

Clinical Practice Guideline

Diffuse Large B-Cell Lymphoma and Related Entities

Diagnosis, Treatment, and Follow-Up

Moritz Ernst, Ulrich Dührsen, Dirk Hellwig, Georg Lenz, Nicole Skoetz, Peter Borchmann

Summary

Background: Diffuse large B-cell lymphoma (DLBCL) is the most common malignant B-cell neoplasm, with an incidence of 5.6 per 100 000 persons per year and a mean age of onset of approximately 65 years. It is an aggressive type of non-Hodgkin's lymphoma requiring urgent treatment with curative intent. Evidence-based guidelines have not been available to date.

Methods: For this first international evidence-based DLBCL-specific guideline, various systematic literature searches were performed. 5 systematic reviews, 21 randomized controlled trials (RCTs), and 36 non-randomized studies were used to formulate 42 recommendations. 142 were formulated on the basis of expert consensus. All recommendations were approved in a structured consensus-finding process.

Results: For staging, combined positron emission tomography and computed tomography (PET/CT) should be performed (evidence: a prospective registry study). For all patients with a new diagnosis of DLBCL and without contraindications, R-CHOP based immunochemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) should be initiated with curative intent (evidence: RCTs). The individual treatment strategy is tailored to the patient's age and risk constellation. Once immunochemotherapy has been completed, PET/CT should be performed again to check for remission. Patients with PET-positive residual disease that is amenable to radiotherapy should be treated with consolidating irradiation (evidence: retrospective cohort study).

Conclusion: This clinical practice guideline on the diagnosis, treatment, and follow-up of patients with DLBCL and related entities provides a standardized clinical management approach, identifies areas where improvement would be desirable, and can serve as a basis for the development of further studies.

Cite this as:

Ernst M, Dührsen U, Hellwig D, Lenz G, Skoetz N, Borchmann P:
Clinical practice guideline: Diffuse large B-cell lymphoma and related entities—
diagnosis, treatment, and follow-up. Dtsch Arztebl Int 2023; 120: 289–96.
DOI: 10.3238/arztebl.m2023.0035

With an incidence of around 5.6 per 100 000 in the general population, diffuse large B-cell lymphoma (DLBCL) is the most commonly occurring non-Hodgkin's lymphoma (1). The median age at onset of the disease is 65 years. DLBCL is found slightly more often in men than in women (ratio 1.2:1) (2). In principle, DLBCL can be treated curatively with immunochemotherapy. One established standard is the R-CHOP regimen, with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (3). An overview of the abbreviations for all treatment schedules can be found in *Table 1*. R-CHOP achieves cure in around 70% of patients with DLBCL (4), and since its introduction in 2002 this regimen has formed the basis for further improvement of the survival rate in numerous studies. However, our knowledge of DLBCL has improved greatly in the intervening years. At the histopathological and molecular level, distinct biological subgroups can be clearly distinguished; these are often small and mostly do not diverge in terms of diagnosis and treatment from the largest group, namely DLBCL, NOS (not otherwise specified) (5). Most important from the point of view of treatment are the subforms of primarily mediastinal large B-cell lymphoma, DLBCL at “immunoprivileged sites” (central nervous system, testicles), and DLBCL associated with infection (human immunodeficiency virus [HIV], *Helicobacter pylori*) (see the section entitled “Related entities” below).

Metabolic imaging by means of positron emission tomography/computed tomography (PET/CT) with F-18 fluorodeoxyglucose has opened the door to more precise definition of the disease stage and adjustment of treatment strategies to the response behavior of individual lymphomas (6–8). Moreover, recent years have seen the advent of several relevant approaches that have the potential to improve the results of first-line therapy in patients that cannot be cured by such treatment. Against this backdrop, the standardization of diagnosis and treatment, definition of risk groups, organization of the numerous new treatment options into evidence-based treatment algorithms, and identification of questions that still need to be resolved are of vital clinical importance.

This clinical practice guideline is the result of cooperation among all relevant professional groups to review and disseminate the available evidence (9).

Department I of Internal Medicine, Faculty of Medicine and University Hospital Cologne, University of Cologne: Moritz Ernst, Prof. Dr. med. Nicole Skoetz, Prof. Dr. med. Peter Borchmann

Clinic for Hematology, University Hospital Essen: Prof. Dr. med. Ulrich Dührsen

Department for Nuclear Medicine, University Hospital Regensburg: Prof. Dr. med. Dirk Hellwig

Department of Medicine A for Hematology, Oncology, and Pneumology, University Hospital Münster: Prof. Dr. med. Georg Lenz

TABLE 1

Treatment schedules

Abbreviation	Meaning
Anti-CD19 CAR T-cell-T	CAR (chimeric antigen receptor) T-cell therapy directed against CD19
APBSCT	Autologous peripheral blood stem cell transplantation
BR	Bendamustine, rituximab
HDCT	High-dose chemotherapy
Pola-BR	Polatuzumab vedotin, bendamustine, rituximab
R-ACVBP	Rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone
(R)-CHOEP	(Rituximab), cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone
(R)-CHOP	(Rituximab), cyclophosphamide, doxorubicin, vincristine, prednisone
R-CHP Polatuzumab	Rituximab, cyclophosphamide, doxorubicin, prednisone, polatuzumab vedotin
R-DHAP	Rituximab, dexamethasone, cytarabine, cisplatin
R-GDP	Rituximab, gemcitabine, dexamethasone, cisplatin
R-Gem-Ox	Rituximab, gemcitabine, oxaliplatin
R-ICE	Rituximab, ifosfamide, carboplatin, etoposide
R-MegaCHOEP	R-CHOEP with dose escalation (cyclophosphamide, doxorubicin, and etoposide)
R-miniCHOP	Low-dose R-CHOP
R2-miniCHOP	R-miniCHOP, lenalidomide
Tafa-Len	Tafasitamab, lenalidomide

Method

The clinical practice guideline was developed under the leadership of the German Society of Hematology and Medical Oncology (DGHO) by an interdisciplinary group formed of clinical and methodological experts, a patient representative, and members of 32 professional associations and other bodies including a patients' organization. The guideline has been issued by the Oncology Guideline Program (OL) of the Association of the Scientific Medical Societies in Germany (AWMF), the German Cancer Society (DKG), and German Cancer Aid (DKH). The guideline was supported by the DKH in the framework of the OL (DKH project number: 70113822). The participants are listed in full in *eMethods 1*.

