BHS Guidelines for the Management of Small Lymphocytic Lymphoma and Chronic Lymphocytic Leukaemia, anno 2020

A. Janssens, MD, PhD

On behalf of the BHS Lymphoproliferative Disease Committee 2019: Marc André, Helène Antoine-Poirel, Christophe Bonnet, Sarah Bailly, Veerle Beckers, Dominique Bron, Alessandra Camboni, Charlotte Caron, Sarah Debussche, Virginie De Wilde, Vanessa Delrieu, Daan Dierickx, Pierre Heimann, Caroline Jacquy, Ann Janssens, Jan Lemmens, Marie Maerevoet, Caressa Meert, Fritz Offner, Kirsten Saevels, Liesbeth Schauvliege, Wilfried Schroyens, Sylvia Snauwaert, Joan Somja, Cécile Springael, Thomas Tousseyn, Eric Van Den Neste, Vanessa Van Hende, Vibeke Vergote, Gregor Verhoef, Inge Vrelust, Alice Wolfromm, Ka Lung Wu.

SUMMARY

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

(BELG J HEMATOL 2020;11(3):108-19)

INTRODUCTION

The Belgian Haematological 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 and 2018.[1-3]

UPDATED RECOMMENDATIONS FOR THE DIAGNOSIS OF SLL/CLL

The diagnosis of CLL requires the presence of at least 5000/µl monoclonal B lymphocytes 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. Gumprecht shadows or smudge cells are frequently seen. Clonality of the B cells (kappa (k) or lambda (l) immunoglobulin (IG) light chains) needs to be confirmed by flow cytometry. Typically, CLL cells co-express the T cell antigen CD5 with B cell antigens.[4,5] The European research initiative on CLL (ERIC) and European society for clinical cell analysis (ESCCA) harmonisation project has selected "required diagnostic markers" and "recommended markers" to refine diagnosis in borderline cases" (*Figure 1*). The required diagnostic markers are strong expression of CD19 (positive > 95% of monoclonal cells), weak expression of CD20, surface IG and k or l IG light chains, together with strong expression of CD23 and CD5 (> 20% of monoclonal cells). In borderline cases, markers as CD43, CD200, ROR1 (positive > 20% of monoclonal cells), weak expression of CD79b and CD81 and no expression of CD10 (positive < 20% of monoclonal cells) are recommended to refine the diagnosis.[6] This immunophenotypic scoring system must help to differentiate CLL better from other leukemic lymphomas compared to

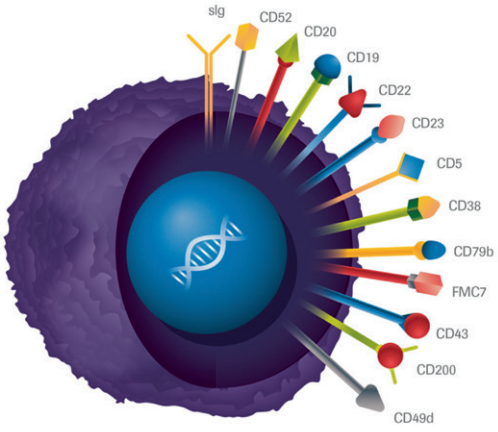
Department of Haematology, University Hospitals Leuven, Leuven, Belgium.

Please send all correspondence to: A. Janssens, MD, PhD, Department of Haematology, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium, tel: 016/346880, email: Ann.janssens@uzleuven.be.

Conflict of interest: A. Janssens received travel grants/consultancy or speaker fees from Janssen, Abbvie, Roche, Celgene, Novartis, Amgen, Sanofi-Genzyme and Gilead.

Keywords: chronic lymphocytic leukaemia, diagnosis, guidelines, prognostic scores, treatment.

FIGURE 1. Immunophenotype of CLL according the ERIC and ESCCA harmonisation project.



"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	Positive <20%
• ROR1	Positive >20%

ERIC: European research initiative on CLL; ESSCA: European society for clinical cell analysis.

previous scoring systems proposed by *Catovsky et al.*[7,8] The term SLL is used for patients with lymphadenopathy and/or splenomegaly but with < 5000/μl monoclonal B cells with a CLL phenotype in the peripheral blood and no cytopenias due to bone marrow infiltration. The diagnosis of SLL, when possible, should be confirmed by histopathology of a lymph node biopsy. In the absence of lymphadenopathy, organomegaly, cytopenia and clinical symptoms, the presence of < 5000/μl monoclonal B lymphocytes in the peripheral blood with a CLL phenotype is defined as monoclonal B cell lymphocytosis (MBL)-CLL type. Bone marrow biopsy is mostly not required for diagnosing CLL, SLL or MBL-CLL type.[4,5]

UPDATED DIAGNOSTIC AND/OR PRETREATMENT WORK-UP (*TABLE 1*)

All guidelines advise to test 17p deletion (del)/*TP53* mutation

TABLE 1. Diagnostic and/or pretreatment work-up.

Mandatory	Potential utility
Personal and familial history Physical examination Biological fitness: PS, comorbidities	Biological fitness: complete geriatric assessment
Complete blood cell count Peripheral blood smear CLL immunophenotype LDH, immunoglobulines, renal function Parameters for hemolysis IGVH mutational status 17p deletion/*TP53* mutation hep B, hep C, CMV, HIV Rx-thorax ECG	β2-microglobulin FISH: 13q deletion, t12, 11q deletion Conventional karyotyping with novel culture techniques Bone marrow aspirate-biopsy when clinically indicated CT neck, abdomen, pelvis
Clinical staging: Rai-Binet	

CLL: chronic lymphocytic leukaemia; LDH: lactate dehydrogenase; IGVH: immunoglobulin heavy chain variable region genes; Hep: hepatitis; CMV: cytomegalovirus; HIV: human immunodeficiency virus; ECG: electrocardiogram; FISH: fluorescence in situ hybridisation; t12: trisomy 12.

