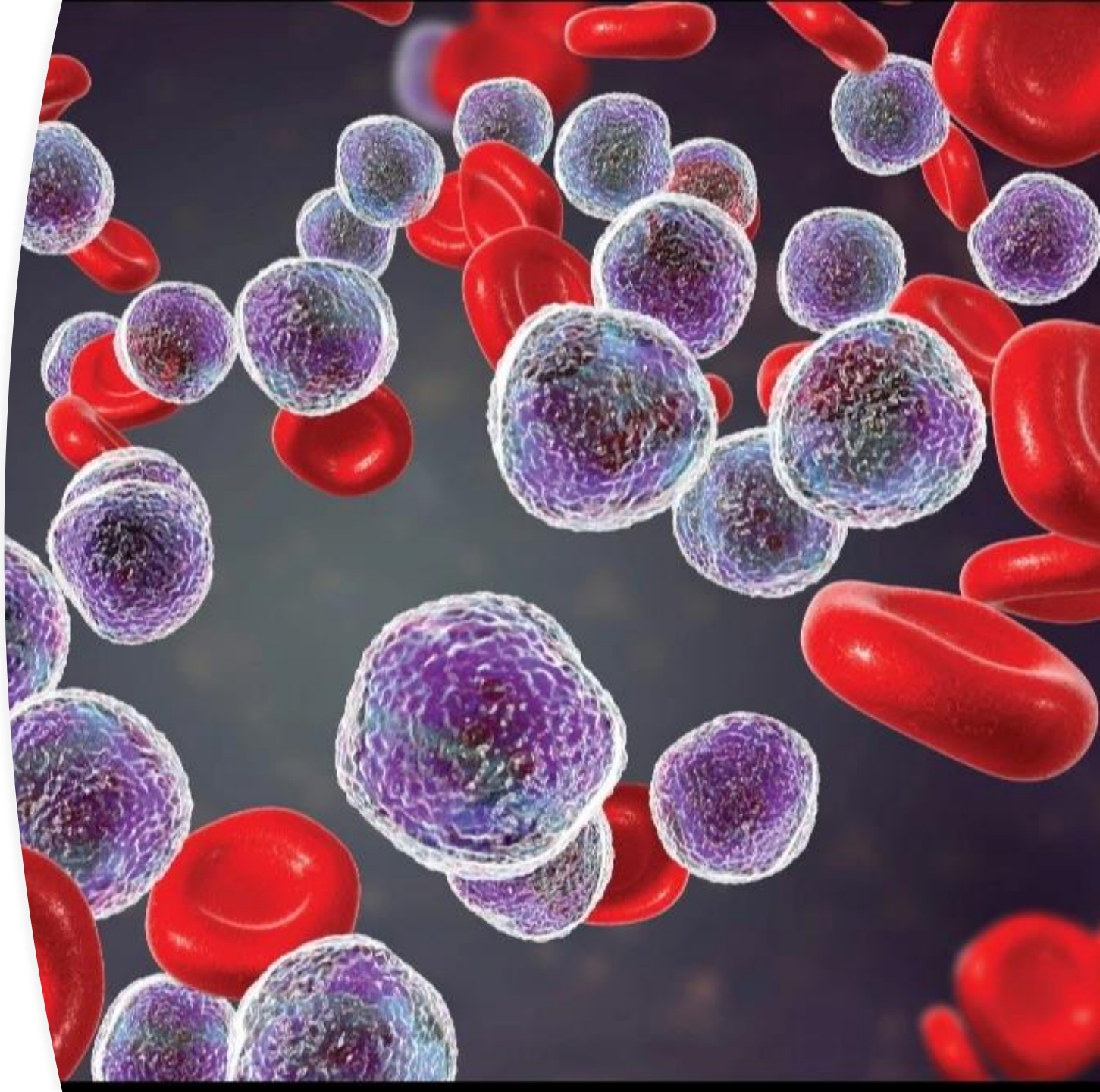
Chronic Lymphocytic Leukemia



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AMPLIFY Study Design

TN CLL (N=867)

Key inclusion criteria
- Age ≥18 years
- TN CLL requiring treatment per iwCLL 2018 criteria[1]
- Without del(17p) or *TP53*[a]
- ECOG PS ≤2

Key exclusion criteria
- CIRS-Geriatric >6
- Significant cardiovascular disease

Stratification
- Age (>65 vs ≤65 years)
- IGHV mutational status
- Rai stage (≥3 vs <3)
- Geographic region

AMPLIFY: randomized, multicenter, open-label, Ph 3 trial

RANDOMIZE 1:1:1

- AV (14 cycles)
- AVO (14 cycles)
- FCR/BR (6 cycles)

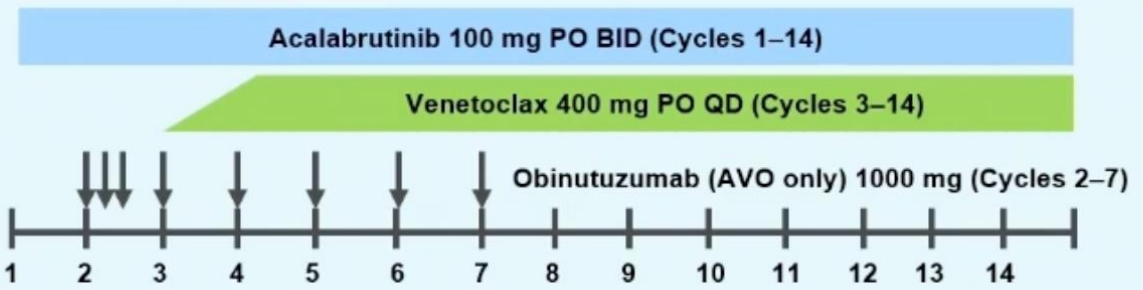
Crossover not built into protocol

Primary endpoint: IRC-assessed PFS (AV vs FCR/BR)

If primary endpoint met, secondary endpoints tested in fixed sequential hierarchy:

1) IRC-PFS (AVO vs FCR/BR)
2) uMRD (AV vs FCR/BR)
3) uMRD (AVO vs FCR/BR)
4) OS (AV vs FCR/BR)
5) OS (AVO vs FCR/BR)

AV and AVO dosing schedule



NCT03836261. Data cutoff: April 30, 2024.
[a]Assayed by central lab.

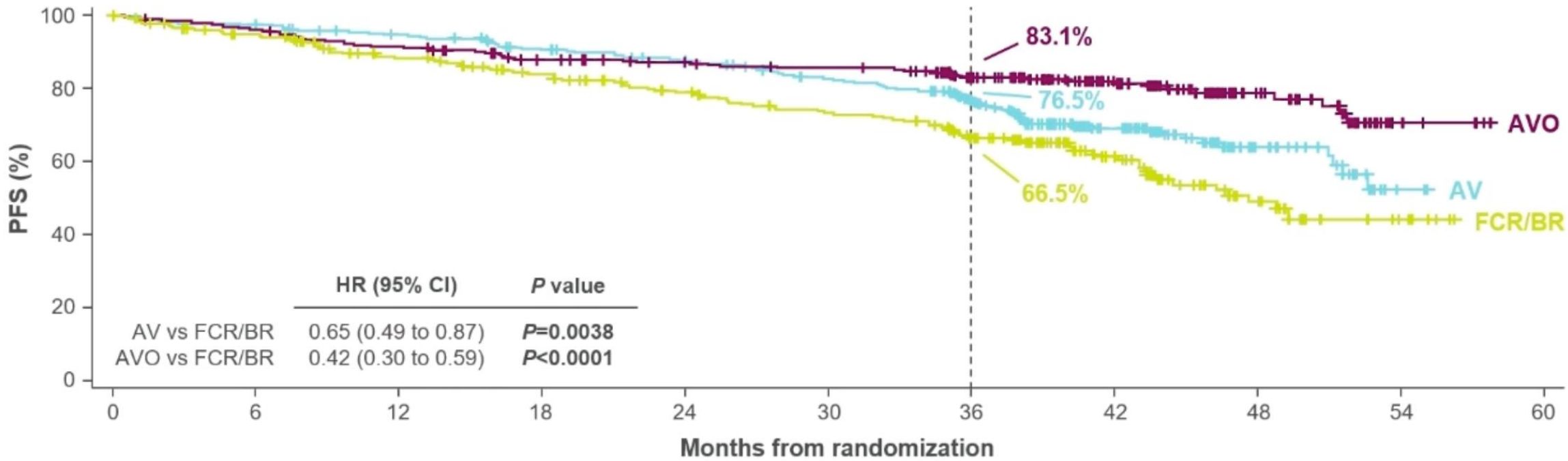
Brown, J et al. ASH 2024 AMPLIFY [Abstract 1009]

Demographics and Baseline Characteristics

Characteristic	AV (n=291)	AVO (n=286)	FCR/BR (n=290)
Age, median (range), yr	61 (31–84)	61 (29–81)	61 (26–86)
≤65 yr	212 (72.9)	210 (73.4)	213 (73.4)
>65 yr	79 (27.1)	76 (26.6)	77 (26.6)
Male sex	178 (61.2)	198 (69.2)	183 (63.1)
ECOG PS score			
0–1	262 (90.0)	272 (95.1)	262 (90.3)
2	28 (9.6)	14 (4.9)	26 (9.0)
Geographic region*			
Europe	184 (63.2)	179 (62.6)	183 (63.1)
North America	50 (17.2)	51 (17.8)	50 (17.2)
Other	57 (19.6)	56 (19.6)	57 (19.7)
Rai stage			
0–II	154 (52.9)	170 (59.4)	163 (56.2)
III–IV	137 (47.1)	116 (40.6)	127 (43.8)
del(11q) present	51 (17.5)	56 (19.6)	46 (15.9)
Unmutated IGHV	167 (57.4)	169 (59.1)	172 (59.3)
Complex karyotype (≥3 aberrations)	45 (15.5)	46 (16.1)	42 (14.5)

Brown, J et al. ASH 2024 AMPLIFY [Abstract 1009]

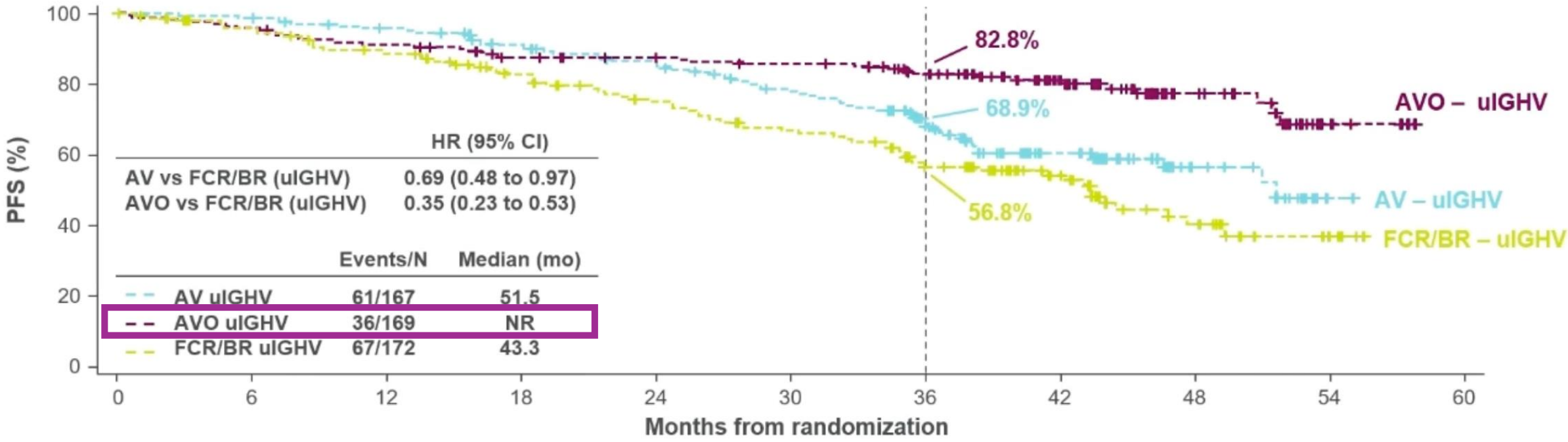
IRC-assessed PFS



Median PFS was NR for AV and AVO, and was 47.6 mo for FCR/BR

Brown, J et al. ASH 2024 AMPLIFY [Abstract 1009]

PFS in the [uIGHV] Subgroup



Unmutated pts may derive particular benefit from the addition of anti-CD20 to the AV doublet

Brown, J et al. ASH 2024 AMPLIFY [Abstract 1009]

Safety Summary

	AV (n=291)	AVO (n=284)	FCR/BR (n=259)
Duration of exposure, median (range), mo	12.9 (1–18)	12.9 (0–18)	5.6 (1–11)
Summary of AEs			
Any AE	270 (92.8)	269 (94.7)	236 (91.1)
Any AE grade ≥3	156 (53.6)	197 (69.4)	157 (60.6)
Any serious AE	72 (24.7)	109 (38.4)	71 (27.4)
Serious AEs leading to death	10 (3.4)	17 (6.0)	9 (3.5)
AE leading to treatment discontinuation	23 (7.9)	57 (20.1)	28 (10.8)

Brown, J et al. ASH 2024 AMPLIFY [Abstract 1009]

Events of Clinical Interest

	AV (n=291)		AVO (n=284)		FCR/BR (n=259)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any ECI	222 (76.3)	136 (46.7)	242 (85.2)	188 (66.2)	185 (71.4)	141 (54.4)
Cardiac events	27 (9.3)	5 (1.7)	34 (12.0)	7 (2.5)	9 (3.5)	3 (1.2)
Atrial fibrillation	2 (0.7)	1 (0.3)	6 (2.1)	2 (0.7)	2 (0.8)	2 (0.8)
Ventricular tachyarrhythmias[a]	2 (0.7)	0	3 (1.1)	0	0	0
Hypertension	12 (4.1)	8 (2.7)	11 (3.9)	6 (2.1)	7 (2.7)	2 (0.8)
Hemorrhage	94 (32.3)	3 (1.0)	86 (30.3)	6 (2.1)	11 (4.2)	1 (0.4)
Major hemorrhage	3 (1.0)	3 (1.0)	8 (2.8)	6 (2.1)	2 (0.8)	1 (0.4)
Neutropenia (any)[b]	108 (37.1)	94 (32.3)	143 (50.4)	131 (46.1)	132 (51.0)	112 (43.2)
Infections (any)	148 (50.9)	36 (12.4)	153 (53.9)	67 (23.6)	82 (31.7)	26 (10.0)
Second primary malignancies	15 (5.2)	5 (1.7)	12 (4.2)	5 (1.8)	2 (0.8)	0
Excl. non-melanoma skin	8 (2.7)	5 (1.7)	7 (2.5)	4 (1.4)	1 (0.4)	0
Tumor lysis syndrome	1 (0.3)	1 (0.3)	1 (0.4)	1 (0.4)	8 (3.1)	8 (3.1)

Brown, J et al. ASH 2024 AMPLIFY [Abstract 1009]

AMPLIFY clinical applications

- AVO compared with AV and CIT
  - deeper remissions (66% ITT, 95% Evaluable)
    - Correlates with PFS
  - ↑ neutropenia
  - ↑ infections
  - ↑ hemorrhage

AVO = preferred in:

1. *uIGHV*
2. *young and fit*

AMPLIFY limitations

- **Mostly low risk TN patients** (although majority IGHV unmutated)
  - **Excluded 17p del or TP53 mutated**
  - Only 15% of pts had complex karyotype
- Comparator arm = CIT
- **Study not powered to detect differences between AV or AVO**
- Excluded pts with CV comorbidities
  - data on CV AE is likely not applicable to pts with CV comorbidities
- **No comparison to BTKi monotherapy or ven / anti– cd20 doublet**

AMPLIFY discussion

- Is this practice changing? In which patients (if any) would you consider using AV or AVO?

- Since AVO had similar incidence of neutropenia as compared with FCR/BR, how do you explain the doubled risk of G3+ infections?

- While this was a frontline study, would you consider using this doublet in the R/R setting? How does this rank with pirtobrutinib, liso-cel, venetoclax re-treatment, other?

