BHS guidelines for the management of small lymphocytic lymphoma and chronic lymphocytic leukaemia, anno 2024

A. Janssens, MD, PhD*

*On behalf of the BHS Lymphoproliferative Disease Committee 2023:
Marc André, Christophe Bonnet, Sarah Bailly, Veerle Beckers, Dominique Bron, Rutgers Callens, Charlotte Caron, Maxim Clauwaert, Sarah Debussche, Ciel De Vriendt, Virginie De Wilde, Vanessa Delrieu, Daan Dierickx, Pierre Heimann, Jan Lemmens, **Marie Maerevoet,** Claire Maquet, Fulvio Massaro, Caressa Meert, **Marie-Christine Ngiribacu,** Fritz Offner, Juliette Rademaekers, Ornella Rizzo, Kirsten Saevels, Liesbeth Schauvliege, Sylvia Snauwaert, Joan Somja, Cécile Springael, Thomas Tousseyn, Eric Van Den Neste, Sam Vandermeeren, Sam Van Hecke, Vanessa Van Hende, Marie Vercruyssen, Vibeke Vergote, Inge Vrelust, Alice Wolfromm, Ka Lung Wu.*

SUMMARY

The Belgian Haematological Society (BHS) Lymphoproliferative disease (LPD) committee updated the existing recommendations on diagnosis, prognostic scores, best strategies for front-line and subsequent-line treatment of small lymphocytic lymphoma (SLL)/chronic lymphocytic leukaemia (CLL), according to robust new data.

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INTRODUCTION

The Belgian Hematology Society (BHS) Lymphoproliferative disease (LPD) committee reviewed the recent literature on diagnosis, prognostic scores and treatment of small lymphocytic lymphoma (SLL)/chronic lymphocytic leukaemia (CLL), to update the recommendations published in 2012, 2015, 2018 and 2020.[1-4]

EPIDEMIOLOGY CLL/SLL

The Belgian Cancer Registry published in 2021 epidemiological data from haematological malignancies in Belgium thanks to incidence registration data from 2004-2018. Haematological malignancies comprise ± 11% of the total cancer burden in Belgium. Epidemiological data on CLL/SLL are found in the chapter on mature B-cell leukaemias and related lymphomas. Data on CLL/SLL (93%), hairy cell leukaemia (5%), B-prolymphocytic leukaemia (<0.5%) and mature B-cell leukaemias, not otherwise specified (2%) are analysed together. This mature B-cell lymphoma group is more frequent in males (M) than in females (F) (M/F ratio: 1.8) and mostly diagnosed in the older population (median age at diagnosis 70 years. Fluctuations in incidence

Department of Haematology, University Hospitals Leuven, Leuven, Belgium.

Please send all correspondence to: A. Janssens, MD, PhD, Department of Haematology, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium, tel: +32 (0)16 346880, email: ann.janssens@uzleuven.be.

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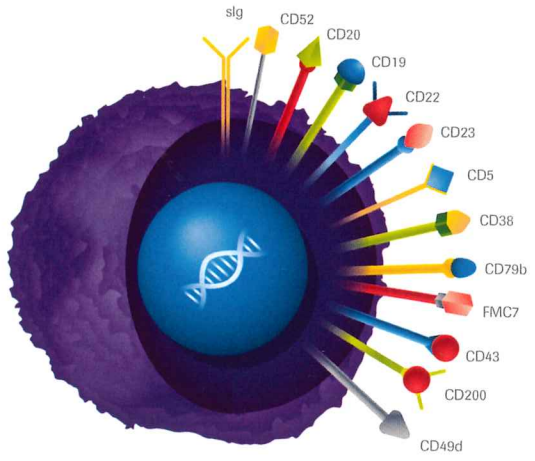
Keywords: Chronic lymphocytic leukaemia, diagnosis, guidelines, prognostic scores, Richter transformation, secondary immune cytopenias, treatment.



"Required" diagnostic markers	
• CD5	Positive >20%
• CD19	Positive >95%
• CD20	Weak
• CD23	Positive >20%
• sIG, κ or λ	Weak
"Recommended" markers to refine diagnosis in borderline cases	
• CD43	Positive >20%
• CD79b	Weak
• CD81	Weak
• CD200	Positive >20%
• CD10	Negative <20%
• ROR1	Positive >20%

FIGURE 1. Immunophenotype of CLL according to the ERIC and ESCCA harmonisation project.
ERIC: European research initiative on CLL; ESSCA: European society for clinical cell analysis.

of CLL/SLL were seen between 2004-2018 ranging from 628-949 newly diagnosed cases. Although we cannot exclude a real increase in incidence, we think that earlier diagnosis and the creation of the entity monoclonal B-cell lymphocytosis (MBL) in the 4th edition of the World Health Organisation (WHO) classification are responsible for the shifts. The five and ten year relative survival of ± 92.5% and 82% have improved over time in both sexes (5-year relative survival 2004-2008 ± 85%).[5] These data are very comparable with the most recently updated Surveillance, Epidemiology, and End Results program of the National Cancer Institute of the United States (US) (based on 2016-2020 cases and deaths). This database highlights that CLL represents 1% of all new cancer cases in the US and that the age-adjusted rate of new CLL/SLL cases was 4.6 per 100,000 and the death rate was 1.1 per 100,000 men and women per year.[6]

DIAGNOSIS OF CLL/ SLL/MBL

Diagnosis of SLL/CLL still follows the international workshop on CLL (iwCLL) guidelines of 2018. The diagnosis requires the presence of at least 5,000 monoclonal B-lymphocytes/microliter (μl) in the blood for the duration of at least three months. Morphologically, the CLL cells are small, round cells with a narrow border of cytoplasm and a dense nucleus with clumped chromatin and indiscernible nucleoli. These typical CLL cells can be admixed with larger cells, cleaved cells or prolymphocytes which may compromise up to 55% of the blood lymphocytes. Gumprecht shadows or smudge cells are frequently seen.[7,8] We must emphasise once more that thanks to the European research initiative on CLL (ERIC) and European society for clinical cell analysis (ESCCA) harmonisation project a panel of CD19, CD5, CD20, CD23, kappa and lambda is usually sufficient to establish the diagnosis. Recommended markers such as CD43, CD79b, CD81, CD200, CD10 and ROR1 may help to refine diagnosis in borderline cases (*Figure 1*). This immunophenotypic scoring system must help to differentiate CLL better from other leukemic lymphomas and eliminate the diagnosis of atypical CLL.[9]

The diagnostic criteria for SLL and MBL-CLL type stay also unchanged.[7,8,10-12] The update of the 4th edition of the WHO classification of haematolymphoid tumours unfortunately gave rise to the 5th edition of the WHO and the International Consensus Committee classification (ICC) of mature lymphoid neoplasms.[10-12] Diagnostic criteria for CLL, SLL and MBL-CLL type are shared by both classifications. The 5th WHO edition proposes to use the term low count MBL without further differentiation and to divide the high count MBL in MBL-CLL/SLL type and MBL-non CLL/SLL type.[11] The ICC classification retains MBL-atypical CLL type for a clone that is CD5 positive but without matching CLL or mantle cell lymphoma with the other immunophenotypic markers.[12]

UPDATED DIAGNOSTIC, PRE-TREATMENT AND POST-TREATMENT WORK-UP

After making the diagnosis of CLL/SLL (blood cell count,

blood smear, CLL immunophenotype, and tissue biopsy) we must complete our **diagnostic work-up** with a personal and familial history and a physical examination (lymph nodes and organomegaly). This gives us an idea on the biological fitness of our patient (performance status (PS), comorbidities). A complete geriatric assessment can have potential utility in older and/or comorbid patients. A marrow aspirate and biopsy generally are not required for the diagnosis of CLL. However, a marrow examination can help clarify whether cytopenias are related or unrelated to leukemic infiltration of the marrow. A marrow examination is frequently mandatory within clinical trials at the start and to confirm complete remission (CR). A lymph node biopsy is generally not required, except in SLL or rare cases in which the diagnosis is difficult to make. A lymph node or tissue biopsy must be performed to establish the diagnosis of Richter transformation (RT). An ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT scan can be useful to identify the best lymphoid area for an excisional biopsy, possibly a core needle biopsy, but never a fine needle aspiration to establish the diagnosis.[7,8]

In the **pre-treatment work-up** it's of utmost importance to consider:

- *patient related factors* (age, PS, comorbidities with a special interest for renal, cardiovascular (CV) and gastrointestinal function, bleeding and infection risk, adherence to treatment and patient preferences);
- *disease related factors* (17p deletion (del)/*TP53* mutation (mut), immunoglobulin heavy chain variable (IGHV) mutational status, complex karyotype (CK), tumour lysis syndrome (TLS) risk);
- and *treatment related factors* (adverse events (AEs), intravenous (IV) *vs.* oral, continuous *vs.* fixed duration (FD), admission to the hospital *vs.* day clinic *vs.* outpatient clinic, duration of response (DoR), time to next treatment (TTNT), overall survival (OS) and economic burden).

A very important patient related factor to consider at the start of treatment is the CV function. A baseline **CV risk assessment** must be done especially in patients who might be Bruton tyrosine kinase inhibitors (BTKis) candidates. This CV risk assessment includes age, sex, race, blood pressure, lipid panel, diabetes mellitus, obesity, smoking (current, former, never), antihypertensive, statin, aspirin treatment, history of CV events and family CV history. In 2022, the European Society of Cardiology published the first cardio-oncology guideline in collaboration with European Hematology Association among others. These recommendations are largely based on expert opinions, as data from clinical trials are simply not (yet) available. Recommendations for baseline CV risk assessment before and monitoring during BTKis are proposed:

- Blood pressure measurement at every clinical visit (and weekly at home during the first three months and later once a mo).
- Electrocardiogram (ECG) before the start and pulse taking at every clinical visit.
- Echocardiography in all patients developing atrial fibrillation (AF).
- Echocardiography at baseline in patients considered at high risk for CV toxicities (M, >65 years, history of hypertension, diabetes mellitus, QTc >480ms, AF, heart failure, cardiomyopathy and severe valvular heart disease).[13]

The disease related factors to highlight are still the *TP53* aberration, IGHV mutational status but also CK and TLS risk. Since the first BHS LPD CLL/SLL management recommendation published in 2012, we advise to test 17p del before the start of "each" new treatment as this aberration can be acquired by clonal evolution. From the 2015 update, this advice was extended to test also *TP53* mut in the absence of a 17p del as the mutated *TP53* ones behave identical to the deleted ones. Today, the ***TP53* aberration** has a lasting predictive and prognostic impact even with our current treatment armamentarium. The novel agents surpass chemoimmunotherapy (CIT) in terms of response, progression free survival (PFS), DoR and OS but still perform inferior compared to those without a *TP53* aberration.[7,8,14]

IGHV mutational status is another strong predictive and prognostic factor that does not change in time and must be performed only once. This DNA sequencing test is however expensive, technically demanding and not widely available. The search for surrogate markers in the past (CD38, ZAP-70, CD49d, etc.) has not been optimal. IGHV status has been included for the first time in our BHS 2020 CLL/SLL treatment algorithm. IGHV testing is reimbursed in Belgium from March 2023 in CLL/SLL with active/advanced disease in the absence of a 17p del/*TP53* mutation and only once. Although the effect of the BTKis seems equal in patients with mutated or unmutated IGHV, the effect of venetoclax (Ven) is still IGHV dependent although less striking than with CIT. Therefore, we advise further testing of the IGHV status in all CLL/SLL patients with active/advanced disease without a 17p del/*TP53* mut especially if a Ven holding regimen or CIT could be a therapeutic option. Assessment of IGHV stereotypes is not recommended in the routine prognostic work-up, although some poor-prognostic subsets have been recognised.[7,8,15] Since the use of novel culture techniques aberrant karyotypes can be found in up to 80% of the CLL samples. Till recently it was unclear if a **CK** has independent predictive or prognostic

value. Also, the definition of CK (≥3 or ≥5 chromosomal aberrations) and the independence of a concomitant *TP53* aberration was not cleared up in CLL.[16] The recent CLL13 trial included only patients without a *TP53* aberration and showed that a CK (≥3 chromosomal aberrations) was found in 12-20% and a high CK (≥5 chromosomal aberrations) in 3-7% of the included patients. A CK was an independent predictive and prognostic factor in those treated with CIT, however in the Ven arms only a high CK was a predictive factor without prognostic significance.[17] Therefore, we can advise to karyotype each CLL patient before the start of any treatment as clonal evolution is not uncommon.

The role of **imaging** is limited in CLL/SLL. A chest radiograph and abdominal ultrasound can be recommended as pre-treatment imaging. CT scans generally are not required pre-treatment or for follow-up evaluation. However, at the start of a Ven holding regimen a CT neck, thorax, abdomen, pelvis must be done to estimate the TLS risk. In clinical trials CT scans are used to evaluate the response to therapy and are done at baseline and at the final response assessment. ^{18}F-FDG PET/CT imaging can be very helpful when CLL transformation is suspected. Standardised uptake values (SUVs.) of <5 are typical of CLL, whereas SUVs. ≥10 are suggestive but not diagnostic of RT and values between five and ten represent a grey area. CLL progression following novel agents might be more metabolically active on ^{18}F-FDG PET compared to progression after CIT.[7,8] As Ven can cause a deep reduction in tumour cells as early as six to eight hours (hrs) following the first dose, we must prevent clinical and/or laboratory **TLS** as much as possible. The first measure to take is to use the recommended ramp-up (5-week dose titration phase: 20 mg-50 mg-100 mg-200 mg-400 mg). Next to titrating the dose, hydration (oral or IV) and anti-hyperuricemic drugs with or without hospitalisation according to risk group assessment is also mandatory to avoid TLS. Three risk groups (high, intermediate and low risk) for TLS are defined according to tumour mass. Tumour mass is assessed by lymphocyte count (< or ≥25000/µl) and measurement of single lymph nodes on CT-scan (<5 cm, between 5-10 cm, ≥10 cm). A "low tumour burden" is defined as single nodes <5 cm "and" a lymphocyte count of <25000/µl. An "intermediate tumour burden" is defined as any single node between 5-10 cm "or" a lymphocyte count ≥25000/µl. A "high tumour burden" is defined as a single node ≥10 cm "or" a single node ≥5 cm "and" a lymphocyte count ≥25000/µl. The risk score is upgraded by the presence of a huge splenomegaly and/or a reduced renal function (Cr Cl <80 ml/min). Additional comorbidities and pre-existing electrolyte abnormalities can increase the risk further. For all patients, blood chemistries should be assessed prior to the initial dose to evaluate kidney function, uric acid and electrolyte (potassium, calcium, phosphorus) abnormalities. Blood chemistries should be reassessed prior to each subsequent dose increase during the titration phase. Blood chemistries should be monitored at 4-6 to 8 hrs, 12 hrs and at 24 hrs after the first 20 and 50 mg of Ven according to risk group. The next Ven dose (d 2 or d 9) should not be administered until the 24 hrs blood chemistry results have been evaluated. Electrolyte abnormalities should be corrected promptly. The same monitoring schedule should be followed at the start of the 100 mg dose or higher in patients who continue to be at TLS risk or have shown problems before.[18] In the recent CLL13 trial, using the above-mentioned TLS prophylaxis, all grade TLS was reported in max 12% of patients treated with Ven (12 cycles) plus obinutuzumab (Ob) (6 cycles) (Ob_6-Ven_{12}) and Ven (12 cycles) plus rituximab (6 cycles) (R_6Ven_{12}). Less than 2% of patients experienced a clinical TLS.[19]

CLINICAL PRESENTATION

Patients with CLL are generally asymptomatic at presentation, and the diagnosis is often made incidentally when lymphocytosis is noted at the time of a routine blood evaluation. At diagnosis, one quarter of patients reveal lymphadenopathies, approximately 15% organomegaly while B symptoms are noticed in only 5%.[7,8] The clinical course of CLL is highly variable. One third of CLL patients never require treatment, another third show disease progression after an initial indolent phase and the remaining third exhibit a progressive disease from the onset and need immediate treatment.[20]

MINIMAL RESIDUAL DISEASE (MRD) IN CLL

Undetectable minimal residual disease (MRD) or minimal measurable disease has been correlated with longer PFS and OS in several haematological diseases. In some situations, MRD analysis is already used as a surrogate for PFS to accelerate access to novel agents. The main laboratory methods available are multi-colour flow cytometry, allele-specific oligonucleotide (ASO)-polymerase chain reaction (PCR) and next generation sequencing (NGS). With CIT, the level of MRD has been correlated with DoR. With continuous BTKi treatment achievement of undetectable (u) MRD seems not be required to achieve long-term control of CLL. When we treat CLL with Ven combinations the depth of MRD is again correlated with PFS and DoR. All recent trials in TN and R/R CLL have incorporated

TABLE 1. Indications for treatment (advanced and/or active disease).

