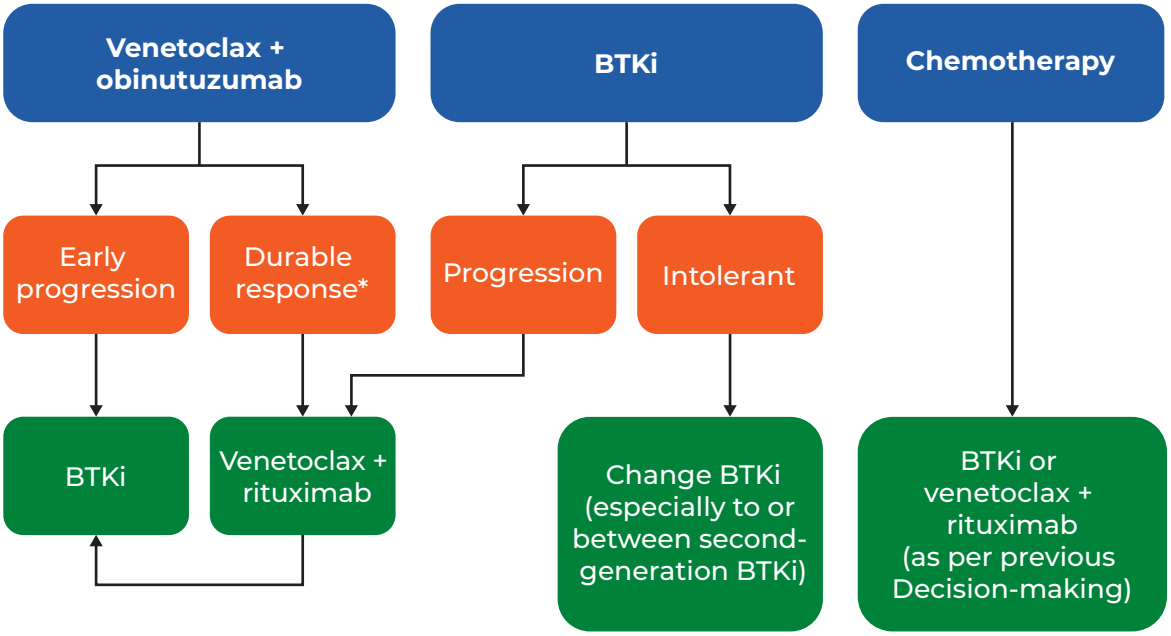
State-of-the-Art Care in CLL/SLL: Best Practices in an Expanding Therapeutic Landscape

When to Initiate Treatment for CLL/SLL: iwCLL Guidelines[1]

- Progressive marrow failure indicated by a CBC (Hb <10 g/dL or platelet counts <100 x 10^9/L)
- Splenomegaly or lymphadenopathy that is massive, progressive, or symptomatic
- Progressive lymphocytosis (increase of ≥50% over 2-mo period, or lymphocyte doubling time <6 mo)
- Autoimmune complications (including anemia or thrombocytopenia poorly responsive to corticosteroids)
- Symptomatic or functional extranodal involvement (eg, skin, kidney, lung, spine)
- Disease-related symptoms (eg, unintentional weight loss, significant fatigue, fevers, or night sweats)

Prior to initiating treatment, mutational status (ie, *TP53* and *IGHV*), age, and fitness should be assessed along with other relevant clinical criteria

Treatment Pathways for CLL/SLL



*Definition of durable response unknown currently. Overall response rate ~70% for patients who have been retreated with venetoclax (16 mo between) in small analysis however these results are limited by selection bias[2]

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AEs Associated with Treatment Options for CLL/SLL

Common AEs that occurred at an incidence ≥30% (BTKi) or ≥20% (venetoclax)

Notable AEs are unique to either the BTKi or venetoclax and require concerted management

BTK Inhibitors[3-5]

- Headache
- Neutropenia
- Thrombocytopenia
- Anemia
- Cardiac arrhythmias, atrial fibrillation
- Hypertension
- Upper respiratory tract infection
- Rash
- Bruising and bleeding, hemorrhage
- Diarrhea
- Musculoskeletal pain
- Fatigue
- Infection

Venetoclax (Plus Obinutuzumab or Rituximab)[6]

- Tumor lysis syndrome
- Neutropenia
- Thrombocytopenia
- Anemia
- Upper respiratory tract infection
- Cough
- Nausea
- Diarrhea
- Musculoskeletal pain
- Edema
- Fatigue

