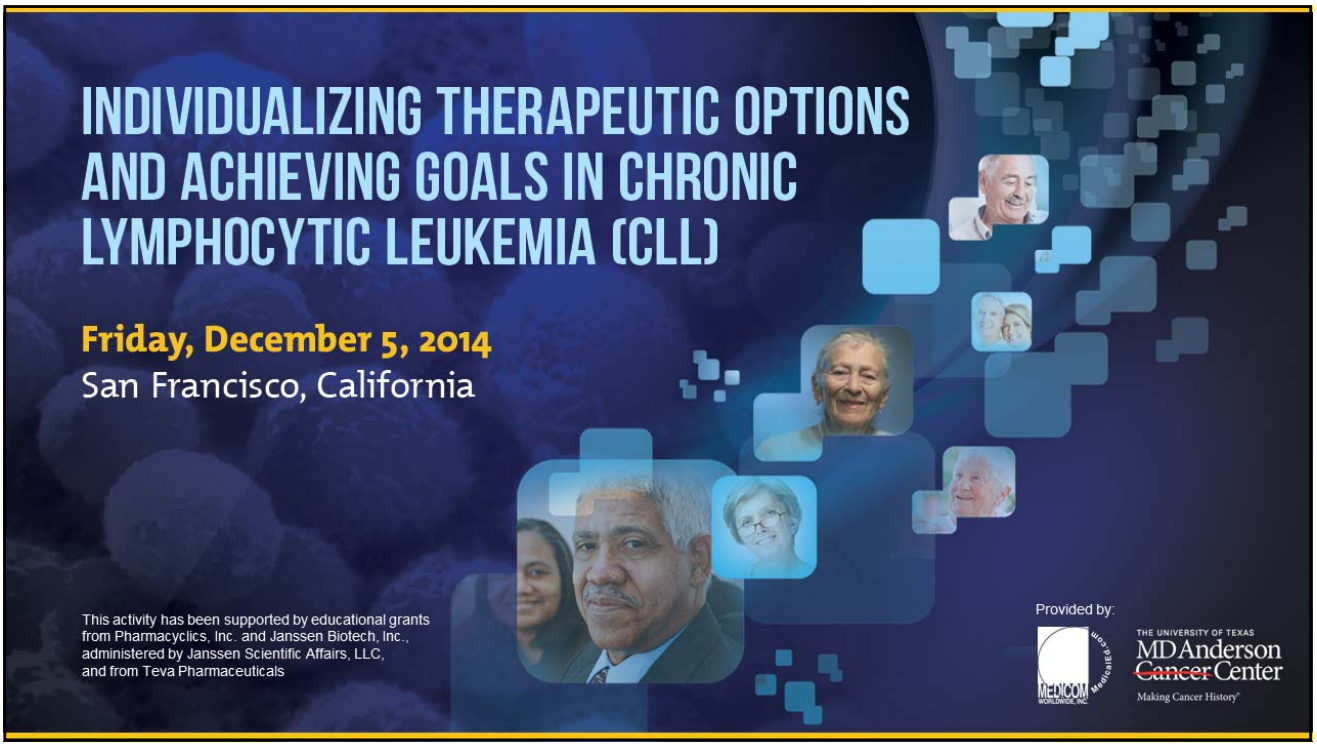
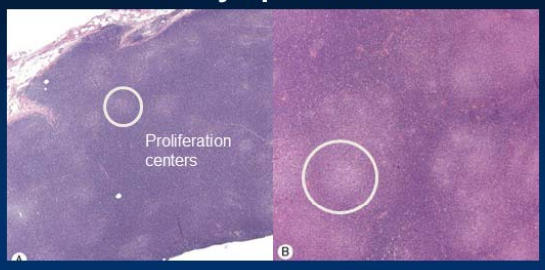


Case Presentation

Jan A. Burger, MD, PhD
Associate Professor
Department of Leukemia
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

In CLL Lymph Nodes, Sites of Proliferation = Sites of BCR Activation

CLL lymph nodes

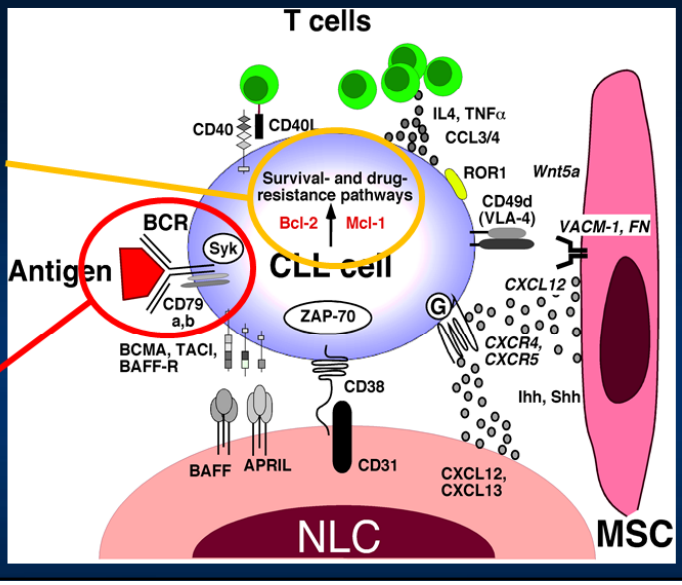


Soma LA, et al. *Human Pathology*. 2006;37:152-159.; Herishanu Y, et al. *Blood*. 2011.

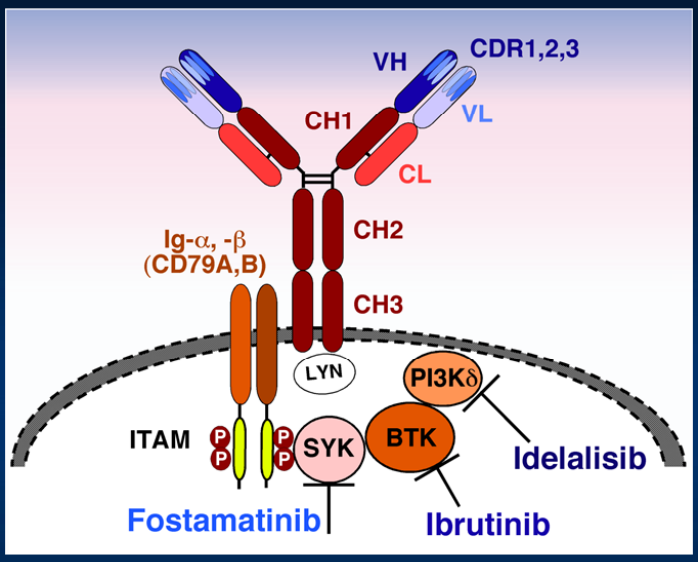
Co-stimulatory Signals in the Tissue Microenvironment

Bcl-2 antagonists (ABT-199)

BCRi



Targets in the BCR Signaling Pathway



Burger JA, Chiorazzi N. *Trends Immunol.* 2013.

BCR-associated Kinases

Kinase	Gene deletion/mutation	Activating receptors in B cells	Function in CLL	Inhibitor(s)
Spleen tyrosine kinase (SYK)	In mice: severe defect of B lymphopoiesis	BCR, integrins, chemokine receptors	Survival and migration via BCR- and chemokine receptor–signaling, chemokine secretion (CCL3, CCL4)	Fostamatinib, PRT2070, GS-9973
Bruton's tyrosine kinase (BTK)	In humans: X-linked agammaglobulinemia (XLA, Bruton's agammaglobulinemia) in mice: X-linked immunodeficiency (xid)	BCR, integrins, chemokine receptors	Survival, proliferation, and migration, BCR signaling, chemokine secretion (CCL3, CCL4)	Ibrutinib, CC292, ONO-4059, ACP-196
PI3Kδ	In mice: deficient antibody responses, lack of B1 cells and marginal zone B cells	BCR, integrins, chemokine receptors	CLL cell survival and migration, chemokine secretion (CCL3, CCL4)	Idelalisib, IPI-145, GS-9820, AMG 319, TGR-1202

Case 1

- 51-year-old male with relapsed CLL and progressive lymphocytosis, lymphocyte doubling time <6 months
- CLL since 1997, previous treatment FCR and bendamustine

PE:	0.5-1 cm cervical nodes No axillary or inguinal nodes or palpable spleen
Lab:	WBC 45,200, 84% lymphocytes Hgb 13.7, platelets 115,000
Flow:	$CD19^+$, $CD5^+$, $CD23^+$ CD20 weakly positive, $CD38^-$
FISH:	11q-, 13q-
IgVH:	Unmutated (1.3% deviation from germline)
CT	Spleen slightly enlarged (15 cm), abdominal nodes up to 2 cm

Case 1 (continued)

- This patient started ibrutinib single agent in 9/2010
- Treatment well tolerated, no relevant side effects
- Lymphocytosis progressed from 45,200 to 94,300/µL in 10/2010, Hb and platelet counts stable

- Which of the following statements are NOT consistent with 11q deletion CLL and response to therapy?
  1. Male gender, presentation at a relatively young age, significant adenopathy, and absence of IGHV mutations (unmutated CLL/U-CLL) is typical in patients with CLL and 11q deletion
  2. A short remission duration after FCR and bendamustine is typical of patients with 11q deletion
  3. The patient is showing signs of early progression on ibrutinib with a short lymphocyte doubling time and alternative therapy should be considered
  4. The minimal side effects of ibrutinib within the first month are characteristic

Case 2

- A 43-year old female with newly diagnosed CLL. Dx in 2012, initially managed with observation
- 02/2014: comes for follow-up, no symptoms

PE	No enlarged lymph nodes or spleen
Lab	WBC 104,500, 79% lymphocytes Hgb 9.7, platelets 26,000, β_2M 2.4
Flow	CD19, CD5, CD23 positive CD20 weakly positive
FISH cytogenetics	Trisomy 12
IgVH	Mutated

Case 2: Treatment Options

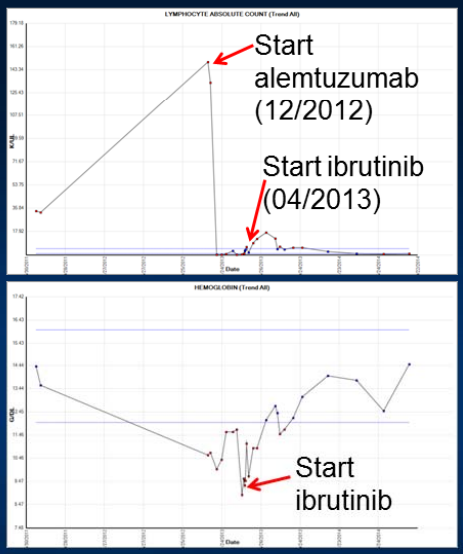
1. Oral steroids, FCR chemoimmunotherapy
2. High-dose Solu-Medrol + rituximab, followed by ibrutinib
3. Bendamustine + rituximab chemo-immunotherapy
4. Obinutuzumab (Gazyva®) + chlorambucil

Case 3

- A 54-year old female with CLL, Dx in 6/2011
- 12/2012: comes for follow-up, complains of fatigue

PE	No enlarged lymph nodes or spleen
Lab	WBC 162,300, 92% lymphocytes Hgb 10.6, platelets 223,000
Flow	CD19, CD5, CD23 positive CD20 weakly positive, CD38-
FISH cytogenetics	Del(17p), del(13q)
IgVH	unmutated

Case 3: Treatment Course



- Symptoms resolved after alemtuzumab (Campath)
- Anemia resolved on ibrutinib, patient continues on ibrutinib to date
- Restaging 8/2014: 10-20% marrow infiltration with del(17p) and del(13q),

Case 3: Allogeneic Stem Cell Transplantation Indicated?

1. Yes, because patient has a median PFS of 28.1 months on ibrutinib due to del(17p), and patients with PD on ibrutinib have very poor outcome
2. No, patient has excellent QOL and allogeneic SCT only should be offered when clinical relapse is noted
3. Initiate donor search, recommendation depends on donor availability, comorbidity, and is an individualized decision process

Prognostic and Predictive Factors in CLL

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Division of Hematology-Oncology
Deputy Director of Research
UC San Diego Moores Cancer Center
La Jolla, California

Chronic Lymphocytic Leukemia (CLL)

- Clinical course of patients with CLL is highly variable
- Many patients are asymptomatic at diagnosis
- CLL is considered incurable, even with current therapy
- Therapy may cause morbidity or mortality
- Current recommendations are to withhold therapy until patients develop disease-related:
  - Symptoms (eg, fatigue, weight loss, enlarged spleen and LN)
  - Complications (eg, impaired marrow or immune function)
  - Clear evidence for disease progression

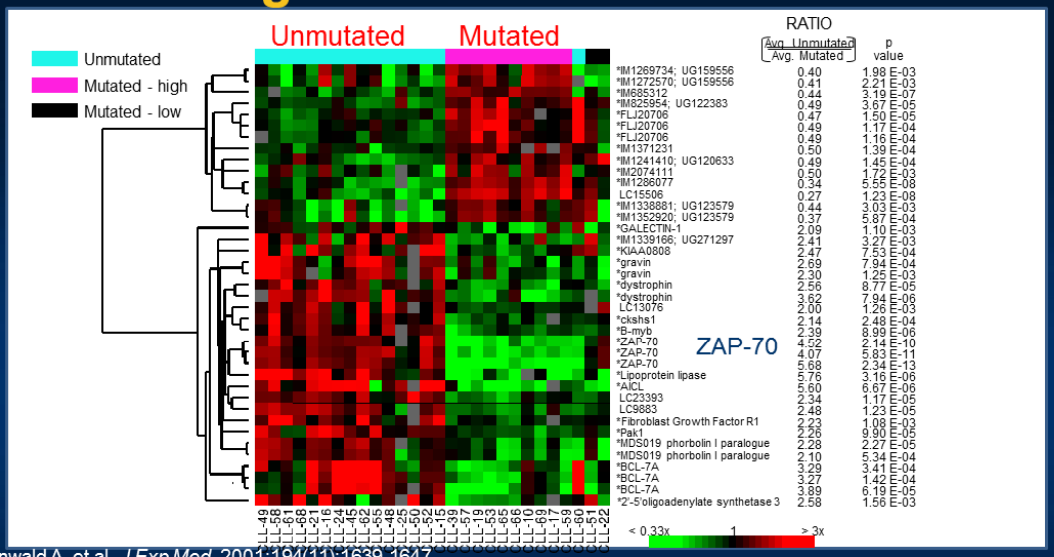
Stage-Independent Prognostic Factors

- Lymphocyte doubling time
  - Fewer than 6 months
- Serum markers
  - TK, β_2M, sCD23
- IgV_H genes
  - Mutations correlate with more benign disease
- $IgV_{H3\text{-}21}$ genes
  - Associated with poor outcome independent of IgV_H mutation status
- ZAP-70
  - Surrogate for IgV_H gene analysis
- CD38
  - Can be proliferative signal and increases survival
- Genomic aberrations detected by FISH
  - As disease progresses, karyotypic evolution may occur
- Differential expression of selected microRNA

β_2M=β_2-microglobulin; FISH=fluorescent in situ hybridization; sCD23=soluble CD23; TK=thymidine kinase; ZAP-70=zeta-chain associated protein kinase 70 kDa.

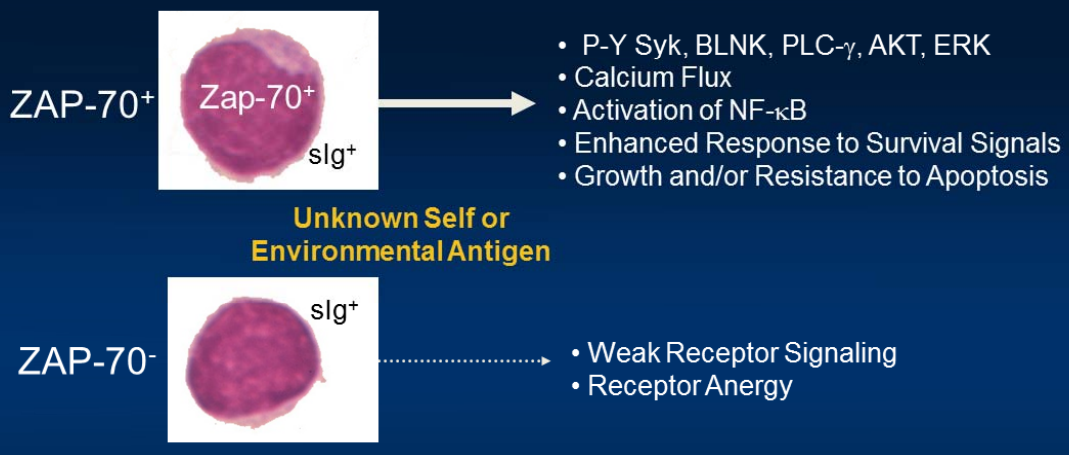
Hamblin T. *Best Pract Res Clin Haematol.* 2007;20:455-468.; Thorselius M, et al. *Blood.* 2006;107:2889-2894.; Montserrat E. *Hematology Am Soc Hematol Educ Program.* 2006;279-284.; Calin GA, et al. *N Engl J Med.* 2005;353:1793.; Stamatopoulos B, et al. *Blood.* 2009;113:5237-5245.; Visone R, et al. *Blood.* 2009;114:3872-3879.

Gene Expression Differences in CLL With or Without IgVH Gene Somatic Mutations



Rosenwald A, et al. *J Exp Med.* 2001;194(11):1639-1647.

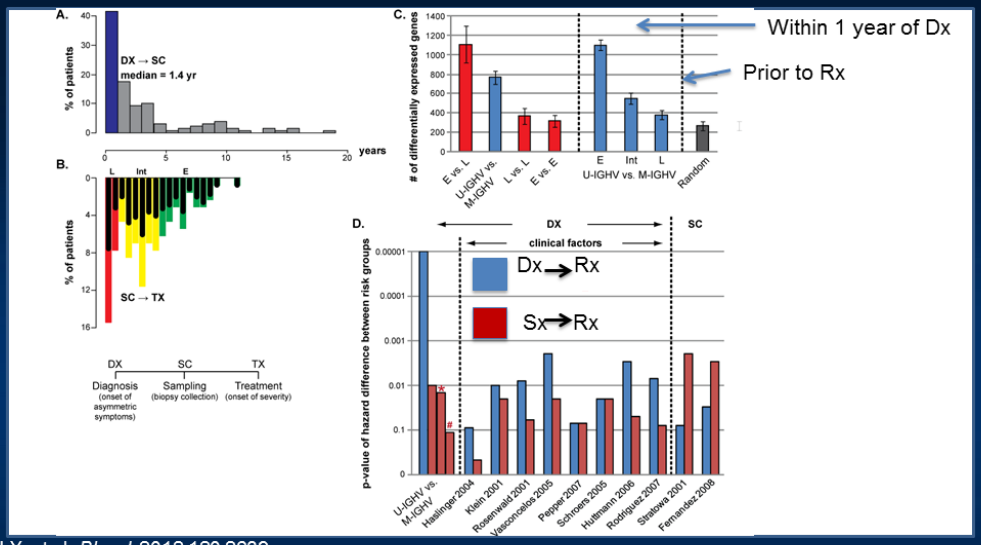
Surface Immunoglobulin Stimulation in ZAP-70+ vs ZAP-70- CLL



Chen L, et al. *Blood.* 2002;100:4609-4614.; Chen L, et al. *Blood.* 2005;105:2036-2041.; Chen L, et al. *Blood.* 2008;111:2685-2692.; Kipps TJ. *Best Pract Res Clin Haematol.* 2007;20:415-424.

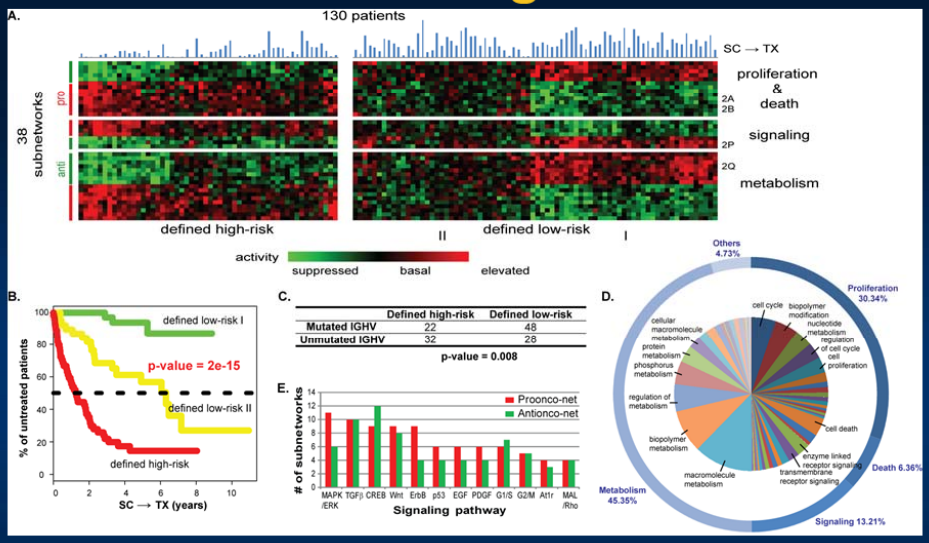
- However, CLL is a dynamic disease
  - Temporal heterogeneity
    - Changes over time in the CLL clone of any one patient
  - Anatomic heterogeneity
    - Changes in CLL depending upon its anatomic location

Gene Expression Differences in CLL With or Without IgVH Gene Somatic Mutations Become Less Apparent Over Time From Dx



Chuang H-Y, et al. *Blood*. 2012;120:2639.

Subnetwork Signatures Associated With Disease Progression



Chuang H-Y, et al. *Blood.* 2012;120:2639.

Subnetworks Associated With Disease Progression

Observation:
Activation of Wnt signaling is correlated with disease progression

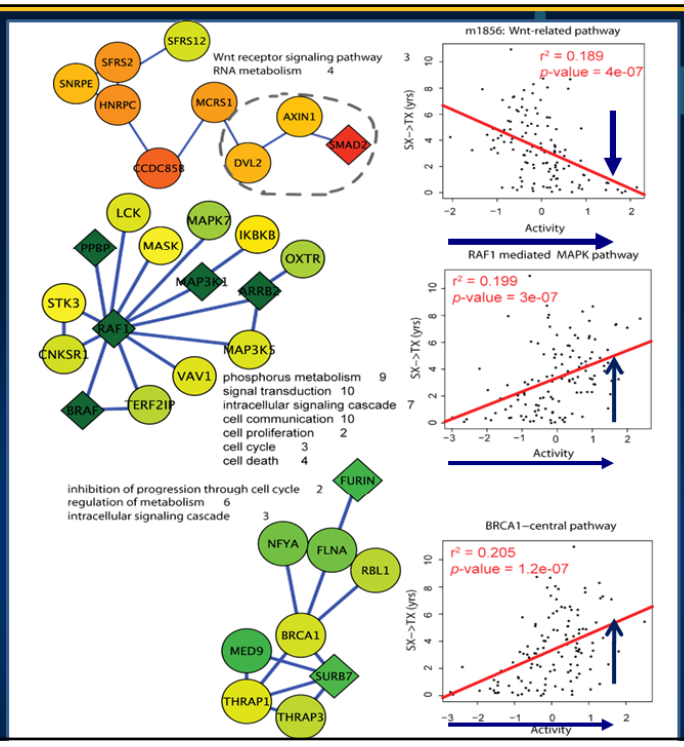
Evidence: Lu, et al. *PNAS*. 2003.
"*CLL with adverse prognostic markers expressed higher levels of Wnt3, Wnt5b and Wnt14*"

Observation:
Treatment-free survival is associated with networks involved
1. Resistance to apoptosis
2. Inhibition of cell cycle progression

Hypothesis:
Disease activity is associated with
1. Reduced resistance to apoptosis
2. Cell cycle progression

➔ Higher turnover rate might correlate with aggressive disease

Chuang H-Y, et al. *Blood.* 2012;120:2639.

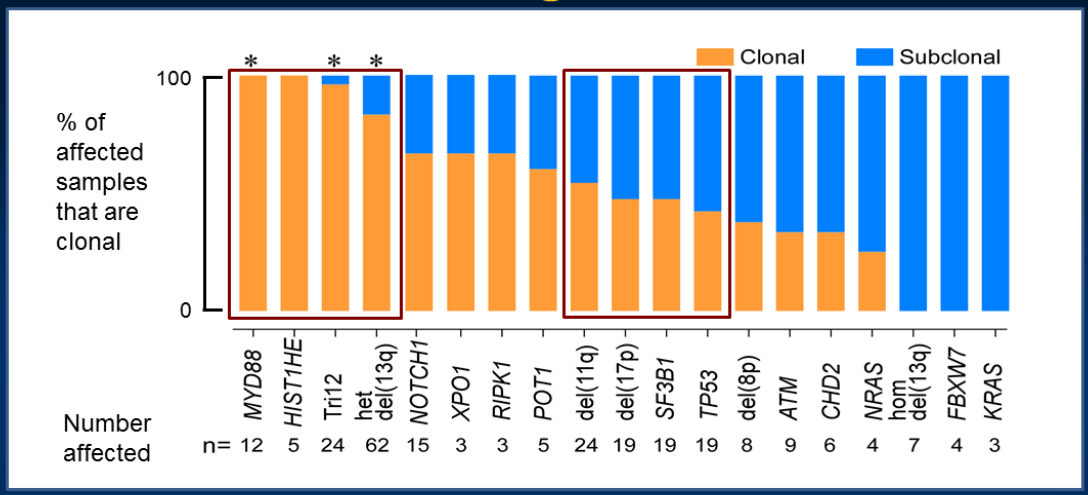


Pathways With Aberrancies/Mutations in CLL

- Notch Signaling
  - *NOTCH1, FBXW7*
- Toll-like Receptors
  - *MYD88, RIPK1*
- DNA Repair and Cell-cycle Control
  - *ATM, TP53, MYC*
- RNA Processing
  - *SF3B1, DDX3X, XPO1*
- Wnt Signaling
  - *ROR1, LEF1, MED12*
- B-cell Receptor Signaling
  - *IGHV, ZAP70, ITPKB, KRAS, NRAS*
- Chromatin Modification
  - *HIST1H1E*
- Regulatory microRNA
  - *miR-15a/miR-6, miR-155, miR-181, miR-150*

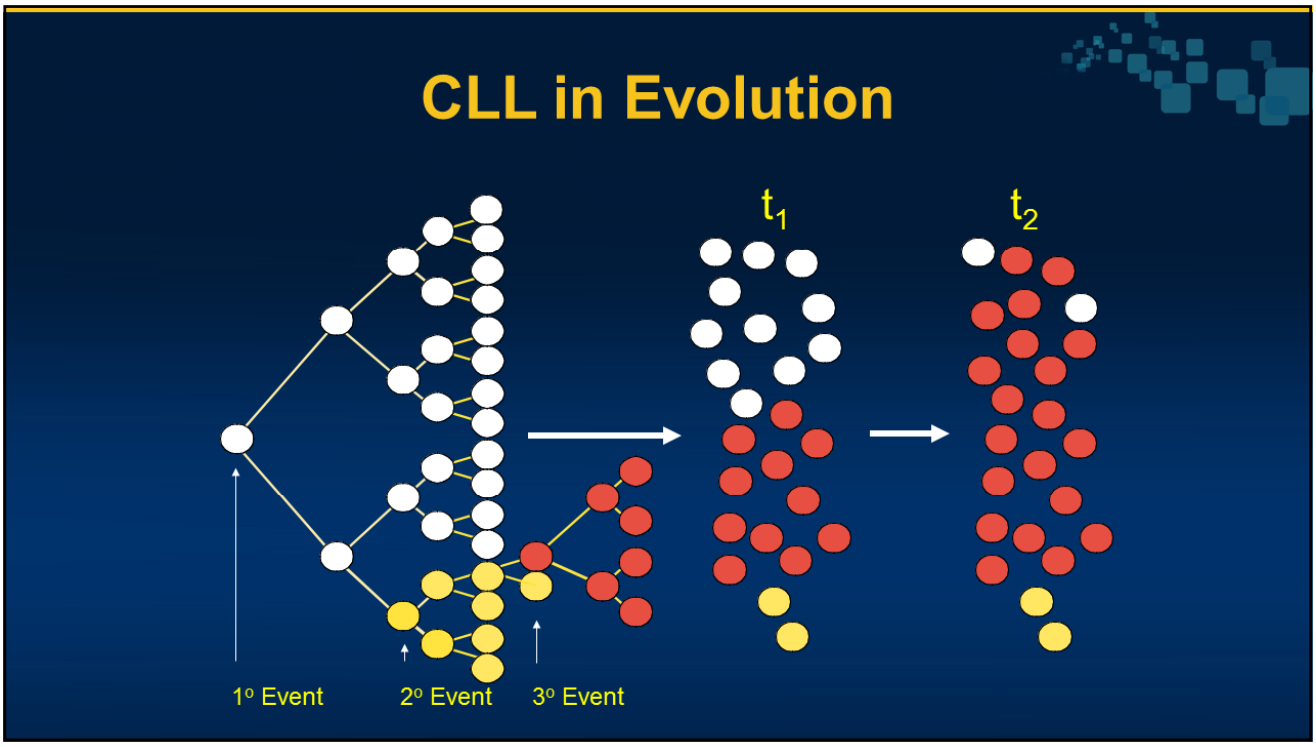
Chuang H-Y, et al. *Blood.* 2012;120:2639,

Early versus Late Drivers of CLL Progression



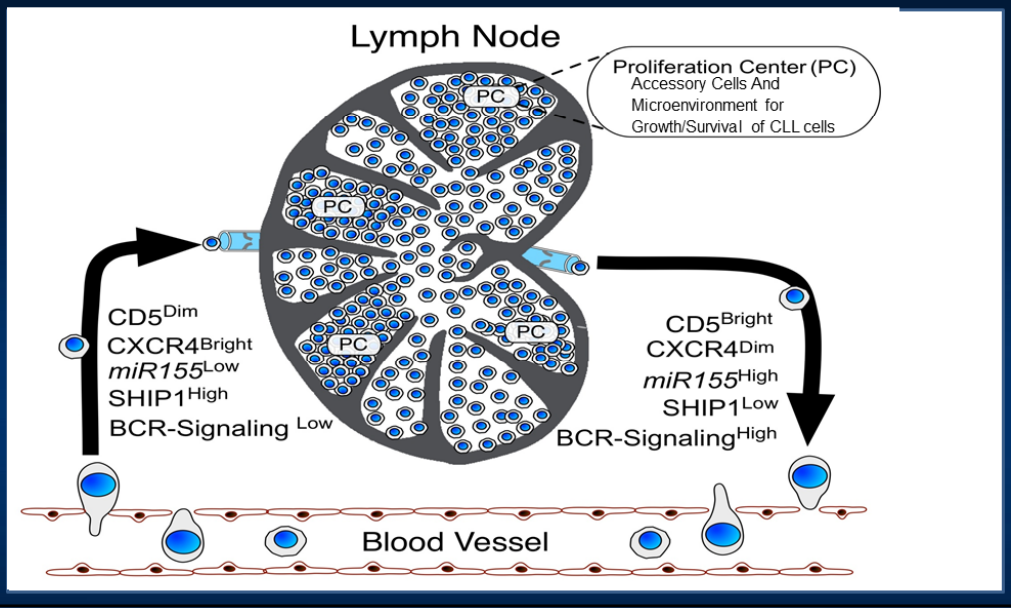
* Higher rate of clonal frequencies, q<0.1

Landau DA, et al. *Cell.* 2013;52:714.

