The Evolving Role of BTKi’s in CLL

June 28, 2022

10 AM PT, 11 AM MT
12 PM CT, 1 PM ET
This program was made possible by grant support from

AstraZeneca  BeiGene

Janssen  pharmacyclics®
Speakers

Matthew S. Davids, MD, MMSc
Associate Director, Center for Chronic Lymphocytic Leukemia
Dana Farber Cancer Institute

Moderator
Brian Koffman, MDCM (retired) MS Ed
Executive Vice President and Chief Medical Officer
CLL Society

Welcome
Robyn Brumble, MSN, RN
Director of Scientific Affairs and Research
CLL Society
The Evolving Role of BTKi’s in CLL

Matthew S. Davids, MD, MMSc
Associate Director, CLL Center
Dana-Farber Cancer Institute
Boston, MA

June 28, 2022
Disclosures
Matthew S. Davids, MD, MMSc

I have the following financial relationships to disclose

• **SAB/Consultant/Honoraria:** AbbVie, BMS, Genentech, Janssen, TG Therapeutics, Celgene, AstraZeneca, Eli Lilly, Adaptive Biosciences, BeiGene, Merck, Ascentage Pharma, Research to Practice, Takeda

• **Institutional Research Funding:** Genentech, Pharmacyclics, TG Therapeutics, BMS, MEI Pharma, Surface Oncology, AstraZeneca, Ascentage Pharma, Novartis
Learning Objectives

- What are BTK inhibitors?
- What is their role in CLL therapy today?
- How do they compare with each other and other treatment options?
- What roles might they play in the future?
Introduction
We Now Have a Diverse Array of Mechanistically Diverse Targeted Therapies for CLL Treatment

- Venetoclax
- Idelalisib
- Duvelisib
- Ibrutinib
- Acalabrutinib
- Zanubrutinib*

• Adapted from Davids & Brown. Leuk Lymphoma. 2012
Milestones in Clinical CLL Research

1950 - Glucocorticoids and alkylating agents introduced

1960 - Fluorouracil and cyclophosphamide introduced

1970 - Nucleoside analogs (Fludarabine) introduced

1980 - Rai and Binet staging

1990 - FCR regimen introduces high CR rates

2000 - Progression-free survival benefit from anti-CD20 mAb obinutuzumab plus chlorambucil vs. rituximab plus chlorambucil or chlorambucil alone

2010 - SYK inhibitor fostamatinib active in CLL

2011 - BTK inhibitor ibrutinib active in refractory, high-risk CLL

2012 - PI3Kδ inhibitor idelalisib active in refractory, high-risk CLL

2013 - Progression-free survival and overall survival benefit from ibrutinib vs. chlorambucil in untreated CLL

2014 - Progression-free survival benefit from venetoclax plus rituximab vs. BR in RR CLL

2015 - Better progression-free survival with ibrutinib with or without rituximab vs. BR in untreated CLL

2016 - Progression-free survival and overall survival benefit from ibritinib plus rituximab vs. FCR in untreated CLL

2017 - Venetoclax plus ibrutinib induces high rates of CR in untreated CLL

2018 - Progression-free benefit from venetoclax plus obinutuzumab vs. chlorambucil plus obinutuzumab in untreated CLL

2019 - BCL2 antagonist venetoclax and second generation BTKi acalabrutinib active in refractory, high-risk CLL

Burger, NEJM, 2020
Frontline BTKi vs Venetoclax + Obinutuzumab: Factors to Consider
Frontline BTKi vs Venetoclax + Obinutuzumab: Factors to Consider

- Convenience (no infusions, TLS monitoring)
- Long-term efficacy data
- Phase III data compared with FCR and BR
- More data for efficacy of Ven at time of ibrutinib progression
Frontline BTKi vs Venetoclax + Obinutuzumab: Factors to Consider

- Convenience (no infusions, TLS monitoring)
- Long-term efficacy data
- Phase III data compared with FCR and BR
- More data for efficacy of Ven at time of ibrutinib progression
- 1-year time-limited therapy
- No known cardiac or bleeding risks
- Less concern for long-term adherence
- Cost-saving
BTK Inhibitors
Mechanism of Action

• Acalabrutinib, Ibrutinib, Zanubrutinib: Form a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity.

• Pirtobrutinib, Nemtabrutinib: 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;17(4):223-233.*
Second Generation BTK Inhibitors Exhibit Differences in Kinase Selectivity

The size of the red circle is proportional to the degree of inhibition.

