Monthly Oncology Tumor Boards:
A Multidisciplinary Approach to Individualized Patient Care

Lymphoma: CLL/SLL

John C. Byrd, MD & Jennifer Woyach, MD
The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute

April 25, 2016

Moderated by Rose K. Joyce
NCCN, Conferences and Meetings Department

This activity is supported by educational grants from BTG; Bristol-Myers Squibb; Celgene Corporation; Genomic Health, Inc.; Lilly; Merck; Novartis Oncology; Prometheus Laboratories; Spectrum Pharmaceuticals, and by a grant from AstraZeneca, and an independent educational grant from Boehinger Ingelheim Pharmaceuticals, Inc.

Faculty Biography

John C. Byrd, MD, is Professor of Medicine and Medicinal Chemistry and Director of the Division of Hematology at The Ohio State University – James Cancer Hospital and Solove Research Institute.

Dr. Byrd earned his medical degree from the University of Arkansas for Medical Sciences. He completed an internship and residency in internal medicine and a fellowship in hematology, oncology, and bone marrow transplantation at the Walter Reed Army Medical Center in Washington, DC. He also completed Translational Laboratory Training at Johns Hopkins University.

Dr. Byrd serves on the editorial boards of various scientific journals. He has authored or co-authored over 400 peer-reviewed manuscripts and nearly 400 abstracts. Dr. Byrd also plays an active role in many professional societies, including the American Society of Clinical Oncology, the National Cancer Institute, the Leukemia and Lymphoma Society, the Lymphoma Research Foundation, and the USA National Cancer Institute-Sponsored Cooperative Oncology Group.

Dr. Byrd is a member of the NCCN ImmunoGen Research Development Committee and the NCCN Non-Hodgkin’s Lymphomas Panel.
Jennifer A. Woyach, MD, is Assistant Professor of Medicine, Division of Hematology in the Department of Internal Medicine at The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute.

Dr. Woyach earned her medical degree from The Ohio State University College of Medicine and Public Health, where she also completed a residency in internal medicine, serving as Chief Resident in her final year. Afterwards, she remained at The Ohio State University to complete a fellowship in hematology and medical oncology and joined the faculty in 2012.

Dr. Woyach has authored or co-authored more than 45 peer-reviewed manuscripts and abstracts. Her research interests include chronic lymphocytic leukemia (CLL) and other hematologic malignancies. Her laboratory research focuses on the role of Bruton’s Tyrosine Kinase (BTK) in the development and expansion of CLL, as well as therapeutic BTK inhibition in CLL using murine and cellular models. Her research also examines resistance to BTK inhibitor therapy. Her clinical research focuses on novel agents in CLL. Dr. Woyach is the Principal Investigator of several active and completed trials for CLL.

Among her achievements, Dr. Woyach is a recipient of the 2015 American Society for Clinical Investigation Young Physician-Scientist Award.

---

**Audience Response Question 1**

A 62 year old man with a 6 year history of stage 0 CLL with slow progression now presents with anemia, increasing lymph node size, normal LDH, and FISH with Trisomy 12 and IGHV mutated status at diagnosis.

The most appropriate therapy for this patient includes all of the following except:

A. Repeat interphase cytogenetics
B. Pursuit of therapy with Fludarabine, Cyclophosphamide, and Rituximab
C. Pursuit of therapy with Bendamustine + Rituximab
D. Bone marrow biopsy and aspirate
E. Direct antibody test
Decisions in CLL: Can Prognostic and Biological Markers Help Manage Patients (2016)

John C. Byrd M.D.
D Warren Brown Chair of Leukemia Research
Professor of Internal Medicine and Medicinal Chemistry
Director, Division of Hematology
The Ohio State University

Chronic Lymphocytic Leukemia

- The most prevalent type of adult leukemia
- Defined by CD5, CD19, CD20, CD23, slg (dim)+ cells in blood; < 5 x 10^9/L cells is monoclonal B-cell lymphocytosis (MBL) which still has many CLL-type complications
- Median age of diagnosis of CLL is approximately 72, with only 10% of patients under age 50.
- More common in men than women (2:1 ratio)
- Environmental predisposition uncertain, although Vietnam Veterans with Agent Orange exposure warrant “service-connected status”
- Genetic predisposition present, with approximately 10% of patients having a first-generation relative with CLL
The Big Question at Diagnosis in Asymptomatic Patients

How will this “bad” leukemia influence my quality of life and life expectancy?

