ASSOCIATION OF COMMUNITY CANCER CENTERS

MULTIDISCIPLINARY CHRONIC LYMPHOCYTIC LEUKEMIA CARE
2018 ASH Updates

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Executive Vice President and Chief Medical Officer

*CLL Society, Inc.*
CLL/SLL
Chronic Lymphocytic Leukemia
Small Lymphocytic Lymphoma
CLL/SLL
ASCO 2015 Cancer Advance of the Year:
Transformation of CLL Treatment
Has everything changed because of:

1. Predictive/Prognostic Testing
2. Targeted Therapies
3. MRD Testing
What I have done to beat those odds despite very high-risk disease

- Refusing some treatments and choosing others
- Getting expert on my team
- Becoming an “expert” patient
- Enrolling in clinical trials
- Getting treatments paid for
- Joining a support group
Disclosure

Consulting: Janssen, Novartis, Verastem Oncology

Stocks: AbbVie, AZN, BGNE, BMY, Celgene, GILD, JNJ, MEIP, MGEN, PTLA, SNSS, TGTX, VO
Disclosure

• I am alive and here today because in 2011 I started on a Phase 1 clinical trial of PCI-32765 now known as ibrutinib.

• I have no detectable CLL today in my blood or bone marrow due to a 2nd clinical trial, this time with CAR-T (JCAR-14).

• I have a bias toward novel therapies, clinical trials, and patient involvement.
Prognosis

11q deletion (later 17p deletion), complex karyotype, CD38+, unmutated, ZAP70+, (now loss of Notch 1, CDKN2A, Dnmt3a, XOP1.)
Kaplan Meier Curve
(or my 1 in 20 chance of living >5 years)

April 11, 2011, as 10.1200/JCO.2010.32.0838
CLL: Epidemiology, Staging, Prognosis
CLL/SLL: Background

- 20,720 estimated new cases in 2019 in the United States alone.
  - 7% of all NHL are CLL/SLL.
- Median age: 71 yrs; more common in males vs. females.
- SLL and CLL considered the same B-cell malignancy.
  - CLL: > 5000 monoclonal lymphocytes in peripheral blood.
  - SLL: presence of lymphadenopathy and/or splenomegaly and < 5000 monoclonal lymphocytes in peripheral blood.
  - One disease with varied presentation; often termed “CLL/SLL.”
- Historical 5-yr survival: 66% (range: few months to normal life span).

CLL Epidemiology

• Causes unknown – more genetics than environment.

• Family studies – higher than expected frequency among first-degree family members with CLL/NHL (5-10% of cases).

• No certain environmental risks:
  • No increase in atomic bomb survivors.
  • No evidence for dietary/lifestyle factors.
  • Japanese in Hawaii incidence = Japanese in Japan.

• However, increased incidence of CLL reported among Chernobyl cleanup workers and veterans exposed to Agent Orange

• US Department of Veterans Affairs has agreed that exposure to Agent Orange is a risk factor for CLL.

• Veterans with CLL can claim benefits if they were previously exposed to Agent Orange while in military service.

CLL Diagnosis (iwCLL)

• Peripheral blood lymphocytosis: ≥5000/μL (≥5 x 10⁹/L).

• Flow cytometry: Monoclonal B cells - light chain restriction, CD19, CD20 (dim), CD23 and also the T-cell marker CD5.

Note:

• CLL cells usually have low levels of CD20, lack expression of CD10, and stain poorly, if at all, with the FMC7 a monoclonal antibody, which recognizes specific epitope of CD20.

• CLL cells also express CD200 (also known as OX-2 membrane glycoprotein), which can help to distinguish CLL from mantle cell lymphoma.

• In addition, the CLL cells of >95% of patients express the onco-embryonic surface antigen ROR1.
# Flow Cytometry

## Common phenotypes of B-cell cancers

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>CD5</th>
<th>CD10</th>
<th>CD19</th>
<th>CD20</th>
<th>CD23</th>
<th>CD79b</th>
<th>FMC-7</th>
<th>CD25</th>
<th>CD11c</th>
<th>CD103</th>
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<tbody>
<tr>
<td>CLL/SLL</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-/+</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-/+</td>
<td>+/-</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Marginal zone lymphoma</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+/-</td>
<td>+/-</td>
<td>-/+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Hairy cell leukemia</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
Figure 18.3 Chronic lymphocytic leukaemia: peripheral blood film showing lymphocytes with thin rims of cytoplasm, coarse condensed nuclear chromatin and rare nucleoli. Typical smudge cells are present.
# CLL Staging Systems

**Rai System**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Risk Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Lymphocytosis, lymphocytes in blood &gt;15,000/mcL and &gt;40% lymphocytes in the bone marrow</td>
<td>Low</td>
</tr>
<tr>
<td>I</td>
<td>Stage 0 with enlarged node(s)</td>
<td>Intermediate</td>
</tr>
<tr>
<td>II</td>
<td>Stage 0-I with splenomegaly, hepatomegaly, or both</td>
<td>Intermediate</td>
</tr>
<tr>
<td>III</td>
<td>Stage 0-II with hemoglobin &lt;11.0 g/dL or hematocrit &lt;33%</td>
<td>High</td>
</tr>
<tr>
<td>IV</td>
<td>Stage 0-III with platelets &lt;100,000/mcL</td>
<td>High</td>
</tr>
</tbody>
</table>

**Binet System**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Hemoglobin ≥10 g/dL and Platelets ≥100,000/mm³ and &lt;3 enlarged areas</td>
</tr>
<tr>
<td>B</td>
<td>Hemoglobin ≥10 g/dL and Platelets ≥100,000/mm³ and ≥3 enlarged areas</td>
</tr>
<tr>
<td>C</td>
<td>Hemoglobin &lt;10 g/dL and/or Platelets &lt;100,000/mm³ and any number of enlarged areas</td>
</tr>
</tbody>
</table>

C: Immune-mediated cytopenias not the basis for these definitions.
Risk Stratification/Prognostic Factors

- Clinical course extremely variable.
- Prognostic factors can help to identify patients who may require therapy relatively soon after diagnosis.
  - Clinical features;
  - Genetics;
  - Molecular; and
  - Biochemical characteristics of the CLL cell.
- Multiple models, nomograms, and prognostic indexes exist – *no single best one.*
Risk Stratification: Prognostic and Predictive Markers

- **Prognostic factors** associated with poorer outcome:
  - Unmutated IgHV ≤ 2% (or VH3.21 even if mutated)
  - ZAP70 expression ≥ 20%
  - CD38 ≥ 30%
  - β2-microglobulin (>3.5 mg per L)
  - Del (17p)/TP53 mutants, Del (11q), complex karyotypes
  - Trisomy 12 (+12) is neutral
  - Male sex
  - Age ≥ 65 years
  - Poor PS from co-morbid conditions

- **Predictive factors:**
  - del17p status
  - TP53 status
  - IgHV mutation status

* Poor prognostic variables still do not impact when to start tx.

