Chronic Lymphocytic Leukemia

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DISCLOSURES

Off-Label Usage
  • Ibrutinib (Pharmacyclics)

Interests
  • None
Chronic Lymphocytic Leukemia

- Most common leukemia in Western world
- Accounts for 30% of adult leukemias
- Median age at diagnosis 65 years
- Median survival ~9 years
- Advanced disease has increased morbidity and mortality, often from infection
Diagnosis of CLL

- Lymphocytosis (small, mature lymphocytes ≥5000/µL)
- Bone marrow involvement of ≥30% lymphocytes
- ≤55% atypical/immature lymphoid cells in peripheral blood
- Clonal expansion of abnormal B lymphocytes
  - Low density of surface Ig (IgM or IgD) with κ or λ light chains
  - B-cell surface antigens (CD19, CD20, CD23); CD20 dim
  - CD5 surface antigen
## Immunophenotypic Differentiation of B-CLL From Other Chronic Lymphoproliferative Disorders

<table>
<thead>
<tr>
<th>Antigen/Marker</th>
<th>CLL</th>
<th>MCL</th>
<th>SLVL</th>
<th>B-PLL</th>
</tr>
</thead>
<tbody>
<tr>
<td>slg intensity</td>
<td>Weak</td>
<td>Strong</td>
<td>Strong</td>
<td>Strong</td>
</tr>
<tr>
<td>CD19/CD20</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CD5</td>
<td>+</td>
<td>+</td>
<td>V</td>
<td>-</td>
</tr>
<tr>
<td>CD23</td>
<td>+</td>
<td>-</td>
<td>V</td>
<td>V</td>
</tr>
<tr>
<td>CD11c</td>
<td>V</td>
<td>-</td>
<td>V</td>
<td>-</td>
</tr>
<tr>
<td>FMC7</td>
<td>V</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CD79b</td>
<td>-</td>
<td>+</td>
<td>V</td>
<td>+</td>
</tr>
<tr>
<td>CD22</td>
<td>-</td>
<td>V</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>
Clinical Course of CLL

- Asymptomatic at diagnosis and for prolonged periods
- Diagnosis often incidental
- Initial symptoms: lymph node ↑/anemia
- Progression: bone marrow impairment, ↑ susceptibility to infection
- Hypogammaglobulinemia ↑ with advanced disease
- Long-term complications: autoimmune phenomena, Richter’s transformation
Autoimmune Complications of CLL

- Autoimmune hemolytic anemia
  - Coombs’ positive
  - Clinical hemolysis
- Pure red cell aplasia
- Immune-mediated thrombocytopenia
- Granulocytopenia
- Other autoimmune diseases uncommon
# The Rai System for Clinical Staging of CLL

<table>
<thead>
<tr>
<th>Stage</th>
<th>System</th>
<th>Features</th>
<th>Median Survival(y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low risk</td>
<td>Lymphocytosis</td>
<td>&gt;10</td>
</tr>
<tr>
<td>I</td>
<td>Intermediate risk</td>
<td>Lymphadendropathy</td>
<td>7</td>
</tr>
<tr>
<td>II</td>
<td></td>
<td>Splenomegaly ± hepatomegaly</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>High risk</td>
<td>Anemia</td>
<td>2-5</td>
</tr>
<tr>
<td>IV</td>
<td></td>
<td>Thrombocytopenia</td>
<td></td>
</tr>
</tbody>
</table>

# Chromosomal Abnormalities in CLL

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Hernandez 1995 n=609</th>
<th>Escudier 1993 n=475</th>
<th>Juliusson 1990 n=391</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any (%)</td>
<td>38</td>
<td>31</td>
<td>56</td>
</tr>
<tr>
<td>+12*</td>
<td>20</td>
<td>26</td>
<td>31</td>
</tr>
<tr>
<td>11q</td>
<td>26</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>14q</td>
<td>19</td>
<td>14</td>
<td>19</td>
</tr>
<tr>
<td>13q</td>
<td>12</td>
<td>7</td>
<td>23</td>
</tr>
<tr>
<td>6q</td>
<td>11</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>+3</td>
<td>2</td>
<td>NR</td>
<td>9</td>
</tr>
</tbody>
</table>

NR = not reported.

