ASSOCIATION OF COMMUNITY CANCER CENTERS

MULTIDISCIPLINARY CHRONIC LYMPHOCYTIC LEUKEMIA CARE

ACCC
Association of Community Cancer Centers

COMPREHENSIVE OVERVIEW OF CHRONIC LYMPHOCYTIC LEUKEMIA

Amy Goodrich, RN, MSN, CRNP-AC

Nurse Practitioner

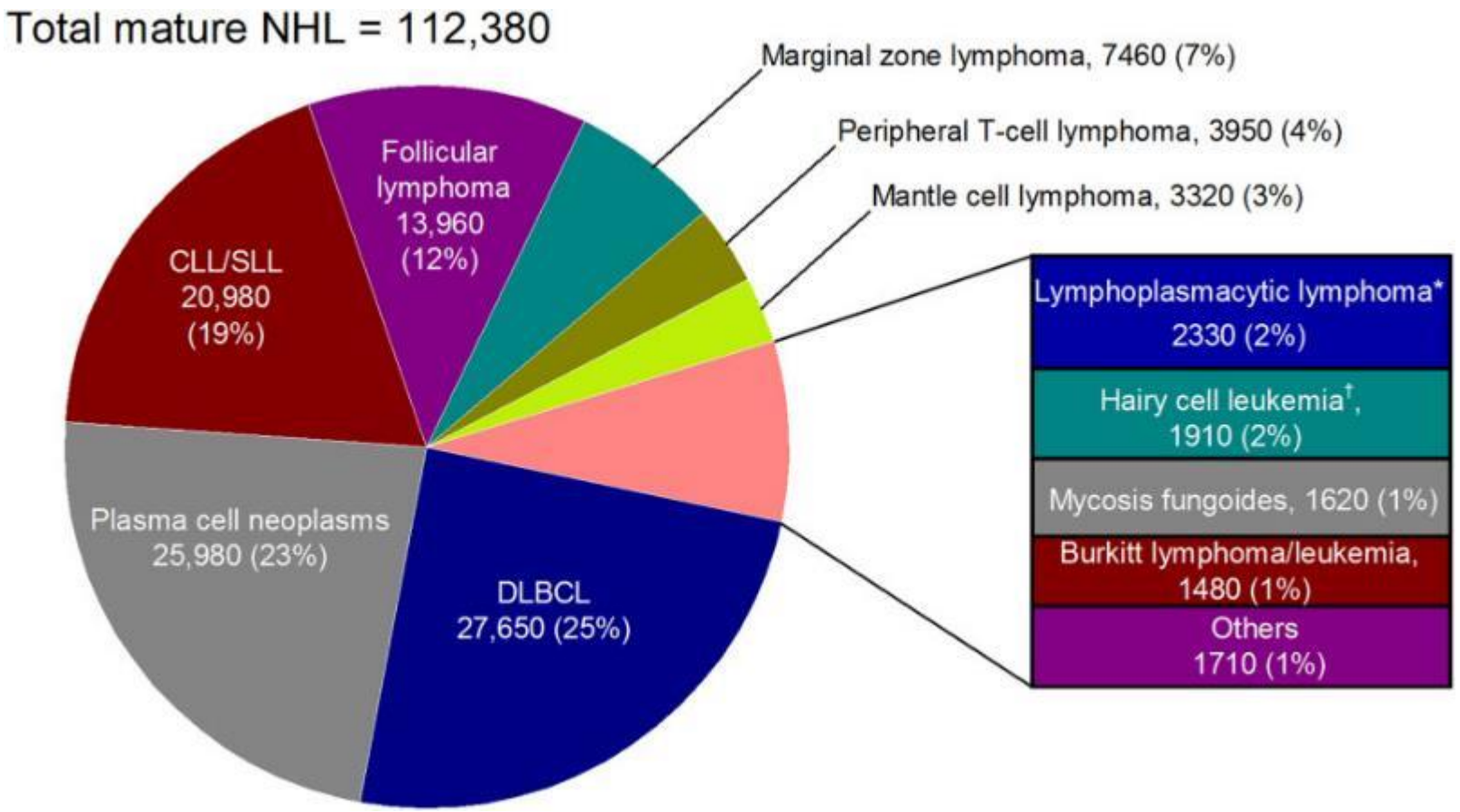
Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University

Baltimore, MD

Learning Objectives

- Review CLL pathophysiology, diagnostic work-up, and staging.
- Identify the mechanism of action for novel agents used for the treatment of CLL.
- Describe best practices for optimizing selection and sequencing of treatments in the upfront and relapsed/refractory settings.
- Anticipate and identify potential adverse events that may be associated with newer agents and how to address to optimize patient outcome.
- Identify issues related to non-adherence.

Incidence of Mature Non-Hodgkin Lymphoid Neoplasia 2016



Teras, L. et al. (2016). 2016 U.S. lymphoid statistics by World Health Organization subtypes. *CA: A Cancer Journal for Clinicians*, 66, 443-459.

CLL/SLL

- Most common leukemia in Western world:
  - 30% of leukemias;
  - Anticipated new cases in 2019 – 20,720;
  - Anticipated deaths in 2019 – 3930.
- A disorder of morphologically mature but immunologically less mature lymphocytes.
- Lymphocyte count ≥5000 for diagnosis.
- Immunophenotype includes CD5+/CD23+.
- Primarily occurs in middle-aged and older adults.
- Considered an indolent disease.
- Large variation in survival between patients-from several months to a normal life expectancy.

National Cancer Institute. (2019). Chronic Lymphocytic Leukemia Treatment-Health Professional Version. cancer.gov/types/leukemia/hp/cll-treatment-pdq.

CLL/SLL

- Most patients diagnosed with early stage disease.
- Approximately 70% will require therapy at some point.
- Considered incurable.
- Anticipate multiple disease relapses and requiring multiple lines of treatment.
- Those with high risk disease have shorter progression free survival (PFS).
  - IGVH-4.2 years.
  - Del(17p)-1 year.

Hilal, T., Betcher, J., & Leis, J. (2018). *Current Hematologic Malignancy Reports*, 13, 237-243.

Presenting Symptoms

- May be incidental finding/asymptomatic in 25-50% of newly diagnosed patients
- Enlarged lymph nodes-most common presenting symptom-80%
- Recurring infections
- Early satiety
- Abdominal discomfort
- Abdominal fullness
- Petechiae
- Mucocutaneous bleeding
- Fatigue
- Night sweats
- Weight loss

National Cancer Institute. (2019). Chronic Lymphocytic Leukemia Treatment-Health Professional Version. cancer.gov/types/leukemia/hp/cll-treatment-pdq

Diagnostic Work-Up

Essential

- Peripheral blood flow cytometry
- Physical exam
- Performance Status
- B symptoms
- CBC with differential/platelets
- Comprehensive metabolic panel
- LDH
- Hepatitis B screen
- CT chest/abdomen/pelvis optional
- Bone marrow biopsy and aspirate, lymph node biopsy optional
- Fertility considerations

Informative for prognosis and/or need for therapy

- FISH:+12; del(11q)*; del(13q)**; del(17p)*
- TP53 sequencing (abnormal*)
- Karyotyping (complex*)
- Molecular analysis for IGHV mutational status (mutated**, unmutated*)
- Beta-2-microglobulin
- Immunoglobulins

National Comprehensive Cancer Network. (2019). B-Cell Lymphomas. Version 1.2019. nccn.org/professionals/physician_gls/pdf/b-cell.pdf.
* unfavorable; ** favorable

CLL Staging Systems

Rai Stage	Modified Rai Stage	Characteristics
0	Low	Lymphocytosis in peripheral blood and bone marrow only
I	Intermediate	Lymphocytosis and enlarged lymph nodes
II		Lymphocytosis and enlarged spleen and/or liver
III	High	Lymphocytosis and anemia (hemoglobin <11g/dL)
IV		Lymphocytosis and thrombocytopenia (platelets <100 X 10^9/L)

Binet Stage	Characteristics
A	Hemoglobin level $\geq$ 10 g/dL, platelet count $\geq$ 100 X 10^9/L, and < 3 enlarged lymphoid sites
B	Hemoglobin level $\geq$ 10 g/dL, platelet count $\geq$ 100 X 10^9/L, and $\geq$ 3 enlarged lymphoid sites
C	Hemoglobin level < 10 g/dL, platelet count < 100 X 10^9/L, or both and any number of enlarged lymphoid sites

Rai, K et al. (1975). *Blood*, 46, 219-234. Binet, J. et al. (1981*). Cancer*, 48, 198-204. Rai, K. In R Gale & K Rai (Eds). (1987). *Chronic Lymphocytic Leukemia: Recent Progress and Future Directions.* New York: Alan R. Liss. Pp. 253-264.

CLL-International Prognostic Index

Prognostic Factor	Points
Del17p on FISH or TP53	4
Unmutated IGHV genes	2
Serum β2 microglobulin >3.5 mg/L	2
Rai Stage I-IV	1
Age >65 years	1

IPI Score	Risk Category	5-Year TFS
0-1	Low Risk	78%
2-3	Intermediate Risk	54%
4-6	High Risk	32%
7-10	Very High Risk	0%

CLL-IPI Working Group. *Lancet Oncology*, 17, 779-790. Parikh, S. (2018). *Blood Cancer Journal,* 8. DOI 10.1038/s41408-018-0131-2

Limitations of CLL-IPI

- Does not include patients treated with novel agents.
- Does not include other important prognostic variables (somatic genetic mutations detected by next-generation sequencing and patient comorbidities).
- Primarily developed to predict OS, it is generally applied in predicting time to first therapy in newly diagnosed previously untreated patients with CLL.

