WELCOME & INTRODUCTIONS

Update on Chronic Lymphocytic Leukemia (CLL)

Program will begin shortly

To register or to view the BCC schedule, visit www.LLS.org/bcc.

Rocky Mountain Blood Cancer Conference
Aurora, CO
May 4, 2019

Texas Blood Cancer Conference
San Antonio, TX
May 18, 2019

UPDATE ON CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

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Department of Leukemia
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, TX
Jan A. Burger, MD, PhD, has no disclosures.

### The Rai System for Clinical Staging of CLL

<table>
<thead>
<tr>
<th>Stage</th>
<th>3-Stage System</th>
<th>Features</th>
<th>Median Survival(y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low risk</td>
<td>Lymphocytosis</td>
<td>&gt;10</td>
</tr>
<tr>
<td>I</td>
<td>Intermediate risk</td>
<td>Lymphadenopathy</td>
<td>7</td>
</tr>
<tr>
<td>II</td>
<td></td>
<td>Splenomegaly ± hepatomegaly</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>High risk</td>
<td>Anemia</td>
<td>2-5</td>
</tr>
<tr>
<td>IV</td>
<td></td>
<td>Thrombocytopenia</td>
<td></td>
</tr>
</tbody>
</table>

Prognostic Factors Associated With Inferior Survival

- Advanced stage at diagnosis
- Short lymphocyte doubling time
- Diffuse pattern of marrow infiltration
- Advanced age/males
- High serum levels of $\beta_2$-microglobulin
- CLL–PLL

Genomic Aberrations In CLL Interphase FISH Results
82% Abnormal

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>No. Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13q deletion</td>
<td>178(55)</td>
</tr>
<tr>
<td>11q deletion</td>
<td>58(18)</td>
</tr>
<tr>
<td>trisomy 12</td>
<td>53(16)</td>
</tr>
<tr>
<td>17p deletion</td>
<td>23(7)</td>
</tr>
<tr>
<td>6q deletion</td>
<td>21(6)</td>
</tr>
</tbody>
</table>

Dohner et al. NEJM 343:1910, 2000
B-Cell Diversity: $V_H$
Rearrangement and Mutation

<table>
<thead>
<tr>
<th>$V_H$</th>
<th>D</th>
<th>$J_H$</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/51</td>
<td>1/27</td>
<td>1/6</td>
<td>$\mu$</td>
</tr>
</tbody>
</table>

Somatic mutations

$V_H$ in B-cell chronic lymphocytic leukemia
- Somatic mutations (<98% homology)
Comparison of CLL Patients With Mutated and Unmutated $V_H$ Genes


Prognostic Factors in CLL

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Bad</th>
</tr>
</thead>
<tbody>
<tr>
<td>$B_2$Microglobulin</td>
<td>increased</td>
</tr>
<tr>
<td>FISH</td>
<td>11q-, 17p-unmutated</td>
</tr>
<tr>
<td>$IGHV$ Mutation Status</td>
<td>positive</td>
</tr>
<tr>
<td>CD38</td>
<td>positive</td>
</tr>
<tr>
<td>ZAP70</td>
<td></td>
</tr>
<tr>
<td>Complex karyotype</td>
<td>predicts for relapse after</td>
</tr>
<tr>
<td>+/- $TP53$ disruption</td>
<td>venetoclax and ibrutinib</td>
</tr>
<tr>
<td>New genomic predictors</td>
<td>$NOTCH1$, $SF3B1$, $RPS15$, and $PAX5$,</td>
</tr>
<tr>
<td></td>
<td>telomere length</td>
</tr>
</tbody>
</table>
Prognostic Factors in CLL

- Constitutional symptoms referable to CLL
- Progressive marrow failure
- Autoimmune anemia +/- thrombocytopenia poorly responsive to steroids or other
- Massive (>6 cm) or progressive splenomegaly
- Massive (>10 cm) or progressive lymphadenopathy
- Progressive lymphocytosis, >50% increase over 2 months or LDT < 6 months.

Hallek et al Blood 2018;131:2745.
CLL
Treatment Options


Alkylating agents
- Chlorambucil
- Cyclophosphamide
Glucocorticoids

Purine nucleosides
- Fludarabine
- Pentostatin
- Cladribine

Purine nucleosides and alkylators

Chemo-immunotherapy
Alemtuzumab
Bendamustine

Kinase inhibitors
Obinutuzumab
BCL-2 antagonists

Survival: Daily Chlorambucil Versus Observation

Conclusion: In elderly CLL patients first-line therapy with fludarabine does not result in a major clinical benefit compared with chlorambucil

Abstract:

