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society of hematologic oncology

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Second line therapy in CLL: what are the best options?

Is two better than one?

Is three better than two?

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Treatments for CLL

1960s

Alkylating agents
- Chlorambucil
- Cyclophosphamide

1970s

Purine nucleosides
- Fludarabine
- Pentostatin
- Cladribine

1980s

Purine nucleosides
and alkylators

1990s

**Chemoimmunotherapy
(FCR, BR)**
Alemtuzumab
Lenalidomide

2000s

2010-2024

BTK inhibitors (**Ibrutinib, Acalabrutinib, Zanubrutinib, Pirtobrutinib**)
PI3K inhibitors (**Idelalisib, Duvelisib**)
BCL-2 inhibitors (**Venetoclax**)
Novel CD20 mAb (**Obinutuzumab**)

CLL lymph nodes: sites of CLL cell proliferation and BCR activation

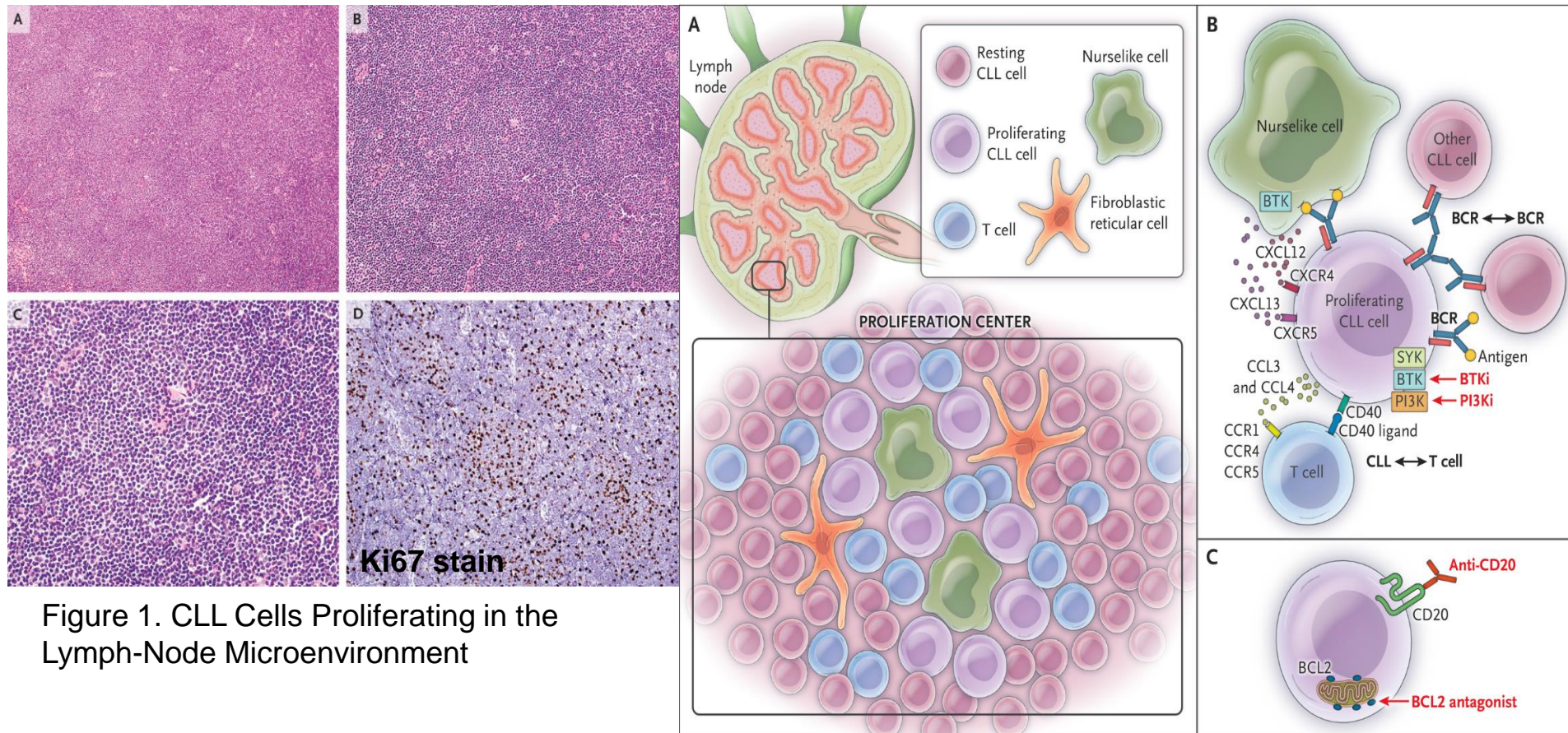
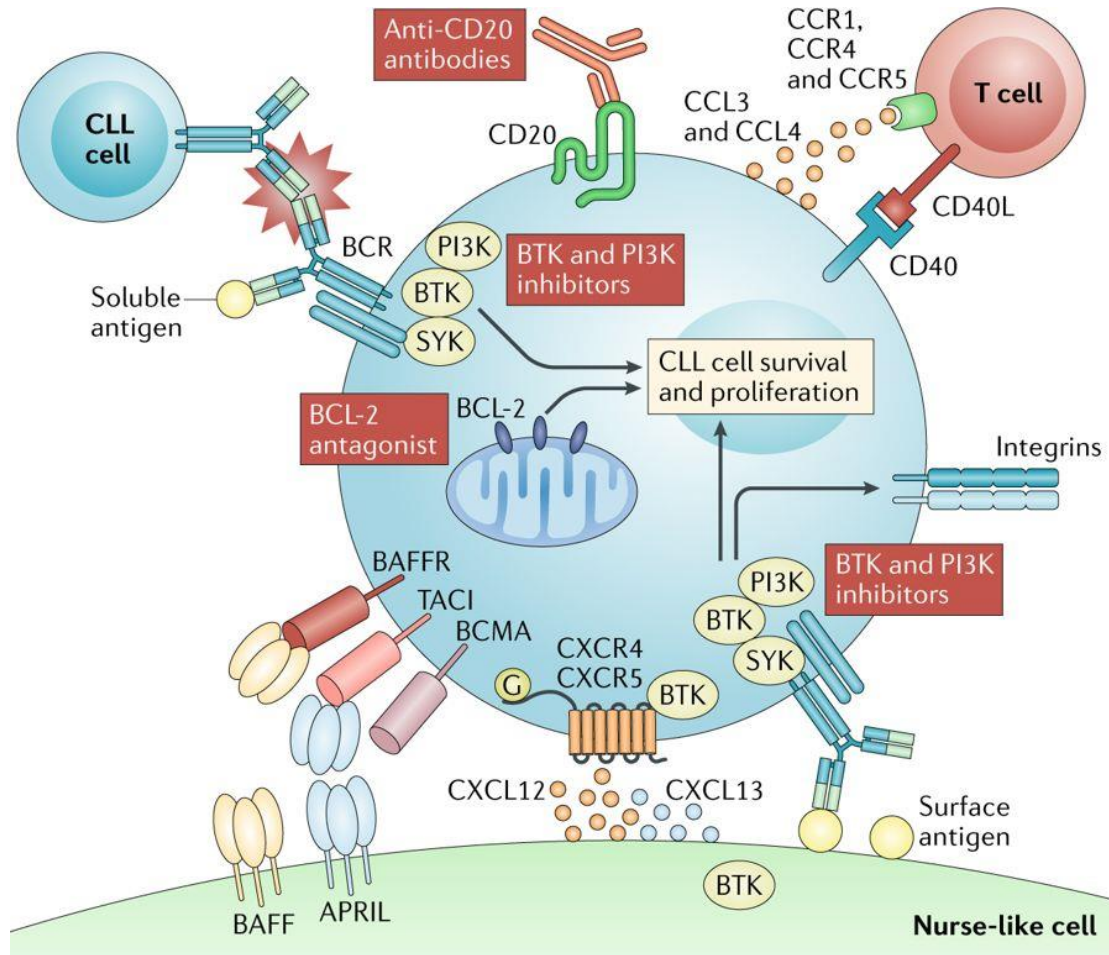
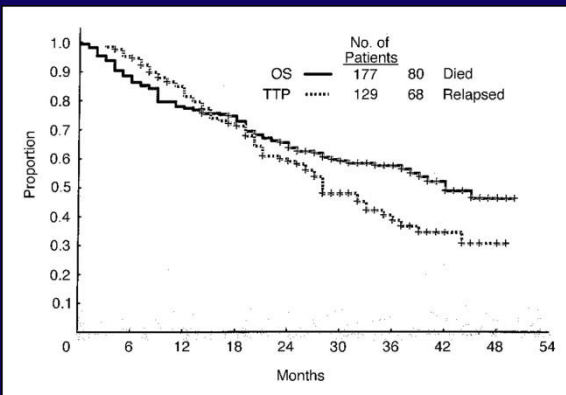
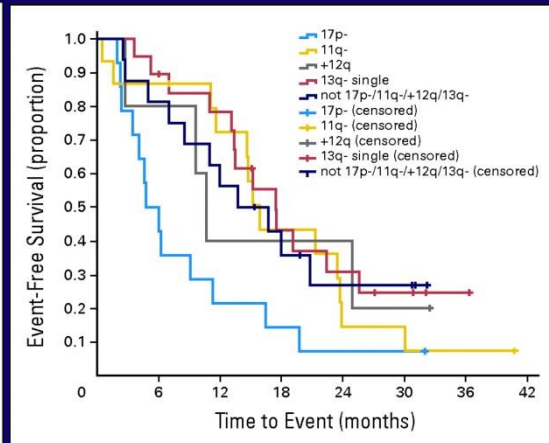
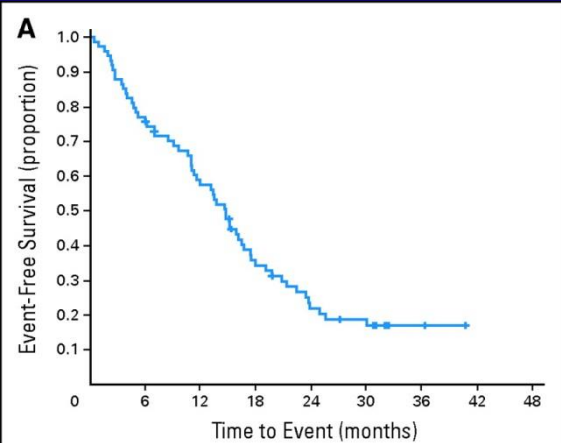


