ON-TOPIC

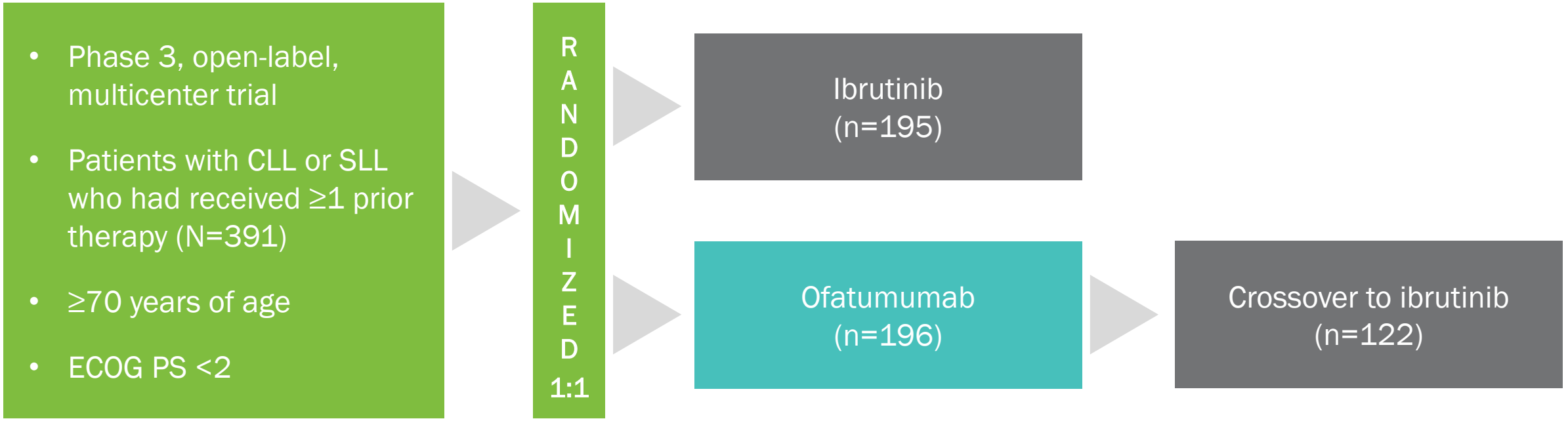
VirtualRoundtable™

ACCREDITED CONTINUING EDUCATION

BTK Battle – Experts Compare and Contrast the Latest Data of BTK Inhibitors for the **Treatment of Hematologic Malignancies**

THIS ACTIVITY IS JOINTLY PROVIDED BY PIM Postgraduate Institute for Medicine | Bio Ascend™

RESONATE Trial: Ibrutinib vs Ofatumumab in Previously Treated CLL/SLL

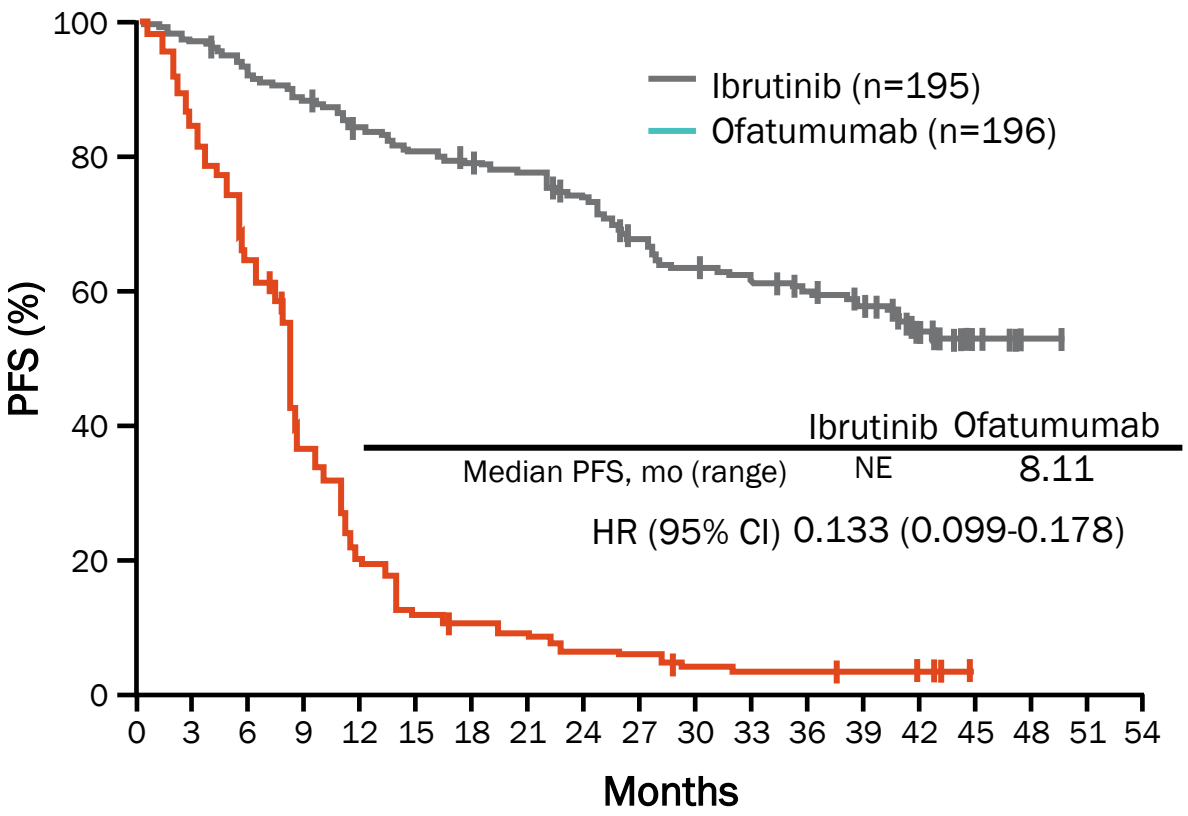


CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SLL, small lymphocytic lymphoma.

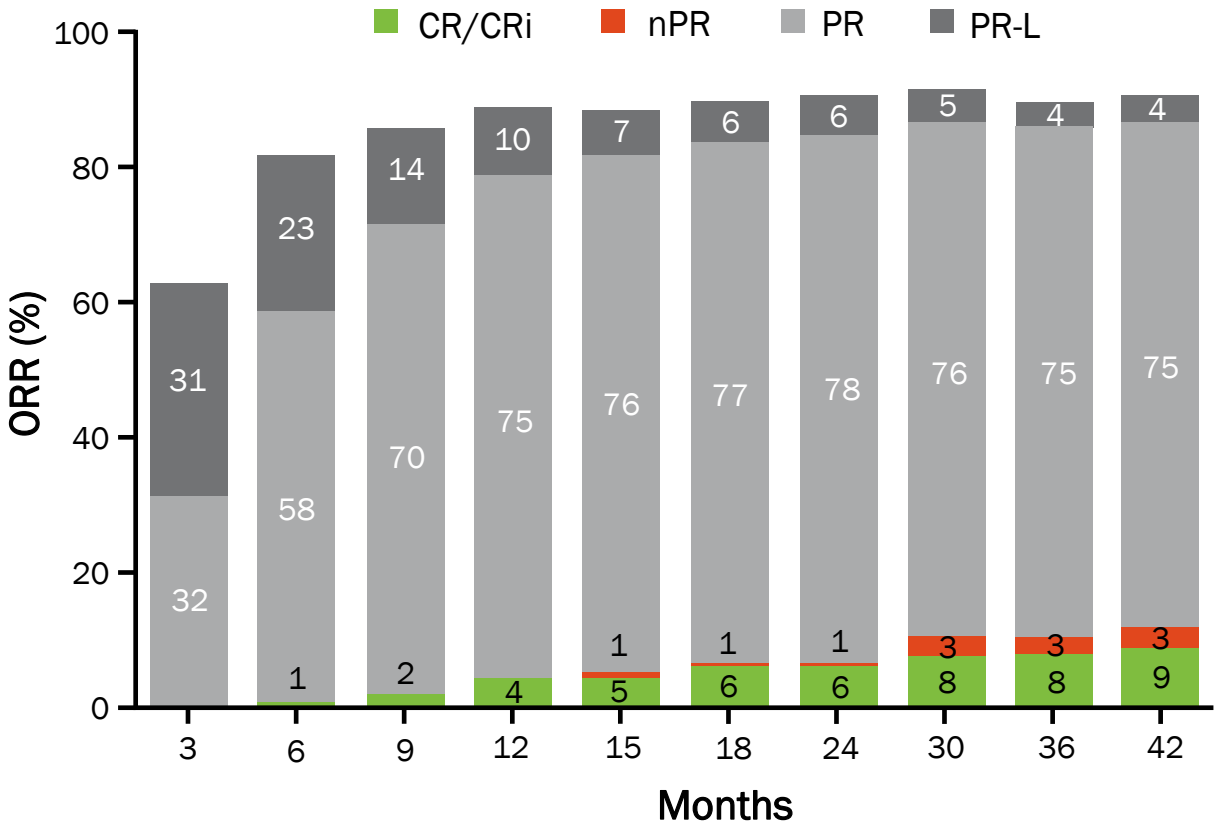
Byrd JC, et al. *N Engl J Med*. 2014;371:213-223.

RESONATE Trial: Long-Term Follow-Up

Long-Term PFS



Best Response



CR, complete response; CRi, complete response with incomplete hematopoietic recovery; NE, not evaluable; nPR, nodular partial response; ORR, overall response rate; PFS, progression-free survival; PR, partial response; PR-L, partial response with lymphocytosis.

Byrd JC, et al. *Blood*. 2019;133:2031-2042.

RESONATE-2 Trial: Ibrutinib vs Chlorambucil in Treatment-Naive Older Patients With CLL/SLL

- Phase 3, randomized, international, open-label trial
- Patients ≥65 years of age with treatment-naive CLL/SLL (N=269)
- ECOG PS ≤2
- No del(17p)

RANDOMIZED 1:1

- Ibrutinib (n=136)
- Chlorambucil (n=133)

Following confirmation of PD, patients randomized to chlorambucil were eligible to cross over to second-line treatment with ibrutinib (investigator's choice)

Primary endpoint: Duration of PFS

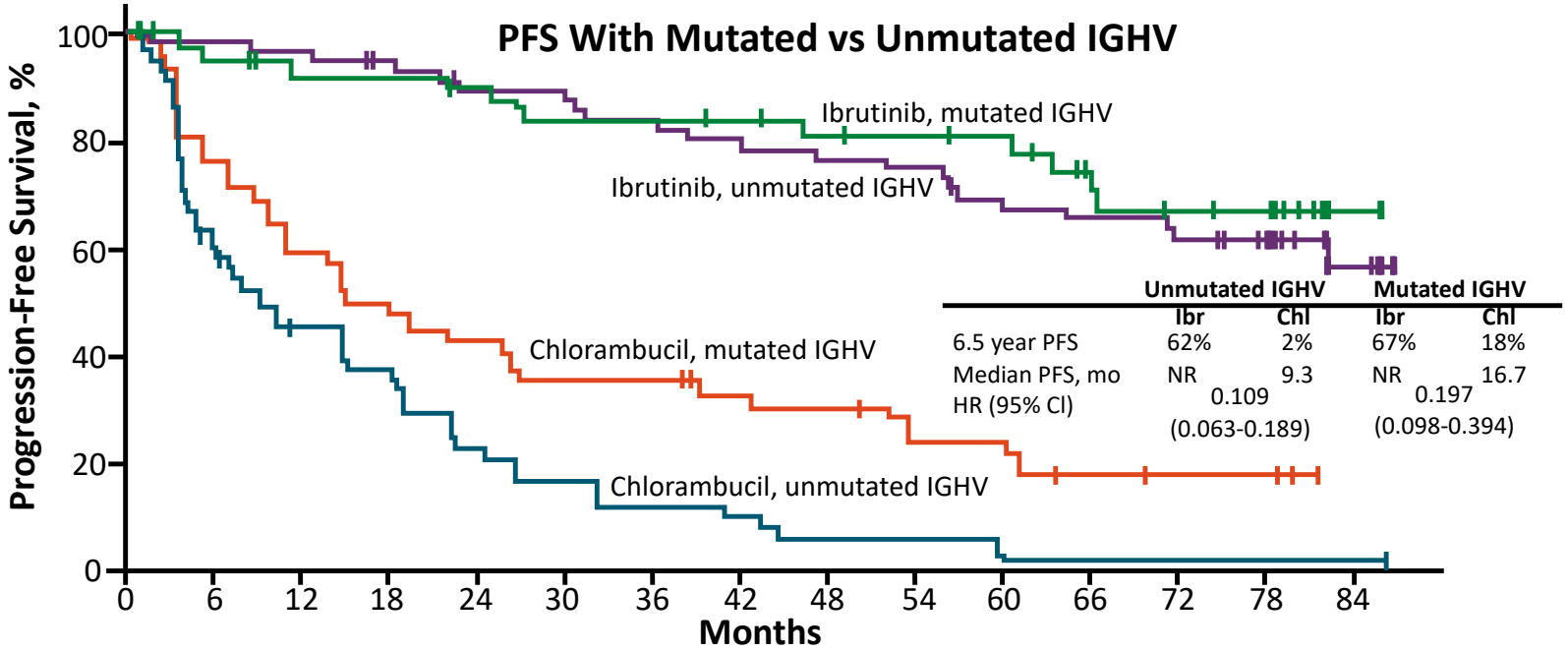
Secondary endpoints: OS, ORR, rate of sustained improvement in hematologic variables, safety

CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; SLL, small lymphocytic lymphoma.

Burger JA, et al. *N Engl J Med*. 2015;373:2425-2437.

RESONATE-2: 7-Year Follow-Up – PFS (Primary Endpoint) – Mutated vs Unmutated *IGHV*

- Primary endpoint PFS: Chlorambucil = 15.0 mo; ibrutinib = NE



Patients at Risk

Ibrutinib, mutated IGHV:	40	37	34	34	32	30	30	29	27	26	25	20	17	16	4
Ibrutinib, unmutated IGHV:	58	58	56	53	49	48	46	43	42	41	36	35	32	26	8
Chlorambucil, mutated IGHV:	42	42	25	21	18	15	15	12	11	8	8	5	4	4	
Chlorambucil, unmutated IGHV:	60	60	23	19	11	8	6	5	3	3	2	1	1	1	1

Chl, chlorambucil; Ibr, ibrutinib; IGHV, immunoglobulin heavy chain variable region gene; NE, not evaluable; PFS, progression-free survival.

Barr PM, et al. ASCO 2021. Abstr #7523.

