CASE 1 time point 1

CASE 1 – Timepoint 1

Patient profile:

Male
Age: 57 y
Weight: 81 kg
Height: 180 cm

Medical history: see comorbidities

Comorbidities:
- sleep apneu
- benign prostate hypertrophy

eGFR 81 mL/min

Current medication:
- Vitamin supplements
- Tamsulosine

Was found to have a raised white blood cell count during medical check-up for work. Referred for investigation.

Patient needs to be an MBL patients for W&W

CASE 1 time point 1

Clinical examination

non votable

1 Blood count

See assets

2 Physical examination

See assets

3 Cell morphology

See assets

4 Immunophenotyping

See assets

Guidelines:

- BHS
- HOVON
- iwCLL
- ESMO
- WHO

Screen What does the available information suggest

- blood count

WBC = 11,740x10^9/L

<u>white blood cell differential:</u>
lymphocytes 50% (5,8 x 10^9/L)
neutrophils 43% (5,0 x 10^9/L)
monocytes 7% (0,8 x 10^9/L)

platelets = 169 x 10^9/L

RBC = 5,37 x 10^{12}/L

Hb = 16,4 g/dl (10,2 mmol/l)
HCT = 46%

Screen What does the available information suggest

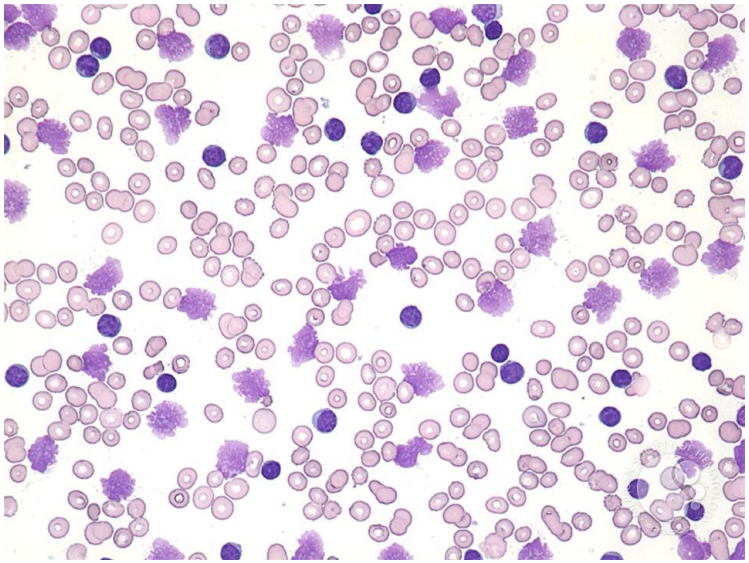
- physical examination

- No lymph nodes in neck, axillae or groins
- No hepatosplenomegaly

Screen What does the available information suggest

- cell morphology

Lymphocytes with dense nucleus with aggregated chromatin, frequent presence of smudge cells



Picture: Peter Maslak, ASH image bank #00001023

Screen What does the available information suggest

- Immunophenotyping

WBC telling	11,74	10**9/L	4.00 - 10.00
B cel merkers			
CD19	27.45	% van leucocyten	
CD19	66.76	% van lymfocyten	
CD10	0.04	% van CD19	
CD20	88.91	% van CD19	
CD23	78.34	% van CD19	
CD79b	3.22	% van CD19	
FMC7	1.08	% van CD19	
Surface immunoglobuline			
sKappa	0.62	% van CD19	
sLambda	97.92	% van CD19	
NK cel merkers			
CD16+CD56	9.43	% van lymfocyten	
T cel merkers			
CD3	29.96	% van lymfocyten	
CD4	13.06	% van lymfocyten	
CD8	12.11	% van lymfocyten	
CD5	94.74	% van CD19	
Niet specifieke merkers			
CD38	17.44	% van CD19	

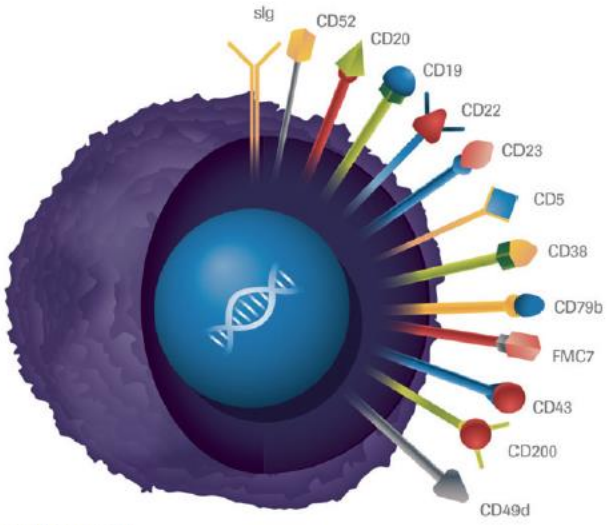
Screen

What does the available information suggest

BHS[1]

Supporting guidelines update

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
• CD43	Positive >20%
• CD79b	Weak
• CD81	Weak
• CD200	Positive >20%
• CD10	Negative <20%
• ROR1	Positive >20%

Rawston et al, Cytometry B Clin Cytom 2018

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

Screen

What does the available information suggest

BHS[2]

Supporting guidelines

Diagnosis

The diagnosis of CLL requires the presence of at least 5000/μl 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 or lambda immunoglobulin (ig) light chains) needs to be confirmed by flow cytometry.[3] Typically, CLL cells co-express the T cell antigen CD5 with B cell antigens. CD19 and CD23 show a strong expression whereas surface ig, CD20 and CD79b are only weakly expressed compared to normal B cells. The immunophenotypic scoring system defined by Moreau et al. is useful to differentiate CLL from other leukaemic lymphomas (CLL score ≥ 3: diagnosis of CLL definitely, CLL score ≤ 2: diagnosis of CLL unlikely, except for some cases with trisomy 12 who could show also an atypical morphology).[4] Bone marrow biopsy is not required for diagnosis.

The term small lymphocytic lymphoma (SLL) is used for patients with lymphadenopathy and/or splenomegaly but with <5000/μl B lymphocytes 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.[3]

In the absence of lymphadenopathy, organomegaly, cytopenia and clinical symptoms, the presence of <5000/μl B lymphocytes in the peripheral blood with a CLL phenotype is defined as monoclonal B-lymphocytosis (MBL)-CLL type.[3]

[2] *Janssens et al. Belg J Hematol 2012;3: 134-143*

HOVON[3]

Supporting guidelines
Update

Screen

What does the available information suggest

Bloedonderzoek:

Hb, leukocyten, trombocyten, leukocytendifferentiatie

Immunofenotypering (zie tabel 1) (SORT C)

Tabel 1: Immunofenotypering bij CLL[1]

Minimaal vereist	
CD19	positief
CD20	doorgaans zwakke expressie
CD5	positief
CD23	positief
Kappa, Lambda	Zwakke expressie, afwijkende ratio
Additionele markers	
CD200	positief
CD43	positief
CD79b	zwak tot negatief

Onderbouwing

Achtergrond- informatie diagnostiek bij diagnose[2]

Bij CLL is er sprake van lymfocytose met in de morfologie van het perifere bloed kapot gestreken lymfocyten en kleine lymfocyten met grumelée kernstructuur.

Voor de diagnose CLL moet bij immunofenotypering het aantal circulerende monoklonale B-cellen >5 x 10^9/l zijn en de immunofenotypering passend bij CLL(o.a. CD19-positief, CD5-positief, CD23-positief).

De diagnose kleincellig lymfocytair lymfoom ('small lymphocytic lymphoma'= SLL) kan gesteld worden, wanneer er lymfadenopathie en/of splenomegalie is, het aantal circulerende monoklonale B-cellen <5 x 10^9/l is en in de lymfklier een celbeeld met lymfoïde cellen met grumelée kernstructuur in combinatie met bij CLL/SLL passende immunofenotypering gezien wordt.

Indien het aantal circulerende monoklonale B-cellen <5 x 10^9/l is, er geen lymfadenopathie of organomegalie is, er geen cytopenie en geen ziektegerelateerde symptomen zijn, dan is er sprake van monoklonale B-lymfocytose.

[3] *Cll richtlijn 2017* http://www.hovon.nl/upload/File/Richtlijnen_BehAdv/richtlijn-cll-hovon_20170607_def_0.pdf

iwCLL[4]

Screen

What does the available information suggest

Supporting guidelines update

1.1. Blood

The diagnosis of CLL requires the presence of ≥5 × 10⁹/L B lymphocytes in the peripheral blood, sustained for at least 3 months. The clonality of these B lymphocytes needs to be confirmed by demonstrating immunoglobulin light chain restriction using flow cytometry. The leukemia cells found in the blood smear are characteristically small, mature lymphocytes with a narrow border of cytoplasm and a dense nucleus lacking discernable nucleoli and partially aggregated chromatin. Gumprecht nuclear shadows, or smudge cells, found as cellular debris, are additional morphologic features commonly associated with CLL. A small percentage of larger or atypical cells or prolymphocytes can be found admixed with morphologically typical CLL cells. Finding ≥55% prolymphocytes would favor a diagnosis of prolymphocytic leukemia; however, this diagnosis remains difficult and is solely based on morphological criteria, because no reliable immunological or genetic marker has been identified. A significant proportion of circulating prolymphocytes (≥10%) seems to indicate a more aggressive form of CLL (with *NOTCH1* or genetic *TP53* aberrations).[6]

CLL or SLL might be suspected in otherwise healthy adults who have an absolute increase in clonal B lymphocytes, but who have <5 × 10⁹/L B lymphocytes in the blood. However, in the absence of lymphadenopathy or organomegaly (as detected by physical examination or imaging studies), or of disease-related cytopenias or symptoms, the presence of <5 × 10⁹/L B lymphocytes is defined as monoclonal B lymphocytosis (MBL).[7] The presence of a cytopenia caused by a typical marrow infiltrate establishes the diagnosis of CLL regardless of the number of peripheral blood B lymphocytes or of the lymph node involvement. MBL has been observed to progress to CLL, requiring treatment at a rate of 1% to 2% per year.[8,9] Subjects with MBL appear to share an increased risk of secondary cancers with CLL patients, in particular of the skin, and should be encouraged to participate in the appropriate screening programs (eg, for carcinomas of the skin or colon).[9]

The definition of SLL requires the presence of lymphadenopathy and the absence of cytopenias caused by a clonal marrow infiltrate. Additionally, the number of B lymphocytes in the peripheral blood should be <5 × 10⁹/L. In SLL, the diagnosis should be confirmed by histopathological evaluation of a lymph node biopsy or biopsy of other tissues. Some patients may present with enlarged lymph nodes that are not suspicious for solid tumors and with peripheral blood B lymphocytes <5 × 10⁹/L that carry a typical CLL immunophenotype (see section 1.2). In these cases, a tissue or lymph node biopsy to establish the diagnosis of SLL may have limited clinical consequences and be omitted.

1.2. Immunophenotype

CLL cells coexpress the surface antigen CD5 together with the B-cell antigens CD19, CD20, and CD23. The levels of surface immunoglobulin, CD20, and CD79b are characteristically low compared with those found on normal B cells.[10-12] Each clone of leukemia cells is restricted to expression of either κ or λ immunoglobulin light chains.[10] The expression of CD5 can also be observed in other lymphoid malignancies, however, such as mantle cell lymphoma.[13] A recent, large harmonization effort has confirmed that a panel of CD19, CD5, CD20, CD23, κ, and λ is usually sufficient to establish the diagnosis.[14] In borderline cases, markers such as CD43, CD79b, CD81, CD200, CD10, or ROR1 may help to refine the diagnosis.[14]

[4] *Hallek Blood 2018 Jun 21;131(25):2745-2760*

ESMO[5]

Screen What does the available information suggest

Supporting guidelines

diagnosis and molecular biology

The diagnosis of CLL is established by the following criteria [1]:

- Presence in the peripheral blood of ≥5000 monoclonal B lymphocytes/μl. The clonality of the circulating B lymphocytes needs to be confirmed by flow cytometry.
- The leukaemia cells found in the blood smear are characteristically small, mature-appearing lymphocytes with a narrow border of cytoplasm and a dense nucleus lacking discernible nucleoli, and having partially aggregated chromatin. Larger, atypical lymphocytes or prolymphocytes may be seen but must not exceed 55%.

CLL cells co-express the CD5 antigen and B-cell surface antigens CD19, CD20 and CD23. The levels of surface immunoglobulin, CD20 and CD79b are characteristically low compared with those found on normal B cells. Each clone of leukaemia cells is restricted to expression of either kappa or lambda immunoglobulin light chains.

Other lymphoma entities to be separated from CLL are leukaemic marginal zone lymphoma, lymphoplasmacytic lymphoma and mantle cell lymphoma (MCL). These tumour cells express B-cell surface antigens and MCL also expresses CD5, but usually not CD23. For cases that express CD23, staining for cyclin D1 or SOX11 and fluorescence *in situ* hybridisation (FISH) for detecting a translocation (11;14) are useful for establishing the diagnosis of MCL. FMC7 may also help differentiating CLL from MCL, but there are also FMC7 positive (atypical) CLL cases. Marginal zone lymphoma or lymphoplasmacytic lymphoma may also be differentiated by a negative or lower CD43 expression in comparison to CLL.

In the World Health Organization classification, small lymphocytic lymphoma (SLL) and CLL are considered to be a single entity. The diagnosis of SLL requires the presence of lymphadenopathy and/or splenomegaly with a number of B lymphocytes in the peripheral blood not exceeding 5×10^9/l. SLL cells show the same immunophenotype as CLL. The diagnosis of SLL should be confirmed by histopathological evaluation of a lymph node biopsy, whenever possible.

In absence of lymphadenopathy, organomegaly, cytopaenia and clinical symptoms, the presence of fewer than 5000 monoclonal B lymphocytes/μl defines 'monoclonal B-lymphocytosis' (MBL) [1], which can be detected in 5% of subjects with normal blood count [2]. Progression to CLL occurs in 1%–2% of MBL cases per year [2].

[5] *Eichhorst Annals of Oncology 2015;26(5): 78–84*

WHO[6]

Screen

What does the available information suggest

Supporting guidelines

Chronic lymphocytic leukemia/small lymphocytic lymphoma and monoclonal B-cell lymphocytosis

The 2008 monograph recognized monoclonal B-cell lymphocytosis (MBL) as the presence of monoclonal B-cell populations in the peripheral blood (PB) of up to <5 x 10^9/L either with the phenotype of chronic lymphocytic leukemia (CLL), atypical CLL, or non-CLL (CD52) B cells in the absence of other lymphomatous features. Found in up to 12% of healthy individuals, in some it may be an extremely small population, but in others associated with a lymphocytosis.[4] Whereas in 2008 it was unknown whether MBL was a precursor of CLL, we now know that MBL precedes virtually all cases of CLL/small lymphocytic lymphoma (SLL).[5] The updated WHO will retain the current criteria for MBL, but will emphasize that "low-count" MBL, defined as a PB CLL count of , <0.5 x 10^9/L, must be distinguished from "high-count" MBL because low count MBL has significant differences from CLL, an extremely limited, if any, chance of progression, and, until new evidence is provided, does not require routine follow-up outside of standard medical care.[6,7] In contrast, high-count MBL requires routine/yearly follow-up, and has very similar phenotypic and genetic/molecular features as Rai stage 0 CLL, although immunoglobulin heavy chain variable region (IGHV)-mutated cases are more frequent in MBL.[8] Also impacting our diagnostic criteria, the revision will eliminate the option to diagnose CLL with , <5 x 10^9/L PB CLL cells in the absence of extramedullary disease even if there are cytopenias or disease-related symptoms. Non-CLL type MBL, at least some of which may be closely related to splenic marginal zone lymphoma, is also recognized.[9,10]

In addition, although other confirmatory studies are necessary, the concept of tissue-based MBL of CLL type will be discussed as there are a subset of cases with lymph node involvement by "SLL" that also do not seem to have a significant rate of progression. In 1 retrospective study, lymph nodes with CLL/SLL in which proliferation centers were not observed and patients in whom adenopathy was <1.5 cm based on computed tomography scans were the best candidates for tissue-based MBL.[11]
Also related to CLL/SLL, there is increasing interest in proliferation centers (PCs) in overt CLL/SLL. We have learned that: PCs can have cyclin D1 expression in up to about 30% of CLL/SLL, they express MYC protein, and, based on 3 of 4 studies, PCs which are large/confluent and/or have a high proliferative fraction are a significant and independent adverse prognostic indicator.

[6] *Swerdlow Blood 2016;127:2375-2390*

CASE 1 time point 1

What would you do next ?

votable

1. CT Scan
2. RX Thorax
3. Ultrasound
4. Bone marrow biopsy
5. Cytogenetics molecular biology
6. No further tests required

Guidelines:

- BHS
- HOVON
- iwCLL
- ESMO

Screen

What Would you do next

BHS[1]

Supporting guidelines Update

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.

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

HOVON[2]

Screen

What Would you do next

Supporting guidelines
Update

Onderzoek om de diagnose CLL te stellen

Aanbevelingen

Bloedonderzoek:
Hb, leukocyten, trombocyten, leukocytendifferentiatie
Immunofenotypering (zie tabel 1) (SORT C)

Tabel 1: Immunofenotypering bij CLL[1]

Minimaal vereist	
CD19	positief
CD20	doorgaans zwakke expressie
CD5	positief
CD23	positief
Kappa, Lambda	Zwakke expressie, afwijkende ratio
Additionele markers	
CD200	positief
CD43	positief
CD79b	zwak tot negatief

Onderbouwing

Achtergrondinformatie diagnostiek vooraf aan therapie[2]

Bij CLL is er sprake van lymfocytose met in de morfologie van het perifere bloed kapot gestreken lymfocyten en kleine lymfocyten met grumelée kernstructuur. Voor de diagnose CLL moet bij immunofenotypering het aantal circulerende monoklonale B cellen >5 x 10^9/l zijn en de immunofenotypering passend bij CLL(o.a. CD19-positief, CD5-positief, CD23-positief) De diagnose kleincellig lymfocytair lymfoom ('small lymphocytic lymphoma'= SLL) kan gesteld worden, wanneer er lymfadenopathie en/of splenomegalie is, het aantal circulerende monoklonale B cellen < 5 x 10^9/l is en in de lymfklier een celbeeld met lymfoide cellen met grumelée kernstructuur in combinatie met bij CLL/SLL passende immunofenotypering gezien wordt. Indien het aantal circulerende monoklonale B cellen <5 x 10^9/l is, er geen lymfadenopathie of organomegalie is, er geen cytopenie en geen ziektegerelateerde symptomen zijn, dan is er sprake van monoklonale B-lymfocytose.

[1] *CLL richtlijn -2017 http://www.hovon.nl/behandeladvies/behandeladvies-leukemie/cll.html*

Onderzoek vooraf aan therapie

Aanbevelingen

Anamnese:
niveau van functioneren ("WHO performance"-score), koorts, gewichtsverlies, nachtzweten en infecties
Lichamelijk onderzoek:
vastleggen van grootte van lymfklieren, lever en milt
Bloedonderzoek: (SORT C)

- Hb, leukocyten, trombocyten, leukocytendifferentiatie
- Nierfunctie, leverfunctie, immuunglobulines, directe antiglobuline test
- Serologie hepatitis B, hepatitis C, HIV
- Cytogenetica (FISH of Comparative genomic hybridization (CGH)-array) voor del (13q), del (11q), del (17p), trisomie 12
- Moleculair onderzoek aanwezigheid TP53-mutatie (tenminste exon 4-10, bij voorkeur bepaald in een ERIC gecertificeerd laboratorium)

Beenmergonderzoek indien trombocytopenie of anemie
(vraagstelling: verdringing of auto-immuun afbraak)
Beeldvorming:
Expert opinion werkgroep:
X thorax (vraagstelling lymfadenopathie, aanwijzing voor infectie, andere longafwijkingen) (SORT C)
Expert opinion werkgroep:
CT hals, thorax, abdomen (achterwege laten indien geen consequenties voor respons evaluatie) (SORT C)

Achtergrondinformatie diagnostiek vooraf aan therapie[2]

Aanvullend onderzoek is erop gericht om stadium van de ziekte vast te stellen, complicaties van de ziekte in kaart te brengen (hemolyse, auto-immuun trombocytopenie, hypogammaglobulinemie) prognostische markers te verkrijgen (Cytogenetisch en moleculair onderzoek) en eventuele actieve of chronische infecties (hepatitis B, C), die kunnen verergeren door de behandeling met monoklonale antistoffen, te diagnosticeren. Beenmergonderzoek kan geïndiceerd zijn ter differentiatie van anemie of trombocytopenie als gevolg van beenmerg-verdringing of door auto-immuun afbraak. In de dagelijkse praktijk kan radiologische beeldvorming zeer beperkt blijven indien bij lichamelijk onderzoek lymfadenopathie en lever-en miltgrootte goed vast te leggen zijn. In studieverband is uitgebreidere beeldvorming (CT hals, thorax, abdomen) veelal wel noodzakelijk ten behoeve van nauwkeurige responsevaluatie.

[2] *Cll richtlijn 2017* http://www.hovon.nl/upload/File/Richtlijnen_BehAdv/richtlijn-cll-hovon_20170607_def_0.pdf

Screen

What Would you do next

iwCLL[3]

Supporting guidelines Update

Table 1. Baseline evaluation of patients with CLL

Diagnostic test	General practice	Clinical trial
Tests to establish the diagnosis		
CBC and differential count	Always	Always
Immunophenotyping of peripheral blood lymphocytes	Always	Always
Assessment before treatment		
History and physical, performance status	Always	Always
CBC and differential count	Always	Always
Marrow aspirate and biopsy	When clinically indicated (unclear cytopenia)	Desirable
Serum chemistry, serum immunoglobulin, and direct antiglobulin test	Always	Always
Chest radiograph	Always	Always
Infectious disease status	Always	Always
Additional tests before treatment		
Molecular cytogenetics (FISH) for del(13q), del(11q), del(17p), add(12) in peripheral blood lymphocytes	Always	Always
Conventional karyotyping in peripheral blood lymphocytes (with specific stimulation)	NGI*	Desirable
TP53 mutation	Always	Always
IGHV mutational status	Always	Always
Serum β_2-microglobulin	Desirable	Always
CT scan of chest, abdomen, and pelvis	NGI	Desirable
MRI, PET scans	NGI	NGI
Abdominal ultrasound†	Possible	NGI

General practice is defined as the use of accepted treatment options for a CLL patient not enrolled on a clinical trial.

CBC, complete blood count; MRI, magnetic resonance imaging; NGI, not generally indicated; PET, positron emission tomography.

*Conventional karyotyping in peripheral blood lymphocytes (with specific stimulation) may be useful before therapy, if established methodology is available.

†Used in some countries to monitor lymphadenopathy and organomegaly.

[3] *Hallek Blood 2018 Jun 21;131(25):2745-2760*

ESMO[4]

Screen What Would you do next

Supporting guidelines Added

Table 1.

Diagnostic and staging work-up

	Pretreatment evaluation	Response evaluation
History, physical examination and performance status	+	+
Complete blood count and differential	+	+
Serum chemistry including serum immunoglobulin and direct antiglobulin test	+	+
Cytogenetics (FISH) for del (17p)/molecular genetics for *TP53* mutation	+	–
Marrow aspirate and biopsy	+[a]	+[b]
Hepatitis B and C, CMV and HIV serology	+	–

[a]Only if clinically indicated.

[b]Only for confirmation of CR within clinical studies.

FISH, fluorescence *in situ* hybridisation; CMV, cytomegalovirus; HIV, human immunodeficiency virus; CR, complete remission.

[4] *Eichhorst Annals of Oncology 2015;26(5): 78–84*

Diagnosis

- MBL

POST-IT: clinical implications of MBL

- Low-count MBL
  - At low risk of progression
  - No clear clinical implications
  - Requires no specific clinical follow-up
- High-count MBL
  - Risk of progression to CLL or SLL requiring treatment is between 1% and 2% per year
  - Significantly higher risk of hospitalization due to serious infections
  - Higher risk of hematologic and nonhematologic cancers
  - Annual complete blood count and periodic lymph node examination are advised

Strati P. & Shanafelt T. Blood 2015; 126(4): 454-462

CASE 1 time point 2

CASE 1 – Timepoint 2

Patient profile:

Male
Age: 59 y
Weight: 81 kg
Height: 180 cm

Medical history:
- MBL diagnosis 2y ago

Comorbidities:
- sleep apneu
- benign prostate hypertrophy

eGFR 81 mL/min

Current medication:
- Vitamin supplements
- Tamsulosine

Patient has asymptomatic CLL

Screen What does the available information suggest

- blood count

WBC = 12,170 x10^9/L

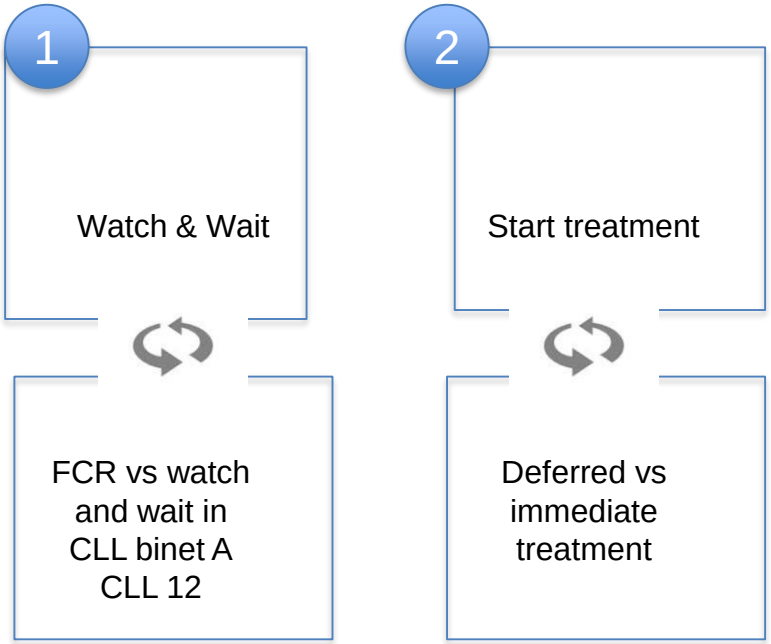
<u>white blood cell differential:</u>
Lymphocytes 53% (6,4 x 10^9/L)
neutrophils 41% (5,0 x 10^9/L)
monocytes 6% (0,7 x 10^9/L)

Hb = 10,143 g/dl (6,3 mmol/l)

CASE 1 time point 2

The patient has been diagnosed with CLL but is asymptomatic. What would you do next?

votable

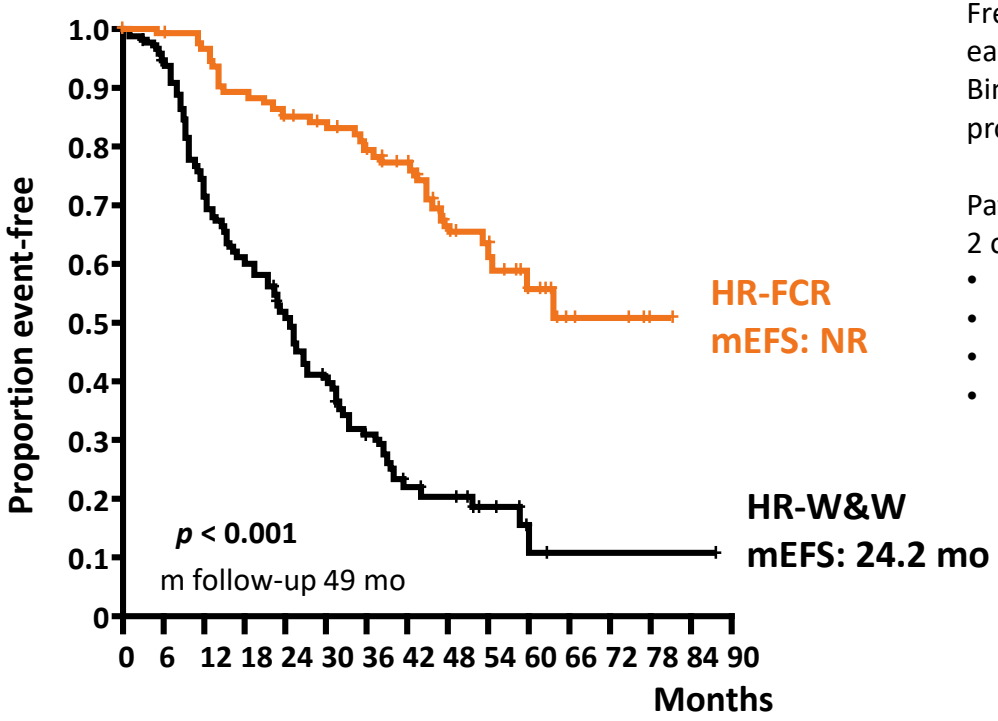


Guidelines:

- BHS
- HOVON
- IwCLL
- ESMO

Screen 1 Diagnosed with CLL, what would you do next ?

- FCR vs watch and wait in CLL Binet A[1]



Endpoint and safety analysis of a randomized German-French cooperative phase III trial comparing the efficacy of early versus deferred FCR therapy in 824 treatment-naive Binet stage A CLL patients with a high risk of disease progression.

Patients were considered high risk if they exhibited at least 2 of 4 prognostic markers:

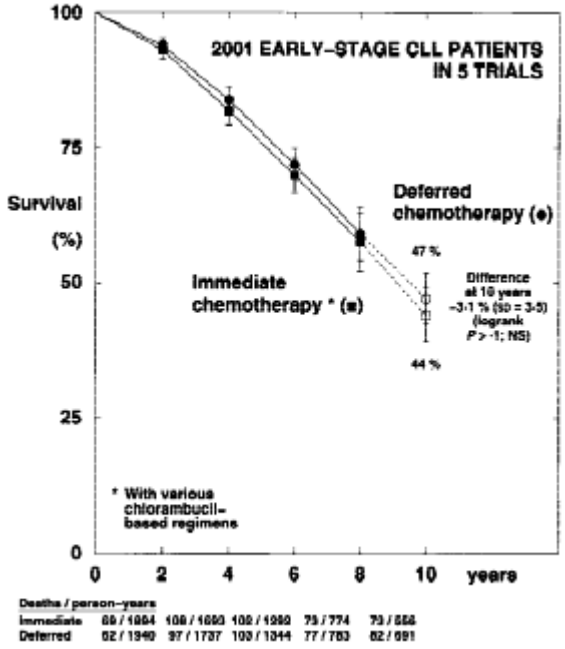
- Lymphocyte doubling time < 12 months
- Serum thymidine kinase > 10 U/l
- Unmutated IGHV
- Unfavorable cytogenetics (11q–, 17p–, tri 12)

Overall survival was not significantly different between HR-FCR and HR-W&W with 181 high-risk patients (90%) being alive at last follow-up. Both, HR-FCR and HR-W&W patients exhibited a significant shorter event-free and overall survival than LR-W&W patients.

[1]*Schweighofer, et al. ASH 2013; Abstract 524 (oral)*

Screen 2 Diagnosed with CLL, what would you do next

- Immediate vs deferred treatment



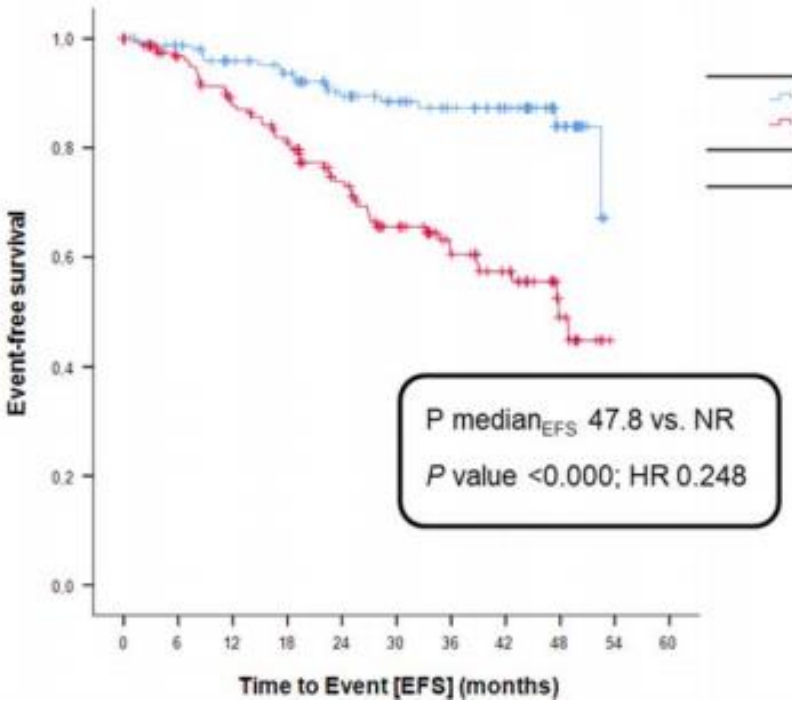
A meta-analysis of randomized trials. Survival rates in trials of immediate versus deferred treatment for chronic lymphocytic leukemia (CLL).[2]

[2]*CLL Trialists' Collaborative Group Journal of the National Cancer Institute, 1999;91(10):861-868*

Screen 1 Diagnosed with CLL, what would you do next ?

- Ibr vs watch and wait in CLL high risk[3]

Figure 1: Event-free survival (intention to treat population)



	total	events	N	%
Ibrutinib	182	18	164	90.1
Placebo	181	55	126	69.9
	363	73	290	79.9

Median observation time= 31 months

Placebo controlled double blinded phase III trial.
CLL Patients with intermediate, high and very high risk were randomized 1:1 to receive ibrutinib 420 mg per day or placebo. EFS was defined as time from randomization until occurrence of active disease according to iwCLL guidelines, new CLL treatment or death

[1]Primary endpoint was event free survival defined as time to symptomatic PD, new treatment and death.

[3]Langerbeins, et al. ICML 2019 Abstract OO7 (oral)

Post IT: infections and secondary malignancies

Risk of infection in W&W

	Cumulative incidence (95 % CI)
5-year cumulative incidence of infection (%)	31.2 (29.0-33.6)
5-year cumulative incidence of treatment (%)	21.9 (20.0-24.0)
5-year cumulative incidence of death (%)	4.9 (3.8-6.0)

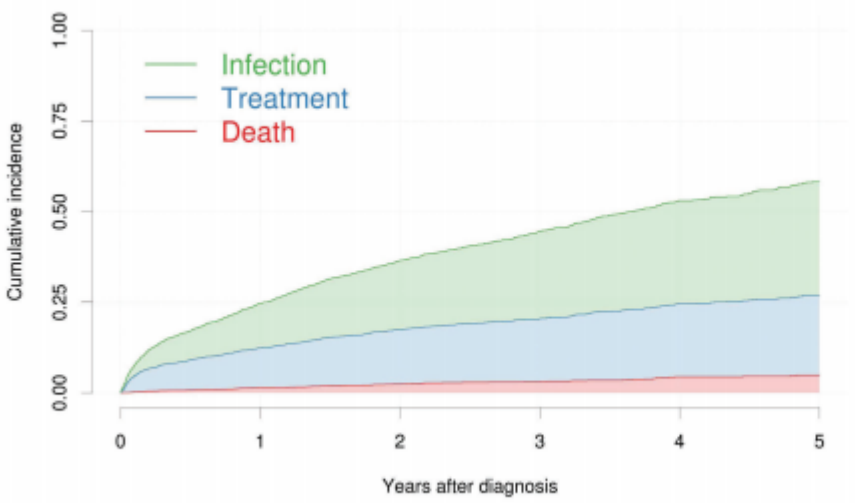
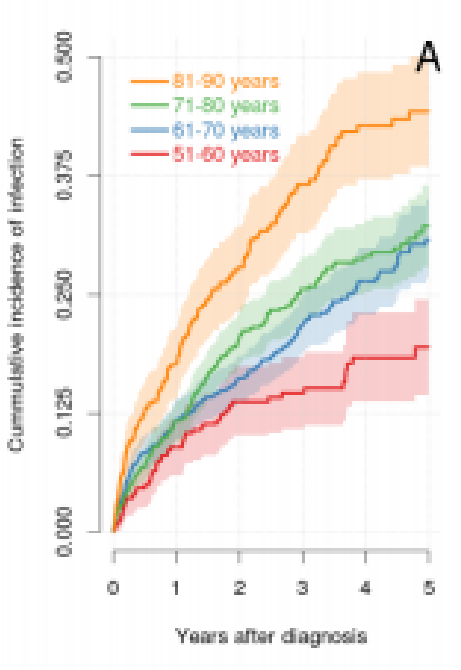


Figure 1 Cumulative incidence for all outcomes. Aalen-Johansen cumulative incidence estimates for the three outcomes stacked on top of each other. Each patient could only have one event, that being whichever came first. Thus, infections subsequent to treatment and *vice versa* were not included. Time zero is the time of diagnosis for all patients.



Andersen et al Haematologica 2018

BHS[1]

Screen Diagnosed with CLL, what would you do next

Supporting guidelines
Update

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

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

HOVON[2]

Screen Diagnosed with CLL, what would you do next

Supporting guidelines

Aanbevelingen

Stadiering volgens Rai en Binet (tabel 2)	(SORT A)
Vaststellen actieve ziekte (tabel 3)	(SORT A)
Vaststellen behandel indicatie (tabel 4)	(SORT A)

Tabel 2: Gereviseerde stadiering volgens Rai en Binet[3]

Stadium	Definitie	Mediane overleving#
Rai		
Laag risico		
Rai 0	Lymfocytose > 15 x 10^9/l	> 10 jaar
Intermediair risico		
Rai I	Lymfocytose en lymfadenopathie	> 8 jaar
Rai II	Lymfocytose en hepato/splenomegalie met/zonder lymfadenopathie	
Hoog risico		
Rai III	Lymfocytose en Hb < 6,9 mmol/l* met/zonder lymfadenopathie/organomegalie	6,5 jaar
Rai IV	Lymfocytose en trombocytopenie <100 x 10^9/l* met/zonder lymfadenopathie/organomegalie	
Binet		
Binet A	Hb ≥ 6,2 mmol/L, trombocyten ≥ 100 x 10^9/L, <3 lymfklierstations	> 10 jaar
Binet B	Hb ≥ 6,2 mmol/L, trombocyten ≥ 100 x 10^9/L, ≥ 3 lymfklierstations	> 8 jaar
Binet C	Hb < 6,2 mmol/L, trombocyten < 100 x 10^9/l*	6,5 jaar

** indien anemie en trombocytopenie niet veroorzaakt wordt door autoantistoffen*

 # op basis van studies zonder "nieuwe middelen"

[4] CLL richtlijn -2017 http://www.hovon.nl/behandeladvies/behandeladvies-leukemie/cll.html

Tabel 3: Criteria voor actieve ziekte[2]

Minstens 1 van de volgende criteria dient aanwezig te zijn:

1.	Minstens 1 van de volgende ziektegerelateerde symptomen: a. Gewichtsverlies ≥10% in voorafgaande 6 maanden b. Extreme vermoeidheid (WHO performance status ≥ 2) c. Koorts ≥38.6 °C gedurende ≥2 weken, in afwezigheid van infecties d. Nachtzweten gedurende meer dan een maand zonder aanwijzing voor infectie
2.	Toenemend beenmergfalen, zich uitend in ontwikkeling van of verergering van anemie en/of trombocytopenie
3.	Auto-immuun anemie en/of trombocytopenie die slecht reageert op behandeling met steroiden
4.	Massale (> 6 cm onder linker ribbenboog) of progressieve splenomegalie
5.	Massale klieren of pakketten (> 10 cm in grootste diameter) of progressieve lymfadenopathie
6.	Progressieve lymfocytose met een stijging > 50% binnen 2 maanden, of een geanticipeerde verdubbelingtijd van minder dan 6 maanden

Tabel 4: Indicaties voor start behandeling[2]

Behandeling Rai 0/ Binet A	Nee
Behandeling Rai I/II of Binet B	Mogelijk (indien actieve ziekte; zie tabel 3)
Behandeling Rai III/IV of Binet C	Ja

Onderbouwing

Achtergrond stadiering[2,3]

Het klinisch stadium volgens Rai en Binet, waarbij het ziekte stadium wordt gebaseerd op aan-of afwezigheid en uitgebreidheid van lymfadenopathie, spleno-en/of hepatomegalie en beenmergverdringing, wordt nog steeds gebruikt om mediane overleving te voorspellen en indicatie voor behandeling vast te stellen.[3] Bij uitgebreid ziektestadium is er altijd een behandelindicatie. Bij vroeg stadium ziekte is er alleen behandelindicatie, indien er actieve ziekte aanwezig is. De criteria voor actieve ziekte bestaan uit ziekte gerelateerde symptomen, beenmergfalen, refractaire auto-immuun anemie of trombocytopenie en de mate en progressie van splenomegalie, lymfadenopathie en lymfocytose.

[2] *CII richtlijn 2017* http://www.hovon.nl/upload/File/Richtlijnen_BehAdv/richtlijn-cll-hovon_20170607_def_0.pdf

iwCLL[3]

Screen Diagnosed with CLL ,What would you do next?

Supporting guidelines
Update

Table 2. Recommendations regarding indications for treatment in CLL

	General practice	Clinical trial
Treat with Rai stage 0	NGI*	RQ
Treat with Binet stage A	NGI*	RQ
Treat with Binet stage B or Rai stage I or II	Possible*	Possible*
Treat with Binet stage C or Rai stage III or IV†	Yes	Yes
Treatment of active/progressive disease	Yes	Yes
Treat without active/progressive disease	No	RQ

General practice is defined as the use of accepted treatment options for a CLL patient not enrolled on a clinical trial. Early therapy of CLL is generally not recommended outside of clinical trials; however, we recognize the need to conduct clinical trials testing the early use of novel agents.

RQ, research question.

*Treatment is indicated, if the disease is active as defined in section 4.

†Anemia and/or thrombocytopenia from CLL-unrelated causes should be excluded.

[3] *Hallek Blood 2018 Jun 21;131(25):2745-2760*

Screen Diagnosed with CLL, what would you do next

Supporting guidelines

- ESMO[4]

management of early disease stage

Binet stage A and B without active disease; Rai 0, I and II without active disease

Previous studies have shown that early treatment with chemotherapeutic agents does not translate into a survival advantage in patients with early-stage CLL [16]. The standard treatment of patients with early disease is a watch-and-wait strategy [I, A]. Blood cell counts and clinical examinations should be carried out every 3–12 months.

Due to the lack of clinical trials, no evidence-based treatment recommendation can be given for localised, early-stage SLL [I, A].

[4]*Eichhorst Annals of Oncology 2015;26(5): 78–84*

CASE 1 time point 2

Follow-up of patient

Non-votable

1. Who is doing the follow up?
2. Frequency of follow-up?
3. Which tests are required during follow-up ?

CASE 1 timepoint 3

Man, 62 years old
Weight: 79 kg
Height: 181 cm

Was diagnosed with CLL three years ago and has been in ‘watch and wait’ since. Three months ago his lymphocyte count was $25x10^9$/L
and this has raised to $70,4x10^9$/L

WBC $77,4x10^9$/L
Lymphocytes 90% ($70,4x10^9$/L)

Hb 11,5 g/dL (7,1 mmol/l)
Platelets $107x10^9$/L

Co-morbidities: sleep apneu, benign prostate hypertrophy

eGFR 87 mL/min

<u>Current medication:</u>
Omega 3 supplements
Vitamin supplements

Performance status – link naar slide 33 met performance status

CIRS – Link naar slide 34 met CIRS

Screen Patient profile changed, what would you do?

Performance status

Performance status

Table 1: ECOG Performance Status categories	
Grade	**Description**
0	**Fully active, able to carry on all pre-disease performance without restriction***
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self care, but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self care. Totally confined to bed chair
5	Dead

Screen Patient profile changed, what would you do?