High tumour load	• Rai 3-4 or Binet C
Disease progression	• Lymphocyte doubling time of less than six months • Massive (>6 cm below costal margin) or progressive or symptomatic splenomegaly • Massive (>10 cm) or progressive or symptomatic lymphadenopathy • Progressive marrow failure leading to cytopenia • Symptomatic functional extranodal disease
Auto-immune problems	• AIHA, AITP, PRCA poorly responsive to corticosteroids
Disease-related problems	• 10% weight loss in six months • Fatigue (PS ≥2) • Fever >38°C for >2 w without infection • Night sweats >1 month

AIHA: immune mediated haemolytic anaemia; AITP: immune mediated thrombocytopenia; PRCA: pure red cell aplasia; PS: performance status.

MRD as a primary or secondary endpoint and some even incorporated it as a stopping rule.

However, today MRD assessment is seldom incorporated in daily clinical practice. In patients treated previously with fludarabine (F), cyclophosphamide (C), R, we could stop treatment after 3-4 cycles if uMRD in the bone marrow was achieved without loss of efficacy but decreasing the AE risk. MRD status after allogeneic stem cell transplant (alloSCT) has been a tool to determine prognosis. With the increasing use of chimeric antigen receptor T-cells (CAR-Ts), MRD will also be a tool to assess disease status. We must be aware that with the available assays we measure MRD in blood and bone marrow but can miss residual disease in lymph nodes. Other MRD techniques such as cell-free DNA may overcome this issue.

We can conclude that MRD status is not a surrogate but another tool for clinical response assessment and prognostication and it remains to be demonstrated whether MRD-driven therapeutic decisions will always be clinically beneficial or sufficient to challenge our CLL treatment paradigms.[21-23]

STAGING AND UPDATED PROGNOSTIC SCORING

The two widely used staging systems are those from Rai (used primarily in the US) and Binet (used in Europe). These clinical staging systems are based on physical examination and complete blood cell counts alone. The value of each system lies mainly in the probability of predicting survival.[24-26] Today 80% of the newly diagnosed patients are staged as Binet A, 13% as Binet B and 7% as Binet C.[27]

With the use of CIT, patients with the most advanced stage (Rai 3-4, Binet C) have a predicted survival time of approximately six years in contrast with one to two years at the time of publication of these staging systems.[24-27] Although clinical staging systems as Rai and Binet remain good prognostic factors, at diagnosis they cannot identify patients with indolent or progressive disease, and they are not able to predict response to treatment.

The international prognostic score for asymptomatic early stage CLL (IPS-E) (n=4933) tried to predict the time to first treatment (TTFT). Unmutated IGHV, lymphocytes >15000/µl and palpable lymph nodes are the three covariates independently correlated with TTFT. A low (score 0), intermediate (score 1) and high risk (score 2-3) group were recognised with a cumulative risk of treatment at five years of 8.4%, 28.4% and 61.2%, respectively. As a lot of our CLL patients today are diagnosed as asymptomatic early stage, the IPS-E can help us to council these patients and plan follow-up visits.[28] Other models were developed to identify patients at high risk for progression and shorter OS. The CLL-international prognostic index (CLL-IPI) for treatment-naïve (TN) patients and the CLL-BALL for relapsing/refractory (R/R) patients seemed to be the most valuable.[29-30] The CLL-IPI defined four patient risk groups with a significant different TTFT and OS. The selected variables were 17p del/*TP53* mut, IGHV, β2 microglobulin, stage and age.[29] CLL-IPI was designed for patients receiving front-line CIT and is currently revisited for the use of targeted treatments.[8,29] The CLL-BALL score was created to predict OS in R/R CLL patients treated with the novel agents (ibrutinib (Ibr), idelalisib (Idela), and Ven but also CIT.

The four selected variables here are β2 microglobulin, haemoglobin, lactate dehydrogenase (LDH) and time from last therapy.[30]

As data show that time from diagnosis to second treatment (TT2T) is better correlated with OS than time from diagnosis to first treatment (TT1T), a risk score model has been developed. The three predictors (unmutated IGHV, β2 microglobulin (>297 nmol/L) and Rai stage (0 *vs.* 1-4) were prognostic for TT2T and OS. These data must be validated but the risk score could help to determine who would benefit from first-line CIT *vs.* targeted therapies. Patients with a risk score of zero or one have a longer TT2T and OS than those with a risk score of three or four and could still be candidates for CIT as frontline treatment according to the authors of this manuscript.[31]

INDICATIONS FOR INITIATION OF TREATMENT (*Table 1*)

In 2018, the international workshop on CLL (iwCLL) updated the 2008 guidelines for the initiation of first-line or further-line treatment and they are summarised in *Table 1*. When substantial disease persists or disease progresses under novel agents, even if the patient stays asymptomatic, starting subsequent therapy, sometimes in overlap with the previous one, can be acceptable to avoid Richter-like acceleration.[7,8]

RECOMMENDATIONS FOR THE TREATMENT OF SLL/CLL ANNO 2024

The role of early intervention *vs.* deferred treatment has been investigated in several randomised clinical trials (RCTs). Treatment of asymptomatic, early stage CLL patients has not been proven beneficial with chemotherapy (chlorambucil (Chl), F or CIT (FCR)) as OS could not be improved. The German CLL Study Group (GCLLSG) CLL12 investigated Ibr *vs.* placebo in asymptomatic TN, early stage CLL with risk factors for early progression (median age 64 years). Although Ibr significantly improved event free survival, PFS and TTNT, OS was not changed and Ibr made CLL patients susceptible to CV toxicities (AF 17.8% *vs.* 7.3%; hypertension 9.7% *vs.* 3.9%) and bleeding complications (27.6% *vs.* 9.6%). Early discontinuation due to AEs was seen in the Ibr arm in 35.5%.[32,33]

OPINION OF BHS-LPD COMMITTEE:

As OS for this CLL population with risk factors for early progression is >20 years without early intervention (placebo-arm), wait-and-see in the absence of active or advanced disease even in the era of targeted agents must still be recommended.

TREATMENT OF TN SLL/CLL ANNO 2024 (*Figure 2*)

In our 2020 update, CIT (FCR, bendamustine (B)-R, Ob-Chl)

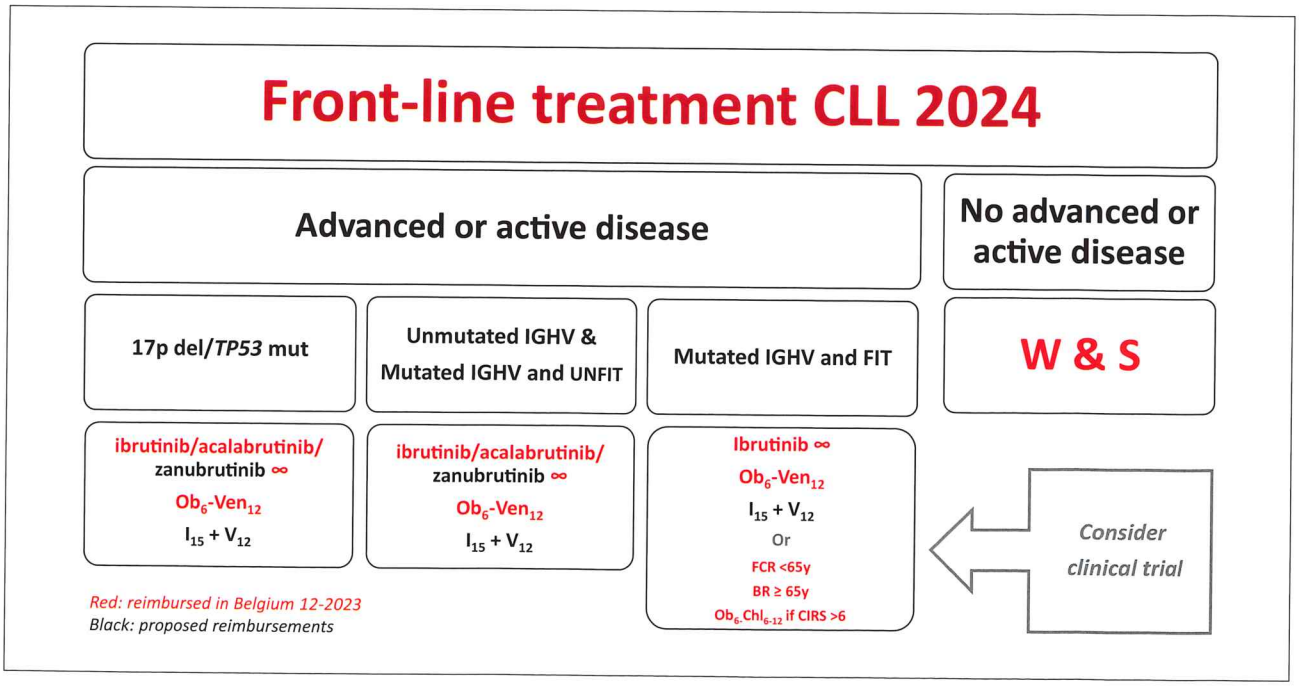


FIGURE 2. Treatment algorithm TN CLL anno 2024 Belgium.

B: bendamustine; Chl: chlorambucil; CIRS: cumulative illness rating scale; del: deletion; mut: mutation; I+V: ibrutinib + venetoclax; IGHV: immunoglobulin heavy chain variable region genes; R: rituximab; Ob: Obinutuzumab; Ven: venetoclax; W & S: wait-and-see; ∞: continuously.

was the only treatment option possible for fit patients. For unfit patients front-line treatment with Ibr became available in February 2020. For patients with a *TP53* aberration continuous treatment with Ibr was already reimbursed August 2015 and continuous Ven was an alternative since November 2017 if the patient was unsuitable for Ibr. We suggested already Ibr as an alternative for CIT in fit patients and Ob_6-Ven_{12} as an additional treatment option for unfit patients and patients with a *TP53* aberration.[4] Acalabrutinib (Acala) was reimbursed from November 2021, as alternative BTKi for TN patients not fit for F and in December 2021 the reimbursement for Ibr was extended to all TN CLL patients in combination with or without R. Ob_6-Ven_{12} acquired finally reimbursement August 2023 for all TN CLL patients according the CLL13 and CLL14 data. We are still waiting for reimbursement of FD Ibr plus Ven (I+V) and continuous treatment of zanubrutinib (Zanu) as an additional alternative BTKi. Ven lost its reimbursed indication as monotherapy from November 2020. A lot of data has been updated or communicated to support the implemented and proposed changes in our treatment algorithm of TN CLL.

TREATMENT OF TN CLL PATIENTS WITH 17P DEL/*TP53* MUT (*Table 2*)

It is common knowledge that patients showing a 17p del/*TP53* mut are poor responders to CIT. The GCLLSG CLL8 trial showed a median PFS and OS of only eleven and 23 months for this subgroup treated with FCR.[34] Our initial Belgian reimbursement of the B-cell receptor (BCR) is, Ibr and Idela (August 2015) and the bcl-2i (Ven) (November 2017) for TN patients with a *TP53* aberration has been approved due to data which revealed better outcomes in R/R CLL than CIT as front-line treatment.

In the meantime, data became available for TN CLL patients carrying a *TP53* aberration treated with these novel agents. The pooled analysis across four studies (PCYC-1122e, RESONATE-2, iLLUMINATE and ECOG-ACRIN E1912) included 89 patients receiving single-agent Ibr (n=45) or Ibr in combination with an anti-CD20 monoclonal antibody (MAB) (n=44). With a median follow-up of 49·8 months, median PFS was not reached (NR). 4 years PFS and OS rates were 79% and 88%, respectively.[35] In ELEVATE TN 73 patients carried a *TP53* aberration and received Acala monotherapy (n=23) or Acala in combination with Ob (n=25). With a follow up of 74.5 months, the 6 years PFS rates in the Acala-Ob and Acala monotherapy arms were 56% and 18% for the Ob_6-Chl_6 arm with a median PFS of 73 months, NR and 17.5 months (hazard ratio for progression or death (HR): 0.28 and 0.23; both p <0.0009). No OS difference has been seen with this follow-up.[36-38] Sequoia Arm C included only 17p del patients (n=111) with or without a *TP53* mutation to be treated with Zanu (median age 70 years). At a median follow-up of 47.9 months, median PFS has not been reached. At 3.5 years, PFS and OS rates were 79.4% and 89.5%, respectively.[39,40]

TABLE 2. TN CLL with a *TP53* aberration: PFS and OS in clinical trials.

TP53 aberration & TN CLL	N	PFS	OS
Ibr (four trials)[35]	89	4 yrs 79%	4 yrs 88%
ELEVATE TN[36-38] Ob_6-Acala *vs.* Acala *vs.* Ob_6-Chl_6	73 25/23/25	4 yrs 74.8%/76.2%/... 6 yrs 56%/56%/18% mPFS 73 mos/NR/17.5 mos	6 yrs 68%/72%/53% (=) mOS NR/NR/74.9 mos
Sequoia Arm C[40] Zanu	111	3.5 yrs 79.5%	3.5 yrs 89.5%
Ob_6-Ven_{12} (CLL14)[41]	25	4 yrs 53% mPFS 51.9 mos	4 yrs 84.5% (entire trial)
Captivate[42] I+V	27	4 yrs 63%	4 yrs 96%

Acala: acalabrutinib; Chl: chlorambucil; CLL: chronic lymphocytic leukaemia; Ibr: ibrutinib; I+V: ibrutinib + venetoclax; mo: month; yrs: years; N= number of patients; NR: not reached; Ob: obinutuzumab; Ob_6-Chl_{12}: obinutuzumab six cycles + chlorambucil twelve cycles; OS: overall survival; PFS: progression free survival; SS: statistical significant; TN: treatment-naïve; Ven: venetoclax; Zanu: zanubrutinib; =: not statistical significant.

TABLE 3. TN FIT CLL without a *TP53* aberration: PFS and OS in clinical trials.

