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Learning Objectives

- Describe the role of the B-cell receptor (BCR) pathway in the survival and proliferation of cancer cells and the rationale for targeting this pathway in CLL/SLL.
- Examine the latest efficacy data on the use of BTK inhibitors in treatment-naïve and relapsed/refractory CLL and review the most recent guideline recommendations for CLL/SLL management.
- Discuss the unique adverse events that may arise with the use of BTK inhibitors and explore evidence-based strategies to ensure the timely recognition and proper management of these adverse events.
- Using a case-based approach, evaluate effective strategies that oncology nurses can employ to optimize therapy, anticipate and manage toxicities, improve adherence to oral chemotherapy and promote collaborative discussion with other members of the oncology care team to ensure optimal CLL patient outcome and shared decision-making.

Targeting the BCR Pathway in CLL: A Novel Approach

Chronic Lymphocytic Leukemia
Overview

- Most common leukemia in the Western world
  - >20,000 new cases/year in the United States with ~4,000 deaths
- Median age at diagnosis = 70
- Heterogeneous disease with wide-ranging clinical course
- Strongest tendency of leukemias for family aggregation
- Incurable with standard chemotherapy
- **Small, mature lymphocytes accumulated in peripheral blood and/or bone marrow (CLL) or primarily in lymph nodes and bone marrow (SLL)**

Brown JR. *Expert Rev Hematol*. 2008; Nosari A. *Mediterr J Hematol Infect Dis*. 2012; https://seer.cancer.gov/statfacts/html/clyl.html; NCCN. CLL/SLL Guidelines. v4.2020.

Chronic Lymphocytic Leukemia
Diagnostic Markers

- Flow cytometry of blood adequate for diagnosis of CLL/SLL
  - Monoclonal B lymphocytes ≥5 x 10^9/L in peripheral blood
- Immunophenotyping identifies surface markers
  - Distinguishes CLL/SLL from other B-cell malignancies
  - Typically: CD5+, CD23+, CD43+/-, CD10-, CD19+, CD20 dim, and cyclin D -

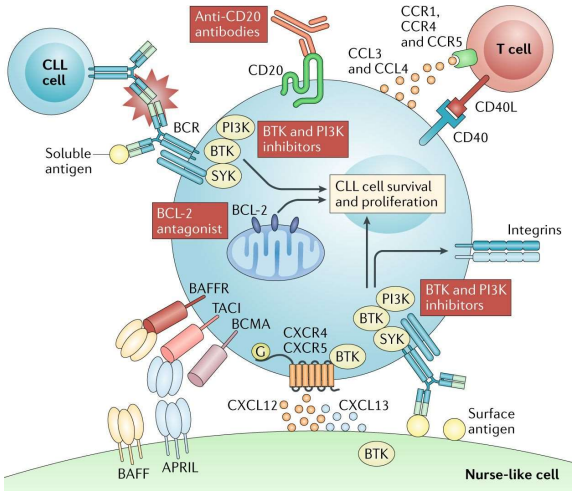
NCCN. CLL/SLL Guidelines. v4.2020.

Genetic Abnormalities in CLL/SLL
Guiding Prognosis & Treatment Modalities

Genomic aberration	Prognosis
Deletions in 13q14	Favorable
Deletions in 14q32.33	Favorable
IGHV mutation	Favorable
Del(6q)	Intermediate
Trisomy 12	Intermediate
Deletion in 17p13	Unfavorable
Deletions in 11q22 (ATM)	Unfavorable
Complex karyotypes	Unfavorable
Elevated beta-2 microglobulin	Unfavorable
TP53 mutation (vs wild-type)	Unfavorable

Yeung CC, Shadman M. *Curr Oncol Rep. 2019;* NCCN. CLL/SLL Guidelines. v4.2020; Gentile M, et al. *Haematologica*. 2009.

CLL is a Complex Disease



Burger JA, O'Brien S. *Nat Rev Clin Oncol*. 2018.

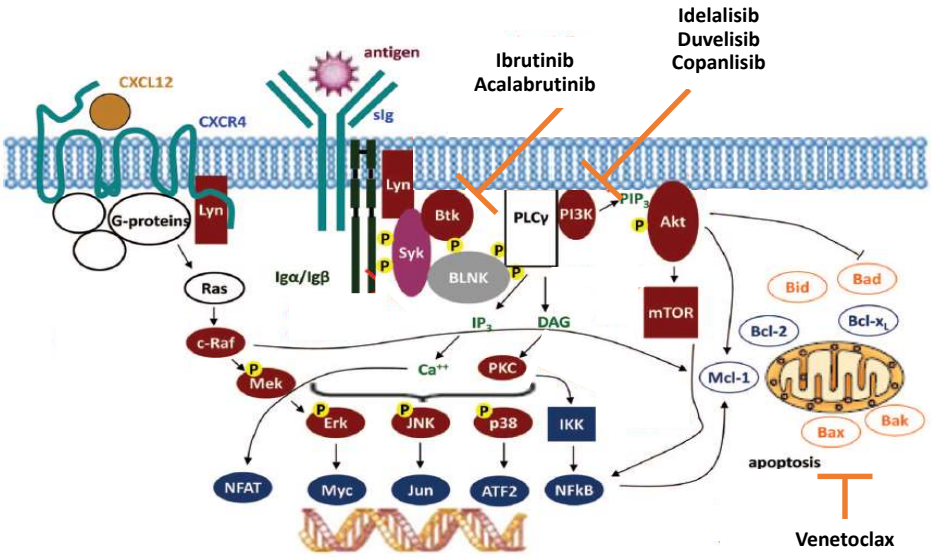
The B-cell Receptor Pathway

- Normal BCR activation → appropriate cell proliferation, differentiation, and antibody production.
- **↑ BCR activation = CLL cell survival and proliferation**
  - Mechanisms of BCR stimulation are typically heterogenous
  - May be caused by ligand independent (tonic) signaling (*IGVH*, ZAP-70 associated with auto-antigen binding)

How can we exploit this increased activation to treat CLL?

