A Pharmacist's Guide to the Safe and Effective Management of BTK and BCL-2 Inhibitors in Chronic Lymphocytic Leukemia

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Educational Objectives

After completion of this activity, participants will be able to:

- Analyze recent advancements and clinical evidence supporting the use of Bruton tyrosine kinase (BTK) and BCL-2 inhibitors in chronic lymphocytic leukemia (CLL) to make informed treatment decisions
- Exercise individualized treatment plans for patients with CLL by integrating guideline recommendations, patient-specific factors, and treatment goals
- Employ strategies to manage toxicities and improve adherence to optimize outcomes in patients with CLL

Pretest Questions

Pretest Question 1

LP is a 68-year-old with newly diagnosed chronic lymphocytic leukemia (CLL) with del(17p) mutation. Past medical history includes well-controlled hypertension and hypercholesterolemia. Which treatment option would be most appropriate as a first-line therapy for LP?

A. Ibrutinib
B. Pirtobrutinib
C. Venetoclax + rituximab
D. Zanubrutinib

Pretest Question 2

In a patient with newly diagnosed CLL, which factor should be taken into consideration when recommending continuous- vs fixed-duration therapy?

A. History of emphysema

B. Patient ethnicity

C. Patient preference

D. Recent shingles infection

Pretest Question 3

Which is an appropriate strategy to safely initiate therapy with venetoclax + obinutuzumab?

A. Perform baseline echocardiogram.
B. Initiate allopurinol concurrently with venetoclax.
C. Monitor blood chemistry during ramp-up.
D. Avoid aspirin and fish oil prior to and during therapy.

Pretest Question 4

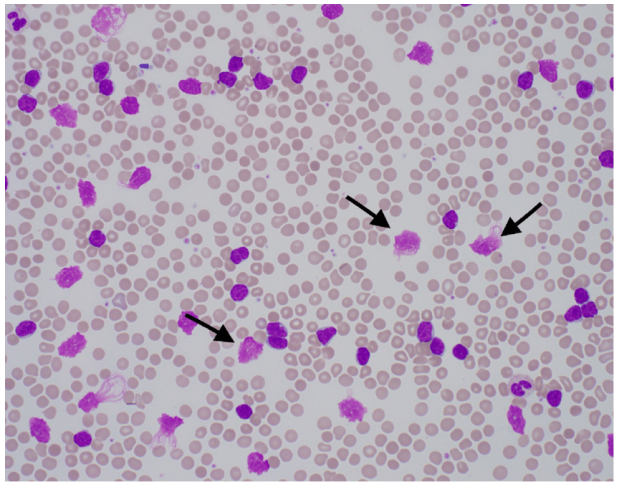
Before participating in this activity, how confident are you in the treatment of CLL with Bruton tyrosine kinase and BCL-2 inhibitors?

A. Not at all
B. Somewhat
C. Moderately
D. Very
E. Extremely

Introduction to Chronic Lymphocytic Leukemia

Background

- Chronic lymphocytic leukemia (CLL) is the most common type of leukemia in adults
- Median age at diagnosis: 70 years
- Disorder of morphologically mature but immunologically dysfunctional B cells
  - 2%-10% of patients with CLL undergo Richter transformation to aggressive lymphomas
- Diagnosis: often asymptomatic at presentation
  - 5%-10% present with B symptoms (fevers, unintentional weight loss, night sweats)
  - Other symptoms may include fatigue, lymphadenopathy, splenomegaly, hepatomegaly, cutaneous manifestations
  - "Smudge cells" seen on peripheral smear
  - Peripheral blood flow cytometry used to confirm diagnosis reveals ≥5 × 10^9/L B lymphocytes sustained for at least 3 months
  - Immunophenotyping commonly reveals CD5, CD19, CD20, CD23



Republished from Jain AG et al. *Cureus*. 2018;10(11):e3570, under the terms of the Creative Commons Attribution License; SEER Cancer stat facts: leukemia - chronic lymphocytic leukemia (CLL). National Cancer Institute. Accessed October 15, 2024. https://seer.cancer.gov/statfacts/html/clyl.html; Mukkamalla SKR et al. Chronic lymphocytic leukemia In: StatPearls [Internet]. StatPearls Publishing. Updated March 7, 2023. Accessed October 15, 2024. https://www.ncbi.nlm.nih.gov/books/NBK470433/

Genetic Markers in CLL

- Molecular cytogenetics and conventional karyotyping identify abnormalities that may guide treatment decisions

Genetic marker	Frequency	Significance
Del(17p)	7%	Aggressive disease and poor response to CIT
TP53 mutation	80% with del(17p)	
Del(13q) as sole abnormality	55%	Favorable prognosis
Unmutated *IGHV*	40%	Aggressive disease
Trisomy 12	16%	Intermediate risk
Del(11q)	18%	High risk

Del(17p)/*TP53* mutation status guides therapy selection

CIT, chemoimmunotherapy.

Chronic lymphocytic leukemia. Leukemia & Lymphoma Society. Accessed October 15, 2024. https://www.lls.org/sites/default/files/file_assets/PS34_CLL_Booklet_2019_FINAL.pdf; NCCN. Clinical Practice Guidelines in Oncology. Chronic lymphocytic leukemia/small lymphocytic lymphoma, version 1.2025. Accessed October 15, 2024. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf

Treatment Overview

- CLL is not curable (except with allogeneic stem cell transplant)
  - Goal of care is most commonly palliation and prolonging survival
- Early-stage asymptomatic CLL: observation is standard of care with monitoring of blood counts and clinical assessment every 3 months
- Treatment required for active disease:

Symptoms
- Fatigue
- Night sweats
- Weight loss

Cytopenias
- Marrow failure: platelets <100k, Hb <10g/dL
- Autoimmune complications

Bulky disease
- Symptomatic organ dysfunction
- LN >10 cm
- Splenomegaly, symptomatic
- Rapid ALC increase

ALC, absolute lymphocyte count; Hb, hemoglobin; LN, lymph node.