Figure 1. CLL Cells Proliferating in the Lymph-Node Microenvironment

CLL and their microenvironment: pathways and targets



CIT for CLL salvage



BR in R/R CLL¹

- ORR 59.0%, CR 9.0%, PR 47.4%, nPR 2.6%, median event-free survival 14.7 months.
- Severe infections in 12.8% of patients. Grade 3/4 neutropenia 23.1%, thrombocytopenia in 28.2%, and anemia in 16.6%

FCR in R/R CLL²

- ORR 73%, CR 25%, PR 32%, nPR 16%, median TTP 28 months
- Grade 3/4 neutropenia 62%, thrombocytopenia in 17%

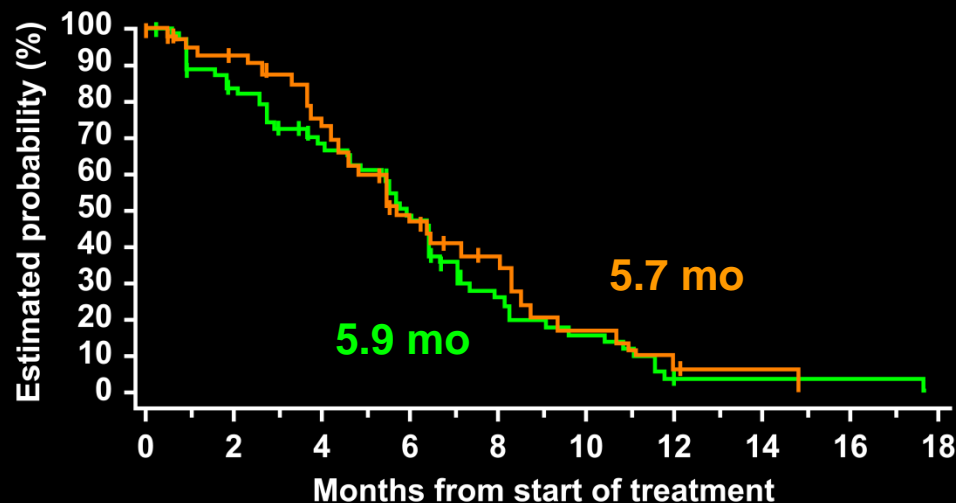
¹ K Fischer *JCO* 29 :3559-3566, 2011

² Wierda W, *JCO* 23:4070-4078, 2005

Ofatumumab in Refractory CLL

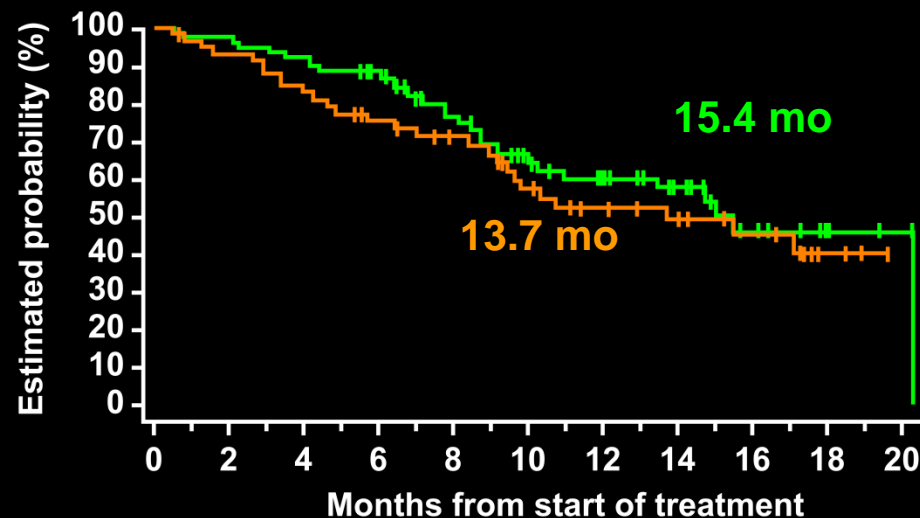
Survival Outcomes

Median progression-free survival*



— DR (n=59)
— BFR (n=79)

Median overall survival**



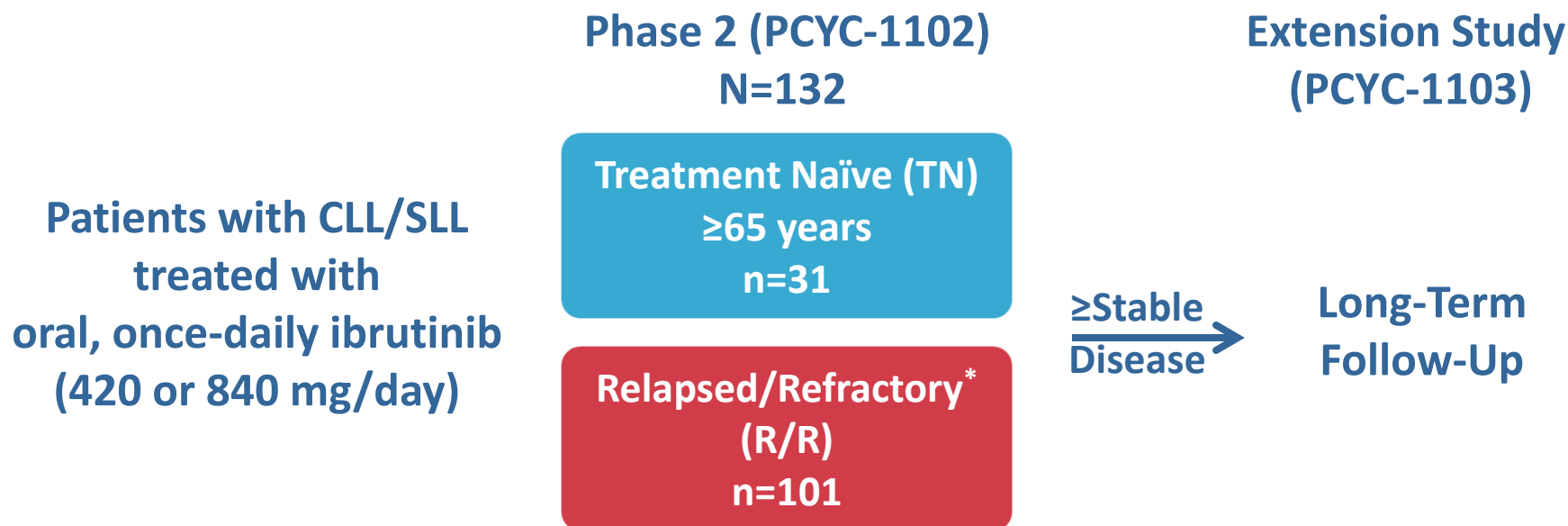
— DR (n=59)
— BFR (n=79)

*Time from start of treatment to progression (assessed by IRC) or death.

