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Chronic Lymphocytic Leukemia (CLL)

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

DGHO DEUTSCHE GESELLSCHAFT FÜR HÄMATOLOGIE UND MEDIZINISCHE ONKOLOGIE

ÖGHO Österreichische Gesellschaft für Hämatologie & Medizinische Onkologie

SSMO SSOM SGMO

SGH+SSH

Publisher

DGHO Deutsche Gesellschaft für Hämatologie und
Medizinische Onkologie e.V.
Bauhofstr. 12
D-10117 Berlin

Executive chairwoman: Prof. Dr. med. Claudia Baldus

Phone: +49 (0)30 27 87 60 89 - 0

info@dgho.de
www.dgho.de

Contact person

Prof. Dr. med. Bernhard Wörmann
Medical superintendent

Source

www.onkopedia-guidelines.info

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Date of document: September 2025

Compliance rules:

- Guideline
- Conflict of interests

Authors: Clemens-Martin Wendtner, Othman Al-Sawaf, Mascha Binder, Peter Dreger, Michael Gregor, Michael Hallek, Ulrike Holtkamp, Henriette Huber, Thomas Nösslinger, Ron Pritzkuleit, Katharina Prochazka, Johannes Schetelig, Simon Schliffke, Ingo Schwaner, Philipp Bernhard Staber, Eugen Tausch, Minna Voigtländer, Thorsten Zenz, Barbara Eichhorst, Stephan Stilgenbauer
Previous authors: Richard Greil, Wolfgang Ulrich Knauf, Eva Lengfelder, Michael Steurer, Bernhard Wörmann

1 Abstract

Chronic lymphocytic leukemia (CLL) is the most common form of leukemia in Central Europe. CLL is clinically and biologically heterogeneous. The median age of onset is 70 years, with a wide age range. The disease may be preceded by monoclonal B-cell lymphocytosis (MBL).

Antineoplastic treatment is only initiated when symptoms appear. The choice of drugs depends on the general condition of the patient, relevant comorbidities, and genetic changes in the CLL cells. Therapy has changed; instead of the previous standard of chemoimmunotherapy, targeted inhibitors that interfere with B-cell receptor signaling or the regulation of programmed cell death are now used as standard. The optimal combinations and sequences of the various CLL therapeutics currently available have not yet been firmly established.

2 Basics

2.1 Definition and basic information

The WHO classification describes CLL as an indolent (lymphocytic) B-cell lymphoma characterized by a leukemic course. In contrast to earlier versions, B-PLL is no longer considered an entity in the current version of the WHO classification (2022) and has been integrated into other entities (prolymphocytic variant of CLL (>15% prolymphocytes), variant of mantle cell lymphoma, splenic B-cell lymphoma/leukemia with prominent nucleoli) [1]. Small lymphocytic lymphoma (SLL) is a B-cell lymphoma that shows the same histological and immunophenotypic picture as CLL, but primarily manifests in lymph nodes, spleen, or other lymphatic organs, while the peripheral blood shows no or only minor involvement (<5,000 B lymphocytes/µl). In the 2022 WHO classification, SLL and CLL are considered to be one entity, and the same treatment recommendations apply to SLL as to CLL.

2.2 Epidemiology

CLL is the most common leukemic disease in Western industrialized countries. According to current data from the US (SEER database), the age-adjusted incidence of CLL was 4.9 per 100,000 inhabitants per year. Approximately 0.6% of people develop CLL during their lifetime. The median age at diagnosis was 70 years. Only 9.1% of patients with CLL were younger than 45 years. Men were more frequently affected (M:F 1.9:1) [2].

While the incidence of CLL has remained stable over the last two decades, mortality has decreased. The 5-year relative survival rate for cases of CLL was 65.1% in 1975 and improved to 87.2% by 2021 [2]. While similar epidemiological data have been reported in Europe, the incidence is lower among the Asian population [3, 4].

2.3 Pathogenesis

CLL has a characteristic immunophenotype but is biologically and clinically heterogeneous. Key elements of pathogenesis are the inhibition of apoptosis and the dysregulation of proliferation. Genome analyses have led to the identification of numerous genetic aberrations and, increasingly, to the differentiation of clinically relevant subgroups with different signaling pathways [5, 6].

The B-cell receptor signaling pathway is of particular importance, as the blockade of critical kinases, including BTK and PI3K, can be used therapeutically. BCL2-dependent signaling pathways are also pathogenetically important for the apoptosis defect in CLL, whereby BH3 mimetics can counteract this effect through their pro-apoptotic action and can therefore be used therapeutically.

The growth and circulation of CLL cells are also determined by interaction with the microenvironment [7].

2.4 Risk factors

The risk of developing CLL is increased by the following factors:

Acquired factors

- According to the German Occupational Diseases Regulation (No. 1318), exposure to organic solvents, e.g., benzene, can be considered a risk factor [8]. However, there is currently no reliable evidence for this or for the significance of other acquired risk factors.

Hereditary factors

- First-degree relatives of CLL patients have an 8.5-fold increased risk of developing CLL and a 1.9- to 2.6-fold increased risk of developing another indolent lymphoma [9, 10]. However, due to the low incidence of these lymphatic neoplasms, the absolute risk of disease among relatives is still low.
- A small group of patients come from families with a strikingly high incidence of CLL and other indolent lymphomas [9, 10]. The genetic basis of this predisposition is not yet fully understood [10].

CLL is usually preceded by an undiagnosed, clinically asymptomatic preliminary stage with proliferation of clonal B cells. These have the biological characteristics of CLL cells and are referred to as monoclonal B-cell lymphocytosis (MBL), see Onkopedia Monoclonal B-cell lymphocytosis. MBL is detectable in >5% of people over the age of 60. The risk of progression to CLL requiring treatment is approximately 1%/year [11]. It depends on the number of monoclonal B lymphocytes [12].

3 Prevention and early detection

There is no evidence for effective preventive measures. Early detection based on the identification of monoclonal B-cell lymphocytosis has not been established. It would only be useful if the early diagnosis of CLL led to a significant improvement in prognosis.

4 Clinical picture

The disease is characterized by lymphocytosis, which is often discovered by chance. As the disease progresses, lymphadenopathy, splenomegaly and hepatomegaly, signs of bone marrow insufficiency, and possibly autoimmune cytopenias may occur. Clinical symptoms may manifest primarily in the form of B symptoms and an increased susceptibility to infection.

5 Diagnosis

5.1 Criteria

According to the criteria of *the International Workshop on CLL (iwCLL) 2018,* the diagnosis of CLL is defined by the fulfillment of the following criteria [13]:

- Detection of at least 5,000 clonal B lymphocytes per µl in peripheral blood for at least three months. Below this value, monoclonal B-cell lymphocytosis (MBL) can be diagnosed if there are no signs of disease (B symptoms, lymphadenopathy, hepatomegaly, splenomegaly, cytopenia, etc.).
- Predominance of small, morphologically mature lymphocytes in the cytological examination of the blood smear.
- Coexpression of the B-cell antigens CD19 and CD23 with the T-cell antigen CD5 in multiparametric immunophenotyping. Another characteristic feature is the relatively weak expression of surface immunoglobulin, CD20, and CD79b. The monoclonal nature of the lymphocytes can be demonstrated by light chain restriction (Igκ or Igλ), preferably by double labeling of CD19/Igκ or CD19/Igλ.

Characteristic findings from microscopy, immunophenotyping, and genetics are presented in the Chronic Lymphocytic Leukemia knowledge database and in the eLCH - eLearning Curriculum Hematology for bone marrow cytology using virtual microscopy (https://ehaematology.com/).

5.2 Diagnostics

The diagnostic procedure depends on the primary constellation of findings, usually characterized by the key finding of lymphocytosis with or without accompanying lymphadenopathy. If CLL is suspected, the following tests are recommended, see table 1 and table 2.

Table 1: Diagnostics for suspected CLL

Test	Comments
Medical history	Poor performance, B symptoms, susceptibility to infection, etc., Previous blood counts/leukocyte counts, family medical history
Physical examination	Lymph node status, determination of spleen and liver size, signs of bleeding and anemia
Blood count	Leukocytes with differential blood count (microscopic differentiation), thrombocytes, hemoglobin, reticulocytes (in case of signs of anemia)
Multiparametric immunophenotyping	• Expression of CD19 and CD23 • Coexpression of CD5 • Weak or absent expression of CD20, CD79b, FMC7 • Monoclonal nature of Igκ or Igλ
Bone marrow puncture	Not usually necessary for diagnosis, but may be indicated during the course of the disease to assess unclear cytopenias or the quality of remission
Lymph node extirpation/biopsy	Only indicated if the immunophenotyping result cannot be clearly classified or if transformation into an aggressive lymphoma is suspected (Richter syndrome)

Table 2: Additional diagnostics before initiating therapy

Examination	Comments
Genetics	• del(17p13)* by FISH (mandatory), other aberrations (11q, 13q, 12, 14q, etc. optional) • *TP53* mutation analysis (Sanger sequencing or NGS, mandatory) • IGHV mutation status (to be determined only once, mandatory) • BCR stereotypes (optional) • Complex karyotype (≥3 aberrations), possibly highly complex karyotype (≥5 aberrations) and translocations (metaphase cytogenetics, optional) • Further genetic testing in cases of atypical phenotype to differentiate from other indolent lymphomas • After long-term BTKi therapy, resistance testing can be informative for the choice of follow-up therapy
Further laboratory analyses	Depending on symptoms and planned therapy, e.g.: • Haptoglobin and Coombs tests if hemolysis is suspected • GFR, especially if venetoclax-containing therapy is planned • Quantitative determination of immunoglobulins if immunodeficiency is suspected • β2-microglobulin (prognostic parameter, see CLL-IPI)
Sonography	Abdomen: spleen, liver, lymph nodes
CT/MRI (neck/thorax/abdomen)	Optional prior to planned venetoclax-containing therapy to assess the risk of tumor lysis
ECG/echocardiogram or cardiological examination	Before initiation of therapy with BTK inhibitors (atrial fibrillation, VES)

Legend:
*Notes: *The data on the unfavorable prognosis of patients with 17p13 deletion are based on molecular cytogenetic analyses using FISH. The group of patients with p53 inactivation due to mutations overlaps significantly with that of patients with del 17p13, but is not completely identical.*

5.3 Classification (staging)

For staging according to Binet (more commonly used in Europe, see table 3) [14] or Rai [15], only a physical examination and a blood count analysis are necessary. The five possible affected lymph node regions (neck, axilla, groin region, spleen, liver; e.g., for staging according to Binet) is primarily performed by palpation. The results of instrumental examinations (organomegaly in sonography, CT) are not relevant for staging, even if in individual cases a lymphoma bulk (e.g., mediastinal, retroperitoneal) may be relevant for treatment.

