Welcome & Introductions

Information for Patients with Chronic Lymphocytic Leukemia

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Disclosure

Susan O’Brien, MD, has affiliations with AbbVie, Johnson & Johnson, Pharmacyclics (Speakers’ Bureau); and TG Therapeutics, Pfizer, Shire, Pharmacyclics, Regeneron, Pronai, Roche (Advisory Board).

What is CLL?

CLL stands for chronic lymphocytic leukemia. It is a type of blood cancer that involves lymphocytes - white blood cells that help fight infections.

In CLL, abnormal lymphocytes build up in the blood and bone marrow. Over time, these abnormal cells crowd the healthy cells. The result is fewer healthy white blood cells, red blood cells and platelets. This leads to problems such as infection, anemia and excess bruising and bleeding. Abnormal lymphocytes may also build up in lymph nodes, the liver or the spleen. This can lead to swelling of these organs.
What are the symptoms of CLL?

Patients are often asymptomatic. Initial symptoms are generally secondary to lymph node enlargement or anemia.

The symptoms we should watch for include:
Weakness, feeling tired, feeling short of breath, weight loss, fever, night sweats

As the disease advances, the following may appear:
- elevated lymphocyte counts;
- progressive lymphadenopathy
- enlarged liver+/spleen;
- more severe anemia,
- low granulocytes or platelets

Understanding medical tests for CLL

CLL cannot be diagnosed by symptoms alone. CLL is usually detected by routine checkups or blood work for other health issues. Medical tests will also tell where CLL is in your body.

Common tests for diagnosis or prior treatment:
• **Physical exam** - the doctor checks for swollen lymph nodes, liver or spleen and other signs of CLL
• **Blood cell counts** - a high white blood cell count in patients with CLL
• **Biopsy**
• **Flow cytometry**—a sample of the cells, taken from blood or bone marrow.

Common tests include also:
• Imaging tests such as x-rays, CT scans or ultrasound
Patients with CLL have a median age at diagnosis of 71 years and most have comorbidities

- 68% of CLL patients are aged ≥ 65 years:
  - Median age at diagnosis is 71 years
  - 40% of patients are aged > 75 years

- 89% of CLL patients have one or more comorbidity:
  - 46% of patients have at least one MAJOR comorbidity

Coexisting medical conditions - Effect on treatment approach

- Treatment strategies are based on the stage of disease and severity of coexisting conditions
- Several tools have been used to define patients into distinct groups; one example from the German Chronic Lymphocytic Leukaemia Study Group (GCLLSG) uses the Cumulative Illness Rating Scale (CIRS) score. Each patient group is then managed differently

<table>
<thead>
<tr>
<th>'Go-go'</th>
<th>'Slow-go'</th>
<th>'No-go'</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completely independent</td>
<td>Some coexisting conditions</td>
<td>Severely handicapped</td>
</tr>
<tr>
<td>No coexisting conditions</td>
<td>Impaired organ function</td>
<td>High severity of coexisting conditions</td>
</tr>
<tr>
<td>Normal life expectancy</td>
<td>Reduced performance status</td>
<td>Reduced life expectancy</td>
</tr>
<tr>
<td>Aggressive immunochemo-therapy</td>
<td>Less aggressive approach</td>
<td>Palliative care</td>
</tr>
</tbody>
</table>

GCLLSG = German CLL Study Group.
Chemoimmunotherapy
Chemotherapy and Antibody Regimens

• FCR: fludarabine, cyclophosphamide and rituximab
• BR: bendamustine and rituximab
• O-chlorambucil: obinutuzumab or ofatumumab and chlorambucil

Why Not Treat CLL at Diagnosis

• Indolent disease
• Patients often asymptomatic
• Median age early 70’s
• Patients often have comorbidities and die of other causes
• Most patients are not cured
**Types of Response in CLL**

**PR:** partial remission. The disease responds, so blood counts improve and lymph nodes (and spleen if enlarged) shrink but they are not normal.

**CR:** complete remission. The disease cannot be found, the blood counts and physical exam are normal, as is the bone marrow.

**MRD:** minimal residual disease. Very sensitive test to look for CLL when blood counts/exam are normal; looks for 1 in 10,000 cells.

The better the response the longer it lasts.

CR lasts longer than PR.

