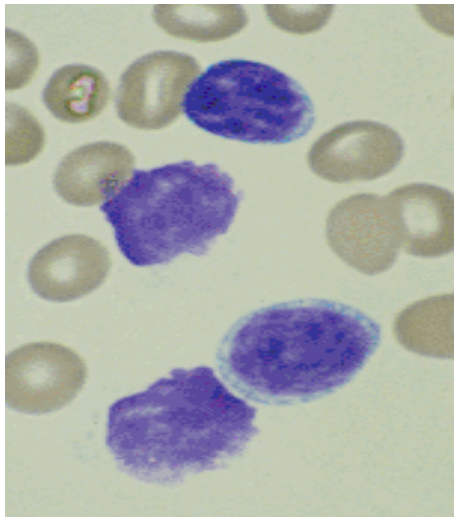
Chronic Lymphocytic Leukemia: ASH 2021 Highlights- BTKis



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Disclosures
Nicole Lamanna, MD

I have the following financial relationships to disclose:

SAB/Consultant/Honoraria: AbbVie, Adaptive Biosciences, Astra-Zeneca, Bei-Gene, Celgene, Genentech, Janssen, LOXO/Eli Lilly, Pharmacyclics

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Targeted Therapy FDA Approvals and Current Status in CLL[1-7]

Agent	Target	Status in CLL/SLL
Ibrutinib	BTK	Approved
Acalabrutinib		Approved
Zanubrutinib		Phase 3 (SEQUOIA)
Pirtobrutinib		Phase 3 (NCT04666038)
Venetoclax	BCL-2	Approved
Idelalisib	PI3K	Approved
Duvelisib		Approved
Umbralisib		Phase 3

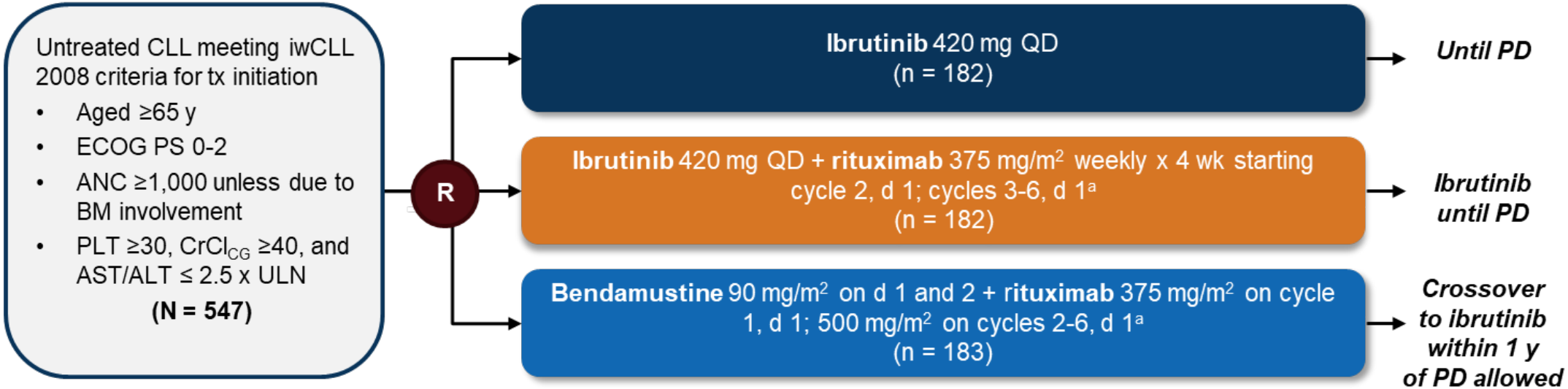
1. Imbruvica (ibrutinib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205552s002lbl.pdf. 2. Calquence (acalabrutinib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/210259s000lbl.pdf. 3. Brukinsa (zanubrutinib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/213217s000lbl.pdf. 4. Venclexta (venetoclax) Prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208573s009lbl.pdf. 5. Zydelig (idelalisib) Prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206545lbl.pdf. 6. Copiktra (duvelisib) Prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/211155s000lbl.pdf. 7. Ukoniq (umbralisib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/213176s000lbl.pdf.

ASH abstracts highlight continued efficacy of BTKis in phase III frontline studies in CLL

- Alliance study
- FLAIR study
- SEQUOIA study

A041202: First-Line Ibrutinib vs Ibrutinib + Rituximab vs Bendamustine + Rituximab in CLL/SLL

- Multicenter, randomized, double-blind phase 3 study

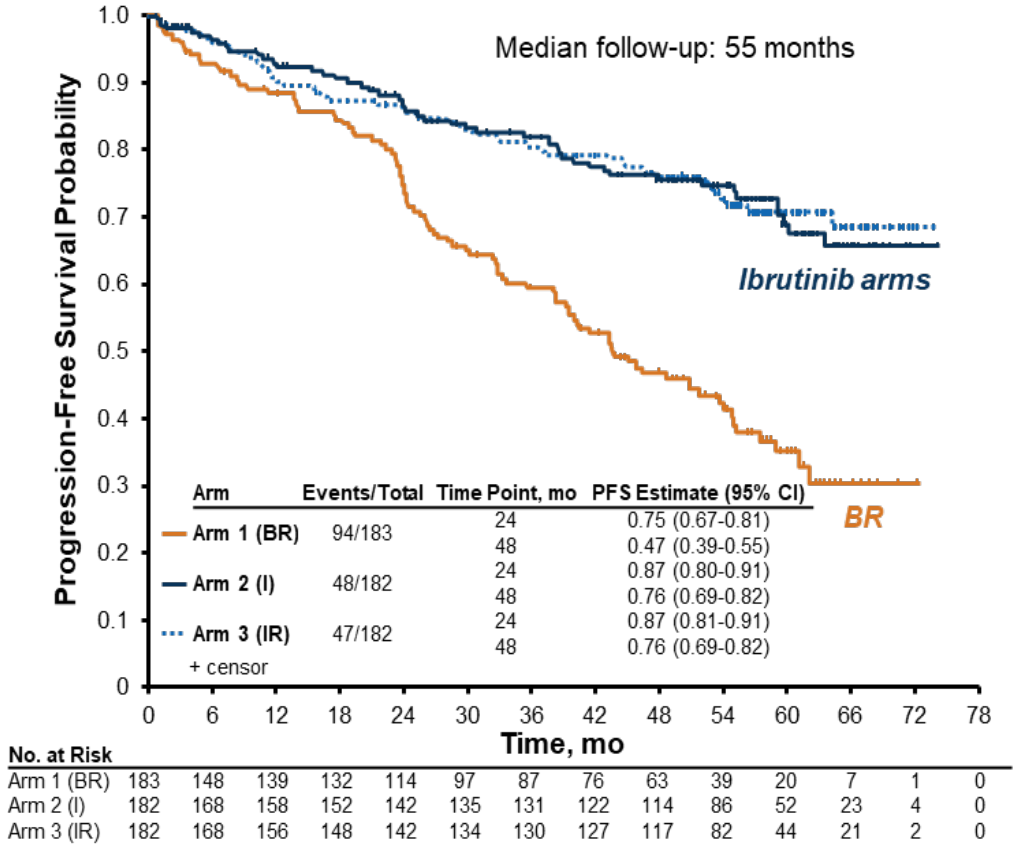


- **Stratified by Rai stage (high vs intermediate risk), del(11q22.3) or del(17p13.1) (presence vs absence), and ZAP-70 methylation (< vs ≥20%)**
- **Primary endpoint:** PFS
  - Two primary comparisons of ibrutinib vs BR and ibrutinib + R vs BR with 90% power to detect HR of 0.586 (estimated 2-y PFS rates: ibrutinib, 75%; BR, 61%) and overall 1-sided α = 0.025 for each comparison
  - If both primary comparisons are significant, third planned comparison of ibrutinib + R versus ibrutinib

1. Woyach JA et al. ASH 2021. Abstract 639.

Long-Term Update From the ALLIANCE Trial Confirms Benefit of Ibrutinib Regimens, Including in *TP53* CLL[1]

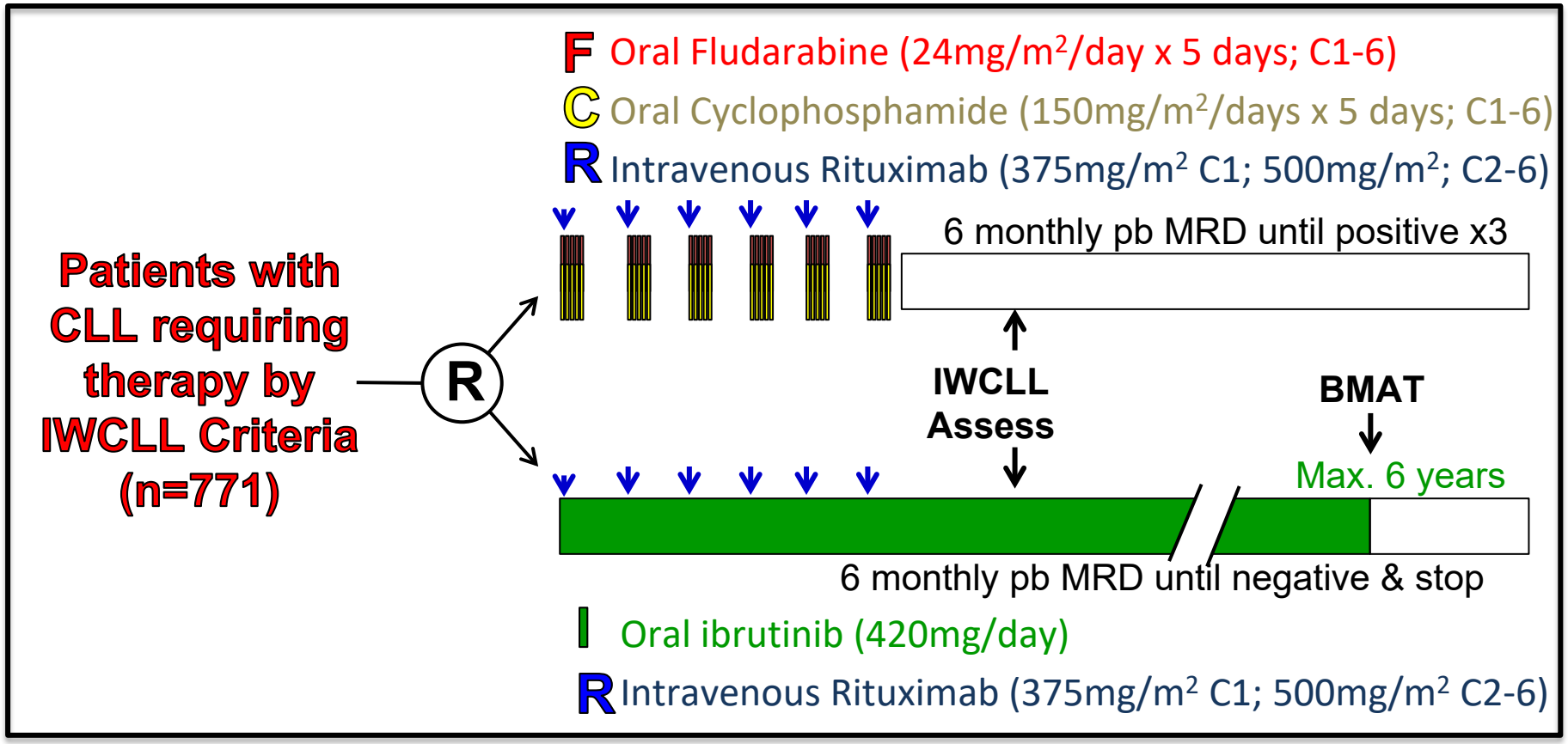
Benefit of ibrutinib regimens over CIT was consistent for all subgroups of patients