*Specific abnormalities are represented as percentage of clonal abnormalities.
## Genomic Aberrations In CLL 
Interphase FISH Results 
82% Abnormal

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>No. Patients</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13q deletion</td>
<td>178</td>
<td>(55)</td>
</tr>
<tr>
<td>11q deletion</td>
<td>58</td>
<td>(18)</td>
</tr>
<tr>
<td>trisomy 12</td>
<td>53</td>
<td>(16)</td>
</tr>
<tr>
<td>17p deletion</td>
<td>23</td>
<td>(7 )</td>
</tr>
<tr>
<td>6q deletion</td>
<td>21</td>
<td>(6 )</td>
</tr>
</tbody>
</table>

Dohner et al NEJM 343:1910, 2000
B-Cell Diversity: $V_H$ Rearrangement and Mutation

$V_H$ in B-cell chronic lymphocytic leukemia
- Somatic mutations (<98% homology)
Comparison of CLL Patients With Mutated and Unmutated $V_H$ Genes

Ig V Gene Mutations and CD38: Newer Prognostic Factors in CLL

Gene Expression Profiling in CLL and ZAP-70

• T cells: 70-kDa, ζ-chain, CD3-receptor–associated PTK
• B cells: usually use Syk-mediated signal transduction

Hamblin T et al. NEJM 2004;351:856-857
Prognostic Value of ZAP-70 in Patients With Stage A Binet CLL: Survival

≥20% ZAP-70–positive cells

<20% ZAP-70–positive cells

(N=44) (P=0.01)

Crespo et al NEJM 2003;348:1764.
ZAP-70 expression by CLL B cells (immunophenotyping)

Rassenti et al
NEJM 351;2004
Time from Diagnosis to Initial Therapy

Percent Of Patients (n = 300)

Years

ZAP70\(^+/\)Unmutated
ZAP70\(^{\text{Neg}}/\)Mutated
ZAP70\(^+/\)Mutated *
ZAP70\(^{\text{Neg}}/\)Unmutated*

Rassenti et al. NEJM 351;2004
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Bad</th>
</tr>
</thead>
<tbody>
<tr>
<td>$B_2M$</td>
<td>increased</td>
</tr>
<tr>
<td>FISH</td>
<td>11q-, 17p-</td>
</tr>
<tr>
<td>VH Mutation Status</td>
<td>unmutated</td>
</tr>
<tr>
<td>CD38</td>
<td>positive</td>
</tr>
<tr>
<td>ZAP70</td>
<td>positive</td>
</tr>
</tbody>
</table>
IWCLL-NCI: Indications to Initiate Treatment for CLL

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

Hallek et al Blood 2008;111:5446-5456
Why Not Treat CLL at Diagnosis

- indolent disease
- patients often asymptomatic
- median age early 70’s
- no cure
Survival: Daily Chlorambucil Versus Observation


*
Chemotherapeutic Options for CLL

- Alkylating agents: chlorambucil, cyclophosphamide, bendamustine
- Corticosteroids
- Nucleoside analogs: fludarabine, cladribine, pentostatin
- Monoclonal antibodies
- Chemoimmunotherapy
Fludarabine for 6 cycles
If CR, PR, SD then Rituximab
q wk x 4

Untreated CLL

Randomize

Fludarabine + Rituximab for 6 cycles
If CR, PR, SD then Rituximab
q wk x 4

Byrd et al JCO 19(8), 2003.
PFS and OS with FR
Genetic Features Predict Early Progression Following Fludarabine and Rituximab


<table>
<thead>
<tr>
<th>FISH (N=104) VH Mutation Status (N=75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17p⁻</td>
</tr>
<tr>
<td>------</td>
</tr>
<tr>
<td>% Pts</td>
</tr>
<tr>
<td>% CR</td>
</tr>
<tr>
<td>PFS (mo)</td>
</tr>
</tbody>
</table>

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

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

ABSTRACT

Purpose
Fludarabine and cyclophosphamide (FC), which are active in treatment of chronic lymphocytic leukemia (CLL), are synergistic with the monoclonal antibody rituximab in vitro in lymphoma cell lines. A chemoimmunotherapy program consisting of fludarabine, cyclophosphamide, and rituximab (FCR) was developed with the goal of increasing the complete remission (CR) rate in previously untreated CLL patients to \( \geq 50\% \).
CLL8 Study Design

Patients with untreated, active CLL and good physical fitness (CIRS ≤ 6, creatinine clearance ≥ 70 ml/min)

