POCKET GUIDELINE

Hematology

Practical management of Chronic Lymphocytic Leukemia in Belgium anno 2020

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This pocket guideline is based on:
Janssens et al. Updated BHS guidelines for the treatment of CLL, MCL and WM anno 2018. BJH 2020

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Index

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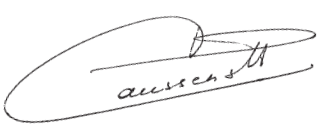
Introduction

The BHS lymphoproliferative working party reviewed in 2019 the recent literature on diagnosis and treatment of SLL/CLL to update the 2012, 2015 and 2017 recommendations. The updated CLL immunophenotype of the ERIC and ESCCA harmonisation project was introduced, as well as the CLL-BALL score for relapsing/refractory patients predicting outcome on novel agents. Concerning treatment, fixed duration rituximab$_6$-venetoclax$_{24}$ has gained already reimbursment for relapsing patients. Recent data confirms the superior outcome of ibrutinib compared to CIT in patients with late relapsing disease and in fit, treatment naïve patients with the greatest benefit seen in the unmutated IGV$_H$ subgroup. Also fixed duration obinutuzumab$_6$-venetoclax$_{12}$ as front-line treatment in unfit patients and those with a p53 dysfunction is superior to CIT. Using the novel agents already for many years, we are convinced that they not only improve duration of response and overall survival but also quality of life.



Prof. Ann Janssens, MD, PhD
Hematology UZ Leuven
President of BHS and member of the BHS Lymphoproliferative working group

Ob$_6$-Ven$_{12}$ not indicated and reimbursed in Belgium 02-2020.

LPD committee members 2019			
Marc André	Sarah Debussche	Marie Maerevoet	Cecile Springael
Helene Antoine Poirel	Vanessa Delrieu	Caressa Meert	Thomas Tousseyn
Sarah Bailly	Virginie De Wilde	Fritz Offner	Eric Van Den Neste
Veerle Beckers	Daan Dierickx	Kirsten Saevels	Vanessa Van Hende
Christophe Bonnet	Pierre Heimann	Liesbeth Schauvliege	Vibeke Vergote
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Alessandra Camboni	Ann Janssens	Sylvia Snauwaert	Alice Wolfromm
Charlotte Caron	Jan Lemmens	Joan Somja	Ka Lung Wu

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

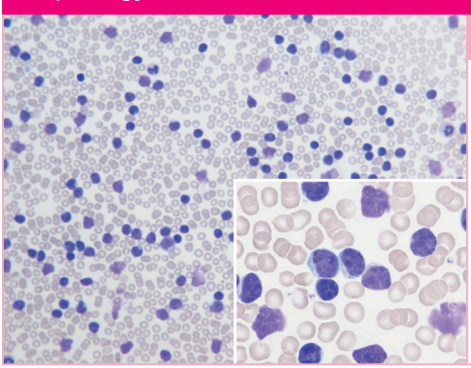
MBL-CLL type vs. SLL vs. CLL

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 2018, Swerdlow et al. Blood 2016

Morphology of CLL



Courtesy: Dr C. Brusselmans, UZ Leuven

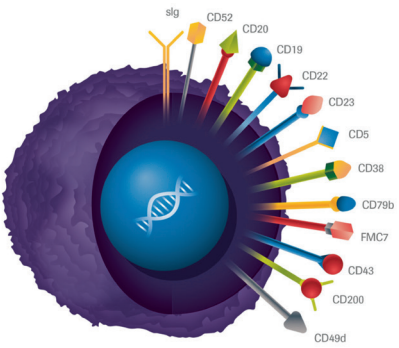
CLL cell characteristics

- 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 2018

Immunophenotype of CLL: ERIC & 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	Negative <20%
• ROR1	Positive >20%

Rawston et al, Cytometry B Clin Cytom 2018

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 IGV_H mutational status 17p deletion/p53 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	

Janssens et al. Updated BHS guidelines for the diagnosis and treatment of CLL. BJH 2020.

