Welcome & Introductions

Chronic Lymphocytic Leukemia (CLL): What Are My Treatment Options?

Welcome to LLS Community
We are a community of blood cancer patients, survivors and caregivers. We’re here to support you, give you trusted information and resources, and help you feel connected. No one should have to face a blood cancer diagnosis alone.

To join LLS Community, visit www.LLS.org/community.

Program will begin shortly

Chronic Lymphocytic Leukemia (CLL): What Are My Treatment Options?

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Chronic Lymphocytic Leukemia (CLL): What Are My Treatment Options?

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Creating a Cancer-free World. One Person, One Discovery at a Time.

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Current Treatment of CLL

Jennifer Woyach, MD
Objectives

- Briefly discuss natural history of CLL
- Discuss useful prognostic markers in CLL
- Discuss criteria for the initiation of therapy
- Discuss specific therapies for CLL
- Discuss what may be coming next

Chronic Lymphocytic Leukemia Background and Natural History

- Most prevalent leukemia (~ 15,000 cases per year)
- Disease of older patients, median age at diagnosis 72 years
- 3:2 male-to-female ratio; Caucasian > African American >>> Asian
- ~ 4,500 deaths per year
- Absolute survival has increased during past 2 decades

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<td>5-Year</td>
<td>54.2%</td>
<td>60.2%</td>
<td>&lt;.0001</td>
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<tr>
<td>10-Year</td>
<td>27.8%</td>
<td>34.8%</td>
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CLL Prognostic Factors

- Heterogeneous disease with survival ranging from months to 25+ years from diagnosis
- Prognostic factors commonly used
  - Stage
  - Lymphocyte doubling time
  - Beta 2 microglobulin
  - IGHV mutational status
  - FISH/Stimulated karyotype
  - TP53 mutation

Rai Staging

<table>
<thead>
<tr>
<th>Rai Stage</th>
<th>Finding</th>
<th>Modified Rai Classification</th>
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<tbody>
<tr>
<td>0</td>
<td>Lymphocytosis</td>
<td>Low Risk</td>
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<tr>
<td>I</td>
<td>Lymphadenopathy</td>
<td>Intermediate Risk</td>
</tr>
<tr>
<td>II</td>
<td>Splenomegaly and/or Hepatomegaly</td>
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<tr>
<td>III</td>
<td>Anemia (&lt;11 g/dL)</td>
<td>High Risk</td>
</tr>
<tr>
<td>IV</td>
<td>Thrombocytopenia (&lt;100 k/uL)</td>
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Category is assigned based on highest risk finding
**IGHV Mutational Status**

- Indicates the divergence of the immunoglobulin heavy chain variable region from the germline sequence.
- Higher levels indicate greater amounts of normal somatic hypermutation, and suggest a more mature precursor cell.
- Currently the strongest predictor of prognosis


**Cytogenetics & Fluorescence In Situ Hybridization**

- Metaphase spread
- A. Normal
- B. Trisomy
- C. Deletion
- D. Translocation

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Implications of FISH/Cytogenetics on Prognosis

- Del(13q), the most common abnormality, indicates indolent disease when detected as the sole abnormality (>50% of pts)
- Trisomy 12 indicates intermediate prognosis (~30% of pts)
- Del(11q) results in loss of the tumor suppressor ATM and is associated with more aggressive disease (~20% of pts)
- Del(17p) results in loss of the tumor suppressor TP53 and is associated with more aggressive disease (~10% of pts)
- Complex karyotype (≥ 3 abnormalities) is associated with more aggressive disease

TP53 Mutation

- Mutations are common in CLL, but most mutations are shared infrequently (2-5% of patients)
- TP53 mutations are seen in about 10-15% of patients at diagnosis.
- 80% of the time, mutations co-exist with del(17p)
Can Prognosis Change Over Time?