**Time from start of treatment to death.

PCYC-1102/1103 Phase 2 Study Design

- Ibrutinib is a first-in-class, once-daily Bruton's tyrosine kinase inhibitor
 - Approved by the US FDA for treatment of patients with CLL/SLL both as first-line treatment and for relapsed/refractory (R/R) disease
 - Allows for treatment without chemotherapy



*R/R includes patients with high-risk CLL/SLL, defined as progression of disease <24 months after initiation of a chemoimmunotherapy regimen or failure to respond

Baseline Characteristics

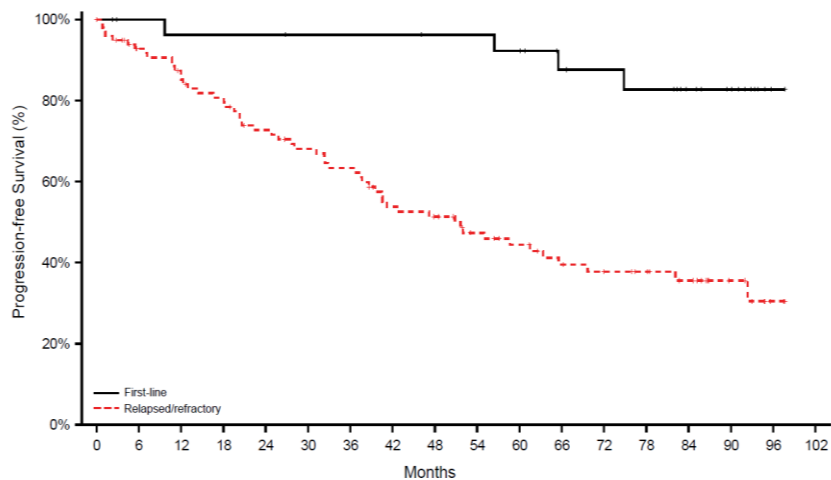
Characteristic	TN (n=31)	R/R (n=101)
Cytogenetic abnormalities		
Del17p	6%	34%
Del11q	3%	35%
Trisomy 12	26%	12%
Del13q	55%	47%
Complex karyotype	13%	37%
Unmutated <i>IGHV</i>	48%	78%
Median lines of prior therapies, n (range)		4 (1–12)
1–2	—	27%
3	—	14%
≥4	—	59%

- The median time on study was 62 months (range, 1–67) for TN patients and 49 months (range, 1–67) for R/R patients.

7-Year Experience With Ibrutinib Monotherapy

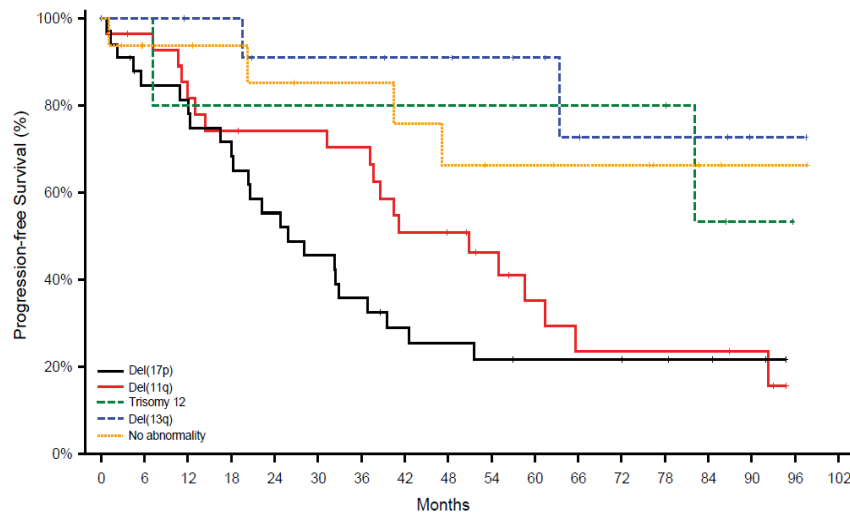
PFS (PCYC 1102/1103)

Progression-Free Survival: TN vs RR



First-line	31	27	26	26	26	25	25	25	24	24	23	19	18	17	13	9	1	0
Relapsed/refractory	101	86	78	72	63	58	54	44	41	34	29	24	22	19	15	8	2	0

PFS in RR CLL: FISH subgroups



Del(17p)	34	26	25	22	17	14	11	8	7	6	5	5	5	4	3	2	0	
Del(11q)	28	26	22	20	19	19	18	13	12	9	6	4	4	4	4	3	0	
Trisomy 12	5	5	4	4	4	4	4	4	4	4	4	4	4	4	2	1	0	
Del(13q)	13	12	11	11	9	9	9	8	8	7	6	4	3	3	3	1	1	0
No abnormality	16	12	12	11	10	9	9	8	7	6	6	5	5	3	2	1	1	0

Median PFS

7-year PFS

TN (n=31)

NR

83%

R/R (n=101)

52 mo

36%

Median PFS

7-year PFS

Del17p (n=34)

26

22%

Del 11q (n=28)

51

23%

Trisomy 12 (n=5)

NR

53%

Del 13q (n=13)

NR

73%

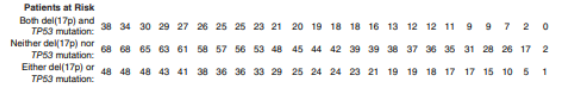
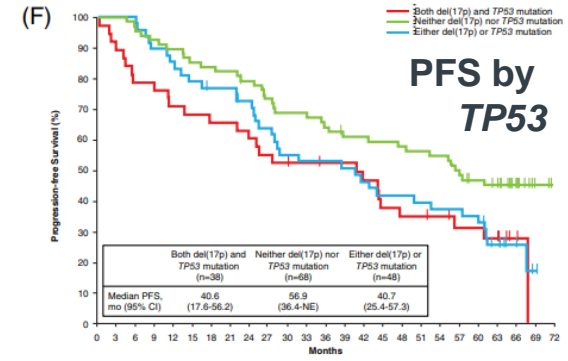
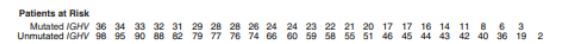
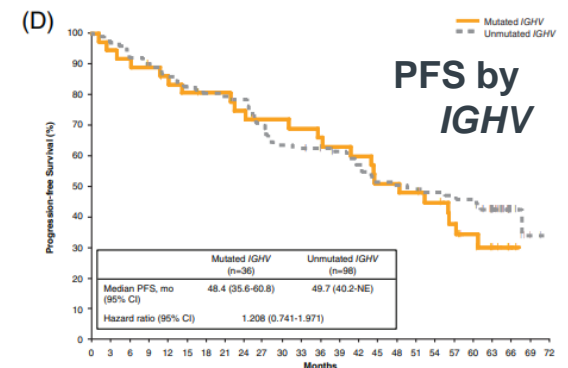
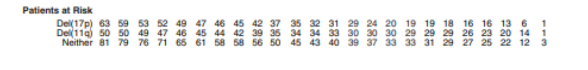
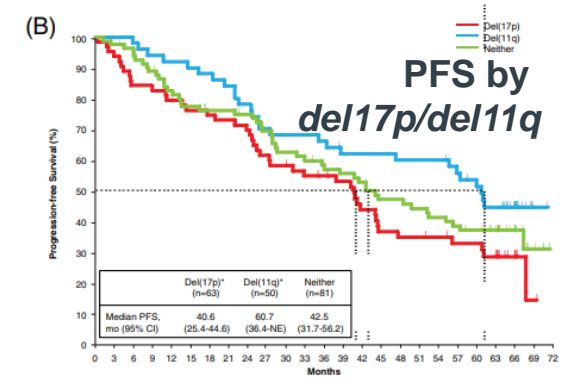
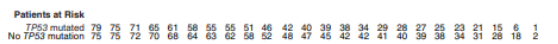
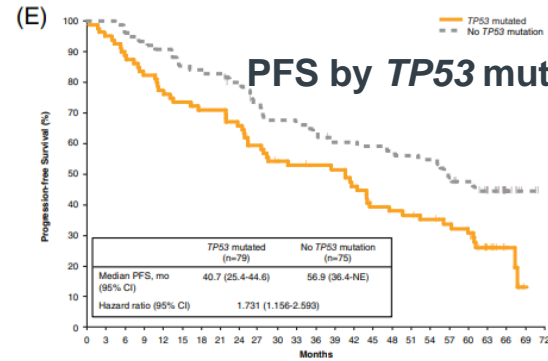
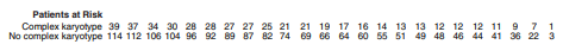
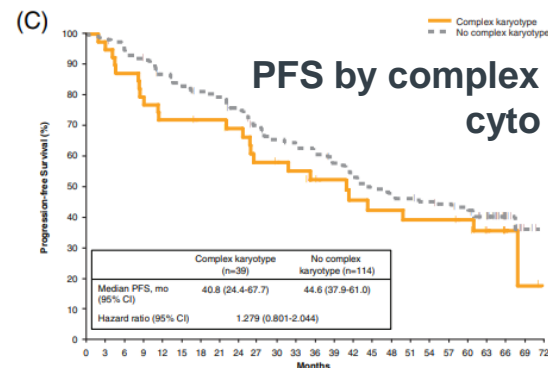
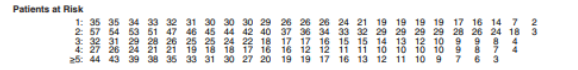
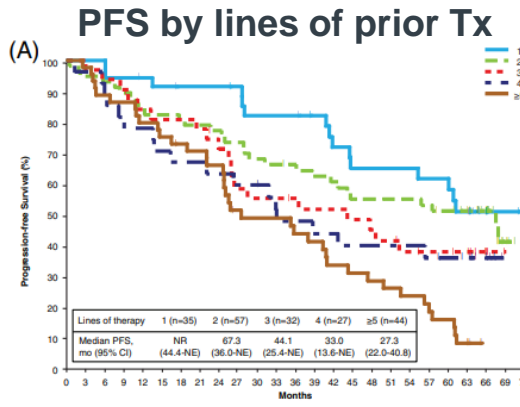
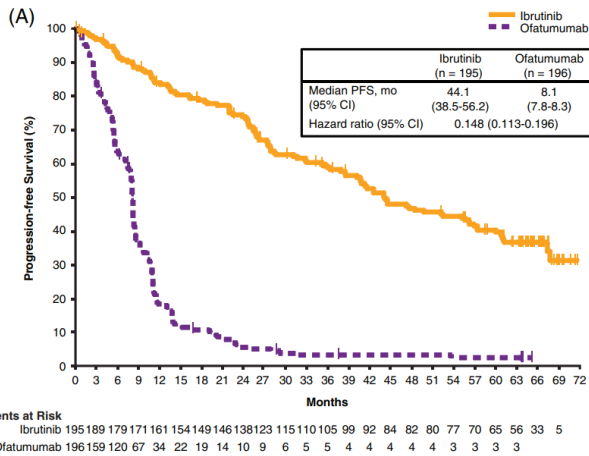
No abnormality

