POCKET GUIDELINE

Hematology

Practical management of Chronic Lymphocytic Leukemia in Belgium

POCKET GUIDELINE

Hematology

Practical management of Chronic Lymphocytic Leukemia in Belgium

This pocket guideline is based on:
Janssens et al. Updated BHS guidelines for the treatment of CLL, MCL and WM anno 2018. BJH 2018

Publisher
Ariez International BV, Westzijde 22, 1506 EE Zaandam, The Netherlands
Tel.: +31(0)75 642 94 20, E-mailadres: editor@bjh.be, Website: www.ariez.nl

This pocket guideline was made possible through funding from Gilead. ONC/BE/18-01//1024 January 2018

Index

POCKET GUIDELINE

Hematology

Practical management of Chronic Lymphocytic Leukemia in Belgium

Introduction

The BHS lymphoproliferative working party reviewed in 2017 the recent literature on diagnosis and treatment of SLL/CLL to update the 2012 and 2015 recommendations on best strategies for front-line and subsequent-line treatment. Today, reimbursement of ibrutinib as front-line treatment has been extended for some patients and venetoclax, the first bcl-2 antagonist available, has gained reimbursement and can be incorporated in the treatment guidelines. We are convinced that the monoclonal antibodies, the BCR inhibitors and the bcl-2 antagonists not only improve duration of response and overall survival but also quality of life.

Prof. Ann Janssens, MD, PhD
Hematology UZ Leuven
Chair of the BHS Lymphoproliferative working group 2013-2018

LPD committee members 2017 - 2018			
Marc André	Virginie De Wilde	Marie Maerevoet	Eric Van Den Neste
Helène Antoine-Poirel	Vanessa Delrieu	Fritz Offner	Vanessa Van Hende
Christophe Bonnet	Daan Dierickx	Liesbeth Schauvliege	Achiel Van Hoof
Dominique Bron	Radu Firescu	Wilfried Schroyens	Vibeke Vergote
Alessandra Camboni	Pierre Heimann	Sylvia Snauwaert	Gregor Verhoef
Charlotte Caron	Caroline Jacquy	Joan Somja	Inge Vrelust
Sarah Debussche	Ann Janssens	Cécile Springael	Ka Lung Wu
Hilde Demuynck	Jan Lemmens	Thomas Tousseyn	

Janssens et al., Updated BHS guidelines for the treatment of CLL, MCL and WM anno 2018. BJH 2018

CLL vs. other chronic B-LPD	
Chronic lymphocytic leukemia/ Small lymphocytic lymphoma	CLL/SLL
B-cell prolymphocytic leukemia	B-PLL
Mantle cell lymphoma	MCL
Follicular lymphoma	FL
Hairy cell leukemia	HCL
Lymphoplasmacytic lymphoma	LPL
Marginal zone B-cell lymphoma • Extranodal MZL (gastric and non-gastric MALT) • Splenic MZL • Nodal MZL	MZL

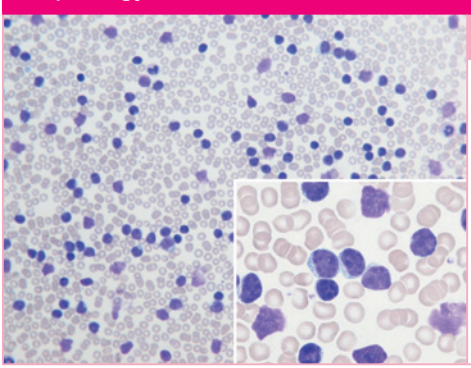
MBL-CLL type vs. SLL vs. CLL

Monoclonal B cell lymphocytosis	Small Lymphocytic Lymphoma	Chronic Lymphocytic Leukemia
Clonal B cells < 5000/µl	Clonal B cells < 5000/µl	**Clonal B cells > 5000/µl**
	Lymph-adenopathies +	Lymph-adenopathies +/-
	Organomegaly +/-	Organomegaly +/-
	Cytopenia due to marrow infiltration +/-	Cytopenia due to marrow infiltration +/-
	Constitutional symptoms +/-	Constitutional symptoms +/-

