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Welcome & Introductions

LEUKEMIA & LYMPHOMA SOCIETY® fighting blood cancers
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Information for Patients with Chronic Lymphocytic Leukemia

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Disclosure

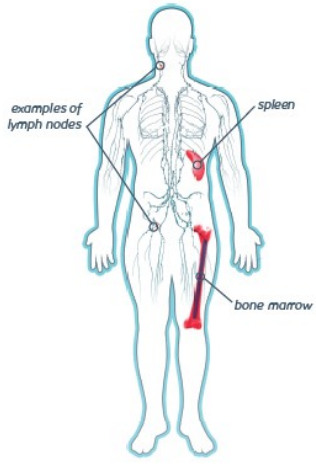
Susan O'Brien, MD, has affiliations with AbbVie, Johnson & Johnson, Pharmacyclics (*Speakers' Bureau*); and TG Therapeutics, Pfizer, Shire, Pharmacyclics, Regeneron, Pronai, Roche (*Advisory Board*).

What is CLL?

CLL stands for **chronic lymphocytic leukemia**. It is a type of blood cancer that involves **lymphocytes** - white blood cells that help fight infections.

In CLL, abnormal lymphocytes build up in the blood and **bone marrow**. Over time, these abnormal cells crowd the healthy cells. The result is fewer healthy white blood cells, red blood cells and **platelets**.

This leads to problems such as infection, **anemia** and excess bruising and bleeding. Abnormal lymphocytes may also build up in **lymph nodes**, the liver or the **spleen**. This can lead to swelling of these organs.



What are the symptoms of CLL?

Patients are often asymptomatic. Initial symptoms are generally secondary to lymph node enlargement or anemia.

The symptoms we should watch for include:

Weakness, feeling tired, feeling short of breath, weight loss, fever, night sweats

As the disease advances, the following may appear:

- elevated lymphocyte counts;
- progressive lymphadenopathy
- enlarged liver+/-spleen;
- more severe anemia,
- low granulocytes or platelets

1. Dierlamm et al. *Cancer Genet Cytogenet*. 1997;94:27-35.

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Understanding medical tests for CLL

CLL cannot be diagnosed by symptoms alone. CLL is usually detected by routine checkups or blood work for other health issues. Medical tests will also tell where CLL is in your body.

Common tests for diagnosis or prior treatment:

• **Physical exam** - the doctor checks for swollen lymph nodes, liver or spleen and other signs of CLL

• **Blood cell counts -** a high white blood cell count in patients with CLL

• **Biopsy**

• **Flow cytometry**—a sample of the cells, taken from blood or bone marrow.

Common tests include also:

• **Imaging tests such as x-rays, CT scans or ultrasound**

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Patients with CLL have a median age at diagnosis of 71 years and most have comorbidities

68% of CLL patients are aged ≥ 65 years:[1]

- Median age at diagnosis is 71 years[1]
- 40% of patients are aged > 75 years[1]

89% of CLL patients have one or more comorbidity:[2]

- 46% of patients have at least one MAJOR comorbidity[2]

1. Howlader N, *et al.* SEER Cancer Statistics Review, 1975-2011. Available at: http://seer.cancer.gov/csr/1975_2011/. Accessed February 2015; 2. Thurmes P, *et al. Leuk Lymphoma* 2008; 49:49–56.

Coexisting medical conditions - Effect on treatment approach

- Treatment strategies are based on the stage of disease and severity of coexisting conditions
- Several tools have been used to define patients into distinct groups; one example from the German Chronic Lymphocytic Leukaemia Study Group (GCLLSG) uses the Cumulative Illness Rating Scale (CIRS) score. Each patient group is then managed differently

'Go-go'	'Slow-go'	'No-go'
• Completely independent • No coexisting conditions • Normal life expectancy → Aggressive immunochemo-therapy	• Some coexisting conditions • Impaired organ function • Reduced performance status → Less aggressive approach	• Severely handicapped • High severity of coexisting conditions • Reduced life expectancy → Palliative care

GCLLSG = German CLL Study Group.

Eichhorst B, *et al. Leuk Lymphoma* 2009; 50:171–178; Leblond V. *Eur Oncol Haematol* 2012; 8:52–57.

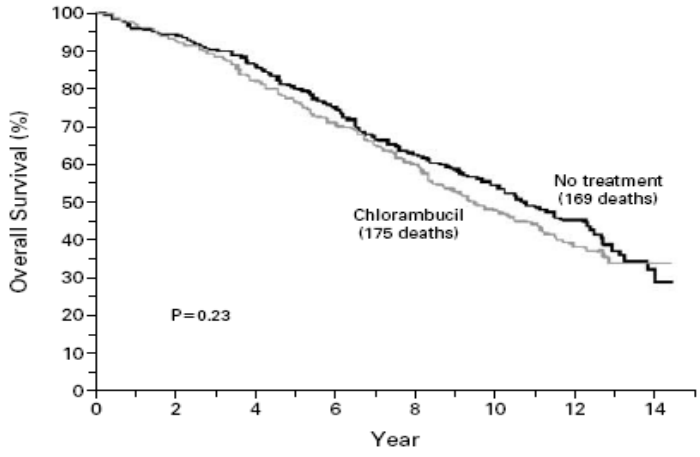
Chemoimmunotherapy Chemotherapy and Antibody Regimens

- **FCR: fludarabine, cyclophosphamide and rituximab**
- **BR: bendamustine and rituximab**
- **O-chlorambucil: obinutuzumab or ofatumumab and chlorambucil**

Why Not Treat CLL at Diagnosis

- **Indolent disease**
- **Patients often asymptomatic**
- **Median age early 70's**
- **Patients often have comorbidities and die of other causes**
- **Most patients are not cured**

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

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Types of Response in CLL

PR: partial remission. The disease responds, so blood counts improve and lymph nodes (and spleen if enlarged) shrink but they are not normal.

CR: complete remission. The disease cannot be found, the blood counts and physical exam are normal, as is the bone marrow.

MRD: minimal residual disease. Very sensitive test to look for CLL when blood counts/exam are normal; looks for 1 in 10,000 cells.

The better the response the longer it lasts.

CR lasts longer than PR.