ECOG-1912 Trial: Ibrutinib + Rituximab vs FCR Chemoimmunotherapy for CLL

- Phase 3, randomized, open-label trial
- Treatment-naive CLL (N=529)
- ≤70 years of age
- ECOG PS 0-2
- CrCl >40 mL/min
- FCR eligible
- No del(17p) by FISH

RANDOMIZED 2:1

Ibrutinib + rituximab (n=354)

Ibrutinib maintenance until PD

Fludarabine + cyclophosphamide + rituximab (n=175)

Primary endpoint: PFS

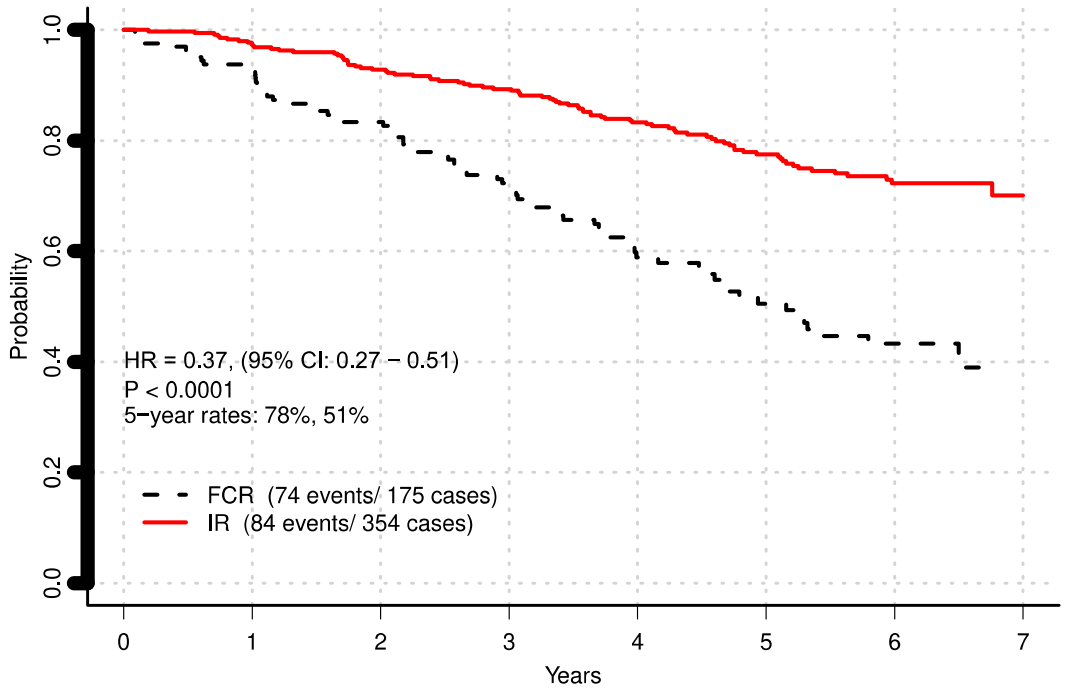
Secondary endpoints: OS, safety

CLL, chronic lymphocytic leukemia; CrCl, creatine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status; FCR, fludarabine, cyclophosphamide, and rituximab; FISH, fluorescence in situ hybridization; OS, overall survival; PD, progressive disease; PFS, progression-free survival.

Shanafelt TD, et al. *N Engl J Med*. 2019;381:432-443.

ECOG-1912 Trial: Results

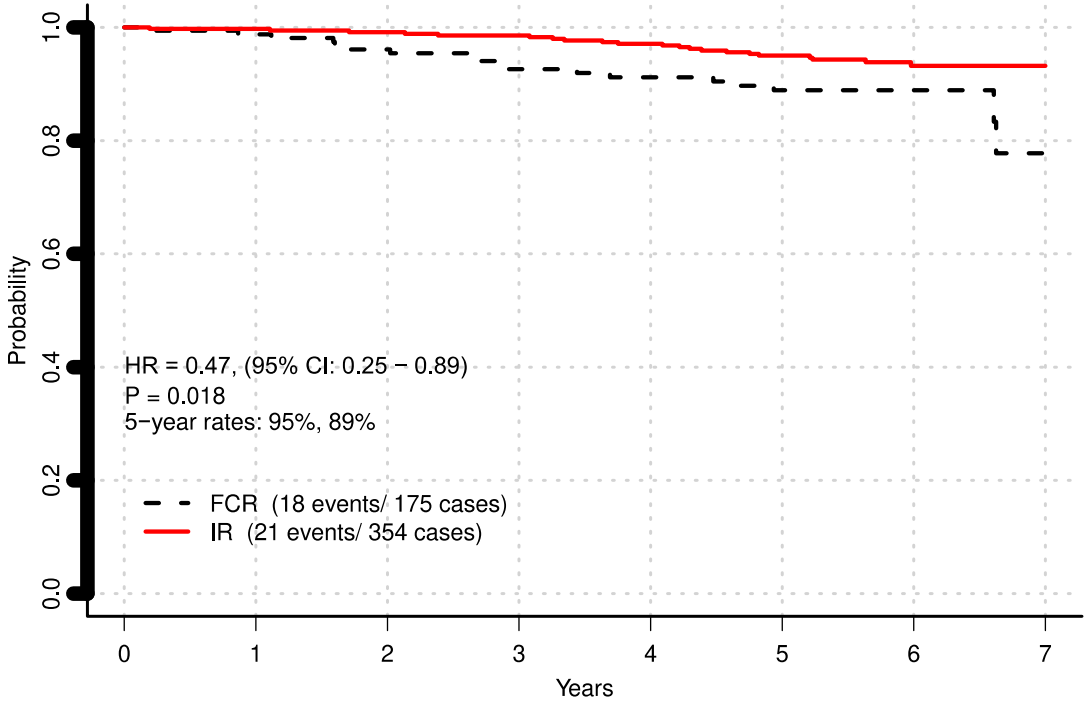
PFS Among All Patients



Number at risk

FCR	175	145	123	98	62	45	21	0
IR	354	339	321	306	248	193	110	7

OS



Number at risk

FCR	175	155	143	131	126	96	47	3
IR	354	347	343	338	329	300	139	20

FCR, fludarabine, cyclophosphamide, and rituximab; IR, ibrutinib and rituximab; ITT, intent-to-treat; OS, overall survival; PFS, progression-free survival.

Shanafelt TD, et al. *Blood*. 2022;140:112-120.

ALLIANCE Trial A041202: Ibrutinib ± Rituximab vs Bendamustine + Rituximab in Untreated CLL

- Phase 3, randomized
- Patients with untreated CLL meeting iwCLL 2008 criteria for treatment initiation (N=547)
- ≥65 years of age
- ECOG PS 0-2
- Patients had
  - CrCl 40 mL/min
  - Bilirubin ≤1.5 x ULN
  - No need for warfarin treatment

RANDOMIZED 1:1:1

- Ibrutinib (n=182)
- Ibrutinib + rituximab (n=182)
- Bendamustine + rituximab (n=183)

Patients in this arm with PD could cross over to ibrutinib within 1 year after progression

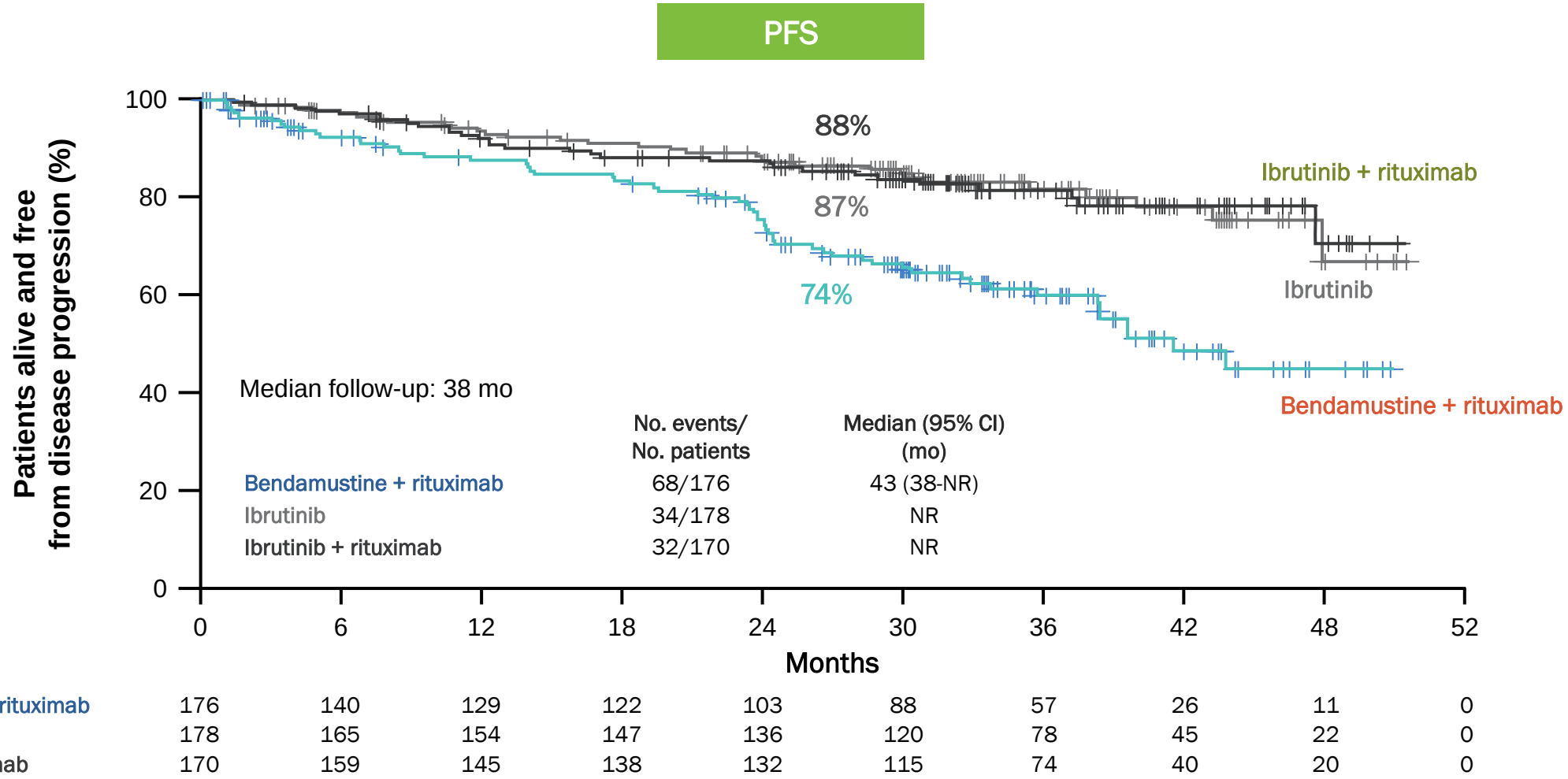
Primary endpoint: PFS

Secondary endpoints: OS, CR, MRD

CLL, chronic lymphocytic leukemia; CR, complete response; CrCl, creatine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; MRD, minimal residual disease; OS, overall survival; PD, progressive disease; PFS, progression-free survival; ULN, upper limit of normal.

Woyach JA, et al. *N Engl J Med*. 2018;379:2517-2528.

ALLIANCE Trial A041202: Results



PFS, progression-free survival.

Woyach JA, et al. *N Engl J Med*. 2018;379:2517-2528.

Real-World Analysis of 616 Ibrutinib-Treated Patients in the United States – Reasons for Discontinuation

Reason for Ibrutinib Discontinuation, %	1L Ibrutinib (n=19)	Ibrutinib in Relapse (n=231)
Toxicity	63.1	50.2
CLL progression	15.8	20.9
Other/unrelated death	5.3	12.1
Physician's or patient's preference	10.5	6.7
RT DLBCL	5.3	4.6
SCT/CAR T cell	0	3.3
Financial concerns	0	0.8
Secondary malignancy	0	0.8
RT Hodgkin lymphoma	0	0.4

1L, first line; CAR, chimeric antigen receptor; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; RT, Richter transformation; SCT, stem cell transplantation.

Mato AR, et al. *Haematologica*. 2018;103:874-879.

ELEVATE-TN Trial: Acalabrutinib ± Obinutuzumab vs Obinutuzumab + Chlorambucil in Treatment-Naive CLL

- Phase 3, randomized, multicenter, open-label trial
- Treatment-naive patients with CLL (N=535)
- ≥65 years of age, or <65 with CIRS score >6 and CrCl <70 mL/min
- Patients stratified by del(17p) status, ECOG PS ≤1 vs 2, geographic region

RANDOMIZED 1:1:1

- Acalabrutinib (n=179)
- Acalabrutinib + obinutuzumab (n=179)
- Obinutuzumab + chlorambucil (n=183)

Until PD or unacceptable toxicity

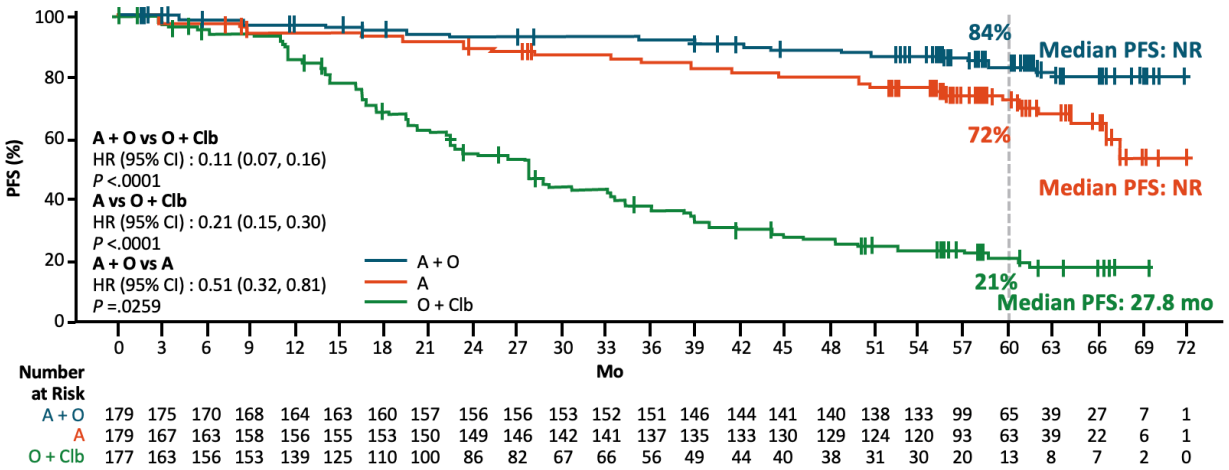
Primary endpoint: PFS per IRC (acalabrutinib/obinutuzumab vs chlorambucil/obinutuzumab)

Secondary endpoints: PFS of acalabrutinib monotherapy vs obinutuzumab/chlorambucil, ORR, TTNT, OS, safety

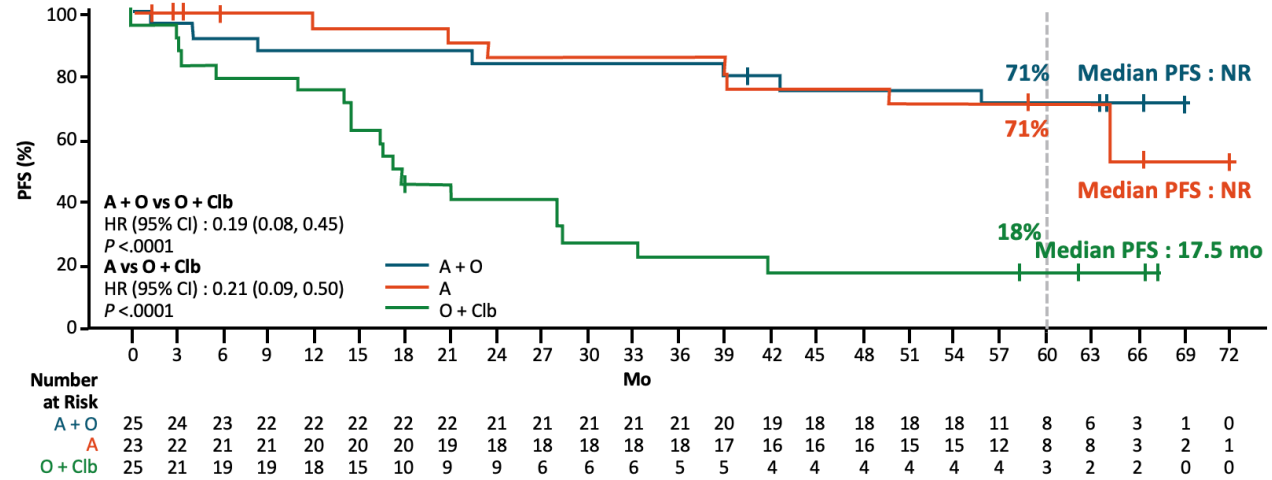
CIRS, cumulative illness rating scale; CLL, chronic lymphocytic leukemia; CrCl, creatine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent review committee; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; TTNT, time to next treatment.

