Risk-Stratified Treatment in Chronic Lymphocytic Leukemia
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Financial Disclosure

The presenters have no financial interests to disclose.
Learning Objectives

1. Assess risk and monitor response to treatment by combining classic leukemia staging methods with novel pathology biomarkers and prognostic factors
2. Discuss strategies for managing side effects of novel therapies, as well as preventing infections
3. Describe best practices for optimizing selection and sequencing of treatments in the upfront and relapsed/refractory settings
4. Explain the role of the advanced practitioner as a member of the collaborative practice team in caring for patients with CLL through the trajectory of their illness
Case Study: Mrs. P

- 7/2008: 71-year-old female with progressive lymphocytosis (dating back to 2005) referred to local hematologist
- Past medical history
  - Diabetes
  - Hypertension and hyperlipidemia
  - Chronic renal insufficiency
  - Primary hyperparathyroidism (secondary to adenoma with intermittent hypercalcemia)
  - Kidney stones
  - Osteoarthritis
  - Gout
  - Vitamin D deficiency
  - Spinal stenosis with related chronic pain
  - Idiopathic pulmonary fibrosis
Case Study: Mrs. P (cont)

- **Subjective**
  - Asymptomatic
  - Intermittent debilitating back pain, followed by a spine specialist and a pain clinic
  - No recent infections

- **Social history**
  - Retired librarian, no chemical/radiation exposure, no military service
  - Married with 2 daughters
  - No smoking or alcohol history

- **Physical exam**
  - No palpable adenopathy
  - No palpable spleen
**CLL Diagnosis**

- **Essential workup for suspected CLL**
  - Laboratory evaluation
    - CBC w/differential, peripheral blood smear, comprehensive panel
  - History
    - Performance status
    - B symptoms
  - Physical exam
    - Physical exam, including nodal regions, Waldeyer’s ring and hepatosplenomegaly
  - Definitive pathology
    - Peripheral blood flow cytometry
    - If flow nondiagnostic, consider lymph node biopsy, excisional or incisional preferred
Case Study: Mrs. P (cont)

- Peripheral blood flow cytometry: 90% of lymphocytes monoclonal, express moderate lambda light chains, and are positive for CD5, CD23 and dim CD20 / negative for CD38, CD10, CD103

<table>
<thead>
<tr>
<th>Test (Unit)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cells (K/µL)</td>
<td>36.0</td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>72</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>12.5</td>
</tr>
<tr>
<td>Platelets (K/µL)</td>
<td>173</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.5</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td>44</td>
</tr>
</tbody>
</table>
What additional tests are needed for Mrs. P’s diagnosis?

A. None, the diagnosis has been established already  JL671
B. Bone marrow biopsy    JL672
C. PET scan   JL673
Other CLL Workup Considerations

- May be useful
  - Recurrent infections
    - Immunoglobulins
  - Anemia
    - Reticulocyte, haptoglobin, direct Coombs’
    - Bone marrow biopsy
  - Suspected tumor lysis or Richter’s transformation
    - LDH
    - Uric acid
    - PET (only if Richter’s transformation suspected)

- Consider
  - Hep B testing for CD20 monoclonal antibody therapy
  - Pregnancy test/sperm banking/address fertility issues
Which of the following tests are considered valuable or informative in determining prognosis and treatment in a patient with chronic lymphocytic leukemia (CLL)?

A. ZAP-70, JAK2 and BCR-ABL  JL674
B. JAK2 and ADMATS13  JL675
C. FISH, IgVH mutational status and karyotype  JL676
D. None of the above  JL677
Case Study: Mrs. P (cont)

- IgVH mutational status: Mutated
- FISH: Normal
- Karyotype: Normal
- No ZAP 70 or B2-microglobulin
- Had recent chest x-ray and abd/pelvis CT for other issues: No lymphadenopathy reported
## CLL Clinical Staging

### Rai Staging System

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Lymphocytosis (&gt; 5.0K/µL)</td>
</tr>
<tr>
<td>I</td>
<td>Lymphocytosis + lymphadenopathy</td>
</tr>
<tr>
<td>II</td>
<td>Lymphocytosis + hepatosplenomegaly +/- LAD</td>
</tr>
<tr>
<td>III</td>
<td>Lymphocytosis + anemia (Hgb &lt; 11 g/dL) +/- LAD or HSM</td>
</tr>
<tr>
<td>IV</td>
<td>Lymphocytosis + thrombocytopenia (Plt &lt; 100K/µL) +/- LAD or HSM</td>
</tr>
</tbody>
</table>

### Binet Staging System

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>&lt; 3 involved lymphoid sites</td>
</tr>
<tr>
<td>B</td>
<td>≥ 3 involved lymphoid sites</td>
</tr>
<tr>
<td>C</td>
<td>Anemia (Hgb &lt; 10 g/dL) or thrombocytopenia (Plt &lt; 100K/µL)</td>
</tr>
</tbody>
</table>

Rai Stage Survival

IgVH Mutational Status

- DNA sequencing for homology to the most similar germ-line gene
- Unmutated ≥ 98% homology
- ~50% of CLL considered unmutated
- Mut = OS ~ 25 years
  - ~80% No therapy
- Unmut = OS ~9 years
  - ~20% No therapy
- *Exception = Mut VH3-21 similar to unmut
- Constant over time

Karyotype

- Historically, karyotyping was limited because CLL has a very low mitotic rate
- Now, B-cell mitogens used to stimulate cell division provide more accurate karyotype
  - CD40-ligand, CpG oligonucleotide, and IL-2
- ~ 25% to 37% of patients will have additional abnormalities detected by karyotype (after FISH)
- Complex karyotype (> 3 abnormalities) repeatedly associated with poor prognosis
- Can change over time

FISH used to probe for common/ significant mutations found in CLL

### CLL FISH Panel

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Associated Gene</th>
<th>Gene Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Del(13q)</td>
<td>pRb</td>
<td>Tumor suppressor/Tumor survival</td>
</tr>
<tr>
<td>Trisomy 12</td>
<td>Multiple</td>
<td>Multiple</td>
</tr>
<tr>
<td>Del(11q)</td>
<td>ATM</td>
<td>Cell division/DNA repair</td>
</tr>
<tr>
<td>Del(17p)</td>
<td>P53</td>
<td>Tumor suppressor</td>
</tr>
</tbody>
</table>

Can change over time

http://AtlasGeneticsOncology.org/Anomalies/tri12ID2024.html
Prognosis by FISH

Clonal Evolution

- New techniques
  - Next generation sequencing
  - Whole exome sequencing
- Clonal evolution is affected by treatment
- Much data
- Not quite ready for standard of care

Others

- **CD38**
  - Detected by flow cytometry
  - Cutoff arbitrarily set at ≥ 30% for high risk
  - Even > 2% correlated with poor prognosis

- **Beta-2-Microglobulin**
  - Correlates with disease stage and tumor burden
  - > 3 generally considered poor prognosis

- **ZAP70**
  - Required for normal T-cell signaling
  - Found aberrantly in CLL cells

- Highly variable: Useful for prognosis but not necessarily treatment decisions

Case Study: Mrs. P (cont)

- Asymptomatic
- Rai Stage 0 CLL/Binet A
- Favorable prognostic findings by FISH
Which of the following is an indication to treat CLL?

