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SPOTLIGHT ON CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

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WELCOMING REMARKS

SPOTLIGHT ON CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

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WELCOMING REMARKS

SPOTLIGHT ON CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

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Occupational Therapist
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Guest on The Bloodline with LLS Podcast Episode:
Improving Quality of Life Through Wellness Practices

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DISCLOSURES

SPOTLIGHT ON CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

Dr. Nicole Lamanna

SAB/Consultant/Honoraria:
AbbVie, Adaptive Biosciences, Astra-Zeneca, Bei-Gene, Bristol Myers Squibb, Celgene, Genentech, Janssen, LOXO/Eli Lilly, Pharmacyclics

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General Characteristics

- Most common adult leukemia – about 30% of adult leukemias
- Relatively long survival makes CLL by far the most prevalent leukemia in the United States: 180,000 patients alive with CLL
- Median survival exceeds 10 years
- Median age at diagnosis 72

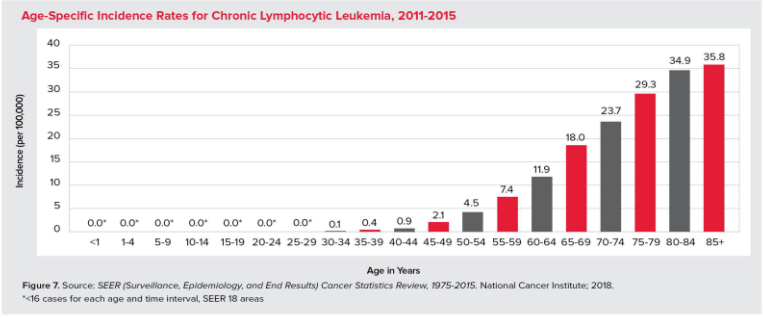

Figure 7. Source: *SEER (Surveillance, Epidemiology, and End Results) Cancer Statistics Review, 1975-2015.* National Cancer Institute; 2018.
*<16 cases for each age and time interval, SEER 18 areas

What is CLL/SLL?

- Leukemia is a type of cancer of the bone marrow and blood
- SLL and CLL considered the same B-cell malignancy
  - CLL: > 5000 clonal B cells in peripheral blood
  - SLL: presence of lymphadenopathy and/or splenomegaly and < 5000 clonal B cells in peripheral blood
- Causes/risk factors:
  - Agent orange exposure
  - Benzene exposure
  - First degree relative of patients with CLL are more likely to develop CLL

Signs and Symptoms

- Most at diagnosis have NO symptoms and often diagnosed incidentally by routine blood work and/or imaging for another reason
- Those who develop symptoms may experience:
  - Fatigue
  - Shortness of Breath
  - Swollen Lymph Nodes or Spleen
  - Infections
  - Weight Loss
  - Night Sweats
  - Easy Bruising

Role of CT Scans

- Computed tomography (CT) scans generally are not required for the initial evaluation or follow-up
- Enlarged lymph nodes detected only by CT do not change Binet or Rai stage
- Minor residual abnormalities on CT scan are less predictive of clinical course than MRD studies on bone marrow

MRD = minimal residual disease.

Hallek et al. Blood. 2008;111(12):5446-5456.
Muntanola et al. J Clin Oncol. 2007;25(12):1576-80.
Eichhorst, et al. Blood. 2011;117(6):1817-21.

Initial Workup of CLL Patients

- All patients at diagnosis:
  - Flow cytometry to confirm CLL diagnosis
- Informative for prognostic and/or therapy determination:
  - Interphase cytogenetics/FISH for: +12, del(13q), del(17)(p13.1), and del(11)(q22.3); del(17p) and del(11q) portend for more aggressive disease
  - IGHV gene status assessment (good lab)
  - β_2-microglobulin
- No CT scan unless symptoms are present; PET scan can be helpful if Richter's suspected
- Bone marrow biopsy and aspirate not necessary in absence of cytopenias

CLL Staging Systems: Rai and Binet Staging Systems

- Take into account:

- Abnormal increase in number of lymphocytes (lymphocytosis)
- Presence of enlarged lymph nodes
- Presence of enlarged spleen and/or liver
- Presence of anemia (abnormal decrease in the number of red blood cells)
- Presence of thrombocytopenia (abnormal decrease in the number of platelets)

Rai Staging System

Stage	Characteristics
Low Risk (Stage 0)	Abnormal increase in the number of lymphocytes in the circulating blood and marrow
Intermediate Risk (Stages I & II)	• Abnormal increase in the number of lymphocytes in the circulating blood and marrow • Enlarged lymph nodes OR • Abnormal increase in the number of lymphocytes in the circulating blood and marrow • Enlarged spleen and/or liver
High Risk (Stages III & IV)	• Abnormal increase in the number of lymphocytes in the circulating blood and marrow • Anemia (hemoglobin < 11 g/dL) OR • Abnormal increase in the number of lymphocytes in the circulating blood and marrow • Thrombocytopenia (platelet counts < 100,000/μL)

Binet Staging System

Stage	Characteristics
A	• No anemia (hemoglobin ≥ 10 g/dL) • No thrombocytopenia (platelets≥ 100,000/mm³) • Less than 3 areas of lymphoid tissue enlargement
B	• No anemia (hemoglobin ≥ 10 g/dL) • No thrombocytopenia (platelets ≥ 100,000/mm³) • 3 or more areas of lymphoid tissue enlargement
C	• Anemia (hemoglobin < 10 g/dL) • Thrombocytopenia (platelets < 100,000/mm³) • Any number of areas of lymphoid tissue enlargement

CLL International Prognostic Indicator (CLL-IPI)

CLL-IPI Category	Risk Score	Treatment Recommendations
Low Risk	0-1	Do not treat
Intermediate Risk	2-3	Do not treat unless the disease is highly symptomatic
High Risk	4-6	Treat except if the patient is asymptomatic
Very high risk	7-10	If decide to treat, do not use chemotherapy but rather novel agents or treatment in clinical trials

Five Prognostic Factors

- TP53 deleted or mutated=4 points
- Unmutated IGHV=2 points
- Serum B-2 microglobulin concentration >3.5mg/L=2 points
- Rai I-V or Binet B-C=1 point
- Patient age>65 years=1 point

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When to Treat?

- **iwCLL criteria**: ***"active disease"***
- Progressive marrow failure with worsening of anemia (hgb<10 g/dL) and/or thrombocytopenia (plts<100)
- Massive or progressive symptomatic splenomegaly or lymphadenopathy
- Absolute white count # not used for treatment (rate of change is progressive lymphocytosis with an increase of >50% over a two-month or lymphocyte doubling time of <6 months suggests progressive disease)
- Symptomatic or functional extranodal involvement (eg, skin, kidney, lung)
- Constitutional symptoms: significant fatigue, night sweats, weight loss, fevers

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Considerations Prior to Initiating Therapy

Anemia or thrombocytopenia	• Exclude GI blood loss • Assess for AIHA/ITP
Symptomatic disease	• Assess for possible lymphoma transformation
Rapidly progressive disease	• Assess for possible lymphoma transformation

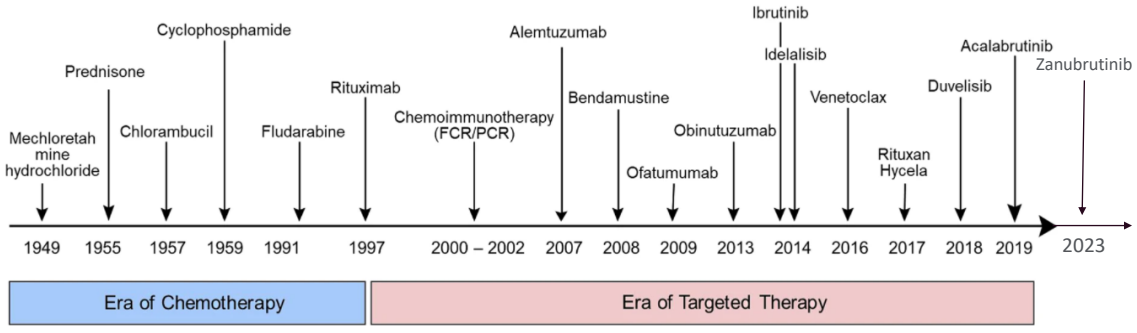
AIHA = autoimmune hemolytic anemia; GI = gastrointestinal; ITP = immune thrombocytopenic purpura.

