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Medical Director, Sue and Ralph Stern Center for Cancer Clinical Trials and Research
Professor of Medicine
University of California Irvine
Orange, CA

Agenda

- Individualized therapy in chronic lymphocytic leukemia (CLL)
- Recently approved and emerging therapies for the treatment of CLL
- Management of potential treatment-related toxicities

Chronic Lymphocytic Leukemia: The Importance of Individualized Therapy

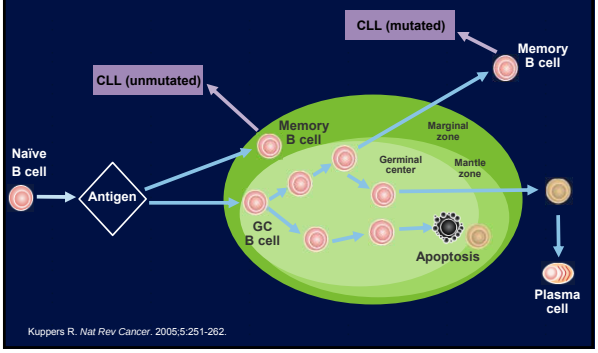
Richard R. Furman, MD

Morton Coleman, MD Distinguished Associate Professor of Medicine
Director, CLL Research Center
Weill Cornell Medical College of Cornell University
New York, NY

Chronic Lymphocytic Leukemia

- Most common type of leukemia in North America
  - Incidence: ~15,000 cases/year
  - Prevalence: ~ 200,000 cases
- More common in Western Europe and North America
- Median age: 72 years old
- Peripheral blood smear demonstrates mature, resting B-cells and smudge cells

CLL: Unmutated vs Mutated



Kuppers R. *Nat Rev Cancer*. 2005;5:251-262.

CLL Diagnostic Criteria (IWCLL)

- Absolute B-lymphocyte count in peripheral blood >5000/mL
  - Small lymphocytic lymphoma (SLL) <5000/mL, with lymphadenopathy or splenomegaly
- 30% of bone marrow involved with lymphocytes
- Co-expression of CD5, CD19/20, and CD23 surface proteins
- Dim expression of CD20 and surface Ig (sIg)
  - Exception: trisomy 12 (role for Notch1?)

Hallek M, et al. *Blood* 2008;111:5446-5456.

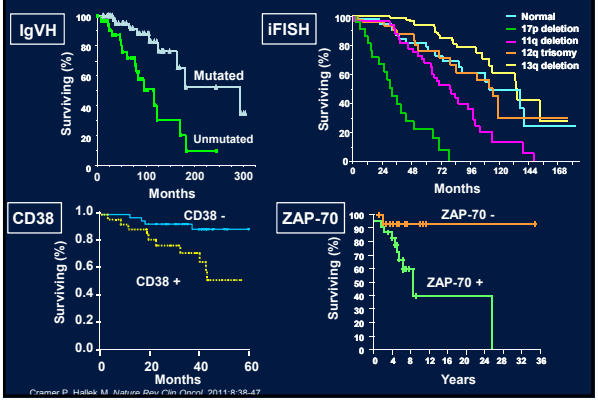
Indications for Treatment of Patients with CLL

- Progressive bone marrow failure (worsening anemia and/or thrombocytopenia; ie, Rai Stage III or IV)
- Massive, progressive, or symptomatic LAD
- Massive, progressive, or symptomatic splenomegaly
- Lymphocyte doubling time of <6 months
- AIHA or ITP poorly responsive to steroids
- Disease related symptoms: weight loss, fevers, fatigue

Clinically Relevant Prognostic Markers (Used Prior to Treatment)

Traditional	Novel
Stage at diagnosis	IgVH mutation status
Lymphocyte doubling time	CD38 expression
Pattern of bone marrow infiltration	ZAP-70 expression
Age	Interphase FISH
Gender	
Karyotype	
β2-microglobulin	
Number of circulating prolymphocytes	

Novel Prognostic Markers in Clinical Practice



Established CLL Treatment Regimens

Treatment-naïve	Relapsed
FR/FCR/PCR	FR/FCR/PCR
Bendamustine + rituximab	Bendamustine + rituximab
Obinutuzumab + chlorambucil	Ofatumumab
Ofatumumab +/- chlorambucil	Alemtuzumab
Alemtuzumab	HDMP + rituximab
HDMP + rituximab	Ibrutinib
Ibrutinib (del 17p)	Idelalisib + rituximab
	Chlorambucil

Factors Impacting Choice of Therapy

Disease-based

- Interphase FISH
  - Del 11q: marked improved response with FC vs F (CLL4)
  - Del 17p
    - Poor response to chemotherapy
    - Genomic instability, risk of Richter's transformation
- V gene family
  - VH4-39: high risk of Richter's transformation?

Factors Impacting Choice of Therapy

Patient-based

- Comorbidities
  - Cumulative Illness Rating Scale (CIRS) score: "go-go" vs "slow-go" vs "no-go"
  - Kidney function
  - Marrow function
- Concerns for tumor lysis
- Autoimmune phenomenon

Cumulative Illness Rating Scale (CIRS)

Body System	
Cardiac (heart only)	Hepatic
Hypertension	Renal
Vascular	Other genitourinary
Respiratory	Musculoskeletal-integumentary
EENT	Neurological
Upper gastrointestinal	Endocrine-metabolic
Lower gastrointestinal	Psychiatric/behavioral

- Comorbidities of each organ system assessed on scale 0-4
- Each organ system receives 1 score equal to highest in that system
- Scores of each system added together

Discussion

Which CLL prognostic markers have been demonstrated to have an impact upon choice of therapy?