R → FCR → 6 courses → Follow up

Updated results of the 2nd analysis
Median observation time 37.7 months

Hallek et al Lancet 2010;376:1164-74
Addition of Rituximab to Fludarabine and Cyclophosphamide

Progression free survival (PFS) 2012

Median observation time 5.9 years

Median PFS
FCR 57 months
FC 33 months

HR 0.59, 95% CI 0.5-0.7, p < 0.0001
Addition of Rituximab to Fludarabine and Cyclophosphamide

Overall survival (OS) 2012

Median observation time 5.9 years

FCR 69.4% alive
Median not reached
FC 62.3% alive
Median 86 months

HR 0.68,
95% CI 0.535-0.858
p=0.001

Fischer K et al. ASH 2012
CLL8 Genetic Analyses: PFS

FC

FCR

Months

Months
Study Design

Previously untreated CLL
Total CIRS score >6 and/or creatinine clearance <70 mL/min
N=780 (planned)

GA101 + chlorambucil x 6 cycles
Primary analysis data cut-off: 07/2012

Chlorambucil x 6 cycles (control arm)
Primary analysis data cut-off: 08/2012

Rituximab + chlorambucil x 6 cycles

- GA101: 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 G-Clb

Goede et al. NEJM. 2014; (370) 1101-10
Study Design

Previously untreated CLL
Total CIRS score >6 and/or creatinine clearance <70 mL/min
N=780 (planned)

590 patients

G-Clb vs. R-Clb
Primary analysis data cut-off: 05/2013

GA101 + chlorambucil x 6 cycles
Chlorambucil x 6 cycles (control arm)
Rituximab + chlorambucil x 6 cycles

Additional 190 patients

Goede et al. NEJM. 2014;(370) 1101-10
Progression-Free Survival (Head-to-Head)

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.
Infusion-related Reactions (IRR) by Cycle

- 7% of patients in the G-Clb arm discontinued owing to grade 3 or 4 IRR
- There were no grade 5 IRR

Goede et al. NEJM. 2014;(370) 1101-10
Bendamustine
Bifunctional Antineoplastic Agent?

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

### Bendamustine vs Chlorambucil as Front-line Therapy in CLL (N=305)

Bendamustine 100 m/m² IV D1, 2 q 4 weeks  
Chlorambucil 0.8 mg/kg PO D1, 15 q 4 weeks

<table>
<thead>
<tr>
<th></th>
<th>Bendamustine</th>
<th>Chlorambucil</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR %</td>
<td>29</td>
<td>&lt;1</td>
</tr>
<tr>
<td>OR %</td>
<td>68</td>
<td>39</td>
</tr>
<tr>
<td>PFS (mos)</td>
<td>21</td>
<td>9</td>
</tr>
<tr>
<td>% Gr. ANC</td>
<td>43</td>
<td>24</td>
</tr>
<tr>
<td>3-4 Plts</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Infection</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>

Knauf et al JCO 2009;27:4378-84
CLL10 Study: FCR VS BR in Front-line

**Design**

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

**Randomization**

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

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

**Non-Inferiority of BR in comparison to FCR for PFS:**

HR ($\lambda$ BR/FCR) less than 1.388

Eichhorst et al. ASH 2013, Abstract 526
### CLL10 Study: FCR VS BR in FrontLine

#### Response to therapy (Best response)

<table>
<thead>
<tr>
<th>Response %</th>
<th>FCR (n=274)</th>
<th>BR (n=273)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR (CR + CRi)</td>
<td>47.4</td>
<td>38.1</td>
<td>0.031</td>
</tr>
<tr>
<td>CR</td>
<td>40.1</td>
<td>36.3</td>
<td></td>
</tr>
<tr>
<td>CRi</td>
<td>7.3</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>50.4</td>
<td>59.7</td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>97.8</td>
<td>97.8</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Eichhorst et al. ASH 2013, Abstract 526
CLL10 Study: FCR VS BR in FrontLine

Minimal residual disease (MRD)