Purpose: Fludarabine and cyclophosphamide (FC), which are active in treatment of chronic lymphocytic leukemia (CLL), are synergistic with the monoclonal antibody rituximab in vitro in lymphoma cell lines. A chemoimmunotherapy program consisting of fludarabine, cyclophosphamide, and rituximab (FCR) was developed with the goal of increasing the complete remission (CR) rate in previously untreated CLL patients to ≥ 50%.
**Response to FC + Rituximab**  
(NCI-WG: 300 Patients)

<table>
<thead>
<tr>
<th>Response*</th>
<th># Pts.</th>
<th>( % )</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>217</td>
<td>(72)</td>
</tr>
<tr>
<td>Nodular PR</td>
<td>31</td>
<td>(10)</td>
</tr>
<tr>
<td>PR</td>
<td>37</td>
<td>(12)</td>
</tr>
<tr>
<td>No Response</td>
<td>13</td>
<td>(4)</td>
</tr>
<tr>
<td>Early Death</td>
<td>2</td>
<td>(1)</td>
</tr>
</tbody>
</table>

* Evaluated 6 months after last course

**Phase III CLL10: Final Analysis of FCR vs BR in Pts With Advanced CLL**

Pts with untreated, active CLL without del(17p) and good physical fitness (CIRS ≤ 6, creatinine clearance ≥ 70 mL/min)  
(N = 564)

- **FCR**
  - Fludarabine 25 mg/m² IV Days 1-3 + 
  - Cyclophosphamide 250 mg/m² Days 1-3 + 
  - Rituximab 375 mg/m² IV Day 0, cycle 1 + 
  - Rituximab 500 mg/m² IV Day 1, cycles 2-6

- **BR**
  - Bendamustine 90 mg/m² IV Days 1-2 + 
  - Rituximab 375 mg/m² Day 0, cycle 1 + 
  - Rituximab 500 mg/m² IV Day 1, cycles 2-6

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

CLL10: PFS (Primary Endpoint) and OS With FCR vs BR in Pts With Advanced CLL

Median 
PFS, Mos

PFS

Mos

P < .001
HR: 1.626
(> 1.388 non-inferiority cut-off)

FCR 55.2
BR 41.7

P = .897

OS at 36 Mos, %

FCR 90.6
BR 92.2

CLL10: Adverse Events With FCR vs BR in Pts With Advanced CLL

<table>
<thead>
<tr>
<th>Adverse Event, %</th>
<th>FCR (n = 279)</th>
<th>BR (n = 278)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>84.2</td>
<td>59.0</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Anemia</td>
<td>13.6</td>
<td>10.4</td>
<td>.20</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>21.5</td>
<td>14.4</td>
<td>.03</td>
</tr>
<tr>
<td>Infection</td>
<td>39.1</td>
<td>26.8</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Secondary neoplasm*</td>
<td>6.1</td>
<td>3.6</td>
<td>.244</td>
</tr>
<tr>
<td>Treatment-related mortality</td>
<td>4.6</td>
<td>2.1</td>
<td>.107</td>
</tr>
<tr>
<td>▪ Infections</td>
<td>2.5</td>
<td>2.1</td>
<td>--</td>
</tr>
<tr>
<td>▪ Secondary neoplasm</td>
<td>1.1</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>▪ Other</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*sAML/MDS: FCR = 6, BR = 1

FCR300 Phase II Trial: Plateau in PFS with FCR as Initial Therapy for CLL

- With extended follow-up, PFS shows plateau at Yrs 10-11


Ibrutinib, Fludarabine, Cyclophosphamide, and Obinutuzumab (iFCG) for Firstline Treatment of Patients with CLL with Mutated IGHV and without TP53 Aberrations


Department of Leukemia, MDACC
ASH 2018, Abstract 185
**Treatment Schema**

**iFCG Courses 1-3**

<table>
<thead>
<tr>
<th>Course 1</th>
<th>Courses 2-3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D1</td>
</tr>
<tr>
<td>Obinutuzumab (mg)</td>
<td>100</td>
</tr>
<tr>
<td>Fludarabine (25 mg/m²)</td>
<td>-</td>
</tr>
<tr>
<td>Cyclophosphamide (250 mg/m²)</td>
<td>-</td>
</tr>
<tr>
<td>Ibrutinib</td>
<td>420 mg daily continuous</td>
</tr>
</tbody>
</table>

Antiviral prophylaxis with acyclovir / valacyclovir was required
PJP prophylaxis was optional
Prophylactic G-CSF was optional in the early part of the trial (now required)

iFCG in IGHV-M CLL, ASH 2018, Abs 185.

