PAVING THE WAY TO NOVEL THERAPIES IN CLL

Real World Patient Cases for the Oncology Pharmacist

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Learning Objectives

- Discuss the molecular pathophysiology associated with the development of CLL, the role of the B-cell receptor (BCR) pathway, and the rationale for therapeutically targeting this pathway.
- Appraise recent clinical safety and efficacy data in novel CLL therapies for use in both monotherapy and combination, focusing on differentiating factors seen among the various agents.
- Assess the latest clinical CLL guideline recommendations for selection and sequencing of therapy, individualized to the patient, including mutation status, performance status, comorbidities, and patient preferences.
- Using a case-based approach, explore the various clinical challenges pharmacists face with the use of CLL novel therapies in practice, including preventing and managing toxicities, promoting patient adherence, and fostering a team-based environment to improve patient care.

Targeting the BCR Pathway in Chronic Lymphocytic Leukemia

A Novel Therapy Revolution

Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma Overview

- Most common leukemia in the Western world[1]
  - >20,000 new cases/year in the United States with ~4,000 deaths
- Primarily occurs in middle-aged and older adults[2]
- Heterogeneous disease with wide-ranging clinical course[3]
  - Most patients diagnosed with early-stage disease
  - Anticipate multiple disease relapses and multiple lines of treatment
  - Those with high-risk disease have shorter median survival
- Incurable with standard chemotherapy
- A disorder of morphologically mature but immunologically less mature lymphocytes[4]
  - CLL: lymphocyte count ≥5000 per mm^3 for diagnosis
  - SLL: presence of lymphadenopathy and/or splenomegaly and lymphocyte count ≤5000 per mm^3 in peripheral blood

CLL, chronic lymphocytic leukemia;
SLL, small lymphocytic lymphoma.

[1]Siegel RL, et al. *CA Cancer J Clin*. 2021;
[2]https://seer.cancer.gov/statfacts/html/clyl.html; [3]Hilal T, et al. *Curr Hematol Malig Rep*. 2018;
[4]https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/cancer-treatment-and-survivorship-facts-and-figures/cancer-treatment-and-survivorship-facts-and-figures-2019-2021.pdf.

Genetic Abnormalities in CLL/SLL Guiding Prognosis and Treatment Modalities

Genomic Alteration	Prognosis
Deletions in 13q14	Favorable
IGHV mutation (vs unmutated)	Favorable (unfavorable)
Trisomy 12	Intermediate
Deletions in 11q22 (ATM)	Unfavorable
Deletion in 17p13	Unfavorable
TP53 mutation (vs wild-type)	Unfavorable
Complex karyotypes (>3 unrelated chromosomal abnormalities)	Unfavorable

*Cytogenetic abnormalities can evolve over time; therefore, re-evaluation of FISH and karyotype is necessary to direct treatment options in patients with indications for treatment.

Yeung CC, Shadman M. *Curr Oncol Rep*. 2019; NCCN. CLL/SLL Guidelines. v4.2021; Gentile M, et al. *Haematologica*. 2009.

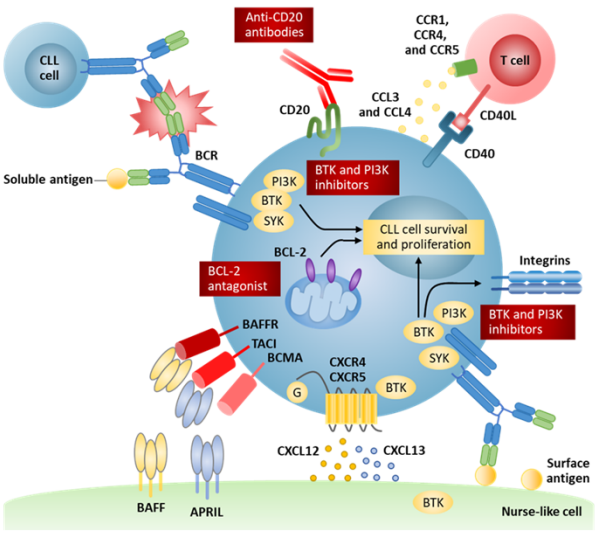
CLL Signs, Symptoms, and Treatment

- In the absence of symptoms, use a "watch and wait" approach, with treatment being beneficial if patient is symptomatic or showing disease progression
  - Severe fatigue
  - Night sweats
  - Weight loss
  - Fever without infection
  - Progressive anemia/thrombocytopenia
  - Progressive bulky disease

"B symptoms"

Brown JR. *Expert Rev Hematol*. 2008; Nosari A. *Mediterr J Hematol Infect Dis*. 2012; NCCN. CLL/SLL Guidelines. v4.2021.

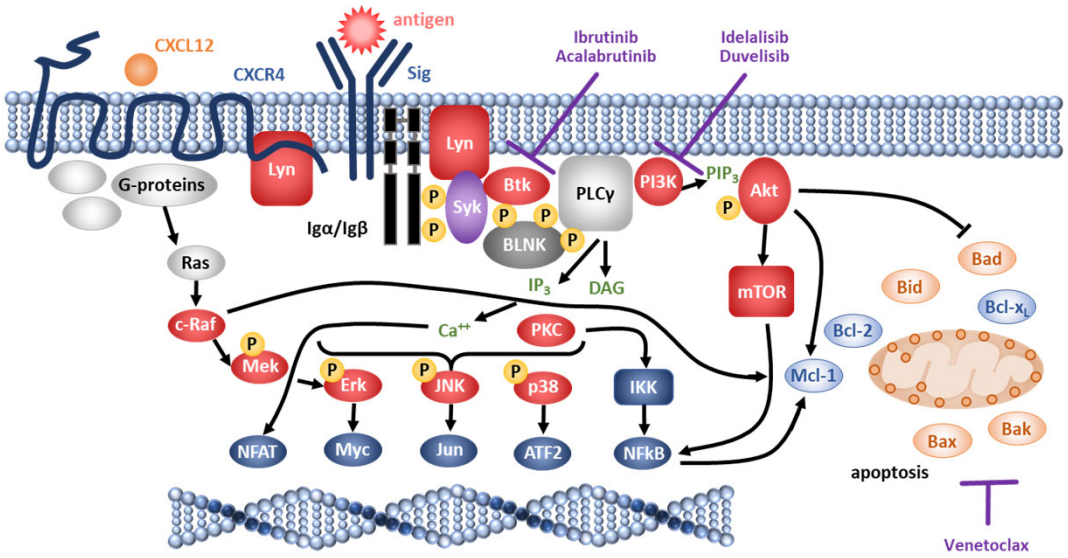
B-cell Receptor (BCR) Pathway



- CLL is a complex disease
- Normal BCR activation → appropriate cell proliferation, differentiation, and antibody production
- ↑ BCR activation = CLL cell survival and proliferation

