How I treat high-risk relapsed refractory CLL patient

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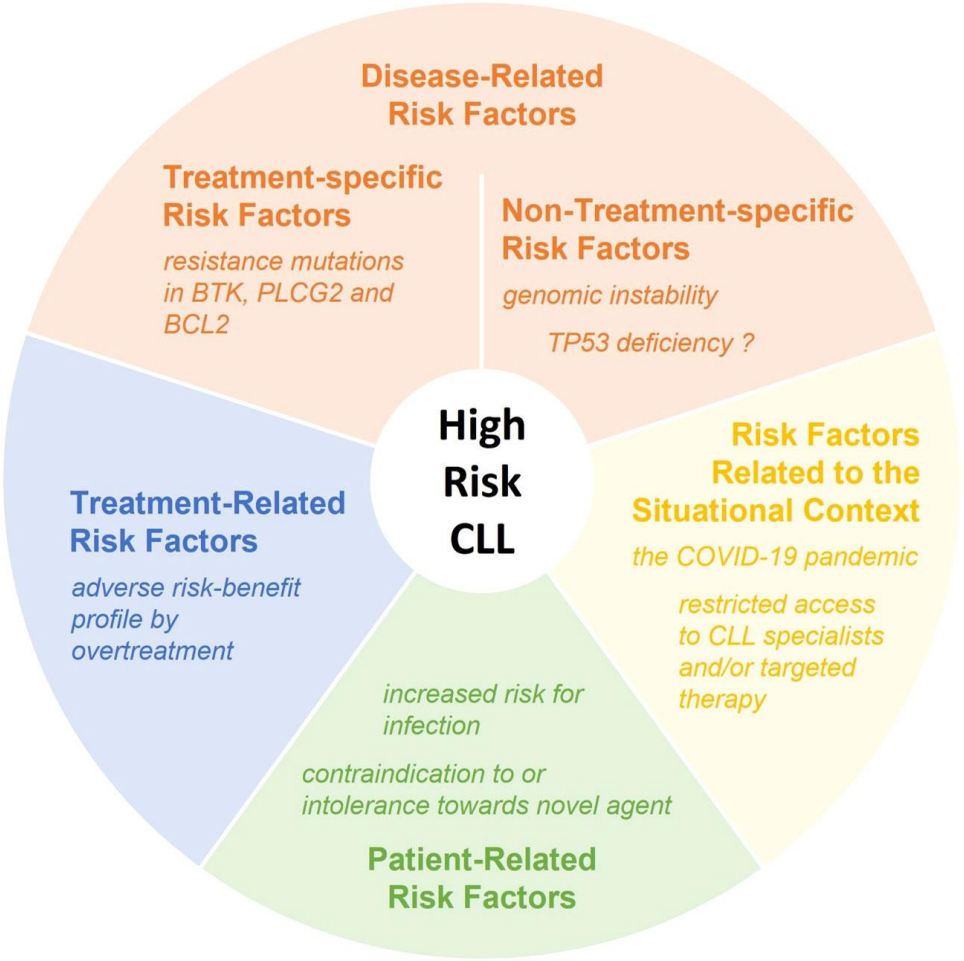
TURIN, 21st September 2023

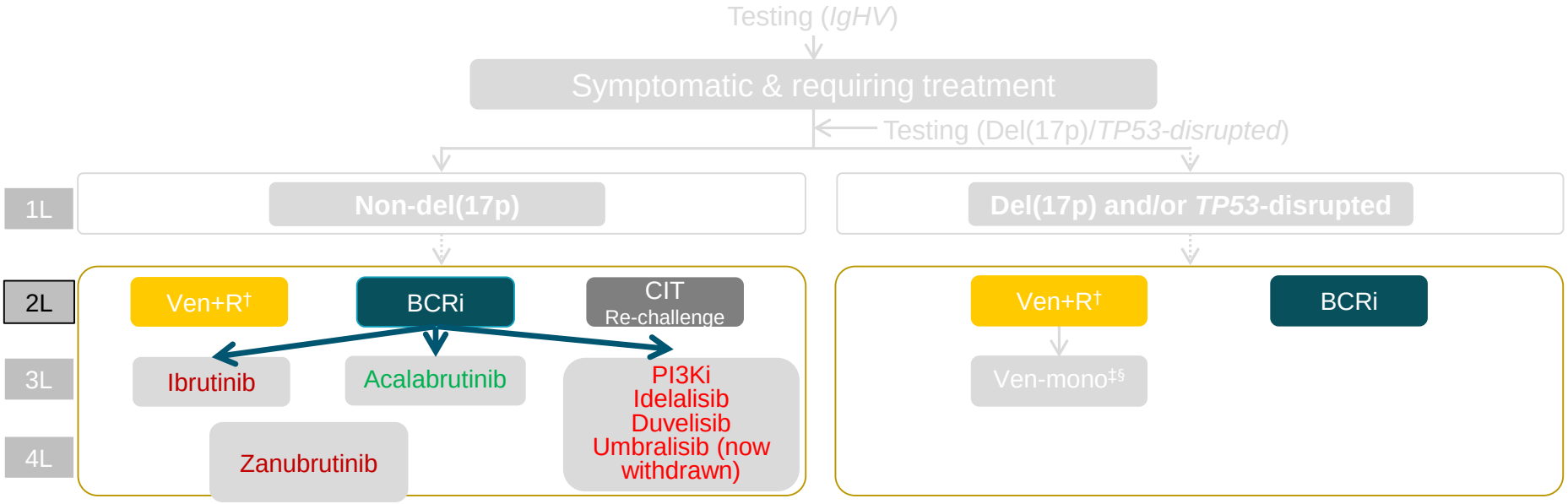
Disclosures of Dr Talha Munir

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Janssen	No	No	Yes	No	Yes	Yes	N/A
AstraZeneca	No	No	Yes	No	No	Yes	N/A
Beigene	No	No	Yes	No	Yes	Yes	N/A
Sobi	No	No	Yes	No	Yes	Yes	N/A
Abbvie	No	No	Yes	No	No	Yes	N/A
Novartis	No	No	No	No	Yes	Yes	N/A
Roche	No	No	Yes	No	No	Yes	N/A

How to define high-risk CLL in era of targeted drugs!



Therapy option for R/R CLL[1–7]



This diagram does not represent all available sequences. Please refer to your local hospital guidelines for the full algorithm of available treatment options.

†Patients treated with Ven+O are not currently eligible for Ven+R as a subsequent therapy. ‡Only if the patient has not progressed during Ven+R. §Venetoclax monotherapy is approved for del(17p) CLL patients unsuitable for BCRi.

BCRi, B cell receptor inhibitor; CIT, chemoimmunotherapy; CLL, chronic lymphocytic leukaemia; *IgHV*, immunoglobulin heavy chain gene; *TP53*, gene coding for p53; Ven, venetoclax; Ven+O, venetoclax + obinutuzumab; Ven+R, venetoclax + rituximab.

1. Eichhorst B, et al. *Ann Oncol* 2015;26(Suppl 5):v78–84; 2. ESMO Clinical Guidelines Committee. *Ann Oncol* 2017;28(Suppl 4):iv149–152; 3. NICE TA561. Technology appraisal guidance – Venetoclax with rituximab for previously treated chronic lymphocytic leukaemia. Available at: https://www.nice.org.uk/guidance/ta561. Accessed: January 2021; 4. NICE. Pathways guidance for lymphoid leukaemia. Available at: https://pathways.nice.org.uk/pathways/blood-and-bone-marrow-cancers/lymphoid-leukaemia.pdf. Accessed: December 2020; 5. Schuh AH, et al. *Br J Haematol* 2018;182:344–359; 6. NHS England National Cancer Drugs Fund List 2020. Available at: https://www.england.nhs.uk/publication/national-cancer-drugs-fund-list/. Accessed: January 2021; 7. BlueTeq Form. VEN3_v1.3 NHS England – Initial funding application – Venetoclax in combination with rituximab for the treatment of previously treated chronic lymphatic leukaemia.

Slide courtesy of Dr Munir.

SEQUENCING IN RELAPSED REFRACTORY CLL

The treatment for relapsed/refractory CLL depends on front-line treatment

Non-Covalent BTK inhibitor

Head-to- head BTKi trials

VS

BCL-2 inhibitor Venetoclax +/- Rituximab

VS

PI3Kinase inhibitor Idelalisib with rituximab

CIT → **?** → **?**

Most patients with RR CLL in the world had CIT upfront but increasingly they will have had novel agents

No definitive comparative data support Ven vs BTKi as first novel agent in novel agent-naive R/R CLL

Speaker's own opinion.

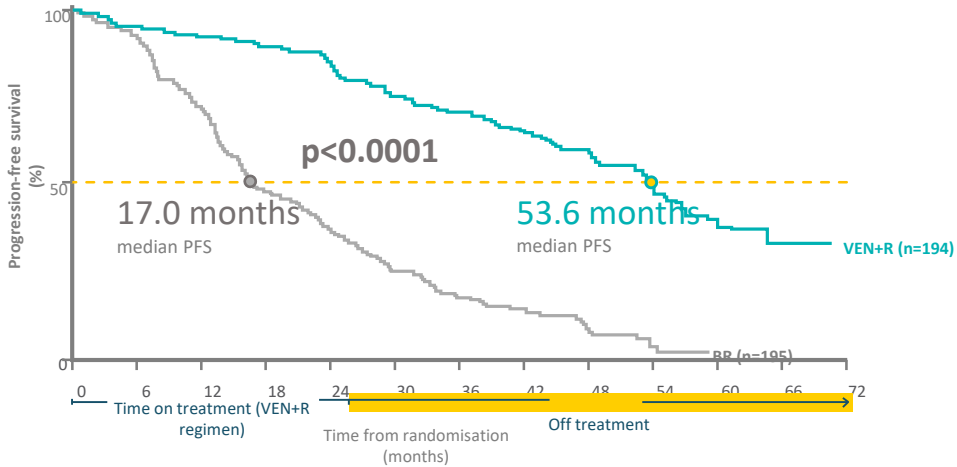
Patients on Landmark Relapsed refractory studies were not treated with prior novel agents n= 9/926

Agent	Study Name (Control Arm)	Number treated	Median (range) prior therapies	Percent on modern chemotherapy free pathways	Percent treated with ≥ 1 BTK, Ven or PI3K-i
Ibrutinib	Resonate (ofatumumab)	195	3 (1 - 12)	0%	0%
Acalabrutinib	ASCEND (investigator's choice: BR or idela-ritux)	155	1 (1 - 8)	0%	0%
Venetoclax monotherapy	Del 17p study (single arm)	107	2 (0 - 10)	Unknown <3.7%	3.7% (n=4)
Venetoclax-rituximab	Murano (BR)	194	1 (1 - >3)	Unknown <2.6%	2.6% (n=5)
Idelalisib-rituximab	STUDY 116 (placebo-ritux)	110	3 (1 – 12)	0%	0%
Duvelisib	DUO	160	2	0%	0%

Slide courtesy of Dr Munir.

RR CLL – What not to do

CIT in RR CLL – Inferior to BTKi and BCL2i

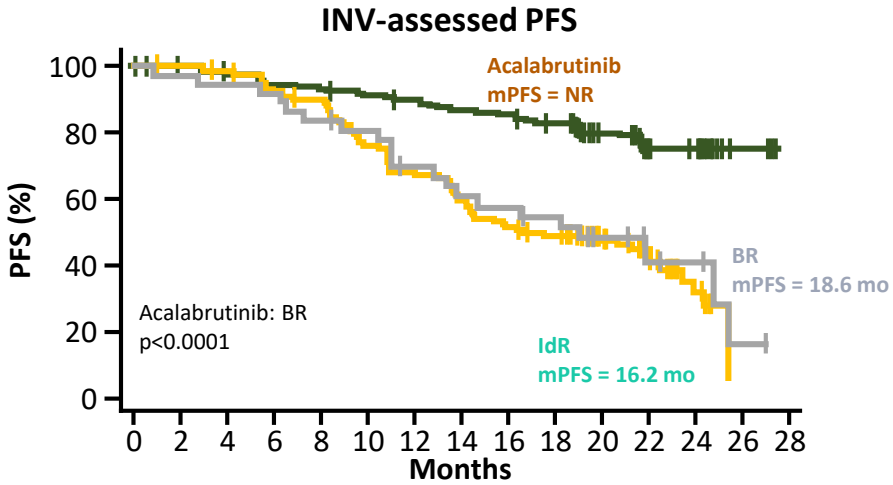


RR CLL treated with time limited VenR vs BR

Median FU 59.2 mo from randomisation

PFS 53.6 vs 17 months in favour VenR

Seymour JF et al. N Engl J Med 2018; 378: 1107–20. 3.
Kater AP: ASH: 2020

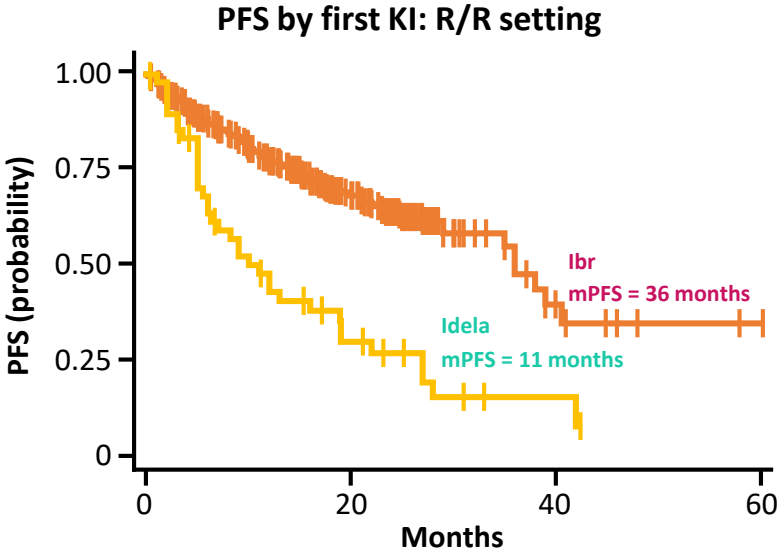


Phase 3 ASCEND Acala vs IdelR / BR R/R CLL

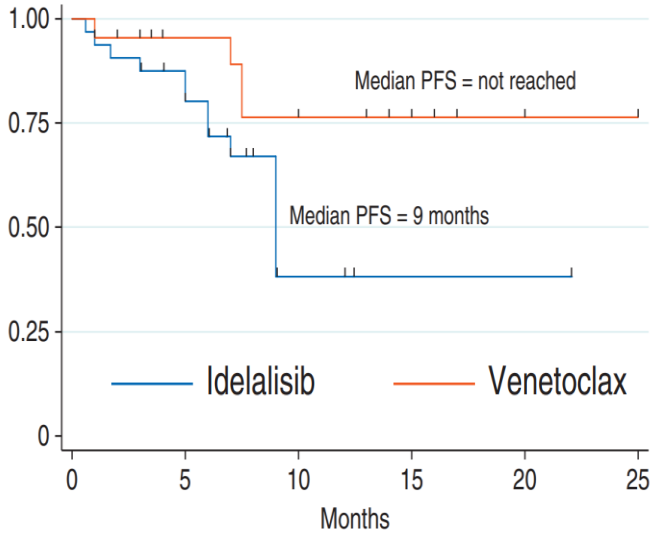
Median follow-up 22 months (N=307)

Ghia P, ASH, 2020

PI3Ki in RR CLL – Inferior to BTKi and BCL2i



Real-world retrospective analysis 683 pts with treatment-naive or R/R CLL



Real world retrospective multicentre analysis. Progression free survival post ibrutinib failure

Mato, Ann Clin Oncol, 2017

The first targeted agent: BTKi vs VenR

Factors to consider in R/R CLL

BTKi

- Convenience (no infusions or need for TLS monitoring)
- Long-term efficacy data in 1L and R/R settings
- Prospective data for Ven after PD on Ibr

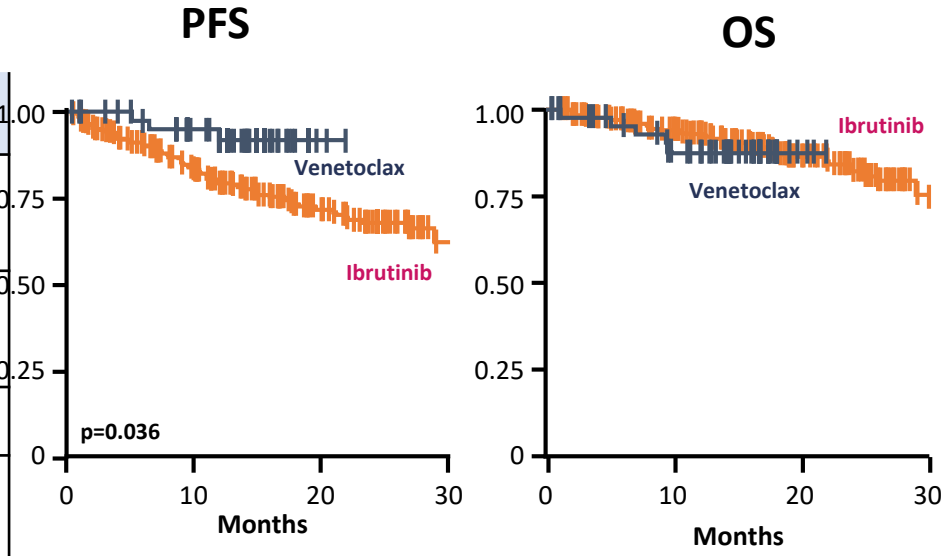
Ven

- Time-limited therapy
- No known cardiac or bleeding risk
- No long-term adherence concerns
- Potential for cost savings

Speaker's own opinion.
Slide courtesy of Dr Munir.

