Crafting the New Treatment Mix in CLL

Pharmacist Insights on Delivering Effective Care With Targeted Therapy

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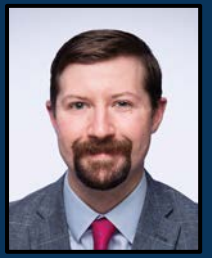

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Targeted Therapy: FDA Approvals and Current Status of BTKi and BCL2i in CLL

Agent	Target	Status in CLL/SLL
Ibrutinib[1]	BTK (covalent)	Approved
Acalabrutinib[2]		Approved
Zanubrutinib[3]		Approved
Venetoclax[4]	BCL2	Approved
Pirtobrutinib[5,a]	BTK (non-covalent)	Phase 3 BRUIN CLL-321 Phase 3 BRUIN CLL-313
Nemtabrutinib[6]		Phase 3 (BELLWAVE-008)

[a] **In January 2023, the FDA approved the non-covalent BTK inhibitor pirtobrutinib for the treatment of adults with R/R MCL after at least two lines of systemic therapy, including a BTK inhibitor[5]**

1. Imbruvica (ibrutinib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205552s002lbl.pdf.
2. Calquence (acalabrutinib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/210259s000lbl.pdf.
3. Brukinsa (zanubrutinib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/213217s007lbl.pdf.
4. Venclexta (venetoclax) Prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208573s009lbl.pdf. 5. Jaypirca (pirtobrutinib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/216059s000lbl.pdf. 6. Woyach J et al. ASH 2023. Abstract 3114.

Delivering Effective Care in the Era of Novel Therapy Can Still Be Challenging

Overreliance on CIT in community settings

informCLL registry, (2015-2018) 840 patients (459 previously untreated; 381 R/R), 96% from community practice settings[1]

CIT was the most commonly used frontline treatment 42%

Toxicity related to targeted therapy

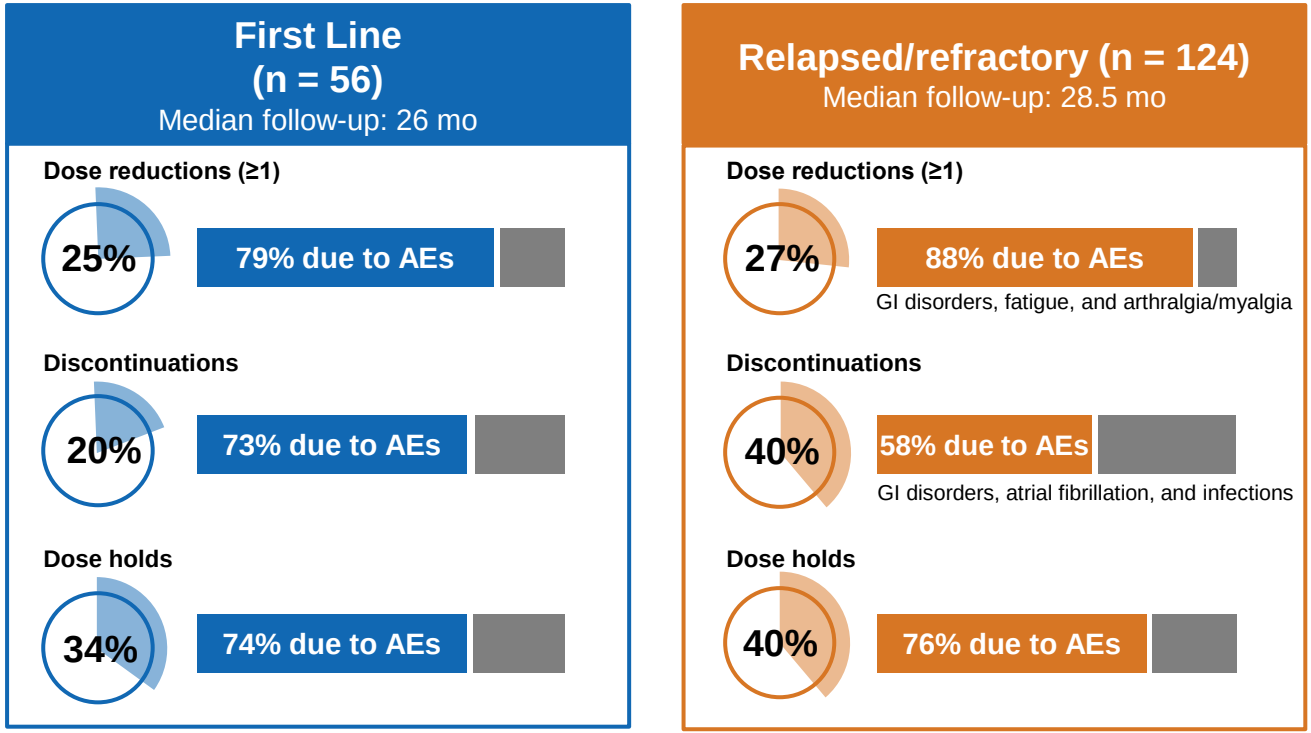
Meta-analysis of 61 trials involving 6,458 patients and 68 treatment arms featuring BTKi regimens (including ibrutinib, acalabrutinib, and zanubrutinib; most trials in CLL/SLL)[2]

Most common all grade AEs: infection (62.2%), hemorrhage (41.5%), and diarrhea (34.3%)

1. Mato A et al. *Clin Lymphoma Myeloma Leuk*. 2020;20:174-183. 2. Wang F et al. ASH 2022. Abstract 4437.

Delivering Effective Care in the Era of Novel Therapy Can Still Be Challenging (Cont'd)

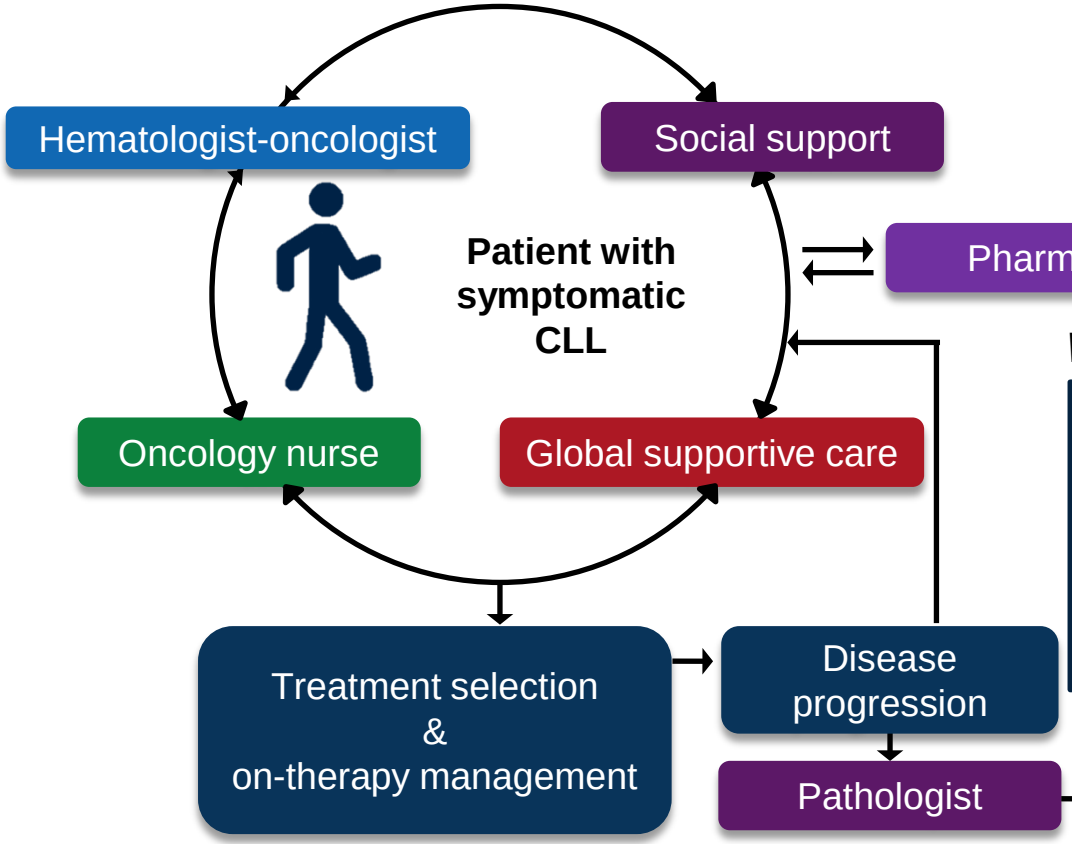
Barriers to the use of BTKi therapy can include toxicity-related dose reductions and discontinuations



