

## CLL Some things you need to know

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## Chronic Lymphocytic Leukemia

- Most common adult leukemia (~15,000 cases per year)
- Median age at diagnosis 72 years
- Causes ~ 4400 deaths per year
- Absolute survival has increased over last 2 decades

American Cancer Society. *Cancer Facts & Figures 2011*; Rai K, et al. *Blood*. 1975;46:219-234; Brenner H, et al. *Blood*. [published online ahead of print February 28, 2008].

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## Diagnosis: NCI-WG

- Small, mature lymphocytes  $\geq 5000/\mu\text{L}$  (BLOOD)
- Lymphocytes  $\geq 30\%$  in (BONE MARROW)
- Clonal expansion of abnormal B lymphocytes (FLOW)
  - Low density of surface Ig (IgM or IgD) with  $\kappa$  or  $\lambda$  light chains
  - B-cell surface antigens (CD19, CD20, CD23); CD20 dim
  - CD5 surface antigen (usually Tcell)

Cheson BD, et al. *Blood*. 1996;87:4990-4997.

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## Staging Systems

<u>Rai</u>	<u>Findings</u>	<u>Survival (mo)</u>
0	Lymphocytosis only	> 120
I	Lymphocytosis + lymphadenopathy	95
II	Lymphocytosis + > spleen and/or liver	72
III	Lymphocytosis + anemia (Hgb < 11.0 g/dL)	30
IV	Lymphocytosis + platelets < 100	30

<u>Binet</u>	<u>Findings</u>	<u>Survival (mo)</u>
A	Hgb $\geq$ 10, Plts $\geq$ 100, < 3 involved areas*	> 120
B	Hgb $\geq$ 10, Plts $\geq$ 100, $\geq$ 3 involved areas*	84
C	Hgb < 10, or Plts < 100	24

\*Involved areas include cervical, axillary, or inguinal nodes, spleen, or liver.

Rai KR, et al. *Blood*. 1975;46:219-234; Binet JL, et al. *Cancer*. 1981;48:198-206.

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## Traditional Prognostic Factors

- Advanced stage at diagnosis
- Short lymphocyte doubling time
- Diffuse bone marrow infiltration
- Older age, males
- Cytogenetic abnormalities

Rozman C, Montserrat E. *N Engl J Med*. 1995;333:1052-1057.  
Cheson BD, et al. *Blood*. 1996;87:4990-4997.

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## Newer Prognostic Factors

- FISH defects
    - 17p deletion
    - 11q deletion
    - 12q trisomy
    - Normal
    - 13q deletions
- } **Hierarchy** ↑
- Unfavorable**  
**Favorable**
- Immunoglobulin heavy chain variable region (IgV<sub>H</sub>)
  - ≤ 2% mutation = unmutated
    - Mutated survival much longer than unmutated
  - CD38 status (≥ 30% = poor outcome)
  - ZAP-70 status (≥ 20% = poor outcome)
  - High serum β2-microglobulin

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## Genetic Aberrations in CLL

### Interphase FISH Results

Chromosomal aberrations detected in 268 of 325 cases (82%)

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

Döhner H, et al. *N Engl J Med.* 2000;343:1910-1916.

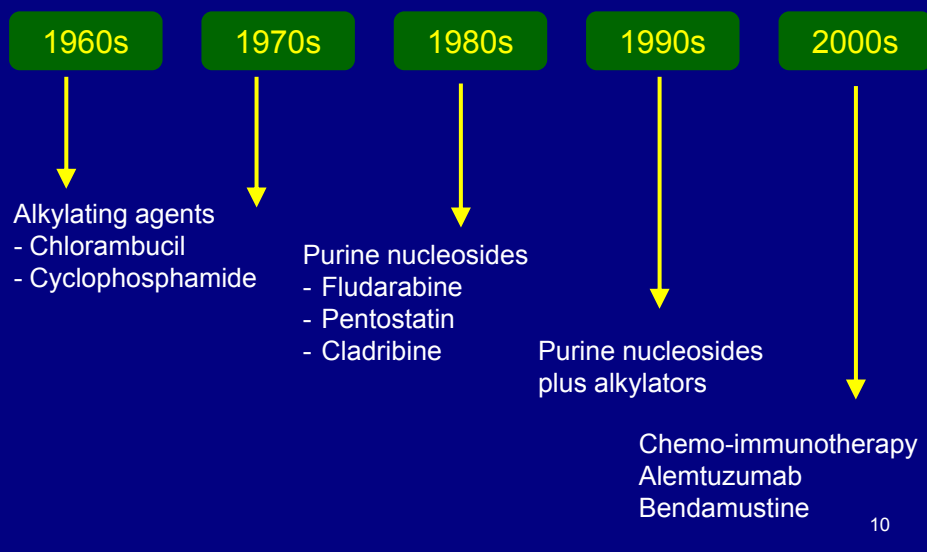
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## International Workshop on Chronic Lymphocytic Leukemia (IWCLL) Indications for Treatment