(mut) before the start of "each" new treatment as it has been shown that chemoimmunotherapy (CIT) in this patient group is inferior to treatment with the novel agents in terms of response, progression free survival (PFS), response duration (DOR) and overall survival (OS).[5,9] Although the effect of the novel agents is as good in patients with mutated or unmutated immunoglobulin heavy chain variable region genes (IGVH), CIT could still be a treatment option for patients with mutated IGVH who prefer a fixed duration of treatment, according data from recent randomised clinical trials (RCTs) *(discussed in treatment of treatment naïve SLL/CLL anno 2020)*. Therefore, we advise testing of the IGVH mutational status in young "and" older patients without a 17p del/*TP53* mutation if CIT could be a therapeutic option. Assessment of IGVH stereotypes however is still not recommended in the routine prognostic work up.[5]

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%.[10,11] The clinical course of CLL is highly variable. One third of CLL patients never require treatment, another third shows disease progression after an initial indolent phase and the remaining third exhibits a progressive disease from the onset and needs immediate treatment.[12,13]

STAGING AND UPDATED PROGNOSTIC SCORING

The two widely used staging systems are those from Rai (used primarily in the United States) 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.[14-16] Today, 80% of the newly diagnosed patients are staged as Binet A, 13% as Binet B and 7% as Binet C.[11] 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.[11,14-17] 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.

Therefore, several models were developed to identify patients at high risk for progression and shorter OS. The CLL-international prognostic index (CLL-IPI) for treatment-naïve patients and the CLL-BALL for relapsing/refractory (R/R) patients seem to be the most valuable. The CLL-IPI defines four patient risk groups with a significant different time to

TABLE 2. CLL-IPI: international prognostic index for treatment-naïve patient.

Variable		HR	Grading
17p del/*TP53* mut	No or Yes	4.2	4
IGVH	Mutated or UnMutated	2.6	2
β2 microglobulin	≤ or > 3.5 mg/dl	2	2
Stage	Rai 0 vs 1-4 Binet A vs B-C	1.6	1
Age	≤ or > 65y	1.7	1

Risk group		%	5y TTFT	5y OS
low	0-1	47	80%	94%
intermediate	2-3	33	47%	91%
high	4-6	18	29%	68%
very high	7-10	3	19%	21%

del: deletion; mut: mutation; IGVH: immunoglobulin heavy chain variable region genes; y: years; HR: hazard ratio; TTFT: time to first treatment; OS: overall survival.

first treatment (TTFT) and OS. The selected variables are 17p del/*TP53* mut, IGVH, β2 microglobulin, stage and age. CLL-IPI was designed for patients receiving front-line CIT (*Table 2*).[18] The CLL-BALL score was created to predict OS in R/R CLL patients treated with the currently approved novel agents (ibrutinib (Ib), idelalisib (Idela) and venetoclax (Ven)) but also CIT. The four selected variables here are β2 microglobulin, haemoglobin, LDH and time from last therapy (*Table 3*).[19] Real-world series of patients with R/R CLL treated with Ib confirm the prognostic power of the CLL-BALL score.[20,21] The future will learn if the BALL score may identify higher risk R/R CLL requiring alternative and more effective therapeutic strategies.

UPDATED INDICATIONS FOR INITIATION OF TREATMENT (*TABLE 4*)

In 2018, the international workshop on CLL (iwCLL) updated the 2008 guidelines for the initiation of treatment. Symptomatic functional extranodal disease was added as indication to start treatment. Criteria for initiating first-line or second-line treatment follow in general similar rules. However, 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.[5]

RECOMMENDATIONS FOR THE TREATMENT OF SLL/CLL ANNO 2020

Treating CLL patients without advanced or active disease is still not recommended regardless of prognostic factors.[5] The role of early intervention *versus* (*vs.*) deferred treatment in patients with high risk disease (11q del and/or 17p del/*TP53* mut and/or unmutated IGVH) has been investigated in several RCTs. The German CLL Study Group (GCLLSG) CLL7 (FCR *vs.* wait and see) and the CLL12 (Ib *vs.* wait and see) showed clearly a longer PFS for the treated patient cohort but without OS benefit today.[22-24]

Before initiating treatment it is of utmost importance to consider patient related factors (age, performance status (PS), comorbidities, renal and bone marrow function and patient wishes), disease related factors (17p del/*TP53* mut, IGVH) and treatment related factors (contraindications to and side-effects from particular treatment modalities, intravenous *vs.* oral treatment, continuous *vs.* fixed duration of treatment). Current data confirm that duration of response to previous treatment becomes less important in the choice between CIT and novel agents.

TREATMENT OF TREATMENT NAÏVE SLL/CLL ANNO 2020 (*FIGURE 2*)

FRONTLINE TREATMENT OF CLL PATIENTS WITH 17P DEL/*TP53* MUT

The most important factor to determine first-line treatment is certainly the presence or absence of a 17p del/*TP53* mut. It is common knowledge that patients showing a 17p del/*TP53* mut are poor responders to CIT. The B cell receptor inhibitors (BCRi), Ib and Idela, have been approved for the treatment of patients with a 17p del/*TP53* mut even as front-line treatment and reimbursed in Belgium since August 2015. Although median (m) PFS and mOS are shorter for

TABLE 3. CLL-BALL: novel agent predictor model for relapsed/refractory patients.

Variable		Grading
β2 microglobulin	< or ≥ 5 mg/dl	1
Anemia	Male: Hb <12g/dl Female: Hb <11g/dl	1
LDH	> ULN	1
Last therapy	< 24 or ≥ 24 months	1
Risk group		**24 months OS %**
low	0-1	90
intermediate	2-3	80
high	4	56

LDH: lactate dehydrogenase; ULN: upper limit of normal; OS: overall survival; Hb: hemoglobin.

TABLE 4. Indications for initiation of treatment.

High tumorload	• Rai 3-4 or Binet C
Disease progression	• Lymphocyte doubling time of less than 6 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 6 months • Fatigue (PS≥2) • Fever >38°C for >2 weeks without infection • Night sweats >1 month

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

patients with the *TP53* aberration, the outcome is still better than for any other treatment available.[25] Since August 2019, Idela lost reimbursement in Belgium for CLL due to safety concerns. Venetoclax (Ven), the first bcl-2 inhibitor (Bcl-2i), as monotherapy can be an alternative in patients unsuitable for Ib as outcome seem comparable with the BCRi (reimbursed in Belgium since November 2017).[26] In the CLL 14 trial, fixed duration obinutuzumab $(Ob)_6$-Ven_{12} also showed a significant PFS benefit in patients with a *TP53* aberration compared to Ob-chlorambucil (Chl) *(details CLL 14 discussed in following paragraph)*.[27] Cross-trial comparisons or direct comparing RCTs have to confirm if Ob_6-Ven_{12} can be a first-line fixed duration treatment alternative to continuous treatment with Ib.

