Chronic Lymphocytic Leukemia (CLL): Diagnosis, Treatment, and Side Effects Management

LEARNING OBJECTIVES

• Describe the various types and subtypes of chronic lymphocytic leukemia (CLL)
• Identify tests used to diagnose disease and monitor treatment of CLL
• Explain the overarching goals of treatment for the types of CLL
• Explain approved and emerging treatment options for CLL, including stem cell transplantation, and the role of clinical trials.
• Describe strategies to manage treatment side effects as well as potential long-term and late effects of treatments for CLL
• Describe the roles of the pharmacist, the nurse and the social worker in treating patients with CLL
FACULTY

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Chronic Lymphocytic Leukemia
CLL/SLL: Background

- More than 20,000 estimated new cases in 2019 in the United States alone[^1^]
  - Most common type of leukemia in adults (37%)
- Median age at diagnosis: 70 yrs[^2^]
- SLL and CLL considered the same B-cell malignancy[^3^]
  - CLL: > 5000 clonal lymphocytes in peripheral blood
  - SLL: presence of lymphadenopathy and/or splenomegaly and < 5000 clonal lymphocytes in peripheral blood
- Historical 5-yr survival: 66% (range: few mos to normal life span)[^4^]

[^3^]: American Cancer Society. Chronic lymphocytic leukemia.

CLL: Prognostic Value of FISH

<table>
<thead>
<tr>
<th>FISH Abnormalities Present in 268/325 Patients (82%)</th>
<th>Lesion</th>
<th>%</th>
<th>Median OS, Mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>del(13q)</td>
<td>55</td>
<td>133</td>
<td></td>
</tr>
<tr>
<td>del(11q)</td>
<td>18</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>Trisomy 12</td>
<td>16</td>
<td>114</td>
<td></td>
</tr>
<tr>
<td>del(17p)</td>
<td>7</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>del(6q)</td>
<td>6</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>18</td>
<td>111</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FISH Abnormality (%)</th>
<th>Patients With Abnormality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>45</td>
</tr>
<tr>
<td>Trisomy 12</td>
<td>15</td>
</tr>
<tr>
<td>del(17p)</td>
<td>10</td>
</tr>
<tr>
<td>del(11q)</td>
<td>20</td>
</tr>
</tbody>
</table>

FISH, fluorescence in situ hybridization; OS, overall survival

CLL: Impact of TP53 Mutations and TP53 Deletion on OS (N = 1148)

- OS effect of TP53 wild type:
  - vs TP53 mut only: $P = .013$
  - vs TP53 del only: $P = .006$
  - vs TP53 mut + del: $P < .001$

Analysis based on cases referred to the Munich Leukemia Laboratory between August 2005 and May 2013

Survival in CLL According to IGHV Mutational Status

- All Patients (n = 84)
- Binet Stage* A Patients (n = 62)

*See Staging Systems slide in Appendix

IGHV, immunoglobulin heavy chain variable region
IWCLL-NCl: Indications to Initiate Treatment for CLL

- Constitutional symptoms referable to CLL
- Progressive marrow failure
- Autoimmune anemia +/- thrombocytopenia poorly responsive to steroids or other
- Massive (>6 cm) or progressive splenomegaly
- Massive (>10 cm) or progressive lymphadenopathy
- Progressive lymphocytosis, >50% increase over 2 months or LDT < 6 months
- NO EARLY TREATMENT, EVEN FOR HIGH-RISK

IWCLL-NCl, International Workshop on Chronic Lymphocytic Leukemia-National Cancer Institute; LDT, lymphocyte doubling time

Treatment Goals for CLL

- Potentially curative treatments: FCR for m-IGHV and allo-HCT
- Majority requiring treatment are older (>70 yo) with comorbidities and more treatment-associated toxicities
- Goals for first-line:
  - Best opportunity for most effective treatment, most eventually relapse and need retreatment:
    - Deeper remission and treatment-free interval, later retreat
    - Maintain disease control on continuous (IBR) treatment

Allo-HCT, allogeneic hematopoietic stem cell transplant; FCR, fludarabine, cyclophosphamide, and rituximab; IBR, ibrutinib

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Essential Tests for Selecting First-Line Treatment in CLL

1. FISH: del(17p) status – can change
   – Know % of cells with deletion

2. TP53 mutation status – can change

3. IGHV mutation status – does not change

Therapeutic Agents for CLL

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>CD20 Antibody</th>
<th>BTK-inhibitor</th>
<th>PI3 kinase-inhibitor</th>
<th>BCL2-inhibitor</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorambucil (Leukeran®)</td>
<td>Rituximab (Rituxan®)</td>
<td>Ibrutinib (Imbruvica®)</td>
<td>Idelalisib (Zydelig®)</td>
<td>Venetoclax (Venclexta®)</td>
<td>Lenalidomide (Revlimid®)</td>
</tr>
<tr>
<td>Fludarabine (Fludara®)</td>
<td>Ofatumumab (Arzerra®)</td>
<td>Acalabrutinib (Calquence®)</td>
<td>Duvelisib (Copiktra®)</td>
<td></td>
<td>CAR T cells</td>
</tr>
<tr>
<td>Cyclophosphamide (Cytoxan®)</td>
<td>Obinutuzumab (Gazyva™)</td>
<td>Zanubrutinib (Brukinsa™)</td>
<td></td>
<td>Umbralisib</td>
<td></td>
</tr>
<tr>
<td>Bendamustine (Treanda®)</td>
<td></td>
<td>Vecabrutinib</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- ARQ 531
- LOXO-305
- CG-806 (Aptose)
First-Line Phase III Randomized Trials

- **RESONATE-2**
  - IBR vs.
  - CHLOR
- **iLLUMINATE** (PCYC-1130) (>65 yo or ≤65 yo with comorbidities)
  - IBR + OBIN vs.
  - CHLOR + OBIN
- **Alliance** (A041202) (>65 yo)
  - IBR vs.
  - IBR + RIT vs.
  - BR
- **ECOG E1912** [<70 yo; non-del(17p)]
  - IBR + RIT vs.
  - FCR
- **CLL14** (CIRS >6; CrCl <70 mL/min)
  - VEN + OBIN vs.
  - CHLOR + OBIN

IBR, ibrutinib (Imbruvica®); CHLOR, chlorambucil (Leukeran®); OBIN, obinutuzumab (Gazyva™); RIT, rituximab (Rituxan®); BR, bendamustine (Treanda®) and rituximab (Rituxan®); FCR, fludarabine (Fludara®), cyclophosphamide (Cytoxan®), and rituximab (Rituxan®); VEN, venetoclax (Venclexta®).

iLLUMINATE (PCYC-1130) Study Design

**Patients (N=229)**
- Previously untreated CLL/SLL
- Requiring treatment per iwCLL criteria
- Age ≥65 years or <65 years old with ≥1 coexisting condition:
  - CIRS >6
  - CrCl <70 mL/min
  - del(17p) or TP53 mutation

**Primary end point**
- PFS by IRC assessment

**Randomize 1:1**
- Ibrutinib – obinutuzumab
  - Ibrutinib 420 mg once daily until PD or unacceptable toxicity + obinutuzumab
  - 1000 mg split on days 1-2, and on day 8 and 15 (cycle 1) then day 1 (total 6 cycles)
- Chlorambucil–obinutuzumab
  - Chlorambucil 0.5 mg/kg on days 1 and 15 *6 cycles* + obinutuzumab 1000 mg split on days 1-2 and on day 8 and 15 (cycle 1) then day 1 *total 6 cycles*