Low-count MBL	High-count MBL
<500/µl	500-5000/µl

Hallek et al. Blood 2008, Swerdlow et al. Blood 2016

Morphology of CLL



Courtesy: Dr C. Brusselmans, UZ Leuven

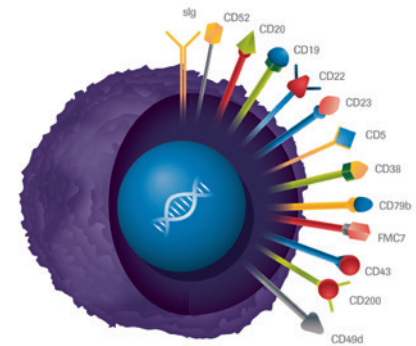
CLL cell characteristics

- small
- mature
- narrow border of cytoplasm
- dense nucleus with partially aggregated chromatin
- no discernible nucleoli
- Gumprecht nuclear shadows or smudge cells
- < 55% prolymphocytes

Microscopy blood smear: easy, rapid and inexpensive

Hallek et al. Blood 2008

Immunophenotype of CLL



CLL score > 3/5	
• CD5	positive
• CD19, CD23	positive
• CD20, CD79b	low expression
• sIG, κ or λ	low expression
• FMC7	negative
• typical CLL	4 to 5/5
• atypical CLL	2 to 3/5
• B-PLL	0 to 1/5
• HCL	0 to 1/5
• FL, SLVL, MCL	0 to 2/5
Moreau EJ et al. Am J Clin Pathol 1997	

CD200 and CD43 positivity can help to differentiate atypical CLL from other LPD

Köhnke et al. Br J Haematol 2017
Rawstron et al. Cytometry B Clin Cytom 2017

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 score LDH, immunoglobulines, renal function Parameters for hemolysis 17p deletion/p53 mutation hep B, hep C, CMV, HIV	CD38-CD49d β2-microglobulin IGV_H mutational status FISH: 13q deletion, t12, 11q deletion Conventional karyotyping with novel culture techniques Bone marrow aspirate and biopsy Rx-thorax, echo abdomen CT neck, thorax, abdomen, pelvis ECG
Clinical staging: Rai-Binet	

Janssens et al. BHS guidelines for the treatment of CLL. BJH 2012

Clinical staging systems

Staging system		Clinical features Lab results
Rai	0 low risk	Lymphocytosis
	I-II intermediate risk	Lymphadenopathy Splenomegaly/Hepatomegaly
	III-IV high risk	Anemia (Hb <11g/dl) Thrombocytopenia (<100000/µl)
Binet	A	<3 areas of lymphadenopathies
	B	≥3 areas of lymphadenopathies
	C	Anemia (Hb <10g/dl) Thrombocytopenia (<100000/µl)

Rai KR et al. Blood 1975
Gale RP et al. UCLA Symposia on Molecular and Cellular Biology, Vol 59, Wiley-Liss, 1987
Binet JL et al. Cancer 1981

Assessment of comorbidity

CIRS (Cumulative Illness Rating Scale) captures numbers and severity of comorbidities

Organ system	If illness/impairment present, please specify:	Score
Heart		⌊_⌋
Blood pressure		⌊_⌋
Vascular		⌊_⌋
Respiratory		⌊_⌋
Ear/nose/throat		⌊_⌋
Upper gastrointestinal		⌊_⌋
Lower gastrointestinal		⌊_⌋
Liver		⌊_⌋
Renal		⌊_⌋
Genitourinary		⌊_⌋
Musculoskeletal		⌊_⌋
Endocrine/metabolic		⌊_⌋
Neurological		⌊_⌋
Psychiatric	Total Score:	⌊_⌋⌊_⌋

www.CIRS.be

Rating strategy
0: no problem
1: current mild problem or past significant problem
2: moderate disability or morbidity requiring first line treatment
3: severe/constant significant disability/"uncontrollable" with first line treatment
4: extremely severe/immediate treatment required end organ failure/severe impairment in function

Parmelee PA, et al. J Am Geriatr Soc. 1995;43(2):130-7.