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:	⌊_⌋⌊_⌋

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) for treatment naïve patients

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

CLL - BALL score for relapsed/refractory patients (novel agent predictor model)

Variable		Grading
B2 microglobulin	< or ≥ 5 mg/dl	1
Anemia	Male: Hb <12g/dl Female: Hb <11/dl	1
LDH	> ULN	1
Last therapy	< 24 or ≥ 24 months	1

Risk group		24 mo OS %
low	0-1	90
intermediate	2-3	80
high	4	56

Soumerai et al. Lancet Haematol 2019

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 • 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 >2w without infection • Night sweats >1m

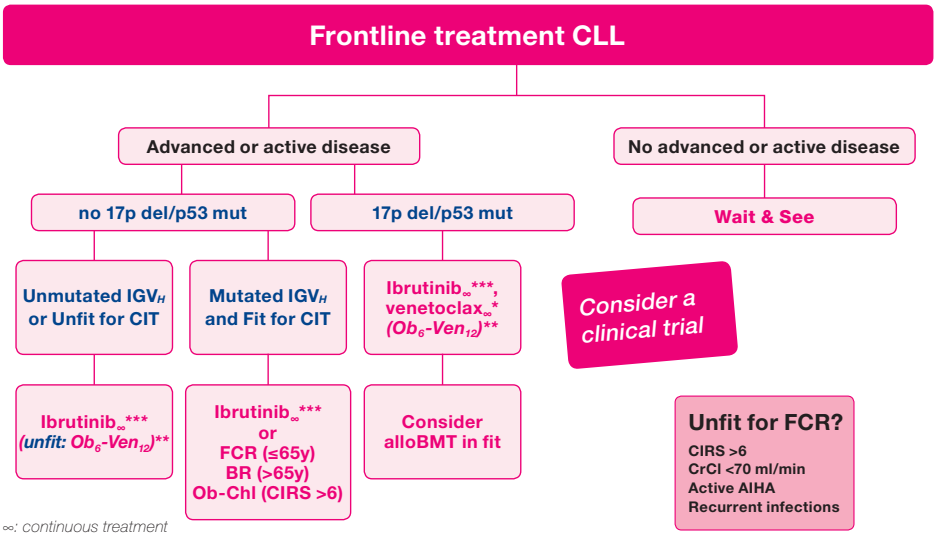
Hallek et al. Blood 2018

Treatment schemes for CLL

		dosage	route	Days(d)/weeks(w)	Cycles (C)
1	**FCR** Fludarabine Cyclophosphamide Rituximab*	 25 mg/m^2 250 mg/m^2 375 (C1)-500(C2-6) mg/m^2	 IV IV IV (SC)	 d1-3 d1-3 d1	 6
2	**BR** Bendamustine Rituximab*	 90 (Frontline)-70 (Relapse) mg/m^2 375 (C1)-500(C2-6) mg/m^2	 IV IV (SC)	 d1-2 d1	 6
3	**Ob-Chl** Obinutuzumab Chlorambucil	 100(d1)-900 (d2)-1000 (d8-15) mg (C1) 1000 mg (C2-6) 10 mg/m^2 or 0.5 (till 0.8) mg/kg	 IV oral	 d1-2-8-15 d1 d1-7 d1 & 15	 6 6 (12) 6 (12)
4	**Ibrutinib$_\infty$**	420 mg	oral	once daily	Continuous treatment
5	**Venetoclax$_\infty$**	Ramp up 20-50-100-200 mg 400 mg	oral	w1-2-3-4 once daily from w5 once daily	Continuous treatment
6	**R$_6$-Ven$_{24}$** Venetoclax Rituximab*	 Ramp up 20-50-100-200 mg 400 mg 375 (C1=w5)-500(C2-6) mg/m^2	 oral IV (SC)	 w1-2-3-4 once daily from w5 once daily w5-9-13-17-21-25	 24 6
7	**Ob$_6$-Ven$_{12}$ **** Obinutuzumab Venetoclax	 100(d1)-900 (d2)-1000 (d8-15) mg (C1) 1000 mg (C2-6) Ramp up 20-50-100-200 mg 400 mg	 IV oral	 d1-2-8-15 d1 w1-2-3-4 once daily From w5 once daily	 6 12