CLL: Outcome From Diagnosis based on Interphase (FISH) Chromosomal Abnormalities

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>% Patients</th>
<th>Median Time to Treatment (months)</th>
<th>Median Overall Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>del(17)(p13.1)</td>
<td>7</td>
<td>9</td>
<td>32</td>
</tr>
<tr>
<td>del (11)(q22.3)</td>
<td>18</td>
<td>13</td>
<td>79</td>
</tr>
<tr>
<td>Trisomy 12</td>
<td>16</td>
<td>33</td>
<td>114</td>
</tr>
<tr>
<td>del(13)(q14)</td>
<td>55</td>
<td>49</td>
<td>133</td>
</tr>
<tr>
<td>None Detected</td>
<td>18</td>
<td>92</td>
<td>111</td>
</tr>
</tbody>
</table>

Overall Survival is Influenced by *IGHV* Gene Mutation Status

- **All Patients**
  - M-24.5 yrs
  - UM-9.75 yrs

- **Binet Stage A Patients**
  - M-24.5 yrs
  - UM-7.75 yrs


Other New Prognostic Factors

- **Stimulated Karyotype** (not regular type)
  - Complexity (> 3 abnormalities) associated with short TFS and poor response to therapy (including transplant and BTK inhibitors)
- **Additional Interphase abnormalities**
  - add 2p—increased risk of Richter’s transformation
  - +8 or amplification of myc—short TFS and OS
- **ZAP-70 methylation** (more reproducible than ZAP-70 protein expression and correlates with favorable outcome)
- **Select mutations associated with rapid progression to treatment**
  - p53
  - NOTCH-1
  - SF3B1
  - BIRC3
All associated with IGHV un-mutated disease
**Initial Work-up of CLL Patients**

- All patients at diagnosis:
  - Flow cytometry to confirm CLL diagnosis
- Informative for prognostic and/or therapy determination
  - Interphase cytogenetics looking for +12, del(13q), del(17)(p13.1) and del(11)(q22.3); del 17p, 2p and del 11q portend for more aggressive disease
  - Unmutated V<sub>H</sub> gene status assessment (good lab)
  - ZAP-70 expression by flow cytometry is not recommended outside clinical trial; Zap-70 methylation may be more reproducible
- Beta-2-microglobulin
- No CT scan unless symptoms are present; PET scan can be helpful if Richter’s suspected
- Bone marrow biopsy and aspirate not necessary in absence of cytopenias

**Complications of CLL**

- Autoimmune complications
- Infections
- Secondary cancers
- Richter’s transformation
When to Treat CLL Patients

- No advantage to treating CLL until symptoms develop irrespective of genomic features
- IWCLL 2008 criteria for treatment (primary and in relapse include
  - Enlarging, symptomatic lymph nodes (> 10 cm)
  - Enlarging, symptomatic spleen (> 6 cm)
  - Cytopenias due to CLL (hemoglobin < 11, platelets < 100)
  - Constitutional symptoms due to disease (fatigue, B-symptoms)
  - Poorly controlled AIHA or ITP
- Absolute lymphocyte count alone is not an indication for treatment unless above 200–300 x 10^9/L or symptoms related to leukostasis.*


How to Differentiate Patients for Treatment

- Age or Functional Status
  - Age 65-70 often used in US
  - CIRS score or creatinine clearance < 60 ml/min often used in Europe

- Genomic Features
  - Del(17p13.1) or not
  - Favorable markers (IgHV mutated with del(13q14) or +12)
CLL8 Study Design

817 Patients with untreated, active CLL and good physical fitness (CIRS ≤ 6, creatinine clearance ≥ 70 ml/min)

- 6 courses

Demographics similar between 2 treatment arms

Updated results of the 3rd analysis
Median observation time 5.9 years

Summary of German CLL8 Study

- Toxicity of FCR similar to FC except for more neutropenia
- FCR versus FC a better therapy for young CLL
  - significantly improves ORR and CR
  - significantly improves PFS (57 versus 33 months, at 5.9 years)
  - significantly improves OS (69.2% vs 62.3% at 5.9 yrs)
- MRD- status at end of therapy most predictive factor for long term PFS and OS
- Majority of genetic groups benefit from FCR therapy except for
  - Del(17p13.1)
  - Normal karyotype (using FISH probes only)

