Concept to Practice: New Advances in the Treatment of Chronic Lymphocytic Leukemia

Locke J. Bryan, M.D.
Assistant Professor of Medicine
Hematology/Oncology; Blood & Marrow Transplant
Disclosures

• No financial disclosures
• Discussion includes off-label and experimental agents
Objectives

• Introduction to CLL/SLL
• Advancements in treatment of CLL/SLL
  – Immunotherapy
  – Revisiting chemoimmunotherapy
  – Targeted agents
• Future directions in treatment of CLL/SLL
**Number of New Cases and Deaths per 100,000:** The number of new cases of chronic lymphocytic leukemia was 4.5 per 100,000 men and women per year. The number of deaths was 1.4 per 100,000 men and women per year. These rates are age-adjusted and based on 2008–2012 cases and deaths.

**Lifetime Risk of Developing Cancer:** Approximately 0.6 percent of men and women will be diagnosed with chronic lymphocytic leukemia at some point during their lifetime, based on 2010–2012 data.
Diagnosis:

**CLL Phenotype**
- CD5 +
- CD10 -
- CD19 +
- CD20 dim
- CD23 +
- sIg dim

**Lymphocytosis (ALC 5X10^9/L)**
- Complete history
- Physical exam
- Blood smear

**Flow cytometry**
- Clonal

**CLL phenotype clone**
- B-cell count
  - ≥ 5X10^9/L CLL
  - <5X10^9/L, LN+ SLL
  - <5X10^9/L, LN- MBL

**Non-CLL phenotype clone**
- B-cell (MCL, FL, SMZ, HCL, LPL)
- T-cell (LGL, MF, T-PLP, T-leu)

**Manage underlying condition**
- Reactive
  - Viral infections (EBV, CMV, mumps, VZV, influenza, hepatitis, rubella, measles, HTLV-I, HIV)
  - Bacterial infections (pertussis, cat scratch disease, rickettsiosis, toxoplasmosis and babesiosis)
  - Autoimmune (CTD)
  - Other (smoking, drugs, stress, splenectomy)

**Lymphoma staging (BM/LN biopsy, CT)**

Diagnosis and Staging:

- **CLL/SLL**
  - Defined as > $5 \times 10^9$/L +/− lymphadenopathy
  - Rai Staging System

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Risk Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Lymphocytosis, peripheral lymphocyte count &gt;15,000/mcL and &gt;40% lymphocytes in bone marrow</td>
<td>Low</td>
</tr>
<tr>
<td>I</td>
<td>Stage 0 disease with enlarge lymph node(s)</td>
<td>Intermediate</td>
</tr>
<tr>
<td>II</td>
<td>Stage 0-I with splenomegaly and/or hepatomegaly</td>
<td>Intermediate</td>
</tr>
<tr>
<td>III</td>
<td>Stage 0-II with Hgb &lt;11 g/dL or Hct &lt;33%</td>
<td>High</td>
</tr>
<tr>
<td>IV</td>
<td>Stage 0-III with platelet count &lt;100,000/mcL</td>
<td>High</td>
</tr>
</tbody>
</table>

# Prognostic Information

## Molecular Study and Flow Cytometry Analysis

<table>
<thead>
<tr>
<th>Prognostic Marker</th>
<th>Molecular Significance</th>
<th>Low Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgVH mutation</td>
<td>Somatic hypermutation</td>
<td>Mutated (&gt;2%)</td>
<td>Unmutated (≤2%)</td>
</tr>
<tr>
<td>Zap-70</td>
<td>Cell activation tyrosine kinase</td>
<td>Negative (&lt;20%)</td>
<td>Positive (≥20%)</td>
</tr>
<tr>
<td>CD38</td>
<td>Cell activation signaling</td>
<td>Negative (&lt;30%)</td>
<td>Positive (≥30%)</td>
</tr>
</tbody>
</table>

## FISH Analysis

<table>
<thead>
<tr>
<th>Favorable</th>
<th>Normal</th>
<th>Unfavorable</th>
</tr>
</thead>
<tbody>
<tr>
<td>del13q – sole abnormality</td>
<td>Normal</td>
<td>del11q (ATM gene)</td>
</tr>
<tr>
<td>trisomy 12</td>
<td>del17p (p53 gene)</td>
<td></td>
</tr>
</tbody>
</table>

## Karyotype

### Unfavorable

Complex karyotype = ≥3 unrelated chromosome abnormalities
Impact of Adverse Cytogenetics in CLL

When to treat?

