

IN PURSUIT OF *YOUR CURE*®

# Mastering the management of BTK and BCL-2 inhibitors in CLL

## The fine-tuning no one tells you about

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@SylvesterCancer

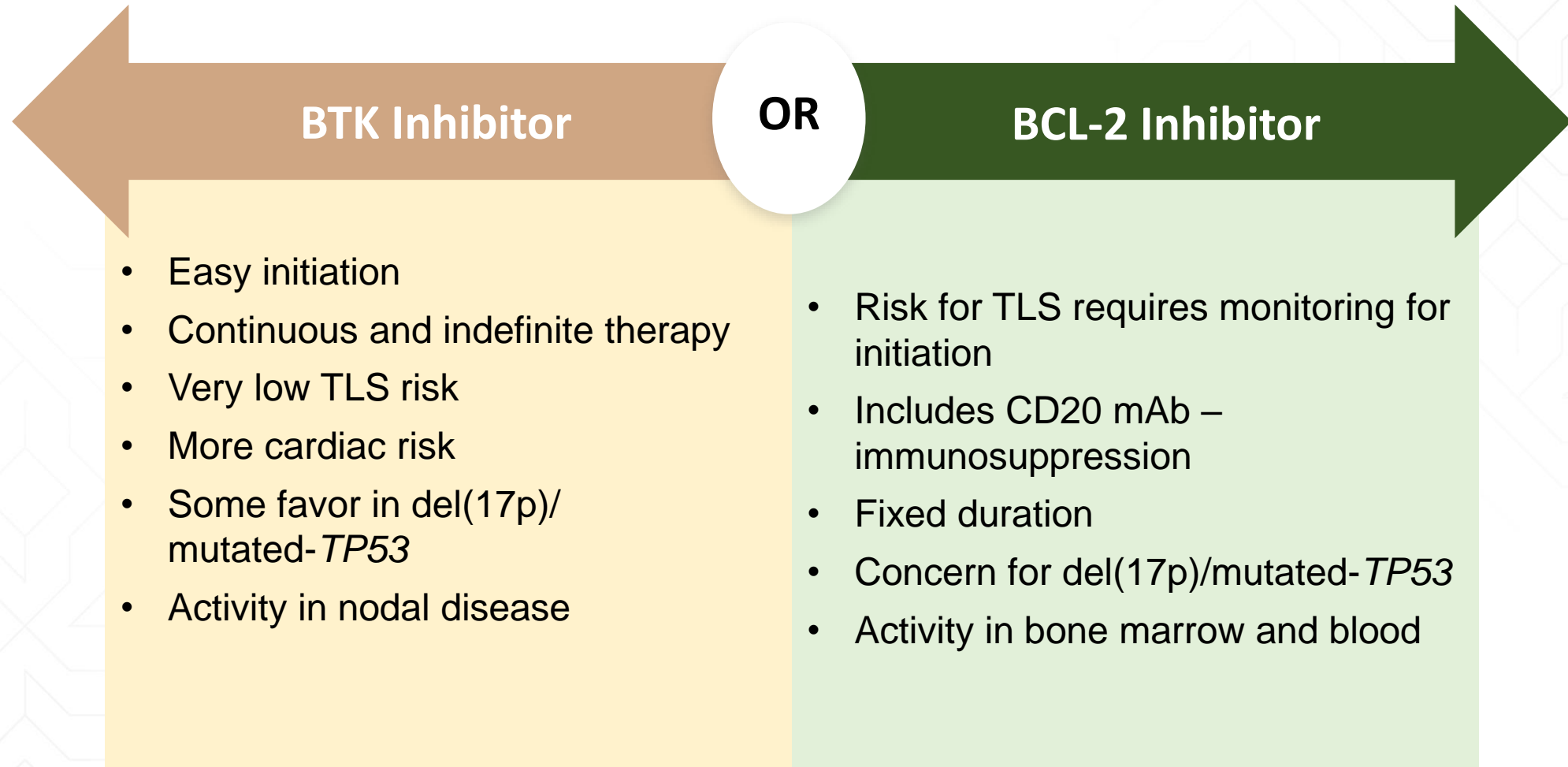


# Disclosures

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- Consulting: Amgen, Kite, SeaGen, Epizyme, Janssen, BeiGene, Abbvie, Incyte, TG Therapeutics, ADC Therapeutics, Lilly, Genentech
- Research Funding: Loxo, BeiGene, Incyte

# CLL Background



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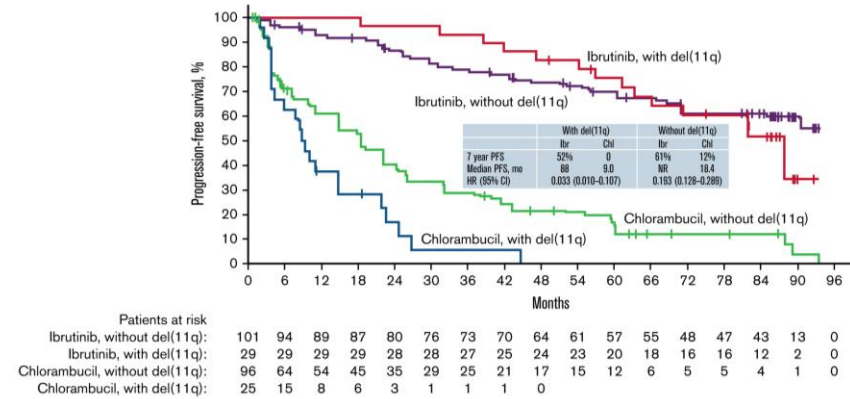
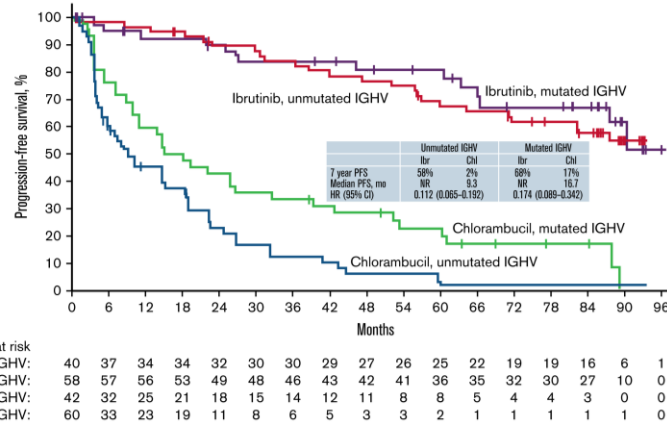
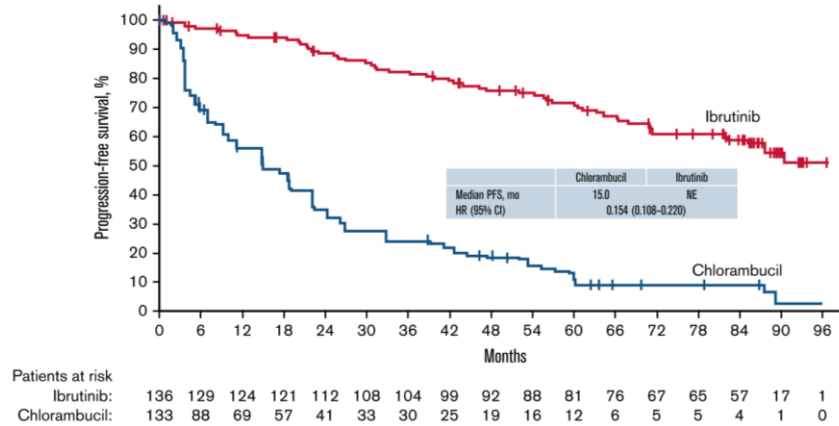
## Considerations in Choice of Treatment

- Patient age, performance status, and comorbidities
- Genetic profile
  - del (17)p
  - *TP53* mutation
  - Complex karyotype
  - *IGHV* mutation
- Regimen risk/benefit profile
- Patient preference
- Response to first-line therapy
  - Agents/classes used first-line
  - Reason for discontinuation (eg, progression or tolerability)

**BTKi – Critical data**

# Ibrutinib in CLL - RESONATE-2 – long term

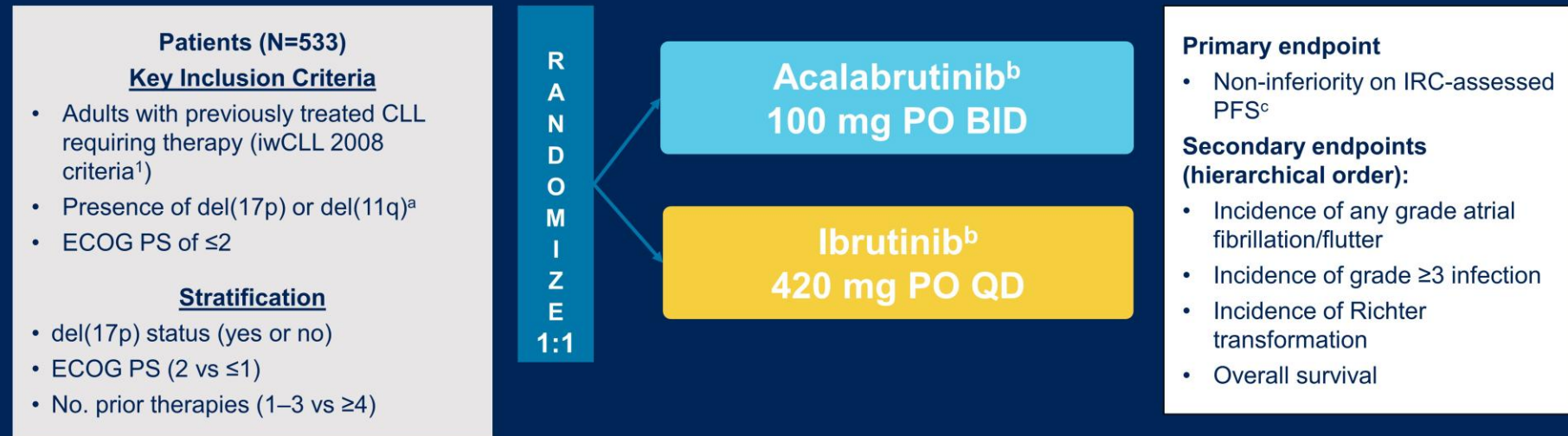
- Phase 3, elderly patients, primary endpoint PFS
  - 8-year follow-up



# Acalabrutinib vs Ibrutinib – ELEVATE-RR

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



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)