From a chart review of 180 CLL patients receiving ibrutinib[1]

1. Hou J-Z et al. *Future Oncol*. 2021;17:4959-4969.

The Hematology-Oncology Management Team and the Role of the Pharmacist



What is the role of the pharmacist?

- Treatment selection
- Medication counseling
- DDI eval/procurement at times
- Long-term monitoring; AE management
- Provision of education

Our Goals for the Activity

- Help you understand the mechanistic/pharmacokinetic profiles and current evidence supporting BTK and BCL2 inhibitor approaches in CLL
- Equip you with the skills you need to develop pharmacist-informed management plans that include targeted agents for TN and R/R CLL
- Provide you with guidance on working collaboratively to address issues such as care coordination, drug–drug interactions, patient counseling, staff education, safety, and dosing considerations

The BTKi Class: The Journey So Far With Covalent Options

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Targeted Options Are Well-Represented in Practice Guidelines for CLL/SLL

NCCN Regimens for TN CLL/SLL Without Del(17p)/*TP53* Mutation[1]

Preferred	• Acalabrutinib ± obinutuzumab (category 1) • Venetoclax + obinutuzumab (category 1) • Zanubrutinib (category 1)
Other recommended (BTKi-based only)	• Ibrutinib (category 1) • Ibrutinib + CD20 mAb or venetoclax (category 2B)

1. NCCN Clinical Practice Guidelines in Oncology. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Version 1.2023. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf.

Targeted Options Are Well-Represented in Practice Guidelines for CLL/SLL

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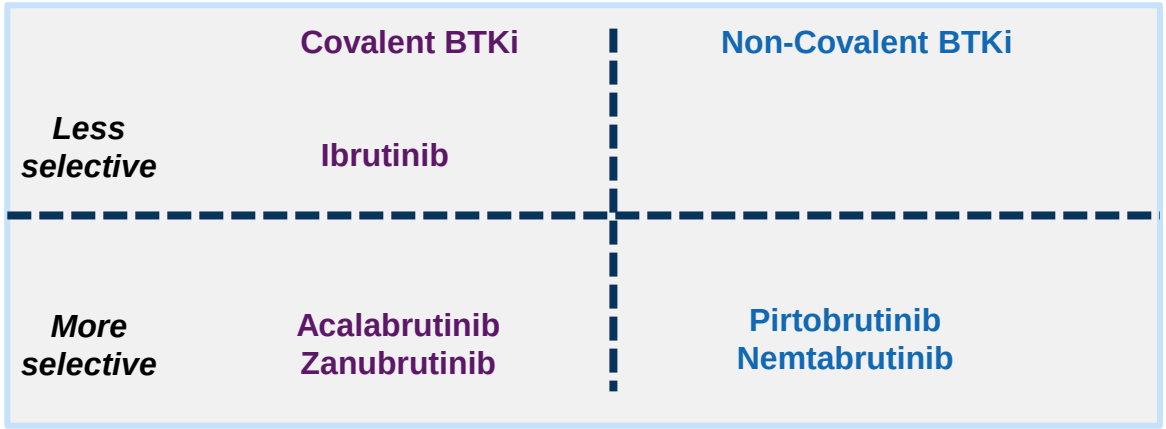
1. NCCN Clinical Practice Guidelines in Oncology. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Version 1.2023. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf.

Longer Follow-Up Confirms Efficacy of Continuous BTKi

	Alliance[1]	ELEVATE-TN[2]	SEQUOIA[3]
	Ibrutinib ± rituximab vs BR	**Acalabrutinib ± G vs G + Clb**	**Zanubrutinib vs BR**
Length of follow-up	4.5 y	5 y	>2 y (26.2 mo)
Efficacy	• 48-mo PFS estimates were **76% for ibrutinib** arms vs 47% for BR	• 60-mo PFS of **84% and 72% (A + G and acalabrutinib)** vs 21% for G + Clb	• 24-mo PFS was **86% with zanubrutinib** vs 70% for BR

1. Woyach J et al. ASH 2021. Abstract 639. 2. Sharman JP et al. ASCO 2022. Abstract 7539. 3. Tam C et al. *Lancet Oncol*. 2022;23:1031-1043.

What Are the Implications of BTKi Selectivity for Off-Target Effects?[1-5]



Less selective BTK inhibitors have more off-target effects, which contribute to more toxicity compared with more selective agents[2]

A hypothesis validated in head-to-head trials

1. Kaptein A et al. ASH 2018. Abstract 1871. 2. Bose P et al. *Expert Opin Drug Metab Toxicol*. 2016;12:1381-1392. 3. Herman SEM et al. *Clin Cancer Res*. 2017;23:2831-2841. 3. Owen C et al. *Curr Oncol*. 2019;26:e233-e240. 4. Mato A et al. *Lancet*. 2021:397:892-901. 5. Brandhuber BJ et al. *Clin Lymphoma Myeloma Leuk*. 2018;18:S216.

ELEVATE-RR: Lower Incidence of Any Grade of AF/Flutter With Acalabrutinib vs Ibrutinib

Key Secondary Endpoint From ELEVATE-RR (Median Follow-Up of 40.9 Months)[1]

Events	Acalabrutinib (n = 266)	Ibrutinib (n = 263)
	Any Grade	
AF/flutter, n (%)	**25 (9.4)**	**42 (16.0)**
Events/100 person-months	0.366	0.721
Median time to onset, mo (range)	28.8 (0.4-52.0)	16.0 (0.5-48.3)
Leading to treatment discontinuation, n (%)	**0**	**7 (16.7)**
AF/flutter incidence among patients without prior history of AF/flutter, n (%)	15/243 (6.2)	37/249 (14.9)

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

ELEVATE-RR: Lower Incidence of Any Grade of Hypertension and Bleeding With Acalabrutinib vs Ibrutinib[1]