CR can be MRD negative or MRD positive. MRD negative remissions last longer then MRD positive remissions

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Other Important Definitions Related to Clinical Trials

PFS: **Progression Free Survival (after treatment)**
Shows how many patients are in remission (disease has not recurred) and alive

OS: **Overall Survival shows how many patients are alive (whether they are in remission or not)**
OS is measured from the start of the therapy

CLL10 Study: FCR VS BR in Front-Line

Design **Patients with untreated, active CLL without del(17p) and good physical fitness (CIRS ≤ 6, creatinine clearance ≥ 70 ml/min)**

Randomization

FCR
Fludarabine 25 mg/m² i.v., days 1-3
Cyclophosphamide 250 mg/m², days 1-3,
Rituximab 375 mg/ m² i.v. day 0, cycle 1
Rituximab 500 mg/m² i.v. day 1, cycle 2-6

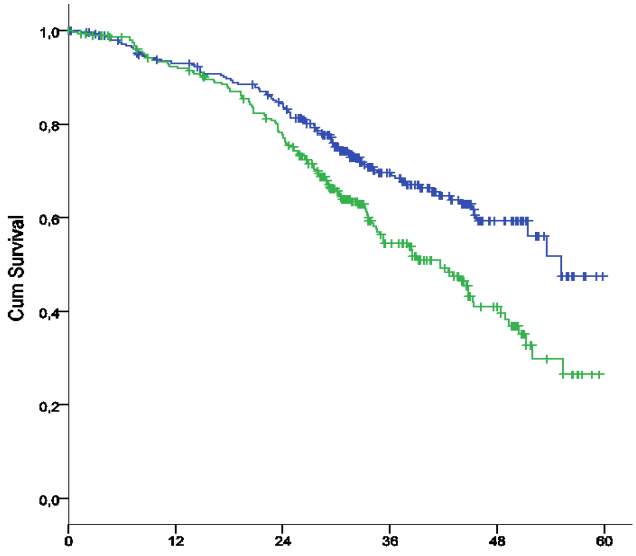
BR
Bendamustine 90mg/m² day 1-2
Rituximab 375 mg/m² day 0, cycle 1
Rituximab 500 mg/m² day 1, cycle 2-6

Non-Inferiority of BR in comparison to FCR for PFS:
HR (λ BR/FCR) less than 1.388

Eichhorst et al ASH 2014

CLL10 Study: FCR VS BR in Front-Line

ITT Progression-free Survival = Primary Endpoint



Median PFS
FCR 55.2 months
BR 41.7 months

P < 0.001
HR = 1.626 = > 1.388

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CLL10 Study: FCR VS BR in Front-Line

Adverse Events CTC ° 3-4 (1st cycle until end of study)

Adverse event	FCR (%) N= 279	BR (%) N=278	p value
Anemia	13.6	10.4	0.20
Infection	39.1	26.8	<0.001
			***sAML/MDS: FCR=6, BR = 1**
TRM	**4.6**	**2.1**	**0.107**
Sec Neoplasm	1.1	0	-

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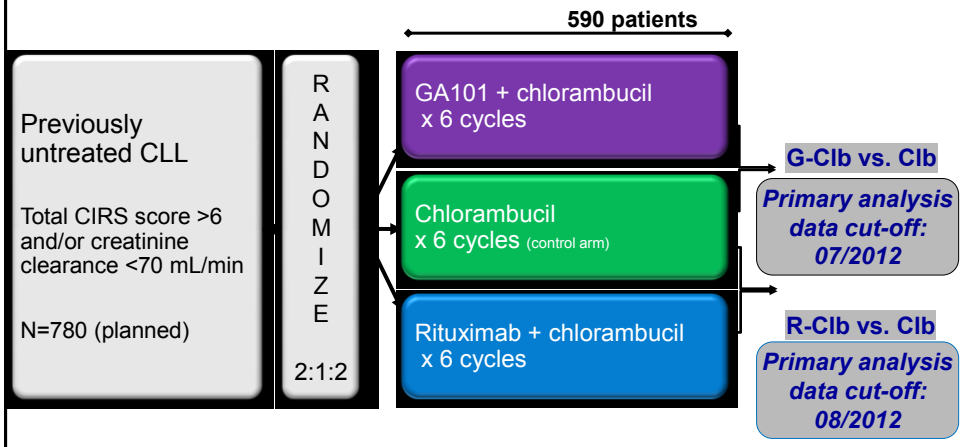
CLL11 Study Design



- GA101: 1000 mg days 1, 8, and 15 cycle 1; day 1 cycles 2–6, every 28 days
- Rituximab: 375 mg/m^2 day 1 cycle 1, 500 mg/m^2 day 1 cycles 2–6, every 28 days
- Chlorambucil: 0.5 mg/kg day 1 and day 15 cycle 1–6, every 28 days
- Patients with progressive disease in the Clb arm were allowed to cross over to G-Clb

Goede et al N Engl J Med 2014 March 2015, 370 (12): 1101-10.

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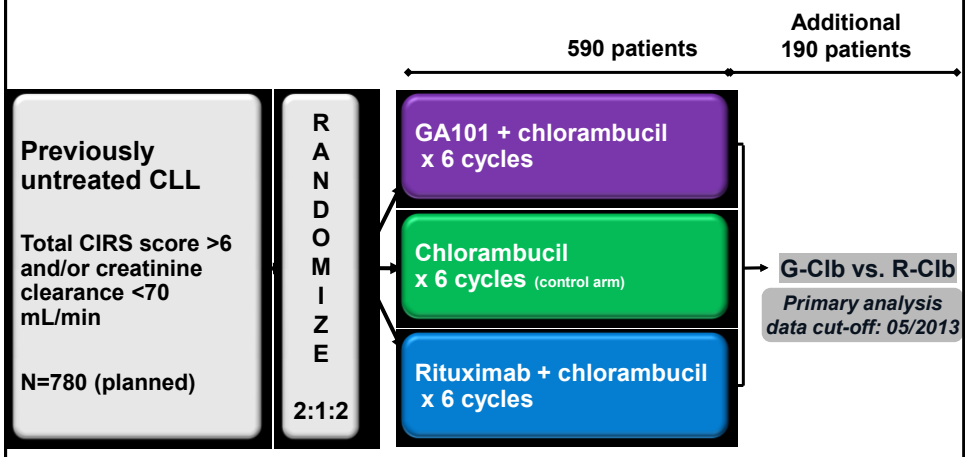
CLL11 Study Design



Goede et al N Engl J Med 2014 March 2015, 370 (12): 1101-10.

