WELCOME & INTRODUCTIONS

Update on Chronic Lymphocytic Leukemia (CLL)

To register or to view the BCC schedule, visit www.LLS.org/bcc.

Rocky Mountain Blood Cancer Conference Aurora, CO **May 4, 2019**	Texas Blood Cancer Conference San Antonio, TX **May 18, 2019**

Program will begin shortly

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DISCLOSURE

Update on Chronic Lymphocytic Leukemia (CLL)

Jan A. Burger, MD, PhD, has no disclosures.

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The Rai System for Clinical Staging of CLL

Stage	3-Stage System	Features	Median Survival(y)
0	Low risk	Lymphocytosis	>10
I	Intermediate risk	Lymphadenopathy	7
II		Splenomegaly ± hepatomegaly	
III	High risk	Anemia	2-5
IV		Thrombocytopenia	

Rai et al. Blood. 1975;46:219-234.

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Prognostic Factors Associated With Inferior Survival

- Advanced stage at diagnosis
- Short lymphocyte doubling time
- Diffuse pattern of marrow infiltration
- Advanced age/males
- High serum levels of β_2-microglobulin
- CLL–PLL

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Genomic Aberrations In CLL Interphase FISH Results 82% Abnormal

Abnormality	No. Patients (%)
13q deletion	178(55)
11q deletion	58(18)
trisomy 12	53(16)
17p deletion	23(7)
6q deletion	21(6)

Dohner et al. NEJM 343:1910, 2000

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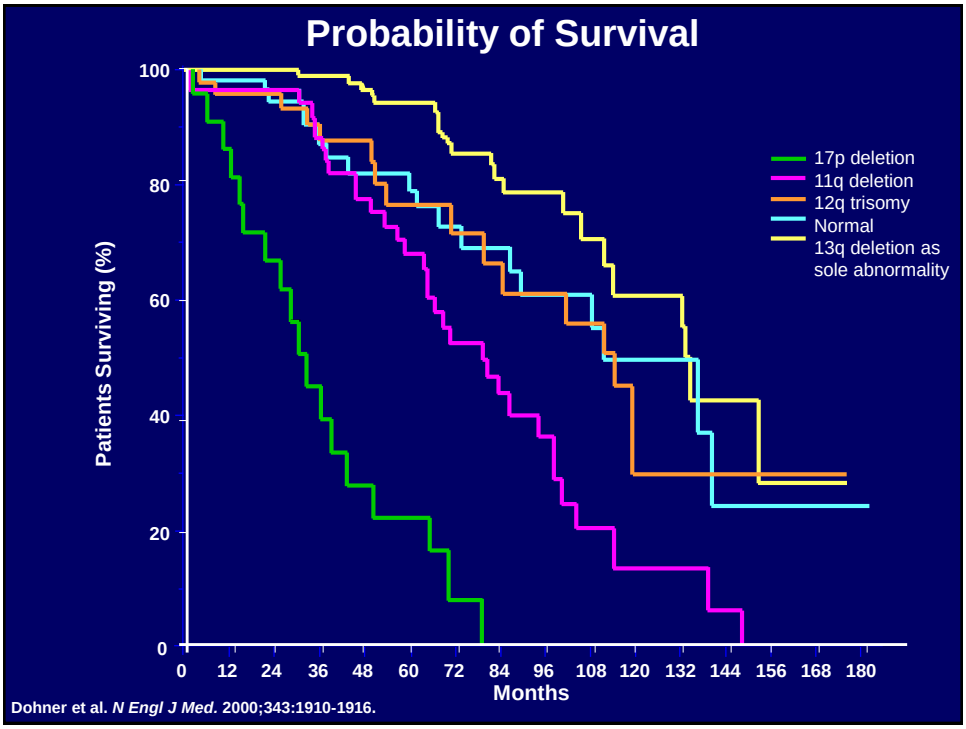

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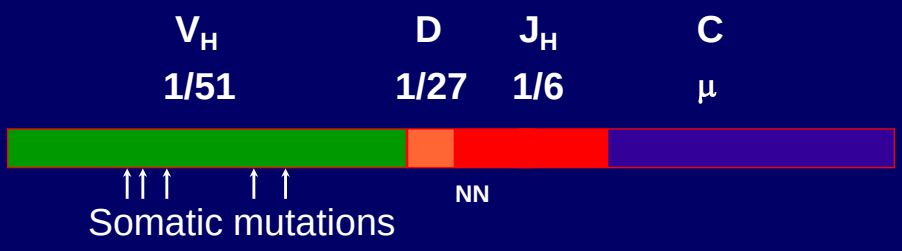
B-Cell Diversity: V_H Rearrangement and Mutation



V_H in B-cell chronic lymphocytic leukemia

- **Somatic mutations (<98% homology)**

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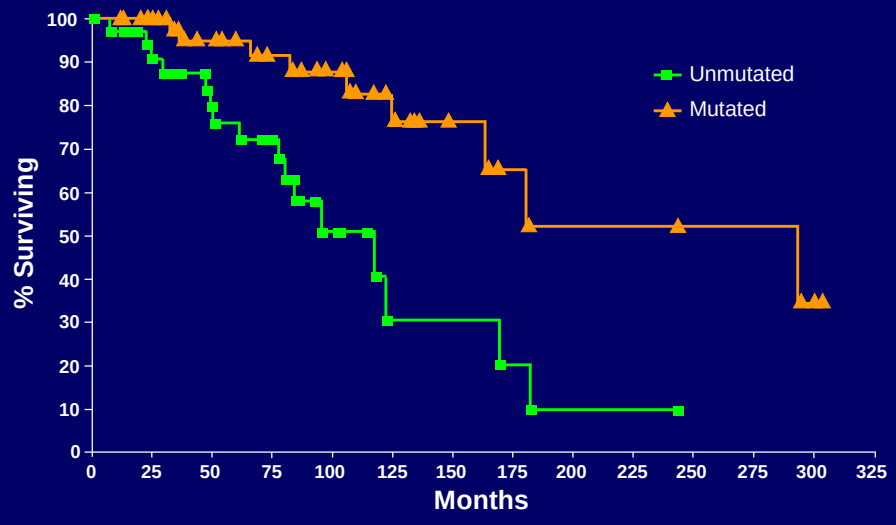
Comparison of CLL Patients With Mutated and Unmutated V_H Genes



Hamblin et al. *Blood.* 1999;94:1848-1854.

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Prognostic Factors in CLL

Parameter	Bad
B_2Microglobulin	increased
FISH	11q-, 17p-
IGHV Mutation Status	unmutated
CD38	positive
ZAP70	positive
Complex karyotype +/- *TP53* disruption	predicts for relapse after venetoclax and ibrutinib
New genomic predictors	*NOTCH1*, *SF3B1*, *RPS15*, and *PAX5*, telomere length

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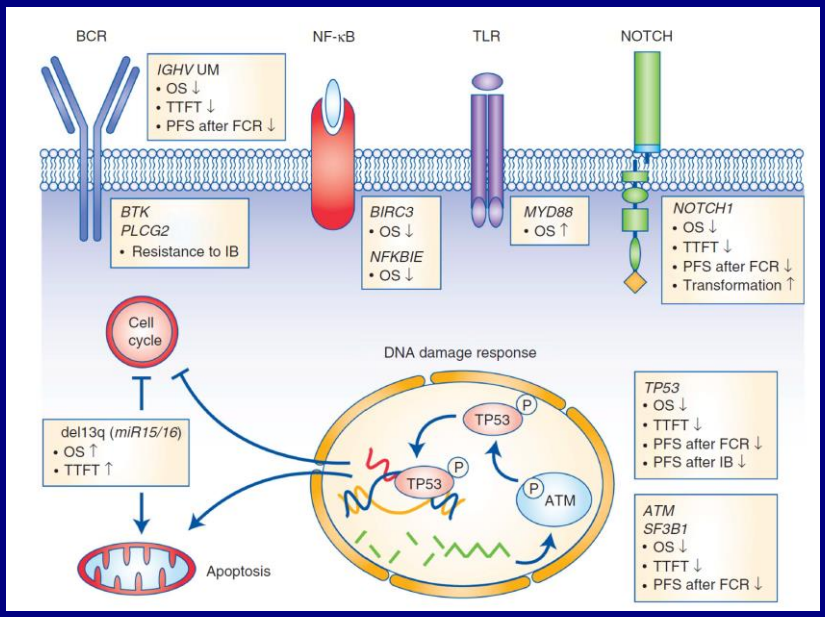
Prognostic Factors in CLL



From: Rossi D British Journal of Cancer **114**:849–854 (2016).

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IWCLL-NCI: Indications to Initiate Treatment for CLL

- **Constitutional symptoms referable to CLL**
- **Progressive marrow failure**
- **Autoimmune anemia +/- thrombocytopenia poorly responsive to steroids or other**
- **Massive (>6 cm) or progressive splenomegaly**
- **Massive (>10 cm) or progressive lymphadenopathy**
- **Progressive lymphocytosis, >50% increase over 2 months or LDT < 6 months.**

Hallek et al Blood 2018;131:2745.

