Overview

- Brief introduction to CLL
  - Epidemiology and clinical features
  - Genetic risk stratification

- Current treatment strategies
  - Standard-of-care chemoimmunotherapy
  - Genetic high-risk disease
  - Elderly patients

- Emerging agents: the “New Face”
  - Immunotherapy: monoclonal antibodies and beyond
  - Targeting B-cell receptor signaling with kinase inhibitors
CLL: Epidemiology

- Most common leukemia (~ 15,000 cases per year)
- Disease of older patients, median age at diagnosis 72 years
- Causes ~ 4,400 deaths per year
- Absolute survival has increased during past 2 decades
- 3:2 male-to-female ratio; white > black >>> Asian
- Relatively long median survival makes CLL by far the most prevalent leukemia

CLL: The Changing Face of Survival

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>5-Year</td>
<td>54.2%</td>
<td>60.2%</td>
</tr>
<tr>
<td>10-Year</td>
<td>27.8%</td>
<td>34.8%</td>
</tr>
</tbody>
</table>

## Rai and Binet Staging Systems

### Rai Findings

<table>
<thead>
<tr>
<th>Stage</th>
<th>Findings</th>
<th>Survival (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Lymphocytosis only</td>
<td>&gt; 150</td>
</tr>
<tr>
<td>I</td>
<td>Lymphocytosis + lymphadenopathy</td>
<td>101</td>
</tr>
<tr>
<td>II</td>
<td>Lymphocytosis + &gt; spleen and/or liver</td>
<td>71</td>
</tr>
<tr>
<td>III</td>
<td>Lymphocytosis + anemia (Hgb &lt; 11.0 g/dL)</td>
<td>19</td>
</tr>
<tr>
<td>IV</td>
<td>Lymphocytosis + platelets &lt; 100</td>
<td>19</td>
</tr>
</tbody>
</table>

### Binet Findings

<table>
<thead>
<tr>
<th>Stage</th>
<th>Findings</th>
<th>Survival (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Hgb ≥ 10, Plts ≥ 100, &lt; 3 involved areas</td>
<td>&gt; 120</td>
</tr>
<tr>
<td>B</td>
<td>Hgb ≥ 10, Plts ≥ 100, ≥ 3 involved areas</td>
<td>84</td>
</tr>
<tr>
<td>C</td>
<td>Hgb &lt; 10 or Plts &lt; 100</td>
<td>24</td>
</tr>
</tbody>
</table>

Rai et al, 1975

Median survival:
- 11 years
- 9 years

Survival rates:
- 32 months
- 11 years
# CLL Outcome from Diagnosis by Interphase FISH Abnormalities

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>% Patients</th>
<th>Median time to Treatment</th>
<th>Median Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Del(17p13.1)</td>
<td>7</td>
<td>9</td>
<td>32</td>
</tr>
<tr>
<td>Del(11q22.3)</td>
<td>18</td>
<td>13</td>
<td>79</td>
</tr>
<tr>
<td>Trisomy 12</td>
<td>16</td>
<td>33</td>
<td>114</td>
</tr>
<tr>
<td>Del(13q14)</td>
<td>55</td>
<td>49</td>
<td>133</td>
</tr>
<tr>
<td>None detected</td>
<td>18</td>
<td>92</td>
<td>111</td>
</tr>
</tbody>
</table>

CLL Prognostic Markers
Mutated vs Unmutated IgV<sub>H</sub> Genes

Overall Survival

Deletion 17p does not always portend rapid disease progression

Phase III CLL8 Trial of FC With or Without Rituximab in Untreated CLL: Study Design

Key eligibility criteria:
- Untreated active CLL
- CIRS score \( \leq 6 \)
- Creatinine clearance \( \geq 70 \text{ mL/min} \)

Primary endpoints:
- PFS
- OS, response, safety

Halleck et al. ASH 2008; abstract 325.
Halleck et al. ASH 2009; abstract 535.
## CLL8 FC v. FCR in Untreated CLL: Efficacy