**Secondary end points include**
- PFS by IRC in high-risk population
- Rate of undetectable MRD
- ORR
- OS
- Infusion-related reactions
- Safety

**After IRC-confirmed PD, patients were allowed to receive single-agent ibrutinib**

*Patients in the chlorambucil-obinutuzumab arm could receive next-line single-agent ibrutinib in crossover following IRC-confirmed PD.*
Superior Progression-Free Survival With Ibrutinib (Imbruvica®) - Obinutuzumab (Gazvy™)

- Median follow-up, 31.3 months (range, 0.2–36.9)
- Estimated PFS at 30 months: 79% with ibrutinib-obinutuzumab vs. 31% with chlorambucil-obinutuzumab
- Even after excluding patients with del(17p): 74% reduction in risk of progression or death with ibrutinib-obinutuzumab


Alliance (A041202) Schema

Untreated patients age ≥65 who meet IWCLL criteria for CLL treatment

Stratify*

Randomize

Bendamustine (Treanda®) 90 mg/m² days 1 and 2 of each 28-day cycle +
Rituximab (Rituxan®) 375 mg/m² day 0 cycle 1, then 500 mg/m² day 1 cycles 2-6
Ibrutinib (Imbruvica®) 420 mg daily until disease progression

Ibrutinib (Imbruvica®) 420 mg daily until disease progression +
Rituximab (Rituxan®) 375 mg/m² weekly for 4 weeks starting cycle 2 day 1, then day 1 of cycles 3-6

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

*See Staging Systems slide in Appendix

Primary Endpoint: Progression-Free Survival
Eligible Patient Population

<table>
<thead>
<tr>
<th>Time (Months)</th>
<th>% Alive and Progression-Free</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>90</td>
</tr>
<tr>
<td>12</td>
<td>80</td>
</tr>
<tr>
<td>18</td>
<td>70</td>
</tr>
<tr>
<td>24</td>
<td>60</td>
</tr>
<tr>
<td>30</td>
<td>50</td>
</tr>
<tr>
<td>36</td>
<td>40</td>
</tr>
<tr>
<td>42</td>
<td>30</td>
</tr>
<tr>
<td>48</td>
<td>20</td>
</tr>
<tr>
<td>52</td>
<td>10</td>
</tr>
</tbody>
</table>

Pairwise Comparisons

I vs BR:
- Hazard Ratio 0.39
- 95% CI: 0.26-0.58
- (1-sided P-value <0.001)

IR vs BR:
- Hazard Ratio 0.38
- 95% CI: 0.25-0.59
- (1-sided P-value <0.001)

IR vs I:
- Hazard Ratio 1.00
- 95% CI: 0.62-1.62
- (1-sided P-value 0.49)

E1912: Study Design

**Arm A – Ibrutinib + Rituximab**
- Cycles 1:
  - Ibrutinib 420 mg PO daily, days 1-28
- Cycles 2-7:
  - Ibrutinib 420 mg PO daily, days 1-28
  - Rituximab 50 mg/m² IV, day 1
  - Rituximab 325 mg/m² IV, day 2
- Cycles 8-35:
  - Ibrutinib 420 mg PO daily, days 1-28

**Arm B – FCR**
- Cycles 1-6:
  - Fludarabine 25 mg/m² IV, days 1-3
  - Cyclophosphamide 250 mg/m² IV, days 1-3
- Cycles 8-35:
  - Rituximab 50 mg/m² IV, day 1, cycle 1
  - Rituximab 325 mg/m² IV, day 2, cycle 1

Planned Accrual: 519

Fludarabine, Fludara®; Ibrutinib (Imbruvica®); Rituximab (Rituxan®)
### Progression-Free Survival

**Intent to Treat**

- **HR** = 0.35 (95% CI 0.22-0.5)
- One sided p<0.00001

**Eligible**

- **HR** = 0.32 (95% CI 0.20-0.51)
- One sided p<0.00001

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### Overall Survival

**Intent to Treat**

- **HR** = 0.17 (95% CI 0.05-0.54)
- One sided p<0.0003

**Eligible**

- **HR** = 0.13 (95% CI 0.03-0.46)
- One sided p<0.0001

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### Causes of Death

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>IR n=354</th>
<th>FCR n=175</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLL</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Unexplained/unwitnessed</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Other: acute/chronic respiratory failure; hx lung adenocarcinoma</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Acute respiratory failure</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Metastatic colon cancer</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Drug overdose</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>4</strong></td>
<td><strong>10</strong></td>
</tr>
</tbody>
</table>

Death during active treatment +30 days: IR (n=3); FCR (n=1)


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### T-MDS/AML AFTER FCR

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Treatment</th>
<th>T-MDS/AML %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MDACC 2004-2012</strong></td>
<td>234</td>
<td>FCR-based</td>
<td>5.1</td>
</tr>
<tr>
<td></td>
<td>131</td>
<td>FCR only</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>MDACC 1999-2003</strong></td>
<td>300</td>
<td>FCR</td>
<td>4.6</td>
</tr>
<tr>
<td><strong>German CLL8</strong></td>
<td>408</td>
<td>FCR</td>
<td>1.5</td>
</tr>
</tbody>
</table>

MDACC, MD Anderson Cancer Center; T-MDS, therapy-related myelodysplastic syndrome; T-AML, therapy-related acute myeloid leukemia

**CLL14: TRIAL DESIGN**

**Safety Run-in Phase**
Venetoclax (Venclexta™) – Obinutuzumab (Gazyva™)

**Previously untreated patients with CLL and coexisting medical conditions**
CIRS >6 and/or CrCl <70 mL/min

1:1 randomization

Follow-up Phase
Primary endpoint: Progression-free survival

Key secondary endpoints: Response, Minimal Residual Disease, Overall Survival

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**CLL14: RESPONSE TO TREATMENT**

Overall response

\[ P = 0.0007 \]

Patients with response (%)

<table>
<thead>
<tr>
<th></th>
<th>Partial response</th>
<th>Complete response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venetoclax-Obinutuzumab (Venclexta™-Gazyva™)</td>
<td>35%</td>
<td>50%</td>
</tr>
<tr>
<td>Chlorambucil-Obinutuzumab (Leukeran™-Gazyva™)</td>
<td>48%</td>
<td>23%</td>
</tr>
</tbody>
</table>

\( P < 0.0001 \)
CLL14: PROGRESSION-FREE SURVIVAL

Hazard ratio 0.35 (95% CI 0.23–0.53), \( P<0.0001 \)

29-months median follow-up

FCR300: PFS by \( IGHV \) Mutation Status (\( IGHV \)-MS)

\( P<0.0001 \)
**CLL10 Study: FCR vs BR in Front-Line**

Progression-free survival by *IGHV*-MS

![Graph showing progression-free survival by *IGHV*-MS](image)

*MS, mutation status.*


**FCR First-Line: 6-Month Landmark PFS by MRD at EoT and *IGHV*-MS**

![Graph showing 6-month landmark PFS by *IGHV*-MS](image)

*EoT, end of treatment.*

*U-MRD, undetectable minimal residual disease.*

### CLL14: Subgroup Analysis for Mutated IGHV by MRD Negativity and by CR Rates

#### Subgroup Analysis for Undetectable PB MRD Rate (ASO-PCR)\(^1\)

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Total N</th>
<th>VenG MRD– (%)</th>
<th>GClb MRD– (%)</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>432</td>
<td>216 75.5</td>
<td>216 35.2</td>
<td>5.67</td>
<td>3.74–8.60</td>
</tr>
<tr>
<td>Mutated IGHV</td>
<td>159</td>
<td>76 73.7</td>
<td>83 43.4</td>
<td>3.66</td>
<td>1.87–7.15</td>
</tr>
</tbody>
</table>