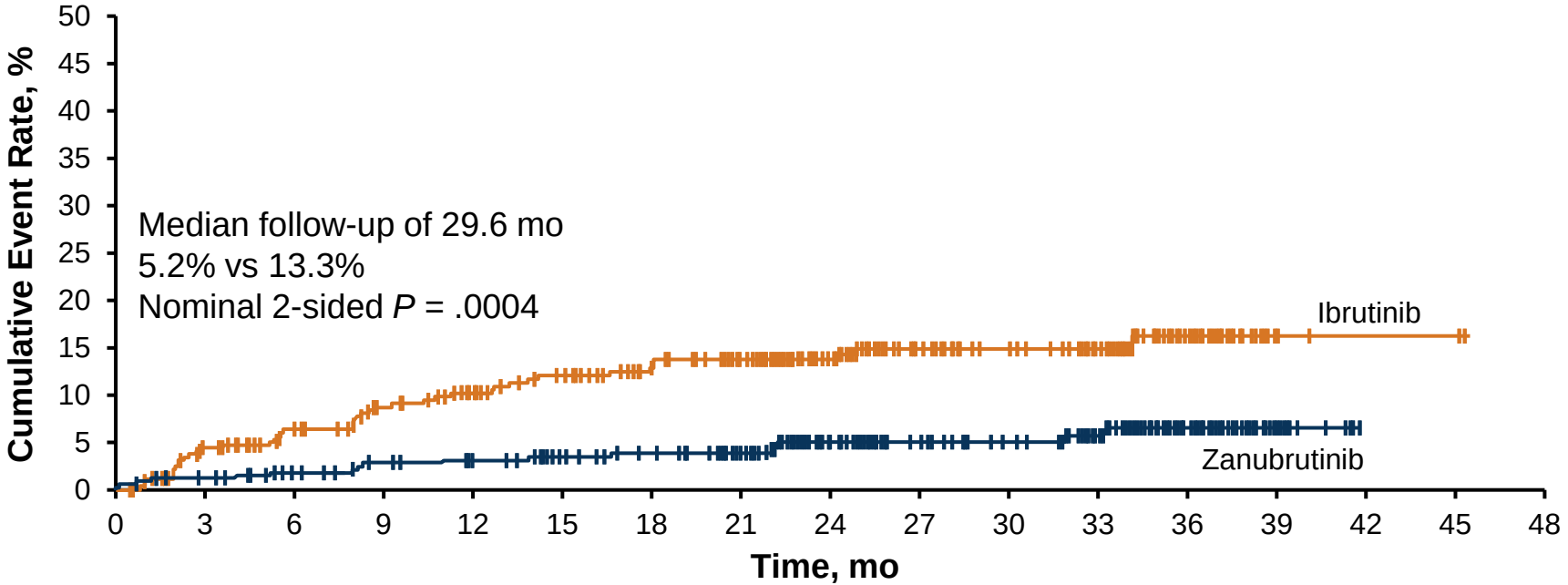
Events, n (%)	Acalabrutinib (n = 266)		Ibrutinib (n = 263)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Cardiac events	64 (24.1)	23 (8.6)	79 (30.0)	25 (9.5)
AF[a]	25 (9.4)	13 (4.9)	42 (16.0)	10 (3.8)
Ventricular tachyarrhythmias	0	0	1 (0.4)	1 (0.4)
Hypertension[b]	**25 (9.4)**	11 (4.1)	**61 (23.2)**	24 (9.1)
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)
ILD/pneumonitis	7 (2.6)	1 (0.4)	17 (6.5)	2 (0.8)
SPMs excluding nonmelanoma skin cancers	24 (9.0)	16 (6.0)	20 (7.6)	14 (5.3)

[a] Includes AF/flutter. [b] Includes hypertension, blood pressure increased, and blood pressure systolic increased.

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

ALPINE: Safety Analysis Showed Lower Rates of AF/Flutter With Zanubrutinib Compared With Ibrutinib[1]

Fewer AF/Flutter Events With Zanubrutinib Versus Ibrutinib



No. at Risk

Zanubrutinib	324	312	302	294	288	277	268	249	199	164	148	120	51	10	0	–	–
Ibrutinib	324	295	278	260	247	230	211	193	153	121	108	89	40	3	2	1	0

1. Brown J et al. ASH 2022. Abstract LBA-6.

ALPINE: Safety Analysis Shows Fewer Serious Cardiac AEs With Zanubrutinib Versus Ibrutinib[1]

Events	Zanubrutinib (n = 324), n (%)	Ibrutinib (n = 324), n (%)
Cardiac AEs	69 (21.3)	96 (29.6)
Serious cardiac AEs	6 (1.9)	25 (7.7)
Cardiac AEs leading to treatment discontinuation	**1 (0.3)**	**14 (4.3)**
Ventricular extrasystoles	1 (0.3)	0
Atrial fibrillation	0	5 (1.5)
Cardiac arrest	0	2 (0.6)[a]
Cardiac failure	0	2 (0.6)
Cardiac failure acute	0	1 (0.3)[a]
Congestive cardiomyopathy	0	1 (0.3)[a]
Myocardial infarction	0	1 (0.3)[a]
Palpitations	0	1 (0.3)
Ventricular fibrillation	0	1 (0.3)

[a] Cardiac deaths. One death not listed due to myocardial infarction with ibrutinib discontinuation due to diarrhea 14 days prior to the fatal event.

1. Brown J et al. ASH 2022. Abstract LBA-6.

The Rapid Emergence of Non-Covalent BTKi

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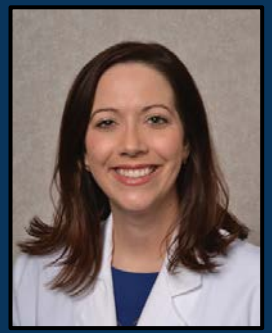
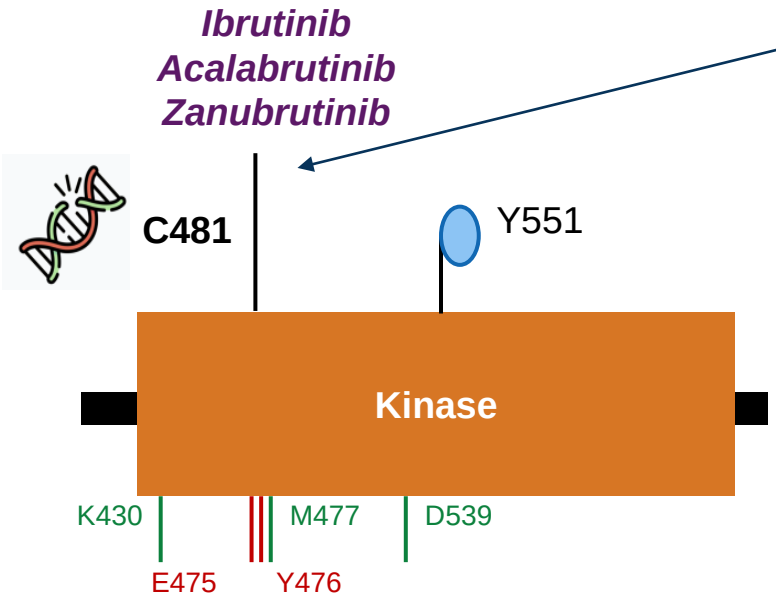