Chronic lymphocytic leukemia. Leukemia & Lymphoma Society. Accessed October 15, 2024. https://www.lls.org/sites/default/files/file_assets/PS34_CLL_Booklet_2019_FINAL.pdf; NCCN. Clinical Practice Guidelines in Oncology. Chronic lymphocytic leukemia/small lymphocytic lymphoma, version 1.2025. Accessed October 15, 2024. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf

Targeted Therapies in CLL

Drug class	Agent	Subclass	Major toxicities
BTKi	**Ibrutinib**	First generation, covalent	Cardiac arrhythmias, HF, myelosuppression, infections, hemorrhage, HTN
	Acalabrutinib	Second generation, covalent	Cardiac arrhythmias, HF, myelosuppression, infections, hemorrhage, HTN, secondary malignancies
	Zanubrutinib	Second generation, covalent	HTN, myelosuppression, hemorrhage, secondary malignancies
	Pirtobrutinib	Third generation, non-covalent	Infections, bleeding, neutropenia
BCL-2i	**Venetoclax**	N/A	TLS, myelosuppression, infections
Anti-CD20 mAb	**Obinutuzumab**	N/A	Infusion reactions
	Rituximab	N/A	Infusion reactions

BCL-2i, B-cell lymphoma 2 inhibitors; BTKi, Bruton tyrosine kinase inhibitors; HF, heart failure; HTN, hypertension; mAb, monoclonal antibody; TLS, tumor lysis syndrome.

Coombs CC. *Curr Hematol Malig Rep*. 2024;19(2):65-74.

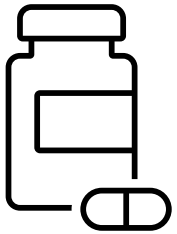
First-Line Treatment

Without del(17p)/*TP53* mutation		*With* del(17p)/*TP53* mutation	
Preferred (all category 1)	Other recommended	**Preferred**	Other recommended
Acalabrutinib ± obinutuzumab	Ibrutinib (category 1)	**Acalabrutinib ± obinutuzumab**	Ibrutinib
Venetoclax + obinutuzumab	Ibrutinib + venetoclax	**Venetoclax + obinutuzumab**	Ibrutinib + venetoclax
Zanubrutinib		**Zanubrutinib**	
CIT options can be considered in certain circumstances		**CIT not recommended as del(17p)/*TP53* mutation associated with low response rates**	

Targeted therapies are the new standard for first-line therapy.

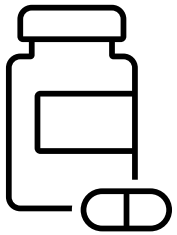
NCCN. Clinical Practice Guidelines in Oncology. Chronic lymphocytic leukemia/small lymphocytic lymphoma, version 1.2025. Accessed October 15, 2024. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf

Preferred First-Line Treatment Options



Acalabrutinib

Continuous BTKi

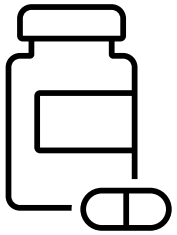


Zanubrutinib

Continuous BTKi

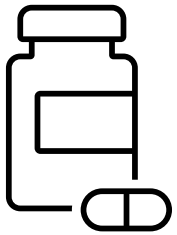
NCCN. Clinical Practice Guidelines in Oncology. Chronic lymphocytic leukemia/small lymphocytic lymphoma, version 1.2025. Accessed October 15, 2024. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf

Preferred First-Line Treatment Options



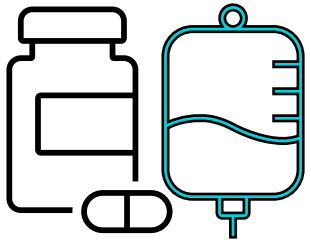
Acalabrutinib

Continuous BTKi



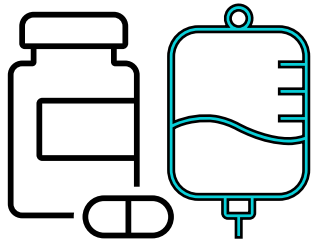
Zanubrutinib

Continuous BTKi



Acalabrutinib + obinutuzumab

Continuous BTKi
+
6 months anti-CD20 mAb



Venetoclax + obinutuzumab

Fixed duration BCL-2i
+
6 months anti-CD20 mAb

NCCN. Clinical Practice Guidelines in Oncology. Chronic lymphocytic leukemia/small lymphocytic lymphoma, version 1.2025. Accessed October 15, 2024. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf

First-Line CLL Pivotal Trials

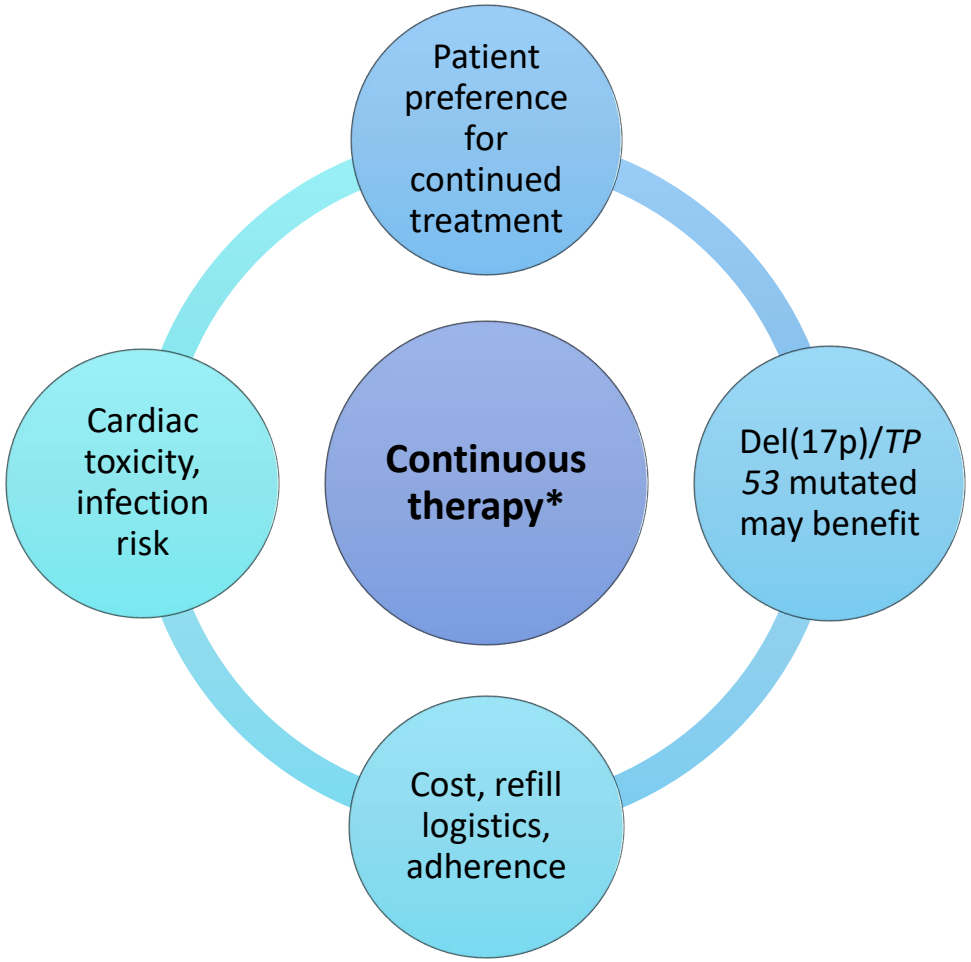
Regimens	Clinical trial	Follow-up	ORR	PFS	OS
Ibrutinib	RESONATE-2	7.4 years	92% (34% CR)	59%	83%
Chlorambucil			37%	9%	78%
Acalabrutinib	ELEVATE-TN	46.9 months	90% (11% CR)	78%	88%
Acalabrutinib + obinutuzumab			96% (31% CR)	87%	93%
Chlorambucil + obinutuzumab			83% (13% CR)	25%	88%
Zanubrutinib, without del(17p)	SEQUOIA	24 months	95% (7% CR)	86%	94%
Bendamustine + rituximab			85% (15% CR)	70%	95%
Zanubrutinib, with del(17p)			90% (6% CR)	89%	94%
Venetoclax + obinutuzumab	CLL-14	76.4 months	NR	76.2 months	78.7%
Chlorambucil + obinutuzumab				36.4 months	69.2%

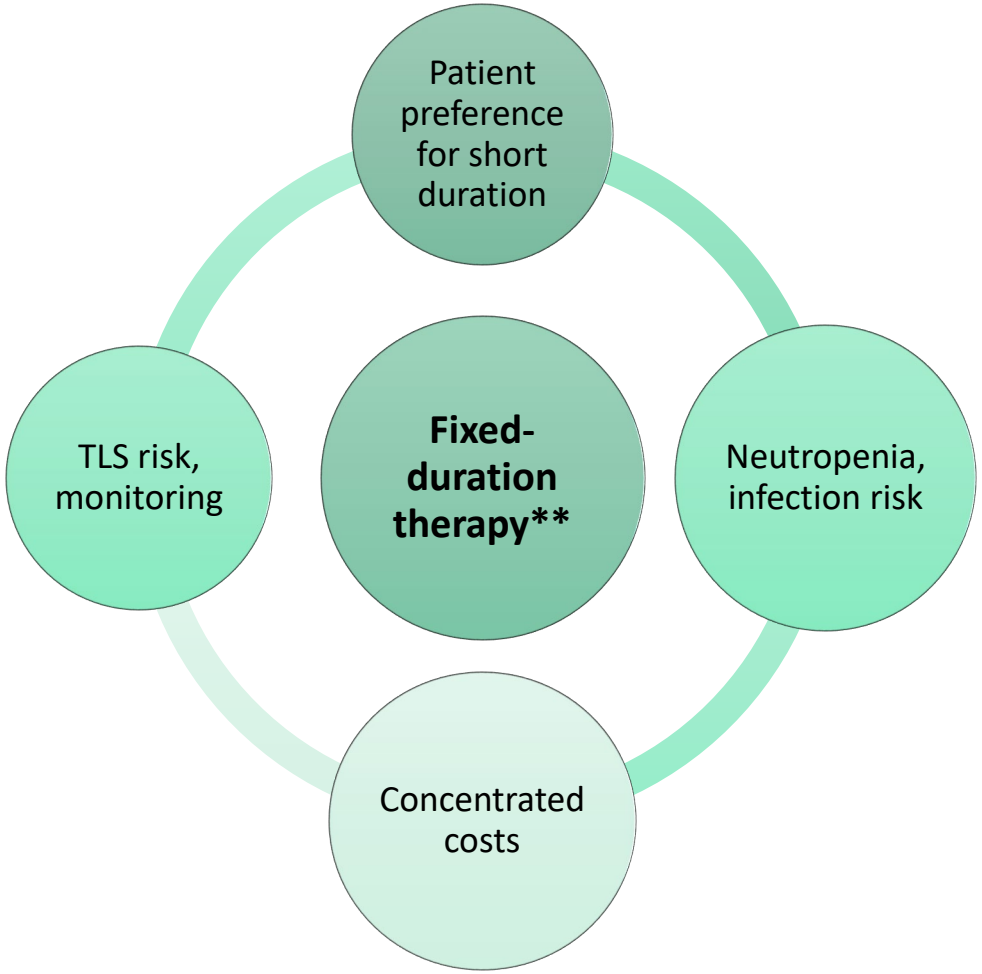
Takeaway: targeted therapies improve outcomes vs CIT.

