Chronic Lymphocytic Leukemia: An Evolving Treatment Landscape

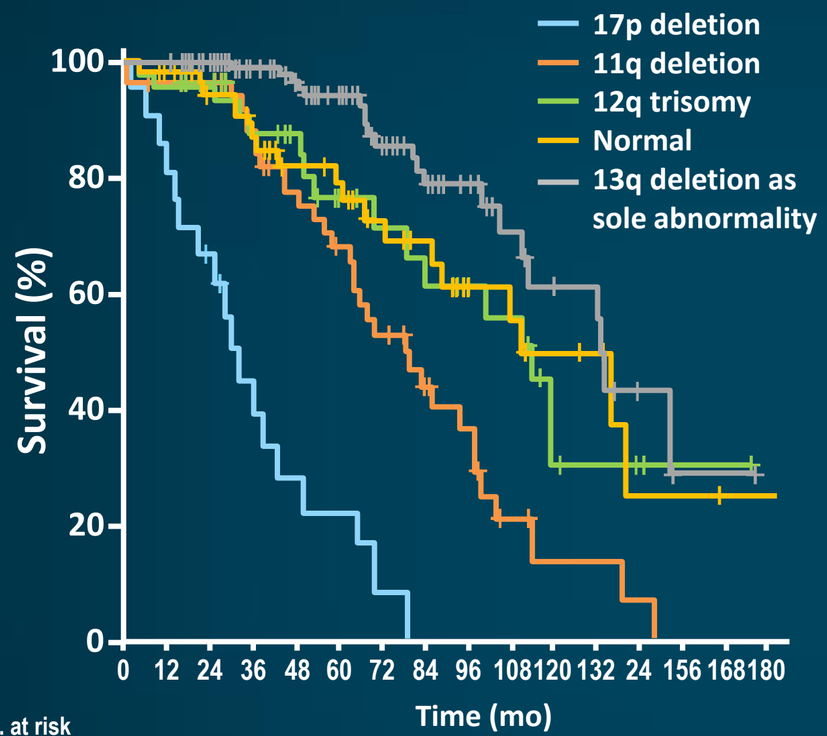
Pre-Read Material

Educational Objectives

- Summarize the safety, effectiveness, and ways of functioning of novel and upcoming treatments for individuals diagnosed with chronic lymphocytic leukemia (CLL)
- Examine and differentiate the effectiveness and safety profiles of both established and innovative Bruton tyrosine kinase (BTK) inhibitors utilized for managing CLL
- Provide an overview of the prevalent adverse effects associated with BTK inhibitors employed in the therapy of CLL, as well as their corresponding management strategies
- Present a summary of the favored and substitute treatment choices for varying stages of therapy in the management of CLL

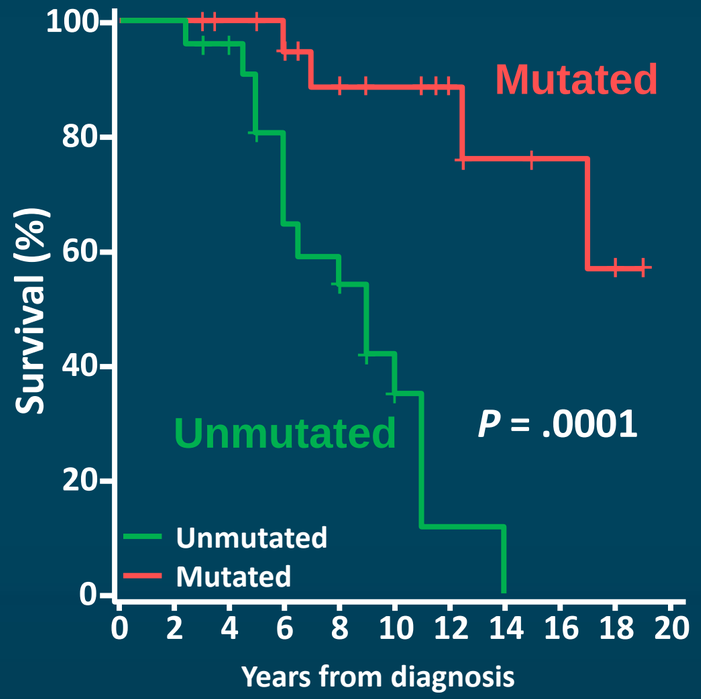
Key Prognostic Markers

FISH[1]

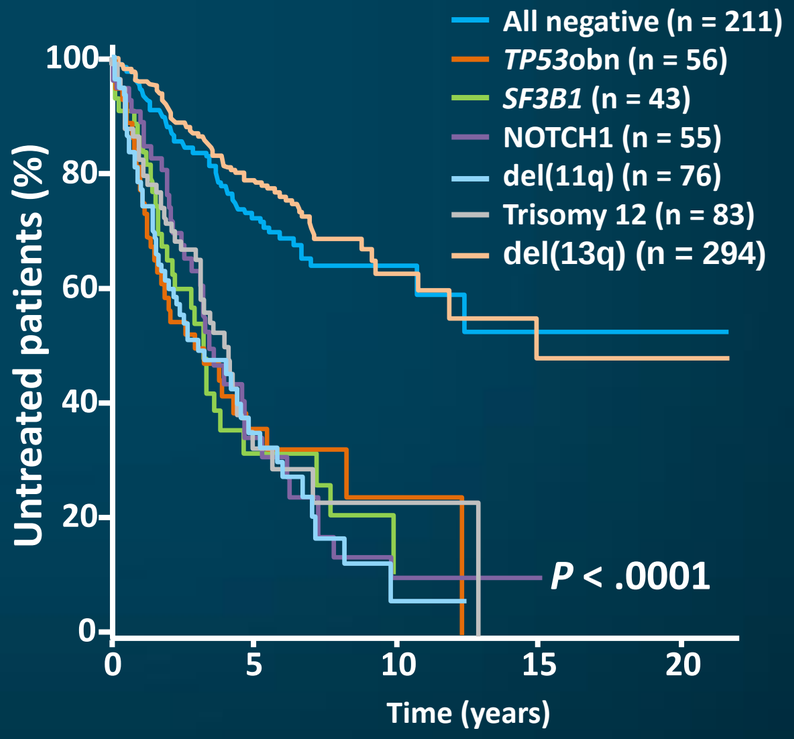


No. at risk															
17p deletion	23	18	13	8	5	4	1	0	0	0	0	0	0	0	0
11q deletion	56	53	47	43	33	27	20	15	10	4	2	2	1	0	0
12q trisomy	47	44	41	29	24	17	14	13	12	11	4	3	2	1	1
Normal	57	51	45	37	30	27	20	17	12	11	6	5	2	2	1
13q deletion as sole abnormality	117	117	106	91	80	63	45	36	24	16	12	11	3	1	1

IGHV[2]



Somatic mutations[3]



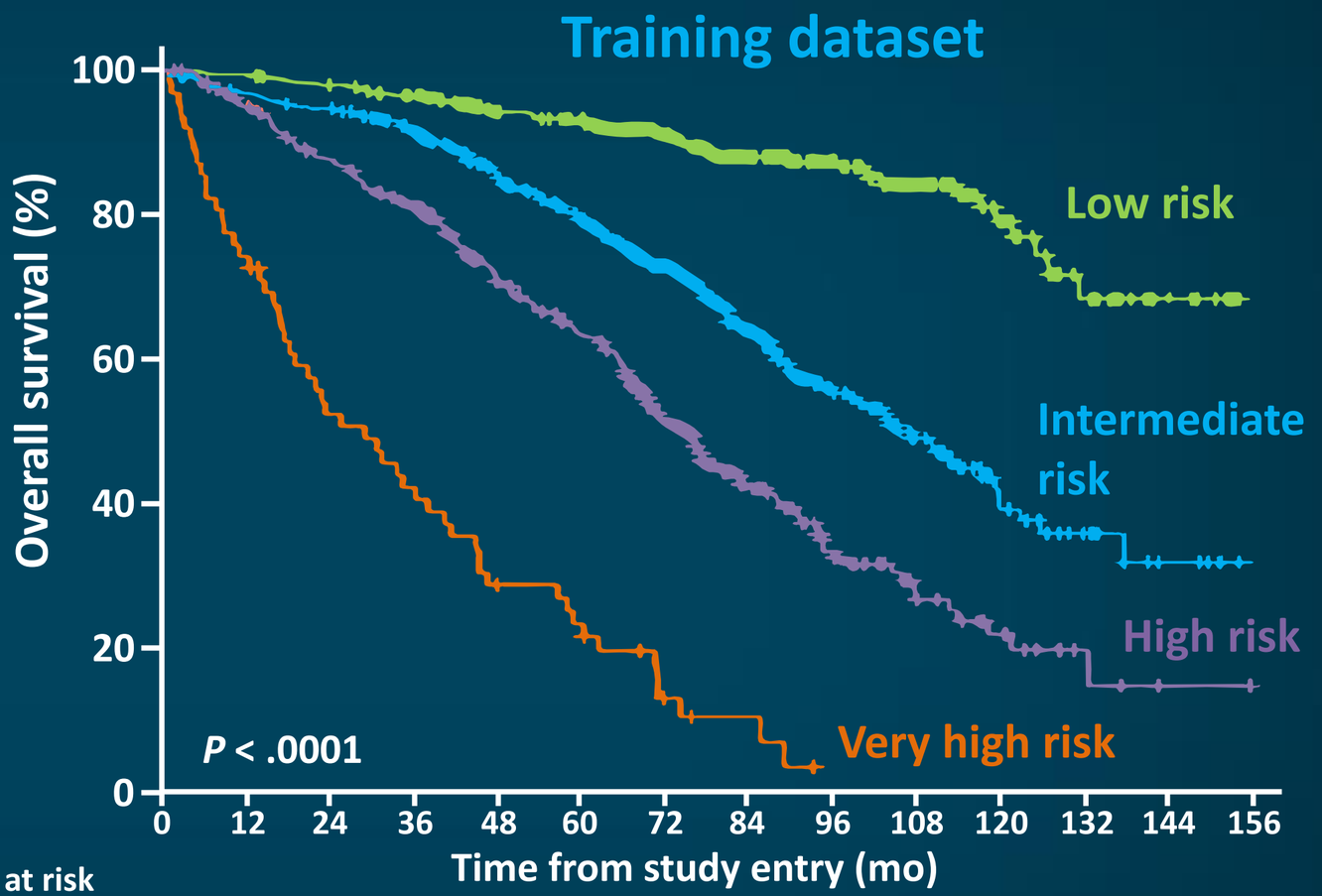
del = deletion; FISH = fluorescence in situ hybridization; IGHV = immunoglobulin heavy chain variable (gene).

1. Döhner H, et al. *N Engl J Med.* 2000;343:1910-1916. 2. Hamblin TJ, et al. *Blood.* 1999;94:1848-1854. 3. Baliakas P, et al. *Leukemia* 2015;29:329-336.