#### Subgroup Analysis for Complete Response Rate\(^2\)

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Total N</th>
<th>VenG CR (%)</th>
<th>GClb CR (%)</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>432</td>
<td>216 49.5</td>
<td>216 23.1</td>
<td>3.26</td>
<td>2.15–4.93</td>
</tr>
<tr>
<td>Mutated IGHV</td>
<td>159</td>
<td>76 51.3</td>
<td>83 34.9</td>
<td>1.96</td>
<td>1.04–3.71</td>
</tr>
</tbody>
</table>

---

**Deeper response rates (MRD negativity and CR) were significantly higher with VenG vs GClb in patients with mutated IGHV.**

---

First-Line Treatment for CLL

<table>
<thead>
<tr>
<th>TP53 Status [del(17p)/TP53]</th>
<th>Age/Fitness</th>
<th>IGHV-MS</th>
<th>First-Line Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deleted and/or Mutated</td>
<td>All</td>
<td>Irrelevant</td>
<td>BTKi ± Obinutuzumab (Gazyva™)</td>
</tr>
<tr>
<td>Intact</td>
<td>Young/Fit</td>
<td>Mutated</td>
<td>BCL2i + Obinutuzumab (Gazyva™)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unmutated</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Older/Unfit</td>
<td>Mutated</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unmutated</td>
<td>BTKi ± Obinutuzumab (Gazyva™)</td>
</tr>
</tbody>
</table>

BTKi, Bruton’s tyrosine kinase inhibitor; BCL2i, BCL-2 inhibitor

Ibrutinib (Imbruvica®) + Venetoclax (Venclexta®)

- Investigator-initiated phase II trial
  - Ibrutinib (Imbruvica®) monotherapy – 3 months
  - Ibrutinib (Imbruvica®) + venetoclax (Venclexta®) – 24 months
  - Option to continue ibrutinib (Imbruvica®) if <CR or MRD+

- Tx-naive with at least 1 high-risk feature:
  - Del(17p) or mutated TP53
  - Del(11q)
  - Unmutated IGHV
  - Age ≥65 yrs

Responses Improve With Ongoing Therapy

Phase 2 CAPTIVATE Study Design (NCT02910583)

Patients (N=164)
Key eligibility:
- Treatment-naïve CLL/SLL
- Active disease requiring treatment per iwCLL criteria
- Age <70 years
- ECOG PS 0–1

Study Populations:
- MRD cohort (N=164): exposure and safety analysis
  - Safety Run-in: first 14 patients completed C15 treatment (12 cycles of I+V);
    no dose-limiting toxicities (DLT) or clinical TLS during first 6 weeks of I+V combination
  - First 30 patients completed C9 treatment (6 cycles of I+V) for MRD evaluation
- Fixed duration cohort (N=159): separate cohort; analysis not shown

Ibrutinib (Imbruvica®) lead-In:
ibrutinib (Imbruvica®) 420 mg once daily for 3 cycles
Followed by I+V:
Add venetoclax (Venclexta®) ramp-up to 400 mg once daily for 12 cycles

Randomization:
- Confirmed undetectable MRD: Double-blind 1:1 randomization, placebo:ibrutinib (Imbruvica®)
- Undetectable MRD not confirmed: 1:1 randomization, ibrutinib: I+V (Imbruvica®)

Confirmed undetectable MRD:
- Stratified by IGHV mutation status.
- Confirmed undetectable MRD for randomization defined as undetectable MRD serially over at least 3 cycles in peripheral blood (PB), and undetectable MRD in both PB and BM.
Bruton Tyrosine Kinase (BTK) Inhibitors

BTK Inhibitors – Dosing

<table>
<thead>
<tr>
<th></th>
<th>Ibrutinib (Imbruvica®)</th>
<th>Acalabrutinib* (Calquence®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA Approval Date</td>
<td>November 2013</td>
<td>October 2017 for mantle cell lymphoma (MCL)</td>
</tr>
<tr>
<td>Usual Starting Dose</td>
<td>420 mg PO once daily</td>
<td>100 mg PO BID</td>
</tr>
<tr>
<td></td>
<td>Take with a glass of water with or without food</td>
<td>Take with water with or without food</td>
</tr>
<tr>
<td>Dose in Hepatic Dysfunction</td>
<td>Child-Pugh A: 140 mg PO daily</td>
<td>Child-Pugh A &amp; B: No recommended dose reductions</td>
</tr>
<tr>
<td></td>
<td>Child-Pugh B: 70 mg PO daily</td>
<td>Child-Pugh C: Not studied</td>
</tr>
<tr>
<td></td>
<td>Child-Pugh C: Avoid use</td>
<td></td>
</tr>
<tr>
<td>Availability</td>
<td>Capsules: 70 mg, 140 mg</td>
<td>Capsules: 100 mg</td>
</tr>
<tr>
<td></td>
<td>Tablets: 140 mg, 280 mg, 420 mg, 560 mg (MCL)</td>
<td></td>
</tr>
</tbody>
</table>

*Acalabrutinib approved for CLL/SLL in sNDA on 11-22-19

# BTK Inhibitors – Drug Interactions

<table>
<thead>
<tr>
<th></th>
<th>Ibrutinib (Imbruvica®)</th>
<th>Acalabrutinib (Calquence®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substrate of</td>
<td>CYP3A</td>
<td>CYP3A, P-gp, BCRP</td>
</tr>
<tr>
<td>Effects on enzymes/transporters</td>
<td>Not a clinically significant inhibitor or inducer</td>
<td>Not a clinically significant inhibitor or inducer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May inhibit BCRP transporter</td>
</tr>
<tr>
<td>Dosing Recommendations with Restricted Concomitant Medications</td>
<td>Moderate CYP3A inh. – 280 mg daily</td>
<td>Moderate CYP3A inh. – 100 mg daily</td>
</tr>
<tr>
<td></td>
<td>Strong CYP3A Inhibitors: Voriconazole (Vfend®)/Posaconazole (Noxafil®) susp. ≤400 mg/day – 140 mg daily</td>
<td>Strong CYP3A inh. – avoid use or interrupt acalabrutinib (Calquence®) if short duration</td>
</tr>
<tr>
<td></td>
<td>Posaconazole (Noxafil®) tabs or IV (any dose) or susp. &gt;400 mg/day – 70 mg daily</td>
<td>Strong CYP3A inducer – avoid use. If cannot avoid, increase to 200 mg BID</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H2-blockers – take acalabrutinib (Calquence®) dose 2 hours prior to H2-blocker</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Short-acting antacids – separate doses by at least 2 hours</td>
</tr>
<tr>
<td>Avoid concomitant use with:</td>
<td>Any other strong CYP3A inhibitors</td>
<td>Proton pump inhibitors</td>
</tr>
<tr>
<td></td>
<td>Strong CYP3A inducers</td>
<td>Grapefruit and Seville oranges</td>
</tr>
</tbody>
</table>

CYP, cytochrome p450; P-gp, P glycoprotein; BCRP, breast cancer resistance protein.


