Advances in Front-Line Treatment of CLL: Is Chemoimmunotherapy Obsolete?

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Faculty Disclosure

• Charlene Kabel declares no existence of a financial interest in any amount related to the content of this activity.

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Learning Objectives

At the conclusion of this activity, participants should be better able to:

1. Compare and contrast the recommended front-line regimens for the treatment of chronic lymphocytic leukemia (CLL)
2. Recognize patient-specific characteristics in the selection of an appropriate front-line treatment regimen for CLL
3. Identify upcoming clinical trials and the potential impact on selection of front-line treatment

Background

• CLL originates in B-lymphocytes
• Most common adult leukemia in Western countries
  • 4.1 new cases per 100,000 people per year in US
  • An estimated 15,000 new cases with 4,500 deaths per year
• Risk factors:
  • Elderly
  • Men
  • First degree relative
• Indolent disease
  • Median overall survival = 10 years

Pathophysiology

- Proliferation and accumulation of mature, CD5+ B-cells
- Blood, bone marrow, lymph nodes, and spleen

<table>
<thead>
<tr>
<th>Prognostic Marker</th>
<th>Frequency at Diagnosis</th>
<th>Overall Survival (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deletion13q (del13q)</td>
<td>55%</td>
<td>15</td>
</tr>
<tr>
<td>Deletion11q (del11q)</td>
<td>25%</td>
<td>6</td>
</tr>
<tr>
<td>Trisomy 12</td>
<td>10-20%</td>
<td>7.5</td>
</tr>
<tr>
<td>Deletion17p (del17p)</td>
<td>5-8%</td>
<td>4</td>
</tr>
<tr>
<td>Unmutated-Immunoglobulin heavy-chain variable region</td>
<td>40%</td>
<td>3.6</td>
</tr>
<tr>
<td>Mutated-Immunoglobulin heavy-chain variable region</td>
<td>60%</td>
<td>&gt;15</td>
</tr>
</tbody>
</table>

- Microenvironment
  - Chemokines, cytokines, and angiogenic factors promote survival of CLL cells

Diagnosis

- ≥ 5000 B-lymphocytes/µL in peripheral blood for ≥ 3 months per flow cytometry
- Immunophenotyping to assess surface antigens:

<table>
<thead>
<tr>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD5</td>
<td>Cyclin D1</td>
</tr>
<tr>
<td>CD19</td>
<td>CD200</td>
</tr>
<tr>
<td>CD20</td>
<td>CD10</td>
</tr>
<tr>
<td>CD23</td>
<td></td>
</tr>
</tbody>
</table>

- Bone marrow and lymph node biopsies are not required for diagnosis
Indications for Treatment

- Cytopenia
- Organomegaly
- Progressive lymphocytosis
- Lymphadenopathy
- Autoimmune process refractory to steroids
- Constitutional symptoms (B-symptoms)


Patient Case

- MT is a 62 year old male recently diagnosed with CLL (del13q, UM-IgHV). His past medical history includes recurrent urinary tract infections, hypertension, controlled atrial fibrillation on anticoagulation, and migraines. He recently developed intolerable night sweats and has palpable cervical lymph nodes requiring treatment for his CLL.

- What FDA approved front-line treatment is best suited for MT?
Guideline Recommendations

- Comorbidities
- Age
- Deletion (17p)

- Cumulative Illness Ratings Index (CIRS)
  - Non-standardized tool to assess fitness for therapy
  - Score ≥ 6 = less fit


FCR: CLL8 Study

**Design:** Prospective, phase III, multicenter, randomized, open-label

**Inclusion Criteria**
- Treatment naïve
- 30-81 years
- Diagnosed with CLL stage C or stage A or B with active disease
- ECOG PS 0-1
- No autoimmune cytopenia

**Cycle 1:**
- Fludarabine 25 mg/m² days 2-4
- Cyclophosphamide 250 mg/m² days 2-4
  ± Rituximab 375 mg/m² day 1

**Cycle 2-6:**
- Fludarabine 25 mg/m² days 1-3
- Cyclophosphamide 250 mg/m² days 1-3
  ± Rituximab 500 mg/m² day 1
  *Given every 4 weeks for 6 total cycles

**Primary Endpoint:**
- PFS

**Select Secondary Endpoints:**
- OS
- Disease-free survival
- Duration of remission

**FC:** Fludarabine + cyclophosphamide
**FCR:** FC + rituximab

ECOG PS, Eastern Cooperative Oncology Group Performance Status; PFS, progression-free survival; OS, overall survival.