How to Differentiate Patients at Time of Treatment?

- Age or functional status (comorbidities)
  - US: Age 65-70 yrs
  - Europe: CIRS score or creatinine clearance < 60 mL/min
- Genomic features – if not done at diagnosis should be done prior to treatment
  - FISH: can change with treatment
    - Presence or not of del(17p) status/TP53 mutation
    - Know % of cells with deletion
  - IGHV mutation status – does not change

Evolution of CLL Therapy

Timeline of US Food and Drug Administration approvals for chronic lymphocytic leukemia.



FCR fludarabine, cyclophosphamide, and rituximab, PCR pentostatin, cyclophosphamide, and rituximab.

Parikh et al., Nature 2020

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Current Treatment Options

- Active observation and monitoring (previously “watch-and-worry”)
- Targeted therapies (ie BTKis, venetoclax, PI3Kis)
- Monoclonal antibody therapies (ie obinutuzumab, rituximab)
- Chemotherapy (ie fludarabine, cyclophosphamide, bendamustine, chlorambucil, pentostatin)
- Chemoimmunotherapy (ie FCR, BR)
- CAR T-cell Therapy
- Stem cell transplantation
- Clinical trials

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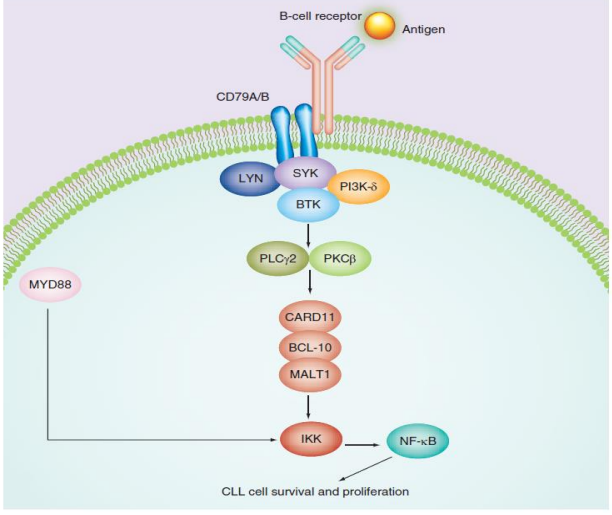
Why it is OK to be in the Active Observation and Monitoring Group!

- Previously 'watch and worry'
- Currently no therapy is yet technically curative
- Historically, early therapy did not change survival (stay tuned…some early intervention studies with targetted therapies in high-risk CLL patients ongoing...)
- Therapies continue to evolve and change
- All therapies have some side effects
- Some patients never need therapy

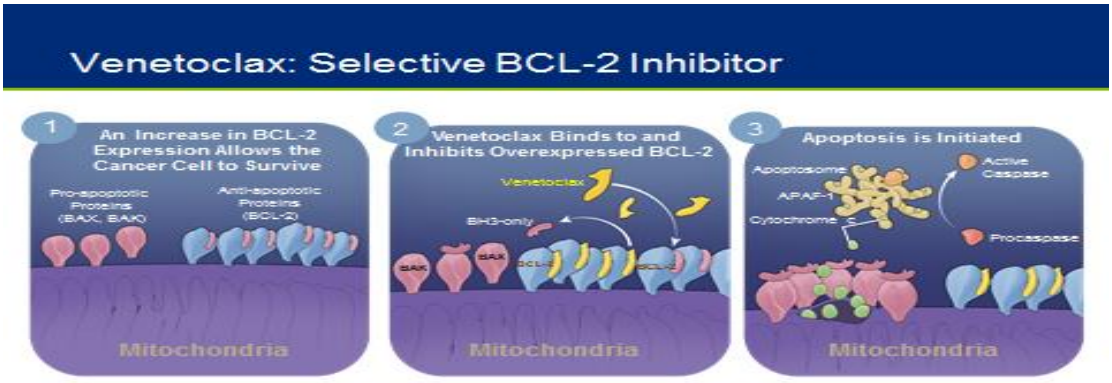
B-Cell Receptor (BCR) Signaling

- BCR: transmembrane receptor located on surface of B lymphocytes
  - Key survival molecule for normal B cells and for most B-cell malignancies
  - In CLL, BCR signaling plays key role in disease pathogenesis
- Mature B cells able to recognize an extensive array of foreign antigens via unique BCR
  - Triggers antigen-specific antibody responses
  - Promotes B-cell differentiation into plasma cells and memory B cells
- BCR stimulation occurs through signaling cascades involving activation of kinases, including SYK, BTK, and PI3K



SYK, spleen tyrosine kinase; BTK, Bruton tyrosine kinase; PI3K, phosphatidylinositol 3-kinase. Burger JA, Wiestner A. *Nat Rev Cancer*. 2018;18(3):148-167. Stevenson FK, et al. *Blood*. 2011;118(16):4313-4320.

Targeting of BCL-2



- Venetoclax is a potent, orally bioavailable agent with a BCR-independent mechanism of action and substantial activity in heavily pre-treated CLL (Roberts AW et al, *NEJM* 2015)

Targeted Therapy: FDA Approvals and Current Status in CLL

Agent	Target	Status in CLL/SLL
Ibrutinib[1]	BTK (covalent)	Approved
Acalabrutinib[2]		Approved
Zanubrutinib[3]		Approved
Pirtobrutinib	BTK (non-covalent)	Phase 3 BRUIN CLL-321 Phase 3 BRUIN CLL-313
Nemtabrutinib		Phase 2
Venetoclax[4]	BCL-2	Approved
Idelalisib[5]	PI3K	Approved
Duvelisib[6]		Approved

Clinical note: In January 2023, pirtobrutinib was approved for the treatment of adult patients with R/R MCL after ≥2 lines of systemic therapy, including a BTK inhibitor[7]

1. Imbruvica (ibrutinib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205552s002lbl.pdf. 2. Calquence (acalabrutinib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/210259s000lbl.pdf. 3.Zanubrutinib prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/213217s007lbl.pdf. 4. Venclexta (venetoclax) Prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208573s009lbl.pdf. 5. Zydelig (idelalisib) Prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206545lbl.pdf. 6. Copiktra (duvelisib) Prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/211155s000lbl.pdf. 7. Jaypirca (pirtobrutinib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/216059s000lbl.pdf.

Modern Goals of Therapy for Patients With CLL

- Modern therapy is very effective but can achieve different goals
- Important to review goals with your care team and empower your 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

Longer Follow-Up Confirms Efficacy of Continuous BTKi versus Traditional Chemoimmunotherapy

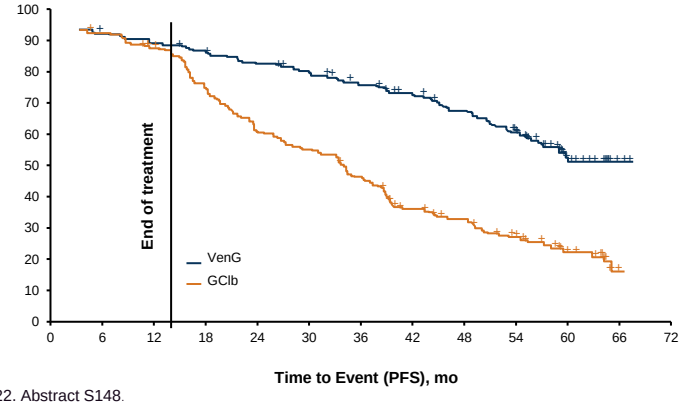
	Alliance[1]	ELEVATE-TN[2]	SEQUOIA[3]
	Ibrutinib ± rituximab vs BR	**Acalabrutinib ± G vs G + Clb**	**Zanubrutinib vs BR**
Length of follow-up	4.5 y	5 y	>2 years (26.2 mo)
Efficacy	• 48-month PFS estimates were 76% for ibrutinib arms vs 47% for BR	• 60-month PFS of 84% and 72% (A+G and acalabrutinib) vs 21% for G + Clb	• 24-mo PFS was 86% with zanubrutinib vs 70% for BR

FDA-approved January 19, 2023 for CLL/SLL

1. Woyach J et al. ASH 2021. Abstract 639. 2. Sharman JP et al. ASCO 2022. Abstract 7539. 3. Tam C et al. *Lancet Oncol*. 2022;23:1031-1043.

