Role of Targeted Therapies in the Management of Chronic Lymphocytic Leukemia: From Clinical Data to Individualized Care

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Disclosures

• During the course of this lecture, Dr. Jacobs may mention the use of medications for both FDA-approved and non-approved indications.

• Dr. Jacobs has no relevant financial relationships to disclose.
Learning Objectives

• Review disease-risk stratification and the use of a prognostic nomogram for estimating time to treatment.

• Examine the first-line management of patients with chronic lymphocytic leukemia (CLL) to maximize adherence while minimizing associated adverse events.

• Discuss the current treatment options for patients with relapsed/refractory CLL and associated limitations.

• Explain the late-stage, clinical trial data for emerging therapies in relapsed/refractory CLL.
Essential Tests at Initial Presentation of CLL: Beyond the Basics

• Diagnostic
  – Peripheral blood-flow cytometry
  – Bone marrow biopsy
    • Conventional karyotyping

• Prognostic
  – Interphase FISH
  – IGHV mutational analysis
  – Tp53 mutational analysis
  – Beta-2 microglobulin
  – LDH

CLL = chronic lymphocytic leukemia; FISH = fluorescence in situ hybridization; IGHV = immunoglobulin heavy-chain variable (region genes); Tp53 = gene providing instructions for making tumor protein p53; LDH = lactate dehydrogenase.
Other Notable Considerations

- Direct anti-globulin test
- Quantitative immunoglobulins
- CT scan of CAP
- Infectious serology

CT = computed tomography; CAP = chest/abdomen/pelvis.
Prognostic Markers in CLL
Prognostic Markers

- Interphase cytogenetics by FISH
- IGHV mutational status
Interphase FISH Correlates With OS

 Patients surviving (%)

 OS = overall survival.

Outcome by Interphase FISH Abnormalities  
(At Diagnosis)

<table>
<thead>
<tr>
<th>Abnormality detected by FISH</th>
<th>Median Time to Treatment (months)</th>
<th>Median OS (months)</th>
<th>Percentage of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Del 17p</td>
<td>9</td>
<td>32</td>
<td>7</td>
</tr>
<tr>
<td>Del 11q</td>
<td>13</td>
<td>79</td>
<td>18</td>
</tr>
<tr>
<td>Trisomy 12q</td>
<td>33</td>
<td>114</td>
<td>16</td>
</tr>
<tr>
<td>Del 13q</td>
<td>92</td>
<td>133</td>
<td>55</td>
</tr>
<tr>
<td>Normal</td>
<td>49</td>
<td>111</td>
<td>18</td>
</tr>
</tbody>
</table>

Prognostic Markers

• Interphase cytogenetics by FISH

• IGHV mutational status
Significance of IGHV

• Mutational status of IGHV predicts clinical outcome in CLL.

• Mutated IGHV is defined as <98% sequence homology to established germline sequence.

• Unmutated IGHV predicts earlier therapy, poorer response, inferior survival, and risk of transformation.

• IGHV correlates with CD38 and ZAP70+ disease.

IGHV Mutational Status Predicts Survival


<table>
<thead>
<tr>
<th></th>
<th>Patients N = 84</th>
<th>Median Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutated</td>
<td>46 (54.8)</td>
<td>293</td>
</tr>
<tr>
<td>Unmutated</td>
<td>38 (45.2)</td>
<td>117</td>
</tr>
</tbody>
</table>

\[P=0.001\]
Prognostic Factors in CLL: Summary

• Interphase-FISH cytogenetic analysis is standard of care at diagnosis and RELAPSE.
  – Chromosomal abnormalities may change with time.
  – Repeat FISH and cytogenetics prior to starting the next therapy to assess for clonal evolution.

• IGHV status does not change with time.

