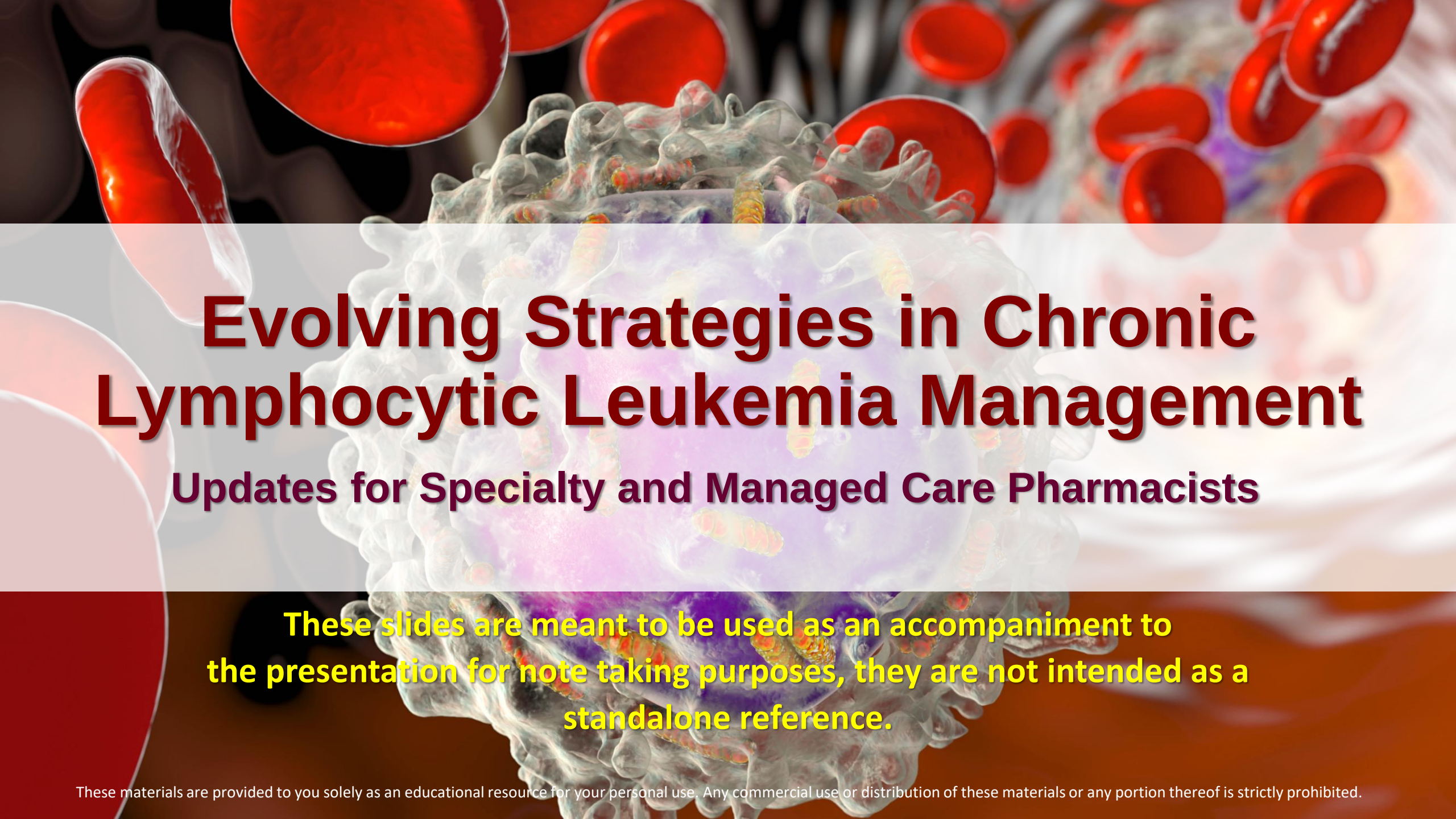
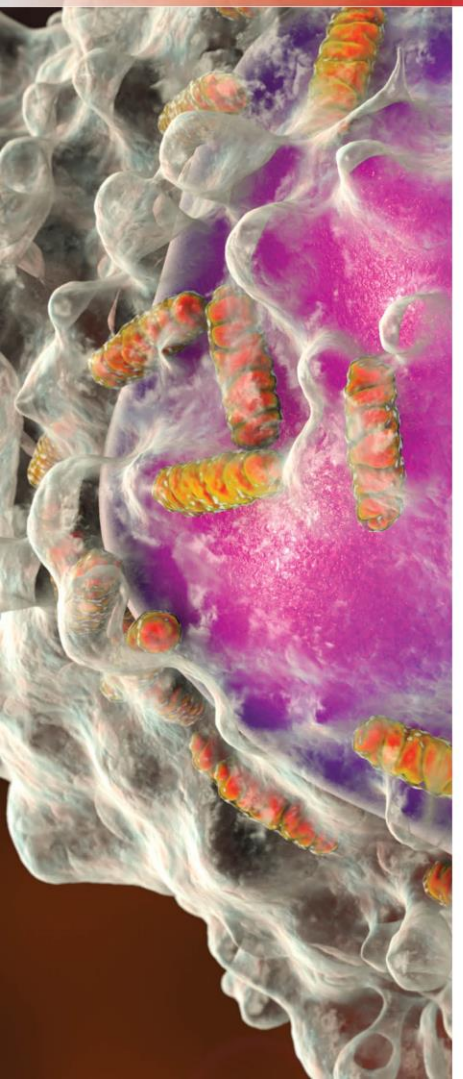


Evolving Strategies in Chronic Lymphocytic Leukemia Management

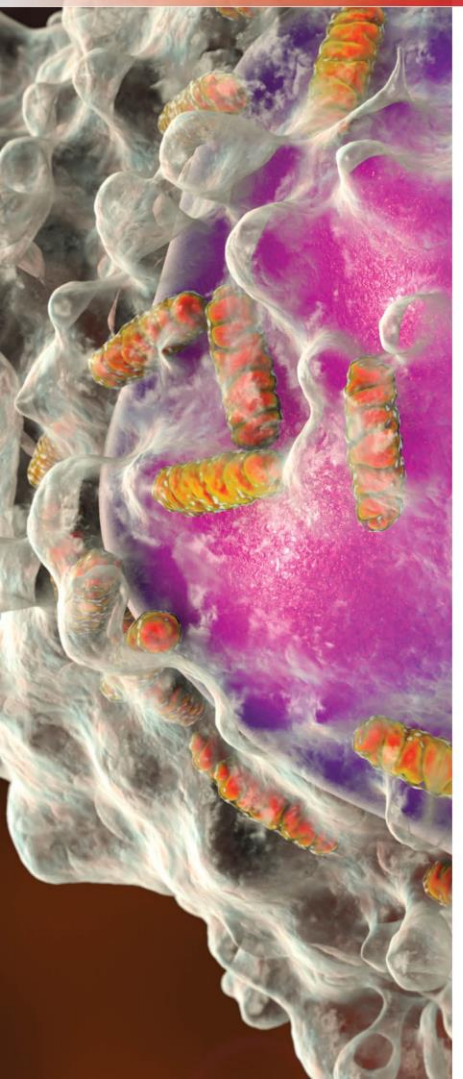
Updates for Specialty and Managed Care Pharmacists

These slides are meant to be used as an accompaniment to the presentation for note taking purposes, they are not intended as a standalone reference.

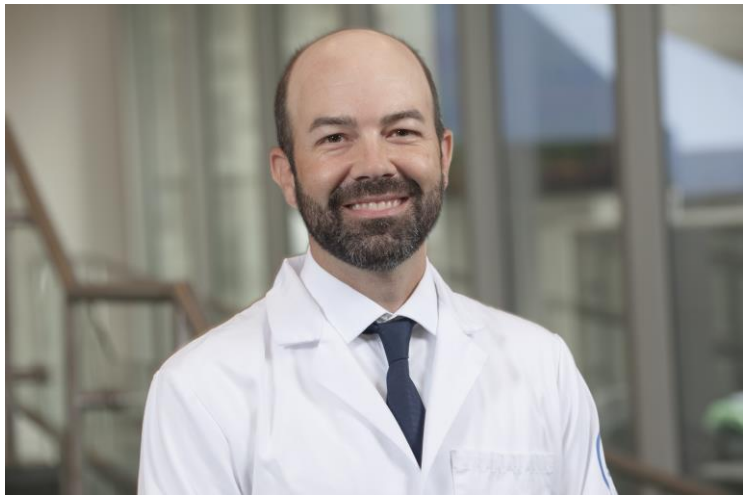


This educational activity is sponsored by Postgraduate Healthcare Education, LLC and is supported by an educational grant from AbbVie and BeiGene

Faculty

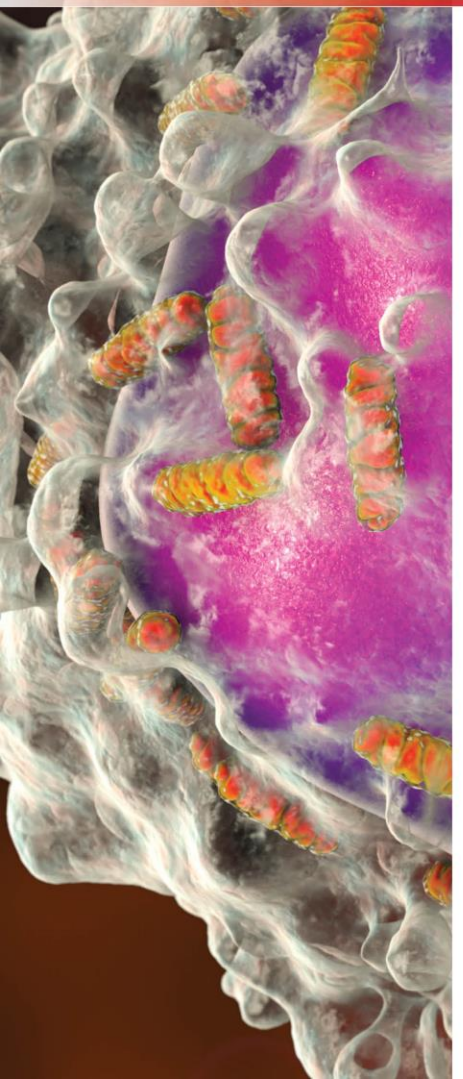


Ryan J. Daley, PharmD, BCOP
Clinical Pharmacy Specialist, Adult Leukemia Services
Memorial Sloan Kettering Cancer Center
New York, NY



Dr. Daley has worked as a Clinical Pharmacy Specialist and Preceptor in Leukemia at Memorial Sloan Kettering Cancer Center since 2013. He received his Doctor of Pharmacy degree from SUNY at Buffalo and completed two ASHP-accredited residencies: a PGY1 Pharmacy Practice Residency at the University of Vermont Medical Center, and a PGY2 Oncology Pharmacy Residency at The University of Texas MD Anderson Cancer Center. Dr. Daley is Board Certified in Oncology Pharmacy and is a member of the Pharmacy Committee for the national cooperative group, The Alliance for Clinical Trials in Oncology.

Disclosures



Dr. Daley has disclosed that he serves as a consultant for Da Volterra (Paris, France) and owns stock in Aprea Therapeutics Inc.

The clinical reviewer, Megan May, PharmD, BCOP has no relevant affiliations or financial relationships with a commercial interest to disclose.