New and Emerging Therapies: Clinical Evidence
DS is 64-year-old male diagnosed with routine lab with a ALC of 35,000. 18 months later, his ALC is 60,000. He now has multiple 2 x 1.5 cm nodes in both axilla and groin. Otherwise, exam and lab are normal. He asks what symptoms or lab might indicate it is time to treat. You tell him:

1. Unexplained fever >38°C x 2 weeks with no infection
2. Unexplained weight loss >10% over 6 months
3. Drenching night sweats >1 month with no infection
4. Severe fatigue
5. Hgb < 10 or platelets <100,000
6. WBC >100,000
7. All the above
8. 1 – 5
CLL Treatment Indications

- No absolute consensus on when/who to start treatment.

- Indications generally include:
  - Significant disease related symptoms:
    - Fevers, night sweats, weight loss;
    - **Severe fatigue**.
  - Threatened end-organ function.
  - Progressive bulky disease:
    - Spleen > 6 cm below cm, lymph nodes > 10 cm.
  - Progressive anemia.
  - Progressive thrombocytopenia.
  - Rapid lymphocyte doubling time.

- **New(superior) therapies have not changed traditional approach as to when to tx.**

- **No recent studies indicate that early intervention prolongs survival.**

- **Presence of del17p does not change approach - ~ 1/3 have indolent course.**
Patients with Mutated IGHV Have Prolonged PFS After FCR

Paradigm Shift
# CLL Treatment: Targeted Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indication in CLL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duvelisib</td>
<td>Third line</td>
</tr>
<tr>
<td>Ibrutinib</td>
<td>First or second line</td>
</tr>
<tr>
<td>Idelalisib</td>
<td>Second line</td>
</tr>
<tr>
<td>Rituximab</td>
<td>First or second line in combination</td>
</tr>
<tr>
<td>Obinutuzumab</td>
<td>First line (with chlorambucil or Ibrutinib)</td>
</tr>
<tr>
<td>Ofatumumab</td>
<td>First line (with chlorambucil)</td>
</tr>
<tr>
<td></td>
<td>Second line (with fludarabine and cyclophosphamide)</td>
</tr>
<tr>
<td></td>
<td>Extended treatment of recurrent or progressive disease</td>
</tr>
<tr>
<td>Venetoclax</td>
<td>Second line</td>
</tr>
</tbody>
</table>
Question

6 months later DS’s Hgb has dropped to 9.3 grams, his nodes have grown and are bothersome. He complains of severe fatigue. At dx, FISH revealed 11q del, and unmutated IgHV.

What test(s) do you need consider before starting therapy?

1. Flow Cytometry
2. Bone Marrow Biopsy
3. CT scan
4. FISH
5. TP53 testing
6. IgHV
B-Cell Receptor Signaling Response

- Survival of resting mature B-cells depends on BCR signaling.
- Some B-cell malignancies depend on tonic BCR signaling for tumor expansion and proliferation.
- BTK inhibitors block BCR signaling, induce apoptosis, and inhibit adhesion of malignant B-cells to microenvironment cells.

- Enhanced antigen-independent B-cell activation more common in CLL that expresses unmutated IGHV.
- Anergy predominates in most cases of CLL that express mutated IGHV.
- Anergic cells less likely to proliferate in response to BCR signaling.
- CLL cells with unmutated IGHV seem to be more sensitive to inhibitors of BCR signaling than CLL cells with mutated IGHV.
- 3 main classes of drugs that inhibit BCR signaling have been evaluated: BTK inhibitors, PI3K inhibitors, and spleen tyrosine kinase (SYK) inhibitors.

Nat Rev Dis Primers.; 3: 16096
On retesting, DS now has 41% 11q del and 9% 17p del. He has no significant comorbidities. Possible RXs include:

1. FCR (fludarabine, cyclophosphamide, and rituximab)
2. FCG (fludarabine, cyclophosphamide, and obinutuzumab/Gazyva)
3. BR (bendamustine and rituximab)
4. Ibrutinib
5. Idelalisib and rituximab
Ibrutinib

• Oral Bruton’s tyrosine kinase inhibitor (BTKi).
• Approved for frontline and relapsed settings.
• Works in patients with or w/o del(17p):
  • No data age < 65 years w/o del(17p) (trial done age >65).
• Increased risk of bleeding (6% severe):
  • ? Mechanism (described as platelet dysfxn);
  • Use with caution or avoid with warfarin/anticoagulation.
• Increased rates of atrial fibrillation.

• Avoid in moderate-to-severe liver disease.
• Lymphocytosis, initially accompanied by a rapid and sustained decrease in lymphadenopathy.
  • Related to inhibition of chemokine receptor signaling, which inhibits migration of CLL cells from blood into lymphoid tissues.
• Secondary resistance develops from binding site mutation – likely also resistant to acalabrutinib.
• Second generation BTKis in clinical trials currently for CLL and approved for MCL/WM.
• Non-covalent binding BTKis in trial for ibrutinib resistance.

• Initial data raised concerns that d/c could lead to worse outcomes.
• New data suggest d/c may be okay, but advice is to continue ibrutinib until next RX in place.

Imbruvica [prescribing information]. Sunnyvale, CA: Pharmacyclics, LLC; 2019
Up to 7 years of follow-up of single-agent Ibrutinib in the Phase 1b/2 PCYC-1102 trial of first line and relapsed/refractory patients with CLL/SLL.

The primary reason for treatment discontinuation in first line pts was AEs (23%), whereas in R/R CLL it was PD (35%).
Ibrutinib Alone or in Combination with Rituximab Produces Superior Progression Free Survival (PFS) Compared with Bendamustine Plus Rituximab in Untreated Older Patients with Chronic Lymphocytic Leukemia (CLL):

Results of Alliance North American Intergroup Study A041202

Background

• Older patients are under-represented on CLL clinical trials unless specifically designed.

• Standard therapies for older patients include chlorambucil plus obinutuzumab and bendamustine plus rituximab.

• Despite widespread use, efficacy of ibrutinib vs. standard chemoimmunotherapy has not been investigated.

