NAVIGATING THE PATIENT JOURNEY IN CHRONIC LYMPHOCYTIC LEUKEMIA

Oncology Nurse Strategies in Therapy Management

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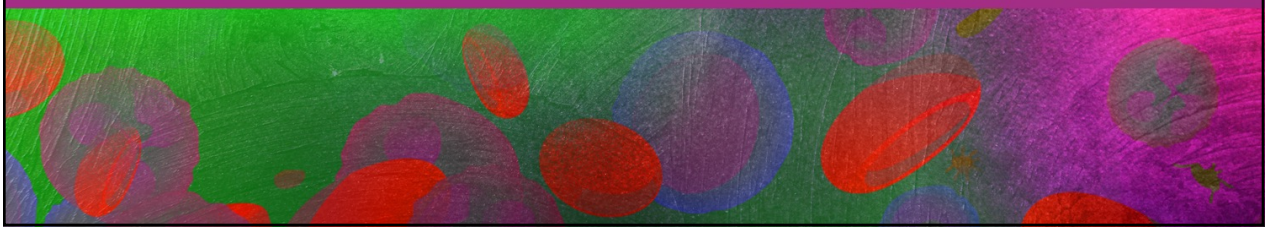
Learning Objectives

- Review the role of the BCR (B-cell receptor) pathway in CLL development and examine currently available and emerging novel therapies targeting the BCR pathway.
- Appraise the appropriate selection and sequencing of CLL therapy based on current guideline recommendations and patient-specific factors, such as line and duration of therapy, clinical presentation, mutation status, among others.
- Discuss unique differences between novel therapies, strategies to properly monitor and manage toxicities, and key counseling points to discuss with patients to ensure minimization of toxicities and optimization of oral adherence.
- Explore strategies to ensure patient understanding and empowerment about the treatment plan and ways to encourage open communication between patient and provider to optimize outcomes.

Exploring the BCR Pathway in Chronic Lymphocytic Leukemia

Novel Therapies At the Forefront



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 mm^3 for diagnosis
  - SLL: presence of lymphadenopathy and/or splenomegaly and lymphocyte count ≤5000 mm^3 in peripheral blood

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

[1]Siegel. *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.

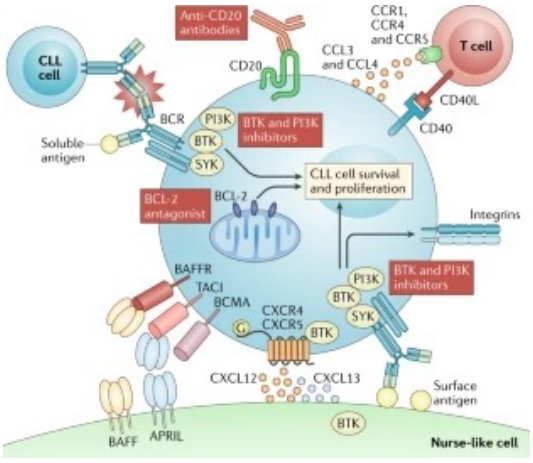
CLL Signs, Symptoms, and Treatment

- In the absence of symptoms, "watch and wait" approach, with treatment being beneficial if CLL is symptomatic.
  - 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.

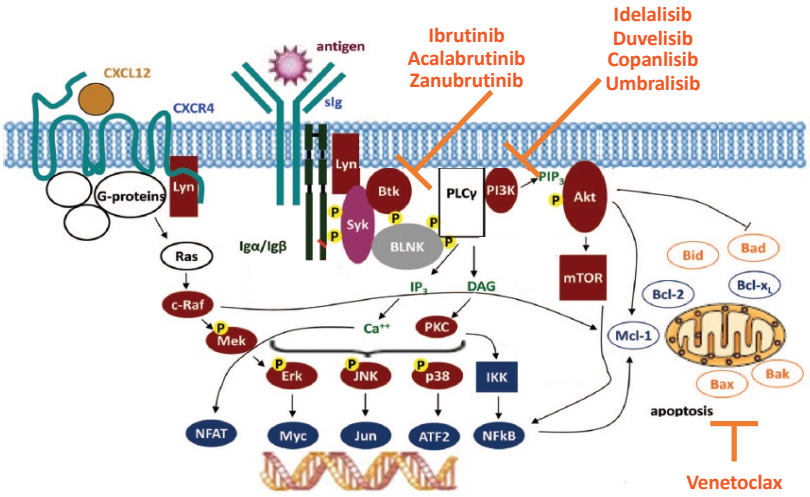
B-cell Receptor (BCR) Pathway



- 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 B-cell Lymphomas



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

BTK Inhibitors

	Ibrutinib	Acalabrutinib
Dose	420 mg orally daily	100 mg orally twice daily
Dosage Form	Tablets: 140 mg, 280 mg, 420 mg, 560 mg Capsules: 70 mg, 140 mg	Capsules: 100 mg
Most common adverse events (≥30%)	Thrombocytopenia, diarrhea, fatigue, musculoskeletal pain, neutropenia, rash, anemia, and bruising	Anemia, neutropenia, upper respiratory tract infection, thrombocytopenia, headache, diarrhea, and musculoskeletal pain
Drug Interactions	CYP3A inhibitors and inducers	CYP3A inhibitors or inducers, gastric acid reducing agents

FDA Prescribing Information.

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.

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.

BCL2 Inhibitor
Venetoclax

Dose	Ramp up for first 5 weeks and then 400 mg daily (ramp-up to reduce risk of tumor lysis syndrome)
Dosage Form	Tablets: 10 mg, 50 mg, 100 mg
Most common adverse events (>20%)	Neutropenia, anemia, diarrhea, upper respiratory track infection, thrombocytopenia, musculoskeletal pain, edema, fatigue, cough, and nausea
Drug Interactions	Strong or moderate CYP3A inhibitors, P-gp inhibitors

FDA Prescribing Information; Thangavadivel S, Byrd JC. *Cancer Discov*. 2019.

Venetoclax CLL Dose Modifications Due to AEs

- 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 • When grade 1, resume at same dose • Consider G-CSF to reduce infection risk in hematologic toxicities
Second and subsequent	• Interrupt therapy • When grade 1, follow dose reduction guidelines • Consider G-CSF to reduce infection risk in hematologic toxicities
Any blood chemistry changes or symptoms suggestive of TLS (high K+, P, LDH, uric acid, low Ca+)	• Withhold next day's dose. If resolved within 24–48 hours of last dose, resume same dose • If requires more than 48 hours to resolve, resume at reduced dose, follow dose reduction guidelines

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

- 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

FDA Prescribing Information.

PI3K Inhibitors

	Idelalisib	Duvelisib
Dose	150 mg orally twice daily	25 mg orally twice daily
Dosage Form	Tablets: 150 mg, 100 mg	Capsules: 25 mg, 15 mg
Most common adverse events (>20%)	Diarrhea, fatigue, nausea, cough, pyrexia, abdominal pain, and rash	Diarrhea or colitis, neutropenia, rash, fatigue, pyrexia, cough, nausea, upper respiratory infection, pneumonia, musculoskeletal pain, and anemia
Drug Interactions	Strong CYP3A inhibitors and inducers, CYP3A substrates	CYP3A inhibitors or inducers, CYP3A substrates

FDA Prescribing Information.