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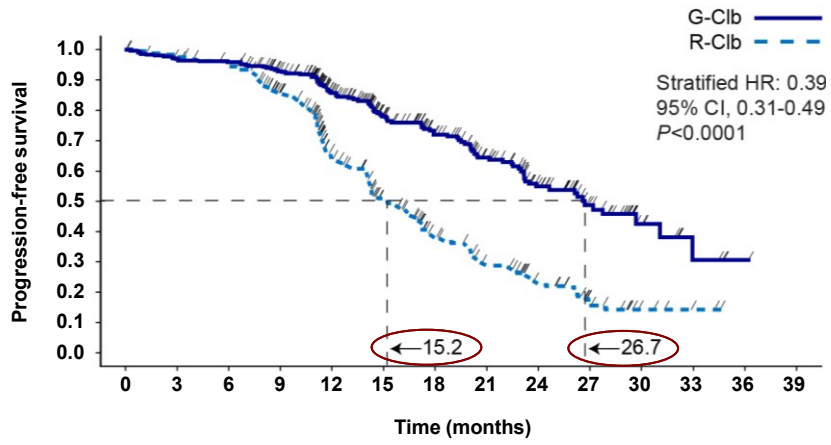
Progression-Free Survival (Head-to-Head)



No. at risk

G-Clb:	330	307	302	278	213	156	122	93	60	34	12	4	1	0
R-Clb:	330	317	309	259	163	114	72	49	31	14	5	2	0	0

Median observation time: G-Clb, 18.8 months; R-Clb, 18.6 months
Type 1 error controlled through closed test procedure; *P* value of the global test was <0.0001
Independent Review Committee-assessed progression-free survival (PFS) was consistent with investigator-assessed PFS

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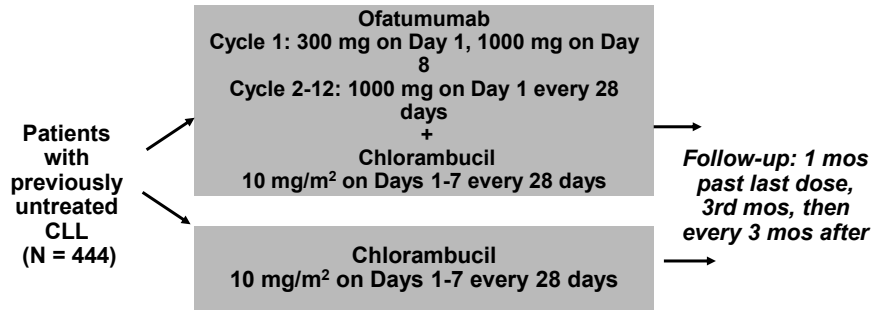
Phase III COMPLEMENT1: Ofatumumab + Chlorambucil vs Chlorambucil Alone



*Minimum 3 cycles or until best response or PD; maximum 12 cycles; no crossover allowed.

Dose rationale: highest PFS and ORR with the lowest toxicity compared with any other chlorambucil treatment

Hillmen P, et al. Lancet. 2015, May 9; 385(9980): 1873-83.

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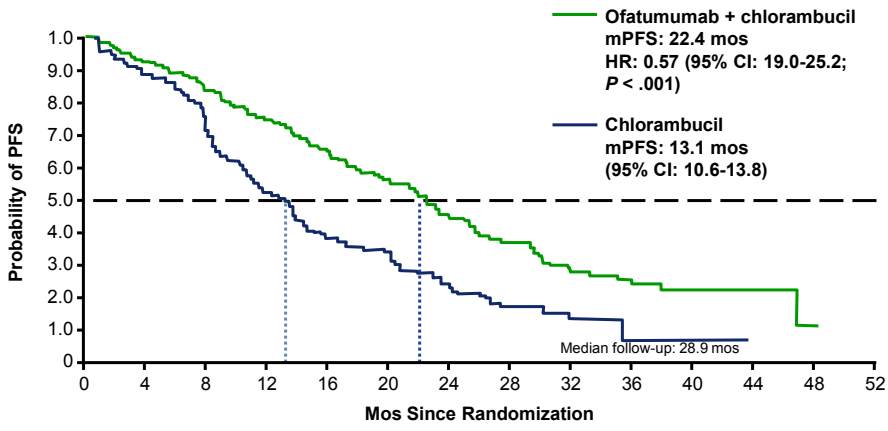
Ofatumumab + Chlorambucil vs Chlorambucil Alone: PFS*



*As assessed by an Independent Review Committee,

Hillmen P, et al. Lancet. 2015, May 9; 385(9980): 1873-83

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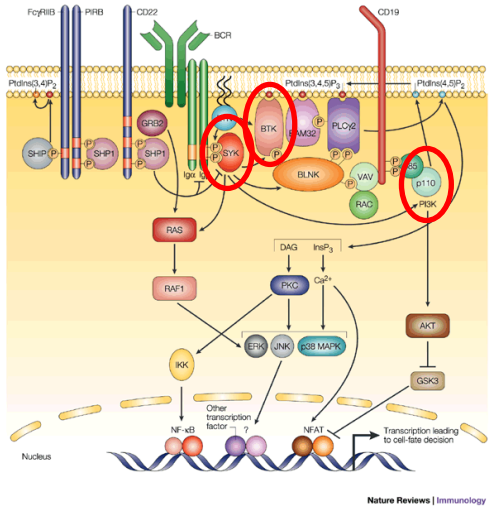
Targeting of BCR Signaling in CLL



- **BCR-associated kinases are targets of new drugs in preclinical and clinical development**
- **Syk (spleen tyrosine kinase) inhibitors: R406, Portola's Syk inhibitors[1]**
- **Btk (Bruton's tyrosine kinase) inhibitors: ibrutinib, CC-292, ONO-4059, ACP196**
- **PI3 kinases: Isoform-Selective Inhibitor of PI 3-Kinases[2], idelalisib, IPI-145, TGR-1202**

[1] Quiroga MP, et al. Blood 114(5):1029-37, 07/2009
[2] Niedermeier M, et al. Blood 113(22):5549-57, 5/2009

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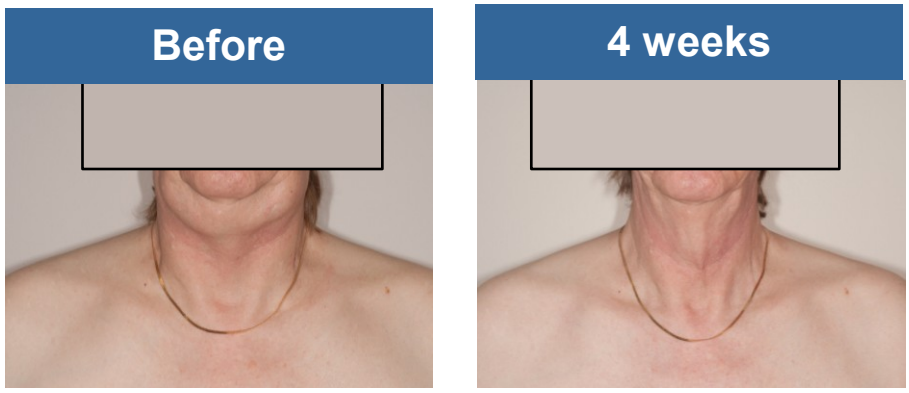
Ibrutinib in Refractory CLL With 11q Deletion