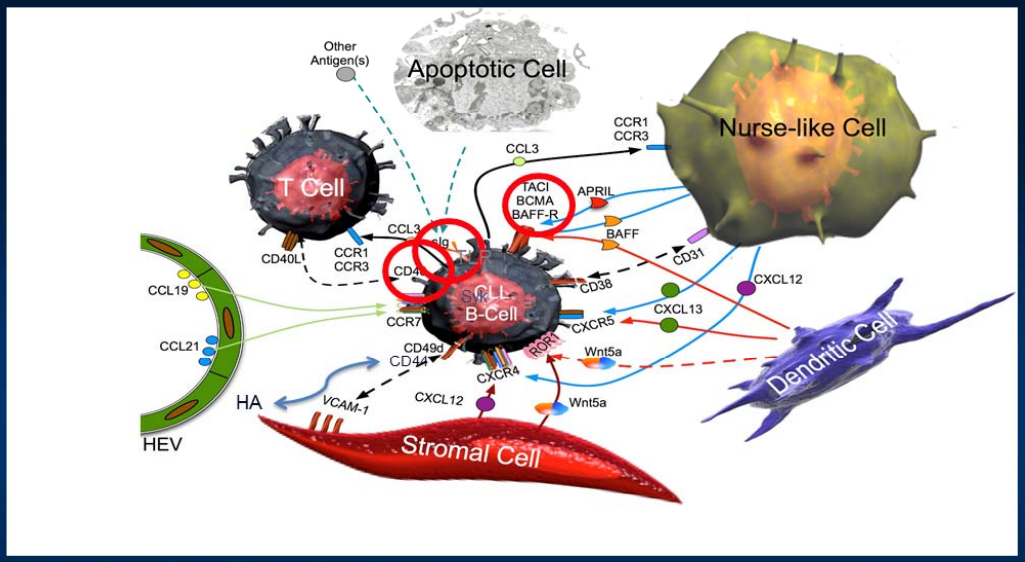


- However, CLL is a dynamic disease
  - Temporal heterogeneity
    - Changes over time in the CLL clone of any one patient
  - Anatomic heterogeneity
    - Changes in CLL depending upon its anatomic location

When CLL Behaves Like a Lymphoma – CLL Cells in the LN

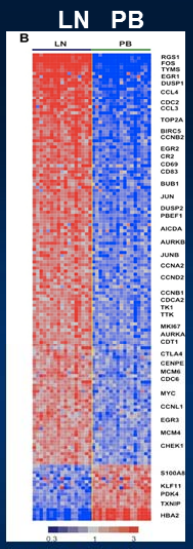


CLL in Proliferation Centers

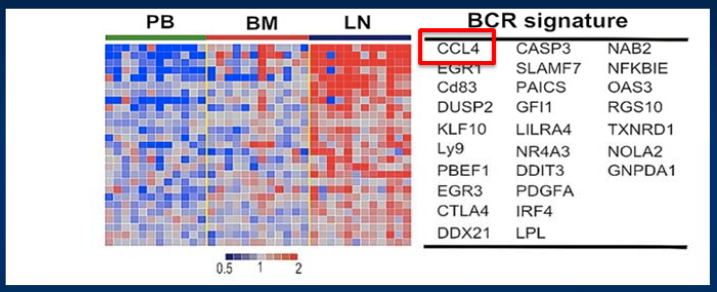


Fecteau J, Kipps TJ. *Front Biosci (Schol Ed)*. 2012;4:61-73.

CLL Cells From the Blood (PB) or Lymph Node (LN) of the Same Patient Have Differences in Gene Expression



Differences in gene signatures suggest that CLL cells in the LN are stimulated via activation of B-cell receptor (BCR) signaling and/or NF-kappaB

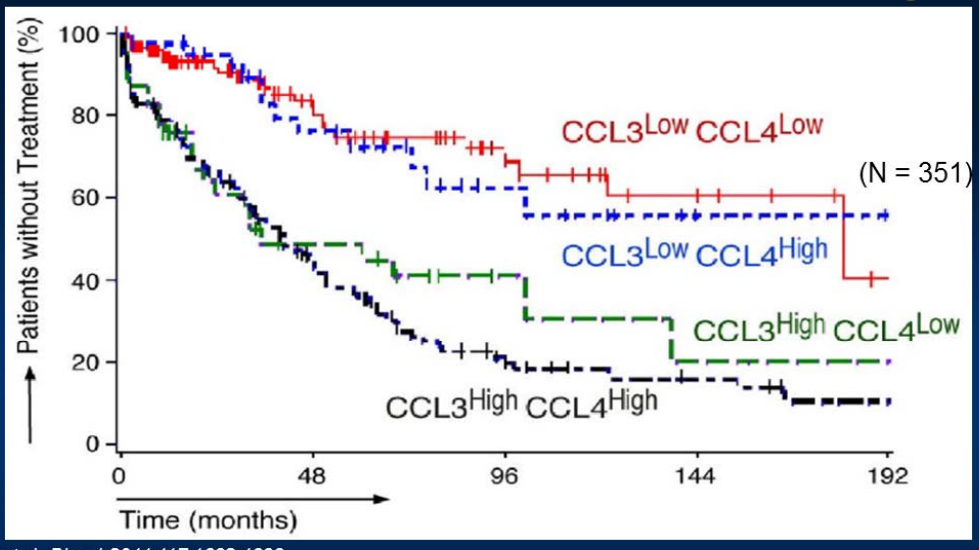


BCR signature

CCL4	CASP3	NAB2
EGR1	SLAMF7	NFKBIE
Cd83	PAICS	OAS3
DUSP2	GFI1	RGS10
KLF10	LILRA4	TXNRD1
Ly9	NR4A3	NOLA2
PBEF1	DDIT3	GNPDA1
EGR3	PDGFA	
CTLA4	IRF4	
DDX21	LPL	

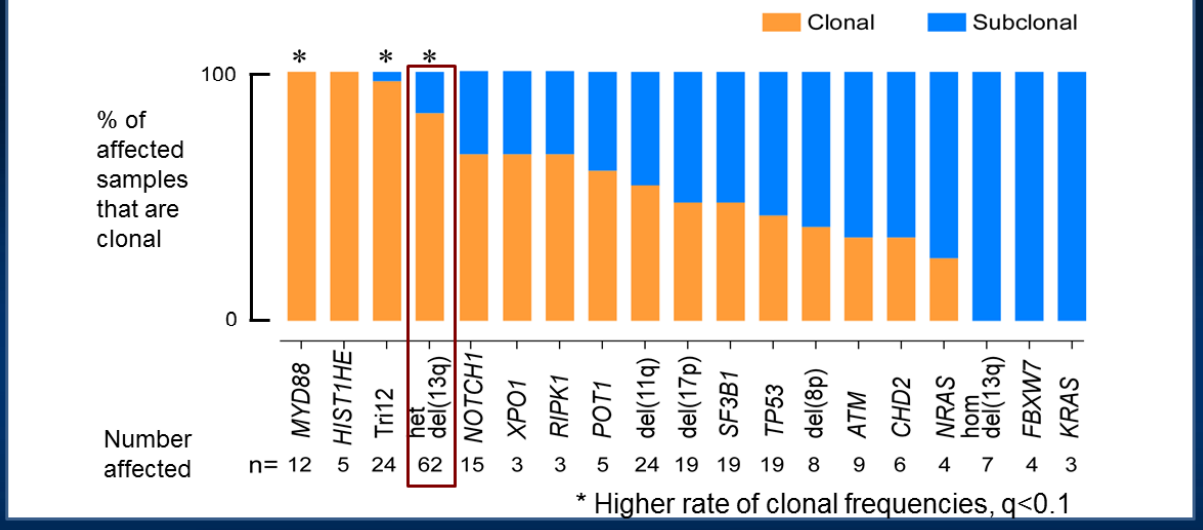
Herishanu, et al. *Blood.* 2011.

Patients With High CCL3 (≥10 pg/mL) Have Shorter Treatment-Free Survival From Diagnosis

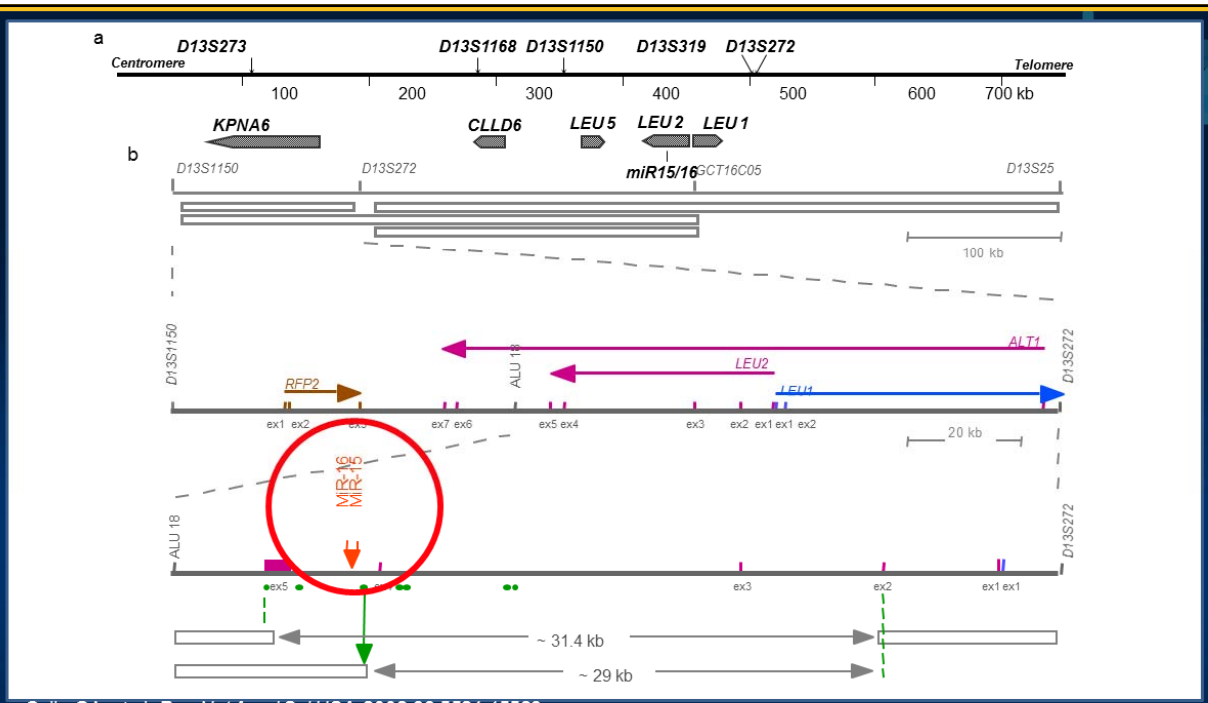


Sivina M, et al. *Blood.* 2011;117:1662-1669.

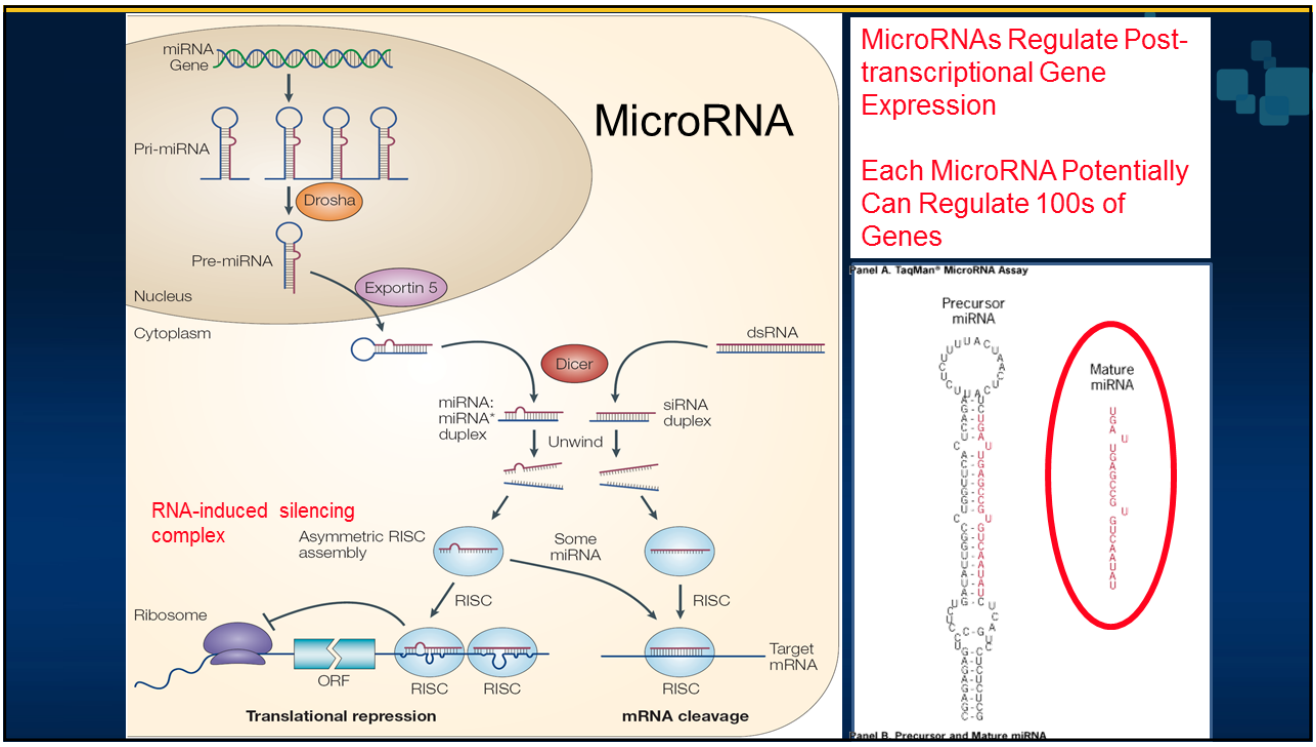
Clonal and Subclonal Drivers in CLL



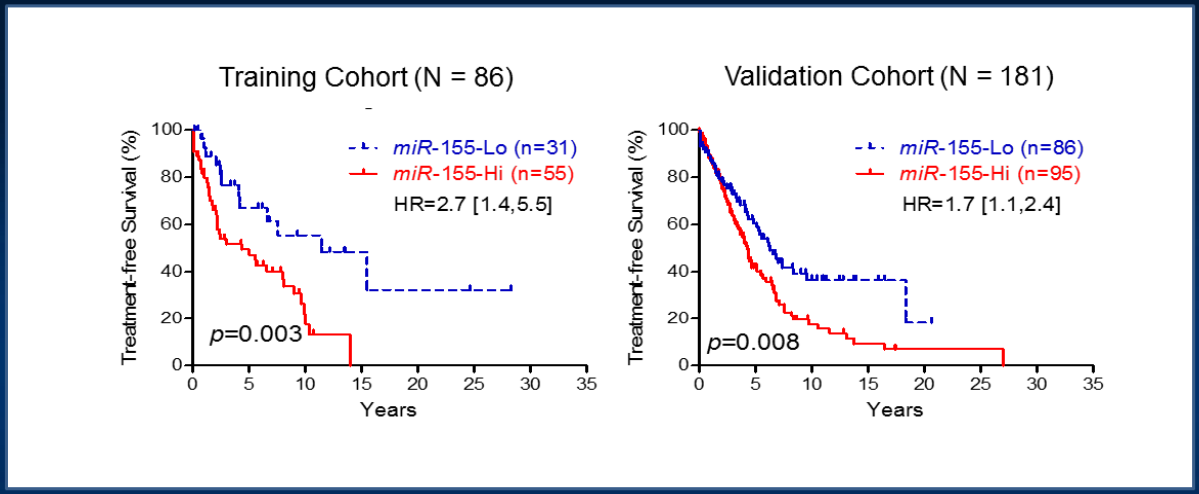
Landau DA, et al. *Cell*. 2013;152:714.



Calin GA, et al. *ProcNat Acad Sci USA*. 2002;99:5524-15529.

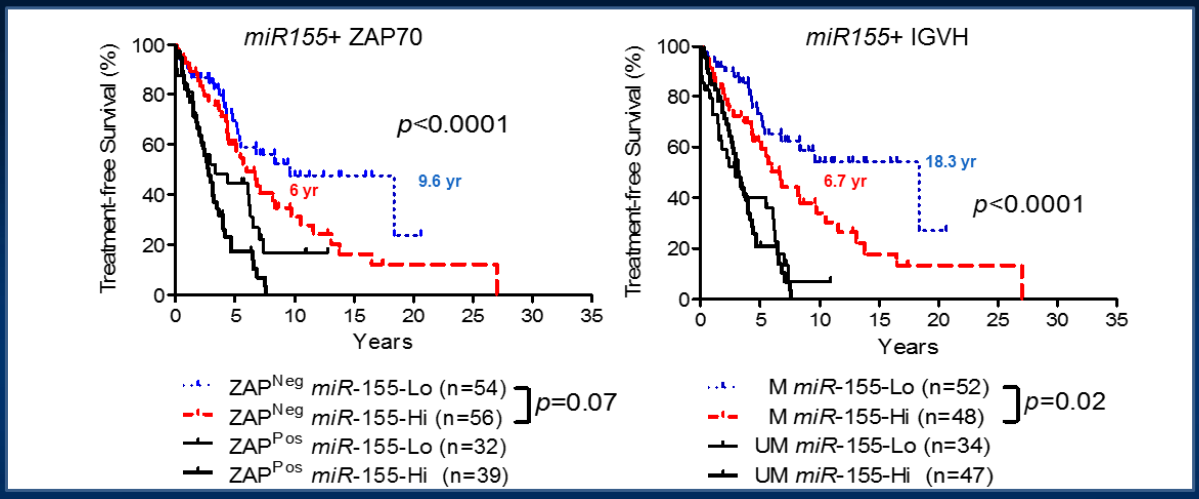


Expression of More Than 2,550 Copies of miR-155 Is Associated With Adverse Clinical Outcome



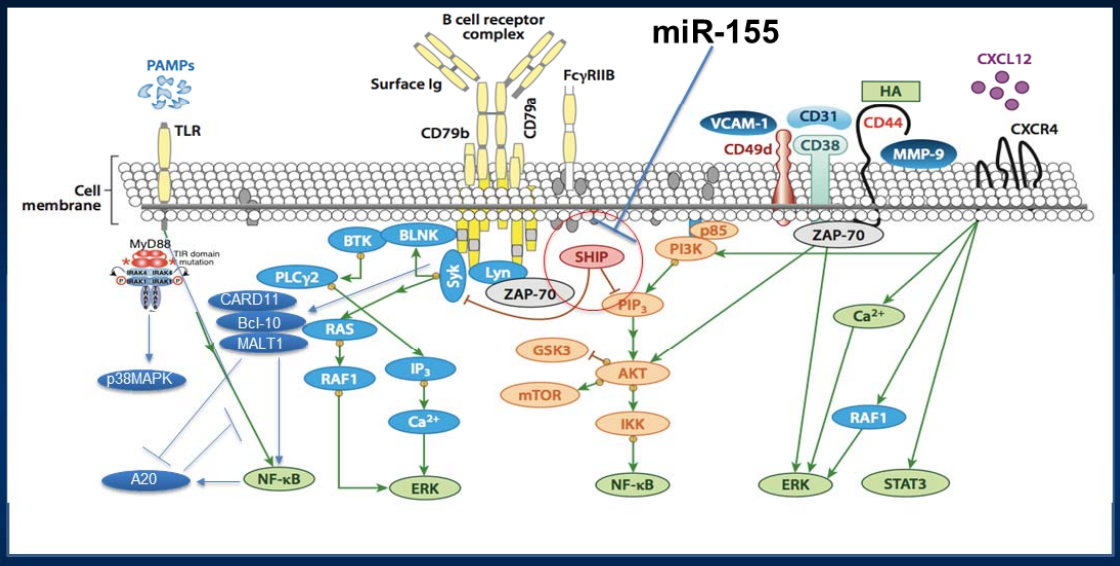
Cui B, et al. *Blood*. 2014;124:546.

High-level Expression of miR-155 Is Associated With Adverse Clinical Outcome

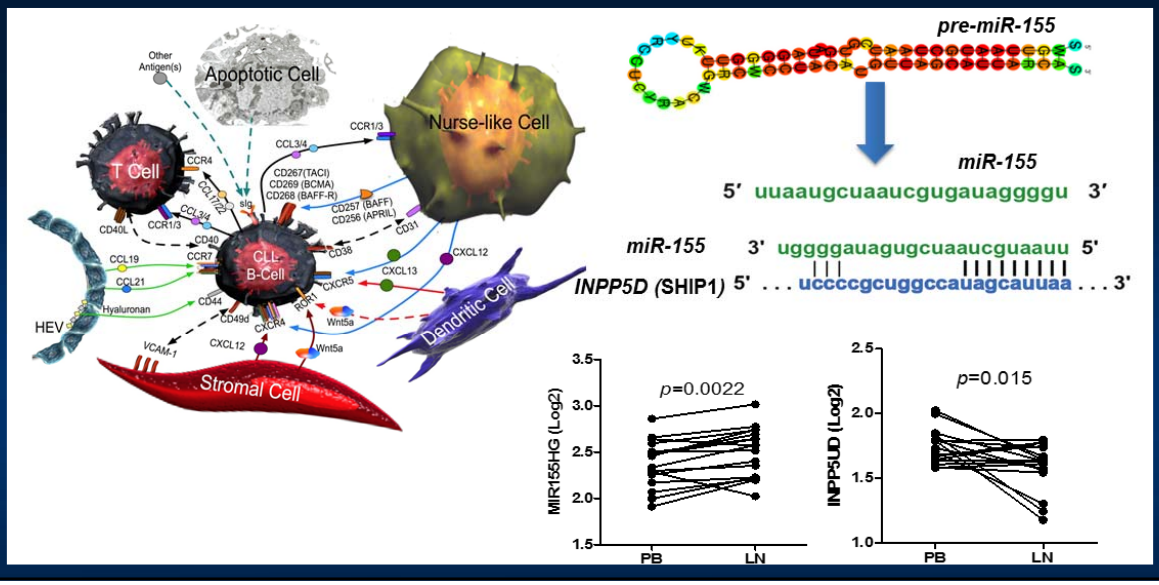


Cui B, et al. *Blood*. 2014;124:546.

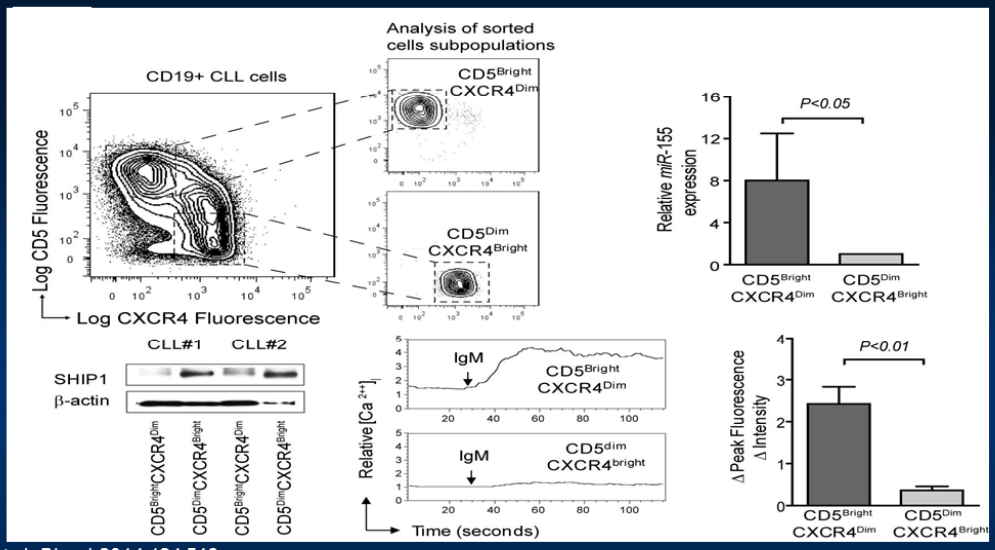
B-cell Receptor Signaling



Expression of Genes Encoding miR-155 or SHIP1 in CLL Cells in Lymph Node (LN) or Peripheral Blood (PB)

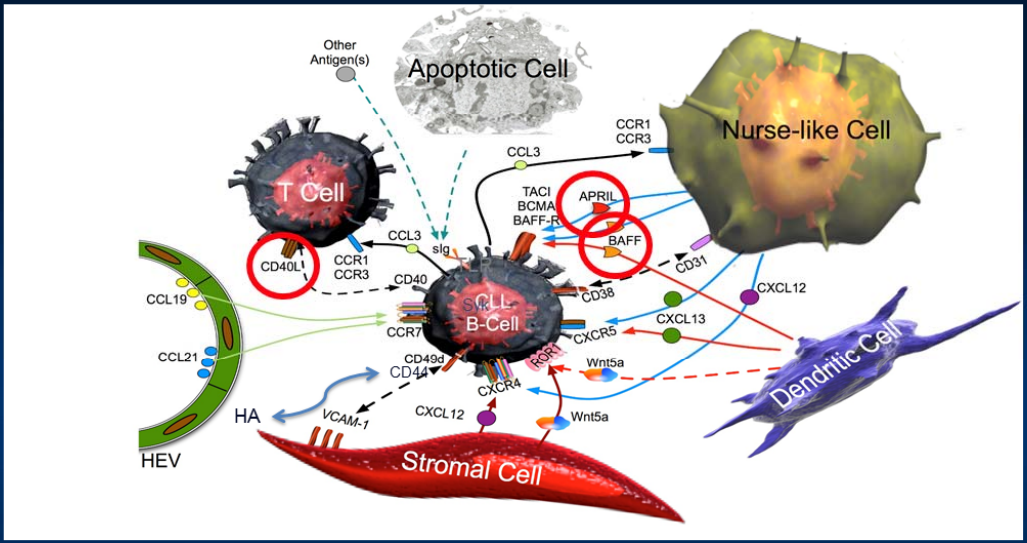


Intraconal Heterogeneity in Expression of miR-155



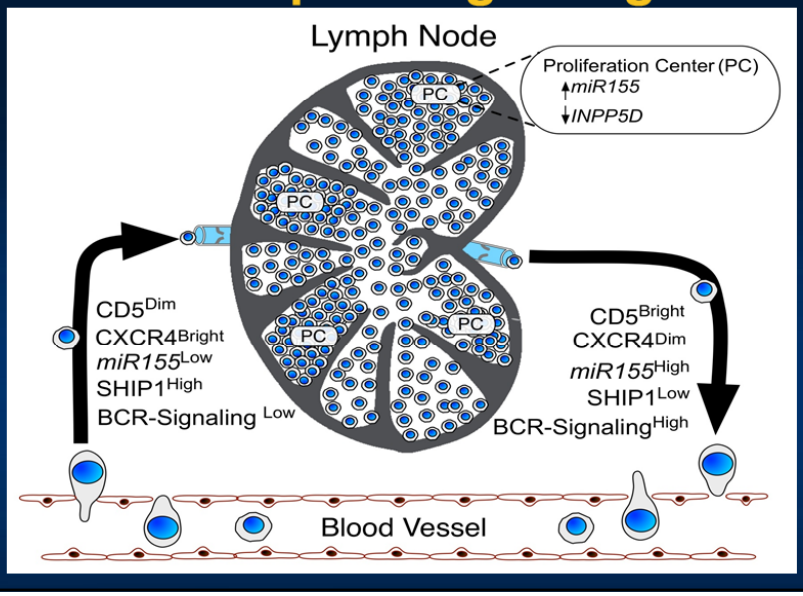
Cui B, et al. *Blood.* 2014;124:546.

CLL Microenvironment

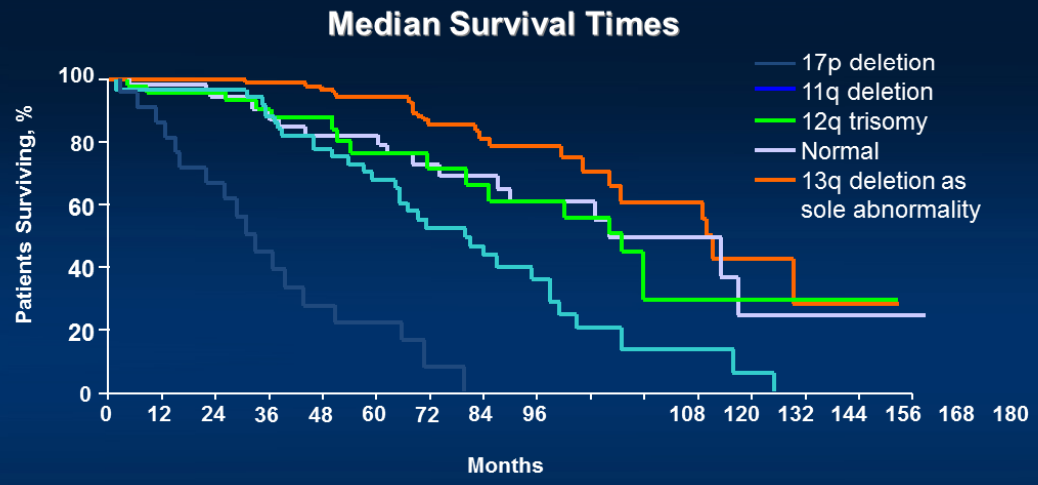


Fecteau J, Kipps TJ. *Front Biosci (Schol Ed)*. 2012;4:61-73.