CLL-IPI Predicted Survival in CIT Era

CLL IPI factors include:

- TP53
- IGHV
- B2M (>3.5 mg/L)
- Clinical stage (0/A vs other)
- Age (>65 years)



No. at risk														
Low risk	341	339	331	320	279	270	224	169	118	81	40	20	8	0
Intermediate risk	474	452	441	415	352	312	232	143	83	52	27	13	5	1
High risk	337	314	284	256	205	178	120	69	40	19	12	4	1	0
Very high risk	62	46	31	25	16	13	5	3	0	0	0	0	0	0

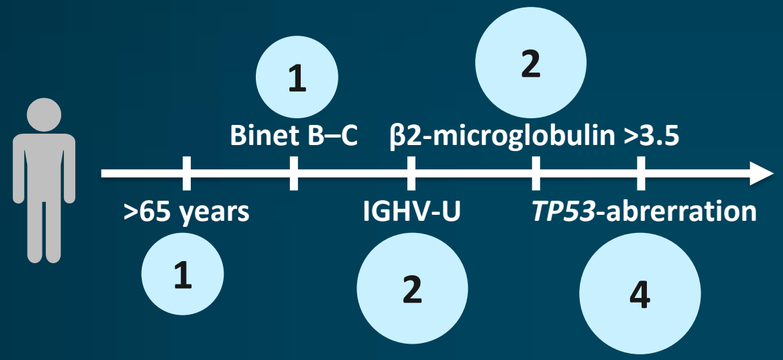
B2M = beta-2 microglobulin; CIT = chemoimmunotherapy; IPI = international prognostic index; TP53 = tumor protein p53.

CLL-IPI working group. *Lancet Oncol.* 2016;17:779-790.

CLL-IPI May Not Be as Useful in Era of Targeted Therapies

Reassessing CLL-IPI in era of targeted therapies

Patients and methods



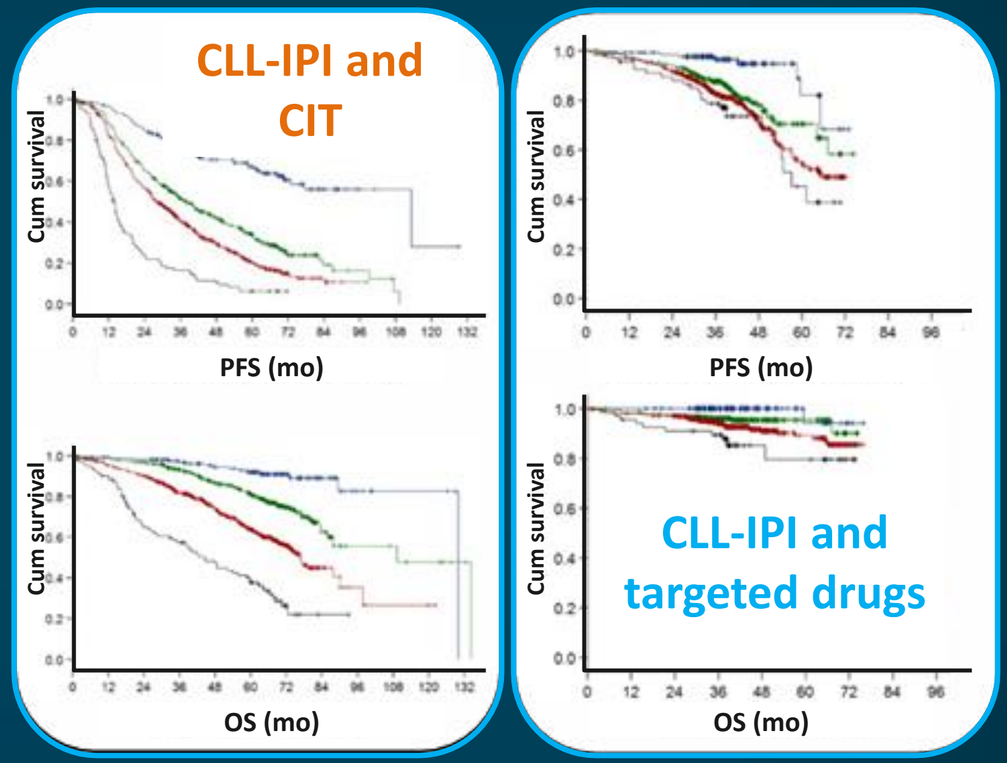
CLL-IPI	
0–1	Low
2–3	Intermediate
4–6	High
7–10	Very high

Patients with TN CLL (n = 2247)

Patients treated with chemo-immunotherapy (n = 1256)

Patients treated with targeted drugs (n = 991)

Main outcomes



Conclusions: **1)** CLL-IPI retains prognostic value for PFS, but its impact appears diminished in predicting OS in CLL patients treated with targeted drugs; **2)** Improved survival with targeted therapies vs CIT underscores need to reevaluate prognostic tools amid treatment shifts

Langerbeins P, et al. *Blood*. 2024;143:2588-2598.

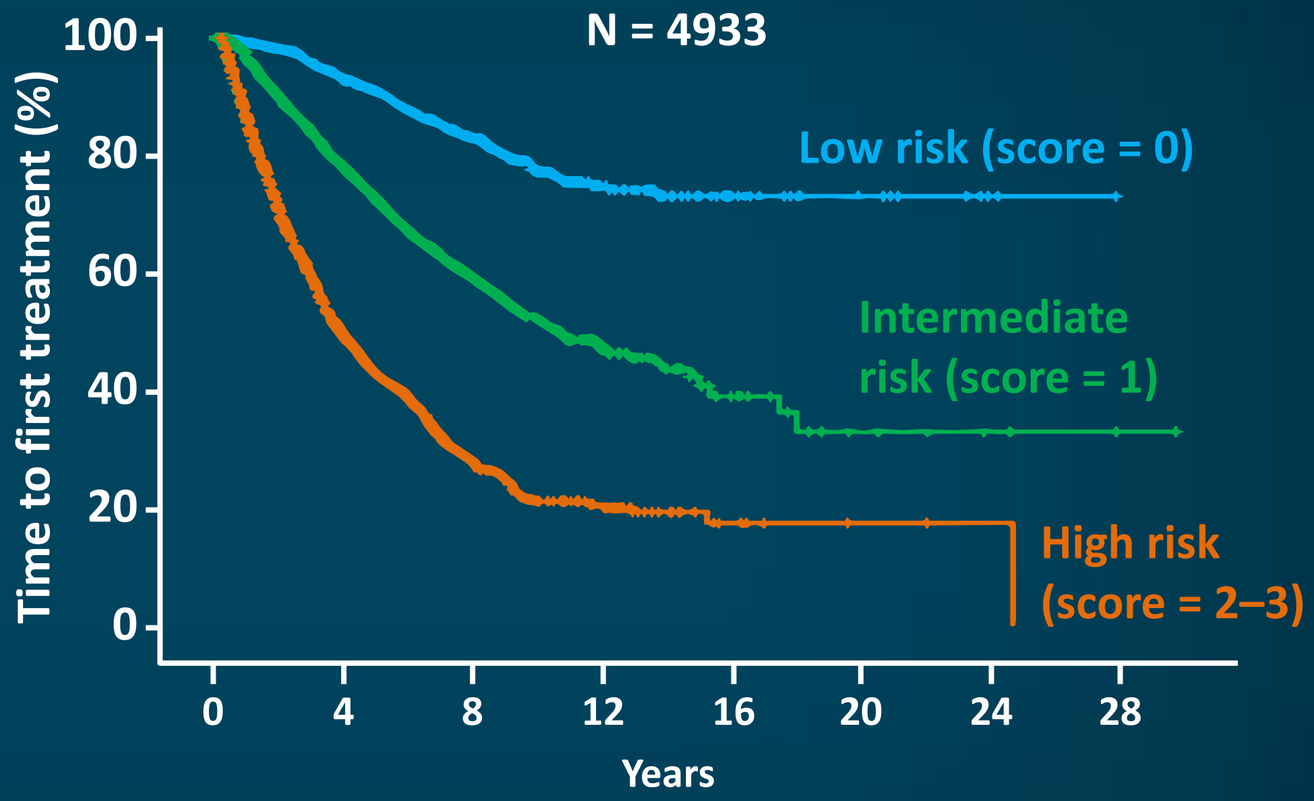
CIT = Chemoimmunotherapy; Cum = cumulative; OS = overall survival; PFS = progression-free survival; TN

IPS-E is a Simple, Robust Prognostic Model for Early-stage CLL

Variable	Points
IGHV unmutated	1
Lymphocytes >15x10^9/L	1
Nodal involvement	1

Risk group	Score
Low risk	0
Intermediate risk	1
High risk	2–3

Cumulative incidence of treatment		
	1 year	5 year
Low risk	<1%	8.4%
Intermediate risk	3.1%	28.4%
High risk	14.1%	61.2%



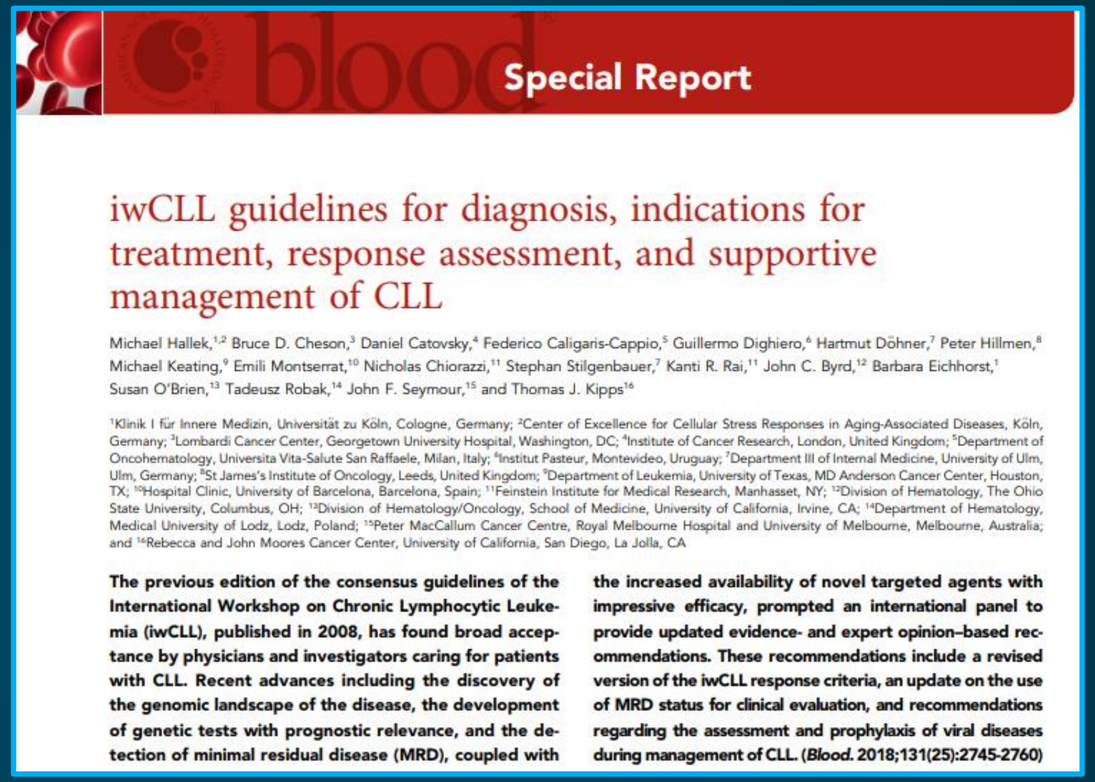
IPS-E = International Prognostic Score for Early Stage CLL.