Sharman JP, et al. *Lancet*. 2020;395:1278-1291.

ELEVATE-TN Trial: PFS 5-Year Follow-Up



Overall

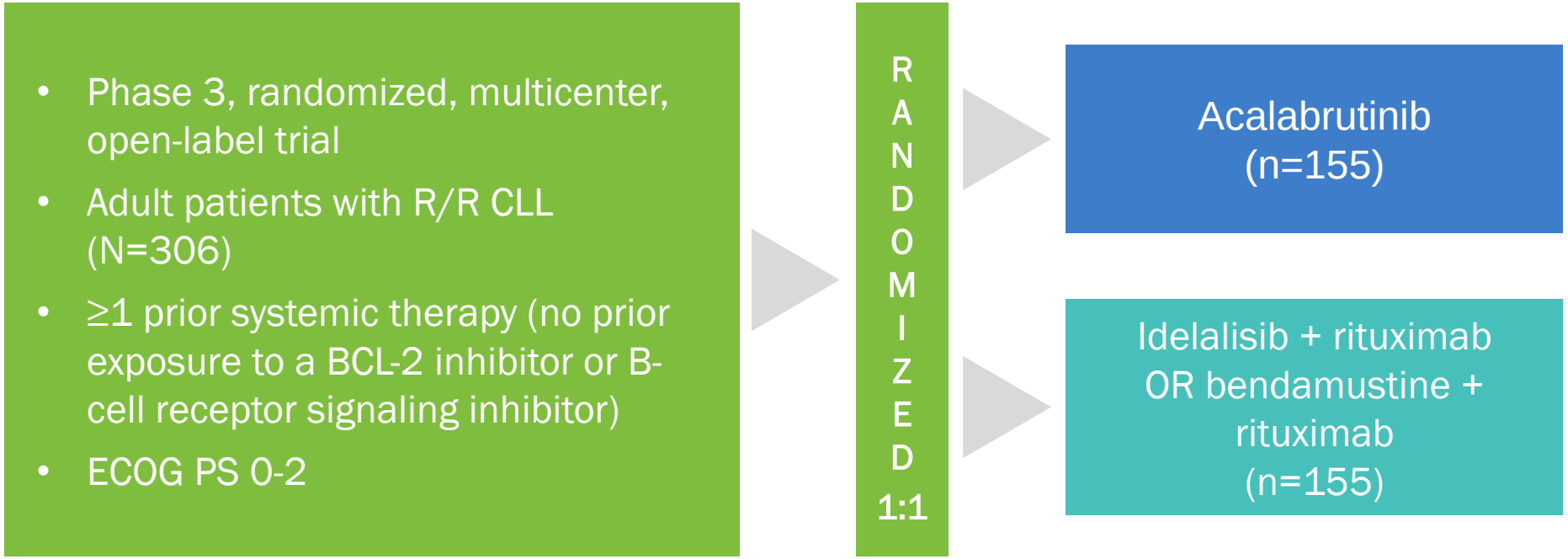


del(17p) and/or *TP53* mutations

A, acalabrutinib; Clb, chlorambucil; NR, not reached; O, obinutuzumab; PFS, progression-free survival.

Sharman J, et al. ASCO 2022. Abstr #7539.

ASCEND Trial: Acalabrutinib vs Rituximab + Idelalisib or Bendamustine in R/R CLL



Primary endpoint: PFS per IRC

Secondary endpoints: ORR, DoR, PFS per investigator, OS

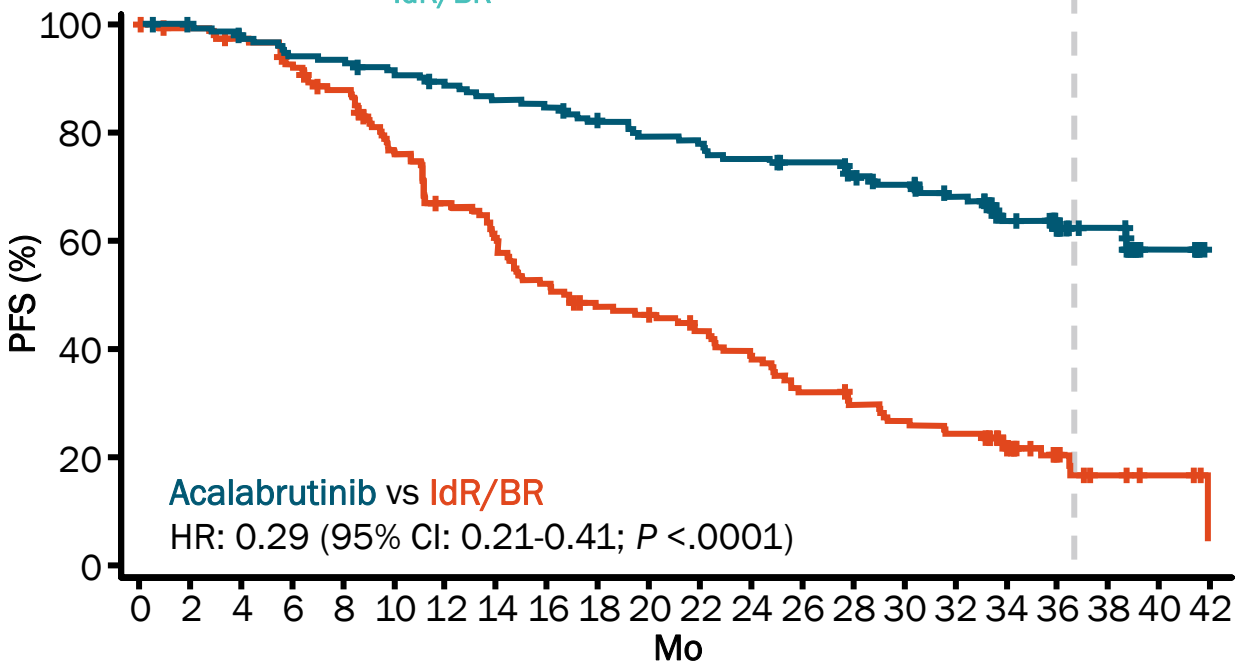
BCL-2, B-cell lymphoma-2; CLL, chronic lymphocytic leukemia; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent review committee; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory.

Ghia P, et al. *J Clin Oncol*. 2020;38:2849-2861

ASCEND: Final PFS by Investigator Assessment

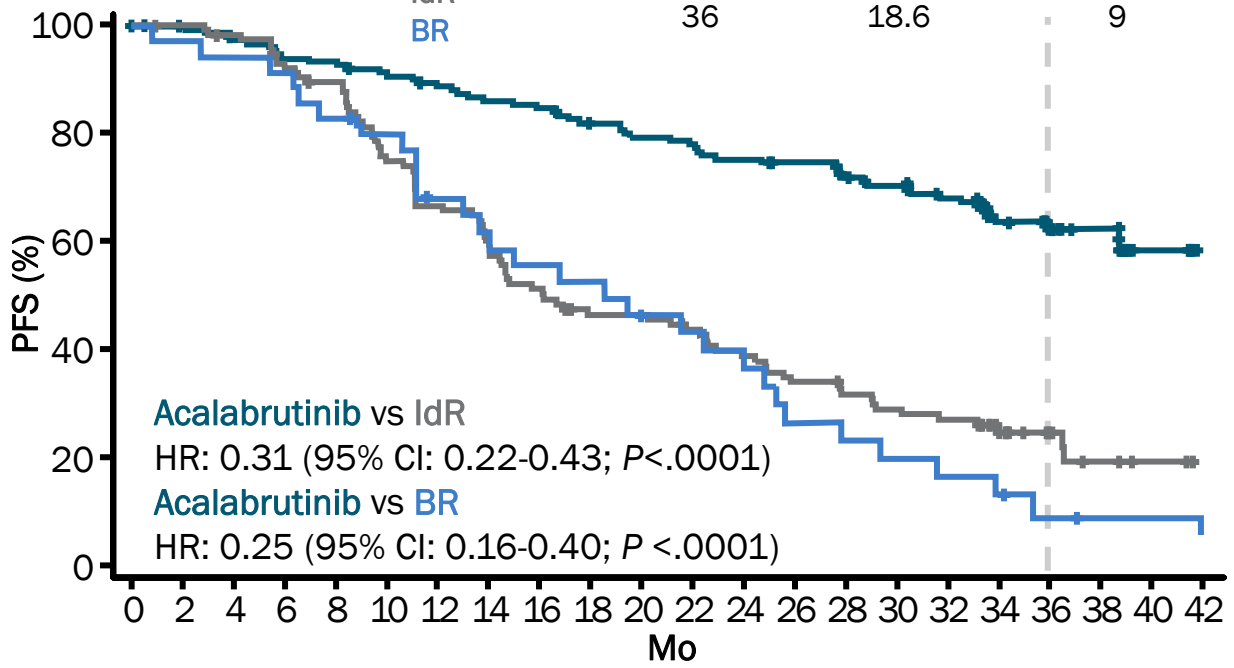
Acalabrutinib vs IdR/BR

	Patients, n	Median PFS, Mo	36-Mo PFS, %
Acalabrutinib	155	NR	63
IdR/BR	155	16.8	21



Acalabrutinib vs IdR vs BR

	Patients, n	Median PFS, Mo	36-Mo PFS, %
Acalabrutinib	155	NR	63
IdR	119	16.2	25
BR	36	18.6	9



Median time on study: acalabrutinib, 36.0 mo; IdR/BR, 35.2 mo

BR, bendamustine/rituximab; IdR, idelalisib/rituximab; PFS, progression-free survival.

Ghia P, et al. *Hemasphere*. 2022;6:e801.

ELEVATE-RR Trial: Ibrutinib vs Acalabrutinib in Patients With High-Risk R/R CLL

- Ongoing phase 3, randomized, multicenter, open-label, noninferiority trial
- Patients with del(17p) or del(11q) CLL with active disease (N=533)
- ≥1 previous line of treatment
- ECOG PS 0-2

Status: Active, not recruiting

RANDOMIZED

- Ibrutinib
- Acalabrutinib

Until PD or unacceptable AE

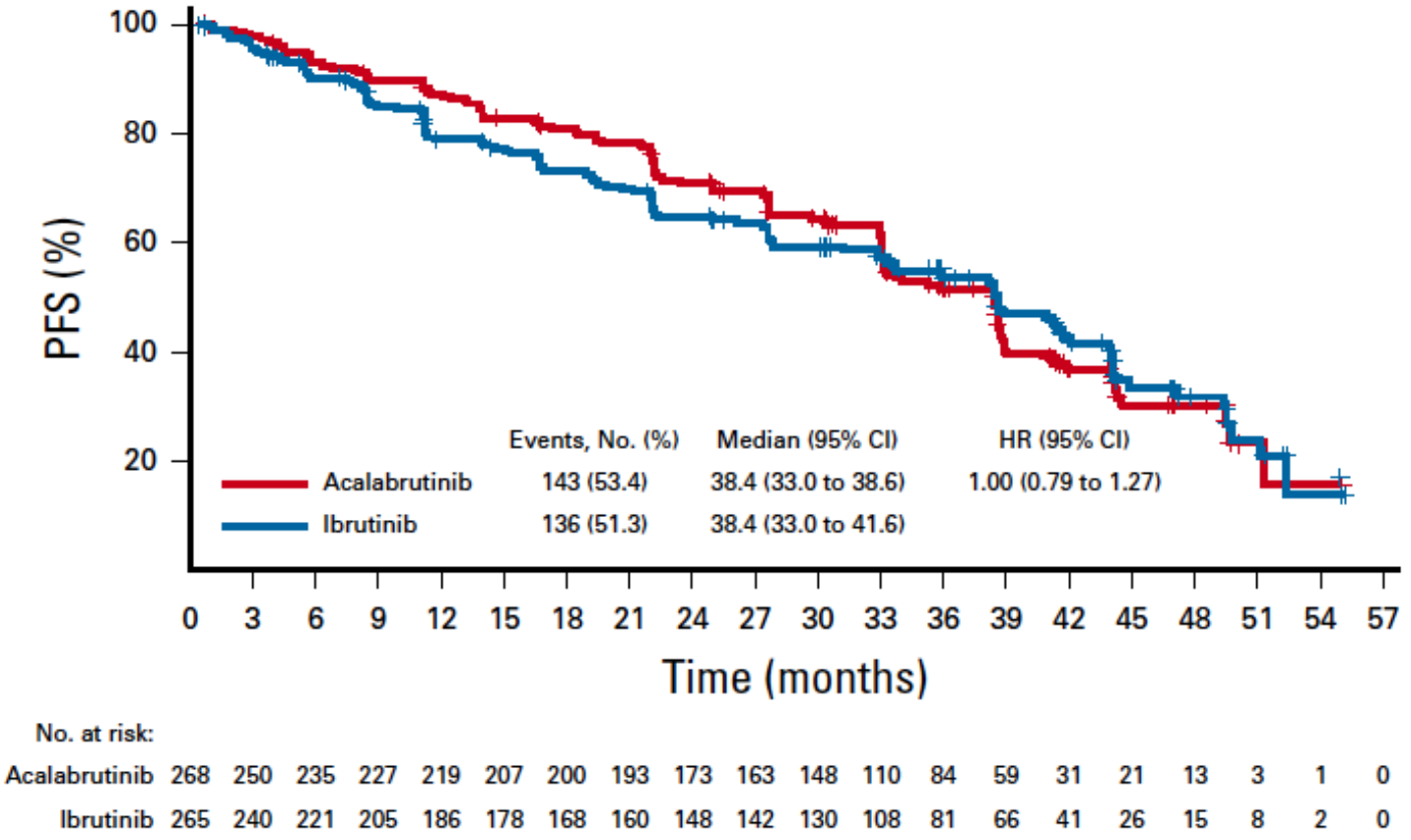
Primary endpoint: PFS

Secondary endpoints: OS, incidence of treatment-emergent AEs, atrial fibrillation, Richter transformation

AE, adverse event; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; OS, overall survival; PD, progressive disease; PFS, progression-free survival; R/R, relapsed/refractory.

