Chronic Lymphocytic Leukemia
Small Lymphocytic Lymphoma
2017 Update

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Swedish Cancer Institute
Seattle, Washington
What is CLL/SLL?
Newly developed defect in the genetic program of a single mature B-lymphocyte -

Bone marrow ——— Blood, lymph

Stages:
- Pluripotent stem cell
- Lymphoid stem cell
- Pre-B-cell
- Mature B-cell
- Activated B-cell
- Plasma cell
CLL vs SLL

- **CLL**: A blood and bone marrow based disease
  - with progressive accumulation of functionally incompetent lymphocytes in the peripheral blood, bone marrow, spleen and lymph nodes.

- **SLL**: If absolute lymphocyte count of <5000/µL at the time of diagnosis
The most prevalent type of adult leukemia

Median age of diagnosis of CLL is ~ 72 yrs, with only 10% of patients younger than 50 yrs of age

More common in men than women (2:1 ratio)

Environmental predisposition uncertain, although Vietnam veterans with Agent Orange exposure warrant “service-connected status”

Genetic predisposition present, with ~ 10% of patients having a first-generation relative with CLL
What are the clinical symptoms?

• Often none!
• Non-specific (night sweats, fever, fatigue, weight loss)
• Related to lymph node of spleen enlargement
• Related to bone marrow involvement (cytopenia)
• Infections
• Skin involvement

• High lymphocyte count does NOT cause symptoms
How do we stage CLL?

Rai Staging:

<table>
<thead>
<tr>
<th>Risk</th>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0</td>
<td>Lymphocytosis in blood or bone marrow</td>
</tr>
<tr>
<td>Intermediate</td>
<td>I</td>
<td>Lymphocytosis + enlarged lymph nodes</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>Lymphocytosis + enlarged liver or spleen with or without lymphadenopathy</td>
</tr>
<tr>
<td>High</td>
<td>III</td>
<td>Lymphocytosis + anemia (Hgb &lt;11 g/dL) with or without enlarged liver, spleen, or lymph nodes</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>Lymphocytosis + thrombocytopenia (platelet count &lt;100,000/microL) with or without anemia or enlarged liver, spleen, or lymph nodes</td>
</tr>
</tbody>
</table>
How do we stage SLL?

Ann Arbor’s staging:

I
II
III
IV

A: No general symptoms
B: General symptoms such as fever, night sweats, weight loss
Prognostic Factors

- FISH defects
  - 17p deletion
  - 11q deletion
  - 12q trisomy
  - Normal
  - 13q deletions

- Immunoglobulin heavy chain variable region ($\text{IgV}_H$)
- CD38 status
- ZAP-70 status
- High serum $\beta_2$-microglobulin and soluble CD23

Genomic aberrations found in approximately 80% of CLL
# Prognostic Factors

## Immunoglobulin Heavy-Chain Variable (IGHV) Region Gene Mutation and Surrogates by Flow Cytometry

<table>
<thead>
<tr>
<th>DNA sequencing&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Outcome Association</th>
<th>Favorable</th>
<th>Unfavorable</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGHV</td>
<td>&gt;2% mutation</td>
<td></td>
<td>≤2% mutation</td>
</tr>
<tr>
<td>Flow Cytometry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD38</td>
<td>&lt;30%</td>
<td></td>
<td>≥30%</td>
</tr>
<tr>
<td>Zap 70</td>
<td>&lt;20%</td>
<td></td>
<td>≥20%</td>
</tr>
</tbody>
</table>

## Interphase Cytogenetics (FISH)<sup>c</sup>

<table>
<thead>
<tr>
<th>Unfavorable</th>
<th>Neutral</th>
<th>Favorable</th>
</tr>
</thead>
<tbody>
<tr>
<td>del(11q)</td>
<td>Normal  +12</td>
<td>del(13q) (as a sole abnormality)</td>
</tr>
<tr>
<td>del(17p)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
B-Cell Diversity

V<sub>H</sub> Rearrangement and Mutation

<table>
<thead>
<tr>
<th>V&lt;sub&gt;H&lt;/sub&gt;</th>
<th>D</th>
<th>J&lt;sub&gt;H&lt;/sub&gt;</th>
<th>C&lt;sub&gt;μ&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/51</td>
<td>1/27</td>
<td>1/6</td>
<td></td>
</tr>
</tbody>
</table>

Somatic mutations

V<sub>H</sub> in B-cell chronic lymphocytic leukemia
What is the initial work-up for CLL patients?

