Project ECHO®

Med Learning Group - Chronic Lymphocytic Leukemia

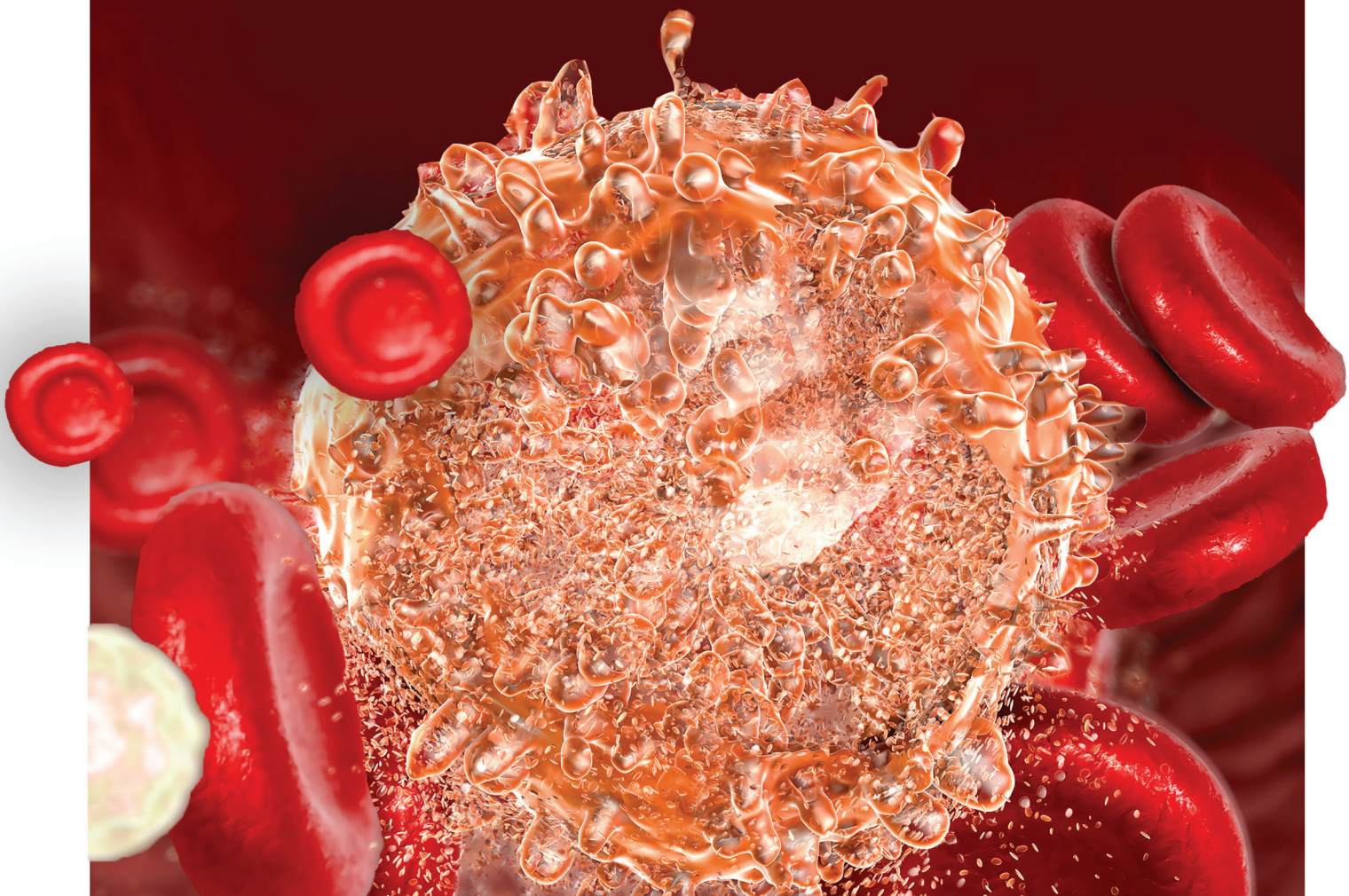
THE CATALYST INITIATIVE

Expanding Knowledge to Improve Clinical Decision-Making and Health Outcomes for Patients with Hematologic Malignancies:

A FOCUS ON CLL

Program Chair

Ryan Jacobs, MD
Principal Investigator of CLL Clinical Trials
Assistant Professor, Atrium Health
Department of Hematology, Lymphoma Section
Levine Cancer Institute
Charlotte, NC



The CATALYST Initiative: Expanding Knowledge to Improve Clinical Decision-Making and Health Outcomes for Patients with Hematologic Malignancies: A Focus on CLL

FACULTY

Ryan Jacobs, MD (PROGRAM CHAIR)
Principal Investigator of CLL Clinical Trials
Assistant Professor, Atrium Health
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PROGRAM OVERVIEW

This case-based live virtual activity is designed to help community oncologists and the multidisciplinary care team choose the optimal treatment for chronic lymphocytic leukemia (CLL) based on patient and disease characteristics, including performance status, organ function, comorbidities, drug interactions, and genetic and molecular biomarkers; monitor for and manage adverse events; and implement SDM into clinical practice to improve patient care and QoL.

TARGET AUDIENCE

This multi-modular educational initiative is intended for US-based hematologists, medical oncologists, and other healthcare providers involved in the management of patients with chronic lymphocytic leukemia.

LEARNING OBJECTIVES

Upon the completion of this program, attendees should be able to:

- Determine how genetic and molecular markers aid in determining treatment strategies for patients with CLL
- Differentiate therapy for the treatment of newly diagnosed or relapsed/ refractory (R/R) CLL based on disease- and patient-specific factors and communicate treatment plans using shared decision-making strategies
- Distinguish adverse events associated with CLL treatment to appropriately prevent and/or manage potential effects

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Purpose: This program would be beneficial for nurses involved in the care of patients with chronic lymphocytic leukemia.
CNE Credits: 1.0 ANCC Contact Hour.

CNE ACCREDITATION STATEMENT

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Awarded 1.0 contact hour of continuing nursing education of RNs and APNs.

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CME Content Review

The content of this activity was independently peer-reviewed.
The reviewer of this activity has nothing to disclose.

CNE Content Review

The content of this activity was peer-reviewed by a nurse reviewer.

Teresa L. Keating, MSN, RN, WHNP
Ultimate Medical Academy/CCM – Lead Nurse Planner

The reviewer of this activity has nothing to disclose

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During this lecture, faculty may mention the use of medications for both FDA-approved and non-approved indications.

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1. Read the CME/CNE information and faculty disclosures.
2. Participate in the live virtual activity.
3. Submit the evaluation form to Med Learning Group.

You will receive your certificate upon completion as a downloadable file.

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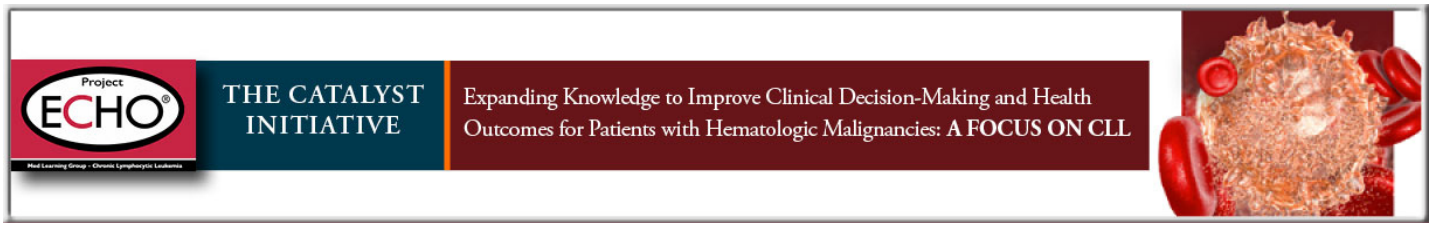
This activity is co-provided by Ultimate Medical Academy/Complete Conference Management (CCM).

This activity is supported by an educational grant from AstraZeneca Pharmaceuticals.



AGENDA

I. **Prognostication and Prediction**
   a. Fluorescence in situ hybridization (FISH)
   b. IgHV mutational status

II. **Treatment Paradigms in CLL**
   a. FCR vs BR
   b. BTK inhibition
   c. Venetoclax
   d. P13K inhibitors
   e. Other approaches

III. **Applying Shared Decision-Making in CLL (Selected Case Studies from the Lightning Round)**
   a. Considering goals of care and patient preferences in the management of CLL
   b. Applying shared decision making to clinical practice

IV. **Case Studies and Questions and Answers**

Expanding Knowledge to Improve Clinical Decision-Making and Health Outcomes for Patients with Hematologic Malignancies: A Focus on CLL

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Learning Objectives

- Determine how genetic and molecular markers aid in determining treatment strategies for patients with CLL
- Differentiate therapy for the treatment of newly diagnosed or relapsed/ refractory (R/R) CLL based on disease- and patient-specific factors and communicate treatment plans using shared decision-making strategies
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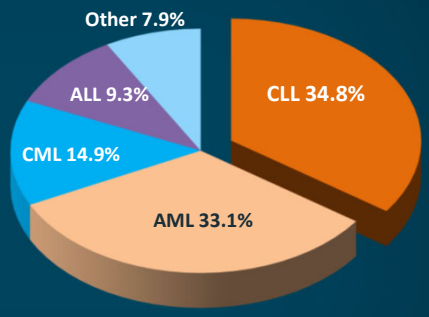
Chronic Lymphocytic Leukemia (CLL)

Definition of CLL—IWCLL (2008)[1]

- Small, monomorphic, mature B-cells
- At least 5000/µL B-cells
- Co-express CD5 and CD23

2021 expected new cases of leukemia in the US by type[2]



- In the US in 2021, an estimated **21,250** patients will be diagnosed with CLL[2]
- Average age of CLL at diagnosis = ~70 years[3]

IWCLL = International Workshop on Chronic Lymphocytic Leukaemia; CD = cluster of differentiation; ALL = acute lymphocytic leukemia; CML = chronic myeloid leukemia.

