
# Optimal Management of Adverse Events (AEs) with BTK and Bcl-2 Inhibitors

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# Treatment Evolution for CLL

**1960s**

Alkylating agents
- Chlorambucil
- Cyclophosphamide

**1970s**

Purine nucleosides
- Fludarabine
- Pentostatin
- Cladribine

**1980s**

**1990s**

Purine nucleosides and alkylators

**2000s**

Chemoimmunotherapy (FCR, BR)
Alemtuzumab
Lenalidomide

**2014-**

BTK inhibitors (Ibrutinib, Acalabrutinib)
PI3K inhibitors (Idelalisib, Duvelisib)
BCL-2 inhibitor (Venetoclax)
Novel CD20 mAb (Obinutuzumab)

**2021+**

BTK inhibitors (Zanubrutinib, Pirtobrutinib)
PI3K inhibitor (Umbralisib)
CAR-T

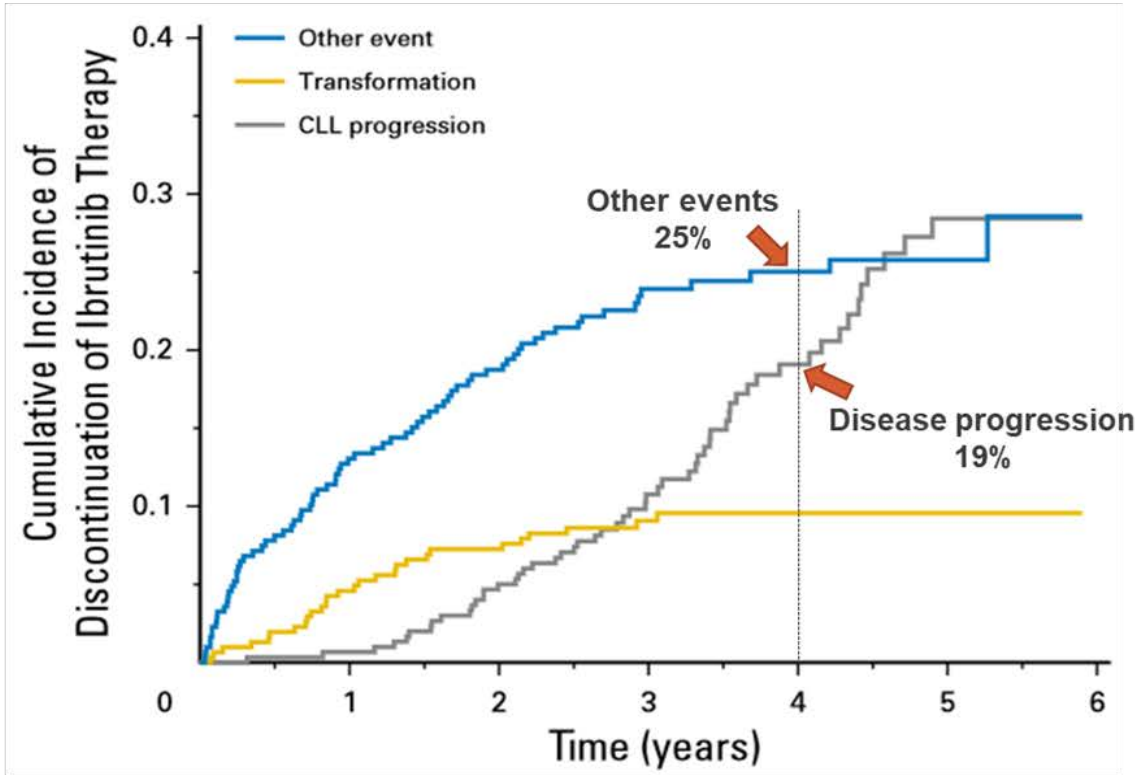
# Pros and Cons of Approved Treatment Approaches in Firstline CLL

| Ibrutinib | Acalabrutinib | Venetoclax + Obinutuzumab |
|---|---|---|
| • **Pro**<br>– 5 yr PFS = 70% (RESONATE-2)<br>– Longer follow-up<br>• **Con**<br>– Indefinite duration<br>– Low CR / U-MRD<br>– Atrial fibrillation, bleeding | • **Pro**<br>– Reduced off-target effects<br>• **Con**<br>– Shorter follow-up<br>– Indefinite duration<br>– Low CR / U-MRD<br>– Atrial fibrillation, bleeding | • **Pro**<br>– Time-limited<br>– High CR / U-MRD<br>• **Con**<br>– Shorter follow-up<br>– TLS logistics<br>– IV administration of obinutuzumab<br>– Neutropenia<br>– Lack of durable remission in del(17p) / *TP53*-m |