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CLL
Treatment Options

1960s | 1970s | 1980s | 1990s | 2000s | 2010s

Alkylating agents
- **Chlorambucil**
- **Cyclophosphamide**

Glucocorticoids

Purine nucleosides
- **Fludarabine**
- **Pentostatin**
- **Cladribine**

Purine nucleosides and alkylators

Chemo-immunotherapy
Alemtuzumab
Bendamustine

Kinase inhibitors
Obinutuzumab
BCL-2 antagonists

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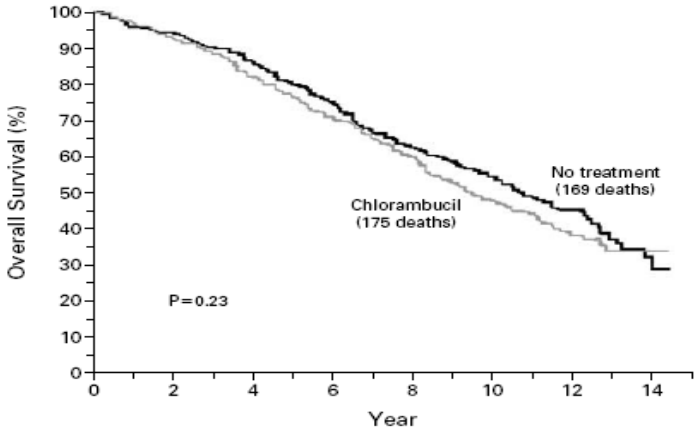
Survival: Daily Chlorambucil Versus Observation



No. at Risk

Chlorambucil	301	296	283	277	264	246	230	205	191	179	132	86	54	26	2
No treatment	308	291	284	266	247	230	213	196	179	159	114	70	39	17	7

Dighiero et al N Eng J Med 338(21):1506-14,1998.

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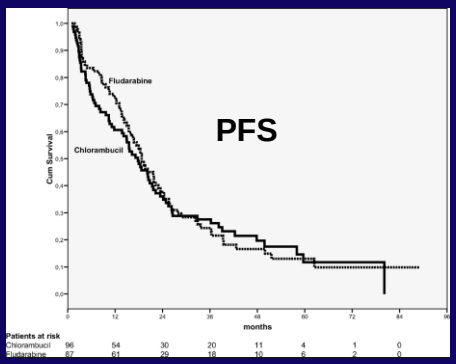
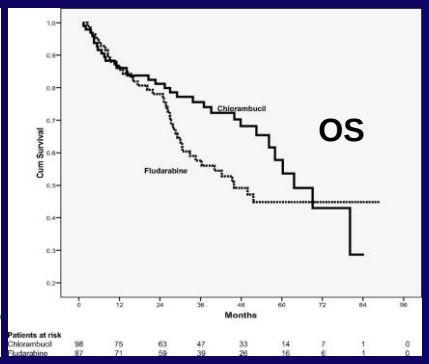
DCLLSG CLL5 trial: CLB vs F





<u>Conclusion:</u> In elderly CLL patients first-line therapy with fludarabine does not result in a major clinical benefit compared with chlorambucil

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VOLUME 23 · NUMBER 18 · JUNE 20 2005

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Early Results of a Chemoimmunotherapy Regimen of Fludarabine, Cyclophosphamide, and Rituximab As Initial Therapy for Chronic Lymphocytic Leukemia

Michael J. Keating, Susan O'Brien, Maher Albitar, Susan Lerner, William Plunkett, Francis Giles, Michael Andreeff, Jorge Cortes, Stefan Faderl, Deborah Thomas, Charles Koller, William Wierda, Michelle A. Detry, Alice Lynn, and Hagop Kantarjian

From the Departments of Leukemia, Hematopathology, Experimental Therapeutics, Blood and Marrow Transplantation, and the Biostatistics and Applied Mathematics, The University of Texas M.D. Anderson Cancer Center, Houston, TX.

Submitted December 9, 2003; accepted November 11, 2004.

A B S T R A C T

Purpose

Fludarabine and cyclophosphamide (FC), which are active in treatment of chronic lymphocytic leukemia (CLL), are synergistic with the monoclonal antibody rituximab in vitro in lymphoma cell lines. A chemoimmunotherapy program consisting of fludarabine, cyclophosphamide, and rituximab (FCR) was developed with the goal of increasing the complete remission (CR) rate in previously untreated CLL patients to ≥ 50%.

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Response to FC + Rituximab (NCI-WG: 300 Patients)

Response*	# Pts.	(%)	
CR	217	(72)	95%
Nodular PR	31	(10)	
PR	37	(12)	
No Response	13	(4)	
Early Death	2	(1)	

*** Evaluated 6 months after last course**

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Phase III CLL10: Final Analysis of FCR vs BR in Pts With Advanced CLL

Pts with untreated, active CLL without del(17p) and good physical fitness (CIRS ≤ 6, creatinine clearance ≥ 70 mL/min) (N = 564)

FCR
Fludarabine 25 mg/m^2 IV Days 1-3 + Cyclophosphamide 250 mg/m^2 Days 1-3 + Rituximab 375 mg/m^2 IV Day 0, cycle 1 + Rituximab 500 mg/m^2 IV Day 1, cycles 2-6

BR
Bendamustine 90 mg/m^2 IV Days 1-2 + Rituximab 375 mg/m^2 Day 0, cycle 1 + Rituximab 500 mg/m^2 IV Day 1, cycles 2-6

- Primary endpoint: noninferiority of BR vs FCR for PFS with HR (λBR/FCR) < 1.388

Eichhorst B, et al. ASH 2014. Abstract 19.

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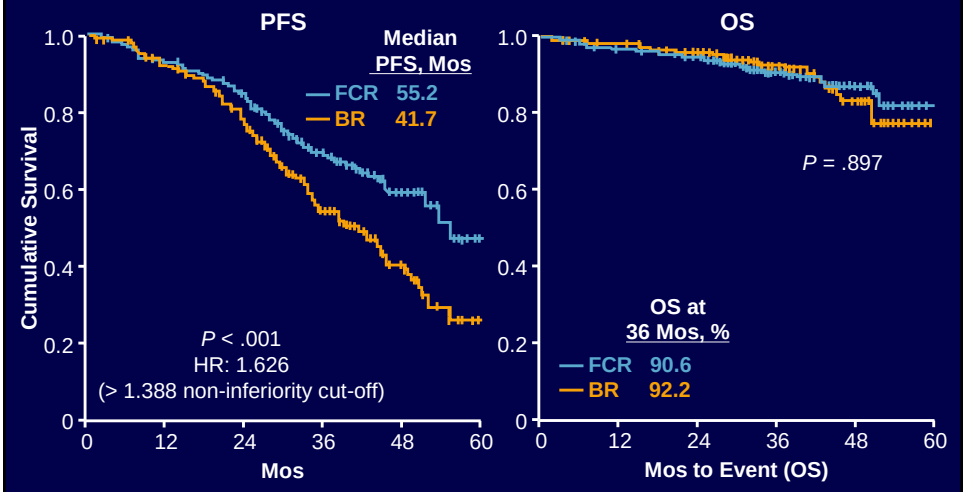
CLL10: PFS (Primary Endpoint) and OS With FCR vs BR in Pts With Advanced CLL



Eichhorst B, et al. ASH 2014. Abstract 19.

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CLL10: Adverse Events With FCR vs BR in Pts With Advanced CLL

Adverse Event, %	FCR (n = 279)	BR (n = 278)	P Value
Neutropenia	84.2	59.0	< .001
Anemia	13.6	10.4	.20
Thrombocytopenia	21.5	14.4	.03
Infection	39.1	26.8	< .001
Secondary neoplasm*	6.1	3.6	.244
Treatment-related mortality	4.6	2.1	.107
▪ Infections	2.5	2.1	--
▪ Secondary neoplasm	1.1	0	--
▪ Other	1.0		

*sAML/MDS: FCR = 6, BR = 1

Eichhorst B, et al. ASH 2014. Abstract 19.

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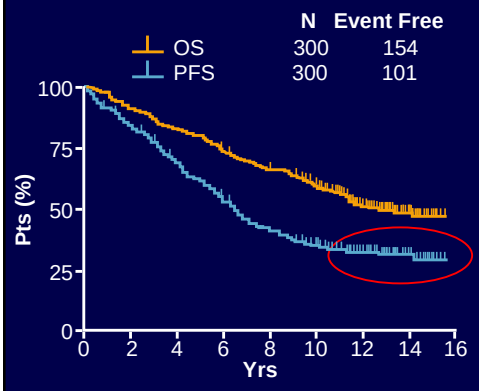
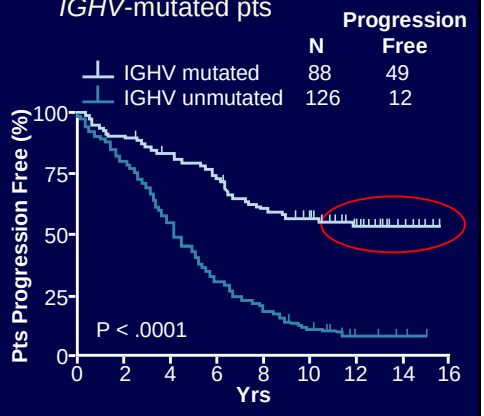
FCR300 Phase II Trial: Plateau in PFS with FCR as Initial Therapy for CLL

- With extended follow-up, PFS shows plateau at Yrs 10-11
- Last relapses occurred around Yr 10, with a plateau in PFS for *IGHV*-mutated pts





Thompson PA, et al. Blood. 2015 Oct 22.

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THE UNIVERSITY OF TEXAS MD ANDERSON CANCER CENTER

Ibrutinib, Fludarabine, Cyclophosphamide, and Obinutuzumab (iFCG) for Firstline Treatment of Patients with CLL with Mutated IGHV and without TP53 Aberrations

Nitin Jain, Philip Thompson, Jan Burger, Alessandra Ferrajoli, Gautam Borthakur, Prithviraj Bose, Zeev Estrov, Tapan Kadia, Koichi Takahashi, Naveen Garg, Xuemei Wang, Rashmi Kanagal-Shamanna, Keyur Patel, Wanda Lopez, Ana Ayala, William Plunkett, Varsha Gandhi, Hagop Kantarjian, Susan O'Brien, Michael Keating, William Wierda

Department of Leukemia, MDACC

ASH 2018, Abstract 185

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Treatment Schema
iFCG Courses 1-3

	Course 1						Courses 2-3		
	D1	D2	D3	D4	D8	D15	D1	D2	D3
Obinutuzumab (mg)	100	900	-	-	1000	1000	1000	-	-
Fludarabine ($25\ mg/m^2$)	-	X	X	X	-	-	X	X	X
Cyclophosphamide ($250\ mg/m^2$)	-	X	X	X	-	-	X	X	X
Ibrutinib	420 mg daily continuous								

Antiviral prophylaxis with acyclovir / valacyclovir was required
PJP prophylaxis was optional
Prophylactic G-CSF was optional in the early part of the trial (now required)

iFCG in *IGHV*-M CLL, ASH 2018, Abs 185.