• Role of Active Surveillance
• Indications for treatment:
  – Significant disease-related symptoms
  – Progressive bulky disease
  – Threatened end-organ function
  – Progressive anemia
  – Progressive thrombocytopenia
Evolution of Treatment for CLL/SLL

- **Before 1985**: Single-agent alkylators
- **1985-1990**: Single-agent purine analogs
- **1990-2000**: Combinations of purine analogs with alkylators
- **2000-2013**: Chemoimmunotherapy
- **After 2014**: Small molecule inhibitors of critical survival pathways
Advances in Treatment

• 2014 was a blockbuster year...

**Patients now have four new options for CLL treatment:**

**2 Targeted Therapies**
- Ibrutinib
  - For relapsed/treatment-resistant CLL
  - Taken orally
  - Less toxic, more effective than prior therapies
  - Delays disease progression
- Idelalisib

**2 Immunotherapies**
- Obinutuzumab
  - For newly diagnosed CLL
  - Highly effective
  - Few serious side effects
  - Delays disease progression
- Ofatumumab
Modern Immunotherapy

**Passive Immunotherapy**
- Engineering of B or T-cell receptors targeting a desired antigen and infused into the patient.

**Active Immunotherapy**
- Enabling the patient’s own immune system to re-engage and re-establish immune surveillance. Concept of avoiding “tumor escape”.

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AUGUSTA UNIVERSITY
Approaches in B-cell Malignancies

**PASSIVE IMMUNOTHERAPY**
- Monoclonal Antibodies
- Conjugated Monoclonal Antibodies
- Radioimmunotherapy
- Allogeneic Stem Cell Transplant
- Adoptive T-cell Transfer (CAR-T)
- Bi-specific B-cell Engagers (BiTE Abs)

**ACTIVE IMMUNOTHERAPY**
- Tumor Vaccines
- In-situ Vaccination
- Immune Checkpoint Inhibitors
CD20 Monoclonal Antibodies

Maloney, et al. NEJM; 2012
# CD20 Monoclonal Antibodies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Antibody Type</th>
<th>Structure</th>
<th>Mechanism of Action ADCC/CDC/PCD</th>
<th>FDA Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>I</td>
<td>Chimeric IgG1</td>
<td>++ / ++ / +</td>
<td>1997</td>
</tr>
<tr>
<td>Ofatumumab</td>
<td>I</td>
<td>Human IgG1 Kappa</td>
<td>+++ / ++++ / ++</td>
<td>2014</td>
</tr>
<tr>
<td>Obinutuzumab</td>
<td>II</td>
<td>Humanized IgG1, glycol-engineered</td>
<td>++++ / - / ++++</td>
<td>2014</td>
</tr>
<tr>
<td>Veltuzumab</td>
<td>I</td>
<td>Humanized IgG1</td>
<td>++ / ++ / +</td>
<td>Phase I/II</td>
</tr>
<tr>
<td>PRO131921</td>
<td>I</td>
<td>Humanized IgG1</td>
<td>++ / ++ / +</td>
<td>discontinued</td>
</tr>
</tbody>
</table>

ADCC: Antibody-dependent cell-mediated cytotoxicity  
CDC: Complement-dependent cytotoxicity  
PCD: Programmed cell death
### Obinutuzumab: CLL11 Trial

**Randomized 1:2:2**

- Front-line therapy
- CLL patients w/ comorbidities
  - CIRS score >6
  - CrCl <70
- Median age 73
- CIRS score 8
- Unmutated IgHV – 60%
- del17p – 8%
  (N=781)

**28-day cycle**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorambucil 0.5 mg/kg PO</td>
<td>on Days 1, 15 x 6 cycles (n = 118)</td>
</tr>
<tr>
<td>Obinutuzumab 1000 mg IV</td>
<td>cycle 1 Days 1, 8, 15; cycles 2-6 Day 1 + Chlorambucil 0.5 mg/kg PO on Days 1, 15 x 6 cycles (n = 333)</td>
</tr>
<tr>
<td>Rituximab 375 mg/m² IV</td>
<td>cycle 1 Day 1; 500 mg/m² cycles 2-6 Day 1 + Chlorambucil 0.5 mg/kg PO on Days 1, 15 x 6 cycles (n = 330)</td>
</tr>
</tbody>
</table>