- All patients at diagnosis
  - Flow cytometry to confirm CLL diagnosis

- Informative for prognostic and/or therapy determination
  - Interphase cytogenetics looking for +12, del(13q), del(17)(p13.1), and del(11)(q22.3); del(17p) and del(11q) portend for more aggressive disease
  - Unmutated VH gene status assessment (good lab)
  - ZAP-70 expression by flow cytometry is not recommended outside clinical trial

- \( \beta_2 \)-microglobulin

- No CT scan unless symptoms are present; PET scan can be helpful if Richter’s suspected

- Bone marrow biopsy and aspirate not necessary in absence of low blood counts
When to start treatment?

- No advantage to treating CLL until symptoms develop regardless of genomic features

- IWCLL 2008 criteria for treatment (in primary and relapse)
  - Enlarging, symptomatic lymph nodes (> 10 cm)
  - Enlarging, symptomatic spleen (> 6 cm below costal margin)
  - Cytopenias due to CLL (hemoglobin < 11 g/dL, platelets < 100,000 cells/µL)
  - Constitutional symptoms due to disease (fatigue, B symptoms)
  - Poorly controlled AIHA or ITP
  - Progressive lymphocytosis with an increase of more than 50 percent over a two-month period or LDT of less than six months
What are the treatment options?

**Chemotherapy**
- fludarabine
- bendamustine
- pentostatin
- cyclophosphamide
- chlorambucil
- ...

**Targeted Antibodies**
- rituximab
- ofatumumab
- obinutuzumab
- alemtuzumab
- others

**Targeted Therapies**
- ibrutinib
- Idelalisib
- ABT199
- others
Targeted Antibodies

- ADCC
- FcyRlla
- CD20 antigen
- Direct effects: Antibody binding induces antiproliferative signaling, apoptosis, and cell-growth inhibition

Complement-mediated lysis
- C1q binding
- MAC

- Ofatumumab binding site
- Rituximab, tositumomab, obinutuzumab binding site

- B-cell NHL (tumor cell)

Antibody structure
- Murine variable sequence
- Human sequence
- Chimeric antibody (rituximab)
- Human antibody (ofatumumab)

Cell membrane
- CD20

Effector cell
“Standard” Treatment

First line Young/Fit without del 17p

- Chemo + Antibodies
  - FCR (fludarabine + cyclophosphamide + rituximab)
  - BR (bendamustine + rituximab)
  - FR (fludarabine + rituximab)
  - PCR (pentostatin + cyclophosphamide + rituximab)
  - Obinutuzumab + chlorambucil
CLL10, Phase III Interim Analysis: FCR vs BR in CLL

Patients with untreated, active CLL without del(17p) and good physical fitness (CIRS ≤ 6, creatinine clearance ≥ 70 mL/min) (N = 561)

FCR
- Fludarabine 25 mg/m^3 IV Days 1-3 +
- Cyclophosphamide 250 mg/m^2 Days 1-3 +
- Rituximab 375 mg/m^2 IV Day 0, cycle 1 +
- Rituximab 500 mg/m^3 IV Day 1, cycles 2-6

BR
- Bendamustine 90 mg/m^3 IV Days 1-2 +
- Rituximab 375 mg/m^2 Day 0, cycle 1 +
- Rituximab 500 mg/m^2 IV Day 1, cycles 2-4

