Received: 14 April 2026 | Accepted: 8 June 2026

DOI: 10.1002/hem3.70422

GUIDELINES - CONSENSUS-BASED

HemaSphere eha

Hodgkin lymphoma: EHA Clinical Practice Guidelines for diagnosis, treatment, and follow-up

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Abstract

Hodgkin lymphoma (HL) is a B-cell-derived malignancy often affecting young adults. Allocation into risk groups is based on staging with positron emission tomography and computed tomography (PET/CT) and the presence or absence of risk factors. Standard treatment for early-stage favorable classic HL (cHL) consists of two cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD), followed by 20 Gy involved-site radiotherapy (IS-RT). Two cycles of escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (eBEACOPP) or a procarbazine-free eBEACOPP variant plus two cycles of ABVD, followed by 30 Gy IS-RT in the case of PET/CT positivity and no further treatment in the case of PET/CT negativity after chemotherapy should be considered in patients with early-stage unfavorable cHL ≤ 60 years. If a less intensive approach is preferred and in individuals > 60 years, four cycles of A(B)VD followed by 30 Gy IS-RT can be given. In advanced cHL, brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone (BrECADD) for four (in the case of PET/CT negativity after two cycles) or six cycles (in the case of PET/CT positivity after two cycles), followed by PET/CT-guided 30 Gy IS-RT should be considered in patients ≤ 60 years. Six cycles of nivolumab and AVD (N-AVD) followed by PET/CT-guided 30 Gy IS-RT represents a less intensive alternative for younger patients and the preferred approach for patients > 60 years. Patients with cHL recurrence should receive checkpoint inhibitor-containing salvage treatment followed by high-dose chemotherapy and autologous stem cell transplantation if eligible. Treatment of nodular lymphocyte-predominant HL differs from cHL in some situations and may contain an anti-CD20 antibody. This guideline aims at providing recommendations for diagnosis, staging, treatment, and follow-up of HL.

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INCIDENCE AND EPIDEMIOLOGY

Hodgkin lymphoma (HL) is a B-cell-derived lymphoid malignancy. The age-standardized incidence in Europe is between 3.5 and 4/100,000/year, the mortality between 0.3 and 0.6/100,000/year.[1] The disease has a bimodal age distribution with one peak in early adulthood and a second peak in individuals aged > 55 years. Men are slightly more often affected than women.[2] Histologically, classic HL (cHL), accounting for ≈95% of cases, is distinguished from nodular lymphocyte-predominant HL (NLPHL), representing ≈5% of cases. Unlike the most recent World Health Organization (WHO) classification that has retained the name NLPHL, the International Consensus Classification proposes nodular lymphocyte-predominant B-cell lymphoma as an alternative name for this entity.[3,4]

DIAGNOSIS, PATHOLOGY, AND MOLECULAR BIOLOGY

Clinical presentation

Patients with cHL typically present with painless lymphadenopathy or symptoms caused by a mediastinal mass. B symptoms (intermittent fever, drenching night sweats, and unintended body weight loss > 10%) are reported in a significant proportion of cases. Pruritus, fatigue, or alcohol-induced lymph node pain occur less frequently.

Histopathology and immunohistochemistry

Histopathology is mandatory for the diagnosis of HL. An excisional lymph node biopsy is recommended and favored over a core needle biopsy. Fine-needle aspiration is insufficient due to the need for architectural assessment and immunophenotyping. The presence of Hodgkin and Reed–Sternberg cells represents the hallmark of cHL. Additional information on histology, immunohistochemistry, and differential diagnoses is summarized in Supplement S1.

Recommendations:

- The diagnosis of HL should be made based on an excisional lymph node biopsy whenever possible and a core needle biopsy if not possible. A fine-needle aspiration is insufficient to establish a robust diagnosis.
- Additional diagnostic work-up depends on uncertainties regarding possible differential diagnoses.

STAGING AND RESPONSE ASSESSMENT

Accurate staging and risk stratification are required for treatment decision-making. The stage according to the Ann Arbor classification is determined by baseline positron emission tomography (FDG-PET) and contrast-enhanced computed tomography (CT) (PET/CT).[5,6] Given its higher sensitivity, PET/CT has superseded the requirement for a bone marrow biopsy at diagnosis.[7] Pretreatment clinical risk factors as defined by different study groups divide early-stage patients into an early-stage favorable and an early-stage unfavorable group. In Stage IIB patients, the presence of certain risk factors can result in the allocation to the advanced-stage group (Table 1). In addition to staging and risk stratification, different baseline examinations are recommended. Given the frequently young age at diagnosis, reproductive counseling before treatment initiation is also important and should be offered to all HL patients with a desire to have children (Table 2).

Information on prognostic scores and the use of PET/CT during and after treatment is summarized in Supplement S2.

TABLE 1 Risk group allocation according to the German Hodgkin Study Group.

Early favorable stages	Stage I/II without risk factors
Early unfavorable stages	Stage I and Stage IIA with ≥1 of the risk factors A–D
	Stage IIB with ≥1 of the risk factors C and D, but not risk factors A and B
Advanced stages	Stage IIB with ≥1 of the risk factors A and B
	Stage III/IV

Note: Risk factors: A, large mediastinal mass ≥ one third of the maximal thoracic width; B, extranodal involvement; C, elevated erythrocyte sedimentation rate (ESR) (>50 mm/h without B symptoms; >30 mm/h with B symptoms); D, involvement of ≥3 nodal areas.

TABLE 2 Diagnostic work-up in Hodgkin lymphoma.

Diagnosis	Lymph node biopsy (excisional lymph node biopsy preferred over core needle biopsy)
Staging and risk stratification	Medical history and physical examination
	Positron emission tomography
	Contrast-enhanced computed tomography
	Full blood cell count
	Blood chemistry
	ESR
Pretreatment examinations	ECG
	Echocardiography or MUGA scan
	Pulmonary function testing
	HBV, HCV, and HIV screening
	Serum pregnancy test (in female patients of reproductive age)
	Reproductive counseling (in patients of reproductive age with a desire to have children

Abbreviations: ECG, electrocardiogram; ESR, erythrocyte sedimentation rate; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MUGA, multi-gated acquisition.

Recommendations:

- PET/CT staging and clinical risk factors should be used for risk group allocation.
- A bone marrow biopsy is not recommended at initial staging if a baseline PET/CT is performed.
- Interim PET/CT should be performed when treating a patient on a pathway that uses data from this timepoint to inform treatment decisions.

MANAGEMENT OF NEWLY DIAGNOSED CHL

Treatment of early-stage cHL

Early-stage cHL includes Stage I/II disease according to the Ann Arbor staging system. Patients with Stage I/II disease without clinical

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risk factors are allocated to the early-stage favorable group, and the majority of those presenting with clinical risk factors to the early-stage unfavorable group (Table 1).