- Binet stage B or Rai stages I or II, with at least one of the following
  - Splenomegaly, when symptomatic, progressive, or massive
  - Lymphadenopathy, when symptomatic, progressive, or massive
  - Progressive lymphocytosis
  - Autoimmune anemia, and/or thrombocytopenia unresponsive to steroids
  - A disease-related symptom (ie, unintentional weight loss significant fatigue, fever, night sweats)
  - Progressive marrow failure
- Binet stage C, Rai stages III or IV

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## Previously Untreated CLL Treatment Options



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## Defining CR in CLL

### Current NCI-WG Criteria

Symptoms	None
Lymphocyte count	$\leq 4000/\mu\text{L}$
Lymph nodes (liver, spleen)	No palpable disease
Neutrophils	$\geq 1500/\mu\text{L}$
Platelets	$> 100,000/\mu\text{L}$
Hemoglobin	$> 11 \text{ g/dL}$
Bone marrow	$< 30\%$ lymphocytes, no nodules

Cheson BD, et al. *Blood*. 1996;87:4990-4997.

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## International Workshop on Chronic Lymphocytic Leukemia (IWCLL)

### Role of CT Scan

- “CT scans generally are *not* required for the initial evaluation or follow-up”
- Enlarged lymph nodes detected only by CT do not change Binet or Rai stage
- Progression in Rai stage 0 predicted by abdominal CT in 1 study, more research needed
- Recommended for clinical trials

Hallek M, et al. *Blood*. [Published online ahead of print January 28, 2008].  
Muntanola A, et al. *J Clin Oncol*. 2007;25:1576-1580.