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iFCG Trial: Study Design

iFCG 3 courses

↓

Ibrutinib for 9 courses (all pts)
+
Obinutuzumab for 3 courses (if CR/CRi with BM U-MRD4)
or
Obinutuzumab for 9 courses (if PR and/or BM MRD^{pos})

↓

After 12 courses
BM U-MRD4 → stop ibrutinib
BM MRD^{pos} → continue ibrutinib

iFCG in *IGHV*-M CLL, ASH 2018, Abs 185.

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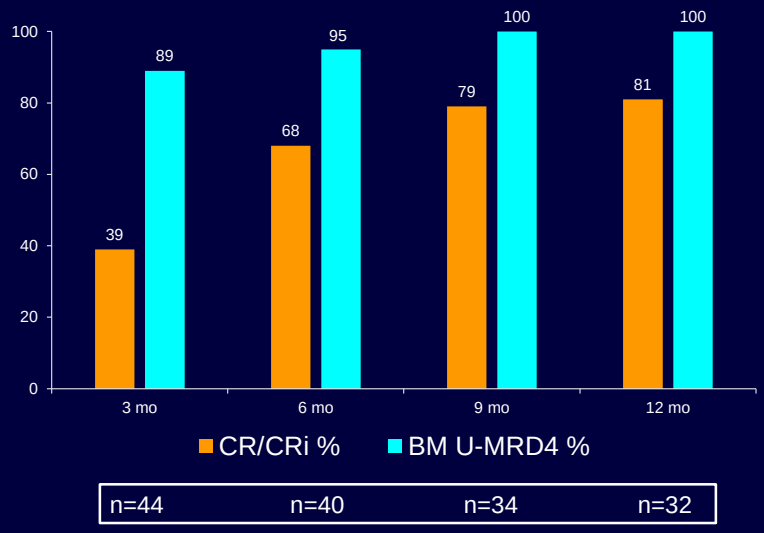
Responses Improve with Time



iFCG in *IGHV*-M CLL, ASH 2018, Abs 185.

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Treatment Discontinuation at 1 Year

- 32 pts reached 1-yr follow-up
  - All 32 had BM U-MRD4 (26 CR/CRi, 6 PR) and discontinued ibrutinib
  - Median follow-up after stopping ibrutinib 13.6 months (range 1.4-20.7)
  - No pt had MRD or clinical relapse

iFCG in *IGHV*-M CLL, ASH 2018, Abs 185

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What About Treatment for Older Patients With CLL?

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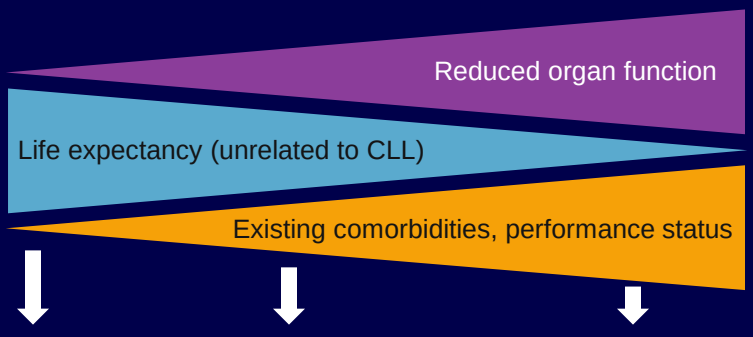
Goals of Frontline Treatment for Older Pts With CLL



Goal:	MRD negative	Good response	Palliation
Priority:	Efficacy	Efficacy and tolerability	Low toxicity

Shanafelt T. Hematology Am Soc Hematol Educ Program. 2013;2013:158-167.

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Phase III CLL11 Trial: Chlorambucil Alone vs With Obinutuzumab vs With Rituximab

Previously untreated CLL pts with comorbidities (CIRS score > 6 and/or CrCl < 70 mL/min) (N = 781)

Chlorambucil
0.5 mg/kg PO on Days 1, 15 x 6 cycles
(n = 118)

Obinutuzumab
1000 mg IV cycle 1 on Days 1, 8, 15; cycles 2-6 on Day 1
Chlorambucil
(n = 333)

Rituximab
375 mg/m^2 IV cycle 1 on Day 1; 500 mg/m^2 cycles 2-6 on Day 1
Chlorambucil
(n = 330)

Goede V, et al. ASH 2013. Abstract 6.
Goede V, et al. N Engl J Med. 2014;370:1101-1110.

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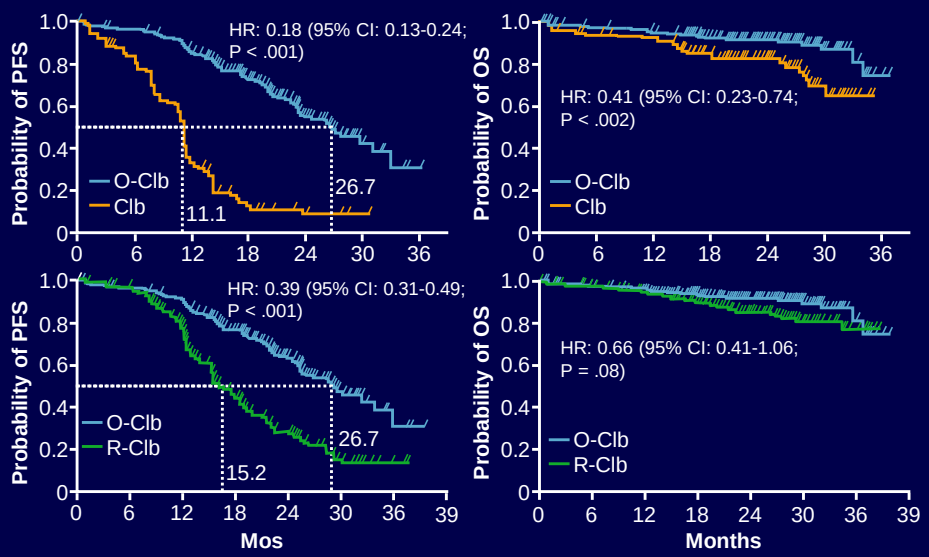
CLL11: Survival with Clb/Obinutuzumab vs Clb Alone or Clb/Rituximab in CLL



Goede V, et al. N Engl J Med. 2014;370:1101-1110.

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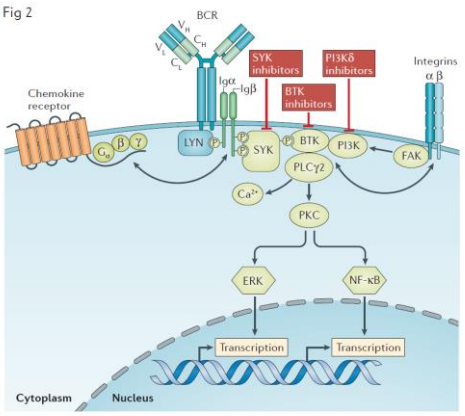
Breakthrough in CLL therapy:
Targeting BCR signaling



Burger & O'Brien Nat Rev Clin Onc 2018.

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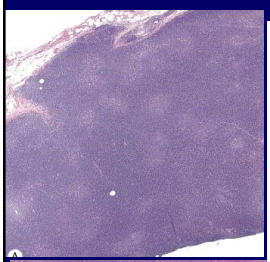
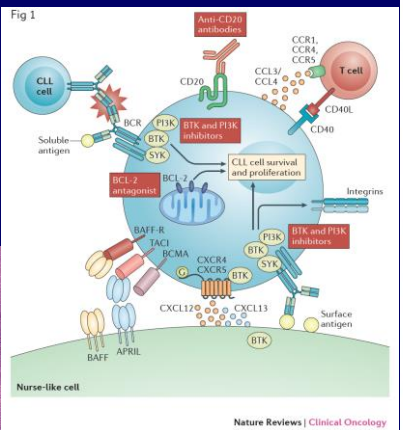
In CLL:
Sites of proliferation = sites of BCR activation



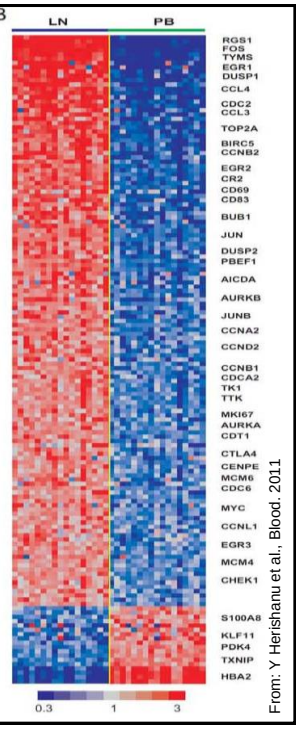
CLL lymph nodes

Proliferation centers

From: Soma LA et al, Human Pathology. 2006;37:152-159



Burger & O'Brien Nat Rev Clin Onc 2018



From: Y Herishanu et al., Blood. 2011

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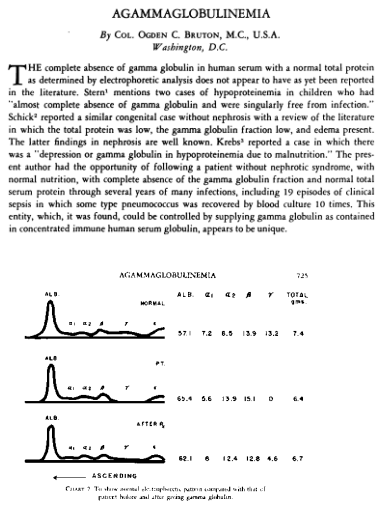
The discovery of agammaglobulinaemia in 1952

Colonel Ogden Bruton (*1908, †2003)
Chief of Pediatrics at the
Walter Reed Army Hospital

From: Ponader & Burger, J Clin Oncol. 32:1830-9, 2013.