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

Treatment in 2020

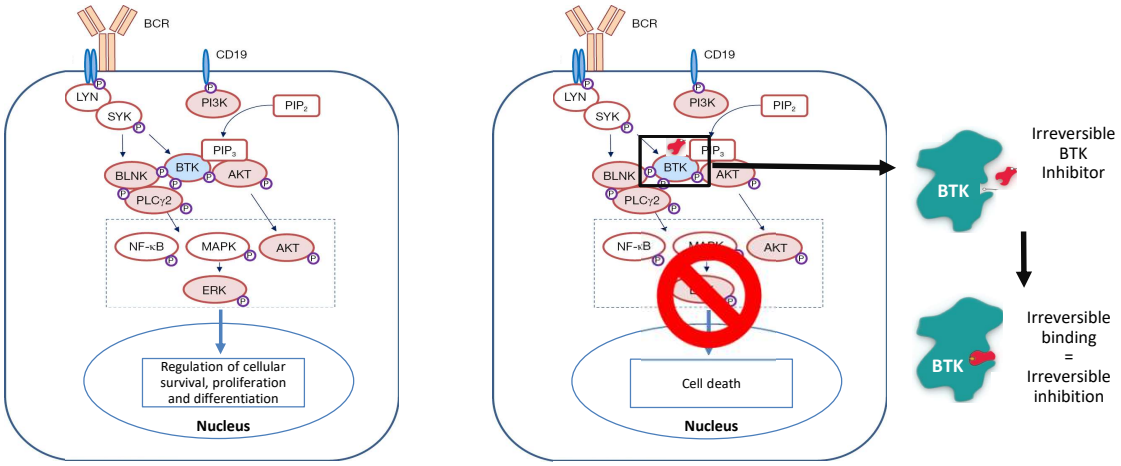


Adapted from Hallek M. *Blood*. 2013; FDA Prescribing Information; Clinicaltrials.gov.

Contemporary Approaches to CLL: Taking a Deep Dive into BTK Inhibition

Bruton's Tyrosine Kinase (BTK)

- **↑ BCR activation = ↑ BTK proteins in CLL cell**
- BTK inhibitors bind to these proteins and hinder the BTK's downstream effects.



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

BTK Inhibitors for the Treatment of CLL/SLL

Therapy	FDA-approved CLL Indication
Ibrutinib	• Approved for CLL/SLL with or without del(17p) • 420 mg tablet PO once daily
Acalabrutinib	• Approved for CLL/SLL • 100 mg tablet PO Q12H
Zanubrutinib	• Under investigation
Tirabrutinib	• Under investigation
Vecabrutinib	• Under investigation

FDA Prescribing Information.

Frontline Treatment without del(17p)/TP53 Mutation

Age and Comorbidities Evaluated

Frail w/ significant comorbidities or ≥65 or younger w/ significant comorbidities

Preferred
- Ibrutinib (category 1)
- Venetoclax + obinutuzumab
- Acalabrutinib ± obinutuzumab

Other recommended regimens
- Bendamustine + anti-CD20 mAb (not recommended for frail patients), chlorambucil + obinutuzumab, HDMP + rituximab, ibrutinib + obinutuzumab, obinutuzumab, chlorambucil, rituximab

<65 and without significant comorbidities

Preferred
- Ibrutinib (category 1)
- Venetoclax + obinutuzumab
- Acalabrutinib ± obinutuzumab

Other recommended regimens
- Bendamustine + anti-CD20 mAb, FCR (preferred for IGHV-mutated CLL), FR, HDMP + rituximab,
- ibrutinib + rituximab, PCR

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

NCCN. CLL/SLL Guidelines. v4.2020.

Frontline Treatment with del(17p)/TP53 Mutation

All Patients

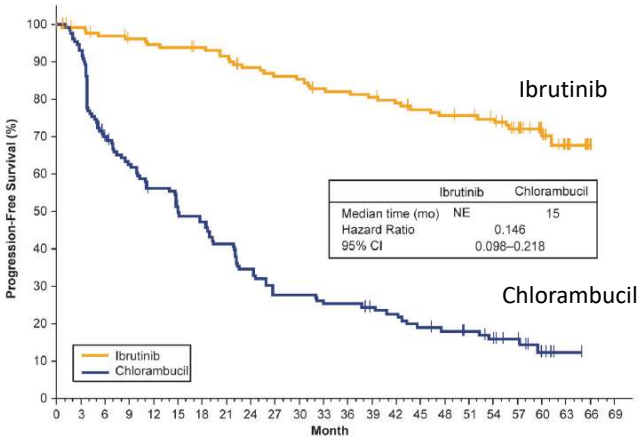
Preferred
- Ibrutinib
- Venetoclax + obinutuzumab
- Acalabrutinib ± obinutuzumab

Other recommended regimens
- Alemtuzumab ± rituximab
- HDMP + rituximab
- Obinutuzumab

NCCN. CLL/SLL Guidelines. v4.2020.

