Thursdays Webinars

EuroBloodNet

HOW TO APPROACH CLL IN OLDER PATIENTS

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ERN-EuroBloodNet subnetwork "Rare lymphoid disorders"

EHA SWG "Aging and hematology" : past

Brussels, BELGIUM

14th of May 2020

Co-funded by the Health Programme of the European Union

European Reference Network for rare or low prevalence complex diseases

Network Hematological Diseases (ERN EuroBloodNet)

CONFLICTS OF INTEREST

Advisory Board: Roche, AbbVie Inc., Amgen Inc., Janssen-Cilag, Gilead

Consulting: None

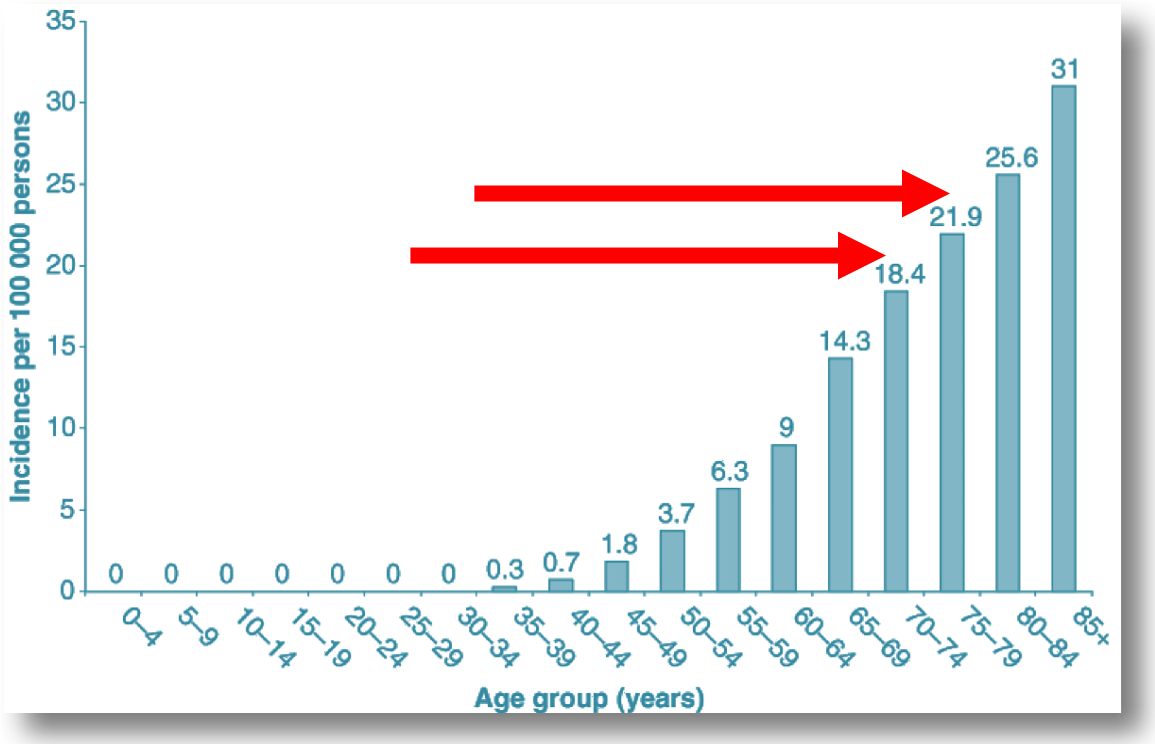
Stockholder : None

Research Funding: Celgene, Roche, Amgen, Abbvie

LEARNING OBJECTIVES OF THE WEBINAR

1. ARE YOU SURE IT IS A CLL?
2. RELEVANT POINTS TO CONSIDER BEFORE TREATMENT?
3. SUMMARY OF FIRST LINE TREATMENT IN OLDER CLL PATIENTS?

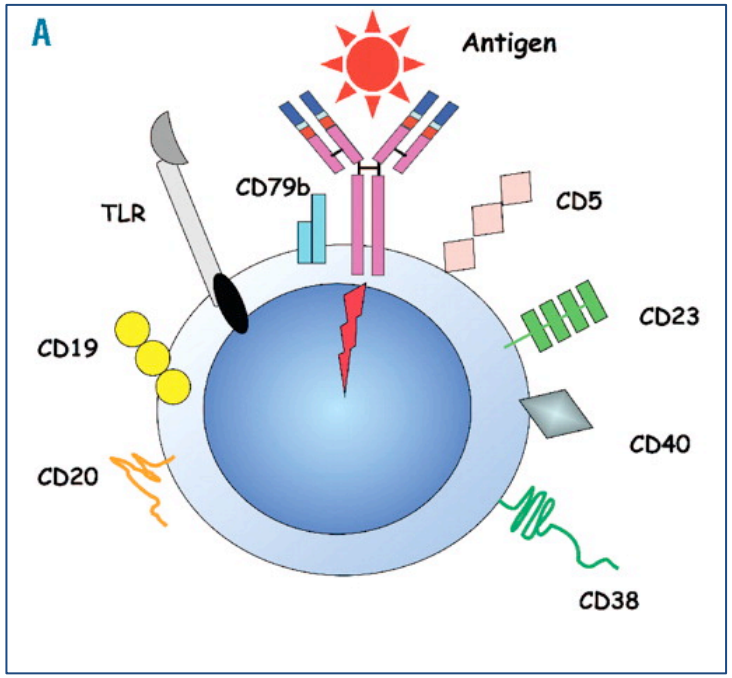
A) ARE YOU SURE IT IS A CLL ?



- Median age is 72y, F>M
- Median age on treatment is 76y
- 55% are diagnosed at 65+y
- CLL remains the primary cause of death in CLL pts
- Real life was far from protocol until recently

Ref : *IWCLL guidelines – Hallek et al; BLOOD 2018 (131) 2745*
ESMO guidelines for CLL – Annals of oncology 2018 (29)25.
SIOG task force elderly – R Stauder et al ;Annals of Oncology 2017 (28) 216

A) ARE YOU SURE IT IS A CLL ?



B-Lymphocytes >5000/uL

CLL score 5/5

- ***Required markers***

CD5	***positive >20%***
CD19,	***positive >95%***
CD23	***positive >20%***
CD20, ~~CD79b~~	***+, low expression***
sIG, k of L	***+, low expression***
~~FMC7~~	***~~negative~~***

- ***Recommeneded markers***

CD43	***Pos >20%***
CD200.	***Pos >20%***
ROR1	***Pos >20%***
CD79b.	*Weak/neg*
CD81.	***Weak/neg***
CD10	*Neg <20%*

Atypical CLL ?

(Score <3/5)

MBL (CLL/MZL/LL)
MCL (t(11-14) Cycl D1)
SLVL/MZL (SM, FMC7+)
B-ProLL. (SM, FMC7+)
Hairy CL (SM,CD25+, BRAFF)
Foll NHL(CD10+;FMC7+)

A. RAWSTON ET AL.
(ERIC & ESCCA)
Cytometry 2018
(94b) 121-128

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A) ARE YOU SURE IT IS A CLL

B) RELEVANT POINTS TO CONSIDER BEFORE TREATMENT :

1. ***DOES THE PATIENT REQUIRE A TREATMENT ?***
2. *How « fit » is the patient ?*
3. *Does the patient present high risk features ?*
4. *Does the patient want a treatment ?*

Ref : *IWCLL guidelines – Hallek et al; BLOOD 2018 (131) 2745*
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1.DOES THE PATIENT REQUIRE A TREATMENT ? .... *COVID19 !!!*

- Evidence of progressive ***marrow failure***
- Massive, progressive, or symptomatic ***splenomegaly***
- Progressive/symptomatic lymphadenopathy or ***massive nodes***
- ***Progressive lymphocytosis***
- ***Autoimmune*** complications
- ***Extranodal*** involvement
- Disease-related symptoms (unintentional weight loss, significant ***fatigue, fevers, night sweats*** for over a month without evidence of infection).