CLL14: 5-Year Follow-Up Shows Efficacy of Frontline Venetoclax/Obinutuzumab vs Chlorambucil/Obinutuzumab[1]

At 5 years after randomization, estimated PFS was 62.6% after VenG and 27% after GClb[2]



1. Al-Sawaf O et al. EHA 2022. Abstract S148.

Choosing between a BTK vs BCL2 inhibitor

BTK Inhibitor[1-4]	BCL2 Inhibitor[4,5]
• Logistically very easy	• Cumbersome initiation/ramp-up
• Indefinite therapy	• Fixed duration
• TLS not of concern	• Risk for TLS requires monitoring
• More cardiac risk/hypertension	• GFR sensitivity
• Some favor in del(17p)/*TP53* mutation	• Question if best for high risk

1. Acalabrutinib PI. 2. Ibrutinib PI. 3. Zanubrutinib PI. 4. Awan. Am Soc Clin Oncol Educ Book. 2020;40:1. 5. Venetoclax PI.

Very-High-Risk CLL With Del17p/*TP53* Aberration-good news…..great drugs

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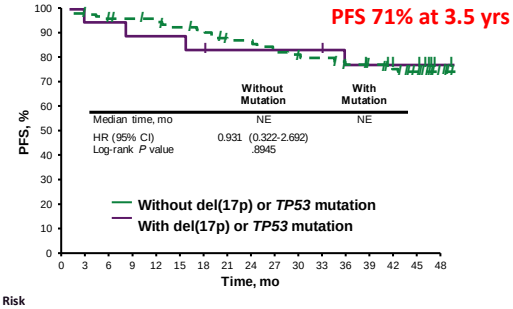
Continuous BTKi in CLL With *TP53* Aberration vs Time-Limited Venetoclax + Obinutuzumab

Ibrutinib

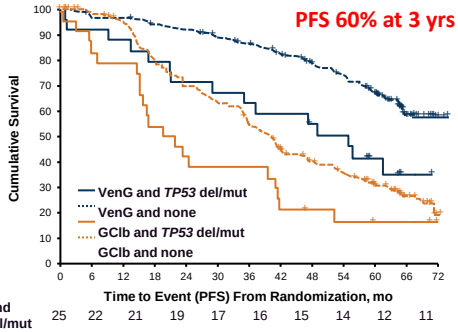
iLLUMINATE: PFS for ibrutinib in elderly patients with *TP53* mutation[1]



No. at Risk																
Without mutation	95	91	88	88	84	83	80	75	73	71	67	67	62	60	52	41	15
With mutation	18	17	17	16	16	15	14	14	14	14	14	13	12	10	7	6	2

Venetoclax + Obinutuzumab

CLL14: PFS for venG in unfit patients with *TP53* mutation[2]



VenG and *TP53* del/mut	25	22	21	19	17	16	15	14	12	11	6	1
VenG and none	184	169	167	161	157	150	142	130	119	109	89	33
GClb and *TP53* del/mut	24	20	19	13	10	9	9	5	4	3	2	2
GClb and none	184	169	160	135	117	106	90	68	58	48	36	18

1. Moreno C et al. *Haematologica*. 2022;107:2108-2120. 2. Al-Sawaf O et al. EHA 2022. Abstract S148.

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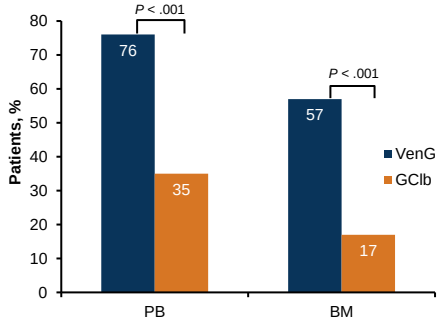
What about MRD (minimal/measurable residual disease) in CLL?

- Not applicable to continuous BTKi
- MRD negativity is associated with longer remissions with fixed duration therapy
- MCF (multicolor flow cytometry) (10-4) in marrow has been the gold standard
- What is the best platform to use?
  - MCF or NGS (next generation sequencing more sensitive - using DNA from a diagnostic sample and than determine dominant sequencing for MRD and track)?
- What should one do with the information?
- Should I monitor MRD serially?

CLL14: VenG Achieved High uMRD and Improved PFS[1,2]

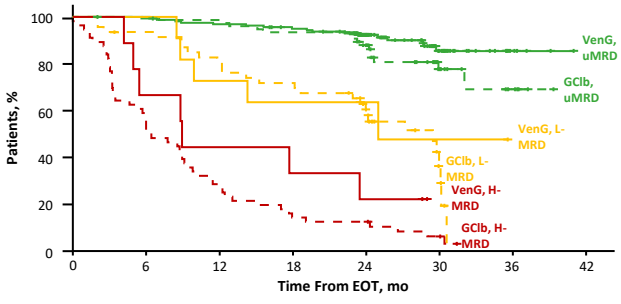
VenG vs GClb as Initial Tx in Patients With CLL and Comorbidities (N = 432)[a]
MRD assessment via clonoSEQ assay

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



In a landmark analysis from EOT, **uMRD patients had longer PFS vs L-MRD or H-MRD (HR = 0.10)**

PFS by PB-MRD Status at EOT
(Median follow-up: 39.6 mo; 2 y after EOT)[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.

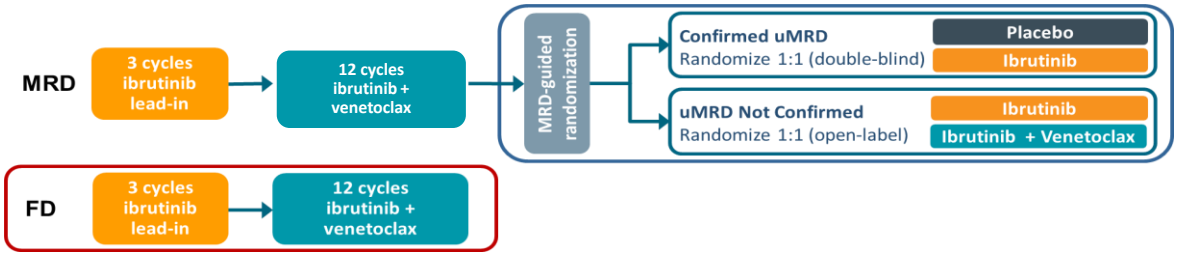
Rationale for Combining BTKi + Venetoclax

- Time-Limited Therapy
- Oral-Oral Combination
- Non-overlapping mechanism of action
- Toxicity profiles non-overlapping
- Act on CLL cells in different compartments
- Synergy in preclinical studies
- High-Risk patients?

Cervantes-Gomez, Clin Cancer Res. 2015; Deng, Leukemia 2017; Slinger, ASH 2017.