1. Hallek M, et al; IWCLL. *Blood.* 2008;111:5446-5456. 2. American Cancer Society (ACS). Cancer Facts & Figures 2021 (www.cancer.org/content/ dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2020/cancer-facts-and-figures-2020.pdf). 3. ACS CLL key statistics (www.cancer.org/cancer/chronic-lymphocytic-leukemia/about/key-statistics.html). Accessed July 7, 2021.

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Prognostic Markers in CLL

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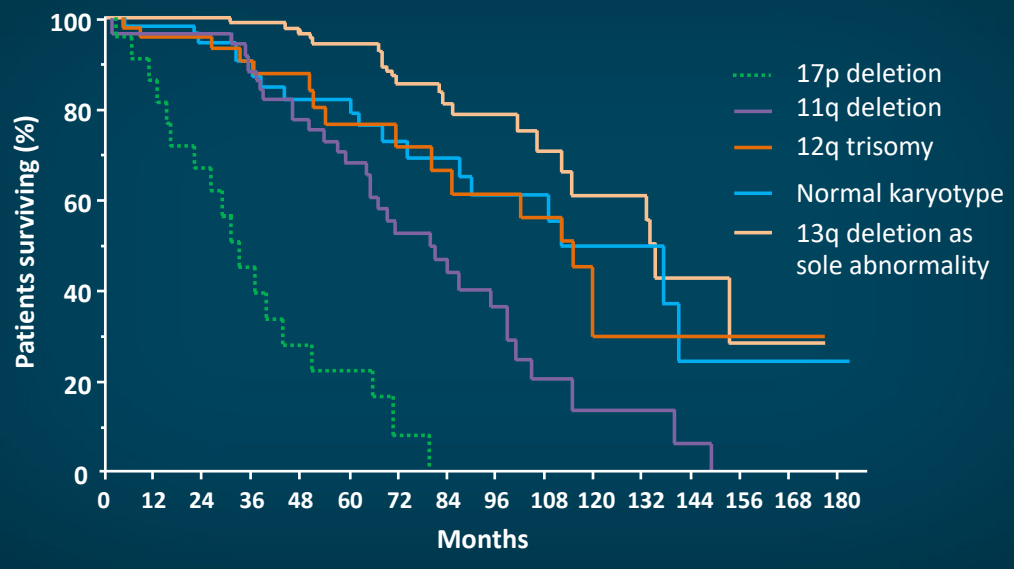
Interphase FISH Correlates With Overall Survival



Döhner H, et al. *N Engl J Med.* 2000;343:1910-1916.

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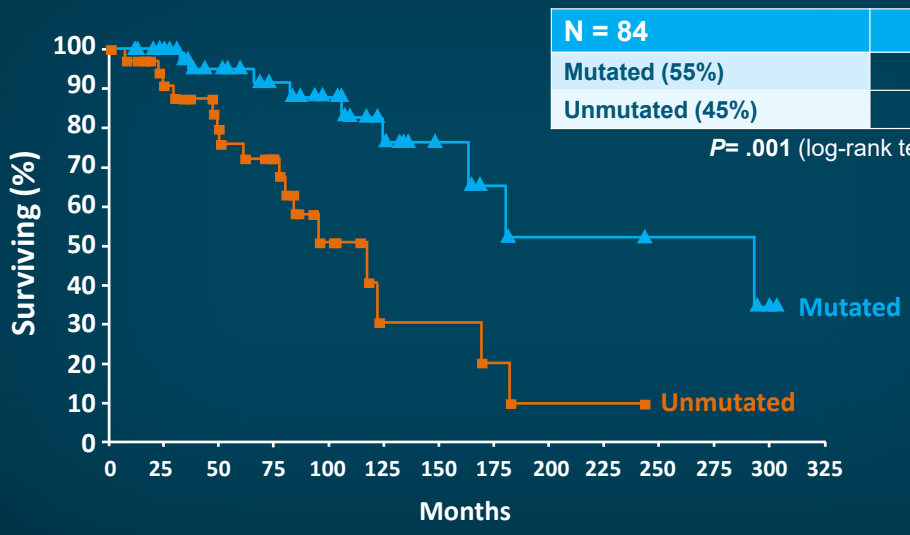
IgHV Mutational Status Predicts Survival



N = 84	Median OS
Mutated (55%)	293 months
Unmutated (45%)	117 months

***P*= .001** (log-rank test)

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

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Prognostic Markers

- Interphase cytogenetics by FISH
- *IgHV* mutational status
- ***TP53* mutation analysis**

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Treatment Paradigms in CLL

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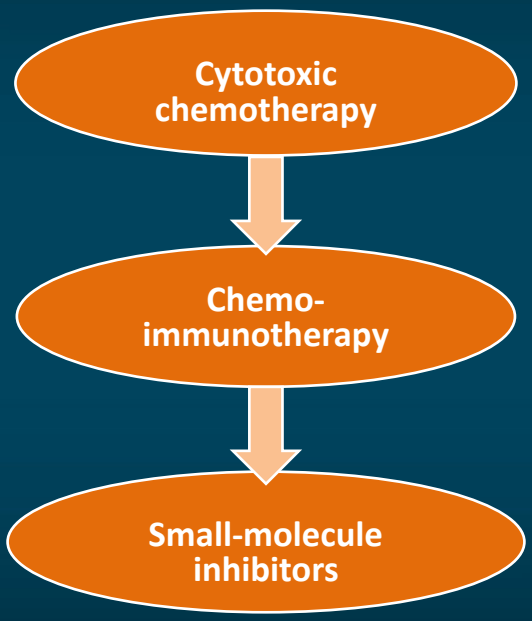
Advances in Therapeutic Paradigms



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Video #1
CLL MOA

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FCR vs BR—CLL10 GCLLSG Trial

	FCR n = 282	BR n = 279	*P* value
ORR (%)	95	96	NS
CR (%)	40	31	.034
Median PFS (months)	55.2	41.7	.003
OS at 3 yrs (%)	91	92	NS
Severe neutropenia (%)	84	59	<.001
Severe infections (%)	39	25	.001
TRM (%)	5	2	—

FCR = fludarabine + cyclophosphamide + rituximab; BR = bendamustine + rituximab; GCLLSG = German CLL Study Group; ORR = overall/objective response rate; CR = complete response/remission; PFS = progression-free survival; yr(s) = year(s); TRM = treatment-related mortality; NS = not significant.

Eichhorst B, et al. *Lancet Oncol.* 2016;17:928-942. Eichhorst B, et al. *Blood.* 2014;124(21): abstract 19.

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Treatment with BTK Inhibition

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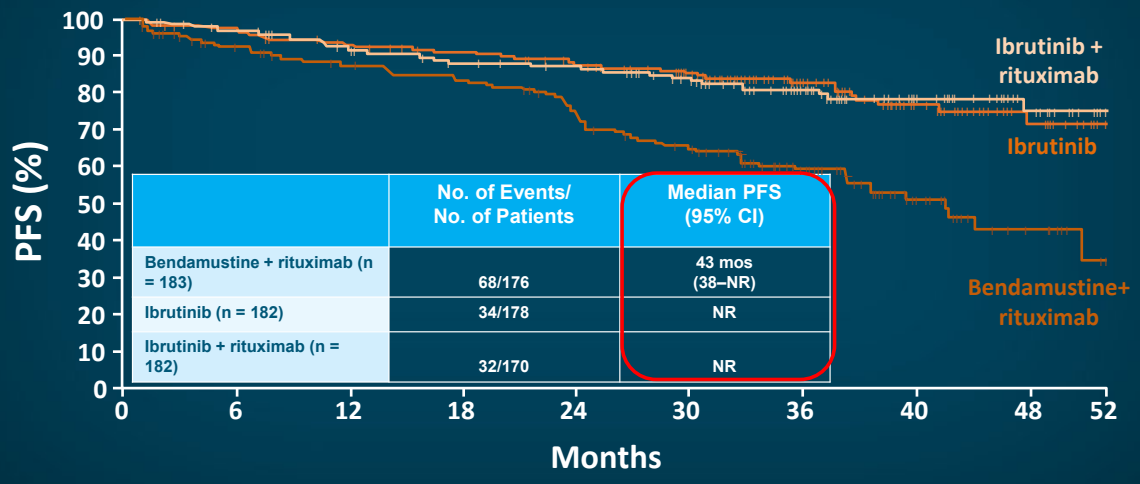
ALLIANCE: Ibrutinib Regimens vs Chemoimmunotherapy in Older Patients with Untreated CLL



	No. of Events/ No. of Patients	Median PFS (95% CI)
Bendamustine + rituximab (n = 183)	68/176	43 mos (38–NR)
Ibrutinib (n = 182)	34/178	NR
Ibrutinib + rituximab (n = 182)	32/170	NR

Woyach JA, et al. *N Engl J Med*. 2018;379:2517-2528.