Discussion

Why is classifying the fitness of patients with CLL relevant?

What tools have been validated for this purpose?

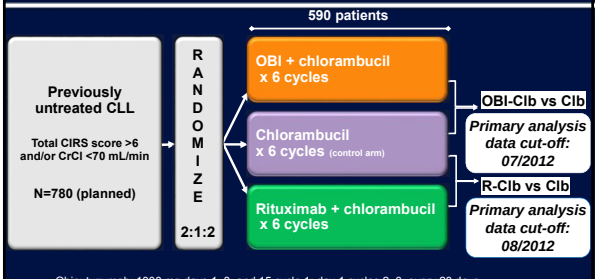
Optimizing Chronic Lymphocytic Leukemia Treatment: Novel and Emerging Therapies

Susan O'Brien, MD
Associate Director for Clinical Science
Chao Family Comprehensive Cancer Center
Medical Director
Sue and Ralph Stern Center for Cancer Clinical Trials and Research
Professor of Medicine
University of California Irvine
Orange, CA

Most Recently Approved Therapies for CLL

Agent	Class	FDA Approval	Indication
Obinutuzumab (IV infusion)	Anti-CD20 MoAb	2013	Previously untreated CLL + chlorambucil
Ibrutinib (oral)	BTK inhibitor (1st in class)	2014	• CLL with ≥1 prior therapy • CLL with 17p deletion
Idelalisib (oral)	PI3K inhibitor (1st in class)	2014	Relapsed CLL + rituximab in patients for whom rituximab alone would be considered appropriate therapy due to other comorbidities

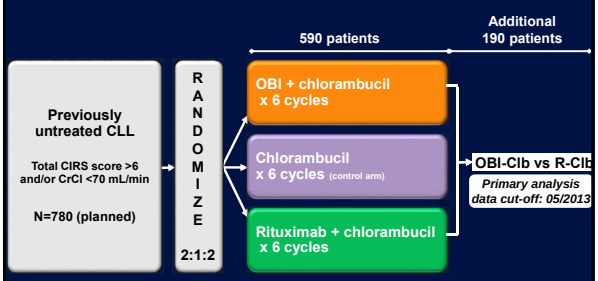
CLL11 Trial: Chlorambucil +/- Rituximab or Obinutuzumab in Previously Untreated CLL



- Obinutuzumab: 1000 mg days 1, 8, and 15 cycle 1; day 1 cycles 2–6, every 28 days
- Rituximab: 375 mg/m² day 1 cycle 1, 500 mg/m² 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 OBI-Clb

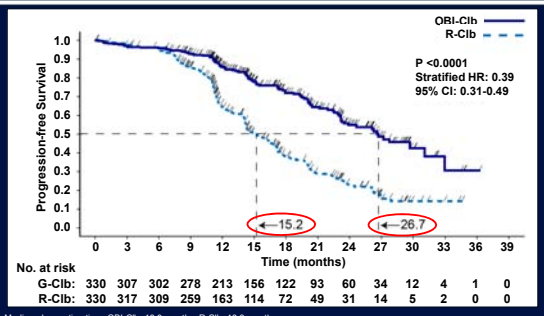
OBI: obinutuzumab; Clb: Chlorambucil; R: rituximab
Goede V, et al. *N Engl J Med.* 2014;370:1101-1110.

CLL11 Trial: Chlorambucil +/- Rituximab or Obinutuzumab in Previously Untreated CLL



OBI: obinutuzumab; Clb: Chlorambucil; R: rituximab
Goede V, et al. *N Engl J Med.* 2014;370:1101-1110.

Progression-free Survival (Head-to-head)



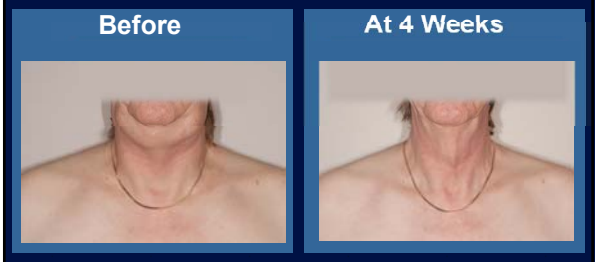
Median observation time: OBI-Clb, 18.8 months; R-Clb, 18.6 months
Independent Review Committee-assessed progression-free survival (PFS) was consistent with investigator-assessed PFS
OBI: obinutuzumab; Clb: Chlorambucil; R: rituximab
Goede V, et al. *N Engl J Med*. 2014;370:1101-1110.

Targeting of BCR Signaling in CLL

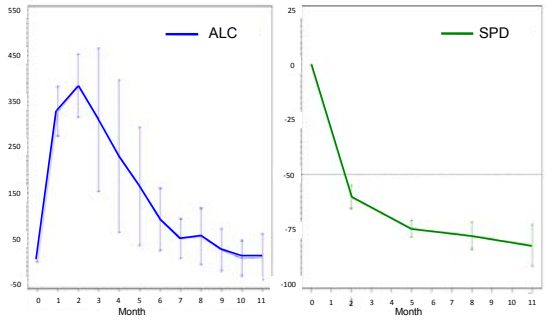
- BCR-associated kinases are targets of new drugs in preclinical and clinical development
  - SYK (spleen tyrosine kinase) inhibitors: R406, Portola's SYK inhibitors
  - BTK (Bruton's tyrosine kinase) inhibitors: ibrutinib, CC-292, ONO-4059, ACP196
  - Isoform-selective inhibitors of PI3Ks: idelalisib, IPI-145, TGR-1202

Quiroga MP, et al. *Blood*. 2009;114:1029-1037; Niedermeier M, et al. *Blood*. 2009;113:5549-5557.

