Chronic Lymphocytic Leukemia:

Diagnosis, Treatment and Side Effect Management

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LEARNING OBJECTIVES

- Describe chronic lymphocytic leukemia (CLL)
- Identify tests used to diagnose disease and monitor treatment of CLL
- Explain the overarching goals of treatment, indications for when to start treatment, and types of treatment for CLL
- Explain approved and emerging treatment options for CLL and the role of clinical trials
- Describe strategies to manage treatment side effects as well as potential long-term and late effects of treatments for CLL
- Describe the healthcare professional's role in managing patients with CLL

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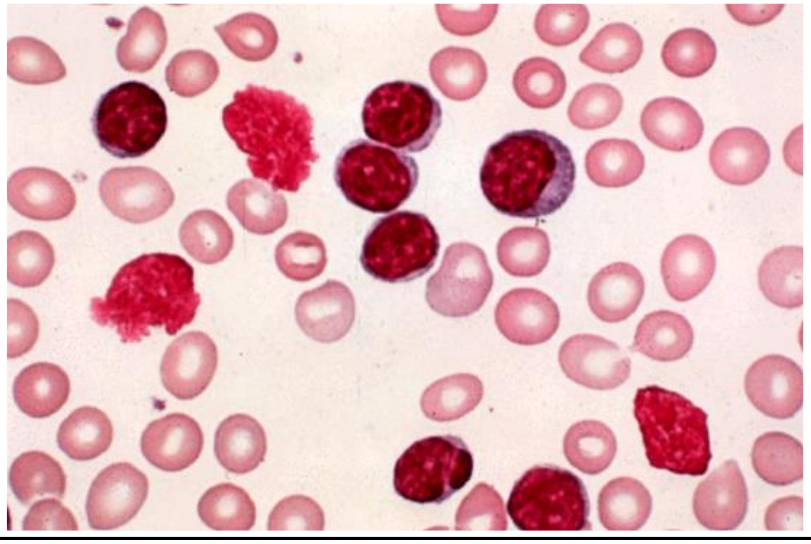
Chronic Lymphocytic Leukemia



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CLL General

- Most common adult leukemia (~ 15,000 cases/yr)
  - 30% of adult leukemias
- Median age at diagnosis 72 years
- Median overall survival > 9 yrs
  (unknown with small molecule inhibitors)
- Survival increased over last 2 decades and continues to improve
- Advanced CLL has increased morbidity and mortality related to infections & other cancers

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CLL Diagnosis

- ALC: >5,000 /μL – mature monoclonal B cells
  - PLL = > 55% prolymphocytes or > 15,000 /μL
- Immunophenotype:
  - $CD5^+$ / $CD19^+$ / $CD23^+$ / surface Ig light chain restricted (κ or λ) - monoclonal
- BM Bx: not required for diagnosis
  - > 30% lymphocytes on aspirate
- Additional testing for prognosis:
  - FISH, IGHV mutation status, stimulated karyotype, serum B2M

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CLL Clinical Course

- Diagnosis often incidental
- Asymptomatic at diagnosis and for prolonged periods
- Initial symptoms: lymph nodes ↑ , fatigue
- Progression: bone marrow impairment (anemia, thrombocytopenia)
- Increased susceptibility to infection
- Progressive hypogammaglobulinemia
- Long-term complications: autoimmune, Richter's transformation, 2nd cancers, infections

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IWCLL-NCI: Indications to Initiate Treatment for CLL

- Constitutional symptoms referable to CLL
- Progressive marrow failure
- Autoimmune anemia +/- thrombocytopenia poorly responsive to steroids or other
- Massive (>6 cm) or progressive splenomegaly
- Massive (>10 cm) or progressive lymphadenopathy
- Progressive lymphocytosis, >50% increase over 2 months or LDT < 6 months
- **NO EARLY TREATMENT, EVEN FOR HIGH-RISK**

Hallek et al Blood 2008;111:5446-5456.

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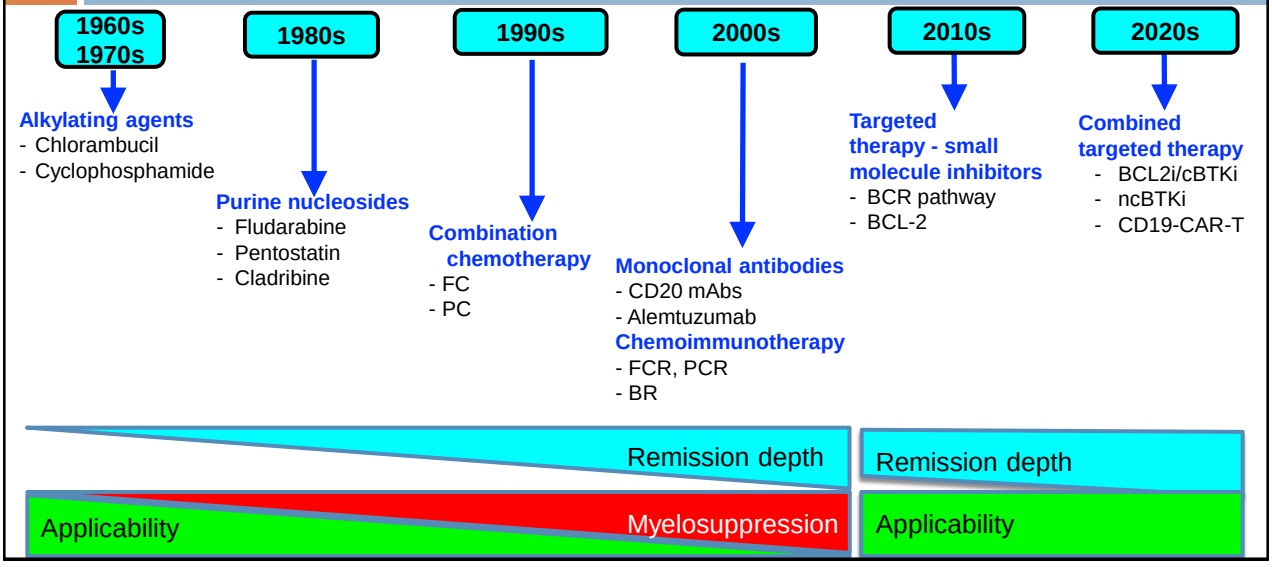
Evolution of First-line Treatments for CLL



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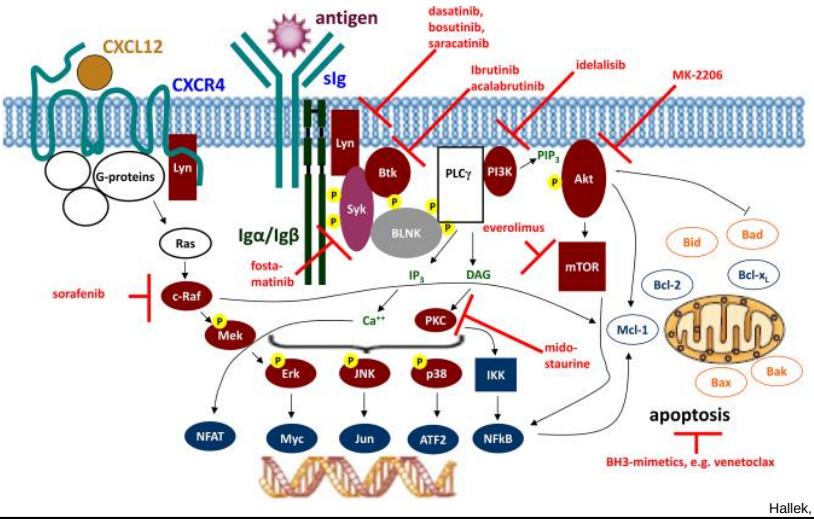
Survival Signaling in CLL: Target of Novel Agents



Hallek, M., Am J Hem. 92:946, 2017.

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Important for Selecting Treatment in CLL

- del(17p) status by FISH: **can change**[2]
  - Know % of cells with deletion
- *TP53* mutation status: **can change**[2]
- IGHV mutation status (for first line): **does not change**[1]
- Age and comorbidities are considerations
- *BTK* and *PLCG2* mutation status (in BTKi treated): **can change**[3]

1. Crombie. Am J Hematol. 2017;92:1393. 2. Chauffaille. Hematol Transfus Cell Ther. 2020;42:261. 3. Hallek. Am J Hematol. 2019;94:1266.

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Therapeutic Agents for CLL

Chemotherapy	CD20 Antibody	BTKi	PI3Ki	BCL-2i	Others
Chlorambucil	Rituximab	Ibrutinib	Idelalisib	Venetoclax	Lenalidomide
Fludarabine	Obinutuzumab	Acalabrutinib	Duvelisib	Sonrotoclax	CD19-CAR-T
Cyclophosphamide	~~Ofatumumab~~	Zanubrutinib	~~Umbralisib~~	Lisaftoclax	
Bendamustine		Pirtobrutinib			
		Nemtabrutinib			
		Tirabrutinib			
		Luxeptinib			
		~~Vecabrutinib~~			

FDA-approved for 1L treatment of CLL in US; FDA-approved for >1L treatment of CLL in US; Not FDA-approved in US

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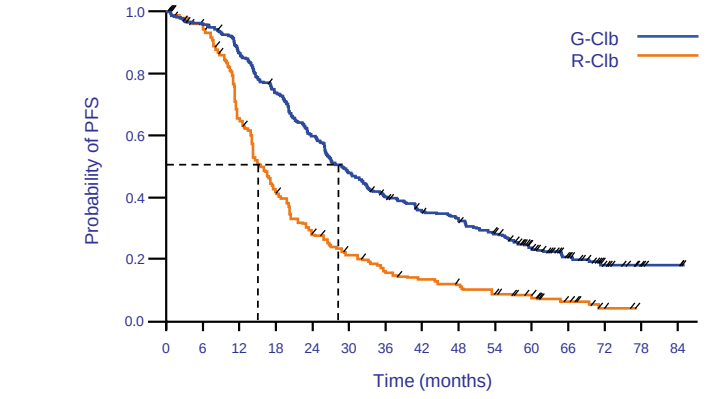
CLL11
PFS: G-Clb vs R-Clb



No. of pts at risk

G-Clb	333	302	270	229	185	149	123	106	98	80	54	33	14	4	2
R-Clb	330	310	209	136	89	67	51	41	35	27	20	10	3	0	0

	G-Clb n=333	R-Clb n=330
Patients with events, n (%)	244 (73.3)	292 (88.5)
5-year PFS, % (95% CI)	23 (19–28)	9 (6–12)
Median PFS, months	28.9	15.7
HR (95% CI), p-value	0.49 (0.41–0.58), p<0.0001	

Median observation time: 59.4 months

Goede, EHA 2018.