<table>
<thead>
<tr>
<th></th>
<th>FCR (n = 388)</th>
<th>FC (n = 371)</th>
<th>HR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>95%</td>
<td>88%</td>
<td>NA</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>CR</td>
<td>44%</td>
<td>22%</td>
<td>NA</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>PR</td>
<td>51%</td>
<td>67%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>SD</td>
<td>4%</td>
<td>8%</td>
<td>NA</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>Median PFS</td>
<td>51.8 months (n = 401)</td>
<td>32.8 months (n = 389)</td>
<td>0.563</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>3-Year OS</td>
<td>87% (n = 408)</td>
<td>82.5% (n = 409)</td>
<td>0.664</td>
<td>.012</td>
</tr>
</tbody>
</table>

- Median observation time: 37.7 months
- FCR significantly improved the CR rate in the patients with del(11q), del(13q), trisomy 12, and unmutated *IGHV* (P < .001) but not in those with del(17p) (P = 0.3)
- The patients achieving a CR had the longest survival

CLL8 FC v. FCR: 6 year follow-up

Second malignancies

- FC arm, 12%; FCR arm, 10% ($P = NS$)
  - Solid tumors, 5.7%
  - Richter transformation, 4.1% 1.5%
  - MDS or AML, 1.5%
- Mean time to onset, 2.4 y after end of treatment
- No significant difference between arms in rates of any type of second malignancy

Late neutropenia (grade 3/4 neutropenia 2 mo or longer after end of treatment)

- FC arm, 9%; FCR arm, 17% ($P = .007$)
- Occurred predominantly during first 12 mo after end of FCR treatment
- No significant difference between arms at 1 y after end of treatment

Fischer et al. 2012 ASH Annual Meeting Abstract #435
Chemoimmunotherapy as Initial Treatment for Patients with Chronic Lymphocytic Leukemia

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CLL8¹ R-FC</th>
<th>MDACC²,³ R-FC</th>
<th>CALGB⁴,⁵ FR</th>
<th>Mayo⁶ PCR</th>
<th>CLL BR</th>
</tr>
</thead>
<tbody>
<tr>
<td>% CR</td>
<td>44</td>
<td>72</td>
<td>47</td>
<td>41</td>
<td>33</td>
</tr>
<tr>
<td>% OR</td>
<td>95</td>
<td>95</td>
<td>90</td>
<td>91</td>
<td>91</td>
</tr>
<tr>
<td>PFS, mo</td>
<td>52</td>
<td>80</td>
<td>42</td>
<td>34</td>
<td>NR</td>
</tr>
</tbody>
</table>

7. Fischer et al. JCO 2012; 30:3209-16
Chemoimmunotherapy yields suboptimal results for del (17p) CLL

<table>
<thead>
<tr>
<th>Regimen</th>
<th>N</th>
<th>ORR (%)</th>
<th>CR (%)</th>
<th>Median PFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FCR-MDA$^{2,3}$</td>
<td>20</td>
<td>70</td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>FCR-CLL8$^1$</td>
<td>21</td>
<td>71</td>
<td>5</td>
<td>11.3</td>
</tr>
<tr>
<td>BR$^4$</td>
<td>7</td>
<td>43</td>
<td>0</td>
<td>&lt;6</td>
</tr>
</tbody>
</table>

4. Fischer et al. JCO 2012; 30:3209-16
CLL20: Alemtuzumab + Dex Followed by Alemtuzumab or Allo-SCT

- 60 patients evaluable for response
- Median follow-up: 11 mo

Patient Subgroup

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fludarabine refractory (n = 25)</td>
<td>52</td>
</tr>
<tr>
<td>Relapsed 17p- (n = 14)</td>
<td>75</td>
</tr>
<tr>
<td>First line 17p- (n = 25)</td>
<td>72</td>
</tr>
</tbody>
</table>

## Chemoimmunotherapy for del (17p) CLL

<table>
<thead>
<tr>
<th>Regimen</th>
<th>N</th>
<th>ORR (%)</th>
<th>CR (%)</th>
<th>Median PFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alemtuzumab</td>
<td>11</td>
<td>n/a</td>
<td>64</td>
<td>10.7</td>
</tr>
<tr>
<td>Alemtuzumab + dexamethasone</td>
<td>22</td>
<td>100</td>
<td>23</td>
<td>n/a</td>
</tr>
<tr>
<td>Alemtuzumab + methylprednisolone</td>
<td>17</td>
<td>88</td>
<td>65</td>
<td>18.3</td>
</tr>
<tr>
<td>Rituximab + methylprednisolone</td>
<td>14</td>
<td>100</td>
<td>25</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Outcome after allo HCT for del (17p) CLL

