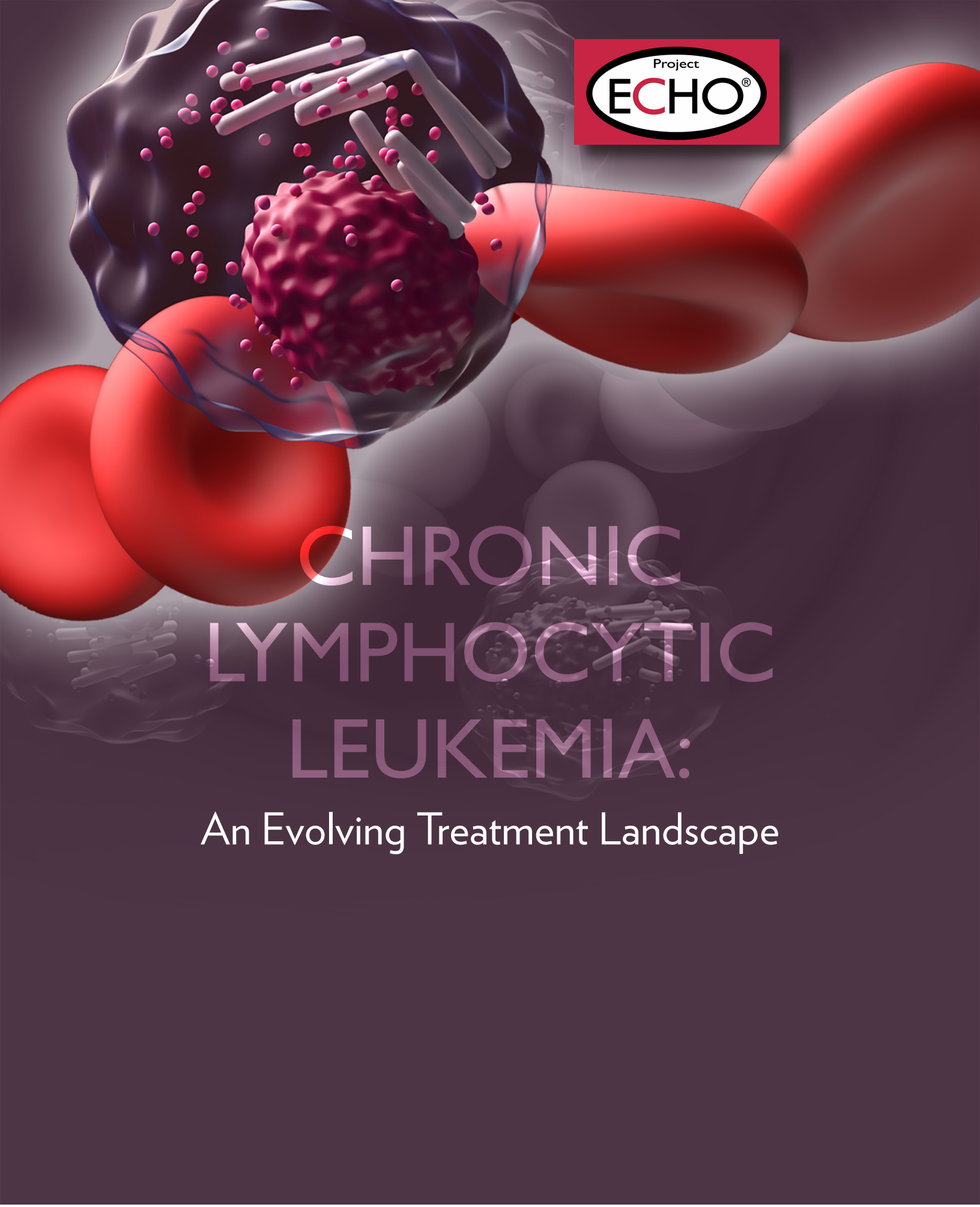

CHRONIC LYMPHOCYTIC LEUKEMIA:

An Evolving Treatment Landscape

This activity is provided by Med Learning Group.
This activity is supported by an educational grant from AstraZeneca Pharmaceuticals.

Chronic Lymphocytic Leukemia: An Evolving Treatment Landscape

PROGRAM CHAIR
Matthew S. Davids, MD, MMSc Clinical Research Director, Division of Lymphoma Dana-Farber Cancer Institute Associate Professor of Medicine Harvard Medical School Boston, Massachusetts

PROGRAM DESCRIPTION

This educational activity is designed for oncologists, hematologists, nurse practitioners, pharmacists, and other multidisciplinary oncology care team members that are involved in the management of patients with chronic lymphocytic lymphoma (CLL). Specifically, the program will help HCPs assess the safety, efficacy, and mechanisms of action of novel and upcoming CLL treatments. This will aid in managing their patients with CLL by differentiating the safety and effectiveness of established and innovative BTK inhibitors, understanding the adverse events specifically associated with these inhibitors, and how to how to manage them. Finally, the program will introduce various favored and substitute treatment options that can be utilized in the management of various stages of CLL.

TARGET AUDIENCE

This activity is designed to meet the educational needs of medical oncologists, hematologists, nurse practitioners, pharmacists, and other multidisciplinary oncology care team members.

LEARNING OBJECTIVES

- Summarize the safety, effectiveness, and ways of functioning of novel and upcoming treatments for individuals diagnosed with CLL
- Examine and differentiate the effectiveness and safety profiles of both established and innovative 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

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

AGENDA:

1. **Introduction**
   - 1.1. CLL fast facts
   - 1.2. Prognostication and prediction
   - 1.3. Brief overview of treatment landscape including Allo-SCT
2. **Treatment-Naïve CLL**
   - 2.1. Introduction to case study
   - 2.2. Clinical trial data of targeted therapies and management of adverse events
     - 2.2.1. BTK inhibitors
     - 2.2.2. BCL2 inhibitors
     - 2.2.3. CD20 monoclonal antibodies
   - 2.3. Case study discussion
3. **Relapsed/refractory (R/R) CLL**
     - 3.1.1. Factors guiding therapy decisions in R/R CLL
     - 3.1.2. Back to case study
     - 3.1.3. Clinical trial data of targeted therapies and management of adverse events
       - 3.1.3.1. Revisiting BTK and BCL2 inhibitors in the R/R setting
     - 3.1.4. Role of MRD in treatment monitoring
     - 3.1.5. Case study discussion
4. **Emerging data and future directions**
     - 4.1.1. Triplet therapy
     - 4.1.2. Noncovalent BTK inhibitors
     - 4.1.3. BTK degraders
     - 4.1.4. CAR-T therapy
     - 4.1.5. Bispecific antibodies
5. **Applying Shared Decision-Making (via the Case Studies)**
   - 5.1. Considering goals of care and patient preferences in the management of CLL
   - 5.2. Patient education on CLL and therapy options
   - 5.3. Applying shared decision-making to clinical practice
6. **Conclusions and Closing Remarks**
7. **Questions and Answers**

Chronic Lymphocytic Leukemia: An Evolving Treatment Landscape

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

CLL Fast Facts

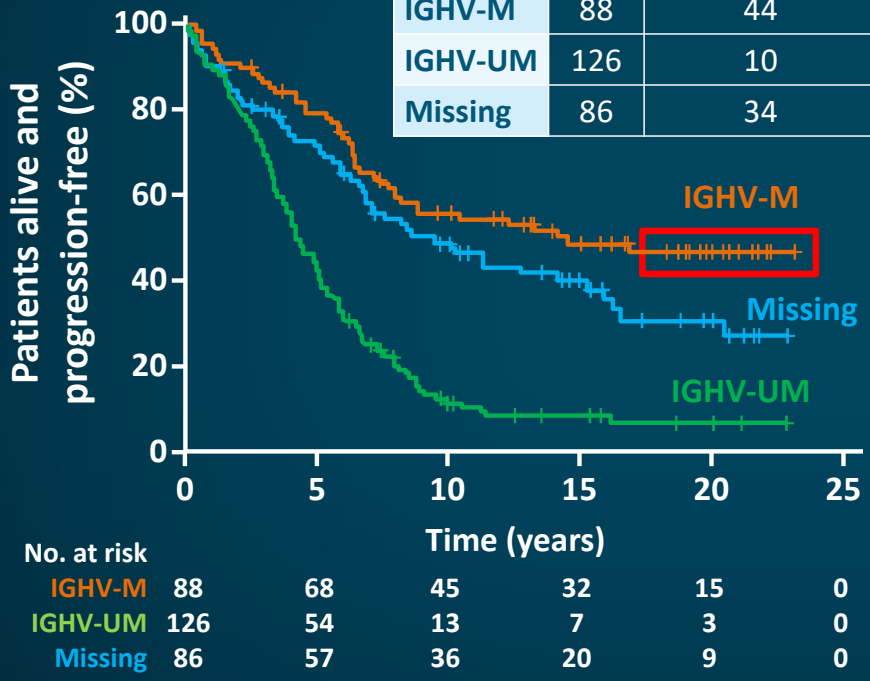
- CLL is a chronic lymphoproliferative disorder of monoclonal B cells
- >80,000 new cases/year worldwide, much higher prevalence
- Median age at diagnosis is 70 years
- Most common presentation is asymptomatic lymphocytosis
- ABC count >5000 (CD5+CD23+CD19+dimCD20+dimIg+)
- Tremendous amount of variation in disease course
- Powerful genetic prognostic markers include FISH, IGHV, and *TP53* mutation status

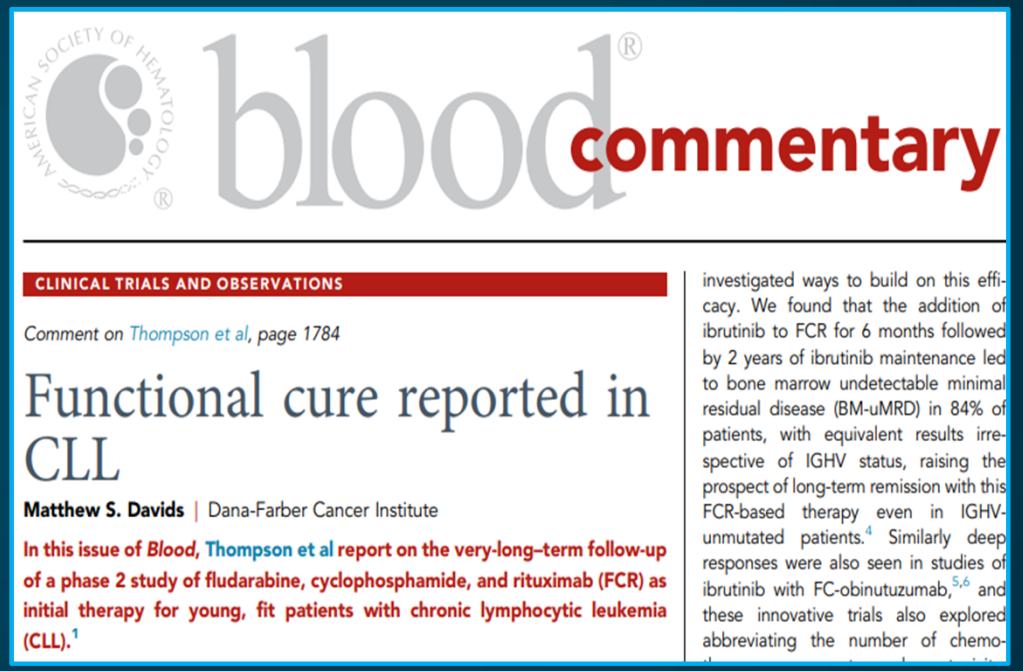
ALC = absolute lymphocyte count; CD = cluster of differentiation; CLL = chronic lymphocytic leukemia; LDT = lymphocyte doubling time.

FCR Can Provide Functional Cure in Mutated IGHV CLL

MDACC—Follow-Up on 300 patients treated with FCR

	N	Without event
IGHV-M	88	44
IGHV-UM	126	10
Missing	86	34




blood commentary

CLINICAL TRIALS AND OBSERVATIONS

Comment on Thompson et al, page 1784

Functional cure reported in CLL

Matthew S. Davids | Dana-Farber Cancer Institute

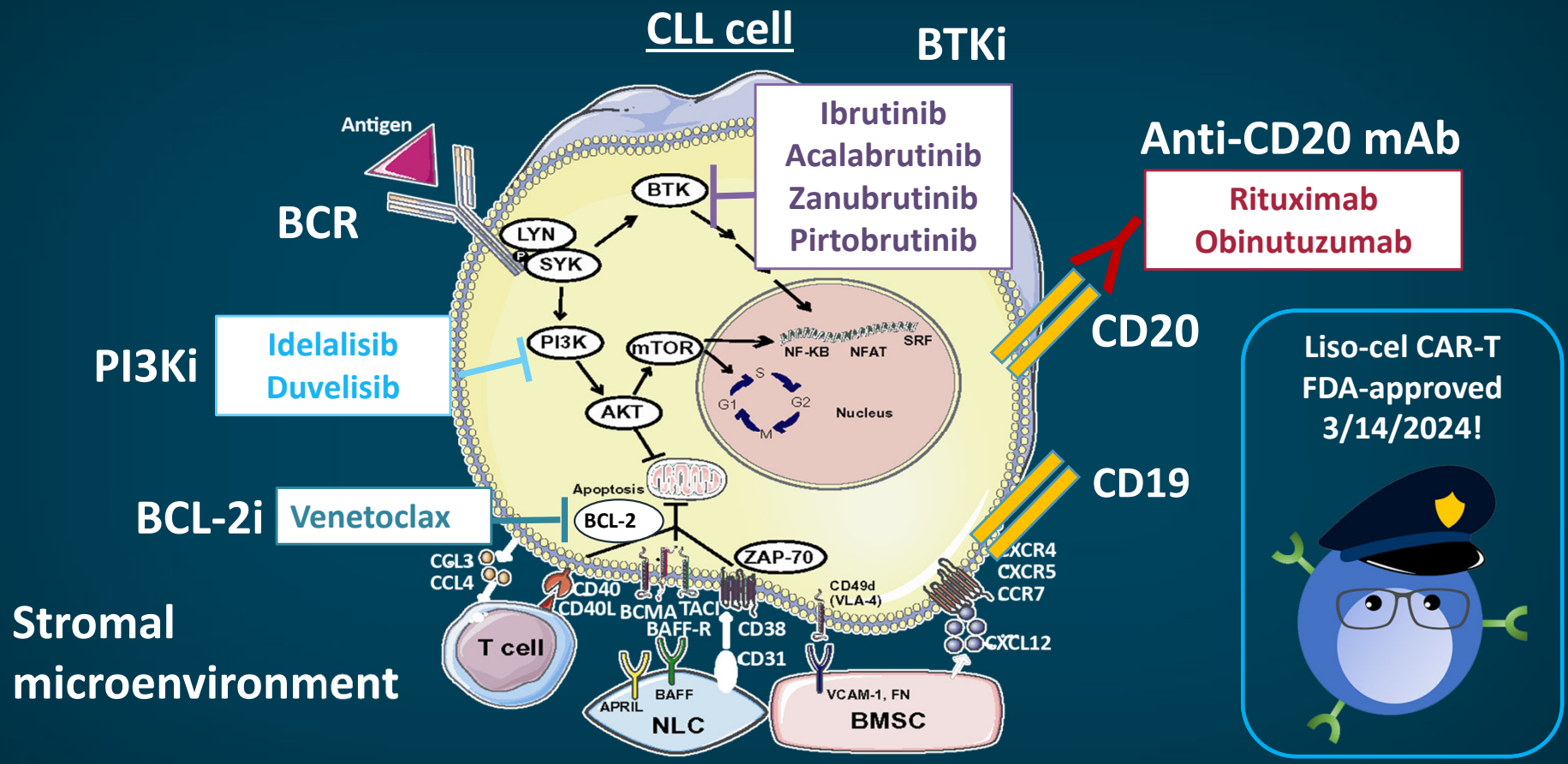
In this issue of *Blood*, Thompson et al report on the very-long–term follow-up of a phase 2 study of fludarabine, cyclophosphamide, and rituximab (FCR) as initial therapy for young, fit patients with chronic lymphocytic leukemia (CLL).[1]

investigated ways to build on this efficacy. We found that the addition of ibrutinib to FCR for 6 months followed by 2 years of ibrutinib maintenance led to bone marrow undetectable minimal residual disease (BM-uMRD) in 84% of patients, with equivalent results irrespective of IGHV status, raising the prospect of long-term remission with this FCR-based therapy even in IGHV-unmutated patients.[4] Similarly deep responses were also seen in studies of ibrutinib with FC-obinutuzumab,[5,6] and these innovative trials also explored abbreviating the number of chemo-

IGHV-M = IGHV mutated; IGHV-UM = IGHV unmutated; MDACC = M D Anderson Cancer Center.

Thompson PA, et al. *Blood.* 2023;142:1784-1788. Davids MS. *Blood.* 2023;142:1761-1763.

A Diverse Array of Novel Agents Are Highly Active in CLL



BCL-2i = B cell lymphoma 2 inhibitor; BCR = B cell receptor; BMSC = bone marrow stromal cells; BTKi = Bruton tyrosine kinase inhibitor; CAR-T = chimeric antigen receptor T cell; mAb = monoclonal antibody; NLC = nurse-like cells; PI3Ki = phosphoinositide 3'-kinase inhibitor.

