

SPECIAL ARTICLE

Lymphomas: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up[☆]

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INTRODUCTION

The treatment landscape for many lymphoma entities continues to evolve rapidly, with multiple recent approvals of novel non-chemotherapy (ChT)-based approaches. The following Clinical Practice Guideline (CPG) provides an overview of the current management landscape for the seven most common systemic diseases [i.e. diffuse large B-cell lymphoma (DLBCL), primary central nervous system lymphoma (PCNSL), follicular lymphoma (FL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), Hodgkin lymphoma (HL) (excluding nodular lymphocyte-predominant HL) and nodal peripheral T-cell lymphoma (PTCL)]. Evidence-based recommendations and therapeutic algorithms are provided for each entity.

INCIDENCE AND EPIDEMIOLOGY

Details regarding the incidence and epidemiology of the seven lymphoma entities covered in this CPG are provided

in the [Supplementary Material Section 1](https://doi.org/10.1016/j.annonc.2025.07.014), available at <https://doi.org/10.1016/j.annonc.2025.07.014>.

DIAGNOSIS, PATHOLOGY AND MOLECULAR BIOLOGY

Details regarding the diagnosis, pathology and molecular biology of the lymphoma entities covered in this CPG are provided in the [Supplementary Material Section 2](https://doi.org/10.1016/j.annonc.2025.07.014), available at <https://doi.org/10.1016/j.annonc.2025.07.014>. Key diagnostic criteria are summarised in [Supplementary Table S1](https://doi.org/10.1016/j.annonc.2025.07.014), available at <https://doi.org/10.1016/j.annonc.2025.07.014>.

Recommendations

- Clinical information should be a mainstay of diagnosis [III, A].
- In general, the diagnosis of lymphoma should rely on surgical biopsy whenever possible to allow adequate histopathological assessment and provide sufficient tissue for immunohistochemistry (IHC) and molecular studies [II, A].
- Diagnosis of DLBCL, PCNSL, FL, MCL, MZL, HL and PTCL should be according to the diagnostic criteria outlined in [Supplementary Table S1](https://doi.org/10.1016/j.annonc.2025.07.014), available at <https://doi.org/10.1016/j.annonc.2025.07.014> [I, A].

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STAGING AND RISK ASSESSMENT

Key recommendations regarding staging and risk assessment for the lymphoma entities covered in this CPG are provided below. Supporting evidence for these recommendations are described in the [Supplementary Material Section 3](https://doi.org/10.1016/j.annonc.2025.07.014), available at <https://doi.org/10.1016/j.annonc.2025.07.014>.

Recommendations

DLBCL

- A baseline electrocardiogram should be carried out on all patients [V, A]. Echocardiogram (or multi-gated acquisition or gated heart pool scan if echocardiogram unavailable) can be considered for all patients [V, B] and is recommended for older patients and those with cardiovascular risk factors [V, A].
- Positron emission tomography (PET)—computed tomography (CT) can be recommended as the standard imaging modality for baseline and response assessment [V, B] and can be considered at interim assessment [V, B].
- Assessment of the central nervous system (CNS) with contrast-enhanced cranial magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) examination can be carried out on a case-by-case basis based on clinical risk factors or presentation [V, B].
- Recommended scoring systems to predict outcomes and stratify patients in clinical trials are the International Prognostic Index (IPI) and the age-adjusted IPI (aIPI) [II, B].
- Assessment of the frail and elderly using the Elderly Prognostic Index can be considered [V, B].
- The CNS-IPI can be calculated when considering patients for CNS prophylaxis [V, B].
- FISH should be carried out to determine the presence of *MYC* rearrangements [V, A]. If *MYC* is rearranged, FISH assessment for *BCL2* rearrangement can be recommended [V, B].
- Cell of origin according to current IHC-based classifications can be reported [V, B].

PCNSL

- Contrast-enhanced cranial MRI is the recommended imaging modality for patients with PCNSL [II, A]. The International Primary CNS Lymphoma Collaborative Group (IPCG) protocol based on 3T or 1.5T MRI is recommended [V, A].
- Spinal cord imaging can be carried out in symptomatic patients or in case of CSF positivity [V, B].
- Unless lumbar puncture is clinically contraindicated, physical—chemical features of CSF as well as conventional cytology and flow cytometry can be assessed in all patients [V, B]. In addition, combined assessment of the *MYD88 L265P* mutation, interleukin-10 levels and PCR for immunoglobulin (Ig) heavy chain variable rearrangement in the CSF may help to discriminate PCNSL from glial neoplasms and non-neoplastic disorders of the CNS [IV, C].

- Ophthalmological assessment by slit lamp fundoscopy should be carried out in all patients to exclude intra-ocular involvement [V, A]. When available, retinal angiography or tomography is advisable [V, C].
- All patients should undergo systemic imaging to exclude extra-CNS disease using PET—CT [V, A].
- If PET—CT is not feasible, contrast-enhanced total-body CT scan, bone marrow (BM) aspiration and biopsy and testicular ultrasound should be carried out [V, A].

FL

- Initial work-up for FL staging should include a BM biopsy and a CT scan of the neck, thorax, abdomen and pelvis [V, A]. BM biopsy is mandatory for staging localised disease [V, A].
- PET—CT can be recommended for routine staging [V, B] and is mandatory to confirm localised stage I/II disease before involved-site radiotherapy (ISRT) [V, A].
- The FL International Prognostic Index (FLIPI) 1 and 2 and the PRIMA Prognostic Index scoring systems can be used for prognostic purposes and stratification in clinical trials [III, B].

MCL

- Formal morphological subtyping of MCL (blastoid, pleomorphic, classical) should be reported whenever histopathological assessment is carried out [V, A].
- Ki-67 percentage values should be reported in all MCL biopsies wherever possible and reported as <30% versus ≥30% as a minimum [V, A].
- *TP53* mutational analysis should be carried out at diagnosis [V, A]. When a new treatment is required, *TP53* mutational analysis can be recommended whenever possible; otherwise p53 expression by IHC could be determined [V, B].
- Staging and reassessment should be carried out using [¹⁸F]2-fluoro-2-deoxy-D-glucose (FDG)—PET—CT or CT alongside BM biopsy with or without aspirate, as clinically appropriate [V, A].
- Risk stratification of patients using the MCL International Prognostic Index (MIPI) or combined MIPI can be recommended, particularly in the context of clinical trials [V, B].

MZL

- Imaging should include complete chest and abdominal CT scan and imaging of the orbits and salivary glands [V, A].
- PET—CT can be recommended in cases where only localised treatment is planned, when clinical and/or laboratory data suggest transformation to high-grade histology and to guide decisions on which lymph node (LN) to target for biopsy [V, B].
- BM aspirate (with morphology and flow cytometry) and biopsy are recommended in nodal MZL (NMZL), splenic MZL (SMZL) and extranodal MZL (EMZL), particularly in non-gastric lymphoma and when local treatment only is planned [V, A].
- Testing for potentially causative relevant micro-organisms can be considered in specific subtypes of mucosa-associated lymphoid tissue (MALT) lymphoma [V, B].

- Clinical and biological prognosticators, i.e. haemoglobin, platelets, lactose dehydrogenase, extra hilar lymphadenopathy, the MZL-IPI and MALT-IPI, may be applied in routine clinical practice to estimate the clinical behaviour of the disease [V, C].

HL

- PET–CT is the recommended imaging modality [IV, A]. Thus, BM examination is not recommended when a patient has undergone staging by PET–CT [IV, E].
- Prognostic factors should be determined to categorise the patient's disease as early-stage favourable, early-stage unfavourable or advanced stage [IV, A].
- For early-stage disease, the risk factors described below should be used [III, A]. If none of these are present, the disease should be categorised as favourable [III, A]:
 - Erythrocyte sedimentation rate (ESR) ≥ 50 mm/h without B symptoms.
 - ESR ≥ 30 mm/h with B symptoms.
 - ≥ 3 LN areas involved.
 - Extranodal disease.
 - Large mediastinal mass (more than one-third of the maximal thoracic width).
- For advanced-stage disease, the International Prognostic Score should be calculated [III, A].

PTCL

- A PET–CT at diagnosis, interim (optional) and end of treatment is the preferred imaging modality for all nodal and extranodal (non-leukaemic) PTCLs [I, B]. If PET–CT is not available, diagnostic CT can be used [V, B].
- In all cases, a BM biopsy is recommended for accurate staging [V, A].
- Additional tests should be carried out in some entities, such as assessment of peripheral blood cells for immunophenotype (e.g. flow cytometry for primary leukaemic entities) [V, A].
- Rebiopsy is recommended at relapse or progression [V, A].
- The IPI is the preferred prognostic tool [IV, B].

DISEASE MANAGEMENT

Key recommendations regarding the management of the lymphoma entities covered in this CPG are provided below and are illustrated in [Figures 1-16](#). Supporting evidence for these recommendations are described in [Supplementary Material Section 4](#), available at <https://doi.org/10.1016/j.annonc.2025.07.014>.

Recommendations

- All patients should be considered for clinical trials wherever possible [V, B].

DLBCL

- All patients should undergo PET staging [V, A] and testing for double-hit lymphoma [V, A].

Limited-stage I-II:

- For patients < 60 years, fit with an IPI 0 and non-bulky disease, four cycles of rituximab–cyclophosphamide–doxorubicin–vincristine–prednisone (R-CHOP) plus two cycles of rituximab (R) is recommended [I, A].
 - This approach can also be considered in patients 60–80 years without additional risk factors [V, B].
- For patients < 80 years, fit with an aalPI 0 and bulk ≥ 7.5 cm, the following first-line treatment options are recommended:
 - Four cycles of R-CHOP without further R if complete metabolic response [CMR; Deauville score (DS) 1–3] achieved after two cycles [I, B].
 - Six cycles of R-CHOP followed by ISRT if DS 4–5 after two cycles [III, B].
- For patients < 80 years with an aalPI ≥ 1 , the following first-line treatment regimens can be recommended:
 - Six cycles of R-CHOP [I, B].
 - Six cycles of R–polatuzumab vedotin–cyclophosphamide–doxorubicin–prednisone (R-Pola-CHP) (IPI ≥ 2) [I, B].
 - Three to four cycles of R-CHOP followed by ISRT [III, B].
- Patients ≥ 80 years should receive six cycles of R plus reduced-dose CHOP (R-miniCHOP) [III, B].
- For patients unsuitable for treatment with anthracyclines, an individualised regimen can be recommended:
 - R–cyclophosphamide–etoposide–vincristine–prednisone (R-CEOP) for six cycles or using an interim PET (iPET)-adapted strategy [III, B].
 - R–cyclophosphamide–non-pegylated liposomal doxorubicin–vincristine–prednisone (R-COMP) for six cycles or using an iPET-adapted strategy [III, B].
 - R–gemcitabine–cyclophosphamide–vincristine–prednisone (R-GCVP) for six cycles or using an iPET-adapted strategy [III, B].
- ISRT can be considered for patients ≥ 80 years according to bulk, distribution, treatment response and radiation risk [IV, B]. Six cycles of dose-attenuated immunochemotherapy (immunoChT) and ISRT can be considered on a case-by-case basis based on dose intensity, response and toxicity assessment [IV, B].

Advanced stage III-IV:

- Fit patients < 80 years with an IPI 0–1 should receive six cycles of R-CHOP [I, A].
- Six cycles of R-Pola-CHP is recommended as an option for fit patients < 80 years with an IPI ≥ 2 [I, A].
- For young patients with a good performance status (PS) and co-existing *MYC-BCL2* rearrangements, treatment intensification can be considered with regimens such as dose-adjusted etoposide–prednisone–vincristine–cyclophosphamide–doxorubicin–R (DA-EPOCH-R) or R–cyclophosphamide–vincristine–doxorubicin–cytarabine–methotrexate (R-CODOX-M)/R–ifosfamide–methotrexate–etoposide–cytarabine (R-IVAC) [IV, B].

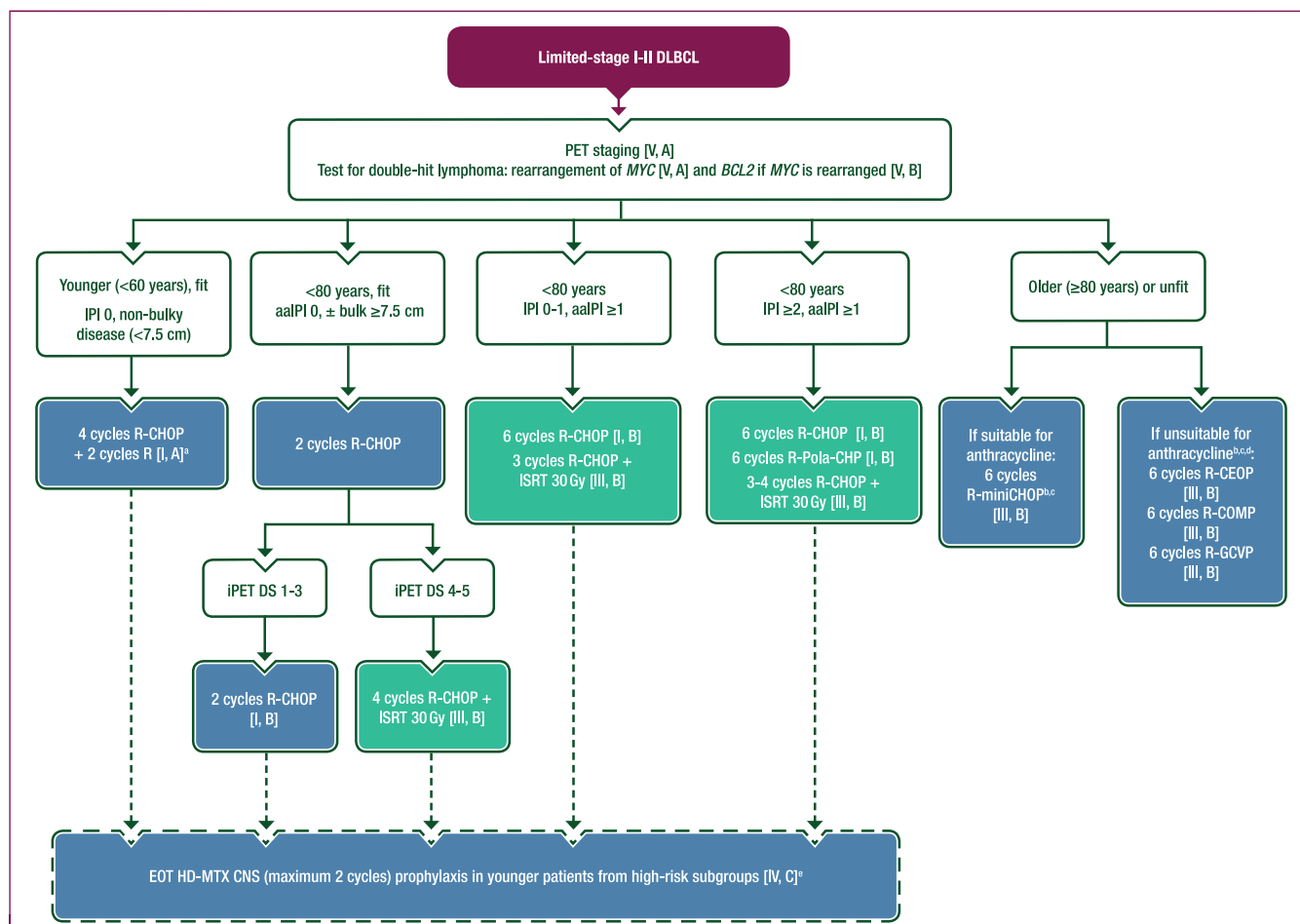


Figure 1. First-line management of stage I-II DLBCL.