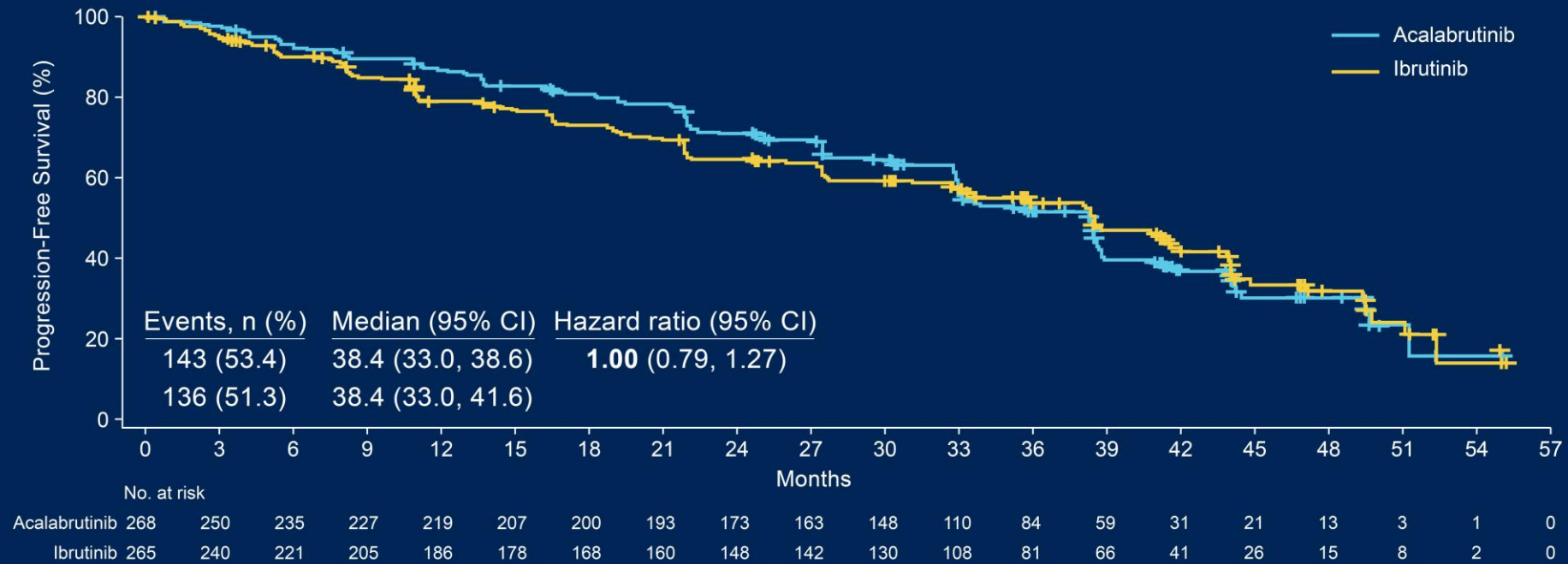
NCT02477696 (ACE-CL-006).

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

Afib/flutter, atrial fibrillation/flutter; BCL-2, B-cell leukemia/lymphoma-2; BCR, B-cell receptor; 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.

# Acalabrutinib vs Ibrutinib – 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.

# Acalabrutinib vs Ibrutinib – ELEVATE-RR

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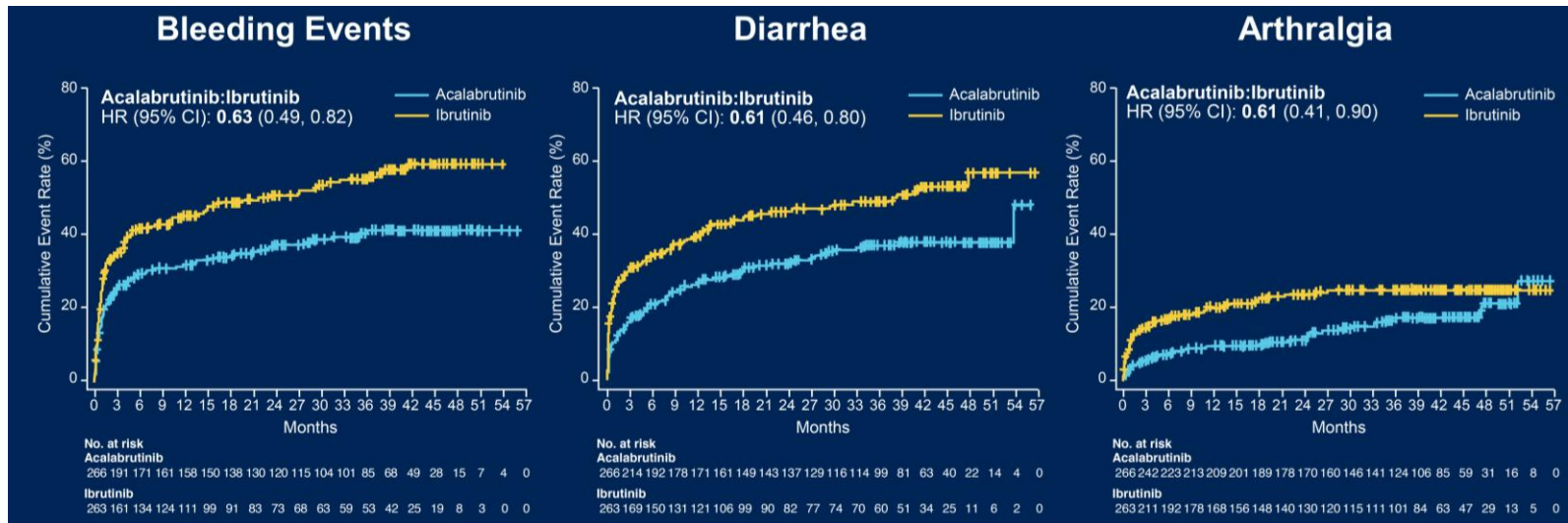
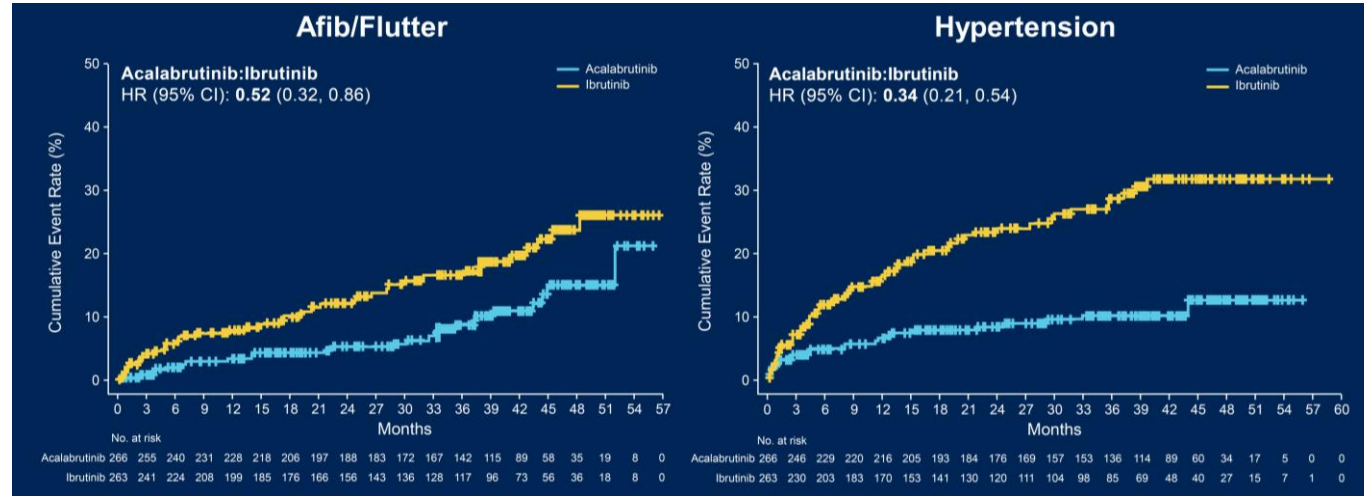
## Secondary Endpoint: Incidence of Any-Grade Atrial Fibrillation/Flutter Significantly Lower With Acalabrutinib

	Any grade	
	Acalabrutinib (n=266)	Ibrutinib (n=263)
Afib/flutter	25 (9.4)*,a	42 (16.0) <sup>a</sup>
Events/100 person-months	0.366	0.721
Time to onset, median (range), months	28.8 (0.4–52.0)	16.0 (0.5–48.3)
Leading to treatment discontinuation <sup>b</sup>	0	7 (16.7)
Afib/flutter incidence among patients without prior history of afib/flutter	15/243 (6.2)	37/249 (14.9)

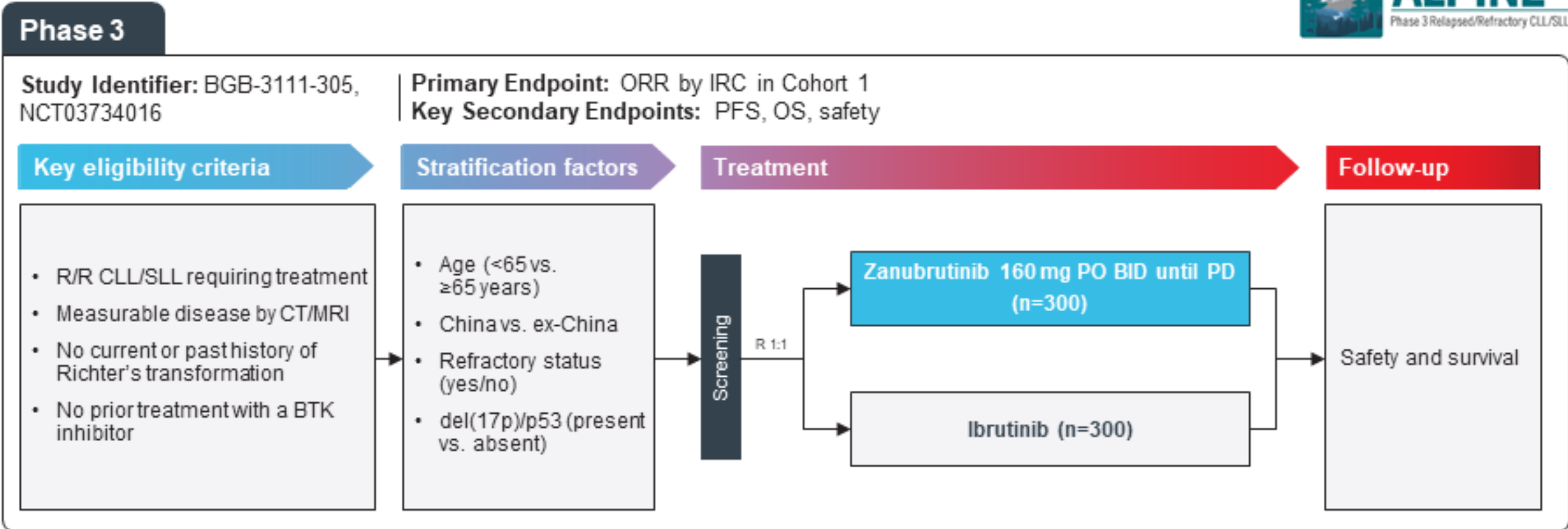
\*Difference in any-grade incidence rates:  $-6.6\%$  (95% CI  $-12.2$  to  $-0.9$ ),  $P=0.02$ .

<sup>a</sup>Grade  $\geq 3$  afib/flutter was reported in 13 (4.9%) in the acalabrutinib arm vs 10 (3.8%) in the ibrutinib arm; <sup>b</sup>Among patients with events of afib/flutter. Afib/flutter, atrial fibrillation/flutter.