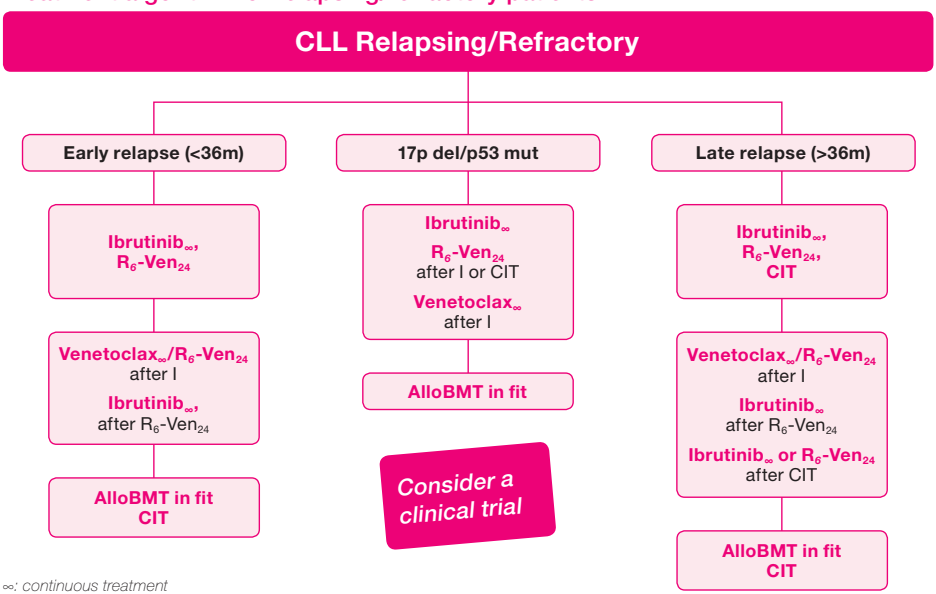
**: Rituximab sc 1600mg fixed dose from the cycle following a cycle wihout any infusion reaction (reimbursed 2018)*
***: Ob$_6$-Ven$_{12}$ not indicated and reimbursed in Belgium 02-2020*

Treatment algorithm for frontline CLL



∞: continuous treatment
*: venetoclax if the patient is unsuitable for ibrutinib
**: Ob_6-Ven_{12} not indicated and reimbursed in Belgium 02-2020
***: ibrutinib∞: only reimbursed in Belgium 02-2020 for patients unfit for CIT
Janssens et al. Updated BHS guidelines for the diagnosis and treatment of CLL, anno 2020. Belg J Hematol. 2020

Treatment algorithm for relapsing/refractory patients



∞: continuous treatment
*: venetoclax if the patient is unsuitable for ibrutinib
Janssens et al. Updated BHS guidelines for the diagnosis and treatment of CLL, anno 2020. Belg J Hematol. 2020

Choice between available btk and bcl-2 inhibitor: factors to be considered

Patient-doctor preference	Ibrutinib-venetoclax: continuous treatment R-venetoclax: fixed duration (24m)	
Hospital contacts	More hospital contacts for venetoclax than for ibrutinib	
Renal impairment	CrCl >25 ml/min: ibrutinib CrCl > 30 ml/min: venetoclax	Monitor more closely for TLS if CrCL between 30-80 ml/min when started on venetoclax
Allopurinol intolerance	Febuxostat oral Rasburicase IV	
Cardiac impairment/ arrhytmia	venetoclax > ibrutinib	Cardiac check up if cardio-vascular risk factors or disease before start ibrutinib
Bleeding	Congenital bleeding disorders / antiplatelet agents / anticoagulant agents: venetoclax preferred over ibrutinib	Assess indication of antiplatelet-anticoagulant therapy
Cost for the community	Fixed duration of treatment costs less than a continuous treatment regimen	

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
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-/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-venetoclax] ↑↑	[ibrutinib-venetoclax] ↑	[ibrutinib-venetoclax] ↓

Assess necessity of concomitant drugs

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

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-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
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. Venclyxto.

Posttreatment work-up outside of clinical trial

Complete Response (at least 2 m after completion of therapy)	**Partial Response** (at least one of the following parameters documented for a minimal duration of 2 m)
Peripheral blood lymphocytes (evaluated by blood and differential count) <4000/µl	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- (<13 cm) 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	Any of the constitutional symptoms

Hallek et al. Blood 2018

Abbreviations

AIHA: auto-ommune 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
ERIC: European research initiative on CLL
ESCCA: European society for clinical cell analysis
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

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