Phase 2 CAPTIVATE Study

- CAPTIVATE (PCYC-1142) is an international, multicenter phase 2 study evaluating first-line treatment with 3 cycles of ibrutinib followed by 12 cycles of combined ibrutinib + venetoclax that comprises 2 cohorts: MRD and FD



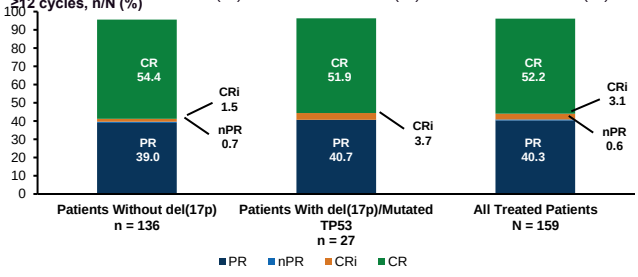
- Results from the MRD cohort demonstrated uMRD in more than two-thirds of patients with 12 cycles of ibrutinib + venetoclax (PB, 75%; BM, 68%), and 30-month PFS rates of ≥95% irrespective of subsequent MRD-guided randomized treatment[1]
- Primary analysis results from the FD cohort of CAPTIVATE was presented at EHA

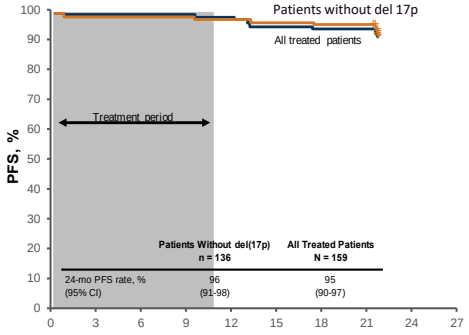
BM, bone marrow; MRD, minimal residual disease; FD, fixed-duration; PB, peripheral blood; PFS, progression-free survival.
Wierda WG et al. ASH 2020, Abstract #123.

CAPTIVATE: FD Ibrutinib + Venetoclax Showed Robust Activity Against TN CLL[1]

The combination achieved durable responses, clinically meaningful PFS, and treatment-free remissions

	Patients Without del(17p) n = 136	Patients With del(17p)/Mutated *TP53* n = 27	All Treated Patients N = 159
Best response, % (95% CI)			
CR/CRi	56 (48-64)	56 (37-74)	55 (48-63)
ORR	96 (92-99)	96 (89-100)	96 (93-99)
Duration of CR ≥12 cycles, n/N (%)	66/76 (87)	13/15 (87)	78/88 (89)





No. at Risk											
All patients	159	155	153	152	152	151	144	144	143	141	
Patients without del(17p)	136	132	130	129	129	128	125	125	124	122	

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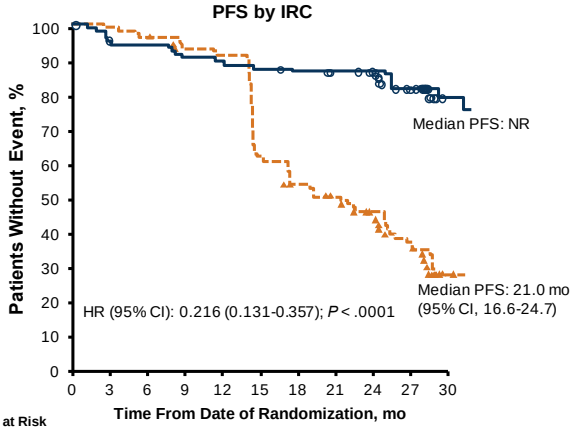
GLOW: Improved PFS and CR With FD I+V vs CIT in TN CLL[1]

Phase 3 assessment of all-oral FD I+V versus GClb in an elderly or unfit TN CLL population[1]

- I+V reduced risk of progression or death by 78% vs GClb
  - HR = 0.216 (95% CI, 0.131-0.357; *P* < .0001)
- CR/CRi rates were significantly higher for I+V vs GClb by both IRC and INV assessments (*P* < .0001)

Led to EMA approval of I+V for adults with previously untreated CLL[2]



No. at Risk											
I+V	106	98	98	94	92	91	89	87	71	59	20
GClb	105	104	101	95	93	63	54	47	36	25	6

1. Kater A et al. *NEJM Evidence*. 2022;1. 2. https://www.bloomberg.com/press-releases/2022-08-04/european-commission-approves-imbruvica-ibrutinib-in-a-fixed-duration-combination-regimen-for-adult-patients-with-previously.

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Characterizing Safety With Novel Time-Limited Combinations[1-3]

Phase 3 GLOW (median follow-up of 28 mo)[1]

- Similar rates of grade ≥3 AEs (76% for I+V, 70% for GClb)
- SAEs in ≥5% of patients for I+V vs GClb: infections (12.3% vs 8.6%) and AF (6.6% vs 0%)
- 2 (1.9%) patients in the I+V arm discontinued ibrutinib due to AF

CAPTIVATE (median follow-up of 27.9 mo)[2]

- Most common grade ≥3 AEs were neutropenia (33%) and hypertension (6%)
- AEs led to dose reductions of ibrutinib only in 9 patients (6%), venetoclax only in 18 patients (11%), and both ibrutinib and venetoclax in 6 patients (4%)

Take-home: Combinations appear to be highly effective, but safety may be a consideration, especially in older patients

1. Kater A et al. EHA 2021. Abstract LB1902. 2. Tam C et al. *Blood*. 2022;139:3278-3289. 3. Al-Sawaf O et al. *Lancet Oncol*. 2020;21:1188-1200.

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How I use MRD in 2023 in CLL?

- Not applicable to continuous BTKi
- Outside of a clinical trial ---- no role for continuous surveillance monitoring in majority of patients as ‘we’ are still trying to figure out best platform and relevance of data to specific patient subtypes in CLL
- Continue therapy in high risk patients [perhaps also in patients who are still responding to therapy]

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What about Intolerance or Resistance to Therapies?

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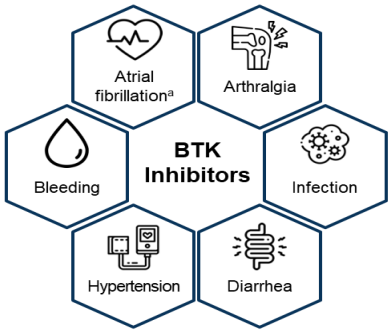
Summing Up the Safety Experience to Date With BTK Inhibitors and Venetoclax in CLL[1,2]

Common Toxicities With BTKi



Additional important AEs: dermatologic changes, fatigue, cytopenias, and ventricular arrhythmia

AEs to Watch With Venetoclax

- TLS
- GI events
- Infections
- Myelosuppression

[a] In 2022 ibrutinib label update for CV events

1. Lipsky A, Lamanna N. *Hematology Am Soc Hematol Educ Program*. 2020;1:336-345. 2. Seymour JF et al. *N Engl J Med*. 2018;378:1107-1120.

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Why Planning for Sequential Therapy Is Always Important for CLL patients

Therapeutic Intolerance and Resistance at Progression

Toxicity/Intolerance[1,2]	Disease Progression[3]
• BTKi discontinuation rates are ~40% in some real-world reports • Largely driven by toxicity (~50% of discontinuations) • Incidence of AEs is greatest in the first 6 months	• Progression on a covalent BTKi is often accompanied by resistance mutations • Mutations such as *BTK* C481S confer resistance to all covalent BTKi

1. Mato AR et al. *Haematologica*. 2018;103:874-879. 2. Aarup K et al. *Eur J Haematol*. 2020;105:646-654. 3. Woyach JA et al. *J Clin Oncol*. 2017;35;1437-1443.

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Sequential Use of Acalabrutinib in Patients With Ibrutinib Intolerance Is an Effective and Safe Option[1]

AE	No. of Patients With Ibrutinib Intolerance[a]	Acalabrutinib Experience for Same Patients, n			
		Total	Lower Grade	Same Grade	Higher Grade
AF	16[b]	2	2	0	0
Diarrhea	7	5	3	2	0
Rash	7	3	3	0	0
Bleeding[c,d]	6	5	3	2	0
Arthralgia	7[e]	2	1	1	0
Total	41	24	18	6	1

[a] Among 60 patients meeting the study enrollment criteria, 41 patients had a medical history of ≥1 (43 events in total) of the following categories of ibrutinib-intolerance events: AF, diarrhea, rash, bleeding, or arthralgia. [b] Includes patients with atrial flutter (n = 2). [c] Events categorized as bleeding included ecchymosis, hemorrhage, epistaxis, contusion, hematuria, and subdural hematoma. [d] All but 1 patient experienced a different type of bleeding event with acalabrutinib compared with ibrutinib treatment. [e] Includes 1 patient with arthritis.