Ibrutinib in Refractory CLL with 11q Deletion

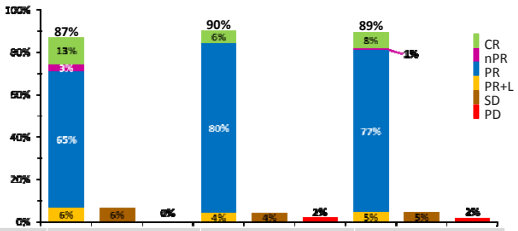


Pattern of Response: Blood Lymphocytes vs Lymph Nodes



SPD: sum of products of lymph node dimension

Best Response
Treatment-naïve and Relapsed Population (Investigator-assessed)

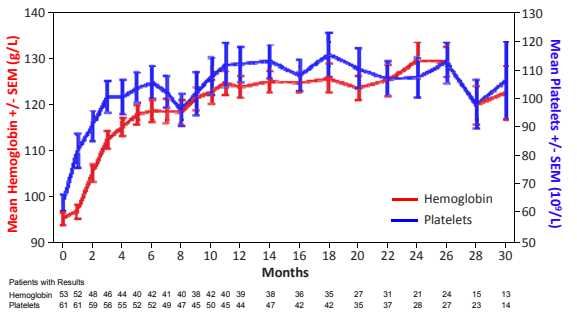


	TN (n=31)	R/R (n=101)	Total (N=132)
30 Month DOR, % (95% CI)	100 (100 to 100)	79.1 (64.2 to 88.4)	85.3 (74.4 to 91.8)
Median DOR, months (range)	NR (0 to 35.0+)	NR (0 to 35.2+)	NR (0 to 35.2+)

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

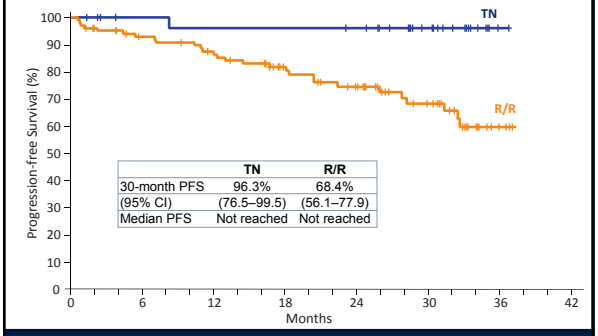
O'Brien S, et al. ASCO; May 30 – June 3, 2014. Chicago, IL. PCYC 1102/1103.

Platelet Counts and Hemoglobin Levels*



*All treated patients with baseline anemia or thrombocytopenia.
O'Brien S, et al. ASCO; May 30 – June 3, 2014. Chicago, IL. PCYC 1102/1103.

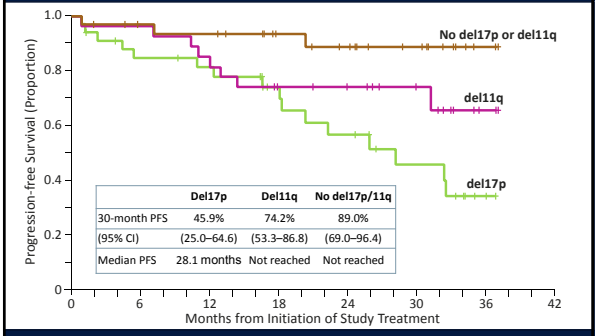
Progression-free Survival



	TN	R/R
30-month PFS	96.3%	68.4%
(95% CI)	(76.5–99.5)	(56.1–77.9)
Median PFS	Not reached	Not reached

O'Brien S, et al. ASCO; May 30-June 3, 2014. Chicago, IL.. PCYC 1102/1103.

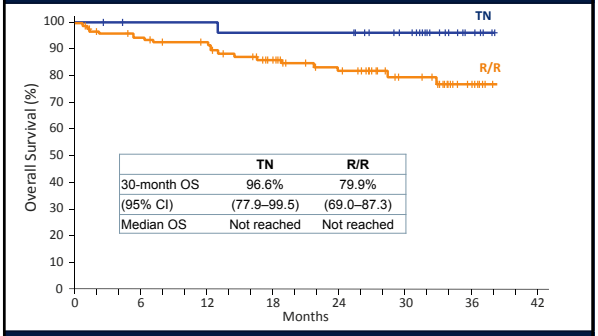
Progression-free Survival by Cytogenetics (FISH) in Relapsed/Refractory Population



	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

O'Brien S, et al. ASCO; May 30- June 3, 2014. Chicago, IL. PCYC 1102/1103.

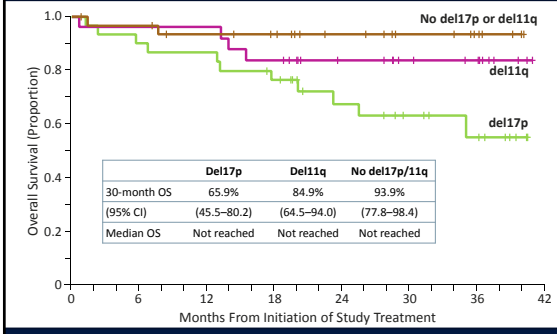
Overall Survival



	TN	R/R
30-month OS	96.6%	79.9%
(95% CI)	(77.9–99.5)	(69.0–87.3)
Median OS	Not reached	Not reached

O'Brien S, et al. ASCO; May 30-June 3, 2014. Chicago, IL. PCYC 1102/1103.