CIRS

CIRS

	Severity				
1. **Heart diseases** (heart only)	0	1	2	3	4
2. **Hypertension** (severity should be evaluated. Involved organs should be considered separately)	0	1	2	3	4
3. **Vascular diseases** (blood, vessels, bone marrow, spleen, lymphatic system)	0	1	2	3	4
4. **Respiratory diseases** (lungs, bronchi, trachea under larynx)	0	1	2	3	4
5. **EENT** (eyes, ear, nose throat, larynx)	0	1	2	3	4
6. **Upper GI tract** (esophagus, stomach, duodenum, biliary tract, pancreas)	0	1	2	3	4
7. **Lower GI tract** (bowel, hernia)	0	1	2	3	4
8. **Liver diseases** (liver only)	0	1	2	3	4
9. **Renal diseases** (kidney only)	0	1	2	3	4
10. **Other genito-urinary diseases** (ureters, bladder, urethra, prostate, genitals)	0	1	2	3	4
11. **Musculo-skeletal system and skin** (muscles, bones, teguments)	0	1	2	3	4
12. **Nervous system diseases** (central and peripheral nervous system not including dementia)	0	1	2	3	4
13. **Endocrine-metabolic diseases** (diabetes, infections, sepsis, toxic state)	0	1	2	3	4
14. **Psychiatric-behavioural diseases** (dementia, depression, anxiety, agitation, psychosis)	0	1	2	3	4

CASE 1 time point 3

The patient profile has changed. What would you do based on these findings ?

votable

1. Start FCR
2. Start other treatment
3. I can not initiate treatment based on this information

Guidelines:

- BHS
- HOVON
- IwCLL
- ESMO

BHS[1]

Screen What Would you do next

Supporting guidelines
Update

BHS[1]

Diagnosis and risk stratification

Criteria to diagnose and stage SLL/CLL have not been changed. The only prognostic factor that predicts treatment resistance and has to be known before the start of treatment, is the presence or absence of a 17p deletion and/or a p53 mutation.

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.

Screen What Would you do next

Supporting guidelines

HOVON[2]

Onderzoek om de diagnose CLL te stellen

Aanbevelingen

Bloedonderzoek:

Hb, leukocyten, trombocyten, leukocytendifferentiatie

Immunofenotypering (zie tabel 1) (SORT C)

Tabel 1: Immunofenotypering bij CLL[1]

Minimaal vereist	
CD19	positief
CD20	doorgaans zwakke expressie
CD5	positief
CD23	positief
Kappa, Lambda	Zwakke expressie, afwijkende ratio
Additionele markers	
CD200	positief
CD43	positief
CD79b	zwak tot negatief

Onderbouwing

Achtergrondinformatie diagnostiek vooraf aan therapie[2]

Bij CLL is er sprake van lymfocytose met in de morfologie van het perifere bloed kapot gestreken lymfocyten en kleine lymfocyten met grumelée kernstructuur. Voor de diagnose CLL moet bij immunofenotypering het aantal circulerende monoklonale B cellen >5 x 10^9/l zijn en de immunofenotypering passend bij CLL(o.a. CD19-positief, CD5-positief, CD23-positief) De diagnose kleincellig lymfocytair lymfoom ('small lymphocytic lymphoma'= SLL) kan gesteld worden, wanneer er lymfadenopathie en/of splenomegalie is, het aantal circulerende monoklonale B cellen < 5 x 10^9/l is en in de lymfklier een celbeeld met lymfoide cellen met grumelée kernstructuur in combinatie met bij CLL/SLL passende immunofenotypering gezien wordt. Indien het aantal circulerende monoklonale B cellen <5 x 10^9/l is, er geen lymfadenopathie of organomegalie is, er geen cytopenie en geen ziektegerelateerde symptomen zijn, dan is er sprake van monoklonale B-lymfocytose.

[1] *CLL richtlijn -2017 http://www.hovon.nl/behandeladvies/behandeladvies-leukemie/cll.html*

Onderzoek vooraf aan therapie

Aanbevelingen

Anamnese:

niveau van functioneren ("WHO performance"-score), koorts, gewichtsverlies, nachtzweten en infecties

Lichamelijk onderzoek:

vastleggen van grootte van lymfklieren, lever en milt

Bloedonderzoek: (SORT C)

- Hb, leukocyten, trombocyten, leukocytendifferentiatie
- Nierfunctie, leverfunctie, immuunglobulines, directe antiglobuline test
- Serologie hepatitis B, hepatitis C, HIV
- Cytogenetica (FISH of Comparative genomic hybridization (CGH)-array) voor del (13q), del (11q), del (17p), trisomie 12
- Moleculair onderzoek aanwezigheid TP53-mutatie (tenminste exon 4-10, bij voorkeur bepaald in een ERIC gecertificeerd laboratorium)

Beenmergonderzoek indien trombocytopenie of anemie

(vraagstelling: verdringing of auto-immuun afbraak)

Beeldvorming:

Expert opinion werkgroep:

X thorax (vraagstelling lymfadenopathie, aanwijzing voor infectie, andere longafwijkingen) (SORT C)

Expert opinion werkgroep:

CT hals, thorax, abdomen (achterwege laten indien geen consequenties voor respons evaluatie) (SORT C)

Achtergrondinformatie diagnostiek vooraf aan therapie[2]

Aanvullend onderzoek is erop gericht om stadium van de ziekte vast te stellen, complicaties van de ziekte in kaart te brengen (hemolyse, auto-immuun trombocytopenie, hypogammaglobulinemie) prognostische markers te verkrijgen (Cytogenetisch en moleculair onderzoek) en eventuele actieve of chronische infecties (hepatitis B, C), die kunnen verergeren door de behandeling met monoklonale antistoffen, te diagnosticeren. Beenmergonderzoek kan geïndiceerd zijn ter differentiatie van anemie of trombocytopenie als gevolg van beenmerg-verdringing of door auto-immuun afbraak. In de dagelijkse praktijk kan radiologische beeldvorming zeer beperkt blijven indien bij lichamelijk onderzoek lymfadenopathie en lever-en miltgrootte goed vast te leggen zijn. In studieverband is uitgebreidere beeldvorming (CT hals, thorax, abdomen) veelal wel noodzakelijk ten behoeve van nauwkeurige responsevaluatie.

[2] *Cll richtlijn 2017* http://www.hovon.nl/upload/File/Richtlijnen_BehAdv/richtlijn-cll-hovon_20170607_def_0.pdf

Screen What Would you do next

iwCLL[3]

Supporting guidelines Update

Table 1. Baseline evaluation of patients with CLL

Diagnostic test	General practice	Clinical trial
Tests to establish the diagnosis		
CBC and differential count	Always	Always
Immunophenotyping of peripheral blood lymphocytes	Always	Always
Assessment before treatment		
History and physical, performance status	Always	Always
CBC and differential count	Always	Always
Marrow aspirate and biopsy	When clinically indicated (unclear cytopenia)	Desirable
Serum chemistry, serum immunoglobulin, and direct antiglobulin test	Always	Always
Chest radiograph	Always	Always
Infectious disease status	Always	Always
Additional tests before treatment		
Molecular cytogenetics (FISH) for del(13q), del(11q), del(17p), add(12) in peripheral blood lymphocytes	Always	Always
Conventional karyotyping in peripheral blood lymphocytes (with specific stimulation)	NGI*	Desirable
TP53 mutation	Always	Always
IGHV mutational status	Always	Always
Serum β_2-microglobulin	Desirable	Always
CT scan of chest, abdomen, and pelvis	NGI	Desirable
MRI, PET scans	NGI	NGI
Abdominal ultrasound†	Possible	NGI

General practice is defined as the use of accepted treatment options for a CLL patient not enrolled on a clinical trial.

CBC, complete blood count; MRI, magnetic resonance imaging; NGI, not generally indicated; PET, positron emission tomography.

*Conventional karyotyping in peripheral blood lymphocytes (with specific stimulation) may be useful before therapy, if established methodology is available.

†Used in some countries to monitor lymphadenopathy and organomegaly.

[3] *Hallek Blood 2018 Jun 21;131(25):2745-2760*

ESMO[4]

Screen

Patient profile changed, what would you do

Supporting guidelines

Table 1. Diagnostic and staging work-up

	Pretreatment evaluation	Response evaluation
History, physical examination and performance status	+	+
Complete blood count and differential	+	+
Serum chemistry including serum immunoglobulin and direct antiglobulin test	+	+
Cytogenetics (FISH) for del (17p)/ molecular genetics for *TP53* mutation	+	–
Marrow aspirate and biopsy	+[a]	+[b]
Hepatitis B and C, CMV and HIV serology	+	–

[a]Only if clinically indicated.
[b]Only for confirmation of CR within clinical studies.
FISH, fluorescence *in situ* hybridisation; CMV, cytomegalovirus; HIV, human immunodeficiency virus; CR, complete remission.

The following additional examinations before treatment are desirable [III, B] [1]:

- Although a bone marrow biopsy is not required for diagnosis, it is recommended for the diagnostic evaluation of unclear cytopaenias, or FISH or molecular genetics if peripheral blood cell lymphocytosis does not allow adequate immunophenotyping
- An extended FISH analysis is recommended before the start of therapy because the detection of additional cytogenetic abnormalities [del(11q) or trisomy 12] may have therapeutic consequences
- Molecular analysis for detecting immunoglobulin heavy chain variable (IGHV) mutation status and better estimation of duration of response
- Imaging studies by computed tomography (CT) scans may be helpful to assess the tumour load or to determine the cause of unclear symptoms in individual patients, but they should not generally be used in asymptomatic patients or for clinical staging. In addition, CT scans may be useful for baseline and final assessment in clinical trials [III, C]. In elderly patients, abdominal ultrasound might be considered instead.

[4]*Eichhorst Annals of Oncology 2015;26(5): 78–84*

CASE 1 time point 3

Which test would provide you with the most valuable information to initiate treatment for this patient?

votable

1. Del17p
   See assets
2. TP53 mutation
   See assets
3. IGHV mutational status
   See assets
4. Option 1, 2, 3
5. Other tests

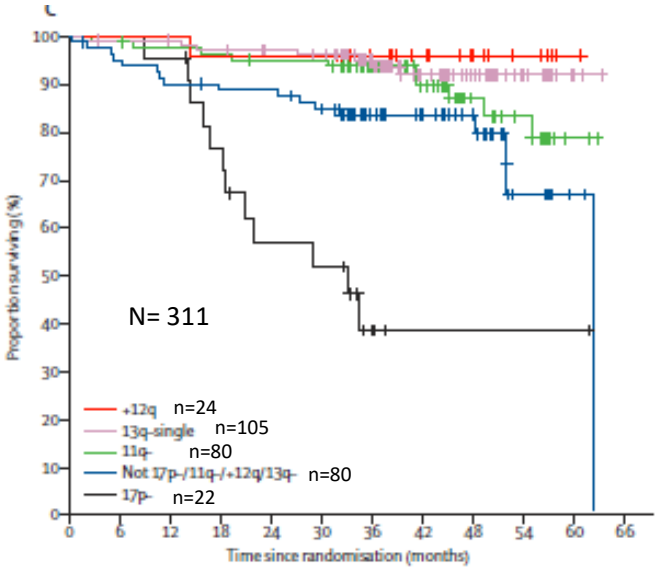
Guidelines:
- BHS
- HOVON
- ERIC

Screen 1 Which test would provide the most valuable information

- FISH (del 17p)

CLL8: FCR vs FC in treatment naive CLL patients

A prospective, randomised, open-label, phase 3 study. Treatment-naïve patients (diagnosed with immunophenotypically confi rmed chronic lymphocytic leukaemia)in Binet stage C, or with confirmed active disease in Binet stages A or B. N= 817

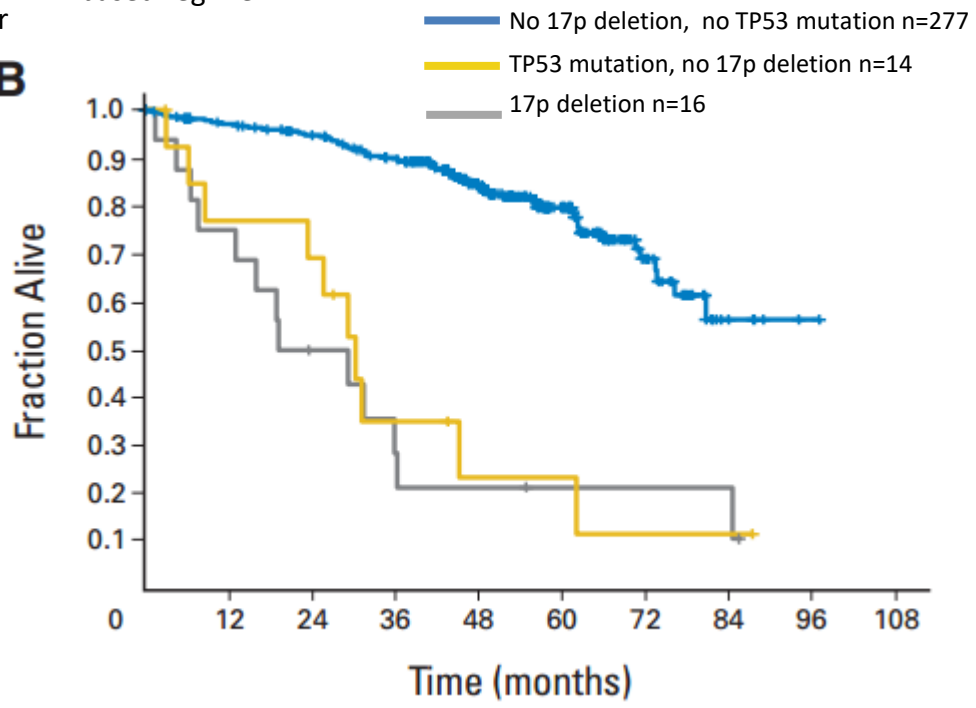


OS# according to genetic subgroups in FCR treated patients[1]

CLL4: FC vs F in treatment naive CLL patients

TP53 mutations were assessed by denaturing high-performance liquid chromatography (exons 2 to 11) in a randomized prospective trial (n 375) with a follow-up of 52.8 months (German CLL Study Group CLL4 trial; fludarabine [F] v F cyclophosphamide [FC]).

OS# according to genetic subgroups in patient treated with F-based regimen[2]



[1]*Hallek, Lancet 2010; 376: 1164–74*

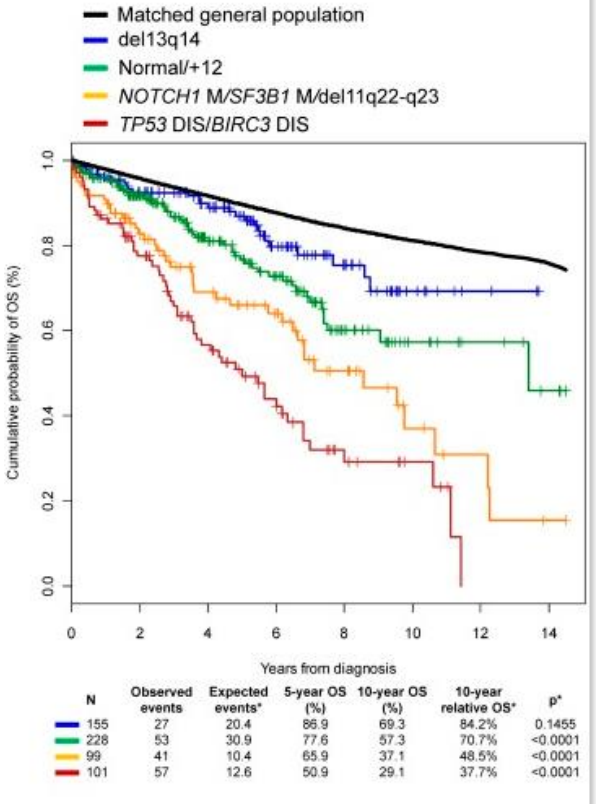
[2]*Zenz* J Clin Oncol 2010;28:4473-4479

Screen 2 Which test would provide the most valuable information

- TP53 mutation

OS* based on an integrated mutational and cytogenetic model

An integrating mutational and cytogenetic model was used to predict the overal survival using both a training validation (n= 583) and a time-dependent design in newly diagnosed and previously untreated CLL



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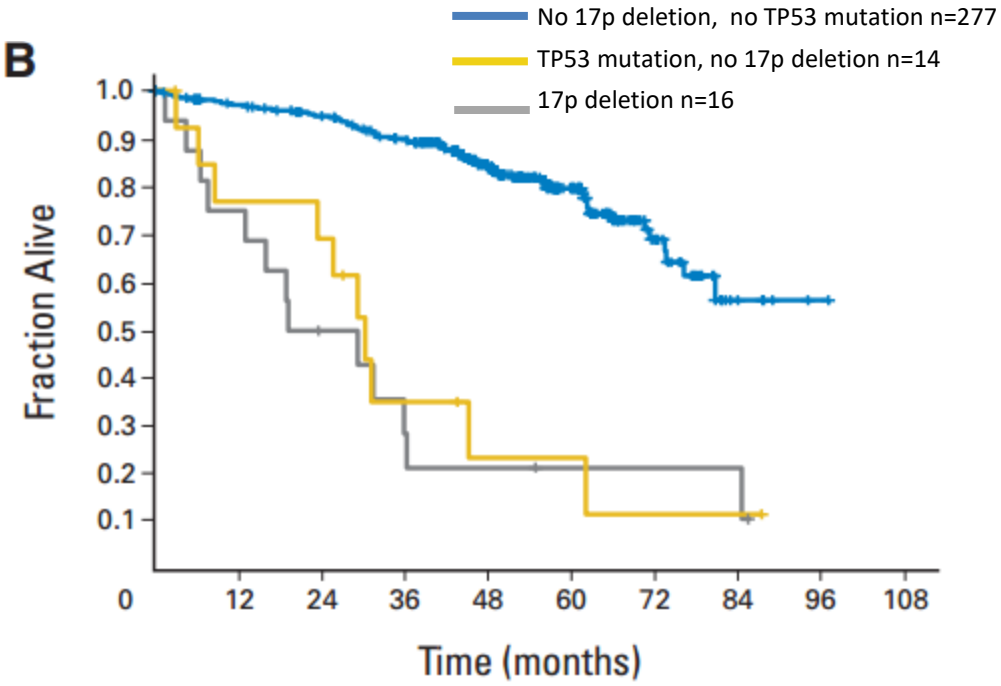
OS# according to genetic subgroups in patient treated with F-based regimen[2]



**Primary endpoint #secondary endpoint*

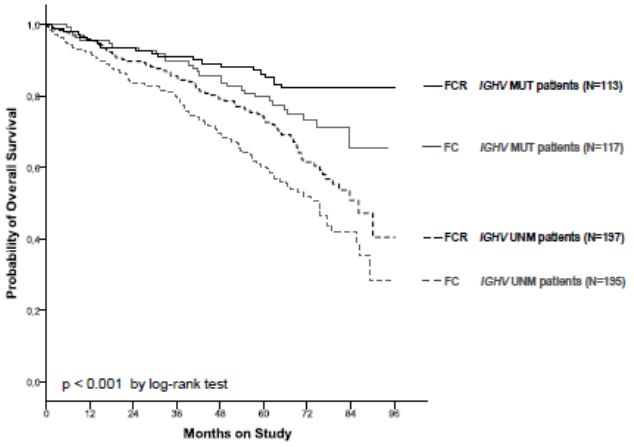
[1] *Rossi Blood 2013; 121:1403-1412*
[2] *Zenz* J Clin Oncol 2010;28:4473-4479

Screen 3 Which test would provide the most valuable information

- Mutational status IGHV

Overall survival[#] in both treatment arms and IGHV MUT and UNM patients[1]

A prospective, randomised, open-label, phase 3 study. Treatment-naive patients (diagnosed with immunophenotypically confirmed chronic lymphocytic leukemia)in Binet stage C, or with confirmed active disease in Binet stages A or B. N= 817

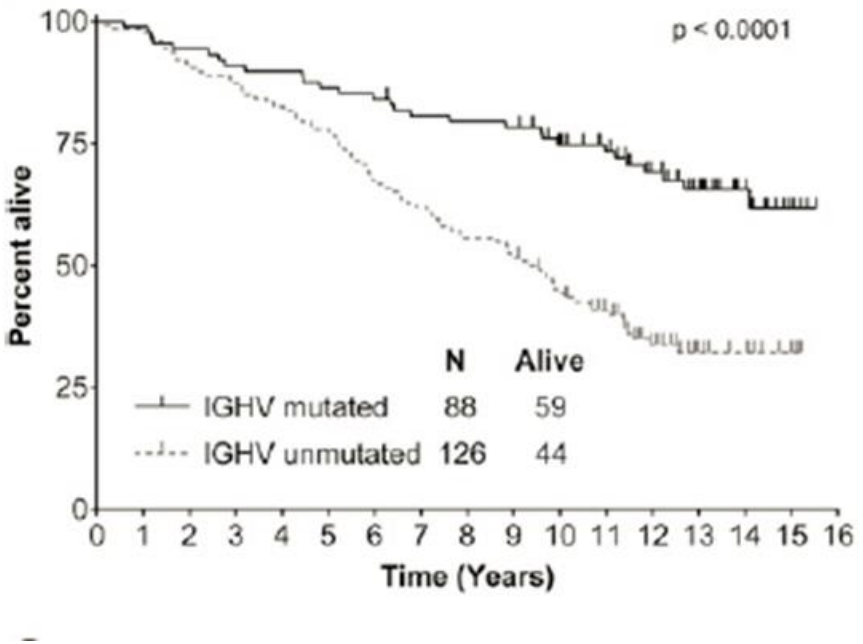


Number at risk	0	12	24	36	48	60	72	84	96
FCR *IGHV* MUT	113	106	104	100	96	89	47	20	1
FC *IGHV* MUT	117	105	96	91	86	76	38	12	0
FCR *IGHV* UNM	197	189	174	161	148	132	67	18	1
FC *IGHV* UNM	195	170	149	137	113	92	45	18	1

[#]secondary endpoint

Estimates of overall survival[#] according to pretreatment mutation status of FCR patients[2]

Post hoc analysis of a single-arm phase II study of FCR as initial therapy in 300 patients with progressive or advanced CLL. Associations between pretreatment characteristics and achievement of CR and MRD-negativity was evaluated



[1]Fischer Blood. 2016;127:208-15

Screen 5 **Which test would provide the most valuable information**

- Other tests

BHS[1]

Screen

Which test is the most valuable for treatment decision

Supporting guidelines

Update

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	

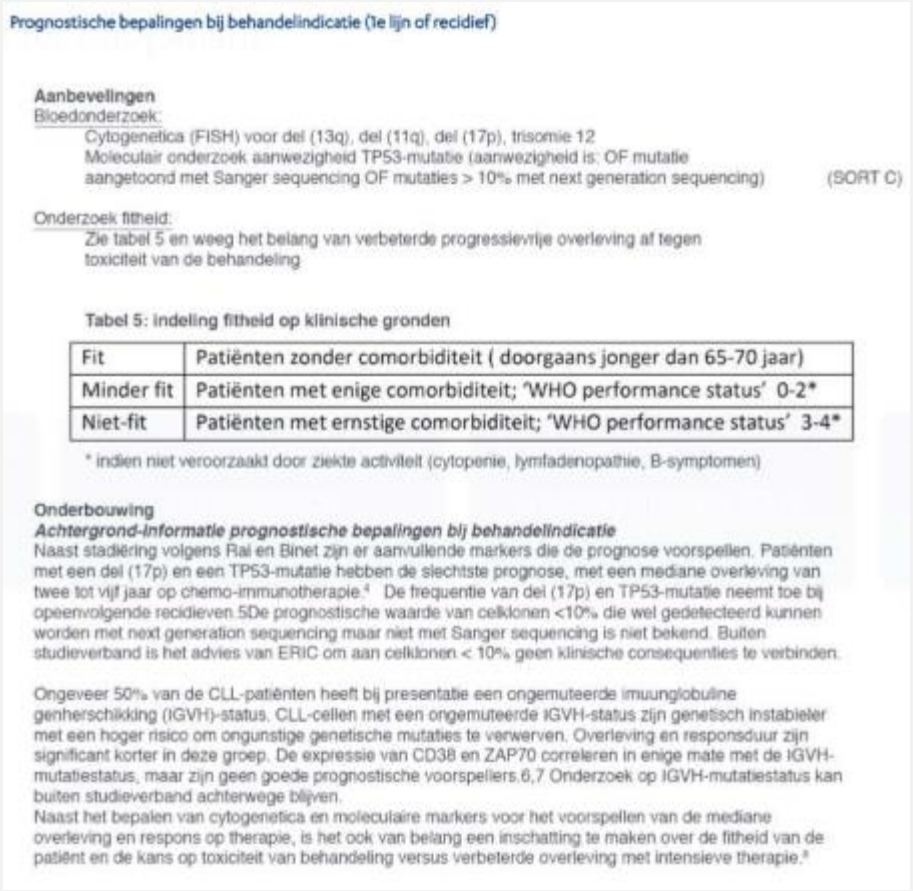
Janssens et al. Updated BHS guidelines for the diagnosis and treatment of CLL. BJH 2020.

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

HOVON[2]

Screen Which test is the most valuable for treatment decision

Supporting guidelines



Prognostische bepalingen bij behandelindicatie (1e lijn of recidief)

Aanbevelingen

Bloedonderzoek:

Cytogenetica (FISH) voor del (13q), del (11q), del (17p), trisomie 12
Moleculair onderzoek aanwezigheid TP53-mutatie (aanwezigheid is: OF mutatie aangetoond met Sanger sequencing OF mutaties > 10% met next generation sequencing) (SORT C)

Onderzoek fitheid:

Zie tabel 5 en weeg het belang van verbeterde progressievrije overleving af tegen toxiciteit van de behandeling

Tabel 5: indeling fitheid op klinische gronden

Fit	Patiënten zonder comorbiditeit (doorgaans jonger dan 65-70 jaar)
Minder fit	Patiënten met enige comorbiditeit; 'WHO performance status' 0-2*
Niet-fit	Patiënten met ernstige comorbiditeit; 'WHO performance status' 3-4*

* indien niet veroorzaakt door ziekte activiteit (cytopenie, lymfadenopathie, B-symptomen)

Onderbouwing

Achtergrond-informatie prognostische bepalingen bij behandelindicatie

Naast stadiëring volgens Rai en Binet zijn er aanvullende markers die de prognose voorspellen. Patiënten met een del (17p) en een TP53-mutatie hebben de slechtste prognose, met een mediane overleving van twee tot vijf jaar op chemo-immunotherapie.[4] De frequentie van del (17p) en TP53-mutatie neemt toe bij opeenvolgende recidieven.5De prognostische waarde van cellonen <10% die wel gedetecteerd kunnen worden met next generation sequencing maar niet met Sanger sequencing is niet bekend. Buiten studieverband is het advies van ERIC om aan cellonen < 10% geen klinische consequenties te verbinden.

Ongeveer 50% van de CLL-patiënten heeft bij presentatie een ongemuteerde imuunglobuline genherschikking (IGVH)-status. CLL-cellen met een ongemuteerde IGVH-status zijn genetisch instabieler met een hoger risico om ongunstige genetische mutaties te verwerven. Overleving en responsduur zijn significant korter in deze groep. De expressie van CD38 en ZAP70 correleren in enige mate met de IGVH-mutatiestatus, maar zijn geen goede prognostische voorspellers.6,7 Onderzoek op IGVH-mutatiestatus kan buiten studieverband achterwege blijven.

Naast het bepalen van cytogenetica en moleculaire markers voor het voorspellen van de mediane overleving en respons op therapie, is het ook van belang een inschatting te maken over de fitheid van de patiënt en de kans op toxiciteit van behandeling versus verbeterde overleving met intensieve therapie.[3]

[2]*Cll richtlijn 2017* http://www.hovon.nl/upload/File/Richtlijnen_BehAdv/richtlijn-cll-hovon_20170607_def_0.pdf

Eric

Screen

Which test is the most valuable for treatment decision

Supporting guidelines
Update

Determining the SHM level is important, not only for general assessment of the disease course in CLL, but also for guiding treatment decisions: put simply, it is not only a prognostic test, but also a predictive test for the use of certain therapies, such as FCR.

Rosenquist et al. Leukemia 2017; 31: 1477-1481

Screen Patient profile changed, what would you do?

Results

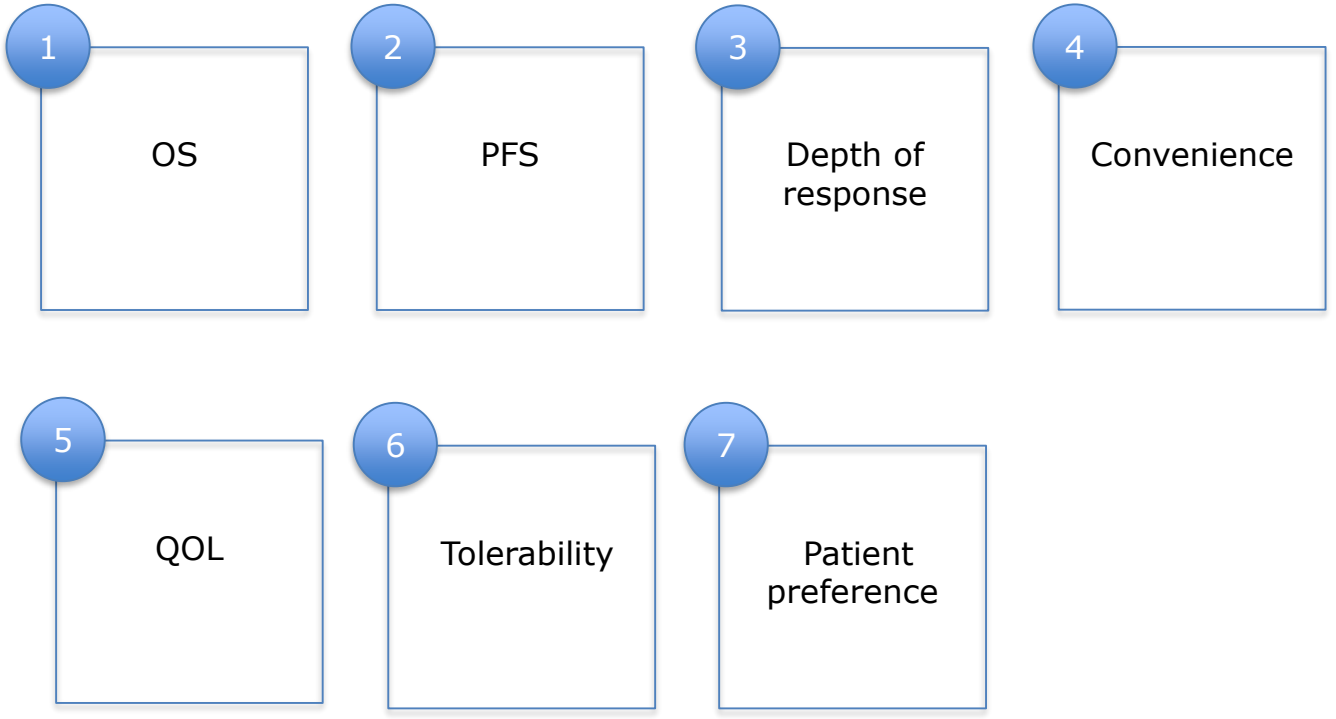
No del17P/TP53 and

IGHV mutation status: mutated

This patient needs treatment, what would drive your decision making?

CASE 1 – timepoint 3

Votable



With the information you have now what treatment would you initiate?

CASE 1 – timepoint 3

Votable

Picture of patient

Performance status

CIRS

No Del 17P/TP53
IGHV Mutated

1

FCR

CLL 8; CLL10
ECOG1912

2

BR

CLL10

3

Ibrutinib R

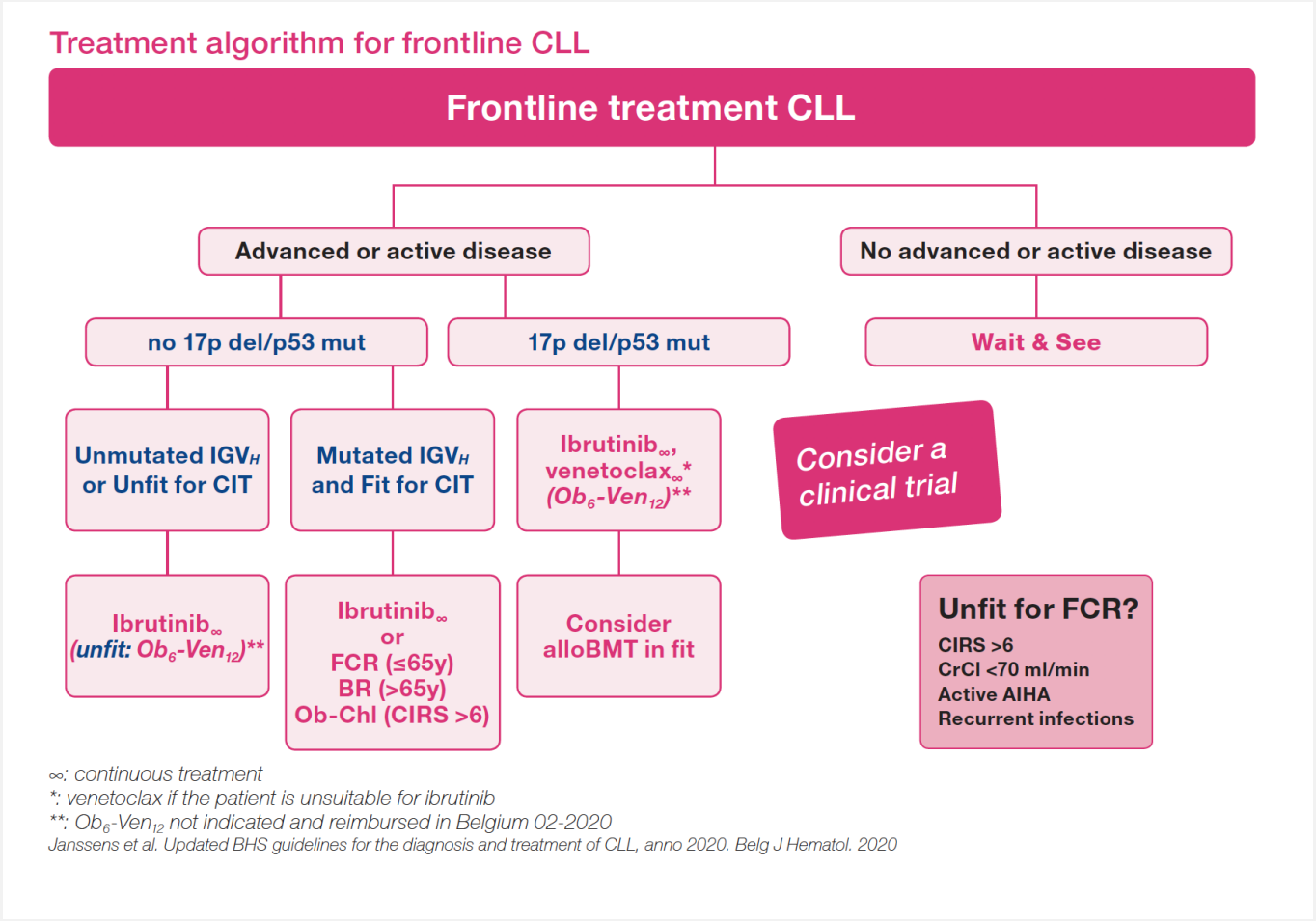
ECOG1912

BHS
HOVON
Hallek
EHA/ESMO

BHS[1]

Screen With the information you have now what treatment would you initiate?

Supporting guidelines update

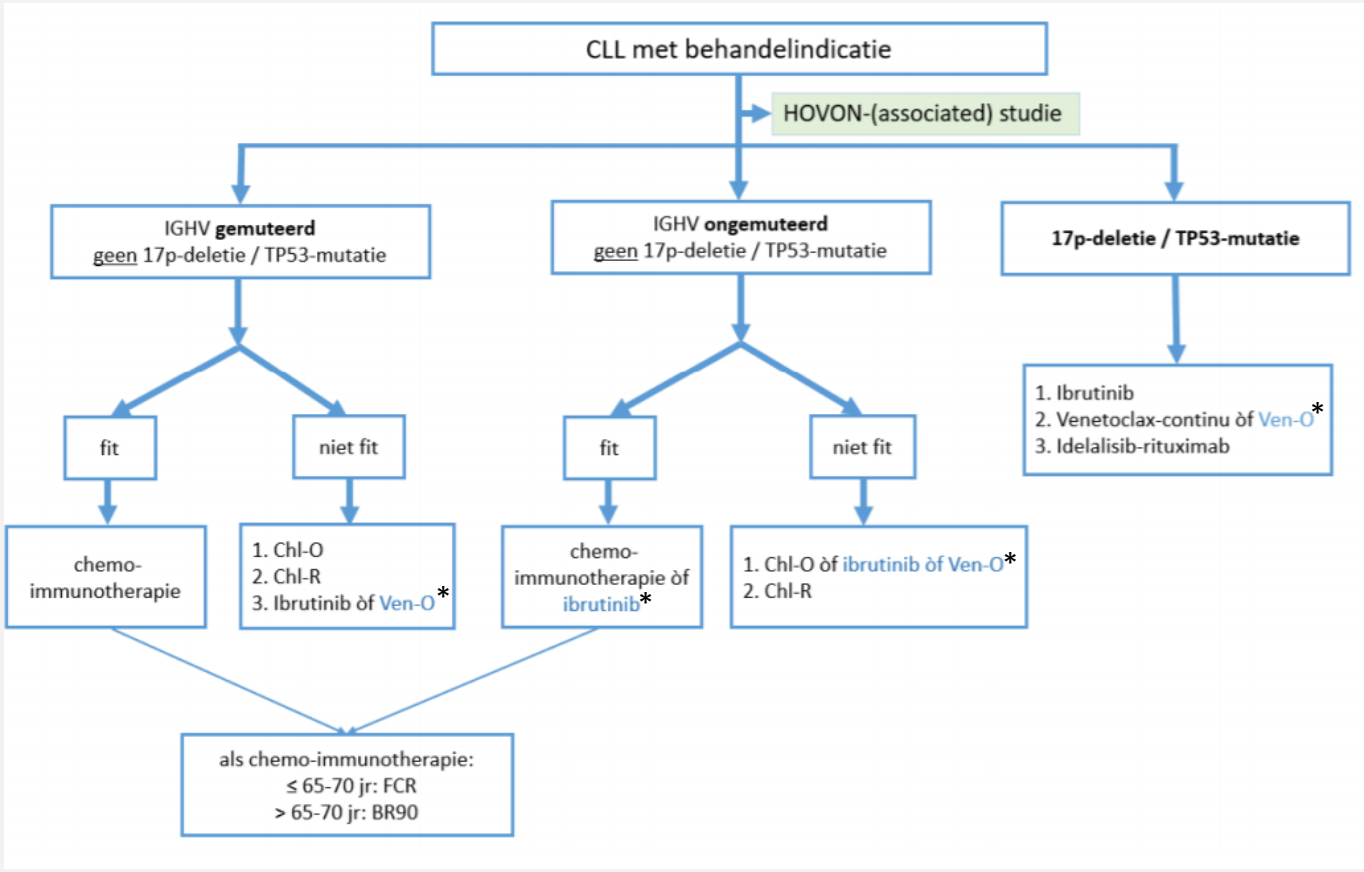


[1] *Janssens et al. Updated BHS guidelines for the diagnosis and treatment of CLL. BJH 2020*

HOVON[2]

Screen With the information you have now what treatment would you initiate?

Supporting guidelines update



*Deze medicatie kan op dit moment nog niet voorgeschreven worden, omdat het ófwel nog niet vergoed wordt ófwel nog geen “indicatie” heeft gekregen.

[2]HOVON CLL Concept richtlijn 2019 http://www.hovon.nl/behandeladvies/behandeladvies-leukemie/cll.html

Hallek[3]

Screen With the information you have now what treatment would you initiate?

Supporting guidelines update

CLL first line treatment (updated June 2019)

Stage	del(17p) or p53mut	Fitness	IGVH	Therapy
Binet A-B, Rai 0-II, inactive disease	Irrelevant	Irrelevant	Irrelevant	None
Active disease or Binet C or Rai III-IV	Yes	Irrelevant	Irrelevant	Ibrutinib or Venetoclax + Obinutuzumab or Idelalisib + Rituximab (if contraindications for ibrutinib)*
	No	Go go	M	FCR (BR above 65 years) or ibrutinib*
			U	Ibrutinib or FCR (BR above 65 years)*
		Slow go	M	Venetoclax + Obinutuzumab or Chlorambucil + Obinutuzumab or Ibrutinib*
			U	Venetoclax + Obinutuzumab or Ibrutinib or Chlorambucil + Obinutuzumab*

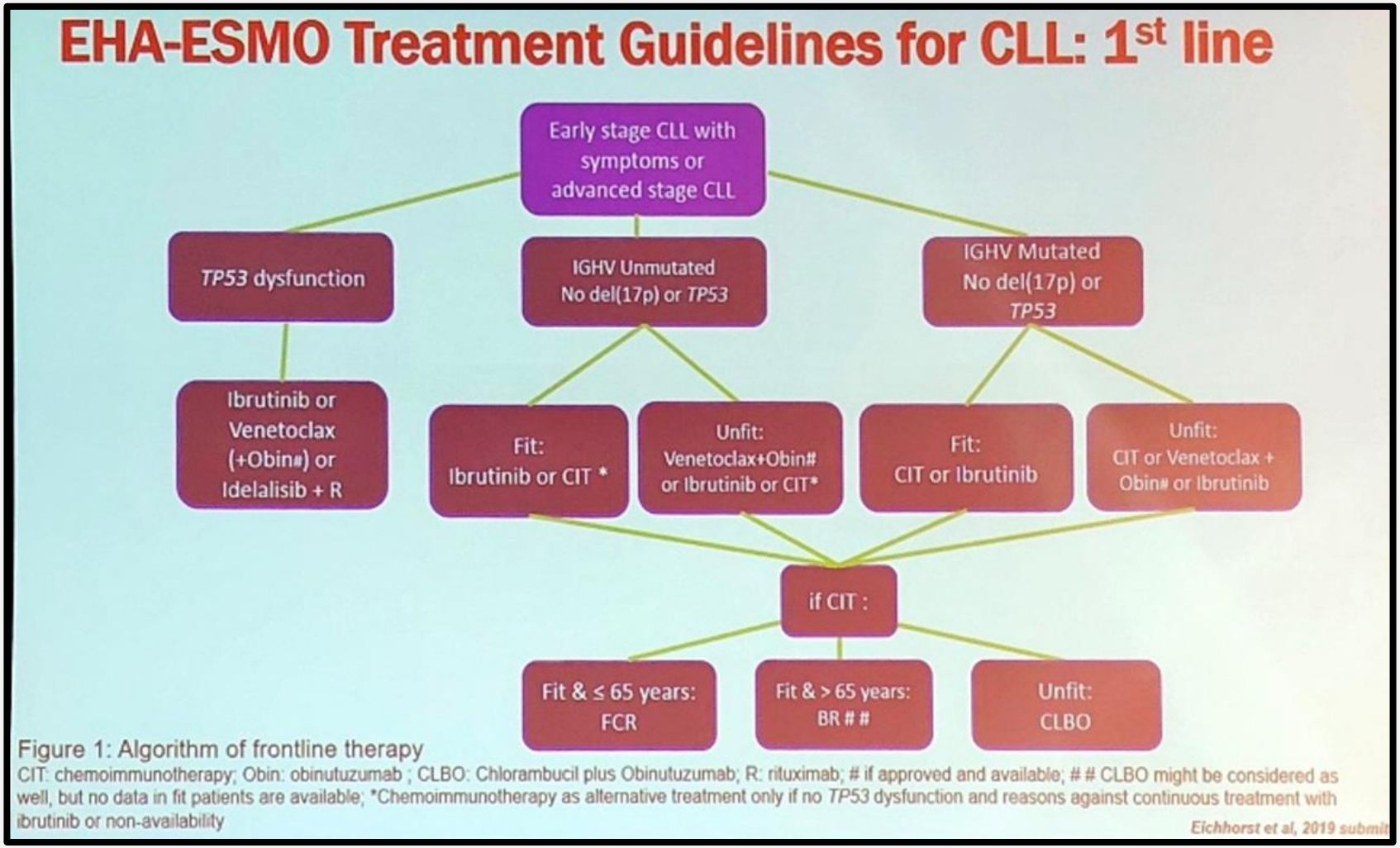
* Consider and discuss with patient: long-term vs fixed (6-12 m) duration therapy, lack of convincing evidence of overall survival differences, specific side effects of each therapeutic option (myelosuppression, infections, secondary malignancies for CIT; cardiac toxicity, bleeding and autoimmune disease for Ibru; TLS and infections for Ven-Obi; autoimmune disease (diarrhea) and opportunistic infections for Idelalisib).