ten Hacken E, et al. *Biochim Biophys Acta*. 2016; Davids M, Brown JR. *Leuk Lymphoma*. 2012; Burger JA, Chiorazzi N. *Trends Immunol.* 2013.

Mechanism of Action for Novel Agents Used in Management of CLL



Adapted from Hallek M. *Blood*. 2013; FDA Prescribing Information; Clinicaltrials.gov.

Navigating the Patient Journey

A Case-based Discussion on CLL Management

NCCN Guidelines
Treatment-naïve CLL

First-line *regardless* of del(17p)/TP53 Mutation

Preferred regimens	
Del(17p)/TP53 mutation? • No (Category 1) • Yes (Category 2A)	**Ibrutinib** **Acalabrutinib** +/- obinutuzumab **Venetoclax** + obinutuzumab

Other regimens (different recommendations based on age, comorbidities, and del(17p)/TP53 status): Alemtuzumab ± rituximab; bendamustine + anti-CD20 mAb; chlorambucil; chlorambucil + obinutuzumab; FCR; FR; HDMP + rituximab; HDMP + rituximab or obinutuzumab; ibrutinib + obinutuzumab; ibrutinib + rituximab; obinutuzumab; rituximab; zanubrutinib (for pts with contraindication to other BTKi)

BR, bendamustine + rituximab; FCR, fludarabine, cyclophosphamide, rituximab;
HDMP, high-dose methylprednisolone; PCR, pentostatin, cyclophosphamide, rituximab.

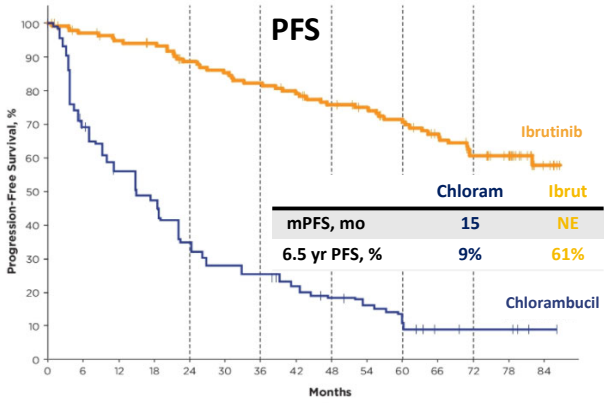
NCCN. CLL/SLL Guidelines. V1.2022.

Phase III RESONATE-2 Trial
Ibrutinib Monotherapy in TN CLL

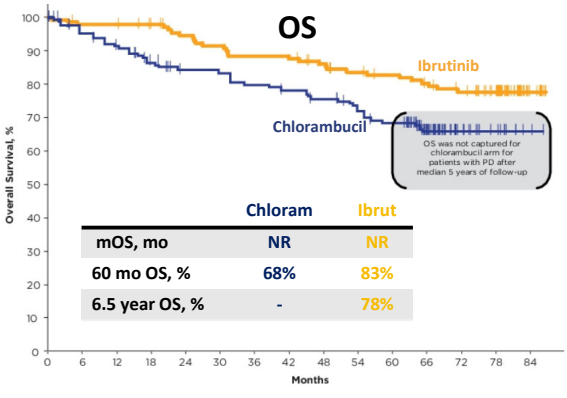
Patient Population
- ≥65 years old
- Excluded del(17p)

Randomized 1:1

Arm A: ibrutinib (n=136)
Arm B: chlorambucil (n=133)



	Chloram	Ibrut
mPFS, mo	15	NE
6.5 yr PFS, %	9%	61%



	Chloram	Ibrut
mOS, mo	NR	NR
60 mo OS, %	68%	83%
6.5 year OS, %	-	78%

Barr PM, et al. *ASCO*. Abstract 7523. 2021.

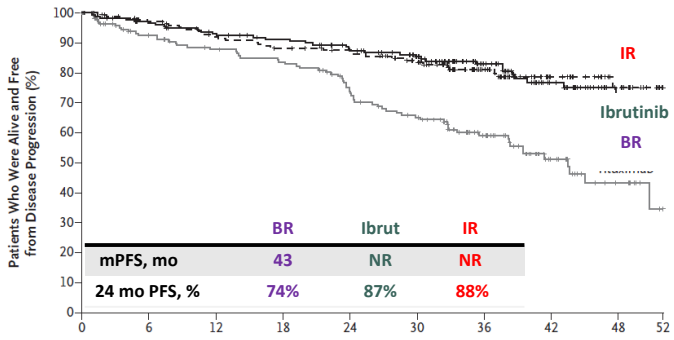
Phase III Alliance A041202 Trial
Ibrutinib Regimens vs Chemotherapy

Patient Population
- ≥65 years old
- Included del(17p) (6%)

Randomized 1:1:1

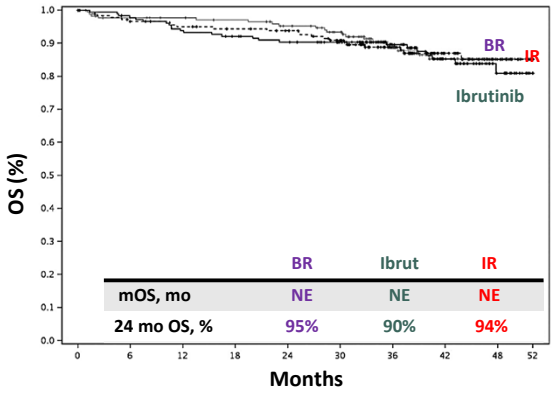
Arm A: ibrutinib (n=182)
Arm B: ibrutinib + rituximab (n=182)
Arm C: bendamustine + rituzumab (n=183)

PFS



	BR	Ibrut	IR
mPFS, mo	43	NR	NR
24 mo PFS, %	74%	87%	88%

OS



	BR	Ibrut	IR
mOS, mo	NE	NE	NE
24 mo OS, %	95%	90%	94%

BR, bendamustine and rituximab; IR, ibrutinib and rituximab; NR, not reached; NE, not estimable.