• CD38 and ZAP70 correlate with IGHV.
Timing of Therapy
## Early Treatment Does Not Improve Survival

<table>
<thead>
<tr>
<th>Start Year</th>
<th>Study Name</th>
<th>Treatment</th>
<th>Death/Patients</th>
<th>Immediate Deaths</th>
<th>Ratio of Annual Death Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>1976</td>
<td>CALGB</td>
<td>Clb</td>
<td>7/22</td>
<td>9/25</td>
<td>-0.5</td>
</tr>
<tr>
<td>1978</td>
<td>MRC-CLL-1</td>
<td>Clb</td>
<td>31/37</td>
<td>32/41</td>
<td>3.7</td>
</tr>
<tr>
<td>1980</td>
<td>FRE-CLL-80</td>
<td>Clb</td>
<td>175/300</td>
<td>169/307</td>
<td>10.1</td>
</tr>
<tr>
<td>1984</td>
<td>MRC-CLL-2</td>
<td>Clb</td>
<td>76/121</td>
<td>73/118</td>
<td>5.2</td>
</tr>
<tr>
<td>1985</td>
<td>FRE-CLL-85</td>
<td>Clb+P</td>
<td>122/457</td>
<td>126/462</td>
<td>-2.0</td>
</tr>
<tr>
<td>1988</td>
<td>PETHEMA</td>
<td>Clb+P</td>
<td>21/77</td>
<td>21/81</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>432/1014 (42.6%)</strong></td>
<td><strong>430/1034 (41.6%)</strong></td>
<td><strong>16.9</strong></td>
<td><strong>212.3</strong></td>
<td></td>
</tr>
</tbody>
</table>

- 99% or ← 95% confidence intervals

Heterogeneity between 6 trials: $\chi^2_5 = 1.7; P>0.1; NS$

Clb = chlorambucil; P = prednisolone; Obs = observed; Exp = expected; NS = not statistically significant.

Indications for Initiating Therapy

Objective laboratory/radiographic findings

- Worsening anemia and/or thrombocytopenia
  - Hemoglobin <11g/dL
  - Platelets <100,000/uL
- Spleen ≥6cm below the left costal margin
- Lymph nodes ≥10cm

Indications for Initiating Therapy (Continued)

Constitutional symptoms

- Unintentional weight loss of ≥10% within the previous 6 months
- Significant fatigue (ECOG PS 2 or worse)
- Fevers >100.5°F for ≥2 weeks without other evidence of infection
- Night sweats for >1 month without evidence of infection

ECOG = Eastern Cooperative Oncology Group.
Review of Standard and Novel Front-Line Strategies
Young, Healthy Patient

(Age ≤65 Years, Non-del 17p/Tp53 Mutated)
FC vs FCR in GCLLSG-8

<table>
<thead>
<tr>
<th></th>
<th>FC (n = 409)</th>
<th>FCR (n = 408)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N = 817</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td>80</td>
<td>90&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>CR</strong></td>
<td>22</td>
<td>44&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>3-year PFS</strong></td>
<td>45</td>
<td>65&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>3-year OS</strong></td>
<td>83</td>
<td>87&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

*<sup>a</sup>P<0.0001; <sup>b</sup>P=0.012

FC = fludarabine + cyclophosphamide; FCR = FC + rituximab; ORR = overall response rate; CR = complete remission; PFS = progression-free survival.

## FCR vs BR—CLL-10 GCLLSG Trial

<table>
<thead>
<tr>
<th></th>
<th>FCR n = 282</th>
<th>BR n = 279</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (%)</td>
<td>98</td>
<td>98</td>
<td>NS</td>
</tr>
<tr>
<td>CR (%)</td>
<td>41</td>
<td>32</td>
<td>0.026</td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>54</td>
<td>43</td>
<td>0.001</td>
</tr>
<tr>
<td>OS at 3 years (%)</td>
<td>91</td>
<td>92</td>
<td>NS</td>
</tr>
<tr>
<td>Severe neutropenia (%)</td>
<td>88</td>
<td>68</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severe infections (%)</td>
<td>40</td>
<td>25</td>
<td>0.001</td>
</tr>
<tr>
<td>TRM (%)</td>
<td>4</td>
<td>2</td>
<td>——</td>
</tr>
</tbody>
</table>

**BR** = bendamustine + rituximab; **TRM** = treatment-related mortality.

CLL10 Trial: Minimal Residual Disease

MRD-negative patients (%)

Interim PB: FCR vs. BR
- FCR: P=0.023
- BR: P=0.024

Final PB: FCR vs. BR
- FCR: P=0.024
- BR: P<0.001

Final BM: FCR vs. BR
- FCR: P<0.001
- BR: P=0.024

No. of patients
- Interim PB: 72/180 vs. 44/156
- Final PB: 137/185 vs. 107/170
- Final BM: 75/129 vs. 31/98

MRD = minimal residual disease; PB = peripheral blood; BM = bone marrow.