Purple: algorithm title; blue: systemic anticancer therapy or their combination; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other aspects of management and non-treatment aspects; dashed arrow: optional branches, colour used as described in the categories above.

aalPI, age-adjusted International Prognostic Index; CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; DS, Deauville score; EOT, end of treatment; HD-MTX, high-dose methotrexate; immunoChT, immunochemotherapy; iPET, interim positron emission tomography; IPI, International Prognostic Index; ISRT, involved-site radiotherapy; PET, positron emission tomography; R, rituximab; R-CEOP, rituximab–cyclophosphamide–etoposide–vincristine–prednisone; R-CHOP, rituximab–cyclophosphamide–doxorubicin–vincristine–prednisone; R-COMP, rituximab–cyclophosphamide–liposomal doxorubicin–vincristine–prednisone; R-GCVP, rituximab–gemcitabine–cyclophosphamide–vincristine–prednisone; R-miniCHOP, rituximab plus reduced-dose cyclophosphamide–doxorubicin–vincristine–prednisone; R-Pola-CHP, polatuzumab vedotin–cyclophosphamide–doxorubicin–prednisone.

^aConsider FLYER approach in patients 60–80 years without additional risk factors [V, B].

^bConsider ISRT consolidation according to bulk, distribution, treatment response and radiation risk [IV, B].

^cSix cycles of dose-attenuated immunoChT and ISRT on a case-by-case basis based on dose intensity, response and toxicity assessment [IV, B].

^dNon-anthracycline-based regimen options (six cycles or using an iPET-adapted strategy) for patients with cardiac comorbidities unsuitable for anthracycline.

^eConsider in limited-stage testicular involvement.

- Clinicians can consider more dose-intense regimens [e.g. R-CODOX-M/R-IVAC or rituximab–cyclophosphamide–doxorubicin–vincristine–etoposide–prednisone (R-CHOEP)] for younger patients (e.g. ≤ 50 years) with a good PS and IPI ≥ 3 , particularly if at higher risk of CNS relapse [III, B].
- Patients ≥ 80 years can receive six cycles of R-miniCHOP [III, B].
 - Full-dose R-CHOP can be considered in extremely fit patients ≥ 80 years on a case-by-case basis [IV, C].
- Patients who are unsuitable for anthracycline can receive one of the following options:
 - Six cycles of R-COMP [III, B].
 - Six cycles of R-GCVP [III, B].
 - Six cycles of R-CEOP [IV, B].
- For patients ≥ 80 years and reversible, significant physiological impairment due to DLBCL disease burden,

corticosteroid pre-phase and/or dose attenuation of cytotoxics for cycle 1 can be considered [III, B].

- FDG-avid residual lesions can be biopsied wherever feasible [IV, B].
- ISRT can be considered on a case-by-case basis in collaboration with a radiation oncologist for patients with an initial isolated bulky lesion (≥ 7 cm) or for those with residual FDG-avid areas suspicious of residual disease [e.g. D4 partial metabolic response (PMR)] at the end of treatment where biopsy is not feasible [II, B].
- End-of-treatment high-dose methotrexate (HD-MTX; two cycles of $3\text{--}3.5\text{ g/m}^2$) may be considered as CNS prophylaxis in highly selected younger patients in ultra-high-risk subgroups (e.g. CNS-IPI 5–6; multiple extranodal sites; renal, adrenal, breast or testicular involvement) regardless of disease stage [IV, C].

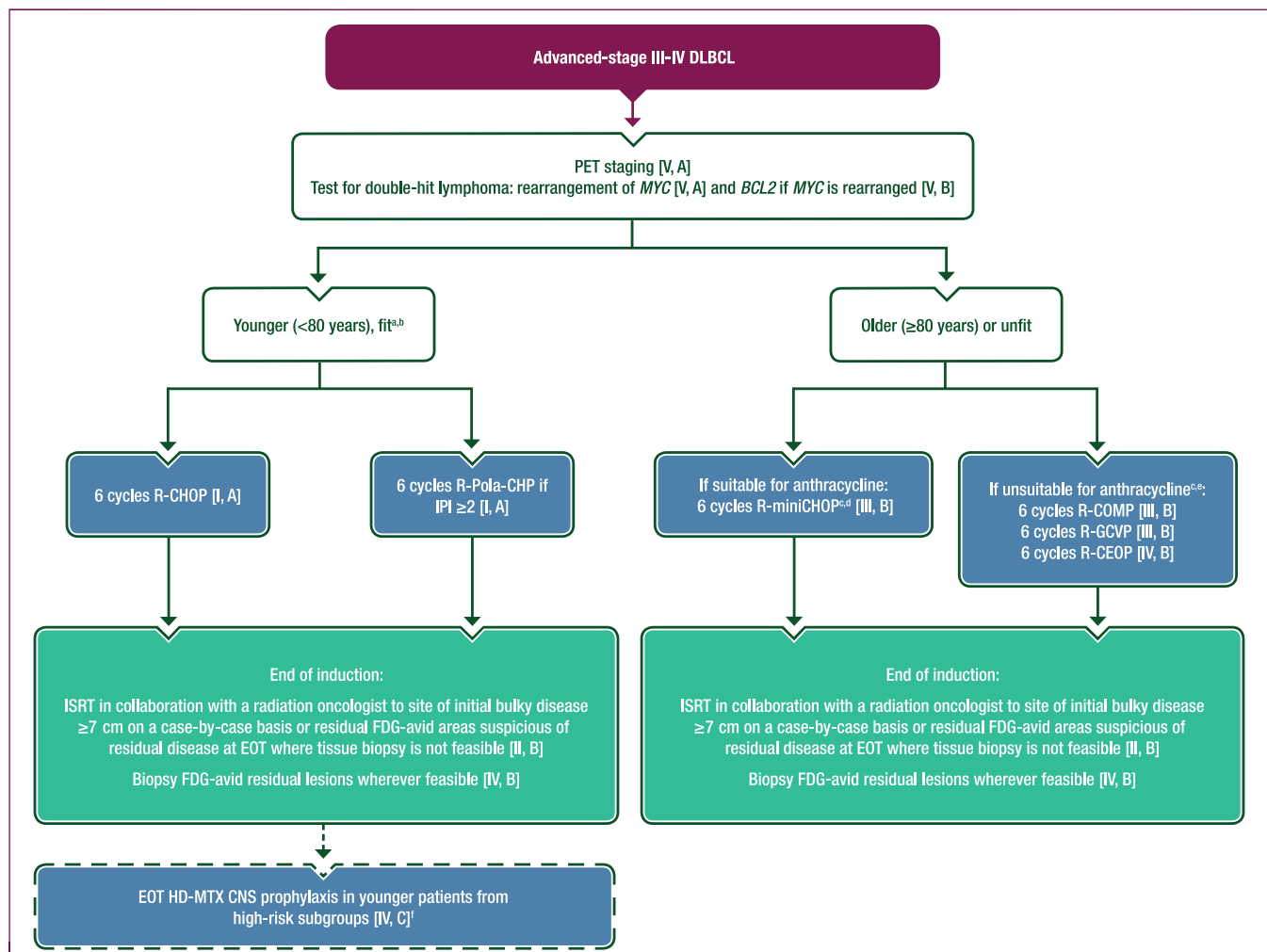


Figure 2. First-line management of stage III-IV DLBCL.

Purple: algorithm title; blue: systemic anticancer therapy or their combination; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other aspects of management and non-treatment aspects; dashed arrow: optional branches, colour used as described in the categories above.

CNS, central nervous system; DA-EPOCH-R, dose-adjusted etoposide—prednisone—vincristine—doxorubicin—rituximab; DLBCL, diffuse large B-cell lymphoma; EOT, end of treatment; FDG, [¹⁸F]2-fluoro-2-deoxy-D-glucose; HD-MTX, high-dose methotrexate; IPI, International Prognostic Index; ISRT, involved-site radiotherapy; PET, positron emission tomography; PS, performance status; R-CEOP, rituximab—cyclophosphamide—etoposide—vincristine—prednisone; R-CHOEP, rituximab—cyclophosphamide—doxorubicin—vincristine—etoposide—prednisone; R-CHOP, rituximab—cyclophosphamide—doxorubicin—vincristine—prednisone; R-CODOX-M, rituximab—cyclophosphamide—vincristine—doxorubicin—cytarabine—methotrexate; R-COMP, rituximab—cyclophosphamide—liposomal doxorubicin—vincristine—prednisone; R-GCVP, rituximab—gemcitabine—cyclophosphamide—vincristine—prednisone; R-IVAC, rituximab—ifosfamide—methotrexate—etoposide—cytarabine; R-miniCHOP, rituximab plus reduced-dose cyclophosphamide—doxorubicin—vincristine—prednisone; R-Pola-CHP, polatuzumab vedotin—cyclophosphamide—doxorubicin—prednisone.

^aConsider treatment intensification (e.g. DA-EPOCH-R or R-CODOX-M/R-IVAC) in patients where MYC is translocated and co-exists with a BCL2 rearrangement [IV, B].

^bConsider more dose-intensive regimens (e.g. R-CODOX-M/R-IVAC or R-CHOEP) for younger patients (e.g. ≤50 years) with a good PS and IPI ≥3, particularly if at higher risk of CNS relapse [III, B].

^cConsider corticosteroid pre-phase and/or dose attenuation of cytotoxics for cycle 1 in patients with reversible, significant physiological impairment due to DLBCL disease burden [III, B].

^dConsider full-dose R-CHOP in extremely fit patients ≥80 years on a case-by-case basis [IV, C].

^eNon-anthracycline-based option for anthracycline-unsuitable patients with cardiac comorbidities.

^fConsider in ultra-high-risk subgroups e.g. CNS-IPI 5-6, multiple extranodal sites, renal, adrenal, breast or testicular involvement [IV, C].

• Relapsed or refractory (r/r) disease:

- Patients should undergo a rebiopsy at each relapse, where feasible, to confirm DLBCL [V, B].
- Patients with early progression of disease (POD, i.e. relapse ≤12 months after completion of first-line treatment) should receive anti-cluster of differentiation (CD) 19 chimeric antigen receptor T-cell (CAR-T) therapy, if suitable [I, A]. Options include:
 - Axicabtagene ciloleucel [I, A].
 - Lisocabtagene maraleucel [I, A].
- Patients with early POD who are unsuitable for CAR-T therapy should receive one of the following:
 - Glofitamab—gemcitabine—oxaliplatin (glofitamab-Gem-Ox) (after one or more line of therapy) [I, A; European Medicines Agency (EMA) approved, not Food and Drug Administration (FDA) approved].
 - Pola—bendamustine—R (Pola-BR) if polatuzumab naive [II, B].
- Patients with late POD (i.e. relapse >12 months after completion of first-line treatment) can receive platinum-based reinduction therapy [I, B] and autologous stem-cell transplantation (ASCT), if suitable.
 - ASCT can only be carried out in patients achieving a DS 4 PMR or CMR after reinduction therapy [IV, B].

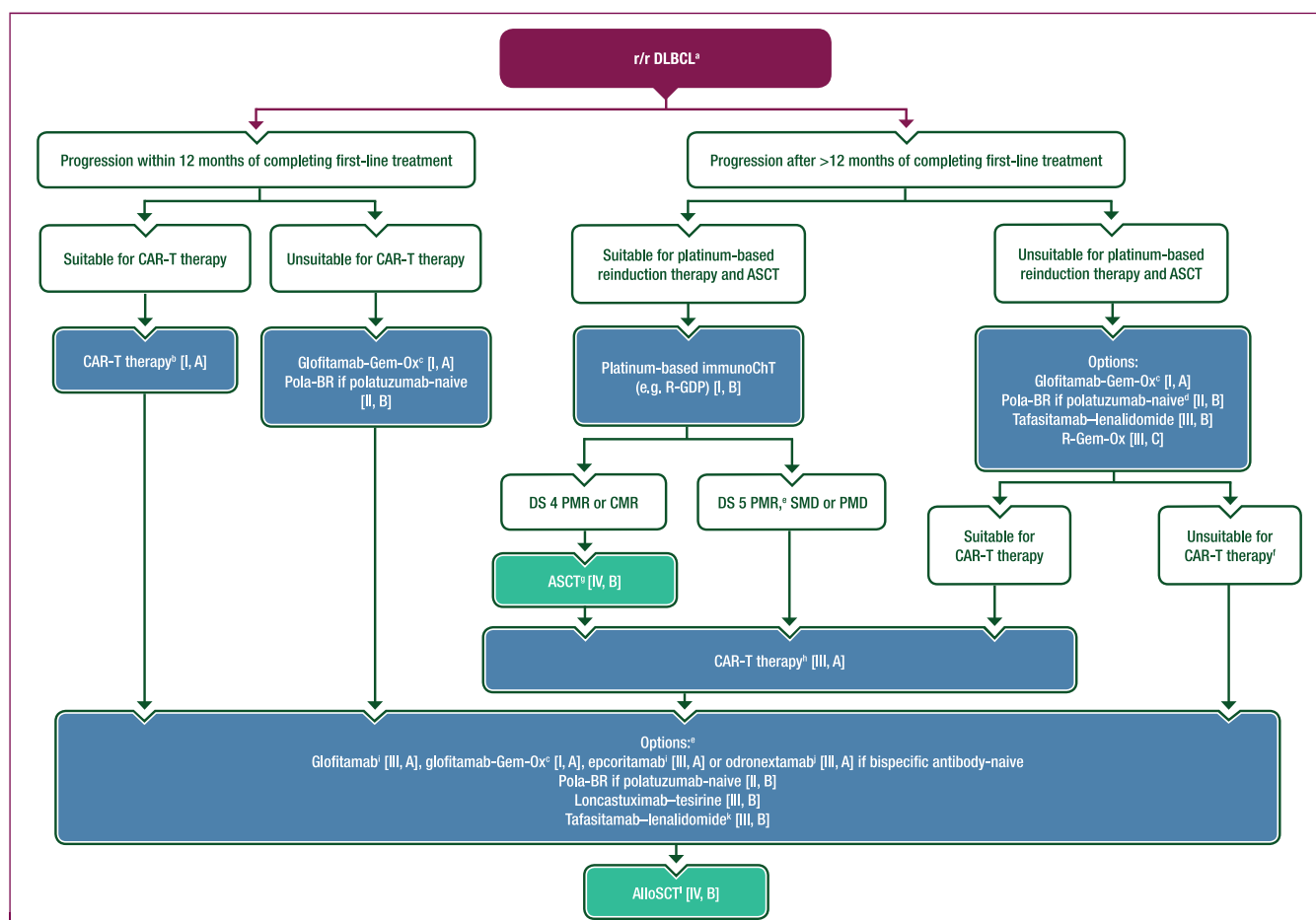


Figure 3. Management of r/r DLBCL.

Purple: algorithm title; blue: systemic anticancer therapy or their combination; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other aspects of management and non-treatment aspects.