With obinutuzumab or rituximab:
Hypersensitivity reaction, Infusion reaction

The Pharmacist's Role in Optimizing CLL Therapy

Drug Interactions

- Thorough medicine reconciliation
- Evaluation of herbal medications
- Instruction to alert pharmacist of new medications

Patient Selection

- Past medical history, comorbid conditions
- Adherence assessment
- Goals of care (ie, desire to stop therapy)
- Affordability of indefinite therapy

Adverse Event Management

- Optimize blood pressure (ibrutinib), TLS management (venetoclax)
- Manage headaches (acalabrutinib), IRRs (CD20 mAb)
- Counsel patients on common and serious adverse events
- Empower patients to self-manage when appropriate
- Provide patient-friendly information (oralchemoedsheets.com)

BTK Inhibitors: Dosing Considerations for CLL/SLL

	Ibrutinib[3]	Acalabrutinib[4]	Zanubrutinib[5]
	Capsules: 70 mg, 140 mg Tablets: 140 mg, 280 mg, 420 mg	100 mg tablets ***formulation can be coadministered with gastric acid–reducing agents****	180 mg capsules
	420 mg once daily	100 mg orally twice daily	160 mg twice daily
	Take with a high-fat, high-calorie meal	With or without food, avoid high-fat meal	With or without food
	Capsules should be swallowed whole with water Do not cut, crush, or chew tablets	Tablet should be swallowed whole with water	Tablet should be swallowed whole with water
	*For missed dose, take as soon as possible on same day and return to normal schedule on next day*	*For missed dose >3 hr past normal time, skip and resume at next scheduled time*	*For missed dose, take as soon as possible on same day and return to normal schedule on next day*

*Acalabrutinib exposures were comparable for tablet vs capsule formulations (AUC_{inf} 567.8 ng h/mL [36.9] vs 572.2 ng h/mL [38.2], C_{max} 537.2 ng/mL [42.6] vs 535.7 ng/mL [58.4], respectively) and tablet can be coadministered with PPIs, food, or via NG tube without affecting the PKs or PDs.[7]

Targeted Therapies: Drug Interactions

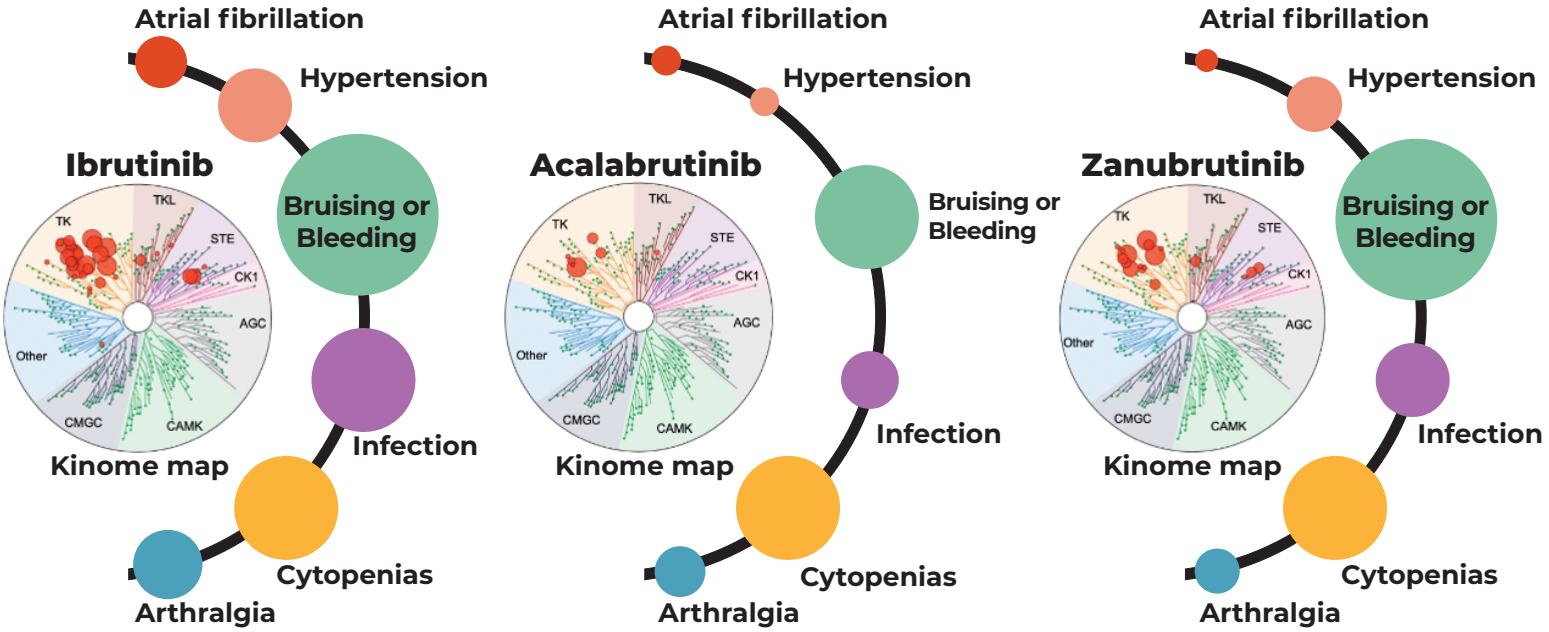
	Ibrutinib[3]	Acalabrutinib[4]	Zanubrutinib[5]
CYP3A4 inhibitors (moderate)	Decrease to 280 mg once daily	Decrease to 100 mg once daily	Decrease to 80 mg twice daily
CYP3A4 inhibitors (strong)	**Avoid*** or hold ibrutinib (if CYP3A4i used ≤7 days)	**Avoid** or hold acalabrutinib for ≥24 hr after last dose of CYP3A4i if used ≤7 days	Decrease to 80 mg once daily
CYP3A4 inducers	**Avoid** *May consider monitoring for reduced efficacy with moderate inducers*	**Avoid** *If unavoidable, increase dose to 200 mg orally twice daily*	**Avoid** *If moderate inducers unavoidable, increase dose to 320 mg twice daily*
P-gp inhibitors	N/A		
Anticoagulants	Consider risk vs benefit and monitor for increased risk of bleeding		
Antiplatelets			
Acid suppressants	N/A	N/A ***with new tablet formulation***	N/A

