Therapeutic Algorithms for Patients with Treatment-Naïve Chronic Lymphocytic Leukemia (CLL)

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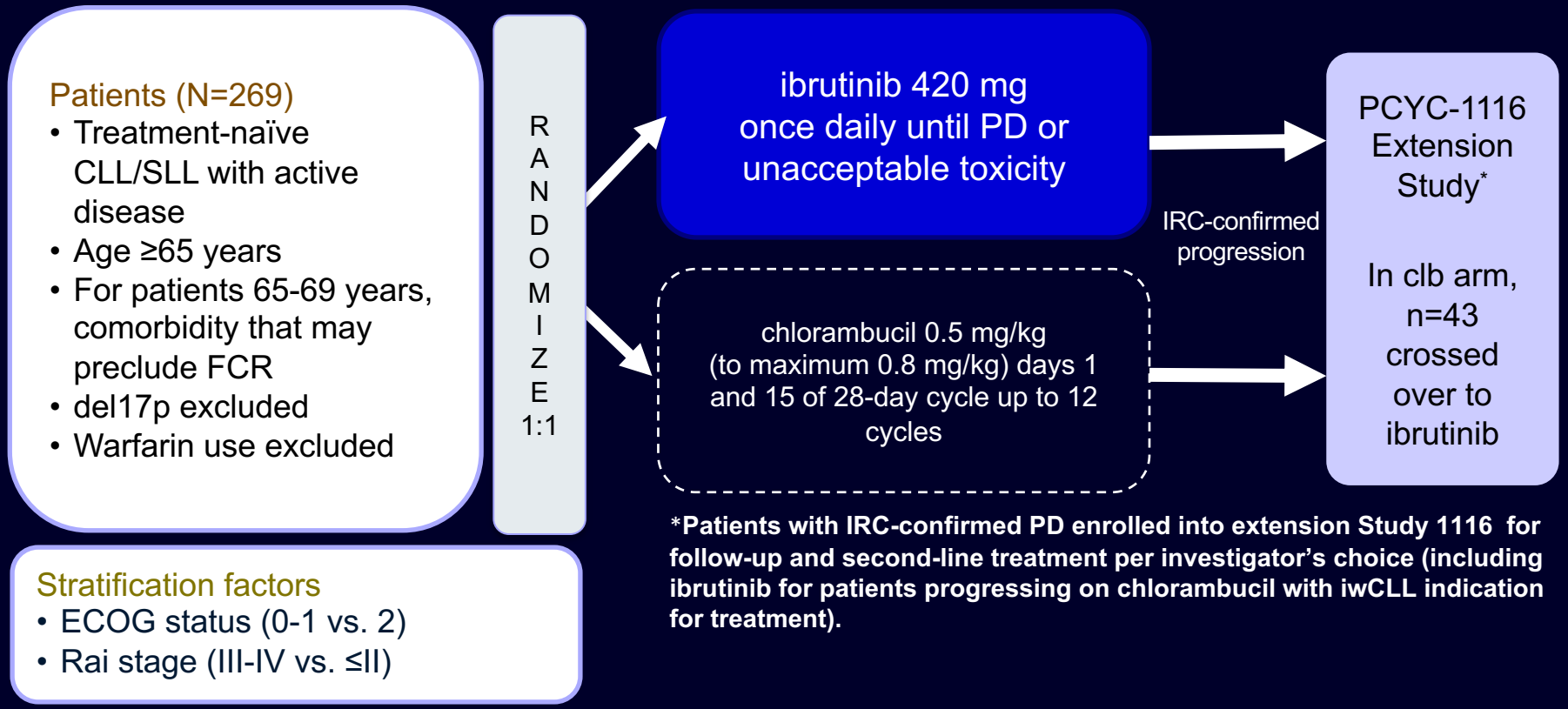
RESONATE-2 (PCYC-1115) Study Design



***Patients with IRC-confirmed PD enrolled into extension Study 1116 for follow-up and second-line treatment per investigator's choice (including ibrutinib for patients progressing on chlorambucil with iwCLL indication for treatment).**

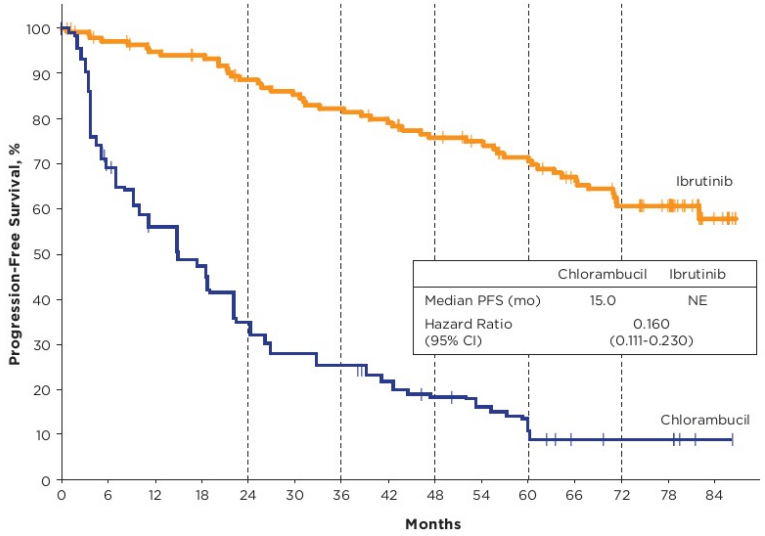
- Phase 3, open-label, multicenter, international study
- Primary endpoint: PFS as evaluated by IRC (2008 iwCLL criteria)[1,2]
- Secondary endpoints: OS, ORR, hematologic improvement, safety

Hallek et al. *Blood.* 2008;111:5446-5456; 2. Hallek et al, *Blood.* 2012; e-letter, June 04, 2012.

Burger, Barr, Robak et al. Leukemia. 2020 Mar;34(3):787-798

RESONATE-2: Long-term PFS Benefit With Ibrutinib

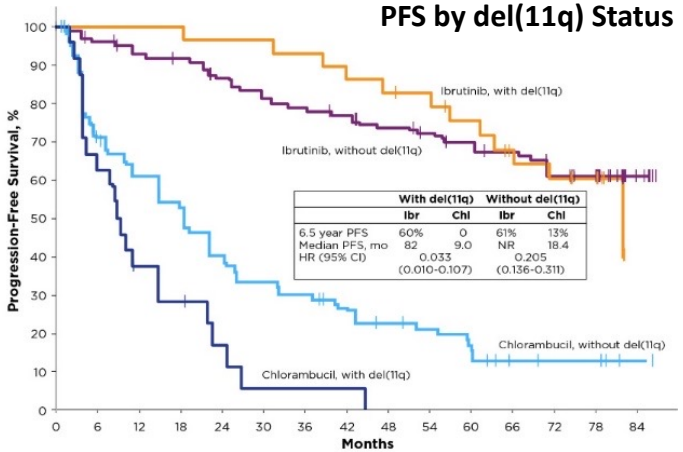
PFS: Ibrutinib vs Chlorambucil



Patients at Risk and PFS

Ibrutinib:	136	129	124	121	112	108	104	99	92	88	81	74	64	56	12
PFS, %:					89		82		76		71		61		
Chlorambucil:	133	88	69	57	41	33	30	25	19	16	12	6	5	5	1
PFS, %:					35		25		18		12		9		

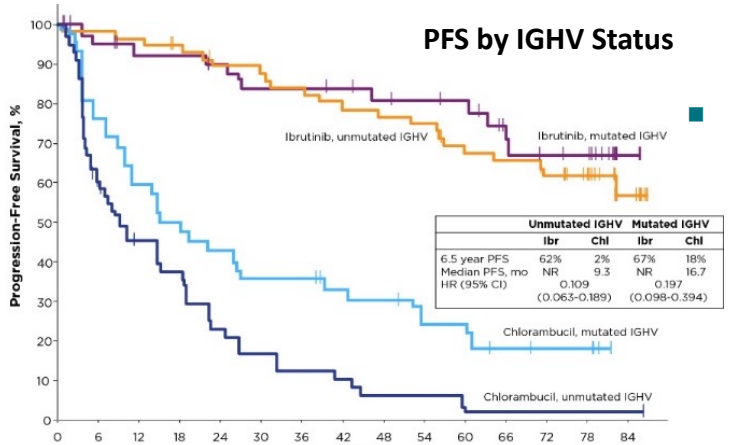
PFS by del(11q) Status



Patients at Risk

Ibrutinib, without del(11q):	101	94	89	87	80	76	73	70	64	61	57	53	45	41	10
Ibrutinib, with del(11q):	29	29	29	29	28	28	27	25	24	23	20	18	16	13	
Chlorambucil, without del(11q):	96	64	54	45	35	29	26	21	17	15	12	6	5	5	1
Chlorambucil, with del(11q):	25	15	8	6	3	1	1	1							

PFS by IGHV Status



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	57	56	53	49	48	46	43	42	41	36	35	32	26	8
Chlorambucil, mutated IGHV:	42	32	25	21	18	15	15	12	11	8	8	5	4	4	
Chlorambucil, unmutated IGHV:	60	33	23	19	11	8	6	5	3	3	2	1	1	1	1

- Median PFS was not reached in the ibrutinib arm
- Ibrutinib-treated patients had an 84% reduction in risk of progression or death
- At 6.5 years, 61% vs 9% of ibrutinib vs chlorambucil patients were estimated to be progression free and alive
- Ibrutinib led to a 97% reduction in risk of PD or death in patients with del(11q) and 80% for those without del(11q) vs chlorambucil
- Ibrutinib led to 89% and 80% reductions in the risk of PD or death in patients with unmutated or mutated IGHV, respectively, vs chlorambucil

HR from stratified Cox regression model; artifact at the end of the curve for ibrutinib patients with del(11q) is due to the extremely low patient numbers at these time points.

