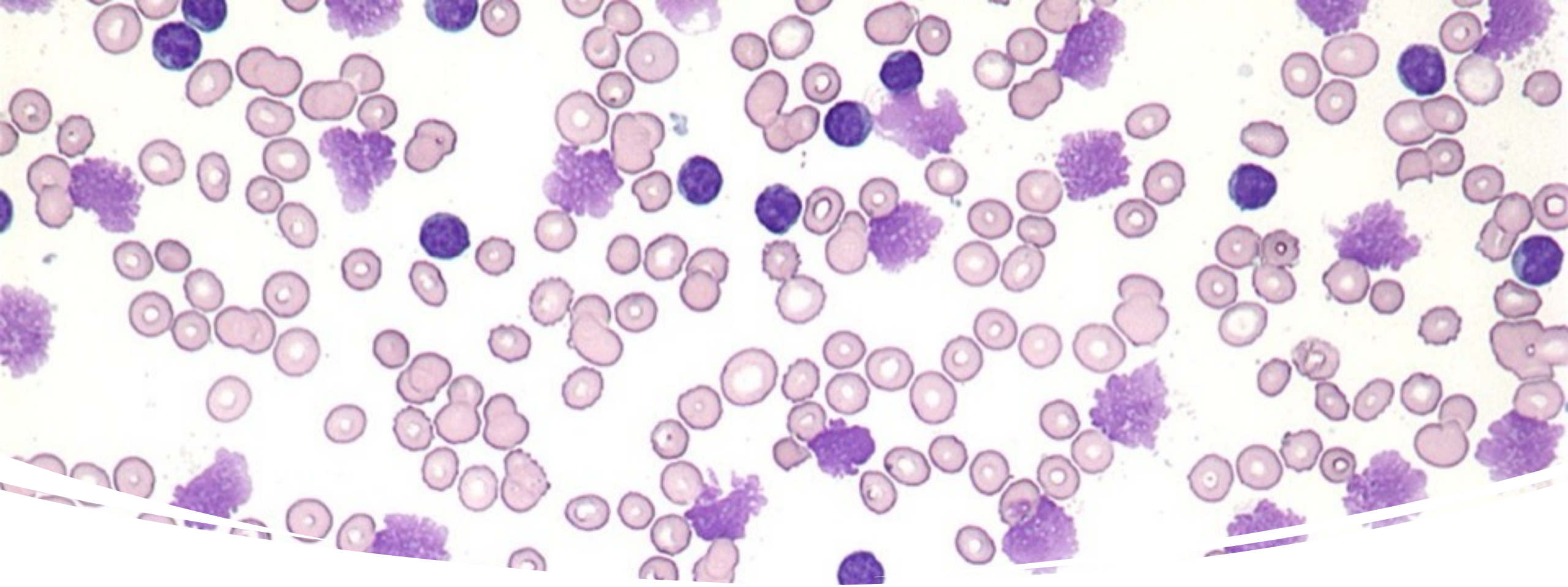


Optimal Management of Adverse Events with BTK and Bcl-2 Inhibitors: Considerations for Special Patient Populations

Matthew S. Davids, MD, MMSc

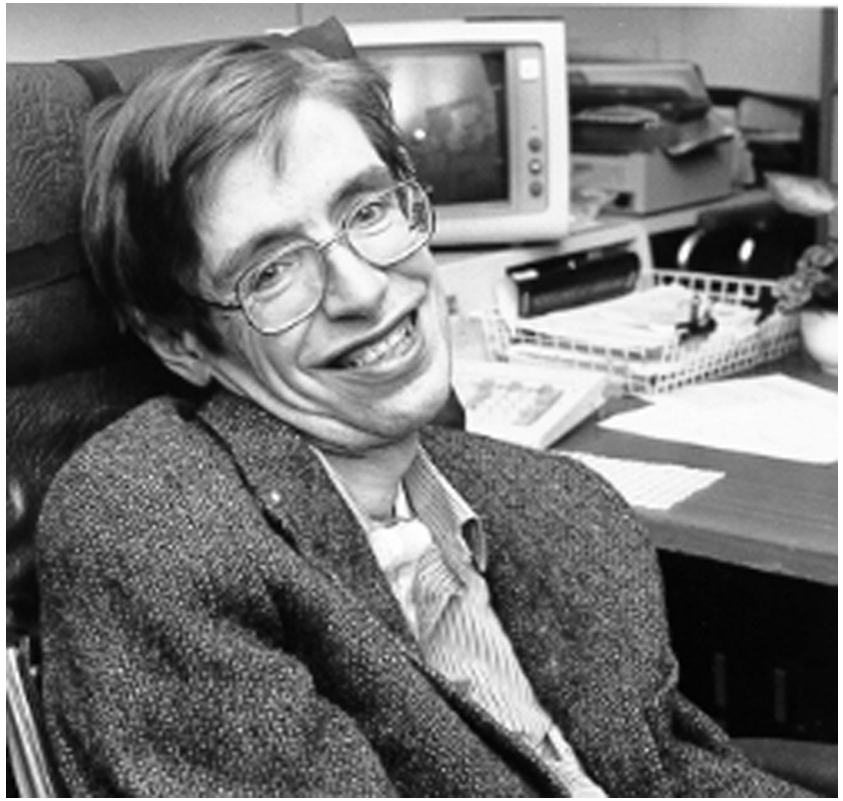
Dana-Farber Cancer Institute | Harvard Medical School