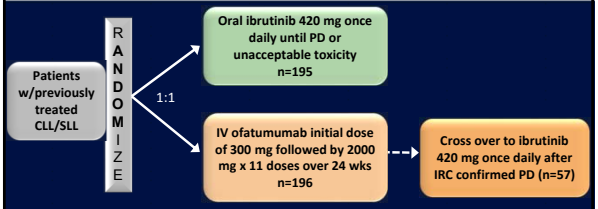
Overall Survival by Cytogenetics (FISH) in Relapsed/Refractory Population



	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	Not reached	Not reached	Not reached

O'Brien S, et al. ASCO; May 30-June 3, 2014. Chicago, IL. PCYC 1102/1103.

RESONATE Trial: Ibrutinib vs Ofatumumab in Previously Treated CLL

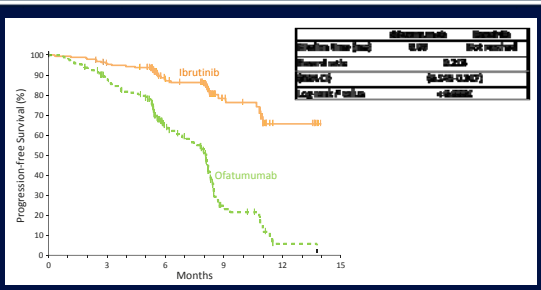


- Primary Endpoint: PFS
- Stratification according to
  - Disease refractory to purine analog chemoimmunotherapy (no response or <12 months)
  - Presence or absence of 17p del
- At time of interim analysis, median time on study was 9.4 months

Protocol amended for cross over with support of Data Monitoring Committee and discussion with health authorities.
PD: progressive disease.

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

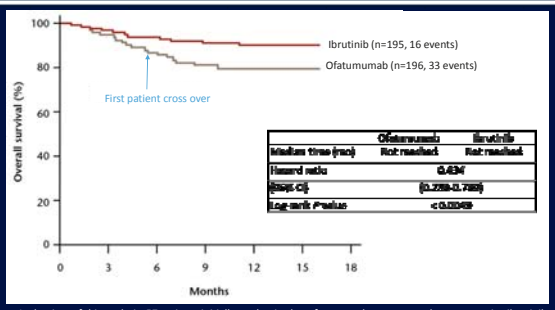
Progression-free Survival



- Richter's transformation was confirmed in 2 patients on each arm
- Another patient on the ibrutinib arm experienced transformation to prolymphocytic leukemia

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

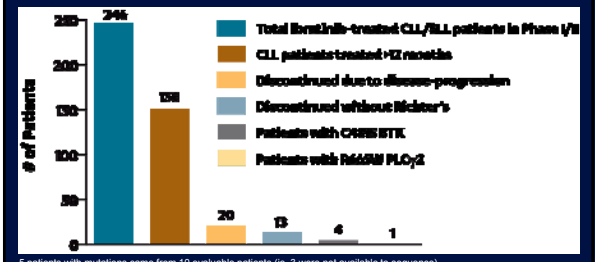
Overall Survival



- At the time of this analysis, 57 patients initially randomized to ofatumumab were crossed over to receive ibrutinib following IRC-confirmed progressive disease

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

Incidence of Acquired Resistance Following Ibrutinib Treatment in CLL Patients



5 patients with mutations came from 10 evaluable patients (ie, 3 were not available to sequence)

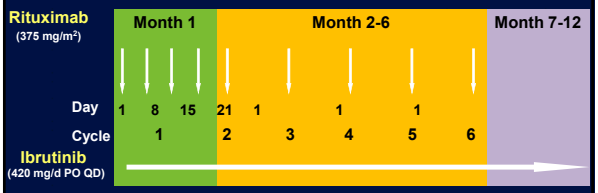
Stilgenbauer S, et al. 12th International Conference on Malignant Lymphoma. June 19-20, 2013. Lugano, Switzerland.

Characteristics of Patients with Acquired SNVs

Pt	Age, years	# of Prior Treatments	Cytogenetics	Ibrutinib Regimen	Days on Ibrutinib	Best Response	Mutation
1	59	5	17p-, +12	560 mg	621	PR	C481S BTK
2	75	2	17p-, complex karyotype	420 mg	673	PR	R665W PLCγ2
3	59	3	11q-	BR x 6 cycles 420 mg	388	CR	C481S BTK
4	51	2	complex karyotype	Ofat x 24 weeks 420 mg	674	CR	C481S BTK
5	69	9	17p-, complex karyotype	840 mg	868	PR	C481S BTK
6	61	4	17p-, complex karyotype	Ofat x 24 weeks 420 mg	505	PR	L845F, R665W, S7054 in PLCγ2 C481S in BTK

Woyach JA, et al. *N Engl J Med*. 2014;370:2286-2294.

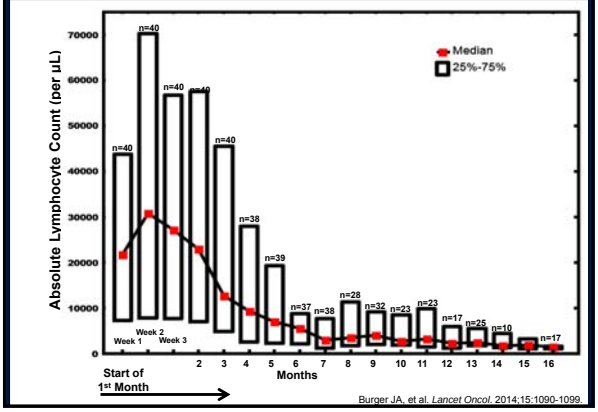
Ibrutinib and Rituximab in High-risk CLL