AlloSCT, allogeneic stem-cell transplantation; ASCT, autologous stem-cell transplantation; CAR-T, chimeric antigen receptor T-cell; CMR, complete metabolic response; DLBCL, diffuse large B-cell lymphoma; DS, Deauville score; EMA, European Medicines Agency; FDA, Food and Drug Administration; glofitamab-Gem-Ox, glofitamab—gemcitabine—oxaliplatin; immunoChT, immunochemotherapy; ISRT, involved-site radiotherapy; PET, positron emission tomography; PMD, progressive metabolic disease; PMR, partial metabolic response; Pola-BR, polatuzumab vedotin—bendamustine—rituximab; R-GDP, rituximab—gemcitabine—dexamethasone—cisplatin; R-Gem-Ox, rituximab—gemcitabine—oxaliplatin; r/r, relapsed or refractory; SMD, stable metabolic disease.

^aRebiopsy at each relapse, where feasible, to confirm DLBCL [V, B].

^bAxicabtagene ciloleucel and lisocabtagene maraleucel are FDA and EMA approved for second-line use.

^cGlofitamab-Gem-Ox is recommended after one or more line of therapy, if available [I, A; EMA approved, not FDA approved].

^dCaution when selecting Pola-BR for patients who may be candidates for CAR-T therapy as a subsequent treatment line. Bendamustine may have an impact on the quality of T cells.

^eConsider DS 5 PMR as failure of second-line platinum-based immunoChT on a case-by-case basis.

^fConsider palliative care at each treatment juncture in appropriately selected patients [V, B].

^gConsider ISRT to initial isolated bulky relapse or residual isolated PET-avid disease before or after ASCT [IV, B].

^hAxicabtagene ciloleucel, lisocabtagene maraleucel and tisagenlecleucel are FDA- and EMA-approved options for patients who have received two or more prior lines of therapy according to availability and patient preference.

ⁱEpcoritamab and glofitamab are FDA and EMA approved for patients who have received two or more prior lines of therapy.

^jEMA approved, not FDA approved.

^kOption for patients relapsing after second- or third-line CAR-T therapy or relapsing after second-line treatment if CAR-T-unsuitable.

^lFor selected young, fit patients who relapse after CAR-T therapy and who obtain a subsequent remission.

- ISRT to the site of initial isolated bulky relapse or residual isolated site of FDG-avid disease before or after ASCT can be considered [IV, B].
- Treatment options for patients with late POD who are unsuitable for platinum-based reinduction and ASCT are the following:
 - Glofitamab-Gem-Ox (after one or more line of therapy) [I, A; EMA approved, not FDA approved].
 - Pola-BR if polatuzumab naïve [II, B].
 - Tafasitamab—lenalidomide [III, B].
 - R-Gem-Ox [III, C].
- Patients relapsing after two or more prior lines of treatment should receive CAR-T therapy, if suitable [III, A]. Options include (according to availability and patient preference) the following:
 - Axicabtagene ciloleucel [III, A].
 - Lisocabtagene maraleucel [III, A].
 - Tisagenlecleucel [III, A].
- Patients relapsing after two or more prior lines of treatment who are unsuitable for CAR-T therapy should receive one of the following, with bispecific antibodies preferred:

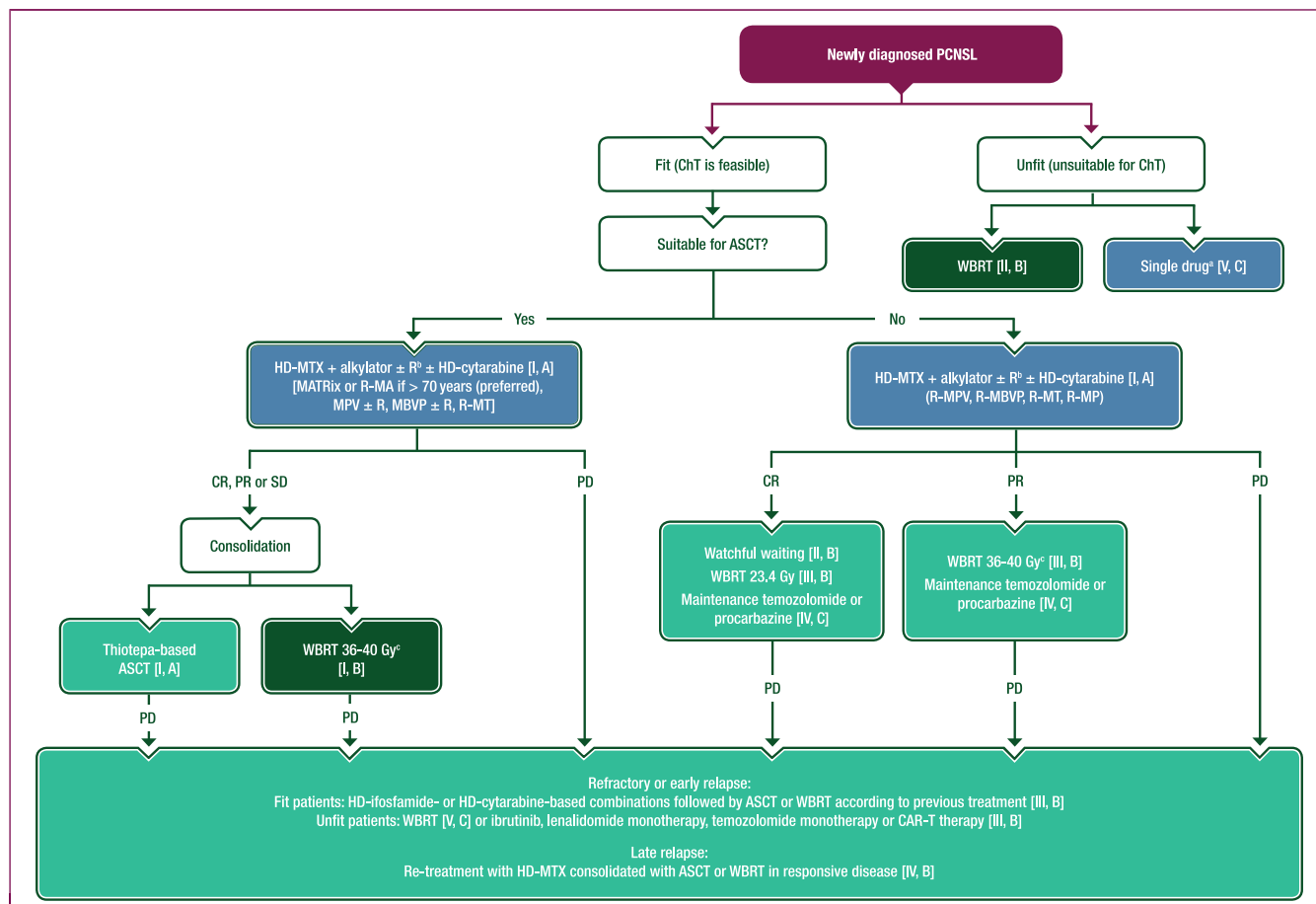


Figure 4. Management of PCNSL.

Purple: algorithm title; dark green: RT; blue: systemic anticancer therapy or their combination; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other aspects of management and non-treatment aspects.

ASCT, autologous stem-cell transplantation; BTKi, Bruton tyrosine kinase inhibitor; CAR-T, chimeric antigen receptor T-cell; ChT, chemotherapy; CR, complete remission; EMA, European Medicines Agency; FDA, Food and Drug Administration; HD, high dose; HD-MTX, high-dose methotrexate; MATRix, high-dose methotrexate–high-dose cytarabine–rituximab–thiotepa; MBVP, methotrexate–carmustine–teniposide–methylprednisolone; MPV, methotrexate–procarbazine–vincristine; PCNSL, primary central nervous system lymphoma; PD, progressive disease; PR, partial response; R, rituximab; R-MA, rituximab–methotrexate–cytarabine; R-MBVP, rituximab–methotrexate–carmustine–teniposide–methylprednisolone; R-MP, rituximab–methotrexate–procarbazine; R-MPV, rituximab–methotrexate–procarbazine–vincristine; R-MT, rituximab–methotrexate–temozolomide; RT, radiotherapy; SD, stable disease; WBRT, whole-brain radiotherapy.

^aDrug options include corticosteroids, alkylators with or without R, BTKis and immunomodulators.

^bR is not EMA or FDA approved in this setting; its use in induction combinations remains a matter of debate and the balance between tolerability and efficacy should be discussed with patients and their carers.

^cFor patients <60 years who are unsuitable for ASCT.

- Glofitamab-Gem-Ox [I, A; EMA approved, not FDA approved] or glofitamab alone [III, A] if bispecific antibody naive.
- Epcoritamab if bispecific antibody naive [III, A].
- Odronektamab if bispecific antibody naive [III, A; EMA approved, not FDA approved].
- Pola-BR if polatuzumab naive [II, B].
- Loncastuximab–tesirine [III, B].
- Tafasitamab–lenalidomide can also be recommended as an option for patients relapsing after second- or third-line CAR-T therapy or relapsing after second-line treatment if CAR-T unsuitable [III, B].
- Allogeneic stem-cell transplantation (alloSCT) can be considered for selected young, fit patients who relapse after CAR-T therapy and who obtain a subsequent remission [IV, B].
- Palliative care can be considered at each juncture in appropriately selected patients [V, B].

PCNSL

• Newly diagnosed:

- For fit patients, induction ChT including HD-MTX is recommended at a minimum of 3 g/m² in a 2- to 4-h infusion [I, A].
- HD-MTX alongside other blood–brain barrier-penetrating cytotoxics assessed in prospective trials are recommended [e.g. HD-MTX–cytarabine–thiotepa–R (MATRix), HD-MTX–procarbazine–vincristine (MPV) with or without R, HD-MTX–carmustine–etoposide–prednisone (MBVP) with or without R, R–MTX–temozolomide (R-MT)] [I, A; R is not EMA or FDA approved in this setting].
 - In patients suitable for ASCT, more intensive regimens are preferred [MATRix or R–MTX–cytarabine (R-MA) if >70 years] [I, A].
 - In non-transplant-eligible patients, options include R-MPV, R-MBVP, R-MT, R–MTX–procarbazine (R-MP) [I, A].

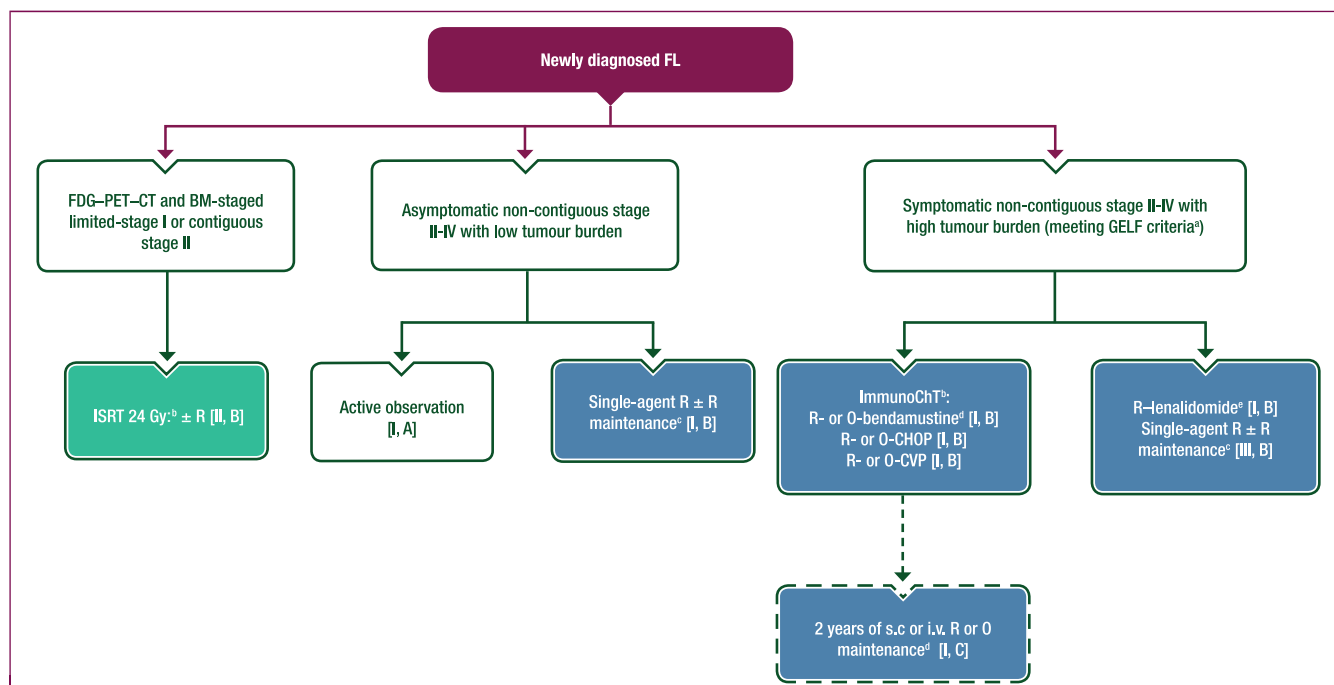


Figure 5. First-line management of FL.

Purple: algorithm title; blue: systemic anticancer therapy or their combination; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other aspects of management and non-treatment aspects; dashed arrow: optional branches, colour used as described in the categories above.

BM, bone marrow; CHOP, cyclophosphamide–doxorubicin–vincristine–prednisone; CT, computed tomography; CVP, cyclophosphamide–vincristine–prednisone; EMA, European Medicines Agency; FDA, Food and Drug Administration; FDG, [¹⁸F]2-fluoro-2-deoxy-D-glucose; FL, follicular lymphoma; GELF, Groupe d'Etude des Lymphomes Folliculaires; immunoChT, immunochemotherapy; ISRT, involved-site radiotherapy; i.v., intravenous; O, obinutuzumab; PCP, pneumocystis pneumonia; PET, positron emission tomography; R, rituximab; s.c., subcutaneous.

^aGELF criteria: tumour >7 cm, three sites >3 cm, systemic or B symptoms, splenomegaly, organ compression, cytopenias, pleural and/or peritoneal effusion.

^bConsider palliative ISRT 4–8 Gy where long-term disease control is less critical than minimising toxicity e.g. elderly or frail patients [IV, B].

^cInduction R 375 mg/m² weekly for 4 weeks; R maintenance every 2 months for 12 doses.

^dCaution with bendamustine in patients ≥70 years and those with respiratory comorbidities and/or alternative immunosuppression. PCP and antiviral prophylaxis can be considered during maintenance after bendamustine [IV, B].

^eNot EMA or FDA approved.

- Judicious dose reduction of MTX and other agents according to renal function and comorbidities is recommended [III, A].
- Intrathecal ChT is not routinely recommended [III, D] except for patients with CSF dissemination who are unable to receive ChT including MTX ≥3 g/m² or for patients with persistence of CSF or meningeal disease at the end of first-line treatment [III, B].
- Thiotepa-based ASCT is recommended as consolidation therapy in fit patients with responsive or stable disease after suitable induction ChT [I, A].
- Consolidation whole-brain radiotherapy (WBRT) at 36–40 Gy can be considered in patients <60 years who achieve a partial response (PR) to induction therapy but who are unsuitable for ASCT [III, B]. This should be avoided in older patients because of the high risk of disabling neurocognitive impairment [I, D].
- A WBRT dose of 23.4 Gy can be recommended as an option for patients >60 years with a complete remission (CR) after induction therapy [III, B]. Longer-term cognitive effects remain incompletely defined.
- Observation can be considered in transplant-ineligible patients with a CR after an established induction therapy [II, B].
- Maintenance temozolomide or procarbazine may also be an option for patients with a CR or PR after induction therapy [IV, C].
- There is no established standard of care (SoC) for patients unfit for ChT. Palliative options include upfront WBRT [II, B], corticosteroids, alkylators with or without R, Bruton tyrosine kinase inhibitors (BTKis) and immunomodulators [V, C].
- r/r disease:
 - Fit patients with refractory or early relapsed PCNSL can be treated with HD-ifosfamide- or HD-cytarabine-based combinations followed by ASCT or WBRT according to previous treatment [III, B].
 - Patients with refractory or early relapsed PCNSL unfit for polyChT may be treated with WBRT [V, C] or ibrutinib, lenalidomide monotherapy, temozolomide monotherapy or CAR-T therapy [III, B].
 - Patients with late relapse of PCNSL can be re-treated with HD-MTX, employing the same or a similar ChT regimen as used in first-line treatment and consolidated with ASCT or WBRT in responsive disease [IV, B].
 - The increased risk of neurotoxicity associated with WBRT may be considered in patients >60 years with r/r PCNSL, especially if HD-MTX has been given [IV, C].