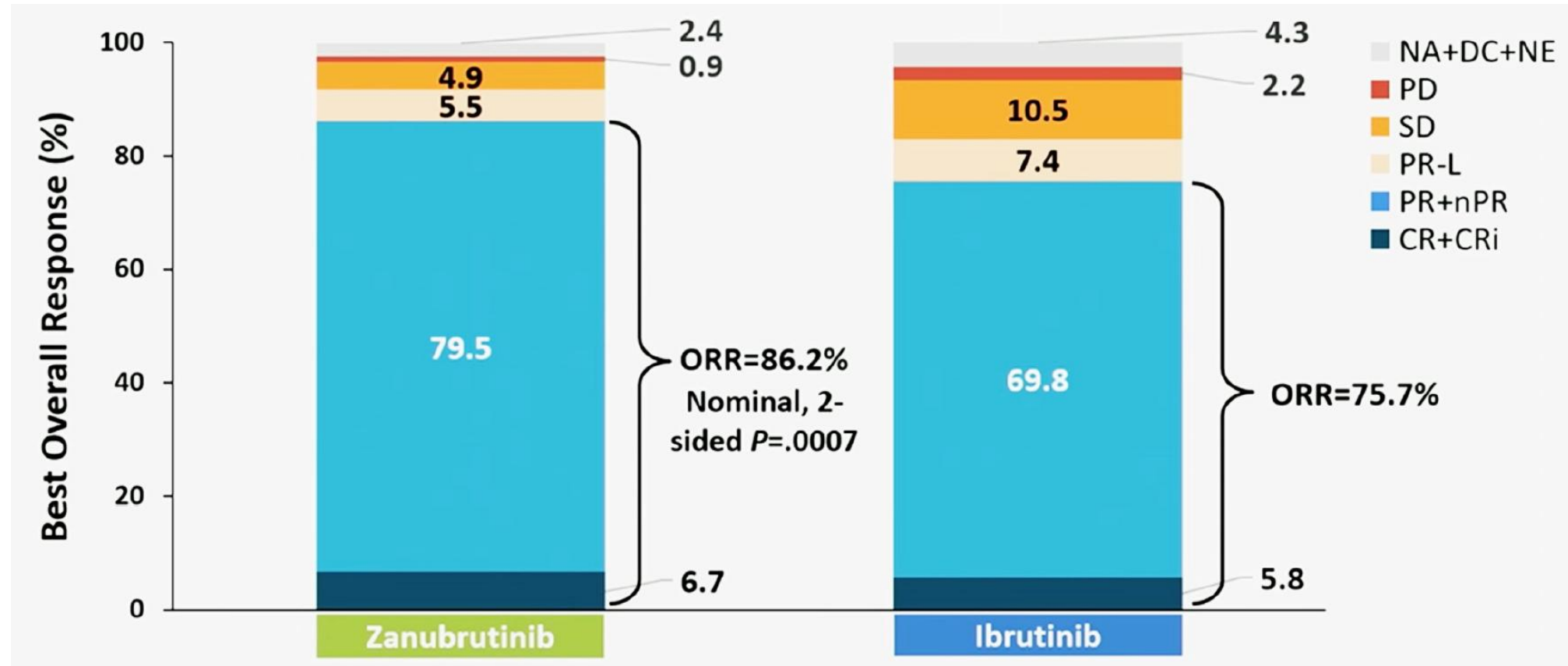
# Acalabrutinib vs Ibrutinib – ELEVATE-RR