Ibrutinib Monotherapy in TN CLL
RESONATE-2 Trial – PFS after 5 Years

- Randomized to ibrutinib or chlorambucil (N=269)
- ≥65 years old (median age 73)
- Excluded del(17p)



Burger JA, et al. *Leukemia*. 2019.

Acalabrutinib Combination
Phase III, ELEVATE-TN Trial

≥65 years or older or <65 years + coexisting conditions

Patient Population
- Randomized 1:1:1
- Median age = 71
- 69% have high CLL-IPI score, 12% have very high CLL-IPI score

Arm 1 (n=179)
Acalabrutinib 100 mg PO BID until disease progression

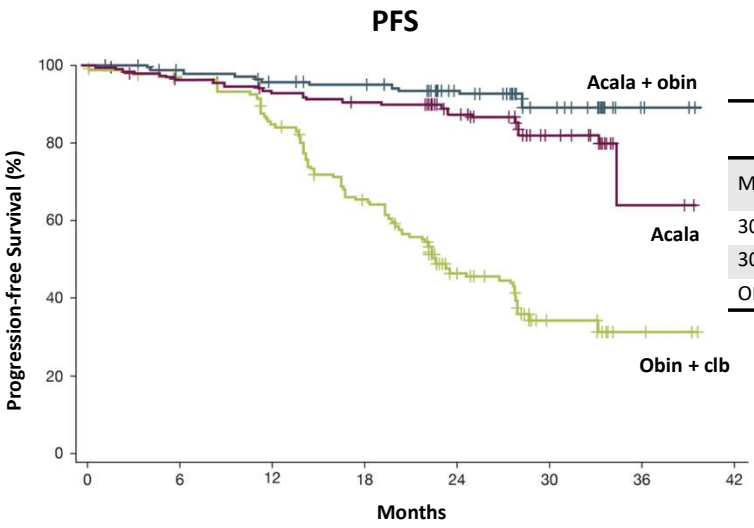
Arm 2 (n=179)
Acalabrutinib 100 mg PO BID until disease progression
Obinutuzumab 100 mg IV day 1, 900 mg day 2
Obinutuzumab 1000 mg day 8, and 15 of cycle 1
Obinutuzumab 1000 mg day 1 of cycles 2–6, every 28 days

Arm 3 (n=177)
Chlorambucil 0.5 mg/kg PO days 1 and 15 of each 28-day cycle for 6 cycles
Obinutuzumab 100 mg IV day 1, 900 mg day 2
Obinutuzumab 1000 mg day 8, and 15 of cycle 1
Obinutuzumab 1000 mg day 1 of cycles 2–6, every 28 days

IPI, international prognostic index.

Sharman JP, et al. *ASH. 2019.* Abstract 31.

Acalabrutinib Combination
Phase III, ELEVATE-TN Trial



	Acala	Acala + obin	Obin + clb
Median PFS, mo	NR	NR	22.6
30 mo PFS*, %	82%	90%	34%
30 mo OS**, %	94%	95%	90%
ORR, %	85%	94%	79%

*Consistent across all subgroups, including del(17p)
**Median OS has not been reached in any arm

Sharman JP, et al. *ASH. 2019*. Abstract 31.

Fit Patients—Phase III E1912
FCR vs IR in <70, <u>without</u> del(17p) CLL

Patient Population
- Median age 58
- ECOG 0–2
- CrCl >40
- Able to tolerate FCR
- No del(17p) by FISH

Randomized 2:1

Arm A: Ibrutinib + Rituximab (n=354)
- **Cycle 1**
  - Ibrutinib 420 mg PO daily, days 1–28
- **Cycle 2**
  - Ibrutinib 420 mg PO daily, days 1–28
  - Rituximab 50 mg/m^2 IV, day 1
  - Rituximab 325 mg/m^2 IV, day 2
- **Cycles 3–7**
  - Ibrutinib 420 mg PO daily, days 1–28
  - Rituximab 500 mg/m^2 IV, day 1
- **Cycle 8+**
  - Ibrutinib 420 mg PO daily, days 1–28

Arm B: FCR (n= 175)
- **Cycles 1–6**
  - Fludarabine 25 mg/m^2 IV, days 1–3
  - Cyclophosphamide 250 mg/m^2 IV, days 1–3
- **Cycle 1**
  - Rituximab 50 mg/m^2 IV, day 1, cycle 1
  - Rituximab 325 mg/m^2 IV, day 2, cycle 1
- **Cycles 2–6**
  - Rituximab 500 mg/m^2 IV, day 1, cycles 2–6

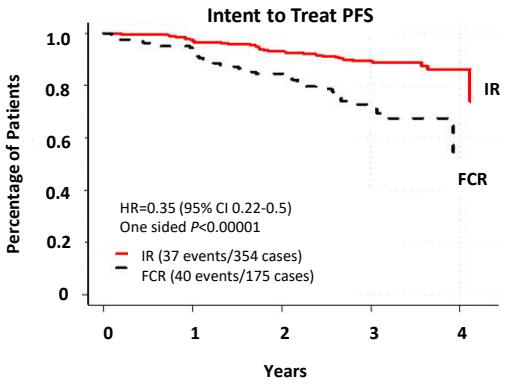
CrCl, creatinine clearance; FISH, fluorescence in situ hybridization.