Patients with benefit after 12 cycles continue on ibrutinib

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

Transient Lymphocytosis



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

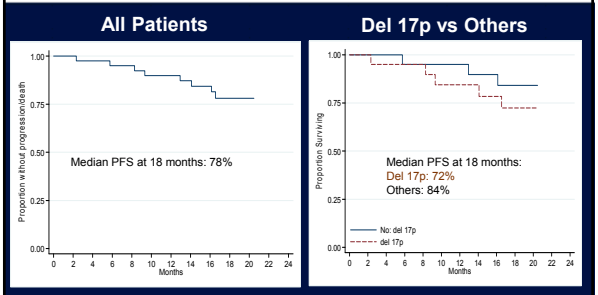
Best Response* (n=40)

	n	%
CR¥	4	10
PR	34	85
OOR	37	95
NR	2	5

*At 12 months or best response before study discontinuation
¥MRD-negative: 1/4, MRD level: 0.1, 0.2, 0.1%

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

Progression-free Survival



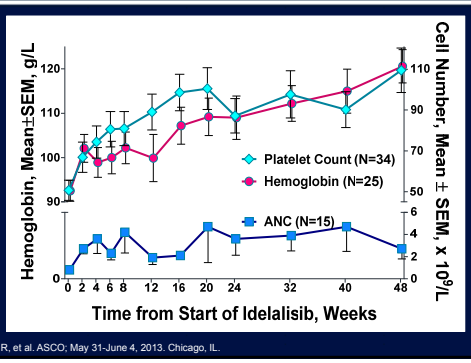
Median follow-up: 17 months

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

Idelalisib in Patient with Refractory CLL and 5 Prior Therapies

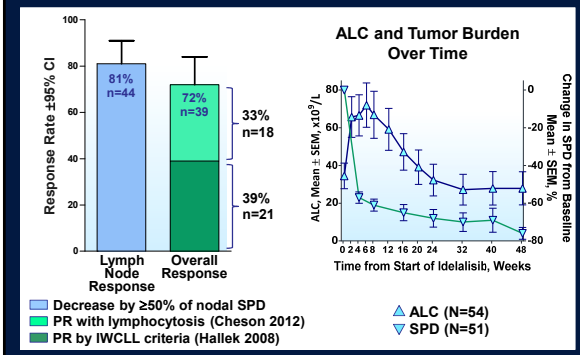
Reductions in peripheral lymphadenopathy

Effect on Baseline Cytopenias



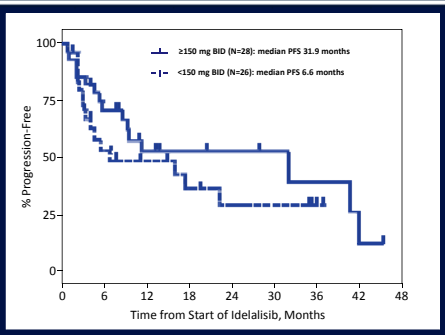
Brown JR, et al. ASCO; May 31-June 4, 2013. Chicago, IL.

Nodal and Overall Response Rates



Brown JR, et al. ASCO; May 31-June 4, 2013. Chicago, IL.

Progression-free Survival by Dose



Brown JR, et al. *Blood*. 2014;123:3390-3397.

Idelalisib + Rituximab in Frontline CLL (Phase 2 Single Arm, Open Label Study)

Subject accrual Oct 2010 through Apr 2012

Primary Study: 101-08

Idelalisib (150 mg BID) x 48 wks

Rituximab (375 mg/m²) 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 S, et al. ASH. December 5-9, 2014. San Francisco, CA.

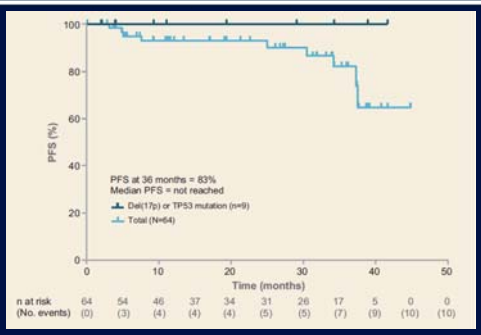
Response

	All Patients (N=64), n (%)	Del17 and/or TP53 Mutation (N=9), n (%)
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

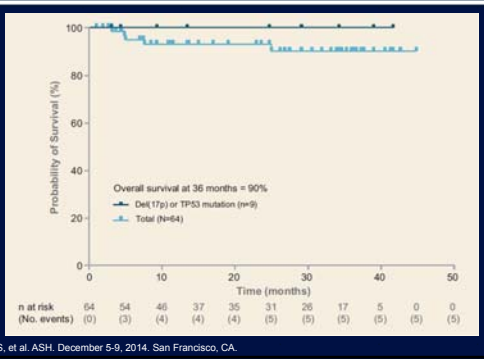
O'Brien S, et al. ASH. December 5-9, 2014. San Francisco, CA.

Progression-free Survival



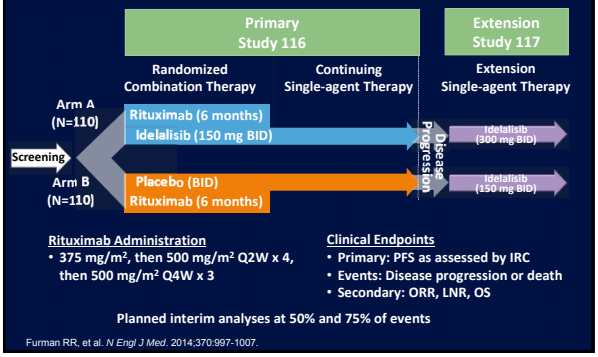
O'Brien S, et al. ASH. December 5-9, 2014. San Francisco, CA.

