Taipei Veterans General Hospital Practice Guidelines Oncology

Non-Hodgkin Lymphoma

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2021年10月16日, 2022年10月16日

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ECOG PERFORMANCE STATUS	
Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982

- Grading for adverse effect from chemotherapy:

CTCAE v5.0

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL*.
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
4	Life-threatening consequences; urgent intervention indicated.
5	Death related to AE.

Diagnosis

- Excisional or incisional biopsy is recommended.
- An FNA biopsy alone is not generally suitable for the initial diagnosis of lymphoma.
- A core needle biopsy is not optimal but can be used under certain circumstances.
- When a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis (immunohistochemistry, flow cytometry, PCR for IGHV and TCR gene rearrangements, karyotype, and FISH for major translocations) may be sufficient for diagnosis.
- Histologic grading cannot be performed on an FNA.

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Staging system for lymphoma (except CLL)

Ann Arbor staging

Stage	Definition
I	Involvement of a single lymph nodes region or a single extralymphatic organ or site (stage I_E)
II	Involvement of two or more node regions on the same side of the diaphragm or localized involvement of an extralymphatic site or organ (stage II_E) and one or more lymph node regions on the same side of the diaphragm
III	Involvement of lymph node regions on both sides of the diaphragm that may also be accompanied by localized involvement of an extralymphatic organ or site (stage III_E) or spleen (stage III_S), or both (stage III_{SE})
IV	Diffuse or disseminated involvement of one or more distant extralymphatic organs with or without associated lymph node involvement
B symptoms	Unexplained fever > 38°C, night sweats, or weight loss > 10% of body weight in the 6 months preceding admission, or a combination of these, is defined as a systemic symptom.
A	Without any B symptoms
X	Bulky disease: tumor >10cm in diameter or > 1/3 widening of the mediastinum

Taipei Veterans General Hospital
Practice Guidelines Oncology

Diffuse Large B-Cell Lymphoma
Primary mediastinal large B-cell lymphoma
Primary CNS lymphoma

Diffuse Large B-Cell Lymphoma
Diagnosis and subtype

Additional test for DLBCL

ESSENTIAL:

- Adequate immunophenotyping to establish diagnosis and GCB versus non-GCB origin
  - ◆ IHC panel: CD20, CD3, CD5, CD10, CD45, BCL2, BCL6, Ki-67, IRF4/MUM1, MYC with or without
  - ◆ Cell surface marker analysis by flow cytometry with peripheral blood and/or biopsy specimen: kappa/ lambda, CD45, CD3, CD5, CD19, CD10, CD20

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- FISH for BCL2, BCL6 rearrangements if MYC positive
- Additional immunohistochemical studies to establish lymphoma subtype
  - IHC panel: cyclin D1, kappa/lambda, CD30, CD138, ALK, HHV8, SOX11
  - Epstein-Barr virus in situ hybridization (EBER-ISH)

Subtype

Subtypes included:

- DLBCL, NOS (includes germinal center and nongerminal center)
- DLBCL coexistent with follicular lymphoma of any grade
- DLBCL coexistent with gastric MALT lymphoma
- DLBCL coexistent with nongastric MALT lymphoma
- Follicular lymphoma grade 3
- Intravascular large B-cell lymphoma
- DLBCL associated with chronic inflammation
- ALK-positive large B-cell lymphomag
- EBV-positive DLBCL, NOS
- T-cell-/histiocyte-rich large B-cell lymphoma
- Large B-cell Lymphoma with with IRF4 rearrangement
- Double expressor DLBCL
- Primary mediastinal large B-cell lymphoma (PMBL);.
- Gray zone lymphoma;
- High-grade B-cell lymphomas with translocations of MYC and BCL2 and/or BCL6 (double-/triple-hit lymphoma);
- High-grade B-cell lymphomas, NOS
- Primary cutaneous DLBCL, leg type

Subtypes not included:

- Primary cutaneous marginal zone lymphoma (PCMZL) and primary cutaneous follicle center lymphoma (PCFCL)
- Primary DLBCL of the CNS
- DLBCL arising from CLL (Richter's transformation)

Diffuse Large B-Cell Lymphoma

Work up

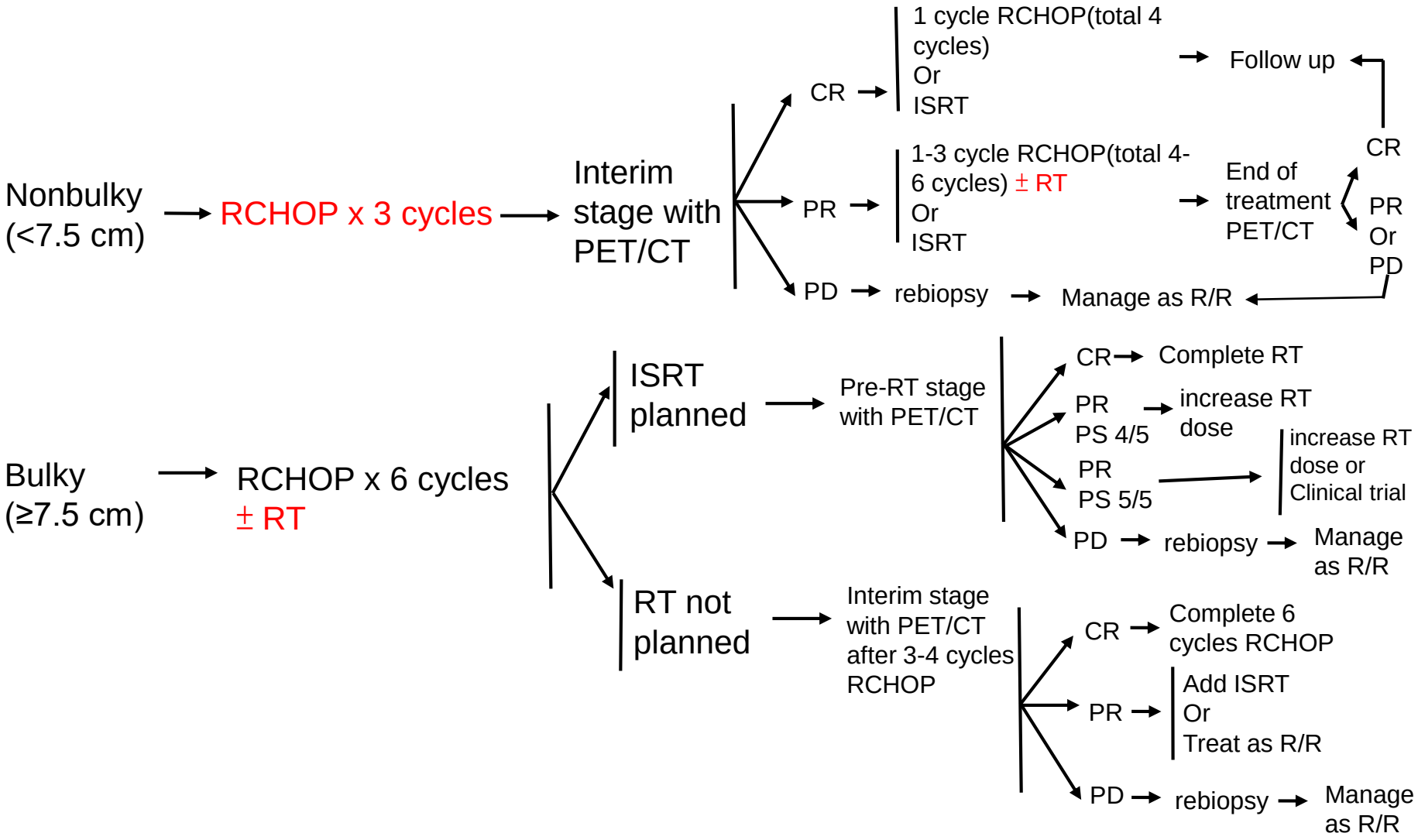
ESSENTIAL:

- Physical exam: attention to node-bearing areas, including Waldeyer's ring, and to size of liver and spleen
- Performance status
- B symptoms
- CBC with differential
- LDH
- Comprehensive metabolic panel
- Uric acid
- PET/CT scan (including neck) and/or C/A/P CT with contrast of diagnostic quality
- Calculation of International Prognostic Index (IPI)
- Hepatitis B testing
- Echocardiogram or MUGA scan if anthracycline or anthracenedione-based regimen is indicated
- Pregnancy testing in women of childbearing age (if chemotherapy or RT planned)

USEFUL UNDER CERTAIN CIRCUMSTANCES:

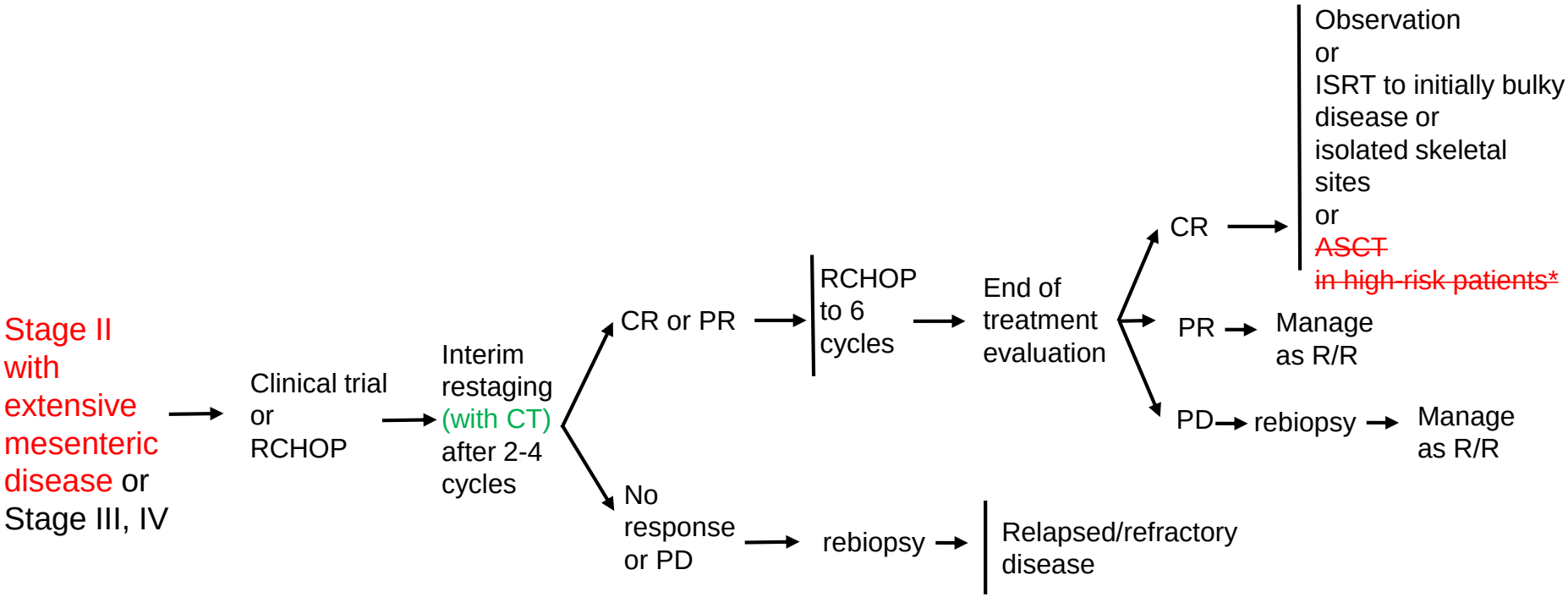
- Head CT/MRI with contrast or neck CT/MRI with contrast
- Discussion of fertility issues and sperm banking
- HIV testing
- Hepatitis C testing
- Beta-2-microglobulin
- Lumbar puncture for patients at risk for CNS involvement, see BCEL-A 2 of 2
- Adequate bone marrow biopsy (>1.6 cm) ± aspirate; bone marrow biopsy is not necessary if PET/CT scan demonstrates bone disease. Bone marrow biopsy with a negative PET/CT scan may reveal discordant lymphoma

Diffuse Large B-Cell Lymphoma
stage I, II



Diffuse Large B-Cell Lymphoma

stage III, IV



* IPI high / high-intermediate risk, may refer to age-adjusted or NCCN-IPI

Diffuse Large B-Cell Lymphoma

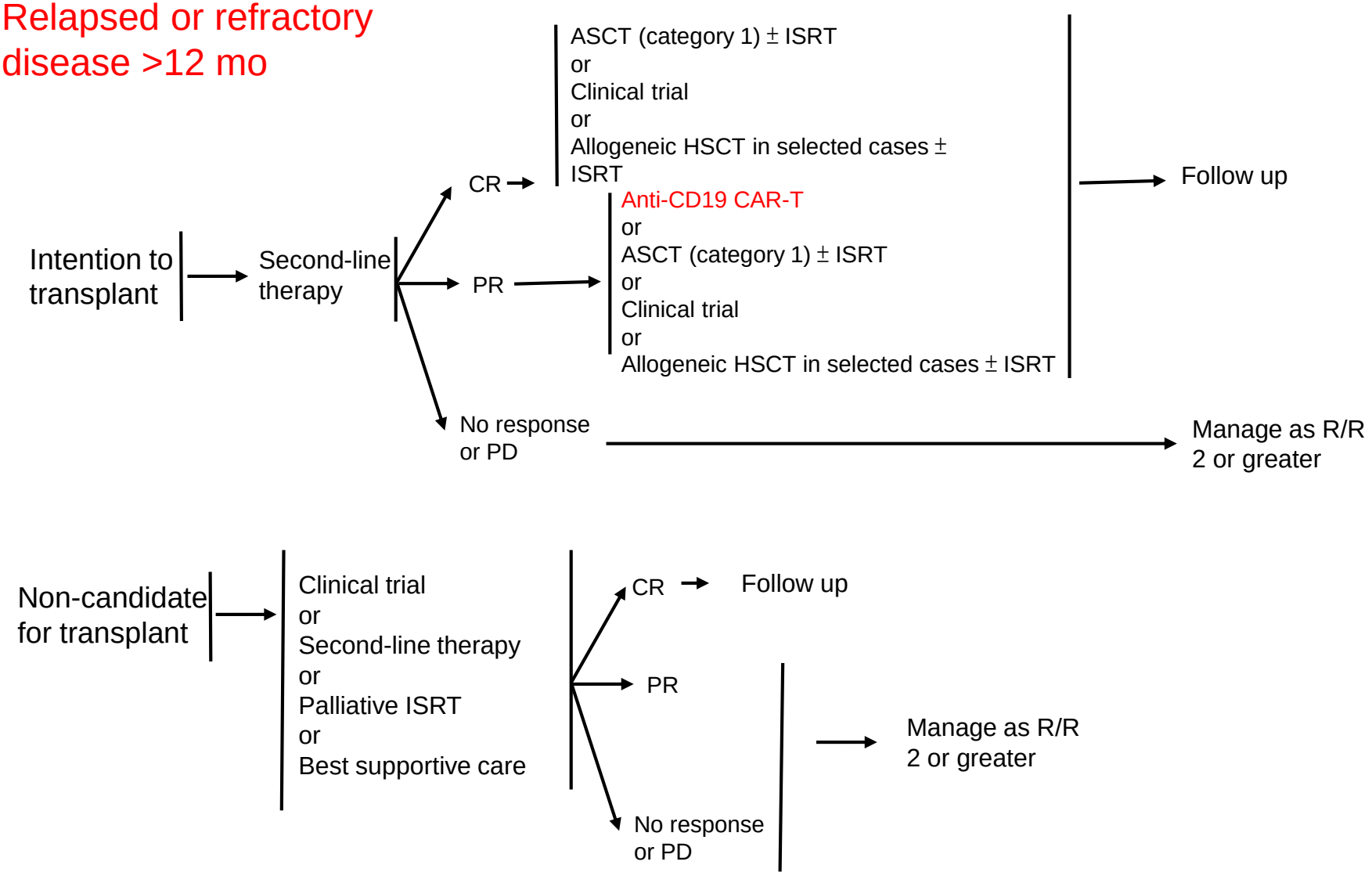
Follow up for CR patients

- H&P and labs, every 3–6 months for 5 years and then yearly or as clinically indicated
- Imaging: C/A/P CT scan with contrast no more often than every 6 months for 2 years after completion of treatment, then only as clinically indicated

Diffuse Large B-Cell Lymphoma

Relapsed/refractory disease

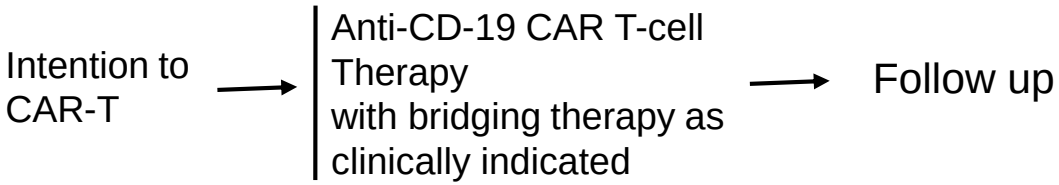
Relapsed or refractory disease >12 mo

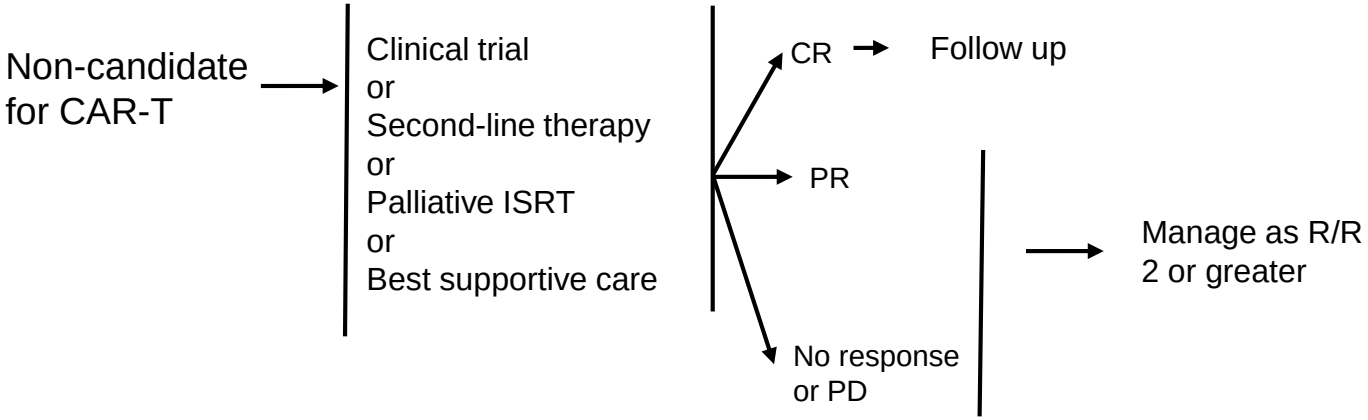


Diffuse Large B-Cell Lymphoma

Relapsed/refractory disease

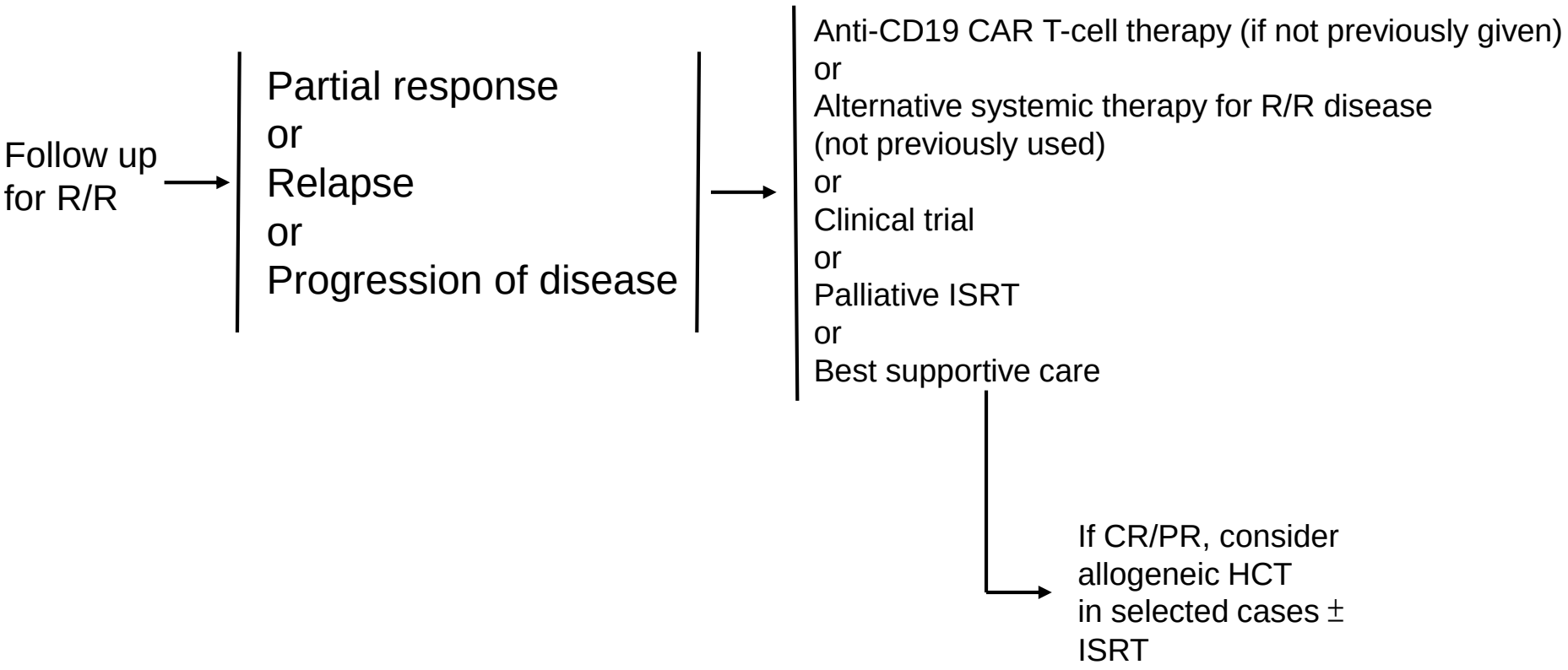
Relapsed or refractory disease <12 mo
or primary refractory





Diffuse Large B-Cell Lymphoma

Relapsed 2 or greater



Diffuse Large B-Cell Lymphoma

PROGNOSTIC MODEL TO ASSESS THE RISK OF CNS DISEASE

CNS-IPI		
Age >60 years	Low risk	0–1
Serum LDH > normal	Intermediate-risk	2–3
Performance status >1	High-risk	4–6 or kidney or adrenal gland involvement
Stage III or IV		
Extranodal involvement >1 site		
Kidney or adrenal gland involvement		

Additional indications for CNS prophylaxis independent of CNS risk score

- Testicular lymphoma
- High-grade B-cell lymphomas (HGBLs) with translocations of MYC and BCL2 and/or BCL6 HGBL, NOS
- Primary cutaneous DLBCL, leg type
- Stage IE DLBCL of the breast
- Kidney or adrenal gland involvement

Treatment add on for risk in CNS disease

- Systemic high-dose methotrexate (3–3.5 g/m2 for 2–4 cycles) during or after the course of treatment
- Intrathecal methotrexate and/or cytarabine (4–8 doses) during or after the course of treatment

Diffuse Large B-Cell Lymphoma

Suggested regimen

First-line Therapy

►Preferred: RCHOP (category 1)

►Others: Dose-adjusted EPOCH + rituximab

For poor LVEF

►DA-EPOCH + rituximab

►RCDOP

►RCEPP(category 2B)

►RCEOP

►RGCVP

FOR VERY FRAIL PATIENTS AND PATIENTS >80 YEARS OF AGE WITH COMORBIDITIES

►RCEPP(category 2B)

►RCDOP

►R-mini-CHOP

►RGCVP

Consolidation (Optimal)

► Lendalidomide maintenance for patients 60–80 y of age (category 2B)

Diffuse Large B-Cell Lymphoma

Suggested regimen

Second-line and Subsequent Therapy

For intention to proceed to transplant

►DHA + platinum ± rituximab
►GDP ± rituximab
►ICE ± rituximab
►ESHAP ± rituximab
►GemOx ± rituximab
►MINE ± rituximab

For non-candidates for transplant

► GemOx ± rituximab
► Pola-BR
► CEOP ± rituximab
► DA-EPOCH ± rituximab
► GDP ± rituximab
► Gemcitabine, vinorelbine ± rituximab (category 3)
► Rituximab

For certain circumstances

► Brentuximab vedotin for CD30+ disease
► Bendamustine ± rituximab (category 2B)
► Ibrutinib (non-GCB DLBCL)
► Lenalidomide ± rituximab (non-GCB DLBCL)

Diffuse Large B-Cell Lymphoma

Suggested regimen

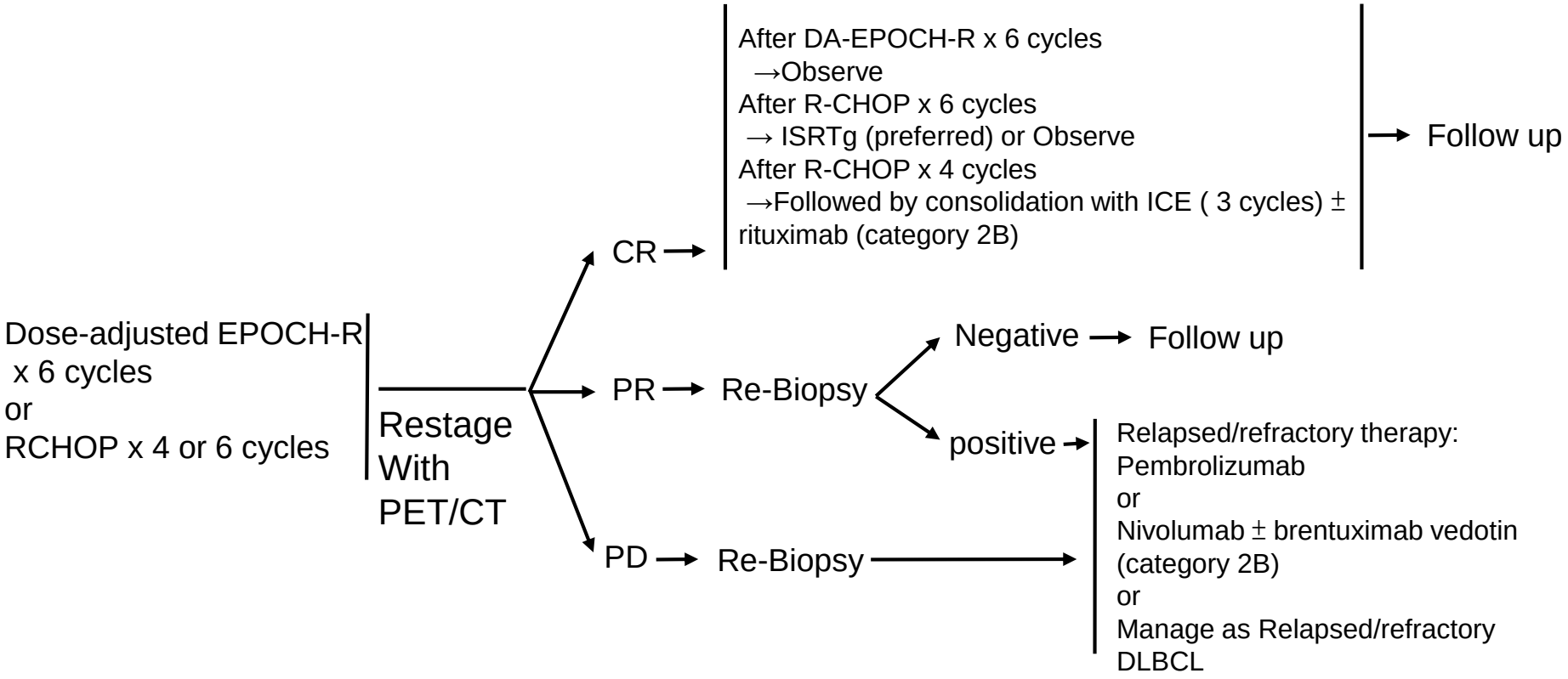
ANTI-CD19 CAR T-CELL THERAPY BRIDGING

- ►DHA + platinum ± rituximab
- ►GDP ± rituximab
- ► GemOx ± rituximab
- ► ICE ± rituximab
- ► Pola-BR (bendamustine should be considered/added only after leukapheresis)

THIRD-LINE AND SUBSEQUENT THERAPY

- ► Selinexor (only after at least two lines of systemic therapy)