Table 3: Staging according to Binet [14]

Stage	Definition
A	Hemoglobin ≥10 g/dL Thrombocytes ≥100,000/µl Less than 3 affected regions[2] (LN[1] , liver, or spleen)
B	Hemoglobin ≥10 g/dL Platelets ≥100,000/µl 3 or more affected regions[2] (LN[1], liver, or spleen)
C	Hemoglobin < 10 g/dL Platelets < 100,000/µl

Legend:
[1] LN = lymph node;
[2] The regions (n=5) include cervical, axillary, and inguinal LN enlargement (unilateral or bilateral), as well as liver and spleen enlargement (detected only by physical examination).

5.4 Prognostic factors

Among the biological prognostic factors, serum β_2 microglobulin (chapter 5.2, table 2) and, at the genomic level, *TP53* aberrations (17p13 deletion (FISH) and *TP53* mutation (Sanger sequencing or NGS)), the mutation status of the variable segments of the immunoglobulin heavy chain genes (IGHV), and the complex karyotype are currently considered to be particularly relevant for prognosis (table 2). Other biomarkers, such as SF3B1/NOTCH1 mutations and other genomic aberrations, require additional prospective validation and are currently not the basis for specific therapeutic considerations outside of clinical trials. Their routine determination is not indicated outside of clinical trials.

In order to better assess the prognosis before initiating first-line therapy, the so-called CLL-IPI (International Prognostic Index) can be determined, whereby the following parameters are required for calculation (https://www.qxmd.com/calculate/cll-ipi): age (≤/> 65 years), Binet stage, β_2 microglobulin (</>3.5 mg/dl), IGHV mutation status, deletion 17p13 (FISH), and *TP53* mutation status [16]. This prognostic index was developed on the basis of immunochemotherapy. It retains its value for targeted therapies in assessing progression-free survival (PFS), but not for overall survival (OS) and is therefore not relevant for the choice of primary therapy [17].

5.5 Differential diagnoses

The most common differential diagnoses are:

- Monoclonal B-cell lymphocytosis (for the risk of progression to CLL, see Onkopedia Monoclonal B-cell lymphocytosis (in German only)).
- Small lymphocytic lymphoma (SLL): Nodal, non-leukemic lymphoma with the microscopic and immunophenotypic profile of CLL
- Reactive lymphocytosis (viral infections, collagenoses).
- Other indolent lymphomas with a leukemic course (follicular lymphoma, see Onkopedia Follicular Lymphoma (in German only); lymphoplasmacytic lymphoma, see Onkopedia Waldenström's Macroglobulemia (in German only) / Lymphoplasmacytic Lymphoma; marginal zone lymphomas, see Onkopedia Marginal Zone Lymphoma (in German only), mantle cell lymphoma, see Onkopedia Mantle Cell Lymphoma (in German only)).
- Hairy cell leukemia (see Onkopedia Hairy Cell Leukemia).

Special attention must be paid to distinguishing it from mantle cell lymphoma due to the similar immunophenotype with coexpression of CD19 and CD5, although mantle cell lymphomas are usually negative for CD23, unlike CLL. In cases of non-classical immunophenotype of CLL,

FISH analysis to rule out the typical aberration of mantle cell lymphomas, i.e., translocation (11;14), or histological examination is indicated.

In patients with rapidly increasing lymphadenopathy or severe B symptoms, Richter transformation should be ruled out by biopsy at any stage of the disease. PET-CT is useful for detecting the most likely location of the transformation.

6 Therapy

6.1 Therapy structure

Therapy is generally indicated in Binet stage C and in Binet stage B or A, if further **criteria for mandatory therapy** are met (active disease according to iwCLL criteria [13]):

- Occurrence/worsening of anemia/thrombocytopenia.
- Massive (>6 cm below the rib cage), progressive, or symptomatic splenomegaly; note: spleen size varies individually depending on body size and weight.
- Massive (>10 cm in diameter), progressive, or symptomatic lymphadenopathy.
- Lymphocyte doubling time of less than 6 months or 50% increase in 2 months, starting from a baseline value of at least 30,000 lymphocytes/µl, and after exclusion of other causes of lymphocytosis.
- Autoimmune cytopenia refractory to standard therapy (corticosteroids).
- One of the following constitutional symptoms:
    - Unintentional weight loss >10% in 6 months
    - Fever >38°C of unknown cause for more than 2 weeks
    - Night sweats for more than one month without evidence of infection
    - Severe fatigue

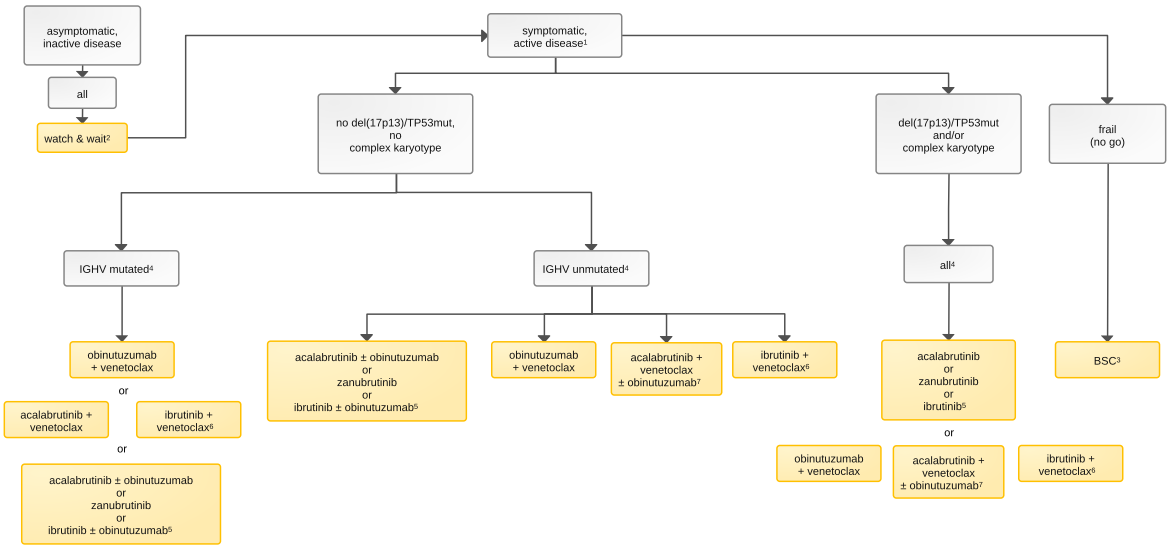
The **structure** of first-line therapy is shown in figure 1, and that of second-line therapy in figure 2.

The **choice of therapy** for CLL is based on specific comorbidity (especially cardiac and renal diseases), concomitant medication (especially anticoagulation), and molecular and cytogenetic status, rather than calendar age. Whenever possible, therapy should be carried out within the framework of clinical trials.

The vertical **ranking** of the individual therapy options shown (figures 1 and 2) corresponds to a prioritization that is not covered by direct comparative, randomized phase III studies with the highest level of evidence. In this respect, it represents a preliminary recommendation from the expert group, which is currently supported by the majority. It should be emphasized, however, that *in practice,* other decision-making factors such as the individual comorbidity profile, adherence aspects, application effort/logistics of the therapeutic intervention, and, above all, patient preference should be taken into account when making the final decision on therapy.

The standard **dosages** for all therapies are based on data from multicenter studies. In cases of advanced age or comorbidity, a dose reduction may be necessary in individual cases, or (more frequently) during the course of therapy as an adjustment to individual side effects. In patients with extensive co-medication, in addition to possible limited compliance, the possible occurrence of drug interactions must also be taken into account.

Figure 1: First-line therapy for CLL



Legend:
palliative therapy approach
[1] Active disease according to the criteria of the IWCLL 2018 [13];
[2] watch & wait – wait-and-see approach;
[3] BSC – best supportive care
[4] The sequence of the following therapies represents one possibility (see chapter 6.1.1.1, chapter 6.1.1.2, and chapter 6.1.1.3.).
Based on the current data, it is not binding. The individual comorbidity profile, adherence aspects, application effort/logistics of the therapeutic intervention, and patient preference for the final therapy decision should be taken into account.
[5] In the event of contraindications to or unavailability of acalabrutinib or zanubrutinib, ibrutinib (+/- obinutuzumab) remains a treatment option, taking into account increased cardiac side effects. Acalabrutinib and zanubrutinib have not been systematically evaluated in younger/fit patients in first-line therapy.
[6] When using I+V, cardiac toxicity must be weighed up, especially in older patients.
[7] When using AV+obinutuzumab, the risk of infectious complications must be weighed, especially in older patients.