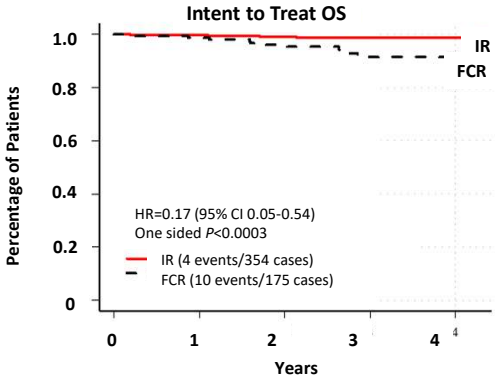
Shanafelt TD, et al. *N Engl J Med.* 2019.

Fit Patients—Phase III E1912

FCR vs IR in <70, without del(17p) CLL

- Improved efficacy
- Less AEs





AE, adverse event; HR, hazard ratio.

Adapted from Shanafelt TD, et al. *N Engl J Med.* 2019.

Patient Selection for Frontline Treatment

- Ibrutinib plays a crucial role in frontline treatment in NCCN Guidelines
  - Regardless of high-risk features
  - With or without comorbidities
- BTK combinations require more research
  - IR combination has not demonstrated benefit over monotherapy in those ≥65 yo
  - Acalabrutinib and ibrutinib combinations with obinutuzumab seem promising
- Alternative combinations such as venetoclax + obinutuzumab have similar PFS
  - Fixed duration may impact preference
  - May also be preferred over ibrutinib in those with cardiac comorbidities or predisposition for AEs

NCCN. CLL/SLL Guidelines. v3.2020.

Ongoing and Future Trials for Frontline CLL

Trial	Patients	Study Arms	Available Data
SEQUOIA Ph III (NCT03336333)	≥65 years old or younger if comorbidities	• Zanubrutinib • Zanubrutinib + venetoclax • Bendamustine + rituximab	• At median f/u of 7 months: ORR of 92%
ASSURE Ph III (NCT04008706)	TN cohort (further stratified by concomitant warfarin use)	• Acalabrutinib	-
EA9161 Ph III (NCT03701282)	All comers, no del(17p)	• Ibrutinib + venetoclax + obinutuzumab • Ibrutinib + obinutuzumab	-
GLOW Ph III (NCT03462719)	≥65 years old or younger if comorbidities	• Ibrutinib + venetoclax • Obinutuzumab + chlorambucil	-
AVO Ph II (NCT03580928)	All comers	• Acalabrutinib + venetoclax + obinutuzumab	• Interim TN cohort data: • 100% PR; 75% CR

www.clinicaltrials.gov; Tam CS, et al. *ASH*. 2019. Abstract 499; Lampson BL, et al. *ASH*. 2019. Abstract 32; Fischer K, et al. *N Engl J Med*. 2019; Jain N, et al. *ASH*. 2019. Abstract 34.

R/R Treatment without del(17p)/TP53 Mutation

Age and Comorbidities Evaluated

Frail w/ significant comorbidities or ≥65 or younger w/ significant comorbidities

Preferred
- Acalabrutinib (category 1)
- Ibrutinib (category 1)
- Venetoclax + rituximab (category 1)
- Idelalisib + rituximab
- Duvelisib

Other recommended regimens
- alemtuzumab ± rituximab, chlorambucil + rituximab, reduced-dose FCR or PCR, HDMP + rituximab, idelalisib, lenalidomide ± rituximab, obinutuzumab, ofatumumab, venetoclax, dose-dense rituximab, BR, BR + ibrutinib, or BR + idelalisib

<65 and without significant comorbidities

Preferred
- Acalabrutinib (category 1)
- Ibrutinib (category 1)
- Venetoclax + rituximab (category 1)
- Idelalisib + rituximab
- Duvelisib

Other recommended regimens
- alemtuzumab ± rituximab, BR, FC + ofatumumab, FCR, HDMP + rituximab, idelalisib, lenalidomide ± rituximab, obinutuzumab, ofatumumab, PCR, venetoclax, BR + ibrutinib, or BR + idelalisib

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

NCCN. CLL/SLL Guidelines. v4.2020.

R/R Treatment with del(17p)/TP53 Mutation

Age and Comorbidities Evaluated

Preferred

- Acalabrutinib (category 1)
- Ibrutinib (category 1)
- Venetoclax + rituximab (category 1)
- Idelalisib + rituximab
- Duvelisib
- Venetoclax

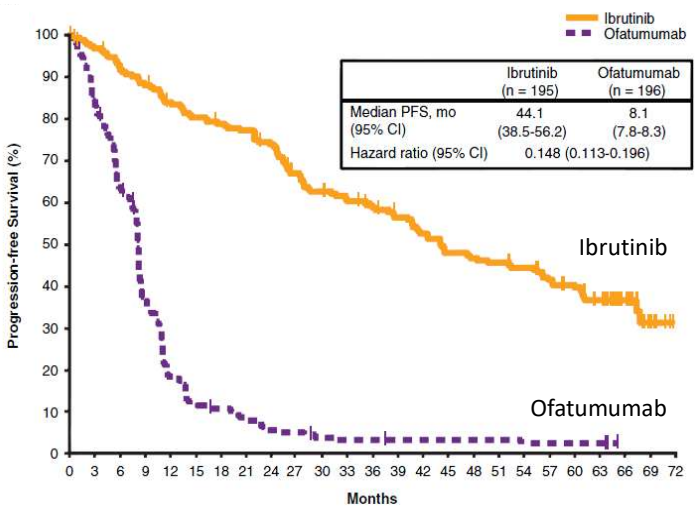
Other recommended regimens

alemtuzumab ± rituximab, HDMP + rituximab, idelalisib, lenalidomide ± rituximab, or ofatumumab

NCCN. CLL/SLL Guidelines. v4.2020.