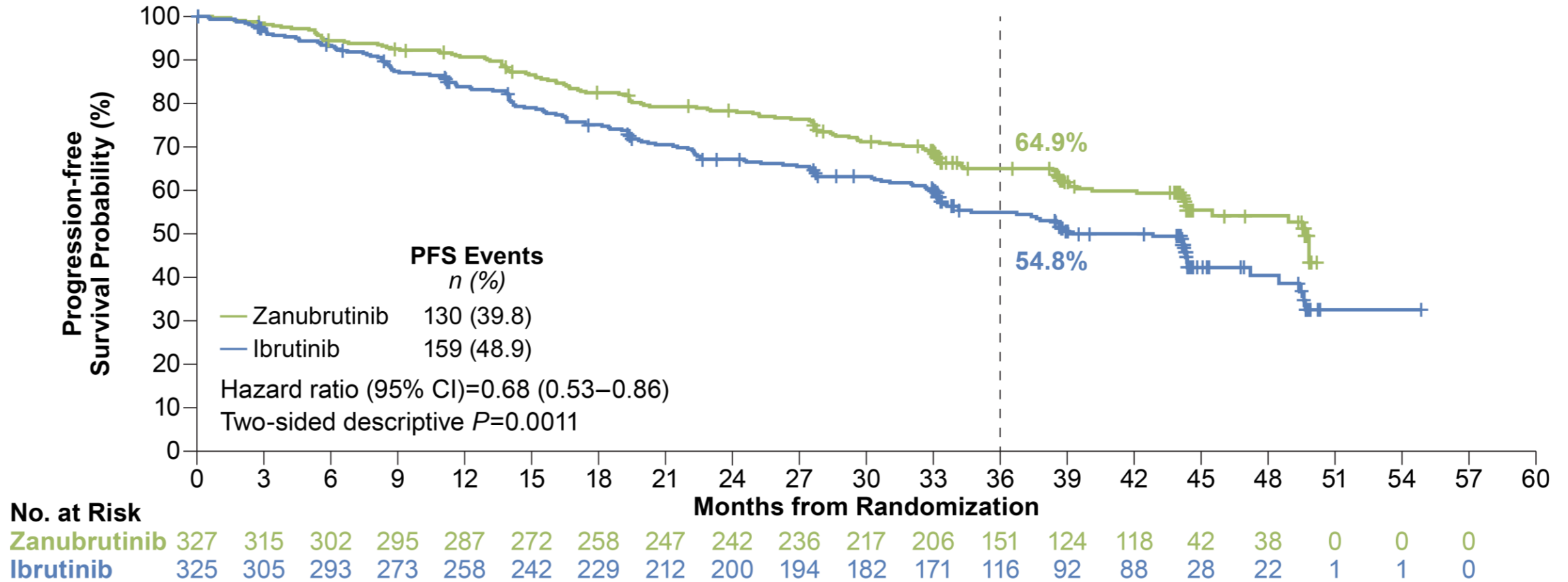
# Zanubrutinib vs Ibrutinib – ALPINE



# Zanubrutinib vs Ibrutinib – ALPINE

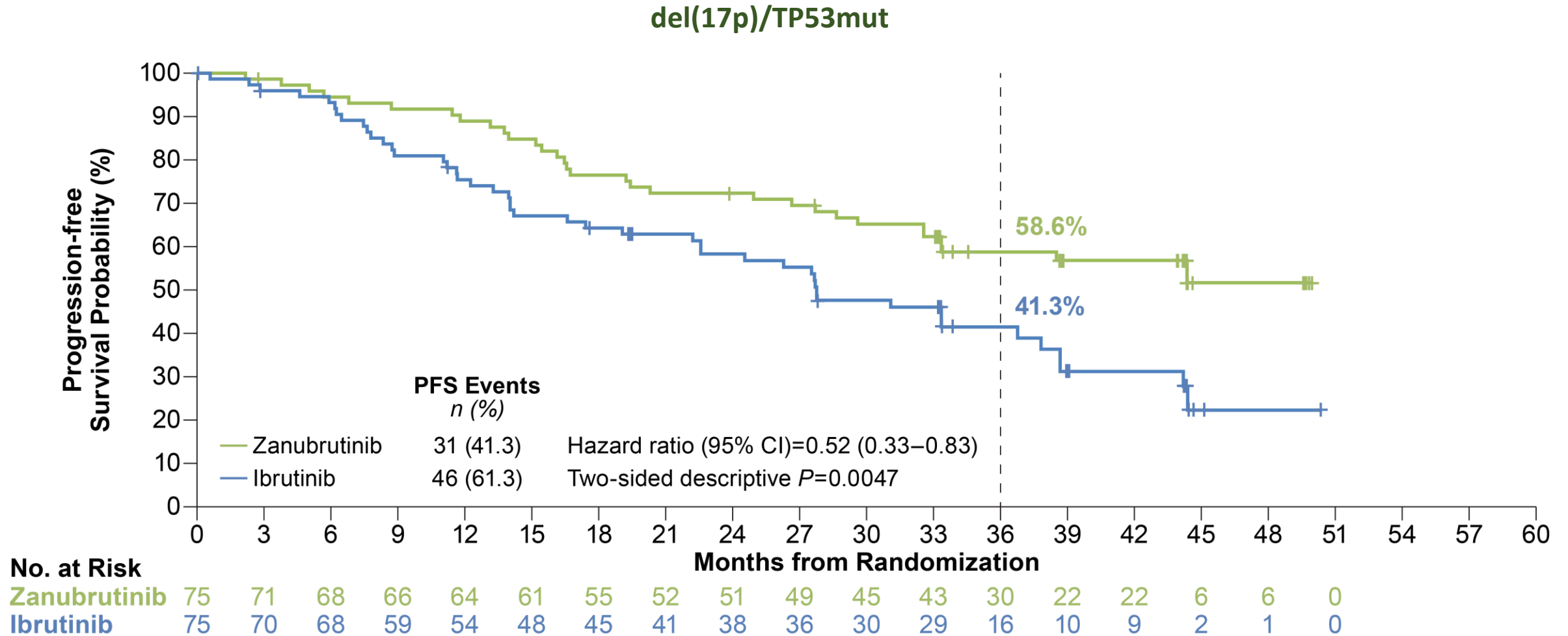


# Zanubrutinib vs Ibrutinib – ALPINE – longer f/u



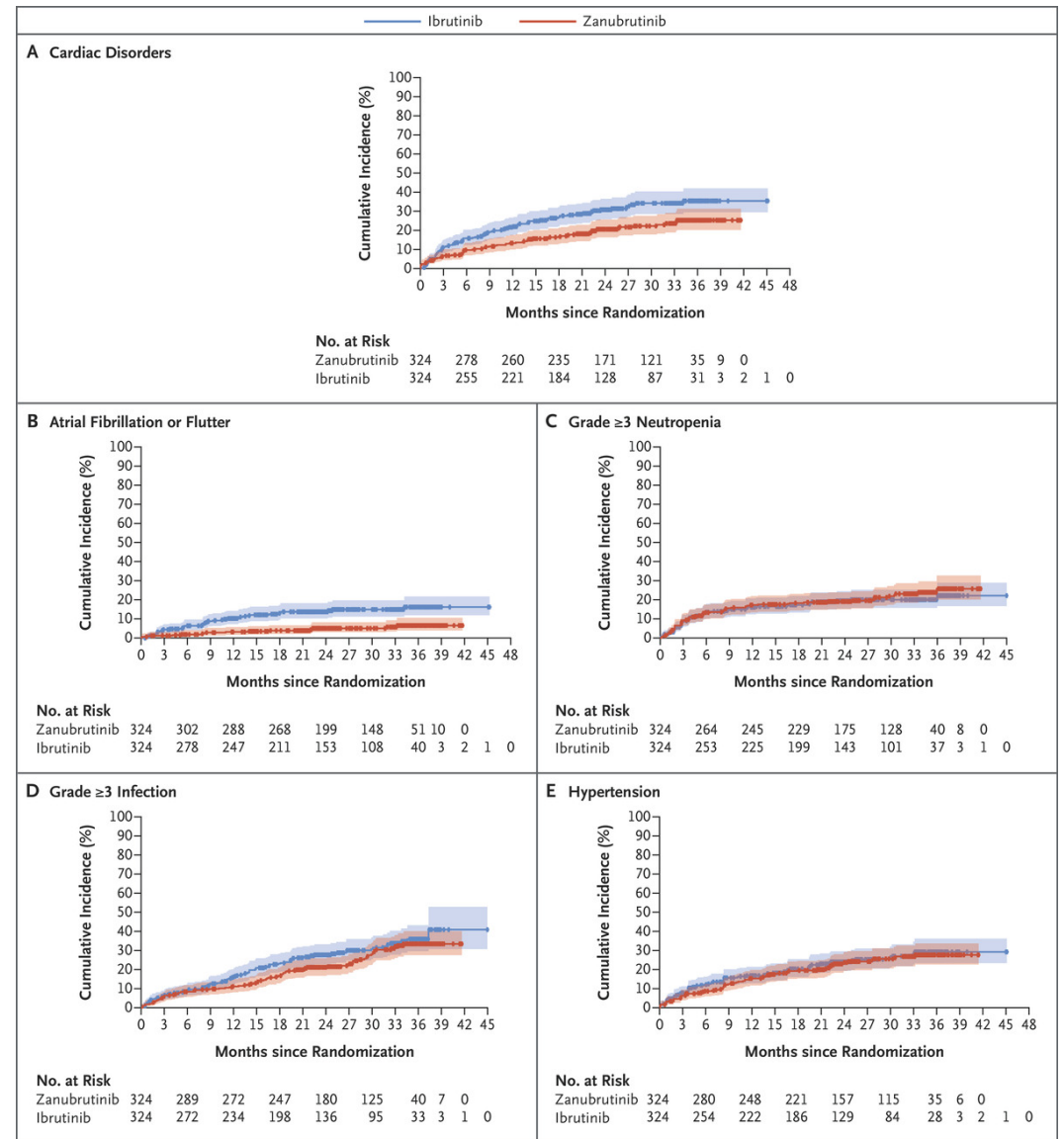
Median study follow-up of 39.0 months

# Zanubrutinib vs Ibrutinib – ALPINE – longer f/u



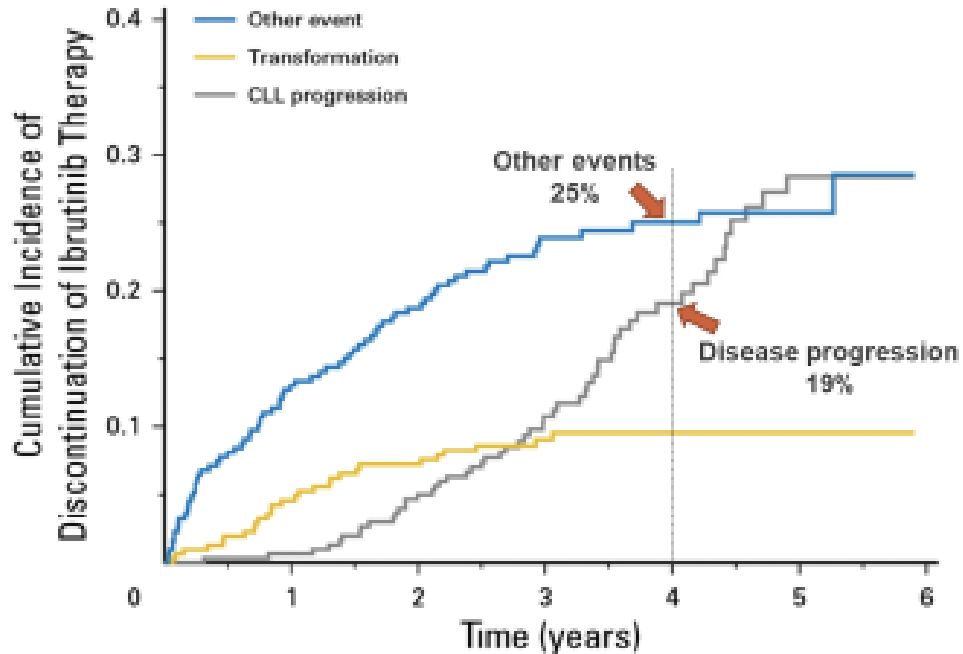
# Zanubrutinib vs Ibrutinib – ALPINE

Cardiac AEs, n (%)	Zanubrutinib (n=324)	Ibrutinib (n=324)
Cardiac AEs	69 (21.3)	96 (29.6)
Serious cardiac AEs	6 (1.9)	25 (7.7)
Cardiac AEs leading to discontinuation	1 (0.3)	14 (4.3)
Ventricular extrasystoles	1 (0.3)	0
Afib	0	5 (1.5)
Cardiac arrest	0	2 (0.6)
Cardiac failure	0	2 (0.6)
Cardiac failure acute	0	1 (0.3)
Congestive cardiomyopathy	0	1 (0.3)
Myocardial infarction	0	1 (0.3)
Palpitations	0	1 (0.3)
Vfib	0	1 (0.3)
Fatal cardiac events	0	6 (1.9)



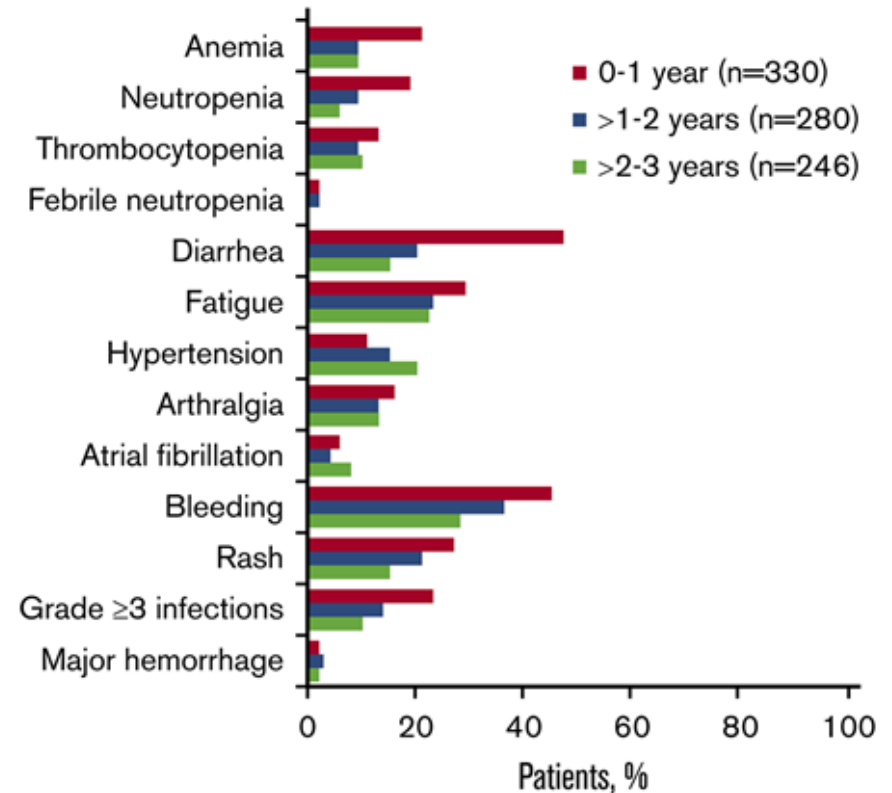
# Ibrutinib long-term effects

Ibrutinib discontinuation from 4 prospective studies<sup>1</sup>



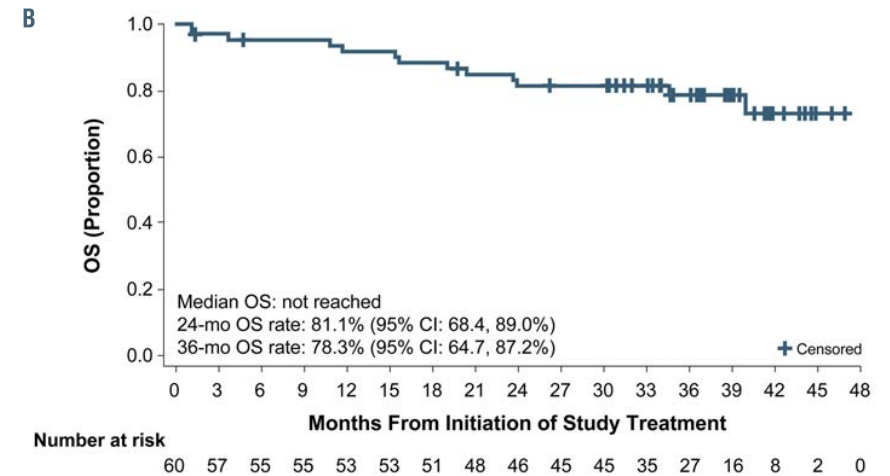
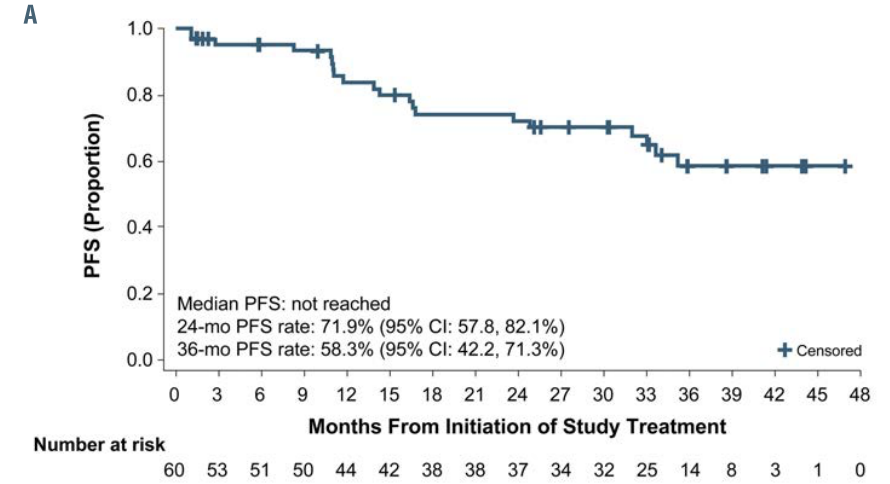
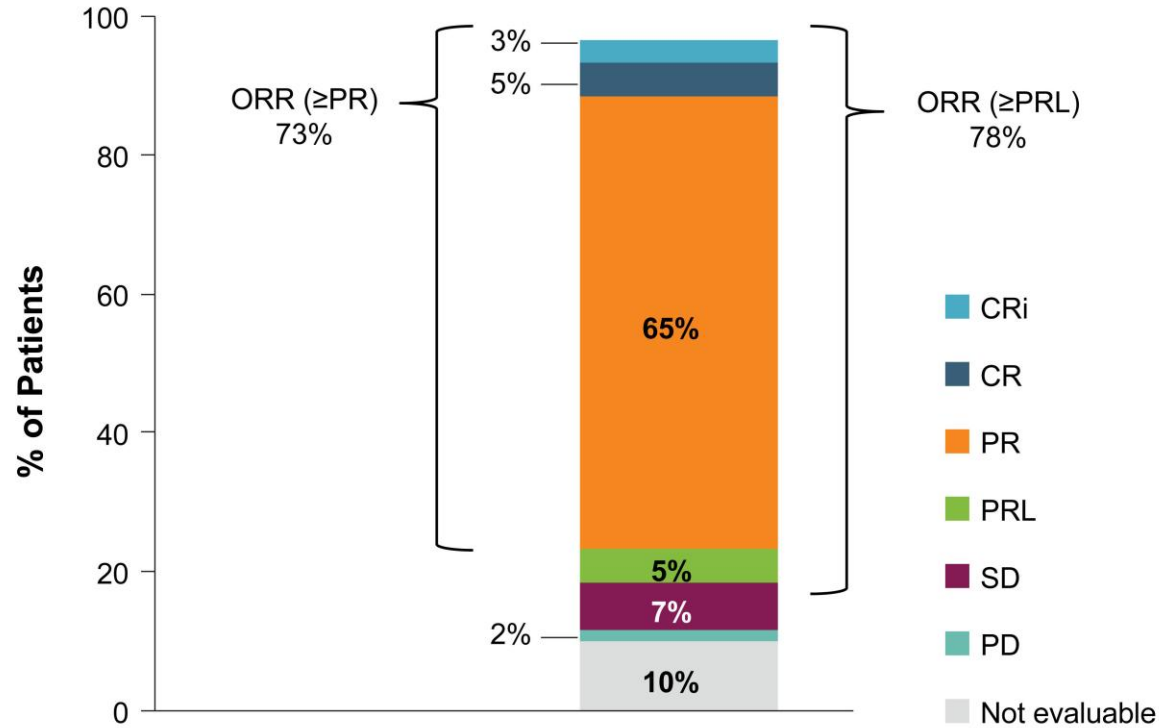
- Ibrutinib discontinuation rates at 5 years
  - Front line = 41%<sup>1</sup>
  - Relapsed/refractory = 54%<sup>2</sup>