Modified from Davids MS, Brown JR. *Leuk Lymphoma*. 2012;53:2362-2370. Lokaj R. Cancernetwork (www.cancernetwork.com/view/fda-approves-liso-cel-for-relapsed-refractory-cll-sll). Accessed 9/13/24.

Treatment-Naïve CLL

Case Study 1A: Frontline Treatment

- Paul is a 64-year-old man with del(11q), IGHV unmutated, *TP53* wildtype CLL who has had progressive anemia and thrombocytopenia with mildly enlarged lymph nodes and worsening fatigue along with 15 lbs of unintentional weight loss over last 6 months; his WBC count is now 84.4, Hgb 9.4 g/dL, and Plts 81K
- His oncologist is now recommending that he initiate frontline CLL treatment
- Paul's medical history is significant for well-controlled hypertension and mild chronic kidney disease with a baseline creatinine of 1.7

Which of the following is a preferred frontline therapy for Paul?

A) Ibrutinib
B) BR
C) Acalabrutinib W2
D) Venetoclax + obinutuzumab
E) FCR

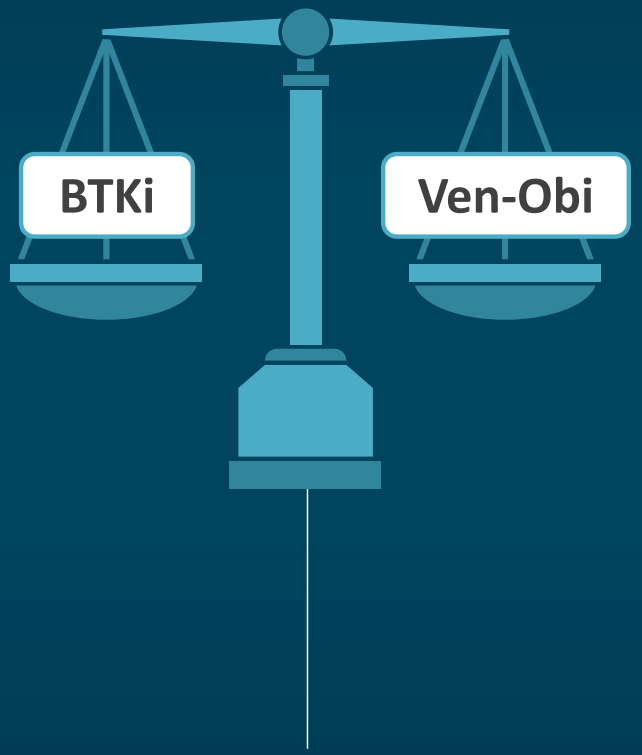
BR = bendamustine and rituximab; Hgb = hemoglobin; Plts = platelets; WBC = white blood count

Slide 7

W2 Answer: C

Writer, 9/26/2024

BTKi vs Ven-Obin in TN CLL: Clinical Considerations



Ven-Obi = venetoclax + obinutuzumab.

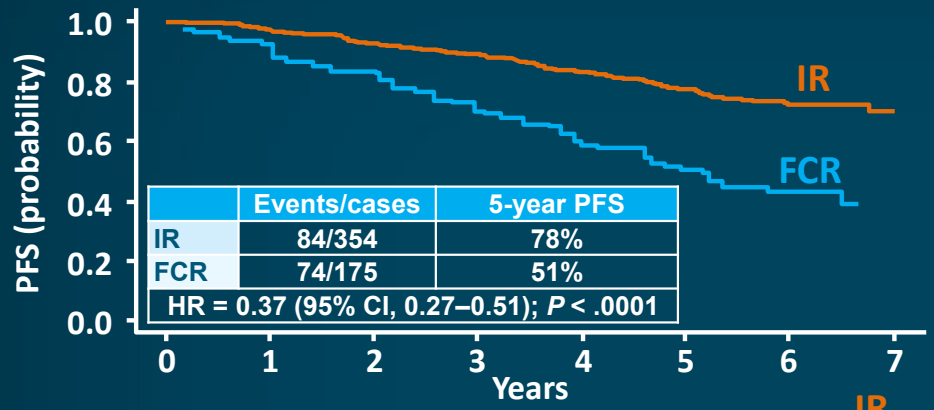
What are the data to support continuous BTKi monotherapy?

Phase 3 Data of IR vs FCR

PFS and Possibly Also OS Benefit of Continuous Ibrutinib-Based Therapy

ECOG 1912 (US)[1]

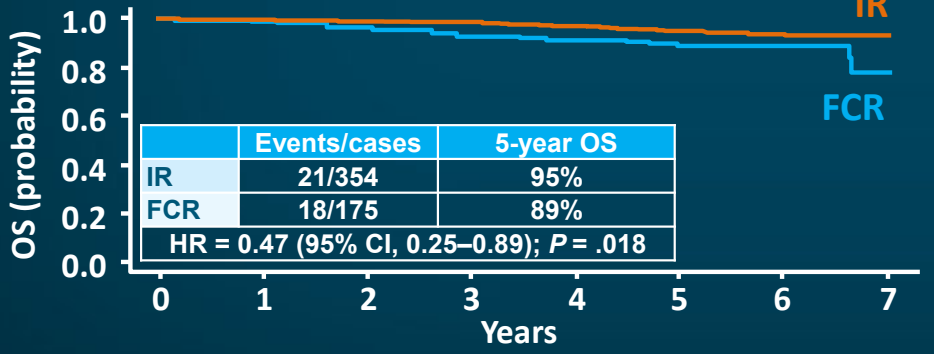
PFS



	Events/cases	5-year PFS
IR	84/354	78%
FCR	74/175	51%

HR = 0.37 (95% CI, 0.27–0.51); *P* < .0001

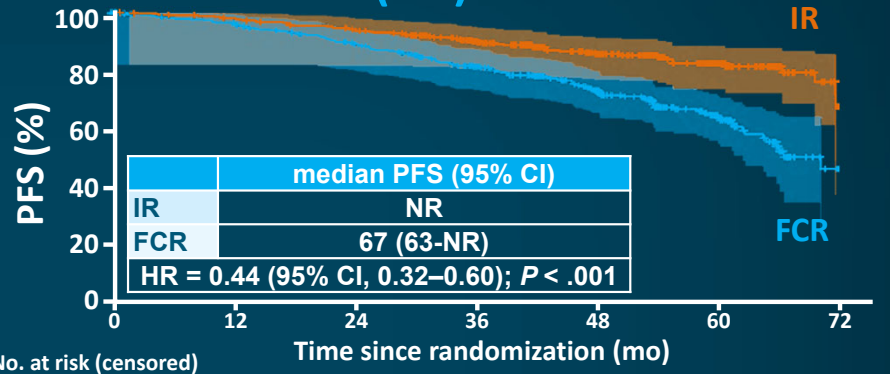
OS



	Events/cases	5-year OS
IR	21/354	95%
FCR	18/175	89%

HR = 0.47 (95% CI, 0.25–0.89); *P* = .018

FLAIR (UK)[2]

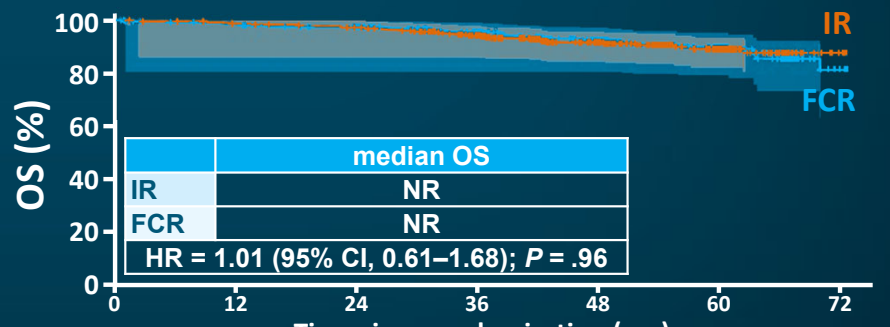


	median PFS (95% CI)
IR	NR
FCR	67 (63-NR)

HR = 0.44 (95% CI, 0.32–0.60); *P* < .001

No. at risk (censored)

FCR	385 (0)	363 (9)	324 (22)	254 (63)	171 (125)	76 (203)	6 (261)
IR	386 (0)	374 (5)	353 (11)	291 (58)	193 (145)	88 (244)	11 (316)



	median OS
IR	NR
FCR	NR

HR = 1.01 (95% CI, 0.61–1.68); *P* = .96

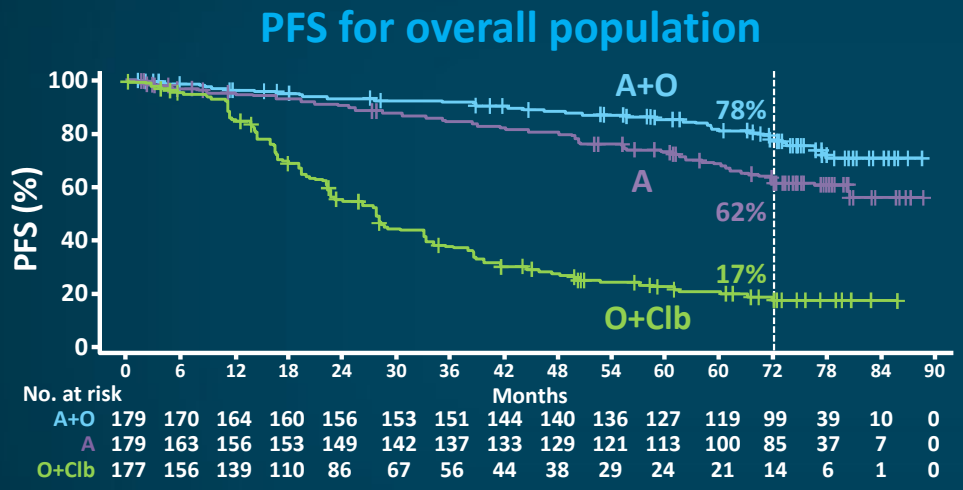
No. at risk (censored)

FCR	385 (0)	369 (10)	351 (26)	290 (81)	202 (163)	94 (266)	12 (344)
IR	386 (0)	377 (5)	365 (12)	305 (61)	210 (150)	95 (261)	13 (342)

ECOG = Eastern Cooperative Oncology Group; FCR = Fludarabine, Cyclophosphamide, Rituximab; IR = Ibrutinib-Rituximab; NR = not reached; UK = United Kingdom.

1. Shanafelt TD, et al. *Blood.* 2022;140:112-120. 2. Hillmen P, et al. *Lancet Oncol.* 2023;24:535-552.

6-Year Follow-Up of ELEVATE-TN: Acalabrutinib ± Obinutuzumab vs Obinutuzumab + Chlorambucil in TN CLL—PFS



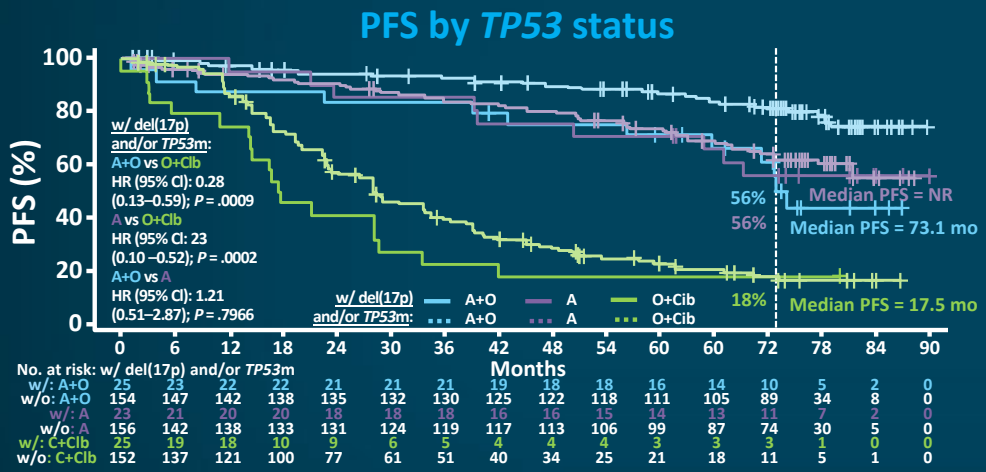
Progression-free survival		
	Median PFS	PFS at 6 years
A+O	NR	78%
A	NR	62%
O+Clb	27.8 mo	17%

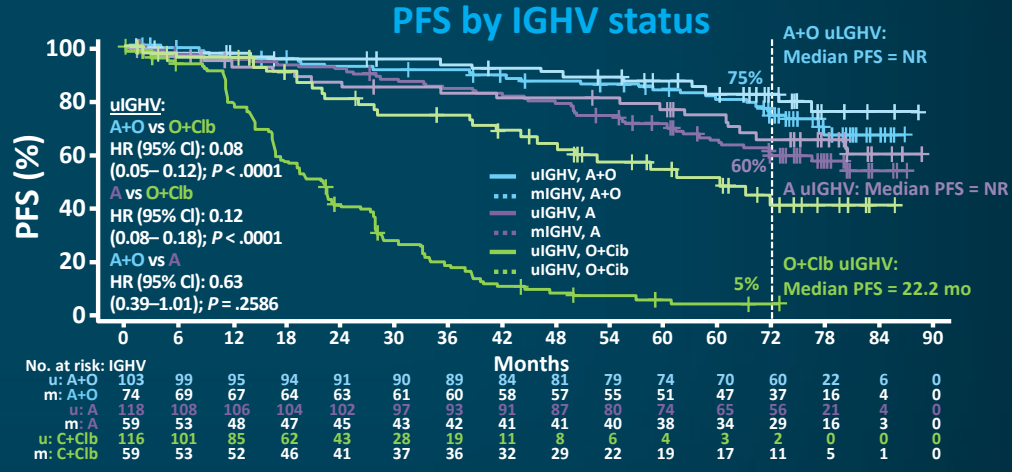
A+O vs O+Clb: HR = 0.14 (95% CI, 0.10–0.20) $P < .0001$
A vs O+Clb: HR = 0.24 (95% CI, 0.17–0.32) $P < .0001$
A+O vs A: HR = 0.58 (95% CI, 0.39–0.86) $P = .0229$

A = acalabrutinib; Clb = chlorambucil; O = obinutuzumab; u = unmutated.

Sharman JP, et al. *Blood*. 2023;142(suppl 1): 636-639.

6-Year Follow-Up of ELEVATE-TN: Acalabrutinib ± Obinutuzumab vs Obinutuzumab + Chlorambucil in TN CLL—PFS





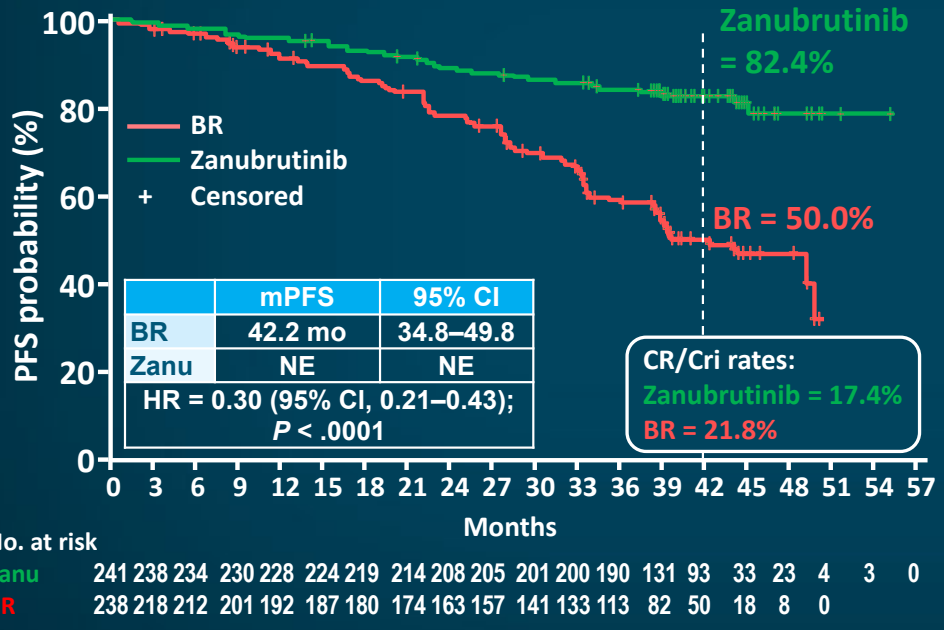
A = acalabrutinib; Clb = chlorambucil; O = obinutuzumab; u = unmutated.

Sharman JP, et al. *Blood*. 2023;142(suppl 1): 636-639.