MiR-155 Can Act As Rheostat for B-cell Receptor Signaling



CLL Genomic Aberrations Detected By FISH Probability of Survival



N=325

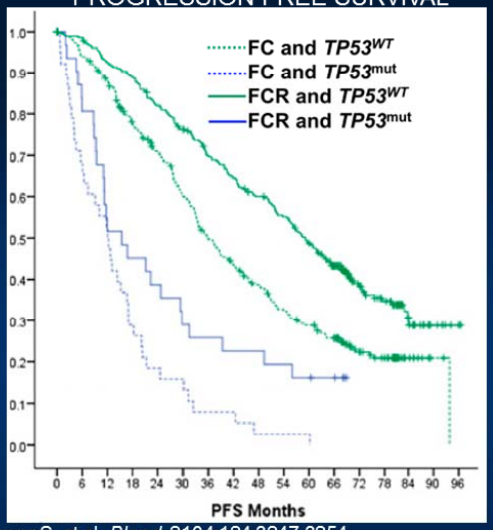
Döhner H, et al. *N Engl J Med.* 2000;343:1910-1916.

Different Types of Response to Chemoimmunotherapy in Patients With Different FISH Cytogenetics

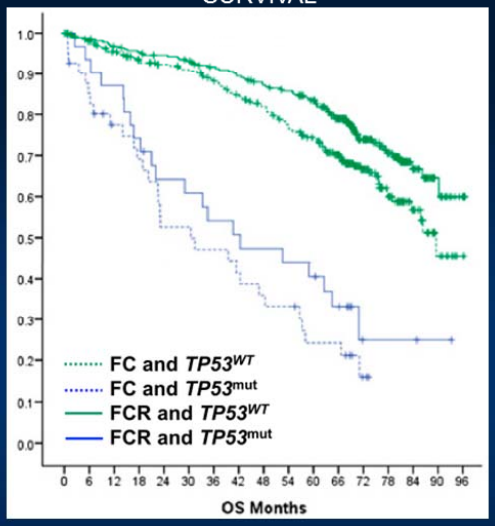
- 17p- p53 mutation
  - Resistant to chemotherapy but sensitive to antibodies, lenalidomide, bcl-2 inhibitors, BCR antagonists or allogeneic transplant
- 11q- ATM deletion and DNA repair defect
  - High CR rate, but short remissions. (Candidates for consolidation therapy?)
- Trisomy 12
  - High expression of CD20 - high CR rate to regimens with anti-CD20 mAbs
  - Can be associated with more aggressive disease with relatively short PFS
- 13q- MiR-15/16 deletion
  - High response rate.
  - Higher incidence of incomplete hemopoietic recovery (CRi)

Impact of TP53 on Outcome in CLL8

PROGRESSION FREE SURVIVAL



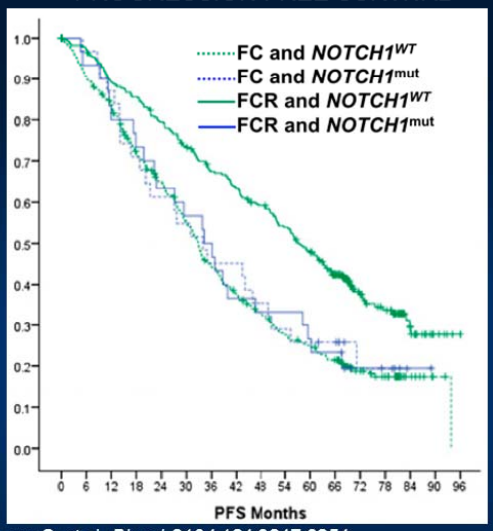
SURVIVAL



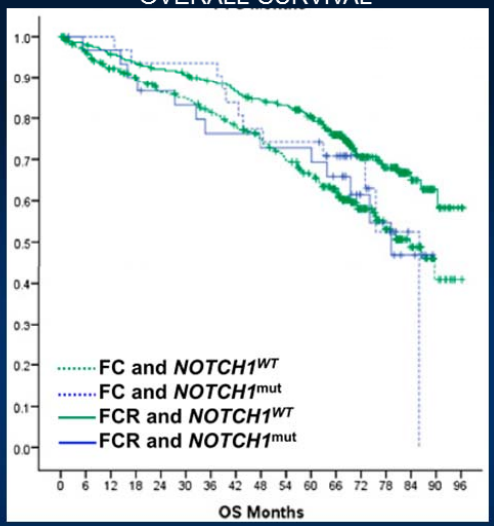
Stilgenbauer S, et al. *Blood.* 2104;124:3247-3254.

Impact of NOTCH1 on Outcome in CLL8

PROGRESSION FREE SURVIVAL

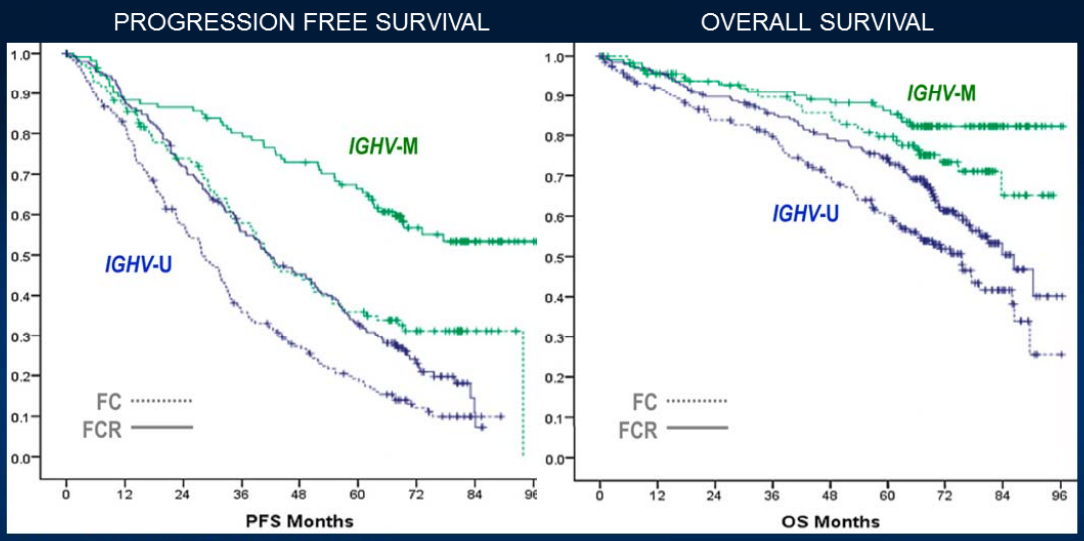


OVERALL SURVIVAL



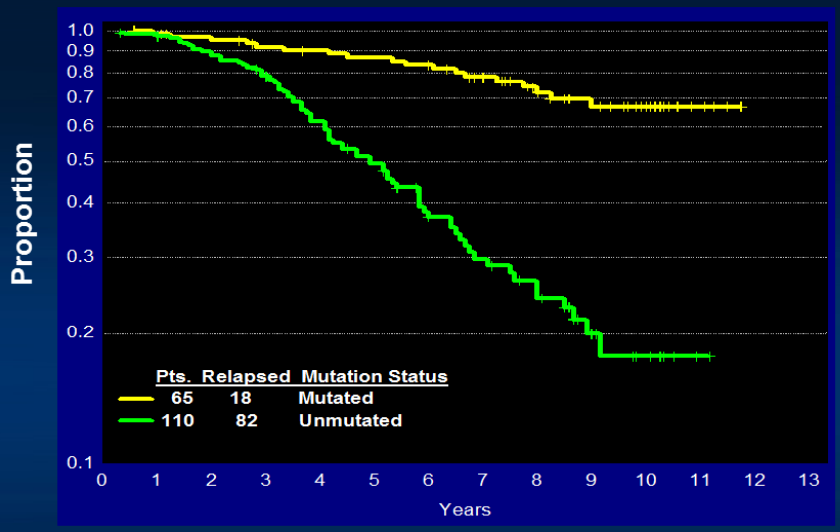
Stilgenbauer S, et al. *Blood.* 2104;124:3247-3254.

Impact of IGHV on Outcome in CLL8



Stilgenbauer S, et al. *Blood.* 2104;124:3247-3254.

FCR Time to Progression by IGHV Mutation Status (Logarithmic Scale)



Wierda W, et al. iwCLL Meeting – Cologne, 2013.

Prognostic Markers

- Fixed markers
  - Do not change over time
    - Ig VH mutation status
    - ZAP-70
  - Most useful in predicting PFS at diagnosis or after therapy
  - Generally do not predict the response to therapy
- Cytogenetic markers – fluorescence in situ hybridization
  - Define distinct prognostic subgroups
  - Certain FISH abnormalities predict poor or short-lived response to chemotherapy – eg, del(17p) or 11q
  - Can change over time or with therapy

Prognostic Markers

- Markers that can change over time
  - Gene expression subnetworks
    - May associate with disease progression
    - May be useful for predicting time from sample collection to therapy
  - Serum beta-2-microglobulin
    - High level associates with more aggressive disease and tumor burden
  - Lymphocyte doubling time
  - Certain genetic mutations
    - NOTCH1, SF3B1, TP53
- Biologic markers and the CLL microenvironment
  - CCL3/CCL4
  - Differential expression of certain microRNA
    - Eg, miR-155, miR-150
  - Provide insight into mechanisms of disease progression
  - Highlight importance of the microenvironment and B-cell receptor signaling to CLL biology

Prognostic Markers

- Newer therapies
  - May change the clinical implication of prognostic markers from bad to good and visa versa
    - FISH cytogenetics
    - Kinase inhibitors might provide greater benefit to patients with bulky disease with "adverse markers" associated with increased B-cell receptor signaling
- A poor prognosis is not due to bad disease, but rather bad medicine

Acknowledgements

- Bing Cui
- Suping Zhang
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UC San Diego Moores Cancer Center
An NCI-designated Comprehensive Cancer Center

California Institute for Regenerative Medicine

Chronic Lymphocytic Leukemia Research Consortium (CRC)

The Value of Traditional Chemoimmunotherapy

Peter Hillmen, MD, FRCP, FRCPath, PhD
Professor, Experimental Hematology
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Question

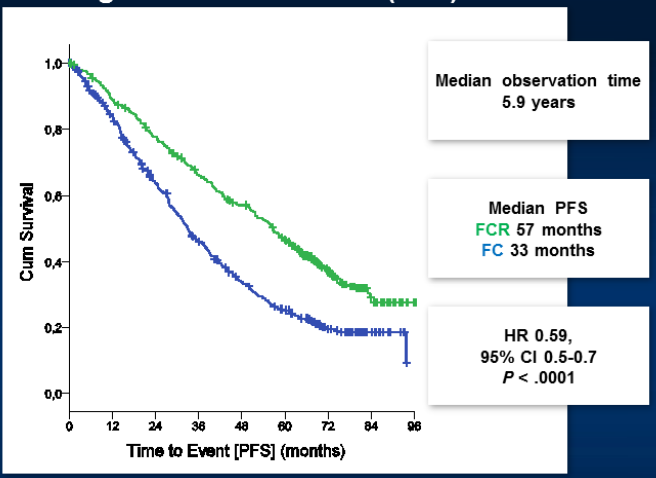
- In your opinion, chemotherapy for fit patients with CLL in 2020 will be:
  1. Rarely used for previously untreated patients
  2. Will remain the gold standard front-line therapy and used for the majority of patients
  3. Will be reserved for patients who fail targeted therapy
  4. Will be used in combination with targeted therapies

Chemoimmunotherapy in CLL

1. **Patients who are fit for fludarabine-based therapy**
2. Patients who are unfit for fludarabine-based therapy
3. Treatment in second or subsequent line of therapy

GCLLSG CLL8: Addition of Rituximab to Fludarabine and Cyclophosphamide

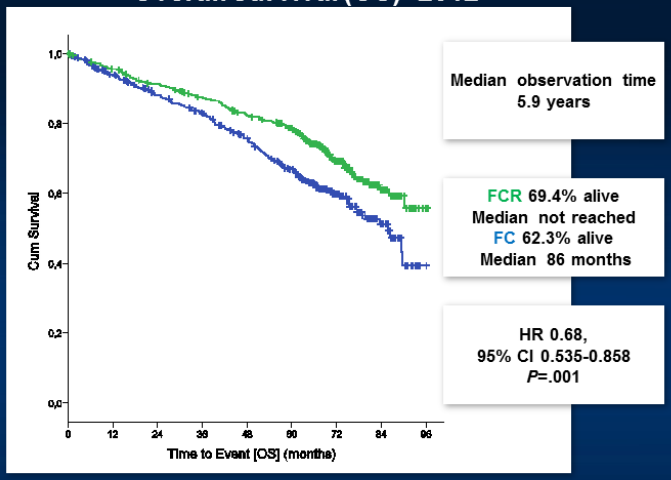
Progression free survival (PFS)* 2012



*Fischer, et al. *Blood.* 2012;120:Abstract 435.; Hallek, et al. *Lancet.* 2010;376(9747):1164-1174.

GCLLSG CLL8: Addition of Rituximab to Fludarabine and Cyclophosphamide

Overall survival (OS)* 2012



*Fischer, et al. *Blood*. 2012;120:Abstract 435.; Hallek, et al. *Lancet*. 2010;376(9747):1164-1174.

Addition of Rituximab to Fludarabine and Cyclophosphamide

Late toxicities after end of treatment (N=800)* 2012

Solid tumor	N	%	*P* value
FCR	26	5.0	0.4
FC	20	6.6	0.4
Richters' transformation	**N**	**%**	***P* value**
FCR	12	3.0	0.1
FC	21	5.3	0.1
AML or MDS	**N**	**%**	***P* value**
FCR	9	2.2	0.1
FC	3	0.8	0.1

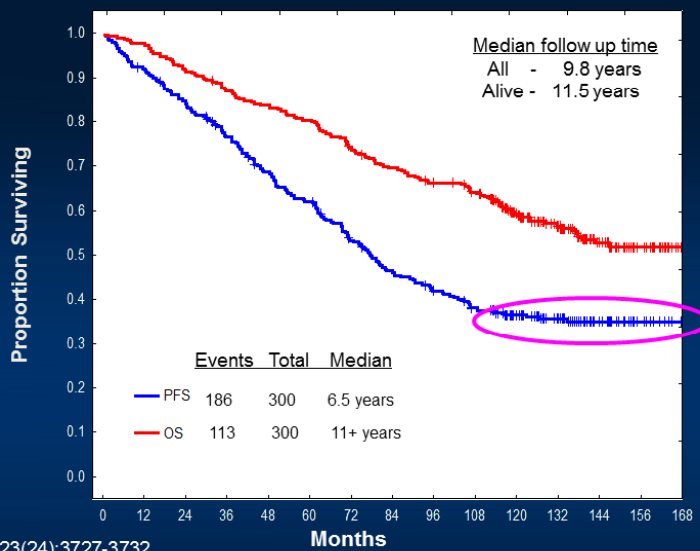
*Fischer, et al. *Blood*. 2012;120:Abstract 435.; Hallek, et al. *Lancet*. 2010;376(9747):1164-1174.

FCR300: 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
Strati, et al. *Blood*. 2014;123(24):3727-3732.

FCR300: Progression-free and Overall Survival



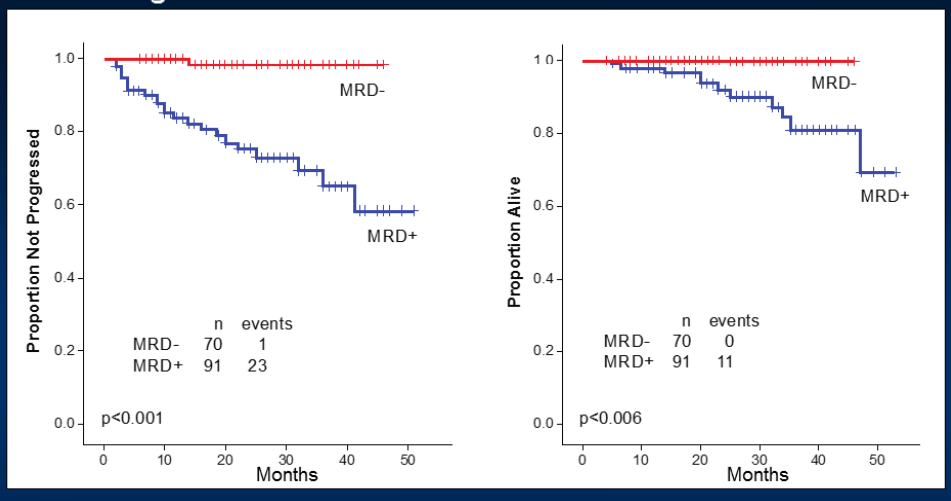
Strati, et al. *Blood*. 2014;123(24):3727-3732.

First-line FCR300: 2008 NCI-WG Response and Bone Marrow MRD Status

NCI-WG Response	n	% of Patients	% MRD-Negative*
CR	154	65	63
CRi	17	7	33
nPR	28	12	0
PR	31	13	17
NR	7	3	0
Overall MRD	161	68	43

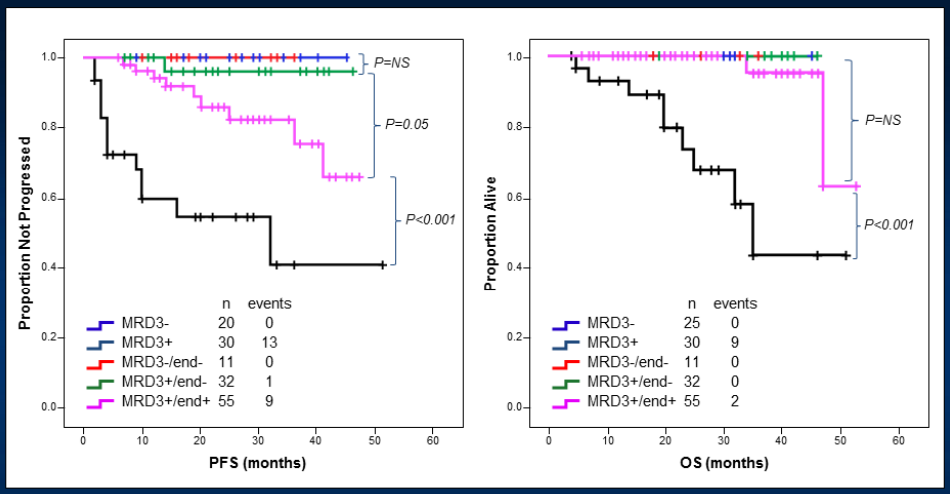
*Bone marrow evaluation by 4-color flow cytometry (sensitivity .01%)
Strati, et al. *Blood*. 2014;123(24):3727-3732.

First-line FCR300: PFS and OS Outcomes by MRD Status



Strati, et al. *Blood*. 2014;123(24):3727-3732.

First-line FCR: PFS and OS Outcomes by MRD Status at Interim and Final Evaluation



Strati, et al. *Blood*. 2014;123(24):3727-3732.

First-line FCR: Multivariable Model for Progression-free Survival

Characteristics	HR (95% CI)	*P*-value
Absence of 17p del	0.08 (0.02-0.3)	<.001
Complete remission	0.2 (0.05-0.6)	.007
Overall remission	0.1 (0.03-0.5)	.003
MRD-negative	0.1 (0.01-0.8)	.03

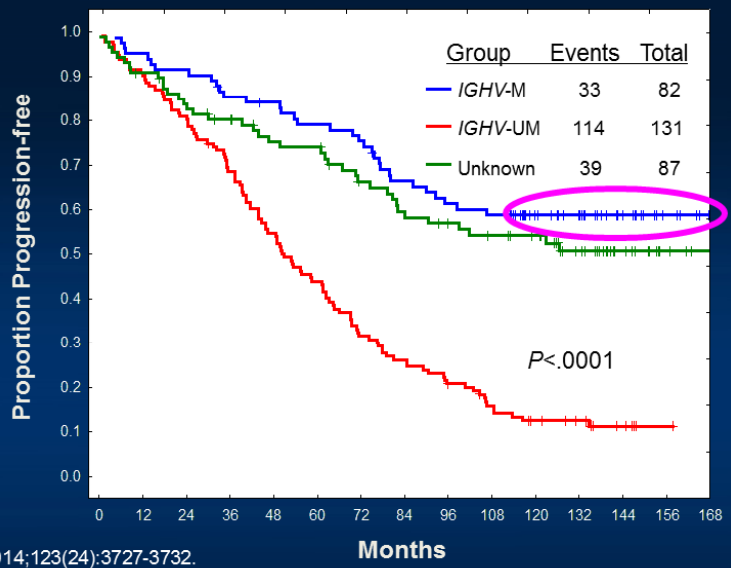
Strati, et al. *Blood*. 2014;123(24):3727-3732.

First-line FCR: Multivariable Model for Bone Marrow MRD-Negative Status

Pretreatment characteristic	OR (95% CI)	*P*-value
IGHV mutated	2.7 (1.1-6.3)	.02
Trisomy 12	2.7 (1.1-7.2)	.05

Strati, et al. *Blood*. 2014;123(24):3727-3732.

FCR300: PFS by IGHV Mutation Status



Strati, et al. *Blood*. 2014;123(24):3727-3732.

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 IV, days 1-3
Cyclophosphamide 250 mg/m², days 1-3
Rituximab 375 mg/m² IV day 0, cycle 1
Rituximab 500 mg/m² IV day 1, cycle 2-6; q 28 days

BR
Bendamustine 90 mg/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. *Blood*. 2013;122:526. Eichhorst B, et al. *Blood*. 2014;124(21): Abstract 19.

CLL10 Study: FCR VS BR in Front-line

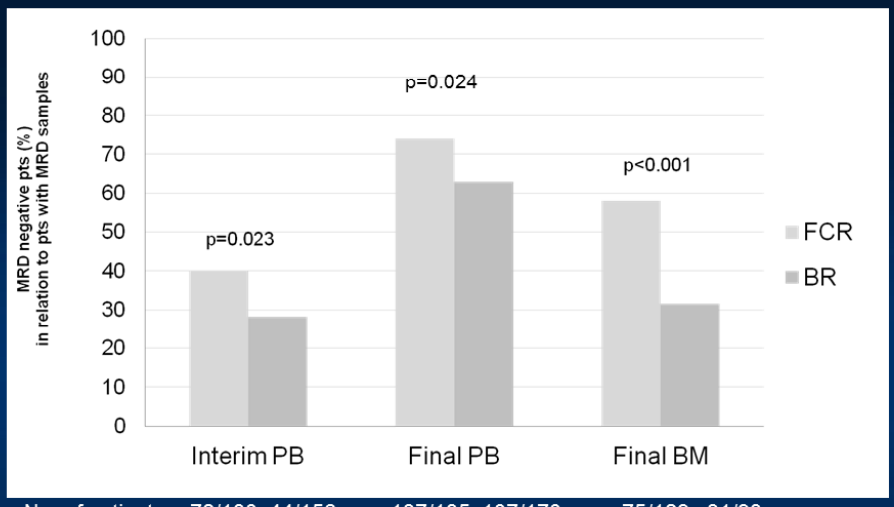
Response to Therapy (Best Response)

Response	FCR n=274	BR n=273	*P* value
CR (CR + CRi)	**47.4%**	**38.1%**	**0.031**
CR	40.1%	36.3%	
CRi	7.3%	1.8%	
PR	50.4%	59.7%	
ORR	**97.8%**	**97.8%**	**1.0**

Eichhorst, et al. *Blood*. 2013;122:526.; Eichhorst B, et al. *Blood*. 2014;124(21): Abstract 19.

CLL10 Study: FCR VS BR in Front-line

Minimal residual disease (MRD)

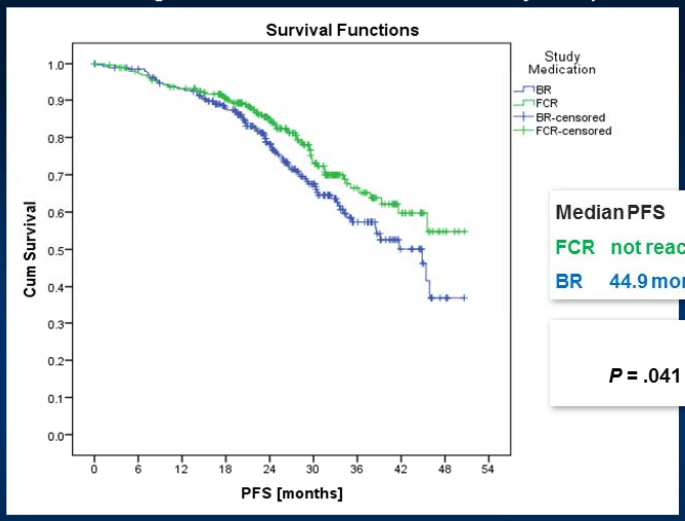


No. of patients: 72/180 44/156 137/185 107/170 75/129 31/98

Eichhorst, et al. *Blood*. 2013;122:526.; Eichhorst B, et al. *Blood*. 2014;124(21): Abstract 19.

CLL10 Study: FCR vs BR in Front-line

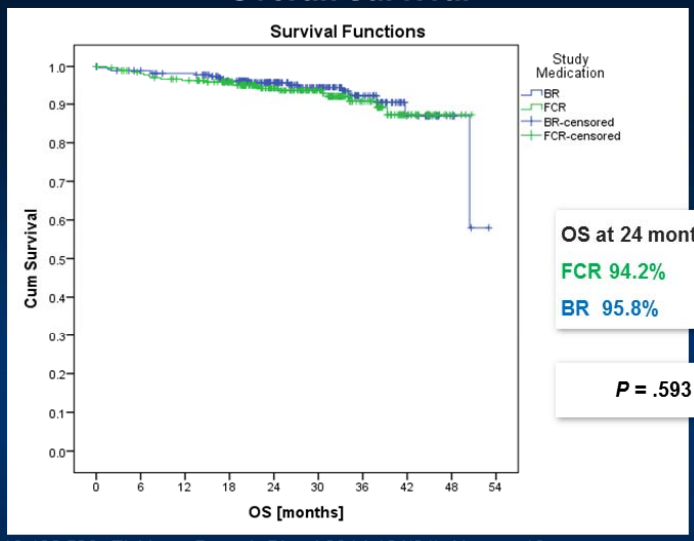
Progression-free survival = Primary endpoint



Eichhorst, et al. *Blood*. 2013;122:526.; Eichhorst B, et al. *Blood*. 2014;124(21): Abstract 19.

CLL10 Study: FCR vs BR in Front-line

Overall survival



OS at 24 months:
FCR 94.2%
BR 95.8%

***P* = .593**

Eichhorst, et al. *Blood*. 2013;122:526.; Eichhorst B, et al. *Blood*. 2014;124(21): Abstract 19.

CLL10 Study: FCR vs BR in Front-line

Adverse events CTC °3-5 (Interval 1st cycle until 3 months after final staging)

Adverse event	FCR (% of pt)	BR (% of pt)	*P* value
All	90.8	78.5	<0.001
Hematological AEs	90.0	66.9	<0.001
Neutropenia	81.7	56.8	<0.001
Anemia	12.9	9.7	0.28
Thrombocytopenia	21.5	14.4	0.036
Infection	39.0	25.4	0.001
TRM	3.9	2.1	0.23

Eichhorst, et al. *Blood*. 2013;122:526.; Eichhorst B, et al. *Blood*. 2014;124(21): Abstract 19.

CLL10 Study: FCR vs BR in Front-line

Conclusion

- Interim analysis shows higher efficacy of FCR with regard to CR rate, MRD negativity and PFS.
- Distribution bias of IGHV status unfavors BR arm.
- FCR induces higher rates of AE (neutropenias, infections).
- Anti-infective prophylaxis to be re-evaluated during chemoimmunotherapy and immediate follow up.

Eichhorst, et al. *Blood*. 2013;122:526.; Eichhorst B, et al. *Blood*. 2014;124(21): Abstract 19.