Results: CLL8 Study

<table>
<thead>
<tr>
<th></th>
<th>FC</th>
<th>FCR</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All CR</td>
<td>22%</td>
<td>44%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age &lt; 65 yrs</td>
<td>20%</td>
<td>45%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age ≥ 65 yrs</td>
<td>24%</td>
<td>43%</td>
<td>0.003</td>
</tr>
<tr>
<td>Del17p</td>
<td>0%</td>
<td>5%</td>
<td>0.43</td>
</tr>
<tr>
<td>Del13q</td>
<td>23%</td>
<td>48%</td>
<td>0.0001</td>
</tr>
<tr>
<td>M-IgHV</td>
<td>21%</td>
<td>50%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

CR, complete remission

- Permission granted to use image for live presentation by M Hallek.

Role of FCR for Patients with Mutated-IgHV

- CLL8 mature data (12.8 years):
  - Significant improvement in patients with M-IgHV status
  - 43.1% of patients achieved MRD negativity → prolonged PFS in M-IgHV

M-IgHV Cohort:
- Median OS = not reached
- Median PFS = not reached
- 12.8 year PFS = 53.9%

UM-IgHV Cohort:
- Median OS = 9.4 years
- Median PFS = 4.2 years
- 12.8 year PFS = 8.9%

BR: CLL10

**Design:** Prospective, phase III, multicenter, randomized, non-inferiority

**Inclusion Criteria:**
- Treatment naive
- 33-81 years
- Diagnosed with CLL & met criteria for treatment per iwCLL
- ECOG PS 0-2
- del17p absent

**Primary Endpoint:**
- Non-inferiority in PFS

**Select Secondary Endpoints:**
- OS
- Overall response
- MRD

**BR:**
- Bendamustine 90 mg/m² days 1-2
- Rituximab 375 mg/m² on day 0 of cycle 1, then 500 mg/m² on day 1 of each cycle

**FCR:**
- Fludarabine 25 mg/m² days 1-3
- Cyclophosphamide 250 mg/m² days 1-3
- Rituximab 375 mg/m² on day 0 of cycle 1, then 500 mg/m² on day 1 of each cycle

**Results: CLL10**

- FCR was statistically superior to BR in most subgroups:
  - PFS in age ≤ 65 years: 53.6 mo. (FCR) vs. 38.5 mo. (BR); p = 0.0004
  - Overall PFS: 55.2 mo. (FCR) vs. 41.7 mo. (BR); p = 0.0003
  - PFS in UM-IgHV: 42.7 mo. (FCR) vs. 33.6 mo. (BR); p = 0.017

- BR was equivalent to FCR in the elderly:
  - PFS in age > 65 years: Not reached (FCR) vs. 48.5 mo. (BR); p = 0.172

**BR should be reserved for elderly patients or those with comorbidities**
Results: CLL10

Safety data in patients > 65 years (niche for BR)

<table>
<thead>
<tr>
<th>Grade 3-5</th>
<th>BR</th>
<th>FCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>61%</td>
<td>88%</td>
</tr>
<tr>
<td>Total infections</td>
<td>26%</td>
<td>47%</td>
</tr>
<tr>
<td>Anemia</td>
<td>13%</td>
<td>14%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>21%</td>
<td>33%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade 3-5</th>
<th>BR</th>
<th>FCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac/Pulmonary</td>
<td>10%</td>
<td>12%</td>
</tr>
<tr>
<td>Laboratory abnormalities</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Secondary malignancy</td>
<td>5%</td>
<td>12%</td>
</tr>
<tr>
<td>Skin reactions</td>
<td>3%</td>
<td>2%</td>
</tr>
</tbody>
</table>