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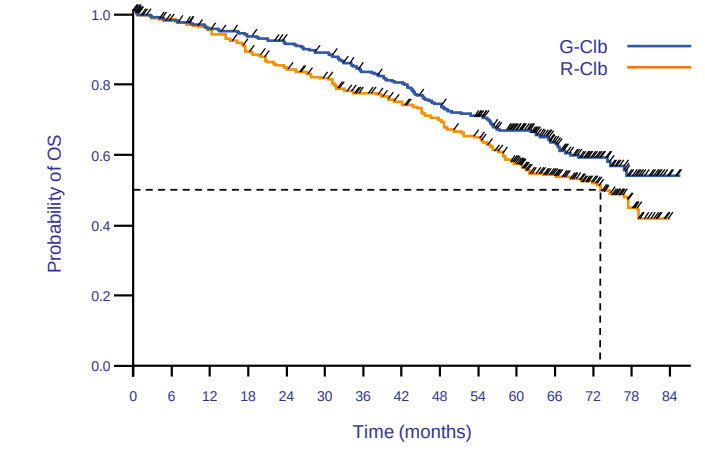
CLL11
OS: G-Clb vs R-Clb



No. of pts at risk

G-Clb	333	310	299	290	279	270	250	239	220	206	171	108	69	28	2
R-Clb	330	314	303	283	263	248	227	212	197	178	147	96	64	22	0

	G-Clb n=333	R-Clb n=330
Patients with events, n (%)	121 (36.3)	147 (44.5)
5-year OS, % (95% CI)	66 (61–72)	57 (51–62)
Median OS, months	NR	73.1
HR (95% CI), p-value	0.76 (0.60–0.97), p=0.0245	

Median observation time: 59.4 months

Goede, EHA 2018.

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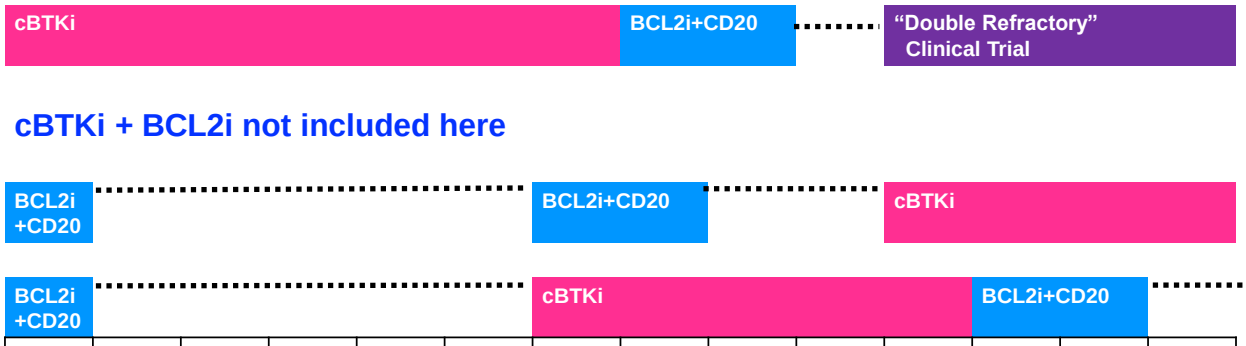
Targeted Therapy Strategy for CLL



Factors affecting timelines:
- Age
- Del(17p)/TP53-m
- Del(11q)
- Complex karyotype
- IGHV-MS

Years

Double Exposed *vs.* Double Refractory:
- Exposed ≠ Refractory
- Refractory=progression on treatment

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BTKi- *vs.* BCL-2i-based Treatment

BTK Inhibitor[1-4]

- Easy initiation
- Continuous and indefinite therapy
- Very low TLS risk
- More cardiac risk
- Some favor in del(17p)/ mutated-*TP53*
- Activity in nodal disease

BCL-2 Inhibitor[4,5]

- Risk for TLS requires monitoring for initiation
- Includes CD20 mAb – immunosuppression
- Fixed duration
- GFR sensitivity
- Concern for del(17p)/mutated-*TP53*
- Activity in BM and blood

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

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First-line Phase III Randomized Trials

- **CLL14** (CIRS >6; CrCl <70 mL/min)
  - **Venetoclax + Obinutuzumab** *vs.*
  - **Chlorambucil + Obinutuzumab**
- **GLOW** (>65yo or ≤65yo with comorbidities)
  - **Ibrutinib + Venetoclax** *vs.*
  - **Chlorambucil + Obinutuzumab**
- **CLL13 / GAIA** [CIRS ≤ 6; non-del(17p)]
  - **Venetoclax + Obinutuzumab** *vs.*
  - **Venetoclax + Ibrutinib + Obinutuzumab** *vs.*
  - **Venetoclax + Rituximab** *vs.*
  - **FCR / BR**
- **RESONATE-2**
  - **Ibrutinib** *vs.*
  - **Chlorambucil**
- **iLLUMINATE** (PCYC-1130) (>65yo or ≤65yo with comorbidities)
  - **Ibrutinib + Obinutuzumab** *vs.*
  - **Chlorambucil + Obinutuzumab**
- **ECOG E1912** [<70yo; non-del(17p)]
  - **Ibrutinib + Rituximab** *vs.*
  - **FCR**
- **Alliance** (A041202) (>65yo)
  - **Ibrutinib** *vs.*
  - **Ibrutinib + Rituximab** *vs.*
  - **BR**
- **ELEVATE-TN** (>65yo or younger with CIRS score >6, or CrCl <70 mL/min)
  - **Acalabrutinib** *vs.*
  - **Acalabrutinib + Obinutuzumab**
  - **Chlorambucil + Obinutuzumab**
- **SEQUOIA** [≥65 yo OR unsuitable for FCR; non-del(17p)]
  - **Zanubrutinib** *vs.*
  - **BR**

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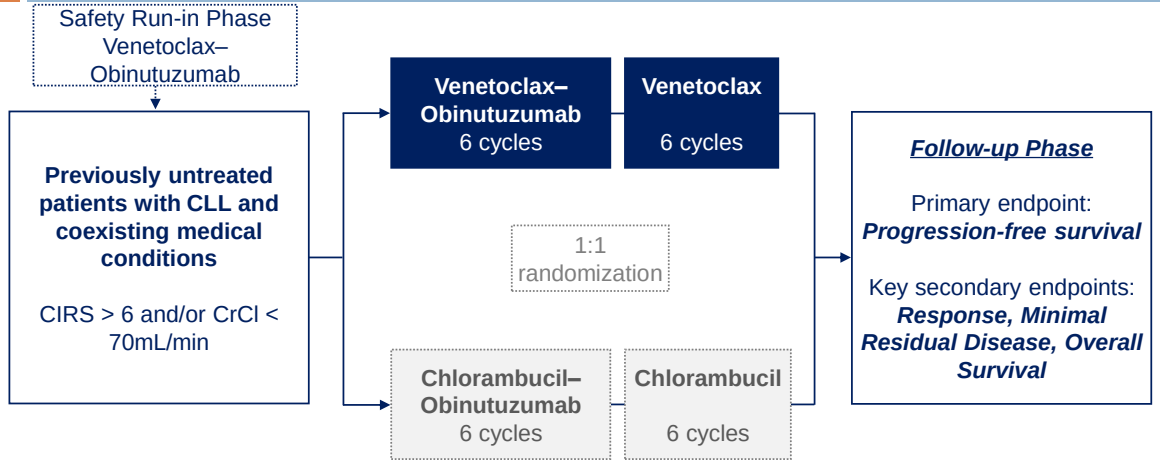
CLL14: Trial Design



Fischer et al., New Engl J Med 2019.

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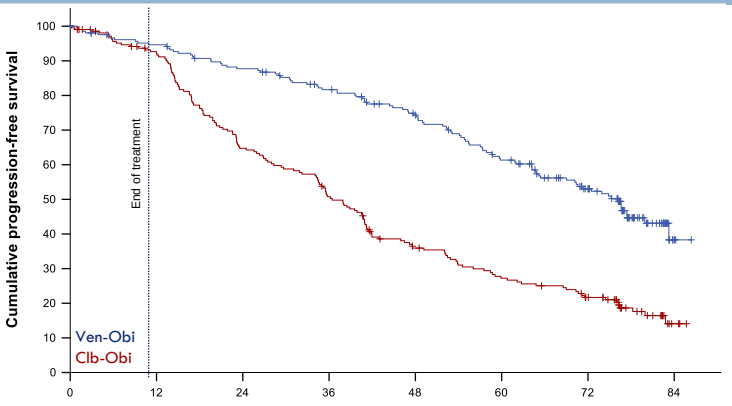
CLL14: Progression-free Survival

Investigator-assessed PFS



Ven-Obi	216	193	177	160	139	112	79	3
Clb-Obi	216	185	130	101	67	50	36	3

Median PFS
Ven-Obi: 76.2 months
Clb-Obi: 36.4 months

6-year PFS rate
Ven-Obi: 53.1%
Clb-Obi: 21.7%

HR 0.40, 95% CI [0.31-0.52]
P<0.0001

Al-Sawaf, O., et al., EHA 2023, Abstract S145

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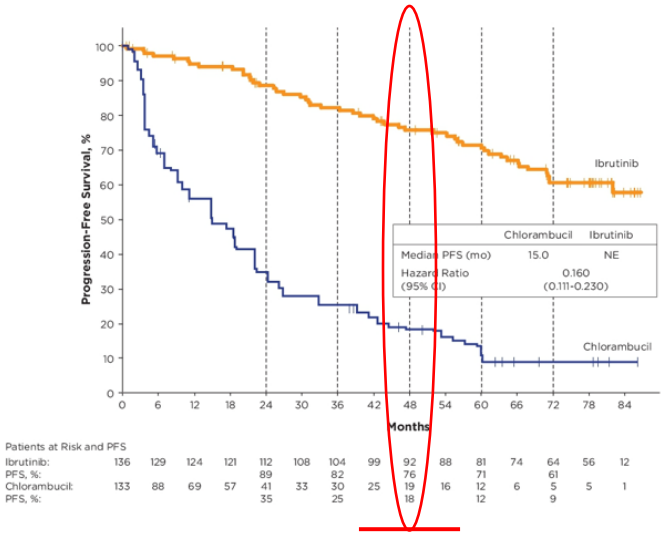
RESONATE-2: First-line, Age >65yrs
Ibrutinib Prolonged PFS Over Chlorambucil



Barr et al. ASCO 2021, Poster 7523.