AGAMMAGLOBULINEMIA

By Col. Ogden C. Bruton, M.C., U.S.A.
Washington, D.C.

THE complete absence of gamma globulin in human serum with a normal total protein as determined by electrophoretic analysis does not appear to have as yet been reported in the literature. Stern[1] mentions two cases of hypoproteinemia in children who had "almost complete absence of gamma globulin and were singularly free from infection." Schick[2] reported a similar congenital case without nephrosis with a review of the literature in which the total protein was low, the gamma globulin fraction low, and edema present. The latter findings in nephrosis are well known. Krebs[3] reported a case in which there was a "depression or gamma globulin in hypoproteinemia due to malnutrition." The present author had the opportunity of following a patient without nephrotic syndrome, with normal nutrition, with complete absence of the gamma globulin fraction and normal total serum protein through several years of many infections, including 19 episodes of clinical sepsis in which some type pneumococcus was recovered by blood culture 10 times. This entity, which, it was found, could be controlled by supplying gamma globulin as contained in concentrated immune human serum globulin, appears to be unique.

AGAMMAGLOBULINEMIA 725

ALB. α_1 α_2 β γ TOTAL gms.

NORMAL 57.1 7.2 8.5 13.9 13.2 7.4

PT. 65.4 5.6 13.9 15.1 0 6.4

AFTER γ_1 62.1 6 12.4 12.8 4.6 6.7

ASCENDING

From: Bruton, OC: *Pediatrics* 1952;9;722-728.

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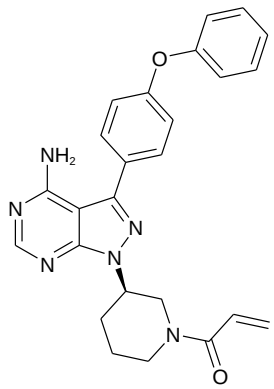
Ibrutinib (PCI-32765)
A Selective Inhibitor of BTK



- Forms a specific bond with cysteine-481 in BTK
- Highly potent BTK inhibition at IC_{50} = 0.5 nM
- Orally administered with once daily dosing resulting in 24-hr target inhibition
- No cytotoxic effect on T-cells or natural killer (NK)-cells
- In chronic lymphocytic leukemia (CLL) cells promotes apoptosis and inhibits CLL cell migration and adhesion

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Marked Reductions in Lymphadenopathy

Before ibrutinib+R (iR) | 2 weeks iR | 9 months iR

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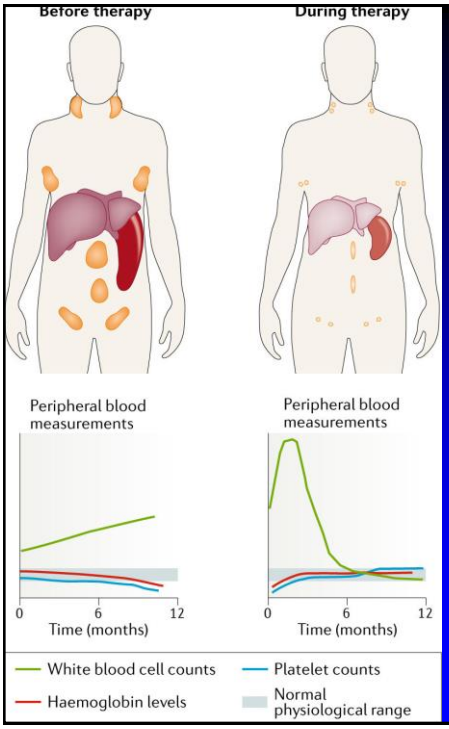

Treatment Related Lymphocytosis in CLL and Mantle Cell Lymphoma (MCL)

- Ibrutinib blocks BTK inducing B-cell apoptosis and disruption of B-cell homing in lymph nodes
- B-cells egress into peripheral blood
- Ibrutinib blocks B-cells from migrating back to lymph nodes resulting in treatment related lymphocytosis

Burger & O'Brien Nat Rev Clin Onc.

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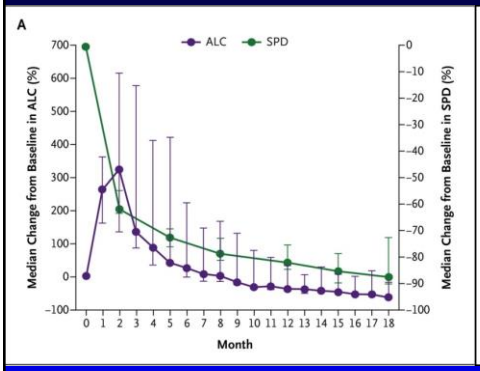
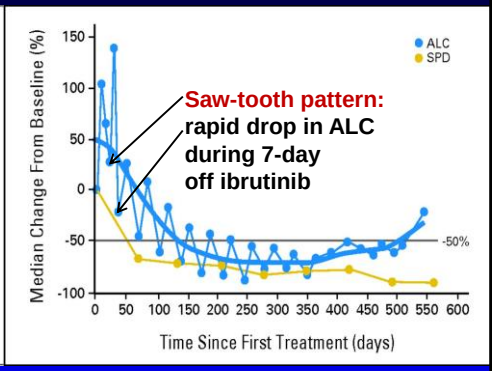
Ibrutinib-induced CLL cell Redistribution: Blood Lymphocytes vs Lymph Nodes



From: Byrd JC et al, NEJM 2013



From: Advani RH et al, JCO 2013

- **Redistribution** of tissue CLL cells into the PB causes early lymphocytosis (up to 3-fold increase)
- **Class effect** of kinase-inhibitors targeting BTK, PI3K, and SYK
- **Saw-tooth pattern** due to re-homing of CLL cells during "off-drug" period

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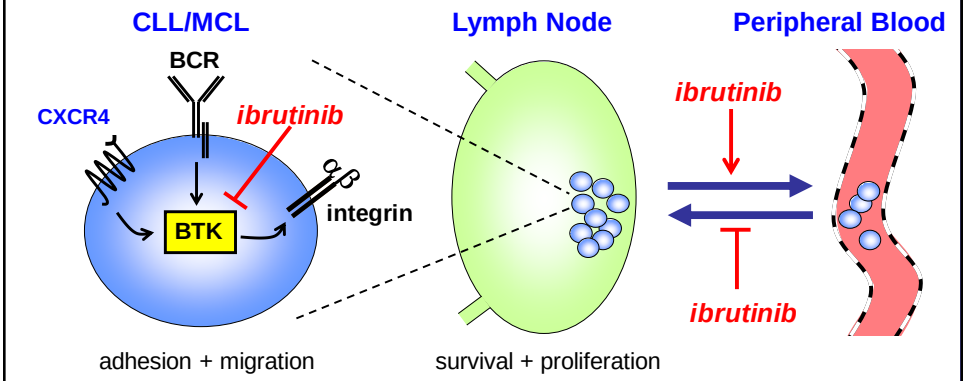
Mechanism of Treatment Related Lymphocytosis in Chronic Lymphocytic Leukemia (CLL) and Mantle Cell Lymphoma (MCL)



- Ibrutinib blocks BTK inducing b-cell apoptosis and disruption of b-cell adhesion in lymph nodes
- B-cells egress into peripheral blood
- Ibrutinib blocks b-cells from migrating back to lymph nodes resulting in treatment related lymphocytosis

de Rooij MFM, et al. *Blood. 2012;* 119:2590-2594.

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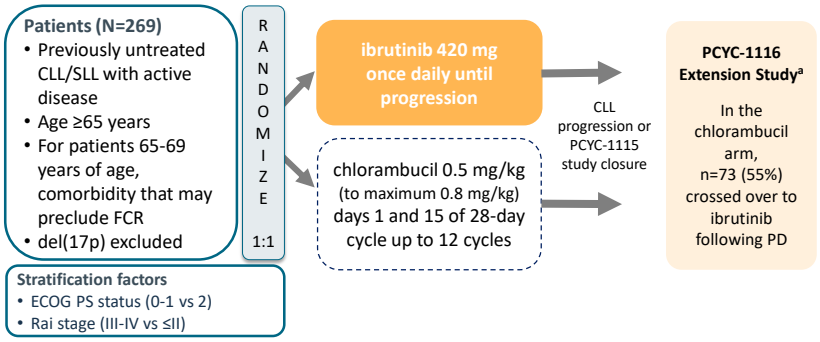
RESONATE-2 (PCYC-1115/1116) Study Design



IRC discontinued after primary analysis

[a]Patients could enroll in separate extension study PCYC-1116 after IRC-confirmed PD or at study PCYC-1115 closure for continuing treatment and follow-up.

ECOG PS, Eastern Cooperative Oncology Group performance status; FCR, fludarabine + cyclophosphamide + rituximab; IRC, independent review committee; PD, progressive disease

DGHO 2018, RESONATE-2 CLL; Burger et al.