CLL - International Prognostic Index (CLL-IPI)

Variable		HR	Grading
17p del/p53 mut	No or Yes	4.2	4
IGV_H	Mut or Unmut	2.6	2
B2 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%

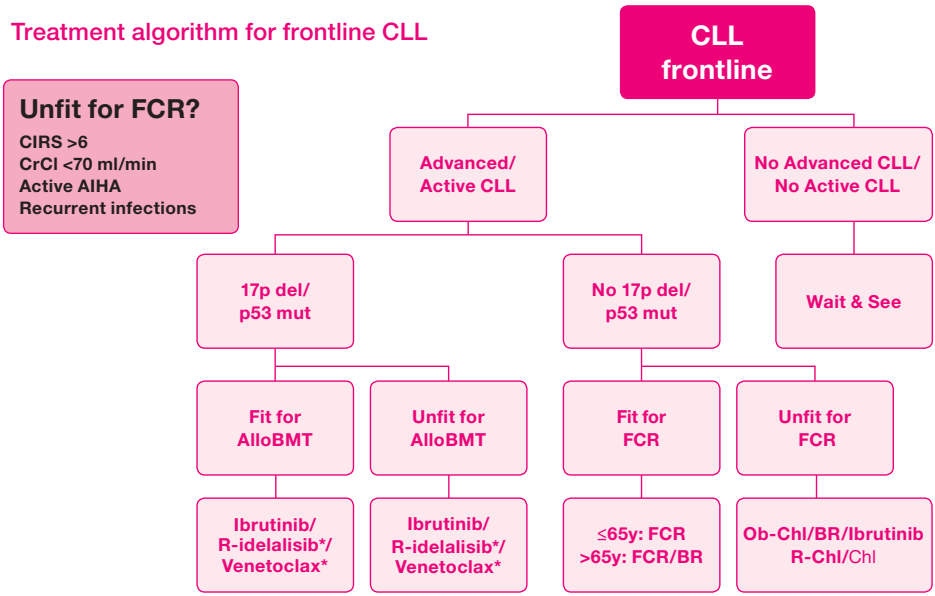
The International CLL-IPI working group. Lancet 2016

Indications for treatment (advanced and/or active disease)

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 (>10cm) or progressive or symptomatic lymphadenopathy • Progressive marrow failure leading to cytopenia
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 >2w without infection • Night sweats >1m

Hallek et al. Blood 2008

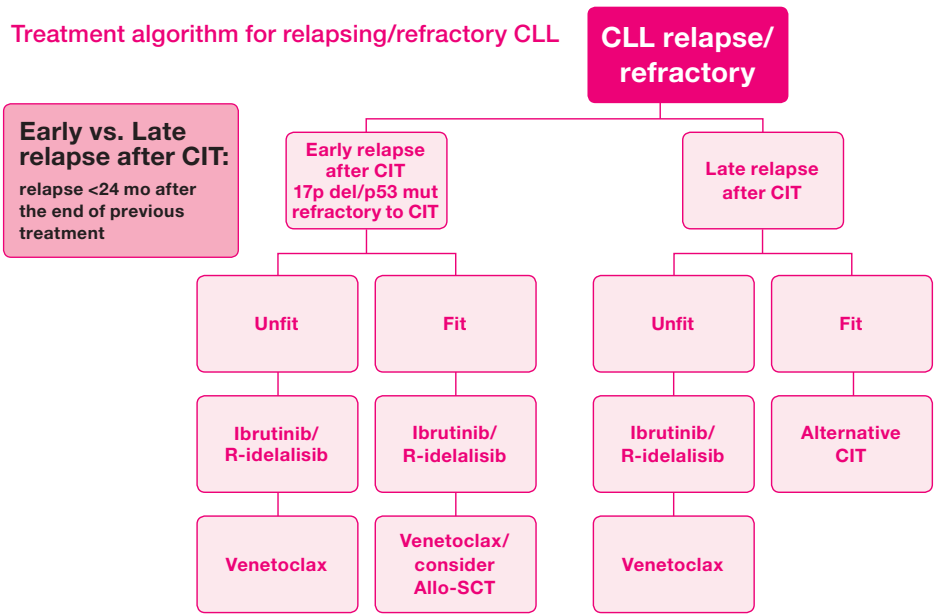
Treatment algorithm for frontline CLL



**: R-idelalisib or venetoclax if the patient is unsuitable for ibrutinib*

Janssens et al. Updated BHS guidelines for the treatment of CLL, MCL and WM anno 2018. BJH 2018