Clinical Case

Shazia Nakhoda, MD

Fox Chase Cancer Center

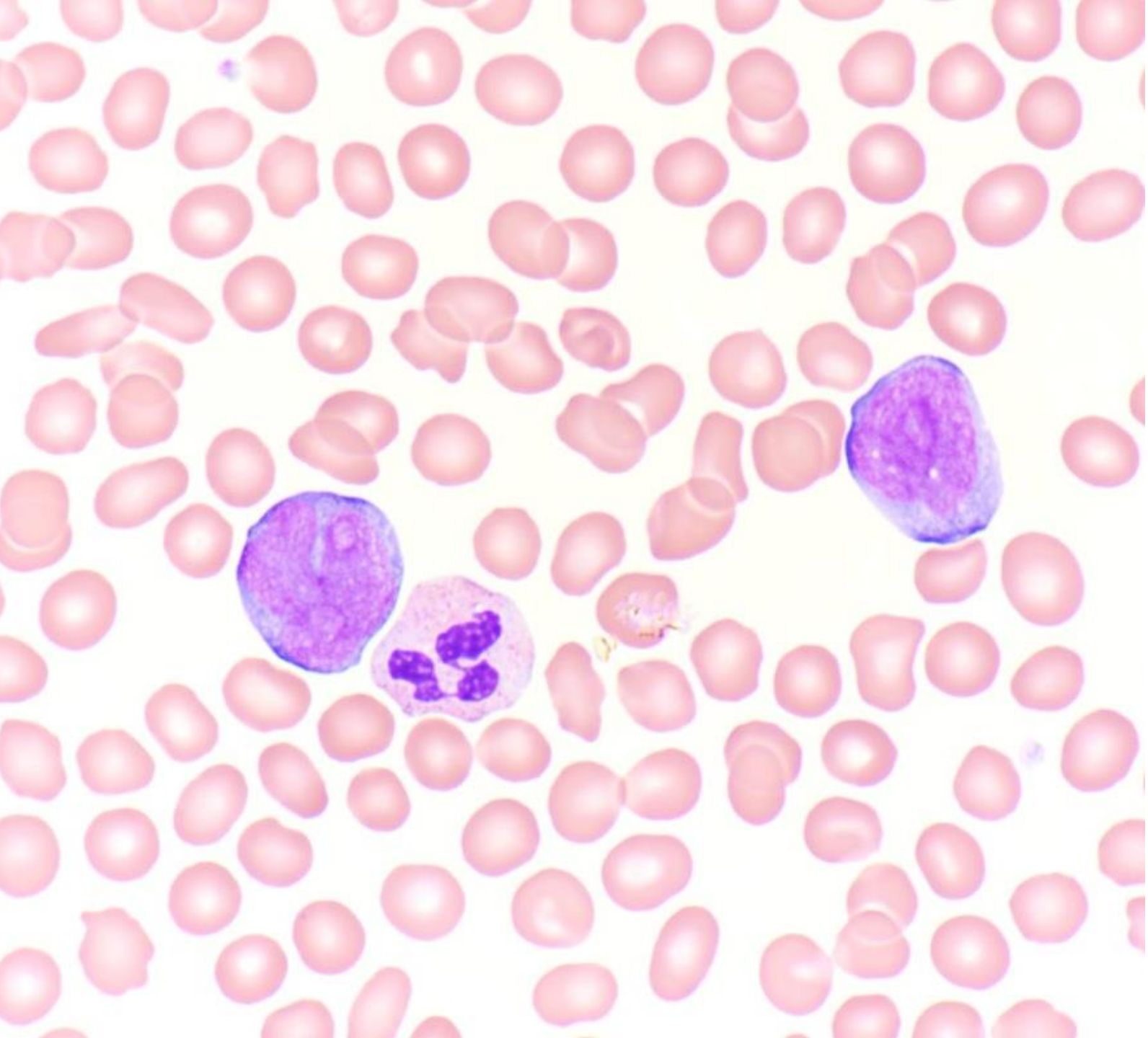
Case

84 M with CLL (IGVH-UM, trisomy 12 on FISH) on ibrutinib x 1 year, bladder cancer, cigarette smoking, and recent new diagnosis of lung adenocarcinoma

- *He had been started on BTKi for indication of progressive cytopenias and disease burden and tolerating treatment well aside from easy bleeding/bruising*
- *At time of evaluation, he had excellent clinical response with resolution of adenopathy, improved lymphocytosis, and mild anemia/thrombocytopenia*

Underwent curative intent lung segmentectomy with mediastinal lymph node dissection. BTKi was held perioperatively

- Path confirmed localized lung adenocarcinoma but also incidentally showed Richter's transformation



Peripheral blood

WBC: 23.7 K/mm3

Peripheral Blood Flow cytometry:

- Gated Lymphs: 38%
- Kappa-restricted B-cells (82%) CD19, CD20(dim)+, CD23+, FMC7-, CD5+, CD79b+, CD38+, CD10-
- **Cytogenomic microarray analysis** (CMA): **trisomy 12** in a mosaic state representing about **30% of cells**.
- **FISH** negative for MYC amplification and rearrangements of BCL6, MYC, BCL2 genes.
- **NGS**: BCOR mutation 29.7%

Case

Post operative course complicated by bleeding complications, empyema, and infections with prolonged admission

- Repeat CT imaging showed no new sites of adenopathy or organomegaly
- Prognostic panel testing (CMA, NGS, and FISH) showed no new changes compared to his baseline at time of treatment initiation a year ago
- Lab work showed mild neutrophilia and lymphocytosis but otherwise no clinical evidence of disease progression

Remained off BTKi at this time and received no DLBCL directed therapies during hospitalization and elected not to resume treatment at discharge

- Outpatient PET/CT showed no evidence of FDG avid disease

2.5 years later on routine follow up off all CLL directed therapies, patient had progressive adenopathy and was ultimately restarted on BTKi with Zanubrutinib

- No further bleeding complications on this therapy and he again achieved excellent disease control

Diagnosis: Pseudo-Richter's Transformation

- Phenomenon seen during BTKi cessation which resolves with resuming BTKi
- Relatively common incidence that is underreported in the literature (small case reports/case series)

Hampel et al Oncologist 2020
Slonim etal Br J Haematol 2020
Shi et al Mayo Clin Proc 2024

Pseudo-Richters's

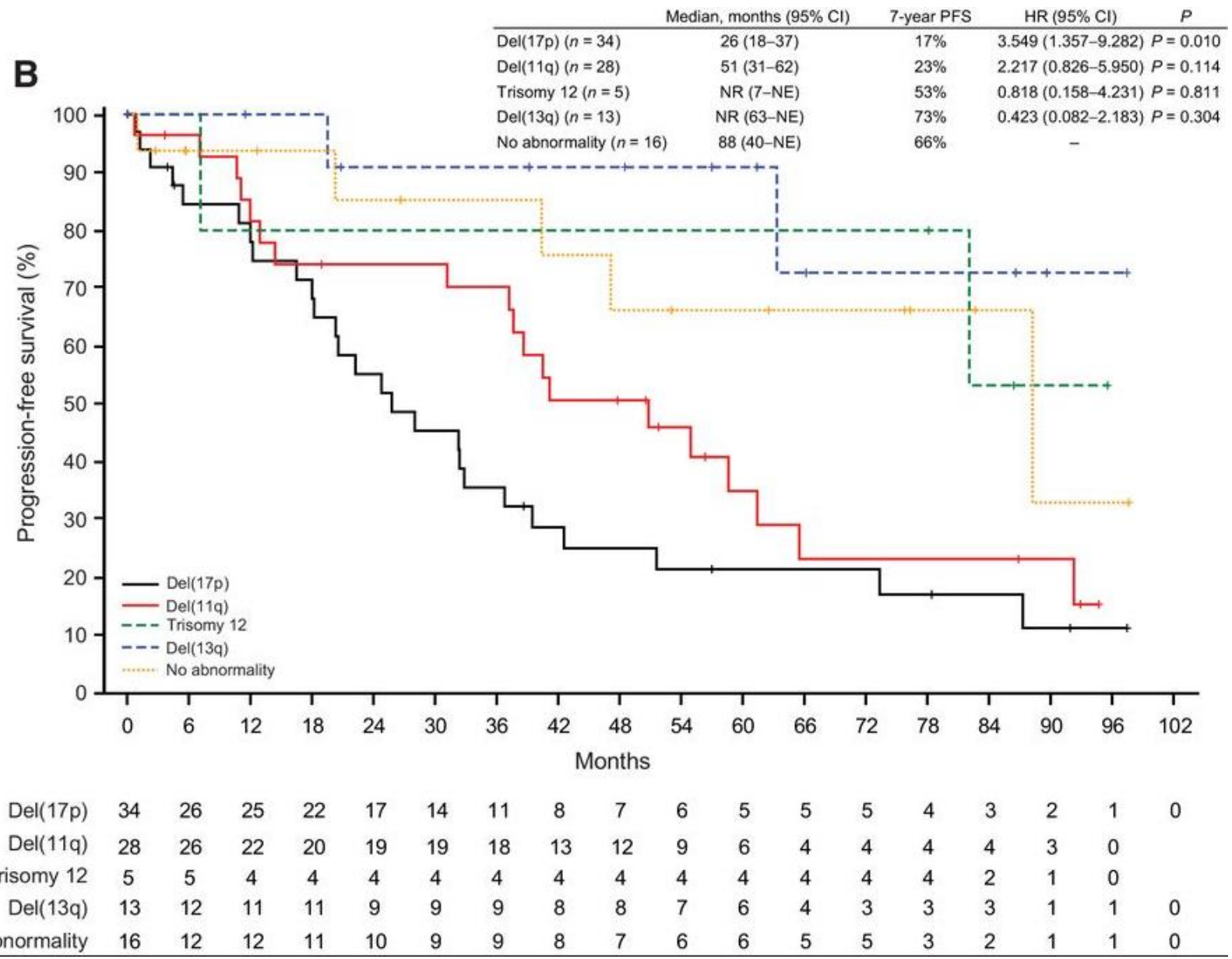
CLL with trisomy 12

- associated with atypical morphology(cleaved nuclei, lymphoplasmacytoid features) and increased proliferation with increased risk of RT
- More common in SLL than CLL
- Traditionally considered "intermediate" prognosis, excellent prognosis in era of targeted agents

Slonim et al Br Haem 2020

Table I. Characteristics of chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL) patients with ibrutinib interruption and "pseudo-Richter transformation" included in this study.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Basic clinical information					
Age at "RT" diagnosis and gender	69 M	82 M	66 M	83 M	70 F
Rai stage prior to Ibr	IV	I	III	I	III
FISH results	+12, 13q−, 11q-, 17p−	17p−	+12	+12, 11q−	+12, 13q−
IgVH mutation status	Unmutated	ND	Unmutated	ND	ND
CD38/ZAP70	−/+	ND	−/+	+/+	+/+
Number of prior therapies	1	0	1	3	0
Prior therapies	FCR	–	Alem-Ofa	Ritux, Ofa, BR	–
Ibrutinib treatment and holding information					
Time from CLL to Ibr	10 years	0·2 years	7 years	8 years	3 years
Time on Ibr before hold	10 months	20 months	37 months	35 months	48 months
Response to Ibr before hold*	PR	PR	PR	PR	PR
Reason for Ibr hold†	Surgery	Surgery	Surgery	Infection	Infection
Duration of Ibr hold	14 days	43 days	12 days	10 days	32 days
Treatment following Ibr hold	Ibr	Ibr	Ibr-G	Ibr-G	Ibr
Response to ibrutinib resumption	PR	PR	PR	PR	PR
Disease progression signs during ibrutinib interruption					
Increased adenopathy	yes	yes	yes	yes	yes
Progressive anaemia/TCP	yes	No	No	yes	no
Increased lymphocytosis	yes	yes	No	yes	yes
B symptoms‡	No	Yes	No	yes	yes
Absolute lymphocyte count (K/μl, reference range 1·5–8·0 K/μl)					
Before Ibr hold	12·8 K	10·8 K	2·8 K	1·2 K	2·2 K
During Ibr hold	7·0 K	18·0 K	1·4 K	11·0 K	13·0 K
After Ibr resumption	4·3 K	3·9 K	4·0 K	0·4 K	2·9 K
LDH (U/l, reference range 0–271 U/l)					
Before Ibr hold	164	ND	164	215	228
Peak value during Ibr hold	255	280	382	1537	1872
After Ibr resumption	151	209	240	188	253
Tissue biopsy (Bx) timing and diagnosis					
Time of Ibr hold to Bx	7 days	10 days	7 days	10 days	13 days
Type of tissue	LN	LN	LN	BM	LN
Bx diagnosis while off Ibr	DLBCL	DLBCL	DLBCL	DLBCL	DLBCL
COO subtype, Hans algorithm	ABC	Unknown	ABC	ABC	ABC
Time of re-Bx from resumption	No re-Bx	No re-Bx	6 months	5 months	3 weeks
Re-Bx diagnosis	–	–	CLL/SLL	CLL/SLL	CLL/SLL



Patient population:
Phase Ib/II PCYC-1102 extension study PCYC-1103 which included patients receiving single-agent ibrutinib in first-line or relapsed/refractory CLL/SLL

Byrd et al Clin Can Research 2020

Long term follow up Data for Frontline Therapies in CLL

Brief Review

Preferred Frontline Therapies for CLL

Acalabrutinib +/- Obinutuzimab (ELEVATE TN)	Zanubrutinib (SEQUOIA)	Venetoclax/Obinutuzumab (CLL14)
• 72 m PFS 78% (A+O) and 62% (A)	• 60 m PFS 76% (non del17p) • 24 m PFS 89% (del17p)	• 72 m PFS 53.1%

Future Directions: BTKi/BCL2 +/- anti-CD20 Ab

Fixed duration Ibr/Ven	Fixed duration Acala/Ven	Fixed duration Zanu/Sonrotoclax
• UK FLAIR: 48 m 86% *excluded del17p • CAPTIVATE: 60 m 70% • GLOW : 36 m 74.6%	• AMPLIFY 36 month PFS 76.5% (AV) and 83.1% (AVO)	• Phase 1: 1 yr PFS 100%

Sharman et al ASH 2023, Tam t al Lancet Onc 2022, Al-Sawaf et al Blood 2024, Tam et al Blood 2022, Niemann et al Lancet Oncol 2023, Hillmen et al Lancet 2023, Brown et al NEJM 2025

• ELEVATE-TN: Study Design

TN CLL (N=535)

Key inclusion criteria

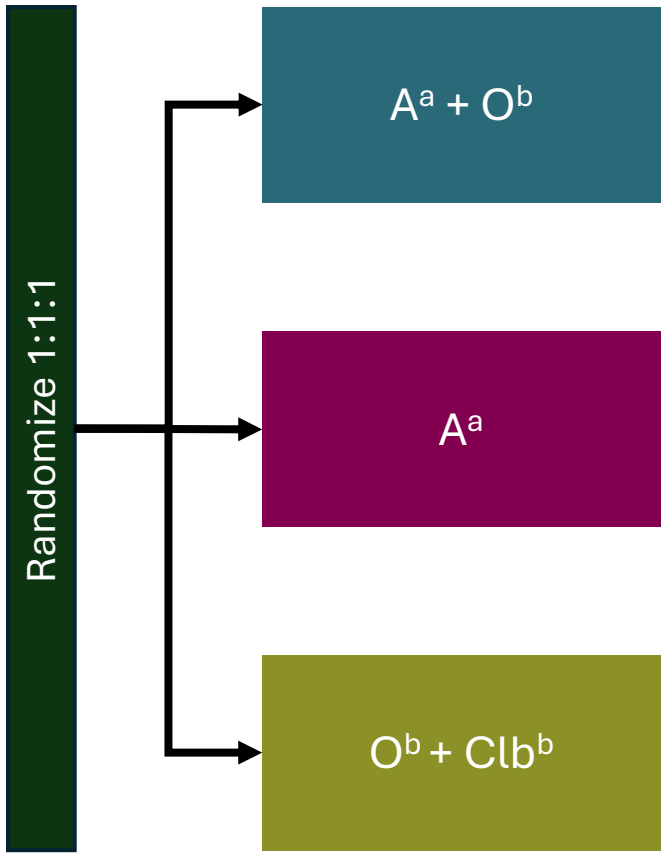
- Age ≥65 years, or >18 to <65 years with:
  - Creatinine clearance 30 – 69 mL/min (by Cockcroft-Gault equation)
  - CIRS-G score >6
- TN CLL requiring treatment per iwCLL 2008 criteria
- ECOG PS ≤2

Key exclusion criteria

- Significant cardiovascular disease

Stratification

- Del(17p), yes vs no
- ECOG PS 0-1 vs 2
- Geographic region



Primary endpoint

- PFS (IRC-assessed): A+O vs O+Clb

Secondary/other endpoints

- PFS (IRC-assessed): A vs O+Clb
- PFS (INV-assessed)
- ORR (IRC- and INV-assessed)
- TTNT
- OS
- uMRD
- Safety

Crossover from O+Clb to A was allowed after IRC-confirmed progression

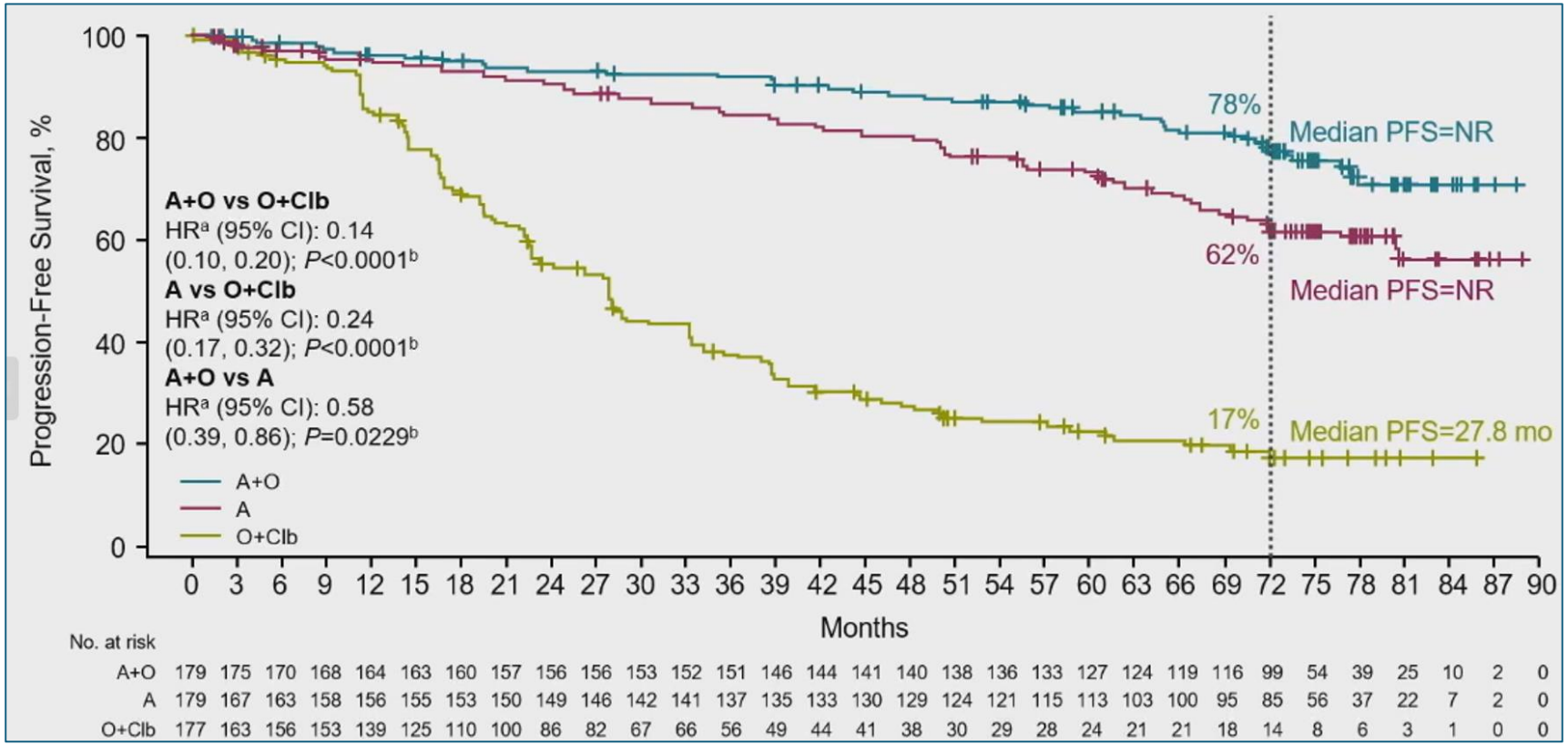
[a]Continued until disease progression or unacceptable toxicity at 100 mg PO BID; [b]Treatments were fixed duration and administered for 6 cycles

Note: After interim analysis, PFS assessments were by investigator only. All analyses are ad-hoc and P-values are descriptive. Data cutoff: March 3, 2023. Patients were enrolled between September 2015 and February 2017.