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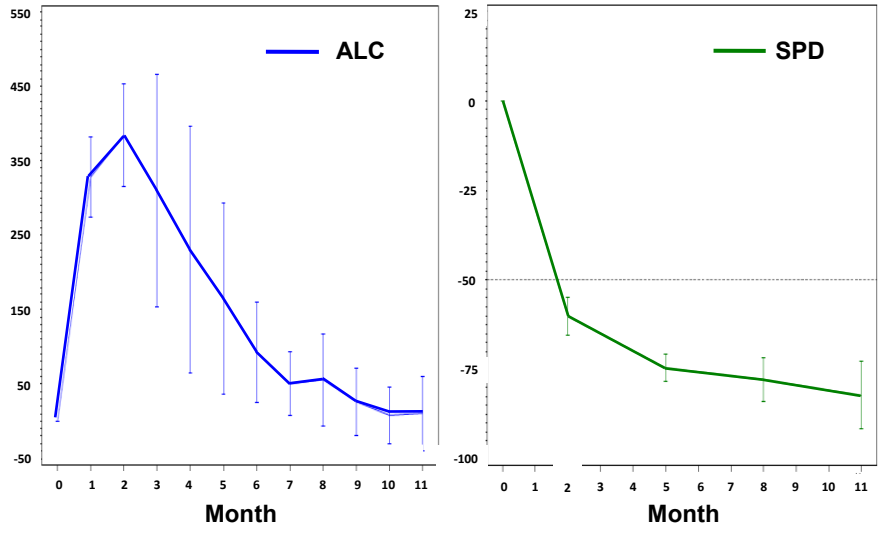
Pattern of Response: Blood Lymphocytes vs. Lymph Nodes



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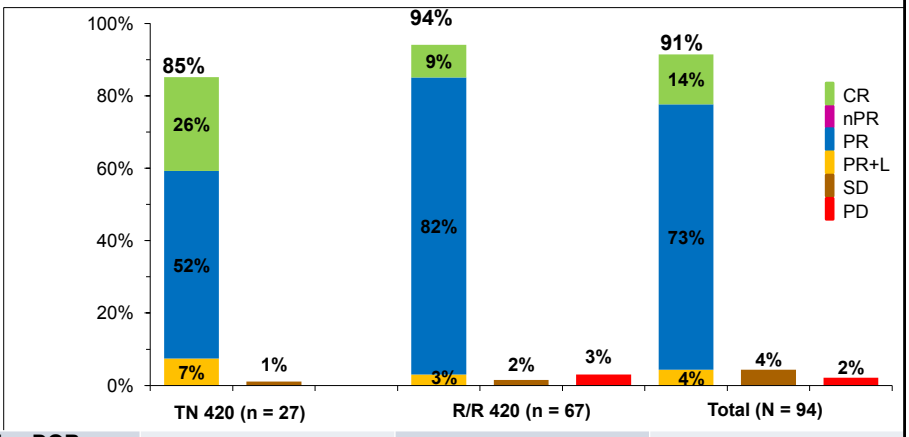
Ibrutinib Phase 2 Best Response (Investigator-Assessed)



	TN 420 (n = 27)	R/R 420 (n = 67)	Total (N = 94)
Median DOR, months (95% CI)*	NR (NE to NE)	NR (35.9 to NE)	NR (NE to NE)
Month 30 (95% CI)*	100% (100 to 100)	82.2% (68.5 to 90.4)	87.3% (77 to 93.2)

*TN: n = 21, R/R: n = 61, total: N = 82.

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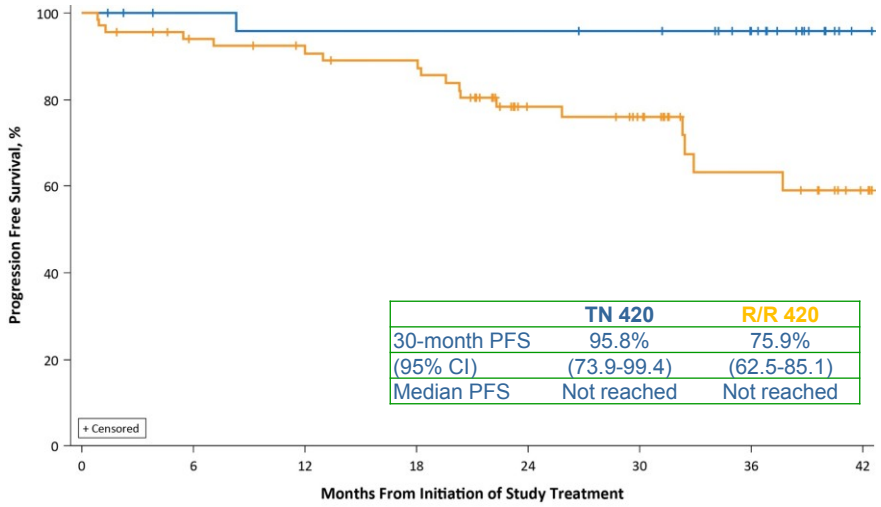
Progression-Free Survival



AACR 2015

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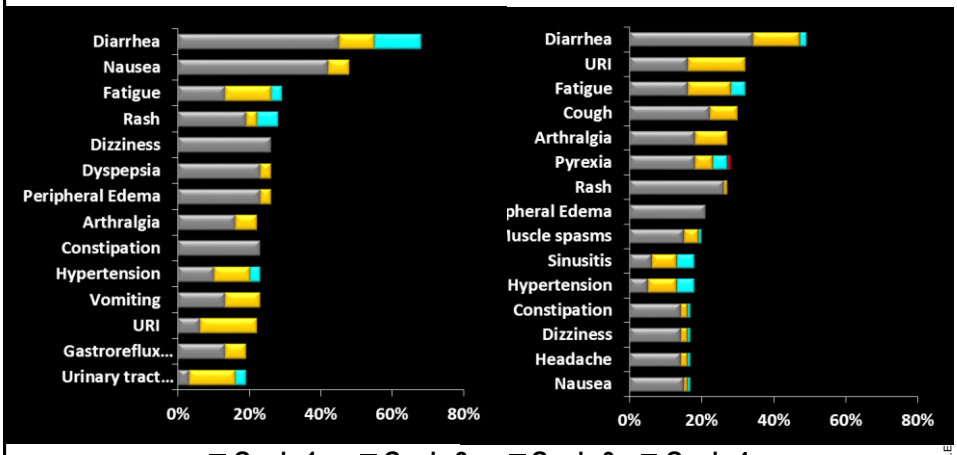
Ibrutinib: Common AEs (All Grades, Regardless of Causality)