[3]Hallek M. Am. J. Hematol. 2019; 94:1266-1287

EHA/ESMO[4]

Screen With the information you have now what treatment would you initiate?

Supporting guidelines update



[4]Eichhorst et al. 2019 submitted

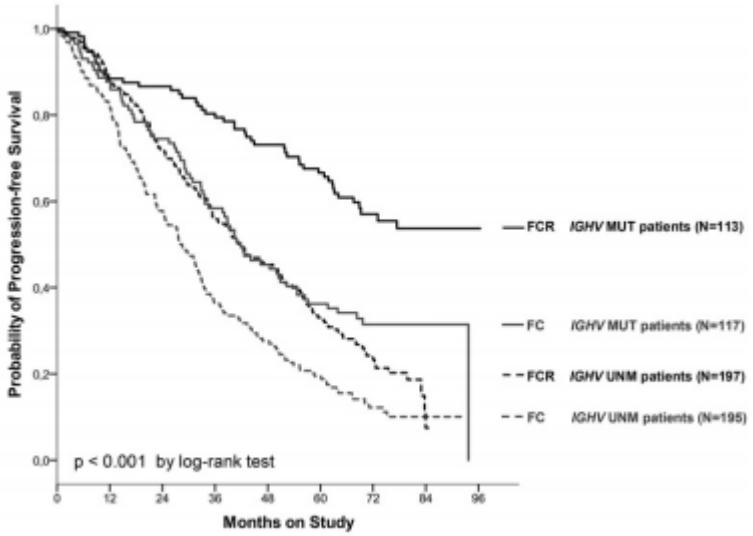
Screen 1 With the information you have now what treatment would you initiate?

FCR

Multicenter Phase III RCT reporting safety and efficacy of FC and FCR treatment of 817 treatment-naïve patients with CLL. With a median follow-up of 5.9 years.

Median PFS was significant longer in the FCR group (56.8 months) than in the FC group (32.9 months) P =0.001*

PFS by IGHV mutation status#



*Primary endpoint #secondary endpoint

Longterm safety data

Long-term safety	FC Cases N (%)	FC Patients N (%)	FCR Cases N (%)	FCR Patients N (%)
Total patients (safety population), N		396		404
Total cases [N (%)] and patients [N (%)] with ≥1 SPM	77 (57)	69 (17)	59 (43)	53 (13)
Secondary malignancies				
Richter's transformation	25 (33)	25 (6)	13 (22)	13 (3)
Solid tumors	29 (38)	28 (7)	26 (44)	24 (6)
Lung	13/29 (45)	13 (3)	5/26 (20)	5 (1)
Prostate	2/29 (7)	2 (1)	6/26 (23)	6 (2)
Renal/bladder	3/29 (10)	3 (1)	4/26 (15)	3 (1)
Colorectal	0/29 (0)	0 (0)	2/26 (8)	2 (<1)
Melanoma	3/29 (10)	3 (1)	5/26 (20)	5 (1)
Breast	1/29 (3)	1 (<1)	2/26 (8)	2 (<1)
Pancreatic	1/29 (3)	1 (<1)	1/26 (4)	1 (<1)
Ovarian/uterine/cervical	0/29 (0)	0 (0)	1/26 (4)	1 (<1)
Liver/gall bladder	1/29 (3)	1 (<1)	0/26 (0)	0 (0)
Thyroid	2/29 (7)	2 (1)	0/26 (0)	0 (0)
Pharyngeal/laryngeal	1/29 (3)	1 (<1)	0/26 (0)	0 (0)
Other	2/29 (7)	2 (1)	0/26 (0)	0 (0)
Hematologic neoplasia	11 (14)	11 (3)	13 (22)	12 (3)
AML/MDS	7/11 (64)	7 (2)	7/13 (54)	6 (2)
Indolent B-non-Hodgkin lymphoma	1/11 (9)	1 (<1)	2/13 (16)	2 (<1)
Aggressive B-non-Hodgkin lymphoma	1/11 (9)	1 (<1)	1/13 (8)	1 (<1)
ALL	0/11 (0)	0 (0)	1/13 (8)	1 (<1)
CML	0/11 (0)	0 (0)	1/13 (8)	1 (<1)
Other	2/11 (18)	2 (<1)	1/13 (8)	1 (<1)
Basalioma, squamous cell	12 (16)	11 (3)	7 (12)	6 (2)
Prolonged neutropenia				
2 months after end of treatment		34 (9)		67 (17)
12 months after end of treatment		14 (4)		16 (4)

Fischer et al. Blood 2016; 127 (2): 208-215

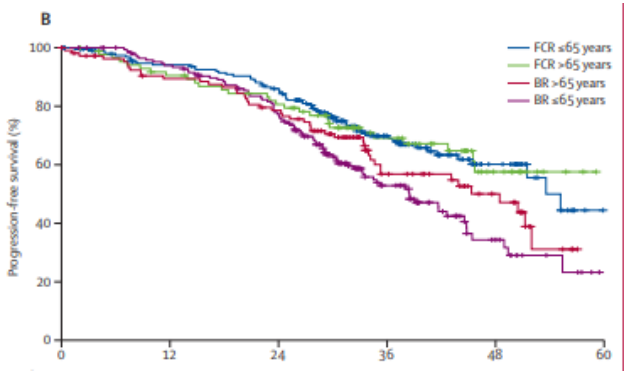
Screen 1 & 2 With the information you have now what treatment would you initiate?

BR

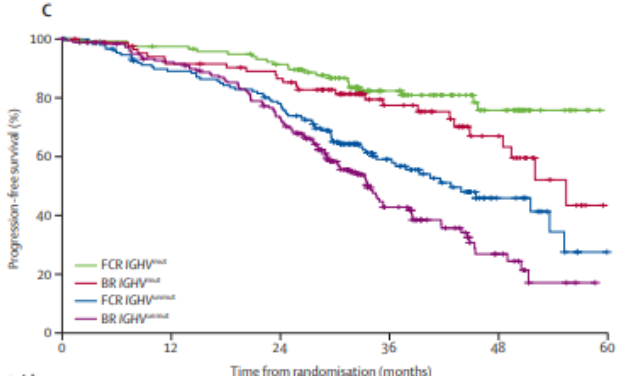
Multicenter phase III RCT with Treatment naive CLL patients without del17P and good physical fitness (Cirs ≤6, CCL ≥ 70ml/min) who were randomized to FCR or BR.

The median observation time for all patients was 35.9 months .Median progression-free survival was 41·7 months with BR and 55·2 months with FCR*

PFS by age#



PFS by IGHV mutation status#



*Primary endpoint
#secondary endpoint

Adverse events	FCR(%) N= 279	BR (%) N= 278	P value
Neutropenia	87.7	67.8	< 0.001
Anemia	14.2	12.0	0.46
Thrombocytopenia	22.4	16.5	0.096
Severe Infection	39.8	25.4	0.001
sec. Neoplasm	6.1	3.6	0.244

Eichhorst et al. Lancet Oncol 2016; 17: 928–42

Screen 3 With the information you have now what treatment would you initiate? IR

A randomized, phase 3 study of IR vs FCR in 529 patients 70 years of age or younger with previously untreated TN CLL . Median FU: 33.6 mo

**Primary endpoint #secondary endpoint ˜ subgroup analysis*

@ 3 years	IR (%)	FCR (%)	HR [95%CI]	P value
PFS*	89.4	72.9	0.35 [0.22 - 0.56]	<0.001
OS#	98.8	91.5	0.17 [0.0 - 0.54]	<0.001
PFS IGHV mutated˜	87.7	88	0.44 [0.14 - 1.36]	NR
PFS IGHV Unmutate˜	90.7	62.5	0.26 [0.14 - 0.50]	NR

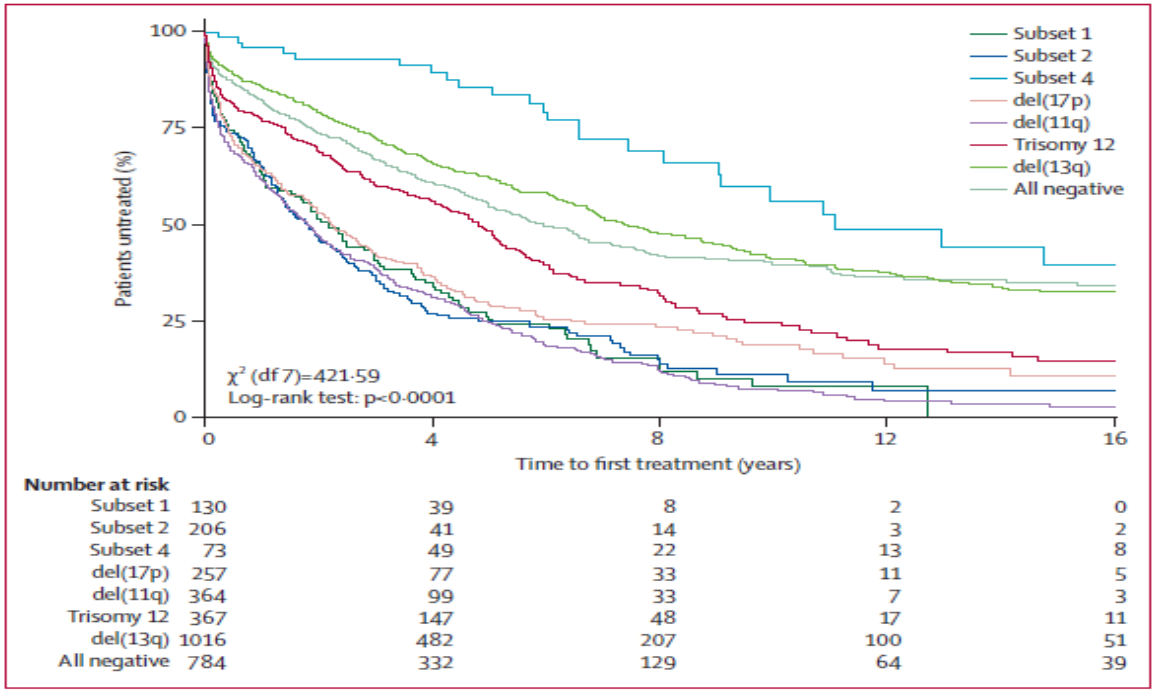
Safety	IR (%)	FCR (%)	P VALUE
All AE Grade ≥3 Regardless of attribution	80.1	79.7	= 0.91
Grade ≥3 Neutropenia	25.6	44.9	<0.001
Grade ≥3 infections+	9.4	9.5	<0.005
Grade ≥3 hypertensions ˜	18.8	8.2	= 0.002
Grade ≥3 Hemorrhage	1.1	0	P = 0.32
Grade ≥3 cardiac events	6.5	1.9	NR
Grade ≥3 atrial fibrillation	3.1	1.3	NR

+Percent of infection complications was lower in the IR arm than in the FCR arm, specifically neutropenic fever (10.5% vs. 20.3%).

Shanafelt TD et al. N Engl J Med. 2019;381:432-43

POST-IT 1 What if patient had a mutated IGHV but subset #2

CASE 1 – timepoint 3



Number at risk

Subset 1	130	39	8	2	0
Subset 2	206	41	14	3	2
Subset 4	73	49	22	13	8
del(17p)	257	77	33	11	5
del(11q)	364	99	33	7	3
Trisomy 12	367	147	48	17	11
del(13q)	1016	482	207	100	51
All negative	784	332	129	64	39

Figure 4: **Immunogenetics refines risk stratification of chronic lymphocytic leukaemia beyond cytogenetic aberrations**

Especially noteworthy in this respect was subset 2, for which we recorded a pronounced clinical aggressiveness that is independent of IGHV gene mutational status and similar to cases with TP53 aberrations, despite the fact that affected patients rarely harbour such abnormalities.

[1] *Baliakas Lancet 2014*

POST-IT 2 not all IGHV3-21 CLL are equal

"Within our series, 437/8593 cases (5%) expressed IGHV3-21 BcR IG.
Of these, 254 (58%) were assigned to subset #2 as they shared homologous VH CDR3 sequences of identical length, whereas the remaining 183 (42%) IGHV3-21-expressing cases exhibited heterogeneous VH CDR3 lengths and amino acid composition ("non–subset #2/IGHV3-21").

CLL stereotyped subset #2 (IGHV3-21/IGLV3-21) is uniformly agressive independently of somatic hypermutation status. The prognosis for non-subset #2/IGHV3-21 CLL resembles that of the remaining CLL cases with similar somatic hypermutation status.

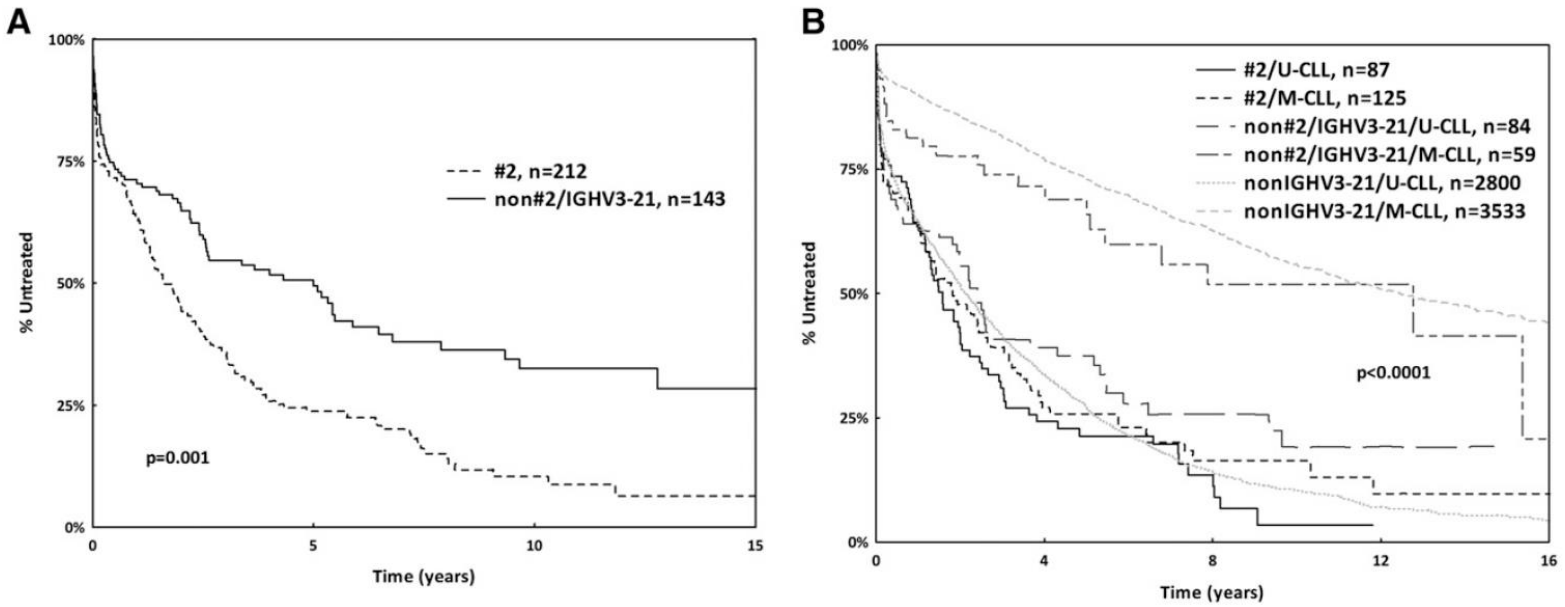


Figure 1. Kaplan Meier curves for TTFT. (A) Subset #2 exhibits significantly shorter TTFT compared with non–subset #2/IGHV3-21 CLL. (B) No difference regarding TTFT between non–subset #2/IGHV3-21 cases and the remaining CLL. Subset #2 exhibits TTFT similar to that of U-CLL independently of IGHV gene mutational status.

Baliakas et al. Blood, 2015;125:856-9

Post IT:ERIC guidelines recommandations

Item	*Recommendations*
Standard cases	
Methodology	Report type of: primers,[a] PCR product analysis, sequencing method, bioinformatics tools
Gene identification	IGHV, IGHD, IGHJ genes and alleles; IGHD may be difficult to precisely identify (due to deletions and/or SHM)
Productive rearrangement	Mutational status determined only for productive rearrangements; if unproductive, mention reasons (out-of-frame junction, stop codon)
IGHV gene: % of nucleotide identity to germ line	Classification: U-CLL $\geqslant$ 98%; M-CLL $<$ 98%; borderline CLL when 97–97.9%
Subset identification	For subsets with well-established prognostic value (subsets #1, #2, #4 and #8)
Difficult cases (frequency[b])	
Double rearrangements (10.5%)	
Productive+non-productive concordant status (7.8%)	Same as standard cases (mutational status defined by the productive rearrangement)
Productive+non-productive discordant status	
Productive U+non-productive M (0.4%)	Mutational status not determined
Productive M+non-productive U (0.2%)	Consider as M-CLL
Double productive	
Concordant status (1.3%)	Same as standard cases
Discordant status (0.7%)	Mutational status not determined
Multiple (more than two) productive rearrangements[c]	Mutational status not determined (unless it can be performed on sorted B-cell clones and predominant clones are easily identified)
Single unproductive rearrangement (0.6%)	Mutational status not determined (after failure of alternative PCR attempts)
Missing anchors (C104/W118) (0.4%)	Mutational status possible if evidence for IG expression on leukemic cells and/or preserved G-X-G motif in VH FR4

Abbreviations: CLL, chronic lymphocytic leukemia; IG, immunoglobulin; M-CLL, mutated CLL; U-CLL, unmutated CLL. [a]Leader primers are the only recommended option. That said, in rare cases when leader primers are unsuccessful at providing a product that can be sequenced and VH FR1 primers are used (discouraged for the determination of SHM status), the report should indicate that the use of VH FR1 primers might underestimate the total number of IGHV somatic hypermutations as a part of the VH domain is missing. [b]All frequencies according to Langerak *et al.*[28] [c]Cases with two or more B-cell clones.[32]

Rosenquist R. Leukemia 2017;31: 1477-1481

How would you evaluate the response?

1. Blood count
2. Physical examination
3. Cell morphology
4. Immunophenotyping
5. MRD level

Guidelines:

- BHS
- HOVON
- iwCLL

Screen How would you evaluate the response?

BHS[1]

Supporting guidelines

Update

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

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

HOVON[2]

Screen How would you evaluate the response?

Supporting guidelines update

Tabel 8: respons[3]

	Parameter	Complete remissie	Partiële remissie	Progressieve ziekte
	Respons definitie:	Alle criteria nodig	Ten minste 2 criteria van 1,2,3 plus 1 criterium van 5a-c (minimale duur van 2 maanden)	Ten minste 1 criterium
1	**Bloed lymfocyten**	<4,0 10^9/l	≥50% afname vanaf start	≥50% toename vanaf start (≥5,0x10^9/cellen)
2	**Lymfadenopathie**	Afwezig (geen >1.5 cm)	≥50% afname vanaf start, geen toename of nieuwe laesies	≥50% toename of nieuw (>1,5 cm)
3	**Hepato/splenomegalie**	Afwezig	≥50% afname vanaf start	≥50% toename of nieuw (>1,5 cm)
4	**B-symptomen**	Afwezig	Niet van toepassing	Niet van toepassing
5a	**Neutrofielen**	>1,5x10^9/l	>1,5x10^9/l	Niet van toepassing
5b	**Trombocyten**	>100x10^9/l	>100x10^9/l or ≥50% toename vanaf start	≥50% afname vanaf start of tot <100x10^9/l secundair aan CLL
5c	**Hemoglobine**	>6,8 mmol/l	>6,8 mmol/l of toename ≥50% na start	Afname van >1,3 mmol/l vanaf start of tot <6,2 mmol/l secundair aan CLL
6	**Beenmerg**	Normocellulair, geen B-lymfoide nodi, <30% lymfocyten	Niet van toepassing	Niet van toepassing
7	**Overig**	Niet van toepassing	Niet van toepassing	CLL- transformatie

Literatuurverantwoording:

Er is gebruik gemaakt van onderstaande richtlijn zonder aanvullende systematische literatuur-analyse: 3.Eichhorst B, Robak T, Montserrat E, Ghia P, Hillmen P, Hallek M, Buske C; ESMO Guidelines Committee. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†.Ann Oncol. 2015 Sep;26 Suppl 5:v78-v84.

[2]*Cll richtlijn 2017* http://www.hovon.nl/upload/File/Richtlijnen_BehAdv/richtlijn-cll-hovon_20170607_def_0.pdf

iwCLL[3]

Screen How would you evaluate the response?

Supporting guidelines
Update

Group	Parameter	CR	PR	PD	SD
A	Lymph nodes	None ≥1.5 cm	Decrease ≥50% (from baseline)*	Increase ≥50% from baseline or from response	Change of −49% to +49%
	Liver and/or spleen size†	Spleen size <13 cm; liver size normal	Decrease ≥50% (from baseline)	Increase ≥50% from baseline or from response	Change of −49% to +49%
	Constitutional symptoms	None	Any	Any	Any
	Circulating lymphocyte count	Normal	Decrease ≥50% from baseline	Increase ≥50% over baseline	Change of −49% to +49%
B	Platelet count	≥100 × 10^9/L	≥100 × 10^9/L or increase ≥50% over baseline	Decrease of ≥50% from baseline secondary to CLL	Change of −49 to +49%
	Hemoglobin	≥11.0 g/dL (untransfused and without erythropoietin)	≥11 g/dL or increase ≥50% over baseline	Decrease of ≥2 g/dL from baseline secondary to CLL	Increase <11.0 g/dL or <50% over baseline, or decrease <2 g/dL
	Marrow	Normocellular, no CLL cells, no B-lymphoid nodules	Presence of CLL cells, or of B-lymphoid nodules, or not done	Increase of CLL cells by ≥50% on successive biopsies	No change in marrow infiltrate

For a detailed description of the response parameters, see section 5.

*Sum of the products of 6 or fewer lymph nodes (as evaluated by CT scans and physical examination in clinical trials or by physical examination in general practice).

†Spleen size is considered normal if <13 cm. There is not firmly established international consensus of the size of a normal liver; therefore, liver size should be evaluated by imaging and manual palpation in clinical trials and be recorded according to the definition used in a study protocol.

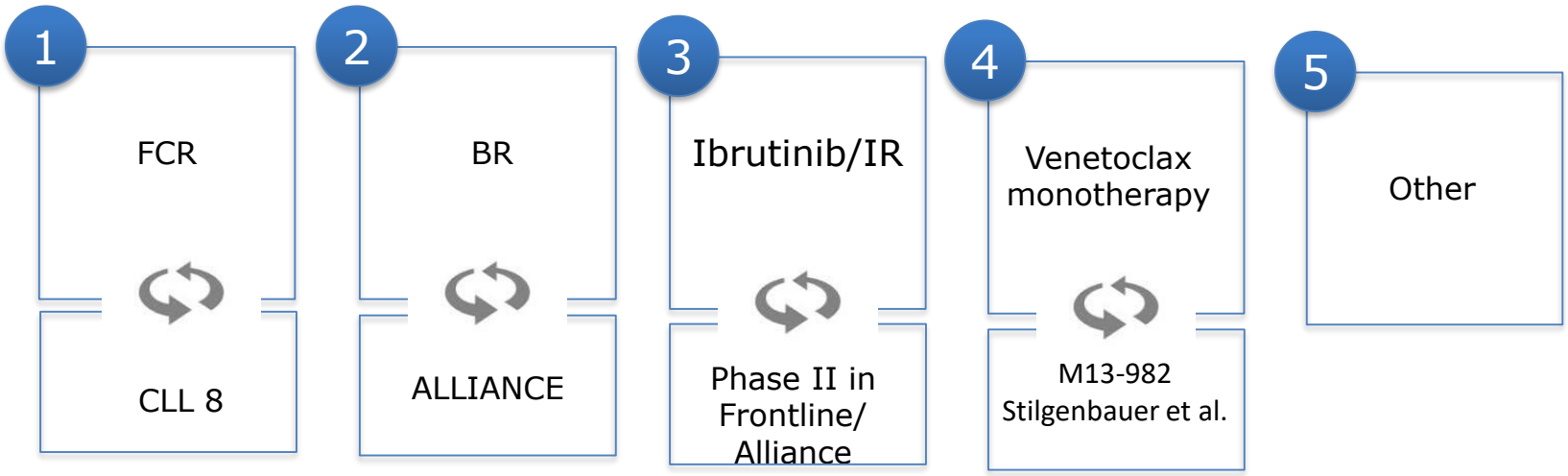
CR, complete remission (all of the criteria have to be met); PD, progressive disease (at least 1 of the criteria of group A or group B has to be met); PR, partial remission (for a PR, at least 2 of the parameters of group A *and* 1 parameter of group B need to improve if previously abnormal; if only 1 parameter of both groups A and B is abnormal before therapy, only 1 needs to improve); SD, stable disease (all of the criteria have to be met; constitutional symptoms alone do not define PD).

[3] *Hallek Blood 2018 Jun 21;131(25):2745-2760*

What if the patient would have del17P/TP53 mutation. Which therapy would you use?

Votable

Keep most of screens

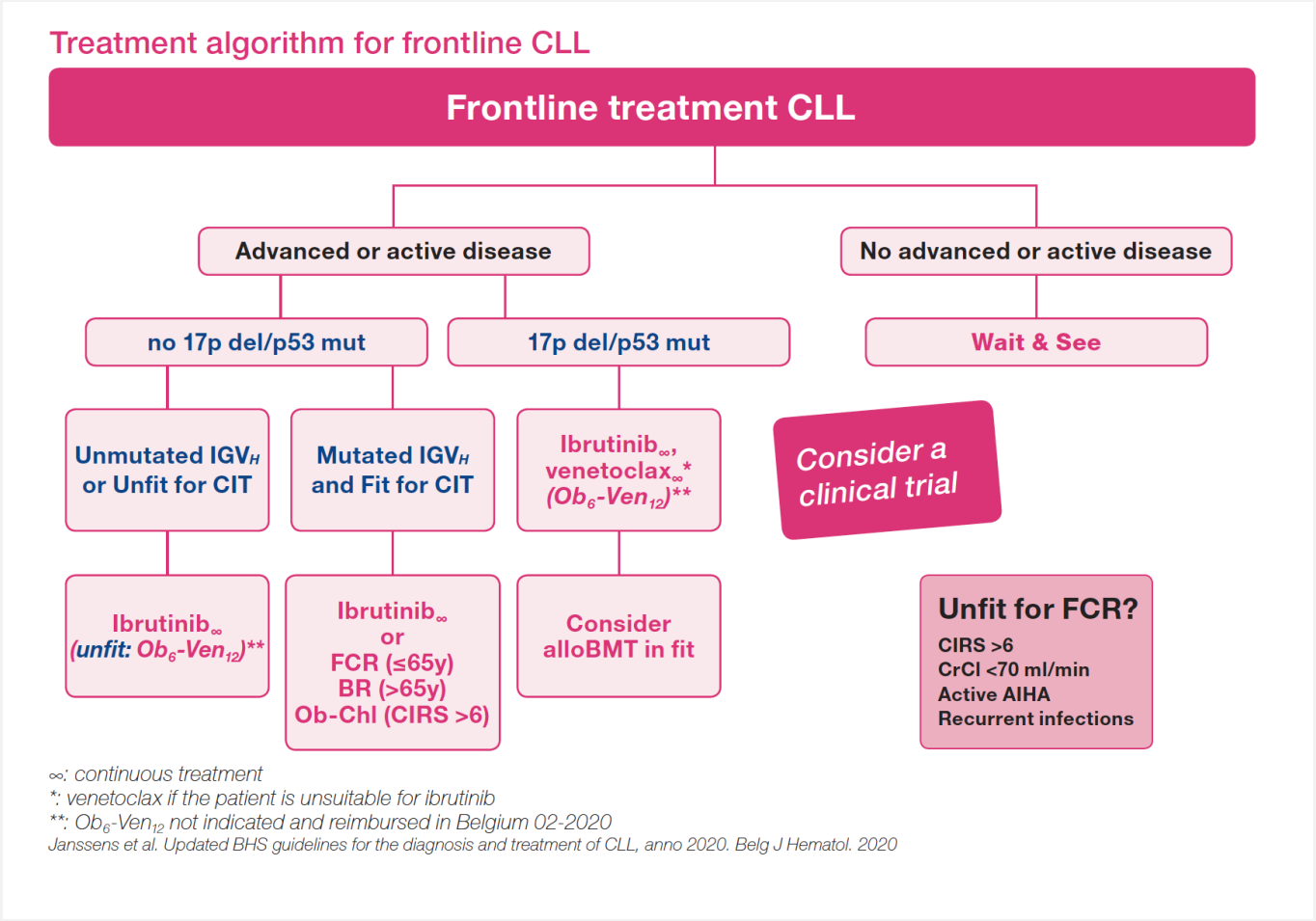


BHS
HOVON
iwCLL/Hallek
EHA/ESMO

BHS[1]

Screen With the information you have now what treatment would you initiate?

Supporting guidelines update

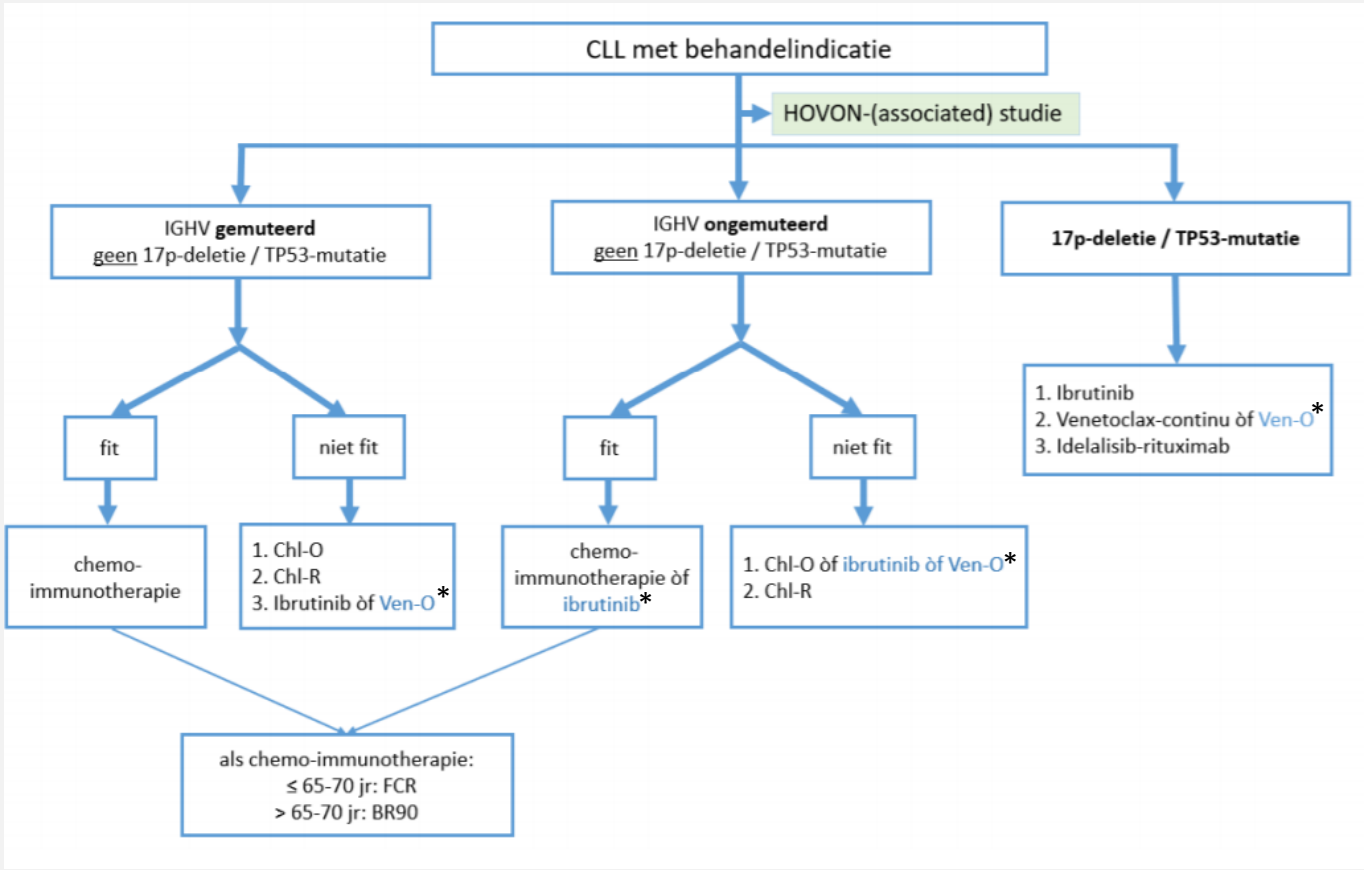


[1] *Janssens et al. Updated BHS guidelines for the diagnosis and treatment of CLL. BJH 2020*

Hovon[2]

Screen With the information you have now what treatment would you initiate?

Supporting guidelines update



*Deze medicatie kan op dit moment nog niet voorgeschreven worden, omdat het ófwel nog niet vergoed wordt ófwel nog geen “indicatie” heeft gekregen.

[2]HOVON CLL Concept richtlijn 2019 http://www.hovon.nl/behandeladvies/behandeladvies-leukemie/cll.html

Hallek[3]

Screen With the information you have now what treatment would you initiate?

Supporting guidelines update

CLL first line treatment (updated June 2019)

Stage	del(17p) or p53mut	Fitness	IGVH	Therapy
Binet A-B, Rai 0-II, inactive disease	Irrelevant	Irrelevant	Irrelevant	None
Active disease or Binet C or Rai III-IV	Yes	Irrelevant	Irrelevant	Ibrutinib or Venetoclax + Obinutuzumab or Idelalisib + Rituximab (if contraindications for ibrutinib)*
	No	Go go	M	FCR (BR above 65 years) or ibrutinib*
			U	Ibrutinib or FCR (BR above 65 years)*
		Slow go	M	Venetoclax + Obinutuzumab or Chlorambucil + Obinutuzumab or Ibrutinib*
			U	Venetoclax + Obinutuzumab or Ibrutinib or Chlorambucil + Obinutuzumab*

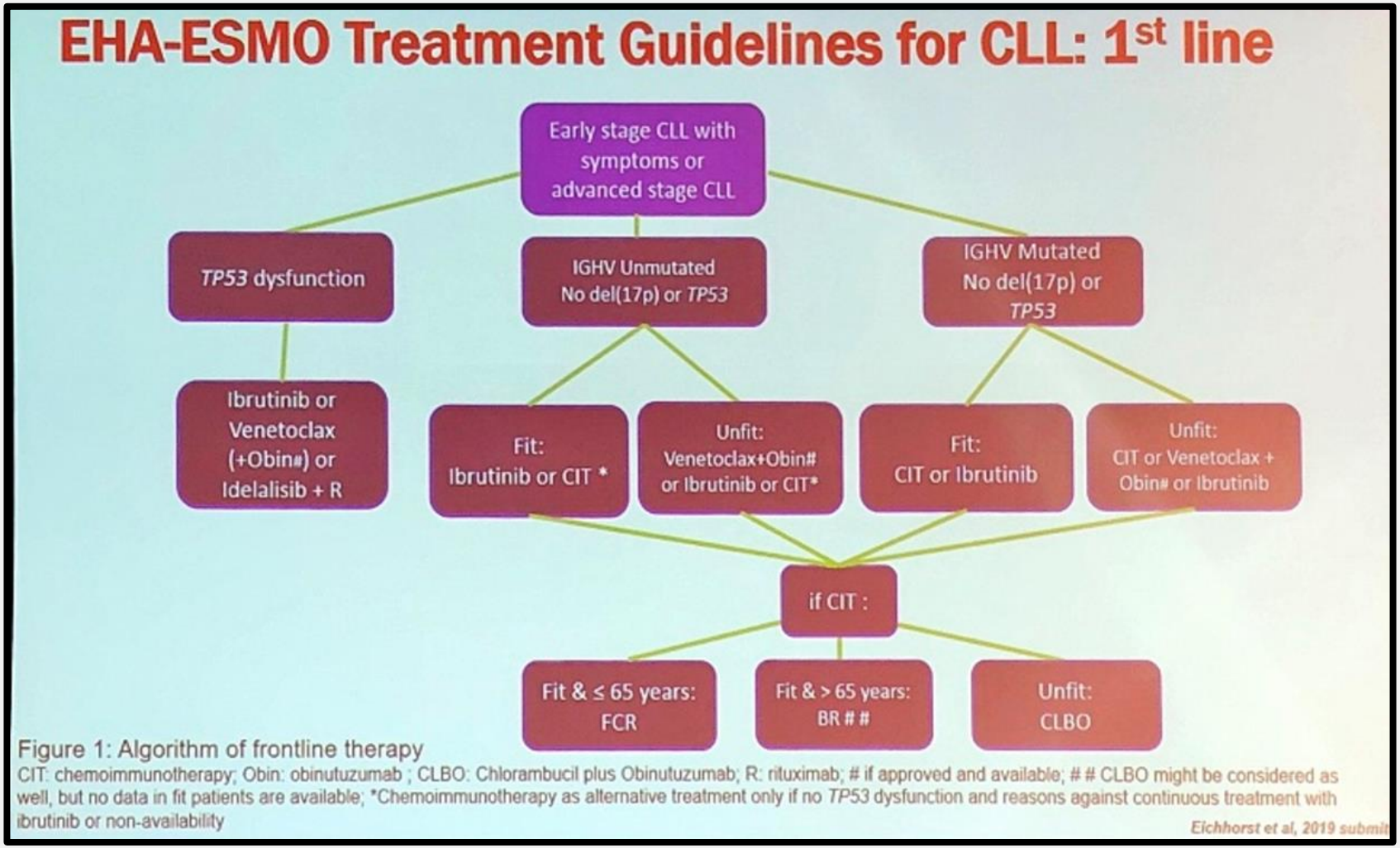
* Consider and discuss with patient: long-term vs fixed (6-12 m) duration therapy, lack of convincing evidence of overall survival differences, specific side effects of each therapeutic option (myelosuppression, infections, secondary malignancies for CIT; cardiac toxicity, bleeding and autoimmune disease for Ibru; TLS and infections for Ven-Obi; autoimmune disease (diarrhea) and opportunistic infections for Idelalisib).

[3]Hallek M. Am. J. Hematol. 2019; 94:1266-1287

EHA/ESMO[4]

Screen With the information you have now what treatment would you initiate?

Supporting guidelines update



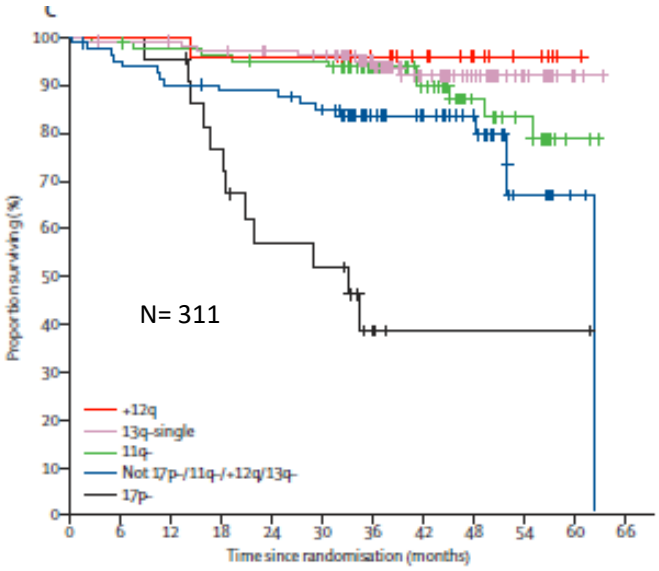
[4]Eichhorst et al. 2019 submitted

Screen 1 With the information you have now what treatment would you initiate?

FCR

Multicenter Phase III RCT reporting safety and efficacy of FC and FCR treatment of 817 treatment-naïve patients with CLL. With a median follow-up of 5.9 years.

Median PFS was significant longer in the FCR group (56.8 months) than in the FC group (32.9 months) P =0.001*



Longterm safety data

Long-term safety	FC Cases N (%)	FC Patients N (%)	FCR Cases N (%)	FCR Patients N (%)
Total patients (safety population), N		396		404
Total cases [N (%)] and patients [N (%)] with ≥1 SPM	77 (57)	69 (17)	59 (43)	53 (13)
Secondary malignancies				
Richter's transformation	25 (33)	25 (6)	13 (22)	13 (3)
Solid tumors	29 (38)	28 (7)	26 (44)	24 (6)
Lung	13/29 (45)	13 (3)	5/26 (20)	5 (1)
Prostate	2/29 (7)	2 (1)	6/26 (23)	6 (2)
Renal/bladder	3/29 (10)	3 (1)	4/26 (15)	3 (1)
Colorectal	0/29 (0)	0 (0)	2/26 (8)	2 (<1)
Melanoma	3/29 (10)	3 (1)	5/26 (20)	5 (1)
Breast	1/29 (3)	1 (<1)	2/26 (8)	2 (<1)
Pancreatic	1/29 (3)	1 (<1)	1/26 (4)	1 (<1)
Ovarian/uterine/cervical	0/29 (0)	0 (0)	1/26 (4)	1 (<1)
Liver/gall bladder	1/29 (3)	1 (<1)	0/26 (0)	0 (0)
Thyroid	2/29 (7)	2 (1)	0/26 (0)	0 (0)
Pharyngeal/laryngeal	1/29 (3)	1 (<1)	0/26 (0)	0 (0)
Other	2/29 (7)	2 (1)	0/26 (0)	0 (0)
Hematologic neoplasia	11 (14)	11 (3)	13 (22)	12 (3)
AML/MDS	7/11 (64)	7 (2)	7/13 (54)	6 (2)
Indolent B-non-Hodgkin lymphoma	1/11 (9)	1 (<1)	2/13 (16)	2 (<1)
Aggressive B-non-Hodgkin lymphoma	1/11 (9)	1 (<1)	1/13 (8)	1 (<1)
ALL	0/11 (0)	0 (0)	1/13 (8)	1 (<1)
CML	0/11 (0)	0 (0)	1/13 (8)	1 (<1)
Other	2/11 (18)	2 (<1)	1/13 (8)	1 (<1)
Basalioma, squamous cell	12 (16)	11 (3)	7 (12)	6 (2)
Prolonged neutropenia				
2 months after end of treatment		34 (9)		67 (17)
12 months after end of treatment		14 (4)		16 (4)

**Primary endpoint #secondary endpoint*

Fisher et al. Blood 2016; 127 (2): 208-215

Screen 2 With the information you have now what treatment would you initiate?