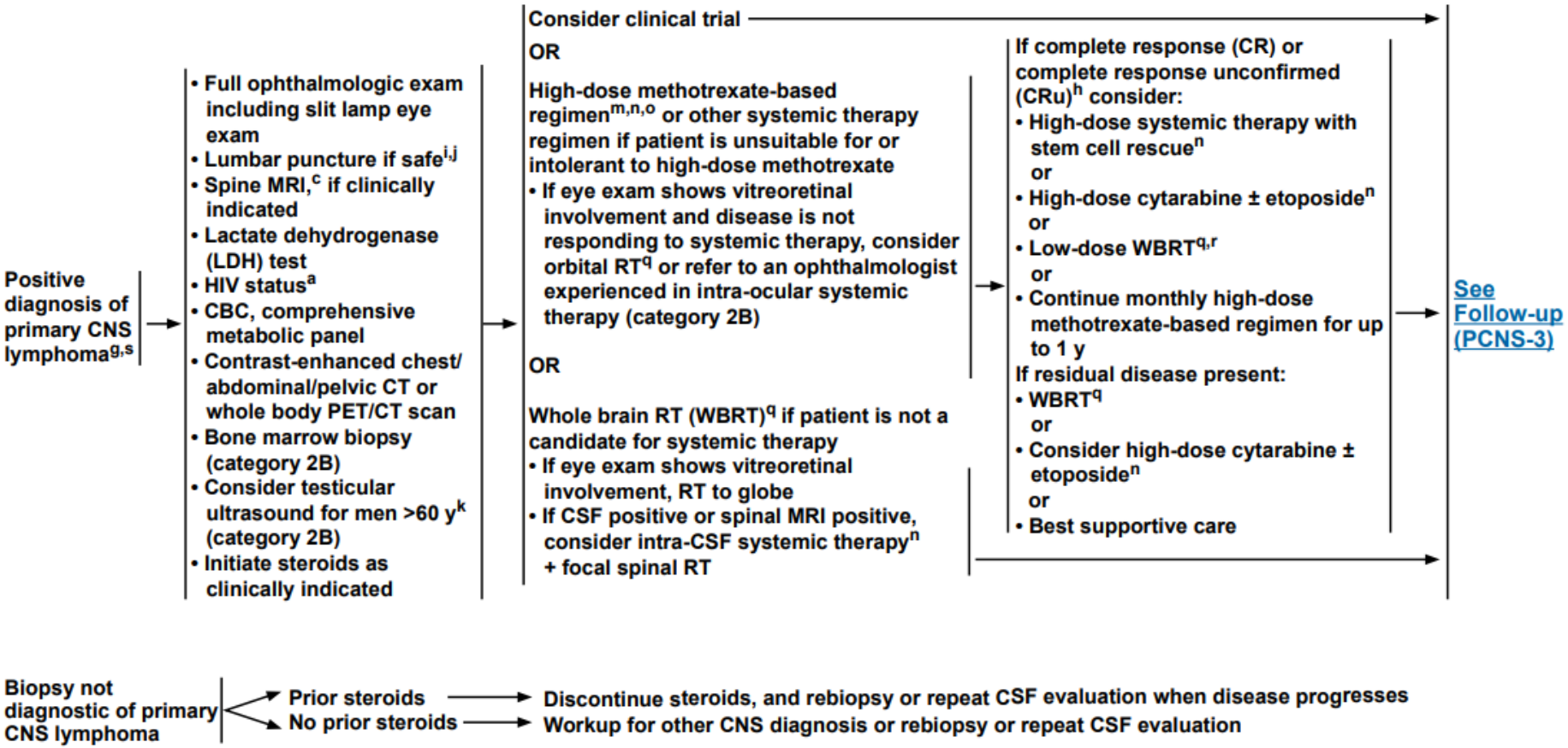
Primary mediastinal large B-cell lymphoma



High-Grade B-Cell Lymphomas

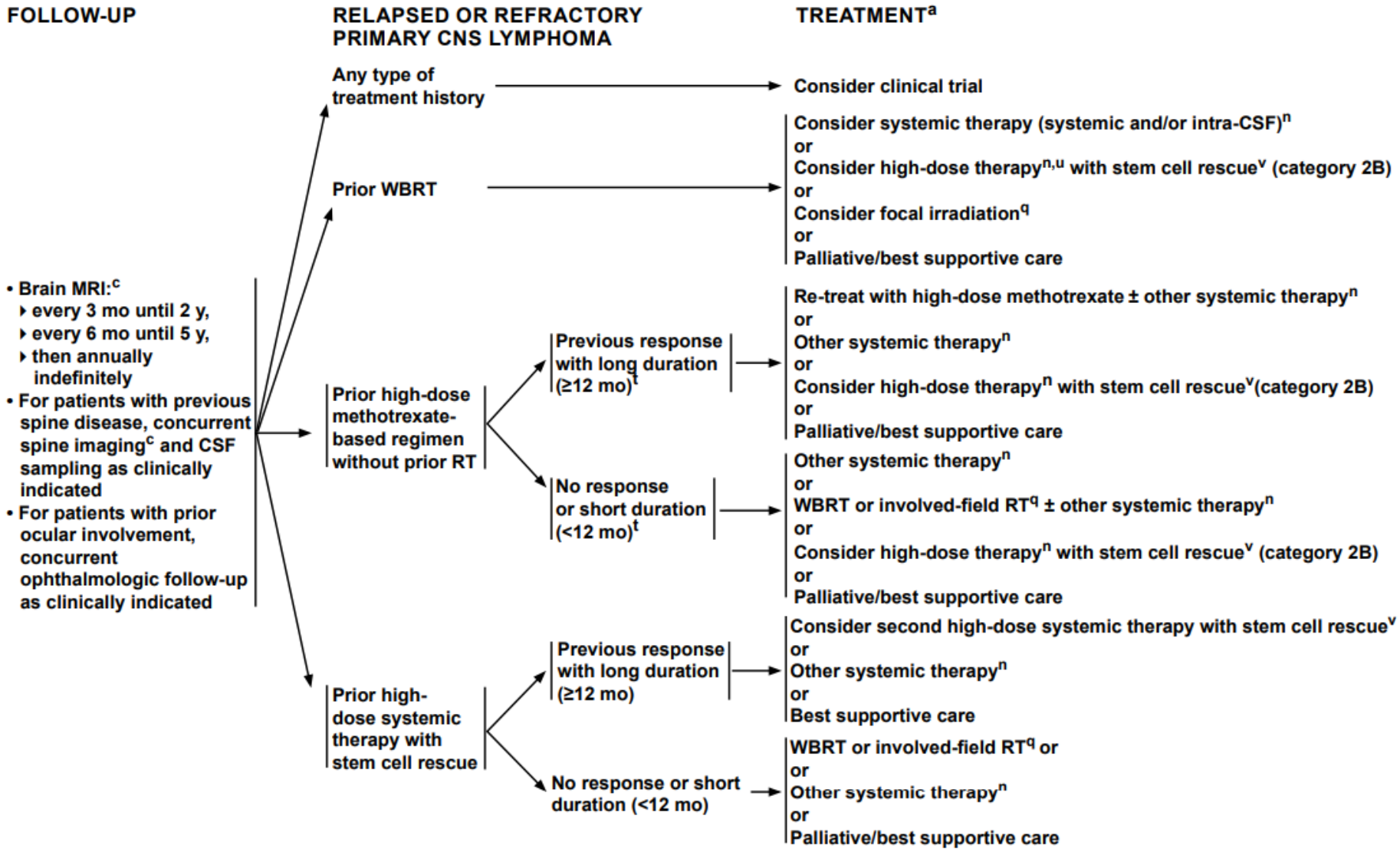
- HGBL NOS
  - Clinical trial is recommended
  - Preferred regimen(While the optimal treatment approach is not established)
    - RCHOP
    - DA-EPOCH-R
    - R-mini-CHOP for frail or elderly patients
    - High toxicity regimen
      - R-HyperCVAD
      - R-CODOX-M/R-IVAC
- HGBL with MYC and BCL2 or BCL6 translocations (Double-/Triple-Hit Lymphomas)
  - Clinical trial is recommended
  - Preferred regimen(While the optimal treatment approach is not established)
    - DA-EPOCH-R
    - R-mini-CHOP for frail or elderly patients
    - High toxicity regimen
      - R-HyperCVAD
      - R-CODOX-M/R-IVAC

Primary CNS lymphoma treatment algorithm



Biopsy not diagnostic of primary CNS lymphoma
- Prior steroids → Discontinue steroids, and rebiopsy or repeat CSF evaluation when disease progresses
- No prior steroids → Workup for other CNS diagnosis or rebiopsy or repeat CSF evaluation

Primary CNS lymphoma treatment algorithm



Taipei Veterans General Hospital Practice Guidelines Oncology

Follicular Lymphoma

Diagnosis

- FL grade 3b is commonly treated as diffuse large B-cell lymphoma *(refer to the DLBCL guideline).*
- The management of FL, grade 3a is controversial and treatment should be individualized.

ESSENTIAL:

Adequate immunophenotyping to establish diagnosis

- IHC panel: CD20, CD3, CD5, CD10, BCL2, BCL6, CD21, or CD23, with or without
- Cell surface marker analysis by flow cytometry with peripheral blood and/ or biopsy specimen: kappa/lambda, CD19, CD20, CD5, CD23, CD10

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- Molecular analysis to detect: antigen receptor gene rearrangements; *BCL2* rearrangements
- Karyotype or FISH: t(14;18); *BCL6*, 1p36, *IRF4/MUM1* rearrangements
- IHC panel: Ki-67; IRF4/MUM1 for FL grade 3, cyclin D1
- NGS panel including *EZH2*, *TNFRSF14* and *STAT6* mutation

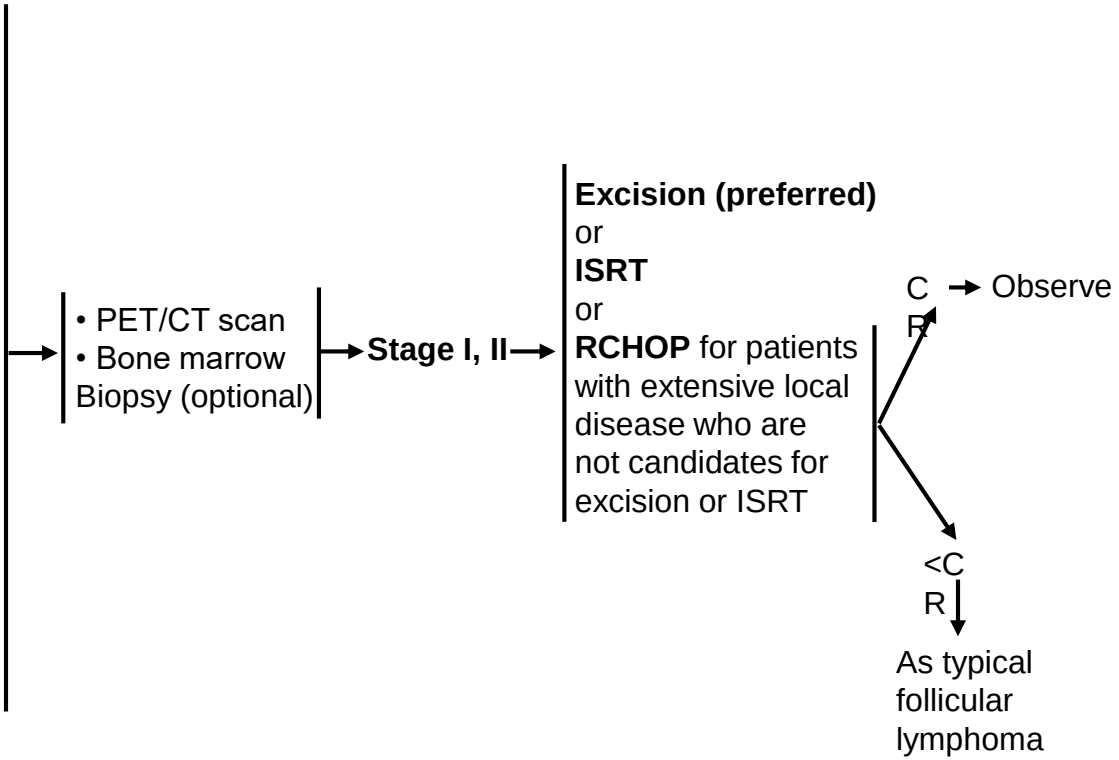
Pediatric-Type Follicular Lymphoma in Adults

Pathologic

- Morphology: expansile follicles, effacement of architecture, absence of diffuse area
- Expresses: BCL6, CD10, ± IRF4/ MUM1 (~20%)
- Proliferation index (Ki-67/MIB-1) >30%
- No rearrangement of *BCL2*, *BCL6*, IRF4/MUM1

Clinical

- Localized disease (stage I, II)
- Head and neck (cervical, submandibular, submental, postauricular, or periparotid lymph nodes) or less common inguinal lymph nodes
- Male sex predominant
- Younger age than typical FL (though can occur in adults older than age 60)



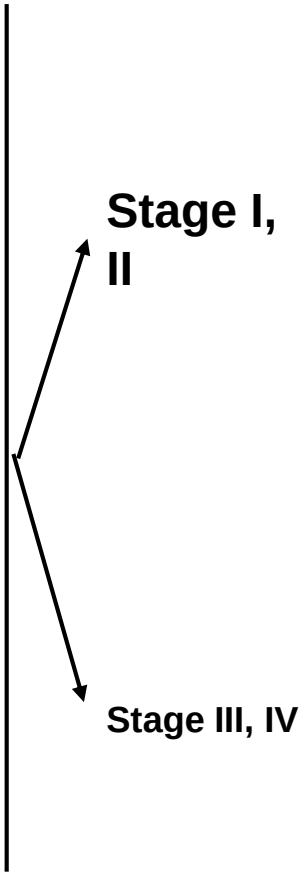
Follicular Lymphoma (grade 1-2) – Workup

ESSENTIAL:

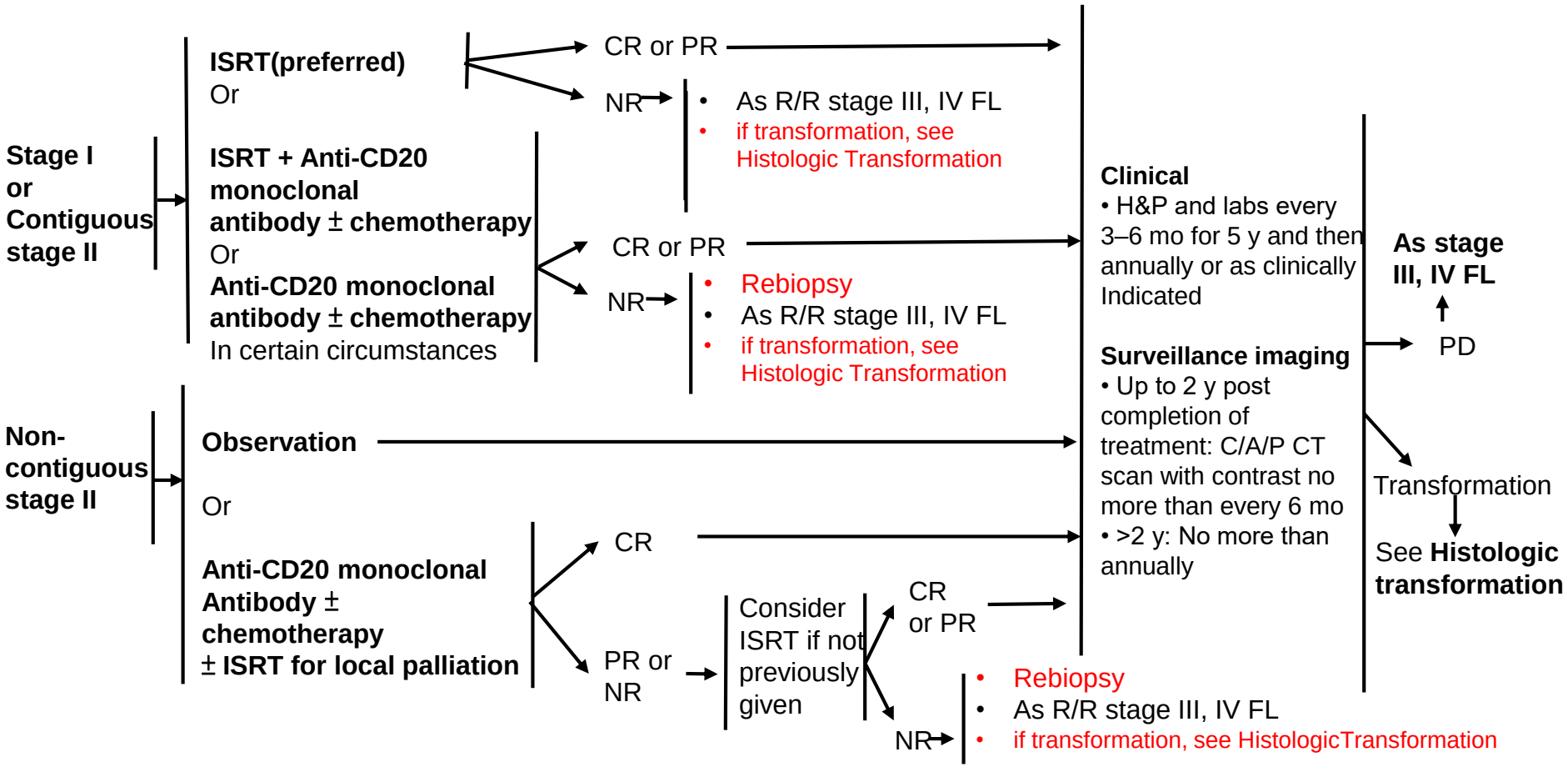
- Physical exam: attention to node-bearing areas, including Waldeyer's ring, and to size of liver and spleen
- Performance status
- B symptoms
- CBC with differential, LDH, comprehensive metabolic panel
- Hepatitis B testing
- PET/CT and/or Chest/abdominal/pelvic (C/A/P) CT with contrast of diagnostic quality
- Whole-body PET/CT scan essential if RT for stage I, II disease or systemic therapy is planned
- Bone marrow biopsy + aspirate (to document clinical stage I–II disease if ISRT planned or to evaluate unexplained cytopenias)
- Pregnancy testing in women of child-bearing age (if chemotherapy or RT planned)

USEFUL IN SELECTED CASES:

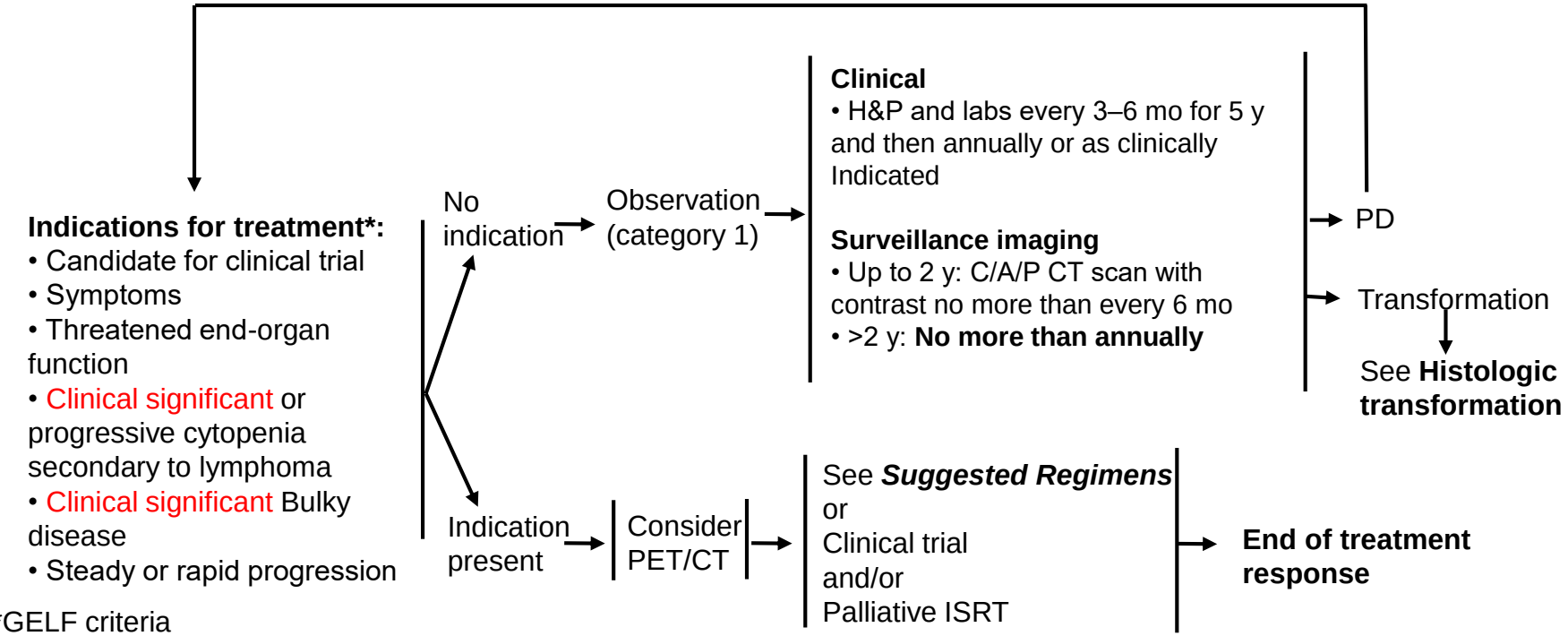
- Echocardiogram or MUGA scan if anthracycline or anthracenedione-based regimen is indicated
- Neck CT with contrast
- Beta-2-microglobulin (necessary for calculation of FLIPI-2)
- Uric acid
- SPEP and/or quantitative immunoglobulin levels
- Hepatitis C testing
- Discussion of fertility issues and sperm banking



Follicular Lymphoma (grade 1-2) – Stage I, II



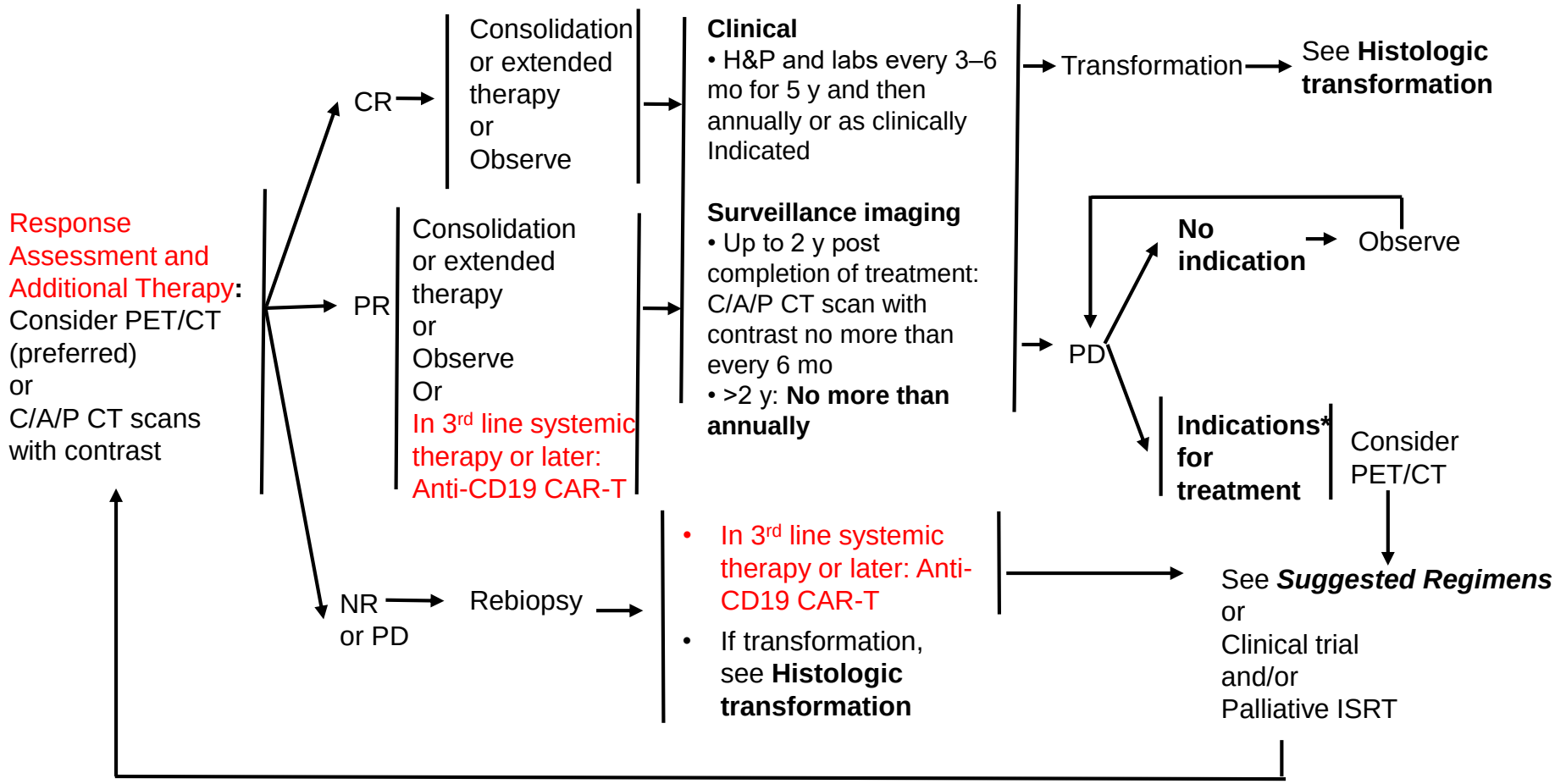
Follicular Lymphoma (grade 1-2) – Stage III, IV



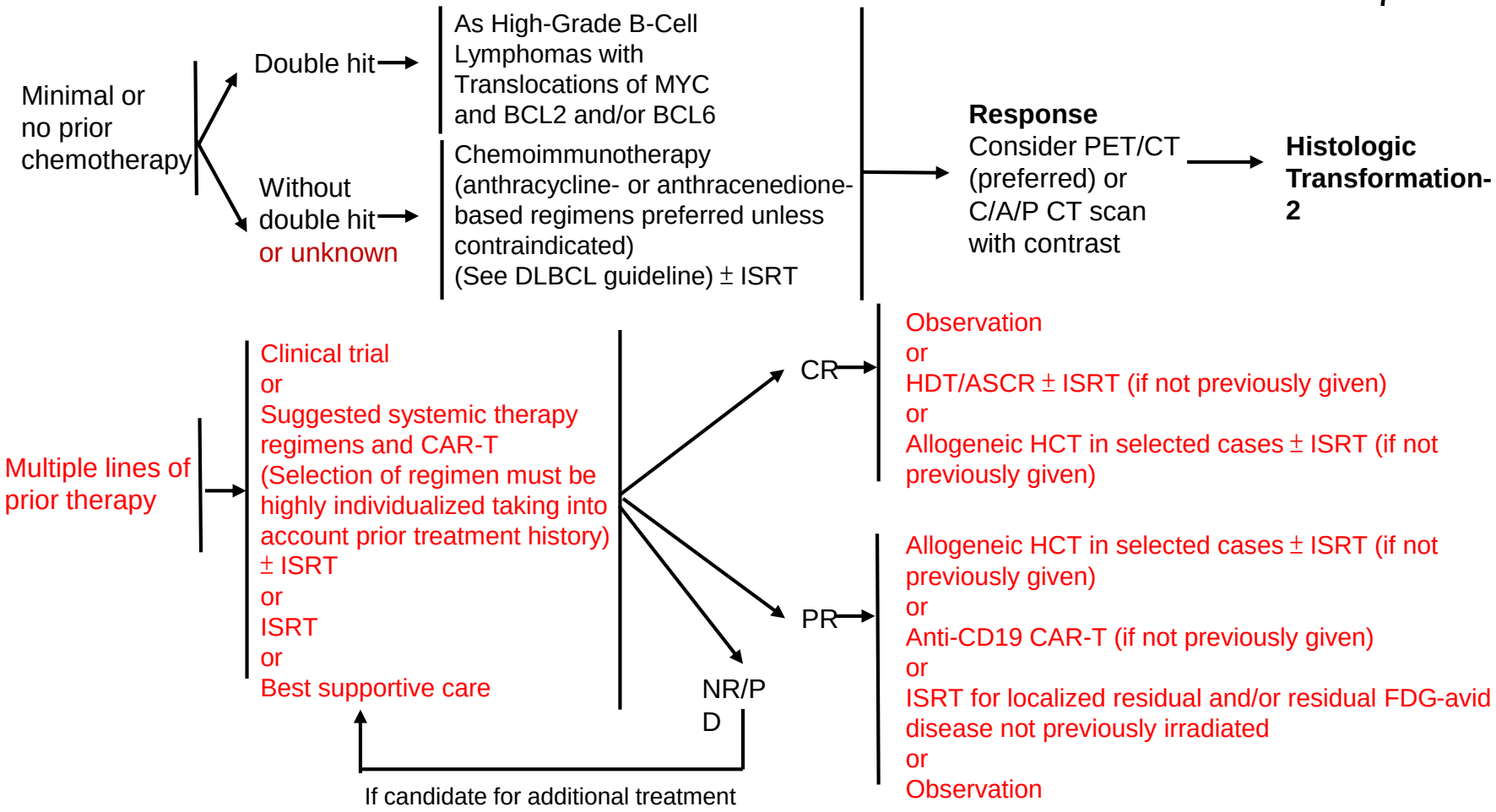
*GELF criteria

- Involvement of ≥3 nodal sites, each with a diameter of ≥3 cm
- Any nodal or extranodal tumor mass with a diameter of ≥7 cm
- B symptoms
- Splenomegaly
- Pleural effusions or peritoneal ascites
- Cytopenias (leukocytes <1.0 x 10^9/L and/or platelets <100 x 10^9/L)
- Leukemia (>5.0 x 10^9/L malignant cells)

Follicular Lymphoma (grade 1-2) – Stage III, IV



Histologic Transformation-1



Histologic Transformation-2

CR → Observation or Clinical trial → Relapsed disease → Biopsy, see histologic transformation after multiple prior therapies

PR /N R/ PD → Second-line therapy
See suggested systemic therapy regimens. Selection of treatment must be based on transplant eligibility

Follicular Lymphoma (grade 1–2)

An TFDA-approved biosimilar is an appropriate substitute for rituximab.

Suggested regimen

First-line Therapy

Preferred regimens (in alphabetical order)

- ►Bendamustine + obinutuzumab or rituximab
- ►CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + obinutuzumab or rituximab
- ►CVP (cyclophosphamide, vincristine, prednisone) + obinutuzumab or rituximab
- ►Lenalidomide + rituximab

Other recommended regimens

- ►Lenalidomide + obinutuzumab (category 2B)
- ►Rituximab (375 mg/m^2 weekly for 4 doses) (consider for low tumor burden)

First-line Therapy for Elderly or Infirm

(if none of the above are expected to be tolerable in the opinion of treating physician)

Preferred regimens

- ►Rituximab (375 mg/m^2 weekly for 4 doses)

Other recommended regimens

- ►Chlorambucil ± rituximab
- ►Cyclophosphamide ± rituximab

Follicular Lymphoma (grade 1–2)

An TFDA-approved biosimilar is an appropriate substitute for rituximab.