This make explain the different “off target” effects.


*Not yet FDA approved for the treatment of CLL
# Summary of FDA-Approved BTK Inhibitors

<table>
<thead>
<tr>
<th>FDA-approved indications</th>
<th>Ibrutinib</th>
<th>Acalabrutinib</th>
<th>Zanubrutinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>• CLL (monotherapy or w/ obinutuzumab or rituximab)</td>
<td>• CLL/SLL (monotherapy or with obinutuzumab)</td>
<td>• R/R MCL</td>
<td></td>
</tr>
<tr>
<td>• R/R MCL</td>
<td>• R/R MCL (monotherapy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• WM</td>
<td>•</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• MZL (after ≥ 1 anti-CD20-based therapy)</td>
<td>•</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• cGVHD</td>
<td>•</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Method of administration

<table>
<thead>
<tr>
<th>Ibrutinib</th>
<th>Acalabrutinib</th>
<th>Zanubrutinib</th>
</tr>
</thead>
<tbody>
<tr>
<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>• MCL and MZL: 560 mg taken orally once daily</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Key toxicities

<table>
<thead>
<tr>
<th>Ibrutinib</th>
<th>Acalabrutinib</th>
<th>Zanubrutinib</th>
</tr>
</thead>
<tbody>
<tr>
<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>
</tbody>
</table>

How Effective are BTKi’s?
8-Year Follow-up of Ibrutinib Monotherapy:
High Rates of OS, ORR and Long-term Tolerability in first-line CLL

PFS (Progression Free Survival)

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

OS (Overall Survival)

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

What Is the Benefit of Adding Anti-CD20 Antibodies to BTK Inhibitors?

<table>
<thead>
<tr>
<th>Trial</th>
<th>ORR (Overall Response Rate)</th>
<th>PFS</th>
</tr>
</thead>
</table>
| Ibrutinib vs ibrutinib + rituximab<sup>1</sup>  
MD Anderson R/R or 1L high risk | 92% vs 92% | 86% vs 86.9% |
| Ibrutinib vs ibrutinib + rituximab<sup>2</sup>  
Alliance Study 1L CLL | 93% vs 94% | NR vs NR |
| Acalabrutinib vs acalabrutinib + obinutuzumab<sup>3</sup>  
ELEVATE-TN | 85% vs 94% | 82% vs 90% (30-mo PFS) |

1L, first line; BTK, Bruton tyrosine kinase; ORR, overall response rate; PFS, progression-free survival; R/R, relapsed/refractory.

4-Year Follow-Up of ELEVATE-TN
Acalabrutinib ± Obinutuzumab vs Obinutuzumab + Chlorambucil in TN (Treatment Naïve) CLL

**Investigator-Assessed PFS**

- **Overall**
  - A+O: 87%
  - A: 78%
  - O+Clb: 25%
  - mPFS = NR

**Overall Survival**

- **A+O**: 93%
- **A**: 88%
- **O+Clb**: 88%
- **mOS = NR**

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>A+O vs O+Clb</td>
<td>0.10 (0.07, 0.17)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>A vs O+Clb</td>
<td>0.19 (0.13, 0.28)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>A+O vs A</td>
<td>0.56 (0.32, 0.95)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>A+O vs O+Clb</td>
<td>0.50 (0.25, 1.02)</td>
<td>0.0604</td>
</tr>
<tr>
<td>A vs O+Clb</td>
<td>0.95 (0.52, 1.74)</td>
<td>0.9164</td>
</tr>
</tbody>
</table>

Acalabrutinib + Obinutuzumab (A+O), Acalabrutinib Monotherapy (A), Obinutuzumab + Chlorambucil (O+Clb)

SEQUOIA (BGB-3111-304)
Arm A & B: Zanubrutinib vs Bendamustine + Rituximab in TN CLL

Progression-Free Survival per IRC Assessment

**Zanubrutinib, unmutated IGHV** vs **BR, unmutated IGHV**
HR, 0.24 (95% CI, 0.13–0.43); \( P < 0.001 \)

**Zanubrutinib, mutated IGHV** vs **BR, mutated IGHV**
HR, 0.67 (95% CI, 0.36–1.22); 2-sided \( P = 0.186 \)

---

BR, bendamustine + rituximab; IRC, independent review committee; PFS, progression-free survival.
ELEVATE-RR Trial: Ibrutinib vs Acalabrutinib in Patients With High-Risk R/R (Relapsed/Refractory) CLL