BR

Multicenter, nonrandomized, phase II study with BR in previously untreated patients with symptomatic CLL regardless of age and fitness. The median observation time for all patients was 27.0 months.

**Primary endpoint*
#secondary endpoint

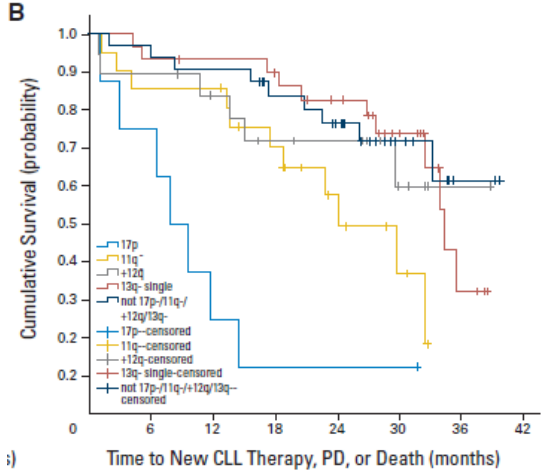
Characteristic	Patients (N = 117) No.	%
Expression of ZAP-70, % (n = 89)		
Median	8.0	
Range	0.0-90.0	
≤ 20	75	84.3
> 20	14	15.7
Expression of CD38, % (n = 91)		
Median	48.0	
Range	12.0-100.0	
≤ 30	11	12.1
> 30	80	87.9
Genomic aberrations by FISH (n = 110)		
17p deletion	8	7.3
11q deletion*	21	19.1
Trisomy 12†	19	17.3
13q deletion‡	32	27.3
Normal§	32	29.1
IGHV mutational status (n = 110)		
Mutated	42	38.2
Unmutated	68	61.8

Abbreviations: FISH, fluorescent in situ hybridization; IGHV, immunoglobulin heavy variable chain.
*Not including 17p deletion.
†Not including 17p deletion or 11q deletion.
‡Not including 17p deletion, 11q deletion, or trisomy 12.
§Not including 17p deletion, 11q deletion, trisomy 12, or 13q deletion (ie, genetic classification according to hierarchical model of Döhner et al.[25]

*

Population	No.	Missing* No.	%	CR No.	%	PR/nPR No.	%	SD No.	%	PD No.	%	ORR No.	%	P	Survival Analysis: Median PFS No.	Months	P	Median EFS Months	P
Total No. of patients	117	3	2.6	27	23.1	76	64.9	11	9.4	0		103	88.0	—		33.8	—	33.9	—
Genetic subgroups																			
Total No. of patients with cytogenetic results and response assessment	108	—		25	23.1	72	66.7	11	10.2	0		97	89.8	—					
17p deletion	8	—		0		3	37.5	5	62.5	0		3	37.5	.001	8	7.9	< .001	7.8	< .001
11q deletion†	20	—		8	40.0	10	50.0	2	10.0	0		18	90.0		21	29.7		24.1	
Trisomy 12‡	19	—		4	21.0	14	73.7	1	5.3	0		18	94.7		19	N/R		N/R	
13q deletion§	30	—		4	13.3	24	80.0	2	6.7	0		28	93.3		30	34.4		34.4	
No abnormalities according to the hierarchical model¶	31	—		9	29.0	21	67.7	1	3.2	0		30	96.8		32	N/R		N/R	

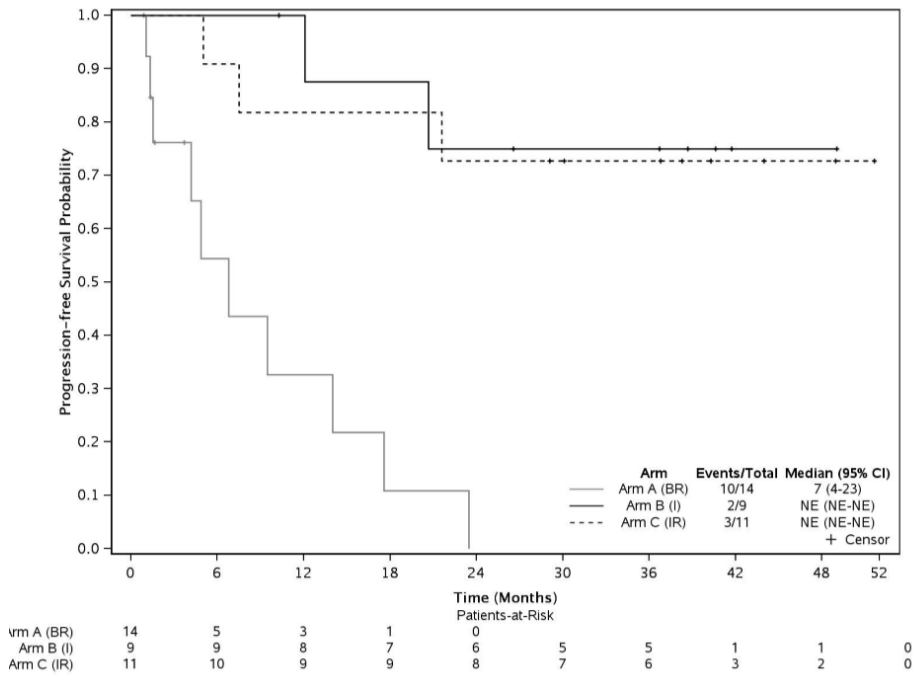
\# B



Fischer et al. Journal of Clinical Oncology 2012; 30(26): 3209-3216

Screen 2 & 3 With the information you have now what treatment would you initiate?

PFS by del17P#



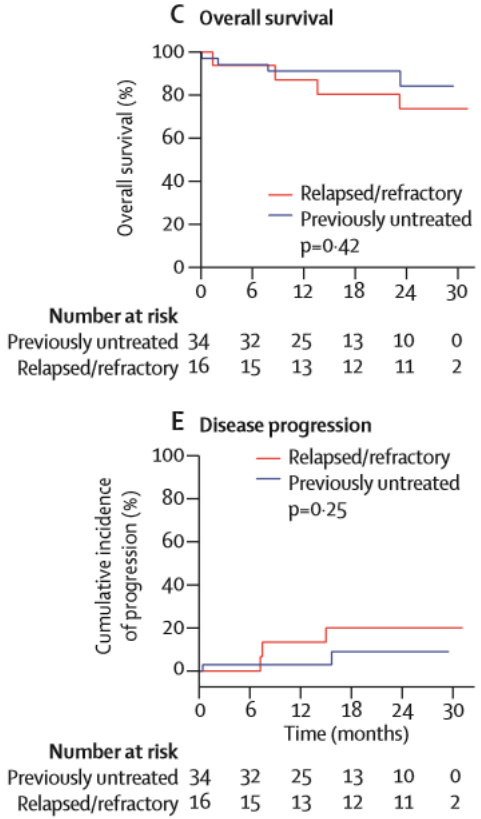
A randomized, phase 3 study of I vs IR vs BR in 547 patients 65 years of age or older with previously untreated TN CLL . Median FU: 38 mo
Primary endpoint: PFS

PFS was substantially longer with ibrutinib or IR compared with BR among patients with del(17p) ($P < 0.001$ for both comparisons)

#subgroup analysis

Woyach et al. New England Journal of Medecine 2018; DOI: 10.1056/NEJMoa1812836

Screen 3 With the information you have now what treatment would you initiate?



single-arm phase 2 study, enrolled 51 CLL patients with TP53 aberrations treated with ibrutinib monotherapy. Both untreated (n=33) and relapsed/refractory CLL (n=15 patients were included.
Primary endpoint: ORR after 6 cycles. Secondary endpoints were safety, OS, PFS, best response, and nodal response

	All evaluable patients (n=48)	Previously untreated patients (n=33)	Relapsed or refractory patients (n=15)
Response at 24 weeks			
Complete response	..	..	..
Partial response	24 (50%)	18 (55%)	6 (40%)
Partial response with lymphocytosis	20 (42%)	14 (42%)	6 (40%)
Stable disease	3 (6%)	..	3 (20%)
Progressive disease	1 (2%)	1 (3%)	..
Best response			
Complete response	5 (10%)	4 (12%)	1 (7%)
Partial response	32 (67%)	23 (70%)	9 (60%)
Partial response with lymphocytosis	8 (17%)	5 (15%)	3 (20%)
Stable disease	2 (4%)	..	2 (13%)
Progressive disease	1 (2%)	1 (3%)	..

Farooqui M. Et al. Lancet Oncol 2015; 16(2):169-176

Screen 4

V monotherapy

Phase II open label study with 158 del(17p) CLL patients with relapsed/refractory or previously untreated CLL (n=153 and n=5, respectively). Median time on study was 26.6 months (range, 0 to 44.2 months).

n (%)	ORR	CR/CRi	nPR/PR	SD	PD	NE
All Patients, N=158	122 (77)	32 (20)	90 (57)	30 (19)	3 (2)	3* (2)
***TP53* mutation, n=55**	38 (69)	10 (18)	28 (51)	16 (29)	1 (2)	0
Unmutated *IGHV*, n=45	39 (87)	7 (16)	32 (71)	4 (9)	1 (2)	1 (2)
>2 prior therapies, n=68	48 (71)	6 (9)	42 (62)	18 (27)	1 (2)	1 (2)
Fludarabine refractory, n=45	35 (78)	11 (24)	24 (53)	10 (22)	0	0
ECOG score of 0, n=69	59 (86)	16 (23)	43 (62)	10 (15)	0	0
ECOG score of 1, n=78	55 (71)	14 (18)	41 (53)	17 (22)	3 (4)	3 (4)
ECOG score of 2, n=11	8 (73)	2 (18)	6 (55)	3 (27)	0	0
Beta-2 microglobulin ≥3 at baseline, n=25	19 (76)	6 (24)	13 (52)	5 (20)	1 (4)	0
Nodes ≥5 cm at baseline, n=76	60 (79)	10 (13)	50 (66)	14 (18)	1 (1)	1 (1)
Nodes ≥10 cm at baseline, n=21	16 (76)	2 (10)	14 (67)	5 (24)	0	0
High TLS risk,† n=62	47 (76)	5 (8)	42 (68)	14 (23)	0	1 (2)

ORR, objective response rate; CR, complete remission; CRi, complete remission with incomplete marrow recovery; nPR, nodular partial remission; PR, partial remission, SD, stable disease; PD, disease progression; NE, not evaluated for response; BCRi, B-cell receptor pathway inhibitor.
*One patient discontinued after the first dose of venetoclax, one patient died after three weeks of treatment due to liver dysfunction not related to venetoclax, and one patient had pseudo obstruction of the small bowel mesentery and retroperitoneum during dose ramp up and discontinued the study.

Stilgenbauer S. et al. *Journal of Clinical Oncology* 36.19 (2018): 1973-1980.

Screen 4

Multicenter phase III RCT with 431 treatment naive CLL patients with coexisting conditions (Cirs >6, CCL < 70ml/min) who were randomized to VG or ChlG. Median follow up 28.1 months.

Table 1. Selected Patient Demographic and Disease Characteristics at Baseline (Intention-to-Treat Population).*

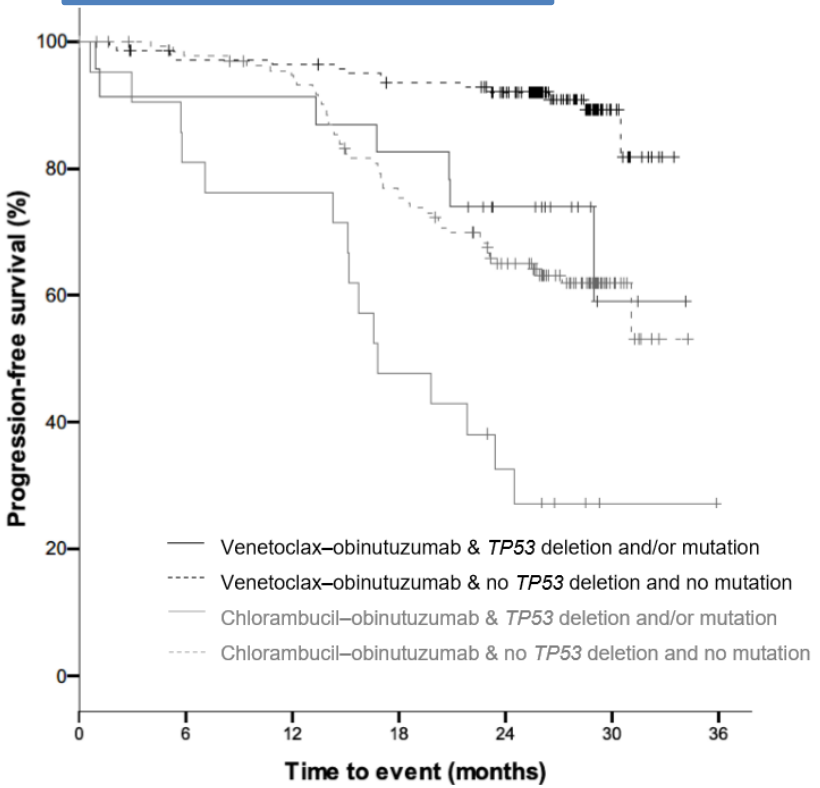
Characteristic	Venetoclax–Obinutuzumab (N=216)	Chlorambucil–Obinutuzumab (N=216)
Age ≥75 yr — no. (%)	72 (33.3)	78 (36.1)
Male sex — no. (%)	146 (67.6)	143 (66.2)
Binet stage — no. (%)†		
A	46 (21.3)	44 (20.4)
B	77 (35.6)	80 (37.0)
C	93 (43.1)	92 (42.6)
Tumor lysis syndrome risk category — no. (%)		
Low	29 (13.4)	26 (12.0)
Intermediate	139 (64.4)	147 (68.1)
High	48 (22.2)	43 (19.9)
Total CIRS score >6 — no. (%)‡	186 (86.1)	177 (81.9)
Calculated creatinine clearance <70 ml/min — no./total no. (%)	128/215 (59.5)	118/213 (55.4)
Cytogenetic subgroup — no./total no. (%)§		
Deletion in 17p	17/200 (8.5)	14/193 (7.3)
Deletion in 11q	36/200 (18.0)	38/193 (19.7)
Trisomy 12	36/200 (18.0)	40/193 (20.7)
No abnormalities	50/200 (25.0)	42/193 (21.8)
Deletion in 13q alone	61/200 (30.5)	59/193 (30.6)
IGHV mutational status — no./total no. (%)		
Mutated	76/200 (38.0)	83/208 (39.9)
Unmutated	121/200 (60.5)	123/208 (59.1)
Could not be evaluated	3/200 (1.5)	2/208 (1.0)
TP53 mutational status — no./total no. (%)		
Mutated	19/171 (11.1)	13/157 (8.3)
Unmutated	152/171 (88.9)	144/157 (91.7)

* There were no significant differences between the groups at baseline. Percentages may not total 100 because of rounding.
† Binet stages indicate the degree of advancement of chronic lymphocytic leukemia and are based on organ and lymph-node involvement, hemoglobin levels, and platelet counts.
‡ Scores on the Cumulative Illness Rating Scale (CIRS) range from 0 to 56, with higher scores indicating more impaired function of organ systems.
§ Cytogenetic subgroups were determined according to the hierarchical model of Döhner et al.[18]

V+G

@ 2 years	VG (%)
PFS *with TP53 aberration*	73.9
PFS *with TP53 aberration*	92.1

PFS by del17P#



" subgroup analysis

Fischer K. et al. N Engl J Med. 2019

What if the patient was 70y old? No del17p/TP53 mutation, mIGHV
Which therapy would you use?

CASE 1 – timepoint 3

Picture of patient

Performance status

CIRS

No Del 17p/TP53 IGHV Mutated

Votable

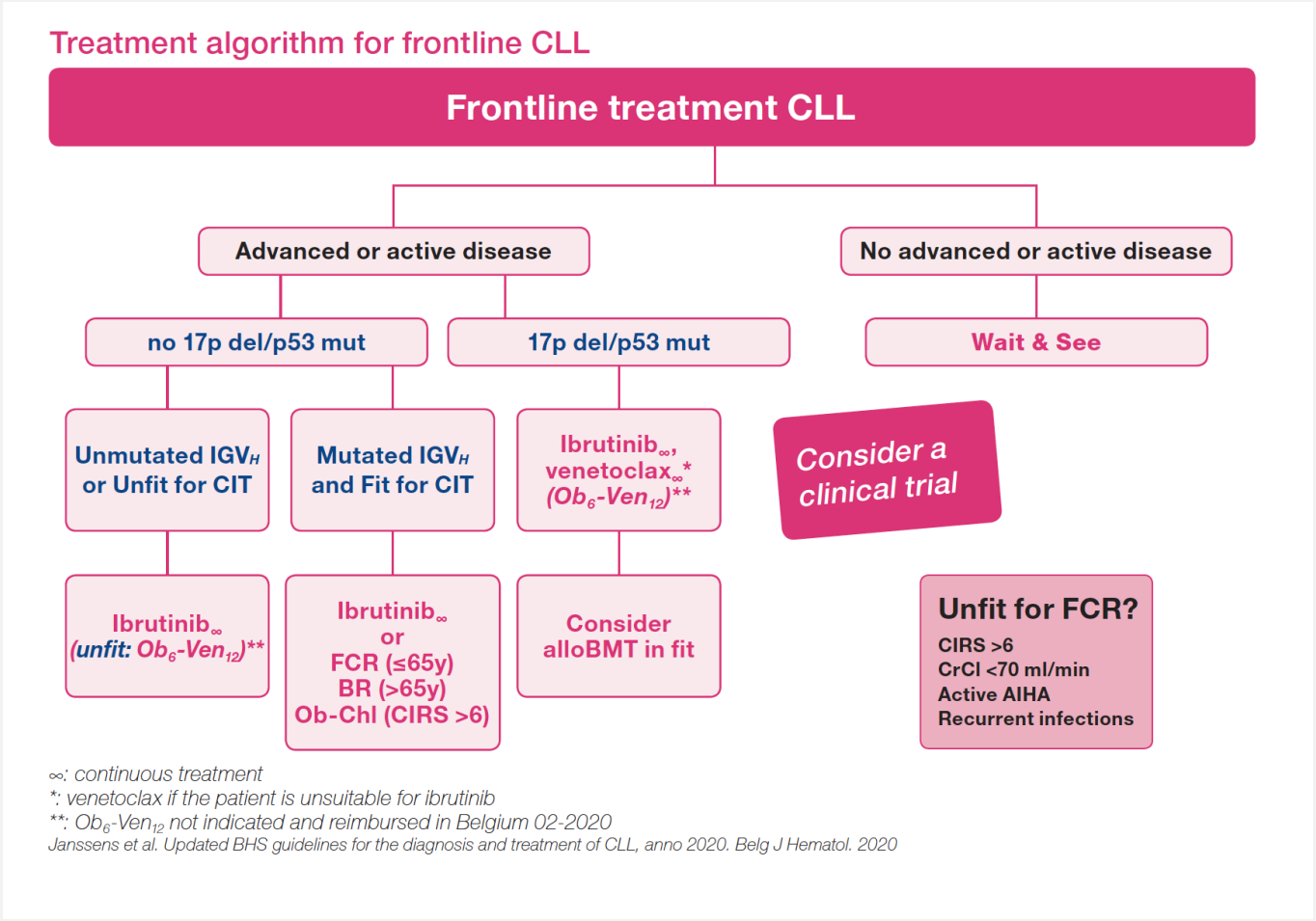
1. FCR → CLL 8; CLL10 ECOG1912
2. BR → CLL10 ALLIANCE
3. Ibrutinib R → ECOG1912 ALLIANCE BURGER
4. Chl+G → CLL11 CLL14 iLLUMINATE
5. VG vs. Chl+G → CLL11 CLL14
6. I → RESONATE-2 ALLIANCE BURGER Tedeschi
7. IG → iLLUMINATE Tedeschi
8. Acalabrutinib (+/- G) → ELEVATE TN

BHS
HOVON
Hallek
EHA/ESMO

BHS[1]

Screen With the information you have now what treatment would you initiate?

Supporting guidelines update

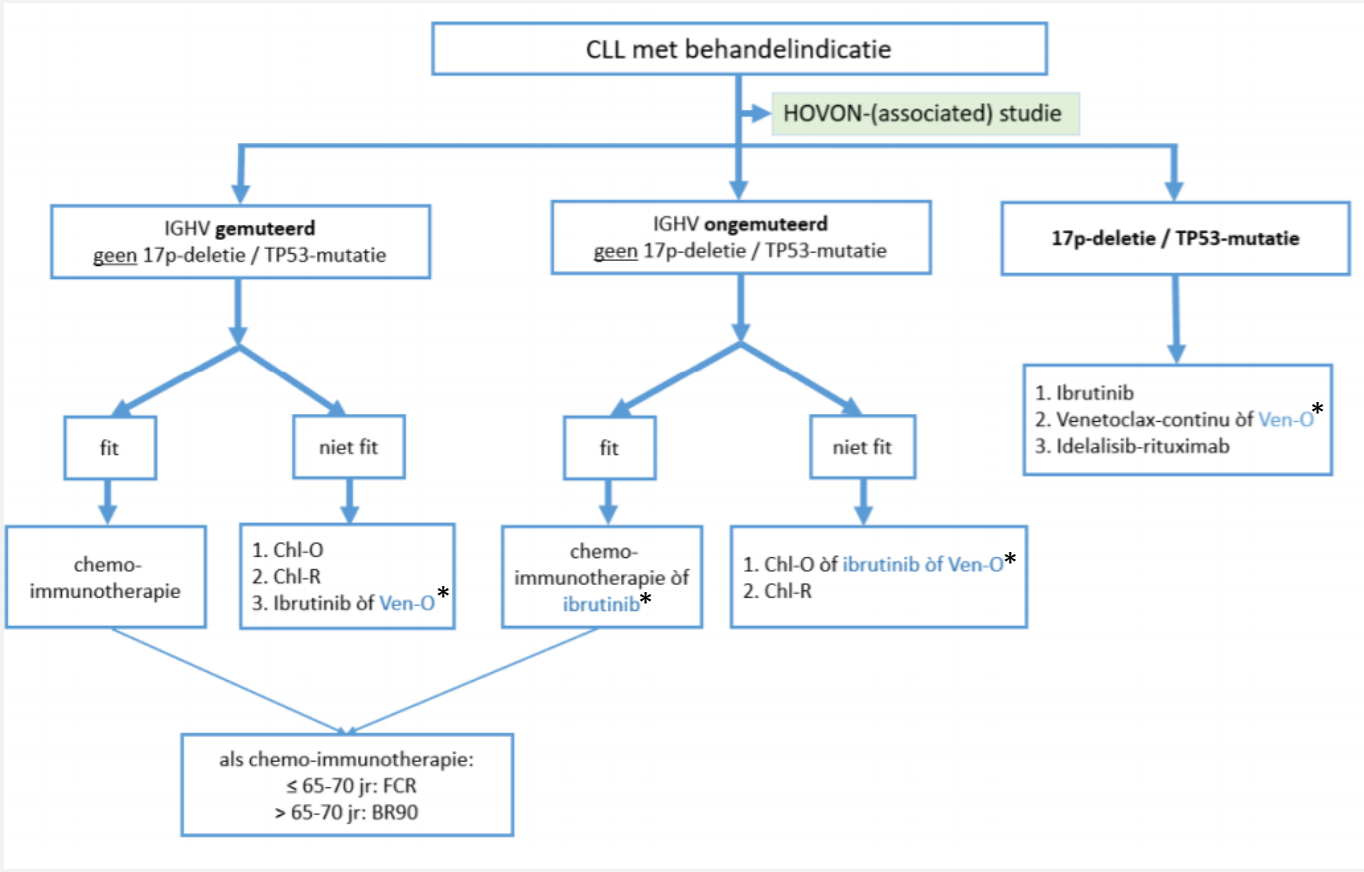


[1] *Janssens et al. Updated BHS guidelines for the diagnosis and treatment of CLL. BJH 2020*

HOVON[2]

Screen With the information you have now what treatment would you initiate?

Supporting guidelines update



*Deze medicatie kan op dit moment nog niet voorgeschreven worden, omdat het ófwel nog niet vergoed wordt ófwel nog geen “indicatie” heeft gekregen.

[2]HOVON CLL Concept richtlijn 2019 http://www.hovon.nl/behandeladvies/behandeladvies-leukemie/cll.html

Hallek[3]

Screen With the information you have now what treatment would you initiate?

Supporting guidelines update

CLL first line treatment (updated June 2019)

Stage	del(17p) or p53mut	Fitness	IGVH	Therapy
Binet A-B, Rai 0-II, inactive disease	Irrelevant	Irrelevant	Irrelevant	None
Active disease or Binet C or Rai III-IV	Yes	Irrelevant	Irrelevant	Ibrutinib or Venetoclax + Obinutuzumab or Idelalisib + Rituximab (if contraindications for ibrutinib)*
	No	Go go	M	FCR (BR above 65 years) or ibrutinib*
			U	Ibrutinib or FCR (BR above 65 years)*
		Slow go	M	Venetoclax + Obinutuzumab or Chlorambucil + Obinutuzumab or Ibrutinib*
			U	Venetoclax + Obinutuzumab or Ibrutinib or Chlorambucil + Obinutuzumab*

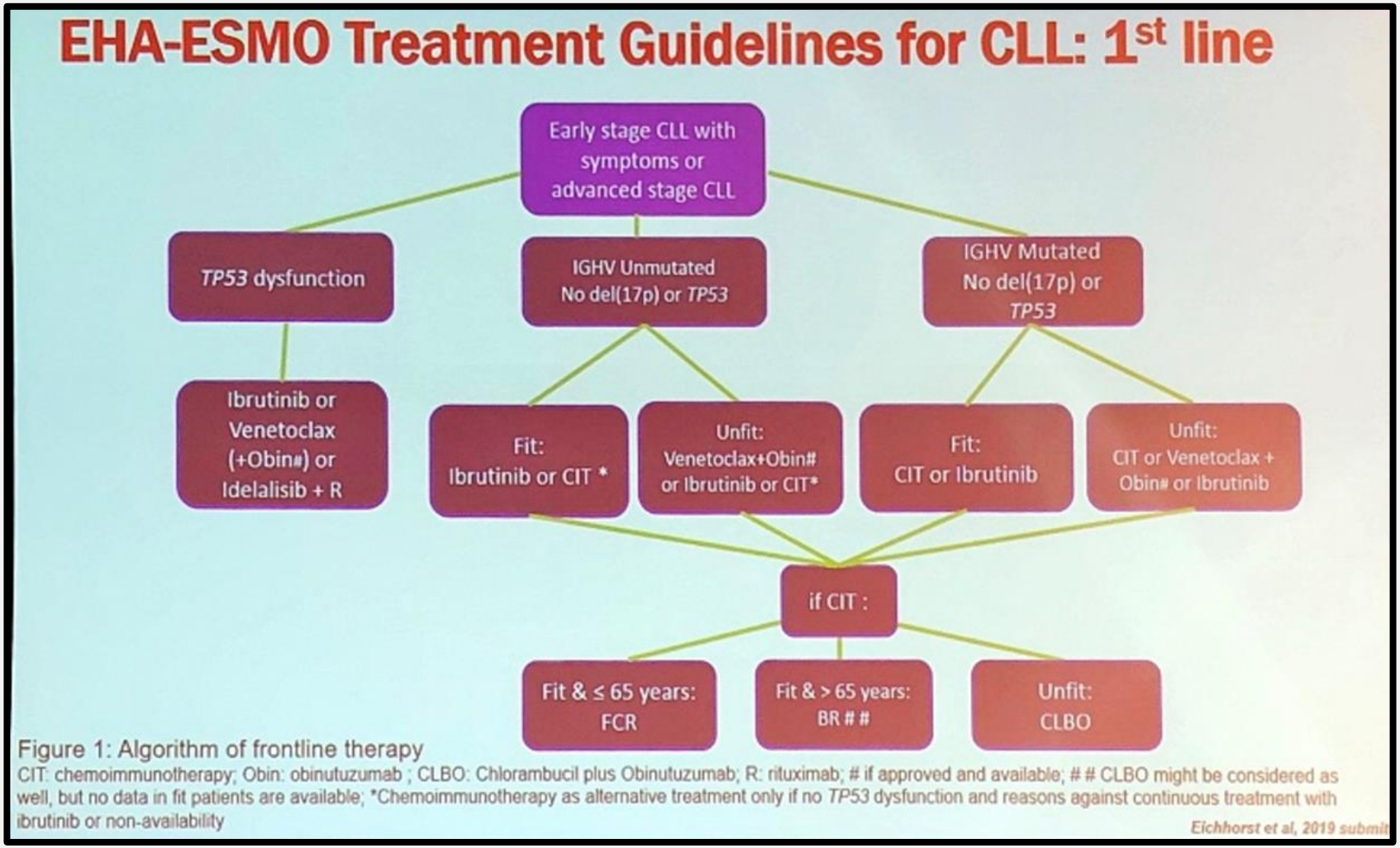
* Consider and discuss with patient: long-term vs fixed (6-12 m) duration therapy, lack of convincing evidence of overall survival differences, specific side effects of each therapeutic option (myelosuppression, infections, secondary malignancies for CIT; cardiac toxicity, bleeding and autoimmune disease for Ibru; TLS and infections for Ven-Obi; autoimmune disease (diarrhea) and opportunistic infections for Idelalisib).

[3]Hallek M. Am. J. Hematol. 2019; 94:1266-1287

EHA/ESMO[4]

Screen With the information you have now what treatment would you initiate?

Supporting guidelines update



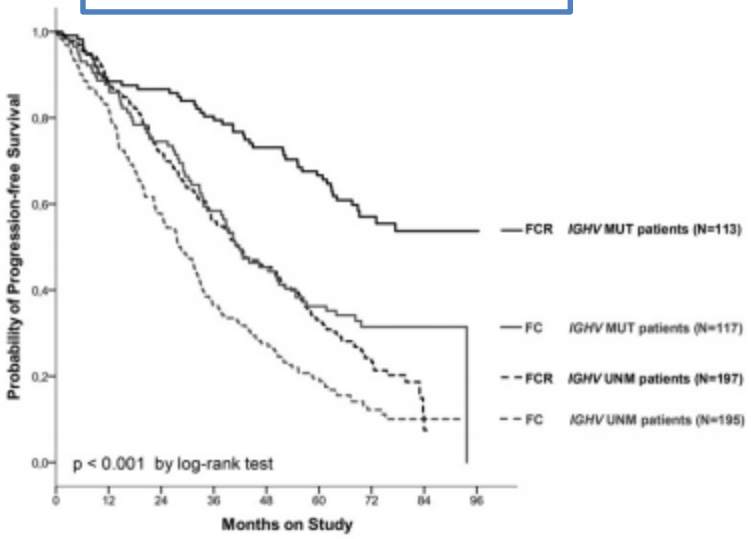
[4]Eichhorst et al. 2019 submitted

Screen 1 With the information you have now what treatment would you initiate?

FCR

Median PFS was significant longer in the FCR group (56.8 months) than in the FC group (32.9 months) P =0.001*

PFS by IGHV mutation status#



**Primary endpoint #secondary endpoint*

Multicenter Phase III RCT reporting safety and efficacy of FC and FCR treatment of 817 treatment-naïve patients with CLL. With a median follow-up of 5.9 years.

Longterm safety data

	FC		FCR	
Long-term safety	**Cases N (%)**	**Patients N (%)**	**Cases N (%)**	**Patients N (%)**
Total patients (safety population), N		396		404
Total cases [N (%)] and patients [N (%)] with ≥1 SPM	77 (57)	69 (17)	59 (43)	53 (13)
Secondary malignancies				
Richter's transformation	25 (33)	25 (6)	13 (22)	13 (3)
Solid tumors	29 (38)	28 (7)	26 (44)	24 (6)
Lung	13/29 (45)	13 (3)	5/26 (20)	5 (1)
Prostate	2/29 (7)	2 (1)	6/26 (23)	6 (2)
Renal/bladder	3/29 (10)	3 (1)	4/26 (15)	3 (1)
Colorectal	0/29 (0)	0 (0)	2/26 (8)	2 (<1)
Melanoma	3/29 (10)	3 (1)	5/26 (20)	5 (1)
Breast	1/29 (3)	1 (<1)	2/26 (8)	2 (<1)
Pancreatic	1/29 (3)	1 (<1)	1/26 (4)	1 (<1)
Ovarian/uterine/cervical	0/29 (0)	0 (0)	1/26 (4)	1 (<1)
Liver/gall bladder	1/29 (3)	1 (<1)	0/26 (0)	0 (0)
Thyroid	2/29 (7)	2 (1)	0/26 (0)	0 (0)
Pharyngeal/laryngeal	1/29 (3)	1 (<1)	0/26 (0)	0 (0)
Other	2/29 (7)	2 (1)	0/26 (0)	0 (0)
Hematologic neoplasia	11 (14)	11 (3)	13 (22)	12 (3)
AML/MDS	7/11 (64)	7 (2)	7/13 (54)	6 (2)
Indolent B-non-Hodgkin lymphoma	1/11 (9)	1 (<1)	2/13 (16)	2 (<1)
Aggressive B-non-Hodgkin lymphoma	1/11 (9)	1 (<1)	1/13 (8)	1 (<1)
ALL	0/11 (0)	0 (0)	1/13 (8)	1 (<1)
CML	0/11 (0)	0 (0)	1/13 (8)	1 (<1)
Other	2/11 (18)	2 (<1)	1/13 (8)	1 (<1)
Basalioma, squamous cell	12 (16)	11 (3)	7 (12)	6 (2)
Prolonged neutropenia				
2 months after end of treatment		34 (9)		67 (17)
12 months after end of treatment		14 (4)		16 (4)

Fisher et al. Blood 2016; 127 (2): 208-215

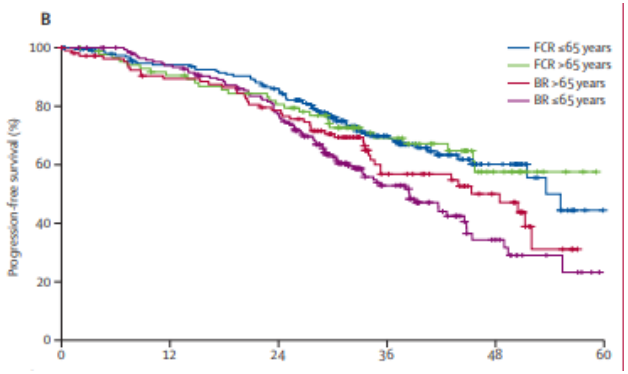
Screen 1 & 2 With the information you have now what treatment would you initiate?

FCR vs BR

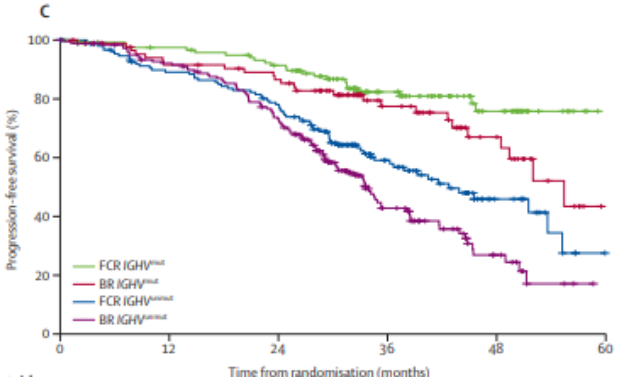
Multicenter RCT with Treatment naive CLL patients without del17P and good physical fitness (Cirs ≤6, CCL ≥ 70ml/min) who were randomized to FCR or BR.

The median observation time for all patients was 35.9 months .Median progression-free survival was 41·7 months with BR and 55·2 months with FCR*

PFS by age#



PFS by IGHV mutation status#



*Primary endpoint
#secondary endpoint

Adverse event	FCR(%) N= 279	BR (%) N= 278	P value
Neutropenia	87.7	67.8	< 0.001
Anemia	14.2	12.0	0.46
Thrombocytopenia	22.4	16.5	0.096
Severe Infection	39.8	25.4	0.001
sec. Neoplasm	6.1	3.6	0.244

Eichhorst et al. Lancet Oncol 2016; 17: 928–42

Screen 1&3 With the information you have now what treatment would you initiate?

FCR/IR

A randomized, phase 3 study of IR vs FCR in 529 patients 70 years of age or younger with previously untreated TN CLL . Median FU: 33.6 mo

@ 3 years	IR (%)	FCR (%)	HR [95%CI]	P value
PFS*	89.4	72.9	0.35 [0.22 - 0.56]	<0.001
OS#	98.8	91.5	0.17 [0.0 - 0.54]	<0.001
PFS IGHV mutated~	87.7	88	0.44 [0.14 - 1.36]	NR
PFS IGHV Unmutated~	90.7	62.5	0.26 [0.14 - 0.50]	NR

**Primary endpoint*
#secondary endpoint
~ subgroup analysis

Safety	IR (%)	FCR (%)	P VALUE
All AE Grade ≥3 Regardless of attribution	80.1	79.7	= 0.91
Grade ≥3 Neutropenia	25.6	44.9	<0.001
Grade ≥3 Infections+	9.4	9.5	<0.005
Grade ≥3 Hypertensions ~	18.8	8.2	= 0.002
Grade ≥3 Hemorrhage	1.1	0	P = 0.32
Grade ≥3 Cardiac events	6.5	1.9	NR
Grade ≥3 Atrial fibrillation	3.1	1.3	NR

+Percent of infection complications was lower in the IR arm than in the FCR arm, specifically neutropenic fever (10.5% vs. 20.3%).

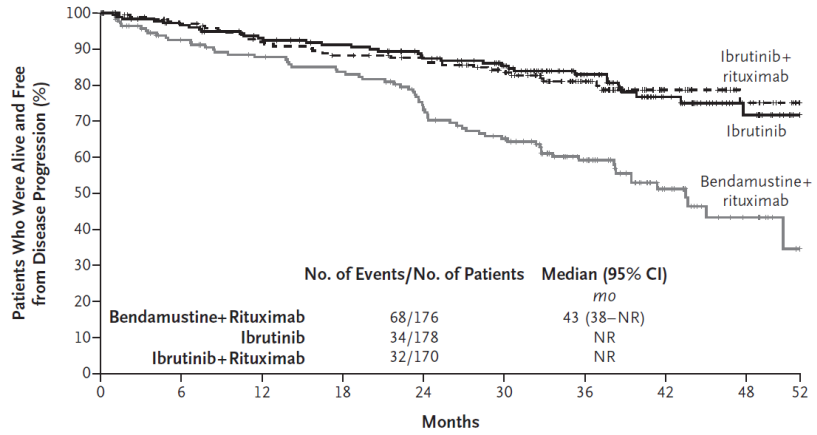
Shanafelt TD et al. N Engl J Med. 2019;381:432-43

Screen 2 & 3 & 6 With the information you have now what treatment would you initiate?

I or IR ALLIANCE

A randomized, phase 3 study of I vs IR vs BR in 547 patients 65 years of age or older with previously untreated TN CLL . Median FU: 38 mo

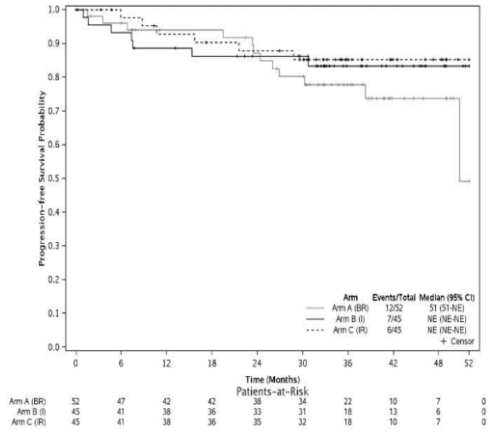
Primary endpoint: PFS



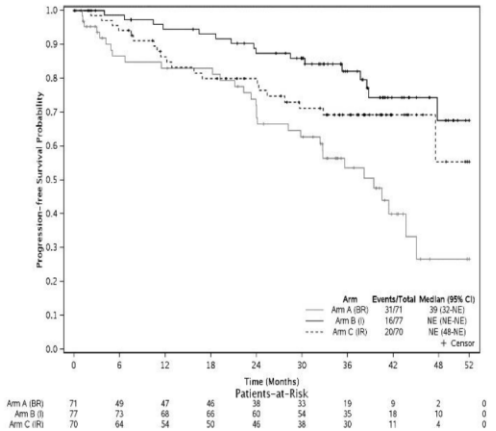
No. at Risk										
Bendamustine+rituximab	176	140	129	122	103	88	57	26	11	0
Ibrutinib	178	165	154	147	136	120	78	45	22	0
Ibrutinib+rituximab	170	159	145	138	132	115	74	40	20	0

Estimated PFS at 2 years (95% CI)	BR	I	IR
	74% (66-80)	87% (81-92)	88% (81-92)

Patients with Mutated IGHV (n=142)



Patients with Unmutated IGHV (n=218)



PFS was longer with ibrutinib-containing regimens among patients with m*IGHV* than with u*IGHV* but there was no significant interaction with IgHV mutation status

Woyach JA, et al. *N Engl J Med.* 2018; 379: 2517-2528

Screen 2 & 3 & 6 With the information you have now what treatment would you initiate?

I or IR ALLIANCE

Hematologic Adverse Events	BR (n=176)	I (n=180)	IR (n=181)	P Value*
Any, n (%)				<0.001
Grade 3	62 (35)	59 (33)	49 (27)	
Grade 4	45 (26)	15 (8)	21 (12)	
Anemia, n (%)				0.09
Grade 3	22 (12)	20 (11)	11 (6)	
Grade 4				
Decreased neutrophil count, n (%)				
Grade 3				
Grade 4				
Decreased platelet count, n (%)				
Grade 3				
Grade 4				

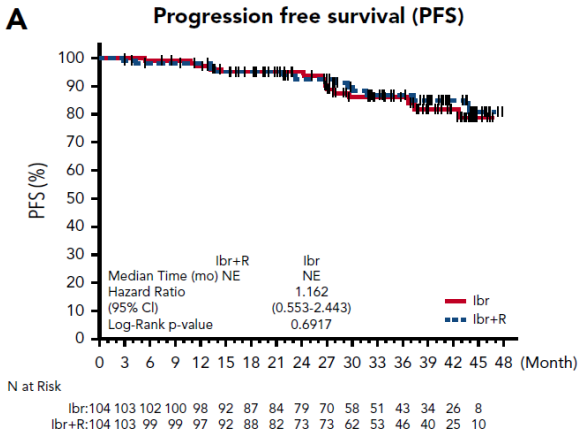
Non-Hematologic Adverse Events	BR (n=176)	I (n=180)	IR (n=181)	P Value*
Any, n (%)				0.04
Grade 3	76 (43)	97 (54)	100 (55)	
Grade 4	20 (11)	12 (7)	12 (7)	
Grade 5	15 (9)	24 (13)	22 (12)	
Bleeding, n (%)				0.46
Grade 3	0	2 (1)	3 (2)	
		(1)	1 (1)	
		0	1 (1)	
				0.62
		(16)	28 (15)	
		(3)	7 (4)	
		(1)	2 (1)	
				<0.001
			(2)	1 (1)	
Atrial fibrillation, n (%)				0.05
Grade 3	5 (3)	15 (8)	10 (6)	
Grade 4	0	2 (1)	0	
Hypertension, n (%)				<0.001
Grade 3	24 (14)	53 (29)	60 (33)	
Grade 4	1 (1)	0	1 (1)	
Secondary cancer, n (%)				0.17
Grade 3	6 (3)	5 (3)	13 (7)	
Grade 4	0	1 (1)	1 (1)	
Grade 5	1 (1)	4 (2)	1 (1)	
Unexplained or unwitnessed death, n (%)				0.24
Grade 5	2 (1)	7 (4)	4 (2)	

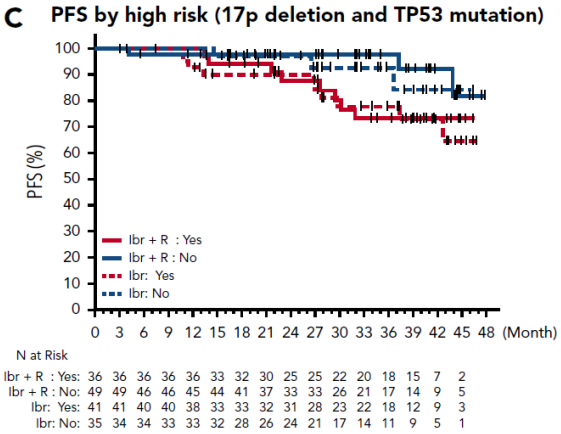
Woyach JA, et al. *N Engl J Med.* 2018; 379: 2517-2528

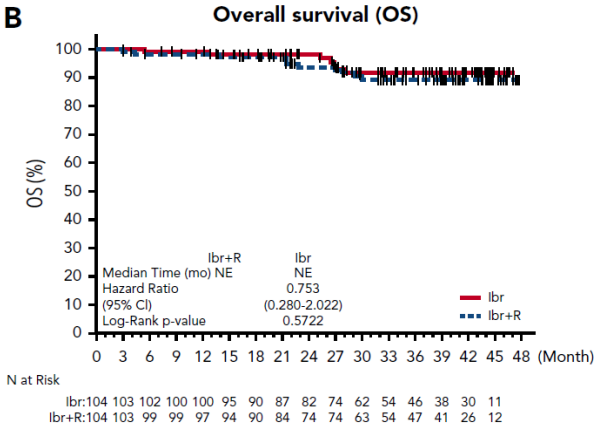
Screen 3 & 6 With the information you have now what treatment would you initiate?