Suggested regimen

First-line consolidation or extended dosing (optional)

Preferred regimens following chemoimmunotherapy

►Rituximab maintenance 375 mg/m^2 one dose every 8–12 weeks for 2 years for patients initially presenting with high tumor burden (category 1)

►Obinutuzumab maintenance (1000 mg every 8 weeks for 12 doses)

Other recommended regimens

►If initially treated with single-agent rituximab, consolidation with rituximab 375 mg/m^2 one dose every 8 weeks for 4 doses

Follicular Lymphoma (grade 1–2)

An TFDA-approved biosimilar is an appropriate substitute for rituximab.

Suggested regimen

Second-line therapy

Preferred regimens (alphabetical order)

- ►Bendamustine + obinutuzumab or rituximab
- ►CHOP + obinutuzumab or rituximab
- ►CVP + obinutuzumabl or rituximab
- ►Lenalidomide + rituximab

Other recommended regimens (alphabetical order)

- ►Lenalidomide (if not a candidate for anti-CD20 monoclonal antibody therapy)
- ►Lenalidomide + obinutuzumab
- ►Obinutuzumab
- ►Rituximab
- ►See Second-line Therapy for DLBCL without regard to transplantability

Follicular Lymphoma (grade 1–2)

An TFDA-approved biosimilar is an appropriate substitute for rituximab.

Suggested regimen

Second-line for Elderly or Infirm

Preferred regimens

►Rituximab (375 mg/m^2 weekly for 4 doses)

Other recommended regimens

►Chlorambucil ± rituximab

►Cyclophosphamide ± rituximab

Second-line consolidation or extended dosing (optional)

Preferred regimens following chemoimmunotherapy

►Rituximab maintenance 375 mg/m^2 one dose every 12 weeks for 2 years (category 1)

►Obinutuzumab maintenance for rituximab-refractory disease (1 g every 8 weeks for total of 12 doses)

Other recommended regimens

►High-dose therapy with autologous stem cell rescue

►Allogeneic hematopoietic cell transplant for highly selected patients

Follicular Lymphoma (grade 1–2)

An TFDA-approved biosimilar is an appropriate substitute for rituximab.

Suggested regimen

Third-line and subsequent therapy

PI3K inhibitors

◊ Copanlisib

EZH2 inhibitors

►Tazemetostat

◊ EZH2 mutation positive

◊ EZH2 wild type or unknown relapsed/refractory disease in patients who have no satisfactory alternative treatment options

Anti-CD19 CAR T-cell therapy

►Axicabtagene ciloleucel

►Tisagenlecleucel

An TFDA-approved biosimilar is an appropriate substitute for rituximab.

Suggested regimen for Histologic Transformation

SYSTEMIC THERAPY REGIMENS[c]		
Intention to proceed to transplant	Preferred regimens • RCHOP (if not previously given) • If previously treated with anthracycline-based regimen (in alphabetical order) ‣ DHA (dexamethasone, cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin) ± rituximab ‣ GDP (gemcitabine, dexamethasone, cisplatin) ± rituximab or (gemcitabine, dexamethasone, carboplatin) ± rituximab ‣ ICE (ifosfamide, carboplatin, etoposide) ± rituximab	
Non-candidates for transplant	Preferred regimens • RCHOP (if not previously given) • If previously treated with anthracycline-based regimen (in alphabetical order) ‣ GemOx ± rituximab ‣ Polatuzumab vedotin-piiq ± bendamustine ± rituximab[d,e] ‣ Tafasitamab-cxix[f] + lenalidomide	Other recommended regimens (in alphabetical order) • CEOP (cyclophosphamide, etoposide, vincristine, prednisone) ± rituximab • GDP ± rituximab or (gemcitabine, dexamethasone, carboplatin) ± rituximab • Loncastuximab tesirine-lpyl[f,g]

ANTI-CD19 CAR T-CELL THERAPY[h,i]
• Histologic transfromation of FL or MZL (all subtypes) ‣ Lisocabtagene maraleucel • Histologic transfromation of FL or nodal MZL ‣ Axicabtagene ciloleucel ‣ Tisagenlecleucel

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Burkitt Lymphoma

Burkitt Lymphoma

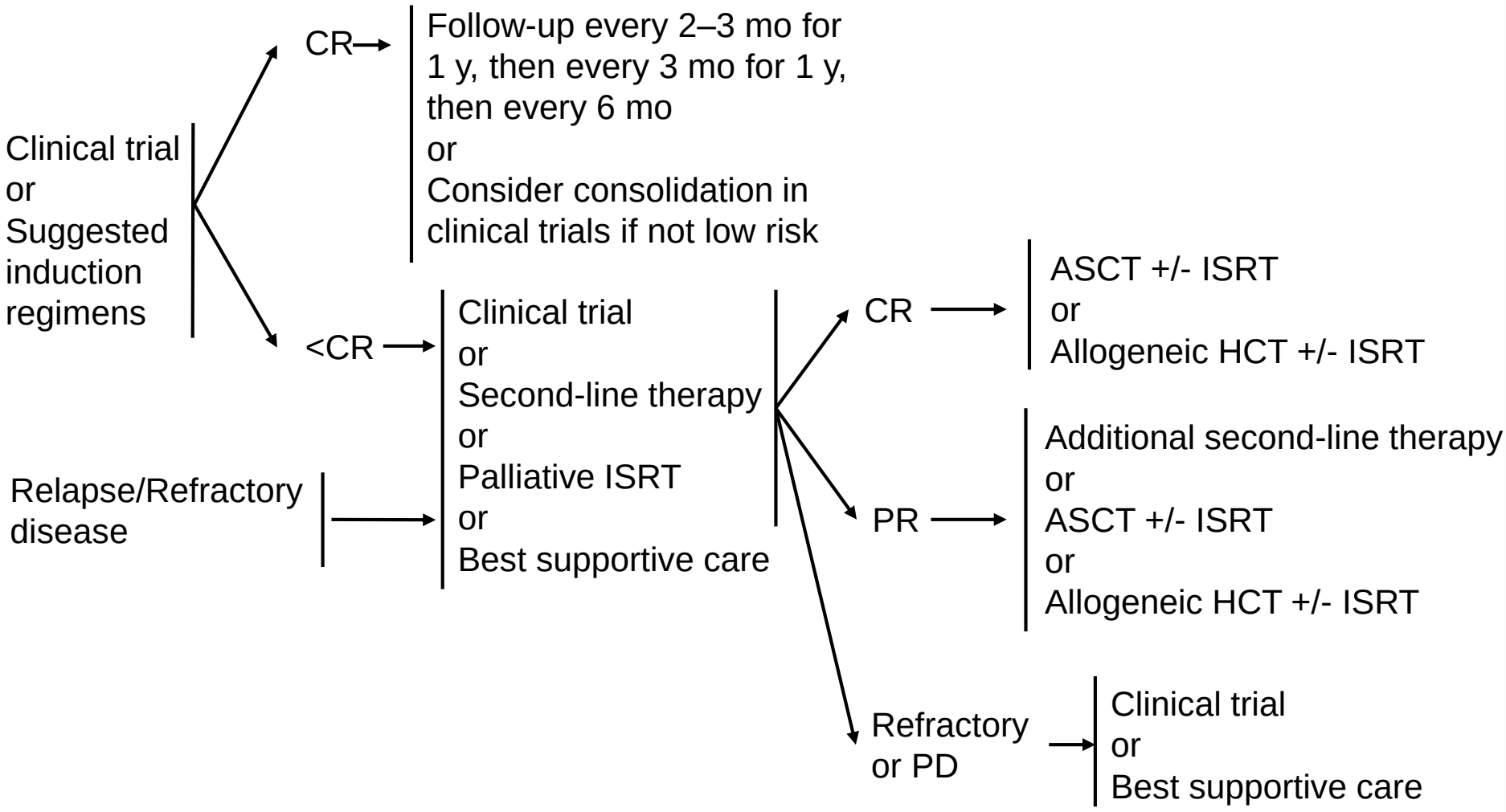
Diagnostic testing

- Adequate immunophenotyping to establish diagnosis
- Karyotype ± FISH: t(8;14) or variants; MYC rearrangement (Optional)
- FISH: BCL2; BCL6 rearrangements or EBER-ISH under certain circumstances (Optional)

Essential evaluation

- History and physical (H&P), B symptoms, performance status
- CBC/DC, LDH, comprehensive metabolic panel, uric acid
- C/A/P CT with contrast or Whole-body PET/CT scan
- Bone marrow biopsy ± aspirate
- Lumbar puncture and CSF flow cytometry
- HIV and Hepatitis B testing
- Echocardiogram or cardiac nuclear medicine scan if anthracycline-based regimen is indicated
- Pregnancy testing

Burkitt Lymphoma



Burkitt Lymphoma

Suggested regimen

Induction Therapy

Low Risk patients (Normal LDH, completely resected abdominal lesion, single extra-abdominal mass <10 cm)

►CODOX-M +/- Rituximab*
►Dose-adjusted EPOCH + Rituximab* + IT MTX
►HyperCVAD / high dose MTX-cytarabine + Rituximab* + IT

High Risk patients

►CODOX-M / IVAC +/- Rituximab*
►HyperCVAD / high dose MTX-cytarabine + Rituximab* + IT
►Dose-adjusted EPOCH + Rituximab* + IT MTX (For patients not able to tolerate aggressive treatments)

** May be adjusted according to availability of rituximab.*

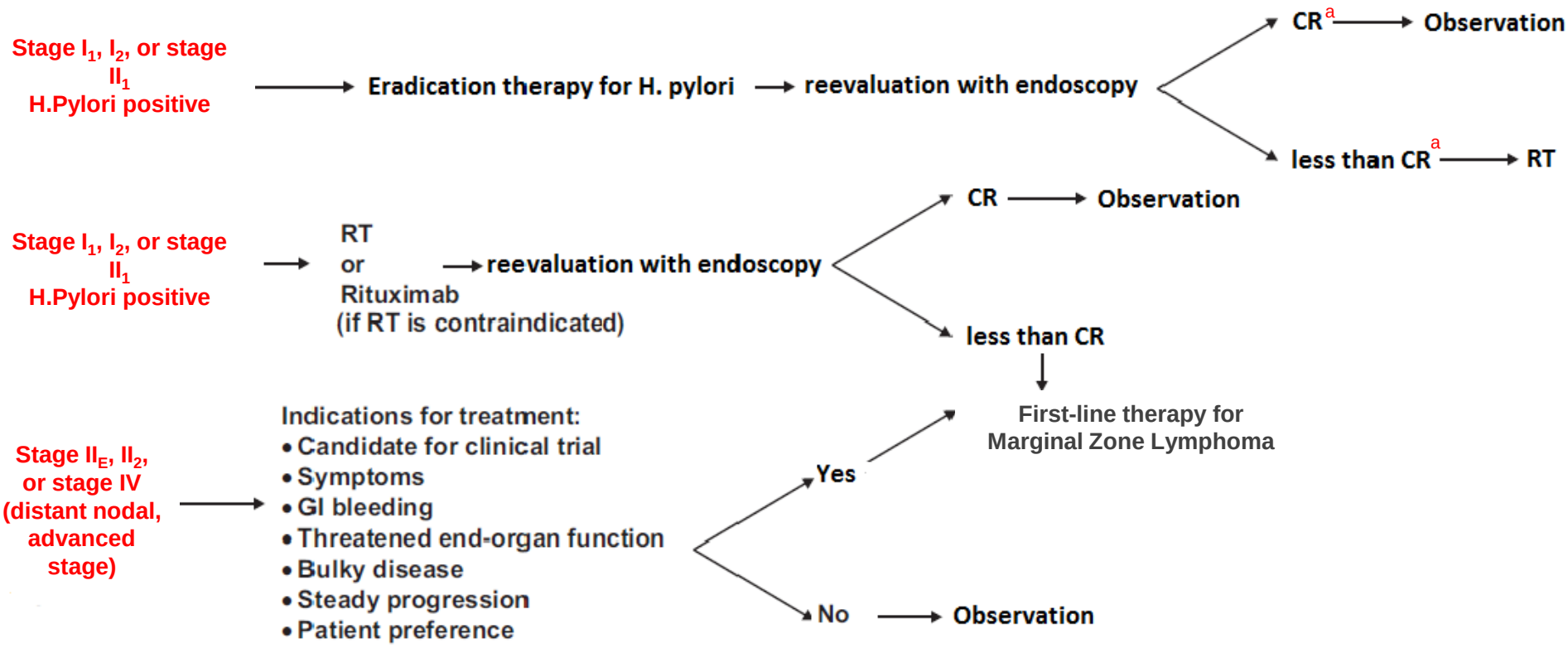
Second-line Therapy

►Dose-adjusted EPOCH + Rituximab + IT MTX
►RICE, IT MTX if not received previously
►RIVAC, IT MTX if not received previously
►RGDP
►High-dose cytarabine + Rituximab
►Other regimens by physician's preference

Taipei Veterans General Hospital Practice Guidelines Oncology

MALT lymphoma

Gastric MALT lymphoma treatment algorithm

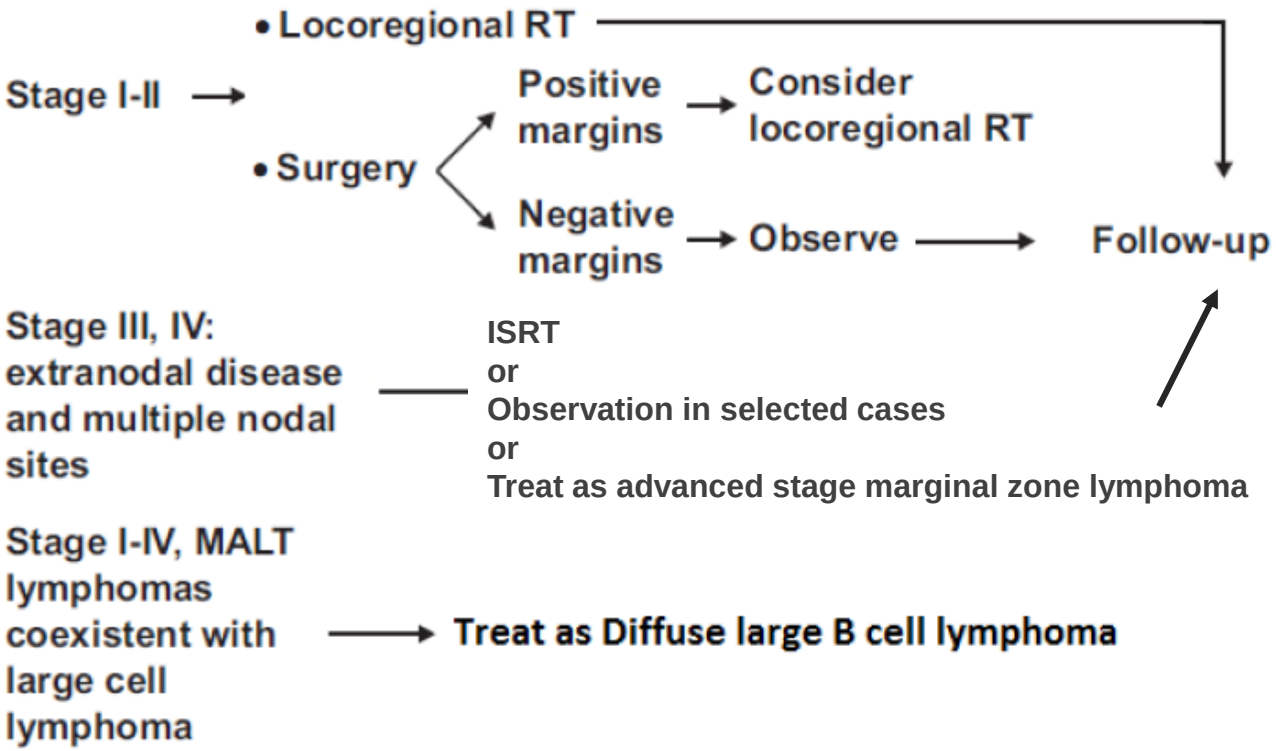


[a]Follow H.pylori, and consider second-line antibiotic treatment if persistent infection

Staging of Gastric MALT Lymphoma: Comparison of Different Systems

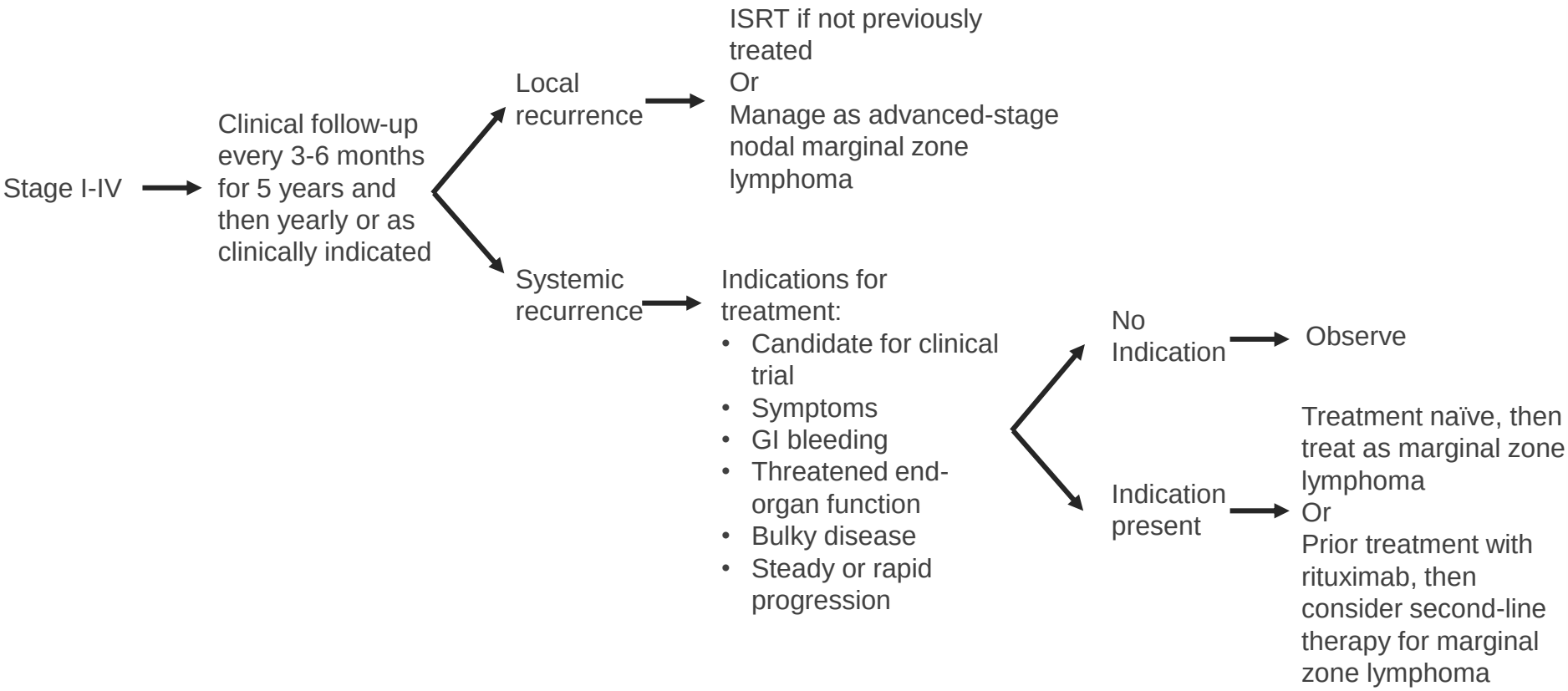
Lugano Staging System for Gastrointestinal Lymphomas		Lugano Modification of Ann Arbor Staging System	TNM Staging System Adapted for Gastric Lymphoma	Tumor Extension
Stage I	Confined to GI tract[a]			
	I_1 = mucosa, submucosa	I_E	T1 N0 M0	Mucosa, submucosa
	I_2 = muscularis propria, serosa	I_E	T2 N0 M0	Muscularis propria
		I_E	T3 N0 M0	Serosa
Stage II	Extending into abdomen			
	II_1 = local nodal involvement	II_E	T1-3 N1 M0	Perigastric lymph nodes
	II_2 = distant nodal involvement	II_E	T1-3 N2 M0	More distant regional lymph nodes
Stage IIE	Penetration of serosa to involve adjacent organs or tissues	II_E	T4 N0 M0	Invasion of adjacent structures
Stage IV[b]	Disseminated extranodal involvement or concomitant supradiaphragmatic nodal involvement		T1-4 N3 M0	Lymph nodes on both sides of the diaphragm/ distant metastases (eg, bone marrow or additional extranodal sites)
		IV	T1-4 N0-3 M1	

Non-gastric MALT lymphoma (Extra-nodal marginal zone lymphoma)



For ocular MALToma if chlamydia infection is proved, systemic antibiotics Doxycycline might be tried before C/T &RT (limited evidence in Taiwan)

Non-gastric MALT lymphoma (Extra-nodal marginal zone lymphoma)



Taipei Veterans General Hospital Practice Guidelines Oncology

Mantle cell lymphoma

Mantle cell lymphoma

ADDITIONAL DIAGNOSTIC TESTING

ESSENTIAL:

- Adequate immunophenotyping to establish diagnosis[a]
  - IHC panel: CD20, CD3, CD5, cyclin D1, CD10, CD21, CD23, BCL2, BCL6, TP53, Ki-67[b] with or without
  - Cell surface marker analysis by flow cytometry peripheral blood and/or biopsy specimen: kappa/lambda, CD19, CD20, CD5, CD23, CD10
- *TP53* sequencing (for patients with typical MCL with an expected aggressive clinical course or particularly if upfront transplant ERTAIN CIRCUMSTANCES:anticipated)[c]

USEFUL UNDER C

- IHC: LEF1 may help distinguish from variant CLL; *SOX11* or *IGHV* sequencing may be useful for determination of clinically indolent[d] MCL; may also help in diagnosis of CCND1- MCL.
- Karyotype or FISH: t(11;14), t(14;18), CLL panel
- Cell surface marker analysis by flow cytometry with peripheral blood and/or biopsy specimen: CD200

WORKUP ESSENTIAL:

- Physical exam: Attention to node-bearing areas, including Waldeyer's ring, and to size of liver and spleen
- Performance status
- B symptoms
- CBC with differential
- Comprehensive metabolic panel
- LDH
- PET/CT scan (including neck) essential if RT planned for stage I, II disease
- PET/CT scan (including neck) and/or C/A/P CT with contrast of diagnostic quality if systemic therapy is planned
- Hepatitis B testing if rituximab contemplated
- Echocardiogram or MUGA scan if anthracycline or anthracycline-based regimen is indicated
- Pregnancy testing in women of childbearing age (if chemotherapy or RT planned)

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- Endoscopy/colonoscopy[f]
- Bone marrow biopsy ± aspirate
- Neck CT with contrast
- Uric acid
- Beta-2-microglobulin
- Hepatitis B and C testing
- Lumbar puncture (for blastic variant or CNS symptoms)
- Discussion of fertility issues and sperm banking

See Stage I, II Induction Therapy (MANT-2)

See Stage II bulky, III, IV Induction Therapy (MANT-3)

[a] Typical immunophenotype: CD5+, CD20+, CD43+, CD23-/+, cyclin D1+, CD10-/+
Note: Some cases of MCL may be CD5- or CD23+. If the diagnosis is suspected, cyclin D1 staining or FISH for t(11;14) should be done. There are rare cases of *CCND1*- MCL (<5%) with an otherwise typical immunophenotype.

[b] Ki-67 proliferation fraction of <30% in lymph nodes is associated with a more favorable prognosis.

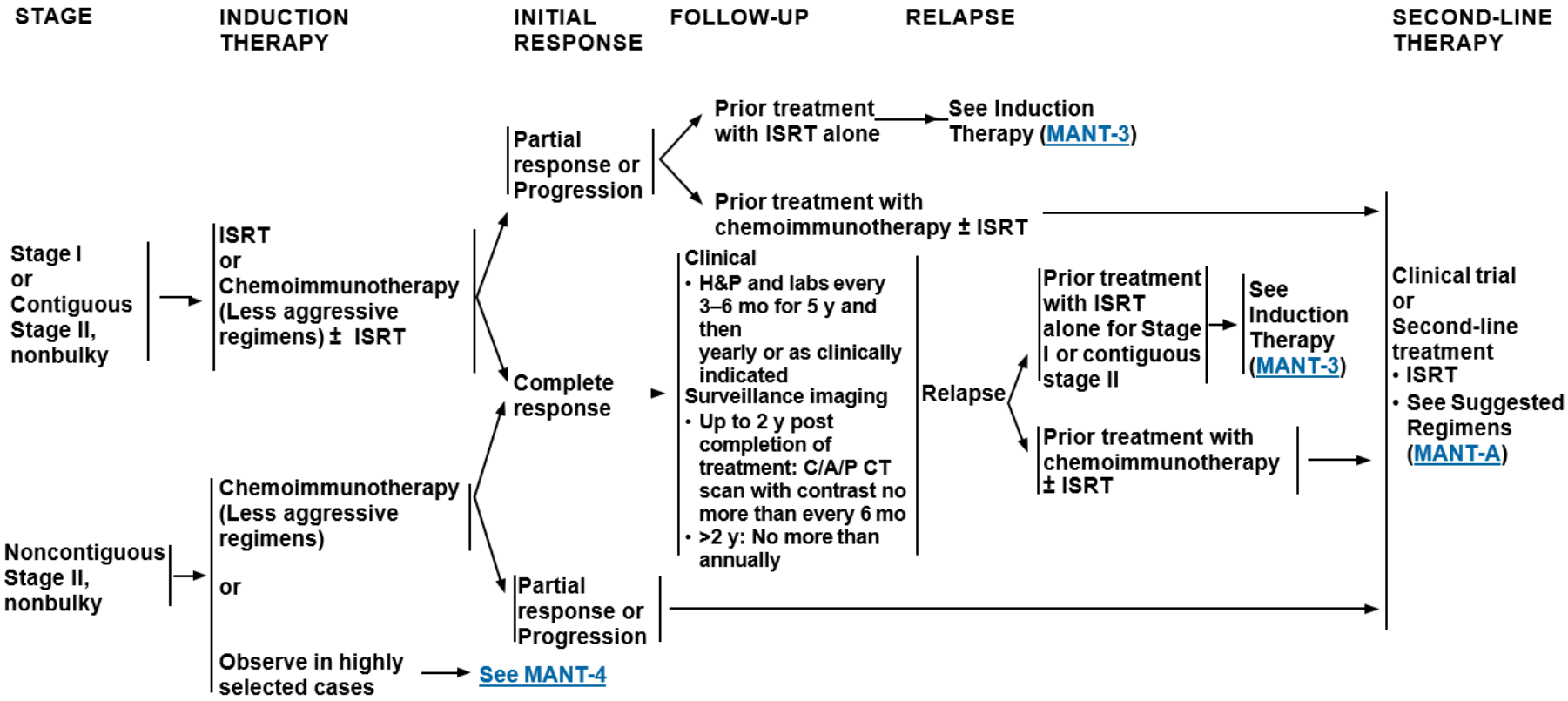
[c] *TP53* mutation has been associated with poor prognosis in patients treated with conventional therapy, including transplant. Clinical trial is strongly suggested for these patients.

[d] Most common biomarker for indolent disease: SOX11- [IGHV mutated]. Typical clinical presentation: leukemic non-nodal CLL-like with splenomegaly, low tumor burden, Ki-67 proliferation fraction <10%.

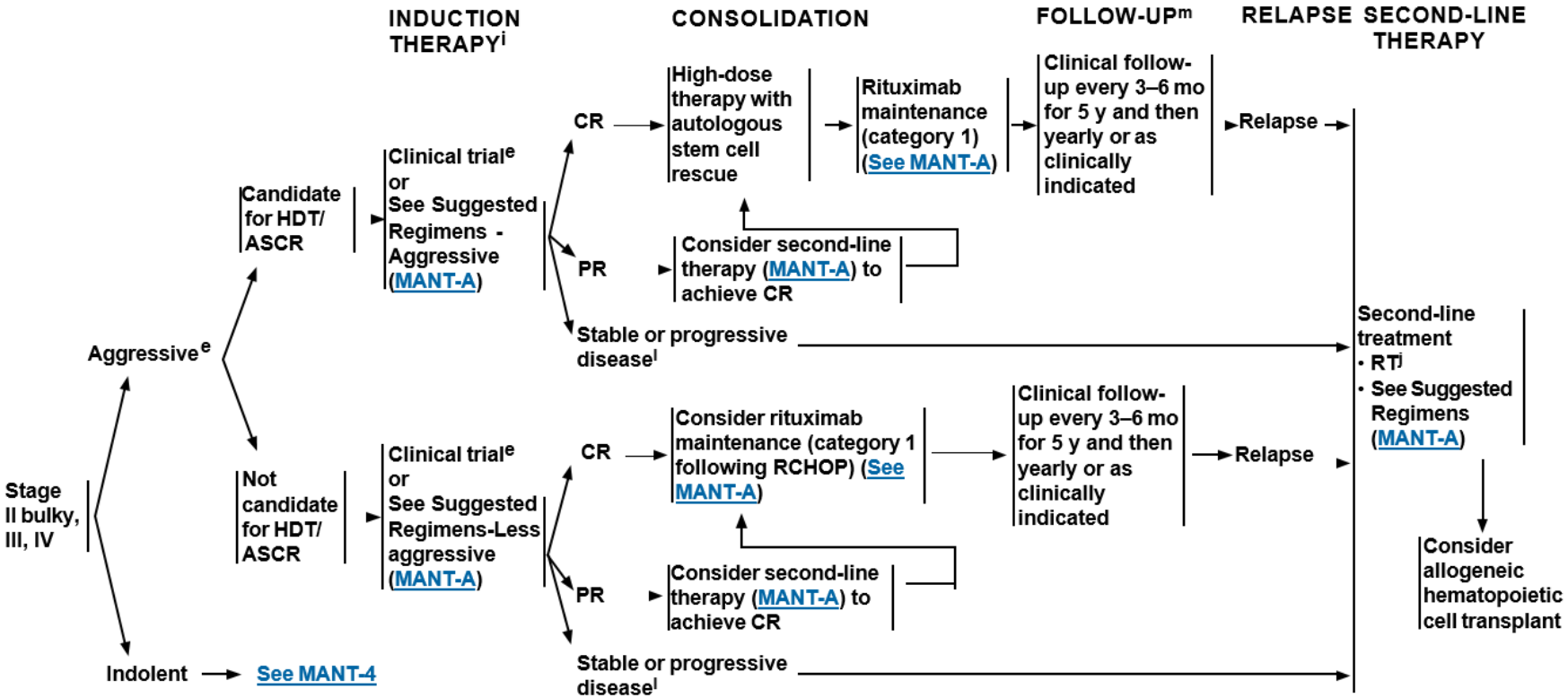
[e] Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen (See NHODG-B). If positive, check viral load and consider consult with gastroenterologist.