Special Considerations for PI3K Inhibitor AE Management

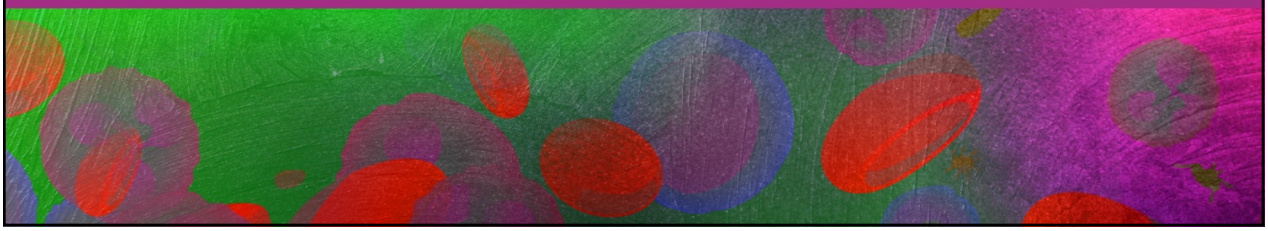
Serious Adverse Events

Toxicity	Idelalisib	Duvelisib
Diarrhea/Colitis	**14%**	**18%**
• Can occur anytime; responds poorly to antimotility agents • **BBW:** Idelalisib and duvelisib		
Pneumonitis	**4%**	**5%**
• Usually treated with steroid therapy • **BBW:** Idelalisib and duvelisib		
Hepatotoxicity (Elevated AST/ALT)	**18%**	8%
• Monitor ALT/AST every 2 weeks for first 3 months of treatment; every 4 weeks for second 3 months of treatment; then every 1–3 months thereafter • **BBW:** Idelalisib		
Cutaneous Reactions	3%	**5%**
• **BBW:** Duvelisib		

Hanlon A, Brander DM. *Hematology Am Soc Hematol Educ Program.* 2020; FDA Prescribing Information.

Collaborative Decision Making and Optimization of Patient Outcomes in CLL

Patient Cases for the Oncology Nurse



Case Study
TN CLL

DG is a 68-year-old female diagnosed CLL/SLL
- Routine blood work found lymphocytosis
- Had mild splenomegaly
- No treatment because she was asymptomatic

Presented at 18-month follow-up with progressive symptoms of bulky lymphadenopathy and fatigue
- CT demonstrates progressive disease
- PET/CT showed low SUV avid bulky adenopathy (max SUV 6.5)
- Biopsy of cervical lymph node demonstrated no Richter's transformation
- **FISH:** del(17p)+, IGHV unmutated

- **PMH:** hypertension, obesity, GERD, coronary artery disease
- **Meds:** lisinopril, omeprazole, multivitamin, aspirin
- **Labs:** WBC 51,000/µL; ALC 48,000/µL, HgB 14.6 g/dL; Plt 250,000/µL
- **SH:** retired, 1 adult child, lives alone

NCCN Guidelines and Trial Data
Treatment-naïve CLL

Preferred 1st-line NCCN Regimens (with or without del17p/TP53)
Ibrutinib
Acalabrutinib + obinutuzumab
Venetoclax + obinutuzumab

Trial	Arms	Clinical Data
RESONATE-2 (Ph III) (≥65 yo, no del17p) N=269	• **Ibrutinib** • Chlorambucil	**60 mo PFS:** 70% vs 12% **60 mo OS:** 83% vs 68%
A041202 (Ph III) (≥65 yo, including del17p) N=547	• **Ibrutinib** • **Ibrutinib**/ritux • BR	**24 mo PFS:** 87% vs 88% vs 74% **24 mo OS:** 90% vs 94% vs 95%
ELEVATE-TN (Ph III) (≥65 yo or <65 yo + comorbidities, including del17p) N=535	• **Acalabrutinib**/obin • **Acalabrutinib** • Chlorambucil/obin	**48 mo PFS:** 87% vs 78% vs 25% **48 mo OS:** 93% vs 88% vs 88%
CLL14 Trial (Ph III) (≥65 yo or <65 yo + comorbidities, including del17p) N=432	• **Venetoclax**/obin • Chlorambucil/obin	**36 mo PFS:** 82% vs 50% **36 mo OS:** 87% vs 87%

NCCN. CLL/SLL Guidelines. v4.2021; Burger JA, et al. *Leukemia.* 2020; Woyach JA, et al. *N Engl J Med.* 2018; Sharman JP, et al. *ASCO.* 2021. Abstract 7509.; Sharman JP, et al. *ASH.* Abstract 31. 2019; Fischer K, et al. *N Engl J Med.* 2019; Al-Sawaf O, et al. *Lancet Oncol.* 2020.

TN CLL
Case Study

PMH: hypertension, obesity, GERD, and coronary artery disease

Meds: lisinopril, diltiazem, omeprazole, multivitamin, and aspirin

Labs: WBC 18,000/µL; ALC 15,500/µL, HgB 10.3 mg/dL; and PLT 145,000/µL

SH: middle-school teacher, married, and 2 adult children and 5 grandchildren

Preferred First-line Therapy with del(17p)/TP53 Mutation

Ibrutinib
Acalabrutinib ± obinutuzumab
Venetoclax + obinutuzumab

TN CLL
Case Study

Discussion regarding treatment options with the patient includes:

- BTK inhibitor treatment with either ibrutinib vs acalabrutinib
- Venetoclax and obinutuzumab

Through shared decision-making, a treatment plan is developed:

- The patient desired oral therapy over IV treatments
- Ibrutinib is prescribed and is covered by insurance

BTK Inhibitor Drug Interactions

- Metabolized by liver, primarily CYP3A4 enzymes

Management		
Strong CYP3A4 inhibitors	Avoid concurrent use with acalabrutinib; if short term (<7 days), consider interrupting ibrutinib and interrupt acalabrutinib; may modify zanubrutinib dose	**CYP3A4 inhibitors:** clarithromycin, erythromycin, itraconazole, fluconazole, posaconazole, voriconazole, ritonavir, indinavir, nelfinavir, darunavir, fosamprenavir, diltiazem, verapamil, amiodarone, dronedarone
Moderate CYP3A4 inhibitors	Reduce BTK inhibitor dose	
Strong CYP3A4 inducers	Avoid concurrent use if possible; if concurrent use is unavoidable, acalabrutinib dose can be increased	**CYP3A4 inducers:** rifampin, carbamazepine, phenytoin, St. John's wort
P-glycoprotein	Avoid concurrent use with ibrutinib if possible	**P-gp substrates:** dabigatran, digoxin, methotrexate
Proton pump inhibitors	**Avoid concomitant use with acalabrutinib**	**PPIs:** omeprazole, esomeprazole
H2-receptor blockers	Take acalabrutinib 2 hours before taking H2RA	**H2RAs:** famotidine, ranitidine
Antacids	Separate dosing from acalabrutinib by at least 2 hours	**Antacids:** calcium carbonate

FDA Prescribing Information; https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers.

TN CLL
Case Study

Discussion regarding treatment options with the patient includes:

- Fixed duration vs. continuous therapy
- Oral vs. intravenous therapy
- Inpatient vs. outpatient treatment
- Treatment side effects
- Past medical hx/current medications
- Co-pay/insurance considerations

Through **shared decision-making**, a treatment plan is developed:

- The patient desired oral therapy over IV treatments
- Ibrutinib is prescribed and is covered by insurance
- Patient had no history of atrial fibrillation, concomitant anti-platelet treatments, or bleeding history

TN CLL
Case Study: Drug Interactions on BTKi

After a review of DG's history and a medication reconciliation:

- Patient wishes to remain on omeprazole therapy
- Because of the omeprazole drug-to-drug interaction, the patient is started on ibrutinib

TN CLL
Case Study

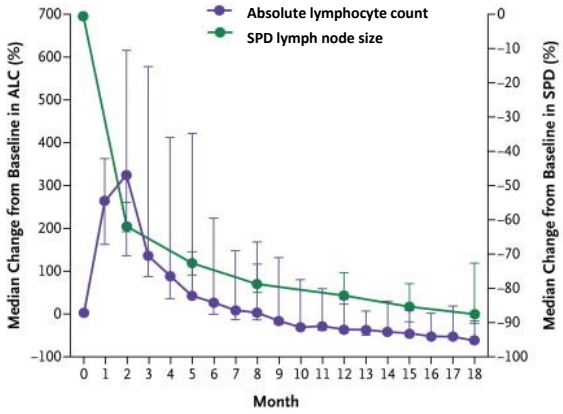
DG is started on ibrutinib 420 mg daily.