Ven vs Ibr as first novel agent in R/R CLL

Baseline characteristics	First novel agent			
	Ibr		Ven ± anti-CD20	
	n=		n=	
Median age at tx, years (range)	382	69 (27–95)	48	65 (39–87)
Median no. of prior tx (range)	385	2 (1–4)	48	2 (1–4)
del(17p), %	255	24	47	34
Complex karyotype, %	157	32	17	24
Elevated LDH, %	189	45	20	45



Retrospective, indirect comparison of ven vs ibr as first novel agent in R/R CLL (N=433)

Median FU 14 mo Ibr, 13.5 mo Ven

Eyre TA, Haematologica 2021
Adapted from AbbVie EHA presentation 2021; Mato

RR CLL – Which BTKi

Ibrutinib vs Acalabrutinib vs Zanubrutinib

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

Patients (N=533)

Key Inclusion Criteria

- Adults with previously treated CLL requiring therapy (iwCLL 2008 criteria[1])
- Presence of del(17p) or del(11q)[a]
- ECOG PS of ≤2

Stratification

- del(17p) status (yes or no)
- ECOG PS (2 vs ≤1)
- No. prior therapies (1–3 vs ≥4)

RANDOMIZE 1:1

- **Acalabrutinib[b] 100 mg PO BID**
- **Ibrutinib[b] 420 mg PO QD**

Primary endpoint

- Non-inferiority on IRC-assessed PFS[c]

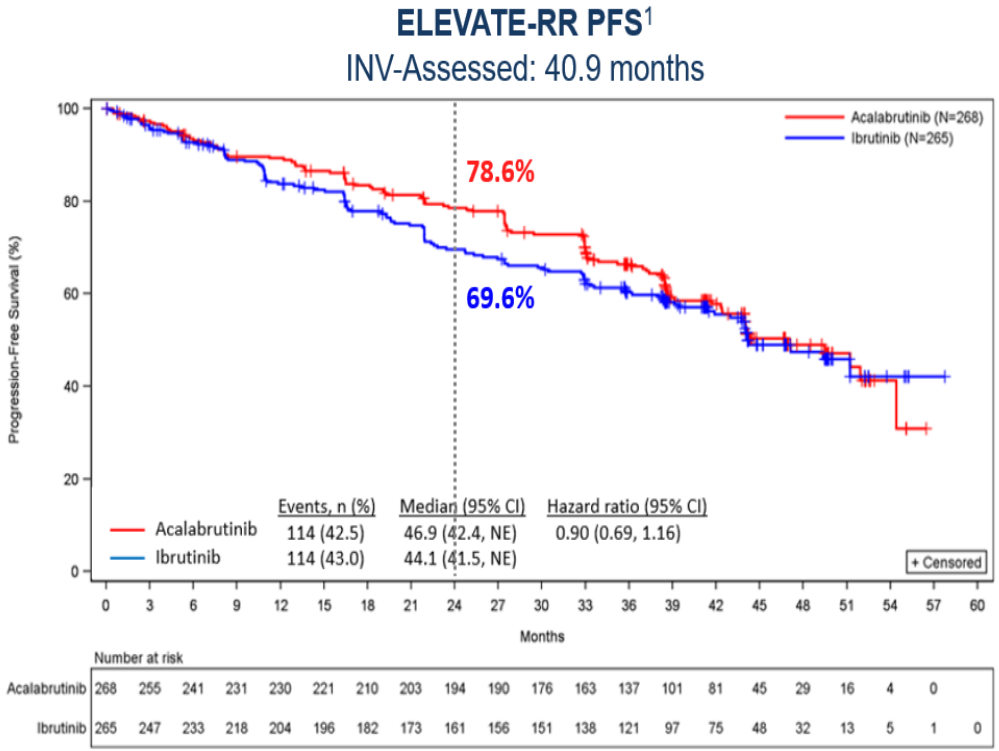
Secondary endpoints (hierarchical order):

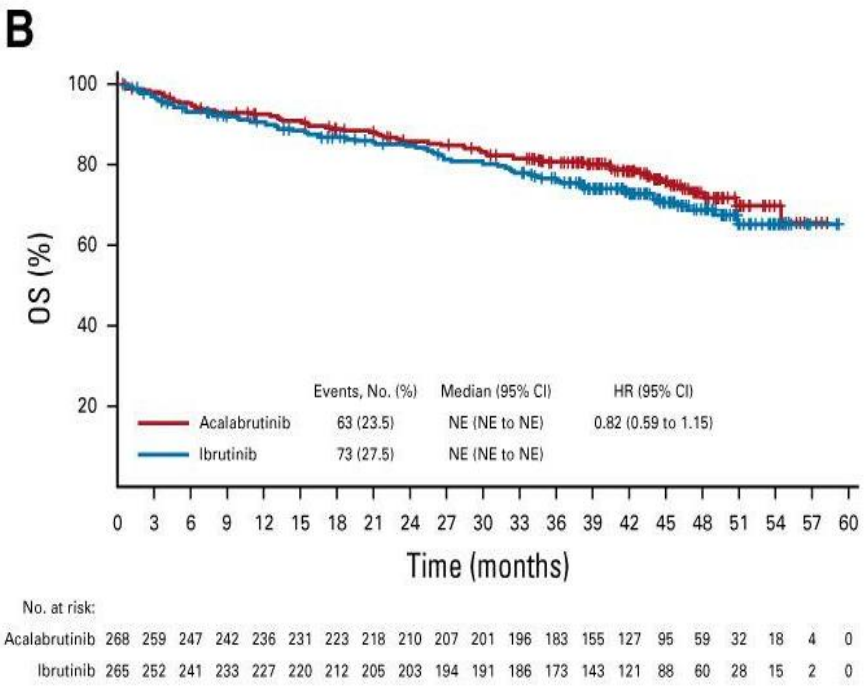
- Incidence of any grade atrial fibrillation/flutter
- Incidence of grade ≥3 infection
- Incidence of Richter transformation
- Overall survival

Key exclusion criteria: Significant CV disease; concomitant treatment with warfarin or equivalent vitamin K antagonist; prior treatment with ibrutinib, a BCR inhibitor, (eg, BTK , PI3K, or Syk inhibitors) or a BCL-2 inhibitor (eg, venetoclax)

NCT02477696 (ACE-CL-006).
[a]By central laboratory testing; [b]continued until disease progression or unacceptable toxicity; [c]conducted after enrollment completion and accrual of ~250 IRC-assessed PFS events.
Afib/flutter, atrial fibrillation/flutter; BCL-2, B-cell leukemia/lymphoma-2; BCR, B-cell receptor; BID, twice daily; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CV, cardiovascular; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent review committee; iwCLL, International Workshop on CLL; PFS, progression-free survival; PI3K, phosphatidylinositol 3-kinase; PO, orally; QD, once daily.
1. Hallek M, et al. *Blood*. 2008;111:5446-56.

Primary Endpoint: Non-inferiority PFS Met (median f/u: 40.9 months)





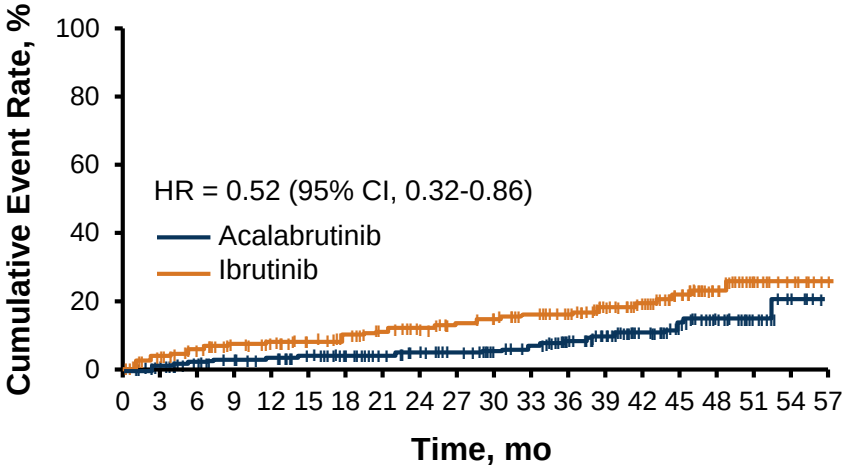
1. Byrd JC et al. *J Clin Oncol*. 2021;39:3441-3452.

Median follow-up: 40.9 months (range, 0.0–59.1).

CI, confidence interval; INV, Investigator; PFS, progression-free survival.

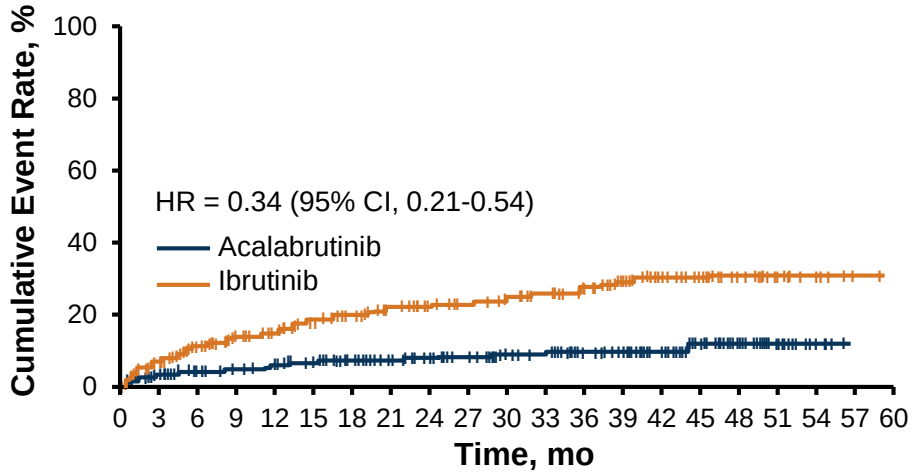
ELEVATE-RR: Cardiac AEs of Interest[1]

Atrial Fibrillation



No. at Risk																			
Acalabrutinib	268	255	240	231	228	218	206	197	188	183	172	167	142	115	89	58	35	19	8	0
Ibrutinib	263	241	224	208	199	185	176	166	156	143	136	128	117	96	73	56	26	18	8	0

Hypertension



No. at Risk																				
Acalabrutinib	266	246	229	220	216	205	193	184	176	169	157	153	136	114	89	60	34	17	5	0	0
Ibrutinib	263	230	203	183	170	153	141	130	120	111	104	98	85	69	48	40	27	15	7	1	0

AEs, adverse events; HR, hazard ratio.

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

ALPINE: Phase 3, Randomized Study of Zanubrutinib vs Ibrutinib in Patients With Relapsed/Refractory CLL or SLL

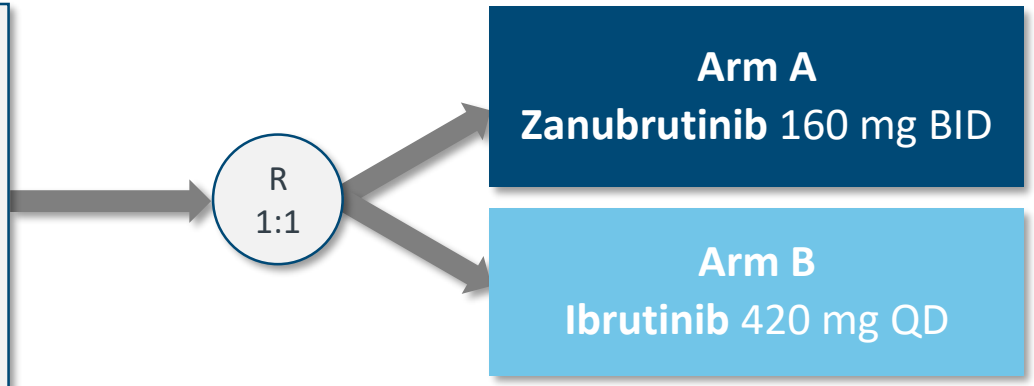
R/R CLL/SLL with ≥ 1 prior treatment
(Planned N=600, Actual N=652)

Key Inclusion Criteria

- R/R to ≥1 prior systemic therapy for CLL/SLL
- Measurable lymphadenopathy by CT or MRI

Key Exclusion Criteria

- Current or past Richter's transformation
- Prior BTK inhibitor therapy
- Treatment with warfarin or other vitamin K antagonists



Stratification Factors

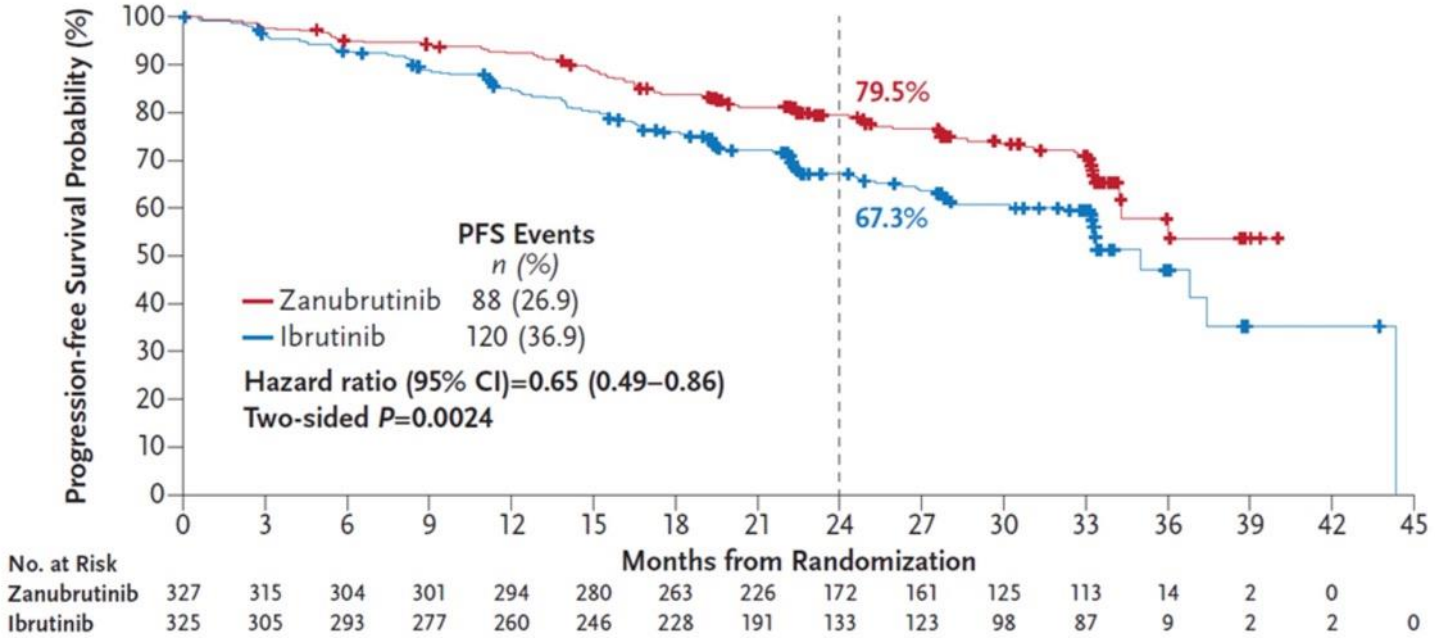
- Age
- Geographic region
- Refractory status
- Del(17p)/*TP53* mutation status

BID, twice daily; BTK, Bruton tyrosine kinase CLL, chronic lymphocytic leukemia; CT, computed tomography; MRI, magnetic resonance imaging; QD, once daily; R, randomized; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma.

ALPINE study. Hillmen et al. LB1900 EHA 2021.

ALPINE:
Primary Endpoint: Improved ORR with Zanubrutinib & PFS as Secondary EP

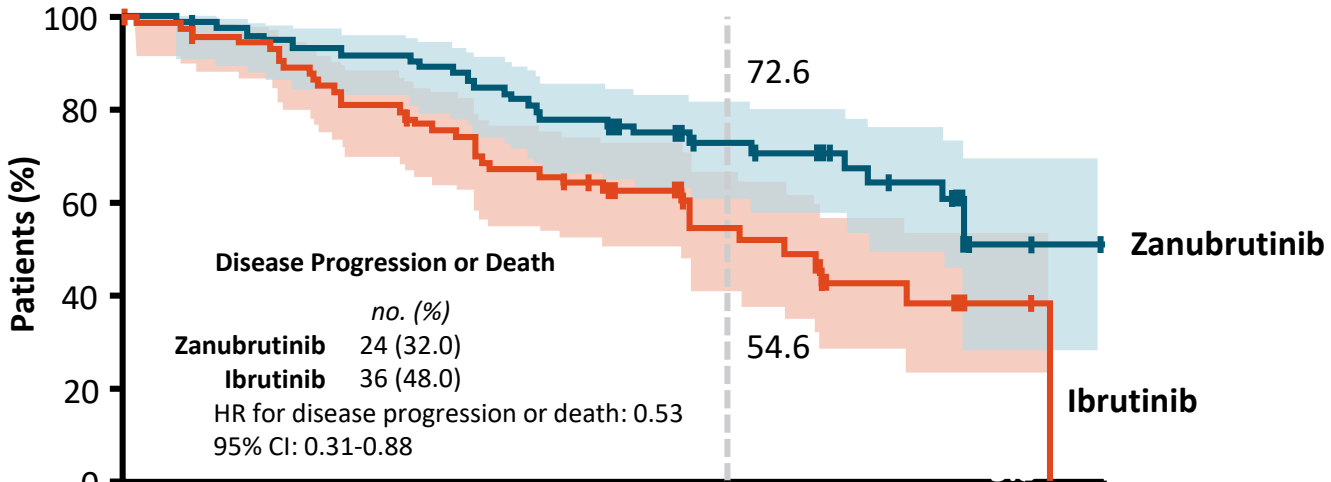
After a median follow-up of 29.6 months, improved PFS with zanubrutinib intent-to-treat population



CLL, chronic lymphocytic leukemia; ORR, overall response rate; PFS, progression-free survival; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma.

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

ALPINE: Investigator-Assessed PFS in Patients With del(17p) and/or *TP53*^{mut}

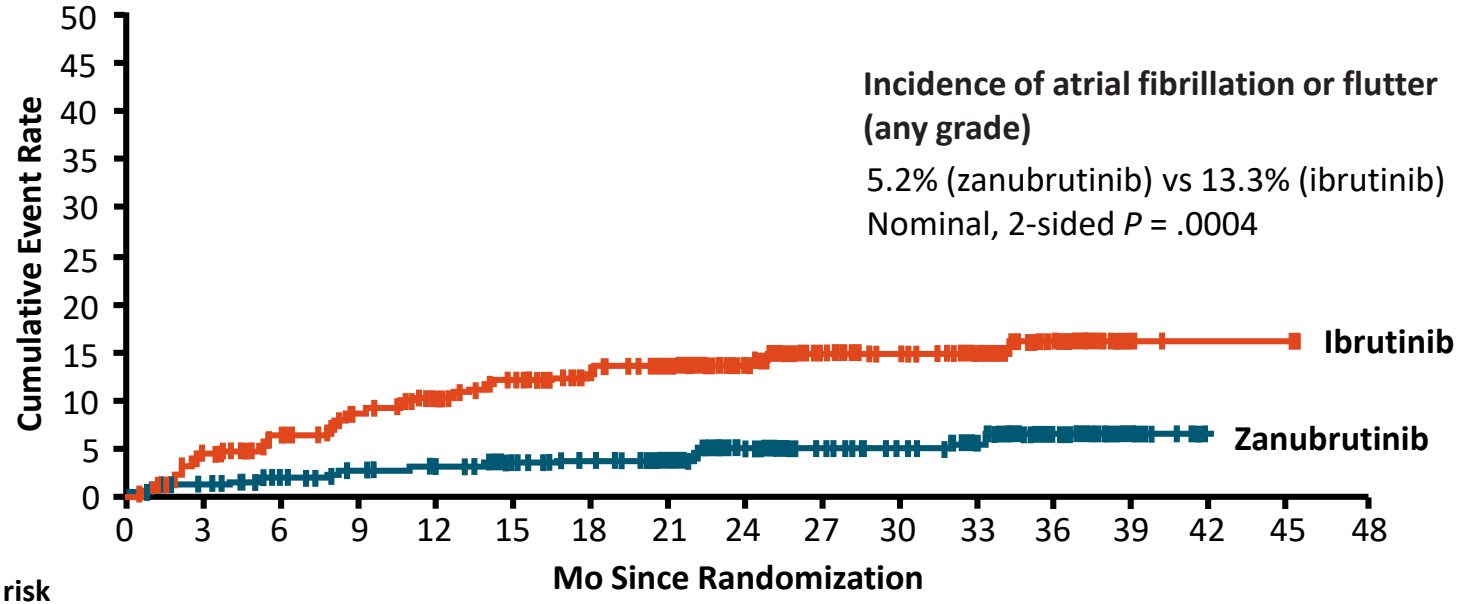


No. at risk

Zanubrutinib	75	71	68	66	64	61	56	47	32	30	21	18	3	0
Ibrutinib	75	70	68	59	55	48	45	34	19	17	10	9	2	0

Brown. ASH 2022. Abstr LBA-6. Brown. NEJM. 2022;[Epub].

ALPINE: Atrial Fibrillation/Flutter



No. at risk																
Zanubrutinib	324	312	302	294	288	277	268	249	199	164	148	120	51	10	0	
Ibrutinib	324	295	278	260	247	230	211	193	153	121	108	89	40	3	2	1	0

Brown. ASH 2022. Abstr LBA-6. Reproduced with permission.