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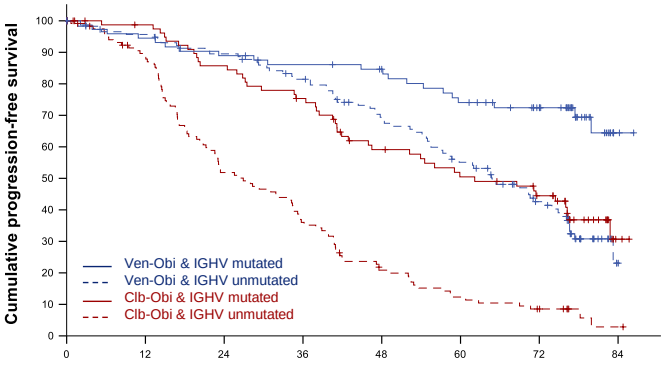
CLL14: Progression-free Survival – IGHV Status

Median observation time 76.4 months



Ven-Obi & IGHV mutated	76	68	64	60	57	49	39	2
Ven-Obi & IGHV unmutated	121	110	101	90	73	57	37	1
Clb-Obi & IGHV mutated	83	76	66	57	42	35	28	2
Clb-Obi & IGHV unmutated	123	101	59	41	22	13	8	1

Median PFS

Ven-Obi & IGHVmut: NR

Ven-Obi & IGHVunmut: 64.8 m

HR 0.38, 95%CI [0.23-0.61], p<0.001

Clb-Obi & IGHVmut: 62.2 m

Clb-Obi & IGHVunmut: 26.9 m

HR 0.33, 95% CI [0.23-0.47], p<0.001

Al-Sawaf, O., et al., EHA 2023, Abstract S145

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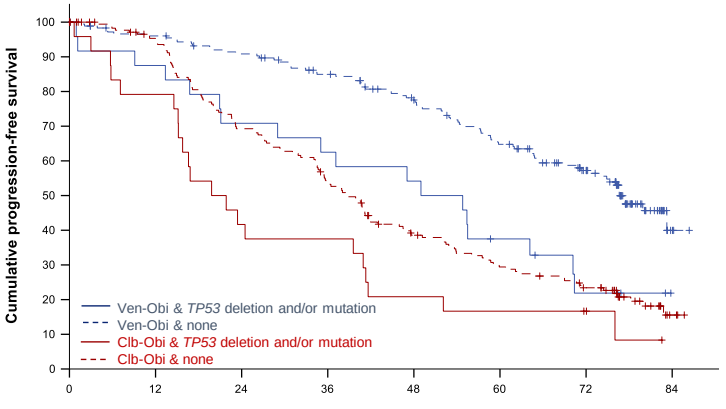
CLL14: Progression-free Survival – *TP53 Status*

Median observation time 76.4 months



Ven-Obi & *TP53* del/mut	25	21	17	15	13	8	4	0
Ven-Obi & none	184	168	157	142	123	101	73	3
Clb-Obi & *TP53* del/mut	24	19	10	9	5	4	3	0
Clb-Obi & none	184	160	117	90	60	45	33	3

Median PFS

Ven-Obi & no *TP53*del/mut: 76.6 m

Ven-Obi & *TP53*del/mut: 51.9 m

HR 2.29, 95% CI [1.37-3.83], p=0.001

Clb-Obi & no *TP53*del/mut: 38.9 m

Clb-Obi & *TP53*del/mut: 20.8 m

HR 1.66, 95% CI [1.05-2.63], p=0.03

Al-Sawaf, O., et al., EHA 2023, Abstract S145.

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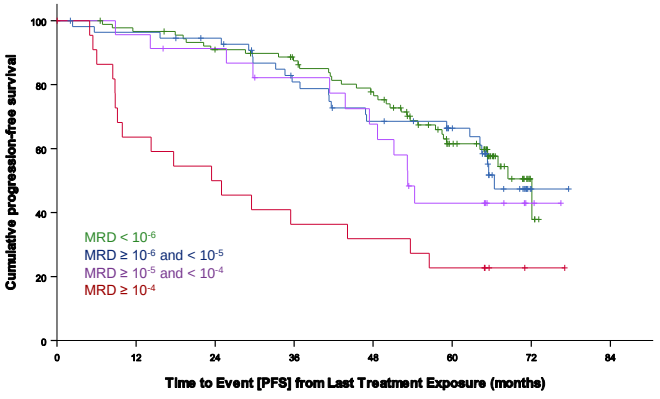
PFS after Ven-Obi According to *MRD Status*

End-of-treatment MRD status in peripheral blood, by NGS



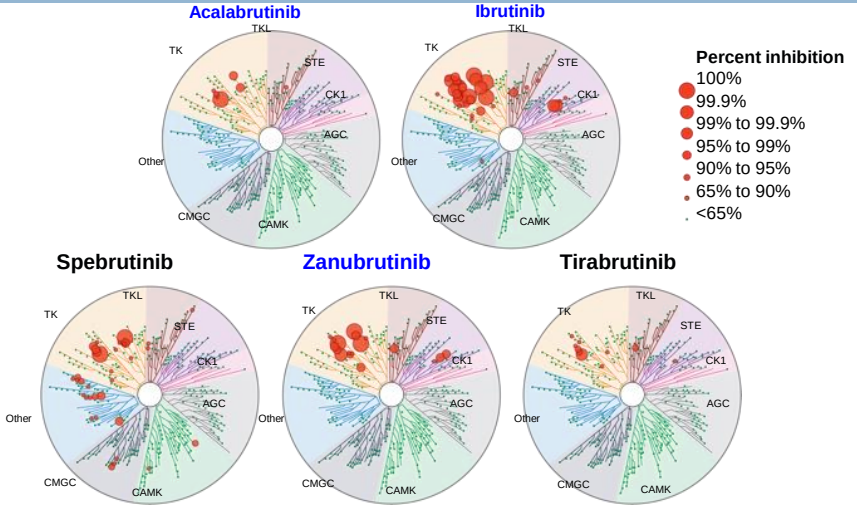
MRD < 10^{-6}	90	86	79	73	63	38	4	0
MRD ≥ 10^{-6} and < 10^{-5}	56	53	50	40	33	26	2	0
MRD ≥ 10^{-5} and < 10^{-4}	23	22	20	17	14	8	2	0
MRD ≥ 10^{-4}	23	14	11	8	7	5	1	0

Depth of remission correlates with **long-term PFS**, indicating the prognostic value of the end-of-treatment MRD status.

Al-Sawaf, O., et al., EHA 2023, Abstract S145.

23

Differences in Overall Kinase Selectivity Among BTKi[1qA]



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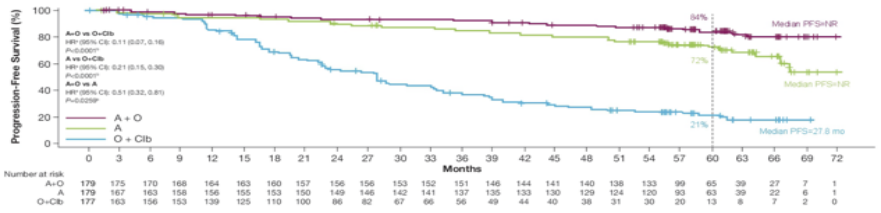
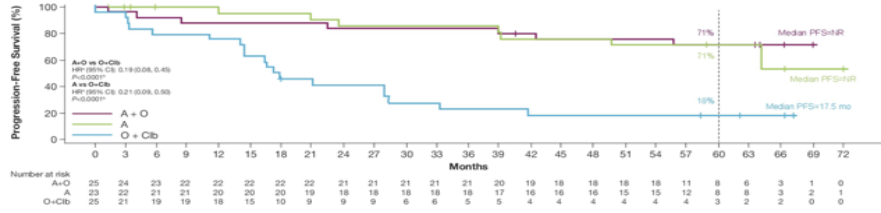
ELEVATE-TN Phase 3 Study: 5-Year Follow-Up PFS

INV-Assessed PFS



INV-Assessed PFS in Patients With del(17p) and/or Mutated *TP53*



Median follow-up:
58.2 months
(range, 0.0-72.0)

Sharman JP, et al. ASCO 2022. Abstract 7539. Sharman JP, et al. EHA 2022. Abstract P666.

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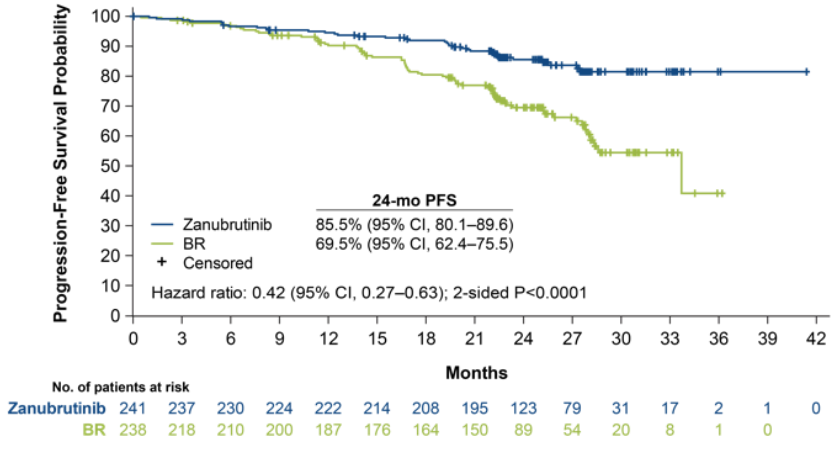
SEQUOIA: Progression-Free Survival Per IRC Assessment



BR, bendamustine + rituximab; IRC, independent review committee; PFS, progression-free survival.

Tam, et al. ASH 2021, Abstract #396.

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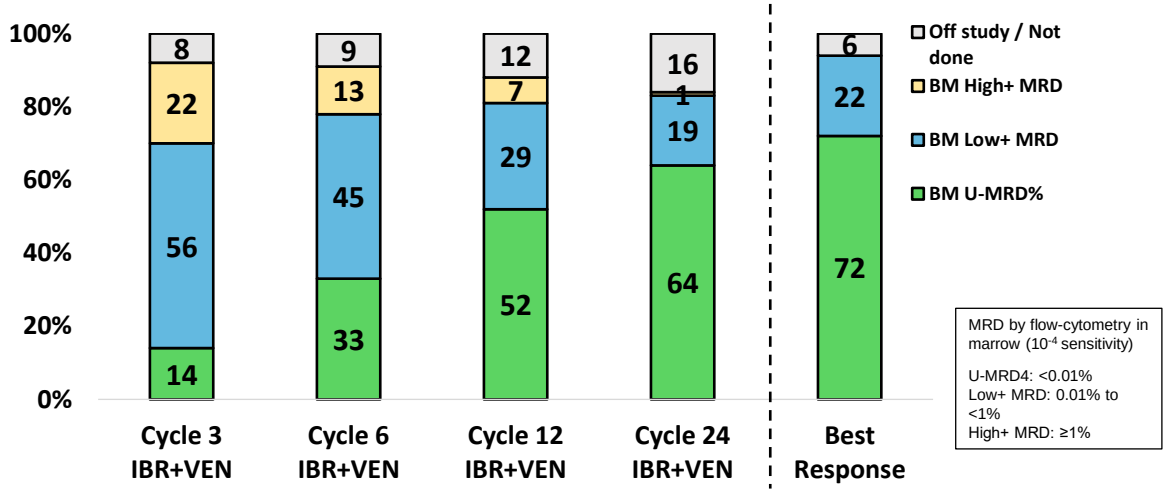
MDACC IBR+VEN: Marrow MRD Response at Serial Time-Points Intent-to-Treat (N=120)



Jain et al. ASH 2022, Abstract #95.

