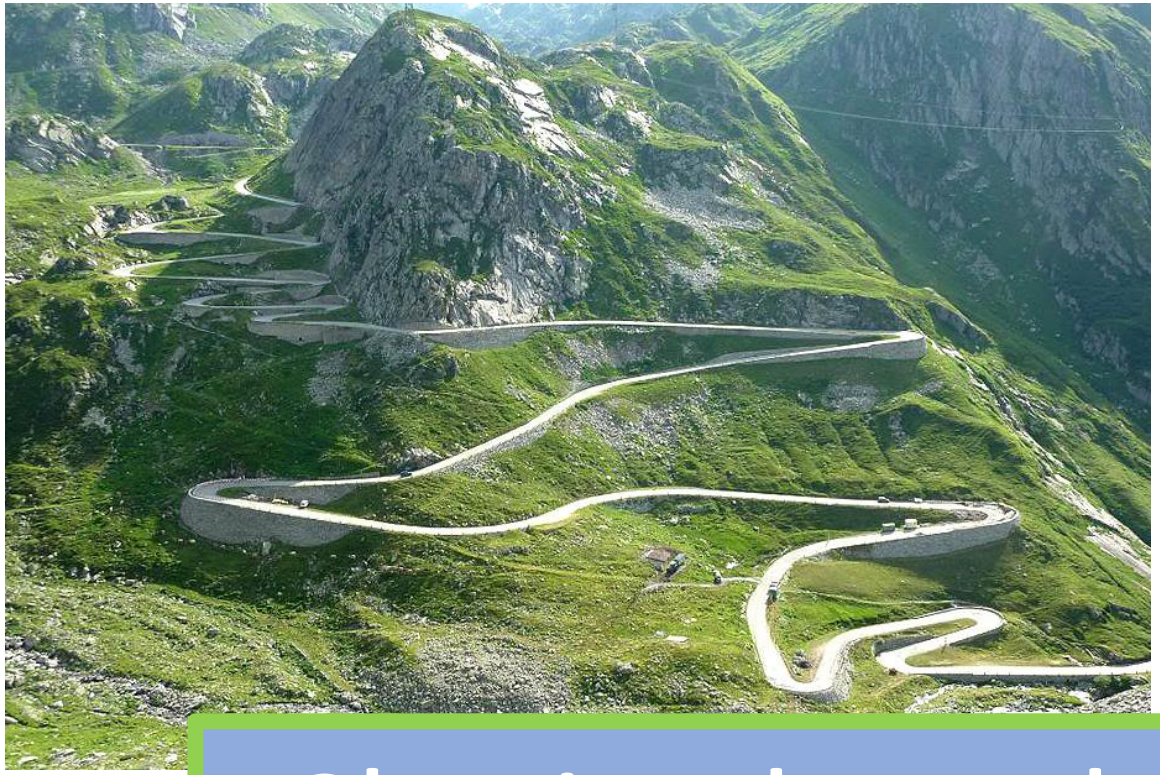
The Israeli CLL Association (ICLLA)
CLL
The Israeli CLL Study Group (ICLLSG)

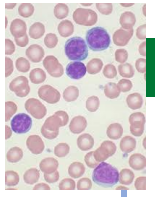
Bnai Zion Medical Center

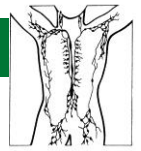


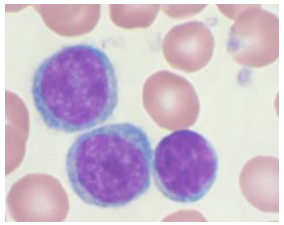
Overview on CLL diagnosis & treatment until today

25/04/2019

Sharing knowledge perspectives and feelings





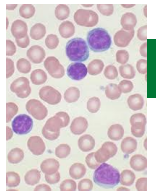


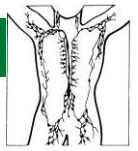
Disclosure statement: Tamar Tadmor

Consulting activity or honoraria:

Roche, Janssen, AbbVie, Takeda, Medison, Gilead

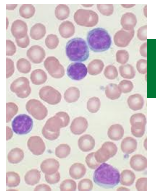
Bnai Zion Medical Center

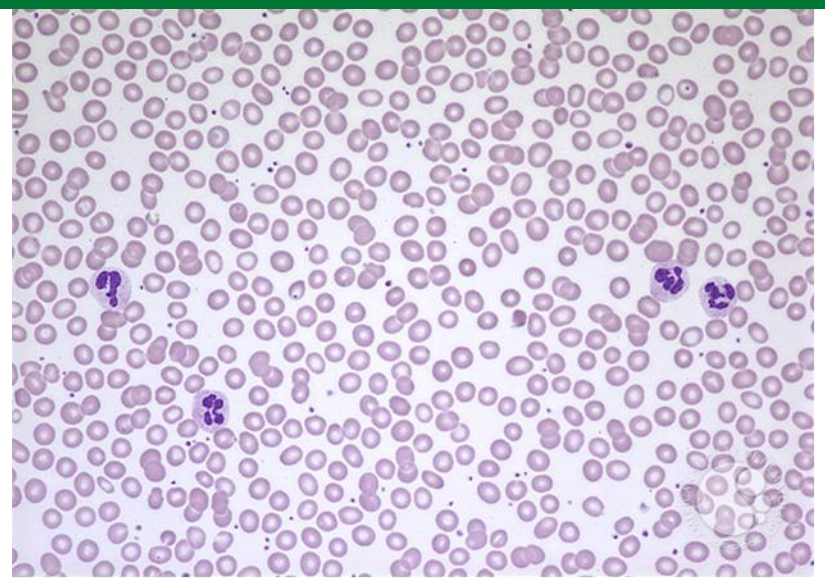


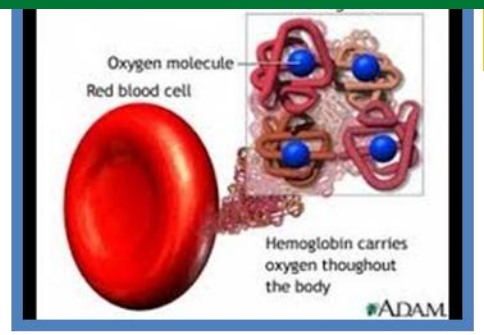


Normal Blood count

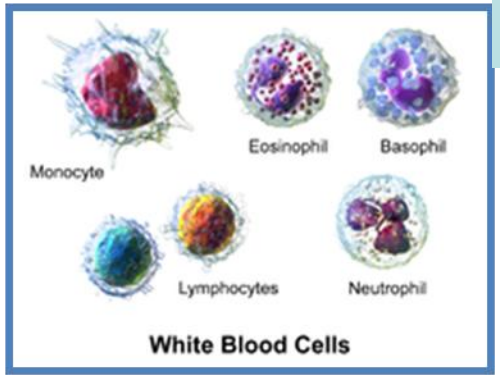
Test	Results	Units	Reference ranges
WBC= white blood cells	7000	/mm3	4.000-11.000
RBC= red blood cells	5.6	/mm3	4.5-6.5
HGB= hemoglobin	14.1	Gr/dl	13.5-17.5
PLT= platelet	255.000	/mm3	150.000-450.000



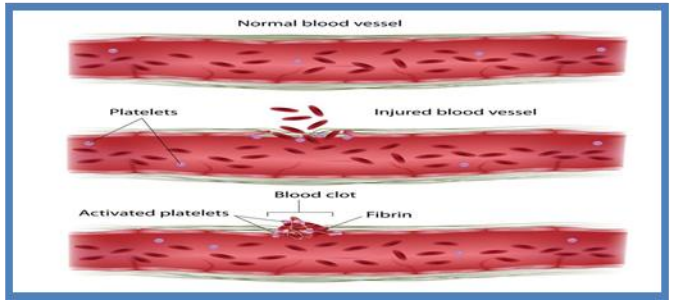




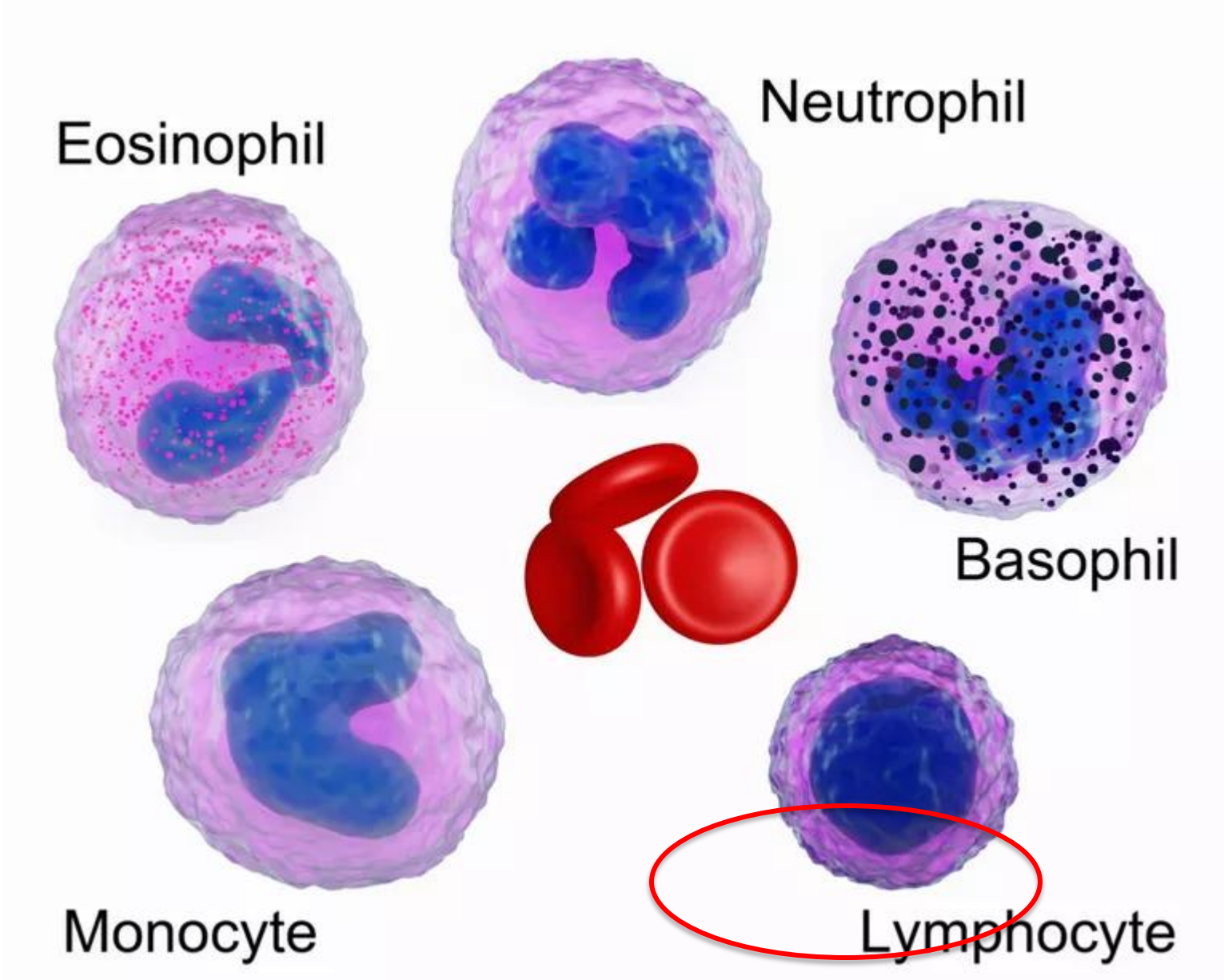
RBC

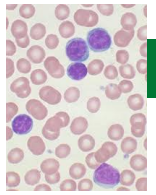


WBC



PLATELET

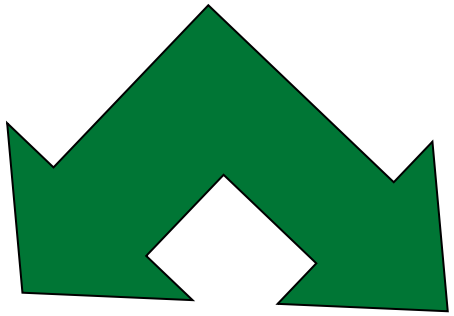

Eosinophil
Neutrophil
Basophil
Monocyte
Lymphocyte



Leukemia =

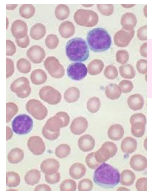
λευκός *leukos* "white" +

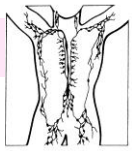
αἷμα *haima* "blood"



Acute Leukemia

Chronic Leukemia





Chronic Lymphocytic Leukemia

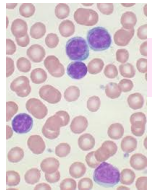
Epidemiological facts:

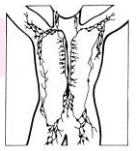
The most frequent leukemia in the western world

4/100000 new cases/ year

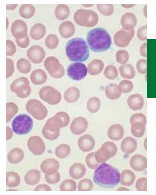
Median age at diagnosis: 72 years

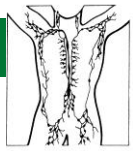
♂ < ♀



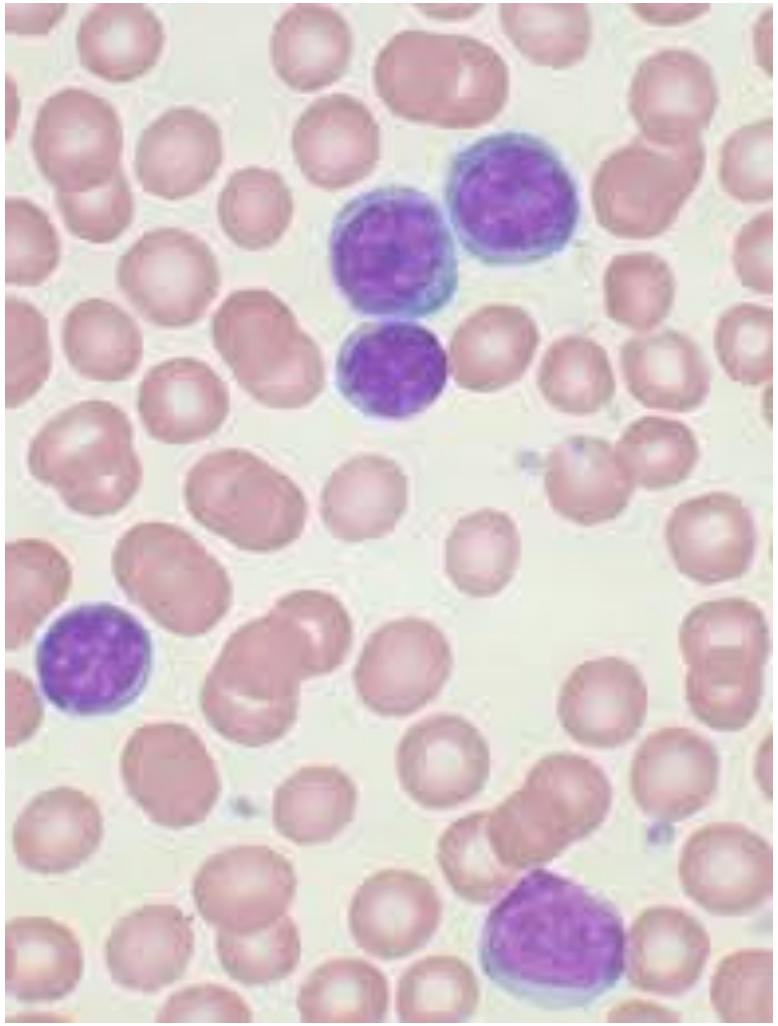


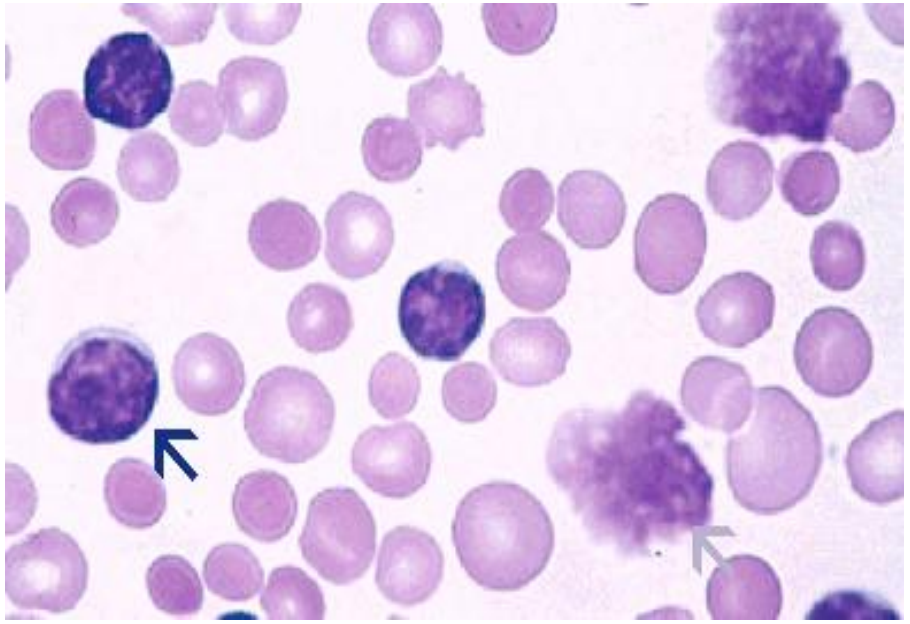
CLL- Diagnosis





Test	Results	Units	Reference ranges
WBC	30000	/mm3	4.000-11.000
RBC	5.6	/mm3	4.5-6.5
HGB	13.2	Gr/dl	13.5-17.5
HCT	45	%	40-52
MCV	90	FL	80-95
MCH	28.8	pg	27-32
MCHC	32	g/dl	31-35
PLT	155.000	/mm3	150.000-450.000
Neutro%	25	%	40-75
Lympho%	70	%	20-45
Mono%	3	%	2-10
Eos%	2	%	1-6
note	Basket cells +++		

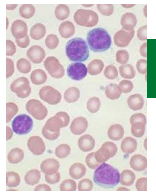


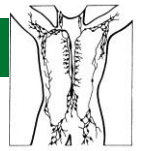


basket cells

Gumprecht cells

smudge cells





blood

2008 111: 5446-5456
Prepublished online January 23, 2008;
doi:10.1182/blood-2007-06-093906

Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute–Working Group 1996 guidelines

Michael Hallek, Bruce D. Cheson, Daniel Catovsky, Federico Caligaris-Cappio, Guillaume Dighiero, Hartmut Döhner, Peter Hillmen, Michael J. Keating, Emili Montserrat, Kanti R. Rai and Thomas J. Kipps

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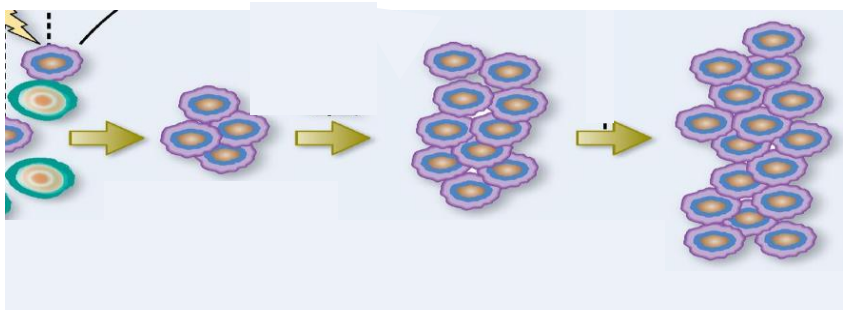
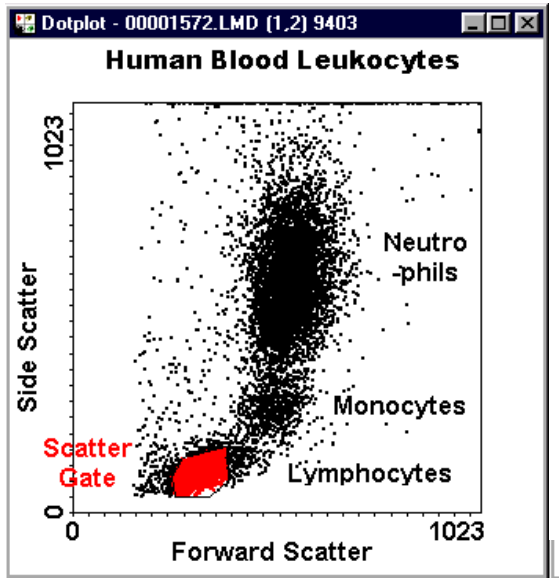
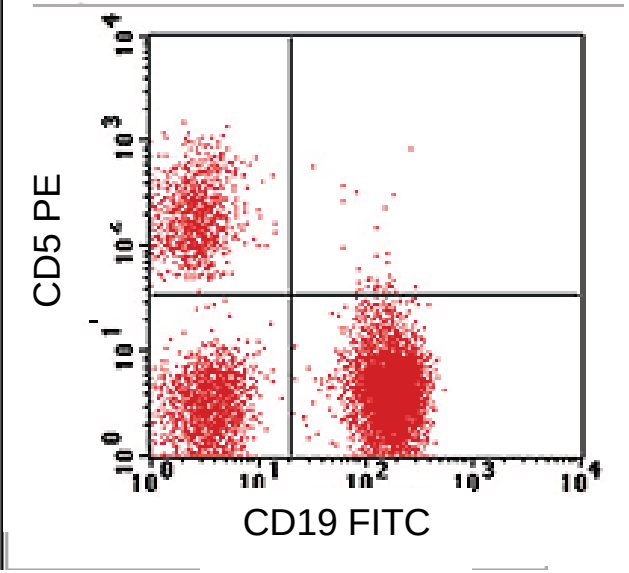
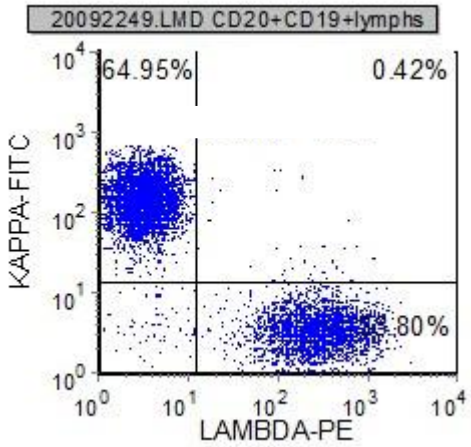
The diagnosis of CLL requires the presence of at least 5×10^9 **B-lymphocytes**/L (5000/µL) in the peripheral blood.

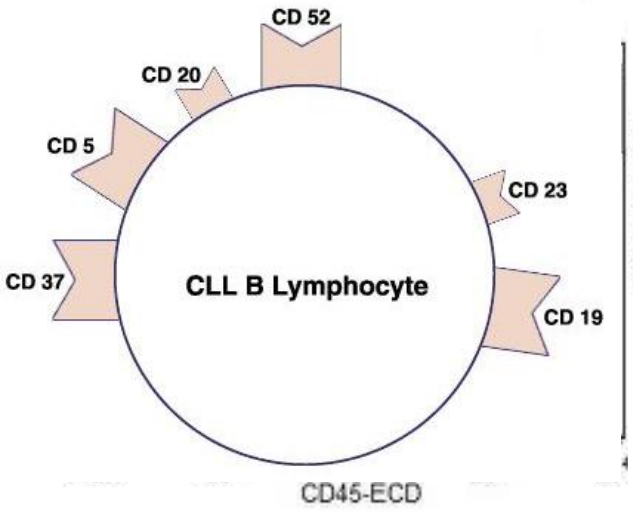
The **clonality** of the circulating B lymphocytes needs to be confirmed by **flow cytometry**

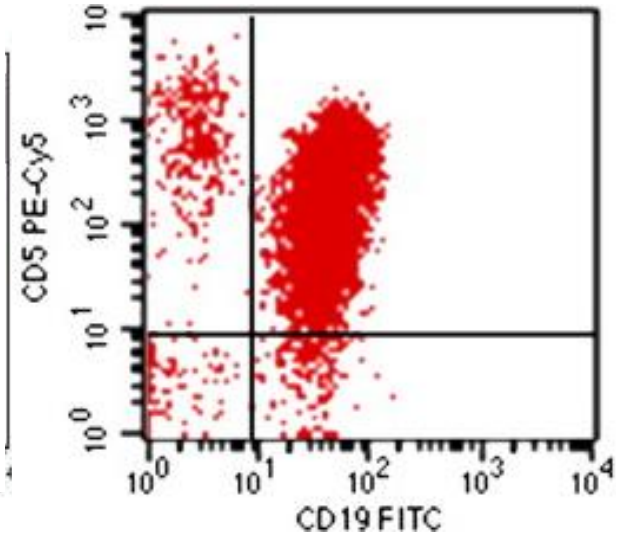


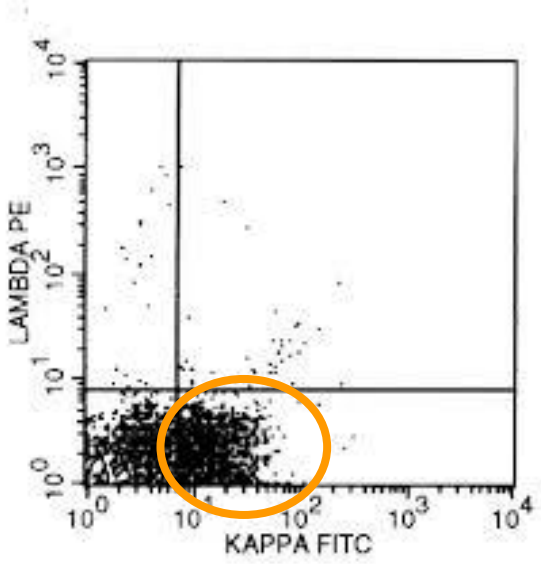

Dotplot - 00001572.LMD (1,2) 9403
Human Blood Leukocytes
Side Scatter
1023
0
Neutro
-phils
Monocytes
Scatter
Gate
Lymphocytes
0
1023
Forward Scatter

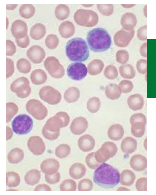

CD5 PE
CD19 FITC


20092249.LMD CD20+CD19+lymphs
64.95%
0.42%
80%
KAPPA-FITC
LAMBDA-PE


CD 52
CD 20
CD 5
CD 23
CD 37
CLL B Lymphocyte
CD 19
CD45-ECD


CD5 PE-Cy5
CD19 FITC


LAMBDA PE
KAPPA FITC



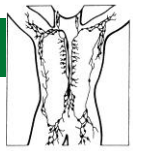
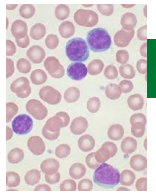


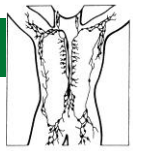
Table 2. Scoring system for diagnosis of chronic lymphocytic leukaemia (CLL)

Marker	Points	
	1	0
CD5	Positive	Negative
CD23	Positive	Negative
FMC7	Negative	Positive
Smlg	Weak	Moderate/strong
CD22/CD79b	Weak/negative	Moderate/strong

Scores in CLL range from 3 to 5 while in the other B-cell disorders they are 0-2.

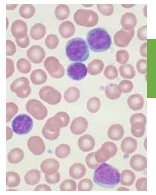
Matutes et al, 2007, Best Practice and Research Clinical Haematology, Vol 20, No. 3 p. 367-384.