Of the publications identified by the systematic literature searches, the data from five systematic reviews, 21 randomized controlled trials (RCT), and 36 non-randomized studies were used to compile 42 evidence-based recommendations directed at answering the key questions (for an example of the search strategy, see *eMethods 2*; for the study selection process, see the *eFigure*). A further 142 recommendations were formulated on the basis of expert consensus. All of the recommendations were approved in a structured consensus-finding process. The different

degrees of recommendation are indicated by "A," "B," and "O". An explanation of their meaning can be found in *Table 2*.

The methods, including the assessment of study quality and certainty of evidence, are described in detail in the guideline report (10). In this article, study results that supplement the evidence prepared formally in the course of guideline compilation are enclosed in braces.

Results

All recommendations can be found in the guideline (9), together with information on other care-related topics, e.g., rehabilitation and follow-up, supportive treatment, psycho-oncology, and exercise therapy. The long version, the short version, and the guideline report are available on the websites of the AWMF and the OL and via the OL's guideline app (11–13). A patient guideline is in preparation.

Diagnosis and other pretherapeutic measures

Biopsy and histopathological diagnosis/tissue harvesting

The procedure of choice to establish the diagnosis of DLBCL is lymph node excision or another form of open biopsy, as long as the intervention is practicable and involves no more than low risk (degree of recommendation: A; expert consensus). In cases where this is impracticable and/or the risk would be high, punch biopsy guided by ultrasonography or computed tomography should be preferred to open biopsy (B; expert consensus). Aspiration cytology should not be used for diagnosis (A; expert consensus).

Molecular diagnosis

For extended diagnostic work-up, particularly to differentiate DLBCL/high-grade B-cell lymphoma with rearrangement of *MYC* and *BCL2* from Burkitt's lymphoma, supplementary cytogenetic (interphase) testing should be performed (B; expert consensus).

Positron emission tomography/computed tomography

If curative treatment is intended, PET/CT with F-18 fluorodeoxyglucose should be carried out to determine how far the tumor has spread (A; PET/CT versus CT-guided first-line treatment: 1-year overall survival hazard ratio [HR] 0.63, 95% confidence interval [0.4; 1.0], result of a prospective registry study of 520 patients including 308 with DLBCL [6]). If cure is not the goal, the measures to establish spread can be scaled down (O; expert consensus).

Bone marrow biopsy

When the treatment goal is cure and PET/CT is used for staging, bone marrow biopsy is unnecessary in the following situations: demonstration of bone marrow involvement by PET/CT, advanced spread (Ann Arbor stage III or IV), limited spread (Ann Arbor stage I or II) but significant bulk (large tumor volume with ≥ 7.5 cm longitudinal diameter), and/or one or more unfavorable

factors on the age-adjusted International Prognostic Index (aaIPI) (A).

Staging

DLBCL should be staged according to its spread using the Lugano modification of the Ann Arbor classification (A; expert consensus).

Clinical prognosis scores

On initial diagnosis of DLBCL, the International Prognostic Index (IPI) should be used to predict what course the disease will take (A; expert consensus). Treatment should be guided by the aaIPI score together with the prognostic factor bulk (A; expert consensus).

Treatment plan

The treatment plan for each individual case of DLBCL should be discussed and approved by an interdisciplinary tumor board (B; expert consensus). Before treatment begins, it should be ascertained whether the treatment can be given in the framework of a clinical study (B; expert consensus).

The onset of treatment with curative intent

If the goal is cure, the treatment of DLBCL should begin as soon as the histological diagnosis is known and supplementary diagnostic testing has taken place (A; expert consensus).

Preservation of fertility

Patients who still intend to have children and are going to be exposed to potentially gonadotoxic chemotherapy or radiotherapy should be informed about all currently available fertility-preserving procedures (A; expert consensus).

First-line treatment

All patients with a new diagnosis of DLBCL and unrestricted treatability receive R-CHOP-based chemotherapy with curative intent. The precise therapeutic strategy depends especially on the individual patient's age and risk constellation. The recommendations are depicted in *Figure 1*.

The first-line treatment of young patients (≤ 60 years)

All young patients with unrestricted treatability who are not in clinical studies should receive immunochemotherapy with curative intent, using R-CHOP or a similar protocol (A; R-CHOP versus CHOP: 3-year overall survival rate 93% [90; 95] versus 84% [80; 88], result of a RCT with 842 patients [15]).

In patients who are at high risk of a central nervous system (CNS) relapse and have no contraindications, prophylactic treatment of the CNS with high-dose systemic methotrexate can be considered (0; expert consensus).

The treatment of young patients with a very favorable prognosis

Young patients with a very favorable prognosis (aaIPI = 0, tumor not bulky) should be treated with

TABLE 2

Grades of recommendation

Strength	Description
A	Strong recommendation
B	Recommendation
0	Recommendation open

four cycles of CHOP in combination with six doses of rituximab (A; four cycles of R-CHOP + two cycles of rituximab versus six cycles of R-CHOP: 3-year overall survival rate 99% [98; 100] versus 98% [96; 99], result of a RCT with 588 patients including 499 with DLBCL [16]).

The treatment of young patients at high risk

Together with the conventional six to eight cycles of R-CHOP, young patients at high risk should be offered one of the following treatment options:

- In aaIPI 1: R-ACVBP
- In aaIPI 2–3: R-CHOEP
- In IPI 2–5: R-CHP polatuzumab

(B).

The recommendations and the evidence on which they are based are displayed in *Table 3*.

Final staging for the planning of continued treatment

After the conclusion of immunochemotherapy in patients with DLBCL, PET/CT should be carried out to check whether remission is present (A; PET/CT versus CT: agreement with reference standard 91.67%, k [weighted coefficient] 0.7 [0.4; 0.9] versus 86.43%, k 0.4 [0.1; 0.8], result of a RCT with 72 patients [21]). NB: In the out-of-hospital setting in Germany, this use of PET/CT is not included in the catalog of services covered by statutory health insurance, so reimbursement of the costs is not guaranteed.