FRONTLINE TREATMENT OF CLL PATIENTS WITHOUT 17P DEL/*TP53* MUT

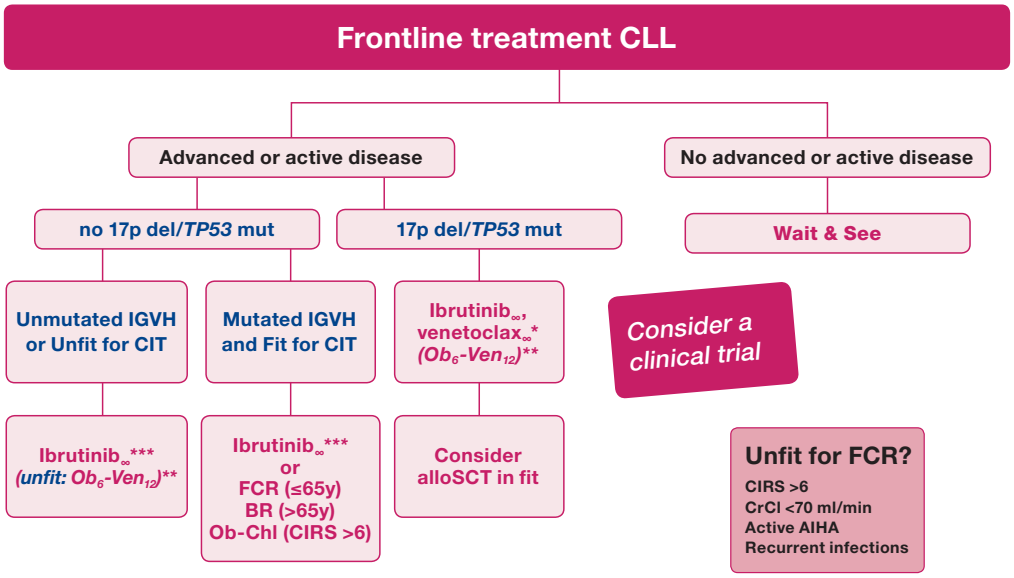
Until today, CIT stayed for a lot of patients the first-line treatment. Fludarabine (F)-cyclophosphamide (C)-rituximab (R) CIT was the standard of care for patients, who were fit, have no major comorbidities (cumulative illness rating scale (CIRS) ≤ 6) and/or a normal renal function (creatinine clearance (Cr Cl) ≥ 70 ml/min) and absence of active autoimmune haemolytic anaemia and recurrent infections).[28] For patients > 65 years, bendamustine (B)-R was an alternative treatment to FCR with similar outcomes but lower toxicities.[29] Even for patients with comorbidities BR seemed a feasible treatment.[30] For unfit (CIRS > 6), elderly patients Ob-Chl improved not only PFS, time to next treatment (TTNT) but also OS compared to R-Chl and Chl.[31] Since May 2017, Ib is reimbursed in Belgium as an alternative treatment option for patients not suitable for fludarabine (F) and without severe, uncontrolled cardiovascular disease according to the Resonate 2 data (phase III RCT comparing Ib to Chl).[32,33]

A lot of data has been presented and published since the 2018 update which substantiate the new proposed treatment recommendations.

In the E1912 phase III RCT, previously untreated CLL patients (N=529) requiring treatment, ≤ 70 years with a good PS, a Cr Cl > 40 ml/min, fit for FCR and no 17p del by FISH were treated with FCR (6 cycles) or Ib-R (Ib-R for six cycles after a single cycle of Ib alone, followed by Ib until disease progression (PD)). CIT induced a higher frequency of complete response (CR) and minimal residual disease (MRD)-negativity than did Ib-R. Nevertheless, PFS was significantly longer for Ib-R with a significant hazard ratio (HR) for progression or death of 0.35 ($p < 0.00001$). Concerning the IGVH status, the PFS difference was only significant for the unmutated subgroup. With a median follow up of 33.6 months, OS was superior for the Ib-R treated patients with a HR for death of 0.17 ($p < 0.0003$). The incidence of ≥ grade 3 adverse events (AEs) was similar in the two groups (+/- 80%) whereas infectious complications of ≥ grade 3 were less common with Ib-R than with FCR (10.5% *vs.* 20.3%, $p < 0.001$).[34]

In the A041202 phase III RCT, previously untreated CLL patients (N=547) requiring treatment, ≥ 65 years with a good PS, a Cr Cl ≥ 40ml/min, no heparin or warfarin, ANC ≥ 1000/µ and platelets ≥ 30000/µ unless due to bone marrow involvement, were treated with Ib until progression, Ib-R 6 cycles followed by Ib until PD or BR 6 cycles. In total, 6% of included patients had a 17p del and 10% a *TP53* mut.

FIGURE 2. Recommendation for treatment of front-line CLL 2020.



∞: continuous treatment.

*: venetoclax if the patient is unsuitable for ibrutinib and *TP53* aberration.

**: Ob_6-Ven_{12} not indicated and reimbursed in Belgium 02-2020.

***: ibrutinib∞: only reimbursed in Belgium 02-2020 for patients unfit for CIT.

del: deletion; mut: mutation; IGVH: immunoglobulin heavy chain variable region genes; CIT: chemoimmunotherapy; FCR: fludarabine, cyclophosphamide, rituximab; BR: bendamustine, rituximab; Chl: chlorambucil, Ob: obinutuzumab; Ven: venetoclax; alloSCT: allogeneic stem cell transplantation; CIRS: cumulative illness rating scale; Cr CL: creatinine clearance; AIHA: immune mediated haemolytic anaemia; y: years.

Cross-over to Ib due to progressive disease (PD) within the first year after BR was allowed and occurred in 30 patients. No significant PFS difference was seen for Ib-R*vs.* Ib. However, PFS was significantly better for Ib and Ib-R compared to BR with a HR of 0.39 and 0.38 (both $p < 0.001$) respectively. With a median follow-up of 38 months, there was no significant difference among the three treatment groups with regard to OS. Concerning again IGVH, the PFS difference between Ib regimens and BR looks more pronounced for the unmutated subgroup. The rate of ≥ grade 3 haematologic AEs was higher with BR (61%) than with Ib or Ib-R (+/- 40%), whereas the rate of ≥ grade 3 non-hematologic AEs was lower with BR (63%) than with the Ib-containing regimens (74% with each regimen). Infectious complications of ≥ grade 3 were seen in 19%, 22% and 27% of BR, Ib and Ib-R treated patients.[35]