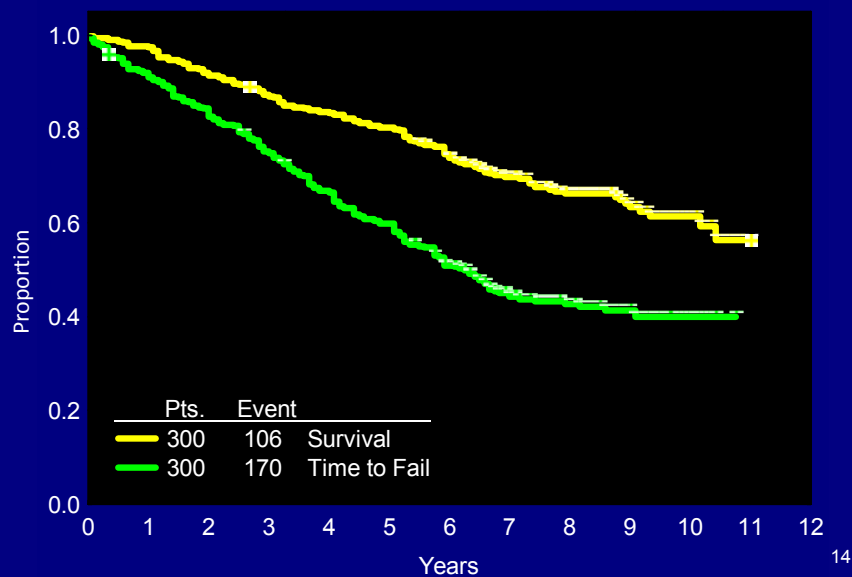
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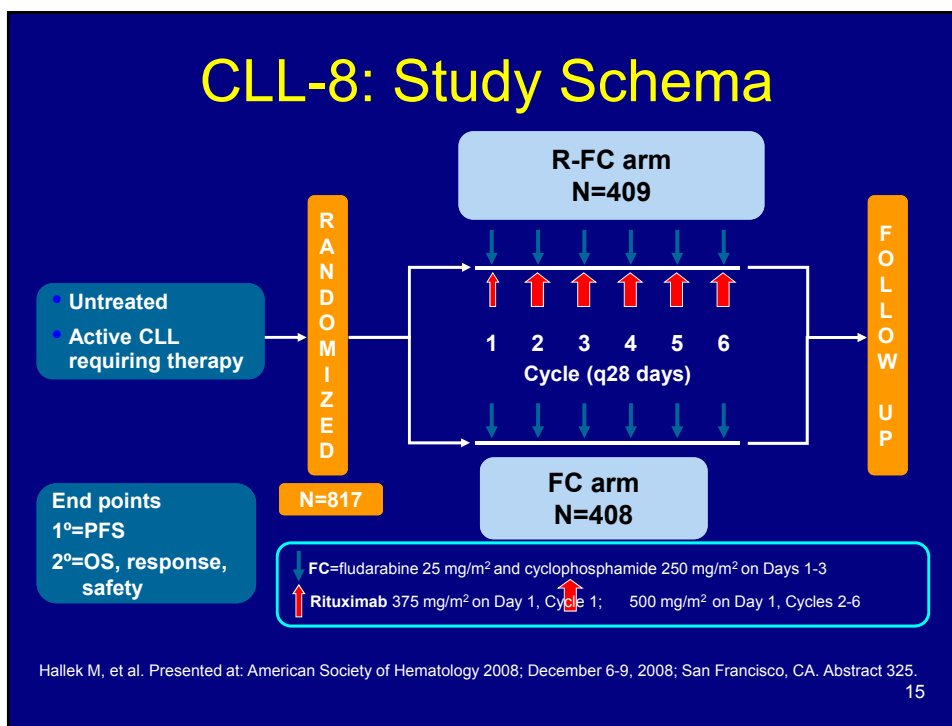
## Response to FC + Rituximab (NCI-WG: 300 Patients)

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

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## FCR-300 Survival and Time to Fail





## Is FCR good for everyone ?

**Mutation status?**

**17p- (p53 mutation)?**

**11q- (ATM deletion)?**

**Age greater than 70 years?**



## FISH CYTOGENETICS AND MUTATION STATUS

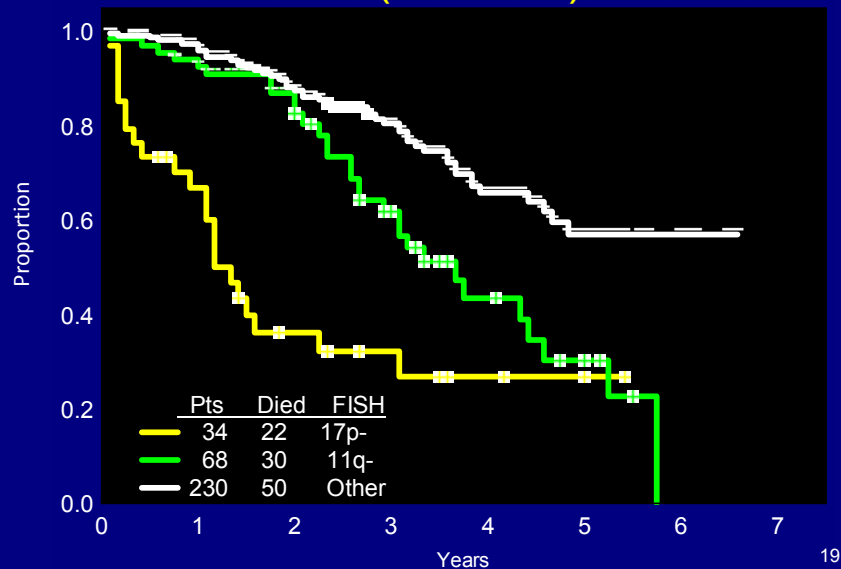
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### Prospective Evaluation of Prognostic Factors Post FCR Study (2004-2010)