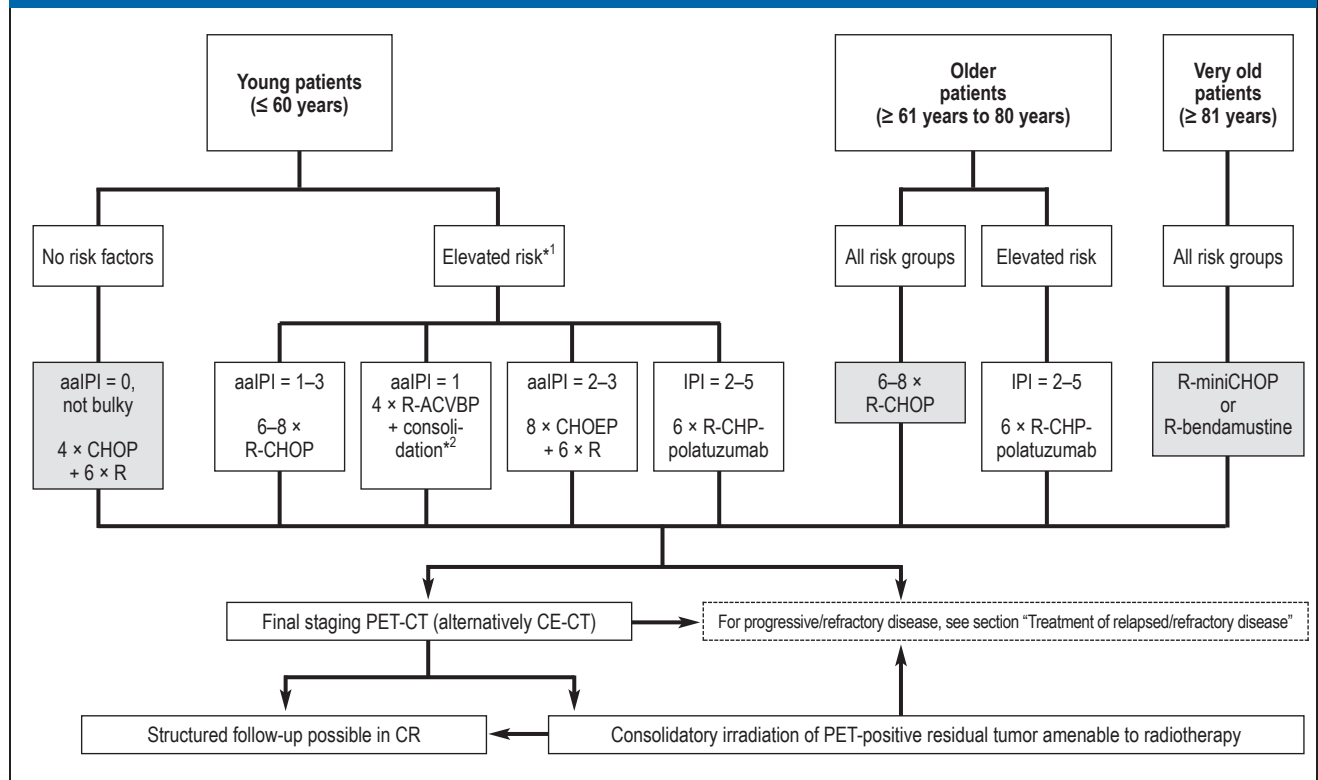
The response to treatment should be assessed with reference to the Lugano classification (B; expert consensus). Against the backdrop of new data on the indication for consolidative radiotherapy, final staging by means of PET/CT is of considerable therapeutic significance (see "Radiotherapy").

Radiotherapy

Patients with PET-positive residual tumor amenable to radiation treatment should receive consolidative radiotherapy (A; radiotherapy versus no radiotherapy: 3-year overall survival rate 80% [71; 87] versus 44% [34; 54], result of a retrospective cohort study with 723 patients [8]).

The treatment should be given in the form of involved-site radiotherapy (A; expert consensus). This is oriented on the lymph nodes originally affected but takes account of the treatment response to systemic therapy, the PET-positive residual tumor, and healthy

FIGURE 1



Treatment algorithm for first-line therapy

*1 The different regimes for young patients with elevated risk have not yet been compared with each other.

*2 In the LNH03–2B study, consolidation comprised two doses of methotrexate, four cycles of rituximab/ifosfamide/etoposide, and finally two cycles of cytarabine (14). aalPI, Age-adjusted International Prognostic Index; CE-CT, contrast-enhanced computed tomography; CR, complete remission; IPI, International Prognostic Index; PET-CT, positron emission tomography/computed tomography; R-ACVBP, rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone; R-Bendamustine, rituximab, bendamustine; CHOEP, cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone; (R)-CHOP, (rituximab), cyclophosphamide, doxorubicin, vincristine, prednisone; R-CHP-polatuzumab, rituximab, cyclophosphamide, doxorubicin, prednisone, polatuzumab vedotin; R-miniCHOP, low-dose R-CHOP regimen

adjacent organs. The safety margins are narrower than with earlier treatment concepts.

Treatment of older patients (> 60 years)

In older patients with a high tumor burden, prephase treatment with prednisone should be given (B; expert consensus). In analogy to young patients, older patients who are fit and have unrestricted treatability should receive potentially curative immunochemotherapy in the form of R-CHOP or a similar regimen (A; R-CHOP versus CHOP: 10-year overall survival rate 43.5% [36.4; 5.4] versus 27.6% [21.4; 34.3], median overall survival 8.4 years [5.4; not reached] versus 3.5 years [2.2; 5.5], result of a RCT with 399 patients [3]; estimated 3-year survival rate [excluding patients with maintenance treatment] 67% versus 58%, HR 0.72 [0.52; 1.00], result of a RCT with 632 patients [22]; 3-year overall survival rate 78.1% [73.2; 83.0] versus 67.7% [62.0; 73.5], result of a RCT with 613 patients including 471 with DLBCL [23]). Additional evidence underlying this recommendation can be found in the guideline.

In IPI 2–5, in analogy to young patients, R-CHP-polatuzumab should be offered (B; for evidence, see the recommendation of R-CHP-

polatuzumab for young patients at high risk). Patients > 80 years of age and those with comorbidities should be offered reduced-dose treatment, e.g., R-miniCHOP or BR (bendamustine, rituximab) (B; 2-year overall survival rate 66% [56.4; 74] versus 65.7% [55.6; 74.1], result of a RCT with 249 patients [24]; {BR median progression survival 10 months, result of a prospective cohort study with 45 patients [25]; median progression-free survival 7.7 months, result of a prospective cohort study with 14 patients [26]}).

Treatment of relapsed/refractory disease

After failure of first-line treatment, the choice is between a treatment strategy with primarily curative and one with primarily palliative intent. It can happen that curative treatment swiftly fails or that palliative treatment leads in individual cases to very long remissions, particularly in third-line or later treatment. The recommendations are depicted in Figure 2.