Primary endpoint: noninferiority of BR vs FCR for PFS HR (ΛBR/FCR) < 1.388

CLL10 FCR vs BR in CLL: Main Findings

- **Median PFS**
  - FCR: not reached
  - BR: 44.9 mos
  - \( P = .04 \)
- **2-yr OS**
  - FCR: 94.2%
  - BR: 95.8%
  - \( P = .59 \)
- **ORR rates identical, but higher CR rates observed with FCR vs BR**
- **Median observation time:** 27.9 mos

<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>.03</td>
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<tr>
<td>CR</td>
<td>40.1</td>
<td>36.3</td>
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</tr>
<tr>
<td>CRi</td>
<td>7.3</td>
<td>1.8</td>
<td></td>
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<tr>
<td>PR</td>
<td>50.4</td>
<td>59.7</td>
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<tr>
<td>ORR</td>
<td>97.8</td>
<td>97.8</td>
<td>1</td>
</tr>
</tbody>
</table>

Treatment

First line older/unfit without del 17p

• CLINICAL TRIALS

• Chemo + Antibodies
  – BR (bendamustine + rituximab)
  – Obinutuzumab + chlorambucil
  – Rituximab + chlorambucil
  – Rituximab
  – Cladribine
  – Fludarabine ± rituximab
  – Chlorambucil
Obinutuzumab

CLL11 Trial: Obinutuzumab + Chlorambucil vs Rituximab + Chlorambucil

Randomized 1:2:2

28-day cycle

Chlorambucil 0.5 mg/kg PO on Days 1, 15 x 6 cycles (n = 118)

Obinutuzumab 1000 mg IV cycle 1 on Days 1, 8, 15; cycles 2-6 on Day 1 + Chlorambucil 0.5 mg/kg PO on Days 1, 15 x 6 cycles (n = 333)

Rituximab 375 mg/m² IV cycle 1 on Day 1; 500 mg/m² cycles 2-6 on Day 1 + Chlorambucil 0.5 mg/kg PO on Days 1, 15 x 6 cycles (n = 330)

Patients who progress on chlorambucil alone allowed to crossover to obinutuzumab + chlorambucil arm

Obinutuzumab

**CLL11: Response and Toxicity**

- **Response**
  - CLB 31% ORR, 0% CR
  - CLB + rituximab 65% ORR, 7% CR \((P < .001)\)
  - CLB + obinutuzumab 78% ORR, 21% CR \((P < .001)\)

- **Toxicity**

<table>
<thead>
<tr>
<th>Grade ≥ 3, %</th>
<th>Obinutuzumab + Chlorambucil ((n = 336))</th>
<th>Rituximab + Chlorambucil ((n = 321))</th>
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<tbody>
<tr>
<td>Any</td>
<td>73</td>
<td>56</td>
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<tr>
<td>Infusion-related reaction</td>
<td>21</td>
<td>4</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>35</td>
<td>27</td>
</tr>
<tr>
<td>Anemia</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Infection</td>
<td>11</td>
<td>13</td>
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</table>

Obinutuzumab

CLL11 Trial: PFS Head-to-Head Comparison

![Graph showing the comparison between Obinutuzumab and Rituximab-chlorambucil in terms of progression-free survival (PFS). The graph indicates a stratified hazard ratio (HR) of 0.39 with a 95% confidence interval (CI) of 0.31-0.49, and a p-value (P) of <.0001.]

- Obinutuzumab-chlorambucil
- Rituximab-chlorambucil

Stratified HR: 0.39
(95% CI: 0.31-0.49;
P < .0001)

Goals of Novel Therapies

• Harness increasing understanding of biology and technology to improve therapy
• Develop “targeted” treatments selective for malignant cells and less toxic to healthy cells
• Recruit the body’s immune system to fight disease
• Help improve the effects of existing treatments in combination
• Induce longer remissions, and ultimately cure, with fewer side effects
Ibrutinib

- **RESONATE study**
- Relapsed/Refractory patients
- Ibrutinib vs. ofatumumab

- Primary endpoint: Progression-free survival
- 9.4 months of follow-up

![Graph showing progression-free survival for Ibrutinib and Ofatumumab]