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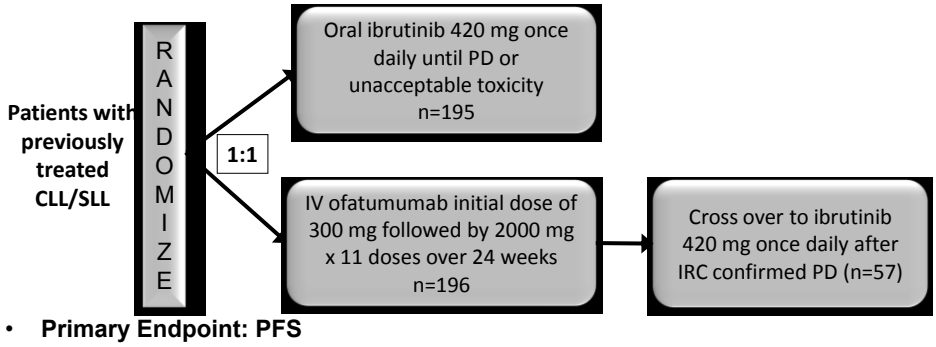
RESONATE™ Phase 3 Study Design



- **Primary Endpoint: PFS**
- **Stratification according to:**
  - **Disease refractory to purine analog chemoimmunotherapy (no response or <12 months)**
  - **Presence or absence of 17p13.1 (17p del)**
- **At time of interim analysis, median time on study was 9.4 months**

Byrd et al N Engl J Med 2014, Jul 17: 371 (3); 213-23

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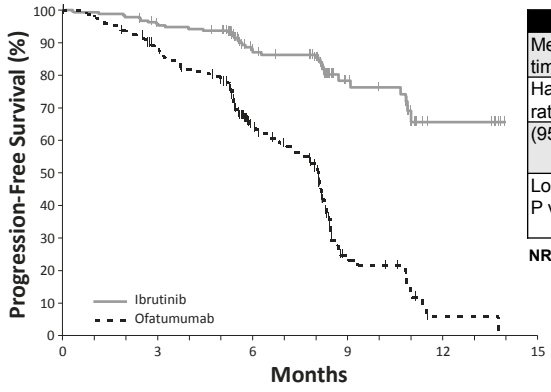
Progression-Free Survival



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

NR, not reached

This represent s a 78% reduction in the risk of PD or death with ibrutinib compared with ofatumumab
Richter's transformation was confirmed in 2 patients on each arm.
Another patient on the ibrutinib arm had transformation to prolymphocytic leukemia

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Safety: Atrial Fibrillation and Bleeding-Related Adverse Events

- **Atrial fibrillation any grade: ibrutinib n=10, ofatumumab n=1**
  - **Discontinuation of ibrutinib in only 1 patient**
    Patients were ≥60 years old (median age 73)
    Most had predisposing risk factors (a prior history of atrial fibrillation or in the setting of a pulmonary infection)

- **Bleeding-related AEs of any grade:**
  most commonly petechiae and ecchymoses
  ibrutinib 44%, ofatumumab 12%
  - **No difference in severe/major bleeding events:**
    ibrutinib n=2, ofatumumab n=3, 1 SDH with ibrutinib
  - **One patient discontinued ibrutinib due to a bleeding AE**
  - **Concomitant anti-platelets or anticoagulants**
    50% ibrutinib and 39% ofatumumab

Byrd et al N Engl J Med 2014, Jul 17: 371 (3); 213-23

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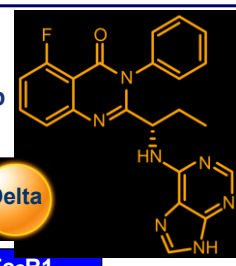
Idelalisib is an Orally Bioavailable Small Molecule that Inhibits PI3K Delta Potently and Selectively

Idelalisib



Class I PI3K Isoform	Alpha	Beta	Gamma	Delta
Cell-Based Activity	PDGF-induced pAKT	LPA-induced pAKT	fMLP-induced CD63+	FcεR1-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™)

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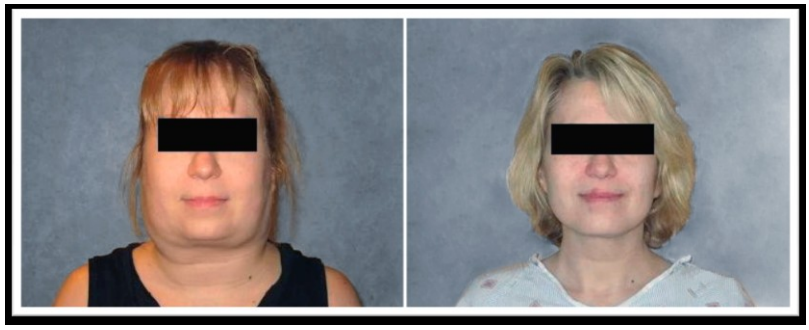
Marked Reductions in Peripheral Lymphadenopathy Were Observed

Pretreatment | With IdelalisibTreatment



38-year-old patient with refractory CLL and 5 prior therapies

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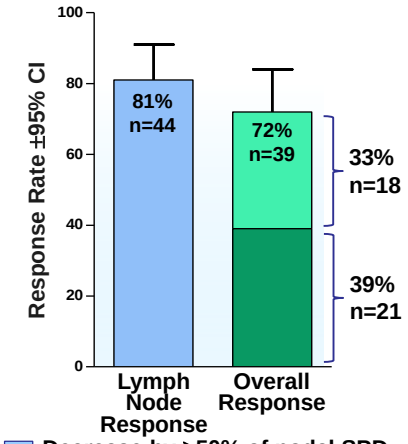
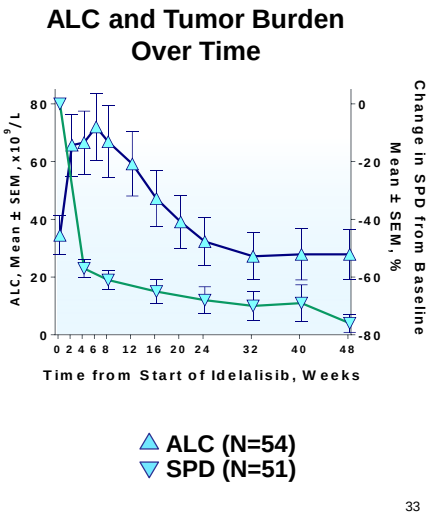
Idelalisib: Nodal and Overall Response Rate