Crossover to obinutuzumab + chlorambucil arm at progression on chlorambucil monotherapy
Obinutuzumab

CLL11 Results

ORR: 78%
CR: 22%
PFS: 26.7 mo
Improved OS

Goede, et al. NEJM; 2014
Table 2. Adverse Events of Grade 3 or Higher, Safety Population.a

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event</td>
<td>175 (73)</td>
<td>58 (50)</td>
<td>125 (56)</td>
<td>58 (50)</td>
<td>235 (70)</td>
<td>177 (55)</td>
</tr>
<tr>
<td>Infusion-related reactions</td>
<td>51 (21)</td>
<td>—</td>
<td>9 (4)</td>
<td>—</td>
<td>67 (20)</td>
<td>12 (4)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>84 (35)</td>
<td>18 (16)</td>
<td>60 (27)</td>
<td>18 (16)</td>
<td>111 (33)</td>
<td>91 (28)</td>
</tr>
<tr>
<td>Anemia</td>
<td>11 (5)</td>
<td>5 (4)</td>
<td>10 (4)</td>
<td>5 (4)</td>
<td>14 (4)</td>
<td>12 (4)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>27 (11)</td>
<td>5 (4)</td>
<td>8 (4)</td>
<td>5 (4)</td>
<td>35 (10)</td>
<td>10 (3)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>13 (5)</td>
<td>0</td>
<td>3 (1)</td>
<td>0</td>
<td>15 (4)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Infections</td>
<td>27 (11)</td>
<td>16 (14)</td>
<td>30 (13)</td>
<td>16 (14)</td>
<td>40 (12)</td>
<td>44 (14)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>8 (3)</td>
<td>4 (3)</td>
<td>11 (5)</td>
<td>4 (3)</td>
<td>13 (4)</td>
<td>17 (5)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>4 (2)</td>
<td>5 (4)</td>
<td>4 (2)</td>
<td>5 (4)</td>
<td>8 (2)</td>
<td>4 (1)</td>
</tr>
</tbody>
</table>

Goede, et al. NEJM; 2014

Table 1. Dose to Be Administered During 6 Treatment Cycles, Each of 28 days Duration, for Patients with CLL

<table>
<thead>
<tr>
<th>Day of treatment cycle</th>
<th>Dose</th>
<th>Rate of infusion (in the absence of infusion reactions/hypersensitivity during previous infusions)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cycle 1</strong> (leading doses)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>100 mg</td>
<td>Administer at 25 mg/hr over 4 hours. Do not increase the infusion rate.</td>
</tr>
<tr>
<td>Day 2</td>
<td>900 mg</td>
<td>Administer at 50 mg/hr. The rate of the infusion can be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr.</td>
</tr>
<tr>
<td>Day 8</td>
<td>1000 mg</td>
<td>If no infusion reaction occurred during the previous infusion and the final infusion rate was 100 mg/hr or faster, infusions can be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr.</td>
</tr>
<tr>
<td>Day 15</td>
<td>1000 mg</td>
<td></td>
</tr>
<tr>
<td><strong>Cycles 2–6</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>1000 mg</td>
<td></td>
</tr>
</tbody>
</table>
Ofatumumab: Complement 1 Trial

- Front-line therapy
- CLL patients w/ comorbidities
- Median age 70
- CIRS score 9
- Unmutated IgHV – 56%
- del17p – 6%  (N=447)

Randomized 1:1

28-day cycle

Chlorambucil 10 mg/m² PO on Days 1-7 x 12 cycles  
(n = 226)

Ofatumumab 1000 mg IV cycle 1 Days 1 (300 mg), 8; cycles 2-12 Day 1 
+ 
Chlorambucil 10 mg/m² PO on Days 1, 15 x 6 cycles  
(n = 221)