Sharman JP et al. ASH 2023. Presentation 636.

- ELEVATE-TN: PFS Was Significantly Higher for A-containing Arms vs O+Clb

  - Median PFS was significantly higher for A+O vs O-Clb and A vs O-Clb

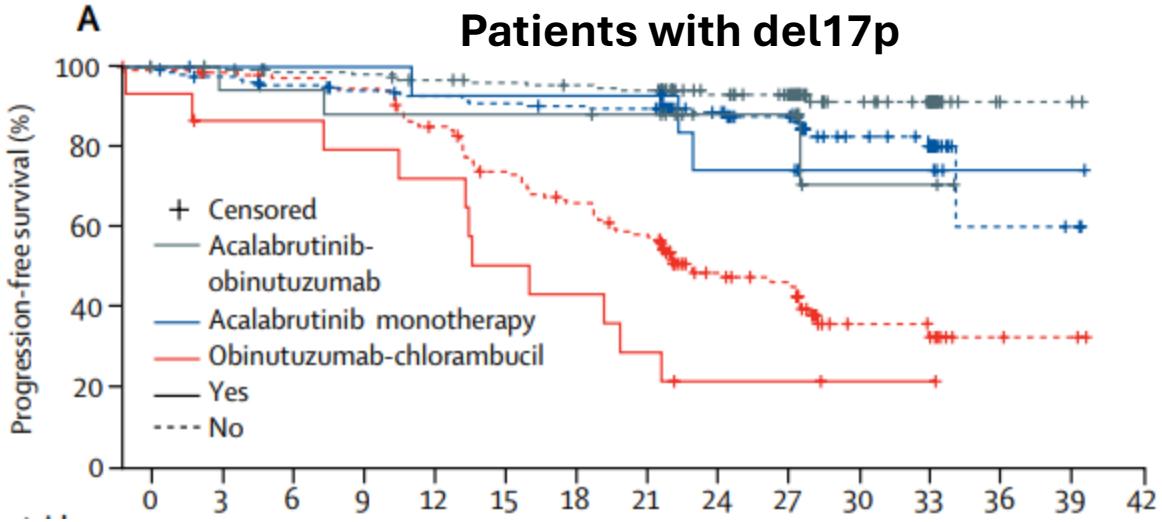


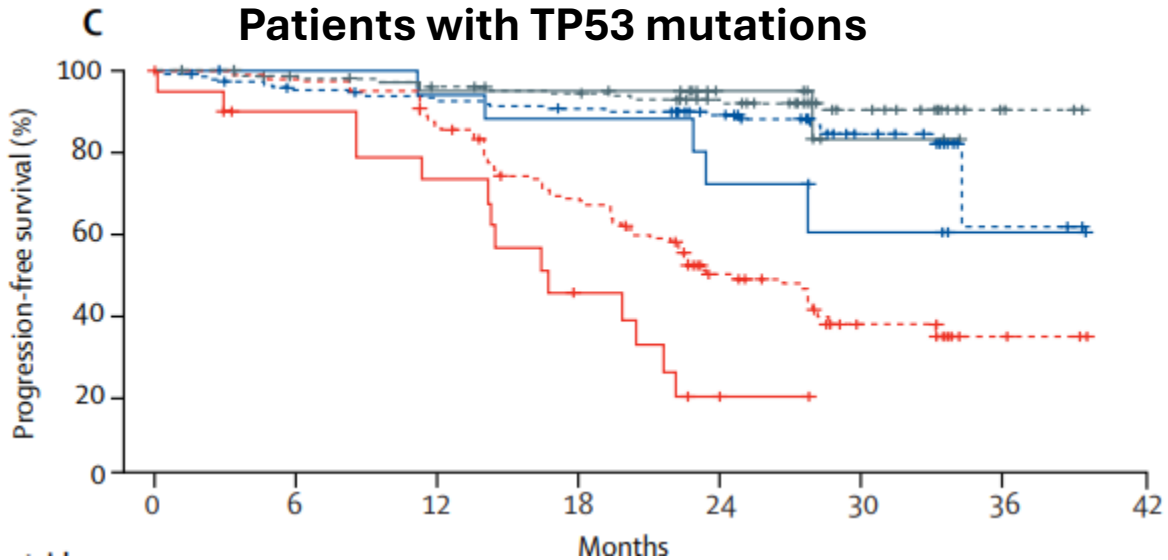
[a]Hazard ratio based on stratified Cox proportional-hazards model; [b]*P* value based on stratified log-ranked test.

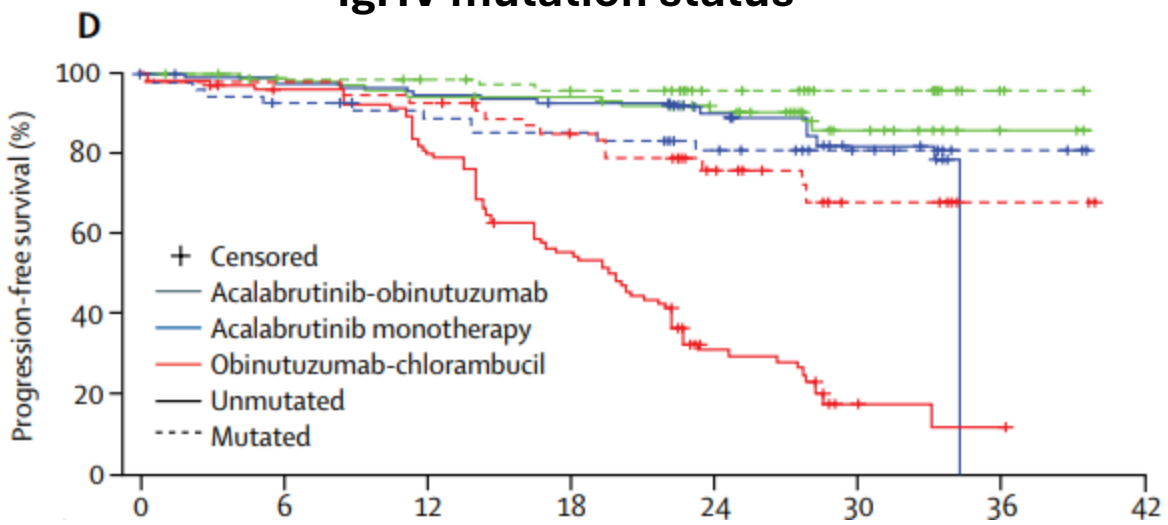
A, acalabrutinib; Clb, chlorambucil; HR, hazard ratio; NR, not reached; O, Obinutuzumab; PFS, progression-free survival.

Sharman JP et al. ASH 2023. Presentation 636.

- ELEVATE-TN: PFS in high risk groups at 4 year follow up

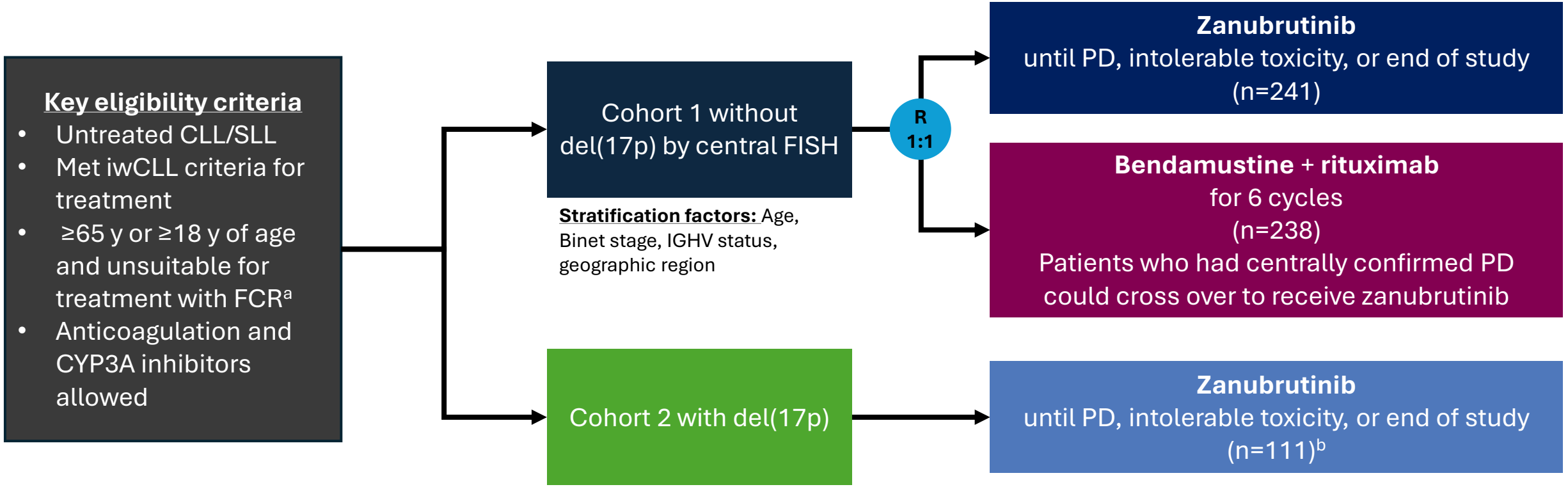






Sharman et al Lancet 2020

- SEQUOIA: Study Design



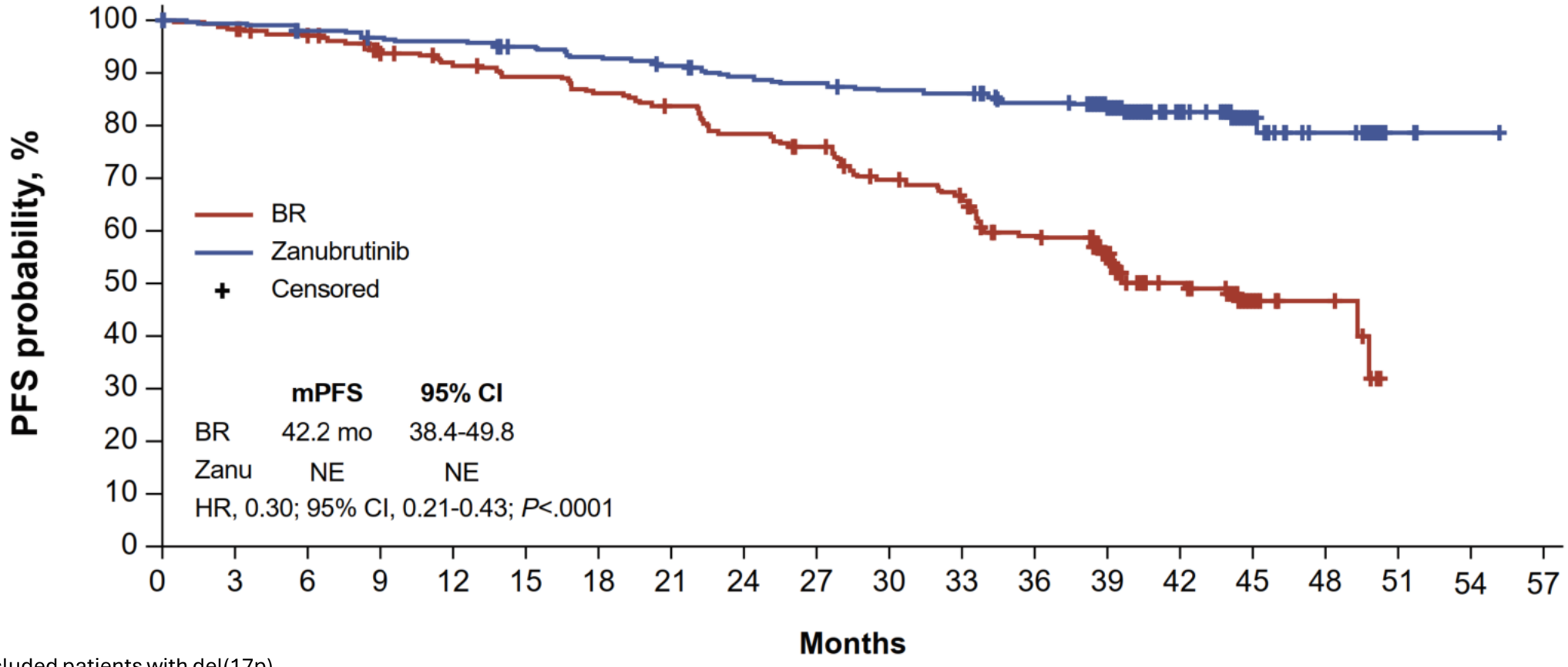
Crossover from BR to Z was allowed after IRC-confirmed progression

[a]Cohort 1 excluded patients with del(17p); [b]One patient without del(17p) was misassigned to the nonrandomly assigned cohort of patients with del(17p).

Munir T, et al. EHA 2023. Presentation 639.

- SEQUOIA Extended Follow-Up: Progression-Free Survival (Cohort 1)

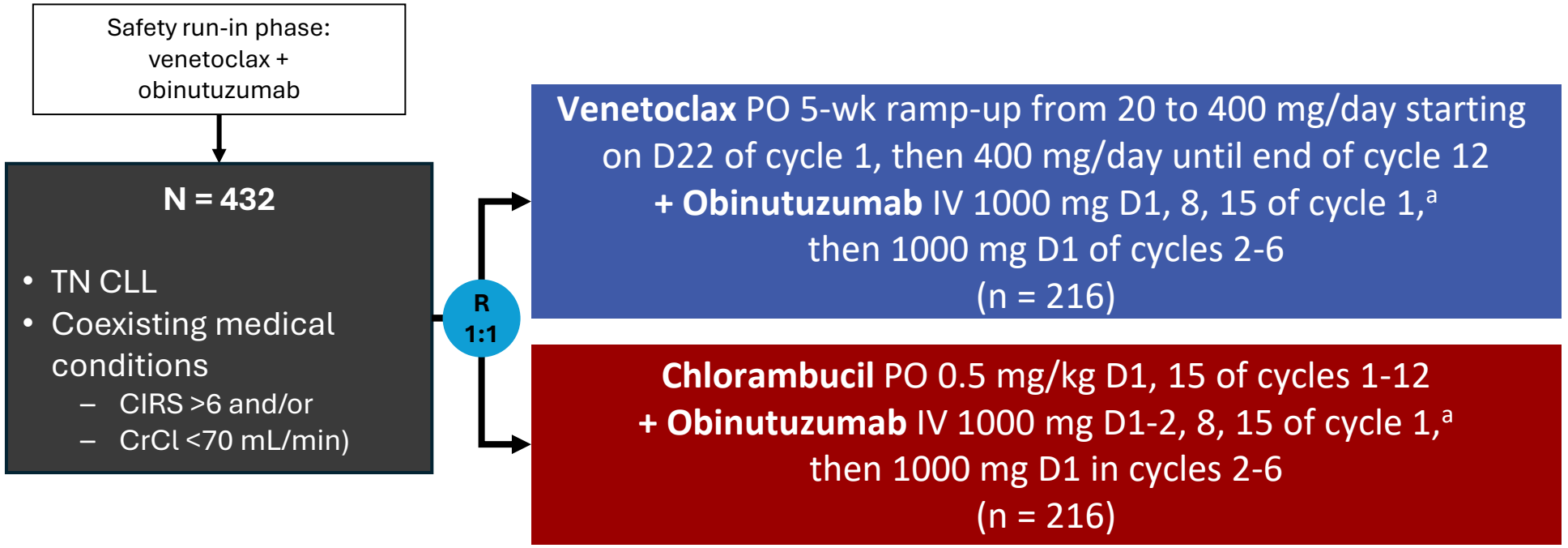
  - Significantly longer mPFS observed for zanubrutinib vs BR In cohort 1[a]



[a]Cohort 1 excluded patients with del(17p)

Munir T, et al. EHA 2023. Presentation 639.