« IwCLL guidelines » for diagnosis, indications for treatment, response assessment, and supportive management »
M Hallek et al. BLOOD 2018 (131) 2745-60

B°RELEVANT POINTS TO CONSIDER BEFORE TREATMENT :

1. Does the patient require a treatment ?
2. **HOW « FIT » IS THE PATIENT ?**
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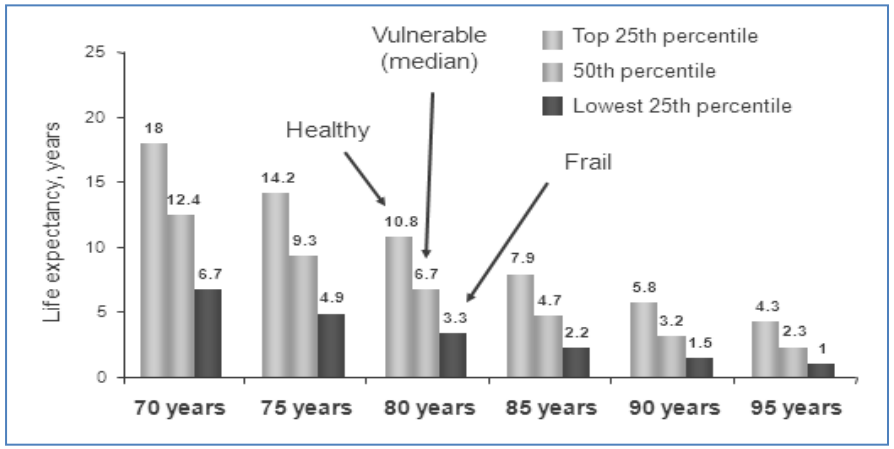
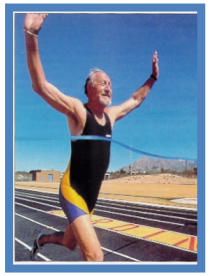
2. OLDER LYMPHOMAS PATIENTS REQUIRES SPECIAL ATTENTION !

- *Life expectancy can reach 10 yrs above 80 yo*



- *Up to 80 y, 75% of patients tolerate chemotherapy*



70 -79 y = 75%
80 -88 y = 20%
90+ y = 5%

- *Marrow reserves are reduced*
- *Neurological tolerance is reduced*
- *Pharmacokinetics is modified*
- *Polymedication is common*
- *Comorbidities (++50%)*, poor PS*, denutrition*,*
- *impaired cognition.. -> Impaired overall Survival !!*

→ **Pt or disease-related ???*

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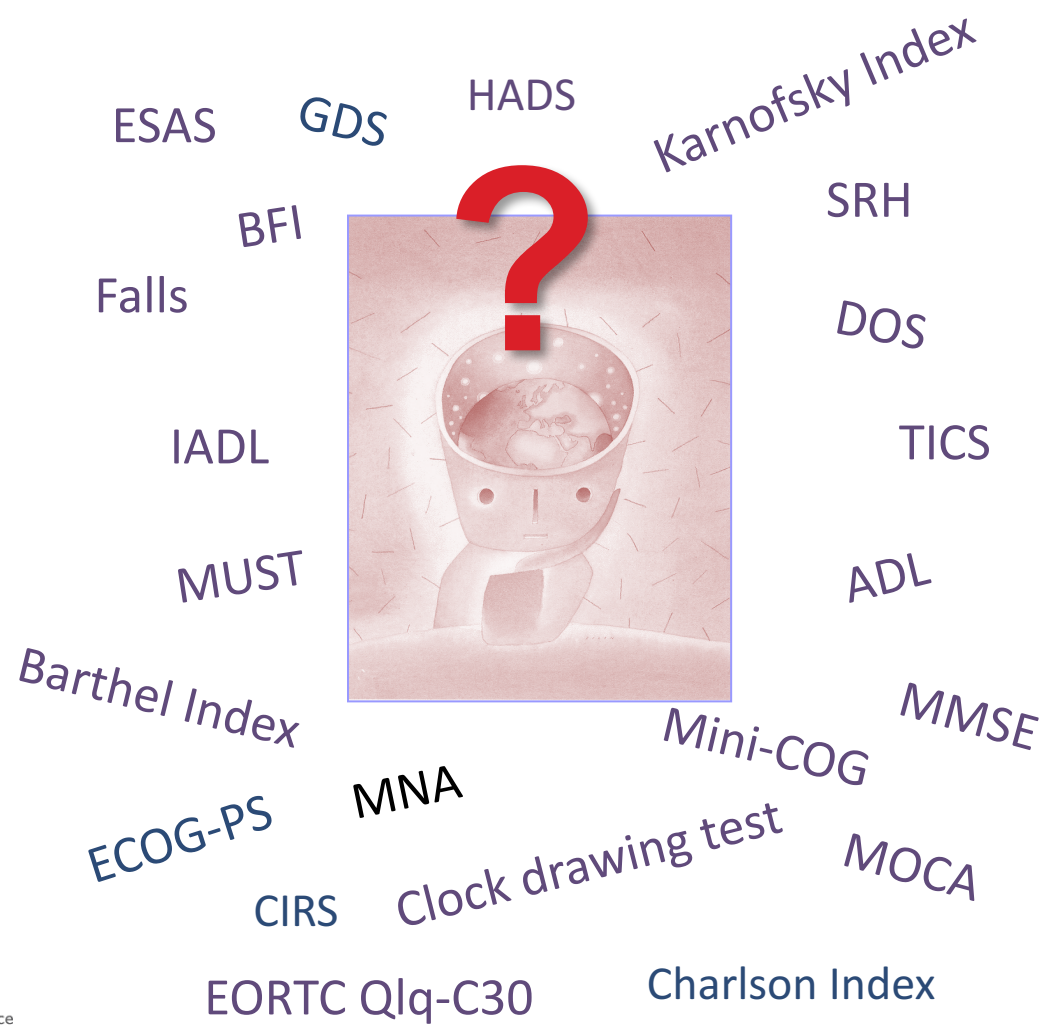
COMPREHENSIVE GERIATRIC ASSESSMENT = « CGA »