6.1.1 First-line therapy

The treatment options in first-line therapy are currently changing and expanding. The following are currently considered **genetic risk factors**:

- del(17p13) or *TP53* mutation
- IGHV unmutated status ($IGHV_{unmut}$)

Various treatment options are available, especially for patients without a high genetic risk profile (without del(17p13) or *TP53* mutation). The selection of options, which are generally chemotherapy-free, is essentially based on existing comorbidities or potential organ toxicities (especially renal or cardiac) as well as possible interactions with medications already prescribed independently of CLL. The relevant results of therapy studies can be summarized as follows:

BTK inhibitors (BTKIs) as monotherapies or in combination with monoclonal anti-CD20 antibodies:

In patients ≥65 years of age with comorbidities, the BTKi **ibrutinib** led to a significant prolongation of both progression-free survival (hazard ratio (HR) 0.16; median not reached) and overall survival (HR 0.16; median not reached) and a significant increase in the remission rate (86% vs. 35%) (RESONATE-2 study) [17].

In the E1912 study, **ibrutinib/rituximab** led to a significant prolongation of progression-free survival (HR 0.352) and overall survival (HR 0.168) compared to fludarabine/cyclophosphamide/

rituximab (FCR) in patients ≤70 years of age (younger and fit patients) [18]. In this study, ibrutinib was given as continuous therapy until disease progression. After a longer follow-up (5 years), a significantly longer PFS (HR 0.27) was documented with ibrutinib/rituximab even in patients with mutated IGHV status (in addition to the quickly recognizable advantage in patients with $IGHV_{unmut}$) [17]. The E1912 study is the only study in which **ibrutinib/rituximab** achieved longer survival compared to chemoimmunotherapy (FCR) [18].

In the ALLIANCE study (randomized comparison of bendamustine plus rituximab (BR) with ibrutinib monotherapy or ibrutinib/rituximab), **ibrutinib** led to a significant prolongation of progression-free survival (HR 0.39) in patients ≥65 years, but not overall survival, not least because of increased toxicity, although follow-up is still relatively short [19]. In addition, the combination of ibrutinib/rituximab shows no advantage over ibrutinib monotherapy. Therefore, ibrutinib is generally recommended as monotherapy, primarily for younger, fit patients.

No data from randomized studies in fit patients <65 years of age are available for the combination of **ibrutinib/obinutuzumab**. Approval was based on data from older patients and patients with comorbidity, see chapter 6.1.1.1.1. EU approval also covers younger patients (corresponding recommendation in figure 1).

No data from randomized studies are currently available for the second-generation BTKi **acalabrutinib** as monotherapy or in combination with obinutuzumab in fit patients <65 years of age. Approval in the ELEVATE-TN study (comparison of acalabrutinib monotherapy with acalabrutinib/obinutuzumab or chlorambucil/obinutuzumab) [20] was based on data from elderly patients and patients with comorbidities. EU approval also covers younger patients (corresponding recommendation in figure 1). Over a longer observation period (5-year update), the CR/CRi rate in the study arm with acalabrutinib and obinutuzumab was 37% with acalabrutinib/obinutuzumab vs. 14% with chlorambucil/obinutuzumab, which translates into an advantage in PFS and overall survival compared to chlorambucil/obinutuzumab [21].

In the ELEVATE-RR recurrence study, a more favorable toxicity profile for acalabrutinib was described in direct comparison to ibrutinib with the same efficacy (in particular, a significantly reduced risk of hypertensive events and atrial fibrillation/flutter).

No data from randomized studies in fit patients <65 years of age are currently available for the second-generation BTKi **zanubrutinib**. Based on the SEQUOIA study (primary therapy in patients aged ≥65 years, randomized comparison of zanubrutinib and BR), EU approval of zanubrutinib for CLL was granted in November 2022 (regardless of fitness and age, first-line and recurrence). In this study, a significant improvement in progression-free survival was documented compared to first-line therapy with bendamustine/rituximab [22].

In a relapse study (ALPINE trial), a direct comparison of zanubrutinib and ibrutinib showed higher efficacy (PFS and overall response rate) and an improved toxicity profile in favor of zanubrutinib with regard to cardiac events (atrial fibrillation/atrial flutter). In addition, this phase III study also showed improved PFS with zanubrutinib compared to ibrutinib (1-year PFS 90% vs. 78%) [23, 24].

By analogy with the data from the recurrence studies (ALPINE, ELEVATE-RR), **a reduced toxicity profile** is also assumed for **zanubrutinib and acalabrutinib** in first-line therapy. In this respect, both substances are recommended in preference to ibrutinib when initiating first-line therapy. Acalabrutinib showed a significantly reduced rate of hypertensive events in the ELEVATE-RR study, but unlike zanubrutinib, it is associated with an increased rate of cephalalgia in the first weeks of therapy.

However, patients already undergoing first-line therapy with ibrutinib without relevant side effects should not be switched to acalabrutinib or zanubrutinib, as current study data indicate

that there are no differences in overall survival between ibrutinib and either of these two substances.

Time-limited combination therapies:

In general, time-limited, i.e., venetoclax-based therapy should be preferred, especially in patients with a long life expectancy and without high-risk characteristics, provided that other factors (e.g., renal function, susceptibility to infection, travel to the treatment center) allow this.

BCL2 inhibitor venetoclax in combination with monoclonal anti-CD20 antibodies:

If long-term therapy is not desired or BTKi therapy is unsuitable (dual platelet aggregation inhibition, severe bleeding tendency, ventricular arrhythmias, possibly severe heart failure), a time-limited therapy based on venetoclax/obinutuzumab (see below) should be chosen as an alternative.

Venetoclax plus obinutuzumab (Venetoclax/Obinutuzumab, VenObi) was approved based on data from patients **of advanced age or with comorbidity**. The time-limited combination therapy consisting of the BCL2 inhibitor venetoclax (12 cycles) plus obinutuzumab (6 cycles) proved to be significantly superior to chemoimmunotherapy with chlorambucil/obinutuzumab in terms of progression-free survival in the CLL14 study (hazard ratio 0.35; median not reached) [25, 26]. After a median observation period of 65.4 months, no difference in overall survival has been observed to date when comparing the two treatment arms [27].
Overall, the combination of venetoclax/obinutuzumab (VenObi) is a very effective but also temporary (12 cycles; planned treatment duration approx. 10.5 months) treatment option in first-line therapy. Patients with **mutated IGHV status** benefit most from this combination therapy, so VenObi is the **primary recommendation** for this low-risk group due to the limited duration of therapy in contrast to continuous BTKi therapy.

Due to its side effect profile, VenObi also proves to be a favorable treatment option for patients with a high cardiac risk profile (especially those with a history of severe arrhythmias). However, VenObi can only be used in exceptional cases in patients with impaired renal function (creatinine clearance <30 ml/min and >15 ml/min) due to a greatly increased risk of tumor lysis syndrome (contraindicated in patients with creatinine clearance below 15 ml/min).

In the CLL13 study by the GCLLSG (randomized comparison **of FCR/BR vs. venetoclax/rituximab vs. VenObi vs. venetoclax/obinutuzumab/ibrutinib),** a significant advantage of **VenObi** in terms of progression-free survival compared to chemoimmunotherapy (FCR, BR) in younger/fit patients has now also been demonstrated [28]. VenObi therefore also represents a good, temporary treatment option for **young/fit patients** with a favorable risk profile ($IGHV_{mut}$, no *TP53* aberration, no complex karyotype). In addition, the triple combination of VenObi + ibrutinib was shown to be superior to the combination of VenObi in terms of prolonging PFS. However, given the lack of difference in overall survival on the one hand and more side effects (including the occurrence of secondary neoplasms) on the other, this combination is not recommended for routine use.

Ibrutinib plus venetoclax:

Ibrutinib/venetoclax (I+V) was approved in August 2022 based on a phase III study (GLOW study), which demonstrated better PFS and OS with I+V compared to a combination of chlorambucil plus obinutuzumab in elderly/comorbid patients [29]. However, the relevant toxicity of the combination in this particular patient population should also be noted, as reflected, for example, in a 14% rate of atrial fibrillation. In addition, data from another study (Phase II CAPTIVATE study), which also included fit patients, were used as a basis for approval. In this study, a good response was also documented in patients with high-risk characteristics (especially with unmu-

tated IGHV status) [30], although direct superiority over other regimens (e.g., venetoclax/obinutuzumab) has not yet been demonstrated.

Monotherapy with ibrutinib over 3 cycles followed by administration of the approved I+V combination over 12 cycles reduced the risk of tumor lysis, allowing the (completely oral) therapy to be administered on an outpatient basis in most cases. I+V is a very effective therapy, but at the same time limited to 15 cycles (approx. 14 months), especially for younger patients with mutated IGHV status who want a time-limited, complete oral therapy. Some data on recurrence after I+V are now also available, which on the one hand show no evidence of the development of BTK or PLCG2 resistance mutations and, on the other hand, also suggest effective retreatment with BTKi [31].