• CLL14 Study Design



Total 28-Day Cycles

- Venetoclax: 12
- Chlorambucil: 12
- Obinutuzumab: 6

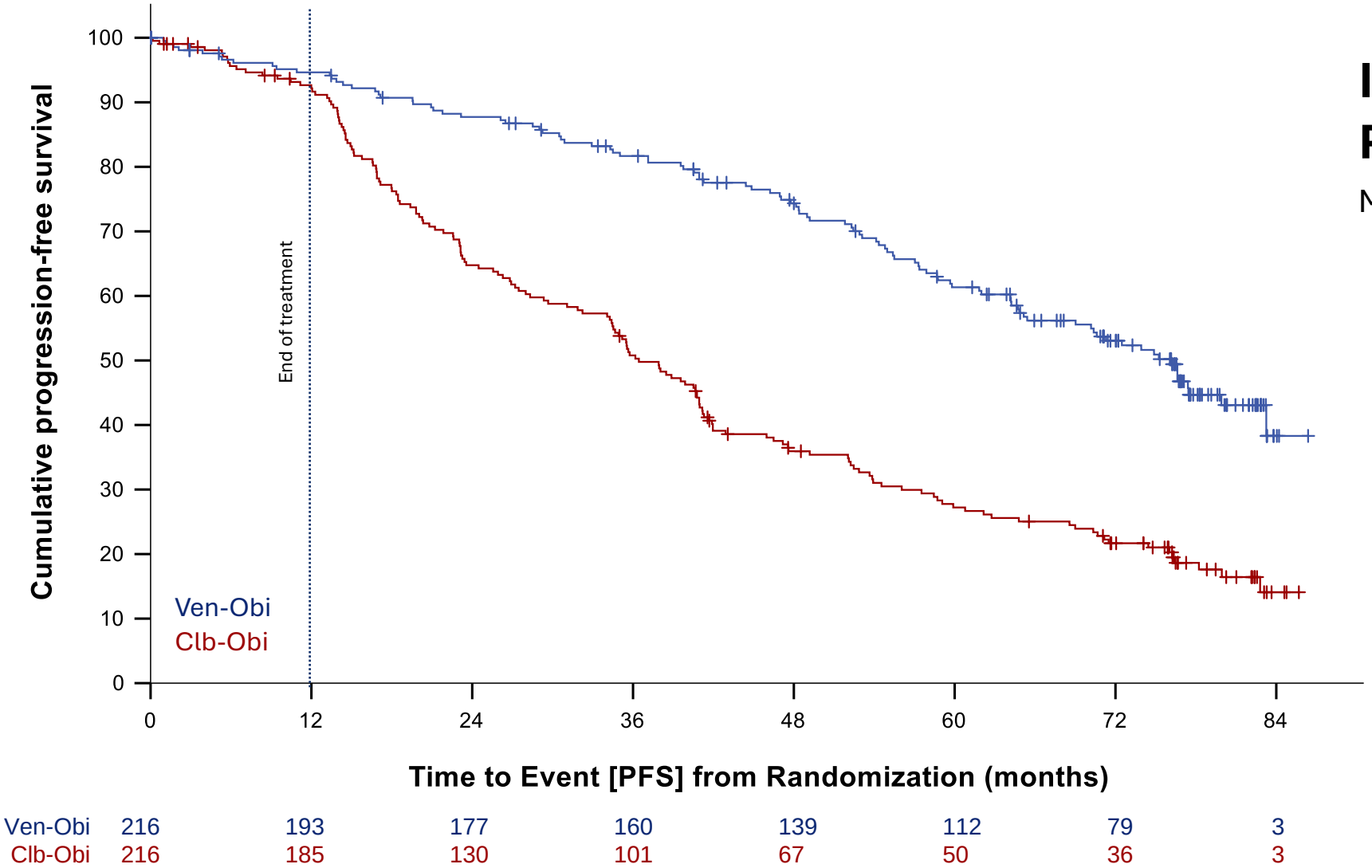
- **Primary endpoint:** investigator-assessed PFS
- **Secondary endpoints:** IRC-assessed PFS, ORR, MRD negativity, OS, event-free survival, DoR, time to new antileukemic treatment

[a]Obinutuzumab also could be administered at 100 mg on Day 1, 900 mg on Day 2, and then 1000 mg on Days 8 and 15 of cycle 1.

CIRS, cumulative illness rating scale; CLL, chronic lymphocytic leukemia; CrCl, creatinine clearance; DoR, duration of response; IRC, independent review committee; MRD, measurable residual disease; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

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

• CLL14: Progression-Free Survival With Extended Follow-up



Investigator-assessed PFS

Median observation time: 76.4 months

Median PFS

- Ven-Obi: 76.2 months
- Clb-Obi: 36.4 months
- HR 0.40 [95% CI 0.31-0.52], *P*<0.0001

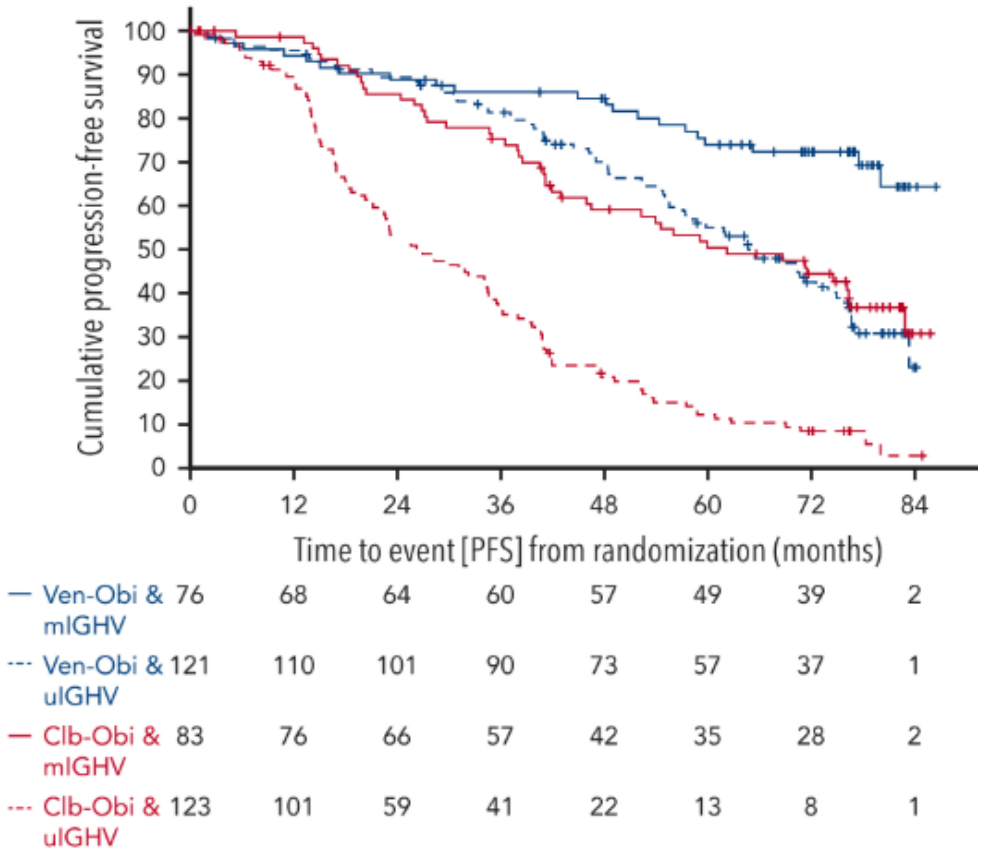
6-year PFS rate

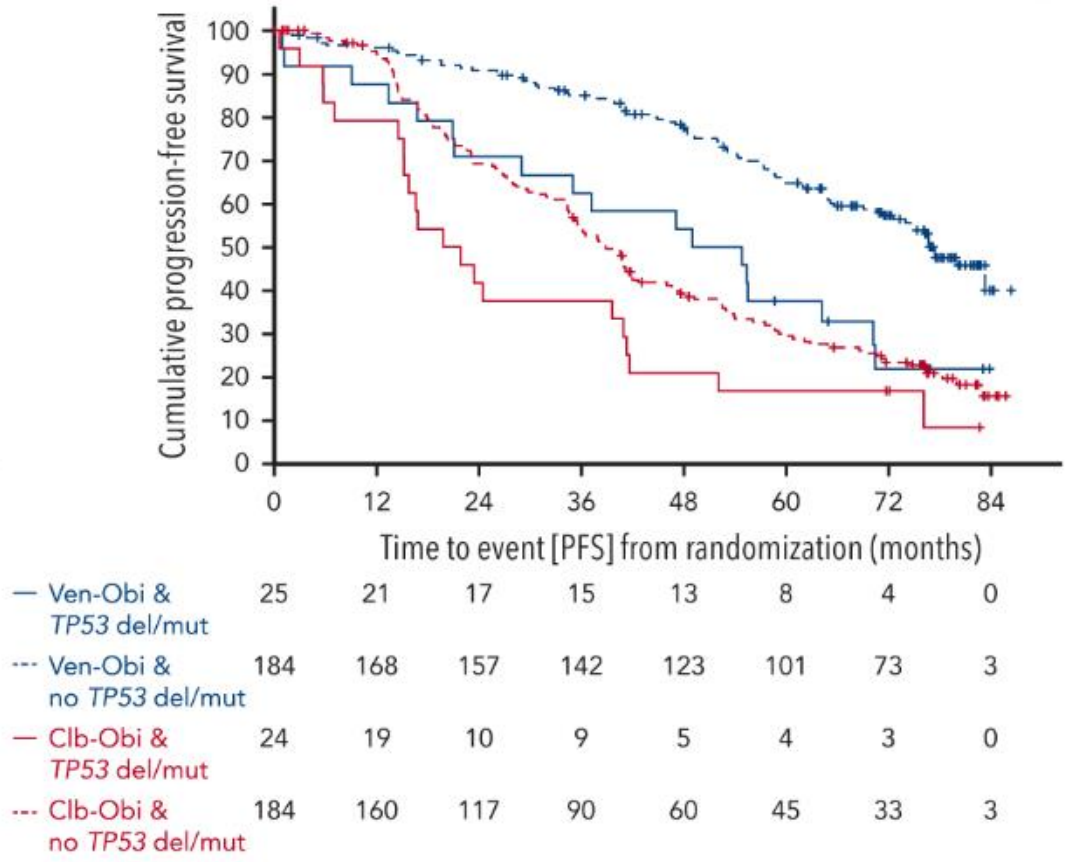
- Ven-Obi: 53.1%
- Clb-Obi: 21.7%

Clb, chlorambucil; CLL, chronic lymphocytic leukemia; CI, confidence interval; HR, hazard ratio; Obi, Obinutuzumab; PFS, progression-free survival; Ven, venetoclax.

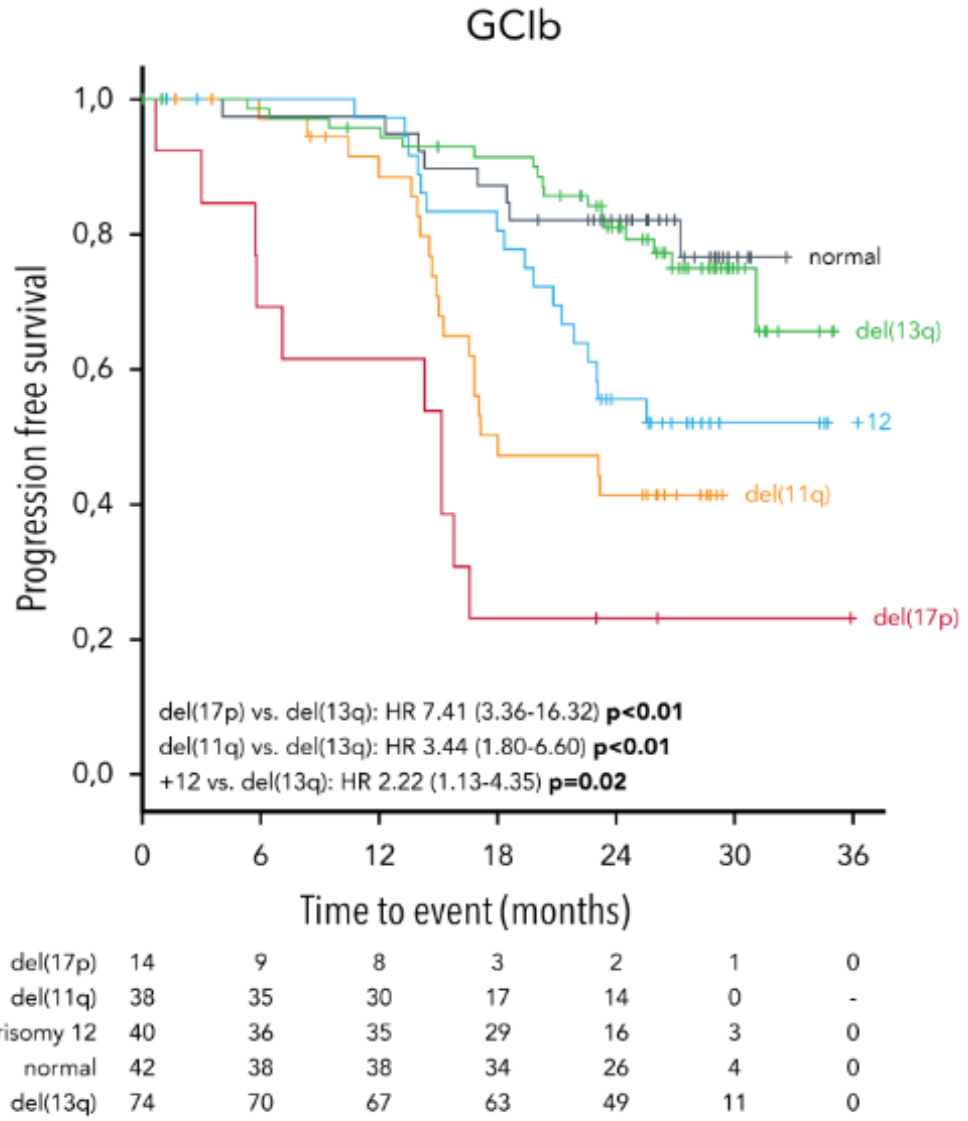
Al-Sawaf O, et al. EHA 2023. Presentation S145.

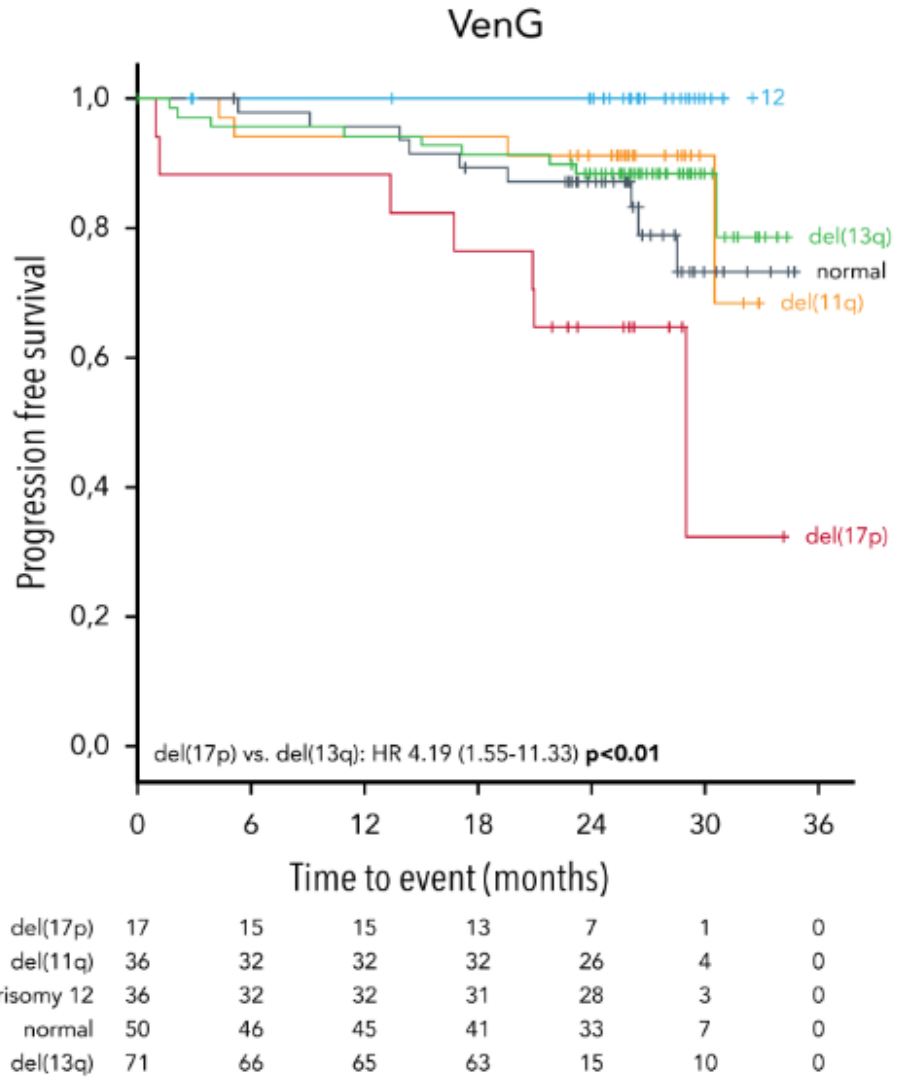
CLL14: Inferior outcomes amongst those with TP53 aberrations and unmutated IgHV





Median PFS in Ven-Obi treated patients: 52 vs. 77 mo
HR 2.29 (95% CI 1.37-3.83); *P*=0.001)





Patient Population: CLL14

Tausch et al Blood 2020

Is switching from one BTK to another appropriate?