The randomized German Hodgkin Study Group (GHSG) HD10 study had compared four and two cycles of ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) each followed by involved-field radiotherapy (RT) at doses of 30 or 20 Gy in patients with early-stage favorable HL. The 5-year progression-free survival (PFS) rates in the most (four cycles of ABVD plus 30 Gy involved-field RT) and least (two cycles of ABVD plus 20 Gy involved-field RT) intensive treatment arms did not differ (93.9% vs. 91.6%). The same was true for the 5-year overall survival (OS) rates (96.9% vs. 96.6%).[8] The results were confirmed by a follow-up analysis indicating 10-year PFS rates of 87.4% and 87.2% and 10-year OS rates of 93.6% and 94.1% after four cycles of ABVD plus 30 Gy involved-field RT and two cycles of ABVD plus 20 Gy involved-field RT, respectively.[9] The question of whether consolidation RT can be omitted in patients with a negative PET/CT after two or three cycles of ABVD was addressed by three randomized studies (RAPID, H10F, and HD16). All three studies demonstrated that PET/CT-negative patients treated with chemotherapy alone had a worse disease control than patients receiving combined-modality treatment (CMT) (RAPID: 3-year PFS 90.8% vs. 94.6%; H10F: 5-year PFS 87.1% vs. 99%; and HD16: 5-year PFS 86.1% vs. 93.4%).[10–12] Follow-up analyses confirmed these results.[13,14] Thus, CMT consisting of two cycles of ABVD followed by consolidation involved-site RT at a dose of 20 Gy is the standard of care for early-stage favorable cHL irrespective of the PET/CT result after two cycles of chemotherapy (Figure 1). However, as outcomes are still good without RT if a complete metabolic remission (CMR) (i.e., Deauville score [DS] ≤ 3) is achieved with chemotherapy, omission of RT can be discussed in patients where the late risks of RT are considered to outweigh the potential benefits of local disease control. The estimation of the risk from RT must be made by a radiation oncologist. With modern techniques, the doses to critical structures such as the heart and lungs are significantly smaller than in the past. The risk of late sequelae may thus be lower than with systemic treatment, especially in cases in which RT is replaced by an increased number of chemotherapy cycles.[15–17] Multidisciplinary discussion should include factors such as age, sex, and disease localization. If RT is omitted, the chemotherapy only approaches from the RAPID, H10F, and HD16 studies should be applied.

In the randomized GHSG HD14 study including patients aged ≤ 60 years with early-stage unfavorable HL, a regimen consisting of two cycles of escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) (eBEACOPP) and two cycles of ABVD ("2 + 2") followed by involved-field RT was associated with improved disease control in comparison with four cycles of ABVD followed by the same RT (10-year PFS 91.2% vs. 85.6%).[18,19] The subsequent randomized HD17 study investigated whether it is possible to omit RT in patients with a negative PET/CT at the end "2 + 2" chemotherapy. At 5 years, there were no PFS differences between the PET/CT-negative patients treated with CMT and chemotherapy alone, respectively (97.7% vs. 95.9%). Hence, RT can be omitted in individuals with a negative PET/CT at the end of systemic treatment if "2 + 2" chemotherapy is applied.[20] Given the results obtained in patients with advanced cHL, replacing eBEACOPP by eBEACOPDac (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and dacarbazine), which was associated with a similar efficacy but a lower risk for acute and

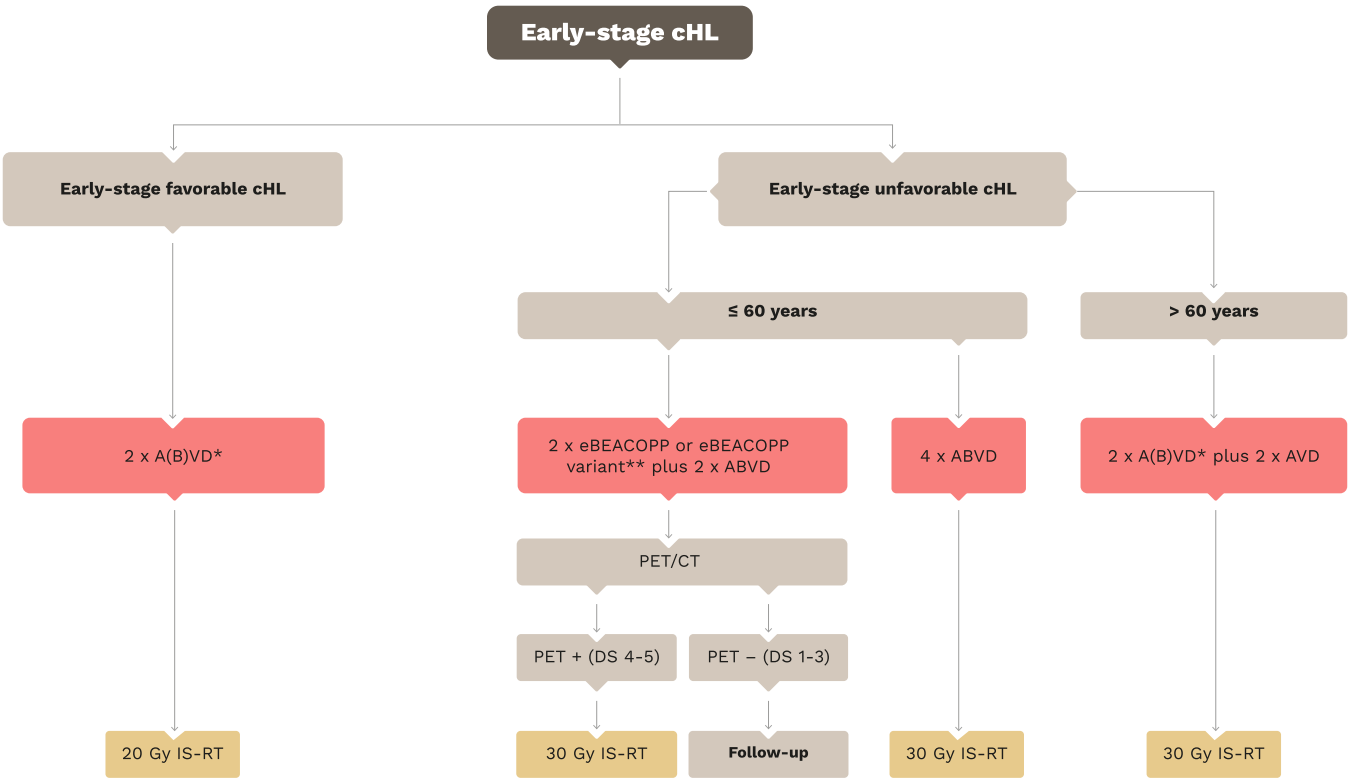

FIGURE 1 **Treatment algorithm for newly diagnosed early-stage classic Hodgkin lymphoma.** *Omission of bleomycin should be considered in patients aged > 70 years. **Escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and dacarbazine (eBEACOPDac) or another procarbazine-free escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (eBEACOPP) variant. ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; cHL, classic Hodgkin lymphoma; CT, computed tomography; DS, Deauville score; IS-RT, involved-site radiotherapy; PET, positron emission tomography.