A. CLL should be treated upon diagnosis in all cases
B. White blood cell count > 100K/µL
C. Anemia with hemoglobin < 12 g/dL
D. Symptomatic splenomegaly
Criteria to Treat CLL

- Eligible for clinical trial
- Significant disease-related symptoms
  - Severe fatigue
  - Night sweats
  - Weight loss
  - Fever without infection
- Threatened end-organ dysfunction
- Progressive bulky disease
  - Spleen > 6 cm below costal margin
  - Lymph nodes > 10 cm
- Progressive anemia or thrombocytopenia

NCCN, 2015.
No “One Size Fits All”

Platelets counts > 100K/µL = minimal clinical risk

In select patients with stable, mild cytopenias, continued observation may be appropriate
  - Hemoglobin < 11 g/dL
  - Platelets < 100K/µL

Autoimmune hemolytic anemia (AIHA) or immune thrombocytopenic purpura (ITP) may be treated for cytopenias alone without treating CLL

NCCN, 2015.
Case Study: Mrs. P (cont)

- Early 2008
  - Profound fatigue
  - Other medical problems stable
  - WBC 174K/µL, hemoglobin 10.1 g/dL, platelets 95K/µL
  - FISH repeated: Continues normal
Audience Response Question

Does this patient need therapy?

A. Yes  JL682
B. No  JL683
Previously Untreated CLL Treatment Schema

**Lab-Based Risk**
- FISH = Del(17p)
- FISH = No Del(17p)

**Clinical Risk**
- Candidate for aggressive therapy
- Not candidate for aggressive therapy (frail/elderly)
- Candidate for aggressive therapy
- Not candidate for aggressive therapy (frail/elderly)
Mrs. P: Initial Treatment Options

<table>
<thead>
<tr>
<th>Initial Therapy – No Del(17p) – No Aggressive Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Obinutuzimab +/- chlorambucil</strong></td>
</tr>
<tr>
<td>Ofatumumab + chlorambucil</td>
</tr>
<tr>
<td>Rituximab + chlorambucil</td>
</tr>
<tr>
<td>Chlorambucil</td>
</tr>
<tr>
<td>Pulse steroids</td>
</tr>
<tr>
<td>Rituximab + bendamustine?</td>
</tr>
<tr>
<td>Aggressive therapy</td>
</tr>
<tr>
<td>FCR, FR, PCR, BR</td>
</tr>
</tbody>
</table>
Obinutuzumab + Chlorambucil

- 781 pts: Median age 73 yr, CIRS score 8
- Randomized to O + chlorambucil, R + chlorambucil, or chlorambucil
- Primary endpoint: PFS
- Median PFS: 26.7 mo (O+C), 16.3 mo (R+C), 11.1 mo (C)
- O + C = Complete response rate = 22.3%

Case Study: Mrs. P (cont)

- Chlorambucil and prednisone initiated in March 2008
- Counts improve without normalization
- Fatigue improves
- October 2009: Presents in local ED with lower GI bleed
- Colonoscopy shows
  - Ischemic colitis
  - Diverticulitis
  - Positive for C. diff
- December 2009
  - WBC 80K/µL, hemoglobin 10.8 g/dL, platelets 49K/µL
  - Reassess
  - New Del(17p) on FISH
  - Further treatment needed
Previously Treated CLL Treatment Schema

**Lab-Based Risk**
- CLL requiring treatment
  - FISH = Del(17p)
  - Candidate for aggressive therapy
  - Not candidate for aggressive therapy (frail/elderly)
  - FISH = No Del(17p)
  - Candidate for aggressive therapy
  - Not candidate for aggressive therapy (frail/elderly)

**Clinical Risk**
Mrs. P: Relapsed/Refractory Options

<table>
<thead>
<tr>
<th>Subsequent Therapy – Del(17p) – No Aggressive Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ibrutinib</strong></td>
</tr>
<tr>
<td><strong>Idelalisib +/- rituximab</strong></td>
</tr>
<tr>
<td>Lenalidomide +/- rituximab</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Aggressive Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-dose methylprednisolone +/- rituximab</td>
</tr>
<tr>
<td>Alemtuzumab +/- rituximab</td>
</tr>
<tr>
<td>Oxaliplatin, fludarabine, cytarabine, rituximab</td>
</tr>
</tbody>
</table>
Case Study: Mrs. P (cont)

- December 2009: Bendamustine (70 mg/m²) and rituximab initiated
- Tolerated very poorly with multiple admissions for nausea, vomiting, dehydration; multiple dose reductions and delays for prolonged neutropenia
- Received 4 cycles
- Post therapy WBC 2K/µL, hemoglobin 12.3 g/dL, Platelets 50K/µL; creatinine 2.0 mL/min
Expected Outcome: BR – Relapsed CLL

- ORR = 59%
  - Del(17p) = 7.1%
- Median follow-up 24 mo
  - EFS = 14.7 mo
  - Del(17p) = 4.8 mo
  - OS = 33.9 mo
  - Del(17p) = 16.3 mo
- Not optimal therapy for del(17p) – especially relapsed

Case Study: Mrs. P (cont)

- 2010–2014
- Notable admission for diarrhea and dehydration due to *C. diff*
  - Asymptomatic a-fib that resolved without intervention after antibiotics, fluid, and electrolyte replacement
- Treated with rituximab 3 times weekly for thrombocytopenia
- Progression within 4–5 months of completing rituximab
- Recurrent infections noted
- Immunoglobulin G < 400
- Monthly IVIG replacement started with improvement of infections
Hypogammaglobulinemia in CLL

- Not well understood
- Disease-related immune defects
- Effects of chemoimmunotherapy
- Incidence ranges from 20% to 70%
- Increased prevalence with length and stage of disease
- Infection is the leading cause of death in patients with CLL

Case Study: Mrs. P (cont)

- February 2014
- WBC 300K/µL, hemoglobin 8.0 g/dL, platelets 86K/µL
- Needs therapy

Subsequent Therapy – Del(17p) – No Aggressive Therapy

<table>
<thead>
<tr>
<th>Ibrutinib</th>
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<tr>
<td>Idelalisib +/- rituximab</td>
</tr>
<tr>
<td>Lenalidomide +/- rituximab</td>
</tr>
</tbody>
</table>
B-Cell Receptor Signaling

http://www.onclive.com/publications/obtn/2013/october-2013/Novel-B-Cell-Receptor-Signaling-Inhibitors-Show-Promise
Expected Outcomes From Ibrutinib

Estimated 30 month OS = 79%

Del(17p) = 65%

Ibrutinib Effects in CLL

- Transient lymphocytosis at initiation = Not an adverse event!!
- AEs expected in $\geq 20\%$
  - Cytopenias
  - Diarrhea
  - Fatigue
  - Musculoskeletal pain
  - Rash
  - Nausea
  - Fever

General Recommendations

- For any \( \geq \) grade 3 adverse event
  - Temporarily discontinue ibrutinib
  - Resume when AE has resolved to \( \leq \) grade 1
  - For 1st occurrence = Resume at same dose
  - For 2nd–3rd occurrence = Reduce by 140 mg (1 tablet)/occurrence
  - For 4th occurrence = Discontinue

- For concurrent use of CYP3A Inhibitors/Inducers
  - Strong inhibitors: Avoid use
    - Anti-retroviral, ketoconazole, posaconazole, voriconazole, clarithromycin
  - Moderate inhibitors: Reduce dose of ibrutinib to 140 mg
    - Fluconazole, ciprofloxacin, erythromycin, calcium channel blockers
  - Strong Inducers: Avoid use
    - Anti-seizure meds

Audience Response Question

Which of the following would exclude this patient from receiving ibrutinib?

