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Diffuse large B-cell lymphoma

Recommendations from the society for diagnosis and therapy of haematological and oncological diseases

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Table of contents

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- Guideline
- Conflict of interests

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1 Summary

Diffuse large B-cell lymphoma (DLBCL) is the most common neoplasm of the lymphatic system. It originates from mature B-cells and is rapidly fatal if left untreated. Rapidly progressive lymph node enlargement and/or extranodal manifestations as well as general symptoms (B symptoms) are characteristic.

The International Prognostic Index allows the assessment of the individual prognosis.

The therapeutic approach is curative. First-line therapy consits of 6 - 8 cycles of the R-CHOP regimen or of protocols similar to R-CHOP. In early stages without any risk factors, a reduction of the number of treatment cycles is possible. The value of radiotherapy is still open. Other unresolved issues are the subject of prospective clinical studies and comprise the application of prognosis- or response-guided therapy, the value of more intensive therapy protocols or the efficacy of new substances.

The cure rate for patients with diffuse large B-cell lymphoma is around 60 to 70%.

2 Basics

2.1 Definition and basic information

The current WHO classification distinguishes diffuse large B-cell lymphoma, not otherwise specified (NOS) from other mature aggressive/blastic B-cell lymphomas [1]. The subtypes of aggressive B-cell lymphomas listed in the WHO classification are differentiated according to clinical parameters (e.g. localization), histological characteristics, immunophenotype. Furthermore, associations with infectious agents or genetic aberrations are of interest. Within the group of diffuse large B-cell lymphomas, NOS, variants can be classified according to morphological criteria (centroblastic, immunoblastic, anaplastic), gene expression ('germinal-center B-cell (GCB)-like', activated B-cell (ABC)-like'), according to immunohistochemical characteristics (in particular CD5, CD30, MYC, BCL2, BCL6, CD10, MUM1) and according to genetic abnormalities (translocation of *MYC*, *BCL2* and/or *BCL6 loci*). More recent genomic classifications allow to distinguish subgroups with characteristic mutation profiles (e.g. EZB, MCD, BN2 or N1 subtype or the C1-C5 clusters) [2].

Treatment of patients with other aggressive large B-cell lymphomas is similar to diffuse large B-cell lymphoma, NOS. They include T-cell/histiocyte-rich large B-cell lymphoma, primary cutaneous diffuse large B-cell lymphoma of the lower extremity ('leg type'), Epstein-Barr virus-positive diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, intravascular

large B-cell lymphoma, the usually CD20-negative plasmablastic lymphoma and follicular lymphoma grade 3b.

Diffuse large B-cell lymphoma, which primarily manifests in the central nervous system (CNS), differs from the aforementioned subtypes in terms of biology and treatment. It is therefore not included in the present recommendations.

2.2 Epidemiology

The incidence of diffuse large B-cell lymphoma is approximately 7 cases per 100,000 inhabitants per year. The disease is more common in Caucasians than in Africans or Asians, and men are more frequently affected than women [3]. The frequency of diagnosis increases with age.

2.3 Pathogenesis

Diffuse large B-cell lymphoma is a heterogeneous diagnostic category. Based on similarities with the presumed cell of origin (COO), the subgroups of germinal center B-cell-like (GCB) and activated B-cell-like (ABC) diffuse large B-cell lymphomas are characterized by the different pattern of gene expression [4]. Ten to 15% of diffuse large B-cell lymphomas cannot be assigned definitively to any of the aforementioned subtypes. Further attempts to reproduce the gene expression patterns by using microarrays or the NanoString technology, using only a few immunohistochemical markers showed heterogeneous results [5]. Subsequent studies, mainly with DNA-based next generation sequencing methods, have identified further molecular subtypes characterized by genetic alterations (mutations, numerical gene copy number changes and chromosomal rearrangements) [2]. The clinical significance of genetic classifications is currently being investigated in clinical studies.

3 Clinical presentation

At the time of diagnosis, rapidly progressive lymph node enlargement and/or extranodal manifestations are usually present. The symptoms depend on the localization of the manifestations and the release of soluble mediators. Bone marrow infiltration, which can be large cell (concordant) or small cell (discordant), is present in 10 to 25 % of cases [1]. Some patients suffer from fever, night sweats and/or weight loss (B symptoms).

4 Diagnosis

4.1 Lymph node tissue

Diagnosis requires a sufficiently large tissue sample, preferably the entire lymph node, for histological, immunohisforochemical, cytogenetic and molecular genetic examinations. As the diagnosis is often difficult, an assessment by an experienced hematopathologist is highly recommended. A rebiopsy is always mandatory in the event of recurrence.

Requirements for routine diagnostics:

A histological analysis is mandatory at the time of diagnosis. Morphology is of particular importance for the correct diagnosis and possible differential diagnoses. If the morphology corresponds to a diffuse large B-cell lymphoma, the following analyses are required for the classification according to the WHO:

- CD20 expression and, if necessary, other B-cell markers if CD20 is negative, to prove the B-cell nature of the malignant cells.

- *MYC* translocations according to the WHO classification. The prognostic relevance of *MYC* translocations with simultaneous *BCL2* translocation appears to depend on the translocation partner [6].
- Determination of the COO subtype, whereby the choice of method is optional. COO subtyping currently has no clear clinical relevance, but is part of the WHO classification.
- Optional: Parallel testing for the expression of MYC and BCL2: if both markers are expressed (currently not uniformly defined) a so-called 'double expressor' status is present. Patients with 'double expressor' lymphoma showed a poorer prognosis in retrospective analyses [7]. The presence of a 'double expressor' status currently has no therapeutic relevance.