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**iFCG Trial: Study Design**

**iFCG 3 courses**

**Ibrutinib for 9 courses (all pts)**

+ **Obinutuzumab for 3 courses (if CR/CRi with BM U-MRD4)**

or

**Obinutuzumab for 9 courses (if PR and/or BM MRD=pos)**

**After 12 courses**

BM U-MRD4 → stop ibrutinib

BM MRD=pos → continue ibrutinib

iFCG in IGHV-M CLL, ASH 2018, Abs 185.
**Responses Improve with Time**

![Bar chart showing responses improve with time](chart)

- **CR/CRi %**
- **BM U-MRD4 %

<table>
<thead>
<tr>
<th>Time</th>
<th>CR/CRi</th>
<th>BM U-MRD4</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mo</td>
<td>39</td>
<td>6</td>
</tr>
<tr>
<td>6 mo</td>
<td>89</td>
<td>68</td>
</tr>
<tr>
<td>9 mo</td>
<td>95</td>
<td>79</td>
</tr>
<tr>
<td>12 mo</td>
<td>100</td>
<td>81</td>
</tr>
</tbody>
</table>

- *n=44*  
- *n=40*  
- *n=34*  
- *n=32*

---

**Treatment Discontinuation at 1 Year**

- **32 pts reached 1-yr follow-up**
  - All 32 had BM U-MRD4 (26 CR/CRi, 6 PR) and discontinued ibrutinib
  
  - Median follow-up after stopping ibrutinib 13.6 months (range 1.4-20.7)

  - No pt had MRD or clinical relapse
What About Treatment for Older Patients With CLL?

**Goals of Frontline Treatment for Older Pts With CLL**

- Reduced organ function
- Life expectancy (unrelated to CLL)
- Existing comorbidities, performance status
- Deep remission
- Effective but less toxic
- Do no harm

<table>
<thead>
<tr>
<th>Goal:</th>
<th>MRD negative</th>
<th>Good response</th>
<th>Palliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Priority:</td>
<td>Efficacy</td>
<td>Efficacy and tolerability</td>
<td>Low toxicity</td>
</tr>
</tbody>
</table>

Phase III CLL11 Trial: Chlorambucil Alone vs With Obinutuzumab vs With Rituximab

Previously untreated CLL pts with comorbidities (CIRS score > 6 and/or CrCl < 70 mL/min) (N = 781)

- Chlorambucil: 0.5 mg/kg PO on Days 1, 15 x 6 cycles (n = 118)
- Obinutuzumab: 1000 mg IV cycle 1 on Days 1, 8, 15; cycles 2-6 on Day 1 (n = 333)
- Rituximab: 375 mg/m² IV cycle 1 on Day 1; 500 mg/m² cycles 2-6 on Day 1 (n = 330)


CLL11: Survival with Clb/Obinutuzumab vs Clb Alone or Clb/Rituximab in CLL

Breakthrough in CLL therapy: Targeting BCR signaling

In CLL: Sites of proliferation = sites of BCR activation
The discovery of agammaglobulinaemia in 1952

Colonel Ogden Bruton (*1908, †2003)
Chief of Pediatrics at the
Walter Reed Army Hospital

Ibrutinib (PCI-32765)
A Selective Inhibitor of BTK

- Forms a specific bond with cysteine-481 in BTK
- Highly potent BTK inhibition at $IC_{50} = 0.5$ nM
- Orally administered with once daily dosing resulting in 24-hr target inhibition
- No cytotoxic effect on T-cells or natural killer (NK)-cells
- In chronic lymphocytic leukemia (CLL) cells promotes apoptosis and inhibits CLL cell migration and adhesion
Marked Reductions in Lymphadenopathy

Before ibrutinib+R (iR) 2 weeks iR 9 months iR

Treatment Related Lymphocytosis in CLL and Mantle Cell Lymphoma (MCL)

- Ibrutinib blocks BTK inducing B-cell apoptosis and disruption of B-cell homing in lymph nodes
- B-cells egress into peripheral blood
- Ibrutinib blocks B-cells from migrating back to lymph nodes resulting in treatment related lymphocytosis

Ibrutinib-induced CLL cell Redistribution: Blood Lymphocytes vs Lymph Nodes

- Redistribution of tissue CLL cells into the PB causes early lymphocytosis (up to 3-fold increase)
- Class effect of kinase-inhibitors targeting BTK, PI3K, and SYK
- Saw-tooth pattern due to re-homing of CLL cells during “off-drug” period

Mechanism of Treatment Related Lymphocytosis in Chronic Lymphocytic Leukemia (CLL) and Mantle Cell Lymphoma (MCL)

- Ibrutinib blocks BTK inducing b-cell apoptosis and disruption of b-cell adhesion in lymph nodes
- B-cells egress into peripheral blood
- Ibrutinib blocks b-cells from migrating back to lymph nodes resulting in treatment related lymphocytosis
Patients (N=269)
- Previously untreated CLL/SLL with active disease
- Age ≥65 years
- For patients 65-69 years of age, comorbidity that may preclude FCR
- del(17p) excluded