CR can be MRD negative or MRD positive. MRD negative remissions last longer then MRD positive remissions.
**Other Important Definitions Related to Clinical Trials**

**PFS:** Progression Free Survival (after treatment)
Shows how many patients are in remission (disease has not recurred) and alive

**OS:** Overall Survival shows how many patients are alive (whether they are in remission or not)
OS is measured from the start of the therapy

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**CLL10 Study: FCR VS BR in Front-Line**

**Design**
Patients with untreated, active CLL without del(17p) and good physical fitness (CIRS $\leq 6$, creatinine clearance $\geq 70$ ml/min)

**Randomization**

- **FCR**
  - Fludarabine 25 mg/m² i.v., days 1-3
  - Cyclophosphamide 250 mg/m², days 1-3
  - Rituximab 375 mg/m² i.v. day 0, cycle 1
  - Rituximab 500 mg/m² i.v. day 1, cycle 2-6

- **BR**
  - Bendamustine 90mg/m² day 1-2
  - Rituximab 375 mg/m² day 0, cycle 1
  - Rituximab 500 mg/m² day 1, cycle 2-6

**Non-Inferiority of BR in comparison to FCR for PFS:**
HR ($\lambda$ BR/FCR) less than 1.388

Eichhorst et al ASH 2014
**CLL10 Study: FCR VS BR in Front-Line**

ITT Progression-free Survival = Primary Endpoint

- **Median PFS**
  - FCR: 55.2 months
  - BR: 41.7 months

- **HR = 1.626**
  - $>$ 1.388

**Adverse Events CTC ° 3-4 (1st cycle until end of study)**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>FCR (%)</th>
<th>BR (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>84.2</td>
<td>59.0</td>
<td>$&lt;$0.001</td>
</tr>
<tr>
<td>Anemia</td>
<td>13.6</td>
<td>10.4</td>
<td>0.20</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>21.5</td>
<td>14.4</td>
<td>0.03</td>
</tr>
<tr>
<td>Infection</td>
<td>39.1</td>
<td>26.8</td>
<td>$&lt;$0.001</td>
</tr>
<tr>
<td>Sec Neoplasm*</td>
<td>6.1</td>
<td>3.6</td>
<td>0.244</td>
</tr>
<tr>
<td>TRM</td>
<td>4.6</td>
<td>2.1</td>
<td>0.107</td>
</tr>
<tr>
<td>Sec Neoplasm</td>
<td>1.1</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

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

**p value**

- **$P < 0.001$**
  - $HR = 1.626 = > 1.388$
CLL11 Study Design

Previously untreated CLL
Total CIRS score >6 and/or creatinine clearance <70 mL/min
N=780 (planned)

590 patients

2:1:2

 GA101 + chlorambucil x 6 cycles

Chlorambucil x 6 cycles (control arm)

Rituximab + chlorambucil x 6 cycles

G-Clb vs. Clb
Primary analysis data cut-off: 07/2012

R-Clb vs. Clb
Primary analysis data cut-off: 08/2012

• GA101: 1000 mg days 1, 8, and 15 cycle 1; day 1 cycles 2–6, every 28 days
• Rituximab: 375 mg/m² day 1 cycle 1, 500 mg/m² day 1 cycles 2–6, every 28 days
• Chlorambucil: 0.5 mg/kg day 1 and day 15 cycle 1–6, every 28 days
• Patients with progressive disease in the Clb arm were allowed to cross over to G-Clb


CLL11 Study Design

Previously untreated CLL
Total CIRS score >6 and/or creatinine clearance <70 mL/min
N=780 (planned)

590 patients

Additional 190 patients

2:1:2

 GA101 + chlorambucil x 6 cycles

Chlorambucil x 6 cycles (control arm)

Rituximab + chlorambucil x 6 cycles

G-Clb vs. R-Clb
Primary analysis data cut-off: 05/2013

Progression-Free Survival (Head-to-Head)

No. at risk
G-Clb: 330 307 302 278 213 156 122 93 60 34 12 4 1 0
R-Clb: 330 317 309 259 163 114 72 49 31 14 5 2 0 0

Median observation time: G-Clb, 18.8 months; R-Clb, 18.6 months
Type 1 error controlled through closed test procedure; P value of the global test was <0.0001
Independent Review Committee-assessed progression-free survival (PFS) was consistent with investigator-assessed PFS

