Chronic Lymphocytic Leukemia (CLL)

Natural History

• Most common type of leukemia
  – ~10,000 cases/year

• Common in the elderly
  – Median age in the 7th decade of life

• Often asymptomatic

• Median survival
  – Low risk (Rai 0): >10 years
  – Intermediate risk (Rai I/II): 5-7 years
  – High risk (Rai III/IV): 1-3 years


CLL impacts survival for all age groups <75
# Chronic Lymphocytic Leukemia Statistics

## At a Glance

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated New Cases in 2020</td>
<td>21,040</td>
</tr>
<tr>
<td>% of All New Cancer Cases</td>
<td>1.2%</td>
</tr>
<tr>
<td>Estimated Deaths in 2020</td>
<td>4,060</td>
</tr>
<tr>
<td>% of All Cancer Deaths</td>
<td>0.7%</td>
</tr>
</tbody>
</table>

## 5-Year Relative Survival

- **86.1%**
- **2010–2016**

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Chronic Lymphocytic Leukemia

How is CLL diagnosed?
Blood Smear in CLL

Blood counts
Blood Smear
Flowcytometry
What is my prognosis?
### Chronic Lymphocytic Leukemia

**Prognostic Factors**

<table>
<thead>
<tr>
<th>Prognostic Feature</th>
<th>Associated With Poor Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD38 expression on CLL cells</td>
<td>High CD38 expression (30%)</td>
</tr>
<tr>
<td>Zap-70 expression on CLL cells</td>
<td>High Zap-70 expression (20%)</td>
</tr>
<tr>
<td>IGHV mutation status Unmutated CLL</td>
<td></td>
</tr>
<tr>
<td>Serum β2 macroglobulin</td>
<td>Elevated (3.5 mg/L)</td>
</tr>
<tr>
<td>FISH cytogenetics</td>
<td>del(17p), del(11q)</td>
</tr>
<tr>
<td>Gene mutations</td>
<td>TP53, NOTCH1, BIRC3, SF3B1, or ATM</td>
</tr>
</tbody>
</table>

**Chromosome Study**

- FISH
- PCR
- Mutation Analysis
- NGS
• Deletions on the long arm of chromosome 13 is most commonly observed (55% of all cases)
  – Isolated del(13q14) is associated with a benign disease course

• 17p deletion and/or TP53 mutation is an adverse prognostic feature, predicting for inferior responses and survival in CLL
  – Lower responses to chemoimmunotherapy

• Important to obtain at diagnosis and should be repeated before subsequent therapies as additional genetic abnormalities may be acquired
Chronic Lymphocytic Leukemia

What are the indications for starting treatment?
NCI-WG Indications to Treat

- Constitutional symptoms referable to CLL
- Progressive marrow failure
- Autoimmune anemia +/- thrombocytopenia poorly responsive to corticosteroids
- Massive or progressive splenomegaly
- Massive or progressive lymphadenopathy
- Progressive lymphocytosis

Observation is appropriate in the absence of indication for therapy
First-Line Treatment

- Chemotherapy
- Monoclonal Antibodies
- Combinations:
  - FCR, BR
- Ibrutinib (Imbruvica)
- Acalabrutinib (Calquence)
- Venetoclax (Venclexta)
- Clinical Trials
Timeline of New Agents for CLL

TN, treatment naïve; R/R, relapsed/refractory; FC, fludarabine and cyclophosphamide (FC)

Not yet approved for CLL

- Ibrutinib
  - TN: Monotherapy; w/Obinutuzumab
  - R/R: Monotherapy

- Obinutuzumab
  - TN: w/Ibrutinib; w/Chlorambucil

- Idelalisib
  - R/R: w/Rituximab

- Venetoclax
  - R/R: Monotherapy & w/Rituximab

- Ofatumumab
  - TN: w/Chlorambucil
  - R/R: Monotherapy; w/FC

- Duvelisib
  - R/R

- Acalabrutinib
  - TN: Monotherapy; w/Obinutuzumab
  - R/R: Monotherapy

- CAR T-cells

Targeted Treatment Options for CLL

Agents listed in bold are FDA approved

- Obinutuzumab
- Ofatumumab
- Rituximab
- Ublituximab
- Copanlisib
- Duvelisib
- Idelalisib
- Umbralisib
- Venetoclax
- Acalabrutinib
- ARQ 531
- Ibrutinib
- LOXO-305
- Tirabrutinib
- Vecabrutinib
- Zanubrutinib

Figure adapted from Crisci, et al. Front. Oncol. 2019. doi.org/10.3389/fonc.2019.00443
BTK Inhibitors