Clinicaltrials.gov. NCT02477696.

ELEVATE-RR Trial: Ibrutinib vs Acalabrutinib in Patients With High-Risk R/R CLL



CLL, chronic lymphocytic leukemia; PFS, progression-free survival; R/R, relapsed/refractory.

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

ELEVATE-RR: AEs of Clinical Interest

Most common grade ≥3 infections: pneumonia (acalabrutinib vs ibrutinib, 10.5% vs 8.7%), sepsis (1.5% vs 2.7%), and urinary tract infections (1.1% vs 2.3%)

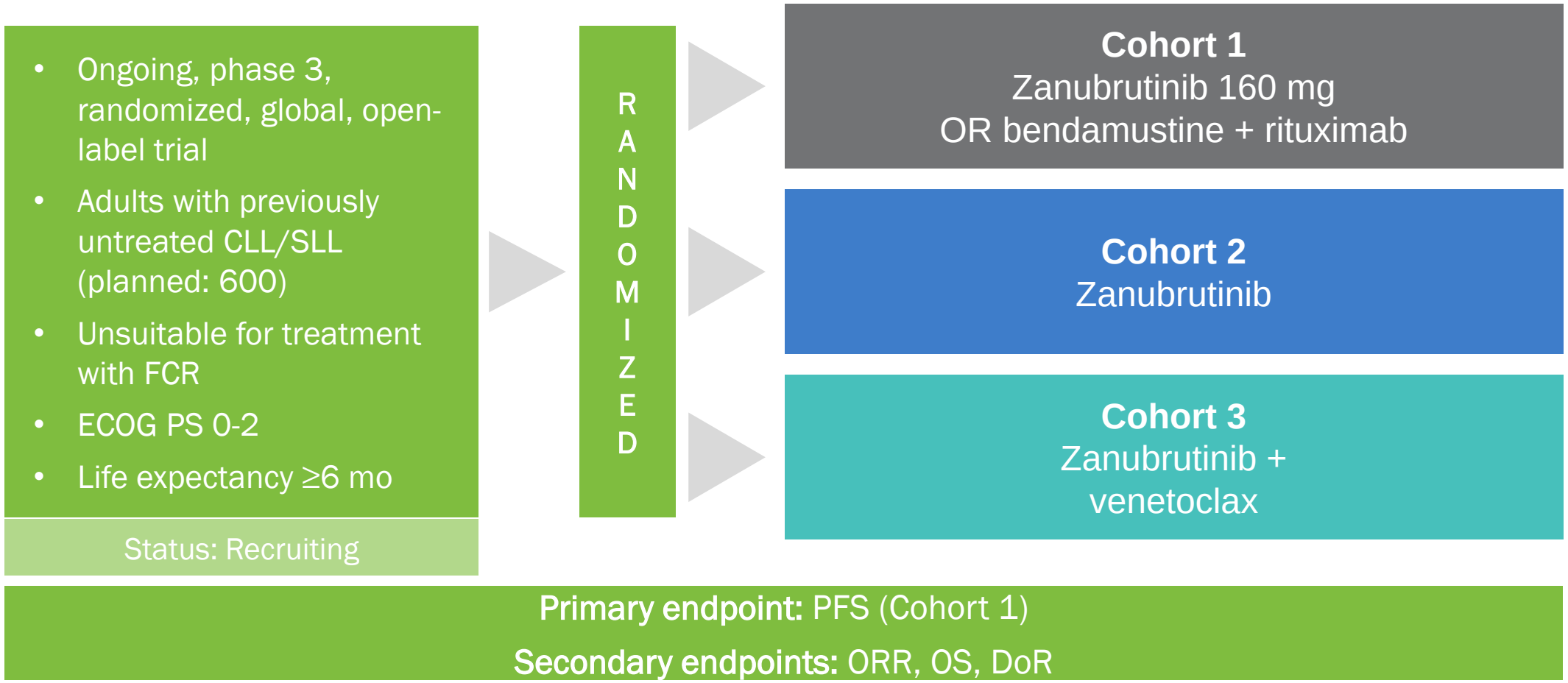
AE, n (%)	Acalabrutinib (n=266)		Ibrutinib (n=263)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Cardiac events	64 (24.1)	23 (8.6)	79 (30.0)	25 (9.5)
• Atrial fibrillation/flutter	25 (9.4)	13 (4.9)	**42 (16.0)[a]**	10 (3.8)
• Ventricular arrhythmias	0	0	3 (1.1)	1 (0.4)
Bleeding events	101 (38.0)	10 (3.8)	**135 (51.3)**	12 (4.6)
• Major bleeding events	12 (4.5)	10 (3.8)	14 (5.3)	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)

AE, adverse event; ILD, interstitial lung disease; NMSC, nonmelanoma skin cancer; SPMs, second primary malignancies.

[a] Bolded numbers statistically significantly higher vs the comparator ($P<0.05$).

Byrd J, et al. ASCO 2021. Abstr #7500.

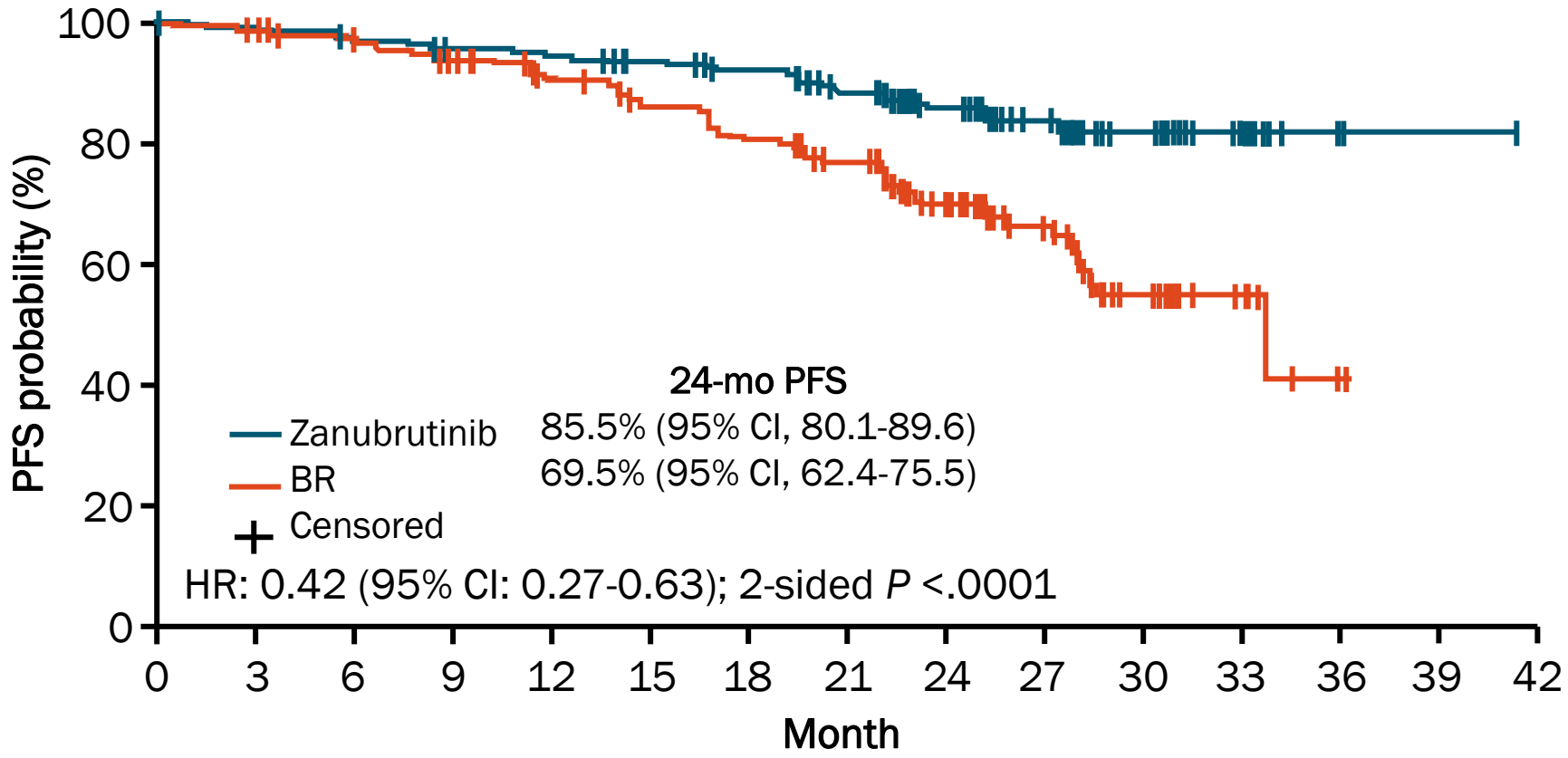
SEQUOIA Trial: Zanubrutinib vs Bendamustine + Rituximab in Treatment-Naive CLL/SLL



CLL, chronic lymphocytic leukemia; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group performance status; FCR, fludarabine, cyclophosphamide, and rituximab; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SLL, small lymphocytic lymphoma.

Clinicaltrials.gov. NCT03336333.

SEQUOIA Trial: Cohort 1 Without del(17p) – IRC-Assessed PFS

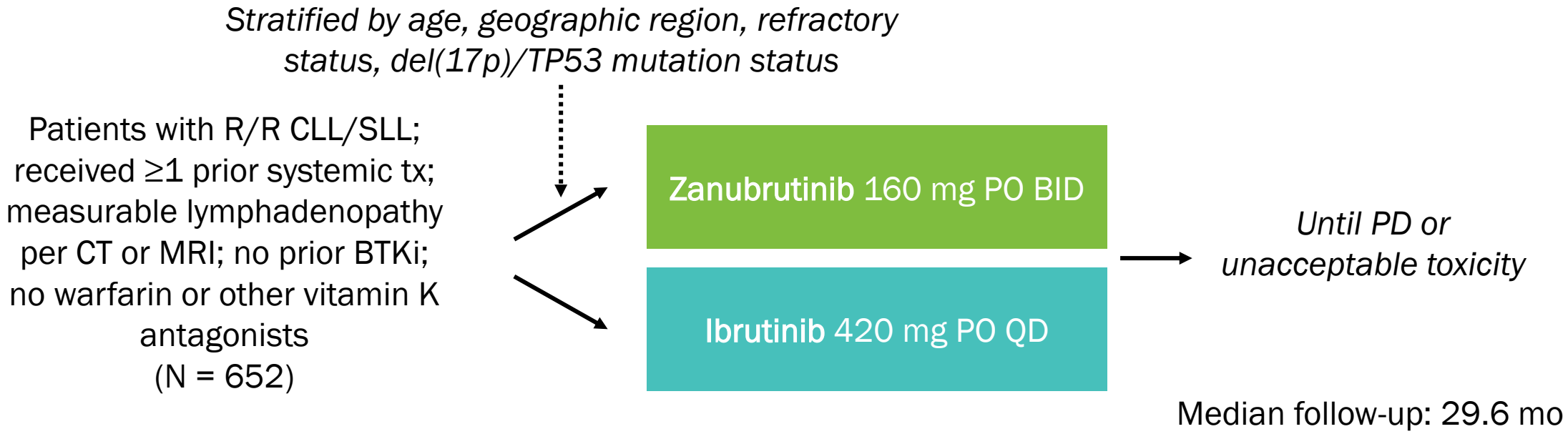


BR, bendamustine/rituximab; IRC, independent review committee; PFS, progression-free survival.

Tam CS, et al. ASH 2021. Abstr #396.

ALPINE: Study Design

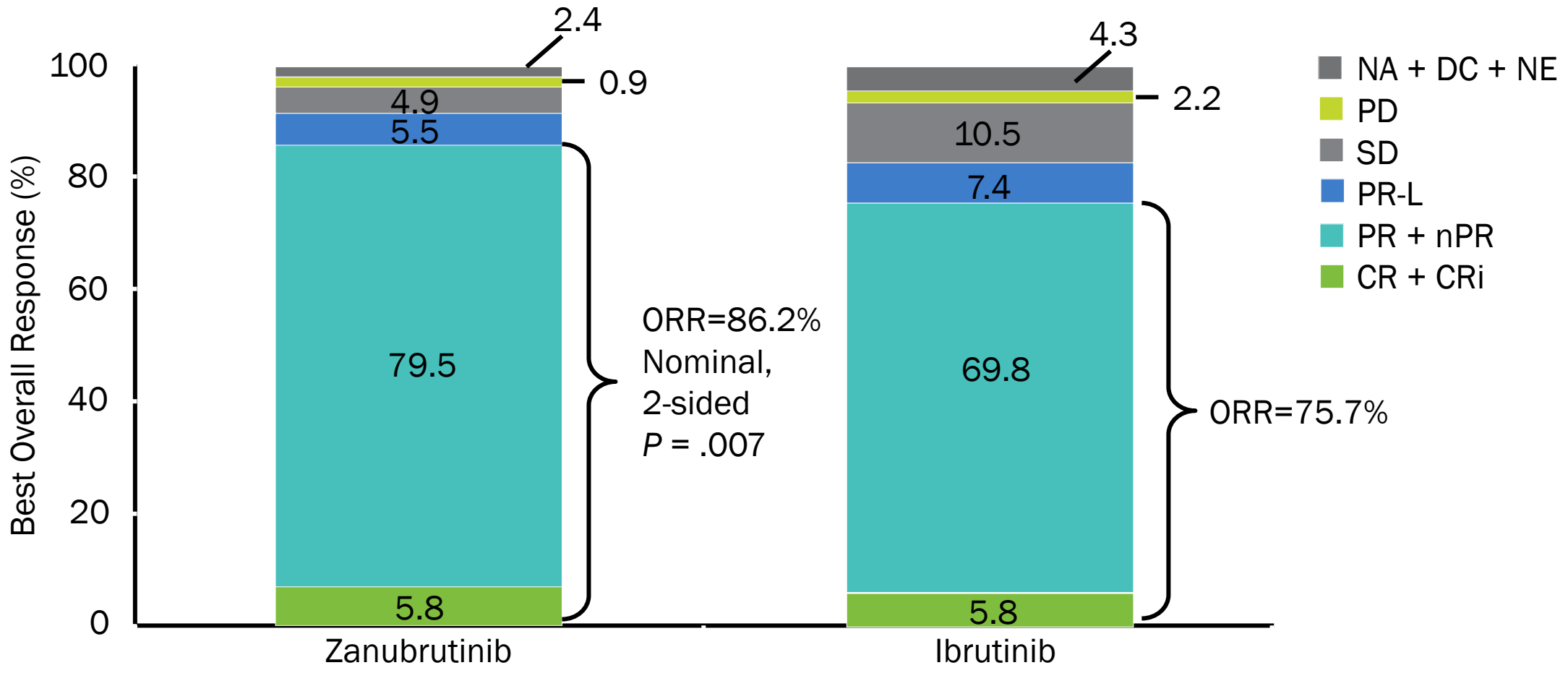
- Randomized, open-label phase III trial (median f/u: 29.6 mo)