Susanne Batesko, MSHE, BSN, RN, Robin Soboti, RPh, and Susan R. Grady, MSN, RN, as well as the planners, managers, and other individuals, not previously disclosed, who are in a position to control the content of Postgraduate Healthcare Education, LLC (PHE) continuing education (CE) activities, hereby state that they have no relevant conflicts of interest and no financial relationships or relationships to products or devices during the past 12 months to disclose in relation to this activity. PHE is committed to providing participants with a quality learning experience and to improve clinical outcomes without promoting the financial interests of a proprietary business.

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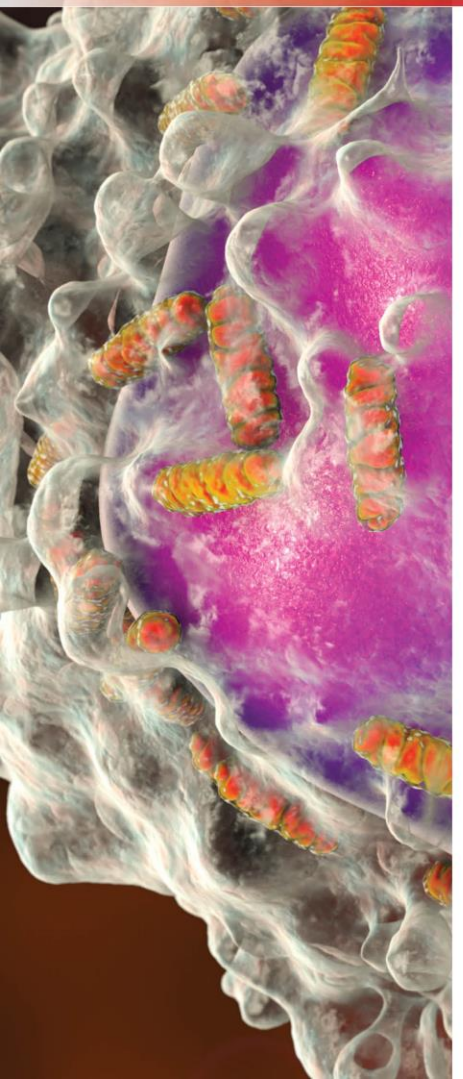
Accreditation



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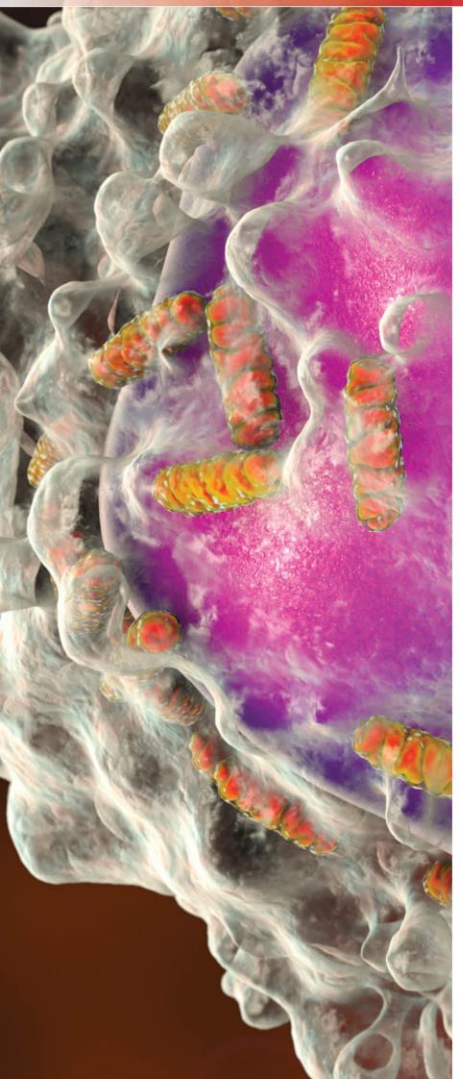
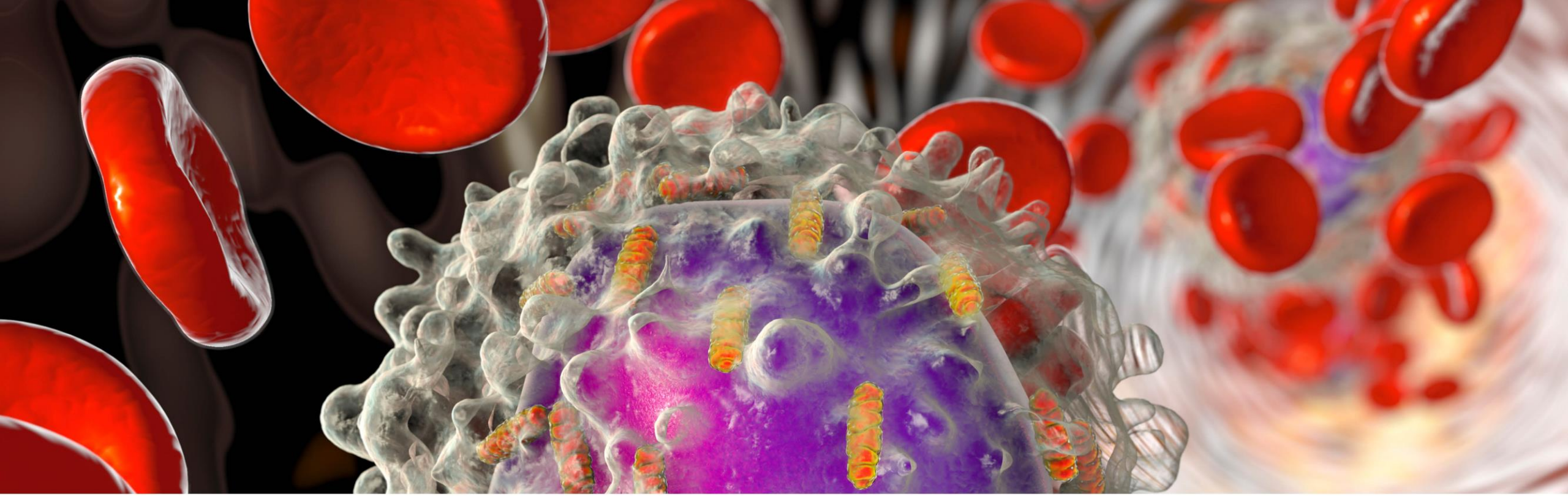
UAN: 0430-0000-23-084-H01-P
Credits: 1.25 hours (0.125 CEUs)
Type of Activity: Application

Learning Objectives



- **Describe** prognostic biomarkers and other clinical features that aid in clarifying initial therapy selection and subsequent lines of treatment for patients with chronic lymphocytic leukemia (CLL)
- **Assess** the efficacy and tolerability of recently approved medications and novel combination regimens for CLL patients, including elderly and high-risk patients
- **Formulate** patient care strategies that address adverse effects and optimize adherence with oral therapies indicated for CLL



Background

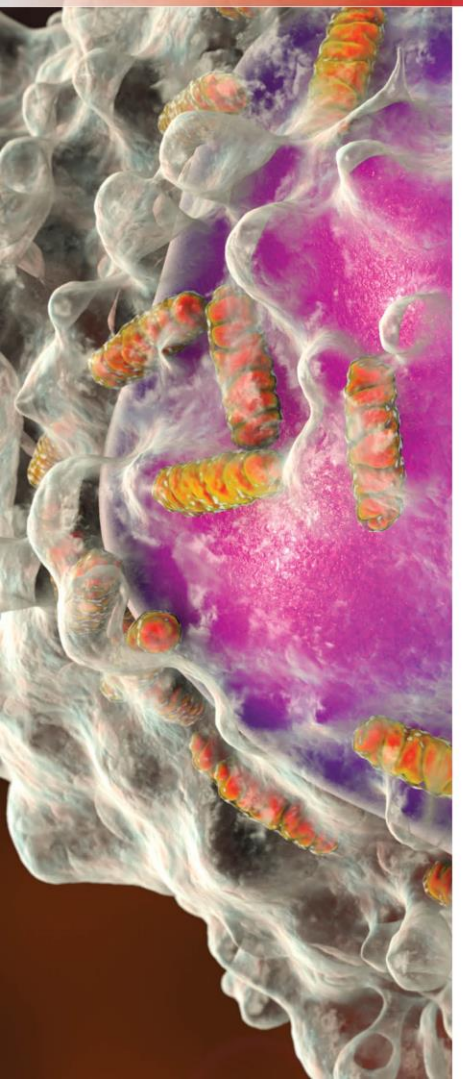
Diagnosis, Epidemiology, & Risk Factors

Epidemiology and Risk Factors

- CLL is the most prevalent adult leukemia in Western countries
  - **2023**: estimated 18,740 new cases of CLL in the United States and 4,490 CLL-related deaths
- Commonly diagnosed between ages 65 and 74 years
  - Median age at diagnosis of 70 years
- Risk factors
  - Older age, male sex, family history, race/ethnicity (more common in North America and Europe), chemical exposures (e.g., Agent Orange, pesticides)
  - Cytogenetics

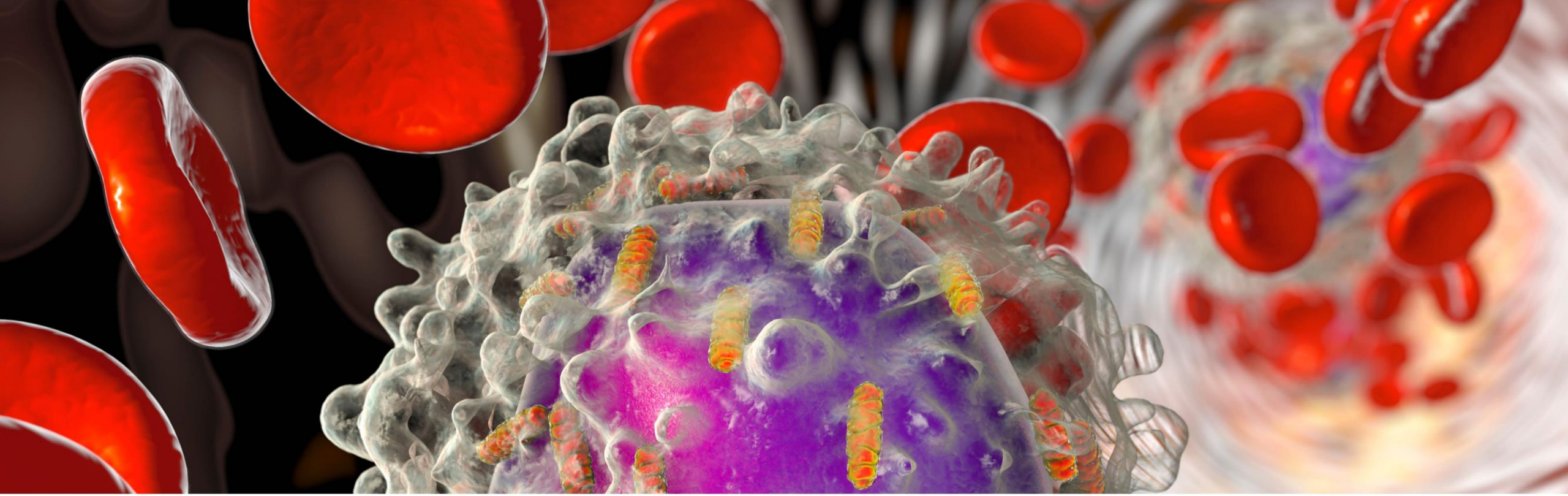
NCCN. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Guidelines (Version 3.2023). Accessed July 1, 2023. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf.; SEER Program. Cancer Stat Facts: Leukemia – Chronic Lymphocytic Leukemia (CLL). Accessed July 1, 2023. https://seer.cancer.gov/statfacts/html/clyl.html.; ACS. What are the risk factors for chronic lymphocytic leukemia? Accessed August 14, 2023. https://www.cancer.org/cancer/types/chronic-lymphocytic-leukemia/causes-risks-prevention/risk-factors.html.