Question

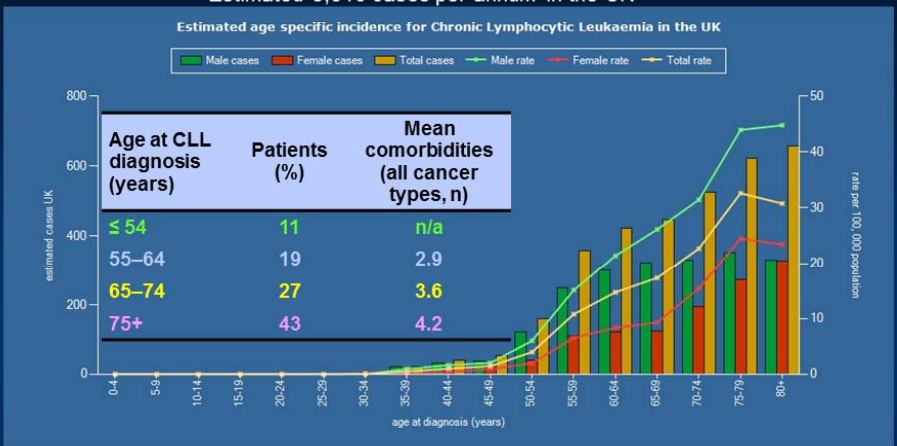
- How do you assess a patients fitness for FCR?
  1. Age only
  2. Application of the Cumulative Index Rating Scale
  3. General clinical assessment
  4. I don't use FCR

Chemoimmunotherapy in CLL

1. Patients who are fit for fludarabine-based therapy
2. **Patients who are unfit for fludarabine-based therapy**
3. Treatment in second or subsequent line of therapy

CLL: Incidence Data (HMRN, Yorkshire, UK)

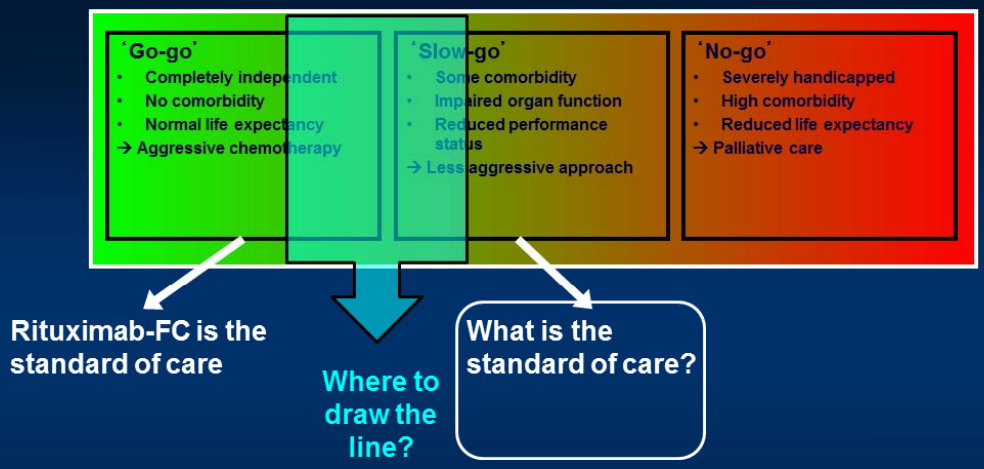
6.4 cases per 100,000.
M:F 1.7
Median age at diagnosis 71years
Estimated 3,610 cases per annum in the UK



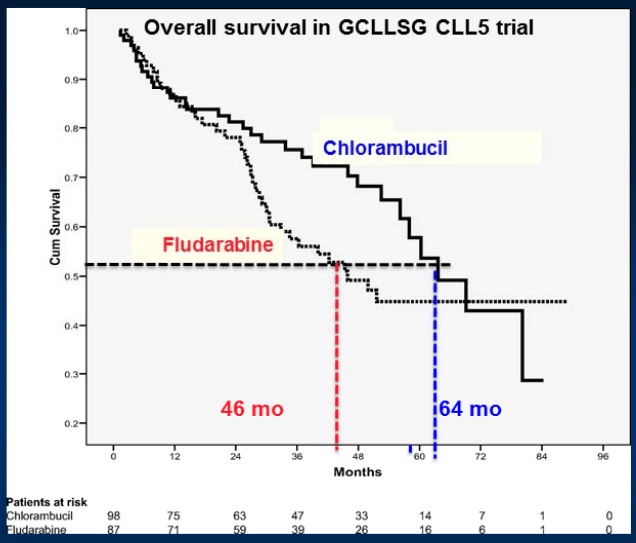
Age at CLL diagnosis (years)	Patients (%)	Mean comorbidities (all cancer types, n)
≤ 54	11	n/a
55–64	19	2.9
65–74	27	3.6
75+	43	4.2

Leeds data (*www.hmrn.org.uk*); Ries LAG, et al. SEER Cancer Statistics Review, 1975–2005.; Available at: *http://seer.cancer.gov/csr/1975_2005/*accessed February 2009., Yancik R, *Cancer.* 1997;80:1273-1283.

The Boundaries Between "Go-Go", "Slow-Go" and "No-Go" Depend on the Therapy

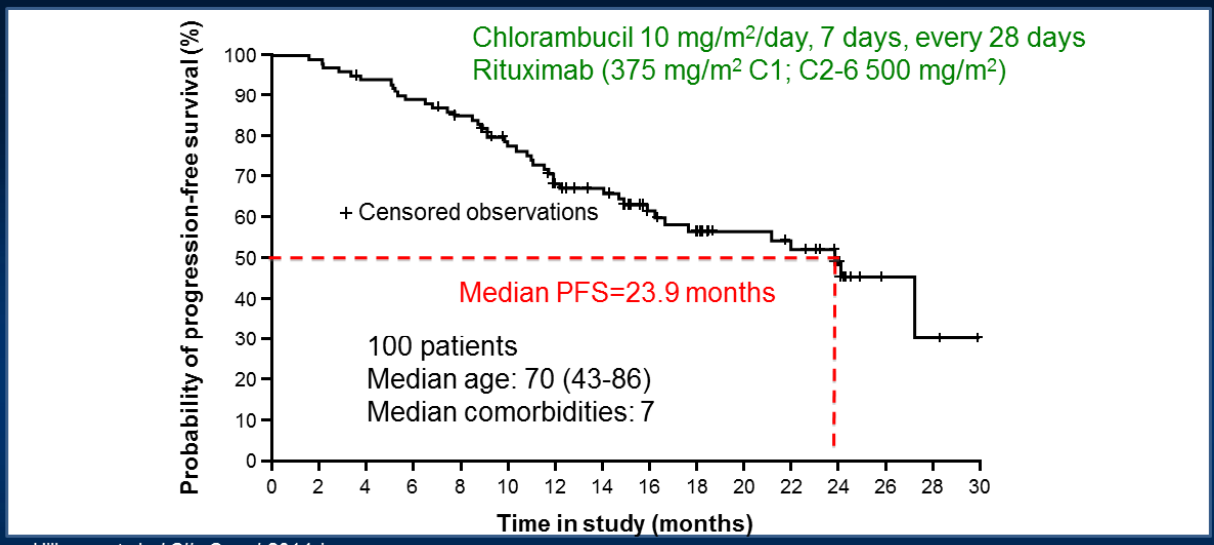


What was the gold standard for elderly patients (>65 yo) with CLL in 2009?



Eichhorst BF et al. *Blood*. 2009;114:3382-3391.

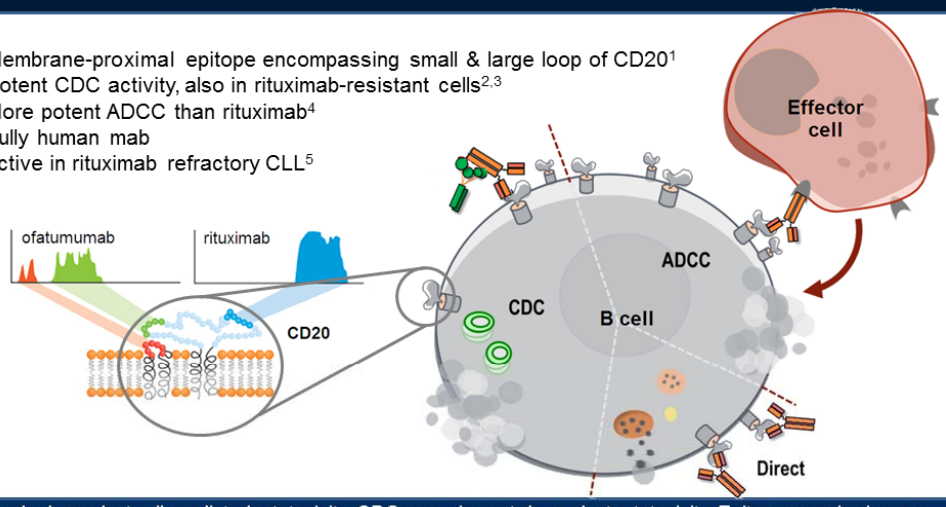
Improved PFS with the Addition of Rituximab to Chlorambucil (R-chlorambucil; NCRI CLL208)



Hillmen, et al. *J Clin Oncol.* 2014; in press.

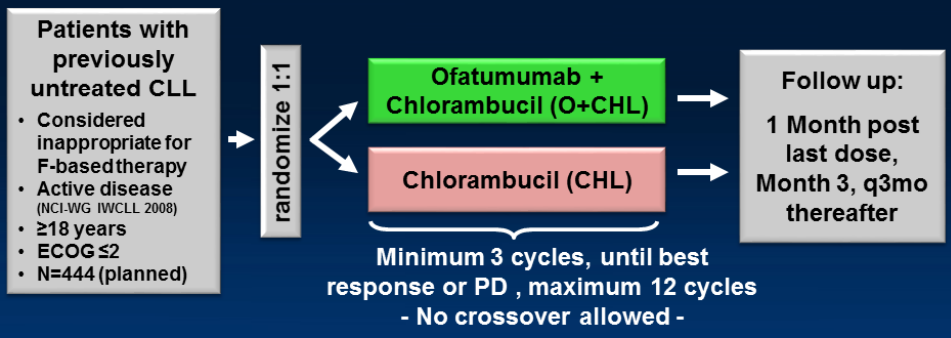
Ofatumumab: Human anti-CD20 Ab

- Membrane-proximal epitope encompassing small & large loop of CD20[1]
- Potent CDC activity, also in rituximab-resistant cells[2,3]
- More potent ADCC than rituximab[4]
- Fully human mab
- Active in rituximab refractory CLL[5]



ADCC=antibody-dependent cell-mediated cytotoxicity; CDC=complement-dependent cytotoxicity; Epitope mapping image: *www.pepscan.com/presto/products-services/epitope-mapping*; Cell image: DAVA Oncology;
[1]Teeling. *J Immunol.* 2006;177:36. [2]Teeling. *Blood.* 2004;104:1793. [3]Barth. *Br J Heam.* 2012;156:490. [4]Craigen. ASH. 2009:Abstract 1725.
[5]Wierda. *Blood.* 2011;18:5126.

COMPLEMENT 1: Ofatumumab in CLL



O: cycle 1 d1 300 mg, d8 1000 mg, cycle 2-12 d1 1000 mg every 28 days

CHL: 10 mg/m^2 d1-7 every 28 days

Dose rationale: evidence of highest ORR and longest PFS with low toxicity compared to any other CHL monotherapy regimen

Hillmen, et al. Manuscript submitted, 2014.

Adverse Event Overview

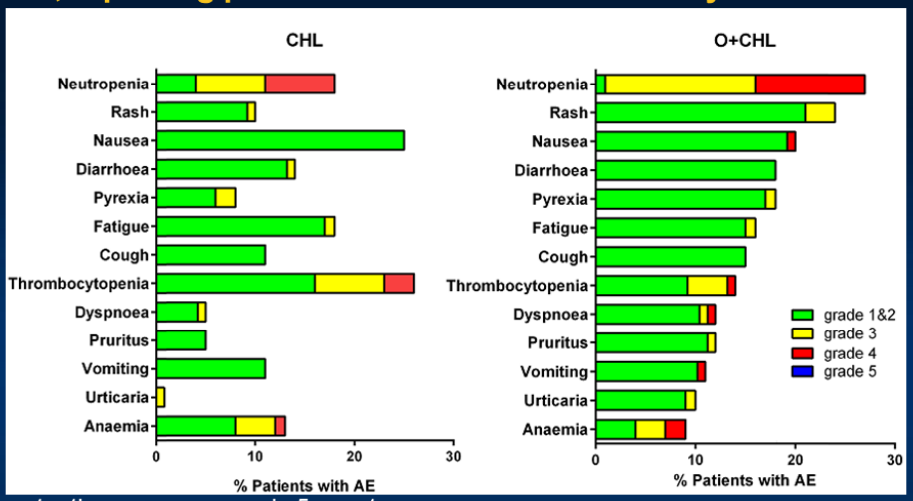
(Reporting period: from first dose to 60 days after last dose[1])

Patient with AE, %	CHL (n=227)	O+CHL (n=217)[2]
AEs, any	87	94
AEs related to study treatment	65	84
AEs leading to WD of treatment	13	13
AEs ≥ Grade 3	43	50
Infusion-related reactions (IRR)[3]	n/a	10
Neutropenia	14	26
Thrombocytopenia	10	5
Anemia	5	5
Infections	12	9
Death (includes death due to PD)	3	4

[1]Data for treatment plus up to 60 days after last dose is reported to allow inclusion of any event that could be caused by the drug prior to its clearance. [2]Safety population is based on the actual treatment subject received, 3 subjects who did not receive any treatment were excluded, CHL population includes 2 subjects from the O+CHL arm who did not receive O. [3]Defined as onset occurring after the start of infusion and within 24 hours of infusion end

Most Common AEs

(As reported by investigator; Cut-off: any grade occurring in ≥10% of patients, reporting period: from first dose to 60 days after last dose)

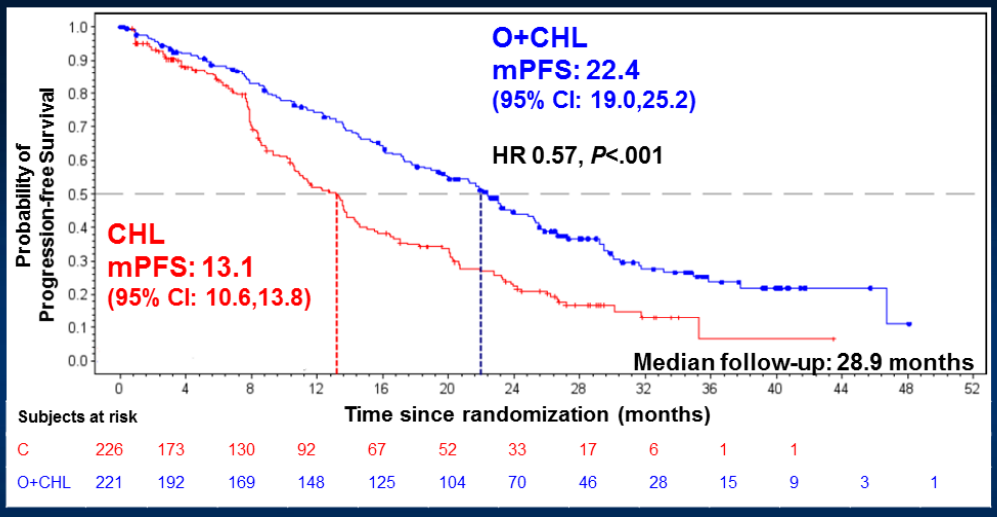


Of listed events, there were no grade 5 events

Hillmen, et al. Manuscript submitted, 2014.

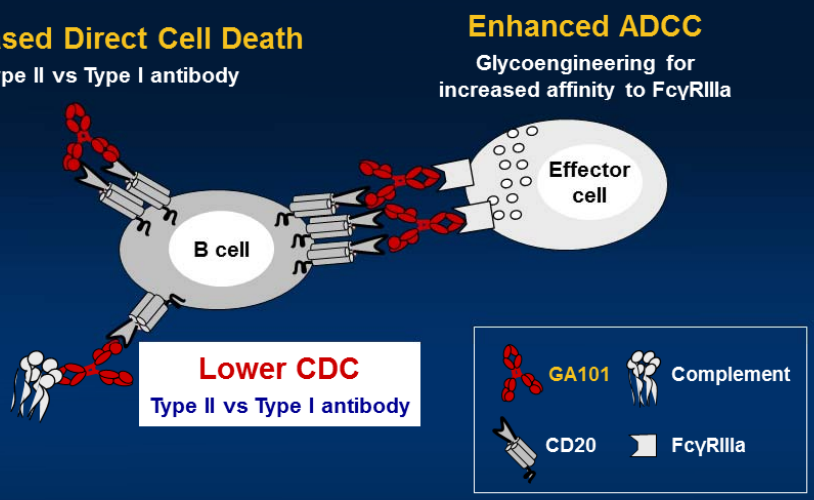
Complement-1: Median PFS (Months)

As Assessed by an Independent Review Committee



Hillmen, et al. Manuscript submitted, 2014.

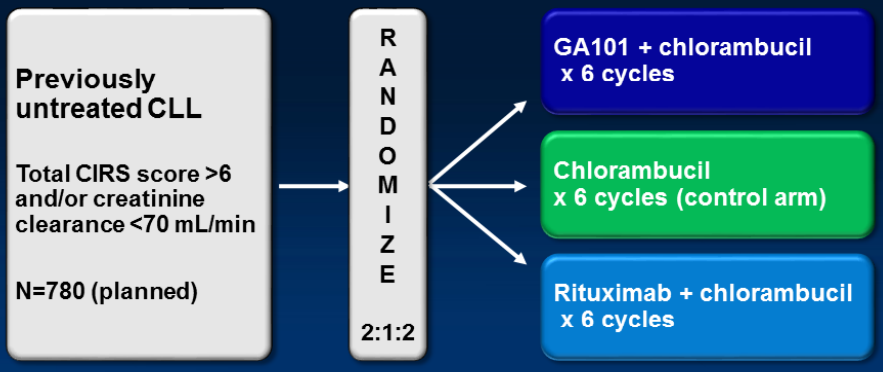
Obinutuzumab (GA101): Anti-CD20 Type II Ab



- ADCC, antibody-dependent cell-mediated cytotoxicity; CDC, complement-dependent cytotoxicity

Mössner, et al. *Blood.* 2010;115:4393-4402.; Goede, **et al.** *Blood.* 2013;122:6.

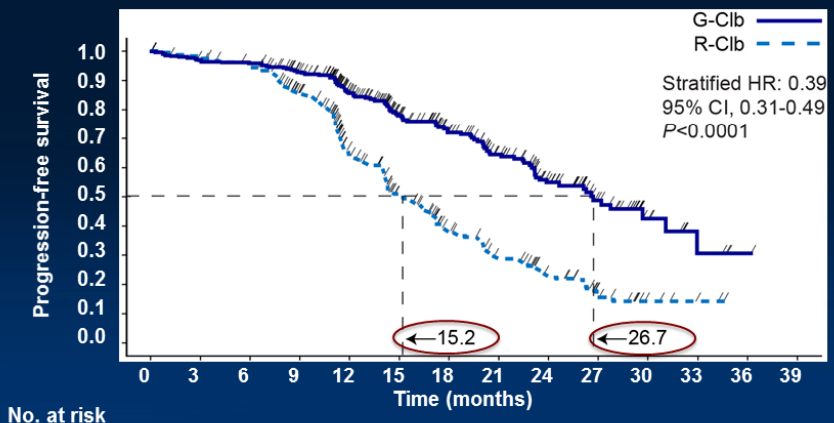
GCLLSG CLL11 Trial: Obinutuzumab in CLL



- 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;370:1101-1110.

GCLLSG CLL11 Trial: PFS for G-Clb vs R-Clb



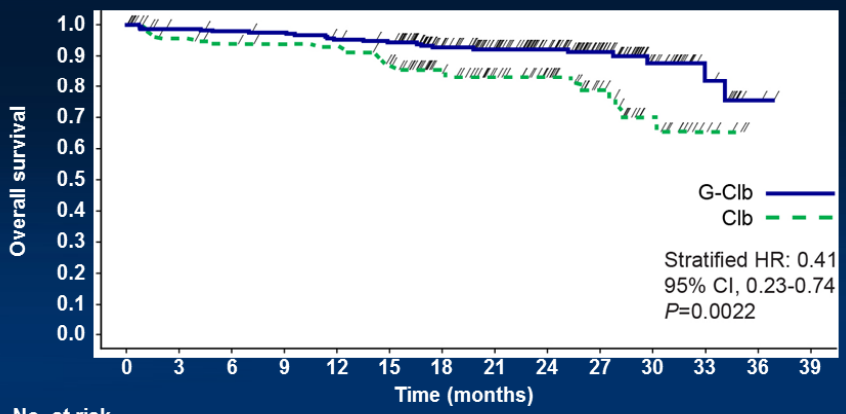
No. at risk

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

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

GCLLSG CLL11 Trial: Overall Survival G-Clb vs Clb



No. at risk

G-Clb:	238	226	223	221	215	211	170	144	115	71	34	14	2	0
Clb:	118	109	105	103	102	94	70	56	44	29	15	5	0	0

Total number of deaths: G-Clb, 22 (9%); Clb, 24 (20%)

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

Adverse Events of Interest

Any AE grade ≥3[b]	G-Clb (n=336)[a] %	R-Clb (n=321)[a] %
	70	55
Infusion-related reaction	20	4
Neutropenia	33	28
Anemia	4	4
Thrombocytopenia	10	3
Infection	12	14
Pneumonia	4	5

[a] Safety population for G-Clb includes 5 patients randomized to R-Clb who received one infusion of GA101 in error
[b] Incidence rate of ≥3% in any treatment arm

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

Chemoimmunotherapy in CLL

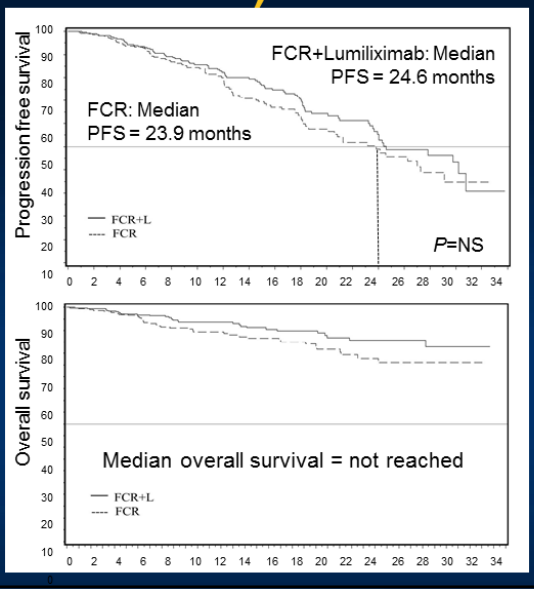
1. Patients who are fit for fludarabine-based therapy
2. Patients who are unfit for fludarabine-based therapy
3. **Treatment in second or subsequent line of therapy**

FCR ± lumiliximab (anti-CD23) in Relapsed CLL (LUCID Trial)

- Randomized trial of FCR ± lumiliximab
- 627 patients, 150 sites, 22 countries, 1 or 2, prior single-agent or combination treatments for CLL
- Med age = 61yo; 70% male

	FCR	FCR+L
No. of patients	311	316
11q del	27%	21%
17p del	8%	9%
VH unmut	50%	52%
2° MDS/AML	4 (1%)	2 (<1%)
ORR	72%	71%
CR	15%	16%
nPR/PR	56%	56%

Awan, et al. *Br J Haematol.* 2014.

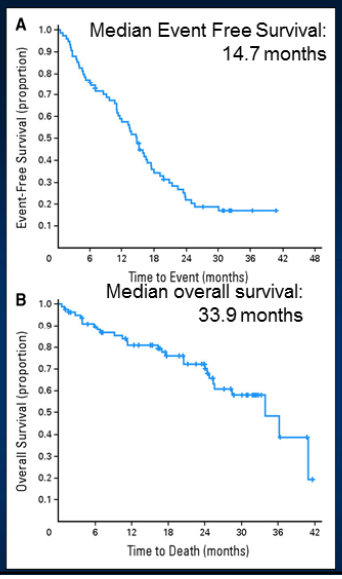


Bendamustine Plus Rituximab in Relapsed CLL

- GCLLSG phase II trial of bendamustine + rituximab in relapsed CLL
- 78 patients, median 2 prior therapies
- Med age = 66yo; 65% male
- 17p del in 14 patients (18%)
- 11q del in 16 patients (20%)
- VH unmutated in 51 (67%)

Response	N = 78	%
ORR	46	59
CR	7	9
PR/nPR	39	50
SD	20	26
PD	5	6
Missing*	7	9

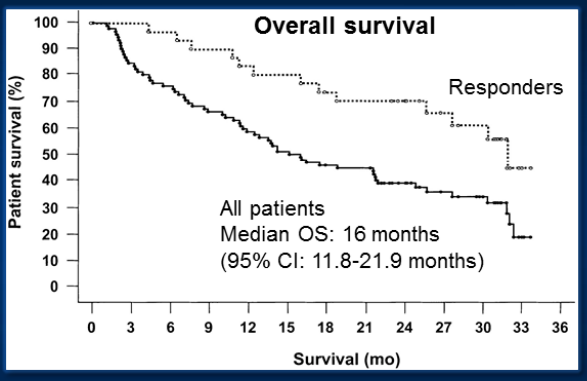
Fischer, et al. *J Clin Oncol.* 2011;29:3559-3566.



Alemtuzumab in Refractory CLL

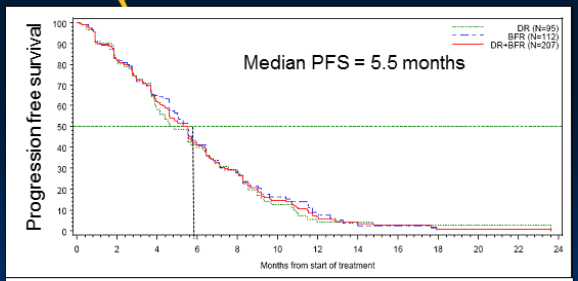
- CAM203 phase II trial of intravenous alemtuzumab in refractory CLL
- 93 patients, median 3 prior therapies
- Failed to respond to or relapsed within 6 months of fludarabine
- Med age = 66yo; 65% male

Response	N = 93	%
ORR	31	33
CR/CRi	8	9
PR/nPR	23	25
SD	16	54

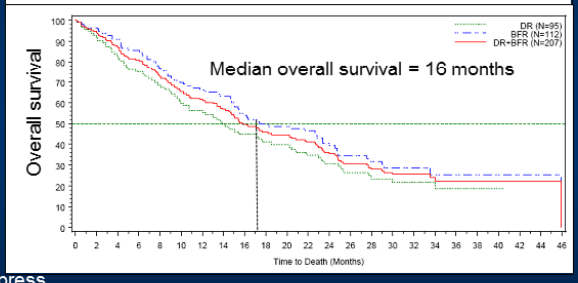


Keating, et al. *Blood*. 2002;99:3554-3561.

Ofatumumab in Refractory CLL (GSK CLL406 Trial)



Refractory to fludarabine and alemtuzumab (n=95)



Refractory to fludarabine, bulky lymph nodes (n=112)

Osterborg, et al. 2014 in press.

Conclusion

1. Patients who are fit for fludarabine-based therapy
   a) FCR remains the gold standard
   b) Some patients remain in remission >15 years out
2. Patients who are unfit for fludarabine-based therapy
   a) Chlorambucil plus anti-CD20 (obinutuzumab or ofatumumab)
   b) Outcomes generally poor and limited options
3. Treatment in second or subsequent line of therapy
   a) Duration of response depends on response to prior therapy
   b) Outcomes are poor with chemo-immunotherapy
   c) Consider novel therapies

Changing Future Treatment Paradigms: The Role of Novel Therapies

Jennifer R. Brown, MD, PhD
Director
Chronic Lymphocytic Leukemia Center
Dana-Farber Cancer Institute
Associate Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Which of the following is not an important potential side effect of idelalisib?

1. Pneumonitis
2. Colitis
3. Bleeding
4. Transaminitis

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2. Colitis
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4. Transaminitis

Which of the following novel agents has shown the highest complete remission rate in relapsed CLL?

1. Ibrutinib
2. ABT-199
3. Idelalisib
4. Obinutuzumab

Which of the following novel agents has shown the highest complete remission rate in relapsed CLL?

1. Ibrutinib
2. ABT-199
3. Idelalisib
4. Obinutuzumab

Which of the following is NOT true of the BCR pathway inhibitors?

1. Nodal response is rapid
2. Side effects are generally mild and manageable
3. Currently these drugs are dosed until progression or adverse event that requires discontinuation
4. The lymphocyte count drops rapidly in most patients
5. Response is preserved even in patients with adverse cytogenetics

Which of the following is NOT true of the BCR pathway inhibitors?