- Primary endpoint: noninferiority and superiority of investigator-assessed ORR
- Secondary endpoints: incidence of atrial fibrillation or flutter, PFS, DoR, OS, TTF, ≥ PR-L rate, PROs, safety

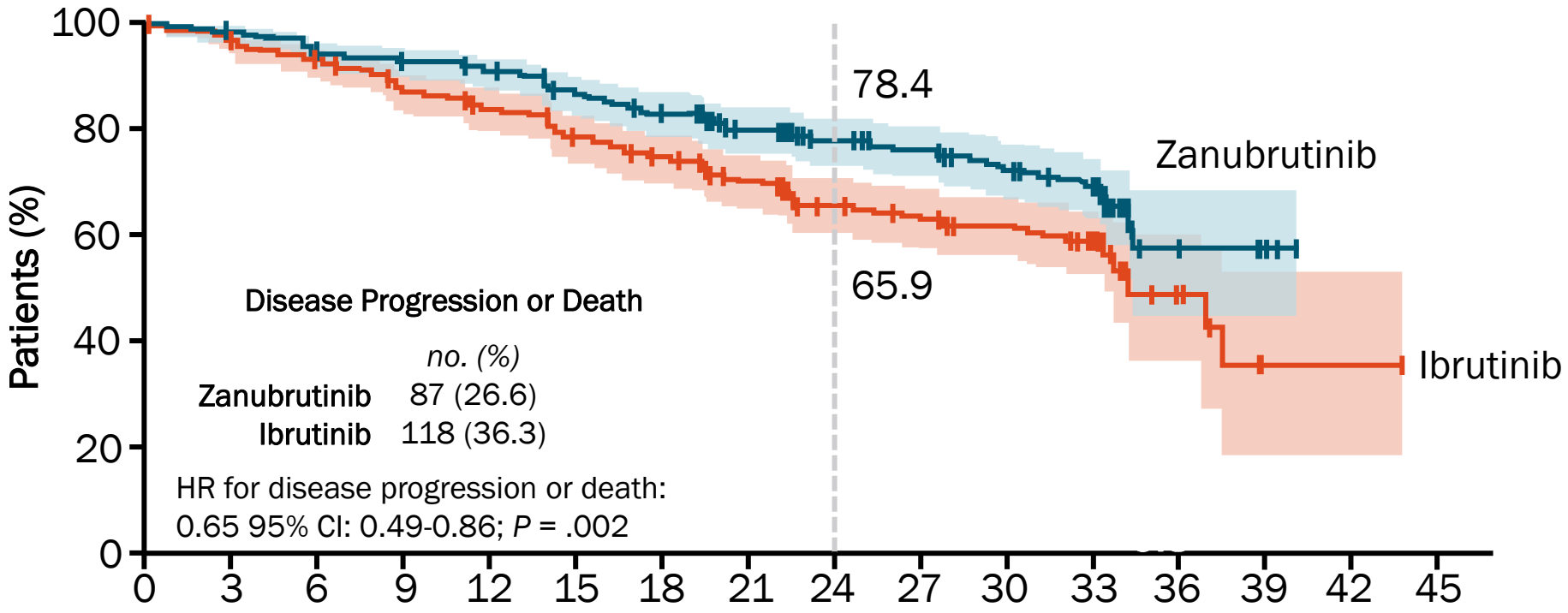
Brown JR, et al. ASH 2022. Abstr LBA-6. Brown JR, et al. *N Engl J Med*. 2022;[Epub].

ALPINE: ORR



Brown JR, et al. ASH 2022. Abstr LBA-6.

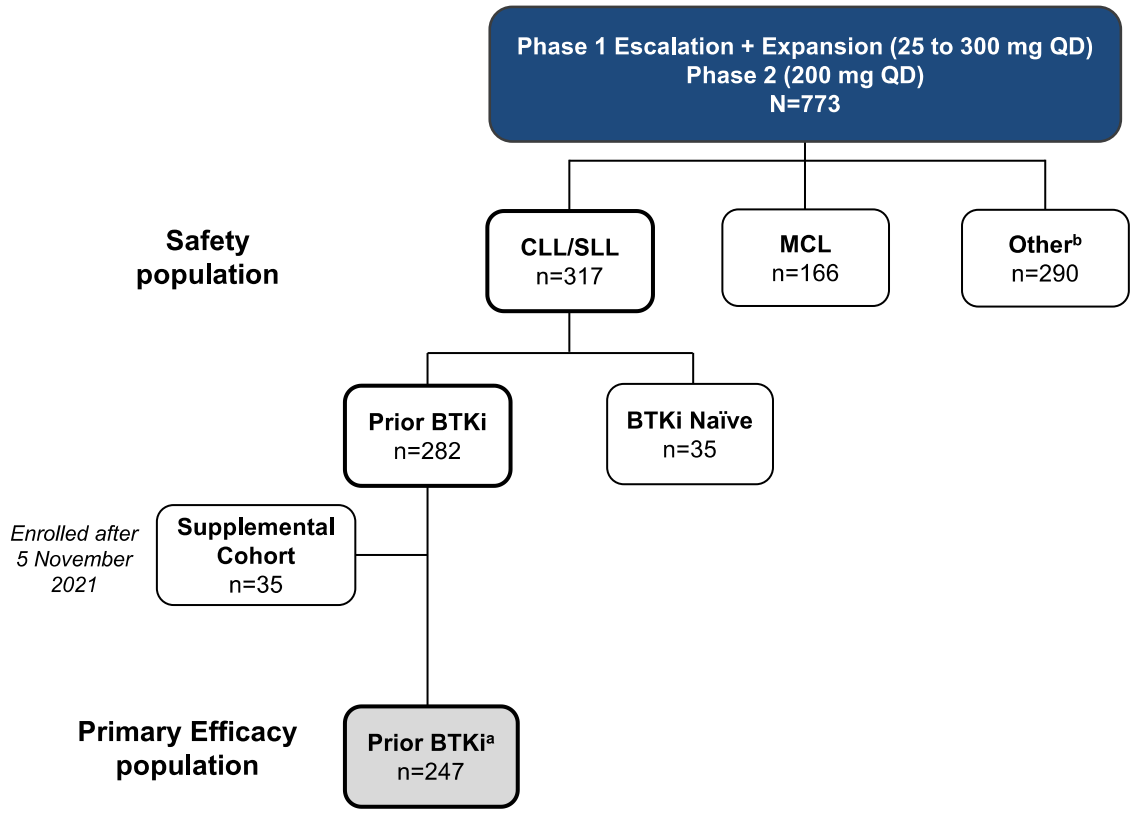
ALPINE: Investigator-Assessed PFS in ITT Population



No. at risk																
Zanubrutinib	327	316	303	297	290	274	260	221	165	158	122	111	12	2	0	
Ibrutinib	325	306	293	273	259	241	227	186	128	121	97	87	9	1	1	0

Brown JR, et al. ASH 2022. Abstr LBA-6. Brown JR, et al. *N Engl J Med*. 2022;[Epub].

Phase I/II BRUIN Study: Design, Eligibility, and Enrollment



Phase 1 3+3 design

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

Eligibility

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

Key endpoints

- Safety/tolerability
- Determine MTD and recommended phase 2 dose
- Pharmacokinetics
- Efficacy according to ORR and DOR (iwCLL) as assessed by IRC

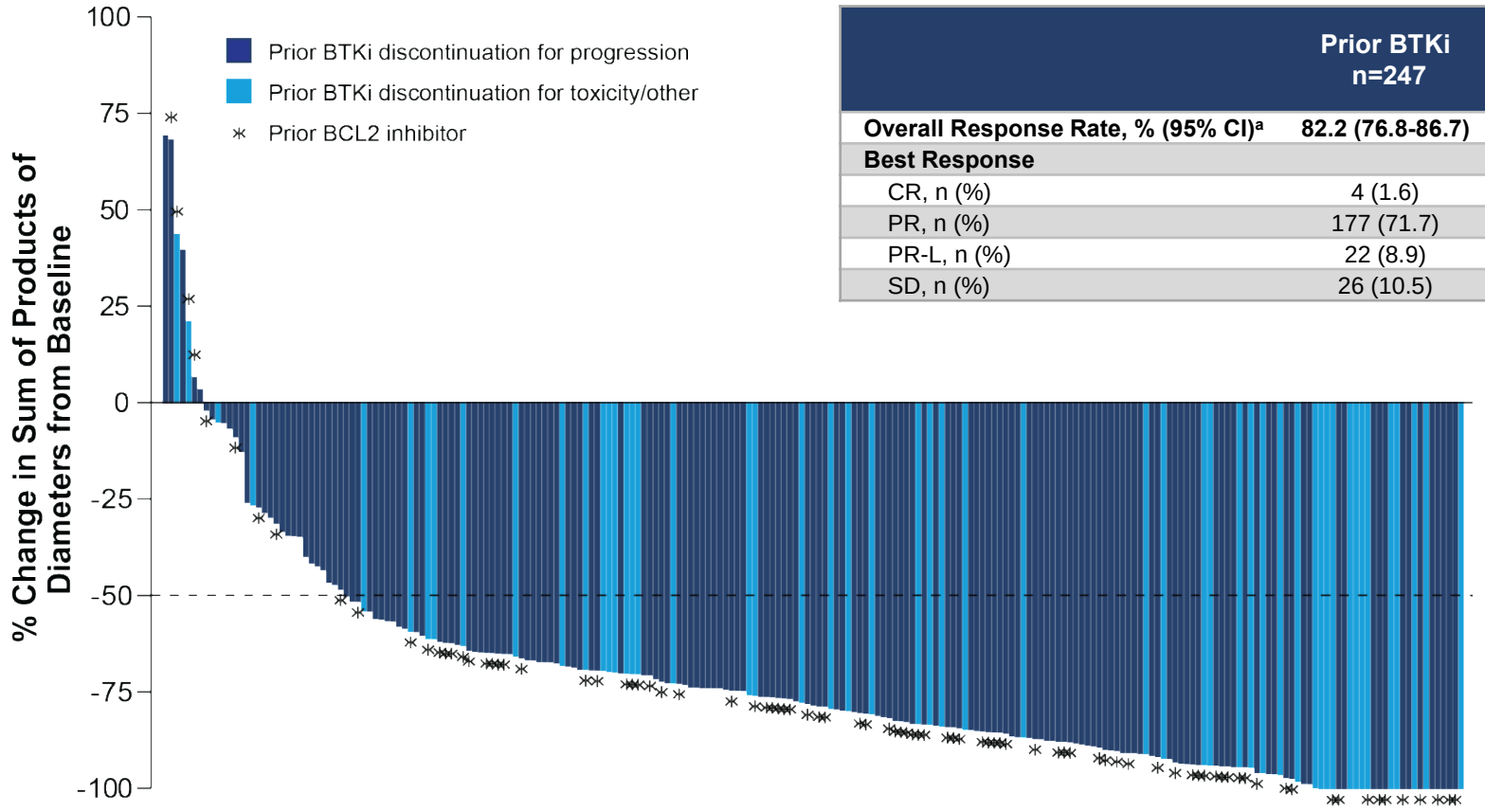
Primary efficacy population[a]

- Enrolled in phase 1 or 2
- Treated with prior BTK inhibitor containing regimen
- Received one or more doses of pirtobrutinib monotherapy

DOR, duration of response: ORR, overall response rate; ECOG PS, Eastern Cooperative Oncology Group Performance Score; MTD, maximum tolerated dose; IRC, independent review committee; QD, daily;
Data cutoff date of 29 July 2022. [a]To ensure adequate follow-up, the primary efficacy population included all CLL/SLL patients who enrolled prior to 5 November 2021. [b]Other includes DLBCL, WM, FL, MZL, Richter transformation, B-PLL, Hairy Cell Leukemia, PCNSL, and other transformation.

Mato AR, et al. ASH 2022. Abstr 961.

BRUIN: Pirtobrutinib Efficacy in CLL/SLL Patients Who Received Prior BTKi Treatment



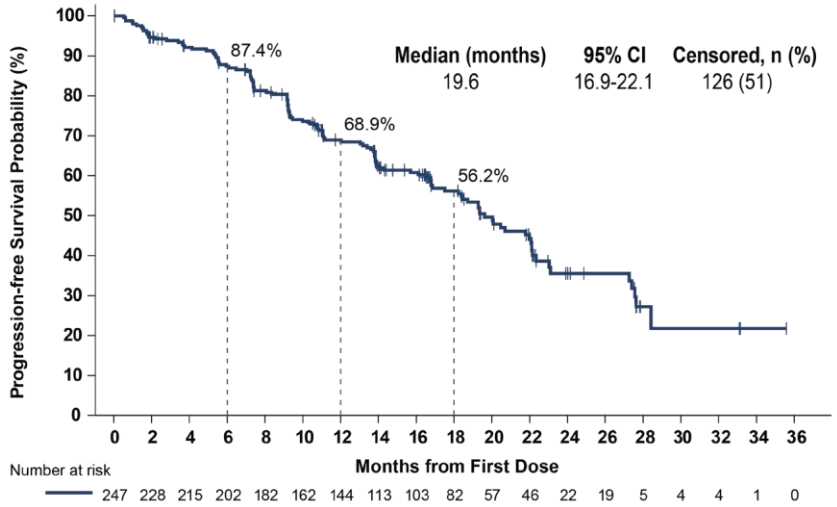
	Prior BTKi n=247	Prior BTKi+BCL2i n=100
Overall Response Rate, % (95% CI)[a]	**82.2 (76.8-86.7)**	**79.0 (69.7-86.5)**
Best Response		
CR, n (%)	4 (1.6)	0 (0.0)
PR, n (%)	177 (71.7)	70 (70.0)
PR-L, n (%)	22 (8.9)	9 (9.0)
SD, n (%)	26 (10.5)	11 (11.0)

Data cutoff date of 29 July 2022. Data for 24 patients are not shown in the waterfall plot due to no measurable target lesions identified by CT at baseline, discontinuation prior to first response assessment, or lack of adequate imaging in follow-up. [a]ORR includes patients with a best response of CR, PR, and PR-L. Response status per iwCLL 2018 according to independent review committee assessment.