Ibrutinib Significantly Extended PFS Compared with Ofatumumab

(RESONATE ~6-year Update)



	Median PFS (months)
All (ibrut vs ofatu)	**44.1 vs 8.11**
Del(17p)	40.6
Del(11q)	60.7
No Del(17p)/Del(11q)	42.5
IGHV mutated	48.4
Unmutated IGHV	49.7
TP53	40.7
No TP53	56.9

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

Phase III ASCEND (ACE-CL-309)
Acalabrutinib in R/R CLL

Patient population
- ≥1 prior therapy for CLL
- ECOG PS ≤2
- Interim analysis planned after ~79 PFS events

Randomized 2:1

Arm 1 (n=155)
Acalabrutinib 100 mg PO twice daily until PD or unacceptable toxicity

Arm 2 (n=155)
Rituximab + physician's choice
- Idelalisib 150 mg PO twice daily (n=119)
- Bendamustine 70 mg/m2 IV (n=36)

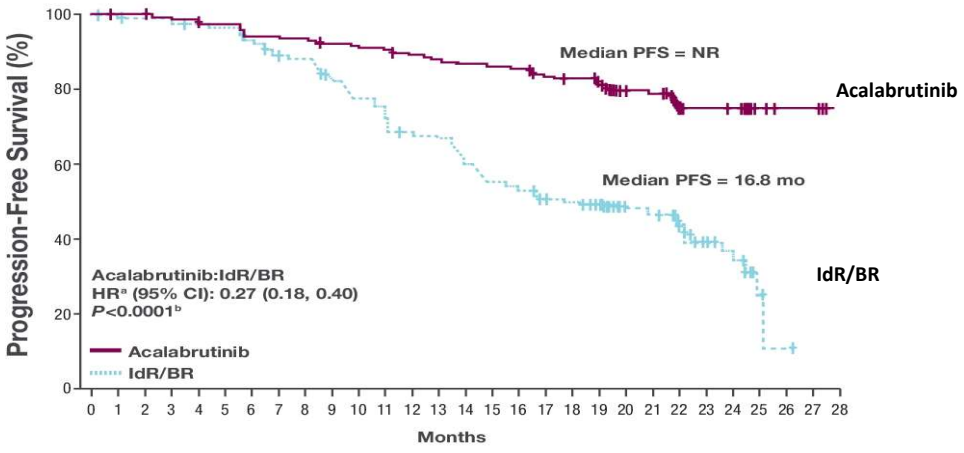
Median follow-up, 16.1 months

Most common AEs (any-acalabrutinib)
- Headache 22%
- Neutropenia 19%
- Diarrhea 18%
- Anemia 15%
- Cough 15%

Ghia P, et al. *EHA*. 2019. Abstract LB2606.

Phase III ASCEND (ACE-CL-309)
Acalabrutinib in R/R CLL

Improved PFS (including high-risk subgroups)



IdR, idealisib and rituximab.

Ghia P, et al. *ASCO*. 2020. Abstract 8015.

Ongoing and Future Trials for R/R CLL

Trial	Patients	Study Arms	Available Data
ALPINE Ph III (NCT03734016)	Relapsed/refractory	• Zanubrutinib • Ibrutinib	—
ACE-CL-006 Ph III (NCT02477696)	Previously treated, high-risk	• Acalabrutinib • Ibrutinib	—
Ph II (NCT04169737)	Relapsed after and/or refractory to ≥1 prior therapy	• Acalabrutinib + obinutuzumab + venetoclax • Acalabrutinib + early obinutuzumab + venetoclax	—
Ph II (NCT02029443)	Relapsed/refractory, ≥1 prior therapy	• Acalabrutinib	• ORR: 94% • CR: 4% • PR: 84% • PD: 1%
Ph II (NCT04116437)	Previously treated, ibrutinib intolerant	• Zanubrutinib	—
Ph II (NCT02756897)	Relapsed/refractory, ≥1 prior therapy (cohort 1)	• Ibrutinib + venetoclax	• After 24 cycles, 67% achieved BM uMRD remission

CR, complete response; PR, partial response; PD, progressive disease; BM uMRD, bone marrow undetectable minimal residual disease.

www.clinicaltrials.gov; Jain N, et al. *ASH*. 2019. Abstract 359; Furman RR, et al. *ASH*. 2019. Abstract 3039.

Treatment Considerations for BTK Inhibitors

BTK Inhibitor Cardiovascular Adverse Event Management

Toxicity	Ibrutinib	Acalabrutinib
Hemorrhage/Bleeding	44% ≥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	5%–77%	3%
• 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	12%	NR
• 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. Version 4.2020.

Risk Factors for Developing Atrial Fibrillation

- Hypertension
- Heart failure
- Diabetes mellitus
- Age
- Obesity
- Excess alcohol consumption
- Valvular heart disease, murmur
- COPD
- Hyperthyroidism
- Obstructive sleep apnea
- Chronic kidney disease
- Acute infections

1. Careful history and assessment—numerous risk score calculators
2. Optimize modifiable factors
3. Reassess on regular basis
4. Educate patient and caregivers

COPD, chronic obstructive pulmonary disease.