Mechanism of Action

• Selective tyrosine kinase inhibitors (TKIs)
• Acalabrutinib, Ibrutinib, Zanubrutinib: Forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity
• Vecabrutinib, LOXO-305, ARQ 531: Noncovalent binding to BTK
• Blocks B-cell receptor signaling and survival, proliferation, and migration of cancerous B cells

Figure from Bond DA et al. Clin Advances Hematol Oncol 2019
## Summary of FDA-Approved BTK Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Ibrutinib</th>
<th>Acalabrutinib</th>
<th>Zanubrutinib</th>
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</thead>
<tbody>
<tr>
<td><strong>FDA-approved indications</strong></td>
<td>• CLL (monotherapy or w/ obinutuzumab or rituximab)</td>
<td>• CLL/SLL (monotherapy or with obinutuzumab)</td>
<td>• R/R MCL</td>
</tr>
<tr>
<td></td>
<td>• R/R MCL</td>
<td>• R/R MCL (monotherapy)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• WM</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• MZL (after ≥ 1anti-CD20-based therapy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• cGVHD</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Method of administration</strong></td>
<td>• CLL/SLL, WM, and cGVHD: 420 mg taken orally once daily</td>
<td>100 mg every 12 hours orally</td>
<td>Once daily (320 mg) or twice daily (160 mg) orally</td>
</tr>
<tr>
<td></td>
<td>• MCL and MZL: 560 mg taken orally once daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Key toxicities</strong></td>
<td>• Bleeding, atrial fibrillation, diarrhea, fatigue, and increased risk for infection</td>
<td>• Headaches, diarrhea, fatigue, infection, anemia</td>
<td>• Diarrhea, infection, fatigue, anemia</td>
</tr>
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8-Year Follow-up of Ibrutinib Monotherapy: High Rates of OS, ORR and Long-term Tolerability in CLL


<table>
<thead>
<tr>
<th></th>
<th>Median, mos (95%CI)</th>
<th>7-year PFS/OS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line (n=31)</strong></td>
<td>NR (NE-NE)</td>
<td>83%</td>
</tr>
<tr>
<td><strong>First-line (n=31)</strong></td>
<td>NR (NE-NE)</td>
<td>84%</td>
</tr>
</tbody>
</table>
Efficacy

- Ibrutinib benefit was also consistent in patients with high prognostic risk (TP53 mutation, 11q deletion, and/or unmutated IGHV)

Safety

- Discontinuation due to AEs decreased over time, with 58% of ibrutinib pts continuing daily treatment

<table>
<thead>
<tr>
<th></th>
<th>Median PFS, mo</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibrutinib</td>
<td>NE</td>
<td>0.146 (0.098-0.218)</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>15.0</td>
<td></td>
</tr>
</tbody>
</table>
Three major studies in the past year that have influenced the first-line therapy of CLL in 2020
Obinutuzumab + Ibrutinib or Chlorambucil in Treatment-Naive CLL/SLL (Phase 3 iLLUMINATE)

First non-chemotherapy combination approved by FDA - January 2019

<table>
<thead>
<tr>
<th></th>
<th>Obinutuzumab + Ibrutinib</th>
<th>Obinutuzumab + Chlorambucil</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR per IRC (per investigator)</td>
<td>88% (91%)</td>
<td>73% (81%)</td>
</tr>
<tr>
<td>CR/CRi per IRC (per investigator)</td>
<td>19% (41%)</td>
<td>8% (16%)</td>
</tr>
<tr>
<td>Patients with undetectable MRD</td>
<td>35%</td>
<td>25%</td>
</tr>
<tr>
<td>OS rate at 30 months</td>
<td>86%</td>
<td>85%</td>
</tr>
</tbody>
</table>

High-risk population (del(17p)/TP53 mutation, del(11q), and/or unmutated IGHV.
IR vs FCR in Pts with Treatment-Naive CLL/SLL (Phase 3 ECOG-ACRIN E1912)

**Primary Endpoints**
PFS, change in QoL

**Treatment-Naive CLL/SLL**
N=529
- CLL (IWCLL criteria), or SLL (WHO criteria)
- Disease requiring treatment
- Age ≤70 years
- No deletion of 17p13
- ECOG PS 0-2

**Randomization**
2:1

**Ibrutinib (QD) + Rituximab (7 cycles)**

**Fludarabine + Cyclophosphamide + Rituximab (6 cycles)**

**1st Interim Analysis**

**PFS (All Randomized)**
HR=0.352; 95% CI, 0.223-0.558; \( P < 0.0001 \)
IR (37 events/354 cases)
FCR (40 events/175 cases)