long-term toxicity or another procarbazine-free eBEACOPP-based protocol may be preferred, although data with these protocols are not available for early-stage unfavorable disease (Figure 1).[21]

In the H10U study for early-stage unfavorable cHL, patients with a negative PET/CT after two cycles of ABVD were randomly assigned between the standard treatment consisting of a total of four cycles of ABVD followed by consolidation RT and a total of six cycles of ABVD alone. In the case of a positive PET/CT after two cycles of ABVD, patients were randomly assigned between standard CMT with a total of four cycles of ABVD plus RT and treatment escalation with two cycles of eBEACOPP followed by RT. In patients with a negative PET/CT, non-inferiority of the chemotherapy alone approach could not be demonstrated (5-year PFS 92.1% vs. 89.6%).[11] Results were confirmed by a follow-up analysis with an extended median follow-up duration close to 10 years.[13] However, as outcomes are still good, six cycles of chemotherapy alone can be offered to selected interim PET/CT-negative patients, bearing in mind that the potential additional chemotherapy-associated short-term and long-term toxicity including cardiac failure and breast cancer that can both be associated with doxorubicin exposure may surpass the risk for adverse events associated with RT.[22,23] Short-term pulmonary toxicity can be reduced by omitting bleomycin from ABVD beyond cycle two as demonstrated by the randomized RATHL study.[24,25] Patients with a positive interim PET/CT receiving intensified treatment had better outcomes than the standard CMT group at 5 years, but this benefit could no longer be observed at 10 years. Treatment intensification to eBEACOPP in patients with early-stage cHL who have a positive PET/CT after two cycles of ABVD should therefore be restricted to selected cases. In individuals aged > 60 years, bleomycin should be included in no more than two chemotherapy cycles as an increased rate of bleomycin-associated toxicity has been observed in this age group if more bleomycin-containing cycles were given. In patients aged > 70 years, omission of bleomycin should be considered (Figure 1).[26–28]

With regard to the radiation volume, involved-site RT is recommended by the International Lymphoma Radiation Oncology Group (ILROG) for both early-stage favorable and early-stage unfavorable cHL. This concept incorporates modern conformal techniques (intensity-modulated RT, volumetric modulated arc therapy, and proton therapy in selected cases such as young adults).[29,30] For patients with mediastinal involvement, deep inspiration breath hold is recommended.[29,31] In the HD17 study, patients with a positive PET/CT after "2 + 2" chemotherapy were randomly assigned between involved-field RT and radiation to a volume which is close to the ILROG definition of involved-site, each at a dose of 30 Gy. The 4-year PFS (96.8% vs. 95.4%) and OS (99.1% vs. 100%) did not differ between the groups. Grade III/IV toxicities such as mucositis were less common in the involved-site RT group (2.6% vs. 8.5%).[32]

Recommendations:

- Early-stage favorable cHL should be treated with two cycles of ABVD followed by 20 Gy involved-site RT (1A).
- Early-stage unfavorable cHL in patients ≤ 60 years should be treated with two cycles of eBEACOPP plus two cycles of ABVD ("2 + 2") followed by 30 Gy involved-site RT only in the case of a positive PET/CT at the end of chemotherapy (1A).
- Two cycles of eBEACOPDac or another procarbazine-free eBEACOPP variant plus two cycles of ABVD, followed by 30 Gy involved-site RT only in the case of a positive PET/CT at the end of chemotherapy, represents an alternative to the original "2 + 2" protocol in early-stage unfavorable cHL (4A).
- Four cycles of ABVD followed by 30 Gy involved-site RT should be given if a less intensive approach not including eBEACOPP or a procarbazine-free eBEACOPP variant is preferred (1A).
- In patients aged > 60 years, the use of bleomycin should be restricted to no more than two treatment cycles; omission of bleomycin should be considered in patients aged > 70 years (3A).

Treatment of advanced cHL

Advanced-stage cHL comprises patients with Stage III/IV disease. In the risk group definition of the GHSG, patients with Stage IIB presenting with large mediastinal mass and/or extranodal manifestations are also included in the advanced-stage group (Table 1). Patients with advanced cHL are usually treated with systemic therapy alone. RT is confined to cases with PET/CT-positive residual disease at the end of systemic therapy. Treatment of the individual patient is chosen based on factors such as age, comorbidities, and fitness.

Treatment of younger patients with advanced cHL (≤60 years)

In the randomized HD21 study including patients aged between 18 and 60 years, BrECADD (brentuximab vedotin (BV), etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone) was more effective and less toxic than eBEACOPP and thus represents the standard approach for younger patients without significant comorbidities. After a median observation time of 5 years, four (in the case of a negative interim PET/CT after two treatment cycles, i.e., DS ≤ 3) or six (in the case of a positive interim PET/CT after two treatment cycles, i.e., DS ≥ 4) cycles of BrECADD resulted in a 5-year PFS of 93.6% as compared to 90.6% with eBEACOPP; the 5-year OS rate was 98% for both protocols.[33] BrECADD was also associated with lower rates of higher grade hematologic toxicities, transfusions, polyneuropathy, and infertility.[34,35] In the randomized SWOG S1826 study that included patients aged between 12 and 84 years, superiority in terms of PFS was demonstrated for the combination of the anti-PD-1 antibody nivolumab and AVD (N-AVD) as compared to BV in combination with AVD (BV-AVD). After a median observation time of 3.1 years, the 3-year PFS after six cycles of N-AVD was 91% (91% for patients between 18 and 60 years), whereas the 3-year PFS with BV-AVD was 82% (85% for patients between 18 and 60 years). Three-year OS rates were 98% and 97%, respectively.[36] Thus, N-AVD represents a less intensive alternative to BrECADD, although longer follow-up may be necessary for final conclusions.