The Challenge of BTK Resistance



Structure of the Bruton tyrosine kinase: focus on the C481 site

***BTK* C481 mutations confer resistance to all covalent BTK inhibitors because they bind at the C481 site**

***BTK* resistance mutations** contribute to disease progression in patients on therapy with covalent BTKi

Non-Covalent BTKi Are Active Against *BTK* C481 Mutations

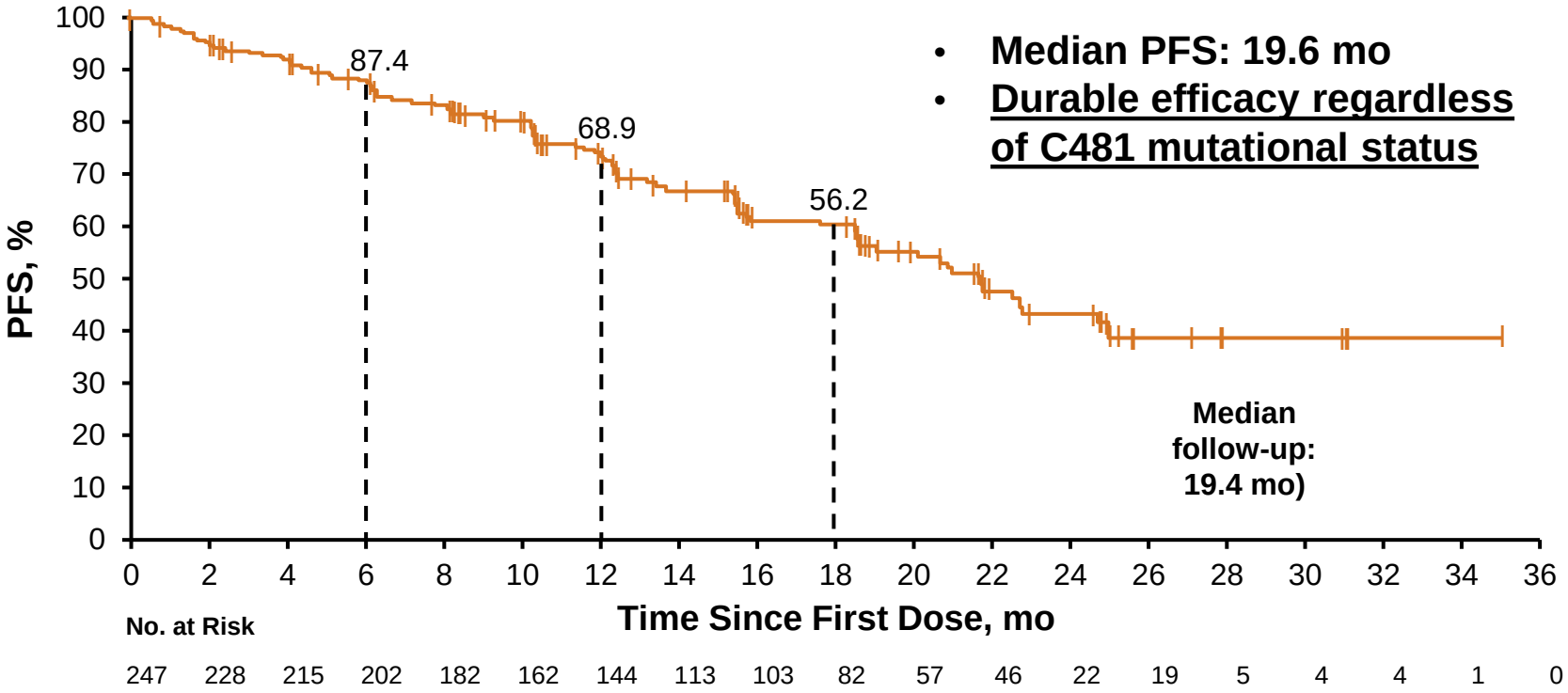
Feature	Ibrutinib	Nemtabrutinib[1,2,a] (in phase 3 trials in CLL/SLL)	Pirtobrutinib[3] (in phase 3 trials in CLL, approved in MCL)
Target	BTK	BTK	BTK
Bond type	Irreversible covalent	Reversible non-covalent	Reversible non-covalent
Requires C481 residue?	Yes	No	No
Active in C481 mutations?	No	Yes	Yes

[a] Investigational.

1. Byrd JC et al. *Oncotarget.* 2018;27:13023-13035. 2. Reiff SD et al. ASH 2016. Abstract 3232. 3. Brandhuber B et al. SOHO 2018. Abstract CLL-200.

BRUIN Update: Robust Response and PFS With Pirtobrutinib in BTKi-Pretreated R/R CLL/SLL Patients[1]

ORR of 82.2% in BTKi-pretreated patients with CLL/SLL



- **Median PFS: 19.6 mo**
- **Durable efficacy regardless of C481 mutational status**

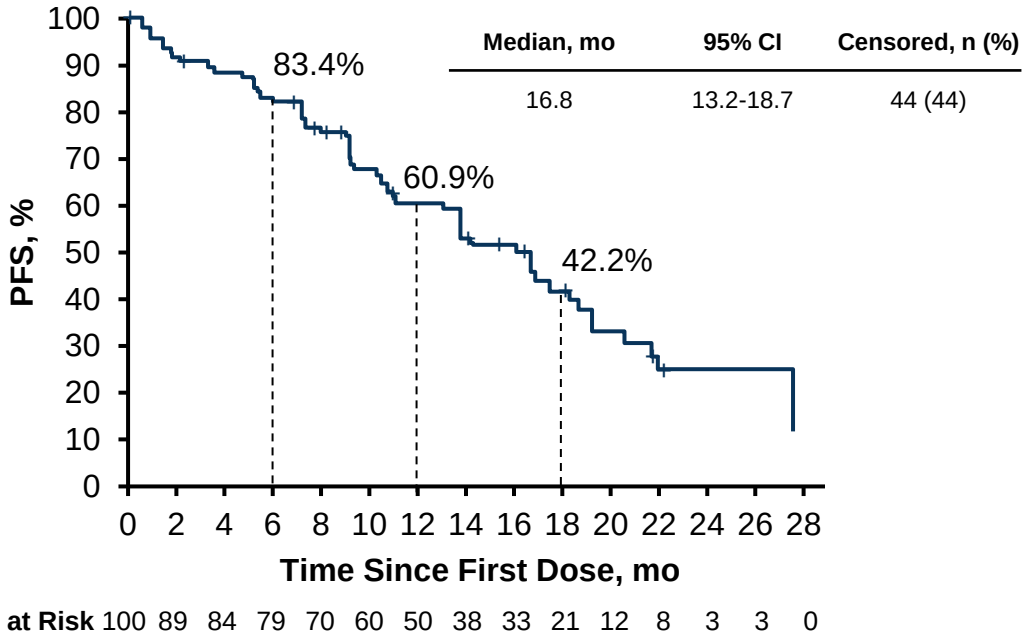
1. Mato A et al. ASH 2022. Abstract 961.

Pirtobrutinib Is Efficacious in Patients With Prior Exposure to BTKi/BCL2 Inhibitor Therapy[1]

ORR of 79% in BTKi/BCL2i pretreated patients with CLL/SLL

Median PFS of 16.8 months in patients with double-exposed disease

Prior BTKi and BCL2i Patients Median Prior Lines = 5



Median follow-up of 18.2 months for patients who received prior BTKi and BCL2i

1. Mato A et al. ASH 2022. Abstract 961.

BRUIN: Pirtobrutinib Is Associated With a Low Rate of *BTK*-Mediated AEs[1]

	All Doses and Patients (N = 773)			
	Treatment-Emergent AEs (≥15%), %		Treatment-Related AEs, %	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
AE				
Fatigue	28.7	2.1	9.3	0.8
Diarrhea	24.2	0.9	9.3	0.4
Neutropenia	24.2	20.4	14.7	11.5
Contusion	19.4	0	12.8	0
Cough	17.5	0.1	2.3	0
COVID-19	16.7	2.7	1.3	0
Nausea	16.2	0.1	4.7	0.1
Dyspnea	15.5	1	3	0.1
Anemia	15.4	8.8	5.2	2.1
AEs of special interest				
Bruising	23.7	0	15.1	0
Rash	12.7	0.5	6	0.4
Arthralgia	14.4	0.6	3.5	0
Hemorrhage/hematoma	11.4	1.8	4	0.6
Hypertension	9.2	2.3	3.4	0.6
AF/flutter	2.8	1.2	0.8	0.1

1. Mato A et al. ASH 2022. Abstract 961.

The Non-Covalent BTKi Nemtabrutinib Is Also Effective in Pretreated CLL/SLL[1]

Patients With CLL/SLL Treated With Nemtabrutinib 65 mg Once Daily (N = 57)