- Median PFS was 44 months with BR, NR for ibrutinib arms (HR = 0.36; *P* < .0001)
- Greater benefit of ibrutinib regimens over CIT noted among patients with *TP53* abnormalities than without (*P* < .001)
- With BR, PFS was worse for those with *TP53* abnormalities versus without (HR = 5.32; *P* <.0001)
- In the ibrutinib arms, no significant difference in PFS by presence or absence of *TP53* abnormalities (HR = 0.99; *P* = .98)

1. Woyach JA et al. ASH 2021. Abstract 639.

Ibrutinib Plus Rituximab vs FCR in Previously Untreated CLL: Results of the Phase III NCRI FLAIR Trial



Primary end-point:
To assess whether IR is superior to FCR in terms of PFS

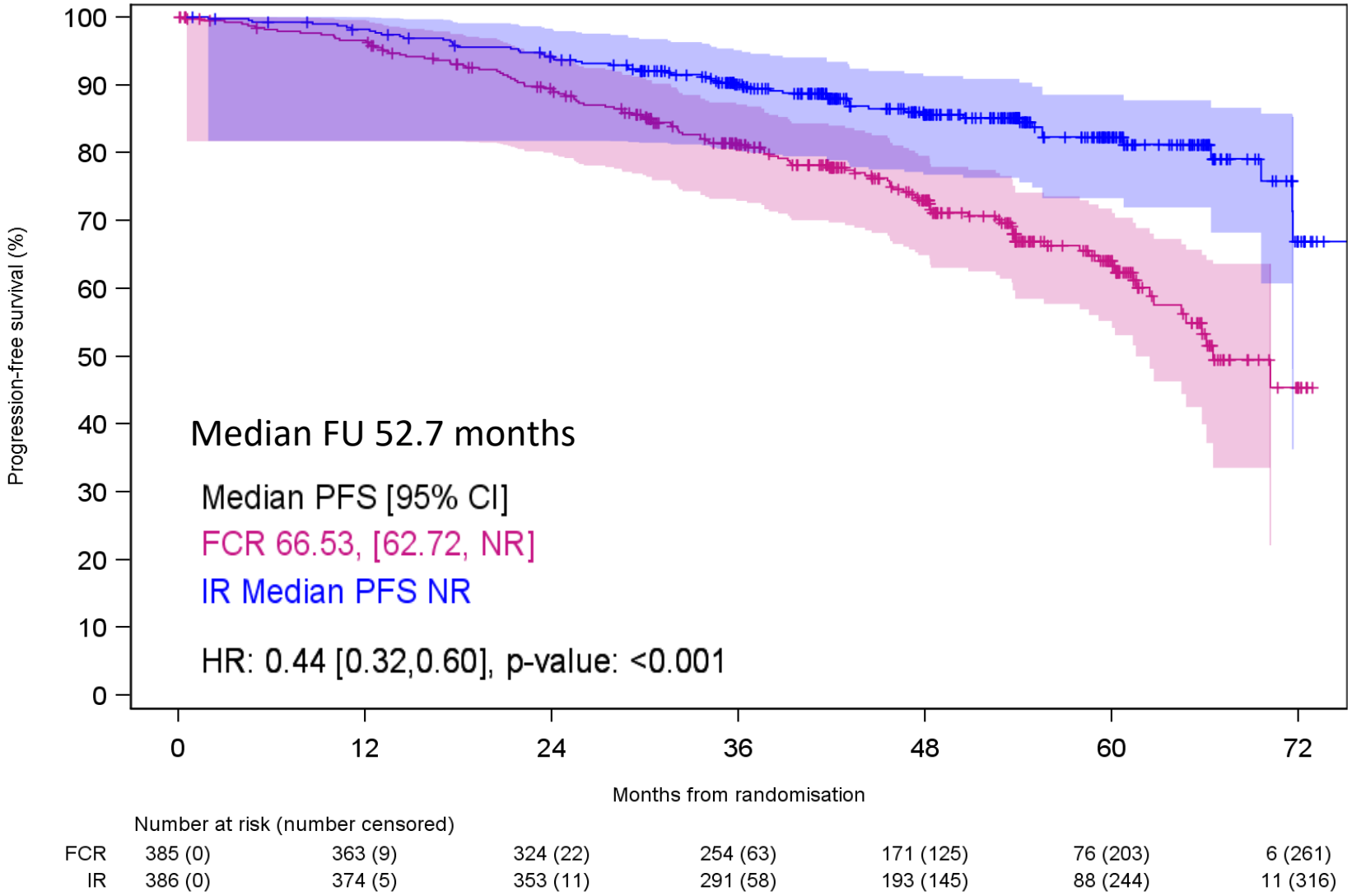
Key secondary end-points:
Overall survival
Response including MRD
Safety and toxicity

Key Inclusion Criteria:
Previously untreated CLL requiring therapy by IWCLL criteria; Considered fit for FCR; ≤75 yrs old

Key Exclusion Criteria:
Prior therapy for CLL; History of Richter's transformation; >20% *TP53* deletion by FISH; Concomitant warfarin (or equivalent) Symptomatic cardiac failure or angina

Hillmen *et al.,* Abstract 642, ASH 2021

FLAIR Primary end-point: Progression Free Survival



Hillmen *et al.,* Abstract 642, ASH 2021

FLAIR IWCLL and MRD Response

IWCLL Response 3-months post treatment with FCR/R

	FCR (n=385)	IR (n=386)
CR	233 (60.5%)	81 (21.0%)
PR	106 (27.6%)	271 (70.2%)
SD/PD/NR	46 (11.9%)	34 (8.8%)

Proportion of participants with MRD negativity* in the bone marrow at 3-months post treatment with FCR/R

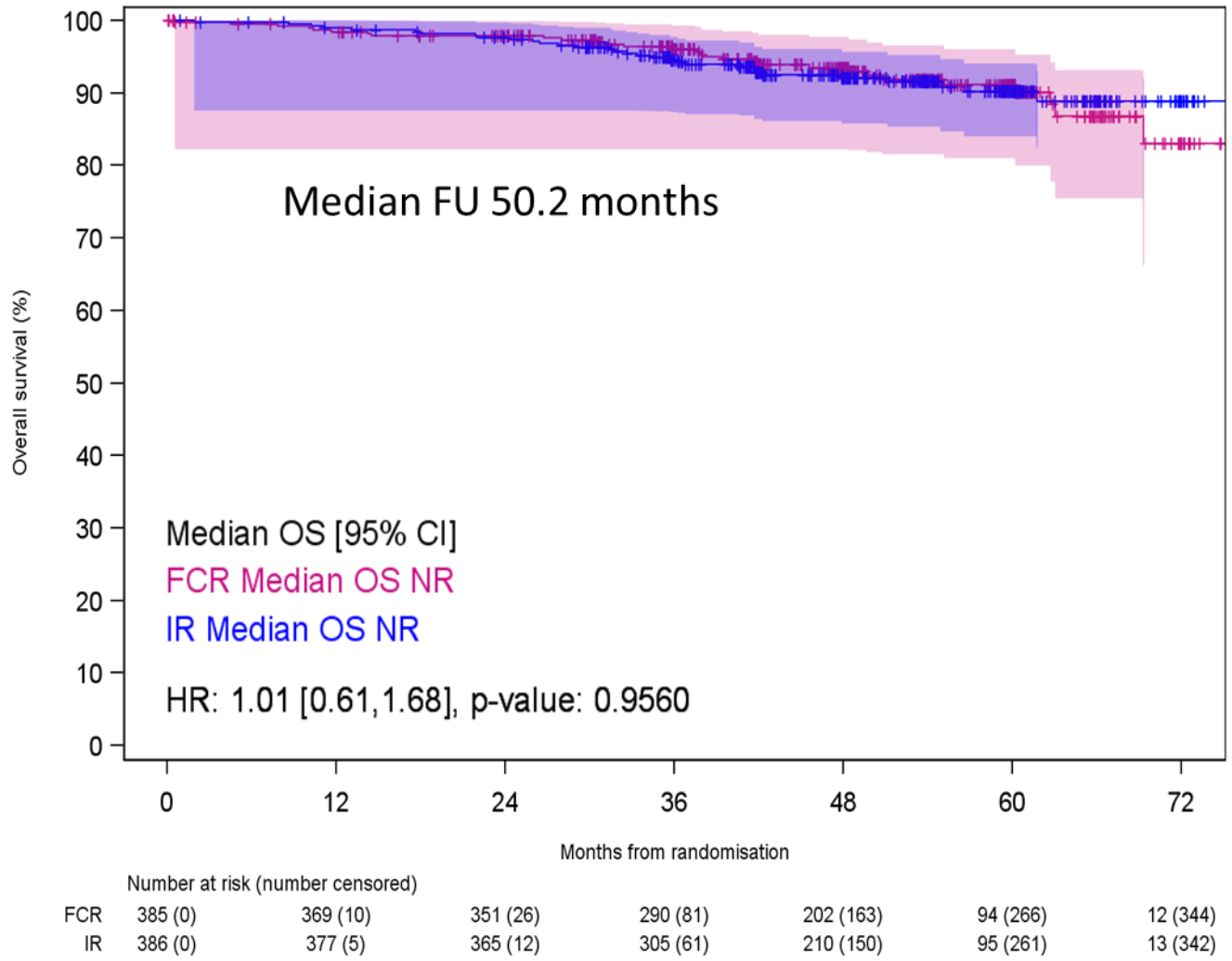
	FCR (n=385)	IR (n=386)
MRD Negative	213 (55.3%)	15 (3.9%)
MRD Positive	140 (36.4%)	357 (92.5%)
N/A	32 (8.3%)	14 (3.6%)

*MRD flow cytometry <1 CLL cell/10,000 (IWCLL criteria)

A greater percentage of participants in the FCR arm became MRD negative in the bone marrow 3-months post-treatment compared to the IR arm (55.3% vs. 3.9%).