Headline ALPINE and ELEVATE RR data

Parameter	ALPINE	ELEVATE - RR
Median Age	67	66
Median prior lines	1	2
% 17p-	13.8 (Z)	45.1 (A)
% Unmutated IGHV	73.1 (Z)	82.1 (A)
Median f-up (months)	29.6	40.9

Data from Byrd et al JCO 2021 and Brown et al NEJM 2023

Headline ALPINE and ELEVATE RR data

Parameter	ALPINE		ELEVATE - RR	
Median Age	67		66	
Median prior lines	1		2	
% 17p-	13.8 (Z)		45.1 (A)	
% Unmutated IGHV	73.1 (Z)		82.1 (A)	
Median f-up (months)	29.6		40.9	
% Discontinuation for AE	**Zanubrutinib** 15.4	**Ibrutinib** 22.2	**Acalabrutinib** 14.7	**Ibrutinib** 21.3
% All grade hypertension	21.9	19.8	8.6	22.8
% All grade AF	5.2	13.3	9.0	15.6
Number of cardiac deaths	0	6	?	?
Number of Ventricular arrythmias / cardiac arrests	?	?	1	5
% 24 month INV-assessed PFS	78.4	65.9	78.6	69.6

Data from Byrd et al JCO 2021 and Brown et al NEJM 2023

RR CLL – Which BTKi

- Very difficult to choose at present
- All analysis are subject to cross-trial comparison
- Efficacy- Zanubrutinib superior to Ibrutinib in terms of PFS with caveats
- Efficacy- Acalabrutinib similar to ibrutinib
- Toxicity- Cardiac signal less pronounced with Acala and Zanu

RR CLL – Fixed duration Ven/Ritux vs Continuous Ven

Final 7-year follow up and retreatment substudy analysis of MURANO: venetoclax-rituximab (VenR)-treated patients with relapsed/refractory chronic lymphocytic leukemia (R/R CLL)

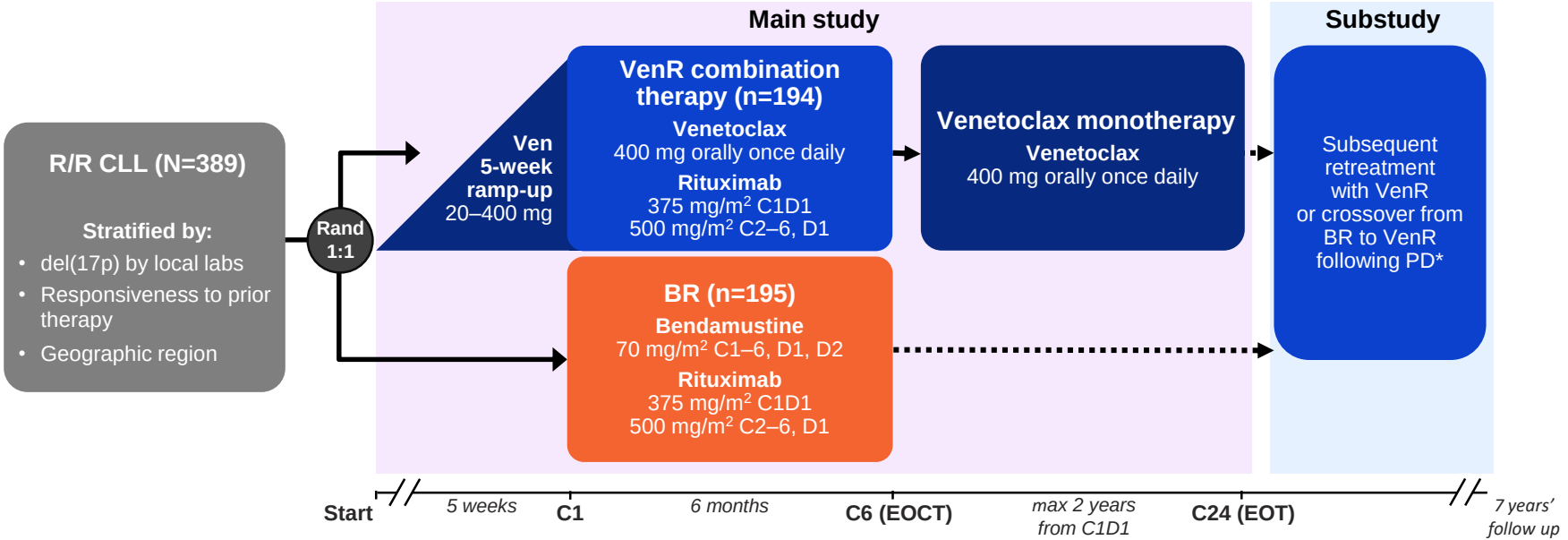
Arnon P Kater[1], Rosemary Harrup[2], Thomas J Kipps[3], Barbara Eichhorst[4], Carolyn J Owen[5], Sarit Assouline[6], Nicole Lamanna[7], Tadeusz Robak[8], Javier de la Serna[9], Ulrich Jaeger[10], Guillaume Cartron[11], Marco Montillo[12], Clemens Mellink[1], Brenda Chyla[13], Maria Thadani-Mulero[14], Marcus Lefebure[14], Yanwen Jiang[15], Rosemary Millen[14], Michelle Boyer[14], John F Seymour[16]

[1]Amsterdam University Medical Centers, Amsterdam, the Netherlands; [2]Royal Hobart Hospital, University of Tasmania, Tasmania, Australia; [3]UCSD Moores Cancer Center, San Diego, CA, USA; [4]University of Cologne, Cologne, Germany; [5]University of Calgary, Calgary, Canada; [6]Segal Cancer Center, Lady Davis Institute, Jewish General Hospital, Montreal, Canada; [7]Columbia University Medical Center, New York, NY, USA; [8]Medical University of Lodz, Lodz, Poland; [9]Hospital Universitario 12 de Octubre, Madrid, Spain; [10]Medical University of Vienna, Vienna, Austria; [11]Centre Hospitalier Universitaire de Montpellier, Montpellier, France; [12]Niguarda Cancer Center, ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy; [13]AbbVie, North Chicago, IL, USA; [14]Roche Products Ltd,Welwyn Garden City, UK; [15]Genentech Inc., South Francisco, CA, USA; [16]Royal Melbourne Hospital, Peter MacCallum Cancer Centre and University of Melbourne, Melbourne, Australia

Presented at the European Hematology Association (EHA) Annual Meeting | June 8–11, 2023

MURANO (NCT02005471): study design and prior findings

- Global, Phase III, open-label, randomized study[1]



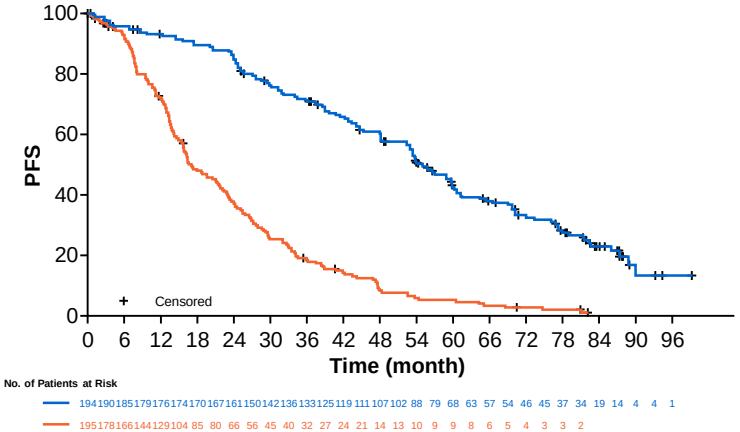
  - Superior PFS and OS was observed with fixed-duration VenR vs BR in patients with R/R CLL[1]
  - At 48 months of follow up, deep responses with uMRD† were associated with favorable PFS[2]

*Investigator-assessed PD according to International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria. †uMRD is defined as <1 CLL cell/10,000 leukocytes.
BR, bendamustine-rituximab; C, cycle; D, day; del(17p), deletion 17p; EOCT, end of combination treatment; EOT, end of treatment; max, maximum; OS, overall survival; PD, progressive disease; PFS, progression-free survival; Rand, randomization; (u)MRD, (undetectable) minimal residual disease.

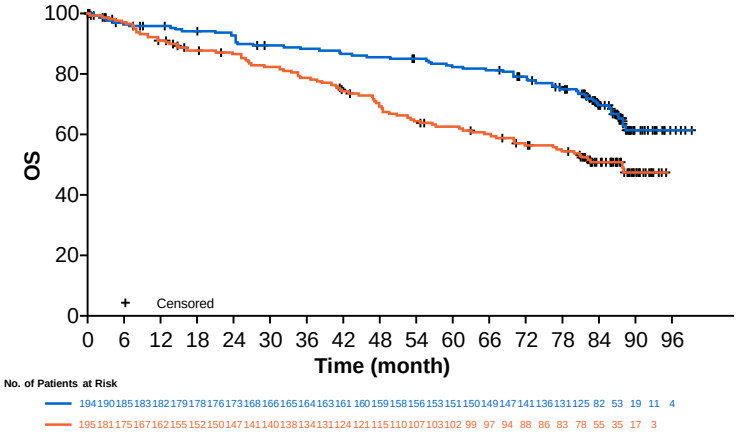
1. Seymour JF, et al. N Engl J Med 2018;378(12):1107–20.
2. Kater AP, et al. J Clin Oncol 2020;38(34)4042–54.

PFS and OS benefits with VenR over BR were sustained at 7 years

	Median PFS (95% CI), months	HR* (95% CI)	7-year PFS (%)
VenR (n=194)	**54.7** (52.3–59.9)	**0.23** (0.18–0.29) Stratified P-value <0.0001†	**23.0**
BR (n=195)	**17.0** (15.5–21.7)		NE



	Median OS (95% CI), months	HR‡ (95% CI)	7-year OS (%)
VenR (n=194)	NE	**0.53** (0.37–0.74) Stratified P-value <0.0002†	**69.6**
BR (n=195)	**87.8** (70.1–NE)		**51.0**



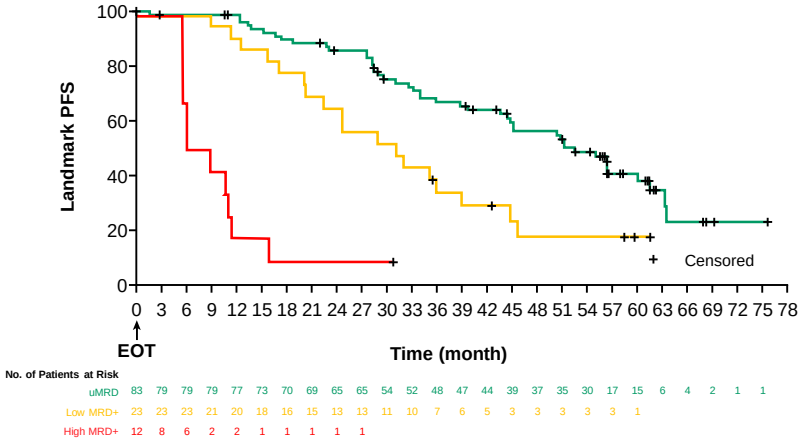
- Median follow up for efficacy (range) was 86.8 months (0.3–99.2) for VenR and 84.4 months (0.0−95.0) for BR
- No new safety signals were identified since the 5-year data cut,[1] with all patients outside of the AE reporting window§

*Stratified HR is presented, unstratified HR=0.25. †P-values are descriptive only. ‡Stratified HR is presented, unstratified HR=0.54. §All AEs were reported until 28 days after the last dose of Ven or 90 days after last dose of R, whichever was longer. After this, only deaths, serious AEs, or AEs of concern that were believed to be Ven-related were reported. AE, adverse event; CI, confidence interval; HR, hazard ratio; NE, not estimable.

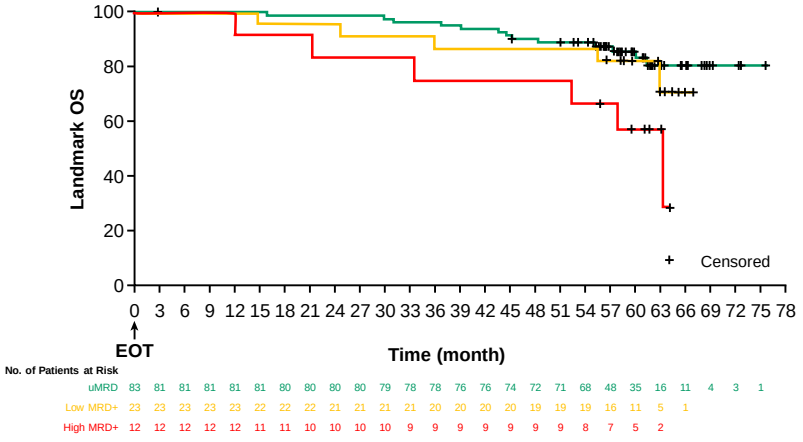
1. Seymour JF, et al. Blood 2022;140(8):839–50.

uMRD at EOT is associated with improved outcomes in the VenR arm

Patients who completed 2 years of Ven without PD*	Median PFS since EOT (95% CI), months	HR (95% CI); P-value†
uMRD (n=83)	**52.5** (44.5–61.5)	
Low MRD+ (n=23)	**29.3** (20.2–37.5)	vs uMRD: **3.46** (1.75–6.86); <0.0001
High MRD+ (n=12)	**4.6** (2.8–8.3)	vs uMRD: **17.22** (5.70–52.00); <0.0001



Patients who completed 2 years of Ven without PD*	Median OS since EOT (95% CI), months	HR (95% CI); P-value†
uMRD (n=83)	**NE** (NE–NE)	
Low MRD+ (n=23)	**NE** (62.7–NE)	vs uMRD: **1.07** (0.34–3.35); NS
High MRD+ (n=12)	**63.1** (51.5–NE)	vs uMRD: **2.39** (0.73–7.80); NS



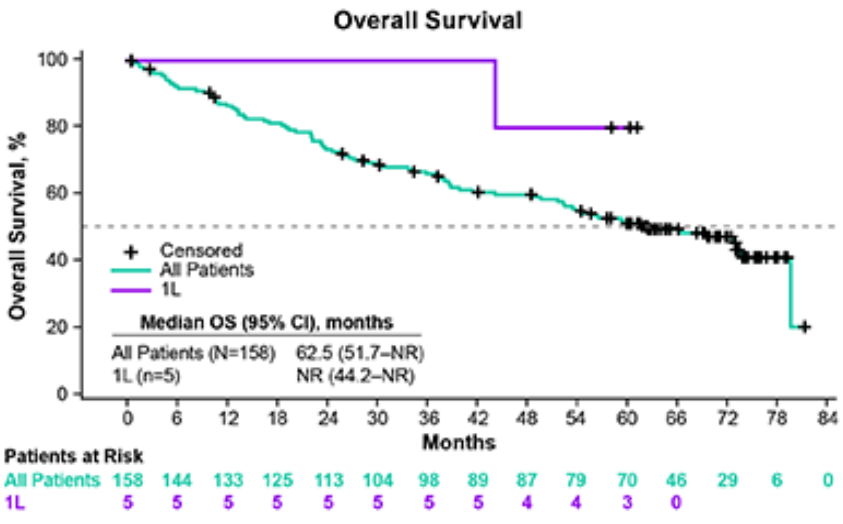
Achievement of uMRD was associated with prolonged PFS in VenR-treated patients

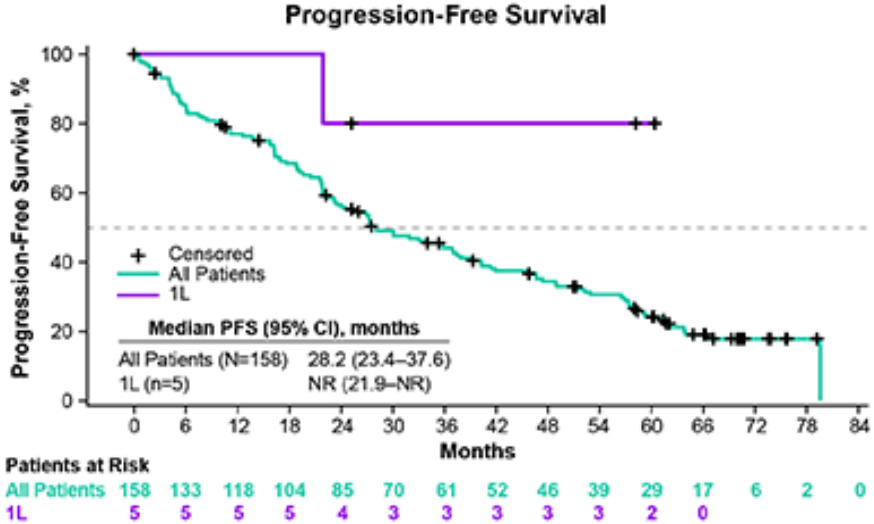
Low MRD+ is defined as ≥1 CLL cell/10,000 leukocytes to <1 CLL cell/100 leukocytes, high MRD+ is defined as ≥1 CLL cell/100 leukocytes. Stratified HR (95% CI) for Low MRD+ vs High MRD+: PFS, 3.22 (1.04–9.97), P=0.0350; OS, 2.27 (0.44–11.69), P=NS.

*Investigator-assessed PD according to iwCLL criteria. †Stratified HRs and P-values are presented, P-values are descriptive only. NS, not significant.

M-13982 trial- Long term FU for 17p deleted CLL

Median Follow-up 70 months



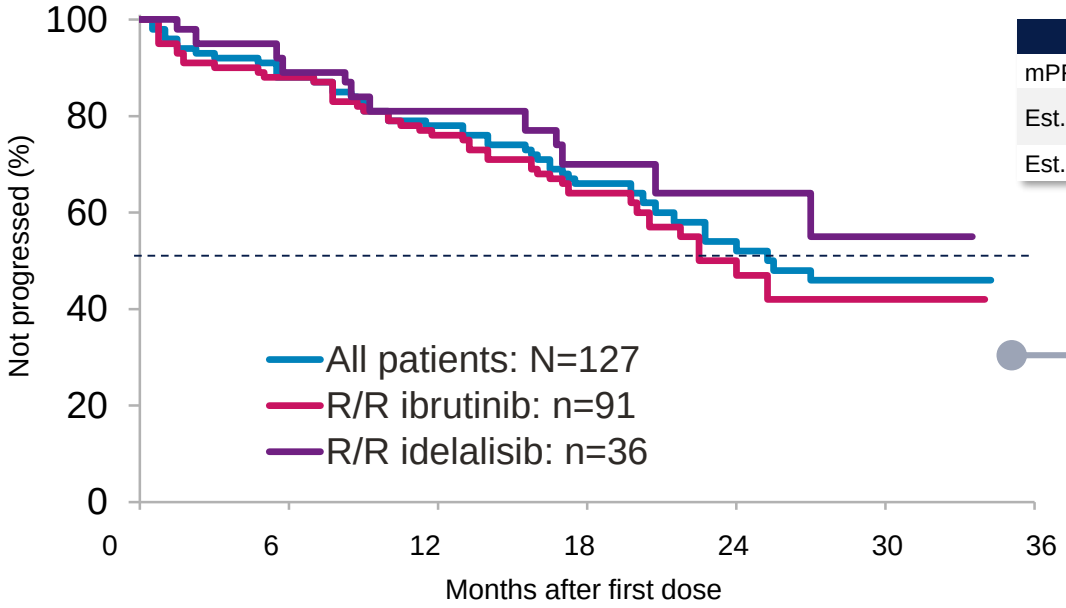


- **48% of pts were alive, 24% were progression-free, and 16% remained on Ven**
- **Except *SF3B1* mutation, other adverse features (eg, >1 *TP53* mutation, *NOTCH1* mutations, unmutated IGHV) did not influence outcomes with Ven treatment in this cohort.**

Stilgenbauer et al. Presented at EHA 2022

Venetoclax monotherapy after BCRi intolerance or progression is effective in R/R CLL

M14-032: PFS with venetoclax after ibrutinib or idelalisib (intolerance or CLL progression; N=127)



	All patients
mPFS, mo	24.7
Est. 18-mo PFS, %	66 (95% CI=56–74)
Est. 24-mo PFS, %	52 (95% CI=40–62)

Only FDA-approved agent with prospective data in BTKi- and PI3Ki-resistant disease

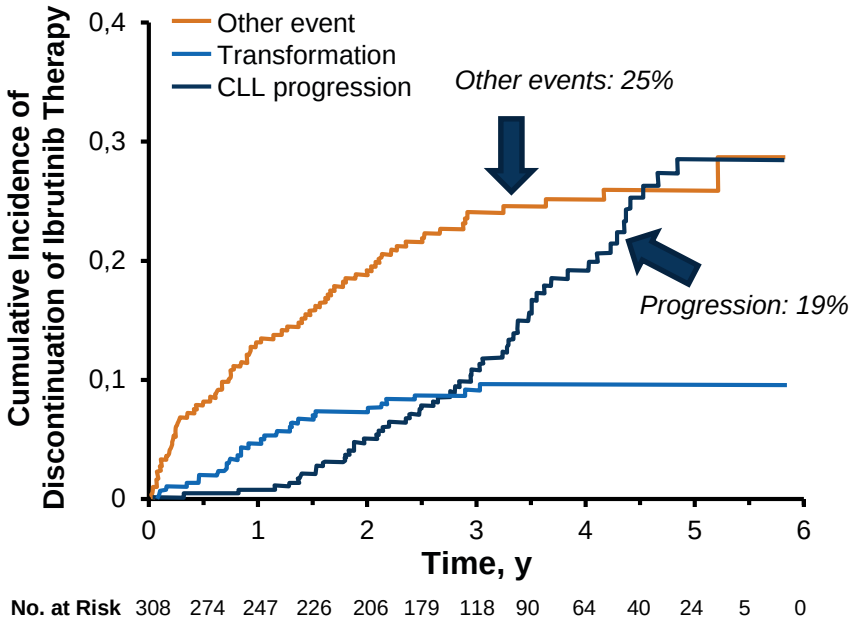
BCRi, B-cell receptor pathway inhibitor; BTKi, Bruton's tyrosine kinase inhibitor; Est., estimated; NR, not reached; PI3Ki, phosphoinositide 3-kinase inhibitor.