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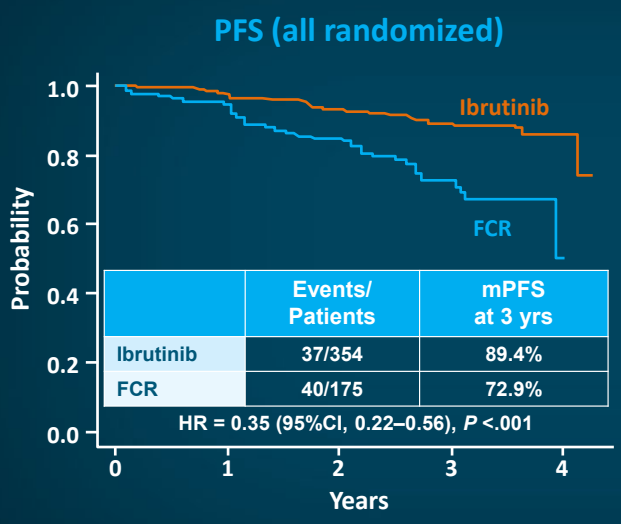
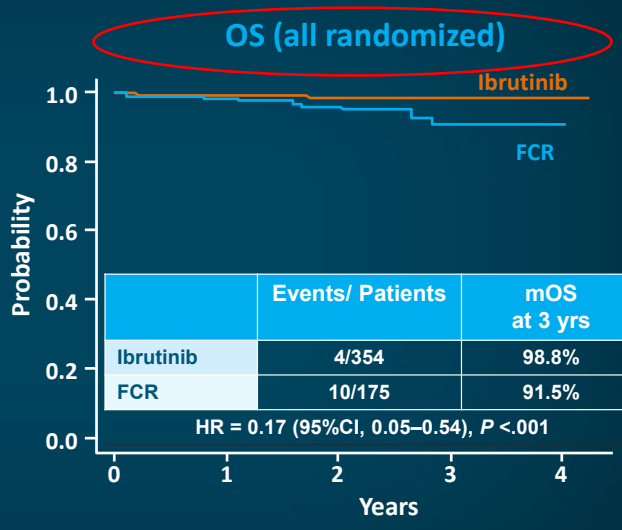
Ibrutinib vs FCR in Untreated Younger Patients with CLL (ECOG)



	Events/ Patients	mPFS at 3 yrs
Ibrutinib	37/354	89.4%
FCR	40/175	72.9%

HR = 0.35 (95%CI, 0.22–0.56), *P* <.001



	Events/ Patients	mOS at 3 yrs
Ibrutinib	4/354	98.8%
FCR	10/175	91.5%

HR = 0.17 (95%CI, 0.05–0.54), *P* <.001

ECOG = Eastern Cooperative Oncology Group; mPFS = median PFS; mOS = median OS.

Shanafelt TD, et al. *N Engl J Med*. 2019;381:432-443.

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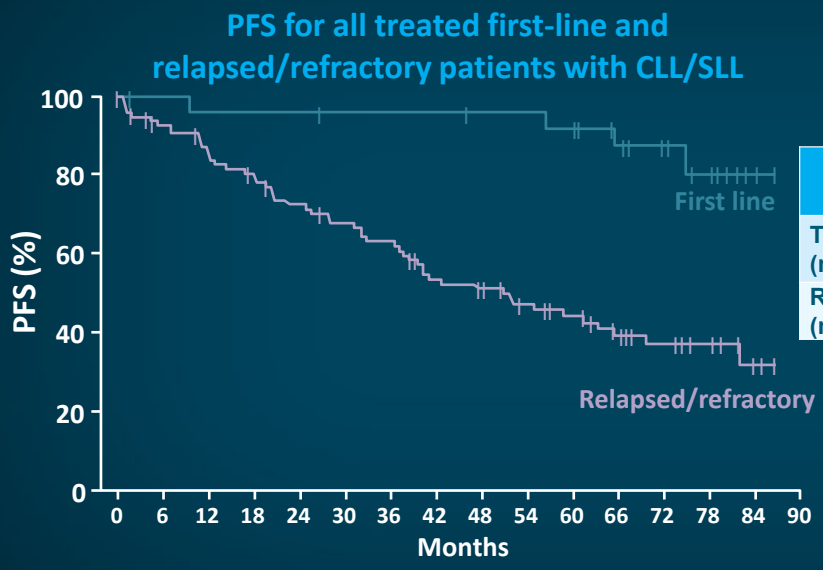
PFS With Long-Term Ibrutinib Use



	Median PFS	7-year PFS
Treatment-naïve (n = 31)	NR	80%
R/R (n = 101)	51 mos	32%

SLL = small lymphocytic lymphoma; R/R = relapsed/refractory; NR = not reached.

Byrd JC, et al. *Blood.* 2018;132(suppl 1):abstract 3133.

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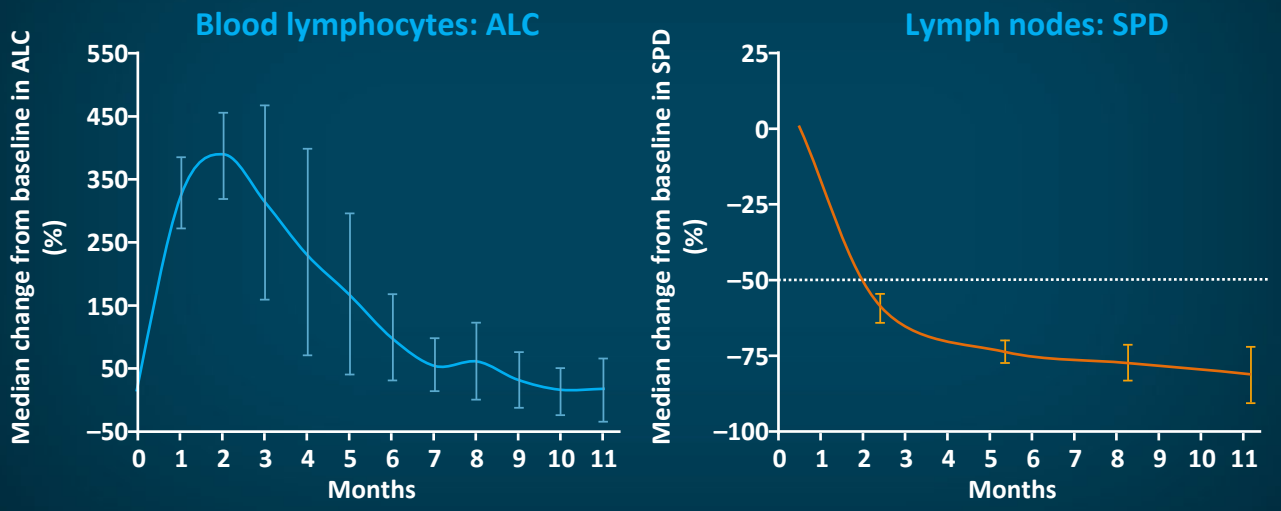
Pattern of Response: Blood Lymphocytes vs Lymph Nodes



ALC = absolute lymphocyte count; SPD = sum of the products of perpendicular diameters of lymph nodes.

Byrd JC, et al. *N Engl J Med*. 2013;369:32-42.

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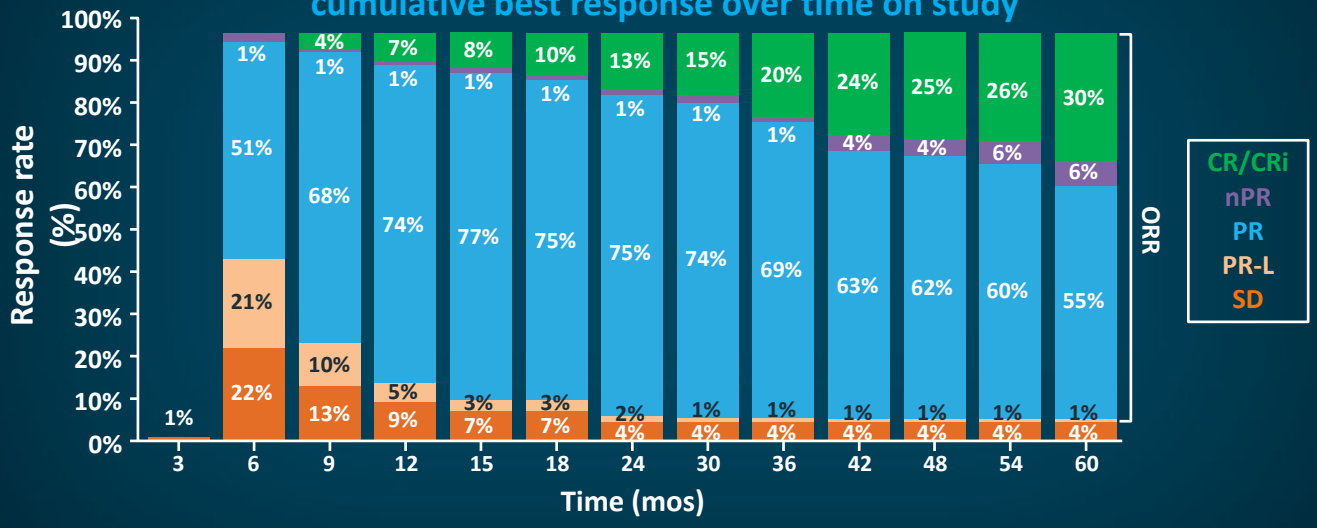
Response Deepens Over Time

RESONATE-2 (ibrutinib monotherapy): cumulative best response over time on study



CR = complete response; CRi = CR with incomplete marrow recovery; PR = partial response/remission; nPR = nodular PR, PR-L = PR with lymphocytosis; SD = stable disease; ORR = overall/objective response rate.