CR, complete response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Sharman JP et al. *Leukemia.* 2022;36(4):1171-1175; Barr P et al. *Blood Adv.* 2022;6(11):3440-3450; Tam CS et al. *Lancet Oncol.* 2022;23(8):1031-1043; Al-Sawaf O et al. *HemaSphere*. 2023;7:suppl e064430a.

Continuous vs Fixed-Duration Therapy





*Ibrutinib, acalabrutinib, zanubrutinib, pirtobrutinib.
**Venetoclax with rituximab or obinutuzumab.

Ravelo A et al. *Blood*. 2023;142(suppl 1):3706; Allan JN et al. *Br J Haematol*. 2022;196(4):947-953.

Second-Line CLL Therapy

CLL/SLL **with** del(17p)/*TP53* mutation

Preferred

- **Acalabrutinib (category 1)**
- **Zanubrutinib (category 1)**
- **Venetoclax ± obinutuzumab**

Other recommended

- Ibrutinib (category 1)
- Venetoclax + rituximab (category 1)
- Ibrutinib + venetoclax (category 2B)

CLL/SLL **without** del(17p)/*TP53* mutation

Preferred

- **Acalabrutinib (category 1)**
- **Zanubrutinib (category 1)**
- **Venetoclax + obinutuzumab**

Other recommended

- Ibrutinib (category 1)
- Venetoclax + rituximab (category 1)
- Venetoclax
- Ibrutinib + venetoclax (category 2B)

Useful in certain circumstances: pirtobrutinib (resistance or intolerance to prior covalent BTKi).*

SLL, small lymphocytic lymphoma.
*NCCN recommendation, not FDA-approved indication.

All category 2A recommendations unless otherwise specified.

NCCN. Clinical Practice Guidelines in Oncology. Chronic lymphocytic leukemia/small lymphocytic lymphoma, version 1.2025. Accessed October 15, 2024. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf

R/R CLL Pivotal Trials

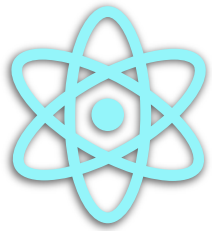
Regimens	Clinical trial	Follow-up	ORR	PFS	OS
Acalabrutinib	ELEVATE-RR	40.9 months	81.0%	38.4 months	NR
Ibrutinib			77.0%	38.4 months	NR
Ibrutinib	ALPINE	36 months	74.8%	54.3%	79.7%
Zanubrutinib			85%	65.8%	82.6%
Venetoclax + rituximab	MURANO	85.7 months	93.3%	54.7 months	69.6%
Bendamustine + rituximab			67.7%	17.0 months	51.0%

Second-generation BTKi and combination BCL-2i + obinutuzumab preferred in second line and beyond.

Kater AP et al. *Hematol Oncol*. 2023;41:239-242; Byrd JC et al. *J Clin Oncol*. 2021;39(31):3441-3452; Brown JR et al. *Blood.* 2023;142(suppl 1):202.

R/R CLL: Treatment Sequencing

Treatment in prior line of therapy



Covalent BTKi

Is progression due to refractory disease or resistance/intolerance?

Progression on treatment

- Venetoclax-based therapy

Resistance/ intolerance

- Different covalent BTKi
- Venetoclax-based therapy
- Pirtobrutinib*

Venetoclax + anti-CD20 mAb

Was there response after completion of treatment or progression/ intolerance while on treatment?

Progression on treatment

Covalent BTKi

Relapse after response

- Re-treatment with venetoclax + anti-CD20 mAb
- Covalent BTK inhibitor

CIT

Does the patient prefer time-limited treatment or continuous therapy?

Fixed duration

Venetoclax-based therapy

Continuous therapy

Covalent BTKi

*NCCN recommendation but not FDA-indicated in the second-line setting.

NCCN. Clinical Practice Guidelines in Oncology. Chronic lymphocytic leukemia/small lymphocytic lymphoma, version 1.2025. Accessed October 15, 2024. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf

Third-Line R/R CLL: After Prior BTKi and Venetoclax

Lisocabtagene maraleucel
(CAR T-cell therapy)

Pirtobrutinib
(non-covalent BTKi)

Both FDA approved for:
CLL/SLL after 2+ lines of treatment including a BTKi and a BCL-2 inhibitor

CAR, chimeric antigen receptor.