Fit TN CLL	N	Median age	PFS	OS
E1912 [43] FCR/Ibr-R_6	529	58 yrs	3 yrs 73%/89% 5 yrs 51%/78%	5 yrs 95%/89% (SS)
CLL13[19,44] CIT/R_6-Ven_{12}/Ob_6-Ven_{12}/ Ob_6-$Ib_{15\text{-}36}$-Ven_{12}	926	61 yrs	3 yrs 75.5%/80.8%/87.7%/90.5% 4 yrs 62%/70.1%/81.8%/85.5% mPFS 59.4 mos/63.4 mos/NR/NR	OS =
FLAIR[45] FCR/Ibr_{6yrs}-R_6	771	62 yrs	4 yrs 73%/85.6% mPFS 67 mos/NR	4 yrs 93%/92.1% (=)
CAPTIVATE[42,46] I+V	159	60 yrs	4 yrs 79% *Unmutated IGHV 73%*	4 yrs 98%
CLL 17 Ibr/Ob_6-Ven_{12} /I+V	926		pending	pending

CLL: chronic lymphocytic leukaemia; Ibr: ibrutinib; I+V: ibrutinib + venetoclax; mo: month; yrs: years; N= number of patients; NR: not reached; Ob: obinutuzumab; Ob_6-Chl_{12}: obinutuzumab six cycles + chlorambucil twelve cycles; OS: overall survival; PFS: progression free survival; R: rituximab; SS: statistical significant; TN: treatment-naïve; Ven: venetoclax; Zanu: zanubrutinib; =: not statistical significant.

The phase III RCT GCLLSG CLL14 compared FD Ob_6-Ven_{12} with Chl (twelve cycles) plus Ob (six cycles) (Ob_6-Chl_{12}) in older or unfit TN CLL patients. Twenty-five patients with a *TP53* aberration were treated with Ob_6-Ven_{12}. With a median follow-up of 76.4 months, median PFS was reached at 51.9 months.[41] The FD cohort of the CAPTIVATE trial treated 27 patients holding a *TP53* aberration with I+V. The four year PFS and OS rates were 63% and 96% for this high-risk group.[42]

OPINION OF BHS-LPD COMMITTEE:

We can conclude that all above mentioned trials confirm excellent and durable responses with the novel agents in monotherapy or in combination with a MAB compared to CIT. However, median PFS and OS stay shorter for patients with a TP53 aberration compared to those without a TP53 aberration. We have no evidence that adding anti-CD20 MABs to BTKis has an added value in this patient population. Continuous BTK inhibition generates prolonged PFS rates compared to FD treatments. At the same time, no data are available from RCTs today where the novel agents or combinations are compared head-to-head. Also, not a lot of data are already communicated on TT2T and time to second PFS (PFS2) in this high-risk CLL population.

TREATMENT OF TN CLL WITHOUT 17P DEL/*TP53* MUT

Clinical trials in TN CLL can be divided in those done in fit and unfit patients.

TREATMENT OF "FIT TN CLL" WITHOUT 17P DEL/*TP53* MUT (*Table 3*)

In the E1912 phase III RCT previously untreated fit CLL patients (n=529), ≤70 years (median age 58 years) with a good PS, a Cr Cl > 40 ml/min and no 17p del by fluorescence in situ hybridisation (FISH) were treated with FCR (six cycles) or Ibr-R_6 (one cycle of Ibr lead-in, six cycles of Ibr-R followed by Ibr until disease progression (PD)). With a median follow-up of 70 months, PFS was significantly longer for Ibr-R_6 with a HR: 0.37; p <0.001 (5 years PFS rates 78% *vs.* 51% for Ibr-R_6 *vs.* FCR). With this longer follow-up, the PFS difference was significant not only for the unmutated but also for the mutated subgroup (both HR: 0.27; p <0.001). The PFS curves were only similar for the CLL IPI low risk group (n=46 (HR: 0.72; p =0.672). OS stayed also superior for the Ibr-R_6 treated patients (HR: 0.47; p =0.018) (5 years OS rates 95% *vs.* 89% for Ibr-R_6 *vs.* FCR) but the benefit was only observed for the unmutated IGHV patients. In total, 60.5% of the Ibr-R_6 treated patients remain on Ibr. 10.5% of patients discontinued therapy due to PD or death and 21.9% discontinued due to AEs. Among Ibr-treated patients who discontinued treatment for a reason other than PD, median PFS was 25 months. Although incidence of ≥ grade 3 AEs was similar in the two groups (± 80%), grade ≥3 infectious complications were less common with Ibr-R_6 than with FCR (10.5% *vs.* 20.3%; p<0.001). AF and other cardiac AEs were reported each in 4.5% of Ibr-R_6 and not in FCR treated patients. Three deaths due

to AML were already reported in the FCR arm.[43]

GCLLSG CLL13, a phase III RCT, assigned fit CLL patients (median age 61 years) without *TP53* aberrations (n=926) to CIT (FCR-BR), R_6-Ven_{12} or Ob_6-Ven_{12} with or without Ibr (Ob_6-Ibr_{15-36}-Ven_{12}). With a median follow-up of 38.8 months, three year PFS was 90.5% in the Ob_6-Ibr_{15-36}-Ven_{12} group and 75.5% in the CIT (HR: 0.32; p <0.001). Only 10% of the Ob_6-Ibr_{15-36}-Ven_{12} patients needed >15 cycles of Ibr monotherapy. Three year PFS was also higher with Ob_6-Ven_{12} (87.7%; HR: 0.42; p <0.001), but not with R_6-Ven_{12}) (80.8%; HR: 0.79; p =0.18) compared to the CIT arm. Grade ≥3 infectious AEs were more common with CIT (18.5%) and Ob_6-Ibr_{15-36}-Ven_{12} (21.2%) than with Ob_6-Ven_{12} (10.5%) or R_6-Ven_{12} (13.2%). Ob_6-Ven_{12} with or without Ibr was superior to CIT as first-line treatment in fit patients with CLL.[19] With a follow-up of 50.5 months, four year PFS rates were 85.5% for Ob_6-Ibr_{15-36}-Ven_{12}, 81.8 % for Ob_6-Ven_{12}, 70.1% for R_6-Ven_{12} and 62% for CIT.[44] Discontinuations due to AEs were seen in 15.3% of CIT, 5.9% of R_6-Ven_{12} , 5.7% of Ob_6-Ven_{12} and 12.6% of Ob_6-Ibr_{15-36}-Ven_{12}. All grades AF were seen in 7.8% of the Ob_6-Ibr_{15-36}-Ven_{12} arm and <2% of the other arms. Hypertension was seen in 12.5% of the Ob_6-Ibr_{15-36}-Ven_{12} arm, 9.3% of the Ob_6-Ven_{12}, 6.7% of R_6-Ven_{12} and 2.8% of CIT arm.[19]

FLAIR is a phase III RCT for patients <75 years old (median age 62 years) with active/advanced disease. Patients with 17p del >20% were excluded. Patients (n=771) were randomised between Ibr_{6years}-R_6 (Ibr for six years and R for six cycles) and FCR (six cycles). After a medium follow-up of 53 months, median PFS was NR for Ibr_{6years}-R_6 and was 67 months for FCR (HR: 0.44; p <0.001). OS was not different for the two groups. There were more unexplained or cardiac sudden deaths (n=8) in the Ibr_{6years}-R_6 arm especially in patients with existing hypertension or a history of cardiac disorders. All grade AF was reported in 5% *vs.* <1% of Ibr_{6years}-R_6 and FCR, respectively. Seven patients developed already MDS/AML in the FCR arm *vs.* only one in the Ibr arm. Discontinuations due to AEs were seen in 28.7% of Ibr_{6years}-R_6 randomised patients.[45]

The FD cohort of CAPTIVATE was a multicentre phase II study of I+V for fit, ≤70 years (median age 60 years) TN CLL/SLL (n=195). Median time on study was 50 months. The four year PFS rate for the total cohort was 79% with a four year OS rate of 98%. The four year PFS rates were lower for patients with unmutated IGHV (73%) or *TP53* aberration (63%). The discontinuation rate was low (4%) and the AF incidence was 9%. Patients with PD after completing FD I+V initiated retreatment with Ibr or I+V with promising responses although the follow-up is short.[42,46]

We must wait at least till 2025 for the results of the GCLLSG CLL17 phase III trial where TN patients (n=926) with advanced/active disease, a good PS and a Cr CL ≥30 ml/min were randomised irrespective of age, *TP53* status and fitness to continuous Ibr, FD Ob_6-Ven_{12} or FD I+V.

OPINION OF BHS-LPD COMMITTEE:

With longer follow-up the E1912 and FLAIR confirmed the PFS benefit of Ibr given continuously compared to SOC being FCR. Today we are not convinced that adding a MAB to Ibr will improve PFS or OS although the depth of response and earlier normalisation of the absolute lymphocyte count will be seen. No data of RCTs with other covalent BTKis (cBTKis) in fit patients are available although we don't expect big differences compared to Ibr. The E1912 trial showed that patients who discontinued Ibr for another reason than PD had an median PFS of 25 months. This means that not all patients discontinuing a BTKi must start immediately with a new treatment line. The CLL13 showed that Ob_6-Ven_{12} as FD treatment improved also PFS compared to FCR or BR. This trial confirmed that Ob is the better MAB to be combined with Ven (twelve cycles). We must optimise our infusion related reaction and TLS approaches when using Ob_6-Ven_{12}. FD I+V shows similar PFS data as Ob_6-Ven_{12} and can be offered as an alternative first-line treatment. Today no data are available from RCTs where continuous BTKis are compared head-to-head to FD treatments. No data are mature on TT2T and PFS2 in this fit population.

TREATMENT OF UNFIT TN CLL WITHOUT 17P DEL/*TP53* MUT (*Table 4*)

The RESONATE-2 was a phase III RCT who assigned TN CLL patients (≥65 years) (median age 72-73 years) without 17p del to Ibr until PD/unacceptable toxicity (n=136) or Chl (0.5-0.8 mg/kg ≤12 cycles) (n=133). With a median follow-up of 82.7 months, the PFS benefit was sustained for Ibr *vs.* Chl (HR: 0.154; 95% confidence interval (CI): 0.108-0.220). The seven year PFS rate was 59% for Ibr *vs.* 9% for Chl. The PFS benefit was also observed for Ibr-randomised patients with 11q del or unmutated IGHV. OS at 7 years was 78% for patients randomised to Ibr. The median OS was 89 months for patients initially treated with Chl despite cross-over to Ibr at PD. With up to eight years of follow-up, 42% of patients remain on Ibr while 24% of patients stopped due to AEs. The yearly incidence of AF and hypertension in the last three years of follow-up varied between 7-9% and 23-25%, respectively.[47]

In the A041202 phase III RCT, previously untreated CLL patients (n=547) requiring treatment, ≥65 years (median age 71 years) with a good PS, a Cr Cl ≥40ml/min, were treated with Ibr until PD, Ibr-R_6 (six cycles of R with Ibr until PD) or BR (six cycles). Six percent of patients had a

TABLE 4. TN UNFIT CLL without a *TP53* aberration: PFS and OS in clinical trials.

UNFIT TN CLL	N	Median age	PFS	OS
Resonate 2[47] Ibr/Chl_{12}	136	72-73 yrs	4 yrs 76%/etc. 7 yrs 59%/9% mPFS NR/15 mos	7 yrs 78%/etc. mOS NR/89 mos (SS)
A041202[48,49] Ibr±R_6/BR	547	71 yrs	4 yrs 76%/48% mPFS NR/44 mos	4 yrs 85-86%/84% (=)
iLLUMINATE[51] Ob_6-Ibr/Ob_6-Chl_6	229	71 yrs	4 yrs 74% mPFS NR/22 mos	4 yrs ±80% both (=)
CLL 14[41,52,53] Ob_6-Ven_{12}/Ob_6-Chl_{12}	432	72 yrs	4 yrs 74%/35% mPFS 76.4 mos/36.4 mos	4 yrs 85.4%/83.1% 6 yrs 78.7%/69.2% (=)
ELEVATE TN[36,38] Ob_6-Acala/Acala/Ob_6-Chl_6	535	70 yrs	4 yrs 87%/78%/25.1% 6 yrs 78%/62%/17% mPFS NR/NR/27.8 mos	4 yrs 92.9%/87.6%/88% 6 yrs 84%/76%/65% (=)
GLOW[57] I+V/Chl_6-Ob_6	211	71 yrs	4.5 yrs 65.8%/19.1% (M 90% U 58%) mPFS NR/21 mos	4.5 yrs 84.5%/63.1% (SS)
Sequoia Arm A-B[40,58] Zanu/BR	479	70 yrs	3.5 yrs 82%/50% mPFS NR/42.8 mos	3.5 yrs 89%/88% (=)

Acala: acalabrutinib; B: bendamustine; CLL: chronic lymphocytic leukaemia; Chl: chlorambucil; Ibr: ibrutinib; I+V: ibrutinib + venetoclax; mo: month; yrs: years; N= number of patients; NR: not reached; Ob: obinutuzumab; Ob_6-Chl_{12}: obinutuzumab 6 cycles + chlorambucil 12 cycles; OS: overall survival; PFS: progression free survival; R: rituximab; SS: statistical significant; TN: treatment-naïve; Ven: venetoclax; years: years; Zanu: zanubrutinib; =: not statistical significant.

17p del and 10% a *TP53* mut. Cross-over to Ibr due to PD within the first year after BR was allowed and occurred in 30 patients. No significant PFS difference was seen for Ibr-R_6 *vs.* Ibr. However, PFS was significantly better for Ibr and Ibr-R_6 (four year PFS 76%) compared to BR (four year PFS 48%) (HR: 0.36; p <0.0001), respectively. With a median follow-up of 55 months, there was no significant difference among the three treatment groups regarding OS. The rate of grade ≥3 haematologic AEs was higher with BR (61%) than with Ibr/Ibr-R_6 (± 40%), whereas the rate of grade ≥3 non hematologic AEs was lower with BR (63%) than with the Ibr-containing regimens (74%). Grade ≥3 infectious complications were seen in 19%, 22% and 27% of BR, Ibr and Ibr-R_6 treated patients.[48,49] The cumulative incidence of AF and hypertension at three year was 19% *vs.* 6% and 73% *vs.* 54% for the Ibr treated patients *vs.* the BR arm.[50]

The iLLUMINATE phase III RCT compared Ob_6-Ibr (Ob six cycles, Ibr till PD) *vs.* Ob_6-Chl_6 (6 cycles) in TN patients (n=229) in need of treatment, ≥65 years or <65 years with at least one of the following criteria (cumulative illness rating scale (CIRS) >6, Cr Cl <70 ml/min, 17p del/*TP53* mut) (median age 71 years). Fourteen percent of all patients showed a 17p del and 13% a *TP53* mut. The final analysis with a median follow-up of 45 months showed the sustained PFS benefit (median PFS NR *vs.* 22 months (HR: 0.25; p <0.0001). The four year PFS rate was 74% for Ob_6-Ibr. A discontinuation rate of 22%, 9-13% and 9% due to AEs was mentioned for Ibr, Ob and Chl, respectively. Cross-over to Ibr was permitted after confirmation of PD to Ob_6-Chl_6 and was started in 50 patients. TTNT was NR for the chemotherapy free regimen and was 33 months for the Ob_6-Chl_6 arm These benefits were seen independent of high-risk features (17p del/*TP53* mut, 11q del, unmutated IGHV). No OS difference was seen at the final analysis. Serious AEs occurred in 58% and 35% of patients treated with Ob_6-Ibr and Ob_6-Chl_6. The most common grade ≥3 AEs in both groups were neutropenia (37% *vs.* 46%) and thrombocytopenia (19% *vs.* 10%). All grades hypertension and AF from time of first dose until 30 days after last dose or initiation of a subsequent treatment was 19% *vs.* 4% and 15% *vs.* 0% for Ob_6-Ibr *vs.* Ob_6-Chl_6.[51]