Cherng HJ, Jain N. Hematol Oncol Clin North Am. 2021;35(4):725-738

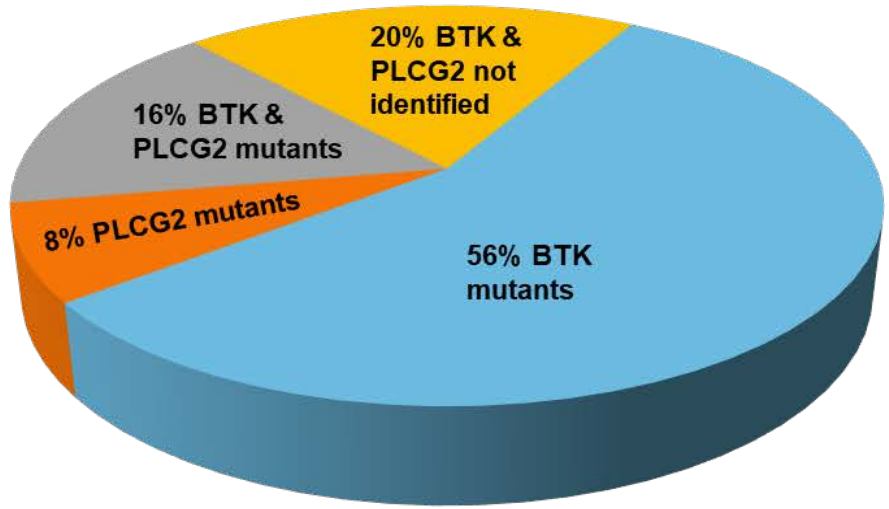
# Resistance and Intolerance Limit Covalent BTK Inhibitor Outcomes

**Ibrutinib discontinuation from 4 prospective studies[1]**




- Ibrutinib discontinuation rates at 5 years
  - Front line = 41%[3]
  - Relapsed/refractory = 54%[1]

**Ibrutinib acquired resistance in patients with progressive CLL[2]**




- BTK C481 mutations are the dominant reason for progressive CLL after covalent BTK inhibitors[1-8]
- BTK C481 mutations prevent covalent BTK inhibitors from effective target inhibition[1-6]

[1]Woyach et al. *J Clin Oncol.* 2017;35:1437-43. [2]Lampson et al. *Expert Rev Hematol.* 2018;11:185-94. [3]Burger et al. *Leukemia.* 2020;34:878-789. [4]Byrd et al. *N Engl J Med.* 2016;374:323-32. [5]Hershkovitz-Rokah et al. *Br J Haematol.* 2018;181:306-19. [6]Woyach et al. *N Engl J Med.* 2014;370:2286–94. [7]Woyach et al. *Blood.* 2019;134(Suppl 1):504. [8]Xu et al. *Blood.* 2017;129:2519–25.

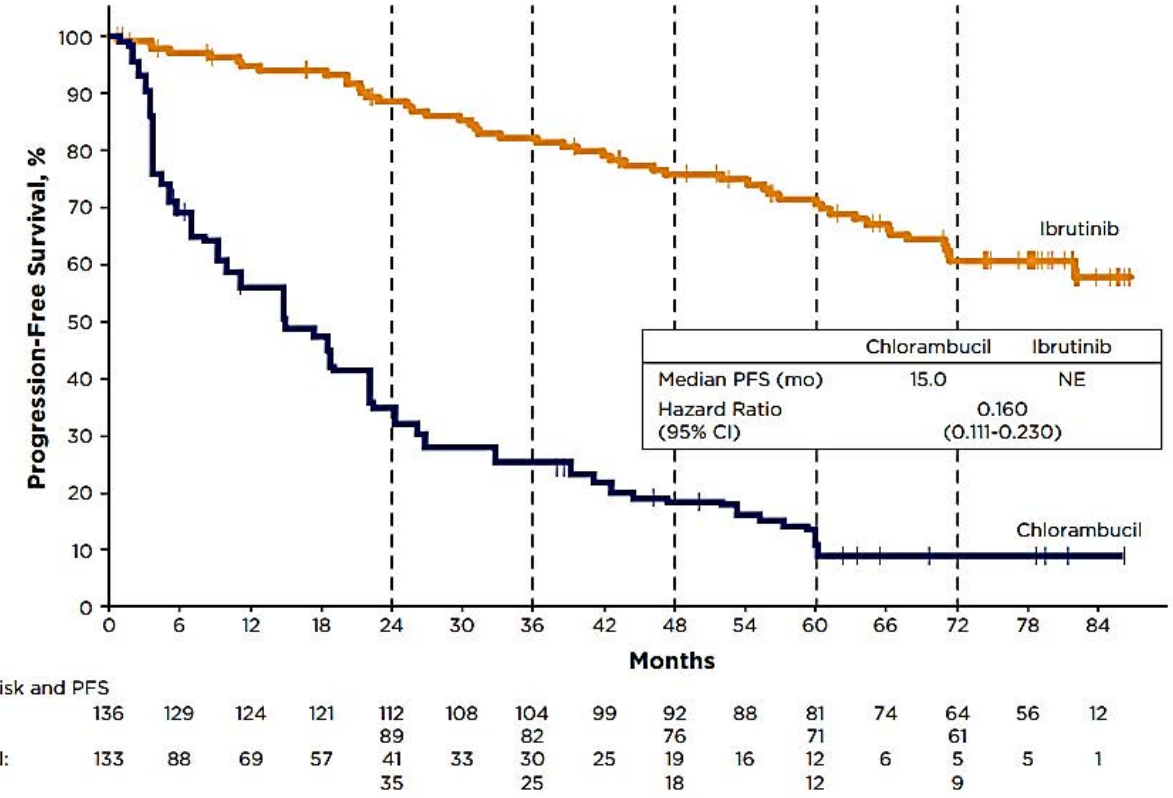
# Duration of Treatment and Outcomes With First-Line Ibrutinib: 7-Year Data from RESONATE-2