Schetelig J et al. JCO 2008;26:5094-5100
CLL5 Protocol of the GCLLSG for Advanced CLL in Older Patients

- CLL, ≥ 65 years, untreated, Binet stage C or B (with symptoms) or A with B-symptoms

- 6 x F
  - F 25 mg/m², D 1–5 IV
  - q 28 d

- Clb (max 12 months)
  - Clb 0.4 mg/kg BW PO
  - Dose escalation up to 0.8 mg/kg BW
  - q 15 d

# CLL5 Protocol: Response According to NCI Criteria

<table>
<thead>
<tr>
<th></th>
<th>Chlorambucil</th>
<th></th>
<th>Fludarabine</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>OR</td>
<td>51</td>
<td>51</td>
<td>67</td>
<td>72</td>
</tr>
<tr>
<td>NR</td>
<td>49</td>
<td>49</td>
<td>26</td>
<td>28</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
<td>93</td>
<td>100</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Chlorambucil</th>
<th></th>
<th>Fludarabine</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>OR</td>
<td>51</td>
<td>51</td>
<td>67</td>
<td>72</td>
</tr>
<tr>
<td>NR</td>
<td>49</td>
<td>49</td>
<td>26</td>
<td>28</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
<td>93</td>
<td>100</td>
</tr>
</tbody>
</table>

$\ p = .011$  

$\ p < .0013$  

$\ p < .001$  

CLL5 Protocol: Survival

Progression defined by the NCI criteria
Median PFS: F 19 months; Clb 18 months

Median observation time = 38 months
Median OS: F 53 months; Clb not reached

CALGB data: fludarabine conveys limited benefit to CLL patients >70 yrs

- PFS/OS benefit of fludarabine differs depending on age.
- PFS/OS is not improved with fludarabine versus chlorambucil in patients ≥70 (versus patients ≤70)
- Response rates to FR are dramatically lower among patients ≥ age 70
  - CR: 51% vs. 77%, \( P = 0.02 \)
  - <50% of patients age ≥70 were able to complete the intended six cycles of FR due to toxicity
  - All patients ECOG PS ≤2

Woyach J et al. JCO (2013)
Phase II Trial of Chlorambucil Plus Rituximab in Patients With Previously Untreated CLL

Eligibility criteria:
• Previously untreated
• Binet stage B/C
• ECOG PS ≤ 2

Chlorambucil 10 mg/m² p.o., days 1-7
Rituximab 375 mg/m², day 1 (cycle 1), 500 mg/m², day 1 (cycles 2-6) q 28 days × 6 cycles

Continuing clinical response

Chlorambucil 10 mg/m² p.o., days 1-7 q 28 days × 6 cycles

- Primary endpoint: Safety
- Secondary endpoints: ORR, PFS, OS, MRD

Hillmen et al. ASH 2010; abstract 697.
### Phase II Trial of Chlorambucil Plus Rituximab in Patients With Previously Untreated CLL

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Rituximab/Chlorambucil (n = 100)</th>
<th>Historical Data on Chlorambucil Alone (n = 200)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>12%</td>
<td>6%</td>
</tr>
<tr>
<td>Overall Response Rate</td>
<td>80%</td>
<td>66%</td>
</tr>
<tr>
<td>Stable Disease/Progressive Disease</td>
<td>17%</td>
<td>30%</td>
</tr>
<tr>
<td>Not Evaluable</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>95% CI for Percentage of Patients Achieving Partial Response or Better</td>
<td>70.8%-87.3%</td>
<td>59.0%-72.5%</td>
</tr>
</tbody>
</table>

- Median PFS: 23.9 months in R-Chl group vs. 18 months in Chl group
- Serious AEs with R-Chl:
  - 57 in 39 patients
  - 13 deaths due to disease progression or treatment-related events

Hillmen et al. ASH 2010; abstract 697.
Ofatumumab in Refractory CLL
Treatment Schedule

Premedication:
- Paracetamol (acetaminophen) 1 g PO or eq
- Antihistamine (cetirizine) 10 mg PO or eq
- Glucocorticoid (prednisolone) 100 mg IV or eq