The GCLLSG CLL 14 trial compared FD Ob_6-Ven_{12} with Ob_6-Chl_{12} in TN CLL patients (n=432) (median age 72 years) with comorbidities (median CIRS score 8-9) and/or a Cr Cl <70 ml/min. After 76.4 months median follow-up, the median PFS for Ob_6-Ven_{12} was reached: median PFS 76.4 months *vs.* 36.4 months for Ob_6-Ven_{12} and Ob_6-Chl_{12}, respectively (HR: 0.40; p <0.0001). Concerning PFS according IGHV and *TP53* aberration, median PFS was NR for mutated IGHV and was 64.8 months for the unmutated ones (HR: 0.38; p <0.001), was NR for those without a *TP53* aberration and was 51.9 months for those with a *TP53* aberration (HR: 2.29; p <0.001). Six year TTNT rate was 65.3% *vs.* 37.1% for Ob_6-Ven_{12} *vs.* Ob_6-Chl_{12} (HR: 0.44; p <0001) with a median TTNT for Ob_6-Chl_{12} of 52.9 months. Median OS was NR. 6 years OS rate is 78.7% *vs.* 69.2% for Ob_6-Ven_{12} and Ob_6-Chl_{12} (HR: 0.69; p <0.052).[41] Treatment discontinuation due to AEs were seen in 16% and 15.4% of Ob_6-Ven_{12} and Ob_6-Chl_{12} treated patients, respectively.[52,53]

The phase III ELEVATE-TN RCT used Ob_6-Acala (Ob six cycles, Acala till PD or intolerance), Acala till PD or intolerance or Ob_6-Chl_6 (six cycles) in untreated patients aged ≥65 years or <65 years if Cr Cl 30-69 ml/min or CIRS >6 with a good PS (n= 535) (median age 70 years). 17p del and *TP53* mut were present in 9% and 11% of patients. At a medium follow-up of 74.5 months, median PFS was prolonged for Ob_6-Acala and Acala compared to Ob_6-Chl_6 (NR *vs.* 27.8 months (HR: 0·14) and NR *vs.* 27.8 months (HR: 0·23) (both p <0.0001)). Estimated six year PFS was 78% with Ob_6-Acala, 62% with Acala and 17% with Ob_6-Chl_6. Cross-over was allowed. 41% of Ob_6-Chl_6 treated patients received Acala at PD. OS was longer for Ob_6-Acala *vs.* Ob_6-Chl_6 (HR: 0.62; p =0.035) while no difference in OS was seen between Acala and Ob_6-Chl_6. Estimated six year OS was 84%, 76% and 75% for Ob_6-Acala, Acala and Ob_6-Chl_6, respectively. Again, the PFS difference for mutated IGHV patients was not significant compared to those who were treated with Ob_6-Chl_6 though the number of patients compared was low. The most common grade ≥3 AE was neutropenia (Ob_6-Acala: 30%, Acala: 9%, Ob_6-Chl_6: 41%). Grade ≥3 infections occurred in 21%, 14% and 8% of patients with Ob_6-Acala, Acala and Ob_6-Chl_6, respectively.[37] With a median follow-up of 74.5 months, AEs led to discontinuation of Acala in the Ob_6-Acala arm in 21% and in the Acala arm in 18% of patients. Treatment was ongoing in 54% and 47% of patients in the Ob_6-Acala and Acala arms.[36-38]

The phase III RCT, GLOW, evaluated the efficacy and safety of FD I+V (Ibr lead-in for three months followed by twelve cycles of combination I+V) and Ob_6-Chl_6 in older patients (median age 71 years) and/or comorbidities (median CIRS score 8-9) without a 17p del or a known *TP53* mutation in TN CLL patients (n=211). With a median follow-up of 34.1 months, PFS was longer for I+V (HR: 0.212; p <0.001). The improvement was consistent across all predefined subgroups including patients >65 years or those with a CIRS >6.[54,55] At a median follow-up of 42 months, OS was significantly improved for the I+V patients (HR: 0.487; p <0.0205).[56] With a median follow up of 55 months, 4.5 years PFS and OS rates were 65.8% and 84.5% *vs.* 19.1% and 63.1% (HR: 0.24; p <0.0001 and HR: 0.42; p =0.0023) for I+V and Ob_6-Chl_6, respectively. The 4.5 years PFS rates were longer in the mutated *vs.* unmutated IGHV patients in the I+V arm (90% *vs.* 58%).[57] The discontinuation rate due to AEs was 10.4% in the I+V arm. Any grade AF occurred in 14.2% *vs.* 1.9% in the I+V and Ob_6-Chl_6 arms. The 4 sudden deaths reported during I+V occurred in patients with a high CIRS and high PS with hypertension, CV disease and/or diabetes.[54-57]

Sequoia arm A+B is a phase III RCT including TN patients >65 years or younger with comorbidities (median age 70 years), with a PS 0-2 and without 17p del (N=479). At a median follow-up of 43.7 months, median PFS was NR for Zanu and was 42.2 months for BR. The 3.5 years PFS rate was 82% for Zanu with a 3.5 years OS rate of 89% and 88% for Zanu and BR, respectively. Treatment discontinuation due to AEs was 8% and 13.5%, respectively in the Zanu and BR arms with a medium follow-up of 26.2 months. Any-grade AF was seen in 5% *vs.* 3% of Zanu *vs.* BR treated patients, respectively. The infection rate was high in both arms (73% *vs.* 63%), bleeding AEs were more frequent in the BTKi arm (49% *vs.* 12%) as haematological toxicities and especially neutropenia were higher in the BR arm (17% *vs.* 57%).[40,58]

OPINION OF BHS-LPD COMMITTEE:

With 6 and 7 years median follow-up the median PFS for Acala and Ibr in the ELEVATE TN and RESONATE-2 trials have still not been reached confirming the great PFS benefit of continuous BTK inhibition in unfit CLL patients. The outcomes of Zanu, with shorter follow-up, look similar. Also in the unfit we miss convincing evidence to add a MAB to the BTKi. With 6 years follow-up the median PFS for Ob_6-Ven_{12} in the CLL14 has been reached. The mPFS of 76.4 months is even better than FCR in young and fit patients. Although the outcome of BTK inhibition is IGHV independent, the median PFS of Ob_6-Ven_{12} is longer in the mutated vs. the unmutated IGHV patients. FD I+V shows also very promising PFS data and even an OS benefit compared to Ob_6-Chl_6. We must wait for the CLL 17 data where continuous BTKis were compared head-to-head to FD treatments indepen-

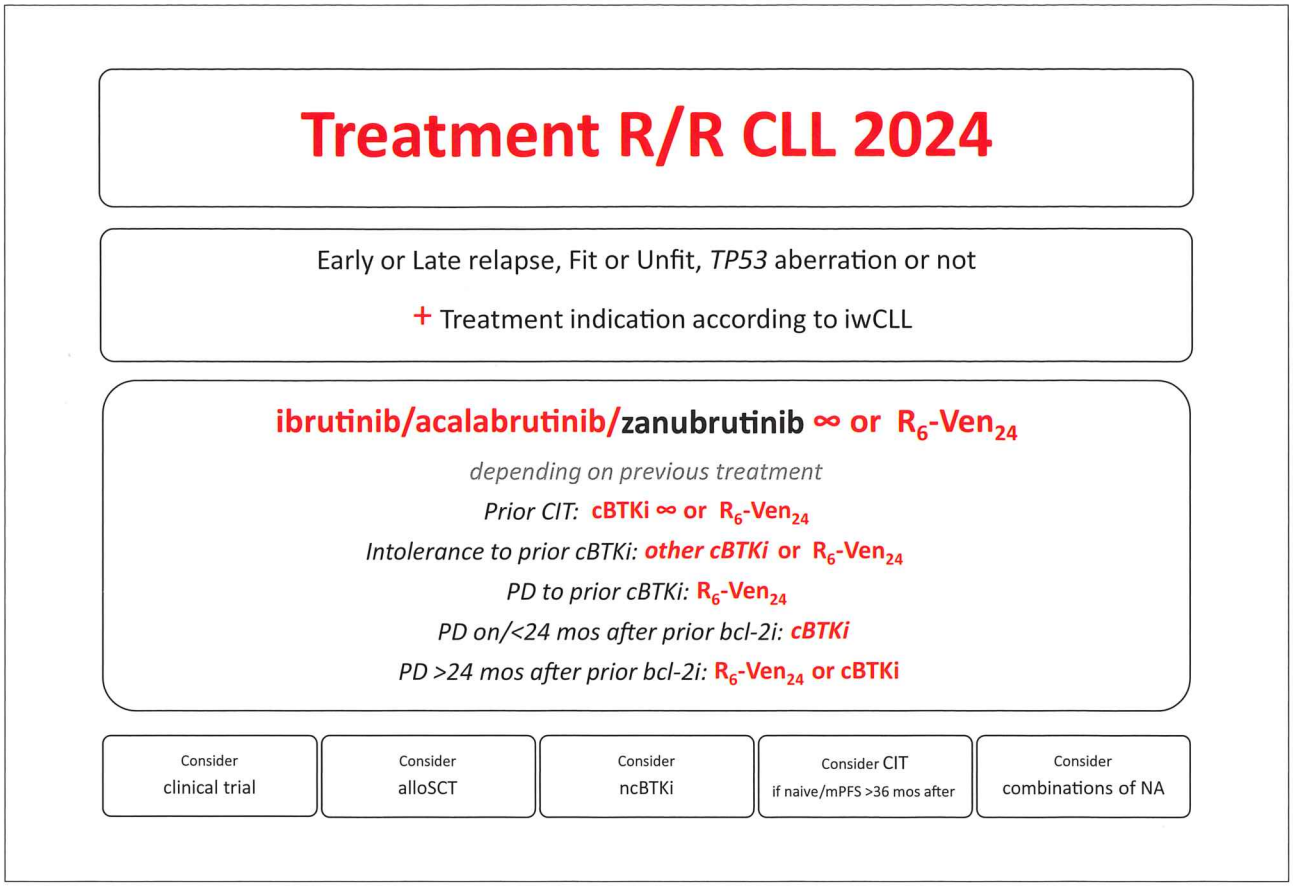


FIGURE 3. Treatment algorithm R/R CLL anno 2024 Belgium.
Acala: acalabrutinib; alloSCT: allogenic stem cell transplantation; BTK: Bruton tyrosine kinase; c: covalent; CIT: chemo-immunotherapy; CLL: chronic lymphocytic leukaemia; i: inhibitor, Ibr: ibrutinib; m: median; mo: month; N= number of patients; NA: novel agents; nc: non-covalent; PD: progressive disease; PFS: progression free survival; R: rituximab; R/R: relapsed/refractory; Ven: venetoclax; yrs: years; Zanu: zanubrutinib;.: ∞: till intolerance or progression.

ent of age and comorbidities to know if one treatment is better than the other. In the meantime, we have three powerful treatment options and selection of the optimal treatment for a particular patient will be multifactorial with special emphasis on CV risks next to infusion related reaction and TLS approaches.

CIT (FCR, BR, OB_6-CHL_{12}) AS FRONTLINE TREATMENT IN CLL IN THE ERA OF NOVEL AGENTS?

As said already, CIT has no place in patients showing a *TP53* aberration as outcomes of continuous BTK inhibition, Ob_{12}-Ven_{12} and I+V surpass the outcomes of CIT.[34] FCR CIT was the standard of care (SOC) for patients, who were fit, have no major comorbidities (CIRS ≤6) and/or a normal renal function (Cr Cl ≥70 ml/min) and absence of active autoimmune haemolytic anaemia (AIHA) and recurrent infections.[34,59] For patients >65 years BR was an alternative treatment to FCR with similar outcomes but lower toxicities.[59] Even for patients with comorbidities BR seemed a feasible treatment.[60] For unfit (CIRS >6), elderly patients Ob-Chl improved not only PFS, TTNT but also OS compared to R-Chl and Chl.[61] Long-term follow-up of some patient cohorts treated with FCR showed previously that ± 50% of young, fit patients with mutated IGHV remain in remission and even cure has been suggested.[62-64] For fit patients FCR was SOC in the E1912 and FLAIR trials while the CLL13 used FCR or BR as SOC. An OS benefit was seen for Ibr-R_6 in the E1912 but not in the FLAIR trial.[43,45] The CLL13 also showed no OS difference although the follow-up is still short.[19] In the E1912 trial the PFS curves for FCR and Ibr-R_6 were only similar for the CLL-IPI low risk group defined as patients without a *TP53* aberration, with mutated IGHV and a normal β2 microglobulin, ≤65years with any stage or >65 years with a Rai 0 or Binet A.[43] A sub-analysis of the CLL13 compared the three year PFS of patients ≤65 years with mutated IGHV and showed identical PFS rates for FCR, Ob_6-Ven_{12} and Ob_6-$Ibr_{15\text{-}36}$-Ven_{12}.[19] A major concern of FCR is the induction

of treatment related myeloid neoplasias (t-MNs) The MD Anderson cancer center reported with a median follow-up of 12.4 years, a prevalence of t-MNs of 4.7% in 300 patients treated with FCR as first-line.[64] E1912 and FLAIR reported also MDS/AML cases with a much shorter follow-up.[43,45] These t-MNs are also difficult to treat.[63] Clinical trials in the unfit or older patients, used BR or a Chl-containing regimen as SOC. An OS benefit for the novel agents was seen only for the Resonate-2 (Ibr) and the Glow (I+V) trials.[47,56,57] Although in every clinical trial a highly significant gain in PFS was seen for the novel agents in patients with unmutated IGHV, the gain was not always significant in patients with mutated IGHV.

OPINION OF BHS-LPD COMMITTEE:

We think that FCR could still be a treatment option for young patients, fit for F with mutated IGHV and absence of CK, 11q or 17p del and prognostic negative NGS aberrations. The risk of t-MN against the risk of cardiac issues must be weighted. For unfit or older patients, CIT (BR, Ob-Chl), could only be an alternative treatment option for mutated IGHV patients if they prefer a time limited treatment or if there are safety issues for BTKis and/or bcl-2is.

SECOND OR SUBSEQUENT-LINE TREATMENT (*Figure 3*)

In our 2020 update, we concluded that Ibr or FD R_6-Ven_{24} were the best therapeutic options for patients with R/R disease after CIT with or without a *TP53* aberration. Till 2020, national and international guidelines supported retreatment with CIT for fit CLL patients showing a late relapse (>2-3 years after previous treatment). For patients unfit, refractory to treatment, experiencing early relapse after CIT the BCRis (Ibr or R-Idela) were reimbursed since August 2015 as outcome compared to anti-CD20 MABs (ofatumumab (Ofa), R) or CIT (BR) was superior. As mentioned before, Idela has lost reimbursement August 2019 for CLL in Belgium due to safety concerns. Ven, the first bcl-2i, was reimbursed as monotherapy November 2017 in R/R CLL with a *TP53* aberration after failure of BCRi or in R/R CLL without a *TP53* aberration after failure of CIT and BCRi. Since September 2019, we can also treat all R/R CLL progressing after Ibr or CIT with a FD of R_6-Ven_{24}. As mentioned already, Ven lost his reimbursed indication as monotherapy in November 2020. In our 2020 update we abandoned CIT from treatment options as we learned from the Helios trial that median PFS after BR for patients

TABLE 5. Treatment of R/R CLL WITH a *TP53* aberration.

R/R CLL with *TP53* aberration	N	Median PFS	Median OS
PCYC 1202-1103[66] Ibr	34	26 mos	57 mos
Resonate/Resonate17/PCYC 1103[67] Ibr	230	2.5 yrs 57%	2.5 yrs 69%
M13-92 + expansion[68] Ven	158	27.2 mos	
Murano[69] Ven_{24}-R_6	53	37.4 mos	5 yrs 70.2%
ELEVATE R/R[70] Ibr/Acala	121/124	27.6 mos/32.9 mos	
ASCEND[71] Acala/ BR or R-Idela	35/13	45.5 mos/11 mos	
ALPINE[72] Ibr/Zanu	75/75	2 yrs 54.6%/72.6%	OS =

Acala: acalabrutinib; B: bendamustine; BTK: Bruton tyrosine kinase; CLL: chronic lymphocytic leukaemia; Ibr: ibrutinib; Idela: idelalisib; mo: month; N= number of patients; OS: overall survival; PFS: progression free survival; R: rituximab; R/R: relapsed/refractory; Ven: venetoclax; years: years; Zanu: zanubrutinib.

relapsing sooner or later than 36 months was only a few months longer while an identical benefit for treatment with Ibr was seen.[65] CIT in R/R CLL can only be a treatment option for patients with a very long response to previous CIT and only if the patient insists on a short, FD of treatment. Acalabrutinib (Acala) was reimbursed from November 2021, as alternative BTKi for all R/R patients.