No crossover allowed; minimum 3 cycles w/ maximum of 12 cycles
Ofatumumab

Complement 1 Results

ORR: 82%
CR: 14%
PFS: 22.4 mo
OS: not reached

Ofatumumab
Complement 1
Results

<table>
<thead>
<tr>
<th></th>
<th>Events/patients</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chlorambucil</td>
<td>Chlorambucil plus ofatumumab</td>
</tr>
<tr>
<td>All patients</td>
<td>151/226</td>
<td>136/221</td>
</tr>
<tr>
<td>Men</td>
<td>90/140</td>
<td>65/142</td>
</tr>
<tr>
<td>Women</td>
<td>61/86</td>
<td>41/79</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>45-55</td>
<td>13/26</td>
<td>11/20</td>
</tr>
<tr>
<td>56-65</td>
<td>26/40</td>
<td>30/51</td>
</tr>
<tr>
<td>&lt;65</td>
<td>47/71</td>
<td>38/69</td>
</tr>
<tr>
<td>≥65</td>
<td>109/155</td>
<td>98/152</td>
</tr>
<tr>
<td>≥70</td>
<td>69/109</td>
<td>70/117</td>
</tr>
<tr>
<td>≥75</td>
<td>82/117</td>
<td>66/104</td>
</tr>
<tr>
<td>Binet stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>51/70</td>
<td>43/77</td>
</tr>
<tr>
<td>B</td>
<td>61/87</td>
<td>51/74</td>
</tr>
<tr>
<td>C</td>
<td>39/69</td>
<td>42/70</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 or 1</td>
<td>37/67</td>
<td>38/59</td>
</tr>
<tr>
<td>≥2</td>
<td>114/159</td>
<td>98/162</td>
</tr>
<tr>
<td>β₂-microglobulin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥3500 g/mL</td>
<td>32/48</td>
<td>33/61</td>
</tr>
<tr>
<td>&gt;3500 g/mL</td>
<td>115/169</td>
<td>101/153</td>
</tr>
<tr>
<td>Immunoglobulin heavy chain status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutated</td>
<td>65/90</td>
<td>38/87</td>
</tr>
<tr>
<td>Unmutated</td>
<td>73/115</td>
<td>87/114</td>
</tr>
<tr>
<td>Laboratory analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17p</td>
<td>11/17</td>
<td>6/10</td>
</tr>
<tr>
<td>11q</td>
<td>18/24</td>
<td>30/39</td>
</tr>
<tr>
<td>17p or 11q</td>
<td>29/41</td>
<td>36/49</td>
</tr>
<tr>
<td>6q or +12q or 13q</td>
<td>76/111</td>
<td>71/119</td>
</tr>
<tr>
<td>No aberration</td>
<td>47/64</td>
<td>33/41</td>
</tr>
<tr>
<td>B-cell ZAP70-positive</td>
<td>72/110</td>
<td>72/100</td>
</tr>
<tr>
<td>B-cell ZAP70-negative</td>
<td>73/103</td>
<td>57/108</td>
</tr>
<tr>
<td>B-cell: T-cell ratio ZAP70-positive</td>
<td>96/135</td>
<td>93/137</td>
</tr>
<tr>
<td>B-cell: T-cell ratio ZAP70-negative</td>
<td>50/78</td>
<td>36/71</td>
</tr>
<tr>
<td>B-cell and B-cell: T-cell ratio ZAP70-positive</td>
<td>55/80</td>
<td>62/81</td>
</tr>
<tr>
<td>B-cell or B-cell: T-cell ratio ZAP70-positive</td>
<td>57/85</td>
<td>41/75</td>
</tr>
<tr>
<td>B-cell and B-cell: T-cell ratio ZAP70-negative</td>
<td>33/48</td>
<td>26/52</td>
</tr>
</tbody>
</table>

Ofatumumab: PROLONG Trial

- Phase III trial
- CLL in CR/PR following 2 or 3 lines of therapy
- No prior maintenance
- 1:1 randomization
- Median age 65
- IgHV unmutated – 50%
- del17p – 2%

Ofatumumab 1000 mg IV
Cycle 1 Day 1 (300 mg) and Day 8 then Q8 wks

CD20 Antibody: Take Home Points

• For older/frail patients with favorable/normal risk cytogenetics
  – Combination w/ chlorambucil
  – Favor obinutuzumab or ofatumumab