Treatment algorithm for relapsing/refractory CLL



Janssens et al. Updated BHS guidelines for the treatment of CLL, MCL and WM anno 2018. BJH 2018

Treatment schemes for CLL

	dosage	route	Days(d)/weeks(w)	Cycles (C)
FCR Fludarabine Cyclophosphamide Rituximab*	 25 mg/m² 250 mg/m² 375 (C1)-500(C2-6) mg/m²	 IV IV IV	 d1-3 d1-3 d1	 6
BR Bendamustine Rituximab*	 90 (Frontline)-70 (Relapse) mg/m² 375 (C1)-500(C2-6) mg/m²	 IV IV	 d1-2 d1	 6
Ob-Chl Obinutuzumab Chlorambucil	 100(d1)-900 (d2)-1000 (d8-15) mg (C1) 1000 mg (C2-6) 10 mg/m² or 0.5 (till 0.8) mg/kg	 IV oral	 d1-2-8-15 d1 d1-7 d1 & 15	 6 6 (12) 6 (12)
R-Chl Rituximab* Chlorambucil	 375 (C1)-500(C2-6) mg/m² 10 mg/m² or 0.5 (till 0.8) mg/kg	 IV oral	 d1 d1-7 d1 & 15	 6 6 (12) 6 (12)
Ibrutinib	420 mg	oral	once daily	Continuous treatment
R-Idelalisib Rituximab* Idelalisib	 375(C1)-500(C2-6) mg/m² 150 mg	 IV oral	 w1-3-5-7-9-13-17-21 twice daily	 8 infusions Continuous treatment
Venetoclax	20-50-100-200 mg 400 mg	oral	w1-2-3-4 once daily from w5 once daily	Continuous treatment

**Rituximab sc 1600mg fixed dose from the cycle following a cycle wihout any infusion reaction (reimbursed 2018)*

Choice between available BCR inhibitors and the bcl-2 inhibitor

Patient preference	Once daily 3 capsules: ibrutinib or 4 tablets: venetoclax Twice daily 1 tablet: idelalisib	
Frontline treatment	ibrutinib/venetoclax > idelalisib	
Renal impairment	CrCl >25 ml/min: ibrutinib/idelalisib/venetoclax CrCl 15-25 ml/min: idelalisib	Monitor more closely for TLS if CrCL between 30-80 ml/min when started on venetoclax
Auto-immune colitis	Ibrutinib/venetoclax > idelalisib	
Cardiac impairment/ arrhytmia	Idelalisib/venetoclax > ibrutinib	Cardiac check up if cardio-vascular risk factors or disease before start ibrutinib
Bleeding	Congenital bleeding disorders: idelalisib/venetoclax > ibrutinib Antiplatelet agents: idelalisib/venetoclax > ibrutinib Anticoagulant agents: idelalisib/venetoclax > ibrutinib	Assess indication of antiplatelet-anticoagulant therapy
Serious pulmonary impairment	ibrutinib/venetoclax > idelalisib	

Janssens. Ibrutinib and idelalisib, the BCR antagonists available for use in daily clinical practice. BJH 2015
Janssens. Venetoclax, the first bcl-2 antaganist available for CLL. BJH 2017