Stratification factors
- ECOG PS status (0-1 vs 2)
- Rai stage (III-IV vs III)

Ibrutinib 420 mg once daily until progression
Chlorambucil 0.5 mg/kg (to maximum 0.8 mg/kg) days 1 and 15 of 28-day cycle up to 12 cycles

PCYC-1116 Extension Study a
In the chlorambucil arm, n=73 (55%) crossed over to ibritunib following PD

IRC discontinued after primary analysis
aPatients could enroll in separate extension study PCYC-1116 after IRC-confirmed PD or at study PCYC-1115 closure for continuing treatment and follow-up.
ECOG PS, Eastern Cooperative Oncology Group performance status; FCR, fludarabine + cyclophosphamide + rituximab; IRC, independent review committee; PD, progressive disease

86% reduction in risk of PD or death for ibritunib vs chlorambucil
48-month overall survival rates: 86% with ibritunib vs 76% with chlorambucil

HR from unstratified Cox regression model
Overall Response Rate in the Ibrutinib Arm

- Response rates consistent with/without del(11q) and regardless of IGHV mutational status
- Investigator-assessed CR/CRi rates was 27% at 48 months, up from 11% at primary analysis
- Sponsor-confirmed CR rate was 16.2% at 48 months, up from 3.7% based on independent review at primary analysis

CR, complete response (sponsor confirmed); CRi, complete response with incomplete blood count recovery; nPR, nodular partial response; PR, partial response; PR-L, partial response with lymphocytosis. Percentages of patients in each category of response may not total the overall proportion with a response because of rounding.

Response rates consistent with/without del(11q) and regardless of IGHV mutational status

Investigator-assessed CR/CRi rates was 27% at 48 months, up from 11% at primary analysis

Sponsor-confirmed CR rate was 16.2% at 48 months, up from 3.7% based on independent review at primary analysis

Overall Response Rate in the Ibrutinib Arm

- Significantly more patients had sustained improvements in hemoglobin or platelets from baseline, and these improvements increased over time
- CLL disease-related symptoms as assessed by the investigator improved more frequently with ibrutinib vs chlorambucil
- Patient-reported outcomes as assessed with FACIT-Fatigue and EQ-5D-5L were improved with ibrutinib

Sustained hematologic improvement is defined as hematological improvement that sustained continuously for ≥56 days without blood transfusion or growth factors which includes: platelet counts >100 x 10⁹/L if baseline ≤100 x 10⁹/L or increase ≥50% over baseline; hemoglobin >11 g/dL if baseline ≤11 g/dL or increase ≥2 g/dL over baseline.

1. Sustained hematologic improvement is defined as hematological improvement that sustained continuously for ≥56 days without blood transfusion or growth factors which includes: platelet counts >100 x 10⁹/L if baseline ≤100 x 10⁹/L or increase ≥50% over baseline; hemoglobin >11 g/dL if baseline ≤11 g/dL or increase ≥2 g/dL over baseline.
2. Defined by change of at least 1 grade from baseline for at least 2 consecutive assessments at any time, as assessed by the investigator.


Improvements in Hematologic Parameters, Patient Symptoms, and Patient-Reported Outcomes

- Significantly more patients had sustained improvements in hemoglobin or platelets from baseline, and these improvements increased over time
- CLL disease-related symptoms as assessed by the investigator improved more frequently with ibrutinib vs chlorambucil
- Patient-reported outcomes as assessed with FACIT-Fatigue and EQ-5D-5L were improved with ibrutinib

Sustained Hematologic Improvement

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2. Defined by change of at least 1 grade from baseline for at least 2 consecutive assessments at any time, as assessed by the investigator.

### Most Frequent Treatment-Emergent Adverse Events (Any Grade\textsuperscript{a,b}) Prevalence by Yearly Interval in First-line Ibrutinib Patients

<table>
<thead>
<tr>
<th>Ibrutinib (n=135)</th>
<th>0-1 year (n=135), %</th>
<th>1-2 years (n=123), %</th>
<th>2-3 years (n=111), %</th>
<th>3-4 years (n=100), %</th>
<th>Total (n=135), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>42</td>
<td>9</td>
<td>12</td>
<td>8</td>
<td>49</td>
</tr>
<tr>
<td>Fatigue</td>
<td>28</td>
<td>22</td>
<td>19</td>
<td>17</td>
<td>34</td>
</tr>
<tr>
<td>Cough</td>
<td>19</td>
<td>11</td>
<td>12</td>
<td>11</td>
<td>33</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>17</td>
<td>14</td>
<td>12</td>
<td>13</td>
<td>27</td>
</tr>
<tr>
<td>Anemia</td>
<td>16</td>
<td>10</td>
<td>8</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>Nausea</td>
<td>20</td>
<td>7</td>
<td>5</td>
<td>3</td>
<td>25</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>15</td>
<td>7</td>
<td>6</td>
<td>6</td>
<td>24</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>14</td>
<td>11</td>
<td>10</td>
<td>7</td>
<td>24</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>13</td>
<td>7</td>
<td>9</td>
<td>9</td>
<td>23</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12</td>
<td>10</td>
<td>14</td>
<td>16</td>
<td>21</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12</td>
<td>4</td>
<td>6</td>
<td>3</td>
<td>20</td>
</tr>
</tbody>
</table>

