ASSOCIATION OF COMMUNITY CANCER CENTERS

MULTIDISCIPLINARY CHRONIC LYMPHOCYTIC LEUKEMIA CARE
Up-to-Date Approaches to Treating the CLL Patient

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Swedish Cancer Institute
Seattle, WA
Chlorambucil, Fludarabine, Bendamustine, Ibrutinib, Ofatumumab, Idelalisib, Duvelisib, Venetoclax, Rituximab, Obinutuzumab, Alemtuzumab, Steroids.
## Treatment Options for CLL

<table>
<thead>
<tr>
<th>Chemotherapy Agents</th>
<th>Anti-CD20 Abs</th>
<th>BCR Inhibitors</th>
<th>BCL-2 Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fludarabine</td>
<td></td>
<td>BTK inhibitors</td>
<td>Venetoclax</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td></td>
<td>Ibrutinib</td>
<td></td>
</tr>
<tr>
<td>Bendamustine</td>
<td></td>
<td>Acalabrutinib</td>
<td></td>
</tr>
<tr>
<td>Chlorambucil</td>
<td></td>
<td>PI3K inhibitors</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Idelalisib</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Duvelisib</td>
<td></td>
</tr>
</tbody>
</table>
## What Do You Need to Know About Your CLL Before Starting Treatment

<table>
<thead>
<tr>
<th></th>
<th>FISH</th>
<th>Karyotype</th>
<th>Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unfavorable</strong></td>
<td>del (17p) del (11q)</td>
<td>Complex (&gt;3 abnormality in more than 1 cell)</td>
<td>Unmutated IGHV (≤ 2%) TP53 NOTCH-1 SF3B1 BIRC3 ATM</td>
</tr>
<tr>
<td><strong>Neutral</strong></td>
<td>Normal +12</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Favorable</strong></td>
<td>del (13q) (sole abnormality)</td>
<td></td>
<td>Mutated IGVH (&gt;2%)</td>
</tr>
</tbody>
</table>

1. TP53 aberration is the most important marker (check before each treatment).
2. IGHV mutational status (one time test).
Indications for Treatment

• Progressive marrow failure.
• Massive, progressive, or symptomatic lymphadenopathy or organomegaly.
• Constitutional symptoms.
• Autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy.
Is Early Treatment Reasonable?

Question:
I have high-risk CLL and the new drugs are much safer and more effective these days. Why can’t I start treatment earlier (at the time of diagnosis)?

Answer:
• Great Question.
• Studies are ongoing – ASH-2019?
• Other studies are being designed.
No Algorithm

Ideal Treatment:

• Cures CLL;
• Helps patients live longer;
• Provides long time periods without treatment and without disease;
• Doesn’t interfere with patient’s work/life;
• Is not forever;
• Has minimal toxicity;
• Does not make patient’s other medical conditions worse.
First Line Treatment
**Before ASH 2018**

**Young and Fit**
- FCR
- most beneficial in pts with mutated IGHV
- ibrutinib for selected patients

**Less Fit**
- BR
- ibrutinib for selected patients

**Unfit**
- ibrutinib
- chlorambucil + obinutuzumab
- ibrutinib for selected patients
FCR vs. IB+R (E1912 Study)

**Study design**

**Arm A – Ibrutinib + Rituximab**
- Cycles 1:
  - Ibrutinib 420 mg PO daily, days 1-28
- Cycle 2:
  - Ibrutinib 420 mg PO daily, days 1-28
  - Rituximab 50 mg/m² IV, day 1
  - Rituximab 325 mg/m² IV, day 2
- Cycles 3-7:
  - Ibrutinib 420 mg PO daily, days 1-28
  - Rituximab 500 mg/m² IV, day 1
- Cycle 8 until progression:
  - Ibrutinib 420 mg PO daily, days 1-28