Median number of infusions: 12 (range, 1–12) for both groups

Ofatumumab in Relapsed CLL
Efficacy

<table>
<thead>
<tr>
<th></th>
<th>Fludarabine/ Alemtuzumab-Re refractory (n = 95)</th>
<th>Bulky Fludarabine-Re refractory (n = 111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response Rate&lt;sup&gt;a&lt;/sup&gt;</td>
<td>51%</td>
<td>44%</td>
</tr>
<tr>
<td>17p-</td>
<td>37% (n =27)</td>
<td>22% (n =18)</td>
</tr>
<tr>
<td>No 17p-</td>
<td>56% (n =64)</td>
<td>49% (n =89)</td>
</tr>
<tr>
<td>Median PFS</td>
<td>5.5 months</td>
<td>5.5 months</td>
</tr>
<tr>
<td>Median Overall Survival</td>
<td>14.2 months</td>
<td>17.4 months</td>
</tr>
<tr>
<td>Responders</td>
<td>23 months</td>
<td>27.6 months</td>
</tr>
<tr>
<td>Nonresponders</td>
<td>10.2 months</td>
<td>15.5 months</td>
</tr>
</tbody>
</table>

<sup>a</sup> Independent of age, Rai stage, 11q- status, prior rituximab, and number of prior regimens

Ofatumumab in Previously Untreated CLL

- Eligibility: age ≥65 years or ineligible/unwilling to receive fludarabine-based therapy
- Treatment plan: 8-weeks induction followed by q2month maintenance x 12 doses
- Cohort 1: 300 mg first dose, 2000 mg subsequent
  Cohort 2: 300 mg first dose, 1000 mg subsequent
- ORR: 62% in cohort 1; 30% in cohort 2
- ORR: del(11q22.3) or del(17p13.1) 33%
- Toxicities were mainly hematologic;
  - G3/4 heme toxicities in 23% of cohort 1 and 21% of cohort 2.
  - G3/4 non-heme toxicities in 16% of cohort 1, 6% of cohort 2

Flinn et al. ASH Annual Meeting 2012. Abstract 719
Ofatumumab in Previously Untreated CLL

**PFS**

- 12 mo PFS: 90% **Cohort 1**
- 76% **Cohort 2**

**OS**

- 15 mo OS: 96%

Flinn et al. ASH Annual Meeting 2012. Abstract 719
### Lenalidomide in CLL Salvage

<table>
<thead>
<tr>
<th></th>
<th>RPCI N = 45</th>
<th>MDACC N = 44</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(32 evaluable)</td>
<td></td>
</tr>
<tr>
<td>Starting dose</td>
<td>25 mg or 5 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>Median dose</td>
<td>TBD&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10 mg</td>
</tr>
<tr>
<td>Response, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>6 (18)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3 (7)</td>
</tr>
<tr>
<td>nPR</td>
<td></td>
<td>1 (2)</td>
</tr>
<tr>
<td>PR</td>
<td>13 (40)</td>
<td>10 (23)</td>
</tr>
<tr>
<td>OR</td>
<td>19 (57.5)</td>
<td>14 (32)</td>
</tr>
<tr>
<td>SD</td>
<td>5 (14)</td>
<td>11 (25)</td>
</tr>
</tbody>
</table>

<sup>a</sup>TBD: To be determined

Phase II Trial of Lenalidomide/Rituximab in Patients With Relapsed CLL: Efficacy

Rituximab: 375 mg/m², days 1, 8, 15, 22 (cycle 1); day 1 (cycles 3-12), q 4 weeks
Lenalidomide: 10 mg/day starting on day 9 of cycle 1, continuing until progression

<table>
<thead>
<tr>
<th>Cycle 6 (n = 44)</th>
<th>Cycle 12 (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>28 (64%)</td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
</tr>
<tr>
<td>nPR</td>
<td>7 (16%)</td>
</tr>
<tr>
<td>PR</td>
<td>21 (48%)</td>
</tr>
<tr>
<td>SD</td>
<td>6 (14%)</td>
</tr>
</tbody>
</table>

- Median OS: not reached; survival rate: 95%
- Median TTF: 12 months
- All patients received prophylaxis for TLS with allopurinol 300 mg/day on days 1-14 of cycle 1; no antibiotic or antiviral prophylaxis was given.
**Treatment Schema**

**Cycle 1**
- **Days 1-8**: Len 2.5 mg/day
- **Days 9-21**: Len 5 mg/day*
- **Days 28-35**: Rituximab 375 mg/m²

**Cycle 2**
- **Days 1-8**: Len 5 mg/day
- **Days 15-28**: Rituximab 375 mg/m² (↑)

**Cycles 3–7**
- **Days 1-21**: Len 10 mg/day*
- **Days 28-35**: Rituximab 375 mg/m² (↑)

*Len dose increased as tolerated.*

Len, lenalidomide.