Mato AR, et al. ASH 2022. Abstr 961.

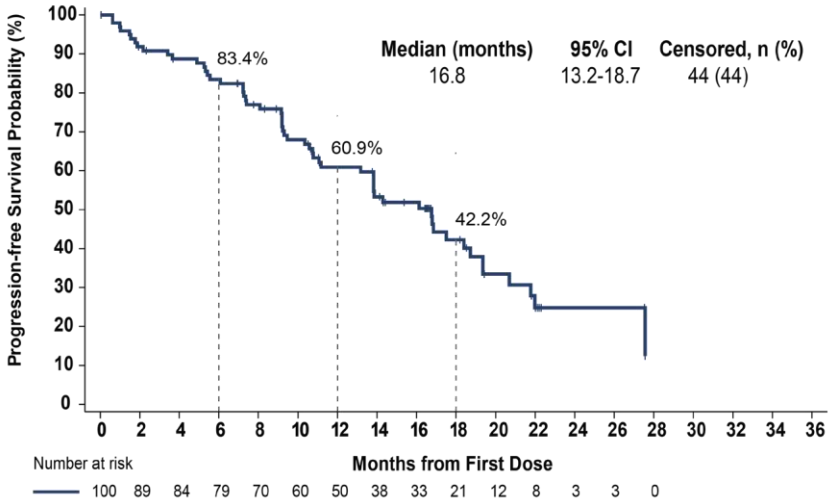
BRUIN: PFS in CLL/SLL Patients Who Received Prior BTKi Treatment

All prior BTKi patients
Median prior lines = 3



- Median follow-up of 19.4 months for patients who received prior BTKi

Prior BTKi and BCL2i patients
Median prior lines = 5

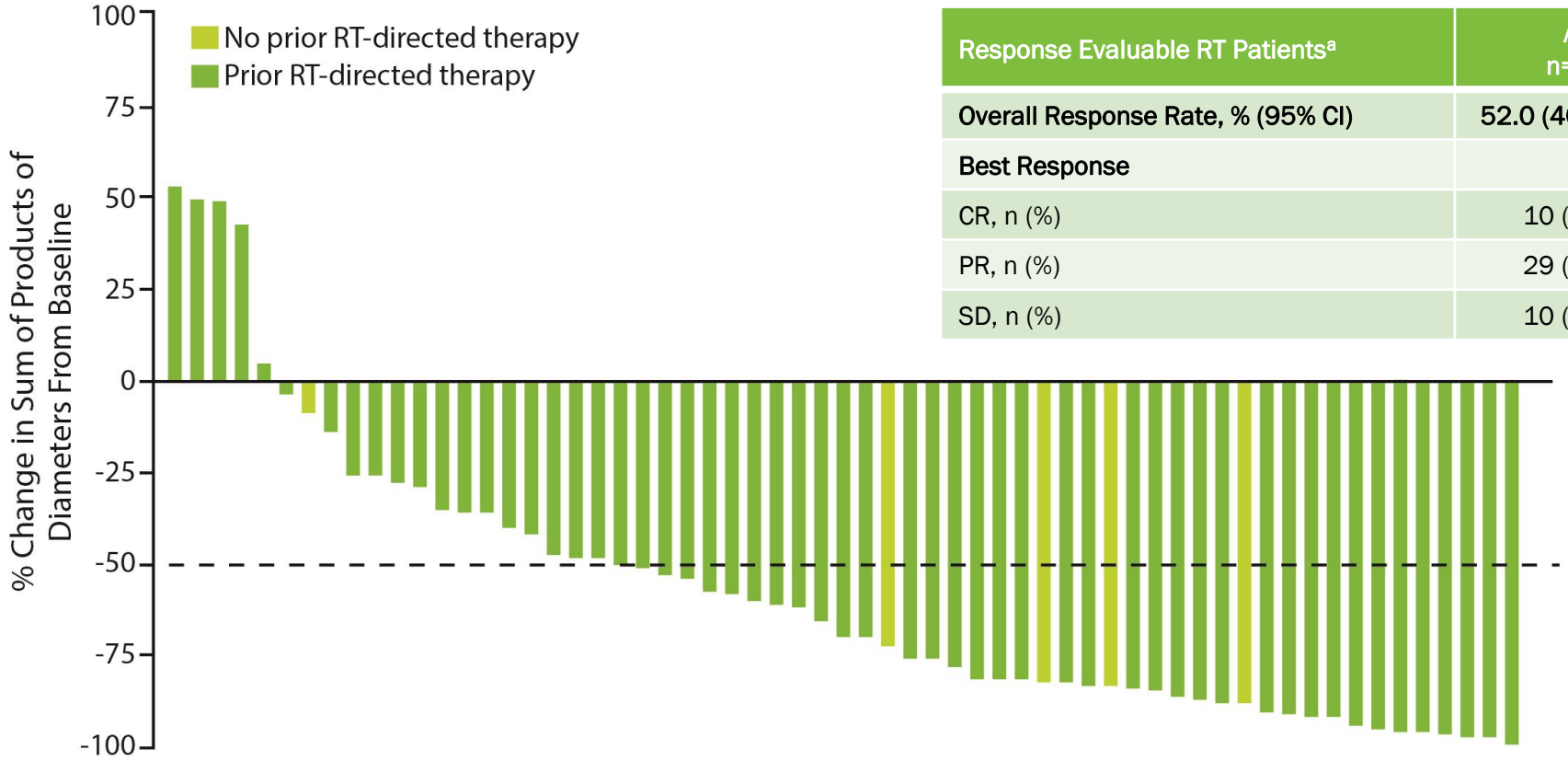


- Median follow-up of 18.2 months for patients who received prior BTKi and BCL2i

Data cutoff date of 29 July 2022. Response status per iwCLL 2018 according to independent review committee assessment.

Mato AR, et al. ASH 2022. Abstr 961.

BRUIN: Pirtobrutinib Efficacy in Richter Transformation Patients



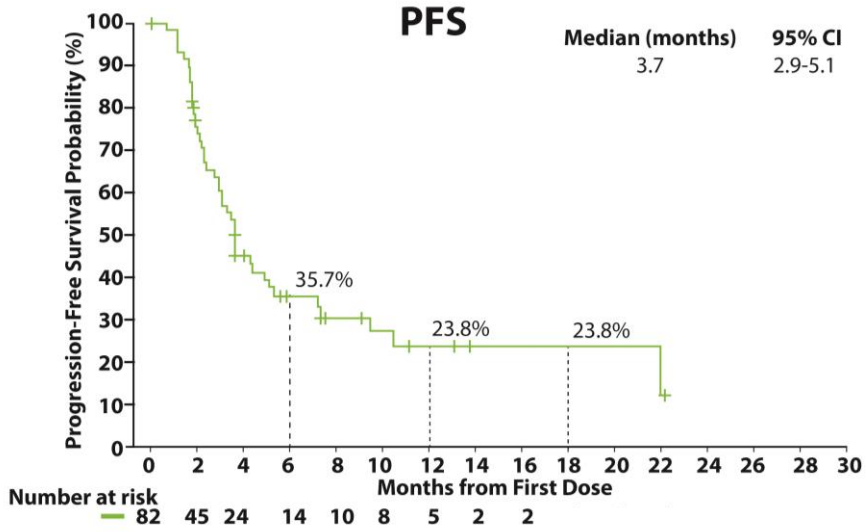
Response Evaluable RT Patients[a]	All n=75	Prior RT Therapy n=68
Overall Response Rate, % (95% CI)	**52.0 (40.2-63.7)**	**50.0 (37.6-62.4)**
Best Response		
CR, n (%)	10 (13.3)	9 (13.2)
PR, n (%)	29 (38.7)	25 (36.8)
SD, n (%)	10 (13.3)	10 (14.7)

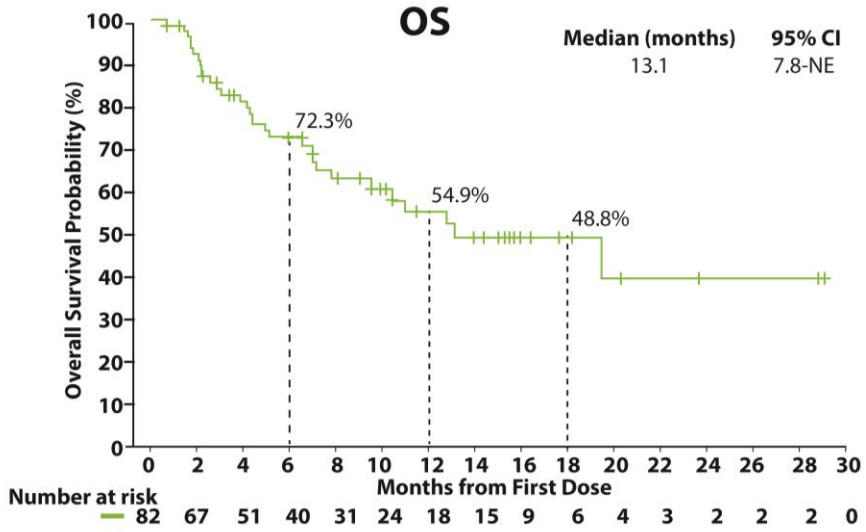
- Among 75 response-evaluable patents, the median time to response was 1.8 months (range, 0.9-9.2), median time on study was 6.7 months (range, 0.7-29.1), and median time on treatment was 3.4 months (range, 0.2-26.7)

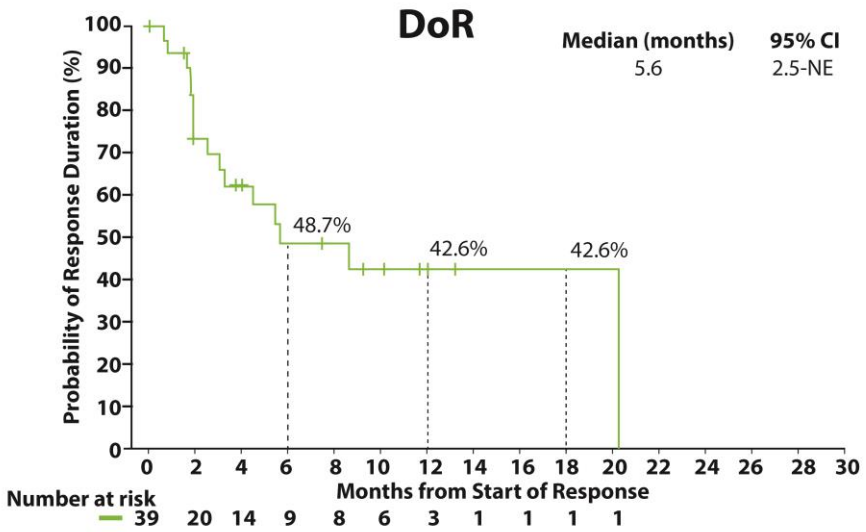
Data cutoff date of 29 July 2022. Data for 14 patients are not shown in the waterfall plot due to no baseline or post-baseline assessment. [a]Response evaluable patients are those who had at least 1 post-baseline response assessment or had discontinued treatment prior to first post-baseline response assessment. Response as assessed by investigator based on Lugano criteria.

Wierda WG, et al. ASH 2022. Abstr 347.

BRUIN: PFS, OS, and DoR in All Richter Transformation Patients







- 6 responding patients were censored for curative intent transplant therapy

Data cutoff date of 29 July 2022. Response as assessed by investigator based on Lugano criteria.

Wierda WG, et al. ASH 2022. Abstr 347.

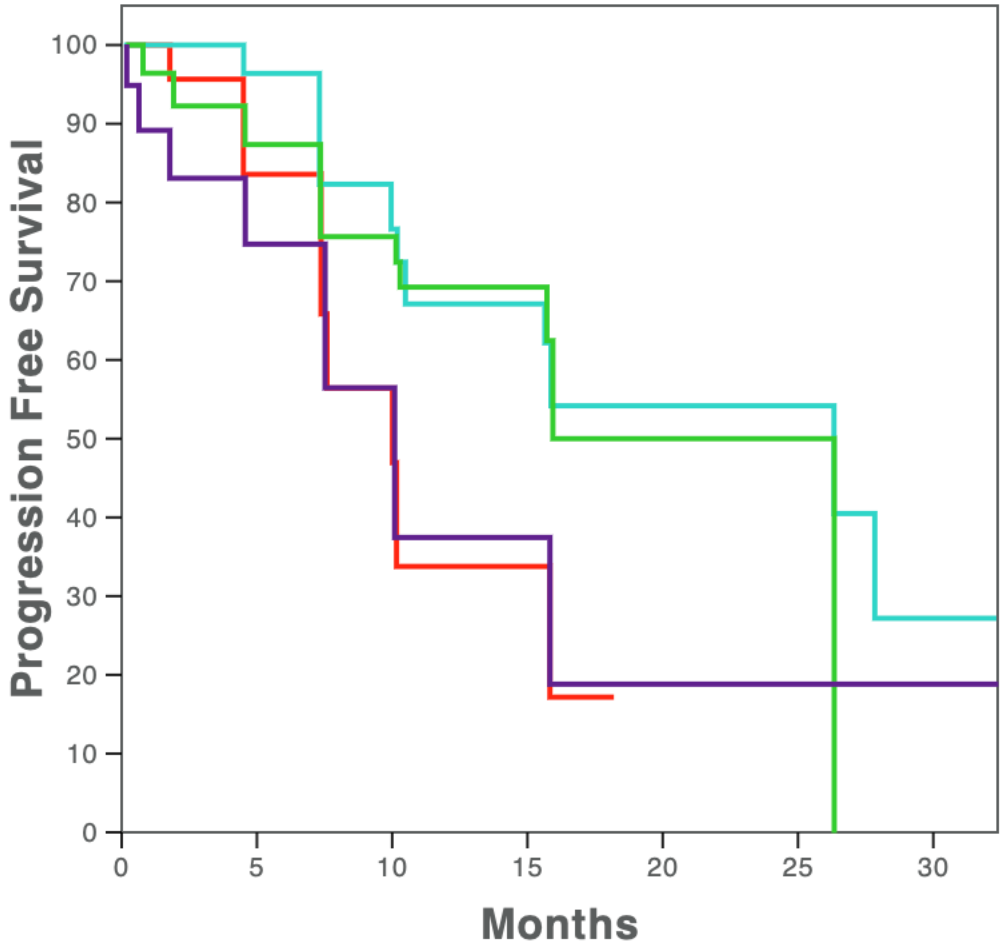
Bellwave-001: ORR and BOR to Nemtabrutinib in Patients With CLL/SLL

	CLL/SLL N = 57	Cohort A n = 25	Cohort B N = 10	Prior BTK and BCL2 inhibitors n = 24	BTK Mutation n = 36	No IGHV Mutation n = 30	Del [17p] n = 19
ORR, n (% [95% CI])[a]	32(56[42-69])	15 (60 [39-79])	4 (40[12-74])	14 (58 [37-78])	21 (58[41-75])	15 (50 [31-69])	10 (53 [29-76])
BOR n (%)							
CR	2 (4)	0 (0)	1 (10)	0 (0)	1 (3)	0 (0)	1 (5)
PR	15 (26)	5 (20)	2 (20)	6 (25)	11 (31)	8 (27)	2 (11)
PR-L	15 (26)	10 (40)	1 (10)	8 (33)	9 (25)	7 (23)	7 (37)
SD	16 (28)	8 (32)	4 (40)	7 (29)	10 (28)	9 (30)	4 (21)
PD	1 (2)	0 (0)	1 (10)	1 (4)	0 (0)	1 (3)	1 (5)
NA	8 (14)	2 (8)	1 (10)	2 (8)	5 (14)	5 (17)	4 (21)

BOR, best overall response; CR, complete response; NA, no assessment; PR, partial response; PR-L, partial response with residual lymphocytosis; SD, stable disease.
[a]Including patients with CR, PR, and PR-L.