**Arm B - FCR**
- Cycles 1-6:
  - Fludarabine 25 mg/m² IV, days 1-3
  - Cyclophosphamide 250 mg/m² IV, days 1-3
- Cycle 1:
  - Rituximab 50 mg/m² IV, day 1, cycle 1
  - Rituximab 325 mg/m² IV, day 2, cycle 1
- Cycle 2-6:
  - Rituximab 500 mg/m² IV, day 1, cycles 2-6

**Randomization**

**E1912**
- ** Eligibility:**
  - Previously untreated CLL
  - Requires treatment (IWCLL 2008)
  - Age ≤ 70
  - ECOG 0-2
  - CrCl>40
  - Able to tolerate FCR
  - No deletion 17p by FISH

**Planned Accrual:** 519

**Disease Progression**

E1912: Results

**Progression-Free Survival**

- IR (37 events/ 354 cases)
- FCR (40 events/ 175 cases)

HR = 0.35 (95% CI 0.22-0.5)
One sided p<0.0001

**Overall Survival**

- IR (4 events/ 354 cases)
- FCR (10 events/ 175 cases)

HR = 0.17 (95% CI 0.05-0.54)
One sided p<0.0003
Progression-Free Survival: IGHV Status

IGHV Unmutated

- HR = 0.44 (95% CI 0.14–1.36)
- One-sided p = 0.07

IGHV Mutated

- HR = 0.26 (95% CI 0.14–0.50)
- One-sided p < 0.00001

<table>
<thead>
<tr>
<th>Years</th>
<th>Number at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 0.0</td>
<td>210</td>
</tr>
<tr>
<td>1 0.2</td>
<td>203</td>
</tr>
<tr>
<td>2 0.4</td>
<td>177</td>
</tr>
<tr>
<td>3 0.6</td>
<td>90</td>
</tr>
<tr>
<td>4 0.8</td>
<td>12</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Years</th>
<th>Number at risk</th>
</tr>
</thead>
<tbody>
<tr>
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<td>71</td>
</tr>
<tr>
<td>1 0.2</td>
<td>64</td>
</tr>
<tr>
<td>2 0.4</td>
<td>43</td>
</tr>
<tr>
<td>3 0.6</td>
<td>14</td>
</tr>
<tr>
<td>4 0.8</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Years</th>
<th>Number at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 0.0</td>
<td>70</td>
</tr>
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<td>1 0.2</td>
<td>67</td>
</tr>
<tr>
<td>2 0.4</td>
<td>59</td>
</tr>
<tr>
<td>3 0.6</td>
<td>25</td>
</tr>
<tr>
<td>4 0.8</td>
<td>2</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Years</th>
<th>Number at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 0.0</td>
<td>44</td>
</tr>
<tr>
<td>1 0.2</td>
<td>38</td>
</tr>
<tr>
<td>2 0.4</td>
<td>31</td>
</tr>
<tr>
<td>3 0.6</td>
<td>18</td>
</tr>
<tr>
<td>4 0.8</td>
<td>0</td>
</tr>
</tbody>
</table>
## A041202: Study Design

- Multicenter, randomized, double-blind phase III study (data cutoff: October 4, 2018)
  - Stratified by Rai stage (high vs intermediate risk), del(11q22.3) or del(17p13.1) (presence vs absence), ZAP-70 methylation (< vs ≥ 20%)

1. **Untreated patients with CLL meeting IWCLL 2008 criteria for tx initiation; aged ≥ 65 yrs; EOGP PS 0-2; ANC ≥ 1000 unless due to BM involvement; PLT ≥ 30; CrCl_{ser} ≥ 40; AST/ALT ≤ 2.5 × ULN; no heparin or warfarin (N = 547)**

### Treatments

<table>
<thead>
<tr>
<th>Ibrutinib 420 mg QD (n = 182)</th>
<th>Ibrutinib 420 mg QD + Rituximab 375 mg/m² wkly x 4 wks starting cycle 2 Day 1; cycles 3-6 Day 1* (n = 182)</th>
<th><strong>Until PD</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>*<em>Bendamustine 90 mg/m² on Days 1, 2 + Rituximab 375 mg/m² on cycle 1 Day 1; 500 mg/m² on cycles 2-6 Day 1</em> (n = 183)</td>
<td><strong>Ibrutinib until PD</strong></td>
</tr>
</tbody>
</table>