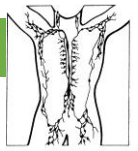




Diagnosis:

- Blood count +Blood smear
- Flowcytometry





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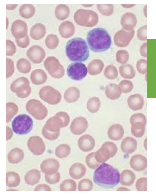
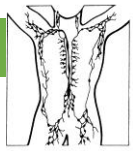
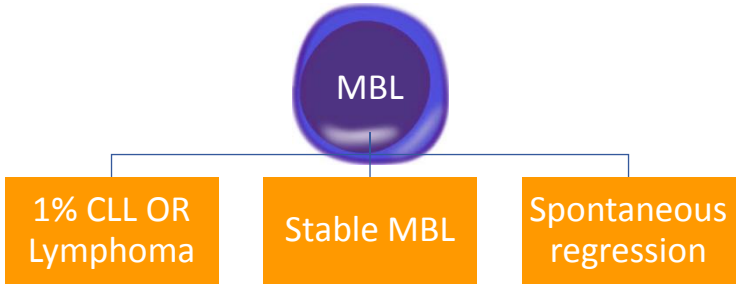
MCV	90	FL	80-95
MCH	28.8	pg	27-32
MCHC	32	g/dl	31-35
PLT	255.000	/mm3	150.000-450.000
Neutro%	27	%	40-75
Lympho%	56	%	20-45
Mono%	6	%	2-10
Eos%	1	%	1-6
Baso%	0	%	<1





MBL
Monoclonal B-cell Lymphocytosis

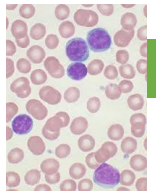


Pre- CLL = MBL

3% of the population

1% /year probability to progress

Follow up only by blood test x 1-2/year

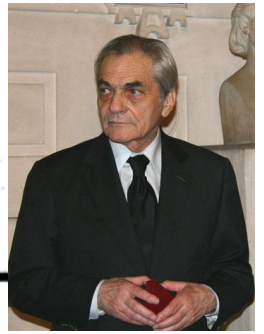


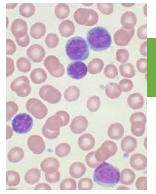
STAGING OF CLL

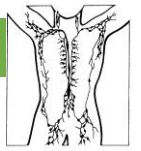
Staging of B Cell CLL and Relation to Survival

Stage	Clinical Features	Median Survival, years
RAI		
0	Lymphocytosis	12
I	Lymphocytosis + adenopathy	9
II	Lymphocytosis + splenomegaly	7
III	Anemia	1–2
IV	Thrombocytopenia	1–2
BINET		
A	No anemia/thrombocytopenia, <3 involved sites	>10
B	No anemia/thrombocytopenia, >3 involved sites	5
C	Anemia and/or thrombocytopenia	2

Kanti R. Rai, MD

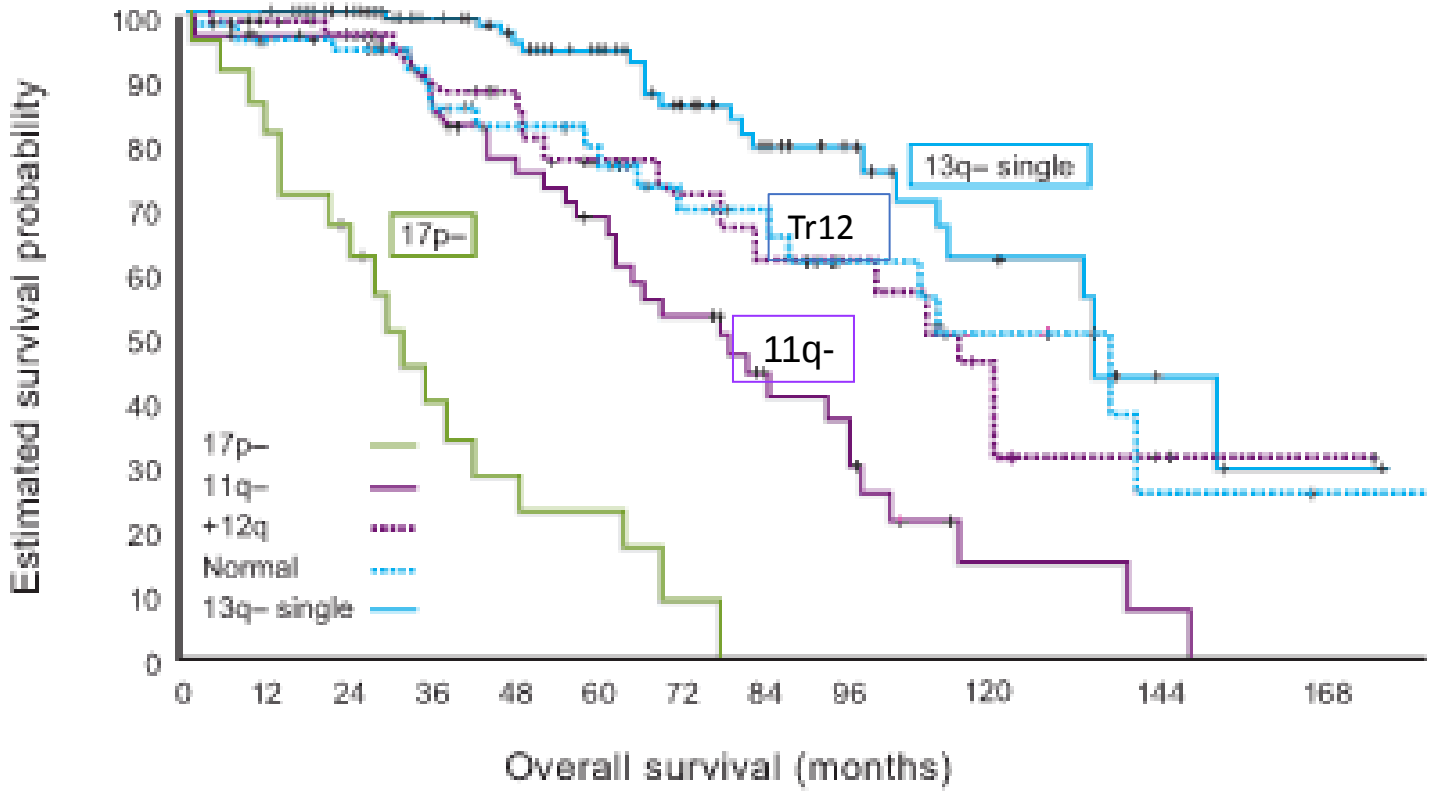




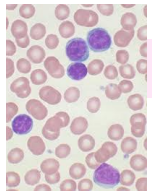


Risk stratification

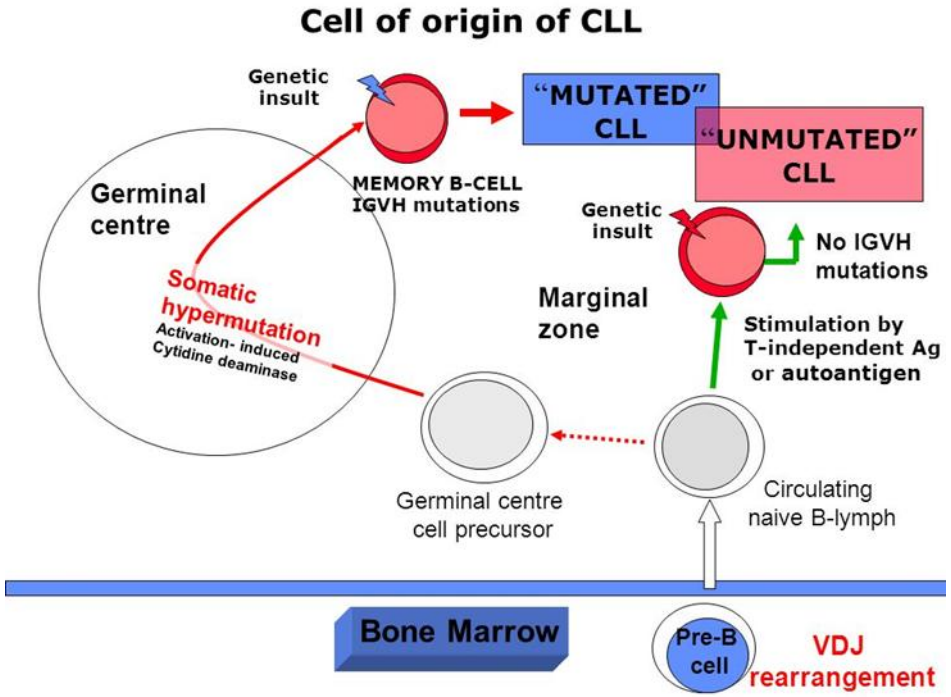
Risk stratification base on FISH analysis



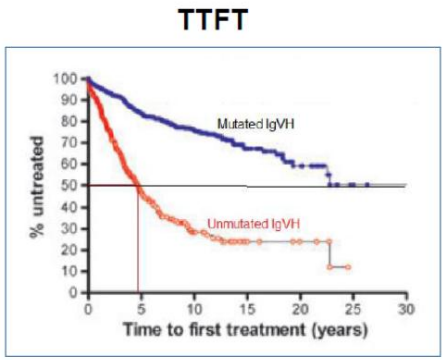
		%	Overall survival
FISH	Deletion 17p	10–7	2-3
	11q Deletion	20	6-8
	Trisomy 12	15	9-11
	Deletion 13q	55	17



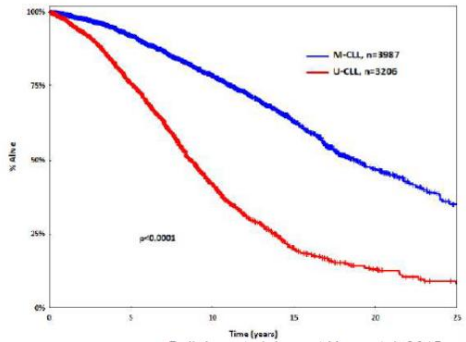
Risk stratification base on mutational status



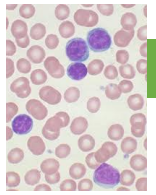
IGHV mutational status in CLL : prognostic value

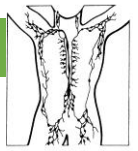


Pepper, BJH, 2011

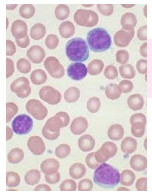


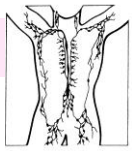
Baliakas et al. Lancet Haematol. 2015





Patients with CLL may have a heterogenous behavior which is mainly related to the biological background and genetic changes that were acquired by the leukemic cells

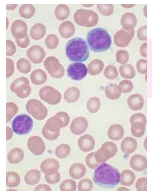


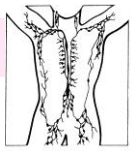


CLL International Prognostic Index (2016)

	Adverse Factor	Grade
Age	>65 years	1
Clinical Stage	Rai I-IV or Binet B-C	1
β_2-microglobulin level	>3.5 mg/L	2
IGHV mutation status	Unmutated (>98% homology with germline)	2
Del(17p) and/or *TP53* mutation	Present	4

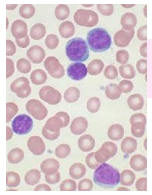
Risk	Score	5-year Overall Survival ($p<0.001$ for all)
Low	0-1	93%
Intermediate	2-3	79%
High	4-6	63%
Very High	7-10	23%

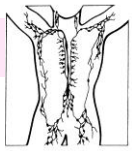




Treatment :

Why not to treat every CLL patient?

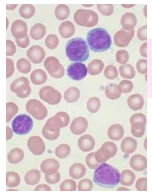


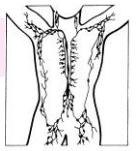


1/3 will never required therapy

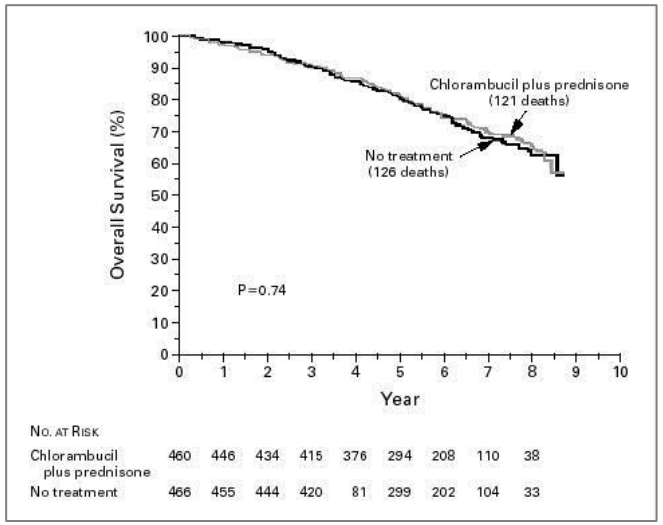
1/3 will required therapy during follow-up

1/3 will required therapy shortly after diagnosis





Dighiero G et al. N Engl J Med 1998



CLL1 HR-Fludarabin (1997-2004)

CLL1 Trial Of The German CLL Study Group (GCLLSG)

Fludarabine or No therapy

No significant difference between both groups in OS was assessed (p= 0.47).

Early Versus Deferred Treatment With Combined Fludarabine, Cyclophosphamide and Rituximab (FCR) Improves Event-Free Survival In Patients With High-Risk Binet Stage A Chronic Lymphocytic Leukemia

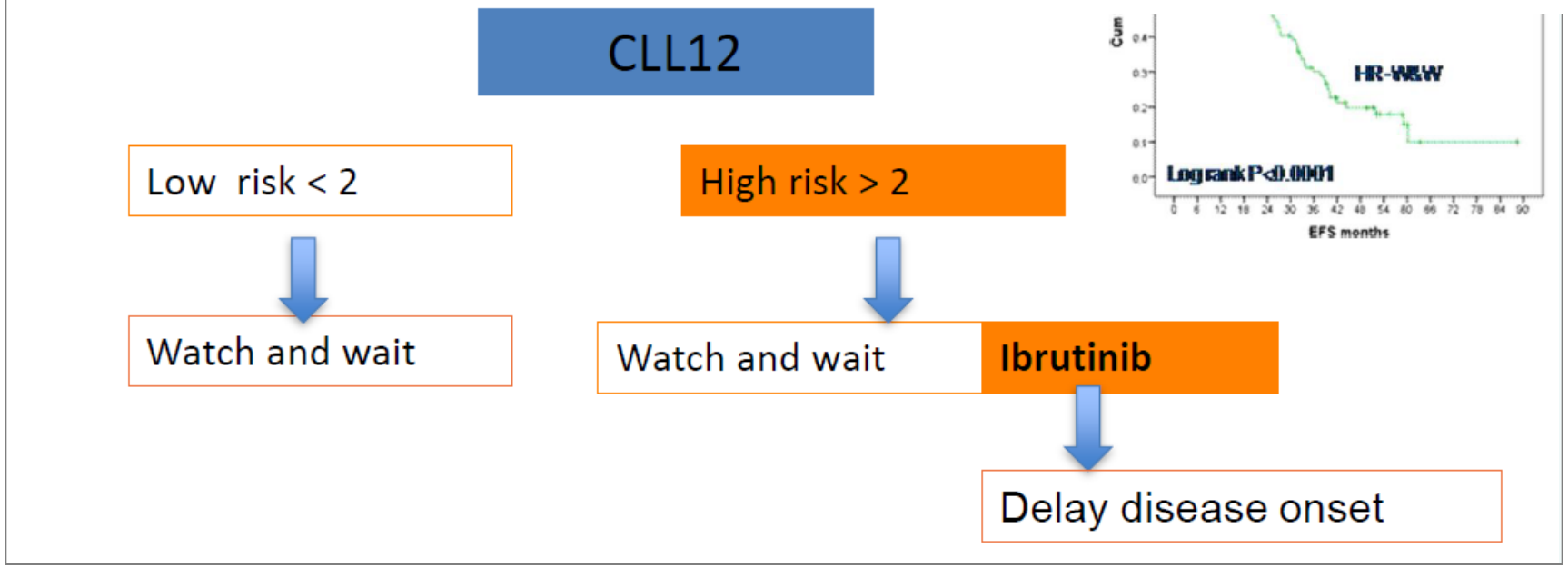
First Results Of a Randomized German-French Cooperative Phase III Trial- CLL7

High risk > 2
200 pts (25.1%)

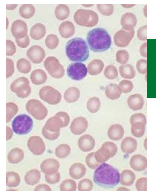
Watch and wait	FCR X 6
101 pts	100 pts (82)

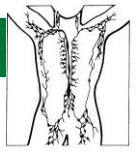
12/2013

- At median follow-up of 49 months, **no benefit in OS.**



Estimated Enrollment:	540
Study Start Date:	April 2014
Estimated Study Completion Date:	April 2022



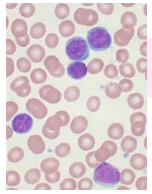


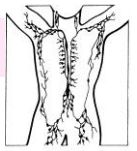
Asymptomatic patients

Binet stage A

Rai stage 0-1

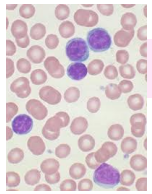
No treatment= follow up by an expert hematologist

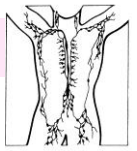




Treatment :

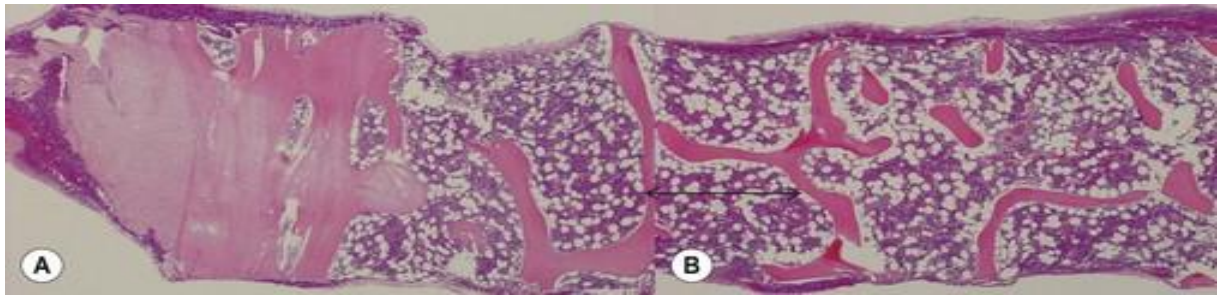
When to start therapy ?

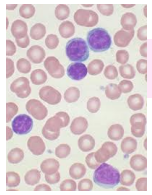


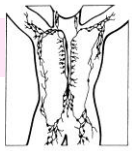


When to treat?

✓=Anemia or thrombocytopenia-progressive BM “insufficiency”

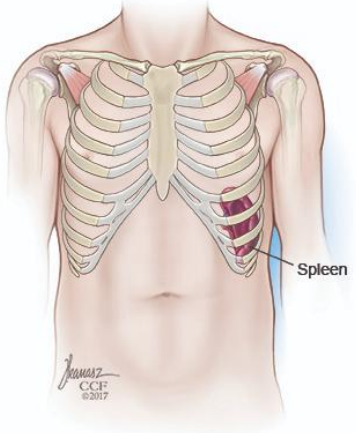


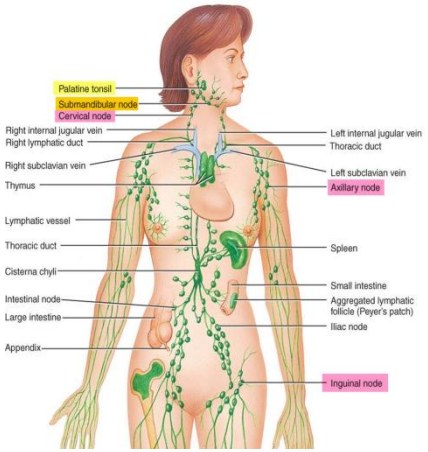


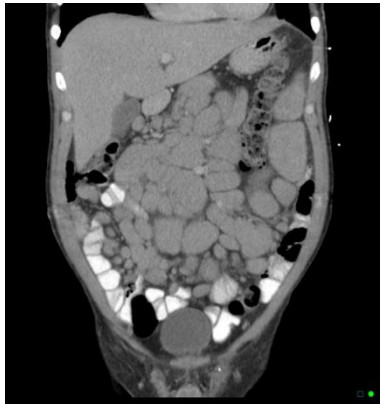


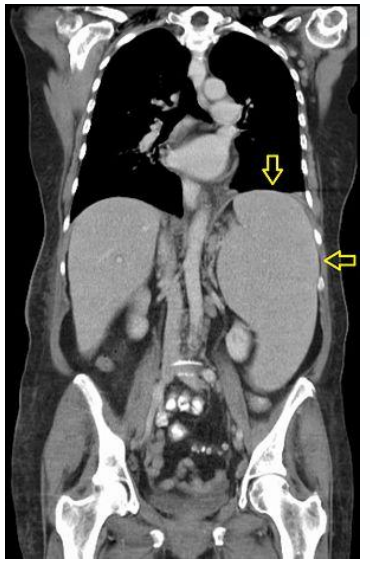
When to treat?

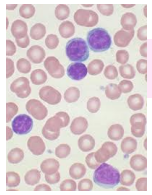
- ✓=Anemia or thrombocytopenia-progressive BM “insufficiency”
- ✓Massive-bulky splenomegaly = 6 cm below the lower costal margin
- ✓Bulky lymphadenopathy or progressive symptomatic lymphadenopathy>10 cm

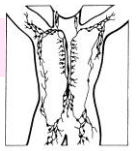










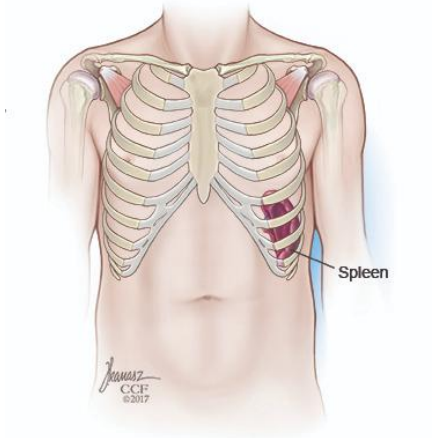


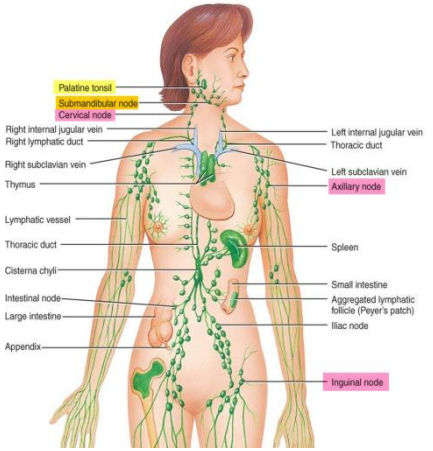
When to treat?

- ✓=Anemia or thrombocytopenia-progressive BM “insufficiency”
- ✓Massive-bulky splenomegaly = 6 cm below the lower costal margin
- ✓Bulky lymphadenopathy or progressive symptomatic lymphadenopathy>10 cm
- ✓Rapid progressive lymphocytosis:

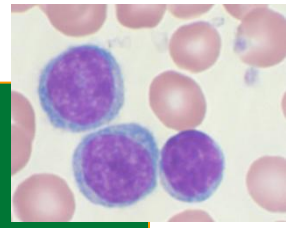
  Increase > 50% in 2 months

  > 100 % in 6 months
- ✓Autoimmune anemia or thrombocytopenia refractory to steroids





Other considerations before we start therapy?



Who is the patient in front of us ?

- Age
- medical history
- medications
- support system

Table 1. The CIRS score

CIRS: Please insert the appropriate grade of illness/impairment

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

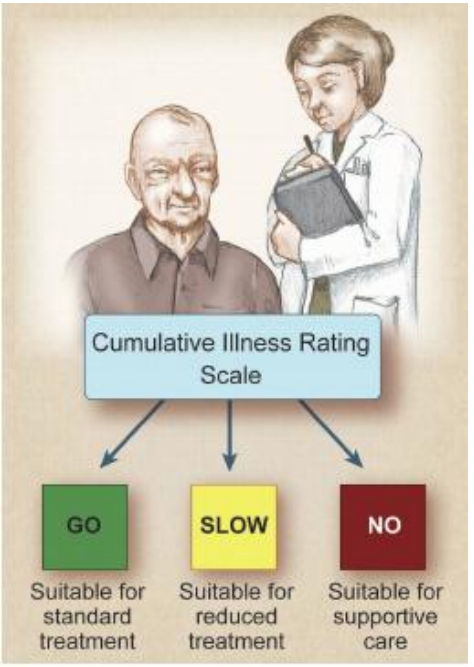
CAT = category; CIRS = Cumulative Illness Rating Scale; NUM = number; SCO = score; TOT = total

CIRS-TOT$_{sco}$

Table 2. Severity rating in the CIRS scoring system

0	No problem affecting that system
1	Current mild problem, does not interfere with normal activity, or past significant problem
2	Interferes with normal activity and/or requires first-line therapy
3	Severe problem and/or constant and significant disability and/or hard-to-control chronic problem
4	Extremely severe problem and/or treatment is urgent and/or severe functional impairment or organ failure

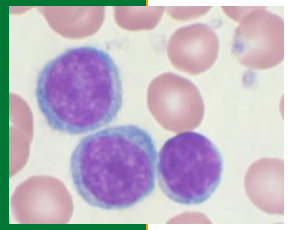
CIRS = Cumulative Illness Rating Scale



Gribben, J. G. Blood 2009;114:3359-3360

Cumulative illness rating scale

Choosing the best treatment



Cumulative illness Rating Scale

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CIRS = Cumulative Illness Rating Scale

CIRS-TOT$_{sco}$

Who is the patient in front of us ?