Woyach JA, et al. ASH 2022. Abstr 3114.

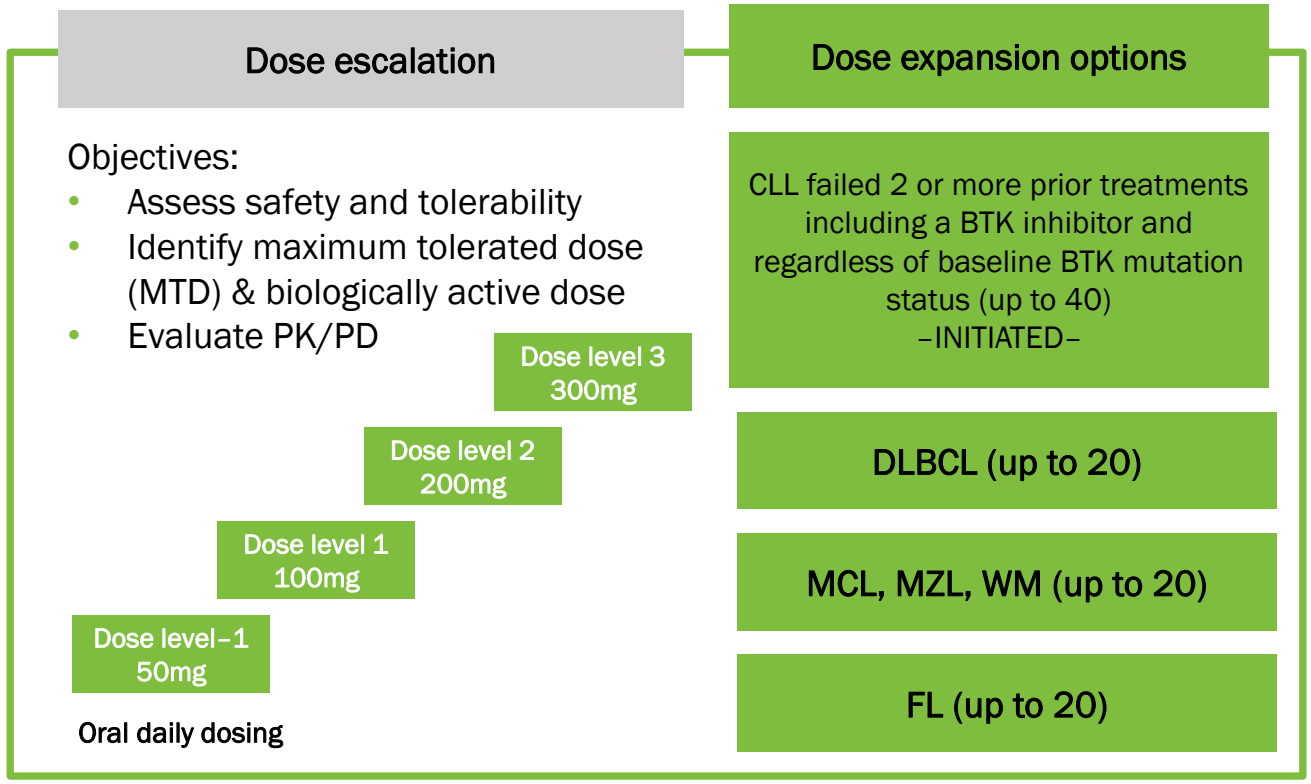
Bellwave-001: Progression-Free Survival



Curves	N	Median (95% CI)
Prior BTK and BCL2 inhibitors	24	10.1 (7.4-15.9)
BTK^C481S mutatION	36	26.3 (10.1-0)
No IGHV mutation	30	15.9 (7.4-0)
Del(17p)	19	10.1 (4.6-0)

Woyach JA, et al. ASH 2022. Abstr 3114.

NX-2127-001: Trial Design



- CLL Phase 1b expansion cohort at 100 mg dose
  - MTD not established
  - 100 mg dose chosen as expansion dose based on PD, clinical activity and safety profile
- Phase 1a dose escalation is ongoing at 200 mg and 300 mg doses for patients with NHL (e.g. DLBCL, MCL, MZL, WM, FL)

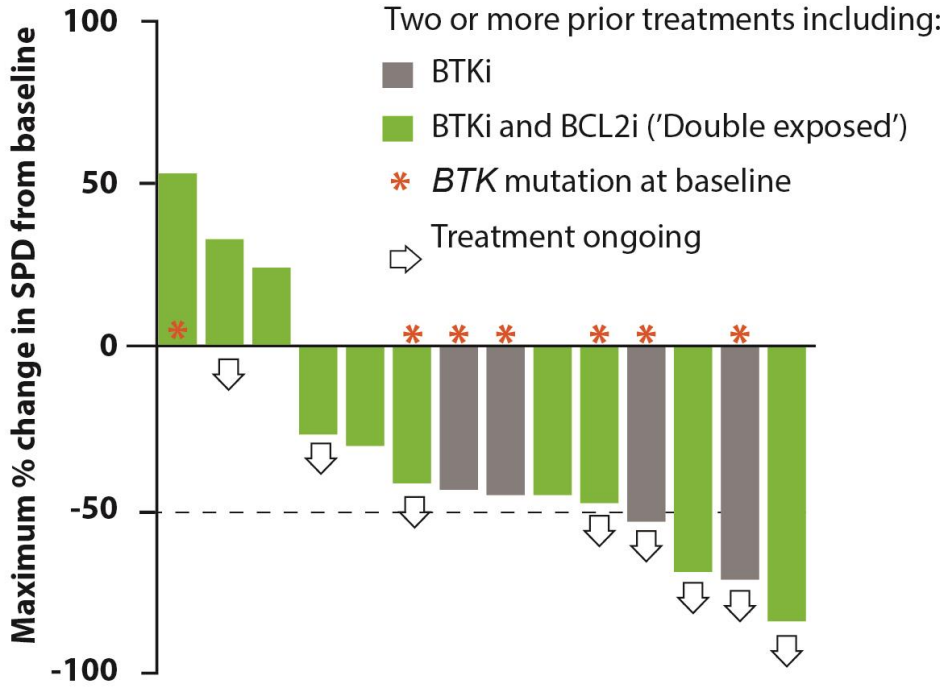
BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PD, pharmacodynamics; PK, pharmacokinetics; WM, Waldenstrom's macroglobulinemia.

Mato AR, et al. ASH 2022. Abstr 965.

NX-2127-001: Preliminary Efficacy (Patients With CLL)

Disease-evaluable patients	n = 15
Objective response rate, [a] % (95% CI)	**33 (12–62)**
Best response, n (%)	
CR	0 (0)
PR	5 (33.3)
SD	5 (33.3)
PD	2 (13.3)
NE[b]	3 (20)

[a]Objective response rate includes CR +Cri + nPR + PR-L + PR.
[b]Patients who discontinued after a single assessment of SD are considered as NE.



*One patient, not shown above, with prior BTKi and BCL2i treatment and with a *BTK* mutation detected at baseline, had no nodal disease at baseline. Their treatment is ongoing with a PR

BCL2i, B-cell lymphoma-2 inhibitor; BTK, Brunton's tyrosine kinase; BTKi, BTK inhibitor; CR, complete response; CRi, complete response with incomplete count recovery; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

Mato AR, et al. ASH 2022. Abstr 965.

NX-2127-001: Safety Summary (TEAEs >15% in All Patients)

Treatment-emergent AEs occurring in >15% of total population, n (%)	Any grade (N=36)	Grade 3+ (N=36)	SAE (N=36)
Fatigue	19 (52.8)	–	–
Neutropenia[a]	14 (38.9)	13 (36.1)	–
Contusion[b]	10 (27.8)	–	1 (2.8)
Thrombocytopenia[c]	9 (25)	3 (8.3)	–
Anemia	8 (22.2)	4 (11.1)	1 (2.8)
Hypertension	9 (25.0)	1 (2.8)	–
Constipation	7 (19.4)	–	–
Dyspnea	7 (19.4)	1 (2.8)	–
Pruritis	7 (19.4)	–	–
Atrial fibrillation/Atrial flutter[d]	6 (16.7)	3 (8.3)	2 (5.6)
Diarrhea	6 (16.7)	–	–
Petechiae	6 (16.7)	–	–
Rash	6 (16.7)	–	–

[a]Aggregate of "neutropenia" and "neutrophil count decreased." [b]Contusion includes episodes of bruising and other similar terms. [c]Aggregate of "thrombocytopenia" and "platelet count decreased." [d]Cases were confounded by risk factors such as: age >80 years (4 cases), history of hypertension (4 cases), male sex (3 cases), and history of prior AF on ibrutinib (2 cases).

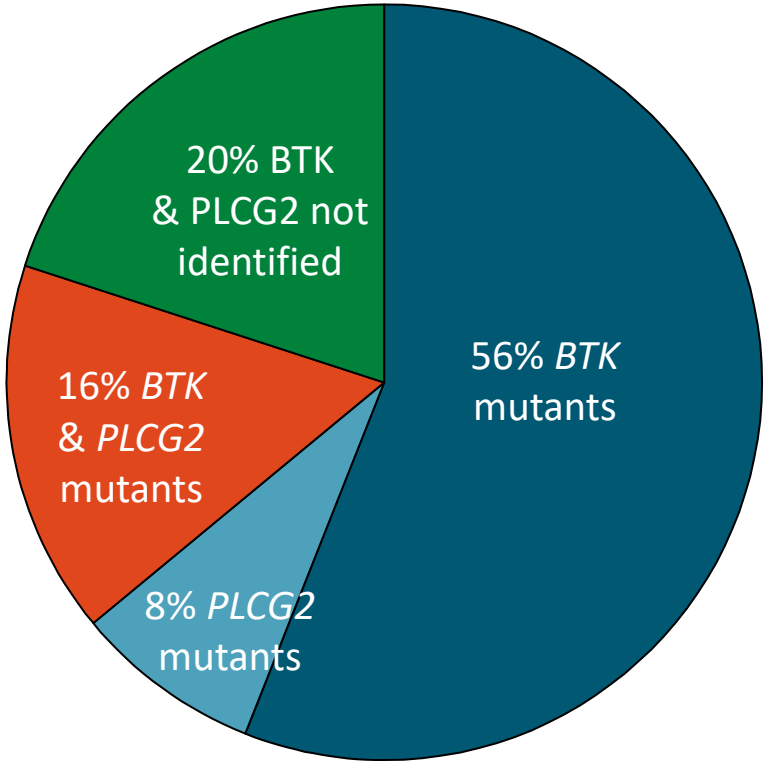
1 DLT of cognitive was observed at 300 mg (CLL); MTD not reached

AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Mato AR, et al. ASH 2022. Abstr 965.

Resistance and Intolerance Limit Covalent BTK Inhibitor Outcomes

Ibrutinib Acquired Resistance in Patients With Progressive CLL[1]

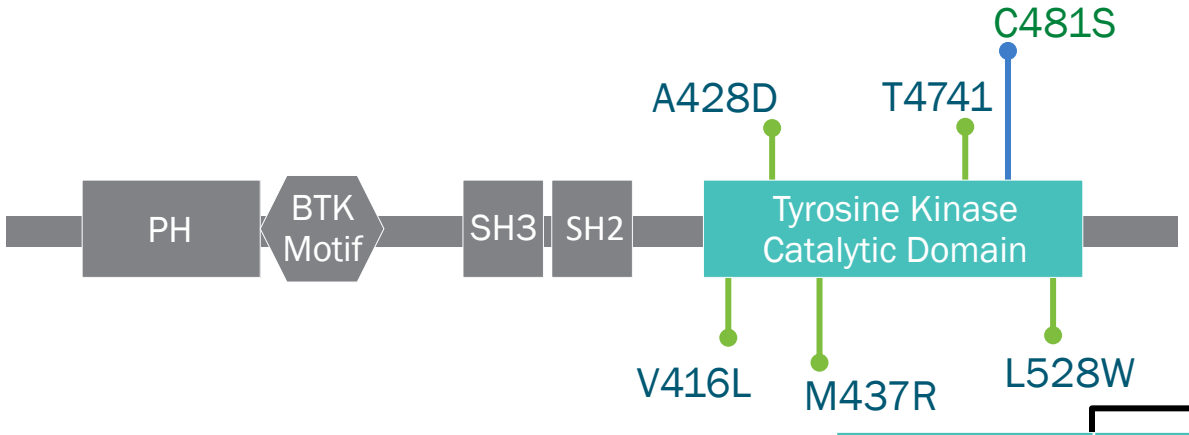


- Ibrutinib discontinuation rate at 5 yr
  - Frontline: 41%[2]
  - R/R: 53.7%[6]
- Appearance of *BTK* C481 mutations dominant reason for progressive CLL after covalent BTKi[1-7]
- *BTK* C481 mutations prevent covalent BTKi from effective target inhibition[1-6]

1. Lampson. *Expert Rev Hematol*. 2018;11:185. 2. Woyach. *J Clin Oncol*. 2017;35:1437. 3. Byrd. *N Engl J Med*. 2016;374:323. 4. Xu. *Blood*. 2017;129:2519.
5. Hershkovitz-Rokah. *Br J Haematol*. 2018;181;306. 6. Burger. *Leukemia*. 2020;34:787. 7. Woyach. ASH 2019. Abstr 642.