[f] Essential for confirmation of stage I–II disease. See Discussion for details.

Mantle cell lymphoma

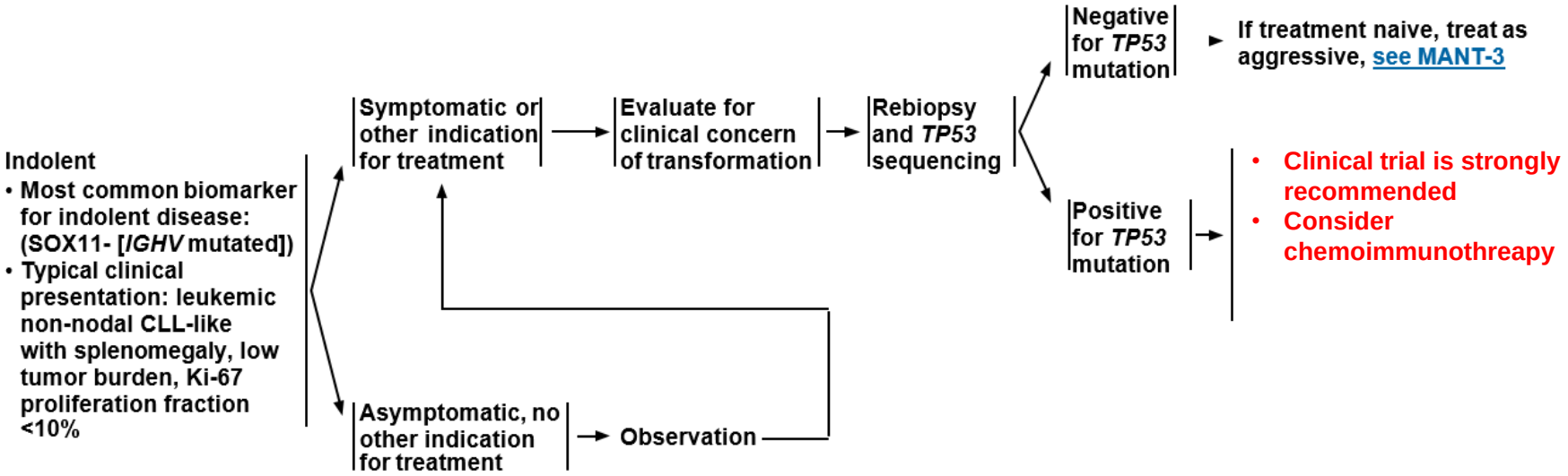


Mantle cell lymphoma



[e] *TP53* mutation has been associated with poor prognosis in patients treated with conventional therapy, including transplant. Clinical trial is strongly suggested for these patients.
[i] Early referral for high-dose therapy with stem cell rescue is advisable for planning purposes.
[m] Follow-up includes diagnostic tests and imaging using the same modalities performed during workup as clinically indicated.
[n] Patients who have achieved near CR can proceed to HDT/ASCR. Patients who have achieved minimal PR with substantial disease should be treated as having stable, refractory disease. Patients who have achieved a very good PR may be treated with additional therapy to achieve CR with the goal of proceeding to HDT/ASCR.
[o] Patients who have achieved a very good PR or better can be observed or consider rituximab maintenance. Patients who have achieved minimal PR with substantial

Mantle cell lymphoma



[e] *TP53* mutation has been associated with poor prognosis in patients treated with conventional therapy, including transplant. Clinical trial is strongly suggested for these patients.
[p] The description represents the most common indolent presentation; however, there are some patients with GI or blood/bone marrow involvement only, which may

SUGGESTED TREATMENT REGIMENS IN MCL
An TFDA-approved biosimilar is an appropriate substitute for rituximab.

First-line Therapy

- **Induction Therapy**
  - Aggressive therapy
    - Preferred regimens
      - **RDHA** (rituximab, dexamethasone, cytarabine) + **platinum** (carboplatin, cisplatin, or oxaliplatin)
      - **Alternating RCHOP/RDHAP** (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)/(rituximab, dexamethasone, cytarabine, cisplatin)
      - **NORDIC regimen** (dose-intensified induction immunochemotherapy with rituximab + cyclophosphamide, vincristine, doxorubicin, prednisone [**maxi-CHOP**]) alternating with rituximab + high-dose cytarabine (R+HiDAC)
      - **HyperCVAD** (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) + **rituximab**
      - **Rituximab, bendamustine followed by rituximab, high-dose cytarabine**
    - Other recommended regimen
      - **Bendamustine + rituximab**
- **Consolidation After Aggressive Therapy**
  - High-dose therapy followed by autologous stem cell rescue
- **Consider Maintenance After HDT/ASCR**
  - Maintenance rituximab every 8 weeks x 3 y

- **Induction Therapy**
  - Less aggressive therapy
    - Preferred
      - **BR** (Bendamustine + rituximab)
      - **VR-CAP** (bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone)
      - **RCHOP**
      - Lenalidomide + rituximab
    - Other recommended regimen
      - **Modified rituximab-HyperCVAD** in patients older than 65 y
      - **RBAC500** (rituximab, bendamustine, cytarabine)

- **Consider Maintenance After Less Aggressive Therapy**
  - Rituximab every 8 weeks until progression or intolerance (following RCHOP; 2–5 y following modified rituximab-HyperCVAD)
  - Prospective trial data suggest no benefit after BR
  - Untested after VR-CAP, RBAC500

SUGGESTED TREATMENT REGIMENS IN MCL

An TFDA-approved biosimilar is an appropriate substitute for rituximab.

Second-line and subsequent therapy

- Preferred regimens
  - BTK inhibitors
    - Acalabrutinib
    - Ibrutinib ± rituximab
    - Zanubrutinib
  - Lenalidomide ± rituximab
- Other regimens
  - Bendamustine + rituximab (if not previously given)
  - Bendamustine + rituximab + cytarabine (RBAC500) (if not previously given)
  - Bortezomib ± rituximab
  - R-DHAP
  - GemOx (gemcitabine + oxaliplatin)
  - Ibrutinib + lenalidomide + rituximab
  - Ibritimib + venetoclax
  - Venetoclax ± rituximab

- Second-line Consolidation
  - Allogeneic hematopoietic cell transplant (nonmyeloablative or myeloablative) in selected cases

- Third-line Consolidation
  - CD19 CAR-T (only given after chemoimmunotherapy and BTK inhibitor)
  - Clinical trial

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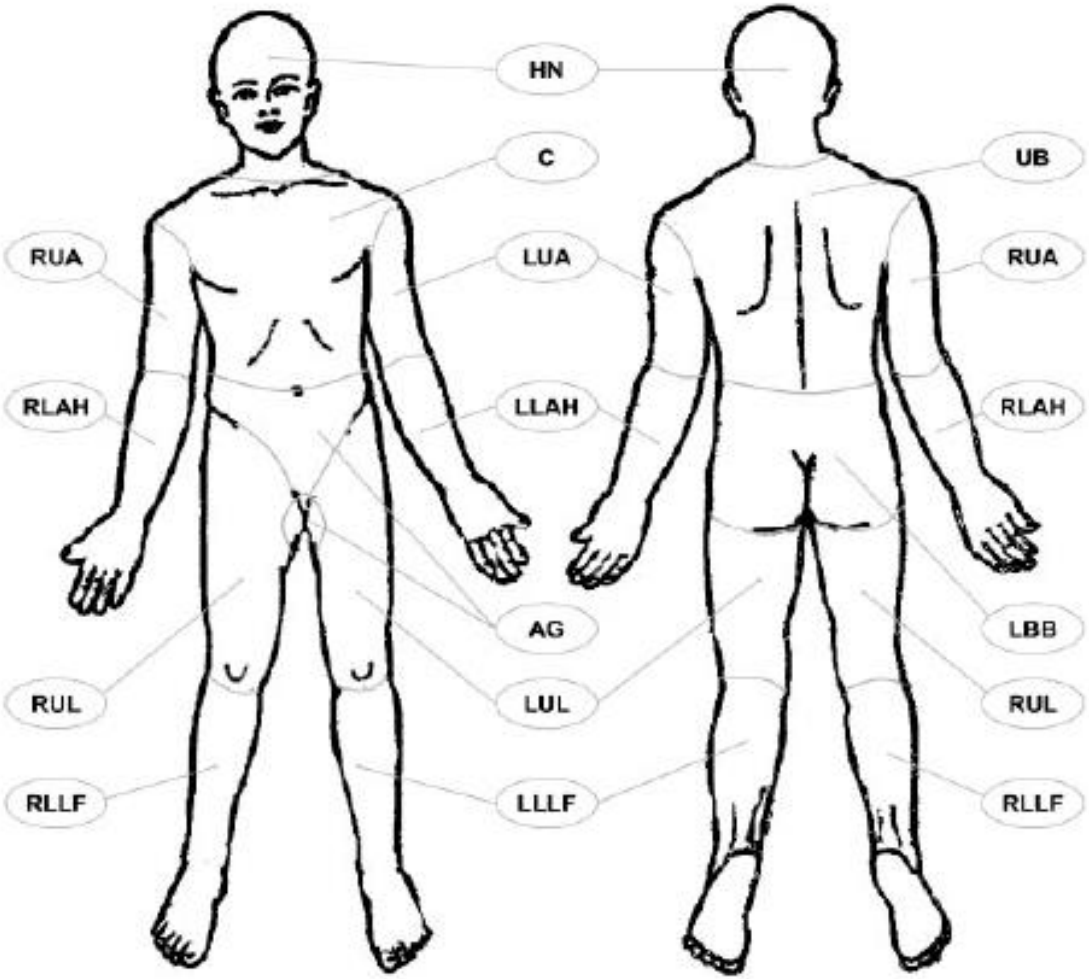
Lymphoblastic lymphoma

Lymphoblastic lymphoma

See guideline for Acute lymphoblastic leukemia

BODY REGIONS FOR THE DESIGNATION OF T (SKIN INVOLVEMENT) CATEGORY

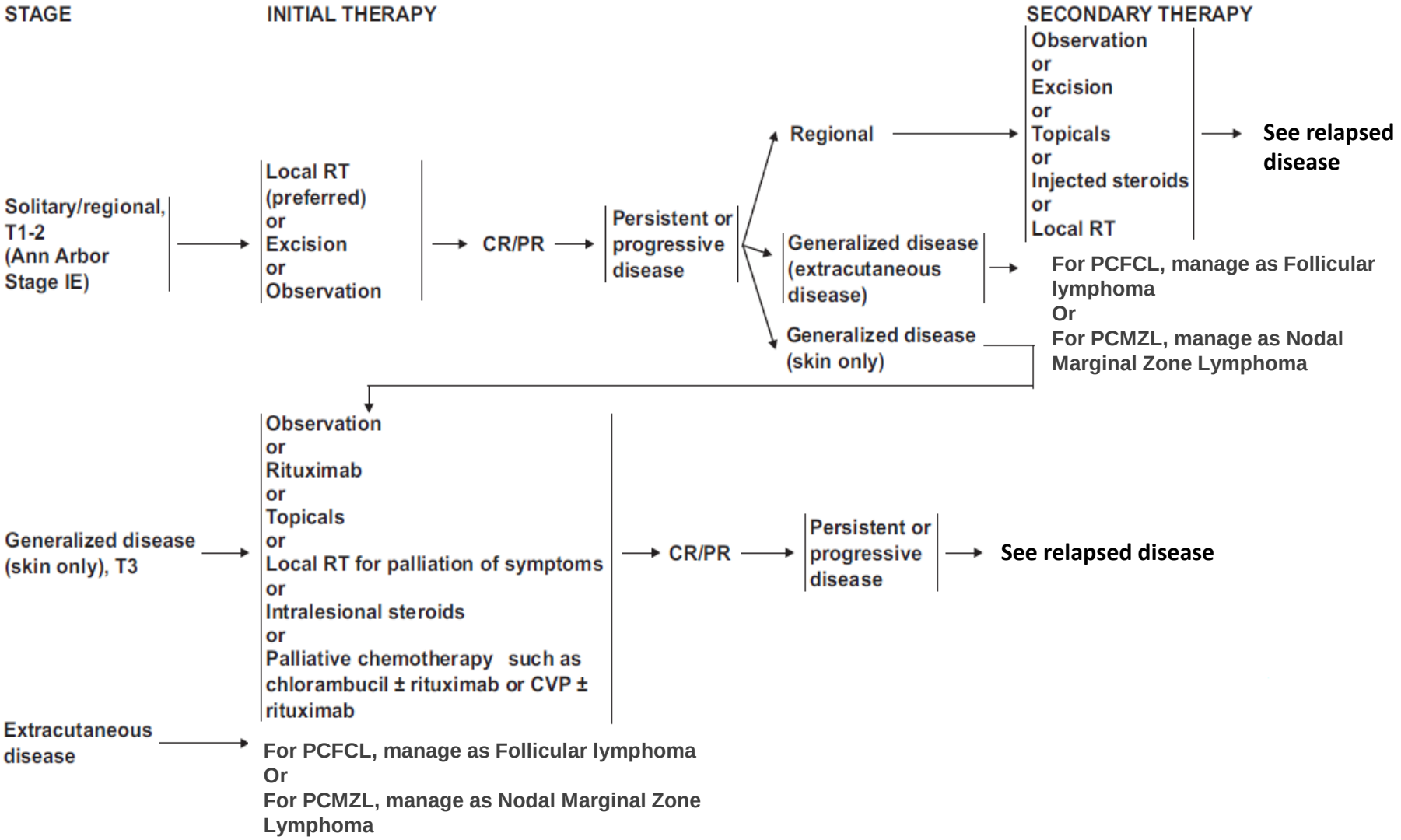


HN	Head & Neck
C	Chest
LUA	Left Upper Arm
LLAH	Left Lower Arm & Hand
AG	Abdominal & Genital
LUL	Left Upper Leg
LLLF	Left Lower Leg & Feet
RUA	Right Upper Arm
RLAH	Right Lower Arm & Hand
RUL	Right Upper Leg
RLLF	Right Lower Leg & Feet
UB	Upper Back
LBB	Lower Back & Buttock

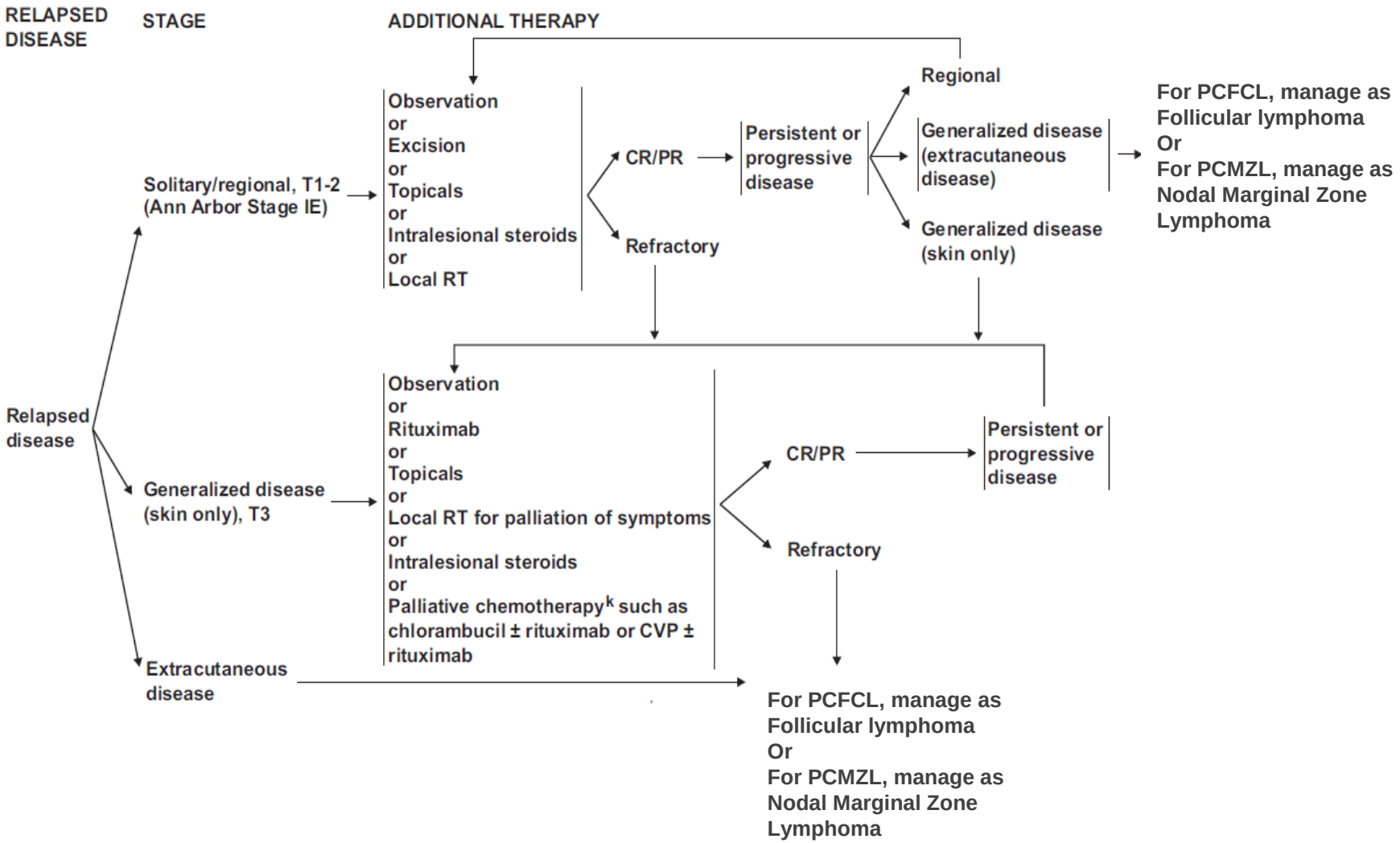
TNM CLASSIFICATION OF CUTANEOUS LYMPHOMA OTHER THAN MF/SS

T	
T1	Solitary skin involvement T1a: a solitary lesion < 5 cm diameter T1b: a solitary > 5 cm diameter
T2	Regional skin involvement: multiple lesions limited to 1 body region or 2 contiguous body regions T2a: all-disease-encompassing in a < 15-cm-diameter circular area T2b: all-disease-encompassing in a > 15- and < 30-cm-diameter circular area T2c: all-disease-encompassing in a > 30-cm-diameter circular area
T3	Generalized skin involvement T3a: multiple lesions involving 2 noncontiguous body regions T3b: multiple lesions involving ≥ 3 body regions
N	
N0	No clinical or pathologic lymph node involvement
N1	Involvement of 1 peripheral lymph node region that drains an area of current or prior skin involvement
N2	Involvement of 2 or more peripheral lymph node regions or involvement of any lymph node region that does not drain an area of current or prior skin involvement
N3	Involvement of central lymph nodes
M	
M0	No evidence of extracutaneous non–lymph node disease
M1	Extracutaneous non-lymph node disease present

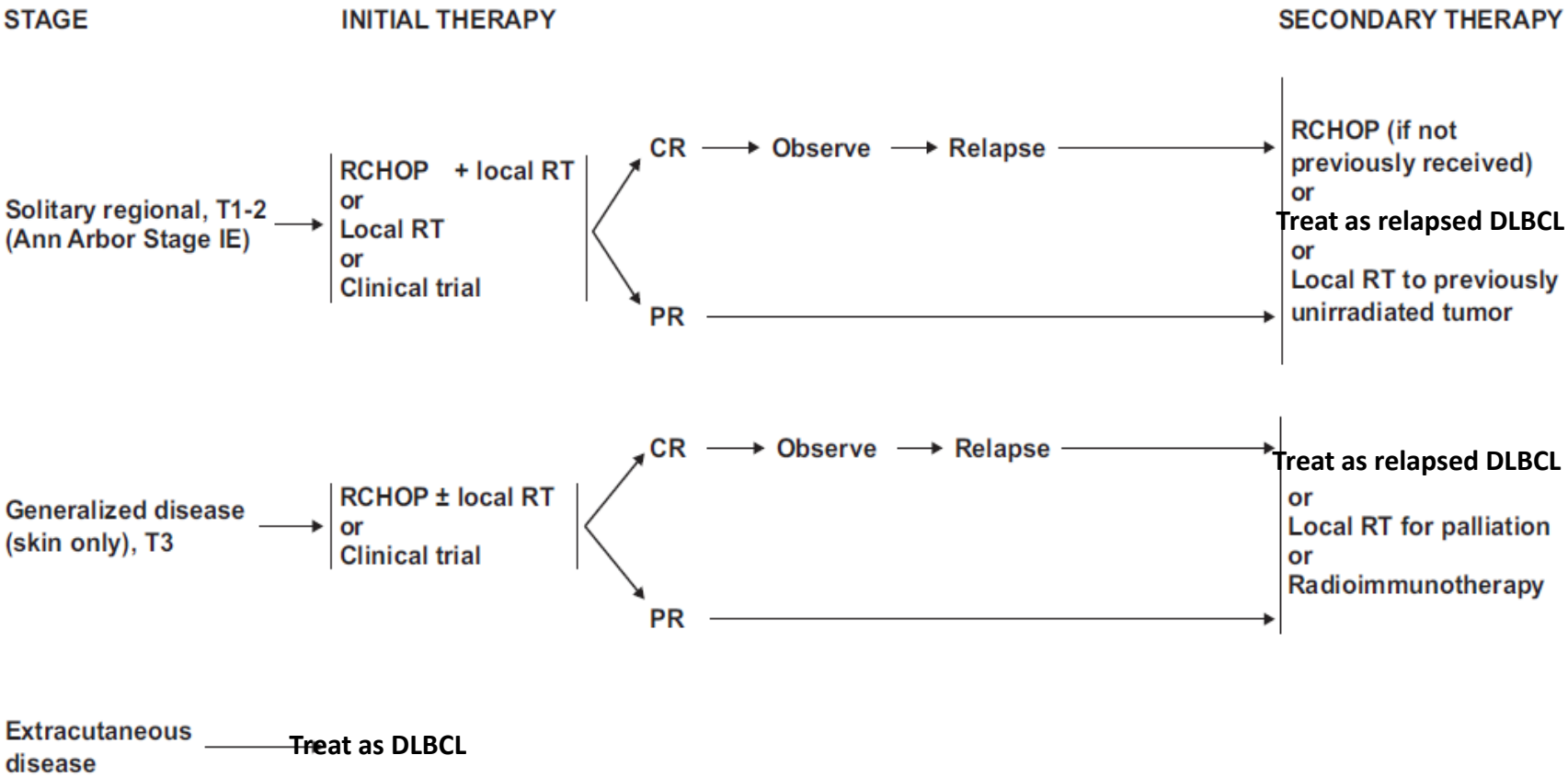
Primary Cutaneous marginal zone lymphoma or follicle center cell lymphoma



Primary Cutaneous marginal zone lymphoma or follicle center cell lymphoma



Primary Cutaneous DLBCL, Leg-type



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Peripheral T-cell lymphoma
Extra-nodal NK/T-cell lymphoma

The 2008 WHO classification of lymphomas: T-cell non-Hodgkin lymphoma

T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK-cells*
Aggressive NK cell leukemia
Systemic EBV⁺ T-cell lymphoproliferative disease of childhood (associated with chronic active EBV infection)
Hydroa vacciniforme-like lymphoma
Adult T-cell leukemia/ lymphoma
Extranodal NK/T cell lymphoma, nasal type
Enteropathy-*associated* T-cell lymphoma
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30⁺ T-cell lymphoproliferative disorder
    Lymphomatoid papulosis
    Primary cutaneous anaplastic large-cell lymphoma
*Primary cutaneous aggressive epidermotropic CD8⁺ cytotoxic T-cell lymphoma**
Primary cutaneous gamma-delta T-cell lymphoma
*Primary cutaneous small/medium CD4⁺ T-cell lymphoma**
Peripheral T-cell lymphoma, not otherwise specified
Angioimmunoblastic T-cell lymphoma
Anaplastic large cell lymphoma (ALCL), ALK⁺
*Anaplastic large cell lymphoma (ALCL), ALK⁻**

Peripheral T-Cell Lymphoma – Diagnosis

- **Adequate immunophenotyping to establish diagnosis**
  - Recommended panel for paraffin section immunohistochemistry: CD20, CD3, CD10, BCL6, Ki-67, CD5, CD30, CD2, CD4, CD8, CD7, CD56, CD57, CD21, CD23, EBER, ALK

    or
  - Cell surface marker analysis by flow cytometry: kappa/lambda, CD45, CD3, CD5, CD19, CD10, CD20, CD30, CD4, CD8, CD7, CD2

- **USEFUL UNDER CERTAIN CIRCUMSTANCES**
  - Molecular genetic analysis to detect: antigen receptor gene rearrangements; t(2;5) and variants
  - Additional immunohistochemical studies to establish lymphoma subtype: βF1, CD279 (PD1)
  - Cytogenetics
  - CXCL-13

Peripheral T-Cell Lymphoma – Subtypes

- Peripheral T-cell lymphoma (PTCL), NOS
- Angioimmunoblastic T-cell lymphoma (AITL)
- Anaplastic large cell lymphoma (ALCL), ALK +
- Anaplastic large cell lymphoma (ALCL), ALK -
- Enteropathy associated T-cell lymphoma (EATL)

Peripheral T-Cell Lymphoma - Prognosis

INTERNATIONAL PROGNOSTIC INDEX

ALL PATIENTS:

- Age > 60 years
- Serum LDH > normal
- Performance status 2-4
- Stage III or IV
- Extranodal involvement > 1 site

INTERNATIONAL INDEX, ALL PATIENTS:

• Low	0 or 1
• Low intermediate	2
• High intermediate	3
• High	4 or 5

Prognostic Index for PTCL-U (PIT)

RISK FACTORS:

- Age > 60 years
- Serum LDH > normal
- Performance status 2-4
- Bone marrow involvement

PROGNOSTIC RISK:

• Group 1	0
• Group 2	1
• Group 3	2
• Group 4	3 or 4

AGE-ADJUSTED INTERNATIONAL PROGNOSTIC INDEX

PATIENTS ≤ 60 YEARS:

- Stage III or IV
- Serum LDH > normal
- Performance status 2-4

INTERNATIONAL INDEX, PATIENTS ≤ 60 YEARS:

• Low	0
• Low/intermediate	1
• High/intermediate	2
• High	3

Modified from NCCN 2022.V2

Treatment Algorithm in PTCL

Except ALK(+) ALCL

- PTCL-NOS
- ALCL, ALK negative[l]
- AITL
- EATL
- MEITL[g]
- Nodal PTCL, TFH
- FTCL

→ Stage I–IV →

Clinical trial (preferred)
or
Multiagent chemotherapy[m]
6 cycles ± ISRTn[n]

→

Restage after 3–4 cycles with PET/CT[h] (preferred) or C/A/P CT scan with contrast[o]

END-OF TREATMENT RESTAGING

END-OF-TREATMENT RESPONSE

ADDITIONAL THERAPY

FOLLOW-UP

CR or PR[p] → Complete planned course of treatment → At completion of treatment, repeat PET/CT[h] (preferred) or C/A/P CT scan with contrast[o]

- CR[p] (PET negative) → Clinical trial or Consider HDT with ASCR[r] or Observe
- PR[p,q] (PET positive)
- Progressive disease[p]

→ Clinical
- H&P for every 3–6 mo for 2 y and then as clinically indicated

Imaging
- Surveillance imaging[h] (no more often than every 6 mo for 2 y and then annually for 5 y or as clinically indicated)