**OS (All Randomized)**
HR=0.168; 95% CI, 0.053-0.538; \( P =0.0003 \)
IR (4 deaths/354 cases)
FCR (10 deaths/175 cases)

**Median follow-up 33.4 months**

**PFS**
- IR was superior to FCR independent of age, sex, PS, stage or del11q23 presence/absence
- IR was superior to FCR for IGHV unmutated, but not mutated patients

**Ibrutinib + Rituximab leads to better disease control & survival compared to FCR**
BR vs IR vs Ibrutinib Alone in Older Patients with Treatment-Naive CLL (Phase 3 ALLIANCE A041202)

**Primary Endpoint**

PFS

**Randomization**

- Ibrutinib (QD)
- Bendamustine + Rituximab (6 cycles)

**Treatment-Naive CLL**

N=523

- CLL (IWCLL criteria)
- CLL requiring treatment (IWCLL criteria)
- Intermediate- or high-risk Rai stage

**1st Interim Analysis**

- No significant OS differences among arms
- Median OS not reached for any arm
- 2-year OS estimates
  - Arm 1 (BR) 95%
  - Arm 2 (I) 90%
  - Arm 3 (IR) 94%

**Bendamustine + Rituximab (6 cycles)**

**Ibrutinib (QD)**

**Patients-at-Risk**

<table>
<thead>
<tr>
<th>Arm</th>
<th>BR</th>
<th>I</th>
<th>IR</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>176</td>
<td>178</td>
<td>170</td>
</tr>
</tbody>
</table>

**% Alive and Progression-Free**

- Arm C (IR)
  - 140/170 = 82.4%
  - 129/178 = 72.8%
  - 134/176 = 76.5%

- Arm B (I)
  - 159/176 = 89.9%
  - 152/165 = 92.6%
  - 147/154 = 95.9%

- Arm A (BR)
  - 145/178 = 81.8%
  - 136/165 = 83.1%
  - 129/154 = 84.2%


**Ibrutinib +/- Rituximab leads to better disease control compared to Bendamustine + Rituximab**
Treatment for Relapsed CLL

- Chemotherapy
- Monoclonal Antibodies
  - Ofatumumab (Arzerra)
  - Alemtuzumab (Campath)
- Ibrutinib (Imbruvica)
- Acalabrutinib (Calquence)
- Venetoclax (Venclexta)
- Clinical Trials
- Stem Cell Transplantation
Ibrutinib is Superior to Ofatumumab in R/R CLL (Phase 3 RESONATE Final Results)

CLL/SLL diagnosis
N=391
- ≥ 1 prior therapy
- ECOG PS 0-1
- Measurable nodal disease by CT

Crossover upon PD (n = 122)

Ibrutinib QD

Ofatumumab (300 mg followed by 2000 mg x 11 doses for 24 wks)

PFS

Ibrutinib: mPFS 44.1 mos
HR: 0.148 (0.113-0.196)

Ofatumumab: mPFS 8.1 mos

OS

Ibrutinib: mOS 67.7 mos
HR: 0.810 (0.602-1.091)

Ofatumumab: mOS 65.1 mos

- Median follow-up 65.3 months
- Long-term treatment with ibrutinib is tolerable and continues to show sustained PFS and OS regardless of high-risk cytogenetics
Acalabrutinib Monotherapy Significantly Improves PFS in R/R CLL (Phase 3 ASCEND)

**Adult patients with R/R CLL**

N = 310

- ≥ 1 prior systemic therapies (no prior exposure to a BCL-2 inhibitor or BCR-signaling inhibitor)
- ECOG PS 0-2
- Stratified by Del(17p), ECOG PS 0-1 vs 2, 1-3 vs ≥ 4 prior tx

**Randomization**

- Acalabrutinib
- Idelalisib + Rituximab or Bendamustine + Rituximab

**Primary endpoint:** IRC-assessed PFS

**Acalabrutinib vs IdR/BR**

- Median follow-up of 16.1 months
- Estimated 12-month PFS was 88% (95% CI, 81% to 92%) for acalabrutinib vs 68% (95% CI, 59% to 75%) for investigator’s choice
Acalabrutinib vs Ibrutinib in R/R High-risk CLL (Phase 3 ELEVATE-CLL R/R)

R/R High-risk CLL
N=533

- ≥ 1 prior therapies for CLL
- ECOG of 0-2
- Active disease meeting ≥1 of the IWCLL 2008 criteria for requiring treatment
- Must have ≥ 1 of the following high-risk prognostic factors:
  - Presence of 17p del by central laboratory
  - Presence of 11q del by central laboratory
  - No prior exposure to ibrutinib or to a BCR inhibitor or a BCL-2 inhibitor

Primary Endpoint
PFS

Randomization

Acalabrutinib

Ibrutinib
Zanubrutinib (BGB-3111) vs Ibrutinib in R/R CLL (Phase III ALPINE)