Age, medical history, medications, support system

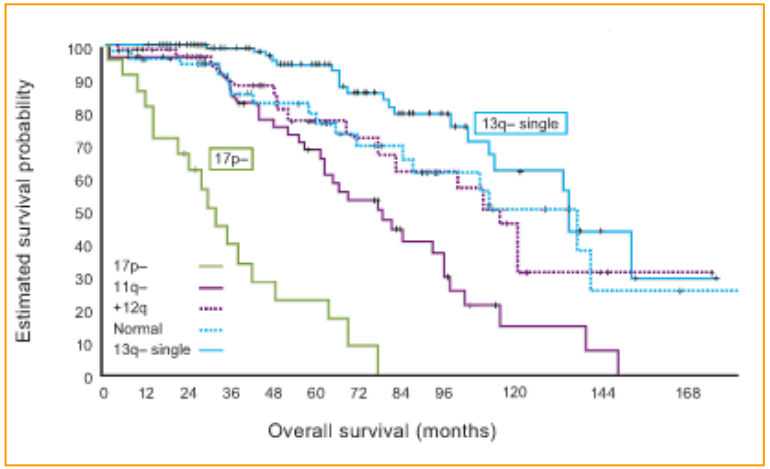
+

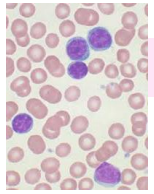
The biology /genetics of his CLL

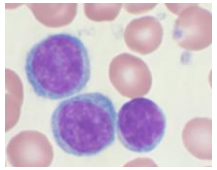
+

What are the available drugs

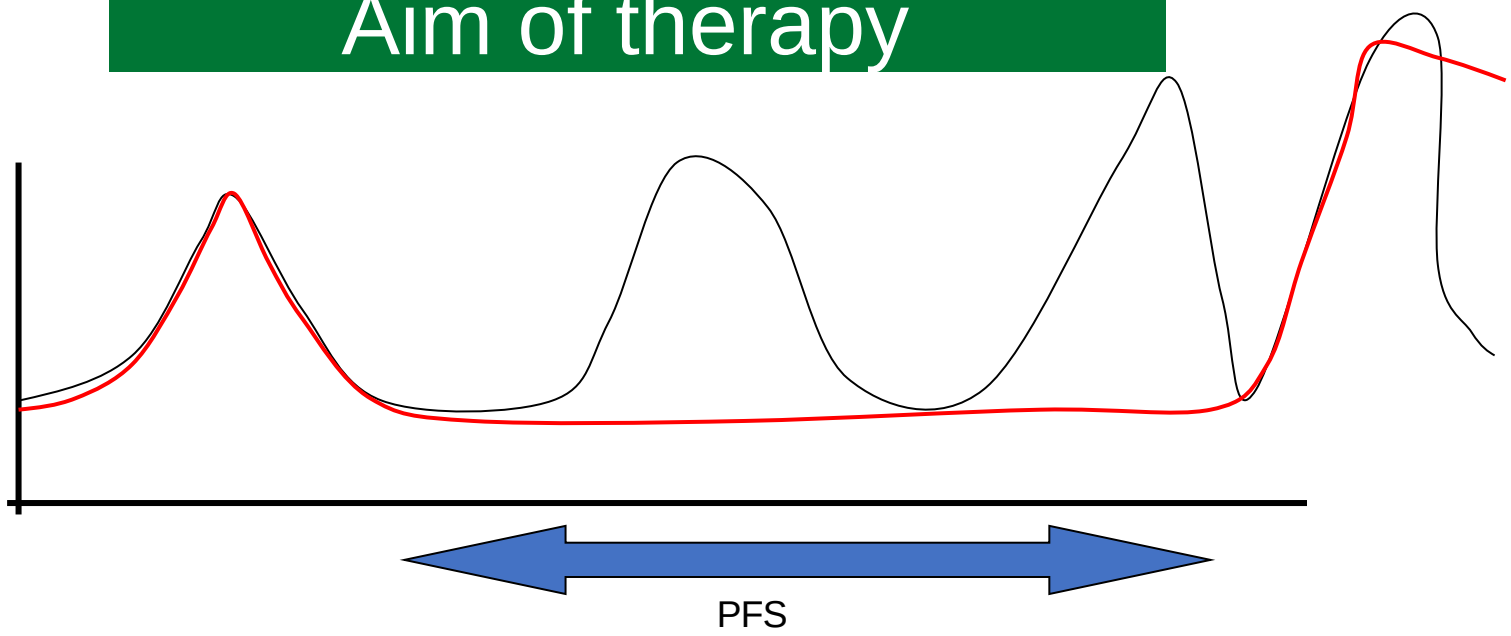
Fit Go Go	Less Fit Slow Go	Unfit No Go

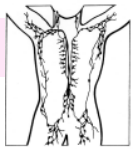


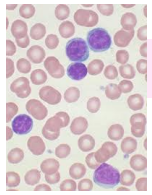


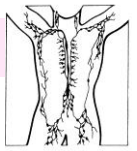


Aim of therapy









Aim of therapy

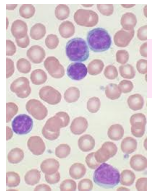
PFS-Progression Free Survival

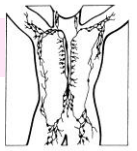
CR complete remission

OS- Overall Survival

Improve quality of life

Achieving MRD= minimal residual disease negative





CLL- Treatment evolution

Chlorambucil+/- (leukeran) prednisone

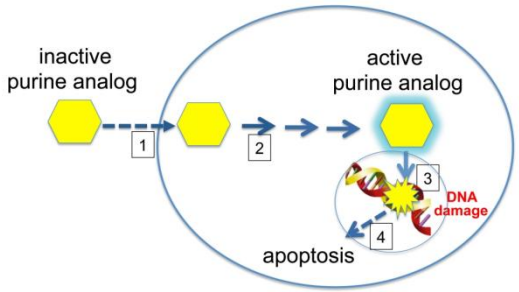
CHOP

CVP

1980-1995

Fludarabine

1996

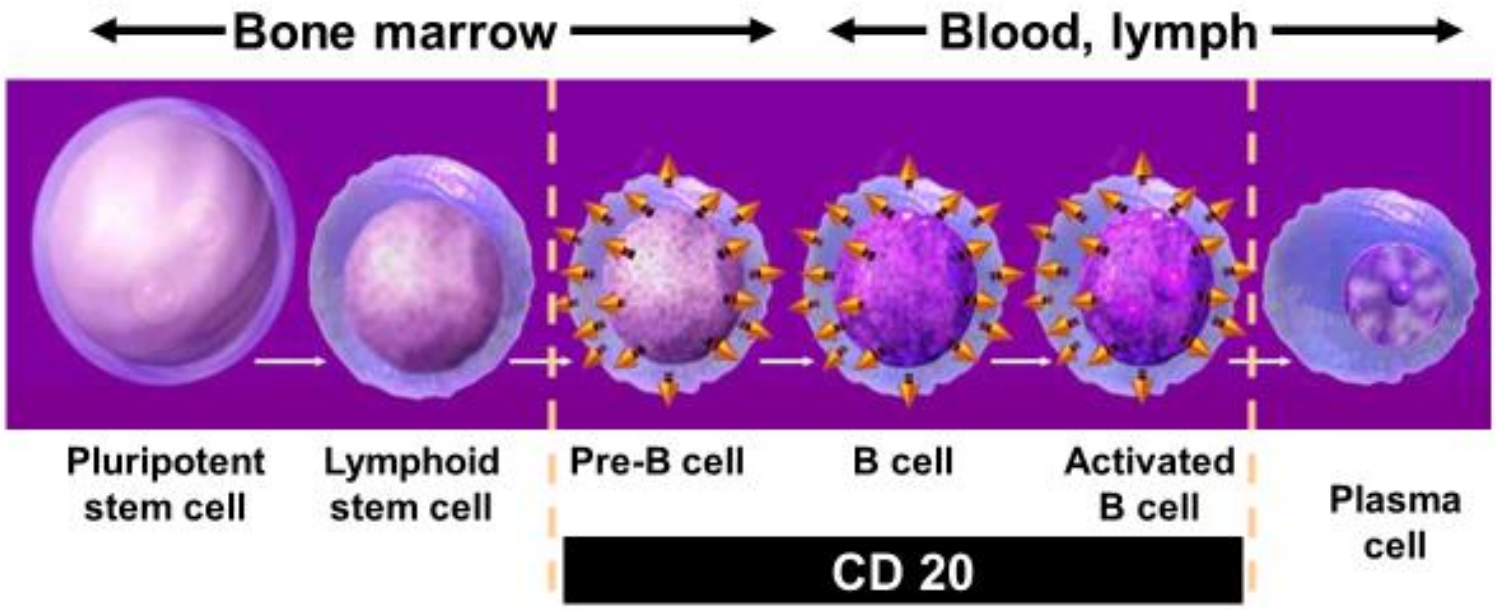


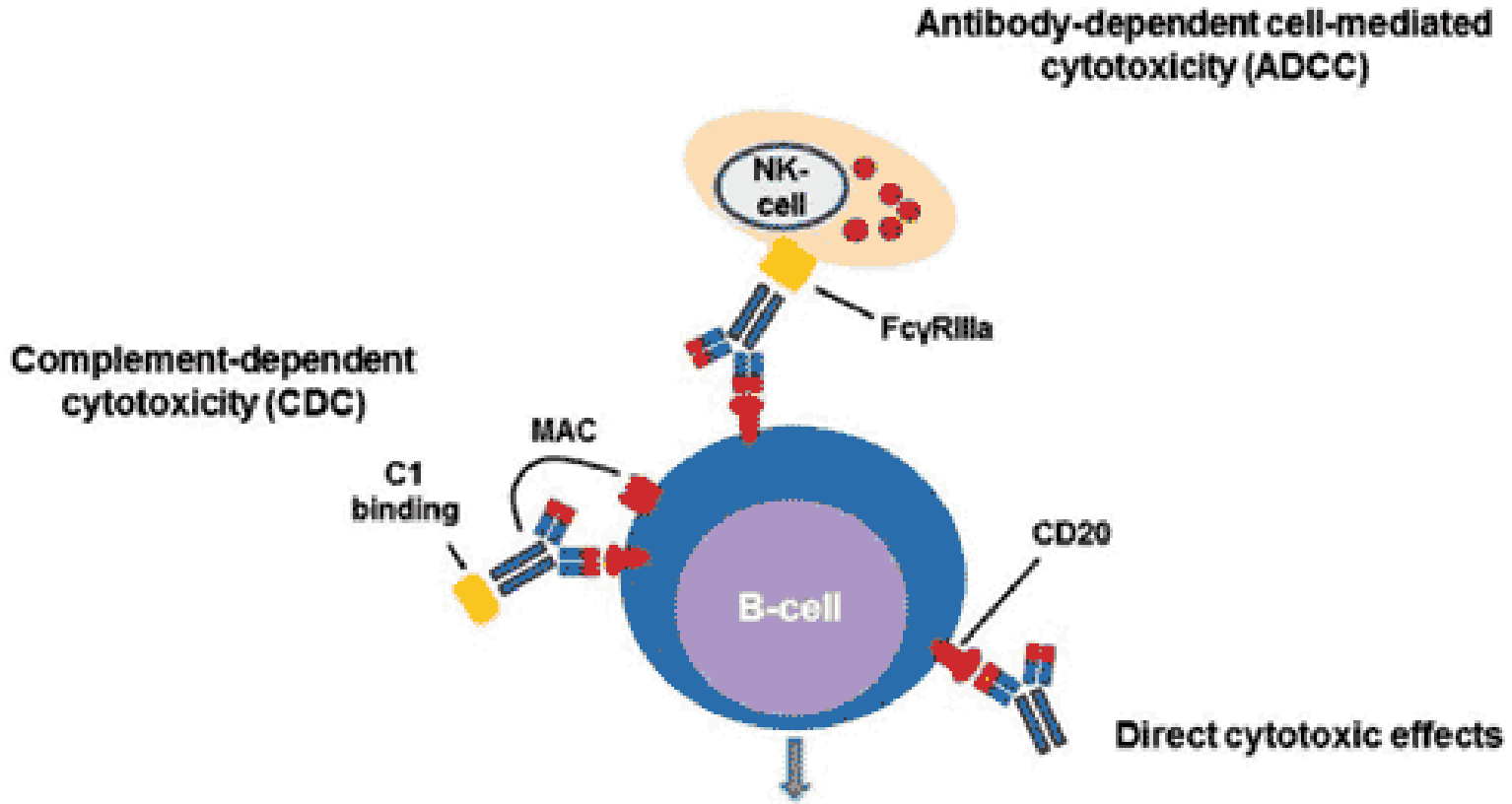
Fludarabine

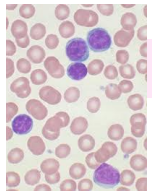
Cyclophosphamide

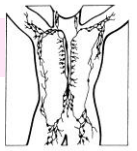
2001

CD20 Expression in B-Cell Development




Antibody-dependent cell-mediated cytotoxicity (ADCC)
NK-cell
FcγRIIIa
Complement-dependent cytotoxicity (CDC)
MAC
C1 binding
CD20
B-cell
Direct cytotoxic effects



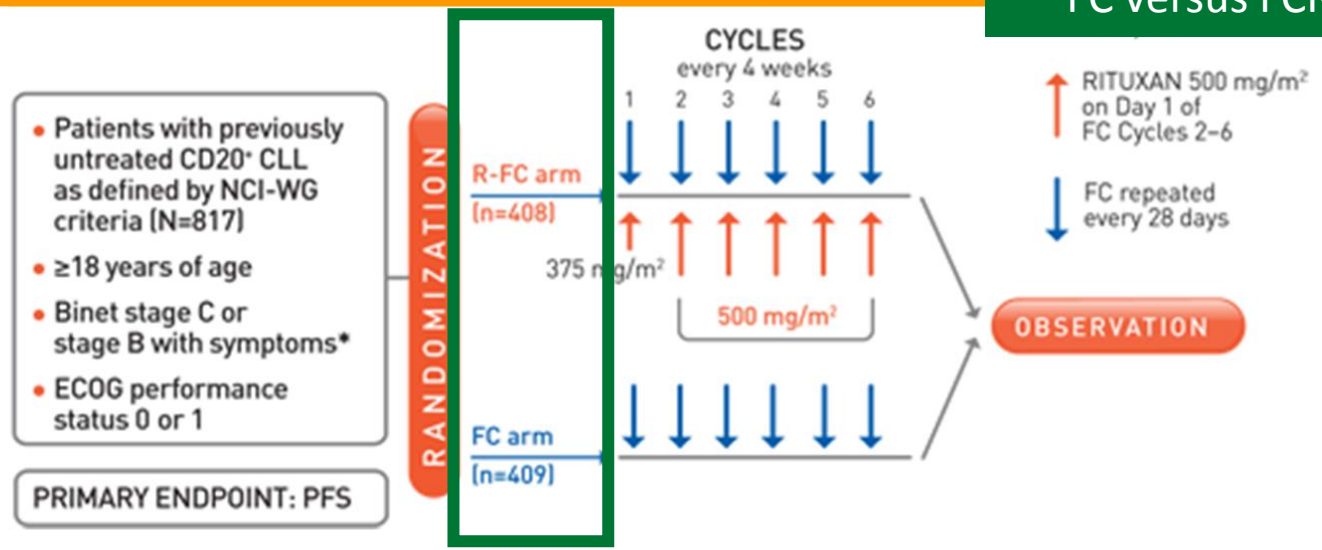


Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial.

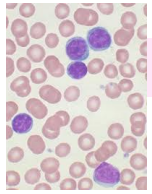
CLL8

CLL8

FC versus FCR



Lancet. 2010 Oct 2;376(9747):1164-74.



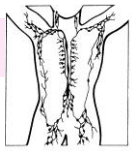
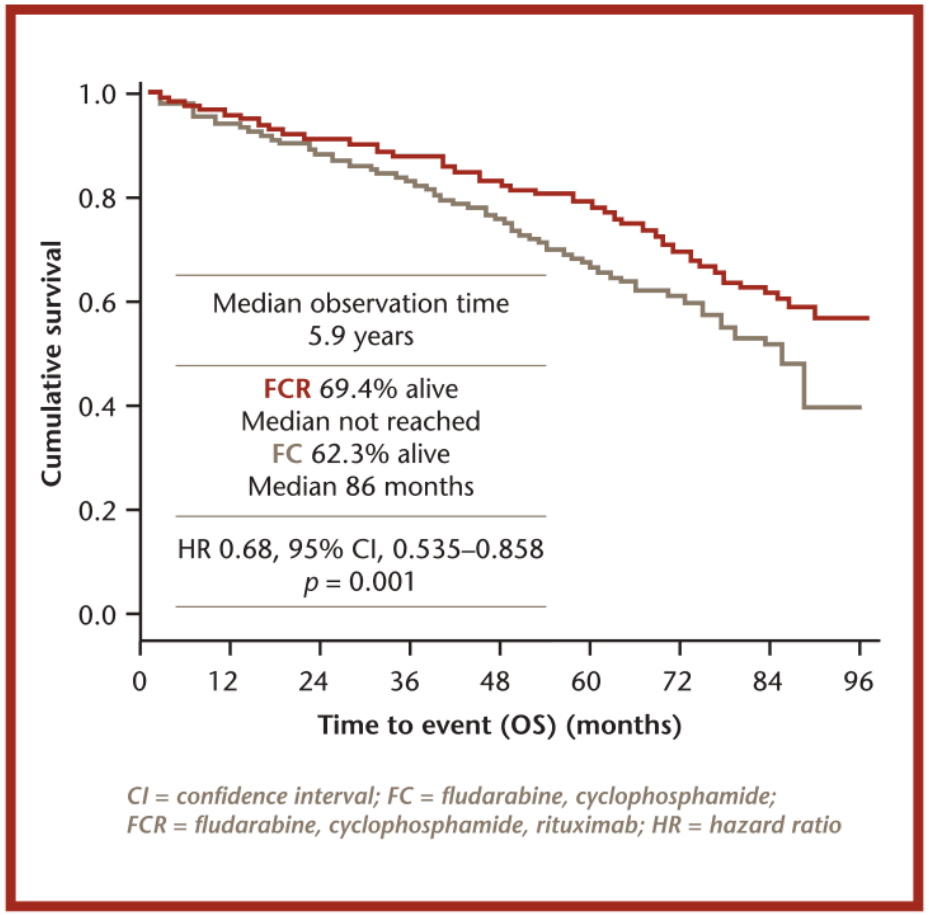
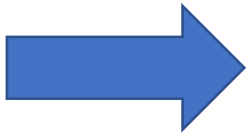
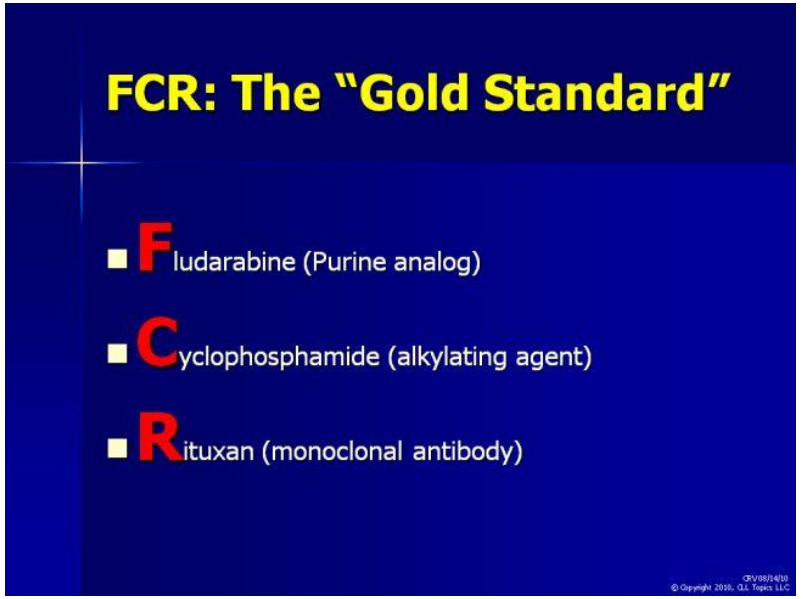


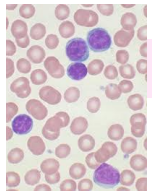
Figure 3. Overall survival

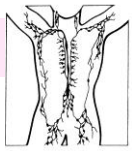


CI = confidence interval; FC = fludarabine, cyclophosphamide; FCR = fludarabine, cyclophosphamide, rituximab; HR = hazard ratio

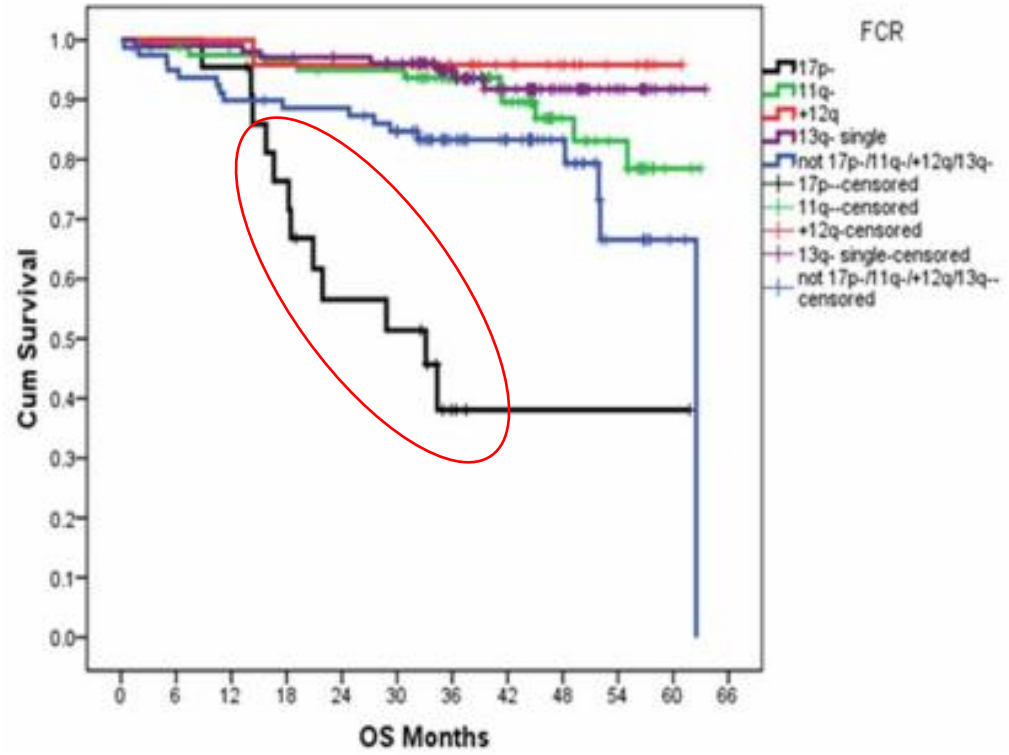


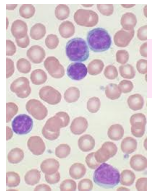


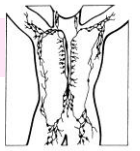




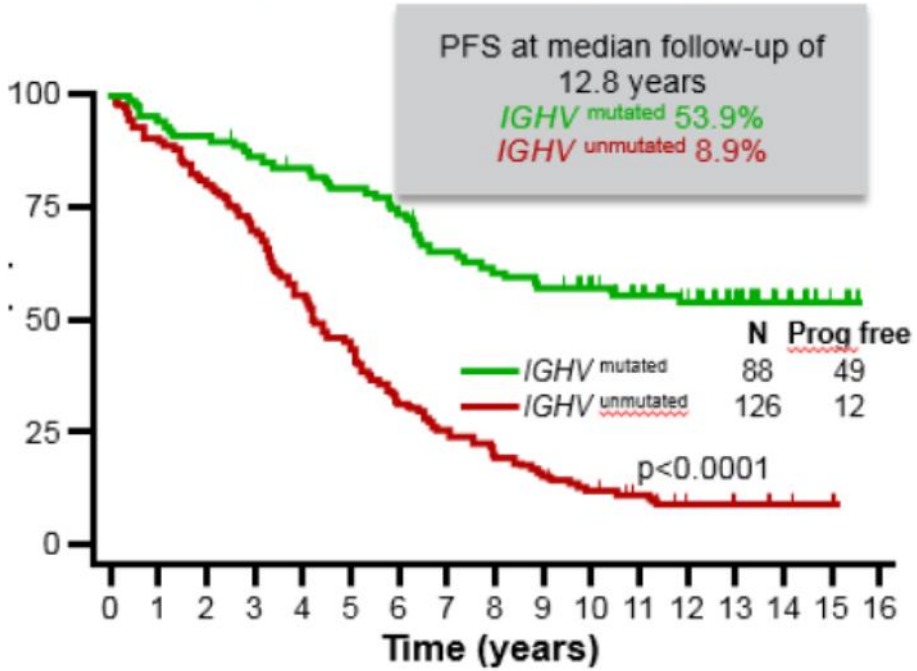
OS for genetic subgroups according to the hierarchical model
FCR







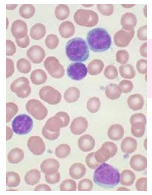
MDACC study of first-line FCR in young, fit patients with CLL (N=300)[2]

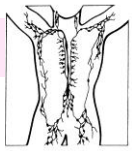


Thompson PA, *et al. Blood* 2016; 127:303–309.

We need to choose who will gain from being treated by FCR regimen:

Mutated IGHV
No 17 p del





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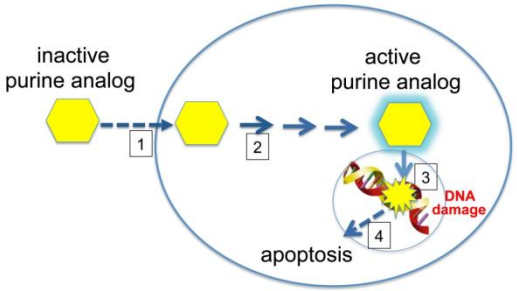


Fludarabine

Cyclophosphamide

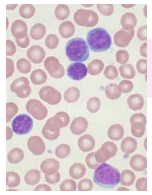
2001

Fludarabine

Cyclophosphamide

Rituximab=FCR

2008-2010



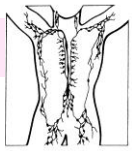


Table 8. Phase II and III studies in first-line CLL*[17,26,34–42]

Treatment regimen	OR (%)	CR (%)	Remission duration
Chlorambucil	40–70	<10	~1 year
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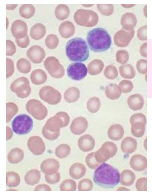
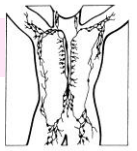
Fludarabine-cyclophosphamide (FC)	75–95	25–40	3–4 years
Fludarabine-cyclophosphamide-rituximab (FCR)	95.1	44.1	~6–7 years

**These regimens have not been compared in head-to-head clinical trials.*
CR = complete response; OR = overall response





CLL- Treatment evolution

Chlorambucil+/- (leukeran) prednisone

CHOP

CVP

Fludarabine-**F**

Fludarabine

Cyclophosphamide= **FC**

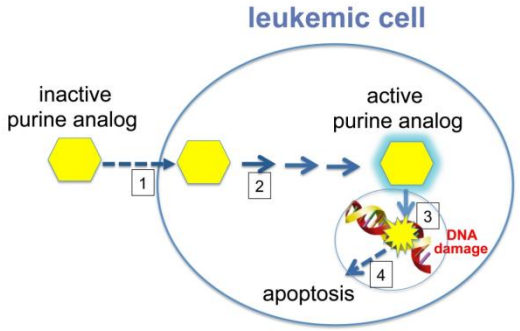
Fludarabine

Cyclophosphamide

Rituximab=FCR

Bendamustine

Rituximab= **BR**



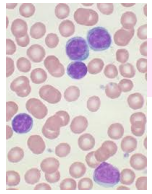
1980-1995

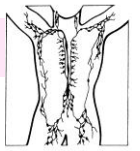
1996

2001

2008-2010

2013-2016





CLL10: Final Analysis of a Phase III Trial of FCR versus BR in Advanced CLL

Eligibility (n = 564)

- Untreated, active
- CLL without del(17p)
- Good physical fitness
- (CIRS ≥6, creatinine clearance ≥70 mL/min)

R

FCR (n = 284)
Fludarabine 25 mg/m² IV days 1-3
Cyclophosphamide 250 mg/m² IV days 1-3
Rituximab 375 mg/m² IV day 0, cycle 1
Rituximab 500 mg/m² IV day 1, cycles 2-6

BR (n = 280)
Bendamustine 90 mg/m² IV days 1-2
Rituximab 375 mg/m² day 0, cycle 1
Rituximab 500 mg/m² IV day 1, cycles 2-6