Condoluci A, et al. *Blood*. 2020;135:1859-1869.

iwCLL Indications for CLL Therapy Initiation Have Not Changed

Indications include:

- Cytopenias
- Bulky or rapidly enlarging lymph node(s) or splenomegaly
- Symptoms (fatigue, fever, night sweats, unintentional weight loss)
- Refractory autoimmune conditions
- ± LDT <6 months



blood

Special Report

iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL

Michael Hallek,[1,2] Bruce D. Cheson,[3] Daniel Catovsky,[4] Federico Caligaris-Cappio,[5] Guillermo Dighiero,[6] Hartmut Döhner,[7] Peter Hillmen,[8] Michael Keating,[9] Emili Montserrat,[10] Nicholas Chiorazzi,[11] Stephan Stilgenbauer,[7] Kanti R. Rai,[11] John C. Byrd,[12] Barbara Eichhorst,[1] Susan O'Brien,[13] Tadeusz Robak,[14] John F. Seymour,[15] and Thomas J. Kipps[16]

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The previous edition of the consensus guidelines of the International Workshop on Chronic Lymphocytic Leukemia (iwCLL), published in 2008, has found broad acceptance by physicians and investigators caring for patients with CLL. Recent advances including the discovery of the genomic landscape of the disease, the development of genetic tests with prognostic relevance, and the detection of minimal residual disease (MRD), coupled with the increased availability of novel targeted agents with impressive efficacy, prompted an international panel to provide updated evidence- and expert opinion–based recommendations. These recommendations include a revised version of the iwCLL response criteria, an update on the use of MRD status for clinical evaluation, and recommendations regarding the assessment and prophylaxis of viral diseases during management of CLL. (*Blood*. 2018;131(25):2745-2760)

If none of the above…

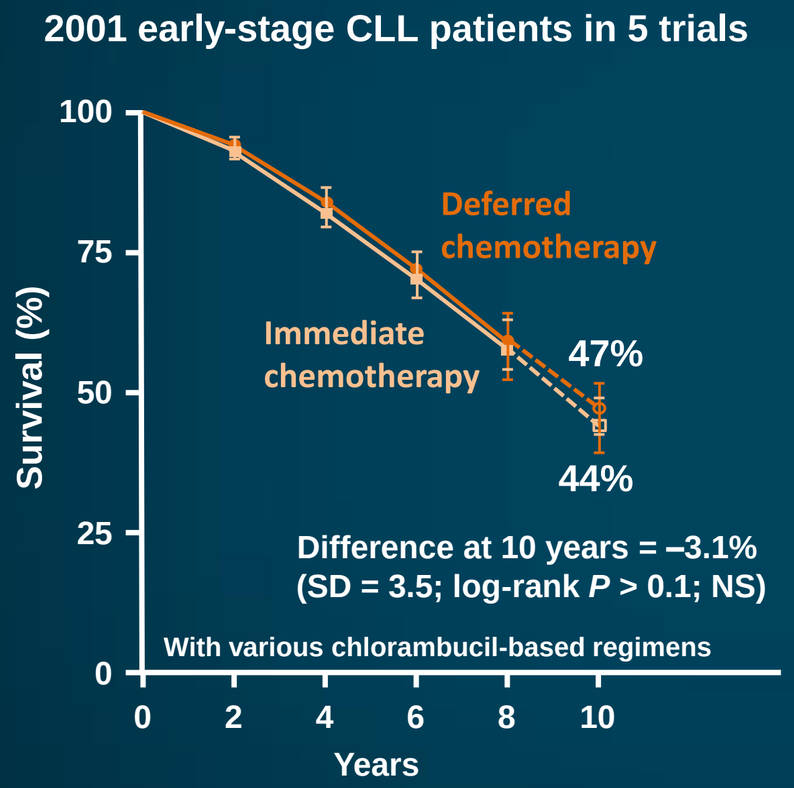
Observation

iwCLL = international workshop on CLL; LTD = Time-limited therapy.

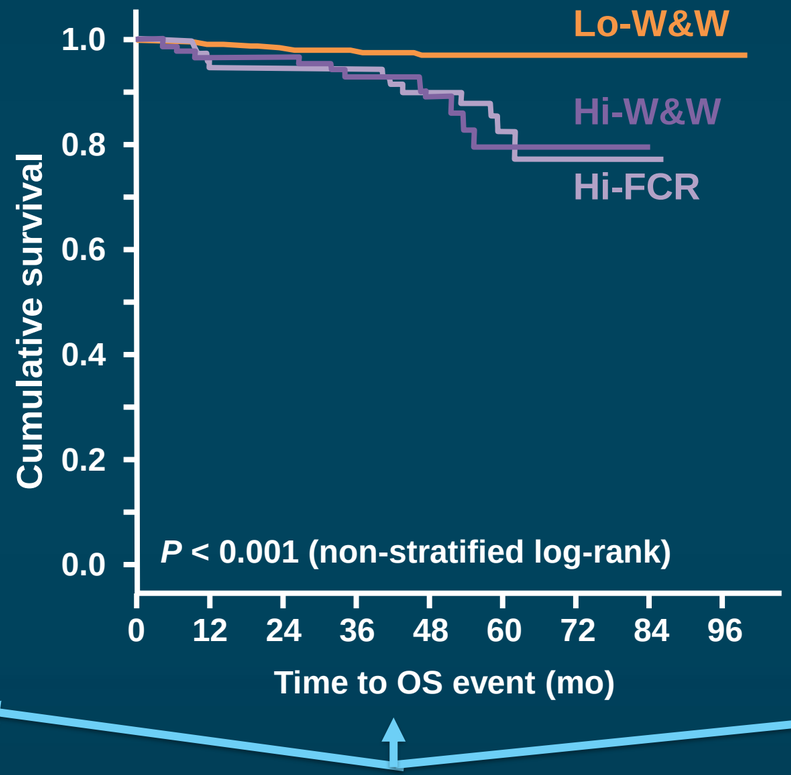
Hallek M, et al. *Blood*. 2018;131:2745-2760.

Several Studies Have Evaluated Early Intervention Strategies in Asymptomatic CLL

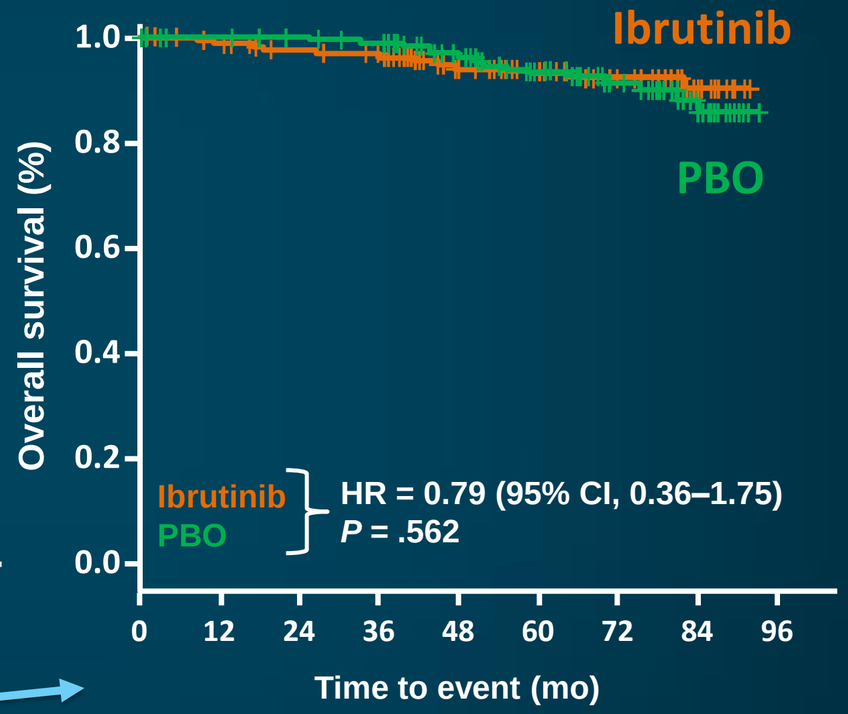
Meta-analysis—OS[1]



CLL7—OS[2]



CLL12—OS[3]



No difference in OS

CI = confidence interval; FCR = fludarabine, cyclophosphamide, rituximab; Hi = high risk; HR = hazard ratio; Lo = low risk; NS = not significant; PBO = placebo; SD = standard deviation; W&W = watch and wait.

1. CLL Trialists' Collaborative Group. *J Natl Cancer Inst*. 1999;91:861-868. 2. Herling CD, et al. *Leukemia*. 2020;34:2038-2050. 3. Langerbeins P, et al. *Hematol Oncol.* 2023;4(suppl 2): 56-58.

Allogeneic Stem Cell Transplant

- Prolonged DFS in advanced, refractory disease and in 17p-/TP53mut (~40% across studies)
- 17p-/TP53mut may lose its negative prognostic effect with AlloSCT
- Factors associated with poor outcome include:
  - >3 lines of therapy
  - Advanced clinical stage
  - Marked lymphadenopathy
  - Refractory disease at time of transplant

Allo-SCT = allogeneic stem-cell transplant; DFS = disease-free survival; mut = mutation.

Gribben JG, *Blood.* 2018;132:31-39.

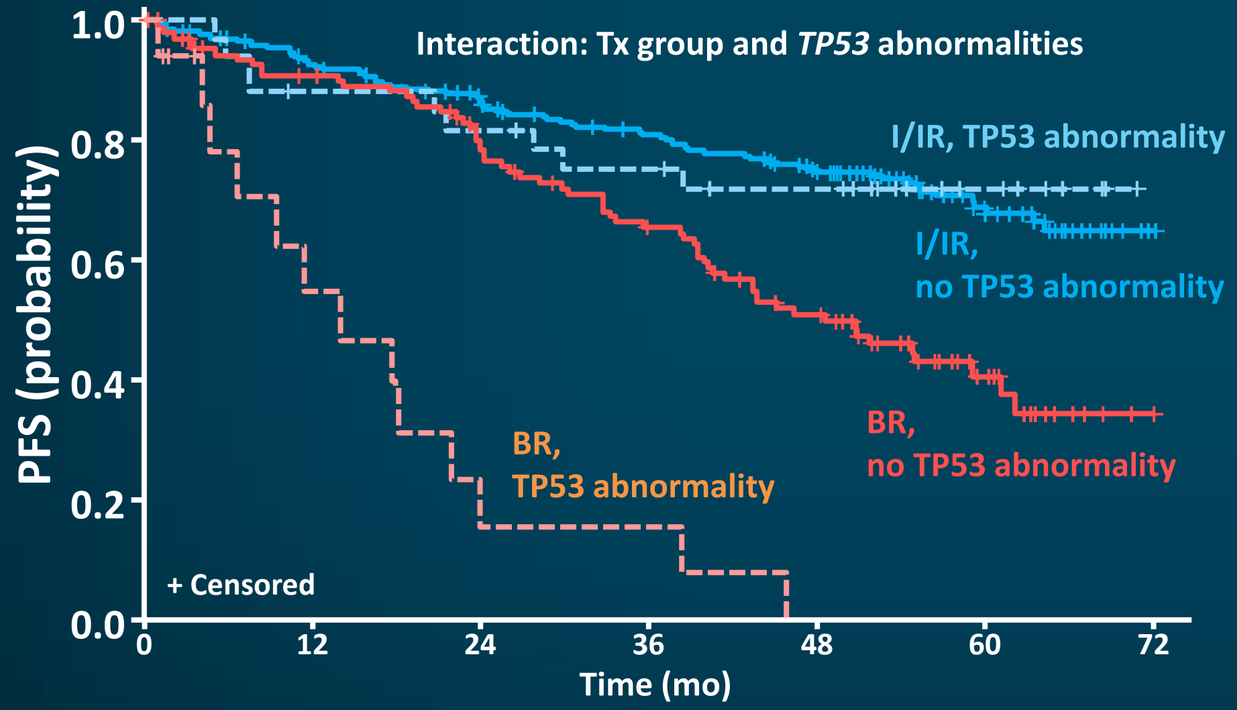
Treatment-Naïve CLL

What are the data to support continuous BTKi monotherapy?