Novel Oral Agents FDA Approved in Front-Line CLL

- Bruton’s tyrosine kinase (BTK) inhibitors:
  - Ibrutinib (Imbruvica®)
  - Acalabrutinib (Calquence®)

- BCL-2 inhibitor:
  - Venetoclax (Venclexta®)
Ibrutinib: RESONATE-2

**Design:** Prospective, phase III, multicenter, randomized, open-label

- **Inclusion Criteria**
  - Treatment naïve
  - Age ≥ 65
  - Diagnosed with CLL or SLL and requiring treatment
  - ECOG PS 0-2
  - del17p absent

- **Primary Endpoint:**
  - PFS

- **Select Secondary Endpoints:**
  - OS
  - Rate of sustained hematologic improvement
  - Safety

- Ibrutinib 420 mg by mouth (PO) daily until progression or toxicity
- Chlorambucil 0.5 mg/kg PO on days 1 and 15 of a 28-day cycle for a maximum of 12 cycles

**Results: RESONATE-2**

- Ibrutinib demonstrated a clear PFS and OS advantage over chlorambucil at a median follow-up of 18.4 mo.
Ibrutinib ± Rituximab: ALLIANCE

Design: Prospective, phase III, multicenter, randomized

Inclusion Criteria
- Treatment naïve
- Age ≥ 65
- Diagnosed with CLL requiring treatment

BR: Bendamustine 90 mg/m² days 1-2
Rituximab 375 mg/m² on day 0 of cycle 1, then 500 mg/m² on day 1 of each cycle
* 6 total 28-day cycles

Ibrutinib 420 mg PO daily until progression or toxicity

Primary Endpoint:
- PFS

Select Secondary Endpoints:
- OS
- Overall response
- MRD

IR: Ibrutinib 420 mg PO daily
Rituximab 375 mg/m² weekly for 4 weeks starting on day 1 of cycle 2, then on day 1 of cycles 3-6

Results: ALLIANCE

Ibrutinib is statistically better than BR in patients ≥ 65 years. The addition of rituximab did not statistically improve outcomes.

MRD negativity at cycle 9
BR (8%) vs. Ibrutinib (1%) vs. Ibrutinib + Rituximab (4%)

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Results: ALLIANCE

More hematologic toxicity and febrile neutropenia with BR

More cardiac toxicity and bleeding with ibrutinib ± rituximab

Ibrutinib + Rituximab: E1912

Design: Prospective, phase III, multicenter, randomized, open-label

Inclusion Criteria
- Treatment naïve
- Age ≤ 70
- Diagnosed with CLL and requiring treatment
- del17p absent

IR: 354
IR: ibrutinib 420 mg by mouth (PO) daily until progression or toxicity
Rituximab 50 mg/m² on day 3 of cycle 2, then 325 mg/m² on day 2 of cycle 2, then 500 mg/m² on day 1 of cycles 3-7

FCR: 175
FCR: Fludarabine 25 mg/m² days 1-3
Cyclophosphamide 250 mg/m² days 1-3
Rituximab 50 mg/m² on day 1 of cycle 1, then 325 mg/m² on day 2 of cycle 1, then 500 mg/m² on day 1 of cycles 2-6

Primary Endpoint:
- PFS

Select Secondary Endpoints:
- OS

**Results: E1912**

**Primary analysis**

**3-year PFS:**
- IR = 89.4%
- FCR = 72.9%
- \( P < 0.001 \)

**3-year OS:**
- IR = 98.8%
- FCR = 91.5%
- \( P < 0.001 \)

**Subgroup analysis**

**3-year PFS in M-IgHV:**
- IR = 87.7%
- FCR = 88%

**MRD negativity at cycle 12**
- IR = 8.3%
- FCR = 59.2%

---

**Ibrutinib + Rituximab and FCR have similar efficacy in the M-IgHV cohort**

Mature Data: E1912

Median time = 45 months

<table>
<thead>
<tr>
<th></th>
<th>36 mo. PFS</th>
<th>45 mo. PFS</th>
<th>36 mo. PFS for M-IgHV</th>
<th>45 mo. PFS for M-IgHV</th>
<th>Grade ≥ 3 adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>IR</td>
<td>89.4%</td>
<td>89%</td>
<td>87.7%</td>
<td>88%</td>
<td>70%</td>
</tr>
<tr>
<td>FCR</td>
<td>72.9%</td>
<td>71%</td>
<td>88%</td>
<td>82%</td>
<td>80%</td>
</tr>
<tr>
<td>P-value</td>
<td>P &lt; 0.0001</td>
<td>P &lt; 0.0001</td>
<td>Not reported</td>
<td>P = 0.086</td>
<td>P = 0.013</td>
</tr>
</tbody>
</table>