Prognostic Factor	Value	Pts.	%CR	%nPR	%OR
FISH	-17p	37	35	5	76
	-11q	75	76	9	97
	Trisomy 12	66	80	11	98
	-13q	100	66	8	98
	Negative	70	71	11	96

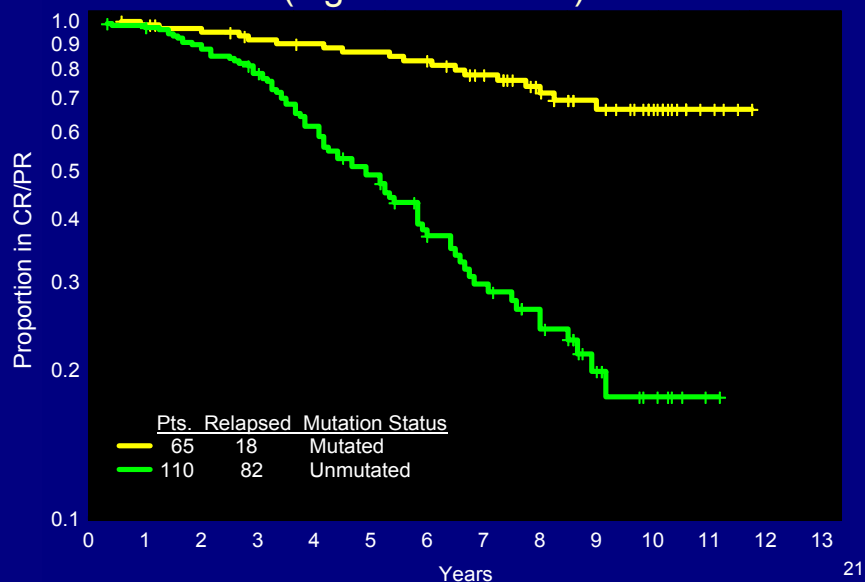
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## Time to Fail Untreated CLL Age <70 by FISH (2004-10)



Mutation status,  
zap70 and CD38 are  
not good predictors of  
probability of CR!

## FCR Time to Progression by Mutation Status (logarithmic scale)

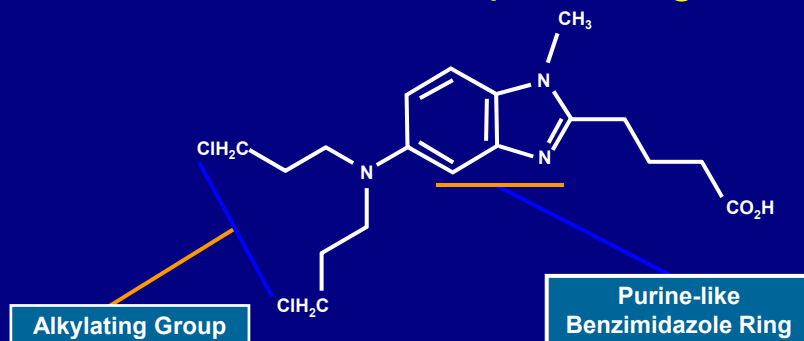


## New Treatments for CLL - 2012

1. Ofatumumab, GA-101, Abt-263, etc
2. Bendamustine, Nelarabine
3. CAL 101(PI3-K Delta inhibitor), BTK Inhibitor,
4. PEITC (Huang), Sapacitabine (Plunkett)
5. Lenalidomide , Flavopiridol, SCH-727965
6. Immuno-therapy (CARs)
7. OFAR (Oxaliplatin)—Richter's
8. Non –ablative allo transplant.

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## Bendamustine Bifunctional Antineoplastic Agent



Available in Germany, 1971 - 1992  
Unique in vitro anti-tumor profile

Rummel M, et al. *J Clin Oncol*. 2005;23:3383-3389.

