Updates in the Management of Chronic Lymphocytic Leukemia

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Disclosures

I have nothing to disclose.
Objectives

Describe the clinical presentation and genetic abnormalities associated with chronic lymphocytic leukemia (CLL)

Evaluate recent clinical trials investigating the efficacy and safety of small-molecule inhibitors in treatment-naïve and relapsed/refractory CLL

Select CLL-directed therapy based on patient-specific and disease-related factors

Provide supportive care recommendations for managing adverse events with small-molecule inhibitors in CLL
Chronic Lymphocytic Leukemia (CLL)

- Most common leukemia in the US; ~21,000 new cases in 2020
- Characterized by small, mature B-lymphocytes that accumulate in the bone marrow and/or peripheral blood
  - Small Lymphocytic Lymphoma (SLL) – histologically the same disease, but accumulation is primarily in lymph nodes
- Median age of diagnosis ~72 years
- Considered incurable with conventional therapies

Clinical Presentation and Natural History

Clinical presentation and natural history can be highly variable

• Asymptomatic lymphocytosis
• Painless adenopathy
• Systemic “B-symptoms”
  • Drenching night sweats
  • Fever without infection
  • Weight loss
• Splenomegaly
• Hepatomegaly

Natural History

• Most will have asymptomatic or indolent disease course
• Subset with aggressive disease
• Possibility of Richter’s transformation

Approaching Treatment

• Observation continues to be the most appropriate course of action for patients with asymptomatic disease

• Indications for treatment
  • Significant disease-related symptoms (fatigue and “B-symptoms”)
  • Threatened end-organ function
  • Progressive bulky disease (spleen >6 cm below costal margin, LNs >10 cm)
  • Progressive bone marrow failure (anemia and/or thrombocytopenia)
  • Progressive lymphocytosis with an increase ≥50% over a 2-month period, or a lymphocyte doubling time <6 months
  • Steroid-refractory autoimmune cytopenias

Considerations for Selecting Treatment

• Patient age (<65 or ≥65)

• Comorbidities and “fitness”
  • No standard tool for determining fitness
  • Cumulative Illness Rating Score (CIRS) – often use >6 as “unfit”
  • Creatinine Clearance - often <70 mL/min as “unfit”

• Genetic abnormalities
  • Presence of del17p or TP53 mutation
  • IGHV mutant vs. unmutated disease
### Genetic Abnormalities in CLL

<table>
<thead>
<tr>
<th>Genomic Aberration</th>
<th>Prognostic Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deletion 13q14</td>
<td>Favorable</td>
</tr>
<tr>
<td>Deletion 14q32.33</td>
<td>Favorable</td>
</tr>
<tr>
<td>Immunoglobulin heavy-chain variable (IGHV) region gene mutation</td>
<td>Favorable</td>
</tr>
<tr>
<td>Deletion 6q</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Trisomy 12</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Deletion 17p13</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>Deletion 11q22 (ATM)</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>Complex karyotypes (≥3 unrelated chromosomal abnormalities)</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>Elevated Beta-2 macroglobulin</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>TP53 mutation</td>
<td>Unfavorable</td>
</tr>
</tbody>
</table>
Del17p and IGHV

• Deletion 17p (del17p) - most important prognostic factor in CLL
  • Reflects loss of tumor suppressor TP53 gene
  • Can be acquired during disease course
  • More likely to progress more rapidly and more often
  • Presence of mutation=the worst outcomes
    • Shorter-treatment free intervals
    • Poor response to chemo(immuno)therapy

• IGHV – important predictor of survival
  • Unmutated=poor prognosis compared to mutated IGHV – independent of disease stage at diagnosis

CLL Treatment Landscape

- Rituximab
- Obinutuzumab
- Ofatumumab
- Venetoclax
- Ibrutinib
- Acalabrutinib
- Idelalisib
- Duvelisib
- Chemotherapy
  - Bendamustine
  - Chlorambucil
  - Cyclophosphamide
  - Fludarabine
  - Pentostatin

### Historic First-line Treatments (circa 2018)

<table>
<thead>
<tr>
<th>&lt;65, no del17p/TP53</th>
<th>≥65, no del17p/TP53</th>
<th>Frail, no del17p/TP53</th>
<th>Del17p/TP53</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FCR</strong>*</td>
<td>Obinutuzumab + chlorambucil*</td>
<td>Obinutuzumab + chlorambucil</td>
<td>Ibrutinib</td>
</tr>
<tr>
<td><strong>FR (except del11q)</strong></td>
<td>Ibrutinib*</td>
<td>Ibrutinib</td>
<td>HDMP+ rituximab</td>
</tr>
<tr>
<td><strong>PCR</strong></td>
<td>Ofatumumab + chlorambucil</td>
<td>Ofatumumab + chlorambucil</td>
<td>Alemtuzumab +/- rituximab</td>
</tr>
<tr>
<td><strong>Bendamustine +/- rituximab</strong></td>
<td>Rituximab + chlorambucil</td>
<td>Rituximab + chlorambucil</td>
<td></td>
</tr>
<tr>
<td><strong>Ibrutinib</strong></td>
<td>Bendamustine +/- rituximab</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*=Category 1 NCCN recommendation