May still be a role for FCR in M-IgHV patients, mature data is needed

Results: E1912

• 27% discontinuation rate → adverse event (14%)
• 20.3 mo. median time on therapy
• Any grade atrial fibrillation: 7.4% (IR) vs. 3.2% (FCR)

<table>
<thead>
<tr>
<th>Grade 3-4</th>
<th>IR</th>
<th>FCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>3.2%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18.8%</td>
<td>8.2%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4.3%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>4.8%</td>
<td>1.3%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade 3-4</th>
<th>IR</th>
<th>FCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>25.6%</td>
<td>45%</td>
</tr>
<tr>
<td>Infection</td>
<td>9.4%</td>
<td>9.5%</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>2.3%</td>
<td>15.8%</td>
</tr>
<tr>
<td>Anemia</td>
<td>4.8%</td>
<td>14.6%</td>
</tr>
</tbody>
</table>
Ibrutinib + Obinutuzumab: iLLUMINATE

Design: Prospective, phase III, multicenter, randomized, open-label

Inclusion Criteria
- Treatment naïve
- Age ≥ 18
- Diagnosed with CLL and requiring treatment
- Unfit for fludarabine-based therapy

Primary Endpoint:
- PFS

Select Secondary Endpoints:
- PFS in high-risk patients
- MRD
- OS
- Safety

IO:
Ibrutinib 420 mg by mouth (PO) daily until progression or toxicity
Obinutuzumab 100 mg IV on day 1, 900 mg on day 2, and 1000 mg on day 8 and 15 of cycle 1, then 1000 mg on day 1 of cycles 2-6

CO:
Chlorambucil 0.5 mg/kg PO days 1 and 15 for 6 cycles
Obinutuzumab 100 mg IV on day 1, 900 mg on day 2, and 1000 mg on days 8 and 15 of cycle 1, then 1000 mg on day 1 of cycles 2-6

Results: iLLUMINATE

Median follow-up = 31.3 mo.

PFS (Intent to Treat):
IO = Not reached
CO = 19 mo.
P< 0.0001

PFS (High-Risk):
IO = Not reached
CO = 14.7 mo.
P< 0.0001
Results: iLLUMINATE

- Higher overall response (OR) and complete response (CR)
  - OR: IO (88%) vs. CO (73%); p = 0.0035
  - CR: IO (19%) vs. CO (8%); p = 0.0096

- Higher MRD negativity
  - IO (35%) vs. CO (25%); (formal statistics not reported)

Safety:

<table>
<thead>
<tr>
<th>Grade 1-2</th>
<th>IO</th>
<th>CO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>7%</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>13%</td>
<td>1%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>31%</td>
<td>10%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>21%</td>
<td>10%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade 3-4</th>
<th>IO</th>
<th>CO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>37%</td>
<td>70%</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>Infusion reactions</td>
<td>2%</td>
<td>8%</td>
</tr>
</tbody>
</table>


Ibrutinib: Real World Tolerability

Design: Multicenter, retrospective cohort

Inclusion Criteria
- Treated with ibrutinib as part of a clinical trial or with commercially available drug
- Treatment from 1/2014-8/2016

Primary Endpoint:
- PFS

Select Secondary Endpoints:
- OS
- Reason for ibrutinib discontinuation

Results: Treatment Discontinuation

- Median follow-up = 17 months
- 42% of patients discontinued ibrutinib
  - Median time = 6 months for intolerance
  - Median time = 10 months for progressive disease
- Toxicity was the main reason for discontinuation