FCR: A Possible Cure for CLL?

- Median PFS was not reached at 12.8 years in the IGHV-mutated group.
- Approximately 50% of IGHV-mutated patients achieved MRD negativity.
- No relapses have been seen beyond 10 years in IGHV-mutated patients.
- FCR vs ibrutinib as preferred front-line therapy?

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>PFS n</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGHV mutated</td>
<td>88</td>
<td>49</td>
</tr>
<tr>
<td>IGHV unmutated</td>
<td>126</td>
<td>12</td>
</tr>
</tbody>
</table>

\[P=0.0001\]

Elderly Patients

(Age >65 Years)
Chemotherapy Options in Elderly Populations

- Avoid fludarabine-based regimens
- Bendamustine + rituximab
  - Slightly higher toxicity rate but feasible in this population

*All patients in the intent-to-treat group.

PD = progression of disease.

Obinutuzumab Plus Chlorambucil
(CLLE-11 Trial)

- Obinutuzumab is an engineered anti-CD20 monoclonal antibody.
- It is well tolerated in patients with co-morbidities and median age of 73.
- Improved PFS when compared with R + Clb and Clb alone

G-Clb = obinutuzumab + chlorambucil; R-Clb = rituximab + chlorambucil.
Obinutuzumab Plus Chlorambucil

![Graph showing survival probability over months for Obinutuzumab Plus Chlorambucil.]

Stratified HR = 0.39
95% CI: 0.31 – 0.49
*P* < 0.001

- **G-Clb**
- **R-Clb**

**Probability of PFS**

**Months**

15.2
26.7

HR = hazard ratio; CI = confidence interval.

Ibrutinib as Front-Line Therapy in CLL
(All Ages)
Targeting Kinases in CLL

BTK = Bruton’s tyrosine kinase; PI3K = phosphatidylinositol-4,5-bisphosphate 3-kinase; PIP3 = phosphatidylinositol—3,4,5-trisphosphate; DAG = diacylglycerol; PKC = protein kinase C; GSK = glycogen synthase kinase; NFAT = nuclear receptor of activated T cells.

Ibrutinib

• Highly potent BTK inhibition at IC50 = 0.5 nM
• Ibrutinib is administered orally with once-daily dosing, resulting in 24-hour target inhibition.
• No cytotoxic effect on T cells or NK cells
• It promotes apoptosis and inhibits migration and adhesion in CLL cells.

NK = natural killer.
Ibrutinib PFS in High-Risk Disease

- **Del(17p)**: 48%
- **Del(11q)**: 74%
- **No del(17p) or del(11q)**: 50%

**Ibrutinib vs Chlorambucil (Resonate-2)**

- Ibrutinib is superior to chlorambucil in patients older than 65 years of age with previously untreated CLL.

  - FDA approval on 3/4/16 for all untreated CLL patients

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**Graph:**

- **Ibrutinib** and **Chlorambucil** PFS (%)

- **Median PFS (months):**
  - Chlorambucil: 18.9
  - Ibrutinib: NR

- **HR (95% CI):** 0.16 (0.09–0.28)

- **P = 0.001**

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**References:**

CLL or SLL stage II-IV

**Treatment?**

- **No indication** → Observe

- **Indication present**
  - **Elderly/fit (>65 years)** →
    - Del17p or TP53 mutation (any age) → Ibrutinib
    - Elderly/fit (>65 years)
      - Consider FCR (preferred for IGHV mutated)
      - Ibrutinib
  - **Elderly + comorbidities** →
    - Ibrutinib (preferred)
    - Obinutuzumab + chlorambucil
  - **Young/fit (<65 years)** →
    - Ibrutinib

*SLL = small lymphocytic lymphoma.*
Novel Treatment of Patients With Relapsed Disease

Kinase Inhibitors

**Median PFS (months)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ofatumumab</td>
<td>8.1</td>
</tr>
<tr>
<td>Ibrutinib</td>
<td>NR&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**HR<sup>b</sup> (95% CI)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ofatumumab</td>
<td>0.22 (0.15–0.32)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Not reached at median follow-up of 9.4 months;<sup>b</sup>HR for progression or death.