• Rituximab improves survival with chemotherapy; impact on ibrutinib not established.
Primary Endpoint: Progression Free Survival

Eligible Patient Population

Pairwise Comparisons

I vs BR:
Hazard Ratio 0.39
95% CI: 0.26-0.58
(1-sided P-value <0.001)

IR vs BR:
Hazard Ratio 0.38
95% CI: 0.25-0.59
(1-sided P-value <0.001)

IR vs I:
Hazard Ratio 1.00
95% CI: 0.62-1.62
(1-sided P-value 0.49)
Del (17p13.1) Subgroup: Progression Free Survival

Intention-to-Treat Patient Population

<table>
<thead>
<tr>
<th>Arm</th>
<th>N</th>
<th>24 Month Estimate</th>
</tr>
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<tbody>
<tr>
<td>BR</td>
<td>14</td>
<td>0%</td>
</tr>
<tr>
<td>I</td>
<td>9</td>
<td>75% (95% CI: 31-93%)</td>
</tr>
<tr>
<td>IR</td>
<td>11</td>
<td>73% (95% CI: 37-90%)</td>
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</table>

Patients-at-Risk

<table>
<thead>
<tr>
<th>Arm</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
<th>36</th>
<th>42</th>
<th>48</th>
<th>52</th>
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<tbody>
<tr>
<td>Arm A (BR)</td>
<td>14</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm B (I)</td>
<td>9</td>
<td>9</td>
<td>8</td>
<td>7</td>
<td>6</td>
<td>5</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Arm C (IR)</td>
<td>11</td>
<td>10</td>
<td>9</td>
<td>9</td>
<td>8</td>
<td>7</td>
<td>6</td>
<td>3</td>
<td>2</td>
<td>0</td>
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</table>

Events/Total

<table>
<thead>
<tr>
<th>Arm</th>
<th>Events/Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>BR</td>
<td>10/14</td>
</tr>
<tr>
<td>I</td>
<td>2/9</td>
</tr>
<tr>
<td>IR</td>
<td>3/11</td>
</tr>
</tbody>
</table>

Censor
Overall Survival
Intention-to-Treat Patient Population

% Alive

Time (Months)

Overall Survival
Intention-to-Treat Patient Population

Arm | N | 24 Month Estimate
---|---|-------------------
BR | 183 | 95% (95% CI: 91-98%)
I  | 183 | 90% (95% CI: 85-94%)
IR | 182 | 94% (95% CI: 89-97%)

Arm A (BR) Events/Total: 20/183
Arm B (I) 24/182
Arm C (IR) 22/182
Censor

Median Follow-up: 38 months
Conclusions

- Ibrutinib or ibrutinib plus rituximab significantly prolongs PFS compared with BR in the frontline setting for older CLL patients.

- Rituximab does not improve PFS over ibrutinib alone.

- BTK inhibition with ibrutinib is not without significant toxicity in older patients, so close monitoring is still warranted.
  - Strategies to discontinue therapy are of great interest.

- Clinical trials for this patient population are still of high clinical interest; the cooperative group setting remains a reasonable avenue to complete these large studies.
  - A041702 (NCT03737981) and EA9161 (NCT03701282).
ECOG-E1912: Ibrutinib vs. Fludarabine, Cyclophosphamide, and Rituximab

- 529 treatment-naïve patients aged ≤70 (without del17p).
- Randomized to ibrutinib/rituximab or FCR.
- At median follow-up of 33.4 months:
  - HR=0.352 (95% CI 0.22-0.5; P<0.001) for PFS or death with ibrutinib/rituximab;
  - HR=0.17 (95% CI 0.05-0.54; P<0.003) for overall survival with ibrutinib/rituximab;
  - Similar findings regardless of IgHV mutation status;
  - Grade ≥3 AEs more common with FCR: 72% vs. 58%; P=0.0042).

Shanafelt et al. Abstract # LBA-4. Presented at the 2018 ASH Annual Meeting, December 4, 2018; San Diego, CA.
Progression Free Survival

Intent to Treat

HR = 0.35 (95% CI 0.22-0.5)
One sided p<0.00001

HR = 0.35 (95% CI 0.22−0.56)
One−sided p = 1.62 · 10^{-6}

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

Number at risk

<table>
<thead>
<tr>
<th>Years</th>
<th>Number at risk</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>354</td>
</tr>
<tr>
<td>1</td>
<td>339</td>
</tr>
<tr>
<td>2</td>
<td>298</td>
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<tr>
<td>3</td>
<td>148</td>
</tr>
<tr>
<td>4</td>
<td>16</td>
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<table>
<thead>
<tr>
<th>Years</th>
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<td>1</td>
<td>147</td>
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<td>2</td>
<td>112</td>
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<tr>
<td>3</td>
<td>50</td>
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<tr>
<td>4</td>
<td>0</td>
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# PFS Sub-Group Analysis

<table>
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<tr>
<th>Group</th>
<th>N</th>
<th>E</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All randomized</td>
<td>529</td>
<td>77</td>
<td>0.35</td>
<td>(0.22, 0.56)</td>
</tr>
<tr>
<td>Eligible</td>
<td>498</td>
<td>72</td>
<td>0.32</td>
<td>(0.20, 0.51)</td>
</tr>
<tr>
<td>Female</td>
<td>173</td>
<td>19</td>
<td>0.30</td>
<td>(0.12, 0.77)</td>
</tr>
<tr>
<td>Male</td>
<td>356</td>
<td>58</td>
<td>0.40</td>
<td>(0.23, 0.67)</td>
</tr>
<tr>
<td>Age &lt; 60</td>
<td>314</td>
<td>51</td>
<td>0.32</td>
<td>(0.18, 0.56)</td>
</tr>
<tr>
<td>Age &gt;= 60</td>
<td>215</td>
<td>26</td>
<td>0.44</td>
<td>(0.20, 0.97)</td>
</tr>
<tr>
<td>ECOG PS 0</td>
<td>335</td>
<td>46</td>
<td>0.26</td>
<td>(0.14, 0.47)</td>
</tr>
<tr>
<td>ECOG PS 1 or 2</td>
<td>194</td>
<td>31</td>
<td>0.61</td>
<td>(0.29, 1.27)</td>
</tr>
<tr>
<td>Rai Stage 0–II</td>
<td>301</td>
<td>41</td>
<td>0.35</td>
<td>(0.18, 0.65)</td>
</tr>
<tr>
<td>Rai Stage III–IV</td>
<td>228</td>
<td>36</td>
<td>0.38</td>
<td>(0.19, 0.74)</td>
</tr>
<tr>
<td>Splenomegaly No</td>
<td>311</td>
<td>39</td>
<td>0.36</td>
<td>(0.19, 0.70)</td>
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<tr>
<td>Splenomegaly Yes</td>
<td>218</td>
<td>38</td>
<td>0.32</td>
<td>(0.17, 0.63)</td>
</tr>
<tr>
<td>Lymphadenopathy No</td>
<td>159</td>
<td>16</td>
<td>0.44</td>
<td>(0.14, 1.42)</td>
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<tr>
<td>Lymphadenopathy Yes</td>
<td>370</td>
<td>61</td>
<td>0.35</td>
<td>(0.21, 0.59)</td>
</tr>
<tr>
<td>Dohner Del(11q22)</td>
<td>117</td>
<td>22</td>
<td>0.24</td>
<td>(0.10, 0.62)</td>
</tr>
<tr>
<td>Dohner Trisomy 12</td>
<td>97</td>
<td>10</td>
<td>0.73</td>
<td>(0.19, 2.89)</td>
</tr>
<tr>
<td>Dohner Normal</td>
<td>106</td>
<td>18</td>
<td>0.78</td>
<td>(0.29, 2.04)</td>
</tr>
<tr>
<td>Dohner Del(13q)</td>
<td>179</td>
<td>19</td>
<td>0.22</td>
<td>(0.08, 0.60)</td>
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<tr>
<td>IGHV Mutated</td>
<td>114</td>
<td>14</td>
<td>0.44</td>
<td>(0.14, 1.35)</td>
</tr>
<tr>
<td>IGHV Unmutated</td>
<td>281</td>
<td>41</td>
<td>0.26</td>
<td>(0.14, 0.50)</td>
</tr>
</tbody>
</table>
Progression Free Survival: IGHV Status