TREATMENT OF R/R CLL PATIENTS WITH 17P DEL/*TP53* MUT (*Table 5*)

The five year follow-up of R/R CLL patients with a 17p del receiving Ibr (PCYC-1102, PCYC-1103 trials) (n=34), showed durable responses with a mPFS of 26 months and a mOS of 57 months.[66] Two hundred and thirty R/R patients with a 17p del from three clinical trials (Resonate, Resonate 17, PCYC-1102) were evaluated. With a median follow-up of 28 months, overall response rate (ORR) was 85% with a 2.5 years PFS and OS of 57% and 69%, respectively.[67] Ven monotherapy acquired reimbursement November 2017 for patients with a *TP53* aberration and progressive or intolerant to Ibr according to the data from the M13-982 trial with expansion cohort (n=158) (only 10% of patients pre-treated with a BCRi). A median PFS of 27.2 months has been shown.[68] Since September 2019 we can also treat these high-risk patients progressing after Ibr or CIT according to the Murano RCT with a FD of R_6-Ven_{24}. This trial included 53 patients with a *TP53* alteration. Median PFS was 37.4 months with a five year OS of 70.2%.[69] Acala was reimbursed from November 2021, as alternative BTKi also for R/R patients with a *TP53* aberration. In the head-to-head phase III RCT ELEVATE R/R, 245 patients with a 17p del were included. One hundred and twenty-four patients were treated with Acala and 121 patients with Ibr. The median PFS was 32.9 months and 27.6 months (HR: 1.00; 95% CI: 0.73-1.38) for the Acala and Ibr treated arms, respectively.[70] In the ASCEND trial, R/R CLL patients, were randomised between Acala (until PD or intolerance) *vs.* investigator choice (R (eight IV infusions) plus Idela (continuously till PD) or BR (six cycles). Thirty-five patients carried a *TP53* aberration. The mPFS was 45.5 months and 11.1 months for those treated with Acala (n=25) and investigator choice (n=13), respectively.[71] Zanu was compared head-to-head to Ibr in the Alpine trial. 23% of each treatment group showed a *TP53* aberration (n=150). The two year PFS was 72.6% *vs.* 54.6% (HR: 0.53; 95% CI: 0.31-0.88) for those treated with Zanu *vs.* Ibr, respectively.[72]

TREATMENT OF R/R CLL PATIENTS WITHOUT 17P DEL/*TP53* MUT (*Table 6*)

The safety and efficacy of Ibr, the first available cBTKi, has been sought in the PCYC-1102, PCYC-1103 trials. 101 R/R CLL patients with a median age of 64 years and a median number of prior treatments of 4 were treated with Ibr. The median PFS and OS were 52 months and 92 months, respectively. The final analysis showed a seven year PFS and OS of 34% and 55% with 21% of patients still on Ibr. Responses to BCRis were confirmed to be independent of IGHV mutational status and the presence of unfavourable genetic aberrations (11q del, CK or novel gene mutations). 24% of patients discontinued treatment due to AEs.[66]

The final analysis of the phase III RCT RESONATE with a median follow-up of 65.3 months was also published. R/R CLL/SLL patients (n=391) with a median age of 67 years and a median number of previous treatments of 3 were treated with Ibr or Ofa. 82% of patients showed high-risk features (17p del/*TP53* mut, 11q del and/or unmutated IGVH). The median PFS remained significantly longer for patients randomised to Ibr *vs.* Ofa (44.1 months *vs.* 8.1 months; HR: 0.15; $p < 0.001$). The PFS benefit was preserved in the high-risk population. OS, censored for cross-over, was better for those initially assigned to Ibr (HR: 0.639; 95% CI: 0.418-0.975). With a median duration of 41 months on Ibr therapy, a cumulatively, all-grade hypertension and AF was noticed in 21% and 12% of patients, respectively. Sixteen percent discontinued Ibr because of AEs.[73]

In the phase III Helios RCT R/R patients (median number of previous treatments two) without a 17p del were treated with BR (six cycles) combined with Ibr or placebo (till PD or intolerance) (n=578) (median age 63-64 years). After a median follow up of 63.7 months, median PFS was significantly better for BR-Ibr (65.1 months *vs.* 14.3 months, HR: 0.23; $p < 0.0001$). In the latest update, analysis of OS corrected for cross-over from placebo to Ibr at PD (160 patients) confirmed the OS advantage of BR-Ibr with median OS still NR for both arms. Reported grade ≥3 AEs in the Ibr and placebo group were similar (77% *vs.* 74%) with the most common grade ≥3 AEs in both groups being neutropenia (54% *vs.* 51%) and thrombocytopenia (15% in each group). Discontinuations due to AEs were reported in 20% of the BR-Ibr *vs.* 11.8% of the BR-placebo treated patients.[65]

The phase III RCT MURANO explored FD R_6-Ven_{24} (R started after ramp-up of Ven) *vs.* BR (six cycles) in R/R CLL (n=389) with a median age of 65 years. ± 27% of patients had a 17p del and/or *TP53* mut. Median number of previous treatments was one. Only 4% of patients were pre-treated with BCRis.[69] After a median follow-up of 59.2 months, median PFS for R_6-Ven_{24} and BR differed significantly (53.6 months *vs.* 17 months, HR: 0.19; $p < 0.0001$). OS showed superiority in the R_6-Ven_{24} arm (HR: 0.40;

p <0.0001) (5 years OS 82.1 *vs.* 62.2%). These OS benefits were observed despite 79% of BR patients received novel agent treatment at PD. Responses were particularly durable in patients who attained uMRD at the end of combination treatment (± mo 9).[74] Median time to MRD recrudescence in peripheral blood was 46 months for all patients and 37 months for those with a *TP53* aberration. Median time to iwCLL progression after MRD recrudescence was seventeen months.[75] The most common grade ≥ 3 AE was neutropenia (R_6-Ven_{24} 58% *vs.* BR 39%) with grade ≥3 infections and TLS occurring in 17.5% and 22% and 3% and 1% of R_6-Ven_{24} and BR treated patients, respectively. Fifteen percent of patients discontinued treatment because of AEs. Premature discontinuation of Ven was associated with suboptimal outcome. Twenty-three percent of patients treated with Ven required a dose reduction without significant impact on outcome highlighting the importance of effective toxicity control to realise the full benefit of Ven treatment.[69]

The ASCEND trial, a phase III RCT, is the first and the only trial comparing a BTKi *vs.* R-Idela head-to-head. Three hundred and ten patients with R/R CLL with a median age of 67 years were randomised between Acala (n=155) (until PD or intolerance) *vs.* investigator choice (R (eight IV infusions) plus Idela (continuously till PD) (n=119) or BR (six cycles) (n=36). The median number of previous treatments was one for the Acala arm and two for the investigator choice arm. Fifty-one percent of patients with confirmed PD on investigator choice (36/68) received Acala monotherapy as cross-over was allowed. Discontinuation due to AEs was observed in 23% of patients on Acala *vs.* 67% in R-Idela and 17% in BR. At a median follow-up of ± 46 months, Acala significantly prolonged median PFS *vs.* R-Idela/BR (NR *vs.* 16.8 months, HR: 0.28; p <0.001) (three year median PFS 62% *vs.* 19% for Acala and R-Idela/BR, respectively). PFS improvement with Acala was observed across all subgroups, including patients with a *TP53* aberration. No difference in OS was seen at time of final analysis (3.5 years median OS 78% *vs.* 65% for Acala and R-Idela/BR, respectively). Any grade AF and hypertension were

TABLE 6. Treatment of R/R CLL WITHOUT a *TP53* aberration.

R/R CLL	N	Median age	Median number of prior treatments	Median PFS	Median OS
PCY 1202-1103[66] Ibr	101	64 yrs	4	52 mos	92 mos
Resonate[77] Ibr/Ofa	391	67 yrs	3	44.1 mos/8.1 mos 56.9 mos (if no *17p del*)	67.7 mos/65.1 mos (SS)
Helios[65] *(No 17p del)* Ibr/BR	578	63-64 yrs	2	65.1 mos/14.3 mos	5 yrs 75.7%/61.2% (SS)
Murano[69] R_6-Ven_{24}/BR	389	65 yrs	1	53.6 mos/17 mos	5 yrs 82.1%/62.2% (SS)
ASCEND[71] Acala/BR-Idela-R	 155/36-119	67 yrs	1 2	NR/16.8 mos 3.5 yrs 78%/19%	3.5 yrs 78%/65% (=)
ELEVATE R/R[70] *(17p/11q)* Ibr/Acala	533	65-66 yrs	2	38.4 mos/38.4 mos	OS =
ALPINE[72] Ibr/Zanu	652	67 yrs	1	2 yrs 65.9%/78.4%	OS =

Acala: acalabrutinib; B: bendamustine; BTK: Bruton tyrosine kinase; CLL: chronic lymphocytic leukaemia; Ibr: ibrutinib; Idela: idelalisib; mo: month; N= number of patients; OS: overall survival; PFS: progression free survival; R: rituximab; R/R: relapsed/refractory; Ven: venetoclax; yrs: years; Zanu: zanubrutinib.

reported in respectively 8% *vs.* 3% *vs.* 3% and 8% *vs.* 6% *vs.* 0% of the Acala, R-Idela and BR arms. This trial confirms not only the superiority of the BTKi over CIT but also over R-Idela in R/R CLL concerning PFS and safety.[71]

At this moment, data from two trials comparing head-to-head cBTKis, Ibr *vs.* Acala and Ibr *vs.* Zanu in R/R CLL are available.[70,72] The phase III RCT BRUIN-CLL-314, investigating pirtobrutinib (Pirto) *vs.* Ibr in patients with BTKi-naive CLL/SLL is ongoing.

Elevate R/R was a non-inferiority, phase III RCT comparing Acala and Ibr in patients with R/R CLL carrying a 17p del or/and an 11q del (n=533) with a median age of 65-66 years and a median number of two prior treatments. No patient was exposed to BCRis or venetoclax. After a medium follow-up of 40.9 months, 46.3% of Acala and 41.1% of Ibr patients remained on treatment. The primary endpoint was reached, meaning that median PFS for Acala was non-inferior to Ibr (median PFS of 38.4 months in both arms HR: 1.00; 95% CI: 0.79-1.27). Median OS was NR in either arm (HR 0.82; 95% CI, 0.59-1.15). All-grade AF and hypertension was significantly lower with Acala *vs.* Ibr (9.4% *vs.* 16.0%; p <0.05 and 8.6% *vs.* 22.8%; p <0.05). Any grade bleeding events, diarrhoea and arthralgias were also less frequent in the Acala arm. Major bleedings were not different. Treatment discontinuations due to AEs occurred in 14.7% and 21.3% of Acala and Ibr-treated patients. This trial concluded that Acala demonstrated similar PFS with fewer CV AEs compared to Ibr.[70] The AE burden score, a score combining grade and duration of AE, was lower for Acala concerning AF, hypertension, haemorrhage and musculoskeletal events and higher for diarrhoea and headache.[76]

The Alpine trial compared Ibr with Zanu in R/R CLL (n=652) with a median age of 67 years and a median number of only one previous treatment. A small number of patients were exposed to Ven (n=15) and phosphatidylinositol 3-kinase (PI3K) or spleen tyrosine kinase (Syk) inhibitors (n=30). The final analysis, after a median follow-up of 29.6 months, showed a better PFS for Zanu (HR: 0.65; p =0.002) (two year PFS 78.4% *vs.* 65.9% for Zanu and Ibr, respectively). This benefit was seen in all pre-specified subgroups. No OS difference was observed with this follow-up period. All grade cardiac events (21.3% *vs.* 29.6%) and all-grade AF (5.2% *vs.* 13.3%) were lower with Zanu *vs.* Ibr. Diarrhoea and muscle cramps were also less frequently reported in the Zanu arm. Any grade of hypertension, bleeding, arthralgia and rash were very similar in the two treatment arms. Any grade of neutropenia was higher in the Zanu arm without an increase of infections. Treatment discontinuations due to AEs occurred in 15.4% and 22.2% of Zanu and Ibr-treated patients. This trial concluded that Zanu demonstrates a superior PFS compared to Ibr across all major subgroups with a lower discontinuation incidence for AEs for Zanu (16.2% *vs.* 22.8%) and fewer cardiac events and cardiac deaths.[72]

BTK INHIBITION

The BTKis have changed without any doubt the treatment journey of newly diagnosed and R/R CLL patients. Ibr has been the first US food and drug administration and European Medicines Agencies approved BTKi (both 2014), followed later by the second-generation being Acala (2019-2020) and Zanu (2023-2022). Ibr, Acala and Zanu are covalent (c) BTKis. The cBTKis bind irreversible the cysteine residue (Cys481) in the ADP-binding pocket of the BTK protein leading to full inhibition and switching off BCR signalling.[77] In the previous chapters we showed that the cBTKis significantly improved PFS and sometimes also OS in fit and unfit TN and R/R CLL. Benefits were maintained among those with high-risk features (unmutated IGHV, 11q del and *TP53* aberrations). As the mode of action of these cBTKis is the same, similar efficacies are expected. Head-to-head trials between cBTKis are only available in R/R CLL.[70,72] BTKi based combination therapies with BR or MAB-FC have been investigated.[65,78-80] Today, we believe from cross-trial comparisons, that adding BR to Ibr does not improve long-term outcomes.[81] Only when rapid debulking is necessary BR can be added. Adding Ibr to MAB-FC was meant to induce deeper and more durable responses, to limit exposure to CIT and to use a FD treatment. Longer follow-up is needed to explore PFS and OS in these trials.[78,79] All cBTKis are given continuously till progression or intolerance due to the limited ability of eradicating the CLL clone. Adherence to this oral treatment is thus crucial for the success. A continuous expensive treatment has also an important impact on the financial burden of the health care systems. Therefore, clinical trials explore cBTKis in combination with Ven as a doublet or in combination with Ven and Ob as a triplet both given as a FD treatment. Since the CLL11 trial, Ob has largely replaced R in CLL because of the improved antibody dependent cellular cytotoxicity and apoptosis leading to improvement of PFS and OS.[61]

In the meantime, we learned that Ibr was not as selective for BTK as initially thought. Acala and Zanu were developed as more selective BTKis. This should be translated in fewer off-target toxicities, discontinuations and an improved efficacy. The ELEVATE R/R trial showed a lower incidence of any grade AF, hypertension and bleeding but also diarrhoea, arthralgia and muscle spasms for Acala

compared to Ibr. Median PFS was similar.[70] The ALPINE trial showed a lower incidence of any grade cardiac events including AF. Diarrhoea and muscle cramps were also less frequently reported in the Zanu arm. The incidence of hypertension, bleeding, arthralgia and rash was similar and the incidence of neutropenia was higher in the Zanu arm. Two year PFS favoured Acala. [72]

Data from a retrospective analysis and a phase II trial showed that patients intolerant to Ibr or Ibr/Acala can switch to Acala or Zanu. Most AEs did not recur or recurred at a lower grade or the same grade. This means that switching cBTKi in case of intolerance can be explored.[82,83]

Due to drug-drug interactions, strong Cyp3A4 inducers and inhibitors, vitamin K antagonists and dual antiplatelet therapy are not recommended to be used concomitantly with any cBTKi. Any cBTKi must be used with caution together with antiplatelet and anticoagulant agents.