Acalabrutinib plus venetoclax +/- obinutuzumab (AV or AVO):

Acalabrutinib/venetoclax (A+V) +/- obinutuzumab (AVO) was approved by the EMA in June 2025 on the basis of a phase III study (AMPLIFY study). This study demonstrated a significantly better PFS in younger/fit patients without *TP53* aberration compared to chemoimmunotherapy (FCR/BR) [32]. Patients with an unmutated IGHV status in particular benefited from the addition of obinutuzumab (AVO regimen) in terms of PFS. In addition, patients receiving AV also showed better overall survival compared to chemoimmunotherapy. AVO was associated with an increased incidence of severe, sometimes fatal, infectious complications (the study was conducted during the COVID-19 pandemic), so that, in contrast to the AV regimen, no survival advantage was seen for AVO compared to chemoimmunotherapy. AV and AVO are therefore recommended as temporary therapies, similar to I+V, especially in low-risk (IGHVmut) and intermediate-risk (IGHVunmut) patients. Data on high-risk patients (*TP53* aberration) are not available from the AMPLIFY study, as this patient group was excluded from the study.

6.1.1.1 Favorable genetic risk profile (mutated IGHV status, no del(17p13)/TP53 mutation, no complex karyotype)

In summary, in patients with **a favorable genetic risk profile** ($IGVH_{mut}$, no *TP53* mutation, no complex karyotype), temporary therapy with **venetoclax/obinutuzumab** (12 cycles) should be used preferentially. Time-limited, purely oral therapy based on **ibrutinib plus venetoclax** or, alternatively, acalabrutinib plus venetoclax is also recommended in first-line therapy, especially for younger patients without concomitant cardiac disease and with mutated IGHV status. In cases of severely impaired renal function (GFR < 30 ml/min) or if purely oral therapy is desired, or in cases of logistical and/or biological problems with regard to the venetoclax dosing phase, primary therapy with a second-generation BTK inhibitor—**acalabrutinib or zanubrutinib**—as oral long-term therapy should be considered in this group. However, the increased cardiotoxicity of ibrutinib compared to second-generation BTKIs should be explicitly pointed out. In cases of severe cardiac comorbidities (including ventricular extrasystoles), venetoclax/obinutuzumab is the preferred recommendation, whereas in cases of renal impairment, BTKi-based therapy should be preferred (figure 1).

In patients who do not want therapy with a signaling pathway inhibitor or are unsuitable for it (e.g., combined severe cardiac and renal comorbidity), chemoimmunotherapy with **chlorambucil/obinutuzumab** or **bendamustine/rituximab** (bendamustine dose reduced to 70 mg/m^2, days 1 and 2) **or FCR** (contraindicated in renal insufficiency). However, the significantly reduced efficacy with shorter PFS compared to BTK or BCL2 inhibitor-based therapy must be explicitly pointed out.
In cases of very **high tumor burden** (hyperleukocytosis, lymphadenopathy >10 cm, etc.), chemotherapy-based tumor debulking with alkylating agents such as bendamustine or cyclophosphamide is also possible on a case-by-case basis [33].

6.1.1.1.1 Poor general condition (frail patients, no go)

For patients in very poor general condition and with a short life expectancy due to comorbidities or general frailty not related to CLL, supportive therapy is the first line of treatment. In selected cases, however, not least on the basis of the FRAIL study, a trial of BTKi-based monotherapy may be attempted, as the therapeutic effect could improve the general condition and thus the frailty *per* se [34].

6.1.1.2 Intermediate genetic risk (unmutated IGHV status, no del(17p) or TP53 mutation, no complex karyotype)

For patients with an unmutated IGHV status without other genetic risk factors (no *TP53* aberration), the treatment options described in chapter 6.1.1.1 are available. The selection of therapy options, which are generally chemotherapy-free, is essentially based on existing comorbidities (especially renal or cardiac) or potential organ toxicities, as well as possible interactions with medications already prescribed independently of CLL.

The available data can be summarized as follows:

Based on the favorable study results, continuous therapy based on second-generation BTK inhibitors (**acalabrutinib +/- obinutuzumab; zanubrutinib**) or time-limited therapy with **venetoclax/obinutuzumab**, **ibrutinib plus venetoclax,** or acalabrutinib plus venetoclax (with obinutuzumab if necessary) is primarily recommended as equivalent (figure 1). Acalabrutinib could be combined with obinutuzumab in this subgroup, as the 6-year follow-up of the ELEVATE-TN study showed a clear difference in PFS (75% vs. 60%), albeit no significant difference in OS, compared to acalabrutinib monotherapy [35]. Furthermore, within the ibrutinib arm of the E1912 study (comparison of ibrutinib/rituximab vs. FCR), no significant difference in PFS was observed between IGHV-mutated and IGHV-unmutated patients after 4 years of observation. In contrast, other randomized studies (ALLIANCE, ILLUMINATE) with BTKIs show a reduced PFS in the group with unmutated IGHV. However, due to the cardiovascular toxicity profile (see chapter 6.1.1.1), therapy with ibrutinib monotherapy is not primarily recommended, in contrast to the second-generation BTKIs acalabrutinib and zanubrutinib, unless patients are young and fit and have no previous cardiac conditions. With time-limited **venetoclax/obinutuzumab**, **ibrutinib plus venetoclax**, or acalabrutinib plus venetoclax (+/- obinutuzumab) or venetoclax/obinutuzumab + ibrutinib, PFS is significantly worse for patients with unmutated IGHV status (compared to $IGHV_{mut}$). However, the median PFS for patients with unmutated IGHV status after one year of therapy is more than 5 years, which means at least 4 years of therapy-free time for half of the patients. The longer time to first PFS with continuous BTKi compared to time-limited venetoclax-based therapy does not show any fundamental superiority in the long term, as (although the evidence is limited) venetoclax-based treatment can be repeated in relapse. The results of a randomized comparison (CLL17 study) between venetoclax/obinutuzumab and continuous BTKi therapy (including unmutated patients) are currently pending.

In cases of severe cardiac comorbidities (including ventricular extrasystoles), **venetoclax/ obinutuzumab** is recommended as the first choice regardless of IGHV status.

The combination of **ibrutinib plus venetoclax** (I+V) can also be used in patients with intermediate risk ($IGHV_{unmut}$) as a temporary therapy (15 cycles). However, data from the GLOW study show a shortened PFS for the I+V arm in patients with $IGHV_{unmut}$ compared to the subgroup of patients with $IGHV_{mut}$. However, the time to next therapy (TTNT) after I+V is approximately 20% after 5 years for both molecularly defined subgroups. For the combination based on **acalabrutinib plus venetoclax**, patients with $IGHV_{unmut}$ also showed a poorer 3-year PFS compared to the $IGHV_{mut}$ subgroup (69% vs. 86%), although this effect was almost offset by

the addition of **obinutuzumab (AVO)** (3-year PFS for AVO: $IGHV_{mut}$ 84% vs $IGHV_{unmut}$ 83%). However, the higher rate of possible infections associated with this triple combination, as described in the AMPLIFY study with regard to COVID-19, must be taken into account, as this tends to be a disadvantage for AVO in terms of OS.

For patients who do not want a signaling pathway inhibitor or are unsuitable for it, the classic treatment with **chlorambucil/obinutuzumab** or **bendamustine/rituximab or FCR** can be used in exceptional cases, with reference to the significantly poorer efficacy (see chapter 6.1.1.1).

Overall, it can therefore be concluded that for the group with intermediate genetic risk ($IGHV_{unmut}$) without simultaneous evidence of high-risk genetics, such as TP53- mutation/ del(17p13)), continuous therapy with a BTKi or, alternatively, temporary therapy in the form of VenObi or I+V or AV can be recommended on an equal footing according to current knowledge. The specific choice depends on individual patient characteristics (comorbidities, co-medication, patient preference, etc.).

6.1.1.3 High genetic risk (del(17p), TP53 mutation)

In cases of CLL requiring treatment with del(17p13)/*TP53* mutation or evidence of a complex aberrant karyotype**,** the **continuous use of BTKIs, primarily acalabrutinib or zanubrutinib** (ibrutinib is also possible as a secondary option in case of contraindications), is recommended regardless of the patient's general condition, taking into account efficacy and side effects. Alternatively, especially in cases where BTKIs are not suitable, the combination of **venetoclax/obinutuzumab** (over 12 cycles) or continuous venetoclax monotherapy can be used in first-line therapy, although the CLL14 study showed significantly poorer PFS and overall survival for venetoclax/obinutuzumab compared to subgroups without *TP53* mutation. Since August 2022, a time-limited combination therapy (over approximately 14 months) in the form of **ibrutinib plus venetoclax** (I+V) has also been approved for first-line therapy of CLL, which also includes patients with high-risk aberrations. In the CAPTIVATE study (chapter 6.1.1.1.1), this subgroup also showed a good response based on a small number of cases (n=27), although PFS is shorter than in patients without *TP53* aberrations (EHA2024) [29, 30]. Formally, the combination of **acalabrutinib plus venetoclax (+/- obinutuzumab; AV/AVO)** has also been approved for patients at highest risk since June 2025, even though the AMPLIFY approval study explicitly excluded patients with *TP53* aberrations. In individual cases, however, AV or AVO can also be used in patients with a high-risk constellation (*TP53* aberration, complex karyotype), even though no detailed data are currently available in the context of a phase III study, but only phase II data for this combination [36].