4.2 Staging

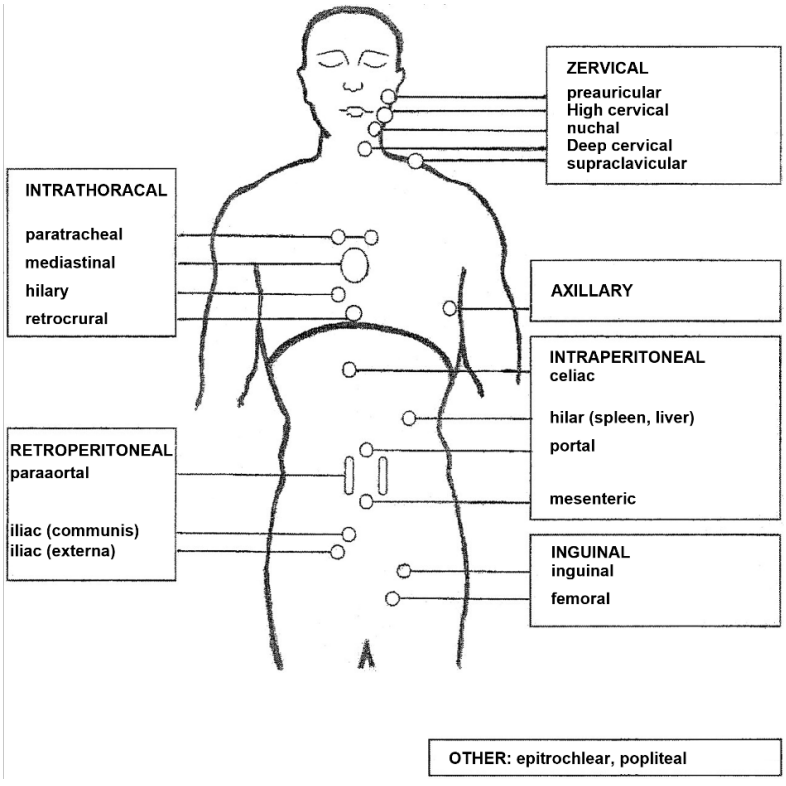
For staging the Ann Arbor classification is used (Table 1) [8]. This requires a history of B-symptoms, a physical examination of the tonsils, lymph nodes, liver, spleen, effusions, visible or palpable masses, computed tomography (CT) with contrast medium of the neck, thorax and abdomen and a bone marrow biopsy (if no PET/CT has been performed for staging; unilateral; aspiration and trephine of at least 2 cm in length). The definition of the lymph node regions is shown in Figure 1.

The detection of lymphoma manifestations is most reliably achieved with positron emission tomography (PET) using the tracer 18-fluorodeoxyglucose (FDG). FDG-PET is the international standard to determine the extent of lymphoma manifestations and for evaluation of treatment results [9]. Usually, whole-body PET/CT is performed, in which pathological glucose accumulations (PET component) are assigned to anatomical structures (CT component). The result of the PET/CT is described using the Lugano classification based on the Ann Arbor classification [9]. PET/CT can provide additional information on bone marrow infiltration and staging at diagnosis leading to so-called 'upstaging' in around 20 % of cases. The metabolically active volume is an additional prognostic and predictive parameter at diagnosis.

Table 1: Ann Arbor classification [8]

Stage	Definition of
I	Involvement of a single lymph node region
I_E	Nodal involvement of a single lymph node region with growth into extranodal tissue (per continuitatem) or presence of a single primary extranodally localized focus
II	Involvement of several lymph node regions on one side of the diaphragm
II_E	Involvement of several lymph node regions on one side of the diaphragm with extention into extranodal tissue (per continuitatem)
III	Involvement of lymph node regions on both sides of the diaphragm
III_E	Involvement of lymph node regions on both sides of the diaphragm with extention (per continuitatem) into extranodal tissue
IV	Diffuse or disseminated involvement of one or more extralymphatic organs: multiple local manifestations in one extralymphatic organ, diffuse infiltration of an entire organ, simultaneous presence of a primary extranodal focus and additional nodal involvement or extranodal manifestations with extention (per continuitatem) from nodal foci or involvement of the liver and/or bone marrow
	Lymphoid structures are: Lymph nodes, tonsils, Waldeyer's pharyngeal ring, Peyer's plaques and the spleen
Suffix S	Involvement of the spleen (considered a lymph node)
Addition A	None of the general symptoms defined under B is present
Addition B	One or more of the following three general symptoms: • Fever above 38° C that cannot be explained otherwise, • Night sweats with change of nightdress that cannot be explained in any other way, • Weigh-loss of more than 10% of body weight within 6 months that cannot be explained in any other way.

Figure 1: Lymph node regions



4.3 Laboratory tests

The laboratory tests include a blood count with differential blood count and clinical chemistry tests to assess liver (bilirubin, GOT, GPT, alkaline phosphatase, gamma-GT) and kidney function (creatinine). Lactate dehydrogenase (LDH) in the serum provides information on cell proliferation and turnover, uric acid on cell decay. A cardiac examination (electrocardiogram, echocardiography) should be done in order to assess subsequent therapy-related complications. Hepatitis and HIV serology are part of the diagnostic program before therapy.

4.4 Prognostic factors

4.4.1 International Prognostic Index (IPI)

The prognosis is estimated using the **International Prognostic Index (IPI).** The IPI includes the factors **age** (≤ vs. > 60 years), **general condition** (ECOG 0 - 1 vs. ≥ 2), **Ann Arbor stage** (I, II vs. III, IV), **involvement of extranodal organs** (0 - 1 vs. ≥ 2 extranodal sites) **and LDH** (≤ vs. > upper normal limit) determining in each case a favorable vs. unfavorable status (corresponding to 0 vs. 1 point, respectively) [10]. Based on the severity, **four risk groups** are distinguished: 0 - 1 points: low risk (overall survival after 3 years: 91%); 2 points: low intermediate (81%); 3 points: high intermediate (65%); 4 - 5 points: high (59%).

The **age-adjusted International Prognostic Index** (aaIPI) is a prognostic score reduced to the factors **general condition, Ann Arbor stage and LDH**, in which the four risk groups mentioned are defined by 0, 1, 2 or 3 unfavorable points. In contrast to the IPI, the aaIPI allows a survival prognosis independent of age.

A further development of the IPI is the 'National Comprehensive Cancer Network' (NCCN) IPI, in which age and LDH activity are divided into 4 or 3 subgroups and only a few extranodal manifestations are evaluated as risk factors [11]. The NCCN-IPI separates the survival curves of the risk groups better than the original IPI. However, it has not yet received general acceptance due to its complexity.

4.4.2 Bone marrow involvement

According to a retrospective study, large cell (concordant) bone marrow infiltration is a risk factor independent of the International Prognostic Index [12]. This does not apply to small cell (discordant) infiltration, which may be a sign of an indolent lymphoma component. In the case of discordant bone marrow infiltration, recurrences can manifest as aggressive or indolent lymphoma. The progression-free survival of patients with discordant infiltration is shortened compared to patients without bone marrow involvement, but the overall survival time does not differ [12].

4.4.3 Bulk

A very large lymphoma manifestation represents a risk factor independent of the International Prognostic Index [13]. The common definition of a 'bulk' in Germany is a diameter ≥7.5 cm [14]. In some countries, a diameter ≥10 cm is required.

4.4.4 Comorbidities

An assessment of comorbidities is highly recommended before starting therapy. Both the 'Charlson Comorbidity Score' and the 'Hematopoietic Cell Transplantation-specific Comorbidity

Index' (HCT-CI) can be used here, whereby the HCT-CI is more accurate with regard to cardiovascular and nephrological comorbidities. Both scores are predictive and prognostic factors. In addition, a comparison of the comorbidities at diagnosis and at relapse can influence the treatment decision if treatment intensification is required in a subsequent relapse or refractoriness [15, 16].