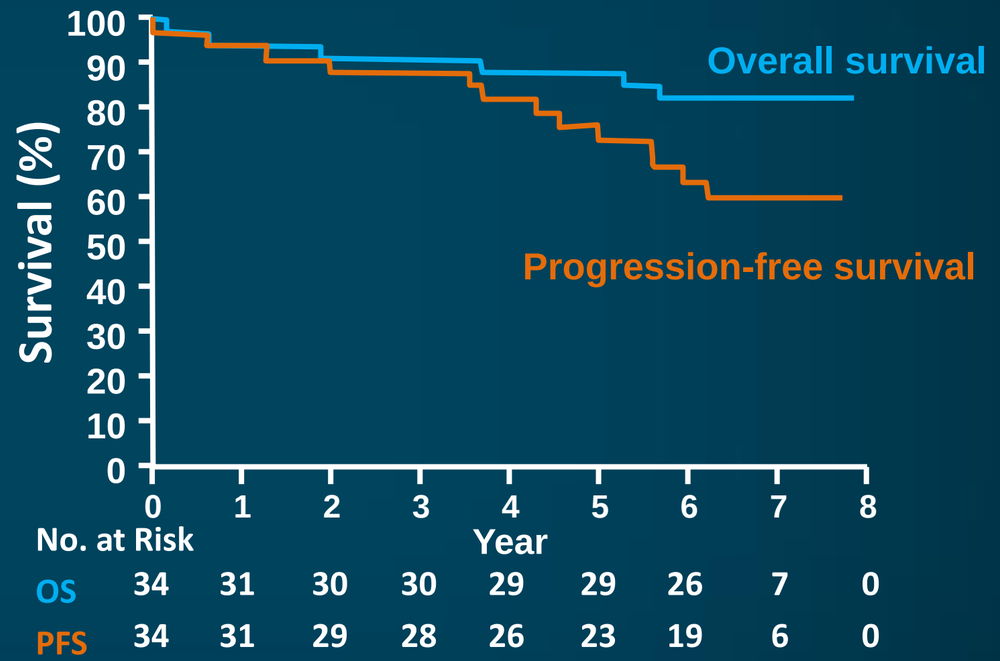
Ibrutinib Can Provide Durable Response, Even for TP53-Aberrant CLL

ALLIANCE: PFS ± *TP53*[1]

Group	Events/total
BR, no TP53 abnormality	63/133
I/IR, no TP53 abnormality	72/264
BR, TP53 abnormality	13/19
I/IR, TP53 abnormality	9/34



NHLBI: OS and PFS[2]

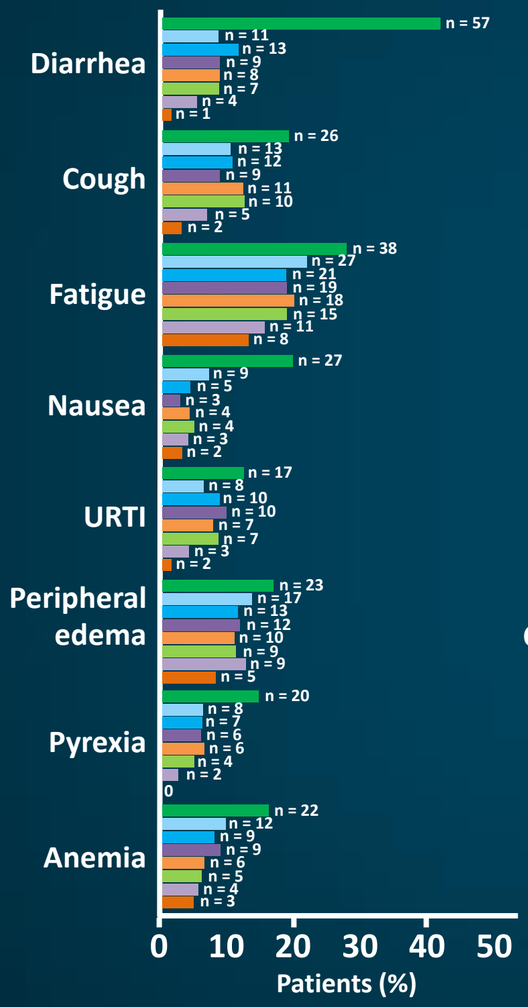


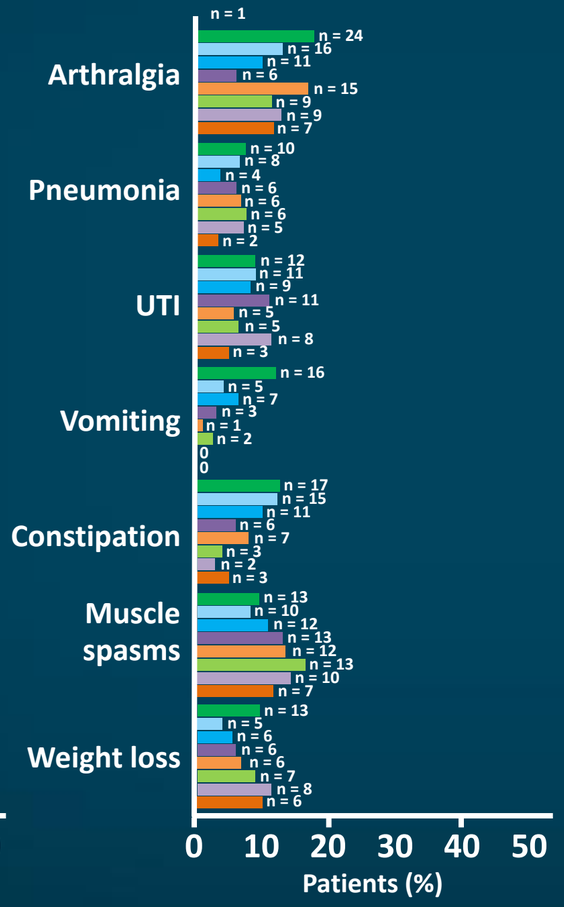
Updated ~10-year OS = 54.1%[3]

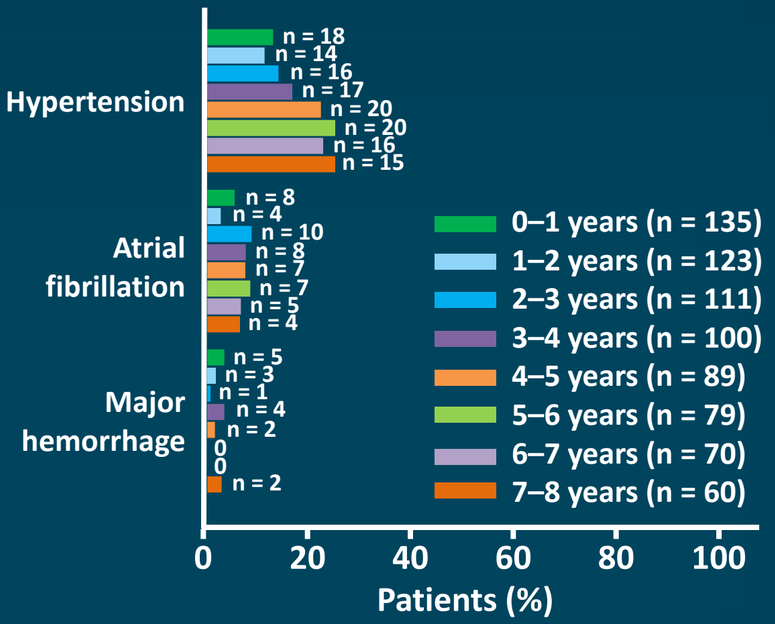
BR = Bendamustine-Rituximab; I/IR = ibrutinib/ibrutinib + rituximab; NHLBI = National Heart, Lung, and Blood Institute; Tx = treatment/therapy.

1. Woyach JA, et al. *Blood*. 2024;143:1616-1627. 2. Ahn IE, et al. *N Engl J Med*. 2020;383:498-500. 3. Itsara A, et al. *Blood*. 2023;142(suppl 1): 201-202.

Discontinuation Rates with Ibrutinib Are Relatively High and Mostly Due to AEs







- 42% of patients were still on ibrutinib at 8 years
- AEs were most common reason for discontinuation (24%)

Discontinuation due to AEs may be even more common in real-world setting (41% discontinuation at median of 17 mo)

AE = adverse event; URTI = upper respiratory tract infection; UTI = urinary tract infection.

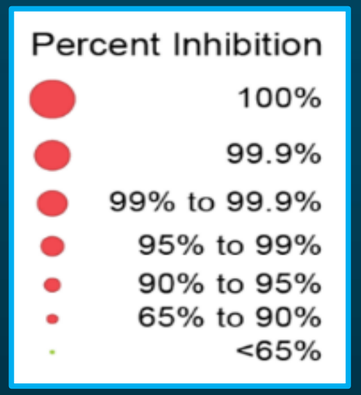
Barr PM, et al. *Blood Adv.* 2022;6:3440-3450. Mato AR, et al. *Haematologica.* 2018;103:874-879.

Different Covalent BTKi Have Different Levels of Specificity for BTK

Ibrutinib

Acalabrutinib

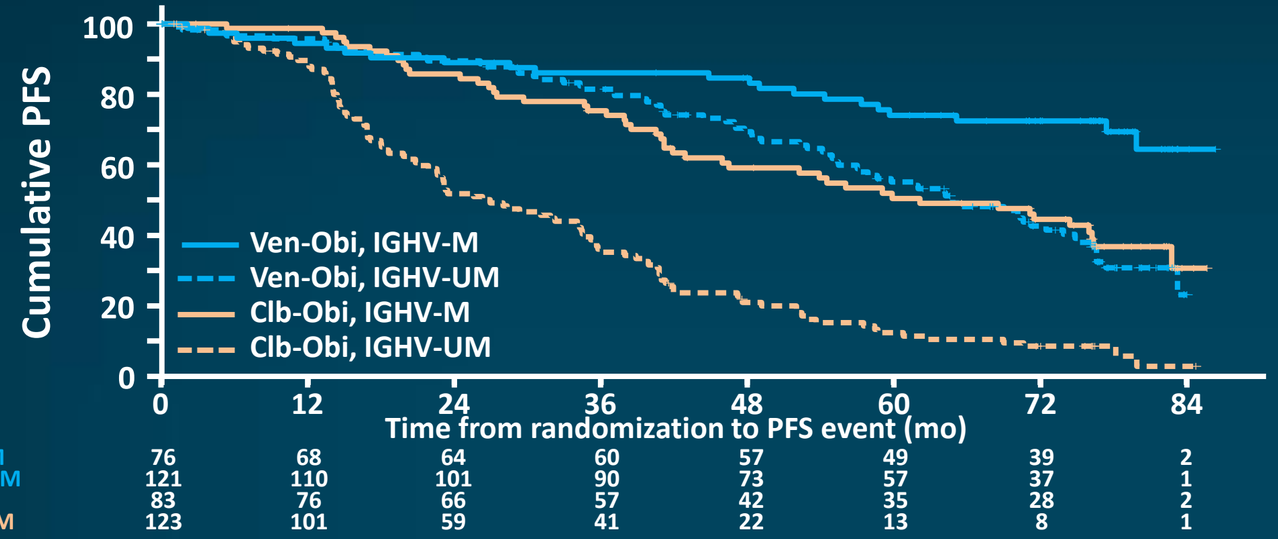
Zanubrutinib



Kaptein A, et al. *Blood*. 2018;132(suppl 1): Abstract 1871.