At 6.5 years, 61% of patients treated with ibrutinib and 9% with chlorambucil were estimated to be progression-free and alive. Sixteen (12%) of 136 patients discontinued ibrutinib due to PD.

## Ibrutinib Dosing and Dose Adjustments

| | Ibrutinib n=136 |
|---|---|
| **Median duration of ibrutinib treatment, months (range)[a]** | 74.0 (0.7–86.8) |
| **Continuing ibrutinib on study, n (%)** | 64 (47) |
| **Discontinued ibrutinib, n (%)** | |
| **AE** | 31 (23) |
| **PD[b]** | 16 (12) |
| **Death** | 11 (8) |
| **Withdrawal by patient** | 9 (7) |
| **Investigator decision** | 4 (3) |

[a]One patient received no doses of ibrutinib;
[b]Two patients discontinued due to Richter's transformation.




***53% discontinuation rate at 7 years; most common reason was adverse event***

Barr et al, ASCO 2021

Regular Article

blood

CLINICAL TRIALS AND OBSERVATIONS

## Outcomes of CLL patients treated with sequential kinase inhibitor therapy: a real world experience

Anthony R. Mato,[1,*] Chadi Nabhan,[2,*] Paul M. Barr,[3] Chaitra S. Ujjani,[4] Brian T. Hill,[5] Nicole Lamanna,[6] Alan P. Skarbnik,[7] Christina Howlett,[7] Jeffrey J. Pu,[8] Alison R. Sehgal,[9] Lauren E. Strelec,[1] Alexandra Vandegrift,[1] Danielle M. Fitzpatrick,[1] Clive S. Zent,[3] Tatyana Feldman,[7] Andre Goy,[7] David F. Claxton,[8] Spencer Henick Bachow,[6] Gurbakhash Kaur,[10] Jakub Svoboda,[1] Sunita Dwivedy Nasta,[1] David Porter,[1] Daniel J. Landsburg,[1] Stephen J. Schuster,[1] Bruce D. Cheson,[4] Pavel Kiselev,[11] and Andrew M. Evens[10]

*Toxicity was the most common reason for ibrutinib discontinuation in front line and R/R settings*

**Table 3. Most common reasons for KI discontinuation in patients who have discontinued ibrutinib or idelalisib**

| | Ibrutinib % (n) | Idelalisib % (n) |
|---|---|---|
| Toxicity | 51 (73) | 52 (18) |
| CLL progression | 28 (40) | 31 (11) |
| RT | 8 (11) | 6 (2) |
| Cellular therapies (chimeric antigen receptor T cells or allogeneic stem cell transplantation) | 2 (3) | 0 (0) |
| Unrelated death/Other | 11 (16) | 11 (4) |

EHA EUROPEAN HEMATOLOGY ASSOCIATION

Ferrata Storti Foundation

## Toxicities and outcomes of 616 ibrutinib-treated patients in the United States: a real-world analysis

Anthony R. Mato,[1] Chadhi Nabhan,[2] Meghan C. Thompson,[1] Nicole Lamanna,[3] Danielle M. Brander,[4] Brian Hill,[5] Christina Howlett,[6,7] Alan Skarbnik,[7] Bruce D. Cheson,[8] Clive Zent,[9] Jeffrey Pu,[10] Pavel Kiselev,[11] Andre Goy,[7] David Claxton,[10] Krista Isaac,[12] Kaitlin H. Kennard,[1] Colleen Timlin,[1] Daniel Landsburg,[1] Allison Winter,[5] Sunita D. Nasta,[1] Spencer H. Bachow,[3] Stephen J. Schuster,[1] Colleen Dorsey,[1] Jakub Svoboda,[1] Paul Barr[13]* and Chaitra S. Ujjani[8]*

Haematologica 2018
Volume 103(5):874-879

- 41% of patients discontinued ibrutinib (med F/U 17 mo).
- Median time to ibrutinib discontinuation was 7 months
- Median time of 6 months for patients who discontinued due to intolerance