2022 ASH CLL Satellite Symposium | Research To Practice

December 9, 2022

Dana-Farber Cancer Institute

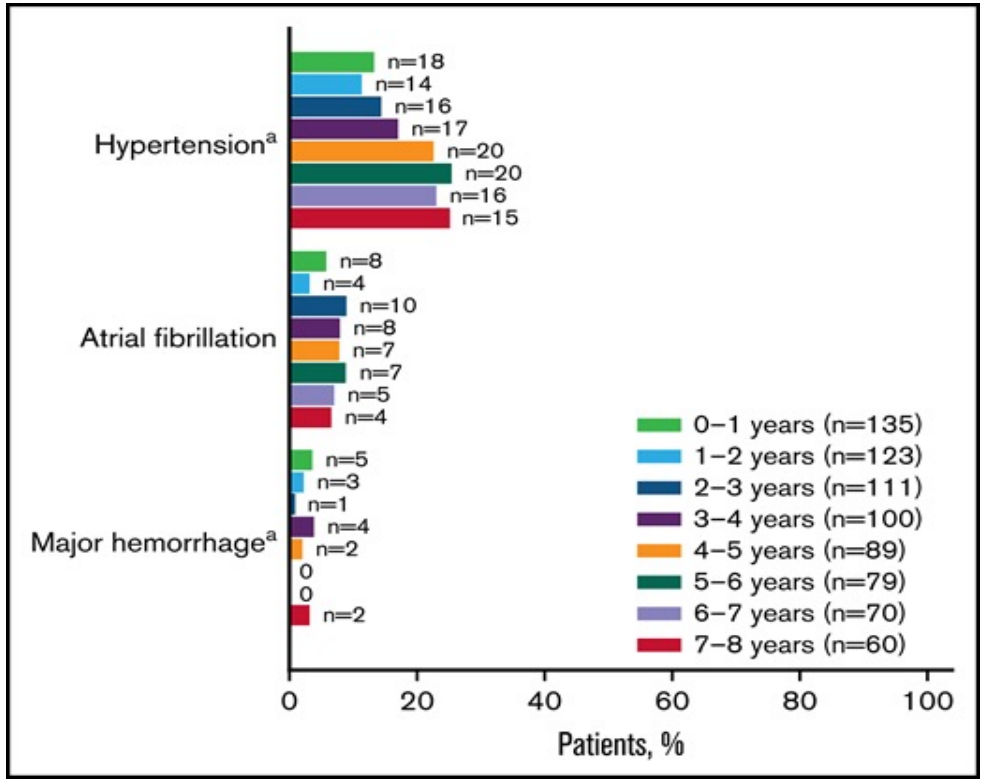
Harvard Medical School

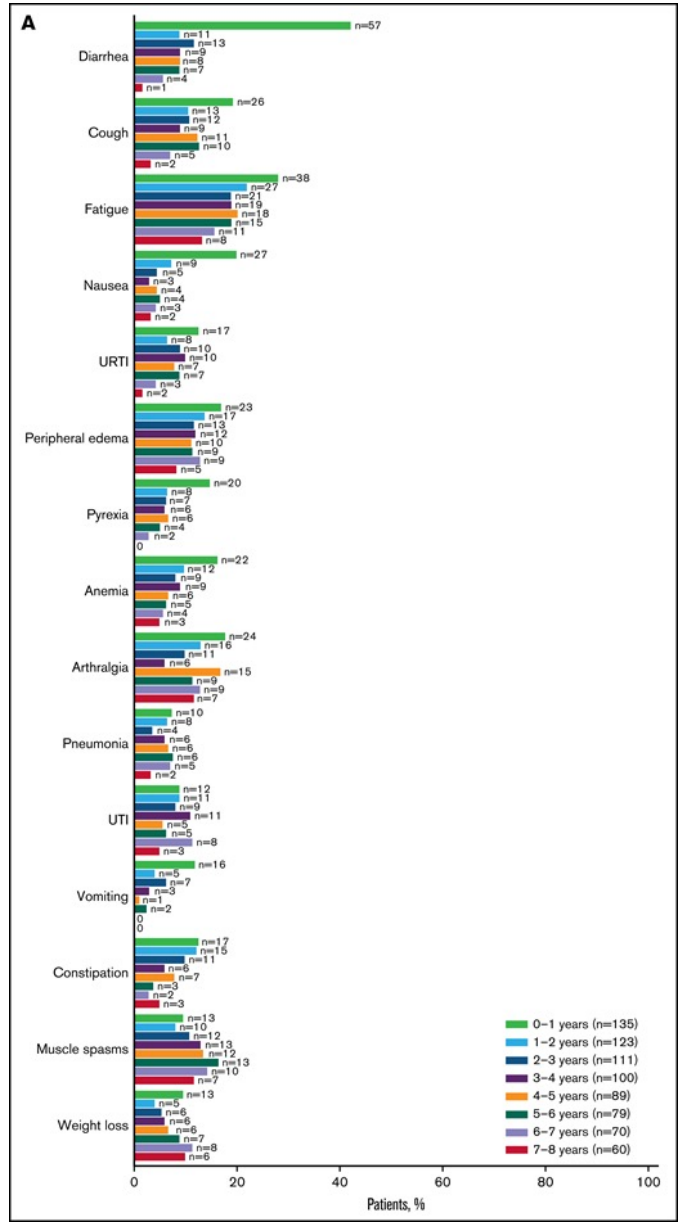


"One of the basic rules of the universe is that nothing is perfect."

Stephen Hawking

RESONATE-2: Discontinuation Rates With Ibrutinib Are High, and Are Due Mostly to AEs





- 42% of patients still on ibrutinib at 8 years
- Most common reason for discontinuation was AEs (24%)

Barr, et al. *Blood Adv.* 2022;6(11):3440-3450

US cooperative group studies suggest Gr 3/4 ibrutinib toxicities may be less in younger patients

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

*including patients with presumed sudden cardiac death

Adapted from Shanafelt et al., ASH, 2018

Reasons for Ibrutinib Discontinuation Outside of Clinical Trials

Most Common Ibrutinib-related Toxicities as Reasons for Discontinuation	
Relapsed CLL (%)	**Front-line CLL (%)**
Atrial fibrillation (12.3)	Arthralgia (41.6)
Infection (10.7)	Atrial fibrillation (25)
Pneumonitis (9.9)	Rash (16.7)
Bleeding (9)	
Diarrhea (6.6)	

Median Times to Ibrutinib Discontinuation Stratified by Toxicity	
Bleeding	8 months
Diarrhea	7.5 months
Atrial fibrillation	7 months
Infection	6 months
Arthralgia	5 months
Pneumonitis	4.5 months
Rash	3.5 months

Mato, et al. *Blood.* 2016;128 (22): 3222

- Ibrutinib discontinuation due to AEs is common in the real-world setting (41% discontinuation at median of 17 mo.)

Mato et al., *Haematologica*, 2018

CLL12: CLL patients commonly have symptoms and complications

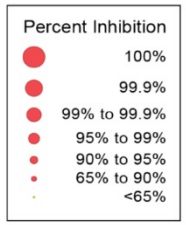
DEUTSCHE STUDIENGRUPPE

	Ibrutinib (n = 158)			Placebo (n = 155)		
	Any grade	Grade 1-2	Grade ≥3	Any grade	Grade 1-2	Grade ≥3
Total no. of events	1593	1426	167	1015*	885	129
Any AE, n (%)	150 (94.9)	70 (44.3)	80 (50.6)	147 (94.8)	80 (51.6)	67 (43.2)
Most common AEs occurring in ≥0% of patients in any treatment group, n (%)†						
Atrial fibrillation	19 (12.0)	9 (5.7)	10 (6.3)	2 (1.3)		2 (1.3)
Diarrhea	50 (31.6)	48 (30.4)	2 (1.3)	28 (18.1)	27 (17.4)	1 (0.6)
Dyspepsia	23 (14.6)	23 (14.6)		4 (2.6)	4 (2.6)	
Nausea	26 (16.5)	26 (16.5)		15 (9.7)	15 (9.7)	
Fatigue	40 (25.3)	39 (24.7)	1 (0.6)	32 (20.6)	31 (20.0)	1 (0.6)
Nasopharyngitis	42 (26.6)	41 (25.9)	1 (0.6)	51 (32.9)	51 (32.9)	
Upper respiratory tract infection	16 (10.1)	15 (9.5)	1 (0.6)	11 (7.1)	11 (7.1)	
Arthralgia	19 (12.0)	18 (11.4)	1 (0.6)	14 (9.0)	13 (8.4)	1 (0.6)
Back pain	16 (10.1)	14 (8.9)	2 (1.3)	17 (11.0)	15 (9.7)	2 (1.3)
Muscle spasms	22 (13.9)			6 (3.9)		
Dizziness	22 (13.9)	20 (12.7)	2 (1.3)	8 (5.2)	8 (5.2)	
Headache	28 (17.7)	28 (17.7)		17 (11.0)	17 (11.0)	
Rash	29 (18.4)	24 (15.2)	5 (3.2)	8 (5.2)	8 (5.2)	
Hematoma	22 (13.9)	20 (12.7)	2 (1.3)	6 (3.9)	6 (3.9)	
Hypertension	16 (10.1)	14 (8.8)	2 (1.3)	7 (4.5)	4 (2.6)	3 (1.9)