- Ongoing phase 3, randomized, multicenter, open-label, noninferiority trial
- Patients with del(17p) or del(11q) CLL with active disease (N=533)
- ≥1 previous line of treatment
- ECOG PS 0-2

Primary endpoint: PFS

Secondary endpoints: OS, incidence of treatment-emergent AEs, atrial fibrillation, Richter transformation

Status: Active, not recruiting

AE, adverse event; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; OS, overall survival; PD, progressive disease; PFS, progression-free survival; R/R, relapsed/refractory

Clinicaltrials.gov. NCT02477696.
ELEVATE-RR Trial: Ibrutinib vs Acalabrutinib in Patients With High-Risk R/R CLL


CLL, chronic lymphocytic leukemia; PFS, progression-free survival; R/R, relapsed/refractory.

ELEVATE-RR: AEs (Adverse Events) of Clinical Interest

- Most common grade ≥3 infections: pneumonia (acalabrutinib vs ibrutinib, 10.5% vs 8.7%), sepsis (1.5% vs 2.7%), and urinary tract infections (1.1% vs 2.3%)

<table>
<thead>
<tr>
<th>AE, n (%)</th>
<th>Acalabrutinib (n=266)</th>
<th>Ibrutinib (n=263)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>Cardiac events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Atrial fibrillation/flutter</td>
<td>25 (9.4)</td>
<td>13 (4.9)</td>
</tr>
<tr>
<td>• Ventricular arrhythmias</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bleeding events</td>
<td>101 (38.0)</td>
<td>10 (3.8)</td>
</tr>
<tr>
<td>• Major bleeding events</td>
<td>12 (4.5)</td>
<td>10 (3.8)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>25 (9.4)</td>
<td>11 (4.1)</td>
</tr>
<tr>
<td>Infections</td>
<td>208 (78.2)</td>
<td>82 (30.8)</td>
</tr>
<tr>
<td>ILD/pneumonitis</td>
<td>7 (2.6)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>SPMs, excluding NMSC</td>
<td>24 (9.0)</td>
<td>16 (6.0)</td>
</tr>
</tbody>
</table>

AE, adverse event; ILD, interstitial lung disease; NMSC, nonmelanoma skin cancer; SPMs, second primary malignancies.

*Bolded numbers statistically significantly higher vs the comparator (P<0.05).

ALPINE Trial: Zanubrutinib vs Ibrutinib in R/R CLL/SLL

- Ongoing, phase 3, randomized, global, open-label trial
- Adults with CLL/SLL relapsed or refractory to ≥1 prior systemic therapy (planned: 600)
- ECOG PS 0-2
- Life expectancy ≥6 mo

Primary endpoint: ORR (up to 36 mo)
Secondary endpoints: PFS, DoR, OS, TTF, safety

Zanubrutinib

Ibrutinib

Status: Active, not recruiting

CLL, chronic lymphocytic leukemia; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group performance status; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; TTF, time-to-treatment failure.

Clinicaltrials.gov. NCT03734016.
ALPINE Trial: Zanubrutinib vs Ibrutinib in R/R CLL/SLL

<table>
<thead>
<tr>
<th>ORR</th>
<th>Zanubrutinib</th>
<th>Ibrutinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>78.3%</td>
<td>62.5%</td>
</tr>
<tr>
<td>del(11q)</td>
<td>83.6%</td>
<td>69.1%</td>
</tr>
<tr>
<td>del(17p)</td>
<td>83.3%</td>
<td>53.8%</td>
</tr>
</tbody>
</table>

PFS by Investigator Assessment

**PFS by Investigator Assessment**

**12-Mo PFS Rate, %**
- Zanubrutinib: 94.9%
- Ibrutinib: 84.0%

**HR (95% CI)**
- Zanubrutinib: 0.40 (0.23–0.69)
- Ibrutinib: 2-sided P = .0007

*Comparison is not from a prespecified analysis. Formal PFS analysis to be performed on all patients once target number of events attained.

CLL, chronic lymphocytic leukemia; KM, Kaplan-Meier; ORR, overall response rate; PFS, progression-free survival; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma.