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

p=0.024

Eichhorst et al. ASH 2013, Abstract 526
CLL10 Study: FCR VS BR in Front-Line

Progression-free survival = Primary endpoint

**Primary endpoint**

- Survival Functions

- **FCR** not reached
- **BR** 44.9 months

**P** = 0.041

Eichhorst et al. ASH 2013, Abstract 526
### CLL10 Study: FCR VS BR in FrontLine

**Adverse Events CTC °3-5**  
(Interval 1st cycle until 3 months after Final staging)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>FCR (% of pt)</th>
<th>BR (% of pt)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>90.8</td>
<td>78.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hematological AEs</td>
<td>90.0</td>
<td>66.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>81.7</td>
<td>56.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anemia</td>
<td>12.9</td>
<td>9.7</td>
<td>0.28</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>21.5</td>
<td>14.4</td>
<td>0.036</td>
</tr>
<tr>
<td>Infection</td>
<td>39.0</td>
<td>25.4</td>
<td>0.001</td>
</tr>
<tr>
<td>TRM</td>
<td>3.9</td>
<td>2.1</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Eichhorst et al. ASH 2013, Abstract 526
Alemtuzumab

- Humanized MoAb targeting CD52 pan-lymphocyte antigen
- 30 mg SQ or IV TIW
- Preferential activity in blood/marrow
- Side infusion reactions with IV
  Effects: minor skin reactions with SQ
- PCP and Herpes prophylaxis needed
- CMV reactivation - 20%
Ofatumumab: Characteristics

- Human CD20 mAb
- Binds a small-loop epitope of CD20
- Potent lysis of B cells
- More effective in vitro CDC versus rituximab
- Effective CDC of cells with low CD20 expression, including CLL cells
- Promising activity in pilot CLL study: ORR 50% in high-dose group (n=27)³

Teeling et al J Immunol 2006: 177;362
Teeling et al Blood 2004: 104;1793
Coiffier et al Blood 2008; 111:1094
Ofatumumab in Refractory CLL Objectives and Key Inclusion Criteria

- Multicenter, open-label, single-arm study: Europe and US
- Overall study objectives: efficacy and safety
- Patient population:

<table>
<thead>
<tr>
<th>Double-Refractory (DR)</th>
<th>Bulky Fludarabine-Refractory (BFR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory to fludarabine-containing regimen (≥2 cycles)</td>
<td>Refractory to fludarabine-containing regimen (≥2 cycles)</td>
</tr>
<tr>
<td>Refractory to alemtuzumab-containing regimen (≥12 doses)</td>
<td>Inappropriate for alemtuzumab due to bulky nodes (&gt;5 cm)</td>
</tr>
</tbody>
</table>

- No upper age limit
- ECOG performance status 0 to 2
- No exclusions for severe cytopenias

Wierda et al JCO 2010;28:1749-55
Ofatumumab in Refractory CLL
Objective Responses

H₀: ORR = 15%

*P < 0.0001 versus H₀ (two-sided exact test).

58%* 47%*

99% CI

DR (n=59)  BFR (n=79)
Ofatumumab in refractory CLL
Survival outcomes

Median progression-free survival*

- Median progression-free survival: 5.7 mo

Median overall survival**

- Median overall survival: 15.4 mo

*Time from start of treatment to progression (assessed by IRC) or death.

**Time from start of treatment to death.
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 inhibitors¹
  • Btk (Bruton’s tyrosine kinase) inhibitors: ibrutinib, CC-292, ONO-4059, ACP196
  • PI3 kinases: Isoform-Selective Inhibitor of PI 3-Kinases², idelalisib, IPI-145, TGR-1202

Targeting of BCR Signaling in CLL

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Targeting of BCR Signaling in CLL

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  - Btk (Bruton’s tyrosine kinase) inhibitors: ibrutinib, CC-292, ONO-4059, ACP196

  - PI3 kinases: Isoform-Selective Inhibitor of PI 3-Kinases\(^2\), idelalisib, IPI-145, TGR-1202

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Ibrutinib in Refractory CLL With 11q Deletion

Before

4 weeks
Pattern of Response:
Blood Lymphocytes vs Lymph Nodes

SPD = sum of products of lymph node dimension
Ibrutinib Inhibits CLL Cell Migration Towards CXCL12 and CXCL13

Hollenriegel et al ASH 2012
Ibrutinib Treatment Reduced Plasma CCL3 and CCL4 Levels in Patients (N=28)