CLL14: 6-year PFS by IGHV and *TP53* Mutation Status

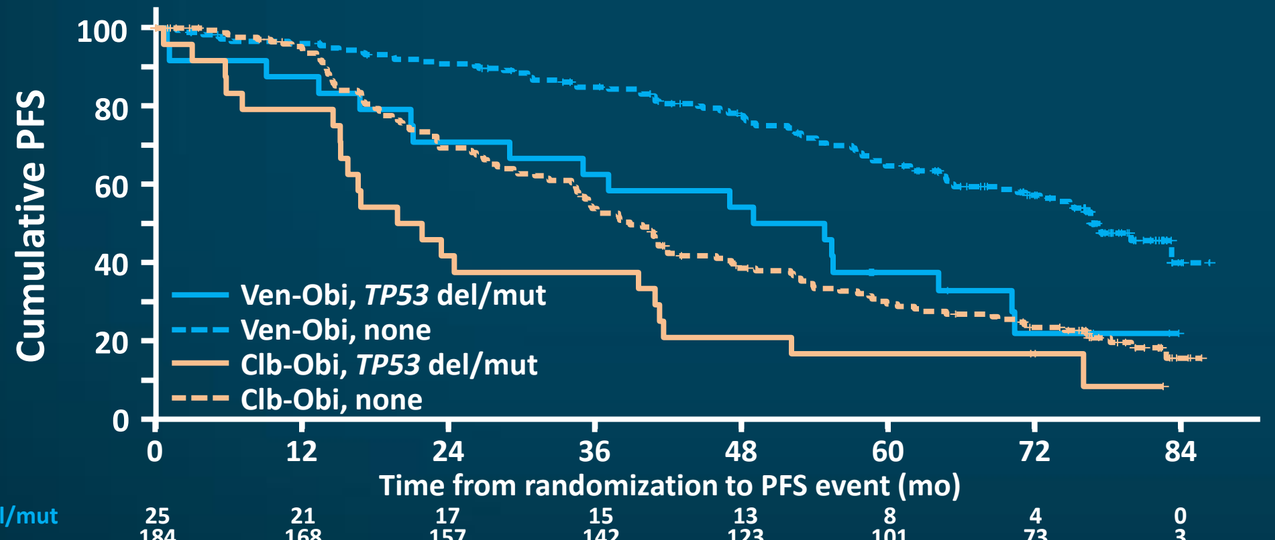
IGHV



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

Median PFS by IGHV mutation status		
	mPFS	HR (95% CI)
Ven-Obi, IGHV-M	NR	0.38 (0.23–0.61) *P* < .001
Ven-Obi, IGHV-UM	64.8 mo	
Clb-Obi, IGHV-M	62.2 mo	0.33 (0.23–0.47) *P* < .001
Clb-Obi, IGHV-UM	26.9 mo	

TP53



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 by TP53 deletion/mutation status		
	mPFS	HR (95% CI)
Ven-Obi, no TP53 D/M	76.6 mo	2.29 (1.37–3.83) *P* = .001
Ven-Obi, TP53 D/M	51.9 mo	
Clb-Obi, no TP53 D/M	38.9 mo	1.66 (1.05–2.63) *P* = .03
Clb-Obi, TP53 D/M	20.8 mo	

Al-Sawaf O, et al. ICML. 2023: Abstract N.025.

Clb = chlorambucil; D/M = deletion and/or mutation; Ven-Obi = Venetoclax-obinutuzumab.

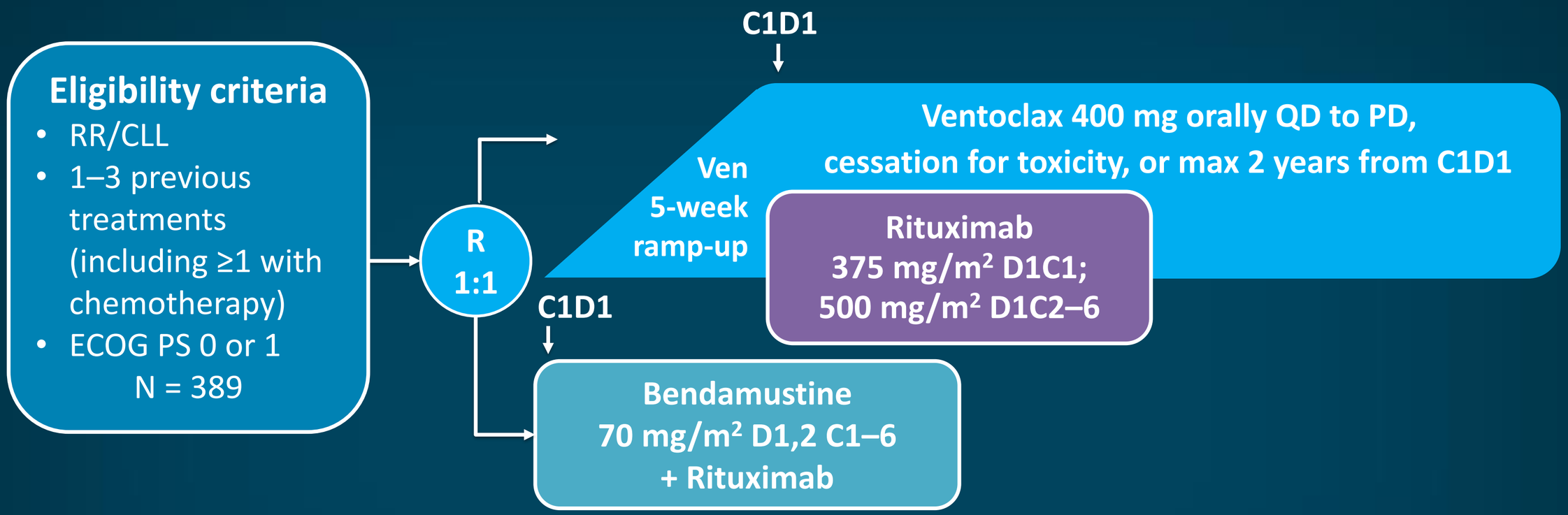
CLL14: 6-year Safety Update

Most frequent adverse events, grade 3 and above				
	Venetoclax-obinutuzumab (n = 212)		Chlorambucil-obinutuzumab (n = 214)	
AEs	During Treatment	After Treatment	During Treatment	After Treatment
Neutropenia	51.9%	3.8%	47.2%	1.9%
Thrombocytopenia	14.2%	0.5%	15.0%	0.0%
Anemia	7.5%	1.9%	6.1%	0.5%
Febrile neutropenia	4.2%	0.9%	3.3%	0.5%
Leukopenia	2.4%	0.0%	4.7%	0.0%
Pneumonia	3.8%	3.3%	3.7%	1.4%
Infusion-related reaction	9.0%	0.0%	9.8%	0.5%
Tumor lysis syndrome	1.4%	0.0%	3.3%	0.0%

Al-Sawaf O, et al. ICML. 2023: Abstract N.025.

Relapsed/Refractory CLL

MURANO: Venetoclax-Rituximab vs BR in R/R CLL—Study Design

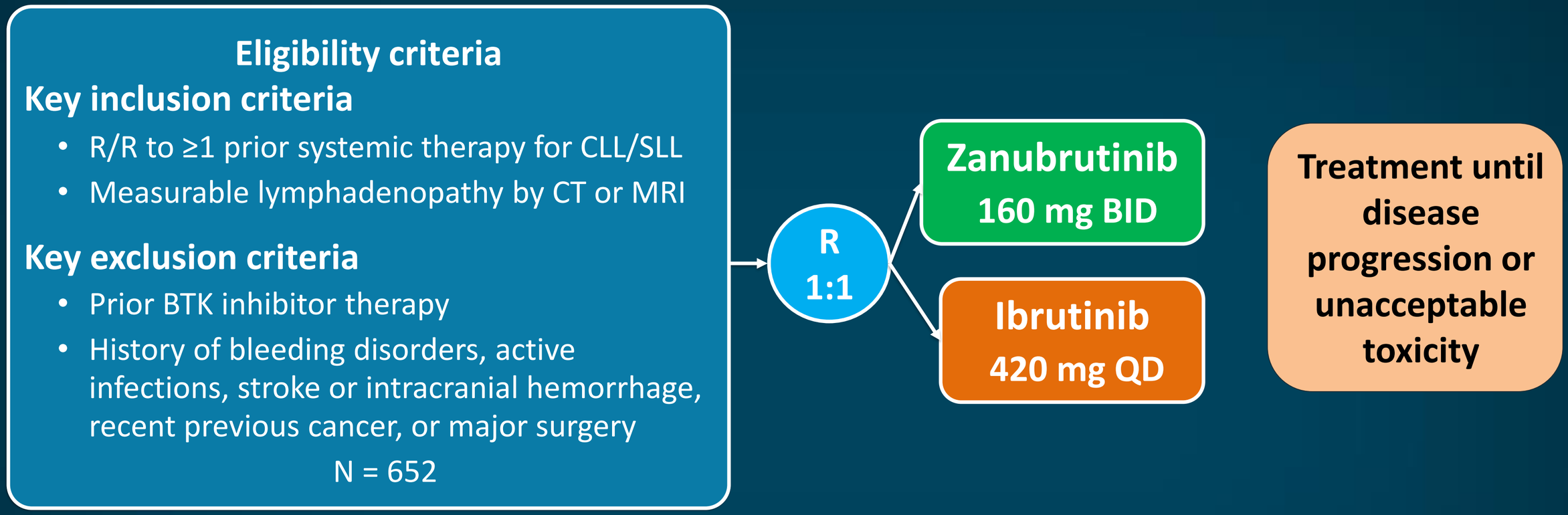


- **Primary endpoint:** INV-assessed PFS
- **Secondary endpoints:** IRC-assessed PFS, INV- and IRC-assessed PFS (patients with del[17p]), ORR, CR, OS, DoR
- **Stratification factors include** del(17p), response to previous therapy, geographic region

BM = bone marrow; C = cycle; D = day; DoR = duration of response; INV = investigator; IRC = independent review committee; max = maximum; ORR = overall/objective response rate; PB = peripheral blood; PD = progressive disease; QD = once daily; R = randomized; Ven = venetoclax.