Recent Data To Consider

- What is the Best Therapy for CLL?
- Long-term Follow Up data for FCR from MDA FCR300 series and German CLL8 study data relative to “curability”
- Ibrutinib data for CLL with del(17)(p13.1) and approval by FDA for initial use in symptomatic CLL
**Ibrutinib: A Potent Irreversible BTK Inhibitor**

- Potent and irreversible BTK inhibition with IC$_{50} =$ 0.5 nM
- Orally bioavailable
- Response noted in 45 (88%) of patients, with 5 (10%) attaining a CR (4 untreated)
- PFS at 24 months is 82% for all patients; 8 (16%) of patients have died—5 with PD, 2 infection, and 1 sudden death

Honigberg et al: PNAS 2010; 107:13075-80
Del(17p)/TP53 mutated CLL: Outcome on Ibrutinib

Ibrutinib versus Chlorambucil (RESONATE-2)

- Phase 3 study in symptomatic, untreated CLL/SLL patients comparing ibrutinib versus chlorambucil (cross-over allowed)
- Eligibility criteria including: 65 years of age, ANC 1 x 10^9/L, platelets 50 x 10^12/L and no del(17)(p13.1)
- Patient Demographics: median age of 73 years (70% ≥ 70 y/o), 45% Advanced Rai stage, 20% del(11)(q22;q23)
- Response: Ibrutinib 86% (4% CR) versus chlorambucil 36% (2% CR)
- Significant PFS and OS with ibrutinib (despite cross-over)
- Toxicity similar between except diarrhea and atrial fibrillation (ibrutinib)
My Approach for Patients < 70

- Repeat interphase cytogenetics, bone marrow
- Clinical trial with strong consideration of non-chemotherapy regimen unless young and with favorable prognostic factors
- Off trial
  - Del(17p13.1): ibrutinib (tissue typing for very young)
  - IGHV mutated: FCR
  - IGHV un-mutated: ibrutinib
- Do not use PCR, rituximab, alemtuzumab, chlorambucil or rituximab maintenance

Approaches to Consider in Older Patients

- No Fludarabine-based regimens (Eichhorst Blood 2009, Woyach J Clin Oncol 2012)
- Bendamustine + Rituximab
  - Slightly higher toxicity rate but feasible in this population
- Chlorambucil + Rituximab
  - ORR 82% (9% CR, 15% nPR) with median PFS of 23.5 months
- High dose methylprednisolone + rituximab
  - Lower steroid dose typically utilized; favored regimen for del(17p)
- Obinutuzumab + chlorambucil: A short standard of care change (now ibrutinib)
### Obinutuzumab

- Humanized monoclonal antibody targeting CD20 with novel properties as compared to rituximab
  - Recognizes unique epitope of CD20 different from rituximab
  - Type II antibody mediating direct CLL cell killing without cross-linking superior to rituximab and ofatumumab
  - Diminished complement mediated lysis as compared to ofatumumab
  - Glycoengineered to mediate enhanced antibody dependent cell-mediated cytotoxicity superior to rituximab and ofatumumab
  - Phase I/II study in relapsed disease shows acceptable safety and ORR 20% (similar to rituximab with IWCLL 2008 criteria)


### CLL11: Study design

- Previously untreated CLL with comorbidities
  - Total CIRS score > 6 and/or creatinine clearance < 70 mL/min
  - Age ≥ 18 years
  - N = 781

- R: GA101: 1,000 mg days 1, 8, and 15 cycle 1; day 1 cycles 2–6, every 28 days
- A: Rituximab: 375 mg/m² day 1 cycle 1, 500 mg/m² day 1 cycles 2–6, every 28 days
- N: Chlorambucil: 0.5 mg/kg day 1 and day 15 cycle 1–6, every 28 days
- D: Patients with progressive disease in the Clb arm were allowed to cross over to G-Clb