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Idelalisib: Adverse Events (≥ 15%) and Selected Lab Abnormalities (N = 54)

AE, n (%)	Any Grade, (%)	Grade ≥ 3, (%)
Fatigue	17 (32)	1 (2)
Diarrhea	16 (30)	3 (6)
Pyrexia	16 (30)	2 (4)
Cough	13 (24)	2 (4)
Back pain	12 (22)	0
Rash	12 (22)	0
URI	12 (22)	0
Pneumonia	11 (20)	10 (19)
Night sweats	10 (19)	0
Chills	9 (17)	0
Laboratory abnormality, n (%)		
AST, increased*	13 (24)	1 (2)
ALT, increased*	10 (19)	1 (2)
*15 subjects total with transaminase elevations		

Brown et al. Blood. 2014 May 29; 123 (22): 3390-7

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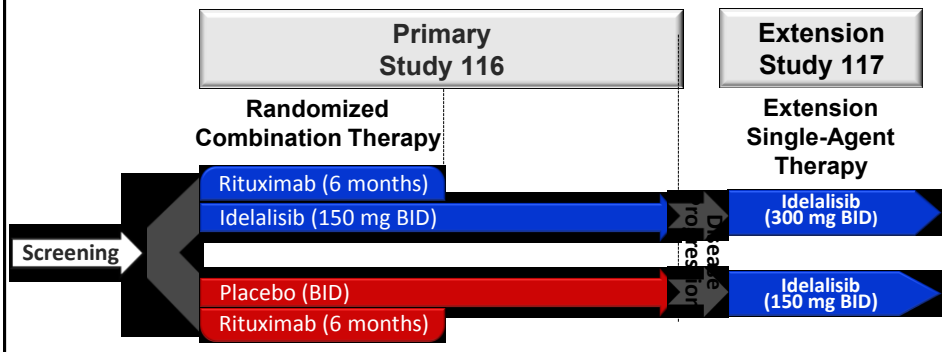
Study 116: Randomized, Double-Blind, Placebo-Controlled



Rituximab administration

- 375 mg/m^2, then 500 mg/m^2 Q2W x 4,
  then 500 mg/m^2 Q4W x 3

Clinical Endpoints

- Primary: PFS as assessed by IRC
- Events: Disease progression or death
- Secondary: ORR, LNR, OS

Planned interim analyses at 50% and 75% of events

Furman et al N Engl J Med 2014, Mar 13, 370 (11): 997-1007

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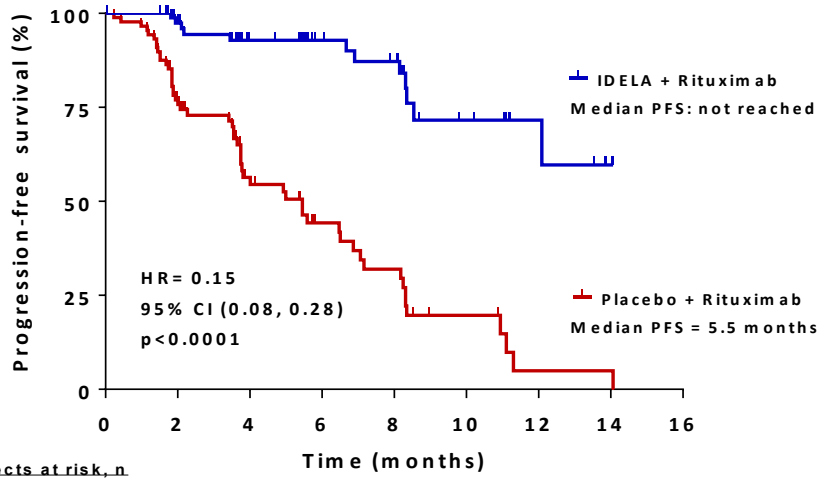
Primary Endpoint: Progression-Free Survival



Subjects at risk, n

IDELA + R:	110	69	44	34	30	14	6	2	0
Placebo + R:	110	62	30	18	13	6	1	1	0

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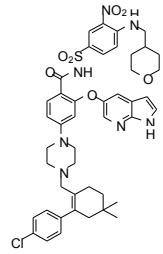
Venetoclax: Potent and Selective Bcl-2 Inhibition

- Small molecule, orally bioavailable
- High affinity for Bcl-2, lower affinity for BCL-xL, Mcl-1
- >100-fold improved functional selectivity for Bcl-2 over Bcl-x_L in assays with tumor cell lines



ABT-199

	Affinity				Cellular Efficacy, EC_{50}, nM				
	TR FRET K_i, nM				FL5.12, 3% FBS			Human tumor cell lines, 10% HS	
Agents	Bcl-2	Bcl-x_L	Bcl-w	Mcl-1	Bcl-2	Bcl-x_L	Functional Selectivity	RS4;11 (Bcl-2)	H146 (Bcl-x_L)
Navitoclax	0.04	0.05	7	>224	20	13	0.6	110	75
ABT-199	< 0.01	48	21	>440	4	261	65	12	3600

S. Jin, P. Kovar, P. Nimmer, M. Smith, Y. Xiao

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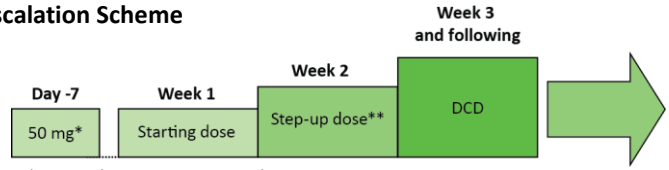
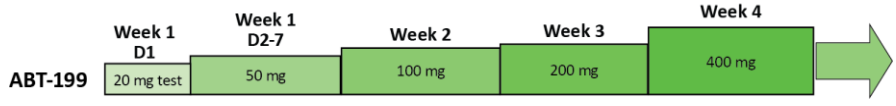
Dosing Schedule of Venetoclax: Dose Escalation Schematic

Dose Escalation Scheme



*3 patients (1 each in cohorts 2, 3, & 5) received ABT-199 20 mg as initial dose.
**Step-up doses range from 100 to 400 mg.
DCD = Designated Cohort Dose