I vs IR Burger

A randomized phase 2 trial of ibrutinib vs ibrutinib + rituximab in R/R CLL patients
Median FU: 36 mo
Primary endpoint: PFS
Secondary endpoint: OS





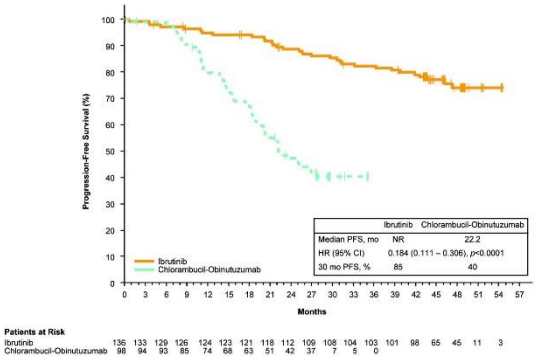


Burger et al. Blood 2019; 133(10):1011-1019

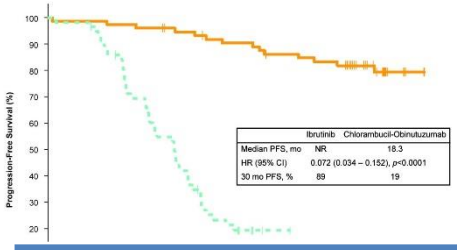
Screen 6 & 7 With the information you have now what treatment would you initiate? I vs Chl+G vs IG Tedeschi

A Cross-trial Comparison of Single-Agent Ibrutinib Versus Chlorambucil-Obinutuzumab in Previously Untreated Patients With Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma
Median follow-up was 48.8 months in the ibrutinib arm of RESONATE-2™ and 31.3 months for both arms of iLLUMINATE
Primary analysis: Investigator-assessed PFS with ibrutinib from RESONATE-2™ vs chlorambucil-G from iLLUMINATE
Secondary analysis: Investigator-assessed PFS in genomic high-risk patients (TP53 mutation, del11q, and/or unmutated IGHV), medical resource utilization during the first 6 months on study treatment

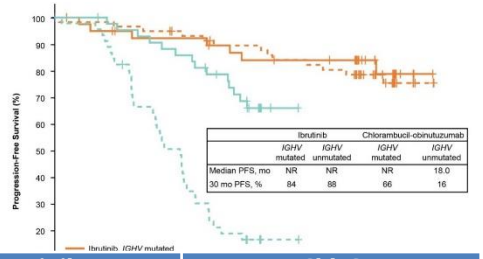
PFS in overall population



PFS in high-risk population



PFS per IGHV mutational status



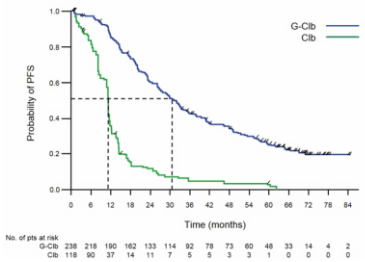
	Ibrutinib N = 135		Chl-G N = 97	
	AE Reporting Period[a]	First 6 Months	AE Reporting Period[a]	First 6 Months
Median duration of treatment, month (range)	46.9 (0.7-54.5)	–	5.1 (0.0-6.3)	–
Any grade ≥ 3 AEs, n (%)	109 (81)	68 (50)	69 (71)	69 (71)
Most common nonhematologic grade ≥ 3 AEs, n (%)[b]				
Pneumonia	16 (12)	4 (3)	4 (4)	3 (3)
Hypertension	10 (7)	5 (4)	4 (4)	4 (4)
Hyponatremia	7 (5)	2 (1)	1 (1)	1 (1)
Infusion-related reaction	0	0	6 (6)	6 (6)
Hematologic grade ≥ 3 AEs, n (%)				
Neutropenia[c]	20 (15)	11 (8)	47 (48)	47 (48)
Anemia	9 (7)	8 (6)	6 (6)	6 (6)
Thrombocytopenia[d]	9 (7)	6 (4)	10 (10)	10 (10)
Febrile neutropenia	5 (4)	1 (1)	7 (7)	7 (7)

Tedeschi A, et al. *Haematologica*. 2019 Aug [Epub ahead of print].

Screen 4 With the information you have now what treatment would you initiate? Chl vs ChlG CLL11

A randomized, open-label phase 3 trial with chlorambucil-obinutuzumab vs chlorambucil in previously untreated patients with CLL and coexisting conditions.
Median observation time G-Clb vs Clb: 62.5 months, G-Clb vs R-Clb: 59.4 months
Primary endpoint: PFS (INV-assessed)
Secondary endpoint: OS

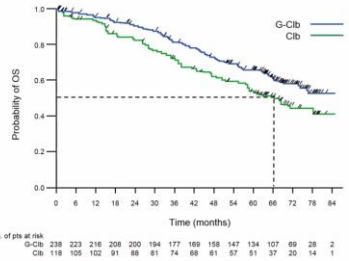
PFS: G-Clb vs Clb



	G-Clb n=238	Clb n=118
Patients with events, n (%)	173 (72.7)	107 (90.7)
5-year PFS, % (95% CI)	25 (19–31)	2 (0–4)
Median PFS, months	31.1	11.1
HR (95% CI), p-value	0.21 (0.16–0.28), p<0.0001	

Median observation time: 62.5 months

OS: G-Clb vs Clb



	G-Clb n=238	Clb n=118
Patients with events, n (%)	93 (39.1)	57 (48.3)
5-year OS, % (95% CI)	66 (60–72)	53 (43–62)
Median OS, months	NR	66.7
HR (95% CI), p-value	0.68 (0.49–0.94), p=0.0196	

Median observation time: 62.5 months

AEs: Overview

	G-Clb vs Clb		G-Clb vs R-Clb	
N (%)	G-Clb n=241	Clb n=116	G-Clb n=336	R-Clb n=321
≥1 AEs (any grade)	228 (95)	96 (83)	316 (94)	290 (90)
Grade 3–5 AEs	179 (74)	59 (51)	241 (72)	191 (60)
Serious AEs	113 (47)	45 (39)	150 (45)	124 (39)
Grade 5 (fatal) AEs	19 (8)	13 (11)	23 (7)	31 (10)
2nd malignancies*	11 (5)	1 (<1)	12 (4)	13 (4)
Infections†	1 (<1)	7 (6)	2 (<1)	2 (<1)

No new safety signals detected

*Neoplasms benign, malignant and unspecified (MedDRA SOC), occurring 6 months after first study drug intake; †all AEs classified as infections and infestations (MedDRA SOC)

AEs: Late onset

	G-Clb vs Clb		G-Clb vs R-Clb	
N (%)	G-Clb n=241	Clb n=116	G-Clb n=336	R-Clb n=321
Prolonged neutropenia,*† n/N	5/184 (3)	8/86 (9)	5/256 (2)	10/268 (4)
Late onset neutropenia,‡§ n/N	37/213 (17)	10/90 (11)	45/297 (15)	36/304 (12)
Second malignancies¶	33 (14)	8 (7)	37 (11)	33 (10)
Squamous cell carcinoma	6 (2)	0 (0)	6 (2)	5 (2)
Basal cell carcinoma	5 (2)	1 (<1)	6 (2)	4 (1)

No new late-onset toxicity detected

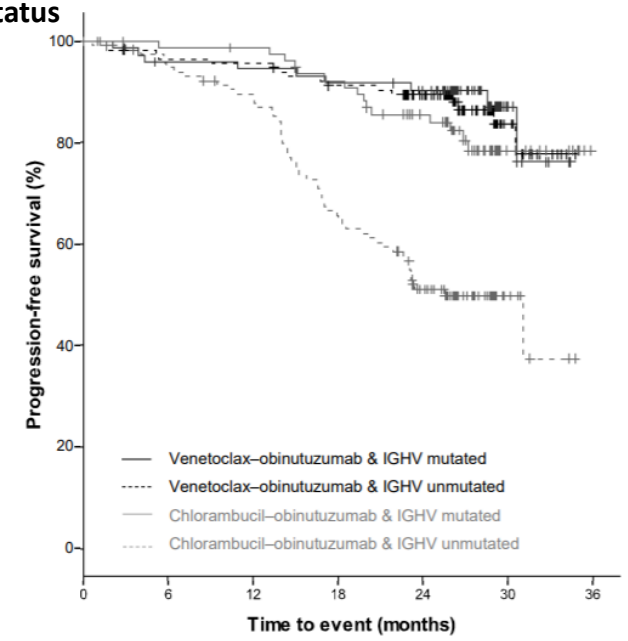
*Neutropenia not resolved within 28 days of treatment completion; †includes patients who completed treatment with a neutrophil assessment available 24–41 days after EOT; ‡neutropenia (<1000 cells/mm³) occurring ≥28 days after treatment completion or discontinuation; §includes patients who completed treatment with a neutrophil assessment available 24–200 days after EOT; ¶second malignancies starting 6 months after initiation of study treatment

Goede V. et al. EHA 2018 abstract and oral presentation S151

Screen 4 & 5 With the information you have now what treatment would you initiate? VG vs ChlG CLL14

A randomized, open-label phase 3 trial with venetoclax-obinutuzumab vs chlorambucil-obinutuzumab previously untreated patients with CLL and coexisting conditions. Median FU: 28.1 mo, Primary endpoint: PFS, Secondary endpoint: OS

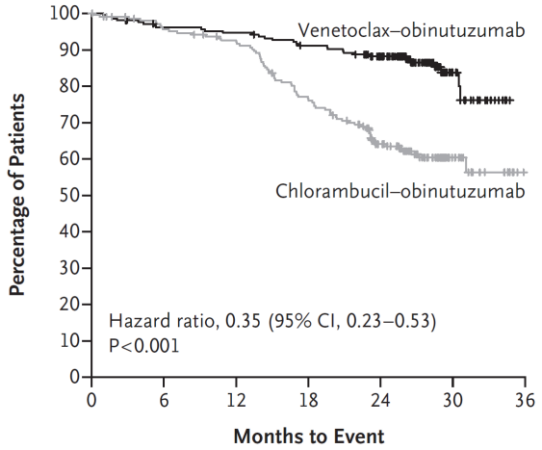
Investigator-assessed progression-free survival according to IGHV mutational status



Patients at risk							
Venetoclax–obinutuzumab & IGHV mutated	76	69	68	66	62	9	0
Venetoclax–obinutuzumab & IGHV unmutated	121	110	109	102	87	16	0
Chlorambucil–obinutuzumab & IGHV mutated	83	77	76	70	56	12	0
Chlorambucil–obinutuzumab & IGHV unmutated	123	109	100	74	50	8	0

Adverse Event	Venetoclax–Obinutuzumab (N=212)†			Chlorambucil–Obinutuzumab (N=214)		
	Maximum Grade 3	Maximum Grade 4	Maximum Grade 3 or 4	Maximum Grade 3	Maximum Grade 4	Maximum Grade 3 or 4
	number of patients (percent)					
Adverse event of grade 3 or 4	81 (38.2)	86 (40.6)	167 (78.8)	93 (43.5)	71 (33.2)	164 (76.6)
Adverse events of grade 3 or 4 that occurred in ≥3% of the patients in either treatment group‡						
Blood and lymphatic system disorders	59 (27.8)	69 (32.5)	128 (60.4)	61 (28.5)	57 (26.6)	118 (55.1)
Neutropenia	52 (24.5)	60 (28.3)	112 (52.8)	56 (26.2)	47 (22.0)	103 (48.1)
Thrombocytopenia	20 (9.4)	9 (4.2)	29 (13.7)	19 (8.9)	13 (6.1)	32 (15.0)
Anemia	16 (7.5)	1 (0.5)	17 (8.0)	13 (6.1)	1 (0.5)	14 (6.5)
Febrile neutropenia	7 (3.3)	4 (1.9)	11 (5.2)	4 (1.9)	4 (1.9)	8 (3.7)
Leukopenia	5 (2.4)	0	5 (2.4)	9 (4.2)	1 (0.5)	10 (4.7)
Infections and infestations	31 (14.6)	6 (2.8)	37 (17.5)	31 (14.5)	1 (0.5)	32 (15.0)
Pneumonia	8 (3.8)	1 (0.5)	9 (4.2)	8 (3.7)	0	8 (3.7)
Injury, poisoning, and procedural complications	21 (9.9)	5 (2.4)	26 (12.3)	29 (13.6)	1 (0.5)	30 (14.0)
Infusion-related reaction	16 (7.5)	3 (1.4)	19 (9.0)	21 (9.8)	1 (0.5)	22 (10.3)
Investigations	26 (12.3)	6 (2.8)	32 (15.1)	16 (7.5)	7 (3.3)	23 (10.7)
Neutrophil count decreased	7 (3.3)	2 (0.9)	9 (4.2)	4 (1.9)	6 (2.8)	10 (4.7)
Aspartate aminotransferase increased	5 (2.4)	0	5 (2.4)	7 (3.3)	0	7 (3.3)
Alanine aminotransferase increased	4 (1.9)	0	4 (1.9)	7 (3.3)	0	7 (3.3)
Metabolism and nutrition disorders§	19 (9.0)	6 (2.8)	25 (11.8)	11 (5.1)	1 (0.5)	12 (5.6)
Hyperglycemia	6 (2.8)	2 (0.9)	8 (3.8)	2 (0.9)	1 (0.5)	3 (1.4)
Gastrointestinal disorders ¶	16 (7.5)	1 (0.5)	17 (8.0)	6 (2.8)	1 (0.5)	7 (3.3)
Diarrhea‖	9 (4.2)	0	9 (4.2)	1 (0.5)	0	1 (0.5)
Cardiac disorders	9 (4.2)	1 (0.5)	10 (4.7)	10 (4.7)	2 (0.9)	12 (5.6)
Neoplasms benign, malignant, and unspecified, including cysts and polyps	10 (4.7)	3 (1.4)	13 (6.1)	7 (3.3)	1 (0.5)	8 (3.7)
Vascular disorders**	12 (5.7)	2 (0.9)	14 (6.6)	7 (3.3)	0	7 (3.3)
General disorders and administration-site conditions ††	14 (6.6)	0	14 (6.6)	6 (2.8)	0	6 (2.8)

A Progression-free Survival, Assessed by Investigator



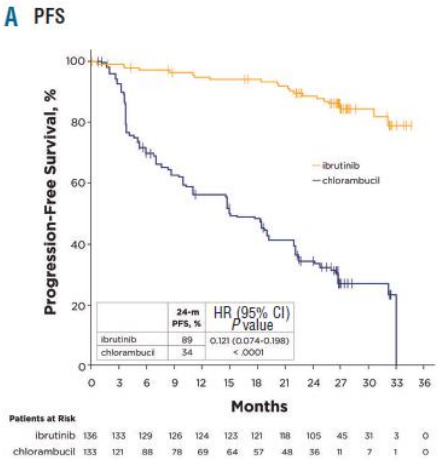
No. at Risk							
Venetoclax–obinutuzumab	216	195	192	183	153	25	0
Chlorambucil–obinutuzumab	216	194	184	152	110	21	0

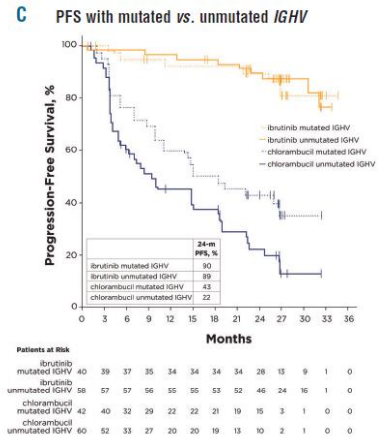
Fischer et al. N Engl J Med 2019;380:2225-36.

Screen 6 With the information you have now what treatment would you initiate?

I vs Chl RESONATE-2

A randomized, open-label phase 3 trial with ibrutinib vs chlorambucil in previously untreated patients with CLL.
Median FU: 36 mo
Primary endpoint: PFS
Secondary endpoint: OS





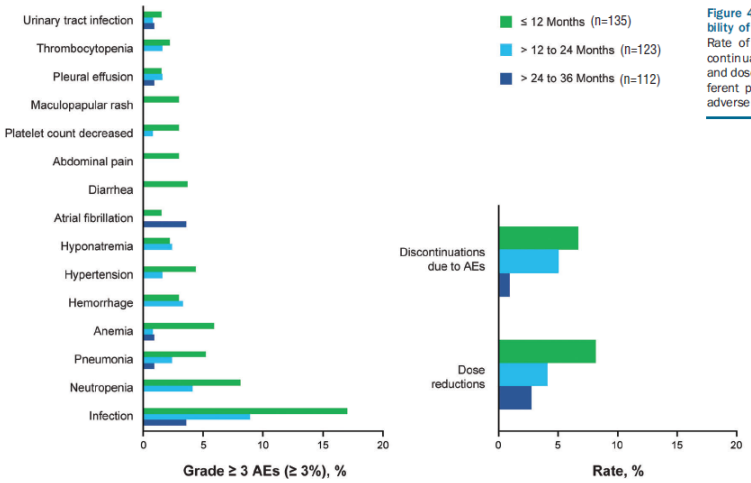


Figure 4. Safety and tolerability of ibrutinib over time. Rate of grade ≥3 AEs, discontinuations due to AEs, and dose reductions over different periods of time. AE, adverse events.

Barr P.M. Haematologica 2018; 103(9): 1502-1510

Screen 4 & 7 With the information you have now what treatment would you initiate?

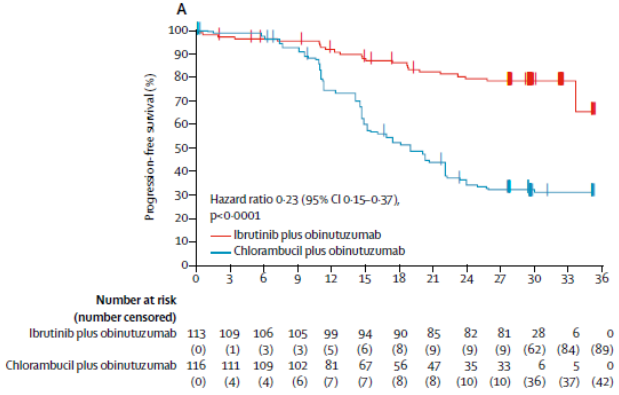
IG vs ChlG iLLUMINATE

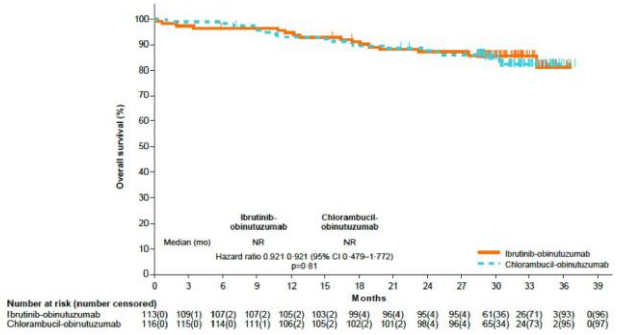
A randomized, open-label phase 3 trial with ibrutinib-obinutuzumab vs chlorambucil-obinutuzumab in previously untreated patients with CLL.

Median FU: 31.3 mo

Primary endpoint: PFS

Secondary endpoint: OS





	Ibrutinib plus obinutuzumab group (n=113)			Chlorambucil plus obinutuzumab group (n=115)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
TEAE period*						
All	25 (22%)	49 (43%)	28 (25%)	29 (25%)	49 (43%)	31 (27%)
Neutropenia	8 (7%)	20 (18%)	21 (19%)	20 (17%)	32 (28%)	21 (18%)
Thrombocytopenia	19 (17%)	17 (15%)	4 (4%)	17 (15%)	6 (5%)	6 (5%)
Diarrhoea	35 (31%)	3 (3%)	0	12 (10%)	0	0
Cough	29 (26%)	1 (1%)	0	14 (12%)	0	0
Infusion-related reaction	26 (23%)	2 (2%)	0	58 (50%)	6 (5%)	3 (3%)
Arthralgia	24 (21%)	1 (1%)	0	12 (10%)	0	0
Pyrexia	20 (18%)	2 (2%)	0	29 (25%)	1 (1%)	0
Fatigue	20 (18%)	0	0	17 (15%)	2 (2%)	0
Back pain	20 (18%)	0	0	11 (10%)	1 (1%)	0
Anaemia	15 (13%)	4 (4%)	0	20 (17%)	9 (8%)	0
Hypertension	15 (13%)	4 (4%)	0	1 (1%)	3 (3%)	1 (1%)
Constipation	18 (16%)	0	0	13 (11%)	1 (1%)	0
Rash maculopapular	15 (13%)	2 (2%)	0	2 (2%)	0	0
Upper respiratory tract infection	15 (13%)	1 (1%)	0	7 (6%)	0	0
Pneumonia	7 (6%)	7 (6%)	1 (1%)	3 (3%)	3 (3%)	1 (1%)
Muscle spasms	15 (13%)	0	0	7 (6%)	0	0
Hyperuricaemia	14 (12%)	0	1 (1%)	0	0	0
Nausea	14 (12%)	0	0	35 (30%)	0	0
Oedema peripheral	14 (12%)	0	0	8 (7%)	0	0
Atrial fibrillation	8 (7%)	6 (5%)	0	0	0	0
Urinary tract infection	10 (9%)	3 (3%)	0	7 (6%)	1 (1%)	0
Insomnia	13 (12%)	0	0	5 (4%)	0	0
Nasopharyngitis	13 (12%)	0	0	4 (3%)	0	0
Conjunctivitis	12 (11%)	0	0	2 (2%)	0	0
Asthenia	11 (10%)	0	0	17 (15%)	0	0
Dyspnoea	9 (8%)	1 (1%)	1 (1%)	15 (13%)	1 (1%)	0
Vomiting	11 (10%)	0	0	14 (12%)	0	0
Headache	9 (8%)	0	0	12 (10%)	1 (1%)	0
Febrile neutropenia	1 (1%)	2 (2%)	3 (3%)	1 (1%)	6 (5%)	1 (1%)
Hyperglycaemia	4 (4%)	2 (2%)	0	3 (3%)	4 (3%)	0
Neutrophil count decreased	1 (1%)	4 (4%)	0	1 (1%)	0	0
Leukopenia	3 (3%)	1 (1%)	0	0	2 (2%)	1 (1%)
Hepatic function abnormal	0	2 (2%)	1 (1%)	0	1 (1%)	0
Acute coronary syndrome	0	3 (3%)	0	0	0	0
Tumour lysis syndrome†	1 (1%)	0	0	4 (3%)	3 (3%)	0

Moreno C. et al. Lancet Oncol 2018
https://doi.org/10.1016/S1470-2045(18)30788-5

Screen 8 With the information you have now what treatment would you initiate? Acala +G vs acala vs ChlG

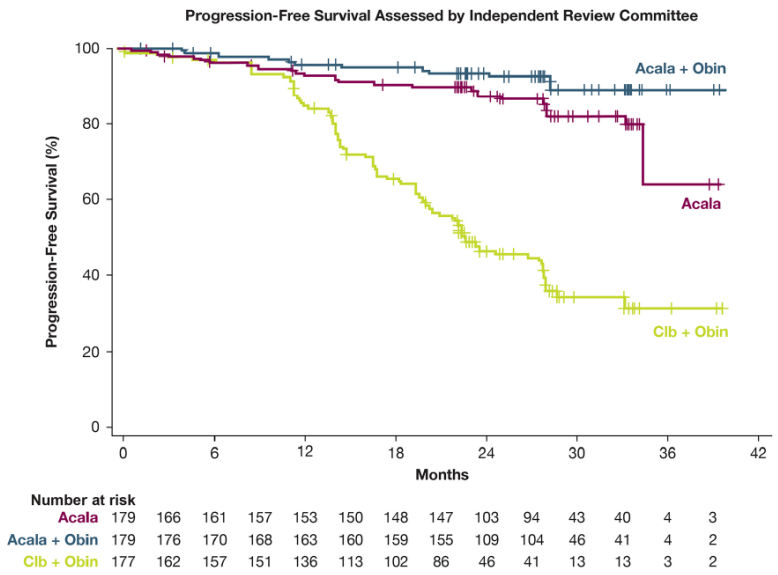
Multicenter, open-label phase 3 trial with acalabrutinib + G vs acalabrutinib vs chlorambucil G in treatment naieve CLL patients

≥65y or <65y with coexisting conditions

Median FU: 28 mo

Primary endpoint: PFS

Secondary endpoint: OS



Median OS was not reached in any arm; (HR [95% CI]; acalabrutinib + O vs O + Clb, 0.47 [0.21-1.06], *P*=0.0577; acalabrutinib vs O + Clb, 0.60 [0.28-1.27], *P*=0.1556).

	Acalabrutinib + Obinutuzumab (n=178)		Acalabrutinib (n=179)		Obinutuzumab + Chlorambucil (n=169)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any, n (%)	171 (96)	125 (70)	170 (95)	89 (50)	167 (99)	118 (70)
Serious, n (%)	69 (39)	58 (33)	57 (32)	53 (30)	37 (22)	33 (20)
Common AEs, n (%)						
Headache	71 (40)	2 (1)	66 (37)	2 (1)	20 (12)	0
Diarrhea	69 (39)	8 (4)	62 (35)	1 (1)	36 (21)	3 (2)
Neutropenia	56 (31)	53 (30)	19 (11)	17 (9)	76 (45)	70 (41)
Nausea	36 (20)	0	40 (22)	0	53 (31)	0
Infusion-related reaction	24 (13)	4 (2)	0	0	67 (40)	9 (5)
Thrombocytopenia	23 (13)	15 (8)	13 (7)	5 (3)	24 (14)	20 (12)
Anemia	21 (12)	10 (6)	25 (14)	12 (7)	20 (12)	12 (7)
Pneumonia	19 (11)	10 (6)	13 (7)	4 (2)	5 (3)	3 (2)
Tumor lysis syndrome[a]	3 (2)	2 (1)	0	0	15 (9)	13 (8)
Febrile neutropenia	3 (2)	3 (2)	2 (1)	2 (1)	9 (5)	9 (5)

[a]By clinical assessment.
AE, adverse event.

Sharman J. et al. ASH Annual Meeting 2019 abstract 31

What if the patient was 70y old and **unfit**? Del17p/TP53 mutation, mIGHV
With the information you have now what treatment would you initiate?

CASE 3 – timepoint 3


Picture of patient


Performance status


CIRS


Del 17P/TP53
IGHV Mutated

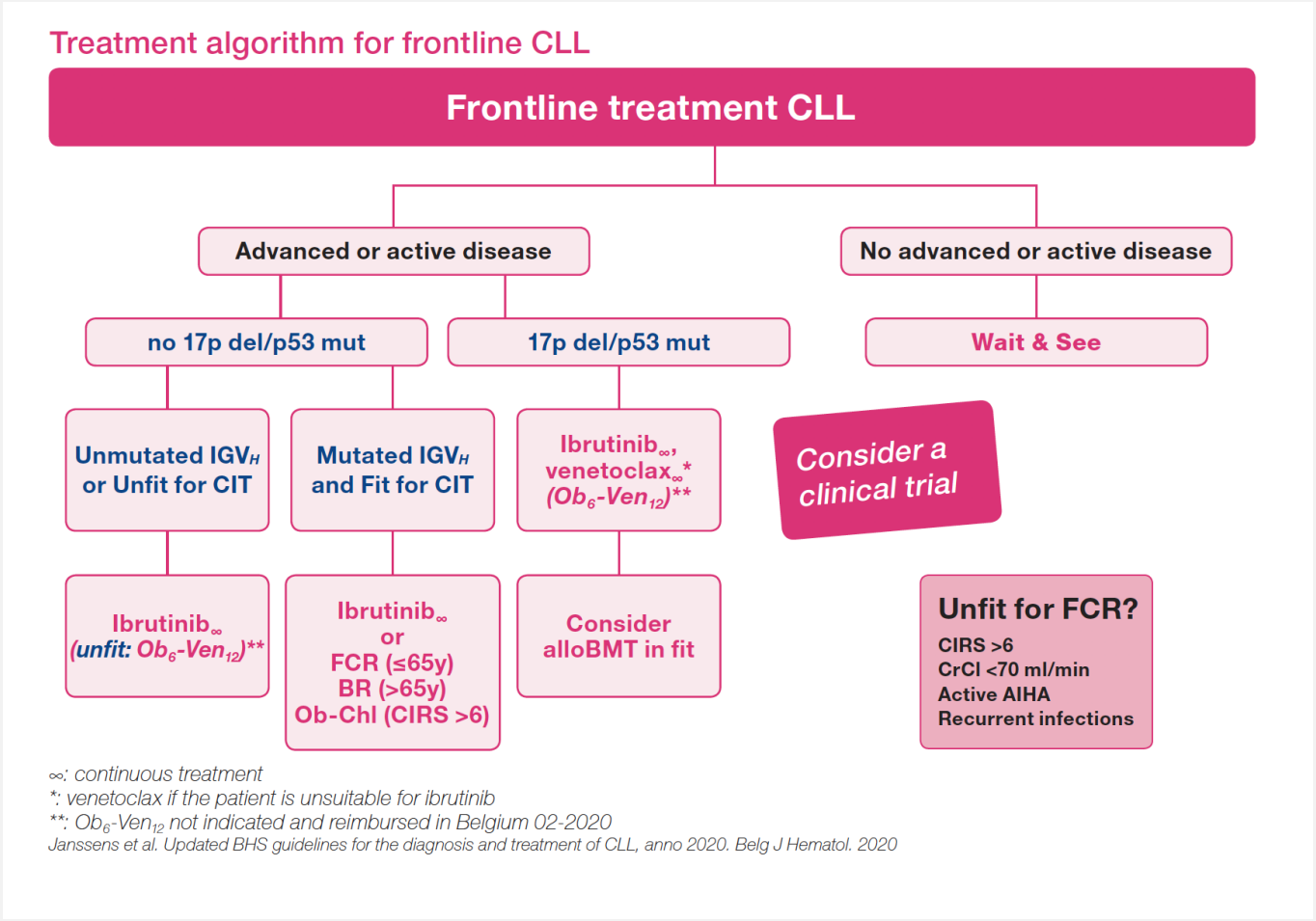
1. Ibrutinib — ALLIANCE
2. Ibrutinib + G — iLLUMUNATE
3. Venetoclax + G — CLL14
4. Venetoclax monotherapy — M13-982 Stilgenbauer et al.
5. Acalabrutinib (+/- G) — ELEVATE TN

BHS
HOVON
Hallek
EHA/ESMO

BHS[1]

Screen With the information you have now what treatment would you initiate?

Supporting guidelines update

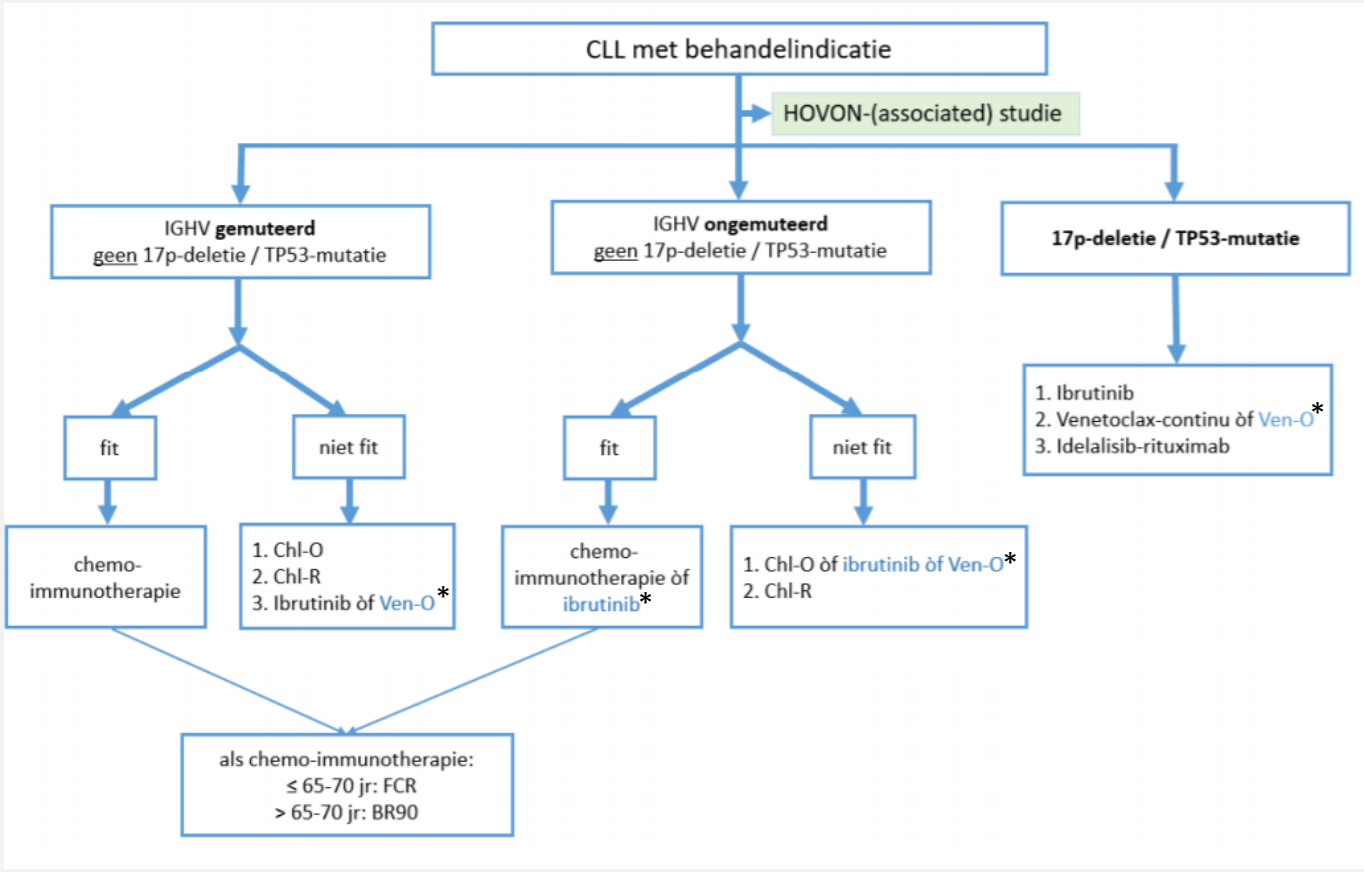


[1] *Janssens et al. Updated BHS guidelines for the diagnosis and treatment of CLL. BJH 2020*

HOVON[2]

Screen With the information you have now what treatment would you initiate?

Supporting guidelines update



*Deze medicatie kan op dit moment nog niet voorgeschreven worden, omdat het ófwel nog niet vergoed wordt ófwel nog geen “indicatie” heeft gekregen.

[2]HOVON CLL Concept richtlijn 2019 http://www.hovon.nl/behandeladvies/behandeladvies-leukemie/cll.html

Hallek[3]

Screen With the information you have now what treatment would you initiate?

Supporting guidelines update

CLL first line treatment (updated June 2019)

Stage	del(17p) or p53mut	Fitness	IGVH	Therapy
Binet A-B, Rai 0-II, inactive disease	Irrelevant	Irrelevant	Irrelevant	None
Active disease or Binet C or Rai III-IV	Yes	Irrelevant	Irrelevant	Ibrutinib or Venetoclax + Obinutuzumab or Idelalisib + Rituximab (if contraindications for ibrutinib)*
	No	Go go	M	FCR (BR above 65 years) or ibrutinib*
			U	Ibrutinib or FCR (BR above 65 years)*
		Slow go	M	Venetoclax + Obinutuzumab or Chlorambucil + Obinutuzumab or Ibrutinib*
			U	Venetoclax + Obinutuzumab or Ibrutinib or Chlorambucil + Obinutuzumab*

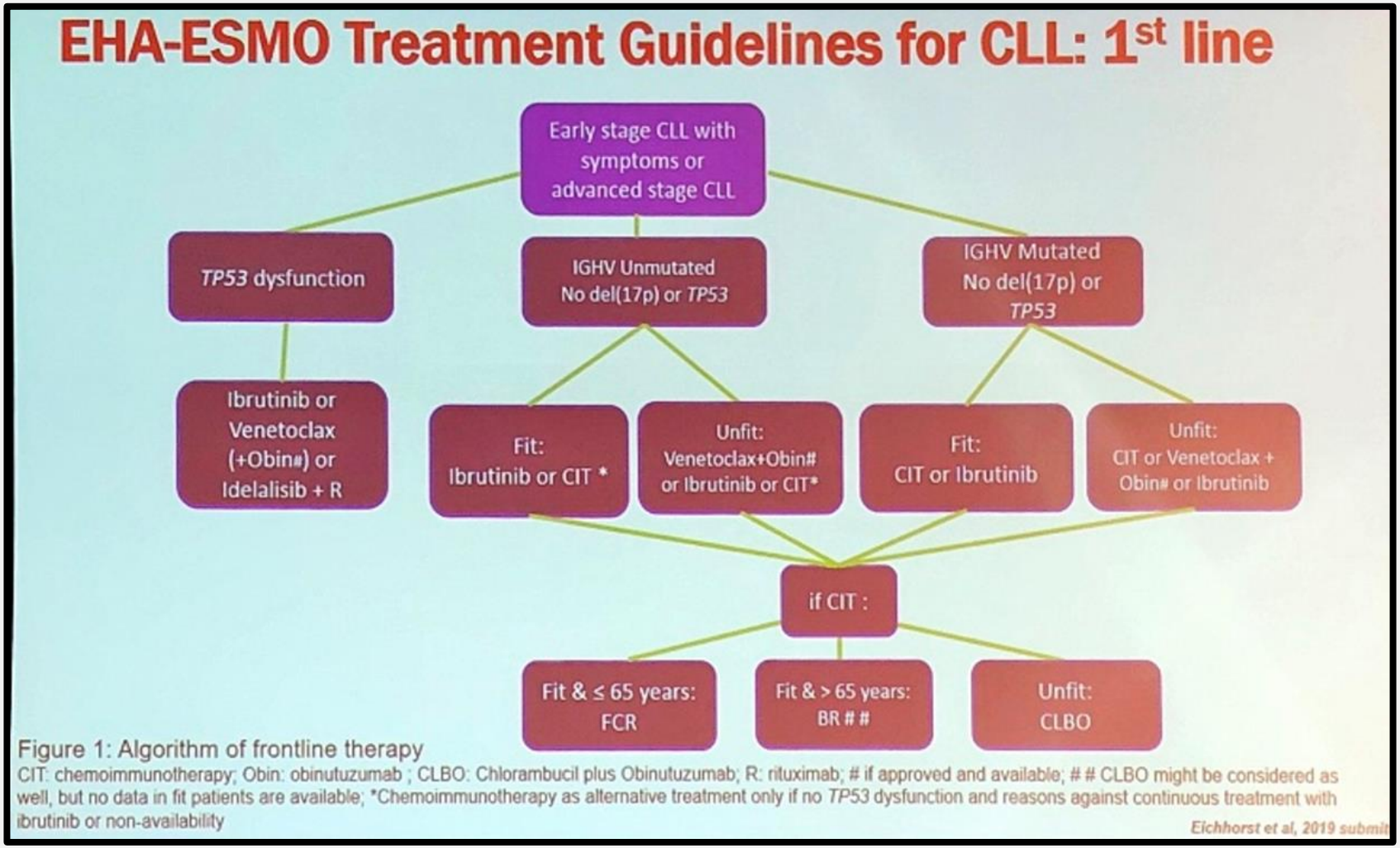
* Consider and discuss with patient: long-term vs fixed (6-12 m) duration therapy, lack of convincing evidence of overall survival differences, specific side effects of each therapeutic option (myelosuppression, infections, secondary malignancies for CIT; cardiac toxicity, bleeding and autoimmune disease for Ibru; TLS and infections for Ven-Obi; autoimmune disease (diarrhea) and opportunistic infections for Idelalisib).

[3]Hallek M. Am. J. Hematol. 2019; 94:1266-1287

EHA/ESMO[4]

Screen With the information you have now what treatment would you initiate?

Supporting guidelines update



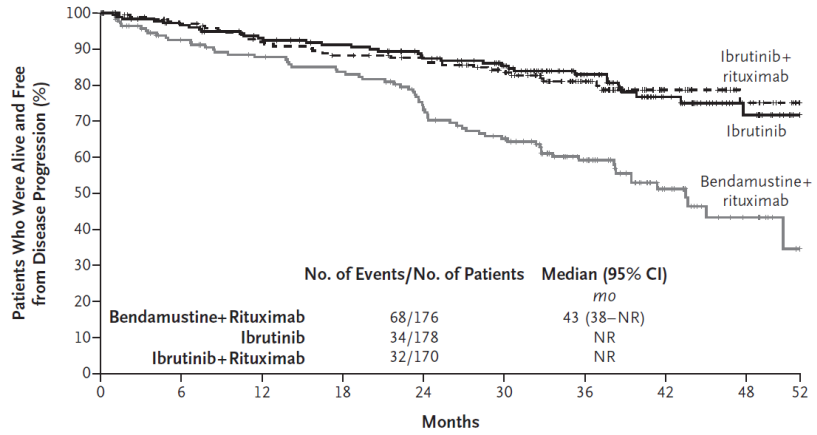
[4]Eichhorst et al. 2019 submitted

Screen 1 With the information you have now what treatment would you initiate?