1. Rogers KA et al. *Haematologica*. 2021;106:2364-2373.

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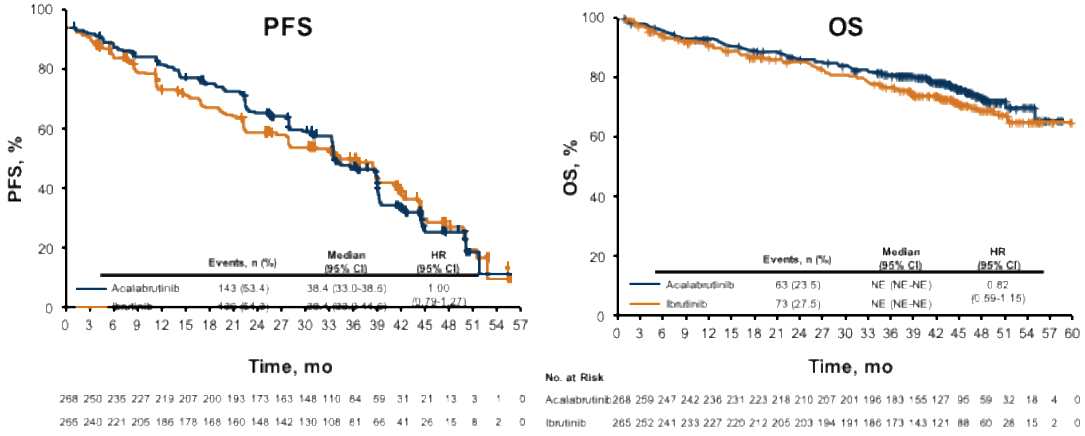
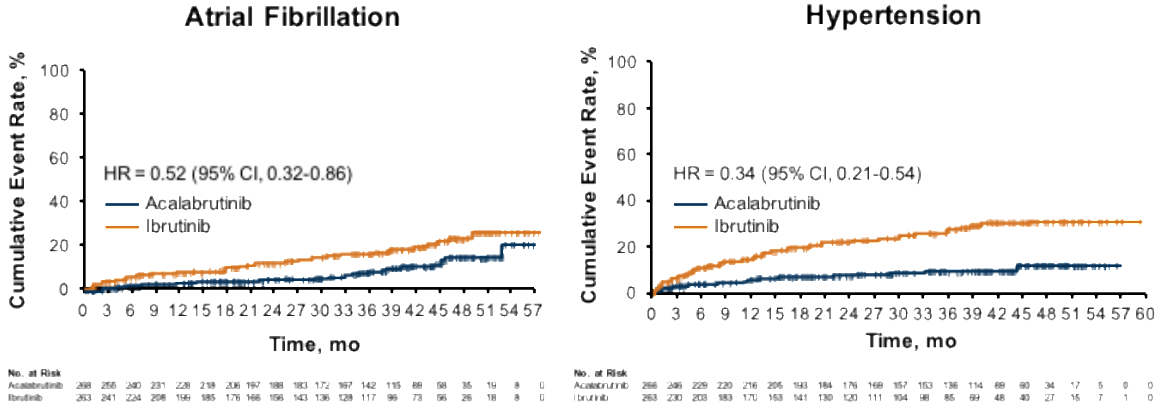
ELEVATE-RR (Acalabrutinib vs Ibrutinib): PFS and OS[1]

After median follow-up of 40.9 mo, PFS with acalabrutinib was noninferior to ibrutinib



1. Byrd JC et al. *J Clin Oncol*. 2021;39:3441-3452.

ELEVATE-RR: Cardiac AEs of Interest[1]



- **Fewer all-grade AF/flutter events with acalabrutinib (25/9.4%) vs ibrutinib (42/16.0%)**

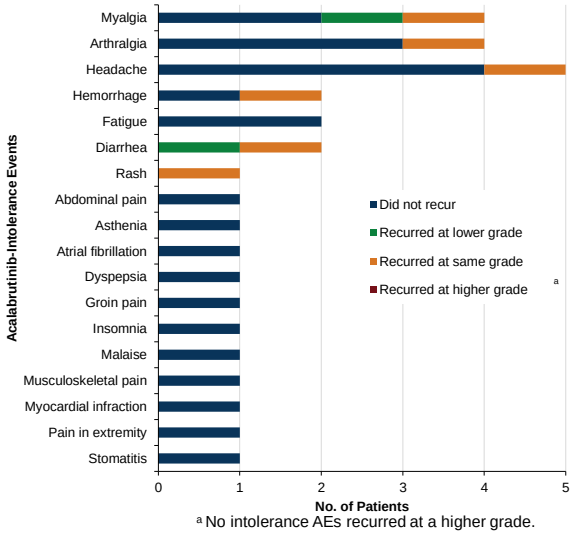
1. Byrd JC et al. *J Clin Oncol*. 2021;39:3441-3452.

Similarly, Zanubrutinib Is Effective in the Setting of BTK Inhibitor Intolerance

- Prior evidence had shown that zanubrutinib was effective in B-cell cancer patients intolerant of ibrutinib or acalabrutinib[1]
- For example, of 87 ibrutinib-intolerant events, 72 intolerant events (83%) did not recur

ASH 2022: zanubrutinib in acalabrutinib-intolerant patients with B-cell malignancies[2]

- Disease was controlled in 13 (93%) of 14 efficacy-evaluable patients treated with zanubrutinib, and 11 (65%) did not experience any recurrence of prior intolerance events

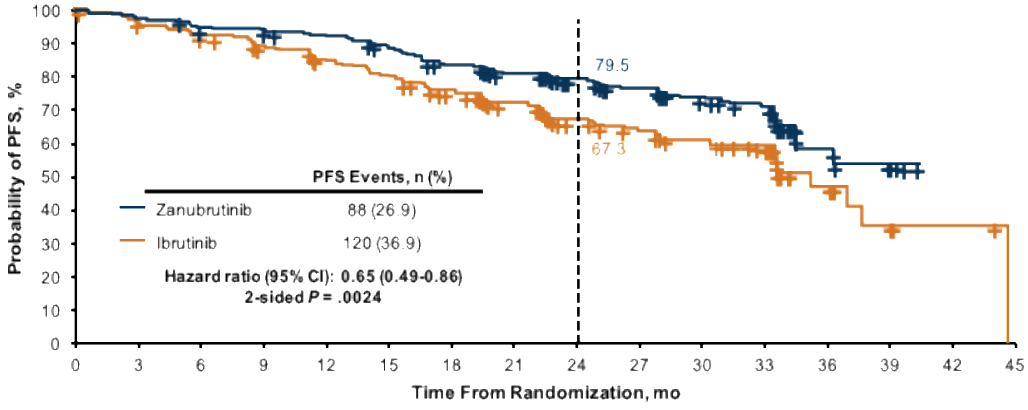


[a] No intolerance AEs recurred at a higher grade.

1. Shadman M et al. ASCO 2021. Abstract e19506. 2. Shadman M et al. ASH 2022. Abstract 1587.

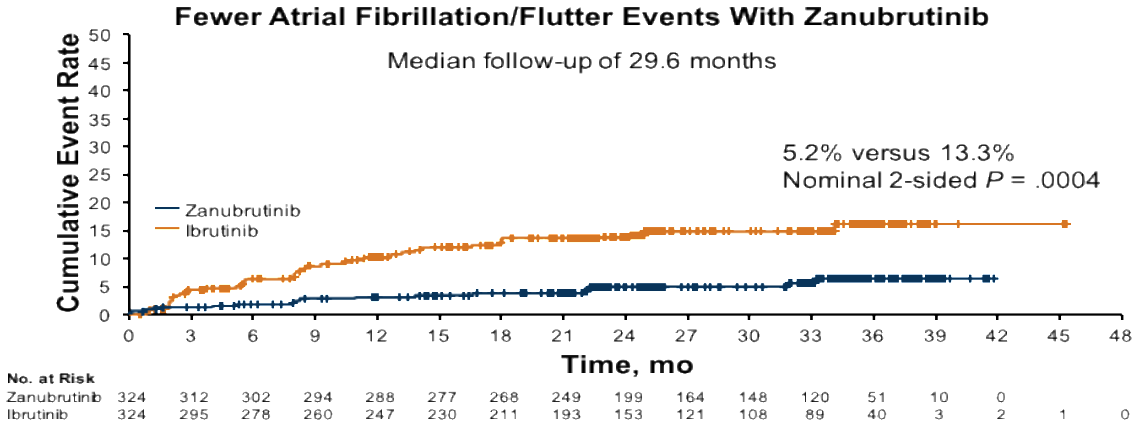
ALPINE: Improved ORR and PFS With Zanubrutinib vs Ibrutinib in R/R CLL/SLL[1]

After a median follow-up of 29.6 months, PFS was improved with zanubrutinib



1. Brown J et al. ASH 2022. Abstract LBA-6.

ALPINE: Safety Analysis Showed Lower Rates of AF/Flutter With Zanubrutinib[1]



1. Brown J et al. ASH 2022. Abstract LBA-6.

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What Strategies Can We Use Against BTK Inhibitor Resistance in CLL?