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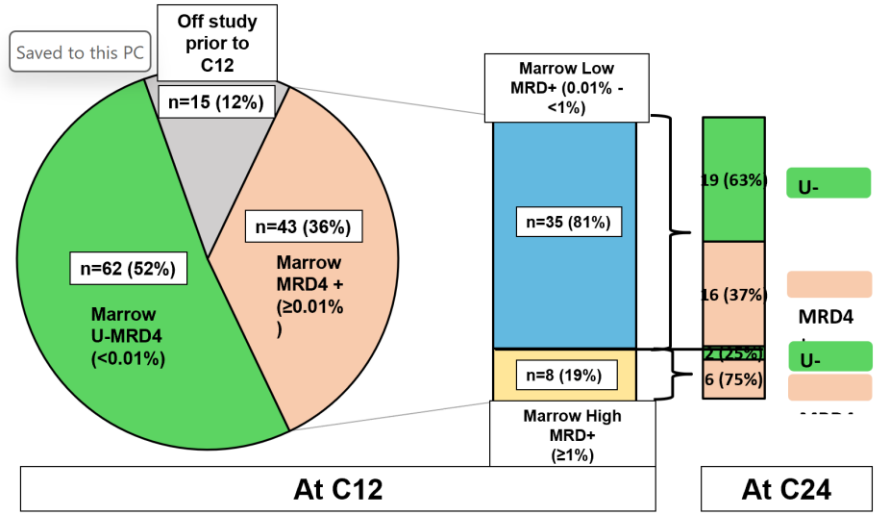
MDACC IBR+VEN: Impact of 2nd Year of Combination Rx



Jain et al. ASH 2022, Abstract #95.

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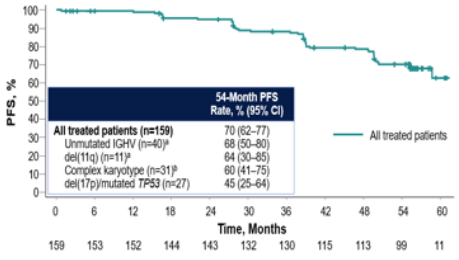
IBR + VEN Regimen Comparisons, ASH 2023

CAPTIVATE, I+V 12 cycles



N=159
Median age = 60 yrs
IGHV-UM = 56%
Del(17p) / *TP53*-m = 17%

4.5 yr PFS = 70%

Ghia, ASH 2023

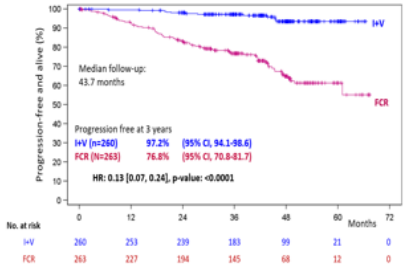
MDACC, I+V 24 cycles

N=1
Median age = 64.5 yrs
IGHV-UM = 86%
Del(17p) / *TP53*-m = 23%

5 yr PFS = 89.8%

Jain, ASH 2023

FLAIR, UK, I+V 2-6 years



N=260
Median age = 62 yrs
IGHV-UM = 48%
Del(17p) = excluded

3 yr PFS = 97.2%

Hillmen, ASH 2023

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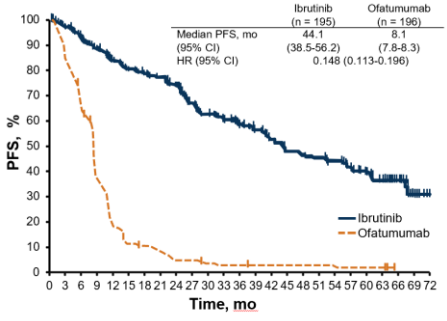
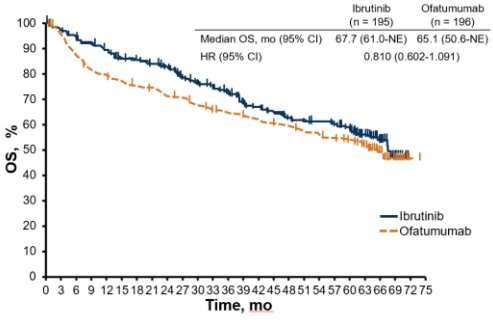
Phase 3 RESONATE Study in Relapsed CLL: Ibrutinib vs Ofatumumab—Outcomes[1-3]





Final RESONATE findings: ibrutinib safety profile remained consistent with prior reports

- Cumulatively, all-grade (grade ≥3) hypertension and atrial fibrillation occurred in 21% (9%) and 12% (6%) of patients, respectively
- 16% discontinued ibrutinib because of AEs
- **Peripheral neuropathy:** all grade = 13%, grade ≥3 = 0.5%
- **CHF:** all grade = 5%, grade ≥3 = 3%
- **Ventricular arrhythmia:** all grade: 1%, no grade ≥3 events

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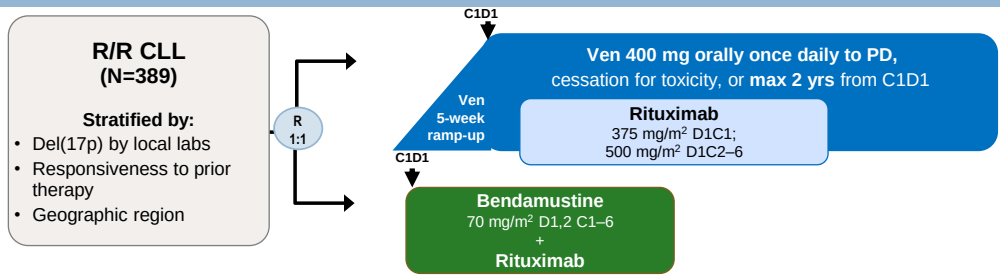
MURANO Study Design



- Primary endpoint: investigator-assessed PFS; secondary endpoints include rate of undetectable MRD (uMRD)
- Clinical response and MRD in PB/BM during Ven single-agent and at follow-up visits were assessed every 3 months for 3 years, then every 6 months thereafter, or until PD
- Primary analysis was pre-planned at 140 PFS events; this follow-up analysis was conducted 1 year later

BM, bone marrow; C, cycle; D, day; PB, peripheral blood; PD, progressive disease; R, randomized

Seymour et al; ASH2018, Abstract 184.
Seymour JF, et al. N Engl J Med 2018;378:1107–20.

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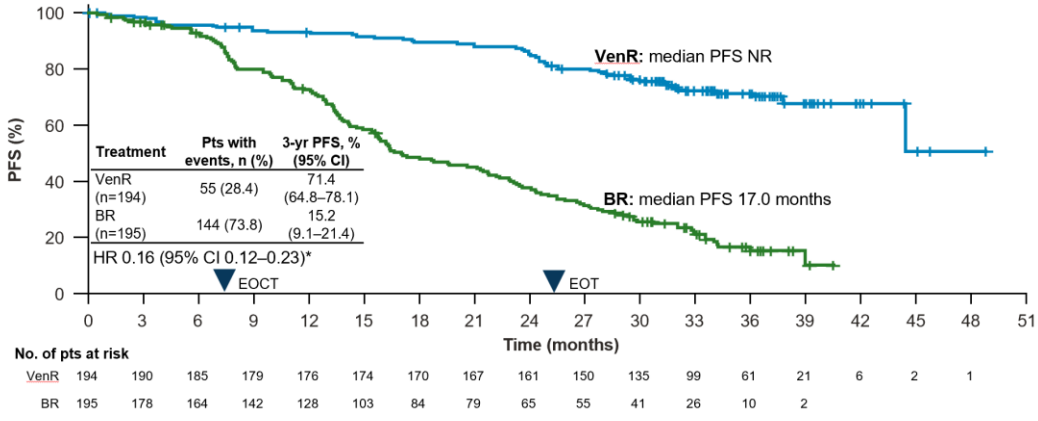
MURANO: Superior PFS with VenR vs BR Maintained with 1 Additional Year of Follow-up: Update

Investigator-assessed PFS



*Stratified HR
Median follow-up 36.0 months (range 0.0–48.6); VenR 36.1 months, BR 35.9 months

Seymour et al; ASH2018, Abstract 184.
Data cut-off date: May 8, 2018.

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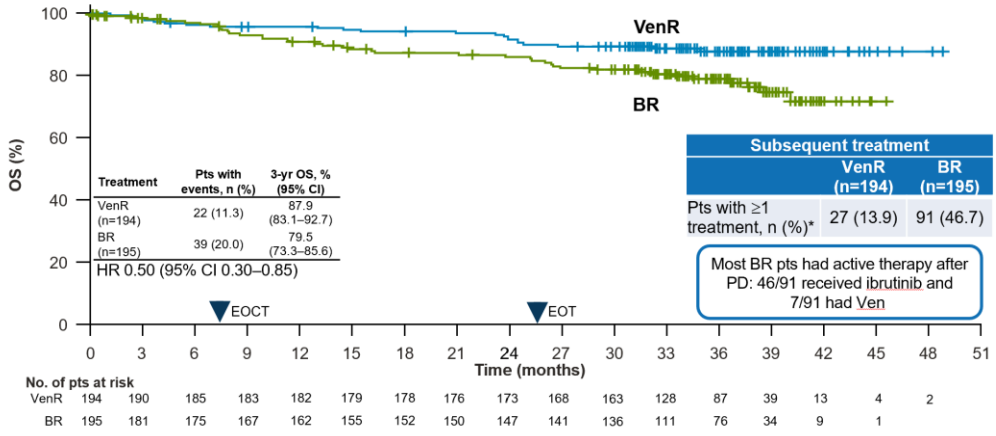
Clinically Meaningful Improvement in OS with VenR vs BR Maintained After 3 Years



*Unstratified HR 0.51 (95% CI 0.30–0.86)
Median follow-up: 36.0 months (range 0.0–48.6). Median per arm: VenR 36.1 months; BR 35.9 months

Seymour et al; ASH2018, Abstract 184.
Data cut-off date: May 8, 2018.