Diagnosis and Staging



- Diagnosis of CLL via peripheral blood
  - Monoclonal B-lymphocytes ≥ 5 x 10^9/L
  - Flow cytometry to confirm B cell clonality
- CLL vs small lymphocytic lymphoma (SLL)
  - Predominance in blood **(CLL)**
  - Predominance in lymph nodes **(SLL)**
- Staging systems
  - **Rai**
    - Low-risk (Stage 0)
    - Intermediate-risk (Stage 1-2)
    - High-risk (Stage 3-4)
  - **Binet**
    - A, B, and C Stages

NCCN. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Guidelines (Version 3.2023). Accessed July 1, 2023. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf.



Prognostic Factors

DNA Sequencing & Cytogenetics

DNA Sequencing

- Immunoglobulin heavy chain variable region (IGHV) status
  - **Mutated** (>2%) → favorable
  - Unmutated (≤2% mutation) → unfavorable
    - Predictor of response rate (RR) and overall survival (OS) with chemoimmunotherapy
      - CLL8, CLL10 clinical trials
- *TP53* status
  - Wild-type → favorable
  - Mutated → unfavorable

NCCN. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Guidelines (Version 3.2023). Accessed July 1, 2023. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf.

Cytogenetics

- Detected by fluorescence in situ hybridization
  - Present in > 80% of treatment-naive patients with CLL

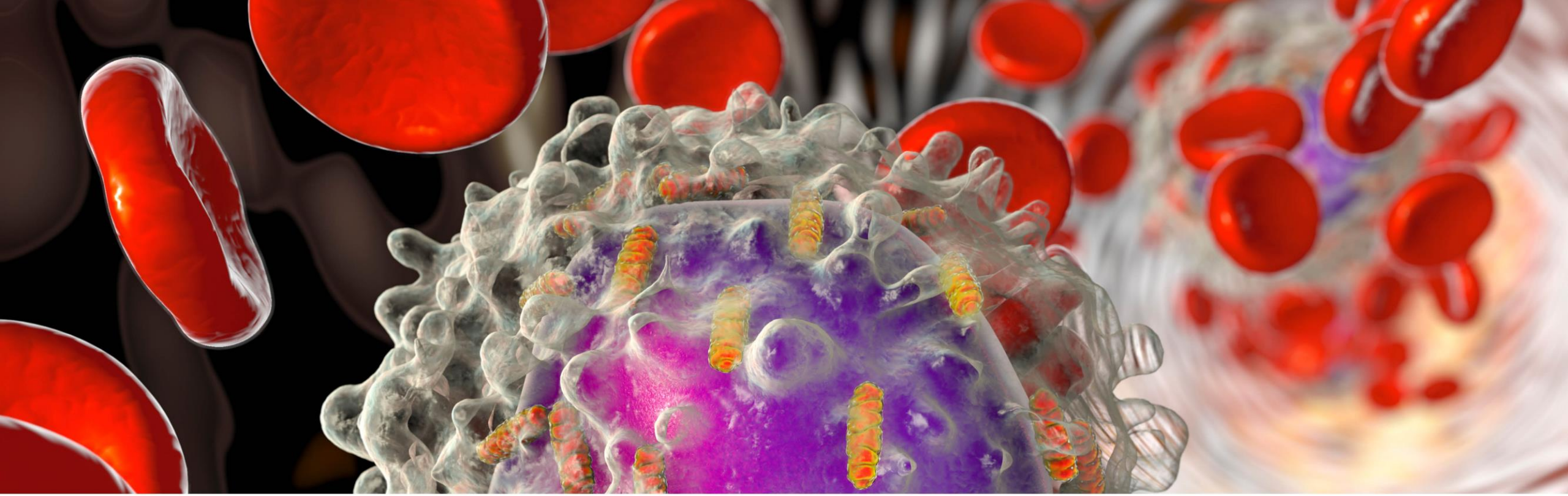
Favorable	Intermediate	Unfavorable
• del(13q)	• Trisomy 12 • Normal cytogenetics	• del(11q) • del(17p) • Complex karyotype

NCCN. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Guidelines (Version 3.2023). Accessed July 1, 2023. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf.

Risk Stratification

- Various prognostic models for risk stratification
  - Age
  - Absolute lymphocyte count
  - Beta-2 microglobulin
  - Cell surface markers (e.g., CD38, ZAP-70)
  - Cytogenetic abnormalities
  - IGHV status
  - LDH
  - Number/size of involved lymph nodes
  - Sex
  - Stage (Rai/Binet)

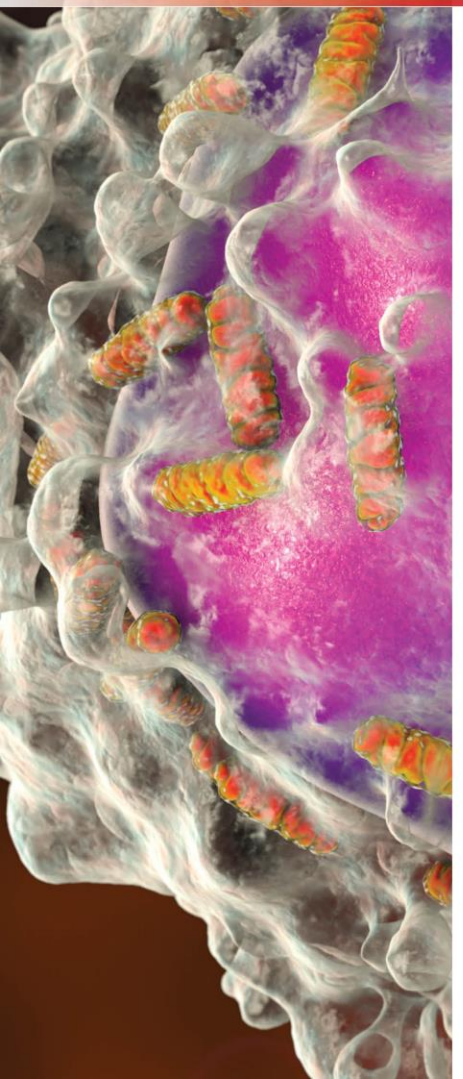
NCCN. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Guidelines (Version 3.2023). Accessed July 1, 2023. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf.



Treatment

Current Options for CLL

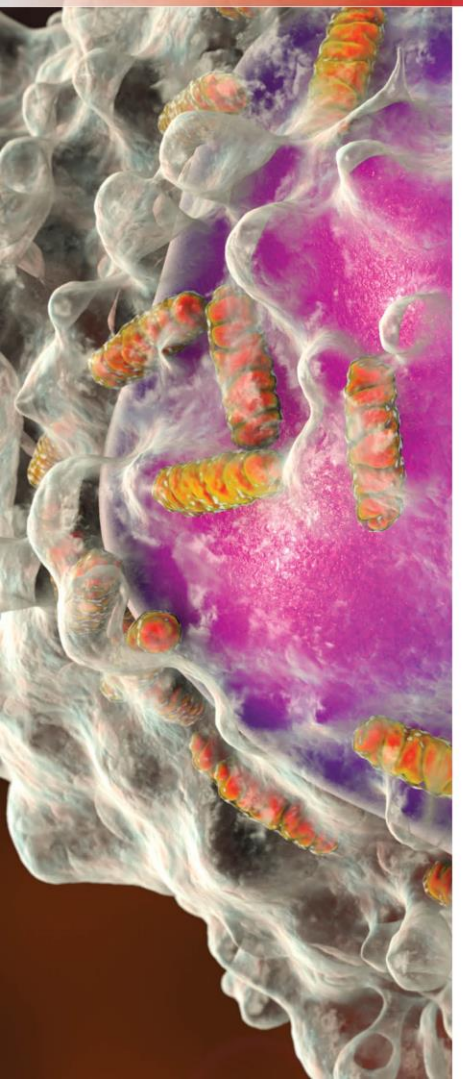
Current Treatment Options



- Chemoimmunotherapy
  - Chemotherapy +/- anti-CD20 monoclonal antibodies (mAbs)
- Anti-CD20 mAb (monotherapy)
- Bruton’s tyrosine kinase (BTK) inhibitors
- B-cell lymphoma 2 (BCL2) inhibitors
- Phosphoinositide 3-kinase (PI3K) inhibitors

NCCN. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Guidelines (Version 3.2023). Accessed July 1, 2023. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf.

Anti-CD20 Monoclonal Antibodies



- Obinutuzumab and rituximab
- **MOA:** complement-dependent cytotoxicity upon binding to CD20 on B-cells
  - Antibody-dependent cellular cytotoxicity and phagocytosis, resulting in cell death
- FDA-approved for use in combination upfront or for R/R CLL
- **Rare/serious AEs:** hypersensitivity/infusion reactions, bone marrow suppression, TLS, hepatitis B reactivation

AEs, adverse effects; FDA, United States Food and Drug Administration; MOA, mechanism of action; R/R, relapsed/refractory; TLS, tumor lysis syndrome.

GAZYVA® [package insert]. Genentech, Inc; 2022.; Rituxan® [package insert]. Genentech, Inc; 2021.

BTK Inhibitors (BTKi)

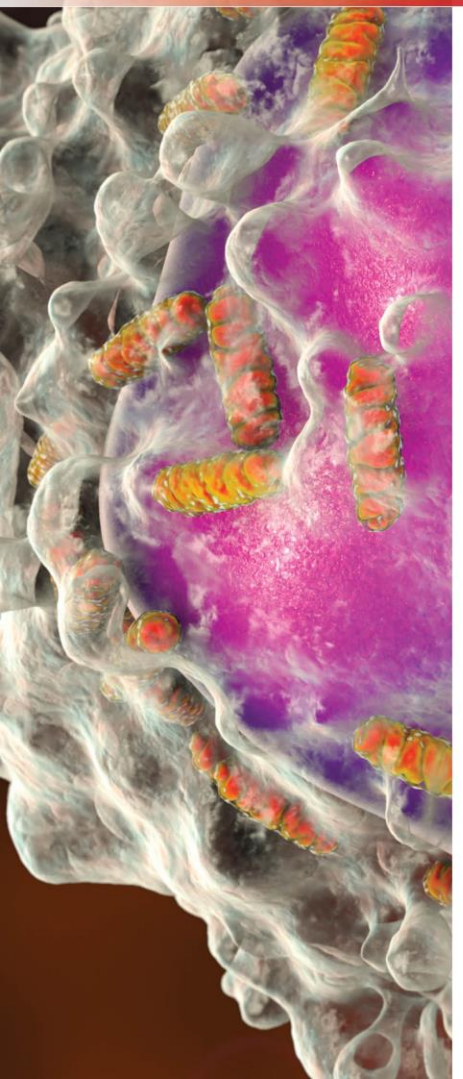
- **MOA:** bind to cysteine 481 (C481) residue of BTK on B-cells

Covalent (irreversible)	Non-covalent (reversible)
• **First generation:** ibrutinib • **Second generation:** acalabrutinib, zanubrutinib • All FDA approved for upfront use or R/R CLL • Cannot bind when C481S mutation occurs	• **FDA approved:** pirtobrutinib (LOXO-305) • For use in R/R mantle cell lymphoma only • **Investigational:** nemtabrutinib (ARQ-531, MK-1026), vecabrutinib (SNS-062) • Clinical activity demonstrated in CLL <u>with</u> (and without) C481S mutation

FDA, United States Food and Drug Administration; MOA, mechanism of action

BRUKINSA® [package insert]. BeiGene, Ltd; 2021.; CALQUENCE® [package insert]. AstraZeneca Pharmaceuticals LP; 2022.; IMBRUVICA® [package insert]. Pharmacyclics LLC; 2023. JAYPIRCA™ [package insert]. Lilly USA, LLC, 2023.