I or IR ALLIANCE

A randomized, phase 3 study of I vs IR vs BR in 547 patients 65 years of age or older with previously untreated TN CLL . Median FU: 38 mo

Primary endpoint: PFS

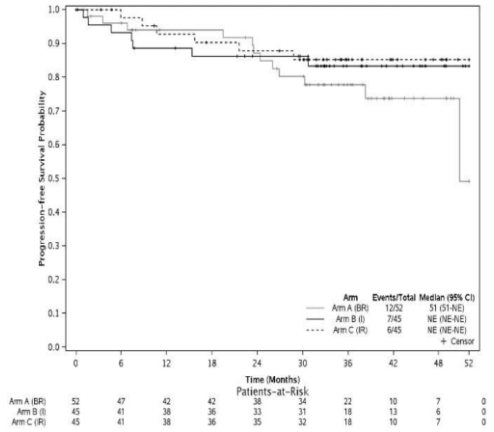


No. at Risk

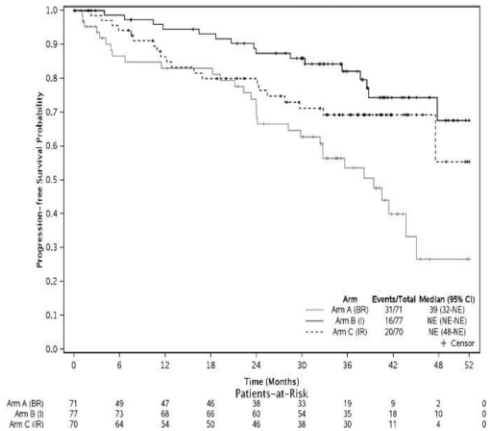
Bendamustine+rituximab	176	140	129	122	103	88	57	26	11	0
Ibrutinib	178	165	154	147	136	120	78	45	22	0
Ibrutinib+rituximab	170	159	145	138	132	115	74	40	20	0

Estimated PFS at 2 years (95% CI)	BR	I	IR
	74% (66-80)	87% (81-92)	88% (81-92)

Patients with Mutated IGHV (n=142)



Patients with Unmutated IGHV (n=218)



PFS was longer with ibrutinib-containing regimens among patients with m*IGHV* than with u*IGHV* but there was no significant interaction with IgHV mutation status

Woyach JA, et al. *N Engl J Med.* 2018; 379: 2517-2528

Screen 3 & 6 With the information you have now what treatment would you initiate?

I or IR ALLIANCE

Hematologic Adverse Events	BR (n=176)	I (n=180)	IR (n=181)	P Value*
Any, n (%)				<0.001
Grade 3	62 (35)	59 (33)	49 (27)	
Grade 4	45 (26)	15 (8)	21 (12)	
Anemia, n (%)				0.09
Grade 3	22 (12)	20 (11)	11 (6)	
Grade 4				
Decreased neutrophil count, n (%)				
Grade 3				
Grade 4				
Decreased platelet count, n (%)				
Grade 3				
Grade 4				

Non-Hematologic Adverse Events	BR (n=176)	I (n=180)	IR (n=181)	P Value*
Any, n (%)				0.04
Grade 3	76 (43)	97 (54)	100 (55)	
Grade 4	20 (11)	12 (7)	12 (7)	
Grade 5	15 (9)	24 (13)	22 (12)	
Bleeding, n (%)				0.46
Grade 3	0	2 (1)	3 (2)	
		(1)	1 (1)	
		0	1 (1)	
				0.62
		(16)	28 (15)	
		(3)	7 (4)	
		(1)	2 (1)	
				<0.001
		(2)	1 (1)	
Atrial fibrillation, n (%)				0.05
Grade 3	5 (3)	15 (8)	10 (6)	
Grade 4	0	2 (1)	0	
Hypertension, n (%)				<0.001
Grade 3	24 (14)	53 (29)	60 (33)	
Grade 4	1 (1)	0	1 (1)	
Secondary cancer, n (%)				0.17
Grade 3	6 (3)	5 (3)	13 (7)	
Grade 4	0	1 (1)	1 (1)	
Grade 5	1 (1)	4 (2)	1 (1)	
Unexplained or unwitnessed death, n (%)				0.24
Grade 5	2 (1)	7 (4)	4 (2)	

Woyach JA, et al. *N Engl J Med.* 2018; 379: 2517-2528

Screen 2 With the information you have now what treatment would you initiate?

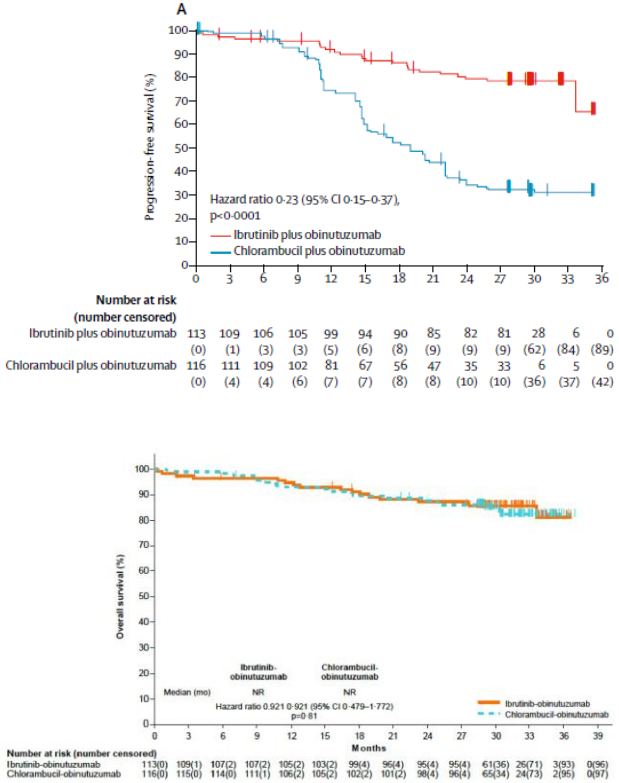
IG vs ChlG iLLUMINATE

A randomized, open-label phase 3 trial with ibrutinib-obinutuzumab vs chlorambucil-obinutuzumab in previously untreated patients with CLL.

Median FU: 31.3 mo

Primary endpoint: PFS

Secondary endpoint: OS



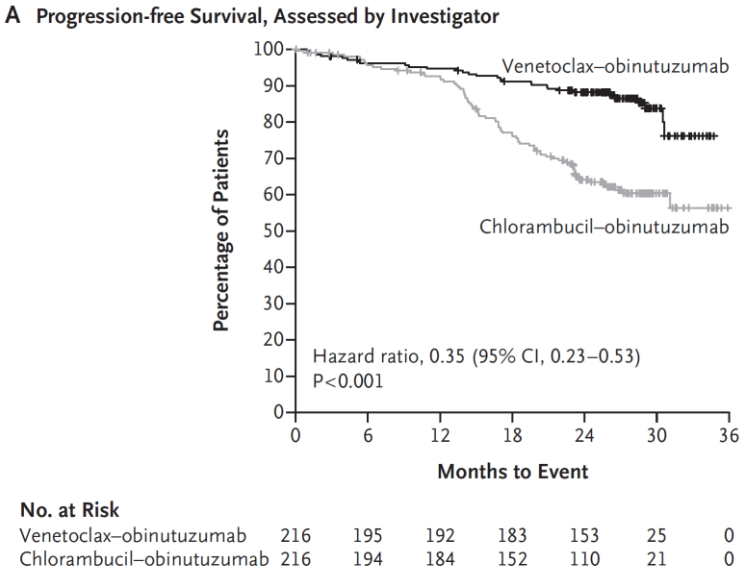
	Ibrutinib plus obinutuzumab group (n=113)			Chlorambucil plus obinutuzumab group (n=115)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
TEAE period*						
All	25 (22%)	49 (43%)	28 (25%)	29 (25%)	49 (43%)	31 (27%)
Neutropenia	8 (7%)	20 (18%)	21 (19%)	20 (17%)	32 (28%)	21 (18%)
Thrombocytopenia	19 (17%)	17 (15%)	4 (4%)	17 (15%)	6 (5%)	6 (5%)
Diarrhoea	35 (31%)	3 (3%)	0	12 (10%)	0	0
Cough	29 (26%)	1 (1%)	0	14 (12%)	0	0
Infusion-related reaction	26 (23%)	2 (2%)	0	58 (50%)	6 (5%)	3 (3%)
Arthralgia	24 (21%)	1 (1%)	0	12 (10%)	0	0
Pyrexia	20 (18%)	2 (2%)	0	29 (25%)	1 (1%)	0
Fatigue	20 (18%)	0	0	17 (15%)	2 (2%)	0
Back pain	20 (18%)	0	0	11 (10%)	1 (1%)	0
Anaemia	15 (13%)	4 (4%)	0	20 (17%)	9 (8%)	0
Hypertension	15 (13%)	4 (4%)	0	1 (1%)	3 (3%)	1 (1%)
Constipation	18 (16%)	0	0	13 (11%)	1 (1%)	0
Rash maculopapular	15 (13%)	2 (2%)	0	2 (2%)	0	0
Upper respiratory tract infection	15 (13%)	1 (1%)	0	7 (6%)	0	0
Pneumonia	7 (6%)	7 (6%)	1 (1%)	3 (3%)	3 (3%)	1 (1%)
Muscle spasms	15 (13%)	0	0	7 (6%)	0	0
Hyperuricaemia	14 (12%)	0	1 (1%)	0	0	0
Nausea	14 (12%)	0	0	35 (30%)	0	0
Oedema peripheral	14 (12%)	0	0	8 (7%)	0	0
Atrial fibrillation	8 (7%)	6 (5%)	0	0	0	0
Urinary tract infection	10 (9%)	3 (3%)	0	7 (6%)	1 (1%)	0
Insomnia	13 (12%)	0	0	5 (4%)	0	0
Nasopharyngitis	13 (12%)	0	0	4 (3%)	0	0
Conjunctivitis	12 (11%)	0	0	2 (2%)	0	0
Asthenia	11 (10%)	0	0	17 (15%)	0	0
Dyspnoea	9 (8%)	1 (1%)	1 (1%)	15 (13%)	1 (1%)	0
Vomiting	11 (10%)	0	0	14 (12%)	0	0
Headache	9 (8%)	0	0	12 (10%)	1 (1%)	0
Febrile neutropenia	1 (1%)	2 (2%)	3 (3%)	1 (1%)	6 (5%)	1 (1%)
Hyperglycaemia	4 (4%)	2 (2%)	0	3 (3%)	4 (3%)	0
Neutrophil count decreased	1 (1%)	4 (4%)	0	1 (1%)	0	0
Leukopenia	3 (3%)	1 (1%)	0	0	2 (2%)	1 (1%)
Hepatic function abnormal	0	2 (2%)	1 (1%)	0	1 (1%)	0
Acute coronary syndrome	0	3 (3%)	0	0	0	0
Tumour lysis syndrome†	1 (1%)	0	0	4 (3%)	3 (3%)	0

Moreno C. et al. Lancet Oncol 2018
https://doi.org/10.1016/S1470-2045(18)30788-5

Screen 3 With the information you have now what treatment would you initiate?

VG vs ChlG CLL14

A randomized, open-label phase 3 trial with venetoclax-obinutuzumab vs chlorambucil-obinutuzumab previously untreated patients with CLL and coexisting conditions.
Median FU: 28.1 mo
Primary endpoint: PFS
Secondary endpoint: OS



Adverse Event	Venetoclax–Obinutuzumab (N=212)†			Chlorambucil–Obinutuzumab (N=214)		
	Maximum Grade 3	Maximum Grade 4	Maximum Grade 3 or 4	Maximum Grade 3	Maximum Grade 4	Maximum Grade 3 or 4
	number of patients (percent)					
Adverse event of grade 3 or 4	81 (38.2)	86 (40.6)	167 (78.8)	93 (43.5)	71 (33.2)	164 (76.6)
Adverse events of grade 3 or 4 that occurred in ≥3% of the patients in either treatment group‡						
Blood and lymphatic system disorders	59 (27.8)	69 (32.5)	128 (60.4)	61 (28.5)	57 (26.6)	118 (55.1)
Neutropenia	52 (24.5)	60 (28.3)	112 (52.8)	56 (26.2)	47 (22.0)	103 (48.1)
Thrombocytopenia	20 (9.4)	9 (4.2)	29 (13.7)	19 (8.9)	13 (6.1)	32 (15.0)
Anemia	16 (7.5)	1 (0.5)	17 (8.0)	13 (6.1)	1 (0.5)	14 (6.5)
Febrile neutropenia	7 (3.3)	4 (1.9)	11 (5.2)	4 (1.9)	4 (1.9)	8 (3.7)
Leukopenia	5 (2.4)	0	5 (2.4)	9 (4.2)	1 (0.5)	10 (4.7)
Infections and infestations	31 (14.6)	6 (2.8)	37 (17.5)	31 (14.5)	1 (0.5)	32 (15.0)
Pneumonia	8 (3.8)	1 (0.5)	9 (4.2)	8 (3.7)	0	8 (3.7)
Injury, poisoning, and procedural complications	21 (9.9)	5 (2.4)	26 (12.3)	29 (13.6)	1 (0.5)	30 (14.0)
Infusion-related reaction	16 (7.5)	3 (1.4)	19 (9.0)	21 (9.8)	1 (0.5)	22 (10.3)
Investigations	26 (12.3)	6 (2.8)	32 (15.1)	16 (7.5)	7 (3.3)	23 (10.7)
Neutrophil count decreased	7 (3.3)	2 (0.9)	9 (4.2)	4 (1.9)	6 (2.8)	10 (4.7)
Aspartate aminotransferase increased	5 (2.4)	0	5 (2.4)	7 (3.3)	0	7 (3.3)
Alanine aminotransferase increased	4 (1.9)	0	4 (1.9)	7 (3.3)	0	7 (3.3)
Metabolism and nutrition disorders§	19 (9.0)	6 (2.8)	25 (11.8)	11 (5.1)	1 (0.5)	12 (5.6)
Hyperglycemia	6 (2.8)	2 (0.9)	8 (3.8)	2 (0.9)	1 (0.5)	3 (1.4)
Gastrointestinal disorders ¶	16 (7.5)	1 (0.5)	17 (8.0)	6 (2.8)	1 (0.5)	7 (3.3)
Diarrhea‖	9 (4.2)	0	9 (4.2)	1 (0.5)	0	1 (0.5)
Cardiac disorders	9 (4.2)	1 (0.5)	10 (4.7)	10 (4.7)	2 (0.9)	12 (5.6)
Neoplasms benign, malignant, and unspecified, including cysts and polyps	10 (4.7)	3 (1.4)	13 (6.1)	7 (3.3)	1 (0.5)	8 (3.7)
Vascular disorders**	12 (5.7)	2 (0.9)	14 (6.6)	7 (3.3)	0	7 (3.3)
General disorders and administration-site conditions ††	14 (6.6)	0	14 (6.6)	6 (2.8)	0	6 (2.8)

Fischer et al. N Engl J Med 2019;380:2225-36.

Screen 4 With the information you have now what treatment would you initiate?

V monotherapy

Phase II open label study with 158 del(17p) CLL patients with relapsed/refractory or previously untreated CLL (n=153 and n=5, respectively). Median time on study was 26.6 months (range, 0 to 44.2 months).

n (%)	ORR	CR/CRi	nPR/PR	SD	PD	NE
All Patients, N=158	122 (77)	32 (20)	90 (57)	30 (19)	3 (2)	3* (2)
***TP53* mutation, n=55**	38 (69)	10 (18)	28 (51)	16 (29)	1 (2)	0
Unmutated *IGHV*, n=45	39 (87)	7 (16)	32 (71)	4 (9)	1 (2)	1 (2)
>2 prior therapies, n=68	48 (71)	6 (9)	42 (62)	18 (27)	1 (2)	1 (2)
Fludarabine refractory, n=45	35 (78)	11 (24)	24 (53)	10 (22)	0	0
ECOG score of 0, n=69	59 (86)	16 (23)	43 (62)	10 (15)	0	0
ECOG score of 1, n=78	55 (71)	14 (18)	41 (53)	17 (22)	3 (4)	3 (4)
ECOG score of 2, n=11	8 (73)	2 (18)	6 (55)	3 (27)	0	0
Beta-2 microglobulin ≥3 at baseline, n=25	19 (76)	6 (24)	13 (52)	5 (20)	1 (4)	0
Nodes ≥5 cm at baseline, n=76	60 (79)	10 (13)	50 (66)	14 (18)	1 (1)	1 (1)
Nodes ≥10 cm at baseline, n=21	16 (76)	2 (10)	14 (67)	5 (24)	0	0
High TLS risk,† n=62	47 (76)	5 (8)	42 (68)	14 (23)	0	1 (2)

ORR, objective response rate; CR, complete remission; CRi, complete remission with incomplete marrow recovery; nPR, nodular partial remission; PR, partial remission, SD, stable disease; PD, disease progression; NE, not evaluated for response; BCRi, B-cell receptor pathway inhibitor.
*One patient discontinued after the first dose of venetoclax, one patient died after three weeks of treatment due to liver dysfunction not related to venetoclax, and one patient had pseudo obstruction of the small bowel mesentery and retroperitoneum during dose ramp up and discontinued the study.

Stilgenbauer, Stephan, et al. *Journal of Clinical Oncology* 36.19 (2018): 1973-1980.

Screen 5 With the information you have now what treatment would you initiate? Acala +G vs acala vs ChlG

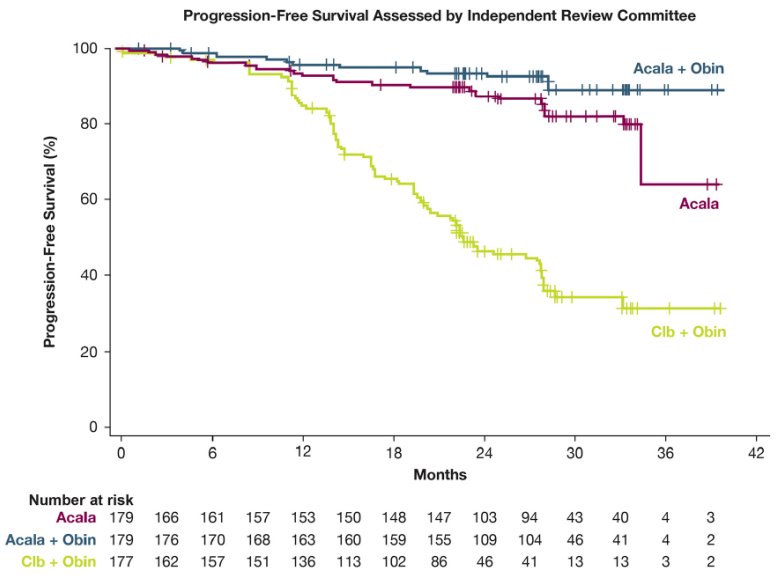
Multicenter, open-label phase 3 trial with acalabrutinib + G vs acalabrutinib vs chlorambucil G in treatment naieve CLL patients

≥65y or <65y with coexisting conditions

Median FU: 28 mo

Primary endpoint: PFS

Secondary endpoint: OS



Median OS was not reached in any arm; (HR [95% CI]; acalabrutinib + O vs O + Clb, 0.47 [0.21-1.06], *P*=0.0577; acalabrutinib vs O + Clb, 0.60 [0.28-1.27], *P*=0.1556).

	Acalabrutinib + Obinutuzumab (n=178)		Acalabrutinib (n=179)		Obinutuzumab + Chlorambucil (n=169)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any, n (%)	171 (96)	125 (70)	170 (95)	89 (50)	167 (99)	118 (70)
Serious, n (%)	69 (39)	58 (33)	57 (32)	53 (30)	37 (22)	33 (20)
Common AEs, n (%)						
Headache	71 (40)	2 (1)	66 (37)	2 (1)	20 (12)	0
Diarrhea	69 (39)	8 (4)	62 (35)	1 (1)	36 (21)	3 (2)
Neutropenia	56 (31)	53 (30)	19 (11)	17 (9)	76 (45)	70 (41)
Nausea	36 (20)	0	40 (22)	0	53 (31)	0
Infusion-related reaction	24 (13)	4 (2)	0	0	67 (40)	9 (5)
Thrombocytopenia	23 (13)	15 (8)	13 (7)	5 (3)	24 (14)	20 (12)
Anemia	21 (12)	10 (6)	25 (14)	12 (7)	20 (12)	12 (7)
Pneumonia	19 (11)	10 (6)	13 (7)	4 (2)	5 (3)	3 (2)
Tumor lysis syndrome[a]	3 (2)	2 (1)	0	0	15 (9)	13 (8)
Febrile neutropenia	3 (2)	3 (2)	2 (1)	2 (1)	9 (5)	9 (5)

[a]By clinical assessment.
AE, adverse event.

Sharman J. et al. ASH Annual Meeting 2019 abstract 31

CASE 2 – Timepoint 1

Patient profile:

Female
Age: 71 y
Unfit

No del17p/TP53 mutation
uIGHV

With the information you have now what treatment would you initiate?

Votable

CASE 2 – timepoint 1

Picture of patient

Performance status

CIRS

No Del 17p/TP53
IGHV Mutated

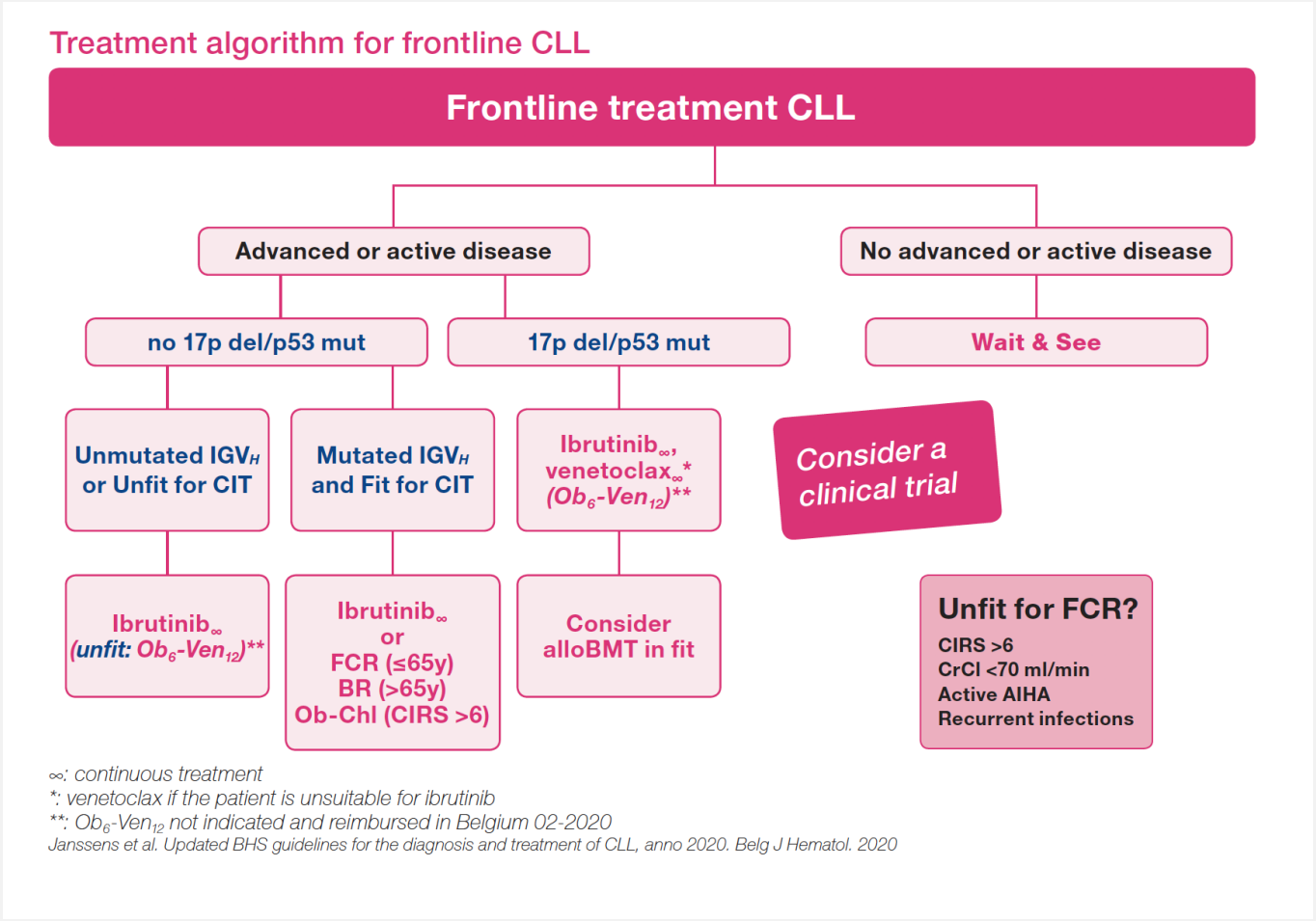
1. I
   - RESONATE-2
   - ALLIANCE
   - BURGER
2. BR
   - CLL10
3. Ibrutinib R
   - ALLIANCE
   - BURGER
4. V+G
   - CLL14
5. Chl+G
   - CLL11
   - CLL14
6. IG
   - iLLUMINATE
7. Acalabrutinib (+/- G)
   - ELEVATE TN

BHS
HOVON
Hallek
EHA/ESMO

BHS[1]

Screen With the information you have now what treatment would you initiate?

Supporting guidelines update

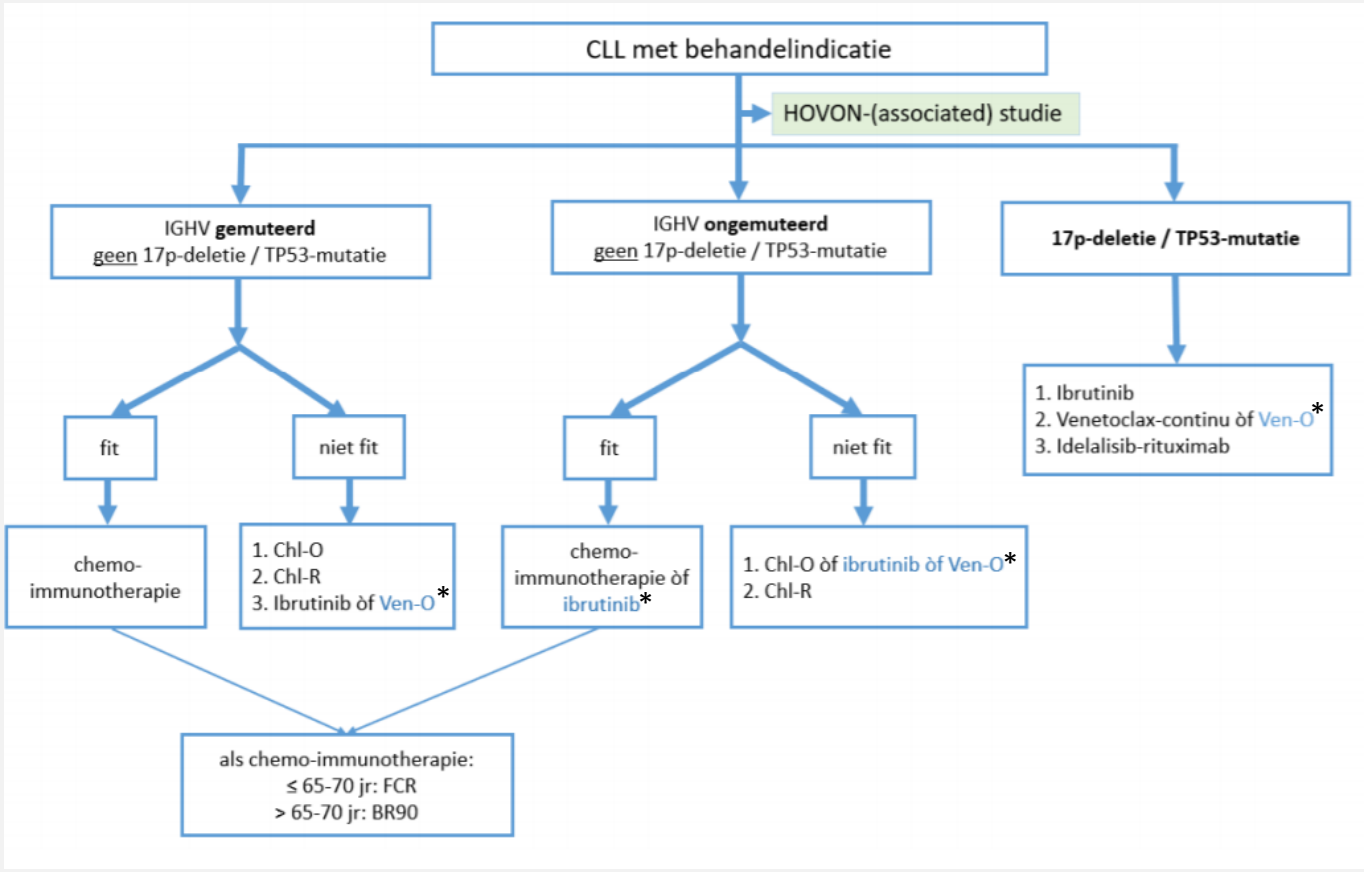


[1] *Janssens et al. Updated BHS guidelines for the diagnosis and treatment of CLL. BJH 2020*

HOVON[2]

Screen With the information you have now what treatment would you initiate?

Supporting guidelines update



*Deze medicatie kan op dit moment nog niet voorgeschreven worden, omdat het ófwel nog niet vergoed wordt ófwel nog geen “indicatie” heeft gekregen.

[2]HOVON CLL Concept richtlijn 2019 http://www.hovon.nl/behandeladvies/behandeladvies-leukemie/cll.html

Hallek[3]

Screen With the information you have now what treatment would you initiate?

Supporting guidelines update

CLL first line treatment (updated June 2019)

Stage	del(17p) or p53mut	Fitness	IGVH	Therapy
Binet A-B, Rai 0-II, inactive disease	Irrelevant	Irrelevant	Irrelevant	None
Active disease or Binet C or Rai III-IV	Yes	Irrelevant	Irrelevant	Ibrutinib or Venetoclax + Obinutuzumab or Idelalisib + Rituximab (if contraindications for ibrutinib)*
	No	Go go	M	FCR (BR above 65 years) or ibrutinib*
			U	Ibrutinib or FCR (BR above 65 years)*
		Slow go	M	Venetoclax + Obinutuzumab or Chlorambucil + Obinutuzumab or Ibrutinib*
			U	Venetoclax + Obinutuzumab or Ibrutinib or Chlorambucil + Obinutuzumab*

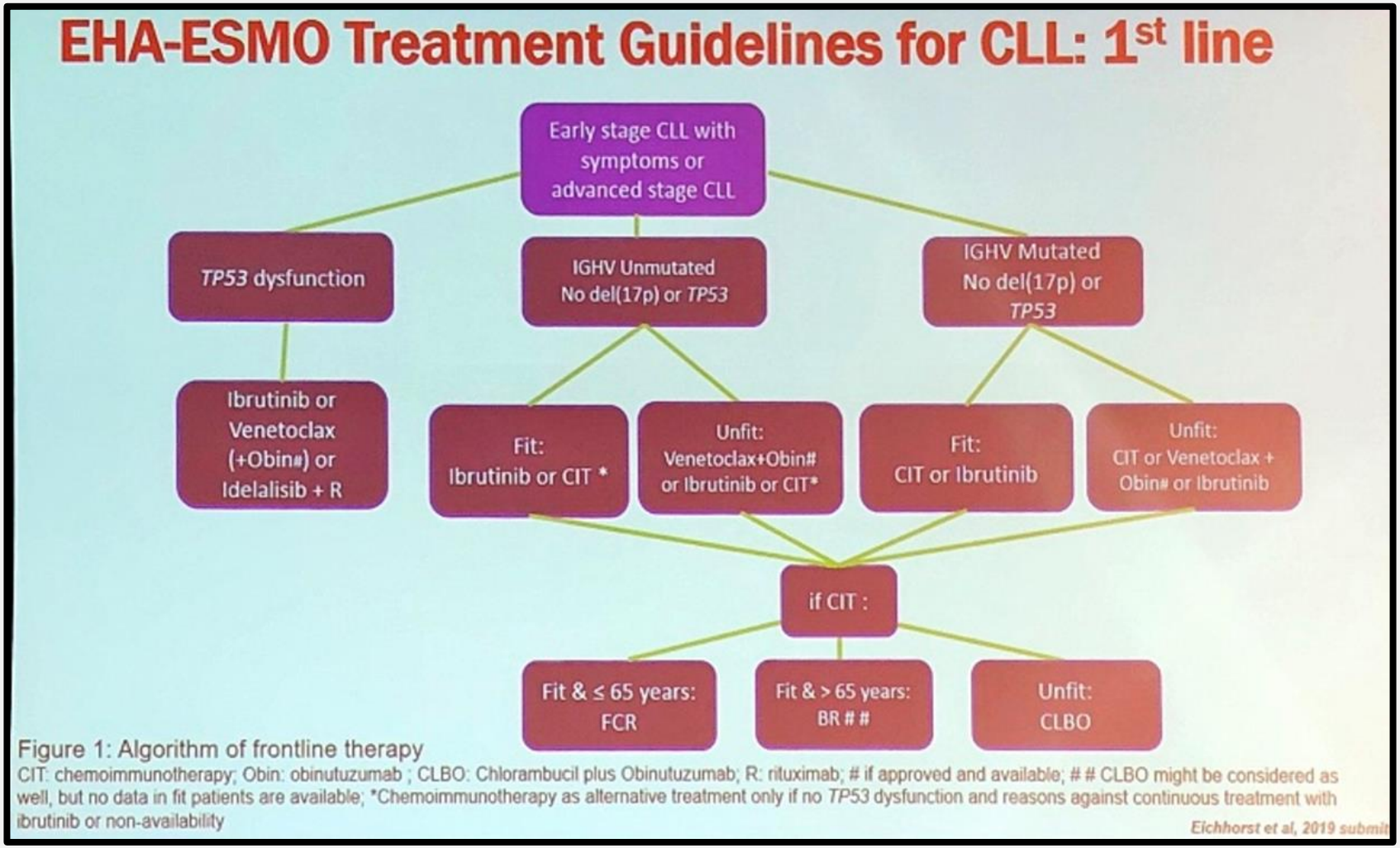
* Consider and discuss with patient: long-term vs fixed (6-12 m) duration therapy, lack of convincing evidence of overall survival differences, specific side effects of each therapeutic option (myelosuppression, infections, secondary malignancies for CIT; cardiac toxicity, bleeding and autoimmune disease for Ibru; TLS and infections for Ven-Obi; autoimmune disease (diarrhea) and opportunistic infections for Idelalisib).

[3]Hallek M. Am. J. Hematol. 2019; 94:1266-1287

EHA/ESMO[4]

Screen With the information you have now what treatment would you initiate?

Supporting guidelines update

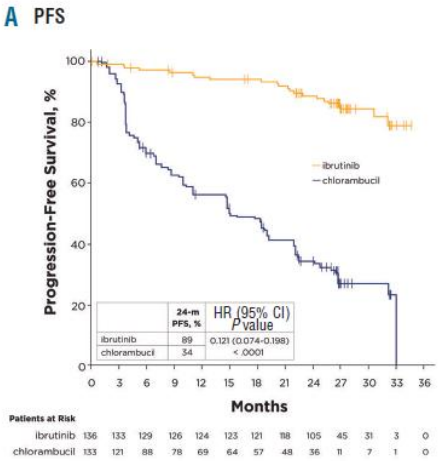


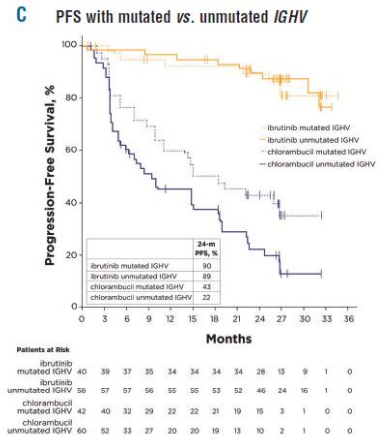
[4]Eichhorst et al. 2019 submitted

Screen 1 With the information you have now what treatment would you initiate?

I vs Chl RESONATE-2

A randomized, open-label phase 3 trial with ibrutinib vs chlorambucil in previously untreated patients with CLL.
Median FU: 36 mo
Primary endpoint: PFS
Secondary endpoint: OS





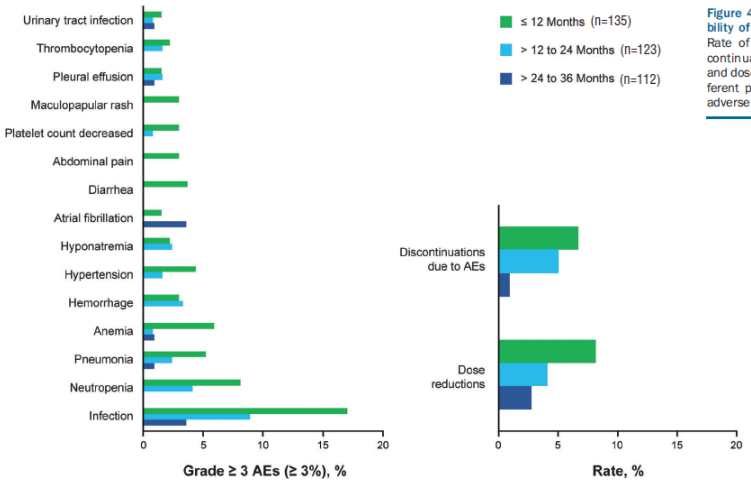


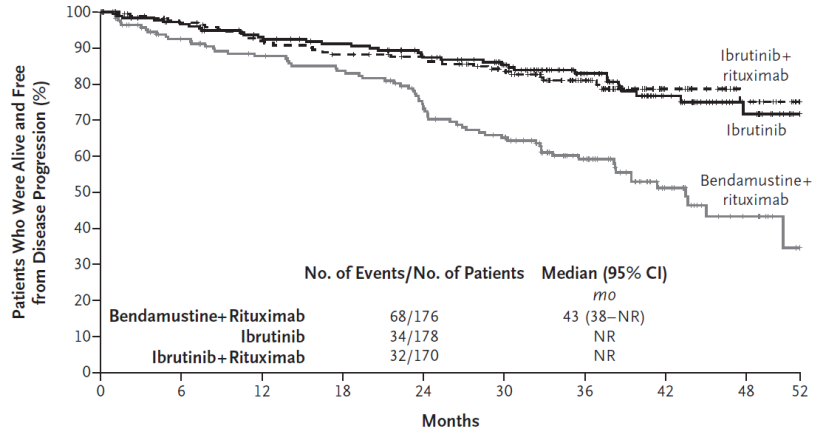
Figure 4. Safety and tolerability of ibrutinib over time. Rate of grade ≥3 AEs, discontinuations due to AEs, and dose reductions over different periods of time. AE, adverse events.

Barr P.M. Haematologica 2018; 103(9): 1502-1510

Screen 1 & 3 With the information you have now what treatment would you initiate? I or IR ALLIANCE

A randomized, phase 3 study of I vs IR vs BR in 547 patients 65 years of age or older with previously untreated TN CLL . Median FU: 38 mo

Primary endpoint: PFS

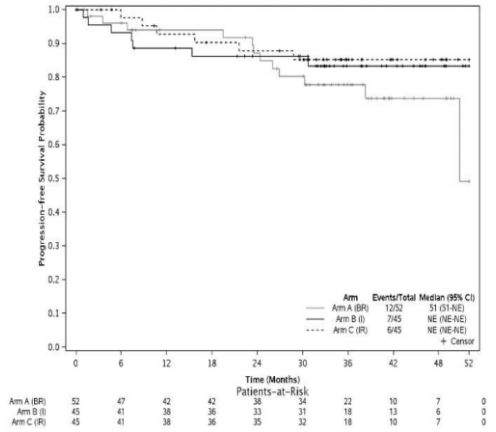


No. at Risk

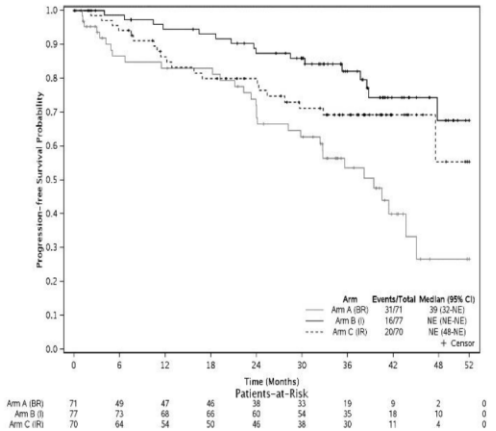
Bendamustine+rituximab	176	140	129	122	103	88	57	26	11	0
Ibrutinib	178	165	154	147	136	120	78	45	22	0
Ibrutinib+rituximab	170	159	145	138	132	115	74	40	20	0

Estimated PFS at 2 years (95% CI)	BR	I	IR
	74% (66-80)	87% (81-92)	88% (81-92)

Patients with Mutated IGHV (n=142)



Patients with Unmutated IGHV (n=218)



PFS was longer with ibrutinib-containing regimens among patients with m*IGHV* than with u*IGHV* but there was no significant interaction with IgHV mutation status

Woyach JA, et al. *N Engl J Med.* 2018; 379: 2517-2528

Screen 1 & 3 With the information you have now what treatment would you initiate?

I or IR ALLIANCE

Hematologic Adverse Events	BR (n=176)	I (n=180)	IR (n=181)	P Value*
Any, n (%)				<0.001
Grade 3	62 (35)	59 (33)	49 (27)	
Grade 4	45 (26)	15 (8)	21 (12)	
Anemia, n (%)				0.09
Grade 3	22 (12)	20 (11)	11 (6)	
Grade 4				
Decreased neutrophil count, n (%)				
Grade 3				
Grade 4				
Decreased platelet count, n (%)				
Grade 3				
Grade 4				

Non-Hematologic Adverse Events	BR (n=176)	I (n=180)	IR (n=181)	P Value*
Any, n (%)				0.04
Grade 3	76 (43)	97 (54)	100 (55)	
Grade 4	20 (11)	12 (7)	12 (7)	
Grade 5	15 (9)	24 (13)	22 (12)	
Bleeding, n (%)				0.46
Grade 3	0	2 (1)	3 (2)	
		(1)	1 (1)	
		0	1 (1)	
				0.62
		(16)	28 (15)	
		(3)	7 (4)	
		(1)	2 (1)	
				<0.001
		(2)	1 (1)	

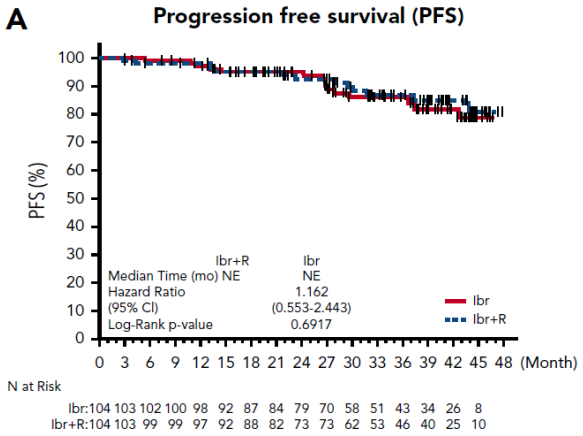
Non-Hematologic Adverse Events	BR (n=176)	I (n=180)	IR (n=181)	P Value*
Atrial fibrillation, n (%)				0.05
Grade 3	5 (3)	15 (8)	10 (6)	
Grade 4	0	2 (1)	0	
Hypertension, n (%)				<0.001
Grade 3	24 (14)	53 (29)	60 (33)	
Grade 4	1 (1)	0	1 (1)	
Secondary cancer, n (%)				0.17
Grade 3	6 (3)	5 (3)	13 (7)	
Grade 4	0	1 (1)	1 (1)	
Grade 5	1 (1)	4 (2)	1 (1)	
Unexplained or unwitnessed death, n (%)				0.24
Grade 5	2 (1)	7 (4)	4 (2)	

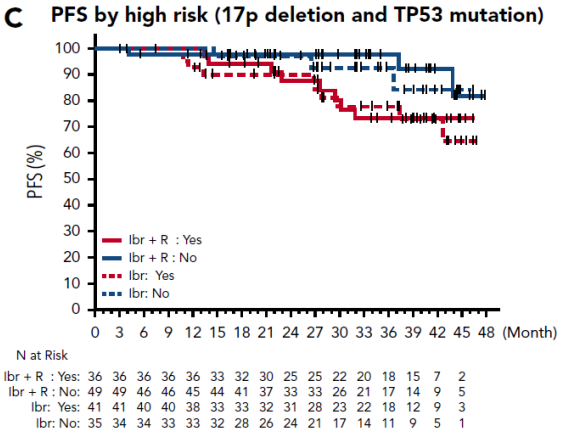
Woyach JA, et al. *N Engl J Med.* 2018; 379: 2517-2528

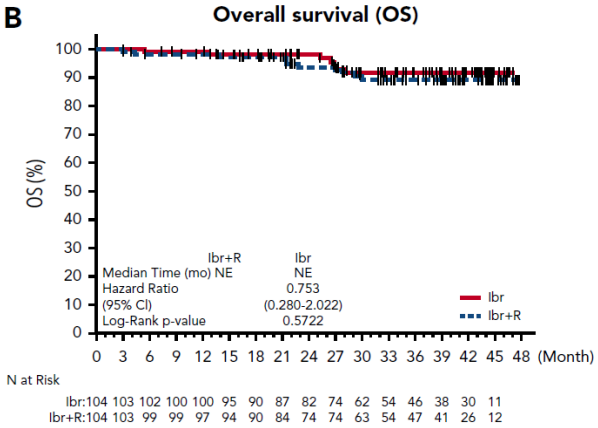
Screen 1 & 3 With the information you have now what treatment would you initiate?