Hollenriegel et al ASH 2012
# Disease Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TN ≥65 yrs n = 31</th>
<th>R/R n = 101</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FISH cytogenetic abnormalities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Del17p</td>
<td>6%</td>
<td>34%</td>
</tr>
<tr>
<td>Del11q</td>
<td>3%</td>
<td>35%</td>
</tr>
<tr>
<td><strong>Median ANC, 10⁹/L (range)</strong></td>
<td>4 (0-19.4)</td>
<td>3 (0-19)</td>
</tr>
<tr>
<td>≤ 1.5 x 10⁹/L</td>
<td>3%</td>
<td>34%</td>
</tr>
<tr>
<td><strong>Median hemoglobin, g/dL (range)</strong></td>
<td>12 (8-16)</td>
<td>12 (6-18)</td>
</tr>
<tr>
<td>≤ 11 g/dL</td>
<td>36%</td>
<td>42%</td>
</tr>
<tr>
<td><strong>Median platelets, 10⁹/L (range)</strong></td>
<td>113 (32-217)</td>
<td>105 (2-310)</td>
</tr>
<tr>
<td>≤ 100 x 10⁹/L</td>
<td>39%</td>
<td>49%</td>
</tr>
</tbody>
</table>

Byrd et al NEJM 2013;369:32
O'Brien et al Lancet Oncol 2014;15:48
Best Response (Investigator-Assessed)

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
### Ibrutinib

#### Best Response by Risk Features

<table>
<thead>
<tr>
<th></th>
<th>Treatment Naive</th>
<th>R/R + HR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>ORR %</td>
</tr>
<tr>
<td>All Patients</td>
<td>31</td>
<td>68</td>
</tr>
<tr>
<td>≥ 70 years age</td>
<td>23</td>
<td>61</td>
</tr>
<tr>
<td>β₂ Microglobulin &gt; 3mg/L</td>
<td>8</td>
<td>63</td>
</tr>
<tr>
<td>Rai Stage III/IV</td>
<td>15</td>
<td>60</td>
</tr>
<tr>
<td>IgV₄ unmutated</td>
<td>17</td>
<td>82</td>
</tr>
<tr>
<td>del(17p13.1) present</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>del(11q22.3) present</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>Bulky disease ≥ 5 cm</td>
<td>6</td>
<td>67</td>
</tr>
<tr>
<td>≥ 3 prior chemo regimens</td>
<td>Not applicable</td>
<td>58</td>
</tr>
<tr>
<td>Purine Analog Refractory</td>
<td>Not applicable</td>
<td>41</td>
</tr>
</tbody>
</table>
Progression-Free Survival

<table>
<thead>
<tr>
<th></th>
<th>TN</th>
<th>R/R</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-month PFS</td>
<td>96.3%</td>
<td>68.4%</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(76.5–99.5)</td>
<td>(56.1–77.9)</td>
</tr>
<tr>
<td>Median PFS</td>
<td>Not reached</td>
<td>Not reached</td>
</tr>
</tbody>
</table>
Progression-Free Survival by Cytogenetics (FISH) in Relapsed/Refractory Population

<table>
<thead>
<tr>
<th>Cytogenetic Abnormality</th>
<th>30-month PFS (95% CI)</th>
<th>Median PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Del17p</td>
<td>45.9% (25.0–64.6)</td>
<td>28.1 months</td>
</tr>
<tr>
<td>Del11q</td>
<td>74.2% (53.3–86.8)</td>
<td>Not reached</td>
</tr>
<tr>
<td>No del17p or del11q</td>
<td>89.0% (69.0–96.4)</td>
<td>Not reached</td>
</tr>
</tbody>
</table>

+ Censored
Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>TN</th>
<th>R/R</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-month OS</td>
<td>96.6%</td>
<td>79.9%</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(77.9–99.5)</td>
<td>(69.0–87.3)</td>
</tr>
<tr>
<td>Median OS</td>
<td>Not reached</td>
<td>Not reached</td>
</tr>
</tbody>
</table>

American Society of Clinical Oncology 2014, PCYC 1102/1108, O'Brien et al.
• Primary Endpoint: PFS
• Stratification according to:
  – Disease refractory to purine analog chemoimmunotherapy (no response or <12 months)
  – Presence or absence of 17p13.1 (17p del)
• At time of interim analysis, median time on study was 9.4 months

Protocol amended for cross over with support of Data Monitoring Committee and discussion with health authorities. Byrd et al NEJM, Epub 5/31/14
Progression-Free Survival

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

- This represents a 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.
Safety: Atrial Fibrillation and Bleeding-related Adverse Events