ALPINE Trial: Zanubrutinib vs Ibrutinib in R/R CLL/SLL

- Cardiac disorders leading to treatment discontinuation: zanubrutinib, n=0; ibrutinib, n=7 (3.4%)

<table>
<thead>
<tr>
<th>AE of Special Interest in Safety Analysis Population, n (%)</th>
<th>Zanubrutinib (n=204)</th>
<th>Ibrutinib (n=207)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>28 (13.7)</td>
<td>5 (2.5)</td>
</tr>
<tr>
<td>Atrial fibrillation and flutter</td>
<td>5 (2.5)</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Major hemorrhagea</td>
<td>73 (35.8)</td>
<td>6 (2.9)</td>
</tr>
<tr>
<td></td>
<td>6 (2.9)</td>
<td>6 (2.9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>34 (16.7)</td>
<td>22 (10.8)</td>
</tr>
<tr>
<td>Infections</td>
<td>122 (59.8)</td>
<td>26 (12.7)</td>
</tr>
<tr>
<td>Neutropenia (low neutrophils)</td>
<td>58 (28.4)</td>
<td>38 (18.6)</td>
</tr>
<tr>
<td>Thrombocytopenia (low platelets)</td>
<td>19 (9.3)</td>
<td>7 (3.4)</td>
</tr>
<tr>
<td>Secondary primary malignancies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Skin cancers</td>
<td>17 (8.3)</td>
<td>10 (4.9)</td>
</tr>
<tr>
<td></td>
<td>7 (3.4)</td>
<td>3 (1.5)</td>
</tr>
</tbody>
</table>

AE, adverse event; CLL, chronic lymphocytic leukemia; CNS, central nervous system; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma.

* Includes serious or grade ≥3 hemorrhage or any-grade CNS hemorrhage.
<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Study Design</th>
<th>Population</th>
<th>Estimated Enrollment</th>
<th>Treatment Arms</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK FLAIR Trial</td>
<td>Phase 3, randomized</td>
<td>Newly diagnosed, aged 18-75 years</td>
<td>1516</td>
<td>Ibrutinib vs ibrutinib + rituximab vs ibrutinib + venetoclax vs FCR</td>
</tr>
<tr>
<td>CLL13 (NCT02950051)</td>
<td>Phase 3, randomized</td>
<td>Newly diagnosed</td>
<td>926</td>
<td>FCR or BR vs venetoclax + rituximab vs venetoclax + obinutuzumab vs venetoclax + ibrutinib + obinutuzumab + venetoclax</td>
</tr>
<tr>
<td>EA9161 (NCT03701282)</td>
<td>Phase 3, randomized, open label</td>
<td>Aged 18-69 years</td>
<td>720</td>
<td>Ibrutinib + obinutuzumab vs ibrutinib + obinutuzumab + venetoclax</td>
</tr>
<tr>
<td>A041702 (NCT03737981)</td>
<td>Phase 3, randomized, open label</td>
<td>Untreated, aged ≥70 years</td>
<td>454</td>
<td>Ibrutinib + obinutuzumab vs ibrutinib + obinutuzumab + venetoclax</td>
</tr>
<tr>
<td>CLL17</td>
<td>Phase 3, randomized</td>
<td>Newly diagnosed, aged ≥18 years</td>
<td>897</td>
<td>Ibrutinib vs ibrutinib + venetoclax vs obinutuzumab + venetoclax</td>
</tr>
<tr>
<td>ACE-CL-311 (NCT03836261)</td>
<td>Phase 3, randomized, global, open label</td>
<td>Aged ≥18 years</td>
<td>780</td>
<td>Acalabrutinib + venetoclax vs acaclabrutinib + venetoclax + obinutuzumab vs standard chemotherapy</td>
</tr>
<tr>
<td>MAJIC</td>
<td>Phase 3, randomized, global, open label</td>
<td>Newly diagnosed, aged ≥18 years</td>
<td>600</td>
<td>MRD-guided acalabrutinib + venetoclax vs MRD-guided venetoclax + obinutuzumab</td>
</tr>
</tbody>
</table>

BR, bendamustine/rituximab; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; FCR, fludarabine, cyclophosphamide, and rituximab; MRD, minimal residual disease. Reference: ClinicalTrials.gov.
Pirtobrutinib (LOXO-305): Selective Noncovalent BTK Inhibitor

- BTK C481 mutations are the principal reason for progressive CLL after treatment with covalent BTK inhibitors
- BTK C481 mutations impair target inhibition by covalent BTK inhibitors
- BTK C481 is where the covalent (irreversible) BTKi bind

Acquired Resistance to Ibrutinib in Patients With Progressive CLL

- 56% BTK mutants
- 16% BTK & PLCG2 mutants
- 8% PLCG2 mutants
- 20% BTK & PLCG2 not identified

BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; PLCG2, phospholipase C gamma 2.