Diagnosis of first relapse

Whenever signs of relapse are observed (e.g., lymph node or organ enlargement, organ dysfunction, pyrexia of unknown origin, night sweats, weight loss, elevated

TABLE 3

Treatment of young patients with elevated risk

Risk status	Recommended treatment	Evidence		
		Comparison	Outcome(s)	Study
aalPI 1	R-ACVBP + consolidation	R-ACVBP versus R-CHOP	3-year overall survival: 92%; 95% CI [87; 95] versus 84%; [77; 89]	RCT, 380 patients, including 317 with DLBCL (14)
aalPI 2–3	8× CHOEP + 6× R	R-CHOEP-14 versus R-MegaCHOEP	10-year overall survival: 72%; [63; 81] versus 59%; [50; 68]	RCT, 262 patients, including 202 with DLBCL (17)
		R-CHOEP-14 versus R-CHOP-14	5-year overall survival: 74% versus 50%; multivariable analysis: HR 0.64, [0.4; 1.0]	Retrospective cohort study, 1304 patients (18)
		R-CHOEP-14 versus R-CHOP-14	4-year overall survival: 75% versus 62%; multivariable analysis: HR 0.5 [0.2; 1.0]	Retrospective cohort study, 159 patients (19)
IPI 2–5	R-CHP polatuzumab	R-CHP polatuzumab versus R-CHOP	2-year overall survival: 88.7%; [85.7; 91.6] versus 88.6%; [85.6; 91.6] Progression-free survival after 2 years: 76.7%; [72.7; 80.8] versus 70.2%; [65.8; 74.6]	RCT, 879 patients (20)

aalPI, Age-adjusted International Prognostic Index; CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; HR, hazard ratio; IPI, International Prognostic Index; R-ACVBP, rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone, consolidated with methotrexate, rituximab, etoposide, ifosfamide, and cytarabine; (R)-CHOEP, (rituximab), cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone; (R)-CHOP, (rituximab), cyclophosphamide, doxorubicin, vincristine, prednisone; R-CHP-polatuzumab, rituximab, cyclophosphamide, doxorubicin, prednisone, polatuzumab vedotin; R-MegaCHOEP, R-CHOEP with dose escalation (cyclophosphamide, doxorubicin, and etoposide); RCT, randomized controlled trial

serum lactate hydrogenase, blood count anomalies), biopsy should ensue with the aim of histological confirmation (A; expert consensus).

When administering potentially curative therapy, PET/CT should be carried out to determine the status before treatment of the relapse, to stage relapsed or refractory disease, and to monitor the response to treatment (A; expert consensus). NB: In the out-of-hospital setting in Germany, PET/CT for this indication is not included in the catalog of services covered by statutory health insurance, so reimbursement of the costs is not guaranteed.

The finding of stable disease or of progressive disease in response to at least two cycles of immunochemotherapy should, if cure is still the goal, prompt reconfiguration of the treatment plan (A; expert consensus).

Second-line treatment with curative intent for patients with early relapse amenable to high-dose therapy

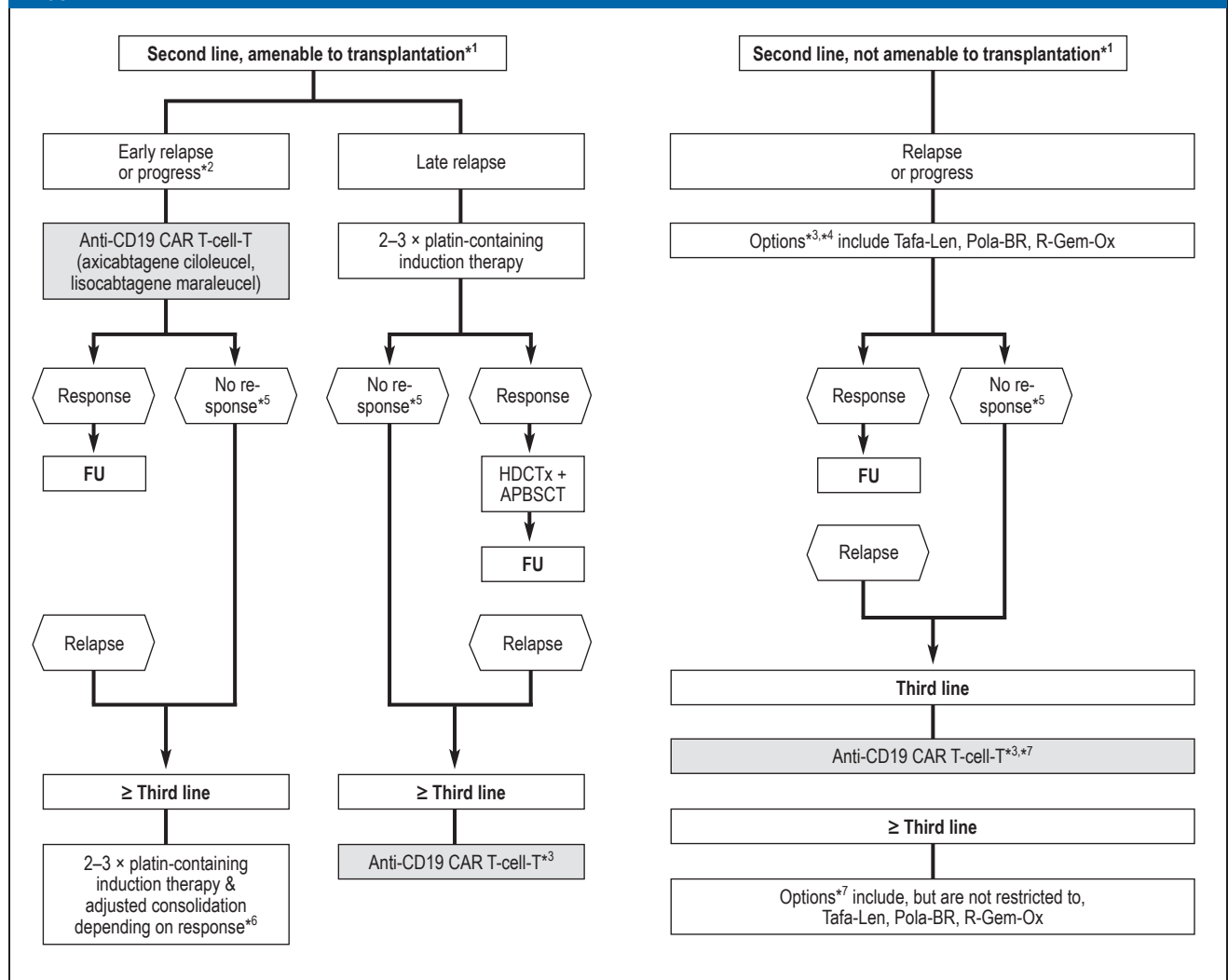
Patients with an early relapse of DLBCL (within 12 months after the end of primary treatment) who are candidates for high-dose treatment should receive anti-CD19 chimeric antigen receptor (CAR) T-cell therapy with axicabtagene ciloleucel or lisocabtagene maraleucel (B; axicabtagene ciloleucel versus high-dose treatment: overall survival [median follow-up 24.9 months] HR 0.73 [0.53; 1.01], result of a RCT with 359 patients including 246 with DLBCL

[28]; lisocabtagene maraleucel versus high-dose treatment: 12-month overall survival rate 79.1% [67.1; 91.1] versus 64.2% [50.5; 77.9], result of a RCT with 184 patients including 102 with DLBCL NOS [29]). NB: The EMA has not yet approved the use of lisocabtagene maraleucel.