NR

66%

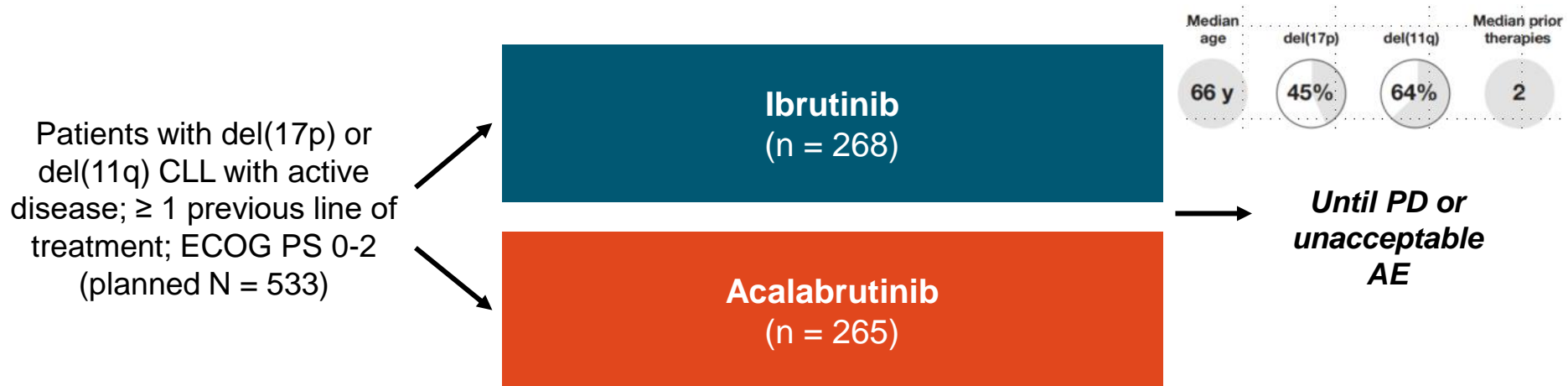
RESONATE trial: Ibrutinib vs. ofatumumab

All patients
PFS 44.1 vs 8.1, months



ELEVATE-RR: Ibrutinib vs Acalabrutinib in Patients With High-Risk Relapsed/Refractory CLL

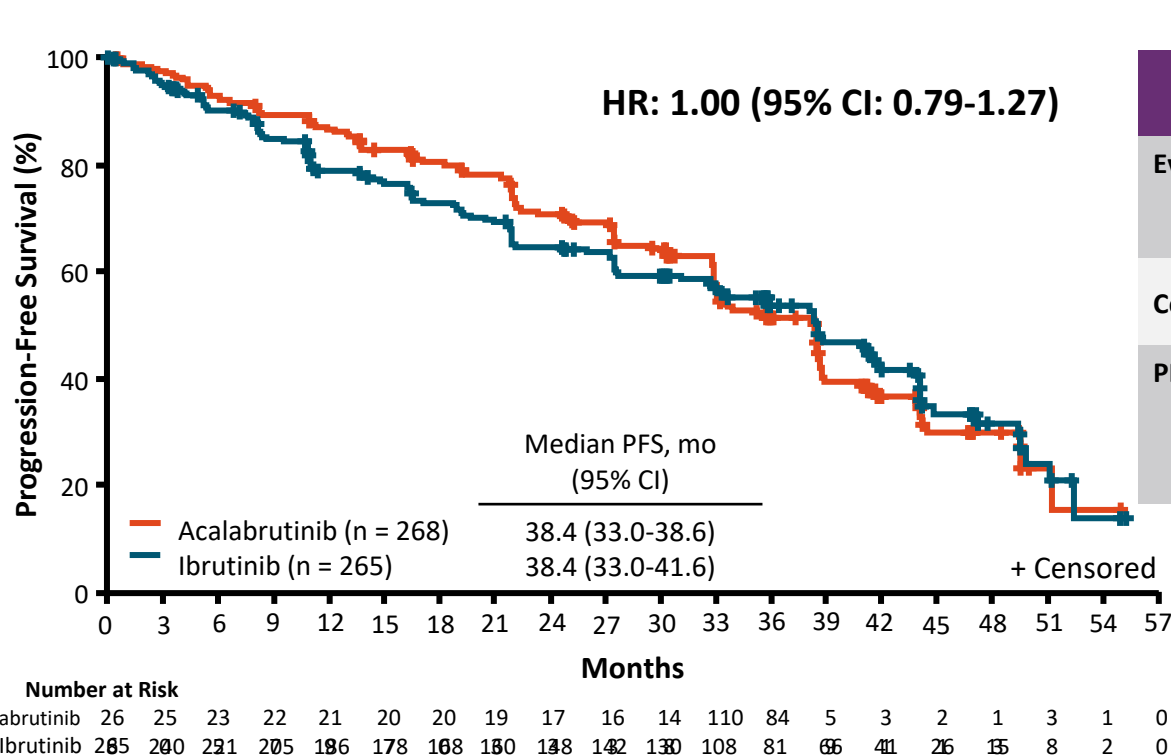
- Final analysis of randomized, multicenter, open-label, noninferiority phase III trial



- Primary endpoint: PFS
- Secondary endpoints: OS; incidence of treatment-emergent AEs, atrial fibrillation; Richter's transformation; grade ≥3 infections
- FPI October 2015 – LPI November 2017 (25 mo)
- Final analysis: 279 IRC PFS events, data cutoff 9/2020

ELEVATE-RR: Noninferiority on IRC-Assessed PFS

- Noninferiority met on IRC-assessed PFS



Median follow-up: 41 months

	Acalabrutinib (n = 268)	Ibrutinib (n = 265)
Events, n (%)	143 (53.4)	136 (51.3)
Death	22 (8.2)	28 (10.6)
PD	121 (45.1)	108 (40.8)
Censored, n (%)	125 (46.6)	129 (48.7)
PFS (95% CI), %		
12 months	86.7 (81.8-90.3)	78.8 (73.1-83.4)
24 months	70.9 (64.8-76.1)	64.5 (58.1-70.2)
36 months	51.4 (44.7-57.8)	53.8 (47.0-60.1)

Noninferiority achieved if upper bound of the 95% CI of HR is less than the prespecified NI margin of 1.429