I vs IR Burger

A randomized phase 2 trial of ibrutinib vs ibrutinib + rituximab in R/R CLL patients
Median FU: 36 mo
Primary endpoint: PFS
Secondary endpoint: OS





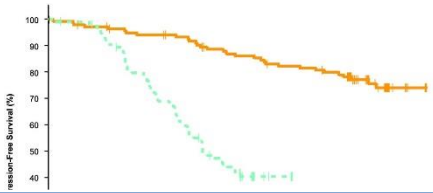


Burger et al. Blood 2019; 133(10):1011-1019

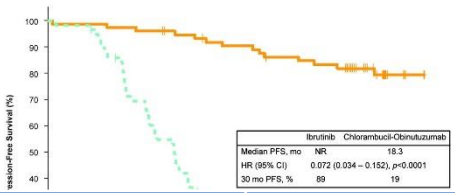
Screen 1 & 3 With the information you have now what treatment would you initiate? I vs IR Tedeschi

A Cross-trial Comparison of Single-Agent Ibrutinib Versus Chlorambucil-Obinutuzumab in Previously Untreated Patients With Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma
Median follow-up was 48.8 months in the ibrutinib arm of RESONATE-2™ and 31.3 months for both arms of iLLUMINATE
Primary analysis: Investigator-assessed PFS with ibrutinib from RESONATE-2™ vs chlorambucil-G from iLLUMINATE
Secondary analysis: Investigator-assessed PFS in genomic high-risk patients (TP53 mutation, del11q, and/or unmutated IGHV), medical resource utilization during the first 6 months on study treatment

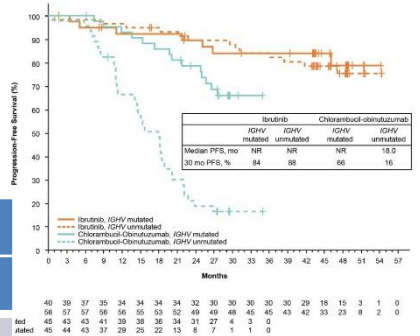
PFS in overall population



PFS in high-risk population



PFS per IGHV mutational status



	Ibrutinib N = 135		Chl-G N = 97	
	AE Reporting Period[a]	First 6 Months	AE Reporting Period[a]	First 6 Months
Median duration of treatment, month (range)	46.9 (0.7-54.5)	–	5.1 (0.0-6.3)	–
Any grade ≥ 3 AEs, n (%)	109 (81)	68 (50)	69 (71)	69 (71)
Most common nonhematologic grade ≥ 3 AEs, n (%)[b]				
Pneumonia	16 (12)	4 (3)	4 (4)	3 (3)
Hypertension	10 (7)	5 (4)	4 (4)	4 (4)
Hyponatremia	7 (5)	2 (1)	1 (1)	1 (1)
Infusion-related reaction	0	0	6 (6)	6 (6)
Hematologic grade ≥ 3 AEs, n (%)				
Neutropenia[c]	20 (15)	11 (8)	47 (48)	47 (48)
Anemia	9 (7)	8 (6)	6 (6)	6 (6)
Thrombocytopenia[d]	9 (7)	6 (4)	10 (10)	10 (10)
Febrile neutropenia	5 (4)	1 (1)	7 (7)	7 (7)

Tedeschi A, et al. *Haematologica.* 2019 Aug [Epub ahead of print].

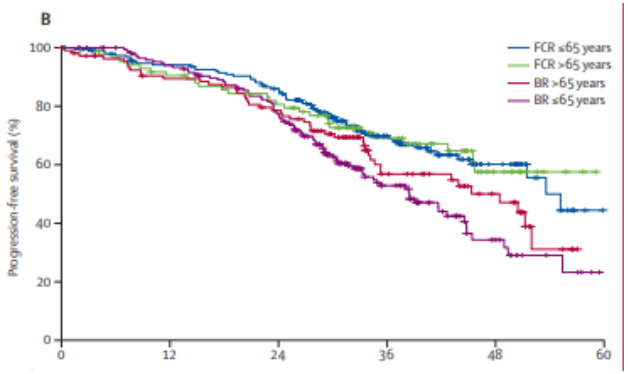
Screen 2 With the information you have now what treatment would you initiate?

FCR vs BR CLL10

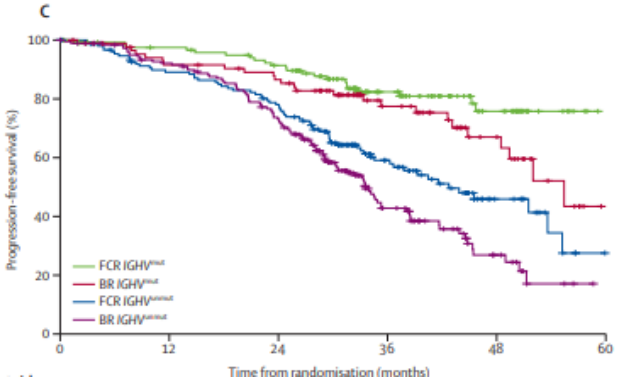
Multicenter RCT with Treatment naive CLL patients without del17P and good physical fitness (Cirs ≤6, CCL ≥ 70ml/min) who were randomized to FCR or BR.

The median observation time for all patients was 35.9 months .Median progression-free survival was 41·7 months with BR and 55·2 months with FCR*

PFS by age#



PFS by IGHV mutation status#



*Primary endpoint
#secondary endpoint

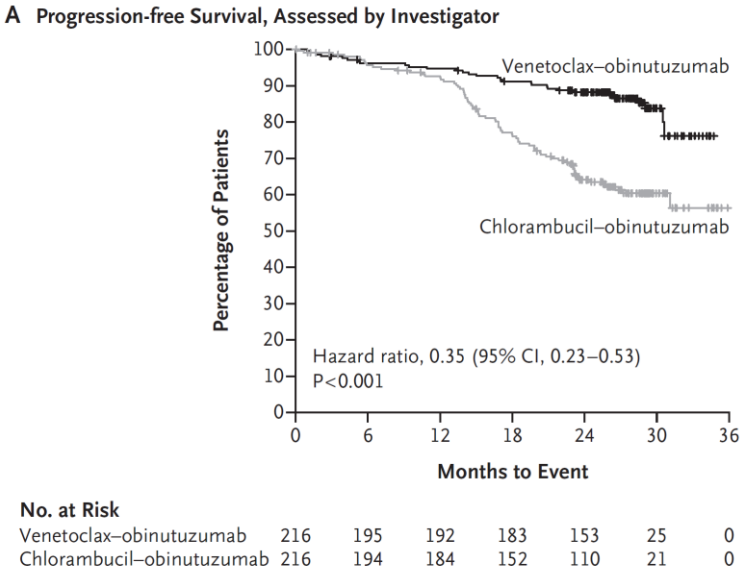
Adverse event	FCR(%) N= 279	BR (%) N= 278	P value
Neutropenia	87.7	67.8	< 0.001
Anemia	14.2	12.0	0.46
Thrombocytopenia	22.4	16.5	0.096
Severe Infection	39.8	25.4	0.001
sec. Neoplasm	6.1	3.6	0.244

Eichhorst et al. Lancet Oncol 2016

Screen 4 & 5 With the information you have now what treatment would you initiate?

VG vs ChlG CLL14

A randomized, open-label phase 3 trial with venetoclax-obinutuzumab vs chlorambucil-obinutuzumab previously untreated patients with CLL and coexisting conditions.
Median FU: 28.1 mo
Primary endpoint: PFS
Secondary endpoint: OS



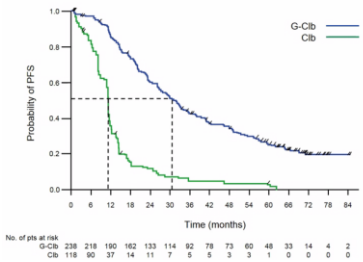
Adverse Event	Venetoclax–Obinutuzumab (N=212)†			Chlorambucil–Obinutuzumab (N=214)		
	Maximum Grade 3	Maximum Grade 4	Maximum Grade 3 or 4	Maximum Grade 3	Maximum Grade 4	Maximum Grade 3 or 4
	number of patients (percent)					
Adverse event of grade 3 or 4	81 (38.2)	86 (40.6)	167 (78.8)	93 (43.5)	71 (33.2)	164 (76.6)
Adverse events of grade 3 or 4 that occurred in ≥3% of the patients in either treatment group‡						
Blood and lymphatic system disorders	59 (27.8)	69 (32.5)	128 (60.4)	61 (28.5)	57 (26.6)	118 (55.1)
Neutropenia	52 (24.5)	60 (28.3)	112 (52.8)	56 (26.2)	47 (22.0)	103 (48.1)
Thrombocytopenia	20 (9.4)	9 (4.2)	29 (13.7)	19 (8.9)	13 (6.1)	32 (15.0)
Anemia	16 (7.5)	1 (0.5)	17 (8.0)	13 (6.1)	1 (0.5)	14 (6.5)
Febrile neutropenia	7 (3.3)	4 (1.9)	11 (5.2)	4 (1.9)	4 (1.9)	8 (3.7)
Leukopenia	5 (2.4)	0	5 (2.4)	9 (4.2)	1 (0.5)	10 (4.7)
Infections and infestations	31 (14.6)	6 (2.8)	37 (17.5)	31 (14.5)	1 (0.5)	32 (15.0)
Pneumonia	8 (3.8)	1 (0.5)	9 (4.2)	8 (3.7)	0	8 (3.7)
Injury, poisoning, and procedural complications	21 (9.9)	5 (2.4)	26 (12.3)	29 (13.6)	1 (0.5)	30 (14.0)
Infusion-related reaction	16 (7.5)	3 (1.4)	19 (9.0)	21 (9.8)	1 (0.5)	22 (10.3)
Investigations	26 (12.3)	6 (2.8)	32 (15.1)	16 (7.5)	7 (3.3)	23 (10.7)
Neutrophil count decreased	7 (3.3)	2 (0.9)	9 (4.2)	4 (1.9)	6 (2.8)	10 (4.7)
Aspartate aminotransferase increased	5 (2.4)	0	5 (2.4)	7 (3.3)	0	7 (3.3)
Alanine aminotransferase increased	4 (1.9)	0	4 (1.9)	7 (3.3)	0	7 (3.3)
Metabolism and nutrition disorders§	19 (9.0)	6 (2.8)	25 (11.8)	11 (5.1)	1 (0.5)	12 (5.6)
Hyperglycemia	6 (2.8)	2 (0.9)	8 (3.8)	2 (0.9)	1 (0.5)	3 (1.4)
Gastrointestinal disorders ¶	16 (7.5)	1 (0.5)	17 (8.0)	6 (2.8)	1 (0.5)	7 (3.3)
Diarrhea‖	9 (4.2)	0	9 (4.2)	1 (0.5)	0	1 (0.5)
Cardiac disorders	9 (4.2)	1 (0.5)	10 (4.7)	10 (4.7)	2 (0.9)	12 (5.6)
Neoplasms benign, malignant, and unspecified, including cysts and polyps	10 (4.7)	3 (1.4)	13 (6.1)	7 (3.3)	1 (0.5)	8 (3.7)
Vascular disorders**	12 (5.7)	2 (0.9)	14 (6.6)	7 (3.3)	0	7 (3.3)
General disorders and administration-site conditions ††	14 (6.6)	0	14 (6.6)	6 (2.8)	0	6 (2.8)

Fischer et al. N Engl J Med 2019;380:2225-36.

Screen 5 With the information you have now what treatment would you initiate? Chl vs ChlG CLL11

A randomized, open-label phase 3 trial with chlorambucil-obinutuzumab vs chlorambucil in previously untreated patients with CLL and coexisting conditions.
Median observation time G-Clb vs Clb: 62.5 months, G-Clb vs R-Clb: 59.4 months
Primary endpoint: PFS (INV-assessed)
Secondary endpoint: OS

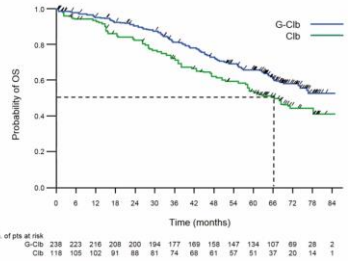
PFS: G-Clb vs Clb



	G-Clb n=238	Clb n=118
Patients with events, n (%)	173 (72.7)	107 (90.7)
5-year PFS, % (95% CI)	25 (19–31)	2 (0–4)
Median PFS, months	31.1	11.1
HR (95% CI), p-value	0.21 (0.16–0.28), p<0.0001	

Median observation time: 62.5 months

OS: G-Clb vs Clb



	G-Clb n=238	Clb n=118
Patients with events, n (%)	93 (39.1)	57 (48.3)
5-year OS, % (95% CI)	66 (60–72)	53 (43–62)
Median OS, months	NR	66.7
HR (95% CI), p-value	0.68 (0.49–0.94), p=0.0196	

Median observation time: 62.5 months

AEs: Overview

	G-Clb vs Clb		G-Clb vs R-Clb	
N (%)	G-Clb n=241	Clb n=116	G-Clb n=336	R-Clb n=321
≥1 AEs (any grade)	228 (95)	96 (83)	316 (94)	290 (90)
Grade 3–5 AEs	179 (74)	59 (51)	241 (72)	191 (60)
Serious AEs	113 (47)	45 (39)	150 (45)	124 (39)
Grade 5 (fatal) AEs	19 (8)	13 (11)	23 (7)	31 (10)
2nd malignancies*	11 (5)	1 (<1)	12 (4)	13 (4)
Infections†	1 (<1)	7 (6)	2 (<1)	2 (<1)

No new safety signals detected

*Neoplasms benign, malignant and unspecified (MedDRA SOC), occurring 6 months after first study drug intake; †all AEs classified as infections and infestations (MedDRA SOC)

AEs: Late onset

	G-Clb vs Clb		G-Clb vs R-Clb	
N (%)	G-Clb n=241	Clb n=116	G-Clb n=336	R-Clb n=321
Prolonged neutropenia,*† n/N	5/184 (3)	8/86 (9)	5/256 (2)	10/268 (4)
Late onset neutropenia,‡§ n/N	37/213 (17)	10/90 (11)	45/297 (15)	36/304 (12)
Second malignancies¶	33 (14)	8 (7)	37 (11)	33 (10)
Squamous cell carcinoma	6 (2)	0 (0)	6 (2)	5 (2)
Basal cell carcinoma	5 (2)	1 (<1)	6 (2)	4 (1)

No new late-onset toxicity detected

*Neutropenia not resolved within 28 days of treatment completion; †includes patients who completed treatment with a neutrophil assessment available 24–41 days after EOT; ‡neutropenia (<1000 cells/mm³) occurring ≥28 days after treatment completion or discontinuation; §includes patients who completed treatment with a neutrophil assessment available 24–200 days after EOT; ¶second malignancies starting 6 months after initiation of study treatment

Goede V. et al. EHA 2018 abstract and oral presentation S151

Screen 6 With the information you have now what treatment would you initiate?

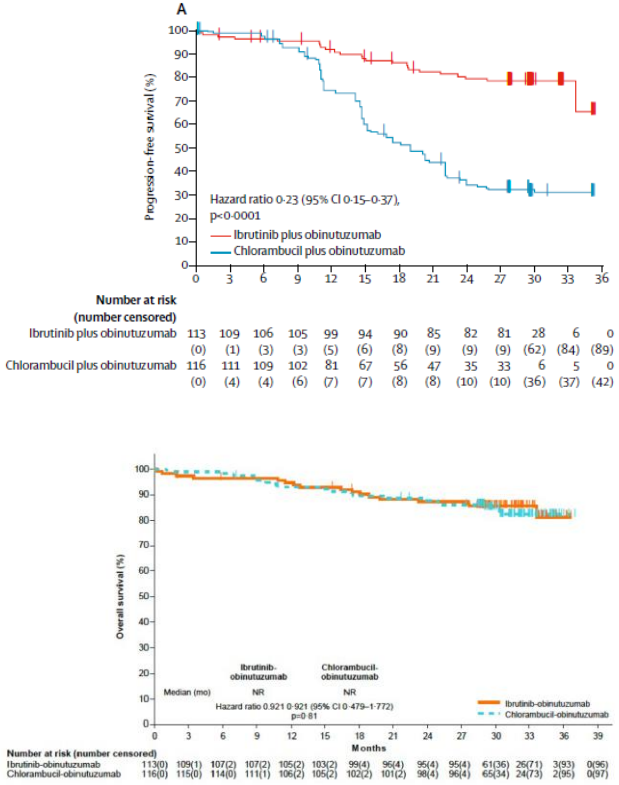
IG vs ChlG iLLUMINATE

A randomized, open-label phase 3 trial with ibrutinib-obinutuzumab vs chlorambucil-obinutuzumab in previously untreated patients with CLL.

Median FU: 31.3 mo

Primary endpoint: PFS

Secondary endpoint: OS



	Ibrutinib plus obinutuzumab group (n=113)			Chlorambucil plus obinutuzumab group (n=115)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
TEAE period*						
All	25 (22%)	49 (43%)	28 (25%)	29 (25%)	49 (43%)	31 (27%)
Neutropenia	8 (7%)	20 (18%)	21 (19%)	20 (17%)	32 (28%)	21 (18%)
Thrombocytopenia	19 (17%)	17 (15%)	4 (4%)	17 (15%)	6 (5%)	6 (5%)
Diarrhoea	35 (31%)	3 (3%)	0	12 (10%)	0	0
Cough	29 (26%)	1 (1%)	0	14 (12%)	0	0
Infusion-related reaction	26 (23%)	2 (2%)	0	58 (50%)	6 (5%)	3 (3%)
Arthralgia	24 (21%)	1 (1%)	0	12 (10%)	0	0
Pyrexia	20 (18%)	2 (2%)	0	29 (25%)	1 (1%)	0
Fatigue	20 (18%)	0	0	17 (15%)	2 (2%)	0
Back pain	20 (18%)	0	0	11 (10%)	1 (1%)	0
Anaemia	15 (13%)	4 (4%)	0	20 (17%)	9 (8%)	0
Hypertension	15 (13%)	4 (4%)	0	1 (1%)	3 (3%)	1 (1%)
Constipation	18 (16%)	0	0	13 (11%)	1 (1%)	0
Rash maculopapular	15 (13%)	2 (2%)	0	2 (2%)	0	0
Upper respiratory tract infection	15 (13%)	1 (1%)	0	7 (6%)	0	0
Pneumonia	7 (6%)	7 (6%)	1 (1%)	3 (3%)	3 (3%)	1 (1%)
Muscle spasms	15 (13%)	0	0	7 (6%)	0	0
Hyperuricaemia	14 (12%)	0	1 (1%)	0	0	0
Nausea	14 (12%)	0	0	35 (30%)	0	0
Oedema peripheral	14 (12%)	0	0	8 (7%)	0	0
Atrial fibrillation	8 (7%)	6 (5%)	0	0	0	0
Urinary tract infection	10 (9%)	3 (3%)	0	7 (6%)	1 (1%)	0
Insomnia	13 (12%)	0	0	5 (4%)	0	0
Nasopharyngitis	13 (12%)	0	0	4 (3%)	0	0
Conjunctivitis	12 (11%)	0	0	2 (2%)	0	0
Asthenia	11 (10%)	0	0	17 (15%)	0	0
Dyspnoea	9 (8%)	1 (1%)	1 (1%)	15 (13%)	1 (1%)	0
Vomiting	11 (10%)	0	0	14 (12%)	0	0
Headache	9 (8%)	0	0	12 (10%)	1 (1%)	0
Febrile neutropenia	1 (1%)	2 (2%)	3 (3%)	1 (1%)	6 (5%)	1 (1%)
Hyperglycaemia	4 (4%)	2 (2%)	0	3 (3%)	4 (3%)	0
Neutrophil count decreased	1 (1%)	4 (4%)	0	1 (1%)	0	0
Leukopenia	3 (3%)	1 (1%)	0	0	2 (2%)	1 (1%)
Hepatic function abnormal	0	2 (2%)	1 (1%)	0	1 (1%)	0
Acute coronary syndrome	0	3 (3%)	0	0	0	0
Tumour lysis syndrome†	1 (1%)	0	0	4 (3%)	3 (3%)	0

Moreno C. et al. Lancet Oncol 2018
https://doi.org/10.1016/S1470-2045(18)30788-5

Screen 5 With the information you have now what treatment would you initiate? Acala +G vs acala vs ChlG

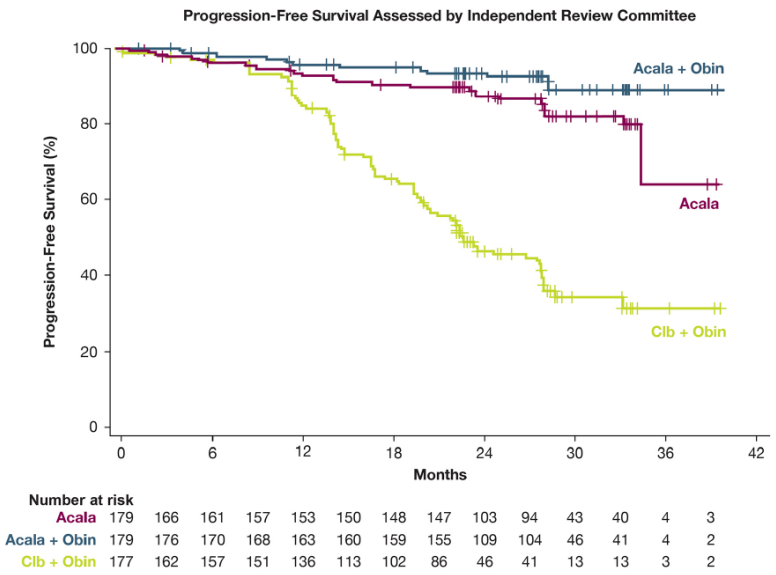
Multicenter, open-label phase 3 trial with acalabrutinib + G vs acalabrutinib vs chlorambucil G in treatment naieve CLL patients

≥65y or <65y with coexisting conditions

Median FU: 28 mo

Primary endpoint: PFS

Secondary endpoint: OS



Median OS was not reached in any arm; (HR [95% CI]; acalabrutinib + O vs O + Clb, 0.47 [0.21-1.06], *P*=0.0577; acalabrutinib vs O + Clb, 0.60 [0.28-1.27], *P*=0.1556).

	Acalabrutinib + Obinutuzumab (n=178)		Acalabrutinib (n=179)		Obinutuzumab + Chlorambucil (n=169)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any, n (%)	171 (96)	125 (70)	170 (95)	89 (50)	167 (99)	118 (70)
Serious, n (%)	69 (39)	58 (33)	57 (32)	53 (30)	37 (22)	33 (20)
Common AEs, n (%)						
Headache	71 (40)	2 (1)	66 (37)	2 (1)	20 (12)	0
Diarrhea	69 (39)	8 (4)	62 (35)	1 (1)	36 (21)	3 (2)
Neutropenia	56 (31)	53 (30)	19 (11)	17 (9)	76 (45)	70 (41)
Nausea	36 (20)	0	40 (22)	0	53 (31)	0
Infusion-related reaction	24 (13)	4 (2)	0	0	67 (40)	9 (5)
Thrombocytopenia	23 (13)	15 (8)	13 (7)	5 (3)	24 (14)	20 (12)
Anemia	21 (12)	10 (6)	25 (14)	12 (7)	20 (12)	12 (7)
Pneumonia	19 (11)	10 (6)	13 (7)	4 (2)	5 (3)	3 (2)
Tumor lysis syndrome[a]	3 (2)	2 (1)	0	0	15 (9)	13 (8)
Febrile neutropenia	3 (2)	3 (2)	2 (1)	2 (1)	9 (5)	9 (5)

[a]By clinical assessment.
AE, adverse event.

Sharman J. et al. ASH Annual Meeting 2019 abstract 31

CASE 3 – Timepoint 1

Patient profile:

Male
Age: 69y

Fit
Symptomatic CLL
Relapsed 13mo post FCR

No del17p/TP53 mutation
mIGHV

With the information you have now what treatment would you initiate?

Votable

CASE 3 – timepoint 1

Picture of patient

Performance status

CIRS

No Del 17P/TP53 IGHV Mutated

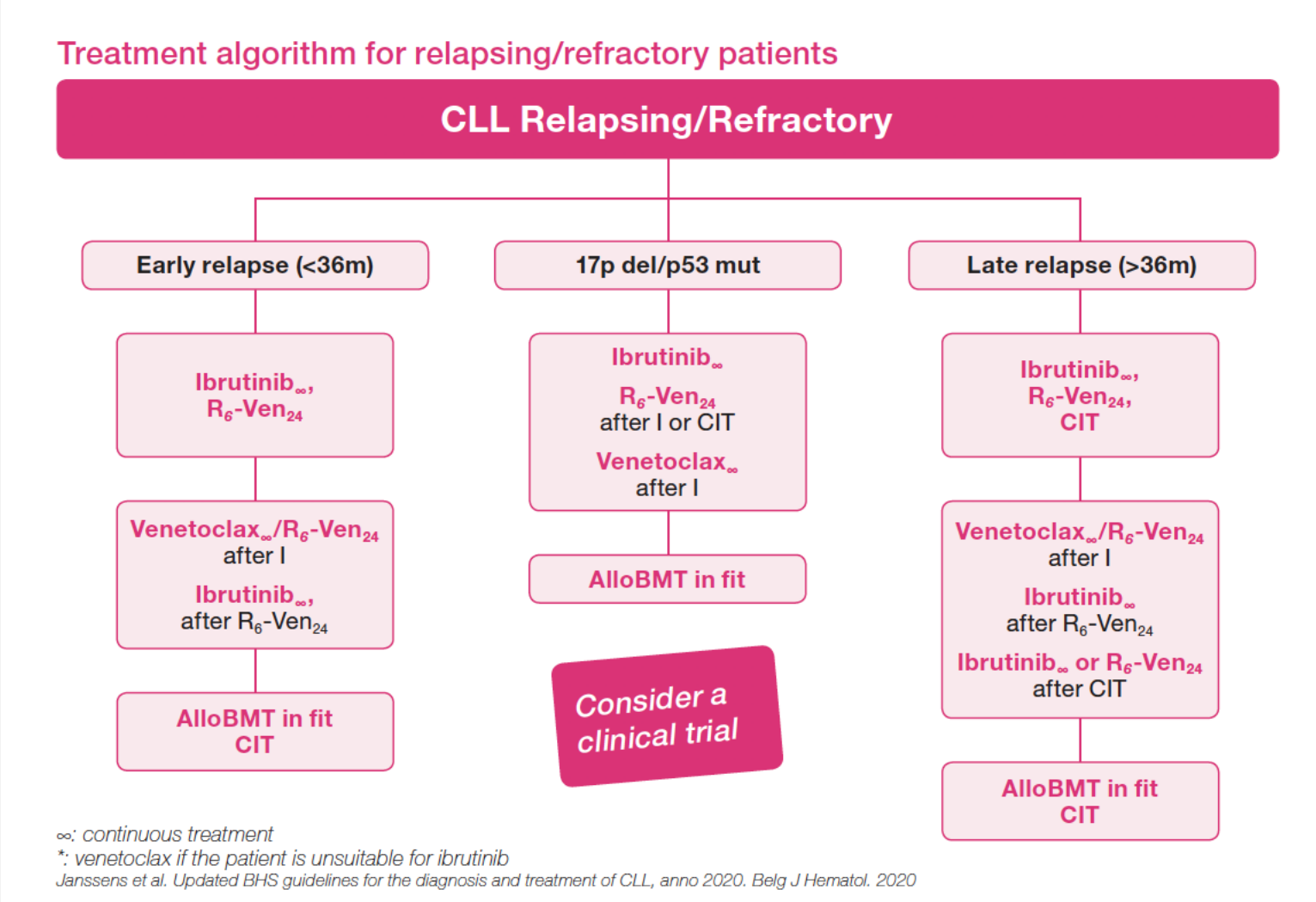
1. FCR → REACH
2. BR → MABLE HELIOS
3. Chl+R → Michallet
4. Ibrutinib → RESONATE HELIOS
5. Venetoclax monotherapy → M13-982 Stilgenbauer et al.
6. V+R → MURANO

BHS
HOVON
Hallek
ESMO

BHS[1]

Screen With the information you have now what treatment would you initiate?

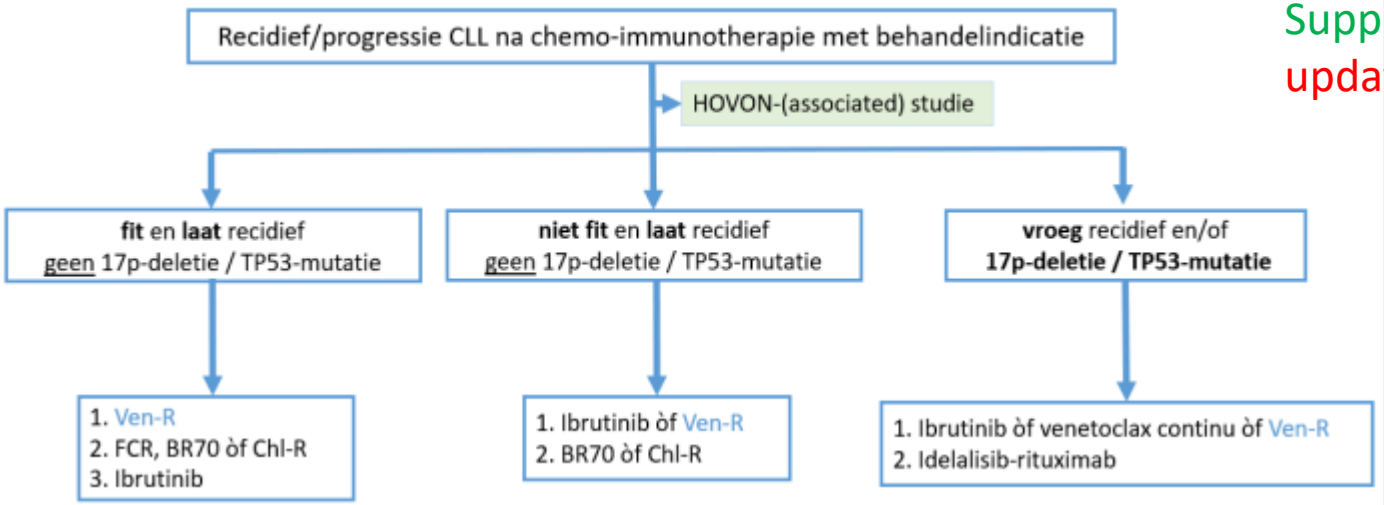
Supporting guidelines update

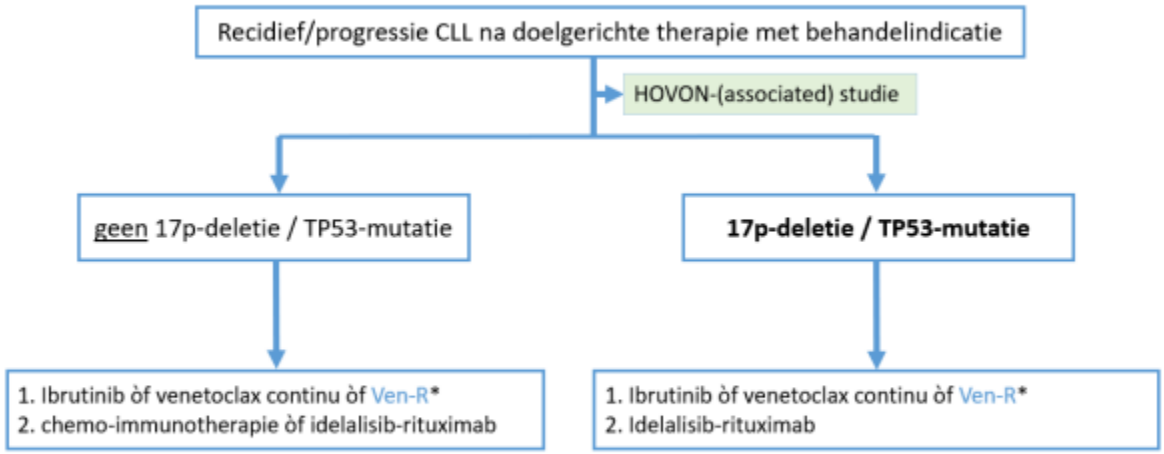


Screen With the information you have now what treatment would you initiate?

HOVON[2]

Supporting guidelines update





http://www.hovon.nl/behandeladvies/behandeladvies-leukemie/cll.html

* switch naar andere doelgerichte therapie. Dus indien recidief/progressie na ibrutinib switch naar venetoclax(-rituximab). Indien recidief/progressie na venetoclax switch naar ibrutinib. Indien langdurige respons op tijdelijke therapie met Ven-R kan herhalen van Ven-R overwogen worden

Hallek[3]

Screen With the information you have now what treatment would you initiate?

Supporting guidelines update

CLL 2L treatment June 2019

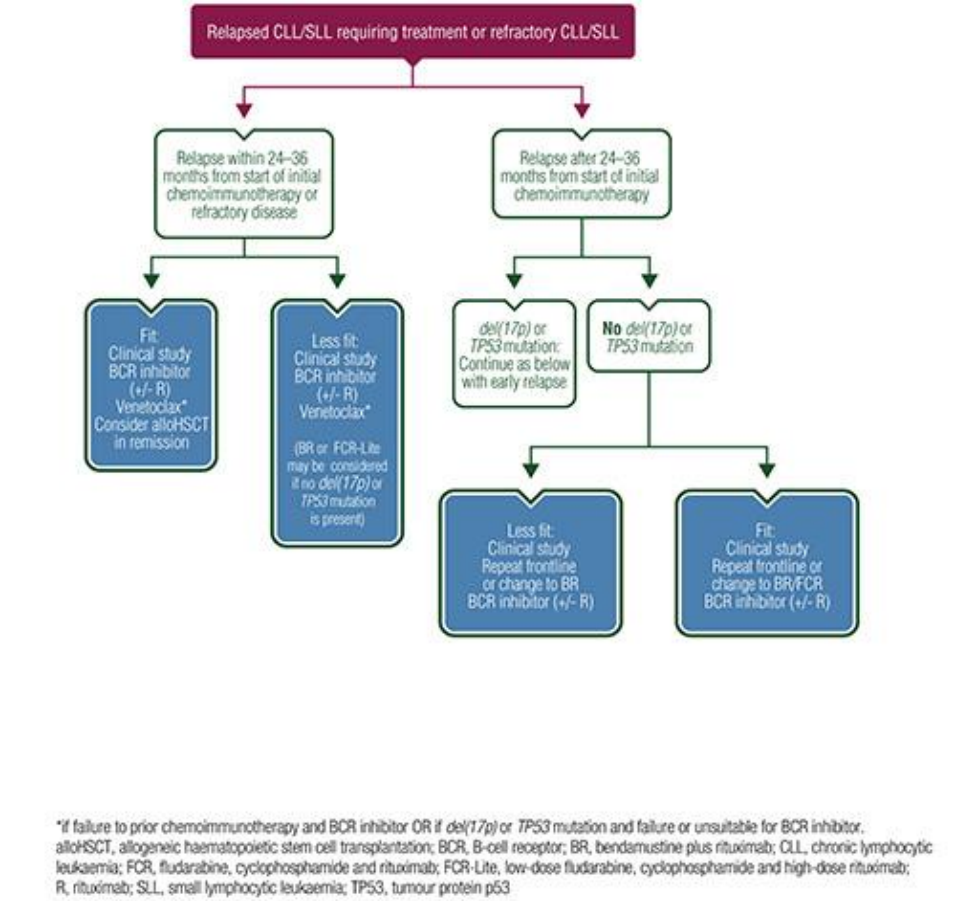
Response to 1L Therapy	Fitness	Therapy
Refractory or progress within 3 years	Go go	Change to one of the following options: Ibrutinib, Idelalisib+R, Venetoclax+Rituximab, FCR or BR, Lenalidomide (+R), Alemtuzumab+Dexamethasone, Fludarabine+Alemtuzumab. Discuss consolidation with allogeneic SCT.
	Slow go	Change to one of the following options: Ibrutinib, Idelalisib + R, Venetoclax +Rituximab, Alemtuzumab+Dexamethasone, FCR-lite, BR, Lenalidomide (+R), High-dose rituximab.
Progress after 3 years	All	Repetition of 1L therapy is possible.

[3]Hallek M. Am. J. Hematol. 2019; 94:1266-1287

ESMO[4]

Screen With the information you have now what treatment would you initiate?

Supporting guidelines update

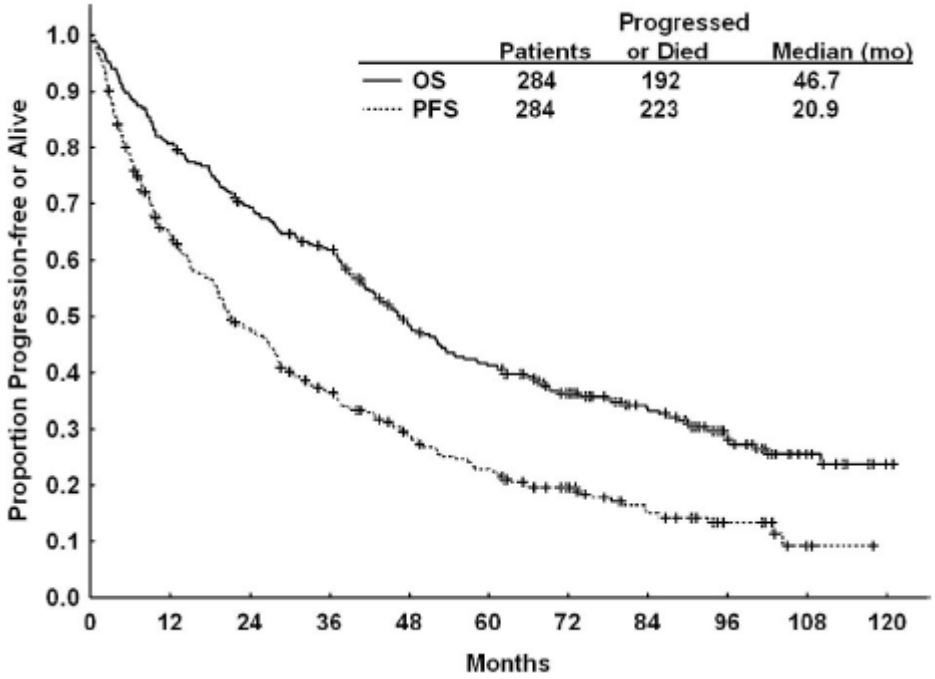


https://www.esmo.org/guidelines/haematological-malignancies/chronic-lymphocytic-leukaemia/eupdate-chronic-lymphocytic-leukaemia-treatment-recommendations

Screen 1 With the information you have now what treatment would you initiate?

FCR

Open-label, phase 2 trial enrolled relapsed CLL patients (N=284) with a median follow-up time for all patients of 43 months (range, 0-122 months).



FCR overall and progression-free survival. Overall survival (OS) and progression-free survival (PFS) for all relapsed/refractory patients treated with fludarabine, cyclophosphamide and rituximab.

Response	Time after last course (2008 IWCLL) 2 mo	6 mo	12 mo	1996 CLL-WG overall
CR, %	18	22	28	30
CRi, %	14	7	1*	
nPR, %	9	10	11	11

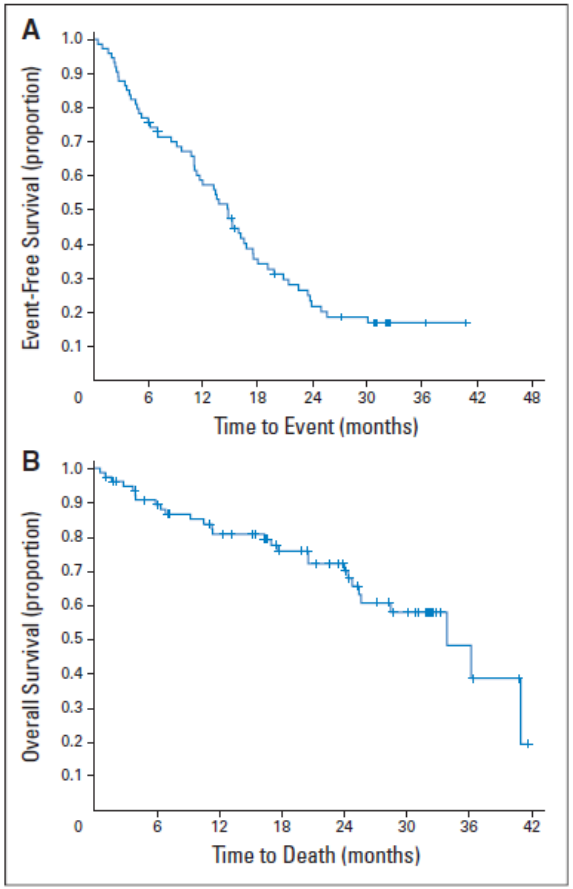
Responses according to 2008 IWCLL criteria.
*Some patients (1%) are in Cri at 12 months due to late-onset neutropenia or thrombocytopenia having achieved CR previously by 1996 CLL-WG criteria

Badoux, Xavier C., et al. "Fludarabine, cyclophosphamide, and rituximab chemoimmunotherapy is highly effective treatment for relapsed patients with CLL." *Blood* 117.11 (2011): 3016-3024.

Screen 2 With the information you have now what treatment would you initiate?

BR

Multicenter phase II trial bendamustine combined with rituximab (BR) in patients with relapsed and/or refractory chronic lymphocytic leukemia (N=78) with a median follow-up of 24 months



A) Event-free survival and B) overall survival for all patients (intent-to-treat population)

Adverse Event	Grade 3 No.	Grade 3 %	Grade 4 No.	Grade 4 %
Adverse events according to treatment courses (n = 353)				
Total courses with at least one grade 3 or 4 event	52	14.7	40	11.3
Hematologic toxicity	46	13.0	40	11.3
Leukopenia	17	4.8	6	1.7
Neutropenia	29	5.4	17	4.8
Thrombocytopenia	23	6.5	19	5.4
Anemia	13	3.7	13	3.7
Tumor lysis syndrome	0	0	0	0
Hemolysis	2	0.6	0	0
Allergic reaction	2	0.6	0	0
Infections	12	3.4	0	0
Other nonhematologic toxicities	14	4.0	3	0.8
Adverse events according to patients (n = 78)				
Total patients with at least one grade 3 or 4 event	21	26.9	19	24.4
Hematologic toxicity	19	24.4	20	25.6
Leukopenia	8	10.3	6	7.7
Neutropenia	7	9.0	11	14.1
Thrombocytopenia	11	14.1	11	14.1
Anemia	9	11.5	4	5.1
Tumor lysis syndrome	0	0	0	0
Hemolysis	2	2.6	0	0
Allergic reaction	2	2.6	0	0
Infections	10	12.8	0	0
Other nonhematologic toxicities	9	11.5	2	2.6

Incidence of CTCAE Grade 3 or 4 adverse events

Fischer, Kirsten, et al. "Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group." *Journal of clinical oncology* 29.26 (2011): 3559-3566.
CTCAE, Common Terminology Criteria for Adverse Events, version 3.0

Screen 3 With the information you have now what treatment would you initiate?