Supported by Current Evidence	Limited Evidence	Not Appropriate
• **Venetoclax:** efficacious, but complicated administration and not appropriate for all patients	• **PI3K inhibitors:** limited benefit in this population and significant toxicity burden	• **Covalent BTK inhibitor retreatment:** only effective in the context of covalent BTK intolerance, not progression
• **Non-covalent BTK inhibitors:** initial evidence suggests potent efficacy against resistance mutations and in the setting of progressive disease	• **Chemoimmunotherapy:** limited benefit in this population, and most current patients have already received these regimens	

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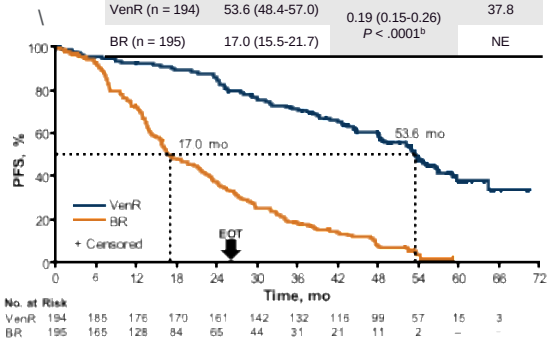
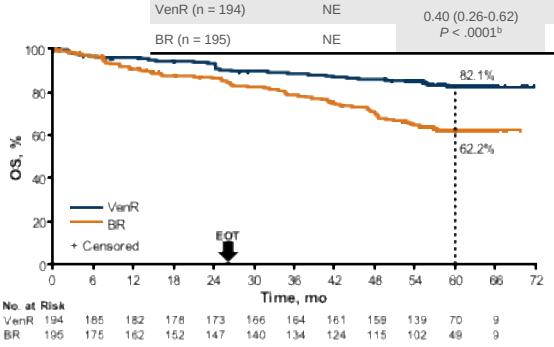
MURANO: VenR Led to Sustained PFS and OS Benefits Over BR 3 Years After EOT[1]

	Median PFS (95% CI), mo	HR[a] (95% CI)	5-Year PFS, %
VenR (n = 194)	53.6 (48.4-57.0)	0.19 (0.15-0.26) *P* < .0001[b]	37.8
BR (n = 195)	17.0 (15.5-21.7)		NE



	Median OS (95% CI), mo	HR[c] (95% CI)	5-Year OS, %
VenR (n = 194)	NE	0.40 (0.26-0.62) *P* < .0001[b]	82.1
BR (n = 195)	NE		62.2

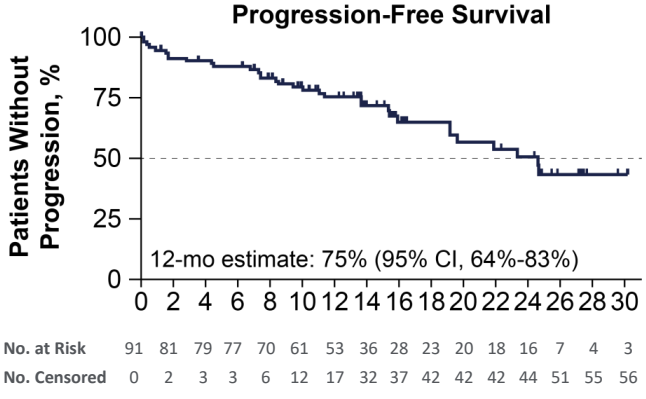


- No new safety signals were identified 3 years after EOT with longer follow-up and patients are outside of the AE reporting window
- Note: low number (5/2.6%) of patients with prior BCRi therapy

[a] Unstratified HR = 0.21. [b] *P* values are descriptive only. [c] Unstratified HR = 0.42.

1. Seymour J et al. *Blood*. 2022;140:839-850.

Venetoclax Monotherapy Is an Active Approach in Ibrutinib-Refractory CLL/SLL[1,2]



- N = 91
- Median of 4 prior therapies
- 47% with del(17p)
- ORR: 70%
- ORR of 61% (28 of 46 patients) in the del(17p) or *TP53*-mutated subset

1. Kater AP et al. ASH 2020. Abstract 125. 2. Jones JA et al. *Lancet Oncol*. 2018;19:65-75.

Mapping Sequential Therapy for CLL patients

If a patient		… then consider
		Venetoclax[1] (PI3Ki may work but are less tested)
Progresses on a BTKi ± resistance mutation	►	Clinical trial: options include noncovalent BTKi (eg, pirtobrutinib, nemtabrutinib),[1,2,a] CAR-T therapy, bispecific monoclonal ABs, BTK degraders, other
Is unable to tolerate ibrutinib or other cBTKi but has responded to therapy	►	Sequencing to acalabrutinib, zanubrutinib[3,4]
Progresses or intolerant to Venetoclax/CD20 antibody	►	Possible re-challenge with venetoclax (depending upon time off therapy); Sequencing to ibrutinib, acalabrutinib, zanubrutinib

[a] Pirtobrutinib/Nemtabrutinib are experimental and only available as part of clinical trials.

1. Jones JA et al. *Lancet Oncol*. 2018;19:65-75. 2. Mato A et al. ASH 2020. Abstract 542. 3. Rogers K et al. *Haematologica*. 2021 Mar 18 [Online ahead of print]. 4. Shadman M et al. ASH 2020. Abstract 2947. 5. Mato A et al. *Clin Cancer Res*. 2020;26:3589-3596.

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Other Therapies on the Horizon for CLL patients

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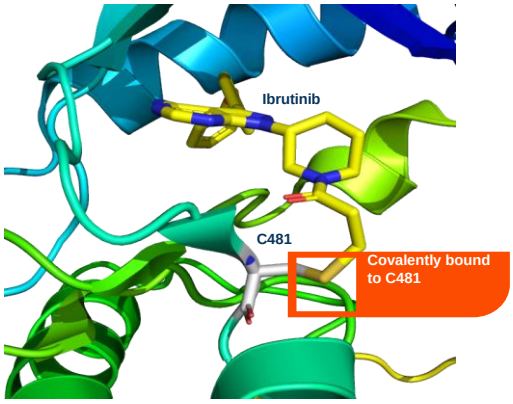
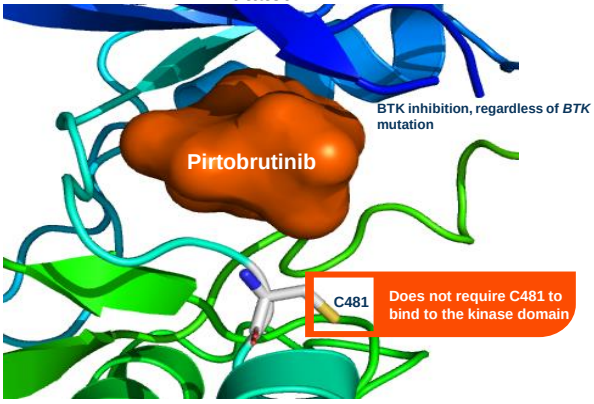
How Noncovalent BTK Inhibitors Overcome Resistance

Covalent BTK Inhibitors (Ibrutinib, Acalabrutinib, and Zanubrutinib) Require WT *BTK* for Activity



Pirtobrutinib Is a Noncovalent BTK Inhibitor That Is Potent Against Both WT and C481-Mutated *BTK*