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

ALPINE Study Design



Primary endpoint: INV-assessed ORR

Secondary endpoints: INV-assessed PFS and incidence of atrial fibrillation or flutter

Stratification factors include age, geographic region, refractoriness, del(17p)/*TP53*

BID = twice daily; CT = computed tomography (scan); MRI = magnetic resonance imaging.

Brown JR, et al. *N Engl J Med.* 2023;388:319-332 and supplement.

Phase 3 ELEVATE-CLL R/R
Acalabrutinib vs Ibrutinib in R/R High-Risk CLL

R/R high-risk CLL

N = 533

- ≥1 prior therapies for CLL
- ECOG PS of 0-2; active disease meeting ≥1 of the IWCLL 2008 criteria for requiring treatment; must have ≥1 high-risk prognostic factors (17p del and/or 11q del by central laboratory)
- No prior exposure to ibrutinib or to BCR or BCL-2 inhibitor

Key points

- Acalabrutinib demonstrated noninferiority to ibrutinib (PFS)
  - At median follow-up of 40.9 mo (range, 0.0–59.1), mPFS was 38.4 mo for both acalabrutinib and ibrutinib (HR = 1.00; 95% CI, 0.79–1.27)
- Incidence of any-grade atrial fibrillation was significantly lower with acalabrutinib vs ibrutinib, at rates of 9.4% vs 16%, respectively

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

Phase 2 Study: Venetoclax + Obinutuzumab Retreatment In Relapsed CLL

Study design

Cohort 1
(N = 60)

Patients who progressed >24 months after 1L VenO completion

→ 6 ycles VenO + 6 cycles Ven monotherapy

Cohort 2
(N = 60)

Patients who progressed >12–24 months after 1L VenO completion

→ 6 cycles VenO + 18 cycles Ven monotherapy

Treatment

28-day cycles:
O: 100 mg (IV) D1, 900 mg D2, 1000 mg D8 and D15 of C1; continuing at 1000 mg IV D1 C2–6

Ven: Once-daily (oral) beginning on D22 of C1 with a 5-week dose ramp-up from 20 mg to a target dose of 400 mg; continuing at 400 mg oral daily C3–12 (Cohort 1) or C3–C24 (Cohort 2)

Endpoints

Primary endpoint
- ORR at EoCT (3 mo after completing VenO)

Secondary endpoints
- CR/CRi at EoCT and EoT (3 mo after completing Ven monotherapy)
- ORR at EoT
- TTR
- DoR
- uMRD (10+) measured in PB at EoCT and EoT
- PFS
- OS
- TTNT
- Safety

Exploratory endpoints
- PROs
- MRD kinetics up to 12 mo post-treatment
- Correlations of igHV, TP53 mutation, and dei(17p) at baseline with treatment outcomes

Objectives

ReVenG study will assess whether patients with CLL who completed first-line venetoclax + obinutuzumab (VenO) can derive clinical benefit with VenO retreatment following disease progression

1. Primary objective is to evaluate ORR of VenO retreatment in patients who progressed >24 months after first-line VenO
2. Secondary objective is to quantify time-to-event efficacy endpoints and to assess safety of VenO retreatment in patients who progressed >24 months after first-line VenO

Study overview

Multicenter

International

Open-label

Phase 2

UP TO **75** patients are planned for enrollment

NCT04895436

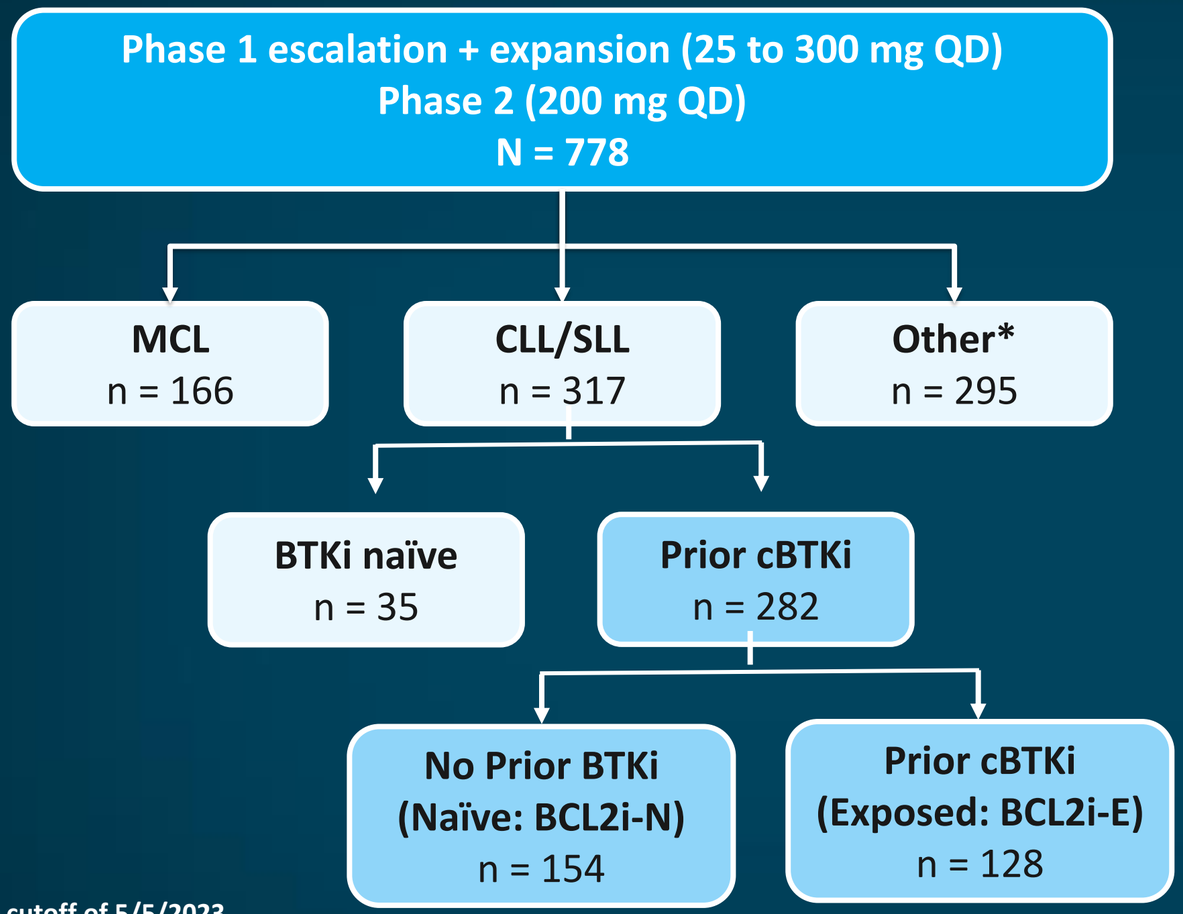
Planned initiation in 12/2021

EoCT = end of combination therapy; IV = intravenous; PB = peripheral blood; PRO = patient-reported outcome; TTR = time to response.

Davids MS et al. *Blood.* 2021;138(suppl 1): Abstract 2634

What can we do for CLL patients who progress after covalent BTKi and venetoclax?

Phase 1/2 BRUIN Study of Pirtobrutinib: Design, Eligibility, and Enrollment



Data cutoff of 5/5/2023
(NCT03740529)

Phase 1 3+3 design

- 28-day cycles
- Intra-patient dose escalation allowed
- Cohort expansion permitted at doses deemed safe

Eligibility

- Age ≥18 years
- ECOG PS 0-2
- Active disease and in need of treatment
- Previously treated

Key endpoints

- Efficacy (ORR according to iwCLL 2018 criteria, DoR, PFS, and OS)
- Safety/tolerability
- Determine MTD and RP2D
- Pharmacokinetics

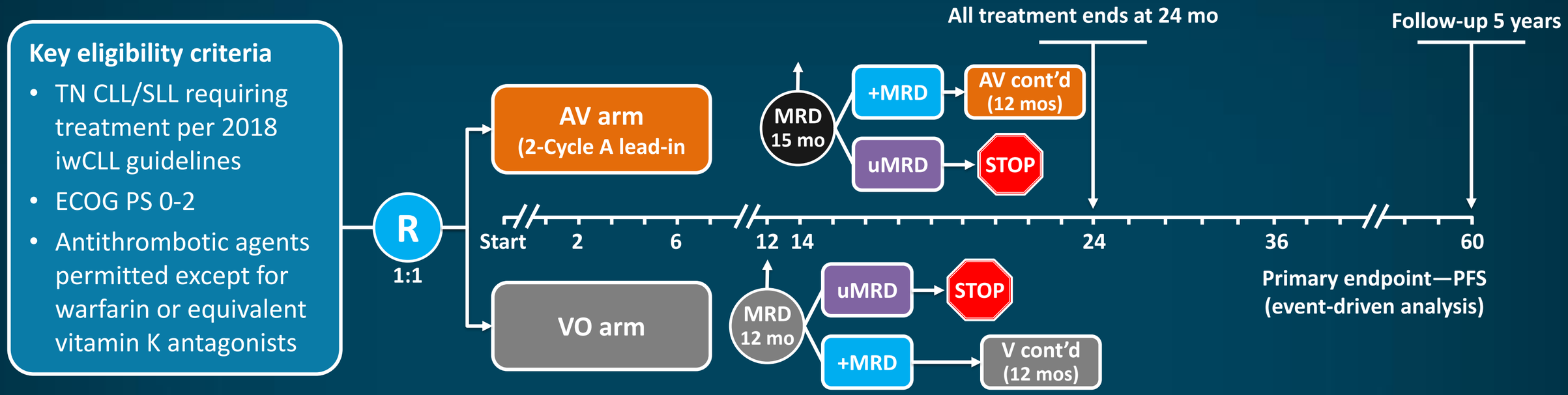
*Other includes diffuse large B-cell lymphoma, Waldenstrom macroglobulinemia, follicular lymphoma, marginal zone lymphoma, B-cell prolymphocytic leukemia, RT, hairy-cell leukemia, primary central nervous system lymphoma, and other transformation.

MCL = mantle-cell leukemia; MTD = minimal threshold detection; RP2D = recommended phase 2 dose.

NCT03740529 (https://clinicaltrials.gov/study/NCT03740529). Accessed 9/10/24. Woyach JA, et al. *Blood.* 2023;142(suppl 1):325-330. Mato AR, et al. *N Engl J Med.* 2023;389:33-44 and supplement.