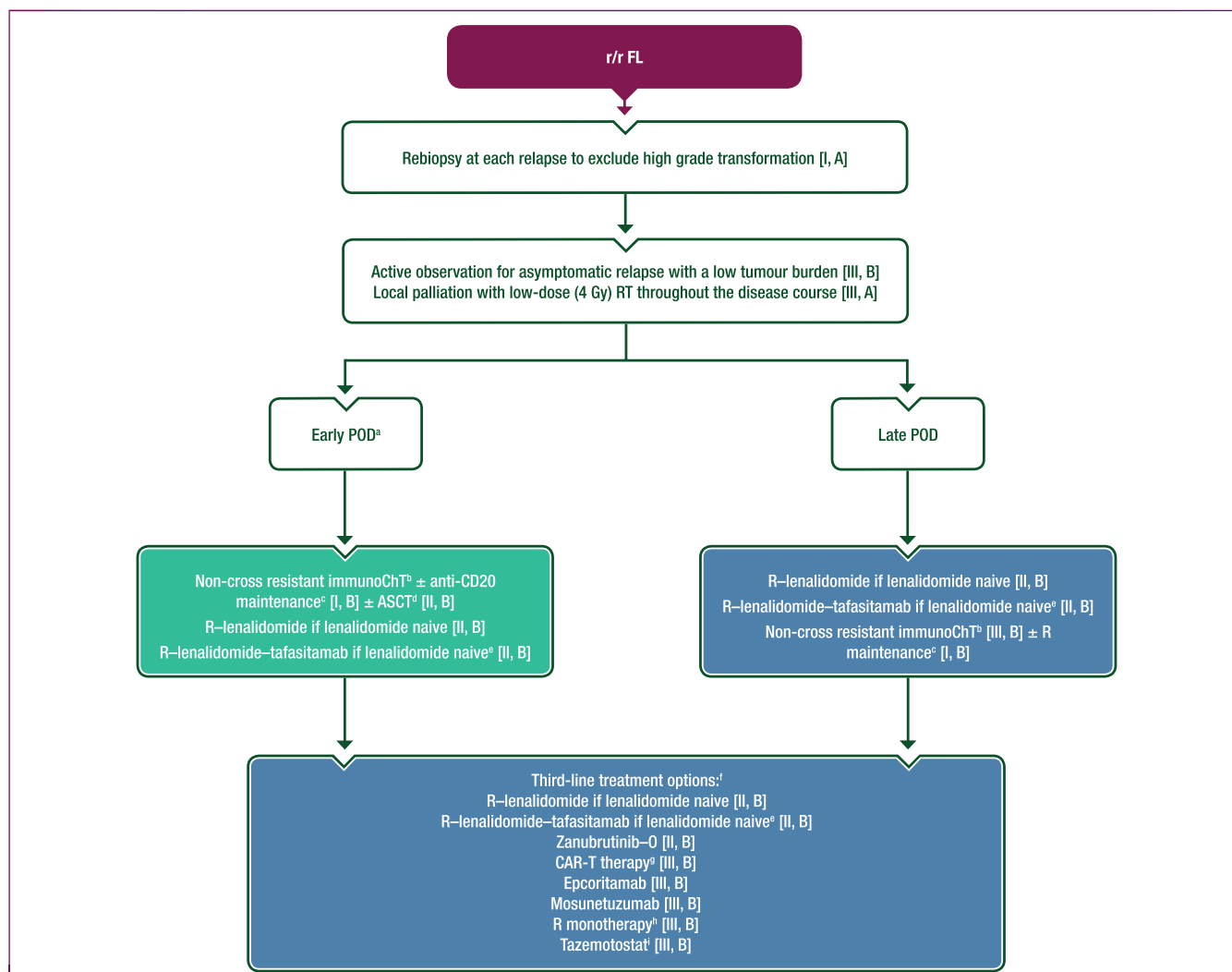


Figure 6. Management of r/r FL.

Purple: algorithm title; blue: systemic anticancer therapy or their combination; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other aspects of management and non-treatment aspects.

AlloSCT, allogeneic stem-cell transplantation; ASCT, autologous stem-cell transplantation; CAR-T, chimeric antigen receptor T-cell; CD, cluster of differentiation; EMA, European Medicines Agency; EZH, enhancer of zeste homologue; FDA, Food and Drug Administration; immunoChT, immunochemotherapy; FL, follicular lymphoma; O, obinutuzumab; POD, progression of disease; R, rituximab; r/r, relapsed or refractory; RT, radiotherapy.

^aRelapse ≤ 24 months after first-line treatment.

^bImmunoChT dependent on prior therapy. O—bendamustine if R refractory [I, B], but if T-cell-engaging therapy is envisioned, bendamustine should be avoided due to its long-term immunosuppression [III, D].

^cConsider R maintenance therapy every 3 months for up to 2 years if not delivered in the first line [I, B]. For early POD, consider O maintenance therapy every 2 months for up to 2 years following O—bendamustine [I, B].

^dConsider ASCT on a case-by-case basis in younger, fit patients with early POD and chemosensitive relapse [II, B].

^eFDA approved, not EMA approved.

^fAlloSCT can be considered in selected younger patients following CAR-T therapy or bispecific antibody therapy or where both are unavailable [IV, B].

^gAxicabtagene ciloleucel: FDA approved after two or more prior lines of therapy, EMA approved after three or more prior lines of therapy; tisagenlecleucel: FDA and EMA approved after two or more prior lines of therapy; lisocabtagene maraleucel: EMA and FDA approved after two or more prior lines of therapy.

^hFor elderly or frail patients after prior long-term remissions.

ⁱFDA approved for EZH-mutated FL, not EMA approved.

FL

• First line:

- Patients with FDG—PET—CT and BM-staged limited-stage I or contiguous stage II FL can be treated with 24 Gy ISRT with or without R as first-line therapy [II, B].
- Palliative ISRT 4–8 Gy can be considered where long-term disease control is less critical than minimising toxicity e.g. elderly or frail patients [IV, B].

- Asymptomatic non-contiguous stage II–IV FL with a low tumour burden should be managed with one of the following first-line options:
 - Active observation [I, A].
 - R induction therapy given weekly for 4 weeks with or without R maintenance therapy given every 2 months for 12 doses [I, B].
- Symptomatic non-contiguous stage II–IV FL with a high tumour burden meeting Groupe d'Etude des

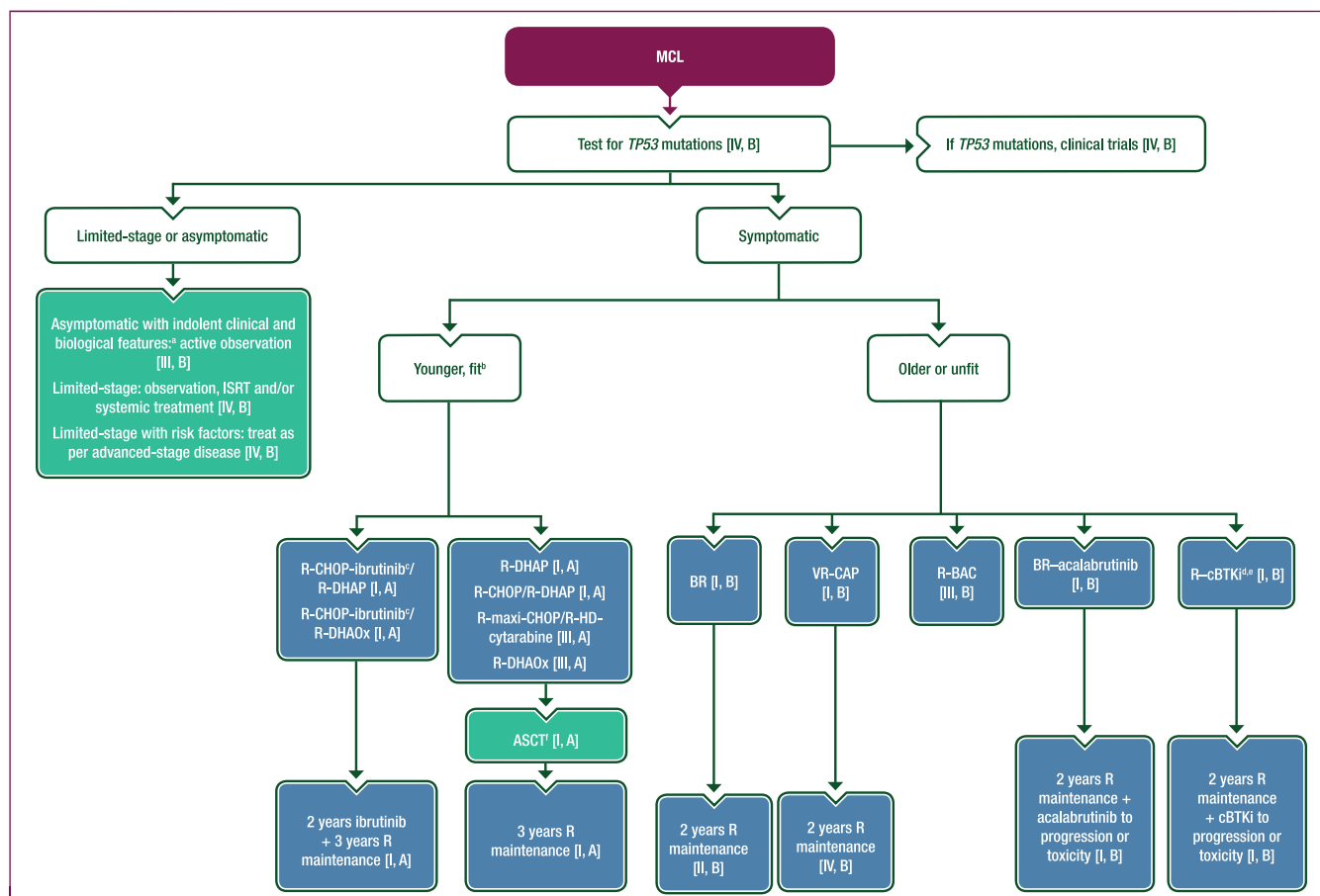


Figure 7. First-line management of MCL.

Purple: algorithm title; blue: systemic anticancer therapy or their combination; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other aspects of management and non-treatment aspects.

ASCT, autologous stem-cell transplantation; BR, bendamustine–rituximab; cBTKi, covalent Bruton tyrosine kinase inhibitor; CD, cluster of differentiation; EMA, European Medicines Agency; FDA, Food and Drug Administration; HD, high dose; ISRT, involved-site radiotherapy; LN, lymph node; MCL, mantle cell lymphoma; MRD, minimal residual disease; R, rituximab; R-BAC, rituximab–bendamustine–cytarabine; R-CHOP, rituximab–cyclophosphamide–doxorubicin–vincristine–prednisone; R-DHA0x, rituximab–dexa-methasone–high-dose cytarabine–oxaliplatin; R-DHAP, rituximab–dexa-methasone–high-dose cytarabine–cisplatin; R-maxi-CHOP, rituximab plus maximum strength cyclophosphamide–doxorubicin–vincristine–prednisone; VR-CAP, bortezomib–rituximab–cyclophosphamide–doxorubicin–prednisone.

^aTypically leukaemic or nodal MCL with LNs ≤ 3 cm, Ki67 $\leq 30\%$, classical or small-cell morphology, no cytopenia or organ compromise.

^bPatients ≤ 65 years (≤ 70 years at physician's discretion). First-line treatment with a cBTKi-containing regimen is preferred.

^cFirst-line ibrutinib is EMA approved, not FDA approved. Other cBTKi considered dependent on availability and preference.

^dNot EMA or FDA approved.

^eEvidence from randomised trials for R–ibrutinib only, although zanubrutinib and acalabrutinib are under investigation alongside anti-CD20 therapy and may represent reasonable alternatives.

^fASCT should be omitted if MRD assessment demonstrates undetectable MRD (10^{-6}) [I, A].

Lymphomes Folliculaires (GELF) criteria can receive one of the following first-line options:

- R– or obinutuzumab (O)–bendamustine [I, B].
- R- or O-CHOP [I, B].
- R- or O-CVP [I, B].
- R–lenalidomide [I, B; not EMA or FDA approved]
- R 375 mg/m² induction therapy given weekly for 4 weeks followed by R maintenance therapy given every 2 months for 12 doses [III, B].
- Following immunoChT induction therapy, maintenance therapy with R or O given every 2 months (subcutaneous or intravenous) for 2 years may be considered [I, C].
- Caution is advised regarding the use of bendamustine in patients ≥ 70 years and those with respiratory comorbidities and/or alternative immunosuppression.

Pneumocystis pneumonia and antiviral prophylaxis can be considered during maintenance after bendamustine [IV, B].

- Extended anti-infection prophylaxis can be considered after bendamustine induction therapy and during maintenance therapy after bendamustine [IV, B].
- r/r disease:
 - At each suspected relapse, rebiopsy is strongly recommended to exclude high-grade transformation [I, A].
 - Asymptomatic, low tumour burden relapse can be managed with observation [III, B].
 - Patients with early symptomatic POD (i.e. relapse ≤ 24 months after completion of first-line treatment) can receive one of the following options:
 - Non-cross-resistant immunoChT [I, B].