A. Absolute requirement for warfarin  
B. History of atrial fibrillation  
C. History of gastrointestinal bleed  
D. Neutrophil count of < 1.0k/uL prior to treatment initiation

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Frequency</th>
<th>Management</th>
</tr>
</thead>
</table>
| Atrial fibrillation       | 6%–9%     | Manage as usual  
Consider need for anticoagulation: Use reversible agent if possible; warfarin not allowed on clinical trials |
Audience Response Question

After initiation of ibrutinib, Mrs. P needs to have a tooth extracted by her dentist 2 weeks from date of clinic visit. Would you recommend any modification of her ibrutinib therapy?

A. No, she can continue ibrutinib daily  JL688
B. Yes, she should hold her ibrutinib dose for 3 days prior to and 3 days following the dental extraction  JL689
C. Yes, she should hold ibrutinib now and resume the day following the surgery  JL690
D. No, she should not have her tooth extracted  JL691

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Frequency (%)</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhage</td>
<td>Up to 6 = Severe</td>
<td>Spontaneous: Hold drug, consider risk/benefit Planned surgery: Hold for 3-7 days prior and after surgery</td>
</tr>
</tbody>
</table>
# Other Specific AE Management

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Frequency</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>71%</td>
<td>Monthly CBC</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>54%</td>
<td>Temporary discontinuation or growth factors as clinically indicated</td>
</tr>
<tr>
<td>Anemia</td>
<td>44%</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>63%</td>
<td>Mild/Moderate: Antidiarrheal agents Severe: Hospitalization, fluids, hold drug</td>
</tr>
<tr>
<td>Rash</td>
<td>27%</td>
<td>Mild: Topical steroid Moderate: Systemic steroid Severe: Hold drug</td>
</tr>
<tr>
<td>Infections</td>
<td>Up to 50%</td>
<td>No standard prophylaxis</td>
</tr>
</tbody>
</table>

Long-Term Follow-up: CLL Patients on Ibrutinib

- Median follow-up 20 mo
  - 232 on therapy, 31 PD, and 45 other
  - Richter's transformation (RT): Early ~ 12 mo = 4.5%
    - Median survival following RT was 3.5 mo
  - CLL progression: late ~ 12 mos = 0.3%
    - Median survival following PD was 17.6 mo
  - Mutations in BTK (C481S) or PLCγ2

Idelalisib + Rituximab

- ORR 81% w/ 93% lymph node response
- Median PFS
  - I + R = not reached
  - R = 5.5 mo

## Most Common AEs

<table>
<thead>
<tr>
<th>Most Common AEs</th>
<th>Any Grade (%)</th>
<th>Grade 3/4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>60</td>
<td>37</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>56</td>
<td>3</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>54</td>
<td>7</td>
</tr>
<tr>
<td>Transaminititis</td>
<td>25-35</td>
<td>5-8</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>35</td>
<td>3</td>
</tr>
<tr>
<td>Nausea</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>23</td>
<td>16</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>21</td>
<td>5</td>
</tr>
<tr>
<td>Chills</td>
<td>21</td>
<td>2</td>
</tr>
<tr>
<td>Rash</td>
<td>18</td>
<td>2</td>
</tr>
</tbody>
</table>

After starting on idelalisib, Mrs. P. develops grade 2 diarrhea with 4-6 liquid stools daily. When she calls your clinic, what should you recommend?

A. Increase fluid intake to 8-10 large glasses of clear liquids daily  JL692
B. Eat frequent small meals (BRAT Diet)  JL693
C. Stop lactose-containing products, high-osmolar supplements, and alcohol  JL694
D. Check stool sample for common infections and if negative, start loperamide  JL695
E. All of the above  JL696

**Audience Response Question**

**Adverse Event**

<table>
<thead>
<tr>
<th>Diarrhea (14% serious to fatal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Management</td>
</tr>
<tr>
<td>Severe (&gt;7 stools/day): Hospitalization fluids, steroids, hold drug. Resume at 100 mg bid</td>
</tr>
<tr>
<td>Life-threatening: Discontinue/DO NOT RESUME</td>
</tr>
</tbody>
</table>

# Idelalisib: Specific AE Management

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>Plt 25–50K/µL: Monitor weekly</td>
</tr>
<tr>
<td></td>
<td>Plt &lt; 25K/µL: Hold until &gt; 25; resume at 100 mg bid</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>ANC &lt; 1K/µL: Monitor weekly</td>
</tr>
<tr>
<td></td>
<td>ANC &lt; 0.5K/µL: Hold until &gt; 0.5; resume at 100 mg bid</td>
</tr>
<tr>
<td>ALT/AST elevations (14% serious to fatal)</td>
<td>5-20× ULN: Hold until &lt;1× ULN; resume at 100 mg bid</td>
</tr>
<tr>
<td></td>
<td>&gt;20× ULN: Discontinue/DO NOT RESUME</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>Discontinue/DO NOT RESUME</td>
</tr>
<tr>
<td>Infections</td>
<td>No standard prophylaxis</td>
</tr>
</tbody>
</table>

Case Study: Mrs. P (cont)

- August 2014: Started on ibrutinib
- WBC increased to peak of 500K/µL for 1 month before slow trend downward
- Initial adverse events: Fatigue and multiple soft stools per day
- AEs improved with time
- Currently: WBC 22K/µL, hemoglobin 10 g/dL, platelets 119K/µL
- Now minimal fatigue and 2 soft stools per day
- Plan is to continue until progressive disease or unacceptable toxicity
Role of the Advanced Practitioner in the Care of Patients With CLL

- Newer agents
  - Frequent up-front monitoring visits
  - Education about expected adverse events
  - Management of adverse events
- Oral drug adherence
- Multidisciplinary care
- Patient/family advocacy
  - Financial
  - Psychosocial
- Long-term survival
  - Continuity of care
  - Long-term and late toxicities
Future Directions

- Venetoclax (ABT-199)
  - BCL-2 inhibitor
  - Phase III study
- ACP-196
  - Second-generation BTK inhibitor
  - Phase III study
- CAR-T cell therapy
  - Phase I/II study
- Multiple others...
Key Takeaways

- Diagnosis and prognosis of CLL patients
  - IgVH, FISH, karyotype
- Selection of therapy
  - Performance status
  - FISH
  - Line of therapy
- Novel therapeutic agents
  - Know exclusion criteria and potential adverse events
- Role of advanced practitioner
  - Long-term follow-up
  - Patient education and advocacy
Questions?
Risk-Stratified Treatment in Chronic Lymphocytic Leukemia

MS. AMY GOODRICH: Thanks everyone for hanging in there with us. I know this is the last session of the day. We are here to talk about CLL. We have no financial disclosures. Here are our learning objectives, which you’ve got in your slides. We’re going to start with a case study and we are going to weave her into the entire program here. Our case study is Mrs. P., diagnosed in 2008. At that time she was 71 years old, with progressive lymphocytosis dating back a few years. She was referred to a local hematologist. Her past medical history, as you can see here, is pretty robust, but you know she’s not an atypical 71-year-old in our country. Subjectively she is asymptomatic. She does have intermittent debilitating back pain due to her spinal stenosis and no recent infections, so she’s good there.