Parikh, S. (2018). *Blood Cancer Journal*, 8. DOI 10.1038/s41408-018-0131-2

Updated 2018 International Workshop on CLL Guidelines to Initiate Therapy (IWCLL)

Any one of the following criteria should be met to initiate CLL therapy:

- Progressive marrow failure, hemoglobin <10 gm/dL or platelet count of <100X 10^9/L;
- Massive (>6 cm below the left costal margin) or progressive or symptomatic splenomegaly;
- Massive (>10 cm in longest diameter) or progressive or symptomatic lymphadenopathy;
- Progressive lymphocytosis with an 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 (e.g., skin, kidney, lung, spine); and
- Disease-related symptoms, including:
  - Unintentional weight loss of >10% within the previous 6 months;
  - Significant fatigue;
  - Fever >38^{o}C for 2 or more weeks without evidence of infection; and
  - Night sweats for >1 month without evidence of infection.

Hallek, M. et al. (2018). *Blood*. https://doi.org/10.1182/blood-2017-09-806398

Case Study

- Mr. H is a 62-year-old male who presents to PCP with fatigue.
- Physical exam reveals axillary adenopathy up to 2 cm.
- Lab results reveals WBC of 27K, lymphocyte count 22K, hemoglobin 11.2, platelet count 115,000, and TSH 7.35.
- PMH remarkable for hypertension and mild COPD (former smoker).
- No recent infection or other change in medical status.
- Started on thyroid replacement therapy.
- Referred to a hematologist.

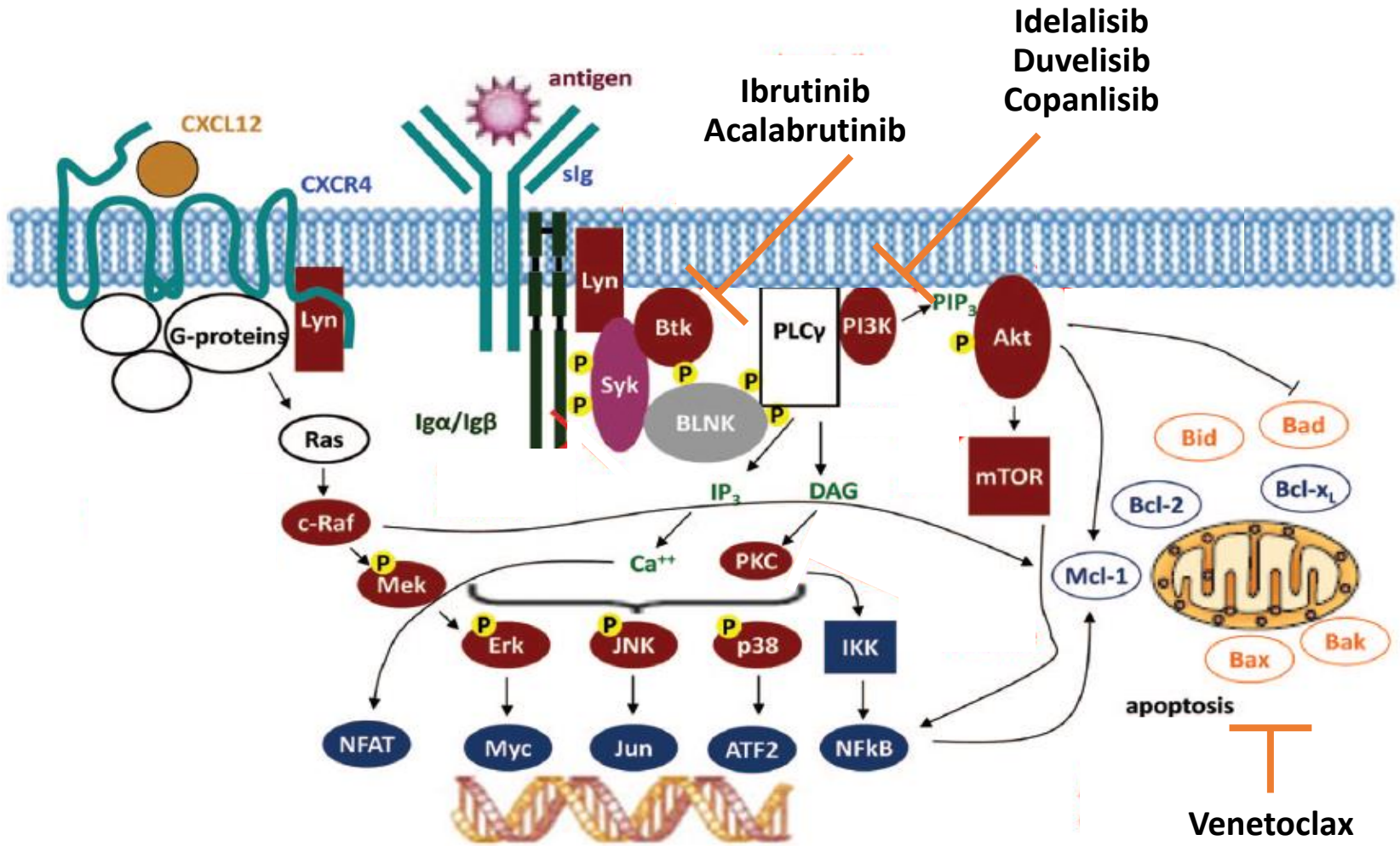
Case Study

- The hematology-oncologist sends B2M, peripheral blood for flow cytometry, IGHV mutational status, and FISH.
- Noted to have typical CLL (CD5+, CD23+, CD19+, CD20 dimly positive) with normal B2 microglobulin, mutated IGHV status, and normal FISH results.
- CT scans reveal up to 2.5 cm axillary, mesenteric and inguinal nodes.
- Stage 2 (Rai), intermediate risk.
- CLL IPI Score = 0, low risk with 5-year TFS 78%.

Case Study

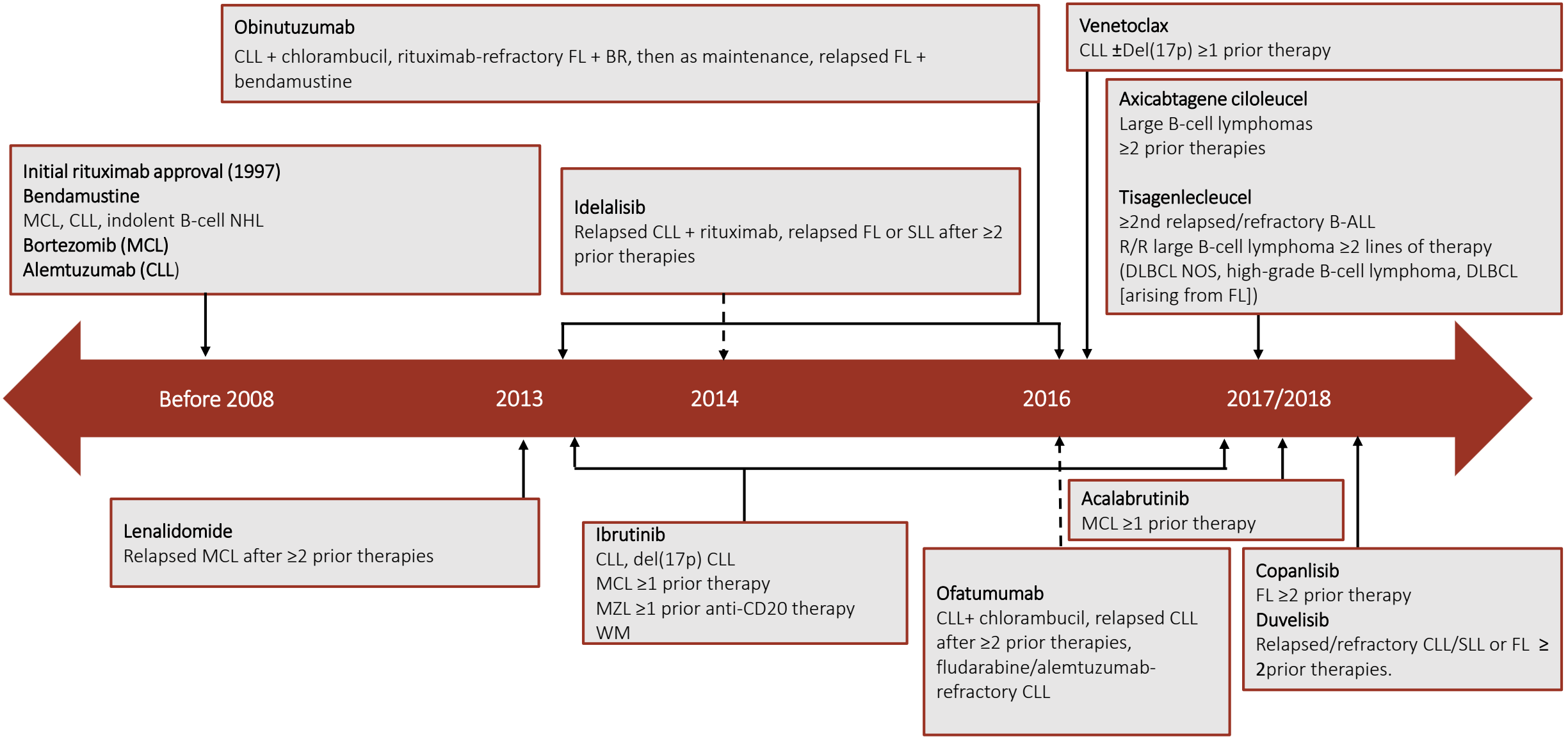
- Does not meet criteria for treatment.
- Fatigue improved with thyroid hormone replacement therapy.
- Active surveillance for CLL.
- Slowly increasing lymphocyte count and increasing mild splenomegaly.
- 6 years later, WBC 110K, ALC 90K, Hgb 10.6, Plts 86K (<100K x 6 months), spleen 5 cm on exam with new fatigue and early satiety.
- Repeat FISH studies show normal findings, TSH WNL.
- Patient now 68 yo and meets criteria for treatment (Plts < 100K, symptomatic splenomegaly).
- After lengthy discussion, patient decides on treatment with ibrutinib.