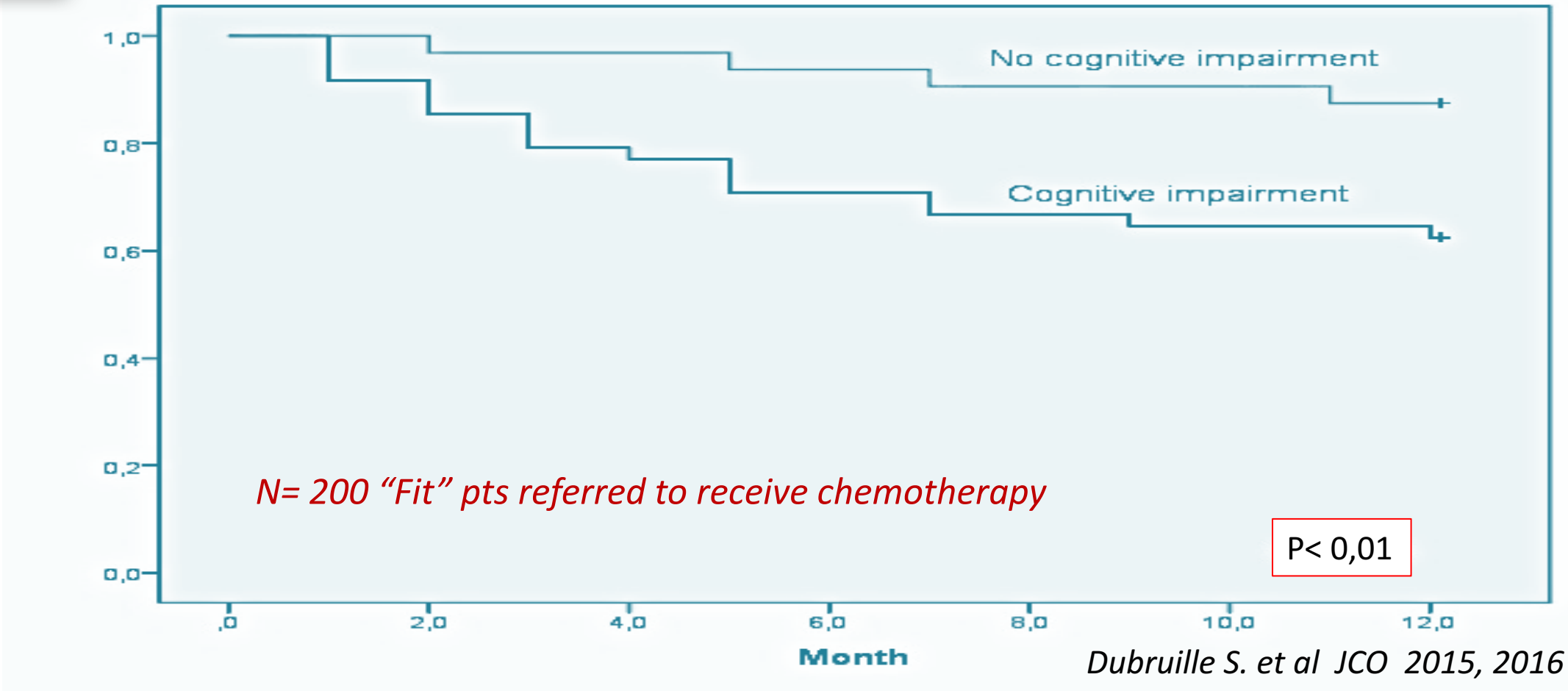


MARKERS OF FRAILTY

- **COGNITION**
  (MMSE/MOCA/IADL)
- **DENUTRITION**
  (MNA, Albumine, BMI
- **PHYSICAL PERFORMANCE**
  (PS, Up & Go)
- **COMORBIDITIES**
  (CIRS, CCI/ RF, GIT..)

→ **Exclude geriatric syndrome**

MILD COGNITIVE IMPAIRMENT IS ASSOCIATED WITH A POORER SURVIVAL IN « CLINICALLY FIT » PATIENTS WITH MALIGNANT HEMOPATHIES.



N= 200 "Fit" pts referred to receive chemotherapy

P< 0,01

Dubruille S. et al JCO 2015, 2016

Fig 2. Kaplan-Meir overall survival estimates between patients without cognitive impairment (MMSE ≥27 and MoCA ≥26) and patients with cognitive impairment (MMSE<27 or MoCA <26) in one-year overall survival.

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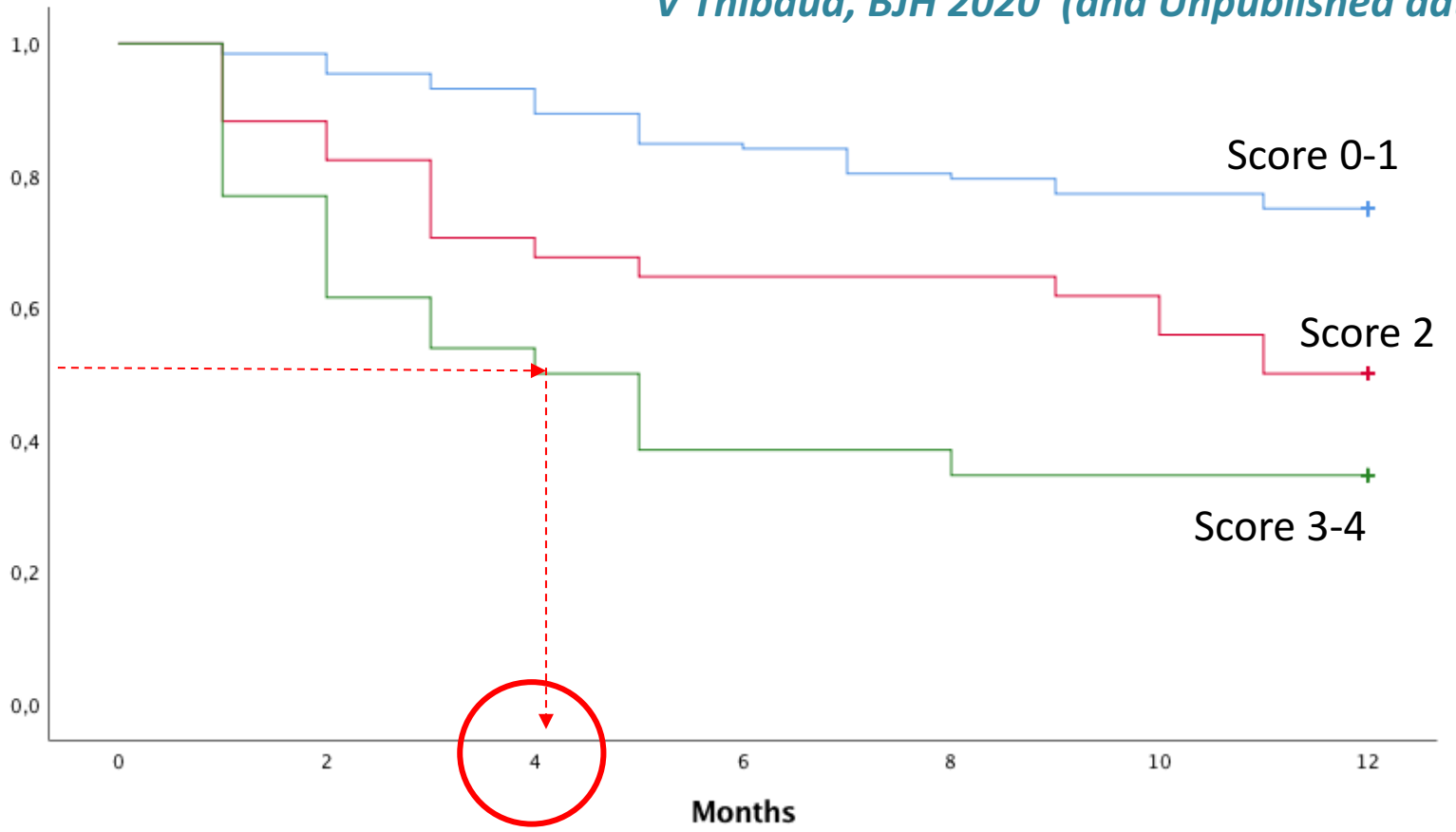
« FRAILTY » SCORING IN MALIGNANT HEMOPATHIES

V Thibaud, BJH 2020 (and Unpublished data)!

Four Independent Prognostic Factors (Score: 1 point/item)

- **ALB < N1**
- **CRP > N1**
- **PT-Rel Comorb>1**
- **MMSE <27**



Pts status	Additive score	N. pts (%)	12 months survival (%)	HR	95% CI			P
Fit	*0-1*	*132 (69)*	*75*					
Vulnerable	*2*	*34 (18)*	*50*	*2.40*	*1.34*	*to*	*4.32*	*0.003*
Frail	*3-4*	*26 (14)*	*35*	*4.12*	*2.28*	*to*	*7.42*	*<0.001*

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B) RELEVANT POINTS TO CONSIDER BEFORE TREATMENT :

1. Does the patient require a treatment ?
2. How « fit » is the patient ?
3. **DOES THE PATIENT PRESENT « HIGH RISK » CLL ?**
4. Does the patient want a treatment ?

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3. DOES THE PATIENT PRESENT HIGH RISK FEATURES : CLL-IPI ?