*James, et al. ASH 2011, Abstract 291*
Final Response to Therapy

- **Arm A (< 65 years)**
  - CR: 20% (90% CI 10–33)
  - ORR: 95% (90% CI 85–99)

- **Arm B (≥ 65 years)**
  - CR: 7% (90% CI 1–22)
  - ORR: 78% (90% CI 61–90)

CRi, CR with incomplete hematopoietic recovery; nPR, nodular PR; PD, progressive disease; PR, partial response; SD, stable disease.

*James, et al. ASH 2011, Abstract 291*
Lenalidomide + Rituximab in First-line CLL

Progression-free Survival

Arm A (< 65 years)
- n=40 patients
- 16 events
- Median PFS: 19 months
- Median follow-up: 18 months

Arm B (≥ 65 years)
- n=29 patients
- 13 events
- Median PFS: 20 months
- Median follow-up: 17 months
Chimeric Antigen Receptor (CAR) T-Cells in Relapsed/Refractory CLL

- CAR contains an extracellular domain targeting CD19, CD3 zeta chain, and costimulatory domain containing 4-1BB or CD28

Porter et al. NEJM (2011) 365: 725-733
Kalos et al. ASH 2012, Abstract 756
Porter et al. ASH 2012, Abstract 717
Grupp et al. ASH 2012, Abstract 2604
Chimeric Antigen Receptor (CAR) T-Cells in Relapsed/Refractory CLL

- N=10; Median age 66
- Chemotherapy 4-7 days pre-infusion
  - FC (1); PC (5) B (4)
- Median dose of CAR cells $1.4 \times 10^8$
- Massive in vivo expansion (1000-10000 fold)
- B cell aplasia
- All responding patients developed cytokine release syndrome
  - IL6, IFN$\gamma$, IL2R
  - Treated with steroids, tocilizumab

## Chimeric Antigen Receptor (CAR) T-Cells in Relapsed/Refractory CLL

<table>
<thead>
<tr>
<th>UPN</th>
<th>Blood</th>
<th>Marrow</th>
<th>Nodes</th>
<th>Expansion</th>
<th>Comments</th>
<th>Max Resp</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>NED</td>
<td>NED</td>
<td>NED</td>
<td>&gt;3 log</td>
<td>MRD* neg</td>
<td>CR 28 mo+</td>
</tr>
<tr>
<td>02</td>
<td>NED</td>
<td>NED</td>
<td>NED</td>
<td>&gt;3 log</td>
<td>MRD* neg</td>
<td>CR 27 mo+</td>
</tr>
<tr>
<td>03</td>
<td>PR</td>
<td>PR</td>
<td>PR</td>
<td>2 log</td>
<td></td>
<td>PR 4 mo</td>
</tr>
<tr>
<td>04</td>
<td>PR</td>
<td>PR</td>
<td>PR</td>
<td>2 log</td>
<td></td>
<td>PR 4 mo</td>
</tr>
<tr>
<td>05</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>&lt;2 log</td>
<td></td>
<td>NR</td>
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<td>06</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>&lt;2 log</td>
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<td>NR</td>
</tr>
<tr>
<td>09</td>
<td>NED</td>
<td>NED</td>
<td>NED</td>
<td>&gt;3 log</td>
<td>MRD* neg</td>
<td>CR 7 mo+</td>
</tr>
<tr>
<td>10</td>
<td>NED</td>
<td>NED</td>
<td>PR</td>
<td>2 log</td>
<td>Bulky nodes</td>
<td>PR 3 mo +</td>
</tr>
<tr>
<td>12</td>
<td>NED</td>
<td>NED</td>
<td>PR</td>
<td>2 log</td>
<td>Bulky nodes</td>
<td>PR 2 mo +</td>
</tr>
<tr>
<td>14</td>
<td>ne</td>
<td>ne</td>
<td>ne</td>
<td></td>
<td></td>
<td>ne</td>
</tr>
</tbody>
</table>