- IGHV mutational status does not change
- Cytogenetic abnormalities and gene mutations can, a process called clonal evolution
  - TP53 abnormalities seen in 10% at baseline, but ~40% later

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<tr>
<th>Category</th>
<th>Reasons for Treatment</th>
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<td>CLL-related symptoms</td>
<td>• Significant B symptoms (eg, night sweats, weight loss, fever without infection, severe fatigue)</td>
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| Tumor burden          | • Progressive lymphadenopathy<br>• Progressive splenomegaly<br>  
  Lymphocyte doubling time <6 months (if ALC >30 x 10⁹/L)<br>• Threatened end-organ function (eg, enlarged lymph node obstructing biliary tree) |
| Bone marrow failure   | • Progressive anemia (Hgb <11 mg/dL)<br>• Progressive thrombocytopenia (platelets <100K) |
| Immune dysfunction    | • Autoimmune anemia and/or thrombocytopenia poorly responsive to corticosteroids or other standard therapy |
Why Don’t We Treat at Diagnosis?

- Multiple clinical trials have investigated this question—none yet have shown a survival advantage to early treatment.
- This remains a question of interest, especially with advances in prognosis (so high risk patients can be targeted) and with newer better tolerated therapies.

Natural history of CLL has been changed by targeted therapy

- Therapies used in the front line setting
  - Ibrutinib
  - Ibrutinib/rituximab
  - Ibrutinib/obinutuzumab
  - Acalabrutinib
  - Venetoclax/obinutuzumab
  - FCR
  - Other CIT (BR, Chlorambucil/obinutuzumab)
Mechanism of BTK Inhibitors

- Ibrutinib or Acalabrutinib

Mechanism of BCL2 Inhibitors

- Venetoclax + Obinutuzumab
How do we choose therapy?
First consideration:

**Targeted therapy** vs **Chemotherapy**

**ECOG 1912**

**Arm A** - Ibrutinib + Rituximab
- Cycle 1:
  - Ibrutinib 420 mg PO daily, days 1-28
  - Rituximab 50 mg/m² IV, day 1
  - Rituximab 325 mg/m² IV, day 2
  - Cycles 3-7:
    - Ibrutinib 420 mg PO daily, days 1-28
    - Rituximab 500 mg/m² IV, day 1

**Arm B** - FCR
- Cycles 1-6:
  - Fludarabine 25 mg/m² IV, days 1-3
  - Cyclophosphamide 250 mg/m² IV, days 1-3
  - Cycle 1:
    - Rituximab 50 mg/m² IV, day 1
    - Rituximab 325 mg/m² IV, day 2
  - Cycles 2-6:
    - Rituximab 500 mg/m² IV, day 1

**Key Points**
- No del(17p)
- Median age 58
- 71% IGHV unmutated

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

Planned Accrual: 519

**E1912 Progression Free Survival and Overall Survival**

**PFS**

- HR = 0.39 (95% CI: 0.26 – 0.57)  
  - FCR: 3-year rate: 89%, 71%
  - IR: 58 events/354 cases

**OS**

- HR = 0.34 (95% CI: 0.15 – 0.79)  
  - FCR: 3-year rate: 99%, 93%
  - IR: 11 events/354 cases

3 yr PFS 89% vs 71%  
3 yr OS 99% vs 93%


**E1912 PFS Based upon IGHV Mutational Status**

**IGHV Mutated**

- HR = 0.42 (95% CI: 0.16 – 1.16)  
  - FCR: 8 events/44 cases  
  - IR: 10 events/70 cases

**IGHV Unmutated**

- HR = 0.28 (95% CI: 0.17 – 0.48)  
  - FCR: 29 events/71 cases  
  - IR: 36 events/218 cases

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**Key Points**
- Median age 71
- 6% del(17p), 10% TP53 mutated
- 61% IGHV unmutated

**Stratification**
- High risk vs intermediate risk Rai Stage
- Presence vs absence of del(11q22.3) or del(17p13.1) on FISH performed locally
- < 20% vs ≥ 20% Zap-70 methylation of CpG 3 performed centrally

**Planed accrual**: 498

IGVH mutated & Zap-70 methylated Subgroups

PFS


ELEVATE TN (ACE-CL-007)

Treatment-naive CLL (N=535)
Age ≥65 or <65 years with coexisting conditions:
• CIRS score >6, or
• creatinine clearance <70 mL/min

Stratification
• del(17p), y vs n
• ECOG PS 0-1 vs 2
• Geographic region (N America, W Europe, or other)