Burger JA, et al. *Leukemia*. 2020;34:787-798.

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Understanding Spectrum of Grade 3/4 AEs With Ibrutinib

Extended Follow-Up

Adverse event, %	≤1 year	>1–2 years	>2–3 years	>3–4 years	>4–5 years	>5–6 years	>6–7 years	Overall study
Hypertension	9	8	19	15	16	16	5	28
Pneumonia	11	10	7	10	6	6	3	24
Neutropenia	11	3	2	1	2	2	0	18
Thrombocytopenia	6	3	2	1	0	0	0	9
Atrial fibrillation	2	3	1	5	5	0	0	9
Diarrhea	3	3	1	3	2	2	0	7
Cellulitis	2	1	6	3	0	2	0	7
Sepsis	2	5	0	3	2	2	0	8
Fatigue	3	2	0	3	0	0	0	6
Decreased lymphocyte count	0	2	6	4	3	6	0	7

Dose reductions due to AEs = 14%; discontinuation due to AEs = 26%

Consider risks and benefits in patients on anticoagulants; monitor for bleeding, fever, infections (evaluate promptly)

AE = adverse event.

O'Brien S, et al. *Blood*. 2018:131:1910-1919 and supplement. Byrd JC, et al. *Clin Cancer Res.* 2020;26:3918-3927.

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Dosing Modifications for Managing Adverse Reactions with Ibrutinib

1st OCCURRENCE	2nd OCCURRENCE	3rd OCCURRENCE	4th OCCURRENCE
Interrupt until resolution to Grade 1 or baseline	Interrupt until resolution to Grade 1 or baseline	Interrupt until resolution to Grade 1 or baseline	DISCONTINUE if adverse reaction persists or reoccurs following 2 dose reductions
RESUME at same dose 420 mg	RESUME at same dose 280 mg	RESUME at same dose 140 mg	

Ibrutinib (Imbruvica®) prescribing information (PI) 2019 (https://imbruvica.com/files/prescribing-information.pdf). Accessed July 7, 2021.

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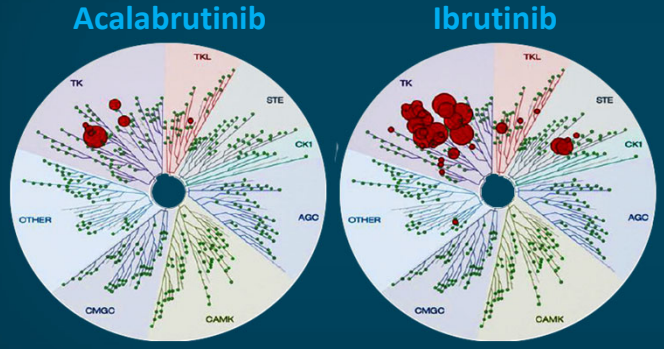
Acalabrutinib (ACP-196)

Acalabrutinib is more selective for BTK with less off-target kinase inhibition compared with ibrutinib *in vitro*

Kinase selectivity profiling at 1 μM



Larger red circles represent stronger inhibition

Recombinant Kinase Inhibition Assays		
Kinase	IC_{50} (nM)	
	Acalabrutinib	Ibrutinib
BTK	5.1	1.5
TEC	93.0	7.0
ITK	>1000	4.9
BMX	46	0.8
TXK	368	2.0
EGFR	>1000	5.3
ErbB2	~1000	6.4
ErbB4	16	3.4
BLK	>1000	0.1
JAK3	>1000	32

IC_{50} = half-maximal inhibitory concentration; TEC = tyrosine kinase (TK) expressed in hepatocellular cancer; ITK = IL2-inducible T-cell kinase; BMX = bone marrow TK on chromosome X; TXK = tyrosine-protein kinase; EGFR = epidermal growth factor receptor; ErbB = erythroblastic oncogene B; BLK = B lymphocyte tyrosine kinase; JAK = Janus kinase.

Herman SEM, et al. *Clin Cancer Res*. 2017;23:2831-2841. Byrd JC, et al. *N Engl J Med*. 2016;374:323-332 and supplement.

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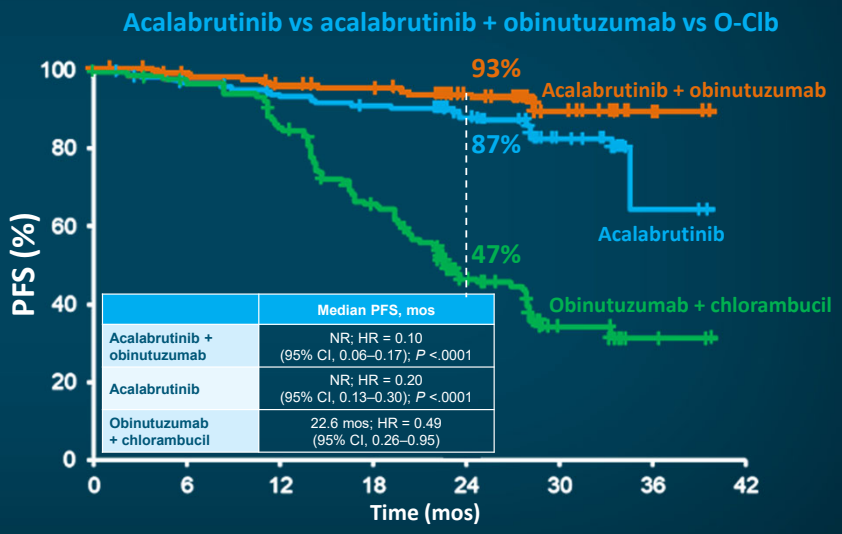
ELEVATE-TN: Acalabrutinib ± Obinutuzumab in Treatment-Naïve Patients With Coexisting Medical Conditions

- Phase 3, open-label trial
- Untreated CLL
- Eligible patients were either ≥65 years or 18 to <65 years with comorbidities

- Median FU = 28.3 mos

Post hoc analysis
HR for PFS between acalabrutinib + obinutuzumab and acalabrutinib monotherapy = 0.49 (95% CI, 0.26–0.95)



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

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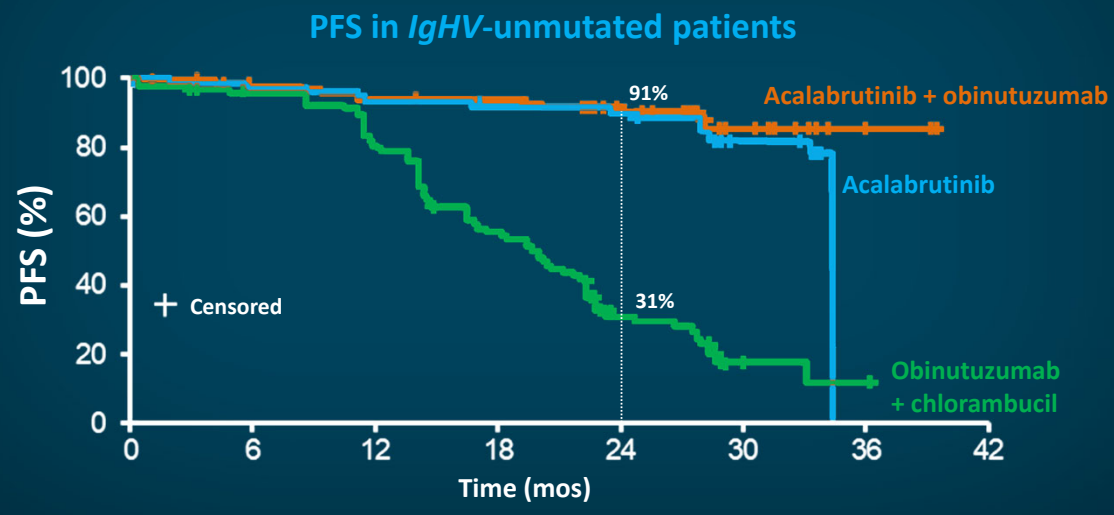
ELEVATE-TN: Acalabrutinib ± Obinutuzumab in Treatment-Naïve Patients With Coexisting Medical Conditions



Modified from Sharman JP, et al. *Lancet*. 2020;395:1278-1291.