Byrd JC, *et al.* ASCO 2018. Abstract 7512 (Poster); Coutre S, *et al. Blood* 2018; **131:**1704–1711; Jones JA, *et al. Lancet Oncol* 2018; **19:**65–75.

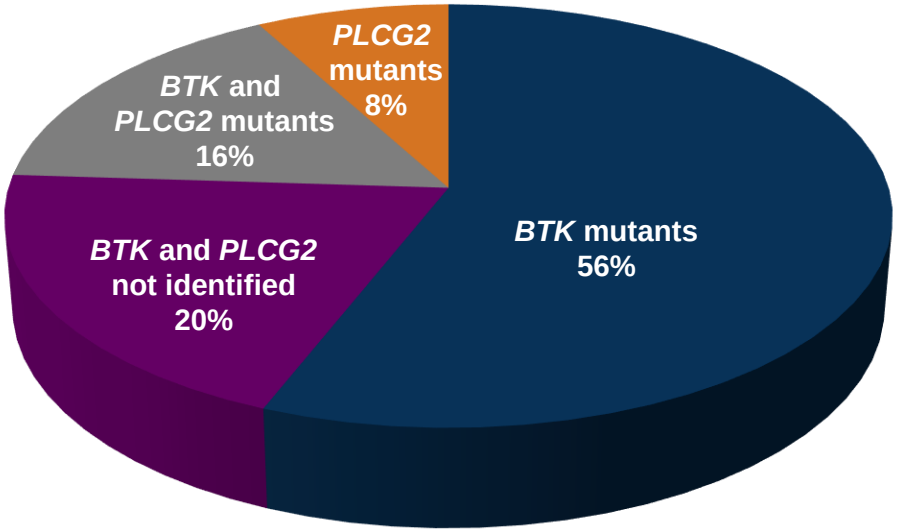
RR CLL – Sequencing

Resistance and Intolerance Limit Outcomes With Covalent BTK Inhibitors in CLL

Ibrutinib Discontinuation Over Four Prospective Studies[1]



Ibrutinib-Acquired Resistance in Patients With Progressive CLL[2]



- *BTK* C481 mutations are the dominant reasons for progressive CLL after covalent BTK inhibitors[1-8]
- *BTK* C481 mutations prevent covalent BTK inhibitors from effective target inhibition[1-6]

BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; PLCG2, phospholipase C gamma 2.

1. Woyach JA et al. *J Clin Oncol*. 2017;35;1437-1443. 2. Lampson BL, Brown JR. *Expert Rev Hematol*. 2018;11:185-194. 3. Burger JA et al. *Leukemia*. 2020;34:787-798. 4. Byrd JC et al. *N Engl J Med*. 2016;374:323-332. 5. Hershkovitz-Rokah O et al. *Br J Haematol*. 2018;181:306-319. 6. Woyach JA et al. *N Engl J Med*. 2014;370:2286-2294. 7. Woyach JA et al. *Blood*. 2019;134(suppl 1):504. 8. Xu L et al. *Blood*. 2017;129:2519-2525.

Venetoclax monotherapy after BCRi intolerance or progression is effective in R/R CLL

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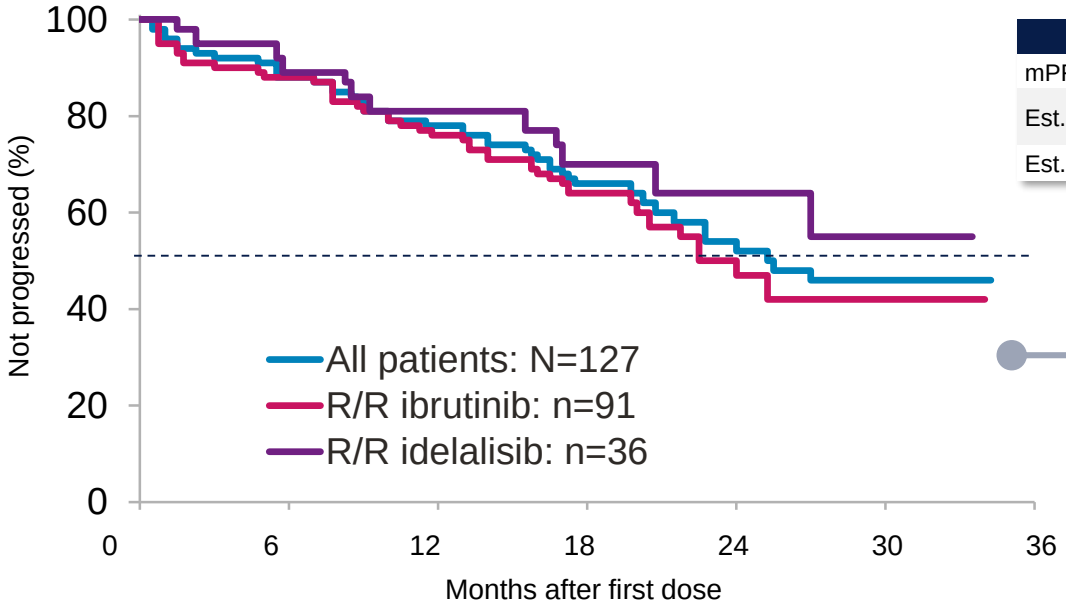

	All patients
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Est. 24-mo PFS, %	52 (95% CI=40–62)

Only FDA-approved agent with prospective data in BTKi- and PI3Ki-resistant disease

Safety disclaimer
Venetoclax had an acceptable safety profile, consistent with other clinical studies of venetoclax monotherapy[3]

BCRi, B-cell receptor pathway inhibitor; BTKi, Bruton's tyrosine kinase inhibitor; Est., estimated; NR, not reached; PI3Ki, phosphoinositide 3-kinase inhibitor.

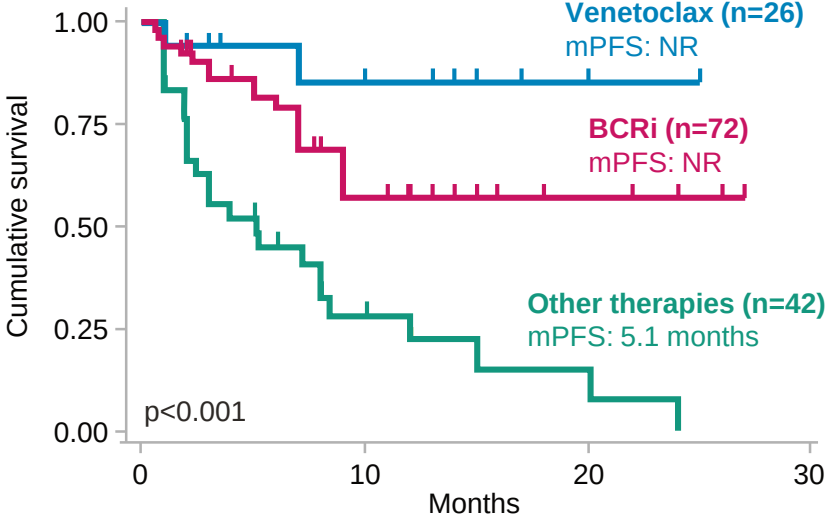
Byrd JC, *et al.* ASCO 2018. Abstract 7512 (Poster); Coutre S, *et al. Blood* 2018; **131:**1704–1711; Jones JA, *et al. Lancet Oncol* 2018; **19:**65–75.

Slide courtesy of Dr Munir.

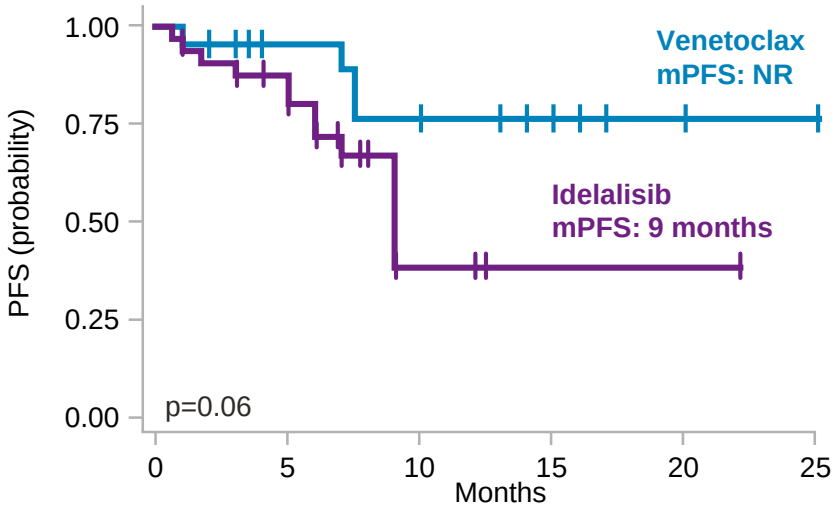
Improved efficacy observed with venetoclax after BCRi

Real-world retrospective analysis of patients with R/R CLL (N=683)[1]

PFS by subsequent therapy after BCRi (PI3Ki or BTKi) discontinuation



PFS by second novel agent in patients with PD on ibrutinib



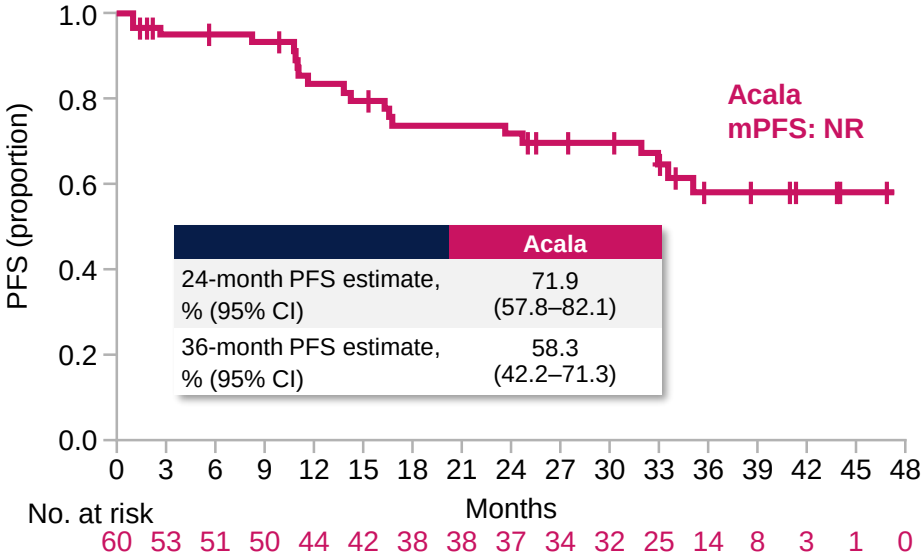
Safety disclaimer - venetoclax
Overall safety profile of venetoclax is based on several clinical trials. Most common AEs of any grade were neutropenia, diarrhoea, and upper respiratory tract infection.
Safety disclaimer - idelalisib
Overall safety profile of idelalisib is based on several clinical trials. Very common AEs include infections, neutropenia, lymphocytosis, diarrhoea, transaminase increase, rash, pyrexia, and triglyceride increase

BCRi, B-cell receptor pathway inhibitor; BTKi, Bruton's tyrosine kinase inhibitor; PI3Ki, phosphoinositide 3-kinase inhibitor; NR, not reached.

Mato AR, *et al. Ann Oncol* 2017; **28:**1050–1056 (incl. suppl.).

Efficacy observed with subsequent BTKi following intolerance with ibrutinib and/or acalabrutinib

ACE-CL-208: PFS with acalabrutinib in ibrutinib-intolerant patients with R/R CLL (N=60)
(median follow-up: 35 months)[1]



* Patients with >90-day study duration included.
BTKi, Bruton's tyrosine kinase inhibitor; ND, not determinable; NE, not evaluable; NR, not reached; PR-L, partial response with lymphocytosis; VGPR, very good partial response.

BGB-3111-215: ORR to zanubrutinib in ibrutinib- and/or acalabrutinib-intolerant patients (N=82)
(median follow-up: 25.2 months)[2]

ORR 71.1%

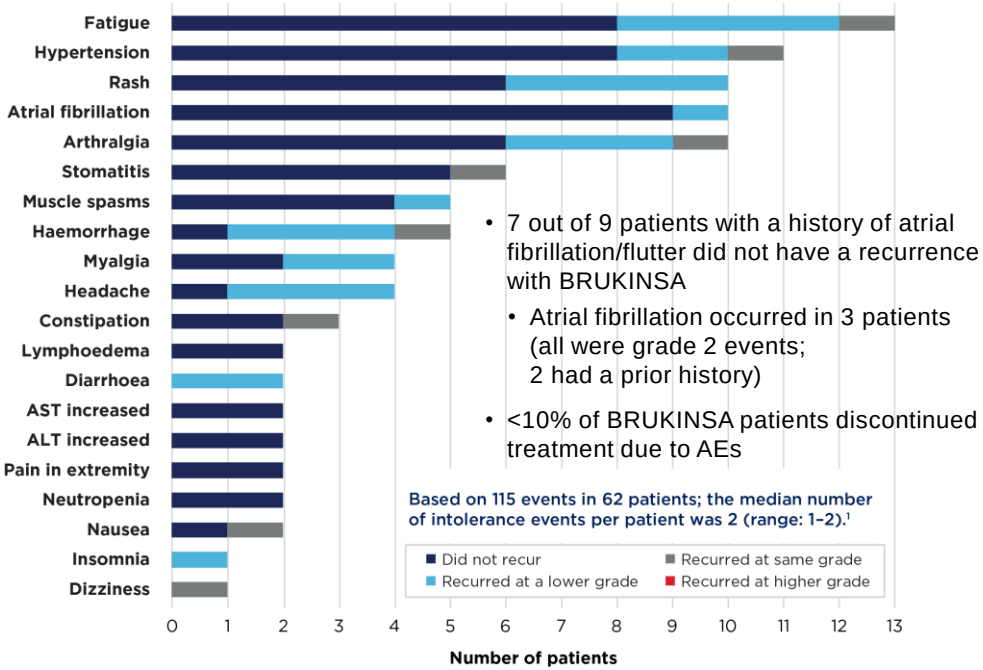
	Ibrutinib intolerant (n=57)	Acalabrutinib ± ibrutinib intolerant (n=25)	Total (N=82)
Patients, n (%)			
Remaining on treatment	39 (68.4)	19 (76.0)	58 (70.7)
Remaining on study	46 (80.7)	21 (84.0)	67 (81.7)
Discontinued from treatment	18 (31.6)	6 (24.0)	24 (29.3)
Adverse event	5 (8.8)	2 (8.0)	7 (8.5)
Progressive disease	6 (10.5)	1 (4.0)	7 (8.5)
Withdrawal by patient	3 (5.3)	2 (8.0)	5 (6.1)
Deaths, n (%)	5 (8.8)	1 (4.0)	6 (7.3)
Median BRUKINSA treatment duration (range), months	26.2 (0.6–36.2)	8.1 (0.5–27.9)	23.7 (0.5–36.2)

- **29% (24/82) patients discontinued treatment due to:**
  - **AEs: Myalgia, stomatitis, penile haemorrhage, COVID-19 pneumonia, ALT rise, AIHA, diarrhoea (n=7)**
  - **Progressive disease (n=7)**
  - **Other (n=10)**

1. Rogers KA, *et al. Haematologica* 2021; **106:**2364–2373;
2. Shadman M et al. Poster presented at EHA 2023; abstract number: P683.

Sequential Use of Acalabrutinib or Zanubrutinib in Patients With Ibrutinib Intolerance Is an Effective and Safe Option[1,2]

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



- 7 out of 9 patients with a history of atrial fibrillation/flutter did not have a recurrence with BRUKINSA
  - Atrial fibrillation occurred in 3 patients (all were grade 2 events; 2 had a prior history)
- <10% of BRUKINSA patients discontinued treatment due to AEs

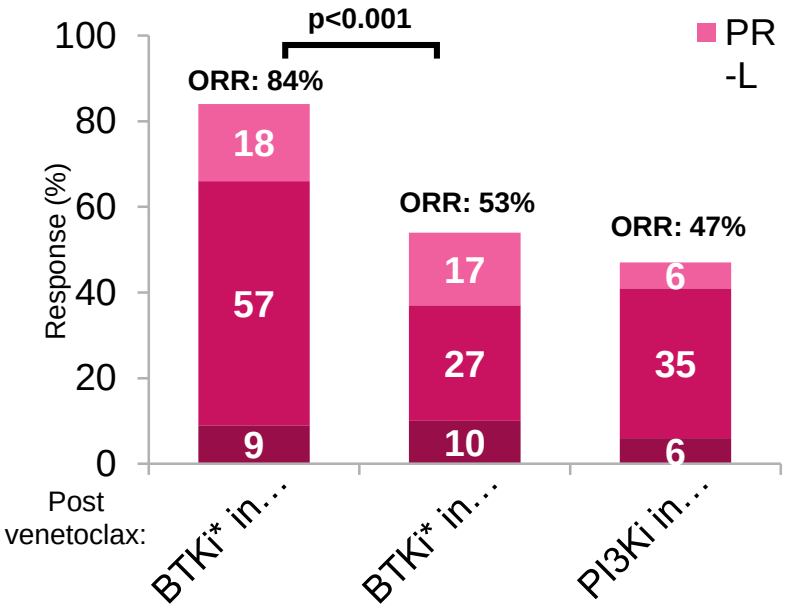
AE, adverse event; AF, atrial fibrillation.