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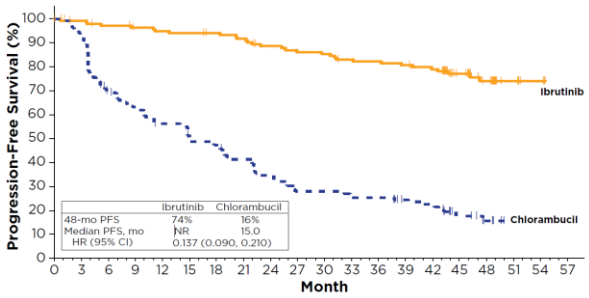
Ibrutinib Prolongs Progression-Free Survival (PFS) Compared With Chlorambucil



- 86% reduction in risk of PD or death for ibrutinib vs chlorambucil
- 48-month overall survival rates: 86% with ibrutinib vs 76% with chlorambucil

HR from unstratified Cox regression model

DGHO 2018, RESONATE-2 CLL; Burger et al.

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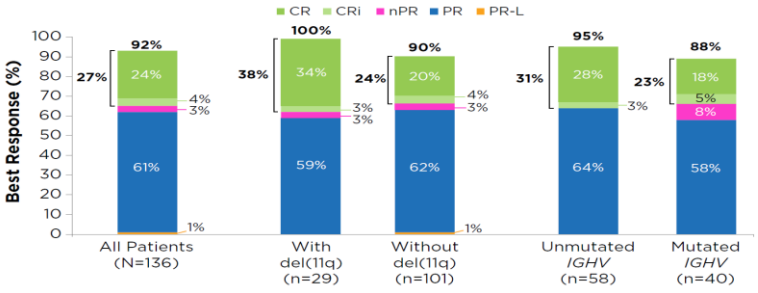
Overall Response Rate in the Ibrutinib Arm



- Response rates consistent with/without del(11q) and regardless of *IGHV* mutational status
- Investigator-assessed CR/CRi rates was 27% at 48 months, up from 11% at primary analysis
- Sponsor-confirmed CR rate was 16.2% at 48 months, up from 3.7% based on independent review at primary analysis

CR, complete response (sponsor confirmed); CRi, complete response with incomplete blood count recovery; nPR, nodular partial response; PR, partial response; PR-L, partial response with lymphocytosis. Percentages of patients in each category of response may not total the overall proportion with a response because of rounding

DGHO 2018, RESONATE-2 CLL; Burger et al.

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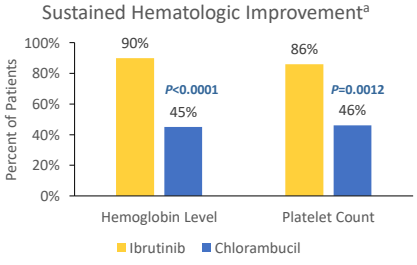
Improvements in Hematologic Parameters, Patient Symptoms, and Patient-Reported Outcomes

- Significantly more patients had sustained improvements in hemoglobin or platelets from baseline, and these improvements increased over time
- CLL disease-related symptoms as assessed by the investigator improved[b] more frequently with ibrutinib vs chlorambucil
- Patient-reported outcomes as assessed with FACIT-Fatigue[1] and EQ-5D-5L[2] were improved with ibrutinib



[a]Sustained hematologic improvement is defined as hematological improvement that sustained continuously for ≥56 days without blood transfusion or growth factors which includes: platelet counts >100 x 109/L if baseline ≤100 x 109/L or increase ≥50% over baseline; hemoglobin >11 g/dL if baseline ≤11 g/dL or increase ≥2 g/dL over baseline.
[b]Defined by change of at least 1 grade from baseline for at least 2 consecutive assessments at any time, as assessed by the investigator.
UIS, Utility Index Score; VAS, Visual Analogue Scale.
1. Yellen SB, et al. J Pain Symptom Manage. 1997;13:63-74.
2. EuroQol Group. Health Policy. 1990;16:199-208.

DGHO 2018, RESONATE-2 CLL; Burger et al.

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Most Frequent Treatment-Emergent Adverse Events (Any Grade[a,b] Prevalence) by Yearly Interval in First-line Ibrutinib Patients

Ibrutinib (n=135)	0-1 year (n=135), %	1-2 years (n=123), %	2-3 years (n=111), %	3-4 years (n=100), %	Total (n=135), %
Diarrhea	42	9	12	8	49
Fatigue	28	22	19	17	34
Cough	19	11	12	11	33
Peripheral edema	17	14	12	13	27
Anemia	16	10	8	10	25
Nausea	20	7	5	3	25
Pyrexia	15	7	6	6	24
Arthralgia	14	11	10	7	24
Upper respiratory infection	13	7	9	9	23
Hypertension	12	10	14	16	21
Vomiting	12	4	6	3	20

[a]All events were Grade 3 or lower, except for 1 case of Grade 4 anemia
[b]Events listed occurred at frequency ≥20%

DGHO 2018, RESONATE-2 CLL; Burger et al.

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Adverse Events of Clinical Interest

Ibrutinib (n=135)	0-1 year (n=135), %	1-2 years (n=123), %	2-3 years (n=111), %	3-4 years (n=100), %
Major hemorrhage (AE term group)	5	5	1	3
Atrial fibrillation	8	1	6	2
Hypertension (AE term group)	18	5	5	4

- Major hemorrhage (AE term group) occurred in 10% of ibrutinib-treated patients
  - None were Grade 5
- Atrial fibrillation occurred in 13% of ibrutinib-treated patients
  - None were Grade 4 or 5
- Hypertension (AE term group) occurred in 24% of ibrutinib-treated patients
  - None were Grade 4 or 5

DGHO 2018, RESONATE-2 CLL; Burger et al.

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Idelalisib: Potent and Selective Inhibitor of PI3Kδ

Idelalisib/ GS-1101

Class I PI3K Isoform	α	β	γ	δ
Cell Type	Mouse embryonic fibroblasts	Mouse embryonic fibroblasts	Human basophils	**Human basophils**
Cell-Based Activity	PDGF-induced pAKT	LPA-induced pAKT	fMLP-induced CD63+	**FceR1-induced CD63+**
EC_{50} (nM)	>20,000	1,900	3,000	**8**

- Selectivity relative to Class I PI3K isoforms involved in insulin signaling and other physiological functions
- No off-target activity against Class II or III PI3K, mTOR, or DNA-PK
- No off-target activity seen in screen of >350 protein kinases (Ambit KINOMEscan™)

Lannutti, et al. Blood, 2011.

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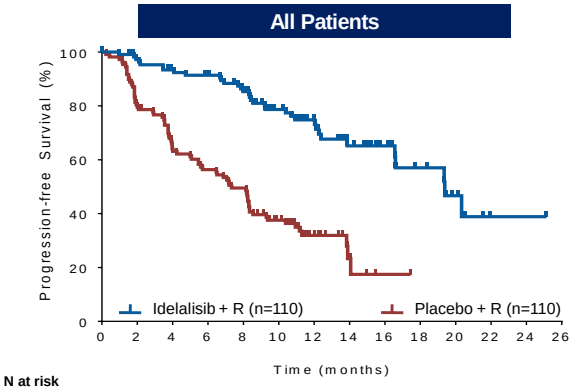
PFS, Including Extension Study*

Idelalisib + R vs Placebo + R



N at risk

IDELA + R	110	102	95	92	83	64	43	26	19	12	7	1	1	0
PBO + R	110	86	66	58	51	33	15	5	1	0	-	-	-	-

	Median PFS (95% CI)	HR (95% CI)	p-value
IDELA + R	19.4 mo (16.6, –)	0.25 (0.16, 0.39)	<0.0001
PBO + R	7.3 mo (5.5, 8.5)		

*Placebo + R includes those patients who received open-label idelalisib after unblinding without prior progression (n=42).

Sharman et al., ASH 2014, Abstract 330.

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March 2016: FDA Halts Six Idelalisib Combination Studies[1]

- Six idelalisib (Zydelig) trials in combination with other therapies have been halted due to reports of an increased rate of adverse events, including death, for patients with hematologic malignancies
- The halted studies were exploring idelalisib in CLL, SLL, and indolent NHL. The FDA announcement follows a similar decision from the European Union, which placed idelalisib under a safety review following infections (PJP, CMV)
- Idelalisib development in frontline CLL on hold
- EMA/PRAC recommends that all patients treated with Zydelig should receive antibiotics to prevent *Pneumocystisjirovecii* pneumonia. Patients should also be monitored for CMV and other infection and have regular blood tests for white cell counts because low counts can increase their risk of infection. Zydelig should not be started in patients with a generalised infection. It should also not be started in previously untreated patients with CLL whose cancer cells have certain genetic mutations (17p deletion or *TP53* mutation).

[1]http://www.fda.gov/Drugs/DrugSafety/ucm490618.htm

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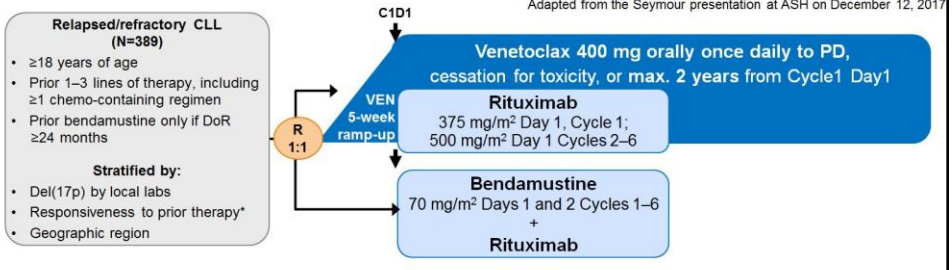
MURANO Study Design

Adapted from the Seymour presentation at ASH on December 12, 2017



Primary Endpoint	INV-assessed PFS
Major Secondary Endpoints	• IRC-CR ⇒ IRC-ORR ⇒ OS (hierarchical testing) • IRC-assessed PFS and MRD-negativity
Key Safety Endpoints	Overall safety profile, focusing on serious adverse events and Grade ≥3 adverse events
Interim Analysis	Approximately 140 INV-assessed PFS events (75% of total information)

NCT02005471
*High-risk CLL – any of following features: del(17p) or no response to front-line chemotherapy-containing regimen or relapsed ≤12 months after chemotherapy or within ≤24 months after chemoimmunotherapy.