ASH 2020 Abstract #2219

Long Term Efficacy of First-Line ibrutinib Treatment for CLL with 4 Years of Follow-Up in Patients with TP53 Aberrations (del(17p) or TP53 Mutation): A Pooled Analysis From 4 Clinical Trials (N=89)

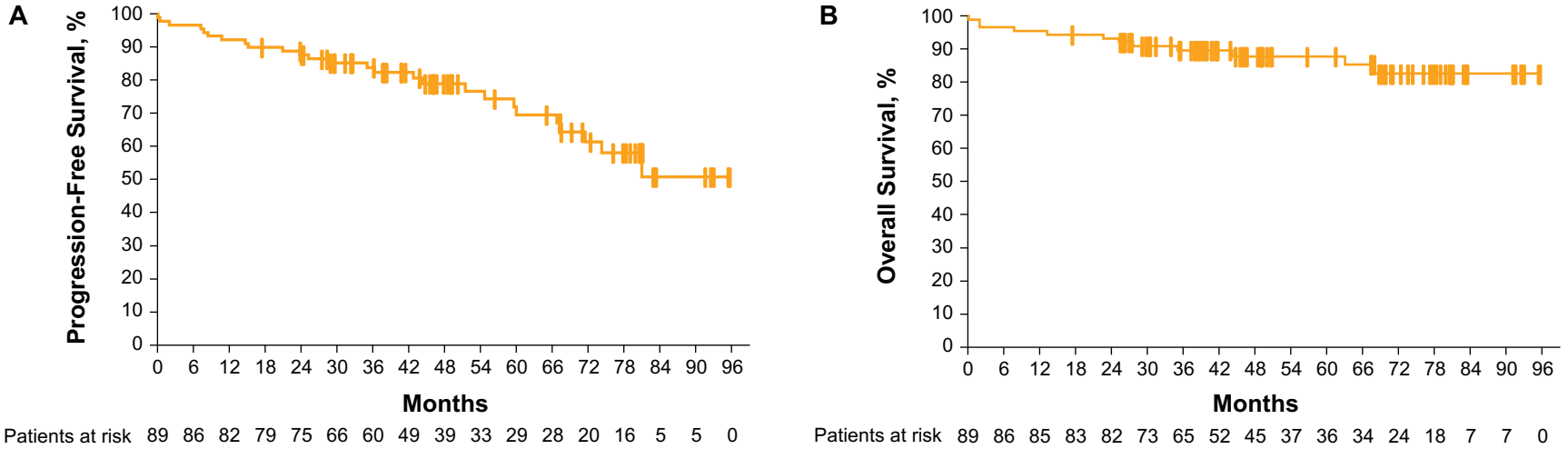
- Pooled data from 4 trials, Phase 1/2 PCYC-1122e trial (NCT01500733), Phase3 ILLUMINATE (I+G), ECOG1912 (I+R), RESONATE-2 (I)
- 53% with 17p deletion, 91% TP53 mutation
- 45 with ibrutinib single agent, 44 ibrutinib with anti-CD20
- Median age 65 (33-87), 53% Rai stage III/IV, 69% unmutated IgHV

Allan J, Shanafelt T, Wiestner A et al. EHA 2020 abstract #2219

RESULTS OF FRONTLINE IBRUTINIB THERAPY IN PATIENTS WITH DEL(17p)/P53 MUTATION

Efficacy

Figure 1. (A) PFS and (B) OS[a] in Patients With *TP53* Aberrations Receiving First-Line Ibrutinib-Based Therapy

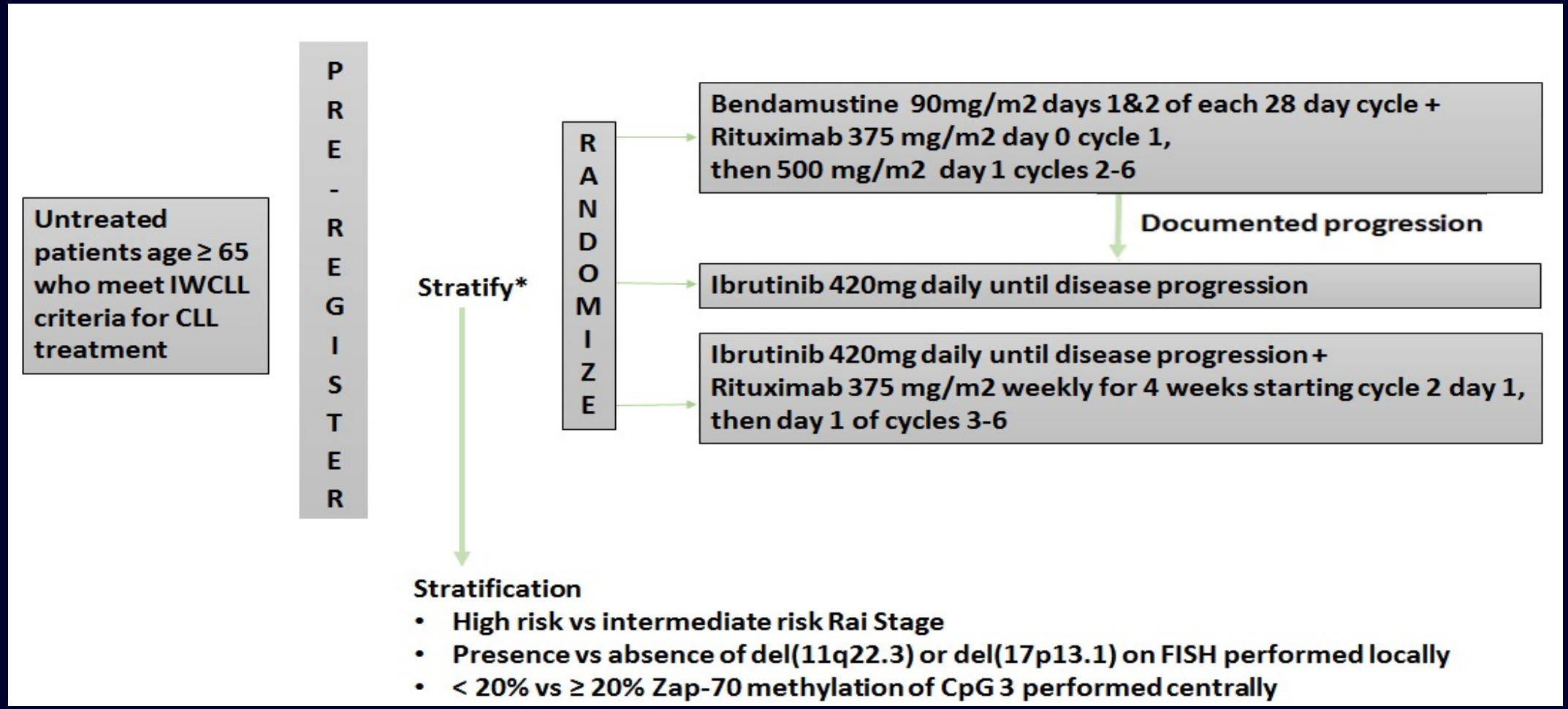


[a]The patient who had the longest follow-up died at 96 months, resulting in an artifact for estimating median OS. This patient's data were suppressed from the plot to correctly represent the population for which the median OS is not estimable.

- In the overall pooled population, the 4-year PFS rate was 79%, the median PFS was not reached (95% CI: 67 mo to not estimable [NE]; **Figure 1A**).
  - For the 47 patients who had either del(17p) only or *TP53* mutation only, median PFS was not reached (95% CI: 60 mo to NE).
  - For the 11 patients who had both del(17p) and *TP53* mutation, median PFS was 42.8 months (95% CI: 7 mo to NE).
- In the overall pooled population, the 4-year OS rate was 88% (**Figure 1B**).
- Most patients (83/89) achieved a response resulting in an ORR of 94%, including 39% who achieved a CR.