SEQUOIA: Phase 3 Open-Label Study of Zanubrutinib vs Bendamustine + Rituximab in TN CLL/SLL—Efficacy

PFS in non-del(17p)

Median follow-up = 43.7 months



	mPFS	95% CI
BR	42.2 mo	34.8–49.8
Zanu	NE	NE
HR = 0.30 (95% CI, 0.21–0.43); *P* < .0001		

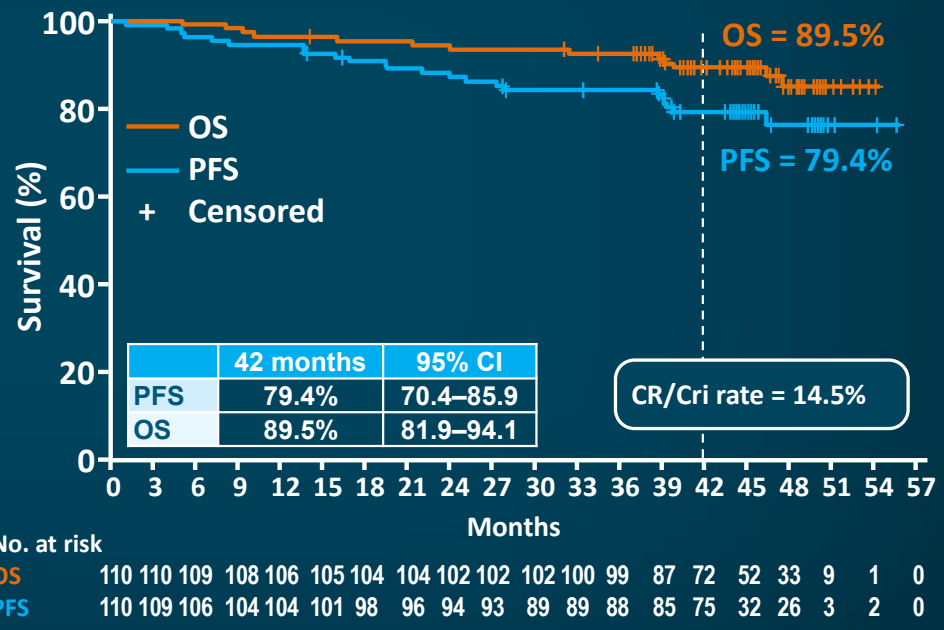
CR/Cri rates:
Zanubrutinib = 17.4%
BR = 21.8%

No. at risk

Zanu	241	238	234	230	228	224	219	214	208	205	201	200	190	131	93	33	23	4	3	0
BR	238	218	212	201	192	187	180	174	163	157	141	133	113	82	50	18	8	0		

PFS in del(17p)

Median follow-up = 47.9 months



	42 months	95% CI
PFS	79.4%	70.4–85.9
OS	89.5%	81.9–94.1

CR/Cri rate = 14.5%

No. at risk

OS	110	110	109	108	106	105	104	104	102	102	102	100	99	87	72	52	33	9	1	0
PFS	110	109	106	104	104	101	98	96	94	93	89	89	88	85	75	32	26	3	2	0

CR = complete remission/response; CRi = CR with incomplete hematologic recovery; del(17p) = chromosome 17p deletion; mPFS = median PFS; NE = not estimable/evaluable; SLL = small lymphocytic lymphoma; Zanu = zanubrutinib.

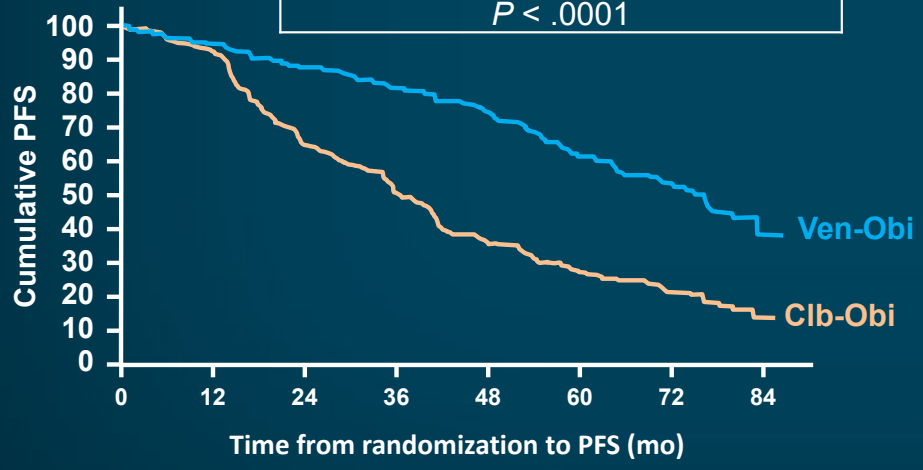
Tam CS, et al. *Lancet Oncol.* 2022;23:1031-1043. Shadman et al., International Conference on Malignant Lymphoma (ICML). 2023: Abstract 154.

What are the data to support time-limited venetoclax combinations?

Fixed Duration Venetoclax-Obinutuzumab (Ven-Obi) vs Clb-Obi
6-Year Follow-Up of CLL14

Progression-free survival

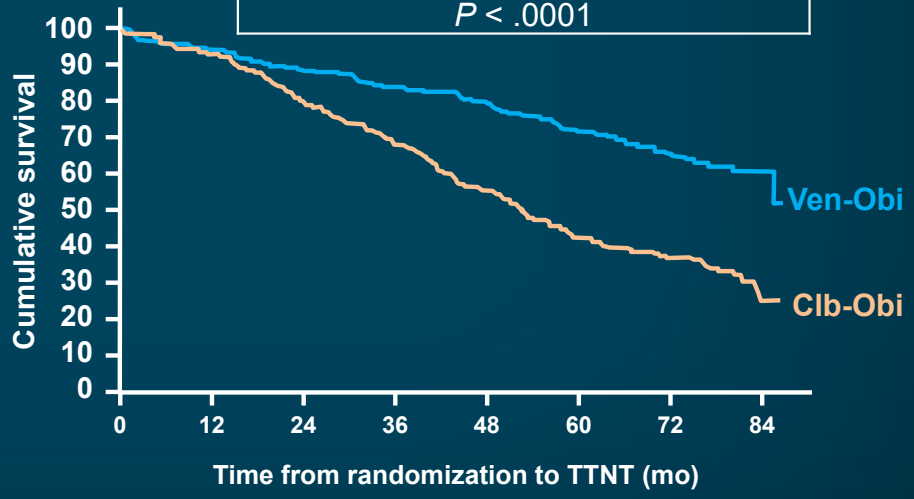
	Median PFS	6-yr PFS
Ven-Obi	76.2 mo	53.1%
Clb-Obi	36.4 mo	21.7%
HR = 0.40 (95% CI, 0.31–0.52) *P* < .0001		



No. at risk								
Ven-Obi	216	193	177	160	139	112	79	3
Clb-Obi	216	185	130	101	67	50	36	3

Time to next treatment (TNTT)

	Median TTNT	6-yr TTNT
Ven-Obi	NR	65.2%
Clb-Obi	52.9 mo	37.1%
HR = 0.44 (95% CI, 0.33–0.58) *P* < .0001		

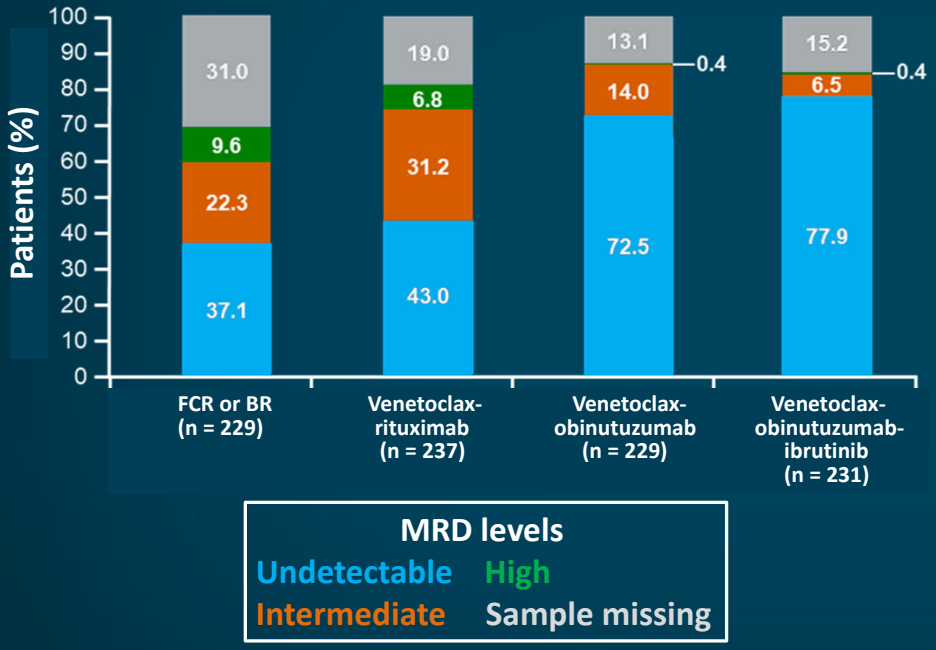


No. at risk								
Ven-Obi	216	195	183	172	161	140	118	20
Clb-Obi	216	194	166	140	111	83	70	10

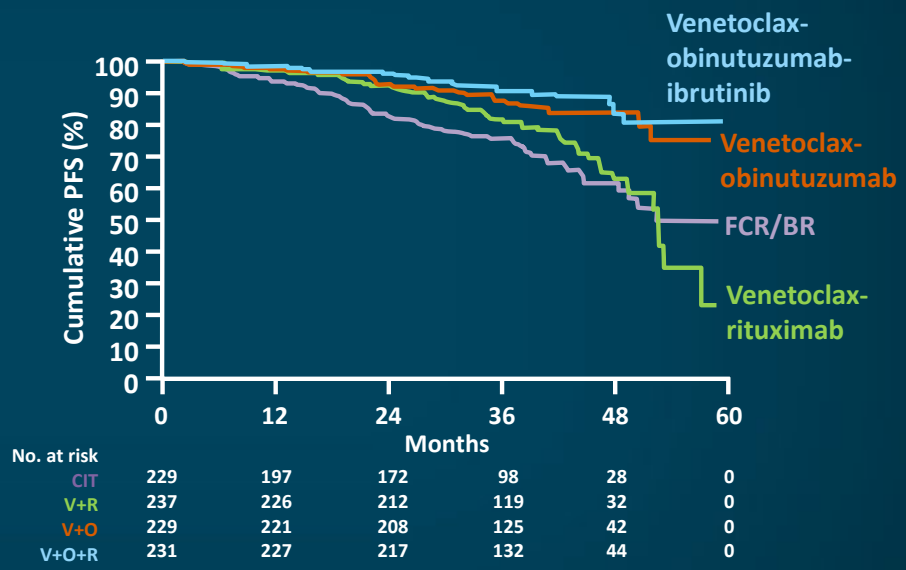
Al-Sawaf O, et al. European Hematology Association (EHA) Hybrid Congress. 2023: Abstract S145.

Venetoclax-Based Time-Limited Treatments vs FCR/BR for 1L Treatment of CLL: GAIA/CLL13 Study

MRD in bone marrow at final restaging



PFS: All patients



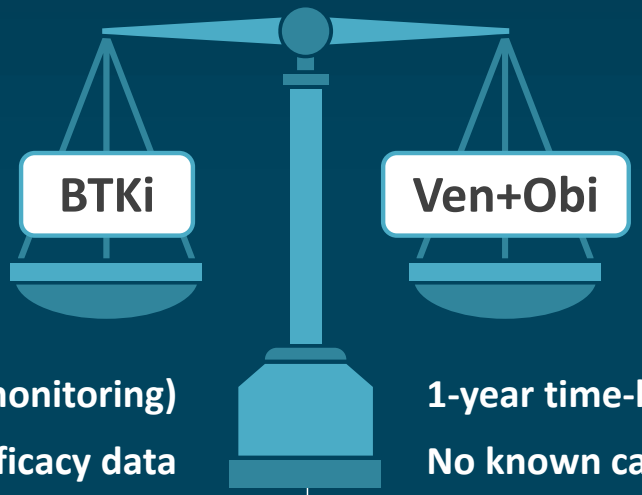
No. at risk						
CIT	229	197	172	98	28	0
V+R	237	226	212	119	32	0
V+O	229	221	208	125	42	0
V+O+R	231	227	217	132	44	0

Most common grade 3 and 4 AEs across all 4 treatment groups were cytopenia and infections

1L = first line; BR = Bendamustine-Rituximab; MRD = minimal residual disease; V+O = venetoclax-obinutuzumab; V+O+R = Venetoclax-obinutuzumab-ibrutinib; V+R = venetoclax-rituximab;\.

Eichhorst B, et al. *N Engl J Med.* 2023;388:1739-1754.

BTKi vs Venetoclax-Obinutuzumab in TN CLL: Clinical Considerations



Convenience (no infusions or TLS monitoring)

Longer-term efficacy data

Prospective data for efficacy of venetoclax at time of ibrutinib progression

Indefinite treatment

Potential for cumulative cardiac toxicity

1-year time-limited therapy

No known cardiac or bleeding risks

Less concern with long-term adherence

Potential for cost savings

Possibility of retreatment

Time-intensive (infusions, venetoclax ramp-up)

TLS = tumor lysis syndrome.

Relapsed/Refractory CLL

Factors Guiding Therapy Decisions in R/R CLL

- Patients relapsing after minimal therapy (mAb, Clb)
- Patients relapsing after effective CIT
  - ***Most of our data are from RESONATE, HELIOS, ASCEND, MURANO, ELEVATE-RR, ALPINE***
- Patients exposed to BTK inhibitors
  - Discontinue for adverse events
  - Progression during therapy
- Patients relapsing after venetoclax
  - Time-limited or during therapy
- Patients relapsing after BTKi and BCL-2

R/R = relapsed/refractory.

Case Study 2A

Paul was started on **frontline acalabrutinib** and achieved a partial remission that lasted ~6 years; at age 70, his WBC rose rapidly to 49.3, Hgb trended back down to 10.1 g/dL, and Plts are 96K; he is noticing some lymph node growth in his neck and is feeling more fatigued

What would you use as second-line therapy for Paul?

A) Zanubrutinib
B) Venetoclax-based therapy
C) BR
D) Idelalisib + rituximab
E) Add rituximab and continue acalabrutinib

W4

Slide 20

W4 Answer: B

Writer, 9/26/2024

MURANO: Phase 3 Study of VenR vs BR in Patients With R/R CLL (5-Year Analysis)

5-year clinical update includes MRD kinetics, with patients off therapy for ~3 years

Results

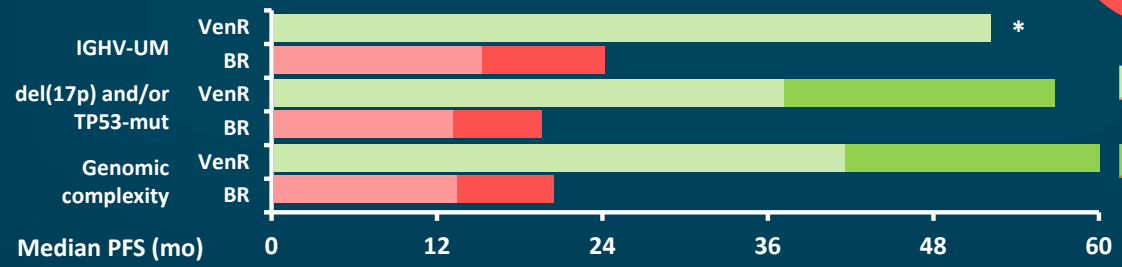
Survival benefits with **VenR vs BR** were sustained

194 patients on VenR

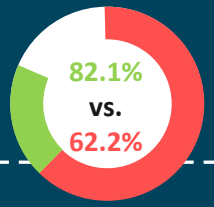
195 patients on BR

Patients with **high-risk cytogenetic** markers, had worse outcomes than those without. Survival remained superior with **VenR** vs **BR,** regardless of cytogenetic markers

5-year median PFS



5-year median OS rates



MRD doubling time post-EoT with VenR was slower compared with BR: Median doubling time of **93 days** with **VenR** and **53 days** with **BR**

Conclusions

Sustained survival, uMRD benefits, and durable responses support 2-year fixed-duration VenR treatment in R/R CLL

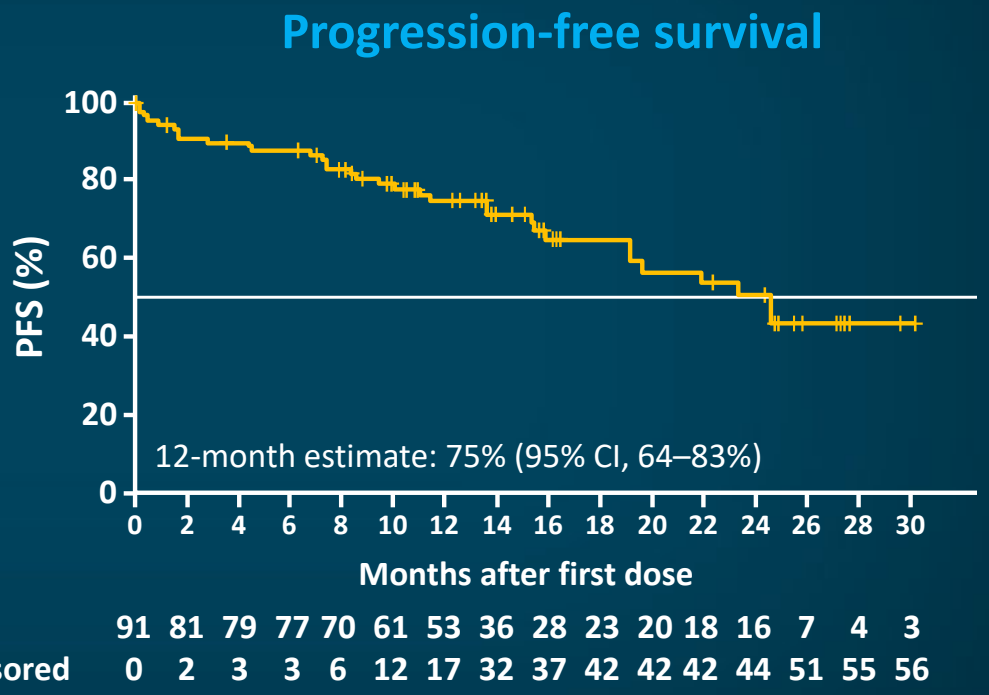
*PFS for patients in the VenR arm with mutated IGHV was not-estimable.