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Patient Demographics

	Venetoclax + Rituximab N=194	Bendamustine + Rituximab N=195
Age, median (range), years	64.5 (28–83)	66.0 (22–85)
Lymphocyte count (×10^9/L), median (range)	43.1 (0.3–703)	54.7 (0.3–536)
Del(17p)*, n/N (%)	46/173 (27)	46/169 (27)
Unmutated IGHV*, n/N (%)	123/180 (68)	123/180 (68)
Mutated *TP53**, n/N (%)	48/192 (25)	51/184 (28)
Number of prior therapies, n (%)		
1	111 (57)	117 (60)
2	57 (29)	43 (22)
3	22 (11)	34 (17)
>3	4 (2)	1 (1)
Prior therapies, n (%)		
Alkylating agent	182 (93)	185 (95)
Purine analog	157 (81)	158 (81)
Anti-CD20 antibody	153 (78)	148 (76)
B-cell receptor pathway inhibitors	5 (3)	3 (2)

*Central lab

As of 8 May 2017

Seymour J, et al. *NEJM.* 2018;378:1107-20

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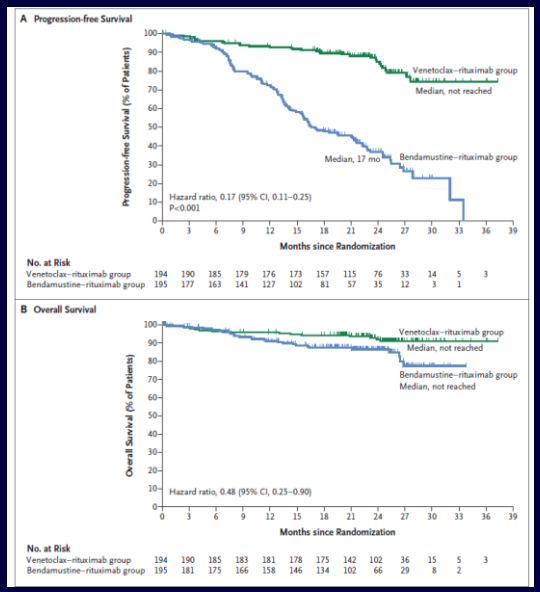
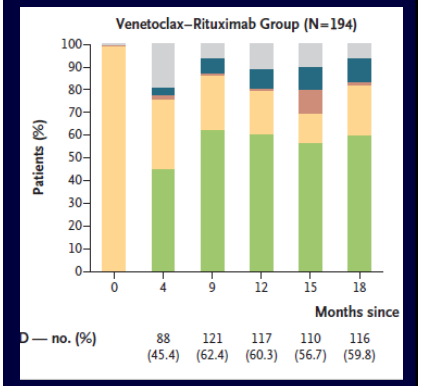
Ven+R vs. BR: PFS and OS



PB-MRD negative



Seymour J, et al. *NEJM.* 2018;378:1107-20.

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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

Jennifer A. Woyach, Amy S. Ruppert, Nyla Heerema, Weiqiang Zhao, Allison M Booth, Wei Ding, Nancy L. Bartlett, Danielle M Brander, Paul M Barr, Kerry A Rogers, Sameer Parikh, Steven Coutre, Arti Hurria, Gerard Lozanski, Sreenivasa Nattam, Richard A. Larson, Harry Erba, Mark Litzow, Carolyn Owen, James Atkins, Jeremy Abramson, Rich Little, Scott E. Smith, Richard M. Stone, Sumithra Mandrekar, John C. Byrd

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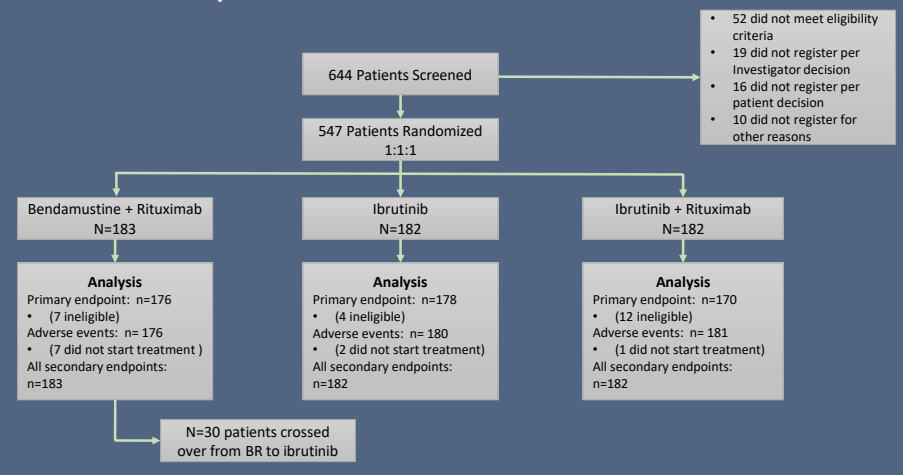
Patient Disposition



Woyach, et al. ASH2018, Abstract 6.

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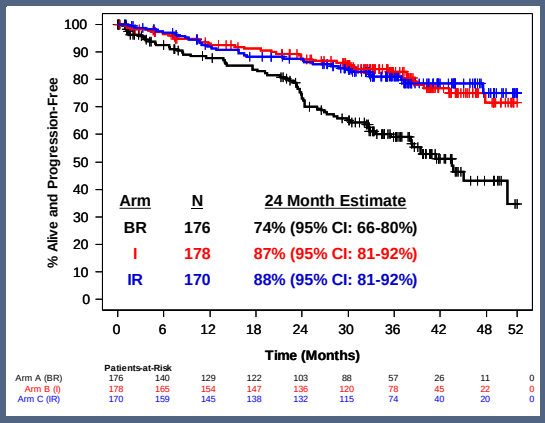
Primary Endpoint: Progression Free Survival
Eligible Patient Population



Pairwise Comparisons

I vs BR:
Hazard Ratio 0.39
95% CI: 0.26-0.58
(1-sided P-value <0.001)

IR vs BR:
Hazard Ratio 0.38
95% CI: 0.25-0.59
(1-sided P-value <0.001)

IR vs I:
Hazard Ratio 1.00
95% CI: 0.62-1.62
(1-sided P-value 0.49)

Woyach, et al. ASH2018, Abstract 6.

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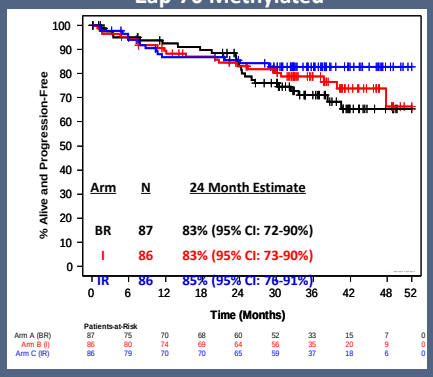
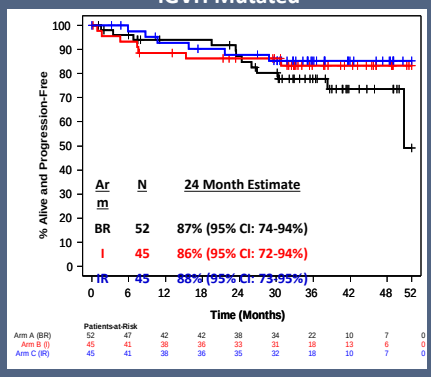
IGVH mutated & Zap-70 methylated Subgroups PFS
Intention-to-Treat Patient Population

Zap-70 Methylated



IGVH Mutated



Woyach, et al. ASH2018, Abstract 6.

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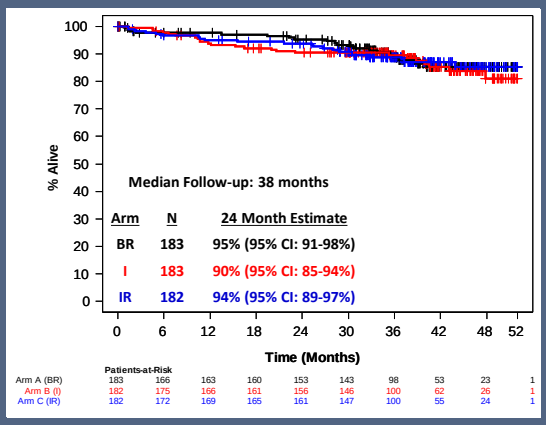
Overall Survival
Intention-to-Treat Patient Population



Woyach, et al. ASH2018, Abstract 6.

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Conclusions

- Ibrutinib or ibrutinib plus rituximab significantly prolongs PFS compared with BR in the frontline setting for older CLL patients
- Rituximab does not improve PFS over ibrutinib alone
- BTK inhibition with ibrutinib is not without significant toxicity in older patients, so close monitoring is still warranted
  - Strategies to discontinue therapy are of great interest
- Clinical trials for this patient population are still of high clinical interest; the cooperative group setting remains a reasonable avenue to complete these large studies
  - A041702 (NCT03737981) and EA9161 (NCT03701282)

Woyach, et al. ASH2018, Abstract 6.