PATIENTS RELATED	DISEASE RELATED CLIN/LAB	DISEASE RELATED CYTOGENETIC	DISEASE REL GENETICS
AGE >65	**Stage Binet B-C**	**Del 17p (>10%)**	TP**53m + (>5%)**
Comorobidities CIRC6+)	**Beta2 micro >3,5**	Del 11q	SF3B1
ECOG <2	CD38 +	Tris 12	NOTCH1
		IGVH UM	ATM

VARIABLE	ADVERSE FACTOR	SCORE
AGE	>65	1
CLINICAL STAGES	B-C	1
DEL17p or TP53m	Deleted or mutated	4
B2 microgl	>3,5mg/l	2
IGVH mut	UnMutated	2

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IWCLL-Lancet Oncol 2016

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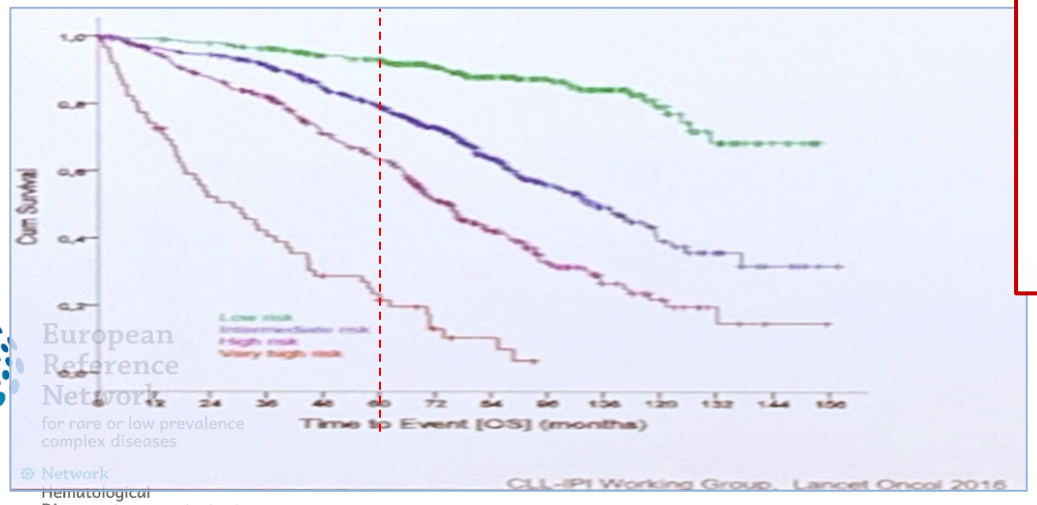
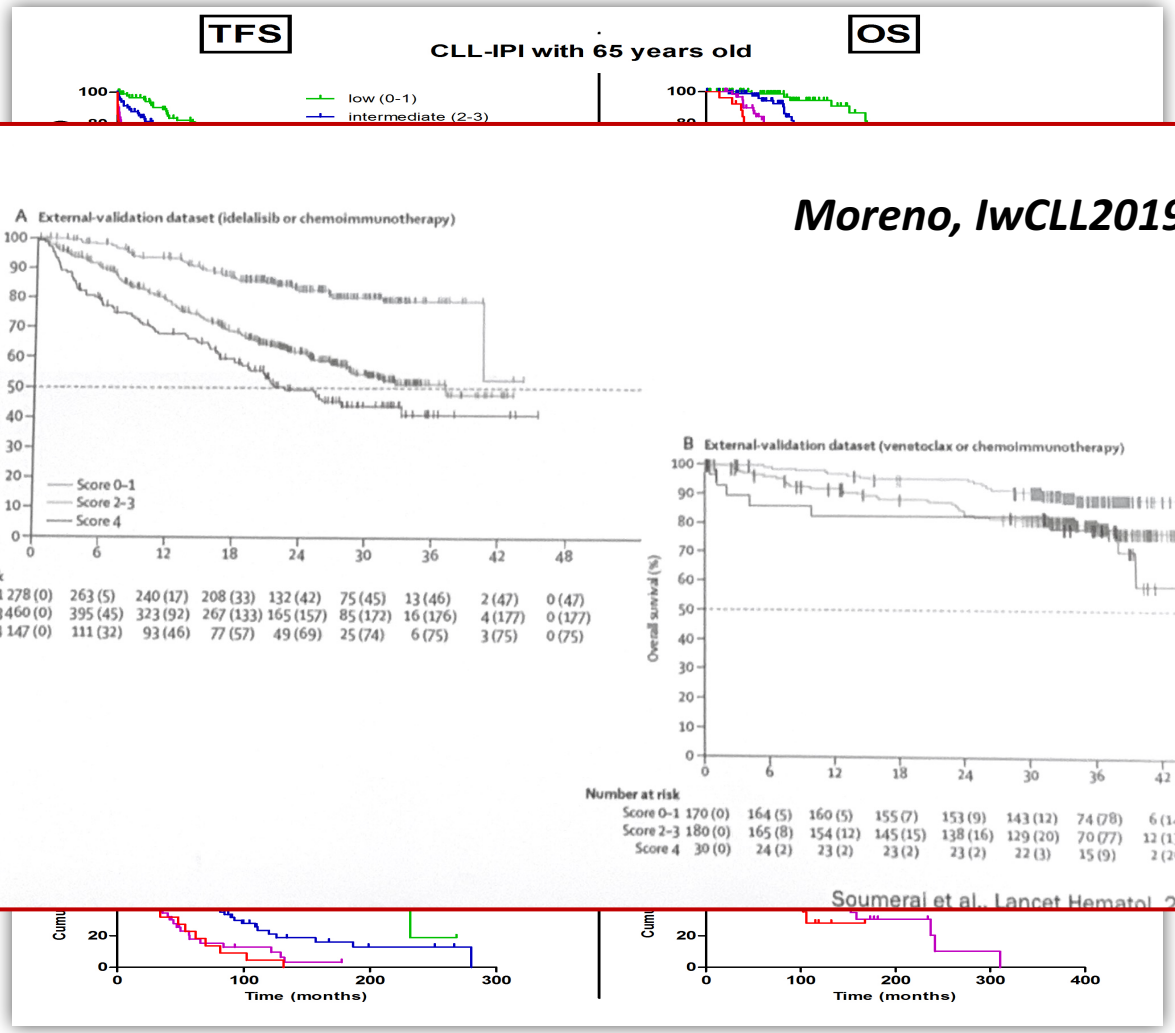
3. DOES THE PATIENT PRESENT HIGH RISK FEATURES : CLL-IPI?

RISKS (R)	SCORE	5 yrs OS (%)	TREATMENT
LOW RISK	0-1	93	W&W
INTERM R	2-3	79	W&W unless symptomatic
HIGH RISK	4-6	64	TREATMENT according to Symptoms
VERY HIGH R	7-10	23	TREATMENT MANDATORY

Lancet oncol 2017





Moreno, IwCLL2019

B.Stamatopoulos- Leukemia 2018

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4. DOES THE PATIENT WANT A TREATMENT ?

« Quality »

Of Life Is

More Important

Than

« Quantity »

Of Life …

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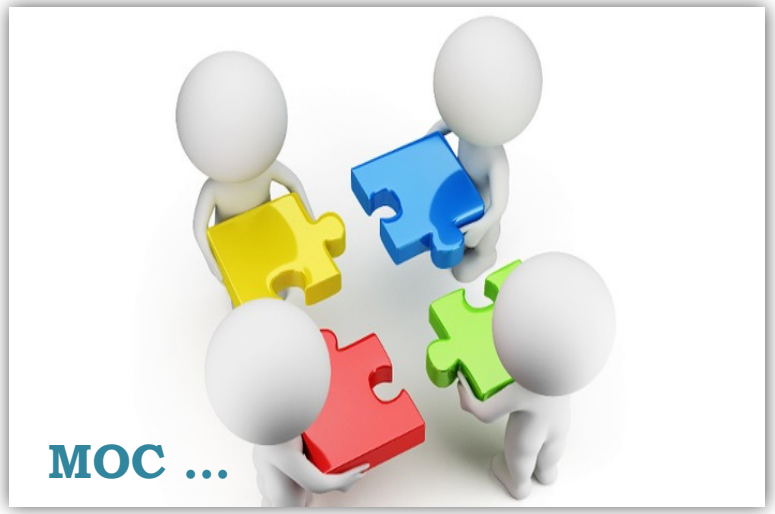
- **CARE GIVERS ?**
- ***Socio-economical status***

- **PATIENT ?** Life Expectancy ?
- **Autonomy (PS/ADL)**
- Comorbidities/Nutrition
- IADL/Cognition/Depression



- **PATIENT EXPECTATIONS !**

- **B-CLL ? – Prognost. Markers?**
- IwCLL Crit for Treat?