Options for younger patients without access to BrECADD or N-AVD include four (in the case of a negative PET/CT after two treatment cycles, i.e., DS ≤ 3) or six (in the case of a positive interim PET/CT after two treatment cycles, i.e., DS ≥ 4) cycles of eBEACOPP-based treatment, six cycles of BV-AVD (for which a survival benefit in comparison with ABVD was demonstrated in the ECHELON-1 study; 6-year OS: 93.9% vs. 89.4%) or two cycles of ABVD followed by four cycles of AVD in those with negative interim PET/CT and eBEACOPP-based treatment or BEACOPP-14 in those with a positive interim PET/CT.[24,25,37–39] An observational study from the United Kingdom reported that the replacement of procarbazine by dacarbazine in eBEACOPP (eBEACOPDac) had resulted in similar efficacy but reduced acute and long-term toxicity in comparison with the original regimen.[21] BrECADD, eBEACOPP, eBEACOPDac, and BV-AVD carry an increased risk of neutropenia and neutropenic fever. Primary prophylaxis with G-CSF and cotrimoxazole is mandatory. In the HD21 protocol, intensified prophylaxis with a quinolone was recommended during aplasia after BrECADD and eBEACOPP.[35] Appropriate treatment for proven or suspected infections is therefore particularly important for individuals treated with these regimens.

In patients with a partial remission according to PET/CT after systemic therapy, involved-site RT at a dose of 30 Gy using modern planning techniques should be considered (Figure 2).[29]

General aspects of the treatment of older patients with advanced cHL (>60 years)

General considerations in the treatment of older cHL patients are outlined in Supplement S3.

Treatment of fit older patients with advanced cHL (>60 years)

Fit older patients were included in randomized studies comparing ABVD and BV-AVD (ECHELON-1 study) and BV-AVD and N-AVD (SWOG S1826 study), respectively. N-AVD was better tolerated and more effective than BV-AVD in this patient group with 3-year PFS rates of 82% versus 58% and 2-year OS rates of 96% versus 85%.[36,40] No improved outcomes in this patient group were demonstrated with BV-AVD in comparison with ABVD. The 5-year PFS rates were 67% versus 62%. At the same time, BV-AVD resulted in higher rates of neutropenia, neutropenic fever, and neuropathy.[41] Taken together, N-AVD should be considered as standard treatment for this patient population (Figure 2). Regimens investigated in Phase II studies include BrECADD and the sequential administration of BV and AVD. In a cohort of very fit patients aged between 61 and 75 years, BrECADD resulted in a 2-year PFS of 92% and a 2-year OS of 91% at the cost of significant hematologic toxicity and infectious complications.[42] The sequential use of BV and AVD resulted in a 2-year PFS of 84% and an OS of 93%, with apparently less hematologic toxicity and infectious complications than with BV-AVD.[43]

For patients who can receive neither BV nor a PD-1 inhibitor but are suitable for multiagent chemotherapy, the standard approach is to administer up to two cycles of ABVD followed by four cycles of AVD for a total of six cycles of systemic treatment. The administration of more than two cycles of ABVD is associated with an unacceptably high incidence of bleomycin-related pulmonary toxicity in older patients.[26,44] Whether bleomycin is given in the first two cycles of chemotherapy should be decided based on the patient´s age (omission in patients aged > 70 years should be considered), preexisting lung conditions, and the result of lung function testing.[27,28]

Treatment of unfit older patients with advanced cHL (>60 years)

For older patients not eligible for multiagent chemotherapy, treatment options are limited, and a cure is unlikely. BV and PD-1 inhibitors given as a single agent are options in this patient group, but neither appears to result in long-term disease control. Additional information on the treatment of older unfit patients is summarized in Supplement S3.

Recommendations:

- Younger patients with advanced cHL should be treated with four (in the case of a negative interim PET/CT after two cycles) or six

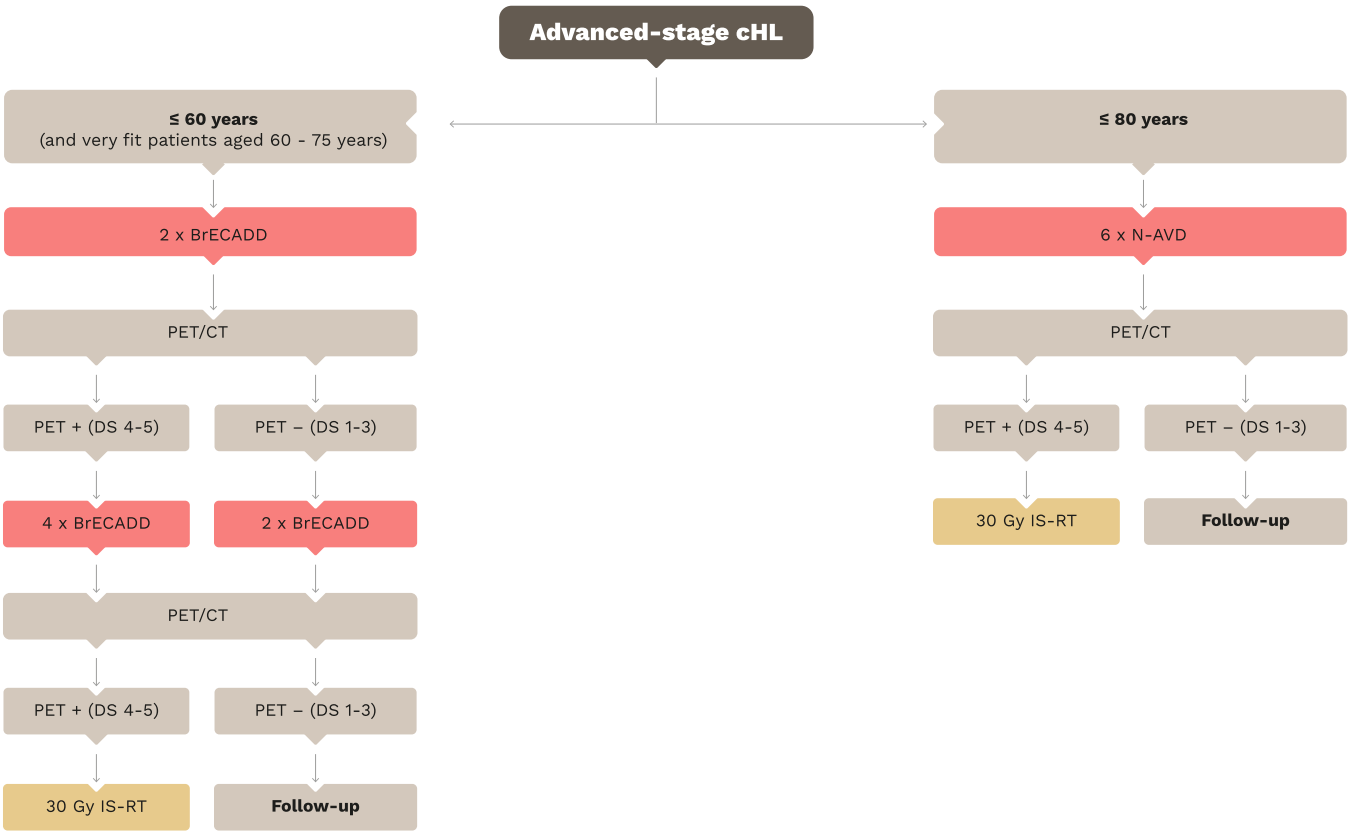

FIGURE 2 **Treatment algorithm for newly diagnosed advanced classic Hodgkin lymphoma.** BrECADD, brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone; cHL, classic Hodgkin lymphoma; CT, computed tomography; DS, Deauville score; IS-RT, involved-site radiotherapy; N-AVD, nivolumab and doxorubicin, vinblastine, and dacarbazine; PET, positron emission tomography.