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ELEVATE-TN Progression-Free Survival
Median follow-up 28.3 months

Kaplan-Meier estimates performed by IRC and all analyses for the intention-to-treat population. No. of events: Acala-G, 14 (7.8%); Acala, 26 (14.5%); G-Clb, 93 (52.5%)
*Post hoc analysis.
*Richter's transformation occurred in: Acala-G n=1, Acala n=5, G-Clb n=1

Hazard ratio (95% CI)
Acala-G vs G-Clb 0.10 (0.06, 0.17) p=0.0001
Acalabrutinib vs G-Clb 0.20 (0.13, 0.30) p<0.0001
Acala-G vs acalabrutinib 0.49 (0.26, 0.95)

CLL14

Key Points
- Median age 72
- 7-9% del(17p), 8-11% TP53 mutated
- 60% IGHV unmutated
What do these trials tell us?

- BTKi +/- anti-CD20 antibody is more effective than chemoimmunotherapy in the treatment of CLL
  - For the subset of IGHV mutated, this may not be true, especially with FCR
- Anti-CD20 antibodies may be better combined with acalabrutinib than ibrutinib
- Venetoclax + obinutuzumab is more effective than chlorambucil + obinutuzumab
- At 2 years, PFS for VO is similar to what is reported for ibrutinib
- Long term results will be critical to determine which regimen is more effective
Second Consideration: How to Choose Between Targeted Therapies?

**Ibrutinib VS Acalabrutinib VS Venetoclax**

**Efficacy Considerations**

- At 2 years, ibrutinib, acalabrutinib, and venetoclax/obinutuzumab appear relatively equivalent
  - There might be a difference in TP53 altered patients
  - IGHV?
- There is much more long-term data with ibrutinib than either venetoclax or acalabrutinib
- Acalabrutinib and ibrutinib are being compared head to head in relapsed CLL, and venetoclax/obin will be compared to ibrutinib, so data on these will be available...someday
Safety Considerations

- Ibrutinib toxicities: Atrial fibrillation (10-15%, more with older patients), Hypertension (7-30% significant), Bleeding (G3+ <5%), Ventricular arrhythmias (<1%, risk factors unclear)
  - There is much more long term data with ibrutinib
- Acalabrutinib toxicities: Atrial fibrillation (<5%), Bleeding (significant <5%)
- Venetoclax toxicities: Neutropenia (significant 50%), Febrile neutropenia (5%), Diarrhea (significant <5%)

Intangibles

- Fixed duration venetoclax/obin vs indefinite BTKi
- More intensive run-in venetoclax/obin vs BTKi
- Once daily ibrutinib vs twice daily acalabrutinib
- Cost

Conclusion: Choice of BTKi vs Venetoclax/obin is patient-specific and involves discussion of data and considerations of pros/cons with each therapy
What is the future of CLL frontline therapy?

- Combination vs single targeted therapy to allow BTKi discontinuation
  - Excellent data from single arm studies of IVO, IV, AVO
- Combinations of CIT and novel therapies: I-FCG, others
- New therapies or strategies

NCTN Study: EA9161

- Age <70
- No del(17p)
- Primary Endpoint: PFS
What happens if the CLL comes back?

- It depends…
  - What do we mean by relapse?
  - What are the prognostic factors?
  - What was the initial treatment?
What was the initial treatment?

- Chemotherapy?

- Venetoclax/obinutuzumab (or other time-limited targeted treatment)?

- Ibrutinib or acalabrutinib given continuously?

If initial treatment was chemotherapy...

- Lots of options!!
  - Ibrutinib
  - Acalabrutinib
  - Venetoclax/rituximab
  - Idelalisib/rituximab
  - Duvelisib
  - Repeat chemotherapy regimen (not my top choice)

But will they work?
Answer: Yes!

- Most of the data we have for outcomes comes from patients who were previously treated with chemotherapy.

- Ibrutinib: Average progression-free survival 52 months
- Acalabrutinib: At 45 months, 62% were progression-free
- Venetoclax/rituximab: At 48 months, 57% were progression-free

If initial treatment was venetoclax/obinutuzumab...