Hillmen *et al.,* Abstract 642, ASH 2021

FLAIR Overall survival



	FCR (n=56)	IR (n=19)
Therapy for Richter's transformation or Hodgkin's		
CHOP-R (5) or ABVD (1)	4	2
Therapy for relapsed CLL		
BTKi	38	0
Idelalisib + R	1	1
Venetoclax + R	8	5
CIT (FCR/BR/ChlR)	4	10
Rituximab	1	1
Targeted therapy for CLL	**47/52 (90%)**	**6/17 (35%)**

Overall survival historical comparison

Surviving at:	FCR FLAIR (2014-2018)	FCR ADMIRE/ARCTIC (2009-2012)
12 months	98.4%	97.5%
24 months	97.9%	92.9%
36 months	96.4%	86.8%
48 months	94.5%	84.2%

Hillmen *et al.,* Abstract 642, ASH 2021

Relative risk of sudden unexplained death or cardiac death, accounting for pre-existing HTN/cardiac disorder at trial entry*, by FLAIR arm

*Defined as being on medication for HTN or CV conditions at study entry

	FCR				IR			
	Sudden unexplained death or cardiac death				Sudden unexplained death or cardiac death			
Hypertension or prior history of cardiac disorder (on treatment at trial entry)		No	Yes	Total		No	Yes	Total
	No	288	2	290	No	276	1	277
	Yes	88	0	88	Yes	100	7	107
	Total	376	2	378	Total	376	8	384
	Relative Risk IE* Fisher's Exact P IE*				Relative Risk 18.1, 95%CI (2.3-146) Fisher's Exact P <0.001			

Meta-analysis

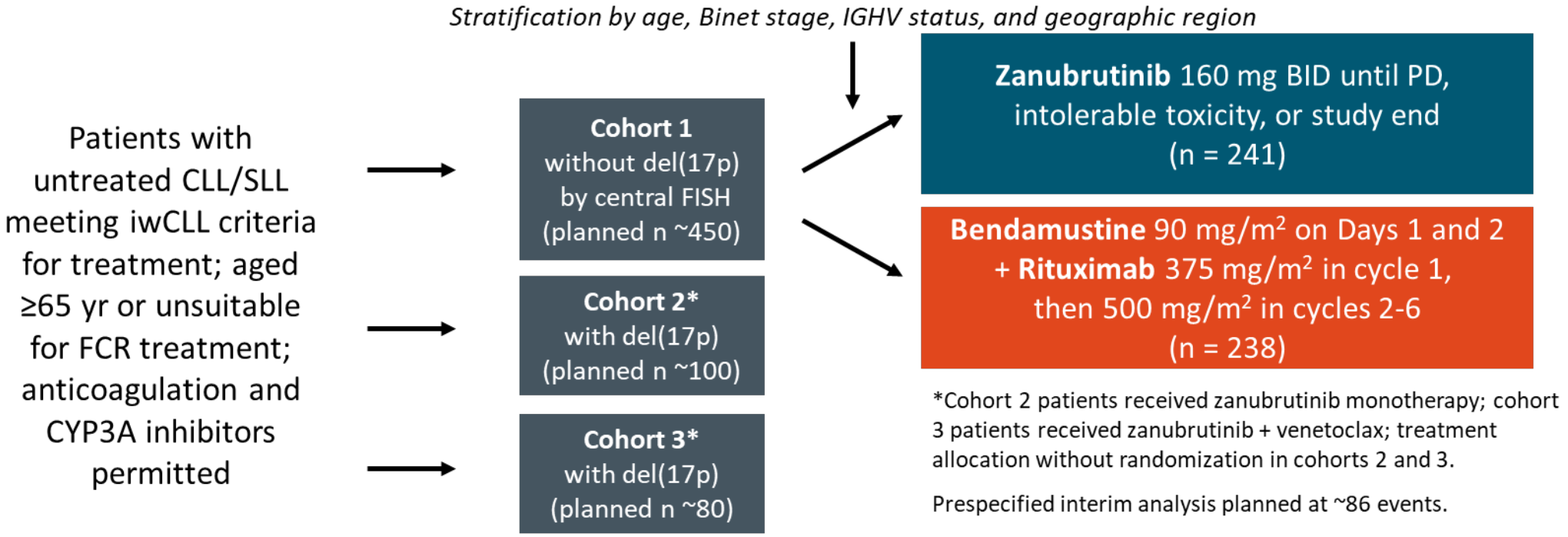
FLAIR is not an outlier for sudden unexplained or cardiac deaths in ibrutinib-containing arms and is consistent with other phase III CLL ibrutinib-containing trials including ALLIANCE, iLLUMINATE, RESONATE, GENUINE and HELIOS.

See poster abstract (#2636) for more details: *'Sudden or Cardiac Deaths on Ibrutinib-Based Therapy Were Associated with a Prior History of Hypertension or Cardiac Disease and the Use of ACE-Inhibitors at Study Entry: Analysis from the Phase III NCRI FLAIR Trial''*, Munir, T.

Hillmen *et al.*, Abstract 642, ASH 2021

SEQUOIA: Study Design

- Multicenter, multicohort, open-label, part-randomized phase III trial



- Primary endpoint (cohort 1): IRC-assessed PFS
- Secondary endpoints (cohort 1): investigator-assessed PFS, ORR, OS, safety

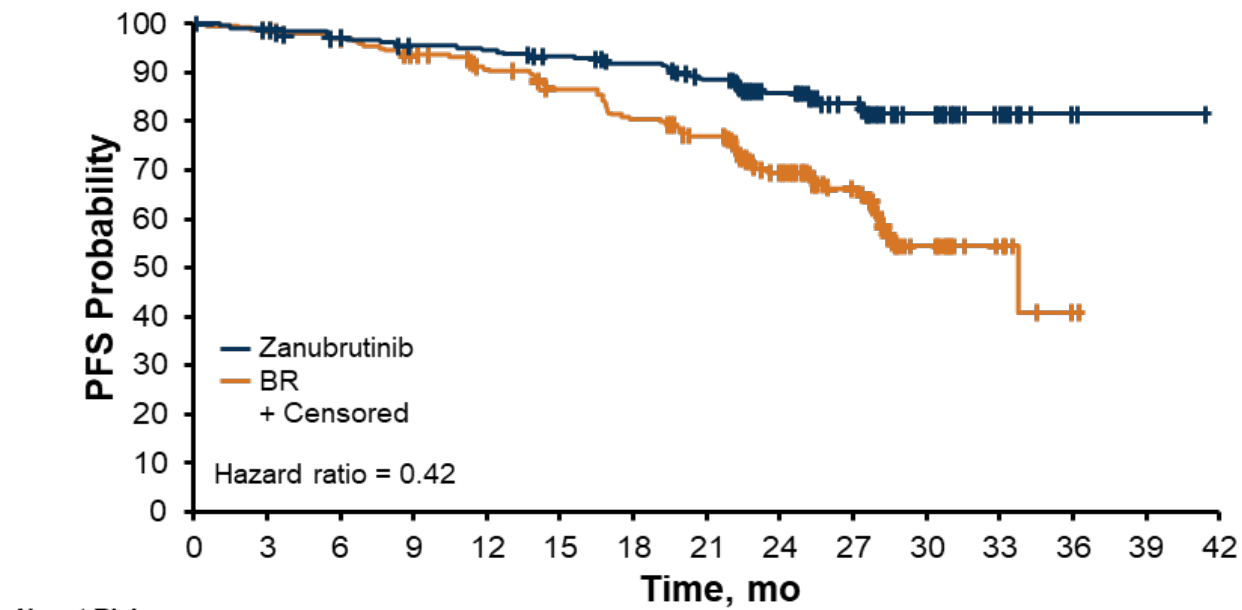
Tam. ASH 2021. Abstr 396.

SEQUOIA: Zanubrutinib Prolongs PFS vs BR in TN CLL

ASH 2021: phase 3 trial of 479 patients with CLL without del(17p); subjects randomized to zanu (n = 241) and BR (n = 238)[1]

After median follow-up of 26.2 mo

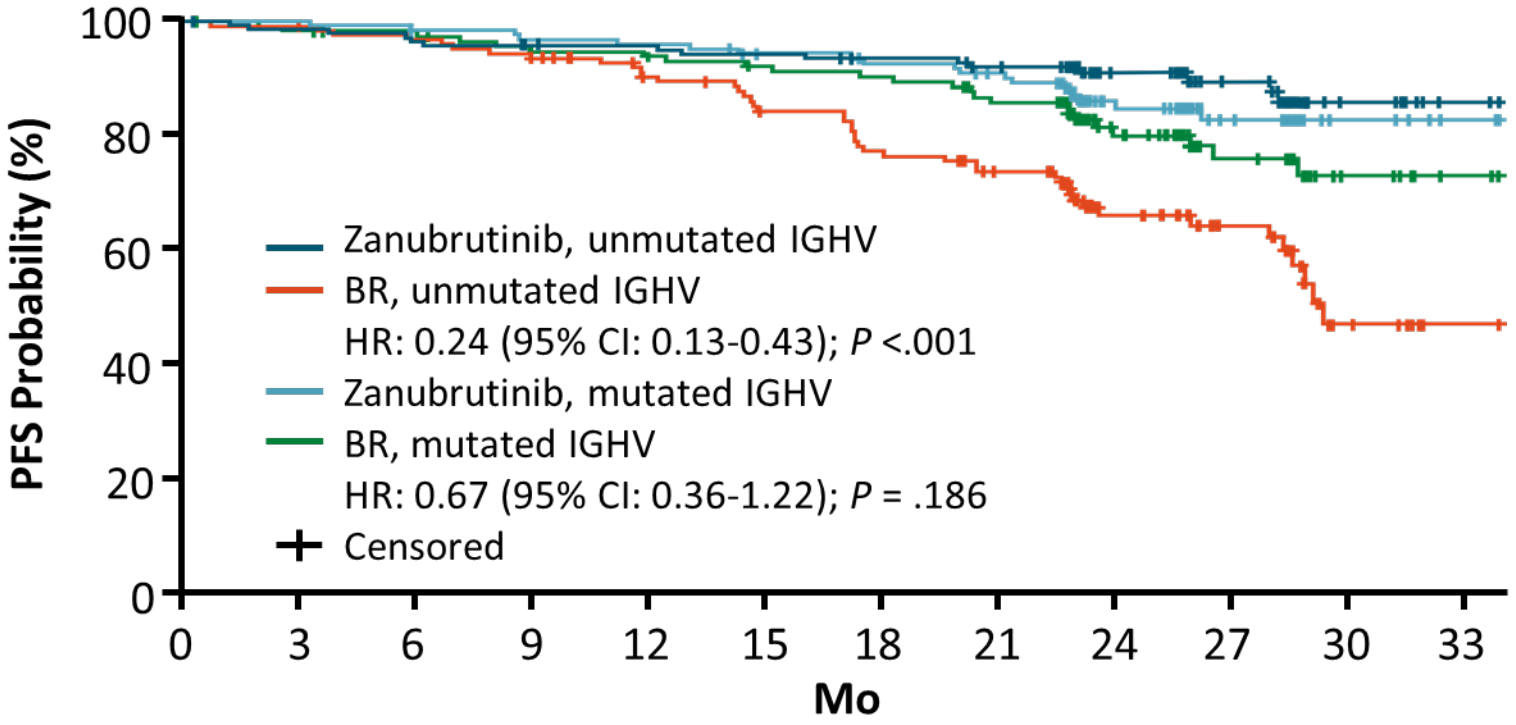
- PFS significantly prolonged with zanu vs BR (HR = 0.42; *P* < .0001)
- Benefit with zanu was observed across subgroups for age, Binet stage, bulky disease, and del(11q)
- **Treatment benefit was also observed for patients with unmutated IGHV (HR = 0.24, 1-sided and 2-sided *P* < .0001),** but not for mutated IGHV