\textsuperscript{a}All events were Grade 3 or lower, except for 1 case of Grade 4 anemia
\textsuperscript{b}Events listed occurred at frequency ≥20%

### Adverse Events of Clinical Interest

<table>
<thead>
<tr>
<th>Ibrutinib (n=135)</th>
<th>0-1 year (n=135), %</th>
<th>1-2 years (n=123), %</th>
<th>2-3 years (n=111), %</th>
<th>3-4 years (n=100), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major hemorrhage</td>
<td>5</td>
<td>5</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>8</td>
<td>1</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18</td>
<td>5</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

- Major hemorrhage (AE term group) occurred in 10% of ibrutinib-treated patients
  - None were Grade 5
- Atrial fibrillation occurred in 13% of ibrutinib-treated patients
  - None were Grade 4 or 5
- Hypertension (AE term group) occurred in 24% of ibrutinib-treated patients
  - None were Grade 4 or 5
**Idelalisib: Potent and Selective Inhibitor of PI3Kδ**

<table>
<thead>
<tr>
<th>Class I PI3K Isoform</th>
<th>α</th>
<th>β</th>
<th>γ</th>
<th>δ</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Mouse embryonic fibroblasts</th>
<th>Mouse embryonic fibroblasts</th>
<th>Human basophils</th>
<th>Human basophils</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Cell-Based Activity</th>
<th>PDGF-induced pAKT</th>
<th>LPA-induced pAKT</th>
<th>fMLP-induced CD63+</th>
<th>FceR1-induced CD63+</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC50 (nM)</td>
<td>&gt;20,000</td>
<td>1,900</td>
<td>3,000</td>
<td>8</td>
</tr>
</tbody>
</table>

* Selectivity relative to Class I PI3K isoforms involved in insulin signaling and other physiological functions
* No off-target activity against Class II or III PI3K, mTOR, or DNA-PK
* No off-target activity seen in screen of >350 protein kinases (Ambit KINOMEscan™)


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**PFS, Including Extension Study***

Idelalisib + R vs Placebo + R

<table>
<thead>
<tr>
<th>N at risk</th>
<th>IDELA + R</th>
<th>PBO + R</th>
</tr>
</thead>
<tbody>
<tr>
<td>110</td>
<td>110</td>
<td>110</td>
</tr>
<tr>
<td>102</td>
<td>86</td>
<td>66</td>
</tr>
<tr>
<td>95</td>
<td>66</td>
<td>58</td>
</tr>
<tr>
<td>92</td>
<td>58</td>
<td>51</td>
</tr>
<tr>
<td>83</td>
<td>51</td>
<td>33</td>
</tr>
<tr>
<td>64</td>
<td>33</td>
<td>15</td>
</tr>
<tr>
<td>43</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>26</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>19</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Median PFS (95% CI)**

<table>
<thead>
<tr>
<th></th>
<th>IDELA + R</th>
<th>PBO + R</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDELA + R</td>
<td>19.4 mo (16.6, -)</td>
<td>7.3 mo (5.5, 8.5)</td>
</tr>
</tbody>
</table>

**HR (95% CI)**

<table>
<thead>
<tr>
<th></th>
<th>IDELA + R</th>
<th>PBO + R</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDELA + R</td>
<td>0.25 (0.16, 0.39)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Placebo + R includes those patients who received open-label idelalisib after unblinding without prior progression (n=42).

Sharman et al., ASH 2014, Abstract 330.
March 2016: FDA Halts Six Idelalisib Combination Studies¹

- Six idelalisib (Zydelig) trials in combination with other therapies have been halted due to reports of an increased rate of adverse events, including death, for patients with hematologic malignancies.
- The halted studies were exploring idelalisib in CLL, SLL, and indolent NHL. The FDA announcement follows a similar decision from the European Union, which placed idelalisib under a safety review following infections (PJP, CMV).
- Idelalisib development in frontline CLL on hold.
- EMA/PRAC recommends that all patients treated with Zydelig should receive antibiotics to prevent *Pneumocystis jirovecii* pneumonia. Patients should also be monitored for CMV and other infection and have regular blood tests for white cell counts because low counts can increase their risk of infection. Zydelig should not be started in patients with a generalised infection. It should also not be started in previously untreated patients with CLL whose cancer cells have certain genetic mutations (17p deletion or *TP53* mutation).