*Some strong CYP3A inhibitors can be coadministered, including voriconazole and posaconazole, with specific ibrutinib dose adjustments. See ibrutinib package insert instructions for more information.

COVID-19 considerations: nirmatrelvir/ritonavir is a strong CYP3A4 inhibitor that interacts with all BTKi and venetoclax

- Consider holding BTKi for duration of 5-day nirmatrelvir/ritonavir course

BTK Inhibitors: Approximate Rate of Select AEs[3-5]



Ibrutinib Dose Modifications[3]

No dose adjustments or discontinuations required for grade 1/2 AEs*

STARTING DOSE	DOSE ADJUSTMENTS		
Grade 2 cardiac failure, grade 3/4 nonhematologic AEs, grade 3/4 neutropenia with infection or fever, or grade 4 hematologic AEs			
420 mg daily (for CLL/SLL)	1st occurrence ***INTERRUPT*** then reduce by 140 mg	2nd occurrence ***INTERRUPT*** then reduce by 140 mg	3rd occurrence DISCONTINUE
Grade 3 Cardiac Arrhythmias			
420 mg daily (for CLL/SLL)	1st occurrence ***INTERRUPT*** then reduce by 140 mg	2nd occurrence DISCONTINUE	
Grade 3 Cardiac Failure or Grade 4 Cardiac Arrhythmias			
420 mg daily (for CLL/SLL)	1st occurrence DISCONTINUE		

Acalabrutinib Dose Modifications[4]

For grade ≥3 nonhematologic AEs, grade 3 thrombocytopenia with bleeding, grade 4 thrombocytopenia, or grade 4 neutropenia lasting longer than 7 days

100 mg BID	1st occurrence ***INTERRUPT*** then resume at current dose once AE resolves to grade 1	2nd occurrence ***INTERRUPT*** then resume at current dose once AE resolves to grade 1	3rd occurrence ***INTERRUPT*** then resume at 100 mg QD once AE resolves to grade 1	4th occurrence DISCONTINUE

Zanubrutinib Dose Modifications[5]

For grade ≥3 nonhematologic AEs, grade 3/4 febrile neutropenia, platelet count decreased to 25,000-50,000/mm^3 with significant bleeding, neutrophil count decreased to <500/mm^3 (lasting more than 10 consecutive days), platelet count decreased to <25,000/mm^3 (lasting more than 10 consecutive days)

320 mg daily (or 160 mg BID)	1st occurrence ***INTERRUPT*** then resume at current dose once AE resolves to grade 1	2nd occurrence ***INTERRUPT*** then resume at 160 mg QD (or 80 mg BID) once AE resolves to grade 1	3rd occurrence ***INTERRUPT*** then resume at 80 mg QD once AE resolves to grade 1	4th occurrence DISCONTINUE

*Would consider if persistent/affecting quality of life.