The patient is laboratory monitored along with clinical follow-up for tolerance.

	Baseline	2 weeks	4 weeks	6 weeks	8 weeks
WBC	18,000/µL	25,000/µL	53,000/µL	75,000/µL	48,000/µL
ALC	17,500/µL	24.000/µL	52,500/µL	74,950/µL	45,500/µL
HgB	10.3 mg/dL	10.5 mg/dL	10.0 mg/dL	10.3 mg/dL	10.3 mg/dL
Platelet	145,000/µL	140,000/µL	135,000/µL	125,000/µL	135,000/µL

Transient Lymphocytosis

Data from patients with CLL being treated with single-agent ibrutinib.



Byrd JC, et al. *N Engl J Med*. 2013; Brown JR. *Blood*. 2015.

TN CLL
Case Study: Drug Interactions on BTKi

DG has been on ibrutinib for one year and has tolerated it well. She now presents with a recurrent vaginal yeast infections after a course of antibiotics for sinusitis. Her gynecologist recommends a course of oral fluconazole.

- It is recommended that her ibrutinib dose be reduced the week she takes flucanazole because of ibrutinib's interaction with CYP3A4 Inhibitors.

TN CLL
Case Study

A few months later, DG calls the clinic because of increased joint pain, especially in her back and legs, which is severely impacting her quality of life. He is no longer able to take her daily walk.

She admits to missing several doses, which has improved her discomfort.

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

Arthralgias/Myalgias with Ibrutinib

- Retrospective analysis of 214 patients treated with ibrutinib
  - Median onset of arthritis/arthralgia: 34.5 months
  - 79% were grade 1-2
  - *Risk factors:* younger age, female gender, first line use of ibrutinib

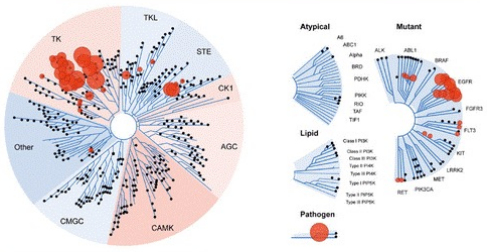
Rhodes JM, et al. *Clin Lymphoma Myeloma Leuk*. 2020.

Not All BTK Inhibitors Created Equal

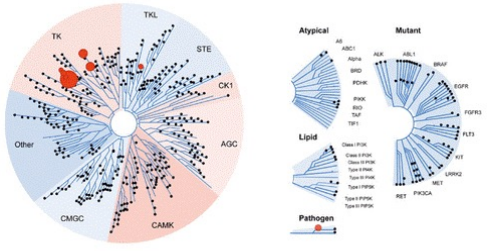
Would switching to acalabrutinib improve tolerance?

BTK Inhibitor Selectivity

Ibrutinib



Acalabrutinib

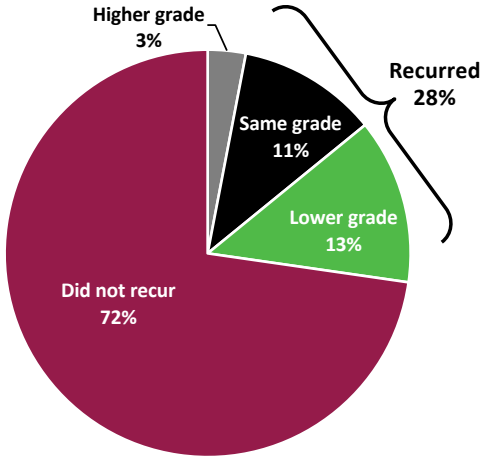


↑ off target binding = ↑ likelihood of toxicities

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

Results in Ibrutinib-intolerant Cohort

- N=33 heavily pretreated patients with CLL treated with acalabrutinib
  - 23 remained on acalabrutinib at median of 19 months on treatment
  - No acalabrutinib dose reductions
- 61 ibrutinib-related AEs associated with intolerance at study entry
  - No recurrence: 72%
  - Recurrence at lower grade than with acalabrutinib: 13%
- ORR: 76%
- Median PFS: not reached
  - 1-year PFS rate: 83.4%



Recurrence of ibrutinib-related adverse events (n=61) during acalabrutinib treatment

Awan FT, et al. *Blood Adv*. 2019.

TN CLL
Case Study

Options are discussed about DG's joint pain

- Continue supportive care with acetaminophen
  - Need to avoid NSAIDs due to increased risk of bleeding
- Short-course of prednisone
- Change to another BTK inhibitor

DG is switched to acalabrutinib per her request

- She then develops severe HA within a week of initiating therapy
- She notes some improvement after a cup of coffee

What would you recommend to DG?

Special Considerations for BTK Inhibitor AE Management

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TN CLL
Case Study

- DG was continued on her current dose of acalabrutinib and trialed on a course of acetaminophen and caffeine to manage the headaches. This was ineffective in adequately relieving her headaches.

- DG goes back on ibrutinib 420 mg daily, uses acetaminophen for a short-time and her arthralgias resolve.

- After 13 months of ibrutinib, she calls the office stating that he is experiencing increase lightheadedness, chest pain, and shortness of breath
  - Instructed to go to nearest ED
  - CT scan without evidence of a PE
  - EKG demonstrates atrial fibrillation in rapid response

Patient Considerations

- Risk factors for this patient developing Afib: hypertension, obesity, and age
- If atrial fibrillation is controlled, it is okay to cautiously begin on ibrutinib
- Anticoagulation considerations
  - Avoid warfarin, may consider LMWH or DOAC using caution with drug interactions
- DG is started on a beta blocker and achieve rates control of her atrial fibrillation
- She is started on apixiban for reduction of stroke risk associated with atrial fibrillation. Aspirin is discontinued.
- She restarts ibrutinib 420 mg daily

TN CLL
Case Study

One year after restarting ibrutinib, DG returns to clinic with complaints of night sweats and severe fatigue.

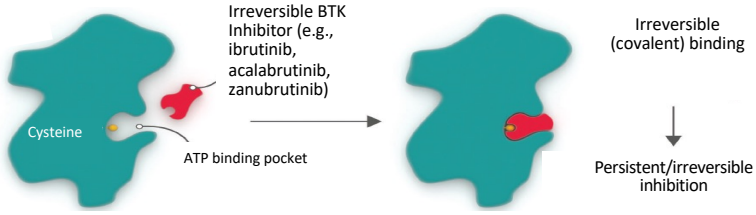
It is confirmed that DG is progressing while on ibrutinib therapy.

- FISH testing finds del(17p)+, unmutated IGHV.
- Molecular analysis reveals C481 mutation.

What is the next step?

When the Binding Site Changes
Mutation Concerns

- Ibrutinib, acalabrutinib, and zanubrutinib 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, 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.