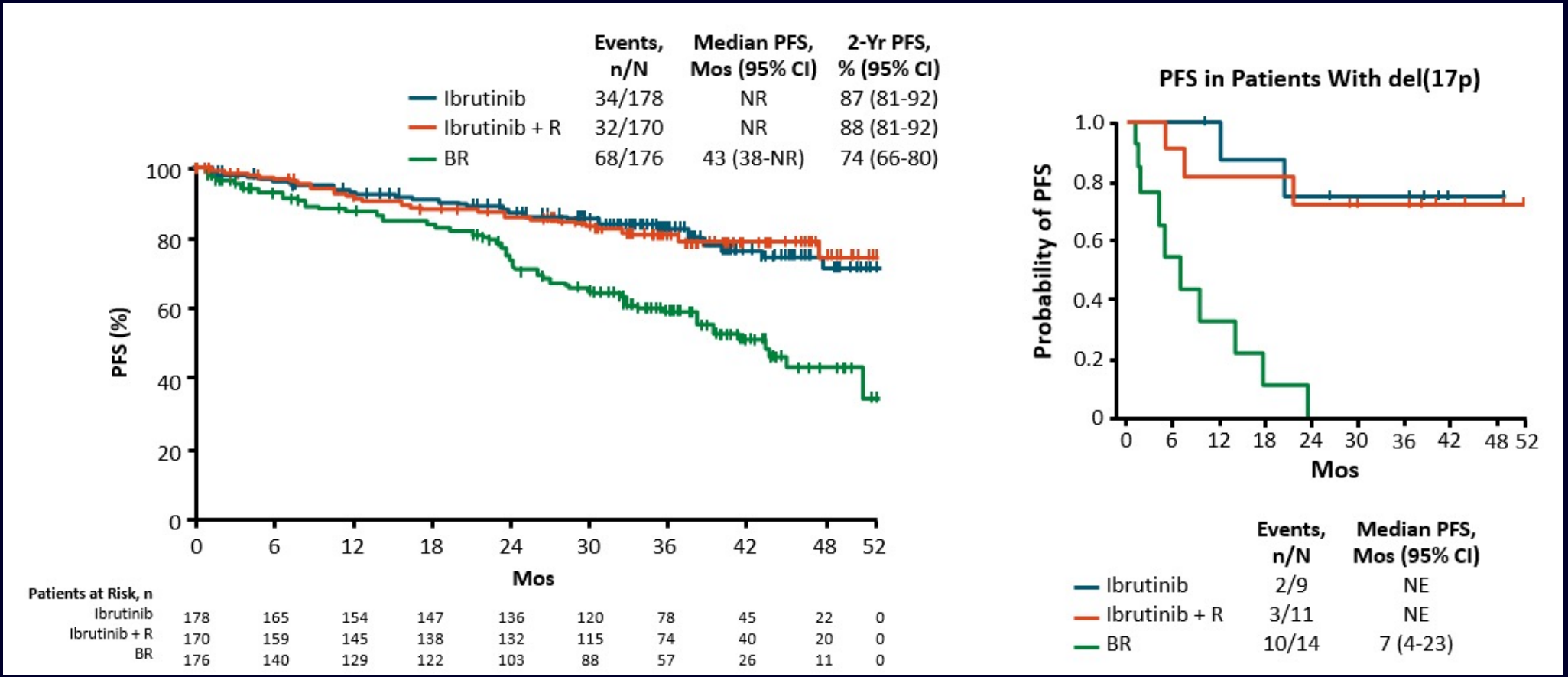
Allan J, Shanafelt T, Wiestner A et al. EHA 2020 abstract #2219

I vs IR vs BR: ALLIANCE A041202 Phase III Trial Design



Woyach. NEJM. 2018;379:2517

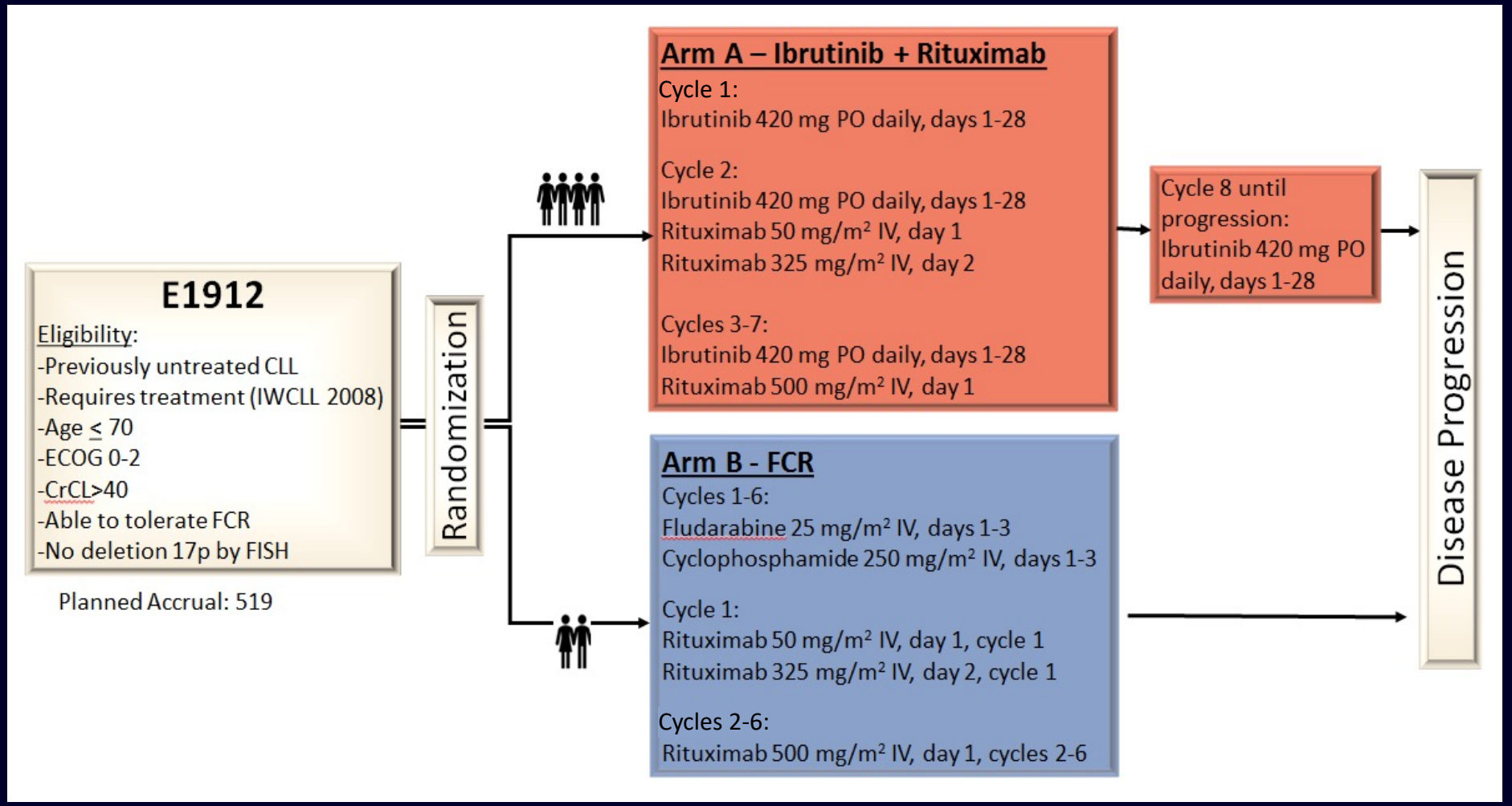
A041202: PFS in ITT and in Patients With del(17p)



Woyach. NEJM. 2018;379:2517

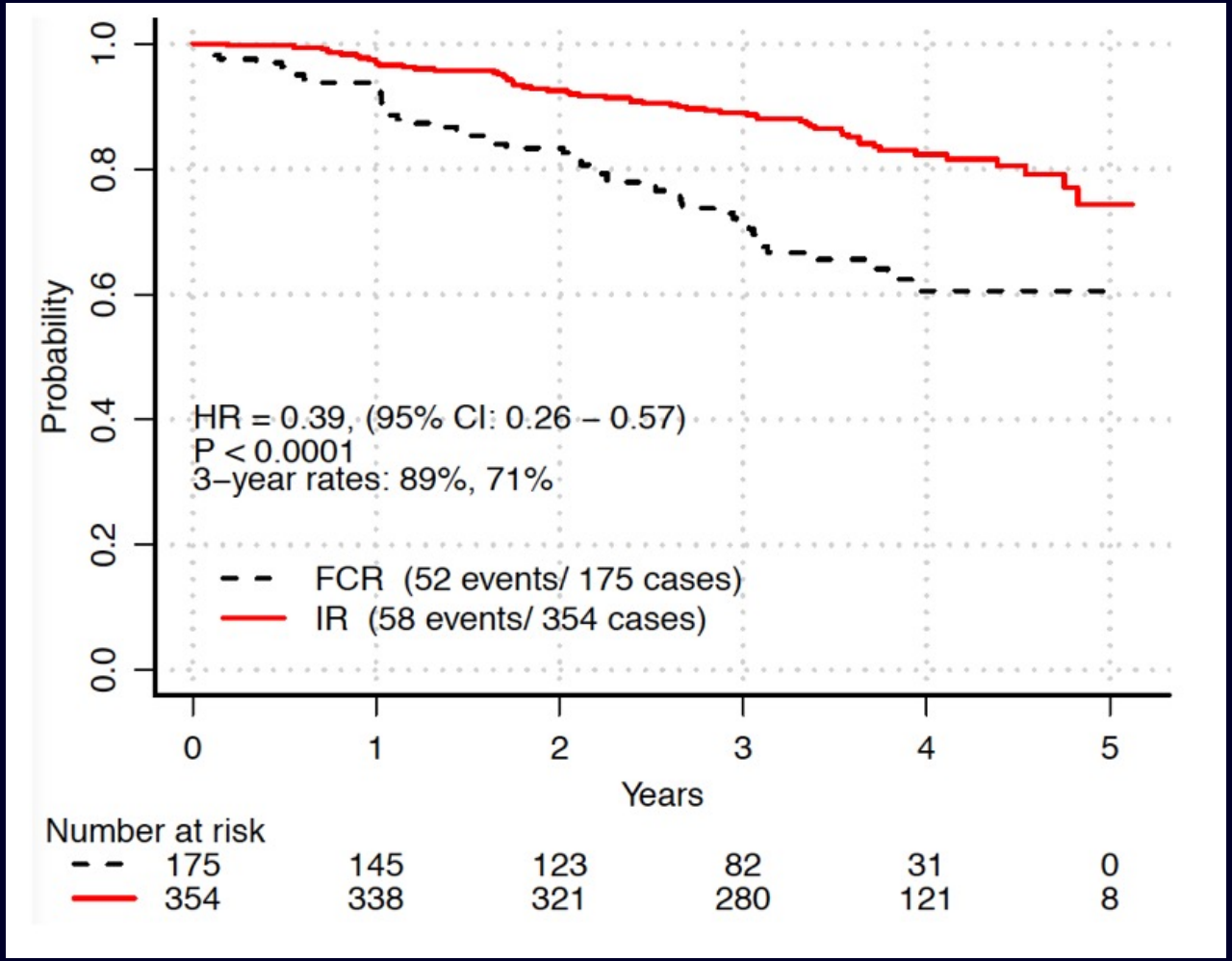
ECOG-E1912

IR vs FCR
Study Design Primary Endpoint: PFS



Shanafelt et al. N Engl J Med. 2019 Aug 1;381(5):432-443.