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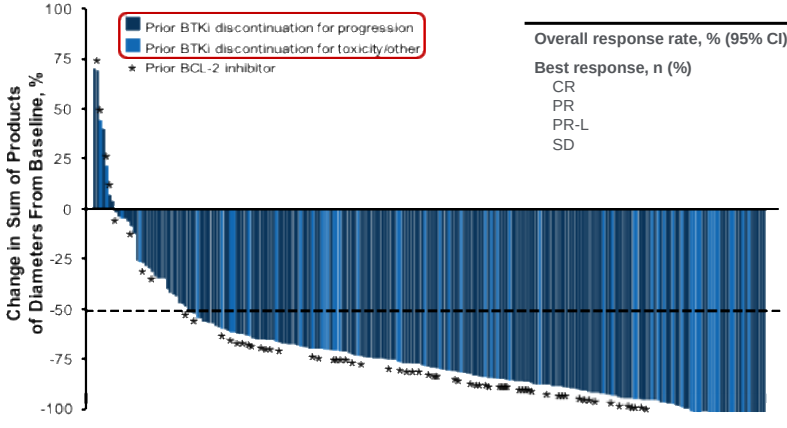
BRUIN Update: Longer Follow-Up Confirms Pirtobrutinib Efficacy in R/R CLL/SLL Patients[1]



	Prior BTKi (n = 247)	Prior BTKi + BCL2i (n = 100)
Overall response rate, % (95% CI)	**82.2 (76.8-86.7)**	**79.0 (69.7-86.5)**
Best response, n (%)		
CR	4 (1.6)	0 (0.0)
PR	177 (71.7)	70 (70.0)
PR-L	22 (8.9)	9 (9.0)
SD	26 (10.5)	11 (11.0)

Pirtobrutinib (200 mg QD) demonstrated durable efficacy in patients treated with a prior covalent BTKi, regardless of

- Prior therapy, reason for prior BTKi discontinuation, or age
- *TP53* mutations, **C481 mutational status**, and/or del(17p)

1. Mato A et al. ASH 2022. Abstract 961.

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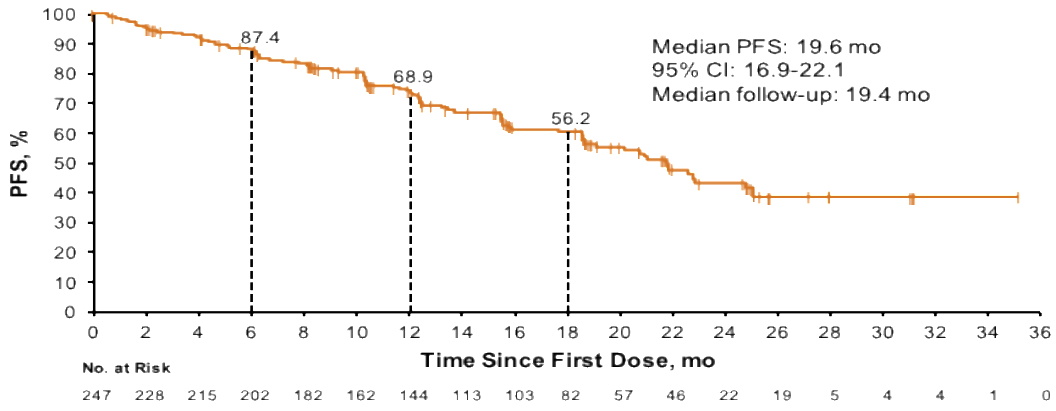
BRUIN Update: Robust PFS in Covalent BTKi-Pretreated R/R CLL/SLL Patients[1]



1. Mato A et al. ASH 2022. Abstract 961.

Pirtobrutinib Is Associated With a Low Rate of BTK-Mediated AEs…

Safety Summary From Longer Follow-Up of the BRUIN Trial (N = 618)[1,2]

	Treatment-Emergent AEs (≥15%), %				
	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade
AE					
Fatigue	13	8	1	–	23
Diarrhea	15	4	<1	<1	19
Neutropenia[a]	1	2	8	6	18
Contusion	15	2	–	–	17
AEs 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 AF 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 A et al. ASH 2021. Abstract 391. 2. Ghia P et al. EHA 2022. Abstract P1101.

Updated Findings Continue to Show Efficacy of Nemtabrutinib in Pretreated CLL/SLL[1]

Patients With CLL/SLL Treated With Nemtabrutinib 65 mg Once Daily (N = 57)

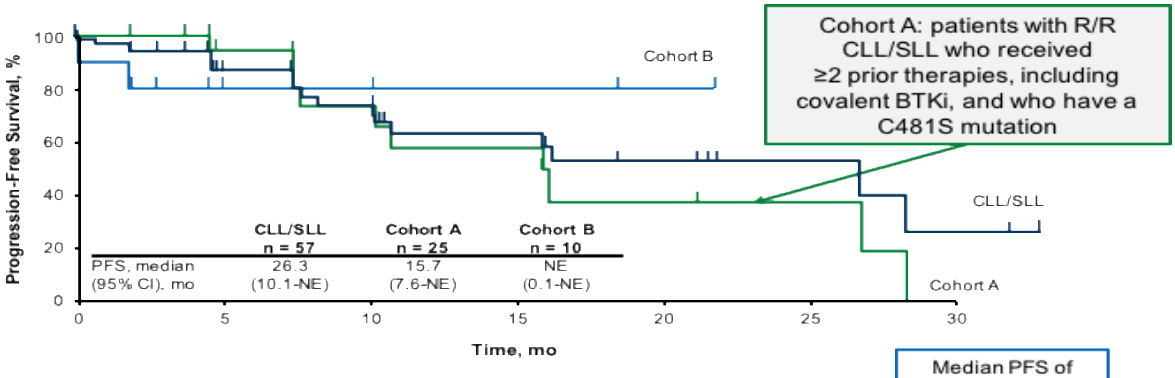
	CLL/SLL With Prior BTK and BCL-2 Inhibitors	C481S-Mutated *BTK*	del(17p)	IGHV Unmutated
n (%)	24 (42)	36 (63)	19 (33)	30 (53)
ORR, % (95% CI)	58 (37-78)	58 (41-75)	53 (29-76)	50 (31-69)
Objective response, n (%)	14 (58)	21 (58)	10 (53)	15 (50)
CR	0	1 (3)	1 (5)	0
PR	6 (25)	11 (31)	2 (11)	8 (27)
PR with residual lymphocytosis	8 (33)	9 (25)	7 (37)	7 (23)
Median DOR, mo	8.5	24.4	11.2	24.4
95% CI	2.7-NE	8.8-NE	5.7-NE	8.5-NE
Median PFS, mo	10.1	26.3	10.1	15.9
95% CI	7.4-15.9	10.1-NE	4.6-NE	7.4-NE

Nemtabrutinib 65 mg continued to show promising and durable antitumor activity with a manageable safety profile in a highly R/R population who had prior therapy with novel agents

ORR of 63% in C481S-mutated disease

1. Woyach J et al. ASH 2022. Abstract 3114.

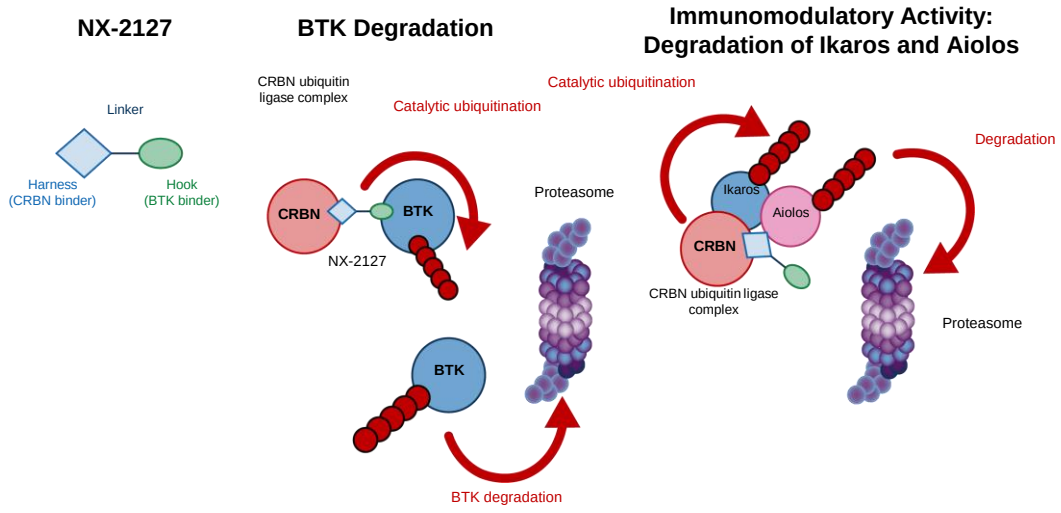
BELLWAVE-001: Nemtabrutinib Demonstrated Durable Clinical Responses in Pretreated CLL[1,a]



[a] Cohort A comprises patients with R/R CLL/SLL who received ≥2 prior therapies, including covalent BTKi, and who have C481S mutation. Cohort B comprises patients with R/R CLL/SLL who received ≥2 prior therapies, are intolerant to BTKi, and have no C481S mutation.