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## Refractory CLL Alemtuzumab US Trial: Toxicity

	All Grades, %	Grade 3 - 4, %
Infusion-related reaction		
Rigors	90	14
Fever	85	20
Nausea	53	0
Vomiting	38	1
Rash	33	0
Dyspnea	28	12
Hypotension	17	2
Infection	55	26
CMV reactivation	8	4
Septicemia	15	10

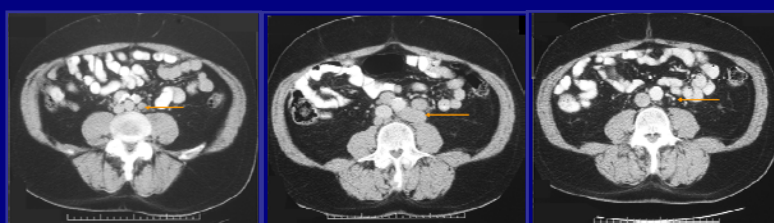
Keating MJ, et al. *Blood*. 2002;99:3554-3561.

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## Tumor Flare Reaction

### Occasional

- Fever
- Bone pain
- ↑ WBC/ALC



Baseline

Flare reaction

Post-treatment

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## Prevention of Tumor Lysis Syndrome

- A lower starting dose of lenalidomide followed by a closely monitored dose escalation scheme
- TLS prophylaxis with hydration and allopurinol
- Increased frequency of safety monitoring for TLS
- Exclusion of patients with a history of renal failure requiring dialysis

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## Lenalidomide in Elderly CLL: Response (2008 NCI-WG Criteria)

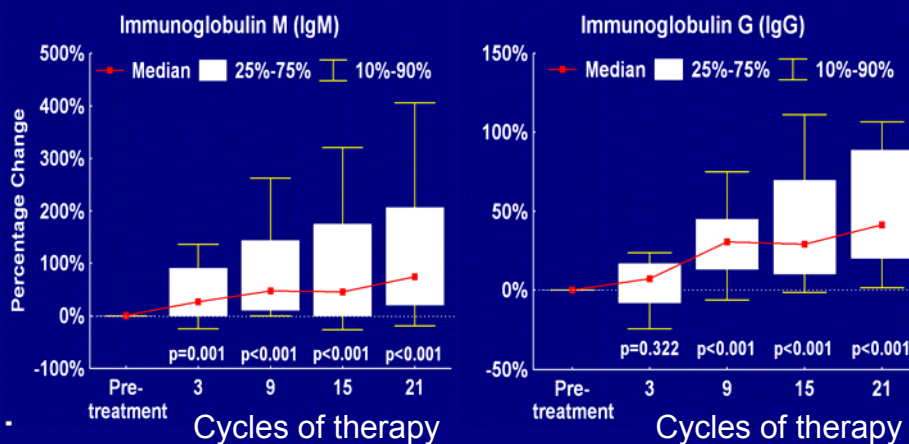
N = 60	NCI Response	
	n patients	%
CR*	6	10
CRi*	3	5
Nodular PR	3	5
PR	25	42
ORR	37	62

\*4 patients (8%) with flow cytometry negative CR

Badoux, X et al. (submitted)

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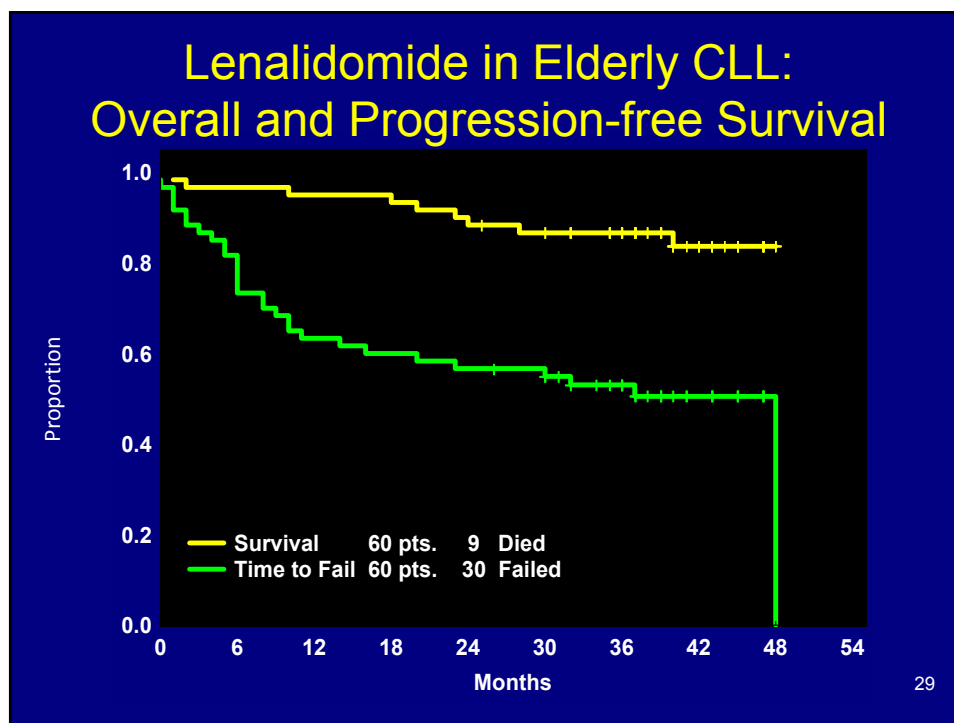
## Lenalidomide in Elderly CLL: Serum Immunoglobulins (n=37)