1. Nodal response is rapid
2. Side effects are generally mild and manageable
3. Currently these drugs are dosed until progression or adverse event that requires discontinuation
4. **The lymphocyte count drops rapidly in most patients**
5. Response is preserved even in patients with adverse cytogenetics

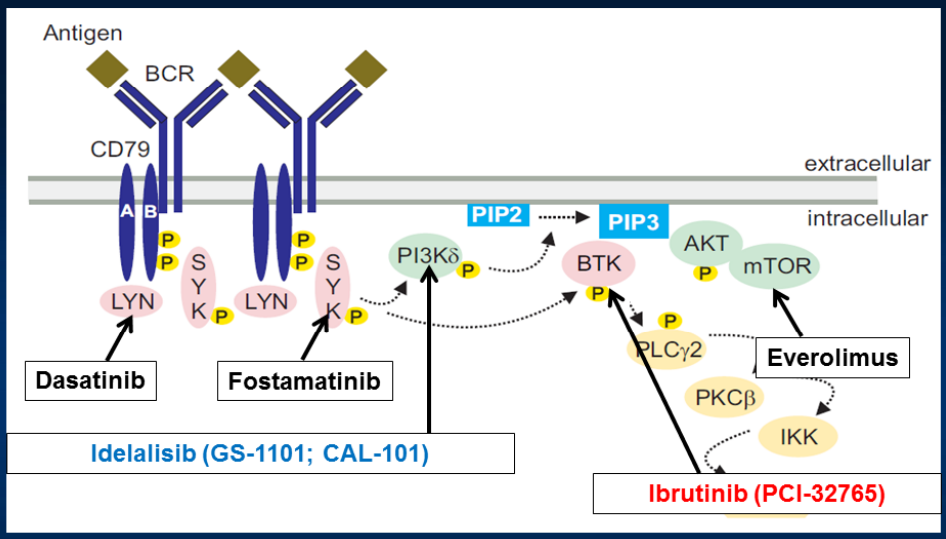
CLL Therapy, ca 2009

	Initial Therapy	Relapsed Therapy
Fit/Young	FCR	Long DOR: Repeat FCR or other CIT
With Comorbidities/ Older	?? Clb, Clb-R, BR, dose-reduced CIT	Long DOR: Repeat; Ofa
With 17p, or Short DOR	?? HDMP + antibody; Alem; Ofa; Lenalidomide AlloSCT	

Novel Agents for CLL

- BCR pathway inhibition:
  - BTK:
    - Ibrutinib (PCI-32765)
  - PI3K:
    - Idelalisib (GS1101, CAL101)
    - IPI-145
- BCL2 inhibition: ABT199

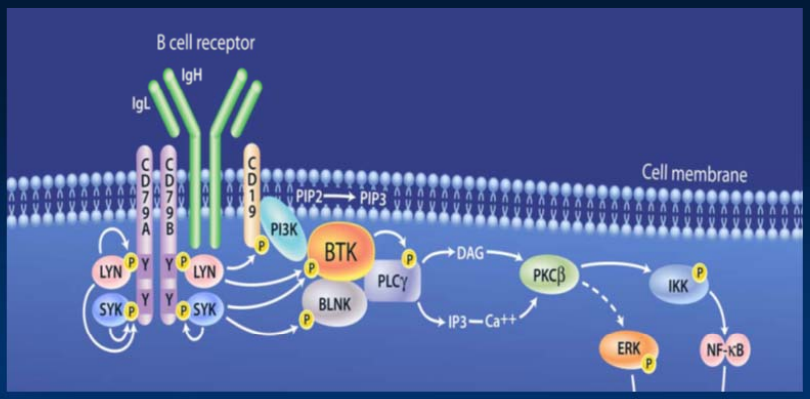
Targeting Kinases in the BCR Pathway



BCR-Directed Agents in Development for CLL

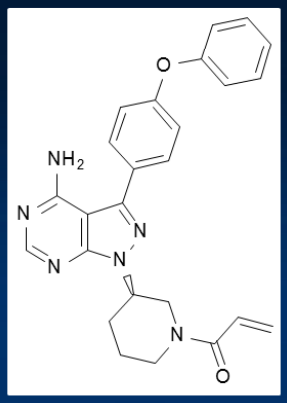
Agent	Sponsor	ORR	Development Phase
BTK Inhibitors			
Ibrutinib	Pharmacyclics, Inc.	71 – 88%	Registration Phase III
CC-292	Celgene Corporation	31-67% (PR)	Phase Ib
ONO-4059	Ono Pharmaceutical	89% (PR)	Phase I
ACP-196	Acerta	—	Phase I
BGB-3111	BeiGene	---	Phase I
PI3Kδ Inhibitors			
Idelalisib	Gilead Sciences	72-100%	Registration Phase III
GS-9820	Gilead Sciences	—	Pending Phase I
AMG 319	Amgen	33% nodal	Phase I
TGR-1202	TG Therapeutics	—	Phase I
IPI-145 (also γ)	Infinity	89% nodal	Phase III
SAR245408 (pan)	Sanofi	40% PR	Phase Ib
Syk Inhibitors			
GS-9973	Gilead Sciences	—	Phase II
Fostamatinib	Rigel Pharmaceuticals	55% nodal	Phase I/II
PRT-2070	Portola	—	Pending Phase I

BTK as a Target in B-Cell Malignancies



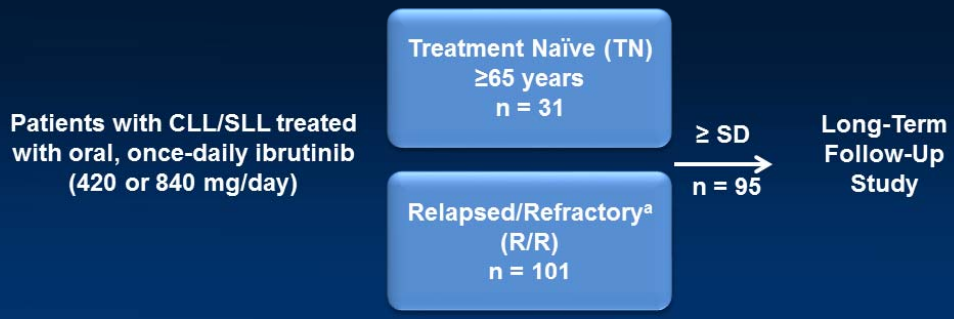
- Mutations in BTK prevent B-cell maturation
- BTK inhibition blocks BCR signaling and induces apoptosis

Ibrutinib (PCI-32765): BTK Inhibitor



- Forms a specific and irreversible bond with cysteine-481 in Btk
- Potent Btk inhibition
  - IC_{50} = 0.5 nM
- Orally available
- Once daily dosing results in 24-hour sustained target inhibition

PCYC-1102/1103 Phase 2 Study Design



- Phase 2 (PCYC-1102) and Extension (PCYC-1103) study
  - 132 patients with treatment-naïve (TN) or relapsed/refractory (R/R) CLL/SLL
  - Three years follow-up

O'Brien, et al. *J Clin Oncol.* 2014;32:5s(suppl; abstr 7014).

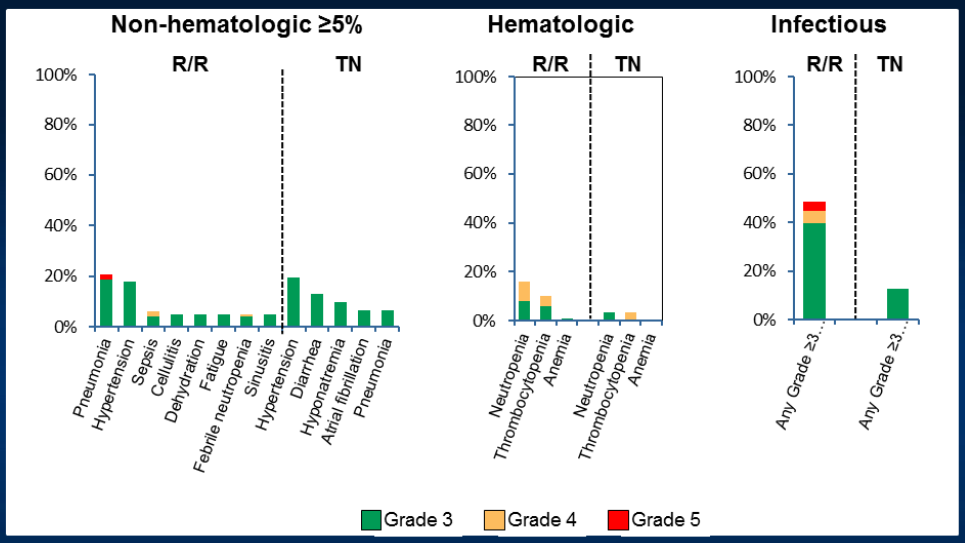
Patient Disposition

Disposition	TN ≥65 years n = 31	R/R n = 101
Median time on study, months (range)	32.1 (2.5–38.1)	26.6 (0.7–37.9)
Duration of study treatment		
≤1 year	5 (16%)	24 (24%)
>1–2 years	1 (3%)	34 (34%)
>2–3 years	25 (81%)	42 (42%)
>3 years	0	1 (1%)
Patients remaining on ibrutinib therapy	25 (81%)	59 (58%)
Primary reason for discontinuation		
Progressive disease	1 (3%)	19 (19%)
Adverse event	3 (10%)	11 (11%)
Consent withdrawal	2 (6%)	3 (3%)
Investigator's decision	0	8 (8%)
Other	0	1 (1%)

64% of total patients remaining on ibrutinib therapy

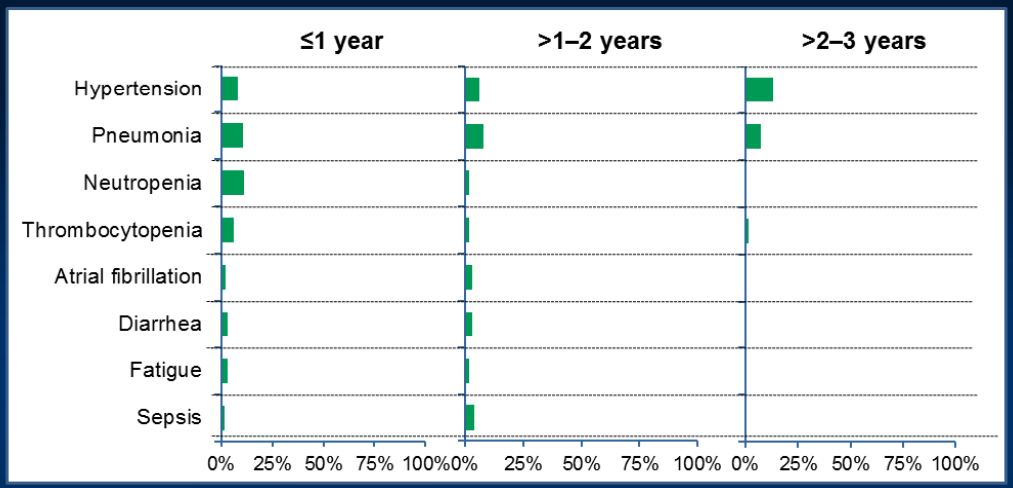
O'Brien, et al. *J Clin Oncol.* 2014;32:5s(suppl; abstr 7014).

Safety: Frequency of Grade ≥3 Adverse Events



O'Brien, et al. *J Clin Oncol.* 2014;32:5s(suppl; abstr 7014).

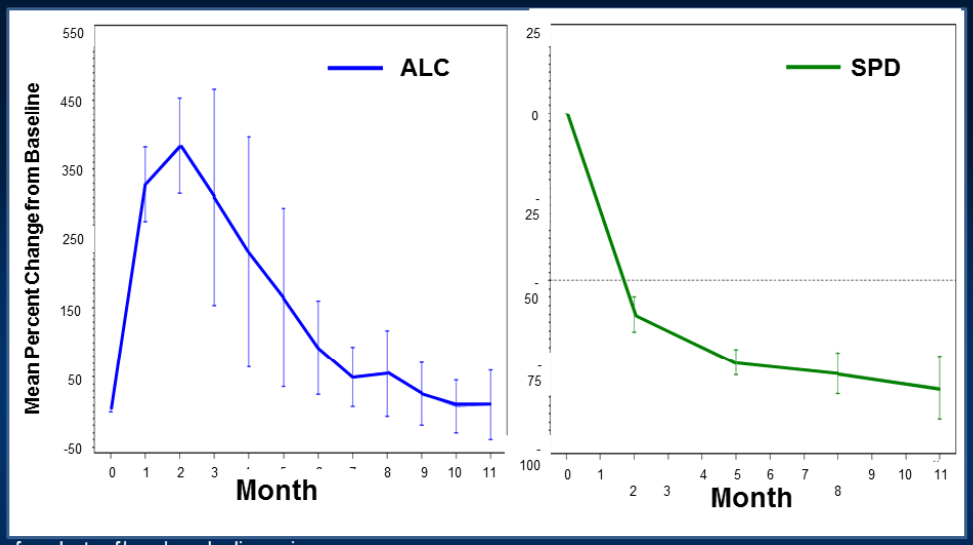
Safety: Grade ≥3 Adverse Events by Time to Event Onset*



*Listed adverse events include those that occurred in ≥5% of patients in all-treated population; denominator for each term and time period can vary based on those at risk

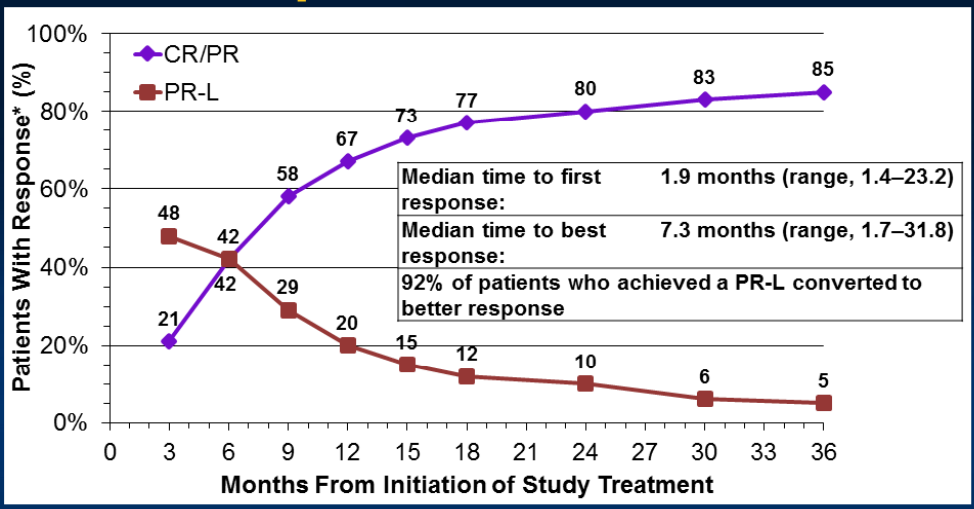
O'Brien, et al. *J Clin Oncol.* 2014;32:5s(suppl; abstr 7014).

Blood Lymphocytes vs. Lymph Nodes



SPD=sum of products of lymph node dimension
O'Brien, et al. *J Clin Oncol.* 2014;32:5s(suppl; abstr 7014).

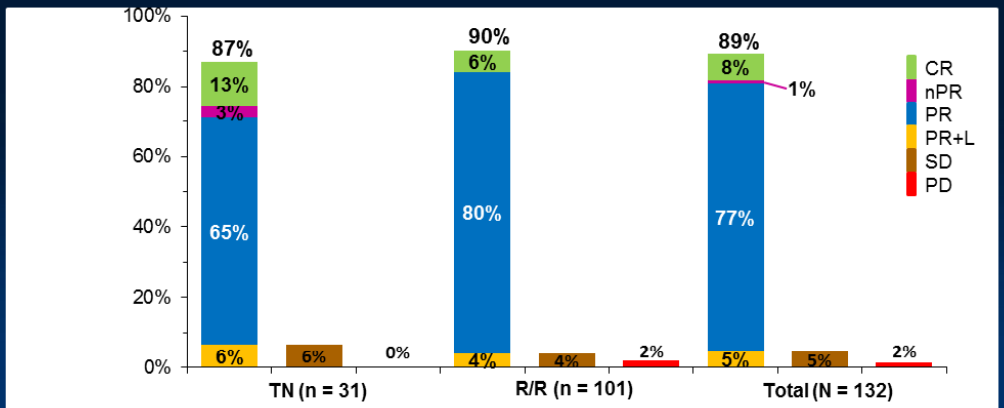
Response Over Time



Best response to ibrutinib improves over time

*Cumulative response as assessed by investigator
O'Brien, et al. *J Clin Oncol.* 2014;32:5s(suppl; abstr 7014).

Best Response (Investigator Assessed)

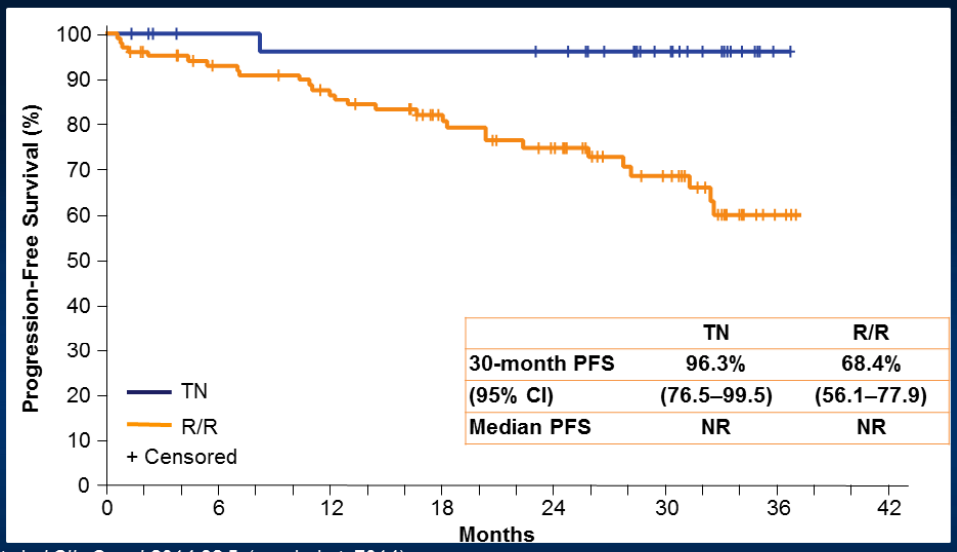


Median DOR in months (range)	NR (0 to 35.0+)	NR (0 to 35.2+)	NR (0 to 35.2+)
Month 30 (95% CI)	100.0% (NE)	79.1% (64.2 to 88.4)	85.3 (74.4 to 91.8)

- 5/6 patients who received prior idelalisib responded to ibrutinib (4PR, 1 PR+L)
- 2/5 responders continue treatment with one additional patient moving on to SCT

O'Brien, et al. *J Clin Oncol.* 2014;32:5s(suppl; abstr 7014).

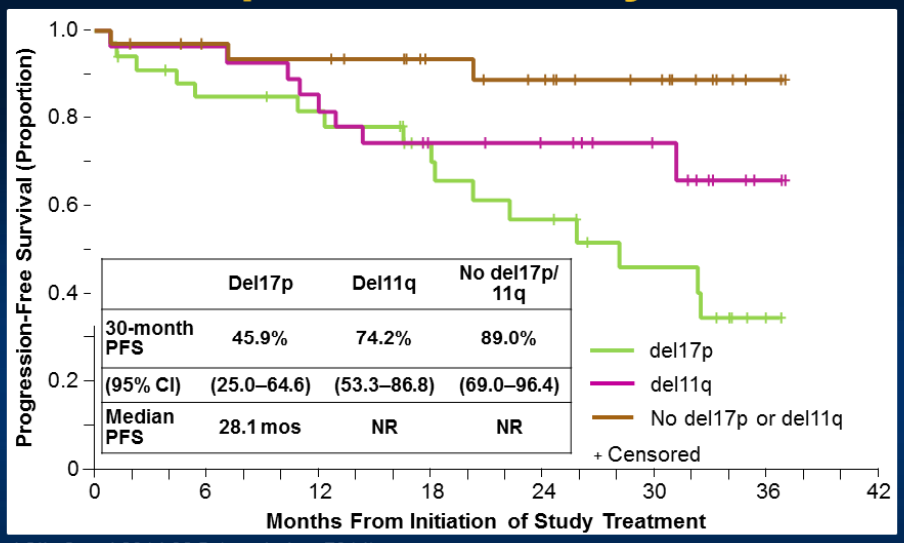
Progression-Free Survival



	TN	R/R
30-month PFS	96.3%	68.4%
(95% CI)	(76.5–99.5)	(56.1–77.9)
Median PFS	NR	NR

O'Brien, et al. *J Clin Oncol.* 2014;32:5s(suppl; abstr 7014).

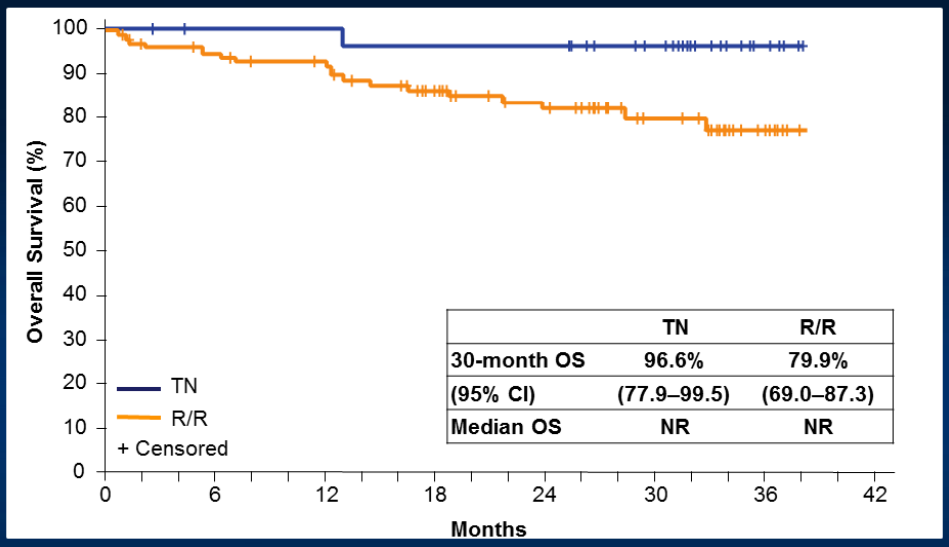
PFS by Cytogenetics (FISH) in Relapsed/Refractory CLL



	Del17p	Del11q	No del17p/ 11q
30-month PFS	45.9%	74.2%	89.0%
(95% CI)	(25.0–64.6)	(53.3–86.8)	(69.0–96.4)
Median PFS	28.1 mos	NR	NR

O'Brien, et al. *J Clin Oncol*. 2014;32:5s(suppl; abstr 7014).

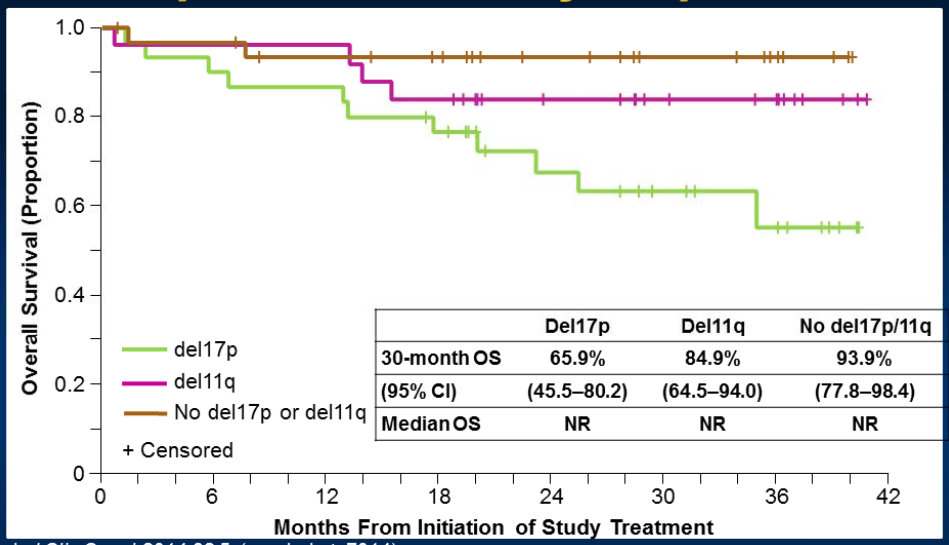
Overall Survival



	TN	R/R
30-month OS	96.6%	79.9%
(95% CI)	(77.9–99.5)	(69.0–87.3)
Median OS	NR	NR

O'Brien, et al. *J Clin Oncol*. 2014;32:5s(suppl; abstr 7014).

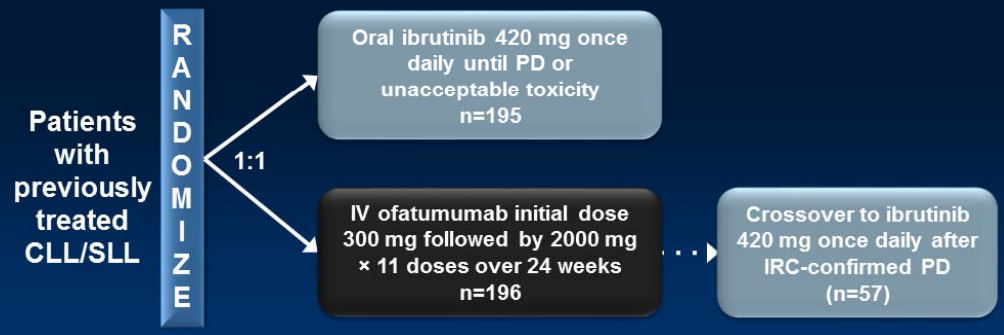
Overall Survival by Cytogenetics (FISH) in Relapsed/Refractory Population



	Del17p	Del11q	No del17p/11q
30-month OS	65.9%	84.9%	93.9%
(95% CI)	(45.5–80.2)	(64.5–94.0)	(77.8–98.4)
Median OS	NR	NR	NR

O'Brien, et al. *J Clin Oncol*. 2014;32:5s(suppl; abstr 7014).

RESONATE™ Phase 3 Study Design



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

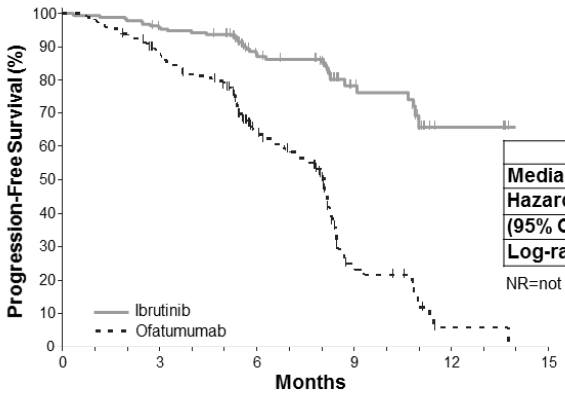
Byrd, et al. *N Engl J Med*. 2014;371(3):213-223.

Baseline Characteristics

	Ibrutinib (N=195)	Ofatumumab (N=196)
CLL/SLL, %	95/5	96/4
Median age, years	67 (30-86)	67 (37-88)
Refractory to purine analogs, %	45	45
Rai stage III/IV, %	56	58
Bulky disease ≥5 cm, %	64	52
Del11q, %	32	30
Del17p, %	32	33
Median prior Rx, n	3 (1-12)	2 (1-13)

Byrd, et al. *N Engl J Med*. 2014;371(3):213-223.

Progression-Free Survival



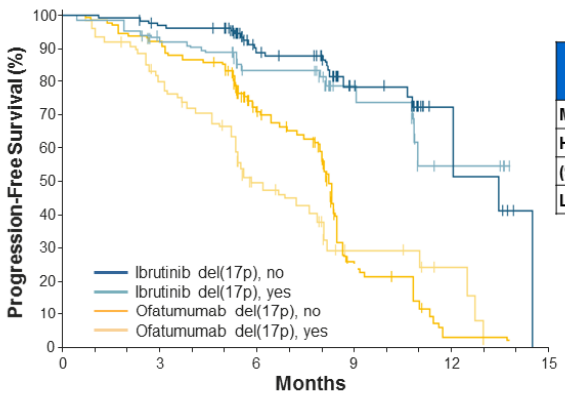
	Ofatumumab	Ibrutinib
Median time (mo)	8.08	NR
Hazard ratio	0.215	
(95% CI)	(0.146-0.317)	
Log-rank *P* value	< 0.0001	

NR=not reached.

- Ibrutinib significantly prolonged PFS; median not reached vs. 8.1 months for ofatumumab
- 78% reduction in the risk of progression or death
- Investigator assessed PFS hazard ratio 0.133 (95% CI: 0.085-0.209) *P* value <.0001
- Richter's transformation was confirmed in 2 patients on each arm. An additional patient on the ibrutinib arm experienced disease transformation to prolymphocytic leukemia

Byrd, et al. *N Engl J Med*. 2014;371(3):213-223.

Progression-Free Survival by del(17p) Status

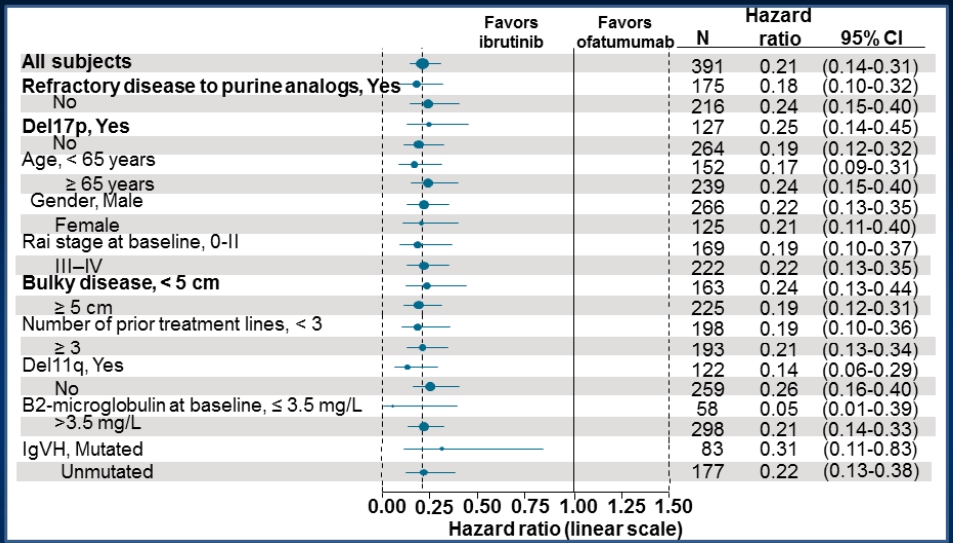


	Ofatumumab del(17p), yes n=64	Ibrutinib del(17p), yes b=63
Median time (mo)	5.8	NR
Hazard ratio	0.247	
(95% CI)	(0.136-0.450)	
Log-rank *P* value	< 0.0001	

- **Ibrutinib significantly prolonged PFS in del(17p) CLL; median NR vs. 5.8 mos for ofatumumab**
- **75% reduction in the risk of progression or death**

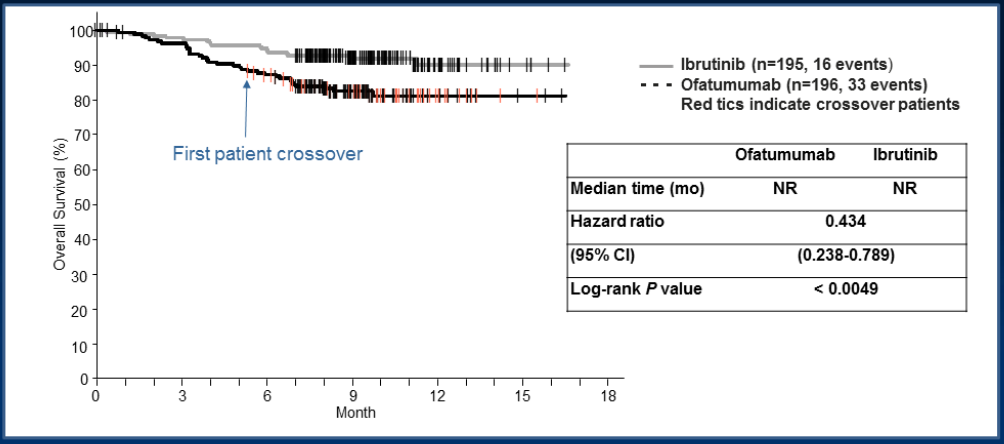
Brown, et al. ASH. 2014.

Progression-Free Survival by Baseline Characteristics and Molecular Features



Byrd, et al. *N Engl J Med*. 2014;371(3):213-223.