4.5 Differential diagnosis

Diffuse large B-cell lymphoma with its variants and subtypes and the diseases related to diffuse large B-cell lymphoma has to be differentiated from lymphomas that manifest similarly, but are treated differently. These include Hodgkin's, Burkitt's and mantle cell lymphomas as well as peripheral T-cell lymphomas. The histological differentiation of diffuse large B-cell lymphoma from other aggressive B-cell lymphomas is based on the WHO classification [1].

5 Therapy

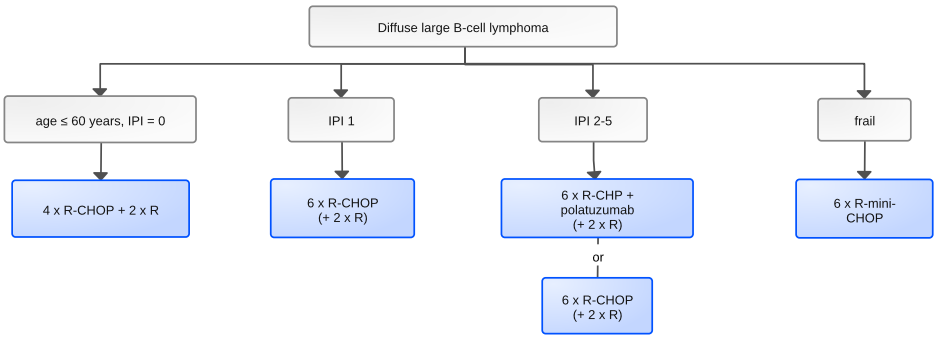
5.1 Therapy structure

Diffuse large B-cell lymphoma and related entities are curable, but rapidly fatal diseases if left untreated. The indication for therapy is therefore linked to the diagnosis. The treatment goal is curation. Exceptions are situations in which comorbidities or other circumstances do not permit a curative approach. The current standard of therapy is based on the results of clinical studies. First-line therapy still consists of immuno-chemotherapy. For relapse therapy, innovative therapy concepts have been established. Two figures depict the therapeutic algorithm: first-line therapy in Figure 2 and management of relapse in Figure 3, respectively. To improve therapy, patients with diffuse large B-cell lymphoma should be treated in prospective studies whenever possible.

Since chemotherapy can cause infertility, patients should be informed about fertility-preserving measures before starting treatment and these should be initiated if necessary.

5.1.1 First-line therapy

Figure 2: Structure of first-line therapy for diffuse large B-cell lymphoma



Involved site radiotherapy should be considered for circumscribed PET-positive residual lymphomas.

The description of the therapy protocols is included in the associated document "Drug-based tumor therapy"

5.1.1.1 Immunochemotherapy

First-line therapy is carried out with 6 cycles of the **CHOP protocol** plus 8 doses of **rituximab (R-CHOP protocol**) or with protocols similar to R-CHOP [17- 19]. The CHOP protocol is equally effective compared to more complex treatment regimens, however R-CHOP is better tolerable [20]. The addition of rituximab improved treatment overall survival in all subgroups [17- 21]. In randomized studies, two variants of the R-CHOP protocol were tested, which provide comparable results in terms of progression-free survival and overall survival [17- 19]: 8 cycles at 21-day intervals or 6 cycles at 14-day intervals followed by 2 additional doses of rituximab. The latter variant requires the administration of G-CSF. Different analyses showed that 6 cycles at 21-day intervals are not inferior to 8 cycles of R-CHOP [22]. Six cycles of R-CHOP-21 are therefore the international standard. In younger patients (60 years and younger) without an IPI risk factor (IPI 0) and without a bulk, treatment should be reduced to 4 cycles of R-CHOP with 2 additional courses of rituximab without any reduction in efficacy [21]. In patients with increased risk (IPI 2-5), 6 courses of R-CHP (CHOP without vincristine) in combination with polatuzumab vedotin followed by two courses of rituximab showed significantly improved progression-free survival compared to standard therapy with 6 courses of R-CHOP and two courses of rituximab (see also comments in chapter 5.1.1.4.3) [23].

For younger high-risk patients, in addition to the treatments described above, intensified protocols can also be used, which are described in chapter 5.1.1.4.3.

5.1.1.2 Maintenance therapy

Maintenance therapy with rituximab is not indicated for diffuse large B-cell lymphoma as it does not improve the treatment results. Similarly, maintenance treatment with other substances such as lenalidomide did not lead to any improvement in overall survival.

5.1.1.3 Irradiation

The potential role of radiotherapy in the treatment of patients with diffuse large B-cell lymphoma has not been defined by the results of randomized studies. Historically, radiotherapy has developed from the sole curative treatment modality to consolidating therapy (involved field radiotherapy) after completion of chemotherapy. Currently, the indication for consolidating radiotherapy depends on the result of a PET/CT scan after completion of chemotherapy. The previously common "Involved Field" treatment of anatomical regions has been replaced by "Involved Site" irradiation of the initial lesion [24].

In the localized stages (I, II) of aggressive lymphomas, randomized studies have shown improved relapse-free survival with consolidating radiotherapy, but no improvement in overall survival [25, 26]. In the advanced stages, however, radiotherapy of PET-positive residual tumors in initial 'bulk lesions' (≥7.5 cm) led to a significant improvement in relapse-free survival and overall survival [14]. Retrospective studies suggest that this also applies to the irradiation of skeletal manifestations. At the end of chemotherapy, consolidating post-irradiation should be considered for individual PET-positive lesions.

The above-mentioned procedure of consolidating radiotherapy for the treatment of PET-positive residual manifestations has found its way into numerous guidelines. With one exception, this approach is not proven by the results of prospective randomized studies, but is based on retrospective analyses with historical controls [27- 29]. General radiotherapy of initial lymphoma manifestations, as previously recommended as an "involved field", is obsolete [30].

5.1.1.4 Open questions in the field of first-line therapy

5.1.1.4.1 Prognosis-guided therapy

It is presently unclear whether patients with aggressive lymphomas that differ in terms of gene expression or genetic subtype may benefit from a modified therapy. The long-term results of the REMoDL-B study showed a significant improvement in progression-free and overall survival with the addition of the proteasome inhibitor bortezomib to R-CHOP in patients with diffuse large B-cell lymphoma of the ABC subtype [31]. In 'double-hit lymphomas', more intensive treatment protocols (e.g. DA-EPOCH-R, Burkitt protocols) led to longer progression-free survival times than R-CHOP in retrospective studies, but there was no difference in overall survival. In this respect, the question of whether patients with 'double-hit lymphoma' benefit from treatment intensification is currently unresolved.

5.1.1.4.2 Response-guided therapy

Whether and under what conditions the result of the interim staging should influence the further treatment strategy is unknown. In a randomized study, interim PET performed after 2 cycles of R-CHOP was of prognostic significance, but in the presence of unfavorable interim PET findings, intensification of treatment did not lead to an improved outcome compared to R-CHOP [20]. In contrast, a PET-guided French phase III trial was able to show that early intensification using high-dose therapy and autologous stem cell transplantation in case of a delayed response (PET still positive after two cycles, negative after four cycles) leading to the same results as standard therapy completed in the case of early PET negativity [32].