<table>
<thead>
<tr>
<th>Table 2. Reasons for Ibrutinib Discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reason for ibrutinib discontinuation</td>
</tr>
<tr>
<td>Toxicity</td>
</tr>
<tr>
<td>Cell progression</td>
</tr>
<tr>
<td>Other/unrelated death</td>
</tr>
<tr>
<td>Physician or patient preference</td>
</tr>
<tr>
<td>RT DLBCL</td>
</tr>
<tr>
<td>Stem cell transplantation/CAR T cell</td>
</tr>
<tr>
<td>Financial concerns</td>
</tr>
<tr>
<td>Secondary malignancy</td>
</tr>
<tr>
<td>RT Hodgkin Lymphoma</td>
</tr>
</tbody>
</table>

RT DLBCL, Richter's Transformation Diffuse Large B-Cell Lymphoma, CAR T-cell Chimeric Antigen Receptor T-cell.
Safety Check

• BTK receptors are expressed in cardiac tissue
• In patients with atrial fibrillation, BTK expression is upregulated

• Ibrutinib directly inhibits BTK signaling pathways involved with direct platelet activation
• Ibrutinib also interferes with platelet GPIb and von Willebrand factor (VWF) signaling inhibiting platelet adhesion to damaged tissue


Acalabrutinib: ELEVATE-TN

**Design:** Prospective, phase III, multicenter, randomized, open-label

**Inclusion Criteria:**
- Treatment naïve
- Age ≥ 65
- Age 18-65 if CrCl 30-69 mL/min or CIRS-G > 6
- ECOG PS 0-2
- Diagnosed with CLL requiring treatment
- Allowed del17p

**Primary Endpoint:**
- PFS by independent review of combination groups containing obinutuzumab only

**Select Secondary Endpoints:**
- PFS by independent review of A vs. CO
- Overall response
- PFS and OS

**A:** Acalabrutinib 100 mg PO twice daily until progression or toxicity

**CO:** Chlorambucil 0.5 mg/kg PO on days 1 and 15 each cycle
Obinutuzumab 100 mg IV on day 1, 900 mg on day 2, 1000 mg on day 8 and 15 of cycle 1, then 1000 mg on day 1 of cycles 2-6

**AO:** Acalabrutinib 100 mg PO twice daily
Obinutuzumab 100 mg IV on day 1, 900 mg on day 2, 1000 mg on day 8 and 15 of cycle 2, then 1000 mg on day 1 of cycles 3-7

Results: ELEVATE-TN

**Median follow-up = 28.3 mo.**

**Median PFS:**
Chlorambucil + obinutuzumab = 22.6 mo.
Acalabrutinib + obinutuzumab = Not reached
Acalabrutinib = Not reached

P< 0.001

Acalabrutinib ± obinutuzumab >> chlorambucil + obinutuzumab in every sub-group analysis including age, performance status, disease status, cytogenetic risk, and IgHV mutation status

MRD negativity: AO (26%) vs. CO (22%)

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Results: ELEVATE-TN

- More adverse events with acalabrutinib + obinutuzumab
  - Any grade: 38.8% (AO) vs. 31.8% (A) vs. 21.9% (CO)
- More drug discontinuation with chlorambucil + obinutuzumab
  - 11.2% (AO) vs. 8.9% (A) vs. 14.1% (CO)

<table>
<thead>
<tr>
<th>Grade 1-2</th>
<th>AO</th>
<th>A</th>
<th>CO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>38.8%</td>
<td>35.8%</td>
<td>11.8%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>34.3%</td>
<td>34.1%</td>
<td>19.5%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>20.8%</td>
<td>15.1%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Infusion reaction</td>
<td>11.2%</td>
<td>0</td>
<td>34.3%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade ≥ 3</th>
<th>AO</th>
<th>A</th>
<th>CO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>3%</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Bleeding</td>
<td>2%</td>
<td>2%</td>
<td>0</td>
</tr>
<tr>
<td>Atrial fibrillation (any grade)</td>
<td>3%</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>29.8%</td>
<td>9.5%</td>
<td>41.4%</td>
</tr>
<tr>
<td>Infection</td>
<td>21%</td>
<td>14%</td>
<td>8%</td>
</tr>
</tbody>
</table>