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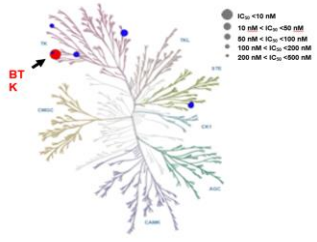
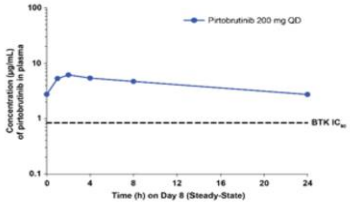
Pirtobrutinib is a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor

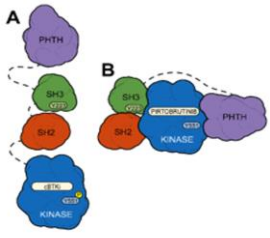
Highly selective for BTK[8-9]



Plasma exposures exceeded BTK IC_{90} throughout dosing interval



Pirtobrutinib may stabilize/maintain BTK in a closed inactive conformation[11]



- Pirtobrutinib is approved in the USA to treat relapsed or refractory MCL after at least two lines of systemic therapy, including prior BTK inhibitor[10]
- Inhibits both WT and C481-mutant BTK with equal low nM potency in *in vitro* models[11] and CLL cells[12]
- Steady state plasma exposure corresponding to 96% BTK target inhibition and a pirtobrutinib-BTK binding complex half-life of about 2 hrs

- In contrast to cBTKi (A), pirtobrutinib (B) appears to stabilize BTK in a closed, inactive conformation, blocking access to upstream kinases and phosphorylation of Y551, thus inhibiting scaffolding interactions that support kinase-independent BTK signaling[11]

[8]Mato et al, *Lancet* 2021. [9]Brandhuber et al. *Clin Lymphoma Myeloma Leuk* 2018.[10]Jaypirca [Prescribing Information]. Indianapolis, IN: Eli Lilly and Company, 2023. [11]Gomez et al. Blood.2023. [12] Aslan B et al. Blood Cancer J 2022.

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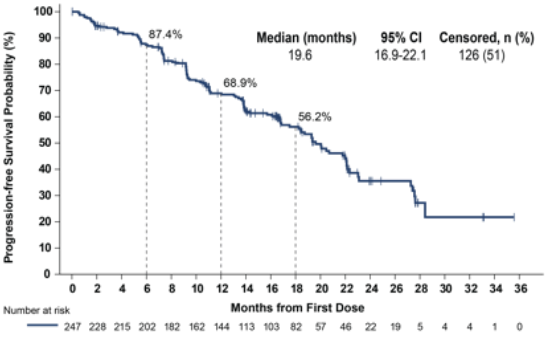
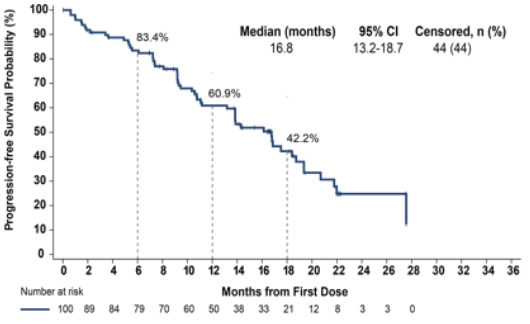
Pirtobrutinib: Progression-Free Survival in CLL/SLL Patients who Received Prior BTKi Treatment

All prior BTKi patients
Median prior lines = 3



- Median follow-up of 19.4 months for patients who received prior BTKi

Prior BTKi and BCL2i patients
Median prior lines = 5



- Median follow-up of 18.2 months for patients who received prior BTKi and BCL2i

Mato et al. ASH 2022, Abstract #961.
Data cutoff date of 29 July 2022. Response status per iwCLL 2018 according to independent review committee assessment.

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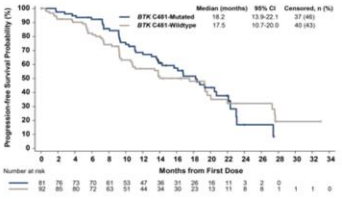
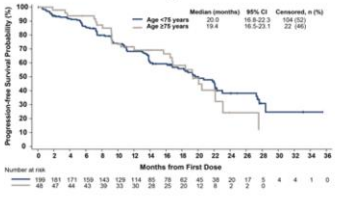
Pirtobrutinib: Progression-Free Survival in CLL/SLL Subgroups

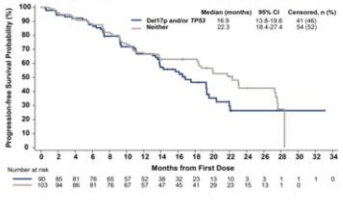
***BTK* C481 mutation status[a,b]**



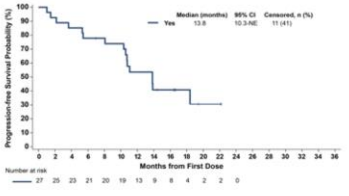
Age



del(17p) and/or *TP53* mutation[a]



Prior BTKi, CIT, BCL2i, and PI3Ki therapy



Data cutoff date of 29 July 2022. Response status per iwCLL 2018 according to independent review committee assessment. [a]*BTK* C481 mutation status, del(17p), and *TP53* mutation status were centrally determined and based on pre-treatment samples. [b]Patients with available mutation data who progressed on any prior BTKi.

Mato et al. ASH 2022, Abstract #961

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TRANSCEND CLL 004: Efficacy Outcomes: DL2 Only

	Full study population at DL2 (n = 88)	BTKi progression/venetoclax failure subset at DL2 (n = 50)
Primary endpoint: IRC-assessed CR/CRi rate per iwCLL 2018, n (%) [95% CI]	17 (19) [12–29]	10 (20) [10–34]
Key secondary endpoints		
IRC-assessed ORR, n (%) [95% CI]	42 (48) [37–59]	22 (44) [30–59]
uMRD rate in blood, n (%) [95% CI]	58 (66) [55–76]	32 (64) [49–77]
Exploratory endpoint: uMRD rate in marrow, n (%) [95% CI]	53 (60) [49–71]	30 (60) [45–74]
Other secondary endpoints		
Best overall response, n (%)		
CR/CRi	17 (19)	10 (20)
PR/nPR	25 (28)	12 (24)
SD	34 (39)	21 (42)
PD	6 (7)	4 (8)
Not evaluable	6 (7)	3 (6)
Time to first response, months, median (range)	1.3 (0.8–17.4)	1.1 (0.8–17.4)
Time to first CR/CRi, months, median (range)	5.5 (0.8–18.0)	2.1 (0.8–18.0)

- **uMRD was achieved in MRD-evaluable patients in the full population at DL2 by:**
  - **15/15 (100%) patients with CR/CRi in blood and 15[a]/16 (94%) in marrow**
  - 24/24 (100%) patients with PR/nPR in blood and 23/23 (100%) in marrow
  - 19/32 (59%) patients with SD in blood and 15/32 (47%) in marrow

[a]One patient had an indeterminate status for MRD, which was considered positive as per FDA guidelines. SD, stable disease.

TRANSCEND CLL 004 uMRD. Poster 3263. Papp et al.6:00—8:00 PM PST, Sunday, December 10, 2023
Siddiqi T, et al. ASH 2023 [Presentation #330]

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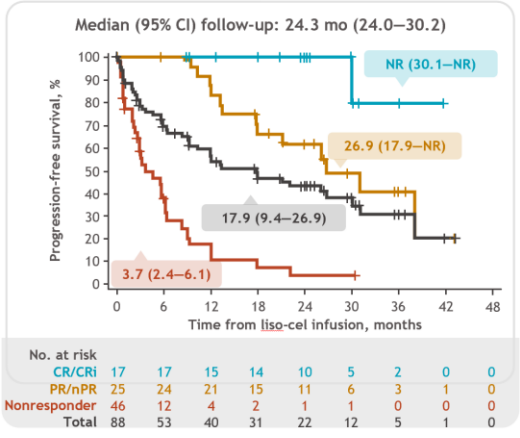
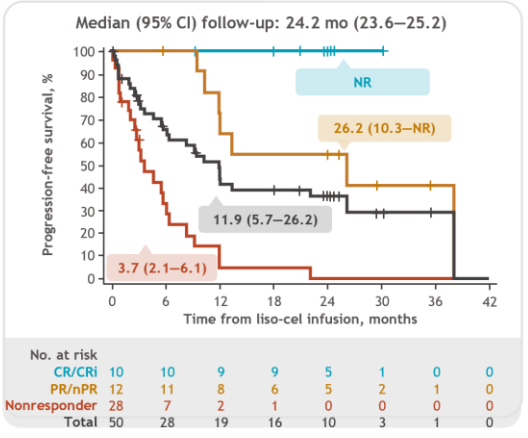
TRANSCEND CLL 004: Progression-free Survival by Best Overall Response

(A) Full study population at DL2 (n = 88)



(B) PEAS (BTKi progression/venetoclax failure subset) at DL2 (n = 50)



Data on KM curves are expressed as median (95% CI, if available).
Siddiqi T, et al. ASH 2023 [Presentation #330]

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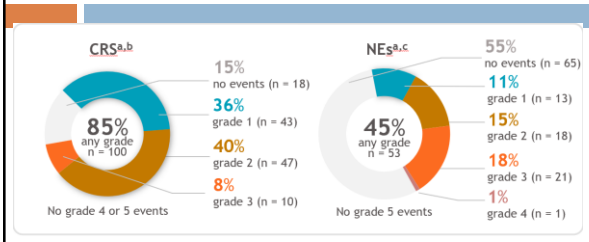
TRANSCEND CLL 004: Safety: Full Study Population (n=118)



	Total (n = 118)	
	CRS	NE
Patients with an event, n (%)	100 (85)	53 (45)
Median (range) time to onset, days	4 (1—18)	7 (1—21)
Median (range) time to resolution, days	6 (2—37)	7 (1—83)
Received tocilizumab and/or corticosteroids for CRS and/or NE	82 (69)	

Other AESIs, n (%)

- Prolonged cytopenias[d]: 64 (54%)
- Grade ≥ 3 infections[e]: 21 (18%)
- Hypogammaglobulinemia[f]: 18 (15%)
- Tumor lysis syndrome: 13 (11%)
- SPM[f]: 11 (9%)
- MAS: 4 (3%)

Deaths due to TEAEs, n = 5 (4%)

- 4 (3%) considered unrelated to liso-cel by investigators (respiratory failure, sepsis, *Escherichia coli* infection, and invasive aspergillosis)
- 1 (1%) considered related to liso-cel by investigators (MAS)

[a]Summed percentages for grouped grades within each graph may not equal the any-grade percentage due to rounding; [b]CRS was graded based on the Lee 2014 criteria; [c]NEs were defined as investigator-identified neurological AEs related to liso-cel; [d]Defined as grade ≥ 3 laboratory abnormalities of neutropenia, anemia, or thrombocytopenia at Day 30 after liso-cel infusion; [e]Includes grade ≥ 3 TEAEs from infections and infestations (System Organ Class) by AE high-level group term; [f]AEs from the 90-day treatment-emergent period, posttreatment-emergent period, and long-term follow-up were included.