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Ibrutinib + Obinutuzumab Versus Chlorambucil + Obinutuzumab as First-Line Treatment in Patients With Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma (CLL/SLL): Results From Phase 3 iLLUMINATE

Carol Moreno, MD, PhD[1]; Richard Greil, MD[2]; Fatih Demirkan, MD[3]; Alessandra Tedeschi, MD[4]; Bertrand Anz, MD[5]; Loree Larratt, MD[6]; Martin Simkovic, MD, PhD[7]; Olga Samoilova, MD[8]; Jan Novak, MD, PhD[9]; Dina Ben-Yehuda, MD[10]; Vladimir Strugov, MD[11]; Devinder Gill, MD, MRCP, FRCPath[12]; John G. Gribben, MD, DSc, FRCP, FRCPath, FMedSci[13]; Emily Hsu, PhD[14]; Cathy Zhou, MS[14]; Fong Clow, ScD[14]; Danelle F. James, MD, MAS[14]; Lori Styles, MD[14]; Ian W. Flinn, MD, PhD[15]

[1]*Hospital de la Santa Creu Sant Pau, Autonomous University of Barcelona, Barcelona, Spain;* [2]*Paracelsus Medical University Salzburg, Salzburg Cancer Research Institute, Cancer Cluster Salzburg, Salzburg, Austria;* [3]*Dokuz Eylul University, Izmir, Turkey;* [4]*ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy;* [5]*Tennessee Oncology, Chattanooga, TN, USA;* [6]*University of Alberta, Edmonton, Alberta, Canada;* [7]*University Hospital Hradec Kralove, Charles University, Hradec Kralove, Czech Republic;* [8]*Nizhny Novogorod Regional Clinical Hospital, Nizhny Novogorod, Russia;* [9]*University Hospital Kralovske Vinohrady and Third Faculty of Medicine, Charles University, Prague, Czech Republic;* [10]*Division of Hematology, Hadassah Ein-Kerem Medical Center, Jerusalem, Israel;* [11]*Almazov National Medical Research Centre, St Petersburg, Russia;* [12]*Princess Alexandra Hospital, Brisbane, Queensland, Australia;* [13]*Barts Cancer Institute, Queen Mary University of London, London, United Kingdom;* [14]*Pharmacyclics LLC, an AbbVie Company, Sunnyvale, CA, USA;* [15]*Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA*

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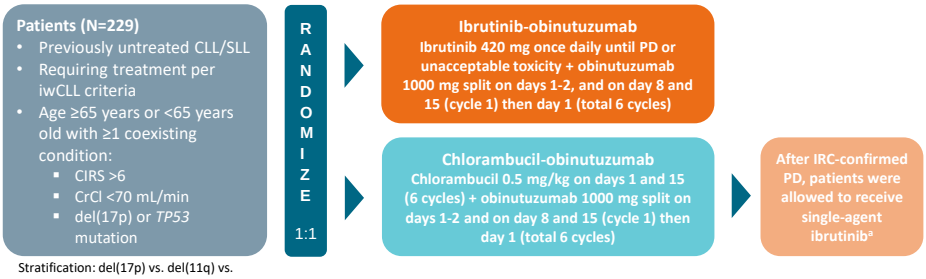
iLLUMINATE (PCYC-1130) Study Design



Stratification: del(17p) vs. del(11q) vs. neither del(17p) or del(11q); ECOG 2 vs 0-1

Primary end point
• PFS by IRC assessment

Secondary end points include
• PFS by IRC in high-risk population
• Rate of undetectable MRD
• ORR
• OS
• Infusion-related reactions
• Safety

CIRS, Cumulative Illness Rating Scale; IRC, independent review committee; iwCLL, International Working Group on CLL; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival.
[a]Patients in the chlorambucil-obinutuzumab arm could receive next-line single-agent ibrutinib in crossover following IRC-confirmed PD.

Moreno et al; ASH2018, Abstract 691.

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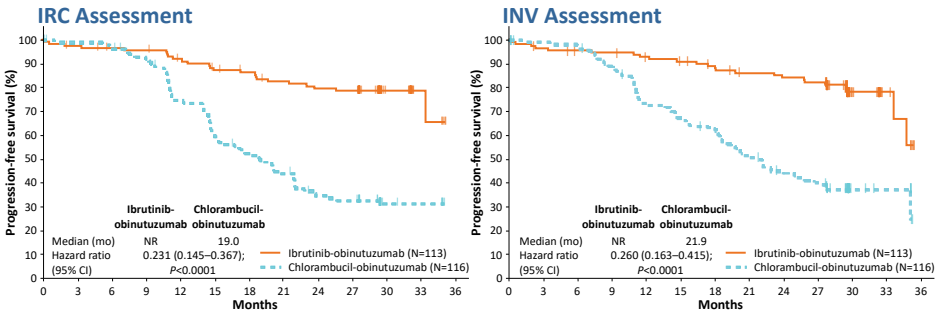
Superior Progression-Free Survival with Ibrutinib-Obinutuzumab



- Median follow-up, 31.3 months (range, 0.2–36.9)
- Estimated PFS at 30 months: 79% with ibrutinib-obinutuzumab vs. 31% with chlorambucil-obinutuzumab
- Even after excluding patients with del(17p): 74% reduction in risk of progression or death with ibrutinib-obinutuzumab

INV, investigator; NR, not reached.

Moreno et al; ASH2018, Abstract 691.

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iLLUMINATE Conclusions

- Ibrutinib-obinutuzumab represents an effective chemotherapy-free treatment option for first-line CLL/SLL, including importantly, for patients with high-risk disease
- Compared with chlorambucil-obinutuzumab, ibrutinib-obinutuzumab provided:
  - 77% reduction in risk of progression or death (ITT population)
  - 85% reduction in risk of progression or death (high-risk CLL population)
  - Consistent benefit across subgroups by high-risk features
  - Higher rates of CR and undetectable MRD
  - Safety profile consistent with AEs expected with individual agents
  - Reduced risk of obinutuzumab-related IRRs
- While single-agent ibrutinib provides PFS rate of 74% at 4 years,[1] combination of ibrutinib-obinutuzumab offers another option to achieve long-term PFS
- This is one of three Phase 3 randomized trials, at ASH 2018, that show superior PFS versus standard-of-care chemoimmunotherapy regimens (bendamustine-rituximab,[2] and fludarabine-cyclophosphamide-rituximab [FCR][3] in first line) and superior OS versus FCR[3]

1. Burger JA, et al. EHA 2018; Abstract PF343; 2. Woyach J, et al. ASH 2018, Abstract #6;
3. Shanafelt T, et al. ASH 2018, Abstract #LBA-4.

Moreno et al; ASH2018, Abstract 691.

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Ibrutinib & Rituximab Improves Progression Free and Overall Survival Relative to FCR in Younger Patients with Previously Untreated Chronic Lymphocytic Leukemia (CLL)

Tait Shanafelt, Xin Victoria Wang, Neil E. Kay, Susan O'Brien, Jacqueline Barrientos , Curt Hanson, Harry Erba, Rich Stone, Mark Litzow, Marty Tallman

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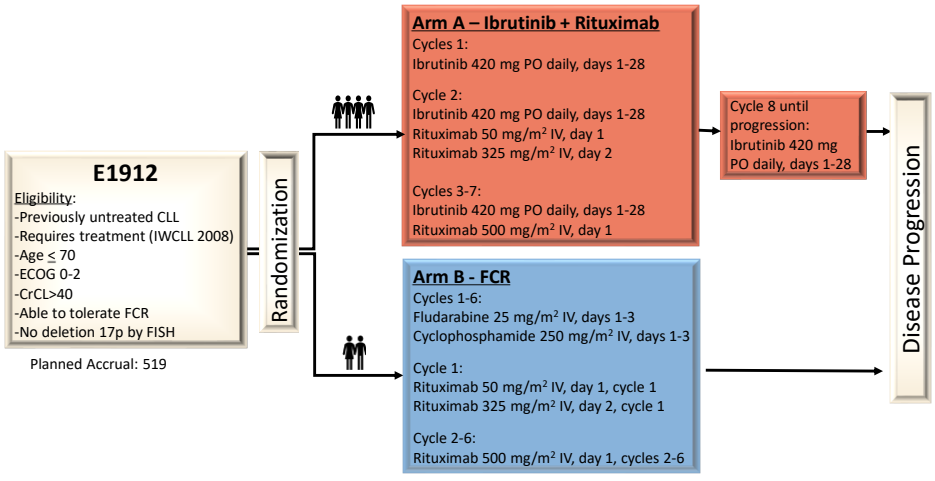
Study design



Shanafelt et al; ASH2018, Abstract LBA-4.

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Patient Characteristics Were Well Balanced

Baseline characteristics		IR n=354	FCR n=175	Total
Median age (y)		58	57	58
Age ≥ 60		41.0%	40.0%	40.6%
Female		33.3%	31.4%	32.7%
ECOG = 0		63.8%	62.3%	63.3%
Rai stage 0		3.1%	5.1%	3.8%
Rai stage I-II		52.8%	53.7%	53.1%
Rai stage III-IV		44.1%	41.1%	43.1%
FISH	11q deletion	22.0%	22.3%	22.2%
	Trisomy 12	19.8%	15.4%	18.3%
	13q deletion	34.2%	33.1%	33.8
B2M >3.5 mg/L		51.9%	48.0%	50.6%
IGHV Unmutated*		75.0%	61.7%	71.1%

* Tested in 437 (82%) patients

Shanafelt et al; ASH2018, Abstract LBA-4.