### Primary endpoint: PFS

- 2 primary comparisons of ibrutinib vs BR and ibrutinib + R vs BR with 90% power to detect HR of 0.586 (estimated 2-yr PFS rates: ibrutinib, 75%; BR, 61%) and overall 1-sided α = 0.025 for each comparison
- If both primary comparisons significant, third planned comparison of ibrutinib + R vs ibrutinib

A041202 (BR vs. IB vs. IB+R): Results

Progression-Free Survival

Overall Survival

<table>
<thead>
<tr>
<th>Patients at Risk, n</th>
<th>BR</th>
<th>BR + R</th>
<th>Ibrutinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mos</td>
<td>103</td>
<td>115</td>
<td>136</td>
</tr>
<tr>
<td>78</td>
<td>65</td>
<td>154</td>
<td>147</td>
</tr>
<tr>
<td>45</td>
<td>147</td>
<td>132</td>
<td>147</td>
</tr>
<tr>
<td>22</td>
<td>136</td>
<td>120</td>
<td>133</td>
</tr>
<tr>
<td>0</td>
<td>120</td>
<td>78</td>
<td>120</td>
</tr>
</tbody>
</table>

Events, n/N: BR 176, BR + R 170, Ibrutinib 178

Median PFS, Mos (95% CI): BR 43 (38-NR), BR + R 43 (NR), Ibrutinib 68 (176-Mos)

2-Yr PF % (95% CI): BR 74 (66%), BR + R 88 (61%), Ibrutinib 87 (61%)

Events, n/N: BR 20, BR + R 22, Ibrutinib 24

Median OS, Mos (95% CI): BR 183, BR + R 182, Ibrutinib 182

2-Yr OS, % (95% CI): BR 95 (91-98), BR + R 94 (89-97), Ibrutinib 90 (85-94)

P ≥ .65 for all pairwise comparisons
# E1912 vs. A041202 Adverse Events

<table>
<thead>
<tr>
<th>Grade 3-5 Treatment-Related AE</th>
<th>E1912: Ibrutinib + R[^3] (n = 352)</th>
<th>041202: Ibrutinib + R[^{1,2}] (n = 181)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, yrs (range)</td>
<td>57 (31-70)</td>
<td>71 (65-86)</td>
</tr>
<tr>
<td>Infection, %</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Bleeding, %</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>7</td>
<td>34</td>
</tr>
<tr>
<td>Deaths during active treatment + 30 days. %</td>
<td>1</td>
<td>7</td>
</tr>
</tbody>
</table>
iILLUMINATE: Study Design

- Randomized, open-label, multicenter phase III trial
  
  Stratified by ECOG PS (0-1 vs 2), del(17p)/del(11q) (+/- vs ++ vs -/+ vs -/-)

  Untreated patients with CLL/SLL needing treatment by iwCLL criteria, ≥ 65 yrs or < 65 yrs with comorbidities* (N = 229)

  **Ibrutinib** 420 mg PO QD continuously + **Obinutuzumab** IV for 6 cycles†
  (n = 113)

  **Chlorambucil** 0.5 mg/kg PO D1,15 for 6 cycles + **Obinutuzumab** IV for 6 cycles†
  (n = 116)

  Ibrutinib continued until PD or unacceptable toxicity

  If IRC-confirmed progression, crossover to next-line single-agent ibrutinib permitted

- Primary endpoint: PFS by IRC in ITT population

- Secondary endpoints: PFS in high-risk patients (positive for del(17p) or TP53 mutation, del(11q), or unmutated IGHV), MRD, ORR, OS, IRRs, safety

iLLUMINATE: Results

Progression-Free Survival

No Overall Survival Benefit

HR: 0.23 (95% CI: 0.15-0.37; P < .0001)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients, n</th>
<th>Median PFS, Mos</th>
<th>30-Mo PFS, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibrutinib + obinutuzumab</td>
<td>113</td>
<td>NR</td>
<td>79 (70-85)</td>
</tr>
<tr>
<td>Chlorambucil + obinutuzumab</td>
<td>116</td>
<td>19.0</td>
<td>31 (23-40)</td>
</tr>
</tbody>
</table>
Venetoclax + obinu vs. CHL + obinu
German CLL14 Study

