Hope Is Here in CLL

Oncology Nurse Strategies for Delivering Effective, Compassionate, and Modern Care to Patients

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CLL SOCIETY

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Indications for Treatment of CLL Have Not Changed and Include Cytopenias, Splenomegaly, Lymphadenopathy

Any one of these criteria should be met to initiate CLL therapy (iwCLL)[1]

- ❑ Progressive marrow failure, Hb <10 gm/dL, or PLT <100 × 10^9/L
- ❑ Massive (≥6 cm below left costal margin) or progressive or symptomatic splenomegaly
- ❑ Massive (≥10 cm in longest diameter) or progressive or symptomatic lymphadenopathy
- ❑ Progressive lymphocytosis + increase of ≥50% over a 2-month period or lymphocyte doubling time of <6 months
- ❑ Autoimmune complications of CLL that are poorly responsive to corticosteroids
- ❑ Symptomatic extranodal involvement (eg, skin, kidney, lung, and spine)
- ❑ Disease-related symptoms

1. Hallek M et al. *Blood*. 2018;131:2745-2760.

Why Are We Here? Despite Progress With Targeted Therapy, CLL Still Presents an Ongoing Challenge

CIT is not a category 1 recommendation in current guidelines

- Yet in the informCLL registry, 40% of patients with unmutated IGHV received CIT, despite decreased efficacy[1]

CLL patients previously treated with both a covalent BTKi and a BCL-2i experience poor outcomes with currently available options

- Median time to discontinuation of the post–BTKi/BCL-2i therapy or death was 5.5 months[2]

1. Mato A et al. *Clin Lymphoma Myeloma Leuk*. 2020;20:174-183. 2. Mato A et al. 63rd American Society of Hematology Annual Meeting and Exposition (ASH 2021). Abstract 3743.

Upfront Choices: Continuous vs Time-Limited Therapy (1)

Nurse Consult 1: Assessing Next Steps for a Patient With High-Risk, Symptomatic CLL

Michael was 72 years old when he was diagnosed with asymptomatic CLL; now 74, he returns to clinic with symptomatic disease, including

- Classic B symptoms, anemia, and abdominal adenopathy
- Comorbid HTN
- CrCl >60 mL/min

Testing shows

- Unmutated IGHV
- *TP53* mutation

What are the next steps?

How should Michael be counseled on his disease and prognosis?

Continuous or fixed-duration therapy?

Explain the Modern Goals of Therapy to Patients With CLL

- Modern therapy is very effective but can achieve different goals
- Be prepared to review goals of care with patients and empower their decision-making

Continuous Therapy	Goal of Therapy
• BTK inhibitors	• Disease control • Prolonged PFS • Independent from response, MRD

Fixed Duration	Goal of Therapy
• Venetoclax + obinutuzumab	• Disease eradication • Prolonged PFS • Undetectable MRD

BTK and BCL-2 Inhibitors Are the Preferred Upfront Treatment Options in TN CLL…[1]

Patients aged ≥65 y
OR
Patients aged <65 y with significant comorbidities (CrCl <70 mL/min)

Preferred regimens

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

Patients aged <65 y without significant comorbidities

Preferred regimens

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

1. NCCN Clinical Practice Guidelines in Oncology. Chronic Lymphocytic Leukemia. Version 2.2022. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf.

… Including in High-Risk Settings[1]

NCCN-Suggested Regimens for CLL With del(17p)/*TP53* Mutations

First-Line Therapy	
Preferred Regimens	**Other Recommended Regimens**
• Acalabrutinib ± obinutuzumab • Ibrutinib • Venetoclax + obinutuzumab • Zanubrutinib	• Alemtuzumab ± rituximab • HDMP + rituximab • Obinutuzumab

Chemoimmunotherapy is NOT recommended

1. NCCN Clinical Practice Guidelines in Oncology. Chronic Lymphocytic Leukemia. Version 2.2022. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf.

Consistent PFS Benefit Across Pivotal 1L Studies Comparing Novel Agents With CIT

Study	Population	Design	PFS Benefit for Experimental Arm?
E1912[1]	"Fit," no del(17p)	FCR x 6 vs IR x 6, then ibrutinib maintenance	**Yes**
ALLIANCE[2]	"Fit," older, del(17p) allowed	3 arm: BR vs IR vs I	**Yes**
iLLUMINATE[3]	Unfit (CIRS >6 or CrCl <70) or *TP53* del/mut	G + Cbl vs G + ibrutinib	**Yes**
ELEVATE-TN[4]	Unfit (CIRS >6 or CrCl <70)	G + Cbl vs acalabrutinib vs G + acalabrutinib	**Yes**
SEQUOIA[5]	Older, no del(17p)	BR vs zanubrutinib	**Yes**
CLL14[6]	Unfit (CIRS >6 or CrCl <70)	G + Cbl vs venG	**Yes**

Continuous therapy **Fixed duration**

1. Shanafelt TD et al. *N Engl J Med*. 2019;381:432-443. 2. Woyach JA et al. *N Engl J Med*. 2018;379:2517-2528. 3. Moreno C et al. *Lancet Oncol*. 2019;20:43-56.
4. Sharman JP et al. *Lancet*. 2020;395:1278-1291. 5. Tam C et al. ASH 2021. Abstract 396. 6. Fischer K et al. *N Engl J Med*. 2019;380:2225-2236.

Longer-Term Evidence Supports Continuous BTKi Therapy…

RESONATE-2	*Ibrutinib versus chlorambucil in TN CLL*
8 years of follow-up[1]	**PFS benefit with ibrutinib** • 59% versus 9% at 7 years • Benefit in del(11q) and unmutated IGHV patients • OS at 7 years was 78% with ibrutinib

Take-home: sustained benefit with first-line ibrutinib treatment for CLL, including for patients with high-risk genomic features

1. Barr PM et al. *Blood Adv*. 2022 Apr 4 [Epub ahead of print].

Longer-Term Evidence Supports Continuous BTKi Therapy… (Cont'd)

ELEVATE-TN[1]	*Acalabrutinib versus acalabrutinib + obinutuzumab versus O-Clb*
4 years of follow-up	**PFS benefit with acalabrutinib** • NR versus 27.8 months • 81% lower risk for disease progression or death with acalabrutinib alone versus O-Clb

Take-home: sustained benefit with use of acalabrutinib regimens versus O-Clb combination in TN CLL

1. Sharman JP et al. 2021 American Society of Clinical Oncology Annual Meeting (ASCO 2021). Abstract 7509.

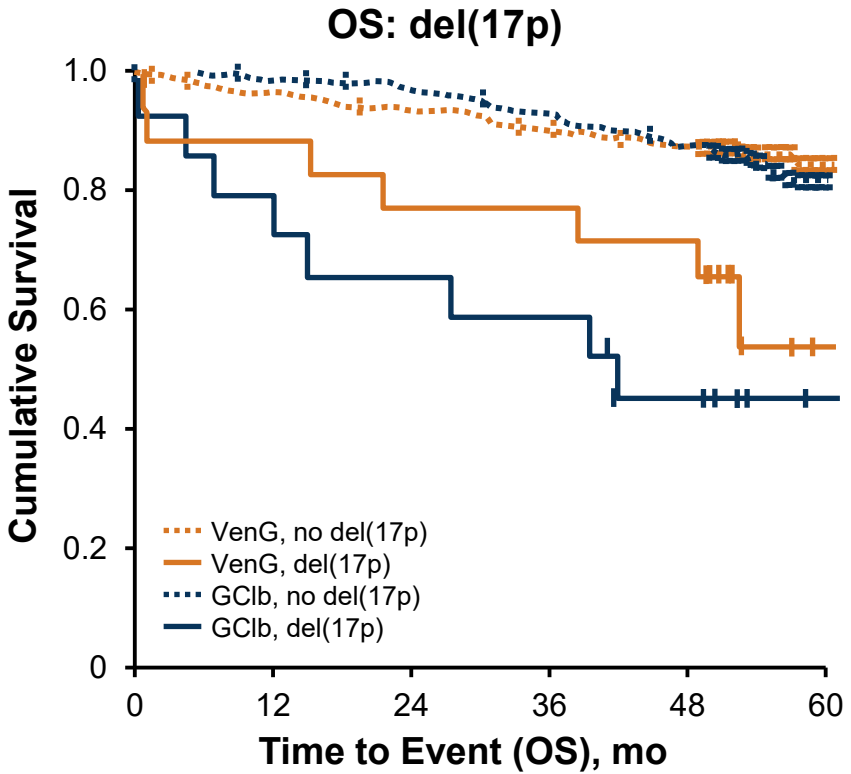
… Including in *TP53* CLL Subgroups

Study	Population	Design	Patients With *TP53*, n	PFS in *TP53* Subgroups
ALLIANCE[1]	Fit, older, del(17p) allowed	3 arms: BR vs IR vs I	51	**Median not established for I or IR vs 7 mo for BR**
iLLUMINATE[2]	Unfit (CIRS >6 or CrCl <70) or *TP53* del/mut	G + Cbl vs G + ibrutinib	29	**Median not reached for I + G vs 11.3 mo for G + Cbl**
ELEVATE-TN[3]	Unfit (CIRS >6 or CrCl <70)	G + Cbl vs acalabrutinib vs G + acalabrutinib	61	**24-mo PFS: 95% for acalabrutinib + G vs 19% for G + Cbl**

1. Woyach JA et al. *N Engl J Med.* 2018;379:2517-2528. 2. Moreno C et al. *Lancet Oncol.* 2019;20:43-56. 3. Sharman JP et al. *Lancet.* 2020;395:1278-1291.

What About Fixed-Duration Venetoclax + Obinutuzumab in *TP53* CLL?

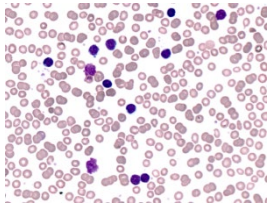
Although fixed-duration venG was effective in the CLL14 trial, the presence of del(17p)/*TP53* was associated with an unfavorable prognosis[1]



1. Tausch E et al. European Hematology Association 2021 Virtual Congress (EHA 2021). Abstract S144.

Explain Prognostic Factors to Patients

Counsel patients on adverse risk factors



Use tools to help patients understand implications for treatment

Prognostic Factor	Is an Adverse Risk Factor When
***TP53* (17p)**	**Mutated and/or deleted**
IGHV status	**Unmutated**
Beta-2 microglobulin	>3.5
Clinical stage	Binet B/C or Rai I-IV
Age	**>65 years**

CLL Society Toolkit: Test Before Treat™ Campaign

Test Before Treat™

- Test FISH and TP53 Mutation before every treatment
- Test IgVH mutation status before the 1st treatment
- Deletion 17p or del(17p) = NO CHEMOTHERAPY
- TP53 mutation = NO CHEMOTHERAPY
- IgVH unmutated = NO FCR
- IgVH mutated = possible FCR

Nurse Consult 1: Recommendations for Michael

Recommendations

- ✓ Counsel Michael on his expected prognosis using appropriate tools and resources
- ✓ Educate on the risks and benefits of continuous versus fixed-duration therapy
- ✓ Continuous BTKi therapy is an excellent choice for this patient
- ✓ Fixed-duration venG is also reasonable assuming different patient preferences and goals of therapy

Michael was 72 years old when he was diagnosed with asymptomatic CLL; now 74, he returns to clinic with symptomatic disease, including

- Classic B symptoms, anemia, and abdominal adenopathy
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- CrCl >60 mL/min

Testing shows

- Unmutated IGHV
- *TP53* mutation

What are the next steps?