The iLLUMINATE phase III RCT compared Ob-Ib (Ob 6 cycles, Ib till PD) *vs.* Ob-Chl (6 cycles) in untreated patients (N=229) in need of treatment, ≥ 65 years or < 65 years with comorbidities (CIRS > 6, Cr Cl < 70 ml/min, 17p del/*TP53* mut). In total, 14% of patients showed a 17p del and 12.5% a *TP53* mut. Cross-over to Ib single-agent was permitted after confirmation of PD to Ob-Chl. After a median follow-up of 31.3 months, mPFS was significantly longer in the Ob-Ib than in the Ob-Chl group (not reached (NR) *vs.* nineteen months) with a significant HR of 0.23 ($p < 0.0001$). In the Ob-Chl arm, 44% of the patients needed sequential treatment compared with 4% in the Ob-Ib arm. TTNT was significantly longer for the chemotherapy free regimen. These benefits were seen independent of high-risk features. The benefit for the unmutated IGVH patients looks greater than for the mutated ones. No OS difference was seen at time of publication. Serious AEs occurred in 58% and 35% of patients treated with Ob-Ib and Ob-Chl. The most common ≥ grade 3 AEs in both groups were neutropenia (37% *vs.* 46%) and thrombocytopenia (19% *vs.* 10%).[36]

The GCLLSG CLL14 compared in a phase III RCT Ob_6-Ven_{12} with Ob-Chl. Patients with previously untreated CLL and comorbidities (CIRS > 6 and/or Cr Cl < 70 ml/min) could be enrolled (N=432). Ob was given for six cycles as Ven and Chl were given for the fixed duration of twelve cycles. After a median follow-up of 28.1 months, PFS was

significantly longer for Ob_6-Ven_{12} with a significant HR of 0.35 ($p < 0.001$). This benefit was also observed in patients with 17p del (9%) and/or *TP53* mut (14%) and in patients with unmutated IGVH. No significant difference was observed for the mutated IGVH subgroup. DOR and TTNT was also better for the chemotherapy free regimen. OS was not different at the time of publication. No difference in ≥ grade 3 neutropenia occurred (53% and 48% for Ob-Ven and Ob-Chl) with also no excess of ≥ grade 3 infections (17.5% and 15.0% respectively).[27]

The phase III ELEVATE-TN RCT used Ob-acalabrutinib (A) (Ob 6 cycles, A till PD or intolerance), A (A till PD or intolerance) or Ob-Chl (6 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). 17p del and *TP53* mut were present in 9% and 11% of patients. At a median follow-up of 28.3 months, mPFS was prolonged for Ob-A and A compared to Ob-Chl (NR *vs.* 22.6 months; HR 0.10 and NR *vs.* 22.6 months; HR, 0.20 (both $p < 0.0001$)). Estimated 2 years PFS was 92.7% with Ob-A and 46.7% with Ob-Chl. Cross-over was allowed. In total, 25% of Ob-Chl treated patients received A at PD. OS was not different at the time of publication. Again, the PFS difference for mutated IGVH patients was not significant compared to those who were treated with Ob-Chl, though the number of patients compared was low. The most common grade ≥ 3 AE was neutropenia (Ob-A 30%, A 9%, Ob-Chl 41%). Grade ≥ 3 infections occurred in 21%, 14% and 8% of patients with Ob-A, A and Ob-Chl respectively.[37]

We are waiting eagerly for the results of the GCLLSG CLL 13 phase III RCT who used standard CIT (FCR or BR), R_6-Ven_{12}, Ob_6-Ven_{12} or Ob_6-Ib_{36}-Ven_{12} in untreated patients in need for treatment without a 17p del/*TP53* mut, good PS and a Cr CL ≥ 70 ml/min (N= 920).[38]

To conclude, all the reviewed RCTs confirm that patients treated with Bruton tyrosine kinase inhibitors (BTKi) till PD or intolerance show a highly significant gain in PFS compared to those treated with CIT. Looking at IGVH mutational status, the gain in PFS benefit was most pronounced for the unmutated IGVH subgroup. So, we feel comfortable to recommend Ib as the best front-line treatment not only for unfit patients but also for fit patients with unmutated IGVH. As not all trials show today a significant PFS benefit for the mutated IGVH subgroups, we think that CIT (FCR, BR, Ob-Chl), could still be an alternative treatment option if these mutated IGVH patients prefer a time limited treatment. Especially FCR could be still the first-line treatment option in young and fit patients with mutated IGVH as long-term follow up of some patient cohorts treated with FCR shows that +/- 50% remain in remission and could be cured.[39-41] At publication of the previous mentioned RCTs, only one trial showed an OS benefit for the BTKi, what could be explained by the short follow-up of the trials and potentiality of cross-over to the novel agent at PD in the other trials.[27,34-37] For the moment, we have no convincing data to recommend adding an anti-CD20 monoclonal to the BTKi as PFS and OS look very similar for the monotherapy *vs.* the combination treatment arms.[35,37] Fixed duration Ob_6-Ven_{12} in patients with unmutated IGVH and/or unfit patients (comorbidities and/or decreased renal function) could be an alternative treatment option.[27]

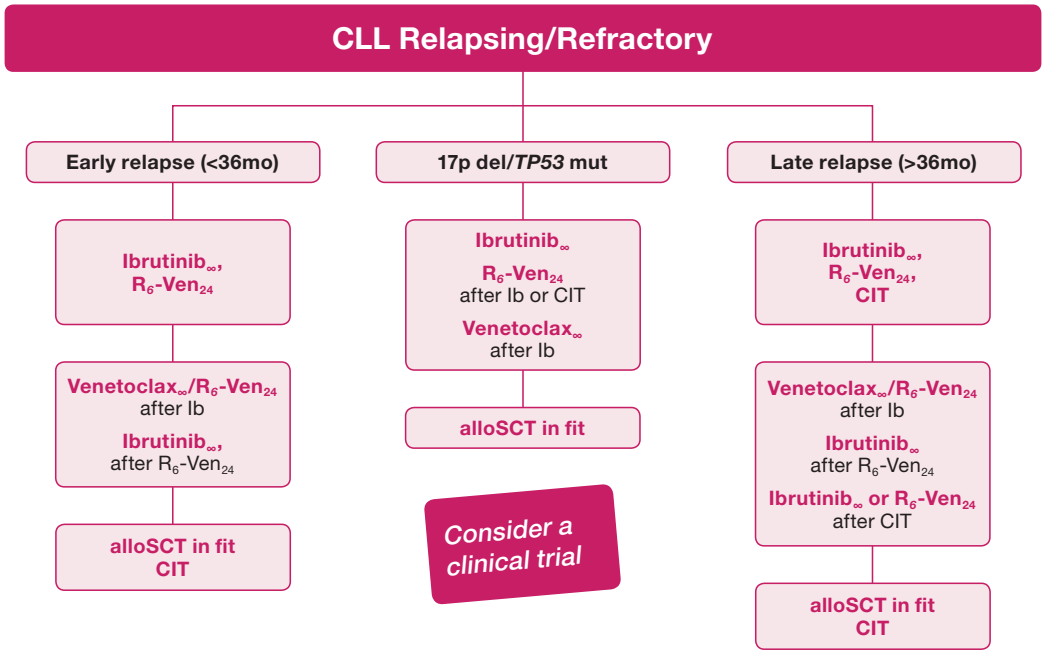
SECOND OR SUBSEQUENT-LINE TREATMENT (*FIGURE 3*)