**IGHV Unmutated**

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

**IGHV Mutated**

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

**Graphical Representation**

- IR (20 events/ 210 cases)
- FCR (21 events/ 71 cases)

**Number at risk**

- IGHV Unmutated:
  - 210
  - 203
  - 177
  - 90
  - 12

- IGHV Mutated:
  - 70
  - 67
  - 59
  - 25
  - 2
Overall Survival

Intent to Treat

HR = 0.17 (95% CI 0.05−0.54)
One sided p<0.0003

Number at risk

<table>
<thead>
<tr>
<th>Years</th>
<th>354</th>
<th>347</th>
<th>318</th>
<th>166</th>
<th>18</th>
</tr>
</thead>
</table>

FCR (10 events/ 354 cases)

Eligible

HR = 0.13 (95% CI 0.03−0.46)
One sided p<0.0001

Number at risk

<table>
<thead>
<tr>
<th>Years</th>
<th>332</th>
<th>327</th>
<th>298</th>
<th>154</th>
<th>18</th>
</tr>
</thead>
</table>

FCR (10 events/ 166 cases)
Conclusions

• Ibrutinib and rituximab provides superior PFS and OS compared to FCR for patients with previously untreated CLL.

• Ibrutinib and rituximab was well tolerated in patients ≤ age 70.

• The need for indefinite therapy should be evaluated in future clinical trials testing novel agent combination therapy.

  • EA9161 (NCT03701282; pts age<70) & A041702 (NCT03737981; pts age>70).
## Grade 3, 4, or 5 Adverse Events ALLIANCE

### During treatment or follow-up (excluding crossover)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>BR n=176</th>
<th>Ibrutinib n=180</th>
<th>IR n=181</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Hematologic -- no. (%)</td>
<td>107 (61)</td>
<td>74 (41)</td>
<td>70 (38)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anemia</td>
<td>22 (13)</td>
<td>21 (12)</td>
<td>11 (6)</td>
<td>0.09</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>71 (40)</td>
<td>27 (15)</td>
<td>39 (22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>26 (15)</td>
<td>12 (7)</td>
<td>9 (5)</td>
<td>0.008</td>
</tr>
<tr>
<td><strong>All Non-hematologic -- no. (%)</strong></td>
<td><strong>111 (63)</strong></td>
<td><strong>133 (74)</strong></td>
<td><strong>134 (74)</strong></td>
<td><strong>0.04</strong></td>
</tr>
<tr>
<td>Bleeding</td>
<td>0 (0)</td>
<td>3 (2)</td>
<td>5 (3)</td>
<td>0.46</td>
</tr>
<tr>
<td>Infections</td>
<td>26 (15)</td>
<td>37 (21)</td>
<td>37 (20)</td>
<td>0.62</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>13 (7)</td>
<td>3 (2)</td>
<td>1 (1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>5 (3)</td>
<td>17 (9)</td>
<td>10 (6)</td>
<td>0.05</td>
</tr>
<tr>
<td>Hypertension</td>
<td>25 (14)</td>
<td>53 (29)</td>
<td>61 (34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Unexplained/unwitnessed death</td>
<td>2 (1)</td>
<td>7 (4)</td>
<td>4 (2)</td>
<td>0.24</td>
</tr>
</tbody>
</table>

- Deaths during active treatment + 30 days: 2 (1%), 13 (7%), 13 (7%).
- Deaths during active treatment + 30 days, up to 6 cycles: 2 (1%), 3 (2%), 6 (3%).
Ibrutinib Adverse Events: ECOG 1912

Randomized Phase III frontline young patients (I vs. I-R vs. FCR)

**TABLE 1.** Grade ≥3-5 Treatment-Related Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Ibrutinib plus Rituximab (n=352)</th>
<th>Fludarabine, Cyclophosphamide, Rituximab (n=158)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>22.7%</td>
<td>43.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anemia</td>
<td>2.6%</td>
<td>12%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2.9%</td>
<td>13.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Infection</td>
<td>7.1%</td>
<td>19%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2.9%</td>
<td>0%</td>
<td>0.04</td>
</tr>
<tr>
<td>Bleeding</td>
<td>1.1%</td>
<td>0%</td>
<td>0.32</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7.4%</td>
<td>1.9%</td>
<td>0.01</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2.6%</td>
<td>0.6%</td>
<td>0.19</td>
</tr>
</tbody>
</table>

Shanafelt et al. Abstract # LBA-4. Presented at the 2018 ASH Annual Meeting, December 4, 2018; San Diego, CA.
Flowchart for Management of Atrial Fibrillation During Ibrutinib Use

Ibrutinib-related atrial fibrillation

- Rate/rhythm control
  - Avoid P-glycoprotein substrates
  - Avoid CYP3A inhibitors

CHA$_2$DS$_2$-VASc ≤ HAS-BLED score
- No need for anticoagulation
  - Continue ibrutinib

CHA$_2$DS$_2$-VASc > HAS-BLED score
- Need for anticoagulation
  - DOAC is preferred over VKA
  - Consider alternative anti-lymphoproliferative disorder treatment options
Summary of Relevant Issues Relating to Bleeding and Anticoagulation During Ibrutinib Treatment

- Cessation of ibrutinib 3-7 days before and after invasive procedures
- Bruising is very common and does not herald major bleeding
- Concomitant antiplatelet therapy does not seem to increase major bleeding
- Concomitant anticoagulation does not seem to increase major bleeding
- Very limited experience with concomitant vitamin K antagonists
- Avoid combined anticoagulation and antiplatelet treatment during ibrutinib use
BCL-2 Inhibitor: Venetoclax

- Orally available, selective, small molecule inhibitor of BCL2:
  - BH3 mimetic: Mimics Bcl-2 homology 3 (BH3) domains of the pro-apoptotic Bcl-2 family members, which neutralize these proteins by binding to their surface hydrophobic grooves.