How should Michael be counseled on his disease and prognosis?

Continuous or fixed-duration therapy?

Nurse Consult: Assuming Michael Is Preparing for Therapy With a BTKi, What Next?

Recommendations

- ✓ Counsel Michael on his expected prognosis using appropriate tools and resources
- ✓ Educate on the risks and benefits of continuous versus fixed-duration therapy
- ✓ Continuous BTKi therapy is an excellent choice for this patient
- ✓ Fixed-duration venG is also reasonable assuming different patient preferences and goals of therapy
- ✓ **Assuming BTKi therapy is chosen, next steps should include counseling on dosing and drug interactions**

Michael was 72 years old when he was diagnosed with asymptomatic CLL; now 74, he returns to clinic with symptomatic disease, including

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What are the next steps?

How should Michael be counseled on his disease and prognosis?

Continuous or fixed-duration therapy?

Ibrutinib Dosing and Administration[1]

Dosing for CLL Differs From MCL

- **CLL**
  - **420 mg by mouth once daily** (as a single agent or combined with BR or obinutuzumab)
  - Administer ibrutinib **before** rituximab or obinutuzumab when given on the same day
- MCL
  - 560 mg by mouth once daily

Administration

- Administer at approximately the same time each day with a full glass of water
- If administered with CYP3A inhibitors, consult prescribing information for dose modifications

Additional Practice Notes

- Reduce dosage to 140 mg once daily for mild hepatic impairment and to 70 mg once daily for moderate hepatic impairment

1. Imbruvica (ibrutinib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210563s000lbl.pdf.

Acalabrutinib Dosing and Administration[1]

Approved Dosing in MCL and CLL

- **100 mg by mouth every 12 hours (twice daily)**

Administration

- Administer with a full glass of water with or without food
- If a dose is missed by more than 3 hours, it should be skipped and the next dose should be taken on the regular schedule

Additional Practice Notes

- Dosage adjustments are recommended when used concomitantly with certain medications (eg, CYP3A inducers and PPIs)

1. Calquence (acalabrutinib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/210259s000lbl.pdf.

Be Prepared to Review Drug Interactions With BTK Inhibitors When Counseling Patients

Coadministration of BTK inhibitors with[1]

	Strong CYP3A4 Inhibitors	Moderate CYP3A4 Inhibitors	Moderate or Strong CYP3A4 Inducers	P-gp Inhibitors	Gastric Acid–Reducing Agents
Ibrutinib	• If necessary, reduce to 140 mg once daily • For short-term use (≤7 d), interrupt ibrutinib	280 mg once daily	Avoid use	No dosage adjustment recommended	No dosage adjustment recommended
Acalabrutinib	Avoid use	100 mg once daily	Avoid use; if necessary, increase to 200 mg twice daily	No dosage adjustment recommended	Avoid PPIs; may decrease AUC by 43%
Zanubrutinib	80 mg once daily	80 mg twice daily	Avoid use	No dosage adjustment recommended	No dosage adjustment recommended

New acalabrutinib maleate salt: immediate-release film-coated tablet and suspension[2]

Clinical effect is expected to be comparable with acalabrutinib capsules at approved dosing, regardless of use of PPIs and ingestion of food

1. Weis TM et al. *J Oncol Pharm Pract.* 2022;10781552221090869. 2. Sharma S et al. ASH 2021. Abstract 4365.

Nurse Consult: An Alternate Scenario in TN CLL

- **What if Michael had presented with a history of cardiac complications/AF or poorly controlled HTN?**
- **Assuming continuous therapy was still preferred, can understanding BTKi safety help us refine our patient care?**

Michael was 72 years old when he was diagnosed with asymptomatic CLL; now 74, he returns to clinic with symptomatic disease, including

- Classic B symptoms, anemia, and abdominal adenopathy
- Comorbid HTN
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Testing shows

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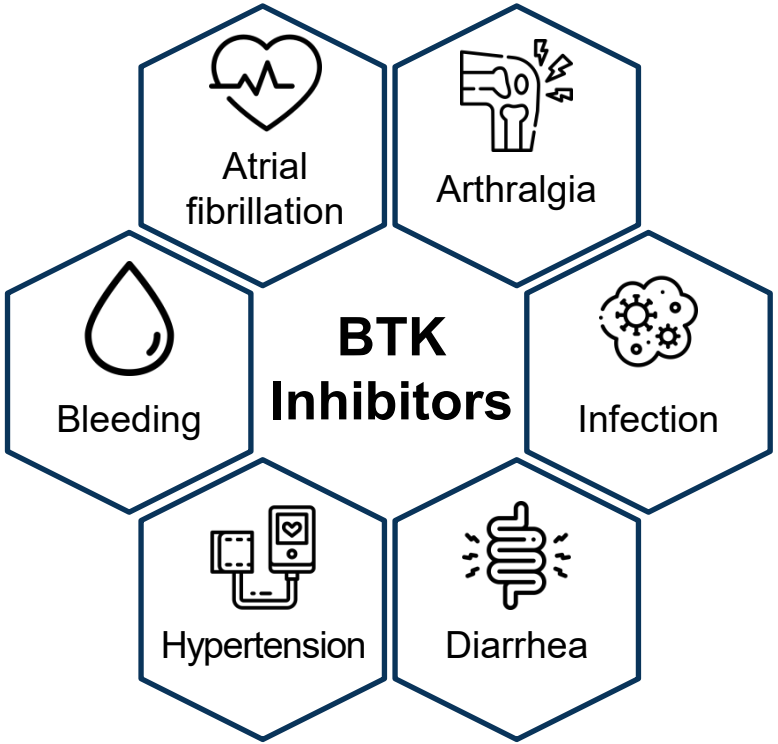
What are the next steps?

How should Michael be counseled on his disease and prognosis?

Continuous or fixed-duration therapy?

Overview of BTK Inhibitor Toxicities in CLL[1]

Common Toxicities



Additional Important Toxicities

- Dermatologic changes
- Fatigue
- Ventricular arrhythmia
- Cytopenias

1. Lipsky A, Lamanna N. *Hematology Am Soc Hematol Educ Program.* 2020;1:336-345.

General BTK Inhibitor Safety Monitoring Approaches[1]

- Don’t give concomitantly with warfarin
- New-onset AF: consider nonwarfarin anticoagulation and monitor
- Monitor for and manage cardiac arrhythmia/AF and treat appropriately
- **Hypertension:** manage with antihypertensives
- Monitor patients for signs of bleeding

- **Arthralgia:** rule out other causes, monitor, and use supportive care for lower-grade events
  - Dose reduce once symptoms affect ADLs and hold dose for higher-grade arthralgia
- Monitor for infections and secondary malignancies

✓ Assess CBCs monthly

✓ Understand risk factors for AF: age >65 years, male sex, diabetes, hypertension, and prior history

1. NCCN Clinical Practice Guidelines in Oncology. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Version 2.2022. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf.

Guidance on AEs More Typically Associated With Second-Generation BTKi[1]

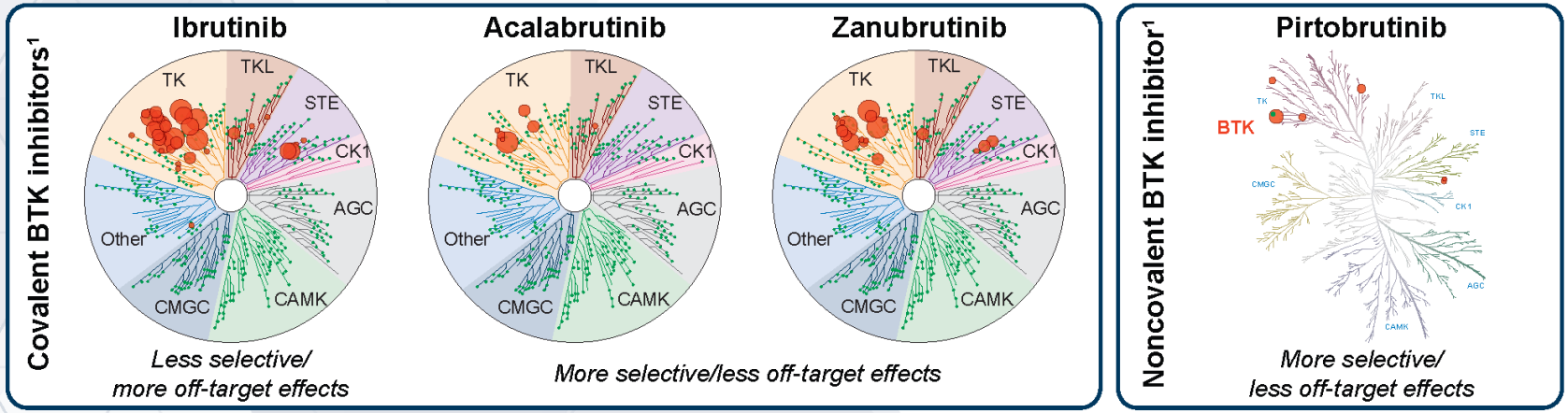
- **Headaches** commonly occur early in therapy **with acalabrutinib**
  - Typically resolve in 1-2 months
  - Manage with acetaminophen + caffeine
  - Dosage reductions/interruptions are not required

- **With zanubrutinib** (not yet approved), be prepared to monitor for **neutropenia**

Example: in a patient experiencing headaches during the first several weeks of therapy, recommend appropriate caffeine consumption and acetaminophen as needed

1. NCCN Clinical Practice Guidelines in Oncology. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Version 2.2022. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf.

What Are the Implications of Covalent and Noncovalent BTKi Selectivity for Off-Target Effects?



Less selective BTK inhibitors (eg, ibrutinib) have more off-target effects, which contribute to more toxicity compared with more selective agents[2]

Potential off-target effects include:

1. Kaptein A et al. ASH 2018. Abstract 1871. 2. Bose P et al. *Expert Opin Drug Metab Toxicol*. 2016;12:1381-1392.

Communication Is Key: Educate Patients on Safety Differences Between BTKi Options

- In head-to-head trials in CLL, more selective second-generation BTKi were associated with less AF
- *Discuss the risks and benefits of continuous BTKi therapy with patients*

	ELEVATE R/R[1]	
	Acalabrutinib (n = 266), n (%)	Ibrutinib (n = 263), n (%)
AF/flutter (any grade)	25 (9.4)	42 (16.0)

	ALPINE[2]	
	Zanubrutinib (n = 204), n (%)	Ibrutinib (n = 207), n (%)
AF/flutter (any grade)	5 (2.5)	21 (10.1)

1. Byrd JC et al. *J Clin Oncol*. 2021;39:3441-3452. 2. Hillmen P et al. EHA 2021. Abstract LB1900.

Upfront Choices: Continuous vs Time-Limited Therapy (2)

Nurse Consult 2: Assessing Next Steps for a Patient With Symptomatic, Good-Prognosis CLL

Sarah is 73 years old with a recent diagnosis of symptomatic TN CLL

- Classic B symptoms, worsening lymphadenopathy
- No major comorbid illnesses
- CrCl >60 mL/min

Testing shows

- Mutated IGHV
- **No *TP53* mutation/del(17p)**

What are the next steps?

How should Sarah be counseled on her disease and prognosis?