Porter et al. ASH Annual Meeting 2012, Abstract 717
B-cell receptor signalling in CLL

Stevenson F K et al. Blood
2011;118:4313-4320
Kinase inhibitors in CLL

Rationale for Targeting PI3K-δ in CLL

- PI3K-δ knock out has B-cell phenotype
- PI3-kinase $\uparrow$ in CLL vs normal B-cells
- PI3K-δ inhibition in CLL cells promotes
  - $\uparrow$ Apoptosis
  - $\downarrow$ Proliferation
  - $\downarrow$ Chemokines
  - $\downarrow$ Microenvironment response

Herman S et al: Blood 2010
CAL-101/GS-1101

- Selective orally available PI3K-δ inhibitor
- Finding eventual dose (150 mg BID) in CLL
- No definitive DLT identified in CLL but transient, reversible transaminitis early in therapy most problematic in NHL

Herman S et al: Blood 2010
GS-1101 Response in CLL

Response Rates

ITT Response Rate

[Exact Binomial 95% CI] %

Overall Response: 84%

Lymph Node Response: 24%

CLL (N=55)

a IWCLL response criteria

b Decrease by 50% in the nodal SPD

Hallek, Blood June 2008

GS-1101 Grade 3-4 Toxicity

Grade 3-4 Adverse Events Occurring in ≥5% of Patients Regardless of Causality (N=55)

CAL-101 (GS-1101) Has Been Evaluated as Monotherapy and Combination Therapy inPatients with Previously Treated CLL

**Designs:** Phase 1-2 dose-ranging trials

**Endpoints:** Recommended dosing regimen, safety, antitumor activity

**Follow-up:** After 48 weeks, patients who continue to benefit can continue GS-1101 single-agent therapy on an extension study

### Phase 1b Single-agent Study
- GS-1101
  - 50 to 350 mg BID

### Phase 1b Combination Study
- GS-1101
  - 100 or 150 mg BID
- Rituximab
  - 375 mg/m² weekly x 8 weeks
- Bendamustine
  - 90 mg/m² Days 1, 2 Q 4 weeks x 6 cycles
Combines of GS-1101 with Rituximab or Bendamustine Significantly Increased Overall Response

- **GS-1101** (N=55)
  - Lymph node response: 84% (n=46)
  - Overall response: 24% (n=13)

- **GS-1101 + R** (N=13)
  - Lymph node response: 77% (n=10)
  - Overall response: 77% (n=10)

- **GS-1101 + B** (N=9)
  - Lymph node response: 89% (n=8)
  - Overall response: 89% (n=8)

---

**a** Decrease by ≥50% in the nodal SPD

**b** Response by IWCLL criteria [Hallek 2008]
Idelalisib Combinations in Relapsed CLL

- R, 375 mg/m² weekly x 8
  - Idelalisib, 100 or 150 mg BID, 48 weeks continuously

- B, 70 or 90 mg/m² D1 + D2, C1-6
  - Idelalisib, 100 or 150 mg BID, 48 weeks continuously
  - B, 70 mg/m² D1 + D2, C1-6
  - R, 375 mg/m² C1-6
  - Idelalisib, 150 mg BID, 48 weeks continuously

**Idelalisib**

<table>
<thead>
<tr>
<th>Combination</th>
<th>Response Rate ±95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>+R (N=19)</td>
<td>90%</td>
</tr>
<tr>
<td>+B (N=18)</td>
<td>79%</td>
</tr>
<tr>
<td>+BR (N=15)</td>
<td>87%</td>
</tr>
</tbody>
</table>

Coutre et al. ASH Annual Meeting 2012, Abstract 191
GS-1101 (Idelalisib; CAL-101) in Relapsed/Refractory CLL

PFS
Median PFS not yet reached
PFS 2 years: 63.4%

OS
Median OS not yet reached
OS 2 years: 84.0%

Coutre et al. ASH Annual Meeting 2012, Abstract 191
Bruton’s Tyrosine Kinase (BTK)  
A critical kinase for lymphoma cell survival and proliferation

- B-cell antigen receptor (BCR) signaling is required for tumor expansion and proliferation
- Bruton’s tyrosine kinase (BTK) is an essential element of the BCR signaling pathway
- Inhibitors of BTK block BCR signaling and induce apoptosis
- Targeted inhibition of BTK is a novel approach for the treatment of B-cell malignancies
Rationale for Targeting BTK in CLL