Safety Check

- Acalabrutinib is a more selective and potent inhibitor of BTK with less off-target inhibition compared to ibrutinib
- Ibrutinib inhibits TEC
  - TEC implicated in cardiac toxicity and inhibition of platelet activation

Comparison of Selected BTK Inhibitor Toxicities

- Hypertension (grade ≥ 3)
  - Ibrutinib = 4%-29%
  - Acalabrutinib = 2-7%
- Atrial fibrillation (any grade)
  - Ibrutinib = 6%-17%
  - Acalabrutinib = 4%
- Bleeding (grade ≥ 3)
  - Ibrutinib
    - Concurrent antithrombotic = 6.1%
    - No antithrombotic = 3.1%
  - Acalabrutinib
    - Concurrent antithrombotic = 3.6%
    - No antithrombotic = 2.7%

- Zanubrutinib
  - Currently not FDA approved for CLL
  - Hypertension (grade ≥ 3) = 3.4%
  - Atrial fibrillation (any grade) = 2%
  - Bleeding (grade ≥ 3) = 2%

Venetoclax: CLL14

Design: Prospective, phase III, multinational, randomized, open-label

**Inclusion Criteria**
- Treatment naïve
- Age ≥ 18 with coexisting conditions
- Diagnosed with CLL and requiring treatment
- CIRS score > 6 or CrCl < 70 mL/min
- Allowed TP53 mutations

**Primary Endpoint:**
- PFS by investigator

**Select Secondary Endpoints:**
- PFS by independent review
- MRD
- Overall and complete response
- OS

VenG:
- Venetoclax 5-week ramp-up to target 400 mg PO daily starting on day 22 of cycle 1 until completion of cycle 12
- Obinutuzumab 100 mg IV on day 1, 900 mg on day 2, and 1000 mg on 15 of cycle 1, then 1000 mg on day 1 of cycles 2-6

ChlorG:
- Chlorambucil 0.5 mg/kg PO days 1 and 15 for 12 cycles
- Obinutuzumab 100 mg IV on day 1, 900 mg on day 2, and 1000 mg on day 15 of cycle 1, then 1000 mg on day 1 of cycles 2-6
Venetoclax: CLL14

Median follow-up = 24 mo.

Survival outcomes

| Investigator PFS: |  
|-------------------|---
| VenG  = 88.2%    |   
| ChlorG = 64.1%   |   
| P < 0.001        |   
| **OS:**          |  
| VenG  = 91.8%    |   
| ChlorG = 93.3%   |   
| P = 0.52         |   

Secondary analysis

| MRD negativity in PB: |  
|-----------------------|---
| VenG  = 75.5%        |   
| ChlorG = 35.2%       |   
| P < 0.001            |   

| MRD negativity in BM: |  
|-----------------------|---
| VenG  = 56.9%        |   
| ChlorG = 17.1%       |   
| P < 0.001            |   

Venetoclax + obinutuzumab has improved overall and complete response compared to chlorambucil + obinutuzumab
Results: CLL14

<table>
<thead>
<tr>
<th>Category</th>
<th>Subgroup</th>
<th>ChlorG</th>
<th>VenG</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td></td>
<td>64.1%</td>
<td>88.1%</td>
<td>0.34</td>
<td>0.23-0.53</td>
</tr>
<tr>
<td>Age (years)</td>
<td>&lt; 75</td>
<td>63.5%</td>
<td>89.7%</td>
<td>0.28</td>
<td>0.16-0.48</td>
</tr>
<tr>
<td></td>
<td>≥ 75</td>
<td>65.1%</td>
<td>84.9%</td>
<td>0.48</td>
<td>0.25-0.93</td>
</tr>
<tr>
<td>Select cytogenetics</td>
<td>del17p</td>
<td>23.1%</td>
<td>64.7%</td>
<td>0.33</td>
<td>0.12-0.89</td>
</tr>
<tr>
<td></td>
<td>del11q</td>
<td>41.3%</td>
<td>91.2%</td>
<td>0.11</td>
<td>0.03-0.38</td>
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<tr>
<td></td>
<td>Trisomy 12</td>
<td>55.6%</td>
<td>100.0%</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td></td>
<td>del13q</td>
<td>78.3%</td>
<td>88.1%</td>
<td>0.45</td>
<td>0.19-1.05</td>
</tr>
<tr>
<td>TP53 deletion ± mutation</td>
<td>Present</td>
<td>32.7%</td>
<td>73.9%</td>
<td>0.31</td>
<td>0.13-0.76</td>
</tr>
<tr>
<td></td>
<td>Not present</td>
<td>65.0%</td>
<td>92.1%</td>
<td>0.23</td>
<td>0.13-0.42</td>
</tr>
<tr>
<td>IgHV</td>
<td>Unmutated</td>
<td>51.0%</td>
<td>89.4%</td>
<td>0.22</td>
<td>0.12-0.38</td>
</tr>
<tr>
<td></td>
<td>Mutated</td>
<td>85.6%</td>
<td>90.3%</td>
<td>0.64</td>
<td>0.28-1.46</td>
</tr>
</tbody>
</table>