Michael Wysota MD, Assistant Professor
Department of Medical Oncology
Division of Hematologic Malignancies and Hematopoietic Stem Cell Transplantation
Thomas Jefferson University Hospital

Summary

- Goals:
  - Review the toxicity profiles of FDA approved front line covalent BTK inhibitors
  - Understand why patients may need to discontinue BTK inhibitors
  - Review options for switching to an alternative covalent BTK inhibitor after BTK toxicity

Case presentation

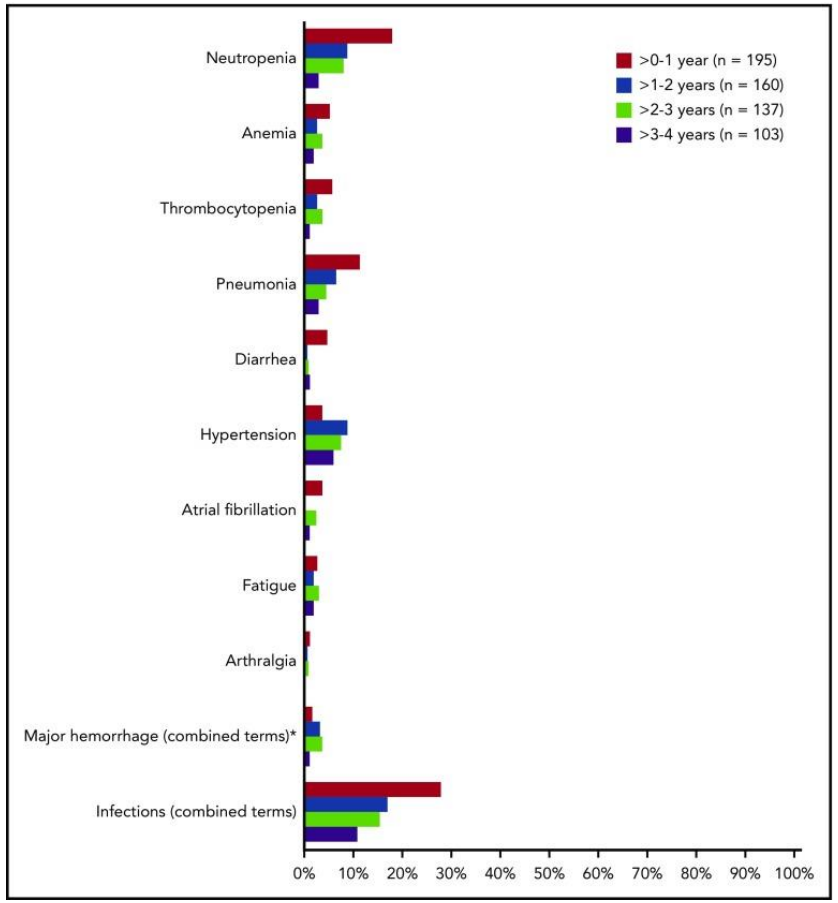
- 64M with PMH prior drug abuse, asthma, bipolar disorder, prior DVT/PE unprovoked on Xarelto and Rai Stage III CLL (IPI-3)
- WBC count at time of diagnosis was 46.6K
  - PB flow demonstrated 85% lymphocytes (CD19, CD20, CD5, CD23, CD38 positive and CD10, CD103 negative) lymphocytes consistent with diagnosis of CLL
  - FISH demonstrated + Trisomy 12, negative for TP53/Del 17p
  - IGHV unmutated
  - His previous oncologist had started patient on Acalabrutinib
    - Patient took Acalabrutinib for 1 week when he reportedly developed blisters in his mouth which resulted in his discontinuation of Acala

Presentation continued

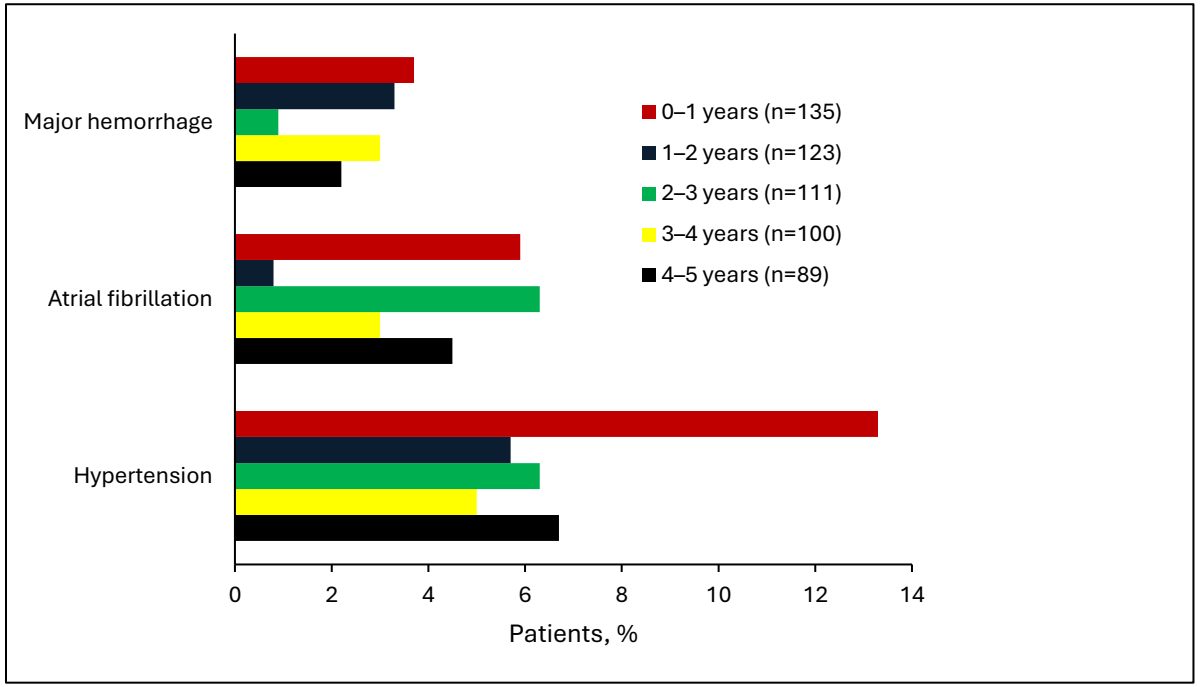
- On presentation ~6 months later:
  - WBC – 103, (~90% lymphocytes), Hgb- 6.8, Plt 98
  - Cr 1.13, Bili and Liver enzymes WNL
  - LDH 409, Uric Acid- 4.2
  - B2m- 6.72
  - CLL IPI-5 - High risk

What Would you do in this situation?

Ibrutinib has several potential toxicities that lead to treatment discontinuation



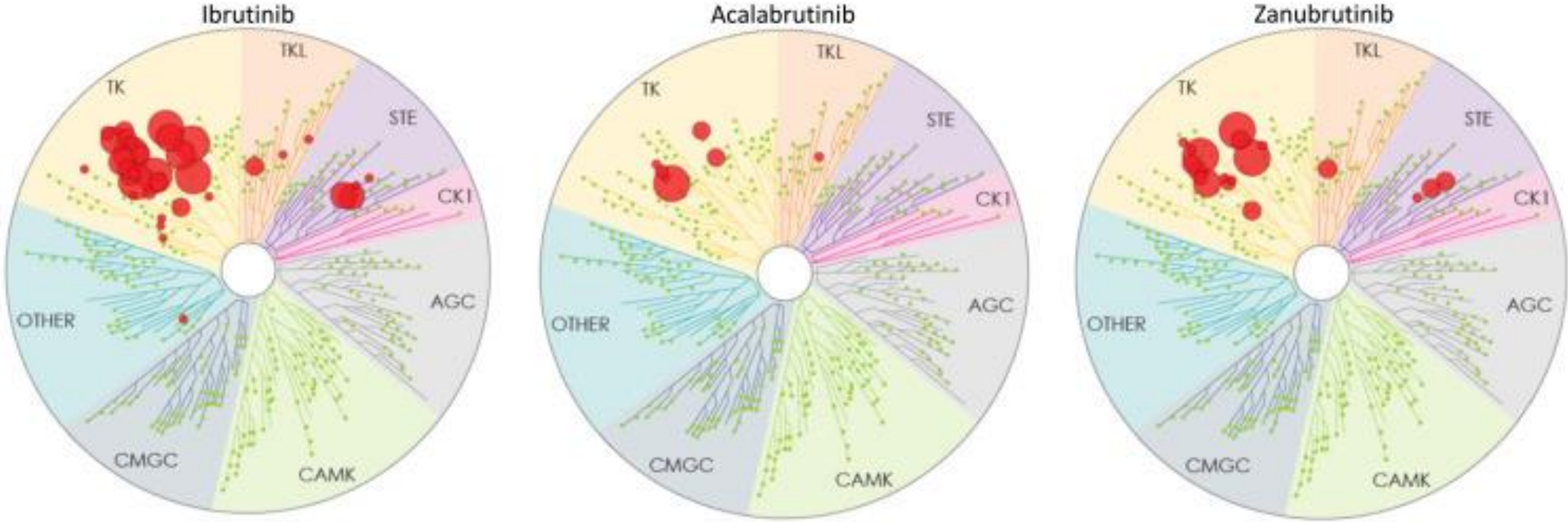
Byrd JC Et al. Long-term follow-up of the RESONATE phase 3 trial of ibrutinib vs ofatumumab. Blood. 2019 May 9;133(19):2031-2042.



Burger JA, Et al.. Long-term efficacy and safety of first-line ibrutinib treatment for patients with CLL/SLL: 5 years of follow-up from the phase 3 RESONATE-2 study. Leukemia. 2020 Mar;34(3):787-798.

First Generation

Second Generation



Percent Inhibition

100%

99.9%

99% to 99.9%

95% to 99%

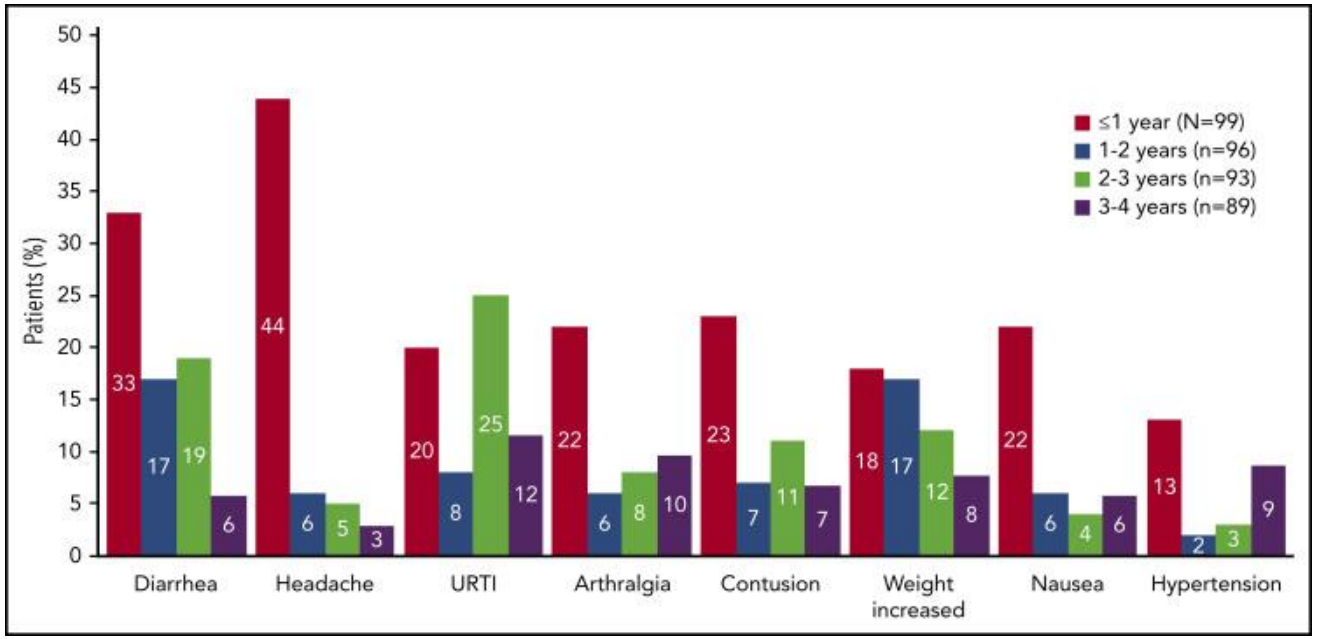
90% to 95%

65% to 90%

<65%

Acalabrutinib has similar but less frequent toxicities relative to ibrutinib

ECI*	All treated patients (N = 99), n (%)	
	All grades	Grade ≥3
Cardiac events	20 (20)†	4 (4)
Atrial fibrillation	5 (5)‡	2 (2)
Ventricular tachyarrhythmias	0	0
Anemia	8 (8)	2 (2)
Leukopenia	9 (9)	9 (9)
Neutropenia	9 (9)	9 (9)
Other leukopenia	1 (1)	1 (1)
Thrombocytopenia	3 (3)	1 (1)
Hemorrhage §	65 (66)	3 (3)
Major hemorrhage‖	4 (4)	3 (3)
Hepatotoxicity	4 (4)	2 (2)
Hypertension	22 (22)	11 (11)
Infections¶, #	83 (84)	15 (15)
Interstitial lung disease/pneumonitis	1 (1)	0
Second primary malignancies	26 (26)	5 (5)
Second primary malignancies, excluding nonmelanoma skin	11 (11)	5 (5)
Tumor lysis syndrome	0	0

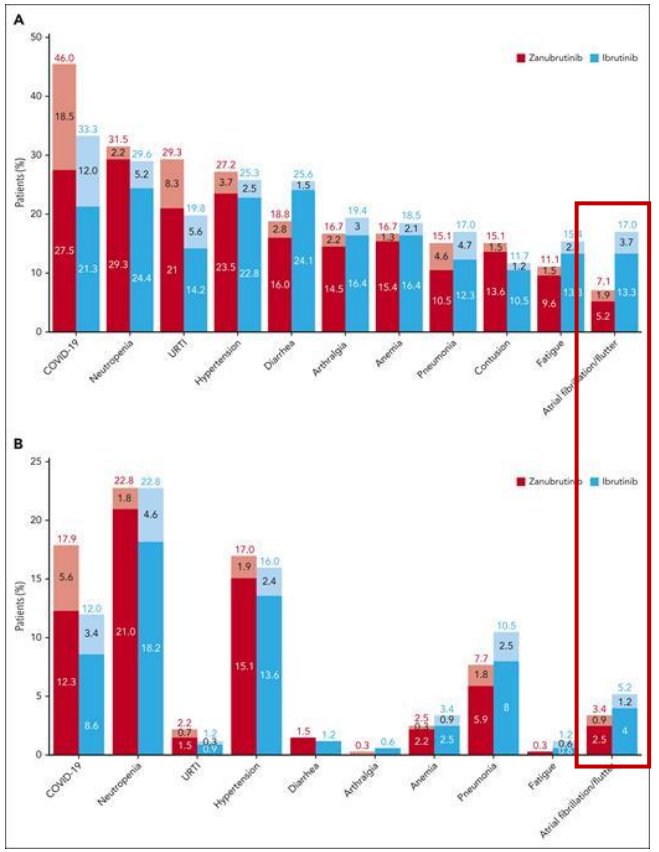


Byrd JC Et. Al. Acalabrutinib in treatment-naive chronic lymphocytic leukemia. Blood. 2021 Jun 17;137(24):3327-3338.