8/16 (50%) patients with IgG<600mg/dl → normalized serum IgG

THE UNIVERSITY OF TEXAS  
MDAnderson  
Cancer Center  
Making Cancer History

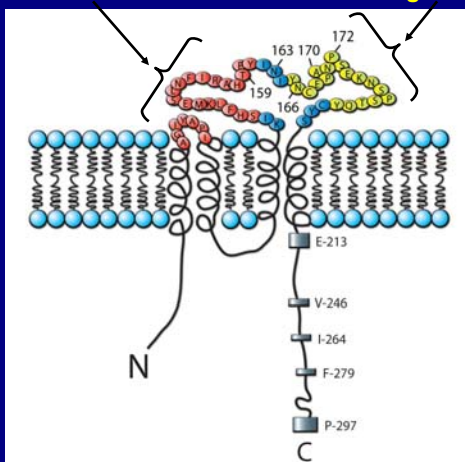
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## NEW ANTIBODIES

# Ofatumumab: Characteristics

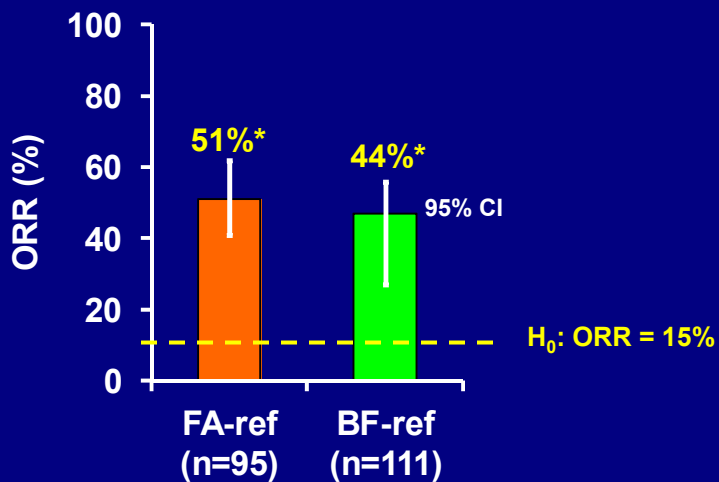
Ofatumumab binding site      Rituximab binding site



- Human CD20 mAb
- Potent lysis of B cells
- More effective *in vitro* CDC versus rituximab
- Effective CDC of cells with low CD20 expression, such as CLL cells

1. Teeling, et al. *J Immunol.* 2006;177;362.      2. Teeling, et al. *Blood.* 2004;104;1793.      31  
 3. Coiffier, et al. *Blood.* 2008;111;1094.

## Ofatumumab in refractory CLL Objective responses by IRC evaluation



\*P<0.0001 versus H<sub>0</sub> (two-sided exact test)