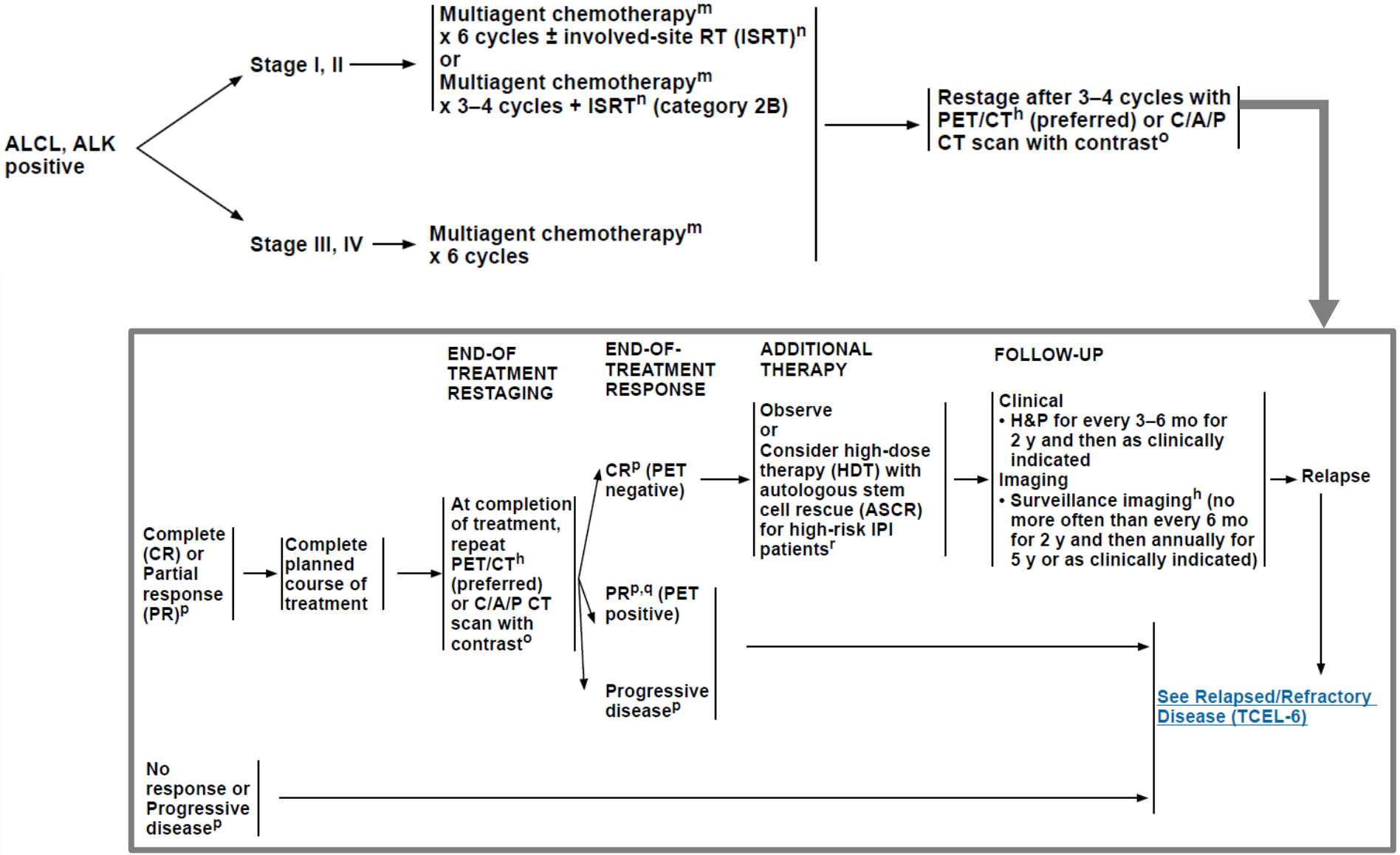
→ Relapse

No response or Progressive disease[p]

→ [See Relapsed/Refractory Disease (TCEL-6)]

Modified from NCCN 2022.V2

Treatment Algorithm in ALK(+) ALCL



Modified from NCCN 2022.V2

First-line regimens in PTCL

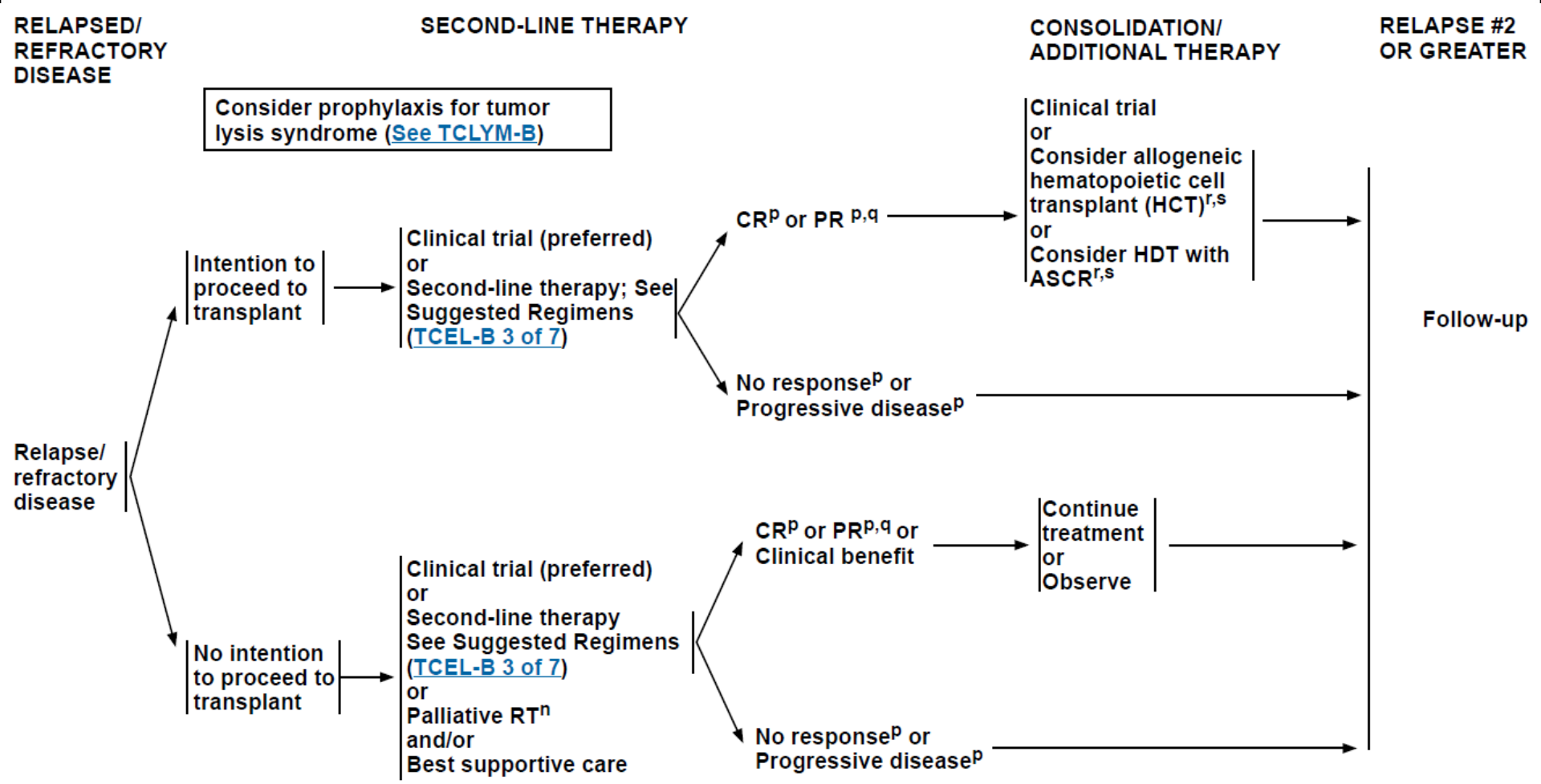
SUGGESTED TREATMENT REGIMENS[a]

	FIRST-LINE THERAPY[b]
ALCL[c]	Preferred regimen • Brentuximab vedotin + CHP (cyclophosphamide, doxorubicin, and prednisone)[d] (category 1) Other recommended regimens • CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) • CHOEP[e] (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone) • Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)
Other histologies (PTCL-NOS; AITL; EATL; MEITL; nodal PTCL, TFH; and FTCL)[f]	Preferred regimens (alphabetical order) • Brentuximab vedotin + CHP (cyclophosphamide, doxorubicin, and prednisone)[d] for CD30+ histologies[g] • CHOEP[e] • CHOP • Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) Other recommended regimens (alphabetical order) • CHOP followed by IVE (ifosfamide, etoposide, epirubicin) alternating with intermediate-dose methotrexate (Newcastle Regimen; studied only in patients with EATL)[h] • HyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) alternating with high-dose methotrexate and cytarabine (category 3)

FIRST-LINE CONSOLIDATION
• Consider consolidation with high-dose therapy and autologous stem cell rescue.

Modified from NCCN 2022.V2

Treatment Algorithm in R/R PTCL



Salvage regimens in PTCL

PTCL-NOS

- Clinical trial preferred

Preferred regimens

- Single agents (alphabetical order)
  - Brentuximab vedotin for CD30+ PTCL[d,g]
  - Pralatrexate
- Combination regimens (alphabetical order)
  - DHAP (dexamethasone, cytarabine, cisplatin)
  - DHAX (dexamethasone, cytarabine, oxaliplatin)
  - ESHAP (etoposide, methylprednisolone, cytarabine) + platinum (cisplatin or oxaliplatin)
  - GDP (gemcitabine, dexamethasone, cisplatin)
  - GemOx (gemcitabine, oxaliplatin)
  - ICE (ifosfamide, carboplatin, etoposide)

Other recommended regimens

- Single agents (alphabetical order)
  - Bendamustine[d]
  - Gemcitabine
  - Lenalidomide[d]
- Combination regimen
  - GVD (gemcitabine, vinorelbine, liposomal doxorubicin)[p]

Modified from NCCN 2022.V2

Salvage regimens in PTCL

Nodal PTCL with TFH phenoty

- Clinical trial preferred

Preferred regimens

- Single agents (alphabetical order)
  - Brentuximab vedotin for CD30+ AITL[d,g]
- Combination regimens (alphabetical order)
  - DHAP (dexamethasone, cytarabine, cisplatin)
  - DHAX (dexamethasone, cytarabine, oxaliplatin)
  - ESHAP (etoposide, methylprednisolone, cytarabine) + platinum (cisplatin or oxaliplatin)
  - GDP (gemcitabine, dexamethasone, cisplatin)
  - GemOx (gemcitabine, oxaliplatin)
  - ICE (ifosfamide, carboplatin, etoposide)

Other recommended regimens

- Single agents (alphabetical order)
  - Bendamustine[d]
  - Gemcitabine
  - Lenalidomide[d]
  - Pralatrexate[n]

Modified from NCCN 2022.V2

Salvage regimens in PTCL

ALCL

- Clinical trial preferred

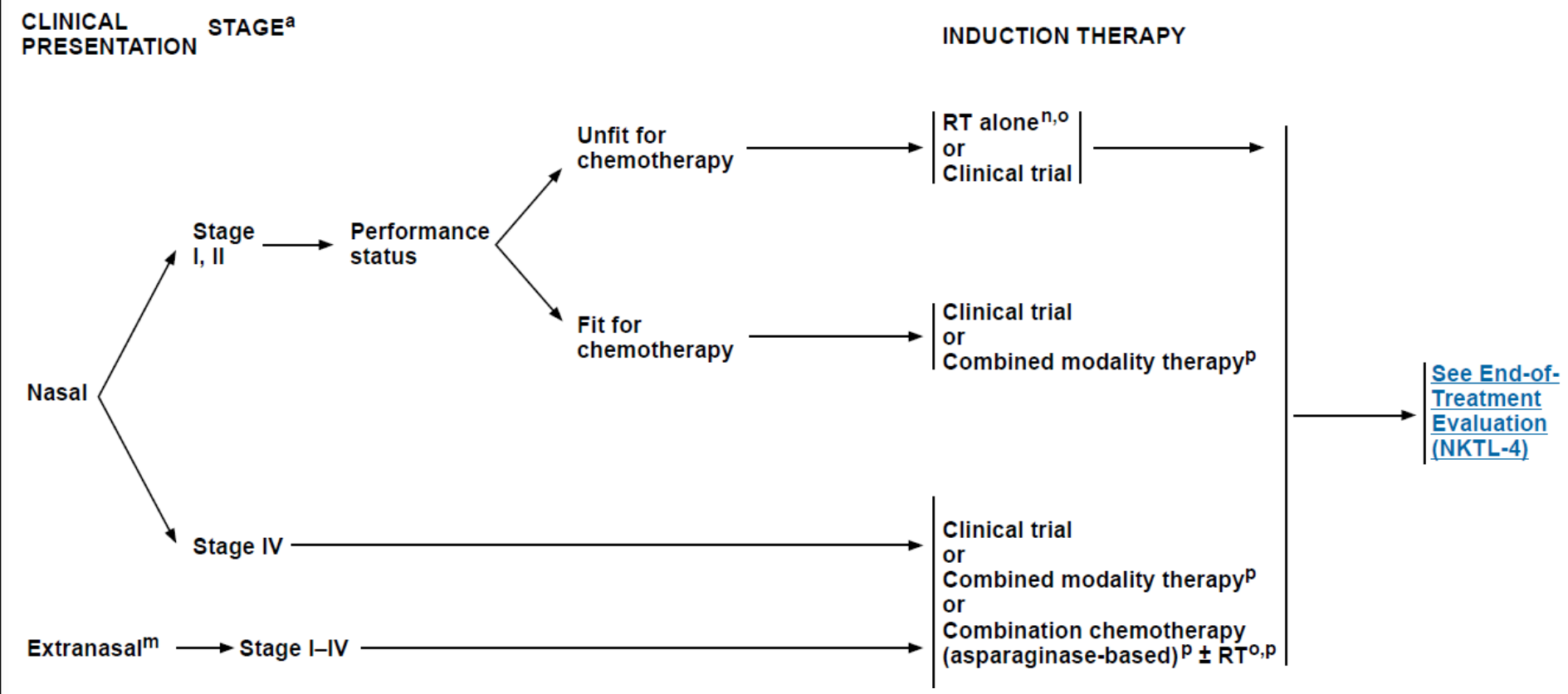
Preferred regimen

- Brentuximab vedotin[d]

Other recommended regimens

- Single agents (alphabetical order)
  - Alectinib (ALK+ ALCL only)[o]
  - Bendamustine[d]
  - Crizotinib (ALK+ ALCL only)
  - Gemcitabine
  - Pralatrexate
- Combination regimens (alphabetical order)
  - DHAP (dexamethasone, cytarabine, cisplatin)
  - DHAX (dexamethasone, cytarabine, oxaliplatin)
  - ESHAP (etoposide, methylprednisolone, cytarabine) + platinum (cisplatin or oxaliplatin)
  - GDP (gemcitabine, dexamethasone, cisplatin)
  - GemOx (gemcitabine, oxaliplatin)
  - ICE (ifosfamide, carboplatin, etoposide)

Treatment Algorithm in ENKTL



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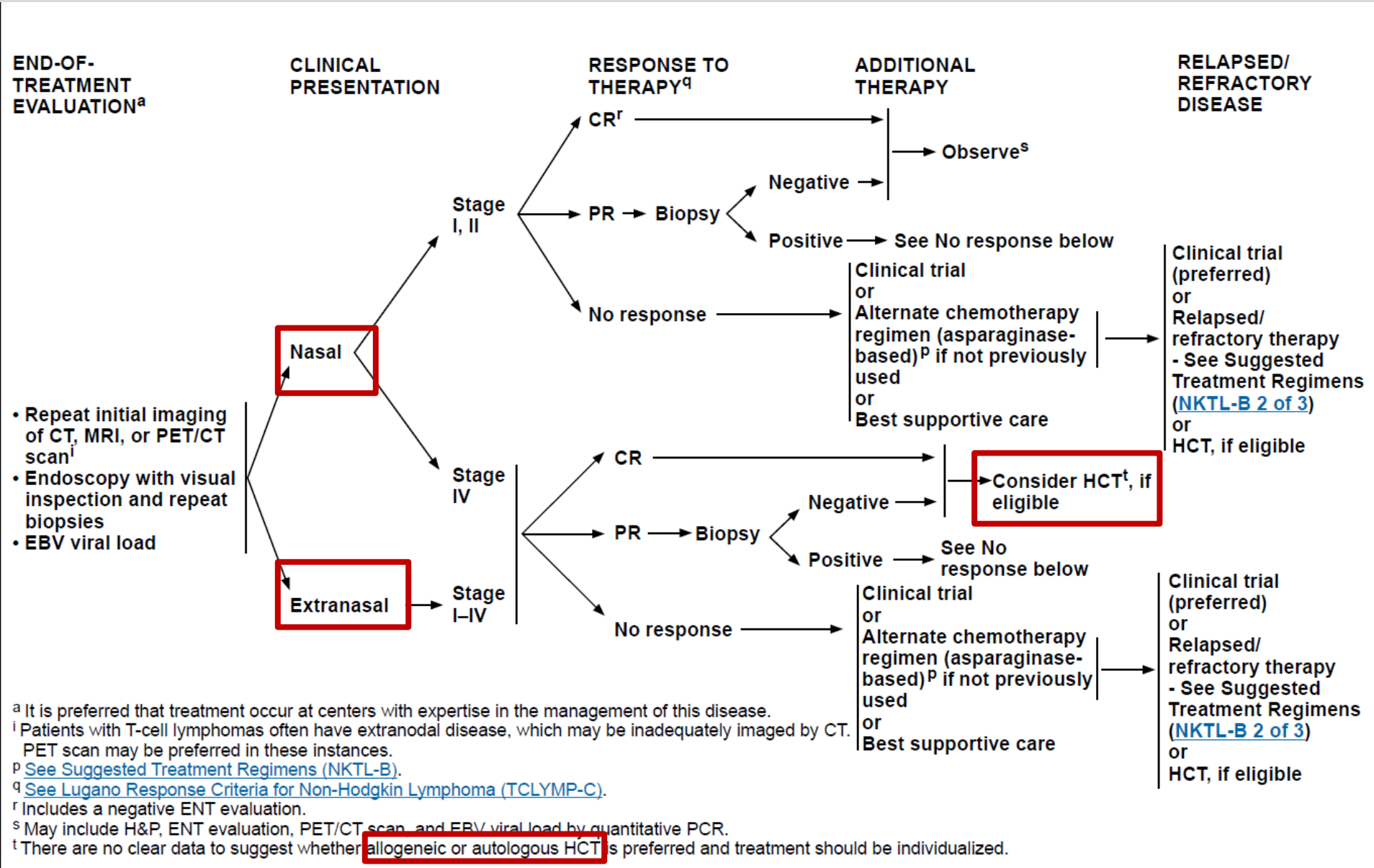
Treatment Algorithm in ENKTL



[a] It is preferred that treatment occur at centers with expertise in the management of this disease.
[i] Patients with T-cell lymphomas often have extranodal disease, which may be inadequately imaged by CT. PET scan may be preferred in these instances.
[p] See Suggested Treatment Regimens (NKTL-B).
[q] See Lugano Response Criteria for Non-Hodgkin Lymphoma (TCLYMP-C).
[r] Includes a negative ENT evaluation.
[s] May include H&P, ENT evaluation, PET/CT scan, and EBV viral load by quantitative PCR.
[t] There are no clear data to suggest whether allogeneic or autologous HCT is preferred and treatment should be individualized.

Modified from NCCN 2022.V2

First-line regimens in ENKTL

INDUCTION THERAPY	
Combination chemotherapy regimen (asparaginase-based)[b,c]	Preferred regimens • Modified SMILE (steroid [dexamethasone], methotrexate, ifosfamide, pegaspargase,[d] and etoposide) x 4–6 cycles for advanced stage • P-GEMOX (gemcitabine, pegaspargase, and oxaliplatin)[d] • DDGP (dexamethasone, cisplatin, gemcitabine, pegaspargase)[d] Useful in certain circumstances • AspaMetDex (pegaspargase, methotrexate, and dexamethasone)[e]
Combined modality therapy	Concurrent chemoradiation therapy (CCRT) Preferred regimen • RT[f] and 3 courses of DeVIC (dexamethasone, etoposide, ifosfamide, and carboplatin) Other recommended regimen • RT[f] and cisplatin followed by 3 cycles of VIPD (etoposide, ifosfamide, cisplatin, and dexamethasone)
	Sequential chemoradiation • For stage I, II, modified SMILE x 2–4 cycles followed by RT[f]
	Sandwich chemoradiation[c] • P-GEMOX x 2 cycles followed by RT[f] followed by P-GEMOX x 2–4 cycles

RT alone (if unfit for chemotherapy)[f]

• RT as a part of initial therapy has an essential role in improved overall and disease-free survival in patients with localized extranodal ENKL, nasal type, in the upper aerodigestive tract.

Substitute asparaginase for pegasparaginase in Taiwan.

Salvage regimens in ENKTL

RELAPSED/REFRACTORY THERAPY

- Clinical trial

Preferred regimens[g,h]
- Pembrolizumab
- Nivolumab

Other recommended regimens (alphabetical order)
- Single agents
  - Brentuximab vedotin for CD30+ disease
  - Pralatrexate
- Combination regimens (alphabetical order)
  - Asparaginase-based combination chemotherapy regimen (NKTL-B 1 of 3) not used in first-line therapy
  - DHAP (dexamethasone, cytarabine, cisplatin)
  - DHAX (dexamethasone, cytarabine, oxaliplatin)
  - ESHAP (etoposide, methylprednisolone, cytarabine) + platinum (cisplatin or oxaliplatin)
  - GDP (gemcitabine, dexamethasone, cisplatin)
  - GemOx (gemcitabine, oxaliplatin)
  - ICE (ifosfamide, carboplatin, etoposide)

Useful in certain circumstances
- RT[f]

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Treatment Algorithm in PTCL

Except ALK(+) ALCL

- PTCL-NOS
- ALCL, ALK negative[l]
- AITL
- EATL
- MEITL[g]
- Nodal PTCL, TFH
- FTCL

→ Stage I–IV →

Clinical trial (preferred)
or
Multiagent chemotherapy[m]
6 cycles ± ISRTn[n]

→

Restage after 3–4 cycles with PET/CT[h] (preferred) or C/A/P CT scan with contrast[o]

END-OF TREATMENT RESTAGING

END-OF-TREATMENT RESPONSE

ADDITIONAL THERAPY

FOLLOW-UP

CR or PR[p] → Complete planned course of treatment → At completion of treatment, repeat PET/CT[h] (preferred) or C/A/P CT scan with contrast[o]

- CR[p] (PET negative) → Clinical trial or Consider HDT with ASCR[r] or Observe
- PR[p,q] (PET positive)
- Progressive disease[p]

Clinical
- H&P for every 3–6 mo for 2 y and then as clinically indicated

Imaging
- Surveillance imaging[h] (no more often than every 6 mo for 2 y and then annually for 5 y or as clinically indicated)

→ Relapse

No response or Progressive disease[p]

→ See Relapsed/Refractory Disease (TCEL-6)

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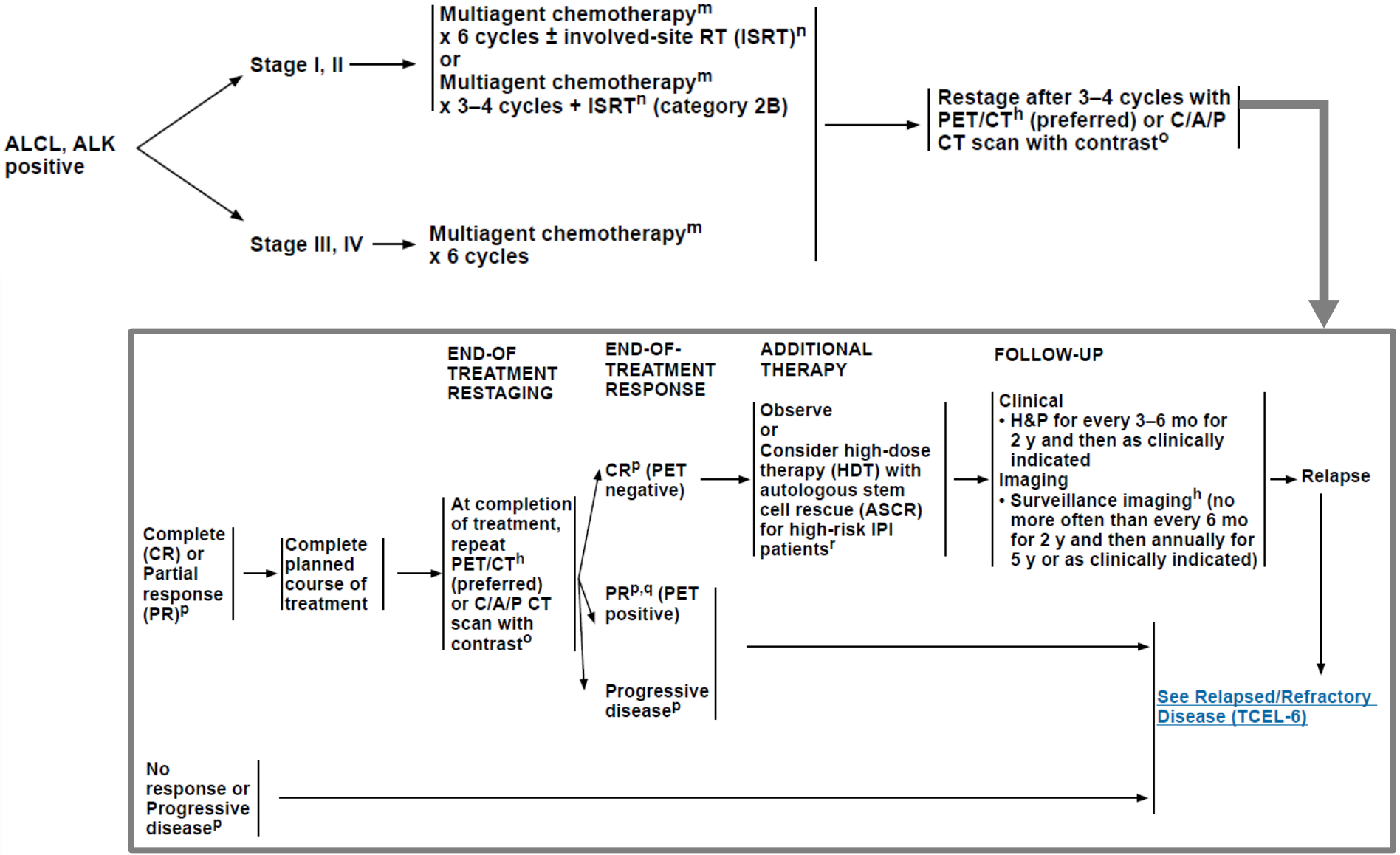
Treatment Algorithm in ALK(+) ALCL



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First-line regimens in PTCL

SUGGESTED TREATMENT REGIMENS[a]

	FIRST-LINE THERAPY[b]
ALCL[c]	Preferred regimen • Brentuximab vedotin + CHP (cyclophosphamide, doxorubicin, and prednisone)[d] (category 1) Other recommended regimens • CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) • CHOEP[e] (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone) • Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)
Other histologies (PTCL-NOS; AITL; EATL; MEITL; nodal PTCL, TFH; and FTCL)[f]	Preferred regimens (alphabetical order) • Brentuximab vedotin + CHP (cyclophosphamide, doxorubicin, and prednisone)[d] for CD30+ histologies[g] • CHOEP[e] • CHOP • Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) Other recommended regimens (alphabetical order) • CHOP followed by IVE (ifosfamide, etoposide, epirubicin) alternating with intermediate-dose methotrexate (Newcastle Regimen; studied only in patients with EATL)[h] • HyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) alternating with high-dose methotrexate and cytarabine (category 3)

FIRST-LINE CONSOLIDATION
• Consider consolidation with high-dose therapy and autologous stem cell rescue.