Zanubrutinib also shows decreased rate of toxicities relative to ibrutinib

	Patients without del(17)(p13·1)			
	Group A, zanubrutinib (n=240*)			
	Grade 1–2	Grade 3	Grade 4	Grade 5
Any	98 (41%)	87 (36%)	28 (12%)	11 (5%)
Serious	16 (7%)	49 (20%)	12 (5%)	11 (5%)
Common adverse events				
Contusion	46 (19%)	0	0	0
Upper respiratory tract infection	39 (16%)	2 (1%)	0	0
Diarrhoea	32 (13%)	2 (1%)	0	0
Arthralgia	30 (13%)	2 (1%)	0	0
Neutropenia	10 (4%)	11 (5%)	16 (7%)	0
Hypertension	14 (6%)	15 (6%)	0	0
Fatigue	25 (10%)	3 (1%)	0	0
Cough	27 (11%)	0	0	0
Headache	26 (11%)	0	0	0
Rash	26 (11%)	0	0	0
Constipation	23 (10%)	1 (<1%)	0	0
Nausea	24 (10%)	0	0	0
Back pain	21 (9%)	0	0	0
Pyrexia	17 (7%)	0	0	0
Vomiting	17 (7%)	0	0	0
Pneumonia	8 (3%)	4 (2%)	0	0
Anaemia	10 (4%)	1 (<1%)	0	0
Basal cell carcinoma	10 (4%)	1 (<1%)	0	0
Thrombocytopenia	5 (2%)	3 (1%)	1 (<1%)	0
Infusion-related reaction	1 (<1%)§	0	0	0
All bleeding adverse events¶	99 (41%)	8 (3%)	0	1 (<1%)
All cardiac adverse events¶	24 (10%)	10 (4%)	0	2 (1%)

Tam CS Et al Zanubrutinib versus bendamustine and rituximab in untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (SEQUOIA): a randomised, controlled, phase 3 trial. Lancet Oncol. 2022 Aug;23(8):1031-1043. doi: 10.1016/S1470-2045(22)00293-5.

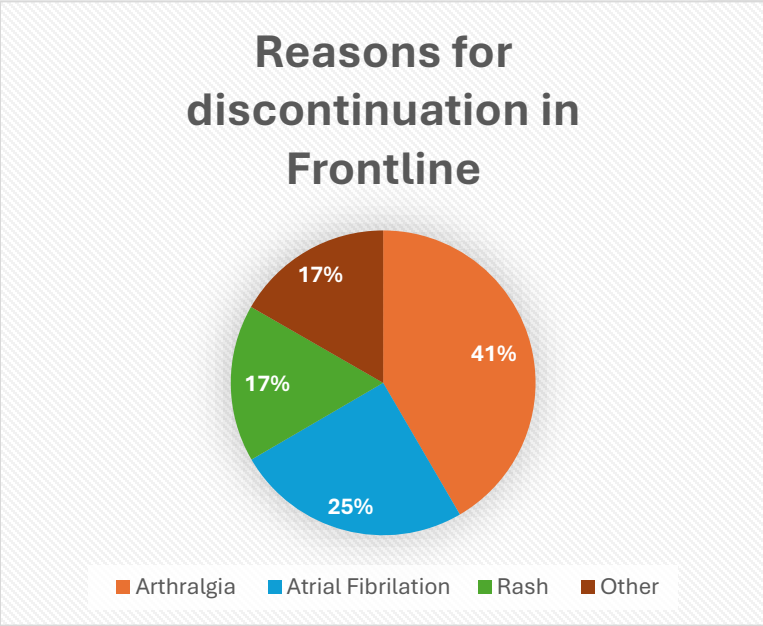


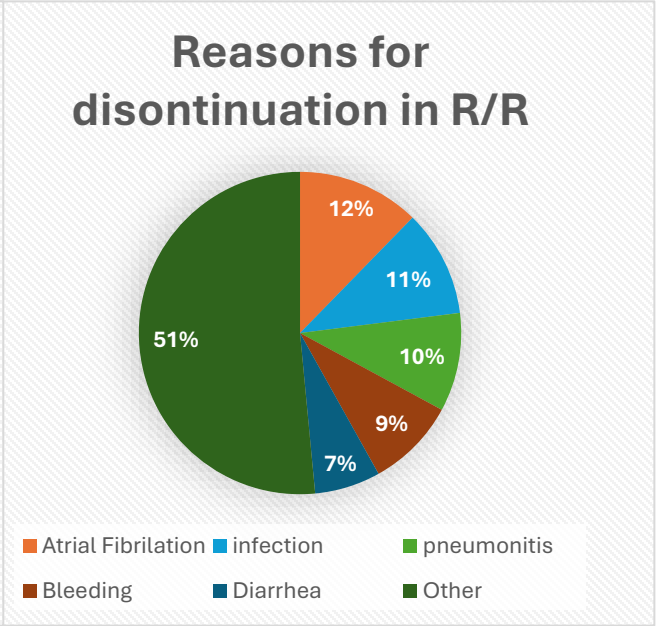
Jennifer R. Brown et al; Sustained benefit of zanubrutinib vs ibrutinib in patients with R/R CLL/SLL: final comparative analysis of ALPINE. *Blood* 2024; 144 (26): 2706–2717.

In a real world cohort a majority of patients discontinued Ibrutinib due to toxicity rather than POD

Reason for ibrutinib discontinuation	Ibrutinib in front-line (n=19)	Ibrutinib in relapse (n=231)
Toxicity	63.1% (n=12)	50.2% (n=116)
CLL progression	15.8% (n=3)	20.9% (n=49)
Other/unrelated death	5.3% (n=1)	12.1% (n=28)
Physician's or patient's preference	10.5% (n=2)	6.7% (n=15)
RT DLBCL	5.3% (n=1)	4.6% (n=10)
Stem cell transplantation/CAR T-cell	0	3.3% (n=8)
Financial concerns	0	0.8% (n=2)
Secondary malignancy	0	0.8% (n=2)
RT Hodgkin lymphoma	0	0.4% (n=1)

CLL: chronic lymphocytic leukemia; RT DLBCL: Richter transformation to diffuse large B-cell lymphoma; CAR T-cell: chimeric antigen receptor T-cell); RT: Richter transformation.





Mato AR, Et al. Toxicities and outcomes of 616 ibrutinib-treated patients in the United States: a real-world analysis. Haematologica. 2018 May;103(5):874-879.

haematologica
Journal of the Ferrata Storti Foundation

Haematologica. 2021 Mar 18;106(9):2364–2373. doi: 10.3324/haematol.2020.272500

Phase II study of acalabrutinib in ibrutinibintolerant patients with relapsed/refractory chronic lymphocytic leukemia

Inclusion

- Patients with CLL intolerant to ibrutinib
- Intolerance defined as
  - Discontinued Ibrutinib to to G3/4 toxicity
  - Discontinued after G2 toxicity that recurred twice or occurred for at least 2 weeks despite supportive care
  - Not suitable for Chemotherapy

Exclusion

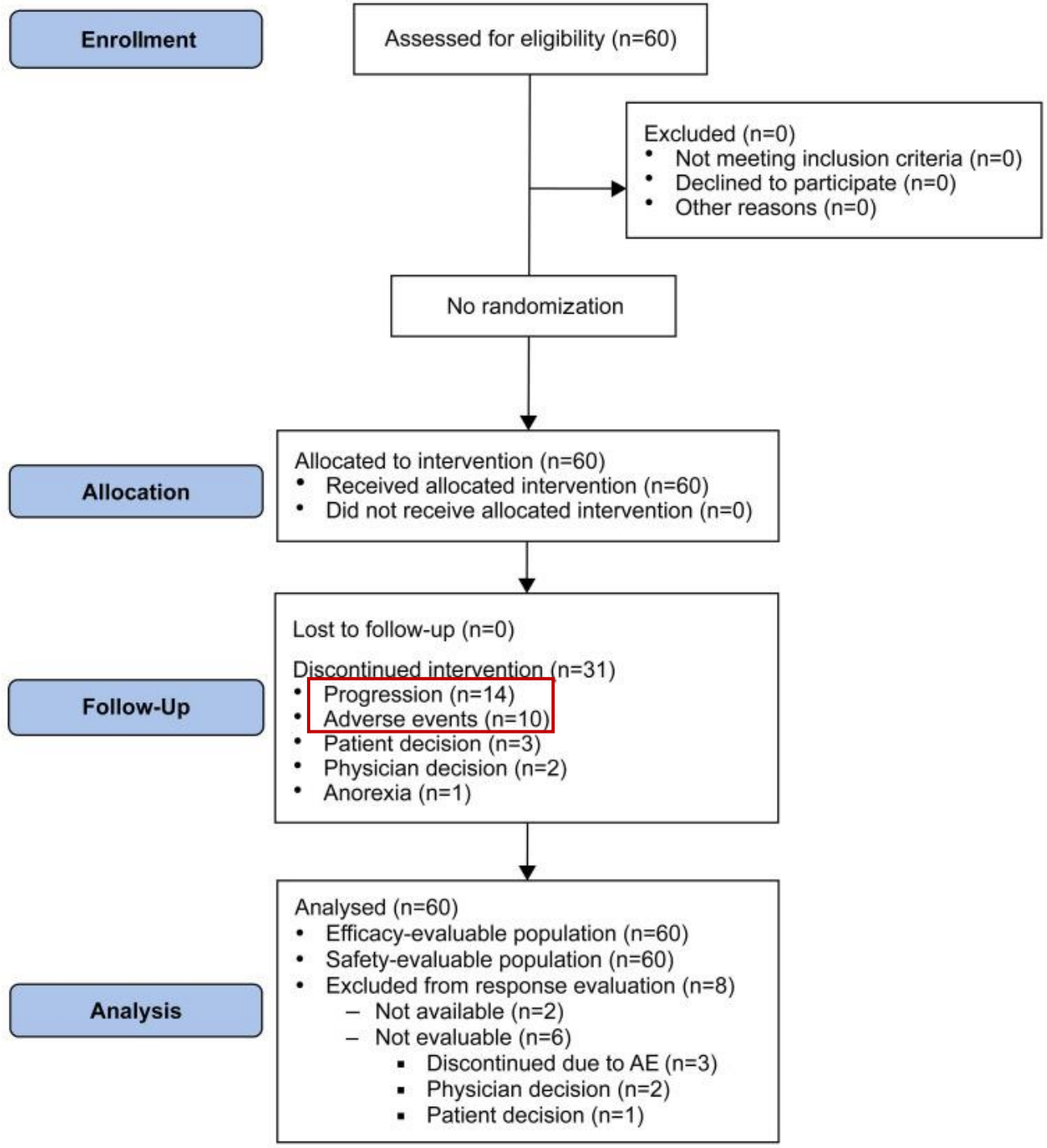
- Any intervening therapy after ibrutinib
- Ongoing G3/4 toxicity
- Richters transformation
- Patients who previously had BCL-2i
- Significant cardiovascular disease
- AC other than warfarin was allowed

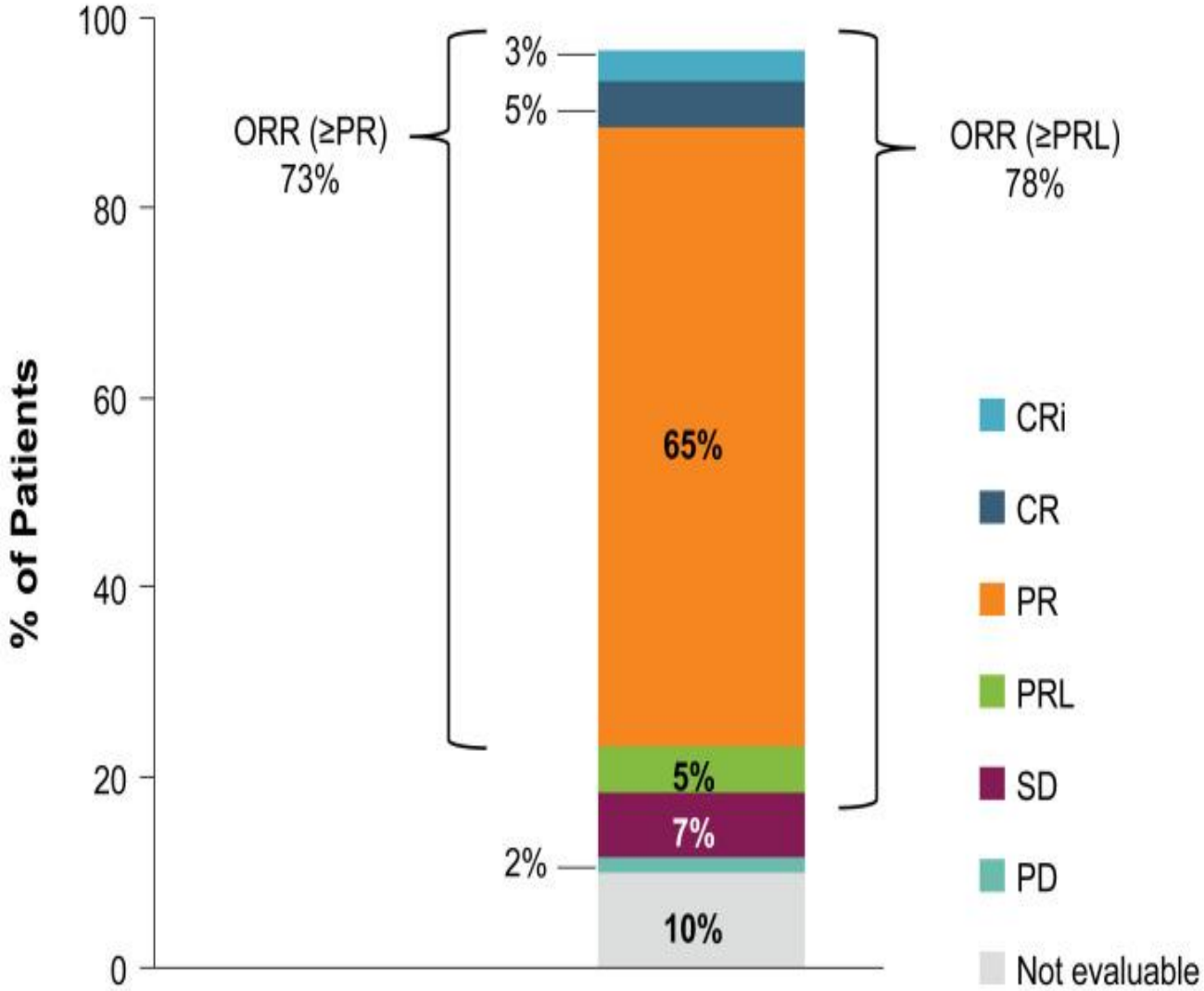
Table S2. Adverse events leading to ibrutinib discontinuation.

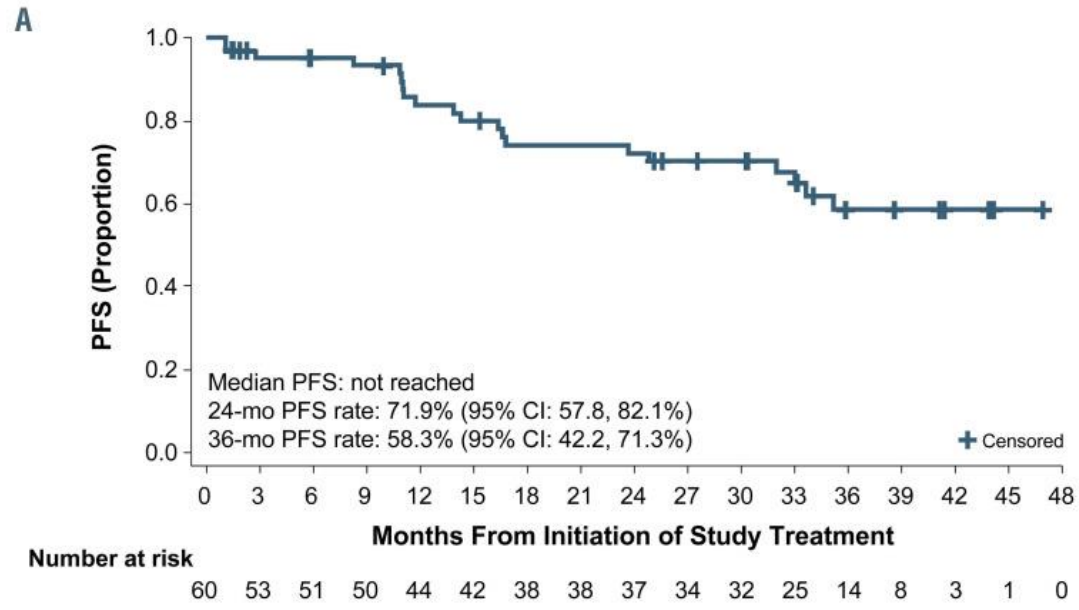
Preferred term	All treated subjects (N=60)			
	All grades[b] n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Patients with ≥1 event[a]	60 (100)	20 (33.3)	36 (60.0)	4 (6.7)
Atrial fibrillation	14 (23.3)	5 (8.3)	8 (13.3)	1 (1.7)
Diarrhea	7 (11.7)	4 (6.7)	3 (5.0)	0
Arthralgia	6 (10.0)	2 (3.3)	4 (6.7)	0
Rash	6 (10.0)	2 (3.3)	4 (6.7)	0
Asthenia	2 (3.3)	2 (3.3)	0	0
Atrial flutter	2 (3.3)	0	2 (3.3)	0
Fatigue	2 (3.3)	0	2 (3.3)	0
Neutropenia	2 (3.3)	0	1 (1.7)	1 (1.7)
Arthritis	1 (1.7)	1 (1.7)	0	0
Aspartate aminotransferase increased	1 (1.7)	0	1 (1.7)	0
Cellulitis	1 (1.7)	0	1 (1.7)	0
Cough	1 (1.7)	1 (1.7)	0	0
Dizziness	1 (1.7)	1 (1.7)	0	0
Ecchymosis	1 (1.7)	1 (1.7)	0	0
Edema	1 (1.7)	1 (1.7)	0	0
Epistaxis	1 (1.7)	0	1 (1.7)	0
Febrile neutropenia	1 (1.7)	0	0	1 (1.7)
Gastritis	1 (1.7)	0	1 (1.7)	0
Gastrointestinal disorder	1 (1.7)	1 (1.7)	0	0
Glaucoma	1 (1.7)	0	0	1 (1.7)
Guillain-Barré syndrome	1 (1.7)	0	1 (1.7)	0
Hematuria	1 (1.7)	1 (1.7)	0	0
Hemorrhage	1 (1.7)	1 (1.7)	0	0
Headache	1 (1.7)	1 (1.7)	0	0
Hypersensitivity	1 (1.7)	0	1 (1.7)	0
Hypertension	1 (1.7)	0	1 (1.7)	0
Liver function test increased	1 (1.7)	1 (1.7)	0	0
Macular edema	1 (1.7)	0	1 (1.7)	0
Myalgia	1 (1.7)	0	1 (1.7)	0
Neutrophil count decreased	1 (1.7)	0	1 (1.7)	0
Pneumonia	1 (1.7)	0	1 (1.7)	0
Pulmonary hemorrhage	1 (1.7)	0	1 (1.7)	0
Rash, maculopapular	1 (1.7)	1 (1.7)	0	0
Retinal hemorrhage	1 (1.7)	1 (1.7)	0	0
Retinal vein occlusion	1 (1.7)	1 (1.7)	0	0
Stent-graft endoleak	1 (1.7)	0	1 (1.7)	0
Stomatitis	1 (1.7)	1 (1.7)	0	0
Thrombocytopenia	1 (1.7)	0	1 (1.7)	0
Uveitis	1 (1.7)	0	1 (1.7)	0