- FDA approved for relapsed del(17p) disease only:
  - Multicenter, open label phase 2;
  - ORR 79%, 8% CR;
  - 12-month PFS was 72%, OS 87%;

- TLS! – Assess risk, use hypouricemic agents, monitor:
  - High-risk patients require hospitalization.

Lancet Oncol. 17, 768–778 (2016)
Fixed Duration of Venetoclax-Rituximab in Relapsed/Refractory Chronic Lymphocytic Leukemia Eradicates Minimal Residual Disease and Prolongs Survival: Post-Treatment Follow-Up of the MURANO Phase III Study

Patients with R/R CLL after 1-3 previous lines of therapy

Venetoclax 5-wk titration, 400 mg PO QD for C1-6 + rituximab (n = 194) vs bendamustine + rituximab (n = 195) for 6 cycles

ORR: 93.3% with venetoclax/R vs 67.7% with BR. Estimated 3-year mPFS 71.4% vs 15.2%
## CAPTIVATE: Efficacy (I+V)

<table>
<thead>
<tr>
<th>Outcome, %</th>
<th>6 Cycles of I+V (n = 30)</th>
<th>9 Cycles of I+V (n = 14)</th>
<th>12 Cycles of I+V (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood MRD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 0.01% (undetectable)</td>
<td>77</td>
<td>86</td>
<td>93*</td>
</tr>
<tr>
<td>0.01% - &lt; 1.0%</td>
<td>13</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>≥ 1.0%</td>
<td>10</td>
<td>NE</td>
<td>--</td>
</tr>
<tr>
<td><strong>Bone marrow MRD†</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 0.01% (undetectable)</td>
<td>--</td>
<td>--</td>
<td>86</td>
</tr>
<tr>
<td>0.01% - &lt; 1.0%</td>
<td>--</td>
<td>--</td>
<td>14</td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td></td>
<td></td>
<td>100 (n = 11)</td>
</tr>
<tr>
<td>CR</td>
<td></td>
<td></td>
<td>36</td>
</tr>
<tr>
<td>CRi</td>
<td>--</td>
<td>--</td>
<td>18</td>
</tr>
<tr>
<td>nPR</td>
<td>--</td>
<td>--</td>
<td>9</td>
</tr>
<tr>
<td>PR</td>
<td></td>
<td></td>
<td>36</td>
</tr>
</tbody>
</table>

*79% with confirmed undetectable MRD. †Assessed only after 12 cycles I + V.

Venetoclax Toxicity

- Tumor lysis syndrome (TLS) is the most important potential early complication.
- Slow, stepped-up dosing and preventive measures can nearly eliminate this risk.
- The most common single agent toxicities include neutropenia, diarrhea, nausea, URI, anemia, fatigue, thrombocytopenia, musculoskeletal pain, edema, and cough.
- Similar toxicity with higher rates when combined with rituximab (MURANO).

<table>
<thead>
<tr>
<th>TLS adverse reactions and relevant common (≥10%) new or worsening laboratory abnormalities occurring at ≥5% (any grade) or ≥2% (grade 3 or 4) higher incidence with VEN+R compared with BR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>TLS</td>
</tr>
<tr>
<td>Laboratory Abnormality</td>
</tr>
<tr>
<td>Hypocalcemia</td>
</tr>
<tr>
<td>Hyperuricemia</td>
</tr>
<tr>
<td>Hyperkalemia</td>
</tr>
</tbody>
</table>
### Murano Toxicity Data Summary

**SUMMARY OF ADVERSE REACTIONS REPORTED WITH INCIDENCE OF ≥10% AND ≥5% HIGHER FOR ALL GRADES OR ≥2% HIGHER FOR GRADE 3 OR 4 IN PATIENTS TREATED WITH VEN+R COMARED WITH BR**

<table>
<thead>
<tr>
<th>Adverse Reaction by Body System</th>
<th>VEN+R followed by single agent VENCLEXTA* (n=194)</th>
<th>BR (n=188)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade ≥3 (%)</td>
</tr>
<tr>
<td><strong>Blood &amp; lymphatic system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia*</td>
<td>65</td>
<td>62</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>40</td>
<td>3</td>
</tr>
<tr>
<td><strong>Infections &amp; infestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection*</td>
<td>39</td>
<td>2</td>
</tr>
<tr>
<td>Lower respiratory tract infection*</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td><strong>Musculoskeletal &amp; connective tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain*</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td><strong>Metabolism &amp; nutrition disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor lysis syndrome</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

*Includes multiple adverse reaction terms.
Venetoclax TLS Risk Assessment

**STEP 1: ASSESS**
PRIOR TO TREATMENT
- Assess Tumor Burden
- Assess Renal Function and Comorbidities
- Assess & Correct Baseline Blood Chemistries

**STEP 2: PREPARE**
2-3 DAYS PRIOR TO FIRST DOSE
- Begin Administering Anti-hyperuricemics 2-3 Days Prior
- Initiate Oral and/or IV Hydration 2 Days Prior*

**STEP 3: INITIATE**
FIRST 5 WEEKS OF TREATMENT
- 5-Week Dose Ramp-up*
- Blood Chemistry Monitoring†
# Venetoclax TLS Management

## Tumor Burden Assessment

<table>
<thead>
<tr>
<th>Low Tumor Burden</th>
<th>Medium Tumor Burden</th>
<th>High Tumor Burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>All LN &lt;5 cm AND ALC &lt;25 x 10⁹/L</td>
<td>Any LN 5 cm to &lt;10 cm OR ALC ≥25 x 10⁹/L</td>
<td>Any LN ≥10 cm OR Any LN ≥5 cm AND ALC ≥25 x 10⁹/L</td>
</tr>
</tbody>
</table>

## Step 2: Prepare 2-3 Days Prior to First Dose

### Anti-hyperuricemics
- **Allopurinol**

### Hydration
- Oral (1.5-2 L)
- Consider additional IV

## Step 3: Initiate First 5 Weeks of Treatment

### Blood Chemistry Monitoring
- **Outpatient**
  - For first dose of 20 mg and 50 mg: Pre-dose, 6 to 8 hours, 24 hours
  - For subsequent ramp-up doses: Pre-dose

- **In hospital**
  - For first dose of 20 mg and 50 mg: Pre-dose, 4, 8, 12, and 24 hours
  - For subsequent ramp-up doses: Pre-dose, 6 to 8 hours, 24 hours

- **Outpatient**
  - For first dose of 20 mg and 50 mg: Pre-dose, 6 to 8 hours, 24 hours

- **In hospital**
  - For first dose of 20 mg and 50 mg: Pre-dose, 4, 8, 12, and 24 hours
  - For subsequent ramp-up doses: Pre-dose, 6 to 8 hours, 24 hours
PI3K Inhibitor: Idelalisib

• Oral inhibitor of phosphoinositide 3'-kinase (PI3K) delta.