Continuous or fixed-duration therapy?

Goals of Therapy May Change Based on the Type of Patient

- Modern therapy is very effective but can achieve different goals
- Be prepared to review goals of care with patients and empower their decision-making

Continuous Therapy	Goal of Therapy
• BTK inhibitors	• Disease control • Prolonged PFS • Independent from response, MRD

Fixed Duration	Goal of Therapy
• Venetoclax + obinutuzumab	• Disease eradication • Prolonged PFS • Undetectable MRD

Assess Barriers When Considering Time-Limited Therapy: Key Questions to Ask

Increased risk for tumor lysis with venetoclax/obinutuzumab

- Can the patient stay adequately hydrated? 1.5-2 L daily?

Ramp-up dosing with venetoclax

- Are they compliant with medications?

Frequent, long clinic visits are required for multiple labs and IV hydration

- Does the patient have transportation to and from clinic?

Potential for infusion reactions with obinutuzumab

- Do they have support at home?

Consistent PFS Benefit Across Pivotal 1L Studies Comparing Novel Agents With CIT

Study	Population	Design	PFS Benefit for Experimental Arm?
E1912[1]	"Fit," no del(17p)	FCR x 6 vs IR x 6, then ibrutinib maintenance	**Yes**
ALLIANCE[2]	"Fit," older, del(17p) allowed	3 arm: BR vs IR vs I	**Yes**
iLLUMINATE[3]	Unfit (CIRS >6 or CrCl <70) or *TP53* del/mut	G + Cbl vs G + ibrutinib	**Yes**
ELEVATE-TN[4]	Unfit (CIRS >6 or CrCl <70)	G + Cbl vs acalabrutinib vs G + acalabrutinib	**Yes**
SEQUOIA[5]	Older, no del(17p)	BR vs zanubrutinib	**Yes**
CLL14[6]	Unfit (CIRS >6 or CrCl <70)	G + Cbl vs VenG	**Yes**

Continuous therapy **Fixed duration**

1. Shanafelt TD et al. *N Engl J Med*. 2019;381:432-443. 2. Woyach JA et al. *N Engl J Med*. 2018;379:2517-2528. 3. Moreno C et al. *Lancet Oncol*. 2019;20:43-56.
4. Sharman JP et al. *Lancet*. 2020;395:1278-1291. 5. Tam C et al. ASH 2021. Abstract 396. 6. Fischer K et al. *N Engl J Med*. 2019;380:2225-2236.

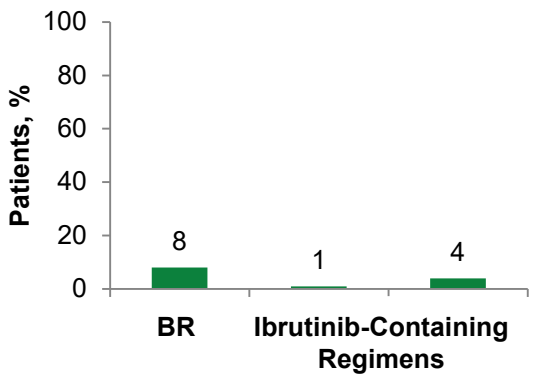
Understand the Efficacy: What If Achieving Disease Eradication Is the Goal of Therapy for Your Patient?

In general, MRD rates have been lower with continuous BTKi therapy, despite excellent overall efficacy

- Multiple ways to measure MRD; examples include flow and NGS

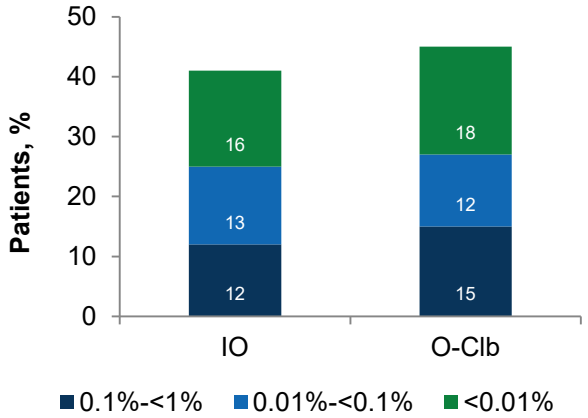
ALLIANCE 202 Trial[1]

BM uMRD at cycle 9 response evaluation



iLLUMINATE Trial[2]

MRD response (PB + BM) at 1 year

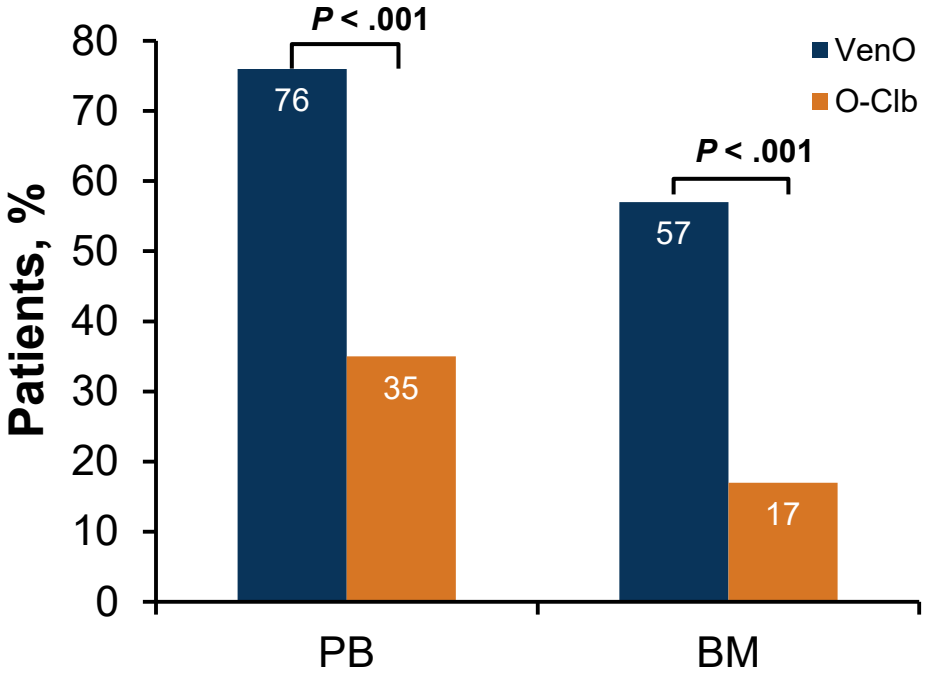


The cumulative rate of PB uMRD increased over time with IO

1. Woyach JA et al. *N Engl J Med.* 2018;379:2517-2528. 2. Moreno C et al. XVIII International Workshop on CLL (iwCLL 2019). Poster 2069.

Understand the Efficacy: What If Achieving Disease Eradication Is the Goal of Therapy for Your Patient? (Cont'd)

uMRD (<10^{-4}) by ASO-PCR 3 mo After EOT[1,a]

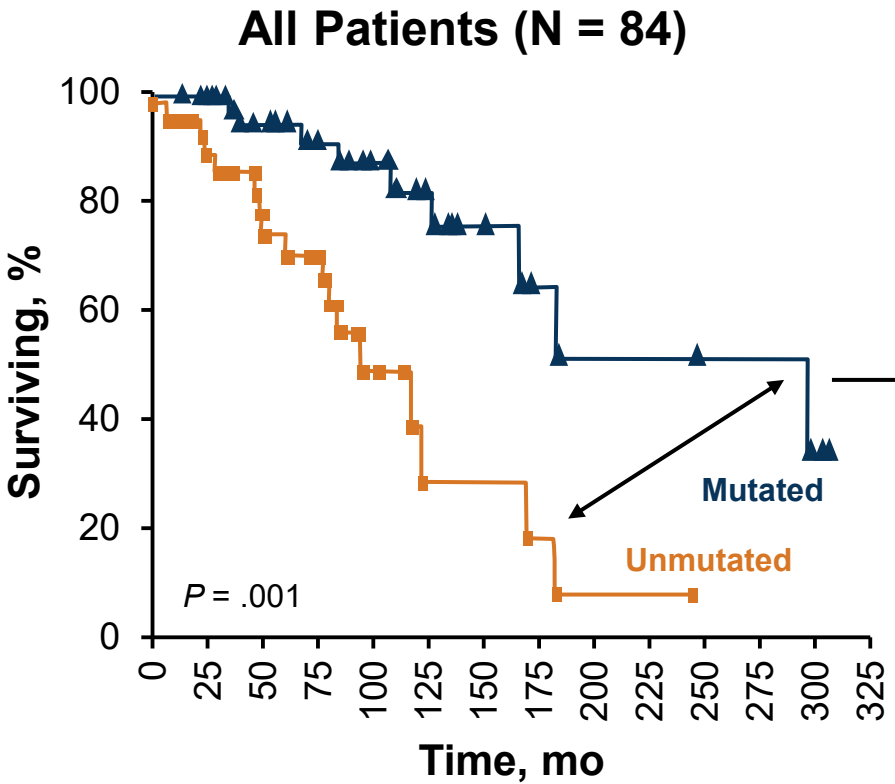


Time-limited venG achieves high uMRD rates and improved PFS; in CLL14, uMRD patients had the longest PFS (HR = 0.10)[2]

[a] Comparison done by Cochran-Mantel-Haenszel tests stratified by Binet stage and geographic region.

1. Fischer K et al. *N Engl J Med*. 2019;380:2225-2236. 2. Al-Sawaf O et al. *Lancet Oncol*. 2020;21:1188-1200.

Mutated IGHV Confers a Favorable Prognosis in CLL[1]



Mutated IGHV has long been recognized as a favorable risk factor

1. Hamblin TJ et al. *Blood*. 1999;94:1848-1854.

Nurse Consult 2: Recommendations for Sarah

Recommendations

- ✓ Counsel Sarah on her expected prognosis using appropriate tools and resources
- ✓ Educate on the risks and benefits of continuous versus fixed-duration therapy
- ✓ Given her circumstances, fixed-duration venG is likely a reasonable option

Sarah is 73 years old with a recent diagnosis of symptomatic TN CLL

- Classic B symptoms, worsening lymphadenopathy
- No major comorbid illnesses
- CrCl >60 mL/min

Testing shows

- Mutated IGHV
- **No *TP53* mutation/del(17p)**

What are the next steps?

How should Sarah be counseled on her disease and prognosis?

Continuous or fixed-duration therapy?

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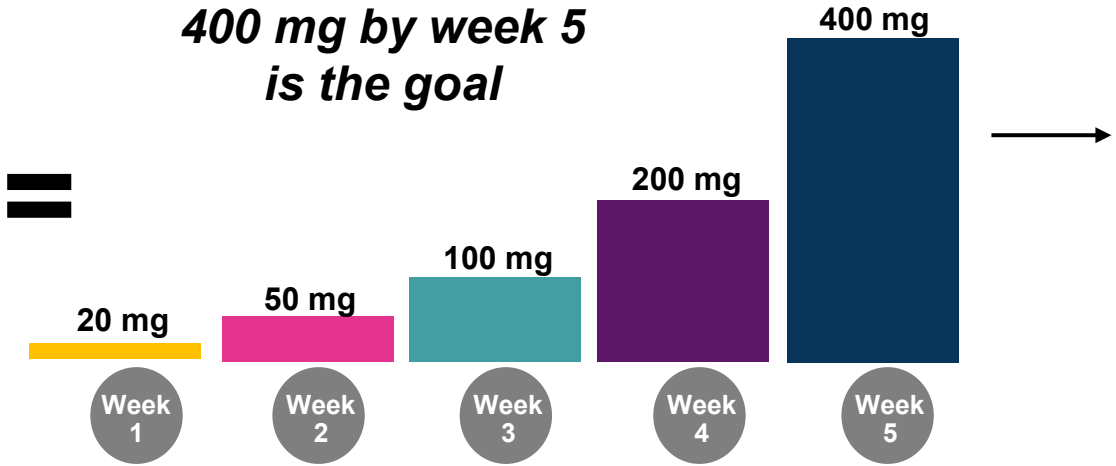
What are the next steps?