• Loss of BTK has B-cell specific phenotype in mice & humans

• Inhibition of BTK inhibits PI3K, MAPK, and NF-κB

• BTK inhibition in CLL cells promotes
  ↑ Apoptosis
  ↓ Proliferation
  ↓ Chemokines
  ↓ Microenvironment response

PCI-32765: A Potent Btk Inhibitor

- Forms a specific and irreversible bond with cysteine-481 in Btk
- Potent irreversible Btk inhibition with $IC_{50} = 0.5 \text{ nM}$
- Inhibits BCR signaling and active in spontaneous canine model of lymphoma
- Orally available
- Once daily dosing results in 24-hr sustained target inhibition

PCYC-1102-CA

Total enrollment 117 patients

Dates enrolled 5/20/10 – 7/27/11

- **Relapsed/Refractory**
  - 420 mg/d (n=27)
  - Median follow-up 12.6 months

- **Treatment Naïve ≥ 65 yrs**
  - 420 mg/d (n=26)
  - Median follow-up 10.1 months

- **Relapsed/Refractory**
  - 840 mg/d (n=34)
  - Median follow-up 9.3 months

- **High-risk Relapsed/Refractory**
  - 420 mg/d (n=25)
  - Median follow-up 2.8 months

- **Treatment Naïve ≥ 65 yrs**
  - 840 mg/d (n=5)
  - Median follow-up 2.8 months
Ibrutinib in Treatment-Naïve CLL

**PCYC-1102-CA**

117 patients
Dates enrolled 20th May 10 – 27th Jul 11

**Treatment Naïve ≥ 65 yrs**
420 mg/d (n=26)
Median follow-up 14.4 months

**Treatment Naïve ≥ 65 yrs**
840 mg/d (n=5)*
Median follow-up 7.4 months

*The 840mg TN cohort was terminated after comparable activity and safety between doses was shown in R/R patients. One patient in this cohort received only 420 mg daily.*
Cumulative Best Response
420 mg/day N=26, Median Follow-up=14.4 mos

O’ Brien et al. ASCO Annual Meeting 2012, Abstract 6515
# Cumulative Best Response by Risk Feature

<table>
<thead>
<tr>
<th>Feature</th>
<th>N</th>
<th>ORR % (n)</th>
<th>CR % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>31</td>
<td>74 (23)</td>
<td>10 (3)</td>
</tr>
<tr>
<td>≥ 70 years age</td>
<td>23</td>
<td>70 (16)</td>
<td>13 (3)</td>
</tr>
<tr>
<td>Hgb &lt; 11 g/dL or PLT &lt; 100K/µL at screening</td>
<td>19</td>
<td>79 (15)</td>
<td>11 (2)</td>
</tr>
<tr>
<td>IgVH unmutated</td>
<td>13</td>
<td>92 (12)</td>
<td>15 (2)</td>
</tr>
<tr>
<td>Del17p present</td>
<td>2</td>
<td>100 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>β2 Microglobulin &gt; 3mg/L</td>
<td>7</td>
<td>86 (6)</td>
<td>29 (2)</td>
</tr>
</tbody>
</table>

O’ Brien et al. ASCO Annual Meeting 2012, Abstract 6515
Ibrutinib in Treatment-Naïve CLL

Estimated Progression-Free Survival

Estimated 15 mo PFS at 420mg/d = 96%

Data cut-off of 13MAR2012

O’Brien et al. ASCO Annual Meeting 2012, Abstract 6515
Marked Response in Rel/Ref CLL

Best Response by Risk Features

<table>
<thead>
<tr>
<th>Risk Feature</th>
<th>n/N</th>
<th>ORR %</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>41/61</td>
<td>67</td>
</tr>
<tr>
<td>≥ 70 years age</td>
<td>13/19</td>
<td>68</td>
</tr>
<tr>
<td>Bulky disease ≥ 5 cm</td>
<td>24/33</td>
<td>73</td>
</tr>
<tr>
<td>Bulky disease ≥ 10 cm</td>
<td>7/10</td>
<td>70</td>
</tr>
<tr>
<td>Hgb &lt; 11 g/dL or PLT &lt; 100K/μL at screening</td>
<td>22/36</td>
<td>61</td>
</tr>
<tr>
<td>IgVH unmutated</td>
<td>31/42</td>
<td>74</td>
</tr>
<tr>
<td>Del 17p</td>
<td>13/20</td>
<td>65</td>
</tr>
<tr>
<td>Del 11q</td>
<td>16/22</td>
<td>73</td>
</tr>
<tr>
<td>β2 Microglobulin &gt; 3mg/L</td>
<td>19/29</td>
<td>66</td>
</tr>
<tr>
<td>Purine Analog Refractory (&lt; 12 mos from any purine analog to next therapy)</td>
<td>17/28</td>
<td>61</td>
</tr>
</tbody>
</table>