• Approved in relapsed setting in combination with rituximab:
  • I-R superior to placebo-R (ORR 81% vs 13%; mOS 20.8 mo vs NR);
  • Works in all subsets del(17p)/TP53, IGHV mutations.

• Also causes lymphocytosis initially (peaks at week 2, resolves by week 12).

• AE: Transaminitis, pneumonitis, colitis (can be severe and occur > 6 months after initiating tx) – black box warnings.

• Prophylaxis for varicella, PCP, test HBV, monitor CMV.

### Toxicity: Idelalisib

<table>
<thead>
<tr>
<th></th>
<th>Previously untreated</th>
<th>Previously treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (number)</td>
<td>64</td>
<td>393</td>
</tr>
<tr>
<td>Diarrhea and/or colitis, any grade</td>
<td>64</td>
<td>14-43</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>42</td>
<td>4-18</td>
</tr>
<tr>
<td>Fatigue, any grade</td>
<td>31</td>
<td>24-36</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>0</td>
<td>2-3</td>
</tr>
<tr>
<td>Cough, any grade</td>
<td>33</td>
<td>13-29</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>2</td>
<td>0-4</td>
</tr>
<tr>
<td>URTI, any grade</td>
<td>NR</td>
<td>14-20</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia, any grade</td>
<td>28</td>
<td>11-22</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>19</td>
<td>6-20</td>
</tr>
<tr>
<td>Pneumonitis, any grade</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>AST and/or ALT increased, any grade</td>
<td>67</td>
<td>24-60</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>23</td>
<td>2-20</td>
</tr>
<tr>
<td>Neutropenia, any grade</td>
<td>53</td>
<td>30-57</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>28</td>
<td>10-43</td>
</tr>
<tr>
<td>Anemia, any grade</td>
<td>23</td>
<td>23-37</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>3</td>
<td>2-11</td>
</tr>
<tr>
<td>Thrombocytopenia, any grade</td>
<td>14</td>
<td>17-30</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>2</td>
<td>5-17</td>
</tr>
<tr>
<td>Febrile neutropenia, any grade</td>
<td>5</td>
<td>3-11</td>
</tr>
</tbody>
</table>

Values represent percentage of patients affected. URTI: upper respiratory tract infection; AST: aspartate transaminase; ALT: alanine transaminase; NR: not reported.
Idelalisib: Summary of Common Adverse Events

• Diarrhea occurs in 2 forms: self-limiting and severe:
  • Self-limiting: usually early onset and responds to common antidiarrheal agents.
  • Severe: responds poorly to antimotility agents but appears to be responsive to budesonide and/or systemic corticosteroids.

• ALT/AST elevations are generally reversible with idelalisib dose interruptions:
  • 74% of patients were able to be retreated with idelalisib without recurrence.

• Pulmonary symptoms should be evaluated for pneumonitis:
  • Discontinue idelalisib with any severity of symptomatic pneumonitis.
  • Some patients were treated with discontinuation of corticosteroids in addition to continuing antibiotics if pneumonitis did not improve.

Duvelisib

- Duvelisib is a first-in-class, oral dual inhibitor of PI3K-δ,γ approved by the US FDA for treatment of adult patients with:
  - relapsed/refractory CLL or SLL after ≥ 2 prior therapies.¹
  - relapsed/refractory FL after at least ≥ 2 prior systemic therapies.¹

Note: This indication is approved under accelerated approval based on overall response rate (ORR); continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

PI3K-δ (delta) inhibition predominantly restricts malignant B-cell growth and survival.¹

PI3K-γ (gamma) inhibition helps modulate the tumor microenvironment, a network of nonneoplastic cells essential to malignant B-cell survival and proliferation.¹,²

Prohibit proliferation and reduce viability in malignant B cells with PI3K-δ inhibition.

Block CXCL12-induced T-cell migration and M2 macrophage polarization with PI3K-inhibition (based on pre-clinical studies).

1. COPIKTRA Prescribing Information, Verastem, Inc.
DUO Patients ≥2 Prior Lines of Therapy:
Duvelisib Demonstrated >7-month Median PFS Advantage vs Ofatumumab*

Progression-Free Survival per IRC¹

Progression-Free Survival per Investigator²

No. at Risk
Duvelisib 95 88 69 60 50 39 13 9 2 2 0
Ofatumumab 101 78 52 39 22 4 2 1 1 1 1 0

Median PFS: 16.4 vs 9.1 months
HR: 0.4 (0.27-0.59)¹²

No. at Risk
Duvelisib 96 89 74 67 53 42 26 24 10 6 4 3 0
Ofatumumab 101 83 55 45 27 12 5 5 3 3 1 1 0

Median PFS: 17.8 vs 9.3 months
HR: 0.35 (0.24-0.51)²

*Kaplan-Meier estimate.
BID, twice a day; HR, hazard ratio; IRC, Independent Review Committee; PFS, progression-free survival
Duvelisib Warnings and Precautions:

Incidence of Serious (Including Fatal) Adverse Experiences and Time to Onset

<table>
<thead>
<tr>
<th>Adverse Experience</th>
<th>Serious (including fatal)</th>
<th>Fatal</th>
<th>Median Onset (all grades)</th>
<th>Range of Onset</th>
<th>75% of Events Occurred By</th>
<th>Median Event Duration and Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td>31%</td>
<td>18/442, 4%</td>
<td>3 months</td>
<td>1 day to 32 months</td>
<td>6 months</td>
<td>Not reported</td>
</tr>
<tr>
<td>Diarrhea or Colitis</td>
<td>18%</td>
<td>1/442, &lt;1%</td>
<td>4 months</td>
<td>1 day to 33 months</td>
<td>8 months</td>
<td>Duration: 0.5 months Range: 1 day to 29 months, 75th Percentile: 1 month</td>
</tr>
<tr>
<td>Cutaneous Reactions*</td>
<td>5%</td>
<td>2/442, &lt;1%</td>
<td>3 months</td>
<td>1 day to 29 months</td>
<td>6 months</td>
<td>Duration: 1 month Range: 1 day to 37 months, 75th Percentile: 2 months</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>5%</td>
<td>1/442, &lt;1%</td>
<td>4 months</td>
<td>9 days to 27 months</td>
<td>9 months</td>
<td>Duration: 1 month 75% resolve by 2 months</td>
</tr>
</tbody>
</table>

*Included drug reaction with eosinophilia and systemic symptoms (DRESS) and toxic epidermal necrolysis (TEN).