Overall Survival



O'Brien S, et al. ASH. December 5-9, 2014. San Francisco, CA.

Idelalisib + Rituximab in Relapsed CLL (Phase 3 Study)



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

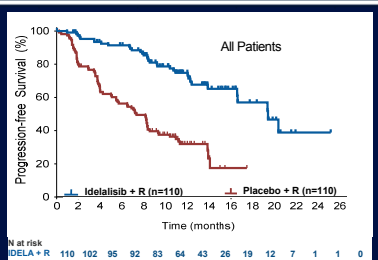
Furman RR, et al. *N Engl J Med*. 2014;370:997-1007.

Key Eligibility

Criteria	Requirement
Relapsed CLL	• CLL progression <24 months since last therapy • Treatment warranted according to IWCLL criteria
Lymphadenopathy	• Presence of ≥1 measurable nodal lesion
Prior therapies	• ≥ 1 anti-CD20 antibody containing therapy or ≥ 2 prior cytotoxic therapies
Appropriate for non-cytotoxic therapy	• CIRS score >6 or creatinine clearance <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;370:997-1007.

Progression-free Survival, Including Extension Study*



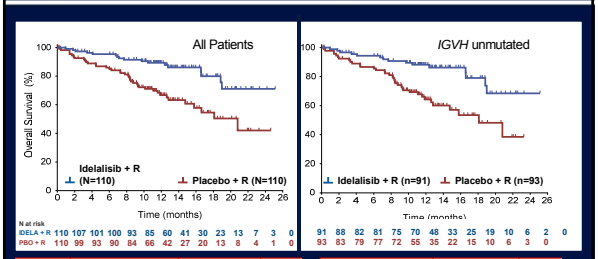
N at risk

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

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

*Placebo + rituximab includes those patients who received open-label idelalisib after unblinding without prior progression (n=42).
Sharman JP, et al. ASH. December 5-9, 2014. San Francisco, CA.

Progression-free Survival, Including Extension Study*



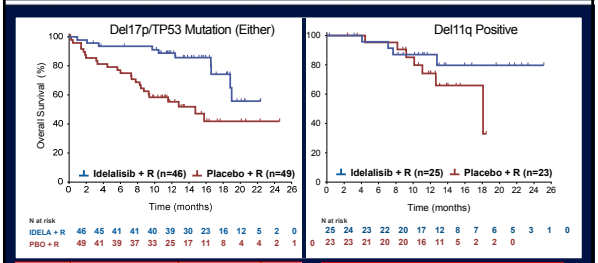
	Median OS (95% CI)	HR (95% CI)	*P*
IDELA + R	NR	0.34 (0.19, 0.6)	0.0001
PBO + R	20.8 mo (14.8, –)		

	Median OS (95% CI)	HR (95% CI)	*P*
IDELA + R	NR (19.0, –)	0.35 (0.19, 0.6)	0.0003
PBO + R	18.1 mo (14.8, –)		

*As randomized, including cross-over

Sharman JP, et al. ASH. December 5-9, 2014. San Francisco, CA.

Progression-free Survival, Including Extension Study*



	Median OS (95% CI)	HR (95% CI)	*P*
IDELA + R	NR (18.8, –)	0.31 (0.15, 0.65)	0.001
PBO + R	14.8 mo (8.4, –)		

	Median OS (95% CI)	HR (95% CI)	*P*
IDELA + R	NR (–, –)	NA	0.21
PBO + R	18.1 (11.1, –)		

*As randomized, including cross-over

Sharman JP, et al. ASH. December 5-9, 2014. San Francisco, CA.

Venetoclax (ABT-199/GDC-0199)

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

	Affinity				Cellular Efficacy EC_{50}, nM				
	TR FRET K_i, nM				FL5.12, 3% FBS			Human Tumor Cell Lines, 10% HS	
Agents	Bcl-2	Bcl-x_L	Bcl-w	Mcl-1	Bcl-2	Bcl-x_L	Functional Selectivity	RS4;11 (Bcl-2)	H146 (Bcl-x_L)
Navitoclax	0.04	0.05	7	>224	20	13	0.6	110	75
ABT-199	<0.01	48	21	>444	4	261	65	12	3600

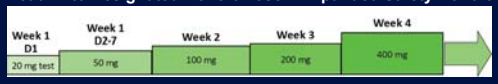
Souers AJ, et al. *Nat Med*. 2013;19:202-208.

Dosing Schedule

Dose Escalation Scheme

*3 patients (1 each in cohorts 2, 3, and 5) received ABT-199 20 mg as initial dose
**Step-up doses range from 100 to 400 mg
DCD: designated cohort dose

Lead-in to Designated Cohort Dose – Expanded Safety Cohort



Seymour JF, et al. EHA. June 13-16, 2013. Stockholm, Sweden.