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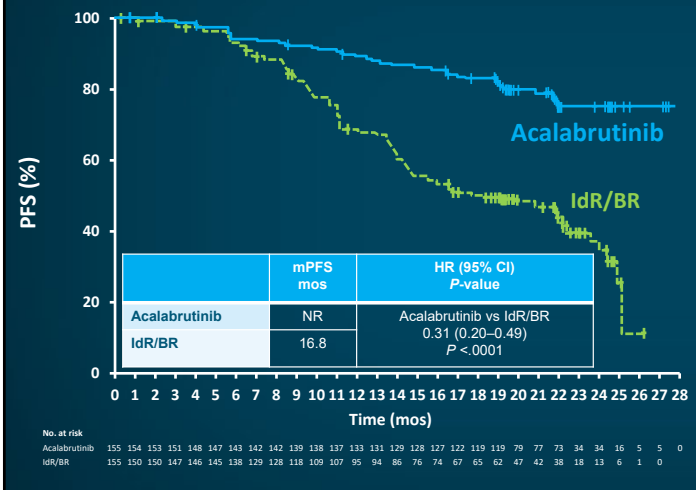
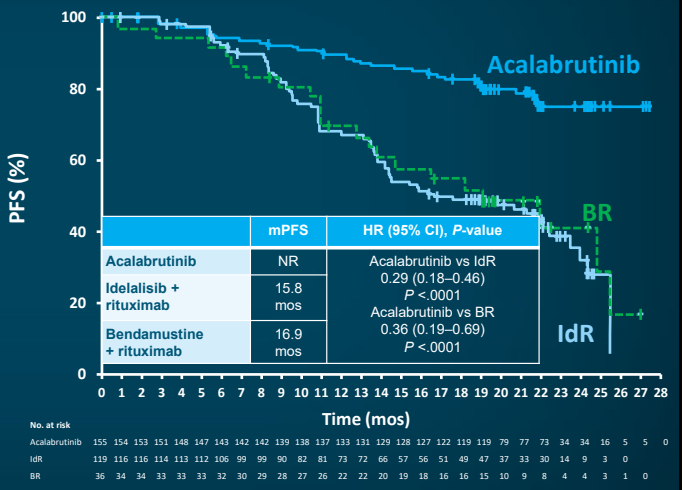
Phase 3 ACE-CL-309/ASCEND: Acalabrutinib Improves PFS in R/R CLL



	mPFS mos	HR (95% CI) *P*-value
Acalabrutinib	NR	Acalabrutinib vs IdR/BR 0.31 (0.20–0.49) *P* <.0001
IdR/BR	16.8	



	mPFS	HR (95% CI), *P*-value
Acalabrutinib	NR	Acalabrutinib vs IdR 0.29 (0.18–0.46) *P* <.0001 Acalabrutinib vs BR 0.36 (0.19–0.69) *P* <.0001
Idelalisib + rituximab	15.8 mos	
Bendamustine + rituximab	16.9 mos	

R = rituximab; IdR = idelalisib + R; BR = bendamustine + R.

Ghia P, et al. *J Clin Oncol.* 2020;38:2849-2861. Ghia P, et al. *J Clin Oncol.* 2020;38(15 suppl): abstract 8015.

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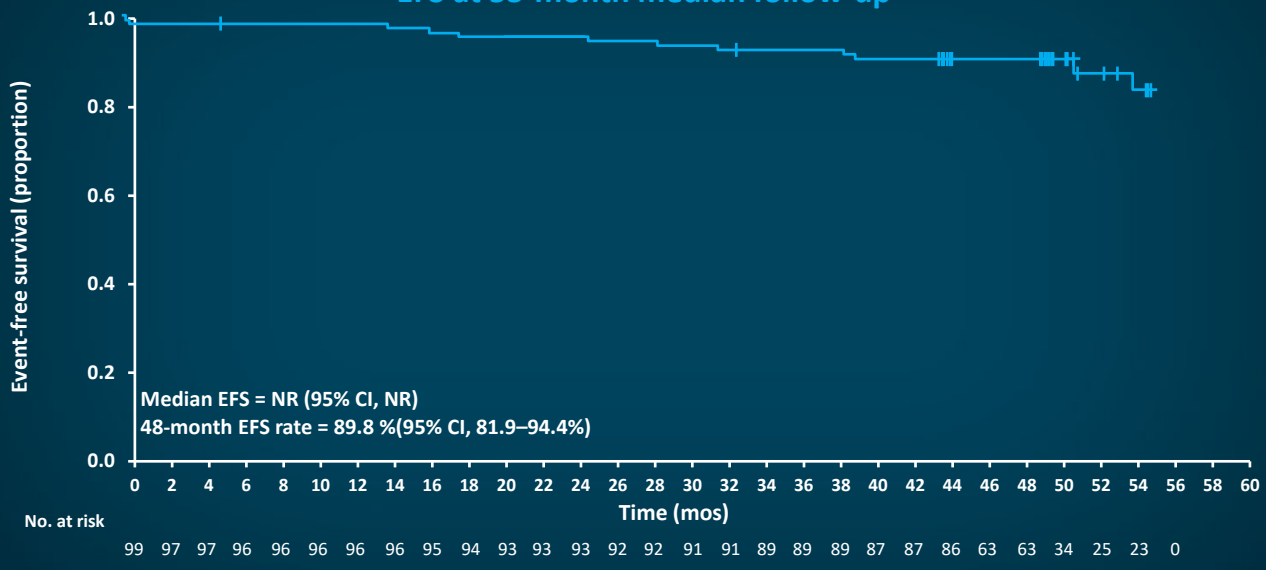
ACE-CL-001: Acalabrutinib in Treatment-Naïve Cohort

EFS at 53-month median follow-up



EFS = event-free survival.

Byrd JC, et al. *Blood.* 2021;137:3327-3338.

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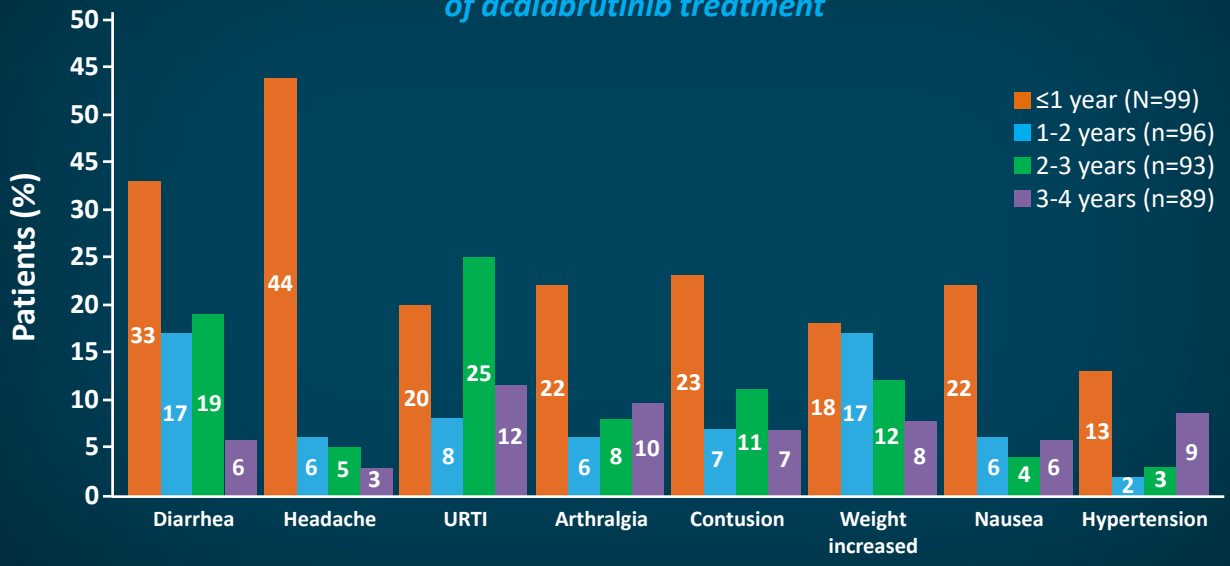
Incidence of AEs on Acalabrutinib by Year

AEs were generally more common within the first year of acalabrutinib treatment



URTI = upper respiratory tract infection.

Byrd JC, et al. *Blood.* 2021;137:3327-3338. Byrd JC, et al. *Blood.* 2018;132(suppl 1): abstract 692.

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ELEVATE-RR: Phase 3 Randomized Non-inferiority Open-Label Trial

Key inclusion criteria

- Adults with previously treated CLL requiring therapy per IWCLL 2008
- Presence of del(17p) or del(11q)
- ECOG PS of ≤2
- No significant CV disease
- No prior treatment with ibrutinib or BTK, PI3K, Syk, or BCL-2 inhibitors

N = 533

RANDOMIZE

1:1

Acalabrutinib 100 mg PO BID

Ibrutinib[b] 420 mg PO QD

Continue until PD or unacceptable toxicity

Primary endpoint: PFS as assessed by IRC

Secondary endpoints: incidence of any grade atrial fibrillation/flutter; incidence of grade ≥3 infection; incidence of Richter transformation; OS

Stratification by del(17p) status (yes or no), ECOG PS (2 vs ≤1), and number of prior therapies (1–3 vs ≥4)

PS = performance status; IRC = independent review committee; OS = overall survival; PO = by mouth; BID = twice daily; QD = once daily.

Byrd JC, et al. *J Clin Oncol.* 2021;39(15 suppl): abstract 7500.

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ELEVATE-RR: Patient Disposition

	Acalabrutinib (n = 268)	Ibrutinib (n = 265)
Duration of follow-up, median (range), mos	41.1 (0.0–58.2)	40.7 (0.2–59.1)
Patients who received treatment	265 (98.9)	264 (99.6)
Patients continuing to receive treatment at data cutoff	124 (46.3)	109 (41.1)
Patients who discontinued treatment	141 (52.6)	155 (58.5)
Reasons for treatment discontinuation		
Disease progression*	82 (30.6)	68 (25.7)
Adverse event	40 (14.9)	59 (22.3)
Consent withdrawn	7 (2.6)	7 (2.6)
Death	5 (1.9)	6 (2.3)
Investigator decision	5 (1.9)	5 (1.9)
Other	2 (0.7)	10 (3.8)

Data cutoff date: September 15, 2020.
*Disease progression includes Richter's transformation.
Byrd JC, et al. *J Clin Oncol.* 2021;39(15 suppl): abstract 7500.