Prevention of infection in CLL during treatment

	PCJ prophylaxis	HSV prophylaxis	CMV PCR monitoring	Hep B screening
Prophylaxis/monitoring When, how long	>2 months after treatment completion and CD4 >200/µl	>2 months after treatment completion and CD4 >200/µl	Each 4 weeks till 2 months after treatment completion	Before start of treatment
Drug choice	Co-trimoxazol 400/80 mg 1 tabl/d Co-trimoxazol 800/160 mg 1 tabl/d 2 times a week (Pentamidine 300 mg aerosol once a month) (Dapsone 100 mg/d) (Atovaquone 1500 mg/d)	Acyclovir 2 x 400mg/d		
History of PCJ/HSV/ CMV infection prior any immunosuppressive treatment	x	x	x	
FCR	x	x		x
R-benda	x if CD4 <200/µl	x if CD4 <200/µl		x
Ob-Chl, R-Chl				x
Ibrutinib				x
R-idelalisib	x		x if CMV serology pos	x
Venetoclax				?
Alemtuzumab	x	x	x if CMV serology pos	x
Prednisone > 20mg/d for 4 weeks	x			x

Maertens J et al. J Antimicrob Chemother 2016, Baden LR et al. J Natl Compr Canc Netw 2012

Prevention of tumor lysis syndrome with venetoclax

5 week dose titration phase: 20-50-100-200-400 mg

Hydration, anti-hyperuricemic drugs, hospitalization and laboratory control according to tumor burden (Consider upgrading risk group if CrCl <80 ml/min, huge splenomegaly, important pre-existing co-morbidities and pre-existing, not corrected, electrolyte or uric acid values)

Low Risk	Median Risk	High Risk
All nodes <5cm* "and" ALC <25000/µl	One node 5-10cm* "or" ALC≥25000/µl	One node≥10cm* "or" One node 5-10cm* with ALC≥25000/µl
2 à 3 d before start 2L oral hydratation allopurinol**	2 à 3 d before start 2L oral hydratation allopurinol** Consider IV fluid	2 à 3 d before start 2L oral hydratation allopurinol or rasburicase if uric acid is elevated IV fluid 150-200ml/h if tolerated
Lab predose at each ramp-up dose Lab at 6-8h, at 24h after 20-50 mg	Lab predose at each ramp-up dose Lab at 6-8h, at 24h after 20-50 mg	Lab predose at each ramp-up dose Lab at 4h, 8h, 12h, 24h after 20-50 mg Lab at 6-8h, 24h at 100-200-400 mg

**: node assessment on CT scan*
***: at least till end of ramp-up*

European Medicines Agency. Summary of Product Characteristics. Venclyxto.
Janssens. Venetoclax, the first bcl-2 antagonist available for CLL. BJH 2017

Ibrutinib and bleeding risk

Increased bleeding risk in combination with
Heparine, low molecular weight heparins
Vitamin K antagonists
Novel oral antagonists (thrombin and factor Xa inhibitors)
Aspirin, nonsteroidal anti-inflammatory drugs
Clopidogrel, ticlopidine, prasugrel
Selective serotonin re-uptake inhibitors (SSRIs)
Fish oil, herbals, vitamin E
Avoid dual antiplatelet treatment
Avoid antiplatelet and anticoagulant combination
Peri-operative management
Minor procedures (central line placement, needle biopsy, thoracocentesis,…): hold ibrutinib for 3d prior and 3d after (not necessary to hold ibrutinib for bone marrow biopsies)
Major surgery: hold ibrutinib 7d prior and 7d after, until healing is reasonable
Platelet transfusion may correct hemostasis when given 4-6h after the last ibrutinib dose in case of significant bleeding or emergent surgery

Assess necessity of concomitant drugs

Discuss bleeding risk with the treating physicians!

Janssens. Ibrutinib and idelalisib, the BCR antagonists available for use in daily clinical practice. BJH 2015
De Weerdt et al. Haematologica 2017

ibrutinib-/idelalisib-/venetoclax-drug interactions

Strong CYP3A4 inhibitors	**Moderate CYP3A4 inhibitors**	**CYP3A4 inducers**
clarithromycin	aprepitant	carbamazepine
telithromycin	ciprofloxacin	phenytoin
ketoconazole	diltiazem	rifampicin
Itraconazole	erytromycin	rifabutin
posaconazole	fluconazole	phenobarbital
voriconazole	verapamil	dexamethasone
HIV medication	diltiazem	St John's wort
Grape fruit (juice)	amiodarone	
Sevilla oranges		
Star fruit		
[ibrutinib-idelalisib-venetoclax] ↑↑	[ibrutinib-idelalisib-venetoclax] ↑	[ibrutinib-idelalisib-venetoclax] ↓

Assess necessity of concomitant drugs

European Medicines Agency. Summary of Product Characteristics. Imbruvica.
European Medicines Agency. Summary of Product Characteristics. Zydelig.
European Medicines Agency. Summary of Product Characteristics. Venclyxto.