Mechanism of Action for Novel Agents Used in Management of B-Cell Lymphomas



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

Mapping Progress in B-Cell Lymphoma Through the Emergence of Novel Agent Classes



Suggested Regimens for Frontline Treatment of CLL/SLL Without del(17p)/TP53 Mutation

Frail with significant comorbidity OR Age≥65 y and younger patients with significant comorbidities	Age<65 y without significant comorbidities	Maintenance therapy
Preferred first-line regimens:	Preferred first-line regimens:	Post first-line
• **Ibrutinib** • **Venetoclax + obinutuzumab**	• **Ibrutinib**	• Consider **Lenalidomide** for high-risk patients
Other recommended regimens:	Other recommended regimens:	
• Bendamustine + CD20 monoclonal antibody (not recommended for frail patients) • Chlorambucil + anti-CD20 monoclonal antibody • **High dose methylprednisolone + rituximab** • **Ibrutinib + obinutuzumab** • **Onibutuzumab** • Chlorambucil • **Rituximab**	• Bendamustine + CD20 monoclonal antibody • FCR (fludarabine, cyclophosphamide, rituximab) • FR (fludarabine, rituximab) • **High dose methylprednisolone + rituximab** • **Ibrutinib + rituximab** • **Venetoclax +obinutuzumab** • PCR (pentostatin, cyclophosphamide, rituximab)	

National Comprehensive Cancer Network. (2019). *CLL/SLL Guidelines*. Version 5.2019. nccn.org/professionals/physician_gls/pdf/cll.pdf.

Suggested Regimens for Frontline Treatment of CLL/SLL Without del(17p)/TP53 Mutation

Frail with significant comorbidity OR Age≥65 y and younger patients with significant comorbidities	Age<65 y without significant comorbidities	Maintenance therapy
Preferred relapsed/refractory regimens:	Preferred relapsed/refractory regimens:	Post second-line
• **Ibrutinib** • **Venetoclax + rituximab** • **Duvelisib** • **Idelalisib + rituximab**	• **Ibrutinib** • **Venetoclax + rituximab** • **Duvelisib** • **Idelalisib + rituximab**	• **Lenalidomide** • **Ofatumumab**
Other recommended regimens	Other recommended regimens	
• **Acalaburtinib** • **Alemtuzumab +/- rituximab** • Chlorambucil + rituximab • Reduced-dose FCR or PCR • **HDMP + rituximab** • **Idelalisib** • **Lenalidomide +/- rituximab** • **Obinutuzumab** • **Ofatumumab** • **Venetoclax** • **Dose-dense rituximab** • Bendamustine, rituximab +/- ibrutinib or idelalisib	• **Acalabrutinib** • **Alemtuzumab +/- rituximab** • Bendamustine + rituximab • FC + ofatumumab • FCR • **HDMP + rituximab** • **Idelalisib** • **Lenalidomide +/- rituximab** • **Obinutuzumab** • **Ofatumumab** • PCR • **Venetoclax** • Bendamustine, rituximab +/- ibrutinib or idelalisib	

National Comprehensive Cancer Network. (2019). *CLL/SLL Guidelines*. Version 5.2019. nccn.org/professionals/physician_gls/pdf/cll.pdf.

Case Study

- Initial increase of lymphocyte count to 150k, with improved palpable nodes and reduced early satiety.
- Lymphocytes trended down over weeks with improvement of hemoglobin and platelet counts.
- Notes bleeding gums with brushing teeth, easy bruising, and intermittent petechiae.
- Mild nausea, well-controlled with ondansetron.
- Loose stools for the first 6 months of ibrutinib, improved with avoiding greasy foods and OTC antidiarrheals.

BTK Inhibitors

	Ibrutinib	Acalabrutinib
Dose	MCL & MZL: 560 mg orally daily CLL/SLL, WM, and cGVHD: 420 mg orally daily	100 mg orally every 12 hours
Dosage Forms	Capsules: 70mg and 140 mg Tablets: 140mg, 280mg, 420mg 560mg	Capsules: 100mg
Most common adverse events (>20%)	Neutropenia, thrombocytopenia, **diarrhea**, anemia, musculoskeletal pain, rash, **nausea**, **bruising**, fatigue, hemorrhage, and pyrexia	Anemia, thrombocytopenia, **headache**, neutropenia, **diarrhea**, fatigue, myalgia, and bruising
Warnings/Precautions	Hemorrhage, infections, cytopenias, cardiac arrhythmias, hypertension, second primary malignancies, tumor lysis syndrome, embryo-fetal toxicity	Hemorrhage, infections, cytopenias, second primary malignancies, atrial fibrillation and flutter
Drug Interactions	CYP3A Inhibitors and Inducers	CYP3A Inhibitors and Inducers Gastric Acid Reducing Agents

AstraZeneca Pharmaceuticals (2017). Calquence Package Insert. azpicentral.com/calquence/calquence.pdf#page=1.
Pharmacyclics LLC. (2018). Imbruvica Package Insert. imbruvica.com/docs/librariesprovider7/default-document-library/prescribing-information.pdf.

Special Considerations for BTK Inhibitor AE Management

Toxicity	Ibrutinib	Acalabrutinib
Hemorrhage/Bleeding	44% ≥Gr3—3%	50% ≥Gr3—2%
• Increased risk of bleeding on concomitant anticoagulant therapy or antiplatelet therapy • Consider risk/benefit of withholding for 3–7 days pre- and post-surgery		
Afib/Flutter	5–77%	3%
• Periodically monitor for cardiac arrhythmias and obtain ECG for those who develop symptoms (palpitations, lightheadedness, syncope, chest pain) or new onset dyspnea • Manage cardiac arrhythmias and manage as appropriate		
Hypertension	12%	NR
• Monitor for new/uncontrolled hypertension • Initiate antihypertensives as needed		

FDA Prescribing Information;
Rogers B, Khan N. *J Adv Pract Oncol.* 2017; NCCN CLL/SLL Guidelines. Version 4.2019.

Special Considerations for BTK Inhibitor AE Management

Toxicity	Ibrutinib	Acalabrutinib
Hemorrhage/Bleeding	44% ≥Gr3—3%	50% ≥Gr3—2%
• Increased risk of bleeding on concomitant anticoagulant therapy or antiplatelet therapy • Consider risk/benefit of withholding for 3–7 days pre- and post-surgery		
Afib/Flutter	5–77%	3%
• Periodically monitor for cardiac arrhythmias and obtain ECG for those who develop symptoms (palpitations, lightheadedness, syncope, chest pain) or new onset dyspnea • Manage cardiac arrhythmias and manage as appropriate		
Hypertension	12%	NR
• Monitor for new/uncontrolled hypertension • Initiate antihypertensives as needed		

FDA Prescribing Information;
Rogers B, Khan N. *J Adv Pract Oncol.* 2017; NCCN CLL/SLL Guidelines. Version 4.2019.

BTK Inhibitors

	BTK Selectivity	Indications
Ibrutinib	√	CLL/SLL (w/ or w/o 17pdel), R/R MCL, WM, R/R MZL, cGVHD
Acalabrutinib	√√√	R/R MCL
Zanubrutinib (BGB-3111)	√√√	Investigational
Tirabrutinib (ONO/GS-4059)	√√√	Investigational

FDA Prescribing Information; Clinicaltrials.gov; Wu J, et al. *J Hematol Oncol*. 2016.