BCL2 Inhibitors



- Venetoclax
  - **MOA:** Selectively inhibits the anti-apoptotic protein B-cell lymphoma 2 (BCL2)
    - Overexpressed in CLL cells
  - FDA approved for upfront use or R/R CLL

FDA, United States Food and Drug Administration; MOA, mechanism of action; R/R, relapsed/refractory

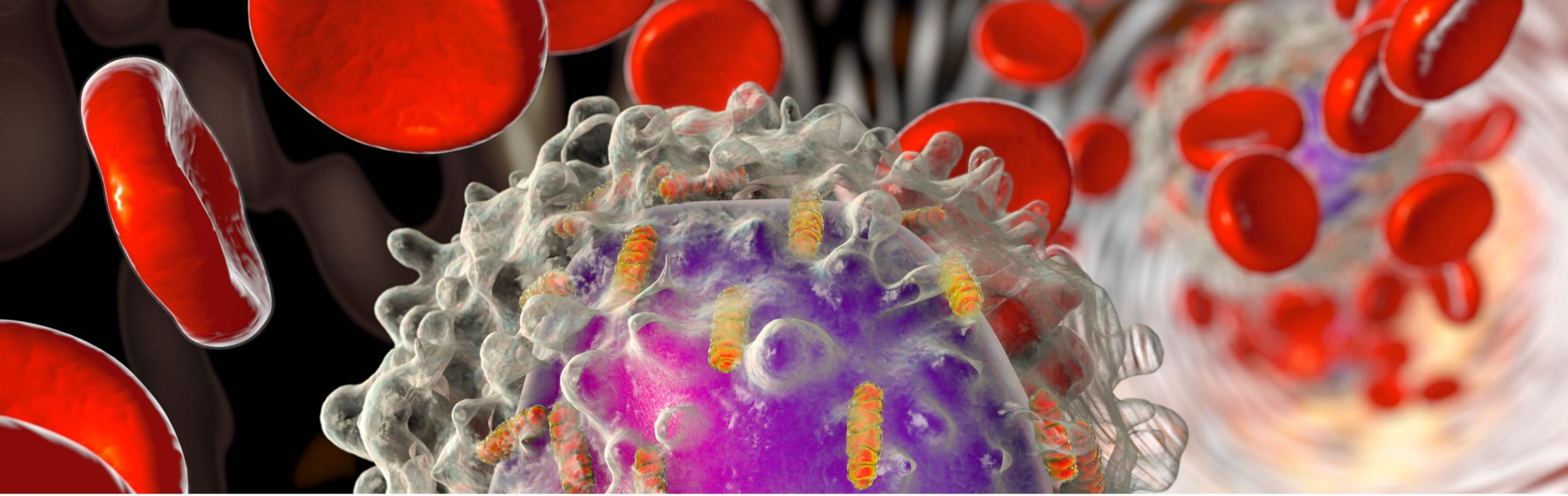
VENCLEXTA® [package insert]. AbbVie Inc.; 2022.

PI3K Inhibitors (PI3Ki)

- **First generation:** idelalisib
  - FDA approved for use in R/R CLL with rituximab
- **Second generation:** duvelisib
  - FDA approved for use in R/R CLL/SLL after > 2 prior therapies
- **MOA:** inhibits the delta isoform of PI3K (PI3Kδ)
  - Highly expressed in malignant lymphoid B-cells

FDA, United States Food and Drug Administration; MOA, mechanism of action

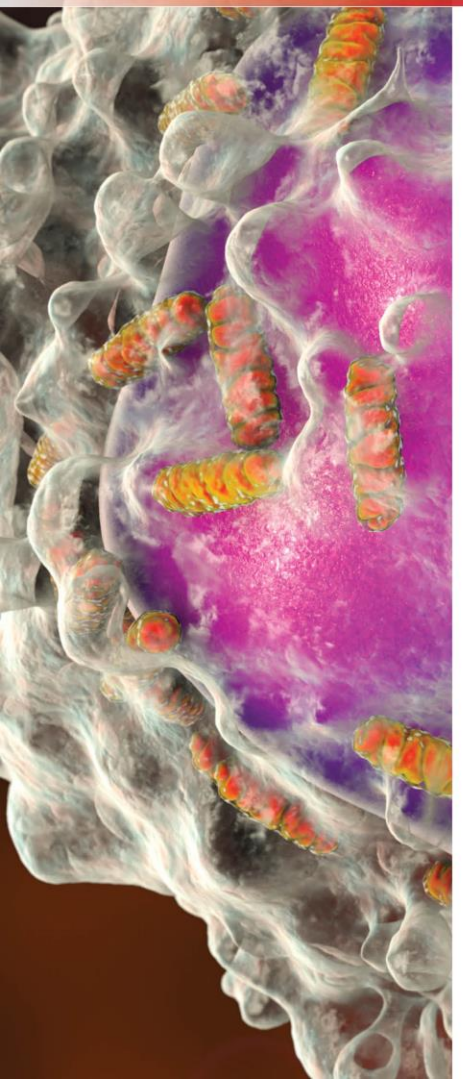
COPIKTRA® [package insert]. Secura Bio, Inc.; 2021.; ZYDELIG® [package insert]. Gilead Sciences, Inc.; 2022.



Clinical Trials

Treatment-Naïve CLL

Treatment-Naive CLL Treatment Options



WITHOUT del(17p)/TP53 mutation	WITH del(17p)/TP53 mutation
• **Acalabrutinib***	• **Acalabrutinib***
• **Acalabrutinib + obinutuzumab***	• **Acalabrutinib + obinutuzumab***
• **Venetoclax + obinutuzumab***	• **Venetoclax + obinutuzumab***
• **Zanubrutinib***	• **Zanubrutinib***
• Ibrutinib	• Alemtuzumab +/- rituximab
• Bendamustine + anti-CD20 mAb (e.g., BR)	• HDMP + rituximab
• Chlorambucil + obinutuzumab	• Ibrutinib
• FCR	• Ibrutinib + venetoclax
• HDMP + rituximab or obinutuzumab	• Obinutuzumab
• Ibrutinib + obinutuzumab	
• Ibrutinib + rituximab	
• Ibrutinib + venetoclax	
• Obinutuzumab	

***preferred regimens**

BR, bendamustine + rituximab; HDMP, high-dose methylprednisolone; mAb, monoclonal antibody

NCCN. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Guidelines (Version 3.2023). Accessed July 1, 2023. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf.

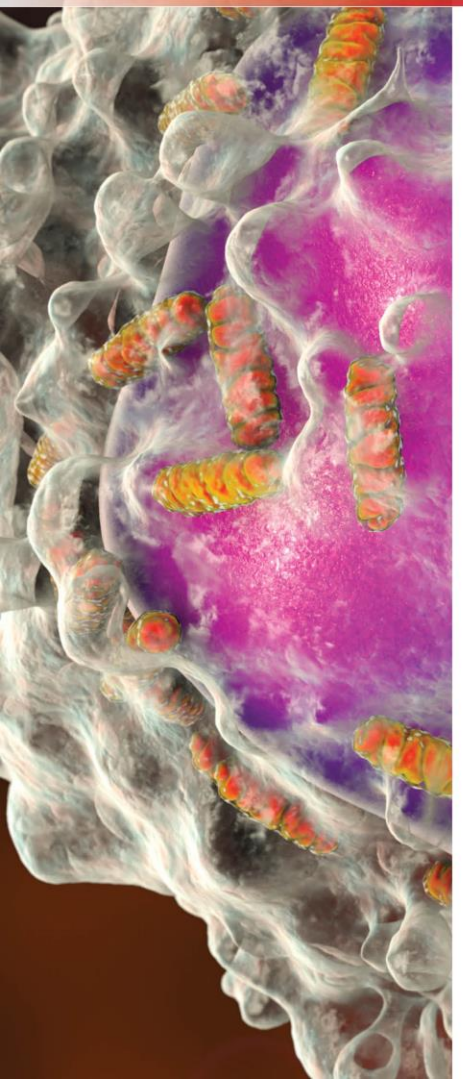
RESONATE-2 (Phase 3)

- Ibrutinib vs chlorambucil
  - ≥65 years of age (median 73 years)
  - Without del(17p)
- **Primary endpoint:** PFS
  - Ibrutinib demonstrated statistically significant longer PFS, OS, and ORR
  - PFS at 6.5 years: 61% ibrutinib vs 9% chlorambucil
- **AEs with ibrutinib (≥20%):** cough, diarrhea, fatigue, nausea
  - Grade 3/4 hemorrhage noted in 4 patients
- Most patients (87%) continued ibrutinib

AEs, adverse effects; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Burger JA, et al. *N Engl J Med.* 2015;373(25):2425-2437.

CLL14 (Phase 3)



- Venetoclax + obinutuzumab (VO) vs chlorambucil + obinutuzumab (CO)
  - ≥65 years of age (median 72 years), with comorbidities or unfit for chemotherapy
  - Fixed duration, no crossover
- **Primary endpoint:** PFS
  - PFS at 24 months: 88.2% (VO) vs 64.1% (CO)
  - PFS at 72 months: 53.1% (VO) vs 21.7% (CO)
- Benefit seen in *TP53* deletion/mutation and unmutated IGHV
- **AEs:** Grade 3/4 neutropenia (52.8%) and infections (17.5%) noted in patients on VO arm
  - Not statistically significant vs CO

AEs, adverse effects; PFS, progression-free survival.

Fischer K, et al. *N Engl J Med*. 2019;380(23):2225-2236.