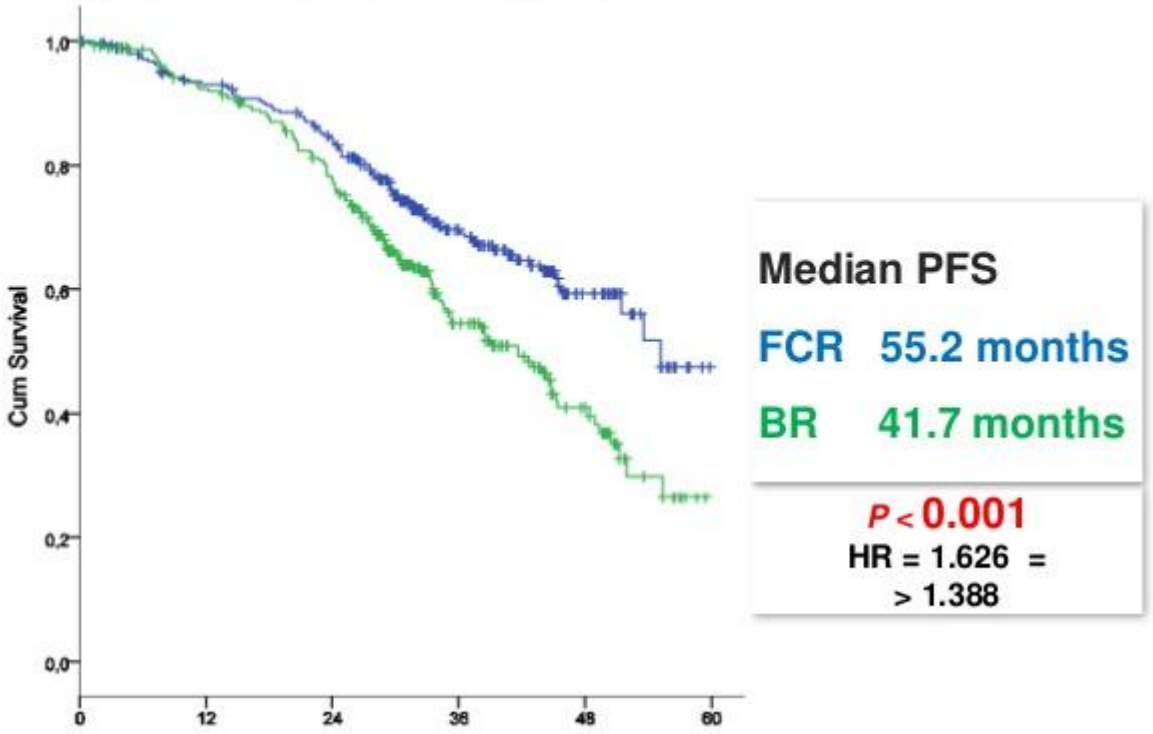
CIRS = Cumulative Illness Rating Scale

Primary endpoint: Noninferiority of BR vs FCR for PFS (hazard ratio BR/FCR < 1.388)

CLL10 STUDY: FCR VS BR IN FRONT-LINE

DEUTSCHE STUDIENGRUPPE

ITT Progression-free survival = Primary endpoint



Median PFS

FCR 55.2 months

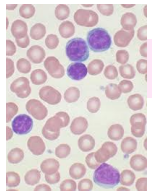
BR 41.7 months

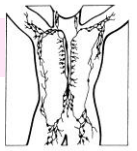
$P < 0.001$

HR = 1.626 = > 1.388

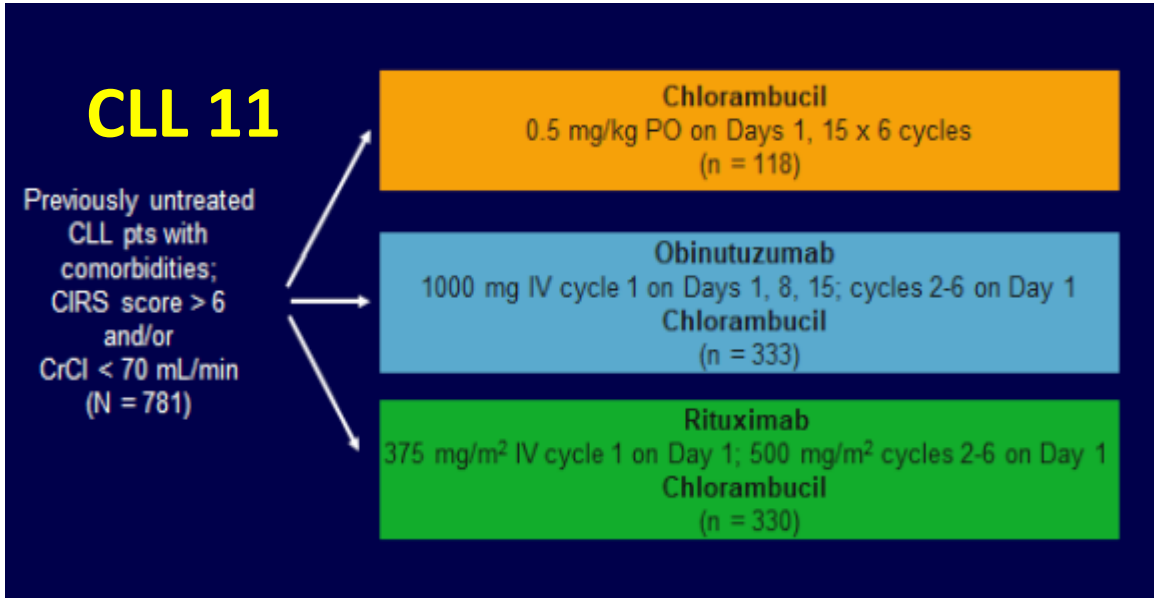
Advantage in PFS <65 years old= FCR

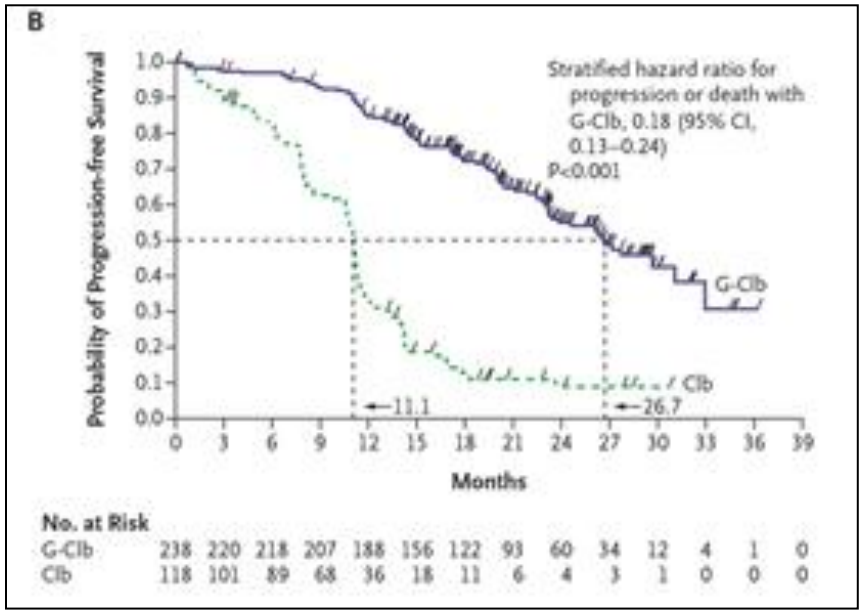
Higher toxicity >65 years old= BR



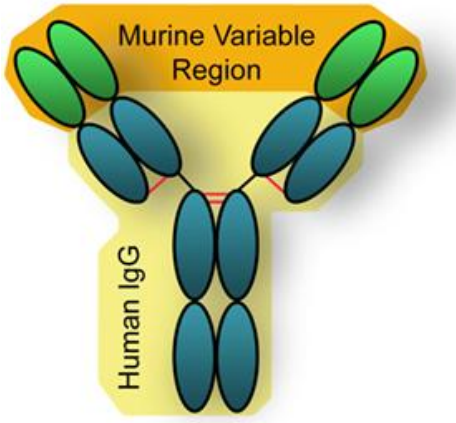


chemo-immunotherapy x Less-FIT patients





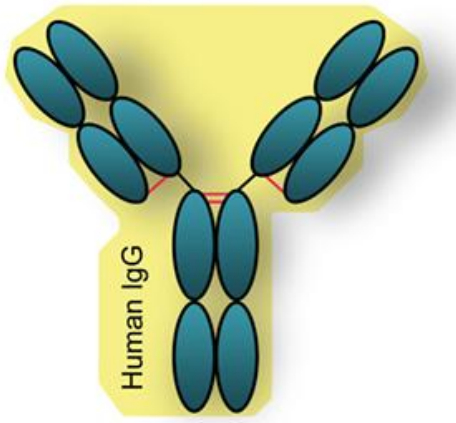
Rituximab



Type I

Direct Killing	+
CDC	+++
ADCC	++
ADP	++

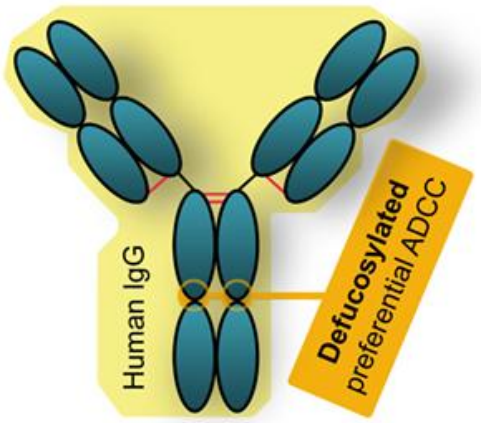
Ofatumumab



Type I

Direct Killing	+
CDC	++++
ADCC	++
ADP	++

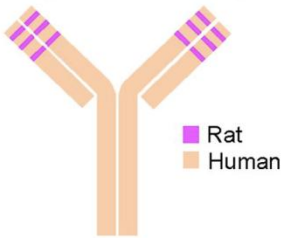
Obinutuzumab



Type II

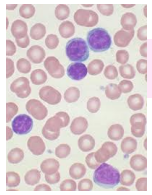
Direct Killing	+++
CDC	+
ADCC	+++
ADP	+++

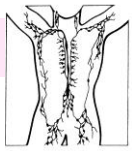
CAMPATH-1H
(Alemtuzumab)



- IgG1:κ mAb
- Anti-CD52
- Lysis of CD52^{+} cells via complement activation, ADCC, and apoptosis

X 17P DEL patients





Chemotherapy + monoclonal antibody anti CD20

= Chemoimmunotherapy

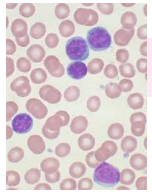
GOLD STANDART treatment x Symptomatic CLL patients

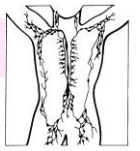
Mabthera= Rituximab		Chlorambucil
Gazyva = Obinutuzumab.	+	Bendamustine
Arzerra= Ofatumumab		Fludarabine + cyclophosphamide

Lunch

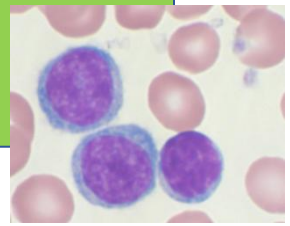
Med appetit

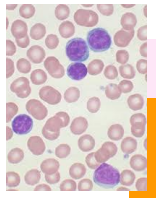
https://kahoot.it/

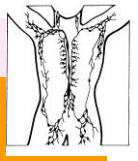




Novel treatments for CLL
Best combination
and future prospective







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CVP
CHOP

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2001 Fludarabine Cytoxan

2008-2010 Fludarabine Cytoxan Rituximab

2013 Bendamustine

2014-2019
Obinutuzumab (Ofatumumab)
Ibrutinib/ (Acalabrutinib)
Venetoclax

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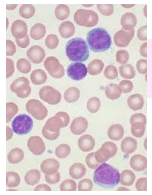
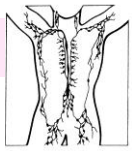
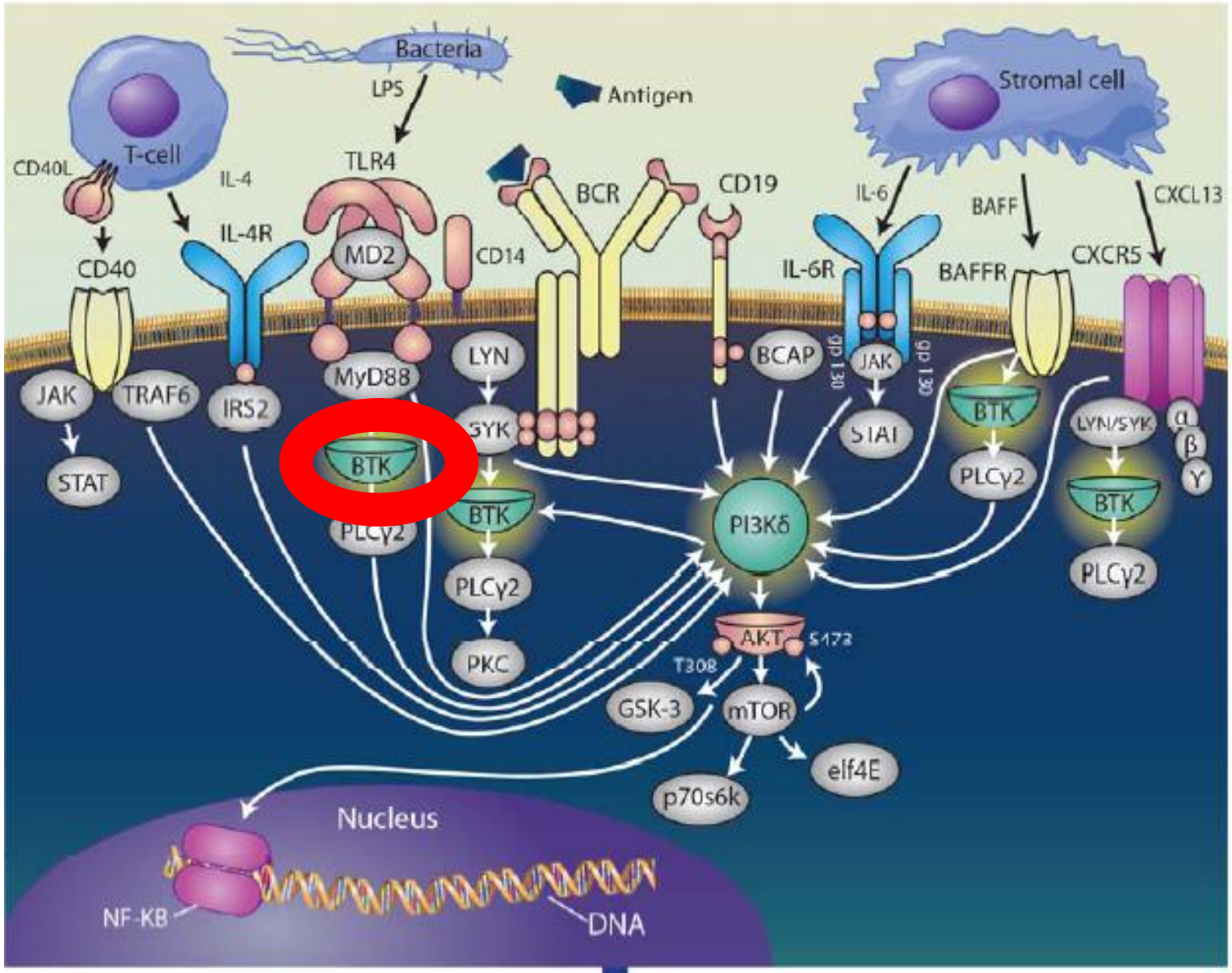


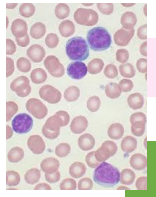


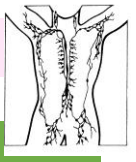
Novel agents :

Biological agents ≠ chemotherapy

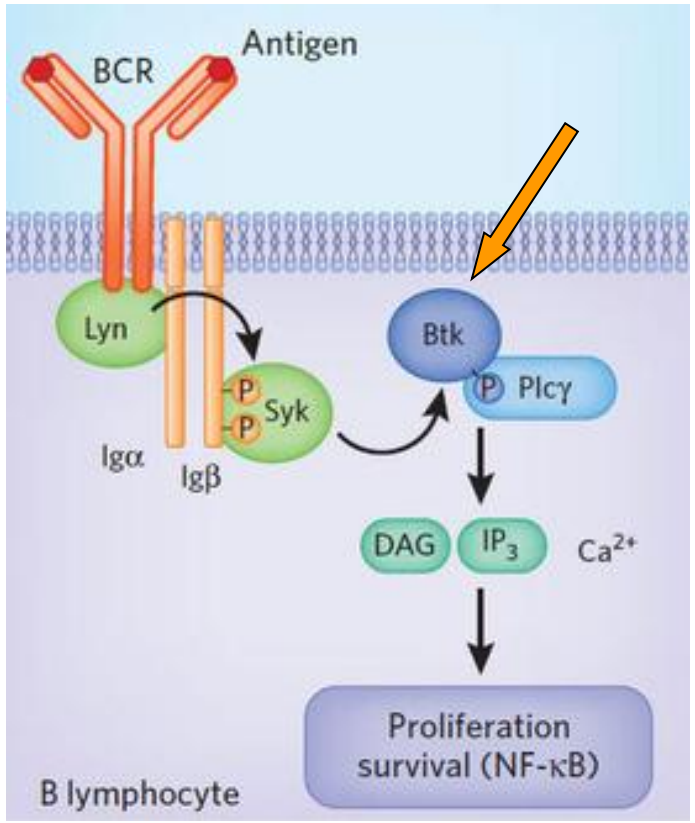
- Selective – act against specific cell
- Activate the immune system to recognize “leukemia cells” as stranger and attack them
- Less long standing side effects
- less immunesuppressive

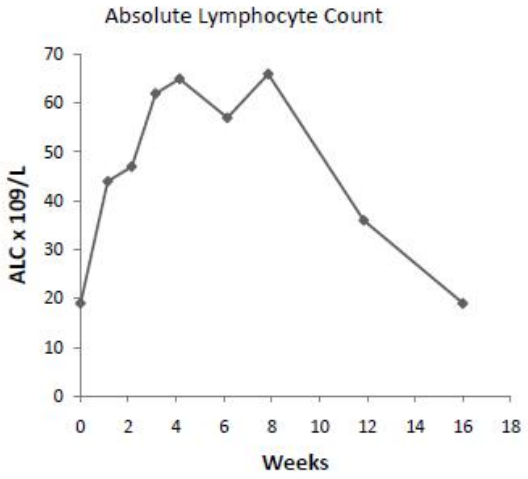

Bacteria
LPS
Antigen
Stromal cell
T-cell
CD40L
IL-4
TLR4
BCR
CD19
IL-6
BAFF
CXCL13
IL-4R
MD2
CD14
IL-6R
BAFFR
CXCR5
CD40
LYN
BCAP
gp130
JAK
gp130
JAK
TRAF6
IRS2
MyD88
SYK
STAT1
BTK
BTK
BTK
LYN/SYK
α
β
γ
PLCγ2
PLCγ2
PLCγ2
PI3Kδ
AKT
S473
T308
PKC
GSK-3
mTOR
elf4E
p70s6k
Nucleus
NF-KB
DNA
Survival, migration, activation, and expansion of B cells

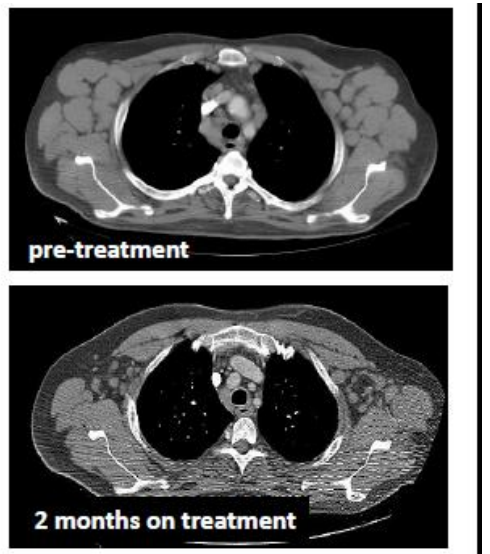


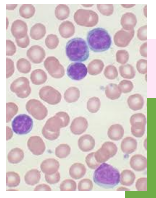


IBRUTINIB

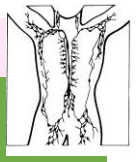

Antigen
BCR
Lyn
Syk
P
P
Igα
Igβ
Btk
P
Plcγ
DAG
IP3
Ca2+
Proliferation
survival (NF-κB)
B lymphocyte

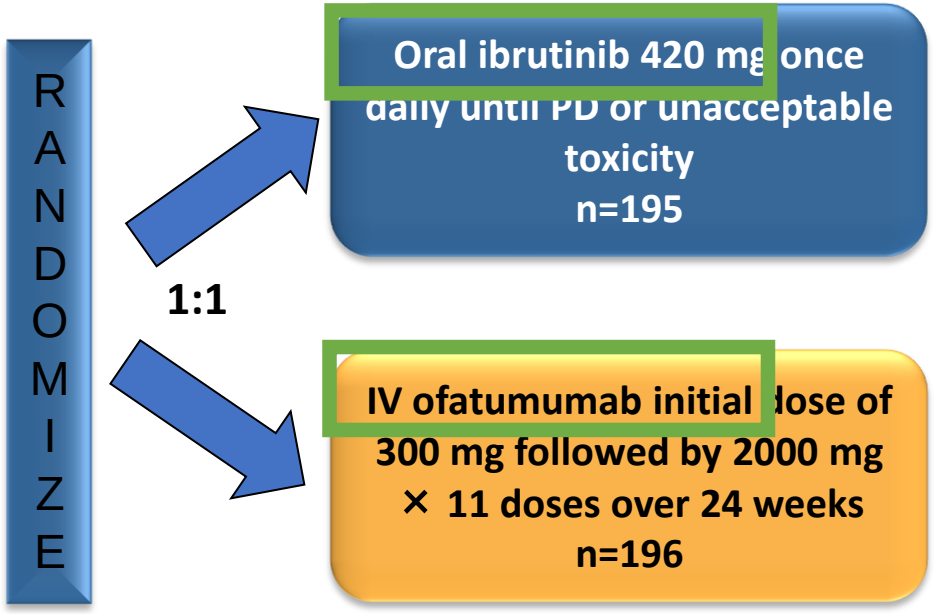

Absolute Lymphocyte Count
ALC x 109/L
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
14
16
18
Weeks


pre-treatment
2 months on treatment



Ibrutinib Pivotal Study: RESONATE

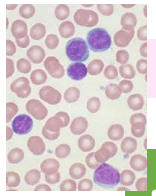


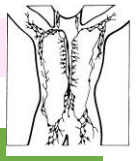


Eligibility: Relapsed and not appropriate for purine analog therapy:

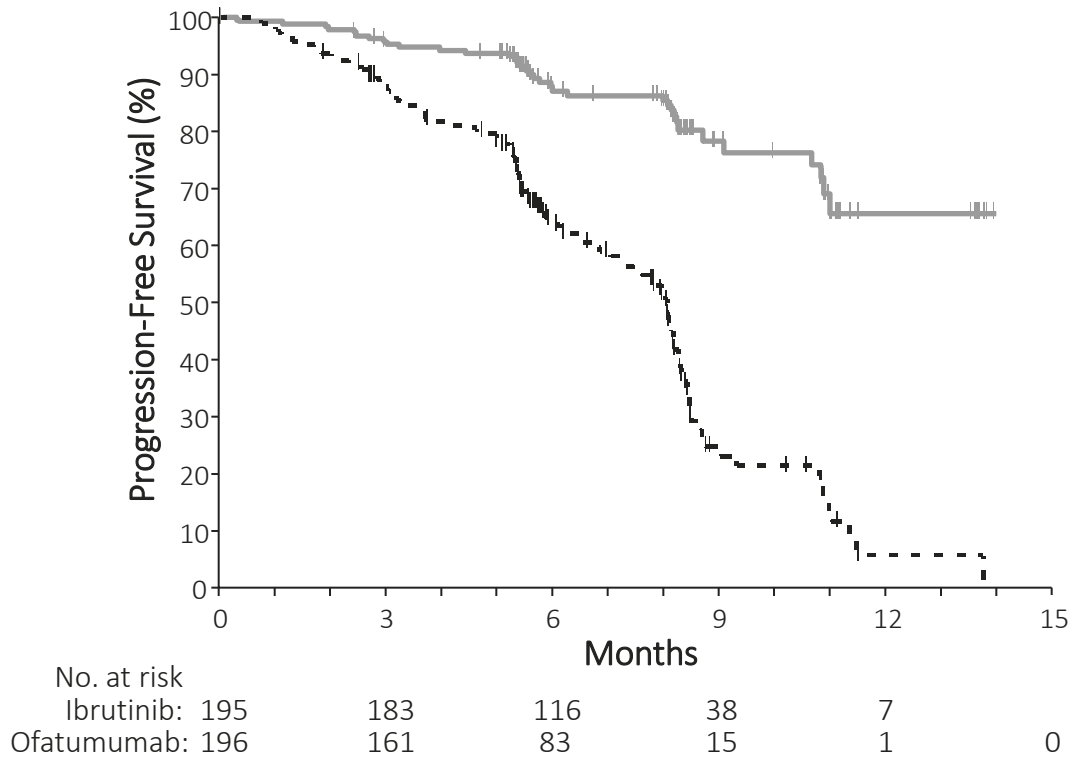
- **Disease progression < 3 years from prior purine analog**
- **Age >70 or age>65 with comorbidities**
- **Relapsed and deletion 17p**
- **purine analog associated AIHA / ITP**

Byrd JC. NEJM 2014; 371:213





RESONATE: Progression Free Survival

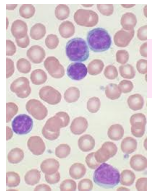


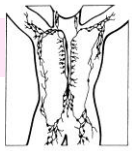
04.2014
FDA approve ibrutinib x relapse CLL

Ibrutinib significantly prolonged PFS
78% reduction in the risk of progression
p value < 0.0001

	Ofatumumab	Ibrutinib
Median PFS (mo)	8.08	NR
Hazard ratio	0.215	
(95% CI)	(0.146-0.317)	
Log-rank *P* value	< 0.0001	