Stuhlinger MC, et al. *Wien Klin Wochenschr*. 2019; Wiczer TE, et al. *Blood Adv*. 2017; https://www.framinghamheartstudy.org/fhs-risk-functions/atrial-fibrillation-10-year-risk/.

Special Considerations for BTK Inhibitor AE Management

Toxicity	Ibrutinib	Acalabrutinib
Infections	≥Gr3—24%	≥Gr3—18%
• 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	33%	32%
• Presents during the first few weeks of therapy and typically resolves by 2 months		
Second Primary Malignancies	9%	11%
• Most common malignancy seen is skin cancer • Advise protection from sun exposure and encourage routine cancer screening		
Arthralgias	24%	16%
• 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	13%	39%
• 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. Version 4.2020.

General BTKi Dose Modifications Due to AEs

- **Ibrutinib:** ≥grade 3 non-hematological toxicities, ≥grade 3 neutropenia with infection or fever, or grade 4 hematological toxicities
- **Acalabrutinib:** ≥grade 3 non-hematological toxicities, grade 3 thrombocytopenia with bleeding, grade 4 thrombocytopenia, and grade 4 neutropenia lasting longer than 7 days

Toxicity Occurrence	Dose Modification		
	Ibrutinib 560 mg	Ibrutinib 420 mg	Acalabrutinib 100 mg
First	Interrupt therapy until resolved to grade 1 or baseline; may be initiated at starting dose		Interrupt therapy until resolved to grade 1 or baseline level; may be resumed at 100 mg daily
Second	Interrupt therapy until resolved to grade 1; restart at 420 mg daily	Interrupt therapy until resolved to grade 1; restart at 280 mg daily	
Third	Interrupt therapy until resolved to grade 1; restart at 280 mg daily	Interrupt therapy until resolved to grade 1; restart at 140 mg daily	
Fourth	Discontinue		

FDA Prescribing Information.

Ibrutinib Drug Interactions

- Metabolized by liver, primarily CYP3A4 substrate, also inhibits P-gp
- Avoid concomitant administration with CYP3A4 inhibitors/inducers and P-gp substrates, if possible
- Prospective trial reported two-thirds of patients on medications that potentially interact with ibrutinib

	Examples
CYP3A4 Inhibitors	Clarithromycin, erythromycin, itraconazole, fluconazole, posaconazole, voriconazole, ritonavir, indinavir, nelfinavir, darunavir, fosamprenavir, diltiazem, verapamil, amiodarone, dronedarone
CYP3A4 Inducers	Rifampin, carbamazepine, phenytoin, St. John's wort
P-glycoprotein	Dabigitran, digoxin, methotrexate

	Management	Dosing Examples
Strong CYP3A4 inhibitors	If short term (<7 days), consider interrupting ibrutinib	• Voriconazole 200 mg PO BID—decrease to 140 mg PO daily • Posaconazole 300 mg tablets daily—decrease to 70 mg PO daily
Moderate CYP3A4 inhibitors	Reduce ibrutinib dose to 280 mg PO daily	

Finnes HD, et al. *Leuk Lymphoma*. 2017; FDA Prescribing Information; https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers.

Acalabrutinib Drug Interactions

- Metabolized by liver, primarily CYP3A enzymes
- Increased gastric pH decreases acalabrutinib solubility

Medication	Acalabrutinib Management
Strong CYP3A4 inhibitors	• Avoid concurrent use if possible • If short term use (up to 7 days), interrupt acalabrutinib
Moderate CYP3A4 inhibitors	• 100 mg PO once daily
Strong CYP3A4 inducers	• Avoid concurrent use if possible • If concurrent use unavoidable, increase acalabrutinib to 200 mg twice daily
Proton pump inhibitors	• Avoid concomitant use
H2-receptor blockers	• Take acalabrutinib 2 hours before taking H_2-receptor blocker
Antacids	• Separate dosing by at least 2 hours

FDA Prescribing Information.

BTKi and Invasive Procedures

What recommendations would you provide regarding BTK inhibitor therapy?

- Both ibrutinib and acalabrutinib recommend holding for 3–7 days pre- and post-invasive procedures
  - For major procedures, hold ibrutinib 7 days prior to procedures and resume at 1–3 days or based on individual factors
- For urgent procedures, platelet transfusion to achieve 50% fresh platelets

Management of bleeding?

- Low grade bleeding—supportive care
- Non-CNS bleeding—hold BTKi and transfuse platelets
- CNS bleeding—individualize considerations for platelet transfusion

CNS, central nervous system.

Shatzel JJ, et al. *J Thromb Haemost*. 2017;
Gribben JG, et al. *Br J Haematol*. 2018; FDA Prescribing Information.

Applying Clinical Trial Data to Clinical Practice: Case-based CLL Treatment Strategies for the Oncology Nurse

Case 1 – TN CLL

JC is a 74-year-old woman diagnosed with CLL 3 years ago. She now requires treatment after presenting with progressive symptoms (bulky disease, B symptoms)

FISH: del(17p)+, del(13q)+, IGHV unmutated

PMHx: atrial fibrillation, GERD, osteoarthritis

Meds: metoprolol, omeprazole, aspirin, multi-vitamin

Labs: CrCl 65 mL/min, WBC 86,000/µL, ANC 1100/µL, platelets 96,000/µL, LDH 380 U/L, uric acid 6.5 mg/dL

EKG: HR 82 bpm, QTc 450 msec, BP 128/72 mmHg

ANC, absolute neutrophil count; GERD, gastroesophageal reflux disease;
iWCLL, International Workshop on CLL; NSR, normal sinus rhythm; QTc, corrected QT interval; WBC, white blood cell.