Adverse Events: ELEVATE – R/R

Event	Acalabrutinib (n = 266)		Ibrutinib (n = 263)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Diarrhea ^{a,b}	92 (34.6)	3 (1.1)	121 (46.0)	13 (4.9)
Headache ^{a,b}	92 (34.6)	4 (1.5)	53 (20.2)	0
Cough ^a	77 (28.9)	2 (0.8)	56 (21.3)	1 (0.4)
Fatigue ^b	54 (20.3)	9 (3.4)	44 (16.7)	0
Arthralgia ^a	42 (15.8)	0	60 (22.8)	2 (0.8)
Hypertension ^{a,b}	23 (8.6)	11 (4.1)	60 (22.8)	23 (8.7)
Contusion ^a	31 (11.7)	0	48 (18.3)	1 (0.4)
Atrial fibrillation ^a	24 (9.0)	12 (4.5)	41 (15.6)	9 (3.4)
Urinary tract infection ^a	22 (8.3)	3 (1.1)	36 (13.7)	6 (2.3)
Back pain ^a	20 (7.5)	0	34 (12.9)	2 (0.8)
Dyspepsia	10 (3.8)	0	32 (12.2)	0

ELEVATE-RR: AEs of clinical interest

AE, n (%)	Acalabrutinib (n = 266)		Ibrutinib (n = 263)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Cardiac events <ul style="list-style-type: none"> ▪ Atrial fibrillation/flutter ▪ Ventricular arrhythmias 	64 (24.1) 25 (9.4) 0	23 (8.6) 13 (4.9) 0	79 (30.0) 42 (16.0) 3 (1.1)	25 (9.5) 10 (3.8) 1 (0.4)
Bleeding events <ul style="list-style-type: none"> ▪ Major bleeding events 	101 (38.0) 12 (4.5)	10 (3.8) 10 (3.8)	135 (51.3) 14 (5.3)	12 (4.6) 12 (4.6)
Hypertension	25 (9.4)	11 (4.1)	61 (23.2)	24 (9.1)
Infections	208 (78.2)	82 (30.8)	214 (81.4)	79 (30.0)
ILD/pneumonitis	7 (2.6)	1 (0.4)	17 (6.5)	2 (0.8)
SPMs, excluding NMSC	24 (9.0)	16 (6.0)	20 (7.6)	14 (5.3)

Detailed Safety Profile of Acalabrutinib vs Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia in the ELEVATE-RR trial

Patients
Previously treated CLL (N = 533)

Randomized 1:1


Acalabrutinib
PO 100 mg BID
n = 266 treated

OR

Ibrutinib
PO 420 mg QD
n = 263 treated

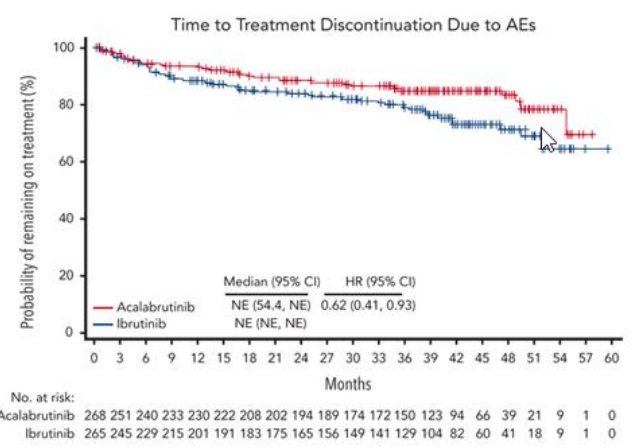
Secondary Safety Analysis

- Exposure-adjusted incidence rates in events per 100 person-months
- Subgroup analyses for ECIs: age, number of prior lines of therapy, prior history of event, AE management
- AE burden score: considers AE duration, recurrence, and grade weighting of the AE in a single score

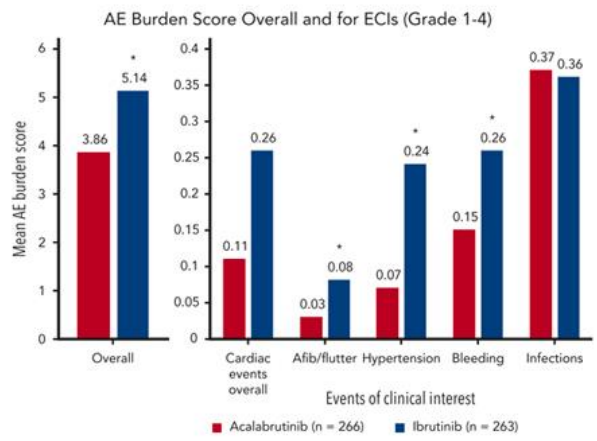
Median time on study  40.9 months

Exposure-adjusted Incidence

- Diarrhea, arthralgia, UTI, back pain, muscle spasms, and dyspepsia incidence rates were 1.5- to 4.1-fold higher with ibrutinib
- Headache and cough incidence rates were 1.6- and 1.2-fold higher, respectively, with acalabrutinib
- Afib/flutter, hypertension, and bleeding incidence rates were 1.6- to 2.8-fold higher with ibrutinib



AE, adverse event; Afib/flutter, atrial fibrillation/atrial flutter; BID, twice daily; CI, confidence interval; CLL, chronic lymphocytic leukemia; ECI, event of clinical interest; HR, hazard ratio; NE, not estimable; PO, orally; QD, once daily; UTI, urinary tract infection.



*Two-sided P-value < .05 without multiplicity adjustment based on Wilcoxon rank-sum test. P-value compares difference in overall distribution rather than mean score.

Conclusions:

- 1) Event-based analyses and AE burden scores demonstrated higher AE burden both overall and specifically for afib/flutter, hypertension, and hemorrhage with ibrutinib vs acalabrutinib
- 2) AE for which both event-based outcomes and AE burden scores were higher with acalabrutinib was limited to headache

ALPINE Study Design

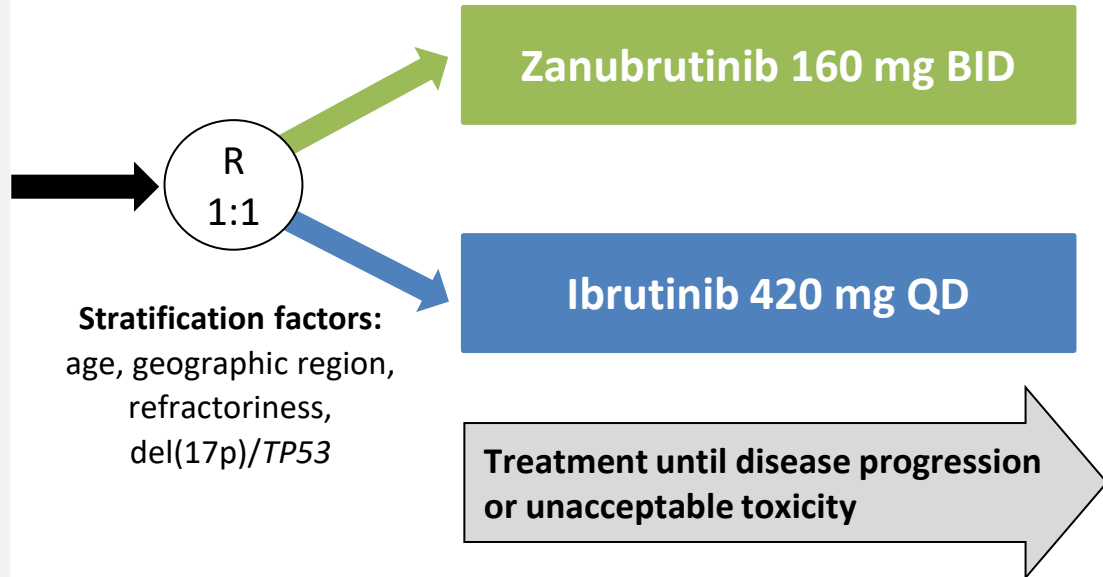
R/R CLL/SLL with ≥ 1 prior treatment
(Planned N=600, Actual N=652)