No. at Risk															
Zanubrutinib	241	237	230	224	222	214	208	195	123	79	31	17	2	1	0
BR	238	218	210	200	187	176	164	150	89	54	20	8	1	0	

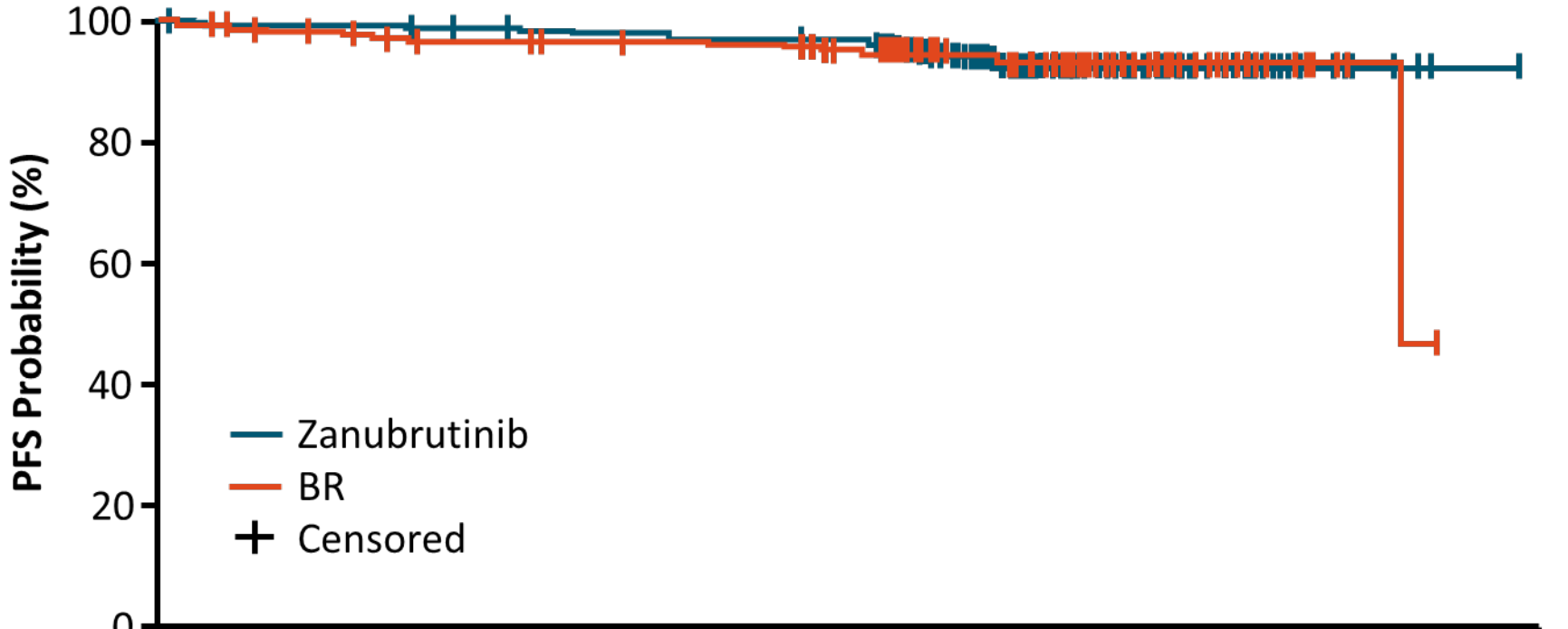
1. Tam C et al. ASH 2021. Abstract 396.

SEQUOIA (Cohort 1): IRC-Assessed PFS by IGHV Status



125	121	117	114	113	112	109	104	68	44	14	6
121	110	106	100	90	82	73	65	39	25	6	1
109	109	106	104	103	97	94	88	53	33	15	10
110	101	98	94	91	88	86	80	47	27	14	7

SEQUOIA (Cohort 1): OS



Zanubrutinib	241	237	230	235	233	231	230	228	179	94	48	22	6	1	0
BR	238	218	217	212	210	209	208	198	141	84	41	16	4	0	

- Median follow-up: 26.2 mo

SEQUOIA (Cohort 1): Summary of AEs

AEs, n (%)	Zanubrutinib (n = 240)*	Bendamustine + Rituximab (n = 227)*
Any AE	224 (93.3)	218 (96.0)
Grade ≥3 AE	126 (52.5)	181 (79.7)
Serious AE	88 (36.7)	113 (49.8)
Fatal AE	11 (4.6)	11 (4.8)
AE leading to dose reduction	18 (7.5)	84 (37.4)
AE leading to dose interruption or delay	111 (46.3)	154 (67.8)
AE leading to discontinuation	20 (8.3)	31 (13.7)

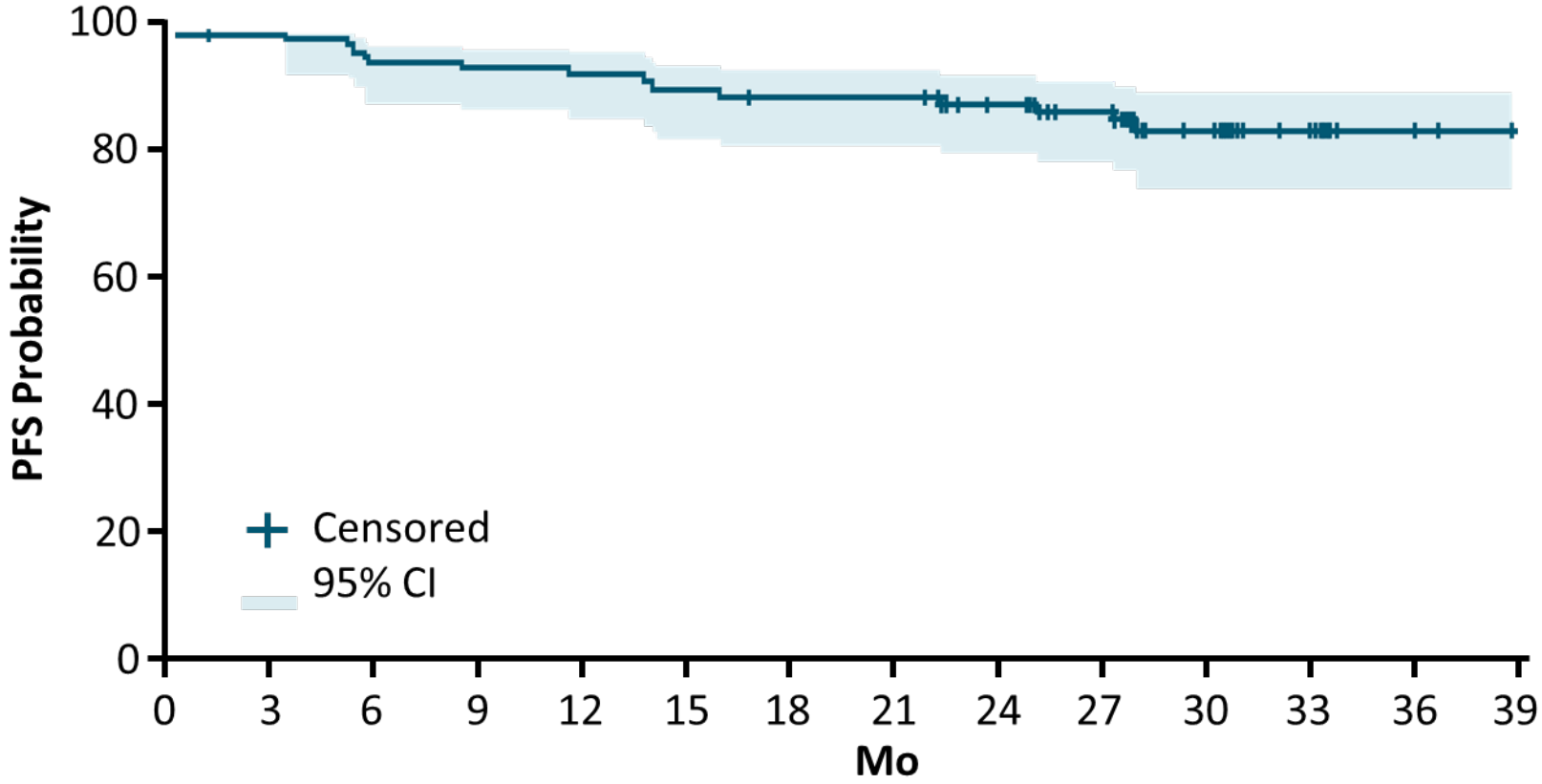
*Safety was assessed in patients who received ≥1 treatment dose; 1 patient in the zanubrutinib arm and 11 patients in the combination arm did not receive treatment.

SEQUOIA (Cohort 1): AEs of Interest

AEs, n (%)	Zanubrutinib (n = 240)*		Bendamustine + Rituximab (n = 227)*	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Anemia	11 (4.6)	1 (0.4)	44 (19.4)	4 (1.8)
Neutropenia	38 (15.8)	28 (11.7)	129 (56.8)	116 (51.1)
Thrombocytopenia	11 (4.6)	5 (2.1)	40 (17.6)	18 (7.9)
Arthralgia	32 (13.3)	2 (0.8)	20 (8.8)	1 (0.4)
Atrial fibrillation	8 (3.3)	1 (0.4)	6 (2.6)	3 (1.3)
Bleeding	108 (45.0)	9 (3.8)	25 (11.0)	4 (1.8)
▪ Major bleeding	12 (5.0)	9 (3.8)	4 (1.8)	4 (1.8)
Diarrhea	33 (13.8)	2 (0.8)	31 (13.7)	5 (2.2)
Hypertension	34 (14.2)	15 (6.3)	24 (10.6)	11 (4.8)
Infections	149 (62.1)	39 (16.3)	127 (55.9)	43 (18.9)
Myalgia	9 (3.8)	0 (0.0)	3 (1.3)	0 (0.0)
Other cancers	31 (12.9)	17 (7.1)	20 (8.8)	7 (3.1)
▪ Dermatologic	16 (6.7)	2 (0.8)	10 (4.4)	2 (0.9)

*Safety was assessed in patients who received ≥1 treatment dose; 1 patient in the zanubrutinib arm and 11 patients in the combination arm did not receive treatment.