BTK Inhibitors

	Ibrutinib	Acalabrutinib	Zanubrutinib (BGB-3111)	Tirabrutinib (ONO/GS-4059)
Major Off-Targets	EGFR, ITK, TEC	Minimal	ITK (weak)	TEC (weak)
Platelet Inhibition	Yes	Minimal	Unknown	Unknown
Afib	Observed	Minimal	Unknown	Observed*
Mechanism of Resistance	BTK/PLCγ2 mutations	BTK mutations reported/TBD	TBD	TBD

*Thought to be unrelated to drug

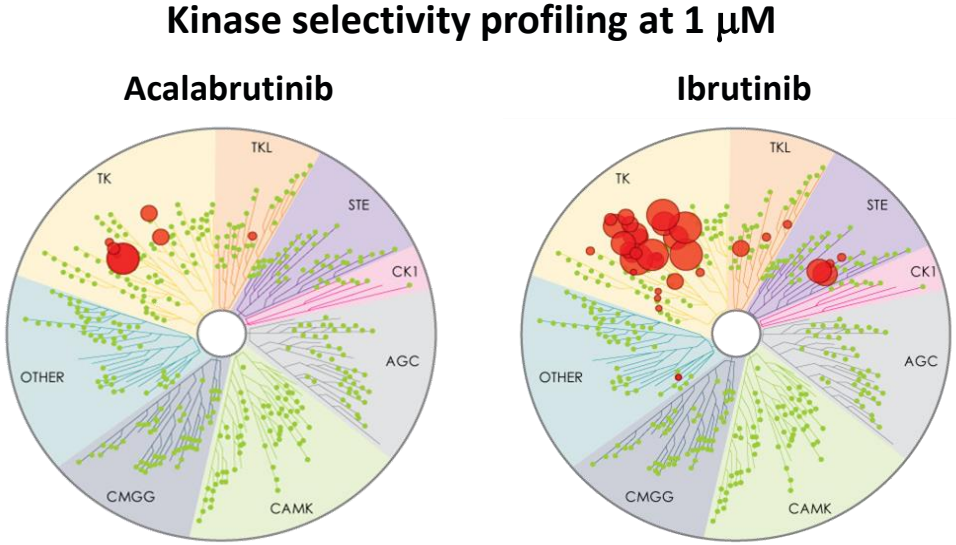
Afib=atrial fibrillation; EGFR=epidermal growth factor receptor; ITK=interleukin-2-inducible T-cell kinase; TEC=tyrosine kinase expressed in hepatocellular carcinoma.

FDA Prescribing Information;
Wu J, et al. *J Hematol Oncol*. 2016;
Byrd JC, et al. *N Engl J Med*. 2016;
Woyach JA, et al. *N Engl J Med*. 2014.

Acalabrutinib
Agent Overview

- Highly-selective, potent kinase inhibitor.
- Designed to minimize off-target activity with minimal effects on TEC, EGFR, or ITK signaling.

Kinase selectivity profiling at 1 μM



The size of the red circle is proportional to the degree of inhibition.

Kinase Inhibition IC_{50} (nM)		
Kinase	**Acalabrutinib**	**Ibrutinib**
BTK	5.1	1.5
TEC	126	10
BMX	46	0.8
TXK	368	2.0
ERBB2	~1000	6.4
EGFR	>1000	5.3
ITK	>1000	4.9
JAK3	>1000	32
BLK	>1000	0.1

Barf T, et al. *J Pharmacol Exp Ther.* 2017.

Ibrutinib in CLL

Efficacy

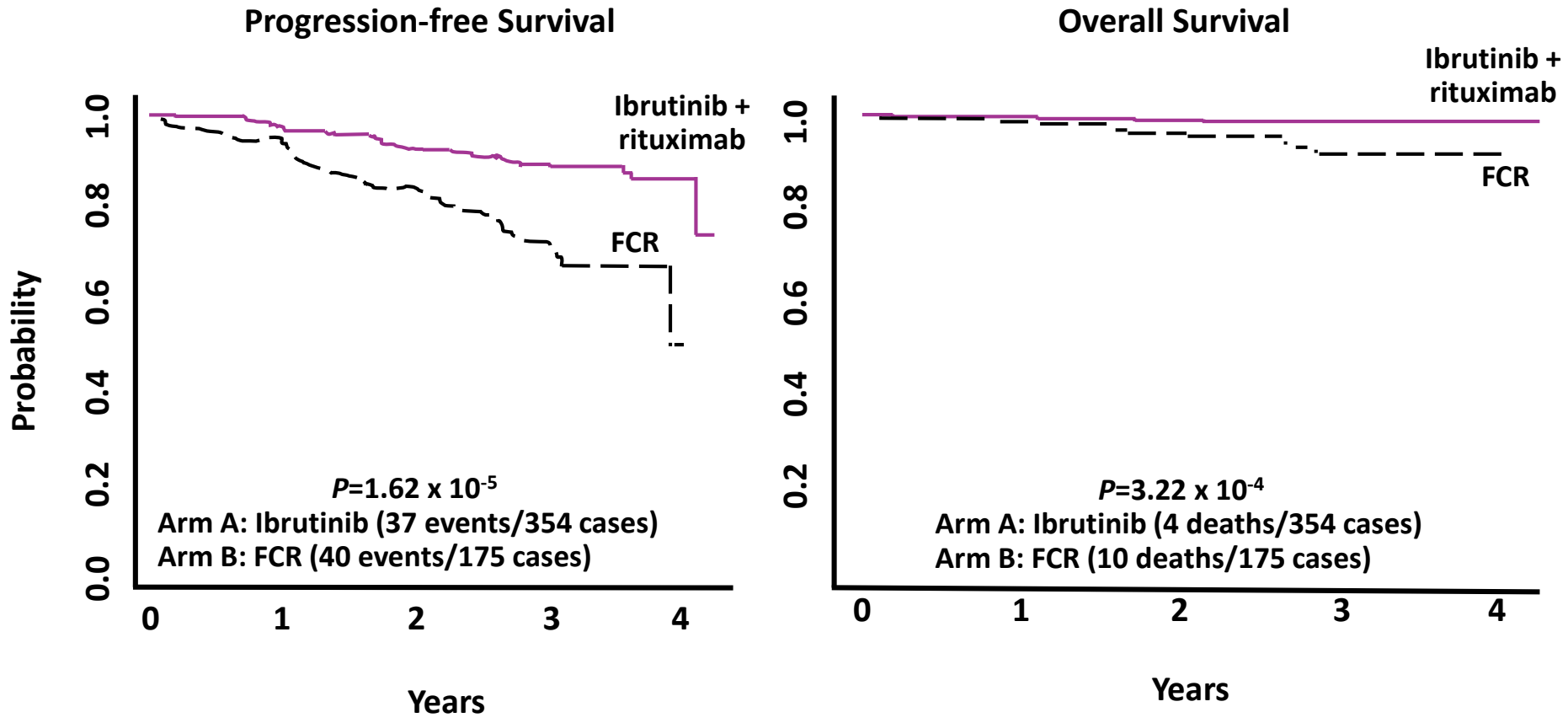
Population	Study	Phase	Follow-Up	Survival
Treatment Naive	PCYC 1102[1] (age ≥65)	1/2	5 yrs	PFS 92% OS 92%
	RESONATE-2[2.3] (vs chlorambucil) (age ≥65)	3	4 yrs	PFS 74% (vs 16% for chlorambucil) OS 95% (vs 84% for chlorambucil)*
Relapsed/ Refractory	PCYC 1102[1]	1/2	5 yrs	PFS 44% OS 60%
	RESONATE[4] (vs ofatumumab)	3	5 yrs	Median PFS 44.1 mos (vs 8.1 mos for ofatumumab) OS data to be presented ASCO 2019
High Risk	RESONATE-17[5] (R/R, del[17p])	2	2 yrs	PFS 63% OS 75%
	Ahn IE, et al[6] (TP53)	2	5 yrs	PFS 74% treatment naïve; 19% R/R OS 85% treatment naïve; 54% R/R

[1]O'Brien S, et al. *Blood*. 2018. Abstract 233. [2]Barr PM, et al. *Haematologica*. 2018. [3]Burger JA, et al. *EHA*. 2018. Abstract PF343. [4]Barr PM, et al. *ASCO*. 2019. Abstract 7510. [5]O'Brien S, et al. *Lancet Oncol*. 2016. [6]Ahn IE, et al. *Blood*. 2018.

*At 2 yr follow-up.