**No. at Risk**

<table>
<thead>
<tr>
<th></th>
<th>Ibrutinib</th>
<th>Ofatumumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>195</td>
<td>196</td>
</tr>
<tr>
<td>3</td>
<td>183</td>
<td>161</td>
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<tr>
<td>6</td>
<td>116</td>
<td>83</td>
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<td>9</td>
<td>38</td>
<td>15</td>
</tr>
<tr>
<td>12</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>15</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Hazard ratio for progression or death, 0.22 (95% CI, 0.15–0.32) P<0.001 by log-rank test
Ibrutinib

Pattern of Response: Blood Lymphocytes vs Lymph Nodes

Ibrutinib in Refractory CLL With 11q Deletion

Images provided by Susan O’Brien, MD.
## Ibrutinib

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>391</td>
<td>0.21 (0.14–0.31)</td>
</tr>
<tr>
<td>Disease refractory to purine analogues</td>
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<tr>
<td>Yes</td>
<td>175</td>
<td>0.18 (0.10–0.32)</td>
</tr>
<tr>
<td>No</td>
<td>216</td>
<td>0.24 (0.15–0.40)</td>
</tr>
<tr>
<td>Chromosome 17p13.1 deletion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>127</td>
<td>0.25 (0.14–0.45)</td>
</tr>
<tr>
<td>No</td>
<td>264</td>
<td>0.19 (0.12–0.32)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>152</td>
<td>0.17 (0.09–0.31)</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>239</td>
<td>0.24 (0.15–0.40)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>266</td>
<td>0.22 (0.13–0.35)</td>
</tr>
<tr>
<td>Female</td>
<td>125</td>
<td>0.21 (0.11–0.40)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>351</td>
<td>0.21 (0.14–0.31)</td>
</tr>
<tr>
<td>Nonwhite</td>
<td>40</td>
<td>0.27 (0.07–0.96)</td>
</tr>
<tr>
<td>Geographic region</td>
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<tr>
<td>United States</td>
<td>192</td>
<td>0.12 (0.07–0.23)</td>
</tr>
<tr>
<td>Europe or other</td>
<td>199</td>
<td>0.34 (0.21–0.56)</td>
</tr>
<tr>
<td>Rai stage at baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0, I, or II</td>
<td>169</td>
<td>0.19 (0.10–0.37)</td>
</tr>
<tr>
<td>III or IV</td>
<td>222</td>
<td>0.22 (0.13–0.35)</td>
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<tr>
<td>ECOG score at baseline</td>
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</tr>
<tr>
<td>0</td>
<td>159</td>
<td>0.26 (0.14–0.48)</td>
</tr>
<tr>
<td>1</td>
<td>232</td>
<td>0.18 (0.11–0.30)</td>
</tr>
<tr>
<td>Bulky disease</td>
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<tr>
<td>&lt;5 cm</td>
<td>163</td>
<td>0.24 (0.13–0.44)</td>
</tr>
<tr>
<td>≥5 cm</td>
<td>225</td>
<td>0.19 (0.12–0.31)</td>
</tr>
<tr>
<td>No. of prior treatment regimens</td>
<td></td>
<td></td>
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<tr>
<td>&lt;3</td>
<td>198</td>
<td>0.19 (0.10–0.36)</td>
</tr>
<tr>
<td>≥3</td>
<td>193</td>
<td>0.21 (0.13–0.34)</td>
</tr>
<tr>
<td>Chromosome 11q22.3 deletion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>122</td>
<td>0.14 (0.06–0.29)</td>
</tr>
<tr>
<td>No</td>
<td>259</td>
<td>0.26 (0.16–0.40)</td>
</tr>
<tr>
<td>β2-microglobulin at baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤3.5 mg/liter</td>
<td>58</td>
<td>0.05 (0.01–0.39)</td>
</tr>
<tr>
<td>&gt;3.5 mg/liter</td>
<td>298</td>
<td>0.21 (0.14–0.33)</td>
</tr>
</tbody>
</table>
Ibrutinib