Management Recommendations for Key AEs

Atrial Fibrillation Management

- Risks include cardiac risk factors, acute infections, and prior history of atrial fibrillation
- Educate patients on their risk and when to call the healthcare team
- Rate control: β-blocker preferred due to CYP drug interactions with verapamil and diltiazem
- Monitor digoxin level for concomitant use with P-gp inhibitor
- Rhythm control; consider drug interactions
- **For controllable** Afib: **continue** therapy; can **consider** switching to alternative BTKi
- **For uncontrollable** Afib: consider alternative therapy

Bleeding Management

- Real-world risks based on multivariate analysis: elevated INR (>1.5) increases risk 4.6x and use of antiplatelet + anticoagulant vs neither increases risk 20x[8]
  - Conflicting data: low bleed incidence despite antiplatelet and/or anticoagulant (comorbidities may be more predictive)[9]
- **Hold BTK inhibitor prior to and after invasive procedures for 3 (minor) to 7 days (major)[3-5]**
  - Reversible impact within 1 wk of discontinuation
  - Platelet transfusion may reverse antiplatelet effects
- **Anticoagulants/antiplatelets are not contraindications[3-5]**
  - Avoid warfarin
  - Consider stopping other medications

Anticoagulation Management

- **Calculate risk**: calculate CHA^2DS^2-VASc and HAS-BLED score (neither scoring system has been validated in patients receiving BTKi)
- **Prevent bleeding**: discuss risk vs benefit based on HAS-BLED score and other factors **avoid warfarin**
- **Prevent stroke**: if CHA^2DS^2-VASc ≥2, consider anticoagulation

Hypertension Management

- **BTK inhibitor may ↑ HTN risk by 13x[10]**
- New or worsened HTN ↑ major CV events but control with antihypertensive ↓ major CV events
- Monitor blood pressure throughout treatment
- Standard management for hypertension, with no specific agent recommended
- BTK inhibitor treatment discontinuation not necessary in most cases
- Adequate management of HTN mitigates CV events

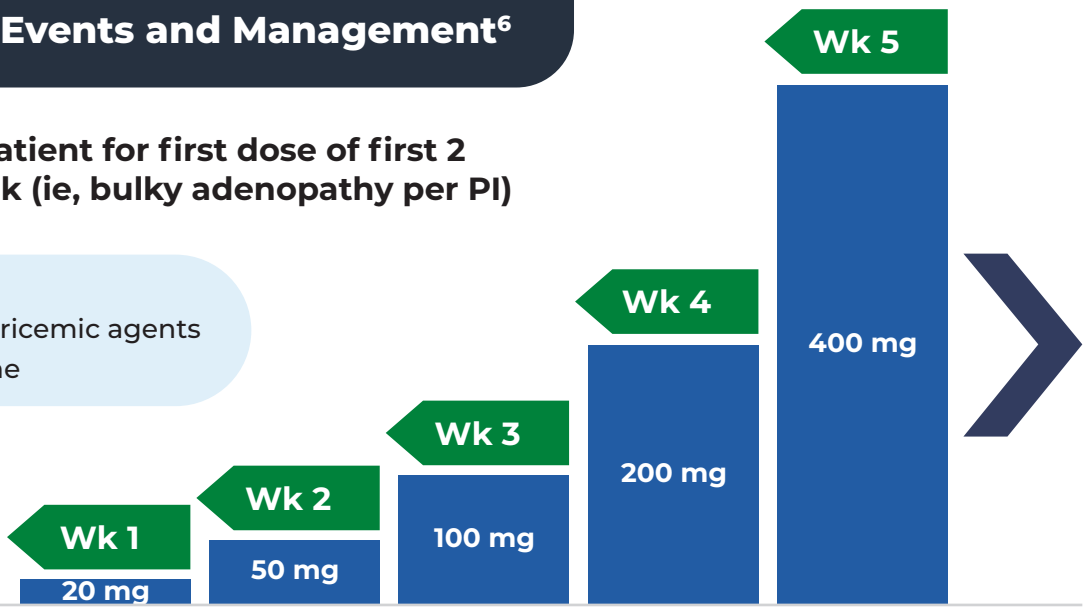
Consider Switching to Another BTK Inhibitor for Intolerance due to AEs