• Role for maintenance ofatumumab in R/R disease that has reached a CR/PR

• Front-line therapy in del11q CLL/SLL for older/frail patients
Alemtuzumab

- CD52 antibody
- Still in the guidelines
- Still available

For del17p CLL/SLL

**ORR**
- Alemtuzumab: 64%
- Chlorambucil: 20%

**PFS**
- Alemtuzumab: 10.7 mo
- Chlorambucil: 2.2 mo


Table 2. Treatment Response by IRRP

<table>
<thead>
<tr>
<th>Response Category</th>
<th>Alemtuzumab (n = 149)</th>
<th>Chlorambucil (n = 148)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients %</td>
<td>No. of Patients %</td>
</tr>
<tr>
<td>Overall responses</td>
<td>124 83.2</td>
<td>82 55.4</td>
</tr>
<tr>
<td>CR</td>
<td>36 24.2</td>
<td>3 2.0</td>
</tr>
<tr>
<td>MRD-negative*</td>
<td>11 7.4</td>
<td>0 0</td>
</tr>
<tr>
<td>Partial response</td>
<td>88 59.1</td>
<td>79 53.4</td>
</tr>
<tr>
<td>Stable disease</td>
<td>9 6.0</td>
<td>42 28.4</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>5 3.4</td>
<td>18 12.2</td>
</tr>
<tr>
<td>Not assessable</td>
<td>11 7.4</td>
<td>6 4.1</td>
</tr>
</tbody>
</table>

Abbreviations: IRRP, independent response review panel; CR, complete response; MRD, minimal residual disease.

*Two MRD-CR patients were determined by the IRRP to be Rai stage 0 at study entry.

From manufacturer website
Alemtuzumab

- CLL206 Trial; n=39 w/ del17p CLL/SLL
- Alemtuzumab 30 mg three times weekly
- Methylprednisolone 1 g/m2 days 1-5 Q4 wks
- ORR – 85%; CR – 36%; PFS – 18.3 mo; OS – 23.5 mo

Pettitt, et al. JCO 2012
Chemoimmunotherapy

FCR – fludarabine / cyclophosphamide / rituximab

  - Update on CLL8 trial

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>FCR 5-year rate, %</th>
<th>FC 5-year rate, %</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients (N = 817)</td>
<td>46.8</td>
<td>25.5</td>
<td>0.59 (0.50-0.69)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years (N = 572)</td>
<td>48.3</td>
<td>25.2</td>
<td>0.57 (0.47-0.70)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>≥65 years (N = 245)</td>
<td>43.2</td>
<td>26.1</td>
<td>0.63 (0.47-0.85)</td>
<td>&lt;.003</td>
</tr>
<tr>
<td>Cyto genetic abnormalities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17p deletion (N = 51)</td>
<td>15.3</td>
<td>0.0</td>
<td>0.47 (0.25-0.90)</td>
<td>.023</td>
</tr>
<tr>
<td>11q deletion (N = 142)</td>
<td>31.4</td>
<td>11.4</td>
<td>0.47 (0.32-0.68)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Trisomy 12 (N = 61)</td>
<td>61.6</td>
<td>23.7</td>
<td>0.41 (0.26-0.81)</td>
<td>.01</td>
</tr>
<tr>
<td>Normal (N = 138)</td>
<td>42.8</td>
<td>37.6</td>
<td>0.83 (0.54-1.26)</td>
<td>.365</td>
</tr>
<tr>
<td>13q deletion (N = 224)</td>
<td>63.3</td>
<td>31.0</td>
<td>0.44 (0.31-0.62)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>IGHV mutational status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UNM (N = 392)</td>
<td>33.1</td>
<td>19.4</td>
<td>0.65 (0.52-0.82)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>MUT (N = 230)</td>
<td>66.6</td>
<td>36.2</td>
<td>0.47 (0.33-0.68)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

OS

- All patients (N = 817) | 78.7               | 66.9              | 0.68 (0.54-0.89) | .001
- Age
  - <65 years (N = 572) | 80.3               | 69.2              | 0.63 (0.47-0.84) | .002
  - ≥65 years (N = 245) | 73.9               | 61.6              | 0.81 (0.54-1.20) | .288
- Sex
  - Female (N = 210)   | 81.3               | 64.5              | 0.56 (0.34-0.93) | .003
  - Male (N = 607)     | 77.8               | 67.8              | 0.71 (0.55-0.93) | <.001
- Cyto genetic abnormalities
  - 17p deletion (N = 51) | 36.0               | 18.2              | 0.64 (0.32-1.25) | .19
  - 11q deletion (N = 142) | 85.8               | 55.1              | 0.35 (0.26-0.61) | <.001
  - Trisomy 12 (N = 61) | 91.5               | 77.4              | 0.54 (0.19-1.55) | .251
  - Normal (N = 138)   | 74.0               | 81.2              | 1.31 (0.73-2.35) | .370
  - 13q deletion (N = 224) | 87.1               | 73.1              | 0.49 (0.28-0.84) | .01