Integrated safety analysis: prevalence of select AEs of clinical interest over time



# Acalabrutinib post Ibrutinib

- Phase 2, discontinue ibrutinib due to intolerance
- Persistent gr 3/4, gr 2 not improving p adjustment
- N=60, median time on ibrutinib 6 mo



# Acalabrutinib post Ibrutinib

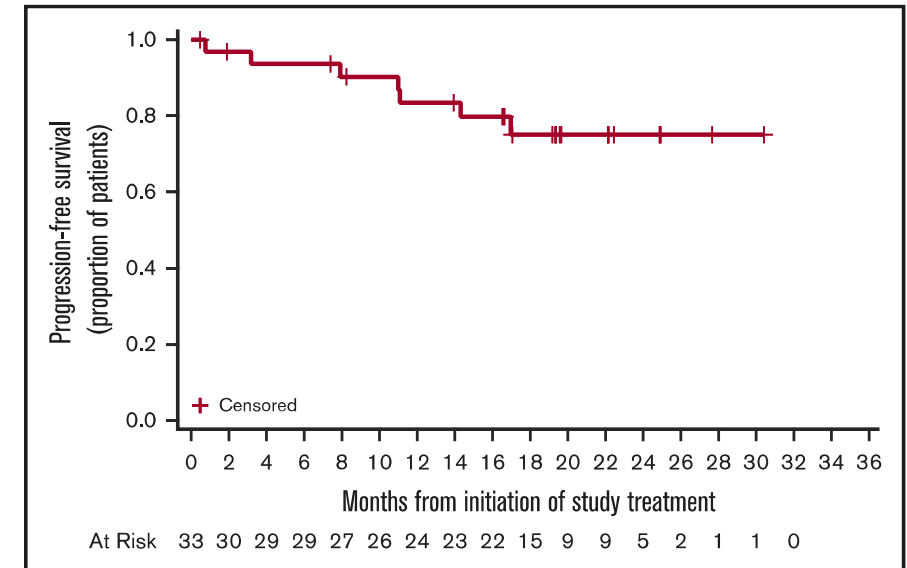
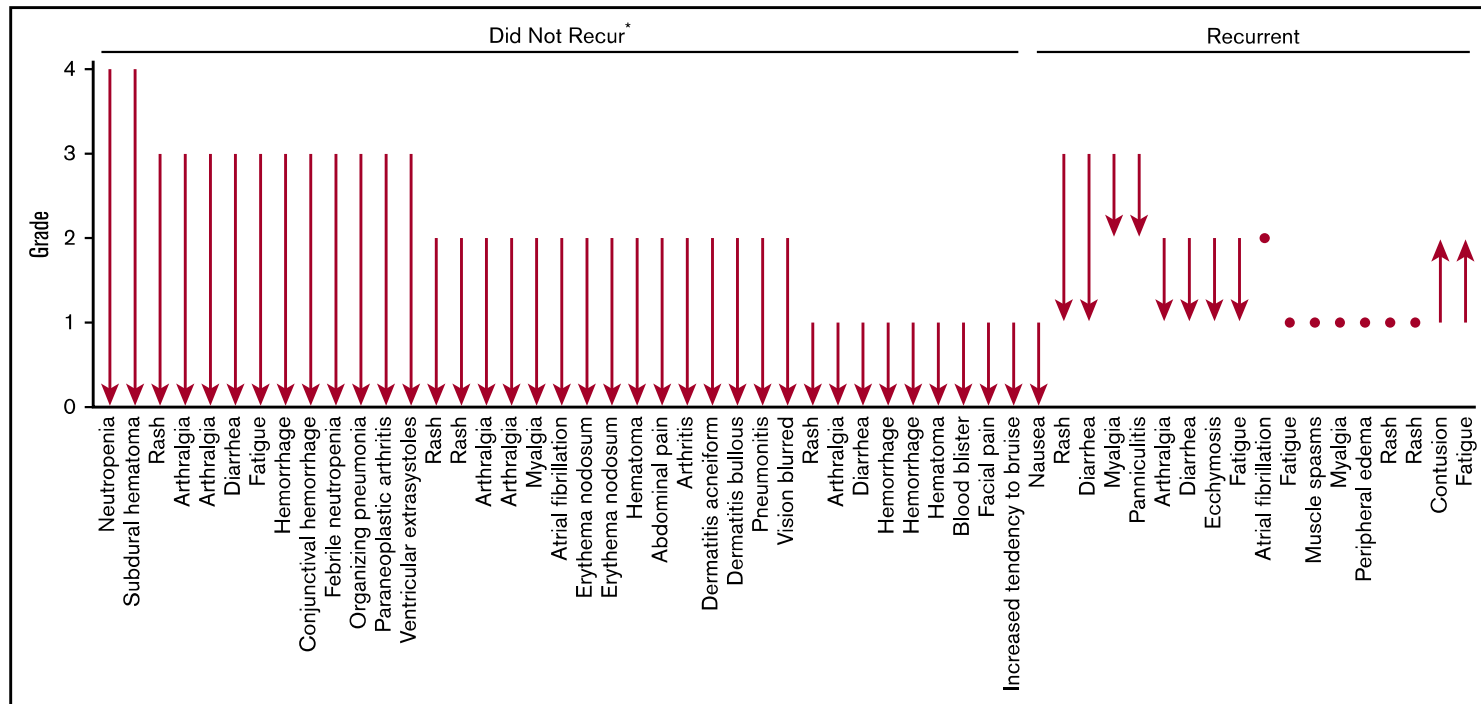
- Phase 2, discontinue ibrutinib due to intolerance
- Persistent gr 3/4, gr 2 not improving p adjustment
- N=60, median time on ibrutinib 6 mo

**Table 3. Ibrutinib-intolerance adverse events and recurrence after acalabrutinib treatment.**

Adverse event	Number of patients with ibrutinib intolerance <sup>a</sup>	Acalabrutinib experience for same patients			
		Total	Lower grade	Same grade	Higher grade
Atrial fibrillation	16 <sup>b</sup>	2	2	0	0
Diarrhea	7	5	3	2	0
Rash	7	3	3	0	0
Bleeding <sup>c,d</sup>	6	5	3	2	0
Arthralgia	7 <sup>e</sup>	2	1	1	0
Total	41	24	18	6	1

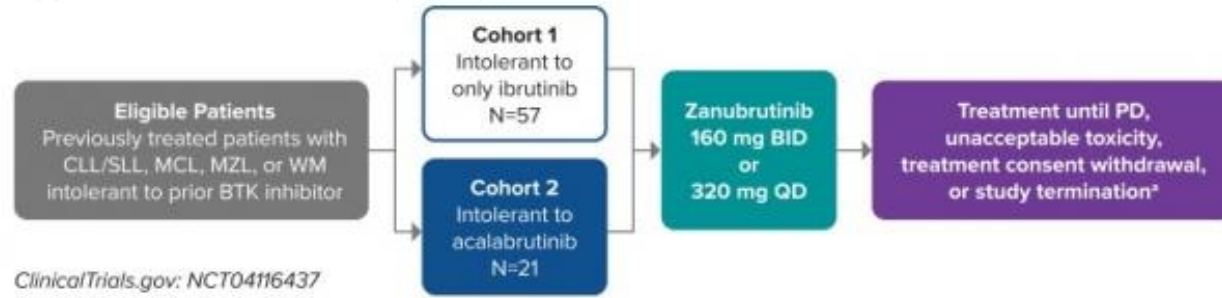
# Acalabrutinib post Ibrutinib

- Phase 2, discontinue ibrutinib due to intolerance
- N=30, median time on ibrutinib 12 mo



# Zanubrutinib post Ibrutinib/Acalabrutinib

Figure 2: BGB-3111-215 Study Design



ClinicalTrials.gov: NCT04116437

\*Study is ongoing.

Table 1. Patient Demographics and Baseline Characteristics

Characteristics	Cohort 1 (prior ibrutinib) (n=57)	Cohort 2 (prior acalabrutinib +/- ibrutinib) (n=10)	Total (N=67)
<b>Indication, n (%)</b>			
CLL	38 (66.7)	5 (50.0)	43 (64.2)
WM	9 (15.8)	2 (20.0)	11 (16.4)
SLL	6 (10.5)	1 (10.0)	7 (10.4)
MCL	2 (3.5)	1 (10.0)	3 (4.5)
MZL	2 (3.5)	1 (10.0)	3 (4.5)
<b>Age, median (range), year</b>	71.0 (49-91)	73.5 (65-83)	71.0 (49-91)
<b>Male, n (%)</b>	30 (52.6)	6 (60.0)	36 (53.7)
<b>ECOG PS 0, n (%)</b>	33 (57.9)	4 (40.0)	37 (55.2)
<b>No. of prior therapy regimens, median (range)</b>	1.0 (1-12)	2.5 (1-5)	1.0 (1-12)
<b>Prior BTKi, n (%)</b>	57 (100)	10 (100)	67 (100)
Ibrutinib monotherapy	49 (86.0)	6 (60.0) <sup>a</sup>	55 (82.1)
Ibrutinib combination therapy	9 (15.8) <sup>b</sup>	0	9 (13.4)
Acalabrutinib monotherapy	0	10 (100)	10 (14.9)
<b>Time on prior BTKi,<sup>c</sup> median (range), months</b>	10.61 (1.1-73.7)	3.33 (0.5-26.9)	—
<b>On-study zanubrutinib dosing regimen</b>			
160 mg bid	35 (61.4)	7 (70.0)	42 (62.7)
320 mg qd	22 (38.6)	3 (30.0)	25 (37.3)

Data Cutoff: 8 September 2021

<sup>a</sup> Six patients had both prior ibrutinib and acalabrutinib therapies. <sup>b</sup> One patient received ibrutinib combination therapy followed by ibrutinib monotherapy. <sup>c</sup> Cumulative ibrutinib exposure for cohort 1 and acalabrutinib for cohort 2.