EHASWG
SCIENTIFIC WORKING GROUPS

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A) ARE YOU SURE IT IS A CLL

B) RELEVANT POINTS TO CONSIDER BEFORE TREATMENT

C) FIRST LINE TREATMENT IN « UNFIT » CLL PATIENTS

1. **CHEMO +/- IMMUNOTHERAPY ?**
2. Btk Inh And Combinations ?
3. BcL2 inh and combinations ?

Ref : *IWCLL guidelines – Hallek et al; BLOOD 2018 (131) 2745*
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CHEMO+/-IMMUNOTHERAPY FOR UNFIT CLL

CLL « UNFIT » for FCR	TRIAL	OR(CR) %	Med PFS (mo)	Med OS (mo)	MRD (% RC	REFERENCES
CLL 5 **(65+)**	**FLU** **CLB**	**50 (14)** **50(4)**	**18** **10**	**46** **64 ***	**NA**	Rai , NEJM 1995 EIchhorst et al Blood 2009
CLL8 **(70+)**	**FCR** **FC**	90(42)	56 36	**50***	NA	Hallek, Lancet On '08, Blood 2016
CLL10 **(65+)**	**FCR vs** **BR**	95 (40) vs 90 (30)	55 **41**	60+ 2*Tu* **NS***	NA	Eichhorst Lancet Onc 2016, 2020
CLL 11 65+/cirs 6+	**Clb vs ChR v** **ChL+ Obin**	**60 (8)** **75 (25)**	**15** **27***	**73** **Not Reached**	**25**	V Goede, NEJM 2014-2018

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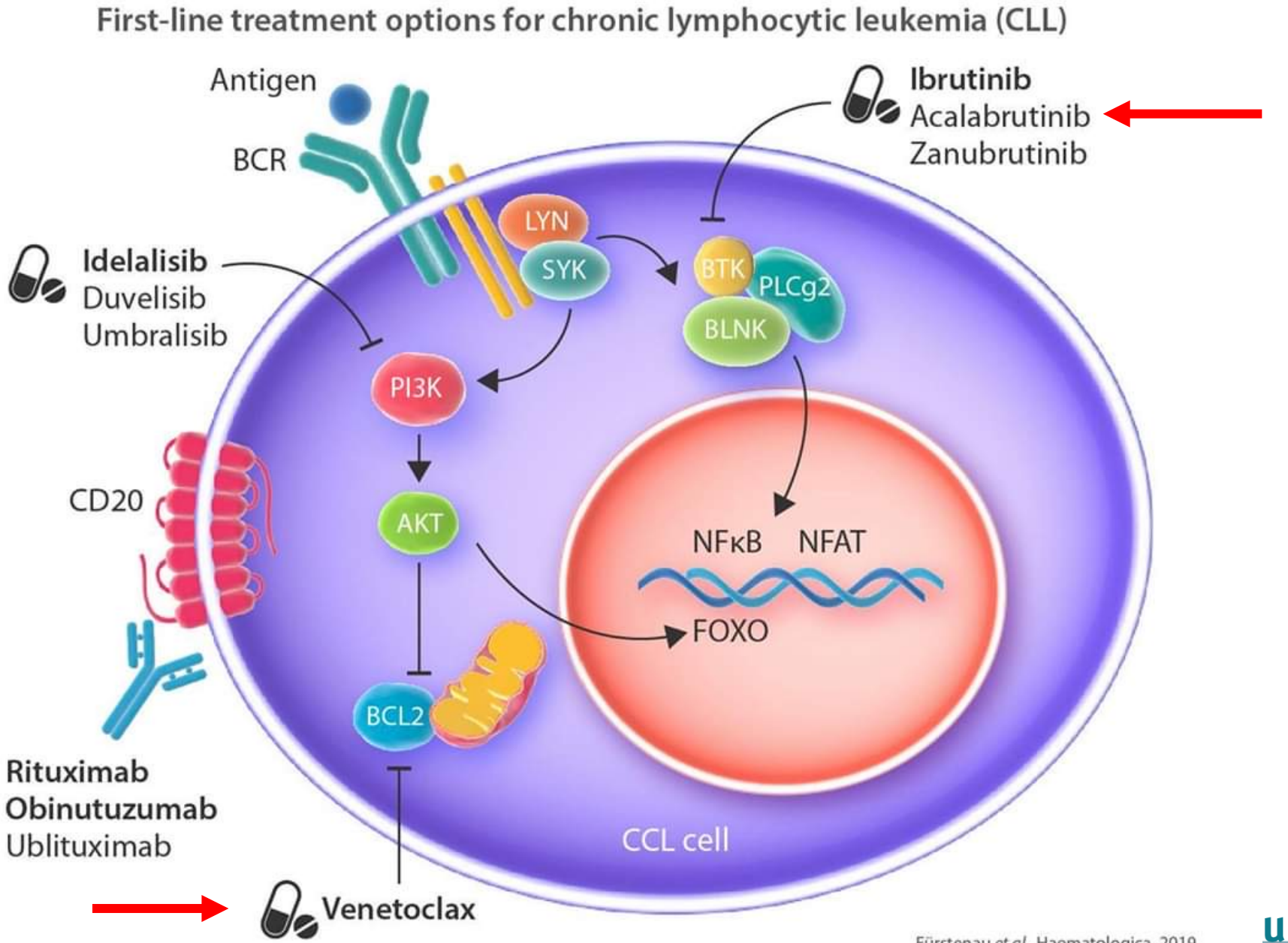
C) FIRST LINE TREATMENT IN « UNFIT » CLL PATIENTS