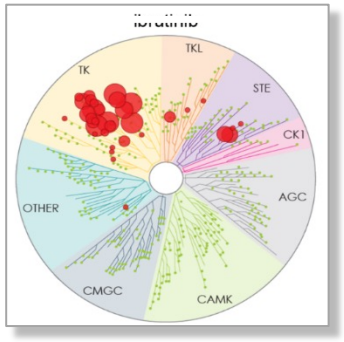
Langerbeins et al., *Blood*, 2022

BTK Inhibitors Exhibit Differences in Kinase Selectivity

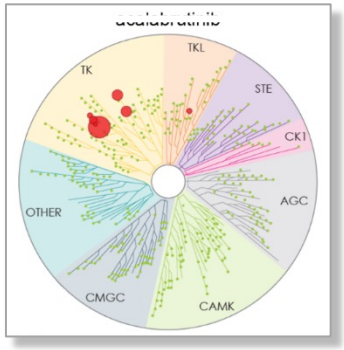
Irreversible



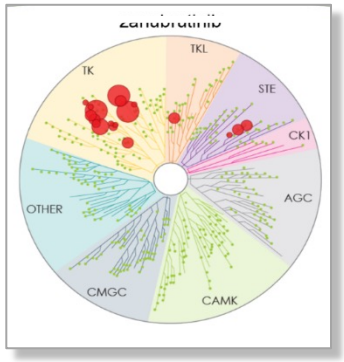
Ibrutinib



Acalabrutinib

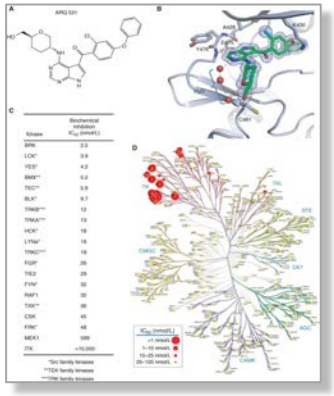


Zanubrutinib

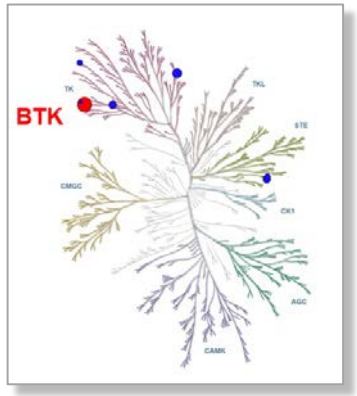


Reversible

Nemtabrutinib



Pirtobrutinib



Do differences in binding and selectivity impact treatment efficacy and risk of adverse events?

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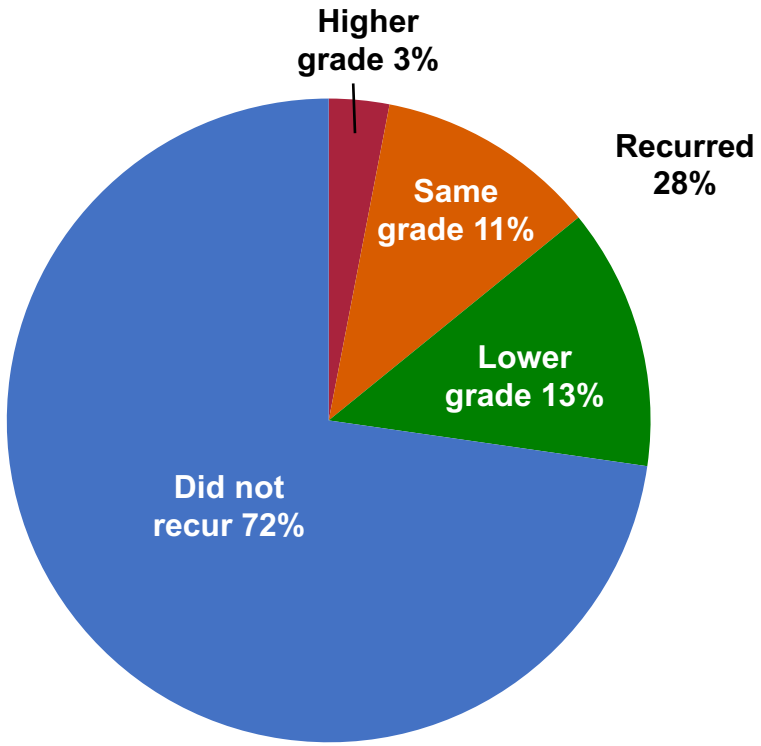
Kaptein A, de Bruin G, Emmelot-van Hoek M, et al. *Blood*. 2018;132(Suppl 1):1871.

Acalabrutinib can be well-tolerated in ibrutinib-intolerant patients

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



Recurrence of Ibrutinib-Related Adverse Events (n=61)
During Acalabrutinib Treatment

- ~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

Awan FT, et al. *Blood.* 2019;3(9):1553-1562.

Phase 2 Trial of Acalabrutinib in Ibrutinib-Intolerant Patients

- Standard-dose acalabrutinib in 60 patients with R/R CLL who were ibrutinib-intolerant
  - Ibrutinib was the most recent systemic therapy for all patients
  - All patients met iwCLL criteria for treatment

	Acalabrutinib (N=60)
ORR	73%
CR	5%
mPFS	NR
24-month PFS	72%
mOS	NR
24-month OS	81%

	Acalabrutinib (N=60)
Most frequent AEs	
Diarrhea	53%
Headache	42%
Contusion	40%
Dizziness	33%
Upper RTI	33%
Cough	30%
AEs leading to discontinuation*	17%

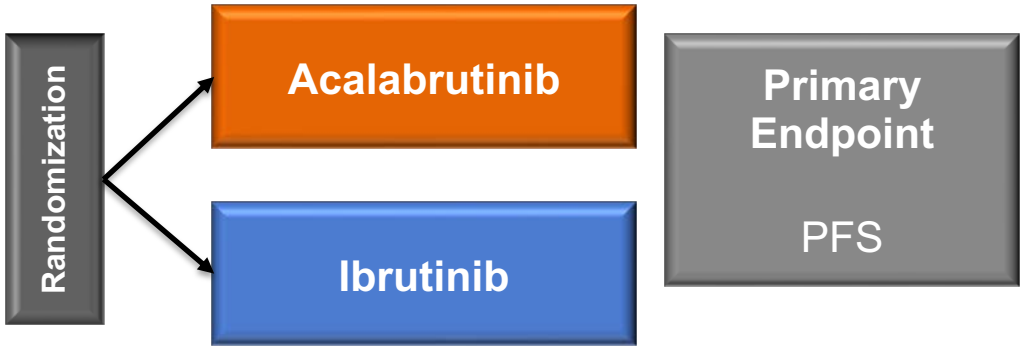
*1 patient discontinued acalabrutinib for the same toxicity (diarrhea) that led to ibrutinib discontinuation

Rogers KA, et al. *Haematologica*. 2021;106(9):2364-2373.