Noncovalent BTK Inhibitors

Mutations Conferring Resistance to BTK Inhibitors



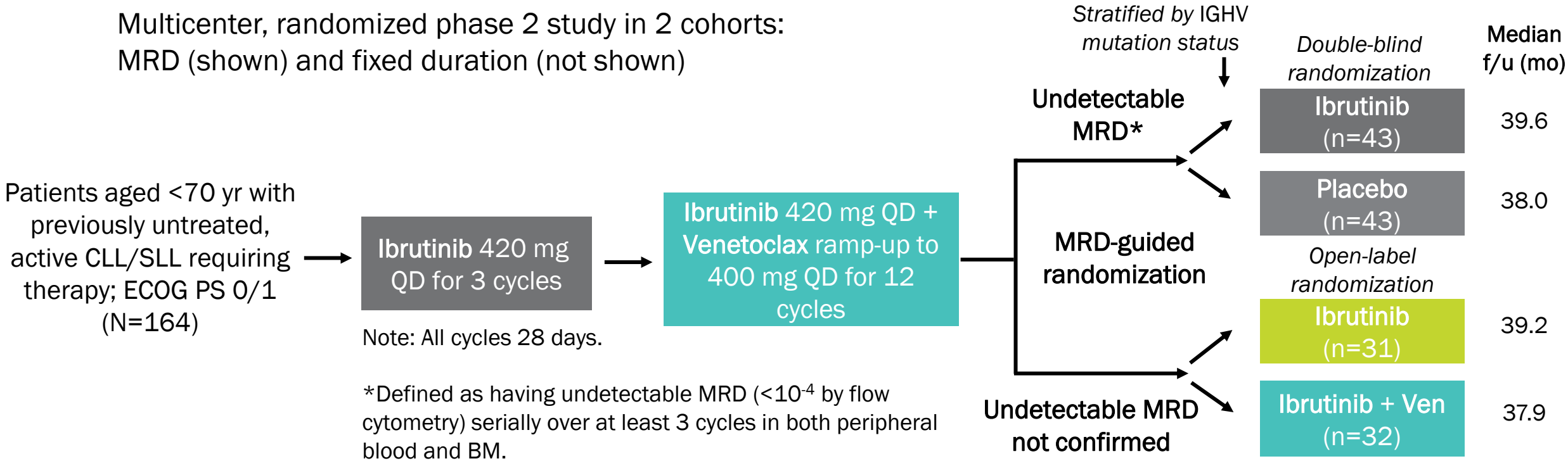
Binding Affinities of BTK Inhibitors

	Noncovalent				Covalent
	Pirtobrutinib	Nemtabrutinib	Vecabrutinib	Fenebrutinib	Ibrutinib
Wild-type	Normal	Normal	Normal	Normal	Normal
A428D	None	Decreased	None	None	None
M437R	Decreased	Normal	Decreased	Decreased	Normal
T4741	Decreased	Decreased	Decreased	Normal	Normal
L528W	None	None	Decreased	Normal	None
C481S	Normal	Normal	Normal	Normal	Decreased

Wang. *N Engl J Med*. 2022;386:735.

CAPTIVATE MRD Cohort: Ibrutinib + Venetoclax in Previously Untreated CLL

Multicenter, randomized phase 2 study in 2 cohorts: MRD (shown) and fixed duration (not shown)



Note: All cycles 28 days.

*Defined as having undetectable MRD ($<10^{-4}$ by flow cytometry) serially over at least 3 cycles in both peripheral blood and BM.

Primary endpoint: 95% to 100% 1-yr DFS rate in patients with confirmed undetectable MRD

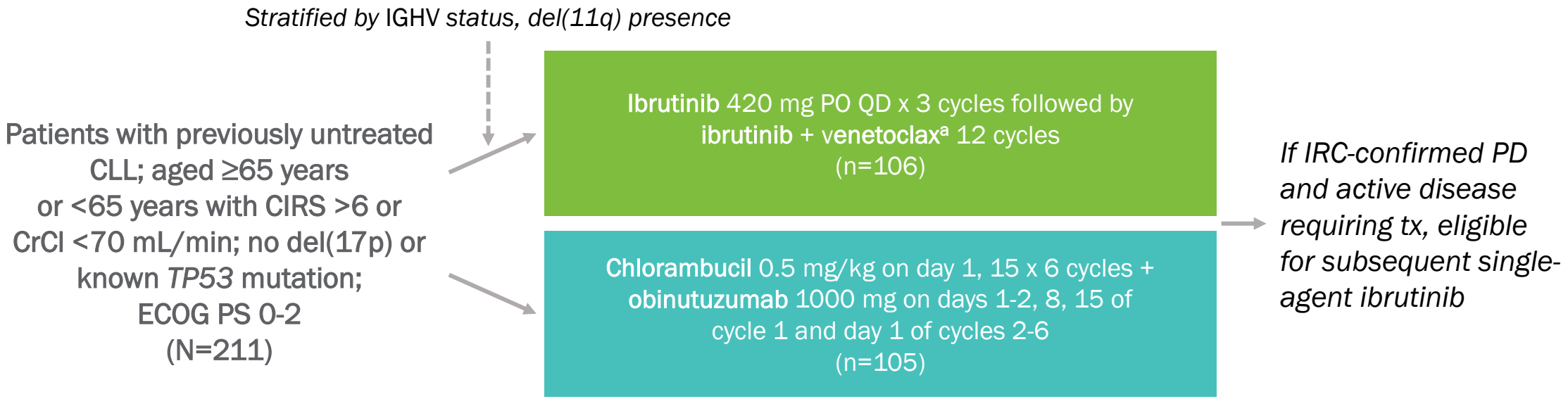
Secondary endpoints: undetectable MRD, response, PFS, safety

BM, bone marrow; CLL, chronic lymphocytic leukemia; DFS, disease-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; f/u, follow-up; Ibr, ibrutinib; IGHV, immunoglobulin heavy chain variable gene; MRD, minimal residual disease; PFS, progression-free survival; QD, once a day; SLL, small lymphocytic lymphoma; Ven, venetoclax.

Ghia P, et al. ASH 2021. Abstr #68.

GLOW: Fixed-Duration Ibrutinib + Venetoclax vs Chlorambucil + Obinutuzumab in Frontline CLL

- International, open-label, randomized phase 3 trial

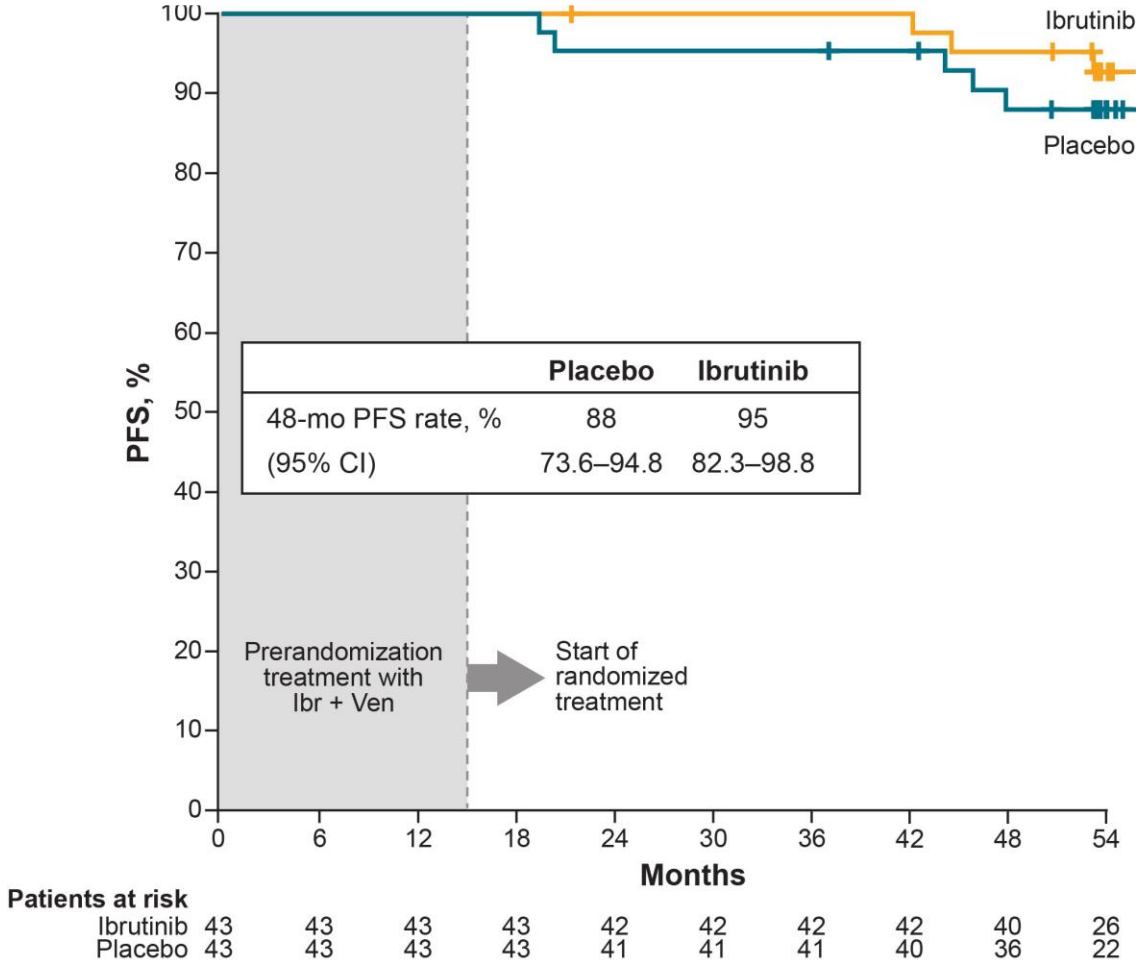


- **Primary endpoint:** PFS per IRC
  - 71 PFS events to detect effect size with HR of 0.5 (80% power, 2-sided α = 0.05)
- **Key secondary endpoints:** uMRD in BM, CR rate per IRC, ORR per IRC, OS, safety

BM, bone marrow; CLL, chronic lymphocytic leukemia; CIRS, cumulative illness rating scale; CR, complete response; CrCl, creatine clearance; ECOG, Eastern Cooperative Oncology Group performance status; IGHV, immunoglobulin heavy chain variable gene; IRC, independent review committee; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PO, by mouth; QD, once a day; tx, treatment; uMRD, undetectable minimal residual disease.

[a] Ramp up from 20 to 400 mg over 5 weeks starting in cycle 4.

CAPTIVATE MRD Cohort: Progression-Free Survival



- At 48 months, PFS was 88% (95% CI, 74-95) with placebo and 95% (95% CI, 82-99) with continued ibrutinib

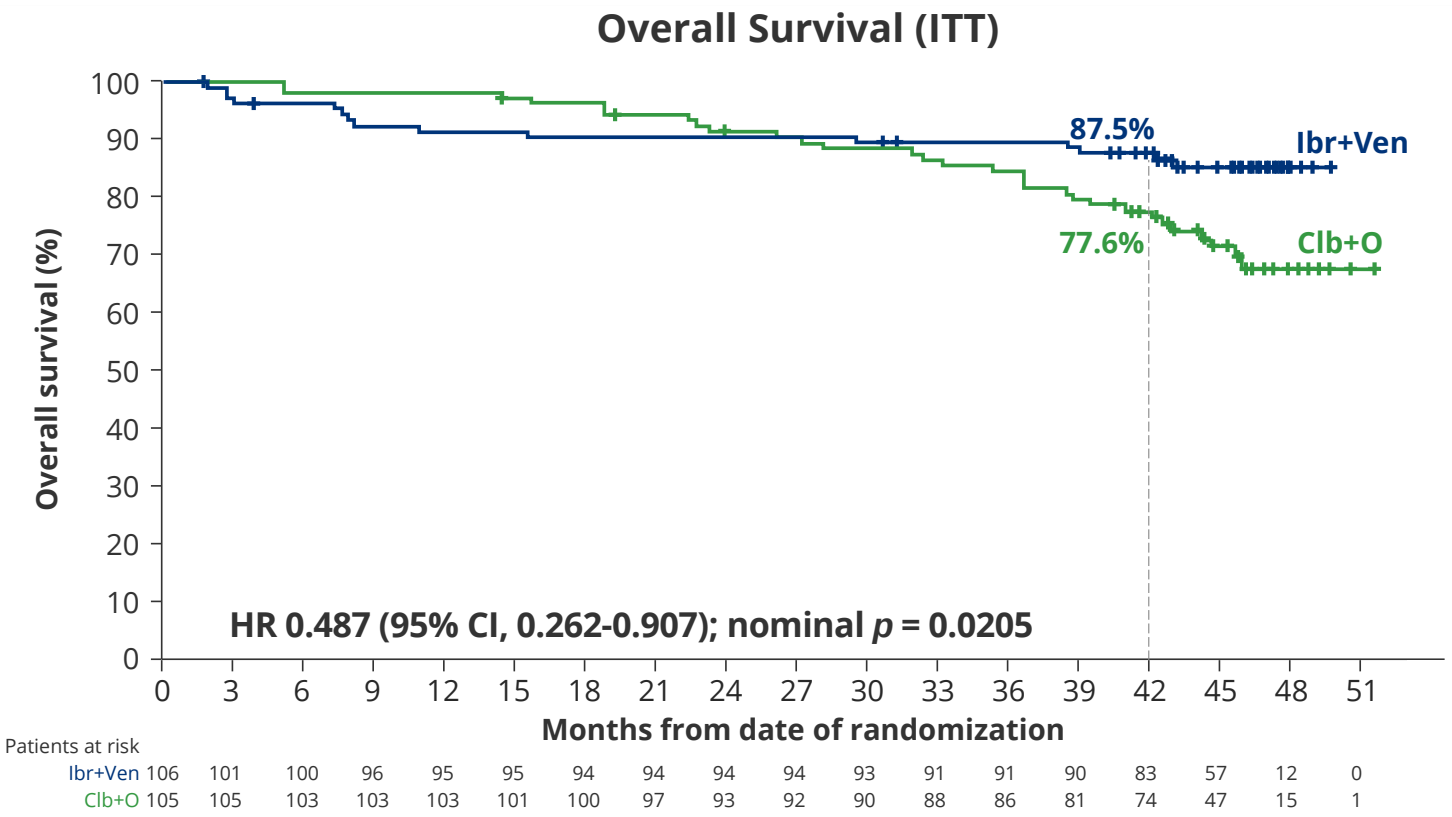
PD and Retreatment Outcomes

- 3 of 7 patients with PD in the placebo arm have initiated retreatment with ibrutinib; all 3 patients had PR
- 2 patients in the ibrutinib arm had PD; none have initiated retreatment

Allan JN, et al. ASH 2022. Abstr 92.

PFS, progression-free survival

GLOW: Ibr+Ven Improved OS vs Clb+O With 4 Years of Study Follow-Up



Median study follow-up: 46 months

- In the Clb+O arm, 39/41 patients requiring subsequent treatment received a BTKi or venetoclax
- The majority of deaths in the Clb+O arm occurred while off any treatment
- More infection-related deaths were seen in the Clb+O arm

Causes of Death

n (%)	Ibr+Ven (N = 106)	Clb+O (N = 105)
PD	1 (0.9)	2 (1.9)
Infections	4 (3.8)	11 (10.5)
Other[a]	10 (9.4)	17 (16.2)
TOTAL	15 (14.2)	30 (28.6)

[a]Cause and number (Ibr+Ven arm, Clb+O arm) of "other" deaths: general/unknown (4,5), cardiac (2,4), CNS (2,3), neoplasm (1,3), euthanasia (1,0), hepatobiliary (0,1), respiratory (0,1).
BTKi, Bruton's tyrosine kinase inhibitor.

Niemann CU, et al. ASH 2022. Abstr 93.