5.1.1.4.3 Complex therapy protocols

In patients under the age of 60 with an intermediate prognosis (aaIPI 1), the **R-ACVBP protocol** proved to be significantly superior to the R-CHOP protocol [33]. The treatment approach is similar to the usual procedure for acute lymphoblastic leukemia. In that protocol, induction with 4 cycles of a dose-intensified R-CHOP variant is followed by consolidation with 2 cycles of high-dose methotrexate, 4 cycles of rituximab/ifosfamide/etoposide and 2 cycles of cytarabine. In younger patients with an unfavorable prognosis (aaIPI 2 or 3), R-ACVBP was not superior to R-CHOP in a randomized, interim PET-guided study [34]. Due to the increased toxicity in older patients, the R-ACVBP protocol has not gained general acceptance. In patients at high risk of central nervous system relapse, the protocol may offer advantages because central nervous system relapses occur less frequently compared to R-CHOP [35].

In the randomized phase 3 POLARIX study, patients aged 18 to 80 years with intermediate- and high-risk (IPI 2-5) were randomized between 6 cycles of R-CHOP and 6 doses of R-CHP in combination with the anti-CD79B antibody-drug conjugate (ADC) polatuzumab vedotin, each followed by two applications of rituximab [23]. Patients treated with **R-CHP-polatuzumab vedotin** in the experimental arm showed a significant improvement in the primary endpoint of progression-free survival at 2 years (76.7% vs. 70.2%) [23]. After a median observation period of 28 months, there was no difference in overall survival. Furthermore, there was no increased toxicity in the experimental arm. Polatuzumab vedotin in combination with R-CHP was approved by the EMA as first-line therapy for the treatment of adults with diffuse large B-cell lymphoma.

The addition of etoposide (100 mg/m² day 1 - 3) to the CHOP protocol led to an improved event-free survival in the pre-rituximab era in younger patients with a good prognosis [36]. After the addition of rituximab, however, the results of CHOP and CHOEP were comparable [18]. In younger patients with an unfavorable prognosis, unexpectedly good results were achieved with the **R-CHOEP protocol.** Patients treated with R-CHOEP achieved a 10-year overall survival of 72% [37]. These results suggest that prognostically unfavorable lymphomas could also benefit from the addition of etoposide under rituximab therapy. A retrospective comparison of the outcomes of younger patients with unfavorable prognosis treated with either R-CHOEP or R-CHP in combination with polatuzumab vedotin showed no differences in progression-free and overall survival, but fewer acute toxicities with R-CHP in combination with polatuzumab vedotin [38]. Despite the methodological limitations, this inter-study comparison limits the use of R-CHOEP in this population. Therefore, R-CHOEP should only be offered to individually selected patients.

In addition to the alkylating agents, anthracyclines, vinca alkaloids and corticosteroids contained in the CHOP protocol, the complex **B-ALL/NHL protocol** of the German ALL Study Group includes the substances methotrexate, cytarabine and etoposide, which penetrate the CNS. Compared to the CHOP protocol, it is associated with higher toxicity (especially mucositis) with comparable therapy-associated mortality. In the event of a poor response to the first two R-CHOP cycles, switching to the B-ALL/NHL protocol under randomized conditions showed no advantage over continuing R-CHOP [20]. In this respect, there is no clear evidence for the use of the B-ALL/NHL protocol in patients with diffuse large B-cell lymphoma.

In view of the importance of **high-dose therapy** with autologous blood stem cell transplantation in patients with lymphoma relapse, numerous attempts have been made to use the procedure as consolidation in front-line therapy, as well. Overall, no advantages could be shown, and in some subgroups the results were contradictory [39]. Outside of clinical trials, consolidating high-dose therapy with autologous blood stem cell transplantation is not recommended as a concept for first-line therapy.

5.1.1.4.4 Rituximab dosage and new CD20 antibodies

In a retrospective study, male patients benefited less from the addition of rituximab to the CHOP protocol than women. This appears to be due to faster rituximab clearance [40]. Increasing the single dose of rituximab from 375 mg/m² to 500 mg/m² improved progression-free survival in male patients compared to a historical control [41]. In a second historical comparison, an improvement in treatment results was achieved in older patients by changing the schedule of rituximab administration [42]. These observations are in contrast to the results of prospective studies [20, 43] and retrospective comparisons, which showed no survival benefit from further rituximab administration. There are no generally accepted recommendations for optimizing the use of rituximab.

New CD20 antibodies such as obinutuzumab [44] or ofatumumab [45] were unable to improve the treatment results achieved with rituximab in diffuse large B-cell lymphoma in randomized studies.

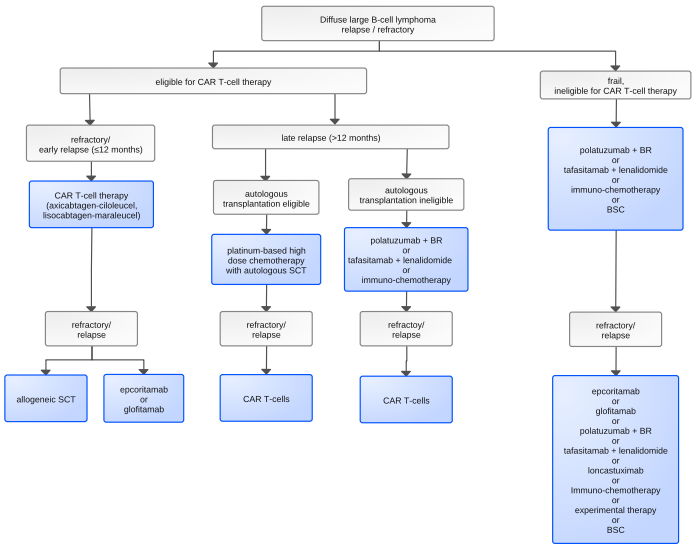
5.1.1.4.5 Vitamin D

Retrospective data suggested that patients with diffuse large B-cell lymphoma and a vitamin D serum concentration below the normal range would have a less favorable disease course than patients with a normal vitamin D concentration [46]. It is unknown whether the treatment out-

come can be improved by vitamin D supplementation, but laboratory-detected reduced vitamin D levels should be compensated.