TN CLL
Case Study

Ibrutinib is discontinued.

Discussion regarding treatment options with the patient includes:

- Idelalisib + rituximab
- Venetoclax + rituximab
- Duvelisib

She opts to proceed with venetoclax and rituximab.

Case Study
R/R CLL

DW is a 73 years old male initially diagnosed with CLL/SLL 13 years ago.
- Treated with FCR x 6 cycles and achieved a CR
- FISH negative for CLL probes, IGHV mutated

Presented to clinic for routine follow-up with increase shortness of breath and coughing
- CT scan revealed increase lymphadenopathy and increasing lymphocytosis
- He has reported increase sinus infections over the last year
- Flow cytometry demonstrated CD5, CD19, dim CD20, CD23, CD24, cyclin D1-
- FISH del11q, mutated IGHV

PMH: hypertension, GERD and atrial fibrillation (currently in rate control)
Meds: aspirin, apixaban, hydrochlorothiazide, omeprazole
Labs: WBC 69,000/µL; ALC 68,000/µL; Hgb 11.3 gm/dL; PLT 153,000/µL

NCCN Guidelines and Trial Data
Relapsed/Refractory CLL

Preferred NCCN Regimens (with or without del17p/TP53)
***Ibrutinib**
***Acalabrutinib**
***Venetoclax** + rituximab
Idelalisib + rituximab
Duvelisib
Venetoclax monotherapy (only for del17p/TP53)

Trial	Arms	Clinical Data
RESONATE (Ph III) (All ages, including del17p) N=391	• **Ibrutinib** • Ofatumumab	**mPFS:** 44.1 vs 8.1 mo **mOS:** 68 vs 65 mo
ASCEND (Ph III) (All ages, including del17p) N=310	• **Acalabrutinib** • **MD Choice:** BR or idelalisib/ritux	**mPFS:** NR vs 16.3 mo **mOS:** NR vs NR
MURANO (Ph III) (All ages, including del17p) N=389	• **Venetoclax**/ritux • BR	**mPFS:** 54 vs 17 mo **5 yr OS:** 82% vs 62%
GS-US-312-0116 (Ph III) (All ages, including del17p + comorbidities) N=220	• **Idelalisib**/ritux • Rituximab	*Initial Study:* **mPFS:** 19.4 vs. 6.5 mo *Extended study with idelalisib alone:* **mOS:** 40.5 mo (IR → I); 34.6 mo (R→I)
DUO (Ph III) (All ages, including del17p) N=210	• **Duvelisib** • Ofatumumab	*Median 22.4 mo f/u:* **mPFS:** 13.3 vs 9.9 mo
NCT01889186 (Ph II) (All ages, only del17p) N=153	• Venetoclax	**ORR:** 77% **24 mo PFS:** 54%

NCCN. CLL/SLL Guidelines. v4.2021; Byrd JC, et al. *Blood.* 2019; Munir T, et al. *Am J Hematol*. 2019; Ghia P, et al. *ASH.* Abstract 3140 2020; Kater AP, et al. *ASH.* Abstract 125. 2020; Kater AP, et al. *J Clin Oncol*. 2019; Furman RR, et al. *N Engl J Med*. 2014; Ghia P, et al. *J Clin Oncol*. 2020; Flinn IW, et al. *Blood*. 2018; Stilgenbauer S, et al. *J Clin Oncol*. 2018.

R/R CLL
Case Study

PMH: hypertension, GERD, atrial fibrillation (currently in rate control)

Meds: aspirin, apixaban, hydrochlorothiazide, omeprazole

Labs: WBC 69,000/µL; ALC 68,000/µL, HgB 11.3 mg/dL; and PLT 153,000/µL

Preferred R/R Therapy without del(17p)/TP53 Mutation

- Ibrutinib
- Acalabrutinib
- Venetoclax + rituximab
- Idelalisib + rituximab
- Duvelisib

R/R CLL
Case Study

After a shared collaborative discussion, DW opts for venetoclax + rituximab. The planned treatment is venetoclax daily (for 2 years) and rituximab (weekly x 4 doses then monthly x 6 months).

During the second week of the venetoclax ramp-up, laboratory tests demonstrate:

Lab	Result
LDH	325 u/L
Calcium	7.5 mg/dL
Phosphorus	8.7 mg/dL
Potassium	5.4 mEq/L
Uric acid	8.1 mg/dL

What do DW's laboratory findings indicate?

Venetoclax CLL Dose Modifications Due to AEs

- 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 • When grade 1, resume at same dose • Consider G-CSF to reduce infection risk in hematologic toxicities
Second and subsequent	• Interrupt therapy • When grade 1, follow dose reduction guidelines below • Consider G-CSF to reduce infection risk in hematologic toxicities
Any blood chemistry changes or symptoms suggestive of TLS (high K+, P, LDH, uric acid, low Ca+)	• Changes in blood chemistries consistent with TLS (requiring prompt management) can occur as early as 6–8 hours after first dose and at each dose increase • Withhold next day's dose. If resolved within 24–48 hours of last dose, resume same dose • If requires more than 48 hours to resolve, resume at reduced dose, as shown below

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

- 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

FDA Prescribing Information.

TLS Prophylaxis Based on Tumor Burden

Best managed if anticipated and prophylaxis is started prior to treatment

Tumor Burden	Prophylaxis	Blood Chemistry Monitoring
Low All LN <5 cm **and** ALC <25 x 10^9/L	• Oral hydration (1.5–2 L) • Allopurinol	**Outpatient** • For first dose of 20 mg and 50 mg: pre-dose, 6–8 hours, 24 hours • For subsequent ramp-up doses: pre-dose
Medium Any LN 5 cm to <10 cm **or** ALC ≥25 x 10^9/L	• Oral hydration (1.5–2 L) and consider additional intravenous • Allopurinol	**Outpatient** • For first dose of 20 mg and 50 mg: pre-dose, 6–8 hours, 24 hours • For subsequent ramp-up doses: pre-dose • For first dose of 20 mg and 50 mg: consider hospitalization for patients with ClCr <80 mL/min
High Any LN ≥10 cm **or** ALC ≥25 x 10^9/L **and** any LN ≥5 cm	• Oral hydration (1.5–2 L) and intravenous (150–200 mL/hour as tolerated) • Allopurinol (consider rasburicase if baseline uric acid is elevated)	**In hospital** • For first dose of 20 mg and 50 mg: pre-dose, 4, 8, 12, 24 hours **Outpatient** • For subsequent ramp-up doses: pre-dose, 6–8 hours, 24 hours

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

Case Study
R/R CLL

Therapy was held for 24 hours. His uric acid and LDH normalized after receiving IV fluids for 6 hours as an outpatient. No further laboratory TLS noted through the ramp up.

DW completed therapy and achieved minimal residual disease (MRD) at the end of treatment.

Strategies to Ensure Patient Understanding and Empowerment about Their Treatment Plan

Seeking	Seeking patient participation
Helping	Helping patient explore treatment options
Assessing	Assessing patient needs and preferences
Reaching	Reaching a decision jointly
Evaluating	Evaluation the patient's decision

Tariman JD, et al. *Clin J Oncol Nurs*. 2020.