Woyach JA, et al. *N Engl J Med*. 2018.

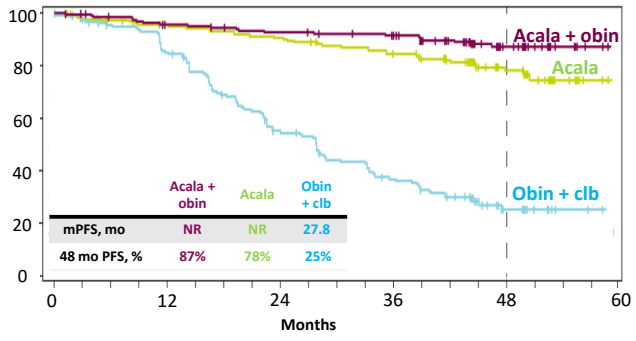
Phase III ELEVATE-TN Trial
Acalabrutinib Combination

Patient Population
- ≥65 years old OR <65 with comorbidities
- Included del(17p) (9%)

Randomized 1:1:1

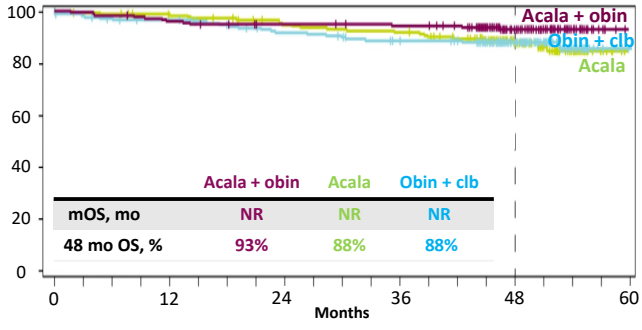
Arm A: acalabrutinib + obinutuzumab (n=179)
Arm B: acalabrutinib (n=179)
Arm C: chlorambucil + obinutuzumab (n=177)

PFS



	Acala + obin	Acala	Obin + clb
mPFS, mo	NR	NR	27.8
48 mo PFS, %	87%	78%	25%

OS



	Acala + obin	Acala	Obin + clb
mOS, mo	NR	NR	NR
48 mo OS, %	93%	88%	88%

Sharman JP, et al. *Lancet*. 2020; Sharman JP, et al. *ASH*. 2019. Abstract 31; Sharman JP, et al. *ASCO*. 2021. Abstract 7509.

Phase III CLL14 Trial

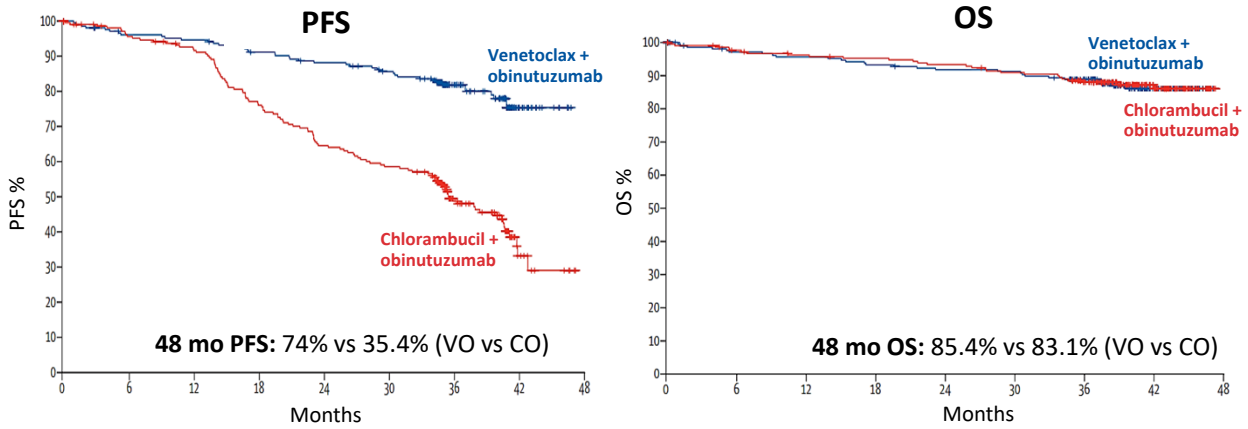
Venetoclax + Obinutuzumab vs Chlorambucil + Obinutuzumab

Patient Population
- ≥65 years old OR <65 with comorbidities
- Included del(17p) (7%)

Randomized 1:1

Arm A: venetoclax + obinutuzumab (n=216)

Arm B: chlorambucil + obinutuzumab (n=216)



Fischer K, et al. *N Engl J Med*. 2019; Al-Sawaf O, et al. *Lancet Oncol*. 2020; Al-Sawaf O, et al. *EHA*. 2021. Abstract S146.

NCCN Guidelines

Treatment-naïve CLL

First-line *regardless* of del(17p)/TP53 Mutation

Preferred regimens

Del(17p)/TP53 mutation?
- No (Category 1)
- Yes (Category 2A)

Ibrutinib

Acalabrutinib +/- obinutuzumab

Venetoclax + obinutuzumab

Other regimens (different recommendations based on age, comorbidities, and del(17p)/TP53 status): Alemtuzumab ± rituximab; bendamustine + anti-CD20 mAb; chlorambucil; chlorambucil + obinutuzumab; FCR; FR; HDMP + rituximab; HDMP + rituximab or obinutuzumab; ibrutinib + obinutuzumab; ibrutinib + rituximab; obinutuzumab; rituximab; zanubrutinib (for pts with contraindication to other BTKi)

BR, bendamustine + rituximab; FCR, fludarabine, cyclophosphamide, rituximab; HDMP, high-dose methylprednisolone; PCR, pentostatin, cyclophosphamide, rituximab.