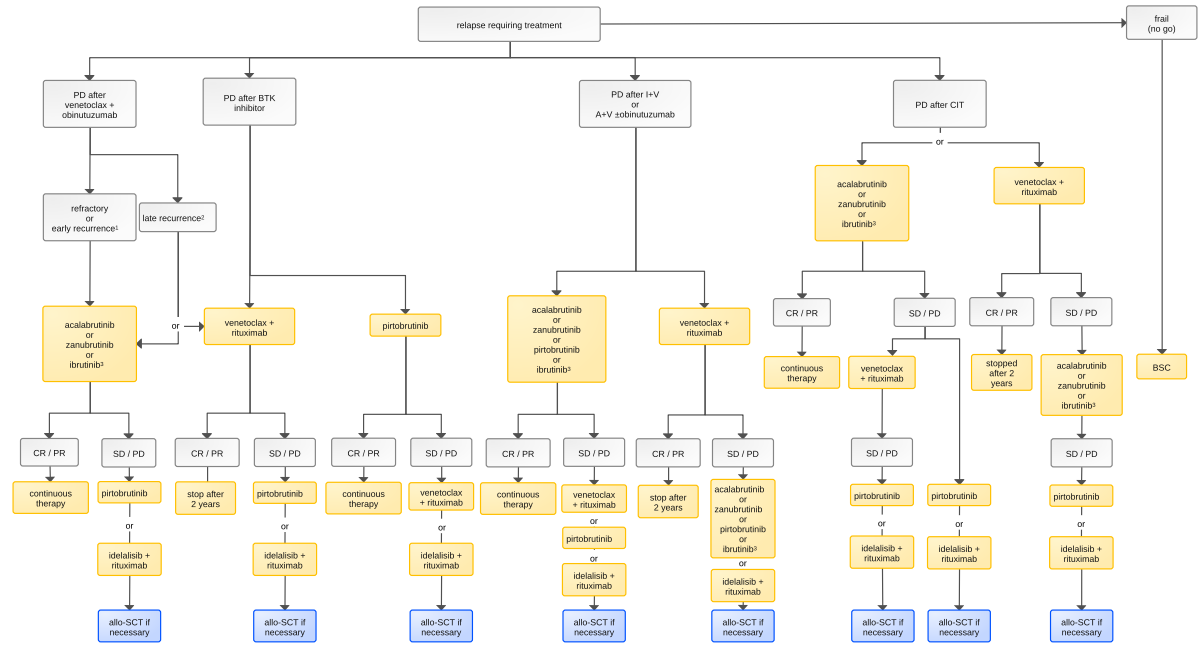
Overall, despite the currently limited data available, continuous therapy based on second-generation BTKIs should be recommended as the primary treatment for patients with a high-risk genetic profile. Otherwise, time-limited therapies (Ven/Obi or I+V or AV or AVO) are also possible and approved based on individual patient characteristics.

6.1.2 Second-line therapy

The **choice of relapse therapy** depends on several individual factors. In addition to the patient's age and comorbidity, these are primarily clinical parameters such as the type of primary therapy, the duration of remission achieved with it, and any changes in the biological characteristics of CLL since the initial diagnosis in terms of clonal evolution (e.g., acquisition of a del(17p13) or *TP53* mutation). After long-term therapy with BTK or BCL2 inhibitors, specific resistance mutations (including in *BTK*, *PLCγ2*, and *BCL2*) may also occur, the detection of which makes it inadvisable to repeat the corresponding therapy. Resistance testing can be

informative, especially when using pirtobrutinib after failure of acalabrutinib or zanubrutinib, as cross-resistance may occur. However, the clinical significance of not all variants is clear. In principle, due to the clear superiority of the new substances (especially BTK and BCL2 inhibitors) over various chemoimmunotherapies in terms of OS, the latter should only be used in very select and exceptional cases of recurrence that have been discussed by a tumor board (patient request, combined cardiac/renal pre-existing conditions, etc.). If a patient has received chemoimmunotherapy as primary therapy, chemoimmunotherapy is not recommended in cases of recurrence, even after a long remission period of >24 months, due to the proven survival benefit (e.g., MURANO study) and the risk of secondary malignancies (including tMDS). Instead, therapy with new substances is favored. An algorithm is shown in figure 2. Whenever possible, therapy should be carried out within the framework of clinical studies.

Figure 2: Treatment of CLL in cases of recurrence and refractoriness



Legend:
palliative therapy approach; curative therapy approach;
CR – complete remission, PD – progression; PR – partial remission; SD – stable disease: according to the criteria of the IWCLL 2018 [13], stable disease is considered a treatment failure; BSC – best supportive care; alloSCT – allogeneic stem cell transplantation,
[1] Early relapse: remission duration less than 2 to 3 years; in the event of progression or early relapse, Richter transformation should be ruled out by means of PET-CT and lymph node histology.
[2] Late relapse: remission duration longer than 2 to 3 years.
[3] If acalabrutinib or zanubrutinib is contraindicated or unavailable, ibrutinib remains a treatment option, taking into account increased cardiac side effects.

Patients who are refractory to ongoing therapy or who achieve a remission duration of less than 3 years and patients who have relapsed with evidence of del(17p13) or a *TP53* mutation have a poor prognosis. Before the introduction of the new substances, their median overall survival was one to two years, calculated from the time of salvage therapy. In these studies, achieving "stable disease" status in patients requiring treatment according to the criteria of the IWCLL 2018 was also considered a treatment failure [13].

Meanwhile, with the covalent **BTK inhibitors** ibrutinib, acalabrutinib, and zanubrutinib, the non-covalent binding BTK inhibitor pirtobrutinib (approved in Germany since March 31, 2025, after at least one prior therapy with covalent BTKi), the **BCL2 inhibitor** venetoclax (plus rituximab), and the **PI3Kdelta inhibitor** idelalisib (plus rituximab), four different drug groups are now available for this patient population. The approval studies mainly included patients with recurrence after chemoimmunotherapy, so that overall, the data available for the use of these new substances in prior therapy with BTK inhibitors or with venetoclax-based regimens is limited.

The most important **current study data** can be presented as follows, although it should be noted that in these studies, prior treatments were mostly chemoimmunotherapy-based, so that the significance with regard to relapse therapy after targeted therapeutics is limited.

- Compared with the anti-CD20 antibody ofatumumab, the BTK inhibitor **ibrutinib** led to a significant prolongation of progression-free survival (HR 0.13; median not reached) and overall survival (HR 0.59) (RESONATE-1 study) [37].
- The BTK inhibitor **acalabrutinib** led to a significant prolongation of progression-free survival (HR 0.31) in patients who had received at least one prior therapy compared to a therapy chosen by the treating physician (idelalisib/rituximab or bendamustine/rituximab) (ASCEND study) [38].
- The BTK inhibitor **zanubrutinib** resulted in a better remission rate (80.4% vs. 72.9%, p=0.0264) and better 2-year PFS (78.4% vs. 65.9%) in patients with relapsed CLL compared to ibrutinib (ALPINE study) [24]. In the subgroup of patients with *TP53* aberration, a significantly better PFS was observed compared to ibrutinib (HR 0.53) [24].
- The non-covalently binding BTK inhibitor **pirtobrutinib** was explicitly tested in the BRUIN-321 study in patients who had all been pretreated with a covalent BTKI and, in half of the cases, also with a BCL2i. Compared to relapse therapy based on bendamustine/rituximab or idelalisib plus rituximab, pirtobrutinib showed significantly better PFS (14 months versus 8.7 months). The time to next treatment (TTNT) was also significantly prolonged with pirtobrutinib (24 months versus 10.9 months) [39].
- The BCL2 inhibitor **venetoclax** in combination with rituximab led to a prolongation of progression-free survival (HR 0.16; median not reached) and overall survival (HR 0.50; median not reached), an increase in the rate of hematological remissions and MRD negativity (MURANO study) [40, 41].
  Venetoclax as monotherapy in patients with relapsed or refractory CLL with evidence of del(17p13) or a *TP53* mutation and after prior treatment with a BCR signaling pathway inhibitor resulted in a remission rate of 79% (single-arm study) [42, 43].

The **recommended treatment for disease recurrence** (see figure 2) depends largely on the previous treatment:

For patients after **first-line treatment with chemoimmunotherapy**, BTK inhibitors are also available as an alternative to the combination of venetoclax/rituximab for second-line therapy. Results from direct comparative studies between venetoclax/rituximab and ibrutinib or acalabrutinib or zanubrutinib are not available. Even though direct data from studies for this patient group are lacking, if a *TP53* aberration is detected, even in recurrence, continuous therapy with a BTKi would in principle be preferred over temporary BCL2i-based treatment (VenR), and in the case of mutated IGHV, temporary therapy with venetoclax/rituximab would be preferred.

In patients who **have previously been treated with BTK inhibitors**, the combination of venetoclax/rituximab (VenR) or venetoclax monotherapy is the preferred standard of care from second-line therapy onwards, regardless of risk classification and fitness, due to its high effectiveness and limited duration of therapy (2 years for VenR). Due to the clear superiority of VenObi over VenR in the first line (see CLL13 study by the GCLLSG), the VenObi regimen (analogous to the CLL14 study) could also be considered on a case-by-case basis and after prior confirmation of cost coverage. Based on EMA approval, pirtobrutinib may now also be used in Germany from the second line onwards in patients who have previously been treated with BTKi (even without prior therapy containing venetoclax). Overall, even in cases of recurrence, the advantages and disadvantages of temporary therapy versus long-term therapy must be considered and discussed with the patient, as is the case with first-line therapy.

Conversely, BTK inhibitors show very good efficacy in patients who **have received prior therapy with venetoclax plus obinutuzumab**. Even after prior treatment with venetoclax plus

obinutuzumab, retreatment with venetoclax (plus rituximab, according to current approval) may be effective, especially in cases of prolonged remission (more than 2 to 3 years). Re-exposure with VenObi in relapse is currently being tested in the ReVenG study. However, there is currently insufficient data on how long remission should last for re-treatment with the BCL2 inhibitor to be useful.