*Regimens are in order by preference.*

Abbreviations: FCR=fludarabine, cyclophosphamide, rituximab, FR=fludarabine, rituximab, PCR=pentostatin, cyclophosphamide, rituximab, HDMP=high-dose methylprednisolone
First-line treatment of CLL without del17p/TP53 mutation (2020)

Age, performance status, and comorbidities

<65 years without significant comorbidities

Preferred
- Ibrutinib (category 1)
- Acalabrutinib ± Obinutuzumab
- Venetoclax + Obinutuzumab

Other recommended
- Bendamustine + antiCD20 mAb
- Fludarabine, cyclophosphamide, rituximab*
- Fludarabine, rituximab
- High-Dose methylprednisolone + rituximab
- Ibrutinib + rituximab
- Pentostatin, cyclophosphamide, rituximab

Frail patients OR Patients ≥65 and younger patients with significant comorbidities

Preferred
- Ibrutinib (category 1)
- Acalabrutinib ± Obinutuzumab
- Venetoclax + Obinutuzumab

Other recommended
- Bendamustine + antiCD20 mAb^*^
- Chlorambucil + Obinutuzumab
- High-Dose methylprednisolone + rituximab
- Ibrutinib + Obinutuzumab
- Obinutuzumab
- Chlorambucil
- Rituximab

*=preferred for IGHV-mutant disease
^=not for frail patients

First-line treatment of CLL with del17p/TP53 mutation (2020)

Treatment-naive CLL
(with del17p or TP53 mutation)

Preferred
Ibrutinib
Acalabrutinib ± Obinutuzumab
Venetoclax + Obinutuzumab

Other recommended
Alemtuzumab ± rituximab
HDMP + rituximab
Obinutuzumab

Bruton’s Tyrosine Kinase (BTK) Inhibitors for Treatment-Naïve CLL
Current State of BTKi in CLL

Ibrutinib
- FDA Approval: CLL/SLL with or without del17p
  - Original CLL approval – 2014
  - First-line approval - 2016
  - Dosing: 420 mg po once daily

Acalabrutinib
- Second generation BTK inhibitor
- FDA Approval: CLL/SLL
  - Approved 11/2019
  - Dosing: 100 mg po twice daily

RESONATE-2: Ibrutinib vs. Chlorambucil

- International, open-label, randomized, phase III trial
- Patients ≥65 years, treatment-naïve CLL (n=269)
  - Exclusion: del17p, concomitant warfarin
- Ibrutinib 420 mg/day until progression vs. chlorambucil 0.5-0.8 mg/kg on days 1 and 15 of 28-day cycle for up to 12 cycles

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Ibrutinib</th>
<th>Chlorambucil</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>Not reached</td>
<td>15.0 months</td>
<td></td>
</tr>
<tr>
<td>5-yr PFS</td>
<td>70%</td>
<td>12%</td>
<td>0.146 (0.098-0.218)</td>
</tr>
<tr>
<td>Median OS</td>
<td>Not reached</td>
<td>Not reached</td>
<td></td>
</tr>
<tr>
<td>5-yr OS</td>
<td>83%</td>
<td>68%</td>
<td>0.450 (0.266-0.761)</td>
</tr>
<tr>
<td>ORR</td>
<td>92%</td>
<td>37%</td>
<td></td>
</tr>
</tbody>
</table>

iLLUMINATE: Obinutuzumab + Ibrutinib or Chlorambucil

- International, open-label, randomized phase III trial

**Patient Population**
- ≥65 years or <65 with comorbidities
- ECOG 0-2
- Del17p – 14%
- TP53 mutation – 13%
- Unmutated IGHV – 58%

**Stratification**
- ECOG 0-1 vs. 2
- del17p

**Obinutuzumab-Ibrutinib (n=113)**
- Ibrutinib 420 mg/day until progression
- Cycle 1: Obinutuzumab 100 mg day 1, 900 mg day 2, 1000 mg days 8, 15
- Cycle 2-6: Obinutuzumab 1000 mg day 1 every 28 days

**Obinutuzumab-Chlorambucil (n=116)**
- Chlorambucil 0.5 mg/kg days 1, 15 q 28 days x6 cycles
- Obinutuzumab dosing as above

- Primary endpoint: IRC-assessed PFS
- Secondary: PFS in high-risk population, ORR/CR, OS, safety

iLLUMINATE Results

- Median PFS: G-I vs. G-C (NR vs. 19 months)
- High-risk CLL: G-I > G-C in PFS (NR vs. 14.7 months; HR 0.15, 95% CI 0.09-0.27, p<0.001)
- 30-mo PFS: G-I (77%) vs. G-C (16%)
- Median OS not reached in either arm
- ORR: 88% G-I vs. 73% G-C
  - CR: 19% G-I vs. 8% G-C
- Did ibrutinib need obinutuzumab?