She’s a retired librarian with a family. She’s a nonsmoker with no adenopathy, and no spleen on exam. What are the elements of an essential work-up? A laboratory evaluation, a CBC with differential, a peripheral smear, and a CMP. What about performance status B symptoms? Administering a physical exam, paying attention to nodes and spleen and liver, and running definitive pathology. For these patients, it really is peripheral blood flow. If there’s any question of what’s going on, then you can consider lymph node biopsies or bone marrows or other sorts of bells and whistles. For her, she has her peripheral blood flow done and, as you can see, she’s got a pretty typical CLL here: CD5 23, CD20 negative, CD38, CD10 and CD103. You can see her counts here. Her white count is elevated, mostly lymphocytes, and her hemoglobin and
platelets are not horrendous. She’s got a little bit of renal insufficiency out of the gate. So what additional tests are needed for her diagnosis? I think I gave it away already.

Let’s move on, okay? Additional things that you could consider if folks are having recurring infections is to look at their immunoglobulins. If they’re anemic, try to figure out if they are having hemolytic anemia by looking at their hemolytic anemia parameters or dipping into the bone marrow. If you are suspecting tumor lysis syndrome or Richter’s, try looking at LDH, uric acid, and PET. If you’re suspecting Richter’s, those spots will be brighter on the PET. Then, of course, hepatitis B testing if you’re going to use CD20, anti CD20 monoclonals. Also, include pregnancy testing, sperm banking, all those good things if it’s a younger patient. Which of the following tests are considered valuable or informative in determining the prognosis and treatment of a patient with CLL? Thank you.

Mrs. P.’s IGVH mutational status is mutated and Dr. Deborah Stephens will be talking about that in a little bit more depth. Her FISH studies are normal, and her karyotype is normal. Her NOSAP 70 or beta 2 microglobulin were done at that time, also. Remember, it’s 2008 and she just went to see a local hematologist. She had a recent chest x-ray done for other purposes and an abdominal CT. She had no adenopathy, so none were repeated.

**DR. DEBORAH STEPHENS**: And I want to go back to the question asking about if more diagnostic tests were needed. A few of you had placed that you need a bone marrow biopsy, and actually for this patient population with the peripheral blood flow cytometry diagnostic of CLL and no other symptoms or
cytopenias, you don’t actually need to do a bone marrow biopsy at diagnosis, which is something that patients are generally very excited about. For this portion of the talk I’m going to be talking a little bit about different prognostic factors. It is going to include a little bit about clinical and more so about lab prognostic factors because there’s a lot of tests out there that you can do. Which ones are the ones that are actually the most important and tell the patient something about what the next few years of their life are going to be like. And what would help you decide upon a different treatment option. The first and the easiest thing that people can do when they meet a patient is do the staging for CLL. What's unique about this type of cancer is that all the staging is done purely based on clinical exam and laboratory findings, because you don’t actually need imaging studies for the diagnosis or staging of CLL.

There are two separate staging systems; one is the Rai staging system and that’s the one that’s used most frequently in the U.S., and the other is the Binet staging system, which is used more frequently in Europe. And I’m going to focus really on the Rai staging system, but I’ve listed the Binet below so you can see it. And basically, a stage 0 means just lymphocytosis; stage I adds lymphadenopathy; stage II adds splenomegaly or hepatomegaly; stage III adds anemia, which means a hemoglobin of less than 11; and, stage IV adds thrombocytopenia, which adds a platelet count of less than 100,000. Here’s a graph that depicts what the survival curves are based upon the stage of the patients. The numbers are a little bit small, but most patients are in the stage I or II category at diagnosis, and that’s the middle line there. You can see the top line
is a Rai stage 0 at diagnosis and they have quite an extended survival of up to 12 years, for a median overall survival for this group—which is quite good survival.

You can see that as compared to the dotted line, which includes patients with stage III or IV at diagnosis, they have a good survival, but it is limited to about a median of eight years in the patient’s first staging. This is something that patients always want to ask about because they always know someone who had breast cancer or something and were told they had stage IV breast cancer. They ask if it means the same thing for their CLL. Now I am going to focus more on the laboratory studies, because as I mentioned, there are a lot of studies that can be sent on these patients. I really want to focus on the ones that are going to mean something clinically and as far as their immediate prognosis or what treatment you might choose. The IGVH mutational status is one of the most important ones of those markers.

This is the immunoglobulin variable heavy chain. In a normal person this mutates with age because what you’re doing is you’re developing different antibodies and trying to attack different antigens that your body might be exposed to. It’s normal for this gene to be mutated. With that being said, the unmutated variety of CLL is the more aggressive one and less developed. We are looking at DNA sequencing, which compares the homology of the most similar germline sequence. A sample is considered unmutated if it has greater than 80% homology to that germline. It’s about 50:50 on a patient if it’s going to be mutated or unmutated. As you can see with the survival curves, it does have a significant impact on the predicted survival. Patients with mutated IGVH status
have an expected overall survival of 25 years, and around 80% of this group may never need therapy for their CLL.

So that is really important for patients as far as planning. Also, you can see that the unmutated patients have an overall survival of only about nine years, and only 20% of them don’t need therapy. In my experience, it’s really a little bit closer to 100% of these patients who go on to need therapy at some point. One exception to this rule is that a mutated version of the VH321 actually behaves clinically similarly to the mutated group and has the worst prognosis. Another thing I like about this prognostic factor is it is constant over time so you don’t have to check it every time you go through a different treatment, and it is something that can be done at diagnosis to give a patient an idea of planning. You know if they are mutated you might want to tell them they don’t want to go to Vegas and spend all their money because they are probably going to be around for a long time.

The next test I want to talk about is something called a karyotype. This is basically where your chromosomes are taken and looked at under a microscope and you can see an example on the screen of actually an abnormal chromosome 12. Because there should only be two arms up there, and there are actually three, this is called trisomy12 CLL. Basically these cells have to be dividing in order to see these different changes in the karyotype. The one thing that has been limited historically, is that CLL is a very slow growing cancer, it is not rapidly dividing, and so we eventually had to come up with ways to stimulate the CLL in the laboratory in order for us to see these chromosomal abnormalities. There’s a
very common test called a FISH panel that I’m going to be talking about next. Actually this karyotype will pick up new abnormalities in about 25% to 40% of patients who are not picked up on the FISH test. This is important because a complex karyotype, or greater than three abnormalities, has been strongly associated with a poor prognosis, and it may affect the patient’s ability to respond to therapy. This can change over time and I’m going to talk a little bit about that in an upcoming slide.