Phase 3 ELEVATE-CLL R/R: Acalabrutinib vs Ibrutinib in R/R High-risk CLL

R/R High-risk CLL
N=533

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



- **Primary Endpoint:**
  - **Acalabrutinib demonstrated noninferiority to ibrutinib** (PFS)
    - At a median follow-up of 40.9 months (range, 0.0-59.1), the mPFS was 38.4 months for both acalabrutinib and ibrutinib (HR, 1.00; 95% CI, 0.79-1.27).

Byrd JC et al. *J Clin Oncol*. 2021;39:3441-3452

ELEVATE-R/R: Lower Incidence of Any Grade A-fib/Flutter, Hypertension, Bleeding With Acalabrutinib vs Ibrutinib[1]

Events, n (%)	Acalabrutinib (n = 266)		Ibrutinib (n = 263)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Cardiac events	64 (24.1)	23 (8.6)	79 (30.0)	25 (9.5)
A-fib[a]	**25 (9.4)**	13 (4.9)	**42 (16.0)**	10 (3.8)
Ventricular tachyarrhythmias	0	0	1 (0.4)	1 (0.4)
Hypertension[b]	**25 (9.4)**	11 (4.1)	**61 (23.2)**	24 (9.1)
Bleeding events	**101 (38.0)**	10 (3.8)	**135 (51.3)**	12 (4.6)
Major bleeding events[a]	12 (4.5)	10 (3.8)	14 (5.3)	12 (4.6)
Infections	208 (78.2)	82 (30.8)	214 (81.4)	79 (30.0)

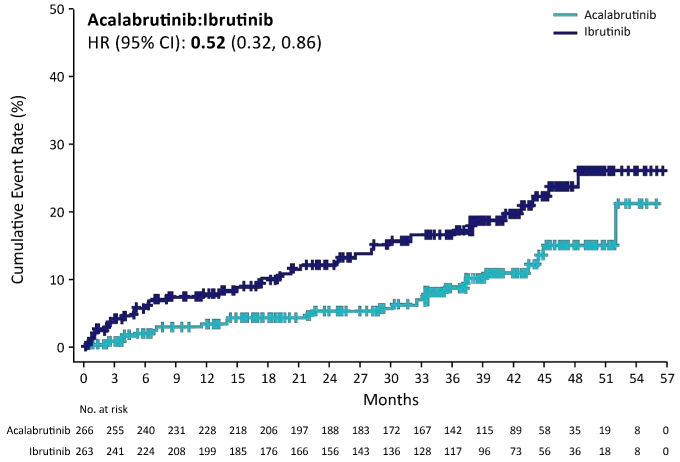
- AEs led to discontinuation in 14.7% of acalabrutinib-treated pts vs 21.3% of ibrutinib-treated pts

[a] Includes A-fib/flutter. [b] Includes hypertension, blood pressure increased, and blood pressure systolic increased.

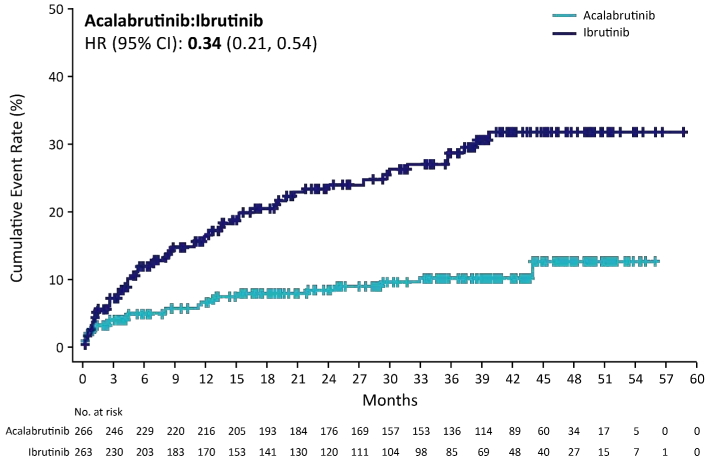
1. Byrd JC et al. *J Clin Oncol*. 2021;39:3441-3452.

Acalabrutinib has an improved AE profile compared to ibrutinib, but toxicities are still common