SEQUOIA (Cohort 2): IRC-Assessed PFS in Patients With del(17p)



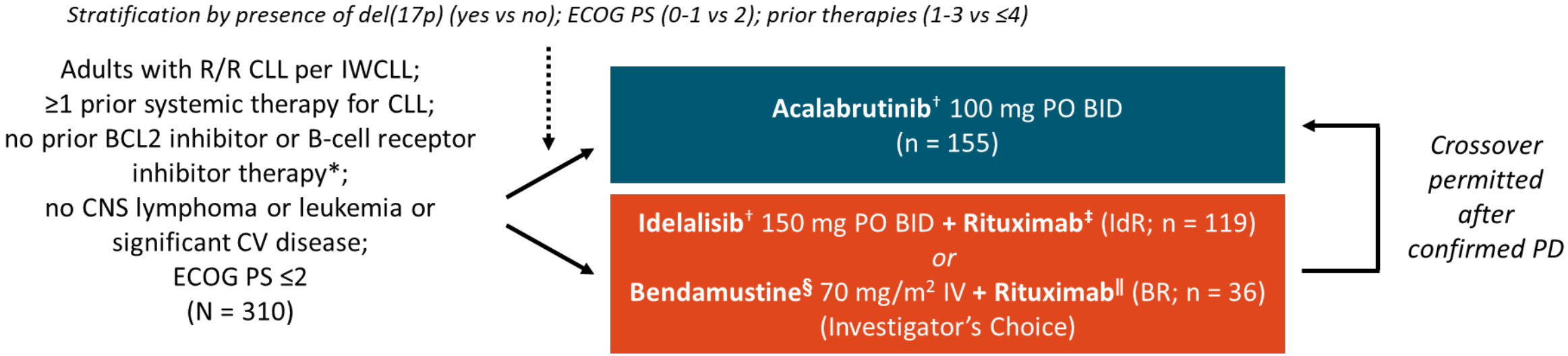
Zanubrutinib	110	109	104	103	102	98	96	96	86	74	37	19	2	0

ASH abstracts highlight continued efficacy of BTKis in phase III relapsed CLL study

- **ASCEND study**

ASCEND: Study Design

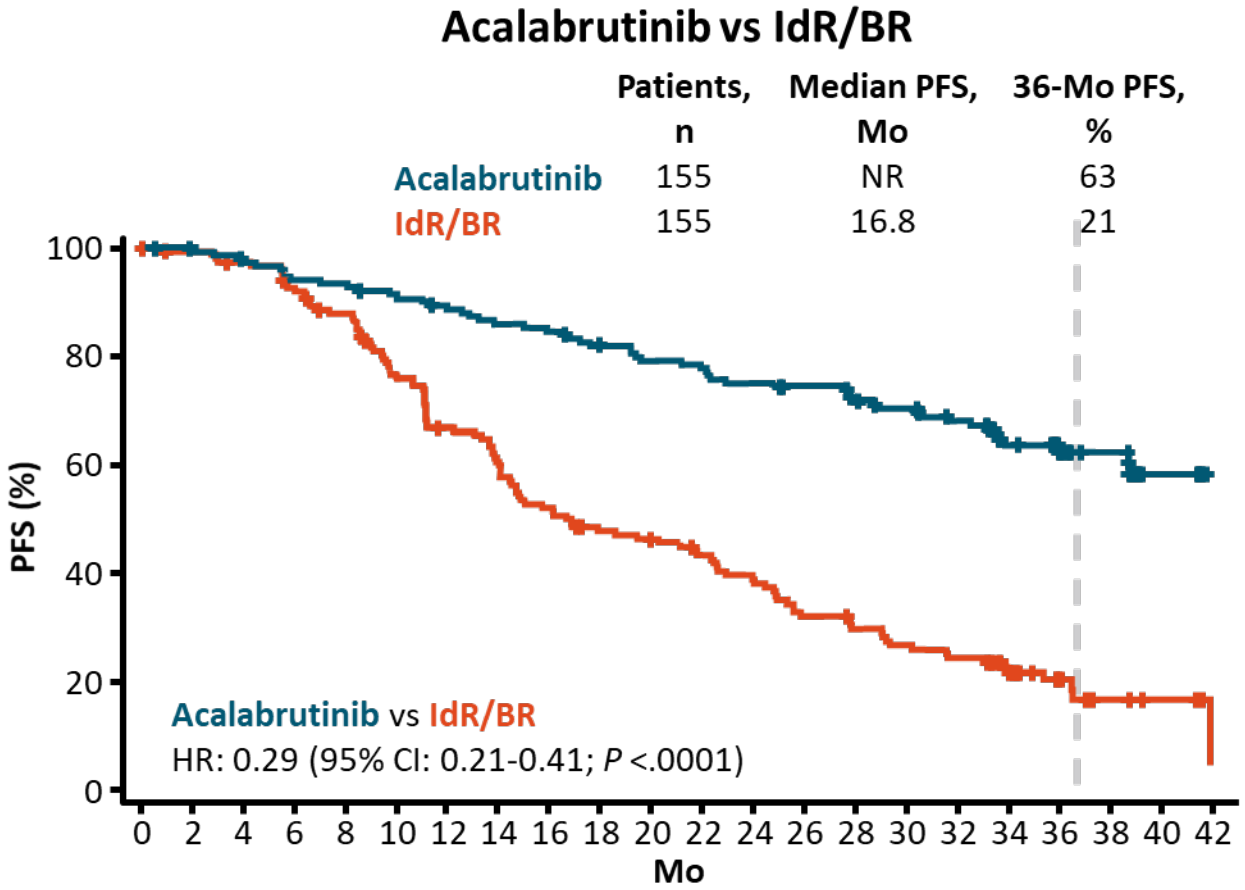
- Global, multicenter, randomized, open-label phase III trial (data cutoff: October 26, 2020)

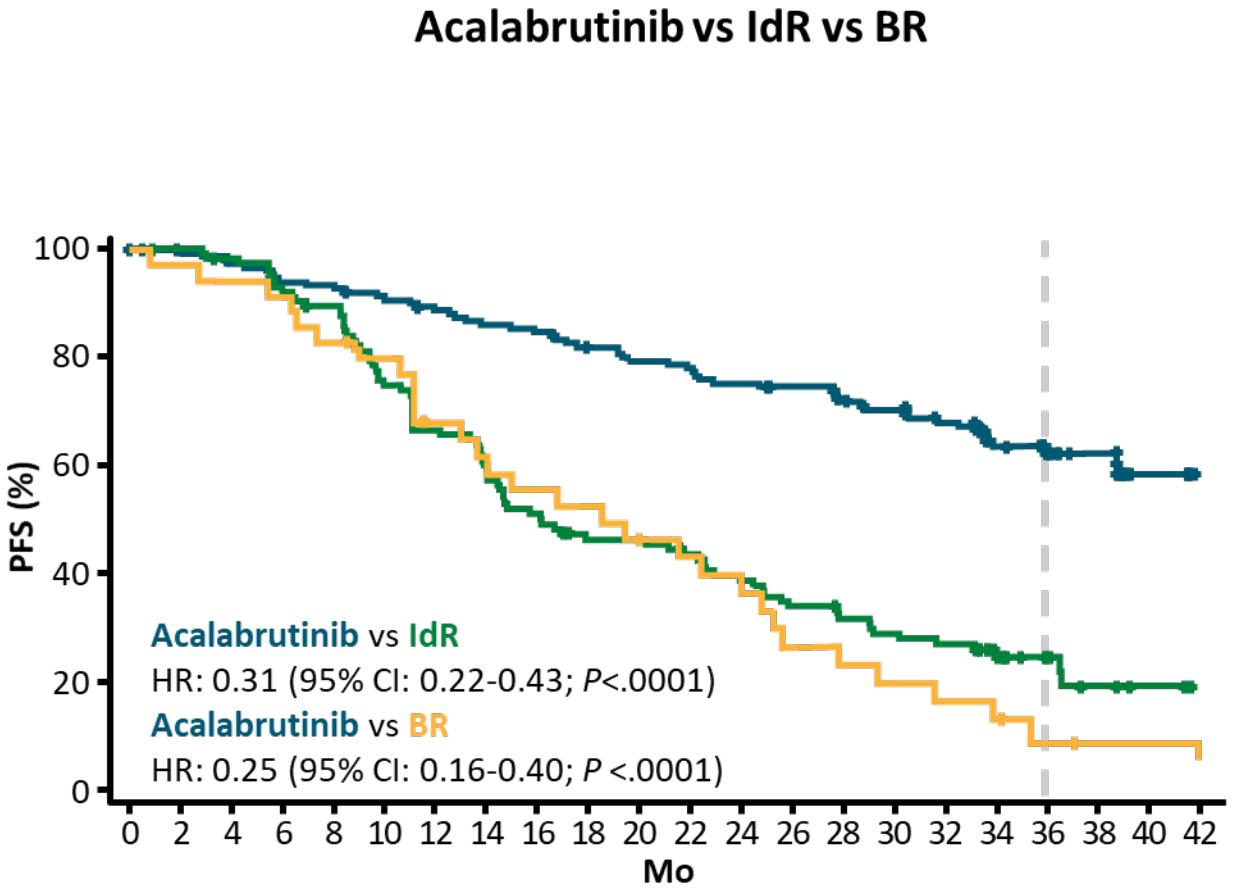


*Prior bendamustine allowed if investigator choice of control treatment was IdR, and if prior response to bendamustine was >24 mo. †Dosed until PD or unacceptable toxicity. ‡Rituximab 375 mg/m^2 IV on Day 1 of cycle 1, then 500 mg/m^2 every 2 wk for 4 infusions, followed by every 4 wk for 3 infusions. §Bendamustine on Days 1 and 2 of cycles 1-6. ‖Rituximab 375 mg/m^2 IV on Day 1 of cycle 1, then 500 mg/m^2 on Day 1 of cycles 2-6.