The one that is most commonly performed and is actually a very important test is the CLL FISH panel. It basically looks at those genetic abnormalities that are most commonly identified or ones that have a significant prognostic effect on patients. And the ones I have listed here are 13q, trisomy 12, 11q and 17p, which are most commonly tested for. This is an abbreviated version of the karyotype because the karyotype looks at all of the chromosomes and this looks just at these very specific parts of the chromosome. Deletion 13q is important because there’s a tumor suppressor gene called the retinoblastoma gene located on that chromosome. Trisomy 12 obviously is a whole chromosome, so it has multiple different genes that are associated with it. Deletion 11q is associated with ataxia telangiectasia mutation, which is responsible for cell division and DNA repair. It is really important if that is missing. Deletion 17p is one of the most important prognostic factors because it carries a very important tumor suppressor gene, TP53. It has a very strong prognostic impact for the patient and affects what treatment you would choose.
This is the survival graph from 2000 when Donor originally published this data in the *New England Journal of Medicine*. Although the numbers are a little small, you can see that the top line represents those patients with deletion 13q as a sole abnormality. These patients actually do better than patients who have a normal karyotype or trisomy 12, which are the next two bars down below and are overlapping. Below that, you have 11q. The very worst prognosis are the patients with 17p, as I mentioned before. And you can see that it has quite a significant impact on the survival of these patients. And when we talk about treatment later, I even use the presence or absence of deletion 17p to choose what therapy I would do. Of course there’s a lot of novel genes that have been identified and some multiple groups have done great work. This is a schematic that was put out by Cathy Wu's group at the Broad Institute, who has done a lot of studies. They are next generation sequencing or whole XM sequencing, and have identified many potential common abnormalities in CLL cells.

This graph represents how CLL changes over time. In the first part you get normal mutations—just through aging or random mutations. In part B you can get some of these specific abnormalities called inducing inciting driver events. These include trisomy 12 and deletion 13q, in additional to mid 88, which is common in many of these cancers. At the top you can see what happens without treatment. You know there are multiple different abnormal clones and they are all dividing at about the same rate. At the bottom you see what can happen. The red cells represent a very bad clone, and typically this is probably something that has deletion 17p, 11q or multiple genetic abnormalities. And when you treat these
patients, the percentage of those cells that survive, because they are chemotherapy resistant, becomes equal with the rest of the population and then they are able to divide in a significant amount. Therefore, when a patient relapses, sometimes you have multiple more cells that have these high-risk genetic features. So, both the karyotype and the FISH panel can change over time. I do check them every time I am moving into a time of treatment for the patient, because if they have developed one of these risk features, it’s going to affect what type of treatment that I would recommend.

And so as I mentioned there’s a lot of new data out there, not much of it is quite yet ready for standard clinical care yet. There are a couple of other ones that I want to mention because they are commonly checked and usually readily available. CD38 is detected on flow cytometry, and on the initial publication really the cut-off of what’s a bad prognosis, was set kind of arbitrarily. In subsequent studies, even a greater than 2% expression is associated with a poor prognosis. Beta 2 microglobulin correlates with disease stage, tumor burden and greater than 3 is generally considered a poor prognosis, and ZAP-70 is something that is required for normal T cell signaling. It is found aberrantly in CLL cells. The thing that I don’t like about these particular prognostic factors is that they change over time. They are highly variable, and ZAP-70 is especially very variable from lab to lab, making it hard to really tell a patient what their prognosis is based upon this since it changes so frequently. And so these are ones that are commonly checked, but in my opinion are not quite as important as far as the patient’s overall outlook.
MS. AMY GOODRICH: So back to our case study. She is asymptomatic, she’s got Rai stage 0 disease, and she’s got favorable prognostics by FISH. Which of the following is an indication to treat CLL? Should it be treated upon diagnosis. Cell count greater than 100,000, anemia with hemoglobin less than 12, or symptomatic splenomegaly? What are the criteria to treat CLL? First and foremost, if you have a clinical trial that a patient fits criteria, then those are always the preferred way to go with a patient. If they have significant disease related symptoms, severe fatigue, night sweats, weight loss, fever without infection, threatened end organ dysfunction, progressive bulky disease, be it nodes or splenomegaly, and then progressive cytopenias, these are all other reasons to treat. How cytopenic is cytopenic enough? For those of you who treat CLL patients and work with more than one physician, you probably know that everyone has a different one size fits all idea. So this really is a quandary many times. Platelet counts over 100,000 really have very minimal clinical risks. In select patients with stable mild cytopenias, continued observation may be appropriate.

We know with hemoglobin less than 11 and platelets less than 100,000, it’s typically the pace of the change that makes the biggest difference and not someone who slides down one or two thousand on their platelets every three or six months. Of course, you’re always looking. You always have to keep autoimmune thrombocytopenia and hemolytic anemia in the back of your mind as well for these patients. Early 2008, she develops profound fatigue. Her other medical problems are stable, so for someone like her with that whole list of other
medical problems, you really have to flesh out a lot of things before you blame it on the CLL. Her white count is rising, her hemoglobin is dropping, as are her platelets, her FISH is repeated and continues to be normal. Does she need therapy, yes or no?

**FEMALE ATTENDEE:** Yeah.

**MS. AMY GOODRICH:** Okay. All right. Thank you.

**DR. DEBORAH STEPHENS:** I agree with you. Based upon the fact that her hemoglobin is low and less than 11, she has profound fatigue that appears to be secondary to progressive CLL. So for somebody with untreated CLL, this is kind of the brief treatment algorithm that I use and it’s loosely based upon NCCN guidelines. So first of all, you decide if they need treatment—and we have already decided that she does. And then I look at lab-based risks. Does she have 17p or no 17p. If she does not have 17p, then I look at her clinical risks. If she is a candidate for aggressive therapy, and if she is definitely not a candidate for aggressive therapy. So in this category there are several treatment options that are currently available. These are a summary of options that I use for patients with initial therapy, no deletion 17p, who can’t tolerate aggressive therapy. You can see listed at the top there are three anti-CD20 monoclonal antibodies that are combined plus or minus with chlorambucil. You could use chlorambucil alone or with pulsed steroids, and some patients if they are borderline, could tolerate bendamustine and rituximab therapy. I’m going to talk a little bit more about obinutuzumab and chlorambucil on the next slide, but I did want to mention if she were a candidate for aggressive therapy and if she were younger, the potential
options are listed below: fludarabine and cyclophosphamide or rituximab, fludarabine and rituximab, pentostatin, cyclophosphamide and rituximab, or bendamustine and rituximab. And comparing these regimens in younger patients, there’s a large on-going phase III clinical trial. At this time and point, it appears that FCR causes progression in increased survival over BR in the younger, healthier patients with CLL.

But going back to our case, although she was diagnosed and needed treatment prior to the approval of this drug, if this were available this would have been a great option for her. Obinutuzumab and chlorambucil are some of the most recently approved drugs for the treatment of CLL. Obinutuzumab is an anti-CD20 monoclonal antibody. How it’s designed to be better than rituximab or ofatumumab is that the portion called the FC portion of the antibody is engineered to better and more effectively bind NK cells to mediate NK cell mediated cytotoxicity. It does it very well. In the phase three clinical trial that it had that got this drug approved, there were 781 patients with a median age of 73 and a SIRS score of 8. And the SIRS score is one that we use to calculate different co-morbidities. The relatively old and sick population would be exactly where our patient would fit. The patients were randomized to receive obinutuzumab and chlorambucil, rituximab and chlorambucil, or chlorambucil alone. And the primary end point of this trial was progression free survival.

And you can see, the survival curves to the right here and the top curve. The purple curve is the obinutuzumab and chlorambucil, and you can see that the median progression free survival was 26.7 months, as compared to 16.3
months shown in the rituximab and chlorambucil arm and the chlorambucil alone was only 11.1 months. Additionally, what was interesting about this trial is that 22% of patients on the obinutuzumab and chlorambucil arm were able to achieve a complete response, which is actually a very good number for a monoclonal antibody therapy.