For patients who relapse after or during primary therapy based on ibrutinib plus venetoclax (I+V) or acalabrutinib plus venetoclax (AV, AVO), initial data are available on retreatment with a BTKi or venetoclax-based therapy. In principle, therefore, only a preliminary recommendation for relapse therapy based on BTKi monotherapy (including pirtobrutinib, venetoclax monotherapy, venetoclax/rituximab, or, in individual cases, idelalisib/rituximab) can be made at this time.

In summary, after pretreatment with venetoclax/obinutuzumab and I+V, retreatment with venetoclax (plus rituximab) or a switch to a BTK inhibitor is possible. Conversely, after treatment failure in the sense of progression under a covalent BTK inhibitor, treatment with venetoclax (+/- rituximab) or with the non-covalent BTK inhibitor pirtobrutinib can be carried out. If intolerance is the cause of first-line failure, a switch to another BTKi may be possible. When using BTKi, second-generation BTKi (acalabrutinib, zanubrutinib) are preferable due to their more favorable side effect profile and, in some cases, better effectiveness (zanubrutinib); ibrutinib is still available as an alternative therapy. No reliable data on the optimal sequence is available to date.

6.1.2.1 Further recommendations in case of progression or early recurrence (less than 3 years)

In cases of clinical progression after the use of BTK inhibitors and BCL2 inhibitors (so-called double-refractory or double-exposed CLL), therapy with the non-covalently binding BTK inhibitor pirtobrutinib may be useful. The BRUIN-321 study, which randomly compared the use of pirtrobrutinib versus idelalisib/rituximab or bendamustine/rituximab, was relevant for approval. Based on n=238 patients, a significantly better median PFS was observed with pirtobrutinib (14 months versus 8.7 months with SOC). The time to next treatment (TTNT) was also significantly longer with pirtobrutinib (24 months vs. 10.9 months with SOC) [39]. On March 31, 2025, the EMA approved pirtobrutinib after BTKi pretreatment, i.e., also for double-refractory patients.

Resistance mutations in BTK and PLCG2 can develop during continuous therapy with covalent BTK inhibitors. The common C481S mutation confers resistance to ibrutinib, acalabrutinib, and zanubrutinib, while pirtobrutinib remains effective. In contrast, mutations at T474 and L528 also lead to resistance to pirtobrutinib. In the BRUIN-321 study, patients with PLCG2 mutations also showed a reduced response. Therefore, testing for resistance mutations is recommended before using pirtobrutinib after prior therapy with a covalent BTKi. However, such testing is not necessary after temporary combination therapy, as resistance mutations are extremely rare in recurrence [44].

Exclusion of **Richter transformation** by PET-CT and lymph node histology.

In patients with transformation of CLL into large B-cell lymphoma (LBCL) in the sense of Richter transformation, chemoimmunotherapy based on R-CHOP can be performed. However, the results are very poor, with survival times of less than 1 year. In biologically young patients, consolidating allogeneic stem cell transplantation is therefore recommended, if possible, especially if LBCL and CLL are clonally related (no independent secondary lymphoma). If the patient is not suitable for allogeneic transplantation, autologous stem cell transplantation may be considered instead [45]. If there are contraindications to allogeneic or autologous stem cell transplanta-

tion, immunotherapy with checkpoint inhibitors (off-label) can also be considered as a salvage option [46]. Recently, high efficacy (ORR 58.3%; 1-year OS 74.7%) has also been reported for the combination of tislelizumab and zanubrutinib (RT1 study) in patients with Richter transformation [47]. Whenever possible, patients should be treated in clinical trials.

Patients with **transformation to Hodgkin lymphoma** should receive chemotherapy as for primary Hodgkin lymphoma.

Allogeneic stem cell transplantation is an option for high-risk patients, see chapter 6.1.3. and figure 2.

6.1.3 Allogeneic stem cell transplantation

The availability of highly effective molecular therapies with the associated improvement in prognosis has greatly relativized the importance of allogeneic stem cell transplantation (allo-SCT) in CLL. However, it remains an option in situations that are associated with a relatively poor prognosis even with modern therapeutic options. Its effectiveness even after prior exposure to signaling pathway inhibitors has been proven [48]. In view of the availability of non-covalent BTK inhibitors, the indication for alloSCT should be even more cautious. It appears to be worth considering primarily in patients with *TP53* alteration or highly complex karyotype who have become refractory to covalent BTKi or venetoclax, or if, regardless of *TP53* status, both substance classes have failed in the sense of "double-refractory CLL" [49].

The indication, timing, and performance of a transplant, including the search for a donor, should be clarified in close cooperation with a transplant center before initiating salvage therapy. An important prognostic factor for achieving long-term disease control is the presence of remission at the time of allogeneic transplantation. If possible, the transplant should be performed within clinical trials.

6.1.4 Autologous stem cell transplantation

High-dose therapy with autologous blood stem cell transplantation can no longer be recommended for the treatment of CLL.

6.1.5 CAR-T cell therapy

CAR-T cell therapy has not been established as a treatment for either untransformed CLL or Richter transformation. On March 15, 2024, Liso-cel was approved by the FDA for patients with BTK inhibitors and BCL2 inhibitors refractory to CLL in the US, based on the CLL004 study, in which an overall response rate of 47% and a CR rate of 18% with promising response durations were achieved in this patient population [50]. However, EMA approval is not currently expected, and the significance of CAR T-cell therapy in relapsed CLL, especially in comparison to allo-HSCT, cannot yet be conclusively assessed. CAR T-cell therapy should therefore be carried out within the framework of clinical trials whenever possible.

In retrospective, multicenter analyses, evidence of efficacy was found for the CAR T-cell products Axi-cel, Tisa-cel, and Liso-cel, which are approved for LBCL, in patients with Richter transformation. However, with 2-year PFS rates of around 30%, the results appear to be somewhat worse than in de novo LBCL [51, 52]. Nevertheless, commercial CAR-T therapy can be considered a potentially curative option in individual cases of recurrence outside of studies, especially if a response to salvage therapy can be achieved and allo-SCT is not an option.

6.1.6 Supportive therapy and treatment of complications

CLL patients often develop infectious complications during the course of the disease, which are exacerbated by the decrease in immunoglobulin concentrations and other mechanisms of acquired immunodeficiency (see Onkopedia secondary immunodeficiencies (in German only)). Particularly careful monitoring with intensive general internal medical treatment, e.g., for chronic or recurrent bronchitis, is indicated. Prophylactic substitution with immunoglobulins reduces the risk of severe infections but has no significant effect on mortality. In June 2018, the EMA updated its guideline in the form of a Summary of Product Characteristics and established the following criteria for substitution with immunoglobulins for patients with secondary immunodeficiency [53]:

- Severe or recurrent infections
- Ineffective antimicrobial therapy
- Evidence of a lack of specific antibody formation (after vaccination) or serum IgG levels <4g/l.

Age-appropriate vaccinations are recommended, see Onkopedia - Vaccinations (in German only), although the formation of specific antibodies may be reduced, and vaccinations should be given before starting therapy whenever possible. Travel vaccinations should only be given after consultation with the attending specialist, as live vaccines, among other things, could endanger the patient.

6.1.7 Therapy for autoimmune phenomena

Autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP) are common concomitant phenomena of CLL [54]. AIHA is usually Coombs-positive. Cold agglutinins with detection of IgM antibodies are the exception. Coombs-negative hemolytic anemias have been described after previous purine analog therapy. Patients should be made aware of the particularly high risk of crises in the context of infections. Pure red cell aplasia (PRCA) is rarely observed. If AIHA or ITP occurs alone without other symptoms of CLL requiring treatment (see above), therapy with corticosteroids is indicated. Otherwise, therapy according to the above algorithms (see tables 1 and 2) is recommended, with a preference for anti-CD20-containing therapies (VenObi, Acalabrutinib-Obi, Venetoclax/Rituximab), although there is little data on the use of targeted substances in patients with autoimmune phenomena [55].

6.2 Drug-based tumor therapy – substances

The results of randomized clinical trials with the individual substances and combinations are summarized in Chronic Lymphocytic Leukemia Study Results (in German only). Information on the approval status of drugs suitable for the treatment of CLL is listed in Chronic Lymphocytic Leukemia Approval Status for Germany, Austria, and Switzerland.

6.2.1 Acalabrutinib

Acalabrutinib is an inhibitor of Bruton's tyrosine kinase (BTK). This kinase plays a central role in the development, differentiation, signal transduction, and survival of B lymphocytes. Acalabrutinib alone or in combination with obinutuzumab led to a significant prolongation of progression-free survival compared to chlorambucil/obinutuzumab (acalabrutinib HR 0.2; acalabrutinib/obinutuzumab HR 0.1) [20]. Acalabrutinib in combination with obinutuzumab also led to an improvement in overall survival compared to chlorambucil/obinutuzumab (HR 0.55, p=0.0474) [56]. Patients with evidence of del(17p13) or a *TP53* mutation benefit from acalabrutinib to

almost the same extent as patients without this risk factor, but the addition of obinutuzumab does not improve the outcome compared to monotherapy.

Severe side effects of acalabrutinib monotherapy in CTCAE grade 3/4 in the ELEVATE-TN study [20] were neutropenia (10%), anemia (7%), thrombocytopenia (3%), and pneumonia (2%). Diarrhea of all grades of severity occurred in 35% of patients. Arrhythmias may occur with acalabrutinib, most commonly atrial fibrillation in 3-4% of patients. Initial diarrhea is often self-limiting. Treatment with acalabrutinib may initially cause lymphocytosis due to the flushing out of leukemia cells from lymphatic compartments. Other clinically relevant side effects include mild bleeding (43%), especially in the form of bruising (24%), and the development or aggravation of arterial hypertension, in 3% of cases at CTCAE grade 3. Acalabrutinib is administered orally.