- **Common side effects:**
  - Thrombocytopenia
  - Neutropenia
  - Diarrhea
  - Anemia
  - Fatigue
  - musculoskeletal pain
  - upper respiratory tract infection
  - Rash
  - Nausea
  - Fever
Idelalisib

Phase III Idelalisib and Rituximab for Previously Treated Patients With CLL

Stratified by del(17p)/TP53 mutation, IGHV mutation status

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

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

*Disease progression,* death, or discontinuation due to AE

†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 and Rituximab for Previously Treated Patients With CLL: PFS

HR: 0.15
(95% CI: 0.08-0.28; P < .001)

Pts at Risk, n
Idelalisib + rituximab 110 69 44 34 30 14 6 2 0
Placebo + rituximab 110 62 30 18 13 6 1 1 0

Idelalisib

Idelalisib: Nodal and ORR

ALC and Tumor Burden Over Time

- ALC, Mean ± SEM (x 10^9/L)
- SPD (n = 51)

Change in SPD From Baseline Mean ± SEM (%)

- 0 to -80

Wks From Start of Idelalisib

81% n = 44
72% n = 39
33% n = 18
39% n = 21

Response Rate ± 95% CI

- Decrease by ≥ 50% of nodal SPD
- PR with lymphocytosis
- PR by IWCLL criteria

Idelalisib

Marked Reductions in Peripheral Lymphadenopathy With Idelalisib

Pretreatment

With Idelalisib Treatment

38-yr-old patient with refractory CLL and 5 previous therapies
Idelalisib

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Idelalisib plus Rituximab</th>
<th>Placebo plus Rituximab</th>
<th>Hazard Ratio for Disease Progression or Death (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>110</td>
<td>110</td>
<td>0.15 (0.08–0.28)</td>
</tr>
<tr>
<td>IGHV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutated</td>
<td>19</td>
<td>17</td>
<td>0.25 (0.07–0.95)</td>
</tr>
<tr>
<td>Unmutated</td>
<td>91</td>
<td>93</td>
<td>0.13 (0.06–0.27)</td>
</tr>
<tr>
<td>17p Deletion or TP53 mutation</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Either</td>
<td>46</td>
<td>50</td>
<td>0.12 (0.05–0.32)</td>
</tr>
<tr>
<td>Neither</td>
<td>64</td>
<td>60</td>
<td>0.17 (0.07–0.43)</td>
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<tr>
<td>17p Deletion</td>
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<tr>
<td>Yes</td>
<td>26</td>
<td>31</td>
<td>0.14 (0.04–0.47)</td>
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<tr>
<td>No</td>
<td>84</td>
<td>79</td>
<td>0.14 (0.07–0.31)</td>
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<tr>
<td>Sex</td>
<td></td>
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<tr>
<td>Male</td>
<td>76</td>
<td>68</td>
<td>0.10 (0.04–0.24)</td>
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<tr>
<td>Female</td>
<td>34</td>
<td>42</td>
<td>0.30 (0.11–0.78)</td>
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<tr>
<td>Age</td>
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<tr>
<td>&lt;65 yr</td>
<td>21</td>
<td>27</td>
<td>0.24 (0.07–0.77)</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>89</td>
<td>83</td>
<td>0.11 (0.05–0.26)</td>
</tr>
</tbody>
</table>
Idelalisib

• **Common side effects:**
  – Fever
  – Fatigue
  – Nausea
  – Chills
  – Diarrhea
  – Thrombocytopenia
  – Neutropenia
  – Anemia
  – Liver enzyme abnormalities
Venetoclax Monotherapy in Rel/Ref CLL and SLL