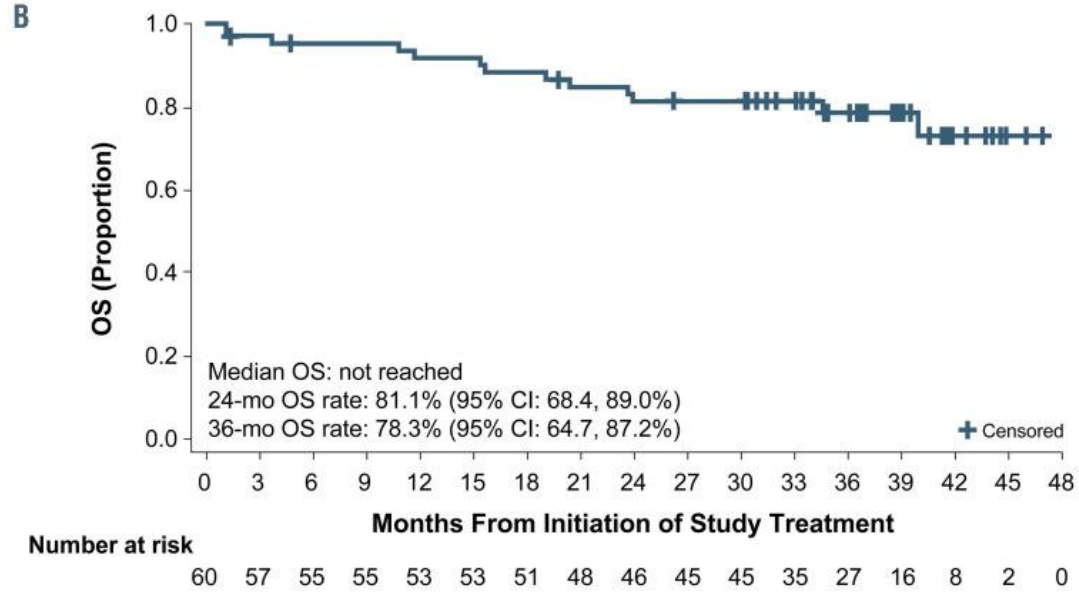
Characteristic	N=60
Age in years, median (range)	69.5 (43-88)
Men, n (%)	38 (63)
ECOG PS ≤1, n (%)	58 (97)
Number of prior systemic therapies, n (%)	
1	14 (23)
2	18 (30)
3	11 (18)
≥4	17 (28)
β2-microglobulin >3 mg/L, n/N (%)	46/58 (79)
Genetic risk features, n/N (%)	
Unmutated *IGHV*	46/58 (79)
del(11q)[a]	14/60 (23)
del(17p)[a]	17/60 (28)
Rai stage III-IV, n (%)	31 (52)
Lymph nodes ≥5 cm, n (%)	19 (32)
Laboratory values, median (range)	
Lymphocyte count, 10^9/L	12.3 (0.9-172.4)
Neutrophil count, 10^9/L	3.3 (0.4-20.1)
Hemoglobin, g/dL	12.2 (7.5-17.3)
Platelet count, 10^9/L	117.5 (37-350)

[a]By fluorescence *in situ* hybridisation testing. ECOG PS: Eastern Cooperative Oncology Group performance status; *IGHV*: immunoglobulin heavy chain gene.




100
80
60
40
20
0
% of Patients
ORR (≥PR)
73%
ORR (≥PRL)
78%
3%
5%
65%
5%
7%
2%
10%
CRi
CR
PR
PRL
SD
PD
Not evaluable


A
PFS (Proportion)
1.0
0.8
0.6
0.4
0.2
0.0
Median PFS: not reached
24-mo PFS rate: 71.9% (95% CI: 57.8, 82.1%)
36-mo PFS rate: 58.3% (95% CI: 42.2, 71.3%)
Censored
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48
Months From Initiation of Study Treatment
Number at risk
60 53 51 50 44 42 38 38 37 34 32 25 14 8 3 1 0


B
OS (Proportion)
1.0
0.8
0.6
0.4
0.2
0.0
Median OS: not reached
24-mo OS rate: 81.1% (95% CI: 68.4, 89.0%)
36-mo OS rate: 78.3% (95% CI: 64.7, 87.2%)
Censored
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48
Months From Initiation of Study Treatment
Number at risk
60 57 55 55 53 53 51 48 46 45 45 35 27 16 8 2 0

Ibrutinib-intolerance adverse events and recurrence after acalabrutinib treatment.

Adverse event	Number of patients with ibrutinib intolerance[a]	Acalabrutinib experience for same patients			
		Total	Lower grade	Same grade	Higher grade
Atrial fibrillation	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

[a]Among 60 patients meeting the study enrollment criteria, 41 patients had a medical history of one or more (43 events in total) of the following categories of ibrutinib-intolerance events: atrial fibrillation, 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 one patient experienced a different type of bleeding event with acalabrutinib compared with ibrutinib treatment. [e]Includes one patient with arthritis.

Clinical Trial > Lancet Haematol. 2023 Jan;10(1):e35-e45.
doi: 10.1016/S2352-3026(22)00320-9. Epub 2022 Nov 16.

Zanubrutinib in patients with previously treated B-cell malignancies intolerant of previous Bruton tyrosine kinase inhibitors in the USA: a phase 2, open-label, single-arm study

Mazyar Shadman [1], Ian W Flinn [2], Moshe Y Levy [3], Ryan F Porter [4], John M Burke [5], Syed F Zafar [6], Jamal Misleh [7], Edwin C Kingsley [8], Habte A Yimer [9], Benjamin Freeman [10], Subramanya S Rao [11], Arvind Chaudhry [12], Praveen K Tumula [13], Mitul D Gandhi [14], Sudhir Manda [15], Dih-Yih Chen [16], Kunthel By [16], Linlin Xu [16], Ye Liu [17], Rocco Crescenzo [16], Adam Idoine [16], Xiaoping Zhang [16], Aileen Cohen [16], Jane Huang [16], Jeff P Sharman [18]

Inclusion

- Adult Patients with CLL, SLL, MCL, WM, MZL intolerant to Acalabrutinib, ibrutinib or both
- For ibrutinib and acalabrutinib intolerance events:
  - 1) 1 or more ≥ Grade 2 nonhematologic toxicities for > 7 days (with or without treatment);
  - 2) 1 or more ≥ Grade 3 nonhematologic toxicity of any duration;
  - 3) 1 or more Grade 3 neutropenia with infection or fever of any duration; or
  - 4) Grade 4 heme toxicity which persists to the point that the investigator chose to stop therapy due to toxicity NOT progression;
- b. For acalabrutinib intolerance events only:
  - 1) 1 or more ≥ Grade 1 nonhematologic toxicities of any duration with ≥ 3 recurrent episodes; or
  - 2) 1 or more ≥ Grade 1 nonhematologic toxicities for > 7 days (with or without treatment);
  - 3) Inability to use acid-reducing agents or anticoagulants (eg, proton pump inhibitors, warfarin) due to concurrent acalabrutinib use.

Exclusion

- Known PML
- MI within 6 months prior to screening
- Other significant cardiac toxicity
- CNS hemorrhage

	Cohort 1 (n=57)	Cohort 2 (n=10)
Indication		
Chronic lymphocytic leukaemia	38 (67%)	5 (50%)
Waldenström macroglobulinaemia	9 (16%)	2 (20%)
Small lymphocytic lymphoma	6 (11%)	1 (10%)
Mantle cell lymphoma	2 (4%)	1 (10%)
Marginal zone lymphoma	2 (4%)	1 (10%)
Age, years	71 (65–79)	74 (70–76)
Sex		
Male	30 (53%)	6 (60%)
Female	27 (47%)	4 (40%)
Ethnicity		
White	54 (95%)	9 (90%)
Multiple	0	1 (10%)
Not reported or unknown	3 (5%)	0
Eastern Cooperative Oncology Group performance status 0	33 (58%)	4 (40%)
Number of previous therapy regimens	1 (1–3)	3 (2–3)
Time on previous BTK inhibitor, months	10·6 (5·6–28·9)*	3·3 (1·4–10·1)†
Baseline cytopenias		
Absolute neutrophil count ≤1·5 × 10^9/L	4 (7%)	0
Haemoglobin ≤11·0 g/dL	7 (12%)	3 (30%)
Platelets ≤100 × 10^9/L	7 (12%)	0
Bulky disease		
Longest diameter <5 cm	33 (58%)	8 (80%)
Longest diameter ≥5 cm	8 (14%)	1 (10%)
No measurable disease	16 (28%)	1 (10%)

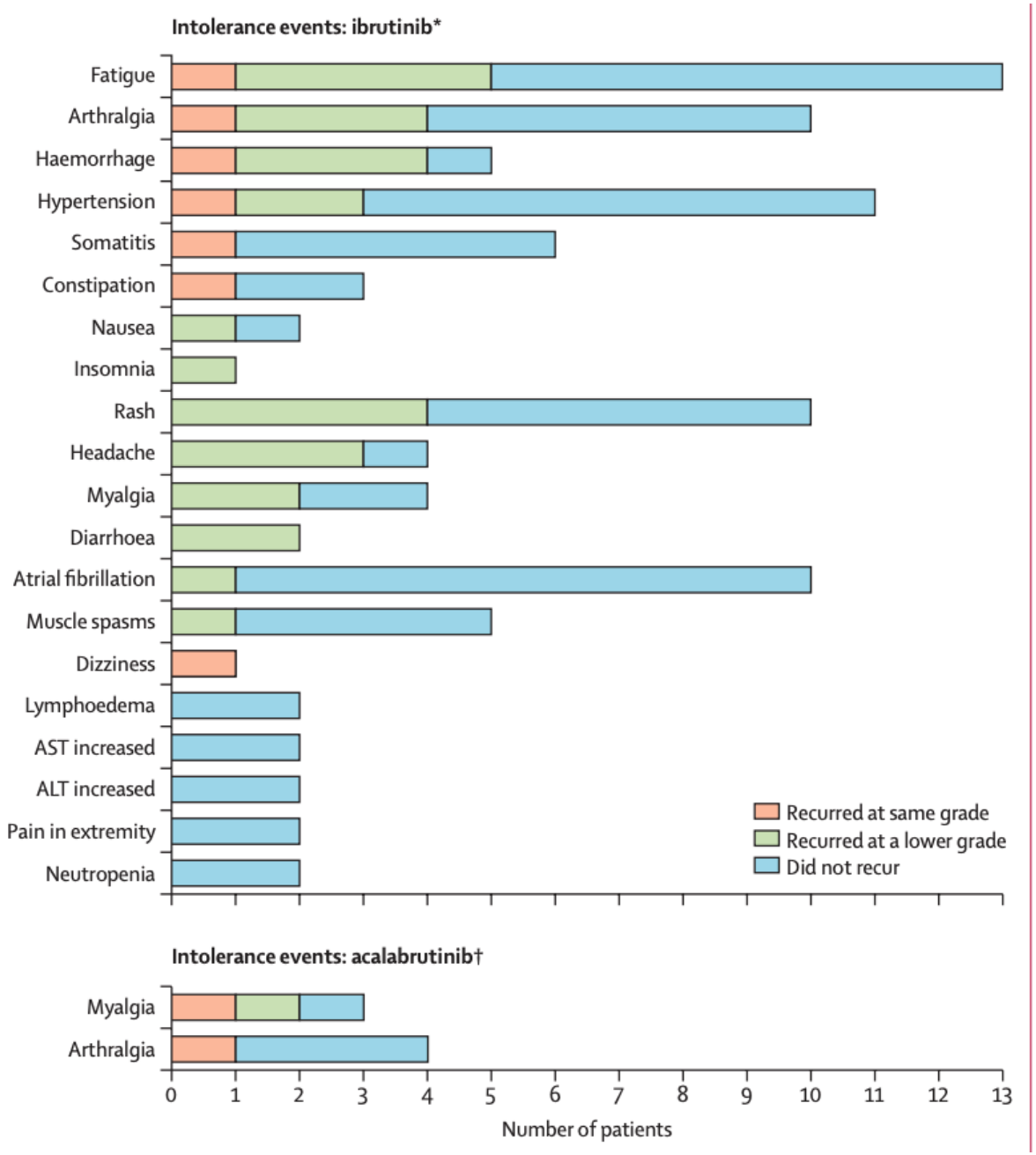
(Table 1 continues in next column)

(Continued from previous column)

	Cohort 1 (n=57)	Cohort 2 (n=10)
Disease staging		
Binet staging for chronic lymphocytic leukaemia		
Stage A	13 (23%)	1 (10%)
Stage B	20 (35%)	4 (40%)
Stage C	5 (9%)	0
Ann Arbor stage for small lymphocytic lymphoma, mantle cell lymphoma, and marginal zone lymphoma		
Stage I	2 (4%)	1 (10%)
Stage II	2 (4%)	0
Stage III	5 (9%)	0
Stage IV	1 (2%)	2 (20%)
Waldenström macroglobulinaemia International Staging System		
Low-risk group	2 (4%)	0
Intermediate-risk group	3 (5%)	1 (10%)
High-risk group	0	0
Unknown	4 (7%)	1 (10%)
Genomic status		
Chronic lymphocytic leukaemia or small lymphocytic lymphoma		
del(11q)	8/44 (18%)	1/6 (17%)
del(17p)	4/44 (9%)	1/6 (17%)
del(13q) nullisomy	5/44 (11%)	1/6 (17%)
TP53 mutation	11/44 (25%)	0
Unmutated *IGHV*	8/44 (18%)	2/6 (33%)
Waldenström macroglobulinaemia		
MYD88 mutation	2/9 (22%)	0
CXCR4 mutation	1/9 (11%)	0
Marginal zone lymphoma		
t(11;18)	0	0
BIRC3 mutation	0	0

Data are n (%), median (IQR), or n/N (%). *BIRC3*=baculoviral IAP repeat containing 3. BTK=Bruton tyrosine kinase. *CXCR4*=C-X-C chemokine receptor type 4. *IGHV*=immunoglobulin heavy chain. *MYD88*=myeloid differentiation primary response 88. NA=not applicable. *TP53*=tumour protein 53. *Ibrutinib. †Acalabrutinb.