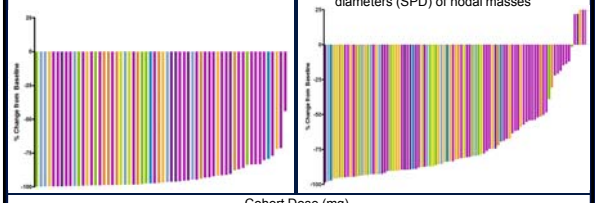
Best Percent Change from Baseline in Blood Lymphocyte Count and Nodal Mass by CT Scan

Blood Lymphocytes (n=60)

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

Nodal Mass by CT Scan (n= 93)

- 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



Cohort Dose (mg)

150 200 300 400 600 800 1200 400 Safety Expansion

Data represents patients with lymphocyte count >5 x 10⁹/L at baseline

Objective Responses

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

Some patients may have more than 1 high-risk marker
¥4 patients have Cri; †D/C: discontinued, first assessment at 6 weeks; *3 patients had confirmatory CT imaging assessments at less than an 8 week interval (5, 6, and 7 weeks)

- As of April 9 2014, 78 patients had 2 CT scans, performed approximately 8 weeks apart n=55 from dose escalation and n=23 from the safety expansion cohort
- A total of 26 patients are not yet evaluable in the SE cohort (12 patients had a PR at their first scan, 14 patients have not yet reached their first assessment)
- The median duration of response has not yet been reached

Conclusions

- Exciting and highly active new agents for the treatment of CLL
  - Obinutuzumab + chlorambucil (FDA-approved September 2013)
  - Ibrutinib (FDA-approved February 2014)
  - Idelalisib + rituximab (FDA-approved July 2014)
  - Venetoclax (ABT-199/GDC-0199): getting closer
  - Next generation BTK, P13K, SYK inhibitors already in trials

Discussion

Do we understand the mechanism of lymphocytosis seen with all of the B-cell inhibitors?

Discussion

Is there an ALC level that you would be concerned about before initiating therapy with a B-cell inhibitor?

Is there an ALC level for which you would intervene during therapy?

Discussion

What do we know about the small cohort of patients who have persistent lymphocytosis with ibrutinib over long periods of time?

Discussion

What combination therapy trials would you like to see, and what would be your first choice?

Discussion

Do you believe that the treatment of CLL will be chemotherapy-free at some point in time?

Managing Treatment-related Toxicities in CLL

Richard R. Furman, MD
Morton Coleman, MD Distinguished Associate Professor of Medicine
Director, CLL Research Center
Weill Cornell Medical College of Cornell University
New York, NY

Novel CLL Therapies: Treatment-related Toxicities

Anti-CD20 Antibodies: Obinutuzumab
- Infusion reactions
- Neutropenia

BTK Inhibitors: Ibrutinib
- Diarrhea
- Bleeding
- Thrombocytopenia
- Atrial fibrillation

PI3K Inhibitors: Idelalisib
- Diarrhea
- Colitis
- Transaminitis
- Pneumonitis

Bcl-2 Mimetics: Venetoclax (ABT-199/GDC-0199)
- Tumor lysis syndrome

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CLL11 Trial: Chlorambucil +/- Rituximab or Obinutuzumab

Adverse Events

Adverse Reaction	Obinutuzumab + Chlorambucil		Rituximab + Chlorambucil	
	Any Grade (%)	Grades 3-4 (%)	Any Grade (%)	Grades 3-4 (%)
Infusion-related reactions	66	20	38	4
Neutropenia	38	33	32	28
Thrombocytopenia	14	10	7	3
Leukopenia	6	4	2	<1
Pyrexia	9	<1	7	<1

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

Infusion-related Reactions (CLL11 Trial)

- First obinutuzumab dose in first 53 patients: 1000 mg on Day 1 of Cycle 1
  - 89% of patients experienced infusion-related reactions

⇩

- Dosing schedule modified to infuse 100 mg on Day 1 and 900 mg on Day 2 of Cycle 1

⇩

- Increased tolerability → infusion-related reactions reduced to 53%
  - Most of these patients (88%) experienced reactions on Day 1, 4% on Day 2, and <3% thereafter

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

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BTK Inhibitors

- Different off-target effects of ibrutinib, ACP-196, and ONO-4059 will likely lead to different toxicities
- Ibrutinib
  - Diarrhea
  - Bleeding
  - Thrombocytopenia
  - Atrial fibrillation

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

RESONATE Trial: Ibrutinib vs Ofatumumab in Previously Treated CLL

Diarrhea

Ibrutinib (n=195)		Ofatumumab (n=191)	
Any Grade, % (n)	Grades 3-4, % (n)	Any Grade, % (n)	Grades 3-4, % (n)
48 (93)	4 (8)	18 (34)	2 (3)

- Lead to dose reduction in 3 patients
- Possibly due to inhibition of EGFR in gut mucosa
- Frequently abates with continued dosing
- May be ameliorated by dose reduction or dosing at bedtime

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

RESONATE Trial: Ibrutinib vs Ofatumumab in Previously Treated CLL

Bleeding
(Including bruising, contusion, petechiae, and hemorrhage)

Ibrutinib		Ofatumumab	
Any Grade, %	Grades 3-4, %	Any Grade, %	Grades 3-4, %
44	1	12	2

- Possibly related to impact of BTK and Tec kinase in platelets (redundant roles)

Thrombocytopenia

Ibrutinib		Ofatumumab	
Any Grade, %	Grades 3-4, %	Any Grade, %	Grades 3-4, %
17	6	12	4

- Long-term thrombocytopenia observed – improved over baseline

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

RESONATE Trial: Ibrutinib vs Ofatumumab in Previously Treated CLL

Atrial Fibrillation

Ibrutinib (n=195)		Ofatumumab (n=191)	
Any Grade, % (n)	Grades 3-4, % (n)	Any Grade, % (n)	Grades 3-4, % (n)
5 (10)	1 (3)	1 (1)	0

- BTK and Tec kinase, both inhibited by ibrutinib, may play a role in myocardial response to the stress of atrial fibrillation
- Unclear whether or not the association between atrial fibrillation and ibrutinib is one that needs to impact upon continued dosing, or if it needs to impact upon management of atrial fibrillation