Ibrutinib and Rituximab vs. FCR in TN CLL/SLL

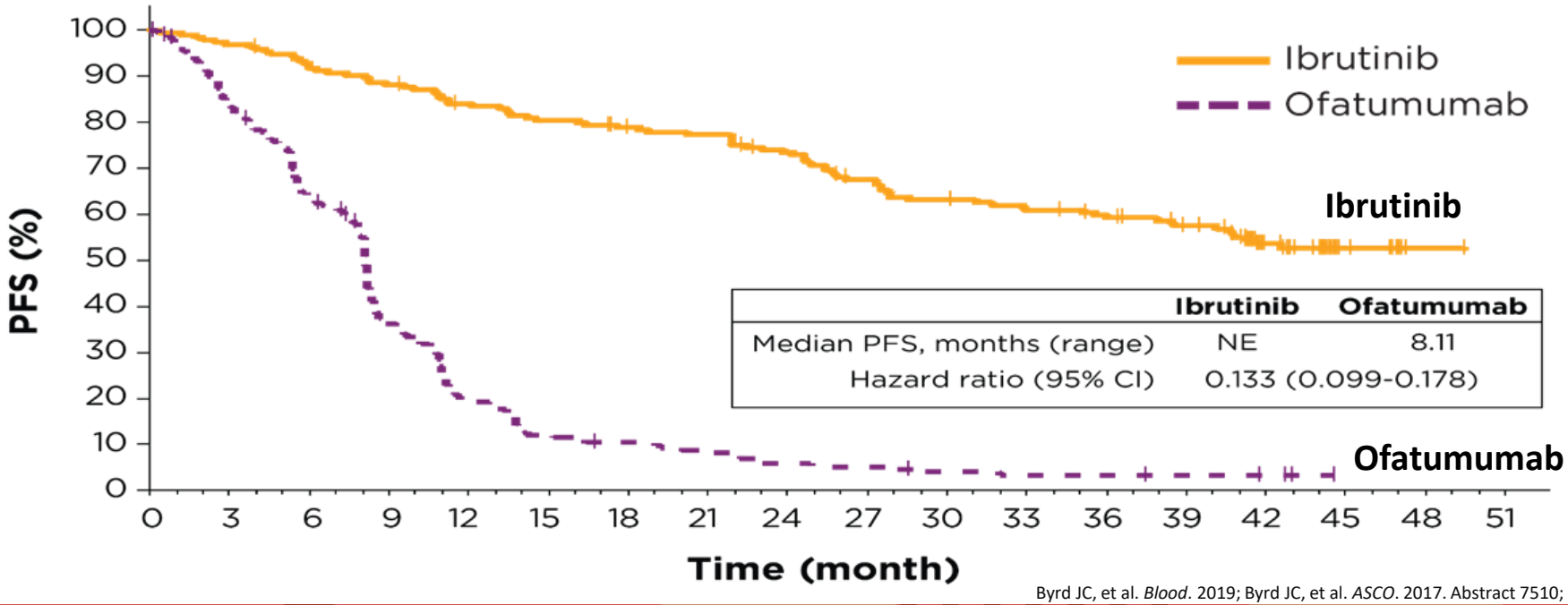
Phase III E1912 Trial



Shanafelt TD, et al. *ASH*. Abstract LBA4. 2018.

Ibrutinib Significantly Extended PFS Compared with Ofatumumab (RESONATE ~4-year Update) in R/R CLL

Updated Results (~6-year Analysis) to be presented at ASCO 2019:
- At a median follow-up of 64 months, median PFS continued to be observed with ibrutinib vs ofatumumab → **44.1 vs 8.1 months** (HR 0.15; 95% CI 0.11-0.20; *P*<0.0001)



Byrd JC, et al. *Blood*. 2019; Byrd JC, et al. *ASCO*. 2017. Abstract 7510; Barr PM, et al. *ASCO*. 2018. Abstract 7510.

Ibrutinib in CLL
Combination Regimens

Study	Population	Regimens	Findings
CLL			
HELIOS[1] (N=578)	R/R	Ibrutinib + BR vs BR	• IRC PFS at 18 mos: 79% vs 24% • No new safety signals

Burger JA, et al[2] (N=206)	High-risk TN and R/R	Ibrutinib + rituximab vs ibrutinib	• No improvement in 2-year PFS or OS with combination therapy
			  • PFS: 94% mono; 93% combo
			  • OS: 98% mono; 94% combo

Jain N, et al[3] (N=72)	High-risk TN and R/R	Ibrutinib + venetoclax	• At 12 mo: 46% R/R and 100% of TN patients were BM MRD negative • TLS risk category lower in 54% of patients at 3 months
Rogers KA, et al[4] (N=25)	TN	Ibrutinib + venetoclax + obinutuzumab	• ORR: 96% • MRD-negative: 58% • No tumor lysis syndrome

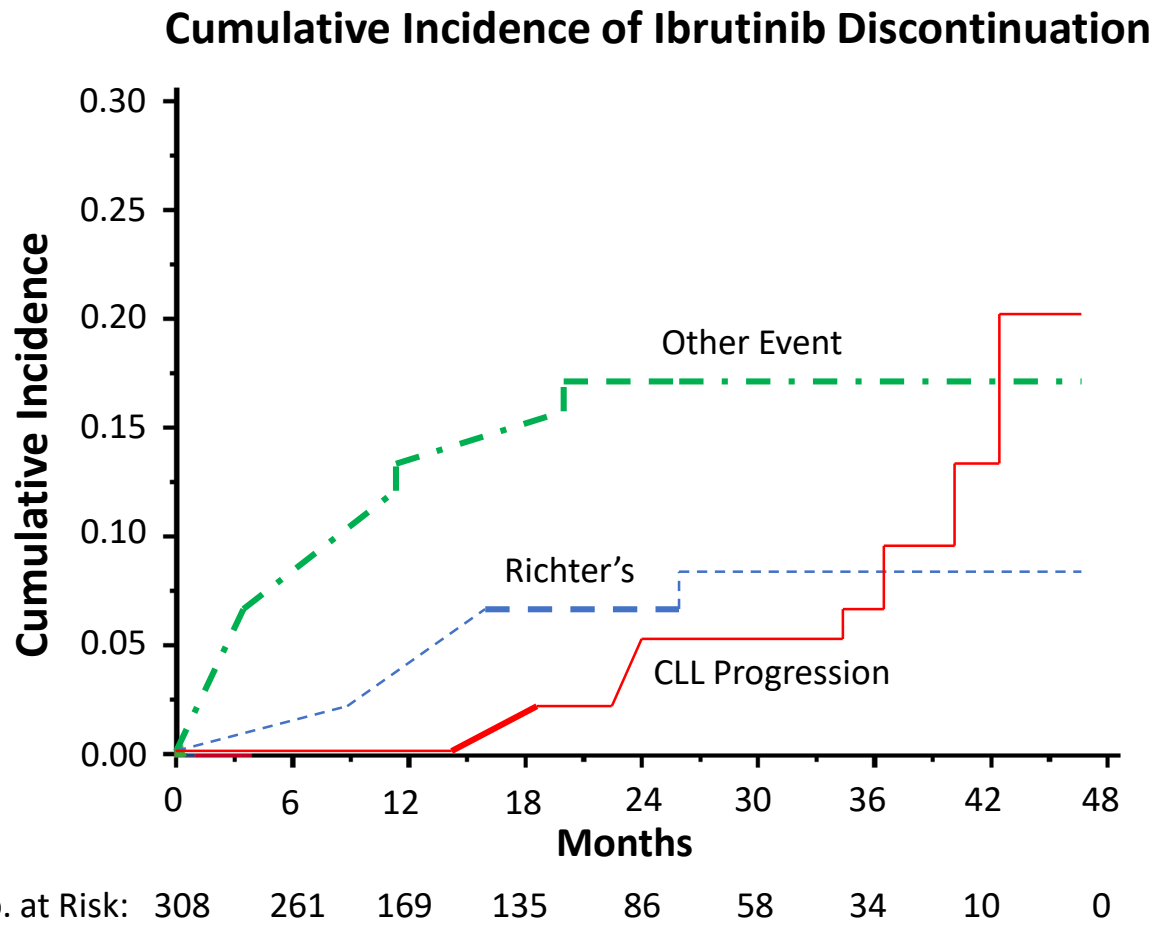
BR=bendamustine + rituximab

[1]Chanan-Kahn A, et al. *Lancel Oncol*. 2016. [2]Burger JA, et al. *ASH*. 2017. Abstract 427. [3]Jain N, et al. *ASH*. 2017. Abstract 429. [4]Rogers KA, et al. *ASH*. 2017. Abstract 431. [5]Jain P, et al. *Br J Haematol*. 2018. [6]Wang ML, et al. *N Engl J Med*. 2013.

Case Study

- After 2.5 years on ibrutinib, he was noted to have increasing lymphocyte count and small palpable nodes.
- States adherence to ibrutinib schedule.
- Trend continues, consistent with progression on ibrutinib.
- FISH studies show del(17p).
- After full review of options, patient decides on treatment with venetoclax + rituximab.
- Ibrutinib continued until venetoclax started, to avoid rapid progression.

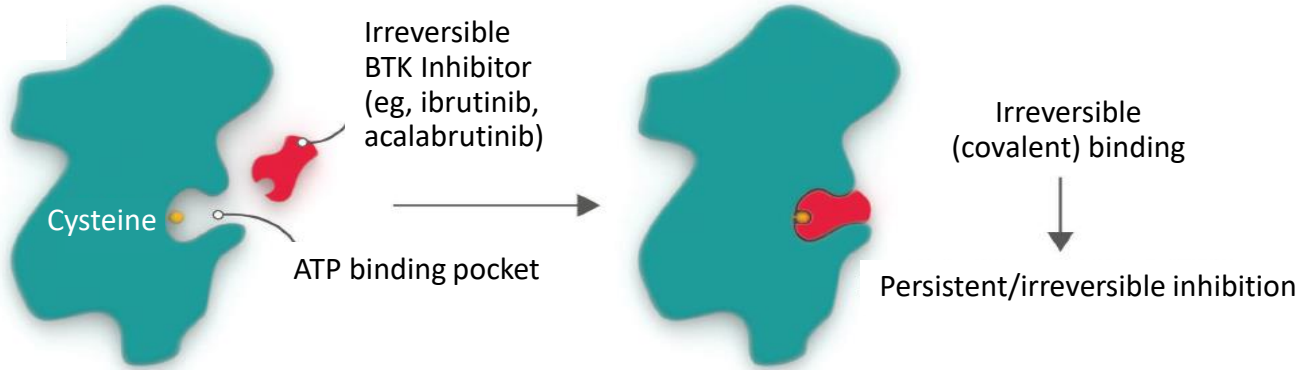
Ibrutinib in CLL
Resistance



- Progressive CLL
  - Almost never occurs during first 12 months.
  - Incidence continues to increase with time.
- Histologic transformation
  - Most commonly to large cell lymphoma (Richter's) or prolymphocytic leukemia.
  - Occurs within first 2 years.
- Poor prognosis
  - Reported median survival of 3–23 months.