AESI, adverse event of special interest; MAS, macrophage activation syndrome; NE, neurological event; SPM, second primary malignancy.

Siddiqi T, et al. ASH 2023 [Presentation #330]

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New Agents for Relapsed / Refractory CLL

- **Old targets – New agents**
  - BTK only degrader (NX-5948; ABBV-101)
  - ncBTKi (TT-01488; LP-168)
  - ngBCL2i (lisaftoclax; BGB-11417; ABBV-453)
  - CD20xCD3 bispecifics (mosunetuzumab; epcoritamab; glofitamab; odronextamab)
- **New targets – New agents**
  - BCL-xL/BCL-2 – (LP-118)
  - PKCb inhibitor – (MS-553)
  - MALT1 (ABBV-525)
  - ROR1 (xCD3 bispecific; CAR-T cells)
  - MCL-1/CDK9 – (Fadraciclib)

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Conclusions

- Outcomes with first-line treatment excellent – focus on finite-duration curative strategies
- Treatment for relapsed disease depends on duration of remission, retreatment with same for long remission
- Refractory disease remains unmet need – promising agents in development
  - Alternative targeted therapies
  - CD19-CAR-T cells
  - Bispecific antibodies
- Richter's transformation remains unmet need

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THANK YOU!

wwierda@mdanderson.org

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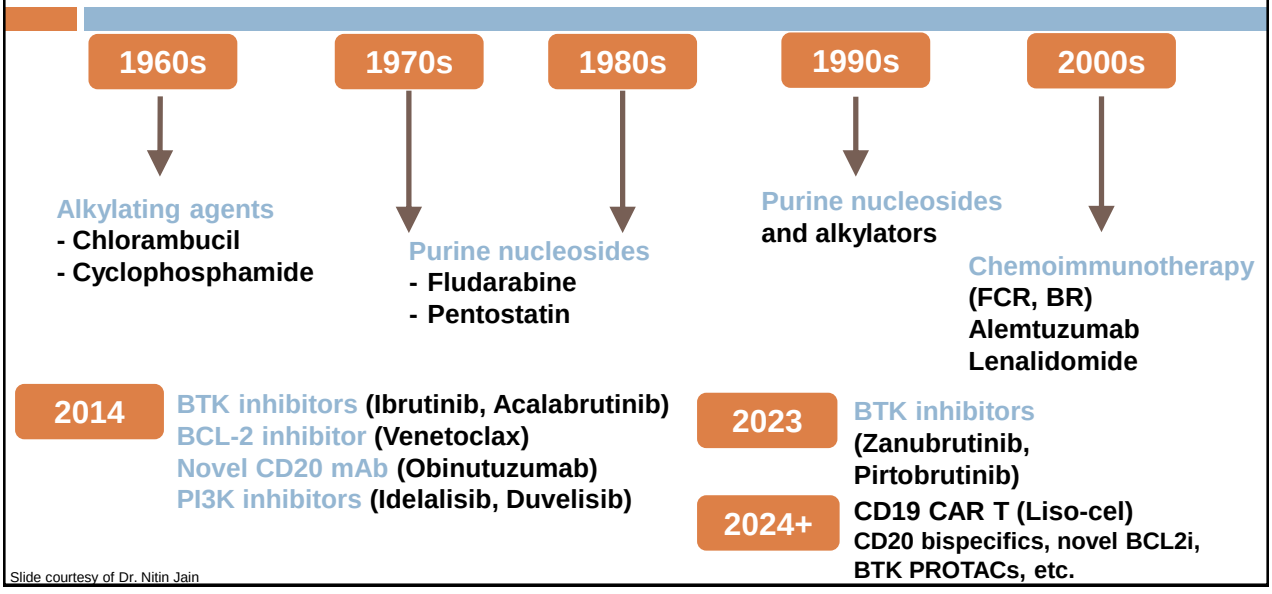
Treatment Evolution in CLL



Slide courtesy of Dr. Nitin Jain

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Treatments

CHEMOIMMUNOTHERAPY

CHEMOTHERAPY
Fludarabine
Cyclophosphamide
Chlorambucil
Bendamustine
Pentostatin

MONOCLONAL ANTIBOIDIES
Rituximab
Obinutuzumab
Alemtuzumab

ORAL TARGETED THERAPIES

BRUTON KINASE INHIBITORS
Covalent
Ibrutinib
Acalabrutinib
Zanubrutinib
Noncovalent
Pirtobrutinib

PHOSPHATIDYLINOSITOL 3-KINASE INHIBITOR
Idelalisib

BCL-2 INHIBITOR
Venetoclax

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Monoclonal Antibodies

	RITUXIMAB (Ritxuan®)	OBINUTUZUMAB (Arezza®)	ALEMTUZUMAB (Campath®)
Target	Anti-CD20 monoclonal antibodies		Anti-CD52 monoclonal antibody
Type	Chimeric human/ mouse	Humanized (Type II)	Humanized
Adverse Effects	Infusion related reactions		
	Tumor lysis syndrome Reactivation of Hepatitis B virus		Infections Skin rash Headache

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BTK Inhibitors: Dosing and Administration

	Ibrutinib[a]	Acalabrutinib[b]	Zanubrutinib[c]	Pirtobrutinib
Dosing	420 mg by mouth once daily	100 mg by mouth twice daily	160 mg by mouth twice daily	200 mg by mouth once daily
Half-life	4 to 6 hours	1 hour	2-4 hours	19 hours
Median T_{max}	1 to 2 hours	0.9 hours	2 hours	2 hours
Dose Forms and Strengths	Cap: 70 mg, 140 mg Tab: 140 mg, 280 mg, 420 mg	Tab*: 100 mg Cap: 100 mg	Cap: 80 mg	Tab: 50 mg, 100 mg
Renal Impairment	No adjustment	No adjustment	No adjustment	≤29 mL/min: 100 mg or 50 mg
Hepatic Impairment				
• **Child-Pugh Class A (mild)**	140 mg daily	No adjustment	No adjustment	No adjustment
• **Child-Pugh Class B (moderate)**	70 mg daily	No adjustment	No adjustment	
• **Child-Pugh Class C (severe)**	Avoid use	Avoid use	80 mg twice daily	

Ibrutinib [PI]. Approved 2013. Revised August 2020; Acalabrutinib [PI]. Approved 2017. Revised November 2019; Zanubrutinib [PI]. Approved 2019. Revised November 2019.

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Drug-Drug Interactions

	Ibrutinib	Acalabrutinib	Zanubrutinib	Pirtobrutinib
Moderate CYP3A4 inhibitor	280 mg daily	100 mg daily	80 mg twice daily	200 mg daily
Voriconazole	140 mg daily	---	80 mg daily	50 mg
Posaconazole	70 mg daily	---		
Strong CYP3A4 inducers	Avoid use	Avoid use. If unable, 200 mg twice daily	Avoid use	Avoid

AE, adverse event; P-gp, P-glycoprotein
Ibrutinib [PI]. Approved 2013. Revised August 2020; Acalabrutinib [PI]. Approved 2017. Revised November 2019; Zanubrutinib [PI]. Approved 2019. Revised November 2019.

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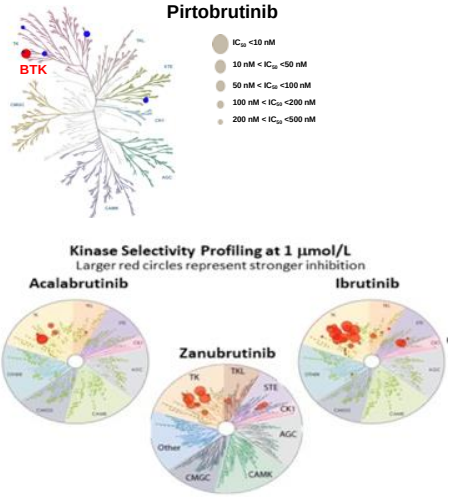
Comparing BTK Inhibitors in CLL
Differences in Inhibition

Kinase	Ibrutinib	Acalabrutinib	Zanubrutinib	Pirtobrutinib
BTK	+++	++	+++	++
TEC - Incr bleeding	+++	+	++	-
ITK - Cytokine productions/ cytotoxic function	+++	-	++	-
EGFR - diarrhea/rash	+++	-	++	-
CSK - A.Fib	++	-	-	?

CSK, C-terminal Src kinase; EGFR, epidermal growth factor receptor; TEC, tyrosine protein kinase



Christensen B. et al. Expert Rev Hematol. 2022;15(4):321-331.
Mato et al, *Lancet* 2021; 397: 892–901. [6]Brandhuber et al. *Clin Lymphoma Myeloma Leuk* 2018; 18(Suppl.1):S216.

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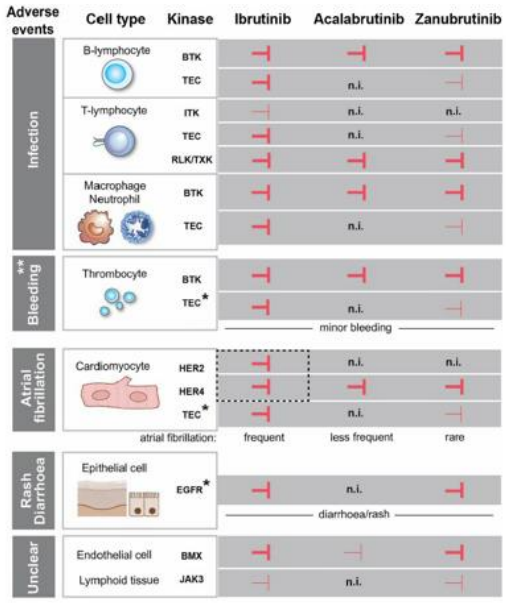

OFF TARGETED EFFECTS OF BTK INHIBITORS

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Non-Cardiac Adverse Events

Adverse Effect	Ibrutinib	Acalabrutinib	Zanubrutinib	Pirtobrutinib
	Incidence (All Grades)			
Diarrhea	31%-46%	35%	21%	26%
Arthralgias/myalgias	16%-23%	16%	13%	23%
Rash	≥30%	10%	13%	12%
Headache	11%-20%	40%	15%	34%
Infection (grade 3)	30%	30%	≤ 23%	34%

a. Byrd JC. JCO. 2021;39(31):3441-3452, b. Tam C. Blood. 2020;136(18):2038-2050, *in Waldenström macroglobulinemia.a