	CLL/SLL With Prior BTK and BCL2 Inhibitors	C481S-Mutated BTK	Del(17p)	IGHV Unmutated
n (%)	24 (42)	36 (63)	19 (33)	30 (53)
ORR, % (95% CI)	58 (37-78)	58 (41-75)	53 (29-76)	50 (31-69)
Objective response, n (%)	14 (58)	21 (58)	10 (53)	15 (50)
CR	0	1 (3)	1 (5)	0
PR	6 (25)	11 (31)	2 (11)	8 (27)
PR with residual lymphocytosis	8 (33)	9 (25)	7 (37)	7 (23)
Median DOR, mo	8.5	24.4	11.2	24.4
95% CI	2.7-NE	8.8-NE	5.7-NE	8.5-NE
Median PFS, mo	10.1	26.3	10.1	15.9
95% CI	7.4-15.9	10.1-NE	4.6-NE	7.4-NE

Nemtabrutinib 65 mg showed promising and durable antitumor activity with a manageable safety profile in a highly R/R population who had prior therapy with novel agents

ORR of 63% in C481S-mutated disease

1. Woyach J et al. ASH 2022. Abstract 3114.

Overview of BCL2 and BCL2/BTKi Combinations in CLL

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Fixed-Duration Venetoclax Regimens Are Effective First-Line and Second-Line Options in CLL

Study	Population	PFS Outcome
CLL14[1] G + Clb vs venG	TN CLL Unfit (CIRS >6 or CrCl <70)	Improved PFS with venG: estimated **5-year PFS of 62.6% vs 27% for GClb**
MURANO[2] VenR vs BR	R/R CLL	Improved PFS with venR; **median PFS of 54 vs 17 mo for BR** HR = 0.19; *P* < .0001

Both venG and venR are included in practice guidelines for TN and R/R CLL, respectively

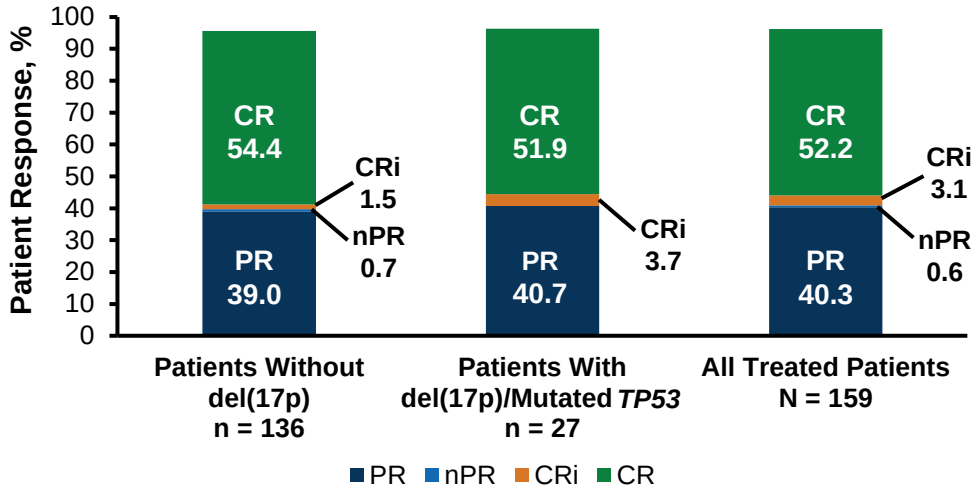
1. Al-Sawaf O et al. EHA 2022. Abstract S148. 2. Seymour J et al. *Blood*. 2022;140:839-850.

CAPTIVATE: FD Ibrutinib + Venetoclax Shows Robust Activity Against TN CLL[1]

Fixed-duration combination of ibrutinib + venetoclax

This strategy achieved durable responses, clinically meaningful PFS, and treatment-free remissions in TN CLL

Similar ORR of 96% in All Patients and Those ± Del(17p)



- Based on these data and the phase 3 GLOW trial, FD ibrutinib + venetoclax was approved in the EU for adults with TN CLL[2]

1. Tam C et al. *Blood*. 2022;139:3278-3289. 2. https://lymphomahub.com/medical-information/fixed-duration-ibrutinib-venetoclax-receives-ec-approval-as-first-line-treatment-for-chronic-lymphocytic-leukemia#.

Characterizing Safety With Novel Time-Limited Combinations[1]

CAPTIVATE (median follow-up of 27.9 mo[2])

- Most common grade ≥3 AEs were neutropenia (33%) and hypertension (6%)
- AEs led to dose reductions of ibrutinib in only 9 patients (6%), venetoclax in only 18 patients (11%), and both ibrutinib and venetoclax in only 6 patients (4%)

Take-home: Combinations appear to be highly effective, but safety may be a consideration, especially in older patients

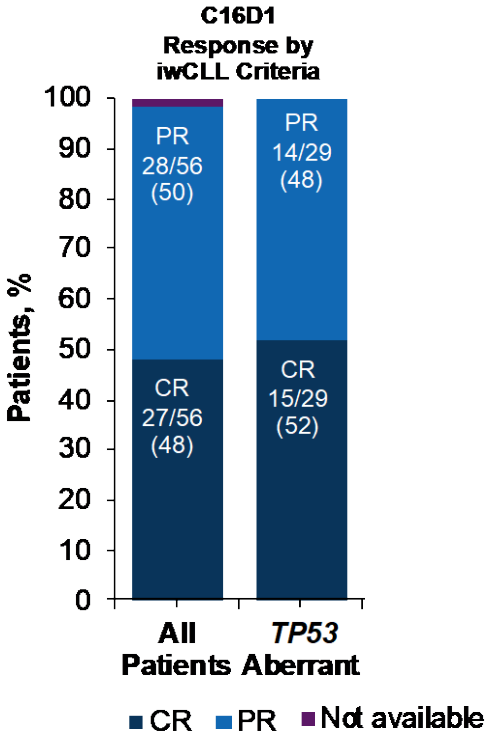
1. Tam C et al. *Blood*. 2022;139:3278-3289.

Time-Limited Acalabrutinib, Venetoclax, and Obinutuzumab (AVO) Is Active in TN CLL

Phase 2 Study Testing AVO in a Population Enriched for High-Risk Features[1]

Take-Homes

- AVO is a highly active, well-tolerated triplet
- 98% ORR by cycle 16, day 1 (48% CR)
- BM-uMRD of 83% in *TP53*-aberrant patients after 15 mo of treatment
- Responses are durable, with 93% PFS in all patients at a median follow-up of nearly 3 y
- Low rates of cardiac and infectious toxicities were observed



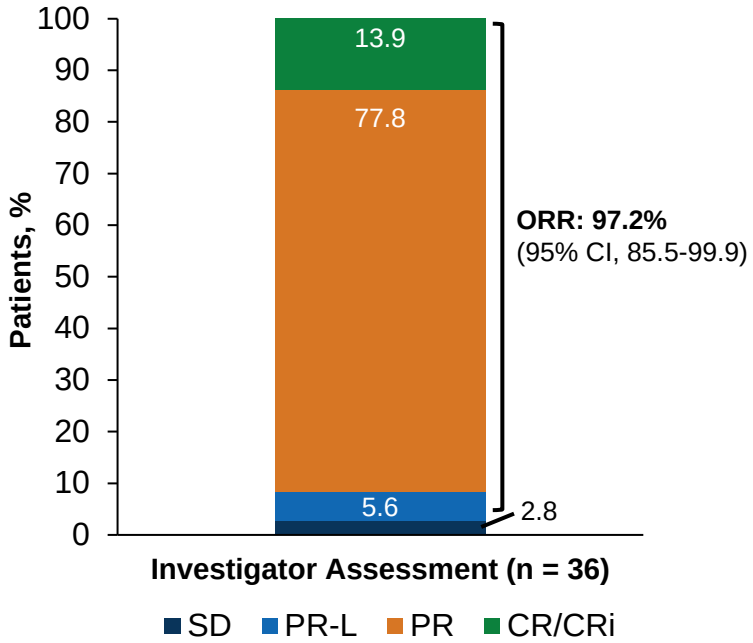
1. Ryan C et al. ASH 2022. Abstract 344.