**DR. ANN GOODRICH:** So that’s our case study and remember this was 2008. She was treated with chlorambucil and prednisone, which is a very old-time regimen. Her counts improved without normalization. Her fatigue improved. So she gets benefit from the chlorambucil and prednisone. By a year later to a year and a half later, she’s in the ED with a lower GI bleed because of the chlorambucil and prednisone, but her colonoscopy shows she’s got ischemic colitis, diverticulitis, and *C. diff*. Later, at the very end of the year, she’s starting to progress again at 80,000, her hemoglobin is in the 10s, and platelets are 49. She gets reassessed because she just comes off the chlorambucil and prednisone and had been doing well and she’s got a new deletion 17p, and further treatment is needed at this time.

**DR. DEBORAH STEPHENS:** For this group of patients, I use a very similar algorithm with different options for patients with relapse CLL. So now she is a CLL patient requiring therapy. She does have deletion 17p and she is still not a candidate for aggressive therapy. In this setting, subsequent therapy for patients with deletion 17p that cannot tolerate aggressive therapy, have several very good options. Unfortunately, for Mrs. P. they weren’t quite ready when she needed this treatment. If this were today and she presented in the same clinical
situation, she would get ibrutinib or idelalisib, which are B cell receptor signaling inhibitors, which we are going to talk about in more detail in the next few slides, or potentially lenalidomide and rituximab. If she were a patient that could get aggressive therapy in addition to the ones listed above, she could potentially get high dose methylprednisolone and rituximab. Chempath is still available off label or Campath is still available off label, or a very aggressive regimen of oxaliplatin, fludarabine, cytarabine, and rituximab. We are very fortunate today to have these less toxic therapies for all of our patients.

**MS. AMY GOODRICH:** By the end of 2009 she needs therapy, and at that time, we didn’t have these newer drugs. She gets started and this was locally on bendamustine and rituximab, and she tolerated it very poorly: multiple admissions, nausea, vomiting, dehydration, dose reductions. She only got four cycles and post therapy her white count was 2,000, hemoglobin 12, platelets 50 and her creatinine took a hit through this whole thing, and then this is when she gets referred in to us.

**DR. DEBORAH STEPHENS:** And I want to try and make that clear. She did not get bendamustine and rituximab. You might have noticed that bendamustine and rituximab was not listed anywhere on my list of treatments for deletion 17p patients and especially in relapse disease. I wanted to show you this slide really to demonstrate why I would not give bendamustine and rituximab to somebody in this patient population. First of all, generally this is the study that first looked at bendamustine and rituximab in relapsed CLL. The overall response rate is about 59%. You can see that for deletion 17p patients it is 7.1%. This
study was published after a median follow-up of about two years. In the general group, the event free survival was 14.7 months while in the deletion 17p group it was only 4.8 months.

As far as overall survival, the general group had a 33 month overall survival, while the deletion 17p only had a 16 month overall survival. You can see the curves. The light blue is the deletion 17p patients, and you know especially for somebody who is old and sick like this lady, you really just give them toxicities. You are not adding any benefit to treating them with bendamustine and rituximab, so I just want to emphasize (and you know we have so many options now) this is not a great therapy for deletion 17p, and I would not use it.

**MS. AMY GOODRICH:** Now I’m going to clump four years together. She sort of starts this downward spiral. She had been admitted for diarrhea, dehydration, *C. diff.*, and she had atrial fibrillation during that hospitalization. It resolved with just correcting her electrolytes and her hydration status. At this point she needed therapy. We were on the verge of killing her because she was so unstable, so we gave her thrice weekly rituximab. This is an old regimen, as well as thrombocytopenia, while trying to figure out if it was immune related or from the CLL. We did a bone marrow and her megakaryocytes were very low. So we sort of got her through that. She progressed pretty quickly. She keeps having these recurring infections. Her immunoglobulins are low. We start replacement therapy of IgG, and many of you in this room know that this is a big issue in patients with CLL. It’s really not well understood. It is disease related in terms of the immune defects, but it’s also treatment related. The incidence is really not
well understood either in the literature. It’s anywhere from 20% to 70%. There’s an increased prevalence the longer you have the disease and the higher the risk is of developing hypogammaglobulinemia. And infection is the leading cause of death in these patients. Looking for it and replacing it is definitely worth the time and the effort.

So February of 2014 she comes in, her white count’s going up, her hemoglobin is low, platelets are low, she needs therapy. So what are we going to do today? Because this is sort of today, 2014, same difference, right?

DR. DEBORAH STEPHENS: Again, I mentioned I’d be talking more about the B cell receptors, signaling inhibitors, which really have been one of the most exciting discoveries for patients with CLL. I’ve shown a picture here of the B cell receptor pathway and basically it is a survival pathway for B lymphocytes, including malignant B cells such as CLL cells. Basically what we are doing is blocking the signals that tell the cells to stay alive and then the cells die. I always explain it to patients as kind of taking the gas out of the car. You can see here that the two drugs that are currently approved are idelalisib, which is a phosphoinositide 3-kinase delta inhibitor, and ibrutinib, which is a bruton tyrosine kinase inhibitor. So you can see these are the survival curves from patients treated on ibrutinib, and you can see the significant difference in, for example, just the one I just showed you for bendamustine and rituximab. The survival curves are pretty flat and this is the same patient population. These are relapsed and refractory patients with CLL. In publication, the estimated 30 month overall survival is 79%, which is outstanding for these patients. You can see below that
the 17p patients still are the ones that are more likely to relapse on these therapies; however, the survival is significantly improved over any of our regimens that we have had in the past.

One thing that I really wanted to point out is that these drugs work a little bit differently than the traditional chemotherapies. This graph shows in green the sum product diameter of lymph node size. You can see that it pretty quickly goes back down to normal after starting therapy; however, the purple line is the absolute lymphocyte count and these drugs do cause a transient lymphocytosis. You can see that it peaks at about two months after therapy. When these drugs initially came out people were stopping the drugs because they thought patients were progressing based on our previous assessment of patients that would be considered a progression. However, something that’s very interesting about the drug is that it worked – you know CLL cells are very comfortable. They like to live in places like the lymph nodes and the spleen, and this drug can really break those bonds. It brings them out into the peripheral blood where it’s easier for them to die off.

And so you see this initial movement of cells out of the spleen and lymph nodes. That’s why the lymph nodes shrink and the peripheral blood count goes up. But I just want to highlight that this is not an adverse event and these patients should not be stopped on therapy because of this. As long as they are otherwise responding, this is exactly what the drug is designed to do and expected to do. As far as adverse events, some of the most common ones experienced by these patients are cytopenias, diarrhea, fatigue, musculoskeletal pain or aches, rashes,
nausea, and fever. And my general recommendations for anyone who experiences a grade 3 adverse event on one of these drugs is to temporarily discontinue the drug, and resume it when it has resolved back to grade 1. For a first occurrence you can restart the drug at the same dose. For second and third occurrence, use your clinical judgment, but you can restart it at a reduced dose. Each pill is 140 mg, so you can reduce by one pill for each occurrence. If there’s a fourth occurrence with a severe side effect, you should discontinue the drug permanently.