Overall Survival



	Ofatumumab	Ibrutinib
Median time (mo)	NR	NR
Hazard ratio	0.434	
(95% CI)	(0.238-0.789)	
Log-rank *P* value	< 0.0049	

- Ibrutinib significantly prolonged OS compared with ofatumumab
  - 57% reduction in the risk of death for the ibrutinib arm
- At the time of this analysis, 57 patients initially randomized to ofatumumab were crossed over to receive ibrutinib following IRC-confirmed PD

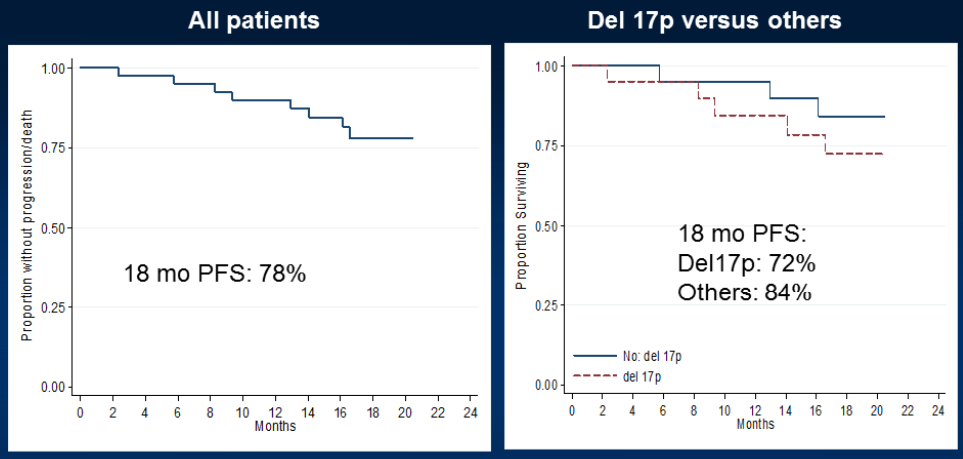
Byrd, et al. *N Engl J Med.* 2014;371(3):213-223.

Safety: Atrial Fibrillation and Bleeding-Related Adverse Events

- Atrial fibrillation of any grade, more common in patients receiving ibrutinib (n=10) vs ofatumumab (n=1)
  - Led to discontinuation of ibrutinib in only one patient
- Bleeding-related AEs of any grade, most commonly petechiae, and including ecchymoses, were more common with ibrutinib than with ofatumumab (44% vs. 12%)
  - The vast majority of ibrutinib events were grade 1
  - No difference in severe/major bleeding events (reported in two patients randomized to ibrutinib and three patients receiving ofatumumab, including one ibrutinib patient with a subdural hematoma)
  - Only one patient discontinued ibrutinib due to a bleeding AE

Byrd, et al. *N Engl J Med.* 2014;371(3):213-223.

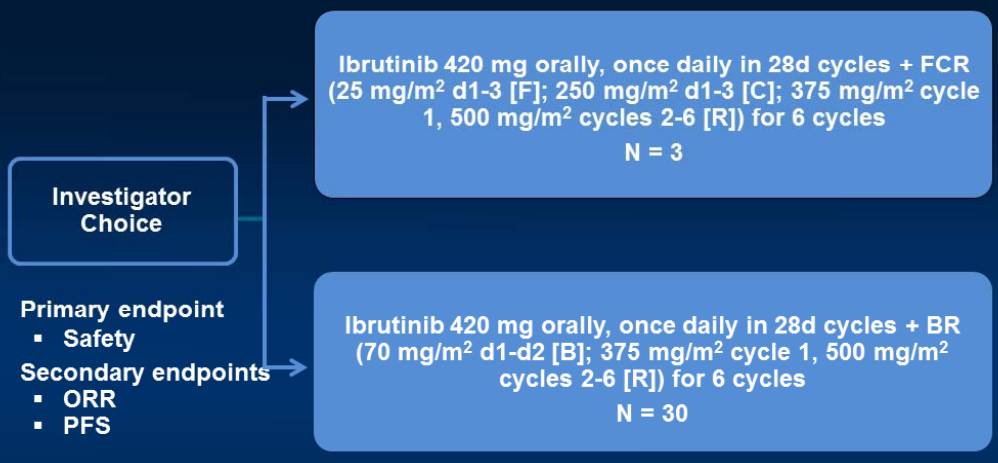
Ibrutinib-Rituximab: PFS in Previously Treated CLL



Median follow-up: 17 months

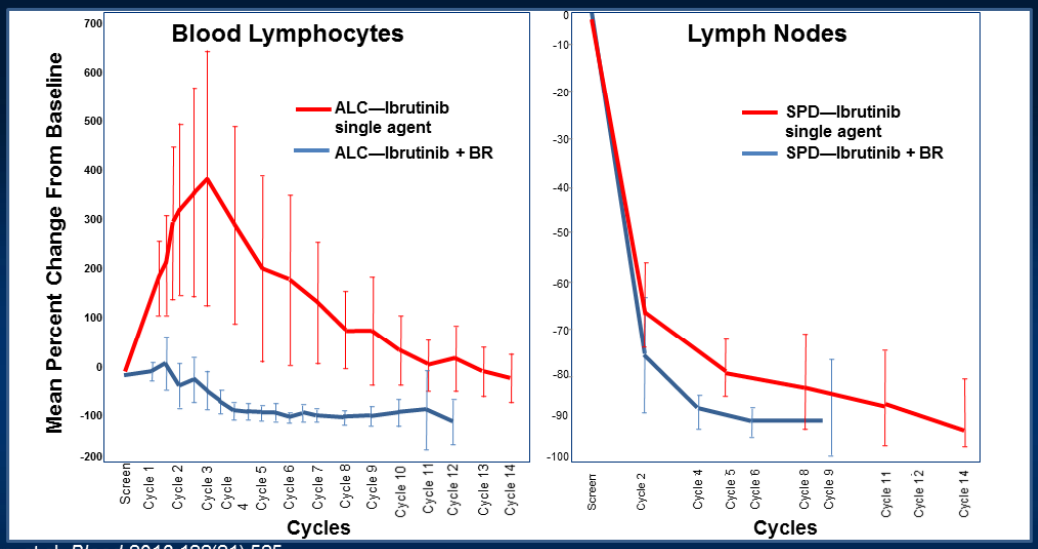
Burger JA, et al. *Lancet Oncol.* 2014;15(10):1090-1099.

PCYC 1108: A Phase 1b Study of Ibrutinib With BR or FCR in Patients With Relapsed/Refractory CLL/SLL



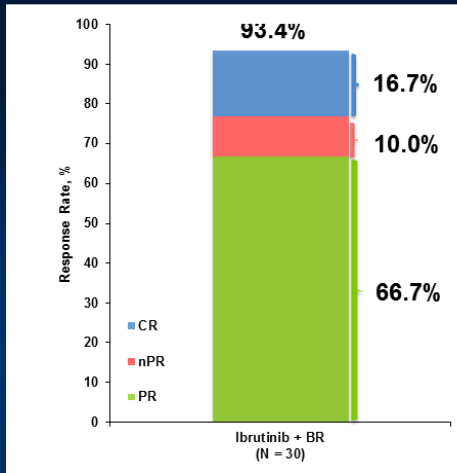
Brown, et al. *Blood.* 2013;122(21):525.

Transient Rise in Lymphocyte Count is Reduced in Combination with BR



Brown, et al. *Blood.* 2013;122(21):525.

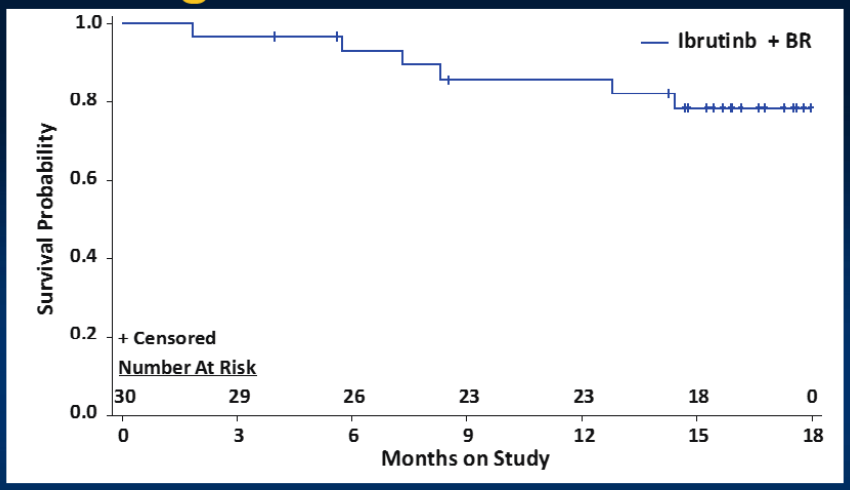
PCYC 1108 Overall Response Rate (ORR)



- Median treatment duration on this study was 16 months, with an ORR of 93.4% (28 responding patients [5 CR, 3 nPR])
- One patient achieved a PR with lymphocytosis (not included in ORR)

Brown, et al. *Blood.* 2013;122(21):525.

PCYC 1108 Progression-Free Survival



18/21 patients who continued on ibrutinib within the extension study are still on treatment ~1 year after the data-cut off without evidence of progression

Brown, et al. *Blood.* 2013;122(21):525.

Limited Experience with Ibrutinib + FCR in Second Line

- Three patients treated, cohort closed due to limited PA-naïve patients in relapsed setting
- Well-tolerated in three patients
  - One SAE – G2 fever and GI bleed
  - All three patients received all 6 cycles of FCR
    - One patient had a dose reduction
- Overall response 100% (3/3) with two confirmed MRD-negative CRs and one MRD-positive CR
- All three patients remain progression free on ibrutinib with 22 month follow-up

Brown, et al. *Blood.* 2013;122(21):525.

Ibrutinib Is Not a Very Specific BTK Inhibitor

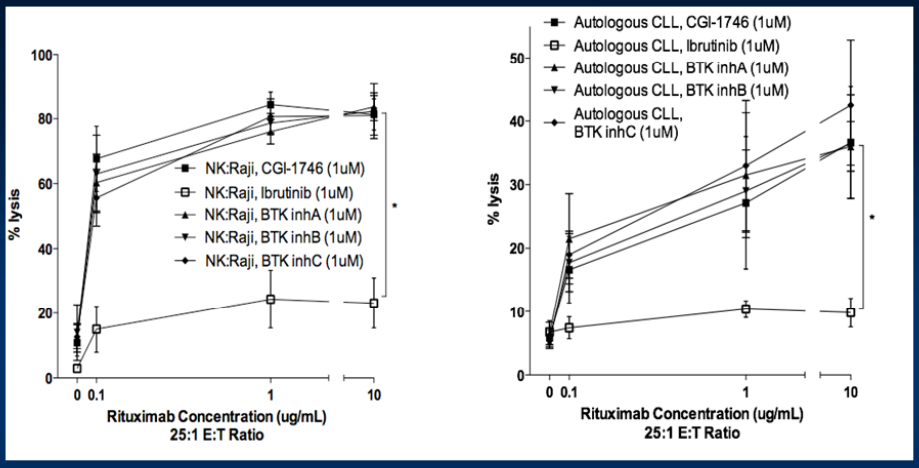
Kinase	IC_{50}, nM	Btk selectivity, fold
BTK	0.5	--
BLK*	0.5	1
BMX*	0.8	1.6
CSK	2.3	4.6
FGR	2.3	4.6
BRK	3.3	6.6
HCK	3.7	7.4
EGFR*	5.6	11.2
YES	6.5	13
ErbB2*	9.4	18.8
ITK*	10.7	21.4
JAK3*	16.1	32.2
FRK	29.2	58.4
LCK	33.2	66.4
RET	36.5	73
FLT3	73	146
TEC*	78	156
ABL	86	172
FYN	96	192
RIPK2	152	304
c-SRC	171	342
LYN	200	400

Honigberg LA, et al. *Proc Natl Acad Sci USA*. 2010;107(29):13075-13080.

Is Greater Specificity Desired?

- **Toxicity:**
  - Rash, diarrhea - ? EGF-R
  - ? Atrial fibrillation
  - ? Bleeding –
    - At least partly BTK dependent
- **Efficacy:**
  - Do other targets contribute?
    - Resistance argues perhaps not
  - ITK inhibition: Impact on ADCC

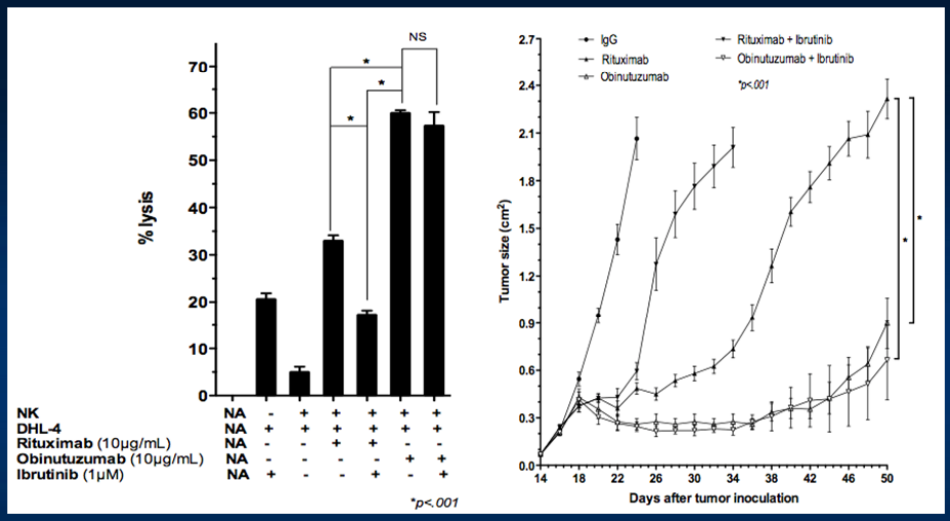
Ibrutinib But Not Alternative BTK Inhibitors Block ADCC by Rituximab



InhA ACP-196; InhB BGB-3111; InhC undisclosed

Rajasekaran, et al. ASH. 2014.

Ibrutinib Does Not Block Activity of Obinutuzumab



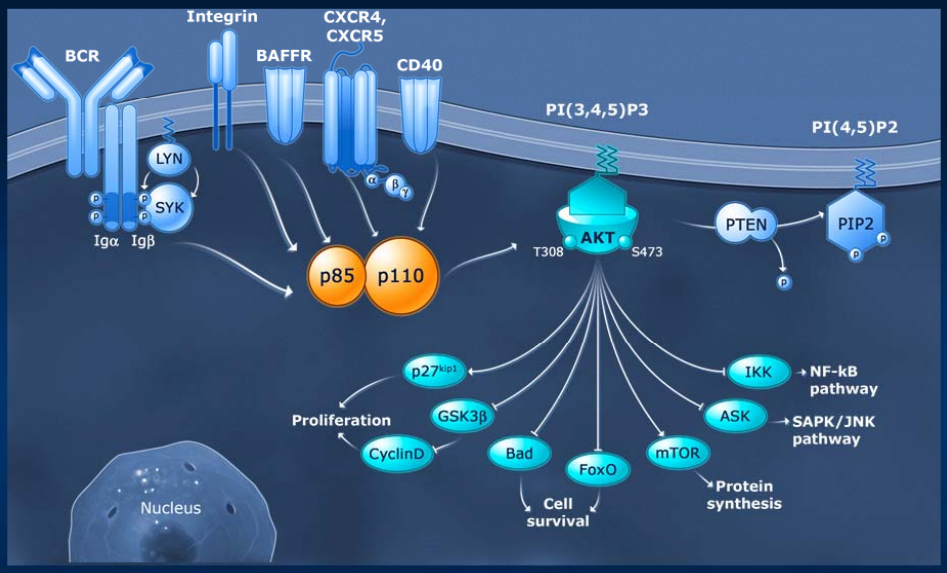
Herter, et al. ASH. 2014.

Mechanisms of Resistance to Ibrutinib

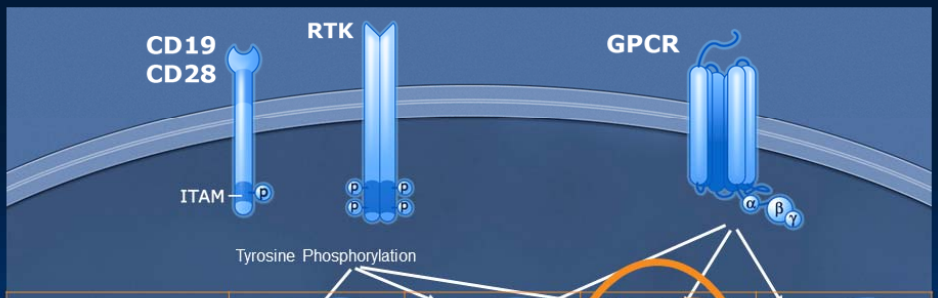
Patient	Age	No. Prior Ther.	Cytogenetics	Study Treatment	Duration on Ibrutinib	Best Response	Identified Mutation
1	59	5	del(17p13.1), +12	560 mg qd	621 days	PR	C481S BTK
2	75	2	del(17p13.1), complex karyotype	420 mg qd	673 days	PR	R665W PLCγ2
3	59	3	del(11q22.3)	BR x 6 cycles, 420 mg qd	388 days	CR	C481S BTK
4	51	2	complex karyotype	Ofatumumab x 24 weeks, 420 mg qd	674 days	CR	C481S BTK
5	69	9	del(17p13.1), complex karyotype	840 mg qd	868 days	PR	C481S BTK
6	61	4	del(17p13.1), complex karyotype	Ofatumumab, x 24 weeks, 420 mg qd	505 days	PR	L845F PLCγ2, C481S BTK

Chang, et al. ASCO. 2013.; Stilgenbauer, et al. *IWCLL*. 2013.; Woyach. *N Engl J Med*. 2014.

PI3K Signaling Pathway As a Target in B Cells



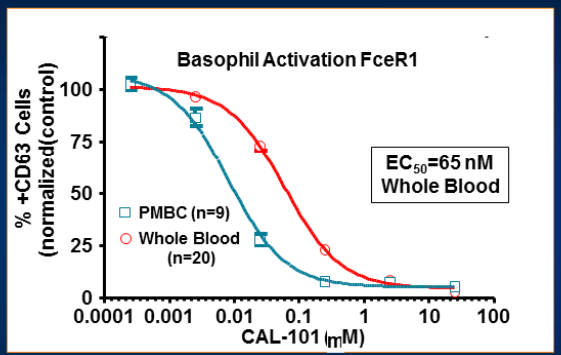
PI3K Delta: Target for B-Cell Diseases

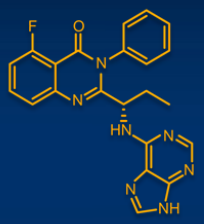


Class I PI3K Isoforms	p85 p110α	p85 p110β	p85 p110δ	p101 p110γ
Isoform	Alpha	Beta	Delta	Gamma
Expression	Broad	Broad	Leukocytes	Leukocytes
Gene KO effect on development	Lethal	Lethal	Benign	Benign
Primary physiological role	Insulin signaling Angiogenesis	unknown	B-cell signaling, development & survival	Neutrophil & T-cell function

Idelalisib (GS-1101) Is Highly Selective for PI3K Delta

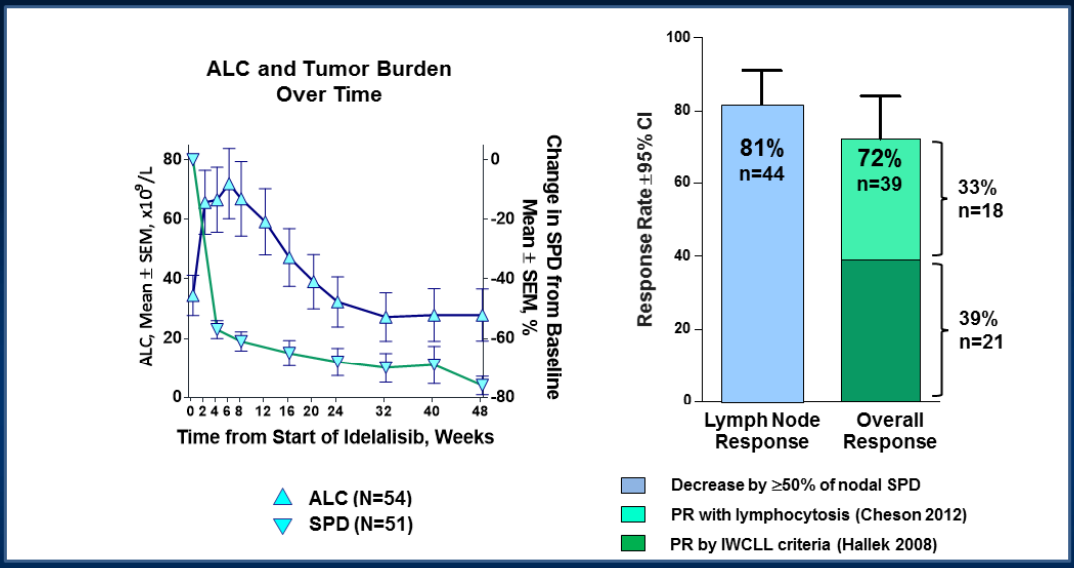
	PI3Kα Alpha	PI3Kβ Beta	PI3Kδ Delta	PI3Kγ Gamma
Assay System	PDGF induced pAKT in fibroblasts	LPA induced pAKT in fibroblasts	FceR1-induced CD63 in basophils	fMLP-induced CD63 in basophils
EC_{50} (nM)	>20,000	1,900	8	3,000





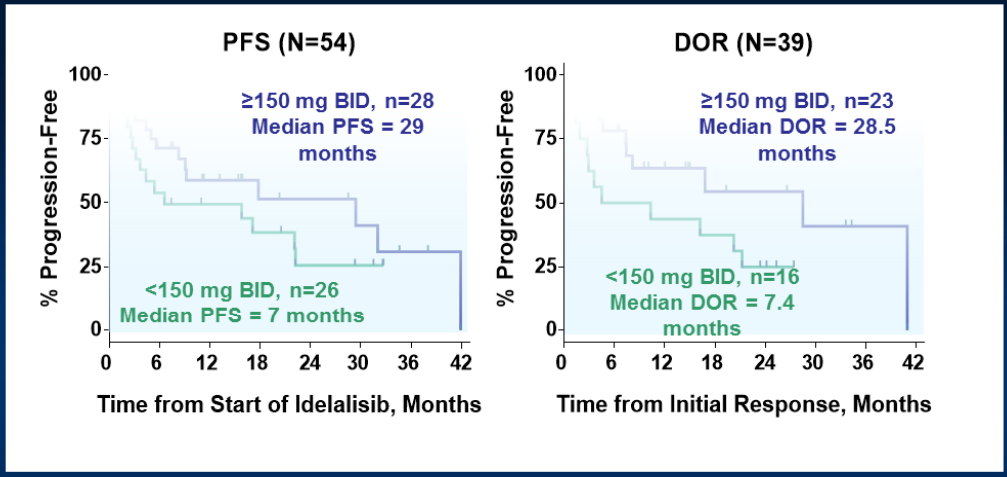
Less than 10-fold shift in EC_{50} in whole blood

Nodal and Overall Response Rate



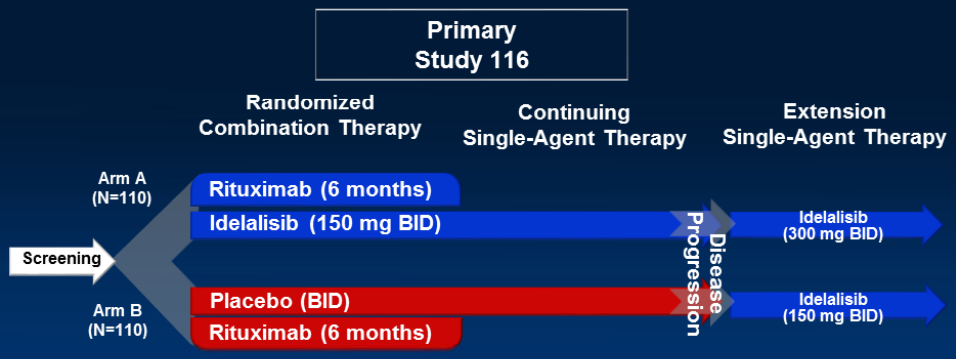
Brown, et al. *Blood.* 2014;123(22):3390-3397.

PFS and DOR by Dose Cohorts



Brown, et al. *Blood.* 2014;123(22):3390-3397.

Gilead Study 116: R-Idela vs R-Placebo



Rituximab administration
- 375 mg/m², then 500 mg/m² Q2W x 4, then 500 mg/m² 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 RR, et al. *N Engl J Med*. 2014;370(11):997-1007.

Key Eligibility

Criteria	Requirement
Relapsed CLL	• CLL progression <24 months since last therapy • Treatment warranted according to IWCLL criteria
Prior therapies	• ≥1 anti-CD20 antibody containing therapy or ≥2 prior cytotoxic therapies
Appropriate for non-cytotoxic therapy	• CIRS score >6 or CrCl <60 ml/min (≥30 mL/min) or Grade 3/4 neutropenia or thrombocytopenia due to prior myelotoxicity
Bone marrow function	• Any grade anemia, neutropenia or thrombocytopenia allowed
Karnofsky score	• ≥40

Furman RR, et al. *N Engl J Med*. 2014;370(11):997-1007.

Baseline Patient Characteristics

	IDELA + R (N=110)	Placebo + R (N=110)
Gender, male, %	69	62
Age, median [range], years	71 [48-90]	71 [47-92]
Rai Stage III-IV, %	64	66
Time since diagnosis, median, years	7.8	8.6
Prior therapies, median [range]	3 [1-12]	3 [1-9]
Prior therapy, agent, %		
Rituximab (R)	91	88
Cyclophosphamide (C)	64	70
Fludarabine (F)	56	64
Bendamustine (B)	58	54
Chlorambucil (Chl)	31	22

Furman RR, et al. *N Engl J Med*. 2014;370(11):997-1007.

Baseline Patient Characteristics

	IDELA + R (N=110)	Placebo + R (N=110)
Cytopenia, Grade 3/4, %		
Anemia	6%	11%
Neutropenia	17%	16%
Thrombocytopenia	16%	29%
ALC, median [range], cells, x 1Kμ/L	32 [0-263]	31 [0-399]
CLL genetics, %		
Unmutated *IGHV*	83	85
Del(17p)/*TP53* mutation	42	46
CIRS score		
Total CIRS score, median [range]	8 [3-18]	8 [1-18]
Subjects with total CIRS score >6, %	88	82
≥1 single organ system score of ≥3, %	35	39
Est. CrCl		
Median [range], ml/min	62 [32-161]	67 [23-199]
Subjects with est. CrCl<60 ml/min, %	44	36

Furman RR, et al. *N Engl J Med*. 2014;370(11):997-1007.

Treatment Disposition

	IDELA + R	Placebo + R
Patients randomized, n (%)	110	110
Received study medication	110 (100)	108 (98)
Continuing on study	83 (76)	50 (46)
Discontinued study, n (%)	27 (25)	60 (55)
Disease progression	7 (6)	41 (37)
Death	5 (5)	9 (8)
Adverse event	5 (5)	6 (6)
Withdrawal by patient	9 (8)	3 (3)
PI decision	1 (1)	1 (1)
Exposure, median [range], months		
Study drug (IDELA or Placebo)	5.0 [0-17]	3.7 [0-15]

Coutre, et al. *J Clin Oncol.* 2014;32:5s(suppl; abstr 7012).

Laboratory Abnormalities of Interest

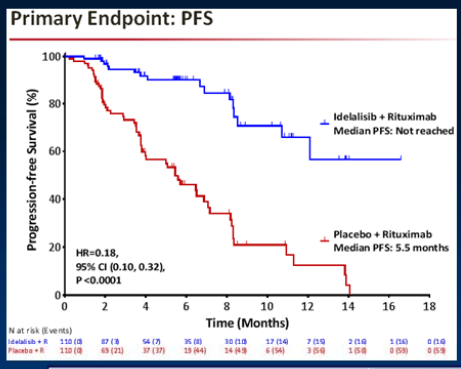
Category, n (%)	IDELA + R (N=110)		Placebo + R (N=108)	
	Any Gr.	Gr. 3/4	Any Gr.	Gr. 3/4
Anemia	32 (29)	8 (7)	35 (32)	18 (17)
Neutropenia	66 (60)	41 (37)	55 (51)	29 (27)
Thrombocytopenia	21 (19)	12 (11)	34 (32)	19 (18)
ALT/AST elevation*	44 (40)	9 (8)	22 (20)	1 (1)

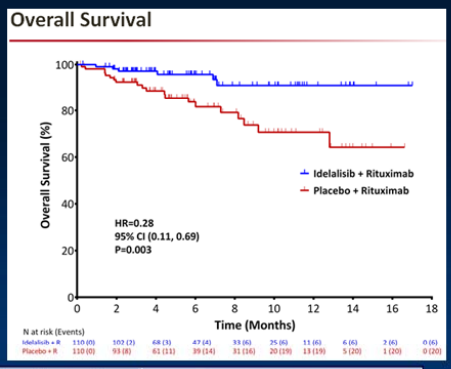
* 7 of the 9 patients in the IDELA + R arm were successfully re-challenged:

- 3 patients at 150 mg BID, 4 at the reduced dose of 100 mg BID
- One patient's transaminase elevation was associated with CLL transformation (Richter) in the liver (progressive disease).

Coutre, et al. *J Clin Oncol.* 2014;32:5s(suppl; abstr 7012).