Zanubrutinib-Venetoclax Combination Is Active in Del(17p) CLL

SEQUOIA Arm D Tested Zanubrutinib-Venetoclax in High-Risk CLL[1]

Of 36 evaluable patients, 14 were treated with the combination therapy for at least 12 months

ORR of 97%



1. Tedeschi A et al. ASH 2021. Abstract 67.

Dosing, Adverse Events, and Drug Interactions With BTKi and BCL2i

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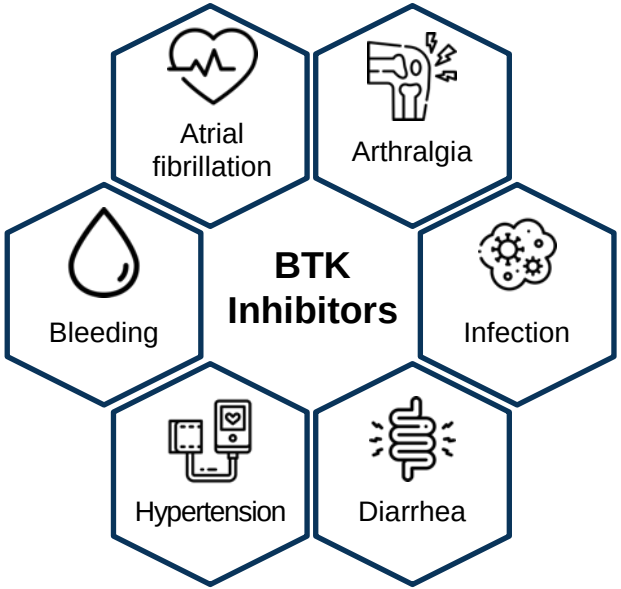
Summing Up the Safety Experience to Date With BTK Inhibitors and Venetoclax in CLL[1,2]

AEs to Note With BTKi



Additional AEs: dermatologic changes, fatigue, cytopenias, and ventricular arrhythmia

AEs to Note With Venetoclax

- TLS
- GI events
- Infections
- Myelosuppression

1. Lipsky A, Lamanna N. *Hematology Am Soc Hematol Educ Program.* 2020;1:336-345. 2. Seymour JF et al. *N Engl J Med*. 2018;378:1107-1120.

Dosing of Covalent BTKi in CLL

	Standard Dose in CLL	Currently Available Dosage Forms
Ibrutinib[1]	420 mg once daily (differs from dose used in MCL)	Capsules, tablets, oral suspension
Acalabrutinib[2]	100 mg twice daily	Tablets
Zanubrutinib[3]	160 mg twice daily or 320 mg once daily	Capsules

1. Imbruvica (ibrutinib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205552s002lbl.pdf. 2. Calquence (acalabrutinib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/210259s000lbl.pdf. 3. Brukinsa (zanubrutinib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/213217s007lbl.pdf.

Be Prepared to Review Dosing and Drug Interactions With BTKi When Counseling Patients

	Coadministration With[1]			
BTKi Dosing in CLL	**Strong CYP3A Inhibitors**	**Moderate CYP3A Inhibitors**	**Moderate or Strong CYP3A Inducers**	**Gastric Acid–Reducing Agents**
Ibrutinib 420 mg once daily	• Reduce to 140 mg once daily • For short-term use (≤7 d), interrupt ibrutinib	Reduce to 280 mg once daily	Avoid use	No dosage adjustment recommended
Acalabrutinib maleate salt (IR film-coated tablet)[2] 100 mg every 12 hours (Capsules discontinued, transition to tablet)	Avoid use	Reduce to 100 mg once daily	Avoid use; if necessary, increase to 200 mg twice daily	**Tablets can be used regardless of use of PPIs and ingestion of food**
Zanubrutinib 160 mg orally twice daily or 320 mg orally once daily	Reduce to 80 mg once daily	Reduce to 80 mg twice daily	Avoid use	No dosage adjustment recommended

1. Weis TM et al. *J Oncol Pharm Pract.* 2022;28:1411-1433. 2. Sharma S et al. ASH 2021. Abstract 4365.

Safety Considerations With Covalent BTKi: Ibrutinib[1]

- **Bleeding:** monitor for bleeding and manage
  - Do not give concomitantly with warfarin; consider non-warfarin anticoagulation
- **Infections:** monitor patients for fever and infections, evaluate promptly, and treat
- **CV events**
  - Evaluate cardiac history and function at baseline
  - Monitor for symptoms of arrhythmias, cardiac function, and cardiac failure
- **Hypertension**
  - Monitor blood pressure
  - Manage with antihypertensives
- **Cytopenias:** check complete blood counts monthly

1. Imbruvica (ibrutinib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210563s000lbl.pdf.

Safety Considerations With Covalent BTKi: Acalabrutinib[1]

- **Certain events, such as AF or HTN, can occur with the BTKi class**
- Head-to-head evidence shows fewer AF/flutter or HTN events with acalabrutinib vs ibrutinib
  - When using acalabrutinib, monitoring for arrhythmias is recommended
- **Monitor for infections, bleeding, and cytopenias (for the latter monitor CBCs regularly)**

- **Headaches commonly occur early in therapy with acalabrutinib and typically resolve in 1-2 months; manage with acetaminophen + caffeine**

Current guidelines and evidence indicate that sequencing to second-generation BTKi can be a useful strategy in settings of ibrutinib-intolerance[2,3]

1. Calquence (acalabrutinib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/210259s000lbl.pdf. 2. NCCN Clinical Practice Guidelines in Oncology. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Version 1.2023. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf. 3. Rogers KA et al. *Haematologica*. 2021;106:2364-2373.

Safety Considerations With Covalent BTKi: Zanubrutinib[1]

- **Certain events, such as AF or HTN, can occur with the BTKi class**
- Head-to-head data show fewer AF/flutter events with zanubrutinib vs ibrutinib
  - When using zanubrutinib, monitoring for arrhythmias is recommended
- **Monitor for infections, bleeding, and cytopenias (monitor CBCs regularly)**

- **Neutropenia with zanubrutinib: for first occurrence, dose interruption is recommended**
  - Once toxicity has resolved to grade 1 or lower or baseline, resume at 160 mg twice daily or 320 mg once daily

Current guidelines and evidence indicate that sequencing to second-generation BTKi can be a useful strategy in settings of ibrutinib-intolerance[2,3]

1. Brukinsa (zanubrutinib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/213217s005lbl.pdf. 2. NCCN Clinical Practice Guidelines in Oncology. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Version 1.2023. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf. 3. Shadman M et al. *Lancet Haematol*. 2023;10:e35-e45.

Non-Covalent BTKi: Dosing and Safety of Pirtobrutinib

Based on MCL labeling and experience in CLL/SLL[1,2]

Dosing

200 mg orally once daily is approved for MCL but is also used in phase 2 testing for CLL/SLL (BRUIN)

Safety

Monitor for arrythmias, infections, bleeding, and cytopenias

Drug Interactions

- **Strong CYP3A inhibitors:** avoid concomitant use; if unavoidable, reduce dose
- **Strong/moderate CYP3A inducers:** avoid concomitant use; if unavoidable increase dose

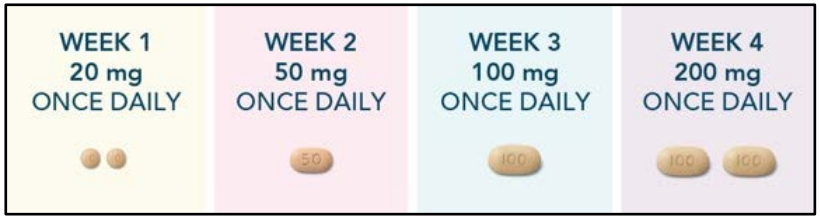
1. Jaypirca (pirtobrutinib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/216059s000lbl.pdf.
2. Mato A et al. ASH 2022. Abstract 961.