¹http://www.fda.gov/Drugs/DrugSafety/ucm490618.htm

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**MURANO Study Design**

- Relapsed/refractory CLL (N=589)
  - ≥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
- Major Secondary Endpoints:
  - IRC-CR vs IRC-ORR vs OS (hierarchical testing)
  - IRC-assessed PFS and MRD- negativity
- Key Safety Endpoints: Overall safety profile, focusing on serious adverse events and Grade ≥3 adverse events
- Interim Analysis: Approximately 140 INV-assessed PFS events (75% of total information)

NCT02854571

*High-risk CLL – any of following features: del(17p) or no response to front-line chemotherapy-containing regimen or relapsed ≤12 months after chemotherapy or within ≥24 months after chemoimmunotherapy.*
**Patient Demographics**

<table>
<thead>
<tr>
<th></th>
<th>Venetoclax + Rituximab N=194</th>
<th>Bendamustine + Rituximab N=195</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, median (range), years</strong></td>
<td>64.5 (28–83)</td>
<td>66.0 (22–85)</td>
</tr>
<tr>
<td><strong>Lymphocyte count (×10⁹/L), median (range)</strong></td>
<td>43.1 (0.3–703)</td>
<td>54.7 (0.3–536)</td>
</tr>
<tr>
<td><strong>Del(17p)*, n/N (%)</strong></td>
<td>46/173 (27)</td>
<td>46/169 (27)</td>
</tr>
<tr>
<td><em><em>Unmutated IGHV</em>, n/N (%)</em>*</td>
<td>123/180 (68)</td>
<td>123/180 (68)</td>
</tr>
<tr>
<td><em><em>Mutated TP53</em>, n/N (%)</em>*</td>
<td>48/192 (25)</td>
<td>51/184 (28)</td>
</tr>
<tr>
<td><strong>Number of prior therapies, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>111 (57)</td>
<td>117 (60)</td>
</tr>
<tr>
<td>2</td>
<td>57 (29)</td>
<td>43 (22)</td>
</tr>
<tr>
<td>3</td>
<td>22 (11)</td>
<td>34 (17)</td>
</tr>
<tr>
<td>&gt;3</td>
<td>4 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td><strong>Prior therapies, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkylating agent</td>
<td>182 (93)</td>
<td>185 (95)</td>
</tr>
<tr>
<td>Purine analog</td>
<td>157 (81)</td>
<td>158 (81)</td>
</tr>
<tr>
<td>Anti-CD20 antibody</td>
<td>153 (78)</td>
<td>148 (76)</td>
</tr>
<tr>
<td>B-cell receptor pathway inhibitors</td>
<td>5 (3)</td>
<td>3 (2)</td>
</tr>
</tbody>
</table>

*C*entral lab

Seymour J, et al. NEJM. 2018;378:1107-20

---

**Ven+R vs. BR: PFS and OS**

PB-MRD negative

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


Patient Disposition

644 Patients Screened
547 Patients Randomized 1:1:1

Bendamustine + Rituximab N=183

Analysis
Primary endpoint: n=176
(7 ineligible)
Adverse events: n=176
(7 did not start treatment)
All secondary endpoints: n=183

Ibrutinib N=182

Analysis
Primary endpoint: n=178
(4 ineligible)
Adverse events: n=180
(2 did not start treatment)
All secondary endpoints: n=182

Ibrutinib + Rituximab N=182

Analysis
Primary endpoint: n=170
(12 ineligible)
Adverse events: n=181
(1 did not start treatment)
All secondary endpoints: n=182

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)


IGVH mutated & Zap-70 methylated Subgroups PFS
Intention-to-Treat Patient Population

Overall Survival
Intention-to-Treat Patient Population

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)
Ibrutinib + Obinutuzumab Versus Chlorambucil + Obinutuzumab as First-Line Treatment in Patients With Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma (CLL/SLL): Results From Phase 3 iLLUMINATE

Carol Moreno, MD, PhD; Richard Greil, MD; Fatih Demirkan, MD; Alessandra Tedeschi, MD; Bertrand Anz, MD; Loren Larratt, MD; Martin Simkovic, MD, PhD; Olga Samolova, MD; Jan Novak, MD, PhD; Dina Ben-Yehuda, MD; Vladimir Strugov, MD; Devinder Gill, MD, MRCP, FRCPath; John G. Gribben, MD, DSc, FRCP, FRCPath, FMedSci; Emily Hsu, PhD; Cathy Zhou, MS; Fong Clow, ScD; Daniele F. James, MD, MAS; Lori Styles, MD; Ian W. Flinn, MD, PhD;