- Small molecule, orally bioavailable
- High affinity for Bcl-2

<table>
<thead>
<tr>
<th>Response, %</th>
<th>Evaluable Patients (n = 56)</th>
<th>del(17p) (n = 17)</th>
<th>Fludarabine Refractory (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>84</td>
<td>82</td>
<td>89</td>
</tr>
<tr>
<td>CR</td>
<td>23</td>
<td>12</td>
<td>22</td>
</tr>
<tr>
<td>PR</td>
<td>61</td>
<td>71</td>
<td>67</td>
</tr>
<tr>
<td>SD</td>
<td>7</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>PD</td>
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<td>--</td>
</tr>
<tr>
<td>Discontinue prior to first assessment</td>
<td>7</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>
Should New Effective Single Agents Replace Chemotherapy as Frontline Therapy in CLL?
FCR300: PFS and OS

Median Follow-up Time
All: 9.8 yrs
Alive: 11.5 yrs

Events | Total | Median
--- | --- | ---
186 | 300 | 6.5 yrs
113 | 300 | 11+ yrs
FCR300: PFS by *IGHV* Mutation Status

<table>
<thead>
<tr>
<th>Group</th>
<th>Events</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>IGHV</em>-M</td>
<td>33</td>
<td>82</td>
</tr>
<tr>
<td><em>IGHV</em>-UM</td>
<td>114</td>
<td>131</td>
</tr>
<tr>
<td>Unknown</td>
<td>39</td>
<td>87</td>
</tr>
</tbody>
</table>

*P* < .0001
Results from the International, Randomized Phase 3 Study of Ibrutinib Versus Chlorambucil in Patients 65 Years and Older with Treatment-Naïve CLL/SLL (RESONATE-2)

(N=269)
- Treatment-naïve CLL/SLL with active disease
- Age ≥65 years
- For patients 65-69 years, comorbidity that may preclude FCR
- del17p excluded
- Warfarin use excluded

**Randomize 1:1**
- Ibrutinib 420 mg once daily until PD or unacceptable toxicity
- Chlorambucil 0.5 mg/kg (max 0.8 mg/kg) days 1 and 15 of 28-day cycle up to 12 cycles

- Phase 3, open-label, multicenter, international study
- **Primary endpoint**: PFS as evaluated by IRC (2008 iwCLL criteria)
- **Secondary endpoints**: OS, ORR, hematologic improvement, safety

- In clb arm, n=43 crossed over to ibrutinib

Tedeschi et al. ASH 2015 Abstract 495
Ibrutinib Prolonged PFS Over Chlorambucil

- 88% reduction in the risk of progression or death for patients randomized to ibrutinib
- Subgroup analysis of PFS revealed benefit was observed across all sub-groups

Ibrutinib Continues to Demonstrate OS Benefit Over Chlorambucil With Longer Follow-Up (n=136) vs (n=133)

ORR in the Ibrutinib Arm

- Ibrutinib CR rates continue to improve over time: increasing from 7% at 12 months to 15% at 24 months to 18% with median follow-up of 29 months.

*Response rates with chlorambucil are the same as in the original report (Burger NEJM 2015)

What is next?
Acalabrutinib Monotherapy in Patients With Ibrutinib Intolerance: Results From the Phase 1/2 ACE-CL-001 Clinical Study

- Acalabrutinib is a highly selective, potent BTK inhibitor
- Minimal off-target effects on TEC, EGFR, or ITK signaling in vitro

<table>
<thead>
<tr>
<th>Kinase</th>
<th>Kinase Inhibition IC50 (nmol/L)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Acalabrutinib</td>
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<tr>
<td>BTK</td>
<td>5.1</td>
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<tr>
<td>TEC</td>
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<td>BMX</td>
<td>46</td>
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<td>TXK</td>
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<td>ERBB2</td>
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<tr>
<td>EGFR</td>
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<tr>
<td>JAK3</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>BLK</td>
<td>&gt;1000</td>
</tr>
</tbody>
</table>

Change in Lymphadenopathy (CT Scan)

Byrd et al. ASH 2015. Abstract 831
Phase 1b Results of a Phase 1b/2 Study of Obinutuzumab, Ibrutinib, and Venetoclax in Relapsed/Refractory CLL

Cycle = 28 days

- Obinutuzumab 1000 mg IV
- Ibrutinib 420 mg daily PO
- Venetoclax (cohort dose) mg daily PO

Response assessed (CT + BMBx)
- After Cycle 8
- 2 months beyond end Cycle 14

Jones et al. Abstract #639, ASH 2016
What about supportive care?