5.1.2 Therapy for progression / refractoriness / relapse

Figure 3: Relapse therapy for diffuse large B-cell lymphoma (first and subsequent relapses)



Legend:
BSC: best supportive care.
The description of the therapy protocols is included in the associated document "Drug-based tumor therapy"

5.1.2.1 Therapy in the first relapse - early recurrence and refractory situation

CAR T-cell therapy:

In recent decades, conventional platinum-containing salvage therapy followed by high-dose therapy with autologous blood stem cell transplantation has been the standard treatment for relapses in younger patients (under the age of 60 years), but also in older patients without therapy-limiting comorbidities [47]. Satisfactory treatment results were only seen if there was a response to conventional-dose induction therapy. This occurred rarely if the **interval** between primary diagnosis and recurrence was **less than 12 months.** Three cycles of the R-DHAP or R-ICE protocol proved to be equivalent as induction therapy [48]. Alternatively, the R-GDP regimen is available, which is equivalent to the R-DHAP protocol with better tolerability [49]. The BEAM protocol was generally used for high-dose chemotherapy [48].

For younger patients with primary refractory disease or **early relapse** (**within 12 months after completion of first-line therapy)** eligible for high-dose therapy**,** the standard of care (high-dose therapy followed by autologous stem cell transplantation) has been compared with anti-CD19 CAR T-cell therapy in phase 3 trials [50- 52]. The ZUMA-7 study showed a significant improvement in event-free and overall survival with axicabtagene-ciloleucel in patients with DLBCL [50]. In the TRANSFORM study, the experimental arm with lisocabtagene-maraleucel also led to a significant improvement in event-free survival, which was followed by the approval of lisocabtagene-maraleucel in patients with DLBCL and other subtypes (high grade B-cell lymphoma (HGBCL), primary mediastinal B-cell lymphoma and follicular lymphoma grade 3B (FL3B)) [51]. Based on these data, treatment with axicabtagene-ciloleucel or lisocabtagene-maraleucel represents the new standard of care for patients with primary refractory disease or early relapse.

CAR T-cell therapy for primary refractory disease or early relapse should also be offered to older patients who may not be able to receive chemotherapy followed by autologous stem cell transplantation, as older patients can also benefit from CAR T-cell therapy to a similar extent as younger patients. The ALYCANTE study in patients who are not capable of receiving high dose chemotherapy showed promising results for therapy with axicabtagene-ciloleucel. The use of lisocabtagene-maraleucel in the PILOT study also showed favorable response rates and survival data in this patient population [53, 54].

5.1.2.2 Therapy in the first relapse - late recurrence

For patients with **late relapse (at least 12 months after completion of first-line therapy) who are eligible for** autologous blood stem cell transplantation, high-dose chemotherapy followed by autologous stem cell transplantation remains the standard of care.

In patients with **late relapse** who are not eligible for an autologous stem cell transplantion due to their age or comorbidities, or patients with early relapse who do not qualify for a CAR T-cell therapy, the treatment goal is often palliative. A curative therapy concept appears possible if the interval between the primary diagnosis and the relapse is long and the disease responds to a new therapy. In addition to the **R-GemOx regimen** [55], more intensive chemotherapy regimens such as **R-DHAP or R-ICE** [48] are also available. Furthermore, the combination of rituximab, bendamustine with the antibody-drug conjugate polatuzumab vedotin (**Pola-BR**) is approved for patients in first or later relapse. The pivotal trial for Pola-BR showed a significant improvement in response rates, progression-free survival and overall survival compared to rituximab and bendamustine [56]. As a further option, a chemotherapy-free treatment option consisting of the anti-CD19 antibody **tafasitamab in combination with lenalidomide** was approved for not high-dose-eligible patients in first relapse [57]. Promising response rates and long-term data were reported in the L-MIND study. However, these data remained unconfirmed by a retrospective real-world analysis [58]. Due to the large number of newly approved treatment modalities, attention to the sequence is becoming increasingly important. When using tafasitamab, the efficacy of downstream CD19-targeted CAR T-cell therapy is unclear. Furthermore, the quality of lymphocyte apheresis after bendamustine is significantly limited in retrospective studies [59].

5.1.2.3 Therapy for second or later relapse

The **three CAR T-cell products axicabtagene-ciloleucel, tisagenlecleucel and lisocabtagene-maraleucel** are currently approved by the EMA (European Medicines Agency) for patients with at least two prior therapies [60, 61, 62]. **According to the approval studies,** the **indication** is for patients with relapsed/refractory diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma or transformed follicular lymphoma. In patients with a second relapse, treatment with CAR T-cells should always be considered.

A CAR T-cell therapy should also be offered to older, possibly co-morbid patients. The ability to use CAR T-cell therapy should be evaluated in a context- and product-specific basis. "Real-world analyses" of all three approved CAR T-cell products in the third and higher treatment lines show no negative influence of age on the success of a CAR T-cell therapy and therefore, no upper age limit is defined for the use of CAR T-cell therapy [63].

With regard to comorbidities, significant negative influences of moderate to severe renal, cardiac and hepatic comorbidities have been described for **axicabtagene-ciloleucel**, which have to be taken into account when determining the indication. Since successful use of axicabtagene ciloleucel in patients with the respective pre-existing comorbidities has been reported in small prospective studies, an absolute contraindication against the use of axicabtagene ciloleucel

does not seem justified. It is futher of note that less toxic treatment modalities with proven curative potential are usually not available in these situations.

Inter-study comparisons and the existing "real-world analyses" show an overall lower toxicity for the substances **tisagenlecleucel and lisocabtagene-maraleucel** compared to axicabtagene-ciloleucel, which resulted in low incidences of non-lymphoma-related mortality and the need for intensive medical treatment [64]. For tisagenlecleucel, an analysis of 1159 patients showed no negative association of comorbidities with survival data [65]. The use of these two CAR T-cell products in their respective approval areas is therefore also possible in the presence of comorbidities due to the lack of less toxic alternatives with proven curative potential.

From the second relapse onwards, the two **bispecific antibodies** epcoritamab and glofitamab are still possible therapeutic options. Usually, they should be used **after failure of CAR T-cell therapy.** Both antibodies induce response rates of between approx. 50 to 60% from the second relapse onwards. Especially patients who achieve a complete remission may remain disease-free in the long term [66, 67]. The two bispecific antibodies differ in terms of application, duration of therapy and structure (epcoritamab, 1xCD20 binding site, glofitamab, 2xCD20 binding site). Epcoritamab is administered subcutaneously for an unlimited period of time until progression or the occurrence of intolerable side effects, while glofitamab is administered intravenously for 12 cycles. The number of patients being cured by epcoritamab and glofitamab cannot be estimated at this time.

A further therapeutic option for patients after failure of CAR T-cell therapy may be allogeneic stem **cell transplantation** in suitable patients - depending on the remission status prior to stem cell transplantation. If a complete metabolic remission cannot be achieved after failure of CAR T-cell therapy, e.g. with a bispecific antibody, allogeneic stem cell transplantation may be considered in individual cases [68].

Furthermore, the anti-CD19 antibody-drug conjugate l**oncastuximab-tesirine is** available therapeutically from the second relapse onwards [69]. Approx. 50% of patients with multiple previously treated diffuse large B-cell lymphoma respond to treatment with loncastuximab-tesirine.