Alliance (A041202): Ibrutinib ± R vs. BR

- International, open-label, randomized phase III trial

**Patient Population**
- ≥65 years or <65 with comorbidities
- ECOG 0-2
- Del17p - 6%
- Del13q - 36%
- TP53 mutation - 10%
- Unmutated IGHV - 61%

**Stratification**
- ECOG 0-1 vs. 2
- Del17p

**Treatment Regimens**

**Ibrutinib-Rituximab (n=182)**
- Ibrutinib 420 mg/day until progression
- Cycle 2: Rituximab 375 mg/m\(^2\) weekly x4
- Cycles 3-6: Rituximab 375 mg/m\(^2\) day 1 q28

**Ibrutinib (n=182)**
- Ibrutinib 420 mg/day until progression

**Bendamustine-Rituximab (n=183)**
- Bendamustine 90 mg/m\(^2\) days 1, 2 q28 x6
- Cycle 1: Rituximab 375 mg/m\(^2\) day 1
- Cycles 2-6: Rituximab 500 mg/m\(^2\) day 1

- Primary endpoint: PFS
- Secondary: OS, ORR/CR, safety

A041202 Results

<table>
<thead>
<tr>
<th></th>
<th>R-Ibr</th>
<th>lb</th>
<th>BR</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-yr PFS</td>
<td>87%</td>
<td>88%</td>
<td>75%</td>
</tr>
<tr>
<td>2-yr OS</td>
<td>94%</td>
<td>90%</td>
<td>95%</td>
</tr>
<tr>
<td>ORR</td>
<td>94%</td>
<td>95%</td>
<td>81%</td>
</tr>
<tr>
<td>CR</td>
<td>12%</td>
<td>7%</td>
<td>26%</td>
</tr>
</tbody>
</table>

- No difference OS between groups, but low event rate, and f/u may be too early
- No significant difference in outcomes between Ibrutinib ± R groups
E1912: R-Ibrutinib vs. FCR

- Multicenter, open-label, randomized phase III trial

**Patient Population**
- ≤70 years
- ECOG 0-2
- CrCl >40 mL/min
- Ability to tolerate FCR
- Del13q – 34%
- Unmutated IGHV – 71%

**Exclusion:** del17p, warfarin

**Stratification**
- Age: <60 vs. 60-70
- ECOG 0-1 vs. 2+
- Rai 0-II vs. III/IV
- Del11q

**R-Ibrutinib (n=354)**
- Cycle 1 until progression: Ibrutinib 420 mg/day
  - days 1-28
- Cycle 2: Rituximab 50 mg/m\(^2\) IV day 1, 325 mg/m\(^2\) IV day 2
- Cycles 3-7: Rituximab 500 mg/m\(^2\) IV day 1

**FCR (n=175)**
- Cycle 1-6: Fludarabine 25 mg/m\(^2\) IV and
  - Cyclophosphamide 250 mg/m\(^2\) IV days 1-3,
  - Rituximab 25 mg/m\(^2\) IV day 1, 325 mg/m\(^2\) IV day 2
- Cycles 2-6: Rituximab 500 mg/m\(^2\) IV day 1

- Primary endpoint: PFS, Secondary: OS, ORR, safety

Long-term Survival with FCR

- Based on CLL biology → not for every patient
  - Best suited for CLL with mutated IGHV and without del17p
  - About half of patients at 8 years will have not yet progressed

Risks with FCR

• FCR can be a difficult regimen to tolerate, requires careful patient selection
• Prolonged neutropenia
  • 2 months after treatment ends ~17%
  • 12 months after treatment ends ~4%
• Risk of infectious complications: grade 3+ ~20%
• Risk of AML/MDS – 1.5% per CLL8 trial, ~5% per long-term phase II data

FCR Finally Considering Retirement?

- 3-yr PFS: R-ibrutinib > FCR
- 3-yr OS: R-ibrutinib > FCR (98.8% vs. 91.5%; HR 0.17, 95% CI 0.05-0.54, p<0.001)
- 45-month follow-up at ASH 2019
  - Sustained PFS and OS benefit
- ORR: R-ibrutinib (96%) > FCR (81%)
  - CR: FCR (30%) > R-I (17%)
- Similar rate of G3+ ADRs R-I (80.1%) vs. FCR (79.7%)
  - G3+ infections with FCR (20.3%) > R-ibrutinib (10.5%)

Maybe not yet...

- No significant PFS difference in mutant IGHV subgroup analysis

FCR Considerations
- Long-term data available
- Potential to “cure” CLL?
- Time-limited therapy
- Very aggressive treatment for perhaps the most indolent CLL disease biology
- Risk of AML/MDS
- Increased risk for serious infections
- Prolonged neutropenia

- Ibrutinib discontinuation rate 72/352 (20.5%) not related to PD
  - Due to ADR: 14%

Ibrutinib Intolerance and ADRs

• Ibrutinib real-world discontinuation rate >20%

• Currently thought that persistent inhibition of BTK is needed → hence need for continuous/indefinite treatment
  • Rapid progression in ~25% of patients with therapy discontinuation
  • Very important to manage BTK inhibitor-induced ADRs to maximize therapy

• Warnings/Precautions: Hemorrhage, Infections, Cytopenias, Cardiac Arrhythmias, Hypertension, Second Primary Malignancies, TLS, Embryo-fetal toxicity
  • Many ADRs are off-target effects (EGFR, TEC, etc)
Bleeding/Hemorrhage

• All-grade bleeding ~40% of patients (often low-grade ecchymoses)
  • Major bleeding in up to 4% of patients

• Mechanism: both on-target and off-target (TEC kinase) inhibition of platelet aggregation via glycoprotein VI