Pirtobrutinib Efficacy in BTK Pre-treated CLL/SLL Patients

Data cutoff date of 16 July 2021. *Patients with >100% increase in SPD. Data for 30 patients are not shown in the waterfall plot due to no measurable target lesions identified by CT at baseline, discontinuation prior to first response assessment, or lack of adequate imaging in follow-up. aEfficacy evaluable patients are those who had at least one post-baseline response assessment or had discontinued treatment prior to first post-baseline response assessment. bORR includes patients with a best response of CR, PR, and PR-L. Response status per iwCLL 2018 according to investigator assessment. Total % may be different than the sum of the individual components due to rounding.

**Efficacy evaluable BTK pre-treated CLL/SLL Patients**

<table>
<thead>
<tr>
<th></th>
<th>n = 252</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response Rate, % (95% CI)</td>
<td>68 (62 – 74)</td>
</tr>
<tr>
<td><strong>Best response</strong></td>
<td></td>
</tr>
<tr>
<td>CR, n (%)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>PR, n (%)</td>
<td>137 (54)</td>
</tr>
<tr>
<td>PR-L, n (%)</td>
<td>32 (13)</td>
</tr>
<tr>
<td>SD, n (%)</td>
<td>62 (25)</td>
</tr>
</tbody>
</table>

BCL2, B-cell lymphoma-2; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CR, complete response; CT, computed tomography; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; ORR, overall response rate; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease; SLL, small lymphocytic lymphoma; SPD, sum of the products of lymph node diameters.

BRUIN: Safety

All doses and patients (n=618)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Any Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>13%</td>
<td>8%</td>
<td>1%</td>
<td>-</td>
<td>23%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15%</td>
<td>4%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>19%</td>
</tr>
<tr>
<td>Neutropeniaa</td>
<td>1%</td>
<td>2%</td>
<td>8%</td>
<td>6%</td>
<td>18%</td>
</tr>
<tr>
<td>Contusion</td>
<td>15%</td>
<td>2%</td>
<td>-</td>
<td>-</td>
<td>17%</td>
</tr>
</tbody>
</table>

AEs of special interestb

| Bruisingc                    | 20%     | 2%      | -       | -       | 22%       |
| Rashd                        | 9%      | 2%      | <1%     | -       | 11%       |
| Arthralgia                   | 8%      | 3%      | <1%     | -       | 11%       |
| Hemorrhagee                  | 5%      | 2%      | 1%      | -       | 8%        |
| Hypertension                 | 1%      | 4%      | 2%      | -       | 7%        |
| Atrial fibrillation/flutterf | -       | 1%      | <1%     | <1%     | 2%h       |

Data cutoff date of 16 July 2021. Total % may be different than the sum of the individual components due to rounding. aAggregate of neutropenia and neutrophil count decreased. bAEs of special interest are those that were previously associated with covalent BTK inhibitors. cAggregate of contusion, petechiae, ecchymosis, and increased tendency to bruise. dAggregate of all preferred terms including rash. eAggregate of all preferred terms including hematoma or hemorrhage. fAggregate of atrial fibrillation and atrial flutter. gRepresents 6 events (all grade 3), including 2 cases of post-operative bleeding, 1 case each of GI hemorrhage in the setting of sepsis, NSAID use, chronic peptic ulcer disease, and one case of subarachnoid hemorrhage in setting of traumatic bike accident. hOf 10 total afib/aflutter TEAEs, 3 occurred in patients with a prior medical history of atrial fibrillation, 2 in patients presenting with concurrent systemic infection, and 2 in patients with both.

96% of patients received ≥ 1 pirtobrutinib dose at or above RP2D of 200 mg daily

1% (n=6) of patients permanently discontinued due to treatment-related AEs

No DLTs reported and MTD not reached

96% of patients received ≥1 pirtobrutinib dose at or above RP2D of 200 mg daily

1% (n=6) of patients permanently discontinued due to treatment-related AEs

AE, adverse event; BTK, Bruton tyrosine kinase; DLT; dose-limiting toxicities; GI, gastrointestinal; MTD, maximum tolerated dose; NSAID, nonsteroidal anti-inflammatory drug; RP2D, recommended phase 2 dose; TEAE; treatment-emergent adverse event.