5.2 Special lymphomas and clinical situations

5.2.1 Primary mediastinal large B-cell lymphoma (PMBL)

5.2.1.1 General information

Primary mediastinal large B-cell lymphoma (PMBL) accounts for around 2 to 4 % of all lymphomas. Due to its different clinical and pathological characteristics it is classified as independent entity by the WHO classification [1]. In terms of molecular pathogenesis, PMBL shares similarities with classical Hodgkin's lymphoma (e.g. often CD30 positivity, constitutive activation of the NF-κB and JAK/STAT signaling pathways and PD-1-mediated immune evasion). PMBLs occur mainly in young women (median age approximately 35 years). Patients with PMBL often present with symptoms of upper airway obstruction or airway compression due to the extent or locally invasive growth of the mediastinal mass.

5.2.1.2 First-line therapy

Patients with PMBL usually receive the same protocols as patients with diffuse large B-cell lymphoma. With these protocols very high cure rates are achieved [70, 71]. However, unlike diffuse large B-cell lymphoma, the optimal chemotherapy regimen for first-line treatment of PMBL has

not yet been determined definitively. Accordingly, there are currently two options in use: R-CHOP and DA-EPOCH-R. With DA-EPOCH-R an overall survival of 97% (95%CI 81-99) after 5 years was achieved in a single-arm study [71]. This regimen contains the same substances as R-CHOEP, but differs in the mode of administration (96-hour continuous infusion of etoposide, vincristine and doxorubicin) and in adjustment of the cytostatic doses based on the granulocyte and platelet nadir of the previous cycle. PMBL patients with a residual lymphoma after first-line chemotherapy treated in real-world evaluations often received an involved field radiotherapy consolidation. A PET-CT scan should clarify whether radiotherapy is necessary after systemic therapy. The IELSG 37 study showed that if PET-CT is negative after systemic therapy, radiotherapy can be omitted [72].

5.2.1.3 Therapy of relapse

The high efficacy of first-line PMBL therapy results in a relatively low proportion of primary refractory or relapsed cases. This rarity hampers the systematic development of optimal therapy of relapsed or refractory patients. Patients with primary refractory disease or early relapse (within 12 months after completion of first-line therapy) should receive CAR T-cell therapy with lisocabtagene maraleucel [73]. Patients with late relapse (more than 12 months after completion of first-line therapy) after initially chemosensitive disease should be treated with platinum-containing salvage therapy (R-DHAP, R-GDP or R-ICE) and, if at least a partial remission is achieved, with high-dose therapy using the BEAM protocol followed by autologous stem cell transplantation. In a primarily chemorefractory situation, it is possible to treat with PD-1 blockade with or without brentuximab vedotin [74- 76]. However, PD-1 blockade has only been approved for this indication in the USA and Switzerland. Anti-CD19 CAR T-cell therapy remains an option for the third line of therapy if CAR T-cell therapy has not yet been administered in the second line of therapy.

5.2.2 Richter Transformation (RT)

Richter transformation (also known as Richter syndrome) is the development of an aggressive lymphoma from chronic lymphocytic leukemia (CLL), which can occur in 2 to 10% of CLLs during the course of the disease. Over 90% of cases have a diffuse large B-cell lymphoma histology, with the remaining cases usually showing histological evidence of Hodgkin's lymphoma. If possible, the presence of a common clonal origin should be investigated to distinguish RT from a de novo secondary lymphoma. Standard therapy for RT with diffuse large B-cell lymphoma histology is 4 to 6 cycles of R-CHOP, with an overall response of only about 40% and a median survival of only about 6 to 8 months [77]. For younger patients with RT, a consolidating allogeneic stem cell transplant is usually recommended. For the few cases with RT and Hodgkin's histology, treatment based on current Hodgkin's protocols is recommended, even if data from larger treatment series are lacking.

Small case series have shown a potential therapeutic benefit of BTK inhibitors such as acalabrutinib and pirtobrutinib in RT, although only very short progression-free survival times of a few months have been described. Checkpoint inhibitors, in particular pembrolizumab, also showed responses when used as monotherapy in RT. These individual therapy options (all off-label) can be considered in cases of reduced fitness or after failure of R-CHOP-based therapies.

Recently, a phase II study of the DCLLSG in RT (RT-1 study) documented a response rate of 58% of treated patients for the combination of the PD-1 inhibitor tislelizumab with the second-generation BTK inhibitor zanubrutinib, with a median progression-free survival of 10 months and approx. 75% of patients still alive after one year [78]. This treatment combination (currently off-label) could therefore be of particular interest for the use of CAR T cells in RT. It is currently being investigated as a further treatment option. Initial results based on axicabtagen-ciloleucel

(among others) indicate high response rates in small case series (ORR of 100% with a CR rate of 63%) with still unclear long-term results.

5.2.3 First-line therapy in the senium

In very elderly patients (> 80 years), the application of the original R-CHOP protocol is often associated with major risks. In these cases the R-miniCHOP protocol is suitable (progression-free survival after 2 years approx. 45 %) (Figure 2) [79].

5.2.4 Central nervous manifestations

During primary therapy with R-CHOP, 2 to 5 % of patients with DLBCL experience a relapse of the disease affecting the central nervous system (CNS).

As central nervous system relapses are rare, general CNS prophylaxis is not recommended. The 'CNS-IPI', which consists of the 5 factors of the IPI and an involvement of the kidneys and/or adrenal glands, is suitable for identifying patients with a high risk of central nervous system recurrence [80]. With 0 - 1 risk factors, the risk of CNS recurrence is < 1 %, with 2 - 3 risk factors 3 % and with 4 - 6 risk factors 10 %. In the high-risk groups, targeted diagnostics (magnetic resonance imaging of the central nervous system, FACS analysis of the cerebrospinal fluid) are recommended. The integration of molecular markers into the 'CNS-IPI' showed that patients with a high 'CNS-IPI' and an ABC or an unclassifiable molecular subtype have a more than 15 % risk of central nervous system relapse [81]. By retrospective analyses no advantage of CNS prophylaxis with high-dose methotrexate for the prevention of CNS relapses was shown [82]. In summary, there is currently no clear evidence for drug-based CNS prophylaxis, e.g. with high-dose methotrexate. Intrathecal prophylaxis is not indicated, as well.

Patients with parallel systemic and central nervous system involvement at diagnosis should be treated with treatment protocols that target both, the peripheral and central nervous system lymphoma, as well. Protocols involving different substances and with different intensities represent the choice here. If possible, autologous stem cell transplantation should be performed [83]. Analogous to primary CNS lymphomas, the CNS penetrating substances should be used.

5.2.5 Testicular lymphoma

Testicular lymphoma is characterized by a high rate of relapse in the central nervous system and contralateral testis. Based on retrospective data, CNS prophylaxis with high-dose methotrexate and irradiation of the contralateral testicle with 30 Gray is recommended in addition to standard therapy [84].