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

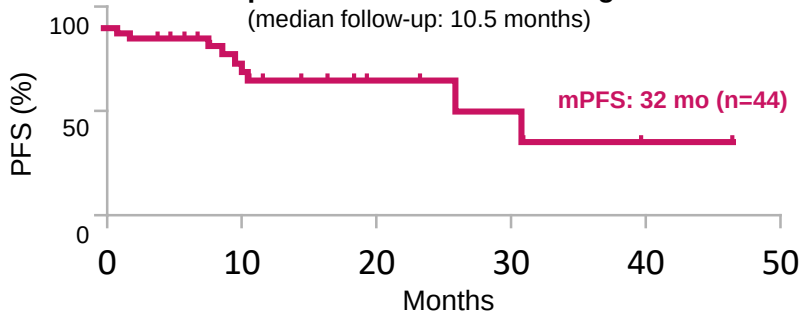
1. Rogers KA et al. *Haematologica*. 2021;106:2364-2373.
2. Shadman M et al. Poster presented at EHA 2023; abstract number: P683.

BTKi therapy after venetoclax is effective in venetoclax-refractory CLL

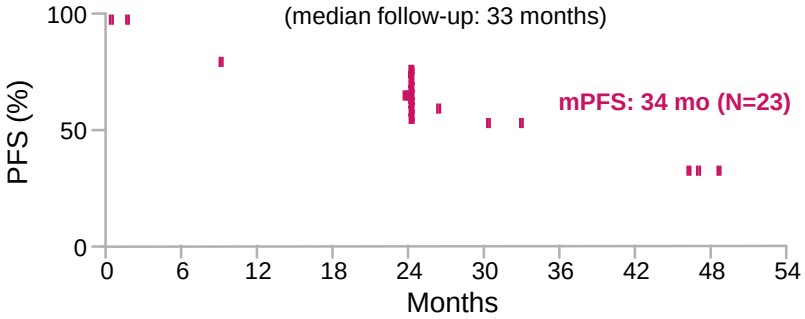
Retrospective cohort study (N=326): Response rates to subsequent therapy after discontinuing venetoclax[1]



Retrospective cohort study (n=44): PFS with BTKi* in BTKi-naive patients after discontinuing venetoclax[1]



Retrospective pooled analysis (N=23): PFS with BTKi† in BCRi-naive patients after PD on venetoclax[2]



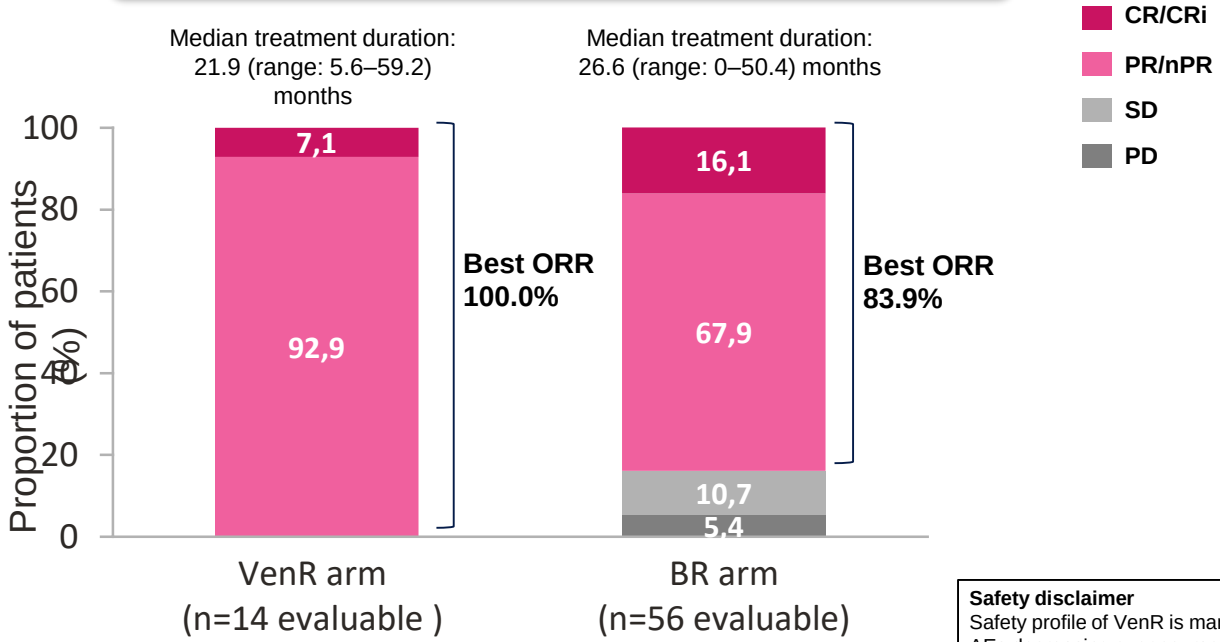
* Ibrutinib or acalabrutinib; † Ibrutinib (n=21) or zanubrutinib (n=2).
BCRi, B-cell receptor pathway inhibitor; BTKi, Bruton's tyrosine kinase inhibitor; PI3Ki, phosphoinositide 3-kinase inhibitor; PR-L, PR with lymphocytosis.

Slide courtesy of Dr Munir.

1. Mato AR, *et al. Clin Cancer Res* 2020; **26:**3589–3596; 2. Lin VS, *et al. Blood* 2020; **135:**2266–2270.

BTKi therapy after fixed-duration venetoclax + anti-CD20 can provide further clinical benefit

MURANO: Best ORR to subsequent BTKi therapy*
(median follow-up: 59 months)

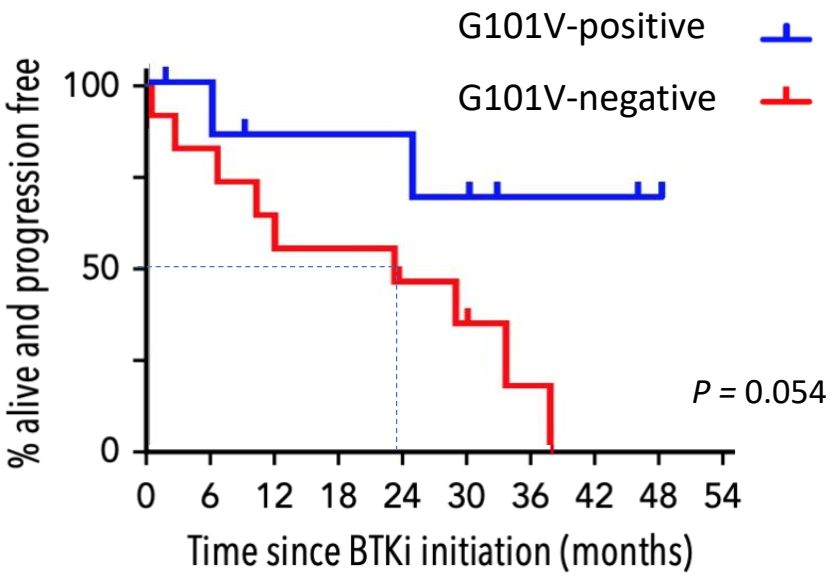


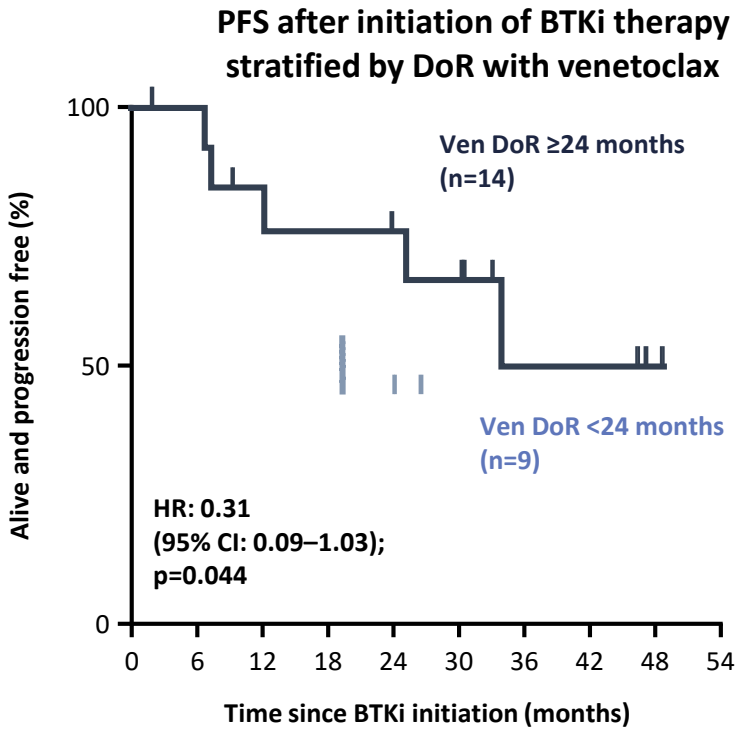
Safety disclaimer
Safety profile of VenR is manageable with rates of Grade 3–4 AEs decreasing over course of treatment, and no new safety signals identified 3 years after treatment

* Responses in patients treated with next line of therapy for insufficient time to have response assessed, or those patients who had no response assessments reported, were considered unevaluable.
B, bendamustine; BTKi, Bruton's tyrosine kinase inhibitor; R, rituximab; Ven, venetoclax.

Harrup R, *et al*. ASH 2020; Abstract 3139 (Poster)
Seymour JF, et al. *Blood* 2022; **140**:839–850..

BTKi in pts with venetoclax-resistant CLL



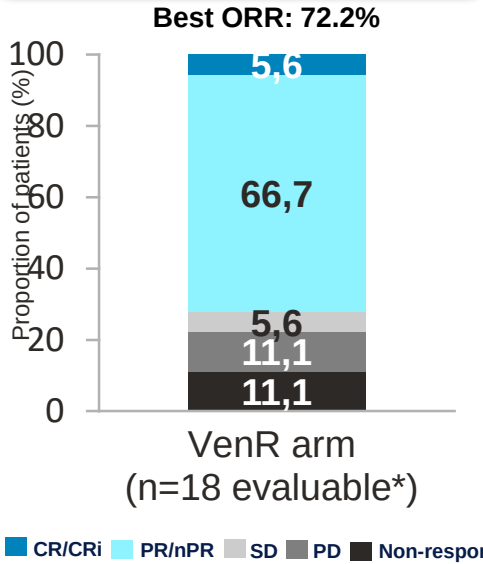


Retrospective, pooled analysis of 23 pts with R/R CLL and PD on venetoclax

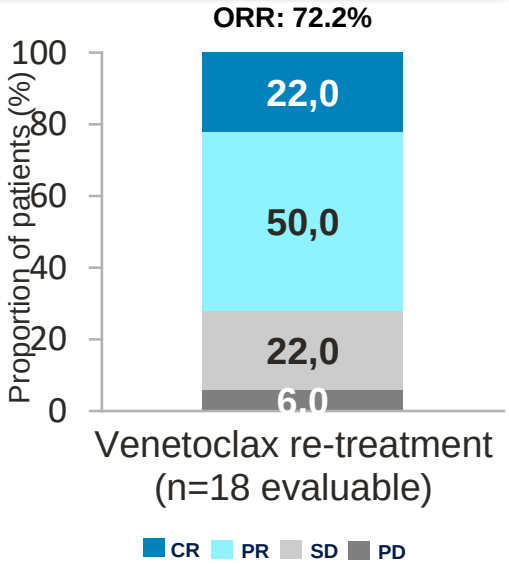
Slide courtesy of Dr Munir
Lin, Blood 2020

Venetoclax-based therapy after venetoclax + anti-CD20 can provide further clinical benefit

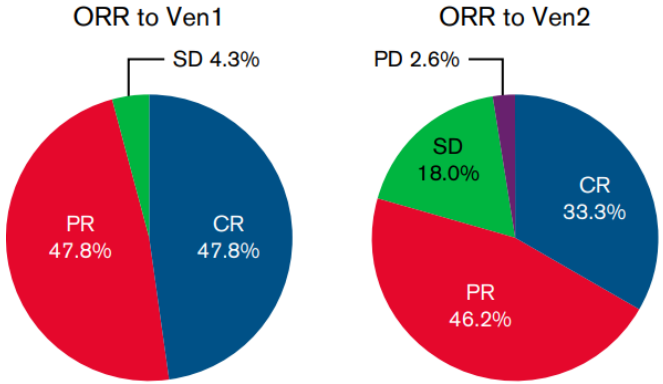
MURANO: ORR with venetoclax regimen after VenR[1]

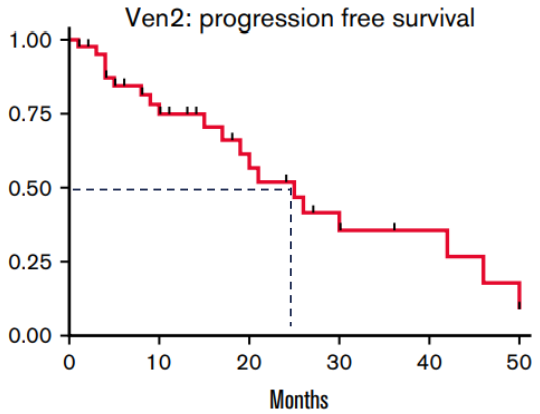


Multicenter, retrospective study (N=25): ORR to venetoclax re-treatment[2]



Safety disclaimer
TLS was a rare event and majority were able to tolerate 400 mg daily[2]

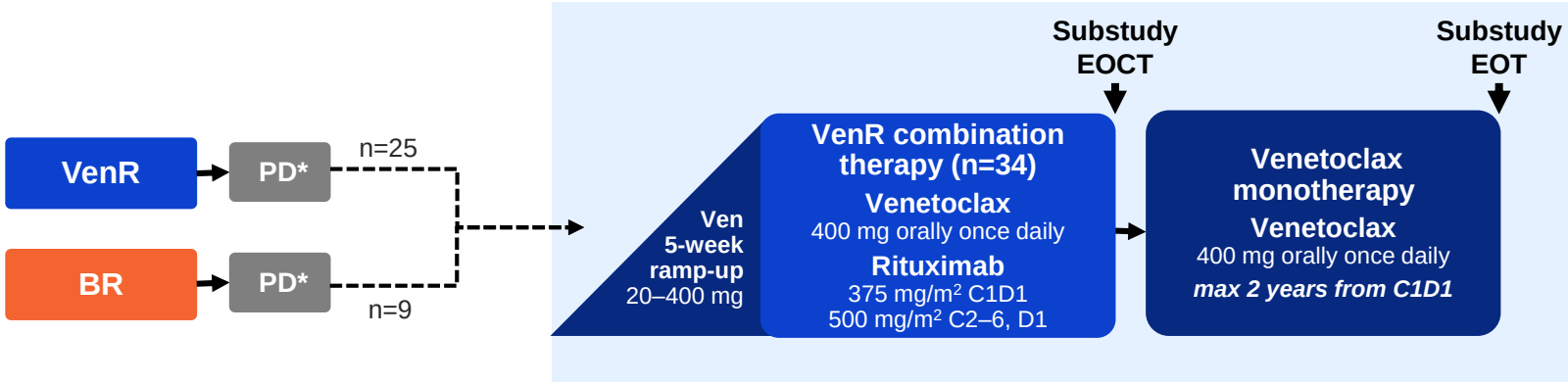




* Median treatment duration: 11.4 (range: 0.7–37.6) months. Responses in patients treated with next line of therapy for insufficient time to have response assessed, or patients who had no response assessments reported were considered unevaluable;
† 28-day cycles, O: 100 mg (IV) D1, 900 mg D2, 1,000 mg D8 and D15 of C1, then 1,000 mg IV D1 C2–6; Ven: 5-week ramp-up (20–400 mg) PO QD D22 of C1, then 400 mg OD C3–12 (Cohort 1) or C3–C24 (Cohort 2).
C, cycle; R, rituximab; Ven, venetoclax.

1. Harrup R, *et al*. ASH 2020. Abstract 3139 (Poster);
2. Thompson MC, *et al.* ASH 2020. Abstract 3136 (Poster);
3. Thompson, Blood Advances, 2022.

MURANO retreatment/crossover substudy



- Out of the 34 patients with PD who entered the substudy, 25 were retreated with VenR
  - Median time (range) from the final study drug dose in the main study to VenR retreatment in the substudy was 2.3 years (1.2–3.1)

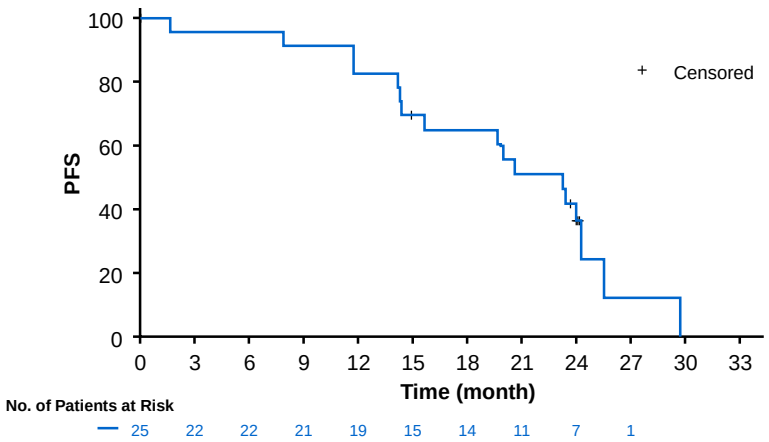
*Investigator-assessed PD according to iwCLL criteria.

VenR retreatment resulted in high response rates, which translated to meaningful PFS amongst retreated patients

- Amongst VenR-retreated patients, median follow up (range) was 33.4 months (2.7–44.0)
  - Median PFS (95% CI) was 23.3 months (15.6–24.3)
  - Best ORR was high at 72.0%; CR rate was 24%
  - Median OS was not reached

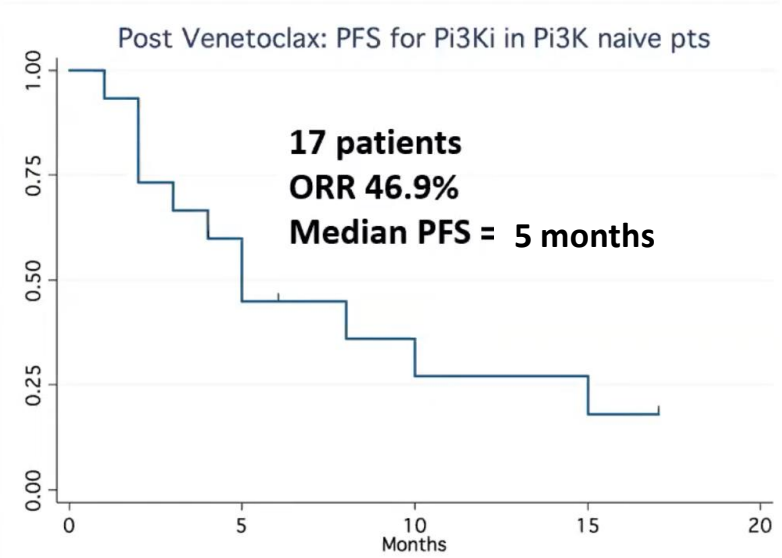
Response rates indicate that VenR retreatment is a viable option for pretreated patients

PFS for VenR-retreated patients in the substudy

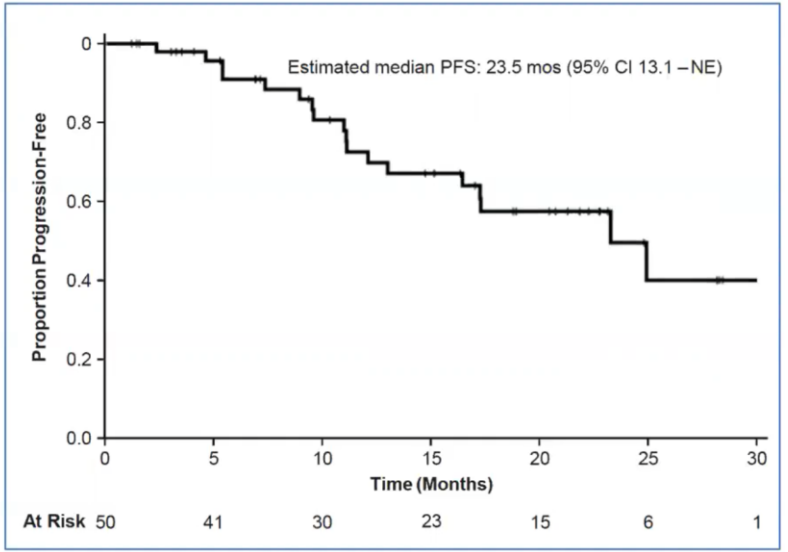


CR, complete response.