NCCN. CLL/SLL Guidelines. V1.2022.

TN CLL
Case Study

Discussion regarding treatment options with the patient includes preferred NCCN therapies for TN CLL:

- BTK inhibitor treatment (ibrutinib or acalabrutinib)
- Venetoclax and obinutuzumab

Drug Interactions with Novel CLL Therapies

LC medications: metformin, diltiazem, omeprazole, multivitamin, and aspirin

	BTK Inhibitors	Venetoclax
Strong CYP3A4 inhibitors	Avoid; if using short term (<7 days), consider interrupting therapy	Contraindicated
Moderate CYP3A4 inhibitors	Reduce dose	↓ dose by ≥50%
CYP3A4 inhibitors: clarithromycin, erythromycin, itraconazole, fluconazole, posaconazole, voriconazole, ritonavir, indinavir, nelfinavir, darunavir, fosamprenavir, diltiazem, verapamil, amiodarone, dronedarone, grapefruit, Seville oranges		
Strong CYP3A4 inducers	Avoid	—
CYP3A4 inducers: rifampin, carbamazepine, phenytoin, St. John's wort		
P-gp inhibitors	Ibrutinib: may increase the concentration of oral P-gp or BCRP substrates with narrow therapeutic index	↓ dose by ≥50%
P-gp substrates: dabigatran, digoxin, methotrexate		
Acid reducing agents	Acalabrutinib: avoid PPIs (omeprazole, esomeprazole); take 2 hours before H2-RAs (ranitidine, famotidine); separate by at least 2 hours from antacids	—

FDA Prescribing Information.

Treatment-Naïve CLL Treatment Considerations

NCCN Preferred Regimens for Treatment Naïve CLL/SLL

	Dose	Route	Duration
Ibrutinib	420 mg daily	PO	Until PD or unacceptable toxicity
Acalabrutinib	100 mg Q12H	PO	Until PD or unacceptable toxicity
Acalabrutinib +obinutuzumab	100 mg Q12H 1000 mg Q28 days*	PO IV	~6 months obinutuzumab then acalabrutinib until PD or unacceptable toxicity
Venetoclax +obinutuzumab	400 mg daily* 1000 mg Q28 days*	PO IV	~1 year** (FIXED DURATION)

Drug Interactions? Adverse Events? — ***Patient preference? Patient Adherence? Transportation?*** — ***Patient preference? Insurance coverage?***

PD, progressive disease.
*Target doses after ramp up; **obinutuzumab cycles 1–6, venetoclax ramp-up on Day 22 of cycle 1, continue venetoclax through cycle 12. FDA Prescribing Information.

Venetoclax Toxicities

All Grades

	Mono	+Obinu	+Ritux
Neutropenia	50	60	65
Diarrhea	43	28	40
URTI	36	17	39
Anemia	33	17	16
Nausea	42	19	21
Fatigue	32	21	2
Musculoskeletal pain	29	—	—

≥40 ≥30 ≥20 ≥10

Grades 3–5

	Mono	+Obinu	+Ritux
Neutropenia	45	56	62
Diarrhea	3	4	3
URTI	1	1	2
Anemia	18	8	11
Nausea	1	—	1
Fatigue	4	2	2
Musculoskeletal pain	2	—	—

≥10 ≥7.5 ≥5 ≥2.5

FDA Prescribing Information.

Venetoclax CLL Dose Modifications Due to AEs

- Consider D/C for those requiring dose reductions less than 100 mg for more than 2 weeks
- During ramp-up phase, continue reduced dose for 1 week before increasing the dose

Grade 3 or 4 non-hematologic toxicities, grade 3 neutropenia with infection or fever, grade 4 hematologic toxicities (except lymphopenia)

Toxicity Occurrence	Dose Modification
First	• Interrupt therapy • Consider G-CSF to reduce infection risk • When grade 1, resume at same dose
Second and subsequent	• Same as above except, when grade 1, follow dose reduction guidelines

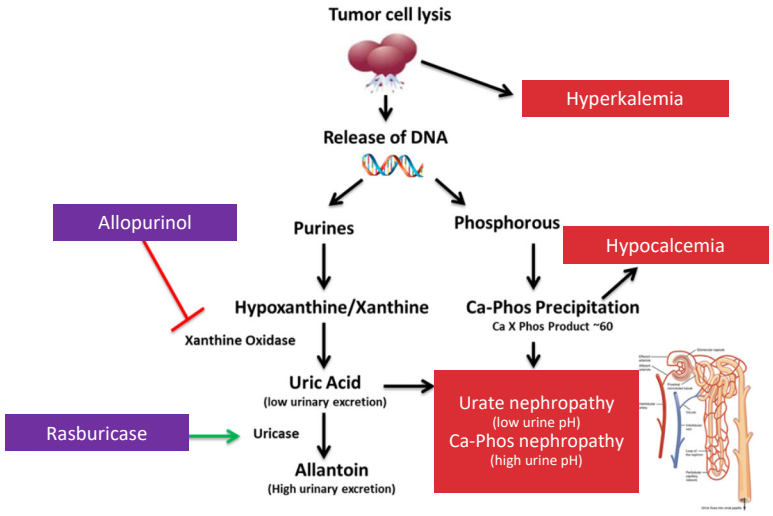
Dose Reduction Guidelines

Dose at Interruption	Restart Dose
400	300
300	200
200	100
100	50
50	20
20	10

Tablets: 10 mg, 50 mg, 100 mg

FDA Prescribing Information.