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Cardiac Adverse Events

BTKi	Mechanism	Approved Indications (United States)	Key Trials	Cardiac Adverse Events		
First Generation						
Ibrutinib	Irreversible, covalent binding to Cysteine-481	CLL/SLL Waldenstrom's Macroglobulinemia Chronic Graft versus Host Disease (GVHD)	RESONATE RESONATE-2 ILLUMINATE	*Arrhythmia*	*AF:* *VA:*	13-16 % 1.9 %
				Hypertension:		9-23 %
				Major Bleeding:		3.9-10 %
Second Generation						
Acalabrutinib	Irreversible, covalent binding to Cysteine-481	CLL/SLL Mantle Cell Lymphoma*	ELEVATE T-N ELEVATE R-R	*Arrhythmia*	*AF:* *VA:*	9.4% 0.4 %
				Hypertension:		9.4 %
				Major Bleeding:		4.5 %
Zanubrutinib	Irreversible, covalent binding to Cysteine-481	CLL/SLL Mantle cell lymphoma* Relapsed/refractory Marginal zone lymphoma** Waldenstrom's Macroglobulinemia	SEQUOIA ASPEN ALPINE	*Arrhythmia*	*AF:* *VA:*	2-5 % 0.2-0.8 %
				Hypertension:		10-23.5 %
				Major Bleeding:		2.9-5.9 %
Third Generation						
Pirtobrutinib	Reversible, non-covalent binding to ATP pocket	Relapsed or Refractory CLL/SLL Mantle Cell Lymphoma***	BRUIN	*Arrhythmia*	*AF:* *VA:*	3.9 % NR
				Hypertension:		2.3 %
				Major Bleeding		2.4 %

Table 1: Overview of BTKi Approved for Use in the United States. *Courtesy of Ng J, Ismail H, Rhodes JM, Copeland-Halperin RS.*

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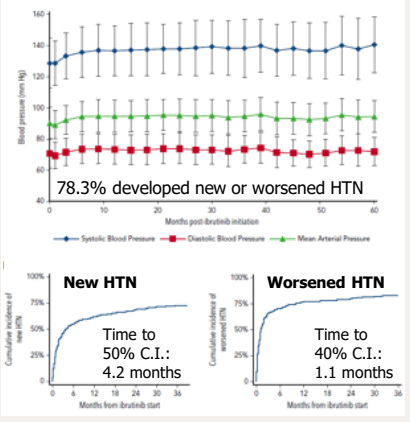
Management of Hypertension

Considerations[a]

- Assess and optimize control of blood pressure at baseline
- Regular monitoring throughout treatment by patient and medical care team
- Initiate antihypertensive agents as needed
  - Consider coordinating care with outside providers (primary care physician, cardiologist, or cardio-oncology [if available])
  - Avoid medications that interact with TKIs known to exacerbate hypertension

Hypertension Following Ibrutinib Initiation in 562 Patients With B-Cell Malignancies[b]



a. Lipsky A, et al. Hematology Am Soc Hematol Educ Program. 2020;2020:336-345; b. Dickerson T, et al. Blood. 2019;134:1919-1928.

52

Management of Atrial Fibrillation

Proposed mechanism	Inhibition of BTK and TEC kinases, which are expressed on cardiac cells that may alter the PI3KT-AKT
Risk factors	Older age (≥ 65 years old), male sex, history of Afib, HTN, HLD, history of pre-existing cardiac disease
MANAGEMENT	
$CHA_2DS_2VASc \leq$ HAS-BLED Score	**$CHA_2DS_2VASc \geq$ HAS-BLED Score**
• Continue BTKi at current dose • Rate/rhythm control	Need to anticoagulate • DOAC preferred • Avoid use of vitamin K antagonist • Consider alternative therapy • Minimize other medications associated with increased bleeding risk
Consider avoiding P-glycoprotein substrates (digoxin) Consider avoiding CYP3A4 inhibitors (verapamil, diltiazem)	

HTN: hypertension; HLD: hyperlipidemia; DOACs: direct oral anticoagulants.

Stephens DM, et al. Blood. 2019;133(12):1298-1307; de Weerdt I, et al. Haematologica. 2017;102:1629-1639; Rhodes J, et al. Curr Oncol Rep. 2018;20:49.

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Other Common and Serious AEs

Adverse Event	Management
Rash	Topical steroids, oral antihistamines
Hair/nail changes	Biotin supplementation, application of nail oil
Diarrhea	Loperamide, hydration, bedtime dosing
Nausea	Bedtime dosing, antiemetics
Arthralgia/myalgia	Exercise, avoid frequent NSAIDs, alternative supplements/treatments
Headache	Caffeine, acetaminophen, avoid NSAIDs/aspirin-containing products
Infection	No standard recommendations for routine screening or prophylaxis practice differs across institutions Monitor closely, be aware of drug-drug interactions with antifungal agents may consider BTK inhibitor hold for severe infection

NSAIDs: nonsteroidal anti-inflammatory drugs.

Lipsky A, et al. Hematology Am Soc Hematol Educ Program. 2020;2020:336-345.

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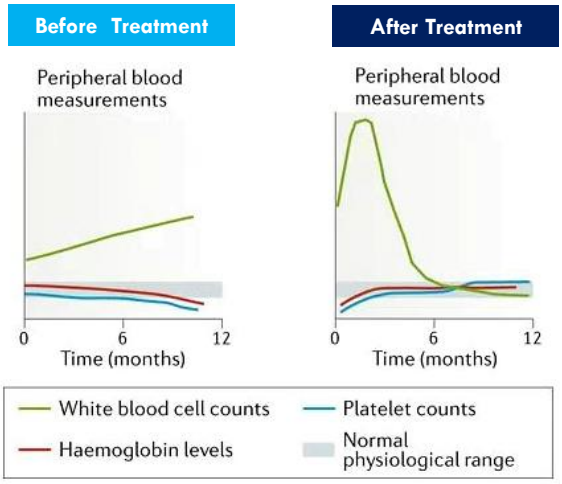
Management of Asymptomatic Lymphocytosis with BTK Inhibitors

- **Onset:** beginning of therapy
- **Proposed mechanism**:
  - Disruption of integrin-mediated adhesions and homing of malignant B cell to the lymphoid microenvironment
- **Management**: continue treatment



Burger J, et al. Nat Rev Clin Oncol. 2018;15:510-527.

55

BTK Inhibitors in CLL: *Patient Education and Adherence*

- Adherence is extremely important[a,b]
  - Missed doses/extended interruptions – potential impact on outcomes
- Overcoming barriers to adherence[a,b]
  - Financial
    - Prescription assistance programs
    - Other financial/institutional resources
  - Patient
    - Education and follow-up strategies
- Pharmacist role in interprofessional approach to patient care

Recommendations for Missed Doses

Ibrutinib[c]	Acalabrutinib[d]	Zanubrutinib[e]
Take as soon as possible on same day; return to normal scheduling the following day	If missed by > 3 hours, omit dose and return to normal schedule	Take as soon as possible on same day; return to normal schedule the following day

Do not administer extra doses to make up for a missed dose

a. Barr PM, et al. Blood. 2017;129:2612-2615; b. Parikh SA, et al. Cancer Med. 2020;9:3390-3399; c. Ibrutinib [PI]. Approved 2013. Revised August 2020; d. Acalabrutinib [PI]. Approved 2017. Revised November 2019; e. Zanubrutinib [PI]. Approved 2019. Revised November 2019.

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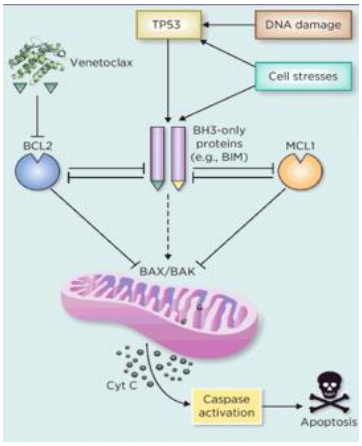

VENETOCLAX

Venetoclax is a selective BCL-2 inhibitor that binds to and inhibits excess BCL2, thereby displacing pro-apoptotic proteins and restoring the apoptotic process

Venetoclax [package insert] 2017
Image adapted from Roberts A. CCR. 2017

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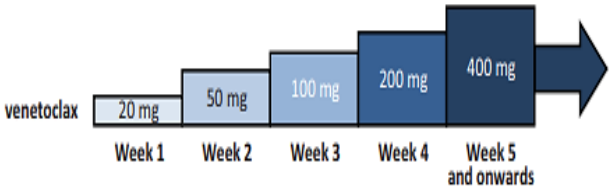
Venetoclax (VENCLEXTA®)

- **Selective BCL-2 inhibitor**
- **Dose: Start with weekly dose escalation**



- **Drug-drug interactions:**

	Management
Strong CYP3A4 inhibitors	Dose reduce by 75%
Moderate CYP3A4 inhibitors	Dose reduce by 50%
P-gp inhibitors	Dose reduce by 50%

Venetoclax [package insert]. 2016.

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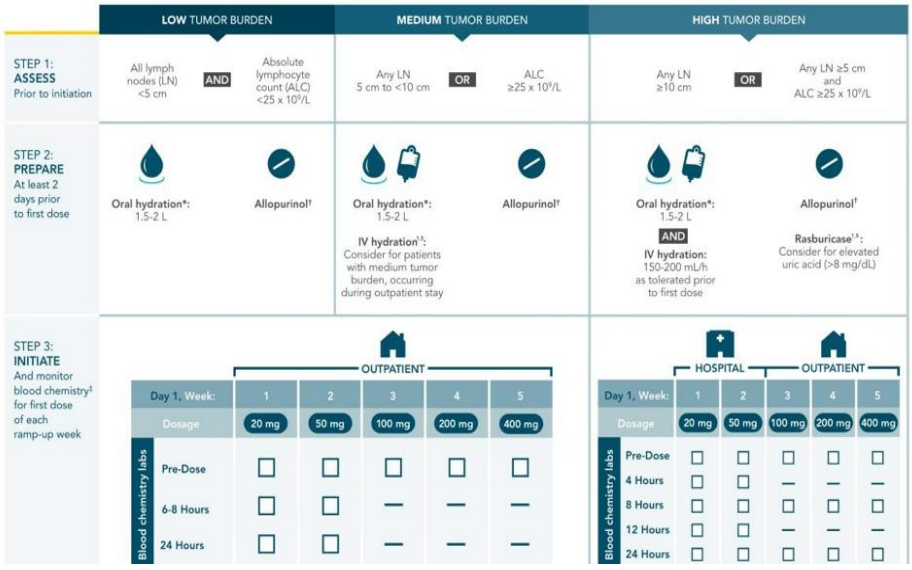

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Venetoclax Adverse Effects

	Cytopenias	Gastrointestinal
INCIDENCE	50%-87% 40%-60% (grade ≥3)	Diarrhea: 43% Nausea: 42%
MANAGEMENT	• Monitor • May require growth-factor support • May need anti-infectives	• Self limiting • Administer within 30 minutes of a meal • Schedule at night • If continues despite supportive care, consider dose reduction

GI= gastrointestinal
Venetoclax [package insert] 2017.