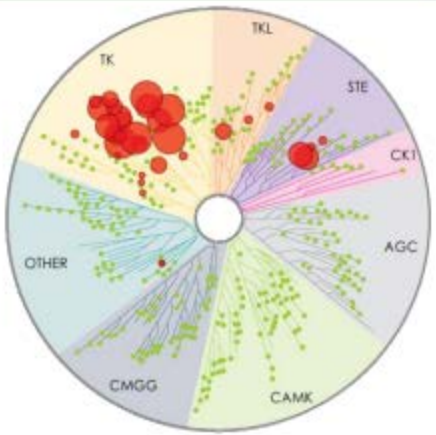
| Most common AEs leading to DC |
|---|
| *A fib* |
| *Infection* |
| *Hematologic* |
| *Bleeding* |
| *Pneumonitis* |

Mato, Nabhan et al, Blood 2016 & Haematologica 2018

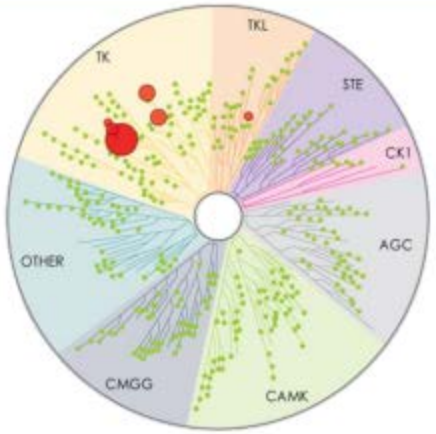
# BTKi Toxicities

- Atrial Fibrillation
- Hypertension
- Bleeding
- Arthralgia/Myalgia/Muscle Cramps
- Rash
- Headaches
- Fatigue
- Infections
- Anticoagulation and antiplatelets
- Drug-drug Interactions: avoid strong or moderate CYP3A4 inhibitors/inducers (elderly=polypharmacy)

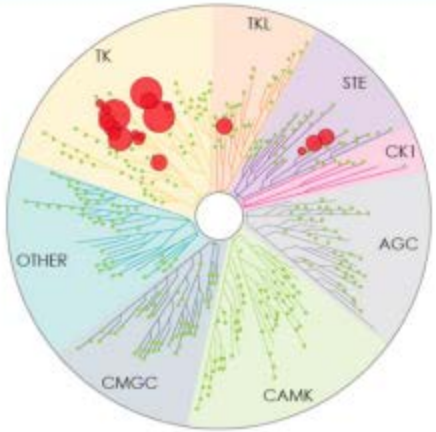
## Ibrutinib




## Acalabrutinib




## Zanubrutinib




$IC_{50}/EC_{50}$ (nM)

| Kinase | Ibrutinib | Acalabrutinib | Zanubrutinib |
|---|---|---|---|
| BTK | 1.5 | 5.1 | 0.5 |
| TEC | 10 | 126 | 44 |
| ITK | 4.9 | > 1000 | 50 |
| BMX | 0.8 | 46 | 1.4 |
| EGFR | 5.3 | > 1000 | 21 |
| ERBB4 | 3.4 | 16 | 6.9 |
| JAK3 | 32 | > 1000 | 1377 |
| BLK | 0.1 | > 1000 | 2.5 |

Slide adapted from Kaptein A et al. ASH 2018. Abs 1871.

# ELEVATE-RR:
## Phase 3 Randomized Non-inferiority Open-Label Trial

**Patients (N=533)**

**Key Inclusion Criteria**

- Adults with previously treated CLL requiring therapy (iwCLL 2008 criteria[1])
- Presence of del(17p) or del(11q)[a]
- ECOG PS of ≤2

**Stratification**

- del(17p) status (yes or no)
- ECOG PS (2 vs ≤1)
- No. prior therapies (1–3 vs ≥4)

RANDOMIZE 1:1

- **Acalabrutinib[b] 100 mg PO BID**
- **Ibrutinib[b] 420 mg PO QD**

**Primary endpoint**

- Non-inferiority on IRC-assessed PFS[c]

**Secondary endpoints (hierarchical order):**

- Incidence of any grade atrial fibrillation/flutter
- Incidence of grade ≥3 infection
- Incidence of Richter transformation
- Overall survival

Key exclusion criteria: Significant CV disease; concomitant treatment with warfarin or equivalent vitamin K antagonist; prior treatment with ibrutinib, a BCR inhibitor (eg, BTK , PI3K, or Syk inhibitors), or a BCL-2 inhibitor (eg, venetoclax)

NCT02477696 (ACE-CL-006).
[a]By central laboratory testing; [b]continued until disease progression or unacceptable toxicity; [c]conducted after enrollment completion and accrual of ~250 IRC-assessed PFS events.
Afib/flutter, atrial fibrillation/flutter; BCL-2, B-cell leukemia/lymphoma-2; BCR, B-cell receptor; BID, twice daily; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CV, cardiovascular; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent review committee; iwCLL, International Workshop on CLL; PFS, progression-free survival; PI3K, phosphatidylinositol 3-kinase; PO, orally; QD, once daily.