Tumor Lysis Syndrome



Symptoms

N/V, SOB, irregular heartbeat, clouding of urine, lethargy, joint discomfort

Treatment

1. Rigorous hydration
2. Management of hyperuricemia
3. Frequent monitoring of electrolytes and aggressive correction

If untreated, may cause acute kidney failure, cardiac arrhythmias, seizures, loss of muscle control, and death.

http://www.learnpicu.com/oncology/tumor-lysis-syndrome; NCCN. CLL/SLL Guidelines. v4.2021.

TLS Prophylaxis and Management

TLS Prophylaxis	Setting	Monitoring Frequency (K, P, Ca, uric acid, CrCl)
Low Tumor Burden (All LN <5 cm and ALC <25 x 10^9/L) • Oral hydration (1.5–2 L) • Allopurinol (consider rasburicase if baseline uric acid is elevated)	Outpatient	• First 20 mg and 50 mg dose: pre-dose, 6–8 hours and 24 hours after dose • Subsequent ramp-up doses: pre-dose
Medium Tumor Burden (Any LN 5 cm to <10 cm or ALC ≥25 x 10^9/L) • As above • Or consider IV hydration	Outpatient*	• As above
High Tumor Burden (Any LN ≥10 cm or ALC ≥25 x 10^9/L and any LN ≥5 cm) • As above • AND IV hydration (150–200 mL/hour as tolerated)	Outpatient or Hospital	• First 20 mg and 50 mg dose: pre-dose, 4, 8, 12, 24 hours post-dose • Subsequent ramp-up doses: pre-dose, 6–8 hours and 24 hours after dose

HOLD next day's dose for any symptoms or changes suggestive of TLS

If resolved in 24–48 hours: resume same dose

If resolved in >48 hours: resume at reduced dose

*Consider hospitalization for CrCl <80 mL/min with first dose of 20 mg and 50 mg.

Stilgenbauer S, et al. *Lancet Oncol*. 2016; FDA Prescribing Information.

NCCN Guidelines
Relapsed/Refractory CLL

Relapsed/Refractory *regardless* of del(17p)/TP53 Mutation*

Preferred regimens (All Category 1)	**Ibrutinib**
	Acalabrutinib
	Venetoclax + rituximab

***Venetoclax** monotherapy is also a preferred recommendation but is Category 2A and for del(17p)/TP53 only

Other regimens (different recommendations based on age, comorbidities, and del(17p)/TP53 status): Alemtuzumab ± rituximab; BR; BR + ibrutinib; chlorambucil + rituximab; dose-dense rituximab; duvelisib; FC + ofatumumab; FCR; HDMP + rituximab; HDMP + rituximab or obinutuzumab; idelalisib ± rituximab; lenalidomide ± rituximab; obinutuzumab; ofatumumab; venetoclax; zanubrutinib (for pts with intolerance or contraindication to other BTKi)

BR, bendamustine + rituximab; FCR, fludarabine, cyclophosphamide, rituximab; HDMP, high-dose methylprednisolone

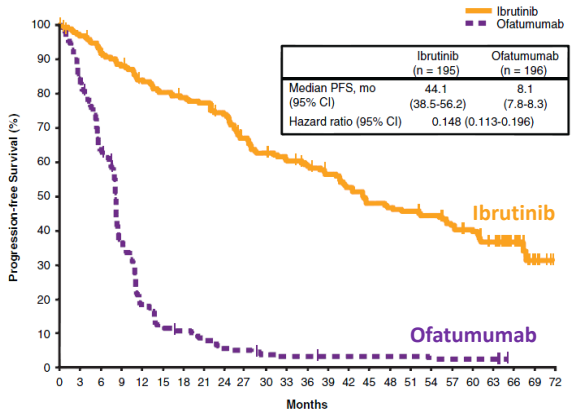
NCCN. CLL/SLL Guidelines. V1.2022.

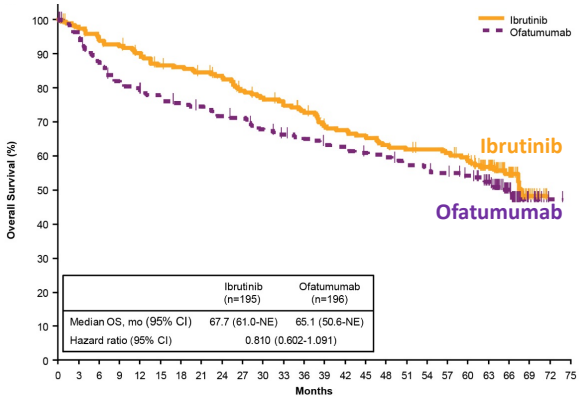
Phase III RESONATE Trial
Ibrutinib vs Ofatumumab

Patient Population
- Median 3 prior therapies
- Included del(17p) (32%)

Randomized 1:1

Arm A: ibrutinib (n=195)
Arm B: ofatumumab (n=196) → crossover to ibrutinib (n=122)





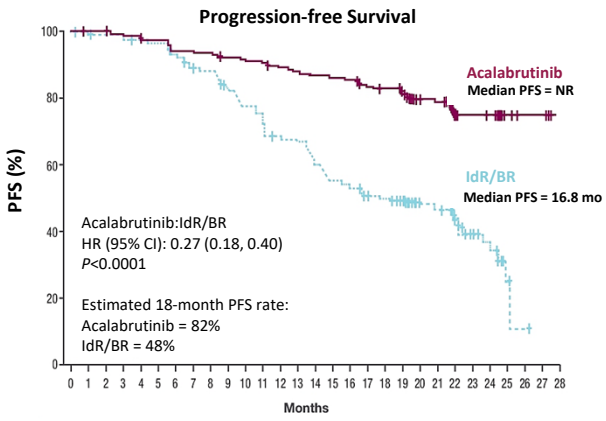
Byrd JC, et al. *Blood*. 2019; Munir T, et al. *Am J Hematol*. 2019.