(in the case of a positive interim PET/CT after two cycles) cycles of BrECADD followed by PET/CT-guided RT (1A).
- If an ABVD-based approach is preferred, six cycles of N-AVD represent an alternative to BrECADD in younger patients with advanced cHL (1A).
- In older patients with advanced cHL who are eligible for multiagent chemotherapy, six cycles of N-AVD should be given (2A).
- Interim PET/CT-guided BrECADD (four or six cycles) optionally followed by PET/CT-guided RT represents an alternative to N-AVD in very fit older patients with advanced cHL (2B).
- If targeted agents are not available, interim PET/CT-guided eBEACOPDac (four or six cycles depending on the result of the PET/CT after two cycles) represents an alternative in younger patients with advanced cHL (4A).
- In older patients with advanced cHL, two cycles of A(B)VD followed by four cycles of AVD represents an alternative to approaches including targeted agents (3A).
- In older patients with advanced cHL who are not eligible for multiagent chemotherapy, possible approaches include combinations of BV with a PD-1 inhibitor or dacarbazine or single-agent conventional chemotherapy (3B).

REFRACTORY AND RELAPSED CHL

Refractory disease is defined as progression during or relapse within 3 months after the end of first-line treatment, early relapse as disease recurrence within 12 months after the end of first-line treatment, and late relapse as disease recurrence 12 or more months after the end of first-line treatment. A biopsy to confirm the progression or relapse should be obtained whenever possible.

Treatment of refractory and relapsed cHL in patients eligible for high-dose chemotherapy and autologous stem cell transplantation

The standard second-line treatment for most patients with refractory and relapsed cHL consists of high-dose chemotherapy (HDCT) and autologous stem cell transplantation (ASCT). This is based on two older randomized studies that had both indicated a reduced relapse rate but no OS benefit after HDCT and ASCT in comparison with conventional chemotherapy.[45,46] Eligibility for HDCT and ASCT should not be based on age alone. Carefully selected fit patients aged > 65 years can also be candidates. The goal of salvage treatment is to achieve a CMR prior to HDCT and ASCT (i.e., DS ≤ 3). A CMR before HDCT and ASCT is associated with a 5-year PFS of approximately 75% versus 25% to 30% in PET-positive (i.e., DS ≥ 4) patients.[47]

Until recently, second-line treatment was based on chemotherapy regimens such as DHAP (dexamethasone, high-dose cytarabine, and cisplatin), ICE (ifosfamide, carboplatin, and etoposide), GVD (gemcitabine, vinblastine, and pegylated liposomal doxorubicin), IGEV (ifosfamide, gemcitabine, vinorelbine, and prednisone), BEGEV (bendamustine, gemcitabine, vinorelbine, and prednisone), and ESHAP (etoposide, methylprednisone, high-dose cytarabine, and cisplatin). These protocols resulted in complete remission rates of up to 55%. The addition of BV (BV-DHAP, BV-ESHAP) improved rates to 70%–80%.[48,49] These rates could be improved further by the use of the PD-1 inhibitors nivolumab or pembrolizumab in combination with chemotherapy (P-GVD, P-ICE, and N-ICE). Such combinations resulted in CMR rates between 87% and 95% and 2-year survival rates up to 96% after HDCT and ASCT.[50–52] The chemotherapy-free combination of BV and nivolumab led to a lower CMR rate (67%), but the estimated 3-year PFS rate was nonetheless 91% for patients proceeding to HDCT and ASCT directly after BV and nivolumab.[53] The limitations of all studies incorporating novel targeted agents include a low overall number of patients and a limited number of patients who had been exposed to BV or PD-1 inhibitors during first-line treatment. Currently, a PD-1 inhibitor used concomitantly with chemotherapy or sequentially with chemotherapy in patients who do not respond sufficiently to single-agent PD-1 inhibitor treatment likely represents the most active option for patients with refractory and relapsed cHL (Figure 3).[52]

If PD-1 inhibitors are not available for second-line treatment, if disease progression occurred during treatment with PD-1 inhibitors or shortly after cessation of PD-1 inhibition as well as in BV-naive patients, BV in combination with chemotherapy represents an option. Single-agent BV may also be considered despite a relatively low CMR rate.[54] In high-risk patients responding to BV-based treatment or conventional chemotherapy, BV maintenance following HDCT and ASCT for up to 16 doses should be considered based on the results from the randomized AETHERA trial (risk factors: primary refractory disease, early relapse, and extranodal involvement at relapse) that had indicated a better 5-year PFS with BV maintenance versus placebo (59% vs. 41%) (Figure 3).[55]

In patients with a partial metabolic remission (PMR) after salvage treatment and before ASCT, respectively, involved-site RT to residual PET-positive areas should be considered. Involved-site RT may also be useful in cases in which local disease control has been a dominant clinical problem. The timing of peri-transplant involved-site RT is variable and controversial, and the decision whether RT is applied before or after ASCT is made individually and aims at avoiding toxicity on engraftment and bone marrow and organ functionality. RT before ASCT has the advantage of yielding maximal cytoreduction prior to transplant. If RT is administered after systemic therapy, the RT volume may be adapted to the post-chemotherapy lymphoma volume (Figure 3).[56,57] If a significant part of the lungs and/or the heart will be irradiated, RT after ASCT reduces the risk for the development of cardio-pulmonary side effects.