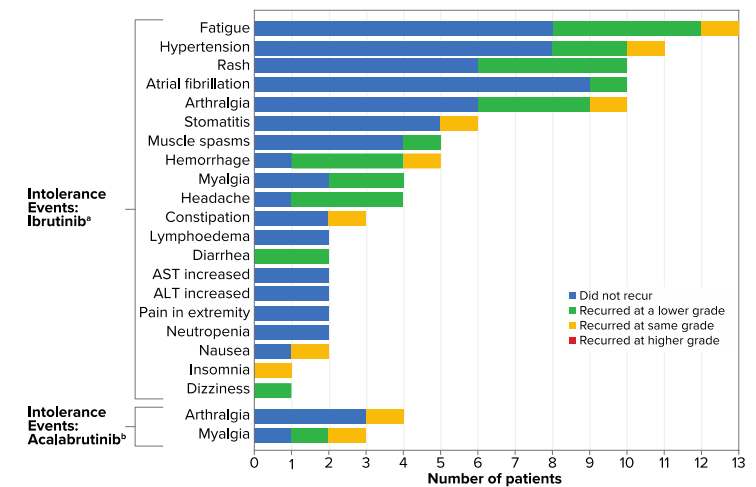
Table 2. Patient Disposition

	Cohort 1 (prior ibrutinib) (n=57)	Cohort 2 (prior acalabrutinib +/- ibrutinib) (n=10)	Total (N=67)
<b>Patients remaining on treatment, n (%)</b>	48 (84.2)	8 (80.0)	56 (83.6)
<b>Patients remaining on study, n (%)</b>	54 (94.7)	10 (100)	64 (95.5)
<b>Patients discontinued from treatment, n (%)</b>	9 (15.8)	2 (20.0)	11 (16.4)
Adverse event	4 (7.0) <sup>a</sup>	1 (10.0) <sup>a</sup>	5 (7.5)
Progressive disease	3 (5.3)	1 (10.0)	4 (6.0)
Physician decision	1 (1.8) <sup>c</sup>	0	1 (1.5)
Withdrawal by patient	1 (1.8) <sup>d</sup>	0	1 (1.5)
<b>Death</b>	1 (1.8) <sup>e</sup>	0	1 (1.5)
<b>Zanubrutinib exposure, median (range), months</b>	11.6 (0.6-20.3)	9.8 (0.5-12.0)	11.1 (0.5-20.3)
<b>Follow-up, median (range), months</b>	12.3 (1.0-22.8)	10.4 (0.5-15.0)	12.0 (0.5-22.8)

<sup>a</sup> Penile bleed, COVID-19 pneumonia (fatal), increased alanine aminotransferase/aspartate transaminase, and autoimmune hemolytic anemia. <sup>b</sup> Myalgia. <sup>c</sup> Patient not responding to treatment. <sup>d</sup> Patient withdrew from study after grade 3 syncope related to diabetes. <sup>e</sup> COVID-19 pneumonia.

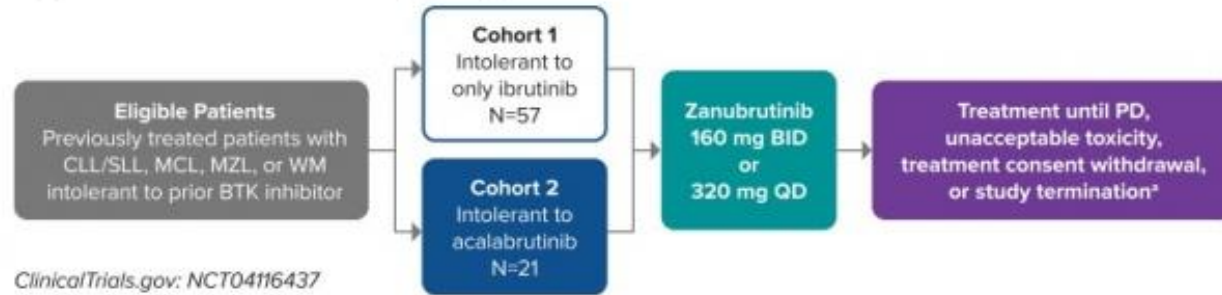
## RESULTS

Figure 3. Recurrence of Ibrutinib and Acalabrutinib Intolerance Events on Zanubrutinib



# Zanubrutinib post Ibrutinib/Acalabrutinib

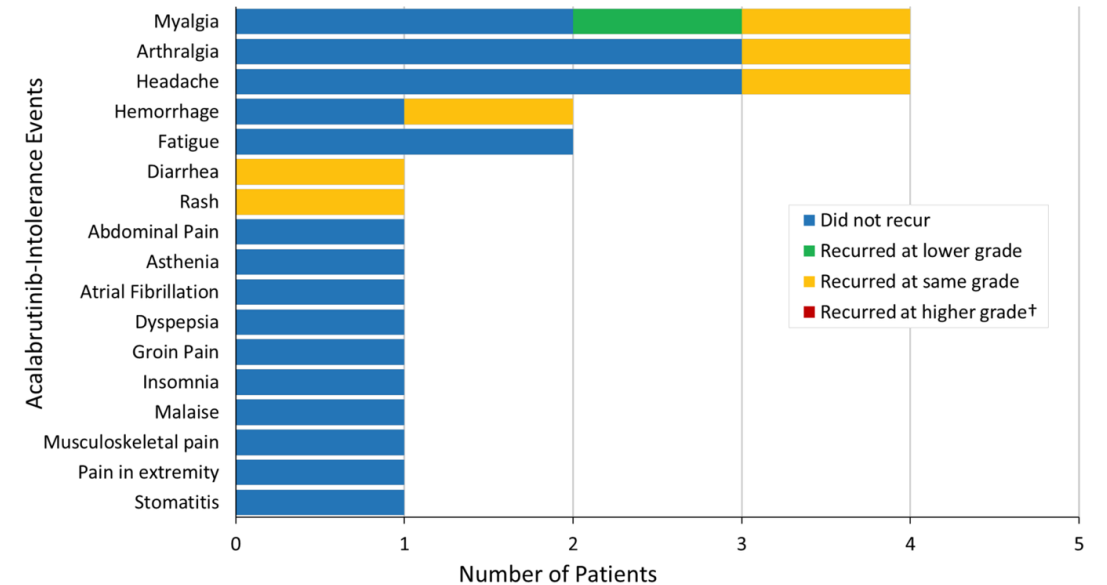
Figure 2: BGB-3111-215 Study Design



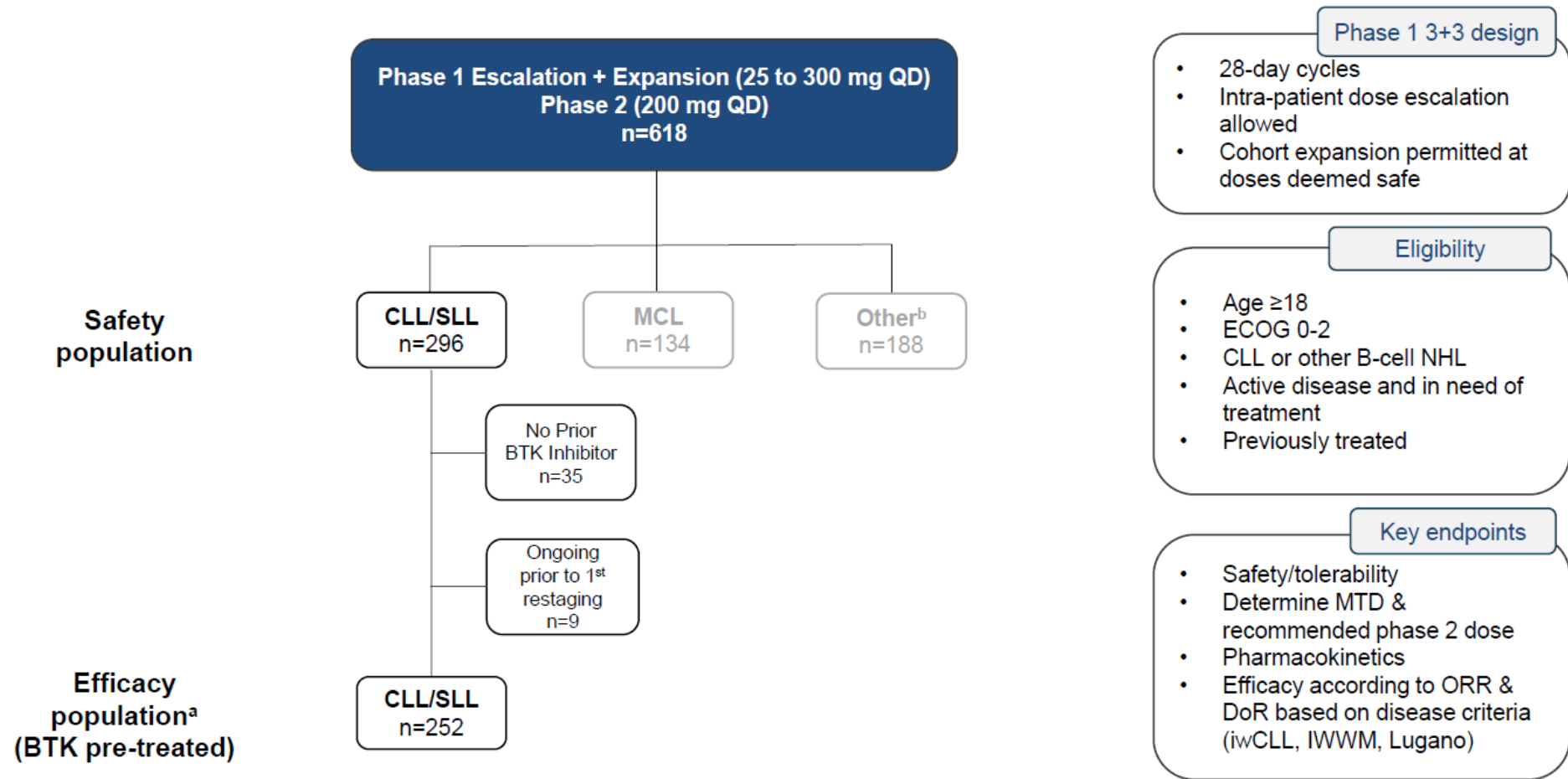
ClinicalTrials.gov: NCT04116437

\*Study is ongoing.

- N=17 (12 CLL/SLL)
- Median acalabrutinib 3.8 mo
- Median zanubrutinib 9.2 mo
- disease controlled in 13 (93%) of 14 evaluable pts