Second-line treatment with curative intent for patients with late relapse amenable to high-dose therapy

Patients with a late relapse who are candidates for high-dose treatment should receive platin-containing induction therapy in combination with rituximab (e.g., R-GDP, R-DHAP, or R-ICE), followed on achievement of remission by autologous hematopoietic stem cell transplantation (B; {high-dose treatment with autologous hematopoietic stem cell transplantation versus conventionally dosed treatment: 5-year overall survival rate 53% versus 32%, $p = 0.038$, result of a RCT with 215 patients with non-Hodgkin's lymphoma [30]}). While the cited study implies an advantage of high-dose treatment with autologous hematopoietic stem cell transplantation over treatment with conventional dosage, evidence from three other RCT comparing various induction therapy protocols (R-GDP, R-DHAP, and R-ICE, among others) was taken into consideration before the recommendation was formulated; these RCT yielded no indication of differences in efficacy among the protocols. The evidence can be found in the guideline.

FIGURE 2



Treatment of relapsed/refractory diffuse large B-cell lymphoma (DLBCL)

*1 There are no validated methods for determining eligibility for HDCT (high-dose chemotherapy). The mortality associated with HDCT can be established by means of the HCT-CI (hematopoietic cell transplantation-specific comorbidity index) (27).

*2 Defined as regression or progression of disease within 12 months after conclusion of the first-line treatment

*3 There exists no direct comparison of the various treatment options. The potential benefits and risks must be weighed up in each individual case when considering the indication. The use of various CAR T-cell treatments depends on their approval status.

*4 Patients with a PET-positive residual tumor following systemic second-line treatment receive consolidatory irradiation.

*5 Response is defined as complete or partial metabolic remission, corresponding to the Lugano criteria.

*6 In chemotherapy-sensitive disease there is the option of consolidation with autologous or allogeneic stem cell transplantation.

*7 In the third and later lines individual consideration of the benefits and risks is necessary; this influences the order of the treatment recommendations.

APBSCT, Autologous peripheral blood stem cell transplantation; anti-CD19 CAR T-cell-T, chimeric antigen receptor (CAR) T-cell treatment directed against CD19; FU, follow-up; HDCT, high-dose chemotherapy; Pola-BR, polatuzumab vedotin, bendamustine, rituximab; R-Gem-Ox, rituximab, gemcitabine, oxaliplatin; Tafa-Len, tafasitamab, lenalidomide

Options for second-line systemic treatment

Patients who are not suitable for high-dose treatment should be offered a less intensive form of immunochemotherapy (e.g., R-Gem-Ox or Pola-BR) or a cytostatic-free combination of drugs (Tafa-Len) to bring about remission (recommendation strength A; Pola-BR versus BR: overall survival [median follow-up 48.9 months] HR 0.42 [0.24; 0.75], result of a RCT with 80 patients [31]; Tafa-Len: median overall

survival [median follow-up 42.7 months] 33.5 months [18.3; not reached], result of a single-arm prospective study with 81 patients [32]).

Treatment of second and later relapses with primarily curative intent

In treatment with primarily curative intent, patients with a second or subsequent relapse or with progressive DLBCL should undergo CAR T-cell therapy, as

long as this has not already been administered as second-line treatment (A; expert consensus).

Related entities

The diagnostic work-up and treatment of entities related to DLBCL are the same as for DLBCL itself. Expert consensus-based recommendations have been formulated for some special situations. In patients with HIV-associated lymphoma, the combined antiretroviral therapy should be continued during treatment of the lymphoma (A; expert consensus). In refractory primarily mediastinal B-cell lymphoma, checkpoint inhibitors with or without brentuximab vedotin are an additional treatment option (B; expert consensus).

In testicular lymphoma the affected testicle should be resected (B; expert consensus) and the contralateral testicle should be irradiated after the end of the course of immunochemotherapy (B; expert consensus). In gastric and duodenal lymphoma, treatment of the lymphoma should be accompanied by pharmacological eradication of *Helicobacter pylori* (B; expert consensus).

In peripheral lymphoma with simultaneous CNS involvement, the anthracycline-containing treatment should be supplemented with a form of systemic therapy that penetrates into the CNS, e.g., a methotrexate-based protocol (A; expert consensus). After the end of this course, consolidatory treatment should be given: preferably high-dose therapy, alternatively irradiation (B; expert consensus). DLBCL located primarily in the CNS with no manifestation elsewhere is not within the scope of the guideline, as it is diagnosed and treated according to different principles.

Research questions

Topics identified as in particularly great need of research were presented systematically in a separate section. They included questions around the following: preservation of fertility; CNS relapse; adjustment of dose intensity to elderly patients' tolerance of chemotherapy and evaluation of geriatric comanagement; use of the total metabolic tumor volume on PET/CT as an instrument for prognosis and treatment guidance; and early prediction of the failure of first-line treatment.

Discussion

This clinical practice guideline is the first evidence-based guideline anywhere in the world specific to DLBCL. It presents the current state of knowledge on the diagnosis, treatment, and follow-up of patients with DLBCL and related entities. By virtue of its evidence- and consensus-based key recommendations together with description of topical research questions it standardizes clinical care, identifies potential for optimization, and provides a basis for the planning of future research.

Acknowledgment

We thank the many committed participants without whose work this guideline could not have been compiled.

Conflict of interest statement

PB has received funding from German Cancer Aid, financial support from

Novartis and Incyte, and consulting fees from Roche, Novartis, Gilead, and BMS/Celgene.

UD has received financial support from Celgene/Bristol-Myers Squibb. He is a member of the data monitoring committee of AvenCell Europe GmbH.