CI, confidence interval

Wierda et al. ASH 2010, Abstract 921

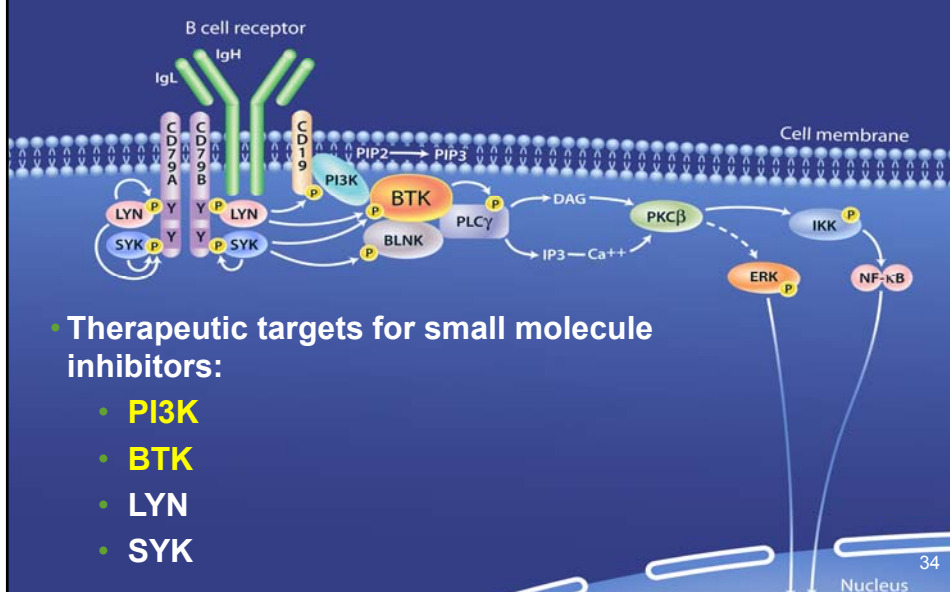
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# B CELL RECEPTOR SIGNALING

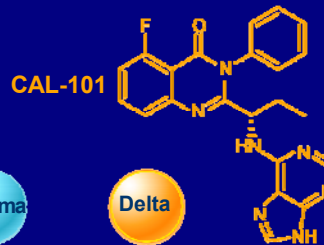
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## B Cell Receptor Signaling Pathway



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## CAL-101 is an Orally Bioavailable Small Molecule that Inhibits PI3K Delta Potently and Selectively



Class I PI3K Isoform	Alpha	Beta	Gamma	Delta
Cell-Based Activity	PDGF-induced pAKT	LPA-induced pAKT	fMLP-induced CD63+	FcεR1-induced CD63+
EC <sub>50</sub> (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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Reference: Lannutti, Blood, 2011