Lead-in to Designated Cohort Dose - Expanded Safety Cohort



Median time on study 10.9 months

Seymour et al. EHA 2014

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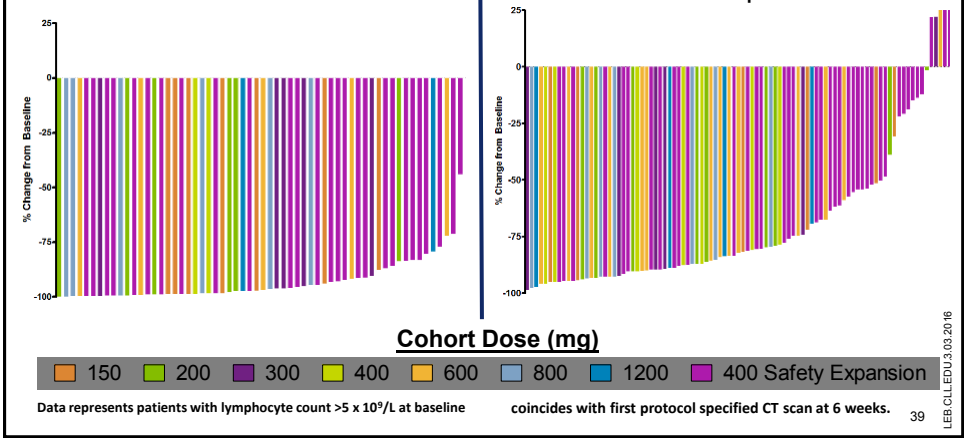
Best Percent Change from Baseline in Blood Lymphocyte Count and Nodal Mass by CT Scan

Blood Lymphocytes (n=60)

- Median Time to 50% reduction: 14 days, range [1 – 49]

Nodal Mass by CT Scan (n= 93)

- The median time to 50% reduction 1.4 months, range [0.65 – 13.7]*
- 78 (84%) evaluable patients had at least a 50% reduction in sum of the product of diameters



Data represents patients with lymphocyte count >5 x 10^9/L at baseline

coincides with first protocol specified CT scan at 6 weeks.

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Objective Responses of Venetoclax Treated Patients

Responses	All n (%), n = 78	del (17p) n (%), n = 19	F-Refractory n (%), n = 41	Unmutated n (%), n = 24
Overall response	60 (77)	15 (79)	31 (76)	18 (75)
Complete response (CR/CRi)#	18 (23)	5 (26)	9 (22)	7 (29)
Partial response*	42 (54)	10 (53)	22 (54)	11 (46)
Stable disease	10 (13)	2 (11)	7 (17)	2 (8)
Disease progression	2 (3)	1 (5)	1 (3)	2 (8)
D/C Prior to assessment+	6 (8)	1 (5)	2 (5)	2 (8)

Some patients may have more than one high risk marker.
#4 patients have CRi; +D/C = discontinued, first assessment at 6 weeks
*3 patients had confirmatory CT imaging assessments at less than an 8 week interval (5, 6, and 7 weeks)

- As of April 9, 78 patients had 2 CT scans, performed approximately 8 weeks apart n=55 from dose escalation and n=23 from the safety expansion cohort
- A total of 26 patients are not yet evaluable in the SE cohort (12 patients had a PR at their first scan, 14 patients have not yet reached their first assessment)
- The median duration of response has not yet been reached

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Minimal Residual Disease (MRD): Preliminary Analyses

- 11/18 patients with CR/CRi assessed for MRD
- Quantification by 4 color flow using local lab
- BM: MRD ⊖ = 6
  - (3 suboptimal cell #)
  - MRD +
  - low level = 4 (0.17%, 0.7%, 0.75%, 1.5%)
- PB: MRD ⊖ = 1 (no BM)
- BM MRD ⊖ 1 F refractory, 17p-
  - 3 F refractory
  - 1 17p

Seymour et al EHA 2014

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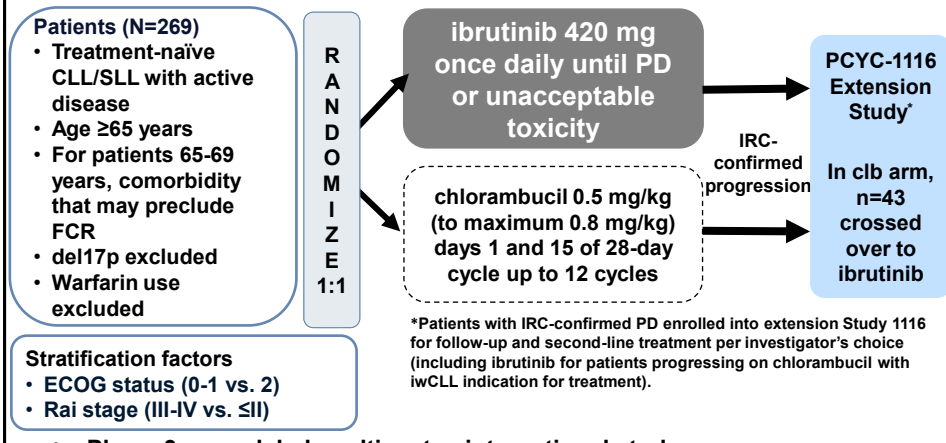
RESONATE™-2 (PCYC-1115) Study Design



- Phase 3, open-label, multicenter, international study
- Primary endpoint: PFS as evaluated by IRC (2008 iwCLL criteria)[1,2]
- Secondary endpoints: OS, ORR, hematologic improvement, safety

1. Hallek et al. *Blood*. 2008;111:5446-5456; 2. Hallek et al, *Blood*. 2012; e-letter, June 04, 2012.

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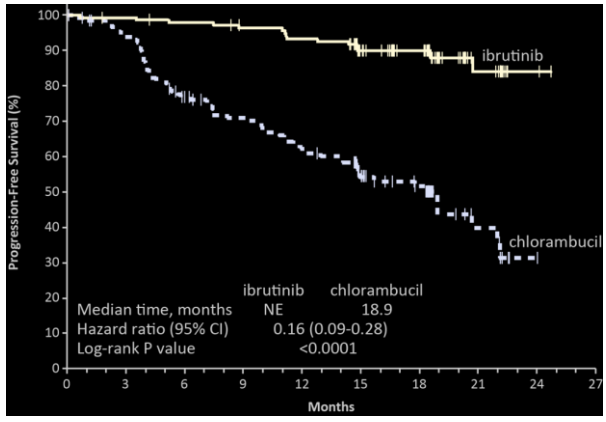
PFS by Independent Assessment



- **84% reduction in risk of progression or death with ibrutinib**
- **18-month PFS rate: 90% with ibrutinib vs. 52% with chlorambucil**
- **Median follow-up: 18.4 months**