Key Takeaways

- Selection and appropriate sequencing of CLL therapy individualized for patients based on current guideline recommendations, trial data, clinical presentation, mutation/performance status, comorbidities, duration of therapy, concurrent medications, and other patient-specific factors.
- Combinations of the novel agents are being studied to improve response rates.
- The use of novel agents is becoming a key component in the treatment of CLL/SLL.
- Understanding each of the unique adverse events that can arise with novel CLL therapies is important in monitoring for and managing toxicities.
- Therapeutic approaches after progression on novel therapies as a result of resistance and strategies to mitigate resistance.
- Shared decision-making is intracule in the likelihood that patients will understand their treatment options, encouraging open communication between patient and provider about any toxicities, scheduled surgeries, new medications, or any concerns that may arise and affect therapy.
- Nurses play a key role in educating patients regarding the proper way to take the novel agents and to monitor adverse events.

Notes

Bibliography and Suggested Reading

Al-Sawaf O, Zhang C, Tandon M, et al. Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (Cll14): follow-up results from a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2020;21(9):1188–1200.

Al – Sawaf O, Zhang C, Robrecht S, et al. Venetoclax – Obinutuzumab for previously untreated chronic lymphocytic leukemia: 4 – year follow – up analysis of the randomized CLL14 study. Abstract S146. Presented at The European Hematology Association Virtual Congress; June 9 – 17, 2021.

American Cancer Society. Cancer treatment and survivorship: facts and figures, 2019–2021. ACA website. 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. Accessed August 2021.

Awan FT, Schuh A, Brown JR, et al. Acalabrutinib monotherapy in patients with chronic lymphocytic leukemia who are intolerant to ibrutinib. *Blood Adv*. 2019;3(9):1553–1562.

Barf T, Covey T, Izumi R, et al. Acalabrutinib (ACP-196): a covalent bruton tyrosine kinase inhibitor with a differentiated selectivity and in vivo potency profile. *J Pharmacol Exp Ther*. 2017;363(2):240–252.

Barr PM, Brown JR, Hillmen P, et al. Impact of ibrutinib dose adherence on therapeutic efficacy in patients with previously treated CLL/SLL. *Blood*. 2017;129(19):2612–2615.

Barr PM, Owen C, Robak T, et al. Up to seven years of follow-up in the RESONATE-2 study of first-line ibrutinib treatment for patients with chronic lymphocytic leukemia. Abstract 7523. Presented at the American Society of Clinical Oncology Annual Meeting; 2021.

Brown JR. How I treat CLL patients with ibrutinib. *Blood*. 2018;131(4):379–386.

Brown JR. Idelalisib has CLL on the run! *Blood*. 2015;126(25):2656–2657.

Burger JA, Barr PM, Robak T, et al. Long-term efficacy and safety of first-line ibrutinib treatment for patients with CLL/SLL: 5 years of follow-up from the phase 3 RESONATE-2 study. *Leukemia*. 2020;34(3):787–798.

Burger JA, Chiorazzi N. B-cell receptor signaling in chronic lymphocytic leukemia. *Trends Immunol*. 2013;34(12):592–601.

Byrd JC, Brown JR, O'Brien S, et al; RESONATE Investigators. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N Engl J Med*. 2014;371(3):213–223.

Byrd JC, Furman RR, Coutre SE, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia [published correction appears in: *N Engl J Med*. 2014;370(8):786]. *N Engl J Med*. 2013;369(1):32–42.

Byrd JC, Harrington B, O'Brien S, et al. Acalabrutinib (ACP-196) in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2016;374(4):323–332.

Byrd JC, Hillmen P, O'Brien S, et al. Long-term follow-up of the RESONATE phase 3 trial of ibrutinib vs ofatumumab. *Blood*. 2019;133(19):2031–2042.

Byrd JC, Smith S, Wagner-Johnston N, et al. First-in-human phase 1 study of the BTK inhibitor GDC-0853 in relapsed or refractory B-cell NHL and CLL [published correction appears in: *Oncotarget*. 2019;10(38):3827–3830]. *Oncotarget*. 2018;9(16):13023–13035.

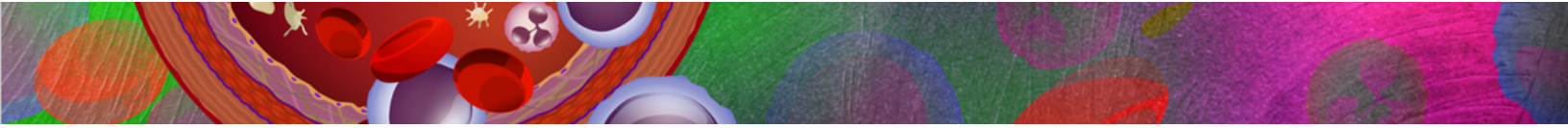
Byrd JC, Wierda WG, Schuh A, et al. Acalabrutinib monotherapy in patients with relapsed/refractory chronic lymphocytic leukemia: updated phase 2 results. *Blood*. 2020;135(15):1204–1213.

Byrd JC, Woyach JA, Furman RR, et al. Acalabrutinib in treatment-naïve chronic lymphocytic leukemia: mature results from phase II study demonstrating durable remissions and long-term tolerability. Abstract 8024. Presented at: 2020 ASCO Virtual Scientific Program; May 29–31, 2020.

Cheah CY, Fowler NH. Idelalisib in the management of lymphoma. *Blood*. 2016;128(3):331–336.

Coutre S, Choi M, Furman RR, et al. Venetoclax for patients with chronic lymphocytic leukemia who progressed during or after idelalisib therapy. *Blood*. 2018;131(15):1704–1711.

Davids MS, Brown JR. Targeting the B-cell receptor pathway in chronic lymphocytic leukemia. *Leuk Lymphoma*. 2012;53(12):2362–2370.



Davids MS, Lampson BL, Tyekucheva S, et al. Updated safety and efficacy results from a phase 2 study of acalabrutinib, venetoclax and obinutuzumab (AVO) for frontline treatment of chronic lymphocytic leukemia (CLL). Abstract 2216. Presented at: ASH Virtual Annual Meeting; December 6, 2020.

Dreger P, Ghia P, Schetelig J, et al; European Research Initiative on CLL (ERIC) and the European Society for Blood and Marrow Transplantation (EBMT). High-risk chronic lymphocytic leukemia in the era of pathway inhibitors: integrating molecular and cellular therapies. *Blood*. 2018;132(9):892–902.

Dreyling M, Jurczak W, Jerkeman M, et al. Ibrutinib versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma: an international, randomised, open-label, phase 3 study. *Lancet*. 2016;387(10020):770–778.

Dreyling M, Morschhauser F, Bouabdallah K, et al. Phase II study of copanlisib, a PI3K inhibitor, in relapsed or refractory, indolent or aggressive lymphoma. *Ann Oncol*. 2017;28(9):2169–2178.

FDA Approved Drug: acalabrutinib. U.S. Food and Drug Administration website. November 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/210259s006s007lbl.pdf. Accessed August 2021.

FDA Approved Drug: copanlisib. U.S. Food and Drug Administration website. February 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/209936s004lbl.pdf. Accessed August 2021.

FDA Approved Drug: duvelisib. U.S. Food and Drug Administration website. July 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211155s001lbl.pdf. Accessed August 2021.

FDA Approved Drug: ibrutinib. U.S. Food and Drug Administration website. December 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/205552s033,210563s010lbl.pdf. Accessed August 2021.

FDA Approved Drug: idelalisib. U.S. Food and Drug Administration website. October 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/205858s014lbl.pdf. Accessed August 2021.

FDA Approved Drug: venetoclax. U.S. Food and Drug Administration website. November 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208573s023lbl.pdf. Accessed August 2021.

FDA Approved Drug: zanubrutinib. U.S. Food and Drug Administration website. November 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/213217s000lbl.pdf. Accessed August 2021.

Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. *N Engl J Med*. 2019;380(23):2225–2236.