Chlorambucil+Rituximab

Open-lable MABLE study rituximab plus bendamustine or chlorambucil for CLL patients (N=241 1st line of therapy and N=116 2nd line of therapy) with a median follow-up of 23.3 (chlorambucil+rituximab)

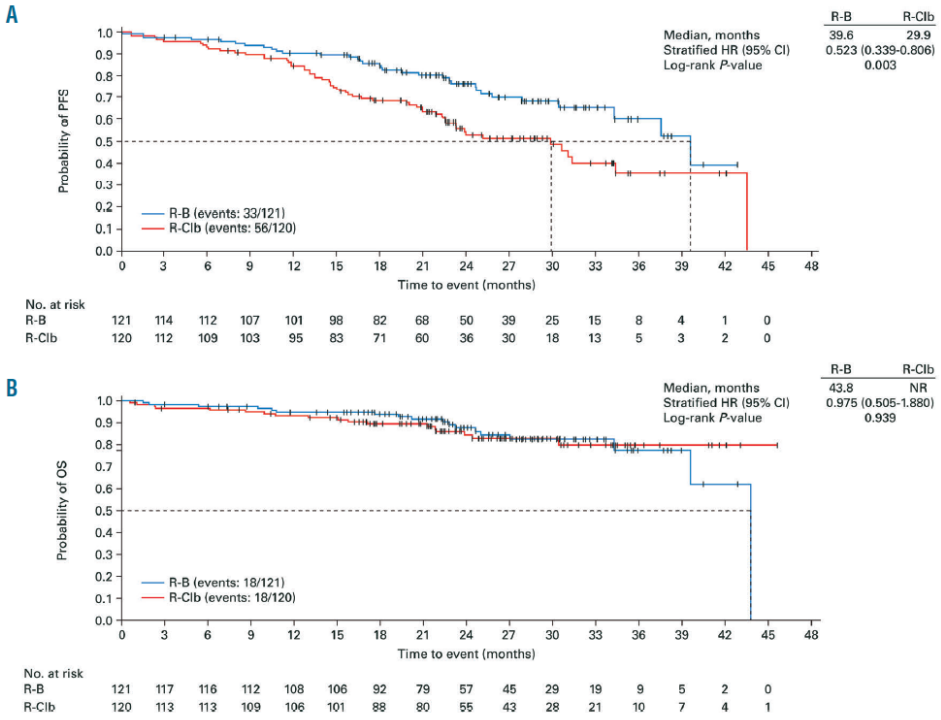


Figure 2. Efficacy in 1L patients. (A) PFS and (B) OS. CI: confidence interval; HR: hazard ratio; NR: not reached; OS: overall survival; PFS: progression-free survival; R-B: rituximab plus bendamustine; R-Clb: rituximab plus chlorambucil.

Table 4. Summary of AEs (safety population).

Patients, n (%)	R-B (N=177)	R-Clb (N=178)
All-grade AEs	173 (98)	173 (97)
Grade ≥3 AEs	132 (75)	113 (64)
SAEs	73 (41)	56 (32)
Most common all-grade AEs[a]		
Blood and lymphatic system disorders	133 (75)	113 (64)
Neutropenia	99 (56)	88 (49)
Leukopenia	42 (24)	31 (17)
Anemia	41 (23)	27 (15)
Thrombocytopenia	37 (21)	44 (25)
Lymphopenia	30 (17)	21 (12)
Gastrointestinal disorders	99 (56)	90 (51)
Nausea	53 (30)	46 (26)
Diarrhea	30 (17)	22 (12)
Constipation	28 (16)	23 (13)
General disorders and administrative site conditions	93 (53)	87 (49)
Pyrexia	37 (21)	17 (10)
Asthenia	29 (16)	34 (19)
Skin and subcutaneous tissue disorders	63 (36)	40 (23)
Rash	29 (16)	9 (5)
Most common grade ≥3 AEs[a]		
Blood and lymphatic system disorders	99 (56)	84 (47)
Neutropenia	76 (43)	65 (37)
Leukopenia	29 (16)	15 (8)
Anemia	18 (10)	12 (7)
Lymphopenia	17 (10)	10 (6)
Thrombocytopenia	17 (10)	16 (9)
Febrile neutropenia	12 (7)	7 (4)
Most common SAEs[b]		
Infections and infestations	33 (19)	15 (8)
Pneumonia	8 (5)	2 (1)
Blood and lymphatic system disorders	25 (14)	15 (8)
Febrile neutropenia	11 (6)	7 (4)

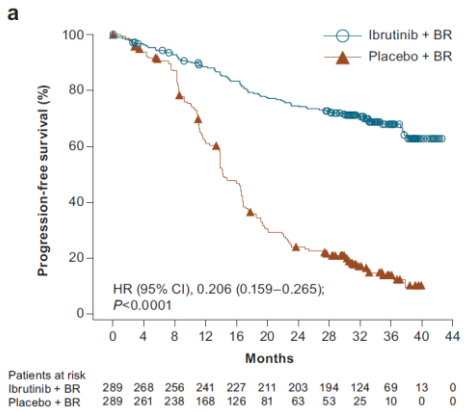
[a]Preferred terms with incidence of ≥15% in either study arm. [b]Preferred terms with incidence of ≥5% in either study arm. Non-serious AEs were reported until 28 days after the end of the last treatment cycle. SAEs unrelated to study treatment were reported until six months after the end of treatment or until the start of new anti- chronic lymphocytic leukemia treatment. Treatment-related SAEs were to be reported indefinitely. AE: adverse event; R-B: rituximab plus bendamustine; R-Clb: rituximab plus chlorambucil; SAE: serious adverse event.

Michallet, Anne-Sophie, et al. *Haematologica* 103.4 (2018): 698-706.

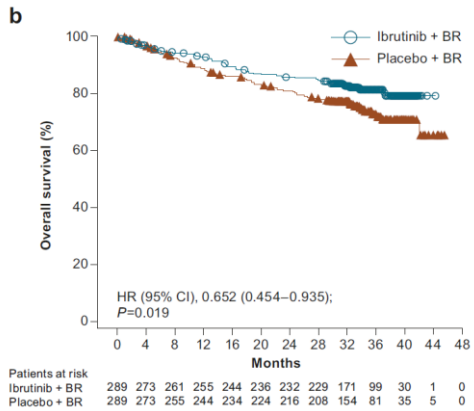
Screen 2 & 4 With the information you have now what treatment would you initiate? Ibrutinib + BR

Randomized, placebo-controlled, phase 3 HELIOS trial of ibrutinib+bendamustine and rituximab (BR) for previously treated chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) without deletion 17p. Overall, 578 patients were randomized 1:1 to either ibrutinib (420 mg daily) or placebo, in combination with 6 cycles of BR, followed by ibrutinib or placebo alone. Median follow-up was 34.8 months (range: 0.1–45.8).

Three-year investigator-assessed progression free survival



Three-year overall survival



Incidence of TEAEs of interest by time to new onset for ibrutinib+BR-treated patients

TEAE, *n* (%)	0–1 year (*n* = 287)	1–2 years (*n* = 216)	2–3 years (*n* = 188)	> 3 years (*n* = 83)
Infection	190 (66.2)	22 (10.2)	4 (2.1)	1 (1.2)
Neutropenia	164 (57.1)	3 (1.4)	0	0
Nausea	105 (36.6)	1 (0.5)	0	0
Diarrhea	98 (34.1)	9 (4.2)	1 (0.5)	2 (2.4)
Thrombocytopenia	86 (30.0)	2 (0.9)	1 (0.5)	0
Bleeding	84 (29.3)	10 (4.6)	4 (2.1)	1 (1.2)
Pyrexia	69 (24.0)	5 (2.3)	4 (2.1)	0
Anemia	64 (22.3)	2 (0.9)	2 (1.1)	0
Fatigue	58 (20.2)	5 (2.3)	3 (1.6)	1 (1.2)
Cough	48 (16.7)	12 (5.6)	4 (2.1)	1 (1.2)
Pneumonia	38 (13.2)	15 (6.9)	7 (3.7)	1 (1.2)
Upper respiratory tract infection	38 (13.2)	17 (7.9)	4 (2.1)	2 (2.4)
Hypertension	27 (9.4)	8 (3.7)	4 (2.1)	0
Atrial fibrillation/ flutter	19 (6.6)	4 (1.9)	6 (3.2)	0

TEAE treatment-emergent adverse event

BR bendamustine and rituximab, CI confidence interval, HR hazard ratio, OS overall survival, PFS progression-free survival

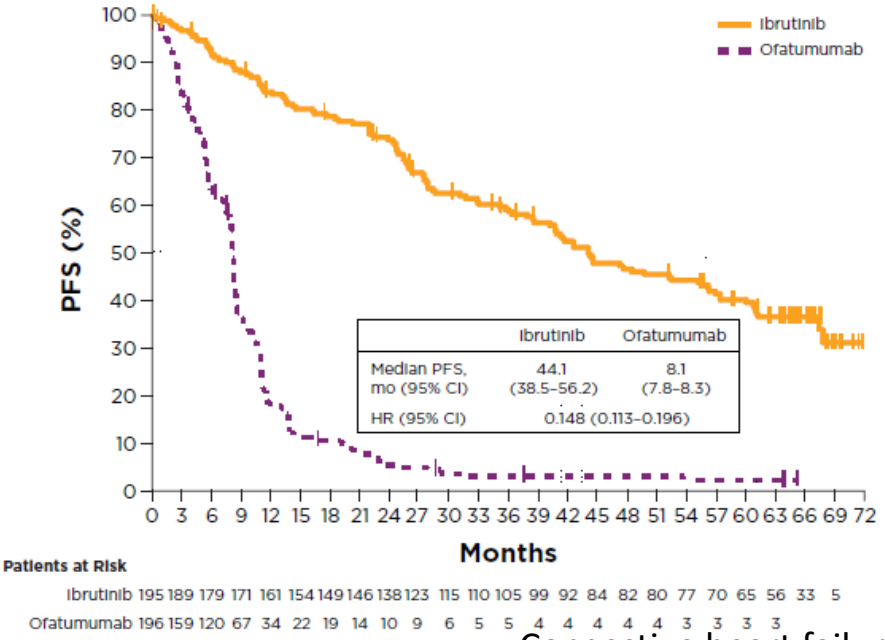
Fraser, G., et al. *Leukemia* 33.4 (2019): 969-980.

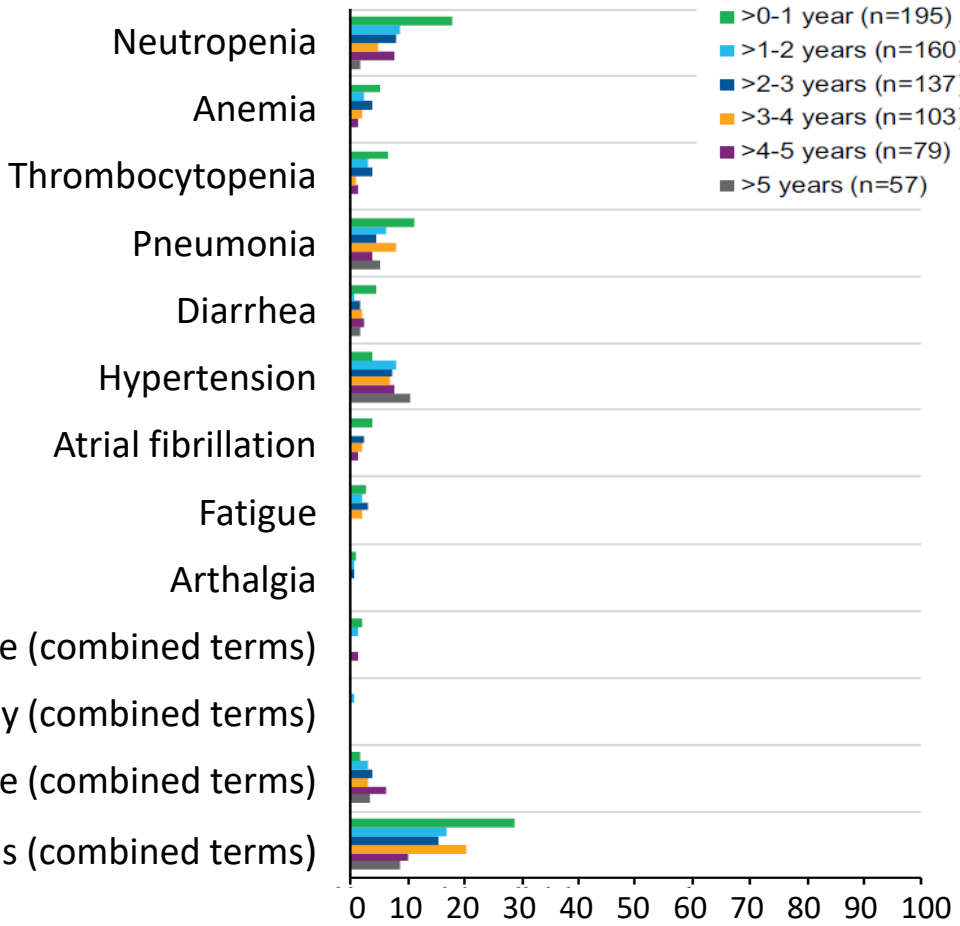
Screen 4 With the information you have now what treatment would you initiate?

Ibrutinib

Multicenter, open-label, randomized phase 3 study that compared ibrutinib to ofatumumab treatment outcomes in previously treated patients with CLL/SLL, including in patients with del(17p) with median follow-up on study of 65.3 months (range, 0.3-71.6) in the ibrutinib arm.

Progression-free survival in the ITT population





Munir T. et al. Am J Hematol. 2019;94:1353–1363

Screen 5 With the information you have now what treatment would you initiate?

V monotherapy

Phase II open label study with 158 del(17p) CLL patients with relapsed/refractory or previously untreated CLL (n=153 and n=5, respectively). Median time on study was 26.6 months (range, 0 to 44.2 months).

n (%)	ORR	CR/CRi	nPR/PR	SD	PD	NE
All Patients, N=158	122 (77)	32 (20)	90 (57)	30 (19)	3 (2)	3* (2)
***TP53* mutation, n=55**	38 (69)	10 (18)	28 (51)	16 (29)	1 (2)	0
Unmutated *IGHV*, n=45	39 (87)	7 (16)	32 (71)	4 (9)	1 (2)	1 (2)
>2 prior therapies, n=68	48 (71)	6 (9)	42 (62)	18 (27)	1 (2)	1 (2)
Fludarabine refractory, n=45	35 (78)	11 (24)	24 (53)	10 (22)	0	0
ECOG score of 0, n=69	59 (86)	16 (23)	43 (62)	10 (15)	0	0
ECOG score of 1, n=78	55 (71)	14 (18)	41 (53)	17 (22)	3 (4)	3 (4)
ECOG score of 2, n=11	8 (73)	2 (18)	6 (55)	3 (27)	0	0
Beta-2 microglobulin ≥3 at baseline, n=25	19 (76)	6 (24)	13 (52)	5 (20)	1 (4)	0
Nodes ≥5 cm at baseline, n=76	60 (79)	10 (13)	50 (66)	14 (18)	1 (1)	1 (1)
Nodes ≥10 cm at baseline, n=21	16 (76)	2 (10)	14 (67)	5 (24)	0	0
High TLS risk,† n=62	47 (76)	5 (8)	42 (68)	14 (23)	0	1 (2)

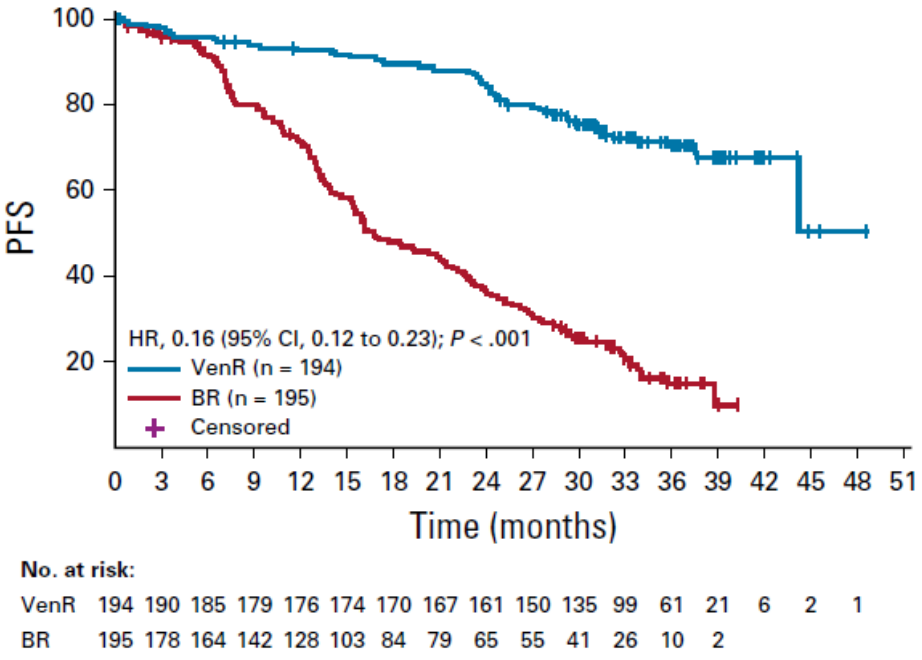
ORR, objective response rate; CR, complete remission; CRi, complete remission with incomplete marrow recovery; nPR, nodular partial remission; PR, partial remission, SD, stable disease; PD, disease progression; NE, not evaluated for response; BCRi, B-cell receptor pathway inhibitor.
*One patient discontinued after the first dose of venetoclax, one patient died after three weeks of treatment due to liver dysfunction not related to venetoclax, and one patient had pseudo obstruction of the small bowel mesentery and retroperitoneum during dose ramp up and discontinued the study.

Stilgenbauer, Stephan, et al. *Journal of Clinical Oncology* 36.19 (2018): 1973-1980.

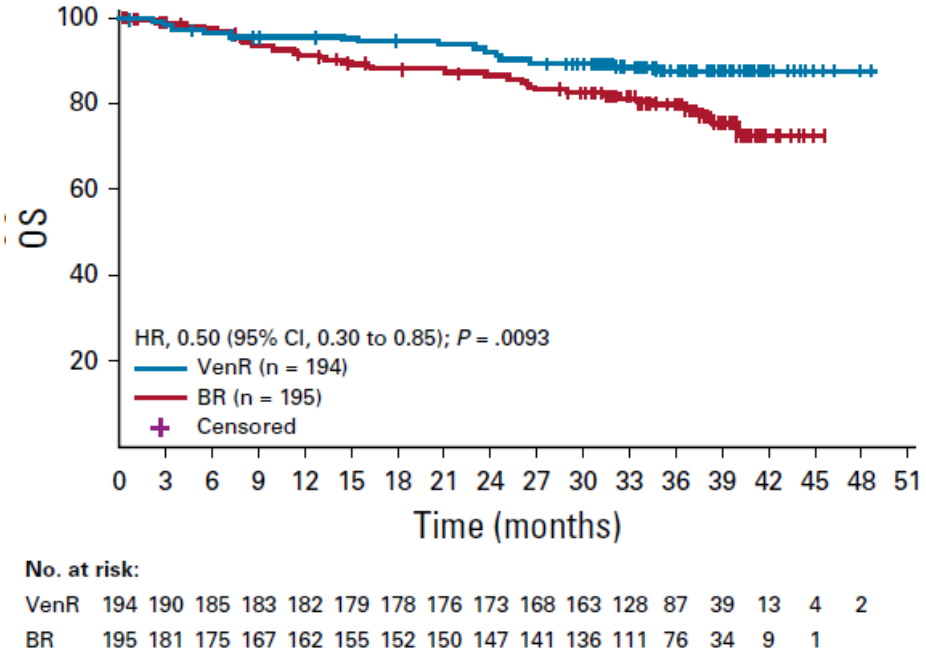
Screen 6 With the information you have now what treatment would you initiate?

Venetoclax + Rituximab

Global, phase III, open-label, randomized study investigating the efficacy and safety of venetoclax-rituximab therapy compared with bendamustine-rituximab in patients with R/R CLL.



Kaplan-Meier plot of investigator progression-free survival (PFS)



Kaplan-Meier plot of overall survival (OS) in the intention-to-treat population with 36-month follow up

Kater, Arnon P., et al. *Journal of Clinical Oncology* 37.4 (2018): 269-277.
BR, bendamustine-rituximab; HR, hazard ratio; VenR, venetoclax-rituximab

Screen 6 With the information you have now what treatment would you initiate?

Venetoclax + Rituximab

Global, phase III, open-label, randomized study investigating the efficacy and safety of venetoclax-rituximab therapy compared with bendamustine-rituximab in patients with R/R CLL.

Event	Venetoclax–Rituximab Group (N=194)	Bendamustine–Rituximab Group (N=188)
Grade 3 or 4 adverse event — no. of patients (%)	159 (82.0)	132 (70.2)
Total no. of events	335	255
Grade 3 or 4 adverse events with at least 2% difference in incidence between groups — no. of patients (%)	130 (67.0)	104 (55.3)
Neutropenia†	112 (57.7)	73 (38.8)
Infections and infestations	34 (17.5)	41 (21.8)
Anemia	21 (10.8)	26 (13.8)
Thrombocytopenia	11 (5.7)	19 (10.1)
Febrile neutropenia	7 (3.6)	18 (9.6)
Pneumonia	10 (5.2)	15 (8.0)
Infusion-related reaction	3 (1.5)	10 (5.3)
Tumor lysis syndrome‡	6 (3.1)	2 (1.1)
Hypotension	0	5 (2.7)
Hyperglycemia	4 (2.1)	0
Hypogammaglobulinemia	4 (2.1)	0
Serious adverse events with at least 2% incidence in either group — no. of patients (%)	90 (46.4)	81 (43.1)
Pneumonia	16 (8.2)§	15 (8.0)
Febrile neutropenia	7 (3.6)	16 (8.5)
Pyrexia	5 (2.6)	13 (6.9)
Anemia	3 (1.5)	5 (2.7)
Infusion-related reaction	1 (0.5)	6 (3.2)
Sepsis	1 (0.5)	4 (2.1)
Tumor lysis syndrome	4 (2.1)	1 (0.5)
Hypotension	0	5 (2.7)
Fatal adverse events — no. of patients (%)	10 (5.2)§	11 (5.9)

Adverse Events

* Before the initiation of the trial drug, only serious adverse events that were considered to have been caused by a protocol-mandated intervention were reported (e.g. serious adverse events related to invasive procedures, such as biopsies). After the initiation of a trial drug, all adverse events, regardless of the relationship to the trial drug, were reported through 28 days after the last dose of trial drug (a maximum of 2 years for the venetoclax-rituximab group) or through 90 days after the las dose of rituximab, whichever was longer. After this period, investigators were to report any deaths, serious adverse events, or other adverse events of concern that were believed to be related to previous treatment with the trial drug.

† A higher percentage of new-onset events of neutropenia occurred during the combincaiton-treatment period than during the ventoclax monotherapy phase (54.1% vs. 11.1%). Protocol-mandated dose interruption for all grade 3 or 4 events of neutropenia occurred in 43.3% of the patients in the venetoclax-rituximab group. In total, 47.9% of the patients in the venetoclax-rituximab group and 43.1% of the patients in the bendamustine-rituximab group received growth factor.

‡ Additional information on the events of the tumor lysis syndrome can be found in the Supplementary Appendix (Table S12)

§ Two serious adverse events of pneumonia that resulted in death occurred in patients who had both disease progression and confirmed Richter's transformation (i.e., conversion into an aggressive lymphoma, typically diffuse large B-cell lymphoma)

Seymour, John F., et al. *New England Journal of Medicine* 378.12 (2018): 1107-1120.

What if the patient has a TP53 mutation?
With the information you have now what treatment would you initiate?

CASE 3 – timepoint 1


Picture of patient


Performance status


CIRS


TP53 mutation
IGHV Mutated

1. Idelalisib+R → Furman 2014
2. Ibrutinib → RESONATE
3. V+R → MURANO
4. Allo-SCT → Gribben 2018
5. Other

BHS
HOVON
iwCLL
ESMO

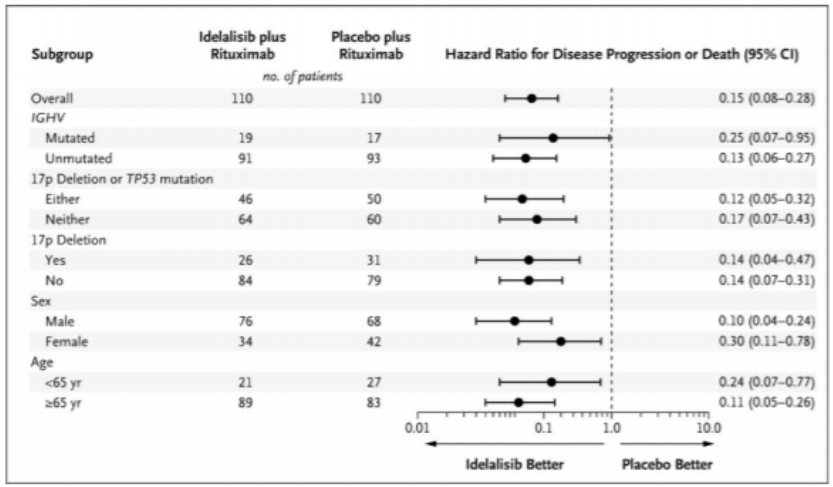
Screen 1 With the information you have now what treatment would you initiate?

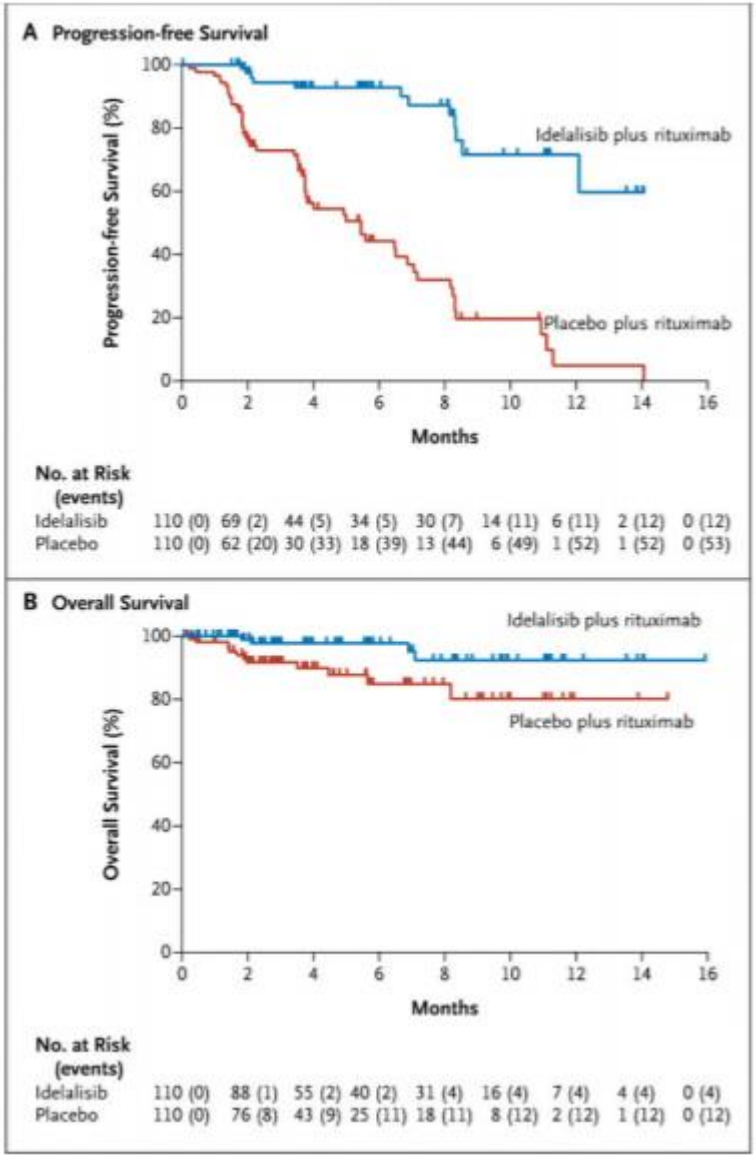
Idelalisib + Rituximab

Multicenter, randomized, double-blind, placebo-controlled, phase 3 study, we assessed the efficacy and safety of idelalisib, an oral inhibitor of the delta isoform of phosphatidylinositol 3-kinase, in combination with rituximab versus rituximab plus placebo.

Progression-free and Overall Survival
At the time the study was stopped, the median duration of progression-free survival among 110 patients receiving idelalisib and rituximab had not yet been reached; among the 110 patients receiving placebo and rituximab, the median duration of progression-free survival was 5.5 months (hazard ratio for progression or death in the idelalisib group, 0.15; 95% confidence interval [CI], 0.08 to 0.28; P

Forest Plot of Progression-free Survival in Prespecified Subgroups
Hazard ratios of less than 1.00 for disease progression or death indicate better results in the idelalisib group.





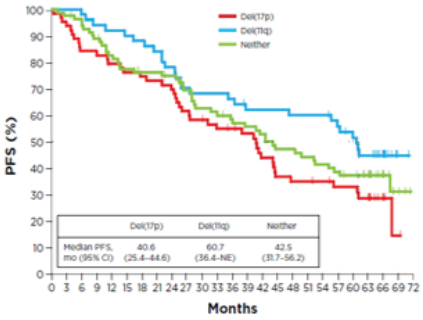
Furman, Richard R., et al. *New England Journal of Medicine* 370.11 (2014): 997-1007.

Screen 2 With the information you have now what treatment would you initiate?

Ibrutinib

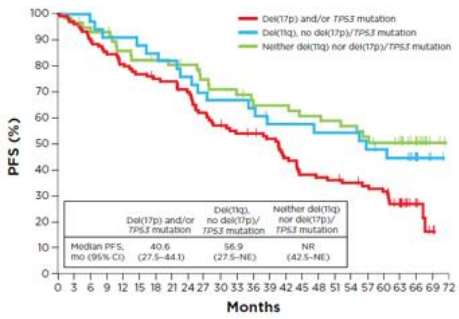
Multicenter, open-label, randomized phase 3 study that compared ibrutinib to ofatumumab treatment outcomes in previously treated patients with CLL/SLL, including in patients with del(17p) with median follow-up on study of 65.3 months (range, 0.3-71.6) in the ibrutinib arm.

PFS by Del(17p) and Del(11q)

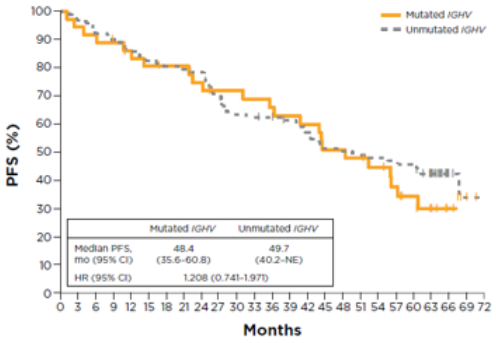


	Ibrutinib	Ofatumumab
Median PFS, mo (95% CI)	44.1 (38.5-56.2)	8.1 (7.8-8.3)
HR (95% CI)	0.148 (0.113-0.196)	

Del(17p)/*TP53* Mutation and Del(11q)



***IGHV* Mutation Status**



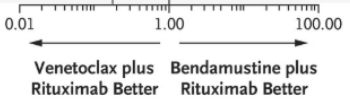
Munir, Talha, et al. *American journal of hematology* (2019).

Screen 3 With the information you have now what treatment would you initiate?

Venetoclax + Rituximab

Global, phase III, open-label, randomized study investigating the efficacy and safety of venetoclax-rituximab therapy compared with bendamustine-rituximab in patients with R/R CLL.

Subgroup	Total No.	Venetoclax–Rituximab Group		Bendamustine–Rituximab Group		Hazard Ratio (95% Wald CI)
		no.	*median (mo)*	*no.*	*median (mo)*	
All patients	389	194	NR	195	17.0	0.17 (0.12–0.26)
Age						
<65 yr	186	97	NR	89	15.4	0.11 (0.06–0.21)
≥65 yr	203	97	NR	106	21.7	0.24 (0.14–0.41)
CLL risk status						
Low	178	90	NR	88	21.6	0.14 (0.07–0.28)
High	211	104	NR	107	15.4	0.19 (0.11–0.30)
Geographic region						
United States and Canada	34	16	NR	18	15.8	0.29 (0.10–0.83)
Australia and New Zealand	86	44	NR	42	24.5	0.34 (0.16–0.72)
Western Europe	131	66	NR	65	17.1	0.11 (0.05–0.23)
Central and Eastern Europe	130	64	NR	66	15.5	0.13 (0.06–0.27)
Asia	8	4	NR	4	13.6	0.28 (0.03–2.69)
No. of previous therapies						
1	228	111	NR	117	16.6	0.14 (0.08–0.24)
2	100	57	NR	43	21.2	0.24 (0.11–0.50)
≥3	61	26	NR	35	10.5	0.24 (0.10–0.57)
Effect of most recent therapy						
CLL refractory to therapy	59	30	NR	29	13.6	0.32 (0.15–0.70)
Relapse of CLL	330	164	NR	166	18.6	0.14 (0.09–0.23)
Chromosome 17p deletion status						
Absent	250	127	NR	123	21.4	0.19 (0.12–0.32)
Present	92	46	NR	46	15.4	0.13 (0.05–0.29)
TP53 mutation status						
Unmutated	277	144	NR	133	21.2	0.15 (0.09–0.25)
Mutated	99	48	NR	51	12.9	0.19 (0.10–0.36)
Baseline *IGHV* mutation status						
Unmutated	246	123	NR	123	15.7	0.16 (0.10–0.26)
Mutated	104	53	NR	51	22.9	0.11 (0.04–0.31)



Kater, A., et al. *Journal of Clinical Oncology* 37.4 (2018): 269-277.

Screen 3 With the information you have now what treatment would you initiate?

Venetoclax + Rituximab

Global, phase III, open-label, randomized study investigating the efficacy and safety of venetoclax-rituximab therapy compared with bendamustine-rituximab in patients with R/R CLL.

Event	Venetoclax–Rituximab Group (N=194)	Bendamustine–Rituximab Group (N=188)
Grade 3 or 4 adverse event — no. of patients (%)	159 (82.0)	132 (70.2)
Total no. of events	335	255
Grade 3 or 4 adverse events with at least 2% difference in incidence between groups — no. of patients (%)	130 (67.0)	104 (55.3)
Neutropenia†	112 (57.7)	73 (38.8)
Infections and infestations	34 (17.5)	41 (21.8)
Anemia	21 (10.8)	26 (13.8)
Thrombocytopenia	11 (5.7)	19 (10.1)
Febrile neutropenia	7 (3.6)	18 (9.6)
Pneumonia	10 (5.2)	15 (8.0)
Infusion-related reaction	3 (1.5)	10 (5.3)
Tumor lysis syndrome‡	6 (3.1)	2 (1.1)
Hypotension	0	5 (2.7)
Hyperglycemia	4 (2.1)	0
Hypogammaglobulinemia	4 (2.1)	0
Serious adverse events with at least 2% incidence in either group — no. of patients (%)	90 (46.4)	81 (43.1)
Pneumonia	16 (8.2)§	15 (8.0)
Febrile neutropenia	7 (3.6)	16 (8.5)
Pyrexia	5 (2.6)	13 (6.9)
Anemia	3 (1.5)	5 (2.7)
Infusion-related reaction	1 (0.5)	6 (3.2)
Sepsis	1 (0.5)	4 (2.1)
Tumor lysis syndrome	4 (2.1)	1 (0.5)
Hypotension	0	5 (2.7)
Fatal adverse events — no. of patients (%)	10 (5.2)§	11 (5.9)

Adverse Events

* Before the initiation of the trial drug, only serious adverse events that were considered to have been caused by a protocol-mandated intervention were reported (e.g. serious adverse events related to invasive procedures, such as biopsies). After the initiation of a trial drug, all adverse events, regardless of the relationship to the trial drug, were reported through 28 days after the last dose of trial drug (a maximum of 2 years for the venetoclax-rituximab group) or through 90 days after the las dose of rituximab, whichever was longer. After this period, investigators were to report any deaths, serious adverse events, or other adverse events of concern that were believed to be related to previous treatment with the trial drug.

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Seymour, John F., et al. *New England Journal of Medicine* 378.12 (2018): 1107-1120.

Screen 4 With the information you have now what treatment would you initiate?

Allo-SCT

Outcome after allo-SCT for CLL in 2589 patients reported by EBMT

	Time after allo-SCT			
	1 y	2 y	5 y	10 y
OS, % (95% CI)	71 (69-73)	62 (60-64)	45 (43-48)	35 (32-38)
Nonrelapse mortality, % (95% CI)	24 (23-26)	30 (28-32)	36 (34-38)	40 (37-42)
Event-free survival, % (95% CI)	62 (60-64)	49 (47-52)	35 (33-37)	28 (25-31)
Incidence of relapse, % (95% CI)	14 (13-25)	21 (19-22)	29 (27-30)	32 (30-25)

Summary of transplant characteristics and survival in selected prospective studies of RIC HSCT in CLL

	Fred Hutchinson Cancer Center[38]	German CLL Study Group[41,45]	MD Anderson Cancer Center[40]	Dana Farber Cancer Institute[39]
Number of patients	82	90	86	76
Conditioning regimen	Flu/low-dose TBI	Flu/Cy ± ATG	Flu/Cy ± R	Flu/Bu
Donors, % (sibling/MUD)	63/37	41/59	50/50	37/63
Median follow-up, mo	60	72	37	61
Median PFS, %	39 (5 y)	38 (6 y)	36 (6 y)	43 (6 y)
Median OS, %	50 (5 y)	58 (6 y)	51 (6 y)	63 (6 y)
Early mortality, % (<100d)	<10	<3	<3	<3
NRM, %	23	23	17	16
Acute grade 3-4 GVHD, %	20	14	7	17
Severe chronic GVHD, %	53	55	56	48

ATG, antithymocyte globulin; Bu, busulfan; Cy, cyclophosphamide; Flu, fludarabine; MUD, matched unrelated donor; R, rituximab; TBI, total body irradiation.

Gribben, John G. *Blood* 132.1 (2018): 31-39.

Screen 5 With the information you have now what treatment would you initiate?

Other

How would you evaluate the response?

1. Blood count
2. Physical examination
3. Cell morphology
4. Immunophenotyping
5. MRD level

Guidelines:
- BHS
- HOVON
- iwCLL

BHS[1]

Screen How would you evaluate the response?

Supporting guidelines update

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

HOVON[2]

Screen How would you evaluate the response?

Supporting guidelines update

Tabel 8: respons[3]

	Parameter	Complete remissie	Partiële remissie	Progressieve ziekte
	Respons definitie:	Alle criteria nodig	Ten minste 2 criteria van 1,2,3 plus 1 criterium van 5a-c (minimale duur van 2 maanden)	Ten minste 1 criterium
1	**Bloed lymfocyten**	<4,0 10^9/l	≥50% afname vanaf start	≥50% toename vanaf start (≥5,0x10^9/cellen)
2	**Lymfadenopathie**	Afwezig (geen >1.5 cm)	≥50% afname vanaf start, geen toename of nieuwe laesies	≥50% toename of nieuw (>1,5 cm)
3	**Hepato/splenomegalie**	Afwezig	≥50% afname vanaf start	≥50% toename of nieuw (>1,5 cm)
4	**B-symptomen**	Afwezig	Niet van toepassing	Niet van toepassing
5a	**Neutrofielen**	>1,5x10^9/l	>1,5x10^9/l	Niet van toepassing
5b	**Trombocyten**	>100x10^9/l	>100x10^9/l or ≥50% toename vanaf start	≥50% afname vanaf start of tot <100x10^9/l secundair aan CLL
5c	**Hemoglobine**	>6,8 mmol/l	>6,8 mmol/l of toename ≥50% na start	Afname van >1,3 mmol/l vanaf start of tot <6,2 mmol/l secundair aan CLL
6	**Beenmerg**	Normocellulair, geen B-lymfoide nodi, <30% lymfocyten	Niet van toepassing	Niet van toepassing
7	**Overig**	Niet van toepassing	Niet van toepassing	CLL- transformatie

Literatuurverantwoording:

Er is gebruik gemaakt van onderstaande richtlijn zonder aanvullende systematische literatuur-analyse: 3.Eichhorst B, Robak T, Montserrat E, Ghia P, Hillmen P, Hallek M, Buske C; ESMO Guidelines Committee. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†.Ann Oncol. 2015 Sep;26 Suppl 5:v78-v84.

[2]*Cll richtlijn 2017* http://www.hovon.nl/upload/File/Richtlijnen_BehAdv/richtlijn-cll-hovon_20170607_def_0.pdf

iwCLL[3]

Screen How would you evaluate the response?

Supporting guidelines
Update

Group	Parameter	CR	PR	PD	SD
A	Lymph nodes	None ≥1.5 cm	Decrease ≥50% (from baseline)*	Increase ≥50% from baseline or from response	Change of −49% to +49%
	Liver and/or spleen size†	Spleen size <13 cm; liver size normal	Decrease ≥50% (from baseline)	Increase ≥50% from baseline or from response	Change of −49% to +49%
	Constitutional symptoms	None	Any	Any	Any
	Circulating lymphocyte count	Normal	Decrease ≥50% from baseline	Increase ≥50% over baseline	Change of −49% to +49%
B	Platelet count	≥100 × 10^9/L	≥100 × 10^9/L or increase ≥50% over baseline	Decrease of ≥50% from baseline secondary to CLL	Change of −49 to +49%
	Hemoglobin	≥11.0 g/dL (untransfused and without erythropoietin)	≥11 g/dL or increase ≥50% over baseline	Decrease of ≥2 g/dL from baseline secondary to CLL	Increase <11.0 g/dL or <50% over baseline, or decrease <2 g/dL
	Marrow	Normocellular, no CLL cells, no B-lymphoid nodules	Presence of CLL cells, or of B-lymphoid nodules, or not done	Increase of CLL cells by ≥50% on successive biopsies	No change in marrow infiltrate

For a detailed description of the response parameters, see section 5.

*Sum of the products of 6 or fewer lymph nodes (as evaluated by CT scans and physical examination in clinical trials or by physical examination in general practice).

†Spleen size is considered normal if <13 cm. There is not firmly established international consensus of the size of a normal liver; therefore, liver size should be evaluated by imaging and manual palpation in clinical trials and be recorded according to the definition used in a study protocol.

CR, complete remission (all of the criteria have to be met); PD, progressive disease (at least 1 of the criteria of group A or group B has to be met); PR, partial remission (for a PR, at least 2 of the parameters of group A *and* 1 parameter of group B need to improve if previously abnormal; if only 1 parameter of both groups A and B is abnormal before therapy, only 1 needs to improve); SD, stable disease (all of the criteria have to be met; constitutional symptoms alone do not define PD).

[3] *Hallek Blood 2018 Jun 21;131(25):2745-2760*