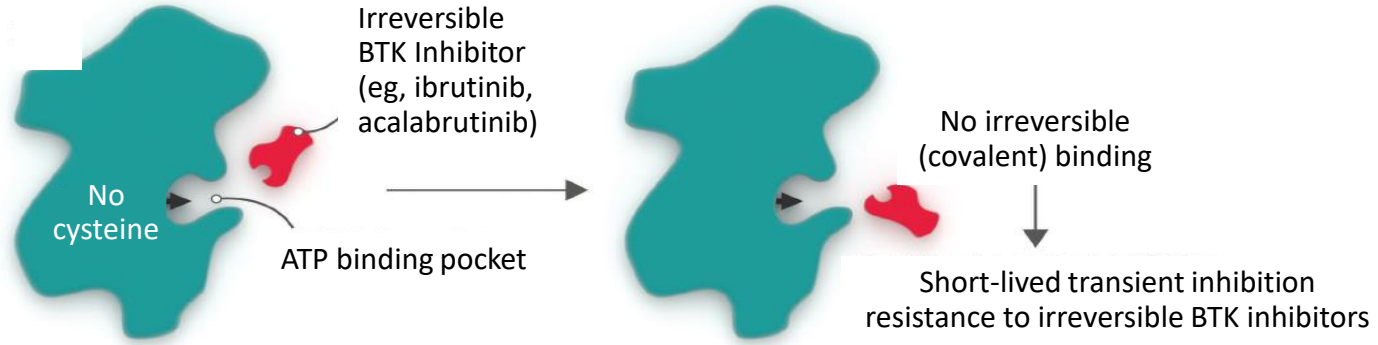
Woyach JA, et al. *Blood.* 2017;
Parikh SA, et al. *ASH.* 2015. Abstract 2935; Maddocks KJ, et al. *JAMA Oncol.* 2015.

Resistance in BTK Inhibitors



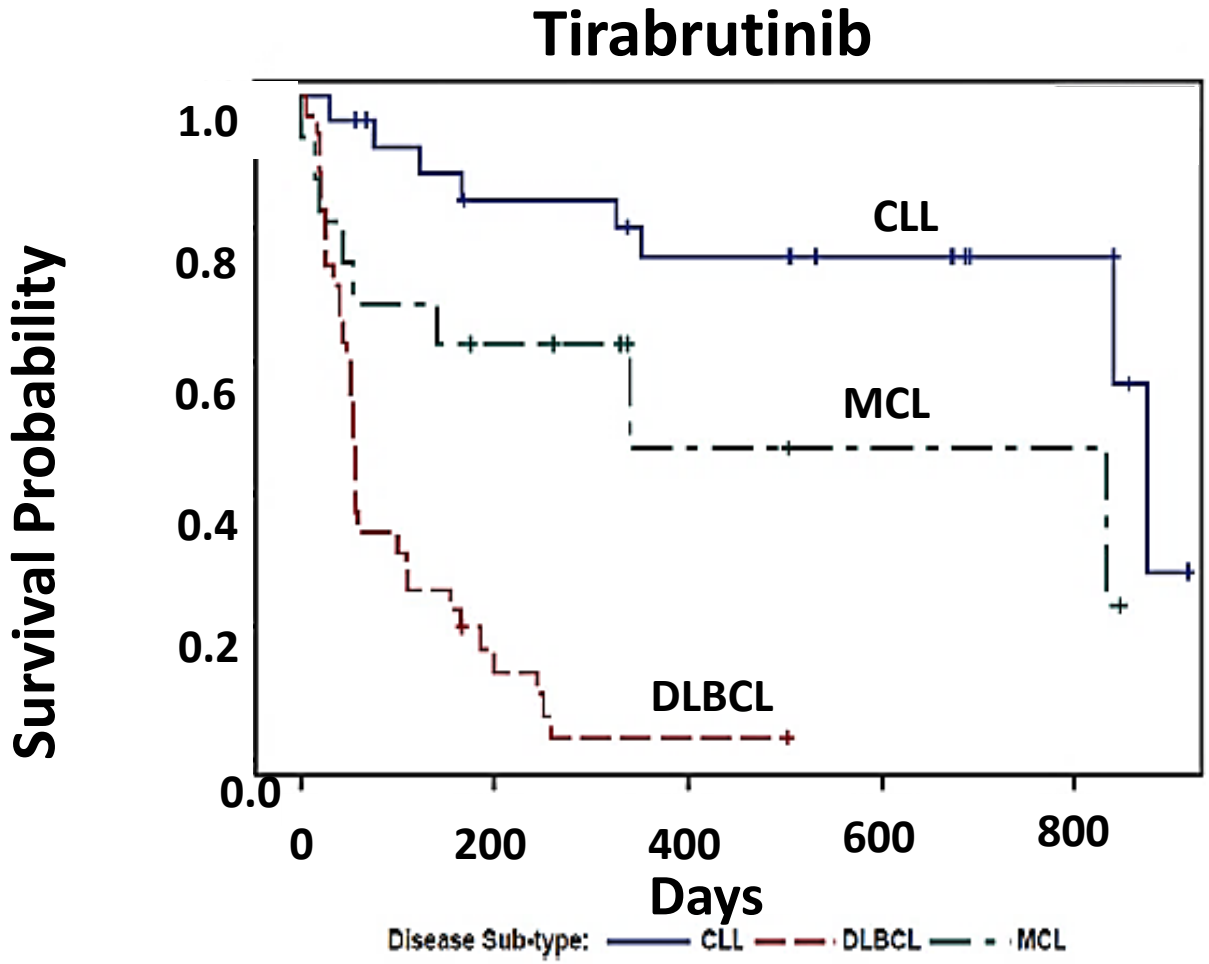
Cys481 Mutation – Resistance to BTK

- ~80% of R/R CLL patients have the C481S mutation (has also observed in acalabrutinib). ***DO NOT use acalabrutinib for ibrutinib-refractory disease (due to the C481 mutation).***
- Reversible BTKis may mitigate resistance (e.g., vecabrutinib, GDC-0853, ARQ-531).



Adapted from Wiestner A. *Haematologica*. 2015; NCCN CLL/SLL Guidelines. v5.2019; Byrd JC, et al. *Oncotarget*. 2018; Wu J, et al. *J Hematol Oncol*. 2016; Woyach JA, et al. *N Engl J Med*. 2014; Byrd JC, et al. *N Engl J Med*. 2016.

BTK Inhibitors
Investigational Agents



Walter HS, et al. *Blood.* 2016.

BTK Inhibitors
Investigational Agents

Zanubrutinib (BGB-3111)

	ORR (CR+PR)	SD
CLL (N=66)	94%	5%
Aggressive Lymphoma* (N=46)	61%	11%
Indolent Lymphoma** (N=16)	50%	50%

*MCL and DLBCL
**FL and MZL

- Most responses were partial.
- No related bleeding or Afib in early evaluation.

Seymour JF, et al. *ICML*. 2017. Abstract 237; Tam C, et al. *ASH*. 2017. Abstract 152.

Suggested Regimens for Treatment of CLL/SLL with del(17p)/TP53 Mutation

First-Line	Relapsed/Refractory	Maintenance Therapy
Preferred regimens:	Preferred regimens:	Post first-line maintenance therapy
• **Ibrutinib** • **Venetoclax + obinutuzumab**	• **Ibrutinib** • **Venetoclax + rituximab** • **Duvelasib** • **Idelalisib + rituximab** • **Venetoclax**	• Consider **Lenalidomide** for high-risk patients with blood minimal residual disease with unmutated IGHV or del(17p)/TP53 mutation) after first-line therapy
Other recommended regimens	Other recommended regimens	Post second-line maintenance therapy
• **Alemtuzumab +/- rituximab** • **HDMP + rituximab** • **Obinutuzumab**	• **Acalabrutinib** • **Alemtuzumab +/- rituximab** • **HDMP + rituximab** • **Idelalisib** • **Lenolidomide +/- rituximab** • **Ofatumumab**	• **Lenalidomide** • **Ofatumumab**

National Comprehensive Cancer Network. (2019). *CLL/SLL Guidelines*. Version 5.2019. nccn.org/professionals/physician_gls/pdf/cll.pdf.