Outcomes

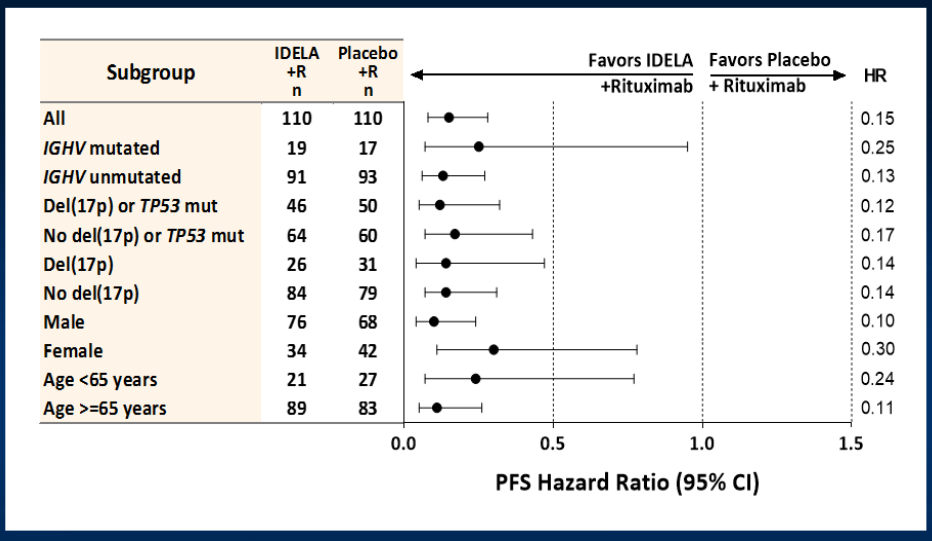




		Idelalisib + rituximab n=110	Placebo + rituximab n=110
PFS	Median (months) (95% CI)	NR (10.7, NR)	5.5 (3.8, 7.1)
	Hazard ratio (95% CI)	0.18 (0.10, 0.32)	
	P value	<0.0001*	

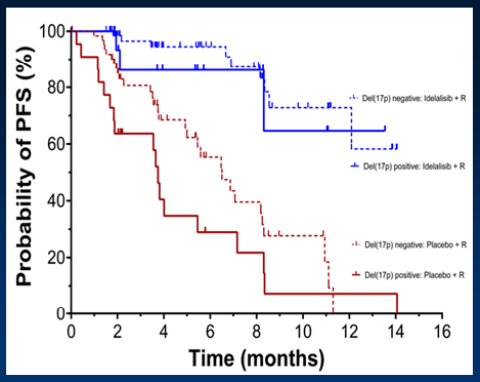
Coutre, et al. *J Clin Oncol.* 2014;32:5s(suppl; abstr 7012).

PFS Analysis in Pre-Specified Subgroups

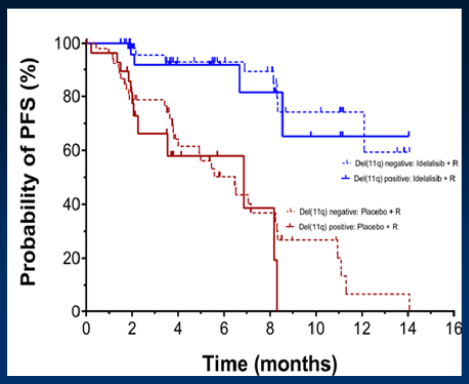


Coutre, et al. *J Clin Oncol.* 2014;32:5s(suppl; abstr 7012).

PFS Outcomes of 17P / 11q Patients



Study arm +/- 17P



Study arm +/- 11Q

Coutre, et al. *J Clin Oncol.* 2014;32:5s(suppl; abstr 7012).

Phase 2 Single Arm, Open-Label Study

Study Schema

Subject Accrual Oct 2010 Through Apr 2012

Primary Study: 101-08

Idelalisib (150 mg BID) x 48 wks

Rituximab (375 mg/m^2) weekly x 8

Extension Study: 101-99

Therapy continues as long as patient receives benefit

Eligibility	• **Age ≥65 years** • **Treatment-naive CLL requiring therapy (IWCLL 2008)** • **No exclusions for cytopenias**
Disease Assessment	• **Investigator determined** • **Weeks 0, 8, 16, 24, 36, 48 and per SOC thereafter**
Endpoints	• **Primary: ORR** • **Secondary: DOR, PFS, safety**

O'Brien SM, et al. *J Clin Oncol.* 2013;31 (suppl; abstr 7005).

Response Assessment

	All Subjects		Del(17p) and/or TP53 mutation	
	N = 64	(%)	N = 9	(%)
Complete Response	**12**	**(19)**	**3**	**(33)**
Partial Response	**50**	**(78)**	**6**	**(67)**
Stable Disease	0		0	
Progressive Disease	0		0	
Not Evaluable	2	(3)	0	
Overall Response	**62**	**(97)**	**9**	**(100)**

Median time to response 1.9 months
24/26 patients with B symptoms resolved by week 16
No on-study progression

O'Brien SM, et al. *J Clin Oncol*. 2013;31(suppl; abstr 7005).

All Cause AEs ≥25% in Primary and Extension Studies; On-Study Lab Abnormalities

Adverse Event	n (%) with any Grade	n (%) with Grade ≥3
Diarrhea**	35 (55)	15 (23)
Pyrexia	27 (42)	2 (3)
Nausea	24 (38)	1 (2)
Rash	24 (38)	5 (8)
Chills	23 (36)	0
Cough	21 (33)	1 (2)
Fatigue	20 (31)	0
Pneumonia	17 (27)	11 (17)

**10 patients reported as Gr 3 colitis, including 6 lacking any AE report of Gr ≥3 diarrhea
Med time to Grade 3 diarrhea/colitis = 9 months

Lab Abnormality*	n (%) with Increase to Grade ≥3
Transaminase elevations	15 (23)
Neutropenia	18 (28)
Anemia	2 (3)
Thrombocytopenia	1 (2)

O'Brien SM, et al. *J Clin Oncol*. 2013;31(suppl; abstr 7005).

AEs Leading to Discontinuation

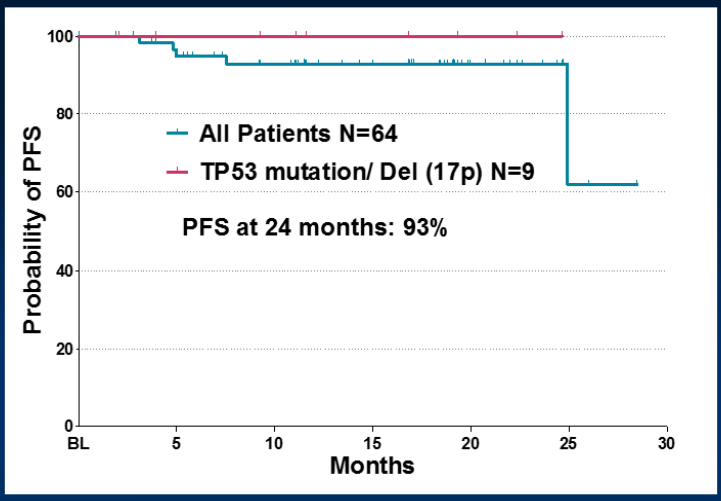
Adverse Event	<24 weeks n = 10*	24-48 weeks n = 6	>48 weeks n = 7	Total n = 23* (%)
Diarrhea/colitis	0	3	5	8 (13)
Respiratory disorders	5	0	0	5 (8)
Rash	3	0	0	3 (5)
Anemia	1	1	0	2 (3)
ALT/AST	1	0	0	1 (2)
Other	2	4	2	8 (13)

Infections in first 48 weeks
- 67% - any Grade
- 23% - Grade ≥3
- 14% - Grade ≥3 pneumonia

Deaths (n = 5)
- Pneumonia/sepsis (1)
- Pneumonia/metastatic melanoma (1)
- Pneumonitis (2)
- Myocardial infarction (1)

O'Brien SM, et al. *J Clin Oncol*. 2013;31 (suppl; abstr 7005).

Progression-Free Survival



*ITT analysis of primary + extension study
Extension study assessments based on standard of care

O'Brien SM, et al. *J Clin Oncol*. 2013;31 (suppl; abstr 7005).

BCR Pathway Inhibitors in Relapsed CLL

	DRUG	N	Nodal Resp	Rate of Incr ALC	ORR	PFS
LYN (?BTK)	Dasatinib	15	47%	NR	20%	TTF 6.7m
SYK	Fostamatinib	11	55%	69%	NR	6.4m
mTOR	Everolimus	22	45%	36%	18%	5.1m
PI3K	Delta: GS1101	55	83%	58%	39% (72%)	16 m (32 m)
	Pan-PI3K: S08	10	60%	50%	40%	NR
	Gamma Delta: IPI-145	52*	98%	64-73%	47%	Too early
BTK	Ibrutinib: PCI-32765	85	88%	78%	71%	75% @ 26m
	CC-292: AVL-292	64*	60%	55%	45%	Too early
	ONO-4059	25*	90%	67%	67%	Too early

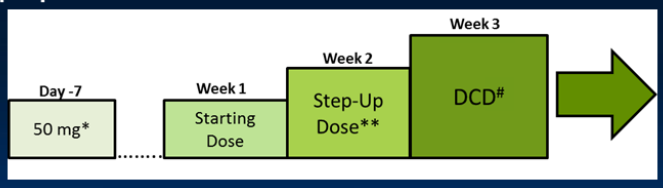
BCL2 Inhibition

- ABT-263: first generation
  - Specific inhibitor BCL2, BCL-XL, BCL-w
  - Dose-limiting toxicity thrombocytopenia
- ABT-199: second generation
  - >100X selectivity relative to BCL-XL
- Ongoing phase 1 study
  - No major thrombocytopenia
  - Primary DLT: tumor lysis syndrome
    - Managed with slow in hospital dose escalation, frequent post-dose labs

ABT-199 Dosing Schema

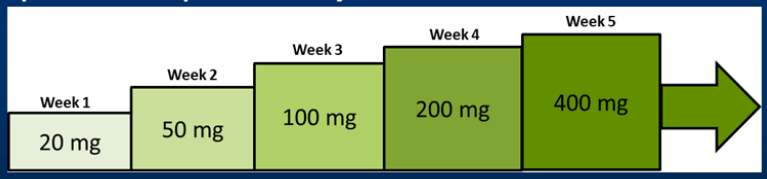
Daily ABT-199 doses increased weekly to the designated cohort dose (DCD)

Initial Ramp-Up Schema: Dose Escalation



* 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 ranges from 150 to 1200 mg

Ramp-Up Schema: Expanded Safety Cohort



Seymour JF, et al. *Haematologica.* 2014;99(suppl 1): ABSSUB-5375.

Patient Characteristics (n=105)

Characteristics		All CLL/SLL
Age, y	Median	66 [36 – 86]
Bulky nodes, n (%)	≥5 cm	58 (55)
	≥10 cm	17 (16)
Number of prior therapies	Median	4 [1 - 11]
IGHV mutation status	Unmutated	36/48 (75)
17p Status	Deleted	23 (22)
	Not Deleted	49 (47)
	Missing	9/24 (31)
Fludarabine, n (%)	Prior Treatment	87 (83)
	Refractory	62 (59)

Seymour JF, et al. *Haematologica.* 2014;99(suppl 1): ABSSUB-5375.

Serious Adverse Events (SAEs) Possibly or Probably Related to ABT-199

SAEs (≥2 patients)	N=105 n (%)
Febrile neutropenia	4 (4)
Tumor lysis syndrome (TLS)*	3 (3)

- Other SAEs (n=1): sudden death* (in the setting of TLS)
- As of April 9, 2014, in the 49 patients treated since modifications were made to the dose ramp-up scheme as well as the tumor TLS prophylaxis and monitoring schedule, no additional events of clinical TLS (or SAEs of TLS) have been reported

Seymour JF, et al. *Haematologica.* 2014;99(suppl 1): ABSSUB-5375.

Adverse Events

All Grades ≥20% of patients	N=105 n (%)
Diarrhea	42 (40)
Neutropenia	38 (36)
Nausea	37 (35)
Upper respiratory tract infection	35 (33)
Fatigue	27 (27)
Cough	21 (20)
Grades 3/4 ≥5% patients	**n (%)**
Neutropenia	35 (33)
Anemia	10 (10)
Febrile neutropenia	7 (7)
Thrombocytopenia	7 (7)
Hyperglycemia	7 (7)
Tumor lysis syndrome (TLS)	7 (7)
Hypokalemia	5 (5)

Seymour JF, et al. *Haematologica.* 2014;99(suppl 1): ABSSUB-5375.

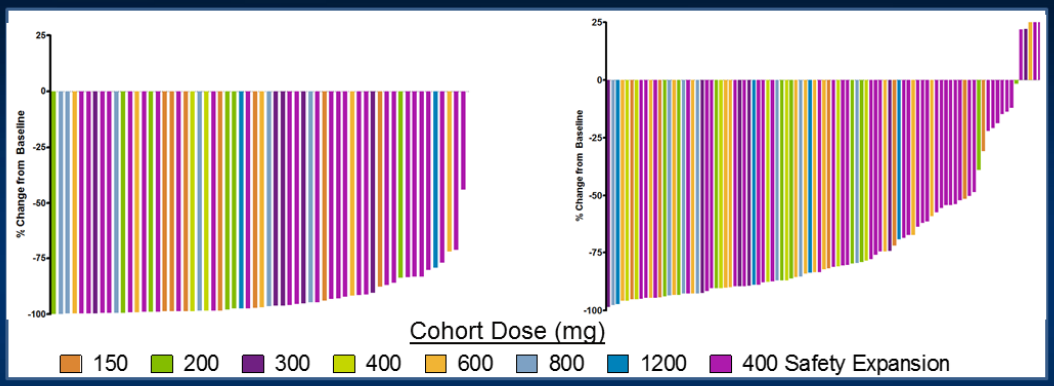
Best Percent Change from Baseline in Blood Lymphocyte Count and Nodal Mass by CT Scan

Blood lymphocytes (n=60)

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

Nodal Mass by CT Scan (n= 93)

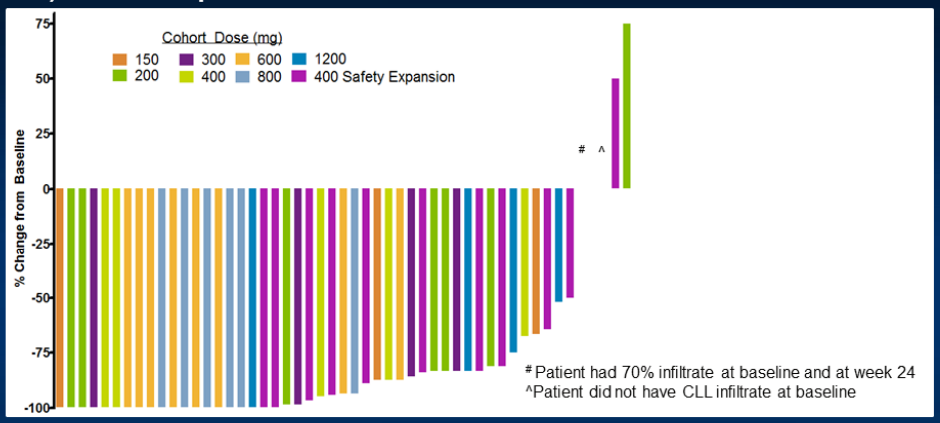
- The median time to 50% reduction 1.4 months, range [0.65 – 13.7]*
- 78 (84%) evaluable patients had at least a 50% reduction in sum of the product of diameters (SPD) of nodal masses



Data represents patients with lymphocyte count >5 x 10^9/L at baseline
*Coincides with first protocol specified CT scan at 6 weeks
Seymour JF, et al. *Haematologica.* 2014;99(suppl 1): ABSSUB-5375.

Best Percent Change from Baseline in Bone Marrow Infiltrate (n=51)

- Median time to 50% reduction: 5.5 months, range [1.9 – 17.4]*
- 46/51 (90%) evaluable patients have had at least a 50% reduction



- Anti-tumor activity of ABT-199 was observed in all tumor compartments

Seymour JF, et al. *Haematologica.* 2014;99(suppl 1): ABSSUB-5375.

Objective Responses of ABT-199 Treated Patients

Responses	All n (%), n = 78	del (17p) n (%) , n = 19	F-Refractory n (%), n =41	IGHV 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)
Stable disease	10 (13)	2 (11)	7 (17)	2 (8)
Disease progression	2 (3)	1 (5)	1 (3)	2 (8)

- The median duration of response has not yet been reached based on current patient enrollment numbers

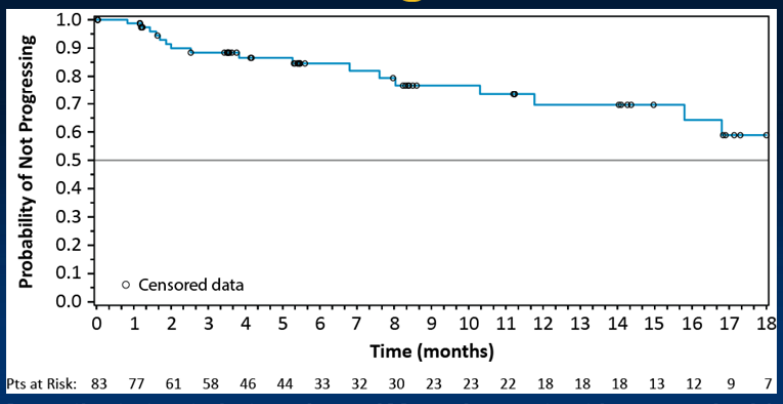
Seymour JF, et al. *Haematologica.* 2014;99(suppl 1): ABSSUB-5375.

Current Status of Enrolled Patients (n=105; April 9, 2014)

- Median time on study
  - Dose escalation patients (all dose levels): 17.1 months, range [0.06 – 29.7]
  - Safety expansion patients: 4.7 months, range [0.52 – 9.3]
- Discontinuations
  - As of April 9, 2014, 105 patients are enrolled and 37 have discontinued for the following reasons:
    - 22 progressive disease (of which 15 were from Richter's)
    - 12 adverse events
    - 3 other (1 need for Coumadin, 2 proceeded to alloSCT)
- Based on the preliminary safety and efficacy profile of ABT-199, 400 mg is currently being explored as the safety expansion dose

Seymour JF, et al. *Haematologica.* 2014;99(suppl 1): ABSSUB-5375.

Progression-Free Survival (PFS) at 400 mg or Higher

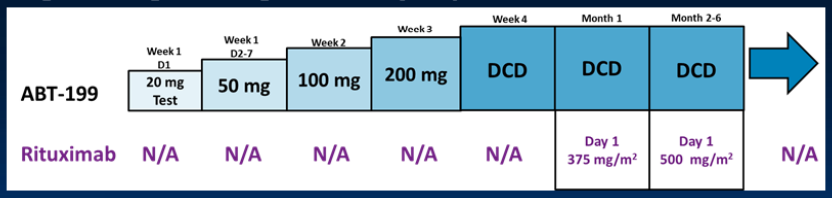


- **Median PFS for patients treated at or above 400 mg has not yet been reached (median follow-up of 5.3 months, range [0.03 – 22])**
- **As of April 9, 2014, the median PFS for all patients is approximately 18 months**

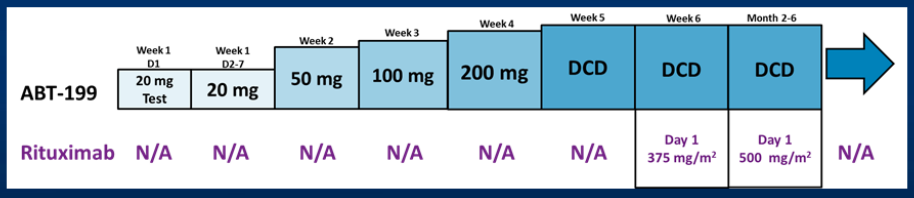
Seymour JF, et al. *Haematologica.* 2014;99(suppl 1): ABSSUB-5375.

Dosing Schedule of ABT-199 and Rituximab – Cohorts 3 – 6

400 mg, 500 mg, 600 mg and safety expansion cohorts dosed with this



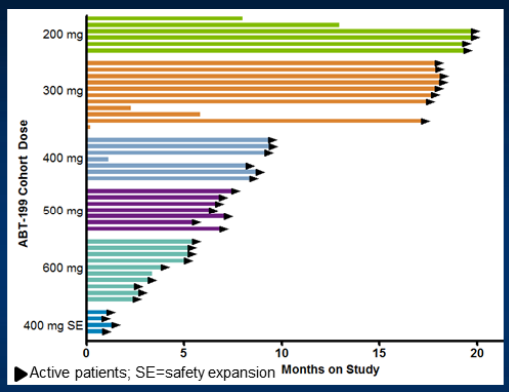
OR: if one or more electrolytes meet Cairo-Bishop criteria and/or if there is ≥30% decrease in ALC with first dose



Roberts AW, et al. *Haematologica.* 2014;99(suppl 1): ABSSUB-4704.

Current Status of Evaluable Patients (April 16, 2014 cut-off)

- Median time on study = 7.5 months, range [0.03 – 19.6]
  - Original dosing regimen = 13.3 months, range (1.5 – 19.6)
  - Amended dosing regimen = 5.1 months, range (0.03 – 9.2)



Discontinuations
- 7 out of 45 patients
- Progressive disease (n = 5)
  - Richter's transformation (4)
  - Progressive CLL (1)
- Adverse event (n = 1)
  - Fatal tumor lysis
- Withdrew consent (n = 1)

Roberts AW, et al. *Haematologica*. 2014;99(suppl 1): ABSSUB-4704.

Responses of Patients Treated with ABT-199 and Rituximab

Response	Evaluable Patients n=25 (%)
Overall response	21 (84)
CR (n=4)/CRi (n=5)*	9 (36)
Disease progression	1 (4)
Discontinued prior to M7 assessment #	2 (8)

- Of the 20 patients on study <7 months (still receiving combination): 5 have a PR, 6 have a PR at first CT; 9 have not yet been evaluated

Roberts AW, et al. *Haematologica*. 2014;99(suppl 1): ABSSUB-4704.

Minimal Residual Disease (MRD)

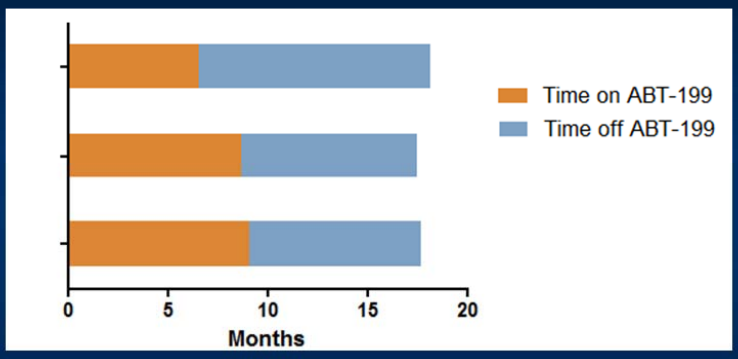
- MRD was assessed by local lab using 4-color flow cytometry in 8/9 CR/CRi patients and six patients with a PR (based on available data)

Patient	Response	Source	Sensitivity	MRD
1	CR	Bone Marrow	10^{-4}	Negative
2	CR	Peripheral Blood	10^{-3}	Negative
3	CR	Bone Marrow	10^{-3}	0.20%
4	CR	Bone Marrow	10^{-3}	Negative
		Peripheral Blood	10^{-3}	Negative
5	CR	Bone Marrow	10^{-4}	Negative
6	CR	Bone Marrow	10^{-4}	Negative
7	CR	Bone Marrow	10^{-4}	0.02%
8	CR	Bone Marrow	10^{-4}	Negative
9	PR	Bone Marrow	10^{-4}	Negative
10	PR	Bone Marrow	10^{-4}	< 1%
11	PR	Bone Marrow	10^{-4}	Negative
12	PR	Peripheral Blood	10^{-4}	Negative
13	PR	Bone Marrow	10^{-4}	Negative
14	PR	Bone Marrow	10^{-4}	Negative

Roberts AW, et al. *Haematologica*. 2014;99(suppl 1): ABSSUB-4704.

Complete Remission: Discontinuation of ABT-199

- Three patients have discontinued ABT-199 after achieving CR/CRi (two with MRD negativity)
- Patients had 1, 3, and 4 prior therapies; one had fludarabine refractory disease
  - Patients are continuing follow-up on study
  - Patients remain in CR at the time of this analysis (8.6, 8.8, and 11.6 months after cessation)



Roberts AW, et al. *Haematologica*. 2014;99(suppl 1): ABSSUB-4704.

Summary

- Several small molecule inhibitors are showing remarkable activity in CLL despite the absence of a genetically activated target
  - Likely due to constitutive pathway activation (BCR, apoptosis)
  - Ibrutinib (approved 2/2014, updated 7/2014)
  - Idelalisib (approved 7/2014)
  - ABT-199

CLL Therapy, ca 2014

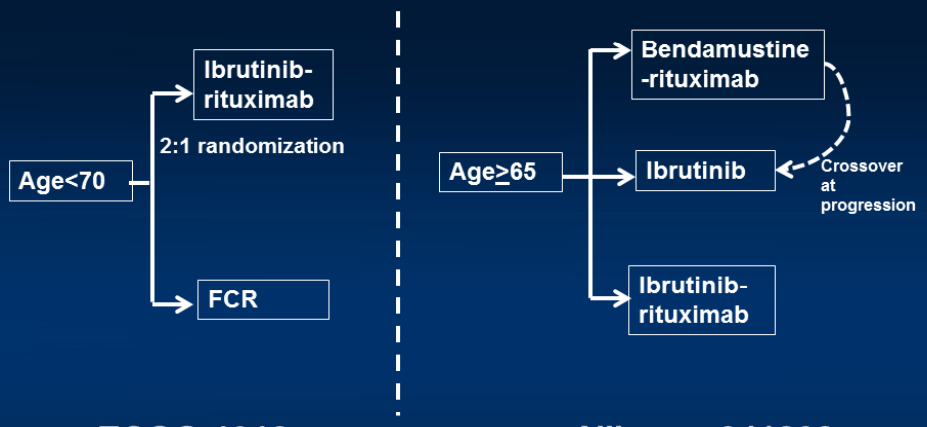
	Initial Therapy	Relapsed Therapy
Fit /Young	FCR (esp mut IGHV) Higher risk: clinical trial	Ibrutinib (Idelalisib+R)
With Comorbidities/ Older	Clb-Obin or Clb-Ofa; BR	Ibrutinib; Idelalisib + R
With 17p	Ibrutinib (HDMP + R/Alem) ?AlloSCT	Ibrutinib Idelalisib + R ?AlloSCT

Ongoing Clinical Trials in CLL

Agent	Initial Therapy	Relapsed Therapy
Ibrutinib	I vs Clb – Ph 3 (RESONATE-2), >65 FCR vs IR – two Ph 3 Ibrutinib – FCR – Ph 2 BR vs IR vs I – Ph 3 I-Obin vs Clb-Obin – Ph 3, >65/Co	I in Del 17p CLL – Ph 2 BR +/- I – Ph 3 I vs IR
Idelalisib	BR+/-Idelalisib Ph 3 Idela-Obin vs Clb-Obin - Ph3, Co Idela-R – Ph 2, Del 17p CLL	BR +/- Idela – Ph 3 Idela-Ofa vs Ofa – Ph 3
ABT-199	ABT199-Obin vs ABT-R vs FCR/BR ABT-Obin vs Clb-Obin	ABT199-R vs BR – Ph 3 ABT199 – Ph 2, Del 17p CLL ABT199 after BCRi
IPI-145		IPI vs Ofa – Ph 3 IPI-145-Obin after BCRi

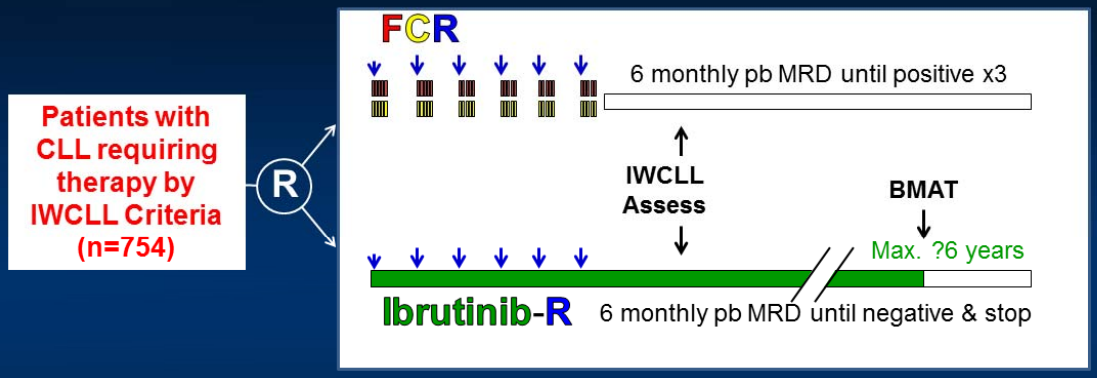
I=Ibrutinib; Co=with comorbidities

US Intergroup: Moving Ibrutinib to Frontline Therapy



UK: Frontline Trial for Patients Fit for FCR: NCRI FLAIR (CLL10) Trial

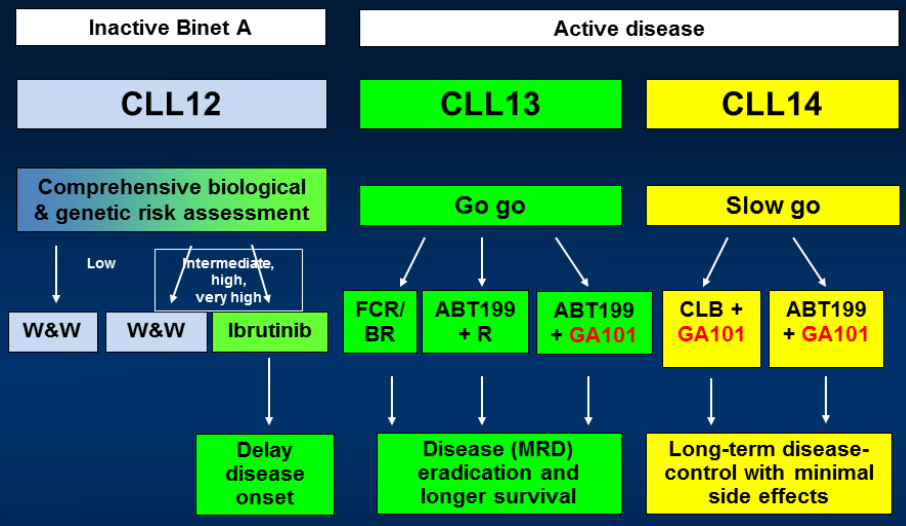
Frontline Therapy in CLL: Assessment of Ibrutinib plus Rituximab



Courtesy of P. Hillmen

Fourth-Generation of GCLLSG Trials

Risk, Stage and Fitness Adapted, Using Targeted Agents



Courtesy of M. Hallek

Summary and Open Questions

- Durability of PRs with single novel agents is unknown
  - Do antibody or chemotherapy combinations add?
    - Currently not clear they add
  - Are relapses more fulminant or more commonly Richter's?
    - Suggested in the early data emerging from ibrutinib and ABT199
- Therapy currently given as continuous single agents, but:
  - Long-term toxicity unknown
  - When patients relapse they will be resistant
- Mechanisms of resistance still being studied
  - Ibrutinib: BTK and PLCγ mutn, clonal evolution ?8p del
  - What does this imply about optimal sequencing of novel agents?