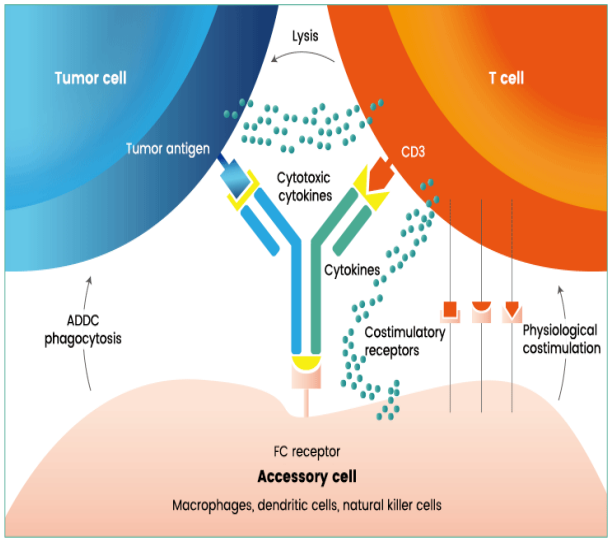
1. Woyach J et al. ASH 2022. Abstract 3114.

Can BTK Degraders Overcome Resistance?



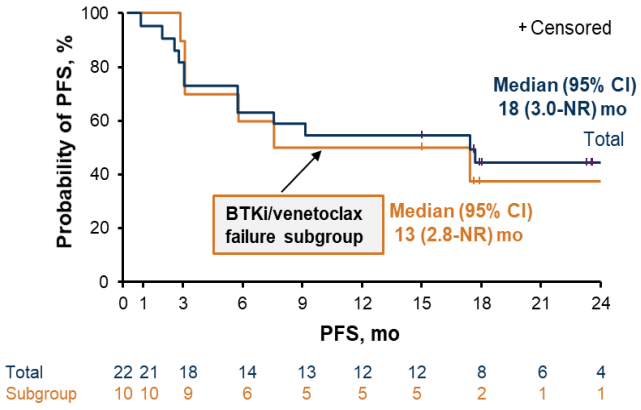
Bispecific Monoclonal Antibodies

- A bispecific antibody is an artificially made protein that will actively bind to two different kinds of antigens.
- Because of its dual specificity, bispecific antibody can support in redirecting T cells to tumor cells, blocking two different signaling pathways simultaneously, dual targeting of different disease mediators, and delivering payloads to targeted sites.
- There are several bispecific antibodies that are being evaluated currently.
  - ie. epcoritamab CD3xCD20



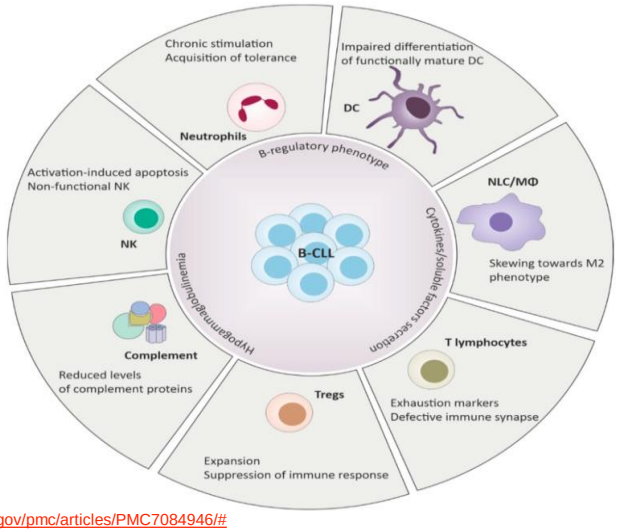
CAR-T Therapy Is Active After Progression on a Covalent BTKi, Including in Double-Refractory CLL

In the TRANSCEND CLL 004 trial, liso-cel was associated with a median PFS of 13 months in patients progressing after BTKi therapy and venetoclax[1]



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

CLL is a Disorder of the Immune System



Arruga F et al. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7084946/#

Clinical Considerations: *Beyond Treatment*

- Routine health care maintenance and age appropriate cancer screening
  - Annual derm screening
  - Colon cancer screening
  - Mammo/Pap
  - PSA (discuss with care team)
- Infections are one of the most common causes of morbidity/mortality in CLL patients
  - Prompt reporting of any signs/symptoms of infections
  - Pneumonia/Bronchitis, Skin infections, urinary tract infections
  - Routine vaccinations to decrease severity of illnesses/decrease hospitalizations
  - Usage of IVIG – ongoing studies to assess impact

Frontline Therapy in CLL, 2023

- Continuous therapy: appealing for patients who want to minimize clinic visits
  - 2nd generation covalent BTKis are demonstrating improved safety profiles compared to ibrutinib
  - At present, data suggest preferred for patients with del17p/TP53 aberrant disease
- Time-limited therapy: appealing for patients who don't want chronic therapy, those with high out of pocket costs with continuous therapy, probably for mutated IGHV as well
  - Whether BTKi - BCL2i +/- antiCD20 improves PFS compared to ven-obin remains completely unanswered and does have increased toxicity. Good clinical trial option for fit younger patients or those with high risk disease.
- Future directions:
  - Fixed-duration combined targeted therapy such as with BTKi + BCL2i (ie goal of deep remission and long PFS; retreat at progression) but toxicity issues need to be monitored and longer follow-up may reveal which patients and disease cohorts may benefit from these combination.
  - Newer therapies: BTK degraders, bi-specific monoclonal antibodies, CART

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ASK A QUESTION

SPOTLIGHT ON CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

Ask a question by phone:

Press star (*) then the number 1 on your keypad.

Ask a question by web:

Click “Ask a question”
Type your question
Click “Submit”

Due to time constraints, we can only take one question per person. Once you’ve asked your question, the operator will transfer you back into the audience line.

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Chat live online: www.LLS.org/InformationSpecialists
Monday to Friday, 10 a.m. to 7 p.m. ET
Email: www.LLS.org/ContactUs
All email messages are answered within one business day.

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Work one-on-one with an LLS Clinical Trial Nurse Navigator who will help you find clinical trials and personally assist you throughout the entire clinical-trial process.
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View our free education videos on disease, treatment, and survivorship. To view all patient videos, please visit **www.LLS.org/EducationVideos**

Patient Podcast

The Bloodline with LLS is here to remind you that after a diagnosis comes hope. To listen to an episode, please visit **www.TheBloodline.org**

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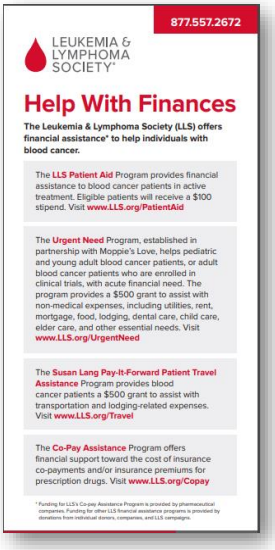

The Leukemia & Lymphoma Society (LLS) offers the following financial assistance programs to help individuals with blood cancers: www.LLS.org/Finances

To order free materials: **www.LLS.org/Booklets**

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