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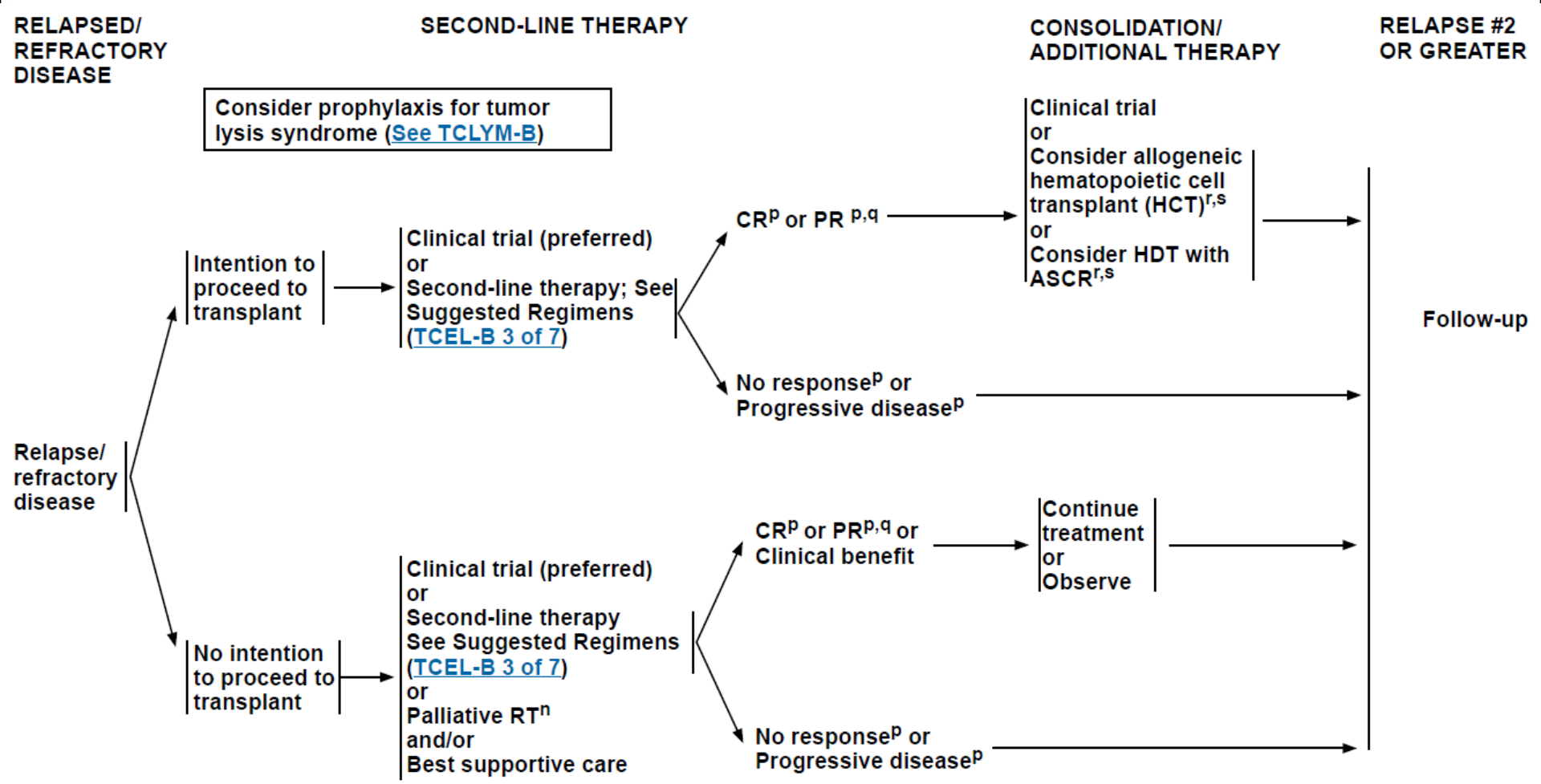
Treatment Algorithm in R/R PTCL



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Salvage regimens in PTCL

PTCL-NOS

- Clinical trial preferred

Preferred regimens

- Single agents (alphabetical order)
  - Brentuximab vedotin for CD30+ PTCL[d,g]
  - Pralatrexate
- Combination regimens (alphabetical order)
  - DHAP (dexamethasone, cytarabine, cisplatin)
  - DHAX (dexamethasone, cytarabine, oxaliplatin)
  - ESHAP (etoposide, methylprednisolone, cytarabine) + platinum (cisplatin or oxaliplatin)
  - GDP (gemcitabine, dexamethasone, cisplatin)
  - GemOx (gemcitabine, oxaliplatin)
  - ICE (ifosfamide, carboplatin, etoposide)

Other recommended regimens

- Single agents (alphabetical order)
  - Bendamustine[d]
  - Gemcitabine
  - Lenalidomide[d]

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Salvage regimens in PTCL

Nodal PTCL with TFH phenotype

- Clinical trial preferred

Preferred regimens

- Single agents (alphabetical order)
  - Brentuximab vedotin for CD30+ AITL[d,g]
- Combination regimens (alphabetical order)
  - DHAP (dexamethasone, cytarabine, cisplatin)
  - DHAX (dexamethasone, cytarabine, oxaliplatin)
  - ESHAP (etoposide, methylprednisolone, cytarabine) + platinum (cisplatin or oxaliplatin)
  - GDP (gemcitabine, dexamethasone, cisplatin)
  - GemOx (gemcitabine, oxaliplatin)
  - ICE (ifosfamide, carboplatin, etoposide)

Other recommended regimens

- Single agents (alphabetical order)
  - Bendamustine[d]
  - Gemcitabine
  - Lenalidomide[d]
  - Pralatrexate[n]

Modified from NCCN 2022

Salvage regimens in PTCL

ALCL

- Clinical trial preferred

Preferred regimen

- Brentuximab vedotin[d]

Other recommended regimens

- Single agents (alphabetical order)
  - Alectinib (ALK+ ALCL only)[o]
  - Bendamustine[d]
  - Crizotinib (ALK+ ALCL only)
  - Gemcitabine
  - Pralatrexate
- Combination regimens (alphabetical order)
  - DHAP (dexamethasone, cytarabine, cisplatin)
  - DHAX (dexamethasone, cytarabine, oxaliplatin)
  - ESHAP (etoposide, methylprednisolone, cytarabine) + platinum (cisplatin or oxaliplatin)
  - GDP (gemcitabine, dexamethasone, cisplatin)
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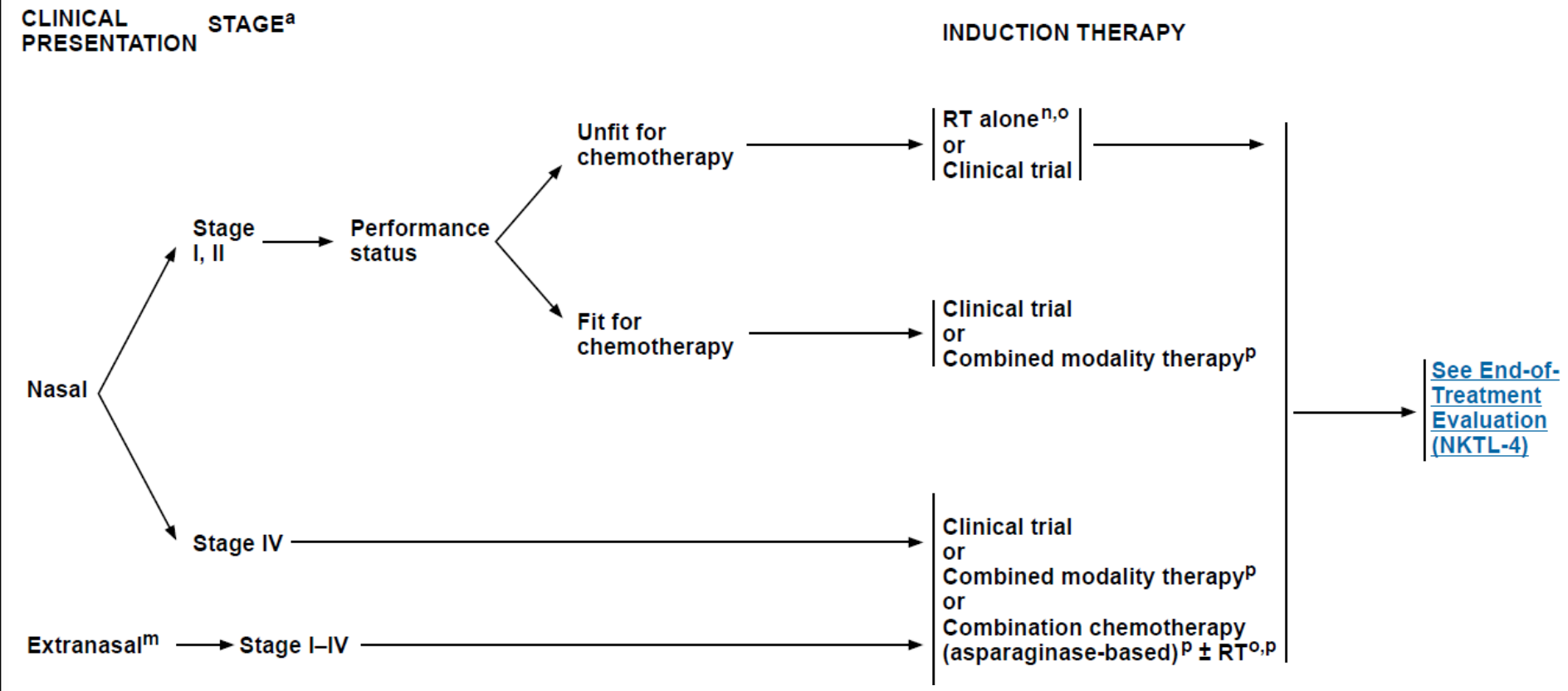
Treatment Algorithm in ENKTL



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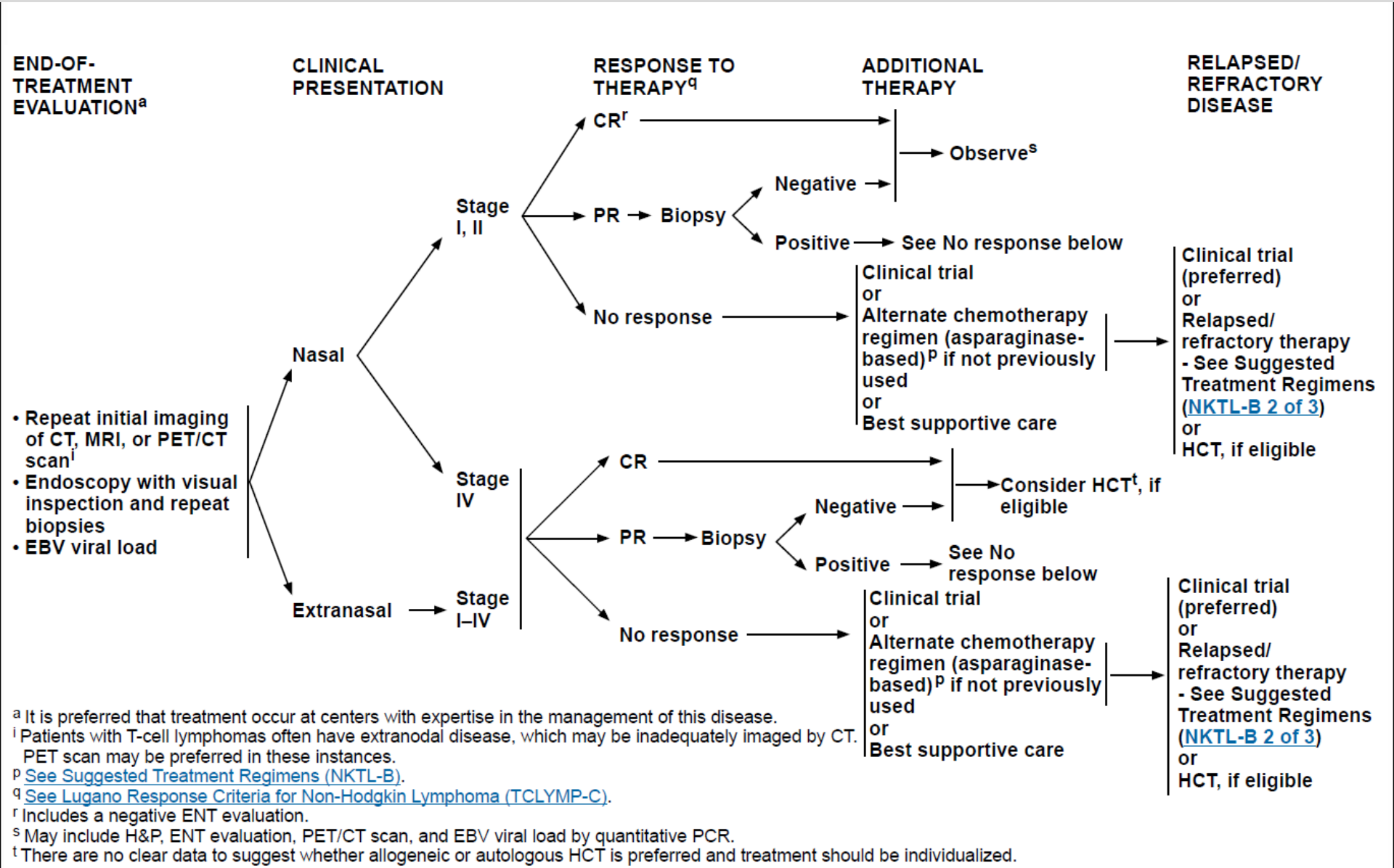
Treatment Algorithm in ENKTL



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First-line regimens in ENKTL

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Salvage regimens in ENKTL

RELAPSED/REFRACTORY THERAPY

- Clinical trial

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- Combination regimens (alphabetical order)
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  - GDP (gemcitabine, dexamethasone, cisplatin)
  - GemOx (gemcitabine, oxaliplatin)
  - ICE (ifosfamide, carboplatin, etoposide)

Useful in certain circumstances
- RT[f]

Mycosis Fungoides/Sezary Syndrome-Staging

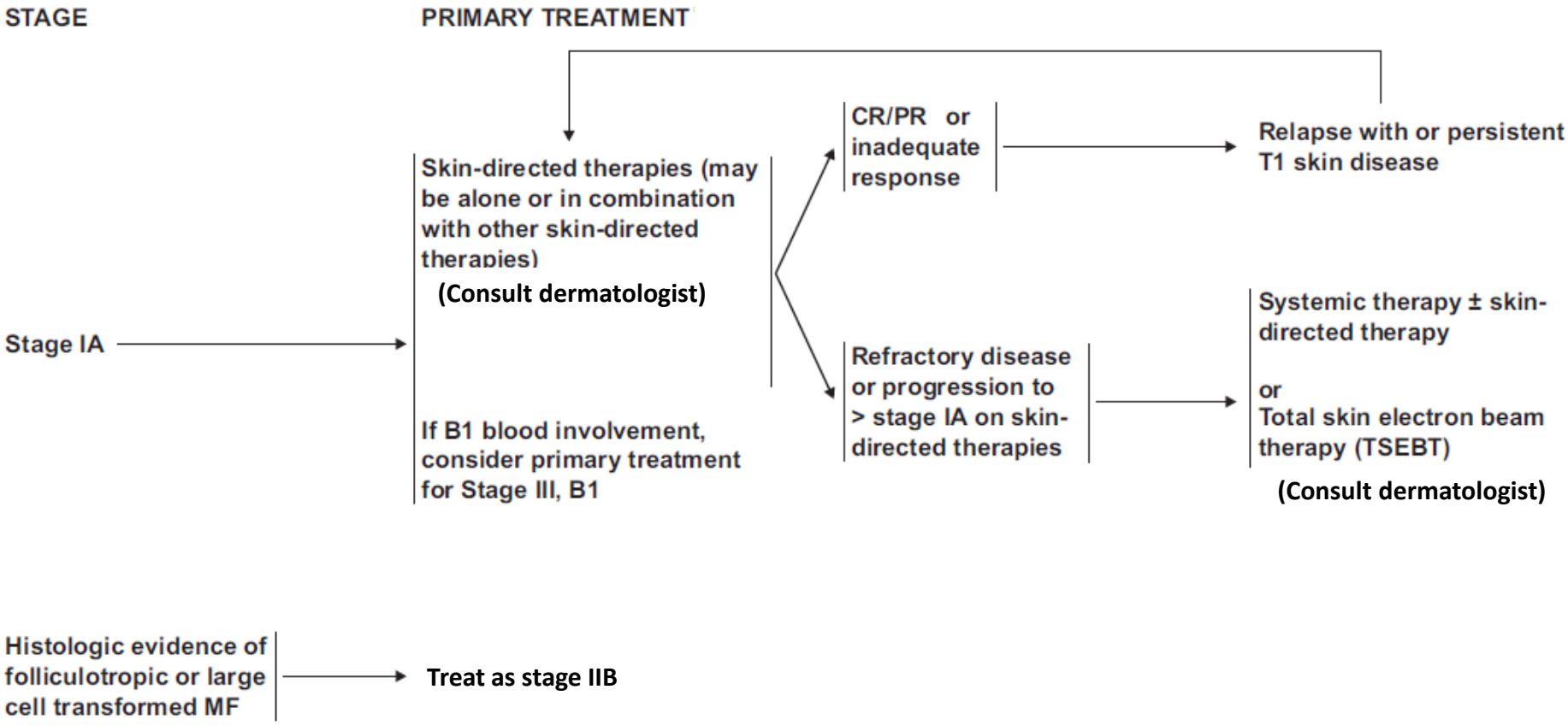
TNMB		TNMB Classification and Staging of Mycosis Fungoides and Sezary Syndrome
Skin	T1	Limited patches, papules and/or plaques covering < 10 % of the skin surface
	T2	Patches, papules and/or plaques[j] covering ≥ 10 % of the skin surface
	T3	One or more tumors (≥ 1 cm in diameter)
	T4	Confluence of erythema ≥ 80 % body surface area
Node	N0	No clinically abnormal peripheral lymph nodes; biopsy not required
	N1	Clinically abnormal peripheral lymph nodes; histopathology Dutch Gr 1 or NCI LN 0-2
	N2	Clinically abnormal peripheral lymph nodes; histopathology Dutch Gr 2 or NCI LN 3
	N3	Clinically abnormal peripheral lymph nodes; histopathology Dutch Gr 3-4 or NCI LN 4
	NX	Clinically abnormal peripheral lymph nodes; no histologic confirmation
Visceral	M0	No visceral organ involvement
	M1	Visceral involvement (must have pathology confirmation and organ involved should be specified)
Blood	B0	Absence of significant blood involvement: ≤ 5 % of peripheral blood lymphocytes are atypical (Sezary) cells
	B1	Low blood tumor burden: > 5 % of peripheral blood lymphocytes are atypical (Sezary) cells but does not meet the criteria of B2
	B2	High blood tumor burden: ≥ 1000/mcL Sezary cells

Mycosis Fungoides/Sezary Syndrome-Staging

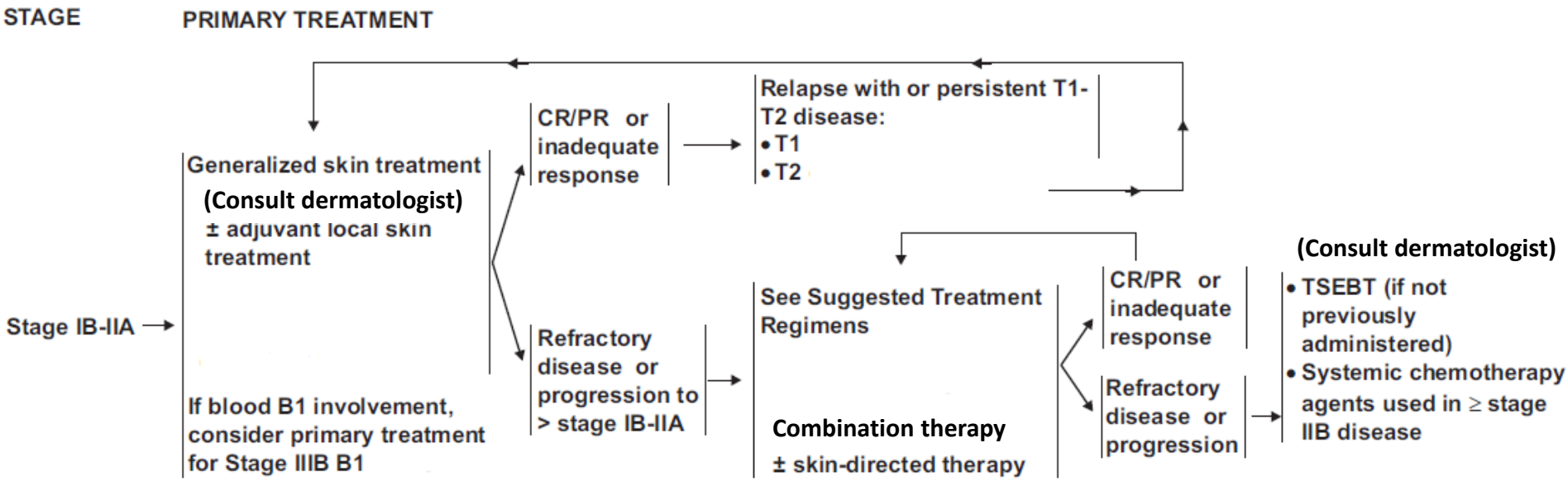
Clinical Staging/Classification of MF and SS

	T	N	M	B
IA	1	0	0	0,1
IB	2	0	0	0,1
IIA	1-2	1,2	0	0,1
IIB	3	0-2	0	0,1
IIIA	4	0-2	0	0
IIIB	4	0-2	0	1
IVA_1	1-4	0-2	0	2
IVA_2	1-4	3	0	0-2
IVB	1-4	0-3	1	0-2

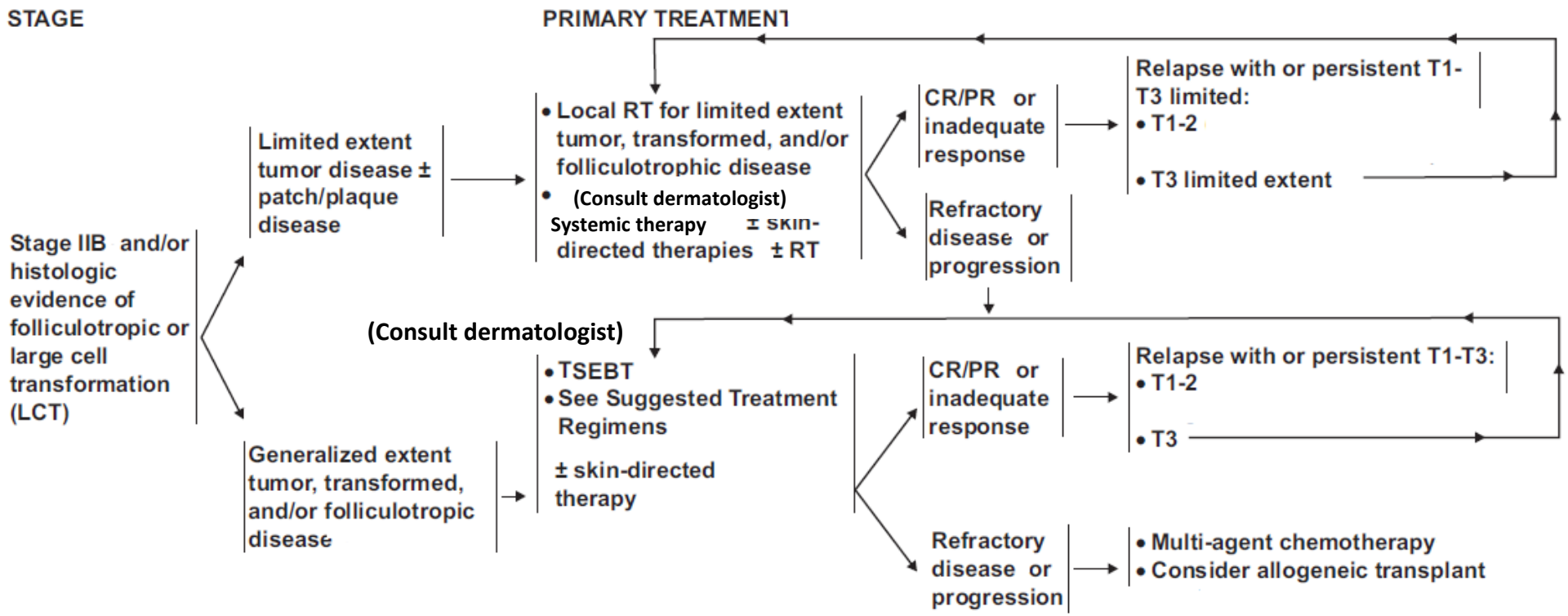
Mycosis Fungoides/Sezary Syndrome- Treatment of stage IA



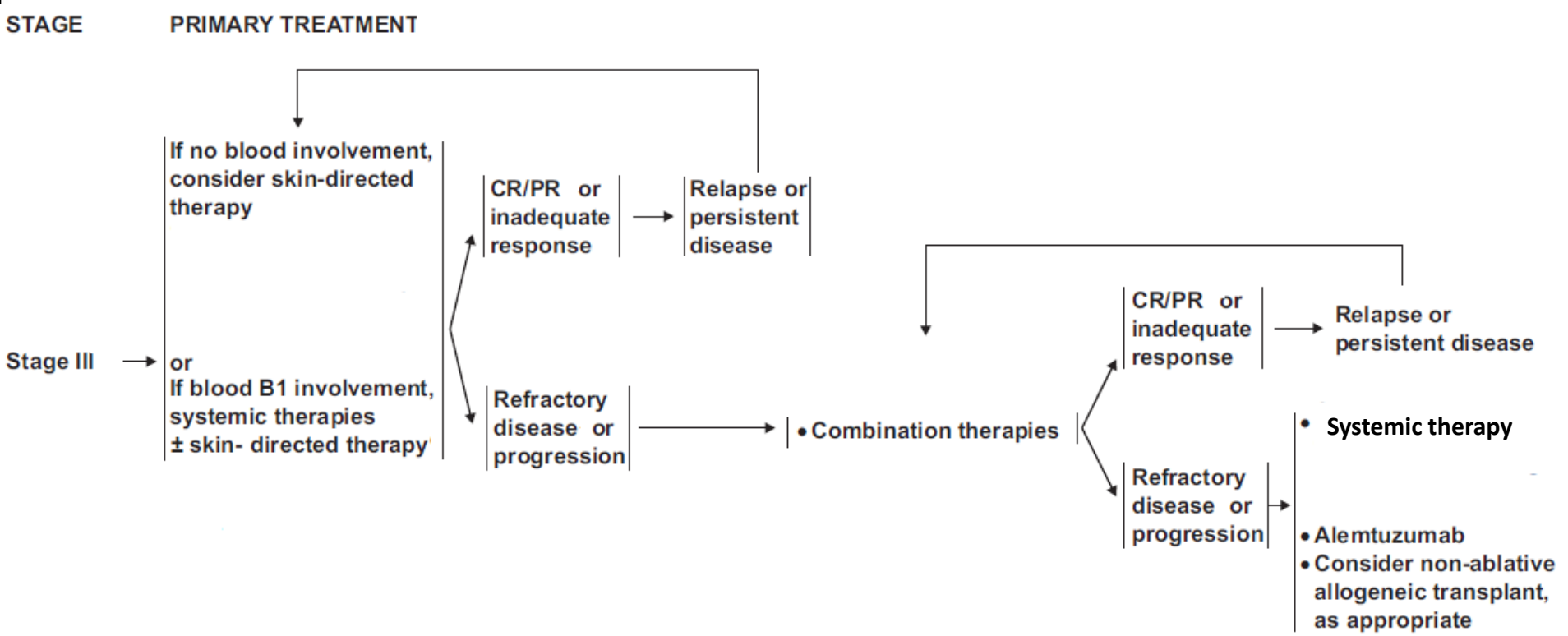
Mycosis Fungoides/Sezary Syndrome- Treatment of stage IB-IIA



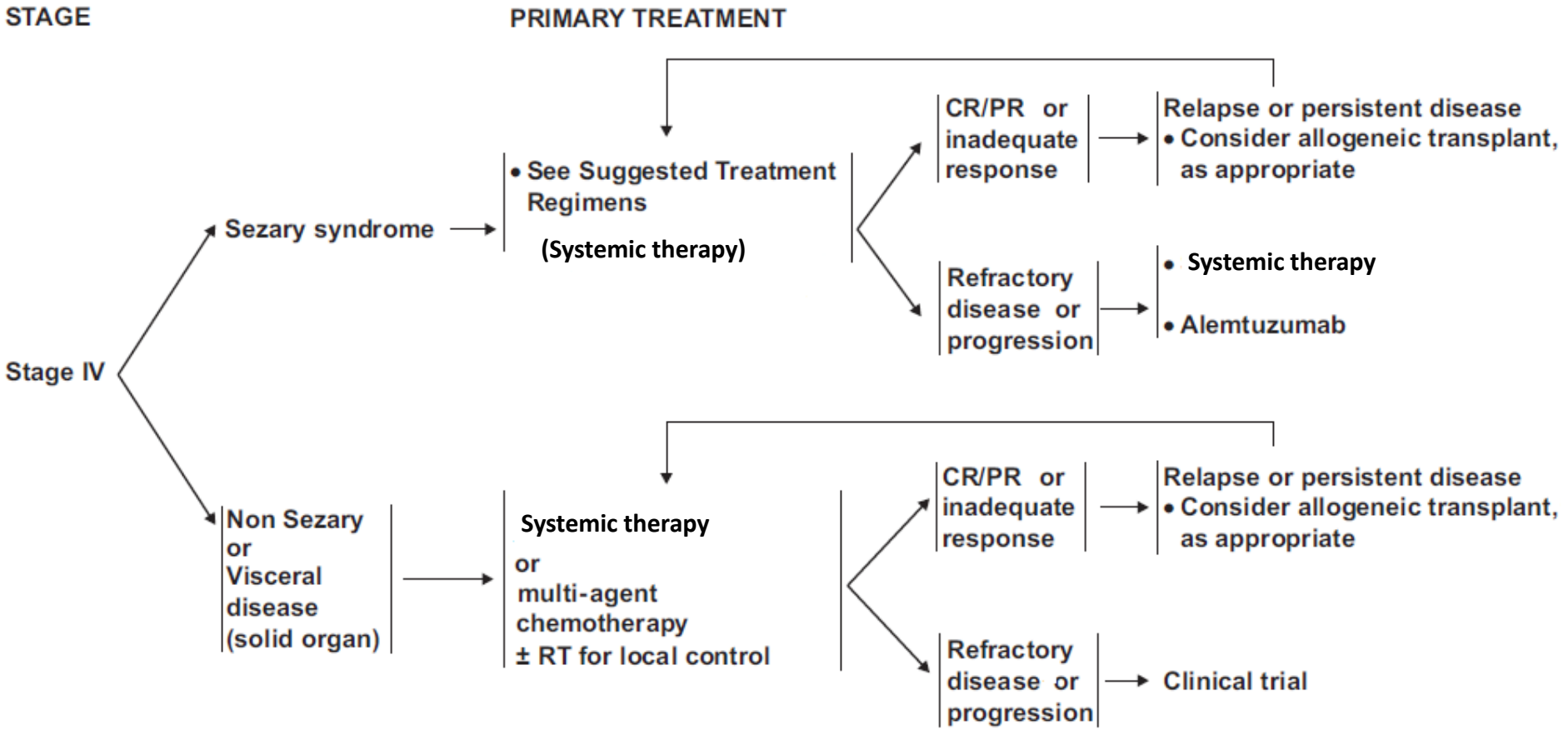
Mycosis Fungoides/Sezary Syndrome- Treatment of stage IIB



Mycosis Fungoides/Sezary Syndrome- Treatment of stage III



Mycosis Fungoides/Sezary Syndrome- Treatment of stage IV



Systemic therapy of Mycosis Fungoides/Sezary Syndrome

Category A

- Retinoids (all-trans retinoic acid) 45 mg/m^2/day PO BID[1]
- Interferons (IFN-alpha) 1.5 to 3 million units SC TIW [2]
- Extracorporeal photopheresis[3]
- Methotrexate 5 to 125 mg IV QW[4]

References

1. Zhang C, Duvic M. Treatment of cutaneous T-cell lymphoma with retinoids. Dermatol Ther 2006;19:264-271.
2. Olsen EA. Interferon in the treatment of cutaneous T-cell lymphoma. Dermatol Ther 2003;16:311-321.
3. Gathers RC, Scherschun L, Malick F, Fivenson DP, Lim HW. Narrowband UVB phototherapy for early stage mycosis fungoides. J Am Acad Dermatol 2002;47:191-197.
4. Zackheim HS, Kashani-Sabet M, Hwang ST. Low-dose methotrexate to treat erythrodermic cutaneous T-cell lymphoma: results in twenty-nine patients. J Am Acad Dermatol 1996;34:626-631.