EoT = end of treatment; uMRD = undetectable MRD; VenR = venetoclax + rituximab.

Seymour JF, et al. *Blood*. 2022;140:839-850.

M14-032: First Prospective Study of Any Treatment for Patients Progressing on BTKi Found That Venetoclax Is Active Post Ibrutinib

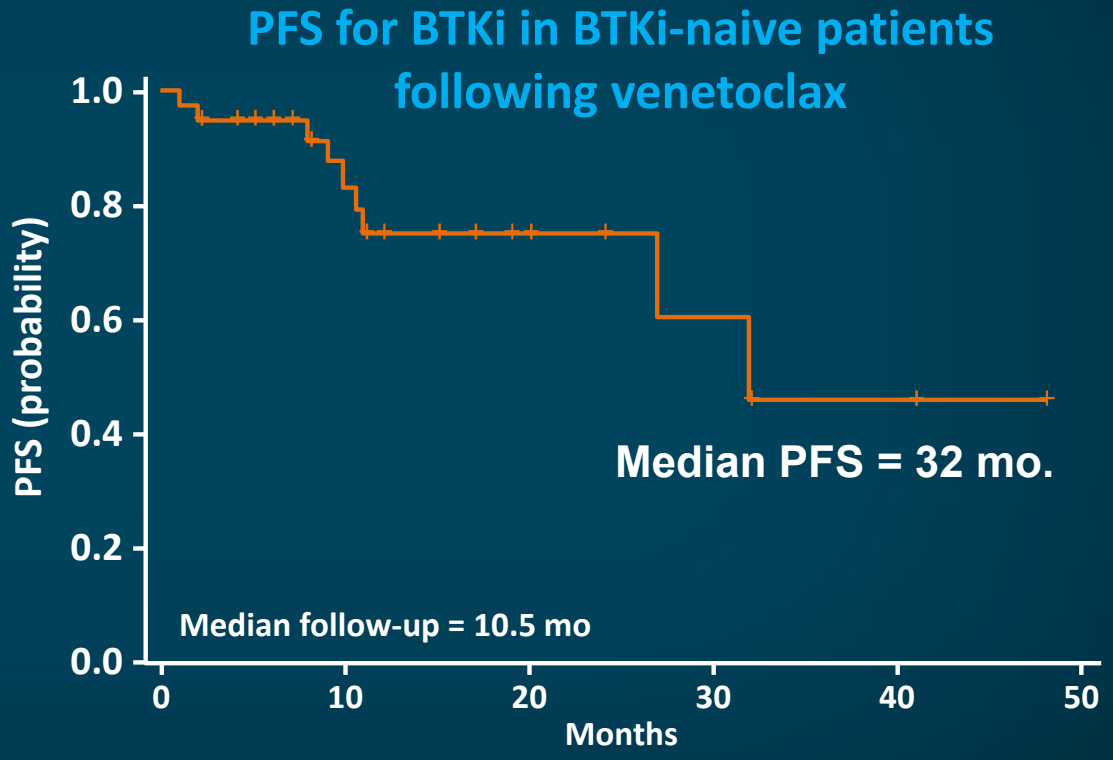
- 91 pts progressed after ibrutinib, treated with venetoclax
- Median 4 prior therapies (range 1–15), del(17p) in 44%
- Overall response rate = 65%, CR/CRi rate = 9%
- Median follow-up = 14 mo



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

After Venetoclax, BTK Inhibition Produces High ORR and Durable Remissions in BTK Inhibitor-Naive Patients

- CLL patients who discontinued venetoclax in first-line (4%) and R/R settings (96%)
- Median of 3 therapies prior to venetoclax
- 40% were BTKi naïve (n = 130)
- ORR to BTKi was 84% (n = 44) in BTKi-naïve patients vs 54% (n = 30) in BTKi-exposed patients



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

Case Study 2B

Paul is started on **1L venetoclax + obinutuzumab** and achieves complete remission with uMRD in blood that lasts ~6 years; at age 70, his WBC rose rapidly to 49.3, Hgb trended down to 10.1 g/dL, and Plts are 96K; he has noticed some lymph node growth in his neck and is feeling more fatigued

What would you use as second-line therapy for Paul?

A) Zanubrutinib
B) Venetoclax-based therapy
C) BR
D) Idelalisib + rituximab

W6

Slide 24

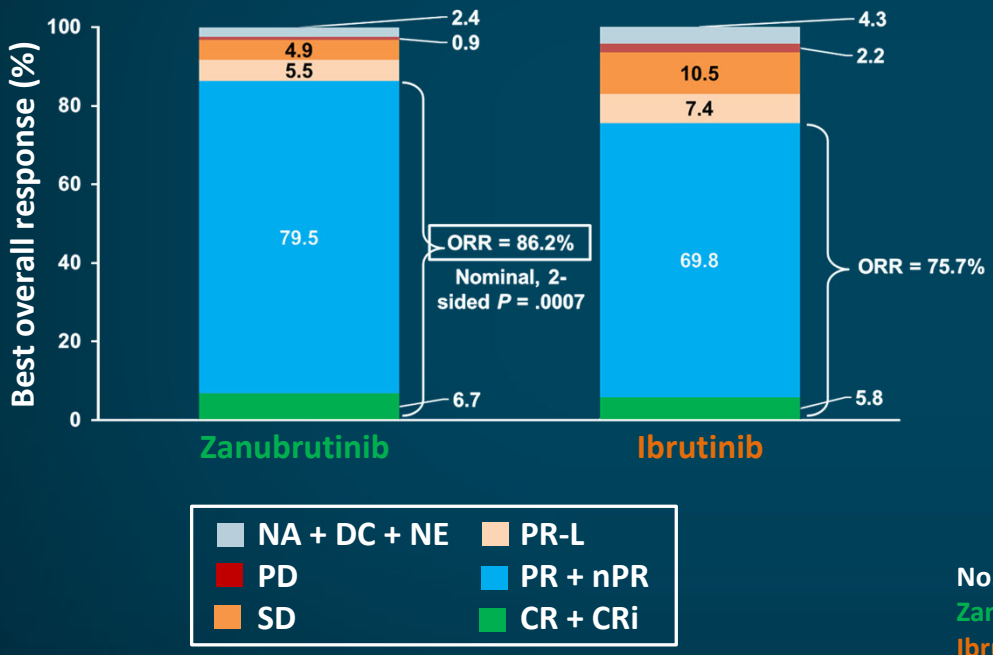
W6 Answer: A

Writer, 9/26/2024

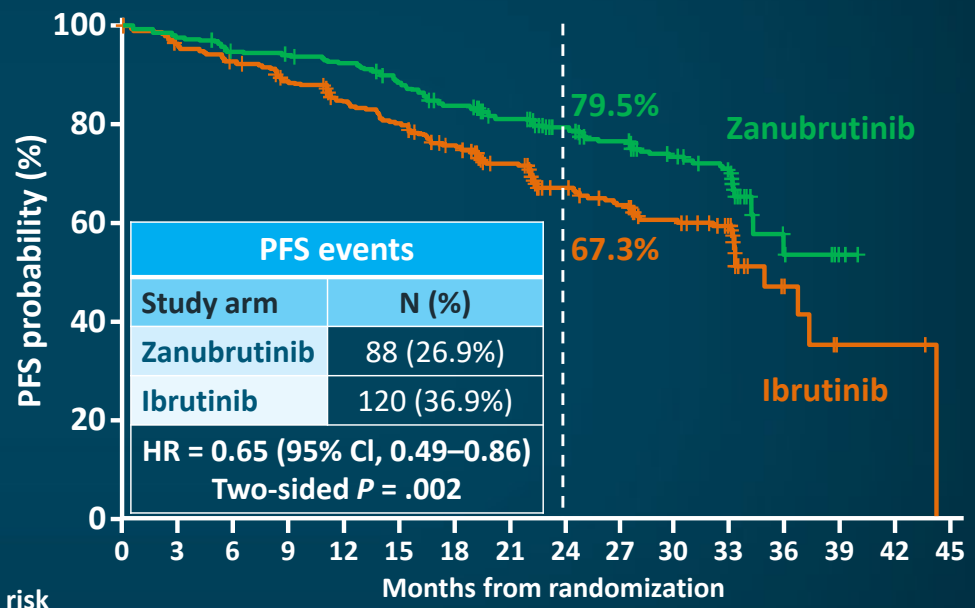
Zanubrutinib PFS by IRC Superior to Ibrutinib

Median study follow-up of 29.6 months

ORR by IRC in ITT population



PFS by IRC in ITT population



No. at risk

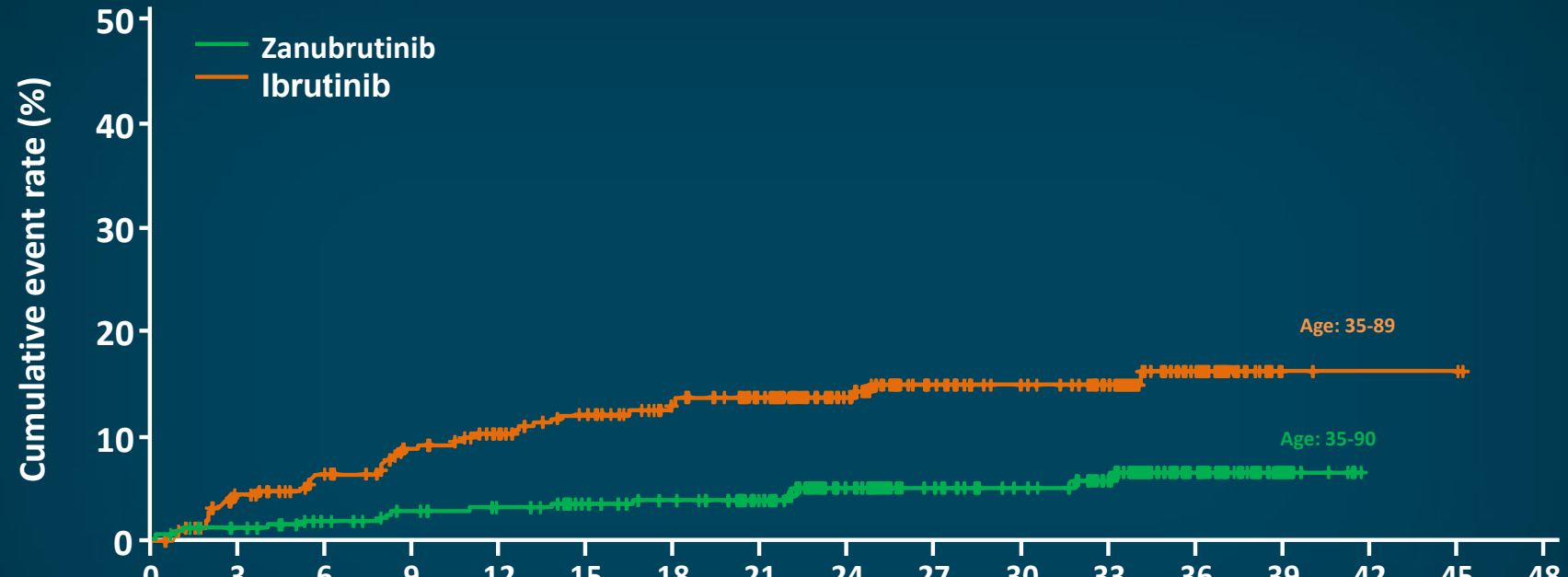
Zanubrutinib	327	315	304	301	294	280	263	261	172	161	125	113	14	2	0	0
Ibrutinib	325	305	293	277	260	246	228	191	133	122	98	87	9	2	2	0

Data cutoff: 8/8/2022.

DC = discontinued; NA = not assessed; nPR = nodular partial response; PR = partial response; PR-L = PR with lymphocytosis; SD = stable disease

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

Fewer Atrial Fibrillation/Flutter Events With Zanubrutinib



No. at risk											
Zanubrutinib	324	302	288	268	199	148	51	10	0	0	0
Ibrutinib	324	278	247	211	153	108	40	3	2	1	0

Data cutoff = 8/8/2022.

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

Zanubrutinib Had Favorable Cardiac Profile

- Lower rate of cardiac events, serious and/or fatal cardiac events, treatment discontinuation (15.4 vs 22.2)

- Lower rate of serious cardiac adverse events reported with zanubrutinib
  - Afib/flutter (n = 2)
  - MI/ACS (n = 2)
  - Congestive heart failure (n = 2)

- **Fatal cardiac events:**
  - **Zanubrutinib, n = 0 (0%)**
  - **Ibrutinib, n = 6 (1.9%)**

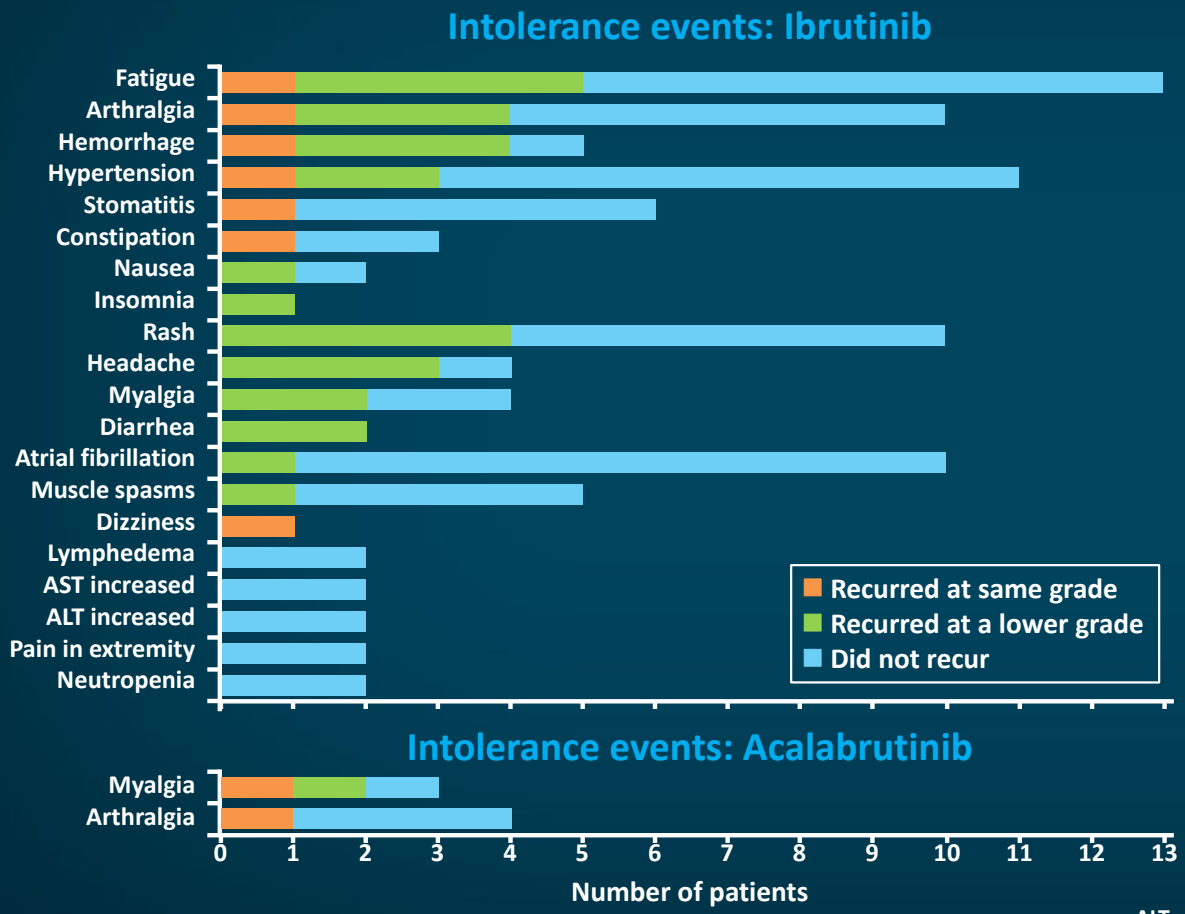
	Zanubrutinib (n = 324)	Ibrutinib (n = 324)
Cardiac adverse events	**69 (21.3%)**	**96 (29.6%)**
Serious cardiac AEs	**6 (1.9%)**	**25 (7.7%)**
Cardiac AEs leading to treatment discontinuation	**1 (0.3)**	**14 (4.3)**
Ventricular extrasystoles	1 (0.3)	0
Atrial fibrillation	0	5 (1.5)
Cardiac arrest	0	2 (0.6)*
Cardiac failure	0	2 (0.6)
Cardiac failure acute	0	1 (0.3)*
Congestive cardiomyopathy	0	1 (0.3)*
Myocardial infarction	0	1 (0.3)*
Palpitations	0	1 (0.3)
Ventricular fibrillation	0	1 (0.3)

***Cardiac deaths: 1 death not listed due to myocardial infarction with ibrutinib discontinuation due to diarrhea 14 days prior to fatal event.**

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

BGB-3111-215: BTKi Intolerance Trial

Low Recurrence of BTKi Intolerance on Zanubrutinib



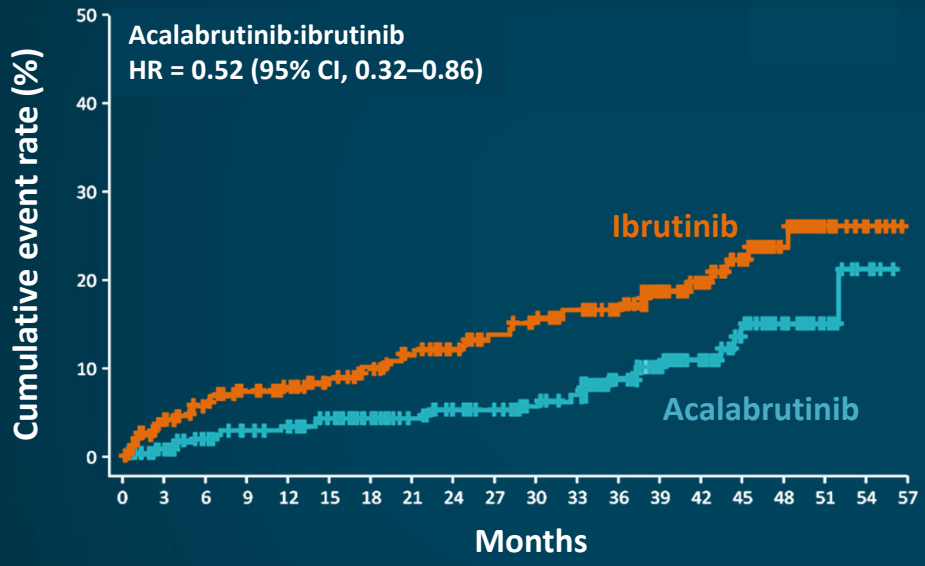
- Intolerable AEs experienced on ibrutinib or acalabrutinib were unlikely to recur with zanubrutinib
  - 72% of ibrutinib and acalabrutinib intolerance events did not recur with zanubrutinib
  - <10% recurrence of prior intolerance event led to zanubrutinib discontinuation
- Zanubrutinib was effective; 90% of disease was controlled or responded to therapy

Shadman M, et al. *Lancet Haematol.* 202310:e35-e45.