Fürstenau *et al.*, Haematologica, 2019

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A) ARE YOU SURE IT IS A CLL

B) RELEVANT POINTS TO CONSIDER BEFORE TREATMENT

C) FIRST LINE TREATMENT IN « UNFIT » CLL PATIENTS

1. Chemo +/- immunotherapy ?
2. **BTK INH AND COMBINATION ?**
3. BcL2 inh and combination ?

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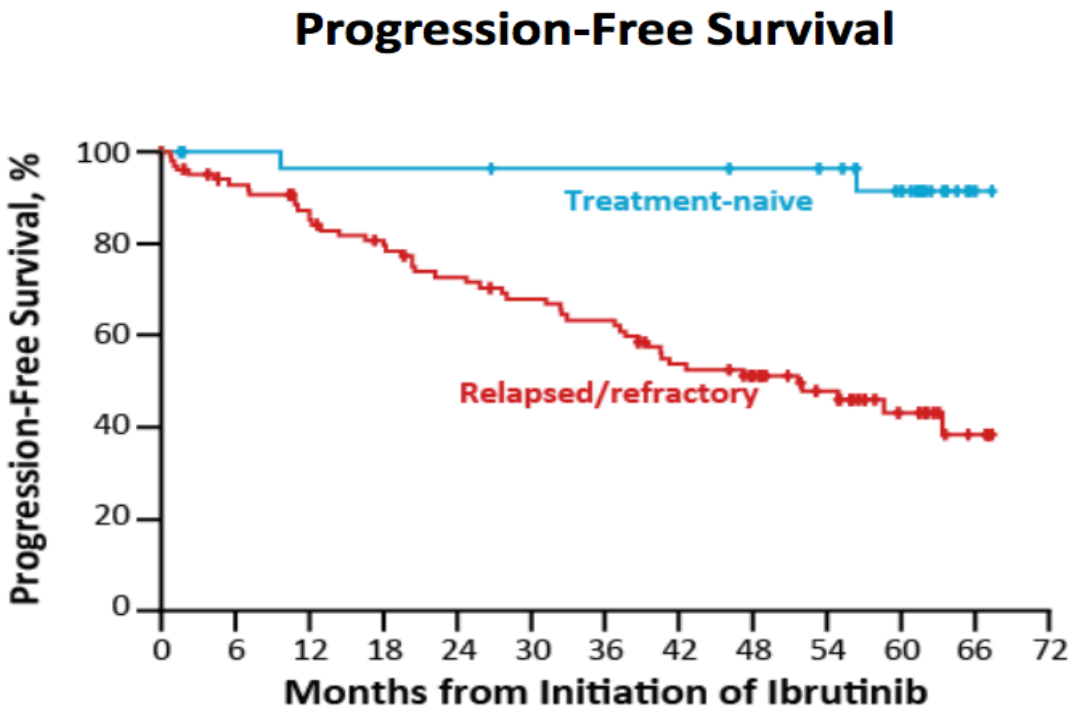
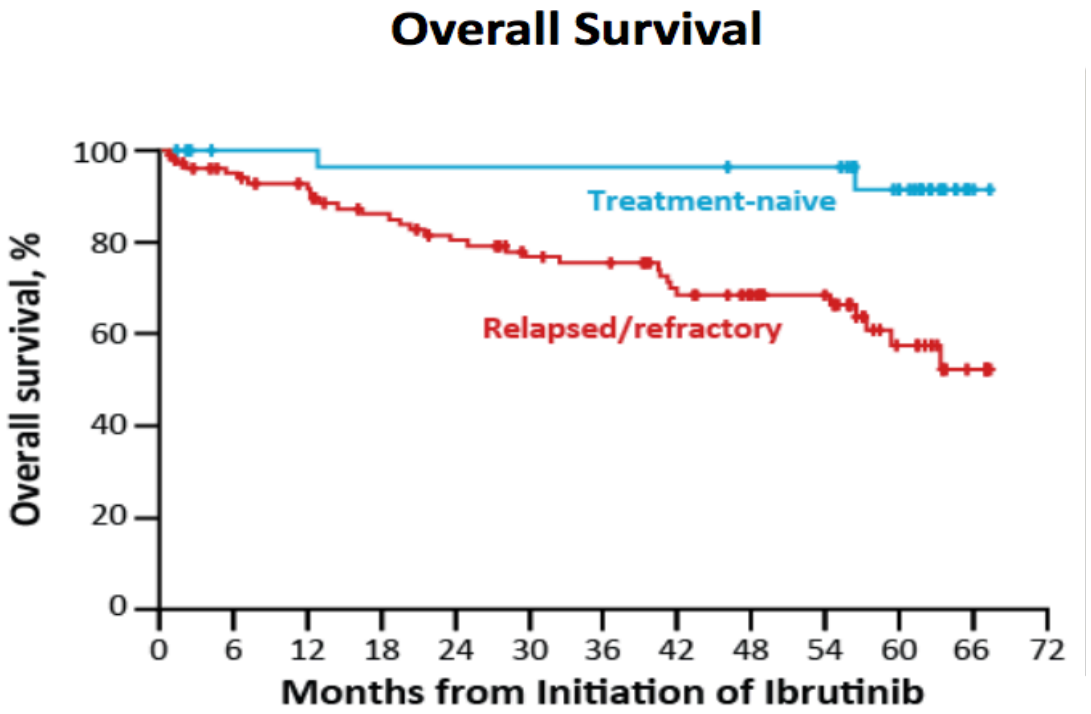
CLL »UNFIT » for FCR	TRIAL	OR(CR) %	Med PFS (Mo)	OS/Yr	Message	Reference
RESONNATE 2 65-90y (n=290)	**IBRU vs CLB**	**90 (18) 50(4)**	**75% PFS/5yrs 12**	**63 vs 83/5y**	**IBRU >> CLB* (PFS & OS)**	**NEJM 2016 IwCLL 2019**
ALLIANCE 65+, 17p del (n=547)	**B+R vs Ibru v Ibru-R**	81(26) vs **94 (10)**	74 % vs **87vs 88%**	NS OS/2 Yr	**IBRU > BR*** IBRU = B Ritux *(No diff in OS Mut CLL/2yr)*	NEJM 2018
ILLUMINATE 65+ (n=229)	**Ob +Chl vs Ob + IBRU**	XXX	**16 vs 77%/30m**	90 /3yrs	**IBRU+Ob > Ob+ Chl *** (PFS not OS)	Lancet Oncol 2019
CLL 14 Unfit= cirs6, CrC<70 (n=432)	**Ob-Chl vs Ob-Venetocl**	**90(58)**	**65** Vs. **88 /24m**	90+/2yr	**Ven = Ob > Ob + Chl * PFS & OS)**	NEJM 2019

IBRUTINIB EXPERIENCE : 7 YEARS FOLLOW-UP





	Median PFS	5-year PFS
TN (n=31)	NR	92%
R/R (n=101)	52 mo	43%

	Median OS	5-year OS
TN (n=31)	NR	92%
R/R (n=101)	NR	57%

Update by O'Brien IWCLL2019

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« ALLIANCE » BR vs Ibru vs Ibru+Ritux

Grade 3, 4, or 5 Adverse Events
During treatment or follow-up (excluding crossover)

Adverse Event	BR N=176	Ibrutinib N=180	IR N=181	P-value
All Hematologic -- no. (%)	**107 (61)**	**74 (41)**	**70 (38)**	**<0.001**
Anemia	22 (13)	21 (12)	11 (6)	0.09
Neutropenia	71 (40)	27 (15)	39 (22)	<0.001
Thrombocytopenia	26 (15)	12 (7)	9 (5)	0.008
All Non-hematologic -- no. (%)	**111 (63)**	**133 (74)**	**134 (74)**	**0.04**
Bleeding	0 (0)	3 (2)	5 (3)	0.46
Infections	26 (15)	37 (21)	37 (20)	0.62
Febrile neutropenia	13 (7)	3 (2)	1 (1)	<0.001
Atrial fibrillation	5 (3)	17 (9)	10 (6)	0.05
Hypertension	25 (14)	53 (29)	61 (34)	<0.001
Unexplained/unwitnessed death	2 (1)	7 (4)	4 (2)	0.24

- Deaths during active treatment + 30 days: 2 (1%), 13 (7%), 13 (7%)
- Deaths during active treatment + 30 days, up to 6 cycles: 2 (1%), 3 (2%), 6 (3%)

Lancet. 2020 Apr 18;395(10232):1278-1291. doi: 10.1016/S0140-6736(20)30262-2.

Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzmab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase 3 trial.

Sharman JP[1], Egyed M[2], Jurczak W[3], Skarbnik A[4], Pagel JM[5], Flinn IW[6], Kamdar M[7], Munir T[8], Walewska R[9], Corbett G[10], Fogliatto LM[11], Herishanu Y[12], Banerji V[13], Coutre S[14], Follows G[15], Walker P[16], Karlsson K[17], Ghia P[18], Janssens A[19], Cymbalista F[20], Woyach JA[21], Salles G[22], Wierda WG[23], Izumi R[24], Munugalavadla V[24], Patel P[24], Wang MH[24], Wong S[24], Byrd JC[25].