1. Hallek M, et al. *Blood*. 2008;111:5446-56.

# Events of Clinical Interest

| Events, n (%) | Any grade | | Grade ≥3 | |
|---|---|---|---|---|
| | Acalabrutinib (n=266) | Ibrutinib (n=263) | Acalabrutinib (n=266) | Ibrutinib (n=263) |
| Cardiac events | 64 (24.1) | 79 (30.0) | 23 (8.6) | 25 (9.5) |
| Atrial fibrillation[a]* | 25 (9.4) | **42 (16.0)** | 13 (4.9) | 10 (3.8) |
| Ventricular arrhythmias[b] | 0 | 3 (1.1) | 0 | 1 (0.4) |
| Bleeding events* | 101 (38.0) | **135 (51.3)** | 10 (3.8) | 12 (4.6) |
| Major bleeding events[c] | 12 (4.5) | 14 (5.3) | 10 (3.8) | 12 (4.6) |
| Hypertension[d]* | 25 (9.4) | **61 (23.2)** | 11 (4.1) | **24 (9.1)** |
| Infections[e] | 208 (78.2) | 214 (81.4) | 82 (30.8) | 79 (30.0) |
| ILD/pneumonitis* | 7 (2.6) | **17 (6.5)** | 1 (0.4) | 2 (0.8) |
| SPMs excluding NMSC | 24 (9.0) | 20 (7.6) | 16 (6.0) | 14 (5.3) |

Higher incidence indicated in **bold yellow** for terms with statistical differences.
*Two-sided P-value for event comparisons <0.05 without multiplicity adjustment.
[a]Includes events with preferred terms atrial fibrillation and atrial flutter.
[b]Includes events with preferred terms torsade de pointes, ventricular arrhythmia, ventricular extrasystoles, ventricular fibrillation, ventricular flutter, ventricular tachyarrhythmia, and ventricular tachycardia.
[c]Defined as any hemorrhagic event that was serious, grade ≥3 in severity, or a central nervous system hemorrhage (any severity grade).
[d]Included events with the preferred terms of hypertension, blood pressure increased, and blood pressure systolic increased.
[e]Most common grade ≥3 infections were pneumonia (acalabrutinib, 10.5%; ibrutinib, 8.7%), sepsis (1.5% vs 2.7%, respectively), and UTI (1.1% vs 2.3%).
ILD, interstitial lung disease; NMSC, nonmelanoma skin cancer; SPMs, second primary malignancies; UTI, urinary tract infection.

# ALPINE: Phase 3, Randomized Study of Zanubrutinib vs Ibrutinib in Patients With Relapsed/Refractory CLL or SLL

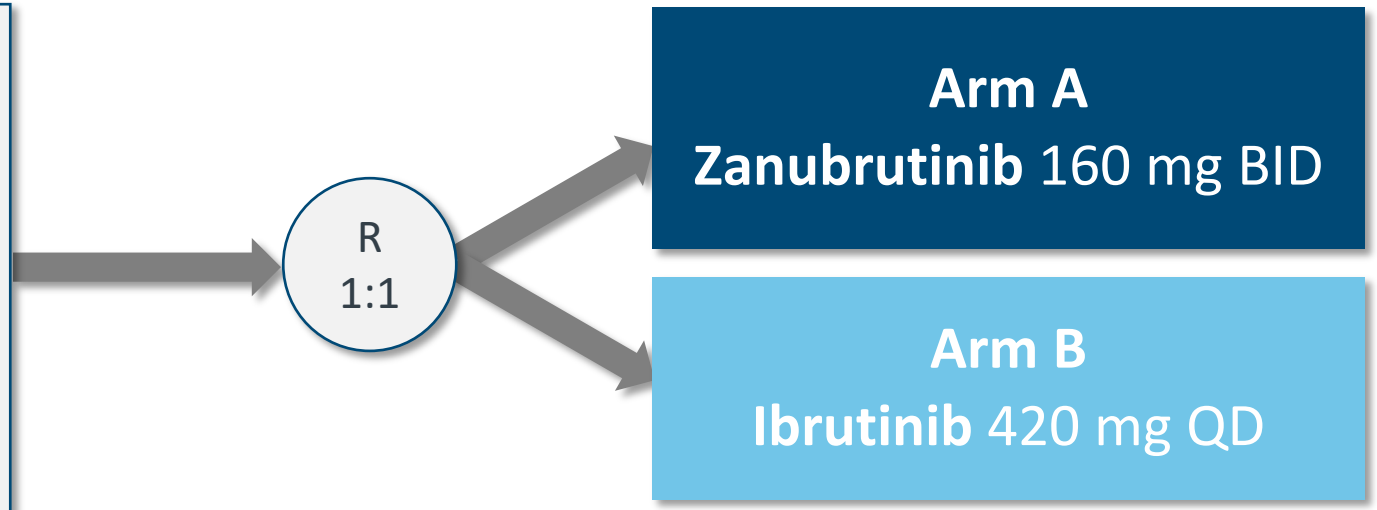
**R/R CLL/SLL with ≥ 1 prior treatment**
(Planned N=600, Actual N=652)