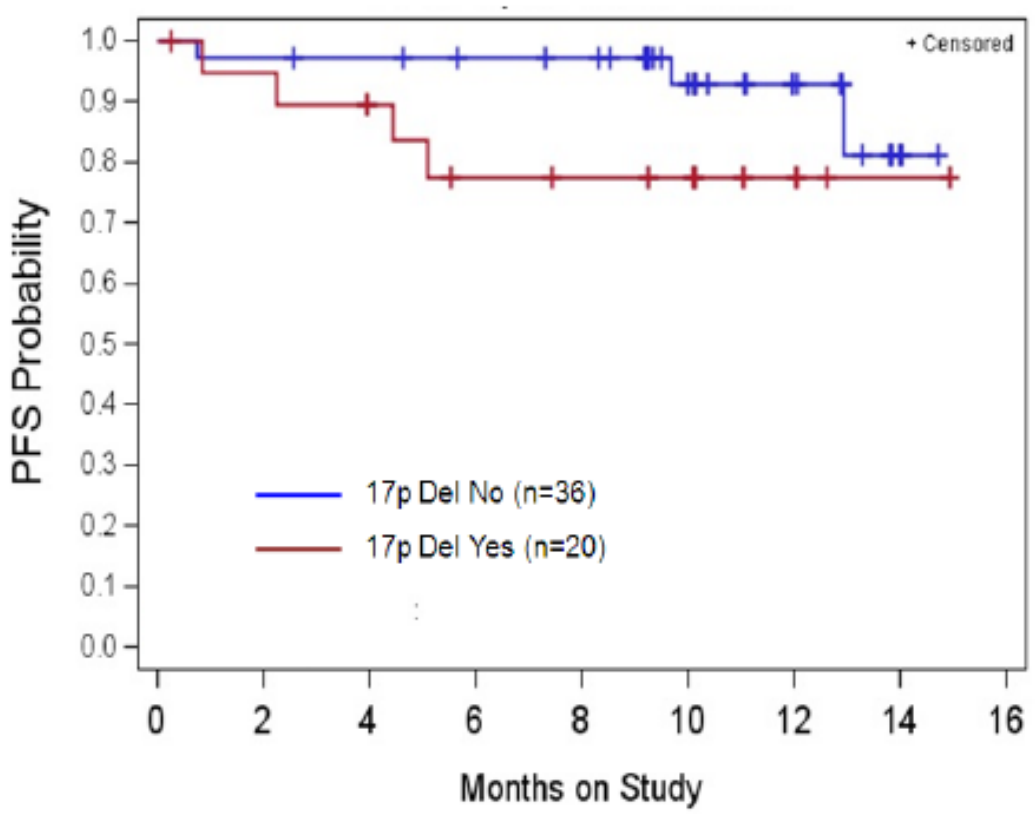
Byrd JC. NEJM 2014; 371:213



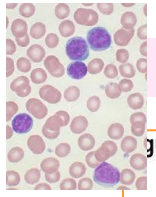


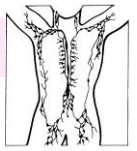
Ibrutinib: Progression-free Survival

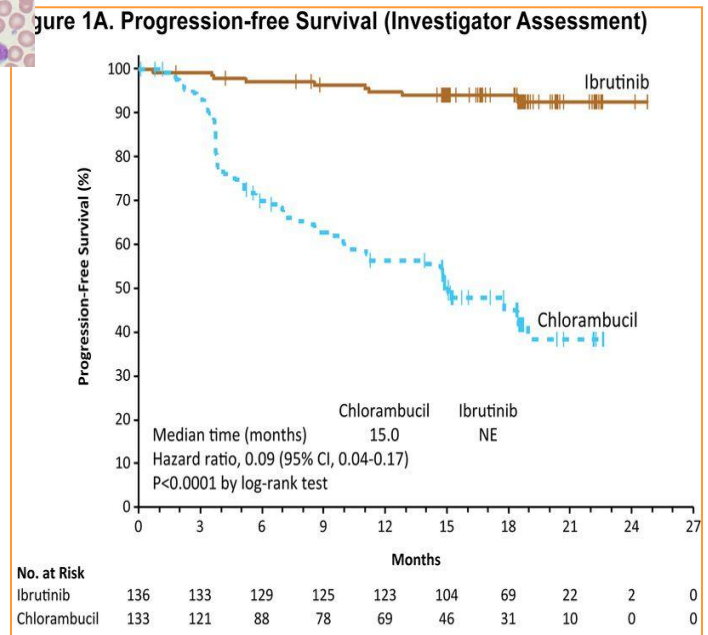
by 17p Del Status

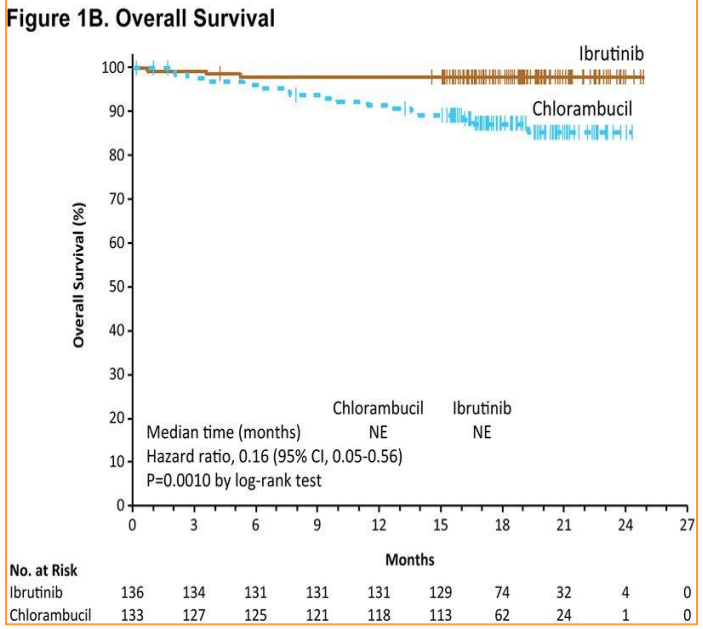


07.2014
FDA approve ibrutinib x CLL 17p del







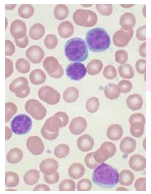


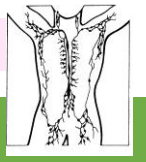
Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia

RESONATE II Investigators-Jan A. Burger ,

N Engl J Med 2015; 373:2425-2437

FDA Approves Imbruvica (ibrutinib) for the First-Line Treatment of Chronic Lymphocytic Leukemia-2016

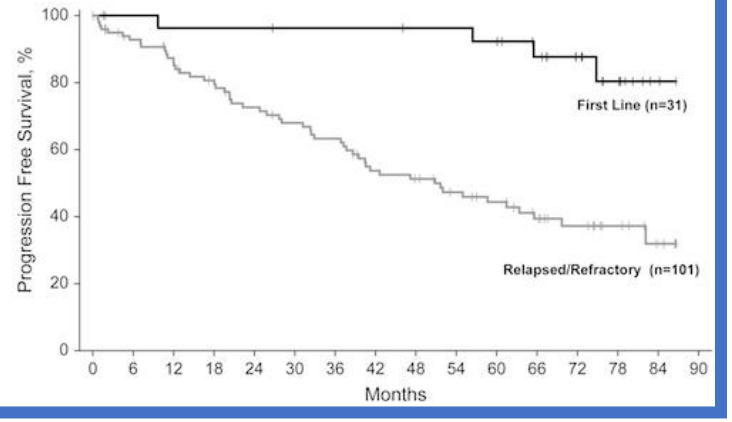




Up to 7 Years of Follow-up of Single-Agent Ibrutinib in the Phase 1b/2 PCYC-1102 Trial of First Line and Relapsed/Refractory Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

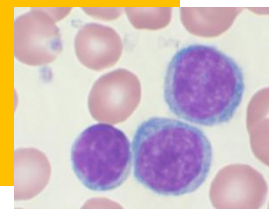
- ORR was 89% for all pts
- **Median DOR was not reached for first line and was 57 mo for R/R pts.**
- Median OS was NR in first line or R/R pts (63, NE),
  with estimated 7 y OS rates of 75% and 52%, respectively.
- Among R/R pts, median PFS trended longer for 27 pts with 1–2 prior lines of therapy (66)
  versus 14 pts with 3 (59) or 60 pts with ≥4 prior lines of therapy (39).
  - PFS

Figure 1. PFS for All-Treated First Line and Relapsed/Refractory Patients with CLL



Outcomes of Ibrutinib-Treated Patients With Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia With High-Risk Prognostic Factors in an Integrated Analysis of 3 Randomized Phase 3 Studies."

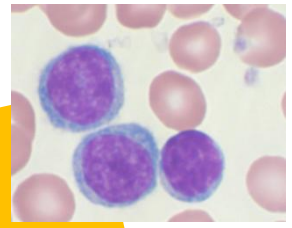
Kipps T. ICML/IwCLL2017



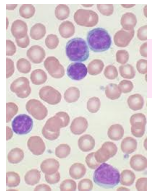
Data from the following trials were pooled
RESONATE (42 months FU),
RESONATE-2 (36 months FU)
HELIOS (32 months FU)

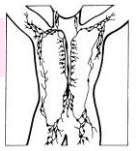
Analyzed based on:
*IGHV mutational status,
*del(11q)
*trisomy 12,
*complex karyotype.
*Impact of del(17p) was not assessed

	IGHV		Trisomy 12		Complex Karyotype		Del 11q	
	Unmut (n=344)	Mut (n-113)	With (n=90)	Without (n=314)	With (n=41)	Without (n=338)	With (n=168)	Without (n=382)
42 months OS%	78	84	82	80	77	78	80	78
Log-rank	0.41		0.92		0.91		0.08	
P value	1.21		1.02		0.96		0.08	



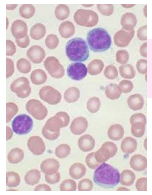
Results suggest that genomic risk factors associated with poor outcomes using traditional therapies have less relevance with ibrutinib treatment

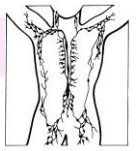




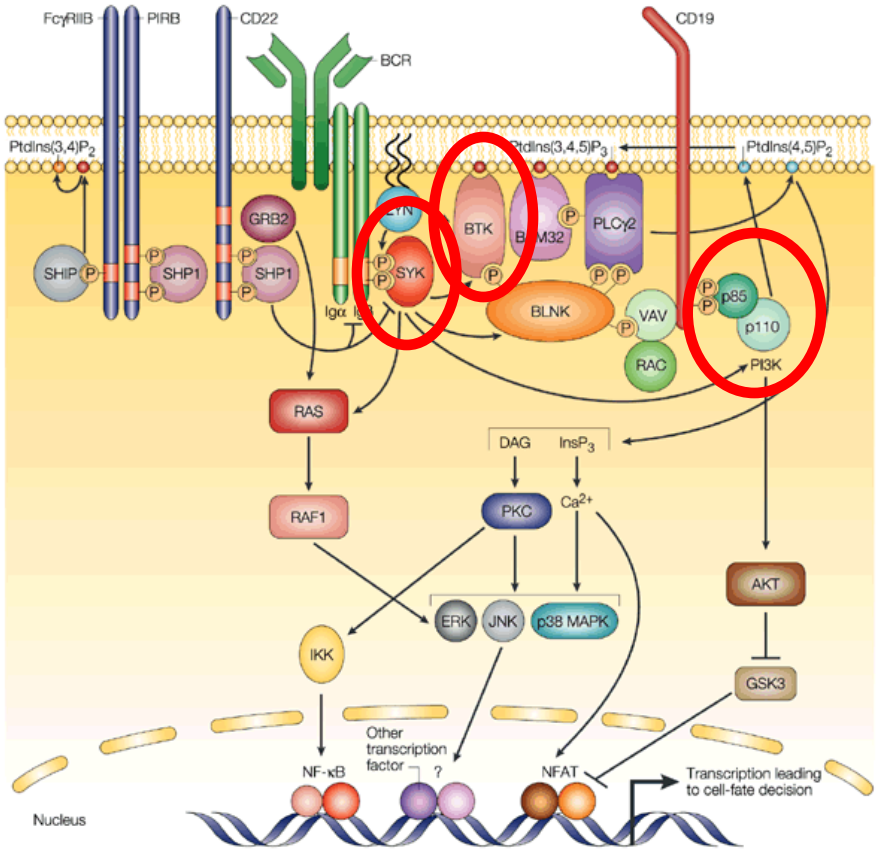
Ibrutinib side effects:

- Diarrhea
- Hypertension
- Invasive fungal infection and other infections
- 7-8 % atrial fibrillation
- Increase bleeding tendency





BCR-associated Kinases: Proven Effective Therapeutic Targets

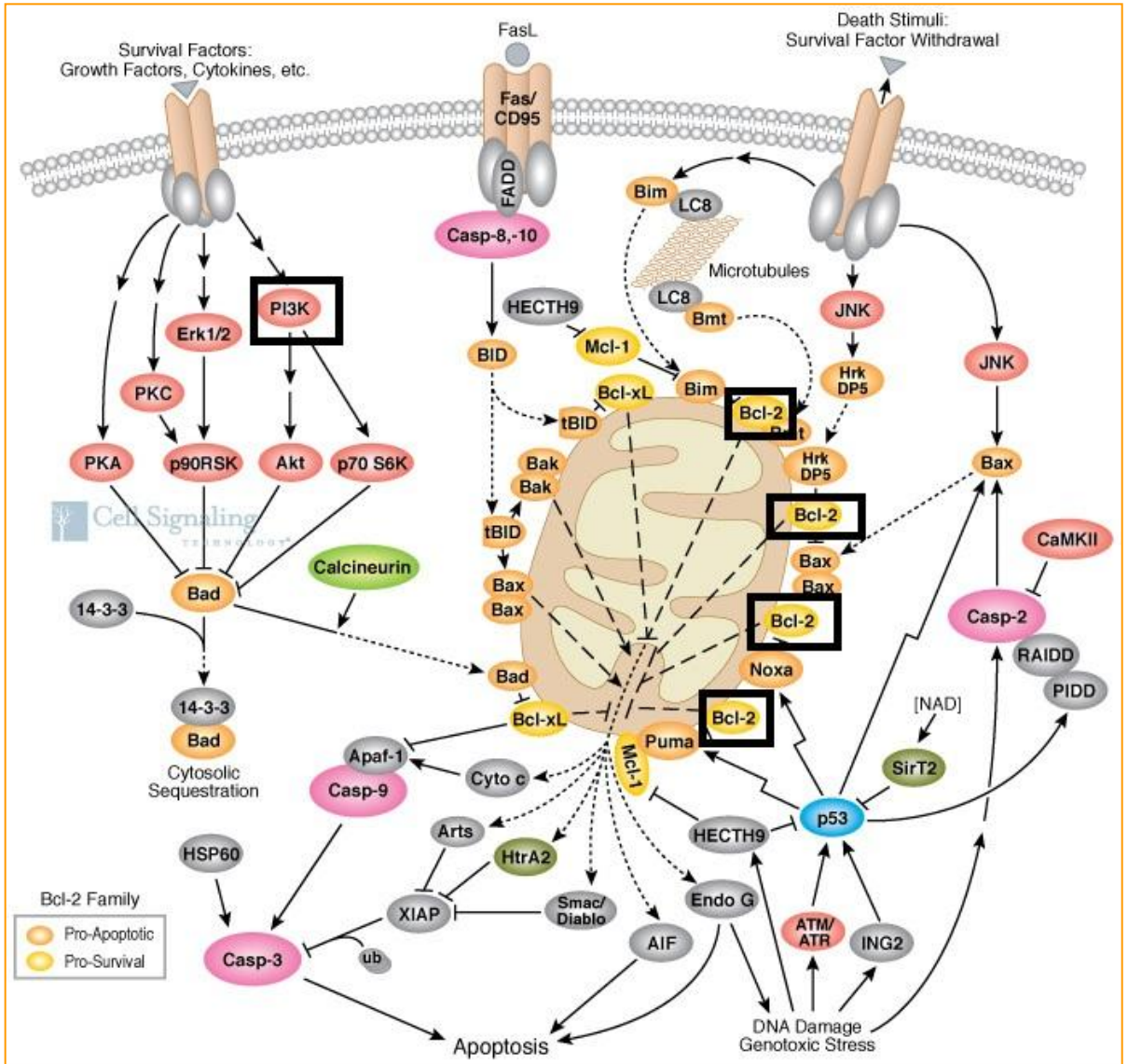


- **Syk (spleen tyrosine kinase):**
  1. **fostamatinib**
  2. **PRT062070**
  3. **GS-9973**
- **Btk (Bruton's tyrosine kinase):**
  1. **ibrutinib**
  2. **CC-292**
  3. **ACP-196**
  4. **ONO-4059**
- **PI3K (phosphatidyl 3-kinase):**
  1. **Idelalisib (GS-1101)**
  2. **Duvelisib (IPI-145)**
  3. **AMG319**

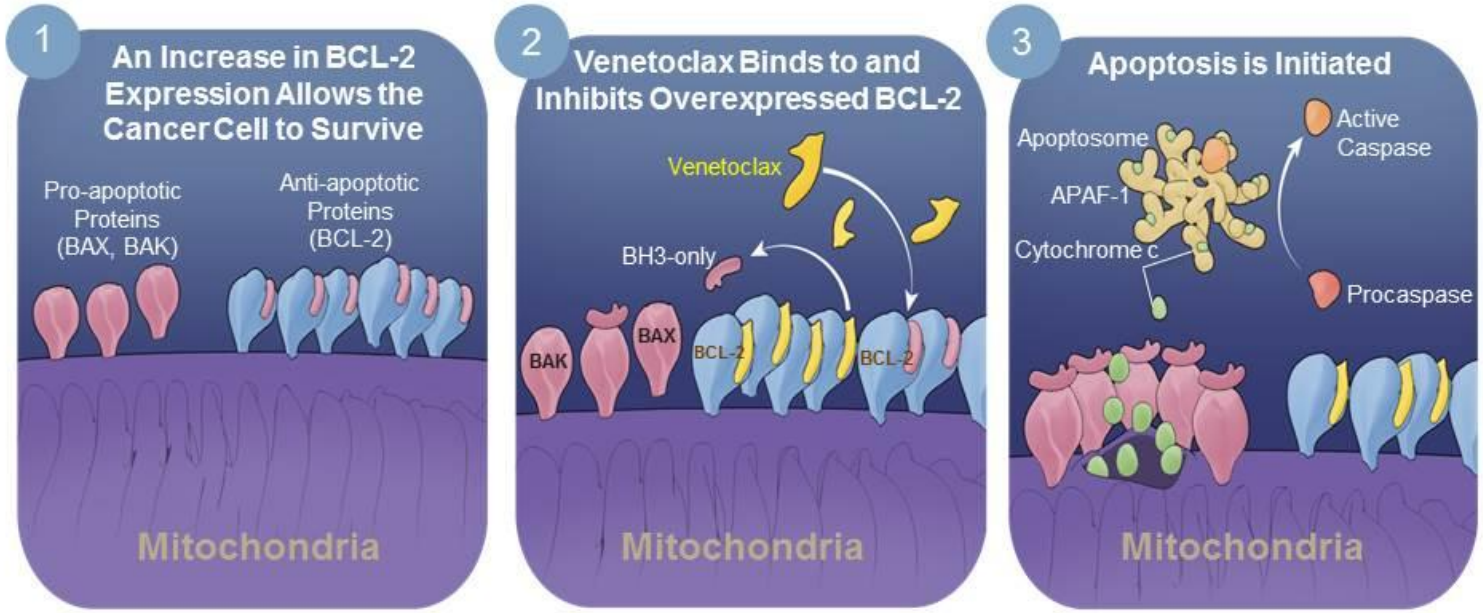
BCL2 INHIBITORS

Proliferation

Apoptosis



Venetoclax: Selective BCL-2 Inhibitor

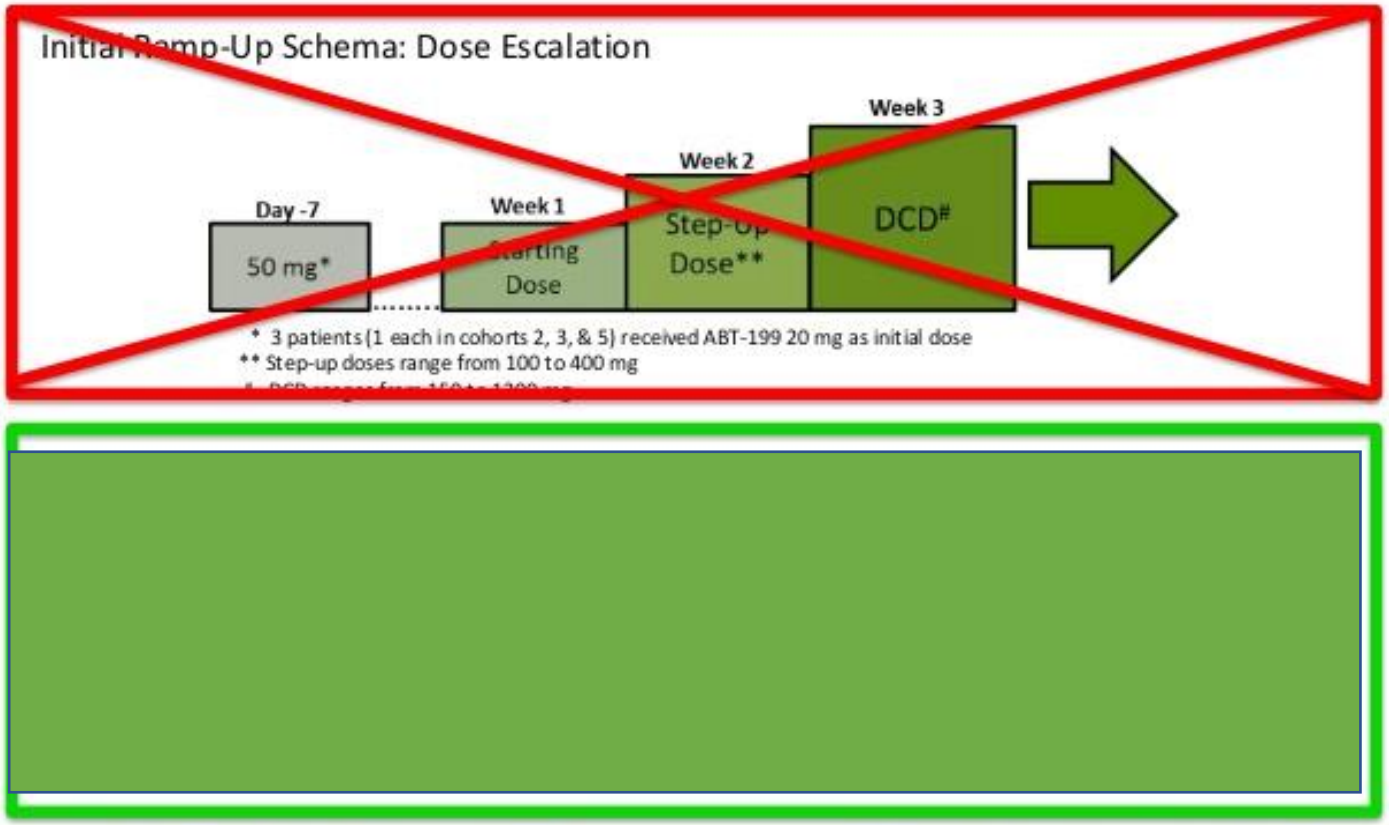


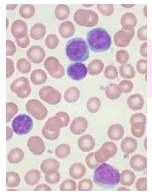
- Venetoclax is a potent, orally bioavailable agent with a BCR-independent mechanism of action and substantial activity in heavily pre-treated CLL (Roberts AW et al, *NEJM* 2015)

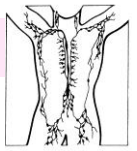
Adapted from Jones et al. Oral Presentation at ASH 2015, Orlando, Florida

ABT-199 (Venetoclax) Dosing Schema

Daily ABT-199 doses increased weekly to the designated cohort dose (DCD)







Venetoclax for Patients With Chronic Lymphocytic Leukemia With 17p Deletion: Results From the Full Population of a Phase II Pivotal Trial.

Venetoclax (VEN) Monotherapy in Relapsed/Refractory (R/R) Chronic Lymphocytic Leukemia (CLL) with Del(17p)

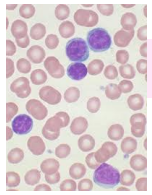
- Phase II study of VEN monotherapy
- N = 107 patients with R/R CLL and del(17p)
- **Primary study endpoint:** Overall response rate (ORR) by independent review committee (IRC)

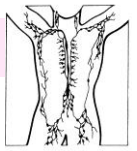
Response (IRC assessed)	N = 107
ORR	79.4%
CR or CRi	7.5%
nPR/PR	72%
Survival rate (12 mo)	
Progression-free survival (PFS)	72%
Overall survival (OS)	86.7%

CR = complete remission; CRi = CR with incomplete bone marrow recovery; nPR = nodular partial remission; PR = partial remission

Stilgenbauer S et al. *Proc ASH* 2015;Abstract LBA-6.

FDA Approves Venetoclax for CLL in Patients With 17p Deletion Who Have Been Treated With at Least One Prior Therapy 2016



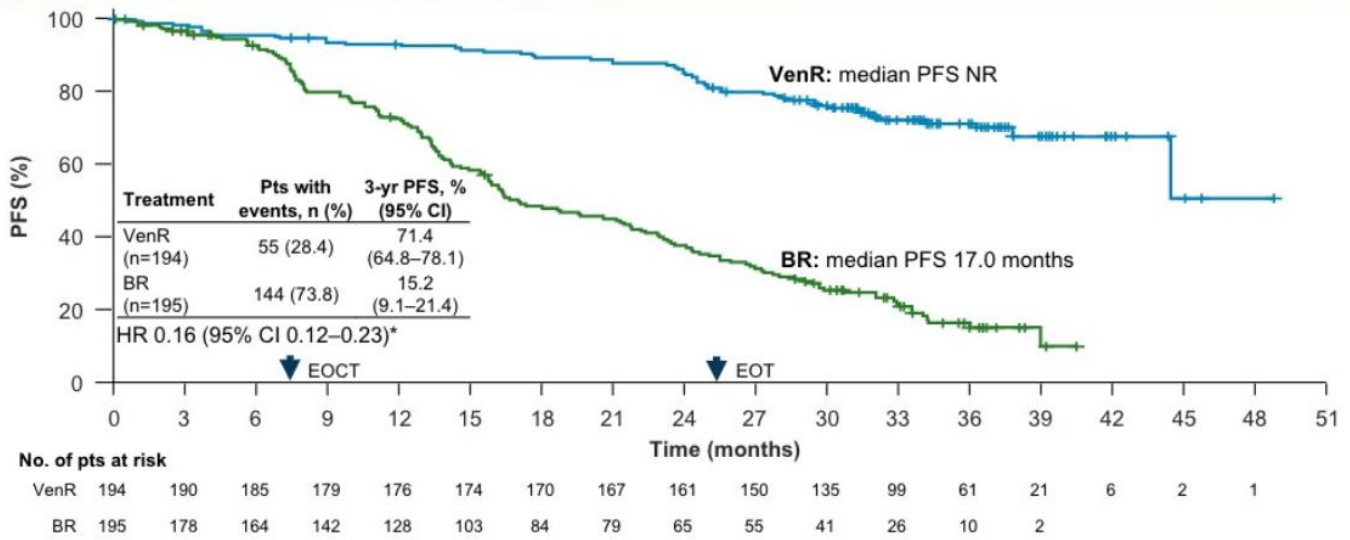


June 8, 2018

FDA Approval of VENCLEXTA® (venetoclax tablets) in Combination with Rituximab as a Fixed Duration Treatment for Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma Patients Who Have Received One Prior Therapy

Superior PFS with VenR vs BR maintained with 1 additional year of follow-up: update

Investigator-assessed PFS



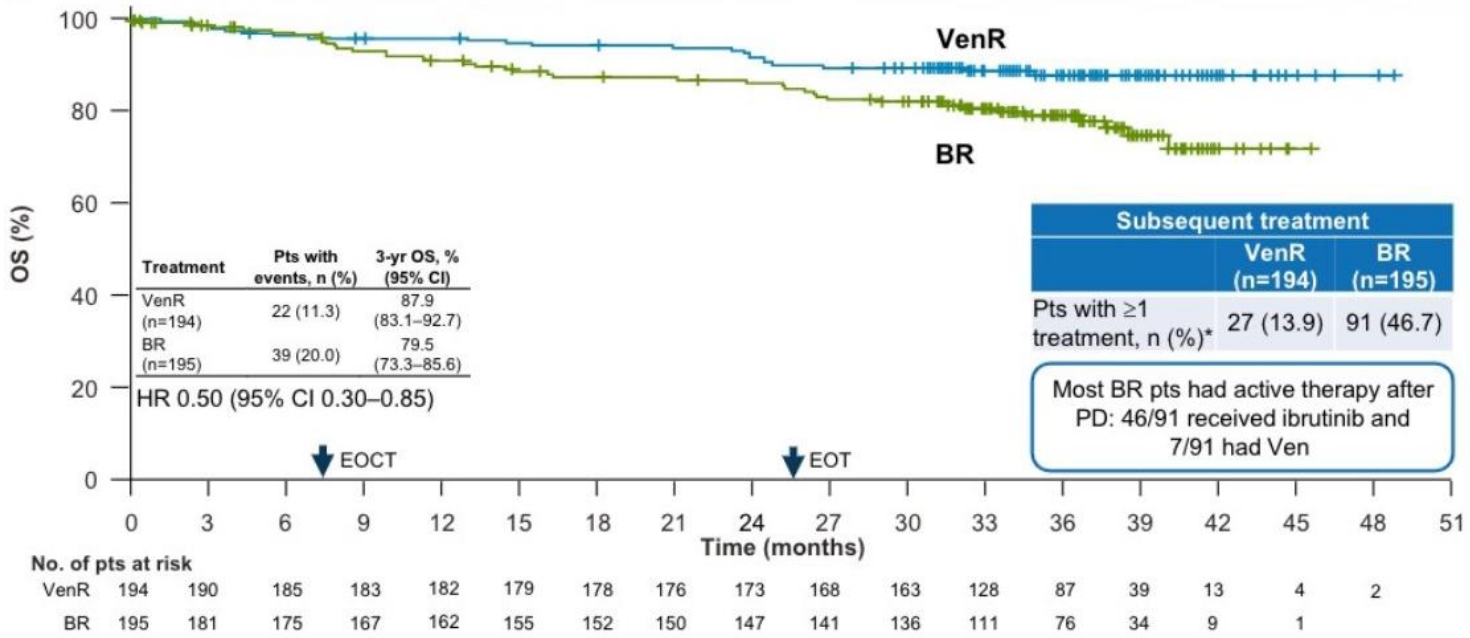
- Median follow-up 36.0 months (range 0.0–48.6); VenR 36.1 months, BR 35.9 months

*Stratified HR

Data cut-off date: May 8, 2018

03/2018

Clinically meaningful improvement in OS with VenR vs BR maintained after 3 years



Treatment	Pts with events, n (%)	3-yr OS, % (95% CI)
VenR (n=194)	22 (11.3)	87.9 (83.1–92.7)
BR (n=195)	39 (20.0)	79.5 (73.3–85.6)

HR 0.50 (95% CI 0.30–0.85)

Subsequent treatment	VenR (n=194)	BR (n=195)
Pts with ≥1 treatment, n (%)*	27 (13.9)	91 (46.7)

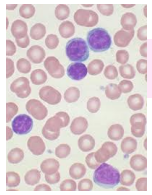
Most BR pts had active therapy after PD: 46/91 received ibrutinib and 7/91 had Ven

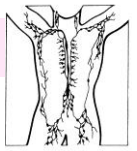
No. of pts at risk

VenR	194	190	185	183	182	179	178	176	173	168	163	128	87	39	13	4	2
BR	195	181	175	167	162	155	152	150	147	141	136	111	76	34	9	1	

*Unstratified HR 0.51 (95% CI 0.30–0.86)
Median follow-up: 36.0 months (range 0.0–48.6). Median per arm: VenR 36.1 months; BR 35.9 months

Data cut-off date: May 8, 2018





Side effects of venetoclax:

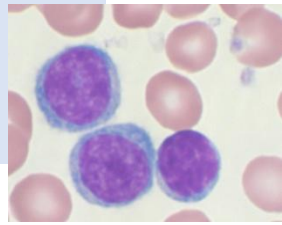
- neutropenia, anemia, thrombocytopenia
- diarrhea, nausea, u
- upper respiratory tract infection,

Serious complications :

- pneumonia,
- tumor lysis syndrome.