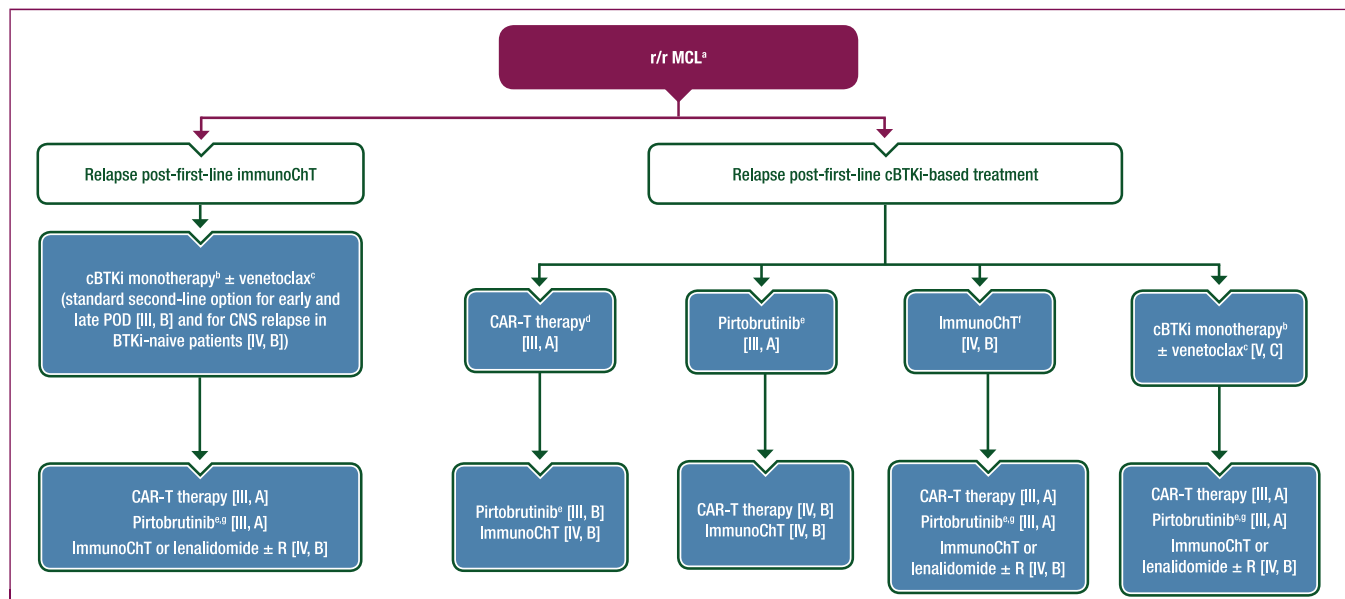


Figure 8. Management of r/r MCL.

Purple: algorithm title; blue: systemic anticancer therapy or their combination; white: other aspects of management and non-treatment aspects.

AlloSCT, allogeneic stem-cell transplantation; BTKi, Bruton tyrosine kinase inhibitor; CAR-T, chimeric antigen receptor T-cell; cBTKi, covalent Bruton tyrosine kinase inhibitor; CNS, central nervous system; EMA, European Medicines Agency; FDA, Food and Drug Administration; immunoChT, immunochemotherapy; MCL, mantle cell lymphoma; POD, progression of disease; R, rituximab; r/r, relapsed or refractory.

^aAlloSCT can be considered in younger, fit patients with r/r MCL in cases where CAR-T therapy is unavailable or has failed [IV, B].

^bIbrutinib: EMA approved, not FDA approved; acalabrutinib and zanubrutinib: FDA approved, not EMA approved.

^cIbrutinib—venetoclax is not EMA or FDA approved but its use could be dictated by patient fitness and MCL biology. Consider cBTKi rechallenge if prior intolerance only or prior fixed-duration cBTKi.

^dCAR-T therapy can be considered if available second line (brexucabtagene autoleucel: FDA approved after one or more prior lines of therapy, not EMA approved at first relapse) for patients at high risk of cBTKi failure. Lisocabtagene maraleucel: FDA approved after two or more prior lines including a cBTKi, not EMA approved.

^ePirtobrutinib: EMA approved after one or more prior line, FDA approved after two or more prior lines of therapy.

^fThe choice of immunoChT is dependent on treatment goals, availability of alternative therapies, prior immunoChT exposure, patient fitness and choice. Bendamustine should be avoided before CAR-T apheresis.

^gThe choice between third-line pirtobrutinib or CAR-T therapy should be according to patient fitness, disease kinetics, patient choice, CAR-T therapy suitability and availability.

- The type of immunoChT is dependent on prior therapy.
- O—bendamustine in R-refractory FL [I, B], but if subsequent T-cell-engaging therapy is envisioned, bendamustine should be avoided due to its long-term immunosuppression [III, D].
 - R—lenalidomide if lenalidomide naïve [II, B].
 - R—lenalidomide—tafasitamab if lenalidomide naïve (FDA approved, not EMA approved) [II, B].
- In younger, fit patients with early POD and chemo-sensitive relapse, ASCT consolidation therapy can be considered [II, B].
- Patients with late symptomatic POD (i.e. relapse >24 months after completion of first-line treatment) can receive one of the following options:
 - R—lenalidomide if lenalidomide naïve [II, B].
 - R—lenalidomide—tafasitamab if lenalidomide naïve (FDA approved, not EMA approved) [II, B].
 - Non-cross-resistant immunoChT [III, B].
- For early or late POD, R maintenance therapy given every 3 months for ≤2 years in patients who did not receive first-line maintenance therapy can be recommended [I, B]. In early POD, O maintenance therapy every 2 months for ≤2 years following O—bendamustine [I, B] can be recommended.
- Later relapses in the third-line setting and beyond can receive one of the following options:
 - R—lenalidomide if lenalidomide naïve [II, B].
 - R—lenalidomide—tafasitamab if lenalidomide naïve (FDA approved, not EMA approved) [II, B].
 - Zanubrutinib—O [II, B].
 - CAR-T therapy [III, B].
 - Axicabtagene ciloleucel: FDA approved after two or more prior lines of therapy, EMA approved after three or more prior lines of therapy.
 - Tisagenlecleucel: FDA and EMA approved after two or more prior lines of therapy.
 - Lisocabtagene maraleucel: EMA and FDA approved after two or more prior lines of therapy.
 - Epcoritamab [III, B].
 - Mosunetuzumab [III, B].
 - R monotherapy (for elderly or frail patients after prior long-term remissions) [III, B].
 - Tazemetostat [III, B; FDA approved for enhancer of zeste homologue (EZH)-mutated FL, not EMA approved].
- In selected younger patients who relapse following CAR-T or bispecific antibody therapy or where both are unavailable, alloSCT can be considered [IV, B].
- Local palliation with low-dose (4 Gy) RT should be considered throughout the FL disease course [III, A].

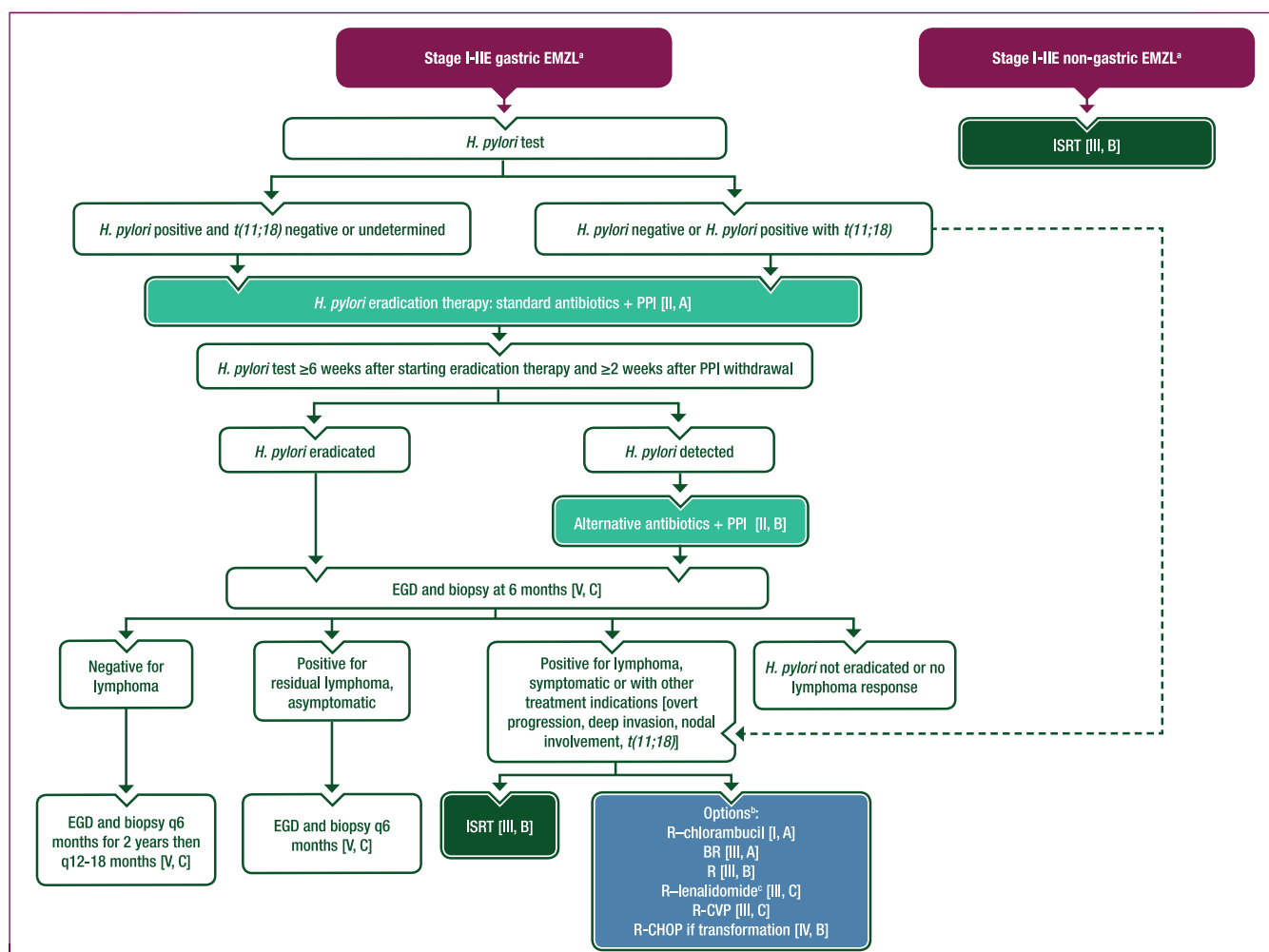


Figure 9. Management of stage I-IIe EMZL.

Purple: algorithm title; dark green: RT; blue: systemic anticancer therapy or their combination; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other aspects of management and non-treatment aspects; dashed arrow: optional branches, colour used as described in the categories above.

BR, bendamustine—rituximab; EGD, oesophagogastrroduodenoscopy; EMA, European Medicines Agency; EMZL, extranodal marginal zone lymphoma; FDA, Food and Drug Administration; *H. pylori*, *Helicobacter pylori*; ISRT, involved-site radiotherapy; PPI, proton pump inhibitor; q, every; R, rituximab; R-CHOP, rituximab—cyclophosphamide—doxorubicin—vincristine—prednisone; R-CVP, rituximab—cyclophosphamide—vincristine—prednisone; RT, radiotherapy.

^aStaging according to Lugano staging system.

^bIf RT not feasible or not indicated.

^cNot EMA or FDA approved.

MCL

• First line:

- In selected patients with newly diagnosed, asymptomatic MCL, a low tumour burden and no high-risk biological features, active observation can be considered [III, B].
- Before first-line treatment, testing for *TP53* mutations can be carried out [IV, B]; patients with *TP53* mutations can be considered for clinical trials [IV, B].
- First-line treatment of limited-stage MCL is not well defined, and observation, ISRT and/or systemic treatment could be considered [IV, B]. If risk factors are present, systemic treatment as per advanced-stage disease can be considered [IV, B].
- Fit patients ≤65 years (up to 70 years at physician's discretion) should receive one of the following first-line options, with a covalent BTKi (cBTKi) within the regimen preferred:
 - R-CHOP—ibrutinib, alternating with either R—dexamethasone—HD-cytarabine—cisplatin (R-DHAP) or R—dexamethasone—HD-cytarabine—oxaliplatin (R-DHAOx) induction therapy [I, A], followed by 2 years of ibrutinib and 3 years of R maintenance therapy [I, A] (first-line ibrutinib is EMA approved, not FDA approved).
 - R plus HD-cytarabine-based induction therapy [R-DHAP [I, A], R-CHOP/R-DHAP [I, A], R plus maximum strength CHOP (R-maxi-CHOP)/R-HD-cytarabine [III, A] or R-DHAOx [III, A]] and ASCT consolidation therapy [I, A] followed by 3 years of R maintenance therapy [I, A].
 - For patients without access to cBTKi integration into the first-line induction therapy regimen who achieve an undetectable minimal residual disease (by clonoSEQ®; Adaptive Biotechnologies, Seattle, WA) following induction therapy, ASCT should be omitted [I, A].

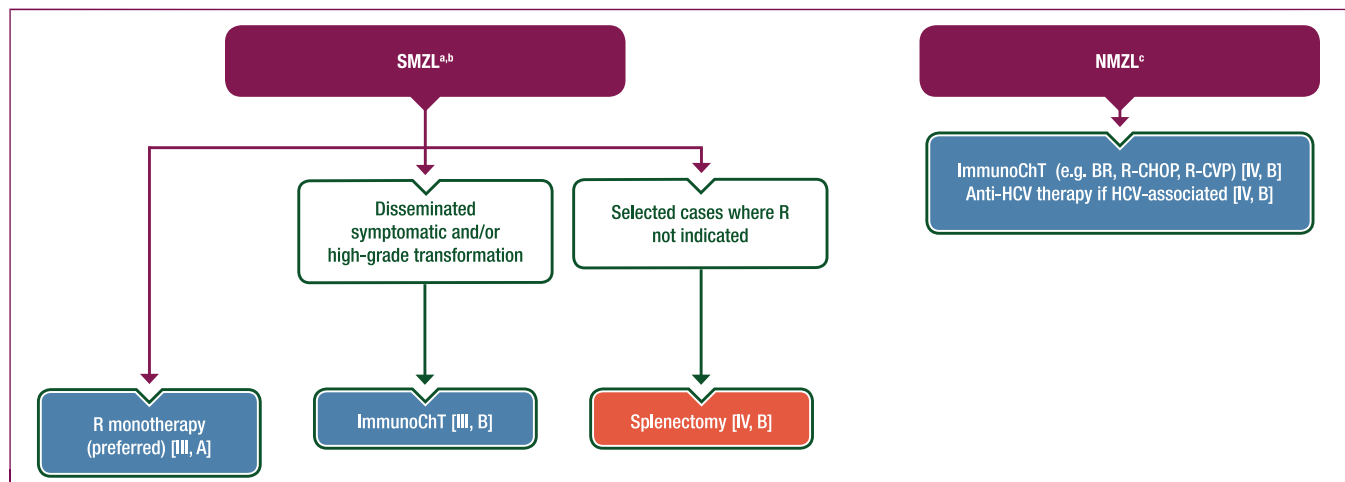


Figure 10. Management of SMZL and NMZL.

Purple: algorithm title; orange: surgery; blue: systemic anticancer therapy or their combination; white: other aspects of management and non-treatment aspects. BM, bone marrow; BR, bendamustine–rituximab; CR, complete remission; FL, follicular lymphoma; HCV, hepatitis C virus; IHC, immunohistochemistry; immunoChT, immunochemotherapy; NMZL, nodal marginal zone lymphoma; R, rituximab; R-CHOP, rituximab–cyclophosphamide–doxorubicin–vincristine–prednisone; R-CVP, rituximab–cyclophosphamide–vincristine–prednisone; SMZL, splenic marginal zone lymphoma.

^aAnti-HCV therapy can be delivered in patients with HCV-associated SMZL [IV, B].

^bSpecific criteria for response assessment are recommended for SMZL: achievement of CR is defined by normal spleen size, normal blood counts, negative flow cytometry on blood and negative IHC on BM biopsy [V, C].

^cTreatment of NMZL should broadly follow the principles applied for FL [IV, B].