**P-values:**

- **P=0.001** by log-rank test

**No. at risk**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibrutinib</td>
<td>195 183 116 38 7</td>
</tr>
<tr>
<td>Ofatumumab</td>
<td>196 161 83 15 1 0</td>
</tr>
</tbody>
</table>

Pattern of Response: Blood Lymphocytes vs Lymph Nodes

Median change from baseline in ALC (%)

Median change from baseline in SPD (%)

ALC = absolute lymphocyte count; SPD = sum of the products of perpendicular diameters of lymph nodes.

Ibrutinib—Long-Term Follow-up

Ibrutinib Discontinuation and Richter’s Transformation (RT)

Cumulative incidence of discontinuation of ibrutinib therapy (%)

No. at risk: 308 261 169 135 86 58 34 10 0

Months

Issues With Ibrutinib

- Disrupts collagen-induced platelet aggregation
- vWF binding

\[ vWF = \text{von Willebrand factor.} \]

Management of Bleeding Issues With Ibrutinib

- Avoid aspirin, NSAIDs, fish oil
- Avoid warfarin
- Can consider alternate anti-coagulants with caution

**NSAID** = non-steroidal antiinflammatory drug.

**Ibrutinib (Imbruvica®)** prescribing information. Available at www.imbruvica.com
Other Issues With Ibrutinib

• Diarrhea
• Fatigue
• Upper respiratory tract infection
• Rash
• Nausea
• Arthralgia
• Atrial fibrillation
• Cytopenias

• Treatment discontinuation due to AEs = 6%
• No evidence of cumulative toxicity or long-term safety

AEs = adverse events.
Ibrutinib (Imbruvica®) prescribing information. Available at www.imbruvica.com
Ibrutinib Has Inferior PFS in Patients With Complex Karyotype

Event-free survival (%)

Time (months)

Neither del(17p) nor del(11q)  del(11q)  del(17p)

P=0.02

P<0.0001

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Event-free</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neither del(17p) nor del(11p)</td>
<td>24</td>
<td>18 (75.0%)</td>
</tr>
<tr>
<td>Del(11q)</td>
<td>28</td>
<td>22 (78.6%)</td>
</tr>
<tr>
<td>Del(17p)</td>
<td>34</td>
<td>17 (50.0%)</td>
</tr>
</tbody>
</table>

No complex karyotype  Complex karyotype

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Event-free</th>
</tr>
</thead>
<tbody>
<tr>
<td>No complex karyotype</td>
<td>35</td>
<td>28 (80.0%)</td>
</tr>
<tr>
<td>Complex karyotype</td>
<td>21</td>
<td>7 (33.3%)</td>
</tr>
</tbody>
</table>

Ibrutinib—Conclusion

• Now approved front-line therapy for all CLL patients
  – May not be the best front-line choice for patients aged <65 years
• Promising responses ~90%
• Low incidence of complete responses, ie, 2–7%
• Response deepens over time.
  – Median time to response: 4 months
  – Median time to best response: 12 months
• Del17p responds, but PFS is shorter.
• Use full dose, and avoid disruptions.
• Avoid using ibrutinib with anticoagulation.
• Follow stopping rules prior to surgical interventions.
Idelalisib

- Selective PI3-K delta inhibitor
- Single-agent response rate of 72%
- 39% PR and 33% PR+L

PR = partial response; PR+L = partial response with treatment-induced lymphocytosis.
Idelalisib in Relapsed/Refractory CLL