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

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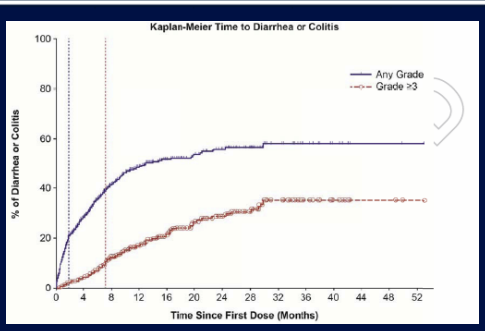
Idelalisib – Diarrhea

- Median time to diarrhea
  - Any grade: 1.5 months (range: 0.0-29.8)
  - Grade 3 or 4: 7.1 months (range: 0.5-29.8)
- Incidence: 14% across all studies
- Pivotal phase 3 study (idelalisib + ritux vs placebo + ritux)
  - Any grade: I + R: 21% vs P + R: 16%
  - Grade 3/4: I + R: 5% vs P + R: 0%
- Most common AE leading to dose reduction/ discontinuation
- Mean time to resolution: 1 month
  - With budesonide: 12.1 days

Sharman JP, et al. ASH. 2014. December 5-9, 2014. San Francisco, CA.

Time to Diarrhea or Colitis



Coutre SE, et al. *Leuk Lymphoma*. 2015 May 19:1-8. [Epub ahead of print]

Diarrhea/Colitis Management

- All cases of diarrhea or colitis resolved with drug withdrawal +/- steroids
- Grade >3 diarrhea: 71 of 106 cases rechallenged with a success rate of 58%
- Expert Panel recommendations (May 2014)
  - 2 types of diarrhea
    - Early: self-limiting, mild to moderate , responsive to antidiarrheal agents
    - Late: watery, without cramps, moderate to severe, not responsive to anti-diarrheal agents; lymphocytic colitis on histology

Coutre SE, et al. *Leuk Lymphoma*. 2015 May 19:1-8. [Epub ahead of print]

Diarrhea/Colitis Management (Grade 1-2)

- Obtain patient history and perform PE to rule out infection
- Stop all lactose-containing products, alcohol, and high osmolar supplements
- Keep adequately hydrated
- Frequent small meals with bananas, rice, applesauce, toast
- Monitor number and character of stools

↓

Administer loperamide (4 mg followed by 2 mg every 4 h or after every loose stool)

↓

Reassess 24-48 h later

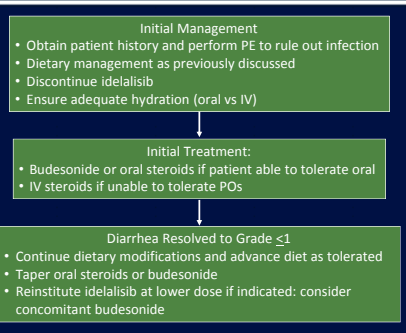
↙ ↘

Diarrhea Resolving
- Advance diet as tolerated
- Discontinue loperamide after 12 h diarrhea-free

Diarrhea Unresolved:
- Follow idelalisib-related diarrhea management

Coutre SE, et al. *Leuk Lymphoma*. 2015 May 19:1-8. [Epub ahead of print]

Diarrhea/Colitis Management (Unresolved Grade 2 or Grade 3/4)



Coutre SE, et al. *Leuk Lymphoma*. 2015 May 19:1-8. [Epub ahead of print]

Idelalisib – Transaminitis

- Elevations of ALT/AST seen within first 12 weeks
- Classically asymptomatic; no hyperbilirubinemia
- Incidence
  - Pivotal CLL trial – idelalisib: 35% vs placebo: 19% (any grade)
  - iNHL trials – idelalisib: 50% (any grade)
- 74% of patients rechallenged at lower dose did not have a recurrence
- Monitoring
  - ALT/AST measurement every 2 weeks x 3 months, followed by every 4 weeks x 3 months, followed by every 1-3 months thereafter

Coutre SE, et al. *Leuk Lymphoma*. 2015 May 19:1-8. [Epub ahead of print]

Idelalisib – Pneumonitis

- Incidence: 3% (24/760) across all trials
  - 19 of 24 reported as serious; 3 fatalities
  - Concomitant viral infections often observed
- Possible role for steroids

Coutre SE, et al. *Leuk Lymphoma*. 2015 May 19:1-8. [Epub ahead of print]

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- Tumor lysis syndrome

Venetoclax (ABT-199/GDC-0199) – Tumor Lysis Syndrome

- Tumor lysis syndrome: primary AE observed
- Initial tumor lysis syndrome seen with flat dosing

⇩

- Stepwise incremental dose escalation

Venetoclax (ABT-199/GDC-0199) – Tumor Lysis Syndrome

- Determination of tumor lysis syndrome risk category
  - Low-risk: LN <5 cm and ALC <25,000
  - Medium-risk: ALC >25,000 or LN 5 cm-10 cm
  - High-risk: LN >10 cm or ALC >25,000 + LN >5 cm

⇩

- Aggressive outpatient oral hydration / inpatient IV hydration (high-risk)
- Prophylaxis with uric-reducing agents
- Frequent laboratory monitoring
- Step-up dosing scheme

Seymour JF, et al. EHA. June 13-16, 2013. Stockholm, Sweden.

Discussion

If diarrhea is associated with both ibrutinib and idelalisib, what are the similarities and differences between the side effects and how would each be managed?

Discussion

How much of an increase in bleeding risk is there with ibrutinib and what is the cause?

Discussion

How do you manage idelalisib-associated transaminitis?

Discussion

What are the risk factors for tumor lysis with venetoclax (ABT-199/GDC-0199) ?

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