The most common serious infections were pneumonia, sepsis, and lower respiratory tract infections. Serious, including fatal, Pneumocystis jirovecii pneumonia (PJP) occurred in 1% of patients. CMV reactivation/infection occurred in 1% of patients.
# Current Treatment Landscape in CLL

## First-line Treatment Options

<table>
<thead>
<tr>
<th>With del(17p)/TP53 mutations</th>
<th>No del(17p)/TP53 mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibrutinib</td>
<td>FCR</td>
</tr>
<tr>
<td>Obinutuzumab</td>
<td>BR</td>
</tr>
<tr>
<td>Clinical trial</td>
<td>Ibrutinib</td>
</tr>
<tr>
<td><em>(if contraindications to ibrutinib)</em></td>
<td>Chlorambucil + obinutuzumab</td>
</tr>
</tbody>
</table>

## Second-line Treatment Options

<table>
<thead>
<tr>
<th>With del(17p)/TP53 mutations</th>
<th>No del(17p)/TP53 mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibrutinib</td>
<td>Ibrutinib</td>
</tr>
<tr>
<td>Venetoclax + rituximab</td>
<td>Venetoclax + rituximab</td>
</tr>
<tr>
<td>Idelalisib + rituximab</td>
<td>Idelalisib + rituximab</td>
</tr>
<tr>
<td>Duvelisib (after 2 prior lines tx)</td>
<td>Duvelisib (after 2 prior lines tx)</td>
</tr>
<tr>
<td>Other options:</td>
<td>Other options:</td>
</tr>
<tr>
<td>Acalabrutinib <em>(off label)</em></td>
<td>Acalabrutinib <em>(off label)</em></td>
</tr>
<tr>
<td>High-dose methylprednisolone + CD20 mAb</td>
<td>Alternate chemotherapy not used first line?</td>
</tr>
<tr>
<td></td>
<td>High-dose methylprednisolone + CD20 mAb</td>
</tr>
</tbody>
</table>

### Three KIs are available:
- Ibrutinib (BTKi), idelalisib (PI3Kδi), and duvelisib (PI3Kδ/γi)
- Also BCL-2 inhibitor: Venetoclax (BCL2i)
Three KIs are available: Ibrutinib (BTKi), idelalisib (PI3Kδi), and duvelisib (PI3Kδ/γi)  
Also BCL-2 inhibitor: Venetoclax (BCL2i)

<table>
<thead>
<tr>
<th>First-line Treatment Options</th>
<th>No del(17p)/TP53 mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>With del(17p)/TP53 mutations</td>
<td>FCR</td>
</tr>
<tr>
<td>Ibrutinib</td>
<td>BR</td>
</tr>
<tr>
<td>Obinutuzumab</td>
<td>Ibrutinib</td>
</tr>
<tr>
<td>Clinical trial</td>
<td>Chlorambucil + obinutuzumab</td>
</tr>
<tr>
<td>(if contraindications to ibrutinib)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Second-line Treatment Options</th>
<th>No del(17p)/TP53 mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>With del(17p)/TP53 mutations</td>
<td>Venetoclax + rituximab</td>
</tr>
<tr>
<td>Ibrutinib</td>
<td>Idelalisib + rituximab</td>
</tr>
<tr>
<td>Venetoclax + rituximab</td>
<td>Duvelisib (after 2 prior lines tx)</td>
</tr>
<tr>
<td>Idelalisib + rituximab</td>
<td>Other options:</td>
</tr>
<tr>
<td>Duvelisib (after 2 prior lines tx)</td>
<td>Acalabrutinib (off label)</td>
</tr>
<tr>
<td>Other options:</td>
<td>High-dose methylprednisolone + CD20 mAb</td>
</tr>
<tr>
<td>Acalabrutinib (off label)</td>
<td></td>
</tr>
<tr>
<td>High-dose methylprednisolone + CD20 mAb</td>
<td></td>
</tr>
</tbody>
</table>

With del(17p)/TP53 mutations: Ibrutinib

No del(17p)/TP53 mutations: Ibrutinib

With del(17p)/TP53 mutations: Ibrutinib, Obinutuzumab

No del(17p)/TP53 mutations: FCR, BR, Ibrutinib, Chlorambucil + obinutuzumab

First-line Treatment Options

Second-line Treatment Options
2016 Treatment Selection Survey
Willingness to Take Lifelong Therapy for Long-Term Control Without Potential for Cure

96% Yes
4% No
CAR-T Cell Therapy
Role in CLL
1) T Cell Collection

2) T Cell Transfection
   1. Binding
   2. Fusion

3) T Cell Adoptive Transfer
   +/− Lymphodepleting conditioning
   3. Integration
   4. Transcription and protein expression
   5. CAR cell membrane insertion

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
Why CARs?

• Best of both worlds of the immune system:
  • B cell specificity;
  • T cell cytotoxicity without presentation.
• Form of Adoptive T cell therapy.
• Synthetically engineered receptors designed to overcome immune tolerance/tumor evasion.
• Targets surface molecules in their native confirmation.
• Engage target independent of antigen presenting cell (APC) and MHC complex.

Ideal CAR Target...

• Tumor specific.
• Universally expressed on only tumor cells.
• Cell surface molecule.
• CD 19:
  • Found on B cell malignant cells (NHL, CLL, ALL, etc.);
  • Expressed on early B cells but NOT stem cells.
Complications of CAR T Cells

- **Cytokine Release Syndrome (CRS)**
  - Typically within 5 days and CRP best predictor.
  - Exponential T cell proliferation leads to IL2, IL6, IFN.
  - Can lead to macrophage activation syndrome and shock/organ failure.
    - Treated with IL6 monoclonal antibodies (Tocilizumab) and steroids.

- **B Cell Aplasia**
  - Immunoglobulin replacement required to keep Ig > 5g/L.

- **Encephalopathy**
  - Unclear pathogenesis.
  - Self limiting.
  - No long-term complications.
  - CAR T cells in CSF in all patients.