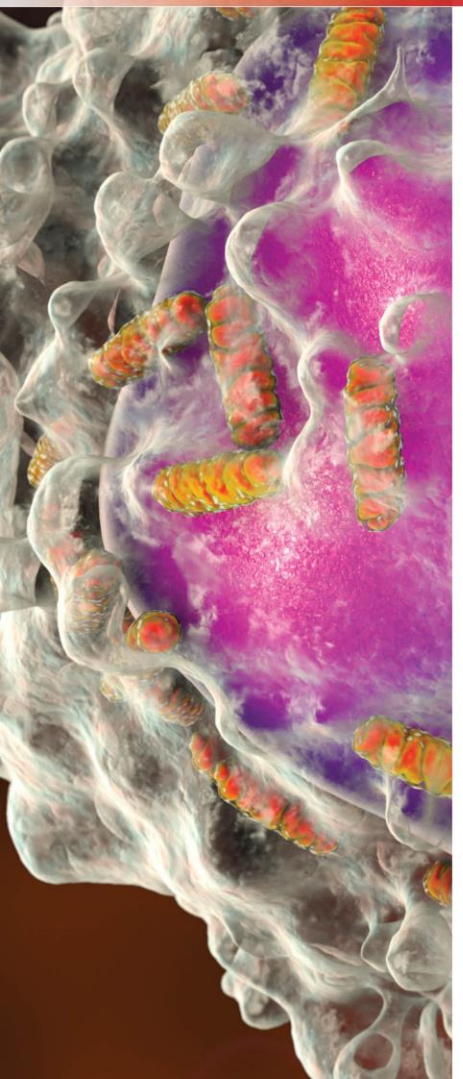
ELEVATE-TN (Phase 3)

- Acalabrutinib (A) vs acalabrutinib + obinutuzumab (AO) vs chlorambucil + obinutuzumab (CO)
  - ≥65 years of age or 18-65 years old with comorbidities
  - Crossover to acalabrutinib allowed for progression on CO
- **Primary endpoint:** PFS
  - PFS at 24 months: 87% (A) vs 93% (AO) vs 47% (CO)
  - PFS at 48 months: 78% (A) vs 87% (AO) vs 25% (CO)
- **Notable AEs (any grade):** headache [37% (A), 40% (AO)], diarrhea [35% (A), 39% (AO)], nausea [22% (A), 20% (AO)]
  - Infusion reactions with obinutuzumab [13% (AO), 40% (CO)]
- **Grade 3/4 AEs:** neutropenia [9% (A), 30% (AO), 41% (CO)] and infections [14% (A), 21% (AO), 8% (CO)]

AEs, adverse effects; PFS, progression-free survival.

Sharman JP, et al. *Lancet*. 2020;395(10232):1278-1291.

AVO (Phase 2)



- Acalabrutinib + venetoclax + obinutuzumab
  - ≥18 years of age (median 63 years)
- **Primary endpoint:** CR with undetectable MRD at Cycle 16, Day 1; prespecified goal of 60%
- ORR of 100%; CR of 46%
- Primary endpoint not met
  - 38% of patients (14 of 37 patients enrolled)
- Similar benefit seen in *TP53* deletion/mutation and unmutated IGHV
- **Grade 3/4 AEs:** overall low incidence
  - Neutropenia (43%)
- Obinutuzumab infusion-related reactions (24%)

AEs, adverse effects; CR, complete response; MRD, minimal residual disease; ORR, overall response rate.

Davids MS, et al. *Lancet Oncol.* 2021;22(10):1391-1402.

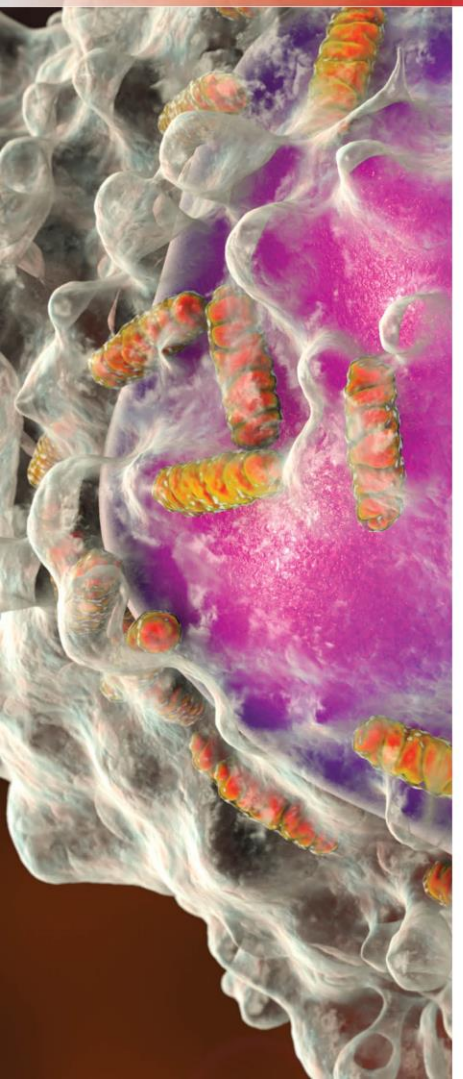
CAPTIVATE (Phase 2)

- Ibrutinib + venetoclax
  - ≤70 years of age (median 60 years)
  - Fixed-duration cohort
    - Ibrutinib lead in (monotherapy x3 cycles) followed by 12 cycles of ibrutinib + venetoclax
- **Primary endpoint:** CR
  - CR rate 55%
  - CR rate of 56% in patients with del(17p)
- **Secondary endpoints:** PFS, OS
  - PFS at 24 months: 95%
  - OS at 24 months: 98%
- **Grade 3/4 AEs:** neutropenia (33%), hypertension (6%)

AEs, adverse effects; CR, complete remission; PFS, progression-free survival; OS, overall survival

Tam CS, et al. *Blood.* 2022;139(22):3278-3289.

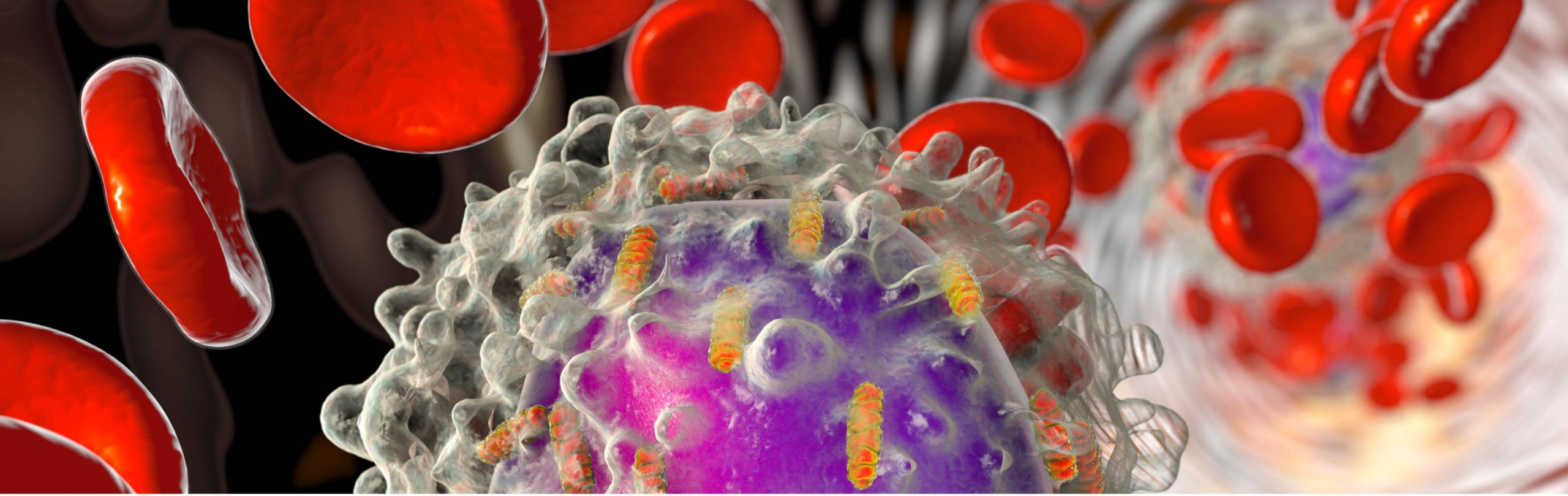
SEQUOIA (Phase 3)



- Zanubrutinib (Z) vs BR vs Z for del(17p)
  - ≥65 years of age or ≥18 years of age with comorbidities
  - Patients with del(17p) included in a separate cohort
    - Assigned to zanubrutinib
- **Primary endpoint:** PFS
  - PFS at 24 months: 86% (Z), 70% (BR); del(17p) cohort 89% (Z)
- **Grade 3/4 neutropenia:** Z (11%), BR (51%), Z for del(17p) (15%)

BR, bendamustine + rituximab; PFS, progression-free survival

Tam CS, et al. *Lancet Oncol*. 2022;23(8):1031-1043.



Clinical Trials

Relapsed/Refractory CLL

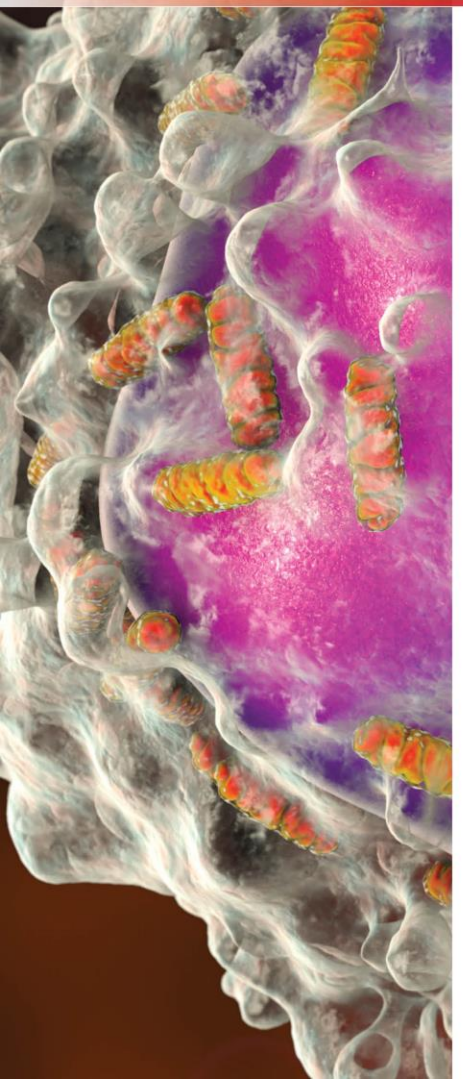
Relapsed/Refractory CLL Treatment Options

WITHOUT del(17p)/TP53 mutation	WITH del(17p)/TP53 mutation
• **Acalabrutinib***	• **Acalabrutinib***
• **Venetoclax + rituximab***	• **Venetoclax +/- rituximab***
• **Zanubrutinib***	• **Zanubrutinib***
• Ibrutinib	• Ibrutinib
• BR	• Alemtuzumab +/- rituximab
• Duvelisib	• Duvelisib
• FCR	• HDMP + rituximab
• HDMP + rituximab or obinutuzumab	• Idelalisib +/- rituximab
• Idelalisib +/- rituximab	• Lenalidomide +/- rituximab
• Lenalidomide +/- rituximab	• Pirtobrutinib
• Obinutuzumab	
• Pirtobrutinib	
• Venetoclax +/- obinutuzumab	

***preferred regimens**

NCCN. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Guidelines (Version 3.2023). Accessed July 1, 2023. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf.

MURANO (Phase 3)



- Venetoclax + rituximab (VR) vs BR
  - ≥18 years of age
  - Fixed duration; no crossover
- **Primary endpoint:** PFS
  - Median PFS of 54 months significantly higher in VR group vs 17 months in the BR group
  - 5-year OS: 82% (VR) vs 62% (BR)
- **Grade 3/4 neutropenia:** higher in **VR** vs BR
  - Grade 3/4 febrile neutropenia or infections higher in **BR** vs VR
- **Grade 3/4 TLS in VR:** 3.1%

OS, overall survival; PFS, progression-free survival; TLS, tumor lysis syndrome

Seymour JF, et al. *N Engl J Med*. 2018;378(12):1107-1120.