Table 1: **Baseline characteristics of all treated patients**


Intolerance events: ibrutinib*
Fatigue
Arthralgia
Haemorrhage
Hypertension
Somatitis
Constipation
Nausea
Insomnia
Rash
Headache
Myalgia
Diarrhoea
Atrial fibrillation
Muscle spasms
Dizziness
Lymphoedema
AST increased
ALT increased
Pain in extremity
Neutropenia
Recurred at same grade
Recurred at a lower grade
Did not recur
Intolerance events: acalabrutinib†
Myalgia
Arthralgia
0 1 2 3 4 5 6 7 8 9 10 11 12 13
Number of patients

Zanubrutinib in CLL/SLL Patients with Previous BTK Inhibitor Use

Table 1: Safety Summary in Patients with CLL/SLL from BGB-3111-215 (N=61)[2]			
	All Patients (N=61)	Cohort 1 (n=44)	Cohort 2 (n=17)
Patients with ≥1 TEAE, n (%)	57 (93.4)	42 (95.5)	15 (88.2)
Grade ≥3	31 (50.8)	24 (54.5)	7(41.2)
Serious	16 (26.2)	12 (27.3)	4 (23.5)
Leading to treatment discontinuation	5 (8.2)	4 (9.1)	1 (5.9)
Leading to dose interruption	30 (49.2)	22 (50)	8 (47.1)
Leading to dose reductions	15 (24.6)	12 (27.3)	3 (17.6)
Leading to death	1 (1.6)	1 (2.3) *	0
Treatment-Emergent Adverse Events in ≥15% of All Patients, n (%)			
Fatigue	18 (29.5)	14 (31.8)	4 (23.5)
COVID-19	14 (23)	13 (29.5)	1 (5.9)
Contusion	13 (21.3)	10 (22.7)	3 (17.6)
Diarrhea	12 (19.7)	8 (18.2)	4 (23.5)
Arthralgia	10 (16.4)	8 (18.2)	2 (11.8)
Cough	10 (16.4)	5 (11.4)	5 (29.4)
Myalgia	10 (16.4)	7 (15.9)	3 (17.6)

Data cutoff: January 3, 2023
* COVID-19 pneumonia

Figure 1: Recurrence of Ibrutinib Intolerance Events with Zanubrutinib[2]

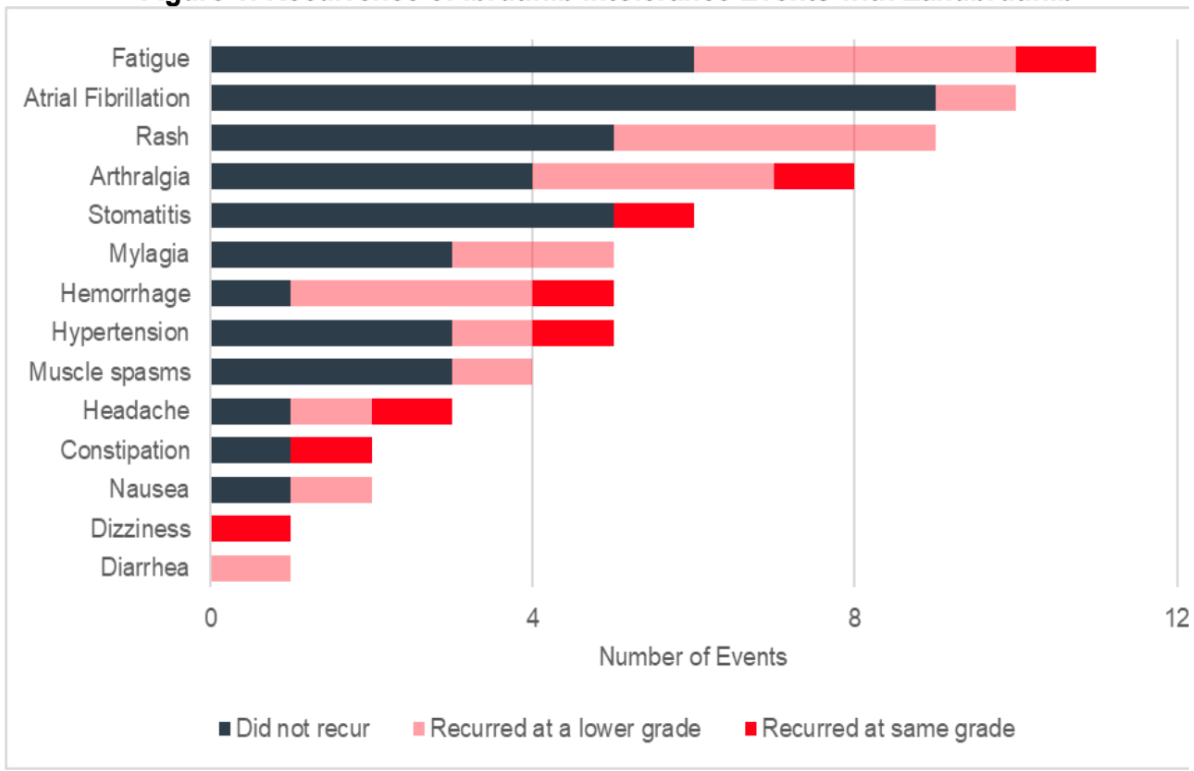


Figure 2: Recurrence of Acalabrutinib Intolerance Events with Zanubrutinib[3]

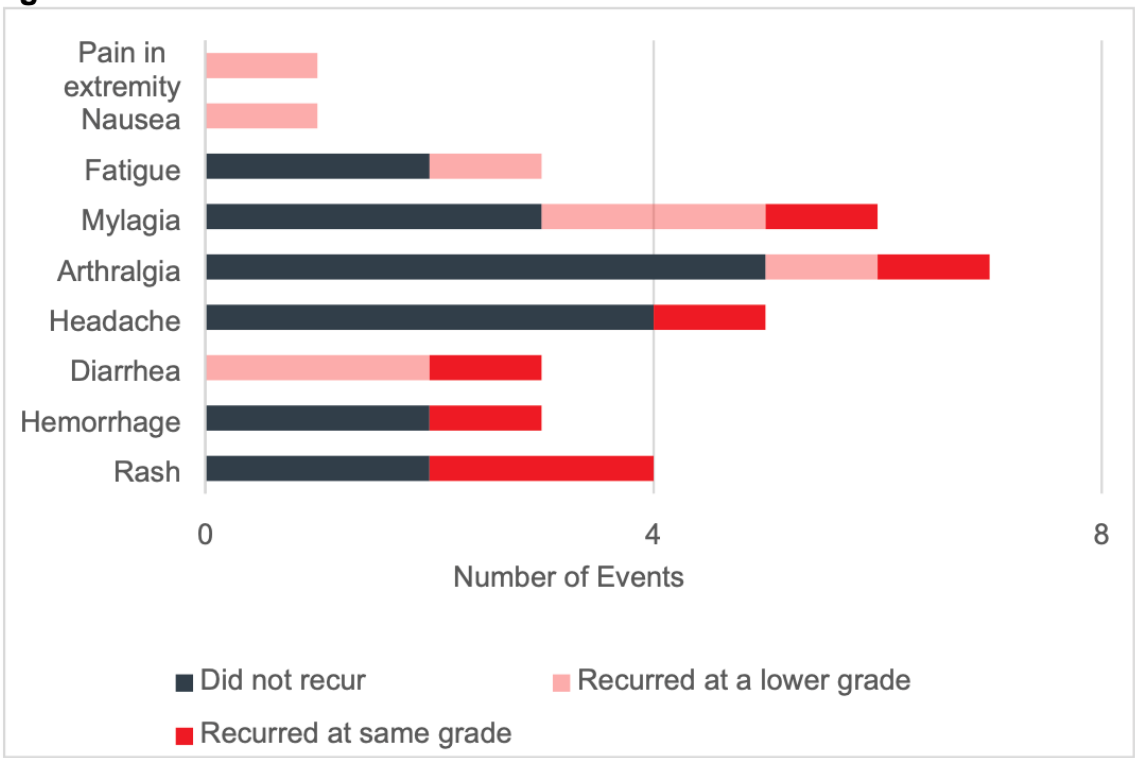


Table 2: Efficacy Outcomes in Patients with CLL/SLL from BGB-3111-215 (N=57)[2]			
	All Patients (N=57)	Cohort 1 (n=43)	Cohort 2 (n=14)
Disease control rate (stable disease or better), n (%, 95% CI)	54 (94.7, 85.4-98.9)	41 (95.3, 84.2-99.4)	13 (92.9, 66.1-99.8)
Overall response rate (better than stable disease), n (%, 95% CI)	41 (71.9, 58.5-83)	31 (72.1, 56.3-84.7)	10 (71.4, 41.9-91.6)
Complete response	1 (1.8)	1 (2.3)	0
Partial response	33 (57.9)	25 (58.1)	8 (57.1)
Partial response with lymphocytosis	7 (12.3)	5 (11.6)	2 (14.3)
Stable disease	13 (22.8)	10 (23.3)	3 (21.4)
Progressive disease	2 (3.5)	1 (2.3)	1 (7.1)
Time to best overall response‡, median (range), months	5.6 (2.6-28.1)	5.7 (2.6-28.1)	2.9 (2.7-8.4)
PFS 12-month event-free rate, % (95% CI)	88.3 (75.7-94.6)	90.3 (76.3-96.3)	74.3 (24.5-93.9)
DOR 12-month event-free rate, % (95% CI)	88 (70.8-95.3)	89.2 (70.1-96.4)	80 (20.4-96.9)
Data cutoff: January 3, 2023			

What if patients progress on BTKi

Real-world evidence of obinutuzumab and venetoclax in previously treated patients with chronic lymphocytic leukemia or small lymphocytic lymphoma

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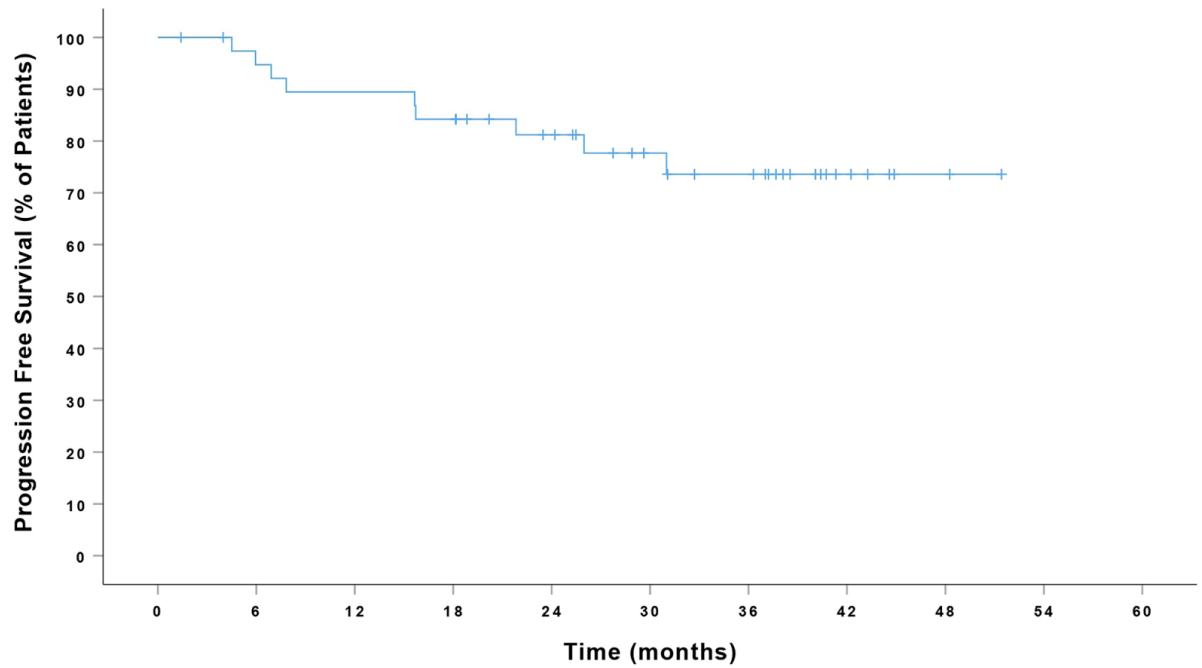
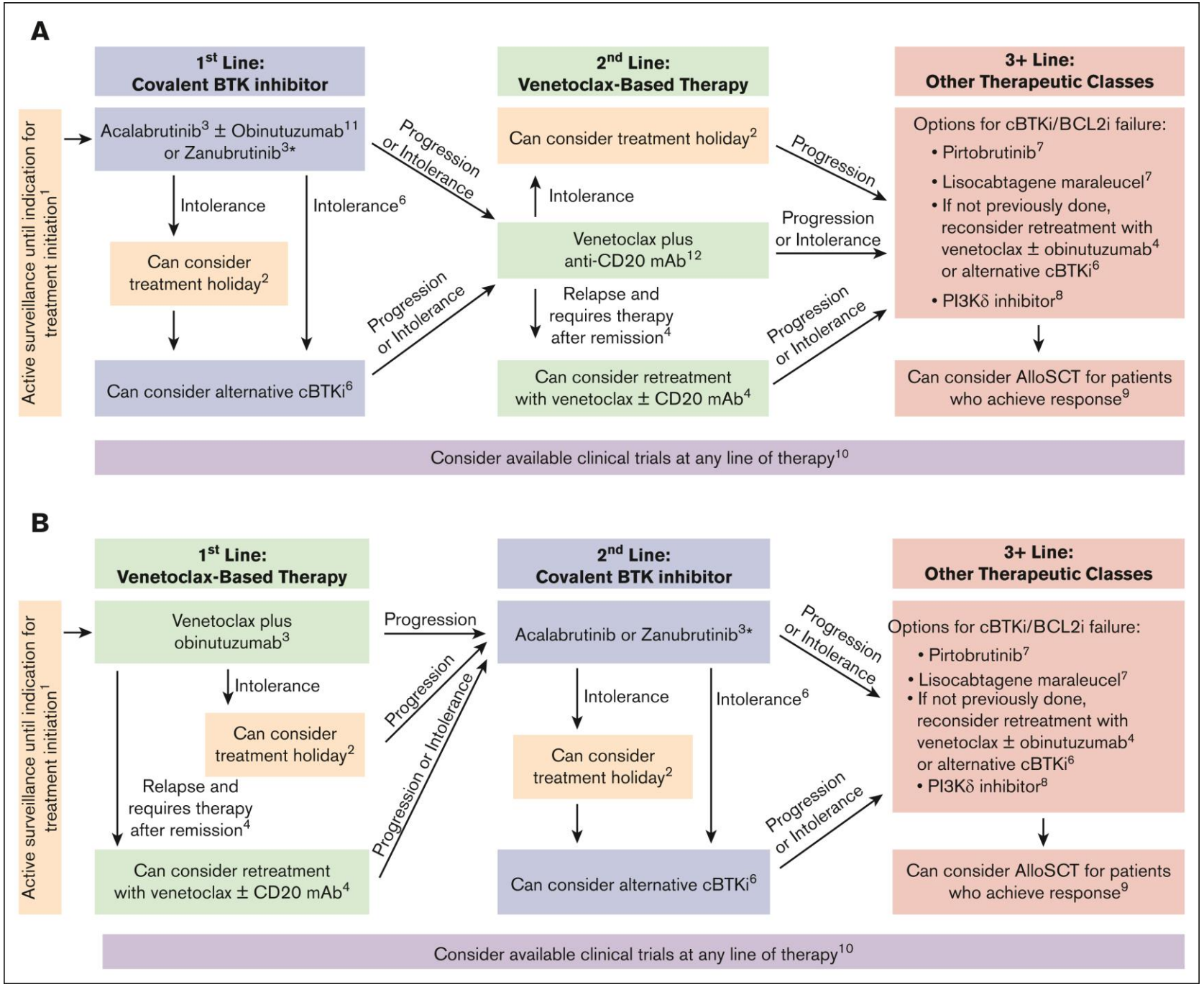
Table 1. Baseline characteristics.

	All patients $N=40$
Age, median (range)	72 (51-94)
Age ≥65 years, n (%)	31 (77.5)
Female sex, n (%)	9 (22.5)
White race, n (%)	37 (92.5)
ECOG PS ≥2, n (%)	4 (10)
Del(17p) or TP53 mutated, n (%)	11/39 (28.2)
TP53 mutated*	7/28 (25)
Del(17p)**	7/39 (17.9)
Unmutated IGHV, n (%)***	21/32 (65.6)
Complex karyotype, n (%)**	11/39 (28.2)
Number of prior lines, median (range)	1 (1-6)
≥2 prior therapies, n (%)	15 (37.5)
Previous cytotoxic chemotherapy, n (%)	28 (70)
Previous chemoimmunotherapy (no BTK/ BCL2 inhibitor)	18 (45)
Previous bendamustine	18 (45)
Previous fludarabine	13 (32.5)
Previous chlorambucil	4 (10)
Previous anti-CD20 monoclonal antibody, n (%)	31 (77.5)
Previous covalent BTK inhibitor therapy, n (%)	22 (55)
Previous cBTKi discontinued for progression	15 (37.5)
Previous cBTKi discontinued for intolerance	7 (17.5)
Previous venetoclax therapy, n (%)	1 (2.5)
CrCl (min/mL), median (range)	57 (22-134)
CrCl ≥80 mL/min, n (%)	7 (17.5)
CrCl ≥60 and <80 mL/min, n (%)	12 (30)
CrCl ≥30 and <60 mL/min, n (%)	19 (47.5)
CrCl <30 mL/min, n (%)	2 (5)
TLS risk assessment, n (%)	
Low	19 (47.5)
Medium	17 (42.5)
High	4 (10)
Pre-obinutuzumab ALC, median (range)	25,500/μL (400-456,000)
Pre-obinutuzumab ALC ≥25,000/μL, n (%)	20 (50)
Baseline maximal tumor dimension (cm), median (range)	2.1 (0.6-22)





Jacob D. Soumerai, Jacqueline Barrientos, Inhye Ahn, Catherine Coombs, Douglas Gladstone, Marc Hoffman, Adam Kittai, Ryan Jacobs, Andrew Lipsky, Krish Patel, Joanna Rhodes, Alan Skarbnik, Meghan Thompson, Daniel Ermann, Patrick Reville, Harsh Shah, Jennifer R. Brown, Deborah M. Stephens; Consensus recommendations from the 2024 Lymphoma Research Foundation workshop on treatment selection and sequencing in CLL or SLL. *Blood Adv* 2025; 9 (5): 1213–1229.

Summary

- If a patient becomes intolerant to a covalent BTK inhibitor during the course of their treatment, it is reasonable to switch to another BTK inhibitor
- Most toxicities, when switching from one covalent BTK inhibitor to another, will not recur or recur at a lower grade
- While there is very little data, it is not recommended to switch from one covalent BTK inhibitor to another in the setting of treatment failure