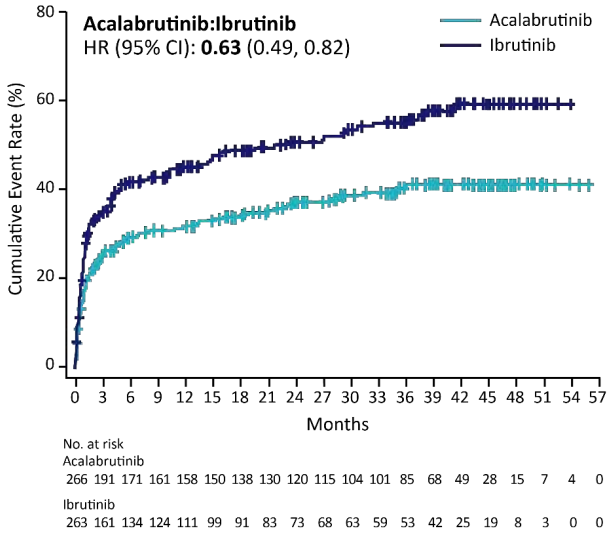
Afib/Flutter



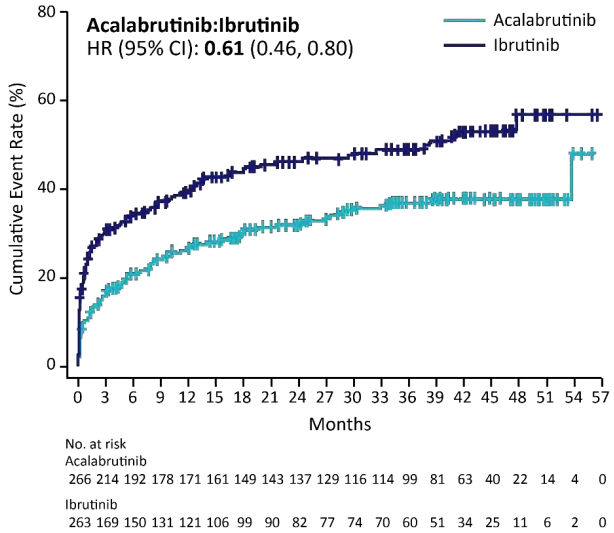
Hypertension



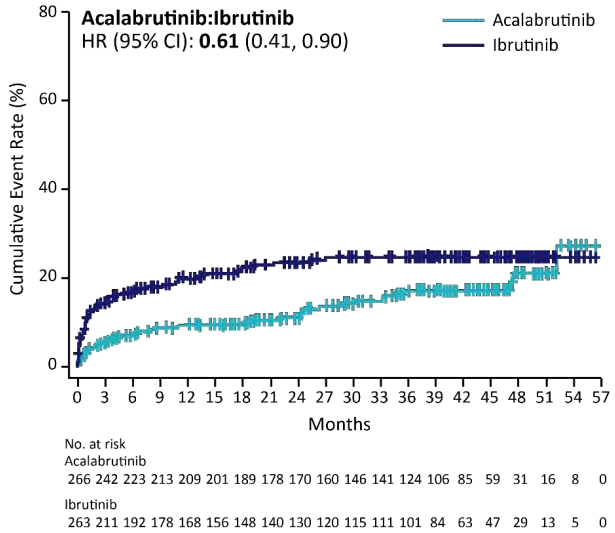
Bleeding Events



Diarrhea



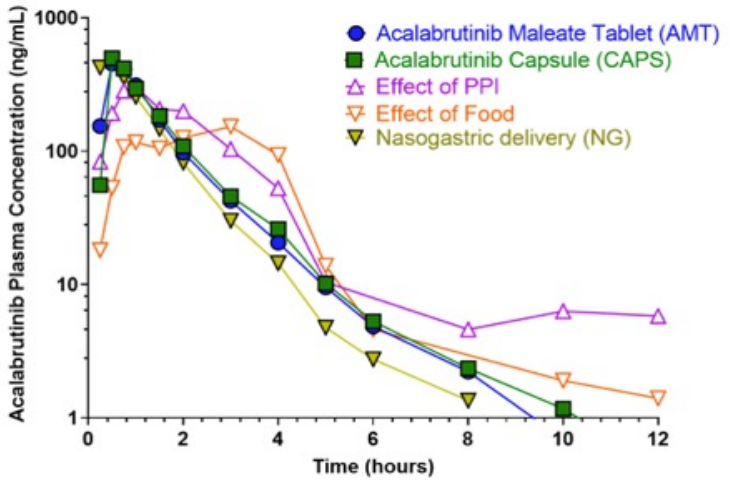
Arthralgia

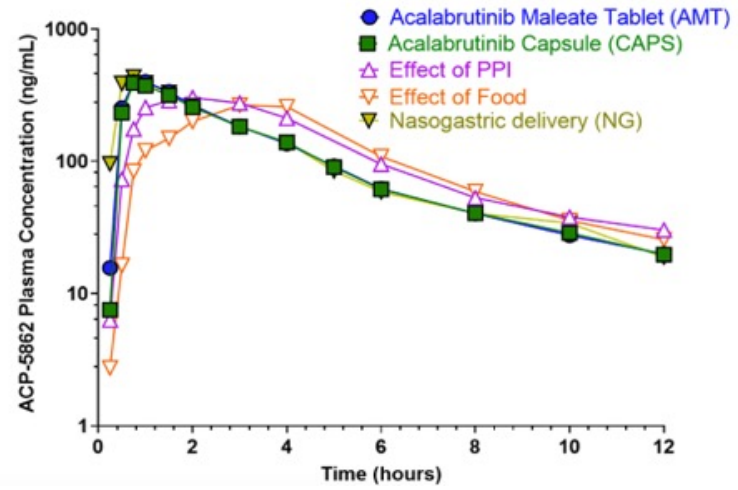


ELEVATE-PLUS: Acalabrutinib Maleate Tablet (AMT) Formulation Allowing Co-administration With PPI and Dosing in Patients Unable to Swallow

- **Three Phase 1, open-label, single-dose, cross-over studies conducted in healthy subjects demonstrated**
  - Similar systemic exposure between AMT and acalabrutinib capsules
  - No clinically relevant differences in acalabrutinib and ACP-5862 exposures was observed following administration of AMT +/- PPI
  - No clinically relevant impact of food on exposures
  - Similar BTK target occupancy
  - No new safety concerns with the AMT

PK Profiles of Acalabrutinib/ACP-5862





ACP-5862, major pharmacologically active metabolite of acalabrutinib.
Sharma S, et al. ASH 2021. Abstract 4365

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

R
1:1

Arm A
Zanubrutinib 160 mg BID

Arm B
Ibrutinib 420 mg QD

Stratification Factors

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

Primary endpoint: ORR

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.