Also should be aware that there are other drugs that may interact with ibrutinib and those include some of the common ones that we use in these patients. These are SIB3 A4 inhibitors or inducers. Strong inhibitors you should really avoid use. Those include antiretroviral drugs used commonly in HIV patients and some of the antifungal agents, which I have listed there. The moderate inhibitors, you can still use ibrutinib, but you should reduce the dose to 140. That includes very commonly used fluconazole and ciprofloxacin and calcium channel blockers. For strong inducers you should also avoid use, and this group mainly includes antiseizure medications. For this audience response question, I just want to highlight a few of the effects of ibrutinib. Which of the following would exclude this patient from receiving ibrutinib: A.) Absolute requirement for warfarin; B.) History of atrial fibrillation; C.) History of GI bleed; or D.) Neutrophil count of less than 1,000 prior to initiation of treatment?

Okay, thank you. And this one is a little bit tougher, so we’ll go through it one by one. My answer is actually answer A, absolute requirement for warfarin.
And the reason why is there has been about a 6% of severe or fatal bleeding in patients on the clinical trials who were receiving both ibrutinib and warfarin at the same time. This is thought to be related to dysfunction of the platelets with ibrutinib. In any patient who has an absolute requirement for Coumadin, such as an artificial heart valve or anything that can be switched to a shorter acting drug such as Lovenox, I would generally choose to give these patients idelalisib, which doesn’t have the bleeding risk. The other big thing that’s been found is a history of atrial fibrillation. Atrial fibrillation has been associated with ibrutinib use in 6% to 9% of patients; however, it’s a little bit hard to sort out because this is exactly the patient population that is going to get atrial fibrillation anyway. And our patient had atrial fibrillation in relationship to a C. diff. infection and dehydration, and that should not exclude her using ibrutinib. For a patient with atrial fibrillation, we manage them as usual with the exception that I don’t use Coumadin to anticoagulate these patients. Some patients could get cardioversion or use other agents.

Although I did mention that there is a risk of bleeding, her history of GI bleed was associated with an infection. Since that has stopped and is stable, it shouldn’t preclude her from getting this drug. A neutrophil count of less than 1,000 is usually related to the CLL and bone marrow infiltration. Patients can start on this drug with a neutrophil count of less than 1,000. Generally that neutrophil count will go up with the drug. I’ll talk a little bit more about management of those in a few slides. This is my next question, after initiation of ibrutinib, Mrs. P. needs to have a tooth extracted by her dentist two weeks from
the date of clinic visit. Would you recommend any modification of her ibrutinib therapy? A.) No, she can continue to receive ibrutinib daily; B.) Yes, she should hold her ibrutinib dose for three days prior and three days post dental extraction; C.) She should hold her ibrutinib now and resume the day following extraction; or D.) No, she should not have her tooth extracted. Okay, this is great. I agree with the majority of the audience that B is the correct answer, and we’ll talk a little bit more in detail about that.

So as I mentioned, about 6% of patients can have severe hemorrhage. Again, typically this was in association with being on a separate blood thinner as well. For spontaneous hemorrhage, you should always hold the drug and really consider the risks and benefit ratio of restarting the drug. For planned surgeries, the drug should be held for three to seven days post and prior to the surgery. I usually make that determination based on how significant the surgery is. Every time I start patients on this drug, I make sure that I mention, because you know they don’t think, You know they’re coming to see you for cancer therapy. They don’t really typically think to mention that they need a tooth extracted or they’re having you know some other minor procedure done. You really need to emphasize that their surgeon needs to be aware of this drug, because it’s relatively new and they surgeon needs to know that they should hold it. They can always call you to get recommendations for holding the drug. I think that this is really important just because this is a drug that’s designed for the patient to take for the rest of their life and the majority of these patients are going to have some
sort of procedure done during that time period, whether it just be, you know, a mole removal, a tooth extraction, or a more major surgery.

I want to briefly address some of the other specific adverse event management for these patients. As far as cytopenias, they happen very frequently, so patients should be getting at least a monthly CBC. The drug can be temporarily discontinued if you reach one of those grade 3 side effects or adverse events. You can use growth factors if needed, and it’s really necessary to keep the patient on the drug. Diarrhea as you can see is quite common and the reason why people get diarrhea is because the drug, in addition to inhibiting Bruton tyrosine kinase, it also inhibits EGFR, which is a common drug target for solid tumor drugs, and can cause diarrhea. So for moderate or severe, you can use antidiarrheal agents and dietary modification. For severe diarrhea, patients should be hospitalized, given fluid, and hold the drug. The next one is a rash, which happens in about a quarter of patients. This is again secondary to that off target side effect of EGFR inhibition. A mild rash can be treated with topical steroids and severe with systemic steroids or holding the drug. You can’t see it down below, but I just mentioned infection can happen in up to 50% of these patients. There’s no standard recommended prophylaxis at this time.

We now have some long term follow-up data of these patients on ibrutinib. There was a group of about 300 patients that was treated on various clinical trials. You can see that at 20 months, 232 of these patients were still on therapy, which is great. But there were 31 patients who did come off for progressive disease. With a closer look at these groups of patients, there were two distinct
groups. One group is our patients that transformed into a more aggressive lymphoma called Richter’s transformation. This seemed to happen early, and it was a higher risk in the first year of therapy of this happening. Once this happened, the survival of the patients was very poor at only 3.5 months. There is another group of these relapse patients that had CLL progression, and the survival was better for these patients at 17.6 months. The reason why they progressed is because they developed mutations at the binding site of ibrutinib or they had downstream activation of other members of the B cell receptor signaling pathways such as PLC gamma 2.

Switching over to idelalisib, which is another inhibitor of the B cell receptor signaling pathway, I wanted to highlight the trial that got this regimen approved for relapsing and refractory patients in combination with rituximab. You can see in this trial, patients were randomized to idelalisib, plus rituximab versus rituximab alone. In the group who received idelalisib, the overall response rate was 81%, but 93% of patients had a lymph node response. The median progression free survival of the idelalisib group was not reached, while the median progression free survival of the rituximab arm was only 5.5 months. So really this looks about as close to what you would see a placebo-controlled trial in Oncology look like. I just put a graph to show some of the common side effects with idelalisib. They include cytopenias, transaminitis, which I will talk more about in a few slides, pneumonia, diarrhea, nausea, and rash. So for our next audience response question, after starting on idelalisib, Mrs. P. develops grade 2 diarrhea with four to six liquid stools daily. When she calls your clinic, what would you
recommend? A.) Increase her fluid intake; B.) Eat frequent small meals and the BRAT diet; C.) Stop lactose containing products, high osmolar supplements, and alcohol; D.) Check a stool sample for common infectious agents, and if negative, start loperamide; or E.) All of the above. So great, I agree, you should do all of the above in this situation.

Diarrhea is one of the adverse events that was reported very frequently in patients receiving idelalisib. This is an inflammatory diarrhea, which resembles something like ulcerative colitis or Crohn’s disease. In 14% of cases, it could be serious to fatal diarrhea. It can occur late, when the patient is on therapy or a year or two out of therapy. In a mild case, like this patient had, I would just recommend dietary modifications and Imodium. In severe or greater than seven stools per day, the patient must be hospitalized and hold the drug. Using your clinical judgment, you may resume the drug at a reduced dose of 100 mg b.i.d. with the standard dose of 150 mg. If you have life-threatening diarrhea, then you should not resume the drug. I wanted to highlight a few other specific management cases as far as cytopenia. If you can see some mild cytopenias, you should be monitoring their counts, and recommending to reduce the dose, if you can’t get the platelet or neutrophil count up. Transaminitis is also a very significant or very severe side effect when it happens. It is also about 14% serious to fatal in that event.