Phase III COMPLEMENT1: Ofatumumab + Chlorambucil vs Chlorambucil Alone

Patients with previously untreated CLL (N = 444)

Ofatumumab
Cycle 1: 300 mg on Day 1, 1000 mg on Day 8
Cycle 2-12: 1000 mg on Day 1 every 28 days +
Chlorambucil
10 mg/m² on Days 1-7 every 28 days

Follow-up: 1 mos past last dose, 3rd mos, then every 3 mos after

*Minimum 3 cycles or until best response or PD; maximum 12 cycles; no crossover allowed.
Dose rationale: highest PFS and ORR with the lowest toxicity compared with any other chlorambucil treatment

**Ofatumumab + Chlorambucil vs Chlorambucil Alone: PFS**

![Graph showing probability of PFS over time for Ofatumumab + Chlorambucil vs Chlorambucil Alone](image)


**Targeting of BCR Signaling in CLL**

- BCR-associated kinases are targets of new drugs in preclinical and clinical development
- Syk (spleen tyrosine kinase) inhibitors: R406, Portola’s Syk inhibitors
- Btk (Bruton’s tyrosine kinase) inhibitors: ibrutinib, CC-292, ONO-4059, ACP196
- PI3 kinases: Isoform-Selective Inhibitor of PI3-Kinases, idelalisib, IPI-145, TGR-1202

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Ibrutinib in Refractory CLL With 11q Deletion

Pattern of Response:
Blood Lymphocytes vs. Lymph Nodes
**Ibrutinib Phase 2 Best Response (Investigator-Assessed)**

<table>
<thead>
<tr>
<th>Category</th>
<th>TN 420 (n = 27)</th>
<th>R/R 420 (n = 67)</th>
<th>Total (N = 94)</th>
</tr>
</thead>
<tbody>
<tr>
<td>nPR</td>
<td>26%</td>
<td>9%</td>
<td>14%</td>
</tr>
<tr>
<td>PR</td>
<td>52%</td>
<td>82%</td>
<td>73%</td>
</tr>
<tr>
<td>PR+L</td>
<td>85%</td>
<td>94%</td>
<td>91%</td>
</tr>
<tr>
<td>SD</td>
<td>7%</td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td>PD</td>
<td>1%</td>
<td>3%</td>
<td>2%</td>
</tr>
</tbody>
</table>

**Median DOR, months (95% CI)**
- NR (NE to NE)
- NR (35.9 to NE)
- NR (NE to NE)

**Month 30 (95% CI)**
- 100% (100 to 100)
- 82.2% (68.5 to 90.4)
- 87.3% (77 to 93.2)

*TN: n = 21, R/R: n = 61, total: N = 82.*

**Progression-Free Survival**

<table>
<thead>
<tr>
<th>Category</th>
<th>TN 420</th>
<th>R/R 420</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-month PFS (95% CI)</td>
<td>95.8% (73.9-99.4)</td>
<td>75.9% (62.5-85.1)</td>
</tr>
<tr>
<td>Median PFS</td>
<td>Not reached</td>
<td>Not reached</td>
</tr>
</tbody>
</table>

AACR 2015
**Ibrutinib: Common AEs**
*(All Grades, Regardless of Causality)*

- **Diarrhea**
- **Nausea**
- **Fatigue**
- **Rash**
- **Dizziness**
- **Dyspepsia**
- **Peripheral Edema**
- **Arthralgia**
- **Constipation**
- **Hypertension**
- **Vomiting**
- **URI**
- **Gastroesophageal reflux**
- **Urinary tract**

**Grade 1**

**Grade 2**

**Grade 3**

**Grade 4**

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**RESONATE™ Phase 3 Study Design**

**Patients with previously treated CLL/SLL**

- **Randomize**
- **1:1**

- **Primary Endpoint:** PFS
- **Stratification according to:**
  - Disease refractory to purine analog chemoimmunotherapy (no response or <12 months)
  - Presence or absence of 17p13.1 (17p del)
- **At time of interim analysis, median time on study was 9.4 months**

**Oral ibritinib 420 mg once daily until PD or unacceptable toxicity**

- **n=195**

**IV ofatumumab initial dose of 300 mg followed by 2000 mg x 11 doses over 24 weeks**

- **n=196**

**Cross over to ibritinib 420 mg once daily after IRC confirmed PD (n=57)**

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Byrd et al N Engl J Med 2014, Jul 17; 371 (3); 213-23
Progression-Free Survival

This represents a 78% reduction in the risk of PD or death with ibrutinib compared with ofatumumab.