Key Inclusion Criteria

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

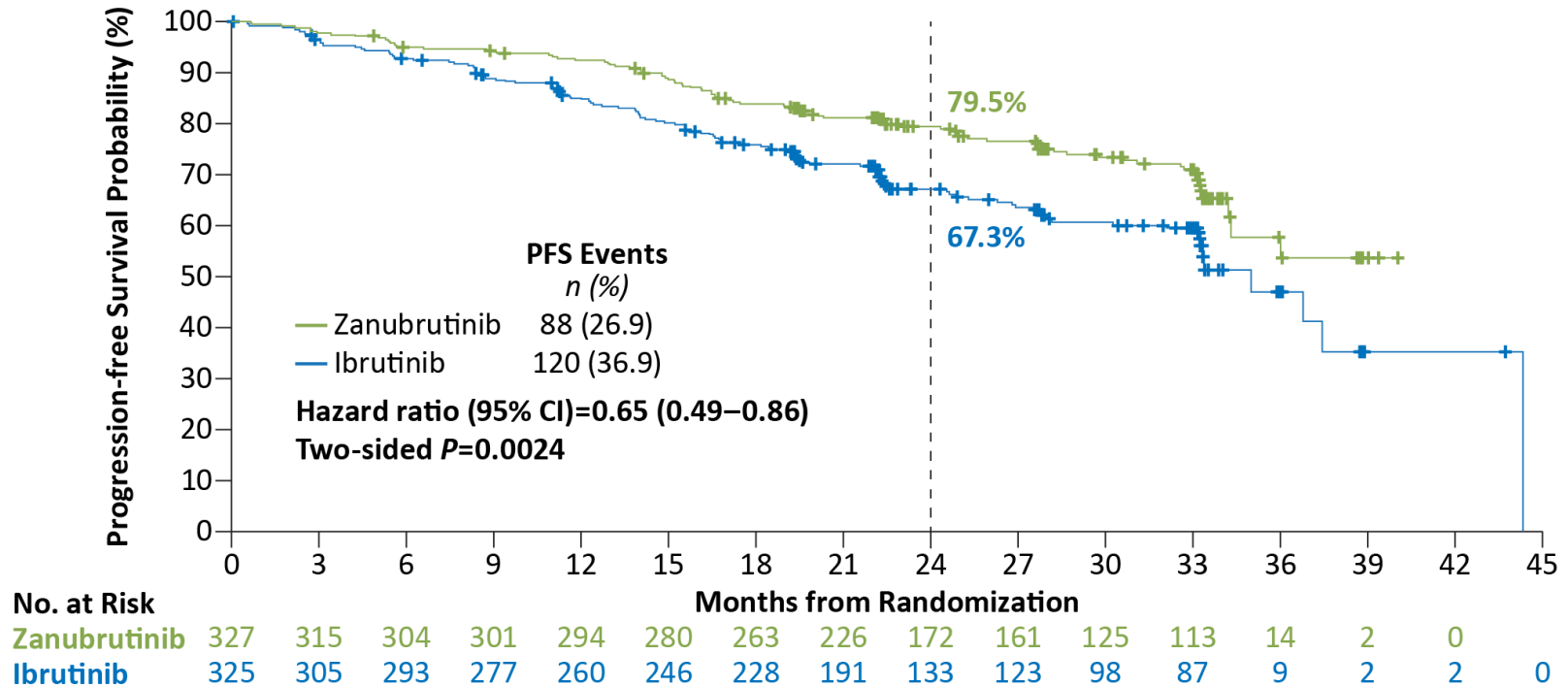
Key Exclusion Criteria

- Prior BTK inhibitor therapy
- Treatment with warfarin or other vitamin K antagonists



Zanubrutinib PFS by IRC Significantly Superior to Ibrutinib

Median study follow-up of 29.6 months



Lower rate of cardiac events, treatment discontinuation, and deaths with Zanubrutinib

Lower rate of serious cardiac adverse events reported with zanubrutinib

- A fib/flutter (n=2)
- MI/ACS (n=2)
- CHF (n=2)

Fatal cardiac events:

- Zanubrutinib, n=0 (0%)
- Ibrutinib, n=6 (1.9%)

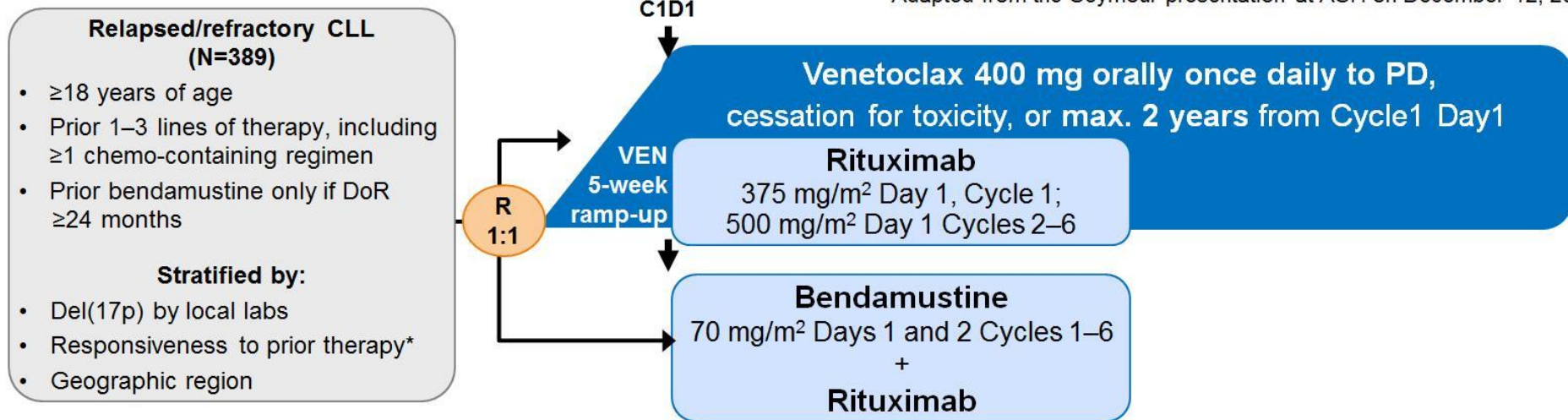
	Zanubrutinib (n=324)	Ibrutinib (n=324)
Cardiac adverse events	69 (21.3%)	96 (29.6%)
Serious cardiac adverse events	6 (1.9%)	25 (7.7%)
Cardiac adverse events leading to treatment discontinuation	1 (0.3)	14 (4.3)
Ventricular extrasystoles	1 (0.3)	0
Atrial fibrillation	0	5 (1.5)
Cardiac arrest	0	2 (0.6)*
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. One death not listed due to myocardial infarction with ibrutinib discontinuation due to diarrhea 14 days prior to the fatal event.

Data cutoff: 8 Aug 2022

MURANO Study Design

Adapted from the Seymour presentation at ASH on December 12, 2017

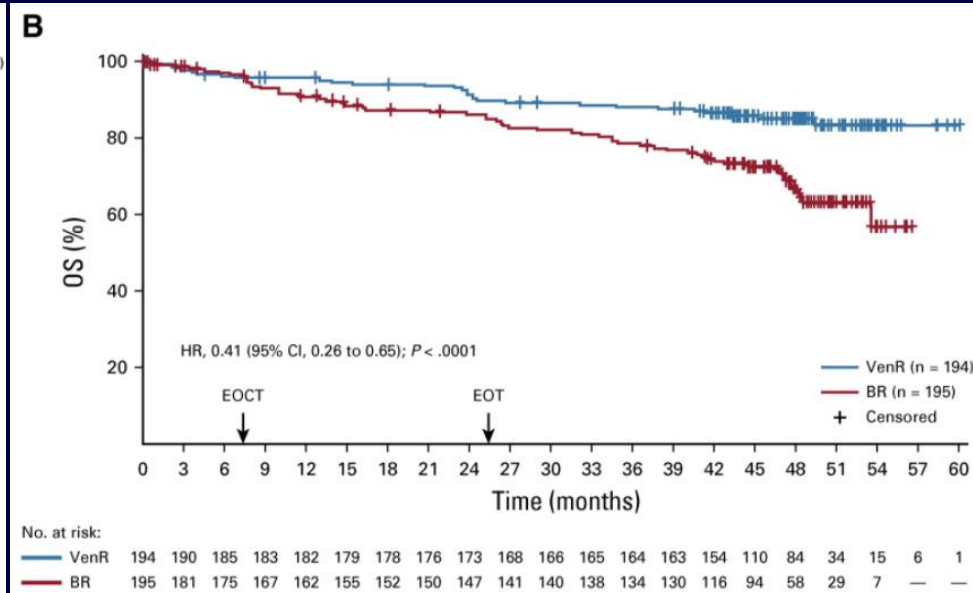
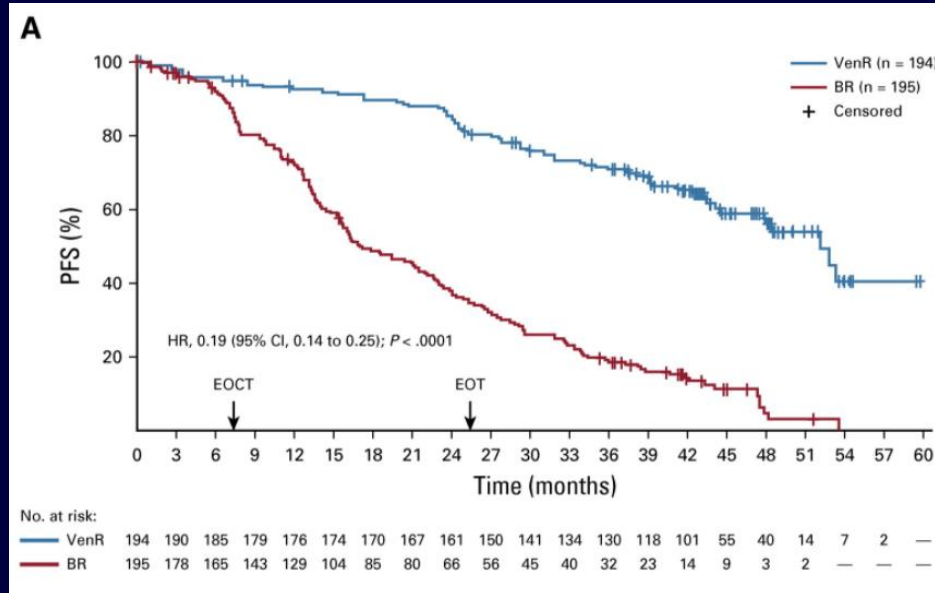