ELEVATE-RR (Phase 3)

- Acalabrutinib (A) vs ibrutinib (I)
  - ≥18 years of age (median 66 years)
  - All patients with del(17p) and/or del(11q)
- **Primary end point:** noninferiority of PFS
  - A determined to be noninferior to I at 40.9-month median follow-up
  - Median PFS of 38.4 months in **both** arms (A and I)
- Decreased rates (any grade) of notable AEs with A vs I
  - Atrial fibrillation/flutter (9.4% vs 16%), arthralgia (15.8% vs 22.8%), bleeding events (38% vs 51.3%), hypertension (8.6% vs 22.8%)
- Incidence of headache increased with A vs I (34.6% vs 20.2%)

AEs, adverse events; PFS, progression-free survival

Byrd JC, et al. *J Clin Oncol*. 2021;39(31):3441-3452.

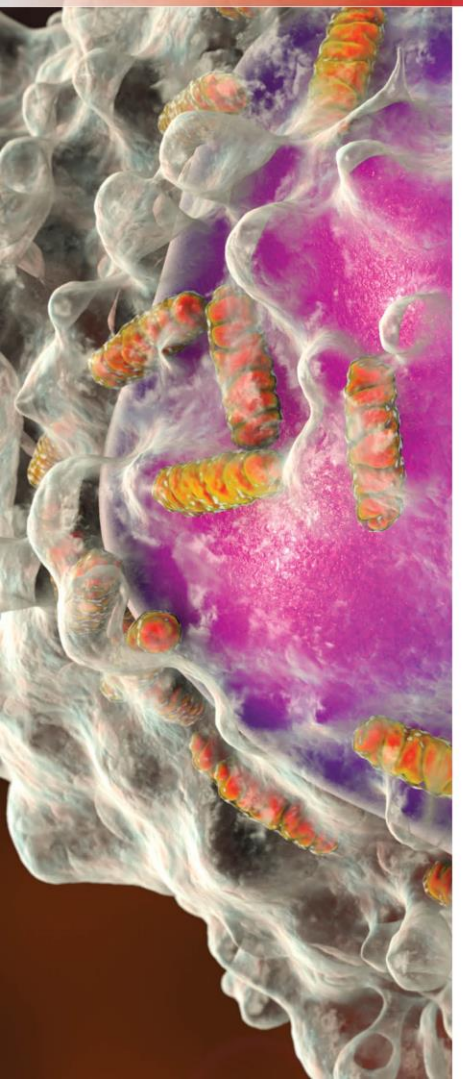
ALPINE (Phase 3)

- Zanubrutinib (Z) vs ibrutinib (I)
  - ≥18 years of age (median 67 years)
- **Primary endpoint:** overall response (CR or CR with incomplete bone marrow recovery, a nodular partial response, or a partial response)
  - ORR: 78% (2% CR; Z) vs 63% (1% CR; I)
- **Secondary endpoints:** PFS and incidence of atrial fibrillation/flutter
  - PFS at 12 months: 95% (Z) vs 84% (I)
  - PFS at 24 months: 78.4% (Z) vs 65% (I)
  - Lower incidence of atrial fibrillation/flutter with Z (5.2% vs 13.3%)
- Notable AEs (Z vs I, grade ≥3)
  - Hypertension (14.8% vs 11.1%), neutropenia (16% vs 13.9%), atrial fibrillation (1.9% vs 3.7%)

AEs, adverse effects; CR, complete remission; ORR, overall response rate; PFS, progression-free survival

Brown JR, et al. *N Engl J Med*. 2023;388(4):319-332.

BRUIN (Phase 1/2)

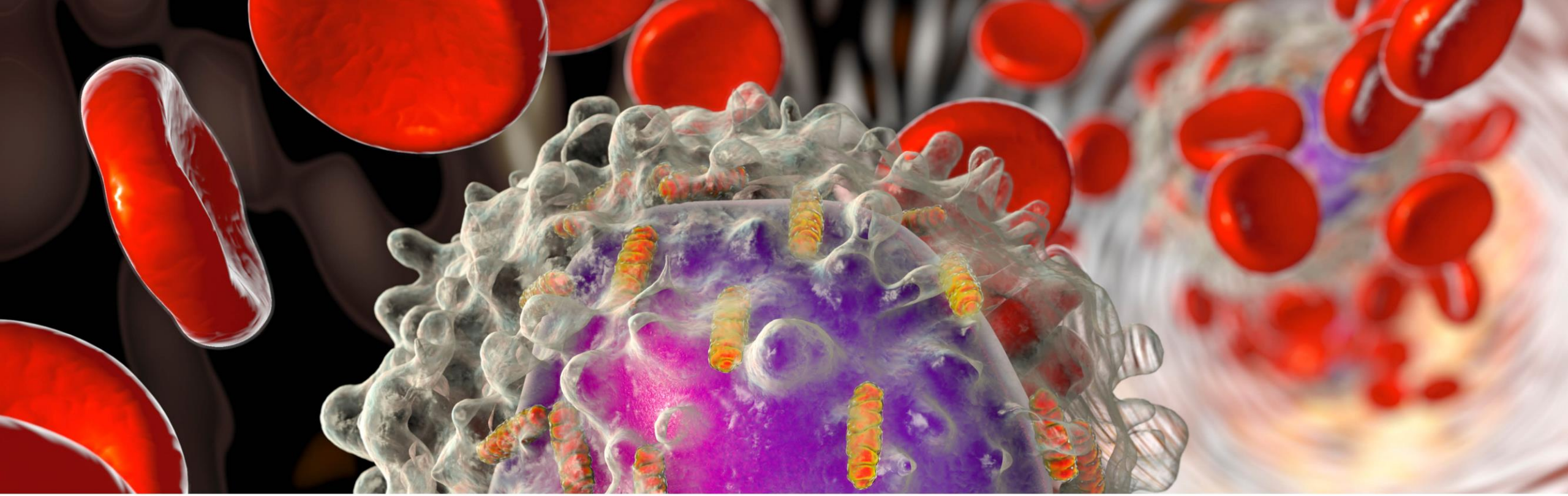


- Pirtobrutinib (open-label; dose-finding)
  - ≥18 years of age
  - Patients with CLL*, mantle cell lymphoma (MCL), Waldenstrom macroglobulinemia (WM), other B-cell lymphomas
    - *All CLL patients previously received covalent BTKi treatment
- **Primary endpoint:** maximum tolerated dose (MTD)
  - Dose levels: 25 mg, 50 mg, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg once per day
  - MTD not achieved
    - Recommended Phase 2 dose of **200 mg daily**
- **Secondary endpoint:** ORR
  - ORR of 82% in CLL patients; ORR of 79% in double-exposed patients (BTKi and BCL2i)
- **AEs:**
  - Fatigue (20%), diarrhea (17%), contusion (13%), neutropenia (13%)
- Decreased rates of notable AEs (any grade) when compared to covalent BTKi
  - Hemorrhage (5%), hypertension (5%), arthralgia (5%), atrial fibrillation/flutter (1%)

AEs, adverse effects; ORR, overall response rate; PFS, progression-free survival

Mato AR, et al. *Lancet*. 2021;397(10277):892-901.

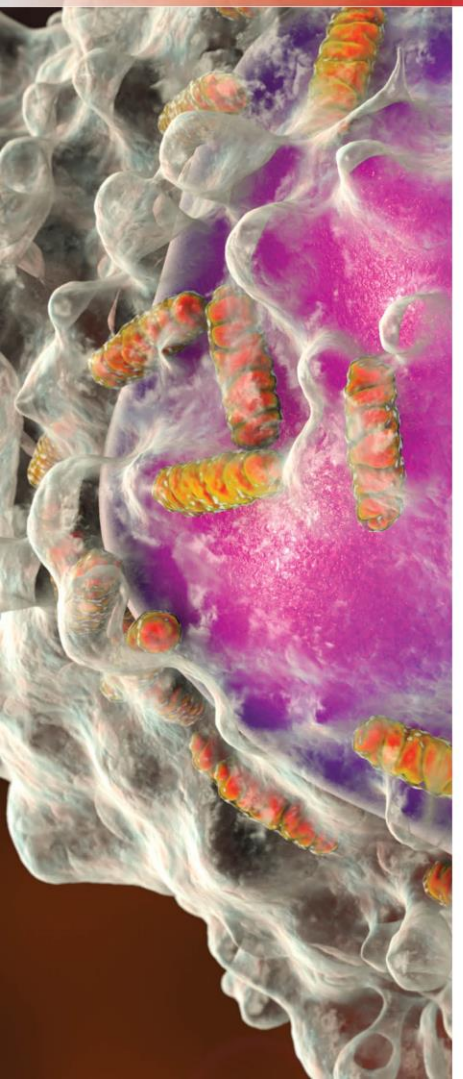
Questions & Answers



Patient Management

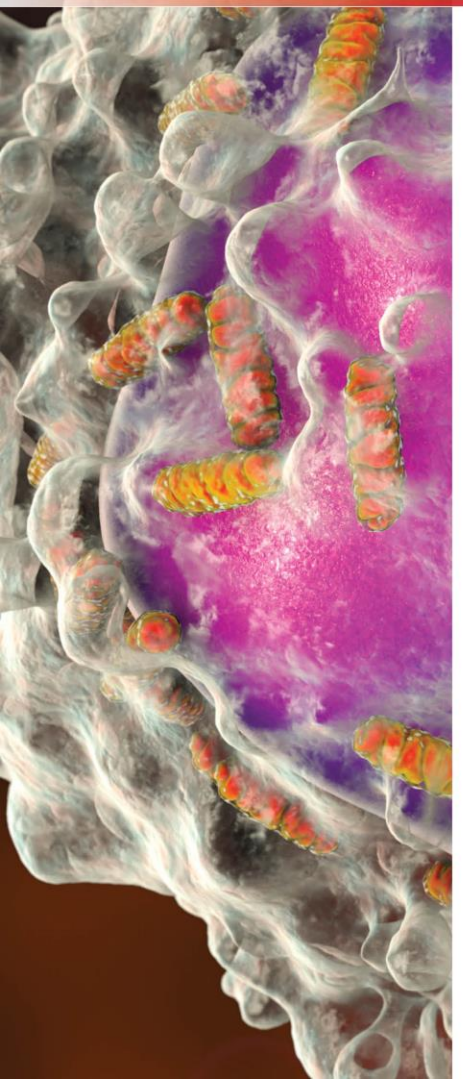
Optimizing Patient Education and Supportive Care

Patient Education



- Adverse effects
- Dose information/adjustments
- Drug-drug interactions
- Supportive care
- Adherence
- Administration
- Medication procurement