6.2.2 Bendamustine

Bendamustine belongs to the nitrogen mustard derivatives. It is an alkylating agent and also has purine antimetabolite properties. In monotherapy in untreated patients, the remission rates were 68% and the progression-free survival was 21.8 months, which was significantly higher than the comparative therapy with chlorambucil (31%, 8.0 months). Bendamustine was used in CLL as monotherapy and in combination with rituximab [57, 58]. Grade 3/4 side effects affect blood formation: neutropenia (23%), thrombocytopenia (12%), anemia (2.5%). Severe infections may occur in combination with rituximab. The side effects require dose adjustments and, if necessary, antibacterial (Pneumocystis jirovecii pneumonia) and antiviral prophylaxis (CMV) with consideration of CD4 lymphocytes. Other common side effects include fever, nausea/vomiting, and skin rash. The bone marrow toxicity of bendamustine is cumulative. Bendamustine is administered intravenously.

6.2.3 Chlorambucil

Chlorambucil is an alkylating agent. It has been used in the treatment of CLL for more than 50 years but should hardly be used today. Chlorambucil monotherapy (0.4 mg/kg body weight every 14 days with a dose increase of 0.1 mg/kg body weight per cycle up to a maximum dose of 0.8 mg/kg body weight) was the appropriate comparative therapy for testing the added benefit of new substances. Chlorambucil is also combined with anti-CD20 antibodies. It is well tolerated. Side effects are dose dependent. The main side effects are hematotoxicity with neutropenia, thrombocytopenia, and anemia. Side effects of CTCAE grade 3/4 are rare and can be avoided by reducing the dose. Chlorambucil is administered orally.

6.2.4 Cyclophosphamide

Cyclophosphamide is effective as a single agent in CLL but is mainly used in combination with fludarabine and rituximab (FCR). The main side effect of cyclophosphamide is hematotoxicity. At higher doses (>1,000 mg), hemorrhagic cystitis may occur, which can be prevented by prophylactic administration of uromitexan. Cyclophosphamide is usually administered intravenously. Cyclophosphamide is also effective in the treatment of autoimmune diseases.

6.2.5 Fludarabine

Fludarabine is a purine analogue. It was synthesized in the late 1960s and has been used to treat CLL since the 1980s. Compared to chlorambucil or combination therapies containing alkylating agents, monotherapy leads to an increase in remission rates but not in survival time. Compared to CHOP, the results for efficacy were not significantly different, but tolerability was significantly better. Side effects of fludarabine monotherapy in CTCAE grade 3/4, occurring in

more than 5% of patients, including neutropenia, anemia, thrombocytopenia, and infections. A critical side effect of fludarabine monotherapy is the increased rate of autoimmune cytopenias, up to pure red cell aplasia.

6.2.6 Ibrutinib

Ibrutinib is an inhibitor of Bruton's tyrosine kinase (BTK). This kinase plays a central role in the development, differentiation, signal transduction, and survival of B lymphocytes. In the approval study, ibrutinib led to a significant prolongation of progression-free survival (hazard ratio 0.22) and overall survival (hazard ratio 0.43) in patients with relapsed or refractory CLL [58]. Patients with evidence of del(17p13) or a *TP53* mutation benefit to almost the same extent as patients without this risk factor. In untreated patients aged ≥65 years, ibrutinib is superior to chlorambucil monotherapy. In addition, ibrutinib-based therapy was shown to be superior to both bendamustine/rituximab [19] and a combination of chlorambucil/obinutuzumab [59] in the first-line treatment of older or less fit patients. Ibrutinib monotherapy was not inferior to the combination of ibrutinib/rituximab [19]. In the context of the E1912 study, the superiority of ibrutinib/rituximab over FCR in the first-line treatment of young/fit CLL patients was also documented [18].

Severe side effects of ibrutinib monotherapy in CTCAE grade 3/4 in the RESONATE studies [37] and in the ALLIANCE study [19] were neutropenia (10-16%), anemia (4-12%), thrombocytopenia (2-7%), pneumonia (4-7%), and diarrhea (4%). Arrhythmias may occur with ibrutinib, most commonly atrial fibrillation in 5-8% of patients. Patients with severe arrhythmias (ventricular tachycardia, higher-degree block) were excluded from the studies. Isolated cases of sudden death and invasive aspergillosis have been reported. Initial diarrhea is often self-limiting. Therapy with ibrutinib initially leads to lymphocytosis due to the flushing out of leukemia cells from lymphatic compartments. Other clinically relevant side effects include skin bleeding (approx. 40%) and the development or aggravation of arterial hypertension. The rate of worsening hypertension is reported to be 78% when a threshold of 130/90 mmHg is assumed in accordance with the criteria of the American College of Cardiology. Based on the threshold of the European Society of Cardiology (ESC), this rate is calculated at 44% [60]. Ibrutinib is administered orally.

6.2.7 Idelalisib

Idelalisib is a selective inhibitor of the delta isoform of phosphatidylinositol 3-kinase (PI3Kδ). This kinase plays an important role in B-cell receptor-induced signal transduction in mature B lymphocytes and in the pathogenesis of CLL. In combination with an anti-CD20 antibody (ofatumumab or rixuximab), idelalisib leads to increases in remission rates to 70-85%, a significant prolongation of progression-free survival (hazard ratio 0.2) and overall survival (hazard 0.34-0.75) [61, 62]. Severe side effects of the combination therapy of idelalisib + rituximab in CTCAE grade 3/4 were neutropenia (34%), thrombocytopenia (10%), anemia (5%), elevated transaminases (5%), diarrhea (4%), fever (3%), fatigue (3%), and chills (2%). In spring 2016, interim results from three ongoing studies on first-line therapy showed an increased number of infection-related deaths in the treatment arm receiving idelalisib. The report by the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) recommends antibiotic prophylaxis for *Pneumocystis jirovecii* and regular monitoring for signs of infection, particularly signs of CMV infection. Idelalisib is administered orally.

6.2.8 Liso-cel

On March 15, 2024, Liso-cel was approved by the FDA for patients with BTKi and BCL2-i refractory CLL in the US, based on the CLL004 study [50]. However, approval in Germany is still

pending. Based on 49 patients receiving a higher dose of CAR-T cells ($100x10^6$, dose level 2), the CLL004 study showed complete remission in 18% of patients. Based on 117 patients, severe cytokine release syndrome (CRS) was observed in 9% of patients, and severe neurological events in 19%. One fatal macrophage activation syndrome was described in this study in one patient.

6.2.9 Obinutuzumab

Obinutuzumab is an anti-CD20 antibody with modified glycosylation. In untreated, comorbid patients, it led to a significant prolongation of progression-free survival (hazard ratio 0.39; median 11.5 months) in combination with chlorambucil compared to chlorambucil-rituximab therapy [63] and, in a later evaluation, also in terms of overall survival (hazard ratio 0.76; median not reached) [64]. Severe side effects of combination therapy with chlorambucil in CTCAE grade 3/4 were infusion-related reactions (21%), neutropenia (35%), thrombocytopenia (11%), and anemia (5%). Obinutuzumab is administered intravenously.

6.2.10 Pirtobrutinib

Pirtobrutinib is a selective, non-covalent binding BTK inhibitor that was evaluated in a Phase I/II study in patients with relapsed/refractory CLL/SLL (BRUIN). In patients who had largely (78%) received a BTKi and, in some cases, venetoclax (40.5%) as prior therapy, a response rate of 73.3% was observed with a median PFS of 19.6 months [65]. The most common side effects reported were infections (71%), bleeding (42.6%), and neutropenia (32.5%). In addition, the following side effects occurred in this study with pirtobrutinib: hypertension (14.2%), atrial fibrillation/flutter (3.8%), and severe hemorrhage (2.2%). The BRUIN-321 study, which randomly compared the use of pirtrobrutinib with idelalisib/rituximab and bendamustine/rituximab, was relevant for approval. Based on 238 patients, a significantly better median PFS was observed with pirtobrutinib (14 months) compared to the standard arm (8.7 months). The time to next treatment (TTNT) was also significantly improved with pirtobrutinib at 24 months (24 months vs. 10.9 months) [39]. The substance was approved by the FDA on December 1, 2023, for double-refractory (BTKi, BCL2i) CLL patients. On March 31, 2025, it was approved by the EMA, whereby pirtobrutinib was already approved for use in patients who had previously been treated with a covalent BTK inhibitor alone, meaning that patients did not necessarily have to be double refractory.

6.2.11 Prednisone/prednisolone

Nowadays, the use of prednisone/prednisolone is limited to the treatment of patients with autoimmune phenomena. Short-term side effects of glucocorticoids include flushing, restlessness, and glucose metabolism disorders. Medium- and long-term side effects correspond to the symptoms of Cushing's syndrome, including osteoporosis and changes in body image. Critical side effects, especially in CLL patients, are infections, particularly of viral and fungal origin, due to increased immunosuppression. Glucocorticoids can be administered orally and intravenously.

6.2.12 Rituximab

Rituximab is a chimeric anti-CD20 antibody. It was first approved for the treatment of patients with indolent lymphomas. Rituximab is effective in monotherapy for CLL, with the effect being dose dependent. In combination with fludarabine and cyclophosphamide (FCR), rituximab was the first substance to significantly prolong overall survival. The most common side effects of rituximab are directly related to the infusion and include fever, chills, nausea, and general malaise. Cytokine release syndrome can lead to severe hypotension with high temperatures,

hypoxia, and the need for intensive care. The occurrence of cytokine release syndrome correlates with tumor mass and depends on the rituximab dosage. Side effects of FCR combination therapy in CTCAE grade 3/4 include cytokine release syndrome (neutropenia (34%), infections (25%), thrombocytopenia (7%), and anemia (4%). Rituximab can be administered intravenously and subcutaneously. Currently, only intravenous administration is approved for CLL.