• Anticoagulation and antiplatelets, medications affecting platelet aggregation → increased risk of bleeding with ibrutinib
  • Avoid warfarin; DOACs and LMWH preferred, but with good monitoring
  • Avoid dual antiplatelets; use lowest doses of aspirin (81 mg) if possible

• Hold ibrutinib at least 3-7 days pre-/post-surgery

Atrial Fibrillation

- Incidence is variable between studies
  - Alliance ~17%, E1912 - ~7%
  - Median time to onset ~3 months, prevalence highest first few months of tx
- Risk factors: ≥65 years, history of hypertension, history of Afib
- Off-target effect - inhibition of cardiac phosphoinositide 3-kinase
- If develops:
  - Consult cardiology; consider rate/rhythm control
  - CHA₂DS₂-VASc: 0-1 requires no AC; >2: consider different CLL therapy?
    - Potential for risk of bleeding > risk of thrombosis?

Hypertension

- All-grade ~20%, high-grade ~8%
- Median time to onset ~ 6 months, incidence remains stable over time
- Retrospective chart review (n=562) found new/worsening HTN in 78% of patients receiving ibrutinib; 18% high-grade HTN (>160/100 mmHg) among those without precedent HTN
  - Risk factors: CLL, baseline SBP, CYP3A4 inhibitor
  - New/worsening HTN associated with risk of major adverse cardiovascular events (arrythmia, MI, CVA, heart failure)
- Monitor blood pressure during therapy; if HTN develops, manage medically

Infectious Complications

• Risk of infections with ibrutinib appears to be highest in first 3 months, and then prevalence decreases over time

• Postulated mechanisms: off-target inhibition of interleukin-2-inducible T-cell kinase $\rightarrow$ impaired immune function

• Reports of increased risk for *Aspergillus fumigatus* and *Pneumocystis jirovecii*
  - No current recommendations for routine prophylaxis

• Consider holding ibrutinib in setting of severe infection
Other Adverse Events

• Arthralgias
  • Likely off-target effect
  • Usually abate >6 months of therapy
  • APAP prn or short pulse prednisone
    • Avoid NSAIDs d/t bleeding risk

• Diarrhea
  • Any grade ~50%, Grade 3+ <5%
  • Early ADR, usually self-limiting
  • Likely off-target EGFR inhibition
  • Loperamide prn if no infection

• Rash: likely off-target EGFR
  • Two main types
    • Non-palpable, asymptomatic petechial rash
    • Palpable, eruptive rash w/ pruritic papules, mimic leucocytoclastic vasculitis
  • Mild-moderate: topical steroids and/or antihistamines
  • Severe: systemic steroids, hold or dose ↓ ibrutinib

Acalabrutinib

• FDA-approved for CLL/SLL in November 2019 based on results of ELEVATE-TN (treatment-naïve) and ASCEND (R/R) phase III trials

• Second generation BTK inhibitor, more selective for BTK than ibrutinib, minimal off-target effects
  • Stronger selectively to BTK over off-target kinases (EGFR, TEC, I2ITCK)
  • Potential less-off target effects → less ADRs?

• Warnings/Precautions: Serious and Opportunistic Infections, Hemorrhage, Cytopenias, Second Primary Malignancies, Atrial Fibrillation and Flutter
ELEVATE-TN: Acalabrutinib ± Obinutuzumab vs. G-Chlorambucil

Patient Population
- ≥65 years or <65 with comorbidities
- ECOG 0-2
- Del17p - 9%
- TP53 mutation - 11%
- Unmutated IGHV - 63%

Stratification
- ECOG 0-1 vs. 2
- Del17p

Exclusion
- Warfarin/VKA use
- Sig. cardiac disease

Obinutuzumab-Acalabrutinib (n=179)
Acalabrutinib 100 mg/BID until progression
Cycle 2: Obinutuzumab 100 mg day 1, 900 mg day 2, 1000 mg days 8, 15
Cycles 3-7: Obinutuzumab 1000 mg day 1 q28

Acalabrutinib (n=179)
Acalabrutinib 100 mg/BID until progression

Obinutuzumab-Chlorambucil (n=177)
Chlorambucil 0.5 mg/kg days 1, 15 every 28 days x6 cycles
Obinutuzumab dosing as above but starts on Cycle 1 Day 1 – x6 cycles

- International, open-label, randomized, phase III trial
- Primary endpoint: IRC-assessed PFS
- Secondary: OS, ORR, safety

ELEVATE Results

• Median PFS improved with acalabrutinib ± G vs. G-Chl

<table>
<thead>
<tr>
<th></th>
<th>G-A</th>
<th>A</th>
<th>G-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-yr PFS</td>
<td>93%</td>
<td>87%</td>
<td>47%</td>
</tr>
<tr>
<td>2-yr OS</td>
<td>95%</td>
<td>95%</td>
<td>92%</td>
</tr>
<tr>
<td>ORR</td>
<td>94%</td>
<td>86%</td>
<td>79%</td>
</tr>
<tr>
<td>CR</td>
<td>13%</td>
<td>1%</td>
<td>5%</td>
</tr>
</tbody>
</table>

• Median follow-up ~28 months

• Median OS not reached in any group

• ELEVATE TN: post-hoc G-acala vs. acala PFS (HR 0.49 95% CI 0.26-0.95)