Primary Endpoint	INV-assessed PFS
Major Secondary Endpoints	<ul style="list-style-type: none"> • IRC-CR ⇒ IRC-ORR ⇒ OS (hierarchical testing) • IRC-assessed PFS and MRD-negativity
Key Safety Endpoints	Overall safety profile, focusing on serious adverse events and Grade ≥3 adverse events
Interim Analysis	Approximately 140 INV-assessed PFS events (75% of total information)

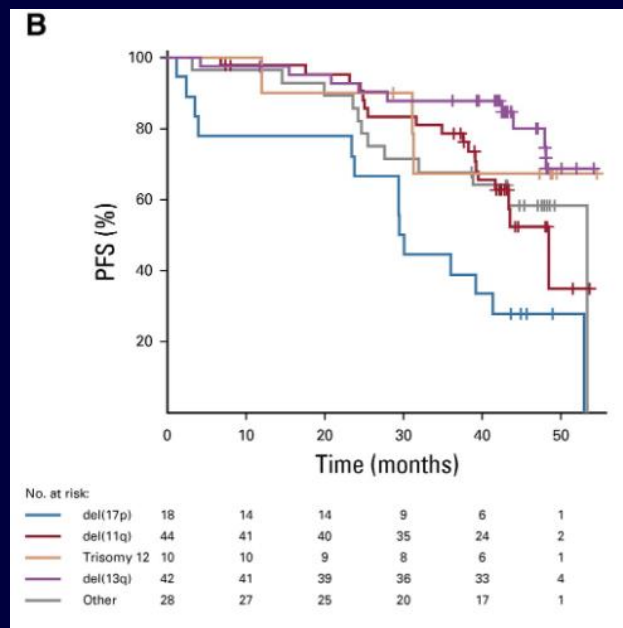
NCT02005471

*High-risk CLL – any of following features: del(17p) or no response to front-line chemotherapy-containing regimen or relapsed ≤12 months after chemotherapy or within ≤24 months after chemoimmunotherapy.

MURANO: Ven+R vs. BR: PFS and OS



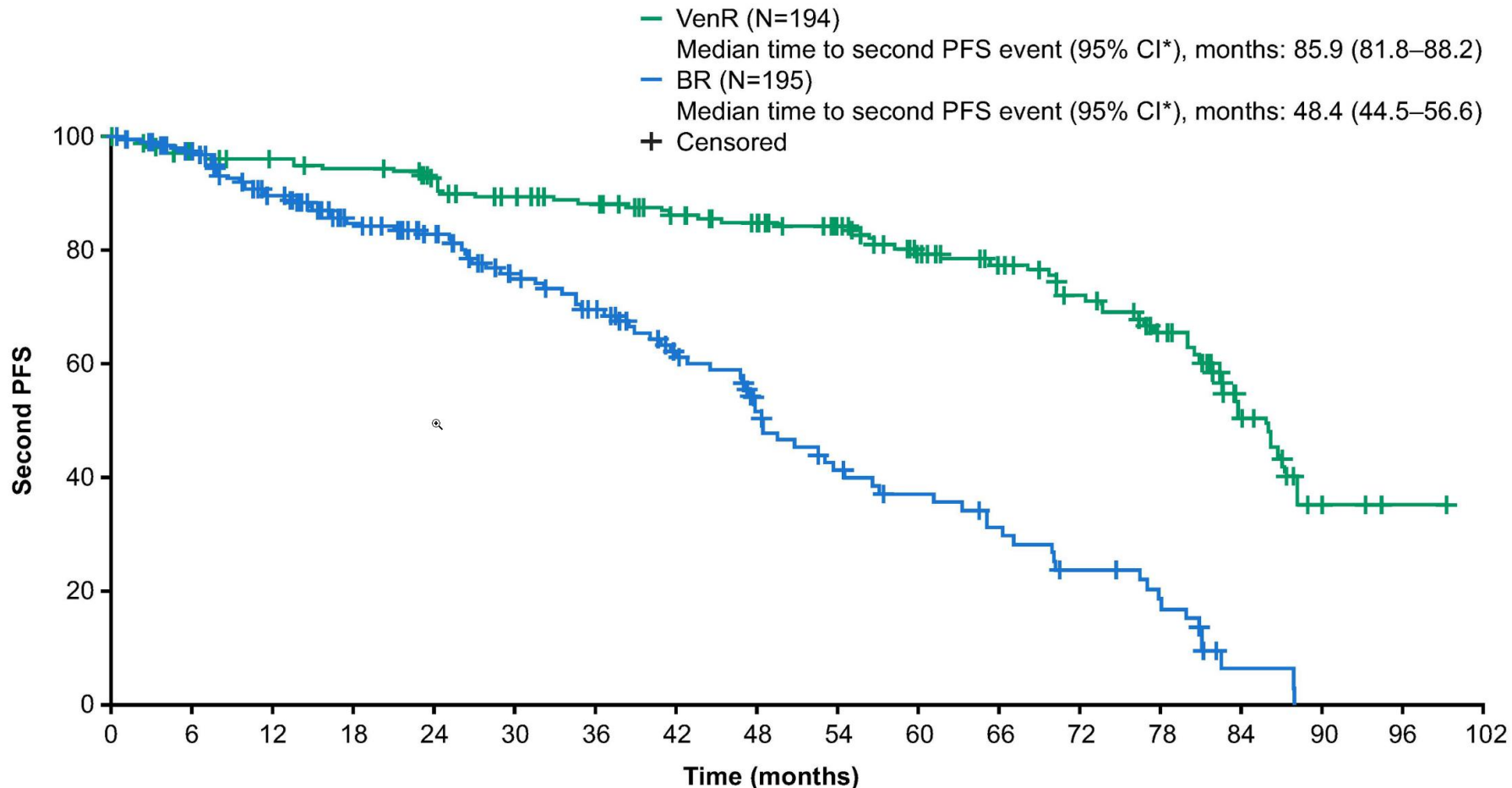
EOCT, end of combination therapy; **EOT**, end of treatment; HR



AP Kater, JCO 38, 4042-4054, 2020.

Seymour J, et al. NEJM. 2018;378:1107-20

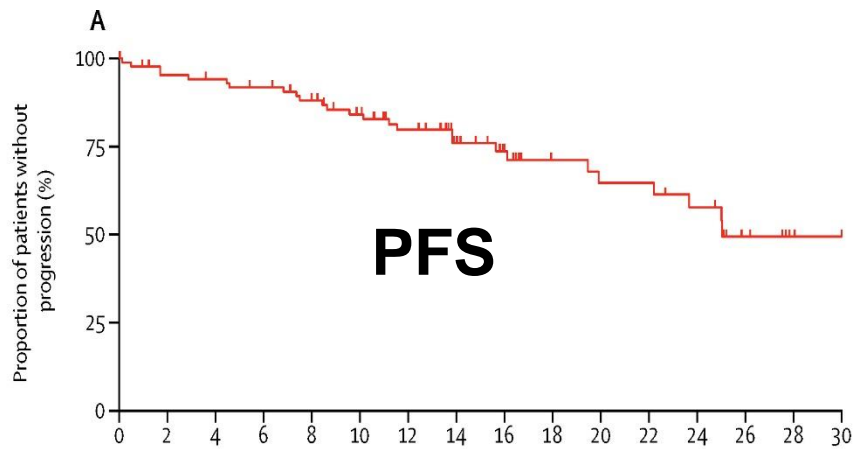
MURANO: Ven+R vs. BR: long-term PFS



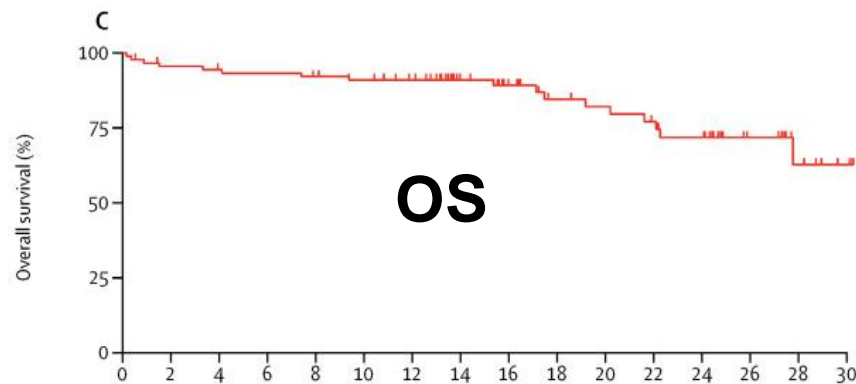
No. of pts at risk

VenR	194	190	185	181	180	177	176	174	166	158	155	149	148	139	134	128	125	117	111	101	91	86	78	74	67	63	52	46	23	16	4	4	1	1
BR	188	181	169	155	145	133	120	116	105	92	83	79	72	63	55	52	41	35	31	28	26	25	21	19	15	14	10	5	2	2				