Adverse Effects: BTKi

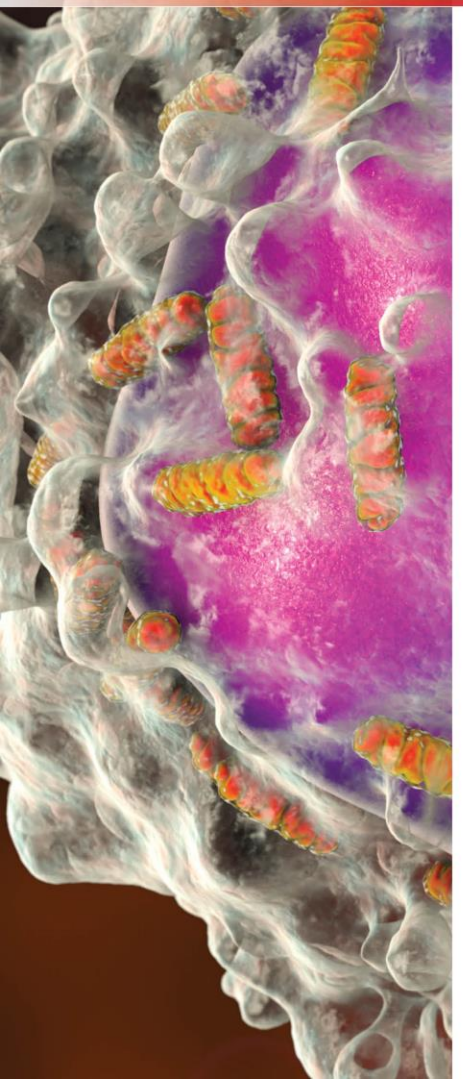


- **Lymphocytosis**
  - Transient, may occur up to 3 months from start of treatment
- **Atrial fibrillation**
  - Prevalence increases with age
  - May occur months to years after initiation
  - Monitor and manage as appropriate
- **Bleeding**
  - May occur in up to 25% of patients
  - Serious, potentially fatal Grade 3/4 hemorrhagic events (e.g., CNS bleeding) reported
  - HOLD BTKi for 3 to 7 days before and after surgical procedures
- **Hypertension**
  - Monitor and manage with anti-hypertensives as appropriate

CNS, central nervous system

BRUKINSA® [package insert]. BeiGene, Ltd; 2021.; CALQUENCE® [package insert]. AstraZeneca Pharmaceuticals LP; 2022.; IMBRUVICA® [package insert]. Pharmacyclics LLC; 2023.

Adverse Effects: BTKi (cont.)



- **Myalgias/arthralgias**
  - Common, often spontaneous resolution
  - Consider treatment hold vs pain management
- **Headache**
  - Early in treatment, may last up to 4 weeks
  - Mild, limited
- **Diarrhea**
  - Mild, resolves quickly
- **Myelosuppression**
  - May hold for high-grade neutropenia, thrombocytopenia
  - Consider filgrastim use/risk for infection
- **Rash**
  - Consider treatment hold followed by dose reduction if high grade

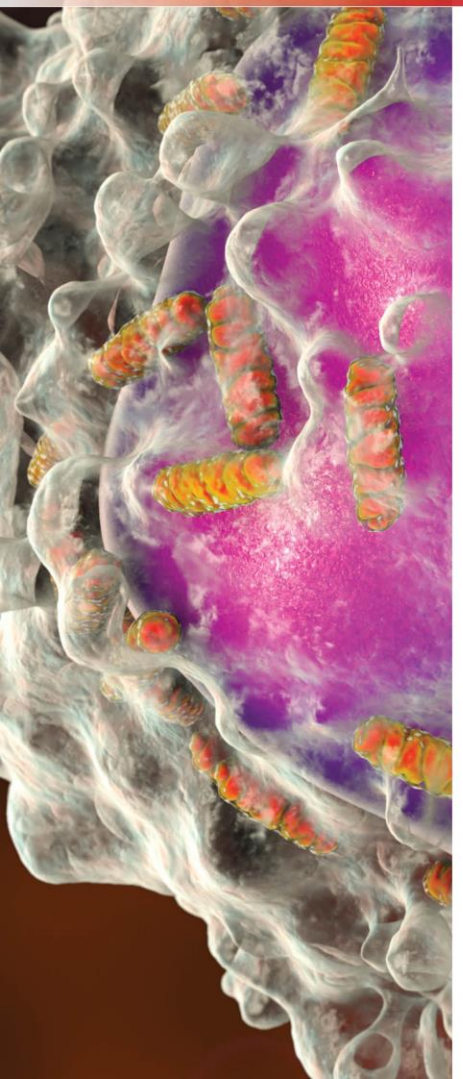
BRUKINSA® [package insert]. BeiGene, Ltd; 2021.; CALQUENCE® [package insert]. AstraZeneca Pharmaceuticals LP; 2022.; IMBRUVICA® [package insert]. Pharmacyclics LLC; 2023.

Adverse Effects: Venetoclax

- **Tumor lysis syndrome**
  - Low/medium tumor burden → **outpatient** ramp-up
  - High tumor burden → **inpatient** ramp-up
- **Myelosuppression**
- Diarrhea
- Nausea
- Fatigue
- Musculoskeletal pain
- Edema

VENCLEXTA® [package insert]. AbbVie Inc.; 2022

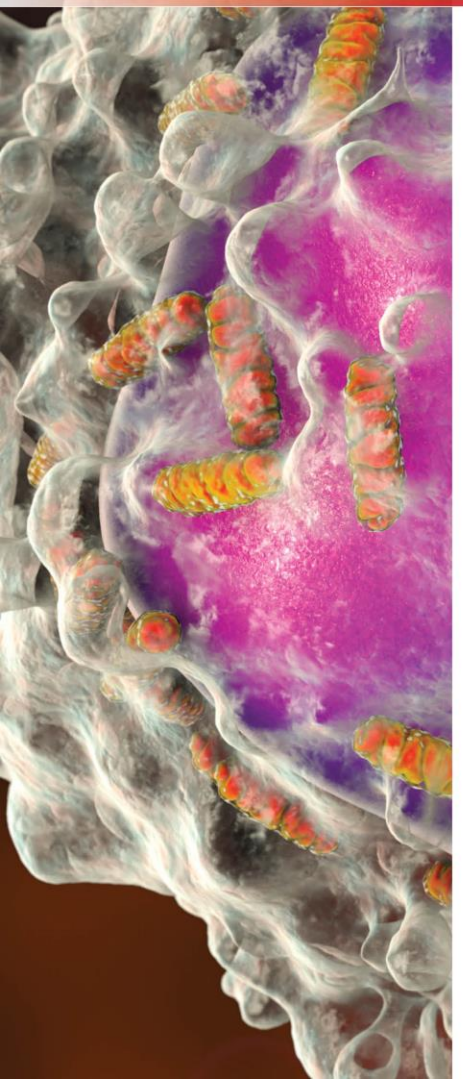
Adverse Effects: PI3Ki



- Fever
- Fatigue
- Pneumonia
- Rash
- Hepatoxicity
- Nephrotoxicity (duvelisib)
- Diarrhea
- Nausea
- Myelosuppression
- Lymphocytosis (duvelisib)
- **Fatal and serious AEs:**
  - Cutaneous reactions, diarrhea/colitis, hepatotoxicity, infections, pneumonitis

COPIKTRA® [package insert]. Secura Bio, Inc.; 2021.; ZYDELIG® [package insert]. Gilead Sciences, Inc.; 2022.

Dose Information



Name	Dose	Formulation(s)
Ibrutinib (Imbruvica®)	420 mg PO daily	capsules, tablets, oral suspension
Acalabrutinib (Calquence®)	100 mg PO BID	tablets (capsules d/c)
Zanubrutinib (Brukinsa®)	160 mg PO BID, 320 mg PO daily	capsules
Venetoclax (Venclexta™)	4-week PO ramp-up (20 mg, 50 mg, 100 mg, 200 mg) to 400 mg PO daily	tablets
Idelalisib (Zydelig®)	150 mg PO BID	tablets
Duvelisib (Copiktra®)	25 mg PO BID	capsules

- Dose adjustments for AEs per product information

AEs, adverse effects; BID, twice daily; d/c, discontinued; PO, by mouth. BRUKINSA® [package insert]. BeiGene, Ltd; 2021.; CALQUENCE® [package insert]. AstraZeneca Pharmaceuticals LP; 2022.; COPIKTRA® [package insert]. Secura Bio, Inc.; 2021.; IMBRUVICA® [package insert]. Pharmacyclics LLC; 2023.; VENCLEXTA® [package insert]. AbbVie Inc.; 2022.; ZYDELIG® [package insert]. Gilead Sciences, Inc.; 2022.

Drug-Drug Interactions: BTKi

- **Moderate/strong CYP3A4 inducers**
  - Avoid with zanubrutinib
  - If strong CYP3A inducer cannot be avoided, increase acalabrutinib to 200 mg twice daily
- **Moderate CYP3A4 inhibitors**
  - Decrease ibrutinib to 280 mg once daily
  - Decrease acalabrutinib to 100 mg once daily
  - Decrease zanubrutinib to 80 mg twice daily
- **Strong CYP3A4 inhibitors**
  - Ibrutinib dose adjustment dependent on concomitant CYP3A4 inhibitor
    - Reduce dose to 70 mg, 140 mg, or avoid completely
  - Avoid w/acalabrutinib
    - If a strong CYP3A4 inhibitor must be used short-term (e.g., anti-infectives for ≤ 7 days), hold acalabrutinib and restart ≥ 24 hours after d/c of strong CYP3A4 inhibitor
  - Decrease zanubrutinib to 80 mg once daily

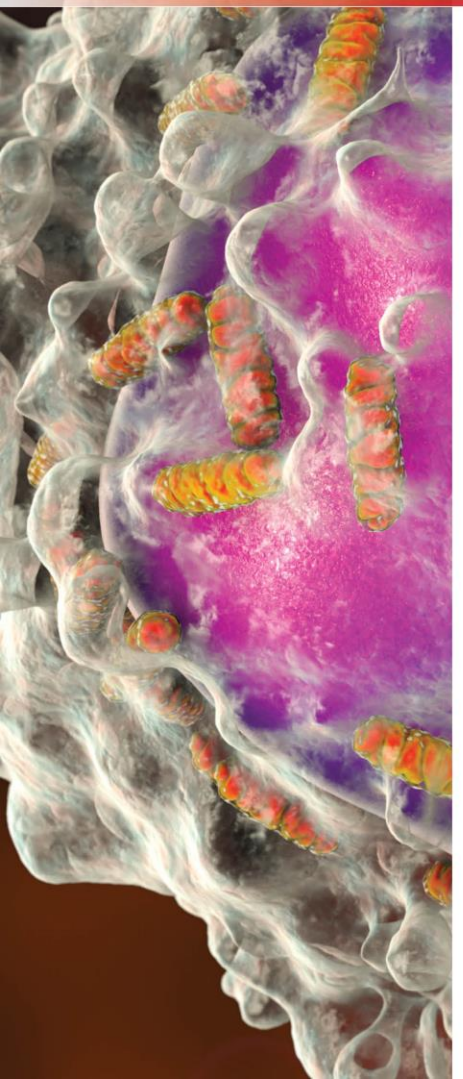
CYP, cytochrome P450; BRUKINSA® [package insert]. BeiGene, Ltd; 2021.; CALQUENCE® [package insert]. AstraZeneca Pharmaceuticals LP; 2022.; IMBRUVICA® [package insert]. Pharmacyclics LLC; 2023.

Drug-Drug Interactions: BTKi (cont.)

- Antiplatelet therapies or anticoagulants
  - Assess risk vs benefit
  - Direct oral anticoagulants (DOACs) preferred
  - **Avoid** warfarin
- Antacids
  - No longer contraindicated with **tablet** formulation of acalabrutinib
  - Does not apply to other BTKi

BRUKINSA® [package insert]. BeiGene, Ltd; 2021.; CALQUENCE® [package insert]. AstraZeneca Pharmaceuticals LP; 2022.; IMBRUVICA® [package insert]. Pharmacyclics LLC; 2023.