Richter’s transformation was confirmed in 2 patients on each arm.

Another patient on the ibrutinib arm had transformation to prolymphocytic leukemia.

Safety: Atrial Fibrillation and Bleeding-Related Adverse Events

- Atrial fibrillation any grade: ibrutinib n=10, ofatumumab n=1
  - Discontinuation of ibrutinib in only 1 patient
    - Patients were ≥60 years old (median age 73)
    - Most had predisposing risk factors (a prior history of atrial fibrillation or in the setting of a pulmonary infection)

- Bleeding-related AEs of any grade:
  - most commonly petechiae and ecchymoses
    - ibrutinib 44%, ofatumumab 12%
  - No difference in severe/major bleeding events:
    - ibrutinib n=2, ofatumumab n=3, 1 SDH with ibrutinib
  - One patient discontinued ibrutinib due to a bleeding AE
  - Concomitant anti-platelets or anticoagulants
    - 50% ibrutinib and 39% ofatumumab

**Idelalisib is an Orally Bioavailable Small Molecule that Inhibits PI3K Delta Potently and Selectively**

<table>
<thead>
<tr>
<th>Class I PI3K Isoform</th>
<th>Alpha</th>
<th>Beta</th>
<th>Gamma</th>
<th>Delta</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell-Based Activity</td>
<td>PDGF-induced pAKT</td>
<td>LPA-induced pAKT</td>
<td>fMLP-induced CD63+</td>
<td>FcεR1-induced CD63+</td>
</tr>
<tr>
<td>EC_{50} (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™)

**Marked Reductions in Peripheral Lymphadenopathy Were Observed**

38-year-old patient with refractory CLL and 5 prior therapies
Idelalisib: Nodal and Overall Response Rate

![Graph showing response rate and adverse events]

Idelalisib: Adverse Events (≥ 15%) and Selected Lab Abnormalities (N = 54)

<table>
<thead>
<tr>
<th>AE, n (%)</th>
<th>Any Grade, (%)</th>
<th>Grade ≥ 3, (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>17 (32)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16 (30)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>16 (30)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Cough</td>
<td>13 (24)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Back pain</td>
<td>12 (22)</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>12 (22)</td>
<td>0</td>
</tr>
<tr>
<td>URI</td>
<td>12 (22)</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>11 (20)</td>
<td>10 (19)</td>
</tr>
<tr>
<td>Night sweats</td>
<td>10 (19)</td>
<td>0</td>
</tr>
<tr>
<td>Chills</td>
<td>9 (17)</td>
<td>0</td>
</tr>
<tr>
<td>Laboratory abnormality, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST, increased*</td>
<td>13 (24)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>ALT, increased*</td>
<td>10 (19)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

*15 subjects total with transaminase elevations

**Study 116: Randomized, Double-Blind, Placebo-Controlled**

### Randomized Combination Therapy
- Rituximab (6 months)
- Idelalisib (150 mg BID)
- Placebo (BID)
- Rituximab (6 months)

### Extension Single-Agent Therapy
- Idelalisib (300 mg BID)
- Idelalisib (150 mg BID)

**Rituximab administration**
- 375 mg/m$^2$, then 500 mg/m$^2$ Q2W x 4,
- then 500 mg/m$^2$ Q4W x 3

**Clinical Endpoints**
- Primary: PFS as assessed by IRC
- Events: Disease progression or death
- Secondary: ORR, LNR, OS

Planned interim analyses at 50% and 75% of events


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**Primary Endpoint: Progression-Free Survival**

- **IDEA + Rituximab**
  - Median PFS: not reached
  - HR = 0.15
  - 95% CI (0.08, 0.28)
  - p < 0.0001

- **Placebo + Rituximab**
  - Median PFS = 5.5 months

**Subjects at risk, n**
- IDEA + R: 110 69 44 34 30 14 6 2 0
- Placebo + R: 110 62 30 18 13 6 1 1 0
Venetoclax: Potent and Selective Bcl-2 Inhibition

- Small molecule, orally bioavailable
- High affinity for Bcl-2, lower affinity for BCL-xL, Mcl-1
- >100-fold improved functional selectivity for Bcl-2 over Bcl-xL in assays with tumor cell lines