How should Sarah be counseled on her disease and prognosis?

Continuous or fixed-duration therapy?

What are the dosing and safety considerations to address?

Venetoclax Dosing and Administration
Clearly Explain the Ramp-Up Dosing Schedule[1]



When used with obinutuzumab: initiate venetoclax (according to the 5-week ramp-up dosing) cycle 1, day 22

When used with rituximab: start rituximab after the patient has completed venetoclax 5-week ramp-up dosing and the patient has received 400 mg once daily for 7 days

1. Venclexta (venetoclax) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/208573s013lbl.pdf.

Monitor for Drug–Drug Interactions: Be Prepared to Modify Venetoclax Dosing[1]

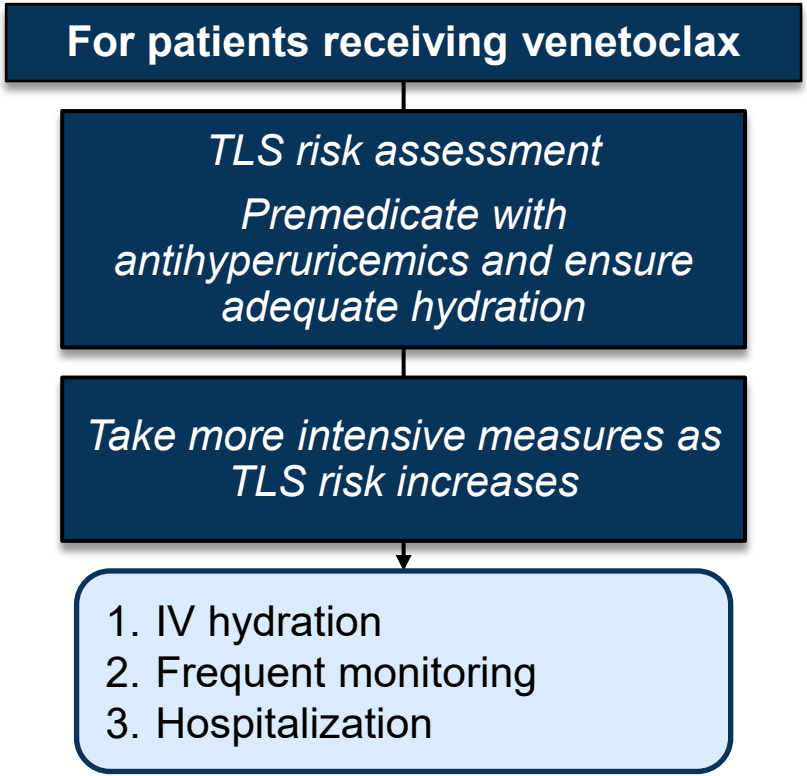
Agent	Venetoclax Dosing Modifications
Moderate CYP3A4 inhibitors	Reduce dose by 50%
Strong CYP3A4 inhibitors	Reduce dose by 75%
CYP3A4 inducers	Avoid concomitant administration; consider switching to alternative agents

1. Richard-Carpentier G, DiNardo CD. *Ther Adv Hematol*. 2019;10:2040620719882822.

TLS With Venetoclax in CLL[1,2]

- Educate patients on the signs and symptoms of hyperuricemia
- Encourage patients to limit foods/fluids containing potassium and phosphorus
- Encourage oral intake of fluids

Watch for hyperuricemia symptoms
Nausea and vomiting
Shortness of breath
Irregular heartbeat
Clouding of urine
Lethargy
Joint discomfort



1. Maloney K, Denno M. *Clin J Oncol Nurs*. 2011;15:601-603. 2. Venclexta (venetoclax) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/208573s013lbl.pdf.

Assuming Our Patient Receives Venetoclax, What Would a TLS Monitoring/Prevention Plan Look Like?[1]

Assess individual patient risk of TLS

- High burden of leukemia involvement in BM
- Elevated pretreatment LDH
- Reduced renal function
- Any LN ≥10 cm or ALC ≥25 x 10^9/L and any LN ≥5 cm

Assess blood chemistry

- Potassium, uric acid, phosphorus, calcium, and creatinine predose; 6-8 hours after each new dose during ramp-up; and 24 hours after final dose level
- Correct preexisting abnormalities prior to initiation of treatment with venetoclax

Prevention of TLS: prophylactic hydration and antihyperuricemic agents (eg, allopurinol)[2] prior to first dose of venetoclax, then continue through ramp-up phase

1. Venclexta (venetoclax) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/208573s013lbl.pdf. 2. Cairo M et al. *Br J Haematol*. 2010;149:578-586.

What Are the Current Recommendations for Hydration and Dosing of Antihyperuricemics?

Hydration	Allopurinol[1,2]	Rasburicase[3,4]
• **Low risk:** normal hydration (1.5 to 2 L daily) • **Intermediate risk:** increased hydration (3 L daily) • **High risk:** increased hydration (3 L daily to 1.5 to 2 L hourly, as tolerated)	• 200 to 400 mg/m^2 daily • Dosage should be adjusted based on renal function	• 0.2 mg/kg as a 30-minute IV infusion daily for up to 5 days • 3 or 6 mg flat doses are useful in clinical practice • No dosage adjustments required based on renal function • Dosing beyond 5 days or administration of ≥1 course not recommended

1. Baldini S et al. *Blood.* 2014;124:5979. 2. Aloprim (allopurinol sodium) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2000/020298Orig1s001.pdf. 3. Trifilio SM et al. *Bone Marrow Transplant*. 2011;46:800-805. 4. Elitek (rasburicase) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/103946s5083lbl.pdf.

Venetoclax: Other AEs of Interest

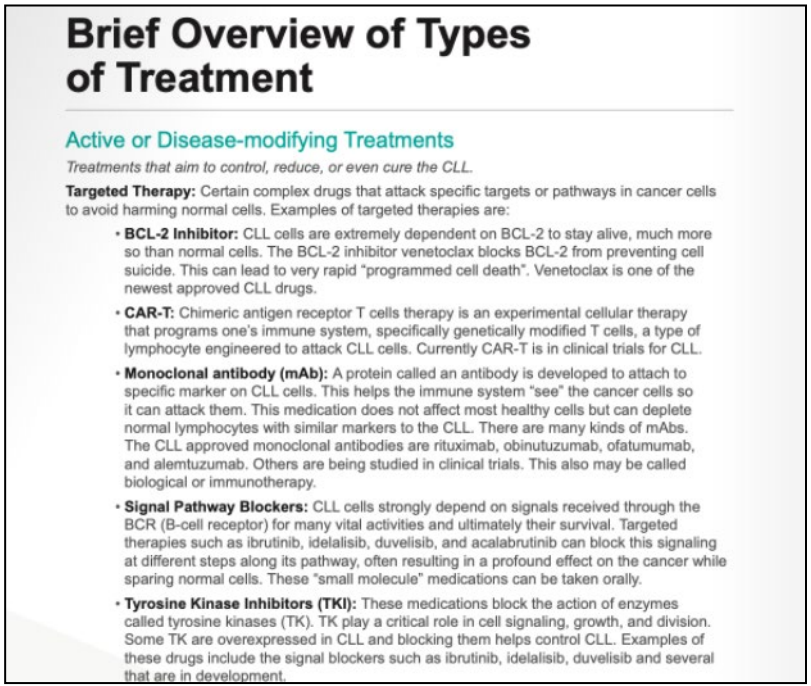
- **Myelosuppression: manage with dose interruption/reduction**
  - For grade ≥3 neutropenia, consider G-CSF and/or antibiotics
- **GI events (diarrhea/nausea)[1,2]**
- **Infection (upper respiratory most common)[1,2]**
- **Autoimmune hemolytic anemia in 7% with monotherapy[1]**
- **Joint pain (12%)**

1. Stilgenbauer S et al. *Lancet Oncol.* 2016;17:768-778. 2. Seymour JF et al. *N Engl J Med*. 2018;378:1107-1120.

Free CLL Society Patient Education Toolkit Binder for Healthcare Providers

- CLL Society is pleased to offer this CLL/SLL Patient Education Toolkit to nurses, which provides valuable handouts across a variety of topics that you can share with patients
- Can be used to explain efficacy and safety information
- Learn more and order at: https://cllsociety.org/patient-education-toolkit/

Includes information on targeted agent classes for use in CLL



Brief Overview of Types of Treatment

Active or Disease-modifying Treatments

Treatments that aim to control, reduce, or even cure the CLL.

Targeted Therapy: Certain complex drugs that attack specific targets or pathways in cancer cells to avoid harming normal cells. Examples of targeted therapies are:

- **BCL-2 Inhibitor:** CLL cells are extremely dependent on BCL-2 to stay alive, much more so than normal cells. The BCL-2 inhibitor venetoclax blocks BCL-2 from preventing cell suicide. This can lead to very rapid "programmed cell death". Venetoclax is one of the newest approved CLL drugs.
- **CAR-T:** Chimeric antigen receptor T cells therapy is an experimental cellular therapy that programs one's immune system, specifically genetically modified T cells, a type of lymphocyte engineered to attack CLL cells. Currently CAR-T is in clinical trials for CLL.
- **Monoclonal antibody (mAb):** A protein called an antibody is developed to attach to specific marker on CLL cells. This helps the immune system "see" the cancer cells so it can attack them. This medication does not affect most healthy cells but can deplete normal lymphocytes with similar markers to the CLL. There are many kinds of mAbs. The CLL approved monoclonal antibodies are rituximab, obinutuzumab, ofatumumab, and alemtuzumab. Others are being studied in clinical trials. This also may be called biological or immunotherapy.
- **Signal Pathway Blockers:** CLL cells strongly depend on signals received through the BCR (B-cell receptor) for many vital activities and ultimately their survival. Targeted therapies such as ibrutinib, idelalisib, duvelisib, and acalabrutinib can block this signaling at different steps along its pathway, often resulting in a profound effect on the cancer while sparing normal cells. These "small molecule" medications can be taken orally.
- **Tyrosine Kinase Inhibitors (TKI):** These medications block the action of enzymes called tyrosine kinases (TK). TK play a critical role in cell signaling, growth, and division. Some TK are overexpressed in CLL and blocking them helps control CLL. Examples of these drugs include the signal blockers such as ibrutinib, idelalisib, duvelisib and several that are in development.

Delivering Optimized Sequential and Combination Therapy and Next Steps for Nurses in CLL Care

Nurse Consult 3: Options for a CLL Patient After Multiple Relapses

John is a 69-year-old patient with CLL who was initially treated with acalabrutinib after meeting criteria for treatment initiation

- Responded well for 4 years
- Subsequently experienced disease progression and treated with venetoclax/rituximab (MURANO regimen)
- After a second relapse, he starts therapy with a PI3Ki—but rapidly progresses

Testing shows

- Unmutated IGHV
- No *TP53* mutation/del(17p)

Would additional therapy with a covalent BTKi or venetoclax be useful?