What kind of side effects are seen with BTKi’s?
CLL12: CLL Patients Commonly Have Symptoms and Complications

<table>
<thead>
<tr>
<th></th>
<th>Ibrutinib n=158</th>
<th>Placebo n=155</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any grade AEs (%)</strong></td>
<td>150 (94.9)</td>
<td>148 (95.5)</td>
</tr>
<tr>
<td><strong>AEs ≥ grade 3 (%)</strong></td>
<td>80 (50.6)</td>
<td>67 (43.2)</td>
</tr>
<tr>
<td><strong>AEs leading to interruption (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Bleeding</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Neoplasia (cancer)</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Infection</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>39</td>
<td>24</td>
</tr>
</tbody>
</table>

Langerbeins et al., *iwCLL*, 2019
Recent US Cooperative Group Studies Suggest Gr 3/4 Ibrutinib Toxicities May Be Less in Younger Patients

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>IR Arm Alliance n=181</th>
<th>IR Arm E1912 N=352</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age</td>
<td>71 yrs</td>
<td>57 yrs</td>
</tr>
<tr>
<td>Age range</td>
<td>65 – 86</td>
<td>31 - 70</td>
</tr>
<tr>
<td>Infection</td>
<td>19%</td>
<td>5%</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>Bleeding</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>34%</td>
<td>7%</td>
</tr>
<tr>
<td>Deaths during active treatment +30 days</td>
<td>7%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Adapted from Shanafelt et al., ASH, 2018
BTKi: Side Effect Management

- Higher bleeding risk with lack of data with platelets < 30K
  - Hold for procedures
    - General guideline: Cataracts (1/1), Colonoscopy (3/3), Cholecystectomy (7/7)
    - Consider platelet transfusion for emergent surgery

- Cardiac disease
  - Difficult to control hypertension
  - Atrial fibrillation

- Active infection
  - Usually hold drug to control infection

- Active autoimmunity can flare before achieving longer term control
BTKi: What to Watch Out For

- Anticoagulants: Avoid if possible. If necessary, use DOACs (Direct oral anticoagulants) instead of warfarin (Coumadin)

- Avoid dual antiplatelet therapy

- Strong/moderate CYP3A inhibitors (i.e. grapefruit, erythromycin, verapamil, goldenseal): Generally avoid, but can reduce dose if needed
• In the setting of active infection it is generally best to hold drug at least until seeing signs of clinical improvement

• For most toxicities requiring drug hold, it is preferable to either rechallenge with full dose or to start back at dose reduction but then get back to full dose

• In general, I am more hesitant to hold drug soon after starting a BTKi or in a patient who is progressing on a novel agent

• I am less concerned about stopping drug in patients who have been on BTKi for at least a few months and are in a good clinical response
General Considerations

• BTKi are infrequently the cause of cytopenias (low blood counts)

• It is generally safe to give growth factor support concomitantly with novel agents

• Patients who have to permanently discontinue a novel agent due to toxicity do not necessarily need to immediately start on a new therapy
General Considerations

Optimizing Adherence to Oral Therapy

• Shared responsibility between clinician and patient\(^1\)
  • Prescriptions will be filled
  • Patient will administer correct dosage at correct time of day
  • Patient will alert clinician of AEs

• Effect of ibrutinib dose adherence on patients’ outcomes evaluated in the RESONATE trial\(^2\)
  • Patients missing ≥8 consecutive days had shorter median PFS
  • Patients with higher DI (dose intensity) demonstrated improved PFS, higher ORR, and trend toward improved OS

AE, adverse event; DI, dose intensity; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Key Takeaways on BTKi Therapy in CLL in 2022

• BTK inhibitors are now a mainstay of therapy in CLL

• Up to 20% of patients discontinue ibrutinib due to side effects

• Next-generation BTKi have similar efficacy as ibrutinib

• These newer agents are associated with reduction in cardiovascular complications (especially afib) and also other side effects

• Reversible BTK inhibitors in development may help overcome resistance mutations

• BTKi have some common side effects but these are manageable for most patients

• With the rapid evolution in this field, active participation in clinical trials remains critical
This program was made possible by grant support from

AstraZeneca  
BeiGene  
Janssen  
pharmacyclics®
Thank You for Attending!

Please take a moment to complete our post-event survey, your feedback is important to us.

If you’re question was not answered, please feel free to email asktheexpert@cllsociety.org.

Join us on July 7th for our new Facebook Live event, July 23rd for our inaugural, virtual 5K Walk/Run event, and August 2nd for our webinar on CAR-T Therapy.

CLL Society is invested in your long life. Please invest in the long life of the CLL Society by supporting our work.

cllsociety.org/donate-to-cll-society/