Sharman, ASH 2019

ELEVATE TN Study Design (ACE-CL-007)

Acalabrutinib = second gen, propiolamide side chain vs acrylamide (ibru)

Treatment-naive CLL (N=535)

Age ≥65 or <65 years with coexisting conditions:
- CIRS score >6, or
- creatinine clearance <70 mL/min

Stratification
- del(17p), y vs n
- ECOG PS 0-1 vs 2
- Geographic region (N America, W Europe, or other)

RANDOMIZE 1:1:1

- **Acalabrutinib[a] + Obinutuzumab (G)[b]**
  [a]100 mg PO BID
  [b]1000 mg IV on D1, 2, 8, and 15 of Cycle 2, + D1 of subsequent 28-day cycles for a total of 6 cycles
- **Acalabrutinib**
  100 mg PO BID
- **Obinutuzumab (G)[c] + Chlorambucil[d]**
  [c]1000 mg IV on D1, 2, 8, and 15 of Cycle 1, + D1 of subsequent 28-day cycles for a total of 6 cycles
  [d]0.5 mg/kg PO on D1 + 15 of each 28-day cycle for 6 cycles

Primary endpoint
- PFS (assessed by IRC) Acala-G vs G-Clb

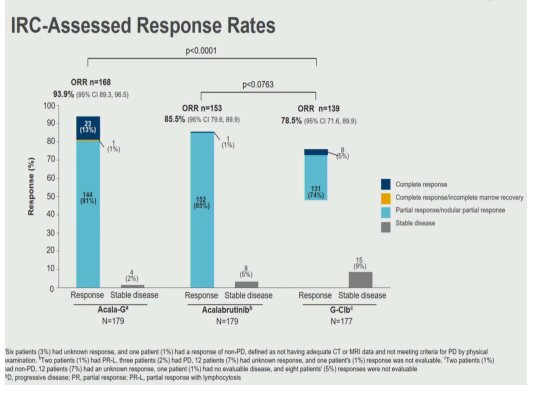
Key secondary endpoints
- PFS acalabrutinib vs G-Clb
- ORR (assessed by IRC and investigator)
- Time to next treatment
- OS
- Safety

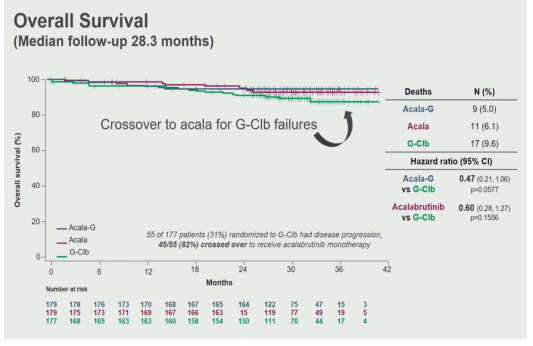
Risk factors balanced
10%17p; 18% 11q
65% mutated

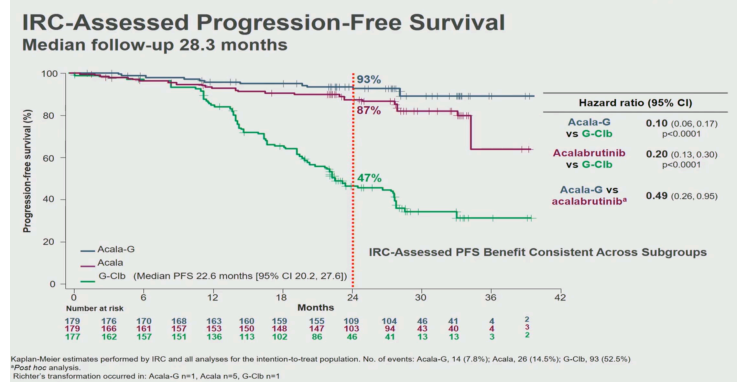
***Crossover** from G-Clb to acalabrutinib was allowed after IRC-confirmed progression*

- Interim analysis was planned based on events (after occurrence of ~111 IRC-assessed PFS events in the combination therapy arms) or after 24 months if the required number of events was not met by this time

Acala, acalabrutinib; CIRS, Cumulative Illness Rating Scale; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent review committee; IV, intravenously;







Kaplan-Meier estimates performed by IRC and all analyses for the intention-to-treat population. No. of events: Acala-G, 14 (7.8%); Acala, 26 (14.5%); G-Clb, 93 (52.5%)
[a]*Post hoc* analysis.
Richter's transformation occurred in: Acala-G n=1, Acala n=5, G-Clb n=1

Adverse Events/Serious Adverse Events

- Greater proportion of subjects with SAE in Acalabrutinib/G arm
- More grade 3 AE's and neutropenia in combination arms
- More infection/grade 3 infection in acalabrutinib arms
- Less IRR in Acalabrutinib/G arm vs Chl/G arm (acala arm starts G cycle 2)
- No grade 3 bleeding in acalabrutinib arm
- Atrial fibrillation 3.6% acalabrutinib arms

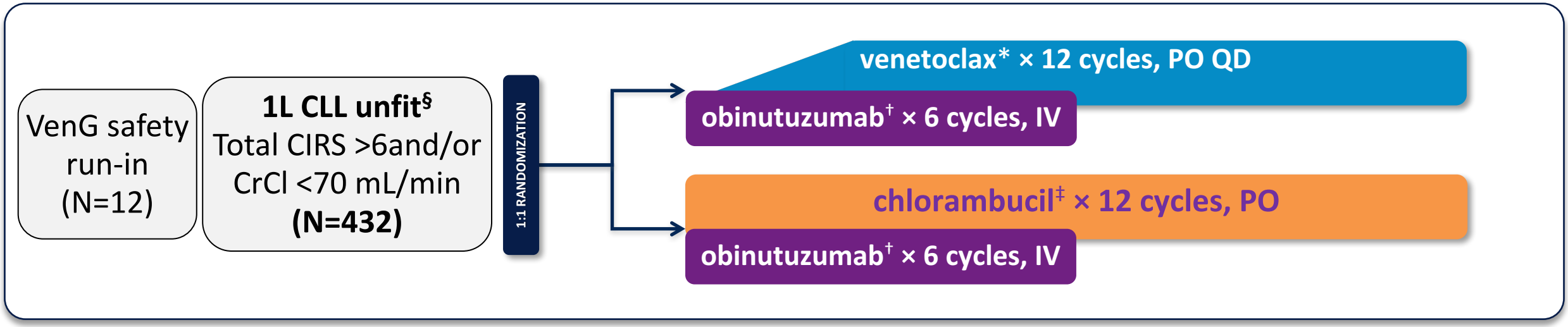
The NEW ENGLAND JOURNAL of MEDICINE

VENETOCLAX + OBINUTUZUMAB (CLL14)
1 YEAR TT IN 1RST LINE UNFIT CLL

N Engl J Med. 2019 Jun 6;380(23):2225-2236. doi: 10.1056/NEJMoa1815281. Epub 2019 Jun 4.

Venetoclax and Obinutuzumab in Patients with CLL and Coexisting Conditions.

Fischer K[1], Al-Sawaf O[1], Bahlo J[1], Fink AM[1], Tandon M[1], Dixon M[1], Robrecht S[1], Warburton S[1], Humphrey K[1], Samoylova O[1], Liberati AM[1], Pinilla-Ibarz J[1], Opat S[1], Sivcheva L[1], Le Dû K[1], Fogliatto LM[1], Niemann CU[1], Weinkove R[1], Robinson S[1], Kipps TJ[1], Boettcher S[1], Tausch E[1], Humerickhouse R[1], Eichhorst B[1], Wendtner CM[1], Langerak AW[1], Kreuzer KA[1], Ritgen M[1], Goede V[1], Stilgenbauer S[1], Mobasher M[1], Hallek M[1].