1Hospital de la Santa Creu Sant Pau, Autonomous University of Barcelona, Barcelona, Spain; 2Paracelsus Medical University Salzburg, Salzburg Cancer Research Institute, Cancer Cluster Salzburg, Salzburg, Austria; 3Dokuz Eylul University, Izmir, Turkey; 4ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; 5University Hospital Hradec Kralove, Charles University, Hradec Kralove, Czech Republic; 6University of Alberta, Edmonton, Alberta, Canada; 7University Hospital Brno, Brno, Czech Republic; 8Nizhny Novgorod Regional Clinical Hospital, Nizhny Novgorod, Russia; 9University Hospital Kralovske Vinohrady and Third Faculty of Medicine, Charles University, Prague, Czech Republic; 10Division of Hematology, Hadassah Ein-Kerem Medical Center, Jerusalem, Israel; 11Almazov National Medical Research Centre, St Petersburg, Russia; 12Princess Alexandra Hospital, Brisbane, Queensland, Australia; 13Barts Cancer Institute, Queen Mary University of London, London, United Kingdom; 14Pharmacyclics LLC, an AbbVie Company, Sunnyvale, CA, USA; 15Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA

iLLUMINATE (PCYC-1130) Study Design

Patients (N=229)
- Previously untreated CLL/SLL
- Requiring treatment per iwCLL criteria
- Age ≥65 years or <65 years old with ≥1 coexisting condition:
  - CIRS >6
  - CrCl <70 mL/min
  - del(17p) or TP53 mutation

Stratification: del(17p) vs. del(11q) vs. neither del(17p) or del(11q), ECOG 2 vs 0-1

Primary end point
- PFS by IRC in high-risk population
- Rate of undetectable MRD
- ORR

Secondary end points include
- OS
- Infusion-related reactions
- Safety

Randomize 1:1

Ibrutinib-obinutuzumab
- Ibrutinib 420 mg once daily until PD or unacceptable toxicity + obinutuzumab 1000 mg split on days 1-2, and on day 8 and 15 (cycle 1) then day 1 (total 6 cycles)

Chlorambucil-obinutuzumab
- Chlorambucil 0.5 mg/kg on days 1 and 15 (6 cycles) + obinutuzumab 1000 mg split on days 1-2 and on day 8 and 15 (cycle 1) then day 1 (total 6 cycles)

After IRC-confirmed PD, patients were allowed to receive single-agent ibrutinib.

Moreno et al; ASH2018, Abstract 691.
Superior Progression-Free Survival with Ibrutinib-Obinutuzumab

- Median follow-up, 31.3 months (range, 0.2–36.9)
- Estimated PFS at 30 months: 79% with ibrutinib-Obinutuzumab vs. 31% with chlorambucil-Obinutuzumab
- Even after excluding patients with del(17p): 74% reduction in risk of progression or death with ibrutinib-Obinutuzumab

INN investigators; NR, not reached.

Moreno et al; ASH 2018, Abstract 691.

iLLUMINATE Conclusions

- Ibrutinib-Obinutuzumab represents an effective chemotherapy-free treatment option for first-line CLL/SLL, including importantly, for patients with high-risk disease
- Compared with chlorambucil-Obinutuzumab, ibrutinib-Obinutuzumab provided:
  - 77% reduction in risk of progression or death (ITT population)
  - 85% reduction in risk of progression or death (high-risk CLL population)
  - Consistent benefit across subgroups by high-risk features
  - Higher rates of CR and undetectable MRD
  - Safety profile consistent with AEs expected with individual agents
  - Reduced risk of obinutuzumab-related IRRs
- While single-agent ibrutinib provides PFS rate of 74% at 4 years,1 combination of ibrutinib-Obinutuzumab offers another option to achieve long-term PFS
- This is one of three Phase 3 randomized trials, at ASH 2018, that show superior PFS versus standard-of-care chemoimmunotherapy regimens (bendamustine-rituximab,2 and fludarabine-cyclophosphamide-rituximab [FCR]3 in first line) and superior OS versus FCR4


Moreno et al; ASH 2018, Abstract 691.
Ibrutinib & Rituximab Improves Progression Free and Overall Survival Relative to FCR in Younger Patients with Previously Untreated Chronic Lymphocytic Leukemia (CLL)

Tait Shanafelt, Xin Victoria Wang, Neil E. Kay, Susan O’Brien, Jacqueline Barrientos, Curt Hanson, Harry Erba, Rich Stone, Mark Litzow, Marty Tallman

**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

**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 1, cycle 1
- Cycle 2-6:
  - Rituximab 500 mg/m² IV, day 1, cycles 2-6