BR – bendamustine / rituximab

- Eichhorst, et al. ASH 2014
  - Update on CLL10 trial

**Select Adverse Events**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>FCR (n = 279)</th>
<th>BR (n = 278)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>84.2%</td>
<td>59.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anemia</td>
<td>13.6%</td>
<td>10.4%</td>
<td>0.20</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>21.5%</td>
<td>14.4%</td>
<td>0.03</td>
</tr>
<tr>
<td>Infection</td>
<td>39.1%</td>
<td>26.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>During therapy (tx) only</td>
<td>22.6%</td>
<td>17.3%</td>
<td>0.12</td>
</tr>
<tr>
<td>During first 5 mo after tx</td>
<td>11.8%</td>
<td>3.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>In patients &lt;65 years</td>
<td>35.2%</td>
<td>27.5%</td>
<td>0.1</td>
</tr>
<tr>
<td>In patients &gt;65 years</td>
<td>47.7%</td>
<td>20.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Secondary neoplasm*</td>
<td>6.1%</td>
<td>3.6%</td>
<td>0.244</td>
</tr>
</tbody>
</table>

* sAML/MDS: FCR (n = 6); BR (n = 1)
B-cell Receptor (BCR) Signaling

- Activated by antigens in tumor microenvironment
- CLL BCRs recognize:
  - Autoantigens
  - Microbial antigens
  - Intrinsic IgHV motifs
- BCR activation promotes CLL cell maintenance/expansion

BTK Pathway in CLL/SLL

- BTK is expressed and functional across non-T-cell hematopoietic lineages
- BTK functions downstream in a variety of receptors
  - Essential element of B cell receptor signaling
  - Chemokine-controlled migration & adhesion
  - Interactions in innate immunity Toll-like receptors,
  - Downstream of Ig FcR and IgE receptor
- Survival of B-cell malignancies requires BTK-dependent signals from BCR

ibrutinib manufacturer slide set
# BTK Inhibitors in CLL/SLL

<table>
<thead>
<tr>
<th>Drug Code</th>
<th>Drug Name</th>
<th>Investigations</th>
<th>FDA Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCI-32765</td>
<td>Ibrutinib</td>
<td>I / II / III</td>
<td>YES</td>
</tr>
<tr>
<td>ACP-196</td>
<td>Acalabrutinib</td>
<td>I / II / III</td>
<td>NO</td>
</tr>
<tr>
<td>AVL/CC-292</td>
<td>Spebrutinib</td>
<td>I</td>
<td>NO</td>
</tr>
<tr>
<td>ONO/GS-4059</td>
<td></td>
<td>I</td>
<td>NO</td>
</tr>
</tbody>
</table>
Ibrutinib: Early Trial Experience

• Phase Ib/II trial – O’brien, et al. Lancet; 2014
  – Symptomatic CLL; age >65 yrs (N=31)
  – Ibrutinib 420 mg vs 840 mg (later discontinued)
  – ORR = 71% w/ 13% CR at median f/u 22.1 mo

  – Both untreated (n=35) and relapsed/refractory (n=16)
  – High risk disease with del17p
  – PFS and OS at 2 yrs: 82% and 80%
Ibrutinib: RESONATE Trial

Randomized 1:1

- Relapsed/refractory CLL/SLL
- Median age 67
- ≥3 prior therapies – 50%
- CIRS score >6 – 38%
- del17p – 32% (N=391)

Primary endpoint = PFS

Ibrutinib 420 mg PO daily
Until progression or toxicity
(n = 195)

Ofatumumab 2000 mg IV
300 mg dose 1, then 2000 mg weekly x7
then Q4wk x 16 doses
(n = 196)

Crossover at progression
Ibrutinib 420 mg PO daily
(n = 57)
Ibrutinib: RESONATE Trial

- Met PFS endpoint
  - 12 month
  - 84% vs 19%

- ORR: 42.6% vs 4.1%
  - Plus 20% PR w/ WBC ct

Ibrutinib: RESONATE-2 Trial

  - Symptomatic CLL/SLL, previously untreated
  - Age >65; median age 73
  - Randomized 1:1; ibrutinib (420 mg) vs chlorambucil
  - ORR 86% vs 35%
  - PFS: not reached vs 18.9 months
  - OS at 2 yrs: 98% vs 85%
Ibrutinib: Take Home Points