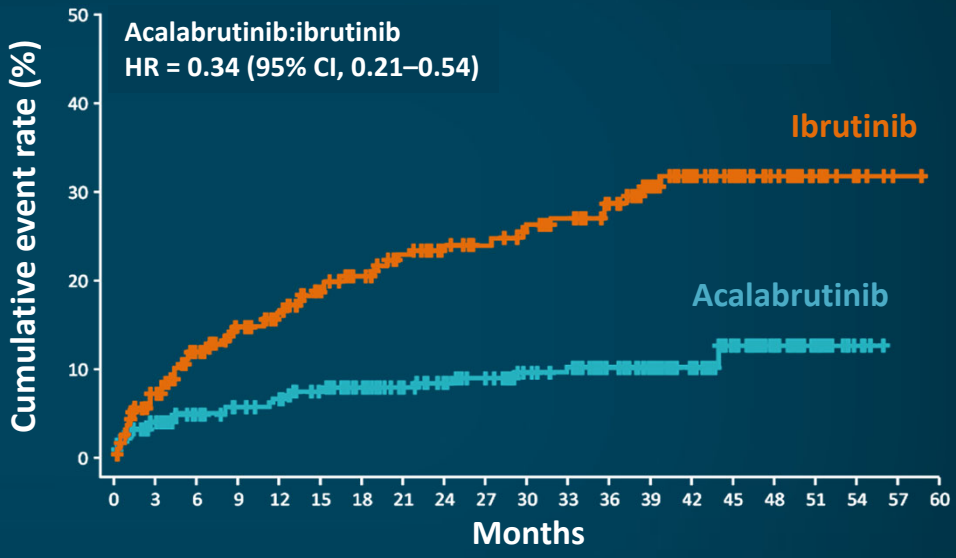
ALT = alanine aminotransferase; AST = aspartate aminotransferase.

ELEVATE RR: Lower Cumulative Incidence of Atrial Fibrillation and Hypertension With Acalabrutinib

Afib/flutter, any grade



Hypertension, any grade



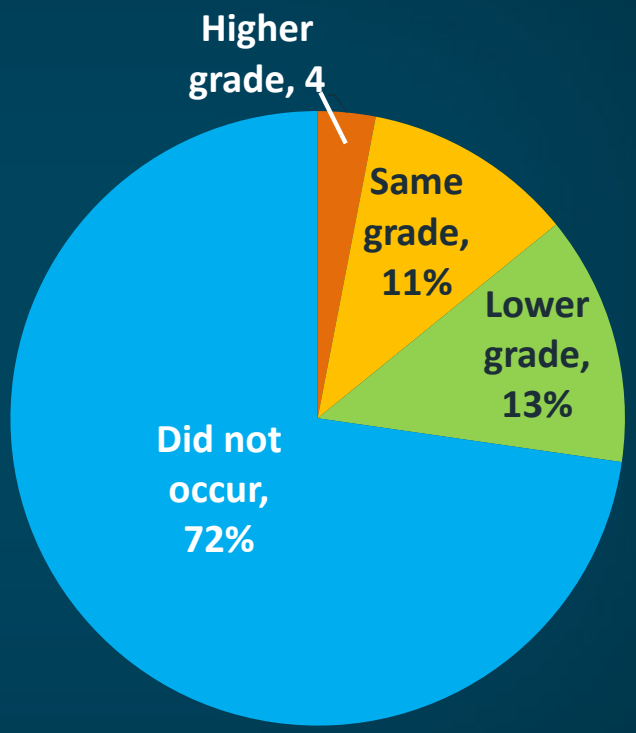
Overall, AEs led to treatment discontinuation in 14.7% of acalabrutinib-treated patients vs 21.3% of ibrutinib-treated patients

Afib = atrial fibrillation.

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

Phase 1/2 ACE-CL-001 Trial: Acalabrutinib in Ibrutinib-Intolerant Cohort

- Among 33 patients who could not tolerate ibrutinib, 23 remained on acalabrutinib
- No acalabrutinib dose reductions occurred
- Of 61 ibrutinib-related AEs, 72% did not recur and 13% recurred at a lower grade with acalabrutinib
- ORR = 76%
- Median PFS = not reached
- 1-yr PFS = 83.4%



Recurrence of ibrutinib-related adverse events (n = 61) during acalabrutinib treatment

Awan FT, et al. *Blood Adv*. 2019;3:15531562.

Retreatment with Venetoclax-Based Regimens After Prior Exposure

MURANO substudy (N = 25)[1]

Retreatment with VenR after VenR

Median prior LOT before first VenR = 2
92% had high-risk features

VenR — **Off treatment** — **VenR2**

Median time off treatment: **2.3 years**

Best ORR = 72.0%

Median PFS = **23.3 mo**

Retreatment 3-year OS = 53.1%

Multicenter retrospective study (N = 46)[2]

Retreatment with venetoclax-based regimens

Median prior LOT = 2 (0–10)
Prior BTKi = 40%

Ven1 — **Off treatment** — **Ven2**

ORR = 95.7%

Median time off Treatment **= 16 mo**

ORR = 79.5%

Median PFS **= 25 mo**

Ven1	Ven 2
Ven mono = 37%	Ven mono = 46%
VenR = 48%	VenR = 28%
VenO = 4%	VenO = 11%
IVen = 2%	IVen = 4%
Other = 9%	Other = 11%

IVen = ibrutinib + venetoclax; LOT = line of therapy; mono = monotherapy; Ven1 = first venetoclax treatment; Ven2 = second venetoclax treatment; VenR = venetoclax + rituximab; VenO = venetoclax + obinutuzumab; VenR2 = retreatment with VenR after VenR.

1. Kater A, et al. *HemaSphere.* 2023;7(suppl 3):229-231 (abstract S201). 2. Thompson MC, et al. *Blood Adv.* 2022;6:4553–4557.

10-year Therapy Timeline for a Typical CLL Patient

77-year-old man with moderate comorbidities needs frontline CLL therapy

Actuarial life expectancy for 77-year-old is 10 years

Covalent BTKi ~8 years → Noncovalent ~2 years → Ven-based

Total duration of CLL therapy: 10 years

1 year treatment: Ven + Obin ~7 years

1 year treatment: Ven + Obin ~3 years → BTKi

Total duration of CLL therapy = 2 years

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

Case Study 3

After starting **zanubrutinib,** Paul achieves a PR which lasts ~3 years. His counts remain relatively normal, but he is now noticing gradual but clear growth of his bilateral cervical and axillary lymph nodes, which are approaching 5 cm in maximum dimension. Paul is becoming more fatigued but is not having B symptoms, and his LDH is normal.

What would you treat Paul with next?

A) Ibrutinib
B) Obinutuzumab monotherapy
C) Duvelisib
D) R-CHOP
E) Pirtobrutinib

W7

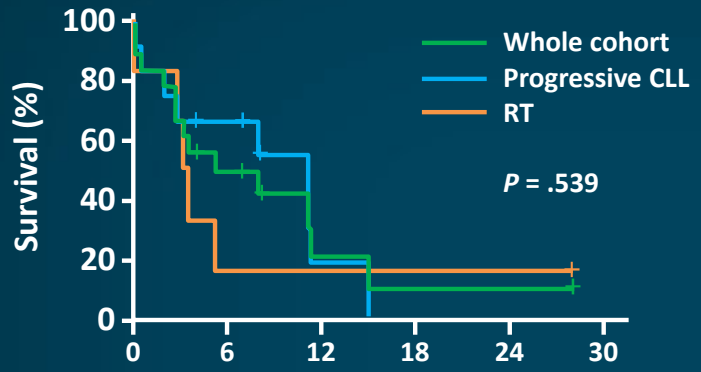
B symptoms = night sweats, fever, unintentional weight loss; LDH = lactate dehydrogenase; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

W7 Answer: E

Writer, 9/26/2024

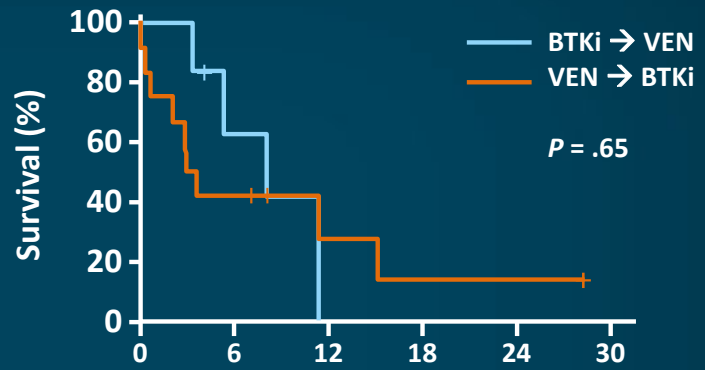
Outcomes for "Double Class Resistant" CLL Are Poor

2011 to 2020: 165 patients treated with Ven or BTKi → 42 double exposed → 18 double refractory



No. at risk						
Whole	18	8	2	1	1	0
CLL	12	7	1	0	0	0
RT	6	1	1	1	1	0

- Whole cohort median OS = 3.6 mo
- No difference in OS between progressive CLL (8.0 mo) and RT (3.3 mo)



No. at risk						
B > V	6	3	0	0	0	0
V > B	12	5	2	1	1	0

- No difference in OS between BTKi → VEN (5.3 mo) and VEN → BTKi (2.9 mo)

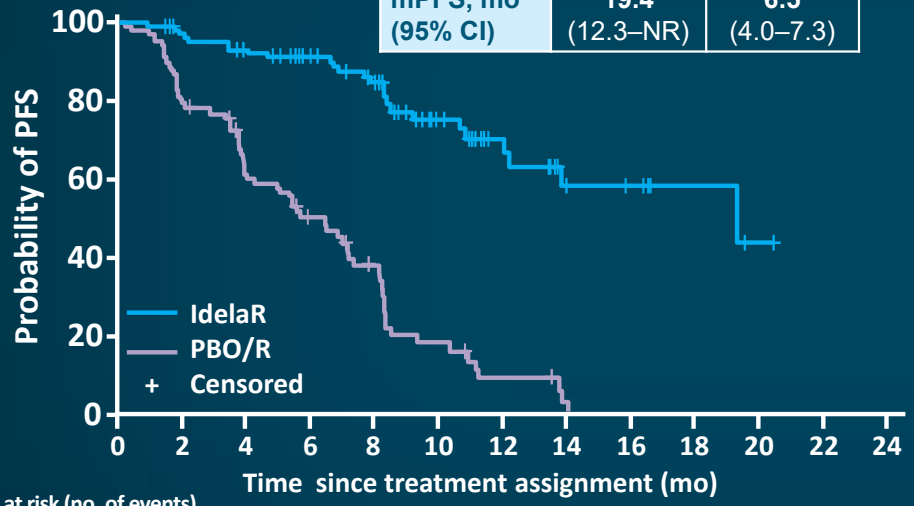
RT = Richter transformation.

Lew TE, et al. *Blood Adv.* 2021;5:4054-4058.

PI3Ki Are Approved for R/R, but Trial Data Are in Post-CIT Population: Toxicity Concerns Remain

Idelalisib + rituximab

	IdelaR (n = 110)	PBO/R (n = 110)
mPFS, mo (95% CI)	19.4 (12.3–NR)	6.5 (4.0–7.3)

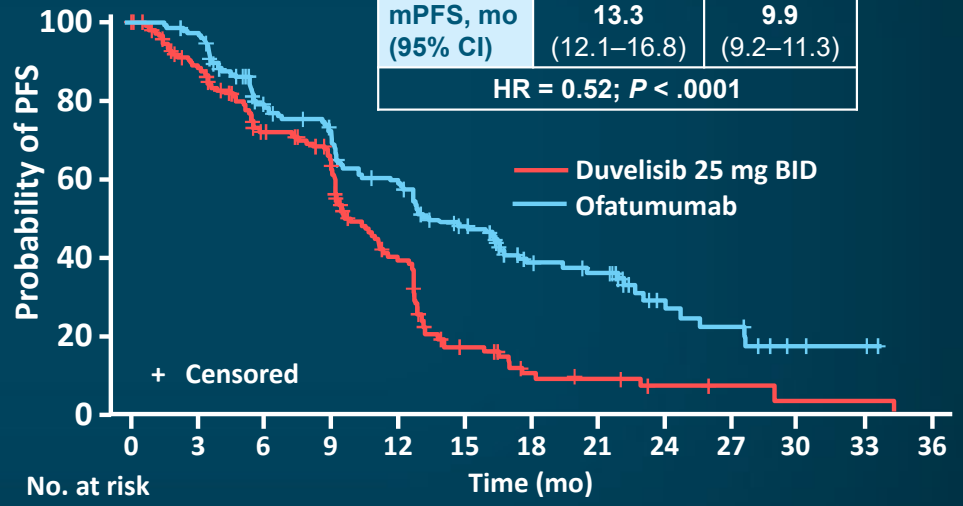


No. at risk (no. of events)

IDELA/R	110 (0)	101 (3)	93 (7)	73 (9)	59 (14)	31 (19)	20 (21)	9 (24)	7 (24)	4 (24)	1 (25)	0 (25)
PBO/R	110 (0)	84 (21)	48 (38)	29 (46)	20 (53)	9 (63)	4 (67)	1 (69)	0 (70)	0 (70)	0 (70)	0 (70)

Duvelisib

	DUV (n = 160)	OFA (n = 159)
mPFS, mo (95% CI)	13.3 (12.1–16.8)	9.9 (9.2–11.3)
HR = 0.52; *P* < .0001		