Emerging Data and Future Directions

Global MAJIC Phase 3 Study Seeks to Define Optimal MRD-Guided Venetoclax Doublet for Frontline CLL Treatment

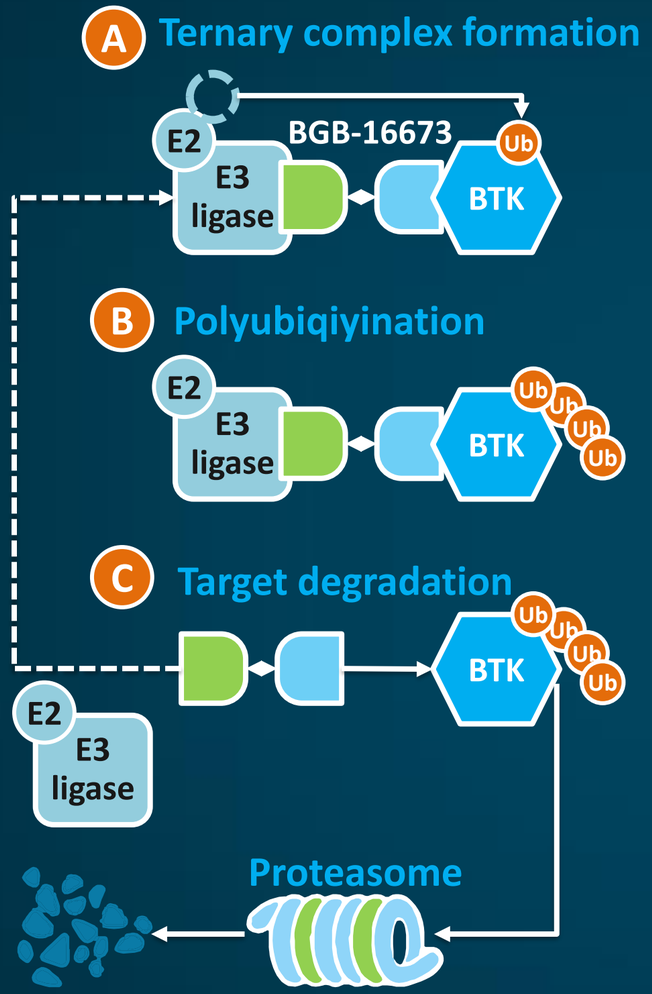


- **Primary endpoint:** INV-assessed PFS
- **Secondary endpoints:** uMRD rates, CR, ORR, EFS, OS, quality of life/PROs, safety
- **Stratified by** age (<65 y vs ≥ 65 y) , del17p and/or TP53 (+ vs –) and IGHV (mutated vs unmutated)
- N = ~600 patients
- Global study with ~40 sites
- First patient in 9/2022 and accrual completed in 3/2024

Davids MS, et al. *Blood.* 2021;138(suppl 1): Abstract 1553. Ryan CE, et al. *Future Oncol.* 2022;18:3689-3699.

EFS = event-free survival.

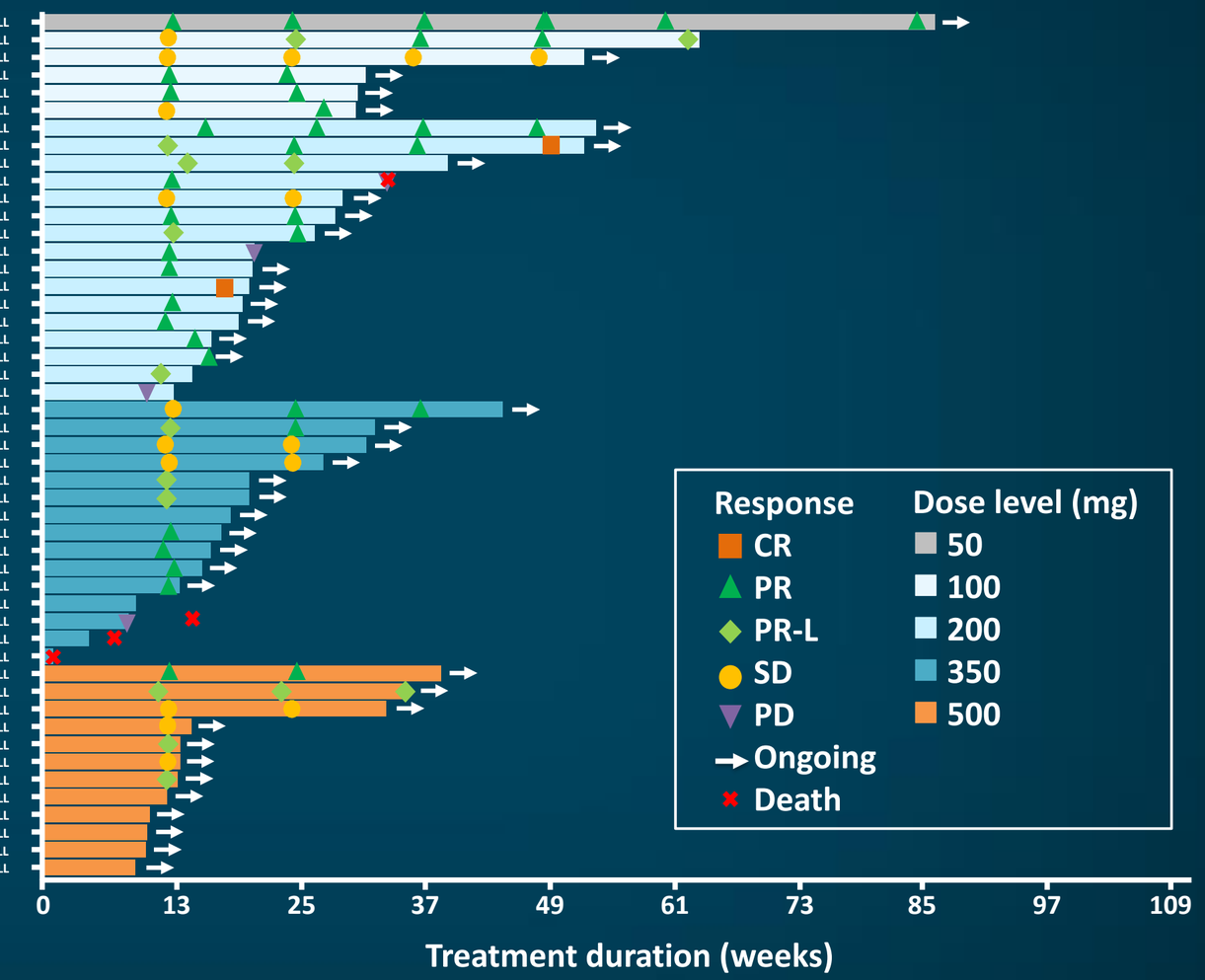
BTK Degraders: BGB-16673



Prior therapy

cBTKI	ncBTKI	BCL2i	BTKi mutations
			–
			–
			C481S, T474I, T474N, T474S
			–
			C481S
			–
			C481S
			–
			C481S
			–
			–
			–
			C481S
			–
			L528S, T474I, A428D
			–
			–
			–
			–
			–
			U
			–
			–
			M437K, A428D, V416L
			C481S
			–
			–
			–
			–
			–
			–
			D43H, E7K
			C481S
			C481S
			–
			C481S
			C481S
			–
			C481S
			–
			–
			U
			–
			–
			–
			T474I
			–
			–
			–

– = absent; U = unknown



- ORR was 72% (31/43) in response-evaluable patients with CLL/SLL
- ORR for 200-mg group was 88%, with 2 patients achieving CR

Parrondo R, et al. *EHA.* 2024 (www.beigenemedical.com/CongressDocuments/Parrondo_BGB-16673-101_EHA_Abstract_2024.pdf). Accessed 9/10/24.

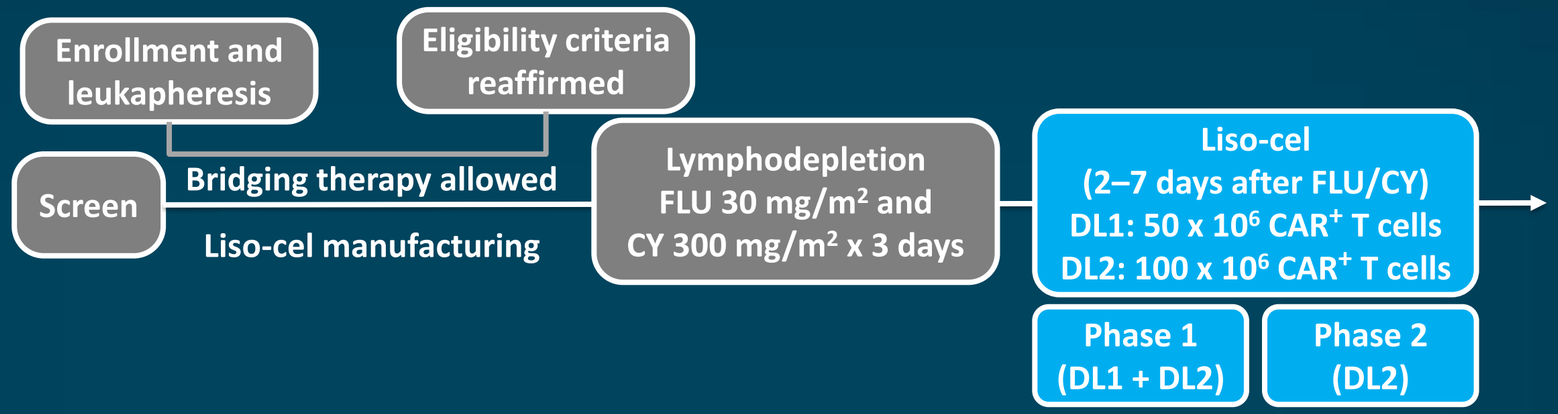
cBTKi = covalent BTKi; ncBTKi = noncovalent BTKi.

CAR-T: Liso-cel

TRANSCEND CLL 004 Study Design: Phase 1/2, Open-label, Multicenter Study

Eligibility criteria

- Age ≥18 years
- R/R CLL/SLL, indication for Tx
- Previously failed/ineligible for BTKi Tx
- Failure of >2 (high risk) or >3 (standard risk) lines of prior Tx
- ECOG PS ≤1
- Adequate bone marrow, organ, and cardiac function
- No RT or active CNS involvement



- **Primary endpoint (PEAS at DL2):** CR/CRi rate per iwCLL 2018 by IRC assessment
- **Key secondary endpoints (PEAS at DL2):** ORR, uMRD rate in blood
- **Other secondary endpoints:** DoR, DoCR, PFS, TTR, TTCR per IRC assessment, OS, uMRD CR in blood, safety
- Primary and key secondary endpoints were tested in prespecified subset of patients with BTKi progression and venetoclax failure (PEAS) at DL2 by following hierarchy: CR/CRi rate (Hy ≤5%), ORR (Hy ≤40%), and uMRD rate in blood (Hy ≤5%)

***Duration of follow-up was increased to 48 mo in protocol amendment (2/16/2021). Patients still in ongoing response per iwCLL 2018 criteria after the 2-year follow-up were followed for safety, disease status, additional anticancer therapies, and survival for an additional 2 years or until progression.**

CNS = central nervous system; CY = cyclophosphamide; DL = dose level; DoCR = duration of complete response/remission; FLU = fludarabine; Hy = null hypothesis; PEAS = primary efficacy analysis set; TTCR = time to complete response/remission.

Siddiqi T, et al. *Lancet*. 2023;402:641-654. NCT03331198. (https://clinicaltrials.gov/study/NCT03331198). Accessed 9/10/24.