Additional idelalisib-drug interactions

Contraindicated	The metabolite of idelalisib (GS-563117) is a strong CYP3A4 inhibitor and may increase the concentration (*check SMPC and consider alternative if possible*)		
simvastatine	Antidepressants Sedatives Neuroleptica	trazodone diazepam, flurazepam, zolpidem quietapine, pimozide	
amiodarone	Anti-gout	colchicine	
midazolam, triamzolam	Cardiovascular drugs	amlodipine, felodipine, diltiazem, nifedipine, nicardipine	disopyramide, lidocaine
sildefanil, tadalafil (PAH)	Anticoagulants	NOACs, warfarine	
	Analgetics	morfine, buprenorphine, fentanyl, cocaine, methadone	
	Glucocorticoids	oral budesonide	
	Anti-infectives	clarithromycine, telitromycine, rifabutin, HCV protease inhibitors	ketoconazole, itraconazole, voriconazole, posaconazole
	Phosphodiesterase inhibitors	sildefanil, tadalafil (erectile dysfunction)	
	Anticonvulsants	carbamazepine	
	Immunosuppressants	cyclosporine, tacrolimus, everolimus	

Assess necessity of concomitant drugs

European Medicines Agency. Summary of Product Characteristics. Zydelig.

Additional venetoclax-drug interactions

venetoclax		
+ Bile acid sequestrants	[venetoclax] ↓	Administer venetoclax 4-6 h after sequestrant
+ warfarin	[warfarin] ↑	Monitor INR
+ digoxin, dabigatran, everolimus, sirolimus	[digoxin, dabigatran, everolimus, sirolimus] ↑	Monitor closely
+ dabigatran		Do not administer at the same moment
+ statins	[statins] ↑	Monitor closely for statin-related toxicity

Assess necessity of concomitant drugs

European Medicines Agency. Summary of Product Characteristics. Venclyxto.

Dose adaptations: ibrutinib-idelalisib-venetoclax

Dose interruptions			
any grade 3 non-hematological toxicity grade 3 neutropenia with infection or fever grade 4 hematological toxicity			
When toxicity improves to grade 1 or completely recovers, drug can be restarted at full dose When toxicity recurs once or more, it is advised to dose reduce the drug In case of neutropenia, intermittent use of short-acting G-CSF can be considered In case of a life-threatening adverse event, consider to discontinue the drug permanently			
Dose adaptations			
Ibrutinib	 + strong CYP3A4 + moderate CYP3A4	420 mg/once daily 140 mg/once daily 280 mg/once daily	280/140 mg once daily
Idelalisib	 + Cyp3A4	150 mg/twice daily Monitor closely for side effects	100 mg twice daily
Venetoclax	 + strong CYP3A4 + moderate CYP3A4	400 mg/once daily 100 mg/once daily 200 mg/once daily	300/200/100/50/20/10 mg

European Medicines Agency. Summary of Product Characteristics. Imbruvica.
European Medicines Agency. Summary of Product Characteristics. Zydelig.
European Medicines Agency. Summary of Product Characteristics. Venclyxto.

Posttreatment work-up

Complete Response outside a clinical trial (at least 2 mo after completion of therapy)	**Partial Response** (at least one of the following parameters documented for a minimal duration of 2 mo)
Absence of clonal lymphocytes in the peripheral blood	Decrease in blood lymphocytes by at least 50%
Absence of significant lymphadenopathy (<1.5cm) by physical examination	Reduction lymphadenopathy >50% (no new node, no increase in any node)
No spleno- or hepatomegaly by physical examination	Reduction hepato-, splenomegaly > 50%
Blood counts above: *(without transfusion - growth factors)* Neutrophils >1500/µl Platelets >100000/µl Hemoglobin >11g/dl	Blood counts: Neutrophils >1500/µl or 50% improvement over baseline Platelets >100000/µl or 50% improvement over baseline Hemoglobin >11g/dl or 50% improvement over baseline
Absence of constitutional symptoms	