No. at risk

DUV	159	126	95	77	43	15	7	6	3	2	1	1	0
OFA	160	149	108	95	78	58	33	29	13	10	3	2	0

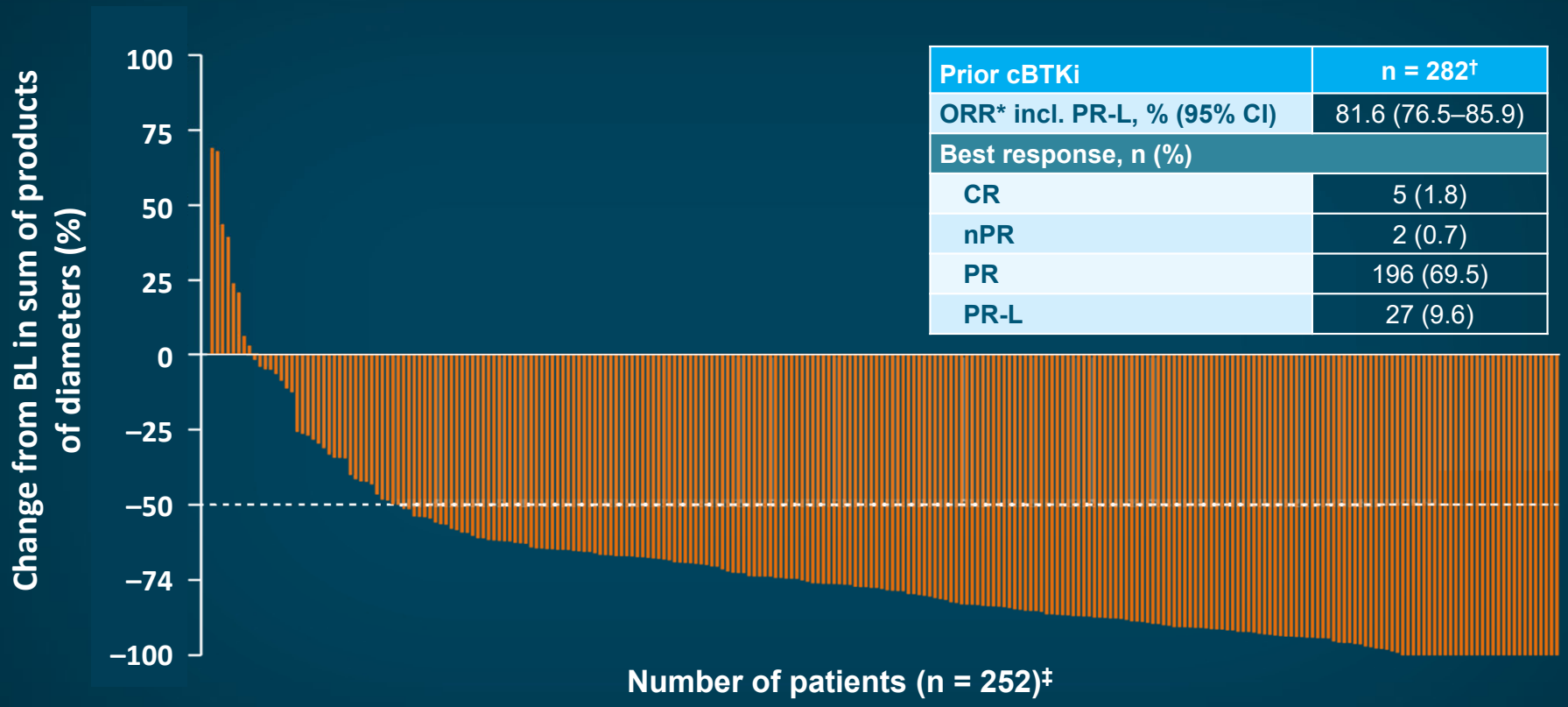
Immune-mediated toxicities include transaminitis, diarrhea/colitis, pneumonitis, infection

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

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

W1

Pirtobrutinib Efficacy in Patients with CLL/SLL Who Received Prior cBTKi



Prior cBTKi	n = 282†
ORR* incl. PR-L, % (95% CI)	81.6 (76.5–85.9)
Best response, n (%)	
CR	5 (1.8)
nPR	2 (0.7)
PR	196 (69.5)
PR-L	27 (9.6)

*ORR including PR-L is number of patients with best response of PR-L or better divided by total number of patients; 14 patients with best response of not evaluable (NE) are included in denominator; †Post-cBTKi patients included subgroup of 19 patients with 1 prior line of cBTKi-containing therapy and 2L therapy of pirtobrutinib, who had ORR including PR-L of 89.5% (95% CI: 66.9-98.7); ‡Data for 30/282 patients are not shown in waterfall plot due to no measurable target lesions identified by CT at BL, discontinuation prior to first response assessment, or lack of adequate imaging in follow-up.

BL = baseline.

Thompson PA, Tam CS. *Blood* (2023) 141 (26): 3137–3142.

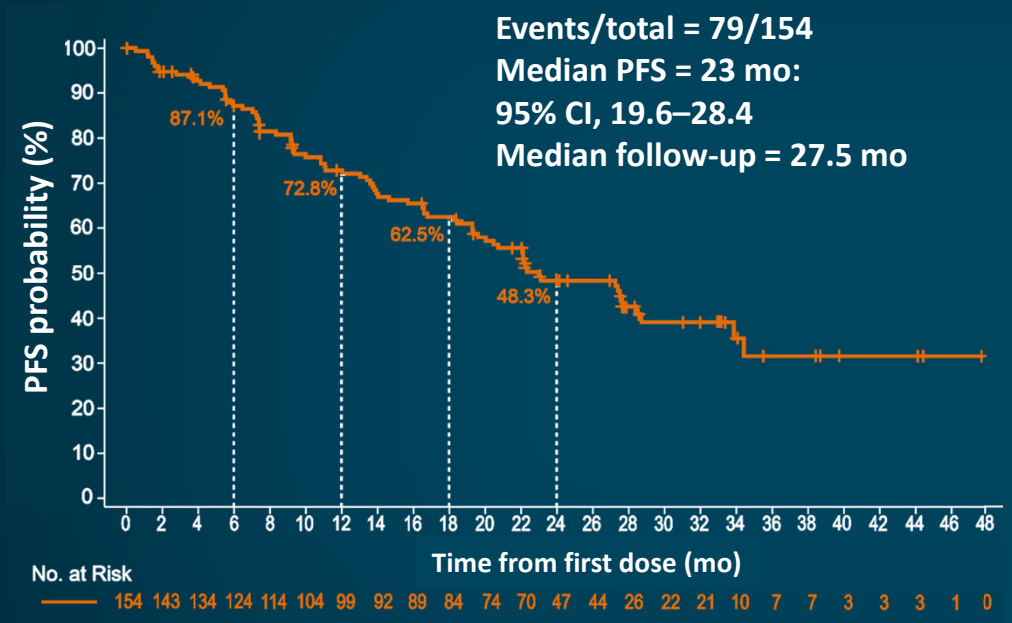
Slide 37

W1 Dr. Davids.Can we get a reference for this slide please?
Writer, 9/19/2024

Pirtobrutinib PFS With Prior cBTKi and With/Without Prior BCL2i

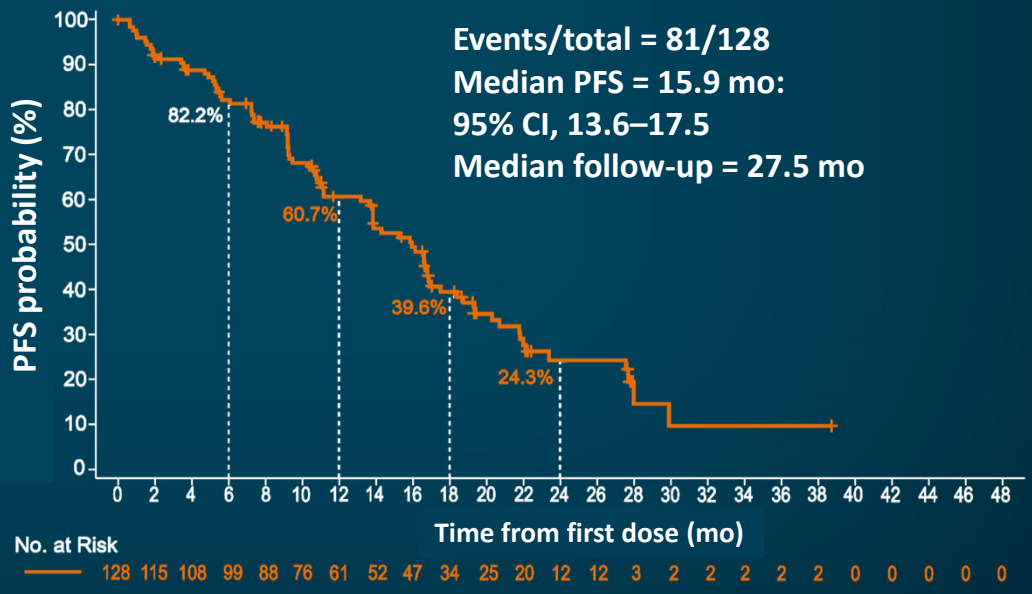
BCL2i-Naive

Events/total = 79/154
Median PFS = 23 mo:
95% CI, 19.6–28.4
Median follow-up = 27.5 mo



BCL2i-Exposed

Events/total = 81/128
Median PFS = 15.9 mo:
95% CI, 13.6–17.5
Median follow-up = 27.5 mo



Woyach JA, et al. *Blood.* 2023;142(suppl 1):325-330.

Pirtobrutinib Safety Profile of Patients Who Received Prior cBTKi

	Treatment-Emergent AEs in Patients with CLL/SLL (N = 317)			
	All cause AEs in ≥20% (%)		Treatment-related AEs (%)	
Adverse event	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Fatigue	31.5	1.9	3.5	0.3
Diarrhea	26.5	0.6	8.8	0.3
Cough	24.3	0.0	1.6	0.0
Contusion	24.3	0.0	16.4	0.0
Covid-19	24.0	5.0	1.6	0.0
AEs of interest	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Infections	71.0	28.1	12.3	3.8
Bleeding	42.6	2.2	23.7	0.9
Neutropenia	32.5	26.8	19.6	14.8
Bruising	30.3	0.0	19.6	0.0
Hemorrhage	21.1	2.2	6.9	0.9
Hypertension	14.2	3.5	3.8	0.3
Atrial fibrillation/flutter	3.8	1.3	1.3	0.3

- Median time on treatment was 18.7 mo (prior cBTKi), 24.3 mo (BCL2i-N) and 15.3 mo (BCL2i-E)
- 11 (3.9%; 9 BCL2i-N, 2 BCL2i-E) patients had treatment-related AEs leading to pirtobrutinib dose reduction
- 7 (2.5%; 4 BCL2i-N, 3 BCL2i-E) patients had treatment-related AEs leading to pirtobrutinib discontinuation

Mato AR, et al. *N Engl J Med.* 2023;389:33-44. Woyach JA, et al. *Blood.* 2023;142(suppl 1):325-330.

Nemtabrutinib is Another Noncovalent BTKi That Is Active in Double-Refractory CLL

Patients with CLL/SLL treated with nemtabrutinib 65 mg QD (N = 57)

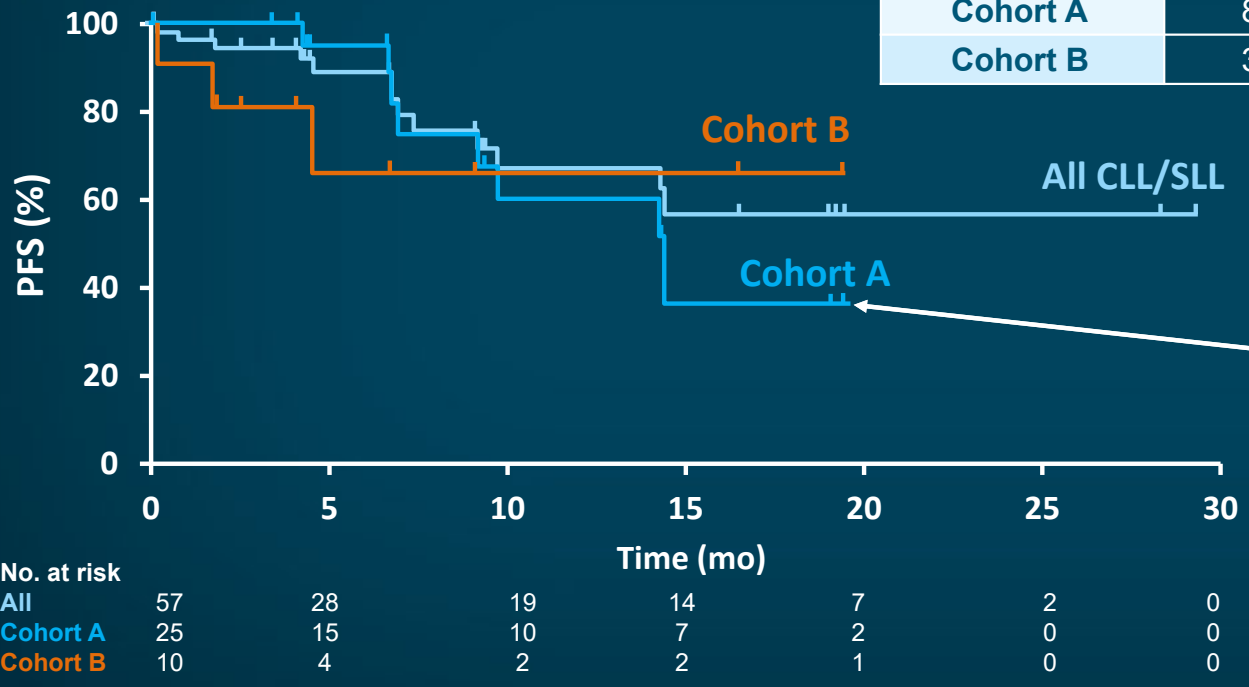
	CLL/SLL with prior BTK and BCL-2 inhibitors	C481S-mutated BTK	del(17p)	IGHV unmutated
n (%)	24 (42)	36 (63)	19 (33)	30 (53)
ORR, % (95% CI)	58 (37–78)	58 (41–75)	53 (29–76)	50 (31–69)
Objective response, n (%) CR PR PR with residual lymphocytosis	14 (58) 0 6 (25) 8 (33)	21 (58) 1 (3) 11 (31) 9 (25)	10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

Woyach JA, et al. *Blood.* 2022;140(suppl 1): 7004-7006 (abstract 3114).

BELLWAVE-001

Nemtabrutinib Is Effective Against BTK Resistance Mutations

	PFS events n/N, %	Median PFS (95% CI), mo
All CLL/SLL	13/57 (23)	NE (10.6–NE)
Cohort A	8/25 (32)	15.7 (7.6–NE)
Cohort B	3/10 (30)	NE (5.0–NE)



No. at risk							
All	57	28	19	14	7	2	0
Cohort A	25	15	10	7	2	0	0
Cohort B	10	4	2	2	1	0	0

Cohort A: patients with R/R CLL/SLL who received ≥2 prior therapies, including covalent BTKi, and who have a C481S mutation

Woyach J et al. HemaSphere. 2022;6(suppl 3):1110-1111 (abstract P682).

BELLWAVE-001: Nemtabrutinib Safety

All Patients at 65 mg QD N = 112		
TRAEs, n (%)	**All**	**Grade ≥3**
Any TRAEs	82 (73)	45 (40)
Selected TRAEs ≥5%		
Dysgeusia	23 (21)	0 (0)
Neutrophil count decreased	22 (20)	19 (17)
Fatigue	14 (13)	2 (2)
Platelet count decreased	13 (12)	5 (4)
Nausea	13 (12)	0 (0)
Hypertension	11 (10)	4 (4)
Diarrhea	11 (10)	2 (2)

TRAE = treatment-related AE.

Woyach JA, et al. *Blood*. 2022;140(suppl 1): 7004-7006 (abstract 3114).

Emerging Data and Future Directions

Phase 3 GLOW Study: Fixed-Duration Ibr+Ven vs Clb+O for TN CLL in Elderly or Unfit Patients

Key eligibility criteria

- Previously untreated CLL
- ≥65 years of age or <65 years with CIRS >6 or CrCl <70 mL/min
- No del(17p) or known *TP53* mutation
- ECOG PS ≤2

R 1:1

Ibrutinib 420 mg PO QD lead-in (3 cycles) followed by **ibrutinib + venetoclax (Ibr+Ven)** (12 cycles; venetoclax ramp-up 20–400 mg over 5 weeks beginning C4)
n = 106

Chlorambucil (Clb) 0.5 mg/kg on D1 and D15 x 6 cycles +
Obinutuzumab (O) 1000 mg D1–2, D8, D15 of C1, and D1 of C2-6
n = 105

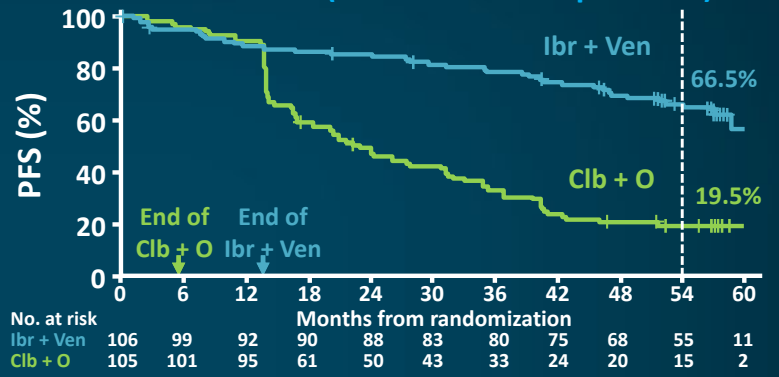
Primary endpoint: IRC-assessed PFS
Secondary endpoints: uMRD rates, CR, ORR OS, TTNT, safety

Safety	Ibr+Ven (n = 106)		Clb+O (n = 105)	
Total number of deaths	19		39	
Reasons for deaths, n	On Tx	Post randomized Tx	On Tx	Post randomized Tx
Infection related	1	3	1	13
Second primary malignancy	1	1	0	7
Cardiac	2	0	0	4
Sudden/unknown	2	3	0	4
Progressive disease	0	1	0	2
Vascular disorders	1	2	0	3
Other	0	2	1	4
Total	7	12	2	37

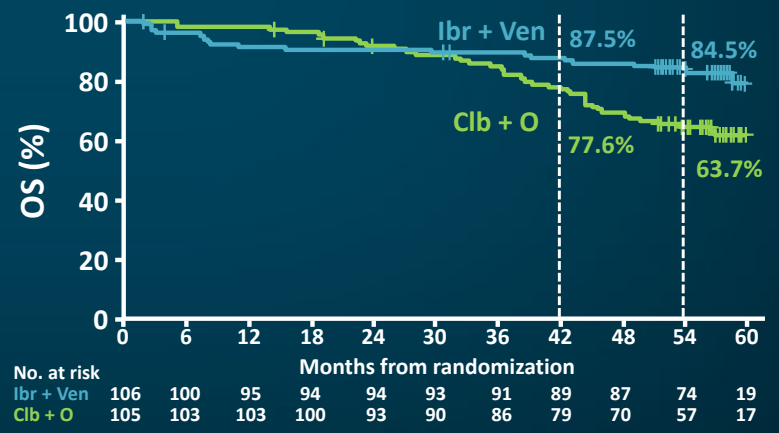
CIRS = Cumulative Illness Rating Scale; CrCl = creatinine clearance; PO = by mouth.