5.2.6 Contraindication against anthracyclines

In cases of advanced heart failure or extensive anthracycline pretreatment, doxorubicin included in the R-CHOP protocol is associated with major risks. The pegylated liposomal doxorubicin formulation is considered to be equipotent but less cardiotoxic. Sensitive heart failure markers (ejection fraction, NT-proBNP) are less likely to reach pathological values with liposomal doxorubicin than with regular doxorubicin. However, under both doxorubicin preparations, clinically manifest heart failure develops rarely and with comparable frequency [85]. An anthracycline-free alternative is to replace doxorubicin with etoposide (50 mg/m² i.v. day 1, 100 mg/m² p.o. days 2 and 3). As an indication of its curative potency, a plateau in the survival curve is observed with R-CEOP, similar to R-CHOP. R-GCVP (gemcitabine instead of doxorubicin) has been studied explicitly in a population with cardiac morbidity including heart failure and coro-

nary heart disease: it resulted in a response rate of 61.3 % and a 2-year progression-free survival of 49.8 % in older patients [86].

5.2.7 Impaired kidney or liver function

As the active metabolites of the substances contained in the R-CHOP protocol are predominantly not eliminated renally, the protocol can generally be applied in cases of impaired renal function. If liver function is impaired, the hepatically eliminated substances doxorubicin and vincristine accumulate. Both drugs should therefore not be given in cases of advanced liver dysfunction or biliary obstruction. Of note, organ dysfunction due to lymphoma is often reversed by one or two cycles of doxorubicin- and vincristine-free chemoimmunotherapy (e.g. rituximab 375 mg/m² day 1; cyclophosphamide 200 mg/m² day 1 - 5; etoposide 100 mg/m² day 1 - 3; prednisone 100 mg day 1 - 5; modification of cyclophosphamide and etoposide treatment according to clinical condition).

5.2.8 Pregnancy and fertility

If an aggressive lymphoma occurs in the first trimester, a termination of pregnancy is recommended, as chemotherapy carried out during the organogenesis phase carries a high risk of malformations. The risk is low in the second and third trimester. The R-CHOP protocol is suitable as a standard treatment regimen. Antimetabolites (e.g. methotrexate) are contraindicated due to the risk of fetal CNS damage. If the lymphoma occurs in late pregnancy and is not very aggressive, treatment can be postponed until after delivery.

A retrospective study showed no disadvantage for the mother if treatment of the lymphoma was not started until after delivery, and only a low risk for the fetus if treatment was carried out in the second or third trimester (stillbirth and malformation rate around 5%) [87]. As prematurity impairs the child's cognitive development, the indication for premature delivery should be strictly determined.

Infertility is primarily caused by alkylants and radiation in the pelvic area. In some men treated with the CHOP protocol, spermatogenesis recovers within 5 to 7 years [88]. As the outcome cannot be predicted in individual cases, sperm preservation should be carried out before chemotherapy if the patient wishes to have children. In women, permanent amenorrhea rarely occurs following treatment with CHOP [89]. However, a reduction in the ovarian reserve with premature menopause (last menstrual cycle before the age of 40) is frequent. The time window for fulfilling the desire to have children is short, especially for patients who have passed the age of 30 at the time of chemotherapy [89].

6 Follow-up

6.1 Monitoring

6.1.1 Interim staging

During first-line or relapse therapy, an interim assessment is usually done with the aim of confirming a potentially successful treatment strategy. Exact time and method of the interim assessment have not yet been defined, nor what degree of tumor reduction is required for the continuation of treatment [9]. In most cases, interim staging with computer tomography is performed after completion of one third or half of the treatment protocol. Interim PET/CT examinations are a prognostic parameter in cases of persistent positivity [20]. Currently, the value of PET/CT-triggered treatment intensification has not been proven [32].

6.1.2 Final examination

The evaluation of the treatment outcome is performed according to international standards. The outcome is evaluated 6 to 8 weeks after the end of treatment using PET/CT. The response categories comprise:

- complete remission (no FDG accumulation),
- partial remission (residual FDG accumulation with a decrease in tumor mass of at least 50 %),
- stable disease (residual FDG accumulation with a decrease in tumor mass of less than 50 %) and
- progressive disease (residual FDG accumulation with an increase in the mass of one or more lymphoma manifestations or new FDG-positive lesion(s) [9].

The Deauville classification is used to quantify the metabolic response. Deauville stages 1 and 2 (FDG activity of residual foci ≤ liver activity) are generally considered complete metabolic remission, while Deauville stages 4 and 5 (residual activity > liver activity) are considered persistent vital lymphoma. The assessment of Deauville 3 is still controversial in aggressive lymphoma. The informative value of interim PET examinations after 2 or 3 cycles of therapy versus PET examinations after completion of therapy and the prognostic significance of the so-called "metabolic tumor volume" are the subject of ongoing studies. If positron emission tomography is not used, the treatment outcome is defined by computed tomography based on the size of residual masses. **The determination of a complete remission requires the absence of any residual masses.** If the remission assessment based solely on CT is unclear, an additional PET/CT is recommended. Details of the difficult response assessment in individual cases has been described in the original literature [9].

6.2 Follow up

Follow-up examinations are important for reintegration into family, work and society, to detect relapses of the disease and to detect and minimize long-term complications, in particular infertility, secondary malignancies and cardiovascular disorders. According to the modified Cotswolds recommendations, follow-up takes place quarterly for the first two years after the end of treatment, every six months for the following three years and every year from the sixth year onwards.

The follow-up examinations focus on the patient's medical history, physical examination and laboratory analyses. Routine CT scans or PET/CT scans are not recommended [9]. The value of less stressful examination procedures, such as ultrasound examination of the abdomen or conventional X-ray examination of the thorax, has not been proven. Imaging procedures are particularly justified if the clinical findings suggest a relapse of the disease or a late complication.

Secondary malignancies (in particular in patients under the age of 45 years) may occur following successful treatment with CHOP-type treatment protocols [90]. In addition to myelodysplasia and acute myeloid leukemia, there is an increased incidence of bronchial carcinomas (increased risk due to concomitant nicotine consumption), colorectal carcinomas, prostate carcinomas, cyclophosphamide-induced urinary bladder carcinomas and Hodgkin's lymphomas. Specific measures for the prevention and detection of secondary malignancies have not been defined, so far.

After treatment with anthracyclines, the risk of an emerging **heart failure is** increased compared to the normal population, especially if chemotherapy was administered in younger age (before the age of 55). Possible individual co-factors which can be reduced are arterial hypertension and nicotine consumption. If chemotherapy and radiotherapy of the mediastinum are

combined, the risk of coronary heart disease or cerebrovascular events increases. For prevention, the control of cardiovascular risk factors (hypertension, hypercholesterolemia, diabetes mellitus, obesity, nicotine abuse) is recommended. When radiating the mediastinum in young patients, early breast cancer screening should be carried out.