# Acalabrutinib Safety

• Acalabrutinib: similar ADR profile as ibrutinib, but slightly lower reported frequencies with certain events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Ibrutinib (Pooled Analysis)</th>
<th>Acalabrutinib (ELEVATE TN)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All-grade</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>22%</td>
<td>2%</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>11%</td>
<td>5%</td>
</tr>
<tr>
<td>Bleeding</td>
<td>55%</td>
<td>5%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>52%</td>
<td>5%</td>
</tr>
<tr>
<td>Headache</td>
<td>17%</td>
<td>2%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>21%</td>
<td>7%</td>
</tr>
<tr>
<td>Infection</td>
<td>83%</td>
<td>31%</td>
</tr>
<tr>
<td>Rash</td>
<td>35%</td>
<td>7%</td>
</tr>
</tbody>
</table>

Acalabrutinib Safety

• Headaches are common (all-grade ~40%)
  • Typically resolve 1-2 months of therapy
  • Can be treated prn with acetaminophen and caffeine supplements
  • Avoid NSAIDs due to bleeding risk

• Similar adverse event management as ibrutinib
  • Avoid concomitant warfarin
  • Consider holding acalabrutinib 3-7 days pre-/post-surgery

• Ibrutinib-intolerant patients initiating acalabrutinib (n=33)
  • 72% of events – ADR did not recur
  • 13% of events – ADR did recur, but at a lower grade
  • Median 19-month follow-up: 70% of patients still on acalabrutinib
BTK Inhibitors in CLL

• BTKi may control disease for very long duration
  • Need to continuously assess for ADRs to optimize QoL and prevent risk of therapy discontinuation
  • Need to understand how risk of BTKi ADRs change over time

• Drug-drug interactions
  • Ibrutinib – CYP3A substrate: reduce dose with moderate inhibitors and voriconazole/posaconazole; avoid strong inducers
  • Acalabrutinib – CYP3A substrate: 100 mg daily with moderate inhibitors; avoid strong inhibitors/inducers
    • ↑ gastric pH=↓ solubility – avoid PPIs; give 2 hours before H2RA, space out 2 hours around antacids

• Medication adherence

• Early, transient lymphocytosis: not progression, but lymphocyte redistribution
Upfront BTK plus Anti-CD20 mAb?

- Alliance showed no benefit with adding R to ibrutinib
  - Single-center R-ibrutinib vs. ibrutinib trial showed no benefit as well in R/R CLL

- ELEVATE TN: post-hoc G-acala vs. acala PFS benefit, but not powered to detect a difference

- Does it matter which mAb?
  - Obinu > Ritux per CLL11 trial

- NCCN consensus: longer PFS likely due to indefinite BTKi and not mAb in first 6 months of therapy

- If going to combine, give BTK first?
  - Lower IRR incidence with BTKi arms

<table>
<thead>
<tr>
<th>All-grade IRR in phase III trials</th>
<th>BTKi + mAb</th>
<th>Chemo + mAb</th>
</tr>
</thead>
<tbody>
<tr>
<td>iLLUMINATE</td>
<td>25%</td>
<td>58%</td>
</tr>
<tr>
<td>Alliance</td>
<td>~14%</td>
<td>~42%</td>
</tr>
<tr>
<td>ELEVATE TN</td>
<td>13.5%</td>
<td>39.6%</td>
</tr>
</tbody>
</table>

NCCN. CLL/SLL. V2.2018.
Venetoclax for Treatment-naive CLL
Venetoclax

• BCL2 (B-cell lymphoma 2) antagonist
  • BCL2: antiapoptotic protein → key regulator of intrinsic apoptotic pathway, overexpressed in CLL
  • By inhibiting BCL2, venetoclax restores apoptosis process in CLL cells

• Originally FDA-approved for R/R del17p CLL (2016) as a single agent – now has broader FDA indication for CLL/SLL
  • Combining with anti-CD20 mAb can help to overcome microenvironment-induced resistance of CLL to venetoclax

• Warnings and Precautions: Tumor Lysis Syndrome, Neutropenia, Infections, Immunization (avoid live vaccines), Embryo-Fetal Toxicity
  • TLS: requires 5-week dose escalation due to rapid reduction in tumor
Ramp-Up and TLS Risk

<table>
<thead>
<tr>
<th>Tumor Burden</th>
<th>LN size/ALC</th>
<th>Prophylaxis</th>
<th>Treatment Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>All LN&lt;5 cm AND ALC&lt;25x10⁹/L</td>
<td>Oral Hydration (1.5-2 L) Allopurinol</td>
<td>Outpatient</td>
</tr>
<tr>
<td>Medium</td>
<td>Any LN 5-10 cm OR ALC≥25x10⁹/L</td>
<td>Oral hydration (1.5-2 L), consider additional IV fluids Allopurinol</td>
<td>Outpatient, consider inpatient for CrCl&lt;80 mL/min</td>
</tr>
<tr>
<td>High</td>
<td>Any LN ≥10 cm OR ALC≥25x10⁹/L AND any LN ≥5 cm</td>
<td>Oral hydration (1.5-2 L) and IV (150-200 mL/hr as tolerated) Allopurinol, may consider Rasburicase for baseline elevated uric acid</td>
<td>Inpatient for 20 mg/50 mg doses Outpatient for rest of ramp-up</td>
</tr>
</tbody>
</table>
## TLS Labs and Monitoring