BCL2 Inhibitor—Venetoclax

Dose	Ramp up for first 5 weeks and then 400 mg daily (ramp-up to reduce risk of tumor lysis syndrome)
Dosage Form	Tablets: 10 mg, 50 mg, 100 mg
Most common adverse events (>20%)	Neutropenia, diarrhea, upper respiratory track infection, thrombocytopenia, musculoskeletal pain, edema, fatigue, cough, and nausea
Drug Interactions	Strong or moderate CYP3A inhibitors, P-gp inhibitors
Resistance	GLy101Val

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

Unique AEs with Venetoclax—TLS

- Venetoclax therapy can cause rapid reduction in tumor and pose a risk for TLS at initiation and during ramp-up phase.
- Changes in blood chemistries consistent with TLS (requiring prompt management) can occur as early as 6-8 hours after first dose and at each dose increase.
- Risk increases in those with comorbidities (e.g., reduced renal function) and increased tumor burden.
- Concomitant use with P-gp inhibitors or strong/moderate CYP3A inhibitors, increases risk of TLS and requires dose adjustment.
- ***Best managed if anticipated and prophylaxis is started prior to treatment.***

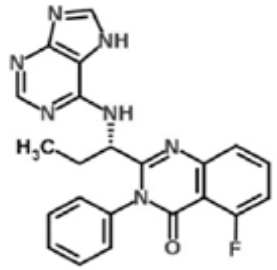
FDA Prescribing Information.

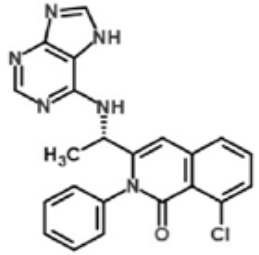
TLS Prophylaxis Based on Tumor Burden

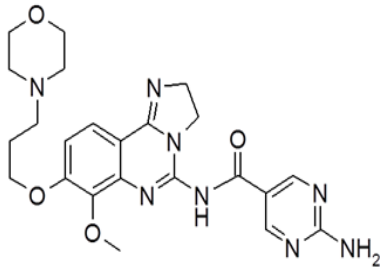
Tumor Burden	Prophylaxis	Blood Chemistry Monitoring
Low All LN <5 cm and ALC <$25x10^9$/L	• Oral hydration (1.5–2 L) • Allopurinol	Outpatient • For first dose of 20 mg and 50 mg: Pre-dose, 6–8 hours, 24 hours • For subsequent ramp-up doses: Pre-dose
Medium Any LN 5 cm to <10 cm or ALC ≥$25x10^9$/L	• Oral hydration (1.5–2 L) and consider additional intravenous • Allopurinol	Outpatient • For first dose of 20 mg and 50 mg: Pre-dose, 6–8 hours, 24 hours • For subsequent ramp-up doses: Pre-dose • For first dose of 20 mg and 50 mg: Consider hospitalization for patients with ClCr <80 mL/min
High Any LN ≥10 cm or ALC ≥$25x10^9$/L and any LN ≥5 cm	• Oral hydration (1.5–2 L) and intravenous (150–200 mL/hour as tolerated) • Allopurinol (consider rasburicase if baseline uric acid is elevated)	In hospital • For first dose of 20 mg and 50 mg: Pre-dose, 4, 8, 12, 24 hours Outpatient • For subsequent ramp-up doses: Pre-dose, 6–8 hours, 24 hours

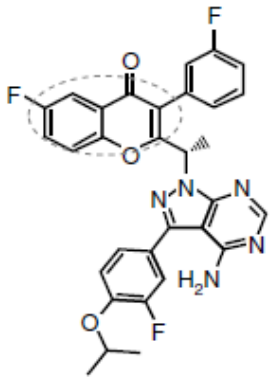
FDA Prescribing Information.

PI3K Inhibitors Are Active in CLL and Other B-Cell Cancers









Idelalisib (IC_{50}-nM)[1]	Duvelisib (IC_{50}-nM)[2]	Copanlisib (IC_{50}-nM)[3]	Umbralisib (IC_{50}-nM)[4]
Oral	Oral	IV	Oral

1. Meadows SA et al. *Blood*. 2012;119:1897-1900. 2. Winkler DG et al. *Chem Biol*. 2013;20:1364-1374. 3. Haike K et al. ASH Meeting on Lymphoma Biology 2014. Abstract 48. 4. Vakkalanka S et al. American Association for Cancer Research Annual Meeting 2014 (AACR 2014). Poster 3741.

PI3K Inhibitors

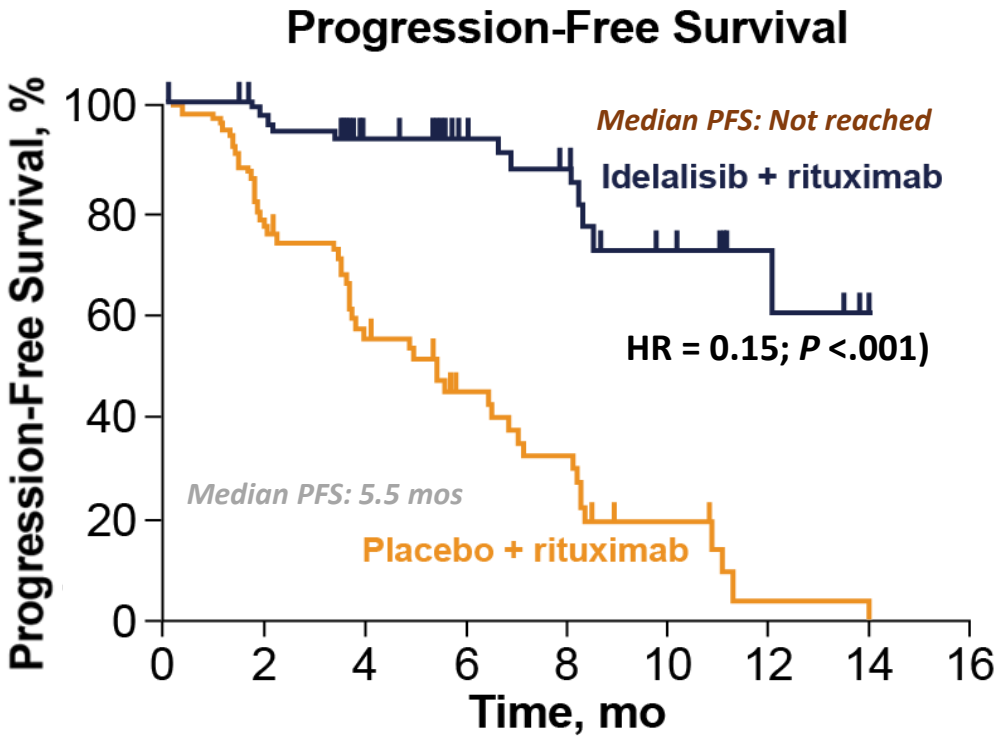
	Idelalisib	Duvelisib	Copanlisib- FL
Dose	150 mg orally twice daily	25 mg orally twice daily	60 mg infusion on D1, 8, and 15 in 28-day cycle
Dosage Form	Tablets: 150 mg, 100 mg	Capsules: 25 mg, 15 mg	For injection as lyophilized solid in single-dose vial for reconstitution
Most Common Adverse Events (>20%)	Diarrhea, fatigue, nausea, cough, pyrexia, abdominal pain, and rash	Diarrhea or colitis, neutropenia, rash, fatigue, pyrexia, cough, nausea, upper respiratory infection, pneumonia, musculoskeletal pain, and anemia	Hyperglycemia, diarrhea, decreased general strength and energy, hypertension, leukopenia, neutropenia, nausea, lower respiratory tract infection, and thrombocytopenia
Drug Interactions	Strong CYP3A inhibitors and inducers, CYP3A substrates	CYP3A inhibitors or inducers, CYP3A substrates	CYP3A inhibitors or inducers

FDA Prescribing Information.

Idelalisib + Rituximab Is Highly Effective in Relapsed/Refractory CLL

Idelalisib + rituximab in CLL

- Patients with relapsed CLL and comorbid conditions (decreased renal function, previous therapy-induced myelosuppression, or major coexisting illnesses)
- **Combination improved PFS vs rituximab alone**



No. at Risk, events

Idelalisib	110 (0)	69 (2)	44 (5)	34 (5)	30 (7)	14 (11)	6 (11)	2 (12)	0 (12)
Placebo	110 (0)	62 (20)	30 (33)	18 (39)	30 (7)	13 (44)	6 (49)	1 (52)	0 (53)