Or should newer options be considered?

In Current Guidelines, BTK Inhibitors and Venetoclax Regimens Are Preferred Options for R/R CLL…

NCCN Recommendations for Second-Line and Subsequent Therapy, No del(17p)/*TP53* Mutations[1]

Patients aged ≥65 y OR Patients aged <65 y with significant comorbidities (CrCl <70 mL/min)	• Acalabrutinib (category 1) • Ibrutinib (category 1) • Venetoclax + rituximab (category 1) • Zanubrutinib
Patients aged <65 y without significant comorbidities	• Acalabrutinib (category 1) • Ibrutinib (category 1) • Venetoclax + rituximab (category 1) • Zanubrutinib

Single-agent venetoclax, idelalisib (+ rituximab), and duvelisib are among the other targeted options recommend

1. NCCN Clinical Practice Guidelines in Oncology. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Version 2.2022. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf.

… Including in High-Risk Settings

NCCN Recommendations for CLL With del(17p)/*TP53* Mutations[1]

Second-Line and Subsequent Therapy	
Preferred Regimens	**Other Recommended Regimens**
• Acalabrutinib (category 1) • Ibrutinib (category 1) • Venetoclax + rituximab (category 1) • Venetoclax) • Zanubrutinib	• Alemtuzumab ± rituximab • Duvelisib • HDMP + rituximab • Idelalisib ± rituximab • Lenalidomide ± rituximab • Obinutuzumab

Chemoimmunotherapy is NOT recommended

1. NCCN Clinical Practice Guidelines in Oncology. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Version 2.2022. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf.

Planning for Sequential Treatment in CLL

If you start with …	… and progression occurs …	… then consider
A covalent BTK inhibitor	▶	Venetoclax[1]
Fixed-duration venetoclax + CD20 antibody	▶	BTK inhibitors[2,3]

1. Jones JA et al. *Lancet Oncol*. 2018;19:65-75. 2. Mato AR et al. *Clin Cancer Res*. 2020;26:3589-3596. 3. Harrup RA et al. ASH 2020. Abstract 3139.

Planning for Sequential Treatment in CLL (Cont'd)

For patients unable to tolerate ibrutinib …	▶	Consider sequencing to a more selective covalent BTKi (acalabrutinib or zanubrutinib) or venetolax[1-3,a]
What about "double-refractory" disease?	▶	A more challenging setting with few approved options

Note: In the setting of progression on a covalent BTKi, sequencing to another covalent BTKi is unlikely to be effective

[a] Zanubrutinib is off-label for CLL but is included in the NCCN Guidelines exactly for these circumstances.

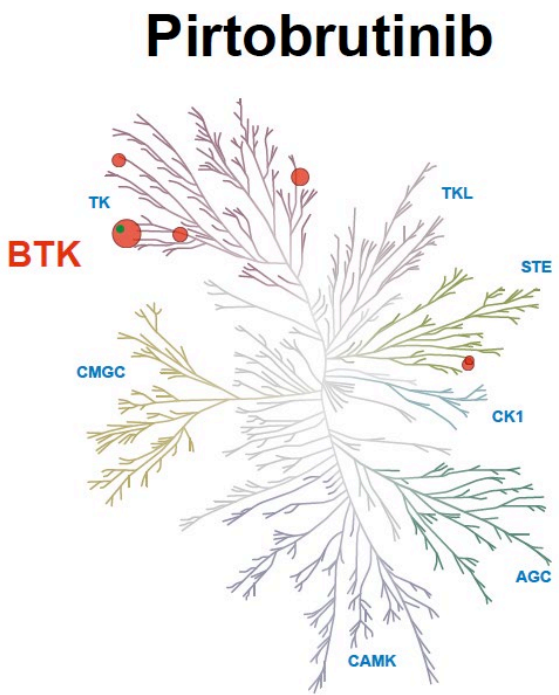
1. Jones JA et al. *Lancet Oncol*. 2018;19:65-75. 2. Rogers KA et al. *Haematologica*. 2021;106:2364-2373. 3. Shadman M et al. ASH 2020. Abstract 2947.

What Strategies Can We Use in Heavily Pretreated or Double-Refractory CLL?

Potential Benefits	Unlikely to Benefit
• **Noncovalent BTK inhibitors:** initial evidence suggests potent efficacy against resistance mutations and in the setting of progressive disease • **CAR-T therapy:** highly active in pretreated CLL	• **PI3K inhibitors:** limited benefit in this population and significant toxicity burden • **Chemoimmunotherapy:** limited benefit in this population • **Covalent BTKi:** patients have already progressed on these agents

Pirtobrutinib[1]

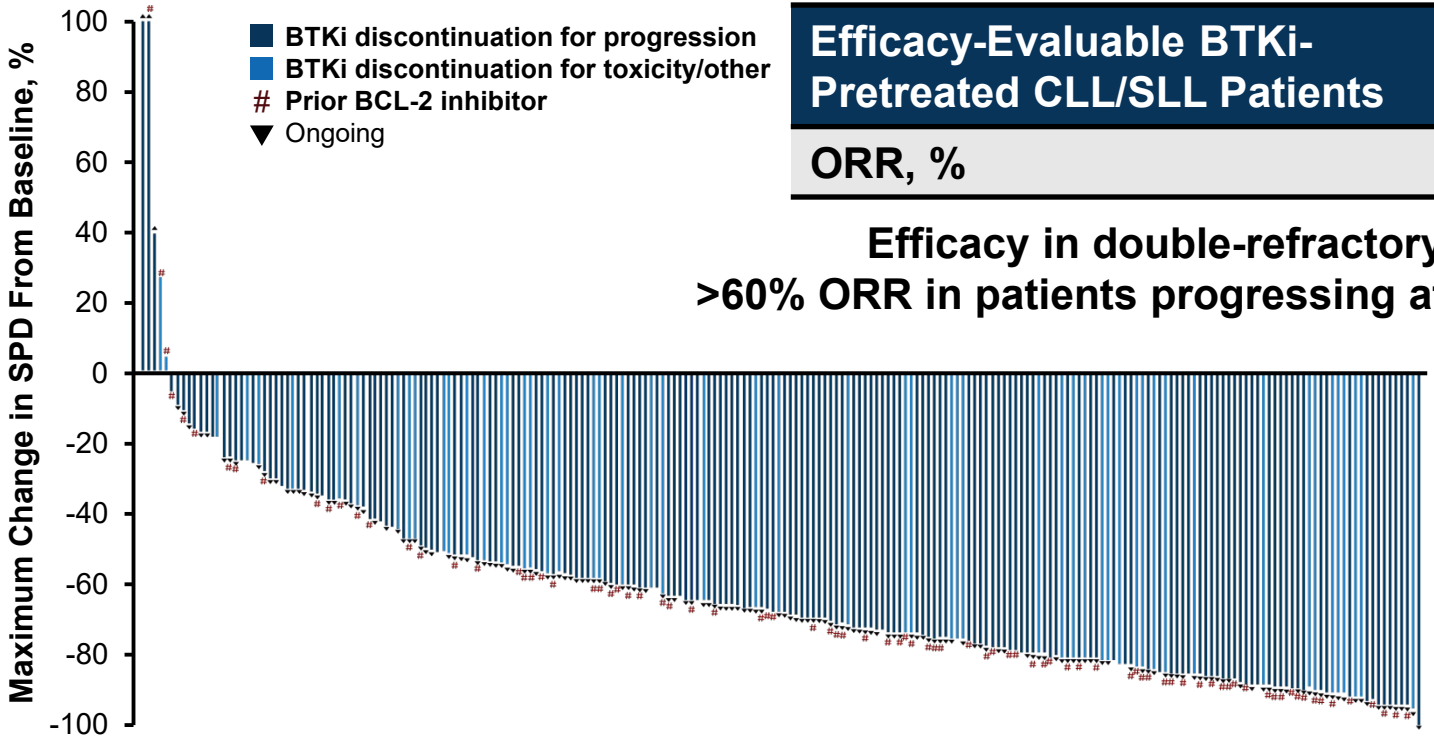
- Pirtobrutinib is a noncovalent, reversible BTK inhibitor
- Highly selective, reducing the potential for off-target toxicities
- Active against *BTK* resistance mutations (eg, C481S)
- Recommended dosage from clinical trials: 200 mg daily



More selective/less off-target effects

1. Mato AR et al. *Lancet*. 2021;397:892-901.

Results From the BRUIN Trial Show Pirtobrutinib Is Active in R/R CLL/SLL[1]



Efficacy-Evaluable BTKi-Pretreated CLL/SLL Patients	N = 252
ORR, %	68

Efficacy in double-refractory disease:
>60% ORR in patients progressing after BTKi + BCL-2i

1. Mato AR et al. ASH 2021. Abstract 391.

Most Data Show That Pirtobrutinib Has a Low Rate of BTK-Mediated AEs

Safety Summary From Longer Follow-Up of the BRUIN Trial (N = 618)[1]

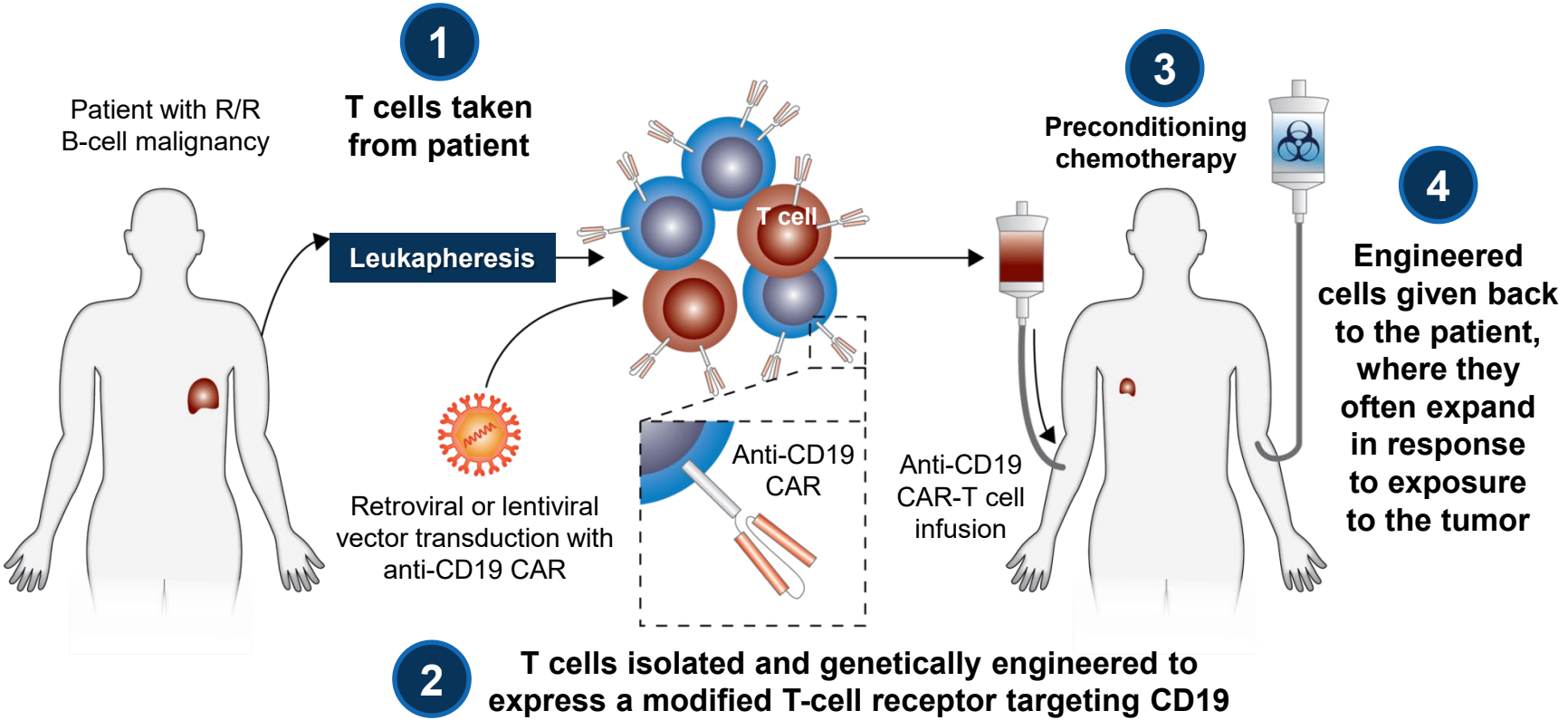
	Treatment-Emergent AEs (≥15%), %				
	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade
Adverse event					
Fatigue	13	8	1	–	23
Diarrhea	15	4	<1	<1	19
Neutropenia[a]	1	2	8	6	18
Contusion	15	2	–	–	17
Adverse events of special interest[b]					
Bruising[c]	20	2	–	–	22
Rash[d]	9	2	<1	–	11
Arthralgia	8	3	<1	–	11
Hemorrhage[e]	5	2	1[g]	–	8
Hypertension	1	4	2	–	7
AF/flutter[f]	–	1	<1	<1	2[h]