**CLL11: Response and Toxicity**

- **Response**
  - CLB 31% ORR, 0% CR
  - CLB + Rituximab 65% ORR, 7% CR $p<0.001$
  - CLB + Obinutuzumab 77% ORR, 22% CR $p<0.001$

- **Toxicity**
  - Grade 3 and 4 infusion related events
    - 20% with Obinutuzumab versus 4% with Rituximab
    - Infusion events with Obinutuzumab early (day 1, within minutes of starting infusion sometime)
  - Grade 3 and 4 neutropenia
    - 33% Obinutuzumab versus 28% with Rituximab
    - No increased risk in serious infections was noted in any arm

---

**MRD Comparison and Impact on Outcome**

![Graph showing MRD comparison](chart.png)

**G-Clb vs Clb: Improved PFS and OS**

- **PFS**
  - Stratifed HR: 0.11
  - 95% CI: 0.13-0.24
  - P=0.0001

- **OS**
  - Stratifed HR: 0.41
  - 95% CI: 0.23-0.74
  - P=0.0022

Total number of deaths: Clb, 24 (20%); G-Clb, 22 (9%)

**Clb vs G-Clb: Overall survival**

- Stratified HR: 0.41
- 95% CI: 0.23-0.74
- P=0.0022

Total number of deaths: Clb, 24 (20%); G-Clb, 22 (9%)

---

Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.
**R-Clb vs G-Clb: Progression-free survival**


**G-Clb vs R-Clb: Overall survival**

**My Approach for Patients > 70**
- Repeat interphase cytogenetics, bone marrow
- Clinical trial with strong consideration of non-chemotherapy regimen with 2nd generation BTK inhibitor (ACP-196) comparing to standard therapy
- Off trial
  - Ibrutinib monotherapy
  - Contraindication to ibrutinib:
    - Obinutuzumab + chlorambucil or
    - Bendamustine + rituximab
- Do not use rituximab, alemtuzumab, chlorambucil or rituximab maintenance

---

**Case 2: Relapsed CLL**

Jennifer Woyach, MD  
Assistant Professor  
The Ohio State University

The James
Case Presentation

Patient is a 72 year old man who received bendamustine plus rituximab (BR) as front-line therapy 2 years ago. He presents with new fatigue limiting his ability to do yardwork at home and adenopathy that has been progressive over the past 3 months.

- FISH shows del(17p), stimulated karyotype shows a complex karyotype with 3 cytogenetic abnormalities
- IGHV is unmutated
- WBC 24.2 with 90% lymphocytes, hgb 13, plt 128

What is the best option for second-line therapy in this patient?

A. Re-treat with BR

B. Fludarabine, Cyclophosphamide, Rituximab (FCR)

C. Ibrutinib

D. Ofatumumab
Answer:
C. Ibrutinib

Alternative Answer Choices
- BR retreatment is expected to have limited efficacy
- FCR not appropriate for 72 year old patient, and efficacy limited in del(17p) CLL
- Ofatumumab is inferior to ibrutinib in relapsed CLL
Ibrutinib

- Forms an irreversible bond with cysteine-481 in Btk
- Also irreversibly binds other kinases with C481
- Once daily dosing results in 24-hr sustained target inhibition
- Pre-clinical activity in NHL and CLL

Herman, Blood 2011
Honigberg, PNAS 2010
PCYC 1102: A Phase Ib/II Study of Ibrutinib in Relapsed CLL

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Median (Range) ≥ 70 years, (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>66 (37 – 82) 35%</td>
</tr>
<tr>
<td>ECOG Status</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>41%</td>
</tr>
<tr>
<td>1</td>
<td>56%</td>
</tr>
<tr>
<td>2</td>
<td>2%</td>
</tr>
<tr>
<td>Median Prior Therapies</td>
<td>4 (1-12)</td>
</tr>
<tr>
<td>β2 Microglobulin &gt; 3mg/L, %</td>
<td>49%</td>
</tr>
<tr>
<td>Rai Stage III/IV at Baseline</td>
<td>65%</td>
</tr>
<tr>
<td>Prognostic Markers, %</td>
<td>85% del(17p13.1) 35% del(11q22.3) 39%</td>
</tr>
</tbody>
</table>