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ELEVATE-RR: Most Common AEs

Events, n (%)	Any grade		Grade ≥3	
	Acalabrutinib (n = 266)	Ibrutinib (n = 263)	Acalabrutinib (n = 266)	Ibrutinib (n = 263)
Diarrhea	92 (34.6)	**121 (46.0)**	3 (1.1)	**13 (4.9)**
Headache	**92 (34.6)**	53 (20.2)	**4 (1.5)**	0
Cough	**77 (28.9)**	56 (21.3)	2 (0.8)	1 (0.4)
URTI	71 (26.7)	65 (24.7)	5 (1.9)	1 (0.4)
Neutropenia	56 (21.1)	65 (24.7)	52 (19.5)	60 (22.8)
Pyrexia	62 (23.3)	50 (19.0)	8 (3.0)	2 (0.8)
Arthralgia	42 (15.8)	**60 (22.8)**	0	2 (0.8)
Hypertension	23 (8.6)	**60 (22.8)**	11 (4.1)	**23 (8.7)**
Anemia	58 (21.8)	49 (18.6)	31 (11.7)	34 (12.9)
Fatigue	54 (20.3)	44 (16.7)	**9 (3.4)**	0
Nausea	41 (17.7)	49 (18.6)	0	1 (0.4)
Confusion	31 (11.7)	**48 (18.3)**	0	1 (0.4)
Pneumonia	47 (17.7)	43 (16.3)	28 (10.5)	23 (8.7)
Atrial fibrillation	24 (9.0)	**41 (15.6)**	12 (4.5)	9 (3.4)
Thrombocytopenia	40 (15.0)	35 (13.3)	26 (9.8)	18 (6.8)

Higher incidence in bold yellow for terms with statistical difference P <.05.
Byrd JC, et al. *J Clin Oncol.* 2021;39(15 suppl): abstract 7500.

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Treatment with Venetoclax

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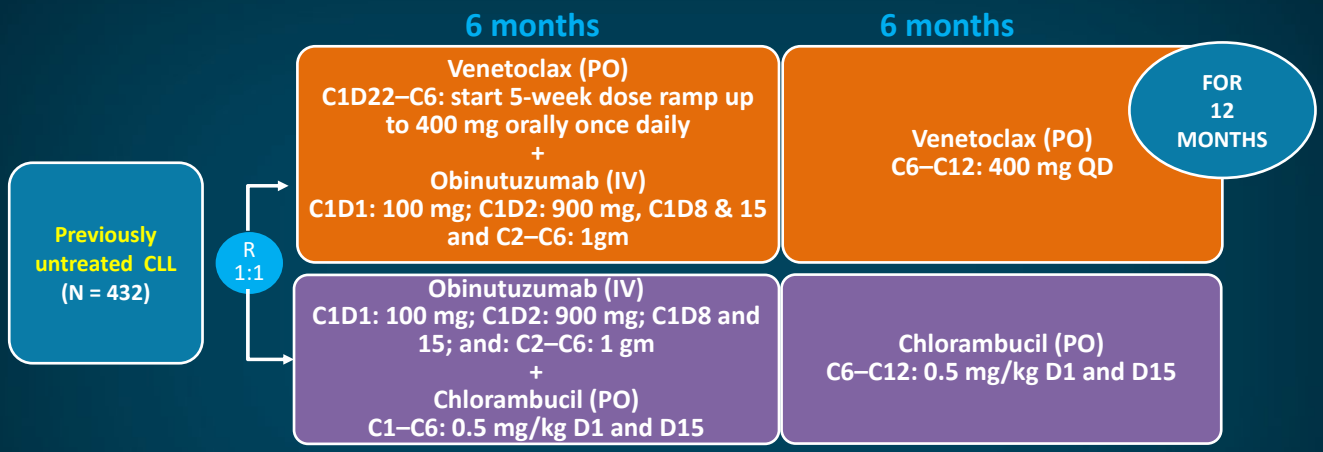
CLL14 Trial: Treatment-Naïve Patients with Coexisting Conditions



- **Primary endpoint:** investigator assessed PFS
- **Key secondary endpoints:** IRC assessed PFS, MRD negativity, ORR, CR, and OS
- **Stratification** according to Binet stage and geographic region

1 cycle = 28 days.
C = cycle; D = day; IV = intravenous.

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

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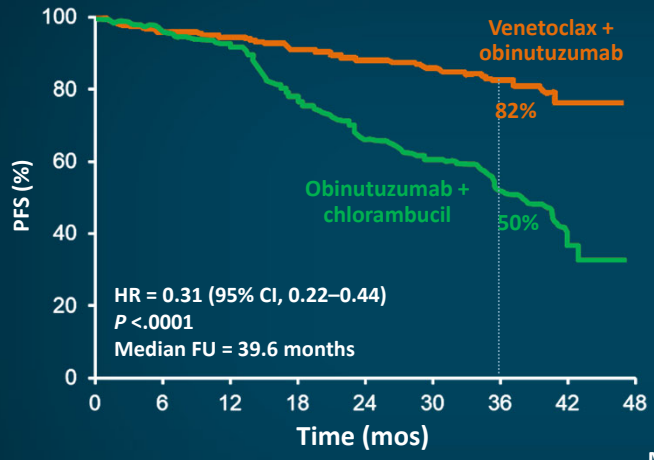
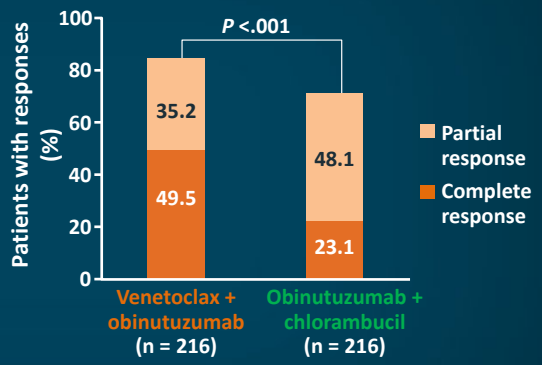
CLL14: Venetoclax + Obinutuzumab for Untreated CLL



Treatment response



MRD

- Venetoclax + obinutuzumab = 75.5% PB (56.9% BM)
- Obinutuzumab + chlorambucil = 35.2% PB (17.1% BM)

PB = peripheral blood; BM = bone marrow.

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

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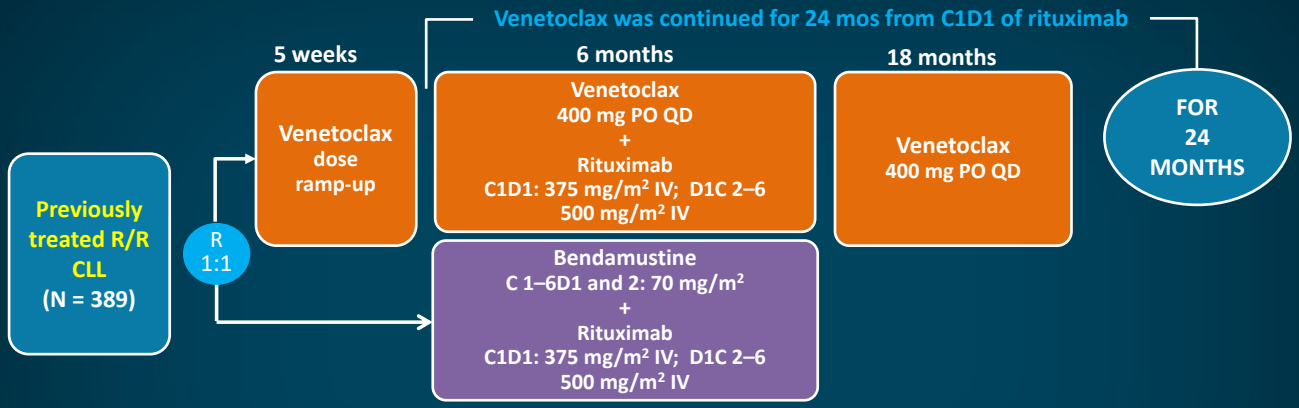
MURANO Study



- **Primary endpoint:** investigator-assessed PFS
- **Secondary endpoints:** IRC-assessed PFS, PFS in patients with del(17p), ORR, CR, OS, duration of response
- **Stratification** by presence/absence of del(17p), responsiveness to prior therapy, and geographic region

First published phase 3 trial involving treatment of CLL with novel small-molecule inhibitors delivered over defined treatment timeline

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

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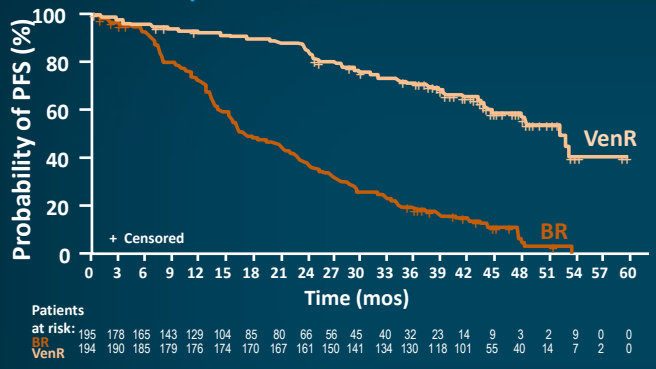
MURANO Study—ASH 2019 Update

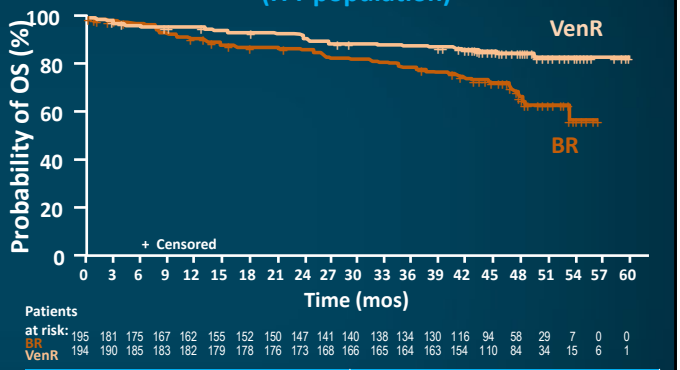
Kaplan-Meier assessments of PFS



	4-year PFS
VenR (n = 194)	57.3%
BR (n = 195)	4.6%

HR = 0.19 (95% CI, 0.14–0.25)
P <.0001

Kaplan-Meier assessments of OS (ITT population)



	4-year OS
VenR (n = 194)	85.3%
BR (n = 195)	66.8%

HR = 0.41 (95% CI, 0.26–0.65)
P <.0001

ITT = intention to treat.