Moreno C, et al. ASH. 2023: Abstract 634; Kater AP, et al. NEJM Evid 2022;1(7).

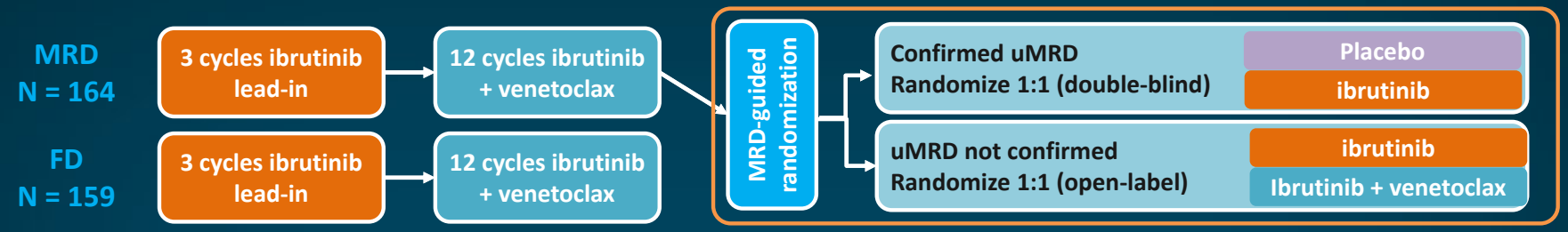
INV-assessed PFS (median follow-up: 57 mo)

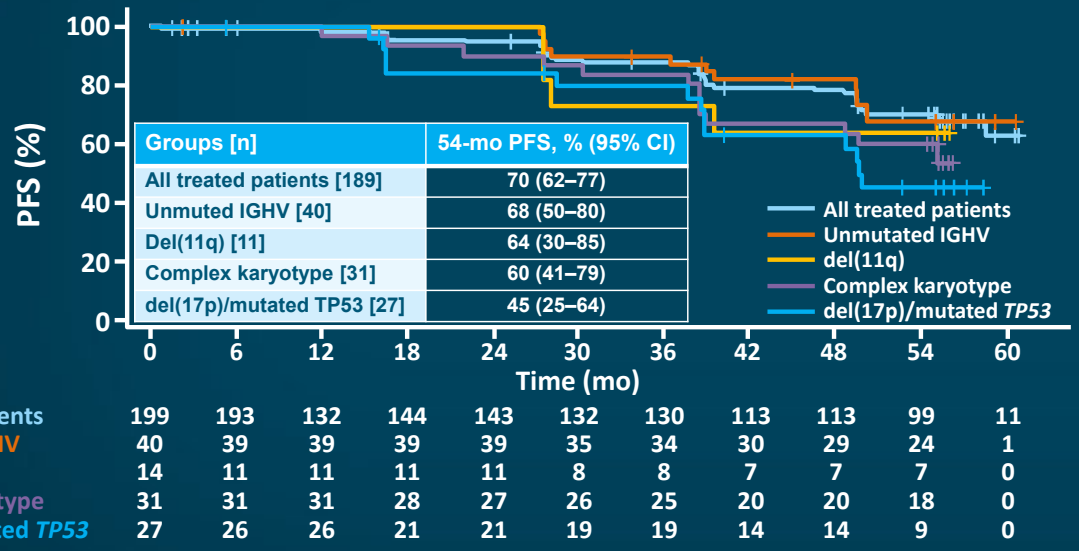


OS (median follow-up: 57 mo)



CAPTIVATE MRD Cohort: 5-year Follow-up and Retreatment Data

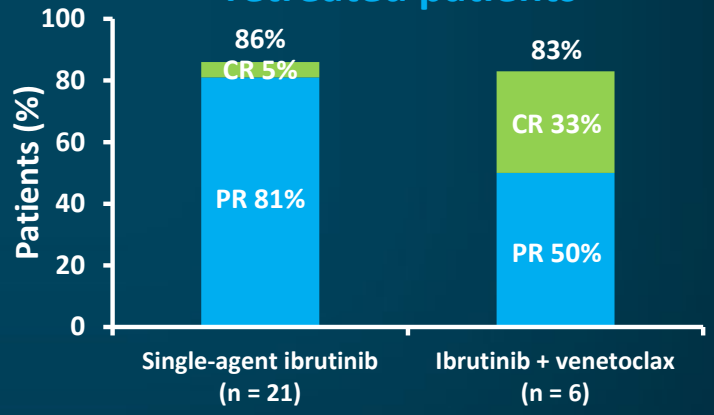




Groups [n]	54-mo PFS, % (95% CI)
All treated patients [189]	70 (62–77)
Unmuted IGHV [40]	68 (50–80)
Del(11q) [11]	64 (30–85)
Complex karyotype [31]	60 (41–79)
del(17p)/mutated TP53 [27]	45 (25–64)

No. at risk											
All treated patients	199	193	132	144	143	132	130	113	113	99	11
Unmutated IGHV	40	39	39	39	39	35	34	30	29	24	1
del(11q)	14	11	11	11	11	8	8	7	7	7	0
Complex karyotype	31	31	31	28	27	26	25	20	20	18	0
del(17p)/mutated *TP53*	27	26	26	21	21	19	19	14	14	9	0

Best response in evaluable retreated patients



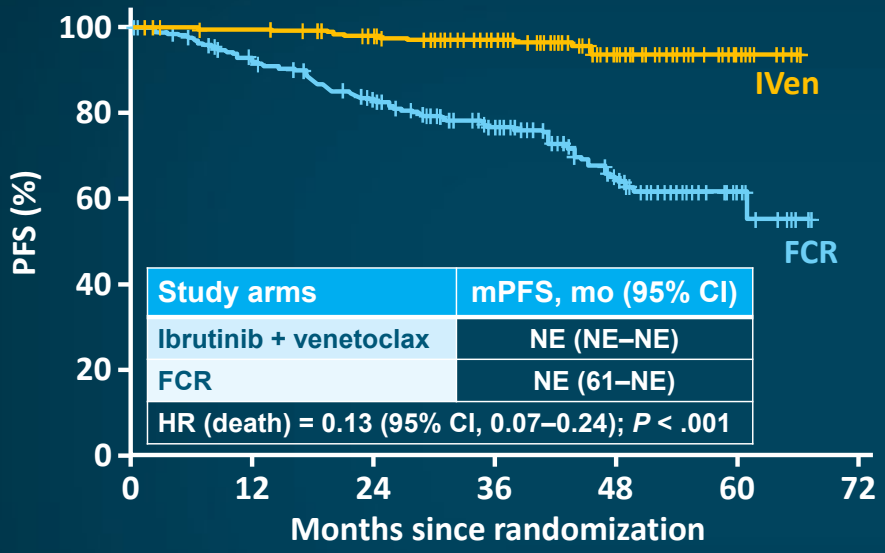
- Median PFS not yet reached for all genetic subgroups except TP53 aberrant
- Retreatment with either ibrutinib monotherapy or repeat IVen was effective for most

Ghia P, et al. ASH. 2023: Abstract 633.

FD = fixed dose.

UK FLAIR: MRD-Guided Ibrutinib + Venetoclax vs FCR

PFS for all patients

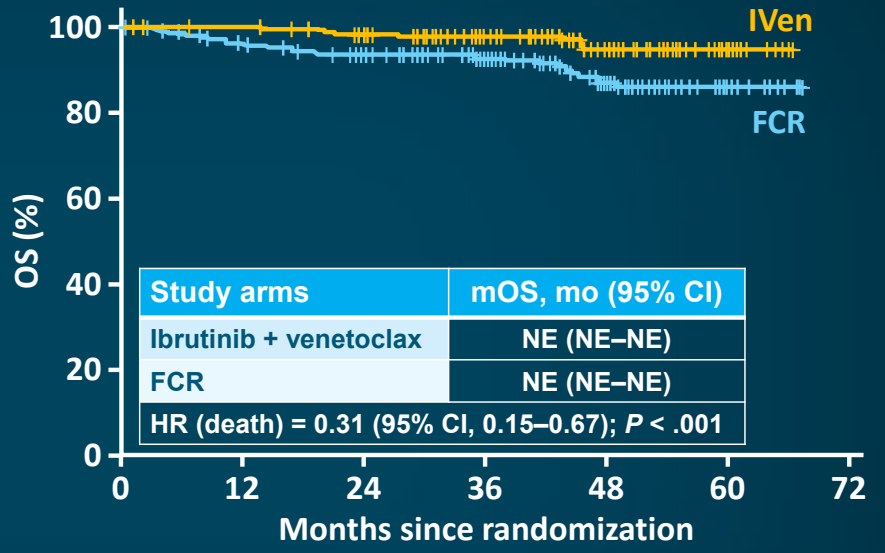


Study arms	mPFS, mo (95% CI)
Ibrutinib + venetoclax	NE (NE–NE)
FCR	NE (61–NE)
HR (death) = 0.13 (95% CI, 0.07–0.24); *P* < .001	

No. at risk (censored)

IVen	260(1)	253 (6)	239 (16)	183 (70)	99 (151)	21 (227)	0 (248)
FCR	263 (2)	227 (18)	194 (28)	145 (63)	68 (126)	12 (177)	0 (188)

OS for all patients



Study arms	mOS, mo (95% CI)
Ibrutinib + venetoclax	NE (NE–NE)
FCR	NE (NE–NE)
HR (death) = 0.31 (95% CI, 0.15–0.67); *P* < .001	

No. at risk (censored)

IVen	260(1)	254 (6)	240 (16)	185 (70)	100 (153)	22 (229)	0 (251)
FCR	263 (2)	234 (19)	213 (34)	166 (80)	79 (162)	15 (223)	0 (238)

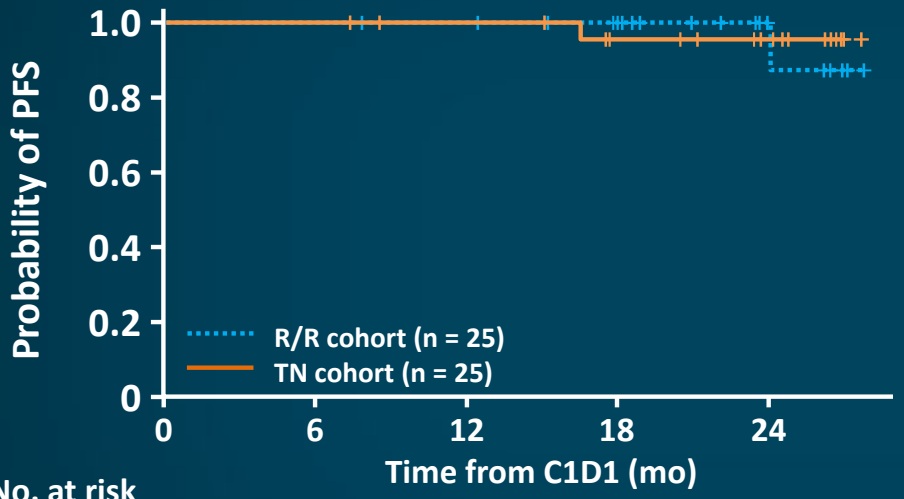
- PFS and OS advantage of MRD-guided IVen vs FCR
- Higher cytopenias and SPM with FCR, higher CV toxicity with IVen (1 Gr 5 event on therapy)

CV = cardiovascular; mOS = median OS; SPM = second primary malignancy.

Munir T, et al. *N Engl J Med.* 2024;390:326-337.

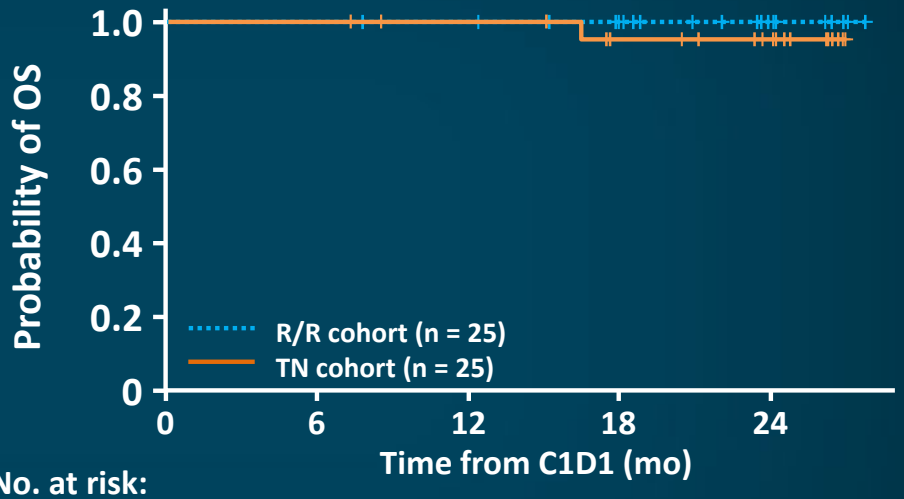
Triplet Therapy With IVO Is Active but Ibrutinib-Related Toxicities Are Observed

Progression-free survival



No. at risk					
R/R cohort	25	24	23	18	8
TN cohort	25	25	23	18	13

Overall survival



No. at risk:					
R/R cohort	25	24	23	18	8
TN cohort	25	25	23	18	13

Cardiovascular toxicities were common: Hypertension = 82%; Afib = 10%

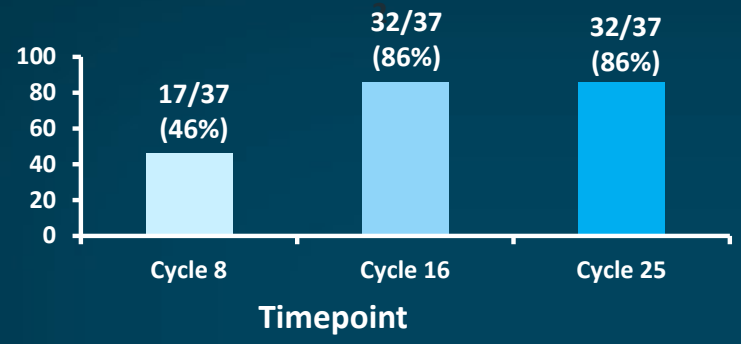
IVO = ibrutinib + venetoclax + obinutuzumab.

Rogers KA, et al. *J Clin Oncol*. 2020;38:3626-3637.

Triplets With More Specific BTKi Are Also Active, Well-tolerated

Phase 2 AVO Trial[1]

Bone marrow MRD Response



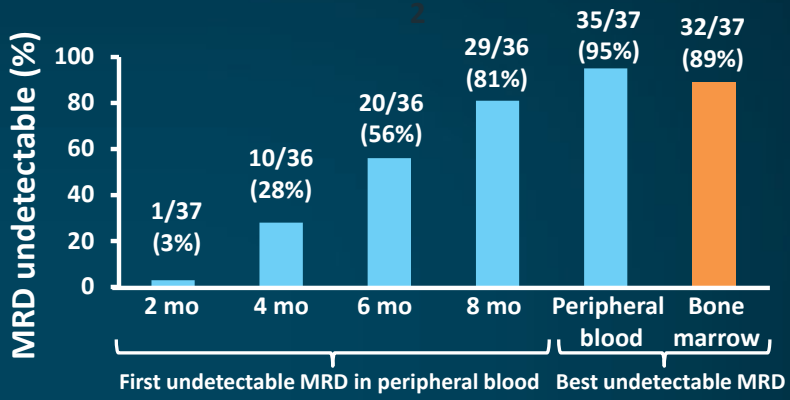
Safety profile

AEs (N = 37), %		All grades	Grade ≥3
Most frequent hematologic	Neutropenia	84	43
	Thrombocytopenia	81	27
	Anemia	59	5
Nonhematologic (≥50%)	Fatigue	89	3
	Headache	76	3
	Bruising	59	0
AEs of special interest	IRR	25	3
	Hypertension	11	0
	Atrial fibrillation	3	3
	Laboratory TLS	5	5

GERD = gastroesophageal reflux disease; IRR = infusion-related reaction.