If the liver function tests are greater than 20 times upper limits of normal, you should discontinue the drug and not resume it. If between 5 and 20, using your clinical judgment, you need to hold the drug. Whether or not you want to
resume it at a reduced dose is a possibility. Patients who develop pneumonitis on idelalisib should absolutely not be restarted on the drug. Again, infections can happen, but there is no standard prophylaxis for idelalisib.

**MS. AMY GOODRICH:** Okay, let’s go back to our case study. In August of 2014, she starts ibrutinib. Her white count was about 300,000 at the time, and it peaked at about 500,000 for about a month. Then the count did this very slow downward trend, which really matches the graph that Debbie showed. Her initial adverse events were fatigue and not really diarrhea, but soft stools. Her adverse events improved over time. Currently her white count is 22, her hemoglobin is 10, and platelets are over 100,000. She’s got minimal fatigue, and we’ve gotten her soft stools under control. You know, because really having four to six stools above normal a day is life altering. Two is okay for her. Then the plan is to continue until progressive disease or unacceptable toxicity.

**DR. DEBORAH STEPHENS:** And we’ll comment before Amy moves on too, that some of these patients do get these high peaks of white blood cell count. Generally, because CLL cells are so small they don’t get the leukostasis like you see with acute myeloid large blast cells. It definitely makes people uncomfortable, but this is definitely seen in these patients.

**MS. AMY GOODRICH:** What’s the role of the advanced practitioner? With our newer agents that we have heard about here and in other talks, really frequent up front monitoring. You’ve got to know for these people have been started on the drug, most of them, the side effects are going to be worse initially and improve over time. Patients need to be educated about side effects because
you know once that diarrhea starts, if they don’t like it, they’re going to stop the
drug. Really tight management of adverse events will only help oral drug
adherence, so these folks really need multidisciplinary care. Especially with Mrs.
P., where she’s got all these other health problems. She is on IgG replacement.
She’s where everyone’s just putting duct tape on her trying to keep her health
together. She’s a very typical CLL patient. Because of patient and family
advocacy, we took out a lot about this lady, including financial and psychosocial
information, Her husband died; she sold her house because she was having so
many infections; she was in and out of rehab; she was living with different family
members; and she was going to a different ER all the time for these infections.
Those of you who went to Laura Adams’ presentation about all the gaps in our
healthcare system will recognize that she really got caught in those a lot.

I was the one tracking down records trying to figure out what the heck was
going on with this lady: of course long-term survival issues, continuity of care,
long-term and late toxicities. Really it’s the people in this room who keep these
people duct taped together.

**DR. DEBORAH STEPHENS:** You know we are seeing a lot of these
patients, who previously would have died from their CLL, are living longer. I think
the advanced practitioner is so very important in the management of these
patients. I wanted to just hit briefly on a couple of the future directions that may
be out there for treatment of CLL. One is very promising and probably will be the
next agent approved by the FDA is venetoclax or ABT-199. It is now in phase
three studies. ACP-196 is a second generation BTK inhibitor that has been
designed to kind of eliminate out those off target side effects that are seen with ibrutinib. It is now in a phase III study, and the first data about that will be coming out at ASH this year. CAR T-cell therapies are a very cool treatment that has been helping a lot of patients with ALL. This is where we basically take people’s T-cells out, design them to attack their own leukemia cells and then put them back in. It has shown a lot of promise in CLL as well. It is still in phase one and phase two studies and it is dangerous up front. You know it only works about half the time in CLL patients, but the patients who it doesn’t work in are not getting graft versus host disease, which is the major complication. You know these are just a few of many others. It’s a very exciting time to be a patient with CLL because there are many novel therapies. Like I said, some of these patients would be dead from their CLL if these new drugs weren’t available. You know there’s more to come. We’re extending the survival of this disease.

I just wanted to highlight a few key takeaways to kind of sum up our lecture. I want you to know how to diagnose and figure out the prognosis of CLL patients. I think that IGBH, FISH, and karyotype are really important for a patient’s daily life and outcome, and what treatment you would recommend. Selection of therapy is based upon performance status, FISH, and what line of therapy. The novel therapeutic agents, just so that you are familiar with exclusion criteria and potential adverse events, the role of the advanced practitioner, the long term follow-up patient education, and advocation. That’s it.

FEMALE MODERATOR: We’ve got a couple minutes for questions, but before we do that can we do the posttest questions, so I don’t forget? Just take a
minute here. Which of the following tests are considered valuable or informative
to determine the prognosis and treatment in a patient with CLL? I’ll give you a
minute there to take your best shot. And then the next question please? A 74-
year-old male patient with CLL is stable on therapy with ibrutinib, plans to have
his tooth extracted by his dentist two weeks from today. Would you recommend
any modification in his ibrutinib therapy? Let’s have you take your best shot here.
I think we have time for one or two questions, and then I’ll give you the
instructions for the rest of the evening and tomorrow. Do we have any questions
for Amy or for Dr. Stephens here?

**MALE ATTENDEE:** Do you use absolute lymphocyte count at all in
determining as far as an absolute number, a doubling time, anything of that sort?

**DR. DEBORAH STEPHENS:** Yes. He was asking if we ever use absolute
lymphocyte count in determination of treatment, and the answer is somewhat. It
used to be part of the NCCN Guidelines to use the lymphocyte doubling count of
less than six months as an indication to start therapy. I would say that has
actually been taken out of the guidelines because patients were being treated a
little bit too early with that recommendation; however, I would say that the patient
whose count is doubling that quickly, usually has something else going on like
thrombocytopenia, anemia, symptomatic splenomegaly. You really kind of have
to just look at where the patient is, what their risk factors are, and how they are
heading I wouldn’t use absolute lymphocyte count as a discrete number to start
treatment. You know I would say patients who are up around 300,000 most likely
are going to need therapy, but there are still some of those patients that I just continue to watch if they are doing well.

**FEMALE ATTENDEE:** Other questions? Do you have any other questions?

**MALE ATTENDEE:** So this gal, she originally did have the 17p deletion, right?

**DR. DEBORAH STEPHENS:** Correct.

**MALE ATTENDEE:** How often you check for new mutations based on clinical gain here?

**DR. DEBORAH STEPHENS:** I check every time that I’m going to do a new therapy. If she has some other reasons for getting treated, I would repeat that FISH panel. It’s really one of the things that’s nice about CLL. It’s easy to study because you can just get these from peripheral blood, and you don’t have to do a bone marrow or other invasive procedure to do it. Outside of her needing additional therapy, I wouldn’t check it unless there would be a reason to act upon that new genetic mutation.

**FEMALE MODERATOR:** Okay. We have a question over here. Sorry.

**MS. HEATHER LEWIN:** I have a patient case question. I’m Heather Lewin from Florida. We have a lot of elderly patients. We have a 90-year-old patient with CLL. We gave her single agent Rituxan. She tolerated it okay, but had a lot of fatigue with that, and now her white count’s starting to rise, hemoglobin is like around 10, and she’s getting somewhat symptomatic from it. What would you choose for second line therapy?
DR. DEBORAH STEPHENS: Any of the ones that I had listed. Ibrutinib, idelalisib and rituximab would be great for somebody like her who is elderly. People actually tolerate these medications very well.

[END]