<table>
<thead>
<tr>
<th>Dose</th>
<th>Low Risk</th>
<th>Medium Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg</td>
<td>Pre-initial dose, and then 6-8, 24 hours post initial dose</td>
<td>Pre-initial dose, and then 6-8, 24 hours post initial dose</td>
<td>Pre-initial dose, and then 4, 8, 12, and 24 hours post initial dose</td>
</tr>
<tr>
<td>50 mg</td>
<td>Pre-initial dose, and then 6-8, 24 hours post initial dose</td>
<td>Pre-initial dose, and then 6-8, 24 hours post initial dose</td>
<td>Pre-initial dose, and then 4, 8, 12, and 24 hours post initial dose</td>
</tr>
<tr>
<td>100 mg</td>
<td>Pre-initial dose</td>
<td>Pre-initial dose</td>
<td>Pre-initial dose, and then 6-8, 24 hours post initial dose</td>
</tr>
<tr>
<td>200 mg</td>
<td>Pre-initial dose</td>
<td>Pre-initial dose</td>
<td>Pre-initial dose, and then 6-8, 24 hours post initial dose</td>
</tr>
<tr>
<td>400 mg</td>
<td>Pre-initial dose</td>
<td>Pre-initial dose</td>
<td>Pre-initial dose, and then 6-8, 24 hours post initial dose</td>
</tr>
</tbody>
</table>

Labs include potassium, phosphorus, uric acid, calcium, creatinine.
CLL14: Obinutuzumab plus venetoclax or chlorambucil

- Multicenter, open-label, randomized phase III trial

**Patient Population**
- CIRS >6 or CrCl <70 mL/min
- Median age 72
- Del17p - 8%
- Del13q – 31%
- Unmutated IGHV – 60%

**Stratification**
- Binet stage
- Geographic region

**Obinutuzumab-venetoclax (n=216)**
- Cycle 1: Obinutuzumab 100 mg day 1, 900 mg day 2, 1000 mg days 8 and 15.
- Venetoclax ramp-up starts on day 22.
- Cycle 2-6: Obinutuzumab 1000 mg day 1 every 28 days
- Cycle 3-12: Venetoclax 400 mg daily

**Obinutuzumab-chlorambucil (n=216)**
- Cycle 1-12: Chlorambucil 0.5 mg/kg days 1, 15 every 28 days
- Obinutuzumab dosing as above.

- Primary endpoint: PFS; Secondary: OS, ORR, CR, uMRD

CLL14 Results

- 3-yr PFS: G-Ven (82%) > G-C (50%)
  - Benefit observed in del17p, TP53 mutation, and unmutated/mutated IGHV

- Median OS NR either group

- ORR: G-Ven (85%) > G-C (71%)
  - CR: G-Ven (46%) > G-C (23%)

- uMRD (<10^-4) 18 months after end of treatment: G-Ven (47%) > G-C (7.4%)

# CLL14 Safety Outcomes

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>G-Venetoclax</th>
<th>G-Chlorambucil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor Lysis Syndrome</td>
<td>1.3%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Neutropenia*</td>
<td>52.8%</td>
<td>48.1%</td>
</tr>
<tr>
<td>Febrile Neutropenia*</td>
<td>5.2%</td>
<td>3.7%</td>
</tr>
<tr>
<td>G-CSF Use</td>
<td>43.5%</td>
<td>45.8%</td>
</tr>
<tr>
<td>Thrombocytopenia*</td>
<td>13.7%</td>
<td>15%</td>
</tr>
<tr>
<td>Anemia*</td>
<td>8%</td>
<td>6.5%</td>
</tr>
<tr>
<td>Infection*</td>
<td>17.5%</td>
<td>15%</td>
</tr>
</tbody>
</table>

*Grade 3/4 toxicity

Frontline Venetoclax Considerations

• Time-limited therapy compared to indefinite BTKi

• Potential for very deep responses
  • Undetectable MRD (\(<10^{-4}\)) in peripheral blood after end of treatment is an important predictor of treatment response and independent predictor of survival

• Reasonable alternative to BTKi for patients who may not tolerate BTKi

• Lack of very long-term follow-up data
  • Ibrutinib has 5-year PFS/OS data in frontline setting
  • Only have f/u data with venetoclax for 2 years following end of treatment
Venetoclax Management

- ADR and drug interaction management different in CLL/SLL vs. AML
- Dose reduce for grade 3 neutropenia plus fever, grade 4 heme toxicity, grade 3+ non-heme toxicity
- If TLS → hold venetoclax, treat TLS, may have to reduce dose if clinical TLS or laboratory TLS >48 hours

<table>
<thead>
<tr>
<th>Drug Interactions</th>
<th>Initiation/Ramp-Up</th>
<th>Steady Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong CYP3A inhibitors</td>
<td>Contraindicated</td>
<td>Posa: venetoclax 70 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other: venetoclax 100 mg</td>
</tr>
<tr>
<td>Moderate CYP3A inhibitors and P-gp inhibitors</td>
<td>Reduce venetoclax dose by 50%</td>
<td></td>
</tr>
</tbody>
</table>
An 80-year patient presents to your clinic with a new diagnosis of CLL now requiring treatment due to progressive and symptomatic anemia. FISH is positive for del13q, del17p, trisomy 12. IGHV is mutated. Which of the following genetic abnormalities represents a poor prognosis and poor response to chemoimmunotherapy?