Median PFS: 15.8 months
Median OS: not reached

Phase III Idelalisib and Rituximab for Previously Treated Patients With CLL

<table>
<thead>
<tr>
<th>Study Arm</th>
<th>N</th>
<th>Median PFS (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idelalisib + R</td>
<td>110</td>
<td>19</td>
</tr>
<tr>
<td>Placebo + R</td>
<td>110</td>
<td>7</td>
</tr>
</tbody>
</table>

Relapsed CLL: Idelalisib + Rituximab

Idelalisib + rituximab
(n = 102)

Placebo + rituximab
(n = 101)

Mut = mutation.
Del(17p)/TP53 mutation (either)

**Idelalisib + R**

**Placebo + R**

IGHV unmutated

**Idelalisib + R**

**Placebo + R**

<table>
<thead>
<tr>
<th>Study Arm</th>
<th>N</th>
<th>Median OS (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idelalisib + R</td>
<td>46</td>
<td>&gt;18</td>
</tr>
<tr>
<td>Placebo + R</td>
<td>49</td>
<td>14.8</td>
</tr>
</tbody>
</table>

*P=0.001*

<table>
<thead>
<tr>
<th>Study Arm</th>
<th>N</th>
<th>Median OS (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idelalisib + R</td>
<td>91</td>
<td>&gt;19</td>
</tr>
<tr>
<td>Placebo + R</td>
<td>93</td>
<td>18.1</td>
</tr>
</tbody>
</table>

*P=0.0003*

Issues with Idelalisib

• Pneumonitis
  – Distinguish from infectious issues
  – Leading cause of discontinuation

• Diarrhea
  – Early onset
  – Late onset
  – Colitis—secondary to T-cell activation

• Transaminitis
# How to Choose Between Ibrutinib and Idelalisib

<table>
<thead>
<tr>
<th>Ibrutinib</th>
<th>Idelalisib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients allergic to rituximab</td>
<td>Patients on anti-coagulation</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>Liver problems</td>
<td>Patients on concurrent azoles (CYP3A Inhibitors)</td>
</tr>
<tr>
<td>Lung problems</td>
<td></td>
</tr>
</tbody>
</table>
• Overall response rate
  – Idelalisib after ibrutinib: 50%
  – Ibrutinib after idelalisib: 77%

• PFS
  – Alternate KI: not reached
    • Median follow-up of 5 months
  – Non-kinase inhibitor: 7 months

KI = kinase inhibitor; Ibr = ibrutinib; Ide = idelalisib.
Kinase inhibitors are effective in patients with untreated and relapsed disease.

Kinase inhibitors are effective in patients who otherwise would have limited therapeutic options.

- This includes patients who have progressed on kinase inhibitors.

Kinase inhibitors are effective in patients with conventional high-risk features.
Relapsed High Risk Patients
(All ages, Del 17p/Tp53 Mutated)
Bcl-2 Pathway

Idelalisib

BCR = B-cell receptor; IgL = immunoglobulin light chain; IgH = immunoglobulin heavy chain; Bcl = B-cell lymphoma; CARD11 = caspase recruiting domain-11; IKKa = inhibitor of NF-κB kinase; MALT1 = mucosa-associated lymphoid tissue translocation protein 1; MAPK = mitogen-activated protein kinase; MAPKK = MAPK kinase; Mcl-1 = myeloid cell leukemia differentiation protein-1; NfkB = nuclear factor κB; P = phosphorylation; PKCb = protein kinase C beta; SFK = SRC family kinase; SYK = spleen tyrosine kinase; Y = tyrosine.
Venetoclax (ABT-199)

- Highly selective inhibitor of Bcl-2
- Bcl-2 is central to the survival of CLL cells.
  - Inhibition triggers apoptosis.
- First in human, phase I dose-escalation study of daily oral venetoclax with expansion cohort
- Relapsed/refractory population
- 89% were considered high risk.

Venetoclax—Tumor Lysis Syndrome (TLS)

- First three patients received 200mg as the initial dose.
  - All three developed tumor lysis.
- Stepwise ramp-up dosing was developed in response.
- Amendment to protocol included TLS prophylaxis and inpatient observation for D1 and D8 for all patients.
- Patients with bulky disease required inpatient observation for all dose escalations.