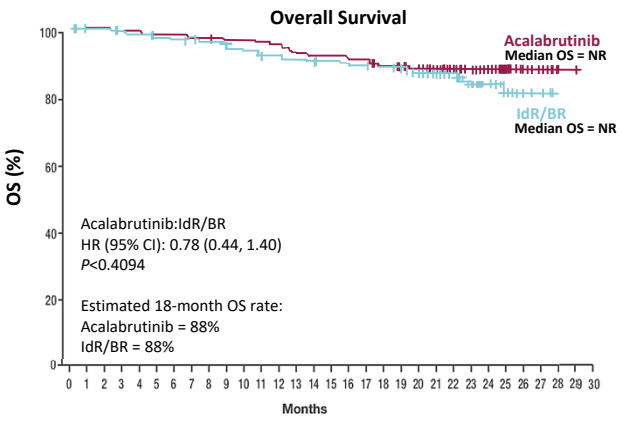
Phase III ASCEND (ACE-CL-309)
Acalabrutinib vs Ritux/BR vs Ritux/IdR

Patient Population
- Median 2 prior therapies
- Included del(17p) (17%)

Randomized 1:1

Arm A: acalabrutinib (n=155)
Arm B: rituximab + idelalisib OR bendamustine (n=155)





IdR, idealisib and rituximab.

Ghia P, et al. ASH Virtual Annual Meeting. 2020. Abstract 3140.

BTK Inhibitor Head-to-Head Trials

Trial	Eligibility	Treatment Arms	Outcomes
ACE-CL-006 *(Phase III)*	• R/R CLL • ECOG PS ≤2 • Del(17p) and/or del(11q) • *Exclusion:* significant CVD, concomitant warfarin, prior BTK or BCL-2 inhibitor, those on PPIs	• Acalabrutinib (n=268) • Ibrutinib (n=265)	• Acalabrutinib non-inferior to ibrutinib with less CV toxicity • mPFS=38.4 months in both arms • mOS=NR in either arm • All grade Afib/flutter: 9.4% vs. 16% (acalabrutinib vs. ibrutinib) • Therapy D/C: 14.7% (acalabrutinib) vs. 21.3% (ibrutinib)

ALPINE *(Phase III)*	• R/R CLL
	• ECOG PS ≤2
	• *Exclusion:* significant CVD, history of severe bleeding disorder, stroke, or intracranial hemorrhage, prior BTK inhibitor
		• Zanubrutinib (n=207)
		• Ibrutinib (n=208)
			• Median f/u of 15 months:
			  • ORR: 78% vs. 63% (Z vs. I)
			  • Del(17p): 83% v. 54%
			  • Del(11q): 84% v. 69%
			  • 12-mo PFS: 95% vs. 84%
			  • 12-mo OS: 97% vs. 93%
			  • Afib/flutter: 2.5% vs. 10.1%

Hillmen P, et al. *EHA.* 2021. Abstract LB1900; Byrd JC, et al. *J Clin Oncol.* 2021.

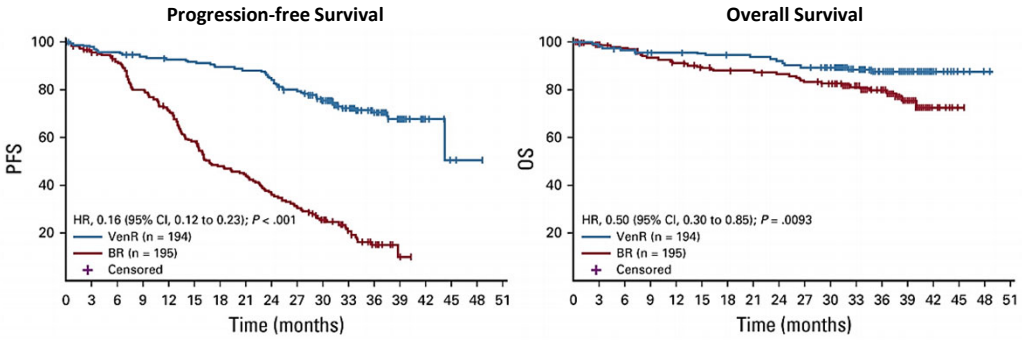
Phase III MURANO Trial
Venetoclax + Rituximab vs BR

Patient Population
- Median 1 prior therapies
- Included del(17p) (24%)

Randomized 1:1

Arm A: venetoclax + rituximab → venetoclax monotherapy (n=194)
Arm B: rituximab + bendamustine (n=194)

Median follow-up of 36 months



Updated results from ASH (median f/u of 59 months):
*PFS and OS benefit were sustained: mPFS = 54 months vs 17 months; 5-year OS=82% vs 62%

Kater AP, et al. *J Clin Oncol.* 2019; Kater AP, et al. ASH Virtual Annual Meeting. 2020. Abstract 125.

Drug Interactions with Novel CLL Therapies

RS medications: lisinopril, hydrochlorothiazide, tamsulosin

	BTK Inhibitors	Venetoclax
Strong CYP3A4 inhibitors	Avoid; if using short term (<7 days), consider interrupting therapy	Contraindicated
Moderate CYP3A4 inhibitors	Reduce dose	↓ dose by ≥50%
CYP3A4 inhibitors: clarithromycin, erythromycin, itraconazole, fluconazole, posaconazole, voriconazole, ritonavir, indinavir, nelfinavir, darunavir, fosamprenavir, diltiazem, verapamil, amiodarone, dronedarone, grapefruit, Seville oranges		
Strong CYP3A4 inducers	Avoid	—
CYP3A4 inducers: rifampin, carbamazepine, phenytoin, St. John's wort		
P-gp inhibitors	Ibrutinib may increase the concentration of oral P-gp or BCRP substrates with narrow therapeutic index	↓ dose by ≥50%
P-gp substrates: dabigatran, digoxin, methotrexate		
Acid Reducing Agents	Acalabrutinib: avoid PPIs (omeprazole, esomeprazole); take 2 hours before H2-RAs (ranitidine, famotidine); separate by at least 2 hours from antacids	—

FDA Prescribing Information.