- For patients unsuitable for HD-cytarabine-based induction therapy and ASCT, one of the following options can be recommended:
 - R–ChT:
 - BR [I, B; preferred] and consider R maintenance therapy for 2 years [II, B].
 - Bortezomib–R–cyclophosphamide–doxorubicin–prednisone (VR-CAP) [I, B] with R maintenance therapy for 2 years [IV, B].
 - R–bendamustine–cytarabine (R-BAC) [III, B] without R maintenance therapy [IV, D].
 - BR–acalabrutinib induction followed by acalabrutinib until progression or toxicity plus 2 years of R maintenance therapy [I, B].
 - R–cBTKi induction therapy (not EMA or FDA approved) followed by 2 years of R maintenance therapy plus cBTKi until progression or toxicity [I, B].
- r/r disease:
 - A cBTKi with or without venetoclax (cBTKi–venetoclax is not EMA or FDA approved) can be offered as standard after first-line immunoChT for the following:
 - Second line rather than later lines in early and late POD [III, B].
 - CNS relapse in BTKi-naïve patients [IV, B].
 - Treatment options after first-line cBTKi-based therapy include:
 - CAR-T therapy (for patients at high risk of cBTKi failure) [III, A].
 - Brexucabtagene autoleucel: FDA approved after one or more prior lines of therapy, not EMA approved at first relapse.
 - Lisocabtagene maraleucel: FDA approved after two or more prior lines of therapy, including a cBTKi; not EMA approved.
 - Pirtobrutinib [III, A; EMA approved after one or more prior line, FDA approved after two or more prior lines of therapy].
 - ImmunoChT [IV, B].
 - cBTKi rechallenge with or without venetoclax (cBTKi–venetoclax is not EMA or FDA approved) if prior intolerance only or prior fixed duration of cBTKi therapy [V, C].
 - Treatment options after second-line immunoChT or cBTKi-based therapy include:
 - CAR-T therapy [III, A].
 - Pirtobrutinib [III, A].
 - ImmunoChT or lenalidomide with or without R [IV, B].
 - Treatment options after second-line CAR-T therapy include:
 - Pirtobrutinib [III, B].
 - ImmunoChT [IV, B].
 - Treatment options after second-line pirtobrutinib include:
 - CAR-T therapy [IV, B].
 - ImmunoChT [IV, B].
 - AlloSCT can be considered in younger, fit patients in cases where CAR-T therapy is unavailable or has failed [IV, B].

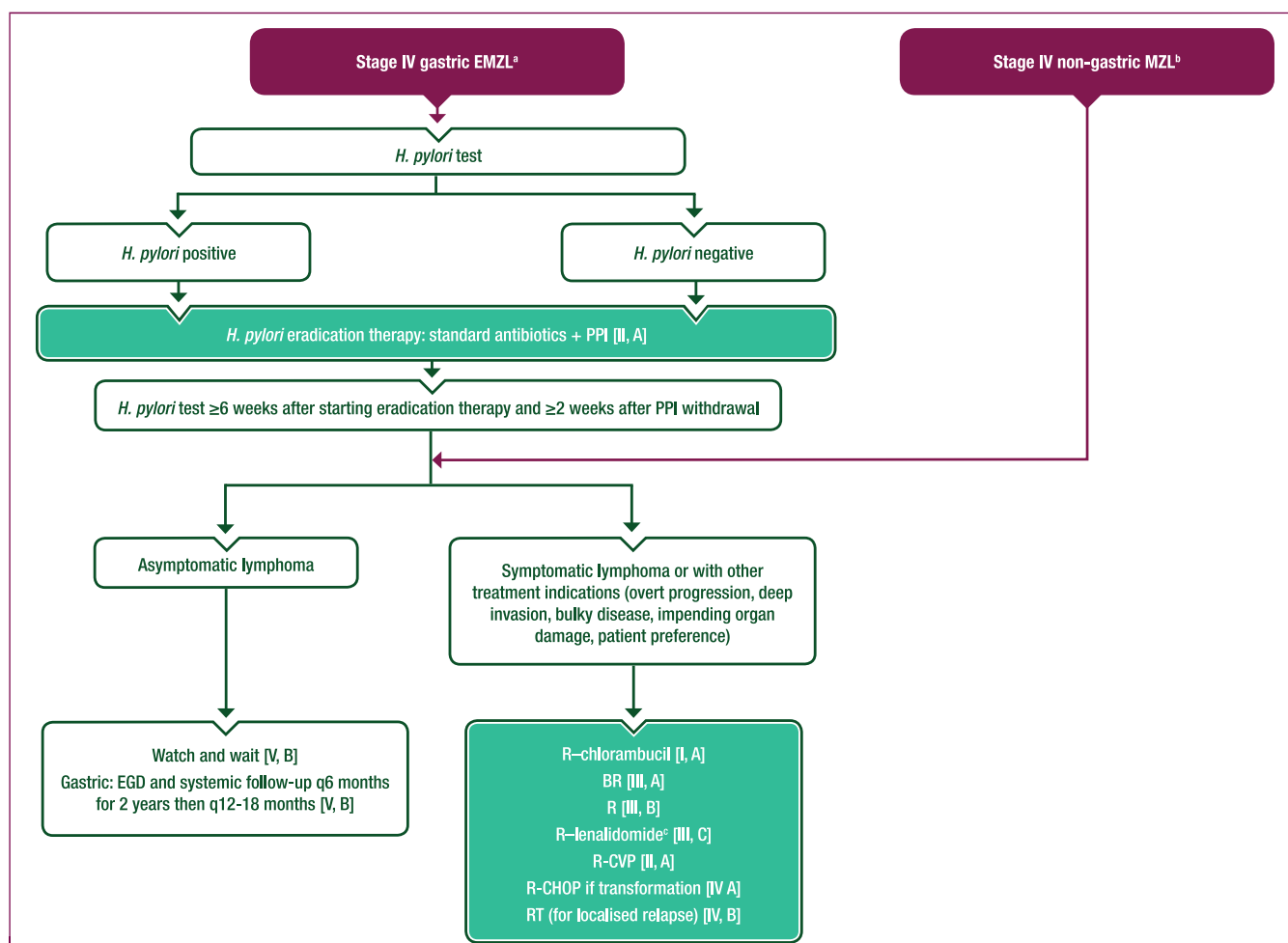


Figure 11. Management of stage IV gastric EMZL and non-gastric MZL.

Purple: algorithm title; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other aspects of management and non-treatment aspects.

BR, bendamustine—rituximab; EGD, oesophagogastroduodenoscopy; EMA, European Medicines Agency; EMZL, extranodal marginal zone lymphoma; FDA, Food and Drug Administration; HCV, hepatitis C virus; *H. pylori*, *Helicobacter pylori*; MZL, marginal zone lymphoma; PPI, proton pump inhibitor; q, every; R, rituximab; R-CHOP, rituximab—cyclophosphamide—doxorubicin—vincristine—prednisone; R-CVP, rituximab—cyclophosphamide—vincristine—prednisone; RT, radiotherapy.

^aStaging according to Lugano staging system.

^bSpecific antimicrobial therapy is indicated in non-gastric MZL where an aetiopathogenetic microorganism (*Campylobacter jejuni*, *Chlamydia psittaci*, HCV) is detected [IV, B].

^cNot EMA or FDA approved.

MZL

- *Helicobacter pylori* (*H. pylori*) eradication treatment should be given to all patients with gastric EMZL [II, A]. In case of *H. pylori* persistence, alternative antibiotics and a proton pump inhibitor can be recommended [II, B]. Oesophagogastroduodenoscopy (EGD) may be recommended after 6 months [V, C].
 - If biopsies are negative for lymphoma, EGD and biopsy may be repeated every 6 months for 2 years then every 12-18 months [V, C].
 - If biopsies are positive at 6 months and the patient is asymptomatic, EGD and biopsy may be repeated every 6 months [V, C].
 - If biopsies are positive or if patients are symptomatic or have other treatment indications [e.g. overt

progression, deep invasion, nodal involvement, *t*-(11;18)], ISRT can be recommended [III, B].

- ISRT can be recommended as the preferred treatment of localised extra-gastric EMZL (24 Gy; lower doses can be considered according to the site and clinical setting) [III, B].
- Specific antimicrobial therapy can be recommended in non-gastric MZL where an aetiopathogenetic microorganism [*Campylobacter jejuni*, *Chlamydia psittaci*, hepatitis C virus (HCV)] is detected [IV, B].
- For patients with asymptomatic stage IV MZL, a watch-and-wait strategy is recommended [V, B]. Patients with stage IV gastric EMZL can undergo EGD and systemic follow-up every 6 months for 2 years then every 12-18 months [V, B].

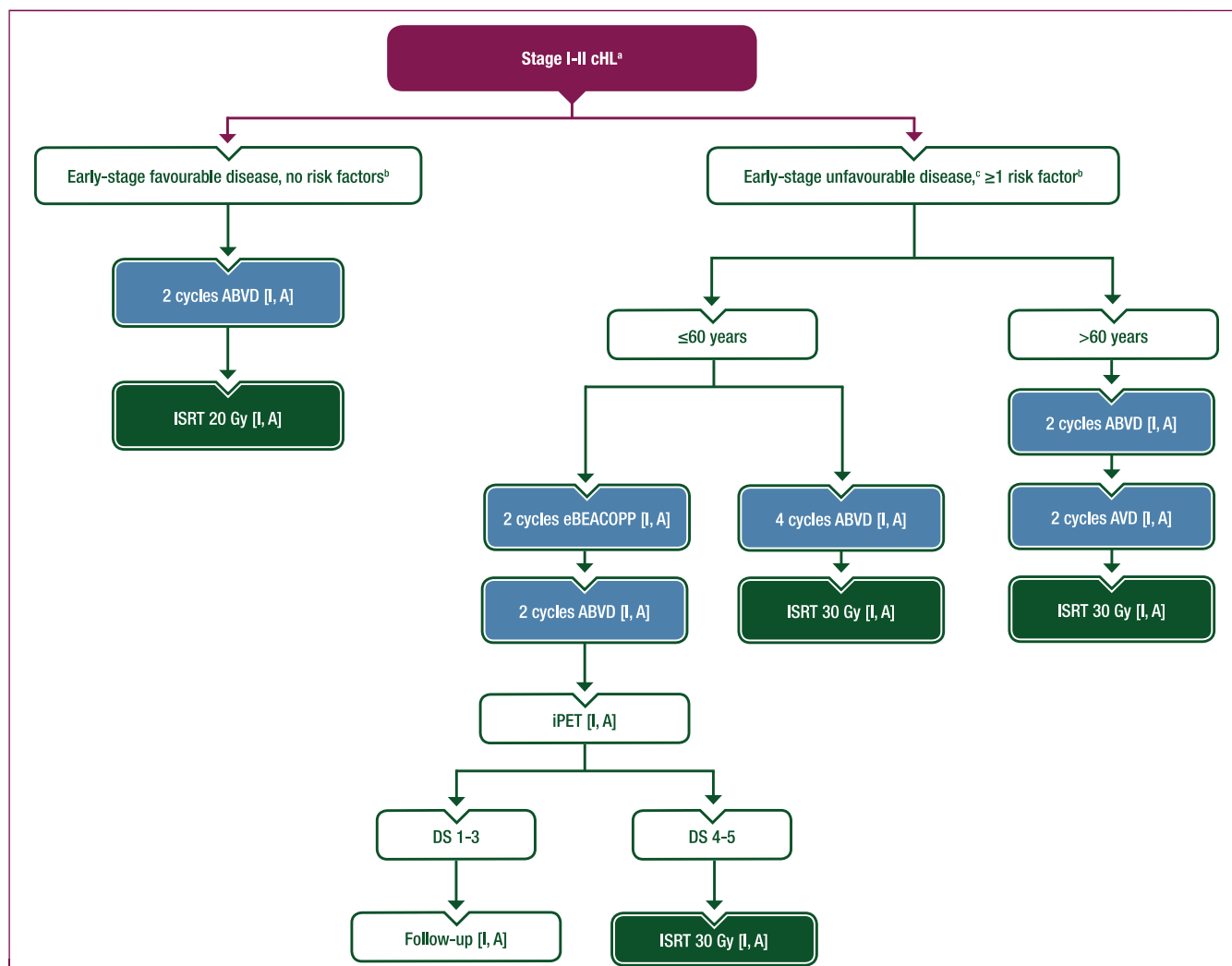


Figure 12. First-line management of stage I-II cHL.

Purple: algorithm title; dark green: RT; blue: systemic anticancer therapy or their combination; white: other aspects of management and non-treatment aspects. ABVD, doxorubicin–bleomycin–vinblastine–dacarbazine; AVD, doxorubicin–vinblastine–dacarbazine; cHL, classic Hodgkin lymphoma; DS, Deauville score; eBEACOPP, escalated doses of bleomycin–etoposide–doxorubicin–cyclophosphamide–vincristine–procarbazine–prednisone; ESR, erythrocyte sedimentation rate; ISRT, involved-site radiotherapy; iPET, interim positron emission tomography; LN, lymph node; RT, radiotherapy.

^aPatients should be offered reproductive counselling, if appropriate [V, A].

^bRisk factors: (i) elevated ESR (>50 mm/h without B symptoms or >30 mm/h with B symptoms); (ii) ≥3 LN areas involved; (iii) extranodal disease; (iv) large mediastinal mass (≥1/3 of the maximal thoracic width).

^cEarly-stage unfavourable disease defined as either: stage I or IIA with one or more risk factor i–iv or stage IIB with risk factor i and/or ii (see footnote b for risk factors).

- Immunotherapy or immunoChT are indicated in patients with symptomatic disseminated EMZL and NMZL, contraindications to RT, relapse after antibiotics or after local therapy or histological transformation of disease. Other indications are overt progression, deep invasion, bulky disease, impending organ damage and patient preference. Options for patients without histological transformation include:
 - R–chlorambucil [I, A].
 - BR [III, A].
 - R monotherapy [III, B].
 - R–lenalidomide [III, C; not EMA or FDA approved].
 - R–CVP [III, C].
- R-CHOP can be recommended as an option for patients with suspected or biopsy-proven histological transformation [IV, B].
- For patients with SMZL, R monotherapy is the preferred initial therapy for most patients [III, A].
- Specific criteria for response assessment may be recommended for SMZL: achievement of CR is defined by normal spleen size, normal blood counts, negative flow cytometry on blood and negative IHC on BM biopsy [V, C].
- ImmunoChT can be indicated when R is ineffective or in the presence of disseminated symptomatic SMZL and/or high-grade transformation [III, B].