NCCN. Clinical Practice Guidelines in Oncology. Chronic lymphocytic leukemia/small lymphocytic lymphoma, version 1.2025. Accessed October 15, 2024. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf

Pirtobrutinib

- Covalent BTKi are susceptible to resistance mutation at the 481-cysteine residue (C481S)
- Pirtobrutinib is a non-covalent BTKi that binds reversibly to BTK and maintains activity against BTK regardless of mutation status
  - Highly selective for BTK with minimal off-target effects
  - Longer half-life compared with covalent BTKi

FDA approved for:
CLL/SLL after 2+ lines of treatment including a BTKi and a BCL-2 inhibitor

NCCN guidelines:
- **Second line if BTKi intolerance or resistance**
- **Third line after BTKi and venetoclax therapies**

Jaypirca. Prescribing information. Eli Lilly and Co; June 2024; NCCN. Clinical Practice Guidelines in Oncology. Chronic lymphocytic leukemia/small lymphocytic lymphoma, version 1.2025. Accessed October 15, 2024. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf

BRUIN Study: Pirtobrutinib in CLL After Covalent BTKi

Phase 1-2, single-arm study

CLL/SLL with 2+ prior therapies (N = 247)

Median 3 prior therapies
- Prior BTKi (100%)
- Prior anti-CD20 mAb (88%)
- Prior chemotherapy (79%)
- Prior BCL-2i (40.5%)
- Prior CAR T (5.7%)

Phase 1: pirtobrutinib 25-300 mg orally daily

Phase 2:Ppirtobrutinib 200 mg orally daily

Outcomes:
- ORR 73.3% (prior BTKi), 70% (double refractory)
- Median PFS 19.6 months (prior BTKi), 16.8 months (double refractory)

AEs:
- Infections (71%)
- Bleeding (42.6%)
- Neutropenia (32.5%)

Accelerated approval for CLL/SLL after 2+ prior lines of treatment.

AE, adverse effect.

Mato AR et al. *N Engl J Med.* 2023;389(1):33-44.

Emerging Trends

Fixed-duration oral doublet therapy
CAPTIVATE: venetoclax + ibrutinib
GLOW: venetoclax + ibrutinib
MAJIC: venetoclax + acalabrutinib (with MRD-guided therapy duration)

Triplet therapy
GAIA-CLL13: obinutuzumab + venetoclax + ibrutinib (7-year follow-up at EHA 2024)

Nemtabrutinib

New BCL-2i
CELESTIAL-TNCLL: sonrotoclax + zanubrutinib vs venetoclax + obinutuzumab
GLORA: lisaftoclax + acalabrutinib

Front-line therapy
AMPLIFY: obinutuzumab + venetoclax + acalabrutinib

BTK degraders
NX-5948 Basket Study in R/R CLL + B-cell malignancies
BGB-16673 in R/R CLL

CAR T-cell therapy
TRANSCEND CLL 004: liso-cel in the third-line setting

Bispecific Abs
EPCORE CLL-1: epcoritamab-bysp in patients with Richter transformation

MRD, minimal residual disease; R/R, relapsed/refractory.

Wierda WG et al. *J Clin Oncol*. 2024;42(16_suppl):7009; Ossorio PS. EHA 2024. Abstract P699; Niemann C et al. *Lancet Oncol*. 2023;24(12):1423-1433; Ma S et al. EHA 2024. Abstract S160; Furstenau M et al. *Lancet Oncol.* 2024;25(6):744-759; Tadmor T et al. *J Clin Oncol.* 2024;42:16_suppl:TPS7088; Jain N et al. EHA 2024. Abstract S164; Opat S et al. EHA 2024. Abstract S156; Lasica M et al. ASCO 2024. Abstract 7078; Davids MS et al. *Blood*. 2022;140(suppl 1):2326-2328; Kater AP et al. EHA 2024. Abstract S163; Siddiqi T et al. *Lancet.* 2023;402(10402):641-654; Linton K et al. EHA 2024. Abstract S155; Parrondo R et al. EHA 2024. Abstract S157.

Doublet Therapy: BTKi + BCL-2 Trials

SEQUOIA (Arm D) Updates:
1L zanubrutinib + venetoclax for del(17p)/TP53 mutated

- n=66 patients with TN CLL/SLL with del(17p) or TP53 mutation

Zanubrutinib 160 mg twice daily x 3 cycles →
Zanubrutinib + venetoclax
(ramp up to 400 mg once daily) for 24 cycles→
Zanubrutinib monotherapy

- At median 31.6 months follow-up, ORR = 100%, CR+CRi = 45%
- Therapy stopping rules based on achievement of undetectable MRD

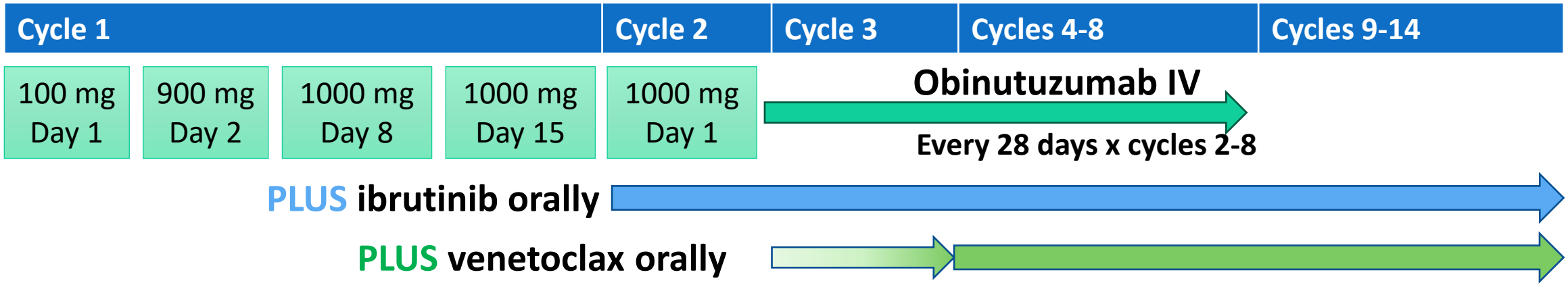
MAJIC:
1L acalabrutinib + venetoclax vs venetoclax + obinutuzumab

- Must have adequate hepatic and renal function
- MRD guided fixed-duration therapy – possibility of adding second year based on MRD status
- Results pending

MRD, minimal residual disease; TN, treatment naive.