- Primary endpoint: PFS
- Secondary endpoints: ORR, OS, safety

ASCEND 3-Yr Update: Investigator-Assessed PFS





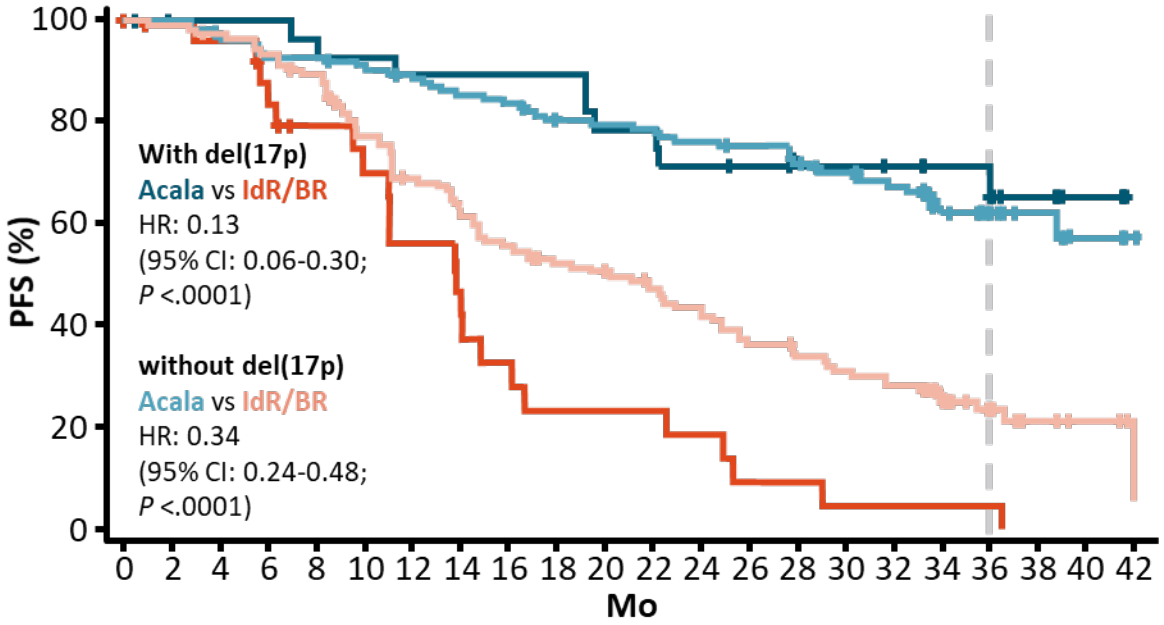
- Median time on study: acalabrutinib, 36.0 mo; IdR/BR, 35.2 mo

Jurczak. ASH 2021. Abstr 393.

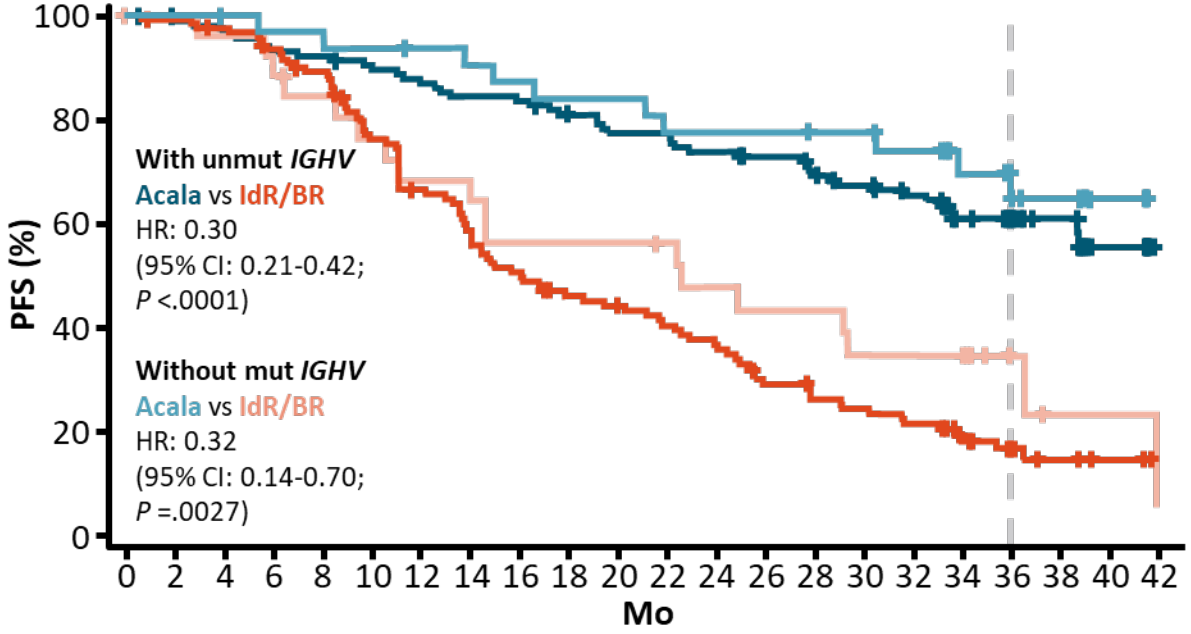
ASCEND 3-Yr Update: Investigator-Assessed PFS in Patients With High-Risk Features

PFS by del(17p)

	Patients, n	Median PFS, Mo	36-Mo PFS, %
Acalabrutinib with del(17p)	28	NR	66
Acalabrutinib without del(17p)	127	NR	62
IdR/BR with del(17p)	26	13.8	5
IdR/BR without del(17p)	129	20.3	24



PFS by *IGHV*



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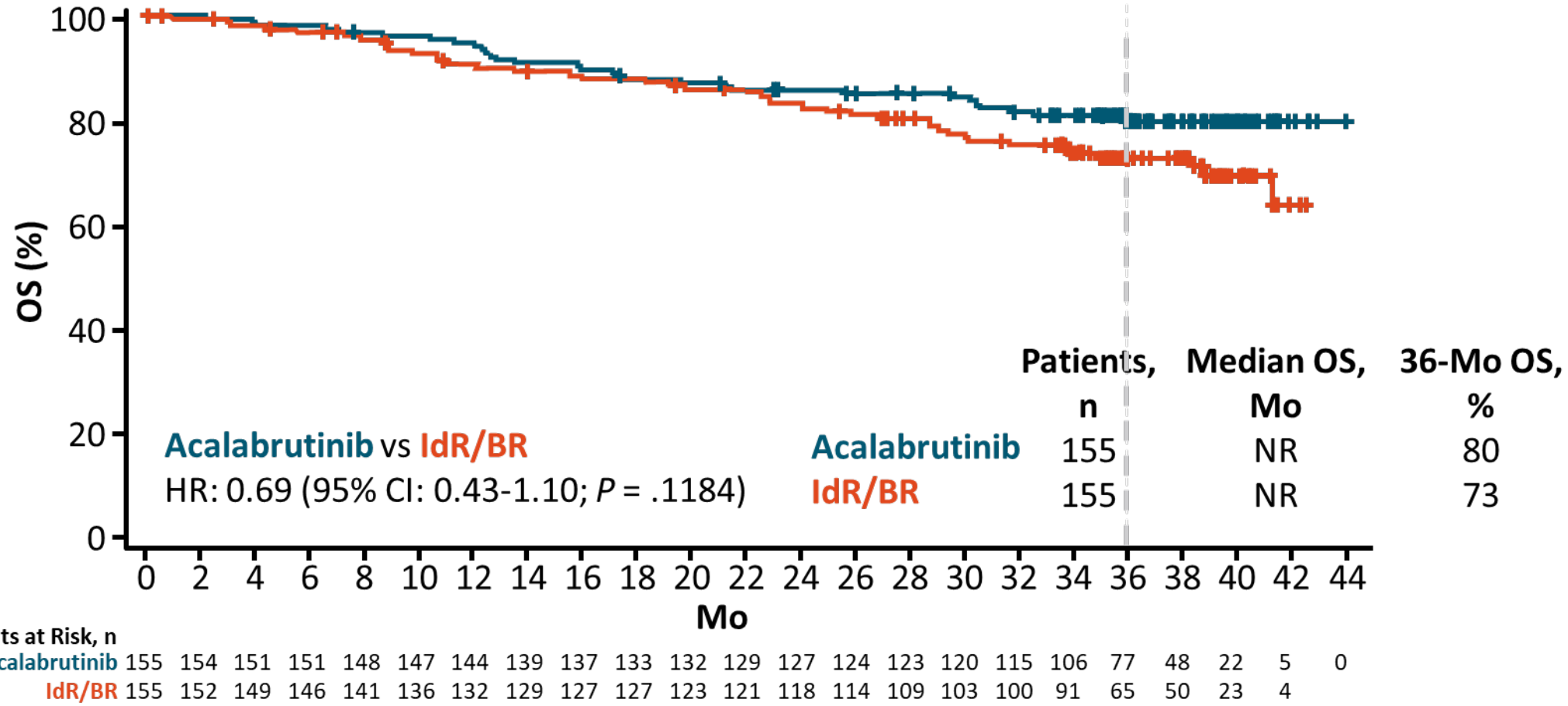
ASCEND 3-Yr Update: OS



- 49% (76/155) of patients receiving IdR/BR crossed over to acalabrutinib

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ASCEND 3-Yr Update: Safety Summary

AEs, n (%)	Acalabrutinib (n = 154)	IdR (n = 118)	BR (n = 35)
Any AEs (all grades)	148 (96)	117 (99)	28 (80)
▪ Grade ≥3	96 (62)	108 (92)	17 (49)
▪ Grade 5	14 (9)	8 (7)	2 (6)
Serious AEs*	59 (38)	74 (63)	9 (26)
Treatment-related AEs	111 (72)	113 (96)	24 (69)
AEs leading to dose reduction	7 (5)	15 (13)	5 (14)
AEs leading to dose withholding	64 (42)	79 (67)	7 (20)
AEs leading to dose d/c	32 (21)	77 (65)	6 (17)
Death within 30 days of last dose	13 (8)[†]	5 (4)[‡]	1 (3)[§]

*Serious AEs reported in ≥5% of patients in any group included: pneumonia (acalabrutinib, 8%; IdR, 9%; BR, 3%); diarrhea (acalabrutinib, 1%; IdR, 15%); pyrexia (acalabrutinib, 2%; IdR, 7%; BR, 3%). [†]Primary causes of death for acalabrutinib: n = 10, AE (n = 1 each, respiratory failure, brain neoplasm, cardiorespiratory arrest, cardiopulmonary failure, pneumonia, neuroendocrine carcinoma, sepsis, bronchitis, cachexia, and neutropenic sepsis); n = 1 each PD, Richter transformation, and unknown. [‡]Primary cause of death for IdR: n = 5, AE (n = 1 each, cardiopulmonary failure, myocardial infarction, pneumonitis, sepsis, and interstitial lung disease). [§]Primary cause of death for BR: n = 1, AE (acute cardiac failure).

Jurczak. ASH 2021. Abstr 393.