# Pirtobrutinib - BRUIN

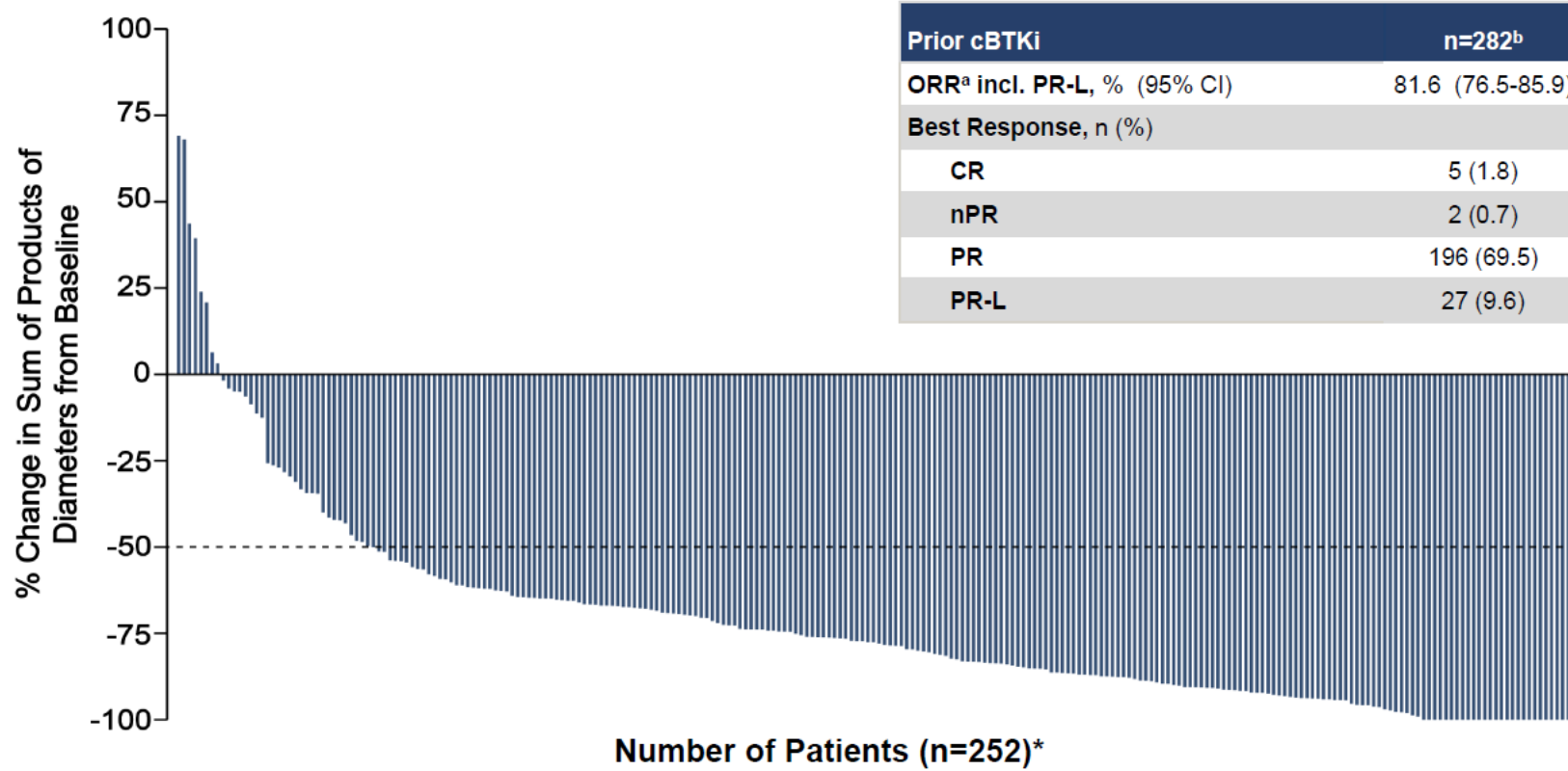


# Pirtobrutinib

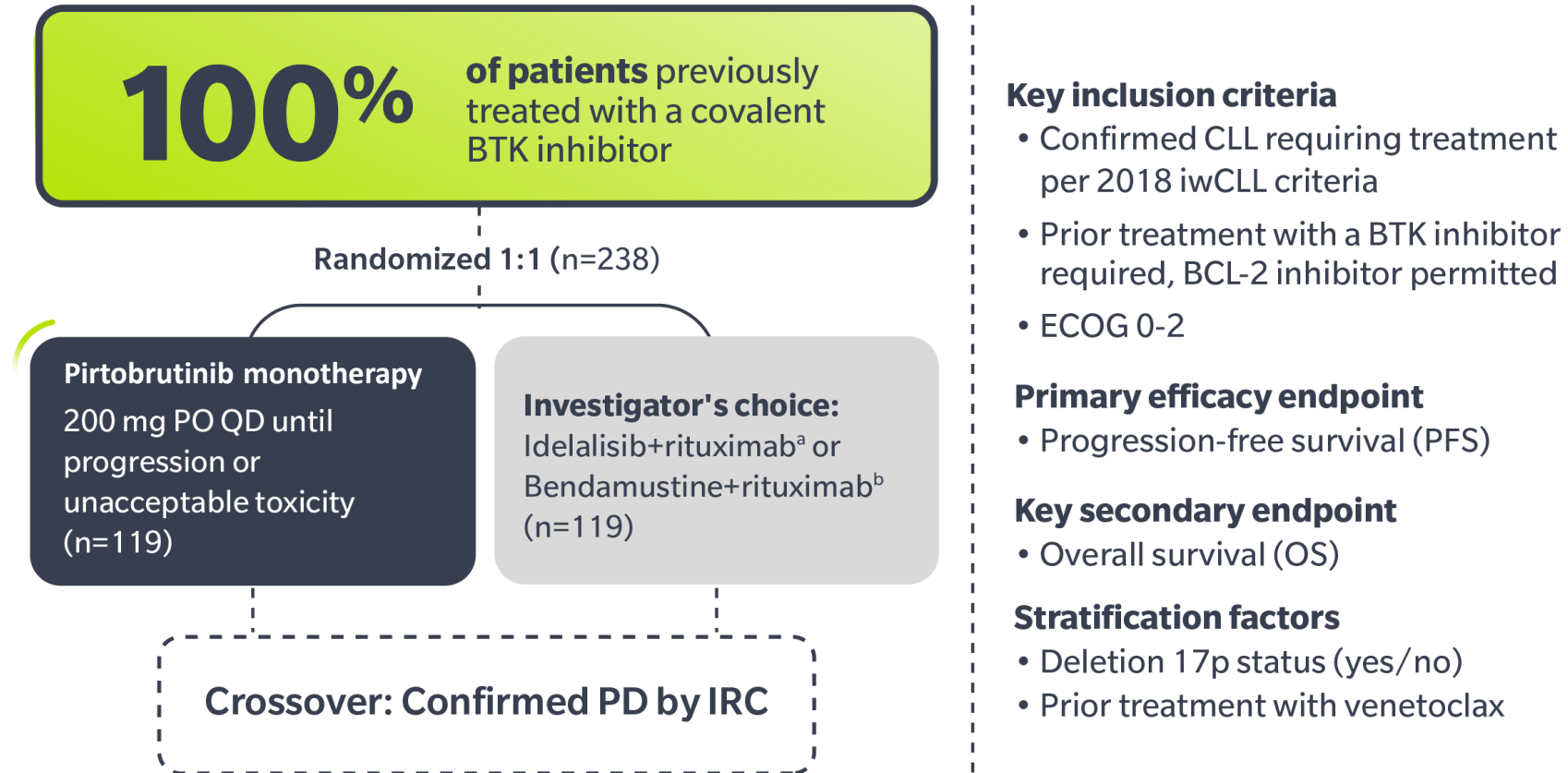
Characteristic	Patients* (N = 247)
Median age (range) - yr	69 (36-88)
Male, n (%)	168 (68.0)
Female, n (%)	79 (32.0)
ECOG performance-status score, n (%) †	
0	133 (53.8)
1	97 (39.3)
2	17 (6.9)
Median number of prior lines of systemic therapy (range)	3 (1-11)
1 line, n (%)	19 (7.7)
2 lines, n (%)	55 (22.3)
3 lines, n (%)	57 (23.1)
4 lines, n (%)	116 (47.0)
Previous therapy, n (%)	
BTK inhibitor‡	247 (100)
Anti-CD20 antibody	217 (87.9)
Chemotherapy	195 (78.9)
BCL2 inhibitor	100 (40.5)
PI3K inhibitor	45 (18.2)
CAR T-cell therapy	14 (5.7)
Allogeneic stem-cell transplantation	6 (2.4)
Reason for discontinuation of any previous BTK inhibitor, n (%) §	
Disease progression	190 (76.9)
Toxic effects or other reason	57 (23.1)

Baseline Molecular Characteristics	Patients* (N = 247)
<i>BTK C481</i>	
Mutated	84/222 (37.8)
Not mutated	138/222 (62.2)
<i>PLCG2</i>	
Mutated	18/222 (8.1)
Not mutated	204/222 (91.9)
High-risk molecular features, n/total, n(%) ¶	
17p deletion	51/176 (29.0)
<i>TP53</i> mutation	87/222 (39.2)
17p deletion, <i>TP53</i> mutation, or both	90/193 (46.6)
Both 17p deletion and <i>TP53</i> mutation	48/170 (28.2)
Unmutated <i>IGHV</i>	168/198 (84.8)
Complex karyotype	24/57 (42)
11q deletion	44/176 (25.0)

# Pirtobrutinib



# Pirtobrutinib – CLL-321 Phase 3 study



<sup>a</sup>Idelalisib: 150 mg PO bid; rituximab IV x 8 (n=82; 69%)

<sup>b</sup>Bendamustine 70 mg/m<sup>2</sup> IV, D1 and D2, cycle 1-6; rituximab IV x 6 (n=37; 31%)

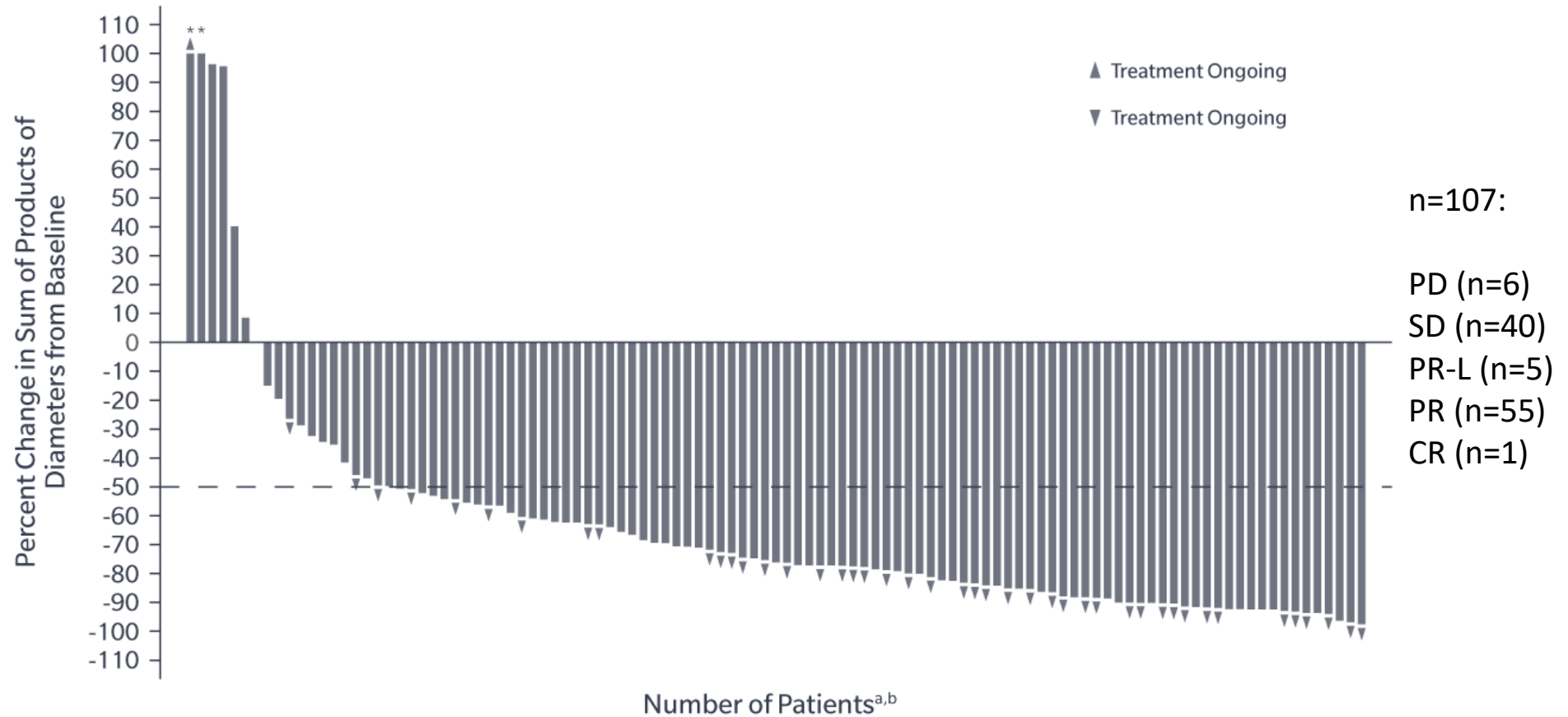
# CLL-321 – Pirtov vs BR/IdR

## Baseline patient characteristics

CLL-321 Select Baseline Patient Characteristics		Pirtobrutinib (n=119)	IdR/BR (n=119)
Age, years	Median (range)	66 (42-90)	68 (42-85)
Sex	Male (%)	70	70
Baseline ECOG PS	0-1 (%)	90	96
	2 (%)	10	4
<b>Prior therapies</b>			
Prior lines of systemic therapy <sup>a</sup>	Median (range)	3 (1-13)	3 (1-11)
Prior BTKi treatment %	Yes	100	100
Discontinuation of any prior BTKi due to <sup>b</sup> %	Progressive disease	71	73
	Toxicity	17	19
	Other	12	7
Prior BCL-2 inhibitor treatment <sup>c</sup> %	Yes	50	52
<b>Mutation Status<sup>d</sup> %</b>			
17p deletion (n/N)	Yes	35 (39/111)	38 (43/112)
IGHV unmutated (n/N)	Yes	93 (90/97)	80 (74/93)
Complex karyotype <sup>e</sup> (n/N)	Yes	72 (53/74)	59 (44/75)
TP53 mutation and/or deletion of 17p (n/N)	Yes	54 (51/94)	54 (53/98)