Ma S et al. EHA 2024. Abstract S160. Niemann C et al. *Lancet Oncol*. 2023;24(12):1423-1433.

GAIA-CLL13: Ibrutinib + Venetoclax + Obinutuzumab



First-line mPFS: 88.5 months (n = 25)

R/R mPFS: 81.8 months (n = 25)

mOS not reached in any cohort

Longer PFS was not observed in patients with uMRD status

IV, intravenous; m, median; uMRD, undetectable minimal residual disease.

Rogers K et al. EHA 2024. Abstract S162. Furstenau M et al. *Lancet Oncol*. 2024;25(6)744-759.

Optimizing Safety of Small Molecule Inhibitors: Pharmacist-Centered Strategies

Cardiac Events With BTK Inhibitors

Agent	Key trials	Bleeding (%)		AF/flutter (%)		HTN (%)	
		Any	Grade ≥3	Any	Grade ≥3	Any	Grade ≥3
Ibrutinib	RESONATE, RESONATE-2, iLLUMINATE	**39**	**4.2**	**7-15**	**3.7**	**19**	**8**
Acalabrutinib	ELEVATE TN	22	3	4.1	1.1	3.2-5	2.8
Zanubrutinib	SEQUOIA, ALPINE	32	3.8	4.4	1.9	14-19	3.4
Pirtobrutinib	BRUIN	42.6	2.2	3.8	1.3	14.2	<1%
Nemtabrutinib*	BELLWAVE-008, BELLWAVE-011	6.4	-	2.1	2.1	**32**	**15**

AF, atrial fibrillation.
*Investigational, not FDA approved.

Lower rates of cardiac events with second- and third-generation BTKi.

Imbruvica. Prescribing information. Janssen Biotech; May 2023; Calquence. Prescribing information. AstraZeneca Pharmaceuticals; August 2022; Brukinsa. Prescribing information. BeiGene USA, Inc; December 2023; Mato AR et al. *N Engl J Med.* 2023;389:33-44; Woyach JA et al. *Cancer Discov*. 2024;14(1)66-75; NCCN. Clinical Practice Guidelines in Oncology. Chronic lymphocytic leukemia/small lymphocytic lymphoma, version 1.2025. Accessed October 15, 2024. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf

Cardiac Events With BTK Inhibitors

Agent	Key trials	Bleeding (%)		AF/flutter (%)		HTN (%)	
		Any	Grade ≥3	Any	Grade ≥3	Any	Grade ≥3
Ibrutinib							**8**
Acalabrutinib							2.8
Zanubrutinib							3.4
Pirtobrutinib							<1%
Nemtabrutinib*	BELLWAVE-011	6.4	-	2.1	2.1	**32**	**15**

Zanubrutinib vs ibrutinib comparative safety (ALPINE)

- Lower rates of AF/atrial flutter
- Similar rates of HTN

Acalabrutinib vs ibrutinib comparative safety (ELEVATE-RR)

- Lower rates of AF/atrial flutter
- Higher rates of headache

*Investigational, not FDA approved.

Lower rates of cardiac events with second- and third-generation BTKi.

Imbruvica. Prescribing information. Janssen Biotech; May 2023; Calquence. Prescribing information. AstraZeneca Pharmaceuticals; August 2022; Brukinsa. Prescribing information. BeiGene USA, Inc; December 2023; Mato AR et al. *N Engl J Med.* 2023;389:33-44; Woyach JA et al. *Cancer Discov*. 2024;14(1)66-75; NCCN. Clinical Practice Guidelines in Oncology. Chronic lymphocytic leukemia/small lymphocytic lymphoma, version 1.2025. Accessed October 15, 2024. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf

Management of Cardiac Toxicities With BTKi

AF

- **Hold therapy with grade 3+ and consider dose reduction or change to second- or third-generation BTKi**
- Avoid warfarin for anticoagulation (DOAC preferred)
- Avoid amiodarone, diltiazem, and verapamil for rate control due to DDI

Patients with baseline low risk (CHA_2DS_2VASC score 0-1) AF can be treated with BTKi

AVOID BTKi in patients with:

- **Family history of sudden cardiac death**
- **Sudden, uncontrolled HTN**
- **Severe or uncontrolled congestive HF**

HTN

- **Hold therapy for grade 3-4 HTN and consider dose reduction or change to second- or third-generation BTKi**
- Manage HTN according to treatment guidelines

Patients with baseline controlled HTN can be treated with BTKi with close monitoring