- Front-line therapy for del17p CLL/SLL
- Front-line alternative for del11q CLL/SLL in older/frail patients
- Excellent second-line option for all subtypes
- Recent approval for consideration in all subtypes as front-line therapy
- Commitment to long-term therapy should be considered with treatment selection
PI3K Pathway in CLL/SLL

# PI3K inhibitors in CLL/SLL

<table>
<thead>
<tr>
<th>Drug code</th>
<th>Drug Name</th>
<th>PI3K isotype</th>
<th>Investigations</th>
<th>FDA Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>GS1101/CAL101</td>
<td>Idelalisib</td>
<td>δ</td>
<td>I / II / III</td>
<td>YES</td>
</tr>
<tr>
<td>IPI-145</td>
<td>Duvelisib</td>
<td>δ / γ</td>
<td>I / II / III</td>
<td>NO</td>
</tr>
<tr>
<td>TGR-1202</td>
<td></td>
<td>δ</td>
<td>I / II / III</td>
<td>NO</td>
</tr>
<tr>
<td>BKM120</td>
<td>Buparlisib</td>
<td>pan</td>
<td>I / II</td>
<td>NO</td>
</tr>
<tr>
<td>AMG 319</td>
<td></td>
<td>δ</td>
<td>I</td>
<td>NO</td>
</tr>
<tr>
<td>SAR245408</td>
<td></td>
<td>pan</td>
<td>I</td>
<td>NO</td>
</tr>
<tr>
<td>GS-9820</td>
<td>Acalisib</td>
<td>pan</td>
<td>I</td>
<td>NO</td>
</tr>
</tbody>
</table>
Idelalisib: Studies 116 and 117

Randomized 1:1

Primary Study 116

Idelalisib 150 mg BID
(N = 110)

Rituximab†
(6 mos)

Placebo BID
(N = 110)

Rituximab†
(6 mos)

Extension Study 117

Idelalisib 300 mg BID

Idelalisib 150 mg BID

Disease progression*, death, or discontinuation due to AE

• Relapsed/refractory CLL/SLL
• Median age 71
• Median CIRS – 8
• del17p – 40%
• Unmutated IgHV – 76%
(N=220)

*Patients with disease progression continued on idelalisib Extension Study 117.
†Rituximab schedule: 375 mg/m², then 500 mg/m² every 2 wks x 4, then 500 mg/m² every 4 wks x 3.
Idelalisib: Study 116

Results

Idelalisib: Take Home Points

• Relapsed/refractory CLL/SLL
  – Use in combination with rituximab

• Alternative when there are contraindications to ibrutinib in relapsed/refractory disease
Safety of Ibrutinib and Idelalisib

Ibrutinib

Dosage

- CLL: The recommended dose of ibrutinib is 420 mg PO daily, continuous and should be continued until time of progression.
- MCL: The recommended dose of ibrutinib is 560 mg PO daily, continuous and should be continued until time of progression.

Lymphocytosis

- CLL: Upon initiation of ibrutinib, transient increase in absolute lymphocyte count is expected in most patients, which does not signify disease progression. This onset of isolated lymphocytosis occurs during the first few weeks of ibrutinib therapy and may persist for several weeks on treatment.
- MCL: Upon initiation of ibrutinib, transient increase in absolute lymphocyte counts occurred in 33% of patients. The onset of isolated lymphocytosis occurs during the first few weeks of ibrutinib therapy and resolves by a median of 8 weeks.
- Grade 2 bleeding events were observed in 6% of patients on ibrutinib; the mechanism is not well understood. Consider the benefit-risk of ibrutinib in patients requiring anti-platelet or anticoagulant therapies. Clinical trials excluded subjects on concurrent warfarin. Ibrutinib should be held 3 days before and after a minor surgical procedure and 7 days before and after a major surgical procedure. Ibrutinib should not be given concomitantly with warfarin.
- New onset atrial fibrillation was reported in 6%–9%, associated with ibrutinib administration.
- Consider non-warfarin anticoagulation
- Monitor carefully
- Consider switching to alternate therapy
- Patients with recurrent atrial fibrillation that is not medically controllable should be changed to idelalisib.
- Hypertension associated with ibrutinib has been uncommonly reported as a basis for discontinuation and should be managed with anti-hypertensives as appropriate. Ibrutinib should only be discontinued for uncontrollable hypertension.