• Recurrent sinus or lung infections:
  – IgG levels
  – Monthly IVIG
• Antibiotic prophylaxis
  – Viral and bacterial
• Vaccination
  – Annual influenza vaccine
  – Pneumococcal vaccine every 5 years
  – Avoid all live vaccines including Zoster

• Autoimmune anemia

• Transfusion
The practice of oncology is undergoing a transformation

- Paradigm shift in Oncology
  - What cures people

- The next five years – How to get to 100%
  - “Thinking outside the box”
New Paradigm

• The immune system is the “agent” that improves outcome and **CURES** people with systemic cancer.

• Fundamental shift in our understanding of cancer.
Breaking Through Cancer's Shield

Experimental treatments indicate that for seven patients, the drugs could stop growth of the cancer without any side effects. So far, the patients have been free of the disease for up to 2 years.

Immunotherapy Cancer Drug Data Show Promise in Prolonging Lives

by Veronica Smith

Drugs designed to unleash the body's own immune system against cancer are showing promise in prolonging lives. Forms of the disease.

Researchers report progress in cancer immunotherapy

They boosted the effectiveness in melanoma patients through...
Breakthrough of the Year
Cancer Immunotherapy
T cells on the attack
Rationale for Immunotherapy

• Immune dysregulation in CLL
  • result of overexpression of checkpoint receptors by T cells and respective ligands on CLL cells

• Checkpoint inhibition may result in correction of immune dysregulation and an anti-leukemia effect
  • GVL is a powerful approach in CLL
    • Success of allogeneic HCT

van Gelder M, Bone Marrow Transplant. 2016 Dec 12
Nivolumab Combined with Ibrutinib for CLL and Richter Transformation - A Phase II Trial

Cohort 1: Relapsed CLL/SLL, or RT

- Screening (Marrow, CT/PET)
- Nivolumab 3mg/kg Q2 wks
- Nivolumab 3mg/kg Q2 wks + Ibrutinib 420 mg daily

- Response Evaluation (bone marrow and imaging)
  - After C1, C3, C6, C9, C12, then Q6 months

Jain et al. Abstract #59, ASH 2016
What about CAR-T cell therapy?

1) T Cell Collection
2) T Cell Transfection
   1. Binding
   2. Fusion
3) T Cell Adoptive Transfer
   3. Integration
4) Patient Monitoring
   a) Disease response
      – CT scans
      – Bone marrow biopsies
      – Peripheral blood flow cytometry
   b) CAR-T Cell persistence
      – Immunohistochemistry of bone marrow biopsy
      – RT-PCR and flow cytometry of blood and bone marrow aspirate
5) CAR cell membrane insertion

CD3 T Cells

1. Binding
2. Fusion
3. Integration
4. Transcription and protein expression
5. CAR cell membrane insertion

+/- Lymphodepleting conditioning
Chimeric antigen receptors

- CARs and CAR-T cells
  - Target surface molecules
  - Enables redirection of engineered T cell subsets to a specified target antigen

Turtle et al, Curr Opin Immunol, 2013
Relapsed after auto HCT

Before RICE

Before CED and CD19 CAR-T cells

Day 28 after CED and CD19 CAR-T cells
Relapsed after HCT

Before CED and CD19 CAR-T cells

Day 27 after CED and CD19 CAR-T cells
Promising Immunotherapy

Conclusions

• Several exciting new approaches
  • approved and in clinical trials

• More selective than chemotherapy Is this the beginning of the end for chemotherapy?
Take home messages

• Take advantage of the recent advancements
• Making the wise choice
• Some of the “older” treatments may still be the best option for you

• Several exciting new agents in clinical trials
  – More selective than chemotherapy but not without toxicity
  – Already second-generation PI3K and BTK inhibitors in clinical trials as well as SYK inhibitors, etc
Questions?

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