PFS at 24 months


- 16% discontinuation
- Grade 3 infection = 5.2%
- Grade 4 infection = 17.5%
- 43.5% used colony stimulating factors
- Tumor lysis syndrome (TLS) = 3 patients (prior to Ven)
- Grade ≥ 3 infusion reaction = 9%
- Richter’s transformation = 2 pts


Results: CLL14
**Time Definitive Therapy Options**

- **FCR or BR**
- **Chlorambucil + Obinutuzumab**
- **Ibrutinib or Acalabrutinib monotherapy**
- **Ibrutinib + Rituximab**
- **Ibrutinib + Obinutuzumab**
- **Acalabrutinib + Obinutuzumab**

**Logistics**

**Chemoimmunotherapy**
- Intravenous administration
- Confirmed compliance
- Lower cost
- Time definitive treatment
- Time defined toxicity
- Physician comfort
- Sequencing in relapse well established

**Novel Targeted Therapy**
- Oral +/- intravenous administration
- Convenient
- Higher cost
- Often indefinite treatment
- Less myelosuppression
- Limited accessibility
- Ongoing sequencing of novel treatments
Refresher- Patient Case

• MT is a 62 year old male recently diagnosed with CLL (del13q, UM-IgHV). His past medical history includes recurrent urinary tract infections, hypertension, controlled atrial fibrillation on anticoagulation, and migraines. He recently developed intolerable night sweats and has palpable cervical lymph nodes requiring treatment for his CLL. His kidney and liver function is within normal limits.

• What FDA approved front-line treatment is best suited for MT?

Patient Case Discussion

• FCR
  • CLL8 and CLL 10 study found improved survival specifically in M-IgHV patients
  • ↑ infection risk with FCR

• Ibrutinib ± CD20 antibody
  • ↑ risk of bleeding, worsening atrial fibrillation, headaches, hypertension

• Acalabrutinib ± obinutuzumab
  • ↑ risk of headaches
  • Lower risk of bleeding and atrial fibrillation in ELEVATE-TN

• Venetoclax + obinutuzumab
  • Likely best treatment option based on the patient’s co-morbidities
Ibrutinib + Venetoclax: CAPTIVATE

**Design:** Prospective, phase III, multicenter, randomized

**Inclusion Criteria**
- Treatment naïve
- Age < 70
- Diagnosed with CLL and requiring treatment

**Primary Endpoint:**
- MRD

**Select Secondary Endpoints:**
- Venetoclax-related tumor lysis syndrome risk
- Pharmacokinetics
- Adverse drug reactions (ADR)

**Ibrutinib 420 mg PO daily**

**Venetoclax 5-week ramp-up to 400 mg PO daily**

Results: CAPTIVATE

Key Demographics
- Median age = 58 years
- TP53 mutation = 20%
- UM-IgHV = 59%

Safety
- Most frequent ADR of any grade:
  - Diarrhea (31% w/ Ibrutinib alone) → 60% w/ combo
  - Arthralgia (22% w/ Ibrutinib alone)
  - Neutropenia (40% w/ combo)
  - Upper respiratory infection (24% w/ combo)
- 20% pts had dose reduction due to adverse event
- 7% of pts discontinued treatment due to adverse event
- Lab TLS = 4 patients (none met clinical TLS)
  - 24% high risk TLS at Cycle 1, Day 1
  - 2% high risk TLS at Cycle 4, Day 1