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

- Bleeding-related AEs of any grade:
  - most commonly petechiae and ecchymoses
  - ibrutinib 44%, ofatumumab 12%
  - No difference in severe/major bleeding events:
    - ibrutinib n=2, ofatumumab n=3, 1 SDH with ibrutinib
  - One patient discontinued ibrutinib due to a bleeding AE
  - Concomitant anti-platelets or anticoagulants
    - 50% ibrutinib and 39% ofatumumab
Idelalisib is an Orally Bioavailable Small Molecule that Inhibits PI3K Delta Potently and Selectively

Class I PI3K Isoform
- Alpha
- Beta
- Gamma
- Delta

Cell-Based Activity
- PDGF-induced pAKT
- LPA-induced pAKT
- fMLP-induced CD63+
- FcεR1-induced CD63+

EC_{50} (nM)
- Alpha: >20,000
- Beta: 1,900
- Gamma: 3,000
- Delta: 8

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

Lannutti, Blood, 2011
Idelalisib Antagonizes BCR-Triggered CLL Cell Migration (Pseudoemperipolesis) Beneath Bone Marrow Stroma Cells
Marked Reductions in Peripheral Lymphadenopathy Were Observed

38-year-old patient with refractory CLL and 5 prior therapies
Idelalisib: Idelalisib Improvement of Baseline Cytopenias

Hemoglobin, Mean ± SEM, g/L

Platelet Count (N=34)
Hemoglobin (N=25)
ANC (N=15)

Time from Start of Idelalisib, Weeks

Cell Number, Mean ± SEM, x 10^9/L

Brown et al. ASCO 2013
Idelalisib: Nodal and Overall Response Rate

Response Rate ±95% CI

Lymph Node Response
- 81% n=44

Overall Response
- 72% n=39
- 33% n=18
- 39% n=21

ALC and Tumor Burden Over Time

Change in SPD from Baseline
Mean ± SEM, %

ALC, Mean ± SEM, x10^9/L

Time from Start of Idelalisib, Weeks

- Decrease by ≥50% of nodal SPD
- PR with lymphocytosis (Cheson 2012)
- PR by IWCLL criteria (Hallek 2008)

ALC (N=54)
SPD (N=51)
Idelalisib: Progression-free Survival by Dose

≥150 mg BID (N=28): median PFS 31.9 months
<150 mg BID (N=26): median PFS 6.6 months
Study 116: Randomized, Double-Blind, Placebo-Controlled

**Primary Study 116**
- **Randomized Combination Therapy**
  - Arm A (N=110)
    - Rituximab (6 months)
    - Idelalisib (150 mg BID)
  - Arm B (N=110)
    - Placebo (BID)
    - Rituximab (6 months)

**Continuing Single-Agent Therapy**
- Disease Progression
  - Idelalisib (300 mg BID)

**Extension Study 117**
- Extension Single-Agent Therapy
  - Idelalisib (150 mg BID)

**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 et al. NEJM 2014, Jan. 22 Epub*
## Study 116: Key Eligibility

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Relapsed CLL</strong></td>
<td>• CLL progression &lt;24 months since last therapy</td>
</tr>
<tr>
<td></td>
<td>• Treatment warranted according to IWCLL criteria</td>
</tr>
<tr>
<td><strong>Lymphadenopathy</strong></td>
<td>• Presence of ≥1 measurable nodal lesion</td>
</tr>
<tr>
<td><strong>Prior therapies</strong></td>
<td>• ≥ 1 anti-CD20 antibody containing therapy or ≥ 2 prior cytotoxic therapies</td>
</tr>
<tr>
<td><strong>Appropriate for non-cytotoxic therapy</strong></td>
<td>• CIRS score &gt;6 or creatinine clearance &lt;60 ml/min (≥30 mL/min) or Grade 3/4 neutropenia or thrombocytopenia due to prior myelotoxicity</td>
</tr>
<tr>
<td><strong>Bone marrow function</strong></td>
<td>• Any grade anemia, neutropenia or thrombocytopenia allowed</td>
</tr>
<tr>
<td><strong>Karnofsky score</strong></td>
<td>• ≥40</td>
</tr>
</tbody>
</table>
Primary Endpoint: Progression-Free Survival

HR = 0.15
95% CI (0.08, 0.28)
p < 0.0001

Median PFS: not reached

Placebo + Rituximab
Median PFS = 5.5 months

Subjects at risk, n
IDELA + R: 110  69  44  34  30  14  6  2  0
Placebo + R: 110  62  30  18  13  6  1  1  0
Hairy Cell Leukemia
Clinical Features

<2% of adult leukemia (500-600 cases/year)