GL has received financial support from Roche, AGIOS, AQUINOX, AstraZeneca, Gilead, Janssen, Bayer, and Morphosys; consulting fees from Roche, Gilead, BMS, Janssen, Bayer, Novartis, AstraZeneca, Takeda, Abbvie, Incyte, Morphosys, Genmab, Karyopharm, Constellation, Genase, Immagine, Hexal/Sandoz, Sobi, PentixaPharm, Miltenyi, and ADC Therapeutics; payments for educational events from Roche, Janssen, Gilead, BMS, Bayer, AstraZeneca, Novartis, Takeda, Abbvie, Incyte, Morphosys, Sobi, and Hexal/Sandoz; and reimbursement of travel costs and congress fees from Janssen, Abbvie, Roche, Novartis, and Morphosys. He is a member of the advisory board for the following: Roche, Gilead, Janssen, Bayer, BMS, Novartis, AstraZeneca, Takeda, Abbvie, Incyte, Morphosys, Genmab, Karyopharm, Hexal/Sandoz, Constellation, ADC Therapeutics, PentixaPharm, and Miltenyi.

The remaining authors declare that no conflict of interest exists.

Manuscript submitted on 15 November 2022, revised version accepted on 2 February 2023

Translated from the original German by David Roseveare

Clinical guidelines are not peer-reviewed in the *Deutsches Ärzteblatt*, as well as in many other journals, because clinical (S3) guidelines are texts which have already been repeatedly evaluated, discussed and broadly consented by experts (peers).

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Corresponding author
 Prof. Dr. med. Peter Borchmann
 Klinik I für Innere Medizin
 Universitätsklinikum Köln
 Kerpener Str. 62
 50937 Köln, Germany
peter.borchmann@uk-koeln.de

Cite this as:
 Ernst M, Dührsen U, Hellwig D, Lenz G, Skoetz N, Borchmann P:
 Clinical practice guideline: Diffuse large B-cell lymphoma and
 related entities—diagnosis, treatment, and follow-up.
Dtsch Arztebl Int 2023; 120: 289–96. DOI: 10.3238/arztebl.m2023.0035

► **Supplementary material**

eMethods and eFigure:
www.aerzteblatt-international.de/m2023.0035

Supplementary material to:

Clinical Practice Guideline: Diffuse Large B-Cell Lymphoma and Related Entities

Diagnosis, Treatment, and Follow-Up

by Moritz Ernst, Ulrich Dührsen, Dirk Hellwig, Georg Lenz, Nicole Skoetz, and Peter Borchmann

Dtsch Arztebl Int 2023; 120: 289–96. DOI: 10.3238/arztebl.m2023.0035

eMETHODS 1

Professional Associations, Organizations, Working Groups, and Participants

Participating professional associations and organizations:

- 1) German Society of Hematology and Medical Oncology (DGHO) (lead management)
- 2) Working Group on Imaging in Oncology
- 3) Working Group on Psycho-Oncology of the German Cancer Society (PSO)
- 4) Infectious Diseases Working Party (AGIHO) of the DGHO
- 5) Working Group for Internal Oncology of the German Cancer Society
- 6) Working Group for Oncological Pharmacology (OPH)
- 7) Working Group on Oncological Rehabilitation and Social Medicine (AGORS)
- 8) Working Group on Prevention and Integrative Oncology (PRIO) in the German Cancer Society
- 9) Working Group Radiation Oncology (ARO)
- 10) Working Group on Supportive Measures in Oncology (AGSMO)
- 11) Professional Association of Hematologists and Oncologists in Private Practice (BNHO)
- 12) Professional Association of German Pathologists (BDP)
- 13) German Society of Andrology (DGA)
- 14) German Society of Surgery (DGCH)
- 15) German Society for Endoscopy and Imaging Procedures (DGE-BV)
- 16) German Society of Specialist Nursing and Functional Services (DGF)
- 17) German Society for Geriatrics (DGG)
- 18) German Society of Gynecology and Obstetrics (DGGG)
- 19) German Society of Internal Medicine (DGIM)
- 20) German Society of Nuclear Medicine (DGN)
- 21) German Society for Palliative Medicine (DGP)
- 22) German Society for Pathology (DGP)
- 23) German Society of Radiation Oncology (DEGRO)
- 24) German Society of Ultrasound in Medicine and Biology (DEGUM)
- 25) German Society of Urology (DGU)
- 26) German Leukemia and Lymphoma Aid (DLH)
- 27) German Network Health Service Research
- 28) German Radiology Society
- 29) German Network for Evidence-Based Medicine (DNEbM)
- 30) German Lymphoma Alliance
- 31) Competence Network Malignant Lymphomas
- 32) German Oncology Nursing Society (*Konferenz Onkologischer Kranken- und Kinderkrankenpflege*, KOK)

Working groups (leaders):

- Epidemiology, Etiology and Risk Factors (Prof. Dr. German Ott)
- Diagnosis I (Prof. Dr. German Ott, Prof. Dr. Lorenz Trümper)
- Diagnosis II (Prof. Dr. Ulrich Dührsen, Prof. Dr. Dirk Hellwig)
- First-Line Treatment (Prof. Dr. Georg Lenz, Prof. Dr. Lorenz Trümper, Prof. Dr. Hans-Theodor Eich)
- Special Subgroups (Prof. Dr. Georg Lenz, Prof. Dr. Lorenz Trümper)
- Treatment of Relapsed/Refractory Disease (Prof. Dr. Peter Borchmann, Prof. Dr. Björn Chapuy, Prof. Dr. Bertram Gläß, Dr. Viola Pöschel, Prof. Dr. Nicole Skoetz, Prof. Dr. Bastian von Tresckow)

- Rehabilitation and Follow-Up (Prof. Dr. Ulrich Dührsen, Dr. Julia Thiemer)
 - Supportive Therapy, Psycho-Oncology, Palliative Medicine, Nutrition, Exercise Therapy, Complementary Medicine (Dr. Markus Horneber, Prof. Dr. Steffen Simon)
 - Research Questions (Moritz Ernst, Prof. Dr. Peter Borchmann)
 - Quality Indicators (Simone Wesselmann*, Johannes Rückher*)
- * External consultants

Participants (in alphabetical order):