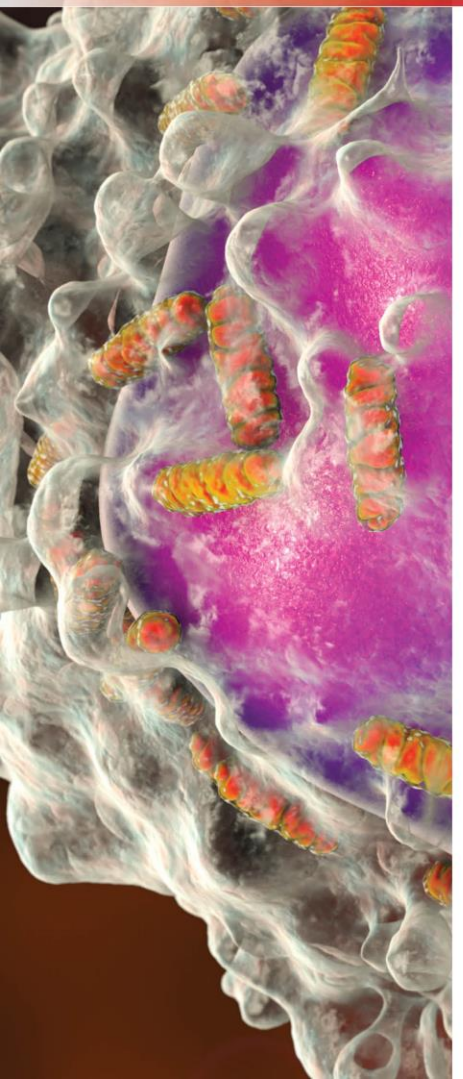
Drug-Drug Interactions: Venetoclax



- **Moderate/strong CYP3A4 inducers**
  - Generally advised to avoid combination
- **Moderate CYP3A4 inhibitors or P-gp inhibitors**
  - Reduce venetoclax dose by at least 50%
  - Resume original venetoclax dose 2 to 3 days after inhibitor discontinuation
- **Strong CYP3A4 inhibitors**
  - Coadministration **contraindicated** during venetoclax *ramp-up*
  - Reduce venetoclax dose during maintenance
    - **Posaconazole:** reduce venetoclax dose to 70 mg
    - Other CYP3A4 inhibitors: reduce venetoclax dose by at least 75%
    - Resume original venetoclax dose 2 to 3 days after inhibitor discontinuation
- **P-gp substrates**
  - Avoid concomitant use
    - If concomitant use is unavoidable, separate dosing of P-gp substrate by ≥6 hours before venetoclax

CYP, cytochrome P450; P-gp, P-glycoprotein; VENCLEXTA® [package insert]. AbbVie Inc.; 2022

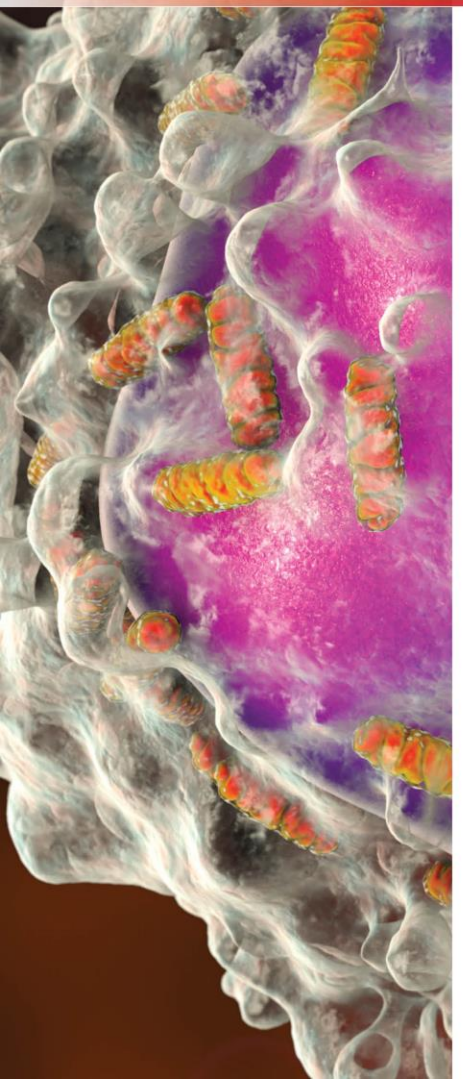
Drug-Drug Interactions: PI3Ki



- **Moderate CYP3A4 inducers**
  - Avoid with duvelisib if possible
    - If used, on day 12 of combination increase duvelisib from 25 mg twice daily to 40 mg twice daily or from 15 mg twice daily to 25 mg twice daily
    - Resume prior duvelisib dose 14 days after stopping inducer discontinuation
- **Strong CYP3A4 inducers**
  - May decrease serum concentration; Avoid
- **Strong CYP3A4 inhibitors**
  - Additional monitoring required when used with idelalisib
  - Reduce the dose of duvelisib to 15 mg twice a day
- **CYP3A4 substrates**
  - Avoid coadministration of sensitive CYP3A4 substrates

CYP, cytochrome P450; COPIKTRA® [package insert]. Secura Bio, Inc.; 2021.; ZYDELIG® [package insert]. Gilead Sciences, Inc.; 2022.

Supportive Care

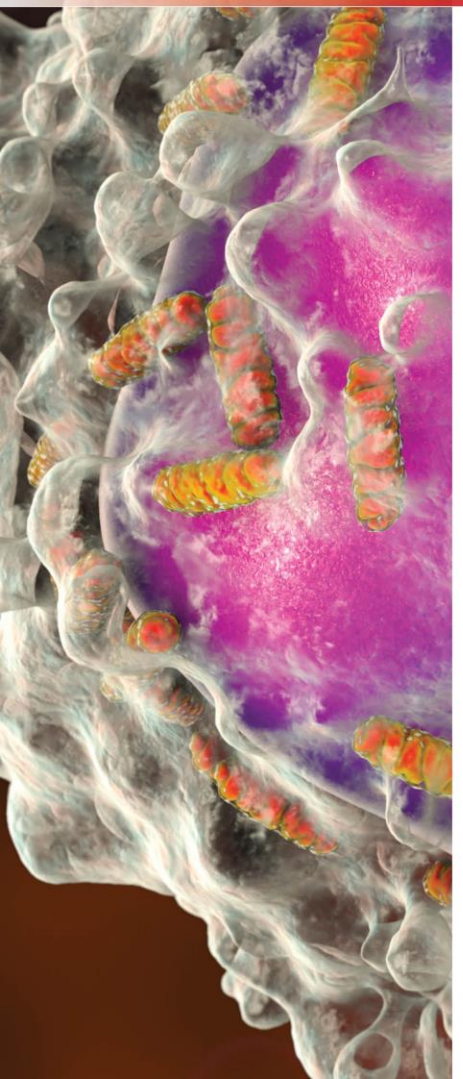


- Anti-infectives
  - Consider PJP and HSV/VZV prophylaxis with BTKi
  - Consider PJP and CMV prophylaxis with PI3Ki
- Hepatitis B virus (HBV) reactivation
  - Prophylaxis for positive hepatitis B surface antigen
  - Treatment with entecavir for positive HBV viral load by quantitative PCR
- TLS prevention for venetoclax
  - Hydration
  - Hyperuricemia prevention
    - G6PD-testing
  - Frequent lab checks

CMV, cytomegalovirus; G6PD, glucose-6-phosphate dehydrogenase; HSV/VZV, herpes simplex virus/varicella zoster virus; PCR, polymerase chain reaction; PJP, Pneumocystis jiroveci pneumonia.

BRUKINSA® [package insert]. BeiGene, Ltd; 2021.; CALQUENCE® [package insert]. AstraZeneca Pharmaceuticals LP; 2022.; COPIKTRA® [package insert]. Secura Bio, Inc.; 2021.; IMBRUVICA® [package insert]. Pharmacyclics LLC; 2023.; VENCLEXTA® [package insert]. AbbVie Inc.; 2022.; ZYDELIG® [package insert]. Gilead Sciences, Inc.; 2022.

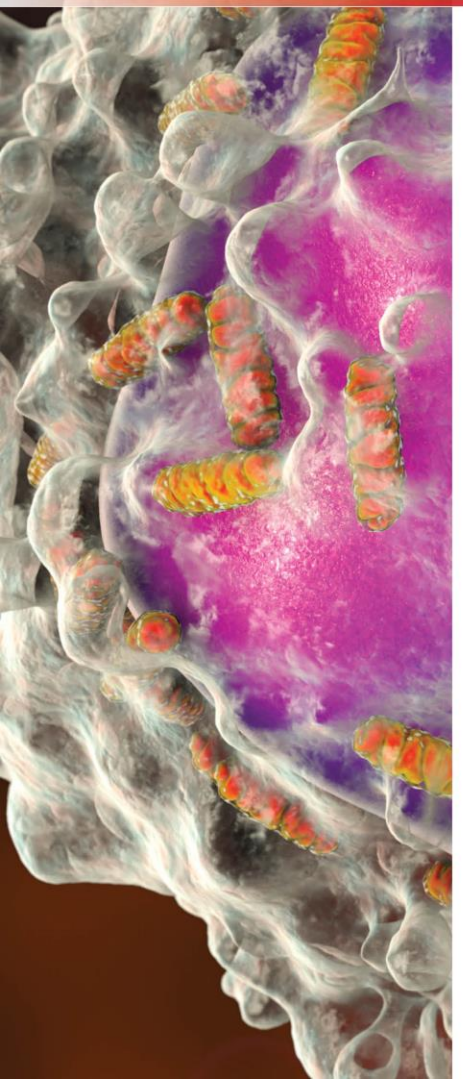
Adherence & Administration



- **Adherence**
  - Retrospective analyses of efficacy trials evaluated the effect of dose intensity on PFS and ORR
  - Higher dose intensity associated with longer median PFS and higher ORR
- **Administration**
  - BTKi, PI3Ki: with or without food
  - Venetoclax: **with** food
  - Swallow whole; do not cut, crush, or chew
  - Avoid grapefruit, grapefruit juice, starfruit, and Seville oranges
- **Storage**
  - Store at 20°C to 25°C (68°F to 77°F)
  - Brief exposure to 15°C to 30°C (59°F to 86°F) permitted

ORR, overall response rate; PFS, progression-free survival; BRUKINSA® [package insert]. BeiGene, Ltd; 2021.; CALQUENCE® [package insert]. AstraZeneca Pharmaceuticals LP; 2022.; COPIKTRA® [package insert]. Secura Bio, Inc.; 2021.; IMBRUVICA® [package insert]. Pharmacyclics LLC; 2023.; VENCLEXTA® [package insert]. AbbVie Inc.; 2022.; ZYDELIG® [package insert]. Gilead Sciences, Inc.; 2022.

Medication Procurement



- Specialty pharmacy
  - Typically utilized/often mandated for dispensing
  - Mail order delivery
- Insurance approval obstacles
  - Prior authorization
  - Appeals
- High cost (“financial toxicity”)
  - Patient financial assistance
    - Copay assistance/coupon card
    - Manufacturer assistance programs
    - Grant support

Questions & Answers

Thank You!