Dosing and Drug–Drug Interactions With Venetoclax[1,2]

Venetoclax standard dose in CLL

- 400 mg once daily with ramp-up dosing to target dose by week 5
- Tablet: 10 mg, 50 mg, and 100 mg

Ramp-Up Dosing Schedule



Strong CYP3A Inhibitors	Moderate CYP3A Inhibitors	Moderate or Strong CYP3A Inducers	P-gp Inhibitors	Gastric Acid Reducing Agents
• Avoid use during initiation and ramp-up phase • After ramp-up, 100 mg once daily	200 mg once daily	Avoid use	200 mg once daily	No dosage adjustment recommended

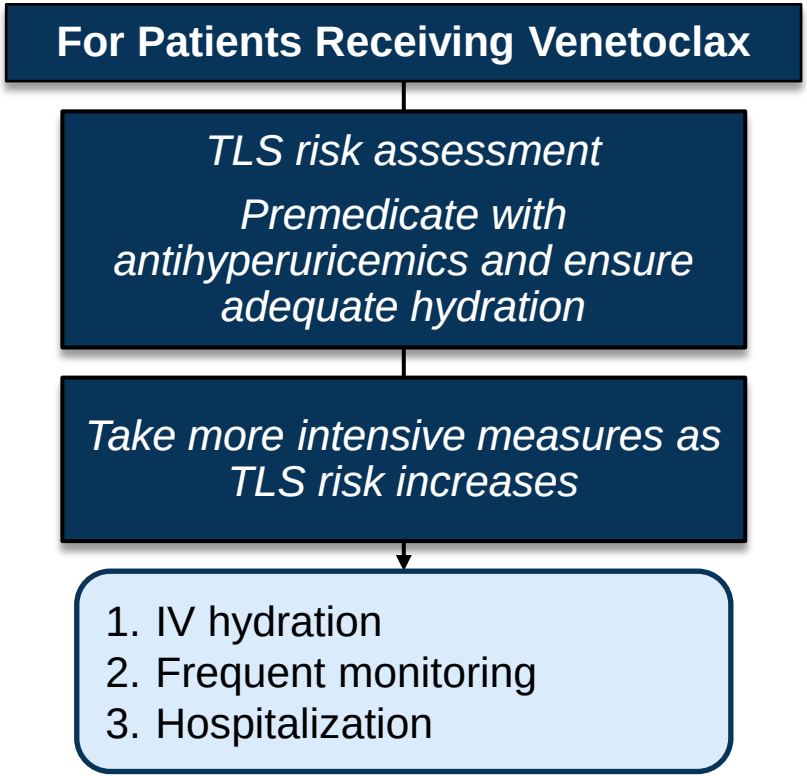
1. Venclexta (venetoclax) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208573s000lbl.pdf.
2. Weis T et al. *J Oncol Pharm Practice.* 2022:1-23.

TLS With Venetoclax in CLL[1,2]

- Encourage patients to limit foods/fluids containing potassium and phosphorus
- Encourage oral intake of fluids

Watch for Hyperuricemia Symptoms	
Nausea and vomiting	Clouding of urine
Shortness of breath	Lethargy
Irregular heartbeat	Joint discomfort

Note: Data suggest that patients who receive venetoclax in the real-world setting may be more likely to have comorbid conditions leading to increased risk of TLS when compared with patients enrolled in RCTs[3]

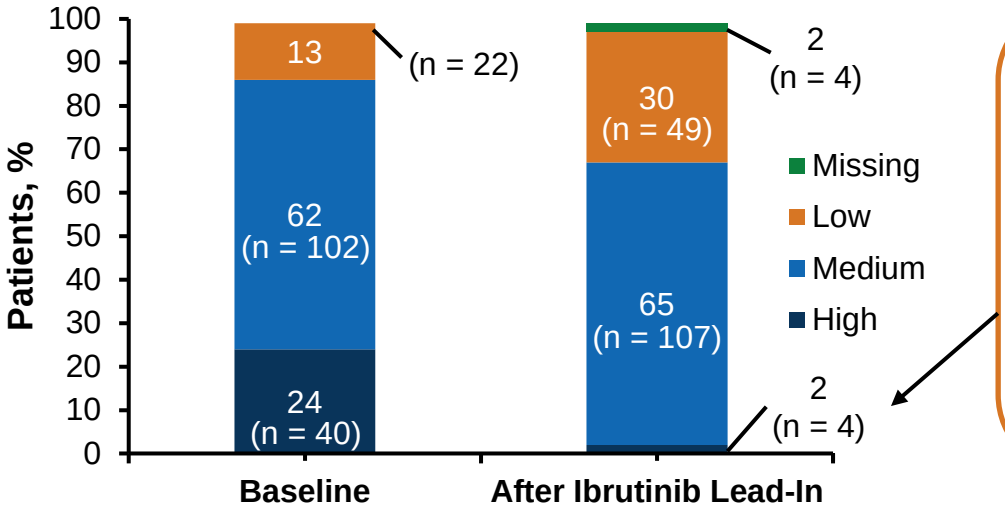


1. Maloney K, Denno M. *Clin J Oncol Nurs*. 2011;15:601-603. 2. Venclexta (venetoclax) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/208573s013lbl.pdf. 3. Mato A et al. *Haematologica*. 2018;103:1511-1517.

The Early Experience With Ibrutinib/Venetoclax: Reductions in TLS Risk Through Effective Debulking

When Ibrutinib-Venetoclax Are Used in Combination, Debulking With Lead-In Ibrutinib Reduced the Severity of TLS[1]

Impact of single-agent ibrutinib lead-in on TLS risk category



Three cycles of single-agent ibrutinib reduced TLS risk category in 90% of patients with high baseline risk and only 2% remained in the high-risk category before initiation of venetoclax ramp-up

1. Wierda W et al. *J Clin Oncol*. 2021;39:3853-3865.

Venetoclax: Other AEs of Interest Include Neutropenia[1-3]

- **Neutropenia: manage with dose interruption/reduction**
  - For grade ≥3 neutropenia, consider G-CSF and/or antibiotics

Grade 3 neutropenia with infection or fever; or grade 4 hematologic toxicities (except lymphopenia)

1st occurrence	• Interrupt treatment • Upon resolution to grade 1 or baseline level, resume venetoclax at the same dose
2nd occurrence	• Interrupt treatment • Upon resolution to grade 1 or baseline level, resume venetoclax at a lower dose

1. Stilgenbauer S et al. *Lancet Oncol.* 2016;17:768-778. 2. Seymour JF et al. *N Engl J Med.* 2018;378:1107-1120.
3. Venclexta (venetoclax) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208573s000lbl.pdf.

Case Forum: Exploring the Role of the Pharmacist on the CLL Team

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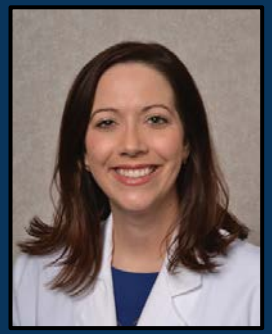

Case 1: Choosing Upfront Therapy & the Role of the Pharmacist

Melissa, a 59-year-old patient presenting with symptomatic higher-risk TN CLL

- **Good PS (0-1)**
- **Unmutated IGHV and complex karyotype**
- **Renal insufficiency (CrCl: 50 mL/min); history of AF and HTN**

Physician recommends a continuous BTKi for this patient, what are next steps for pharmacists?