---

# BTK Inhibitors – Warnings

<table>
<thead>
<tr>
<th></th>
<th>Ibrutinib (Imbruvica®)</th>
<th>Acalabrutinib (Calquence®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Arrhythmias</td>
<td>Atrial fibrillation: 4%</td>
<td>Atrial fibrillation: 3%</td>
</tr>
<tr>
<td></td>
<td>Rare ventricular arrhythmias</td>
<td>Obtain an EKG in symptomatic patients</td>
</tr>
<tr>
<td></td>
<td>Caution in patients with cardiac history</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Obtain an EKG in symptomatic patients</td>
<td></td>
</tr>
<tr>
<td>Cytopenias</td>
<td>Grade 3 and 4 events can occur</td>
<td>Grade 3 and 4 events can occur</td>
</tr>
<tr>
<td></td>
<td>Monitor blood counts monthly</td>
<td>Monitor blood counts monthly</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>Major bleeding: 4%; all grades: 39%</td>
<td>Major bleeding: 2%; all grades: 50%</td>
</tr>
<tr>
<td></td>
<td>Concomitant antiocoagulants increase risk</td>
<td>Concomitant antiocoagulants increases risk</td>
</tr>
<tr>
<td></td>
<td>Consider holding ibrutinib at least 3-7 days prior to and postsurgical procedures depending on risks of surgery, bleeding, and ibrutinib interruption</td>
<td>Consider holding acalabrutinib at least 3-7 days prior to and postsurgical procedures depending on surgery and bleeding risks</td>
</tr>
</tbody>
</table>

EKG, electrocardiogram.

BTK Inhibitors – Warnings*

<table>
<thead>
<tr>
<th></th>
<th>Ibrutinib (Imbruvica®)</th>
<th>Acalabrutinib (Calquence®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td>Grade 3 or greater: 24% Cases of progressive multifocal leukoencephalopathy (PML), hepatitis B reactivation, invasive fungal infections &amp; Pneumocystis jirovecii pneumonia (PJP)</td>
<td>Grade 3 or greater: 18% Cases of PML, hepatitis B reactivation, and invasive fungal infections have been reported</td>
</tr>
<tr>
<td>Secondary Malignancies</td>
<td>10% occurrence rate Most common – non-melanoma skin cancers</td>
<td>11% occurrence rate Most common – non-melanoma skin cancers</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Any grade: 12% Grade 3 or greater: 5% Monitor blood pressure periodically</td>
<td>Not listed as a warning</td>
</tr>
<tr>
<td>Tumor lysis syndrome</td>
<td>Rarely occurs</td>
<td>Not listed as a warning</td>
</tr>
</tbody>
</table>


*Embryo-Fetal Toxicity: Based on findings in animals, BTK Inhibitors can cause fetal harm when administered to a pregnant woman. Advise women to avoid becoming pregnant and to use contraception. See Full PI for each drug for more specifics.

BTK Inhibitors – Other Common Side Effects

Non-lab events occurring in ≥20% of patients in Ibrutinib (Imbruvica®) clinical trials
- Rash
- Musculoskeletal pain
- Fatigue
- Pyrexia
- Cough
- Diarrhea
- Nausea
- Advise patients about the possibility of lymphocytosis after initiating treatment
  - Occurs within the first month of therapy and can persist for several weeks. Not progression!

Non-lab events occurring in ≥20% of patients in Acalabrutinib (Calquence®) clinical trials
- Headache
  - Occurs early and typically resolves with continued therapy
- Fatigue
- Myalgia
- Diarrhea
- Bruising


*Embryo-Fetal Toxicity: Based on findings in animals, BTK Inhibitors can cause fetal harm when administered to a pregnant woman. Advise women to avoid becoming pregnant and to use contraception. See Full PI for each drug for more specifics.
Venetoclax (Venclexta®) Dosing

- Inhibits the B-cell lymphoma 2 (BCL2) protein, which is overexpressed in CLL leading to prolonged cell survival
- Inhibition of BCL2 by venetoclax (Venclexta®) restores apoptosis
- CLL dosing (requires a ramp-up at initiation):
  - Each dose should be taken with a meal and water
  - Week 1: 20 mg PO daily x 7 days
  - Week 2: 50 mg PO daily x 7 days
  - Week 3: 100 mg PO daily x 7 days
  - Week 4: 200 mg PO daily x 7 days
  - Week 5 and thereafter: 400 mg PO daily, continuously
- Dosing in hepatic impairment:
  - Child-Pugh C: Decrease dose by 50%
- See prescribing information for modifications for toxicity
- Availability:
  - Tablets: 10 mg, 50 mg, 100 mg
Venetoclax (Venclexta®) Drug Interactions

- Substrate of CYP3A, P-gp; inhibitor of P-gp and BCRP; weak inhibitor of CYP2C9 (may affect warfarin)
- Dosing recommendations for specific concomitant medications:
  - Concomitant strong or moderate CYP3A inhibitors and P-gp inhibitors are contraindicated during ramp-up or require a venetoclax (Venclexta®) dose reduction
  - Concomitant posaconazole – 70 mg PO daily (82.5% reduction)
  - Other strong CYP3A inhibitor – 100 mg PO daily (75% reduction)
  - Moderate CYP3A inhibitor or P-gp inhibitor – 200 mg PO daily (50% reduction)
  - P-gp substrate – administer at least 6 hours before venetoclax (Venclexta®) dose
- Advise patient to avoid grapefruit, Seville orange, and starfruit consumption while taking venetoclax (Venclexta®)

Venetoclax (Venclexta®) Warnings

- Tumor lysis syndrome (TLS)
  - Fatal and serious TLS events have occurred in patients with high tumor burden (rate 2% after ramp-up schedule/aggressive prophylaxis instituted)
  - See prescribing information for risk assessment and TLS prophylaxis guidance based on risk
- Neutropenia
  - Grade 3 or 4 neutropenia occurred in approximately 63% of patients in clinical trials
  - Monitor counts periodically during therapy
- Infections
  - Fatal and serious infections have occurred
- Embryo-Fetal Toxicity
  - May cause embryo-fetal harm when administered to a pregnant woman. Advise females of reproductive potential to avoid pregnancy during treatment
- Immunization
  - Do not administer live attenuated vaccines prior to, during, or after treatment until B-cell recovery occurs. Advise patients that vaccinations may be less effective.
Venetoclax (Venclexta®): Other Common Side Effects

• Events (non-lab) occurring in 20% or greater of patients in clinical trials
  • Edema
  • Upper respiratory tract infections
  • Musculoskeletal pain
  • Fatigue
  • Cough
  • Diarrhea
  • Nausea

• Venetoclax (Venclexta®): does not cause lymphocytosis compared to some of the other oral agents being discussed

Anti-CD20 Monoclonal Antibodies

• Three anti-CD20 monoclonal antibodies currently on the market:
  • Rituximab [Rituxan® (IV)] and rituximab (Rituxan®)/hyaluronidase (SQ) (chimeric)
  • Ofatumumab [Arzerra® (human)]
  • Obinutuzumab [Gazyva™ (humanized)]

• Toxicities profiles are fairly similar:
  • Infusion-related reactions (follow premedication recommendations)
  • Injection site reactions (SQ)
  • Tumor lysis syndrome
  • Mucocutaneous reactions (rituximab)
  • Cytopenias
  • Risk of infections (eg, hepatitis B reactivation, PML)
  • Add minimal overlapping toxicity when combined with other agents, such as chemotherapy or oral targeted agents
  • Based on human data, RITUXAN® can cause fetal harm due to B-cell lymphocytopenia in infants exposed to rituximab in-utero. Advise pregnant women of the risk to a fetus. Females of childbearing potential should use effective contraception while receiving RITUXAN® and for 12 months following the last dose of RITUXAN®
  • ARZERRA® (ofatumumab) may cause fetal B-cell depletion based on findings from animal studies and the drug’s mechanism of action There are no data on ARZERRA use in pregnant women to inform a drug-associated risk. See full PI.
  • GAZYVA™ is likely to cause fetal B-cell depletion based on findings from animal studies and the drug’s mechanism of action There are no data with GAZYVA™ use in pregnant women to inform a drug-associated risk. See full PI.