The standard conditioning regimen in refractory and relapsed cHL is BEAM (carmustine, etoposide, cytarabine, and melphalan), and stem collection should be performed early.[45,46]

Patients with late relapse after initial treatment for early-stage favorable cHL can be considered for second-line treatment with intensive conventional chemotherapy optionally combined with novel targeted agents and RT.[58]

Recommendations:
- Relapsed and refractory disease should be confirmed by biopsy whenever possible (3A).
- HDCT followed by ASCT represents the standard approach for most patients with refractory and relapsed cHL who are eligible for this approach (2A).
- In countries in which PD-1 inhibitors are available and reimbursed, salvage treatment before HDCT and ASCT should consist of a PD-1 inhibitor combined with chemotherapy either concomitantly or sequentially if response to the PD-1 inhibitor given as a single agent is insufficient (3B).
- For BV-naive patients in countries in which BV but no PD-1 inhibitors are available and reimbursed or in patients not eligible for treatment with PD-1 inhibitors, BV in combination with chemotherapy is recommended as salvage treatment before HDCT and ASCT (2A).
- BV maintenance following ASCT is recommended for high-risk patients (1A).
- If no CMR is achieved after salvage therapy, options include third-line treatment or ASCT with RT to PET-positive sites and/or BV maintenance (3B).

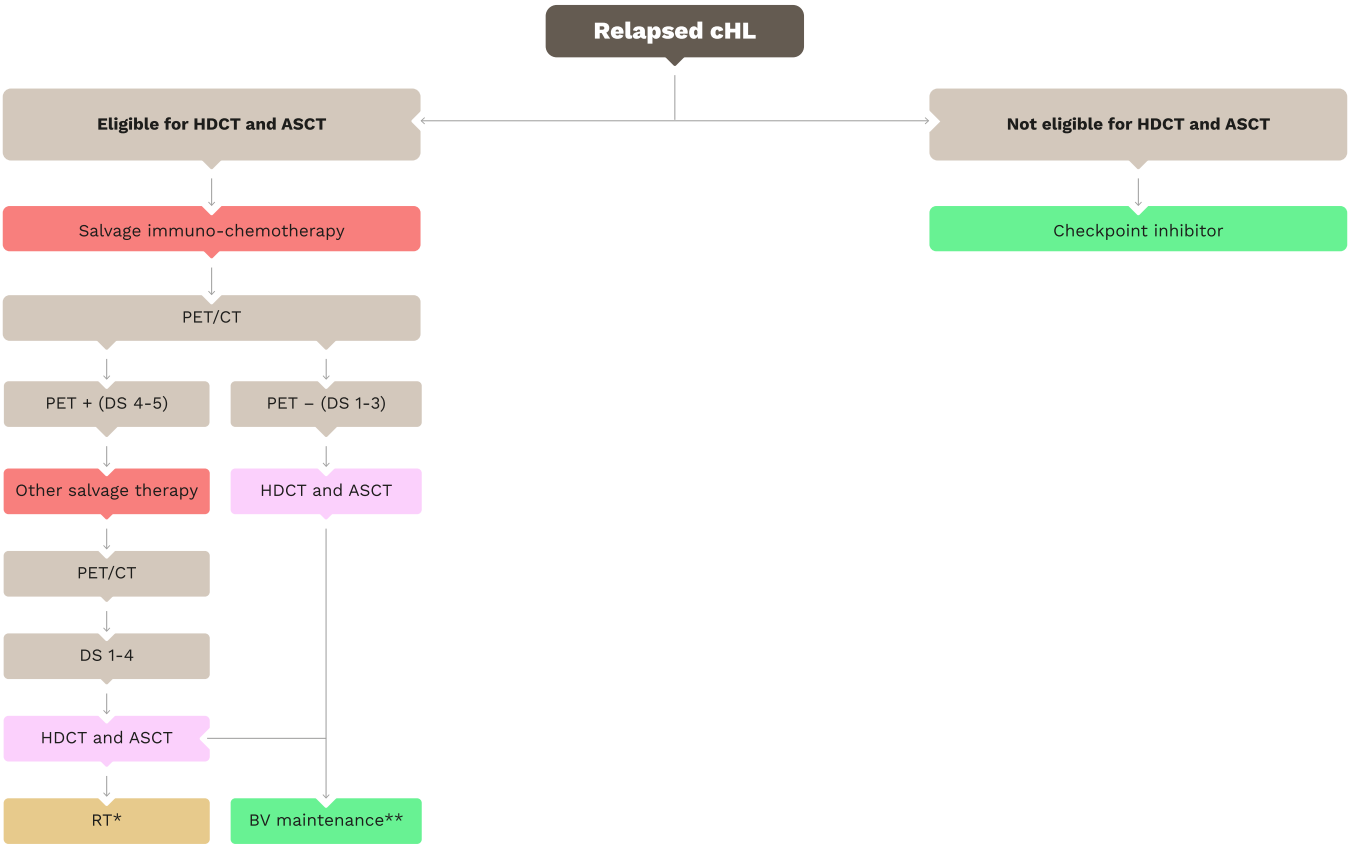

FIGURE 3 **Treatment algorithm for refractory and relapsed classic Hodgkin lymphoma.** *Radiotherapy (RT) should be considered to positron emission tomography (PET)/computed tomography (CT)-positive residual lymphoma after salvage therapy if high-dose chemotherapy (HDCT) and autologous stem cell transplantation (ASCT) are conducted without reaching a complete metabolic remission. RT is mostly performed after HDCT and ASCT but is also possible before. **Brentuximab vedotin (BV) maintenance should be considered in patients with high-risk characteristics if they did not have BV treatment or if they had responded to BV before. cHL, classic Hodgkin lymphoma; DS, Deauville score.

- RT to PET-positive sites should be considered prior to or following ASCT (3A).
- Selected patients (i.e., individuals with late relapse after initial treatment for early-stage favorable cHL) may be considered for second-line treatment with conventional chemotherapy optionally combined with novel agents and RT (3C).

Patients with relapse after HDCT and ASCT

For patients who had been exposed to BV and PD-1 inhibitors, the choice of treatment at disease recurrence after HDCT and ASCT is challenging. Entry into a clinical trial is encouraged whenever possible. Otherwise, the treatment to which the patient was most sensitive can be administered, and a donor search for allogeneic stem cell transplantation (alloSCT) should be initiated. If at least a PMR is achieved, alloSCT represents a potentially curative option. However, the potential benefit has to be balanced against the complications associated with this treatment modality.[57]