**Dose-escalation cohort**

<table>
<thead>
<tr>
<th>Day -7</th>
<th>Wk 1</th>
<th>Wk 2</th>
<th>Wk 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mg</td>
<td>50 mg</td>
<td>Step-up dose</td>
<td>Target group dose</td>
</tr>
</tbody>
</table>

**Expansion cohort**

<table>
<thead>
<tr>
<th>Wk 1</th>
<th>Wk 2</th>
<th>Wk 3</th>
<th>Wk 4</th>
<th>Wk 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg</td>
<td>50 mg</td>
<td>100 mg</td>
<td>200 mg</td>
<td>400 mg</td>
</tr>
</tbody>
</table>

## Venetoclax—Dose-Limiting Toxicities

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>TLS n (%)</th>
<th>Neutropenia n (%)</th>
<th>Muscle Spasms n (%)</th>
<th>Vomiting n (%)</th>
<th>Thrombocytopenia n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>200&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3 (100)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>150</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>200</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
</tr>
<tr>
<td>300</td>
<td>1 (14)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>400</td>
<td>0</td>
<td>0</td>
<td>1 (14)</td>
<td>1(14)</td>
<td>1 (14)</td>
</tr>
<tr>
<td>600</td>
<td>0</td>
<td>1(7)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>800</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1200</td>
<td>1 (20)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup>Initial cohort prior to protocol amendment instituting dose ramp up; <sup>b</sup>sudden death.

Overall response rate was 79% (n = 116).
Complete remissions occurred in 20%.
Minimal residual disease negativity was achieved in 5%.
Overall response rate did not vary on the basis of the number of previous therapies or other usual risk factors.
Venetoclax (ABT-199) — Response (Continued)

- Median duration of follow-up was 17 months.
- 15-month PFS was 69% in the 400mg group.
- 51% of patients remain on treatment at the time of publication.
- Richter’s transformation occurred in 16% (n = 18).
- 2-year overall survival was 84%.

Patients with 17p deletion had:

- Overall response rate: 71%
- Complete response rate: 16%
- Approved by the FDA for second line therapy in patients with 17p deletion on 4/11/16

Emerging Data on New Targeted Therapies
Acalabrutinib (ACP-196)

• More selective, second-generation, irreversible BTK inhibitor
• Designed to improve on the safety and efficacy of first-generation BTK inhibitors.
• Ibrutinib irreversibly inhibits alternative kinase targets in addition to BTK.
  – EGFR, TEC, ITK, TXK
  – Responsible for rash, diarrhea, bleeding, afib.

EGFR = epidermal growth factor receptor; TEC = tyrosine kinase expressed in hepatocellular carcinoma; ITK= interleukin-2-inducible T-cell kinase; TXK = T-cell X chromosome kinase; afib = atrial fibrillation.

## Adverse Events With Acalabrutinib

<table>
<thead>
<tr>
<th>Condition</th>
<th>All Grades (%)</th>
<th>Grades 1–2 (%)</th>
<th>Grades 3–4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>43</td>
<td>43</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>39</td>
<td>38</td>
<td>2</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>23</td>
<td>20</td>
<td>3</td>
</tr>
<tr>
<td>URI</td>
<td>23</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>21</td>
<td>18</td>
<td>3</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>21</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>20</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>Contusion/petechiae</td>
<td>34</td>
<td>34</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>16</td>
<td>15</td>
<td>2</td>
</tr>
</tbody>
</table>

URI = upper respiratory infection.
Acalabrutinib (ACP-196)—BTK Occupancy

- Low rates of adverse events allowed safe administration of twice-daily dosing.
- Full target coverage may reduce drug resistance.