R/R CLL Treatment Considerations

NCCN Preferred Regimens for R/R CLL/SLL

	Dose	Route	Duration
Ibrutinib	420 mg daily	PO	Until PD or unacceptable toxicity
Acalabrutinib	100 mg Q12H	PO	Until PD or unacceptable toxicity
Venetoclax + rituximab	400 mg daily* + 500 mg/m^2 Q28 days*	PO IV	~2 years** (fixed duration)
Venetoclax (del17p+)	400 mg daily*	PO	Until PD or unacceptable toxicity

*Target doses after ramp up.
**Venetoclax 5-week ramp-up plus one week on target dose of 400 mg, then begin rituximab for cycles 1–6, venetoclax for cycles 1–24.

FDA Prescribing Information.

R/R CLL
Case Study

Discussion regarding treatment options with the patient includes preferred NCCN therapies for R/R CLL:

- BTK inhibitor treatment (ibrutinib or acalabrutinib)
- Venetoclax and rituximab

Patient prefers avoidance of infusion center or hospitalization if possible.

R/R CLL
Case Study

Discussion regarding treatment options with the patient includes preferred NCCN therapies for R/R CLL:

- BTK inhibitor treatment (ibrutinib or acalabrutinib) ***PO***
- Venetoclax and rituximab ***PO/IV***

Through shared decision-making, a treatment plan is developed. Ibrutinib is prescribed and is covered by insurance.

Special Considerations for BTK Inhibitor AE Management

Toxicity	Ibrutinib	Acalabrutinib	Zanubrutinib
Infections	≥Gr3, 21%	≥Gr3, 19%	≥Gr3, 11%
• Cases of progressive multifocal leukoencephalopathy (PML), pneumocystis jirovecii pneumonia (ibrutinib), and infections due to hepatitis B reactivation (acalabrutinib) have occurred • Monitor and evaluate patients for fever and infections; treat appropriately			
Lymphocytosis	66%	26%	41%
• Presents during the first few weeks of therapy and typically resolves by 2 months			
Second Primary Malignancies	10%	12%	9%
• Most common malignancy seen is skin cancer • Advise protection from sun exposure and encourage routine cancer screening			
Arthralgias	24%	16%	14%
• Usually occurs early in the treatment course • APAP or short course of prednisone therapy; anti-inflammatory agents, such as ibuprofen, should be avoided to minimize bleeding • Transition to a selective BTKi, such as acalabrutinib can diminish or resolve this toxicity			
Headache	18%	39%	4%
• Usually observed early in therapy and typically resolves over 1–2 months • Generally well managed with analgesics, such as acetaminophen and caffeine supplements			

FDA Prescribing Information; Stephens DM, et al. *Blood*. 2019; Rogers B, Khan N. *J Adv Pract Oncol.* 2017; NCCN. CLL/SLL Guidelines. v4.2021.

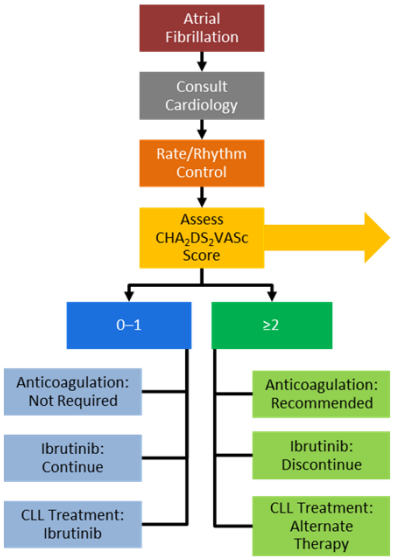
Special Consideration for BTK Inhibitor Cardiovascular AE Management

Toxicity	Ibrutinib	Acalabrutinib	Zanubrutinib
Hemorrhage/Bleeding	32% ≥Gr3, 4%	22% ≥Gr3, 3%	50% ≥Gr3, 2%
• Increased risk of bleeding on concomitant anticoagulant therapy or antiplatelet therapy • Consider risk/benefit of withholding for 3–7 days pre- and post-surgery			
Afib/Flutter	≥Gr3, 4%	≥Gr3, 1.1%	≥Gr3, 2%
• Periodically monitor for cardiac arrhythmias and obtain ECG for those who develop symptoms (palpitations, lightheadedness, syncope, chest pain) or new onset dyspnea • Manage cardiac arrhythmias and manage as appropriate			
Hypertension	19%	5%	12%
• Monitor for new/uncontrolled hypertension • Initiate antihypertensives as needed			

FDA Prescribing Information; Rogers B, Khan N. *J Adv Pract Oncol.* 2017; NCCN. CLL/SLL Guidelines. v4.2021.

BTK Inhibitor Toxicity Management
Atrial Fibrillation

- Baseline CV risk assessment before starting therapy; consider alternate therapy in high-risk CVE (CHA_2D_2-VASc Score) needing anticoagulation
- For new AF
  - CHA_2D_2-VASc Score 0–1: most clinicians favor continuing BTKi
  - CHA_2D_2-VASc Score ≥2: consider holding until AF control or BTKi discontinuation
- Periodically monitor for cardiac arrhythmias and obtain ECG for those who develop symptoms or new onset dyspnea
  - Consider beta-blockers over CYP3A4 inhibitors or P-gp substrates, which interact with BTKis
  - For anticoagulation, consider low-dose apixaban (2.5 mg BID given CYP3A4 interaction) or enoxaparin; avoid warfarin



CHA_2DS_2-VASc Scoring	
Risk Factor	**Points**
CHF	1
Hypertension	1
Age 65–74 years	1
Age ≥75 years	2
Diabetes mellitus	1
History of stroke/TIA	2
Vascular disease	1
Female gender	1

Stephens DM, et al. *Blood*. 2019; Wiczer TE, et al. *Blood Adv*. 2017; Lipsky A, et al. *Hematology Am Soc Hematol Educ Program.* 2020; FDA Prescribing Information; NCCN. CLL/SLL Guidelines. v4.2021.