Co-administration with CYP3A inhibitors and inducers

- Avoid concomitant administration of ibrutinib/idelalisib with strong or moderate inhibitors of CYP3A.
- For strong CYP3A inhibitors used short-term (eg, antifungals and antibiotics for 7 days or less; eg, ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin) consider interrupting ibrutinib/idelalisib therapy during the duration of inhibitor use. Avoid strong CYP3A inhibitors that are needed chronically.
- If a moderate CYP3A inhibitor must be used, reduce the ibrutinib/idelalisib dose. Patients taking concomitant strong or moderate CYP3A4 inhibitors should be monitored more closely for signs of ibrutinib/idelalisib toxicity.

- Avoid concomitant use of strong CYP3A inducers (eg, carbamazepine, rifampin, phenytoin, St. John’s Wort). Consider alternative treatments with less CYP3A induction.

Idelalisib

- The recommended dose of idelalisib is 150 mg PO twice daily, per prescribing recommendations.
- Fatal and/or serious hepatotoxicity, severe diarrhea or colitis, pneumonitis, and intestinal perforation have been observed in patients treated with idelalisib.
- Hepatotoxicity: Monitor hepatic function prior to and during treatment. Interrupt (if ALT/AST > 5 x ULN [upper limit of normal]) and when resolved may resume at a reduced dose (100 mg PO twice daily).
- Diarrhea or Colitis: Monitor for the development of severe diarrhea or colitis. Interrupt until resolution and then reduce or discontinue idelalisib. Severe diarrhea and colitis can be managed with systemic or nonabsorbable steroids.
- Pneumonitis: Monitor for pulmonary symptoms and bilateral interstitial infiltrates. Discontinue idelalisib.
- Intestinal perforation: Discontinue idelalisib if intestinal perforation is suspected.
- Lymphocytosis
- CLL: Upon initiation of idelalisib, transient increase in absolute lymphocyte count is expected in most patients, which does not signify disease progression. This onset of isolated lymphocytosis occurs during the first few weeks of idelalisib therapy and may persist for several weeks on treatment.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Ibrutinib Pattern of Response

Safety of Ibrutinib and Idelalisib

**Ibrutinib**

- **Bleeding issues:**
  - Careful in patients on anticoagulation
  - Hold drug prior to surgical procedures
- **Atrial fibrillation:**
  - Reason for alternative?
- **Hypertension:**
  - Monitor/treat

**Idelalisib**

- **Toxicities:**
  - Hepatotoxicity
    - Follow LFTs
  - Diarrhea/colitis
  - Pneumonitis
  - Intestinal perforation
- **Infections:**
  - PCP prophylaxis
  - CMV reactivation

<table>
<thead>
<tr>
<th>Combined Studies 123/124/125</th>
<th>ZYDELIG (N = 664)</th>
<th>Control (N = 402)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Deaths</td>
<td>49 (7.4%)</td>
<td>14 (3.5%)</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>2.29 (1.26, 4.18)</td>
<td></td>
</tr>
</tbody>
</table>

Gilead drug letter 3/2016
Treatment Targets

## SYK Inhibitors

<table>
<thead>
<tr>
<th>Drug Code</th>
<th>Drug Name</th>
<th>Investigations</th>
<th>FDA Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>R788</td>
<td>Fostamatinib</td>
<td>I / II</td>
<td>NO</td>
</tr>
<tr>
<td>GS-9973</td>
<td>Entospletinib</td>
<td>I / II</td>
<td>NO</td>
</tr>
<tr>
<td>PRT-062070</td>
<td>Cerdulatinib</td>
<td>I</td>
<td>NO</td>
</tr>
</tbody>
</table>

## BCL-2 Targeted Agents

<table>
<thead>
<tr>
<th>Drug Code</th>
<th>Drug Name</th>
<th>Investigations</th>
<th>FDA Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>GDC-0199/ABT-199</td>
<td>Venetoclax</td>
<td>I / II</td>
<td>NO</td>
</tr>
<tr>
<td>SPC2996</td>
<td></td>
<td>I / II</td>
<td>NO</td>
</tr>
<tr>
<td>G3139</td>
<td>Oblimersen</td>
<td>I / II</td>
<td>NO</td>
</tr>
<tr>
<td>GX15-070MS</td>
<td>Obatoclax</td>
<td>I</td>
<td>NO</td>
</tr>
<tr>
<td>ABT-263</td>
<td>Navitoclax</td>
<td>I / II</td>
<td>NO</td>
</tr>
</tbody>
</table>
Thank You
Questions?