Open Questions

- No evidence to support earlier therapy, which might incur risk of clonal evolution
- What is the future role of chemotherapy?
  - Particularly FCR which leads to long-term PFS in a subset of low risk mut IGHV patients
- Can we find safe, novel-novel combinations that generate meaningful improvement in CR?
  - Studies in planning will assess these novel agent combinations, eg, BCR inhibitors + BCL2 antagonists
  - Potential for high costs could be mitigated by shorter duration therapy

Which of the following is not an important potential side effect of idelalisib?

1. Pneumonitis
2. Colitis
3. Bleeding
4. Transaminitis

Which of the following is not an important potential side effect of idelalisib?

1. Pneumonitis
2. Colitis
3. **Bleeding**
4. Transaminitis

Which of the following novel agents has shown the highest complete remission rate in relapsed CLL?

1. Ibrutinib
2. ABT-199
3. Idelalisib
4. Obinutuzumab

Which of the following novel agents has shown the highest complete remission rate in relapsed CLL?

1. Ibrutinib
2. **ABT-199**
3. Idelalisib
4. Obinutuzumab

Which of the following is NOT true of the BCR pathway inhibitors?

1. Nodal response is rapid
2. Side effects are generally mild and manageable
3. Currently these drugs are dosed until progression or adverse event that requires discontinuation
4. The lymphocyte count drops rapidly in most patients
5. Response is preserved even in patients with adverse cytogenetics

Which of the following is NOT true of the BCR pathway inhibitors?

1. Nodal response is rapid
2. Side effects are generally mild and manageable
3. Currently these drugs are dosed until progression or adverse event that requires discontinuation
4. **The lymphocyte count drops rapidly in most patients**
5. Response is preserved even in patients with adverse cytogenetics

Cases Revisited

Jan A. Burger, MD, PhD
Associate Professor
Department of Leukemia
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Case 1

- 51-year-old male with relapsed CLL and progressive lymphocytosis, lymphocyte doubling time <6 months
- CLL since 1997, previous treatment FCR and bendamustine

PE:	0.5-1 cm cervical nodes No axillary or inguinal nodes or palpable spleen
Lab:	WBC 45,200, 84% lymphocytes Hgb 13.7, platelets 115,000
Flow:	$CD19^+$, $CD5^+$, $CD23^+$ CD20 weakly positive, $CD38^-$
FISH:	11q-, 13q-
IgVH:	Unmutated (1.3% deviation from germline)
CT	Spleen slightly enlarged (15 cm), abdominal nodes up to 2 cm

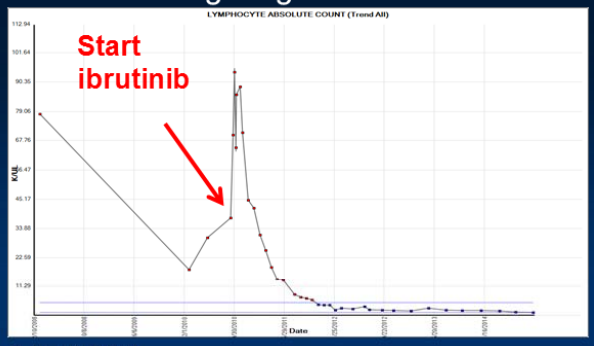
Case 1 (continued)

- This patient started ibrutinib single agent in 9/2010
- Treatment well tolerated, no relevant side effects
- Lymphocytosis progressed from 45,200 to 94,300/µL in 10/2010, Hb and platelet counts stable

- Which of the following statements are NOT consistent with 11q deletion CLL and response to therapy?
  1. Male gender, presentation at a relatively young age, significant adenopathy, and absence of IGHV mutations (unmutated CLL/U-CLL) is typical in patients with CLL and 11q deletion
  2. A short remission duration after FCR and bendamustine is typical of patients with 11q deletion
  3. The patient is showing signs of early progression on ibrutinib with an increasing lymphocyte count and needs be switched to another type of therapy
  4. The minimal side effects of ibrutinib within the first month are characteristic

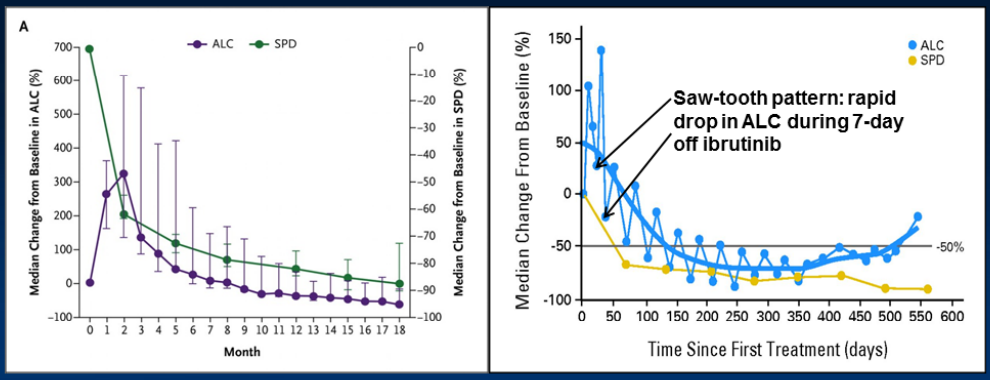
Case 1 (continued)

- This patient started ibrutinib single agent in 9/2010



  - Normalization of ALC in 11/2011
  - CT 4/2011: no residual disease
  - 11/2012: BMA in CR, MRD 3.5%
  - 04/2014: BMA in CR, MRD 2.6%

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



- 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

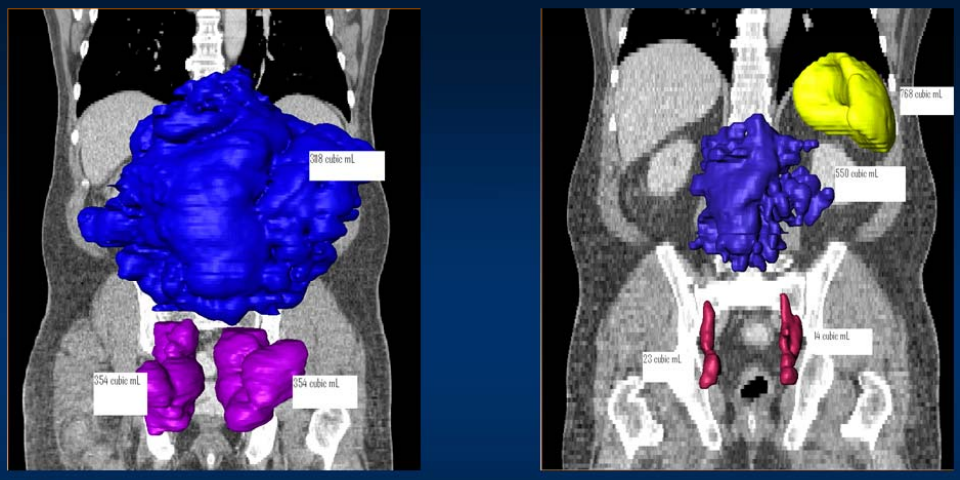
Byrd JC, et al. *N Engl J Med.* 2013.; Advani RH, et al. *J Clin Oncol.* 2013.

Marked Reductions in Peripheral Lymphadenopathy During Ibrutinib Therapy

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

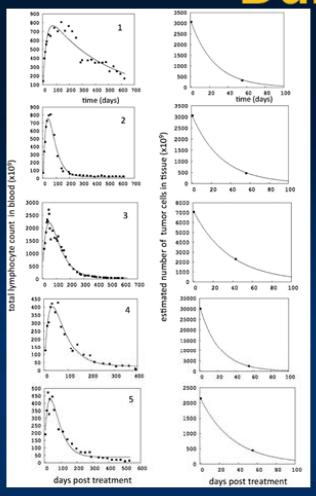
Volumetric Changes During Ibrutinib Therapy

Before ibrutinib | **3 months on ibrutinib**



Wodarz D, et al. *Blood*. 2014.

Dynamics of PB and Tissue CLL Cells During Ibrutinib Therapy



- During ibrutinib therapy, 1.7% of blood and 2.7% of tissue CLL cells die per day
- The fraction of CLL cells that redistribute into the blood during ibrutinib treatment represents 23.3% ± 17% of the tissue disease burden

- Serial ALC (left column)
- Serial volumetric analysis (right column) of CLL disease burden

Wodarz D, et al. *Blood*. 2014.

Case 2

- A 43-year old female with newly diagnosed CLL. Dx in 2012, initially managed with observation
- 02/2014: comes for follow-up, no symptoms

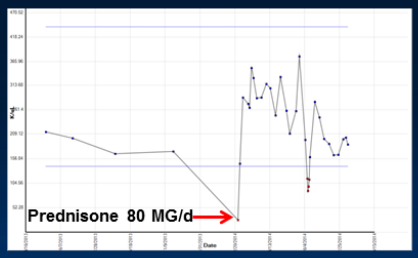
PE	No enlarged lymph nodes or spleen
Lab	WBC 104,500, 79% lymphocytes Hgb 9.7, platelets 26,000, β_2M 2.4
Flow	CD19, CD5, CD23 positive CD20 weakly positive
FISH cytogenetics	Trisomy 12
IgVH	Mutated

Case 2: Treatment Options

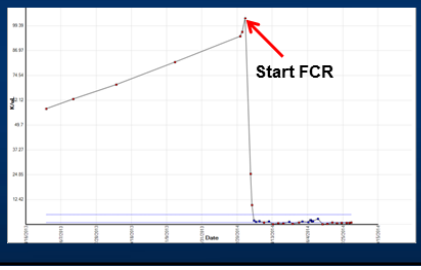
1. Oral steroids, FCR chemo-immunotherapy
2. High-dose Solu-Medrol + rituximab, followed by ibrutinib
3. Bendamustine + rituximab chemo-immunotherapy
4. Obinutuzumab (Gazyva®) + chlorambucil

Case 2: Treatment Course

Platelet counts



Lymphocyte counts



- ITP and progressive CLL
- After 4 cycles FCR: MRD-negative

Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Eradication of bone marrow minimal residual disease may prompt early treatment discontinuation in CLL

Paolo Strati,[1] Michael J. Keating,[1] Susan M. O'Brien,[1] Jan Burger,[1] Alessandra Ferrajoli,[1] Nitin Jain,[1] Francesco Paolo Tambaro,[2] Zeev Estrov,[1] Jeffrey Jorgensen,[3] Pramoda Challagundla,[3] Stefan H. Faderl,[1] and William G. Wierda[1]

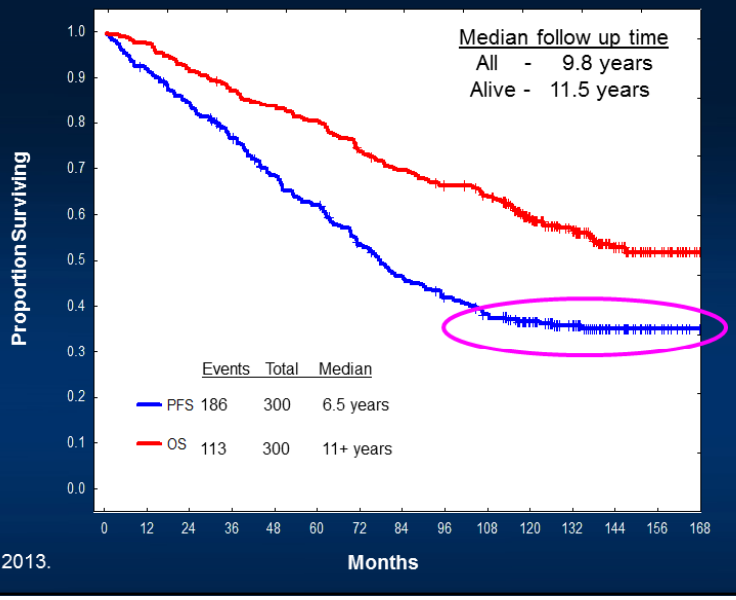
[1]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Dipartimento di Patologia Generale, Seconda Università degli Studi di Napoli, Napoli, Italy; and [3]Department of Hematopathology, The University of Texas MD Anderson Cancer Center, Houston, TX

Key Points

- MRD eradication is a desirable end point in chronic lymphocytic leukemia.
- Early MRD eradication may prompt treatment discontinuation.

The high complete remission rate with first-line combined fludarabine, cyclophosphamide, and rituximab (FCR) begs the question of the value of minimal residual disease (MRD)–negative status as a treatment end point. We report on 237 patients with chronic lymphocytic leukemia who received first-line FCR. MRD was prospectively assessed by 4-color flow cytometry in bone marrow after course 3 and at final response assessment. After course 3 and at final response assessment, 17% and 43% of patients were MRD negative in bone marrow, respectively. A mutated immunoglobulin heavy chain variable gene and trisomy 12 were independently associated with MRD-negative status both after 3 courses of FCR and at final response assessment in multivariable analyses (MVAs). MRD-negative status was independently associated with significantly longer progression-free survival (PFS) and overall survival (OS) in MVA ($P = .03$ and $.02$, respectively). This association was confirmed also on landmark MVA at the time of MRD assessment ($P = .04$ and $.05$, respectively). MRD-negative patients had comparable PFS and OS, independent of the number of courses received or interim staging. Early MRD eradication may be a desirable goal, prompting consideration of early discontinuation of treatment. This trial was registered at www.clinicaltrials.gov as #NCT00759798. (*Blood*. 2014;123(24):3727-3732)

FCR300: Progression-free & Overall Survival



Wierda, et al. *iWCLL*. 2013.

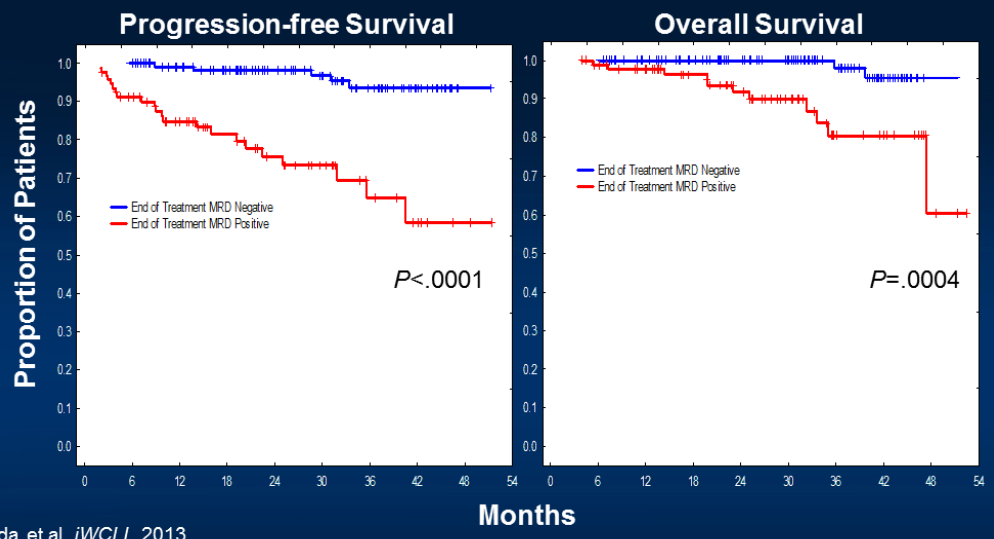
First-line FCR: NCI-WG Response & Bone Marrow MRD-free Status

NCI-WG Response	No.	% of Patients	% MRD-Negative*
CR	153	65	75
nPR	29	12	4
PR	48	20	44
NR	7	3	0
Overall MRD	220	93	59

* Bone marrow evaluation by 4-color flow cytometry (sensitivity .01%)

Wierda, et al. *iWCLL.* 2013.

First-line FCR: PFS & OS by MRD Status



Wierda, et al. *iWCLL.* 2013.

First-line FCR: Multivariable Model for BM MRD-free Status (N=181)

Pretreatment Characteristic	*P*-value
IGHV – Mutated	.003
Rai Stage – 0-II	.016
Trisomy 12	.02
No 17p del	.04

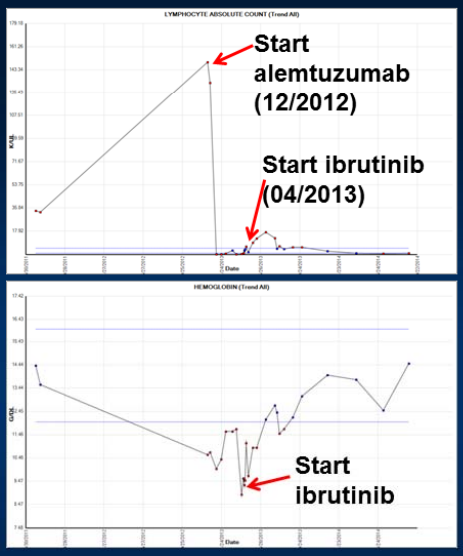
Wierda, et al. *iWCLL.* 2013.

Case 3

- A 54-year old female with CLL, Dx in 6/2011
- 12/2012: comes for follow-up, complains of fatigue

PE	No enlarged lymph nodes or spleen
Lab	WBC 162,300, 92% lymphocytes Hgb 10.6, platelets 223,000
Flow	CD19, CD5, CD23 positive CD20 weakly positive, CD38-
FISH cytogenetics	Del(17p), del(13q)
IgVH	unmutated

Case 3: Treatment Course

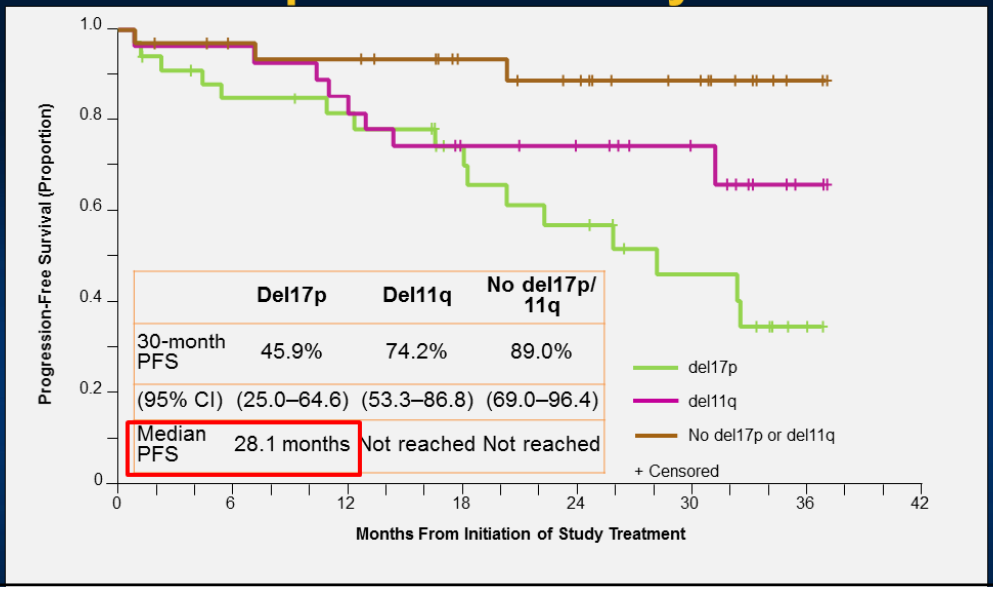


- Symptoms resolved after alemtuzumab (Campath)
- Anemia resolved on ibrutinib, patient continues on ibrutinib to date
- Restaging 8/2014: 10-20% marrow infiltration with del(17p) and del(13q)

Case 3: Allogeneic Stem Cell Transplantation Indicated?

1. Yes, because patient has a median PFS of 28.1 months on ibrutinib due to del(17p), and patient with PD on ibrutinib have very poor outcome
2. No, patient has excellent QOL and allogeneic SCT only should be offered when clinical relapse is noted
3. Initiate donor search, recommendation depends on donor availability, comorbidity, and is an individualized decision process

PFS with Ibrutinib by Cytogenetics (FISH) in Relapsed/Refractory CLL



	Del17p	Del11q	No del17p/ 11q
30-month PFS	45.9%	74.2%	89.0%
(95% CI)	(25.0–64.6)	(53.3–86.8)	(69.0–96.4)
Median PFS	28.1 months	Not reached	Not reached

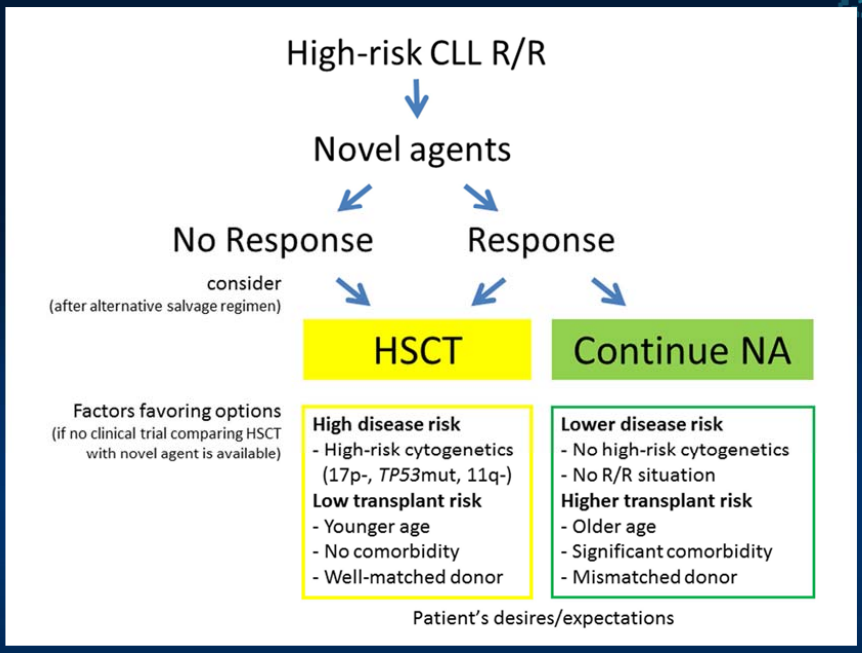
Allo-SCT Candidates Prior to Available BCR-Inhibitors

- Relapsed CLL with "short" remission
- Fludarabine-refractory CLL
- Relapsed del(17p) CLL
- Del(17p) CLL – first remission
- Partial response or less with first-line FCR
- Richter's transformation

Novel Agents vs HSCT in High-risk CLL

- As long as the risks and benefits of different treatment strategies are not settled, all patients with high-risk CLL should be considered for treatment with BCRi/BCL2a
- For those patients responding to these agents there are two treatment possibilities:
  - Performing an HSCT
  - To continue on the novel drug
- Individual disease-specific and transplant-related risk factors, along with patient's preferences, should be taken into account when advising one of these treatments over the other

Dreger P, et al. *Blood*. 10-2014 [Epub ahead of print]



Dreger P, et al. *Blood*. 10-2014 [Epub ahead of print]

Panel Discussion

What is the Future of Treatment – ASH Trials to Watch

Jan A. Burger, MD, PhD
Associate Professor
Department of Leukemia
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Conclusions

- Several exciting new agents approved and in clinical trials
- More selective than chemotherapy but not without toxicity
- Ibrutinib FDA approved - 2014
- Idelalisib FDA approved July 2014
- BCL2 antagonist ABT-199 and 2nd generation P13K and BTK inhibitors in clinical trials as well as SYK inhibitors

Complex Karyotype is a Stronger Predictor than Del(17p) for Inferior Outcome in Relapsed or Refractory CLL Patients Treated with Ibrutinib-Based Regimens

Philip A. Thompson, et al. Abstract #22
Saturday, December 6, 2014: 12:45 PM Ballroom 104

- 100 patients with R/R CLL treated with ibrutinib-based therapy at MD Anderson (2010-2013)
- Overall response rate, including partial remission with persistent lymphocytosis, was 95% with 16% complete responses
- In multivariable analysis (MVA), only complex metaphase karyotype was significantly associated with event-free survival (EFS)
- Fludarabine-refractory CLL and complex metaphase karyotype were independently associated with inferior overall survival (OS)
- Del(17p) was not significantly associated with EFS or OS

What's New at ASH 2014

Chemo-immunotherapy (CIT)
- Frontline FCR Shows Superior Efficacy in Comparison to BR (CLL10 Study; oral presentation, Saturday 12PM, Abstract 19)

Antibodies:
- Rituximab Maintenance after CIT Improves PFS (oral presentation, Saturday 12:15PM, Abstract 20)
- Ofatumumab Maintenance Prolongs PFS in Rel CLL (oral presentation, Sat 12:30 PM, Abstract 21)

Ibrutinib:
- Ibrutinib in R/R CLL with 17p Deletion (RESONATE™-17 Trial; oral presentation, Monday, 7:00 AM, Abstract 327)
- Deuterated Water Labeling in Patients with CLL/SLL treated with the BTK inhibitor Ibrutinib (oral presentation, Monday, 7:15 AM, Abstract 326)

Idelalisib:
- 2nd Interim Analysis of a Ph 3 Idelalisib + Rituximab for Relapsed CLL: Analysis in high-risk CLL subpopulations (oral presentation, Monday, 8:15 AM, Abstract 330)
- Update on Ph 2 Study of Idelalisib + Rituximab in Treatment-Naïve CLL/SLL (Poster on Sunday, Abstract 1994)

ABT-199:
- ABT-199 + Rituximab in Patients with R/R CLL (oral presentation, Monday, 7:00 AM, Abstract 325)
- Phase 1b ABT-199 with BR in R/R or Untreated CLL (Poster on Sunday, Abstract 3337)
- Phase 1b Study ABT-199 + Obinutuzumab in R/R or Untreated CLL (Poster on Monday, Abstract 4687)

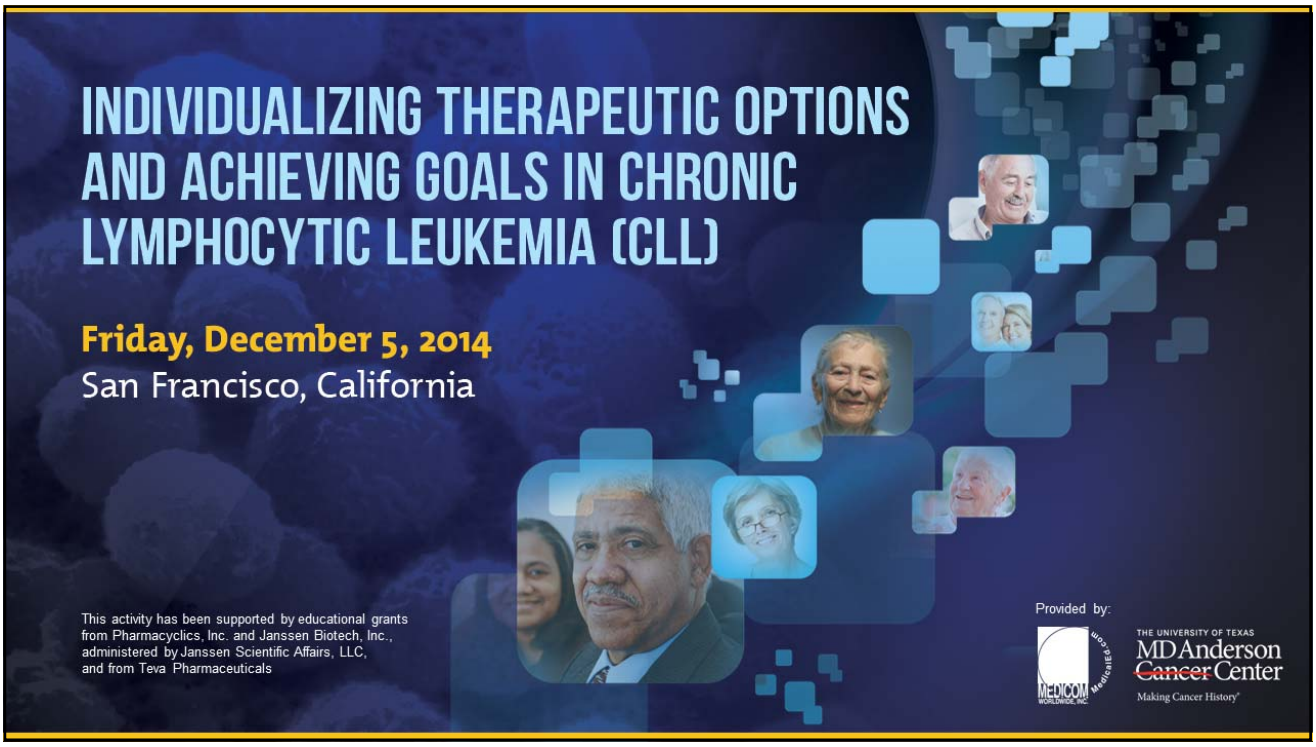
ONO-4059:
- Single Agent Activity in High Risk Chronic CLL (Poster on Monday, Abstract 3328)

IPI-145:
- Activity of Duvelisib (IPI-145) in Patients Previously Treated with Ibrutinib (Poster on Sunday, # 3335)
- Activity in Patients with Relapsed/Refractory CLL (Poster on Sunday, Abstract 3334)

Thank you!

Dept. of Leukemia, MDACC

jaburger@mdanderson.org


INDIVIDUALIZING THERAPEUTIC OPTIONS AND ACHIEVING GOALS IN CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)
Friday, December 5, 2014
San Francisco, California
This activity has been supported by educational grants from Pharmacyclics, Inc. and Janssen Biotech, Inc., administered by Janssen Scientific Affairs, LLC, and from Teva Pharmaceuticals
Provided by:
MEDICOM WORLDWIDE, INC.
THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®