Chemoimmunotherapy

• Chemoimmunotherapy = Anti-CD20 monoclonal antibody + alkylating agent +/- purine nucleoside analog
  • Alkylating agents – bendamustine (Treanda®), cyclophosphamide (Cytoxan®), chlorambucil (Leukeran®)
  • Purine analogs – fludarabine, pentostatin
  • Anti-CD20 monoclonal antibodies – rituximab (Rituxan®), ofatumumab (Azerra®), obinutuzumab (Gazyva®)

• Alkylating agents crosslink DNA strands leading to impaired DNA replication and transcription, and ultimately cell death

• Purine analogs inhibit DNA synthesis by inhibiting critical enzymes involved in the process, such as DNA polymerase and adenosine deaminase

• Anti-CD20 monoclonal antibodies attach to the CD20 antigen expressed on CLL cells and activate antibody-dependent cellular and complement-dependent cytotoxicity

• Up to 6 cycles of chemotherapy may be given with cycles repeated every 28 days
  • Chlorambucil regimens may be given for up to 12 cycles
  • After completion of cycles, patients are observed until progression
Chemoimmunotherapy Side Effects

• Major toxicities associated with chemoimmunotherapy are myelosuppression and infections
  • Infection prophylaxis is indicated, and growth factor support may be necessary
  • FCR > BR > Clb-R
• Chemotherapy-induced nausea and vomiting can be managed per the guidelines
  • Ensure patients have a PRN antiemetic for home
• Tumor lysis syndrome is also a risk in patients with high tumor burden
  • Assess patient’s TLS risk and provide appropriate prophylaxis
• Secondary malignancies are also a long-term risk of chemoimmunotherapy
• Potential risks to fetal health must be weighed against risks of delaying treatment in pregnant women. Pregnancy should be avoided during treatment and after as indicated by prescribing information.

PRN, “as needed”

R/R CLL
Phase III RESONATE: Ibrutinib (Imbruvica®) vs Ofatumumab (Arzerra®) in R/R CLL/SLL

- Stratified by refractory to purine analogue chemoimmunotherapy (no response or relapsed within 12 mos); presence or absence of 17p13.1 (17p del)

Patients with CLL/SLL diagnosis; ≥1 prior therapy; ECOG PS 0/1; measurable nodal disease (N = 391)

Ibrutinib (Imbruvica®)
420 mg/day PO until PD or unacceptable toxicity (n = 195)

Ofatumumab (Arzerra®)
IV starting dose of 300 mg followed by 2000 mg x 11 doses for 24 wks (n = 196)

Crossover to Ibrutinib (Imbruvica®)
420 mg/day following PD (n = 122)

- At time of interim analysis, median time on study was 9.4 mos

Protocol amended for crossover with support of data-monitoring committee and discussion with health authorities.


RESONATE: PFS (Primary Endpoint) and OS

Ibrutinib, (Imbruvica®); ofatumumab, (Arzerra®)

Phase III ASCEND Trial of Acalabrutinib (Calquence®) vs Idelalisib (Zydelig®) + Rituximab (Rituxan®) or BR in R/R CLL

- International, randomized, open-label phase III trial
- Primary endpoints: PFS per IRC
- Secondary endpoints: ORR, DoR, PFS per investigator, OS
- Interim analysis planned after ≈79 PFS events


ASCEND: PFS by IRC Review (Primary Endpoint)

<table>
<thead>
<tr>
<th>Patients at Risk, n</th>
<th>PFS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acalabrutinib (n = 155)</td>
<td>88</td>
</tr>
<tr>
<td>IdR/BR (n = 155)</td>
<td>68</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mos</th>
<th>Patients at Risk, n</th>
<th>Median PFS, mos</th>
<th>HR (95% CI)</th>
<th>1-yr PFS rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acalabrutinib</td>
<td>155</td>
<td>153 153 149 147 146</td>
<td>16.5</td>
<td>0.31 (0.20-0.49; P &lt; .0001)</td>
</tr>
<tr>
<td>IdR/BR</td>
<td>155</td>
<td>150 150 146 144 142</td>
<td>NR</td>
<td>88</td>
</tr>
</tbody>
</table>

acalabrutinib, (Calquence®); NR, not reached
## BTK Inhibitors in Clinical Development

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism</th>
<th>Disease</th>
<th>Current Phase</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibrutinib (Imbruvica&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>irBTKi-C481</td>
<td>MCL, CLL</td>
<td>Approved (CLL/MCL)</td>
<td>Being tested in combinations</td>
</tr>
<tr>
<td>Acalabrutinib (Calquence&lt;sup&gt;™&lt;/sup&gt;)</td>
<td>irBTKi-C481</td>
<td>MCL, CLL</td>
<td>Approved (MCL); III (CLL)</td>
<td>To be filed for FDA approval in newly diagnosed and R/R CLL*</td>
</tr>
<tr>
<td>Zanubrutinib (Brukinsa&lt;sup&gt;™&lt;/sup&gt;)</td>
<td>irBTKi-C481</td>
<td>MCL, CLL</td>
<td>III (CLL); I/II (MCL)</td>
<td>Under FDA review for R/R MCL**</td>
</tr>
<tr>
<td>Ono-/GS-4059</td>
<td>irBTKi-C481</td>
<td>CLL, NHL</td>
<td>I completed</td>
<td>No clear plan</td>
</tr>
<tr>
<td>Spebrutinib</td>
<td>irBTKi-C481</td>
<td>CLL</td>
<td>I/Ib</td>
<td>No clear plan</td>
</tr>
<tr>
<td>M7583</td>
<td>irBTKi-C481</td>
<td>Heme malignancies</td>
<td>I/II</td>
<td>Early development</td>
</tr>
<tr>
<td>Evobrutinib</td>
<td>irBTKi-C481</td>
<td>Autoimmune</td>
<td>II</td>
<td>Autoimmune development</td>
</tr>
<tr>
<td>Fenebrutinib</td>
<td>rBTKi</td>
<td>CLL, NHL</td>
<td>I completed</td>
<td>Autoimmune development</td>
</tr>
<tr>
<td>Vecabrutinib</td>
<td>rBTKi</td>
<td>CLL</td>
<td>I/II</td>
<td>Early development for CLL</td>
</tr>
<tr>
<td>ARQ-531</td>
<td>rBTKi</td>
<td>Heme malignancies</td>
<td>I</td>
<td>Early development</td>
</tr>
<tr>
<td>LOXO-305</td>
<td>rBTKi</td>
<td>CLL</td>
<td>I</td>
<td>Early development; plan for CLL</td>
</tr>
</tbody>
</table>

*FDA approved for CLL, November 2019; **FDA approved for MCL, November 2019.