In our previous guidelines, treatment for patients with R/R disease in need for treatment was mainly selected depending on presence or absence of a 17p del/*TP53* mut, fitness and DOR to the previous treatment (< or > 24 à 36 months).[2,3] Until now, retreatment with CIT was only recommended for fit patients showing a late relapse after previous CIT. For patients unfit, treatment refractory, experiencing early relapse after CIT or showing a 17p del/*TP53* mut, treatment with the BCRi (Ib or R-Idela) was reimbursed since August 2015 as outcome compared to monoclonal antibodies or CIT was superior.[3,42-44]

TREATMENT OF R/R CLL PATIENTS WITH 17P DEL/*TP53* MUT

As mentioned already, Ib or R-Idela were the best treatment choices compared to other treatment regimens when a patient acquires a *TP53* aberration after CIT and has a treatment indication.[3] Idela however has lost reimbursement for CLL in Belgium in August 2019 due to safety concerns. The 5 year follow-up of R/R CLL patients with a 17p del receiving ibrutinib (PCYC-1102, PCYC-1103 trials) (N=34), showed durable responses with a mPFS of 26 months and a mOS of 57 months.[45] A total number of 230 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 an estimated 30-months PFS and OS of 57% and 69%, respectively.[46] Ven monotherapy acquired reimbursement in November 2017 for patients with a *TP53* aberration and progressive or intolerant to Ib according the data from the M13-982 trial with expansion cohort (N=158). A mPFS of 27.2 months has been shown.[47] Since September 2019, we can also treat these high-risk patients progressing after Ib or CIT according to the Murano RCT with a fixed duration of R (6 cycles) and Ven (24 months) (R_6-Ven_{24}) as no difference in PFS is seen between patients with or without the *TP53* alteration (*Murano data discussed in following paragraph*).[48]

FIGURE 3. Recommendation for treatment of relapsed/refractory CLL 2020.



∞: continuous treatment.

mo: month; del: deletion; mut: mutation; R: rituximab; Ven: venetoclax; Ib: ibrutinib; alloSCT: allogeneic stem cell transplantation; CIT: chemoimmunotherapy.

TREATMENT OF R/R CLL PATIENTS WITHOUT 17P DEL/*TP53* MUT

Until recently, national and international guidelines supported retreatment with CIT for fit CLL patients showing a late relapse (> 24 or 36 months after previous treatment). For patients unfit, treatment refractory, experiencing early relapse after CIT the BCRi (Ib or R-Idela) were reimbursed since August 2015 as outcome compared to monoclonal antibodies or CIT was superior.[3,42-44] As mentioned before, Idela has lost reimbursement in August 2019 for CLL in Belgium due to safety concerns.

The five year follow-up of R/R CLL patients receiving ibrutinib (PCYC-1102, PCYC-1103 trials) (N=101), showed durable responses with a mPFS of 52 months and a five year OS of 57% and an excellent tolerability.[45] The updated seven year PFS and OS were 32% and 52% respectively with 21% of patients still on Ib.[49] Responses to BCRi seem independent of IGVH mutational status and the presence of unfavourable genetic aberrations (11q del, complex karyotype or novel gene mutations).[50]

The final results of the phase III RESONATE RCT treating R/R CLL/SLL patients with single-agent Ib (median follow up on study of 65.3 months in the Ib arm) or ofatumumab (Ofa) (N=391) were published. In total, 82% of patients included showed high-risk features (17p del/*TP53* mut, 11q del and/or unmutated IGVH). The mPFS remained significantly longer for patients randomised to Ib *vs.* Ofa (44.1 *vs.* 8.1 months; HR: 0.15). The PFS benefit was preserved in the high-risk population. OS, censored for crossover, was significantly better with Ib *vs.* Ofa (HR: 0.639). With a median of 41 months on Ib therapy, the safety profile showed a cumulatively, all-grade (grade ≥3) hypertension and atrial fibrillation occurring in 21% (9%) and 12% (6%) of patients, respectively.[51]

In the phase III Helios RCT, R/R patients without a 17p del were treated with BR (6 cycles) combined with Ib or placebo (till PD or intolerance) (N= 578).[43] After a median follow up of 34.8 months, mPFS was significantly better for BR-Ib (NR *vs.* 14.3 months, HR 0.021 ($p < 0.0001$)). In the recent update, analysis of OS corrected for cross-over from placebo to Ib at PD (160 patients) confirmed the OS advantage of BR-Ib with mOS still not reached for both arms.[52] Although cross-trial comparisons are difficult to interpret, for the moment no difference in mPFS or mOS is suspected for BR-Ib *vs.* Ib single-agent, suggesting that addition of BR to Ib does not improve long-term outcomes compared with single-agent Ib.[53] In the appendix of the primary analysis of this trial, we found a subgroup PFS analysis for patients