PI3Ki in Post BTKi and Venetoclax patients[1]



2nd generation PI3Ki Umbralisib in BTKi/PI3Ki intolerance[2]



USE OF PI3Ki AFTER OTHER TARGETED DRUGS IS LIMITED AND LONG TERM CONTROL OF DISEASE IS POOR

Safety disclaimer
Most common (≥5%) grade ≥3 AEs on umbralisib (all causality) were neutropenia (18%), leukocytosis (14%), thrombocytopenia (12%), pneumonia (12%), and diarrhea (8%). Six patients (12%) discontinued umbralisib because of an AE[2]

1. Mato et al. Clin Cancer Res. 2020; 26(14): 3589–3596.
2. Mato et al Blood. 2020 Dec 1:blood.2020007376.

Umbralisib is not EMA-approved for the treatment of CLL.

CASE STUDY

How to treat and when: 63-years-old male now

1988
CLL diagnosis; on watch and wait

2006: Assessment
IgHV unmutated
FISH- No abnormality

2008: Need for treatment
FCR x 6 → MRD-Negative CR
CLL cell 0.01% in bone marrow

2011: MRD relapse
1 log increase every 18 months

2012: Clinical relapse
Clinical relapse- BR X 6 → PR

2013: Early relapse
Ibrutinib on PCYC 1116 → PR

2018: Need for treatment
Venetoclax with rituximab → MRD-Negative CR

2019: MRD relapse
1 log increase every 12 weeks

Long discussion with patient:
- Allogeneic stem cell transplant
- Cellular therapies

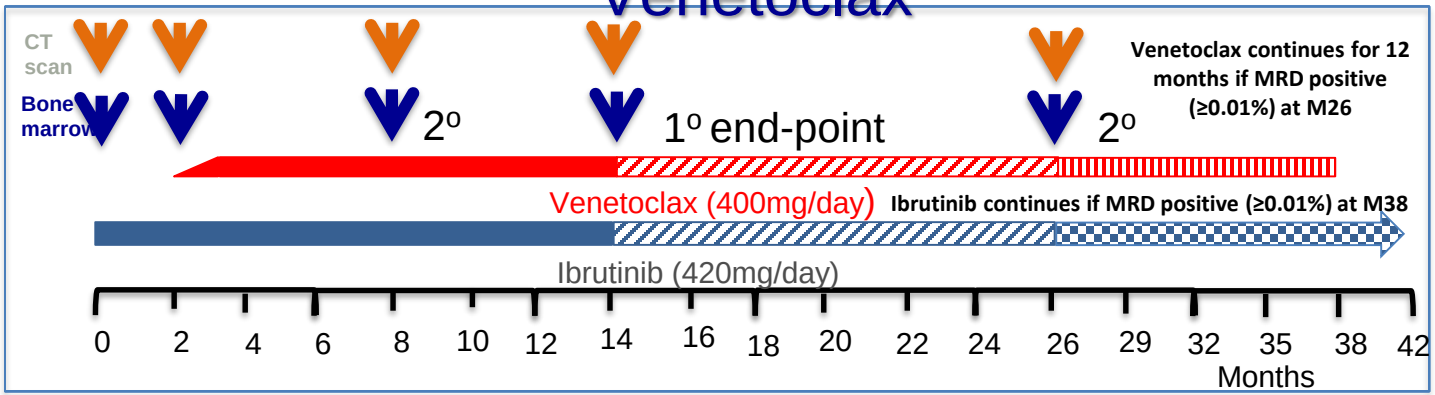
Patient refused Allogeneic SCT

CLL, chronic lymphocytic leukaemia; CR, complete response; FCR, fludarabine, cyclophosphamide + rituximab; Ig, immunoglobulin; *IgHV*, immunoglobulin heavy chain gene; MRD, minimal residual disease; BR, Bendamustine + rituximab

Case courtesy of Dr. Munir.

RR CLL – Could we do better?? MRD directed duration of therapy

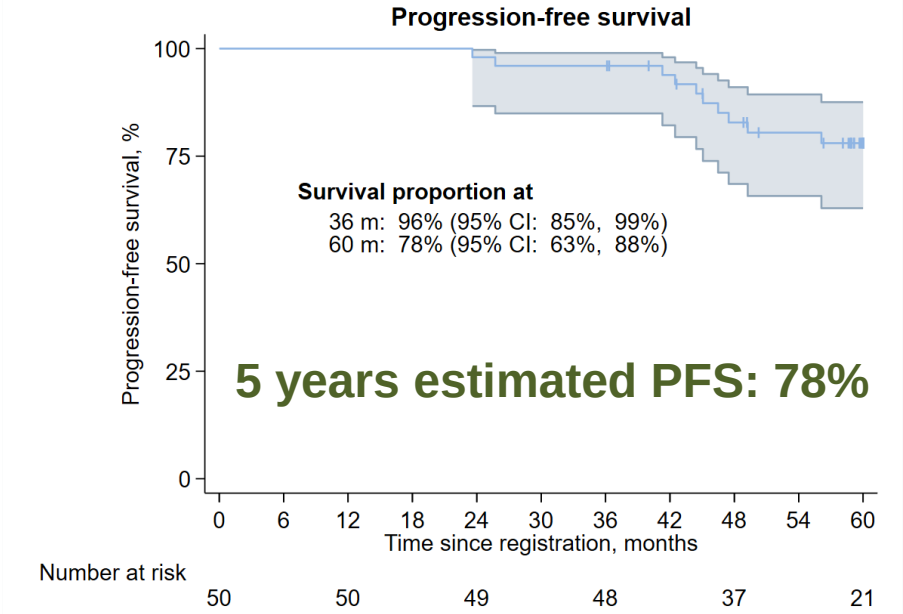
Treatment Schedule and Stopping Rules- Amendment allowed addition of 3rd year of Venetoclax

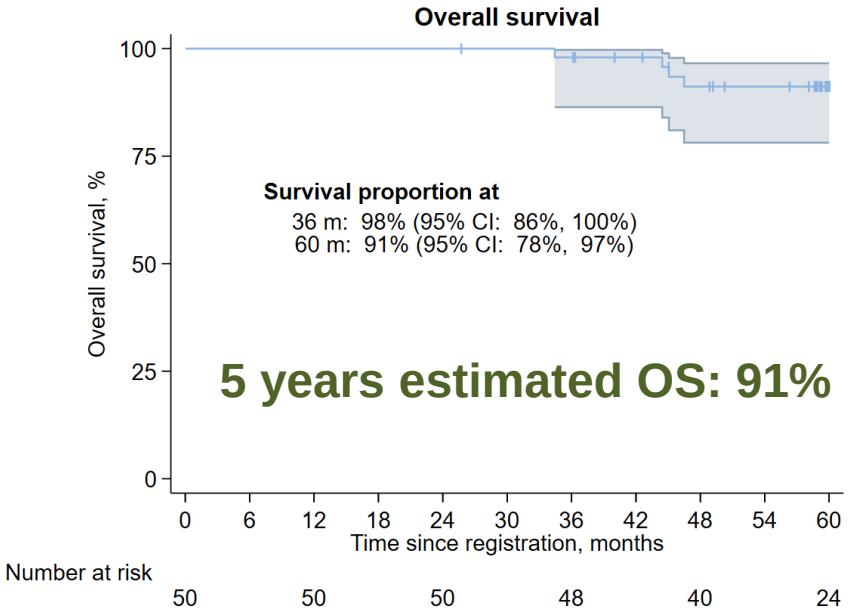


<u>Duration of VEN therapy</u>: 3 consecutive MRD4 (<0.01% CLL) in PB confirmed in BM:
MRD <0.01% at M8 → stop I+V at M14; MRD <0.01% at M14 → stop I+V at M26
MRD negative (<0.01%) at M26 → stop I+V at M26, if MRD positive (≥0.01%) continue IBR till PD
<u>Amendment:</u> if MRD positive (≥0.01%) at M26, Additional Ven for 12 months.

Progression Free and Overall Survival (n=50)

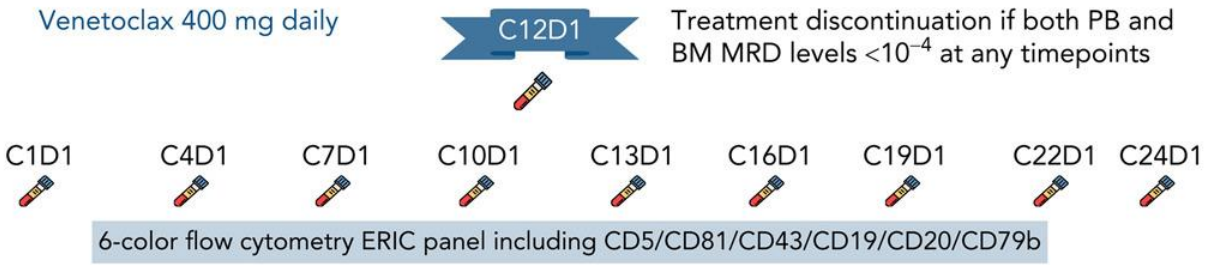
Median PFS and OS not reached by 60 months

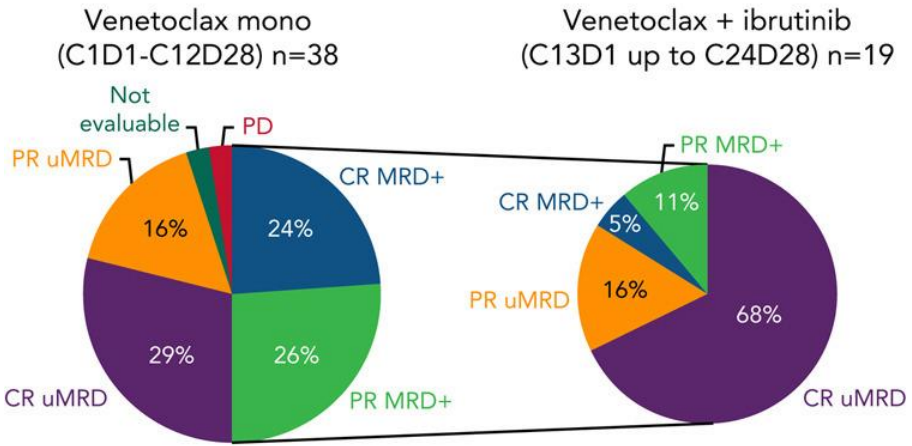


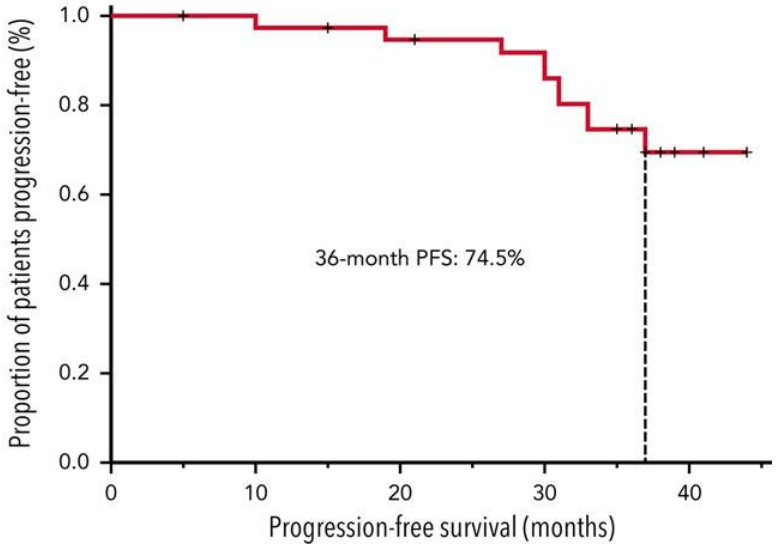


Date of data lock: 01-Nov-2022

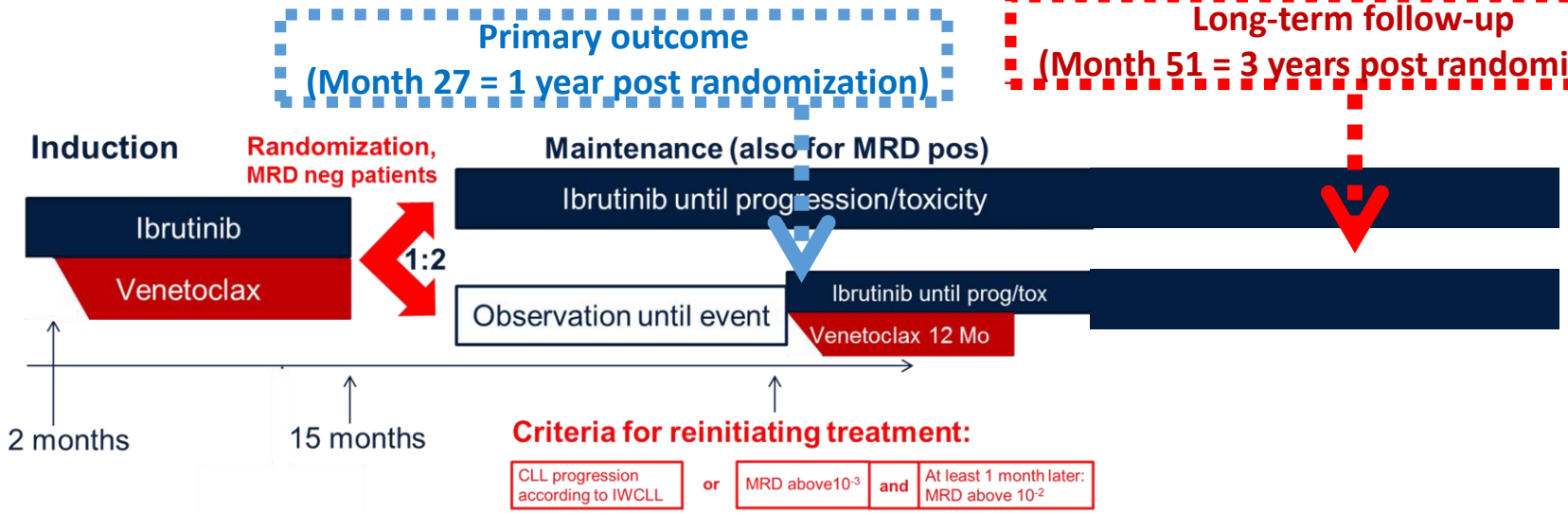
IMPROVE- Minimal residual disease–driven treatment intensification with sequential addition of ibrutinib to venetoclax in R/R CLL[1]







1. Scarfo et al. Blood 2022; 140 (22): 2348–2357.



Primary analysis, when the last patient reached 27 months, showed a favorable benefit-risk profile of MRD based cessation and reinduction:

– Primary endpoint was reached: PFS at 12 months post stopping therapy in arm B = 98%[1]

1. Kater, Lancet Oncol 2022

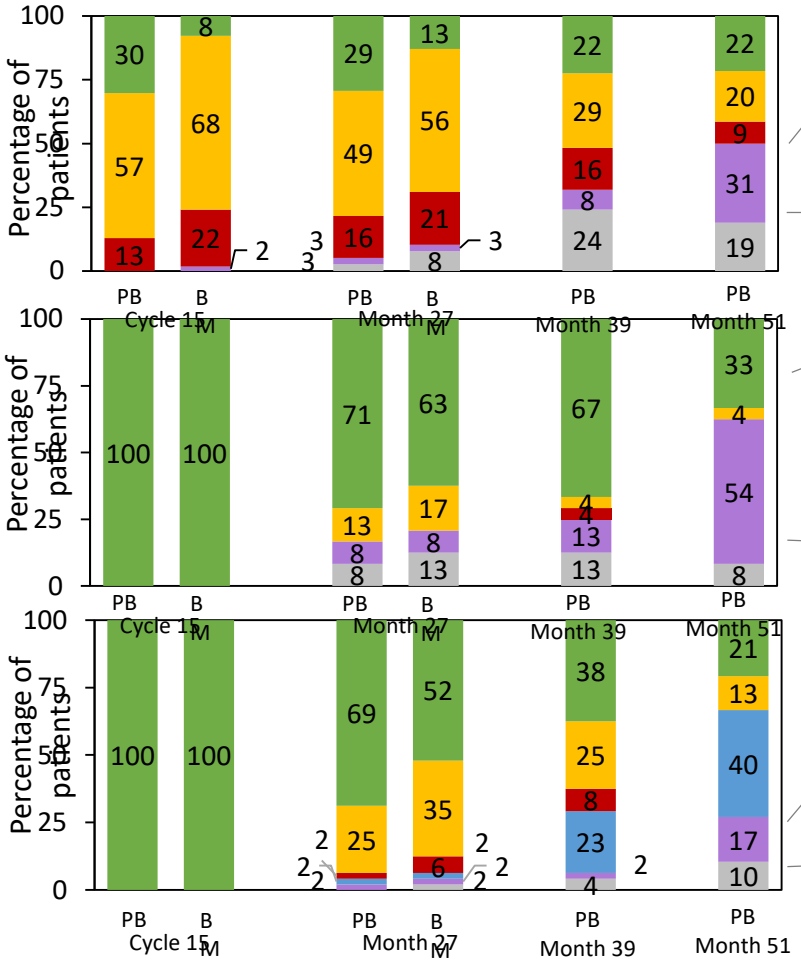
72 patients (32%) achieved uMRD and at least PR after 1 year of I + V combination

MRD responses from randomization + 3 years (Month 51)

Non randomized (N=116)

Arm A: uMRD randomized to continued ibrutinib (N=24)

Arm B: uMRD randomized to observation (N=48)



Off protocol patients and reason:

36 (31%) =
3 deaths
19 toxicities (16%)
2 progression
2 refusal
10 other reasons

13 (54%) =
1 death
6 toxicities (25%)
1 progression
2 refusal
3 other reasons

8 (17%) =
2 deaths
1 toxicity (2%)
1 progression
4 other reasons

<u>Over 3 years after start of observation:</u>

19/48 (40%) patients had MRD conversion (≥MRD2) and reinitiated treatment.