Durability of Responses on Continuous Therapy and Following Drug Cessation in Deep Responders with Venetoclax and Rituximab."

Danielle Brander; Duke Cancer Institute IWCLL 2017



49 patients with venetoclax plus rituximab

↓

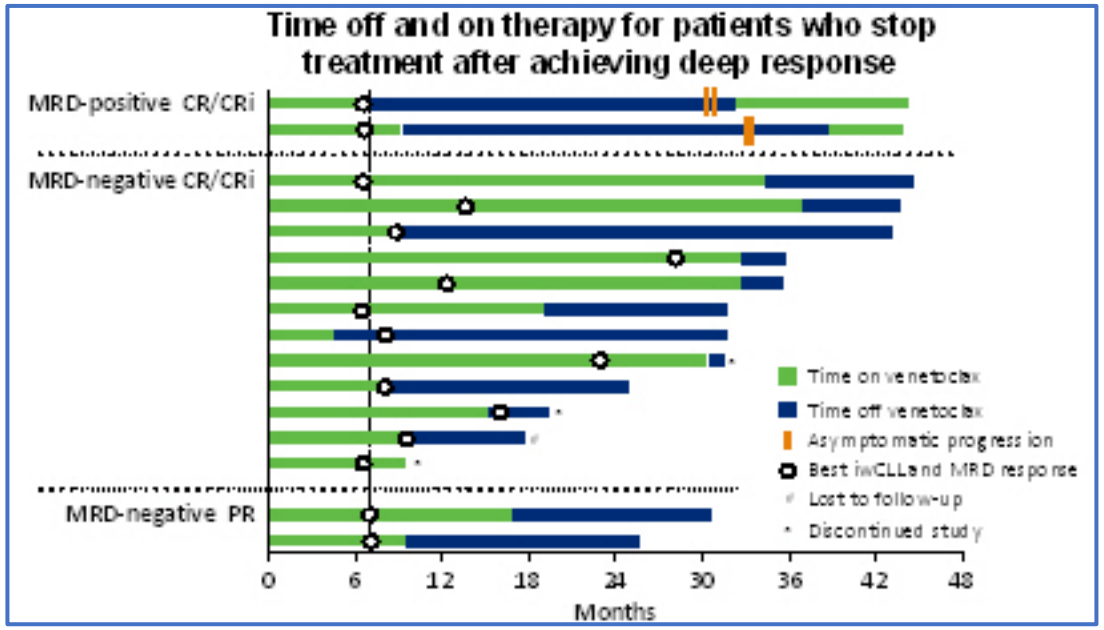
Tx till complete remission (CR) or minimal residual disease (MRD)-achieved

↓

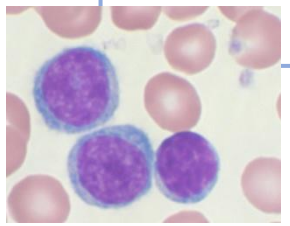
Discontinue venetoclax

↓

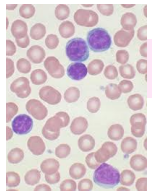
Patients with progressive disease after discontinuation could reinitiate the same combination.

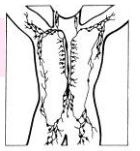


12 Patients had durable remissions after elective treatment cessation (10 ongoing)
None of the patients who achieved MRD-negativity have progressed off therapy (median time 20 months)



Possible to discontinue venetoclax after achieving a deep response and to maintain treatment –free remission

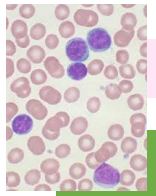


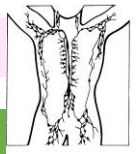


Both Ibrutinib and venetoclax are effective drugs

BUT

Are they more effective than std treatment in newly diagnosed symptomatic CLL patients?





Alliance Study Design

- Multicenter, randomized, double-blind phase III study

Untreated patients with CLL meeting IWCLL 2008 criteria for tx initiation;
- aged ≥ 65 yrs;
- EGOG PS 0-2;
- ANC ≥ 1000 unless due to BM involvement;
- PLT ≥ 30; $CrCl_{CG}$ ≥ 40; AST/ALT ≤ 2.5 x ULN; no heparin or warfarin
(N = 547)

Ibrutinib 420 mg QD (n = 182)	***Until PD***
Ibrutinib 420 mg QD + **Rituximab** 375 mg/m^2 wkly x 4 wks starting cycle 2 Day 1; cycles 3-6 Day 1* (n = 182)	***Ibrutinib until PD***
Bendamustine 90 mg/m^2 on Days 1, 2 + **Rituximab** 375 mg/m^2 on cycle 1 Day 1; 500 mg/m^2 on cycles 2-6 Day 1* (n = 183)	***Crossover to ibrutinib w/n 1 yr of PD allowed***

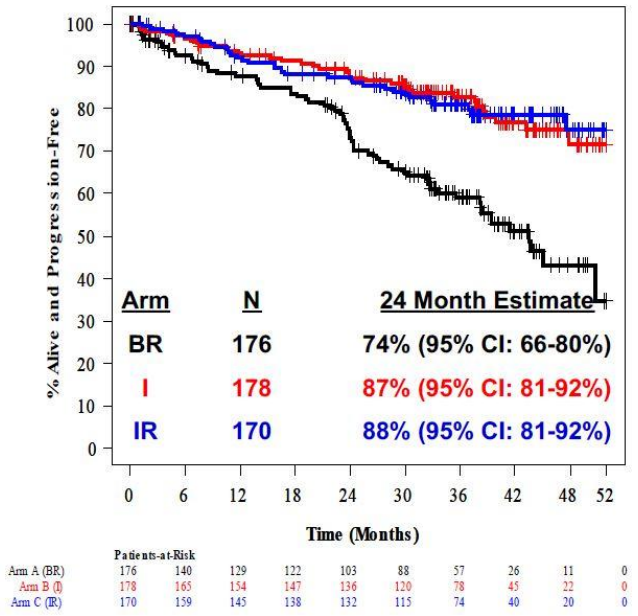
*28-day cycles.

- Primary endpoint: PFS
  - 2 primary comparisons of ibrutinib vs BR and ibrutinib + R vs BR with 90% power to detect HR of 0.586 (estimated 2-yr PFS rates: ibrutinib, 75%; BR, 61%) and overall 1-sided α = 0.025 for each comparison
  - If both primary comparisons significant, third planned comparison of ibrutinib + R vs ibrutinib

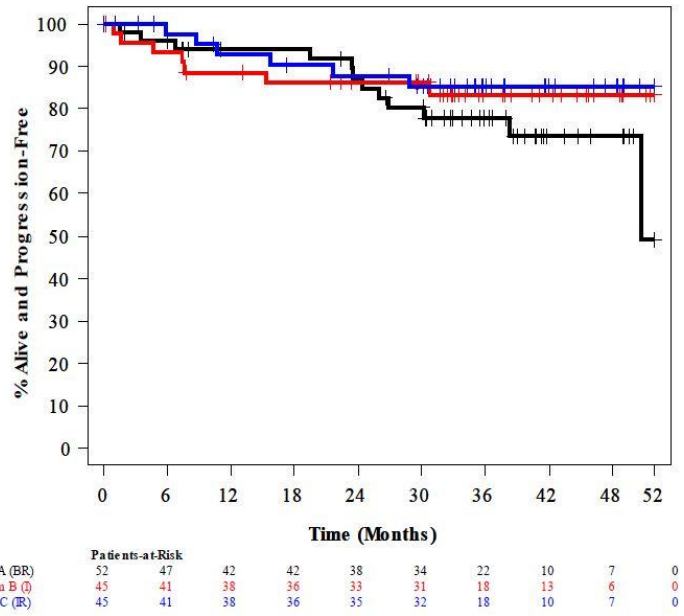
Woyach. ASH 2018. Abstr 6. Woyach. NEJM. 2018;[Epub].

ALLIANCE A041202

PFS all patients

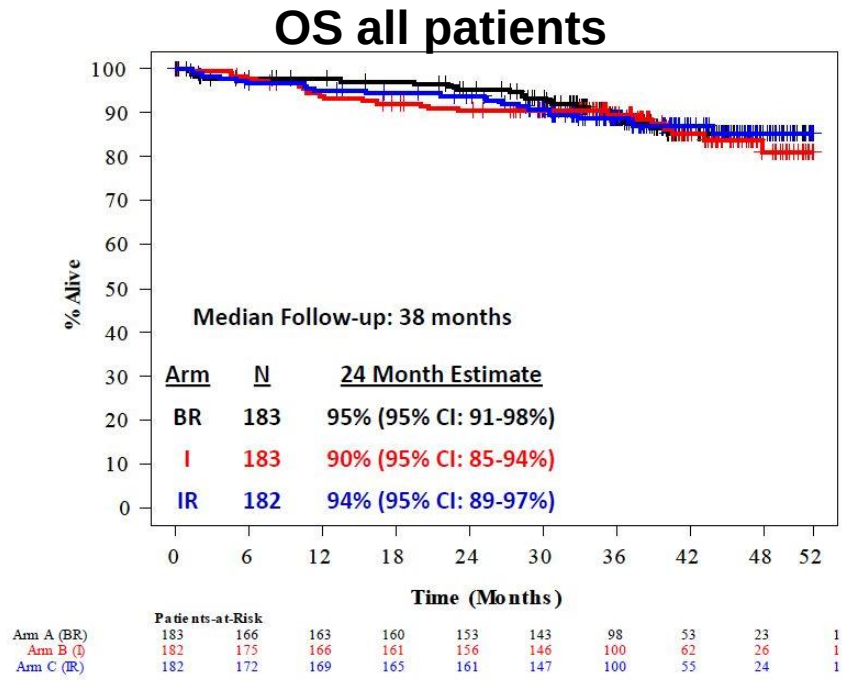


PFS IGHV mutated



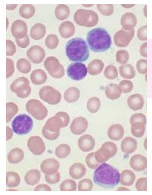
ASH 2018, I. Jennifer A. Woyach al., 6 Ibrutinib Alone or in Combination with Rituximab Produces Superior Progression Free Survival (PFS) Compared with Bendamustine Plus Rituximab in Untreated Older Patients with Chronic Lymphocytic Leukemia (CLL): Results of Alliance North American Intergroup Study A041202

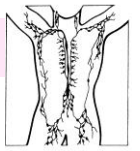
3. ALLIANCE A041202



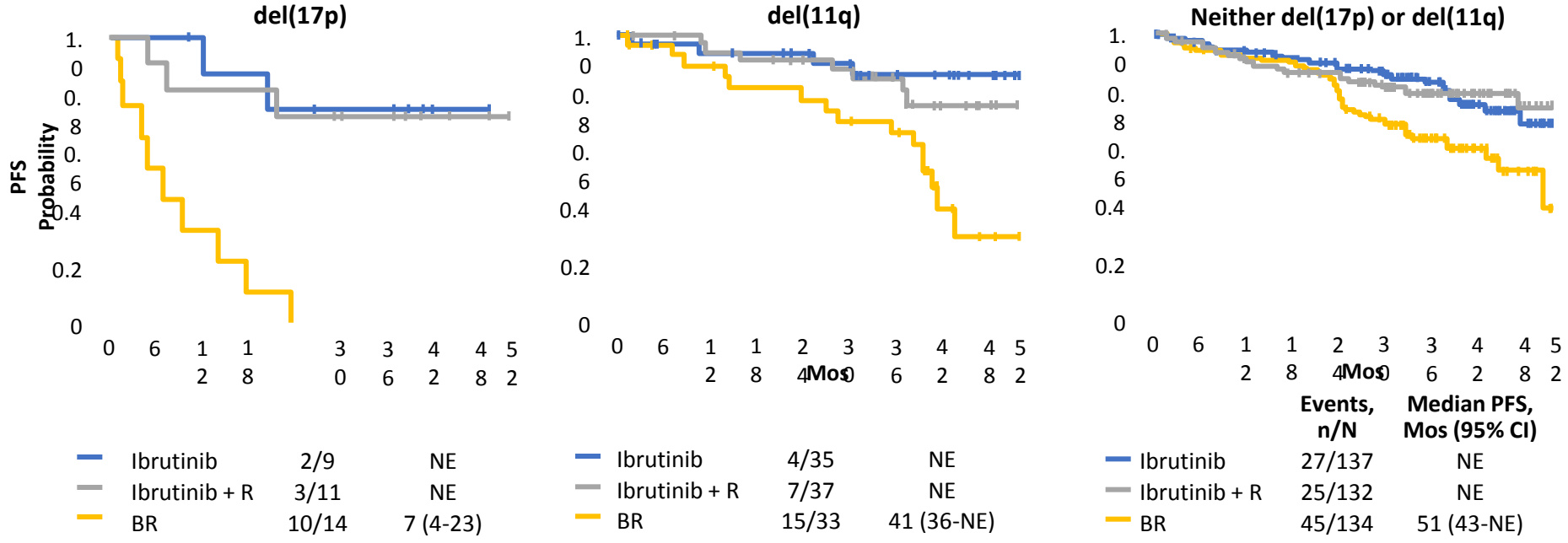
→ No significant difference in overall survival (OS) between treatment arms.

ASH 2018, I. Jennifer A. Woyach al., 6 Ibrutinib Alone or in Combination with Rituximab Produces Superior Progression Free Survival (PFS) Compared with Bendamustine Plus Rituximab in Untreated Older Patients with Chronic Lymphocytic Leukemia (CLL): Results of Alliance North American Intergroup Study A041202





A041202: PFS by del(17p) and del(11q) Status



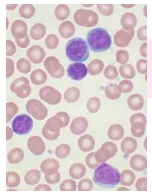
Woyach. NEJM. 2018;[Epub].

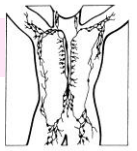
A041202: Safety

Grade 3-5 AEs During Treatment or Follow-up,* n (%)	Ibrutinib (n = 180)	Ibrutinib + R (n = 181)	BR (n = 176)	*P* Value
Any hematologic	74 (41)	70 (38)	107 (61)	< .001
▪ Anemia	21 (12)	11 (6)	22 (13)	.09
▪ Neutropenia	27 (15)	39 (22)	71 (40)	< .001
▪ Thrombocytopenia	12 (7)	9 (5)	26 (15)	.008
Any nonhematologic	133 (74)	134 (74)	111 (63)	.04
▪ Bleeding	3 (2)	5 (3)	0	.46
▪ Infections	37 (21)	37 (20)	26 (15)	.62
▪ Febrile neutropenia	3 (2)	1 (1)	13 (7)	< .001
▪ Atrial fibrillation	17 (9)	10 (6)	5 (3)	.05
▪ Hypertension	53 (29)	61 (34)	25 (14)	< .001
Death				
▪ Unexplained/unwitnessed	7 (4)	4 (2)	2 (1)	.24
▪ During active treatment + 30 days	13 (7)	13 (7)	2 (1)	--
▪ During active treatment + 30 days, up to 6 cycles	3 (2)	6 (3)	2 (1)	--

*Excludes crossover.

Woyach. ASH 2018. Abstr 6. Woyach. NEJM. 2018;[Epub].

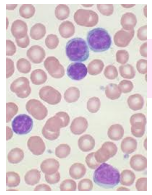


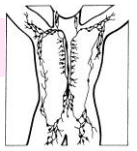


A041202: Conclusions

- In older patients with CLL, first-line ibrutinib ± R significantly prolonged PFS vs BR (both $P < .001$), with no additional PFS benefit with addition of R to ibrutinib
  - Median PFS: ibrutinib, NR; ibrutinib + R, NR; BR, 43 mos
  - 2-yr PFS: ibrutinib, 87%; ibrutinib + R, 88%; BR, 74%
- Ibrutinib associated with important toxicities in this older cohort, with investigators recommending close monitoring with ibrutinib in this setting
  - Significantly higher rates of HTN ($P < .001$) and atrial fibrillation ($P = .05$) with ibrutinib-based tx
  - BR exhibited significantly higher rates of febrile neutropenia ($P < .001$), neutropenia ($P < .001$), and thrombocytopenia ($P = .008$)
- Investigators concluded that further large clinical trials are needed in this patient population (eg, A041702, EA9161), with identification of discontinuation strategies of significant interest

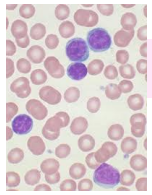
Woyach. ASH 2018. Abstr 6. Woyach. NEJM. 2018;[Epub]. NCT03737981. NCT03701282.

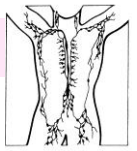




iLLUMINATE: Phase III Trial of Ibrutinib + Obinutuzumab vs Chlorambucil + Obinutuzumab in Previously Untreated CLL/SLL

Moreno. ASH 2018. Abstr 691.
Moreno. Lancet Oncol. 2018;[Epub].



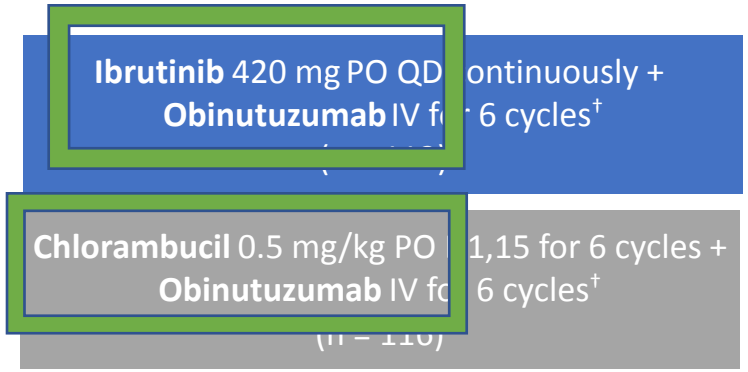


iLLUMINATE: Study Design

- Randomized, open-label, multicenter phase III trial

Stratified by ECOG PS (0-1 vs 2), del(17p)/del(11q) (+/+ vs +/- vs -/+ vs -/-)

Untreated patients with CLL/SLL needing treatment by iwCLL criteria, ≥ 65 yrs
or
< 65 yrs with comorbidities*
(N = 229)



Ibrutinib continued until PD or unacceptable toxicity

If IRC-confirmed progression, crossover to next-line single-agent ibrutinib permitted

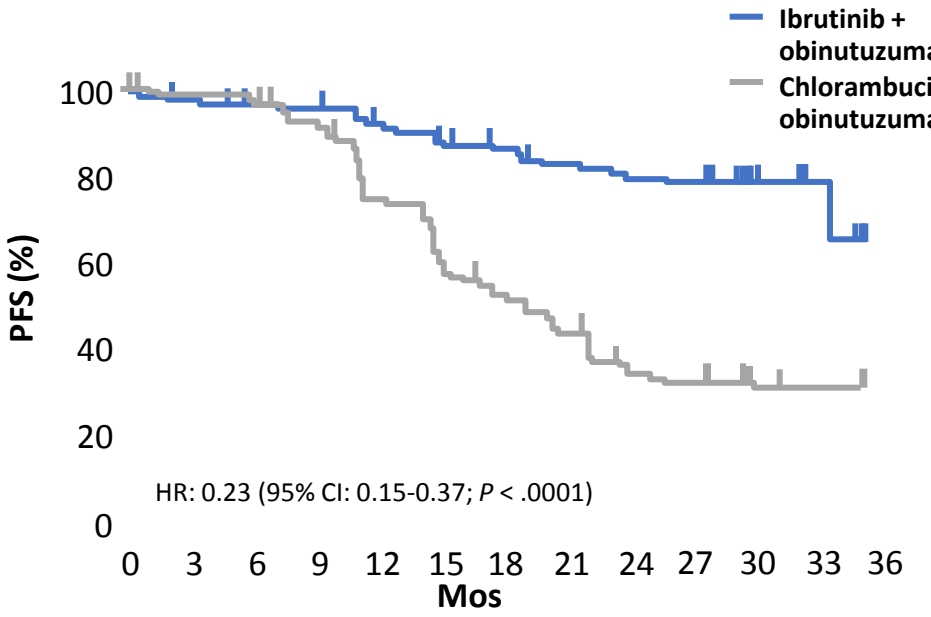
*Cumulative Illness Rating Score > 6, creatinine clearance < 70 mL/min, and/or del(17p)/*TP53* mutation.
†Cycle 1: 100 mg, Days 1; 900 mg, Day 2; 1000 mg, Days 8, 15. Cycle 2-6: 1000 mg, Day 1.

- Primary endpoint: PFS by IRC in ITT population
- Secondary endpoints: PFS in high-risk patients (positive for del(17p) or *TP53* mutation, del(11q), or unmutated *IGHV*), MRD, ORR, OS, IRRs, safety

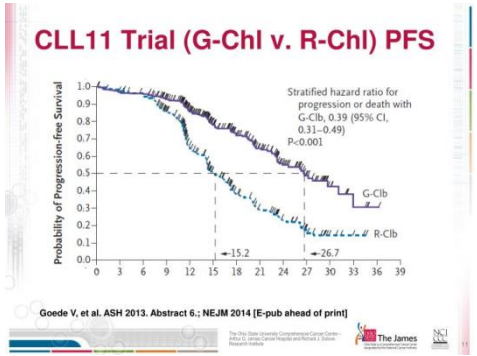
Moreno. ASH 2018. Abstr 691. Moreno. Lancet Oncol. 2018;[Epub].

iLLUMINATE: IRC-Assessed PFS in ITT Population

	Patients, n	Median PFS, Mos	30-Mo PFS, % (95% CI)
Ibrutinib + obinutuzumab	113	NR	79 (70-85)
Chlorambucil + obinutuzumab	116	19.0	31 (23-40)



Patients at Risk, n (number censored)													
Ibrutinib + obinutuzumab	113	109	106	105	99	94	90	85	82	82	28	6	0
	(0)	(1)	(3)	(3)	(5)	(6)	(8)	(9)	(9)	(9)	(62)	(84)	(89)
Chlorambucil + obinutuzumab	116	111	109	102	81	67	56	47	35	33	6	5	0
	(0)	(4)	(4)	(6)	(7)	(7)	(8)	(8)	(10)	(10)	(36)	(37)	(42)



Moreno. Lancet Oncol. 2018;[Epub].

iLLUMINATE: Secondary Efficacy Endpoints

	All Patients		High-Risk Patients	
Outcome	**Ibrutinib + Obinutuzumab (n = 113)**	**Chlorambucil + Obinutuzumab (n = 116)**	**Ibrutinib + Obinutuzumab (n = 73)**	**Chlorambucil + Obinutuzumab (n = 75)**
ORR (per IRC), %	88	73	90	68
▪ CR/CRi	19	8	14	4
Median DoR, mos	NR (29.7-NE)	18.1 (15.2-NE)	NR (NE-NE)	11.8 (10.4-15.9)
MRD undetectable in BM or PB, %	35	25	27	15
▪ BM	20	17	--	--
▪ PB	30	20	--	--

- At follow-up of 31.3 mos, median OS not reached in either arm; HR: 0.92 (95% CI: 0.48-1.77)
  - 30-mo OS: 86% (95% CI: 77-91) for ibrutinib arm, 85% (95% CI: 77-90) for chlorambucil arm

- 4/113 (4%) in the ibrutinib arm vs 51/116 (44%) in the chlorambucil arm initiated subsequent therapy, with median time to next treatment not reached in either arm
  - Need for second-line therapy reduced with ibrutinib (HR: 0.06; 95% CI: 0.02-0.18)

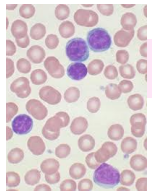
Moreno. Lancet Oncol. 2018;[Epub].

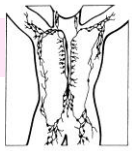
iLLUMINATE: Serious AEs

Serious AE	Ibrutinib + Obinutuzumab (n = 113)	Chlorambucil + Obinutuzumab (n = 115)
Any, n (%)	65 (58)	40 (35)
Ibrutinib related, n (%)	30 (27)	--
▪ Pneumonia, n	5	--
▪ Atrial fibrillation, n	5	--
▪ Febrile neutropenia, n	4	--
Chlorambucil related, n (%)	--	21 (18)
▪ Febrile neutropenia, n	--	7
▪ Tumor lysis syndrome, n	--	4
Obinutuzumab related, n (%)	17 (15)	27 (23)
▪ Febrile neutropenia, n	3	7
▪ Thrombocytopenia, n	3	--
▪ IRR, n	--	8
▪ Tumor lysis syndrome, n	--	5
▪ Pyrexia, n	--	4

Moreno. Lancet Oncol. 2018;[Epub].