For PD-1 inhibitor-naive patients, treatment with a PD-1 inhibitor for up to 2 years is recommended.[59] When PD-1 inhibitors are used as a single agent, the median PFS is approximately 14 months.[59–61] The first response assessment in patients treated with a PD-1 inhibitor should be performed after four cycles using the LYRIC criteria to exclude pseudo progressions and avoid premature cessation of treatment.[62] However, the LYRIC criteria have not been validated prospectively and are challenging to use in the daily practice. Other methods such as measurements of serum thymus and activation-related chemokine (TARC) or circulating tumor DNA (ctDNA) may improve the assessment of response but are investigational and not broadly available. Whether alloSCT should be offered to all patients achieving a response to treatment with a PD-1 inhibitor is controversial. Patients with an early complete response with PD-1 inhibition have the highest probability to obtain long-term disease control.[61] However, patients should be informed that even in the case of achieving a CMR, the median duration of response is no longer than 2.5–3 years, and most patients relapse after discontinuation of treatment.[60,61] Among patients who undergo alloSCT, the administration of PD-1 inhibitors prior to transplantation has improved the outcomes from a historical 2-year OS of 65% to a rate of 82%.[63] However, roughly 40% of patients develop acute GvHD Grade II–IV and 20% Grade III–IV complications.[64] Administration of PD-1 inhibitors should be discontinued at least 6 weeks before alloSCT.[57,65]

Recommendations:

- The treatment strategy for patients with relapse after HDCT and ASCT should be chosen individually and adapted to the previous treatment (3A).
- AlloSCT should be discussed with all eligible patients responding to treatment, for example, PD-1 inhibitors, taking into account individual risks and potential benefits (3B).

- AlloSCT should be discussed with all fit patients who are refractory to or who progress on or after PD-1 inhibitor therapy (3A).

Treatment of patients with refractory and relapsed cHL not eligible for HDCT and ASCT

There is no standard treatment approach for patients with refractory or relapsed cHL not eligible for HDCT and ASCT. Treatment should be chosen individually taking into account performance status, age, comorbidities, and prior treatment. For most patients, treatment based on PD-1 inhibitors should be preferred over BV, especially if BV was used during first-line treatment. Information on the treatment of patients with refractory or relapsed cHL not eligible for HDCT and ASCT is summarized in Supplement S3.

Recommendations:

- PD-1 inhibitors given as a single agent represent the preferred treatment for patients with refractory or relapsed cHL not eligible for HDCT and ASCT (2A).
- Chemotherapy alone or in addition to PD-1 inhibitors can be given (2B).
- If patients are not eligible for PD-1 inhibitors or treatment with PD-1 inhibitors is not reimbursed, single-agent BV for up to 16 cycles is recommended, especially in individuals who are BV-naive (2A).
- In patients with localized relapse, RT alone or together with a PD-1 inhibitor can be considered (3A).

FOLLOW-UP, LONG-TERM IMPLICATIONS, AND SURVIVORSHIP

Long-term management of adult HL survivors involves monitoring for relapse, treatment-related complications, and routine health maintenance. The structure and duration of survivorship care largely depend on the overall organization of different health care systems and the coordination of patient care. Patient education for practical self-management strategies and structured survivorship care plans are important cornerstones of follow-up.

Imaging with PET/CT, CT, or magnetic resonance imaging (MRI) scan (in the case PET/CT or CT cannot be carried out or initial staging was also conducted using MRI) is carried out after the end of treatment to confirm the remission status. Thereafter, patients should be followed clinically. Surveillance imaging with PET/CT or CT is not indicated unless clinical symptoms occur.[5,6]

Follow-up intervals and examinations are adjusted to the different health care systems. In general, follow-up evaluations should seek clinical findings that suggest disease relapse or treatment-related complications. Therefore, history, physical examination, and laboratory analysis including full blood cell count, erythrocyte sedimentation rate, and blood chemistry screening should be carried out at follow-up visits.

Thyroid function (thyroid-stimulating hormone) should be evaluated once a year if the neck was irradiated. Furthermore, testosterone and estrogen levels should be monitored, particularly in younger patients who had intensive chemotherapy. Monitoring of luteinizing hormone and follicle-stimulating hormone should be considered in premenopausal female patients. Where possible, blood pressure measurement and lipid testing should be performed annually for all patients.[66]

Patients should be actively asked about symptoms indicating the existence of long-term toxicity, especially second malignancies, heart and lung disease, chronic fatigue, neuropsychiatric sequelae (including anxiety and depression), neuropathy, bone health, sexual dysfunction, and fertility problems. The social impact related to work life or financial situation should be included as topics during follow-up care. Relevant patient-reported outcome measures may help to identify patient concerns. Risk awareness and lifestyle counseling for cancer and cardiovascular risk prevention should be discussed at follow-up visits.

Particular attention should be paid to breast cancer screening in female patients who had received RT including dose exposure to the breasts before the age of 36 years. These patients should have a mammography and/or a breast MRI annually starting 8 years after RT, but not earlier than at age 25 years.[67] The fact that the breast cancer risk also correlates with the cumulative doxorubicin dose should also be considered when planning breast cancer screening for the individual patient.[23] Other regular cancer screening should be conducted due to the persistently increased risk for the development of second hematologic and solid malignancies after HL treatment.[68,69]

Recommendations:

- Survivorship care should be conducted according to structured plans adjusted to the different health care systems and the patient's individual risk for late toxicities (4B).

NODULAR LYMPHOCYTE-PREDOMINANT HODGKIN LYMPHOMA

As in cHL, the malignant cells in NLPHL (LP cells) also constitute only ≈1% of the cellularity in the tumor tissue. The LP cells have a preserved B-cell phenotype with consistent positivity for CD20 and B-cell receptor signaling.[70] LP cells from a subset of NLPHL cases recognize bacterial antigens such as those from *Moraxella catarrhalis* and *Rothia mucilaginosa* via their B-cell receptors.[71,72] JAK-STAT and NF-κB signaling are active in LP cells.[70] BCL6 is often rearranged.[73] NLPHL is associated with a more pronounced male predominance, the median age at initial diagnosis is slightly higher, patients are more often diagnosed in early stages, and the clinical course is usually more indolent than in cHL.[74,75] The recently developed lymphocyte-predominant International Prognostic Score (LP-IPS) including the risk factors age (≥45 years), stage (Stage III/IV disease), hemoglobin (<10.5 g/dL), and splenic involvement allows the discrimination of risk groups regarding PFS, OS, the risk of lymphoma-specific death, the risk of NLPHL-specific death, and the risk of transformation into aggressive B-NHL, respectively.[76]