Kater AP, et al. *J Clin Oncol.* 2020;38:4042-4054.

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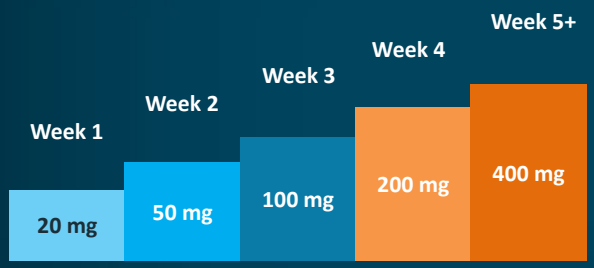
Venetoclax

Tumor lysis syndrome and Other AEs

5-week dose escalation



Assess TLS risk in all patients preparing for venetoclax therapy

Premedicate with antihyperuricemics and ensure adequate hydration

As overall TLS risk increases, employ more intensive measures

1. IV hydration
2. Frequent monitoring
3. Hospitalization

TLS = tumor-lysis syndrome.

National Community Oncology Dispensing Association (NCODA) Positive quality intervention: venetoclax risk stratification, dosing, and dispensing procedure (www.ncoda.org/wp-content/uploads/2018/05/PQI-Venetoclax-12-2019.pdf). Accessed July 19, 2021.

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Venetoclax + Obinutuzumab: Safety

164/212 patients (77.4%) completed study treatments

Venetoclax dose reductions due to AEs: 43 patients (20%) → Most common was neutropenia

Discontinuation due to AEs: 33 patients (16%) → Most common was neutropenia

Most Frequent ≥Grade 3 AEs		
	During treatment	After treatment
Neutropenia	51.9%	4%
Thrombocytopenia	13.7%	0.5%
Anemia	7.5%	1.5%
Febrile neutropenia	4.2%	1.0%
Infusion-related reactions	9.0%	—
TLS	1.4%	—
Neoplasms	1.4%	6.4%

Al-Sawaf O, et al. *Lancet Oncol*. 2020;21:1188-1200.

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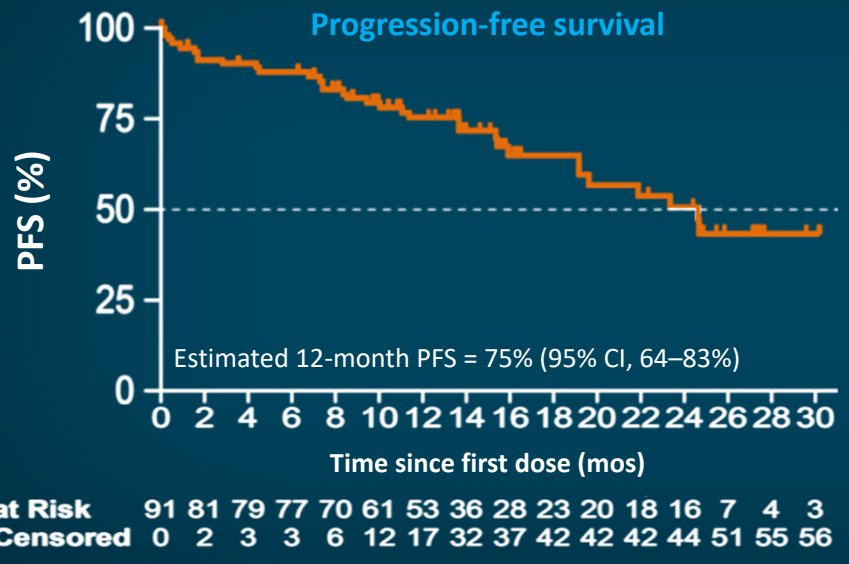
Venetoclax in Ibrutinib-Refractory/Intolerant Patients



- Median of 4 prior therapies
- 47% del(17p)
- ORR* = 70%

*in main cohort.

Jones JA, et al. *Lancet Oncol*. 2018;19:65-75.

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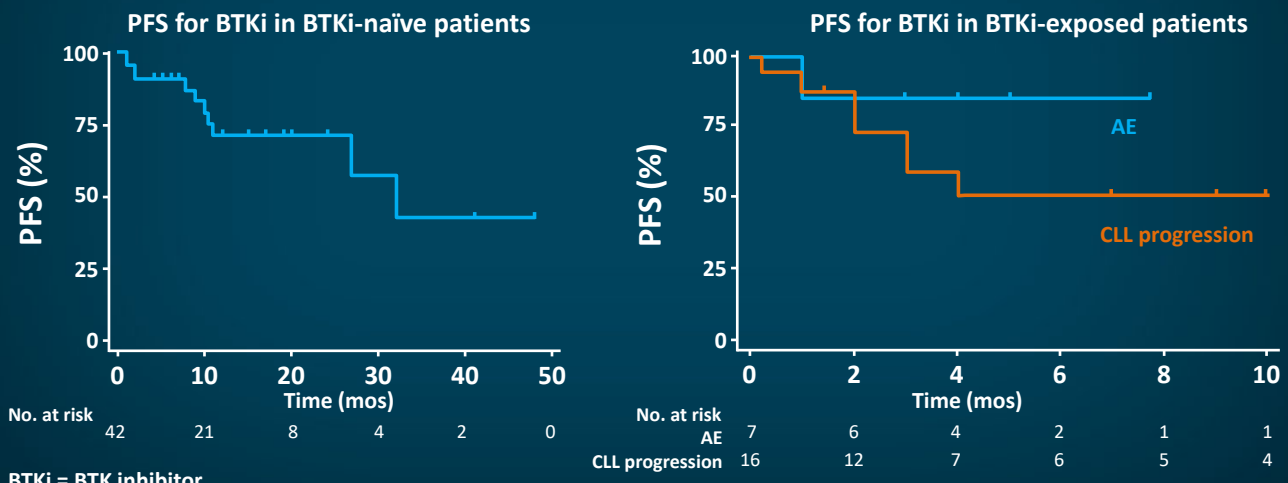
Post-Venetoclax Use of BTKi in CLL
Patients Sequencing to Subsequent Treatment (N = 326)[1]

BTKi-naïve patients: BTKi therapy results in high ORR and durable remissions

For BTKi-exposed patients, BTK inhibition is NOT effective in setting of BTKi resistance



BTKi = BTK inhibitor.

Mato AR, et al. *Clin Cancer Res*. 2020;26:3589-3596.

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Treatment Paradigm in CLL

Continuous therapy

- BTK inhibitors (ibrutinib, acalabrutinib)

Goal of therapy

- Disease control
- Prolonged PFS
- Independent from response, MRD

Fixed duration

- Venetoclax + obinutuzumab

Goal of therapy

- Disease eradication
- Prolonged PFS
- Undetectable MRD

MRD = minimal residual disease; PFS = progression-free survival.

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Treatment with PI3K Inhibitors and Other Approaches

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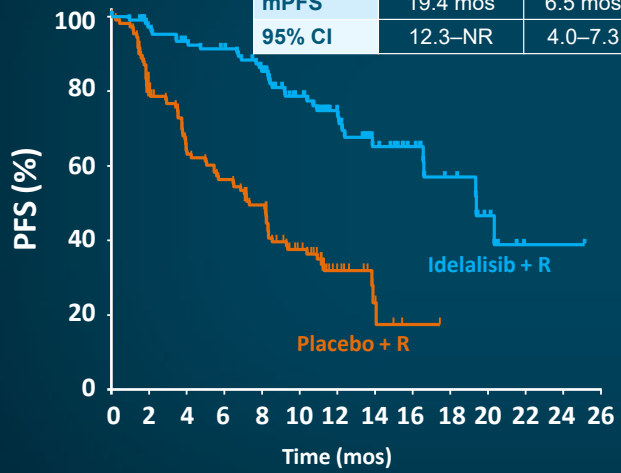
Trials of PI3K Inhibitors in CLL

Phase 3 trial of idelalisib + R vs R[1]

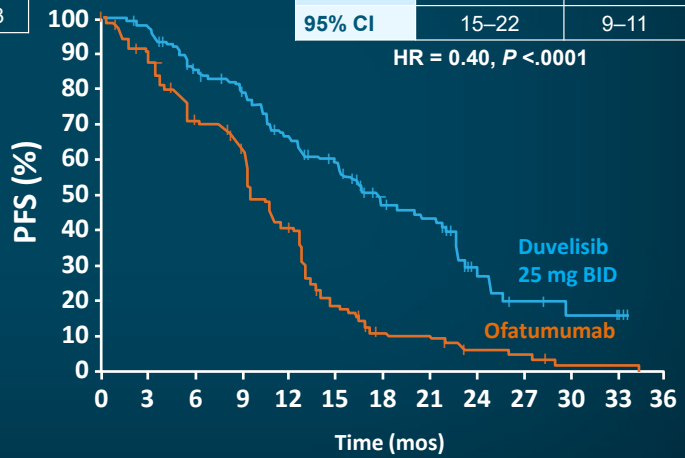
	IR	R
mPFS	19.4 mos	6.5 mos
95% CI	12.3–NR	4.0–7.3



Phase 3 DUO trial of duvelisib vs ofatumumab[2]

	DUV	OFA
mPFS	17.6 mos	9.7 mos
95% CI	15–22	9–11

HR = 0.40, *P* <.0001



IR = idelalisib + rituximab; DUV = duvelisib; OFA = ofatumumab.