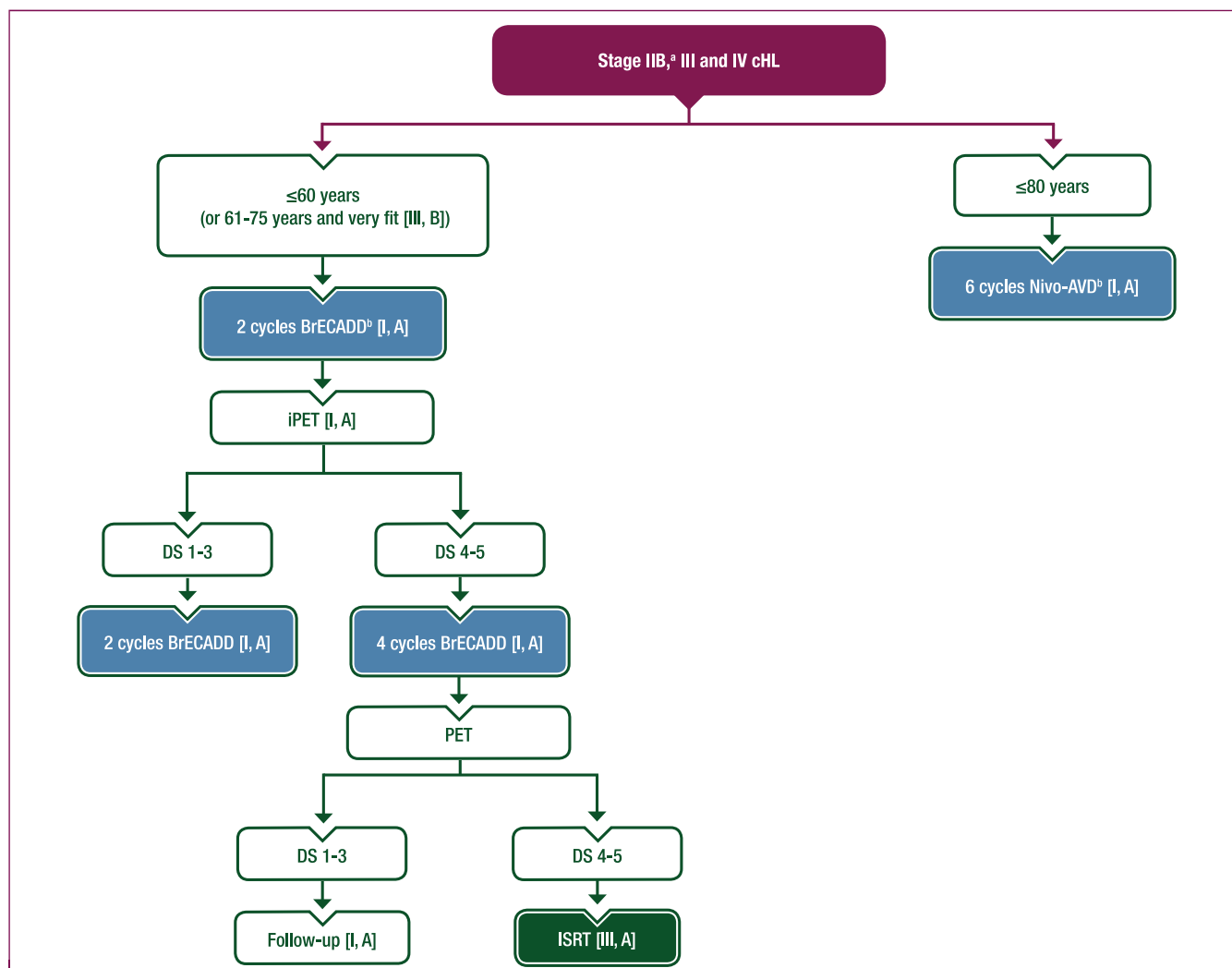


Figure 13. First-line management of stage IIB with risk factors, III and IV cHL.

Purple: algorithm title; dark green: RT; blue: systemic anticancer therapy or their combination; white: other aspects of management and non-treatment aspects. ABVD, doxorubicin—bleomycin—vinblastine—dacarbazine; BrECADD, brentuximab vedotin—etoposide—cyclophosphamide—doxorubicin—dacarbazine—dexamethasone; BV-AVD, brentuximab vedotin—doxorubicin—vinblastine—dacarbazine; cHL, classic Hodgkin lymphoma; DS, Deauville score; eBEACOPDac, escalated bleomycin—etoposide—doxorubicin—cyclophosphamide—vincristine—prednisone—dacarbazine; EMA, European Medicines Agency; FDA, Food and Drug Administration; iPET, interim positron emission tomography; ISRT, involved-site radiotherapy; Nivo-AVD, nivolumab—doxorubicin—vinblastine—dacarbazine; PD-1, programmed cell death protein 1; PET, positron emission tomography; RT, radiotherapy.

^aStage IIB cHL with risk factors: large mediastinal mass or extranodal disease.

^bBrECADD and Nivo-AVD are preferred treatments for patients ≤60 years [I, A; BrECADD: EMA approved, not FDA approved; Nivo-AVD: not EMA or FDA approved]. BrECADD with or without ISRT as part of the depicted iPET-adapted strategy can also be considered for very fit patients 61–75 years on a case-by-case basis [III, B]. Nivo-AVD is considered the favoured option for patients 60–80 years [I, A]. If Nivo-AVD is unavailable and BrECADD is unsuitable, BV-AVD represents a third treatment option [I, A]. If BV and PD-1 inhibitors are not available, standard treatment options are ABVD [I, A] or eBEACOPDac [IV, B].

- Anti-HCV therapy can be delivered in patients with HCV-associated SMZL [IV, B].
- Splenectomy can be considered in selected cases of SMZL when R is not indicated or is ineffective [IV, B].
- Treatment of NMZL should broadly follow the principles applied for FL [IV, B].
- ImmunoChT can be recommended for NMZL (e.g. BR, R-CHOP, R-CVP) [IV, B].
- Anti-HCV therapy can be delivered in patients with HCV-associated NMZL [IV, B].
- Treatment options for r/r MZL in need of treatment include R—lenalidomide [I, B; FDA approved, not EMA

approved], immunoChT [III, B], ibrutinib (not EMA or FDA approved) [III, B] and zanubrutinib [III, B]. RT can be considered for localised relapse [IV, B].

HL

- First line, stage I-II:
 - Patients should be offered reproductive counselling, if appropriate [V, A].
 - For patients with favourable classic HL (cHL), the SoC is two cycles of doxorubicin—bleomycin—vinblastine—dacarbazine (ABVD) [I, A] followed by 20 Gy ISRT [I, A].

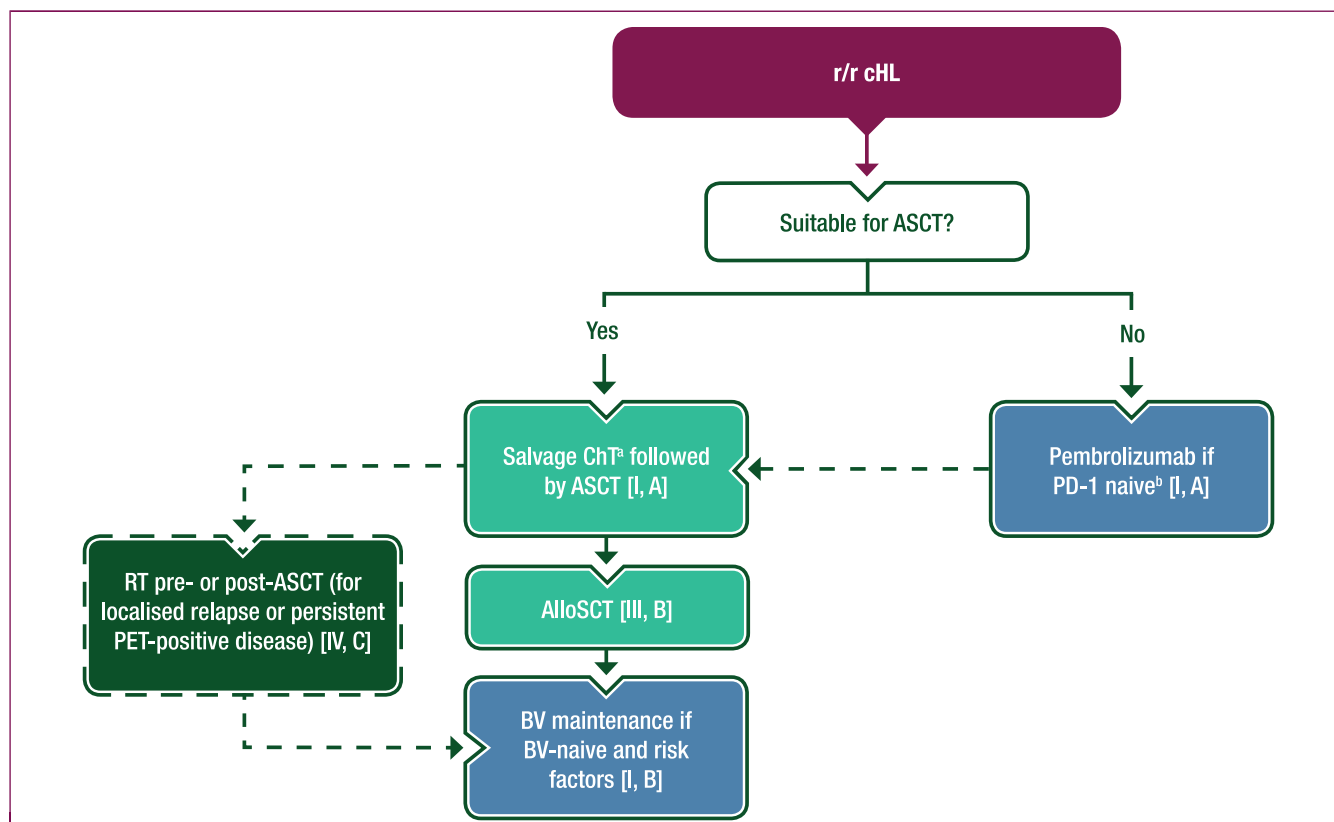


Figure 14. Management of r/r cHL.

Purple: algorithm title; dark green: RT; blue: systemic anticancer therapy or their combination; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other aspects of management and non-treatment aspects; dashed arrow: optional branches, colour used as described in the categories above.

AlloSCT, allogeneic stem-cell transplantation; ASCT, autologous stem-cell transplantation; BEGEV, bendamustine–gemcitabine–vinorelbine; BV, brentuximab vedotin; cHL, classic Hodgkin lymphoma; ChT, chemotherapy; DHAP, dexamethasone–cytarabine–cisplatin; ESHAP, etoposide–cytarabine–cisplatin–methylprednisolone; GDP, gemcitabine–dexamethasone–cisplatin; GVD, gemcitabine–vinorelbine–liposomal doxorubicin; ICE, ifosfamide–carboplatin–etoposide; PD-1, programmed cell death protein 1; PET, positron emission tomography; r/r, relapsed or refractory; RT, radiotherapy.

^aThe following salvage ChT options can be recommended [III, B]: DHAP, ESHAP, GDP, ICE, BEGEV or GVD. Integrating novel agents (e.g. PD-1 inhibitors, BV) may be reasonable depending on availability [III, B].

^bPatients who are chemo-refractory who subsequently respond to pembrolizumab may be considered for ASCT [IV, C].

- Treatment options for patients ≤ 60 years with unfavourable cHL include:
 - Two cycles of escalated bleomycin–etoposide–doxorubicin–cyclophosphamide–vincristine–procarbazine–prednisone (eBEACOPP) [I, A] followed by two cycles of ABVD [I, A] and then iPET [I, A]. If the DS is 4–5 at iPET, patients should receive 30 Gy ISRT [I, A]. If the DS is 1–3 at iPET, no further treatment is required [I, A].
 - Four cycles of ABVD [I, A] followed by 30 Gy ISRT [I, A].
- Patients > 60 years of age with unfavourable cHL should be treated with two cycles of ABVD [I, A] followed by two cycles of doxorubicin–vinblastine–dacarbazine (AVD) [I, A] and then 30 Gy ISRT [I, A].
- First line, stage IIB with risk factors (extranodal disease and/or large mediastinal mass), stage III and IV:
 - Fit patients ≤ 60 years should be treated with two cycles of brentuximab vedotin–etoposide–cyclophosphamide–doxorubicin–dacarbazine–dexamethasone (BrECADD) [I, A; EMA approved, not FDA approved] followed by iPET [I, A].
 - If the iPET is negative (DS 1–3), two additional cycles of BrECADD should be given [I, A].
 - If the iPET is positive (DS 4–5), patients should receive four additional cycles of BrECADD [I, A].
 - Patients with PET-positive disease at the end of ChT should receive ISRT [III, A].
 - For patients with PET-negative disease at the end of ChT, no further treatment is required [I, A].
 - This approach can also be considered for very fit patients 61–75 years on a case-by-case basis [III, B].
 - Six cycles of nivolumab (Nivo)-AVD represents an alternative treatment option for patients ≤ 60 years and is considered the favoured option for patients 60–80 years [I, A; not EMA or FDA approved].
 - Patients ≤ 60 years can be treated with brentuximab vedotin (BV)-AVD in cases where Nivo-AVD is unavailable and BrECADD is clinically unsuitable [I, A].
 - If BV and programmed cell death protein 1 (PD-1) inhibitors are not available, standard treatment options are ABVD [I, A] or escalated bleomycin–etoposide–doxorubicin–cyclophosphamide–vincristine–prednisone–dacarbazine (eBEACOPDac) [IV, B], depending on tolerability.

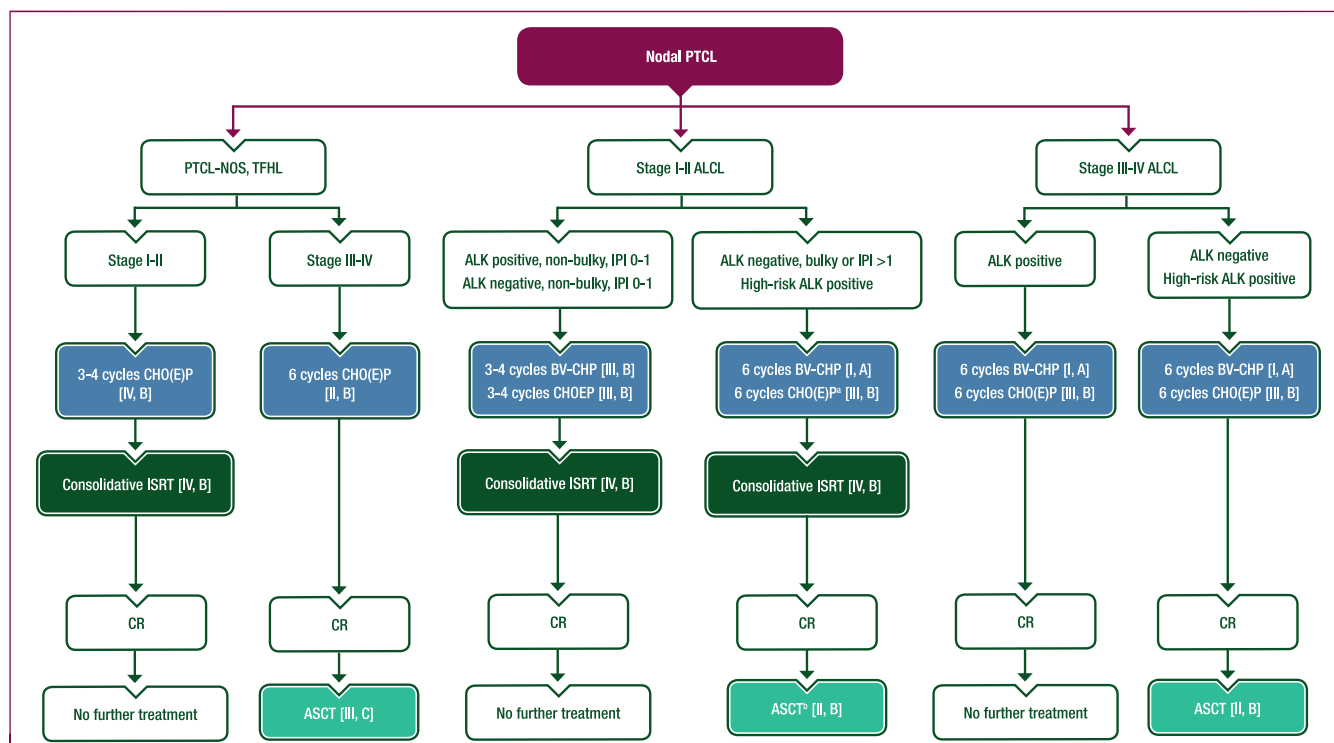


Figure 15. Management of nodal PTCL.