Co-administration of the Acala capsules with proton-pump inhibitors (PPIs) was not recommended due to significant decreased absorption of Acala. However, the absorption of acalabrutinib maleate tablets is not influenced anymore by PPIs providing a similar exposure independent of PPI administration.[84] The tablets are available and reimbursed in Belgium from October 1st, 2023.

In the meantime, reversible, non-covalent (nc) inhibitors have been developed. The ncBTKis do not bind the cysteine residue but bind reversible the ADP-binding pocket through hydrogen, ionic bonds and hydrophobic interactions and can overcome the resistance of cBTKis. Pirto and nemtabrutinib are the most advanced ncBTKis in clinical development. The limited available data show durable responses in heavily pre-treated patients especially with BTK C481S or similar mutations. Also, some AEs typically associated with cBTKis occur relatively infrequent (bleeding, hypertension, AF). With a short median follow-up (16.5 months), only 2.8% of patients discontinued Pirto due to AEs.[85]

OPINION OF BHS-LPD COMMITTEE:

Selection of the most appropriate cBTKi is a multifactorial process. Comorbidities of the patient, expected AEs of the particular BTKi, co-medication, ease of administration (once vs. twice a day) and desired outcome must be weighted. The help of trained clinical pharmacists is crucial for patient safety as they inform, teach, review and manage difficult pharmacotherapeutic issues.

RESISTANCE TO NOVEL AGENTS

Primary resistance to BTKis seem to exist in 10-15% of CLL patients and the underlying mechanisms are unknown. *TP53* aberrations and CK increase the risk of progression also when treated with BTKis. Loss of efficacy due to development of secondary resistance to BTKis is the reason of discontinuation in 10-20% of patients. Frequency of resistance seems similar for all cBTKis. As said already, cBTKis bind irreversible the cysteine residue (Cys481) in the ADP-binding pocket to inhibit the BTK protein and switch off BCR signalling completely. Variants in Cys481 (C481S most frequent) lead to reversible and unstable bonds and diminished inhibition of BTK as phosphorylation of BTK can occur. The ncBTKis do not bind the cysteine residue but bind reversible the ADP-binding pocket and can overcome the resistance of the cBTKis. In the meantime, other acquired mutations have been found that cluster in the catalytic domain of BTK. These mutations can also confer resistance to ncBTKis (for example L528W induces resistance to c- and ncBTKis). It is not exceptional that multiple BTK mutations are found in the same patient. Therefore, sequencing the entire BTK gene rather than hot spot locations is recommended today. CLL progression seems a relative late event during cBTK inhibition with a prevalence of 5% at two years and >20% at four years. Resistant clones are detected ± 8-9 months prior to progression. Gain of function mutations in the gene of the downstream kinase PLCγ2 is another mechanism of resistance leading to autonomous BCR signalling downstream of BTK which cannot be suppressed by any BTKi. PLCγ2 and BTK mutations can also co-exist in resistant patients.[85]

The other class of novel agents used in CLL are the bcl-2is with Ven being the first available and approved agent. As Ven inhibits only bcl-2, the relative expression of non-bcl-2 (MCL-1, BCL-XL) anti-apoptotic proteins *vs.* bcl-2 may determine primary or acquired resistance. The mode of action of Ven is binding the bcl-2 protein, releasing Bim and inducing apoptosis. Mutations in bcl-2 (Gly101Val most frequent) cause huge reduction in affinity of Ven for bcl-2. Also here, multiple mutations in bcl-2 or non-bcl-2 anti-apoptotic proteins can be found in the same patient. Clonal evolution with the acquisition of a *TP53* aberration or CK is also a mechanism for Ven resistance. Less deep and/or sustained responses are seen in patients harbouring a *TP53* aberration and treated with Ven. Clinical trials are ongoing using novel, more potent bcl-2is which hopefully can overcome Gly101Val mutations.[86]

OPTIMAL SEQUENCING OF THE NOVEL AGENTS

In the meantime, more data on sequencing of the novel agents in R/R CLL became available from real-world retrospective reviews. Data of the efficacy of novel agents at first

relapse after novel agents as frontline treatment however stay sparse. The sequencing will depend on the reason of BTKi discontinuation (intolerance *vs.* progression), previous treatments and responses. The UK (n=105) and Italian (n=76) retrospective real-world data showed better outcomes for patients switching for intolerance compared to those switching for PD.[88,89]

SEQUENCING AFTER BTKIS: INTOLERANCE *vs.* PROGRESSIVE DISEASE

For most patients with responding disease who discontinued a cBTKi because of **intolerance**, rechallenge with another cBTKi or starting a bcl-2i can be recommended. However, before starting the next treatment observation till the iwCLL criteria of PD are met must also be advised. The choice between BTK or bcl-2 inhibition will depend on the specific AE and grade of AE that led to treatment discontinuation. The risk of bleeding is lower with Acala and Zanu compared with Ibr, but bleeding is a class effect of BTKis. So, if serious bleeding is the issue, rechallenge with a cBTKi is probable not the best treatment option. The same for CV issues. Switching to another cBTKi or to bcl-2 inhibition will depend on kind and grade of CV AE. If a patient is highly affected by Acala-induced headache, not quickly resolving with caffeine or paracetamol, switching to another cBTKi can be a reasonable approach. Arthralgias and diarrhea are more common with Ibr than with the second-generation cBTKis. So, switching from Ibr to either Acala or Zanu could be a treatment option.[70,72,77,82,83] Do not forget to explore first dose reductions before switching to another agent.

For patients with non-responding disease or experiencing disease **progression** on any of the cBTKis, rechallenge with another cBTKi cannot be recommended as their mode of action and outcomes are similar. For this population, switching to the bcl-2i, Ven, is the only reasonable option. A phase II trial (n=91) showed a median PFS of 24 months.[90]

SEQUENCING AFTER BCL-2: INTOLERANCE *vs.* PROGRESSIVE DISEASE

For patients with responding disease who discontinued a bcl2-i because of **intolerance**, a cBTKi can be started at clinical progression per iwCLL if BTKi-naïve or non-resistant to cBTKis previously.

For patients with **non-responding or progressive** disease **on** Ven, a cBTKi is recommended in the non BTKi resistant patients and an ncBTKi for double refractory patients, if available. Enrolment in a clinical trial must be offered, if possible.

For patients with **progression after** a Ven-based treatment, retreatment with a Ven-based regimen or treatment with a cBTKi can be considered. Retreatment with a Ven-based regimen looks more appropriate if progression occurs later than 24 months after the previous Ven-based treatment. In the sub-study of Murano (n=34), 25 pts received VenR retreatment, 92.0% of whom had high-risk features (unmutated IGHV, genomic complexity, *TP53* aberrations). Best ORR was 72.0% and median PFS was 23.3 months. Median time from the last Ven dose in the main study to Ven ramp-up in the sub-study was 2.3 years. 32% of patients achieved uMRD at the end of combination treatment, but no patient retained uMRD at the end of treatment.[91] The ongoing phase II ReVenG trial include patients with a minimum PFS of twelve months after the previous Ob_6Ven_{12} treatment. The cohort with a PFS >24 months will be retreated with twelve months of Ob_6Ven_{12}. The other cohort with a PFS between 12-24 months will be treated with 24 months of Ob_6Ven_{24}.[92] Responses seem also more durable with cBTKis at **progression after** a Ven-based treatment when patients progressed after an initial deep response (CR or uMRD) and >24 months after the previous Ven-based regimen. The observed median PFS and OS were 34 months and 42 months, respectively (n=23).[93]

TREATMENT OF DOUBLE EXPOSED OR DOUBLE REFRACTORY PATIENTS

Double exposed CLL patients are patients who have been treated with a cBTKi and a bcl-2i. Double-refractory CLL patients are today defined as: PD on a cBTKi and PD on Ven-R/Ob or PD within 24 months after Ven-R/G or vice versa or PD on I+V or within 24 months after the completion of I+V. Outcomes of double exposed or double refractory patients are poor with a median time to subsequent treatment failure or death of less than six months. So, double exposed and double refractory CLL patients are a new urgent medical need problem.[94]

The phase I-II BRUIN trial treated CLL patients (n=247) with a median age of 69 years, a median number of previous treatments of three, with Pirto, an ncBTKi. All patients were exposed to cBTKis, 75% showing PD and 25% intolerance. Forty percent of patients were also exposed to bcl-2is. Median PFS was 22.1 months for those only exposed to cBTKis and 16.8 months for those double exposed. Responses were identical in BTK mutated or unmutated patients. Only 2.8% of patients discontinued treatment due to AEs. The most common AEs reported were infections, bleeding and neutropenia. With a median follow-up of 16.5 months, typically BTKi associated AEs as hypertension, AF, major haemorrhage occurred infrequently. No cases of sudden cardiac deaths or ventricular fibrillation or tachycardia were reported.[85]

Inclusion in a clinical trial with ncBTKis, bispecific antibodies, CAR-Ts, or alloSCT are options for these hard-to-treat patients. As a lot of these patients today have not been exposed to CIT, CIT could be a potential option in CIT naïve patients without a TP53 aberration. CIT could also be an option for CIT exposed patients with a long response to CIT (>3 years). Combining novel agents can also give some responses.[95]

CELLULAR TREATMENT: ALLOGENEIC STEM CELL TRANSPLANTATION (ALLOSCT) AND CHIMERIC ANTIGEN RECEPTOR T CELLS (CAR-TS)

The European Society for Blood and Marrow Transplantation (EBMT) reported on the outcome of alloSCT (n=2589) from 2000-2010. At five years there was an OS of 45%, a PFS of 35%, a non-relapse mortality (NRM) of 36% and a relapse rate of 29%. Thanks to the improvements in patient and donor selection, reduced intensity conditioning, donor lymphocyte infusions, graft *vs.* host disease (GVHD) prophylaxis and supportive care we believe that alloSCT has become more effective and safer today.[96] Due to the availability of the novel agents EBMT saw that the yearly number of alloSCT dropped from >450 in 2011 to ± 100 in 2019.[97] The National Comprehensive Cancer Network recently narrowed the EBMT 2018 recommendations for alloSCT in CLL to R/R CLL exposed or refractory to BTK- and bcl-2is. Especially the double refractory population have a very short OS and represents a population with a high unmet medical need. The other lasting indication for alloSCT is RT and will be discussed later. The ideal moment to perform the transplant is while the CLL remains well controlled. However, in double refractory patients, limited data are available to guide pre-transplantation bridging. Responses have been seen with agents as ncBTK-, PI3Kis, alemtuzumab, bispecific antibodies, CIT, combinations of BTK- and bcl-2is, etc. With longer follow-up we must be aware that alloSCT can cure only a minority of patients, meaning that disease surveillance is warranted as late relapses can occur even more than twenty years after transplant. As these long-term survivors have a persistent elevated risk of NRM follow-up for late toxicities must be offered. As CLL is predominantly a disease of the older adult population, only a small fraction of patients will be eligible for alloSCT especially if they fulfil the definition of double exposed or double refractory patients.[96] Knowing that the survival of this patient group is <6 months, we hope that other cellular therapies than alloSCT become a treatment option soon. Although the first case report of successful CAR-T treatment in CLL was already published in 2011 and multiple cases with sustained remissions were reported since then, we have no access to an approved CAR-T cell product for the treatment of CLL today. We are waiting for the results of ongoing clinical trials using optimised CAR-T constructs and methods to enhance T-cell function (+ Ibr, + PD-1- or PD-L1 inhibitor) and to improve persistence of T-cells.[98] Liso-cel has been studied the most widely in CLL, also in double exposed and double refractory patients. The TRANSCEND CLL 004 study reported data on 49 double refractory patients. The median follow-up was almost twenty months. ORR was 43% with a CR of 18%. Responses were seen mostly already at day 30 and were durable (median DoR 35.3 months), median PFS was 11.9 months and median OS 30.3 months. The safety profile was reported manageable with low grades of cytokine release syndrome ≥ grade 3 and neurological AEs.[99] A phase III RCT comparing Liso-cel with Idela-R or BR will start enrolling patients soon. CAR-T cells targeting other antigens than CD19 (CD20, BAFF-R, CD37) or more than one antigen (CD19 + CD20) are developed and tested. B-cell aplasia and hypogammaglobulinemia are toxicities encountered with CD19 CAR-Ts as normal B-cells are depleted. To limit this specific immunosuppression CAR-Ts expressing the light chain of the malignant cells would spare the B-cells expressing the other light chain or expressing ROR-1 or FC receptor immunoglobulin M which are both not expressed on normal B-cells. Allogeneic donor or allogeneic off the shelf CAR-Ts are also under investigation and could be ideal in cases of autologous production difficulties and rapid PD. These allogeneic CAR-T cells should have an improved T-cell quality compared to the autologous CAR-Ts of most CLL patients. Donor alloCAR-Ts require HLA compatibility and off the shelf alloCAR-T products need techniques to minimise rejection of non-HLA matched products. Natural killer CAR cells are another promising new tool in the arsenal of cellular therapies although a lot of further research is needed to be conducted.[100]

RICHTER TRANSFORMATION (RT)

The 5th WHO classification of haematolymphoid tumours propose to use the term Richter transformation (RT) over Richter syndrome.[11] The ICC classification emphasises the need to distinguish accelerated CLL (expanded proliferation centres) from diffuse large B-cell lymphoma (DLBCL) (sheets of large B-cells) and reversible proliferation of sheets of large cells (Richter-like) in patients in which BTK inhibition has been temporarily interrupted.[12]

Transformation of CLL to DLBCL (>90%) or Hodgkin's disease (<10%) is known as RT. The development of RT

may represent either a clonal progression of the CLL or a de novo development of an independent lymphoid malignancy.[101,102] RT is not a rare event in the natural history of CLL since the cumulative incidence at ten years is about 10%.[103] A rapidly enlarging lymph node, new fevers, drenching night sweats, unintentional weight loss, elevation of LDH or calcium, new or worsening cytopenias, no response to treatment are signs/symptoms that should raise suspicion for RT. A PET-CT scan and review by an experienced haematopathologist of an excisional biopsy, if possible, of the most FDG-avid lymph node must prove or exclude RT. We must be aware that patients treated with the novel agents can have PET-CT scans highly suspected to have RT although the lymph node biopsies show only accelerated CLL. Although we have witnessed unprecedented progress in the management of CLL, the outcomes of RT classified as DLBCL clonally related to the CLL (80%) with R-based chemotherapy (CHOP, OFAR, EPOCH, etc.) remain dismal. The few patients with a DLBCL non-clonally related to the CLL (<20%), have a prognosis with CIT identical to de novo DLBCL. At this moment data (ORR, PFS, and OS) from a few non-randomised trials support to add Ven to the induction CIT regimen (R-CHOP, R-EPOCH). As the median survival time with CIT alone is less than one year, and with adding Ven less than two years, young and fit patients, responding to induction treatment are still candidates for alloSCT. The results from small patient RT series treated with c- and ncBTK inhibitors show moderate and no durable responses (Pirto: mDoR 8.6 months). The results of PD-1 blockade as monotherapy are less promising than initially reported. No prospective data on anti-CD19 directed CAR-T therapies in R/R RT are available although data from again some case series hold promise. A clinical trial with brexu-cel is now enrolling (ZUMA-25). Also, the initial results with bi-specific antibodies as glofitamab and epcoritamab appear promising. A lot of trials with various combinations of BTK-, bcl-2-, PI3K-, immune check point inhibitors and CIT are running. The outcome of Hodgkin variant of RT is slightly better. These patients must be treated with a Hodgkin specific chemotherapy regimen. Rituximab is a potential additional therapeutic option for patients whose Hodgkin cells express the CD20 antigen.[101,102]

AUTOIMMUNE COMPLICATIONS

The proportion of CLL patients who present with autoimmune cytopenia (AIC) at some point during the disease varies between 4-10%. Autoimmune haemolytic anaemia (AIHA) (7-10%) and immune thrombopenia (ITP) (1-5%) seem more common than pure red cell aplasia (PRCA) (1%) and autoimmune neutropenia (AIN) (<0.2%). AIC may complicate CLL from diagnosis to disease progression. When there is no active/advanced CLL we can manage the AIC separately. Corticosteroids remain the treatment of choice. Today, especially for AIHA, it is recommended to add rituximab (weekly for four weeks) early to taper steroids more rapidly when haemoglobin is stabilising. Blood transfusions can be necessary in the acute phase and recombinant erythropoietin can accelerate recovery. Patients refractory to steroids and rituximab or patients with active/advanced CLL must be started additionally on a CLL directed therapy. High responses have been seen with C or B regimens in the past. In the meantime, BTK inhibition or Ven regimens have also shown to improve or overcome the immune cytopenias. Alternative immunosuppression (cyclosporine, mycophenolate mofetil, and azathioprine), splenectomy and alemtuzumab should be considered only in patients failing to respond. For ITP the AIHA management can be copied. Intravenous immunoglobulins can be added to steroids in case of deep thrombopenia with bleeding symptoms. Case series have shown that thrombopoietin receptor agonists are efficacious also in CLL mediated ITP. Splenectomy for ITP is also discouraged. Granulocyte-colony-stimulating factor (G-CSF) can overcome neutropenia in AIN.[104,105]

SUPPORTIVE CARE

It is important to counsel patients about the increased risk of infections and secondary primary malignancies (SPMs) during their MBL-CLL journey.