PCYC-1102-CA
Total enrollment 86 relapsed/refractory patients
Dates enrolled 20th May 10 – 27th Jul 11

Response by IWCLL 2008 Criteria

Progression-Free Survival


30 month PFS 69%

Phase III PFS

<table>
<thead>
<tr>
<th></th>
<th>Ofatumumab</th>
<th>Ibrutinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time (mo)</td>
<td>8.08</td>
<td>NR</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.215</td>
<td></td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(0.146-0.317)</td>
<td></td>
</tr>
<tr>
<td>Log-rank P value</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
</tbody>
</table>

78% reduction in the risk of progression or death

### Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>Ofatumumab</th>
<th>Ibrutinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time (mo)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.434</td>
<td>0.238-0.789</td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log-rank P value</td>
<td>0.0049</td>
<td></td>
</tr>
</tbody>
</table>

57% reduction in death with ibrutinib


### Case, Continued

The patient starts ibrutinib and sees dramatic initial improvement in lymph node size and fatigue. He initially has joint pain and heartburn, which are well controlled with over-the-counter medications, and improve over time. He has to hold ibrutinib for a short time due to a planned foot surgery, but otherwise is compliant with ibrutinib.

After 14 months of therapy all lymph nodes have resolved and patient is feeling well. WBC remains elevated at 36.3, with 90% lymphocytes
What should be done about the persistently elevated lymphocyte count?

A. Observation only

B. Add rituximab weekly for 4 weeks

C. Add idelalisib

Answer:

A. Observation Only
**Pattern of response with Ibrutinib**


**Prolonged Lymphocytosis Following Ibrutinib**

- Lymphocytosis in 77% of patients
- Median time to normalization 6.2 months (95% CI: 4.4-8.1)
- Prolonged lymphocytosis (PR-L) defined as lymphocytosis not normal or ≤ by 50% within 12 months
- At 12 months, 17 pts (20%) were PR-L, 49% PR/CR

Prolonged Lymphocytosis Following Ibrutinib

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CR/PR patients (n=42)</th>
<th>PR-L patients (n=17)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range)</td>
<td>66.0 (37-82)</td>
<td>67.0 (55-75)</td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td>30 (71.4%)</td>
<td>13 (76.5%)</td>
<td>0.759</td>
</tr>
<tr>
<td>Median baseline WBC (range, 10^9/L)</td>
<td>12.3 (1.7-308.1)</td>
<td>31.6 (3.8-122.0)</td>
<td>0.482</td>
</tr>
<tr>
<td>Median peak WBC (range, 10^9/L)</td>
<td>51.5 (5.2-619.1)</td>
<td>156.3 (29.1-361.1)</td>
<td>0.006</td>
</tr>
<tr>
<td>Rai stage at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate (II)</td>
<td>11 (26.2%)</td>
<td>6 (35.3%)</td>
<td></td>
</tr>
<tr>
<td>High (III/IV)</td>
<td>28 (66.7%)</td>
<td>11 (64.7%)</td>
<td>0.753</td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (7.2%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>FISH abnormalities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trisomy 12</td>
<td>6 (14.3%)</td>
<td>0</td>
<td>0.175</td>
</tr>
<tr>
<td>Del13q</td>
<td>15 (35.7%)</td>
<td>12 (70.6%)</td>
<td>0.010</td>
</tr>
<tr>
<td>Del11q</td>
<td>15 (35.7%)</td>
<td>7 (41.2%)</td>
<td>0.444</td>
</tr>
<tr>
<td>Del17p</td>
<td>13 (31.0%)</td>
<td>3 (17.6%)</td>
<td>0.364</td>
</tr>
<tr>
<td>IgVH Mutated</td>
<td>5 (11.9%)</td>
<td>7 (41.2%)</td>
<td>0.015</td>
</tr>
<tr>
<td>Zap-70 methylated at CpG3</td>
<td>11 (26.2%)</td>
<td>7 (41.2%)</td>
<td>0.487</td>
</tr>
</tbody>
</table>


PR-L is not associated with inferior PFS compared with PR/CR at 12 months

The patient’s lymphocytosis resolved after 19 months of therapy. He does well for 37 months, but then the lymphocyte count begins to rise and lymph nodes in the neck become palpable. He meets criteria for disease progression.