Byrd et al. ASH Annual Meeting 2012, Abstract 189
Ibrutinib Phase Ib Relapsed/Refractory: PFS by Genetic Risk Feature

Byrd et al. ASH Annual Meeting 2012, Abstract 189
Ibrutinib in CLL -- Safety

Byrd et al. ASH Annual Meeting 2012, Abstract 189
## OSU 10053: Ibrutinib + Ofatumumab

<table>
<thead>
<tr>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Cycle 3</th>
<th>Cycle 4</th>
<th>Cycle 5-8</th>
<th>Cycle 9+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibrutinib 420 mg/day</td>
<td>Ibrutinib 420 mg/day</td>
<td>Ibrutinib 420 mg/day</td>
<td>Ibrutinib 420 mg/day</td>
<td>Ibrutinib 420 mg/day</td>
<td>Ibrutinib 420 mg/day</td>
</tr>
<tr>
<td>Ofatumumab D1, 8, 15, 22</td>
<td>Ofatumumab D1, 8, 15, 22</td>
<td>Ofatumumab D1, 8, 15, 22</td>
<td></td>
<td>Ofatumumab D1</td>
<td></td>
</tr>
</tbody>
</table>

### Eligibility:
- Relapsed/Refractory CLL
- \( \geq 2 \) priors (including nucleoside analog)
- CD20+ >10%

**Cycle Length = 28 days**

Jaglowski et al. ASCO Annual Meeting 2012, Abstract 6508
Ibrutinib Mediates Transient Rise in Lymphocyte Count that is Diminished in Combination with ofatumumab

**Blood Lymphocytes**

- ALC—PCYC 1102: Ibrutinib single agent relapsed/refractory
- ALC—Ibrutinib + ofatumumab

**Lymph Nodes**

- SPD—PCYC 1102: Ibrutinib single agent relapsed/refractory
- SPD—Ibrutinib + ofatumumab

Mean Percent Change From Baseline

Cycles

- Screen
- Cycle 1
- Cycle 2
- Cycle 3
- Cycle 4
- Cycle 5
- Cycle 6
- Cycle 7
- Cycle 8
- Cycle 9

ofatumumab added to ibrutinib
# OSU 10053: Best Response

<table>
<thead>
<tr>
<th></th>
<th>CLL/SLL/PLL (N=24)</th>
<th>Richter’s (N=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># (%)</td>
<td># (%)</td>
</tr>
<tr>
<td>CR</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>23 (96)</td>
<td>2 (67)</td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td>100 %</td>
<td>67%</td>
</tr>
<tr>
<td>SD</td>
<td>0</td>
<td>1 (33)</td>
</tr>
<tr>
<td>PD</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NE</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Median Follow-up = 9.8 months (5.2 – 12.9 months)  
24 (89%) patients remain on study  
3 Patients have discontinued:  
1 allo HSCT, 1 death (Richter’s), 1 PD (Richter’s)

Jaglowski et al. ASCO Annual Meeting 2012, Abstract 6508
Ibrutinib + Rituximab in High-risk CLL

High-risk disease (del17p or TP53 mutation [treated or untreated], or PFS < 36 months after frontline FCR, or relapsed del11q CLL)

- median age of 65 (range 35–82); median of 2 prior therapies
- 31 patients unmutated IGHV, 1 patient mutated IGHV
- 19 del17p or TP53 mutation (4 without prior tx), 13 del11q

Burger et al. ASH Annual Meeting 2012, Abstract 187
Ibrutinib + Rituximab in High-Risk CLL

Burger et al. ASH Annual Meeting 2012, Abstract 187
Creating a cancer-free world. One person, one discovery at a time.