Bone Marrow (BM) MRD negativity = 72%

Efficacy
- 92% pts completed 15 cycles
- ORR = 97%
- Peripheral blood (PB) MRD negativity = 75%

AVO: Acalabrutinib + Venetoclax + Obinutuzumab

Inclusion Criteria
- Treatment naïve
- Diagnosed with CLL and
met criteria for treatment per iwCLL
- ECOG PS 0-2
- CrCl ≥ 50 mL/min
- ANC ≥ 500 mm$^3$
- Platelets ≥ 30,000/mm$^3$

Primary Endpoint:
- Rate of BM MRD negative CR at 15 cycles

Selected Secondary Endpoint:
- Adverse events

Acalabrutinib (A): 100 mg PO BID
Obinutuzumab (G): 100 mg IV on day 1, 900 mg on day 2, and 1000 mg on days 8 and 15 of cycle 1, then 1000 mg IV on day 1 of cycles 2-6
Venetoclax (Ven): 5-week ramp-up to 400 mg PO daily
Results: AVO

**Key Demographics**
- Median age = 63 years
- UM-IgHV = 62%
- TP53 aberrant = 27%

**Efficacy**
- 24 patients had restaging at cycle 8
- Overall response rate (ORR) = 100%
  - Partial response (PR) = 75%
  - Complete response (CR) = 25%
- PB MRD- = 65%
- BM MRD- = 50%
- BM MRD- CR = 13%

**Safety**
- Frequent any grade adverse events:
  - Fatigue (81%)
  - Headache (76%)
  - Bruising (43%)
  - Infusion-related reactions (22% → 3% grade ≥ 3)
- Frequent grade ≥ 3 adverse events:
  - Neutropenia (32%)
  - No febrile neutropenia
- TLS = 2 patients
  - 97% medium-high risk TLS at Cycle 1, Day 1
  - 9% medium-high risk TLS at Cycle 4, Day 1
- 1 case of grade 3 A. fib
- No hemorrhage

---

**Clinical Trials**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism</th>
<th>Phase</th>
<th>Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAR-T</td>
<td>Anti-CD19</td>
<td>1</td>
<td>Relapsed / refractory</td>
</tr>
<tr>
<td>LOXO-305</td>
<td>BTK inhibitor</td>
<td>1/2</td>
<td>Relapsed / refractory</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>Checkpoint inhibitor</td>
<td>2</td>
<td>First line, relapsed / refractory</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Checkpoint inhibitor</td>
<td>2</td>
<td>First line, relapsed / refractory</td>
</tr>
<tr>
<td>Ublituximab</td>
<td>Anti-CD20 MoAb</td>
<td>3</td>
<td>First line, relapsed / refractory</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 / 1b</td>
<td>Relapsed / refractory</td>
</tr>
<tr>
<td>Umbralisib</td>
<td>Dual inhibitor of PI3Kδ and CK1ε</td>
<td>2</td>
<td>First line, relapsed / refractory</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Addition to current therapy</td>
</tr>
<tr>
<td>Zanubrutinib</td>
<td>BTK inhibitor</td>
<td>3</td>
<td>Relapsed / refractory</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>First line</td>
</tr>
</tbody>
</table>

Pending Research Questions

- Sequencing
- MRD negativity
- Length of therapy
- Early discontinuation
- Combination treatment

Key Takeaways

- FCR is preferred over BR
  - FCR is equivalent to BR in age ≥ 65
- Ibrutinib is preferred over BR
  - Including age ≥ 65
- Ibrutinib is preferred over FCR
  - Ibrutinib is equivalent to FCR in M-IgHV
- Acalabrutinib ± obinutuzumab is preferred over chlorambucil + obinutuzumab
  - Including M-IgHV and elderly
- Venetoclax + obinutuzumab is preferred over chlorambucil + obinutuzumab
  - Including elderly
Thank You