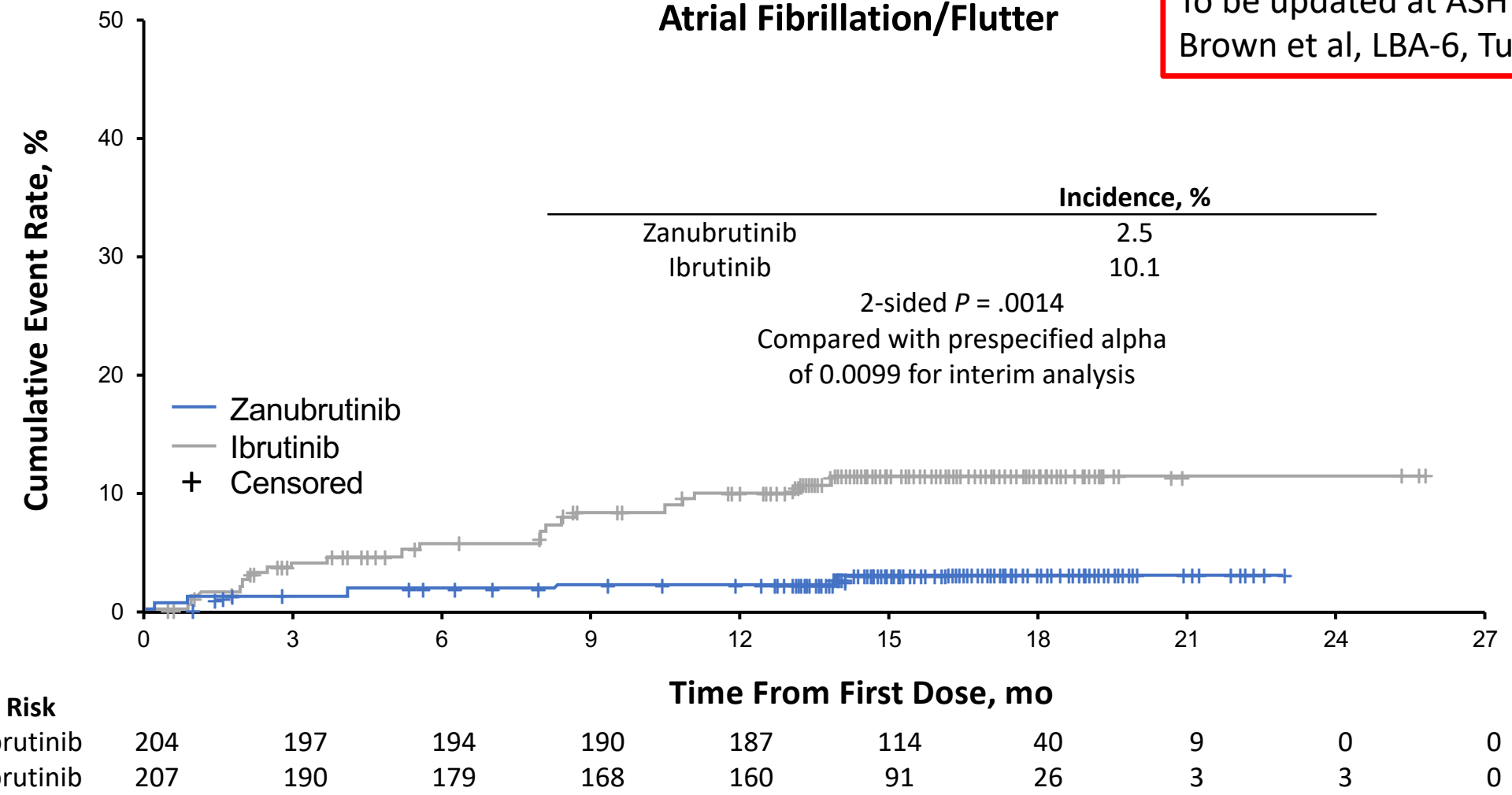
Additional AEs of Special Interest

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	73 (35.8)	6 (2.9)	75 (36.2)	6 (2.9)
Major hemorrhage[b]	6 (2.9)	6 (2.9)	8 (3.9)	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	17 (8.3)	10 (4.9)	13 (6.3)	4 (1.9)
Skin cancers	7 (3.4)	3 (1.5)	10 (4.8)	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 hemorrhages that were serious or grade ≥3 or CNS hemorrhages of all grades.
[c] Pooled terms including neutropenia, neutrophil count decreased, and febrile neutropenia; thrombocytopenia and platelet count decreased.

ALPINE: Safety Analysis with Lower Rates of A-fib/Flutter With Zanubrutinib

To be updated at ASH 2022:
Brown et al, LBA-6, Tues AM Dec. 13

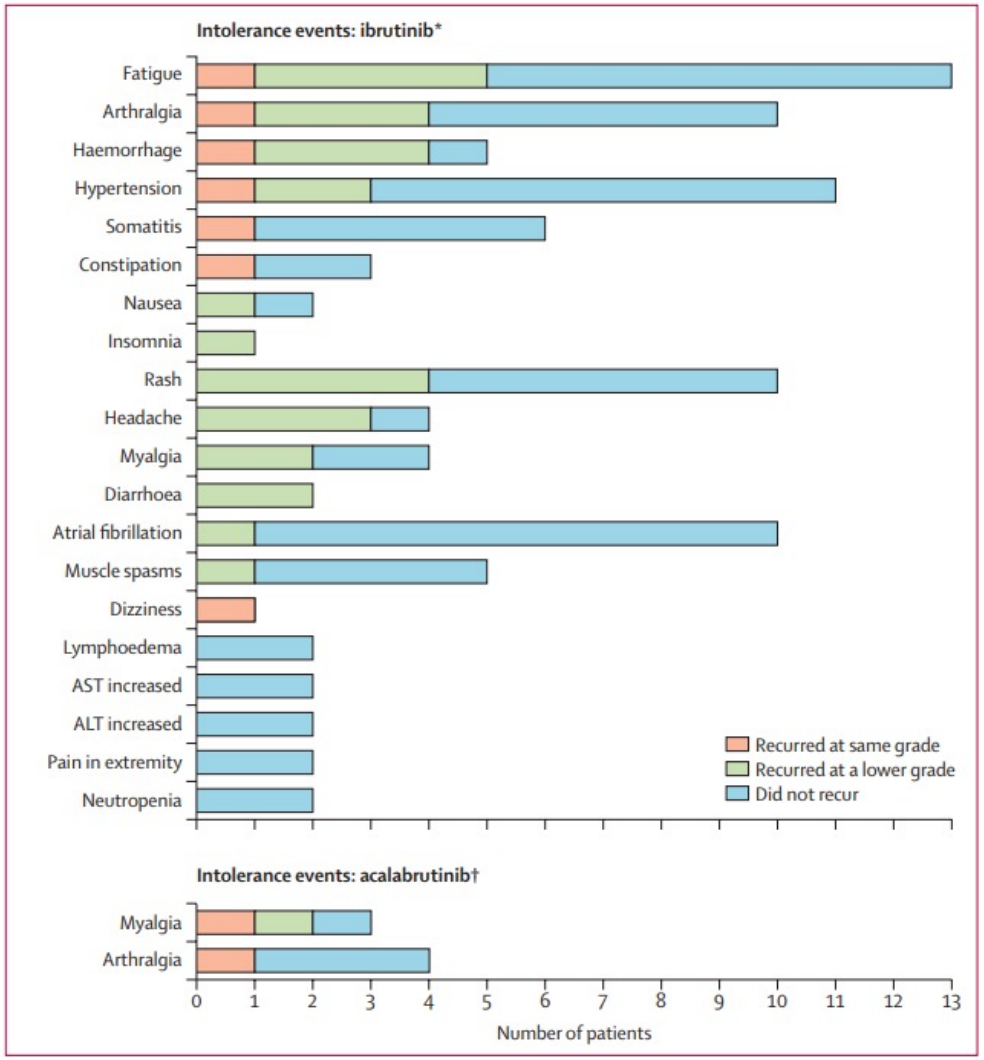


Overall AEs leading to treatment discontinuation: 16 in zanubrutinib group (8%) vs 27 for ibrutinib (13%)

Hillmen P et al. EHA 2021. Abstract LB1900.

A phase 2 study of zanubrutinib in patients with previously treated B-cell malignancies intolerant of previous BTKi

Recurrence and change in severity of ibrutinib and acalabrutinib intolerance events during treatment with zanubrutinib



Shadman et al., *Lancet Haem*, 2022

Tips for BTKi toxicity management[1]

- Avoid warfarin when anticoagulation needed
- Hypertension: proactively manage with antihypertensives
- Monitor for and manage cardiac arrhythmia/a-fib; treat appropriately
- Monitor patients for signs of bleeding

- Headaches commonly occur early in therapy with acalabrutinib and typically resolved in 1-2 months (manage with acetaminophen + caffeine)
- Monitor for neutropenia (particularly with zanubrutinib), use GCSF prn
- Monitor for infections and secondary malignancies
- Hold perioperatively depending on how significant the procedure is

1. NCCN Clinical Practice Guidelines in Oncology. Chronic Lymphocytic Leukemia. Version 2.2022. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf.