E1912: IR vs FCR
Progression Free Survival



ASH 2019

ELEVATE-TN Study Design

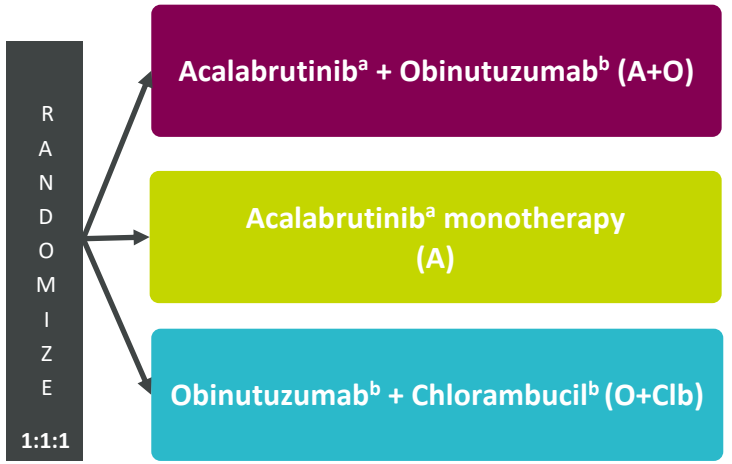
TN CLL (N=535)

Key Inclusion Criteria

- Age ≥65 years, or >18 to <65 years with comorbidities
  - Creatinine clearance 30–69 mL/min (by Cockcroft-Gault equation)
  - CIRS-G score >6
- Untreated CLL
  - Requiring treatment per iwCLL 2008 criteria[1]
- ECOG PS score ≤2
- Adequate hematologic, hepatic, and renal function

Stratification

- del(17p), y vs n
- ECOG PS 0–1 vs 2
- Geographic region (N America, W Europe, or other)



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)
- Time to next treatment
- OS
- uMRD
- Safety

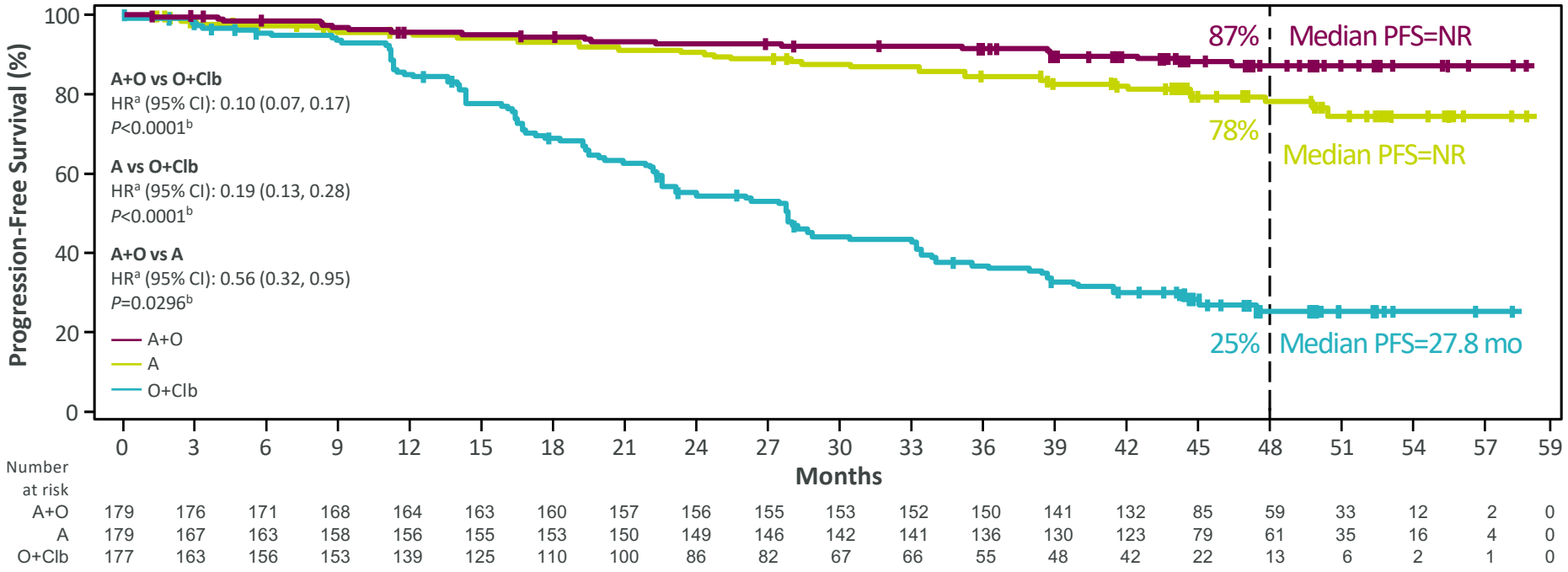
***Crossover** from O+Clb to A was allowed after IRC-confirmed progression*

Note: After interim analysis,[2] PFS assessments were by investigator only

Key exclusion criteria: Significant cardiovascular disease (uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or QTc >480 msec at screening)

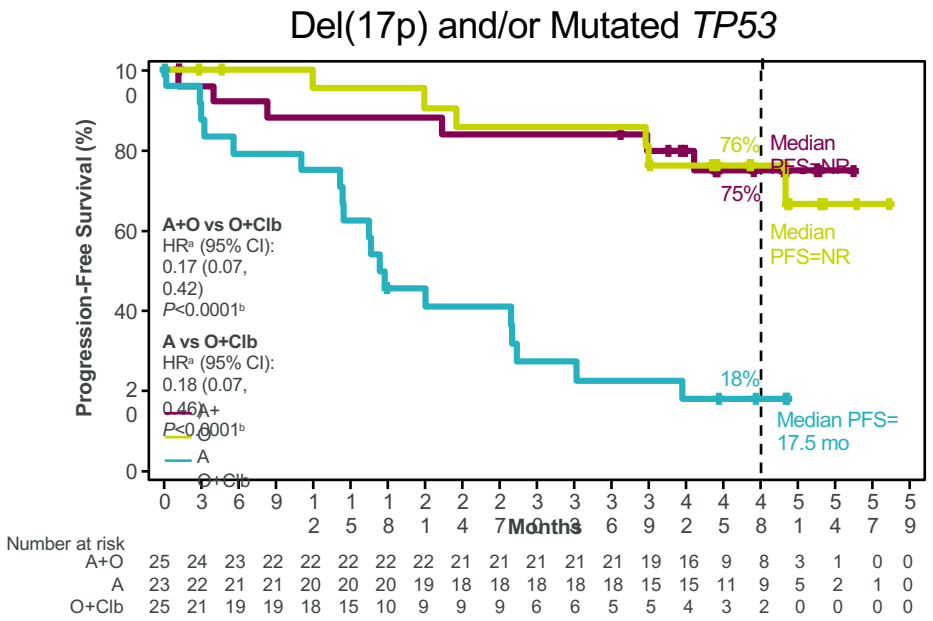
NCT02475681.
Data cutoff: September 11, 2020.
[a]Continued until disease progression or unacceptable toxicity at 100 mg PO BID; [b]Treatments were fixed duration and administered for 6 cycles.
A, acalabrutinib; CIRS-G, Cumulative Illness Rating Scale-Geriatric; Clb, chlorambucil; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; INV, investigator; IRC, independent review committee; O, obinutuzumab; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TN, treatment-naïve; uMRD, undetectable minimal residual disease.
1. Hallek M, et al. *Blood*. 2008;111:5446-56. 2. Sharman J, et al. *Lancet*. 2020;395:1278-91.

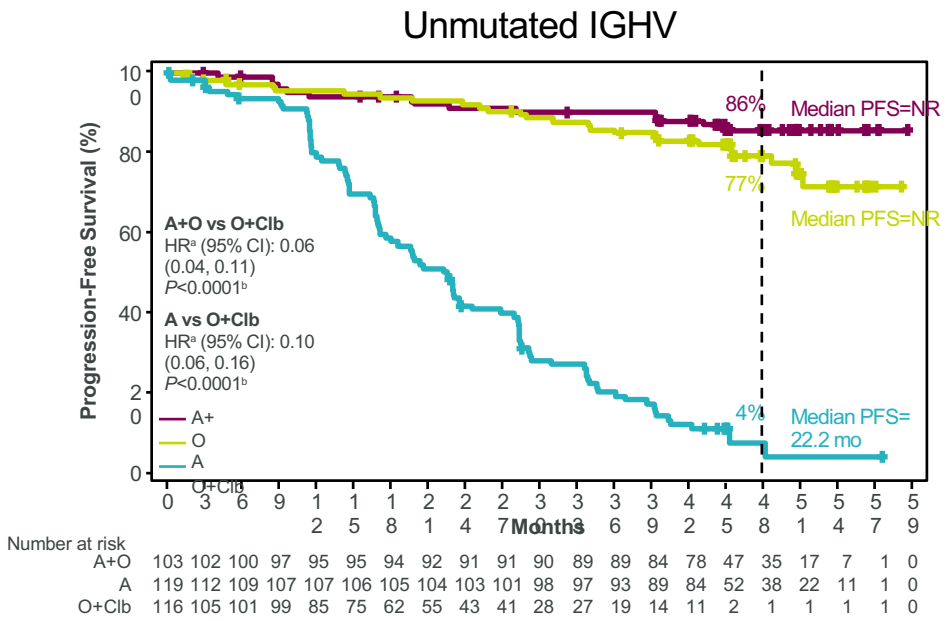
ELEVATE-TN: Investigator-assessed PFS Overall



[a]Hazard ratio was based on stratified Cox-Proportional-Hazards model; [b]*P*-value was based on stratified log-rank test.
A, acalabrutinib; CI, confidence interval; Clb, chlorambucil; HR, hazard ratio; NR, not reached; O, obinutuzumab; PFS, progression-free survival.