- Many options for targeted therapies
  - Ibrutinib
  - Acalabrutinib
  - Venetoclax/rituximab
  - Idelalisib/rituximab
  - Duvelisib

- Could also consider repeating initial therapy depending on remission duration

But will they work?
Answer: Probably

- No clinical trials have been performed specifically to address second-line therapy in patients previously on venetoclax/obinutuzumab
  - But, there is no reason why other therapies would not work

- Recent data from ASH 2019 shows that BTK inhibitors are effective after venetoclax. PI3K inhibitors are less so, but still have activity
- Repeating venetoclax is not clearly effective (yet)

If initial treatment was ibrutinib or acalabrutinib…

- Options remain for targeted therapies
  - Acalabrutinib
  - Venetoclax/rituximab
  - Idelalisib/rituximab
  - Duvelisib

But will they work?
**Answer is dependent on context of progression**

- If progression occurs after ibrutinib discontinued for toxicity, treatment with acalabrutinib is effective.
- If progression occurs after acalabrutinib discontinued for toxicity, other treatments (venetoclax, PI3K inhibitor) are likely effective.
- If progression occurs during treatment with ibrutinib/acalabrutinib, venetoclax has been shown to be effective. PI3K inhibitors less so.

**Exciting Treatments/Strategies Currently in Trials**

- New ways to target the B cell receptor signaling pathway
- New antibody treatments
- Harnessing the immune system to combat CLL
New ways to target the B cell receptor signaling pathway

New Antibody Targets

New Antibody Techniques:
- Bispecific antibodies
Harnessing the Immune System

CAR-T cells (or CAR-NK cells)

Thank You!
Q&A SESSION
Chronic Lymphocytic Leukemia (CLL): What Are My Treatment Options?

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

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

Due to time constraints, we can only take one question per person. Once you’ve asked your question, the operator will transfer you back into the audience line.

RESOURCES

• Information Specialists
  Master’s level oncology professionals, available to help cancer survivors navigate the best route from diagnosis through treatment, clinical trials and survivorship.
  – Email: infocenter@LLS.org
  – Toll-Free Phone: 1-800-955-4572

• Clinical Trial Support Center
  Work one-on-one with an LLS Clinical Trial Nurse Navigator who will personally assist you throughout the entire clinical-trial process. Clinical Trial Nurse Navigators are registered nurses with expertise in blood cancers.
  – Email: www.LLS.org/CTSC

• Additional Information about Leukemia:
  – www.LLS.org/leukemia
FREE LLS EDUCATION & SUPPORT RESOURCES

- **Education Booklets about CLL:**
  - [www.LLS.org/booklets](http://www.LLS.org/booklets)

- **Weekly Chronic Lymphocytic Leukemia Online Chat:**
  - [www.LLS.org/chat](http://www.LLS.org/chat)

- **Telephone/Web Programs:**
  - [www.LLS.org/programs](http://www.LLS.org/programs)

- **Additional LLS Information about Coronavirus:**
  - [www.LLS.org/coronavirus](http://www.LLS.org/coronavirus)

- **LLS Podcast,** *The Bloodline with LLS*
  - Listen in as experts and patients guide listeners in understanding diagnosis, treatment, and resources available to blood cancer patients: [www.thebloodline.org](http://www.thebloodline.org)

- **Education Videos**
  - Free education videos about survivorship, treatment, disease updates and other topics: [www.LLS.org/educationvideos](http://www.LLS.org/educationvideos)

- **Patti Robinson Kaufmann First Connection Program**
  - Peer-to-peer program that matches newly diagnosed patients and their families: [www.LLS.org/firstconnection](http://www.LLS.org/firstconnection)

- **Nutrition Consults**
  - Telephone and email consultations with a Registered Dietitian: [www.LLS.org/nutrition](http://www.LLS.org/nutrition)

- **What to Ask**
  - Questions to ask your treatment team: [www.LLS.org/whattoask](http://www.LLS.org/whattoask)

- **Other Support Resources**
  - LLS Community, discussion boards, blogs, support groups, financial assistance and more: [www.LLS.org/PatientSupport](http://www.LLS.org/PatientSupport)
THANK YOU

We have one goal: A world without blood cancers