Challenges of CAR-T Cell Therapy

• Unclear how well it will work against solid tumor or even large nodes.
  – Problem of T cells entering tumor site.
• Will tumors lose target antigen and develop resistance?
• Technical and regulatory challenges of producing genetically modified CAR-T cells for each patient.
• Exhaustion of transferred T cells:
  – Use CRISPR gene editing to delete PD-1 from T cells;
  – Increased risk of autoimmune reactions from endogenous TCRs;
  – Use CRISPR to delete TCRs;
  – Result is PD-1- T cells expressing tumor-specific CAR.
CD19-Targeted CAR-T Therapy in Patients with Ibrutinib-Refactory CLL

### Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All Patients (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>60 (40–73)</td>
</tr>
<tr>
<td>Prior fludarabine + R regimen, %</td>
<td>18 (100)</td>
</tr>
<tr>
<td>Prior ibrutinib</td>
<td>18 (100)</td>
</tr>
<tr>
<td>Ibrutinib-refractory, n (%)</td>
<td>11 (61)</td>
</tr>
<tr>
<td>Ibrutinib-intolerant, n (%)</td>
<td>3 (17)</td>
</tr>
<tr>
<td>Venetoclax-refractory, n (%)</td>
<td>4 (22)</td>
</tr>
<tr>
<td>Complex karyotype, n (%)</td>
<td>12 (67)</td>
</tr>
<tr>
<td>del(17p), n (%)</td>
<td>11 (61)</td>
</tr>
<tr>
<td>Median abnormal B-cells in BN, % (range)</td>
<td>77 (0.4–96)</td>
</tr>
</tbody>
</table>

At day 28, 11/13 (85%) of patients who received Cy/Flu lymphodepletion and 2x10^6 CAR-T cells/kg had complete elimination of marrow disease*

* By flow cytometry; † 4 weeks after last CAR-T infusion.

### Response (n=17)†

- **ORR**
  - All (N=17): 76%
  - Ibrutinib-ref/intolerant (n=13): 50%
  - Venetoclax-refractory (n=4): 50%

- **Patients**
  - CR: 29%
  - PR: 23%

### PFS

- **Non CR (n=8)**
- **CR (n=5)**

Transcend CLL 004 Phase 1 Study: Lisocabtagene Maraleucel (LISO-CEL; JCAR017) CD19-Targeted Defined Cell Product

- Liso-cel demonstrated promising activity in a heavily pretreated patient population with high-risk CLL, all of whom had received prior ibrutinib.
- Liso-cel toxicities were manageable at both dose levels tested – Low rates of grade 3 CRS (6.3%) and neurologic events (18.8%).
- High best ORR (81.3%) and a CR/CRi rate (43.8%).
  - Responses have deepened over time at 3- and 6-month follow-up – CR continues in 5 of 6 patients with at least 3 months of follow-up.
- Early uMRD4 responses were observed in a majority of patients (73.3%) and were maintained at 3 and 6 months.
Conclusions

• CAR-T cells are exciting addition to our ability to treat CLL and other cancers.
• The quality of CARs is improving and further data is accumulating.
• However, long-term data (Persistence of CARs) is lacking.
• The cause of toxicity is not clear.
• More questions than answers at presence. Where/when/how to use them.
The Amazing Transformation of CAR-T!

The story of change from exhausted T-cell to life-saving SUPERHERO!

Story and text by Brian & Patty Koffman
Will Koffman, Illustrator

Supported by JUNO Therapeutics
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Wait a minute...

I am being pulled out of my person.

Now I'm being spun around like crazy!
And to add insult to injury, I'm being attacked by viruses that are inserting new messages into my DNA, my instructional code.
I'm changed...

I am transformed....

...focused, powerful!
I am part me, part another creature, like the ancient mythical chimera that was part lion, part goat and part snake. In my case it's part human and part virus. The virus is helping me to build a new receptor to recognize a marker on the surface of B-cells - CD-19. I am a Chimeric Antigen Receptor-T cell, a CAR-T or Car-ty as I like to be called.

My new CAR has a target element, spacer, transmembrane domain, co-stimulatory domain and signaling domain to supercharge me!
Understanding U-MRD
Undetectable Minimal Residual Disease (U-MRD) CLL

- Complete eradication of leukemia is desired end point.
- Sensitive multicolor flow cytometry, PCR or NGS, can detect MRD in many patients with complete clinical response.
- Substantial evidence that therapies able to eradicate MRD usually lead to improved clinical outcome.
- Techniques for assessing MRD have become well-standardized.
- 6-color flow cytometry (MRD flow), allele-specific oligonucleotide PCR, or high-throughput sequencing using the ClonoSEQ assay are reliably sensitive to < 1 CLL cell /10,000 leukocytes.
- Typical flow cytometry–based assay: 6 markers (ie, CD19, CD20, CD5, CD43, CD79b, and CD81) increasingly commercially available.

Blood. 2018;131(25):2745-2760
Undetectable Minimal Residual Disease (U-MRD) CLL, Cont’d

• Patients have undetectable MRD (U-MRD) if blood or marrow <1 CLL cell/10,000 leukocytes.

• Peripheral blood generally used for assessment; marrow will have detectable CLL when also found in peripheral blood.

• Some therapies preferentially clear blood but not marrow (such as monoclonal antibodies); therefore, may be important to confirm that marrow is MRD-neg when blood is MRD-neg.

• Preferred term now is U-MRD.
Minimal Residual Disease (MRD) Is Independent Predictor of 10-year Survival in CLL

Retrospective analysis of bone marrow MRD status after various therapies in UK 1996-2007

Upfront MRD(-) vs. MRD (+): 10-year PFS 65% vs 10%, 10-year OS 70% vs 30%

The CLL Toolkit provides health care providers with CLL-specific educational materials to supplement the education that is taking place verbally in their physician-patient dialogue.

- Binder format;
- Just-in-time handouts on various topics;
- Meets the patient where they are in the CLL journey;
- Supplemental online materials for updates, re-orders, and surveys.

SIGN UP FOR A FREE COPY TODAY!
cllsociety.org/kit
The CLL Society, Inc.

- 501C3 non-profit founded by family physician and CLL patient and his CLL caregiver.
- Focus on patient and caregiver education, support, and research.
- Dedicated to addressing the unmet needs of the CLL and related blood cancer communities.
- The primary source of reliable CLL-specific information:
  - Over 1.3 Million website visits since 2015;
  - ~ 5000 patients and caregivers on mailing list;
  - > 800 original articles with conference coverage including ASH, ASCO & EHA;
  - Research presented at ASCO, ASH and EHA including the largest survey of CLL patients.
- World-renowned CLL physicians on our Medical Advisory Board.
Has everything changed because of:

1. Predictive/Prognostic Testing  YES
2. Targeted Therapies          YES
3. MRD Testing                Not Yet
If I had an hour to solve a problem and my life depended on the solution, I would spend the first 55 minutes determining the proper question to ask.

Albert Einstein (1879 - 1955) Physicist & Nobel Laureate
Thank You

Brian Koffman, MDCM, FCFP, DABFP, MS Ed
Executive Vice President and Chief Medical Officer

CLL Society, Inc.