CAR-T: Liso-cel—Efficacy Outcomes

Efficacy	Full study population at DL2 (n = 87)	BTKi progression/venetoclax failure subset at DL2 (n = 49)
Primary endpoint: IRC-assessed CR/CRi rate (95% CI) per iwCLL 2018, %	18 (11–28)	18 (9–32); *P* =.0006
Key secondary endpoints		
IRC-assessed ORR (95% CI), %	47 (36–58)	43 (29–58); *P* = .39
uMRD rate in blood (95% CI), %	64 (53–74)	63 (48–77)
Exploratory endpoint: uMRD rate in marrow (95% CI), %	59 (48–69)	59 (44–73)
Other secondary endpoints		
Best overall response, n (%)		
CR/CRi	16 (18)	9 (18)
PR/nPR	25 (29)	12 (24)
SD	34 (39)	21 (43)
PD	6 (7)	4 (8)
Not evaluable	6 (7)	3 (6)
Median (range) time to first response, mo	1.5 (1.0–3.1)	1.2 (1.0–3.0)
Median (range) time to first CR/CRi, mo	4.4 (3.0–7.5)	3.0 (1.2–3.3)

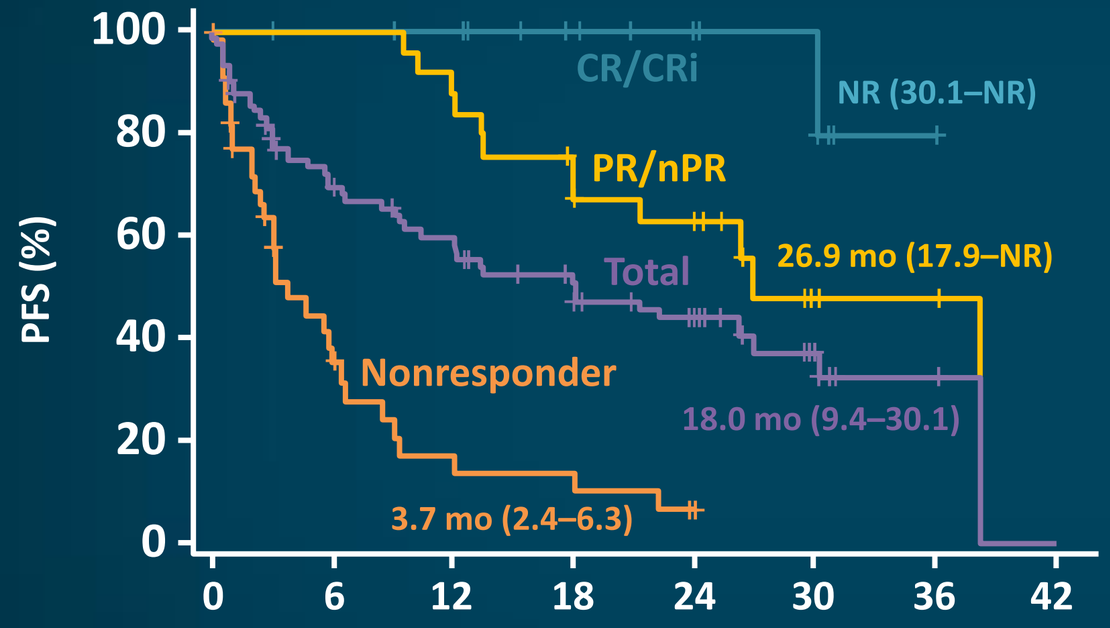
- All MRD-evaluable responders were uMRD in blood and marrow
- 12 of 20 MRD-evaluable patients with SD were uMRD in blood

Siddiqi T, et al. *Lancet.* 2023;402:641-654.

CAR-T: Liso-cel—Progression-Free Survival

Full study population at DL2 (n = 87)

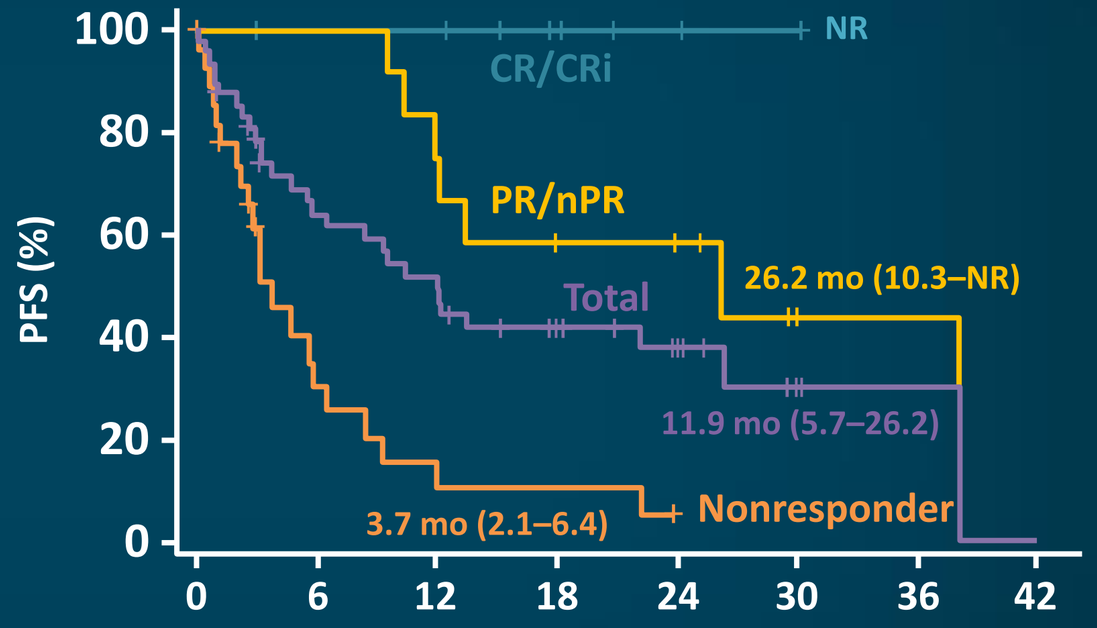
Median (95% CI) follow-up = 24.0 mo (18.3–26.4)



No. at risk								
CR/CRI	16	15	14	10	6	5	1	0
PR/nPR	25	25	22	15	11	3	2	0
Nonresponder	46	11	4	3	1	0	0	0
Total	87	51	40	28	18	8	3	0

PEAS (BTKi progression/venetoclax failure subset) at DL2 (n = 49)

Median (95% CI) follow-up = 20.8 mo (17.6–25.2)



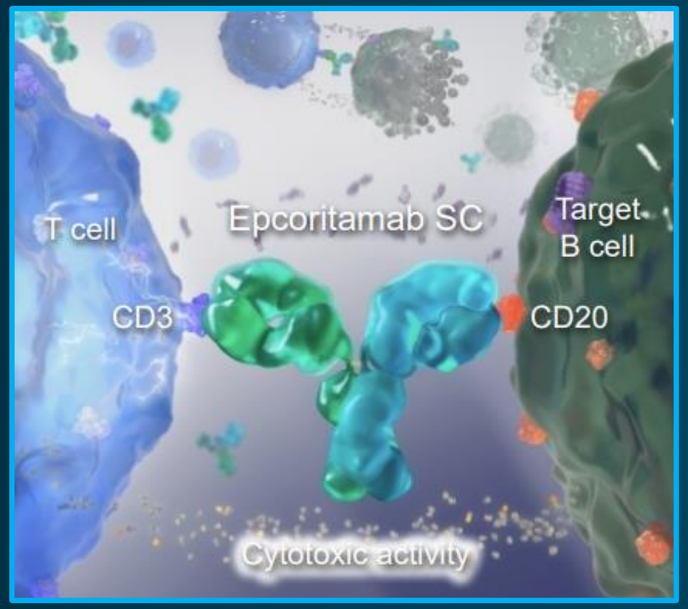
No. at risk								
—	9	8	8	5	2	1	0	0
—	12	12	9	6	5	1	1	0
—	28	6	2	2	0	0	0	0
—	49	26	19	13	7	2	1	0

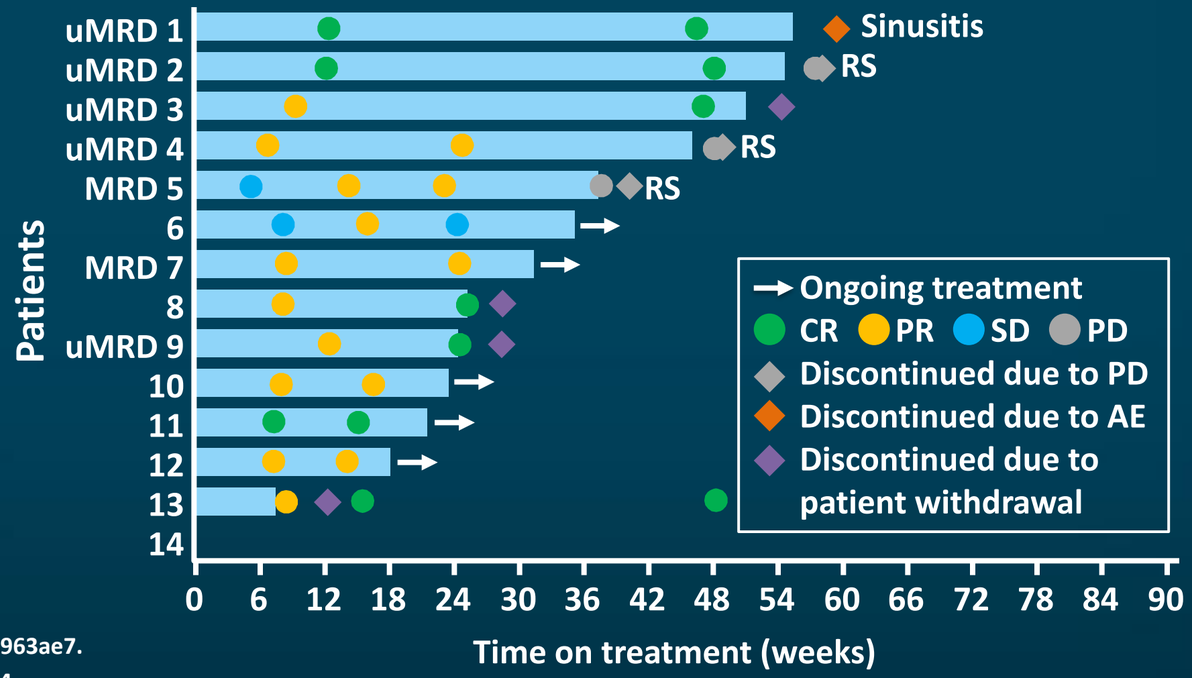
Siddiqi T, et al. *Lancet.* 2023;402:641-654 and supplement.

Data on Kaplan-Meier curves are expressed as median (95% CI, if available).

Bispecific Abs Also Hold Promise in CLL

Response, n (%)	Total efficacy evaluable n = 21	*TP53* aberration n = 14	Double-Exposed n = 17
Overall response	**13 (62)**	**9 (64)**	**9 (53)**
CR	7 (33)	4 (29)	5 (29)
PR	6 (29)	5 (36)	4 (24)
SD	4 (19)	2 (14)	4 (24)
PD	1 (5)	1 (7)	1 (6)
NE/no assessment	3 (14)	2 (14)	3 (18)





	Evaluable n = 21
Median TTR, mo (range)	**1.9** (1.6–3.7)
Median TTCR, mo (range)	**3.6** (1.6–10.8)
Estimated DoR at 9 mo,%	83
Estimated PFS at 9 mo, %	67
Estimated OS at 9 mo, %	81

RS = Richter's syndrome.

Kater et al., *iwCLL*. 2023 (https://de170d6b23836ee9498a-9e3cbe05dc55738dcbe22366a8963ae7.ssl.cf1.rackcdn.com/2501058-1432618-002.pdf). Accessed 9/10/24.

We look forward to seeing you at our TeleECHO sessions to discuss Chronic Lymphocytic Leukemia!