ASCEND 3-Yr Update: AEs of Clinical Interest

AEs of Clinical Interest, n (%)	Acalabrutinib (n = 154)		IdR (n = 118)		BR (n = 35)	
	Any	Grade ≥3	Any	Grade ≥3	Any	Grade ≥3
Atrial fibrillation	10 (7)	2 (1)	4 (3)	1 (1)	1 (3)	1 (3)
Hemorrhage	46 (30)	4 (3)	10 (9)	3 (3)	2 (6)	1 (3)
▪ Major hemorrhage*	5 (3)	4 (3)†	3 (3)‡	3 (3)‡	1 (3)	1 (3)
Hypertension	11 (7)	7 (5)	6 (5)	1 (1)	0	0
Infections	100 (65)	38 (25)	83 (70)	37 (31)	17 (49)	4 (11)
Second primary malignancies excluding non-melanoma skin carcinomas	11 (7)	8 (5)	2 (2)	1 (1)	2 (6)	2 (6)
Tumor lysis syndrome	1 (1)	1 (1)	1 (1)	1 (1)	0	0

*Major hemorrhage: any serious or grade ≥3 hemorrhage, or CNS hemorrhage of any grade. †Includes n = 1 each of grade 4 GI hemorrhage, grade 3 GI hemorrhage, grade 4 ITP , and grade 3 intestinal hemorrhage. ‡Includes n = 1 each of grade 3 GI hemorrhage, grade 3 and grade 4 ITP, and grade 3 hematuria.

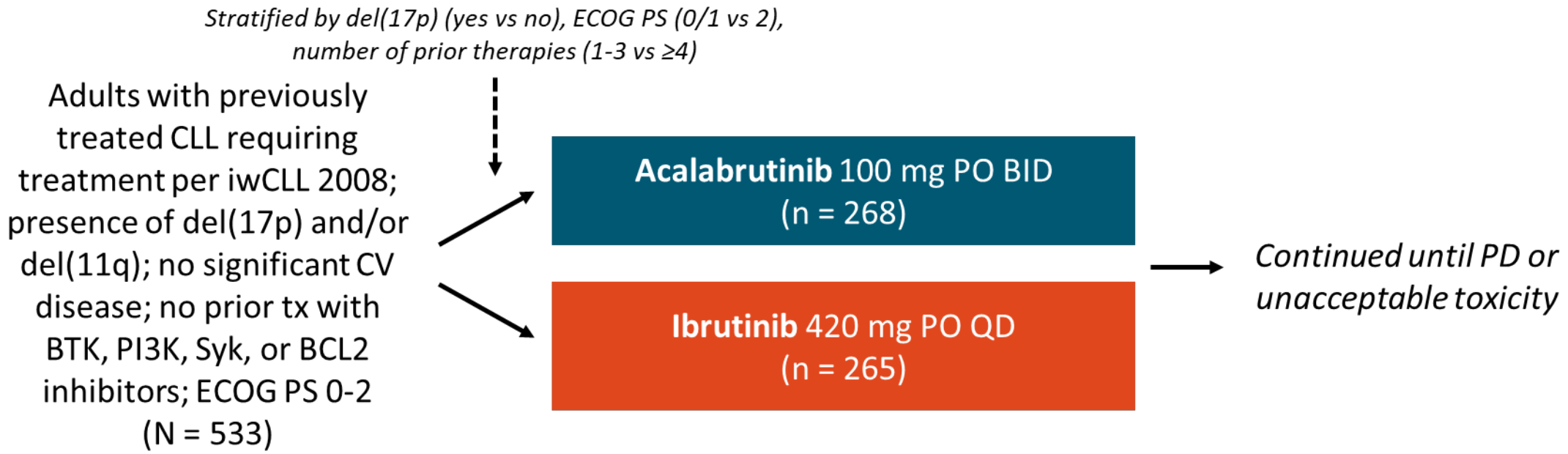
Jurczak. ASH 2021. Abstr 393.

HEAD TO HEAD COMPARISONS OF BTKis in RR CLL

- ELEVATE-RR
- ALPINE

ELEVATE-RR: Study Design

- Randomized, open-label phase III noninferiority trial



- Primary endpoint: noninferiority of IRC-assessed PFS
- Secondary endpoints: any-grade atrial fibrillation/flutter, grade ≥3 infection, Richter transformation, OS
- Median follow-up: 40.9 mo

Seymour. ASH 2021. Abstr 3721.

ELEVATE-RR AEs: Selected Common AEs Incidence, Exposure-Adjusted Incidence, and Time With Event

Common AEs (Incidence ≥10%)	Incidence, %				Exposure-Adjusted Incidence*				Exposure-Adjusted Time With Event†			
	Any Grade		Grade ≥3		Any Grade		Grade ≥3		Any Grade		Grade ≥3	
	Acala	Ibr	Acala	Ibr	Acala	Ibr	Acala	Ibr	Acala	Ibr	Acala	Ibr
Diarrhea	35	46‡	1	5‡	1.9	2.8	<0.1	0.2	6.7	9.6	<0.1	0.1
Headache	35‡	20	2‡	0	1.8	1.1	<0.1	0	7.8	5.4	<0.1	0
Cough	29‡	21	1	<1	1.3	1.1	<0.1	<0.1	5.6	4.9	<0.1	<0.1
Fatigue	20	17	3‡	0	0.9	0.9	0.1	0	7.4	7.0	0.6	0
Arthralgia	16	23‡	0	1	0.6	1.3	0	<0.1	7.5	10.4	0	<0.1
Back pain	8	13‡	0	1	0.3	0.5	0	<0.1	1.9	3.2	0	0.1
Muscle spasms	6	13‡	0	1	0.2	0.7	0	<0.1	0.8	10.0	0	0.1
Dyspepsia	4	12‡	0	0	0.1	0.5	0	0	1.0	2.4	0	0

*Reported as events per 100 person-mo. †Reported as mo with event per 100 person-mo. ‡2-sided *P* <.05 without multiplicity adjustment.

- Incidence of diarrhea, arthralgia, back pain, muscle spasm, and dyspepsia statistically higher with Ibr vs Acala
- Incidence of headache and cough statistically higher with Acala vs Ibr

Seymour. ASH 2021. Abstr 3721.

ELEVATE-RR AEs: Events of Clinical Interest Incidence, Exposure-Adjusted Incidence, and Time With Event

Event of Clinical Interest	Incidence, %				Exposure-Adjusted Incidence*				Exposure-Adjusted Time With Event†			
	Any Grade		Grade ≥3		Any Grade		Grade ≥3		Any Grade		Grade ≥3	
	Acala	Ibr	Acala	Ibr	Acala	Ibr	Acala	Ibr	Acala	Ibr	Acala	Ibr
Cardiac events	24	30	9	10	1.2	1.9	0.4	0.5	7.1	13.0	0.4	0.2
▪ Afib/flutter	9	16‡	5	4	0.4	0.7	0.2	0.1	1.3	3.8	0.3	0.1
HTN	9	23‡	4	9‡	0.4	1.2	0.1	0.4	4.1	15.0	1.6	4.0
Bleeding events	38	51‡	4	5	2.4	3.8	0.1	0.2	13.7	24.6	0.1	0.1
▪ Major events	5	5	4	5	0.2	0.2	0.1	0.2	0.1	0.3	0.1	0.1
Infections	78	81	31	30	8.9	10.4	1.6	2.0	14.6	15.6	1.5	1.1

*Reported as events per 100 person-mo. †Reported as mo with event per 100 person-mo. ‡2-sided *P* <.05 without multiplicity adjustment.

- Incidence of afib/flutter, HTN, and bleeding statistically higher with Ibr vs Acala
- Exposure-adjusted time with these events was also higher with Ibr vs Acala

Seymour. ASH 2021. Abstr 3721.

ELEVATE-RR AEs: Incidence of Afib/Flutter and HTN by Subgroup

Incidence by Subgroup, %	Any-Grade Afib/Flutter		Any-Grade HTN	
	Acala (n = 266)	Ibr (n = 263)	Acala (n = 266)	Ibr (n = 263)
Age				
▪ <65 yr	3.2	7.4	8.9	23.1
▪ ≥65 yr	14.8	23.2	9.9	23.2
Prior lines of therapy				
▪ 1-3	9.7	15.7	10.1	24.6
▪ ≥4	7.1	18.5	3.6	11.1
No prior history of event	6.2	14.9	6.6	22.8

- The risk of new-onset afib/flutter and HTN was markedly reduced with Acala vs Ibr in patients with no prior history of such events
  - Afib/flutter: HR: 0.37 (95% CI: 0.20-0.67)
  - HTN: HR: 0.23 (95% CI: 0.11-0.48)

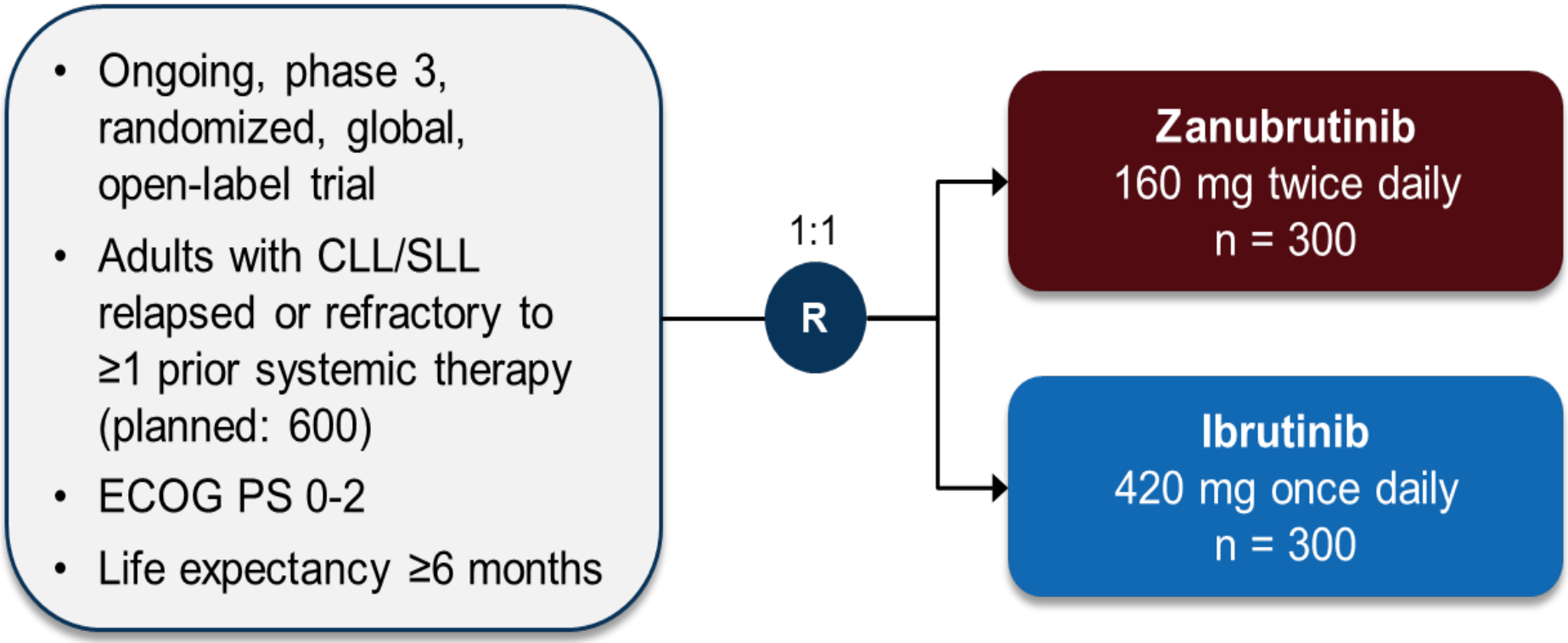
Seymour. ASH 2021. Abstr 3721.