Phase 2 BOVen Trial[2]

MRD Response

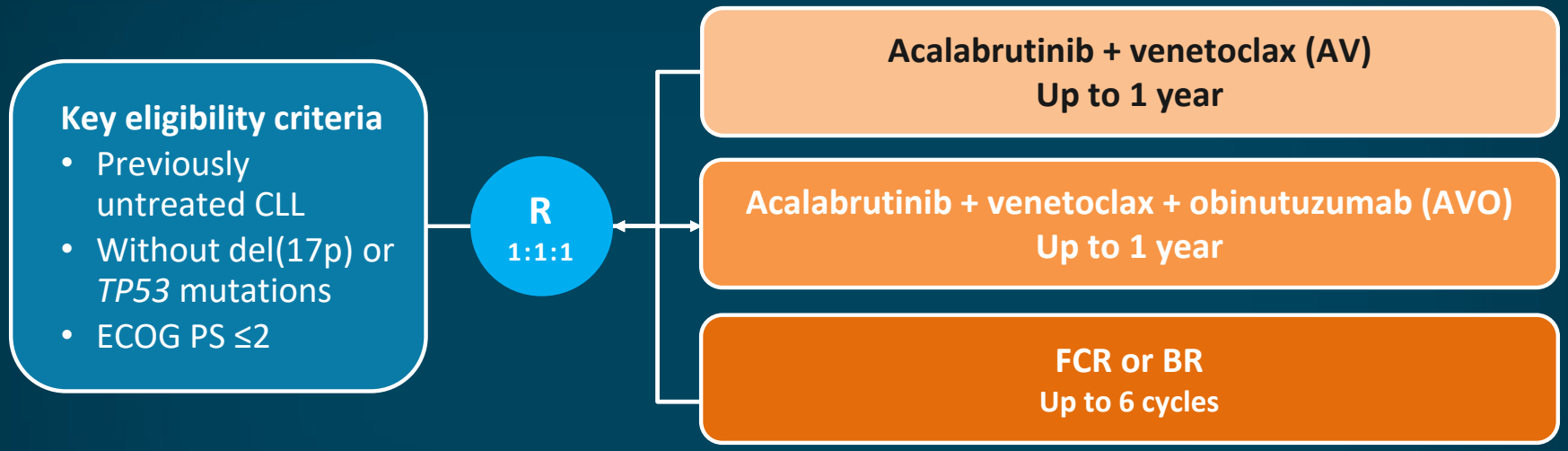


Safety profile

	Grade 1–2	Grade 3	Grade 4
Thrombocytopenia	20 (51%)	3 (8%)	0
Fatigue	20 (51%)	1 (3%)	0
Neutropenia	13 (33%)	2 (5%)	5 (13%)
Bruising	20 (51%)	0	0
Diarrhea	18 (46%)	0	0
IRR	15 (39%)	1 (3%)	1 (3%)
Anemia	16 (41%)	0	0
Cough	14 (36%)	0	0
Rash	10 (26%)	3 (8%)	0
Nausea	12 (31%)	0	0
Constipation	11 (28%)	0	0
Nasal congestion	10 (26%)	0	0
GERD	10 (26%)	0	0
Insomnia	9 (23%)	0	0
Myalgia	9 (23%)	0	0
Arthralgia	8 (21%)	0	0

1. Davids MS, et al. *Lancet Oncol*. 2021;22:1391-1402. 2. Soumerai JD, et al. *Lancet Haematol*. 2021;8:e879-e890.

AMPLIFY (ACE-CL-311): Phase 3 Study of Acalabrutinib + Venetoclax ± Obinutuzumab vs FCR/BR in TN CLL Without Del(17p) or TP53 Mutations



- **Primary endpoint:** PFS (IRC assessed) of AV vs FCR/BR
- **Key secondary endpoints:** PFS (IRC assessed) of AVO vs FCR/BR and PFS (INV assessed) of AV vs FCR/BR

BR = bendamustine, rituximab; FCR = fludarabine, cyclophosphamide, rituximab

NCT03836261. (https://clinicaltrials.gov/ct2/show/NCT03836261). Accessed 9/10/24.

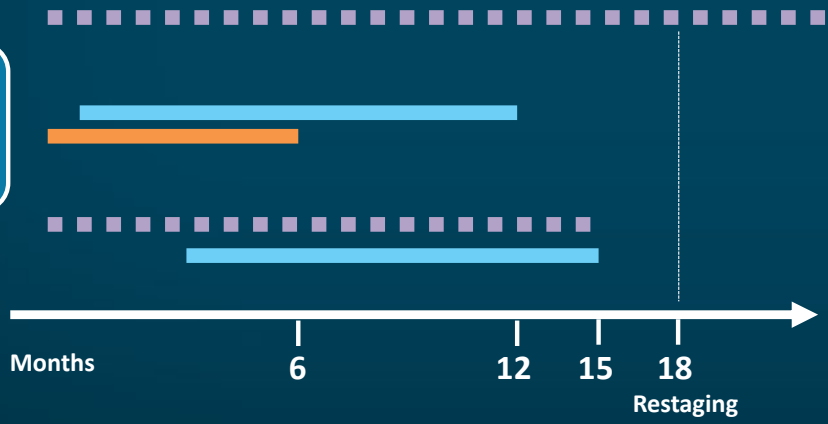
CLL17 Trial Is Comparing Continuous BTKi to Time-Limited Venetoclax-Based Doublets

CLL17[1,2]

Phase 3 trial in 1L CLL, including those with adverse prognostic factors

- **Ibrutinib monotherapy**
- **Venetoclax + Obinutuzumab**
- **Venetoclax + Ibrutinib**

Stratification by fitness, del(17p)/*TP53*^{mut}, IGHV
Randomization[2]



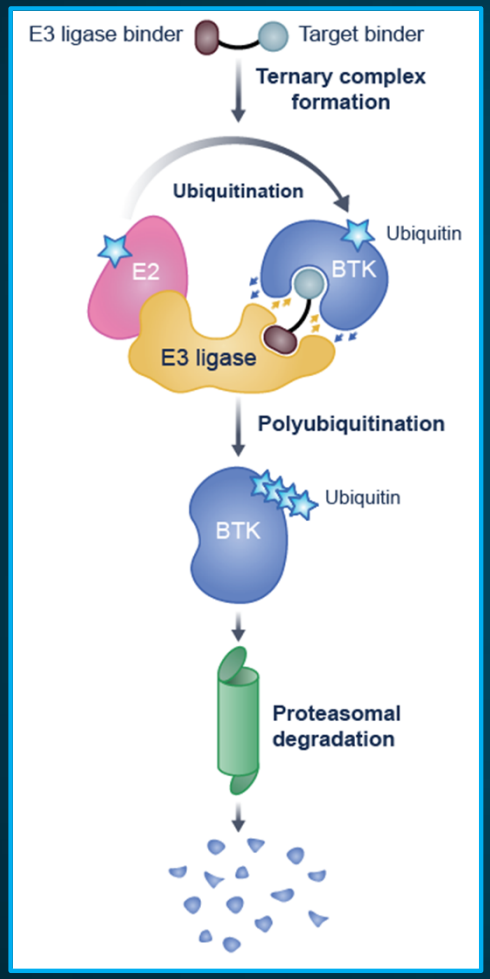
Ibrutinib D1 420 mg PO daily until PD or intolerance

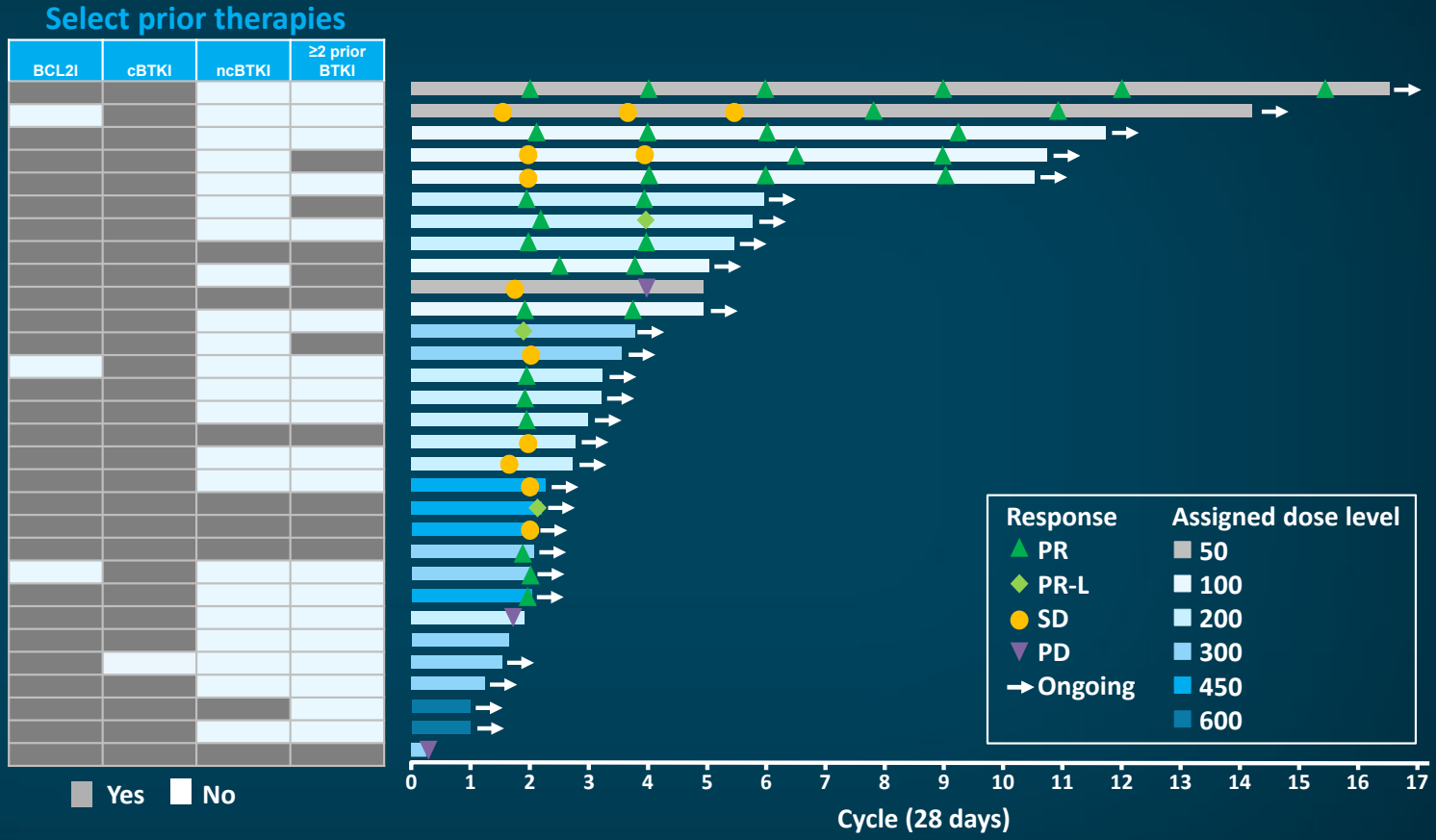
Venetoclax 400 mg PO daily (C1 D22–C12 D28)
Obinutuzumab 1000 mg IV (C1 D1(2)/8/15, C2–6 D1)

Ibrutinib 420 mg PO daily (C1 D1–C15 D28)
Venetoclax 400 mg PO daily (C5 D1–C15 D28)

1. NCT04608318. (www.clinicaltrials.gov/ct2/show/NCT04608318). 2. DCLLSG. CLL17 Trial (www.dcllsg.de/en/trial/cll17/CLL17_Synopsis_v1.2_20200923.pdf). URLs accessed 9/10/24.

BTK Degraders: NX-5948





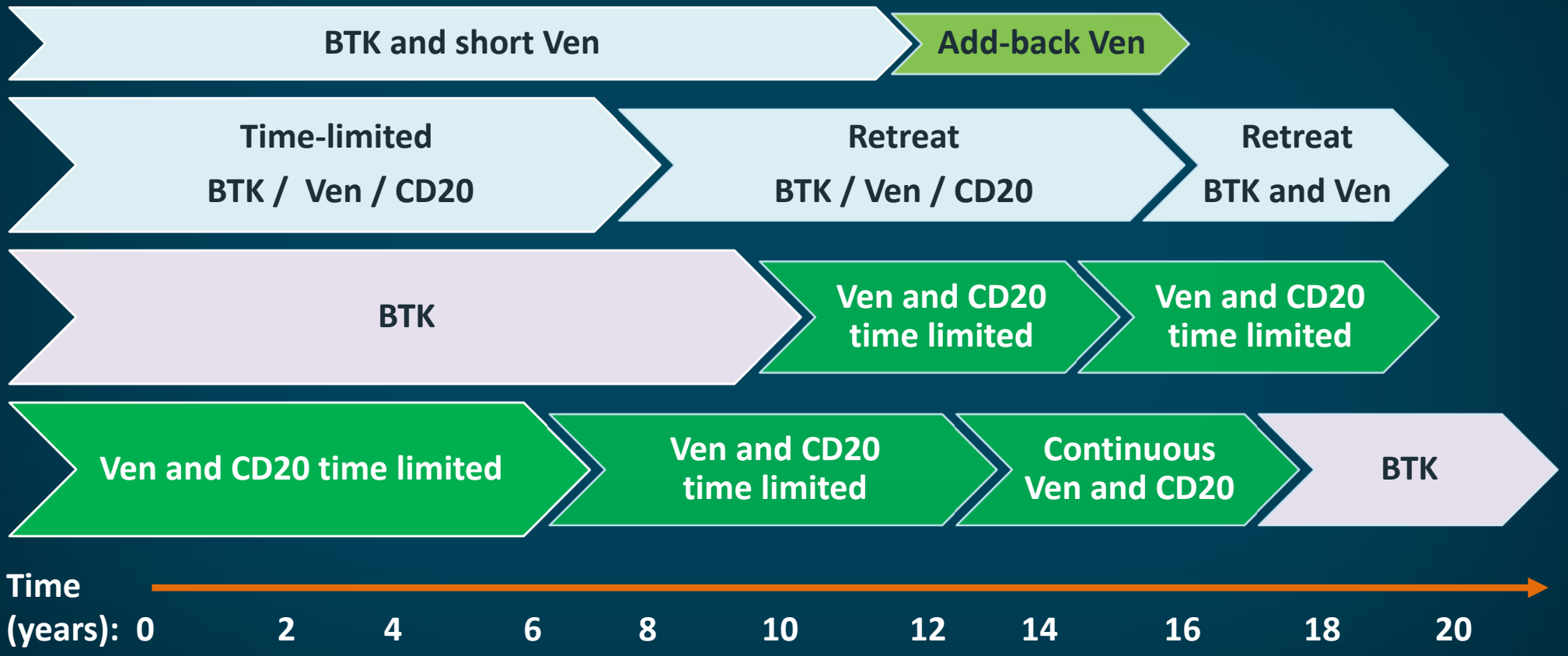
CLL disease-evaluable patients, n = 26	
ORR, % (95% CI)	69.2 (48.2–85.7)

Linton K, et al. *EHA*. 2024 (www.nurixtx.com/wp-content/uploads/2024/06/EHA-2024-Oral-FINAL.pdf). Accessed 9//10/24.

Other Novel Therapies in Development

- Noncovalent BTK inhibitors (e.g. Nemtabrutinib)
- BTK degraders (e.g. NX-5948 and BGB-16673)
- CAR-T with (e.g. Liso-cel)
- Bispecific antibodies (e.g. Epcoritamab)

Many Active Sequences in CLL Present Opportunities and Challenges



Importance of Shared Decision-Making in CLL

Introduce choice

- Planning step
- Identify problem
- Offer choice
- Check reaction
- Ensure patients understand your respect for their preferences and uncertainty in treatment

Describe options

- Determine what the patient already knows
- List and describe options, including risks and benefits
- Use decision aids to help patients understand their options and make value-based decisions
- Teach-back to determine understanding

Help make decisions

- Focus on preferences
- Agree on a treatment plan
- Ensure patient understands that plan can be modified and decisions can be reviewed at any time

Modified from Elwyn G, et al. *J Gen intern Med*. 2012;27:1361-1367.

Key Take-Aways for Frontline

- Role of CIT in CLL is very limited
- Continuous BTKi is a highly effective approach
- 2nd-generation BTKi (acalabrutinib and zanubrutinib) now preferred over ibrutinib
- Venetoclax + obinutuzumab is time-limited, with durable benefit and potential for retreatment
- Discussions of continuous vs time-limited therapy should be individualized
- Venetoclax + BTKi (± CD20) data are maturing, but combination is not yet approved in the US
- MRD-guided therapy duration may be on the horizon

Key Take-Aways for R/R CLL

- Patients with progression on BTKi or continuous venetoclax are best treated with the other agent
- 2nd generation BTKi (acalabrutinib and zanubrutinib) are safer than ibrutinib and possibly more efficacious (zanubrutinib)
- Patients who stop BTKi for AEs can receive next-generation cBTKi (or venetoclax)
- Patients with progression on covalent BTKi should **NOT** be treated with another covalent BTKi
- Patients who received time-limited venetoclax ± anti-CD20 antibody can be retreated

Key Take-Aways for R/R CLL (Contd)

- Progression on both BTKi and venetoclax is challenging clinical scenario
- Noncovalent BTKi, such as pirtobrutinib and nemtabrutinib, are promising in this population
- BTK degraders are also showing early promise
- CAR-T with liso-cel is active in a minority of double-refractory patients; bispecific antibodies are on horizon
- Active participation in clinical trials remains critical

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REFERENCE TOOLKIT:

REFERENCE	LINK
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