Infections remains a major cause of morbidity and mortality in CLL patients. Data have shown that 25-50% of all CLL deaths can be related to infectious complications. We know also that the immune dysfunction in CLL is complex and affects the innate and adaptive immune systems. Hypogammaglobulinemia, one of the immune functions we can measure, is seen already in 25% of patients at diagnosis and can go up to 85% during the CLL journey. As these dysfunctions are not frequently reversible with CLL directed treatment, we must focus on preventing infections. Repeated infections are not considered an indication for starting CLL therapy by iwCLL.

The substitution of IV or subcutaneous immunoglobulins is only reimbursed in Belgium in patients with hypogammaglobulinemia and severe or recurrent infections in need for antibiotics.

Another way to prevent infectious complications is to vaccinate. Reasonable levels of seroconversion or seroprotection can be achieved in CLL although less than in non-immunocompromised patients. We generally start

with the recommended vaccinations as soon as possible after the diagnosis of CLL and even MBL. According international guidelines and the recommendations of the Belgian Superior Health Council we advise to vaccinate against flu (yearly tetravalent standard dose or high dose), COVID-19 (booster 2023), pneumococci (for example: 20-valent conjugate vaccine followed each five years by the 23-valent polysaccharide vaccine till the age of 85), herpes zoster reactivation (two doses with an interval of at least two months) and ten yearly boosters against tetanus, diphtheria and whooping cough. Live vaccines are contraindicated in CLL patients because severe or even fatal complications have been reported (available live attenuated vaccines: yellow fever, rotavirus, varicella, rubella, mumps, measles, dengue, nasal flu vaccine). Although the Belgian Superior Health council recommend the high dose flu vaccine, it is not reimbursed at this moment. The herpes zoster reactivation vaccine is reimbursed from November 2023 for all haematological malignancies if treatment has been given in the past five years. Shingles or herpes zoster is a painful reactivation of the varicella virus. One in three persons will develop shingles in their lifetime and the risk increases with advancing age and with immunosuppression. The most significant complication of shingles is post-herpetic neuralgia which may occur in up to 20% of those who get shingles. Shingrix® has shown to reduce not only the reactivation but also post-herpetic neuralgia. For flu and COVID-19 we also advice to vaccinate the close contacts of our patients to reduce the risk of passing the viruses to the immunocompromised ones.[106] The prevention strategies we know well from the COVID-19 pandemic as hand hygiene, keeping distance, improving ventilation and wearing high-quality masks, will decrease the transmission rate of any viral infection. We must still inform our patients to report any COVID-19 infection to their physician immediately as the antiviral agent, Paxlovid®, remains effective against the latest viral strains of COVID-19.

Growth factors such as G-CSF and erythropoiesis-stimulating factors (EPO) can be given in patients under myelosuppressive therapy with deep or prolonged neutropenia or anaemia according to the Belgian reimbursement criteria.

Prophylaxis against *Pneumocystis Jirovecii* (PCJ) and herpes simplex reactivation were standard for patients with a history of these infections and during T-cell depleting therapies (FCR, alemtuzumab, BR if <200 CD4 cells/μl). Prolonged high dose steroids require also PCJ prophylaxis. There is no recommended antibacterial nor antifungal prophylaxis in CLL patients treated with the novel agents (BTKis or bcl-2is). However, in frail patients with comorbidities and/or prolonged neutropenia and /or prolonged steroid therapy we must have a high suspicion of infection and can consider prophylactic antifungal therapy keeping drug-drug interactions in mind. We recommend Hepatitis B (HBV) screening before the start of treatment. Antiviral prophylaxis must be started in HBV carriers treated with anti-CD20 MABs which must be maintained for twelve to eighteen months after the last dose. For HBV carriers treated with the novel agents, monitoring of the PCR load each three to six months can be recommended [107]

Several retrospective studies confirm the elevated risk for solid and haematological malignancies in CLL patients.[108,109] In an Australian cohort, 44.9% of CLL patients had at least one SPM, and apart from skin cancer, was associated with a reduced OS.[110] When we want to consolidate the OS benefits induced by the novel agents, we must optimise routine surveillance activities to counteract this excess in mortality (breast cancer screening program Flanders and colorectal cancer screening program of Belgium, skin cancer screening by a dermatologist, awareness of cancer red flags).

FUTURE TREATMENT APPROACHES

Although responses and DoR are exceptionally high and long with the available novel agents, the challenge stays to identify the best sequence or combination to achieve long-term CLL control with optimal quality of life. We are waiting for the results of trials exploring FD doublets and triplets *vs.* continuous BTK inhibition. Trials with MRD as one of their endpoints, will learn if achievement of uMRD can alter our treatment plan. We mentioned already that double-exposed and double refractory patients are a new urgent medical need in CLL. Therefore, the search for new agents or combinations must continue and patients must be still encouraged to enter clinical trials. We wait eagerly for more mature results concerning the ncBTKis (Pirto, nemtabrutinib). Also new promising bcl-2is (lisaftoclax and sonrotoclax) and dual bcl-2/bcl-xl inhibitors are entering the clinic. Another new class of drugs are the BTK degraders. These drugs ubiquitinate BTK, Ikaros and Aialos and make degradation by the proteasome possible. These molecules seem to work in CLL patients resistant to c-, ncBTKis and bcl-2is.

Although PI3Kis were very effective in CLL, the severe toxicity profile associated with the first-generation inhibitors (Idela and duvelisib), combined with the availability of other more tolerable agents, have limited their use. However, further investigation could be useful to optimise administration schedules of the currently approved PI3Kis and to develop next-generation agents with improved tolerability, so that this class of agents can be considered

KEY MESSAGES FOR CLINICAL PRACTICE

1. No treatment is necessary for patients "without" active and/or advanced disease, regardless of prognostic factors.
2. Continuous BTKis, FD Ob_6-Ven_{12} or FD I+V are the preferred treatment options for TN CLL. Patient, disease and treatment related factors must be considered to choose the optimal treatment for that particular patient (*Figure 2*).
3. CIT can still be an excellent treatment option for a small percentage of patients who are fit for F with mutated IGHV and no adverse prognostic genomic aberrations. The risk of t-MN must be weighed against cardiac issues.
4. Continuous BTKis and FD R_6-Ven_{24} are the preferred treatment choices for R/R CLL. Treatment choice will depend certainly on patient, disease and treatment related factors but also on previous treatments (*Figure 3*).
5. Double exposed and double refractory patients are the new urgent medical need problem in CLL. The ncBTKis look very promising.
6. AlloSCT must still be considered in a selected group of patients.
7. Patients must be encouraged to enter clinical trials exploring new agents or combinations. We expect a lot from the bispecific antibodies and optimised CAR-constructs.

as an effective and safe treatment option in multi-refractory patients.[111]

We also expect a lot from clinical trials exploring the T-cell redirecting therapies. Clinical trials using optimised CAR-T constructs and methods to enhance T-cell function and to improve persistence of T-cells are on their way. The same is true for several bispecific antibodies.

CONCLUSION

This manuscript, the fifth publication on BHS LPD committee CLL guidelines in twelve years, confirms that management of CLL stays a continuous evolving field.

We propose once more to use in the diagnostic work-up the ERIC-ESCCA immunophenotypic scoring system to differentiate CLL better from other leukaemic lymphomas and get rid of the diagnosis of atypical CLL.[6-8]

Before starting any treatment in active/advanced CLL we advise to exclude a CK and a 17p del/*TP53* mut by FISH and NGS. In the absence of a *TP53* aberration the IGHV mutational status can be checked, but only once. Depending on the NGS panel used, information on the mutation status of BTK, PLCy2 and bcl-2 can also be obtained.

The criteria to start treatment in first-line or at relapse are not changed and starting treatment is only necessary in patients with active or advanced disease.

After implementing the recent reimbursements and reviewing the recent literature, the BHS LPD committee proposes updated recommendations for treatment of naïve and R/R CLL in *Figures* 2 and 3.

The selection of the most appropriate treatment for one patient at that particular time-point stays a multifactorial process. Patient, disease and treatment related factors must be considered altogether. Comorbidities of the patient, expected AEs of the treatment, co-medication, ease of administration, treatment duration and desired outcome must be weighted. We must not forget that Chl monotherapy or supportive care to control symptoms can still be a justifiable treatment option for frail patients.

Using the novel agents for almost a decade, we encounter a new urgent medical need being how to treat patients after BTK and bcl-2 inhibition. We hope that the ncBTKis, bispecific antibodies and CAR-Ts expand our therapeutic armamentarium soon. AlloSCT should still be considered according to international BMT recommendations. Patients must be encouraged to enter clinical trials exploring new agents as monotherapy or in combinations.

REFERENCES

1. Janssens A, et al. BHS guidelines for the treatment of chronic lymphocytic leukaemia anno 2012. Belg J Hematol. 2012;3:134-143.
2. Janssens A, et al. Updated BHS guidelines for the treatment of chronic lymphocytic leukaemia anno 2016. Belg J Hematol. 2015;6:195-202.
3. Janssens A, et al. Updated BHS guidelines for the treatment of chronic lymphocytic leukaemia, mantle cell lymphoma and Waldenström macroglobulinemia anno 2018. Belg J Hematol. 2018;9:101-12.
4. Janssens A. BHS Guidelines for the Management of Small Lymphocytic Lymphoma and Chronic Lymphocytic Leukaemia, anno 2020. Belg J Hematol. 2020;11:108-19.
5. https://kankerregister.org/media/docs/cijfersoverkanker/HaematoPublication_FINAL_09062021.pdf
6. https://seer.cancer.gov/statfacts/html/clyl.html
7. Hallek M, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood. 2018; 131:2745-60
8. Hallek M, et al. Chronic lymphocytic leukaemia: 2022 update on diagnostic and therapeutic procedures. Am J Hematol. 2021;96:1679-705.
9. Rawstron A, et al. Reproducible diagnosis of chronic lymphocytic leukaemia by flow cytometry: An European Research Initiative on CLL (ERIC) & European Society for Clinical Cell Analysis (ESCCA) Harmonisation project. Cytometry B Clin Cytom. 2018;91:121-8.
10. Swerdlow S, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127:2375-90.
11. Alaggio R, et al. The 5th edition World Health Organisation classification of Haematolymphoid tumours: Lymphoid neoplasms. Leukemia. 2022;36: 1720-48.
12. Campo E, et al. The international Consensus classification of mature lymphoid neoplasms: a report from the clinical advisory committee. Blood. 2022;140:1229-53.
13. Lyon A, et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). Eur Heart J. 2022;43:4229-361.
14. Malcikova J, et al. ERIC recommendations for TP53 mutation analysis in chronic lymphocytic leukaemia-update on methodological approaches and results interpretation. Leukemia. 2018;32:1070-80.
15. Agathangelidis A, et al. Immunoglobulin gene sequence analysis in chronic lymphocytic leukaemia: the 2022 update of the recommendations by ERIC, the European Research Initiative on CLL. Leukemia. 2022;36:1961-8.
16. Kitai A, et al. The impact of increasing karyotypic complexity and evolution on survival in patients with CLL treated with ibrutinib. Blood. 2021;138: 2372-82.
17. Fürstenau M, et al. High karyotypic complexity is an independent prognostic factor in patients with CLL treated with venetoclax combinations. Blood. 2023;142:446-59.
18. Janssens A. Venetoclax, the first available bcl-2 antagonist for chronic lymphocytic leukaemia. Belg J Haematol. 2017;8:265-71.
19. Eichhorst B, et al. First-line venetoclax combinations in chronic lymphocytic leukaemia. N Eng J Med. 2023;388:1739-54.
20. Galle V, et al. Is it possible to predict who may never need treatment for B-CLL? Belg J Haematol. 2018;9:124-9.
21. Fürstenau M, et al. Minimal residual disease assessment in CLL: Ready to use in clinical routine? Hemasphere. 2019;3:5.
22. Benintende G, et al. Measurable residual disease in chronic lymphocytic leukaemia. Front Oncol. 2023;13:1112616.
23. Fisher A, et al. The evolving use of measurable residual disease in chronic lymphocytic leukaemia clinical trials. Front Oncol. 2023;13:1130617.
24. Rai K, et al. Clinical staging of chronic lymphocytic leukaemia. Blood. 1975; 46:219-34.
25. Rai K. A critical analysis of staging in CLL. In: Gale R, Rai K, eds. Chronic Lymphocytic Leukemia: recent progress and future directions. New York: Alan R. Liss. 1987:252-64.
26. Binet J, et al. A new prognostic classification of chronic lymphocytic leukaemia derived from a multivariate survival analysis. Cancer. 1981;48:198-206.
27. Abrisqueta P, et al. Improving survival in patients with chronic lymphocytic leukaemia (1980-2008): the Hospital clinic of Barcelona experience. Blood. 2009;114:2044-50.
28. Condoluci A, et al. International prognostic score for asymptomatic early-stage chronic lymphocytic leukaemia. Blood. 2020;135:1859-69.
29. The International CLL-IPI working group. An international prognostic index for patients with chronic lymphocytic leukaemia (CLL-IPI): a meta-analysis of individual patient data. Lancet. 2016;17:779-90.
30. Soumerai, JD, et al. Prognostic risk score for patients with relapsed or refractory chronic lymphocytic leukaemia treated with targeted therapies or chemoimmunotherapy: a retrospective, pooled cohort study with external validations. Lancet Haematol. 2019;6:e366-74.
31. Bantilan K, et al. Time to second treatment can be used to predict overall survival in chronic lymphocytic leukaemia: identifying risk factors to help guide treatment selection. Leuk Lymphoma. 2023;64:300-11.
32. Langerbeins P, et al. The CLL12 trial: ibrutinib vs. placebo in treatment-naïve early-stage chronic lymphocytic leukaemia. Blood. 2022;139:177-87.
33. Langerbeins P, et al. Ibrutinib versus placebo in patients with asymptomatic, treatment-naïve early stage chronic lymphocytic leukaemia (CLL): final results of the phase 3, double-blind, placebo-controlled CLL12 trial. Hemasphere. 2023;7(S3)S200:226.
34. Hallek M, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. Lancet. 2010;376:1164-74.
35. Allan J, et al. Long-term efficacy of first-line ibrutinib treatment for chronic lymphocytic leukaemia in patients with TP53 aberrations: a pooled analysis from four clinical trials. Br J Haematol. 2022;196:947-53.
36. Sharman J, et al. Efficacy and safety in a 4-year follow-up of the ELEVATE-TN study comparing acalabrutinib with or without obinutuzumab versus obinutuzumab plus chlorambucil in treatment-naïve chronic lymphocytic leukaemia. Leukemia. 2022;36:1171-5.
37. Sharman J, et al. Acalabrutinib ± Obinutuzumab vs. Obinutuzumab + Chlorambucil in treatment naive chronic lymphocytic leukaemia: 5-year follow-up of ELEVATE-TN. EHA. 2022;P666.