---

### Phase III Trial of Venetoclax (Venclexta<sup>®</sup>) + Rituximab (Rituxan<sup>®</sup>) vs BR in R/R CLL/SLL (MURANO): Study Design

- **Multicenter, randomized, open-label phase III trial**
  - Stratified by del(17p), prior tx response, *geographic region*
  - Adult patients with R/R CLL, 1-3 prior tx lines (with ≥1 CT-containing regimen), prior bendamustine (Treanda<sup>®</sup>) permitted if DoR ≥24 mos (N = 389)

- **Venetoclax (Venclexta<sup>®</sup>) dose ramp-up:**
  - 20-400 mg PO QD for 5 wks then 400 mg PO QD for cycles 1-6 + Rituximab (Rituxan<sup>®</sup>) 375 mg/m² on day 1 of cycle 1, then 500 mg/m² on day 1 of cycles 2-6 (n = 194)

- **Bendamustine (Treanda<sup>®</sup>)** 70 mg/m² on Days 1, 2 of cycles 1-6 + Rituximab (Rituxan<sup>®</sup>) 375 mg/m² on Day 1 of cycle 1, then 500 mg/m² Day 1 of cycles 2-6 (n = 195)

- **28-day cycles**
  - Venetoclax (Venclexta<sup>®</sup>) monotherapy until PD, unacceptable toxicity, or maximum of 2 yrs from day 1 of cycle 1
  - *High-risk CLL defined as del(17p); no response to first-line CT-containing tx; or relapsed in ≤12 mos after CT or in ≤24 mos after chemoimmunotherapy.*

- **Primary endpoint:** investigator-assessed PFS
- **Secondary endpoints:** IRC-assessed PFS and MRD negativity, IRC-assessed CR → ORR → OS (hierarchical testing), safety

Seymour. NEJM. 2018;378:1107. NCT02005471.
MURANO: Updated PFS and OS

- Median follow-up: 36.0 mos

Status Off Therapy, n (%) | uMRD (n = 83) | Low MRD (n = 23) | High MRD (n = 14) | Missing (n = 10)
---|---|---|---|---
Progression free | 81 (97.6) | 20 (87.0) | 3 (21.4) | 10 (100)
Progressive disease | 2 (2.4) | 3 (13.0) | 11 (78.6) | 0

EOT, end of treatment; MRD, minimal residual disease; uMRD, undetectable minimal residual disease

MURANO: Predictors of Disease Progression at EOT

Univariate analysis of clinical and cytogenetic risk factors in VenR pts who completed therapy without progression

<table>
<thead>
<tr>
<th>Characteristic, n/N (%)</th>
<th>Patients With PD</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood MRD status at EOT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Undetectable</td>
<td>2/83 (2.4)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>▪ Low</td>
<td>3/23 (13.0)</td>
<td></td>
</tr>
<tr>
<td>▪ High</td>
<td>11/14 (78.6)</td>
<td></td>
</tr>
<tr>
<td>del(17p) and/or TP53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ At least one present</td>
<td>10/43 (23.3)</td>
<td>.01</td>
</tr>
<tr>
<td>▪ Neither present</td>
<td>5/78 (6.4)</td>
<td></td>
</tr>
<tr>
<td>del(11q)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ No</td>
<td>13/80 (16.3)</td>
<td>.03</td>
</tr>
<tr>
<td>▪ Yes</td>
<td>1/38 (2.6)</td>
<td></td>
</tr>
<tr>
<td>del(11q) without del(17p)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ No</td>
<td>7/58 (12.1)</td>
<td>.25</td>
</tr>
<tr>
<td>▪ Yes</td>
<td>1/32 (3.1)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic, n/N (%)</th>
<th>Patients With PD</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGHV mutation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ No</td>
<td>13/84 (15.5)</td>
<td>.14</td>
</tr>
<tr>
<td>▪ Yes</td>
<td>2/38 (5.3)</td>
<td></td>
</tr>
<tr>
<td>No. previous therapies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ ≤1</td>
<td>9/78 (11.5)</td>
<td>.79</td>
</tr>
<tr>
<td>▪ ≥2</td>
<td>7/52 (13.5)</td>
<td></td>
</tr>
<tr>
<td>Bulky disease (largest lymph node diameter)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ &lt;5 cm</td>
<td>9/67 (13.4)</td>
<td>1.0</td>
</tr>
<tr>
<td>▪ ≥5 cm</td>
<td>7/53 (13.2)</td>
<td></td>
</tr>
<tr>
<td>Nodal status at EOCT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ &lt;1.5 cm</td>
<td>5/64 (7.8)</td>
<td></td>
</tr>
<tr>
<td>▪ ≥1.5 to &lt;2 cm</td>
<td>2/23 (8.7)</td>
<td>.08</td>
</tr>
<tr>
<td>▪ ≥2 cm</td>
<td>9/39 (23.1)</td>
<td></td>
</tr>
</tbody>
</table>

BCL-2 Coding Mutation Detected in 7 Patients With CLL-Type Progression on Venetoclax (Venclexta®)

- **BCL-2 c.302G>T, p.(Gly101Val)** detected in samples from 7 of 15 patients sequenced at CLL-type progression on venetoclax (Venclexta®)

**Phase III Trial of Idecalisib (Zydelig®) + Rituximab (Rituxan®) in Relapsed CLL: Final Results of PFS (Primary Endpoint) and OS**

- Phase III trial in patients with relapsed CLL after at least 1 prior line of tx
  - Primary study 116 with idecalisib (Zydelig®) /rituximab (Rituxan®) followed by extension study 117 with single-agent idecalisib (Zydelig®)

  ![Graph of PFS and OS](image)

  **Sharman. JCO. 2019;37:1391.**

**Phase III DUO Trial of Duvelisib (Copiktra®) vs Ofatumumab (Arzerra®) in R/R CLL**

- Duvelisib is a dual inhibitor of PI3K delta and PI3K gamma
  - Administered orally twice daily
  - Prolonged PFS compared with ofatumumab in the DUO study
  - FDA approved for patients with R/R CLL/SLL and ≥2 previous therapies in September 2018

  ![Graph of PFS and OS](image)

Phosphatidylinositol 3-Kinase (PI3K) Inhibitors

PI3K Inhibitors – Dosing

<table>
<thead>
<tr>
<th></th>
<th>Idelalisib (Zydelig®)</th>
<th>Duvelisib (Copiktra®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzyme isoform(s) inhibited</td>
<td>PI3K delta</td>
<td>PI3K delta and gamma</td>
</tr>
<tr>
<td>FDA Approval Date</td>
<td>July 2014</td>
<td>September 2018</td>
</tr>
<tr>
<td>Usual Starting Dose</td>
<td>150 mg PO BID continuously Take with or without food</td>
<td>25 mg PO BID continuously Take with or without food</td>
</tr>
<tr>
<td>Dose in Hepatic Dysfunction</td>
<td>No dose adjustments are recommended but limited data in patients with baseline AST or ALT &gt; 2.5 x ULN or bilirubin &gt; 1.5 x ULN. Monitor for toxicity.</td>
<td>No specific recommendations as no effect of Child-Pugh A, B, or C hepatic impairment on duvelisib exposure was seen</td>
</tr>
<tr>
<td>Availability</td>
<td>Tablets: 100 mg, 150 mg</td>
<td>Capsules: 15 mg, 25 mg</td>
</tr>
</tbody>
</table>

AST, aspartate aminotransferase; ALT, alanine aminotransferase; ULN, upper limit of normal.