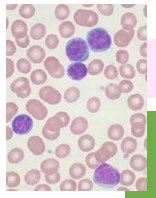
- Deaths due to AEs
  - 10/113 (9%) in ibrutinib arm over median of 2.5 yrs of treatment
  - 2/115 (3%) in chlorambucil arm over median of 5 mos of treatment
- Treatment-related deaths
  - 1 patient with sudden death due to ibrutinib
  - 1 patient with neuroendocrine carcinoma of the skim due to chlorambucil

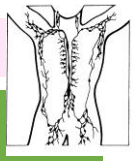




Phase III E1912: First-line Ibrutinib + Rituximab vs Standard-of-Care FCR in Younger Patients With Previously Untreated CLL

Shanafelt. ASH 2018. Abstr LBA-4. NCT02048813.





E1912: Study Design

- Primary analysis of randomized, open-label phase III trial (data cutoff: October 24, 2018)

Stratified by age (< vs ≥ 60 yrs), ECOG PS (0/1 vs 2), stage (III-IV vs I-II), del(11q22.3) vs other

Patients with previously untreated CLL requiring treatment per IWCLL 2008, aged ≤ 70 yrs, ECOG PS 0-2, CrCl > 40 mL/min, ability to tolerate FCR, no del(17p) by FISH (N = 529)

2 → **Ibrutinib** 420 mg PO QD for cycles 1-7 + **Rituximab** 50 mg/m^2 IV on Day 1, cycle 2, then 325 mg/mg^2 on Day 2, cycle 2, then 500 mg/m^2 on Day 1, cycles 3-7 (n = 354)

1 → **Fludarabine** 25 mg/m^2 IV on Days 1-3 for cycles 1-6 + **Cyclophosphamide** 250 mg/m^2 IV on Days 1-3 for cycles 1-6 + **Rituximab** 50 mg/m^2 IV on Day 1, cycle 1, then 325 mg/mg^2 on Day 2, cycle 1, then 500 mg/m^2 on Day 1, cycles 2-6 (n = 175)

Ibrutinib maintenance until PD

28-day cycles.

- Primary endpoint: PFS
  - Study has 80% power to detect PFS HR for ibrutinib + R vs FCR of 0.67 using stratified log-rank test, with prespecified boundary of 2.87 for first PFS interim analysis corresponding to 1-sided *P* = .0025
- Secondary endpoints: OS, safety

Shanafelt. ASH 2018. Abstr LBA-4. NCT02048813.

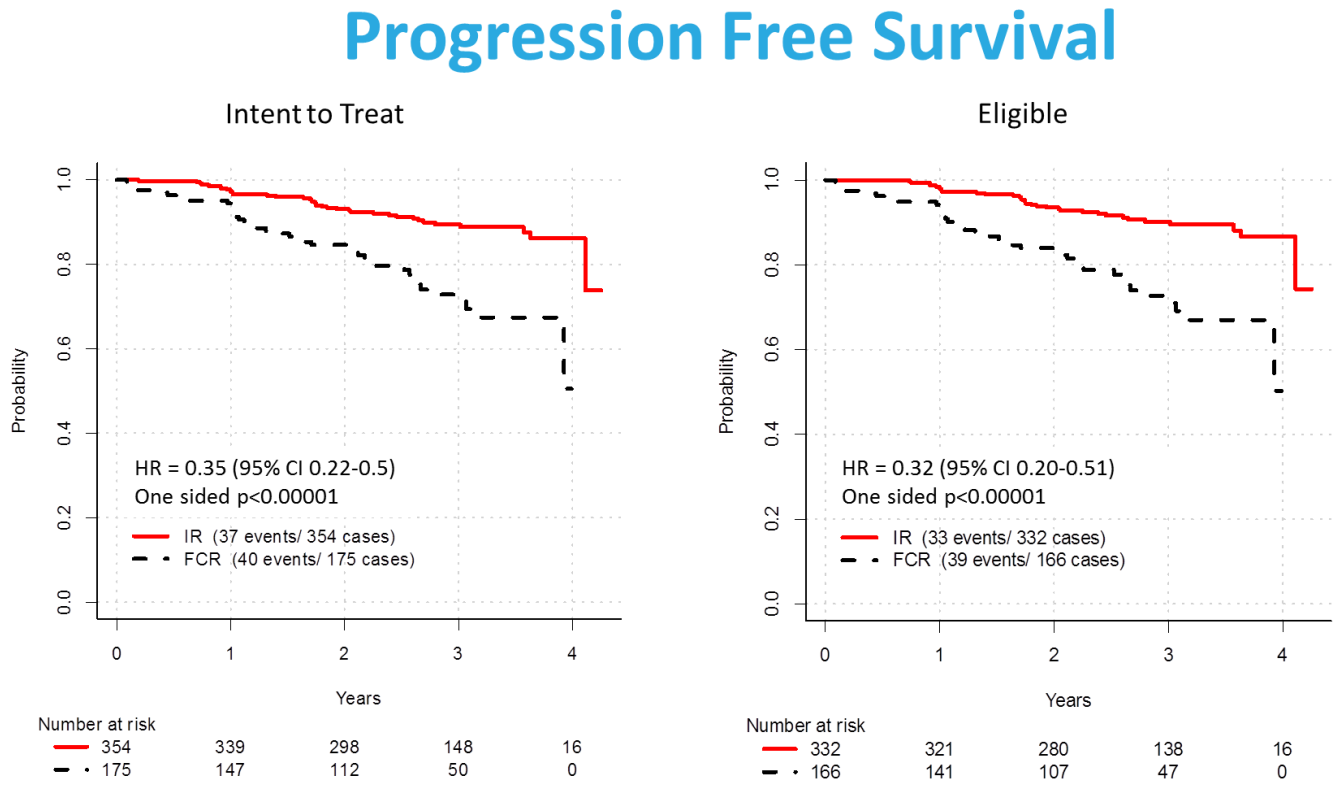
E1912: Baseline Characteristics

Characteristic, %	Ibrutinib + R (n = 354)	FCR (n = 175)
Median age, yrs	58	57
Age ≥ 60 yrs	41.0	40.0
Female	33.3	31.4
ECOG PS of 0	63.8	62.3
Rai stage		
▪ 0	3.1	5.1
▪ I-II	52.8	53.7
▪ III-IV	44.1	41.1
FISH analysis		
▪ del(11q)	22.0	22.3
▪ Trisomy 12	19.8	15.4
▪ del(13q)	34.2	33.1
> 3.5 mg/L	51.9	48.0
Unmutated *IGHV**	75.0	61.7

*Assessed in 437 patients (82%).

Shanafelt. ASH 2018. Abstr LBA-4.

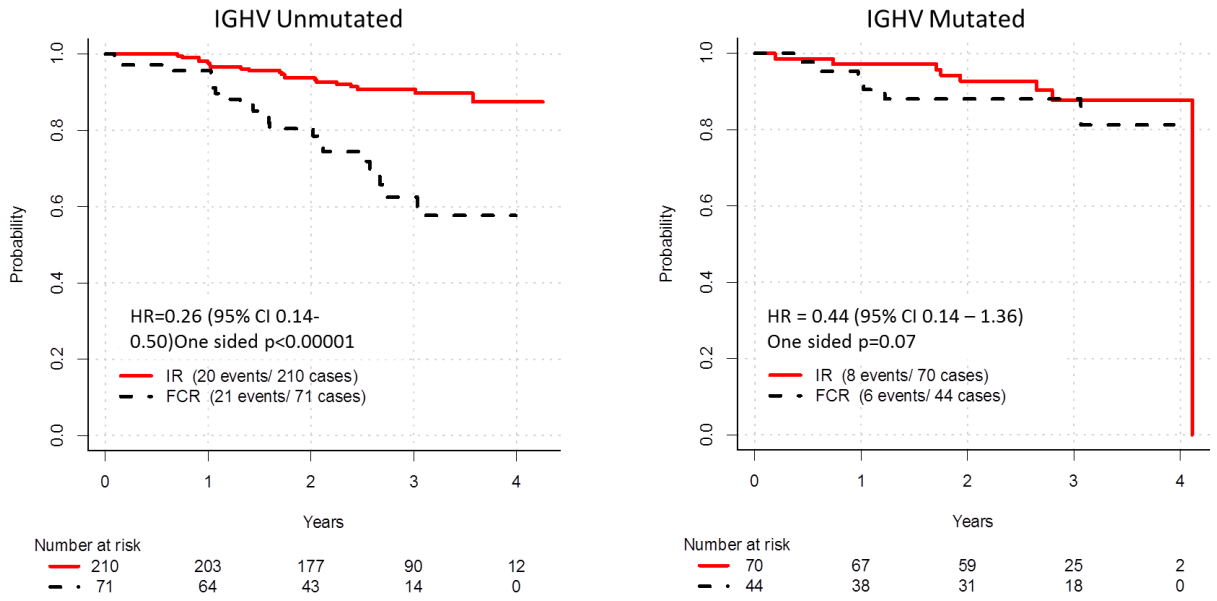
2. ECOG-ACRIN E1912



ASH 2018, Tait D. Shanafelt, MD et al., LBA-4 A Randomized Phase III Study of Ibrutinib (PCI-32765)-Based Therapy Vs. Standard Fludarabine, Cyclophosphamide, and Rituximab (FCR) Chemoimmunotherapy in Untreated Younger Patients with Chronic Lymphocytic Leukemia (CLL): A Trial of the ECOG-ACRIN Cancer Research Group (E1912)

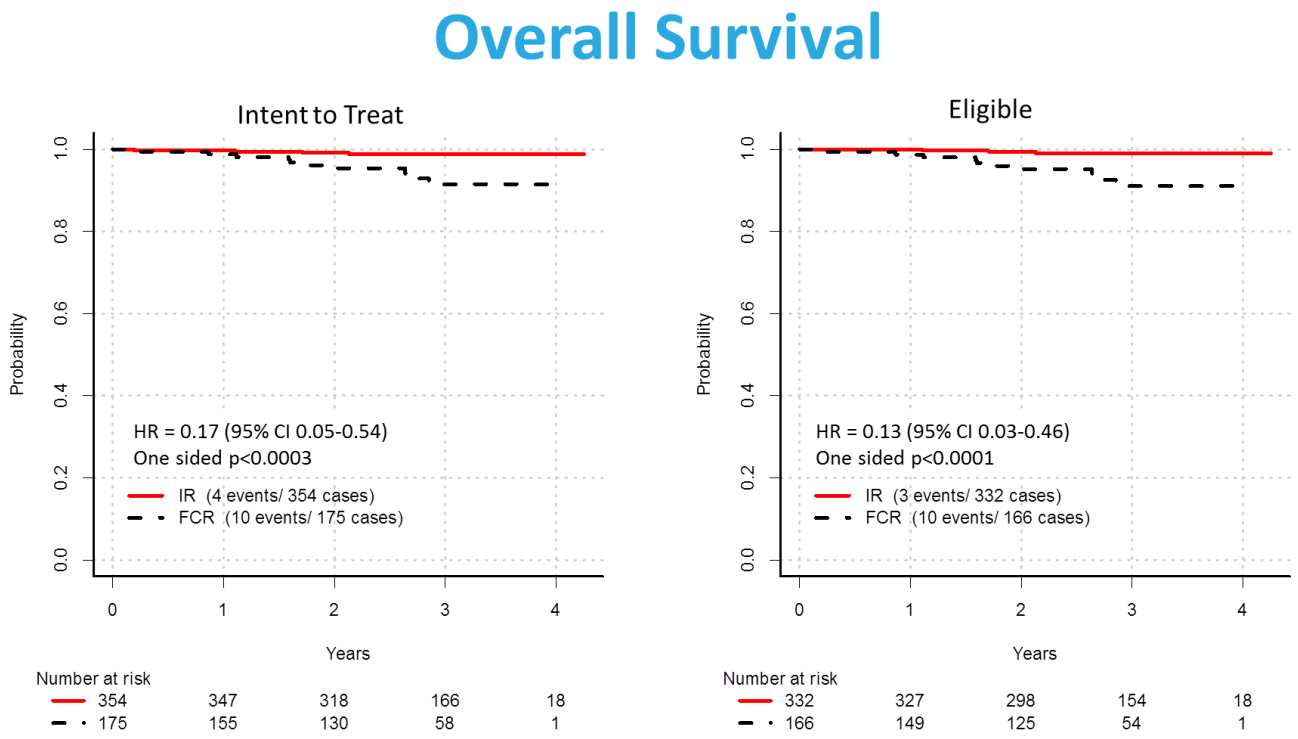
2. ECOG-ACRIN E1912

Progression Free Survival: IGHV Status



ASH 2018, Tait D. Shanafelt, MD et al., LBA-4 A Randomized Phase III Study of Ibrutinib (PCI-32765)-Based Therapy Vs. Standard Fludarabine, Cyclophosphamide, and Rituximab (FCR) Chemoimmunotherapy in Untreated Younger Patients with Chronic Lymphocytic Leukemia (CLL): A Trial of the ECOG-ACRIN Cancer Research Group (E1912)

2. ECOG-ACRIN E1912



ASH 2018, Tait D. Shanafelt, MD et al., LBA-4 A Randomized Phase III Study of Ibrutinib (PCI-32765)-Based Therapy Vs. Standard Fludarabine, Cyclophosphamide, and Rituximab (FCR) Chemoimmunotherapy in Untreated Younger Patients with Chronic Lymphocytic Leukemia (CLL): A Trial of the ECOG-ACRIN Cancer Research Group (E1912)

E1912: Grade 3-5 Treatment-Related AEs Throughout Observation

Grade 3-5 Treatment-Related AE Throughout Observation, %	Ibrutinib + R (n = 352)	FCR (n = 158)	*P* Value
Any grade ≥ 3 AE	58.5	72.1	.004
Neutropenia	22.7	43.7	< .001
Anemia	2.6	12.0	< .001
Thrombocytopenia	2.9	13.9	< .001
Any infection	7.1	19.0	< .001
▪ Infection	5.4	8.2	.24
▪ Neutropenic fever	2.3	15.8	< .001
Atrial fibrillation	2.9	0.0	.04
Bleeding	1.1	0.0	.32
Hypertension	7.4	1.9	.01
Diarrhea	2.6	0.6	.19

- With ibrutinib + R vs FCR, significantly higher rates of AF, HTN (both $P < .05$); significantly lower rates of grade ≥ 3 AEs, myelosuppression, any infection, neutropenic fever (all $P \leq .004$)

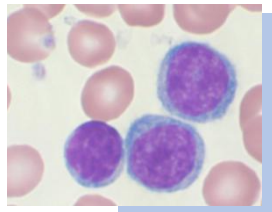
Shanafelt. ASH 2018. Abstr LBA-4.

E1912: Conclusions

- In this primary analysis of a phase III trial, first-line ibrutinib + R showed statistically significant improvement in PFS and OS vs standard-of-care FCR in younger patients with previously untreated CLL (all $P \leq .00003$)
  - HR for PFS in ITT population: 0.35 (95% CI: 0.22-0.50)
  - HR for OS in ITT population: 0.17 (95% CI: 0.05-0.54)
- Ibrutinib + R was well tolerated in this younger patient population
  - Rate of grade ≥ 3 AEs was 58.5% with ibrutinib + R vs 72.1% with FCR ($P = .004$)
  - With ibrutinib + R vs FCR, low but still significantly higher rates of atrial fibrillation (2.9% vs 0%; $P = .04$) and hypertension (7.4% vs 1.9%; $P = .01$)
- Study investigators proposed evaluating need for indefinite treatment in future studies of novel combination therapy
  - Phase III trials assessing ibrutinib + obinutuzumab ± venetoclax in adults: adults aged < 70 yrs, EA9161 (NCT03701282); adults aged ≥ 70 yrs, A041702 (NCT03737981)

Shanafelt. ASH 2018. Abstr LBA-4.

Slide credit: clinicaloptions.com



Drugs and Regimens available x CLL

Chemotherapy

Fludarabine+cyclophosphamide
Bendamustine
Chlorambucil

Immunotherapy

Anti CD20: Rituximab
Ofatumumab
Obinutuzumab
Ublituximab
Anti CD52: Alemtuzumab
Anti CD37: Otelrtuzumab
AGS67E
Anti ROR1: Cirmtuzumab
Anti CD19: MOR00208

BCRi/pi3k inhibitors

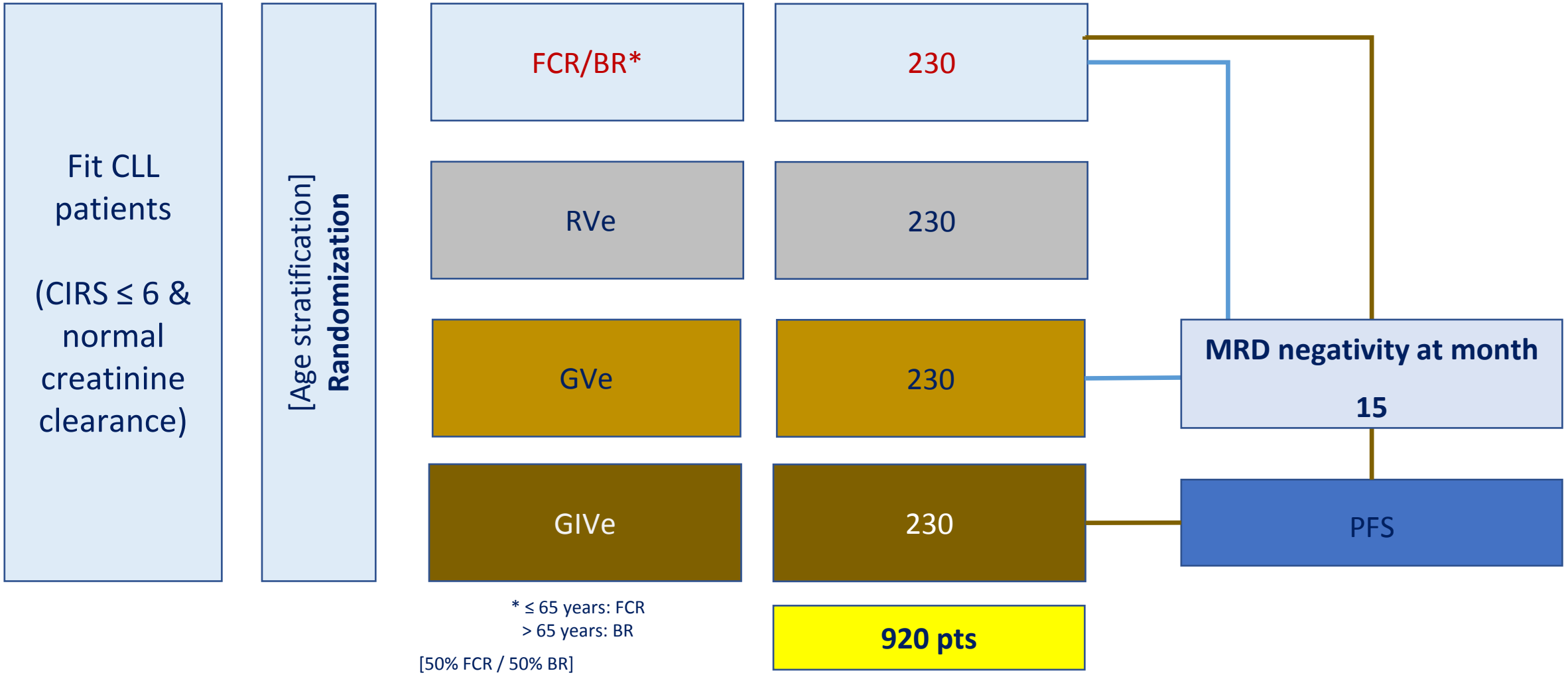
Ibrutinib
Idelalisib
Acalabrutinib
TGR-1202 (umbralisib)
Duvelisib
BGB-3111
ACP-319

BCL2

Venetoclax

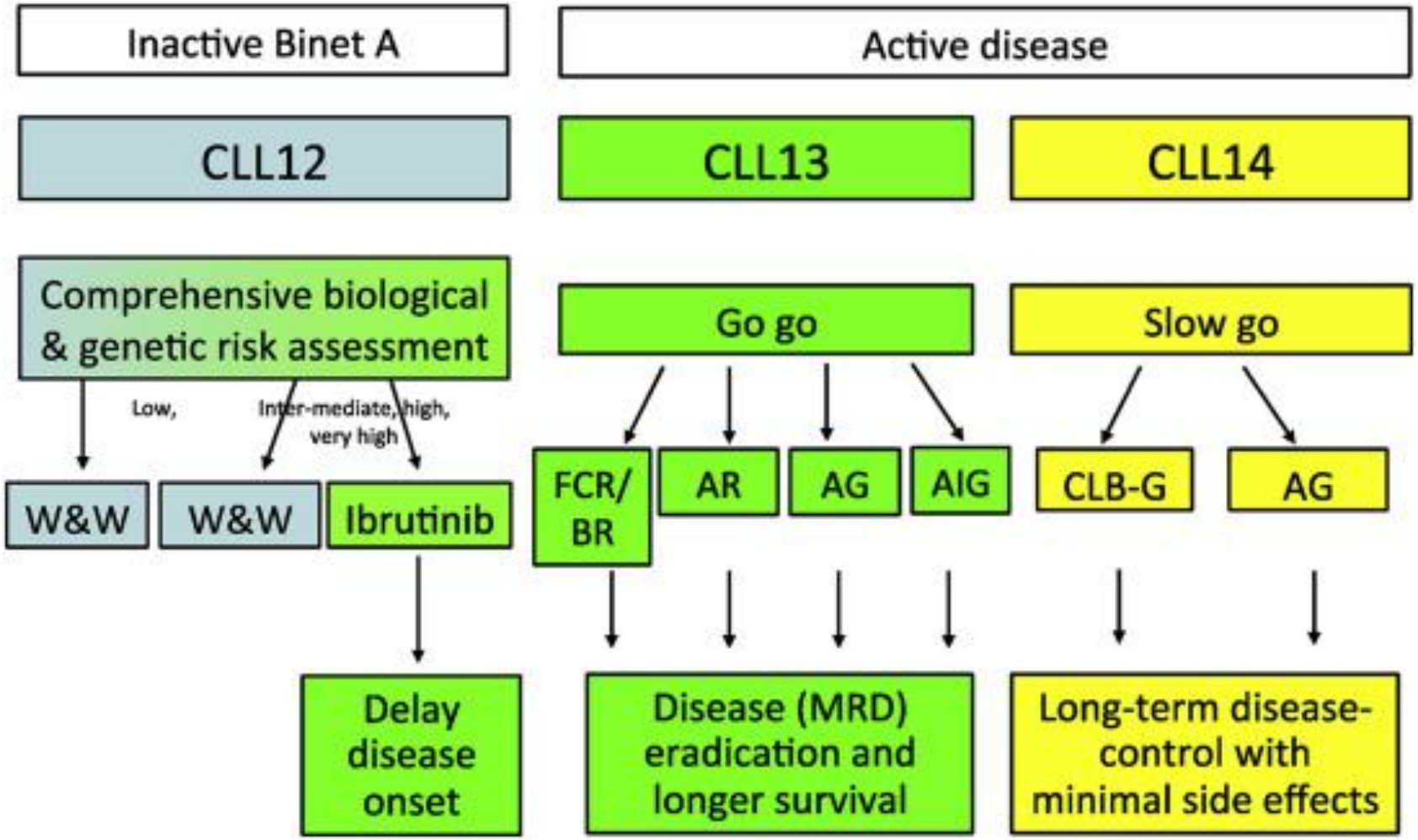
Fit Patients:
GAIA study

Standard chemoimmunotherapy vs. ABT-199 + R vs. ABT-199 + G vs. ABT-199 + I + G

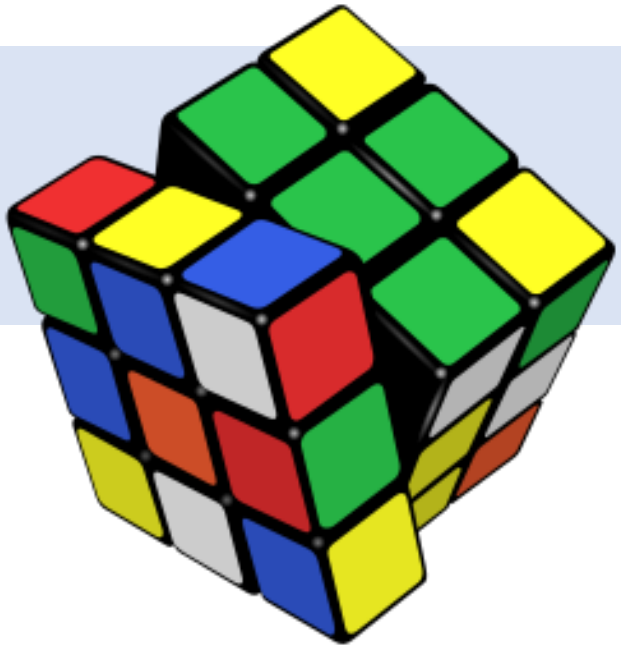


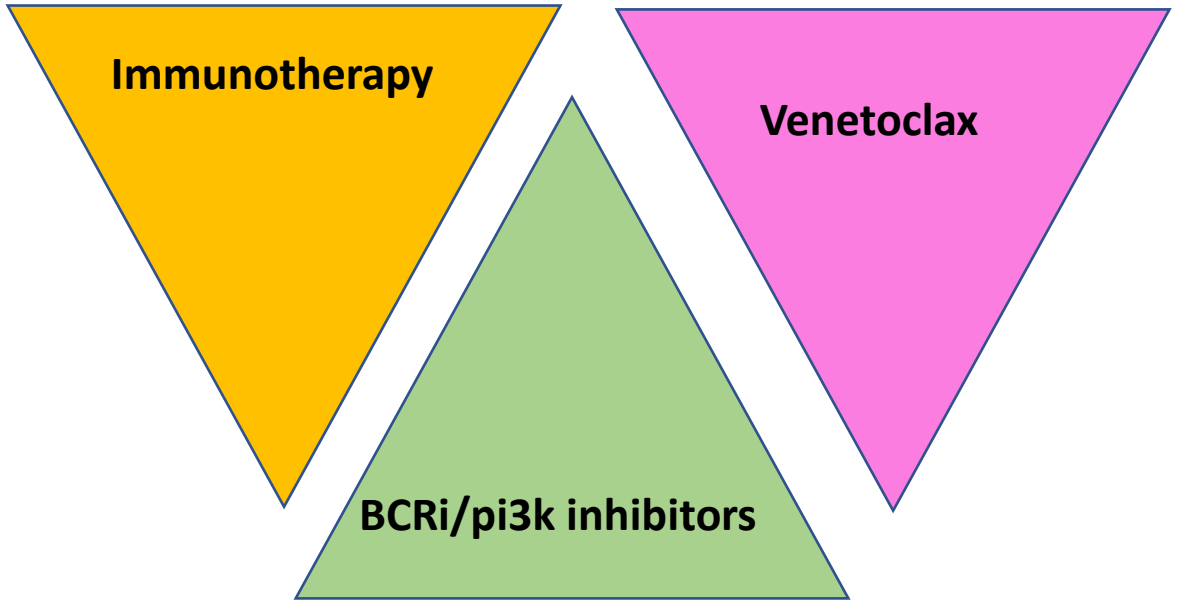
Fourth Generation of GCLLSG Trials

Risk, Stage and Fitness Adapted, Using Targeted Agents



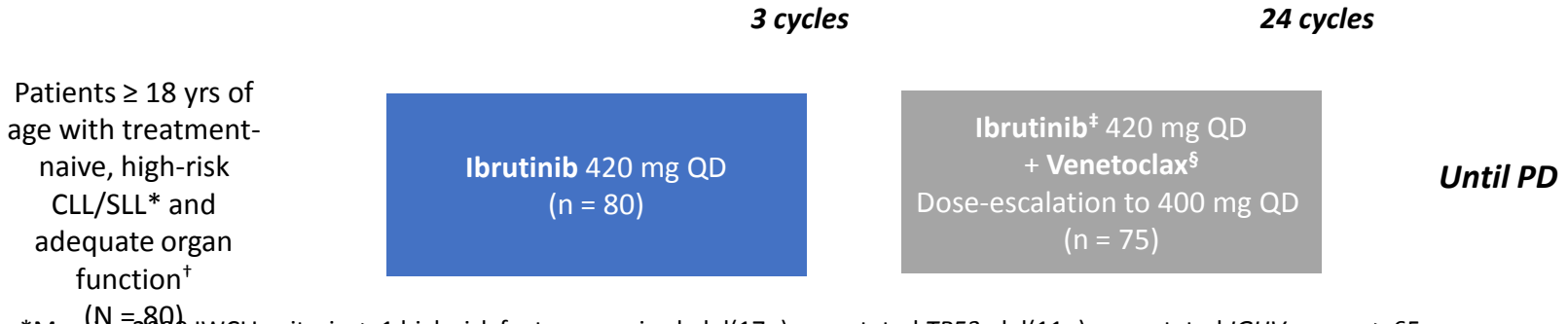
Best combination of therapy?