**Key Inclusion Criteria**

- R/R to ≥1 prior systemic therapy for CLL/SLL
- Measurable lymphadenopathy by CT or MRI

**Key Exclusion Criteria**

- Current or past Richter's transformation
- Prior BTK inhibitor therapy
- Treatment with warfarin or other vitamin K antagonists




**Stratification Factors**

- Age
- Geographic region
- Refractory status
- Del(17p)/*TP53* mutation status

BID, twice daily; BTK, Bruton tyrosine kinase' CLL, chronic lymphocytic leukemia; CT, computed tomography; MRI, magnetic resonance imaging; QD, once daily; R, randomized; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma.

# Additional AEs of Special Interest

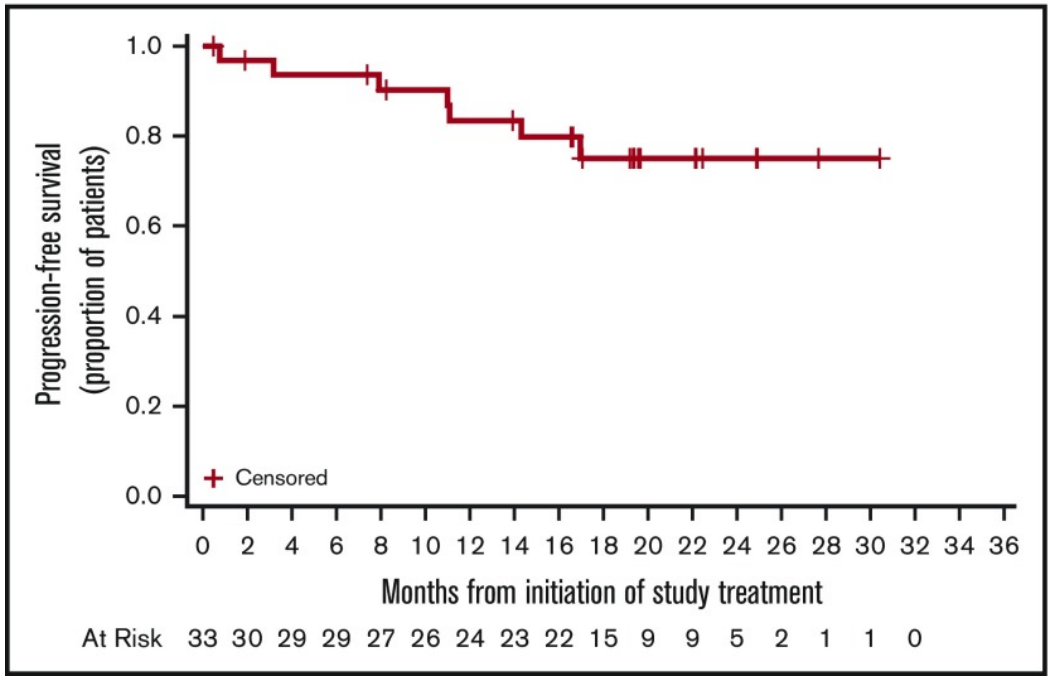
| Safety Analysis Population | Zanubrutinib (n=204), n (%) | | Ibrutinib (n=207), n (%) | |
|---|---|---|---|---|
| | Any Grade | Grade ≥3 | Any Grade | Grade ≥3 |
| Cardiac disorders[a] | 28 (13.7) | 5 (2.5) | 52 (25.1) | 14 (6.8) |
| **Atrial fibrillation and flutter (key 2º endpoint)** | **5 (2.5)** | **2 (1.0)** | **21 (10.1)** | **4 (1.9)** |
| Hemorrhage<br>Major hemorrhage[b] | 73 (35.8)<br>6 (2.9) | 6 (2.9)<br>6 (2.9) | 75 (36.2)<br>8 (3.9) | 6 (2.9)<br>6 (2.9) |
| Hypertension | 34 (16.7) | 22 (10.8) | 34 (16.4) | 22 (10.6) |
| Infections | 122 (59.8) | 26 (12.7) | 131 (63.3) | 37 (17.9) |
| Neutropenia[c] | 58 (28.4) | 38 (18.6) | 45 (21.7) | 31 (15.0) |
| Thrombocytopenia[c] | 19 (9.3) | 7 (3.4) | 26 (12.6) | 7 (3.4) |
| Secondary primary malignancies<br>Skin cancers | 17 (8.3)<br>7 (3.4) | 10 (4.9)<br>3 (1.5) | 13 (6.3)<br>10 (4.8) | 4 (1.9)<br>2 (1.0) |