What first-line treatment should JC start on?

All Patients with del(17p) and/or TP53

Preferred
- Ibrutinib
- Acalabrutinib ± obinutuzumab
- Venetoclax + obinutuzumab

Other recommended regimens
- Alemtuzumab ± rituximab
- HDMP + rituximab
- Obinutuzumab

NCCN. CLL/SLL Guidelines. v4.2020.

Case 1
Patient Considerations

- Thorough history and physical, medication reconciliation, and cardiac assessment/consult
- If atrial fibrillation controlled, okay to cautiously begin on ibrutinib
- Not on anticoagulation at this time, if required, consider other therapy options
  - Avoid warfarin, may consider LMWH or DOAC using caution with drug interactions
- Bleeding risk
  - Use antiplatelet agents with caution, alternative agents if possible, avoid dual antiplatelet agents, if aspirin required, use lowest dose (81 mg) possible
  - Avoid use of concurrent anticoagulation and antiplatelet therapy
- Ibrutinib may control disease for long duration, must consistently assess, prevent, and treat common side effects to avoid unnecessary discontinuation

Brown JR. *Blood*. 2018; Salem JE, et al. *J Am Coll Cardiol*. 2019; Shatzel JJ, et al. *J Thromb Haemost*. 2017; Stephens DM, et al. *Blood*. 2019.

Case 1 – TN CLL

JC was started on ibrutinib 420 mg PO once daily and responded well to therapy. After a year of ibrutinib therapy, she began to consistently experience elevated blood pressure (>160/90).

What should be done for JC at this time?

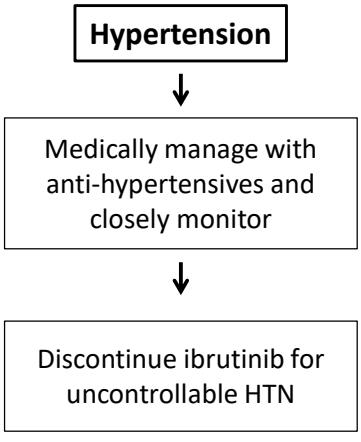
BTK Inhibitor Cardiovascular Adverse Event Management

Toxicity	Ibrutinib	Acalabrutinib
Hemorrhage/Bleeding	44% ≥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	5%–77%	3%
• 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	12%	NR
• 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. Version 4.2020.

Outcomes Analysis
Ibrutinib and Hypertension

- Most AEs decrease over time *except* hypertension
  - 8% during first year
  - 15% in year 2
  - 20% in year 3
  - 19% in years >3



O'Brien SM, et al. *Am J Hematol.* 2019; NCCN. CLL/SLL Guidelines. v4.2020.

Case 1 – TN CLL

JC was started on antihypertensives, which successfully stabilized her blood pressure. A few months later, JC returns to clinic with complaints of night sweats and severe fatigue.

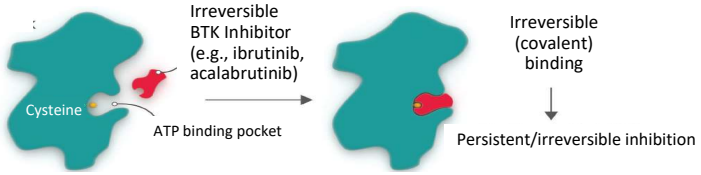
It is confirmed that JC is progressing while on ibrutinib therapy. Molecular analysis *reveals C481 mutation*.

FISH: del(17p)+, del(13q)+, IGHV unmutated

Meds: metoprolol, omeprazole, aspirin, multi-vitamin

When the Binding Site Changes
Mutation Concerns

- Ibrutinib and acalabrutinib both 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 **both ibrutinib and acalabrutinib.** Do not use acalabrutinib when there is resistance to ibrutinib.

Adapted from Wiestner A. *Haematologica*. 2015; NCCN CLL/SLL Guidelines. v4.2020; 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.

What Is Next?
Overcoming Inhibition

BTK inhibitor	Mechanism	Selectivity for BTK	Phase of development
Zanubrutinib	Covalent, Irreversible	Moderate	II/III
Tirabrutinib	Covalent, Irreversible	High	I/II
Vecabrutinib	Non-covalent, Reversible	Moderate	I/II
LOXO-305	Non-covalent, Reversible	High	I
ARQ-531	Non-covalent, Reversible	Low	I

Reversible, non-covalent BTKis may mitigate resistance

- Trial with ARQ 53, found cytotoxicity at 72 hours against ibrutinib resistant cell lines
- Activity in heavily pretreated patients with BTK mutations
- Well tolerated

Reiff SD, et al. *Cancer Discov*. 2018;
Woyach JA, et al. *EHA*. 2018. Abstract PF355; Bond DA, Woyach JA. *Curr Hematol Malig Rep*. 2019.

Case 2
Previously Treated

EP is a 64-year-old male who has new symptoms of increasing cervical lymphadenopathy, fatigue, and left upper quadrant fullness.