Which of the following mutations are most likely to have been acquired in this patient?

A. BTK mutation  
B. NOTCH1 mutation  
C. MyD88 mutation  
D. FLT3 mutation

Answer:  
A. BTK mutation
Whole exome sequencing (WES) identifies resistance mutation profile

Table 1. Characteristics of Six Patients with Resistance to Ibrutinib.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)</th>
<th>Prior Therapies (no.)</th>
<th>Baseline Cyto genetic Features</th>
<th>Study Treatment and Daily Dose</th>
<th>Duration of Ibrutinib Treatment (days)</th>
<th>Best Response</th>
<th>Time to First Response (days)</th>
<th>Identified Mutations of Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>59</td>
<td>3</td>
<td>del(17p13.1), trisomy 12</td>
<td>Ibrutinib, 560 mg</td>
<td>621</td>
<td>Partial</td>
<td>70</td>
<td>C481S mutation in BTK</td>
</tr>
<tr>
<td>2</td>
<td>59</td>
<td>3</td>
<td>del(11q22.3)</td>
<td>Bendamustine–rituximab for 6 cycles; Ibrutinib, 400 mg</td>
<td>388</td>
<td>Complete</td>
<td>70</td>
<td>C481S mutation in BTK</td>
</tr>
<tr>
<td>3</td>
<td>61</td>
<td>2</td>
<td>complex karyotype</td>
<td>Ofatumumab for 24 wk; Ibrutinib, 420 mg</td>
<td>674</td>
<td>Complete</td>
<td>85</td>
<td>C481S mutation in BTK</td>
</tr>
<tr>
<td>4</td>
<td>69</td>
<td>9</td>
<td>del(17q13.1), complex karyotype</td>
<td>Ibrutinib, 840 mg</td>
<td>868</td>
<td>Partial</td>
<td>133</td>
<td>C481S mutation in BTK</td>
</tr>
<tr>
<td>5</td>
<td>61</td>
<td>4</td>
<td>del(17q13.1), complex karyotype</td>
<td>Ofatumumab for 24 wk; Ibrutinib, 420 mg</td>
<td>505</td>
<td>Partial</td>
<td>85</td>
<td>L845F, R665W, and S707Y mutations in PLCγ2 and C481S mutation in BTK</td>
</tr>
<tr>
<td>6</td>
<td>75</td>
<td>2</td>
<td>del(17q13.1), complex karyotype</td>
<td>Ibrutinib, 420 mg</td>
<td>673</td>
<td>Partial</td>
<td>159</td>
<td>R665W mutation in PLCγ2</td>
</tr>
</tbody>
</table>

* We used fluorescence in situ hybridization to detect del(17p13.1), del(11q22.3), centromere 12, and del(13q14.3) and metaphase analysis of stimulated C-banded cells to determine complexity.
† Doses are given for ibrutinib only.

C481S mutation causes ibrutinib to inhibit BTK reversibly

Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.
With confirmed CLL progression after ibrutinib, you plan to continue ibrutinib until next therapy can be initiated. What is the best option for next-line therapy?

A. FCR  
B. R-CHOP  
C. Ofatumumab  
D. Clinical Trial

**Answer:**  
D. Clinical Trial
Survival is poor following relapse

- **BCL2** is antiapoptotic protein over-expressed in CLL and other malignancies
- **Venetoclax** is BH3 mimetic which antagonizes BCL2
- Phase I study in CLL
  - **ORR** 77% (30% CR, Cri)
  - **PFS** 25 mo in escalation cohort


Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.
Venetoclax Shows Preliminary Efficacy in Ibrutinib Resistance

- 41 ibrutinib-refractory patients treated with venetoclax
- ORR 61% (3 CR)
- Follow-up is short

Case 2 Conclusions

- BTK inhibitors and other targeted therapies have shown exceptional efficacy in the relapse setting and are standard of care
- Lymphocytosis with BCR signaling antagonists is asymptomatic, does not indicate relapse or predict poor PFS, and does not require intervention
- Relapse on ibrutinib is most often associated with mutations in BTK or PLCG2 and is associated with poor prognosis
- Clinical trials should be sought for patients who relapse on BTK inhibitors