- Prof. Dr. Freerk Baumann^h
- Dr. Walter Baumann (27*¹)^g
- Dr. Christian Berdel^d
- Dr. Moritz Bewarder
- Prof. Dr. Peter Borchmann (1*¹, 31*²)^{e, f, i, j}
- PD Dr. Bettina Böttcher (18*²)^{c, g, i}
- PD Dr. Geothy Chakupurakal (11)^g
- Prof. Dr. Björn Chapuy^{e, f}
- Prof. Dr. Markus Dietlein^{c, g}
- Prof. Dr. Christoph Frank Dietrich (15*¹)
- Prof. Dr. Ulrich Dührsen (19*¹)^{b, c, g, i, j}
- Prof. Dr. Hans-Theodor Eich (23*¹)^d
- Moritz Ernstⁱ
- Dr. Birte Friedrichs (1*²)^{d, e}
- Dr. Fabian Frontzek^{d, e, i}
- Dr. Christina Gerlach (21*²)^{h, j}
- Prof. Dr. Bertram Glaß (30*¹)^{b, d, f}
- PD. Dr. Valentin Goede (17*¹)
- Elke Goldhammer (16)
- Prof. Dr. Christian Görg (24*²)
- PD Dr. Jirka Grosse^c
- Dr. Vitaly Heidt (27*²)
- Prof. Dr. Gerhard Held (31*¹)^{d, e}
- Prof. Dr. Dirk Hellwig (20*¹)^{c, f, g, i, j}
- Prof. Dr. Klaus Herfarth (9*², 23*²)
- Dr. Pia Heußner (3*¹)^{c, h}
- Dr. Ulrike Holtkamp (26*¹)^{c, g, h, j}
- Dr. Markus Horneber (10*¹)^h
- Prof. Dr. Kai Hübel^e
- Prof. Dr. Andreas Hüttmann^d
- Dr. Dominic Kaddu-Mulindwa
- Dr. Lukas Käsmann (8*²)
- Prof. Dr. Wolfram Klapper (12/22*²)^c
- Prof. Dr. Frank-Michael Köhn (13*¹, 25*²)^{c, g}
- Prof. Dr. Sabine Kliesch (25*¹)^{c, g}
- Prof. Dr. Carsten Kobe (20*²)^{c, g}
- Prof. Dr. Georg Lenz (1*¹)^{b, d, e}
- PD Dr. Rüdiger Liersch (11)^e
- Prof. Dr. Oliver Micke (8*¹)
- Dr. Michael Oertel^{d, j}
- Prof. Dr. German Ott (12/22*¹)^{a, b}
- Kerstin Paradies (32*¹)
- PD Dr. Thorsten Persigehl (2*¹, 28*²)^{c, g}
- Prof. Dr. Dawid Pieper (29*²)
- Dr. Viola Pöschel (1*¹, 6*²)^{d, f}
- Dr. Anne Pralong^h
- Prof. Dr. Christina Rieger (4*¹)^h
- Prof. Dr. Christian Rübe (9*²)
- PD Dr. Hans Schlößer (14)^b
- Prof. Dr. Heinz Schmidberger (9*¹)
- PD Dr. Martin Schmidt-Hieber (4*²)
- Dr. Tilman Schöning (6*¹)^h

- Prof. Dr. Steffen Simon (21*¹)^h
- Prof. Dr. Nicole Skoetz (29*¹)^{f, j}
- Dr. Julia Thiemer (7*¹)^g
- PD Dr. Lorenz Thurner
- Prof. Dr. Bettina Toth (13*², 18*¹)^{c, g}
- Dr. Hannes Treiber^{d, e}
- PD Dr. Corinna Trenker (24*¹)
- Prof. Dr. Lorenz Trümper (5*¹)^{b, d, e}
- Prof. Dr. Lale Umutlu (2*², 28*¹)^{c, g}
- Prof. Dr. Jörg Janne Vehreschild (4*²)
- Prof. Dr. Bastian von Tresckow^f
- PD Dr. Ulrich Wedding (17*²)^{c, d, i}
- Dr. Rebecca Wurm-Kuczera^{d, e}

The numbers in parentheses identify the representatives of professional associations/organizations

*¹ Voting representative

*² Deputy

^a Working Group on Epidemiology, Etiology, and Risk Factors

^b Working Group on Diagnosis I

^c Working Group on Diagnosis II

^d Working Group on First-Line Treatment

^e Working Group on Special Subgroups

^f Working Group on Treatment of Relapsed/Refractory Disease

^g Working Group on Rehabilitation and Follow-Up

^h Working Group on Supportive Therapy, Psycho-Oncology, Palliative Medicine, Nutrition, Exercise Therapy, Complementary Medicine

ⁱ Working Group on Research Questions

^j Working Group on Quality Indicators

eMETHODS 2

Example of Search Strategy—Randomized Controlled Trials and Systematic Reviews

Cochrane Central Register of Controlled Trials (Central, 2020, Issue 03) in the Cochrane Library
(search conducted on 24.03.2020) (1760 records)

#Searches

- 1 HGBCL:ti,ab,kw
- 2 „high grade“ NEAR/2 lymphom*):ti,ab,kw
- 3 (aggressive* NEAR/2 lymphom*):ti,ab,kw
- 4 MeSH descriptor: [Lymphoma, Large B-Cell, Diffuse] explode all trees
- 5 ((large cell* NEAR/3 lymphom*) or (b-cell NEAR/3 lymphom*) or (bcell NEAR/3 lymphom*) or (lymphoid* NEAR/3 lymphom*) or (histiocytic* NEAR/3 lymphom*) or (plasmablastic* NEAR/3 lymphom*)):ti,ab,kw
- 6 diffuse*:ti,ab,kw
- 7 #5 and #6
- 8 DLBCL:ti,ab,kw
- 9 #1 or #2 or #3 or #4 or #7 or #8

Embase Ovid (1972 up to 24.03.2020) (2051 records)