A. del13q
B. del17p
C. Trisomy 12
D. Mutant IGHV

www.pollev.com/sallybarbour693

text SallyBarbour693 to 22333

www.pollev.com/sallybarbour693
Which of the following genetic abnormalities represents a poor prognosis and poor response to chemoimmunotherapy?

- del13q
- del17p
- Trisomy 12
- Mutant IGHV
You are discussing treatment options with your patient. Given his high-risk cytogenetics and now having an indication for treatment, which of the following is the most appropriate regimen for him to initiate?

A. Fludarabine, cyclophosphamide, rituximab (FCR)
B. Chlorambucil
C. Ibrutinib
D. Ibrutinib, rituximab

Text SallyBarbour693 to 22333
www.pollev.com/sallybarbour693
You are discussing treatment options with your patient. Given his high-risk cytogenetics and now having an indication for treatment, which of the following is the most appropriate regimen for him to initiate?

- Fludarabine, cyclophosphamide, rituximab (FCR)
- Chlorambucil
- Ibrutinib
- Ibrutinib, rituximab
Relapsed/Refractory CLL
### R/R without del17p/TP53 mutations

<table>
<thead>
<tr>
<th></th>
<th><strong>Preferred</strong></th>
<th><strong>Other recommended</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>&lt;65 years without</strong></td>
<td>Acalabrutinib* • Ibrutinib* • Venetoclax + rituximab • Duvelisib •</td>
<td>Alemtuzumab ± rituximab • FC + ofatumumab • FCR • HDMP-rituximab • Idelalisib •</td>
<td></td>
</tr>
<tr>
<td><strong>significant comorbidities</strong></td>
<td>Idelalisib + rituximab</td>
<td>Lenalidomide ± rituximab</td>
<td></td>
</tr>
<tr>
<td><strong>Frail OR ≥65 years or</strong></td>
<td>Acalabrutinib* • Ibrutinib* • Venetoclax + rituximab • Duvelisib •</td>
<td>Alemtuzumab ± rituximab • Chlorambucil + rituximab • Reduced-dose FCR • HDMP-</td>
<td></td>
</tr>
<tr>
<td><strong>younger with comorbidities</strong></td>
<td>Idelalisib + rituximab</td>
<td>rituximab • Reduced-dose PCR • Venetoclax • Dose-dense rituximab • BR ± ibrutinib</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>or idelalisib</td>
<td></td>
</tr>
</tbody>
</table>

*=Category 1 NCCN recommendation

Abbreviations: BR=bendamustine, rituximab, FCR=fludarabine, cyclophosphamide, rituximab, FC=fludarabine, cyclophosphamide, PCR=pentostatin, cyclophosphamide, rituximab, HDMP=high-dose methylprednisolone
R/R CLL with del17p/TP53 mutation

<table>
<thead>
<tr>
<th>Preferred</th>
<th>Other recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acalabrutinib*</td>
<td>Alemtuzumab ± rituximab</td>
</tr>
<tr>
<td>Ibrutinib*</td>
<td>HDMP + rituximab</td>
</tr>
<tr>
<td>Venetoclax + rituximab*</td>
<td>Idelalisib</td>
</tr>
<tr>
<td>Duvelisib</td>
<td>Lenalidomide ± rituximab</td>
</tr>
<tr>
<td>Idelalisib + rituximab</td>
<td>Ofatumumab</td>
</tr>
<tr>
<td>Venetoclax</td>
<td></td>
</tr>
</tbody>
</table>

*=Category 1 NCCN recommendation
Abbreviations: HDMP=high-dose methylprednisolone
MURANO: Rituximab + Venetoclax or Bendamustine

Patient Population
- ≥18 years
- ECOG 0-1
- Prior 1-3 lines of therapy, including ≥1 chemo-containing regimen
- Prior bendamustine if duration of response ≥ 24 months

Stratification
- Del17p
- Responsiveness to prior line of therapy

1:1

5-week Venetoclax ramp-up

R-Venetoclax (n=194)
Venetoclax 400 mg daily x2 years starting with Cycle 1
Cycle 1: Rituximab 375 mg/m² Day 1
Cycles 2-6: Rituximab 500 mg/m² Day 1 q 28 days

R-Bendamustine (n=195)
Cycle 1-6: Bendamustine 70 mg/m² Days 1, 2
Rituximab as above. Every 28-day cycles.