**BTK occupancy, all cohorts**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg QD</td>
<td>100%</td>
<td>89%</td>
</tr>
<tr>
<td>175 mg QD</td>
<td>87%</td>
<td>99%</td>
</tr>
<tr>
<td>250 mg QD</td>
<td>92%</td>
<td>100%</td>
</tr>
<tr>
<td>400 mg QD</td>
<td>95%</td>
<td>100%</td>
</tr>
<tr>
<td>100 mg BID</td>
<td>99%</td>
<td>99%</td>
</tr>
</tbody>
</table>

**BTK occupancy, 100 mg, twice-daily cohort**

<table>
<thead>
<tr>
<th>Time of assessment</th>
<th>BTK occupancy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1, 4 hr after dosing</td>
<td>97%</td>
</tr>
<tr>
<td>Day 2 before dosing</td>
<td>95%</td>
</tr>
<tr>
<td>Day 8 before dosing</td>
<td>97%</td>
</tr>
<tr>
<td>Day 8, 4 hr after dosing</td>
<td>99%</td>
</tr>
<tr>
<td>Day 28 before dosing</td>
<td>97%</td>
</tr>
<tr>
<td>Day 28, 4 hr after dosing</td>
<td>99%</td>
</tr>
</tbody>
</table>

QD = once daily; BID = twice daily.

Acalabrutinib (ACP-196)—Change in ALC and SPD

- Median of three previous therapies for CLL
- 31% had chromosome 17p deletion.
- 75% had unmutated immunoglobulin heavy-chain variable genes.

- Median follow-up of 14.3 months
- Overall response rate was 95%.
- No cases of Richter’s transformation
- Only one case of CLL progression has occurred.

Targeting Kinases in CLL

Entospletinib (GS-9973)

- Oral, selective inhibitor of spleen tyrosine kinase (Syk)
  - Syk is a cytoplasmic protein that is predominantly expressed in cells of hematopoietic lineage.
  - Syk signaling elicits a range of diverse biologic functions, including cellular development, function, proliferation, differentiation, and adhesion.

- Multicenter phase II
  - 41 patients, relapsed/refractory CLL

Entospletinib (GS-9973)—Response

- Overall response rate: 61%
- Nodal response: 7.3%
- No complete responses
- Only one patient with refractory disease (2.4%)
- No difference in ORR between subgroups
- Median follow-up of 7.7 months

**Table: Objective Response Rate with 95% CI**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No.</th>
<th>Objective Response Rate with 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>41</td>
<td>0.61 (0.45-0.76)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>28</td>
<td>0.68 (0.48-0.84)</td>
</tr>
<tr>
<td>Female</td>
<td>13</td>
<td>0.46 (0.19-0.75)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>7</td>
<td>0.57 (0.18-0.90)</td>
</tr>
<tr>
<td>≥65</td>
<td>34</td>
<td>0.62 (0.44-0.78)</td>
</tr>
<tr>
<td>No. of Prior Therapies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;4</td>
<td>28</td>
<td>0.61 (0.41-0.78)</td>
</tr>
<tr>
<td>≥4</td>
<td>13</td>
<td>0.62 (0.32-0.86)</td>
</tr>
<tr>
<td>IGHV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutated</td>
<td>8</td>
<td>0.63 (0.24-0.91)</td>
</tr>
<tr>
<td>Unmutated</td>
<td>31</td>
<td>0.61 (0.42-0.78)</td>
</tr>
<tr>
<td>17p Del or TP53 Mutation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Either</td>
<td>10</td>
<td>0.40 (0.12-0.74)</td>
</tr>
<tr>
<td>Neither</td>
<td>29</td>
<td>0.69 (0.49-0.85)</td>
</tr>
</tbody>
</table>

Entospletinib (GS-9973)—PFS and DoR

- Median PFS was 13.8 months.
- Median duration of response has not been reached.

DoR = duration of response.

Oltlertuzumab (TRU-016)

- Novel humanized anti CD-37 protein
- CD-37 is involved in the regulation of B-Cell function
  - Present in high levels of B-cell leukemias and lymphomas
- Phase I dose escalation study with expansion cohort
- Administered weekly x 8 weeks, followed by monthly
- Patients with relapsed/refractory CLL

Otlertuzumab (TRU-016)—Response

- Median number of prior therapies: 4 in dose-escalation group and 1 in expansion group
- 25 patients (30%) had deletion 17p.
- Lymphocyte reduction of ≥50% was observed in 76% of patients.
- Lymph-node reduction of ≥50% was observed in 20% of patients.