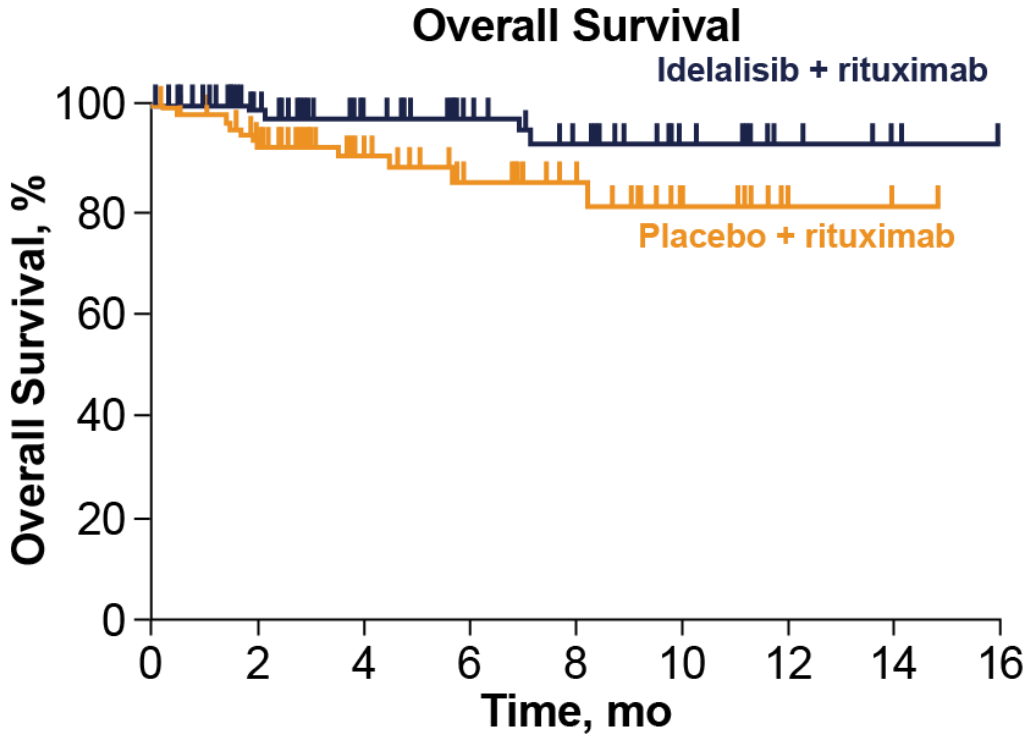
1. Furman RR et al. *N Engl J Med*. 2014;370:997-1007.

Idelalisib + Rituximab Is Highly Effective in Relapsed/Refractory CLL

Idelalisib + rituximab in CLL

- Combination also improved OS and response vs rituximab alone
- ORR: 81% vs. 13%; *P* < .001
- 1-Year OS: 92% vs. 80%; HR = for 0.28; *P* = .02

Take home: Idelalisib + rituximab more effective than rituximab in CLL patients less able to undergo chemotherapy



No. at Risk, events

Idelalisib	110 (0)	88 (1)	55 (2)	40 (2)	31 (4)	16 (4)	7 (4)	4 (4)	0 (4)
Placebo	110 (0)	76 (8)	43 (9)	25 (11)	18 (11)	8 (12)	2 (12)	1 (12)	0 (12)

Furman RR et al. *N Engl J Med*. 2014;370:997-1007.

PI3K Inhibitor Specific Toxicities and Management

Toxicity	Idelalisib	Duvelisib
ALT/AST Elevation		
3–5x ULN (grade 2)	Maintain dose and monitor weekly until ≤1x ULN	Maintain dose and monitor weekly until <3x ULN
>5–20x ULN (grade 3)	Hold and monitor weekly until ≤1x ULN; resume at 100 mg BID	Hold and monitor weekly until <3x ULN; resume at same dose for first occurrence, reduce to 15 mg for second
>20x ULN (grade 4)		D/C therapy
Copanlisib Specific Toxicities and Management		
Hyperglycemia—41%		
Pre-dose FBG ≥160 mg/dL OR random NFBG ≥200 mg/dL	Hold until FBG is ≤160 mg/dL or random NFBG is ≤200 mg/dL	
Pre-dose FBG or post-dose BG >500 mg/dL	First occurrence: hold until is ≤160 mg/dL or random NFBG is ≤200 mg/dL; reduce dose to 45 mg Subsequent occurrences: hold until is ≤160 mg/dL or random NFBG is ≤200 mg/dL; reduce dose to 30 mg. If persistent at 30 mg, D/C	
Hypertension—26%		
Pre-dose BP ≥150/90	Hold until <150/90 based on two consecutive BP measurements at least 15 min apart	
Post-dose BP ≥150/90 (non-life threatening)	If anti-hypertensive treatment not required, continue; if required, reduce dose. D/C if BP remains uncontrolled (>150/90) despite antihypertensive treatment	
Post-dose elevated BP with life-threatening consequences	D/C drug	

FDA Prescribing Information.

Case Study

- Tolerates venetoclax ramp-up without tumor lysis syndrome.
- Counts begin to improve and nodes start to reduce in size toward the end of ramp-up.
- Rituximab monthly x 6 post ramp-up.
- Remains on venetoclax with no progression and no toxicity.

Safety
Concomitant Medications

- Avoid co-administration with strong CYP3A4 inhibitors/inducers.
  - If CYP3A inhibitors are to be used short-term (such as anti-infectives for up to 7 days, interrupt therapy).
- Dose reductions are recommended when BTK inhibitor is co-administered with moderate CYP3A inhibitors.
- Acalabrutinib: Avoid co-administration with proton pump inhibitors (e.g., omeprazole), take 2 hours before taking H2-receptor antagonists (e.g., ranitidine), and separate dosing by at least 2 hours with antacids.

CYP3A4/5 Inhibitors*	CYP3A4/5 Inducers*
Clarithromycin	Carbamazepine
Itraconazole	Phenytoin
Ketoconazole	Rifampin
Ritonavir	St. John's wort
Erythromycin	Modafinil
Diltiazem	Rufinamide
Fluconazole	
Grapefruit juice	
Seville oranges	
Verapamil	
Cimetidine	

*Not a complete list

FDA Prescribing Information;
fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm.

Adherence
A New Challenge in Era of Targeted Therapies

- New standards of oncologic therapy require new mindset for patient management.
  - Therapy moving from the controlled, clinic setting to the home.
  - Therapy moving from short term to long term, possibly lifetime.
- With these changes, cancer care more closely follows the chronic disease model.
  - Substantial number of patients struggle to adhere to oral anti-cancer regimens.
- Studies of Americans with cancer suggest that most prefer learning detailed information about their disease and its prognosis in a direct and honest manner.
  - However, many patients have little understanding of their disease prognosis, treatment options, or sources of support.

Stacey D, et al. *Cochrane Database Syst Rev*. 2017; Greer JA, et al. *The Oncologist*. 2016; ahrq.gov/professionals/education/curriculum-tools/shareddecisionmaking/index.html.

Cost
The Prohibitive Economics of Cancer Therapy

- In 2015, direct medical costs from cancer in the U.S. were estimated at $80.2 billion.
- Average cost of newly-approved therapies is ~$10,000/month.
- With the emerging role of targeted therapies, prices continue to climb.
  - As of 2011, the mean monthly insurance payment for targeted oral anticancer medications was $7,370.
  - Approximately 9% of Americans are uninsured, resulting in an elevated bankruptcy rate among cancer patients.
  - Annual cost-per-patient routinely exceeds $100,000.
- Clinical impact is significant.
  - Limits access to care.
  - 31.6% of patients recently diagnosed with cancer will alter their prescription drug use for financial reasons, compared to just 21.4% of patients with no history of cancer.

Zheng Z, et al. *Cancer.* 2017; Ya-Chen TS, et al. *J Clin Oncol.* 2015; am.asco.org/cost-cancer-drugs-should-be-part-treatment-decisions; cancer.org/cancer/cancer-basics/economic-impact-of-cancer.html.

Adherence

Using Shared Decision-Making (SDM) to Overcome Barriers

- Improved satisfaction with clinical communication and treatment has been shown to strongly predict adherence to oral anticancer therapy.
- Analysis from the RESONATE study on the effect of adherence to ibrutinib found:
  - Sustained adherence to daily dosing was necessary to achieve optimal outcomes.
  - PFS was shorter in patients missing ≥8 consecutive doses compared to those who missed <8 days.

Barriers to Adherence
Personal • Emotional/mental status • Social support • Disease attitudes/expectations • Socioeconomic status
Treatment-Related • Complexity of treatment • Immediacy/evidence of benefits • Side effects • Cost ***"Financial Toxicity"***
Healthcare System • Relationship with providers • Communication with providers • Patient education • Satisfaction with care • Convenience of care

Jacobs JM, et al. *J Oncol Pract*. 2017; Barr PM, et al. *Blood.* 2017; Fessele KL. *Clin J Oncol Nurs*. 2017.

Improving Adherence
ONS Toolkit
Communications Approaches

Traditional Counseling	Motivational Interviewing
• HCP is the healthcare expert • Assumes patient lacks knowledge • Tells patient what to do • Hopes patient follows instructions	• HCP develops partnership with patient • Exchanges information to facilitate an informed decision • Patient has the right to decide own care
• HCP provides definitive information • Directives are presumed to be non-negotiable	• HCP provides information to patient for the purpose of developing discrepancy between present behavior and goal
• HCP dictates healthcare behavior	• HCP and patient negotiate behavior and reach agreement
• Goal is to motivate the patient	• Goal is to access motivation and elicit patient's commitment to change behavior
• HCP persuades patient to change behavior	• HCP understands and accepts patient's actions
• HCP expects respect from patient	• HCP must earn respect from patient

ons.org/practice-resources/toolkits/oral-adherence.

Key Takeaways

- Each of the novel agents have unique adverse events.
- Nurses play a key role in educating patients regarding the proper way to take the novel agents and to monitor for adverse events.
- Nurses also are key in the management of adverse events associated with treatment of malignancies.
- Oncology nurses are in a unique position to evaluate and address barriers to adherence and improve patient outcomes.