Ibrutinib + Venetoclax in CLL: Study Design

- Investigator-initiated phase II trial
  - Median follow-up: 14.8 mos (range: 5.6-27.5)



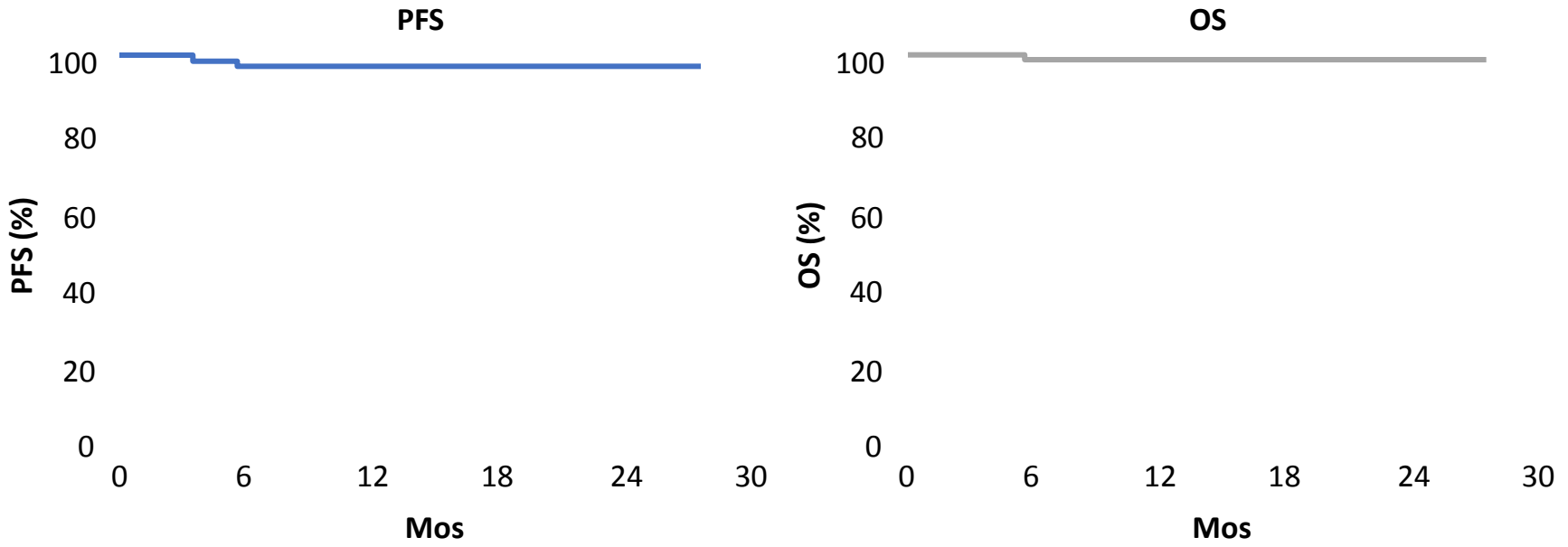
*Meeting 2008 IWCLL criteria; ≥ 1 high risk feature required: del(17p) or mutated *TP53,* del(11q), unmutated *IGHV,* or age ≥ 65 yrs.
†GFR > 50 mL/min; ALT/AST ≤ 3.0 x ULN; total bilirubin ≤ 1.5 x ULN; platelets > 20 K/µL.
‡Ibrutinib stopped at cycle 24 if BM MRD negative (by flow cytometry at 10^{-4}), or if BM MRD positive, until PD.
§Wk 1: 20 mg QD; Wk 2: 50 mg QD; Wk 3: 100 mg QD; Wk 4: 200 mg QD; Wk 5-27: 400 mg QD.
Response evaluations Q3M in Yr 1, Q6M in Yr 2. Any LN > 1.5 cm by CT considered PR.

- Primary endpoint: CR/CRi by 2008 IWCLL criteria

Jain. ASH 2018. Abstr 186.

Slide credit: clinicaloptions.com

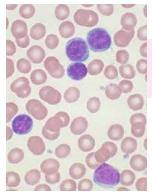
Ibrutinib + Venetoclax in CLL: Survival

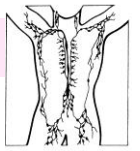


- No patients experienced CLL progression, 1 patient with Richter transformation to DLBCL

Jain. ASH 2018. Abstr 186. Reproduced with permission.

Slide credit: clinicaloptions.com





- CHEMOTHERAPY FREE era for CLL patients
- Effective in all cytogenetic subtypes/risk groups
- Tolerated in all ages
- Use chronically by tablets

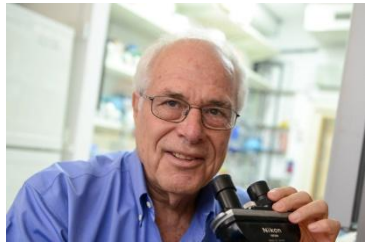
The NEW ENGLAND JOURNAL of MEDICINE

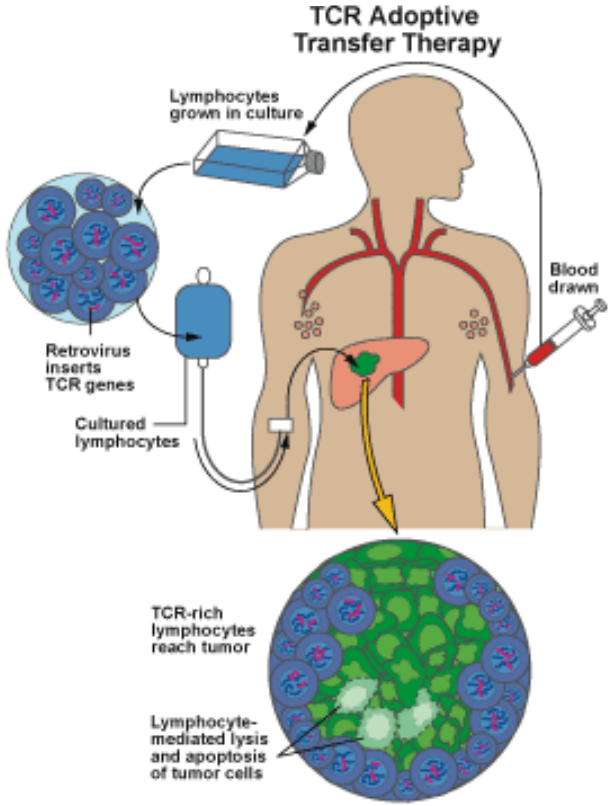
BRIEF REPORT

Chimeric Antigen Receptor–Modified T Cells in Chronic Lymphoid Leukemia

David L. Porter, M.D., Bruce L. Levine, Ph.D., Michael Kalos, Ph.D., Adam Bagg, M.D., and Carl H. June, M.D.

N Engl J Med 2011; 365:725-733





Risk factors associated with Richter's transformation in patients with chronic lymphocytic leukaemia: protocol for a retrospective population-based cohort study.
Hleuhel MH, Ben-Dali Y, Da Cunha-Bang C, Brieghel C, Clasen-Linde E, Niemann CU, Andersen MA.
BMJ Open. 2019 Mar 3;9(3

Limited value of routine follow-up visits in chronic lymphocytic leukemia managed initially by watch and wait: A North **Denmark** population-based study.
Nørgaard CH, Søgaard NB, Biccler JL, Pilgaard L, Eskesen MH, Kjartansdottir TH, Bøgsted M, El-Galaly TC.
PLoS One. 2018 Dec 27;13(12):e0208180. doi: 10.1371/journal.pone.0208180. eCollection 2018.

Epidemiology of bloodstream infections in patients with chronic lymphocytic leukemia: a longitudinal nation-wide cohort study.
Andersen MA, Moser CE, Lundgren J, Niemann CU.
Leukemia. 2019 Mar;33(3):662-670. doi: 10.1038/s41375-018-0316-5. Epub 2018 Dec 13.

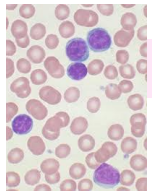
Automated shape-based clustering of 3D immunoglobulin protein structures in chronic lymphocytic leukemia.
Polychronidou E, Kalamaras I, Agathangelidis A, Sutton LA, Yan XJ, Bikos V, Vardi A, Mochament K, Chiorazzi N, Belessi C, Rosenquist R, Ghia P, Stamatopoulos K, Vlamos P, Chailyan A, Overb Marcatili P, Hatzidimitriou A, Tzovaras D.
BMC Bioinformatics. 2018 Nov 20;19(Suppl 14):414. doi: 10.1186/s12859-018-2381-1

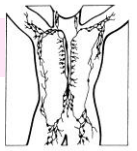
Venous thromboembolism in chronic lymphocytic leukemia: a Danish nationwide cohort study.
Gade IL, Riddersholm SJ, Christiansen I, Rewes A, Frederiksen M, Enggaard L, Poulsen CB, Bergmann OJ, Gillström DB, Pedersen RS, Nielsen L, Eriksen HH, Torp-Pedersen C, Kristensen SR, Severinsen MT.
Blood Adv. 2018 Nov 13;2(21):3025-3034. doi: 10.1182/bloodadvances.2018023895.

Cytomegalovirus-associated haemophagocytic lymphohistiocytosis: a rare cause of febrile neutropenia during cancer chemotherapy.
Bergmann K, Møller HEH, Bergmann OJ.
BMJ Case Rep. 2018 Sep 14;2018. pii: bcr-2018-225592. doi: 10.1136/bcr-2018-225592.

Chronic lymphocytic leukemia patients with heterogeneously or fully methylated LPL promotor display longer time to treatment.
Daugaard I, Hussmann D, Kristensen L, Kristensen T, Kjeldsen TE, Nyvold CG, Larsen TS, Møller MB, Hansen LL, Wojdacz TK.
Epigenomics. 2018 Sep;10(9):1155-1166. doi: 10.2217/epi-2018-0020. Epub 2018 Sep 5.

Cardiovascular disease in chronic myelomonocytic leukemia: do monocytosis and chronic inflammation predispose to accelerated atherosclerosis?
Elbæk MV, Sørensen AL, Hasselbalch HC.
Ann Hematol. 2019 Jan;98(1):101-109.



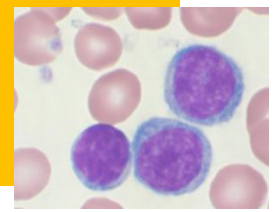


Thank you

TAK

Outcomes of Ibrutinib-Treated Patients With Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia With High-Risk Prognostic Factors in an Integrated Analysis of 3 Randomized Phase 3 Studies."

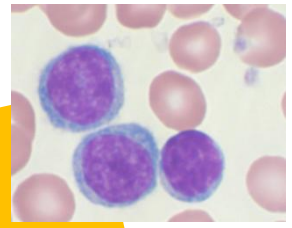
Kipps T. ICML/IwCLL2017



Data from the following trials were pooled
RESONATE (42 months FU),
RESONATE-2 (36 months FU)
HELIOS (32 months FU)

Analyzed based on:
*IGHV mutational status,
*del(11q)
*trisomy 12,
*complex karyotype.
*Impact of del(17p) was not assessed

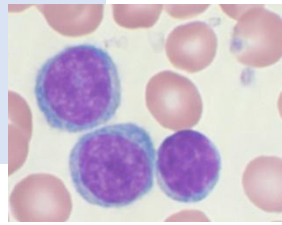
	IGHV		Trisomy 12		Complex Karyotype		Del 11q	
	Unmut (n=344)	Mut (n-113)	With (n=90)	Without (n=314)	With (n=41)	Without (n=338)	With (n=168)	Without (n=382)
42 months OS%	78	84	82	80	77	78	80	78
Log-rank	0.41		0.92		0.91		0.08	
P value	1.21		1.02		0.96		0.08	



Results suggest that genomic risk factors associated with poor outcomes using traditional therapies have less relevance with ibrutinib treatment

Durability of Responses on Continuous Therapy and Following Drug Cessation in Deep Responders with Venetoclax and Rituximab."

Danielle Brander; Duke Cancer Institute IWCLL 2017



49 patients with venetoclax plus rituximab

↓

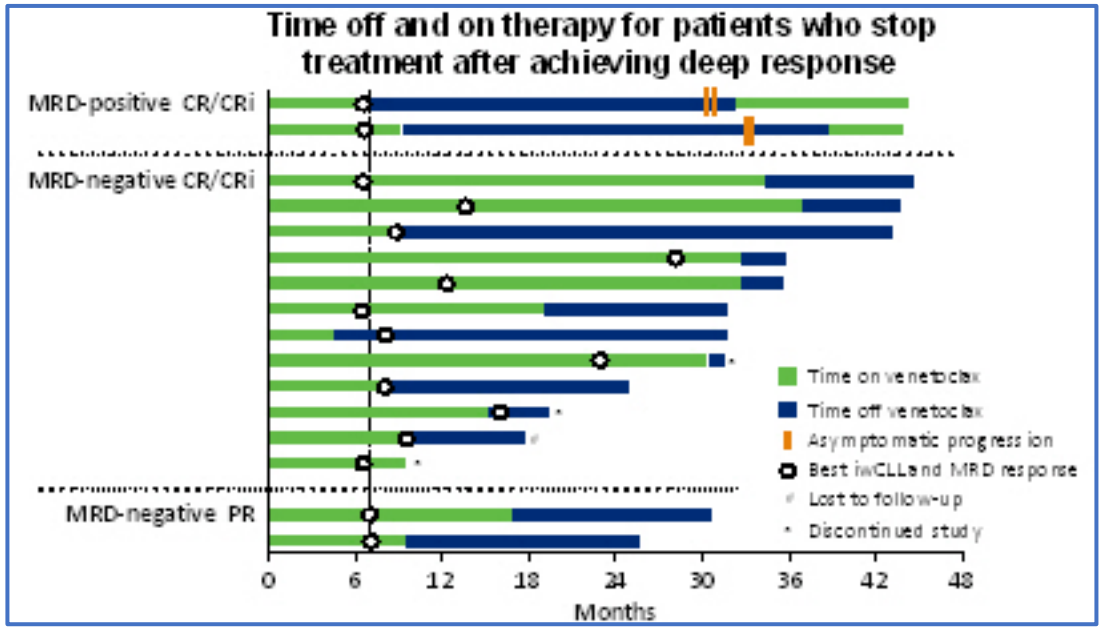
Tx till complete remission (CR) or minimal residual disease (MRD)-achieved

↓

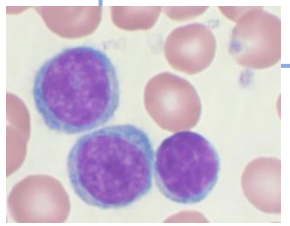
Discontinue venetoclax

↓

Patients with progressive disease after discontinuation could reinitiate the same combination.



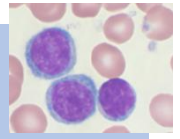
12 Patients had durable remissions after elective treatment cessation (10 ongoing)
None of the patients who achieved MRD-negativity have progressed off therapy (median time 20 months)

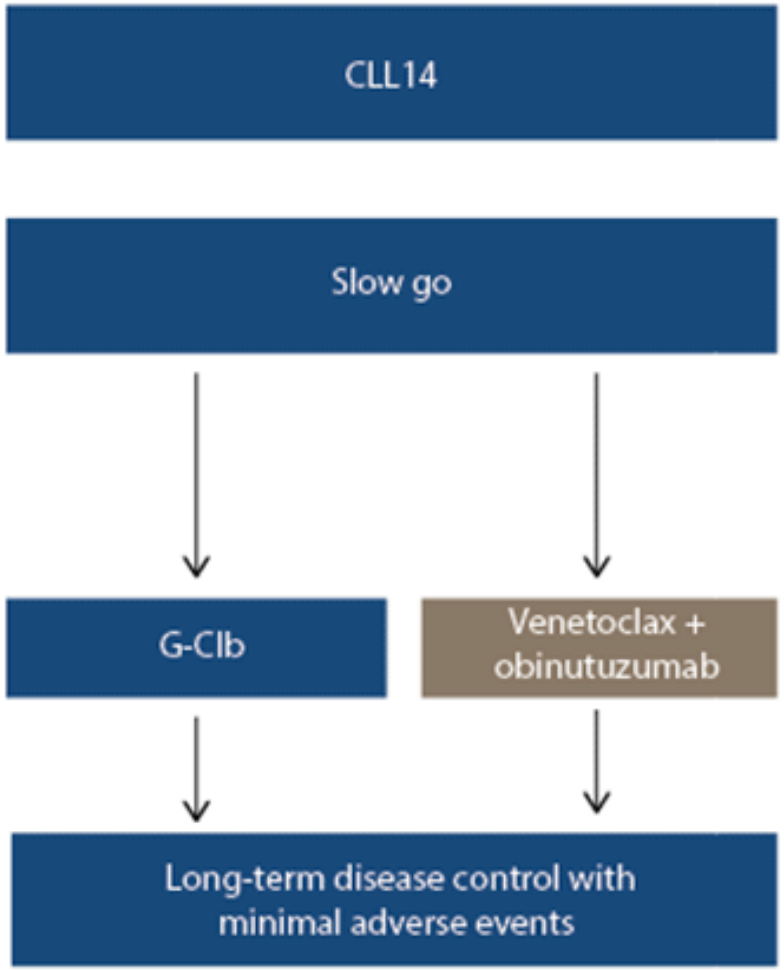


Possible to discontinue venetoclax after achieving a deep response and to maintain treatment –free remission

CLL14: (the successor trial to CLL11)

A Prospective, Open-Label, Multicenter Randomized Phase III Trial to Compare the Efficacy and Safety of Obinutuzumab and Venetoclax with Obinutuzumab and Chlorambucil in Patients with Previously Untreated CLL / *Kirsten Fischer*





- **12 previously untreated patients** with coexisting medical conditions assessed by cumulative illness rating scale (**CIRS) total score > 6** and/or estimated creatinine clearance (CrCl) < 70 mL/min requiring treatment

STUDY DESIGN:

- All patients received **6 cycles of obinutuzumab and venetoclax** followed by **6 additional cycles of venetoclax**.
- Obinutuzumab was administered intravenously with 100 mg on day 1, 900 mg on day 2 (option to deliver 1000 mg on day 1), 1000 mg on day 8 and day 15 of cycle 1 and 1000 mg on day1 for cycles 2-6.
- A gradual weekly dose ramp-up of venetoclax with 20 mg, 50 mg, 100 mg, 200 mg up to 400 mg was administered **starting at day 22** of cycle 1

Figure 1

	TOTAL N (%)
All patients, N	13
Demographic and baseline characteristics	
Gender, N (%)	
Male	8 (61.5)
Female	5 (38.5)
Age (years), N (%)	
Median (range)	75.0 (59 – 88)
≥ 70	11 (84.6)
Binet Stage, N (%)	
A	2 (15.4)
B	4 (30.8)
C	7 (53.8)
CIRS Score (total)	
Median (range)	8 (6 – 14)
CrCl (ml/min)	
Median (range)	57.6 (30.3 – 108.2)

CrCl, creatinine clearance

- No clinical TLS was reported.
- Two patients developed laboratory TLS
- None of the protocol defined stopping criteria for the safety run-in phase of the study were met.
- Neither event resulted in interruption or dose modification of study treatment.
- Rapid reduction in the peripheral lymphocyte count was observed in all 12 patients treated with the combination regimen

- **The randomized phase of the CLL14 trial ended in Aug 2016**

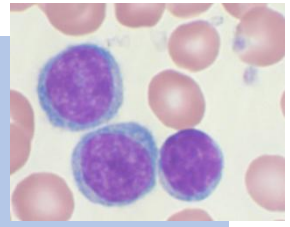
Conclusion:

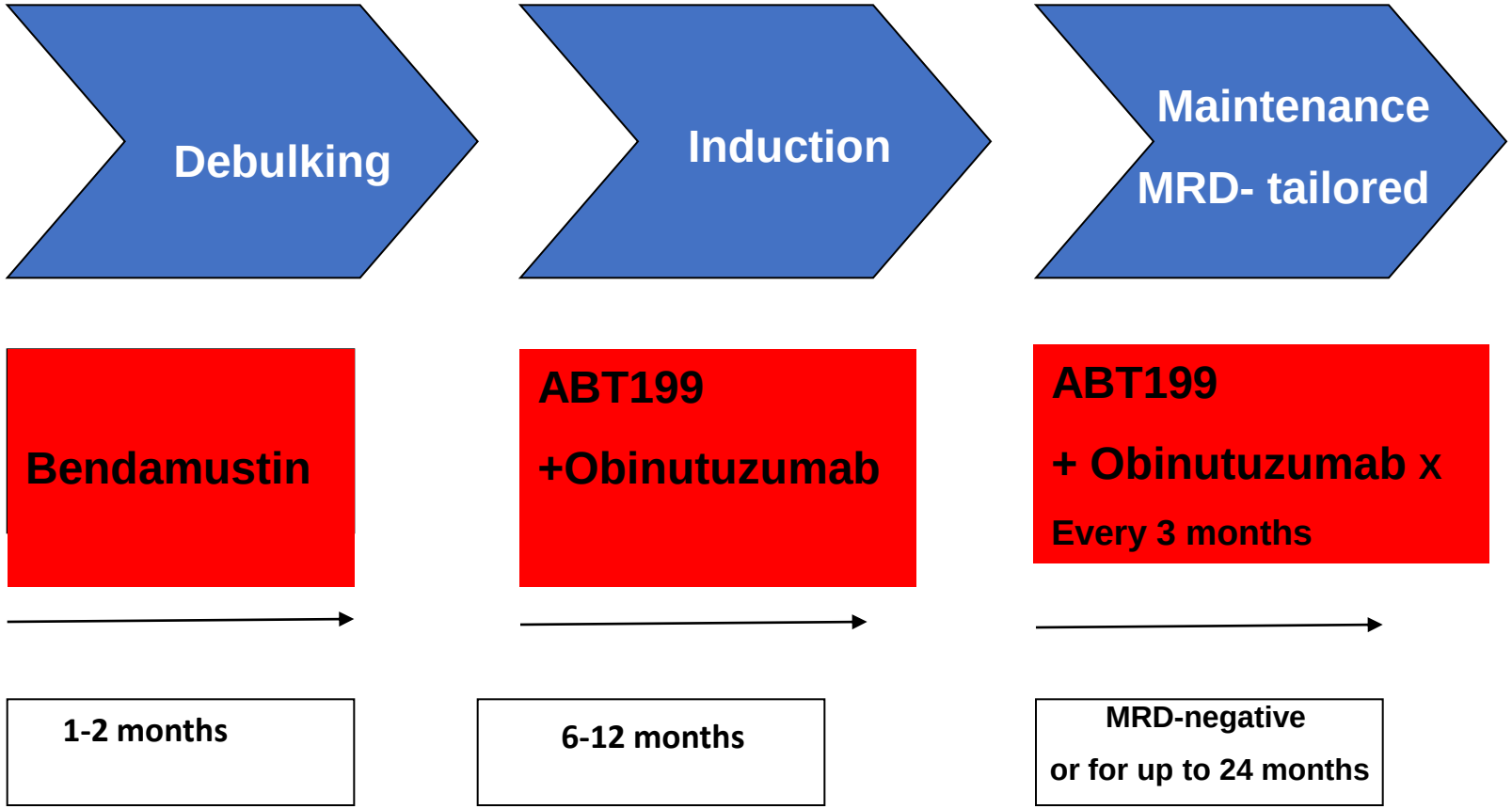
These preliminary data suggest that VEN + G can be safely administered in pts with CLL with no difference in tolerability between R/R and TN subgroups.

A phase 3 study evaluating VEN+G is ongoing.

BAG trial of GCLLSG/sequential triple-T”

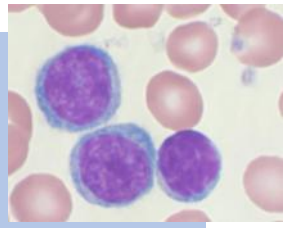
Paula Cramer/EHA-1233





BAG trial of GCLLSG/sequential triple-T”

EHA-1233



- 66 pts were enrolled; 34 pts were treatment-naïve and 29 had R/R CLL (median number of prior therapies: 2, range: 1-8).
- Median age was 59 (28-77)years
- Median CIRS score was 2 (0-14)
- 11 of 59 pts (19%) had a del(17p) and 45 of 61 (74%) had an unmutated IGHV status.

Results:

- 60 pts completed 6 induction cycles with G and A.
- All TN (100%) and all but two of the R/R pts (93%) responded with an ORR of 97% at the end of induction
- MRD negativity ($<10^{-4}$ by flow cytometry) in peripheral blood (pb) was achieved in 56 pts (89%);

Conclusion:

Very efficacious in a heterogeneous study population and well tolerated except

for 3 fatal septicaemias in R/R pts.

A041202: Study Design

- Multicenter, randomized, double-blind phase III study (data cutoff: October 4, 2018)

Stratified by Rai stage (high vs intermediate risk), del(11q22.3) or del(17p13.1) (presence vs absence), ZAP-70 methylation (< vs ≥ 20%)

Untreated patients with CLL meeting IWCLL 2008 criteria for tx initiation; aged ≥ 65 yrs; EGOG PS 0-2; ANC ≥ 1000 unless due to BM involvement; PLT ≥ 30; $CrCl_{CG}$ ≥ 40; AST/ALT ≤ 2.5 x ULN; no heparin or warfarin (N = 547)

Ibrutinib 420 mg QD (n = 182)	***Until PD***
Ibrutinib 420 mg QD + **Rituximab** 375 mg/m^2 wkly x 4 wks starting cycle 2 Day 1; cycles 3-6 Day 1* (n = 182)	***Ibrutinib until PD***
Bendamustine 90 mg/m^2 on Days 1, 2 + **Rituximab** 375 mg/m^2 on cycle 1 Day 1; 500 mg/m^2 on cycles 2-6 Day 1* (n = 183)	***Crossover to ibrutinib w/n 1 yr of PD allowed***

*28-day cycles.

- Primary endpoint: PFS
  - 2 primary comparisons of ibrutinib vs BR and ibrutinib + R vs BR with 90% power to detect HR of 0.586 (estimated 2-yr PFS rates: ibrutinib, 75%; BR, 61%) and overall 1-sided α = 0.025 for each comparison
  - If both primary comparisons significant, third planned comparison of ibrutinib + R vs ibrutinib

Woyach. ASH 2018. Abstr 6. Woyach. NEJM. 2018;[Epub].