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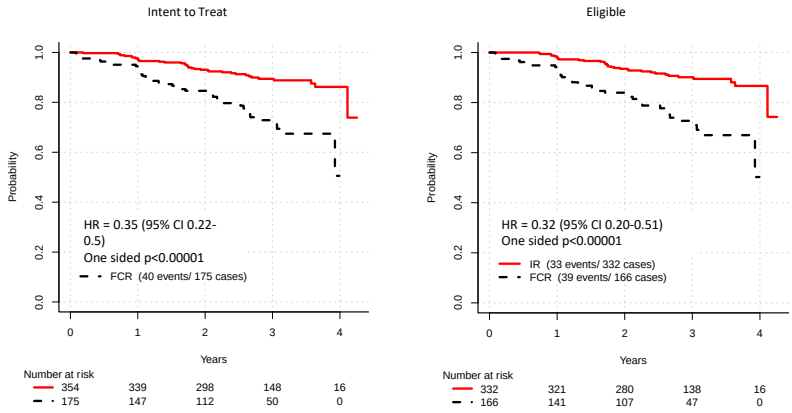
Progression Free Survival



Shanafelt et al; ASH2018, Abstract LBA-4.

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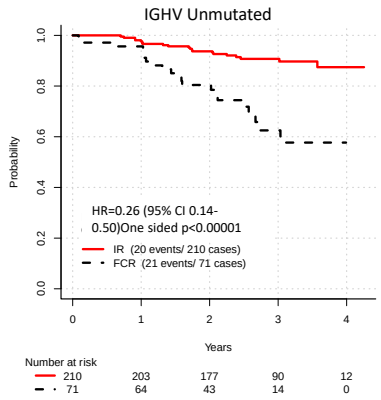
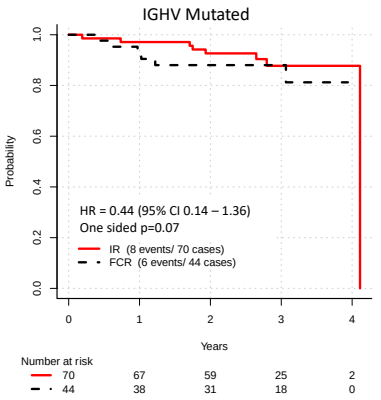
Progression Free Survival: IGHV Status





Shanafelt et al; ASH2018, Abstract LBA-4.

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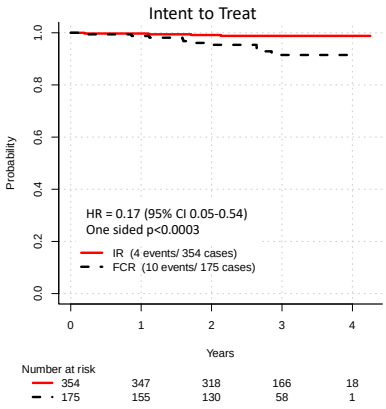
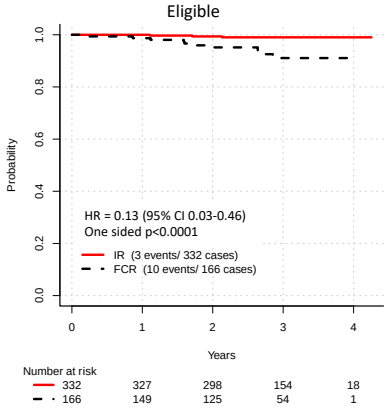
Overall Survival





Shanafelt et al; ASH2018, Abstract LBA-4.

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Why Eliminate Chemotherapy for CLL?

- Myelosuppression and risk for infection
- Immune cell depletion and risk for infection
- Risk for developing refractory, higher-risk CLL through clonal evolution
- Risk for secondary hematologic malignancies (MDS/AML)
- Risk for CLL transformation events
- Risk for second cancers?
- We have better treatment

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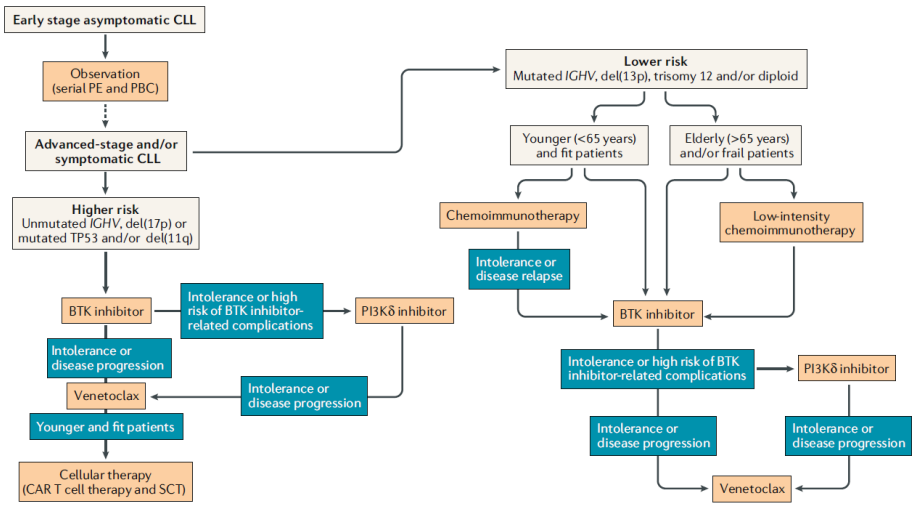
Algorithm for management of patients with CLL



Burger & O'Brien Nat Rev Clin Onc 2018.

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Thank you!

Collaborators:

- **Würzburg University: A Rosenwald, E Hartmann**
- **CLLGRF: F Caligaris-Cappio, N Chiorazzi, Z Estrov, N Kay**
- **MDACC: M Keating, W Wierda, S O'Brien, H Kantarjian, V Gandhi, A Ferrajoli, K Balakrishnan**
- **UCSD: T Kipps, L Rassenti**
- **UC Irvine: D Wodarz, N Komarova**
- **DFCI, Broad I: C Wu, DA Landau**

My laboratory: Mariela Sivina, Julia Hoellenriegel, Stefan Koehrer, Ekaterina Kim, Elisa ten Hacken, Shubhchintan Randhawa

Funding: CPRIT, MD Anderson Moonshot, Leukemia & Lymphoma Society

Dept. of Leukemia, MDACC

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Q&A SESSION

Update on Chronic Lymphocytic Leukemia (CLL)

- **Ask a question by phone:**
  - Press star (*) then the number 1 on your keypad.
- **Ask a question by web:**
  - Click "Ask a question"
  - Type your question
  - Click "Submit"

Due to time constraints, we can only take one question per person. Once you've asked your question, the operator will transfer you back into the audience line.

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- **Free telephone/web programs: www.LLS.org/programs**
- **Live, weekly online chats: www.LLS.org/chat**
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- **Information about leukemia: www.LLS.org/leukemia**

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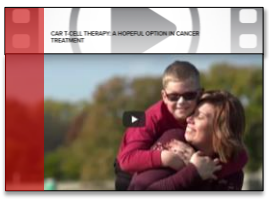
- **LLS Patient Podcast, *The Bloodline with LLS***

  Listen in as experts and patients guide listeners in understanding diagnosis, treatment, and resources available to blood cancer patients: **www.thebloodline.org**



- **Education Videos**

  Free education videos about survivorship, treatment, disease updates, and other topics: **www.LLS.org/educationvideos**

- **Patti Robinson Kaufmann First Connection Program**

  Peer-to-peer program that matches newly diagnosed patients and their families: **www.LLS.org/firstconnection**

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LLS EDUCATION & SUPPORT RESOURCES

- **Free Nutrition Consults**

  Telephone and e-mail consultations with a registered dietitian: **www.LLS.org/nutrition**

- **What to Ask**

  Questions to ask your treatment team: **www.LLS.org/whattoask**

- **Other Support Resources**

  LLS community, blogs, support groups, financial assistance, and more: **www.LLS.org/support**

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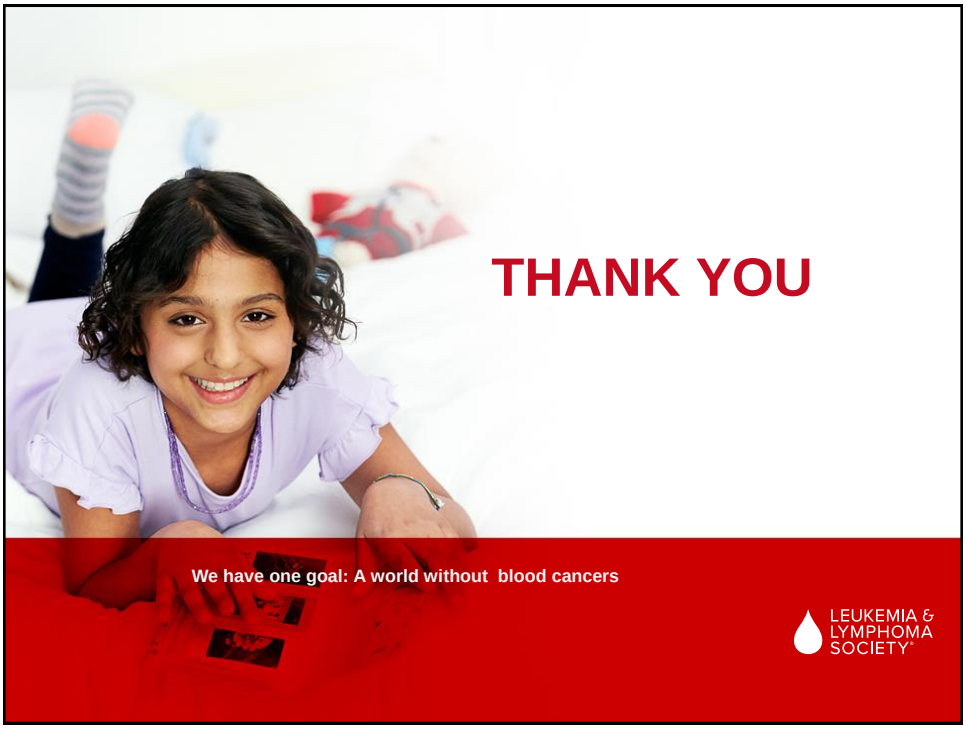

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