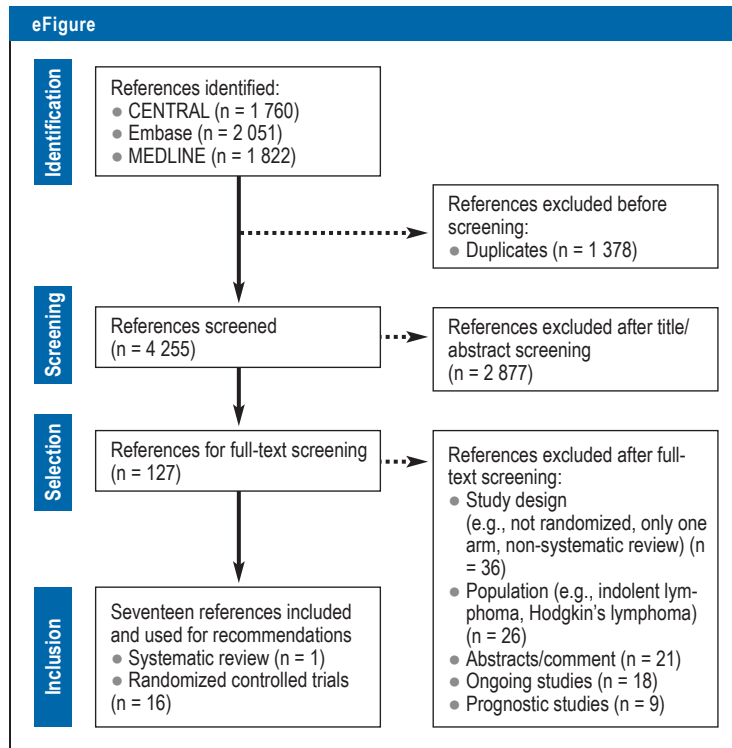
#Searches

- 1 ((high grade* adj2 (malignanc* or lymphom*)) or HGBCL).tw,kw.
- 2 (aggressive* adj3 lymphom*).tw,kw.
- 3 or/1–2
- 4 exp DIFFUSE LARGE B CELL LYMPHOMA/
- 5 intravascular large b cell lymphom*.tw,kw. (((large cell* adj3 lymphom*)
- 6 or (b-cell adj3 lymphom*) or (bcell adj3 lymphom*) or (lymphoid* adj3 lymphom*) or (histiocytic* adj3 lymphom*) or (plasmablastic* adj3 lymphom*)) adj3 diffuse*).tw,kw.
- 7 DLBCL.tw,kw.
- 8 (histiocytic* adj1 lymphom*).tw,kw.
- 9 or/4–8
- 10 RANDOMIZED CONTROLLED TRIAL/
- 11 CONTROLLED CLINICAL STUDY/
- 12 random*.ti,ab.
- 13 RANDOMIZATION/
- 14 INTERMETHOD COMPARISON/
- 15 placebo.ti,ab.
- 16 (compare or compared or comparison).ti.
- 17 (open adj label).ti,ab.
- 18 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.
- 19 DOUBLE BLIND PROCEDURE/
- 20 parallel group\$1.ti,ab.
- 21 (crossover or cross over).ti,ab. ((assign\$ or match or matched or allocation) adj5 (alternate or group\$1 or
- 22 intervention\$1 or patient\$1 or subject\$1 or participant\$1)).ti,ab.
- 23 (controlled adj7 (study or design or trial)).ti,ab.
- 24 (volunteer or volunteers).ti,ab.
- 25 trial.ti.
- 26 or/10–25
- 27 (ANIMAL EXPERIMENT/ or ANIMAL EXPERIMENT/) not (HUMAN EXPERIMENT/ or HUMAN/)
- 28 26 not 27
- 29 (meta-analysis or systematic review).tw.
- 30 (3 or 9) and (28 or 29)
- 31 limit 30 to embase

Medline Ovid (1946 up to 24.03.2020) (1822 records)

#Searches

- 1 ((high grade* adj2 (malignanc* or lymphom*)) or HGBCL).tw,kf.
- 2 (aggressive* adj3 lymphom*).tw,kf.
- 3 or/1–2
- 4 exp LYMPHOMA, LARGE B-CELL, DIFFUSE/
- 5 ((large cell* adj3 lymphom*) or (b-cell adj3 lymphom*) or (bcell adj3 lymphom*) or (lymphoid* adj3 lymphom*) or (histiocytic* adj3 lymphom*) or (plasmablastic* adj3 lymphom*)).tw,kf.
- 6 diffuse*.tw,kf.
- 7 5 and 6
- 8 DLBCL.tw,kf.
- 9 (histiocytic* adj1 lymphom*).tw,kf.
- 10 4or 7 or 8 or 9
- 11 3 or 10
- 12 randomized controlled trial.pt.
- 13 controlled clinical trial.pt.
- 14 randomi?ed.ab.
- 15 placebo.ab.
- 16 clinical trials as topic.sh.
- 17 randomly.ab.
- 18 trial.ti.
- 19 or/12–18
- 20 exp ANIMALS/ not HUMANS/
- 21 19 not 20
- 22 CLINICAL TRIAL, PHASE III/
- 23 („Phase 3“ or „phase3“ or „phase III“ or P3 or „PIII“).ti,ab,kw.
- 24 (22 or 23) not 20
- 25 21 or 24
- 26 (review or review,tutorial or review, academic).pt.
- 27 (medline or medlars or embase or pubmed or cochrane).tw,sh.
- 28 (scisearch or psychinfo or psycinfo).tw,sh.
- 29 (psychlit or psyclit).tw,sh.
- 30 cinahl.tw,sh.
- 31 ((hand adj2 search\$) or (manual\$ adj2 search\$)).tw,sh.
- 32 (electronic database\$ or bibliographic database\$ or computeri?ed database\$ or online database\$).tw,sh.
- 33 (pooling or pooled or mantel haenszel).tw,sh.
- 34 (peto or dersimonian or der simonian or fixed effect).tw,sh.
- 35 (retraction of publication or retracted publication).pt.
- 36 or/27–35
- 37 26 and 36
- 38 meta-analysis.pt.
- 39 meta-analysis.sh.
- 40 (meta-analys\$ or meta analys\$ or metaanalys\$).tw,sh.
- 41 (systematic\$ adj5 review\$).tw,sh.
- 42 (systematic\$ adj5 overview\$).tw,sh.
- 43 (quantitativ\$ adj5 review\$).tw,sh.
- 44 (quantitativ\$ adj5 synthesis\$).tw,sh.
- 45 (quantitativ\$ adj5 synthesis\$).tw,sh.
- 46 (methodologic\$ adj5 review\$).tw,sh.
- 47 (methodologic\$ adj5 overview\$).tw,sh.
- 48 (integrative research review\$ or research integration).tw.
- 49 or/38–48
- 50 37 or 49
- 51 11 and (25 or 50)



Flow chart: Example of study selection process: randomized controlled trials and systematic reviews

This flow chart shows the study selection process for the identification of randomized controlled trials and systematic reviews conducted to answer various questions. The other articles included (guidelines, systematic reviews, randomized controlled trials, and non-randomized studies including registry studies), which were identified in separate searches (sources: CENTRAL, Embase, MEDLINE, GIN, and the websites of the German Institute for Quality and Efficiency in Health Care (IQWiG) and the German Federal Joint Committee (G-BA) are not presented here. All of the searches that were performed are described in detail in the guideline report.