Venetoclax was generally well tolerated in phase 1, although specific toxicities were noted

Adverse events, serious adverse events and toxicity in the 116 study patients

Adverse event*	Any Grade [n (%)]	Grade 3 or 4 [n (%)]
Any	**115** (99)	**96** (83)
Diarrhea	**60** (52)	**2** (2)
Upper respiratory tract infection	**56** (48)	**1** (1)
Nausea	**55** (47)	**2** (2)
Neutropenia	**52** (45)	**48** (41)
Fatigue	**46** (40)	**4** (3)
Cough	**35** (30)	**0**
Pyrexia	**30** (26)	**1** (1)
Anemia	**29** (25)	**14** (12)
Headache	**28** (24)	**1** (1)
Constipation	**24** (21)	**1** (1)
Thrombocytopenia	**21** (18)	**14** (12)
Arthralgia	**21** (18)	**1** (1)
Vomiting	**21** (18)	**2** (2)
Peripheral oedema	**18** (16)	**0**
Pyrexia	**17** (15)	**10** (9)

Serious adverse event†	Any Grade [n (%)]	Grade 3 or 4 [n (%)]
Any	**52** (45)	
Febrile neutropenia	**7** (6)	
Pneumonia	**5** (4)	
Upper respiratory tract infection	**4** (3)	
Immune thrombocytopenia	**3** (3)	
Tumor lysis syndrome	**3** (3)	
Diarrhea	**2** (2)	
Fluid overload	**2** (2)	
Hyperglycaemia	**2** (2)	
Prostate cancer	**2** (2)	
Pyrexia	**2** (2)	

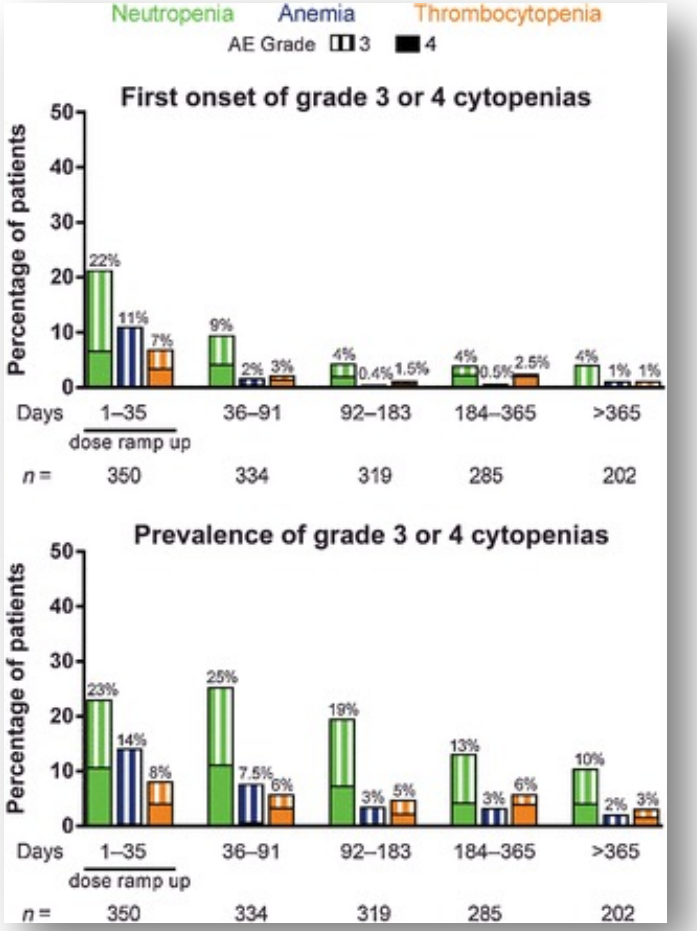
Toxicity	Any Grade (%)	Grade 3 or 4 (%)
Neutropenia	**45**	**41**
GI	**52**	**2**
TLS	**3**	**3**

*Listed are adverse events that were reported in at least 15% patients. Preexisting grade 1/2 abnormalities not reported, unless grade increased during the study.
†Listed are serious adverse events that were reported in at least two patients. Excluded are serious adverse events that were related to disease progression in two patients.

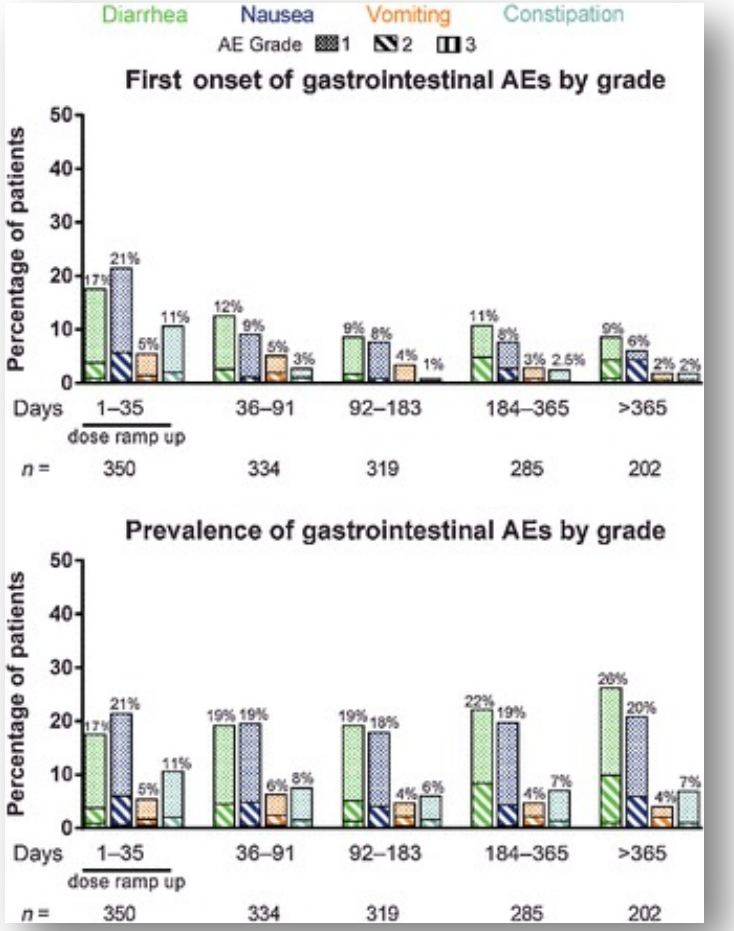
Roberts AW, Davids MS, et al. *N Engl J Med* 2016;374:311–322.