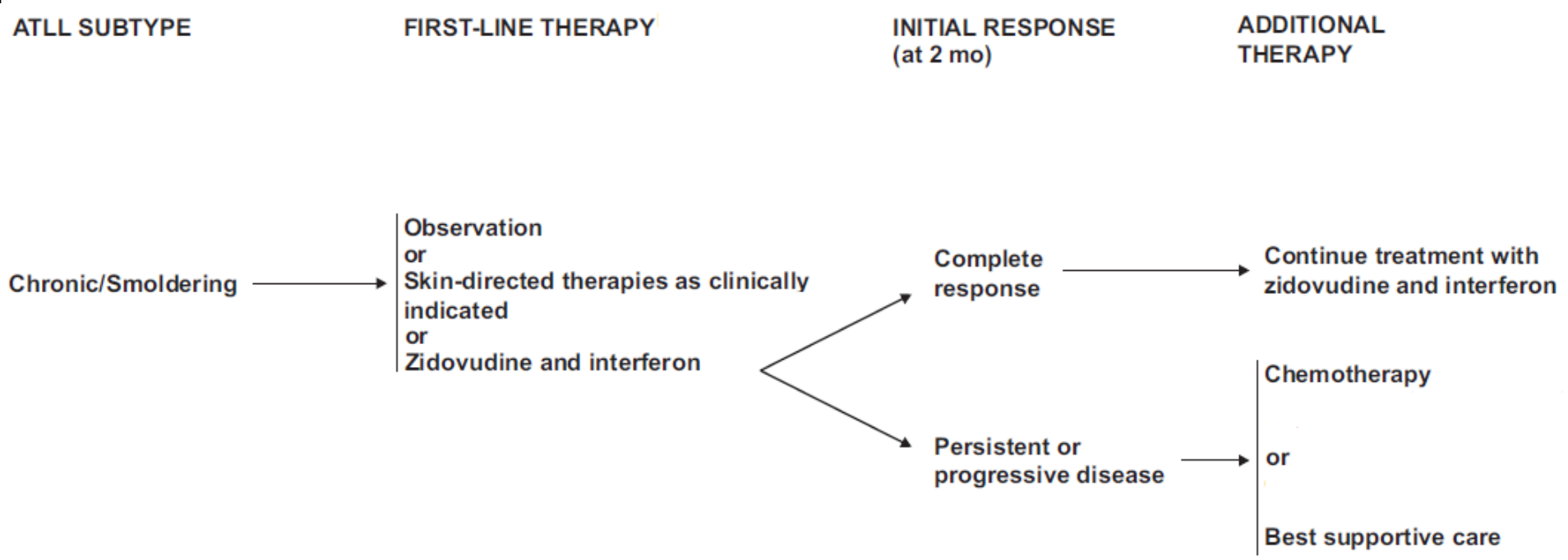
Taipei Veterans General Hospital Practice Guidelines Oncology

Adult T-cell Leukemia/Lymphoma

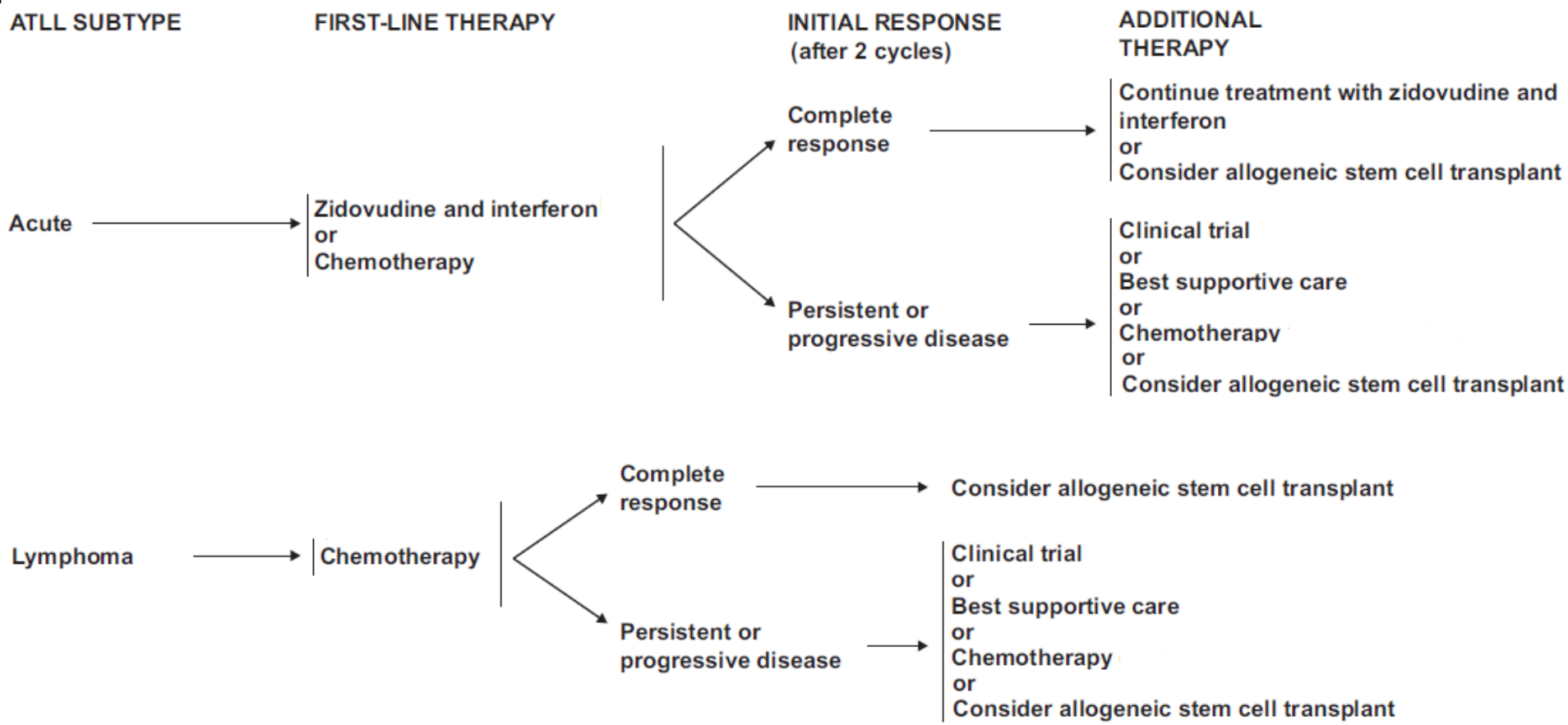
Adult T-cell Leukemia/Lymphoma - Diagnosis

- **ESSENTIAL:**
  - Complete skin examination
  - HTLV-1 serology: ELISA
  - Peripheral blood smear analysis for atypical cells(ALC > 4000/μL in adults) in acute and chronic subtypes
  - Flow cytometry on peripheral blood
  - Serum Calcium level
- **USEFUL IN CERTAIN CIRCUMSTANCES:**
  - If ELISA is positive confirmatory Western Blot
  - Biopsy of lymph nodes (excisional), skin biopsy, GI tract, or bone marrow biopsy is required if:
    - Diagnosis is not established on peripheral blood, or
    - Ruling out an underlying infection (tuberculosis, histoplasmosis, toxoplasmosis, etc.)
    - If biopsy performed, the recommended panel for paraffin section immunohistochemistry: CD3, CD4, CD7, CD8, and CD25

Adult T-cell Leukemia/Lymphoma



Adult T-cell Leukemia/Lymphoma



Suggested chemotherapy regimen
-**CHOP**
-**Dose-adjusted EPOCH**
-**hyperCVAD/MTX-Ara-C**

Non-Hodgkin lymphoma- Commonly used combination chemotherapy regimen

- **CVP Q3W x 8 cycles[1]**
  Cyclophosphamide 750 mg/m2 iv d1
  Vincristine 1.4 mg/m2 (max 2 mg) iv d1
  Prednisone 40 mg/m2 po qd d1-5

- **R-CVP Q3W x 8 cycles[1]**
  Rituximab 375 mg/m2 iv d1
  Cyclophosphamide 750 mg/m2 iv d1
  Vincristine 1.4 mg/m2 (max 2 mg) iv d1
  Prednisone 40 mg/m2 po qd d1-5

- **CVP + maintenance R Q3W x 6-8 cycles[2]**
  Cyclophosphamide 1000 mg/m2 iv d1
  Vincristine 1.4 mg/m2 (max 2 mg) iv d1
  Prednisone 100 mg po qd d1-5
  Followed by
  Rituximab 375 mg/m2 iv qw x 4, q6m x 4 (2 years)

Non-Hodgkin lymphoma- Commonly used combination chemotherapy regimen

- **CHOP Q3w x 6-8 cycles[3]**
  Cyclophophamide 750 mg/m2 iv d1
  Doxorubicin 50 mg/m2 iv d1
  Vincristine 1.4 mg/m2 (max 2 mg) iv d1
  Prednisone 100 mg po qd d1-5

- **R-CHOP Q3w x 6-8 cycles[4]**
  Rituximab 375 mg/m2 iv d1
  Cyclophophamide 750 mg/m2 iv d1
  Doxorubicin 50 mg/m2 iv d1
  Vincristine 1.4 mg/m2 (max 2 mg) iv d1
  Prednisone 100 mg po qd d1-5

- **R-miniCHOP Q3W x 6-8 cycles (optional)**
  Rituximab 375 mg/m2 iv d1
  Cyclophophamide 400 mg/m2 iv d1
  Doxorubicin 25 mg/m2 iv d1
  Vincristine 1mg iv d1
  Prednisone 40 mg/m2 po qd d1-5

Non-Hodgkin lymphoma- Commonly used combination chemotherapy regimen

- **B-R**
  - **Follicular lymphoma 1st line: [6]**

    Bendamustine 90 mg/m2 iv day 1-2 (self-pay)
    Rituximab 375 mg/m2 iv day 1

  - **DLBCL 1st line (optional):[7]**

    Bendamustine 100-120 mg/m2 iv day 1-2 (self-pay)
    Rituximab 375 mg/m2 iv day 1

- **R-CHOP + maintenance R[4]**

  R-CHOP x 6 cycles, followed by Rituximab 375 mg/m2 iv q3m x 2 yrs

Non-Hodgkin lymphoma- Commonly used combination chemotherapy regimen

- **R-GemOx Q2W x 8 cycles[11]**
  Rituximab 375 mg/m2 iv d1
  Gemcitabine 1000 mg/m2 iv at 10 mg/m2/min d2
  Oxaliplatin 100 mg/m2 iv over 2 hrs d2

Non-Hodgkin lymphoma- Commonly used combination chemotherapy regimen

- **ICE Q4W x 2 cycles[12]**
  Ifosfamide 1000 mg/m2/d iv over 1 h d1-2 (hours 0 and 1)
  Etoposide 150 mg/m2/d iv over 11 hrs after ifosfamide d1-2 (hours 1-11)
  Carboplatin 200 mg/m2/d iv over 1 h after etoposide d1-2 (hours 11-12)
  Etoposide 150 mg/m2/d iv over 11 hrs after carboplatin d1-2 (hours 12-24)
  Mesna 333 mg/m2 iv 30 minutes before ifosfamide, repeat 4 and 8 hrs after ifosfamide

- **RICE Q2W x 3 cycles[12]**
  Rituximab 375 mg/m2 iv d1
  Ifosfamide 5000 mg/m2 mixed with Mesna 5000 mg/m2 iv over 24 hrs d2
  Carboplatin AUC 5 (max 800mg) iv d2
  Etoposide 100 mg/m2/d iv d1-3
  Filgrastim 5 ug/kg sc qd d5-12

Non-Hodgkin lymphoma-
Commonly used combination chemotherapy regimen

- **ESHAP Q3-4W x 6-8 cycles[13]**
  Etoposide 40 mg/m2/d iv over 1 hr d1-4
  Methylprednisolone 500 mg/d iv over 15 min d1-5
  Cisplatin 25 mg/m2/d civi d1-4
  Cytarabine 2000 mg/m2 iv over 2 hr d5

- **EPOCH Q3w x 6-8 cycles[14]**
  Etoposide 50 mg/m2/d civd d1-4
  Prednisone 60 mg/m2/d po d1-5
  Vincristine 0.4 mg/m2/d civi d1-4
  Doxorubicin 10 mg/m2/d civi d1-4
  Cyclophosphamide 750 mg/m2 iv over 15 min d5

Non-Hodgkin lymphoma- Commonly used combination chemotherapy regimen

- **Dose-adjusted EPOCH Q3W x 6-8 cycles[15]**
  Etoposide 50 mg/m2/d civi d1-4
  Prednisone 60 mg/m2/d po d1-5
  Vincristine 0.4 mg/m2/d civi d1-4
  Doxorubicin 10 mg/m2/d civi d1-4
  Cyclophosphamide 750 mg/m2 iv over 15 min d5

Dose-adjustment paradigm based on twice weekly CBC
If nadir ANC > 500/uL, 20% increase in Etoposide, Doxorubicin and Cyclophosphamide above last cycle
If nadir ANC < 500/uL on 1 or 2 measurements, same doses as last cycle
If nadir ANC < 500/uL on at least 3 measurements, or nadir platelet < 25,000/uL on 1 measurement, 20% decrease in Etoposide, Doxorubicin and Cyclophosphamide below last cycle

Non-Hodgkin lymphoma-
Commonly used combination chemotherapy regimen

- **DHAP Q3-4W[17]**
  Dexamethasone 40 mg po qd d1-4
  Cisplatin 100 mg/m2 iv over 24 hrs d1
  Cytarabine 2000 mg/m2 iv q12 hrs for 2 doses d2

Non-Hodgkin lymphoma- Commonly used combination chemotherapy regimen

- **CODOX-M/IVAC[18]**
- **Cycle 1 and 3 (CODOX-M)**
  Cyclophosphamide 800 mg/m2 iv d1
  Cyclophosphamide 200 mg/m2/d iv d2-5
  Doxorubicin 40 mg/m2 iv d1
  Vincristine 1.5 mg/m2 iv d1, 8 for cycle 1 and d1, 8, 15 for cycle 3
  Methotrexate 1200 mg/m2 iv over 1 h d10, then 240 mg/m2 per hour civi for the next 23 hrs
  Leucovorin 50 mg iv q6h begins 36 hrs from the start of MTX till MTX level < 0.05 uM
  Filgrastim begins 24 hrs from the start of Leucovorin till ANC > 1000/mL
  CNS prophylaxis:
  Intrathecal Cytarabine 70 mg d1 and 3, Methotrexate 12 mg d15
  CNS treatment:
  Cycle 1: Intrathecal Cytarabine 70 mg d1, 3 and 5, Methotrexate 12 mg d15 and 17
  Cycle 3: Intrathecal Cytarabine 70 mg d1 and 3, Methotrexate 12 mg d15

Non-Hodgkin lymphoma- Commonly used combination chemotherapy regimen

- **CODOX-M/IVAC[18]**
- **Cycle 2 and 4 (IVAC)**
  Ifosfamide 1500 mg/m2/d iv d1-5
  Etoposide 60 mg/m2/d iv d1-5
  Cytarabine 2000 mg/m2 iv q12h d1 and 2 (total 4 doses)
  Filgrastim begins 24 hrs after completion of chemotherapy till ANC > 1000/mL
  CNS prophylaxis:
  Intrathecal Methotrexate 12 mg d5
  CNS treatment:
  Cycle 2: Intrathecal Methotrexate 12 mg d5, Cytarabine 70 mg d7 and 9
  Cycle 4: Intrathecal Methotrexate 12 mg d5

Non-Hodgkin lymphoma- Commonly used combination chemotherapy regimen

- **Hyper-CVAD/MTX-Ara-C Q3W[19]**
- **Cycle 1,3,5,7 (3-4 wks/cycle)**
  Cyclophosphamide 300 mg/m2 iv over 2 hrs q12 hrs x 6 doses d1-3
  Mesna 600 mg/m2/d civi d1-3 to start 1 h before cyclophosphamide till 12 hrs after completion of cyclophosphamide
  Vincristine 2 mg iv d4, 11
  Doxorubicin 50 mg/m2 iv over 24 hrs (over 48 hrs if LVEF < 50%) d4
  Dexamethasone 40 mg po or iv qd d1-4 and d11-14
- **Cycle 2,4,6,8 (3-4 wks/cycle)**
  Methotrexate 200 mg/m2 iv over 2 hrs followed by 800 mg/m2 civi over 22 hrs d1
  Cytarabine 3 g/m2 (1 g/m2 for patients over 60 years old) iv over 2 hrs q12 hrs x 4 doses d2-3
  Leucovorin 50 mg iv q6 hrs starting 12 hrs after completion of MTX till MTX level < 0.05 uM
- **Intrathecal chemotherapy**
- **Prophylaxis**
  Methotrexate 12 mg d2 of each cycle for a total of 3-4 treatments
  Cytarabine 100 mg d8 of each cycle for a total of 3-4 treatments
  Therapeutic
  Intrathecal chemotherapy twice a week (Methotrexate 12 mg and Cytarabine 100 mg respectively) till no more cancer cells in CSF, then decrease intrathecal chemotherapy to once a week x 4, followed by Methotrexate 12 mg d2, Cytarabine 100 mg d8 for the remaining chemotherapy cycles

References

1. Marcus R, Imrie K, Solal-Celigny P, et al. Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. J Clin Oncol 2008;26:4579-4586.
2. Hainsworth JD, Litchy S, Burris HA, III, et al. Rituximab as first-line and maintenance therapy for patients with indolent Non-Hodgkin's lymphoma. J Clin Oncol 2002;20:4261-4267.
3. Hiddemann W, Kneba M, Dreyling M, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood 2005;106:3725-3732.
4. Czuczman MS, Weaver R, Alkuzweny B, et al. Prolonged clinical and molecular remission in patients with low-grade or follicular non-Hodgkin's lymphoma treated with rituximab plus CHOP chemotherapy: 9-year follow-up. J Clin Oncol 2004;22:4711-4716.
5. The Lancet Oncology, Volume 12, Issue 5, Pages 460 - 468, May 2011
6. Rummel MJ *et al*. Bendamustine plus rituximab (B-R) versus CHOP plus rituximab (CHOP-R) as first-line treatment in patients with indolent and mantle cell lymphomas (MCL): updated results from the StiL NHL1 study. *J Clin Oncol*. 2012;30(suppl; abstr 3).
7. Walter E, *et al*. Leuk Lymphoma. 2012 Nov;53(11):2290-2. doi: 10.3109/10428194.2012.682311. Epub 2012 May 22

References

8. Levine AM, Tulpule A, Smith L, Espina BM, Mohrbacher AF, Feinstein DI. Results of a pilot trial of fludarabine, mitoxantrone and rituxan in mantle cell lymphoma [abstract]. Blood 2005;106:Abstract 945.
9. Forstpointner R, Dreyling M, Repp R, et al. The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared to FCM alone in patients with relapsed and refractory follicular and mantle cell lymphom - results of a prospective randomized study of the German low grade lymphoma study group (GLSG). Blood 2004;104:3064-3071.
10. Wohrer S, Drach J, Hejna M, et al. Treatment of extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) with mitoxantrone, chlorambucil and prednisone (MCP). Ann Oncol 2003;14:1758-1761.
11. Lopez A, Gutierrez A, Palacios A, et al. GEMOX-R regimen is a highly effective salvage regimen in patients with refractory/relapsing diffuse large-cell lymphoma: A phase II study. Eur J Haematol 2008;80:127-132.
12. Zelenetz AD, Hamlin P, Kewalramani T, et al. Ifosfamide, carboplatin, etoposide (ICE)-based second-line chemotherapy for the management of relapsed and refractory aggressive non -Hodgkin's lymphoma. Ann Oncol 2003;14[suppl 1]:i5-10.
13. Velasquez WS, McLaughlin P, Tucker S, et al. ESHAP - an effective chemotherapy regimen in refractory and relapsing lymphoma: a 4-year follow-up study. J Clin Oncol1994;12:1169-1176.

References

14. Wilson WH, Bryant G, Bates S, et al. EPOCH chemotherapy: toxicity and efficacy in relapsed and refractory non-Hodgkin's lymphoma. J Clin Oncol 1993;11:1573-582
15. Dunleavy K, Shovlin M, Pittaluga S, et al. DA-EPOCH Chemotherapy is highly effective in ALK -positive and ALK-negative ALCL: Results of a prospective study of PTCL subtypes in adults [abstract]. Blood 2011;118:Abstract 1618
16. Rodriguez MA, Cabanillas FC, Velasquez W, et al. Results of a salvage treatment program for relapsing lymphoma: MINE consolidated with ESHAP. J Clin Oncol. 1995 Jul;13(7):1734-41.
17. Delarue R, Haioun C, Ribrag V, et al. CHOP and DHAP plus rituximab followed by autologous stem cell transplantation (ASCT) in mantle cell lymphoma (MCL): a phase II study from the GELA. Blood 2013;121:48-53.
18. Wang ES, Straus DJ, Teruya-Feldstein J, et al. Intensive chemotherapy with cyclophosphamide, doxorubicin, high-dose methotrexate/ifosfamide, etoposide, and high-dose cytarabine (CODOX-M/IVAC) for human immunodeficiency virus-associated Burkitt lymphoma. Cancer 2003;98:1196-1205.
19. Thomas DA, Kantarjian HM, Faderl S, et al. Hyper-CVAD and rituximab for de novo Burkitt lymphoma/leukemia [abstract]. Blood 2011;118:Abstract 2698.
20. Attenuated immunochemotherapy regimen (R-miniCHOP) in elderly patients older than 80 years with diff use large B-cell lymphoma: a multicentre, single-arm, phase 2 trial. Lancet Oncol 2011; 12: 460–68

Commonly used single agent chemotherapy regimen

- **Chlorambucil[1]**
  Chlorambucil 10 mg po qd
- **Cyclophosphamide[2]**
  Cyclophosphamide 100 mg/m2 po qd
- **Fludarabine Q4W[3]**
  Fludarabine 25 mg/m2 iv qd d1-5
- **Rituximab Q2M x 4 cycles[4]**
  375 mg/m2 iv qw x 4 followed by 375 mg/m2 iv
- **Bendamustine Q3W x 12 cycles[5]**
  Bendamustine 120 mg/m2 iv over 30-60 min d1 and 2
- **Bortezomib Q3W[6]**
  Bortezomib 1.3-1.5 mg/m2 iv d1, 4, 8 and 11
- **Temsirolimus QW[7]**
  Temsirolimus 250 mg iv over 30 min qw for a total of 12 months or 2 months after CR
  Premedication Diphenhydramine 25-50 mg iv
- **High dose Methotrexate QM x 11 cycles[8]**
  Methotrexate 8 g/m2 iv over 4 hrs q2w till CR or up to 8 cycles, followed by 8 g/m2 iv

References

1. Rai KR, Peterson BL, Appelbaum FR, Kolitz J, Elias L, Shepherd L, Hines J, Threatte GA, Larson RA, Cheson BD, Schiffer CA (2000). "Fludarabine compared with chlorambucil as primary therapy for chronic lymphocytic leukemia.". N Engl J Med 343 (24): 1750–7
2. Shanafelt TD, Lin T, Geyer SM; et al. (June 2007). "Pentostatin, cyclophosphamide, and rituximab regimen in older patients with chronic lymphocytic leukemia". Cancer 109 (11): 2291–8.
3. Cohen BJ, Moskowitz C, Straus D et al. Cyclophosphamide/fludarabine (CF) is active in the treatment of mantle cell lymphoma. Leuk Lymphoma 2001;42:1015-1022.
4. Morales AV, Advani R, Horwitz SM, et al. Indolent primary cutaneous B-cell lymphoma: experience using systemic rituximab. J Am Acad Dermatol 2008;59:953-957.
5. Robinson KS, Williams ME, van der Jagt RH, et al. Phase II multicenter study of bendamustine plus rituximab in patients with relapsed indolent B-cell and mantle cell Non-Hodgkin's Lymphoma. J Clin Oncol 2008; 26:4473-4479.
6. Goy A, Bernstein SH, Kahl BS, et al. Bortezomib in patients with relapsed or refractory mantle cell lymphoma: updated time-to-event analyses of the multicenter phase 2 PINNACLE study. Ann Oncol 2009;20:520-525.
7. Phase I Trial of the Pan-PI3K Inhibitor Pilaralisib (SAR245408/XL147) in Patients with Chronic Lymphocytic Leukemia (CLL) or Relapsed/Refractory Lymphoma Clin. Cancer Res. Jul 15, 2015:3160-3169
8. Escalon MP, Liu NS, Yang Y, et al. Prognostic factors and treatment of patients with T-cell non -Hodgkin lymphoma: the M. D. Anderson Cancer Center experience. Cancer 2005;103:2091-2098.

Taipei Veterans General Hospital Practice Guidelines Oncology

Hodgkin Lymphoma

Staging

Definitions of Stages in Hodgkin's Disease

Stage I Involvement of a single lymph node region (I) or localized involvement of a single extralymphatic organ or site (I_E).

Stage II Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of a single associated extralymphatic organ or site and its regional lymph node(s), with or without involvement of other lymph node regions on the same side of the diaphragm (II_E).

Note: The number of lymph node regions involved may be indicated by a subscript (eg, II_3).

Stage III Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by localized involvement of an associated extralymphatic organ or site (IIIE), by involvement of the spleen (III_S), or by both (III_{E+S}).

Stage IV Disseminated (multifocal) involvement of one or more extralymphatic organs, with or without associated lymph node involvement, or isolated extralymphatic organ involvement with distant (nonregional) nodal involvement.

A. No systemic symptoms present

B. Unexplained fevers >38°C; drenching night sweats; or weight loss >10% of body weight (within 6 months prior to diagnosis)

Risk Factor	GHSG	EORTC	NCCN
Age		≥50	
Histology			
ESR and B symptoms	>50 if A; >30 if B	>50 if A; >30 if B	≥50 or any B symptoms
Mediastinal mass	MMR > .33	MTR > .35	MMR > .33
# Nodal sites	>2*	>3*	>3
E lesion	any		
Bulky			>10 cm

GHSG = German Hodgkin Study Group EORTC = European Organization for the Research and Treatment of Cancer
MMR = Mediastinal mass ratio, maximum width of mass/maximum intrathoracic diameter
MTR = Mediastinal thoracic ratio, maximum width of mediastinal mass/intrathoracic diameter at T5-6

Definitions of Lymph Node Regions

		Ann Arbor	EORTC	GHSG
Supradiaphragmatic Nodal Regions	R Cervical/SCL			
	R ICL/Subpectoral			
	R Axilla			
	L Cervical/SCL			
	L ICL/Subpectoral			
	L Axilla			
	Mediastinum			
	R Hilum			
	L Hilum			
Infradiaphragmatic Nodal Regions	Celiac/Spleen hilar			
	Paraortic			
	Mesenteric			
	R Iliac			
	L Iliac			
	R Inguinal/Femoral			
	L Inguinal/Femoral			

International Prognostic Score (IPS) 1 point per factor (advanced disease)

- **Albumin <4 g/dL**
- **Hemoglobin <10.5 g/dL**
- **Male**
- **Age ≥45 years**
- **Stage IV disease**
- **Leukocytosis (white blood cell count at least 15,000/mm$_3$)**
- **Lymphocytopenia (lymphocyte count less than 8% of white blood cell count, and/or lymphocyte count less than 600/mm$_3$)**

PET 5-POINT SCALE (DEAUVILLE CRITERIA)

PET 5-POINT SCALE (DEAUVILLE CRITERIA)

Score		PET/CT Scan Result
Negative	1	No uptake
	2	Uptake ≤ mediastinum
	3	Uptake > mediastinum but ≤ liver
Positive	4	Uptake moderately higher than liver and visually above adjacent background activity
	5	Uptake markedly higher than liver and/or new lesions
	X[a]	New areas of uptake unlikely to be related to lymphoma

Diagnosis/workup

- Excisional biopsy (recommended)
- Core needle biopsy may be adequate if diagnostic
- Immunohisto-chemistry evaluation

Essential:

- **H&P including: B symptoms (unexplained fever >38°C; drenching night sweats; or weight loss >10% of body weight within 6 mo of diagnosis), alcohol intolerance, pruritus, fatigue, performance status, examination of lymphoid regions, spleen, liver**
- **CBC, differential, platelets**
- **Erythrocyte sedimentation rate (ESR)**
- **Comprehensive metabolic panel, lactate dehydrogenase (LDH), and liver function test (LFT)**
- **Pregnancy test for women of childbearing age**
- **Diagnostic CT (contrast-enhanced)**
- **PET/CT scan (skull base to mid-thigh)**
- **HIV and hepatitis B/C testing**
- **Counseling: Fertility, smoking cessation, psychosocial**

Useful in selected cases:

- **Fertility preservation**
- **Diagnostic neck CT with contrast, if neck is PET/CT+ or if neck RT contemplated**
- **Pulmonary function tests (PFTs incl. diffusing capacity [DLCO]) if ABVD or escalated BEACOPP are being used**
- **Pneumococcal, H-flu, meningococcal vaccines, if splenic RT contemplated**
- **HTLV I/II**
- **Chest x-ray (encouraged, especially if large mediastinal mass)**
- **Adequate bone marrow biopsy if there are cytopenias and negative PET**
- **Evaluation of ejection fraction if doxorubicin-based chemotherapy is indicated**
- **MRI or PET/MRI (skull base to mid-thigh) with contrast unless contraindicated**