[a] Aggregate of neutropenia and neutrophil count decreased. [b] AEs of special interest are those that were previously associated with covalent BTK inhibitors. [c] Aggregate of contusion, petechiae, ecchymosis, and increased tendency to bruise. [d] Aggregate of all preferred terms, including rash. [e] Aggregate of all preferred terms, including hematoma or hemorrhage. [f] Aggregate of atrial fibrillation and atrial flutter. [g] Represents 6 events (all grade 3), including 2 cases of postoperative bleeding; 1 case each of GI hemorrhage in the setting of sepsis, NSAID use, and chronic peptic ulcer disease; and 1 case of subarachnoid hemorrhage in the setting of traumatic bike accident. [h] Of 10 total AF/atrial flutter TEAEs, 3 occurred in patients with a prior medical history of AF, 2 in patients presenting with concurrent systemic infection, and 2 in patients with both.

1. Mato AR et al. ASH 2021. Abstract 391.

Assessing the CAR-T Option in CLL

Overview of CAR-T Cell Therapy[1,2]



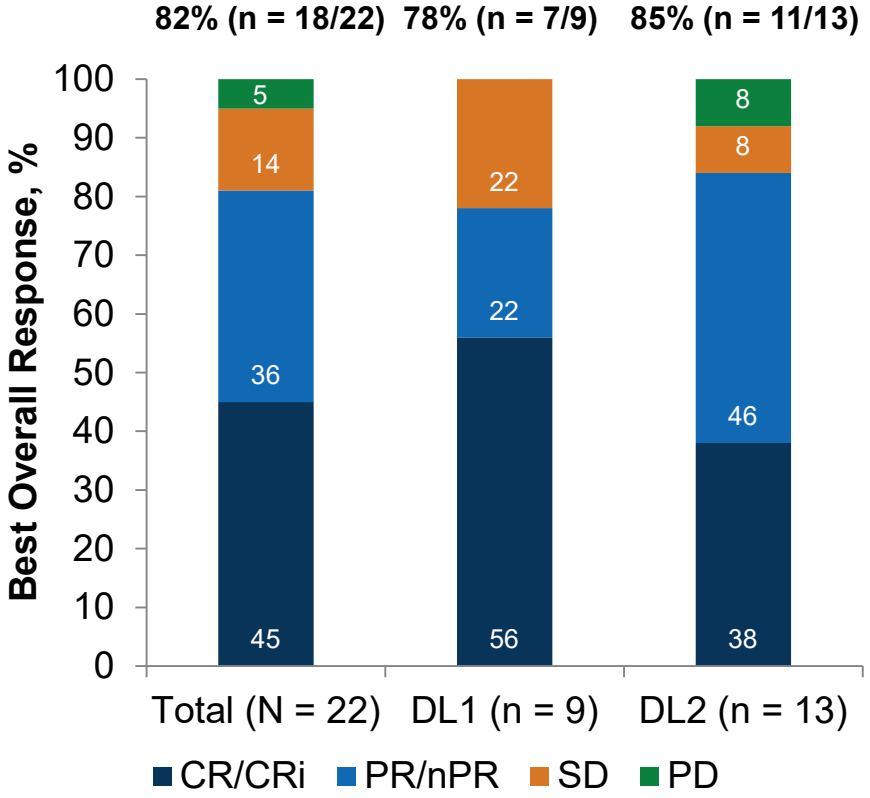
1. https://labiotech.eu/immuno-oncology-history-car-t-nyt/. 2. Levine BL. *Cancer Gene Ther*. 2015;22:79-84.

Robust Efficacy of Liso-Cel in Pretreated CLL Patients[1]

In the TRANSCEND CLL 004 trial, patients

- **Failed or were ineligible for BTKi**
- **Had high-risk disease: failed ≥2 prior therapies**
- **Had standard-risk disease: failed ≥3 prior therapies**

In this heavily pretreated population: high rates of response (82% ORR)



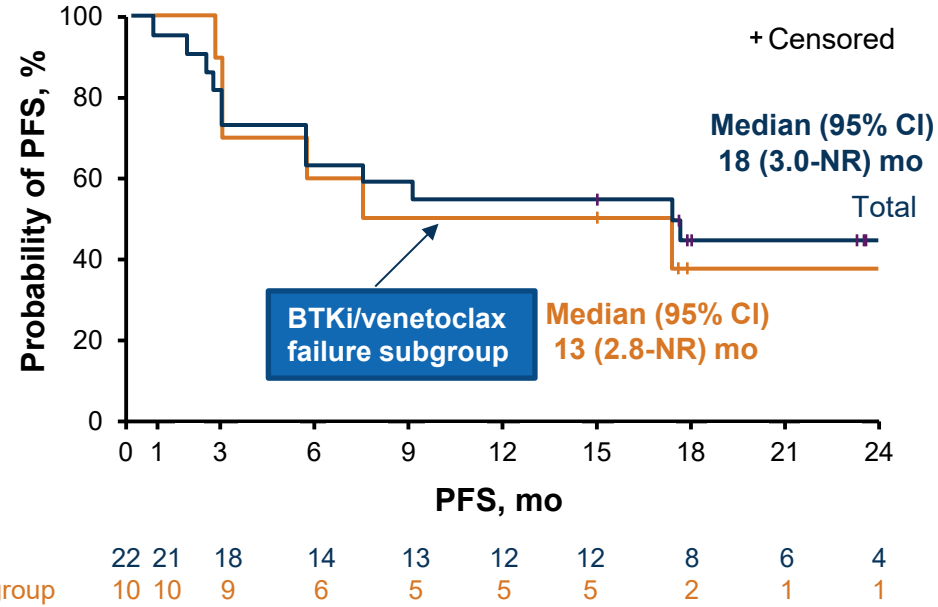
1. Siddiqi T et al. *Blood*. 2022;139:1794–1806.

Robust Efficacy of Liso-Cel in Pretreated CLL Patients[1] (Cont'd)

In the TRANSCEND CLL 004 trial, patients

- **Failed or were ineligible for BTKi**
- **Had high-risk disease: failed ≥2 prior therapies**
- **Had standard-risk disease: failed ≥3 prior therapies**

In this heavily pretreated population: median PFS of 18 months (13 months in double-refractory patients)



1. Siddiqi T et al. *Blood*. 2022;139:1794–1806.

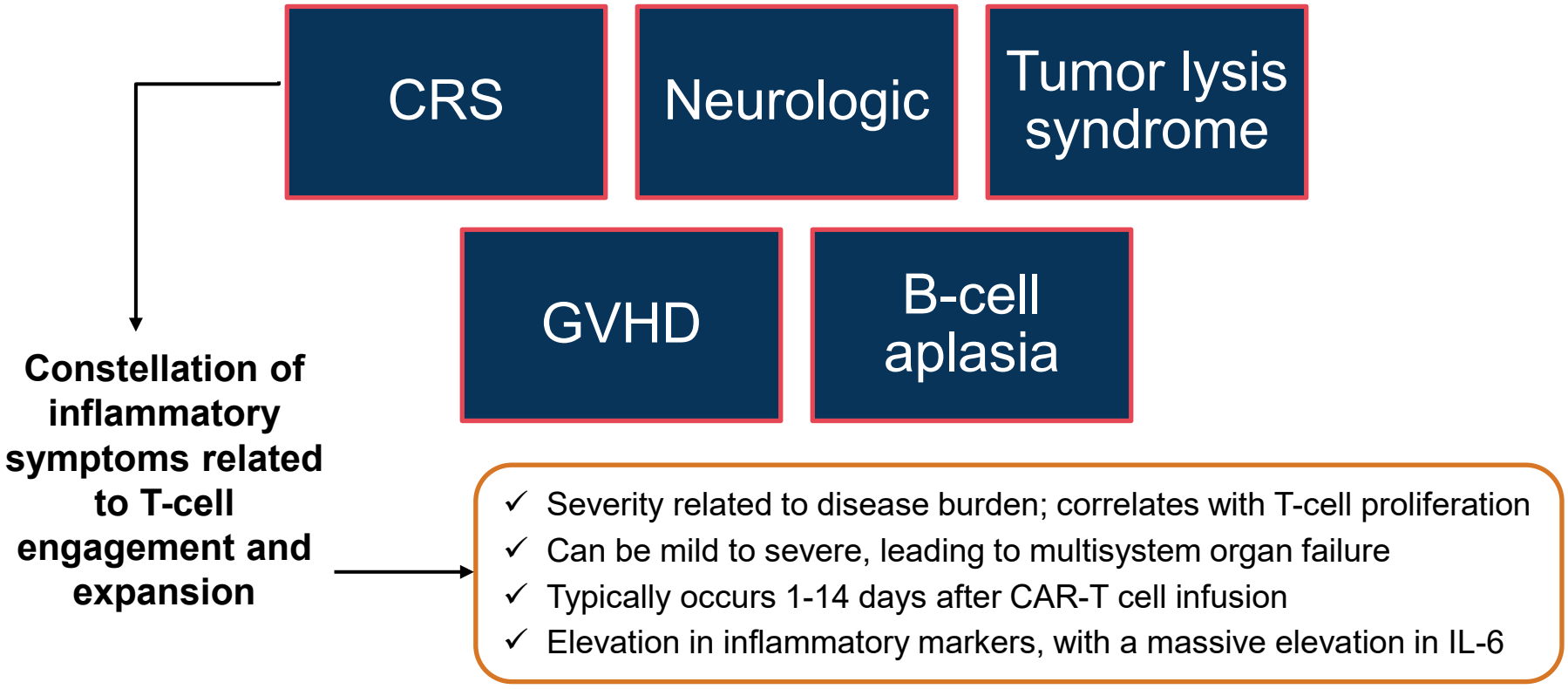
Treatment-Emergent AEs With Liso-Cel Included CRS and Neurologic Toxicity[1]