Venetoclax risks tend to decrease over time

Cytopenias



GI Toxicities



- **2/166 (1.4%) of patients treated with current dosing algorithm had biochemical laboratory changes in TLS parameters, but none had clinical TLS**

Davids MS et al., *Clin Cancer Res*, 2018

Phase 3 CLL14 study: Safety profile of ven + obin was favorable, especially after completion of therapy

Most frequent ≥ grade 3 adverse events	Venetoclax-obinutuzumab (N=212)	
	During Treatment	After Treatment
Neutropenia	51.9%	4.0%
Thrombocytopenia	13.7%	0.5%
Anemia	7.5%	1.5%
Febrile neutropenia	4.2%	1.0%
Infusion-related reaction	9.0%	0.0%
Tumor lysis syndrome	1.4%	0.0%
Neoplasms	1.4%	6.4%

Al-Sawaf et al, EHA 2020

Tips for venetoclax toxicity management

- For neutropenia (e.g. ANC <1,000), it is helpful to give growth factor support (pegfilgrastim when available) and continue venetoclax
  - Individualized frequency based on patient response
- For diarrhea, infectious etiologies should be ruled out and then anti-diarrheals can be used while continuing venetoclax
- For nausea: adjust dose timing and use antiemetics
- Dose interruption and dose reduction can be used for persistent toxicities despite the above measures
- Does **not** need to be held perioperatively

Davids MS. *Blood* 2017;130:1081–1088

CAPTIVATE-FD Cohort: Ibrut + Ven well-tolerated in a young, fit population

Median Age = 60

Treatment-Emergent AEs	All treated patients (n = 159), n (%)	
	Any grade	Grade 3/4
Most common AEs		
Diarrhea	99 (62)	5 (3)
Nausea	68 (43)	2 (1)
Neutropenia	66 (42)	52 (33)
Arthralgia	53 (33)	2 (1)
Hypertension	25 (16)	9 (6)
Neutrophil count decreased	16 (10)	8 (5)
Other AEs of clinical interest		
Atrial fibrillation	7 (4)	2 (1)
Major hemorrhage	3 (2)	2 (1)
Laboratory safety parameters		
Hematology		
Neutrophils decreased	115 (72)	60 (38)
Platelets decreased	94 (59)	20 (13)
Hemoglobin decreased	31 (19)	0
Chemistry		
Corrected calcium decreased	61 (38)	1 (1)
Potassium increased	39 (25)	4 (3)
Uric acid increased	34 (21)	34 (21)
Creatinine increased	27 (17)	0

Tam et al., *Blood*, 2022

GLOW: Ibrut + Ven had more toxicities in an older, more comorbid population

Median Age = 71

Treatment exposure — mo, median (range)	**13.8 (0.7–19.5)**	
Adverse events — n (%)	Grade 3/4	Grade 5
Patients with ≥1 adverse events	73 (68.9)	7 (6.6)
Neutropenia	37 (34.9)	0
Infections and infestations	16 (15.1)	2 (1.9)
Diarrhea	11 (10.4)	0
Hypertension	8 (7.5)	0
Atrial fibrillation	7 (6.6)	0
Thrombocytopenia	6 (5.7)	0
Hyponatremia	6 (5.7)	0
Cardiac failure	3 (2.8)	1 (0.9)
Sinus node dysfunction	1 (0.9)	1 (0.9)
Cholestasis	1 (0.9)	0
Sudden death	0	2 (1.9)
Ischemic stroke	0	1 (0.9)
Malignant neoplasm	0	1 (0.9)
Cardiac arrest	0	1 (0.9)
Tumor lysis syndrome	0	0

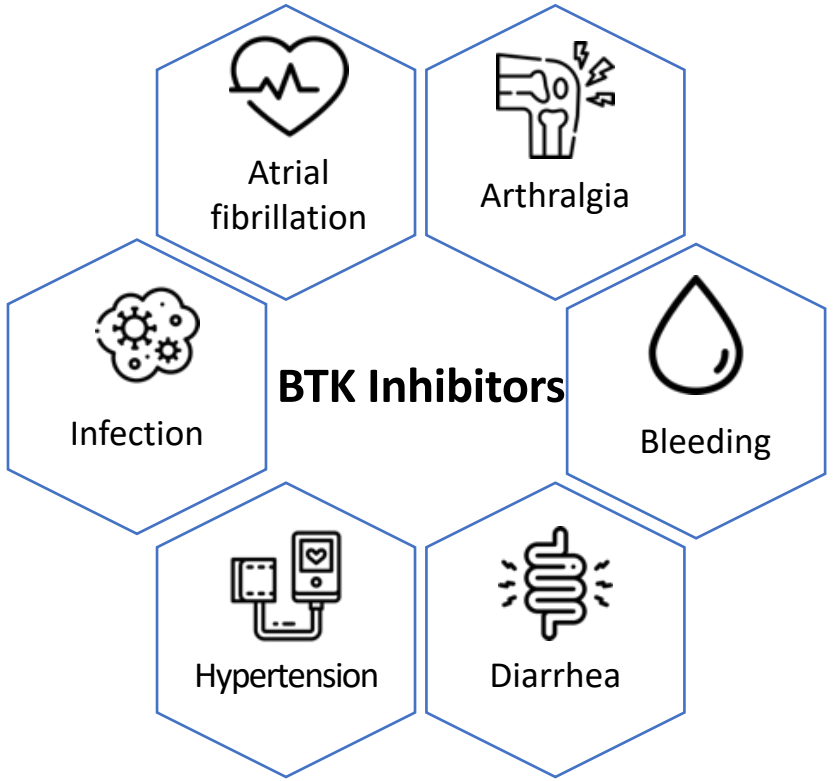
Kater et al., *NEJM Evid*, 2022

General tips for AE Management in CLL

- In the setting of active infection it is generally best to hold drug at least until seeing signs of clinical improvement (possible exception of mild COVID-19)
- For most toxicities requiring drug hold, it is preferable to either re-challenge with full dose or to start back at dose reduction but then get back to full dose
- I am more hesitant to hold drug soon after starting a novel agent or in a patient who is progressing on a novel agent
- I am less concerned about stopping drug in patients who have been on novel agents for at least a few months and are in a good clinical response
- 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

Summary of AEs with Targeted Agents in CLL

AEs With BTKi



Additional important AEs: dermatologic changes, fatigue, cytopenias, and ventricular arrhythmias

AEs With Venetoclax

- **TLS**
- **GI events**
- **Infections**
- **Myelosuppression**

APPENDIX

Editorial Review

Optimal Management of Adverse Events with BTK and Bcl-2 Inhibitors: Considerations for Special Patient Populations — Dr Davids

- Incidence of side effects (eg, hemorrhage, atrial fibrillation, infections, cytopenias, hypertension, headache) with ibrutinib, acalabrutinib and zanubrutinib in published clinical trials
  - Slides 4, 6, 9, 11, 15
- Implications for clinical decision-making of results from the Phase III ELEVATE-RR and ALPINE studies evaluating acalabrutinib and zanubrutinib, respectively, versus ibrutinib for previously treated disease
  - Slides 10-18 (indirectly)
- Pharmacokinetics, pharmacodynamics and safety of the maleate tablet formulation of acalabrutinib compared to standard capsules
  - Slide 13
- Frequency of tumor lysis syndrome and other adverse events with venetoclax therapy in CLL clinical trials
  - Slides 19-22
- Incidence and severity of clinically relevant toxicities encountered when combining BTK and Bcl-2 inhibitors
  - Slides 23-24
- NOTE: Slides 25-26 are summary of BTK and Bcl-2 inhibitors and general tips for AE management in CLL

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RESEARCH
TO PRACTICE

NO RECOMMENDED CHANGES