<table>
<thead>
<tr>
<th>Agents</th>
<th>Bcl-2</th>
<th>Bcl-xL</th>
<th>Bcl-w</th>
<th>Mcl-1</th>
<th>Bcl-2</th>
<th>Bcl-xL</th>
<th>Functional Selectivity</th>
<th>RS4;11 (Bcl-2)</th>
<th>H146 (Bcl-xL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Navitoclax</td>
<td>0.04</td>
<td>0.05</td>
<td>7</td>
<td>&gt;224</td>
<td>20</td>
<td>13</td>
<td>0.6</td>
<td>110</td>
<td>75</td>
</tr>
<tr>
<td>ABT-199</td>
<td>&lt;0.01</td>
<td>48</td>
<td>21</td>
<td>&gt;440</td>
<td>4</td>
<td>261</td>
<td>65</td>
<td>12</td>
<td>3600</td>
</tr>
</tbody>
</table>


Dosing Schedule of Venetoclax: Dose Escalation Schematic

- Day -7
- 50 mg

**Day 1**
- Starting dose
- Week 1

**Week 2**
- Step-up dose**
- Dose Escalation Dose (DCD)

**Week 3 and following**

**Lead-in to Designated Cohort Dose - Expanded Safety Cohort**

**ABT-199**
- Week 1 D1
- 20 mg test

**Week 1 D2-7**
- 50 mg

**Week 2**
- 100 mg

**Week 3**
- 200 mg

**Week 4**
- 400 mg

*3 patients (1 each in cohorts 2, 3, & 5) received ABT-199 20 mg as initial dose.
**Step-up doses range from 100 to 400 mg.
DCD = Designated Cohort Dose

Median time on study 10.9 months

Seymour et al. EHA 2014
**Nodal Mass by CT Scan (n= 93)**

- The median time to 50% reduction: 1.4 months, range [0.65 – 13.7]*
- 78 (84%) evaluable patients had at least a 50% reduction in sum of the product of diameters (SPD) of nodal masses*
  - *coincides with first protocol specified CT scan at 6 weeks.

**Blood Lymphocytes (n=60)**

- Median Time to 50% reduction: 14 days, range [1 – 49]

**Best Percent Change from Baseline in Blood Lymphocyte Count and Nodal Mass by CT Scan**

![Graph showing percent change from baseline for blood lymphocytes and nodal mass by CT scan]

**Objective Responses of Venetoclax Treated Patients**

<table>
<thead>
<tr>
<th>Responses</th>
<th>All (n=78)</th>
<th>del (17p) (n=19)</th>
<th>F-Refractory (%) (n=41)</th>
<th>Unmutated (%) (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response</td>
<td>60 (77)</td>
<td>15 (79)</td>
<td>31 (76)</td>
<td>18 (75)</td>
</tr>
<tr>
<td>Complete response (CR/CRI)*</td>
<td>18 (23)</td>
<td>5 (26)</td>
<td>9 (22)</td>
<td>7 (29)</td>
</tr>
<tr>
<td>Partial response*</td>
<td>42 (54)</td>
<td>10 (53)</td>
<td>22 (54)</td>
<td>11 (46)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>10 (13)</td>
<td>2 (11)</td>
<td>7 (17)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Disease progression</td>
<td>2 (3)</td>
<td>1 (5)</td>
<td>1 (3)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>D/C Prior to assessment*</td>
<td>6 (8)</td>
<td>1 (5)</td>
<td>2 (5)</td>
<td>2 (8)</td>
</tr>
</tbody>
</table>

Some patients may have more than one high risk marker.

*4 patients have CRI; *D/C = discontinued, first assessment at 6 weeks

*3 patients had confirmatory CT imaging assessments at less than an 8 week interval (5, 6, and 7 weeks)

- As of April 9, 78 patients had 2 CT scans, performed approximately 8 weeks apart
  n=55 from dose escalation and n=23 from the safety expansion cohort
- A total of 26 patients are not yet evaluable in the SE cohort (12 patients had a PR at their first scan, 14 patients have not yet reached their first assessment)
- The median duration of response has not yet been reached
Minimal Residual Disease (MRD): Preliminary Analyses