## PCI-32765 Novel Small Molecule Btk Inhibitor

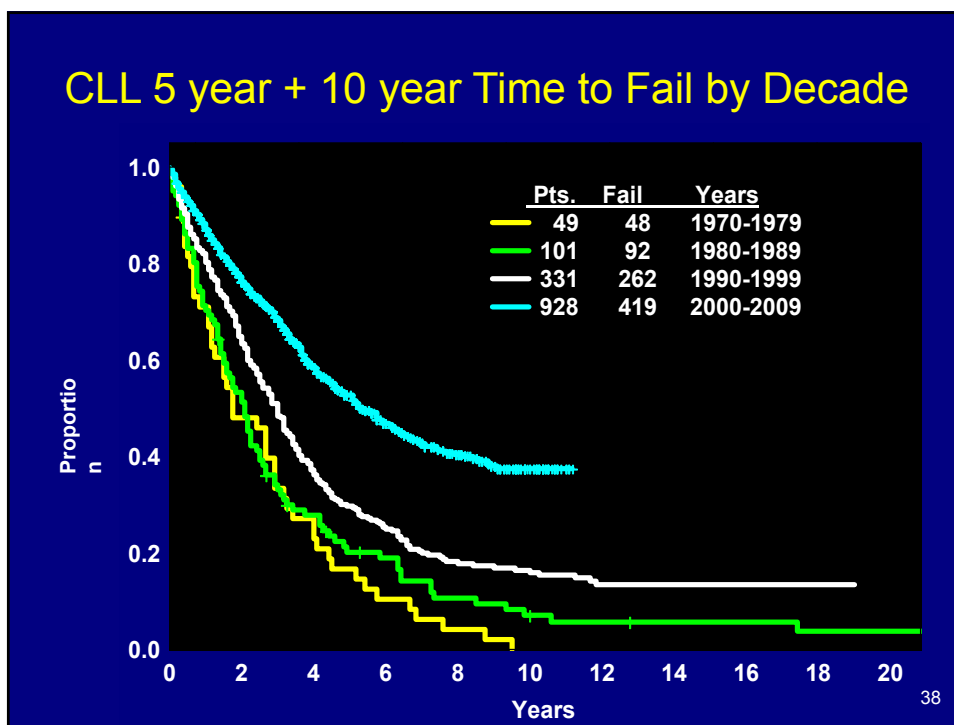
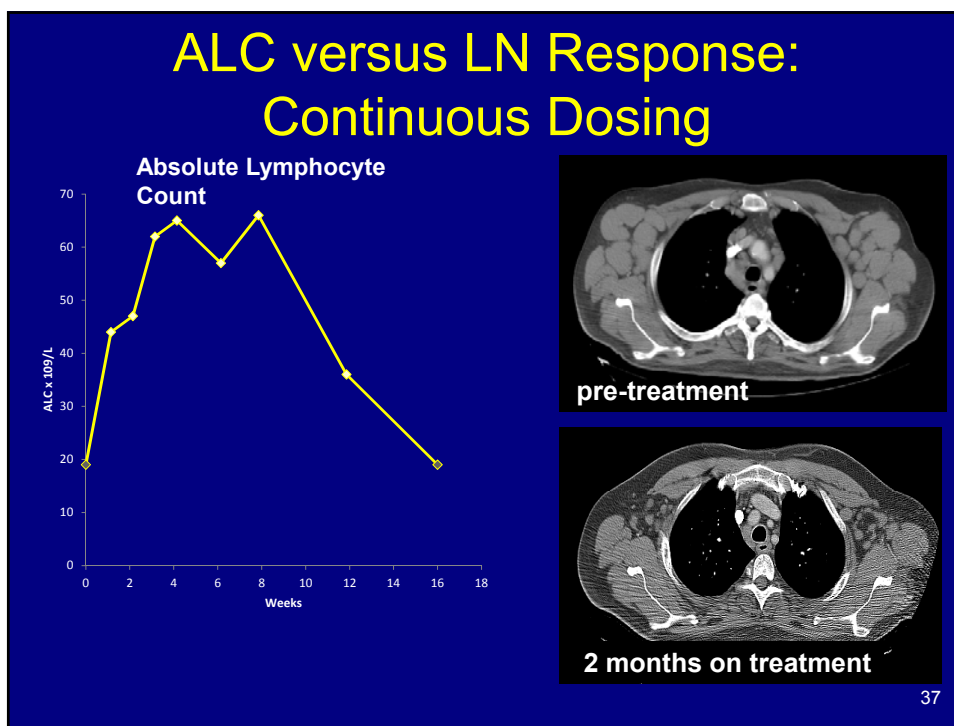
- Forms a specific and irreversible bond with cysteine-481 in Btk
- Potent Btk inhibition
  - IC<sub>50</sub> = 0.5 nM
- Orally available



Burger, et al. ASH 2010, Abstract 57.

PCI-32765

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## Frontline treatment of CLL 2015

- Induction with BCR Tyrosine kinase inhibitor
- Test for MRD with flow, plasma DNA, Mirs and other serum markers
- Consolidation with CARs or genetic specific therapies
- NST allogeneic transplants later

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## OTHER ISSUES REMAINING IN CLL

- AUTO-IMMUNE COMPLICATIONS
- RICHTER'S TRANSFORMATION
- HYPO GAMMA-GLOBULINEMIA
- SECOND CANCERS
- INFECTION OCURRENCE AND PREVENTION
- MARROW FAILURE

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## Question and Answer Session

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The Leukemia & Lymphoma Society's (LLS) Co-Pay Assistance Program offers financial assistance to qualified CLL patients to help with treatment-related expenses and insurance premiums. Patients may apply online or over the phone with a Co-Pay Specialist.

- **WEBSITE:** [www.LLS.org/copay](http://www.LLS.org/copay)
- **TOLL-FREE PHONE:** (877) LLS-COPAY

For more information about CLL and other LLS programs, please contact an LLS Information Specialist.

- **TOLL-FREE PHONE:** (800) 955-4572
- **EMAIL:** [infocenter@LLS.org](mailto:infocenter@LLS.org)