General BTKi Dose Modifications Due to AEs

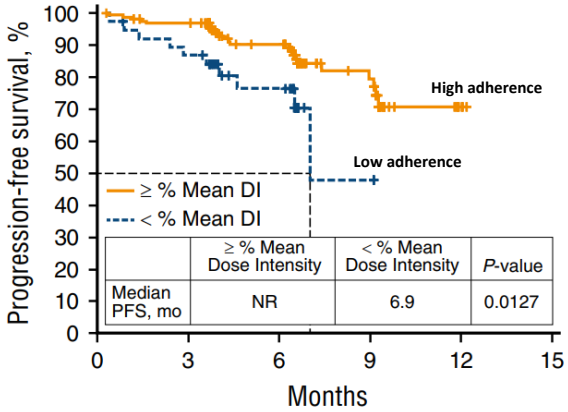
- ≥Grade 3 non-hematological toxicities (all)
- **Neutropenia:** ≥grade 3 neutropenia with infection or fever (ibrutinib), grade 3 febrile neutropenia (zanubrutinib), grade 4 neutropenia lasting longer than 7 days/10 days (acalabrutinib/zanubrutinib)
- **Thrombocytopenia:** grade 3 thrombocytopenia with bleeding (acalabrutinib) for 10 days (zanubrutinib), grade 4 thrombocytopenia (acalabrutinib), ≥grade 4 hematological toxicities (ibrutinib)

Toxicity Occurrence	Dose Modification		
	Ibrutinib	Zanubrutinib	Acalabrutinib
First	Interrupt therapy until resolved to grade 1 or baseline; may be initiated at starting dose		Interrupt therapy until grade 1 or baseline level; then resume at starting dose
Second	Interrupt therapy until resolved to grade 1; restart at reduced dose		
Third	Interrupt therapy until resolved to grade 1; resume at reduced dose		
Fourth	Discontinue		

FDA Prescribing Information.

Therapy Interruption on Efficacy
Importance of Managing Toxicities

- Missed doses → worsened outcomes
- **Prevention and early recognition/management of toxicities** is <u>paramount</u> to decrease likelihood of therapy interruption (either from patient non-adherence or clinician-guided dose modifications)
  - Encourage frequent and open communication with patients to improve outcomes



	≥ % Mean Dose Intensity	< % Mean Dose Intensity	*P*-value
Median PFS, mo	NR	6.9	0.0127

Missed ibrutinib doses for ≥8 days was associated with worsened PFS.

Minimize BTKi toxicities and avoid therapy interruption to maintain efficacy.

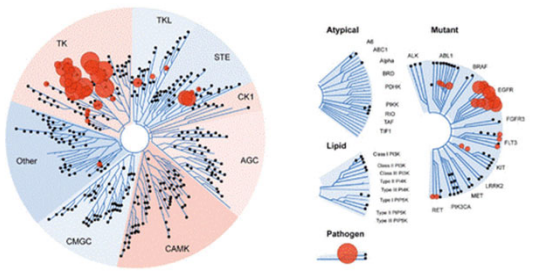
Barr PM, et al. *Blood*. 2017.

Not All BTK Inhibitors Created Equal

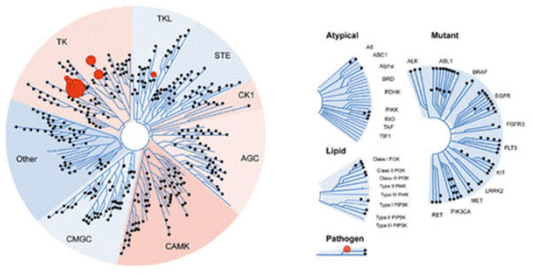
Would switching to acalabrutinib improve tolerance?

BTK Inhibitor Selectivity

Ibrutinib



Acalabrutinib

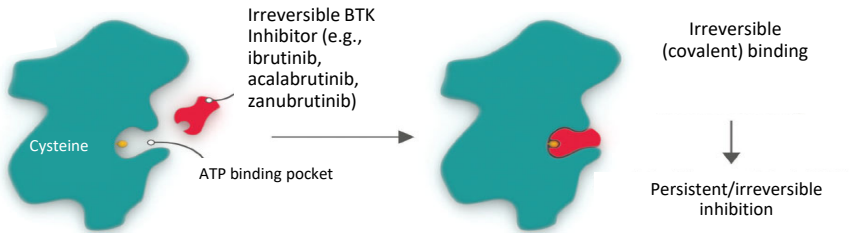


↑ off target binding = ↑ likelihood of toxicities

Owen C, et al. *Curr Oncol*. 2019.

When the Binding Site Changes
Mutation Concerns

- Ibrutinib, acalabrutinib, and zanubrutinib all covalently bind to BTK at the cysteine 481 (C481) amino acid



- Acquired resistance occurs due to this binding site mutation (cysteine to serine change so BTKi can no longer bind)
- If C481S mutation develops, resistance will occur with **ibrutinib, acalabrutinib, and zanubrutinib**

Adapted from Wiestner A. *Haematologica*. 2015; NCCN. CLL/SLL Guidelines. v4.2021; Byrd JC, et al. *Oncotarget*. 2018; Wu J, et al. *J Hematol Oncol*. 2016; Byrd JC, et al. *N Engl J Med*. 2016; Woyach JA, et al. *N Engl J Med.* 2014; Woyach JA. *Blood.* 2018.

R/R CLL
Case Study

Discussion regarding treatment options with the patient includes preferred NCCN therapies for R/R CLL:

- Venetoclax and rituximab ***PO/IV***
- Venetoclax monotherapy ***PO***

Patient still expresses desire for oral therapy over IV treatment. Patient is started on venetoclax monotherapy.

Conclusions

- CLL is the most common leukemia in the Western world, primarily manifesting in the elderly.
- Novel therapies targeting the BCR pathway have become a mainstay in the treatment of CLL.
- Treatment selection should be individualized to the patient and selected based on mutation status, performance status, comorbidities, and patient preferences.
- Fixed-duration and chemoimmunotherapy free approaches are now options in both the front line and relapsed/refractory setting.
- Prevention and early recognition/management of toxicities associated with oral therapies is vital to decrease likelihood of therapy interruption.