		No AE recurrence or lower grade recurrence
33 patients intolerant to **ibrutinib** experiencing 61 AEs[11]	**Acalabrutinib (phase II expansion)**	**85%**
66 patients intolerant to **ibrutinib** experiencing 72 AEs[12]	**Acalabrutinib (phase II)**	**85%**
67 patients intolerant to **ibrutinib** (n = 57; 115 AEs) or **acalabrutinib** (n = 10; 18 AEs) experiencing 133 AEs[13]	**Zanubrutinib (phase II)**	**93%**

Venetoclax: Adverse Events and Management[6]

Assess risk for TLS → inpatient for first dose of first 2 ramp-up doses if high risk (ie, bulky adenopathy per PI)

Monitor: TLS labs per PI
Prevent: hydration, antihyperuricemic agents
Treat: per institutional guideline



Venetoclax: TLS Management[6]

RISK	ASSESS RISK DISEASE CHARACTERISTICS	MANAGEMENT PLAN
Low risk	No bulky adenopathy ALC <25 x 109/L	Outpatient: • Oral hydration (1.5-2.0 L/day) and allopurinol • Lab monitoring: predose, 6-8 hr, 24 hr at first dose of 20 mg and 50 mg and then predose at subsequent ramp-up doses
Intermediate risk	Bulky adenopathy: ≥5 cm and <10 cm or ALC: ≥25 x 109/L	Outpatient: • Oral hydration (1.5-2.0 L/day), IV (PRN), and allopurinol • Lab monitoring: predose, 6-8 hr, 24 hr at first dose of 20 mg and 50 mg and then predose at subsequent ramp-up doses • If creatinine clearance <80 mL/min, consider inpatient admission for first 2 dose escalations
High risk	Bulky adenopathy: ≥10 cm or bulky adenopathy: ≥5 cm and ALC ≥25 x 109/L	Inpatient for first dose of first 2 ramp-up doses: • Oral hydration and IV as tolerated • Allopurinol (consider rasburicase based on baseline uric acid)

Additional factors to consider: baseline uric acid, LDH, potassium, phosphorous, sCr, calcium

Venetoclax: Hematologic Toxicity Management[6]

Grade 3 neutropenia with infection or fever or Grade 4 hematologic toxicity

- **First occurrence:**
  Interrupt treatment
  Resume at *same dose* once resolved to grade ≤1 or baseline
  Consider growth factor
- **Second and subsequent occurrences:**
  Interrupt treatment
  Resume at *lower dose* level once resolved to grade ≤1 or baseline
  Consider growth factor

Dose at Interruption	Reduced Dose Level
400 mg	300 mg
300 mg	200 mg
200 mg	100 mg
100 mg	50 mg
50 mg	20 mg
20 mg	10 mg

Consider discontinuation for patients who require dose reductions to <100 mg for more than 2 wk

Targeted Therapies: Drug Interactions[6]

Avoid grapefruit juice!

	Venetoclax
CYP3A4 inhibitors (moderate)	Reduce dose by 50%
CYP3A4 inhibitors (strong)	**Avoid** during initiation and ramp-up Reduce dose by at least 75% after ramp-up phase
CYP3A4 inducers	**Avoid**
P-gp inhibitors	**Avoid**, if possible, or reduce dose by 50% and separate dosing by ≥6 hr
Anticoagulants	May increase warfarin concentration
Antiplatelets	N/A
Acid suppressants	

COVID-19 considerations:
nirmatrelvir/ritonavir is a strong CYP3A4 inhibitor that interacts with all BTKi and venetoclax

- Consider dose reduction or dose hold for venetoclax during 5-day nirmatrelvir/ritonavir course, depending on clinical scenario

Strategies to Improve Patient Adherence to Oral Therapy

While Receiving BTK Inhibitors

Follow up with patients weekly during their first mo of BTK inhibitor therapy

Then, consider follow-up every 3 mo during the first yr with a consistent point of contact

Most patients will be seen less frequently by their physician at this point in their care

While Receiving Venetoclax

Weekly office visits until ramp-up dosing is complete

After the patient is stabilized, reach out monthly and then every 3 mo until the full course of venetoclax therapy is complete

Regular follow-up and monitoring of patients is critical with oral therapy to identify any AEs early and for appropriate AE management

Regular follow-up can improve patient outcomes and adherence, and regular touch points allows us to stay up to date on any new medications the patient may need to begin

References

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