- 11/18 patients with CR/CRi assessed for MRD
- Quantification by 4 color flow using local lab
- BM: MRD ⊗ = 6
  (3 suboptimal cell #)
  MRD +
  low level = 4 (0.17%, 0.7%, 0.75%, 1.5%)
- PB: MRD ⊗ = 1 (no BM)
- BM MRD ⊗ 1 F refractory, 17p-
  3 F refractory
  1 17p

Seymour et al EHA 2014

RESONATE™-2 (PCYC-1115) Study Design

Patients (N=269)
- Treatment-naïve CLL/SLL with active disease
- Age ≥65 years
- For patients 65-69 years, comorbidity that may preclude FCR
  - del17p excluded
  - Warfarin use excluded

Randomize 1:1

Stratification factors
- ECOG status (0-1 vs. 2)
- Rai stage (III-IV vs. I-II)

ibritinib 420 mg once daily until PD or unacceptable toxicity

chlorambucil 0.5 mg/kg (to maximum 0.8 mg/kg) days 1 and 15 of 28-day cycle up to 12 cycles

IRC-confirmed progression

In clb arm, n=43 crossed over to ibritinib

PCYC-1116 Extension Study

*Patients with IRC-confirmed PD enrolled into extension Study 1116 for follow-up and second-line treatment per investigator’s choice (including ibritinib for patients progressing on chlorambucil with iwCLL indication for treatment).

Phase 3, open-label, multicenter, international study
- Primary endpoint: PFS as evaluated by IRC (2008 iwCLL criteria)1,2
- Secondary endpoints: OS, ORR, hematologic improvement, safety

PFS by Independent Assessment

- 84% reduction in risk of progression or death with ibrutinib
- 18-month PFS rate: 90% with ibrutinib vs. 52% with chlorambucil
- Median follow-up: 18.4 months

Overall Survival

- 84% reduction in risk of death with ibrutinib
- 24-month OS rate: 98% with ibrutinib and 85% with chlorambucil
- 3 deaths on ibrutinib arm vs. 17 deaths on chlorambucil arm
**FCR300: Progression-Free & Overall Survival**

Median follow up time:
- All: 9.8 yrs
- Alive: 11.5 yrs

**FCR300: PFS by IGHV Mutation Status**

<table>
<thead>
<tr>
<th>Group</th>
<th>Events</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGHV-M</td>
<td>33</td>
<td>82</td>
</tr>
<tr>
<td>IGHV-UM</td>
<td>114</td>
<td>131</td>
</tr>
<tr>
<td>Unknown</td>
<td>39</td>
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**Oral Small Molecules in CLL**

- **Ibrutinib** FDA approved
  - Initial therapy
  - Recurrence after chemotherapy

- **Idelalisib** FDA approved
  - In combination with rituximab for recurrence

- **Venetoclax** FDA approved
  - Recurrence in patients with 17p deletion

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**Considerations for Ibrutinib vs Chemoimmunotherapy as Initial Therapy for CLL**

- **Pills vs IV**

- **Defined time on therapy**
  - FCR or BR: 6 months
  - Chlorambucil based: 6-12 months
  - Ibrutinib: indefinite

- **Long term results**
  - Ibrutinib: 4 years follow-up is too short to talk about cure
  - FCR: over 10 years, may be a cured group

- **Cost to patient**
  - Chemotherapy based: none
  - Ibrutinib: copay
Q&A Session

Dr. O’Brien’s slides are available for download at www.LLS.org/programs

After the program, the audio replay and program transcript will also be available at the link above.

Information for Patients with Chronic Lymphocytic Leukemia

The Leukemia & Lymphoma Society (LLS) offers:

- **Online Chats**: Online moderated chat forums: [www.LLS.org/chat](http://www.LLS.org/chat)
- **What to ask**: Questions to ask your treatment team: [www.LLS.org/whattoask](http://www.LLS.org/whattoask)
- **Free education materials**: [www.LLS.org/booklets](http://www.LLS.org/booklets)
- **Past CLL education programs**: [www.LLS.org/programs](http://www.LLS.org/programs)
- **Leukemia Links**: Monthly online publication that delivers news and links detailing latest leukemia research and studies: [www.LLS.org/signup](http://www.LLS.org/signup)
- **Information Resource Center**: Speak one-on-one with an Information Specialist who can assist you through cancer treatment, financial, and social challenges.
  - **EMAIL**: infocenter@LLS.org
  - **TOLL-FREE PHONE**: (800) 955-4572