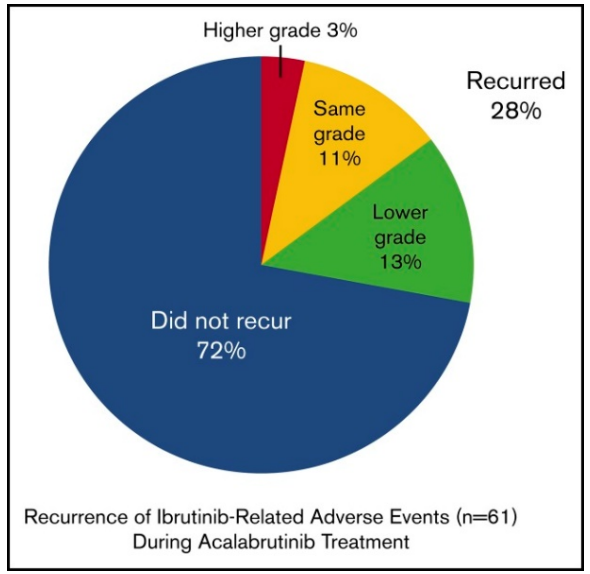
AE, adverse events. All events are of any grade unless otherwise specified.
[a] Cardiac disorders leading to treatment discontinuation: zanubrutinib 0 patients and ibrutinib 7 (3.4%) patients.
[b] Includes serious or grade ≥3 hemorrhage and CNS bleeding of all grades .
[c] Pooled terms including neutropenia, neutrophil count decreased, and febrile neutropenia; thrombocytopenia and platelet count decreased.

# Acalabrutinib in Ibrutinib-Intolerant Patients

**Subset analysis of patients with ibrutinib intolerance enrolled in phase 1/2 ACE-CL-001 (n = 33)**

- Median duration of prior ibrutinib, 11.6 months
- ~70% of patients remained on acalabrutinib after a median of 19 months
  - 3 patients had discontinued acalabrutinib due to AEs; 4 patients discontinued due to progressive disease




- Median duration of response was not reached
- Median PFS was not reached
- 1-year PFS was 83.4% (95% CI, 64.5%-92.7%)

Awan FT, et al. *Blood.* 2019

UNIKLINIK KÖLN
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DEUTSCHE STUDIENGRUPPE

Abstract S146

# VENETOCLAX-OBINUTUZUMAB FOR PREVIOUSLY UNTREATED CHRONIC LYMPHOCYTIC LEUKEMIA: 4-YEAR FOLLOW-UP ANALYSIS OF THE RANDOMIZED CLL14 STUDY

**Othman Al-Sawaf**, Can Zhang, Sandra Robrecht, Maneesh Tandon, Anesh Panchal, Anna-Maria Fink, Eugen Tausch, Matthias Ritgen, Karl-Anton Kreuzer, Su Young Kim, Clemens-Martin Wendtner, Barbara Eichhorst, Stephan Stilgenbauer, Yanwen Jiang, Michael Hallek, Kirsten Fischer

June 11th, 2021
Clinical trials with targeted therapies in CLL

# MOST FREQUENT ≥ GRADE 3 ADVERSE EVENTS

| | Venetoclax-obinutuzumab (N=212) | | Chlorambucil-obinutuzumab (N=214) | |
|---|---|---|---|---|
| | **During Treatment** | **After Treatment** | **During Treatment** | **After Treatment** |
| Neutropenia | 51.9% | 4.0% | 47.2% | 1.9% |
| Thrombocytopenia | 13.7% | 0.5% | 15.0% | 0.0% |
| Anemia | 7.5% | 1.5% | 6.1% | 0.5% |
| Febrile neutropenia | 4.2% | 1.0% | 3.3% | 0.5% |
| Leukopenia | 2.4% | 0.0% | 4.7% | 0.0% |
| Pneunomia | 3.3% | 3.0% | 2.8% | 1.4% |
| Infusion-related reaction | 9.0% | 0.0% | 9.8% | 0.5% |
| Tumour lysis syndrome | 1.4% | 0.0% | 3.3% | 0.0% |

# TLS Prophylaxis with Venetoclax

| | Hydration | Anti-hyperuricemic | Labs |
|---|---|---|---|
| **Low risk**<br>LN <5cm<br>AND<br>ALC <25 | Oral (1.5-2L) | Allopurinol | Outpatient<br><br>20/50mg: Pre-dose, 6-8hr, 24 hr<br>100/200/400mg: Pre-dose |
| **Medium risk**<br>LN 5 to <10cm<br>OR<br>ALC ≥25 | Oral (1.5-2L)<br>Consider additional IV | Allopurinol | Outpatient<br><br>20/50mg: Pre-dose, 6-8hr, 24 hr<br>100/200/400mg: Pre-dose<br><br>If GFR <80: admit for 20/50mg |
| **High risk**<br>LN ≥10cm<br>OR<br>ALC ≥25 and LN ≥5cm | Oral (1.5-2L) and IV (150-200 ml/hr as tolerated) | Allopurinol;<br>Consider rasburicase if elevated uric acid | Admit<br>20/50mg: Pre-dose, 4, 8, 12, 24 hr<br><br>Outpatient<br>100/200/400mg: Pre-dose, 6-8 hr, 24hr |