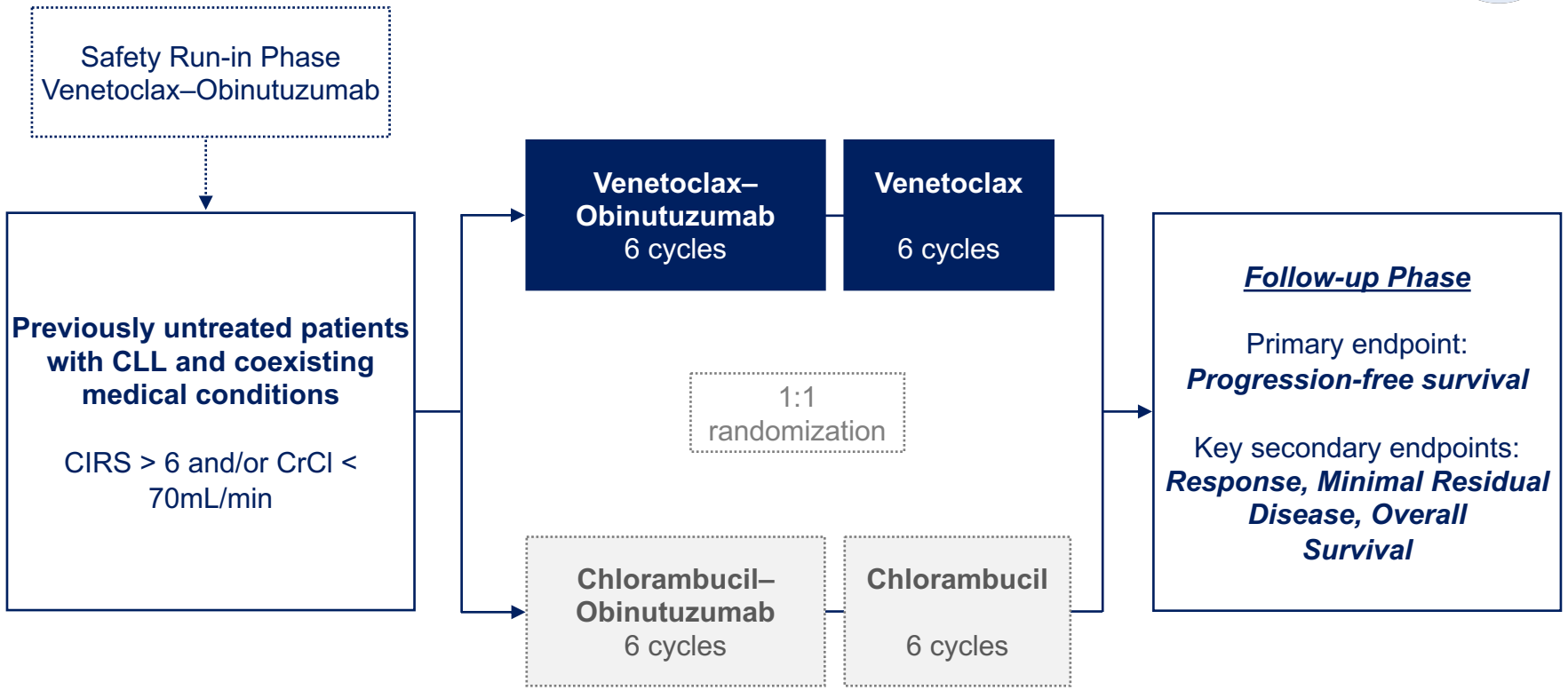
ELEVATE-TN: Investigator-assessed PFS in Patients With del(17p) and/or Mutated *TP53* OR Unmutated IGHV





[a]Hazard ratio was based on unstratified Cox-Proportional-Hazards model. [b]*P*-value was based on unstratified log-rank test.
A, acalabrutinib; CI, confidence interval; Clb, chlorambucil; HR, hazard ratio; IGHV, immunoglobulin heavy chain variable region; NR, not reached; O, obinutuzumab; PFS, progression-free survival.

Abstract S146
VENETOCLAX-OBINUTUZUMAB FOR PREVIOUSLY UNTREATED CHRONIC LYMPHOCYTIC LEUKEMIA: 4-YEAR FOLLOW-UP ANALYSIS OF THE RANDOMIZED CLL14 STUDY



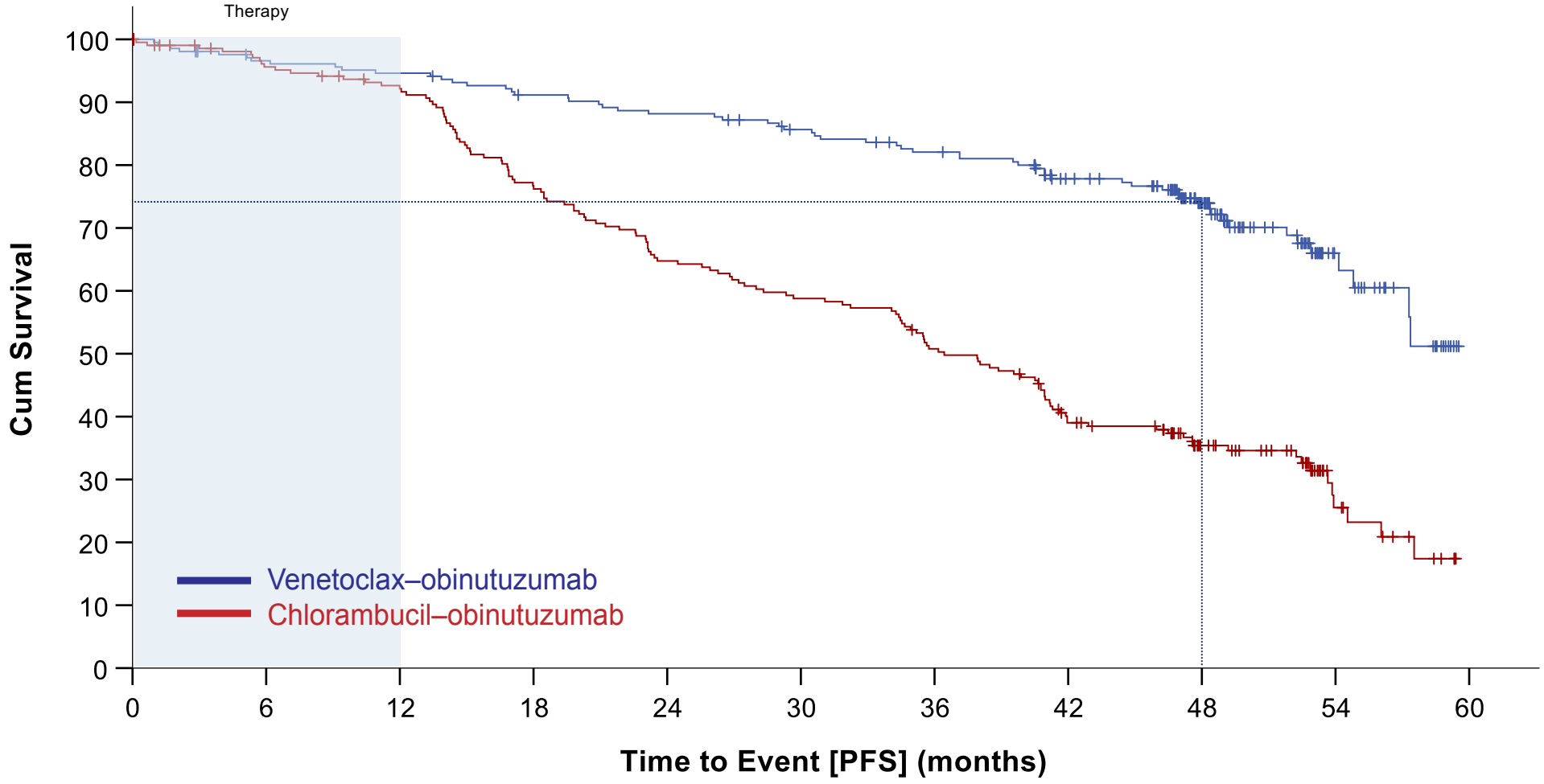
Al-Sawaf O et al. EHA 2021; Abstract S146.