Purple: algorithm title; dark green: RT; blue: systemic anticancer therapy or their combination; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other aspects of management and non-treatment aspects.

ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase; ASCT, autologous stem-cell transplantation; BV-CHP, brentuximab vedotin–cyclophosphamide–doxorubicin–prednisolone; CHOEP, cyclophosphamide–doxorubicin–vincristine–etoposide–prednisolone; CR, complete remission; IPI, International Prognostic Index; ISRT, involved-site radiotherapy; NOS, not otherwise specified; PTCL, peripheral T-cell lymphoma; RT, radiotherapy; TFHL, follicular helper T-cell lymphoma.

*Alternative for patients with stage I-II high-risk ALK-positive ALCL.

^bFor patients with stage I-II ALK-positive ALCL with high-risk features (e.g. IPI 3-4 and/or bulky extranodal disease and/or unconfirmed suspected residual disease activity) [II, B].

• r/r disease:

- Patients should receive salvage ChT followed by ASCT [I, A]. The following salvage ChT options can be recommended [III, B]: DHAP, etoposide–cytarabine–cisplatin–methylprednisolone (ESHAP), gemcitabine–dexamethasone–cisplatin (GDP), ifosfamide–carboplatin–etoposide (ICE), bendamustine–gemcitabine–vinorelbine (BEGEV) or gemcitabine–vinorelbine–liposomal doxorubicin (GVD). Integrating novel agents (e.g. PD-1 inhibitors, BV) may be reasonable depending on availability [III, B]. RT either before or after ASCT may be considered for localised relapse and/or for persistent PET-positive disease [IV, C].
- BV maintenance therapy in BV-naïve patients with high-risk features after ASCT can be considered [I, B].
- In patients unsuitable for or relapsing after ASCT who are PD-1 inhibitor- and BV-naïve, pembrolizumab is favoured over BV [I, A].
- Patients who are chemo-refractory who subsequently respond to pembrolizumab may be considered for ASCT [IV, C].
- AlloSCT can be considered in suitable patients after ASCT [III, B].

PTCL

- First-line treatment of PTCL not otherwise specified (NOS) or follicular helper T-cell lymphoma (TFHL):
 - CHOP or CHOP-like ChT with or without etoposide can be offered as first-line induction therapy [II, B].
 - For patients with stage I-II, non-bulky PTCL NOS or TFHL and a favourable pre-therapeutic risk profile, an abbreviated course of ChT [e.g. three to four cycles of CHO(E)P] can be considered, followed by consolidative ISRT (e.g. 30-40 Gy) [IV, B].
 - For patients with stage III-IV disease, six cycles of CHO(E)P can be recommended [II, B], followed by consideration of consolidative ASCT in responding patients [III, C].
- First-line treatment of anaplastic lymphoma kinase (ALK)-negative anaplastic large-cell lymphoma (ALCL):
 - In patients with limited-stage, non-bulky disease and a favourable pre-therapeutic risk profile, abbreviated ChT [e.g. three to four cycles of BV–cyclophosphamide–doxorubicin–prednisolone (BV-CHP) or CHOEP] [III, B] followed by consolidative ISRT (e.g. 30-40 Gy) [IV, B] can be recommended.

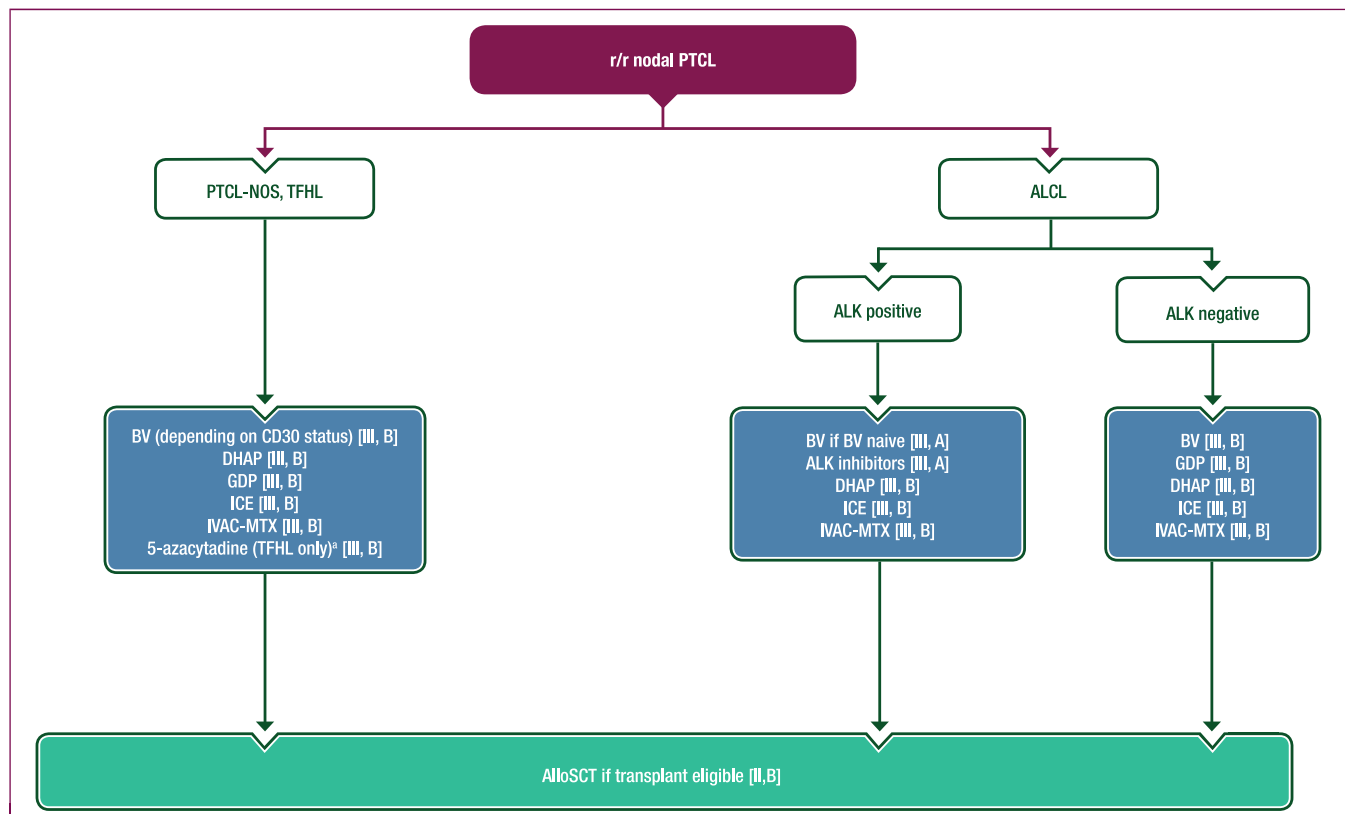


Figure 16. Management of r/r nodal PTCL.

Purple: algorithm title; blue: systemic anticancer therapy or their combination; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other aspects of management and non-treatment aspects.

ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase; alloSCT, allogeneic stem-cell transplantation; BV, brentuximab vedotin; CD, cluster of differentiation; DHAP, dexamethasone–cytarabine–cisplatin; EMA, European Medicines Agency; FDA, Food and Drug Administration; GDP, gemcitabine–dexamethasone–cisplatin; ICE, ifosfamide–carboplatin–etoposide; IVAC-MTX, ifosfamide–methotrexate–etoposide–cytarabine–methotrexate; NOS, not otherwise specified; PTCL, peripheral T-cell lymphoma; r/r, relapsed or refractory; TFHL, follicular helper T-cell lymphoma.

^aNot EMA or FDA approved.

- All other ChT-eligible patients should be offered six cycles of BV-CHP [I, A].
 - Six cycles of CHO(E)P is an alternative for patients with advanced-stage disease [III, B].
- Consolidative ISRT can be recommended for patients with stage I-II, bulky or IPI >1 disease after six cycles of BV-CHP or CHO(E)P [IV, B].
- Consolidative ASCT in first CR can be considered for transplant-eligible, chemosensitive patients with stage III-IV disease [II, B].
- First-line treatment of ALK-positive ALCL:
 - In patients with limited-stage, non-bulky disease and a favourable pre-therapeutic risk profile, abbreviated ChT (e.g. three to four cycles of BV-CHP or CHOEP) [III, B] followed by consolidative ISRT (e.g. 30-40 Gy) in responding patients [IV, B] can be recommended.
 - All other ChT-eligible patients should be offered six cycles of BV-CHP [I, A].
 - Six cycles of CHO(E)P is an alternative for patients with stage I-II high-risk (bulky disease, IPI ≥2 or age >40 years) or advanced-stage disease [III, B].
 - Consolidative ISRT can be recommended for patients with stage I-II, high-risk disease after six cycles of BV-CHP or CHO(E)P [IV, B].
 - ASCT is generally not recommended for patients with stage III-IV low-risk disease [III, D]. It can, however, be considered for patients with stage I-IV disease with high-risk features (e.g. IPI 3-4 and/or bulky extranodal disease and/or unconfirmed suspected residual disease activity) [II, B].
- r/r disease:
 - Options for r/r PTCL NOS and TFHL include 5-azacytidine (for TFHL only), BV (depending on CD30 status), DHAP, GDP, ICE and IVAC-MTX [III, B; 5-azacytidine not FDA or EMA approved].
 - Options for r/r ALK-negative ALCL include BV, DHAP, GDP, ICE, IVAC-MTX [III, B].
 - For patients with r/r ALK-positive ALCL, BV is recommended if not received as first-line therapy [III, A].
 - For patients with ALK-positive ALCL refractory to BV, ALK inhibitors should be considered [III, A]. ChT (e.g. DHAP, ICE or IVAC-MTX) is also an option [III, B].
 - For transplant-eligible patients with PTCL or ALCL, consolidation with alloSCT can be considered [II, B].

FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP

Key recommendations regarding follow-up for the lymphoma entities covered in this CPG are provided below. Supporting evidence for these recommendations are described in the [Supplementary Material Section 5](https://doi.org/10.1016/j.annonc.2025.07.014), available at <https://doi.org/10.1016/j.annonc.2025.07.014>. Long-term follow-up will vary according to country, hospital policy and resources. Clinicians should also consult their local guidelines regarding follow-up.

Recommendations

DLBCL

- For patients treated to CMR in the first-line setting, routine surveillance with PET–CT or diagnostic CT is generally not recommended [III, D].
- After first-line systemic treatment, history and physical examination should be carried out every 3–6 months for 2 years [V, B]. Follow-up can be discontinued after 2–5 years in asymptomatic patients [V, B].

PCNSL

- Follow-up imaging with cranial MRI can be considered in patients eligible for intensive salvage therapies, at 3-month intervals in the first 2 years after treatment completion and then every 6 months for another 3 years [V, B]. After 5 years, annual cranial MRIs may be considered [V, C].
- Ophthalmological examination can be carried out annually if not involved initially, and 3 monthly if involved initially or in patients with visual deterioration [V, B].
- CSF assessment should only be carried out in the case of suspected or confirmed relapse [V, B].
- Neurocognitive function and quality of life can be assessed on an annual basis, at least within clinical trials [V, B].

FL

- After local RT, history and physical examination should be carried out every 6 months for 2 years and annually thereafter if clinically indicated [V, A].
- Evaluation of thyroid function should be carried out at 1, 2 and 5 years in patients who have undergone irradiation of the neck [V, A].
- After systemic treatment, history and physical examination is suggested every 3–6 months for 2 years and every 6–12 months thereafter [V, C].
- Minimal adequate radiological or other examinations can be carried out every 6 months for 2 years [III, B] and are optional annually ≤ 5 years [III, C]. Regular CT scans are not mandatory outside of clinical trials, and PET–CT should generally not be used for surveillance [V, D].
- Adequate prophylaxis (antibiotics and/or IgG supplementation) can be recommended for patients with symptomatic recurrent infections and should take prior treatment into consideration (e.g. with bendamustine

[IV, B]. Annual seasonal influenza and coronavirus disease (COVID)-19 vaccination may be considered [V, C].

MCL

- Asymptomatic patients with disseminated MCL managed by a watch-and-wait strategy should generally be monitored every 3–6 months by physical examination, imaging (as clinically required), blood counts and biochemistry [V, B].
- After first-line systemic treatment, history and physical examination should generally be carried out every 3–6 months [V, B]. Follow-up should generally not be discontinued given the continued pattern of relapse with long follow-up [V, D].
- Adequate prophylaxis (antibiotics and/or IgG supplementation) is required for patients with symptomatic recurrent infections and should take prior treatment into consideration (e.g. CAR-T therapy, bendamustine) [V, B]. Annual seasonal influenza and COVID-19 vaccination may be considered [V, C].

MZL

- Asymptomatic patients with disseminated MZL (SMZL and NMZL) managed by a watch-and-wait strategy should be monitored every 3–6 months by physical examination, imaging (as clinically required), blood counts and biochemistry [V, B].
- Patients with EMZL at non-gastric sites can be re-evaluated with clinical examination, laboratory work-up and imaging or biopsy of residual lesions, if indicated, every 3 months for the first 2 years and every 6 months thereafter [V, C].
- In patients with gastric MZL, sequential evaluation of gastric biopsies remains an essential follow-up procedure, particularly in patients with persistent *H. pylori* infection [V, B].

HL

- History, physical examination and laboratory analysis should generally be carried out every 3 months for the first year, every 6 months until year 4 and annually thereafter [V, B].
- Routine surveillance with PET–CT or diagnostic CT is generally not recommended for patients in CR [III, D].
- Thyroid function should be evaluated annually in patients who have undergone irradiation of the neck [V, A].
- Female patients who were ≤ 40 years at the time of chest or axillary irradiation should undergo mammography once a year starting 8–10 years after RT [V, A]. Those who were ≤ 30 years should undergo a breast MRI in addition to mammography [V, A].

PTCL

- Follow-up may include history and physical examination every 3 months for 1 year and every 6 months for 2–4 further years [V, C].
- Routine surveillance with PET–CT or diagnostic CT is generally not recommended for patients in CR [III, D].

- Follow-up can be discontinued after 3 years in non-transplanted asymptomatic patients [V, B] and after 5 years in asymptomatic patients who have received ASCT [V, B] if the patient is in an ongoing CR. In patients who have received alloSCT, the general guidelines for alloSCT should be applied [V, A].

METHODOLOGY

This CPG was developed in accordance with the ESMO standard operating procedures for CPG development (<https://www.esmo.org/guidelines/esmo-guidelines-methodology>). All recommendations provided are based on current scientific evidence and the authors' collective expert opinion. Where recommendations for multiple different treatment options exist, prioritisation is illustrated by ordering these options according to level of evidence (LoE) and grade of recommendation (GoR); and where equal, by alphabetical order. The relevant literature has been selected by the expert authors. The FDA/EMA or other regulatory body approval status of new therapies/indications is reported at the time of writing this CPG. LoEs and GoRs have been applied using the system shown in [Supplementary Table S2](#), available at <https://doi.org/10.1016/j.annonc.2025.07.014>.¹ Statements without grading were considered justified standard clinical practice by the authors. For future updates to this CPG, including Express Updates and Living Guidelines, please see the ESMO Guidelines website: <https://www.esmo.org/guidelines/esmo-clinical-practice-guidelines-haematological-malignancies>.

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