- No late or delayed AEs of concern have emerged with longer follow-up

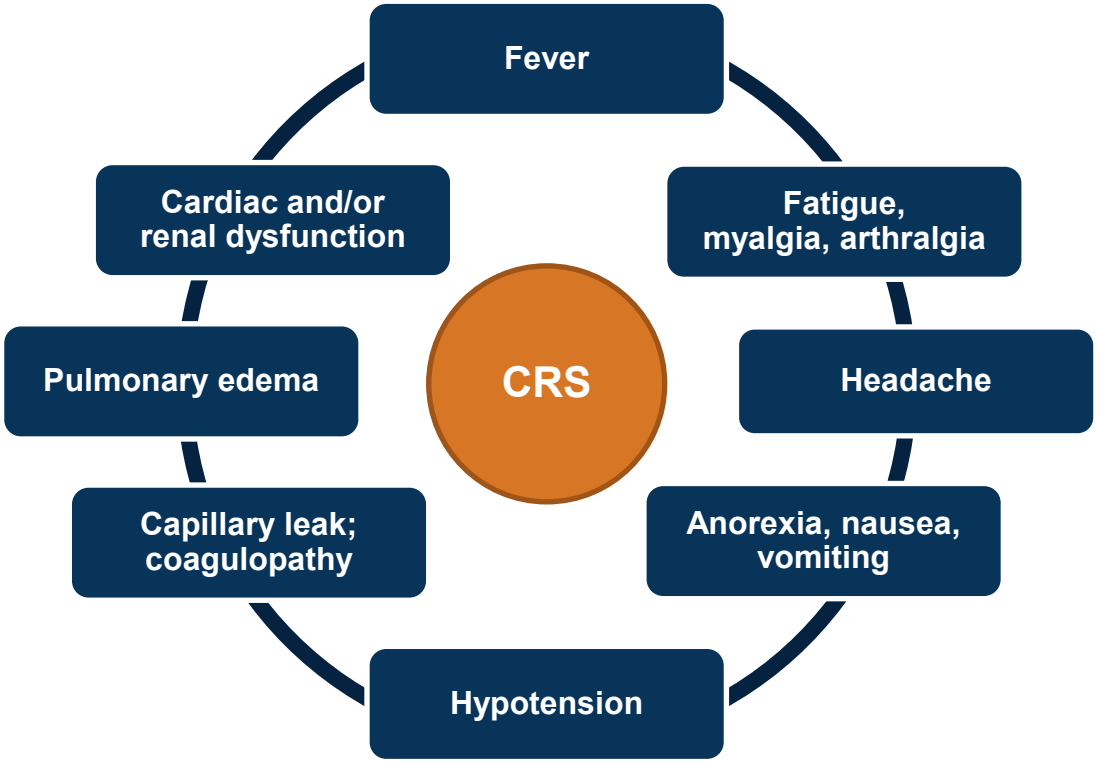
Parameter	Monotherapy Cohort (N = 23)	BTKi Progression/Venetoclax Failure Subgroup (n = 11)
Common grade 3/4 TEAEs, n (%)		
Anemia	17 (74)	7 (64)
Thrombocytopenia	16 (70)	6 (55)
Neutropenia/neutrophil count decrease	16 (70)	8 (73)
Leukopenia	10 (43)	2 (18)
CRS		
All-grade CRS, n (%)	17 (74)	7 (64)
Median time to CRS onset, days (range)	3 (1-10)	1 (1-10)
Median duration of CRS, days (range)	12 (2-50)	15 (5-50)
Grade 3 CRS, n (%)	2 (9)	2 (18)
NEs		
All-grade NEs, n (%)	9 (39)	5 (46)
Median time to NE onset, days (range)	4 (2-21)	4 (2-21)
Median duration of NE, days (range)	20.5 (6-50)	38 (6-50)
Grade ≥3 NEs, n (%)	5 (22)	3 (27)

1. Siddiqi T et al. ASH 2020. Abstract 546.

Overview of CAR-T Cell Therapy Adverse Events



Take-Homes on Managing CRS[1]

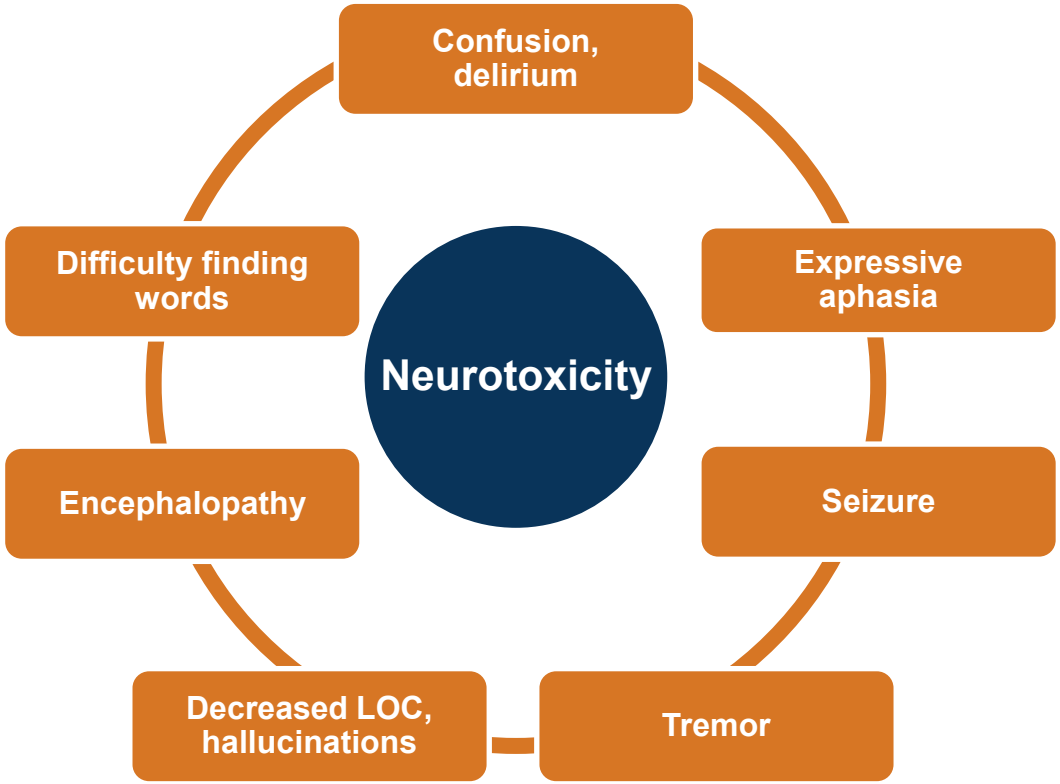


- **Goal:** prevent multisystem organ failure but do not stop the CAR-T cells from working
- **Treatment**
  - Supportive care
  - Tocilizumab: monoclonal antibody to IL-6 receptor; blocks IL-6–mediated inflammatory effects
  - Steroids (if no improvement with tocilizumab)

1. Lee DW et al. *Blood*. 2014;124:188-195.

Neurotoxicity[1,2]

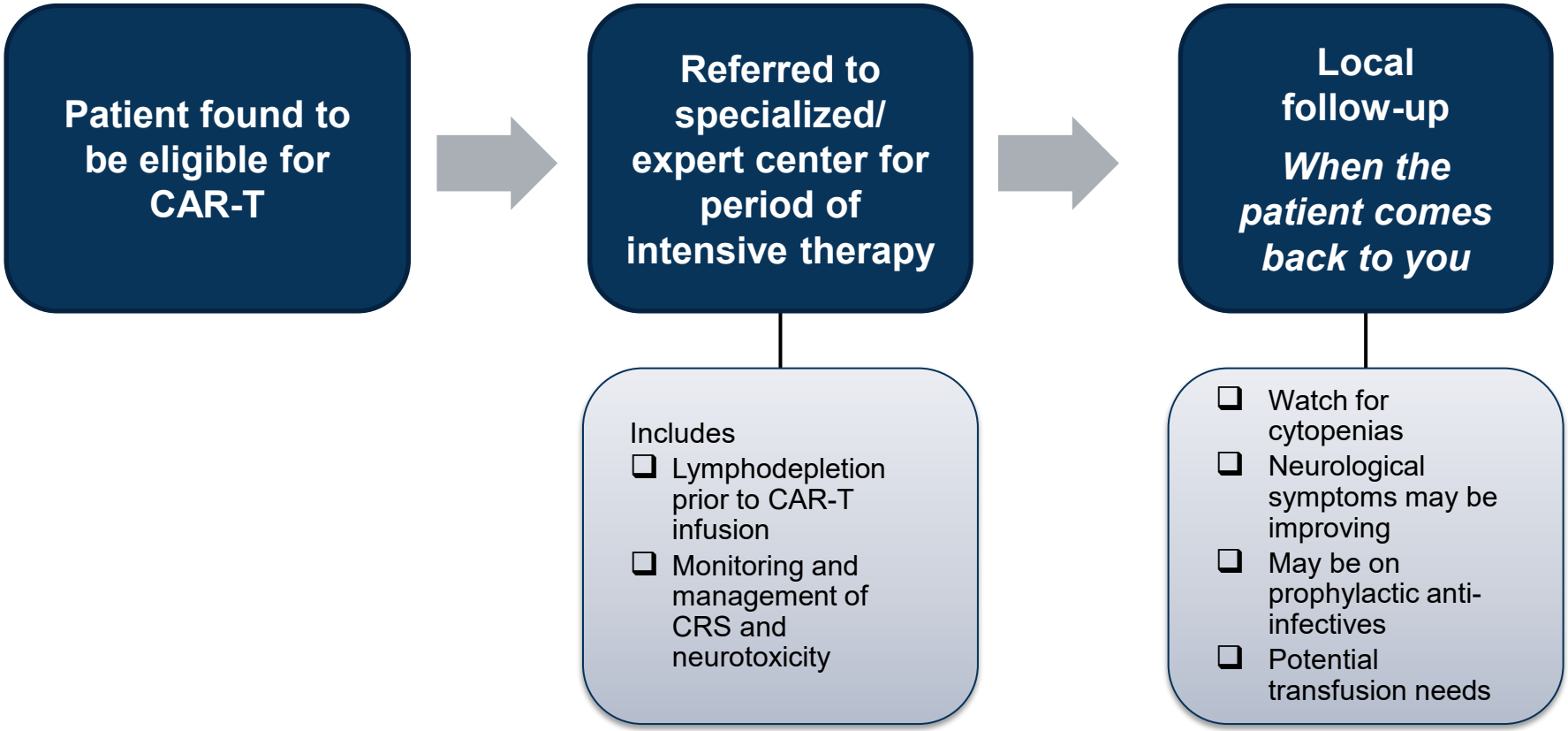
- **Cause: unclear**
  - Cytokine mediated
  - T-cell mediated
- **Risk factors: unclear**
  - High disease burden
  - Concurrent CRS
- **Treatment**
  - Supportive care
  - Levetiracetam



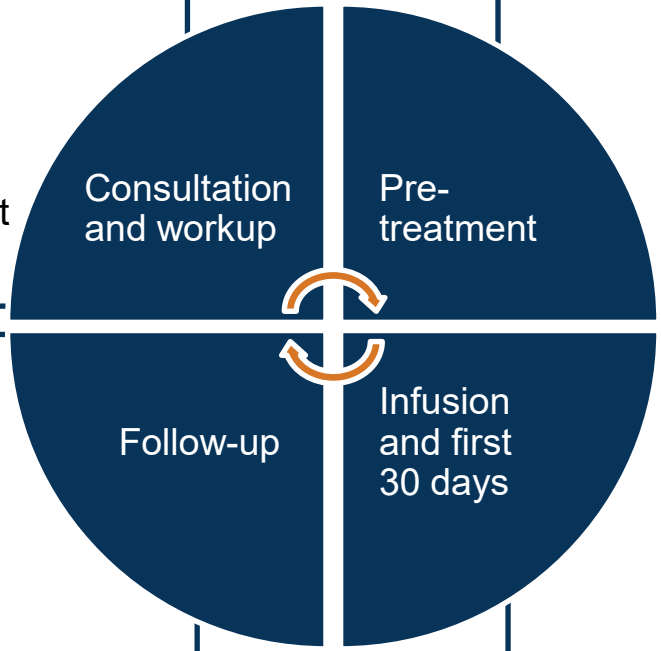
1. Maude SL et al. *Blood*. 2015;125:4017-4023. 2. Bonifant CL et al. *Mol Ther Oncolytics*. 2016;3:16011.