Flinn IW, Hillmen P, Montillo M, et al. The phase 3 DUO trial: duvelisib vs ofatumumab in relapsed and refractory CLL/SLL. *Blood*. 2018;132(23):2446–2455.

Flinn IW, Miller CB, Ardeshna KM, et al. Dynamo: a phase II study of duvelisib (IPI-145) in patients with refractory indolent non-hodgkin lymphoma. *J Clin Oncol*. 2019;37(11):912–922.

Finnes HD, Chaffee KG, Call TG, et al. Pharmacovigilance during ibrutinib therapy for chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) in routine clinical practice. *Leuk Lymphoma*. 2017;58(6):1376–1383.

Framingham Heart Study. Framingham Heart Study AF score (10-year risk). FHS website. https://framinghamheartstudy.org/fhs-risk-functions/atrial-fibrillation-10-year-risk/. Accessed June 2021.

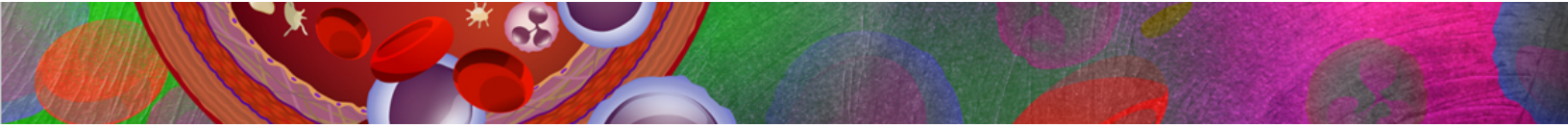
Furman RR, Sharman JP, Coutre SE, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2014;370(11):997–1007.

George B, Chowdhury SM, Hart A, et al. Ibrutinib resistance mechanisms and treatment strategies for B-cell lymphomas. *Cancers (Basel)*. 2020;12(5).

Ghia P, Pluta A, Wach M, et al. Acalabrutinib (Acala) versus idelalisib plus rituximab (IdR) or bendamustine plus rituximab (BR) in relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL): ASCEND final results. Abstract 3140. Presented at: 2020 ASH Virtual Annual Meeting; December 5–8, 2020.

Ghia P, Pluta A, Wach M, et al. Acalabrutinib (Acala) versus idelalisib plus rituximab (IdR) or bendamustine plus rituximab (BR) in relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL): ASCEND final results. Abstract 8015. Presented at: 2020 ASCO Virtual Scientific Program; May 29–June 2, 2020.

Ghia P, Pluta A, Wach M, et al. Ascend: phase III, randomized trial of acalabrutinib versus idelalisib plus rituximab or bendamustine plus rituximab in relapsed or refractory chronic lymphocytic leukemia. *J Clin Oncol*. 2020;38(25):2849–2861.



Ghia P, Pluta A, Wach M, et al. Ascend phase 3 study of acalabrutinib vs investigator's choice of rituximab plus idelalisib (IDR) or bendamustine (BR) in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL). Abstract LB2606. Presented at: 24th EHA Congress; June 16, 2019; Amsterdam.

Gopal AK, Kahl BS, de Vos S, et al. PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. *N Engl J Med*. 2014;370(11):1008–1018.

Hallek M. Signaling the end of chronic lymphocytic leukemia: new frontline treatment strategies [published correction appears in: *Blood*. 2014;123(26):4153]. *Blood*. 2013;122(23):3723–3734.

Hallek M, Cheson BD, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. *Blood*. 2018;131(25):2745–2760.

Handunnetti SM, Anderson MA, Burbury K, et al. Three-year update of the phase II ABT-199 (venetoclax) and ibrutinib in mantle cell lymphoma (AIM) study. Abstract 756. Presented at: 2019 ASH Annual Meeting; December 7–10, 2019; Orlando, Florida.

Hanlon A, Brander DM. Managing toxicities of phosphatidylinositol-3-kinase (Pi3k) inhibitors. *Hematology Am Soc Hematol Educ Program*. 2020;2020(1):346–356.

Hendriks RW. Drug discovery: new BTK inhibitor holds promise. *Nat Chem Biol*. 2011;7(1):4–5.

Hilal T, Betcher JA, Leis JF. Economic impact of oral therapies for chronic lymphocytic leukemia-the burden of novelty. *Curr Hematol Malig Rep*. 2018;13(4):237–243.

International CLL-IPI working group. An international prognostic index for patients with chronic lymphocytic leukaemia (CLL-IPI): a meta-analysis of individual patient data. *Lancet Oncol*. 2016;17(6):779–790.

Jerkeman M, Eskelund CW, Hutchings M, et al. Ibrutinib, lenalidomide, and rituximab in relapsed or refractory mantle cell lymphoma (PHILEMON): a multicentre, open-label, single-arm, phase 2 trial. *Lancet Haematol*. 2018;5(3):e109–e116.

Jerkeman M, Hutchings M, Raty R, et al. Ibrutinib-lenalidomide-rituximab in patients with relapsed/refractory mantle cell lymphoma: final results from the Nordic Lymphoma Group MCL6 (PHILEMON) phase II trial. Abstract 623. Presented at: 2020 ASH Virtual Annual Meeting; December 5–8, 2020.

Jin F, Robeson M, Zhou H, et al. The pharmacokinetics and safety of idelalisib in subjects with moderate or severe hepatic impairment. *J Clin Pharmacol*. 2015;55(8):944–952.

Jones JA, Mato AR, Wierda WG, et al. Venetoclax for chronic lymphocytic leukemia progressing after ibrutinib: an interim analysis of a multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2018;19(1):65–75.

Kaptein A, de Bruin G, Emmelot-van Hoek M, et al. Potency and selectivity of BTK inhibitors in clinical development for B-cell malignancies. *Blood.* 2018;132(Suppl 1):1871.

Kater AP, Kipps TJ, Eichhorst B, et al. Five-year analysis of MURANO study demonstrates enduring undetectable minimal residual disease (uMRD) in a subset of relapsed/refractory chronic lymphocytic leukemia (R/R CLL) patients (pts) following fixed-duration venetoclax-rituximab (VenR) therapy (Tx). Abstract 125. Presented at: 2020 ASH Virtual Annual Meeting; December 5–8, 2020.

Kater AP, Seymour JF, Hillmen P, et al. Fixed duration of venetoclax-rituximab in relapsed/refractory chronic lymphocytic leukemia eradicates minimal residual disease and prolongs survival: post-treatment follow-up of the murano phase III study. *J Clin Oncol*. 2019;37(4):269–277.

Kittai AS, Woyach JA. Resistance mechanisms to targeted agents in chronic lymphocytic leukemia. *Cancer J*. 2019;25(6):428–435.

Lampson BL, Kasar SN, Matos TR, et al. Idelalisib given front-line for treatment of chronic lymphocytic leukemia causes frequent immune-mediated hepatotoxicity. *Blood*. 2016;128(2):195–203.

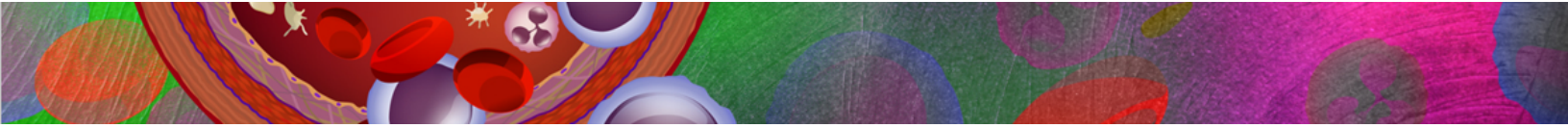
Leppa S, Santoro A, Demeter J, et al. Long-term follow-up of patients (Pts) with relapsed or refractory (R/R) follicular lymphoma (FL) treated with copanlisib. Abstract 7553. Presented at: American Society of Clinical Oncology Annual Meeting; May 31–June 4, 2019; Chicago, Illinois.