relapsing sooner or later than 36 months after previous treatment. The benefit for treatment with Ib seen for late relapse seemed as great as for early relapse while mPFS for treatment with BR was only a few months longer than for those with early relapse.[43] These data confirm that CIT must be reserved for patients with at least a very long response to previous CIT and only if the patient insists on a short, fixed duration of treatment. Reported grade 3-4 AEs in the Ib 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).[43]
The phase III RCT MURANO explored fixed duration R_6-Ven_{24} (R started after the ramp up of Ven) *vs.* BR (6 cycles) in R/R CLL (N= 389). Around 27% of patients had a 17p del and/or *TP53* mut. Median number of previous treatments was one. Approximately 4% of patients were pre-treated with a BCRi.[48] After a median follow-up of 48 months, mPFS for R_6-Ven_{24} and BR differed significantly (NR *vs.* 17 months, HR of 0.19 ($p < 0.0001$). OS showed superiority in the R_6-Ven_{24} arm with a HR 0.41 ($p < 0.0001$). These OS benefits were observed despite 79% of BR patients received novel agent treatment at PD.[54] Responses were particularly durable in patients who attained undetectable (u)MRD at the end of combination treatment (+/- months 9).[55] Twenty-four months after cessation of R_6-Ven_{24} 86% of the uMRD, 61% of the low level MRD and 7% of the high-level MRD patients remained progression free.[54] Median time to MRD recrudescence in peripheral blood was 46 months for all patients and 37 months for those with a *TP53* aberration. Time to iwCLL progression after MRD recrudescence was 17 (14-27) months.[56] The most common seen grade ≥ 3 AE was neutropenia (R_6-Ven_{24} 58% *vs.* BR 39%) with grade ≥ 3 infections and tumour lysis syndrome occurring in 17.5% and 22% and 3% and 1% of R_6-Ven_{24} and BR treated patients, respectively.[48]
The ASCEND trial, a phase III RCT, compared the efficacy and safety of A monotherapy (until PD or intolerance) *vs.* investigator choice (R (8 IV infusions)- Idela (continuously till PD) or BR (6 cycles) in R/R CLL (N=310). In total, 17% of patients showed a 17p del and 24% a *TP53* mut. Fifty-one percent of patients with confirmed PD on investigator choice (36/68) received A monotherapy as cross-over was allowed. Discontinuation due to AEs was observed in 11% of patients on A *vs.* 49% in Idela, 12% R in R-Idela, 11% in B and 17% R in BR. At a median follow-up of 16.1 months, A significantly prolonged mPFS *vs.* R-Idela/BR (NR *vs.* 16.5 months, HR 0.31 ($p < 0.0001$)). PFS improvement with A was observed across all subgroups, including patients with a *TP53* aberration. No difference in OS was seen at time of presentation. AEs of interest were atrial fibrillation (5.2% *vs.* 3.3% of patients on A *vs.* R-Idela/BR), bleeding (26% *vs.* 7.2%; including major haemorrhage (1.9% *vs.* 2.6%)) and grade ≥ 3 infections (15% *vs.* 24%). 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. This was the first trial comparing a BTKi *vs.* R-Idela head to head.[57]
Ven single agent gained already reimbursement to treat CLL patients refractory to Ib or Idela or progressive after Ib/Idela discontinuation due to responses seen in the M14-032 trial (N=64). The PFS at one year was 72%.[58] In the meantime, more data on optimal sequencing of the novel agents in CLL became available from real-world retrospective reviews. In the setting of BCRi failure (N=683), alternative BCRi or Ven appear superior to CIT. The use of Ven upon Ib failure might be superior to Idela due to higher ORR (79% *vs.* 46%) and longer PFS (HR 0.6 ($p = 0.06$)).[59] Data in the setting of Ven failure are less mature and only available in abstract form. A US multicentre, retrospective, chart-review analysis explored outcomes of Ib post-Ven in Ib-naïve patients (N=26). The ORR to Ib was 56.0% with time to progression varying from three to 53 months (N=10). Another retrospective analysis reviewed 326 patients who discontinued Ven and focused on subsequent treatments with BTKi, phosphoinositol 3 kinase inhibitors (PI3Ki) and cellular therapy (chimeric antigen receptor T cells (CAR-Ts) or allogeneic stem cell transplantation (SCT). For BTKi naïve patients, BTKi results in high ORR (84%) and durable remissions (mPFS 32 months). For BTKi exposed patients, BTK inhibition is not effective in the setting of previous BTKi resistance (mPFS four months) but should be considered if prior BTKi intolerance. PI3Ki following Ven does not appear to result in durable remissions even in PI3Ki naïve patients (ORR 47%, mPFS five months). No new safety signals arose. Twelve out of eighteen patients who received CAR-T after Ven responded but with only a mPFS of nine months. Median PFS was not reached for nineteen patients who underwent alloSCT post Ven. We conclude that BTKi in naïve or previously responsive patients and alloSCT following Ven appear to be the most effective treatment strategies with durable responses.[60]

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

Reduced intensity (RIC) allogeneic SCT should still be considered as a reasonable therapeutic option for high-risk CLL patients. However, as the treatment landscape is changing, the definition of high-risk patients is also a changing field. The latest proposal by ERIC and European Society for Blood and Marrow Transplantation (EBMT) defines R/R CLL

KEY MESSAGES FOR CLINICAL PRACTICE

1. No treatment is necessary for patients "without" active and/or advanced disease, regardless of prognostic factors (*Figure 2*).
2. Ib should be the preferred first-line treatment for patients "with and without" a *TP53* aberration; for fit patients with mutated IGIV, CIT could still be an alternative treatment. *(Ib not reimbursed for fit patients without TP53 aberration at publication)* (*Figure 2*).
3. Ib or fixed-duration R_6-Ven_{24} are the best therapeutic options for patients with R/R disease after CIT with or without an acquired *TP53* aberration (*Figure 3*).
4. Real world data affirm that at progression Ven after Ib and Ib after Ven can induce high and durable responses (*Figure 3*).
5. RIC allogeneic SCT should still be considered after remission induction with a novel agent according the ERIC & EBMT recommendations.
6. Patients must be encouraged to enter clinical trials exploring new agents or combinations.

patients after CIT and on a BTKi or Bcl-2i as high-risk I or high-risk II depending on treatment response and *TP53* aberration. High risk I patients have a 17p del/*TP53* mut and are responding to the first novel agent. Once maximum disease control has been achieved, a consolidating allogeneic SCT could be performed immediately only if ≤ 65 years, no comorbidities and a well-matched donor available. The allogeneic SCT should be deferred if > 65 years and/or multiple or severe comorbidities and/or partially matched donor available and the novel agent continued till treatment failure. High-risk II patients have no response to the first novel agent and are responding to an alternative novel agent. Patients who are frail or have no donor should continue till treatment failure. An allogeneic SCT could be considered in responding high-risk II patients with a well or partially matched donor or some permitted comorbidities. 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 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 and to improve persistence of T cells. When access to a CAR-T product becomes available, this cellular therapy could be offered to patients now ineligible for allogeneic SCT. When relapse or progression is seen after cellular therapy, alternative novel agents/ combinations or alternative cellular therapies can be considered or reconsidered.[62]

FUTURE TREATMENT APPROACHES

Although responses and DOR are exceptionally high and long with the use of 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. Longer follow-up of clinical trials exploring stopping treatment after a well-defined time period and/or at the achievement of MRD negativity will learn how long-lasting remissions will be and if cure is possible. The search for new agents or combinations must continue and patients must be still encouraged to enter clinical trials.