N = 400

- R/R to ≥ 1 prior therapies for CLL
- Active disease meeting ≥1 of the IWCLL 2008 criteria for requiring treatment
- No prior BTX tx
- Stratified by age (< 65 vs ≥ 65 years), refractory status (yes vs no), geographic region, and del(17p)/TP53 mutation status (present vs absent)

Primary Endpoint
ORR

Zanubrutinib

Ibrutinib

Summary of BTK Inhibitors for R/R CLL

- Ibrutinib and Acalabrutinib monotherapies are FDA approved therapies for R/R CLL

**Ibrutinib**

<table>
<thead>
<tr>
<th></th>
<th>Median PFS, mos (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibrutinib</td>
<td>44.1 (38.5-58.2)</td>
<td>0.148 (0.113-0.196)</td>
</tr>
<tr>
<td>Ofatumumab</td>
<td>5.1 (7.8-8.3)</td>
<td></td>
</tr>
</tbody>
</table>

**Acalabrutinib**

<table>
<thead>
<tr>
<th></th>
<th>Median PFS, mos (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acalabrutinib</td>
<td>NR</td>
<td>0.27 (0.18-0.40), p &lt; .0001</td>
</tr>
<tr>
<td>IdR/BR</td>
<td>16.8</td>
<td></td>
</tr>
</tbody>
</table>

Targeted Treatment Options for CLL

Agents listed in bold are FDA approved

Obinutuzumab
Ofatumumab
Rituximab
Ublituximab

Copanlisib
Duvelisib
Idelalisib
Umbralisib

Acalabrutinib
ARQ 531
Ibrutinib
LOXO-305
Tirabrutinib
Vecabrutinib
Zanubrutinib

Venetoclax

Figure adapted from Crisci, et al. Front. Oncol. 2019. doi.org/10.3389/fonc.2019.00443
Venetoclax in CLL: Response

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>CR, %</th>
<th>ORR, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>116</td>
<td>20</td>
<td>79</td>
</tr>
<tr>
<td>Del(17p)</td>
<td>31</td>
<td>16</td>
<td>71</td>
</tr>
<tr>
<td>No del(17p)</td>
<td>60</td>
<td>18</td>
<td>80</td>
</tr>
</tbody>
</table>
Venetoclax+Rituximab is an Effective Treatment Option for R/R CLL (Phase 3 MURANO)

Adult patients with R/R CLL (N = 389)
- CLL (IWCLL diagnostic criteria)
- Previously tx w/1-3 lines of therapy, including ≥1 standard chemotherapy-containing regimen

Venetoclax (5-week ramp-up + 6 cycles) + Rituximab (6 cycles)

Primary Endpoints
- PFS, PD rate

Venetoclax + Rituxan leads to better disease control compared to BR

<table>
<thead>
<tr>
<th></th>
<th>Venetoclax + Rituxan (VEN + R)</th>
<th>Bendamustine + Rituximab (BR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, mos</td>
<td>NR (17)</td>
<td>0.17 (0.12–0.23)</td>
</tr>
<tr>
<td>P Value</td>
<td>&lt; .0001</td>
<td>--</td>
</tr>
<tr>
<td>1-yr PFS, %</td>
<td>92.7</td>
<td>72.5</td>
</tr>
<tr>
<td>2-yr PFS, %</td>
<td>84.9</td>
<td>36.3</td>
</tr>
<tr>
<td>4-yr PFS, %</td>
<td>57.3</td>
<td>4.6</td>
</tr>
</tbody>
</table>

V + R consistently favored across subgroups including del(17p) status, TP53 status, baseline IGHV status, & number of prior treatments

Venetoclax+Obinutuzumab vs Chlorambucil+Obinutuzumab in Treatment-naïve Patients with CLL and Comorbidities (Phase III CLL14)

- Venetoclax/obinutuzumab produced significantly longer PFS than chlorambucil/obinutuzumab (HR 0.35, \( P < .001 \))
  - 2-yr PFS rate: 88% vs 64%
- PFS benefits observed regardless of IGHV or TP53 status
- Venetoclax/obinutuzumab induced rapid and durable MRD negativity
- The safety profile of venetoclax/obinutuzumab was manageable
  - No significant difference in grade 3/4 neutropenia, infections, or all-cause mortality

On May 15, 2019, the FDA approved Venetoclax + Obinutuzumab for adult patients with CLL or SLL
Take Home Points: CLL 2020

• Significant improvements in the management of CLL in the past decade
• Importance of personalized therapy based on patient & disease characteristics
• Non-chemotherapy options for first-line & subsequent therapies
• Encourage participation in Clinical Trials