What Would the CAR-T Process Look Like in CLL?

Based on the NHL Experience …



Get to Know the CAR-T Management Team



- CAR-T MD
- **CAR-T nurse coordinator**
- Financial services
- Social work
- Education specialist

- CAR-T MD and coordinator
- Manufacturer
- Apheresis
- Cell therapy lab
- **Outpatient nurses and infusion center**

- CAR-T MD
- **CAR-T nurse coordinator**
- **Outpatient nurses**
- Referring MD/staff

- CAR-T inpatient team
- Pharmacists
- Cell therapy lab
- **Inpatient and outpatient nurses**
- Neurology, CCM, ED
- Nutrition, PT

Research
- Sponsors and affiliates
- PI
- **Nurse coordinator**
- CRA
- Data
- Regulatory

Other
- Schedulers
- Lodging
- Data: FACT, CIBMTR

Nurse Consult 3: Recommendations for John

Recommendations

- ✓ Be honest: In John's case, it's unlikely conventional options are going to be useful
- ✓ Educate on the potential of clinical trial therapy
- ✓ Offer resources for trial enrollment/information
- ✓ Trial-based options could include CAR-T therapy (eg, liso-cel) or noncovalent BTKi (pirtobrutinib)

John is a 69-year-old patient with CLL who was initially treated with acalabrutinib after meeting criteria for treatment initiation

- Responded well for 4 years
- Subsequently experienced disease progression and treated with venetoclax/rituximab (MURANO regimen)
- After a second relapse, he starts therapy with a PI3Ki—but rapidly progresses

Testing shows

- Unmutated IGHV
- No *TP53* mutation/del(17p)

Would additional therapy with a covalent BTKi or venetoclax be useful?

Or should newer options be considered?

Use patient-appropriate tools to educate on the potential of novel modalities such as CAR-T

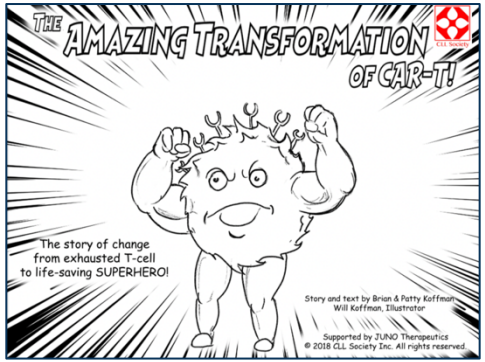
CLL Society Tools for Patient Education: *Resources for Understanding CAR-T Therapy*

Talk to your patients: CLL Society offers dedicated CAR-T resources, available at: www.cllsociety.org/CAR-T

- Extensive resource library
- CAR-T blog
- 1-page informational brochure
- CAR-T comic book

Welcome to the CAR-T Resource Library

Free CAR-T Therapy Brochure for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) Patients



The CAR-T Blog

Coming Full Circle: How to Prepare for the Future of CLL Care

Many Studies Are Testing BTKi and Venetoclax Combinations

CAPTIVATE[1]

- Assessed fixed-duration and MRD-guided ibrutinib/venetoclax

→ High rates of uMRD with fixed-duration therapy, including in patients with high-risk disease features

GLOW was a phase 3 trial of fixed-duration ibrutinib/venetoclax[2]

→ Improved PFS and CR with fixed-duration ibrutinib and venetoclax versus CIT

Triplets combining multiple novel agents are also being tested

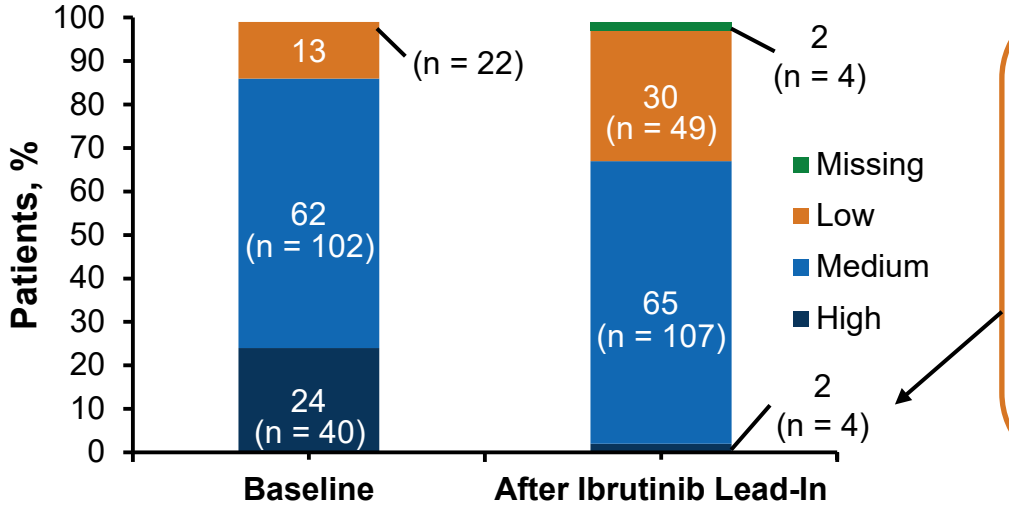
→ Ibrutinib, acalabrutinib, or zanubrutinib plus venetoclax and obinutuzumab

1. Wierda W et al. iwCLL 2021. 2. Kater A et al. EHA 2021. Abstract LB1902.

The Early Experience With Ibrutinib/Venetoclax: Reductions in TLS Risk Through Effective Debulking

- In the CAPTIVATE trial, the safety profile of ibrutinib/venetoclax was consistent with known AEs for each agent alone (no new safety signals observed)[1]
- **Debulking with lead-in ibrutinib reduced the severity of TLS**

Impact of single-agent ibrutinib lead-in on TLS risk category



Three cycles of single-agent ibrutinib reduced TLS risk category in 90% of patients with high baseline risk and only 2% remained in the high-risk category before initiation of venetoclax ramp-up

1. Wierda W et al. *J Clin Oncol*. 2021;39:3853-3865.

What Does This Mean for Nurses? How Can Nurses Prepare for Novel Combinations?

- **Different issues may arise with BTKi/venetoclax combinations**
  - Two distinct AE profiles—be prepared for both or newer, more severe manifestations (particularly with triplets)
  - Financial assistance programs may be available, many resources can help (CLL Society)

- **Educate patients and caregivers**
  - They will have questions as they experience these newer modalities
  - They will ask you questions they don't ask doctors—be prepared and know how to answer and where to direct queries

Take-Homes

- The CLL treatment landscape continues to change quickly: be adaptable and use the skills we've learned over years of using novel therapy in CLL
- Newer drugs are coming, including within existing drug classes
- Be prepared for unique modalities: CAR-T therapy
- Newer targeted combinations will change our focus, so stay vigilant and be prepared

Audience Q&A

PeerView
Live

Please remember to complete and submit your Post-Test and Evaluation for CE credit.

PeerView.com/CLL-Survey-QWZ

Thank you and have a good day.

PeerView
Live

Abbreviations

AF: atrial fibrillation

AKI: acute kidney injury

ALC: absolute lymphocyte count

ALL: acute lymphocytic leukemia

ASO: antisense oligonucleotide

axi-cel: axicabtagene ciloleucel

BCL-2: B cell lymphoma 2

BCL-2i: B cell lymphoma 2 inhibitor

BM: bone marrow

BR: bendamustine plus rituximab

brexu-cel: brexucabtagene autoleucel

BTK: Bruton tyrosine kinase

BTKi: Bruton tyrosine kinase inhibitor

CAR: chimeric antigen receptor

CAR-T: chimeric antigen receptor T cell

Cbl: chlorambucil

CCM: certified case manager

CD19: cluster of differentiation 19

CIBMTR: Center for International Blood and Marrow Transplant Research

CIRS: Cumulative Illness Rating Scale

CIT: chemoimmunotherapy

CLL: chronic lymphocytic leukemia

COVID-19: coronavirus disease 2019

CR: complete response

CRA: clinical research associate

CrCl: creatinine clearance

CRi: complete remission with incomplete hematologic recovery

CRP: C-reactive protein

CRS: cytokine-release syndrome

Abbreviations

CYP3A: cytochrome P3A

del(17p): deletion 17p

DIC: disseminated intravascular coagulation

DL1: dose level 1

DL2: dose level 2

EOT: end of treatment

FACT: Foundation for the Accreditation of Cellular Therapy

FCR: fludarabine, cyclophosphamide, and rituximab

FL: follicular lymphoma

G: obinutuzumab

G-CSF: granulocyte colony-stimulating factor

GVHD: graft-versus-host disease

HTN: hypertension

I: ibrutinib

IGHV: immunoglobulin heavy-chain gene

IL-6: interleukin 6

IR: ibrutinib + rituximab

iwCLL: International Workshop on Chronic Lymphocytic Leukemia

LDH: lactate dehydrogenase

liso-cel: lisocabtagene maraleucel

LN: lymph node

LOC: level of consciousness

MCL: mantle cell lymphoma

MRD: minimal residual disease

NCCN: National Comprehensive Cancer Network

NE: not evaluable

NGS: next-generation sequencing

NHL: non-Hodgkin lymphoma

nPR: nodular PR

Abbreviations

NR: not reached

O-Clb: obinutuzumab plus chlorambucil

ORR: overall response rate

P-gp: P-glycoprotein

PB: peripheral blood

PD: progressive disease

PI3K: phosphatidylinositol-4,5-bisphosphate 3-kinase

PI3Ki: phosphatidylinositol-4,5-bisphosphate 3-kinase inhibitor

PLT: platelet

PPI: proton pump inhibitor

PR: partial response

PT: physical therapy

R/R: relapsed/refractory

SD: stable disease

SLL: small lymphocytic lymphoma

TEAE: treatment-emergent adverse event

tisagen: tisagenlecleucel

TLS: tumor lysis syndrome

TN: treatment naïve

TP53: tumor protein 53

uMRD: undetectable minimal residual disease

VenG: venetoclax plus obinutuzumab