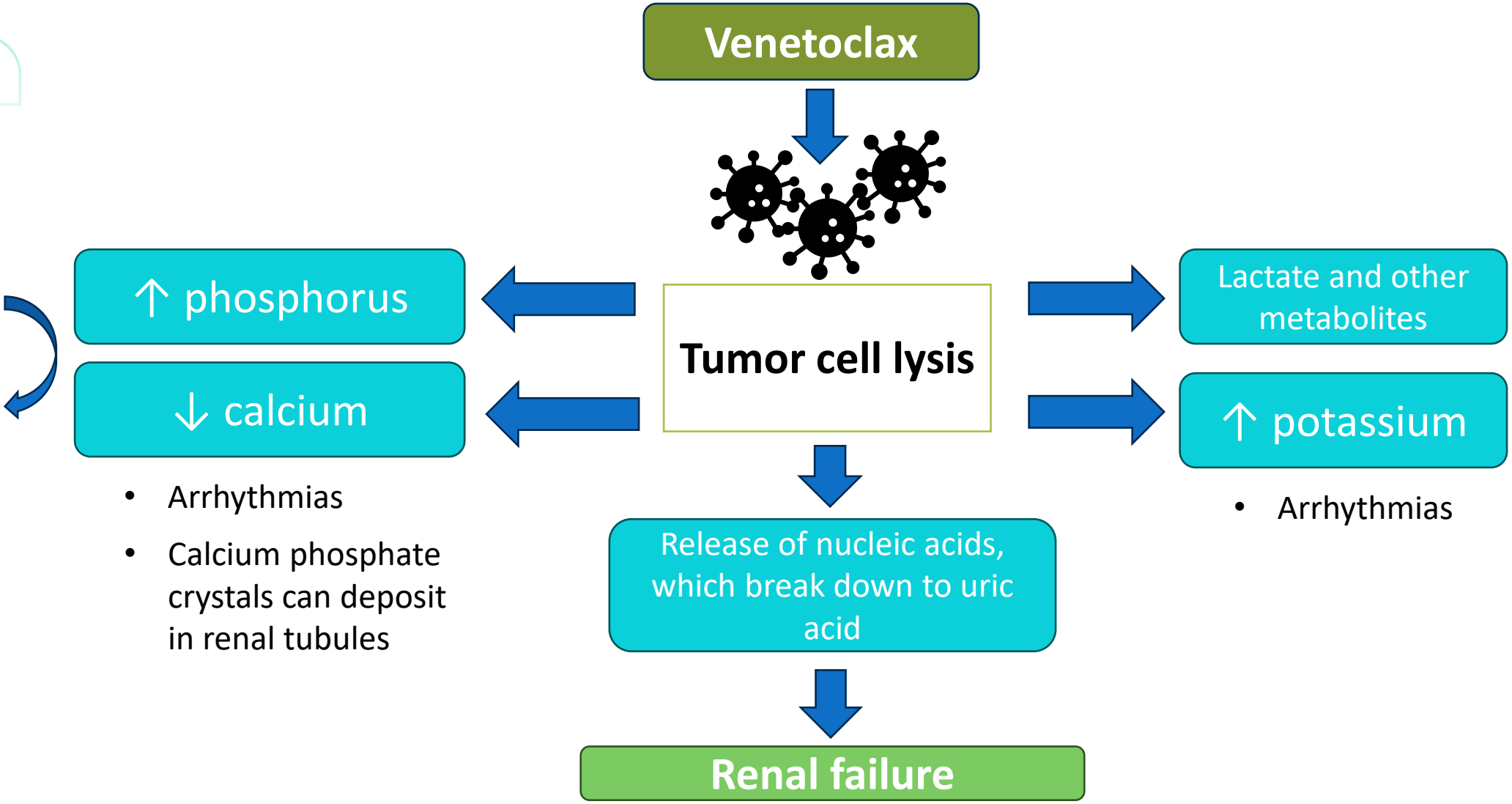
Bleeding

- **Hold therapy for 3-7 days before and after surgery**
- **Hold BTKi and anticoagulation if major bleeding occurs**
- Avoid NSAIDs, aspirin, and fish oil while on therapy

DDI, drug-drug interaction; DOAC, direct oral anticoagulant; NSAID, nonsteroidal anti-inflammatory drug.

Awan FT et al. *Blood Adv*. 2022;6(18):5516-5525; Quartermaine C et al. *JACC CardioOncol*. 2023;5(5):570-590.

Tumor Lysis Syndrome With Venetoclax



Adeyinka A et al. Tumor lysis syndrome. StatPearls [Internet]. StatPearls Publishing. Updated October 31, 2022. Accessed October 15, 2024. https://www.ncbi.nlm.nih.gov/books/NBK518985/; Venetoclax. Prescribing information. Genentech; July 2024.

BCL-2 Inhibitors: Clinical Pearls

- Venetoclax inhibits BCL-2, leading to cell apoptosis
- Trials have shown durable responses in high-risk population with combination anti-CD20 agent + venetoclax
- Ramp-up dosing and obinutuzumab pretreatment may reduce TLS risk
- Start venetoclax on cycle 1 day 22 if in combination with obinutuzumab

Ramp-up dosing:
Week 1: 20 mg once daily
Week 2: 50 mg once daily
Week 3: 100 mg once daily
Week 4: 200 mg once daily
Week 5: 400 mg once daily

Logistical considerations:
- Patient able to make frequent clinic visits for monitoring
- Access to inpatient facility for TLS management if needed

Venclexta. Prescribing information. AbbVie Inc; July 2024; A guide for healthcare professionals initiating venclexta for patients with CLL/SLL. AbbVie Inc, Genentech. Accessed October 15, 2024. https://www.venclextahcp.com/content/dam/gene/venclextahcp/cll/pdfs/VENCLEXTA-Treatment-Guide.pdf

TLS Risk Management With BCL-2 Inhibitors

Baseline assessment: CT scan, ALC, blood chemistry (K, Phos, Ca, UA), renal clearance