Media Release

Basel, 01 November 2018

Phase III data showed that Venclexta/Venclyxto plus Gazyva/Gazyvaro reduced the risk of disease worsening or death in people with previously untreated chronic lymphocytic leukaemia with co-morbidities

- The phase III CLL14 study compared Venclexta/Venclyxto in combination with Gazyva/Gazyvaro to standard-of-care Gazyva/Gazyvaro plus chlorambucil
- Data will be submitted to health authorities and presented at an upcoming medical meeting
Summary of Frontline CLL Studies for First Line
ASH 2018

• Ibrutinib is standard of care for first line.
• There is no benefit in adding rituximab to ibrutinib.
• Benefit not clear in patients with a mutated IGHV gene.
• The only patients in whom FCR may not be the wrong answer:
  • young (<65) and fit (no-comorbidities);
  • mutated IGHV;
  • without del17p or TP53 mutation;
  • without del11q.
• Important to remember: ibrutinib> BR but no OS benefit.

Waiting to see the CLL14 study results – May change the current standard.
Relapsed CLL
## Relapsed CLL

<table>
<thead>
<tr>
<th></th>
<th>Ibrutinib</th>
<th>Venetoclax</th>
<th>Idelalisib/Duvelisib</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>BTK</td>
<td>BCL-2</td>
<td>PI3K delta / Delta+Gamma</td>
</tr>
<tr>
<td><strong>Regimen</strong></td>
<td>Single agent</td>
<td>With R</td>
<td>With Rituximab (idela)</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>420 mg po daily</td>
<td>Ramp-up ➔ 2 years!</td>
<td>150 mg po BID (idela) 25 mg po BID (develisib)</td>
</tr>
<tr>
<td><strong>Addition of Anti CD20 Ab</strong></td>
<td>No major benefit Faster “response”</td>
<td>Recommended R/R label</td>
<td>R/R label</td>
</tr>
<tr>
<td><strong>Major side effect (concern)</strong></td>
<td>Bleeding (anticoagulation) - rare</td>
<td>TLS (initially)</td>
<td>Colitis (diarrhea) Infections (FDA alert)</td>
</tr>
<tr>
<td><strong>Other side effects</strong></td>
<td>• Body pain • Fatigue • Hypertension • A fib</td>
<td>• Neutropenia</td>
<td>• Pneumonitis • Transaminitis • PJP • CMV</td>
</tr>
<tr>
<td><strong>FDA label for CLL</strong></td>
<td>• Everybody</td>
<td>• del 17 p after 1 line • R/R</td>
<td>• R/R (after 2 lines)</td>
</tr>
</tbody>
</table>
Ibrutinib vs. Venetoclax for Relapsed CLL

• No head-to-head studies.
• Both reasonable options.
• Both superior to idelalisib (based on toxicity profile).

In favor of Venetoclax

• **Fixed treatment duration.**
• **After the first 4-5 weeks, seems to be better tolerated.**
• Higher rate of CR and MRD negativity.
• **Treatment holiday/hold is expected (not proven yet).**
• Preferred in patients with A fib, bleeding issues, HTN.