Undetectable MRD by ASO-PCR	**Venetoclax-Obinutuzumab**	**Chlorambucil-Obinutuzumab**	*P* value
Number of patients, N	**216**	**216**	
Peripheral blood			
Undetectable (<10^{-4})	**76 %**	**35 %**	**< 0.001**
Undetectable (<10^{-4}) in complete response	42 %	14 %	< 0.001
Bone marrow			
Undetectable (<10^{-4})	**57 %**	**17 %**	**< 0.001**
Undetectable (<10^{-4}) in complete response	34 %	11 %	< 0.001

By ASO-PCR 3 months after completion of treatment
Concordance BM vs. Blood: 86.8% for both treatment groups

CLL14: PROGRESSION-FREE SURVIVAL

Median observation time: 52.4 months



Median PFS

Ven-Obi: not reached

Clb-Obi: 36.4 months

4-year PFS rate

Ven-Obi: 74.0%

Clb-Obi: 35.4%

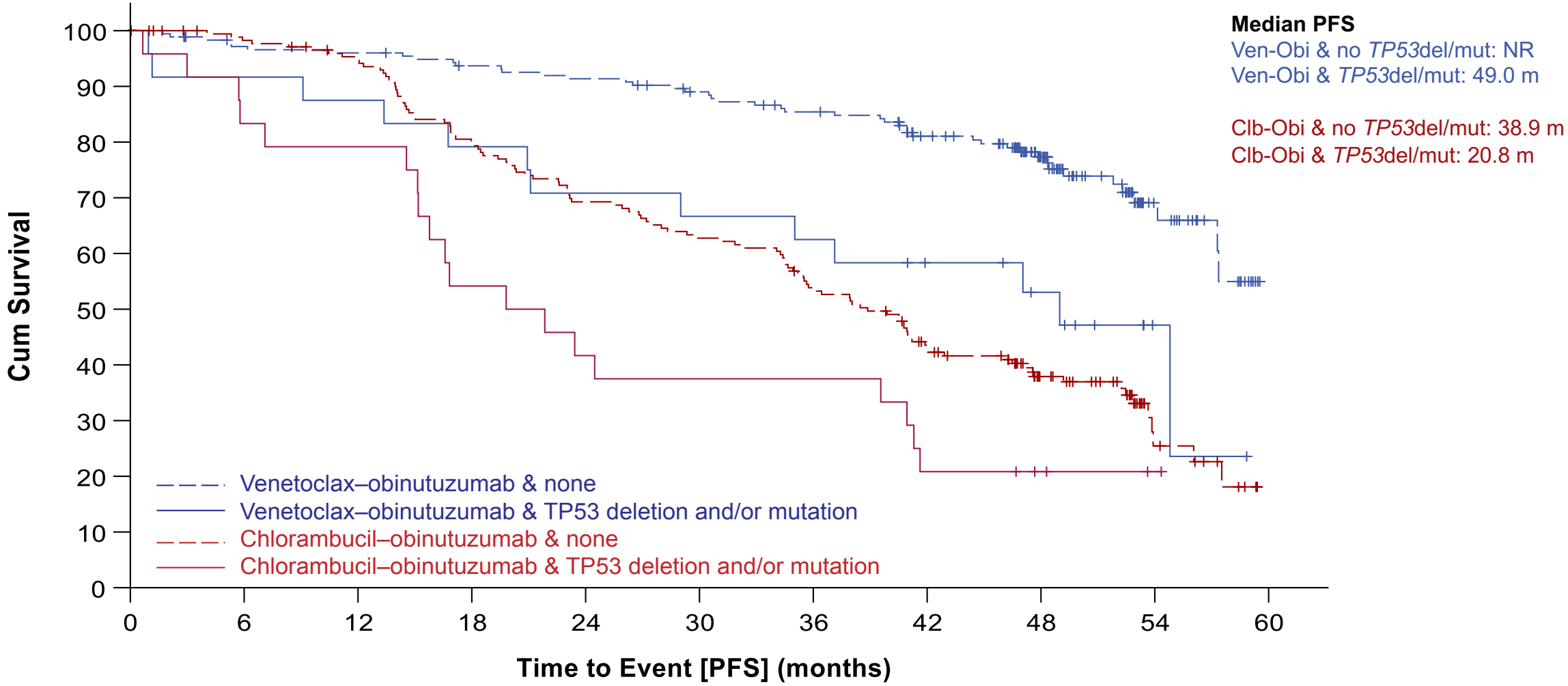
HR 0.33, 95% CI [0.25-0.45]

P<0.0001

Al-Sawaf O et al. EHA 2021; Abstract S146.

CLL14: PROGRESSION-FREE SURVIVAL – *TP53* status

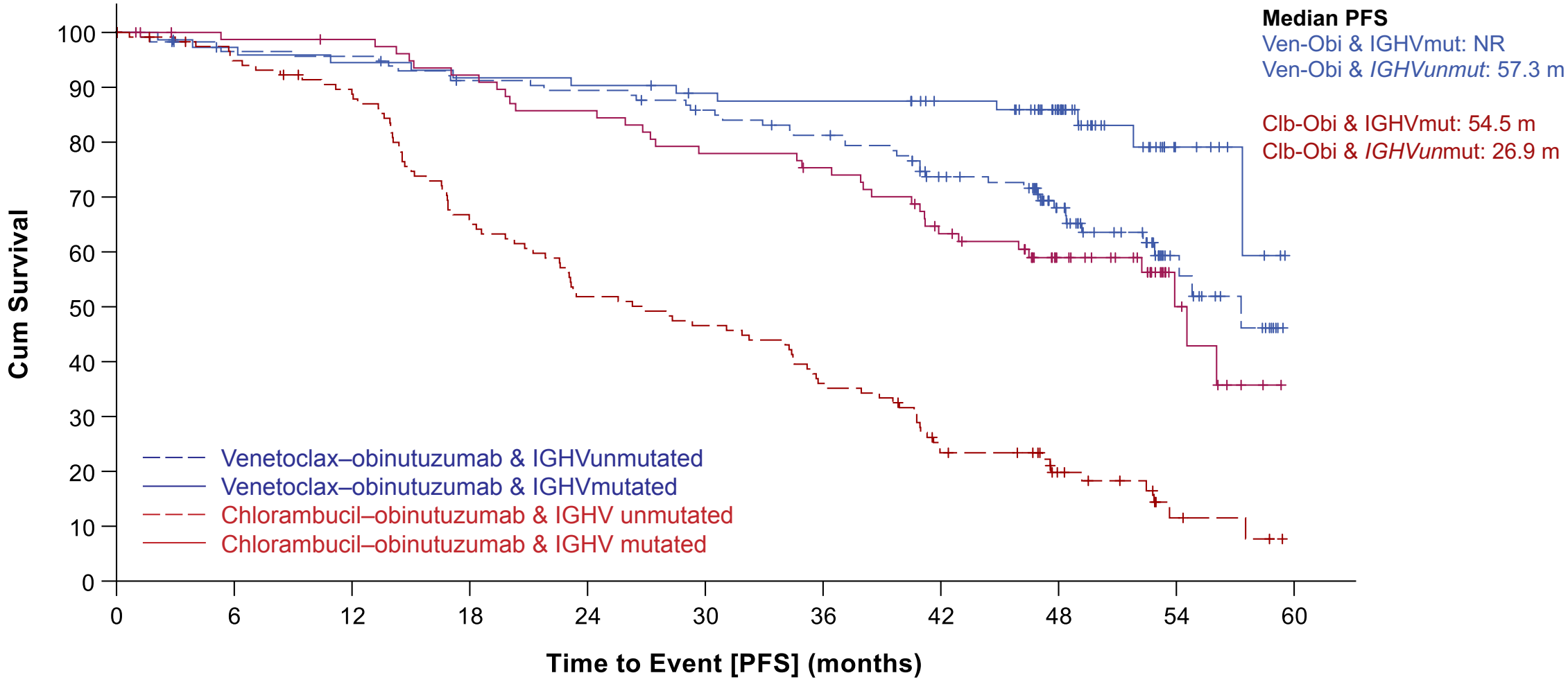
Median observation time: 52.4 months



Al-Sawaf O et al. EHA 2021; Abstract S146.

PROGRESSION-FREE SURVIVAL – IGHV status

Median observation time: 52.4 months



Al-Sawaf O et al. EHA 2021; Abstract S146.

CLL14: Most Frequent ≥ Grade 3 Adverse Events

	Venetoclax-obinutuzumab (N=212)		Chlorambucil-obinutuzumab (N=214)	
	During Treatment	After Treatment	During Treatment	After Treatment
Neutropenia	51.9%	4.0%	47.2%	1.9%
Thrombocytopenia	13.7%	0.5%	15.0%	0.0%
Anemia	7.5%	1.5%	6.1%	0.5%
Febrile neutropenia	4.2%	1.0%	3.3%	0.5%
Leukopenia	2.4%	0.0%	4.7%	0.0%
Pneunomia	3.3%	3.0%	2.8%	1.4%
Infusion-related reaction	9.0%	0.0%	9.8%	0.5%
Tumour lysis syndrome	1.4%	0.0%	3.3%	0.0%

Al-Sawaf O et al. EHA 2021; Abstract S146.