Chimeric Antigen Receptor-Modified T Cells

- Lentiviral vector expressing a chimeric antigen receptor with specificity for the B-cell antigen CD19
- Coupled with CD137 and CD3-zeta (costimulatory receptors in T Cells)
- Transduced into autologous T cells and reinfused

Chimeric Antigen Receptor-Modified T Cells
(Contrast-Enhanced CT Scans)

Axial

Coronal

Before therapy

1 month of treatment

3 months of treatment

Pembrolizumab

- MC1485 trial: phase II trial in relapsed/refractory CLL
- 16 patients (5 with Richter’s transformation)
- 5 patients had progressed on ibrutinib.
- 4/5 patients with Richter’s transformation had a response.
  - 1 complete response
  - Immature PFS data
- 2 non-Richter’s patients had stable disease and continued on therapy at the last follow-up.

Summary

• Early results with kinase inhibitors are extremely promising.
• Similar agents are also in clinical development.
  – Monoclonal antibodies
    • Ublituximab (CD20)
  – PI3K inhibitors
    • TGR 1202
    • Duvelisib/IPI145
• Novel combinations are being tested.
  – Obinutuzumab + venetoclax (CLL-14)
  – Bendamustine + rituximab + (venetoclax/ibrutinib/idelalisib)
• Cost and prescription coverage and long-term side effects may be issues, especially with combinations.
Case Studies
Case 1—Cal

• Cal is a 77-year-old male with 13q deleted, IGHV-unmutated CLL, who presents for follow-up for his CLL.
  – He also has CAD, hypertension, mild CHF, and hyperlipidemia.

• He was previously treated with FCR 6-years ago and achieved a complete remission that lasted for 4 years. He was followed with watchful waiting after his relapse until now when he started having progressive fatigue, lymphadenopathy, and splenomegaly.

• His lab evaluation reveals:
  – WBC count: 105,000 cells/µL
  – Hemoglobin: 10.5 mg/dL
  – Platelet count: 96,000 cells/µL

CAD = coronary artery disease; CHF = congestive heart failure; WBC = white blood cell.
Case 1—Question

What is the best choice of therapy for Cal?

A. Chlorambucil
B. Fludarabine + rituximab
C. Fludarabine + cyclophosphamide + rituximab
D. Bendamustine + rituximab
E. Chlorambucil + obinutuzumab
F. Chlorambucil + ofatumumab
G. Idelalisib + rituximab
H. Ibrutinib
Case 1—Question

What is the best choice of therapy for Cal?

A. Chlorambucil
B. Fludarabine + rituximab
C. Fludarabine + cyclophosphamide + rituximab
D. Bendamustine + rituximab
E. Chlorambucil + obinutuzumab
F. Chlorambucil + ofatumumab
G. Idelalisib + rituximab
H. Ibrutinib
Case 2—Fred

- Fred is a 57-year-old male who was diagnosed with del17p, IGHV-unmutated CLL 6 months ago.
- He now presents with progressive fatigue, lymphadenopathy in the axillary and inguinal regions, and palpable splenomegaly of 7cm below the costal margin.
- His only significant past medical history is for hypertension, for which he takes hydrochlorothiazide.
- His lab evaluation reads:
  - WBC count: 88,000 cells/µL
  - Hemoglobin: 9.8 mg/dL
  - Platelet count: 102,000 cells/µL
Case 2—Question 1

- You decide to start Fred on ibrutinib.
- Ibrutinib places Fred at increased risk for all of the following EXCEPT ____?

A. Diarrhea
B. Atrial fibrillation
C. Bruising
D. Bleeding
E. Colitis
F. Nausea
G. Rash
Case 2—Question 1

• You decide to start the patient on ibrutinib.
• Ibrutinib places this patient at increased risk for all of the following EXCEPT ____?

A. Diarrhea
B. Atrial fibrillation
C. Bruising
D. Bleeding
E. Colitis
F. Nausea
G. Rash
Questions and Answers