Lipsky A, Lamanna N. Managing toxicities of Bruton tyrosine kinase inhibitors. *Hematology Am Soc Hematol Educ Program*. 2020;2020(1):336–345.

Maddocks KJ, Ruppert AS, Lozanski G, et al. Etiology of ibrutinib therapy discontinuation and outcomes in patients with chronic lymphocytic leukemia. *JAMA Oncol*. 2015;1(1):80–87.

Mato AR, Hill BT, Lamanna N, et al. Optimal sequencing of ibrutinib, idelalisib, and venetoclax in chronic lymphocytic leukemia: results from a multicenter study of 683 patients. *Ann Oncol*. 2017;28(5):1050–1056.

Mato AR, Nabhan C, Thompson MC, et al. Toxicities and outcomes of 616 ibrutinib-treated patients in the United States: a real-world analysis. *Hematologica.* 2018;103(5):874–879.



Merolle MI, Ahmed M, Nomie K, Wang ML. The B-cell receptor signaling pathway in mantle cell lymphoma. *Oncotarget*. 2018;9(38):25332–25341.

Moia R, Patriarca A, Schipani M, et al. Precision medicine management of chronic lymphocytic leukemia. *Cancers (Basel)*. 2020;12(3).

Moreno C, Griel R, Demirkan F, et al. Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukemia (iLLUMINATE): a multicentre, randomized, open-label, phase 3 trial. *Lancet Oncol.* 2019;20:43–56.

Munir T, Brown JR, O'Brien S, et al. Final analysis from RESONATE: up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. *Am J Hematol*. 2019;94(12):1353–1363.

National Comprehensive Cancer Network. NCCN guidelines: B-cell lymphomas. Version 4.2021; May 5, 2021. NCCN website. https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed June 2021.

National Comprehensive Cancer Network. NCCN guidelines: chronic lymphocytic leukemia/small lymphocytic lymphoma. Version 4.2021; April 29, 2021. NCCN website. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf. Accessed June 2021.

National Institutes of Health, National Cancer Institute (SEER). Cancer stat facts: leukemia—chronic lymphocytic leukemia (CLL). SEER website. https://seer.cancer.gov/statfacts/html/clyl.html. Accessed June 2021.

Nodzon, L. Minimal residual disease in chronic lymphocytic leukemia: highlights from SOHO 2020. *J Adv Pract Oncol*. 2021;12(Suppl 1):20–22.

O'Brien S, Jones JA, Coutre SE, et al. Ibrutinib for patients with relapsed or refractory chronic lymphocytic leukaemia with 17p deletion (RESONATE-17): a phase 2, open-label, multicentre study. *Lancet Oncol*. 2016;17(10):1409–1418.

Owen C, Berinstein NL, Christofides A, Sehn LH. Review of Bruton tyrosine kinase inhibitors for the treatment of relapsed or refractory mantle cell lymphoma. *Curr Oncol*. 2019;26(2):e233–e240.

Parikh SA. Chronic lymphocytic leukemia treatment algorithm 2018. *Blood Cancer J*. 2018;8(10):93.

Parmar S, Patel K, Pinilla-Ibarz J. Ibrutinib (Imbruvica): a novel targeted therapy for chronic lymphocytic leukemia. *P T*. 2014;39(7):483–519.

Puri KD, Di Paolo JA, Gold MR. B-cell receptor signaling inhibitors for treatment of autoimmune inflammatory diseases and B-cell malignancies. *Int Rev Immunol*. 2013;32(4):397–427.

Raedler LA. Zydelig (Idelalisib): first-in-class pi3 kinase inhibitor approved for the treatment of 3 hematologic malignancies. *Am Health Drug Benefits*. 2015;8(Spec Feature):157–162.

Rhodes JM, LoRe VA 3rd, Mato AR, et al. Ibrutinib-associated Arthralgias/Myalgias in Patients With Chronic Lymphocytic Leukemia: Incidence and Impact on Clinical Outcomes. *Clin Lymphoma Myeloma Leuk*. 2020;20(7):438-444.

Roeker LE, Mato AR. Approaches for relapsed CLL after chemotherapy-free frontline regimens. *Hematology Am Soc Hematol Educ Program* 2020;2020(1):10–17.

Rogers KA, Thompson PA, Allan JN, et al. Phase 2 study of acalabrutinib in ibrutinib (IBR)-intolerant patients (Pts) with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL). Abstract 7530. Presented at: 2019 ASCO Annual Meeting; June 3, 2019; Chicago, Illinois.

Rule S, Jurczak W, Jerkeman M, et al. Ibrutinib versus temsirolimus: 3-year follow-up of patients with previously treated mantle cell lymphoma from the phase 3, international, randomized, open-label RAY study. *Leukemia*. 2018;32(8):1799–1803.

Salem JE, Manouchehri A, Bretagne M, et al. Cardiovascular toxicities associated with ibrutinib. *J Am Coll Cardiol*. 2019;74(13):1667–1678.

Salles GA, Schuster SJ, De Vos S, et al. Idelalisib efficacy and safety in follicular lymphoma patients from a phase 2 study. Abstract 8529. Presented at: American Society of Clinical Oncology Annual Meeting; May 29–June 2, 2015; Chicago, Illinois.

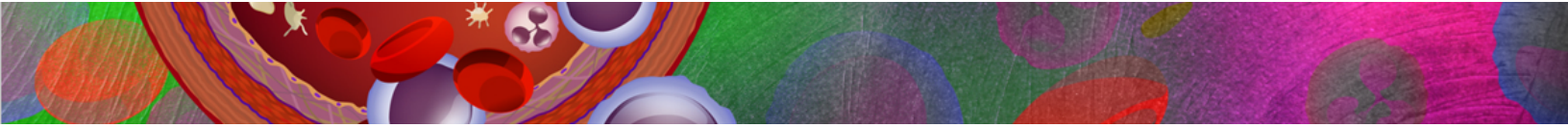
Scott LJ. Venetoclax: a review in relapsed/refractory chronic lymphocytic leukemia. *Target Oncol*. 2019;14(5):493–504.

Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax-rituximab in relapsed or refractory chronic lymphocytic leukemia. *N Engl J Med*. 2018;378(12):1107–1120.

Shadman M, Sharman JP, Levy MY, et al. Phase 2 study of zanubrutinib in patients with relapsed/refractory B-cell malignancies intolerant to ibrutinib/acalabrutinib. Abstract 2947. Presented at: 2020 ASH Annual Meeting (virtual); December 5–8, 2020.

Shanafeld TD, et al. Ibrutinib and rituximab provides superior clinical outcome compared to FCR in younger patients with chronic lymphocytic leukemia: extended follow-up from the E1912 trial. Abstract 33. Presented at: 2019 ASH Annual Meeting; December 7–10, 2019; Orlando, Florida.

Shanafelt TD, Wang XV, Kay NE, et al. Ibrutinib–rituximab or chemoimmunotherapy for chronic lymphocytic leukemia. *N Engl J Med*. 2019;381(5):432–443.