In favor of Ibrutinib

• Longer track record.
• Easier to start.
• **More information about salvage options if stops working.**
Ven-R vs. BR in relapsed CLL (MURANO Study)

Relapsed/refractory CLL (N=389)
- ≥18 years of age
- Prior 1–3 lines of therapy, including ≥1 chemo-containing regimen
- Prior bendamustine only if DoR ≥24 months

Stratified by:
- Del(17p) by local labs
- Responsiveness to prior therapy*
- Geographic region

Primary Endpoint | INV-assessed PFS
---|---

C1D1

Venetoclax 400 mg orally once daily to PD, cessation for toxicity, or max. 2 years from Cycle1 Day1

R 1:1

VEN 5-week ramp-up

Rituximab
- 375 mg/m² Day 1, Cycle 1;
- 500 mg/m² Day 1 Cycles 2–6

Bendamustine
- 70 mg/m² Days 1 and 2 Cycles 1–6 +
- Rituximab

Seymour, NEJM, 2018
Ven-R vs. BR in relapsed CLL (MURANO Study)

**Graph:**
- Progression-Free Survival (%)
- Median PFS = 18.1 months
- VenR (N=194)
- BR (N=195)
- HR 0.19, 95% CI 0.13–0.28, P<0.0001

**Table:**
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Pts with events, n (%)</th>
<th>1-yr PFS %</th>
<th>2-yr PFS %</th>
</tr>
</thead>
<tbody>
<tr>
<td>VenR (n=194)</td>
<td>35 (18.0)</td>
<td>91.2</td>
<td>82.8</td>
</tr>
<tr>
<td>BR (n=195)</td>
<td>106 (54.4)</td>
<td>74.1</td>
<td>37.4</td>
</tr>
</tbody>
</table>

Seymour, NEJM, 2018
What Happens After Stopping Venetoclax?

- 10 months follow-up after stopping venetoclax.
- Only 12% of patients relapsed.
- Some still don’t need treatment.
- Relapse was less likely if there was minimal detectable disease at the end of 2 years.

Kater, JCO, 2019
Combination Therapies
# Ongoing Combination Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Regimen</th>
<th>MRD neg</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDACC</td>
<td>TN and R/R</td>
<td>Venetoclax + Ibrutinib</td>
<td>18 months: 69% (TN)</td>
<td>Jain, ASH18</td>
</tr>
<tr>
<td>The OSU</td>
<td>TN</td>
<td>Venetoclax + Ibrutinib + Obinutuzimab</td>
<td>EOT: 67% (TN); 50% (Relapsed)</td>
<td>Rogers, ASH18</td>
</tr>
<tr>
<td>TAP CLARITY</td>
<td>R/R</td>
<td>Venetoclax + Ibrutinib</td>
<td>6 cycles</td>
<td>Hillmen, ASH17</td>
</tr>
<tr>
<td>CAPTIVATE</td>
<td>TN</td>
<td>Venetoclax + Ibrutinib</td>
<td>12 cycles: 81%</td>
<td>Wierda, ASCO18,#1142</td>
</tr>
</tbody>
</table>
EA9161 Study

Schema

Arm A
- Ibrutinib:
  Cycles 1-19: d1-d28 420mg PO daily
- Obinituzumab:
  Cycle 1: d1 100mg IV
d2 900mg IV
d8 1000mg IV
d15 1000mg IV
  Cycles 2-6: d1 1000mg IV
- Venetoclax:
  Cycle 3: d1-d7 20mg PO daily
d8-d14 50mg PO daily
d15-d21 100mg PO daily
d22-d28 200mg PO daily
  Cycles 4-14: d1-d28 400mg PO daily

Arm B
- Ibrutinib:\n  Cycles 1-19: d1-d28 420mg PO daily
- Obinituzumab:
  Cycle 1: d1 100mg IV
d2 900mg IV
d8 1000mg IV
d15 1000mg IV
  Cycles 2-6: d1 1000mg IV

Stratification
- Age: < 65 yrs vs. ≥ 65 yrs and < 70yrs
- PS: 0, 1, vs. 2
- Stage: 0, 1, or 2 vs. 3, 4
- del11q22.3 (ATM) vs. other
A041702 Study
1. Clinical trials are highly recommended until CLL is cured.

2. Treatment algorithms are for physicians, make your own algorithm.

3. We are officially in the “chemo-free” era for CLL but for selected patients, chemo may still be reasonable.

4. The goal is to cure CLL with a “chemo-free” regimen and with fixed-duration.

5. Combination therapy will most likely be the future – we will find out!
Thank You