Etiology/molecular abnormalities unknown

Median age     mid- fifties

Male : female  4 : 1

Presenting features
  constitutional    60%
  cytopenia - related  25%
  incidental        25%
# Hairy Cell Leukemia

## Clinical Features

<table>
<thead>
<tr>
<th>Physical</th>
<th>% Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>splenomegaly</td>
<td>90</td>
</tr>
<tr>
<td>hepatomegaly</td>
<td>20</td>
</tr>
<tr>
<td>adenopathy</td>
<td>10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hematologic</th>
<th>% Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>cytopenia</td>
<td>70</td>
</tr>
<tr>
<td>leukocytosis</td>
<td>10</td>
</tr>
<tr>
<td>circulating HC</td>
<td>70</td>
</tr>
</tbody>
</table>
Aspirate Smear
Hairy Cell Leukemia

Phenotype:

B-cell: CD19, CD20, surface Ig, FMC – 7, Unique

T-cell: CD25 (IL2R), Monocytic, CD11c, CD103

Molecular: BRAF V600E mutations
Hairy Cell Leukemia
Historical Data

- Median survival 4 years
- Infectious deaths
- Splenectomy

Improvement in:

all counts          40 - 60%
one parameter        90%
response with BM cell.  < 85%
<table>
<thead>
<tr>
<th><strong>Hairy Cell Leukemia - Therapy</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IFN</strong></td>
</tr>
<tr>
<td>ORR 75-85%. CR 0-30%</td>
</tr>
<tr>
<td>Flu-like symptoms, fatigue, neurotoxicity</td>
</tr>
<tr>
<td><strong>Pentostatin</strong></td>
</tr>
<tr>
<td>Nucleoside analog</td>
</tr>
<tr>
<td>4mg/m², IV q week – 2 weeks</td>
</tr>
<tr>
<td>ORR 87-97%. CR 59-82%</td>
</tr>
<tr>
<td>Rash, nausea, renal insufficiency</td>
</tr>
<tr>
<td><strong>Cladribine</strong></td>
</tr>
<tr>
<td>Nucleoside analog</td>
</tr>
<tr>
<td>0.1 mg/kg x 7 CI or</td>
</tr>
<tr>
<td>0.12 mg/kg/day x 5 days (2 hrs)</td>
</tr>
<tr>
<td>ORR 97-100%, CR 76-95%</td>
</tr>
</tbody>
</table>
Fig. 1. disease-free survival (DFS) after first-line therapy, comparing pentostatin with cladribine. The seven nonresponders (to pentostatin) are excluded. Log-rank test $P = 0.55$.

Else et al Cancer 104:2442, 2005
Figure 2. Overall survival, comparing first-line treatment with pentostatin and cladribine. Log-rank test $P = 0.34$.

Else et al Cancer 104:2442, 2005
<table>
<thead>
<tr>
<th></th>
<th>Zenhausern</th>
<th>Thomas</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients:</strong></td>
<td>25</td>
<td>15</td>
</tr>
<tr>
<td><strong>Schedule:</strong></td>
<td>4 weeks</td>
<td>8-12 weeks</td>
</tr>
<tr>
<td><strong>OR:</strong></td>
<td>80%</td>
<td>80%</td>
</tr>
<tr>
<td><strong>CR:</strong></td>
<td>32%</td>
<td>53%</td>
</tr>
<tr>
<td><strong>F/U:</strong></td>
<td>27 mos</td>
<td>32 mos</td>
</tr>
<tr>
<td></td>
<td>8 PD</td>
<td>5 PD</td>
</tr>
</tbody>
</table>

Zenhausern et al Haematologica 93:1426, 2008  
Thomas et al JCO 102:3906, 2003
Recombinant Immunotoxins

- **Moxetumomab**
  - Anti-CD22 + truncated Pseudomonas exotoxin
  - previously treated HCL
    - N=28, CR 46%, PR 40%
    - Median DFS not reached
      - 65% at 3 years
  - Kreitman et al. JCO 30:1822;2012

- **LMB-2**
  - Anti-CD25 + truncated Pseudomonas exotoxin
  - Phase I included 4 HCL - 1 CR (duration > 11 months), 3 major responses (98-99% reduction in circulating HC)
  - Toxicity: fever, elevated LFTs, diarrhea, N/V, transient cardiomyopathy
  - Kreitman et al. JCO 18:1622; 2000