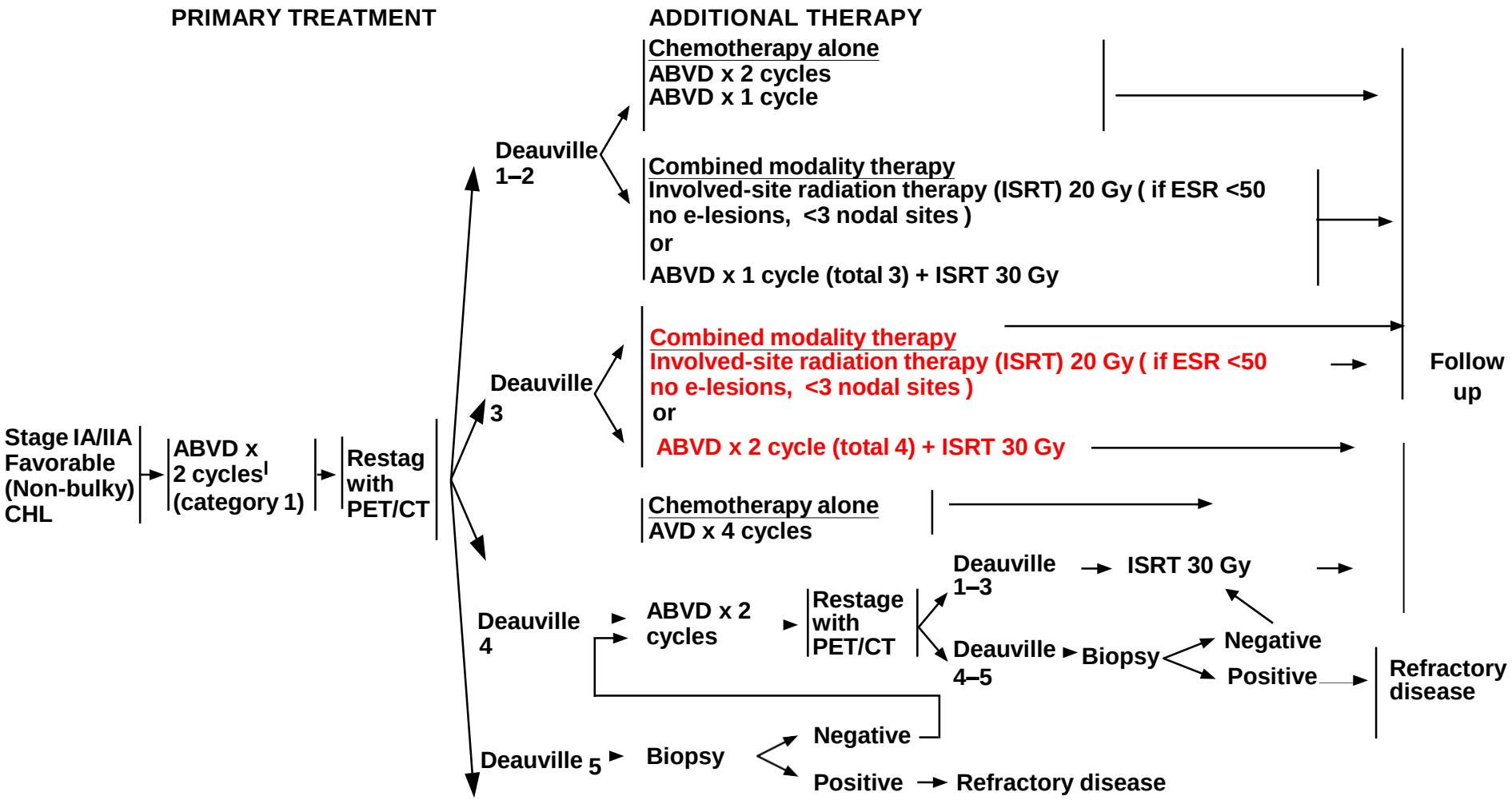
Classic Hodgkin Lymphoma (CHL)

Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL)

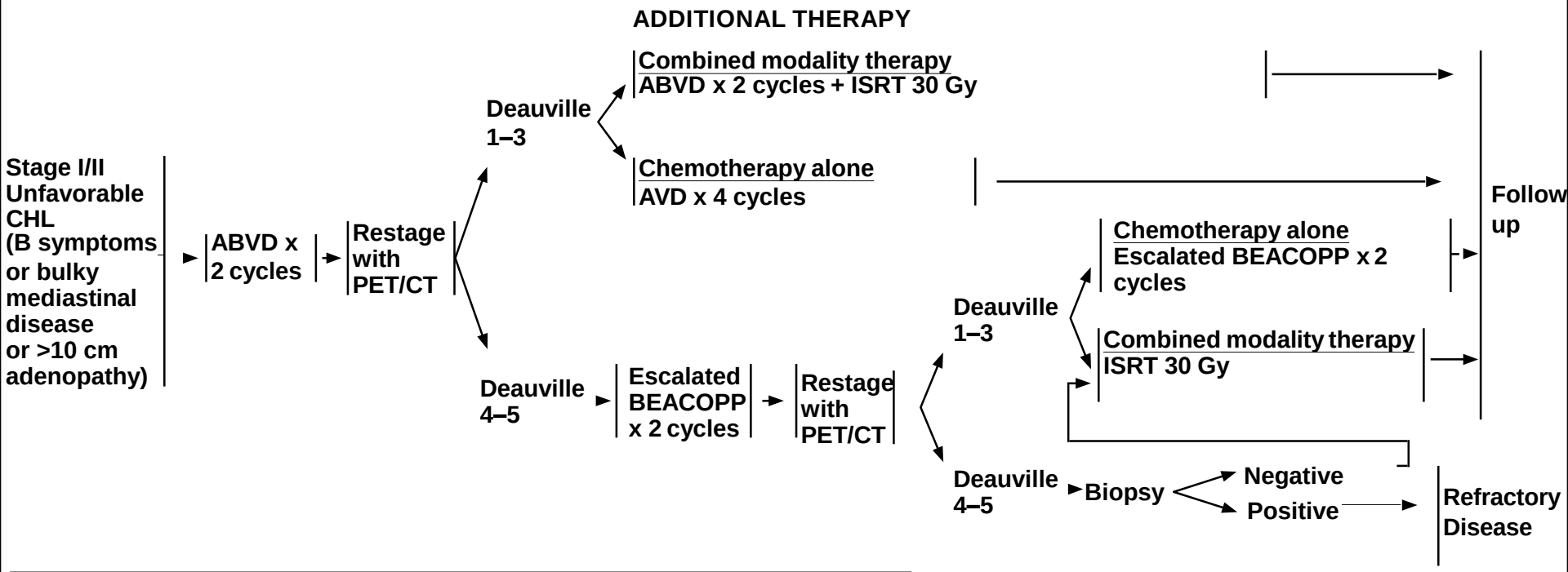
- Clinical staging/risk classification of classic Hodgkin lymphoma (CHL)

Clinical Stage	Bulky Mediastinal Disease[j] or >10 cm Adenopathy	ESR >50 or # Sites >3	Type
IA/IIA	No	No	Favorable Disease
	No	Yes	Favorable/Unfavorable Disease
	Yes	Yes/No	Unfavorable Disease
IB/IIB	Yes/No	Yes/No	Unfavorable Disease
III–IV	Yes/No	N/A	Advanced Disease

Stage IA,IIA favorable



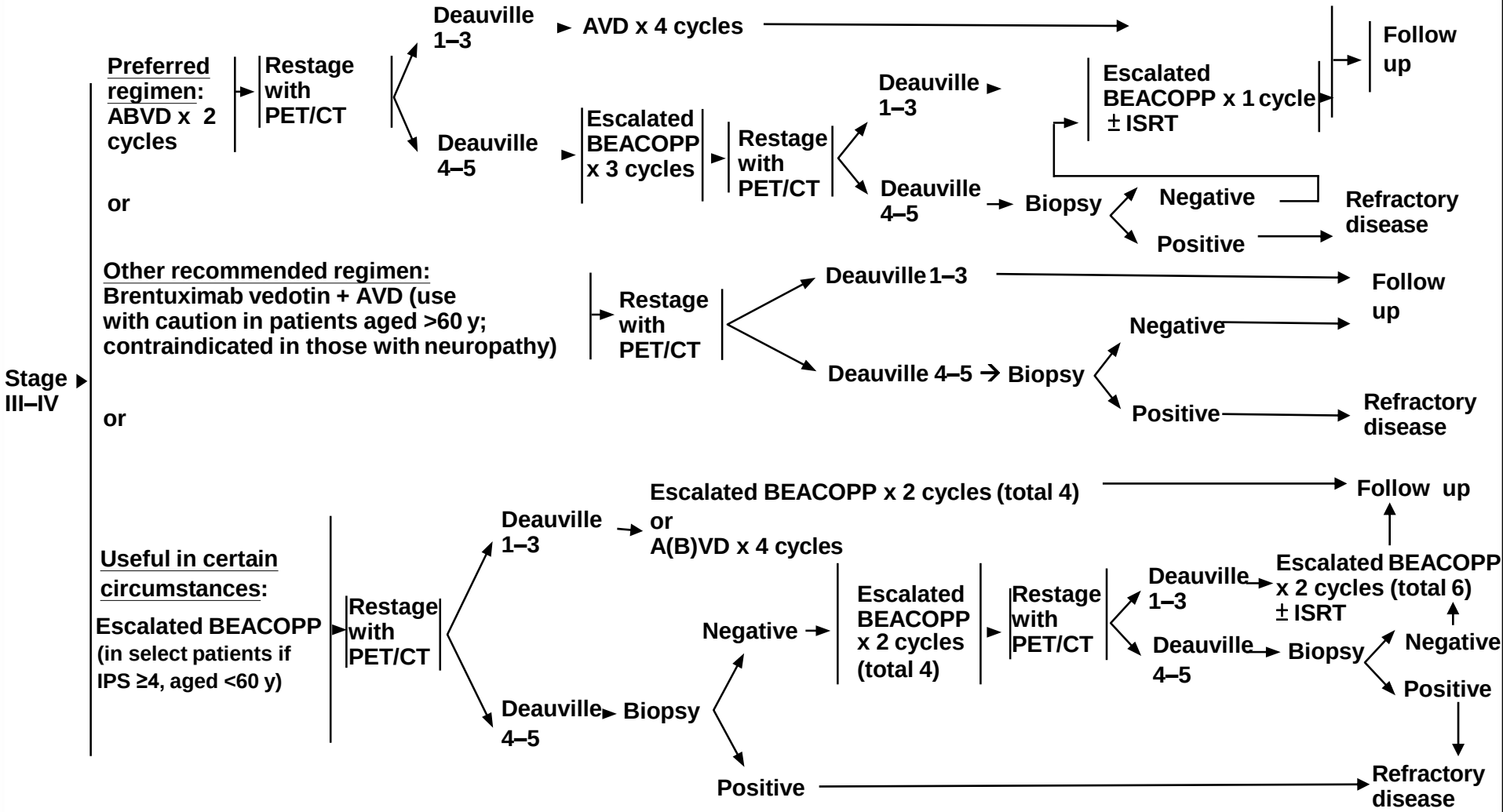
Stage I/II unfavorable (B symptom or bulky disease)



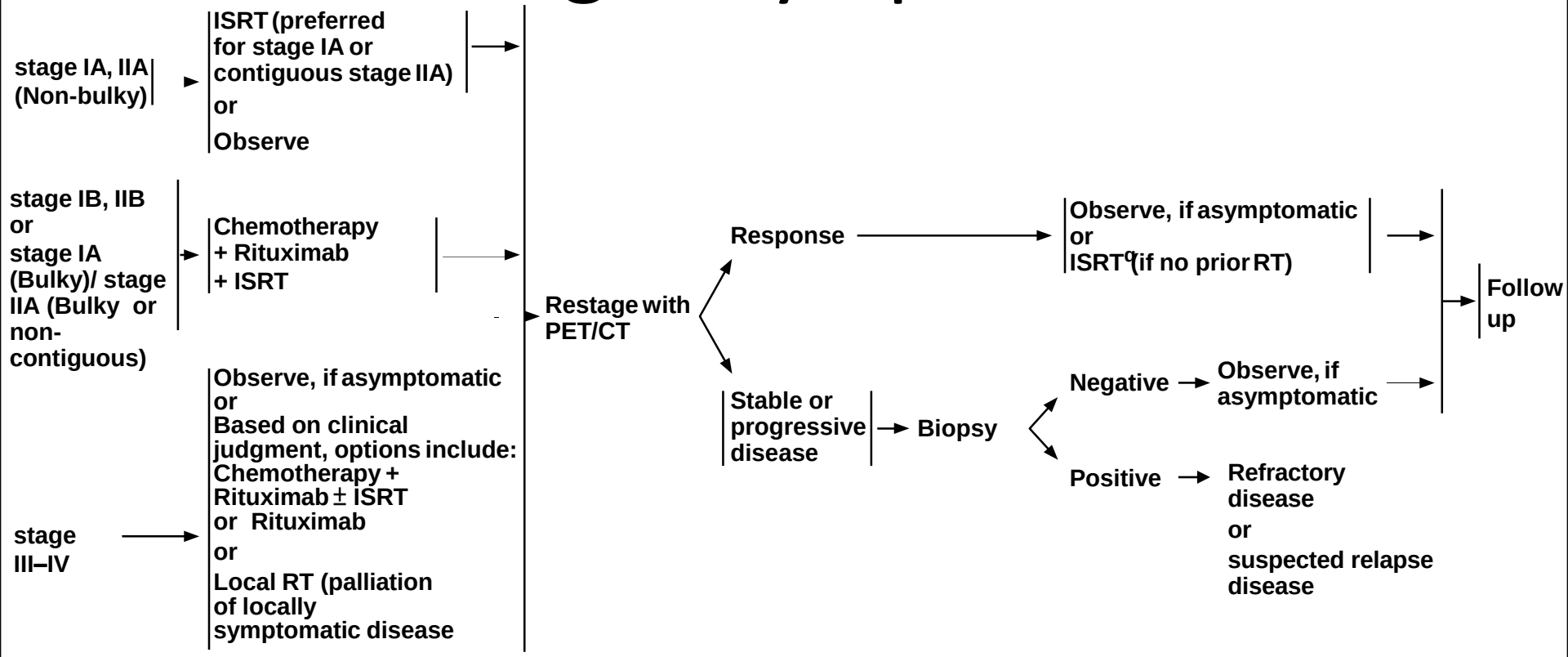
Special considerations for Deauville 4–5 after ABVD x 2 cycles:

- The degree of abnormality of a Deauville 4 score is quite variable and may influence further therapy (eg, If only focally positive, it may be feasible to continue with 2 more cycles of ABVD and then repeat the PET scan.). For a scan that remains positive throughout the area(s) of initial disease, the consensus is to escalate therapy (with consideration of biopsy, especially if an easily accessible site).
- A Deauville 5 score should prompt re-biopsy, especially if a readily accessible site, which would then inform subsequent therapy. If a biopsy is not performed, treatment should be escalated.

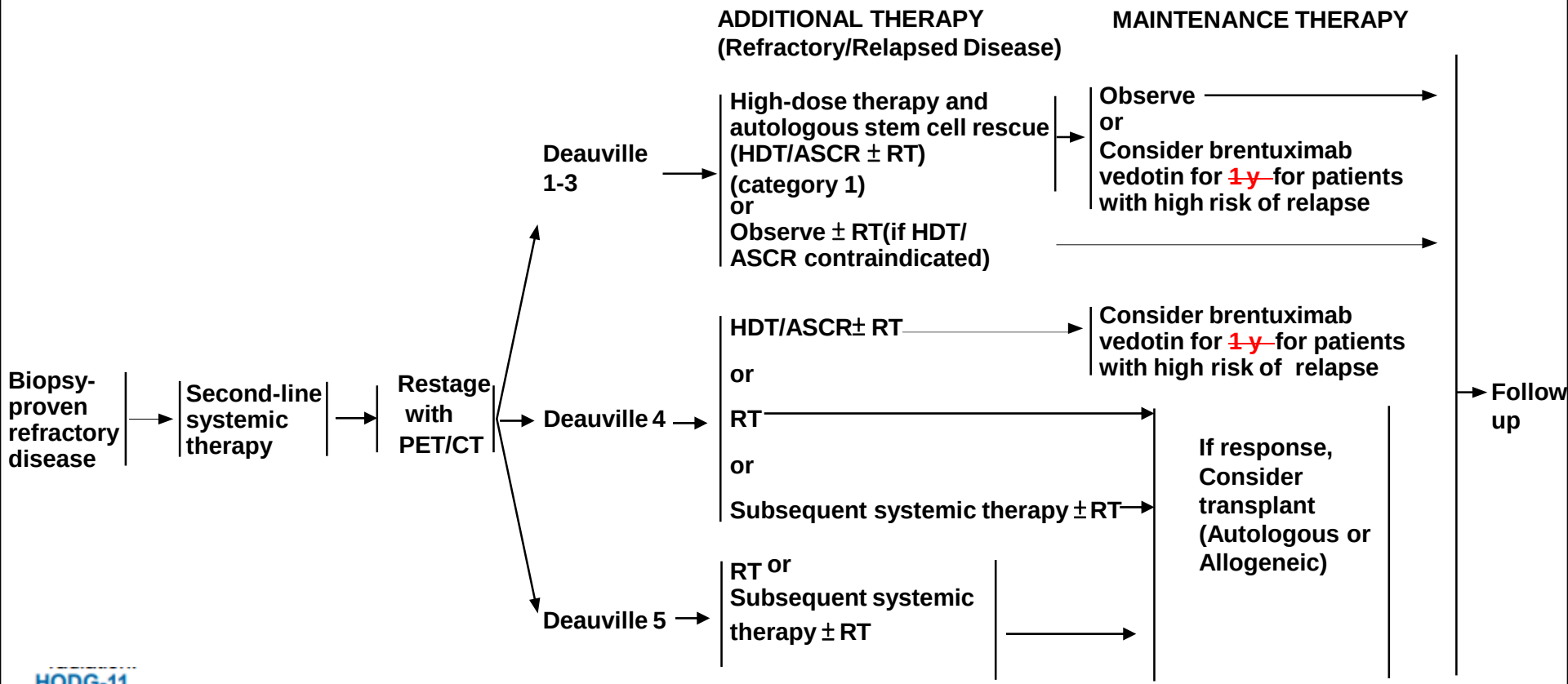
Stage III/IV CHL



Nodular lymphocyte-predominant Hodgkin lymphoma



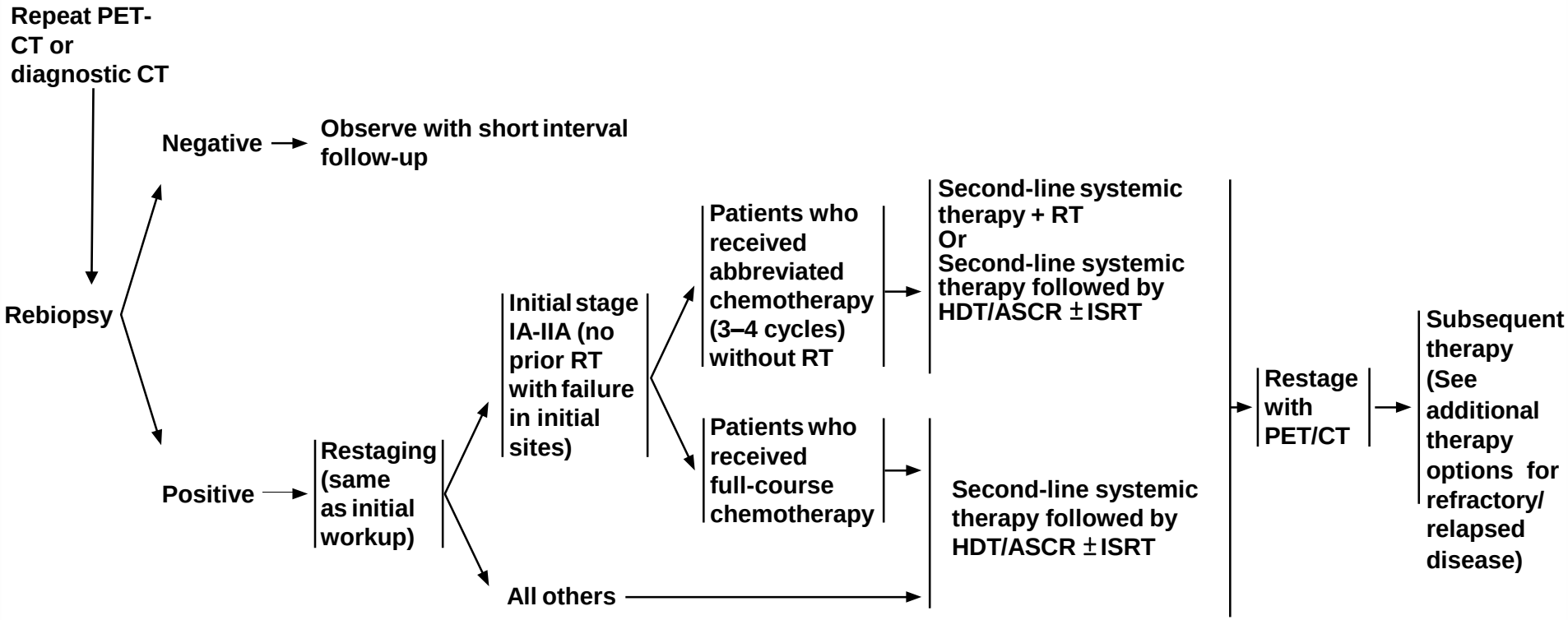
Classic Hodgkin lymphoma Refractory disease



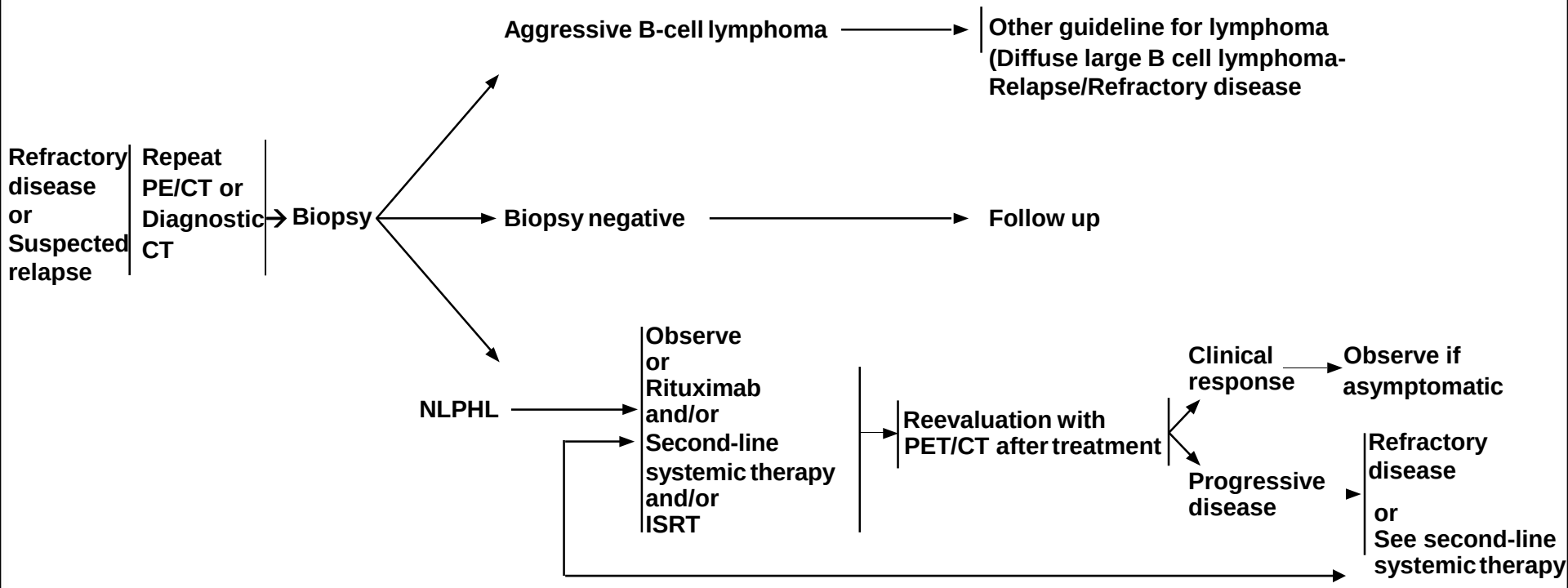
HODG-11

- Maintenance Therapy, Recommendations modified as follows:
  - Deauville 1–3: Observe or *Consider* brentuximab vedotin *maintenance* ~~for 1 y~~ for patients with high risk of relapse
  - Deauville 4: *Consider* brentuximab vedotin *maintenance* ~~for 1 y~~ for patients with high risk of relapse

Classic Hodgkin lymphoma suspected relapse



Nodular lymphocyte-predominant Hodgkin lymphoma refractory or suspected relapse



Regimens for Hodgkin lymphoma

- **ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) ± ISRT**
- **Escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone)**
- **Escalated BEACOPP followed by ABVD with ISRT**
- **Brentuximab vedotin + AVD (doxorubicin, vinblastine, and dacarbazine)**

.

Nodular Lymphocyte-Predominant Hodgkin Lymphoma

Regimens

ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) + rituximab

CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab

CVbP (cyclophosphamide, vinblastine, prednisolone) + rituximab

Rituximab

Chemotherapy for relapse or refractory disease

Relapsed/Refractory Disease

	Second-Line and Subsequent Therapy (in alphabetical order)	Third-Line and Subsequent Therapy (in alphabetical order)
CHL	• Brentuximab vedotin • Brentuximab vedotin + bendamustine • Brentuximab vedotin + nivolumab • DHAP (dexamethasone, cisplatin, high-dose cytarabine) • ESHAP (etoposide, methylprednisolone, high-dose cytarabine, cisplatin) • Gemcitabine/bendamustine/vinorelbine • GVD (gemcitabine, vinorelbine, liposomal doxorubicin) • GVD + pembrolizumab • ICE (ifosfamide, carboplatin, etoposide) • ICE+ brentuximab vodetin • ICE + nivolumab • IGEV (ifosfamide, gemcitabine, vinorelbine) • Pembrolizumab (for patients not candidates for transplant)	• Bendamustine • Bendamustine + carboplatin + etoposide • C-MOPP (cyclophosphamide, vincristine, procarbazine, prednisone) • Everolimus • GCD (gemcitabine, cisplatin, dexamethasone) • GEMOX (gemcitabine, oxaliplatin) • Lenalidomide • MINE (etoposide, ifosfamide, mesna, mitoxantrone) • Mini-BEAM (carmustine, cytarabine, etoposide, melphalan) • Nivolumab • Pembrolizumab
NLPHL	• R (rituximab) + Bendamustine • R + DHAP • R + ESHAP • R + ICE • R + IGEV * If not previously used: R-ABVD R-CHOP R-CVbP	

Principle of checkpoint inhibitor (CPI) for relapse or relapse

- **CPI are recommended for any patients with CHL that has relapsed or progressed after HDT/ASCR ± brentuximab vedotin.**
- **CPI are also an option for patients with relapsed/refractory CHL who are transplant-ineligible based on comorbidity or failure of second-line chemotherapy.**
- **Post-allogeneic transplant, patients can receive either nivolumab or pembrolizumab. There are limited data regarding the use of CPI following allogeneic transplantation; CPI should be used with caution before allogeneic transplantation due to increased risk of GVHD (graft- versus-host disease) and other immunologic complications.**

Management of classic Hodgkin lymphoma in older adults (age>60)

- **CHL in older adult patients is associated with poorer disease outcomes. B-symptoms, poor performance status, mixed cellularity, histologic subtype, EBV+ disease, and medical comorbidities are more frequent in this population.**
- **Standard chemotherapy regimens are associated with dose reductions, treatment toxicity, and treatment-related mortality in older patients.**
- **There are limited prospective data evaluating alternatives to standard therapies for older patients. Selection of standard versus alternate first-line therapy for an older patient should be based on clinical judgment, with the goal of minimizing toxicity while maximizing efficacy.**
- **The regimens listed below should be considered in older patients to lessen/minimize toxicity. These regimens have not been proven to overcome the poorer disease outcomes observed in the older patients.**
- **Clinical trial is recommended when available.**
- **ISRT alone is an option when systemic therapy is not considered feasible or safe.**

Stage I–II Favorable Disease

- **A(B)VD (2 cycles) ± AVD (2 cycles) + ISRT (preferred)**
- **CHOP (4 cycles) + ISRT**

Stage I–II Unfavorable or Stage III–IV Disease

- **A(B)VD (2 cycles) followed by AVD (4 cycles), if PET scan is negative after 2 cycles of ABVD.**
  - **Patients with a positive PET scan after 2 cycles of ABVD need individualized treatment.**
- **Brentuximab vedotin followed by AVD, conditionally followed by brentuximab vedotin in responding patients with CR or PR**
- **Brentuximab vedotin + DTIC (dacarbazine)**
- **CHOP (6 cycles) ± ISRT**

Relapsed or Refractory Disease

- **Outcomes are uniformly poor for patients with relapsed or refractory disease.**
- **No uniform recommendation can be made, although clinical trials or possibly single-agent therapy with a palliative approach is recommended.**
- **Individualized treatment is necessary. Palliative therapy options include: Bendamustine, Brentuximab vedotin, ISRT. Nivolumab, Pembrolizumab or other second-line and subsequent therapy options**

Follow up after completion of treatment and monitor

- **Complete response should be documented including reversion of PET to "negative" within 3 months following completion of therapy.**
- **It is recommended that the patient be provided with a treatment summary at the completion of therapy, including details of radiation therapy (RT), organs at risk (OARs), and cumulative anthracycline dosage given.**
- **Follow-up with an oncologist is recommended and should be coordinated with the primary care physician (PCP), especially during the first 5 y after treatment to detect recurrence, and then annually due to the risk of late complications including second cancers and cardiovascular disease Late relapse or transformation to large cell lymphoma may occur in NLPHL.**
- **The frequency and types of tests may vary depending on clinical circumstances: age and stage at diagnosis, social habits, treatment modality, etc. There are few data to support specific recommendations; these represent the range of practice at NCCN Member Institutions.**

- **<u>Follow-up After Completion of Treatment Up to 5 Years</u>**
- **Interim H&P: Every 3–6 mo for 1–2 y, then every 6–12 mo until year 3, then annually.**
- **Annual influenza vaccine and other vaccines as clinically indicated**
- **Laboratory studies:**
  - **CBC, platelets, ESR (if elevated at time of initial diagnosis), chemistry profile as clinically indicated.**
  - **Thyroid-stimulating hormone (TSH) at least annually if RT to neck.**
- **Consider neck/chest/abdomen/pelvis CT scan with contrast no more often than every 6 mo for the first 2 y following completion of therapy, or as clinically indicated after 2 y, especially in NLPHL where late relapse may occur. PET/CT only if last PET was Deauville 4–5, to confirm complete response.**
- **Counseling: Reproduction, health habits, psychosocial, cardiovascular, breast self-examination, skin cancer risk, end-of-treatment discussion.**
- **Surveillance PET should not be done routinely due to risk for false positives. Management decisions should not be based on PET scan alone; clinical or pathologic correlation is needed.**