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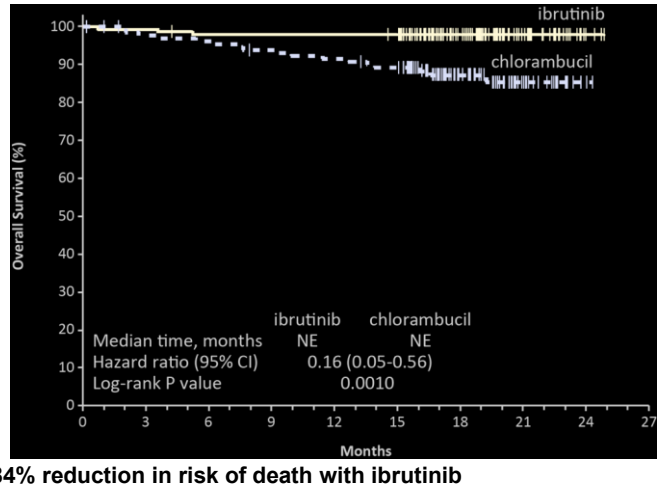
Overall Survival



- **84% reduction in risk of death with ibrutinib**
- **24-month OS rate: 98% with ibrutinib and 85% with chlorambucil**
- **3 deaths on ibrutinib arm vs. 17 deaths on chlorambucil arm**

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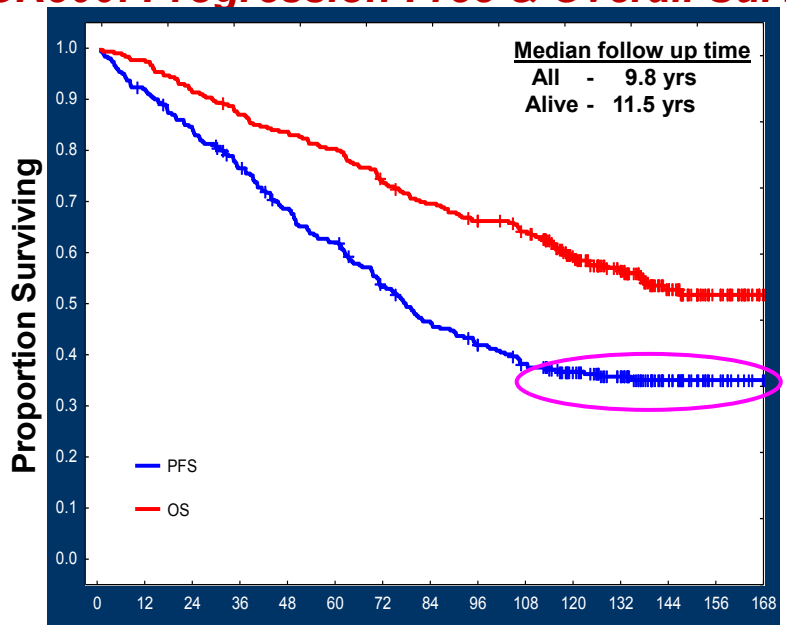
FCR300: Progression-Free & Overall Survival



Wierda et al. iWCLL 2013

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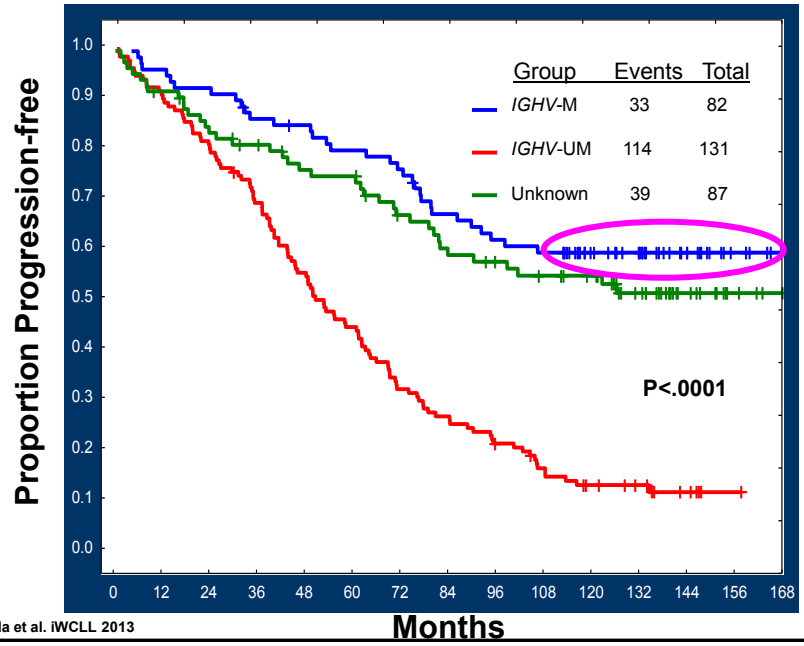
FCR300: PFS by IGHV Mutation Status



Wierda et al. iWCLL 2013

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Oral Small Molecules in CLL

- Ibrutinib FDA approved
  - Initial therapy
  - Recurrence after chemotherapy
- Idelalisib FDA approved
  - In combination with rituximab for recurrence
- Venetoclax FDA approved
  - Recurrence in patients with 17p deletion

Considerations for Ibrutinib vs Chemoimmunotherapy as Initial Therapy for CLL

- Pills vs IV
- Defined time on therapy
  - FCR or BR 6 months
  - Chlorambucil based 6-12 months
  - Ibrutinib: indefinite
- Long term results
  - Ibrutinib: 4 years follow-up is too short to talk about cure
  - FCR: over 10 years, may be a cured group
- Cost to patient
  - Chemotherapy based : none
  - Ibrutinib : copay

Information for Patients with Chronic Lymphocytic Leukemia

LEUKEMIA & LYMPHOMA SOCIETY® fighting blood cancers — someday is today®

Q&A Session

Dr. O'Brien's slides are available for download at
www.LLS.org/programs

After the program, the audio replay and program transcript will also be available at the link above.

Information for Patients with Chronic Lymphocytic Leukemia

LEUKEMIA & LYMPHOMA SOCIETY® fighting blood cancers — someday is today®

The Leukemia & Lymphoma Society (LLS) offers:

- **Online Chats:** Online moderated chat forums**: www.LLS.org/chat**
- **What to ask:** Questions to ask your treatment team: **www.LLS.org/whattoask**
- **Free education materials: www.LLS.org/booklets**
- **Past CLL education programs: www.LLS.org/programs**
- **Leukemia Links**: Monthly online publication that delivers news and links detailing latest leukemia research and studies**: www.LLS.org/signup**
- **Information Resource Center:** Speak one-on-one with an Information Specialist who can assist you through cancer treatment, financial, and social challenges.
  - **EMAIL: infocenter@LLS.org** **TOLL-FREE PHONE: (800) 955-4572**