- International, open-label, randomized, phase III trial
- Primary endpoint: PFS, Secondary: OS, ORR, safety
MURANO Results

- Prior therapies: ~2% BCRi, ~95% alkylator, ~80 purine analogues
- 2-year PFS: R-Ven (84.9%) > BR (36.3%)
- Benefit seen across all subgroups (including del17p)

ASCEND: Acalabrutinib in R/R CLL

**Stratification**
- Del17p (27%)
- ECOG 0-1 vs. 2
- Prior treatment: 1-3 vs. ≥4

**Acalabrutinib 100 mg BID (n=155)**

**IdR or BR (n=155)**
- Idelalisib 150 mg BID plus rituximab (n=119) OR Bendamustine 70 mg/m2 plus rituximab (n=36)

<table>
<thead>
<tr>
<th></th>
<th>Acalabrutinib</th>
<th>IdR/BR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS*</td>
<td>Not reached</td>
<td>16.5 months</td>
</tr>
<tr>
<td>12-month PFS</td>
<td>88%</td>
<td>68%</td>
</tr>
<tr>
<td>12-month OS</td>
<td>94%</td>
<td>91%</td>
</tr>
<tr>
<td>ORR</td>
<td>81%</td>
<td>75%</td>
</tr>
</tbody>
</table>

*HR 0.31, 95% CI 0.20-0.49; p<0.0001
One of the first trials to compare small-molecule inhibitors (BTKi vs. PI3Ki).
DUO: Duvelisib vs. Ofatumumab

• Duvelisib – new phosphatidylinositol 3-kinase (PI3K) inhibitor

• Phase III trial: Duvelisib 25 mg BID until PD vs. Ofatumumab
  • Median ~2 prior lines of treatment; excluded prior BTKi/PI3Ki
  • Del17p and/or *TP53* mutation ~32% of patients

• Median PFS: Duvelisib > Ofa (13.3 vs. 9.9 months; HR 0.52; p<0.0001)
  • Median OS not reached in either arm

• ORR: Duvelisib - 74% vs. Ofatumumab - 45%
  • ORR was regardless of del17p status

• Led to the FDA-approval of duvelisib for R/R CLL/SLL after at least 2 prior lines of therapy

Duvelisib

• Dual inhibitor of PI3K-δ, γ → different actions for different PI3K isoforms
  • PI3K-δ: blocks survival and proliferation of malignant B cells
  • PI3K-γ: tumor microenvironment, supports malignant B-cell maintenance

• Boxed warnings: serious infections (31%), diarrhea/colitis (18%), cutaneous reactions [SJS, TEN, DRESS] (5%), pneumonitis (5%)

• Diarrhea/colitis – median time to onset ~4 months
  • Mild-to-mod: antidiarrheals, may need to hold therapy
  • Severe/unresponsive: budesonide, hold treatment

• *Pneumocystis jirovecii* (PJP) prophylaxis; consider CMV prophylaxis
  • Continue *PJP* prophylaxis until absolute CD4+ T-cell count >200 cells/μl

• CYP3A substrate – avoid strong inducers, reduce to 15 mg BID with strong inhibitors, caution with other CYP3A substrates
A 71-year patient presents to your clinic with new-onset severe B-symptoms and splenomegaly. Up until now, his CLL has been well-controlled with ibrutinib since 2016. He has no high-risk cytogenetics on FISH; his CLL is significant for unmutated IGHV. Which of the following regimens is the most appropriate to initiate?

A. Rituximab-venetoclax  
B. Bendamustine-rituximab  
C. Full-dose fludarabine, cyclophosphamide, rituximab  
D. No change in treatment is indicated
Which of the following regimens is the most appropriate to initiate?

- Rituximab-venetoclax
- Bendamustine-rituximab
- Full-dose fludarabine, cyclophosphamide, rituximab
- No change in treatment is indicated
Your patient will be initiated R-venetoclax per the MURANO trial. His absolute lymphocyte count is $32 \times 10^9/L$ and his largest lymph node measures at 6.4 cm. His estimated creatinine clearance is 60 mL/min. What is this patient’s risk for tumor lysis syndrome and where should he initiate venetoclax?

A. Low risk – treat as outpatient
B. Medium risk – treat as outpatient
C. High risk – treat as outpatient
D. High risk – admit inpatient for 20 mg and 50 mg doses
What is this patient's risk for tumor lysis syndrome and where should he initiate venetoclax?

- Low risk – treat as outpatient
- Medium risk – treat as outpatient
- High risk – treat as outpatient
- High risk – admit inpatient for 20 mg and 50 mg doses
Pipeline

• BTKi and venetoclax combinations
  • Phase II data with ibrutinib/venetoclax x2 years – 88% CR, 61% MRD(-)
  • SEQUIOA phase III trial: zanubrutinib vs. zanu/venetoclax vs. BR (1st line)
  • GLOW phase III: ibrutinib/venetoclax vs. obinutuzumab-chlorambucil (1st line)

• Phase III: ibrutinib vs. acalabrutinib – NCT02477696 (R/R)

• Emerging BTK inhibitors to address BTKi resistance
  • Vecabrutinib, LOXO-305, ARQ 531

• Novel time-limited therapies: ublituximab, umbralisib, venetoclax combo

• CAR-T/ibrutinib combinations (phase I/II - TRANSCEND-CLL-004)
  • Preliminary data suggests ibrutinib may improve CAR-T efficacy and lower rates of cytokine release syndrome

Conclusion

• Significant advancements in the past several years have been made in the treatment of CLL

• Pharmacists can play an integral role in the care of CLL patients by assisting in the proper selection of CLL-directed therapy, preventing and managing adverse events, managing drug-drug interactions, and optimizing medication adherence

• The landscape of how we treat CLL is likely to continue to evolve and change in the next several years
Questions?

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Donald.moore1@atriumhealth.org