6.2.13 Venetoclax

Venetoclax blocks the anti-apoptotic B-cell lymphoma 2 protein (BCL2), thereby inducing programmed cell death. In one of the two non-randomized approval studies, venetoclax led to partial or complete remission in 75% of pretreated patients with del17p or *TP53* mutation. In patients without del17p or *TP53* mutation but after pretreatment with an inhibitor of the BCR signaling pathway (ibrutinib or idelalisib), 67% achieved partial or complete remission. Furthermore, venetoclax shows clinical activity in patients after prior treatment with chemoimmunotherapy and BCR inhibitor, regardless of TP53 aberration status [40, 42]. Furthermore, data from a randomized study comparing venetoclax with bendamustine were published in the context of the MURANO study, showing that response rates, including MRD negativity rates, and progression-free survival were significantly improved in favor of the venetoclax/rituximab combination (time-limited therapy over a total of 2 years), regardless of TP53 status [42]. Venetoclax is approved as monotherapy in the first-line treatment of patients with 17p or TP53 mutations, provided that a patient is not suitable for ibrutinib therapy. The combination of venetoclax/obinutuzumab (limited to a total treatment duration of approximately 10.5 months, corresponding to 12 cycles of venetoclax) was approved by the FDA and EMA in 2020 based on data from the CLL14 study [26]; for national regulations.

The most common side effects of venetoclax are neutropenia, diarrhea, nausea, anemia, upper respiratory tract infections, fatigue, and increased blood phosphate levels. Severe side effects may include febrile neutropenia, pneumonia, and initial tumor lysis syndrome. To avoid tumor lysis syndrome, a dose escalation schedule for the first few weeks has been included in the prescribing information. It starts at 20 mg and reaches the target dose of 400 mg in the fifth week. Venetoclax is administered orally.

6.2.14 Zanubrutinib

Zanubrutinib is a second-generation Bruton's tyrosine kinase (BTK) inhibitor with more specific kinase inhibition compared to ibrutinib. In the SEQUOIA study, zanubrutinib monotherapy in patients >65 years of age or patients <65 years of age with comorbidities and untreated CLL led to a significant prolongation of progression-free survival compared to bendamustine/rituximab (zanubrutinib HR 0.3), but not overall survival. Patients with evidence of del(17p13) or a *TP53* mutation benefit to almost the same extent as patients without this risk factor; the same applies to unmutated IGHV status.

Severe side effects of zanubrutinib monotherapy in CTCAE grade 3/4 in the SEQUOIA study [22] included neutropenia (11%), anemia (0.4%), thrombocytopenia (2.1%), infections (16.3%), and pneumonia (1.7%). Diarrhea of all degrees of severity occurred in 13.8% of patients. Arrhythmias may occur with zanubrutinib, most commonly atrial fibrillation in 1.7% of patients. Therapy with zanubrutinib may initially lead to lymphocytosis due to the flushing out of leukemia cells from lymphatic compartments. Other clinically relevant side effects include mild bleeding (28.3%), especially in the form of bruising (24.2%), and the development or aggravation of arterial hypertension, in 6.3% of cases at CTCAE grade 3. Zanubrutinib is administered orally.

7 Rehabilitation

Patients should be informed at an early stage about the options for outpatient and inpatient rehabilitation measures as well as other entitlements under social welfare law. The patient's wishes regarding the rehabilitation clinic should be taken into account (in Germany according to §9 SGB IX). Nevertheless, a clinic with a focus on oncology should be recommended in order to ensure optimal rehabilitation success.

8 Follow-up

Follow-up care for asymptomatic patients should include a blood count at intervals of approximately 3-6 months, in addition to a clinical examination of the lymph nodes, liver, and spleen. Radiological examinations using computed tomography or magnetic resonance imaging are generally not necessary in the follow-up care of patients in remission. Attention should be paid to the occurrence of autoimmune cytopenias (autoimmune hemolytic anemia, immune thrombocytopenia) and infections. Furthermore, rapid lymph node enlargement, B symptoms, and/or an increase in LDH should give cause to rule out not only a recurrence of CLL but also a transformation into a highly malignant lymphoma (Richter transformation). If CLL recurrence is clinically suspected, molecular (cyto)genetic testing should be repeated to reliably rule out newly occurring and therapy-relevant high-risk aberrations (especially del17p13 or *TP53* mutation, complex karyotype).

Information on COVID-19 can be found in the Onkopedia COVID-19 guideline (in German only). There are no changes to therapy or monitoring and follow-up examinations as a result of the SARS-CoV-2 pandemic.

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14 Links

Malignant Lymphoma Competence Network

www.kompetenznetz-leukaemie.de

German Leukemia & Lymphoma Aid Association

www.leukaemie-hilfe.de

German CLL Study Group

www.dcllsg.de

15 Authors' Affiliations

PD Dr. Dr. med. Othman Al-Sawaf
Universitätsklinikum Köln
Klinik I für Innere Medizin
Kerpener Str. 62
50937 Köln
othman.al-sawaf@uk-koeln.de

Prof. Dr. med. Mascha Binder
Universitätsspital Basel
Medizinische Onkologie
Klinikum 2
Petersgraben 4
4031 Basel
mascha.binder@unibas.ch

Prof. Dr. med. Peter Dreger
Universitätsklinikum Heidelberg
Medizinische Klinik und Poliklinik V
Im Neuenheimer Feld 410
69120 Heidelberg
peter.dreger@med.uni-heidelberg.de

Prof. Dr. med. Barbara Eichhorst
Universität zu Köln
Klinik I für Innere Medizin
Kerpener Str. 62
50937 Köln
barbara.eichhorst@uk-koeln.de

Dr. med. Michael Gregor
Luzerner Kantonsspital
Departement Medizin
Hämatologische Abteilung
Spitalstr.
CH-6000 Luzern 16
michael.gregor@luks.ch

Prof. Dr. med. Michael Hallek
Universitätsklinikum Köln
Klinik I für Innere Medizin
Kerpener Str. 62; Haus 16
50937 Köln
michael.hallek@uk-koeln.de

Dr. med. Ulrike Holtkamp
DLH
Deutsche Leukämie- und Lymphomhilfe e.V.
Thomas-Mann-Str. 40
53111 Bonn
u.holtkamp@leukaemie-hilfe.de

Dr. med. Henriette Huber
Städtisches Klinikum Karlsruhe
Medizinische Klinik III
Moltkestr. 90
76133 Karlsruhe
henriette.huber@klinikum-karlsruhe.de

Dr. Thomas Nösslinger
Mein Hanusch-Krankenhaus Wien
3. Medizinische Abteilung für Hämatologie und Onkologie
Heinrich-Collin-Str. 30
A-1140 Wien
thomas.noesslinger@oegk.at

Dr. Ron Pritzkuleit
Institut für Krebsepidemiologie
Krebsregister Schleswig-Holstein
Ratzeburger Allee 160
23538 Lübeck
ron.pritzkuleit@krebsregister-sh.de

PD Dr. Dr. med. Katharina Prochazka
Medizinische Universität Graz
Klinische Abteilung für Hämatologie
Auenbruggerplatz 38
A-8036 Graz
katharina.prochazka@medunigraz.at

Prof. Dr. med. habil. Johannes Schetelig
Universitätsklinikum
Carl Gustav Carus Dresden
Station MK1-KMT
Medizinische Klinik I
Fetscherstr. 74
01307 Dresden
johannes.schetelig@uniklinikum-dresden.de

Dr. med. Simon Schliffke
Onkologie Lerchenfeld GbR
Lerchenfeld 14
22081 Hamburg
simon.schlieffke@onkologie-lerchenfeld.de

Dr. med. Ingo Schwaner
Onkologische Schwerpunktpraxis
Kurfürstendamm 65
10707 Berlin
ingo.schwaner@onkologie-kurfuerstendamm.de

Prof. Dr. Philipp Bernhard Staber
Universitätsklinikum des Saarlandes
Klinik für Innere Medizin I
Kirrberger Str. 100
66421 Homburg
philipp.staber@uks.eu

Prof. Dr. med. Stephan Stilgenbauer
Universitätsklinikum Ulm
Comprehensive Cancer Center Ulm (CCCU)
Albert-Einstein-Allee 23
89081 Ulm
stephan.stilgenbauer@uniklinik-ulm.de

Dr. Eugen Tausch
Klinik für Innere Medizin III
Universitätsklinikum Ulm
Albert-Einstein-Allee 23
89081 Ulm
Eugen.Tausch@uniklinik-ulm.de

PD Dr. med. Minna Voigtländer
Universitätsklinikum Hamburg-Eppendorf
Zentrum für Onkologie
II. Medizinische Klinik und Poliklinik
Martinistr. 52
22041 Hamburg
m.voigtlaender@uke.de

Prof. Dr. med. Clemens-Martin Wendtner
LMU Klinikum
Medizinische Klinik und Poliklinik III
Campus Innenstadt
Ziemssenstr. 1
80336 München
clemens.wendtner@med.uni-muenchen.de

Prof. Dr. med. Thorsten Zenz
UniversitätsSpital Zürich
Zentrum für Hämatologie und Onkologie
Rämistr. 100
CH-8091 Zürich
thorsten.zenz@usz.ch

16 Disclosure of Potential Conflicts of Interest

according to the rules of the responsible Medical Societies.