CONCLUSION

This manuscript, being the fourth publication on BHS LPD committee CLL guidelines in less than 10 years, is the best evidence that management of CLL is a continuous evolving field. We propose to use in the diagnostic work-up the ERIC-ESCCA immunophenotypic scoring system instead of the *Catovsky and colleagues*' system to differentiate CLL better from other leukaemic lymphomas.[6-8] We also advise testing the IGVH mutational status in young "and" older patients without a 17p del/*TP53* mut if CIT could be a therapeutic option. Although initiating treatment is mostly only necessary in patients with active or advanced disease, in the era of novel agents, starting subsequent therapy, sometimes in overlap with the previous one, can be acceptable to avoid Richter-like acceleration when substantial disease persists or disease progresses.[5]

After reviewing the recent literature, we feel comfortable to recommend Ib as the best front-line treatment. Only for the mutated IGVH subgroup, we think that CIT could still be an alternative treatment option if these patients prefer a time limited treatment.[34-37] Fixed duration Ob_6-Ven_{12} in patients with a *TP53* aberration, unmutated IGVH and/or unfit could certainly be an alternative first-line treatment option in the future.[27] Chl monotherapy or supportive care to control symptoms could still be a justifiable treatment option for frail patients.

For patients with R/R disease after CIT, Ib or fixed-duration R_6-Ven_{24} are the best therapeutic options independent of the presence or absence of an acquired *TP53* aberration and the time from last therapy.[42-56] Real world data affirm that at progression Ven after Ib and Ib after Ven can induce again durable responses.[58-61] Although the outcomes with the available novel agents are exceptionally good, the challenge stays to achieve even longer CLL control without impairment of quality of life. Therefore, in selected patients, cellular therapies as allogeneic SCT should still be considered according the ERIC & EBMT recommendations and patients must be encouraged to enter clinical trials exploring new agents, combinations or treatment strategies.[62]

REFERENCES

1. Janssens A, et al. BHS guidelines for the treatment of chronic lymphocytic leukaemia anno 2012. Belg J Hematol. 2012;3:134-43.
2. Janssens A, et al., on behalf of the BHS Lymphoproliferative Working Party. 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. Swerdlow S, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127:2375-90.
5. Hallek M, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood. 2018;131:2745-60.
6. Rawstron A, et al. Reproducible diagnosis of chronic lymphocytic leukemia 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.
7. Matutes E, et al. The immunological profile of B-cell disorders and proposal of a scoring system for the diagnosis of CLL. Leukemia. 1994;8:1640-5.
8. Moreau E, et al. Improvement of the chronic lymphocytic leukemia scoring system with the monoclonal antibody SN8 (CD79b). Am J Clin Pathol. 1997;108:378-82.
9. Malcikova J, et al. ERIC recommendations for TP53 mutation analysis in chronic lymphocytic leukemia-update on methodological approaches and results interpretation. Leukemia. 2018;32:1070-80.
10. Doubek M, et al. Modern and conventional prognostic markers of chronic lymphocytic leukaemia (CLL) in the everyday haematological practice. Eur J Haematol. 2011;87:130-7.
11. Abrisqueta P, et al. Improving survival in patients with chronic lymphocytic leukemia (1980-2008): the Hospital clinic of Barcelona experience. Blood. 2009;114:2044-50.
12. Dighiero G. CLL Biology and prognosis. Hematology Am Soc Hematol Educ Program. 2005;278-84 .
13. Galle V, et al. Is it possible to predict who may never need treatment for B-CLL? Belg J Hematol. 2018;9:124-9.
14. Rai K, et al. Clinical staging of chronic lymphocytic leukemia. Blood. 1975;46:219-34.
15. 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.
16. Binet J, et al. A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. Cancer. 1981;48;198-206.
17. Shanafelt T. Predicting clinical outcome in CLL: how and why. Hematology Am Soc Hematol Educ Program. 2009;421-9.
18. 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;779-790.
19. Soumerai, 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.
20. Gentile M, et al. External Validation of a Novel Risk Model (BALL Score) in Real-World Relapsed/Refractory Chronic Lymphocytic Leukemia Patients Receiving Ibrutinib. A Campus CLL Study. Blood. 2019;134(suppl 1):4308.
21. Ysebaert L, et al. Real-World Ibrutinib Validation of the Ball Score to Predict Overall Survival: A Filo Group Study in R/R CLL Patients. Blood. 2019;134 (suppl 1):1741.
22. Schweighofer C, et al. Early versus deferred treatment with combined fludarabine, cyclophosphamide and rituximab (FCR) improves event-free survival in patients with high-risk Binet stage A chronic lymphocytic leukemia-first results of a randomized German-French Cooperative Phase III Trial. Blood. 2013;122(21):524.
23. Langerbeins P, et al. The CLL12 trial protocol: a placebo-controlled double-blind Phase III study of ibrutinib in the treatment of early-stage chronic lymphocytic leukemia patients with risk of early disease progression. Future Oncol. 2015; 11:1895-1903.
24. Langerbeins P, et al. Ibrutinib versus placebo in patients with asymptomatic treatment-naïve early stage CLL: primary endpoint results of the phase 3 double bind randomized CLL12 trial. Haematol Oncol. 2019;37(S2):38-40 .
25. O'Brien S, et al. Efficacy and safety of ibrutinib in patients with relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma with 17p deletion: results from the phase II RESONATE 17 trial. Blood. 2014;124(21): 327.
26. Stilgenbauer S, et al. Venetoclax for Patients With Chronic Lymphocytic Leukemia With 17p Deletion: Results From the Full Population of a Phase II Pivotal Trial. J Clin Oncol. 2018;36:1973-80.
27. Fischer K, et al. Venetoclax and Obinutuzumab in Patients with CLL and Coexisting Conditions. N Eng J Med. 2019;380:2225-36.
28. Hallek M, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukemia: a randomised, open-label, phase 3 trial. Lancet. 2010;376:1164-74.
29. Eichhorst B, et al. First-line chemoimmunotherapy with bendamustine and rituxi-