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Counseling Patients About AEs
The Role of Nurses, Pharmacists, and Patient Educators

Include what to expect on key AEs

Review ways to self-manage AEs

Discuss ways to determine if an AE is serious and needs to be addressed immediately

Discuss and help minimize financial burden of prescriptions

Educate about additional factors to be aware of:

- Avoiding specific foods
- Reporting any new medications
- Planning any surgical procedures

Friesen-Storms JH, et al. Int J Nurs Stud. 2015;52:393-402; Kane HL, et al. CA Cancer J Clin. 2014;64:377-88; Kawasaki Y Clin J Oncol Nurs. 2014;18:701-6; Erçalışkan A, et al. Blood Adv. 2021;5:3344-3353.

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Role of the Oncology Nurse in CLL

Jackie Broadway-Duren, PhD, DNP, FNP-BC

Department of Leukemia

The University of Texas MD Anderson Cancer Center

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Definition of an Oncology Advanced Practitioner

- Oncology Advanced Practitioners – non-physician providers with expert clinical knowledge and specialized training to care for patients with cancer. Types of APs include:
  - Nurse Practitioners
  - Clinical Nurse Specialists
  - Physician Assistants
- Registered Nurses

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Roles of Oncology Nurse Practitioners

- Physical Assessment (H&P) – evaluate patients physical and emotional status
- Procedurists – Perform certain procedures for assessment of disease, such as bone marrow biopsies, lumbar punctures.
- Educators – educate patients on disease, treatments, and drug side effects
- Patient advocates
- Diagnostician - order scans, xrays, and other procedures as needed for patient care

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Characteristics of the Nurse Practitioner Role in Oncology

- Direct and comprehensive patient-centered care
- Manage treatment plans
- On-going assessment of symptoms
- Advocating for patients with cancer
- Works collaboratively with interdisciplinary cancer care teams
- Provides family support

Oncology Nursing Society (ONS, 2024). https://www.ons.org.

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Symptom Management

- Experts in symptom management caused by cancer treatments i.e., BTK inhibitors
- Offer various strategies for management of drug adverse events
- Provide detailed explanation of treatment drugs and regimen
- Prescribe necessary drugs for patients
- Review treatment diaries/encourage compliance

(ONS, 2024).

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Manage Survivorship Clinics

- Survivorship clinics provide care to patients who have either completed therapy or are stable, not needing acute care
- Survivorship begins with cancer diagnosis
- Designed to monitor for recurrent cancers, relapsed cancers, preventive care (vaccines, cancer screenings), and surveillance

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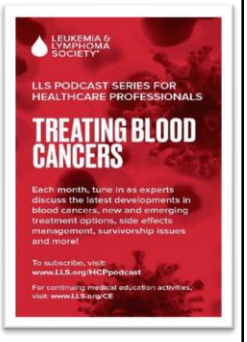
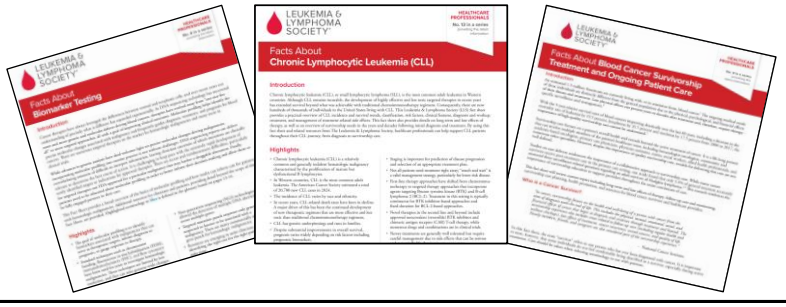
FREE LLS RESOURCES FOR HEALTHCARE PROFESSIONALS

- ❑ Free CME & CE courses www.LLS.org/CE
- ❑ Fact Sheets www.LLS.org/HCPbooklets
- ❑ Videos for HCPs www.LLS.org/HCPvideos
- ❑ Podcast series for HCPs www.LLS.org/HCPpodcast





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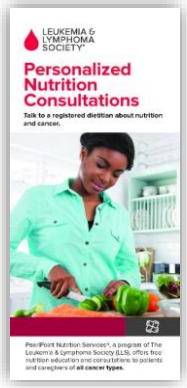
FREE LLS RESOURCES FOR PATIENTS

- **Information Specialists** – Personalized assistance for managing treatment decisions, side effects, and dealing with financial and psychosocial challenges (IRC)
  - www.LLS.org/IRC
- **Nutrition Education Services Center** – one-on-one consultation with a registered dietician for patients/caregivers of all cancer types (NESC)
  - www.LLS.org/Nutrition
- **Clinical Trial Nurse Navigators** – RNs and NPs provide personalized service for patients seeking treatment in a clinical trial, sift through and provide information to bring back to their HC team (CTSC)
  - www.LLS.org/CTSC
- **Reach out Monday–Friday, 9 am to 9 pm ET**
  - Phone: (800) 955-4572
  - Live chat: www.LLS.org/IRC
  - Email: infocenter@LLS.org
  - HCP Patient Referral Form: www.LLS.org/HCPreferral



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HERE TO HELP: LLS COMMITMENT

to providing education & resources to help patients access clinical trials

CLINICAL TRIAL SUPPORT CENTER

- A team of highly trained nurses and nurse practitioners experienced with hematological malignancies and clinical research.
- Provide education to patients about clinical trials, treatment options, and other disease specific information.
- Provide patients, families, and their caregivers with a professional, detailed, individualized search to discuss with their HCP.
- Provide guidance and serve as advocates throughout the clinical trial process. Help make connections between the patient and the trial site to facilitate enrollment as appropriate.
- Provide a personal connection and develop long term relationships to help better serve our patients.

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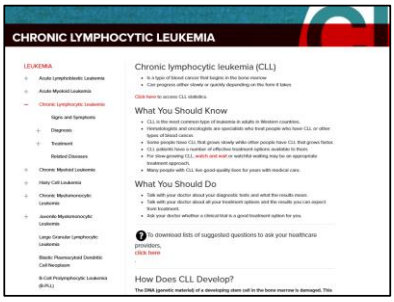
FREE LLS RESOURCES FOR PATIENTS AND CAREGIVERS

- **Webcasts, Videos, Podcasts, booklets**:
  - www.LLS.org/Webcasts
  - www.LLS.org/EducationVideos
  - www.LLS.org/Podcast
  - www.LLS.org/Booklets
  - **www.LLS.org/Leukemia**



- **Support Resources**
  - Financial Assistance: www.LLS.org/Finances
    - Urgent Need
    - Patient Aid
    - Travel Assistance
  - Other Support: www.LLS.org/Support
    - LLS Regions
    - Online Weekly Chats Facilitated by Oncology SW
    - LLS Community Social Media Platform
    - First Connection Peer to Peer Program

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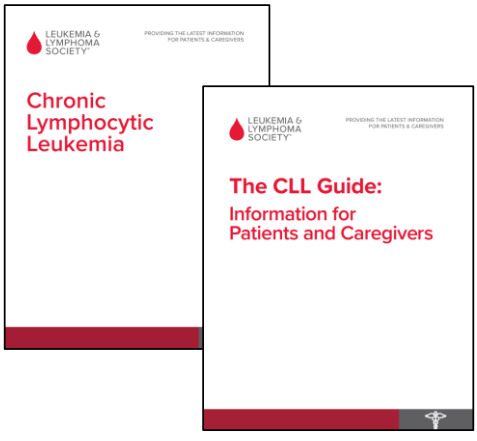
FREE LLS RESOURCES FOR YOUR PATIENTS



BOOKLETS AND FACT SHEETS

English – www.LLS.org/Booklets
Spanish – www.LLS.org/Materiales

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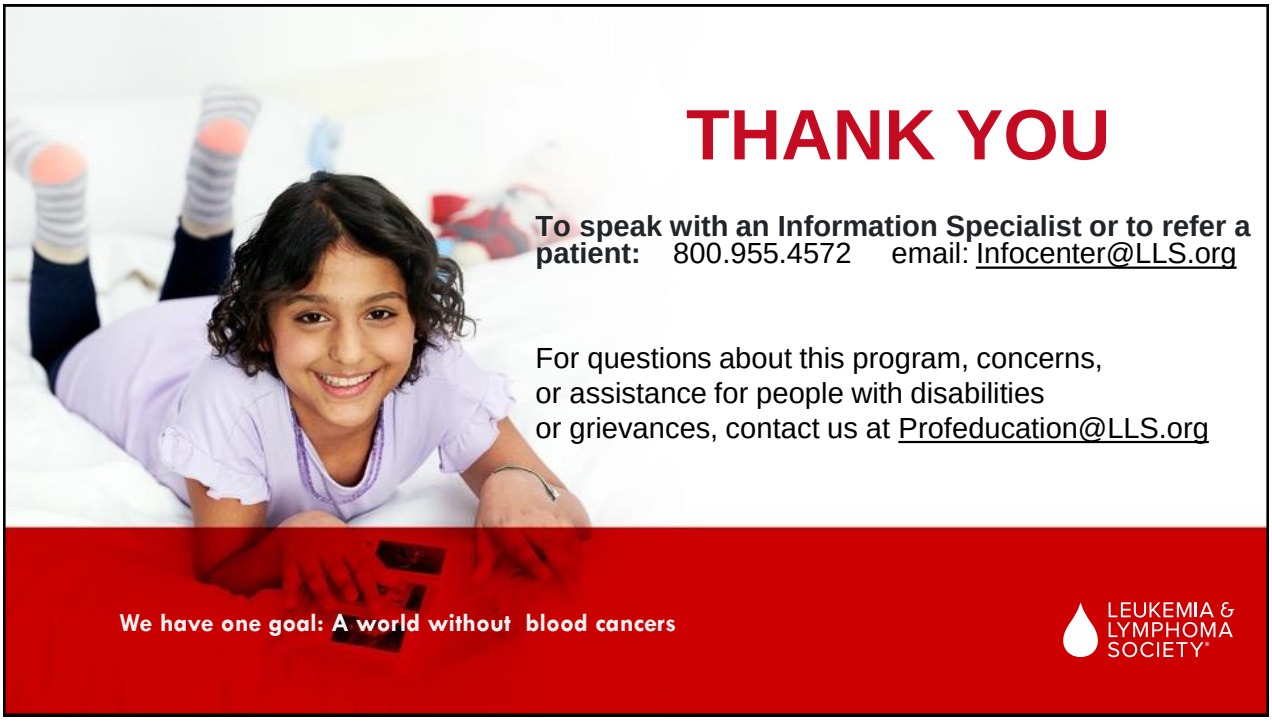
THANK YOU
To speak with an Information Specialist or to refer a patient: 800.955.4572 email: Infocenter@LLS.org
For questions about this program, concerns, or assistance for people with disabilities or grievances, contact us at Profeducation@LLS.org
We have one goal: A world without blood cancers
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