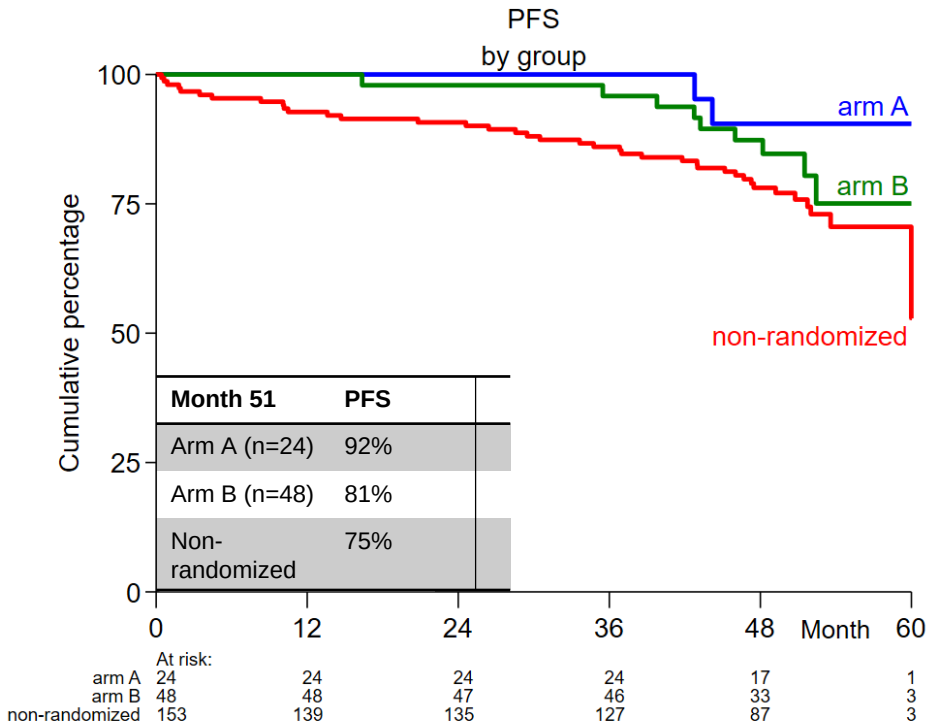
Median time to MRD conversion = 24 months after start of observation (range 6-35)

MRD relapsed patients enriched for:

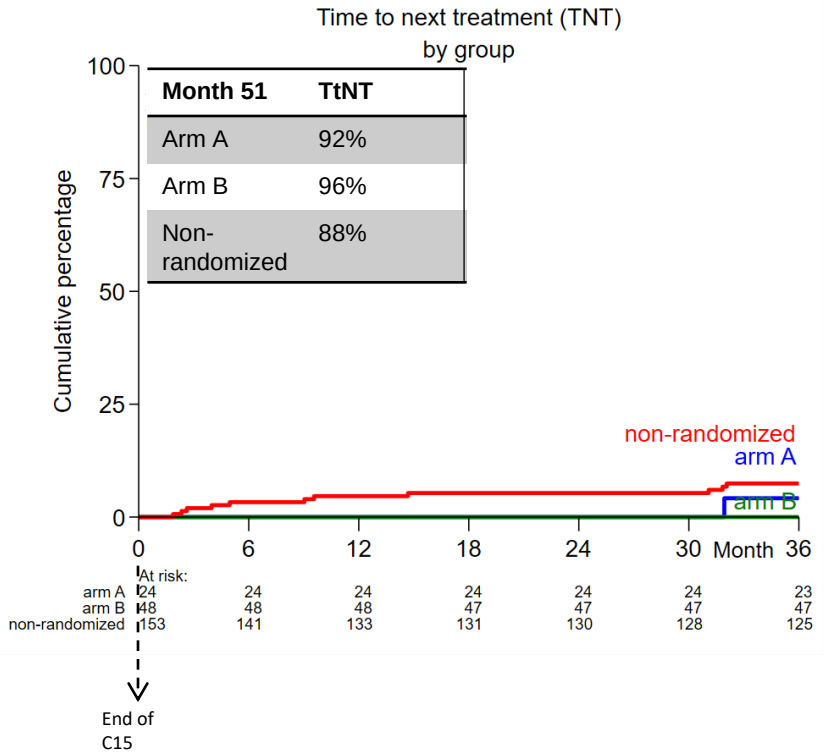
- TP53 abberations
- genomic complexity (≥3 aberrations)

Data cut off January 2023

PFS

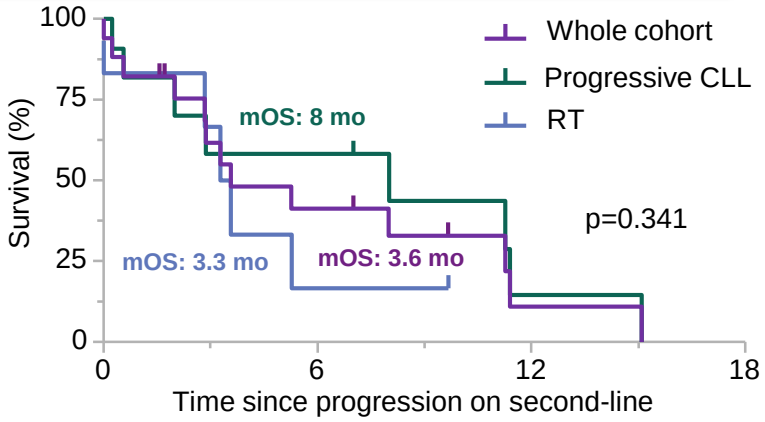


Time to Next Treament



Poor outcomes in patients with double class-resistant CLL

OS after the development of PD on 2L targeted therapy (N=17)

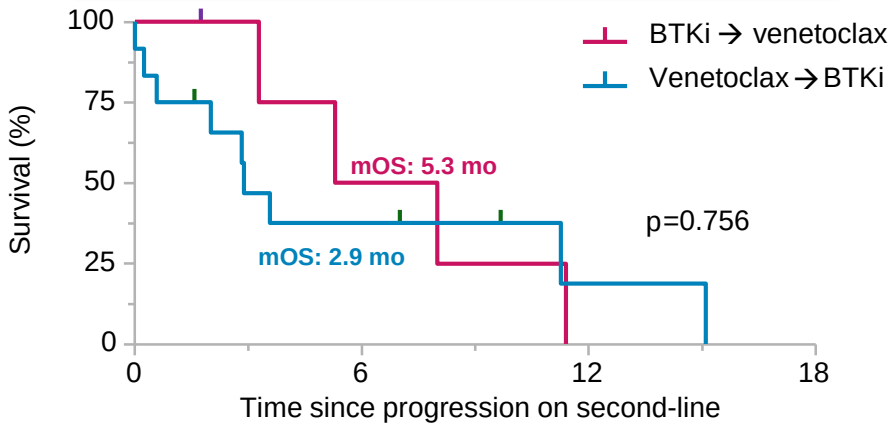


No. at risk:

Whole	17	9	6	4	1
CLL	11	5	5	3	1
RT	6	4	1	1	

No difference in OS between progressive CLL (8 months) and RT (3.3 months)

OS after the development of PD on 2L targeted therapy, stratified by prior sequencing of targeted agents (N=17)



No. at risk:

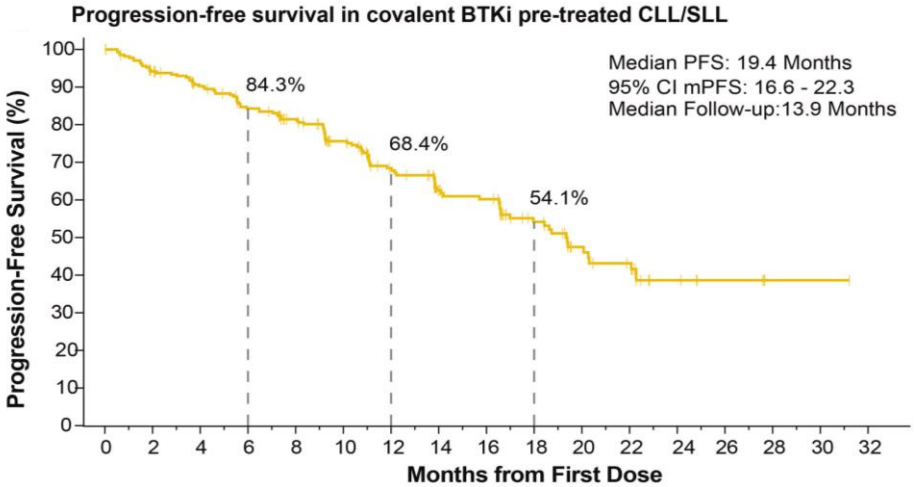
B→V	5	4	2	1	
V→B	12	5	4	3	1

BTKi, Bruton's tyrosine kinase inhibitor; RT, Richter's transformation.

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

Pirtobrutinib

- BRUIN-CLL
  - Phase 1/2, open-label, pirtobrutinib monotherapy, N=170
  - Median 3 prior therapies
  - 25% del17p, 30% *TP53*mut, 88% unmutated IGHV



		BTKi pre-treated CLL/SLL, n	Response Evaluable Cohort, n	ORR, % (95% CI)	Median PFS, months (95% CI)	Estimated 12-month PFS rate, % (95% CI)	Estimated 18-month PFS rate, % (95% CI)
Overall		276	273	74 (68-79)	19.4 (16.6-22.3)	68 (62-74)	54 (46-61)
Age	≥75	57	56	71 (58-83)	20.1 (15.7- NE)	78 (63-87)	62 (44-75)
	<75	219	217	74 (68-80)	18.7 (16.6- NE)	66 (58-73)	52 (43-60)
At least prior BTKi and BCL2i	Yes	122	119	73 (64-81)	14.1 (11.1-18.7)	58 (47-68)	42 (29-55)
	No	154	154	74 (66-81)	22.1 (18.4-NE)	75 (67-82)	62 (52-70)
Del(17p) and/or *TP53* mutation	Yes	99	98	80 (70-87)	16.6 (13.8-22.1)	69 (58-78)	47 (33-59)
	No	107	107	67 (58-76)	19.4 (14.1-NE)	66 (55-75)	58 (46-68)
BTK C481 status*	Mutated	85	85	81 (71-89)	17.0 (13.8-20.3)	69 (57-79)	49 (35-61)
	Unmutated	91	91	65 (54-75)	20.3 (13.8-NE)	63 (52-73)	54 (40-65)
Reason for Prior BTKi discontinuation	Disease progression	206	205	73 (66-79)	18.6 (13.9-20.3)	66 (58-73)	50 (41-59)
	Intolerance & Other	68	66	76 (64-85)	NE (18.4-NE)	77 (64-86)	67 (51-79)

*Pts with available mutation data who progressed on any prior covalent BTKi, excluding those who were covalent BTKi intolerant.
Del(17p)- deletion 17p; PFS- median progression-free survival; DOR- median duration of response; CI- confidence interval; ORR- overall response rate; N- number of patients; n- number of response evaluable patients in sample; NE- not evaluable

- ORR 74% (n=232): 1% CR, 64% PR, 8% PR with lymphocytosis
- 20% Grade 3/4 neutropenia, hypertension (3%) and hemorrhage (2%), 1% afib

Mato AR, Woyach JA, Brown JR, et al. Efficacy of Pirtobrutinib in Covalent BTK-Inhibitor Pre-Treated Relapsed / Refractory CLL/SLL: Additional Patients and Extended Follow-up from the Phase 1/2 BRUIN Study. Blood. 2022;140(Supplement 1):2316-2320.

Nemtabrutinib

- BELLWAVE-001
  - Phase 1/2, open-label
  - Cohort A: R/R CLL/SLL with ≥2 prior therapies, including a covalent BTKi, with a C481 mutation
  - Cohort B: R/R CLL/SLL with ≥2 prior therapies, intolerant to a BTKi, without a C481 mutation
  - Median of 4 prior therapies
  - 63% C481S mutation; 65% *TP53* mutation or del(17p); and 47% IGHV mutation
  - Among all patients with B-cell malignancies treated with twice daily 65 mg nemtabrutinib,
  - 73% had any-grade treatment-related AEs
    - Grade 3 or 4 AEs occurred in 45 pts (40%); 17% neutrophil count decreased
    - The most common AEs of special interest: hypertension (30%) and arthralgia (20%)

Pts with CLL/SLL treated with nemtabrutinib 65 mg QD
n = 57

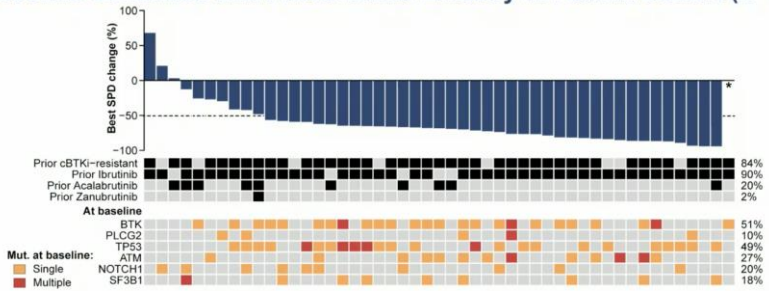
	Cohort A	Cohort B	CLL/SLL with prior BTK and BCL2 inhibitors	C481S-mutated BTK	del(17p)	*IGHV*-unmutated
n (%)	25 (44)	10 (18)	24 (42)	36 (63)	19 (33)	30 (53)
ORR (95% CI), %	60 (39-79)	40 (12-74)	58 (37-78)	58 (41-75)	53 (29-76)	50 (31-69)
Objective response, n (%)						
CR	0 (0)	1 (10)	0 (0)	1 (3)	1 (5)	0
PR	5 (20)	2 (20)	6 (25)	11 (31)	2 (11)	8 (27)
PR with residual lymphocytosis	10 (40)	1 (10)	8 (33)	9 (25)	7 (37)	7 (23)
Median duration of response, months, 95% CI	13.9 5.5-NE	NE NE-NE	8.5 2.7-NE	24.4 8.8-NE	11.2 5.7-NE	24.4 8.5-NE
Median PFS, months, 95% CI	15.7 7.6-NE	NE 0.1-NE	10.1 7.4-15.9	26.3 10.1-NE	10.1 4.6-NE	15.9 7.4-NE

NE, not estimable.

Woyach J, Awan IWFF, Eradat H, Brander DM, Tees M, Parikh S. Updated analysis of BELLWAVE-001: A phase 1/2 open-label dose-expansion study of the efficacy and safety of nemtabrutinib for the treatment of B-cell malignancies. Abst P628. Paper presented at: European Hematology Association Congress, June 8-11, 2023; Frankfurt, Germany.

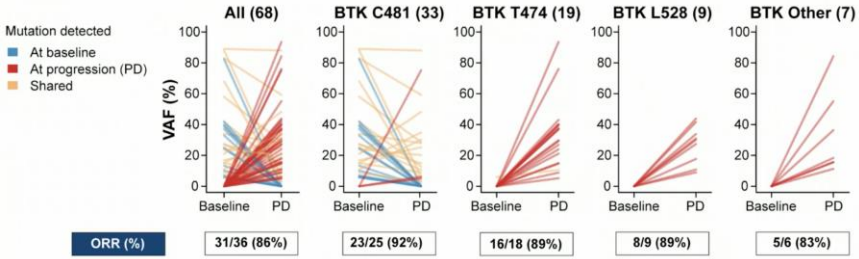
BTK mutations on Non-Covalent BTKi inhibitor are BTK non-C481 mutations

Baseline Genomics and Pirtobrutinib Efficacy in Patient Cohort (n=49)



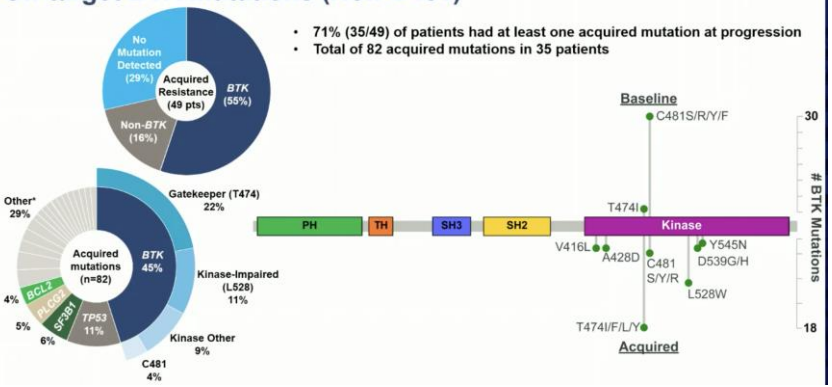
- The most common mutations at baseline were in *BTK* (51%), *TP53* (49%), *ATM* (27%), *NOTCH1* (20%), *SF3B1* (18%), and *PLCG2* (10%)
- A total of 31 *BTK* mutations in 25 patients were detected at baseline: C481S (n=23), C481R (n=4), C481Y (n=2), C481F (n=1), T474I (n=1)
- Pirtobrutinib efficacy was observed regardless of type of prior cBTKi and baseline *BTK* mutational status
- ORR for the resistant population (N=49) was 80% (95%CI 66-90%)

Majority of *BTK* Acquired Mutations were *BTK* T474, L528



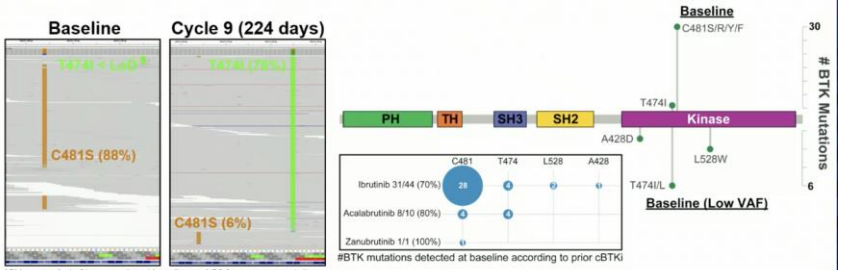
- Decrease/clearance of C481 clones observed at progression on pirtobrutinib in 92% (22/24) patients[a]
- *BTK* C481R/S/Y, T474, L528, other kinase mutations arose at/near progression (n=27 patients[b])
- ORR were similar across groups regardless of the acquired BTK mutation

Acquired Resistance to Pirtobrutinib Mostly Converged Around On-target *BTK* Mutations (Non-C481)



- 71% (35/49) of patients had at least one acquired mutation at progression
- Total of 82 acquired mutations in 35 patients

Several *BTK* Mutations Were Found at Low VAF at Baseline

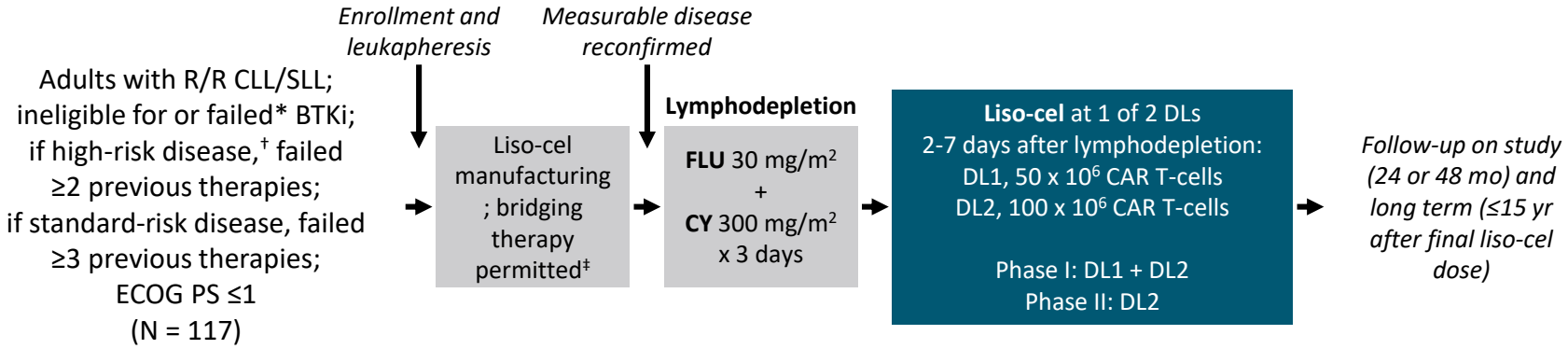


- 9/37 (24%) acquired non-C481 BTK mutations at PD (median VAF at PD: 40% [range, 9-84]) pre-existed at baseline at low VAFs (1-3%)[a]
- These patients had similar responses to pirtobrutinib (6/8, 75% ORR [95%CI, 35-97], median time on pirtobrutinib of 11.2 months (range (3.9-14.5m)) and included patients that received prior ibrutinib (n=4), acalabrutinib (n=3), and ibrutinib + acalabrutinib (n=1)

Brown et al. HemaSphere 7():p e6233246, August 2023

TRANSCEND CLL 004: Study Design

- Multicenter, open-label phase I/II trial



*Ineligibility defined as need for full-dose anticoagulation or arrhythmia history; failure defined as best response of SD/PD, PD after response, or d/c due to unmanageable toxicity. †High-risk disease defined as complex cytogenetic abnormalities, del(17p), *TP53* mutation, or unmutated *IGHV*. ‡Liso-cel manufacturing was not successful for 1 patient.