Hallek et al. Blood 2008

Abbreviations

AIHA	auto-immune hemolytic anemia
BCR	B-cell receptor
CIRS	cumulative illness rating scale
CIT	chemo-immunotherapy
CLL	chronic lymphocytic leukemia
CLL-IPI	CLL international prognostic index
CrCl	creatinine clearance
HR	hazard ratio
ITP	immune thrombocytopenic purpura
LPD	lymphoproliferative disorder
MALT	mucosa associated lymphoid tissue
MBL	monoclonal B-cell lymphocytosis
MZL	marginal zone B-cell lymphoma
OS	overall survival
PAH	pulmonary arterial hypertension
PRCA	pure red cell aplasia
PS	performance status
SLL	small lymphocytic lymphoma
TTFT	time to first treatment

References

Baden LR, Bensinger W, Angarone M, et al. Prevention and treatment of cancer-related infections. J Natl Compr Canc Netw. 2012;10(11):1412-45.

Binet JL, Auquier A, Dighiero G, et al. A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. Cancer. 1981;48(1):198-206.

De Weerdt I, Koopmans SM, Kater AP, et al. Incidence and management of toxicity associated with ibrutinib and idelalisib: a practical approach. Haematologica. 2017;102(10):1629-39.

European Medicines Agency. Summary of Product Characteristics. Imbruvica. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003791/WC500177775.pdf

European Medicines Agency. Summary of Product Characteristics. Venclyxto. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004106/WC500218800.pdf

European Medicines Agency. Summary of Product Characteristics. Zydelig. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003843/WC500175377.pdf

Gale RP (Author), Rai KR (Editor). Chronic Lymphocytic Leukemia: Recent Progress and Future Direction. UCLA Symposia on Molecular and Cellular Biology, New Series, Vol 59, Wiley-Liss, 1987.

Hallek M, Cheson B, Catoversusky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukaemia: a report from the international workshop on updating the National Cancer Institute-Working Group 1996 guidelines. Blood. 2008;111:5446-56.

Janssens A, Van Den Neste E, Schroyens W, et al. BHS guidelines for the treatment of chronic lymphocytic leukaemia anno 2012. Belg J Hematol. 2012;3:134-43.

Janssens. Ibrutinib and idelalisib, the BCR antagonists available for use in daily clinical practice. Belg J Hematol. 2015;6(5):216-24.

Janssens et al. Updated BHS guidelines for the treatment of CLL anno 2016. Belg J Hematol 2015.

Janssens. Venetoclax, the first bcl-2 antaganist available for CLL. Belg J Hematol. 2017;8(7):265-71.

Janssens et al. Updated BHS guidelines for the treatment of CLL, MCL and WM anno 2018. Belg J Hematol. 2018.

Köhnke T, Wittmann VK, Bücklein VL, et al. Diagnosis of CLL revisited: increased specificity by a modified five-marker scoring system including CD200. Br J Haematol 2017;179(3):480-87.

Maertens J, Cesaro S, Maschmeyer G, et al. ECIL guidelines for preventing Pneumocystis jirovecii pneumonia in patients with haematological malignancies and stem cell transplant recipients. J Antimicrob Chemother. 2016;71(9):2397-404.

Moreau EJ, Matutes E, A'Hern RP, et al. Improvement of the chronic lymphocytic leukemia scoring system with the monoclonal antibody SN8 (CD79b). Am J Clin Pathol. 1997 Oct;108(4):378-82.

Parmelee PA, Thuras PD, Katz IR, et al. Validation of the Cumulative Illness Rating Scale in a geriatric residential population. J Am Geriatr Soc. 1995;43(2):130-7.

Rai KR, Sawitsky A, Cronkite EP, et al. Clinical staging of chronic lymphocytic leukemia. Blood. 1975;46(2):219-34.

Rawstron AC, Kreuzer KA, Soosapilla 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 2017. [Epub ahead of print]

Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127(20):2375-90.

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(6);779-90.