- Cycle 8 until progression: Ibrutinib 420 mg PO daily, days 1-28

Planned Accrual: 519

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

Randomization

Disease Progression

**Patient Characteristics Were Well Balanced**

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>IR n=354</th>
<th>FCR n=175</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (y)</td>
<td>58</td>
<td>57</td>
<td>58</td>
</tr>
<tr>
<td>Age ≥ 60</td>
<td>41.0%</td>
<td>40.0%</td>
<td>40.6%</td>
</tr>
<tr>
<td>Female</td>
<td>33.3%</td>
<td>31.4%</td>
<td>32.7%</td>
</tr>
<tr>
<td>ECOG = 0</td>
<td>63.8%</td>
<td>62.3%</td>
<td>63.3%</td>
</tr>
<tr>
<td>Rai stage 0</td>
<td>3.1%</td>
<td>5.1%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Rai stage I-II</td>
<td>52.8%</td>
<td>53.7%</td>
<td>53.1%</td>
</tr>
<tr>
<td>Rai stage III-IV</td>
<td>44.1%</td>
<td>41.1%</td>
<td>43.1%</td>
</tr>
<tr>
<td>FISH</td>
<td>11q deletion 22.0%</td>
<td>22.3%</td>
<td>22.2%</td>
</tr>
<tr>
<td></td>
<td>Trisomy 12 19.8%</td>
<td>15.4%</td>
<td>18.3%</td>
</tr>
<tr>
<td></td>
<td>13q deletion 34.2%</td>
<td>33.1%</td>
<td>33.8</td>
</tr>
<tr>
<td>B2M &gt;3.5 mg/L</td>
<td>51.9%</td>
<td>48.0%</td>
<td>50.6%</td>
</tr>
<tr>
<td>IGHV Unmutated*</td>
<td>75.0%</td>
<td>61.7%</td>
<td>71.1%</td>
</tr>
</tbody>
</table>

* Tested in 437 (82%) patients

**Progression Free Survival**

- **Intent to Treat**
  - HR = 0.35 (95% CI 0.22-0.5)
  - One sided p=0.00001

- **Eligible**
  - HR = 0.32 (95% CI 0.20-0.51)
  - One sided p=0.00001

**Progression Free Survival: IGHV Status**

- **IGHV Unmutated**
  - HR = 0.26 (95% CI 0.14–0.50)
  - One-sided p = 0.0001
  - Number at risk: 210, 203, 177, 90, 12

- **IGHV Mutated**
  - HR = 0.44 (95% CI 0.14–1.36)
  - One-sided p = 0.07
  - Number at risk: 70, 67, 59, 25, 2

**Overall Survival**

- **Intent to Treat**
  - HR = 0.17 (95% CI 0.05–0.54)
  - One-sided p = 0.0033
  - Number at risk: 324, 347, 318, 166, 18

- **Eligible**
  - HR = 0.13 (95% CI 0.03–0.46)
  - One-sided p = 0.0001
  - Number at risk: 323, 327, 298, 154, 18

Why Eliminate Chemotherapy for CLL?

- Myelosuppression and risk for infection
- Immune cell depletion and risk for infection
- Risk for developing refractory, higher-risk CLL through clonal evolution
- Risk for secondary hematologic malignancies (MDS/AML)
- Risk for CLL transformation events
- Risk for second cancers?
- We have better treatment

Algorithm for management of patients with CLL


67

68
Thank you!

Collaborators:
- Würzburg University: A Rosenwald, E Hartmann
- CLLGRF: F Calgaris-Cappio, N Chlorazzi, Z Estrov, N Kay
- UCSD: T Kipps, L Rassenti
- UC Irvine: D Wodarz, N Komarova
- DFCI, Broad I: C Wu, DA Landau

My laboratory: Mariela Sivina, Julia Hoellenriegel, Stefan Koehler, Ekaterina Kim, Elisa ten Hacken, Shubhchintan Randhawa

Funding: CPRIT, MD Anderson Moonshot, Leukemia & Lymphoma Society

Dept. of Leukemia, MDACC

Q&A SESSION
Update on Chronic Lymphocytic Leukemia (CLL)

- Ask a question by phone:
  – Press star (*) then the number 1 on your keypad.

- Ask a question by web:
  – Click “Ask a question”
  – Type your question
  – Click “Submit”

Due to time constraints, we can only take one question per person. Once you’ve asked your question, the operator will transfer you back into the audience line.
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• Information about leukemia: www.LLS.org/leukemia

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  [www.LLS.org/educationvideos](http://www.LLS.org/educationvideos)

• Patti Robinson Kaufmann First Connection Program
  Peer-to-peer program that matches newly diagnosed patients and their families:
  [www.LLS.org/firstconnection](http://www.LLS.org/firstconnection)
• Free Nutrition Consults
  Telephone and e-mail consultations with a registered dietitian: www.LLS.org/nutrition

• What to Ask
  Questions to ask your treatment team: www.LLS.org/whattoask

• Other Support Resources
  LLS community, blogs, support groups, financial assistance, and more: www.LLS.org/support

THANK YOU