PMH: diagnosed with CLL 3 years ago and treated with FCR, achieving a complete response; hypertension; diabetes; multivessel coronary artery disease s/p stents (requiring prolonged dual antiplatelet therapy); and GERD

Disease: del(11q), unmutated IGHV, and *TP53* wild type

Meds: aspirin, ticagrelor, lisinopril, hydrochlorothiazide, metformin, and pantoprazole

Labs: CrCl 52 ml/min, Hb 11.2 gm/dL, WBC 55,000/ µL, ANC 1600/µL, and Plt 147,000/µL

R/R Treatment without del(17p)/TP53 Mutation

Age and Comorbidities Evaluated

Frail w/ significant comorbidities or ≥65 or younger w/ significant comorbidities		<65 and without significant comorbidities	
Preferred	**Other recommended regimens**	**Preferred**	**Other recommended regimens**
Acalabrutinib (category 1) Ibrutinib (category 1) Venetoclax + rituximab (category 1) Idelalisib + rituximab Duvelisib	alemtuzumab ± rituximab, chlorambucil + rituximab, reduced-dose FCR or PCR, HDMP + rituximab, idelalisib, lenalidomide ± rituximab, obinutuzumab, ofatumumab, venetoclax, dose-dense rituximab, BR, BR + ibrutinib, or BR + idelalisib	Acalabrutinib (category 1) Ibrutinib (category 1) Venetoclax + rituximab (category 1) Idelalisib + rituximab Duvelisib	alemtuzumab ± rituximab, BR, FC + ofatumumab, FCR, HDMP + rituximab, idelalisib, lenalidomide ± rituximab, obinutuzumab, ofatumumab, PCR, venetoclax, BR + ibrutinib, or BR + idelalisib

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

NCCN. CLL/SLL Guidelines. v4.2020.

Case 2

Previously Treated

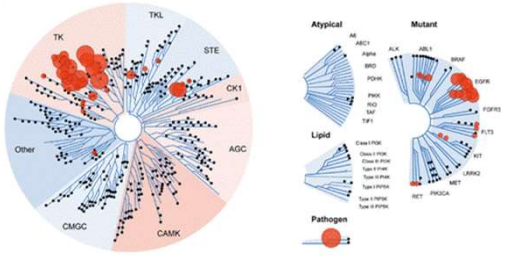
EP starts ibrutinib 420 mg once daily. Within two months of initiating therapy, EP began to experience joint pain that severely impacted his quality of life. He is unable to take his morning jog because of the discomfort.

Case 2
Previously Treated

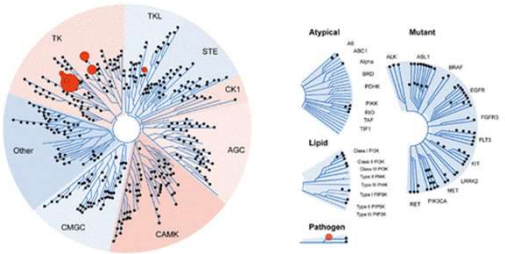
Would a switch to acalabrutinib improve tolerance?

BTK Inhibitor Selectivity

Ibrutinib



Acalabrutinib



↑ off target binding = ↑ likelihood of toxicities

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

Case 2
Previously Treated

Would a switch to acalabrutinib improve tolerance?

- In 33 ibrutinib-intolerant patients, 72% of adverse events did not recur while on acalabrutinib therapy and 13% recurred at a lower grade[1]
- Preliminary results suggest acalabrutinib is an effective option in ibrutinib intolerant patients. Direct comparative studies underway.[1,2]

[1]Awan FT, et al. *Blood Adv*. 2019; [2]Rogers KA, et al. *ASCO*. 2019. Abstract 7530.

Case 2
Previously Treated

- EP was treated with multiple courses of steroids to treat the arthralgia experienced with ibrutinib. Unfortunately, his joint pain would continue to come back. EP noted that he had missed a "couple doses here and there" in hopes that it would alleviate the pain.
- EP was switched to acalabrutinib 100 mg PO every 12 hours. His arthralgia dissipated within a couple of weeks of therapy. EP calls the clinic stating that he has been having headaches more frequently than usual. He wants to know if this has anything to do with his acalabrutinib treatment.

Considerations to Ensuring BTKi Therapy Success

- Continued medication access
  - Unfunded, private insurance, Medicare part D
  - Pharmaceutical company support/programs, prior authorization/appeal support, utilization of approved compendia for off-label use
- Reinforce patient and caregiver education
  - Compliance
  - Adverse events
- Ongoing reassessment of new medications, OTC
  - Dosing/drug interactions

BTK Inhibitors and COVID-19

- Patients with severe COVID-19 have hyperinflammatory immune response regulated by macrophage activation.
  - BTK regulates macrophage signaling and activation
- Early clinical data/case studies demonstrate that BTKis can protect against lung injury and improve pulmonary function in these patients.
- Roschewski M, et al. *Sci. Immunol*. 2020.
  - N=19 hospitalized patients with severe COVID-19 treated with acalabrutinib for 10-14 days
  - Measures of inflammation (C-reactive protein and IL-6) normalized quickly for patients
  - 72.7% on supplemental oxygen were discharged on room air
  - 50% of ventilated patients were extubated (25% of which were discharged on room air)

Treon SP, et al. *Blood*. 2020; Roschewski M, et al. *Sci. Immunol.* 2020; https://www.astrazeneca.com/media-centre/press-releases/2020/astrazeneca-initiates-calavi-clinical-trial-with-calquence-against-covid-19.html.

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