First Results of a Head-to-Head Trial of Acalabrutinib versus Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia

John C. Byrd[1]; Peter Hillmen[2]; Paolo Ghia[3]; Arnon P. Kater[4]; Asher Chanan-Khan[5]; Richard R. Furman[6]; Susan O'Brien[7]; Mustafa Nuri Yenerel[8]; Arpad Illes[9]; Neil Kay[10]; Jose A. Garcia-Marco[11]; Anthony Mato[12]; Javier Pinilla-Ibarz[13]; John F. Seymour[14]; Stephane Lepretre[15]; Stephan Stilgenbauer[16]; Tadeusz Robak[17]; Priti Patel[18]; Kara Higgins[18]; Sophia Sohoni[18]; Wojciech Jurczak[19]

[1]The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA; [2]St. James's University Hospital, Leeds, UK; [3]Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milano, Italy; [4]Amsterdam University Medical Center, Amsterdam, on behalf of Hovon, Netherlands; [5]Mayo Clinic Jacksonville, Jacksonville, FL, USA; [6]Weill Cornell Medicine, New York Presbyterian Hospital, New York, NY, USA; [7]Chao Family Comprehensive Cancer Center, University of California-Irvine, Irvine, CA, USA; [8]Istanbul University, Istanbul, Turkey; [9]University of Debrecen, Debrecen, Hungary; [10]Mayo Clinic Rochester, Rochester, MN, USA; [11]Hospital Universitario Puerta de Hierro-Majadahonda, Madrid, Spain; [12]University of Pennsylvania, Philadelphia, PA, USA; [13]Moffit Cancer Center, Tampa, FL, USA; [14]Peter MacCallum Cancer Centre, Royal Melbourne Hospital and University of Melbourne, Victoria, Australia; [15]Centre Henri Becquerel and Normandie University UNIROUEN, Rouen, France; [16]University of Ulm, Ulm, Germany; [17]Medical University of Lodz, Lodz, Poland; [18]AstraZeneca, South San Francisco, CA, USA; [19]Maria Sklodowska-Curie National Research Institute of Oncology, Krakow, Poland

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

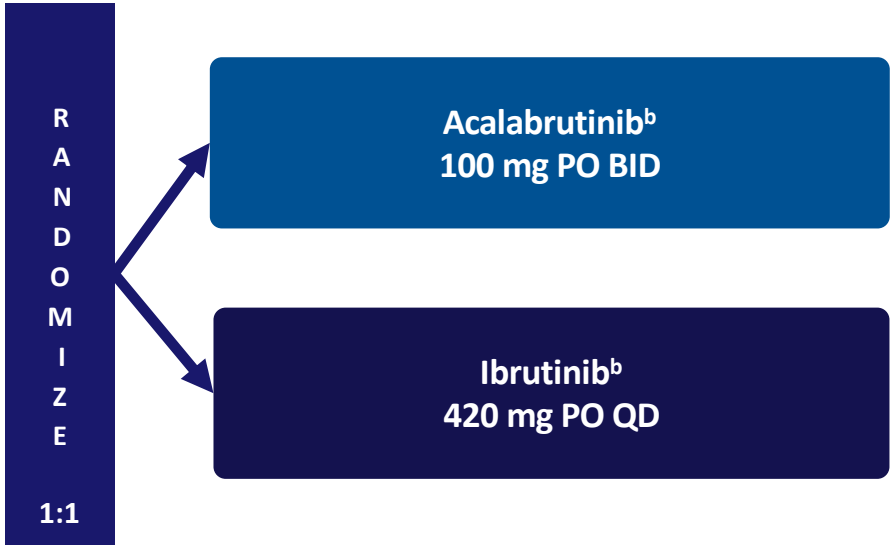
Patients (N=533)

Key Inclusion Criteria

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

Stratification

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



Primary endpoint

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

Secondary endpoints (hierarchical order):

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

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

NCT02477696 (ACE-CL-006).

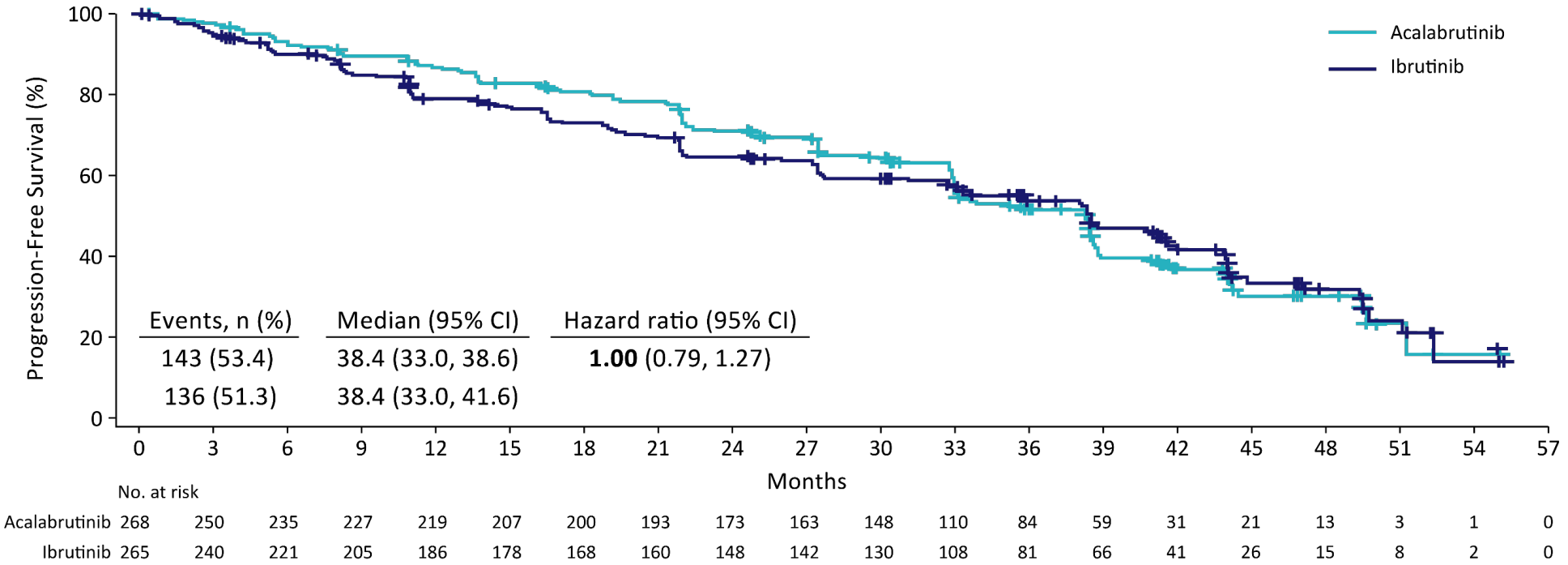
[a]By central laboratory testing; [b]continued until disease progression or unacceptable toxicity; [c]conducted after enrollment completion and accrual of ~250 IRC-assessed PFS events.

Afib/flutter, atrial fibrillation/flutter; BCL-2, B-cell leukemia/lymphoma-2; BID, twice daily; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CV, cardiovascular; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent review committee; iwCLL, International Workshop on CLL; PFS, progression-free survival; PI3K, phosphatidylinositol 3-kinase; PO, orally; QD, once daily.

1. Hallek M, et al. *Blood*. 2008;111:5446-56.

ELEVATE-RR

Primary Endpoint: Non-inferiority Met on IRC-Assessed PFS



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

CI, confidence interval; IRC, independent review committee; PFS, progression-free survival.

ELEVATE-RR

Events of Clinical Interest

Events, n (%)	Any grade		Grade ≥3	
	Acalabrutinib (n=266)	Ibrutinib (n=263)	Acalabrutinib (n=266)	Ibrutinib (n=263)
Cardiac events	64 (24.1)	79 (30.0)	23 (8.6)	25 (9.5)
Atrial fibrillation[a]*	25 (9.4)	**42 (16.0)**	13 (4.9)	10 (3.8)
Ventricular arrhythmias[b]	0	3 (1.1)	0	1 (0.4)
Bleeding events*	101 (38.0)	**135 (51.3)**	10 (3.8)	12 (4.6)
Major bleeding events[c]	12 (4.5)	14 (5.3)	10 (3.8)	12 (4.6)
Hypertension[d]*	25 (9.4)	**61 (23.2)**	11 (4.1)	**24 (9.1)**
Infections[e]	208 (78.2)	214 (81.4)	82 (30.8)	79 (30.0)
ILD/pneumonitis*	7 (2.6)	**17 (6.5)**	1 (0.4)	2 (0.8)
SPMs excluding NMSC	24 (9.0)	20 (7.6)	16 (6.0)	14 (5.3)

Higher incidence indicated in **bold blue** for terms with statistical differences.
*Two-sided P-value for event comparisons <0.05 without multiplicity adjustment.
[a]Includes events with preferred terms atrial fibrillation and atrial flutter.
[b]Includes events with preferred terms torsade de pointes, ventricular arrhythmia, ventricular extrasystoles, ventricular fibrillation, ventricular flutter, ventricular tachyarrhythmia, and ventricular tachycardia.
[c]Defined as any hemorrhagic event that was serious, grade ≥3 in severity, or a central nervous system hemorrhage (any severity grade).
[d]Included events with the preferred terms of hypertension, blood pressure increased, and blood pressure systolic increased.
[e]Most common grade ≥3 infections were pneumonia (acalabrutinib, 10.5%; ibrutinib, 8.7%), sepsis (1.5% vs 2.7%, respectively), and UTI (1.1% vs 2.3%).
ILD, interstitial lung disease; NMSC, nonmelanoma skin cancer; SPMs, second primary malignancies; UTI, urinary tract infection.

FIRST INTERIM ANALYSIS OF ALPINE STUDY: RESULTS OF A PHASE 3 RANDOMIZED STUDY OF ZANUBRUTINIB VS IBRUTINIB IN PATIENTS WITH RELAPSED/REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA/ SMALL LYMPHOCYTIC LYMPHOMA

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

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

Key Inclusion Criteria

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

Key Exclusion Criteria

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

R
1:1

Arm A
Zanubrutinib 160 mg BID

Arm B
Ibrutinib 420 mg QD

Stratification Factors

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

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

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ORR by Investigator Assessment

	Zanubrutinib (n=207), n (%)	Ibrutinib (n=208), n (%)
Primary endpoint: ORR (PR+CR)	162 (**78.3**) 95% CI: 72.0, 83.7	130 (**62.5**) 95% CI: 55.5, 69.1
	Superiority 2-sided *P*=0.0006 compared with pre-specified alpha of 0.0099	
CR/CRi	4 (1.9)	3 (1.4)
nPR	1 (0.5)	0
PR	157 (75.8)	127 (61.1)
ORR (PR-L+PR+CR)	*183 (88.4)*	*169 (81.3)*
PR-L	21 (10.1)	39 (18.8)
SD	17 (8.2)	28 (13.5)
PD	1 (0.5)	2 (1.0)
Discontinued or new therapy prior to 1st assessment	6 (2.9)	9 (4.3)

	del(17p) (n=24), n (%)	del(17p) (n=26), n (%)
ORR (PR+CR)	20 (83.3)	14 (53.8)

CR, complete response; CRi, complete response with incomplete bone marrow recovery; D/C, discontinuation; DOR, duration of response; NE, not evaluable; nPR, nodular partial response; ORR, overall response rate; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease.