Pharmacokinetic Considerations With BTKi and BCL2i in CLL[1]

Agent Half-Life, h	Metabolism and Transport	Active Metabolite	Elimination	Dosing for Renal Impairment	Dosing for Hepatic Dysfunction
Ibrutinib 4-6	• Hepatic via CYP3A4 (major), CYP2D6 (minor)	Yes, PCI-45227 (15-fold less potent inhibition of BTK)	• Feces (80%) • Urine (<10%)	• No dosage adjustment recommended	• Child-Pugh A: 140 mg daily • Child-Pugh B: 70 mg daily • Child-Pugh C: avoid use
Acalabrutinib 0.6-2.8 (parent drug) 6.9 (active metabolite)	• Hepatic via CYP3A4 (major) • P-gp substrate (minor), BCRP substrate (minor)	Yes, ACP-5862 (2-fold less potent inhibition of BTK)	• Feces (84%) • Urine (12%)	• No dosage adjustment recommended	• Child-Pugh C: avoid use
Zanubrutinib 2-4	• Hepatic via CYP3A4 (major) • Induces CYP3C19 (weak) and CYP3A4 (weak)	No	• Feces (87%) • Urine (8%)	• No dosage adjustment recommended	• Child-Pugh C: 80 mg twice daily
Venetoclax 26	• Hepatic via CYP3A4 (major), P-gp (minor)	Yes, M27 (58-fold less potent inhibition of BCL2)	• Feces (>99%)	• No dosage adjustment recommended • Use with caution and monitor for increased risk of TLS	• Child-Pugh A: No dosage adjustment recommended • Child-Pugh B: No dosage adjustment recommended • Child-Pugh C: Reduce venetoclax dose by 50%

1. Weis T et al. *J Oncol Pharm Practice.* 2022:1-23.

Case 1: Choosing Upfront Therapy & the Role of the Pharmacist

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- **Renal insufficiency (CrCl: 50 mL/min); history of AF and HTN**

Physician recommends a continuous BTKi for this patient; recommended next steps include:

- ❑ Check medication interactions
- ❑ Evaluate comorbidities
- ❑ Discuss with patient dosing, safety profiles, and potential drug interactions

Case 1: Choosing Upfront Therapy & the Role of the Pharmacist

Melissa, a 59-year-old patient presenting with symptomatic higher-risk TN CLL

- **Good PS (0-1)**
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- **Renal insufficiency (CrCl: 50 mL/min); history of AF and HTN**

+

History of AF & CV risk factors (HTN)
Given risk factors, a second-generation BTKi (acalabrutinib or zanubrutinib) is recommended for this patient

Case 1 Continued: Therapeutic Considerations at Progression

Melissa, a 59-year-old patient presenting with symptomatic higher-risk TN CLL

- **Good PS (0-1)**
- **Unmutated IGHV and complex karyotype**
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Patient progresses after 3 years on a covalent BTKi

If fixed-duration venetoclax-rituximab is recommended, what are the next steps?

Case 1 Continued: Therapeutic Considerations at Progression

Melissa, a 59-year-old patient presenting with symptomatic higher-risk TN CLL

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Patient progresses after 3 years on a covalent BTKi

If fixed-duration venetoclax-rituximab is recommended, what are the next steps?

- ❑ Risk-stratify for TLS
- ❑ Care coordination/review logistics for time-limited therapy, as this generally requires more participation from patients
- ❑ Note: logistics and toxicity differ with venR and when using venG **in the upfront setting** (eg, more neutropenia)

Case 2: Role of the Pharmacist in AE Management

David, a 70-year-old patient with symptomatic CLL and unmutated IGHV

- **Receiving treatment with a covalent BTKi**
- **After 4 months, he experiences painful arthralgias (grade 2)**

What strategies should be considered for this event?

Case 2: Role of the Pharmacist in AE Management

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- **After 4 months, he experiences painful arthralgias (grade 2)**

What strategies should be considered for this event?

General recommendations for BTKi

- ❑ Supportive care: acetaminophen and topical diclofenac
- ❑ Avoid NSAIDs due to bleeding risk
- ❑ Prednisone is an option (lower dose)

If ibrutinib is used

- ❑ Dose holds/holidays appear to be more effective than reductions[1]
- ❑ For persistent arthralgia, sequencing to a more selective BTKi is an option[2,3]

1. Rhodes JM et al. *Clin Lymphoma Myeloma Leuk*. 2020;20:438-444.
2. Shadman M et al. *Lancet Haematol*. 2023;10(1):E35-45. 3. Rogers KA et al. *Haematologica*. 2021;106:2364-2373

Key Principles for Pharmacy Practice & AE Management

- Regardless of line of therapy, collaborative discussions are necessary for the development of a comprehensive treatment plan

- A pharmacist provides chart reviews at various times in the patient journey to monitor for tolerability
  - Eg, HTN management, medication list updates, and refills timeframe

- When AEs occur, a strategy and plan for supportive care, dose hold, and/or therapy change is crucial to ensure ongoing compliance

Case 2 Revisited: What Happens After Progression On Multiple Targeted Agent Classes?

David, a 70-year-old patient with symptomatic CLL and unmutated IGHV

- **Initial treatment with covalent BTKi**
- **Progression at 4 years**
- **Treated with venR, but progression 2 years after EOT**

How can pharmacists help prepare this patient for next steps?

Case 2 Revisited: What Happens After Progression On Multiple Targeted Agent Classes?

David, a 70-year-old patient with symptomatic CLL and unmutated IGHV

- **Initial treatment with covalent BTKi**
- **Progression at 4 years**
- **Treated with venR, but progression 2 years after EOT**

How can pharmacists help prepare this patient for next steps?

- ❑ Double-exposed disease remains a challenge
- ❑ Discuss the potential of clinical trial enrollment
- ❑ Potential for off-label non-covalent BTKi, given pirtobrutinib approval in MCL
- ❑ Ven retreatment is being explored

Case 3: Preparing for BTKi-Venetoclax Combinations

George, 70-year-old patient with symptomatic CLL

- **Fit, no major comorbid illnesses**
- **Unmutated IGHV, but no *TP53* mutation**

What are the pharmacist's responsibilities should this patient receive a fixed-duration BTKi-venetoclax combination?

Case 3: Preparing for BTKi-Venetoclax Combinations

George, 70-year-old patient with symptomatic CLL

- **Fit, no major comorbid illnesses**
- **Unmutated IGHV, but no *TP53* mutation**

What are the pharmacist's responsibilities should this patient receive a fixed-duration BTKi-venetoclax combination?

- ❑ Prepare for the additive toxicity profile with BTKi-VEN doublets or triplets
- ❑ Counseling on all-oral therapy
- ❑ Lead-in debulking for TLS, followed by VEN escalation
- ❑ Financial considerations

Final Pharmacist Take-Homes

- Oral targeted therapies, alone or in combination with anti-CD20 monoclonal antibodies, are largely supplanting chemoimmunotherapy in the treatment of newly diagnosed and relapsed/refractory CLL

- Emerging data supports a role for non-covalent BTK inhibitors, as well as time-limited combination therapies, in the future management of CLL

- Pharmacists are uniquely equipped for adverse event monitoring and management; patient support and education; and creating individualized therapy plans for patients with CLL receiving BTK and BCL2 inhibitors

Audience Q&A