1. Sharman JP, et al. *J Clin Oncol.* 2019;37:1391-1402. 2. Flinn IW, et al. *Blood.* 2018;132:2446-2455.

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Adverse Events with Idelalisib and Duvelisib

- Severe pneumonitis
  - Distinguish from infectious issues
    - Idelalisib: 4%
    - Duvelisib: 5%
- Diarrhea
  - Can be early and/or late onset
    - Idelalisib: 32%; 11% Gr 3/4
    - Duvelisib: 50%; 23% Gr 3/4*
  - Colitis (secondary to T-cell activation)
    - Idelalisib: 14–20%†
    - Duvelisib: 50%; 23% Gr 3/4*
- AST/ALT elevations
  - Idelalisib: 28%/39%; 5%/9% Gr 3/4
  - Duvelisib: 37%/40%; 6%/8% Gr 3/4
- Infections
  - Frontline idelalisib trials discontinued due to increased deaths
  - PJP and CMV prophylaxis now considered standard
    - Occurs in <1%

*reported as diarrhea OR colitis; †did not report separately from severe diarrhea.

Gr = grade; AST = aspartate aminotransferase; ALT = alanine aminotransferase; PJP = *Pneumocystis jirovecii* pneumonia; CMV = cytomegalovirus.

Idelalisib (Zydelig®) PI 2020 (www.gilead.com/~/media/Files/pdfs/medicines/oncology/zydelig/zydelig_pi.pdf FDA. 2016 (www.fda.gov/drugs/drug-safety-and-availability/ fda-alerts-healthcare-professionals-about-clinical-trials-zydelig-idelalisib-combination-other). Duvelisib (Copiktra®) PI 2019 (https://copiktra.com/pdf/verastem/COPIKTRA-PI-072019.pdf). Accessed July 19, 2021.

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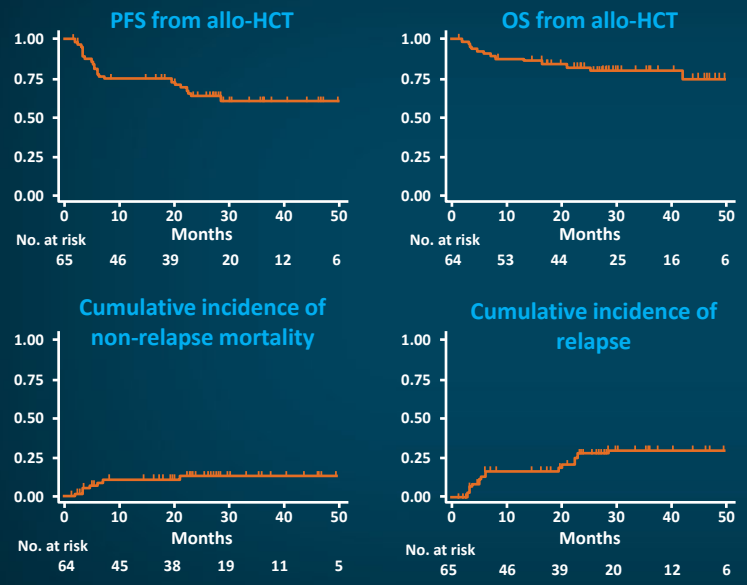
Allogeneic Stem-Cell Transplantation for CLL in Era of Novel Agents



- N = 65, median age at allo-HCT = 60 years
- CLL status prior to transplant:
  - CR = 26%
  - PR = 66%
  - SD = 5%
  - PD = 3%
- RIC = 95%; ablative = 5%
- Lines of therapy = 3 (1–9); 1 (1–3) novel
- 82% progression on ≥1 novel agent
- Median PFS and OS not reached after allo-HCT (median FU = 27 mos)
- 24-mo PFS = 63%; 24-mo OS = 81%

Allo-HCT = allogeneic hematopoietic stem-cell transplantation; RIC = reduced-intensity conditioning.

Roeker LE, et al. *Blood Adv*. 2020;4:3977-3989.

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Applying Shared Decision Making in CLL

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5 Essential Steps of Shared Decision-Making
SHARE Approach

It's all about communication!

AHRQ Share Approach (www.ahrq.gov/sites/default/files/publications/files/share-approach_factsheet.pdf). Accessed July 7, 2021.

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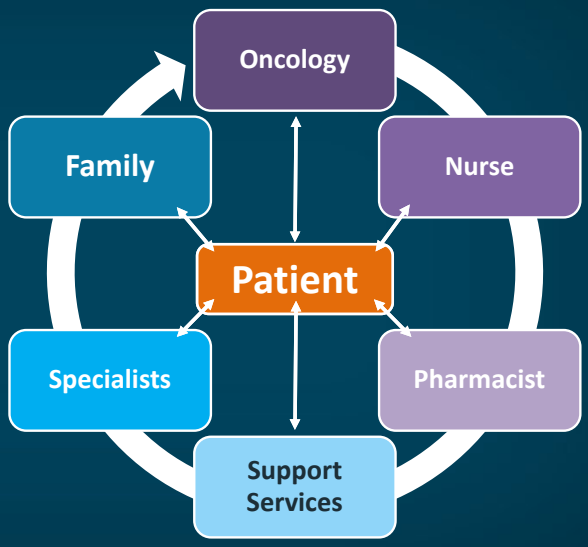
Shared Decision-Making (SDM) in Oncology

Collaborative care

- Interconnection of essential players
- Patient-centered
- Communication is **KEY!**



Adapted from National Quality Forum (NQF). National Quality Partners PlaybookTM: Shared Decision Making in Healthcare. Washington, DC: NQF;2018.

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Summary Points

- Early results with small-molecule inhibitors are extremely promising
- Small-molecule inhibitors provide favorable treatment options for majority of CLL patients, most notably high-risk, elderly, and/or comorbid patients and those with relapsed disease
- Cost, prescription coverage, and long-term side effects may be issues
- Novel combinations delivered over defined treatment timelines offer hope for deep responses and long treatment-free intervals
- Important to incorporate SDM components when developing care plans with patients, family members, and/or caregivers

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Case Study: Treatment Naïve Patient

- 64-year-old male veteran referred from PCP with elevated WBC and painful lymphadenopathy (LAD)
- Previously untreated
- IgHV-mutated
- FISH + del(11q)
- Other selected findings:
  - WBC: 117.3 X 10^9/L
  - Lymphocytes: 109.2 X 10^9/L
  - Hgb: 9.6 g/dL
  - CT C/A/P: LAD above and below the diaphragm, largest node 4cm R inguinal node. Spleen 18cm.

How would you manage this patient?

WBC = white blood count; Hgb = hemoglobin; ANC = absolute neutrophil count.

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Case Study: Previously Treated

- 70-year-old female, previously treated with BR and then ibrutinib, but discontinued after 2 years due to rash
- During routine follow-up, the patient reported increasing fatigue
- She has cervical lymphadenopathy on exam, ~4 cm, spleen is palpable 6 cm below the costal margin, and she has normal kidney function
- Laboratory results:
  - ALC: 112,000 cells/mL
  - Hgb: 10.8 g/dL
  - Platelets: 75,000 cells/mm^3

What treatment option(s) should you consider?

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Case Study: Second Opinion

- 77-year-old male presents for second opinion regarding his CLL. Local oncologist recommended BR. No prognostic workup done previously.
- Previously untreated
- IgHV-unmutated
- FISH + del(17p)
- Other selected findings:
  - WBC: 154 X 10^9/L
  - Hgb: 9.2 g/dL
  - Platelets: 75,000 cells/mm3
  - Palpable LAD non painful LAD in the cervical and axillary chains

How would you manage this patient?

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Case Study: Symptomatic Progression

- 66-year-old male with CLL who has previously been treated with FCR, ibrutinib, and venetoclax + rituximab. Now with symptomatic progression.
- IgHV-unmutated
- FISH + del 17p and Tp53 mutated (new findings)
- Other selected findings:
  - WBC: 33 X 10^9/L
  - Hgb: 8.9 g/dL
  - Plt: 87,000 cells/mm^3
  - CT C/A/P: LAD above and below the diaphragm, largest node 6 cm R axillary node. Spleen 16cm.

What would you manage this patient?

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Thank you

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