38. Sharman J, et al. Acalabrutinib+/- Obinutuzumab vs. Obinutuzumab + chlorambucil in treatment-naïve chronic lymphocytic leukaemia: 6-year follow-up of ELEVATE-TN. Abstract ASH 2023.
39. Tam C, et al. Zanubrutinib monotherapy for patients with treatment naïve chronic lymphocytic leukaemia and 17p deletion. Haematologica. 2020; 106:2354-63.
40. Shadman M, et al. Zanubrutinib (zanu) versus Bendamustine + Rituximab (BR) in patients (pts) with treatment-naïve (TN) CLL/SLL: extended follow-up of the Sequoia study. Hematol Oncol. 2023;41(S2):235-8.
41. Al Sawaf O, et al. Venetoclax-Obinutuzumab for previously untreated chronic lymphocytic leukaemia: 6-year results of the randomised CLL14 study. Hemasphere. 2023;7(S3):S145.
42. Ghia P, et al. Fixed-duration Ibrutinib + Venetoclax in chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL): 4-y follow-up from the FD cohort of the phase 2 Captivate study. Hematol Oncol. 2023;41 (Abstract 155):238.
43. Shanafelt T, et al. Long-term outcomes of ibrutinib-rituximab and chemoimmunotherapy in CLL: updated results of the E1912 trial. Blood 2022; 140:112-120
44. Furstenau M, et al. First-line venetoclax combinations in fit patients with CLL: 4-year follow-up and NGS-based MRD analysis from the phase 3 GAIA/CLL13 trial. ASH 2023.
45. Hillmen P, et al. Ibrutinib and rituximab versus fludarabine, cyclophosphamide, and rituximab for patients with previously untreated chronic lymphocytic leukaemia (FLAIR): interim analysis of a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2023;24:535-52.
46. Alan J, et al. Outcomes in patients with high-risk features after fixed duration ibrutinib plus venetoclax: phase II CAPTIVATE study in first-line chronic lymphocytic leukaemia. Clin Cancer Res. 2023;29:2593-601.
47. Barr P, et al. Up to 8-year follow-up from RESONATE-2: first-line ibrutinib treatment for patients with chronic lymphocytic leukaemia. Blood Advances. 2022;6:3440-50.
48. Woyach J, et al. Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL. N Engl J Med. 2018;379:2517-28.
49. Woyach J, et al. Long-Term Results of Alliance A041202 Show Continued Advantage of Ibrutinib-Based Regimens Compared with Bendamustine Plus Rituximab (BR) Chemoimmunotherapy. Blood. 2021;138(S1):639.
50. Ruppert A, et al. A Prospective Economic Analysis of Early Outcome Data From the Alliance A041202/ CCTG CLC.2 Randomised Phase III Trial Of Bendamustine-Rituximab Compared With Ibrutinib-Based Regimens in Untreated Older Patients With Chronic Lymphocytic Leukemia. Clin Lymphoma Myeloma Leuk. 2021;21:766-74.
51. Moreno C, et al. First-line treatment of chronic lymphocytic leukaemia with Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab: final analysis of the randomised, phase III iLLUMINATE trial. Haematologica. 2022;107:2108-20.
52. Fischer K, et al. Venetoclax and Obinutuzumab in Patients with CLL and Coexisting Conditions. N Eng J Med. 2019;380:2225-36.
53. Al-Sawaf O, et al. Minimal residual disease dynamics after venetoclax-obinutuzumab treatment: extended off-treatment follow-up from the randomised CLL14 study. J Clin Oncol. 2021;36:4049-60.
54. Kater A, et al. Fixed-duration ibrutinib-venetoclax in patients with chronic lymphocytic leukaemia and comorbidities. NEJM Evidence. 2022;1(7).
55. Munir T, et al. Impact of minimal residual disease on progression free survival outcomes after fixed-duration ibrutinib-venetoclax versus chlorambucil-obinutuzumab in the GLOW study. J Clin Oncol. 2023;41(21):3689-99.
56. Niemann C, et al. Efficacy of fixed-duration ibrutinib-venetoclax in previously untreated CLL: 4-year follow-up from the phase 3 GLOW study. Lancet Oncol. Submitted.
57. Moreno C, et al. First-Line Fixed-Duration Ibrutinib plus Venetoclax (Ibr+Ven) versus Chlorambucil plus Obinutuzumab (Clb+O): 55-Month Follow-up from the GLOW Study. ASH 2023.
58. Tam C, et al. Zanubrutinib versus bendamustine and rituximab in untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (SEQUOIA): a randomised controlled, phase 3 trial. Lancet Oncol. 2022;23:1031-43.
59. Eichhorst B, et al. First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. Lancet Oncol. 2016; 17:928-42.
60. Kleeberg U, et al. Bendamustin-rituximab combination is a safe and effective, ambulatory treatment for elderly patients with chronic lymphocytic leukaemia: retrospective real-world analysis by age from a German registry and review of the literature. Anticancer Res. 2016;36:2827-38.
61. Goede V, et al. Overall survival benefit of obinutuzumab over rituximab when combined with chlorambucil in patients with chronic lymphocytic leukaemia and comorbidities: final survival analysis of the CLL11 study. EHA library. 2018;215923:S151.
62. Rossi D, et al. Molecular prediction of durable remission after first-line fludarabine-cyclophosphamide-rituximab in chronic lymphocytic leukaemia. Blood. 2015;126:1921-4.
63. Fischer K, et al. Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: updated results of the CLL8 trial. Blood. 2016;127:208-15.
64. Thompson P, et al. Fludarabine, cyclophosphamide, and rituximab treatment achieves long-term disease-free survival in IGHV-mutated chronic lymphocytic leukaemia. Blood. 2016;127:303-9.
65. Fraser G, et al. Final 5-year findings from the phase 3 HELIOS study of ibrutinib plus bendamustine and rituximab in patients with relapsed/refractory chronic lymphocytic leukaemia/small lymphocytic lymphoma. Leuk Lymphoma. 2020;61:3188-97.
66. Byeard J, et al. Ibrutinib Treatment for First-Line and Relapsed/Refractory Chronic Lymphocytic Leukemia: Final Analysis of the Pivotal Phase Ib/II PCYC-1102 Study. Clin Cancer Res. 2020;26:3918-27.
67. Jones J, et al. Evaluation of 230 patients with relapsed/refractory deletion 17p chronic lymphocytic leukaemia treated with ibrutinib from 3 clinical trials. Br J Haematol. 2018;182:504-12.
68. Stilgenbauer S, et al. Venetoclax for patients with chronic lymphocytic leukaemia with 17p deletion: results from the full population of a phase II pivotal trial. J Clin Oncol. 2018;36:1973-80.

69. Seymour JF, et al. Venetoclax-rituximab in relapsed or refractory chronic lymphocytic leukaemia. N Eng J Med. 2018;378:1107-20.
70. Byeard J, et al. Acalabrutinib Versus Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia: Results of the First Randomised Phase III Trial. J Clin Oncol. 2021;39:3441-52.
71. Ghia P, et al. Acalabrutinib Versus Investigator's Choice in Relapsed/Refractory Chronic Lymphocytic Leukemia: Final ASCEND Trial Results. Hemasphere. 2022;6:e801.
72. Brown J, et al. Zanubrutinib or ibrutinib in relapsed or refractory chronic lymphocytic leukaemia. N Eng J Med. 2023;388:319-32.
73. Munir T, et al. Final analysis from RESONATE: Up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukaemia or small lymphocytic lymphoma. Am J Hematol. 2019;94:1353-63.
74. Kater A, et al. Venetoclax plus rituximab in relapsed chronic lymphocytic leukaemia: 4-year results and evaluation of impact of genomic complexity and gene mutations from the MURANO phase III study. J Clin Oncol. 2020;38:4042-54.
75. Seymour J, et al. Enduring undetectable MRD and updated outcomes in relapsed/refractory CLL and fixed-duration venetoclax-rituximab. Blood 2022;140:839-850
76. Seymour J, et al. Detailed safety profile of acalabrutinib vs. ibrutinib in previously treated chronic lymphocytic leukaemia in the ELEVATE-RR trial. Blood. 2023;142:687-99.
77. Alu A, et al. BTK inhibitors in the treatment of hematological malignancies and inflammatory diseases: mechanisms and clinical studies. J Hematol Oncol. 2022;15:135.
78. Davids M, et al. Ibrutinib plus fludarabine, cyclophosphamide, and rituximab as initial treatment for younger patients with chronic lymphocytic leukaemia: a single-arm, multicentre, phase 2 trial. Lancet Haematol. 2019;6:e419-28.
79. Jain N, et al. Ibrutinib, fludarabine, cyclophosphamide, and obinutuzumab (iFCG) regimen for chronic lymphocytic leukaemia (CLL) with mutated IGHV and without TP53 aberrations. Leukemia. 2021;35:3421-9.
80. Michallet A, et al. A fixed-duration immunochemotherapy approach in CLL: 5.5-year results from the phase 2 ICLL-07 FILO trial. Blood Adv. 2023;7:3936-45.
81. Hillmen P, et al. Comparing single-agent ibrutinib, bendamustine plus rituximab (BR) and ibrutinib plus BR in patients with previously treated chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL): an indirect comparison of the RESONATE and HELIOS trials. Blood. 2015; 126:2944.
82. Awan F, et al. Acalabrutinib monotherapy in patients with chronic lymphocytic leukaemia who were intolerant to ibrutinib. Blood Adv. 2019;3:1553-62.
83. Shadman M, et al. Zanubrutinib in patients with previously treated B-cell malignancies intolerant of previous Bruton tyrosine kinase inhibitors in the USA: a phase 2, open-label, single-arm study. Lancet Haematol. 2023; 10:e35-45.
84. Pepin X, et al. Acalabrutinib Maleate Tablets: The Physiologically Based Biopharmaceutics Model behind the Drug Product Dissolution Specification. Mol Pharmaceutics. 2023;20:2181-93.
85. Mato A, et al. Pirtobrutinib after a covalent BTK inhibitor in chronic lymphocytic leukaemia. N Eng J Med. 2023;389:33-44.
86. Nakhoda S, et al. Resistance to Bruton tyrosine kinase inhibition in chronic lymphocytic leukaemia and non-Hodgkin lymphoma. Br J Haematol. 2023; 200:137-49.
87. Liu J, et al. Mechanisms of venetoclax resistance and solutions. Front Oncol. 2022;12:1005659.
88. Eyeare T, et al. The efficacy and safety of venetoclax therapy in elderly patients with relapsed, refractory chronic lymphocytic leukaemia. Br J Haematol. 2020;188:918-23.
89. Innocenti I, et al. Venetoclax in CLL patients who progress after B-cell receptor inhibitor treatment: a retrospective multi-centre Italian experience. Br J Haematol. 2019;187:e1-32.
90. Jones J, et al. Venetoclax for chronic lymphocytic leukaemia progressing after ibrutinib: an interim analysis of a multicentre, open-label, phase 2 trial. Lancet Oncol. 2018;19:65-75.
91. Kater A, et al. Final 7-year follow up and retreatment substudy analysis of Murano: venetoclax-rituximab (VenR)-treated patients with relapsed/refractory chronic lymphocytic leukaemia (R/R CLL). Hemasphere. 2023;S201.
92. Davids M, et al. ReVenG: A Phase 2 Study of Venetoclax Plus Obinutuzumab Retreatment in Patients With Relapsed Chronic Lymphocytic Leukemia. Blood. 2021;138(S1):2634.
93. Lin V, et al. BTK inhibitor is effective in patients with CLL resistant to venetoclax. Blood. 2020;135:2266-70.
94. Aronson J, et al. Approach to a patient with "double refractory" chronic lymphocytic leukaemia: "Double, double toil and trouble" (Shakespeare). Am J Hematol. 2022;97:S19-25.
95. Lew T, et al. How I treat chronic lymphocytic leukaemia after venetoclax. Blood. 2021;138:361-9.
96. Puckrin R, et al. The role of allogeneic hematopoietic cell transplantation for chronic lymphocytic leukaemia: A review. Front Oncol. 2023;12:1105779.
97. Tournillac O, et al. The European landscape on allogeneic hematopoietic cell transplantation for chronic lymphocytic leukaemia between 2009 and 2019: a perspective from the chronic malignancies working party of the EBMT. Bone Marrow Transplant. 2023;58(6):621-4.
98. Lemal R, et al. State-of-the-art for CAR T-cell therapy for chronic lymphocytic leukaemia in 2019. J Immunother Cancer. 2019;7:202.
99. Siddiqi T, et al. Lisocabtagene maraleucel (liso-cel) in R/R chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL): primary analysis of TRANSCEND CLL 004. Hematol Oncol. 2023;41(S2).
100. Coombs C, et al. Cellular therapies in chronic lymphocytic leukaemia and Richter's transformation: recent developments in chimeric antigen receptor T-cells, natural killer cells and allogeneic stem cell transplant. Cancers. 2023;15:1838.
101. Audil H, et al. Richter transformation of chronic lymphocytic leukaemia-are we making progress? Cur Hematol Malig Rep. 2023:18:144-57.
102. Ryan C, et al. Practical management of Richter transformation in 2023 and beyond. ASCO Educational Book 2023.
103. Al-Sawaf O, et al. Richter transformation in chronic lymphocytic leukaemia (CLL)- a pooled analysis of German CLL study group (GCLLSG) front line treatment trials. Leukemia. 2021;35:169-76.

104. Fatizzo B, et al. Autoimmune cytopenias in chronic lymphocytic leukaemia: focus on molecular aspects. Front Oncol. 2020;9:1435.
105. Vitale C, et al. Pre-existing and treatment-emerging autoimmune cytopenias in patients with CLL treated with targeted drugs. Blood. 2021; 137:3507-17.
106. Wang K, et al. Vaccination efficacy in patients with chronic lymphocytic leukaemia. Leuk Lymphoma. 2023;64:42-56.
107. Rivera D, et al. Managing the Risk of Infection in Chronic Lymphocytic Leukemia in the Era of New Therapies. Current Oncology Reports. 2022;24: 1003-14.
108. Kumar V, et al. Trends in the risk of second primary malignancies among survivors of chronic lymphocytic leukaemia. Blood Cancer J. 2019;9:75.
109. van der Straten L, et al. Risk of second primary malignancies in patients with chronic lymphocytic leukaemia: a population-based study in the Netherlands, 1989-2019. Blood Cancer J. 2023;13:15.
110. Shen Y, et al. Second primary malignancies in chronic lymphocytic leukaemia: Skin, solid organ, haematological and Richter's syndrome. EJHaem. 2022;3:129-38.
111. Skanland S, et al. PI3K inhibitors in chronic lymphocytic leukaemia: where do we go from here? Haematologica. 2023;108:9-21.