mab 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.
30. Kleeberg U, et al. Bendamustin-rituximab combination is a safe and effective, ambulatory treatment for elderly patients with chronic lymphocytic leukemia: retrospective real-world analysis by age from a German registry and review of the literature. Anticancer Res. 2016;36:2827-38.
31. Goede V, et al. Overall survival benefit of obinutuzumab over rituximab when combined with chlorambucil in patients with chronic lymphocytic leukemia and comorbidities: final survival analysis of the CLL11 study. EHA library. 2018;215923:S151.
32. Burger J, et al. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. N Eng J Med. 2015;373:2425-37.
33. Burger J, et al. Long-term efficacy and safety of first-line ibrutinib treatment for patients with CLL/SLL: 5 years of follow-up from the phase 3 RESONATE-2 study. Leukemia. 2020;34:787-98.
34. Shanafelt T, et al. Ibrutinib-Rituximab or Chemoimmunotherapy for Chronic Lymphocytic Leukemia. N Engl J Med. 2019;381:432-43.
35. Woyach J, et al. Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL. N Engl J Med. 2018;379:2517-28.
36. Moreno C, et al. Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iLLUMINATE): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2019;20:43-56.
37. Sharman J, et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab in treatment-naïve chronic lymphocytic leukemia: the randomized, controlled, phase 3 ELEVATE TN trial. Lancet. 2020;395:1278-91.
38. Von Tresckow J, et al. The GAIA (CLL13) trial- an international, randomized, four-arm study for first line treatment of physically fit CLL. Integr Cancer Sci Therap. 2017;4(5):1-2.
39. Rossi D, et al. Molecular prediction of durable remission after first-line fludarabine-cyclophosphamide-rituximab in chronic lymphocytic leukemia Blood. 2015;126: 1921-4.
40. 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.
41. Thompson P, et al. Fludarabine, cyclophosphamide, and rituximab treatment achieves long-term disease-free survival in IGHV-mutated chronic lymphocytic leukemia. Blood. 2016;127:303-9.
42. Byrd J, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphocytic lymphoid leukemia. N Eng J Med. 2014:371:214-23.
43. Chanan-Khan A, et al. Ibrutinib combined with bendamustine and rituximab compared with placebo, bendamustine, and rituximab for previously treated chronic lymphocytic leukaemia or small lymphocytic lymphoma (HELIOS): a randomised, double-blind, phase 3 study. Lancet Oncol. 2016;17:200-11.
44. Zelenetz A, et al. Idelalisib or placebo in combination with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukemia: interim results from a phase 3, randomized, double blind, placebo-controlled trial. Lancet Oncol. 2017;18:297-311.
45. O'Brien S, et al. Single-agent ibrutinib in treatment-naïve and relapsed/refractory chronic lymphocytic leukemia: a 5-year experience. Blood. 2018;131:1910-19.
46. 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.
47. Stilgenbauer S, et al. Venetoclax for patients with chronic lymphocytic leukemia with 17p deletion: results from the full population of a phase II pivotal trial. J Clin Oncol. 2018;36:1973-80.
48. Seymour JF, et al. Venetoclax-rituximab in relapsed or refractory chronic lymphocytic leukemia. N Eng J Med. 2018;378:1107-20.
49. Byrd J, et al. Up to 7 Years of Follow-up of Single-Agent Ibrutinib in the Phase 1b/2 PCYC-1102 Trial of First Line and Relapsed/Refractory Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Blood. 2018; 132(suppl 1):3133.
50. Kipps T, et al. Long-term studies assessing outcomes of ibrutinib therapy in patients with del(11q) chronic lymphocytic leukemia. Clin Lymphoma Myeloma Leuk. 2019;19:715-22.
51. Munir T, et al. Final analysis from RESONATE: Up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. Am J Hematol. 2019;94:1353-63.
52. Fraser G, et al. Updated results from the phase 3 HELIOS study of ibrutinib, bendamustine, and rituximab in relapsed chronic lymphocytic leukemia/small lymphocytic lymphoma. Leukemia. 2019;33:969-80.
53. Hillmen P, et al. Comparing single-agent ibrutinib, bendamustine plus rituximab (BR) and ibrutinib plus BR in patients with previously treated chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL): an indirect comparison of the RESONATE and HELIOS trials. Blood. 2015;126(23):2944.
54. Seymour J, et al. Four-Year Analysis of Murano Study Confirms Sustained Benefit of Time-Limited Venetoclax-Rituximab (VenR) in Relapsed/Refractory (R/R) Chronic Lymphocytic Leukemia (CLL). Blood. 2019;134(suppl 1):335.
55. Kater A, et al. Fixed duration of venetoclax-rituximab in relapsed/refractory chronic lymphocytic leukemia eradicates minimal residual disease and prolongs survival: post-treatment follow-up of the Murano Phase III study. J Clin Oncol. 2019;37:269-77.
56. Lew T, et al. Undetectable peripheral blood MRD should be the goal of venetoclax in CLL, but attainment plateaus after 24 months. Blood Adv. 2020;4:165-73.
57. Ghia P, et al. Acalabrutinib vs Rituximab Plus Idelalisib (IdR) or Bendamustine (BR) by Investigator Choice in Relapsed/Refractory (RR) Chronic Lymphocytic Leukemia: Phase 3 ASCEND Study. Haematol Oncol. 2019;37(2):86-7.
58. Jones J, et al. Venetoclax monotherapy for patients with chronic lymphocytic leukaemia who relapsed after or were refractory to ibrutinib or idelalisib. Blood. 2016;128(suppl 1):637.
59. Mato A, et al. Optimal sequencing of ibrutinib, idelalisib, and venetoclax in chronic lymphocytic leukemia: results from a multicenter study of 683 patients. Ann Oncol. 2017;28:1050-6.
60. Brown J, et al. Outcomes of Ibrutinib (Ibr) Therapy in Ibr-Naïve Patients (pts) with Chronic Lymphocytic Leukemia (CLL) Progressing after Venetoclax (Ven). Blood. 2019;134(Suppl 1):4320.
61. Mato A, et al. Efficacy of Therapies Following Venetoclax Discontinuation in CLL: Focus on B-Cell Receptor Signal Transduction Inhibitors and Cellular Therapies. Blood. 2019;134(Suppl 1):502.
62. Dreger P, et al. High-risk chronic lymphocytic leukemia in the era of pathway inhibitors: integrating molecular and cellular therapies. Blood. 2018;132:892-902.
63. Lemal R, et al. State-of-the-art for CAR T-cell therapy for chronic lymphocytic leukemia in 2019. J Immunother Cancer. 2019;7(1):202.