Primary endpoint:
- Investigator-assessed PFS

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

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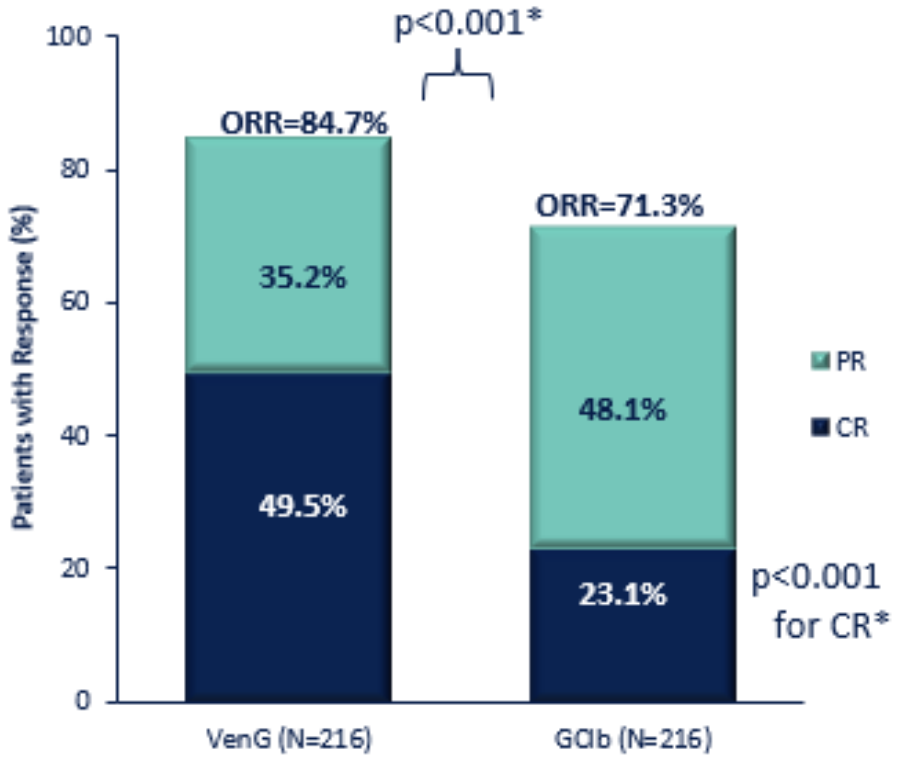
for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

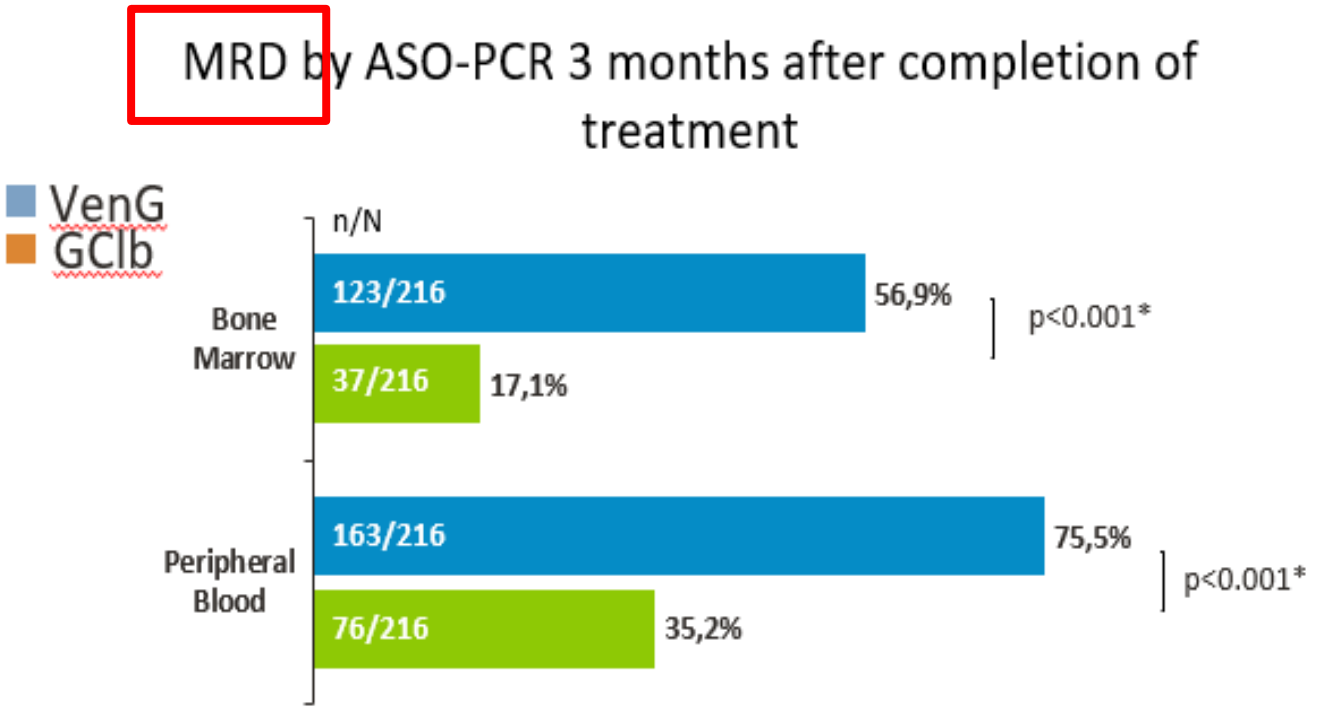
Thursdays Webinars

CLL14 - VENETOCLAX + OBINUTUZUMAB (VEN-G):

"1 YEAR " TT IN 1RST LINE "UNFIT" CLL

Overall and Complete Response Rates were Significantly Higher with VenG than GClb





- Overall and complete response rates were significantly higher with VenG than with GClb (84.7% vs 71.3% [p<0.001]; 49.5% vs 23.1% [p<0.001], respectively)

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

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CLL14 Adverse Events

Adverse Event	Chlorambucil Obinutuzumab N=212	Venetoclax Obinutuzumab N=214
All Hematologic -- no. (%)		
Anemia	14 (6.5)	17 (8)
Neutropenia	103 (48.1)	112 (52.8)
Thrombocytopenia	32 (15)	29 (13.7)
All Non-hematologic -- no. (%)		
Infections	32 (15)	37 (17.5)
Febrile neutropenia	8 (3.7)	11 (5.2)
Diarrhea	1 (0.5)	9 (4.2)
Neoplasms, benign or malignant	8 (3.7)	13 (6.1)

What do you mean by « Unfit » in CLL…

- **UNFIT FOR FCR:** 65^{+} y, GF > 70%, Active infection , UM IVIG gene, TP53m
- **UNFIT FOR BR:** Unmut IGIV, $TP53^{m}$, Poor autonomy, Acute infection
- **UNFIT FOR CLB + OBINUT:** $TP53^{m}$, Unmut IVIG, Geriatric syndrome

- **UNFIT FOR IBRUTINIB:** BTK^{m}, $PLCG2^{m}$, Arythmia, uncontroled HT, warfarin (mech.valve, cardiac Thrombus, APLS…)
- **UNFIT FOR VENETOCL + OBINUTUZ** : Heart Failure or Renal Failure, geriatric syndrome

ALGORITHM TREATMENT OF OLDER PATIENTS WITH CLL

Front-line treatment CLL

Advanced or active disease

No advanced or active disease

no 17p del/p53 mut

17p del/p53 mut

W & S**

Unfit for FCR
M ou UM IGVH

Fit for FCR
Mutated IGVH

Ibrutinib, Venetoclax*

Benefit : Risk Analysis

BR / Ob – Chl

Ibru /VEN-G

FCR,
>65j: FCR/BR

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TAKE HOME MESSAGES

- Older patients requires specific attention! Supportive Care +++
- Ibrutinib/Acalabrutinib are Superior to Chemoimmunotherapy
- Intermittent BTKi is under investigation
- Ven- G is more effective than ChL- G and very similar to Ibru
- Long term toxicity is now critical to define the best option in first line