PI3K Inhibitors – Drug Interactions

<table>
<thead>
<tr>
<th>Substrate of</th>
<th>Idealisib (Zydelig®)</th>
<th>Duvelisib (Copiktra®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effects on enzymes/transporters</td>
<td>Strong inhibitor of CYP3A</td>
<td>Moderate inhibitor of CYP3A</td>
</tr>
<tr>
<td>Dosing Recommendations with Restricted Concomitant Medications</td>
<td><strong>Strong CYP3A inhibitor</strong> – avoid use. If not possible, monitor patient more closely for side effects</td>
<td><strong>Strong CYP3A inhibitor</strong> – 15 mg BID</td>
</tr>
<tr>
<td></td>
<td><strong>Sensitive CYP3A substrates</strong> – avoid use</td>
<td><strong>Sensitive CYP3A substrates</strong> – use with caution</td>
</tr>
</tbody>
</table>

Avoid concomitant use with:

- Strong CYP3A inducers
- Sensitive CYP3A substrates


PI3K Inhibitors – Warnings

<table>
<thead>
<tr>
<th>Effect</th>
<th>Idealisib (Zydelig®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatotoxicity</td>
<td>Fatal/serious hepatotoxicity: 18%</td>
</tr>
<tr>
<td></td>
<td>Avoid concomitant agents that are liver toxic</td>
</tr>
<tr>
<td></td>
<td>Monitor AST and ALT:</td>
</tr>
<tr>
<td></td>
<td>• Every 2 weeks for the first 3 months, then</td>
</tr>
<tr>
<td></td>
<td>• Every 4 weeks for the next 3 months, then</td>
</tr>
<tr>
<td></td>
<td>• Every 1 to 3 months thereafter</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4 ALT and AST elevations: 8% and 2%, respectively</td>
</tr>
<tr>
<td></td>
<td>Avoid concomitant agents that are liver toxic</td>
</tr>
<tr>
<td></td>
<td>Monitor AST and ALT periodically</td>
</tr>
<tr>
<td>Diarrhea/Colitis</td>
<td>Grade 3 or higher diarrhea or colitis: 14%</td>
</tr>
<tr>
<td></td>
<td>Responds poorly to antimotility agents; slow to respond to treatment interruption with or without corticosteroids</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>Pneumonitis: 4%</td>
</tr>
<tr>
<td></td>
<td>Onset ranged from within the first month to 15 months into therapy</td>
</tr>
<tr>
<td></td>
<td>Do not rechallenge</td>
</tr>
<tr>
<td></td>
<td>Fatal/serious pneumonitis: 5%</td>
</tr>
</tbody>
</table>

# PI3K Inhibitors – Warnings

<table>
<thead>
<tr>
<th></th>
<th>Idelalisib (Zydelig®)</th>
<th>Duvelisib (Copiktra®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td>Fatal and/or serious infections: 21% Cases of cytomegalovirus (CMV) reactivation and</td>
<td>Serious/fatal infections: 31% Cases of CMV reactivation and <em>Pneumocystis jirovecii</em></td>
</tr>
<tr>
<td></td>
<td><em>Pneumocystis jirovecii</em> pneu monia have been reported</td>
<td>pneumonia have been reported</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Grade 3 or 4 neutropenia: 25% Monitor blood counts every 2 weeks for the first 6</td>
<td>Grade 3 or 4 neutropenia: 42% Monitor blood counts every 2 weeks for the first 2</td>
</tr>
<tr>
<td></td>
<td>months, then as clinically indicated. Monitor weekly when ANC is less than 1K</td>
<td>months, then as clinically indicated. Monitor weekly when ANC is less than 1K</td>
</tr>
<tr>
<td>Cutaneous reactions</td>
<td>Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have occurred.</td>
<td>Serious/fatal cutaneous reactions: 5% Drug reaction with eosinophilia and systemic</td>
</tr>
<tr>
<td></td>
<td>Do not rechallenge if SJS or TEN occurs</td>
<td>symptoms (DRESS) and TEN have occurred</td>
</tr>
<tr>
<td>Intestinal perforation</td>
<td>Rare occurrence, not always in the setting of diarrhea/colitis Do not rechallenge</td>
<td>Not listed as a warning</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>Rare occurrence</td>
<td>Not listed as a warning</td>
</tr>
<tr>
<td>Embryo-fetal toxicity</td>
<td>May cause fetal harm. Avoid pregnancy while taking; use effective contraception</td>
<td>Can cause fetal harm when administered; conduct pregnancy testing before initiating</td>
</tr>
<tr>
<td></td>
<td>during and at least 1 month after treatment</td>
<td>treatment. Advise females, and males with female partners of reproductive potential,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>to use effective contraception during treatment and for at least 1 month after the</td>
</tr>
<tr>
<td></td>
<td></td>
<td>last dose</td>
</tr>
</tbody>
</table>

ANC, absolute neutrophil count; CMV, cytomegalovirus.


---

# PI3K Inhibitors – Other Common Side Effects

**Non-lab events occurring in ≥20% of patients in idelalisib (Zydelig®) clinical trials**
- Rash
- Pneumonia
- Fatigue
- Pyrexia
- Cough
- Diarrhea
- Nausea
- Advise patients about the possibility of lymphocytosis after initiating treatment
  - Occurs within the first month of therapy and can persist for several weeks. Not progression!

**Non-lab events occurring in ≥20% of patients in duvelisib (Copiktra®) clinical trials**
- Fatigue
- Pyrexia
- Upper respiratory tract infection
- Diarrhea
- Nausea
- Rash
- Pneumonia
- Cough

### Additional Patient Support

#### Infection Monitoring and Prophylaxis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Newly Diagnosed CLL</th>
<th>Relapsed/Refractory CLL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibrutinib (Imbruvica&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>HSV, HBV*</td>
<td>HSV, HBV*</td>
</tr>
<tr>
<td>Acalabrutinib (Calquence&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>---</td>
<td>HSV, HBV*</td>
</tr>
<tr>
<td>Venetoclax (Venclexta&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>HSV</td>
<td>HSV</td>
</tr>
<tr>
<td>Idelalisib (Zydelig&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>---</td>
<td>HSV, PJP, HBV*, CMV**</td>
</tr>
<tr>
<td>Duvelisib (Copiktra&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>---</td>
<td>HSV, PJP, HBV*, CMV**</td>
</tr>
<tr>
<td>CD20 monoclonal antibodies</td>
<td>HBV*</td>
<td>HBV*</td>
</tr>
<tr>
<td>Chemoimmunotherapy</td>
<td>HSV, PJP, HBV*, CMV**# Consider bacterial/fungal during periods of neutropenia</td>
<td>HSV, PJP, HBV*, CMV**# Consider bacterial/fungal during periods of neutropenia</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>---</td>
<td>HSV/VZV, PJP, HBV*, CMV** Consider fungal</td>
</tr>
</tbody>
</table>

*Patients should be screened for hepatitis and those patients HBsAg positive should receive prophylaxis

**Monitor for CMV reactivation weekly using quantitative PCR while on therapy and for a period of time after.

#Fludarabine-based chemoimmunotherapy.

CMV, cytomegalovirus; HSV, herpes simplex virus; HBV, hepatitis B virus; PJP, Pneumocystis jirovecii pneumonia; VZV, varicella zoster virus

Medication Access

• Oral agents present unique challenges with regard to patient access to the medication
  • Most patients will not be able to start a new therapy on the day the prescription is written
  • Challenges in scheduling concomitant IV medication if combination therapy planned
• Prescriptions may require prior authorization, which can delay the start of therapy
• Covered prescriptions may still have high copays that necessitate applications to programs/foundations for financial assistance
• Patients without prescription coverage must rely on manufacturer’s assistance programs to acquire free drug
• Many members of the healthcare team may need to assist the patient in obtaining access to the medication

Medication Adherence

• The transition to oral therapies as the backbone of CLL therapy has highlighted the importance of monitoring patient adherence to therapy
  • Therapy is continuous with no defined end point
• Data in other disease states as well as CLL demonstrate the importance of adherence on outcomes
• A retrospective analysis of patients receiving Ibrutinib on the RESONATE study evaluated the effect of dose intensity on CLL outcomes
  • Patients that maintained high dose intensity with ibrutinib therapy had improved PFS
  • Treatment interruptions of greater than 7 days were associated with increased PFS events
• Members of the healthcare team should assess patient’s adherence to therapy at each visit at a minimum
  • More frequent assessments may be necessary at therapy initiation and when managing toxicities

Oral CLL Therapies – Patient Counseling Points

• When initiating therapy, encourage patients to reach out for any barriers acquiring the medication
• Stress adherence to prescribed dose, taking at the same time(s) each day
• Educate patients on the common or serious side effects
• Remind patients to report any changes to medical problems and concomitant medications to healthcare teams

Nursing Considerations in CLL

JACKIE BROADWAY-DUREN, DNP, APRN, FNP-BC
Who Are Oncology Nurses?