- **Primary endpoint**: CR/CRi per iwCLL 2018 (IRC)
- **Key secondary endpoints**: ORR, uMRD rate

Siddiqi. ASCO 2023. Abstr 7501. Siddiqi. Lancet. 2023;[Epub]. NCT03331198.

TRANSCEND CLL 004: Efficacy

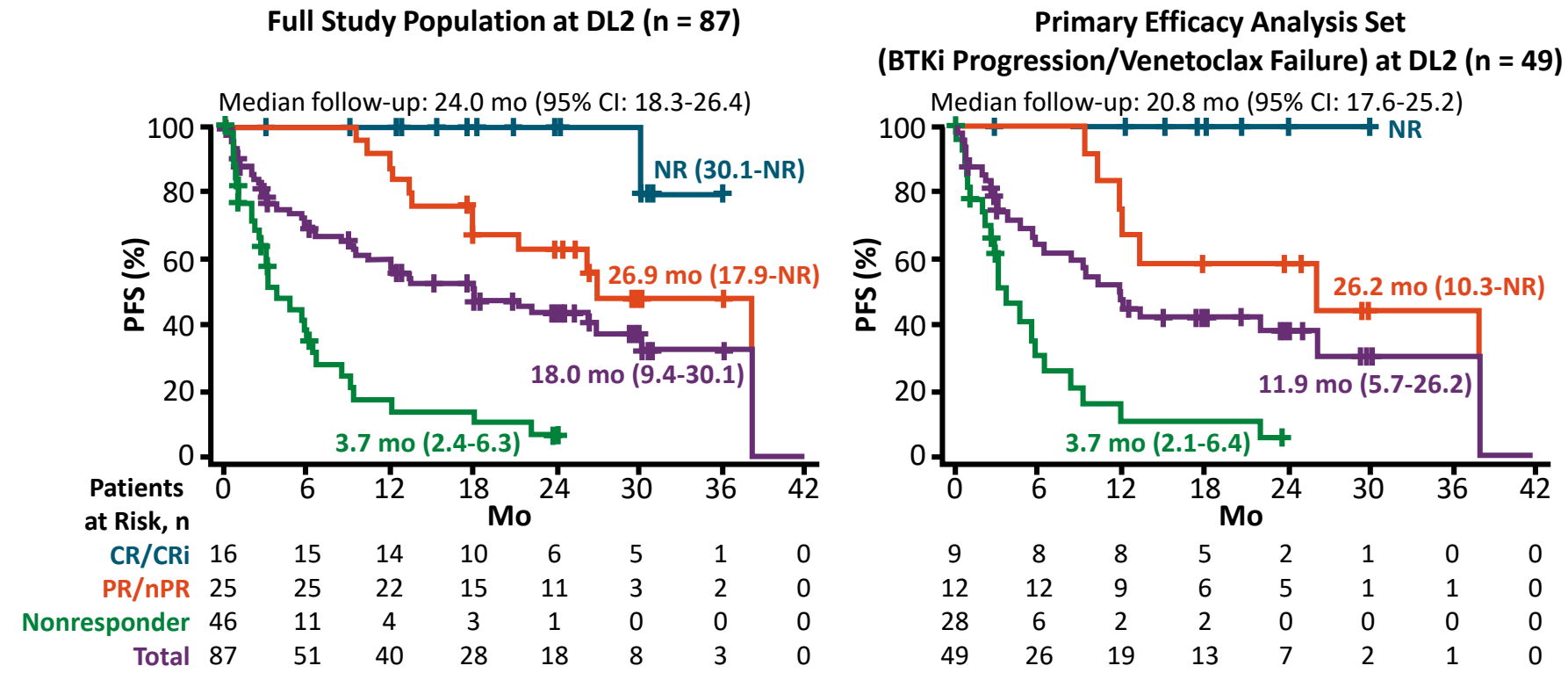
Outcome	Full Study Population at DL2 (n = 87)	BTKi Progression/Venetoclax Failure Subset at DL2 (n = 49)
IRC-assessed CR/CRi rate, % (95% CI)* (primary endpoint)	18 (11-28)	18 (9-32; 1-sided *P* = .0006)
IRC-assessed ORR, % (95% CI)	47 (36-58)	43 (29-58; 1-sided *P* = .3931)
uMRD rate in blood, % (95% CI)	64 (53-74)	63 (48-77)
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 time to first response, mo (range)	1.5 (0.8-17.4)	1.2 (0.8-17.4)
Median time to first CR/CRi, mo (range)	4.4 (1.1-17.9)	3.0 (1.1-6.1)
uMRD rate in marrow, % (95% CI) (exploratory endpoint)	59 (48-69)	59 (44-73)

*By iwCLL 2018 criteria.

- All MRD-evaluable responders were uMRD in blood and BM; n = 12/20 MRD-evaluable patients with SD had uMRD in blood

Siddiqi. ASCO 2023. Abstr 7501. Siddiqi. Lancet. 2023;[Epub].

TRANSCEND CLL 004: PFS by Best Overall Response

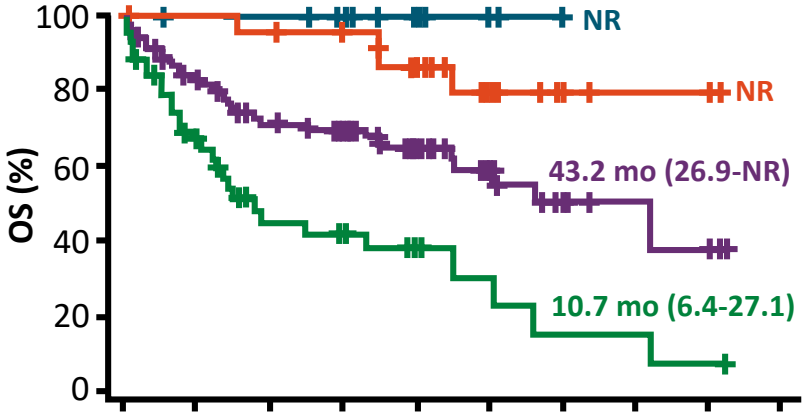


Siddiqi. ASCO 2023. Abstr 7501. Siddiqi. Lancet. 2023;[Epub]. Reproduced with permission.

TRANSCEND CLL 004: OS by Best Overall Response

Full Study Population at DL2 (n = 87)

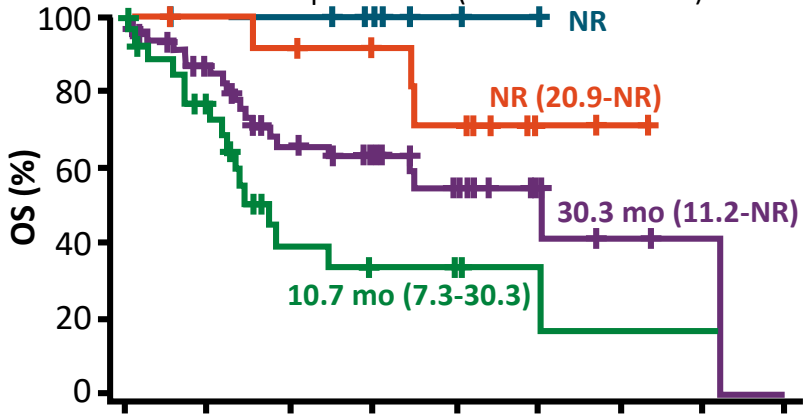
Median follow-up: 24.2 mo (95% CI: 23.3-29.7)



Patients at Risk, n										
CR/CRi	16	15	15	13	7	5	2	0	0	0
PR/nPR	25	25	24	21	16	9	5	2	2	0
Nonresponder	46	26	15	12	8	4	2	2	1	0
Total	87	66	54	46	31	18	9	4	3	0

Primary Efficacy Analysis Set (BTKi Progression/Venetoclax Failure) at DL2 (n = 49)

Median follow-up: 20.8 mo (95% CI: 17.8-25.2)



9	8	8	6	2	1	0	0	0
12	12	11	9	7	2	1	0	0
28	18	7	4	4	2	1	1	0
49	38	26	19	13	5	2	1	0

Siddiqi. ASCO 2023. Abstr 7501. Siddiqi. Lancet. 2023;[Epub]. Reproduced with permission.

TRANSCEND CLL 004: TEAEs of Special Interest

TEAEs of Special Interest, n (%)	Full Study Population (n = 117)
Any-grade CRS	99 (85)
▪ Grade 1/2	43 (37)/46 (39)
▪ Grade 3	10 (9)
▪ Grade 4/5	0
▪ Median time to first onset/resolution, d (range)	4.0 (1-18)/6.0 (2-37)
Any-grade neurologic event*	53 (45)
▪ Grade 1/2	13 (11)/18 (15)
▪ Grade 3	21 (18)
▪ Grade 4	1 (1)
▪ Grade 5	0
▪ Median time to first onset/resolution, d (range)	7.0 (1-21)/7.0 (1-83)

TEAEs of Special Interest, n (%)	Full Study Population (n = 117)
Other AEs	
▪ Prolonged cytopenia	63 (54)
▪ Grade ≥3 infections	20 (17)
▪ Hypogammaglobulinemia	18 (15)
▪ Tumor lysis syndrome	13 (11)
▪ Second primary malignancy	11 (9)
▪ Macrophage activation syndrome	4 (3)

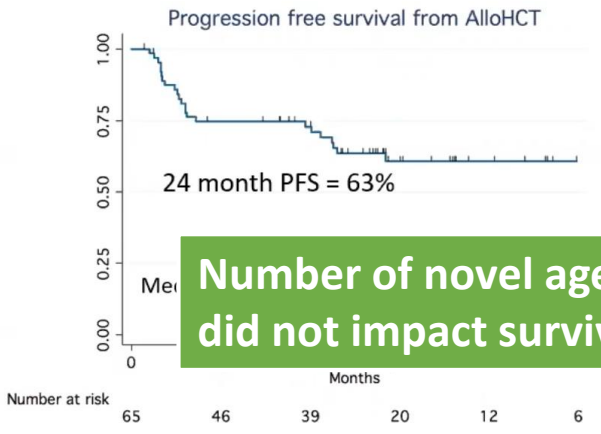
anemia (52%), and thrombocytopenia (41%)

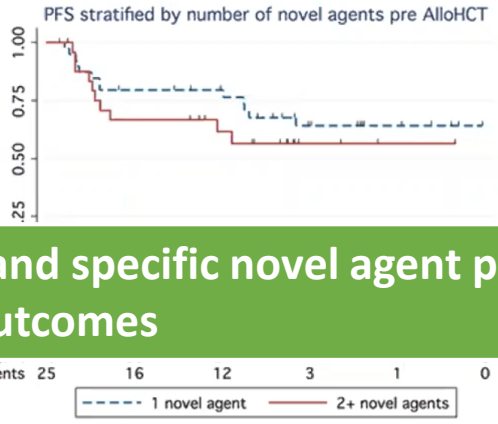
- 5 deaths due to TEAEs: 4 considered unrelated, 1 related (macrophage activation syndrome) to study treatment
- Tocilizumab and/or corticosteroids administered in n = 81 (69%) for management of CRS and/or neurologic event

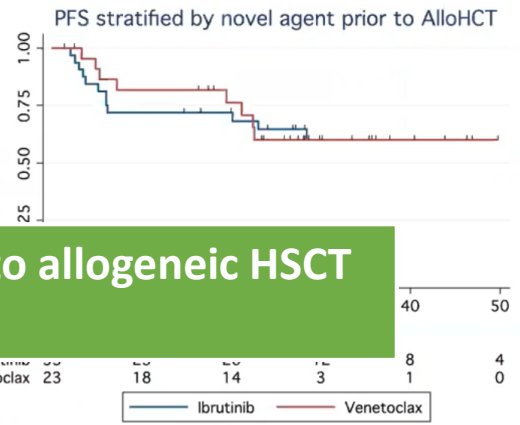
*Neurologic events defined by investigator.

Siddiqi. ASCO 2023. Abstr 7501. Siddiqi. Lancet. 2023;[Epub].

ALLOGENEIC TRANSPLANT IN NOVEL AGENTS ERA







Number of novel agents and specific novel agent prior to allogeneic HSCT did not impact survival outcomes

Multivariable analyses				
HCT-CI (≥1 vs 0)	3.3	1.1-9.9	.035	64
Donor (related vs unrelated)	2.2	0.94-5.2	.07	64

Adapted from Roeker et al, Blood Adv, 2020

Safety disclaimer
Prior NAs do not appear to impact the safety of alloHCT, and survival outcomes are similar regardless of number of NAs received, prior chemoimmunotherapy exposure, or NA immediately preceding alloHCT.

CASE STUDY

Case 2: How to treat and when: 63-years-old male now

1988 — CLL diagnosis; on watch and wait

2006: Assessment — *IgHV* unmutated
FISH- No abnormality

2008: Need for treatment — FCR x 6 → MRD-Negative CR
CLL cell 0.01% in bone marrow

2011: MRD relapse — 1 log increase every 18 months

2012: Clinical relapse — Clinical relapse- BR X 6 → PR

2013: Early relapse — Ibrutinib on PCYC 1116 → PR

2018: Need for treatment — Venetoclax with rituximab → MRD-Negative CR

2019: MRD relapse — 1 log increase every 12 weeks

Long discussion with patient:
- Allogeneic stem cell transplant
- Cellular therapies

Patient refused Allogeneic SCT

Accepted Allogeneic SCT after 18 months on Pirto but progressed and died due to Covid

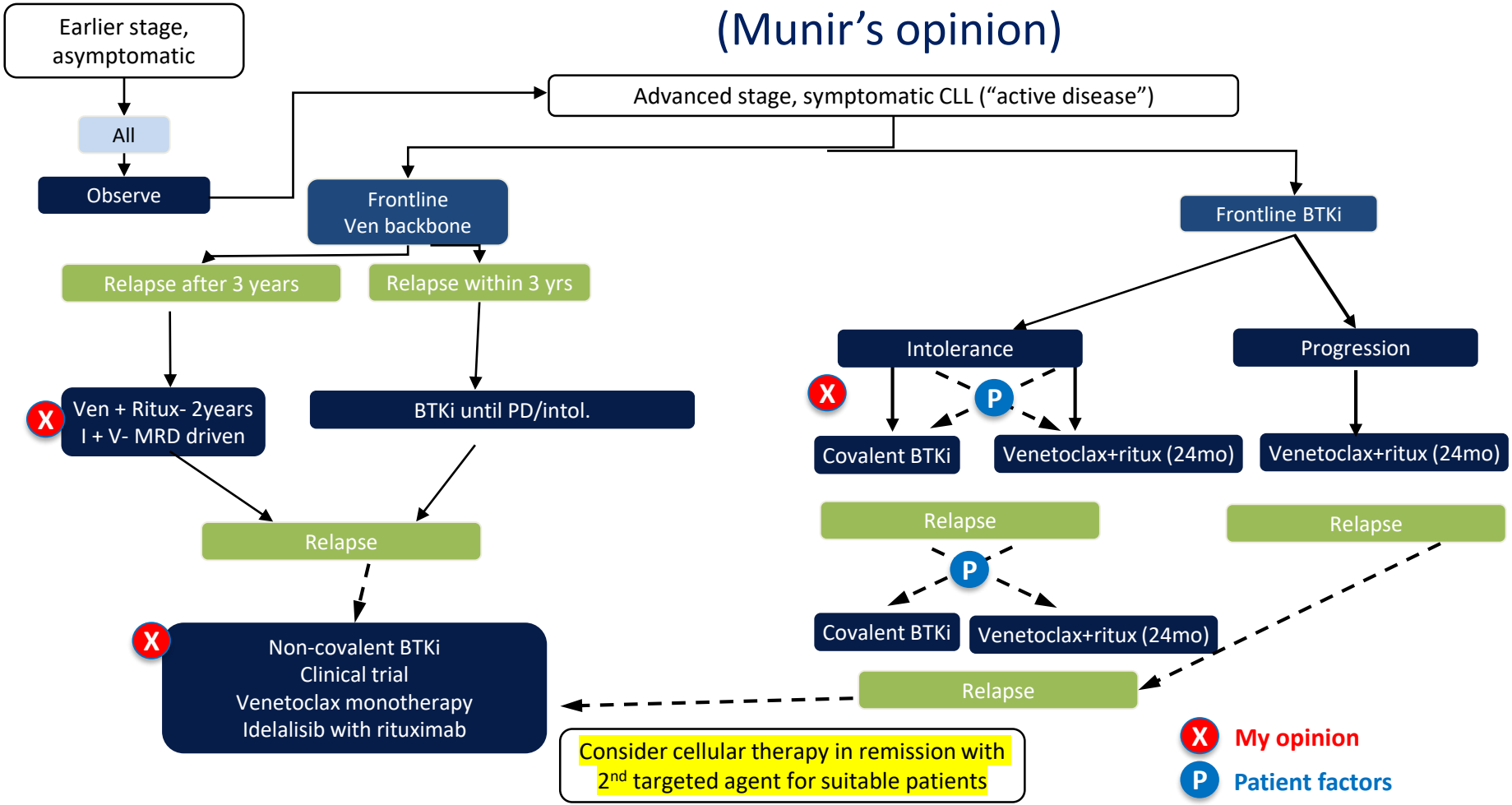
Early relapse:
- Poor response to Campath and Methylprednisolone
- Poor response to Idelalisib
- Recruited on Bruin study

Good response
? Next steps

CLL, chronic lymphocytic leu
immunoglobulin; *IgHV*, immu

Case courtesy of Dr. Munir.

R/R CLL treatment algorithm- 2023 (Munir's opinion)



Future directions and trial

- Phase 3 trials- LOXO 20022 (VEN+R vs VEN+R+Pirto)

Early phase trials:

- BTK degraders (NURIX 2127/5948, BGB-16673)
- PKC-Beta inhibitor
- Bispecific antibodies (EPCORE)
- CDK9 inhibitors
- MALT-1 inhibitor

Conclusions

- CLL care has transformed over the last decade with the advent of novel agents allowing
  - Avoidance of traditional CIT toxicities
  - In some case better clinical responses
  - Potentially less drive to develop resistance mutations related to DNA damage

- Sequencing of the multitude of available therapeutic options remains indeterminant in many instances and must be individualised to
  - Patient preferences
  - Patient comorbidities
  - Features of the CLL itself – disease bulk, high-risk genetic features
  - ? MRD status

- Addressing these questions will help prevent development of double class resistant disease and ultimately improve the lives of our patients

Acknowledgements

Thank you to all patients who participated in the trial along with their families and to research staff at all participating centres.

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Members of the independent Data Safety Monitoring Board and the Trial Steering Committee.
Support from Janssen, Pharmacyclics and Abbvie.