ELEVATE-RR AEs: Cumulative Incidence of Afib, HTN, and Bleeding

Cumulative Incidence	Any-Grade Afib/Flutter		Any-Grade HTN		Any-Grade Bleeding	
	Acala (n = 266)	Ibr (n = 263)	Acala (n = 266)	Ibr (n = 263)	Acala (n = 266)	Ibr (n = 263)
Treatment duration, mo						
▪ 6	2.0	5.5	4.6	11.6	29.4	42.1
▪ 12	3.2	7.7	6.3	16.3	32.0	45.4
▪ 18	4.1	9.7	7.7	20.0	34.2	49.1
▪ 24	5.1	11.8	8.2	22.9	37.7	51.0
▪ 30	5.6	15.4	9.3	25.6	38.8	53.8
▪ 36	8.5	16.0	9.8	28.0	40.7	55.3

Seymour. ASH 2021. Abstr 3721.

ALPINE Trial: Zanubrutinib vs Ibrutinib in R/R CLL/SLL[1]

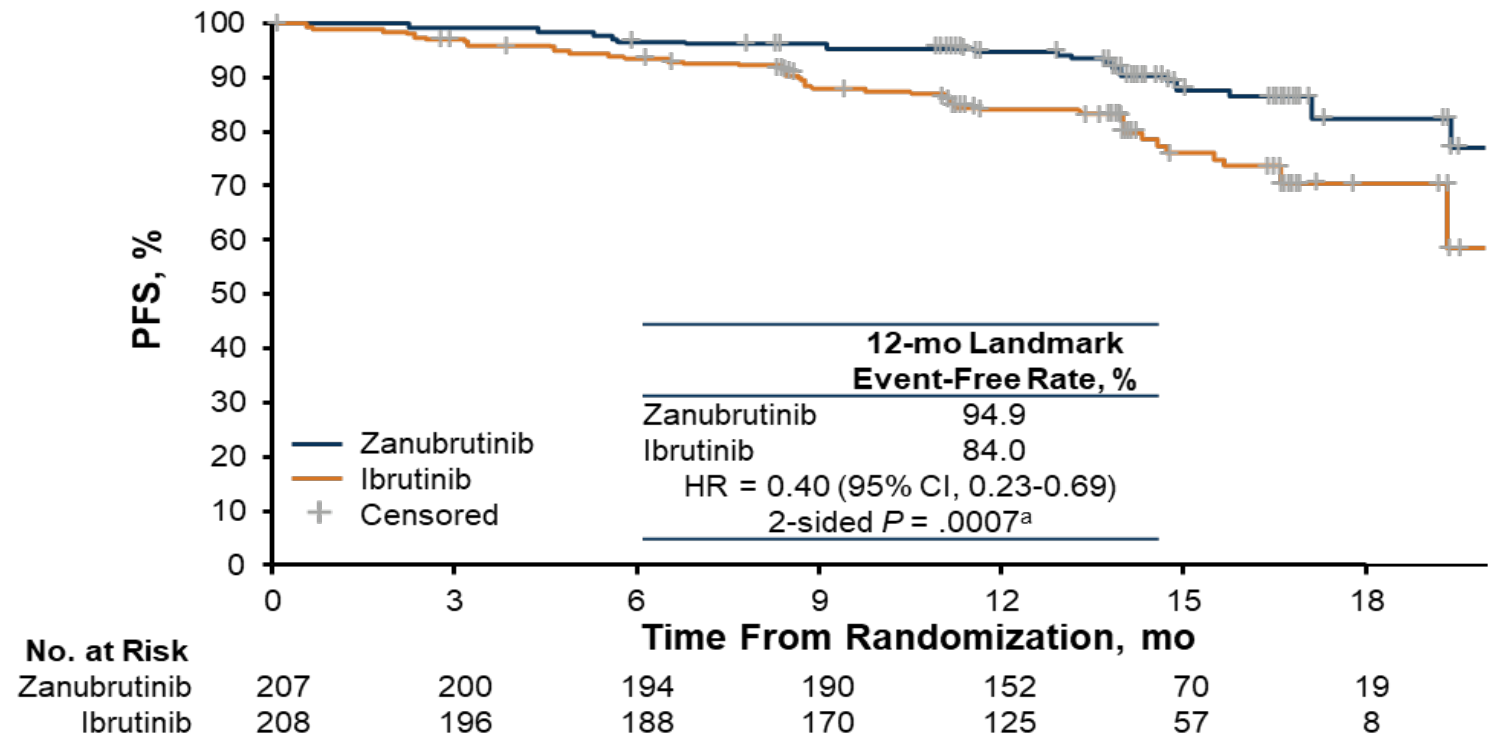


- **Primary endpoint:** ORR (up to 36 months)
- **Secondary endpoints:** PFS, DOR, OS, TTF, and safety

1. Hillmen P et al. EHA 2021. Abstract LB1900.

ALPINE: Improved ORR and PFS With Zanubrutinib vs Ibrutinib in R/R CLL/SLL[1]

- ORR improved with zanubrutinib: 78.3 vs 62.5 for ibrutinib
- Superiority 2-sided *P* = .0006 compared with prespecified alpha of .0099

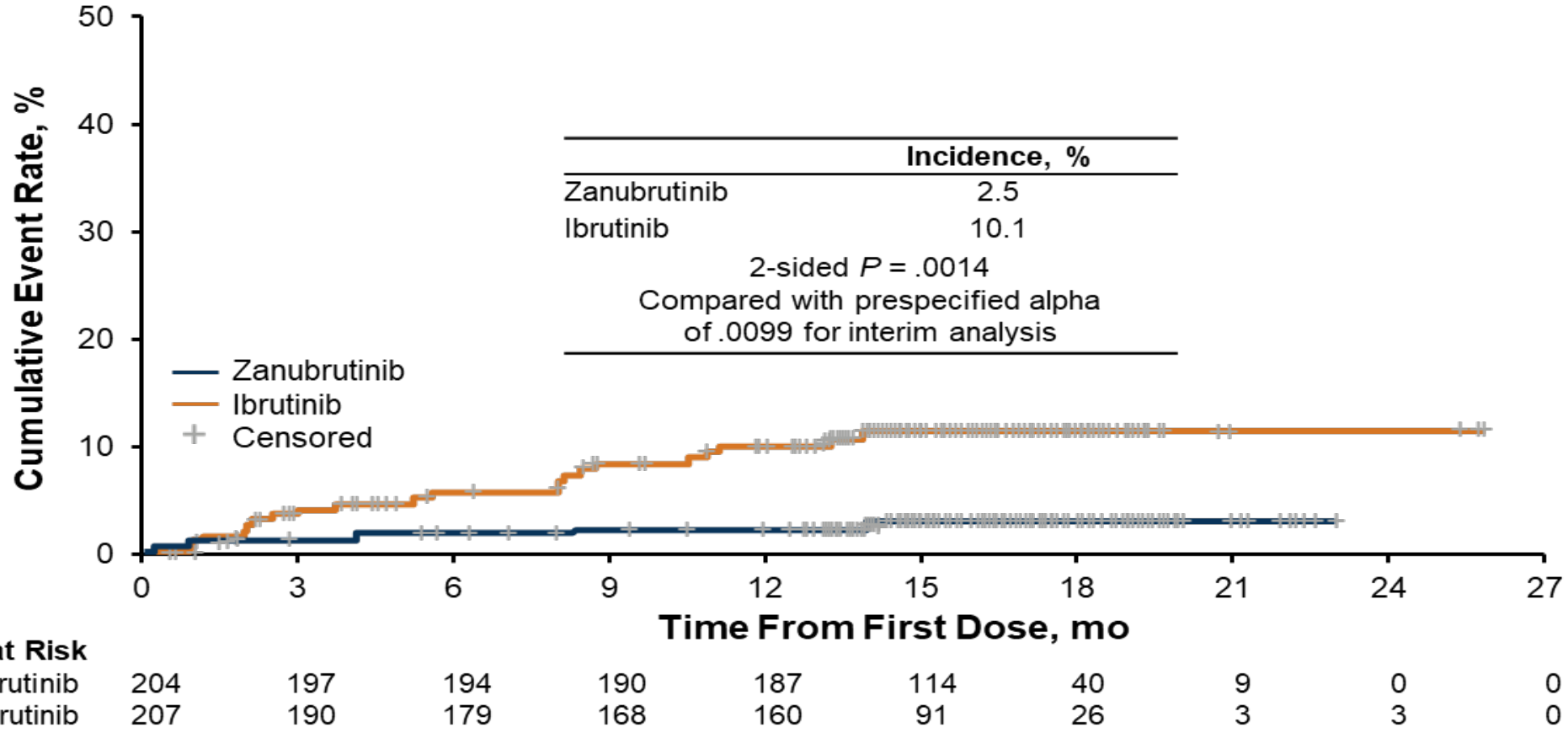


Median PFS follow-up was 14 months for both zanubrutinib and ibrutinib arms

[a] Not a prespecified analysis; formal analysis of PFS will be based on all patients when the target number of events is reached.

1. Hillmen P et al. EHA 2021. Abstract LB1900.

ALPINE: Safety Analysis Showed Lower Rates of AF/Flutter With Zanubrutinib[1]



1. Hillmen P et al. EHA 2021. Abstract LB1900.

Conclusions:

- Long-term follow-up of ongoing BTKi studies continue to yield excellent PFS outcomes in CLL patients both in upfront and relapsed setting and in high risk patients (ie del17p/p53, unmutated IGHV)
- Adverse events of interest with BTKis: CV, HTN, bleeding, infections need to be respected and managed appropriately
- Follow-up of ongoing randomized clinical trial data will provide a more direct comparison to assess for advantages in the toxicity profile of one BTKi agent over another


THANK YOU!