# FIXED-DURATION IBRUTINIB PLUS VENETOCLAX (I+V) VERSUS CHLORAMBUCIL PLUS OBINUTUZUMAB (CLB+O) FOR FIRST-LINE TREATMENT OF CHRONIC LYMPHOCYTIC LEUKEMIA (CLL): PRIMARY ANALYSIS OF THE PHASE 3 GLOW STUDY

Arnon P. Kater,[1] Carolyn Owen,[2] Carol Moreno,[3] George Follows,[4] Talha Munir,[5] Mark-David Levin,[6] Ohad Benjamini,[7] Ann Janssens,[8] Anders Osterborg,[9] Tadeusz Robak,[10] Martin Simkovic,[11] Don Stevens,[12] Sergey Voloshin,[13] Vladimir Vorobyev,[14] Munci Yagci,[15] Loic Ysebaert,[16] Rui Qin,[17] Sriram Balasubramanian,[18] Natasha Schuier,[19] Kurt Baeten,[20] Donne Bennett Caces,[17] Carsten U. Niemann[21]

[1]Amsterdam University Medical Centers, Amsterdam, Netherlands; [2]Tom Baker Cancer Centre, Calgary, Canada; [3]Hospital de la Santa Creu i Sant Pau, Autonomous University of Barcelona, Spain; [4]Addenbrookes Hospital, Cambridge, UK; [5]St James's Hospital, Leeds, UK; [6]Albert Schweitzer Hospital, Dordrecht, Netherlands; [7]Sheba Medical Center, Ramat Gan, Israel; [8]UZ Leuven Gasthuisberg, Leuven, Belgium; [9]Karolinska University Hospital, Stockholm, Sweden; [10]Medical University of Lodz, Copernicus Memorial Hospital, Lodz, Poland; [11]University Hospital Hradec Kralove, Hradec Kralove, Czech Republic; [12]Norton Cancer Institute, Louisville, KY, USA; [13]Russian Scientific and Research Institute of Hematology and Transfusiology, St. Petersburg, Russia; [14]S.P. Botkin Moscow City Clinical Hospital, Moscow, Russia; [15]Gazi Universitesi Tip Fakultesi, Ankara, Turkey; [16]Institut Universitaire du Cancer Toulouse Oncopole, Toulouse, France; [17]Janssen Research & Development, Raritan, NJ, USA; [18]Janssen Research & Development, San Diego, CA, USA; [19]Janssen Research & Development, Düsseldorf, Germany; [20]Janssen Research & Development, Beerse, Belgium; [21]Rigshospitalet Copenhagen University Hospital, Copenhagen, Denmark

# Summary of Safety and TLS Risk Reduction

## Grade 3 or Higher AEs in ≥5% of Patients

| | I+V (N = 106) | Clb+O (N = 105) |
|---|---|---|
| Median exposure, mos (range) | 13.8 (0.7-19.5) | 5.1 (1.8-7.9) |
| Any, % | 75.5 | 69.5 |
| Neutropenia[a] | 34.9 | 49.5 |
| Infections[b] | 17.0 | 11.4 |
| Thrombocytopenia | 5.7 | 20.0 |
| Diarrhea | 10.4 | 1.0 |
| Hypertension | 7.5 | 1.9 |
| Atrial fibrillation | 6.6 | 0 |
| Hyponatremia | 5.7 | 0 |
| TLS | 0 | 5.7 |

[a]Includes 'neutrophil count decreased'; grade ≥3 febrile neutropenia: 1.9% for I+V vs 2.9% for Clb+O

[b]Includes multiple preferred terms

- After 3 cycles of ibrutinib lead-in, <2% of patients remained at risk for TLS based on high tumor burden
- 2 (1.9%) patients in I+V arm discontinued ibrutinib due to atrial fibrillation
- SAEs in ≥5% of patients for I+V vs Clb+O: Infections (12.3% vs 8.6%) and atrial fibrillation (6.6% vs 0%)
- Rate of secondary malignancies at time of analysis: 8.5% for I+V vs 10.5% for Clb+O
  - NMSC: 3.8% vs 1.9%
  - Other: 4.7% vs 8.6%

EHA 2021, Kater AP, et al.

TLS, tumor lysis syndrome; AE, adverse event; SAE, serious AE; NMSC, non-melanoma skin cancer

# Thank you!

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