Patients with newly diagnosed Stage IA NLPHL without clinical risk factors are appropriately treated with involved-site RT alone at a dose of 30 Gy. This is not only true for patients with residual disease after lymph node surgery but also for those who had a complete lymph node resection.[77] The addition of chemotherapy does not improve outcomes in this patient group. An analysis comprising patients with Stage IA NLPHL without clinical risk factors who had been treated within prospective studies revealed 8-year PFS and OS rates of 91.9% and 99% after 30 Gy limited-field RT alone.[78] Of note, the involved-site RT volumes irradiated in this RT alone approach are larger than the involved-site RT volumes in CMT approaches.[29] Most data on the treatment of newly diagnosed NLPHL other than Stage IA without clinical risk factors derive from studies that included individuals with both cHL and NLPHL. An analysis comprising patients with newly diagnosed NLPHL treated within prospective randomized GHSG studies investigating ABVD and BEACOPP variants partly followed by consolidation RT indicated 10-year PFS rates between 69.8% and 79.7% and 10-year OS rates between 87.4% and 96.2% depending on the risk profile.[79] A large multicenter retrospective analysis has demonstrated a PFS advantage for patients with newly diagnosed Stage II to IV NLPHL who had chemotherapy in combination with the anti-CD20 antibody

rituximab (5-year PFS 89.6% with chemotherapy plus rituximab vs. 72.7% with chemotherapy alone).[80] Hence, a brief chemotherapy with ABVD optionally combined with rituximab (two cycles in early favorable stages other than Stage IA without clinical risk factors; four cycles in early unfavorable stages), and followed by consolidation RT represents a very active treatment option in early-stage NLPHL. Given the intensity of BEACOPP-based chemotherapy, the consistent CD20 positivity of the LP cells, and the mostly indolent clinical course, anti-CD20 antibody-containing protocols usually given in indolent B-NHL represent an alternative to cHL approaches especially in advanced NLPHL. Smaller retrospective analyses have indicated high response and PFS rates for R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), BR (bendamustine, rituximab), and R-CVP (rituximab, cyclophosphamide, vincristine, and prednisone).[81–83] However, results from prospective studies and long-term follow-up are not available for these approaches when used in NLPHL. Selected patients such as those with asymptomatic advanced-stage disease may also be managed with active surveillance.[84]

Patients with suspected NLPHL recurrence should have a biopsy to confirm the diagnosis given a 10-year transformation rate into aggressive B-NHL of ≈10%.[85,86] Once NLPHL histology has been confirmed, the choice of salvage treatment depends on factors such as time to relapse, previous treatment, and stage at relapse. Patients with a long interval between initial treatment and NLPHL recurrence, relapse after low-intensity first-line treatment (e.g., RT alone or approaches including limited amounts of chemotherapy), and/or localized disease at relapse can often be salvaged successfully with single-agent anti-CD20 antibody treatment, RT alone, or conventional chemotherapy optionally combined with an anti-CD20 antibody and/or RT. Only a minority of patients (e.g., patients with early relapse after intensive first-line treatment) require second-line treatment with HDCT and ASCT.[87,88]

Given the lack of CD30 on LP cells, the CD30-directed antibody–drug conjugate BV does not play a role in the treatment of NLPHL. The same is true for checkpoint inhibitors targeting the PD-1/PD-L1 axis.

Recommendations:

- Patients with Stage IA NLPHL without clinical risk factors should be treated with 30 Gy involved-site RT alone (2A).
- In early stages other than Stage IA without clinical risk factors, approaches also used in cHL optionally combined with an anti-CD20 antibody should be considered as available data indicate very good outcomes (2A).
- In advanced NLPHL, the management strategy for the individual patient should be chosen based on factors such as age, lymphoma burden, affected sites, and systemic symptoms; it can range from active surveillance to intensive chemotherapy in combination with an anti-CD20 antibody (4B).
- In histologically confirmed NLPHL recurrence, treatment should be chosen individually based on factors such as age, previous treatment, and stage at relapse. Treatment options range from single-agent anti-CD20 antibody treatment to HDCT and ASCT (4B).
- BV and PD-1 inhibitors should not be used in NLPHL (5A).

METHODOLOGY

Different aspects of the development of the guidelines are summarized in Supplement S4.

AUTHOR CONTRIBUTIONS

Dennis A. Eichenauer: Conceptualization; investigation; writing—original draft; methodology; visualization; writing—review and editing; resources; supervision. **Marc André**: Resources; investigation; writing—original draft. **Peter Borchmann**: Resources; investigation; writing—original draft. **Graham P. Collins**: Investigation; resources; writing—original draft. **Ian Doherty**: Investigation; writing—original draft. **Hans-Theodor Eich**: Resources; investigation; writing—original draft. **Massimo Federico**: Resources; investigation. **Alexander Fossa**: Investigation; writing—original draft; resources. **Sylvia Hartmann**: Investigation; resources; writing—original draft. **Martin Hutchings**: Investigation; writing—original draft; resources. **Timothy Illidge**: Investigation; writing—original draft; resources. **Carsten Kobe**: Investigation; writing—original draft; resources. **Wouter J. Plattel**: Investigation; writing—original draft; resources. **Lena Specht**: Investigation; writing—original draft; Resources. **Anna Sureda**: Investigation; writing—original draft; resources. **Jan M. Zaucha**: Investigation; writing—original draft; resources. **Joseé M. Zijlstra**: Investigation; writing—original draft; resources. **Igor Aurer**: Conceptualization; investigation; writing—original draft; writing—review and editing; methodology; visualization; resources; supervision.

CONFLICT OF INTEREST STATEMENT

M.A. received honoraria for advisory work from Beigene, Bristol Myers-Squibb, Gilead, Incyte, Sobi, and Takeda and travel grants from AbbVie, AstraZeneca, Bristol Myers-Squibb, Celgene, Gilead, Roche, and Takeda. G.P.C. received honoraria for speaker and advisory work from Takeda and research funding from BMS. M.H. served as consultant or advisor for or received honoraria from AbbVie, Arvinas, AstraZeneca, Bristol Myers-Squibb, Genmab, Johnson&Johnson, Roche, and Takeda and received institutional research support from AbbVie, AstraZeneca, Bristol Myers-Squibb, Genentech, Genmab, Incyte, Johnson&Johnson, Merck, Novartis, Roche, Seattle Genetics, and Takeda. T.I. received honoraria for speaker and advisory work from Takeda. L.S. received honoraria for speaker and advisory work from Kyowa Kirin. A.S. received honoraria from Takeda, BMS/Celgene, and MSD, served as consultant for Takeda, BMS/Celgene, and MSD, and received research funding from Takeda. Ja.M.Z. served as consultant or advisor for or received honoraria from AbbVie, AstraZeneca, Bristol Myers-Squibb, Pfizer, Johnson&Johnson, Roche, and Takeda and received institutional research support from Bristol Myers-Squibb, Roche. and Takeda. Jo.M.Z. received honoraria and research funding from Takeda, AbbVie, and Roche. I.A. received honoraria or served as a consultant or speaker for AbbVie, AstraZeneca, Beigene/BeOne, Eli Lilly, Johnson&Johnson, Novartis/Sandoz, Pfizer, Roche, Sobi, and Takeda. The other authors declare no potential conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

FUNDING

This research received no funding.

SUPPORTING INFORMATION

Additional supporting information can be found in the online version of this article.

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