Registered nurses (RNs) have varied levels of educational preparation

- Associate degree
- Bachelor’s degree
- Doctorate degrees
- DNP/PhD
- Many oncology nurses are oncology certified (OCN)
- Have specialized training applicable to area of specialty

Rationale for Nurses in CLL

- Nurses are vital to oncology patient care
- Deliver high-quality clinical services
- Contribute to improved patient outcomes
- Serve in multifaceted roles in CLL patient care

Nursing Roles in CLL Patient Care

Patient Care

Advocate

Oncology Nurse Roles

Educator

Research Study Coordinators

Interprofessional Team Member

As a member of the interprofessional team, nurses:

- Triage patients based on symptoms
- Assist in patient education for oral therapies
- Assist in coordinating treatment schedules and patient appointments
- Administer IV infusions (i.e., antibody therapy)
- Collaborate with physicians, APPs, pharmacists, social work, and patient advocates in coordinating patient care
Role of the RN in Patient Care

- Review medications during each clinic visit
- Provide initial review of systems with each clinic visit
- Administer outpatient injections (vaccine) and monitor patients for side effects
- Perform bedside nursing for hospitalized patients (Richter’s)
- Work with multidisciplinary teams to ensure patient needs are met

Nurse Educator Role in CLL

- RNs provide pertinent patient education
- RNs provide written drug side effect information
- Instruct patients on oral drug adherence and assist in patient follow-up
- APRNs educate patients with specific disease-related information and mechanism of action of various therapies (e.g., MAB, BTK inhibitors)
Patient Advocacy in CLL

- Transitional care – collaborate with patient’s community providers
- Facilitate prior authorizations
- Collaborate with specialty pharmacies to ensure patient medications are delivered on time
- Care coordination is an integral component of the oncology nurse’s job
- Assist with communication among patients, family members, and other disciplines
- Prepare patients and caregivers on expectations for clinic and treatments

Research Nurse Role in CLL

- Collaborate with the interprofessional team members to determine best treatment recommendations
- Research nurses (RNs) educate patients regarding research protocols, specific drug information, and study requirements
- Register patients for research protocols
- Obtain consent for research studies
- Monitor adverse events of therapy and report to PI, attending physician/APP
- Collaborate with pharmaceutical and FDA sponsors of research studies and report adverse events using grading scales
Advanced Practice Nurses (APRNs) in CLL

- APRNs perform physical examinations, order and interpret laboratory and radiologic diagnostic tests, and order blood products and growth factors as indicated
- APRNs consent patients for treatments for off-protocol therapy
- Collaborate with physicians and pharmacists regarding appropriate treatments
- APRNs assist in managing adverse drug effects (AEs) by:
  - Monitoring lab data with intervention as indicated (TLS)
  - Prescribe appropriate medications or needed intervention to manage AEs

Integration of Interprofessional Roles

- New patient presents to clinic with new diagnosis of B CLL
- The RN is the first point of contact upon patient entering clinic
- The RN does initial review of systems (ROS), reviews and updates medications
- The RN hands the patient off to the APRN or PA (APP)
- The APRN assesses the patient, including past medical history, past cancer therapies, performs H&P and medication review, and orders appropriate tests
- The attending physician is then given a report on the patient, and further evaluation and decisions are made with team input
RESOURCES FOR YOU & YOUR PATIENTS

FROM THE LEUKEMIA & LYMPHOMA SOCIETY (LLS)

WWW.LLS.ORG

LLS RESOURCES FOR HEALTHCARE PROFESSIONALS

Online and in-person CE/CME webinars, symposia & rounds
Free CME & CE  www.LLS.org/CE

Podcast series for healthcare professionals
Conversations with experts about diagnosing & treating blood cancers  www.LLS.org/HCPpodcast

HCP palm card – User friendly links to resources for you & your patients
www.LLS.org/CE
LLS RESOURCES FOR PATIENTS AND CAREGIVERS

- **Information Specialists** – disease information, emotional support, financial, travel & co-pay assistance, support through local LLS patient access staff. Also send free materials to patients & HCPs

- **Nutrition Consultations** – One-on-one consultations from certified dietitian

  Specialists can serve as a resource for your HCP team
  M - F, 9 am to 9 pm ET:
  - Phone: (800) 955-4572
  - Live chat: [www.LLS.org/InformationSpecialists](http://www.LLS.org/InformationSpecialists)
  - Email: [infocenter@LLS.org](mailto:infocenter@LLS.org)

- **Additional support for patients & caregivers** – [www.LLS.org/Support](http://www.LLS.org/Support)

- **Booklets on disease, treatment, & support** - [www.LLS.org/Booklets](http://www.LLS.org/Booklets)

- **Webinars, videos, in-person programs** - [www.LLS.org/Programs](http://www.LLS.org/Programs) & [www.LLS.org/Educationvideos](http://www.LLS.org/Educationvideos)

CLINICAL TRIAL NURSE NAVIGATORS

Help patients find and enroll in clinical trials based on highly detailed individualized assessments

[www.LLS.org/Navigation](http://www.LLS.org/Navigation)

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patients provided with in-depth clinical trial navigation and support in past year
We have one goal: A world without blood cancers

Appendix
Rai and Binet Staging Systems and CLL International Prognostic Index

Table 3A. Rai Staging System

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk (Stage 0)</td>
<td>Abnormal increase in the number of lymphocytes in the circulating blood and marrow</td>
</tr>
<tr>
<td>Intermediate Risk (Stages I &amp; II)</td>
<td>- Abnormal increase in the number of lymphocytes in the circulating blood and marrow&lt;br&gt;- Enlarged lymph nodes&lt;br&gt;- Abnormal increase in the number of lymphocytes in the circulating blood and marrow&lt;br&gt;- Enlarged spleen and/or liver</td>
</tr>
<tr>
<td>High Risk (Stages III &amp; IV)</td>
<td>- Abnormal increase in the number of lymphocytes in the circulating blood and marrow&lt;br&gt;- Anemia (hemoglobin &lt; 11 g/dL)&lt;br&gt;- Abnormal increase in the number of lymphocytes in the circulating blood and marrow&lt;br&gt;- Thrombocytopenia (platelet counts &lt; 100,000/μL)</td>
</tr>
</tbody>
</table>

Table 3B. Binet Staging System

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>- No anemia (hemoglobin &gt; 10 g/dL)&lt;br&gt;- No thrombocytopenia (platelets &gt; 100,000/μL)&lt;br&gt;- Less than 3 areas of lymphoid tissue enlargement</td>
</tr>
<tr>
<td>B</td>
<td>- No anemia (hemoglobin ≥ 10 g/dL)&lt;br&gt;- No thrombocytopenia (platelets ≥ 100,000/μL)&lt;br&gt;- 3 or more areas of lymphoid tissue enlargement</td>
</tr>
<tr>
<td>C</td>
<td>- Anemia (hemoglobin &lt; 10 g/dL)&lt;br&gt;- Thrombocytopenia (platelets &lt; 100,000/μL)&lt;br&gt;- Any number of areas of lymphoid tissue enlargement</td>
</tr>
</tbody>
</table>

Chronic Lymphocytic Leukemia Booklet, The Leukemia & Lymphoma Society- LLS.org