	Baseline features	Prevention	Hospitalization
Low	LN <5 cm **AND** ALC <25 x 10^9/L	Starting **before** venetoclax: ❑ Allopurinol starting 2-3 days before ❑ Oral hydration (1.5-2 L/day) starting 2 days before During therapy: ❑ Monitor blood chemistry and creatinine clearance at 6-8 hours and 24 hours after each ramp-up step ❑ Consider IV hydration for high-risk TLS and/or rasburicase with elevated uric acid	Outpatient
Medium	LN 5-10 cm **OR** ALC ≥25 x 10^9/L		Outpatient or inpatient if comorbidities
High	LN ≥10 cm **OR** any LN ≥5 cm **AND** ALC >25 x 10^9/L		Inpatient ramp-up for IV hydration and TLS monitoring

Venclexta. Prescribing information. AbbVie Inc; July 2024; A guide for healthcare professionals initiating venclexta for patients with CLL/SLL. AbbVie Inc, Genentech. Accessed October 15, 2024. https://www.venclextahcp.com/content/dam/gene/venclextahcp/cll/pdfs/VENCLEXTA-Treatment-Guide.pdf

Venetoclax and Cytopenias

- Pooled analysis of venetoclax monotherapy, most common any-grade AEs:
  - Diarrhea (41%)
  - Cytopenias (neutropenia: 40%, anemia: 31%, and thrombocytopenia: 21%)
- Cytopenias were the most common grade 3/4 AEs

- Neutropenia was the most common reason for dose interruption or reduction
- First onset of hematologic toxicities commonly occurs during ramp-up
- Incidence of new hematologic events was low after the first 3 months

Dose interruption or granulocyte colony-stimulating factor led to resolution of cytopenias in most cases.

	Action
First occurrence	Hold treatment and resume at same dose once neutropenia resolves to grade 1 or baseline
Second and subsequent occurrences	Hold and resume at lower dose once neutropenia resolves

Davids MS et al. *Clin Cancer Res*. 2018;24(18):4371-4379; Venetoclax. Prescribing information. Genentech; July 2024.

Venetoclax Interactions

DDIs

- Substrate of BCRP/ABCG2, CYP3A4 (major), and P-glycoprotein/ABCB1 (minor)
- Co-administration of strong CYP3A4 inhibitors (ie, posaconazole) contraindicated during ramp-up for patients with CLL
- Dosage reduction of venetoclax required with concomitant strong CYP3A4 inhibitors

Drug-food interactions

- Take venetoclax with food and water
- Avoid concomitant intake of grapefruit juice, Seville oranges, or starfruit

Venetoclax. Prescribing information. Genentech; July 2024.

Infection Risk With CLL

Hepatitis B screening
- Initiate entecavir if needed for prophylaxis

Vaccinations
- Avoid live vaccines
- Recommended:
  - Annual influenza vaccine
  - Pneumococcal vaccine* for all patients treated with BTKi
  - Respiratory syncytial virus vaccine
  - COVID-19 vaccine

Antimicrobial prophylaxis
- Consider herpes simplex virus prophylaxis in patients receiving:
  - BTKi (acalabrutinib/ibrutinib)
  - Purine analogs
  - Bendamustine
  - Alemtuzumab
- Consider *Pneumocystis jirovecii* pneumonia prophylaxis for patients receiving:
  - BTKi (acalabrutinib/ibrutinib)
  - PI3K inhibitors
  - Purine analogs
  - Bendamustine
  - Alemtuzumab

*Recombinant, adjuvanted.

NCCN. Clinical Practice Guidelines in Oncology. Chronic lymphocytic leukemia/small lymphocytic lymphoma, version 1.2025. Accessed October 15, 2024. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf

Conclusion

- Recent approvals have significantly impacted the treatment landscape of CLL
- Emerging data on front-line doublet (BCL-2i + BTKi) and triplet (BCL-2i + BTKi + anti-CD20 mAb) therapy may change treatment algorithm in near future
- Pharmacists play an important role in the management of BTKi-associated cardiac toxicities and in the management of venetoclax-related AEs

Additional Resources

Resources	
Chronic Lymphocytic Leukemia Society	www.cllsociety.org
Shadman M. Diagnosis and treatment of chronic lymphocytic leukemia: a review. *JAMA*. 2023;329(11):918-932.	
Bennett R, Seymour JF. Update on the management of relapsed/refractory chronic lymphocytic leukemia. *Blood Cancer J*. 2024;14(1):33.	

Posttest Questions

Posttest Question 1

LP is a 68-year-old with newly diagnosed chronic lymphocytic leukemia (CLL) with del(17p) mutation. Past medical history includes well-controlled hypertension and hypercholesterolemia. Which treatment option would be most appropriate as a first-line therapy for LP?

A. Ibrutinib
B. Pirtobrutinib
C. Venetoclax + rituximab
D. Zanubrutinib

Posttest Question 2

In a patient with newly diagnosed CLL, which factor should be taken into consideration when recommending continuous- vs fixed-duration therapy?

A. History of emphysema

B. Patient ethnicity

C. Patient preference

D. Recent shingles infection

Posttest Question 3

Which is an appropriate strategy to safely initiate therapy with venetoclax + obinutuzumab?

A. Perform baseline echocardiogram.
B. Initiate allopurinol concurrently with venetoclax.
C. Monitor blood chemistry during ramp-up.
D. Avoid aspirin and fish oil prior to and during therapy.

Posttest Question 4

After participating in this activity, how confident are you in the treatment of CLL with Bruton tyrosine kinase and BCL-2 inhibitors?

A. Not at all
B. Somewhat
C. Moderately
D. Very
E. Extremely

Thank you!