Sharman JP, Banerji V, Fogliatto LM, et al. Phase 3 study of acalabrutinib combined with obinutuzumab or alone versus obinutuzumab plus chlorambucil in patients with treatment-naive chronic lymphocytic leukemia: results from ELEVATE-TN. Abstract 31. Presented at: 2019 ASH Annual Meeting; December 7–10, 2019; Orlando, Florida.

Sharman JP, Coutre SE, Furman RR, et al. Final results of a randomized, phase III study of rituximab with or without idelalisib followed by open-label idelalisib in patients with relapsed chronic lymphocytic leukemia. *J Clin Oncol*. 2019;37(16):1391–1402.

Sharman JP, Egyed M, Jurczak W, et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzmab for treatment-naive chronic lymphocytic leukaemia (Elevate TN): a randomised, controlled, phase 3 trial. *Lancet*. 2020;395(10232):1278–1291.

Sharman JP, Egyed M, Jurczak W, et al. Acalabrutinib ± obinutuzumab versus obinutuzumab + chlorambucil in treatment-naïve chronic lymphocytic leukemia: Elevate-TN four-year follow up. Abstract 7509. Presented at: ASCO Virtual Meeting 2021; June 4 – 8, 2021.

Shatzel JJ, Olson SR, Tao DL, et al. Ibrutinib-associated bleeding: pathogenesis, management, and risk reduction strategies. *J Thromb Haemost.* 2017;15(5):835–847.

Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. *CA Cancer J Clin*. 2021;71(1):7–33.

Song Y, Zhou K, Zou D, et al. Treatment of patients with relapsed or refractory mantle-cell lymphoma with zanubrutinib, a selective inhibitor of bruton's tyrosine kinase. *Clin Cancer Res*. 2020;26(16):4216–4224.

Stephens DM, Byrd JC. How I manage ibrutinib intolerance and complications in patients with chronic lymphocytic leukemia. *Blood*. 2019;133(12):1298–1307.

Stilgenbauer S, Eichhorst B, Schetelig J, et al. Venetoclax for patients with chronic lymphocytic leukemia with 17p deletion: results from the full population of a phase II pivotal trial. *J Clin Oncol*. 2018;36(19):1973–1980.

Stilgenbauer S, Eichhorst B, Schetelig J, et al. Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study. *Lancet Oncol*. 2016;17(6):768–778.

Stühlinger MC, Weltermann A, Staber P, et al. Recommendations for ibrutinib treatment in patients with atrial fibrillation and/or elevated cardiovascular risk. *Wien Klin Wochenschr*. 2020;132(3-4):97–109.

Tam CS, Robak T, Ghia P, et al. Zanubrutinib monotherapy for patients with treatment naïve chronic lymphocytic leukemia and 17p deletion. *Hematologica.* October 13, 2020. [Epub ahead of print.]

Tam CS, Trotman J, Opat S, et al. Phase 1 study of the selective BTK inhibitor zanubrutinib in B-cell malignancies and safety and efficacy evaluation in CLL. *Blood*. 2019;134(11):851–859.

Tariman JD, Tarvainis A, Webber-Ritchey KJ, Simonovich SD. Shared decision-making competency: provider-specific factors in hematology-oncology clinical practice. *Clin J Oncol Nurs*. 2020;24(4):346–351.

Tausch E, Close W, Dolnik A, et al. Venetoclax resistance and acquired BCL2 mutations in chronic lymphocytic leukemia. *Haematologica.* 2019;104(9):e434–e437.

ten Hacken E, Burger JA. Microenvironment interactions and B-cell receptor signaling in chronic lymphocytic leukemia: implications for disease pathogenesis and treatment. *Biochim Biophys Acta*. 2016;1863(3):401–413.

Thangavadivel S, Byrd JC. Gly101Val BCL2 mutation: one step closer to understanding venetoclax resistance in CLL. *Cancer Discov*. 2019;9(3):320–322.

U.S. Food and Drug Administration. Drug development and drug interactions: table of substrates, inhibitors, and inducers. FDA website. https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers. Accessed June 2021.

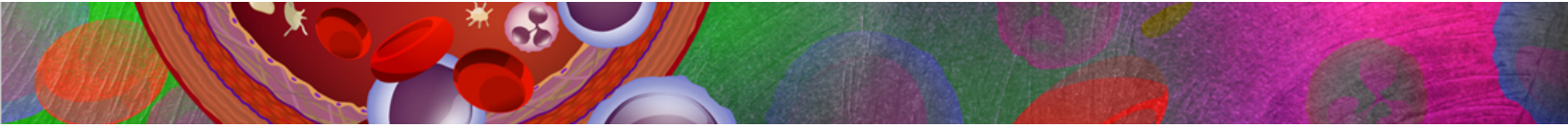
Wang M, Rule S, Zinzani PL, et al. Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): a single-arm, multicentre, phase 2 trial. *Lancet*. 2018;391(10121):659–667.

Wang M, Rule S, Zinzani PL, et al. Acalabrutinib monotherapy in patients with relapsed/refractory mantle cell lymphoma: long-term efficacy and safety results from a phase 2 study. Abstract 2040. Presented at: ASH Virtual Annual Meeting; December 5–8, 2020.

Wang ML, Blum KA, Martin P, et al. Long-term follow-up of MCL patients treated with single-agent ibrutinib: updated safety and efficacy results. *Blood*. 2015;126(6):739–745.

Wang ML, Lee H, Chuang H, et al. Ibrutinib in combination with rituximab in relapsed or refractory mantle cell lymphoma: a single-centre, open-label, phase 2 trial. *Lancet Oncol*. 2016;17(1):48–56.

Wen T, Wang J, Shi Y, et al. Inhibitors targeting Bruton's tyrosine kinase in cancers: drug development advances. *Leukemia*. 2021;35:312–332.



Whang JA, Chang BY. Bruton's tyrosine kinase inhibitors for the treatment of rheumatoid arthritis. *Drug Discov Today*. 2014;19(8):1200–1204.

Wiczer TE, Levine LB, Brumbaugh J, et al. Cumulative incidence, risk factors, and management of atrial fibrillation in patients receiving ibrutinib. *Blood Adv*. 2017;1(20):1739–1748.

Wiestner A. The role of B-cell receptor inhibitors in the treatment of patients with chronic lymphocytic leukemia. *Haematologica*. 2015;100(12):1495–507.

Woyach JA. Ibrutinib and aspergillus: a BTK-targeted risk. *Blood*. 2018;132(18):1869–1870.

Woyach JA, Furman RR, Liu T-M, et al. Resistance mechanisms for the Bruton's tyrosine kinase inhibitor ibrutinib. *N Engl J Med*. 2014;370(24):2286–2294.

Woyach JA, Ruppert AS, Heerema NA, et al. Ibrutinib regimens versus chemoimmunotherapy in older patients with untreated CLL. *N Engl J Med*. 2018;379(26):2517–2528.

Wu J, Liu C, Tsui ST, Liu D. Second-generation inhibitors of Bruton tyrosine kinase. *J Hematol Oncol*. 2016;9(1):80.

Xu W, Yang S, Zhou K, et al. Treatment of relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma with the BTK inhibitor zanubrutinib: phase 2, single-arm, multicenter study. *J Hematol Oncol*. 2020;13(1):48.

Yeung CCS, Shadman M. How to choose the best treatment and testing for chronic lymphocytic leukemia in the tsunami of new treatment options. *Curr Oncol Rep*. 2019;21(8):74.

Young RM, Phelan JD, Wilson WH, Staudt LM. Pathogenic B-cell receptor signaling in lymphoid malignancies: new insights to improve treatment. *Immunol Rev*. 2019;291(1):190–213.