6.3 COVID-19

Information on COVID-19 can be found in the Onkopedia COVID-19 guideline. The SARS-CoV-2 pandemic has not resulted in any changes with regard to treatment or check-ups and follow-up examinations.

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10 Active studies

Malignant lymphoma competence network: http://www.lymphome.de

14 Links

German Leukemia and Lymphoma Aid e. V.

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16 Disclosure of Potential Conflicts of Interest

according to the rules of DGHO, OeGHO, SGH+SSH, SGMO

Author	Employer[1]	Consulting / Expert opinion[2]	Shares / Funds[3]	Patent / Copyright / License [4]	Fees[5]	Funding of scientific research[6]	Other financial relations[7]	Personal relationship with authorized representatives[8]
Chapuy, Björn	ab 1.10.2021 Charité, Universitätsmedizin Berlin, Campus Benjamin Franklin vorher: Universitätsmedizin Göttingen	**Yes** AbbVie, ADC, BMS, Incyte, Janssen, Regeneron, Roche, Sobi	**No**	**No**	**Yes** AbbVie, Ars tempi, Astra Zeneca, BMS, Incyte, Janssen, Gilead, KML, Roche, Sandoz, Sobi, Ono	**Yes** Gilead Oncology Award (mit S. Dietrich) 2021 BC ist Leiter der GLA IIT R-Pola-Glo, die vom IKF gesponsort wird und finanzielle Zuwendungen von der ROCHE bekommt.	**Yes** Roche (An/Abreise zum EHA 2022)	**No**
Glaß, Bertram	Helios Klinik Berlin-Buch	**Yes** Roche, Kite/Gilead, Celgene/BMS, Novartis, Miltenyi, Lonca, Abbvie, JAZZ, Jannssen, Incyte	**No**	**No**	**Yes** Roche, BMS, Kite, Abbvie, Jannssen, Incyte	**Yes** Roche, Riemser	**No**	**No**
Keil, Felix	Vorstand der 3. Medizinischen Abteilung Hämatologisch-onkologisches Zentrum 1140 Wien, Heinrich-Collin-Straße 30	**Yes** Roche, Incyte, Novartis, Gilead: Advisory Boards.	**No**	**No**	**Yes** AbbVie, Amgen, AstraZeneca, Beigene, Celgene/BMS, Incyte, Janssen, Novartis, Roche	**Yes** AbbVie, AstraZeneca, Celgene/BMS, Takeda	**No**	**No**
Klapper, Wolfram	Universitätsklinikum Schleswig-Holstein - Campus Kiel Institut für Pathologie, Sektion für Hämatopathologie	**Yes** Roche	**No**	**No**	**No**	**Yes** AMgen, Takeda, Roche, Janssen, InCyte, Regeneron	**No**	**No**
Lenz, Georg	Universitätsklinikum Münster	**Yes**	**No**	**No**	**Yes** Roche, Gilead, Janssen, Celgene/BMS, Novartis, AstraZeneca, Takeda, Abbvie, Morphosys, Incyte, Sobi, Hexal/Sandoz, Beigene	**Yes** Roche, Gilead, Janssen, Bayer, AstraZeneca, Morphosys, AGIOS, AQUINOX, Verastem, Acerta	**Yes** Roche, Gilead, Janssen, Celgene/BMS, Novartis, AstraZeneca, Takeda, Abbvie, Morphosys, Incyte, Beigene, Sobi	**No**

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		Roche, Gilead, Janssen, Celgene/ BMS, Bayer, Novartis, AstraZeneca, Takeda, Abbvie, Morphosys, Incyte, Genmab, Karyopharm, Constellation, ADC Therapeutics, Miltenyi, PentixaPharm, Sobi, Immagene, Genase, Lilly, Hexal/ Sandoz, MSD, Beigene						
Nickelsen, Maike	Selbständige Tätigkeit seit 01.04.2023	**Yes** Advisory Boards: AbbVie, Amgen, Astra Zeneca, BMS, Incyte, Janssen, Lilly, Roche, SoBi,	**No**	**No**	**Yes** Vortragstätigkeit: AbbVie, Amgen, BMS, Incyte, Janssen, Roche, SoBi	**No**	**Yes** Reise- und Kongresskosten: BMS, Lilly, Roche	**No**
Urban, Novak	Inselspital / Universitätsspital Bern	**Yes** Astra Zeneca, Ideogen, Roche, Beigene, Gilead, Kyowa Kirin, Incyte, Takeda, Pierre Fabre, Celgene/ BMS	**No**	**No**	**Yes** Gilead, Takeda, Celgene/ BMS, H & O Communication	**No**	**No**	**No**
Schmidberger, Heinz	Universitätsmedizin Mainz	**No**	**No**	**No**	**No**	**No**	**No**	**No**
Schmitt, Clemens A.	Johannes Kepler Universität Linz Kepler Universitätsklinikum Linz Charité - Universitätsmedizin Berlin	**Yes**	**No**	**No**	**Yes**	**Yes** Janssen: Forschungsunterstützung	**No**	**No**

Author	Employer[1]	Consulting / Expert opinion[2]	Shares / Funds[3]	Patent / Copyright / License [4]	Fees[5]	Funding of scientific research[6]	Other financial relations[7]	Personal relationship with authorized representatives[8]
		Roche: Advisory Board, Sprecherhonorare Janssen: Advisory Board, Sprecherhonorare und Forschungsunterstützung Takeda: Advisory Board BMS/Celgene: Advisory Board Astra Zeneca: Advisory Board Abbvie: Advisory Board Roche: Advisory Board, Sprecherhonorare Janssen: Advisory Board, Sprecherhonorare und Forschungsunterstützung Takeda: Advisory Board BMS/Celgene: Advisory Board Astra Zeneca: Advisory Board Abbvie: Advisory Board			Roche: Advisory Board, Sprecherhonorare Janssen: Advisory Board, Sprecherhonorare Takeda: Advisory Board BMS/Celgene: Advisory Board Astra Zeneca: Advisory Board Abbvie: Advisory Board			
Wendtner, Clemens-Martin	München Klinik Schwabing Ludwig-Maximilians-Universität (LMU) München	**Yes** Hoffmann-La Roche, Janssen-Cilag, AbbVie, GSK, BeiGene, AstraZeneca, Lilly	**No**	**No**	**Yes** Hoffmann-La Roche, Janssen-Cilag, AbbVie, GSK, BeiGene, AstraZeneca, Lilly	**Yes** Hoffmann-La Roche, Janssen-Cilag, AbbVie, GSK, BeiGene, AstraZeneca, Lilly	**No**	**No**

Legend:

[1] - Current employer, relevant previous employers in the last 3 years (institution/location).

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