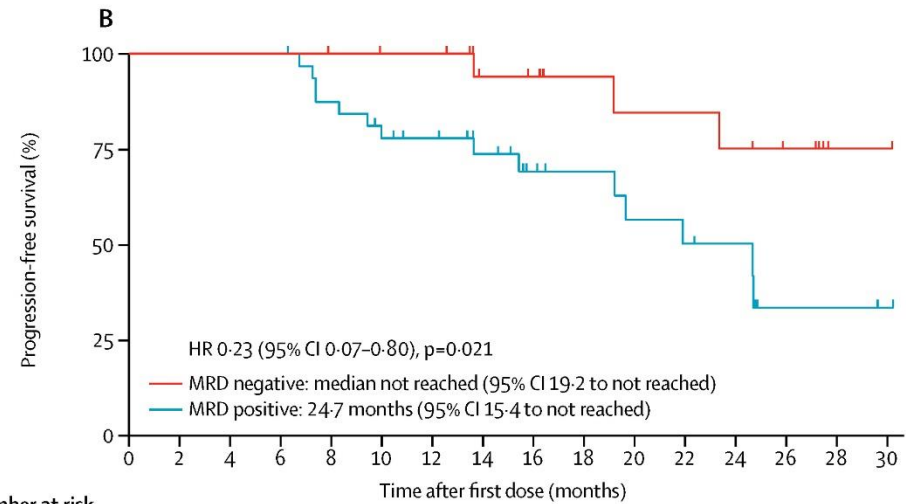
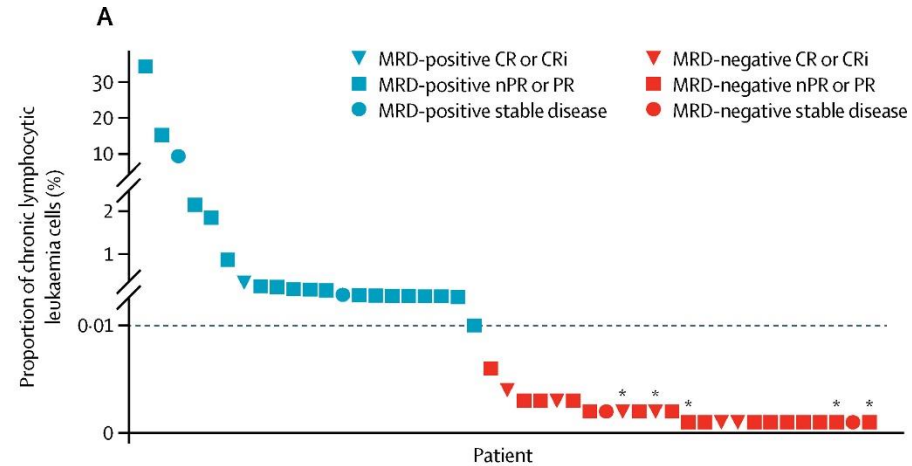
Venetoclax for CLL progressing after ibrutinib



Number at risk 91 83 80 77 72 63 54 39 31 23 21 21 17 9 5 4
(number censored) (0) (6) (7) (8) (11) (17) (22) (38) (43) (49) (50) (51) (58) (62) (63)



Number at risk 91 85 83 82 80 77 73 54 44 35 33 30 26 41 8 4
(number censored) (0) (2) (3) (3) (4) (6) (10) (29) (38) (45) (46) (47) (49) (61) (67) (71)



	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30
MRD negative	24	24	24	24	24	23	23	15	14	11	10	10	9	6	2	2
(number censored)	(0)	(1)	(1)	(1)	(1)	(2)	(2)	(3)	(10)	(13)	(13)	(13)	(13)	(16)	(20)	(20)
MRD positive	33	33	33	33	30	26	23	19	14	12	10	9	7	3	3	2
(number censored)	(0)	(1)	(1)	(1)	(1)	(2)	(4)	(7)	(11)	(13)	(13)	(14)	(15)	(17)	(17)	(18)

Acalabrutinib, Venetoclax, and Obinutuzumab in Relapsed CLL: Final Efficacy and Circulating Tumor DNA (ctDNA) Analysis of the CLL2-BAAG Trial

Study Design and Exposure (ClinicalTrials.gov Identifier: NCT03787264)

Phase 2 CLL2-BAAG study

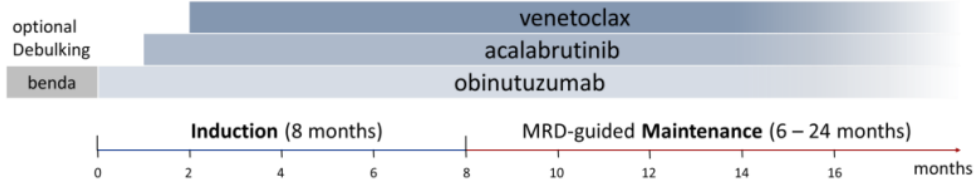


46 patients with r/r CLL

- Unmutated IGHV: 75.6%
- TP53 aberration(s): 31.8%
- Prior BTKi/venetoclax: 40.0%

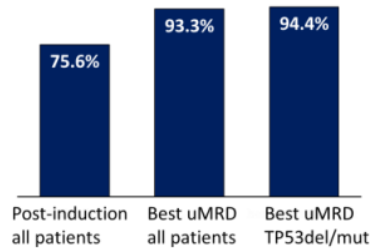
Median time to uMRD: 5.4 months

Median treatment duration: 14.7 months

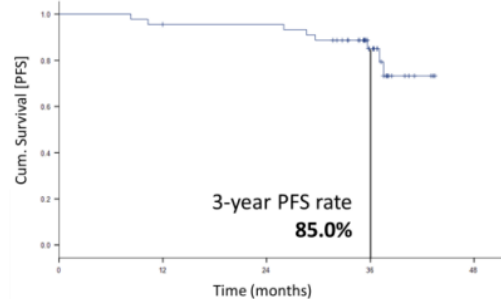


Main Findings (median follow-up 36.3 months)

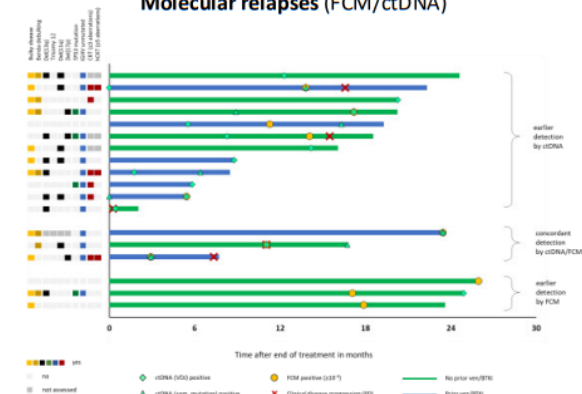
PB undetectable MRD rates



Progression-free survival



Molecular relapses (FCM/ctDNA)



Conclusions: Time-limited acalabrutinib, venetoclax, and obinutuzumab induced deep and ongoing remissions in patients with relapsed/refractory CLL, including those with *TP53* aberrations and prior BTKi/venetoclax exposure.

Fürstenau et al. DOI: 10.xxxx/*blood*.2024xxxxxx

**Blood
Visual
Abstract**

Strategies for treating Relapsed CLL

Initial Therapy Chemoimmunotherapy	Initial Therapy Venetoclax- Based	Initial Therapy BTKi
<ul style="list-style-type: none">• Acalabrutinib• Zanubrutinib• Ibrutinib*• Venetoclax/rituximab	<p>Completion of Therapy >2 years ago</p> <ul style="list-style-type: none">• Venetoclax/rituximab**• Acalabrutinib• Zanubrutinib• Ibrutinib*	<p>Intolerant to Previous BTKi</p> <ul style="list-style-type: none">• Alternate BTKi• Venetoclax/rituximab
	<p>Completion of Therapy <2 years ago or intolerant to venetoclax⁺</p> <ul style="list-style-type: none">• Acalabrutinib• Zanubrutinib• Ibrutinib*	<p>Relapse on BTKi Therapy</p> <ul style="list-style-type: none">• Venetoclax/rituximab



Thank you!

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