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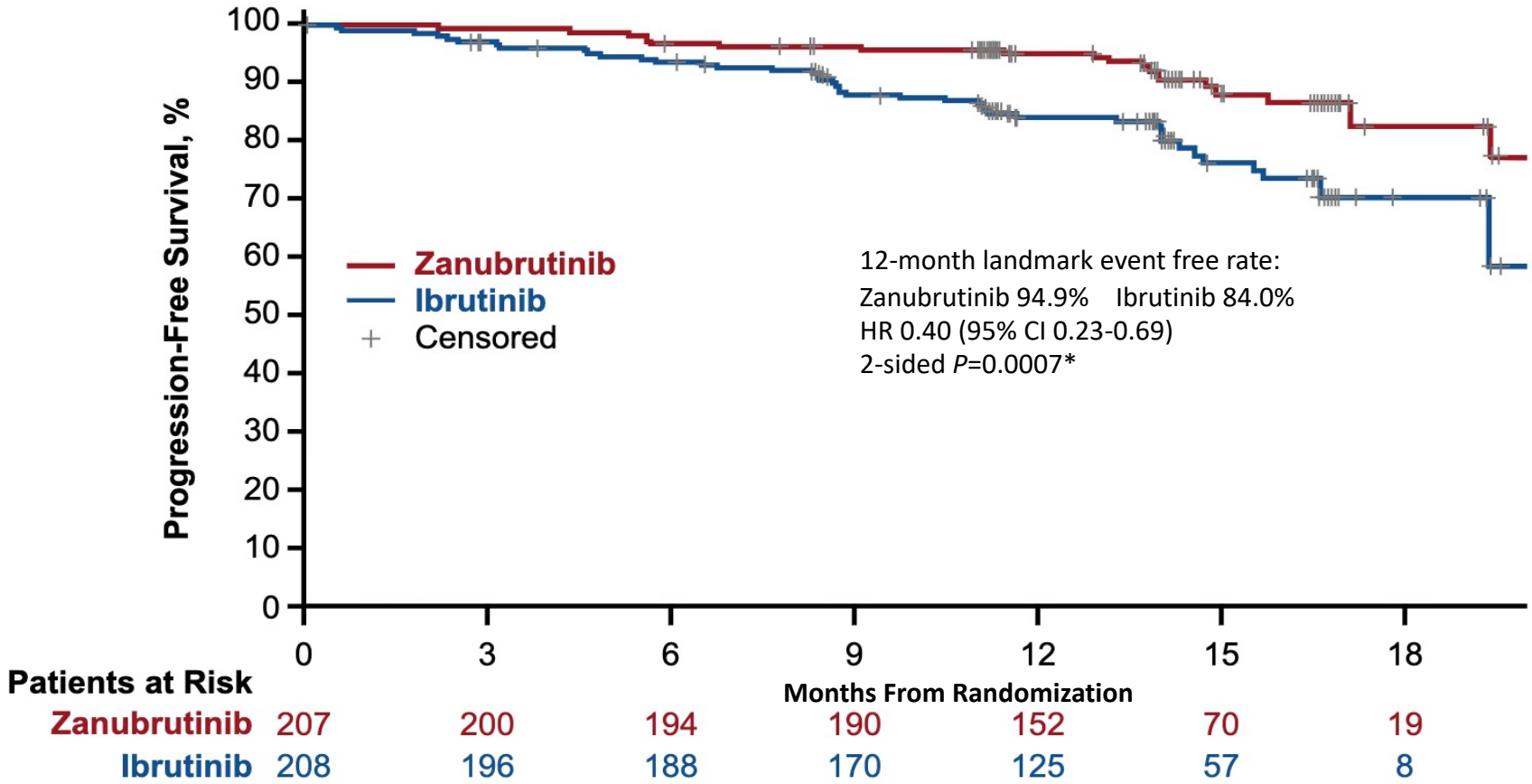
PFS by Investigator Assessment



*Not a prespecified analysis; formal analysis of PFS will be based on all patients when the target number of events is reached.
Median PFS follow-up was 14.0 months for both zanubrutinib and ibrutinib arms by reverse KM method.
PFS, progression-free survival.

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Additional AEs of Special Interest

Safety Analysis Population	Zanubrutinib (n=204), n (%)		Ibrutinib (n=207), n (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Cardiac disorders[a]	28 (13.7)	5 (2.5)	52 (25.1)	14 (6.8)
Atrial fibrillation and flutter (key 2º endpoint)	**5 (2.5)**	**2 (1.0)**	**21 (10.1)**	**4 (1.9)**
Hemorrhage Major hemorrhage[b]	73 (35.8) 6 (2.9)	6 (2.9) 6 (2.9)	75 (36.2) 8 (3.9)	6 (2.9) 6 (2.9)
Hypertension	34 (16.7)	22 (10.8)	34 (16.4)	22 (10.6)
Infections	122 (59.8)	26 (12.7)	131 (63.3)	37 (17.9)
Neutropenia[c]	58 (28.4)	38 (18.6)	45 (21.7)	31 (15.0)
Thrombocytopenia[c]	19 (9.3)	7 (3.4)	26 (12.6)	7 (3.4)
Secondary primary malignancies Skin cancers	17 (8.3) 7 (3.4)	10 (4.9) 3 (1.5)	13 (6.3) 10 (4.8)	4 (1.9) 2 (1.0)

AE, adverse events. All events are of any grade unless otherwise specified.
[a] Cardiac disorders leading to treatment discontinuation: zanubrutinib 0 patients and ibrutinib 7 (3.4%) patients.
[b] Includes hemorrhages that were serious or grade ≥3 or CNS hemorrhages of all grades.
[c] Pooled terms including neutropenia, neutrophil count decreased, and febrile neutropenia; thrombocytopenia and platelet count decreased.

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Positive Topline Results Announced from the Phase 3 SEQUOIA Trial Comparing Zanubrutinib to Bendamustine Plus Rituximab (BR) in Patients with Treatment-Naïve Chronic Lymphocytic Leukemia

"**The SEQUOIA trial met the primary endpoint at interim analysis, with Zanubrutinib significantly prolonging progression-free survival compared to chemoimmunotherapy, and safety and tolerability consistent with its known profile.**

SEQUOIA is the second positive global Phase 3 trial of Zanubrutinib in chronic lymphocytic leukemia, following ALPINE in the relapsed or refractory setting.

With a median follow-up of 25.8 months, the SEQUOIA trial met the primary endpoint of progression-free survival (PFS) as assessed by independent review committee (IRC), as Zanubrutinib achieved a highly statistically significant improvement in PFS compared to B+R.

In addition, the trial demonstrated a statistically significant improvement in PFS per investigator assessment, a secondary endpoint.

Zanubrutinib was also generally well-tolerated, consistent with its known safety profile."

https://www.businesswire.com/news/home/20210729006225/en/BeiGene-Announces-Positive-Topline-Results-from-Phase-3-SEQUOIA-Trial-Comparing-BRUKINSA%C2%AE-Zanubrutinib-to-Bendamustine-Plus-Rituximab-in-Patients-with-Treatment-Na%C3%AFve-Chronic-Lymphocytic-Leukemia

Conclusions

- BTKi +/- obin is an excellent continuous therapy option
  - Ibrutinib frontline PFS is 61% at 6.5 years
  - Ibrutinib produces longer PFS compared to every chemoimmunotherapy in frontline therapy
  - High-risk (del)11q patients have a favorable outcome with ibrutinib
  - In P53 aberrant patients, 4-year PFS is 79% with ibrutinib and 75% with acalabrutinib
  - Acalabrutinib +/- obin produced a 4-year PFS of 78-87% months
- Venetoclax + Obin produces a 4-year PFS of 74% with only one year of therapy; in P53 aberrant patients median PFS was 49 months
- In Elevate-RR, ibrutinib and acalabrutinib have overlapping PFS curves as assessed by IRC, less atrial fibrillation and HTN with acalabrutinib
- In ALPINE, interim analysis showed higher ORR, longer PFS and less atrial fibrillation with Zanu compared to ibrutinib, by investigator assessment

Case 2: A 71-year-old patient with CLL

A 71-year-old man presents to an oncologist after CBC done as part of preop work for knee replacement shows lymphocytosis, patient is asymptomatic

PMH: kidney stones, no labs done in many years

PE: 1-2 cm cervical nodes, 2 cm axillary nodes, shotty inguinal nodes, no hepatosplenomegaly

CBC: ALC 48,000, Hgb 12.6, Plts 120

Flow: consistent with CLL, CD38 negative

FISH: 13q deletion, IGHV mutated

Case 2 (continued)

12 months later

Patient has mild fatigue, occasional night sweats

PE: 2-3 cm cervical nodes, 3-4 cm axillary nodes, 1 cm inguinal nodes, 2 cm palpable spleen

CBC: ALC 62,000, Hgb 11.8, Plts 113

Plan: continue observation

Case 2 (continued)

24 months from diagnosis

Patient has increasing fatigue and night sweats

PE: 3 cm cervical nodes, 4 cm axillary nodes, 2 cm inguinal nodes, 5 cm palpable spleen

CBC: ALC 74,000, Hgb 11.2, Plts 101

Repeat FISH: 13 deletion, P53 wild type

Plan: order abdominal CT to assess TLS risk and then start venetoclax and obinutuzumab