# CLL-321 – Pirto vs BR/IdR

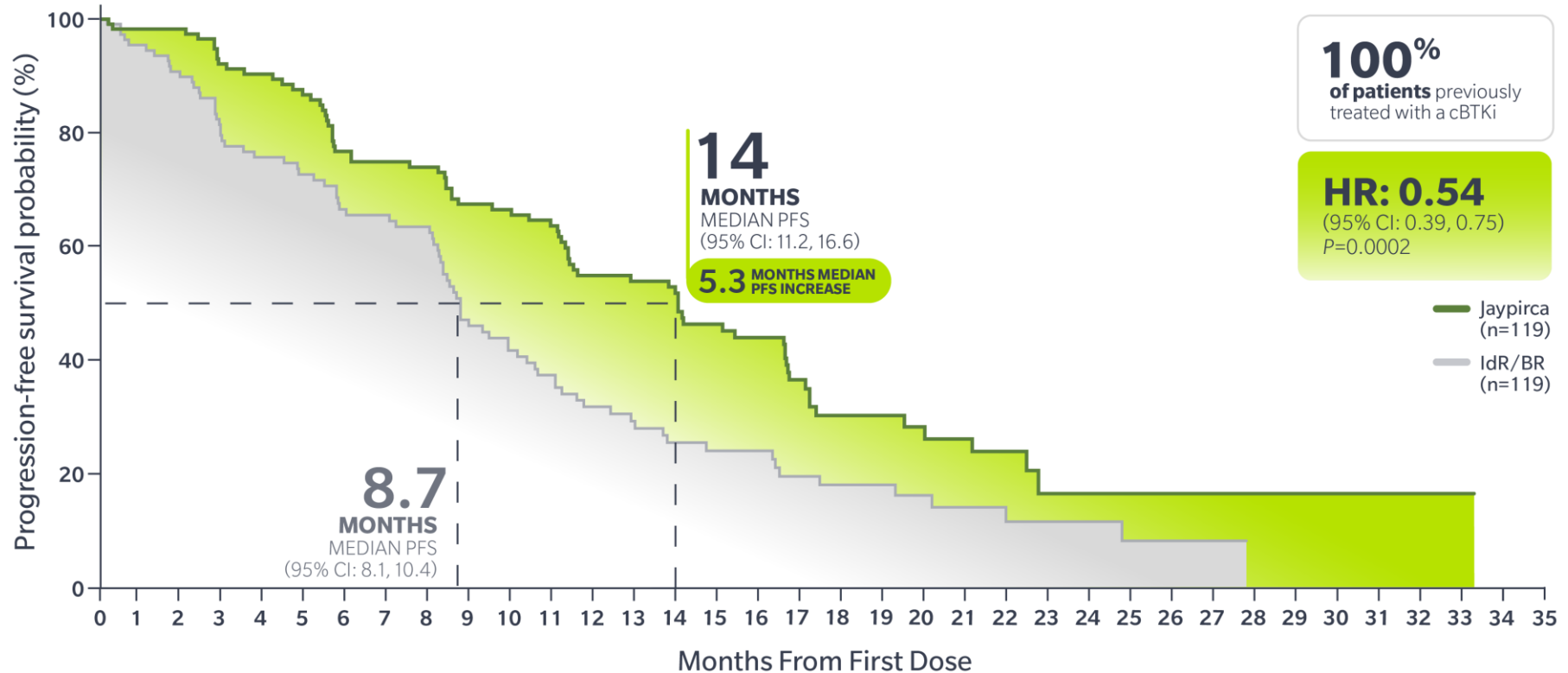
## Pirtobrutinib best change from baseline in tumor size (n=107)



\* Indicates patients with >100% increase in SPD, and the corresponding % changes from baseline are 155.0, 108.1, respectively.

# CLL-321 – Pirto vs BR/IdR

## Progression-free survival



### Number at risk

Jaypirca

119 114 113 103 100 95 84 80 79 71 69 66 54 53 44 39 36 23 19 19 12 12 10 4 4 3 3 3 3 3 3 2 2 1 0 0

IdR/BR












119 98 92 78 73 68 60 59 57 42 37 33 25 22 18 16 16 12 10 9 7 5 5 3 3 2 1 1 0 0 0 0 0 0 0 0 0

**Median F/U – 19.4 mos (pirtobrutinib), 17.7 mos (IdR/BR)**

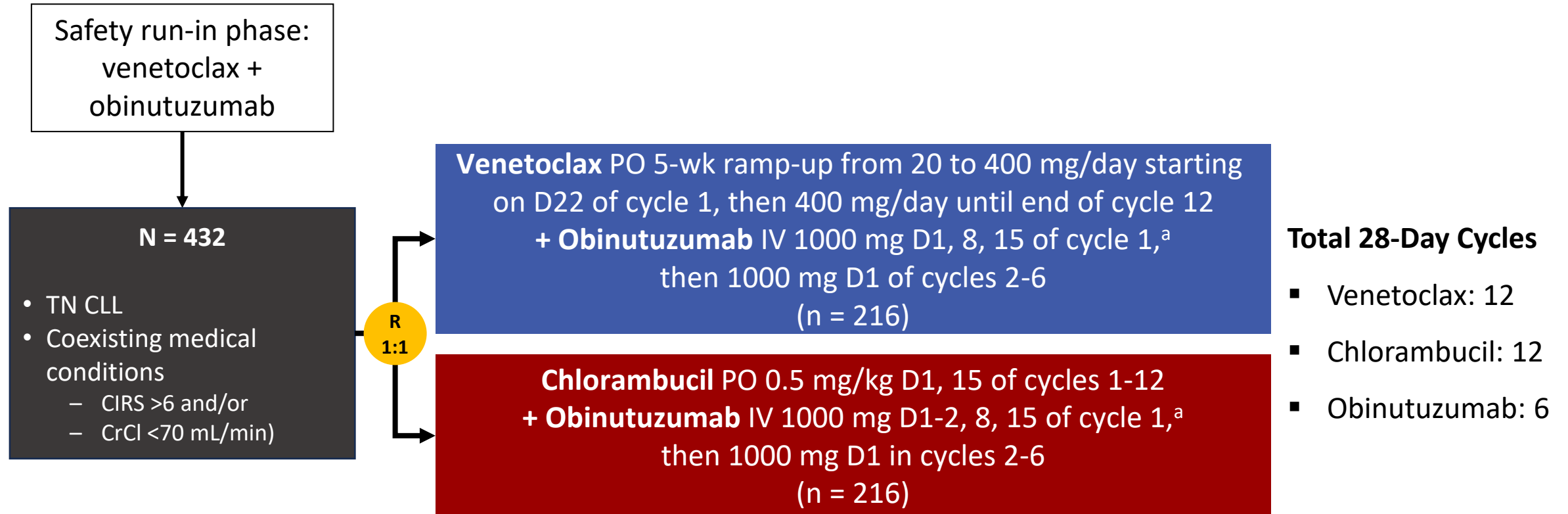
**BCL2i – Critical data**

# Venetoclax

## TLS

	LOW TUMOR BURDEN	MEDIUM TUMOR BURDEN	HIGH TUMOR BURDEN																																																																											
<b>STEP 1: ASSESS</b> Prior to initiation	All lymph nodes (LN) <5 cm <b>AND</b> Absolute lymphocyte count (ALC) <25 x 10 <sup>9</sup> /L	Any LN 5 cm to <10 cm <b>OR</b> ALC ≥25 x 10 <sup>9</sup> /L	Any LN ≥10 cm <b>OR</b> Any LN ≥5 cm and ALC ≥25 x 10 <sup>9</sup> /L																																																																											
<b>STEP 2: PREPARE</b> At least 2 days prior to first dose	 Oral hydration*: 1.5-2 L  Allopurinol <sup>†</sup>	 Oral hydration*: 1.5-2 L  <b>IV hydration<sup>1,20</sup></b> : Consider for patients with medium tumor burden, occurring during outpatient stay  Allopurinol <sup>†</sup>	 Oral hydration*: 1.5-2 L  <b>AND</b> <b>IV hydration:</b> 150-200 mL/h as tolerated prior to first dose  Allopurinol <sup>†</sup> <b>Rasburicase<sup>1,20</sup></b> : Consider for elevated uric acid (>8 mg/dL)																																																																											
<b>STEP 3: INITIATE</b> And monitor blood chemistry <sup>‡</sup> for first dose of each ramp-up week	 <b>OUTPATIENT</b> <table border="1"> <thead> <tr> <th>Day 1, Week:</th> <th>1</th> <th>2</th> <th>3</th> <th>4</th> <th>5</th> </tr> </thead> <tbody> <tr> <td>Dosage</td> <td>20 mg</td> <td>50 mg</td> <td>100 mg</td> <td>200 mg</td> <td>400 mg</td> </tr> <tr> <td rowspan="4">Blood chemistry labs</td> <td>Pre-Dose</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> <tr> <td>6-8 Hours</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td>—</td> <td>—</td> <td>—</td> </tr> <tr> <td>24 Hours</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td>—</td> <td>—</td> <td>—</td> </tr> </tbody> </table>		Day 1, Week:	1	2	3	4	5	Dosage	20 mg	50 mg	100 mg	200 mg	400 mg	Blood chemistry labs	Pre-Dose	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6-8 Hours	<input type="checkbox"/>	<input type="checkbox"/>	—	—	—	24 Hours	<input type="checkbox"/>	<input type="checkbox"/>	—	—	—	 <b>HOSPITAL</b>  <b>OUTPATIENT</b> <table border="1"> <thead> <tr> <th>Day 1, Week:</th> <th>1</th> <th>2</th> <th>3</th> <th>4</th> <th>5</th> </tr> </thead> <tbody> <tr> <td>Dosage</td> <td>20 mg</td> <td>50 mg</td> <td>100 mg</td> <td>200 mg</td> <td>400 mg</td> </tr> <tr> <td rowspan="5">Blood chemistry labs</td> <td>Pre-Dose</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> <tr> <td>4 Hours</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td>—</td> <td>—</td> <td>—</td> </tr> <tr> <td>8 Hours</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> <tr> <td>12 Hours</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td>—</td> <td>—</td> <td>—</td> </tr> <tr> <td>24 Hours</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>		Day 1, Week:	1	2	3	4	5	Dosage	20 mg	50 mg	100 mg	200 mg	400 mg	Blood chemistry labs	Pre-Dose	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	4 Hours	<input type="checkbox"/>	<input type="checkbox"/>	—	—	—	8 Hours	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	12 Hours	<input type="checkbox"/>	<input type="checkbox"/>	—	—	—	24 Hours	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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	For the first doses of 20 mg and 50 mg, consider hospitalization for patients with medium tumor burden and CLcr <80 mL/min; for these patients, see table to the right for monitoring in hospital.																																																																													

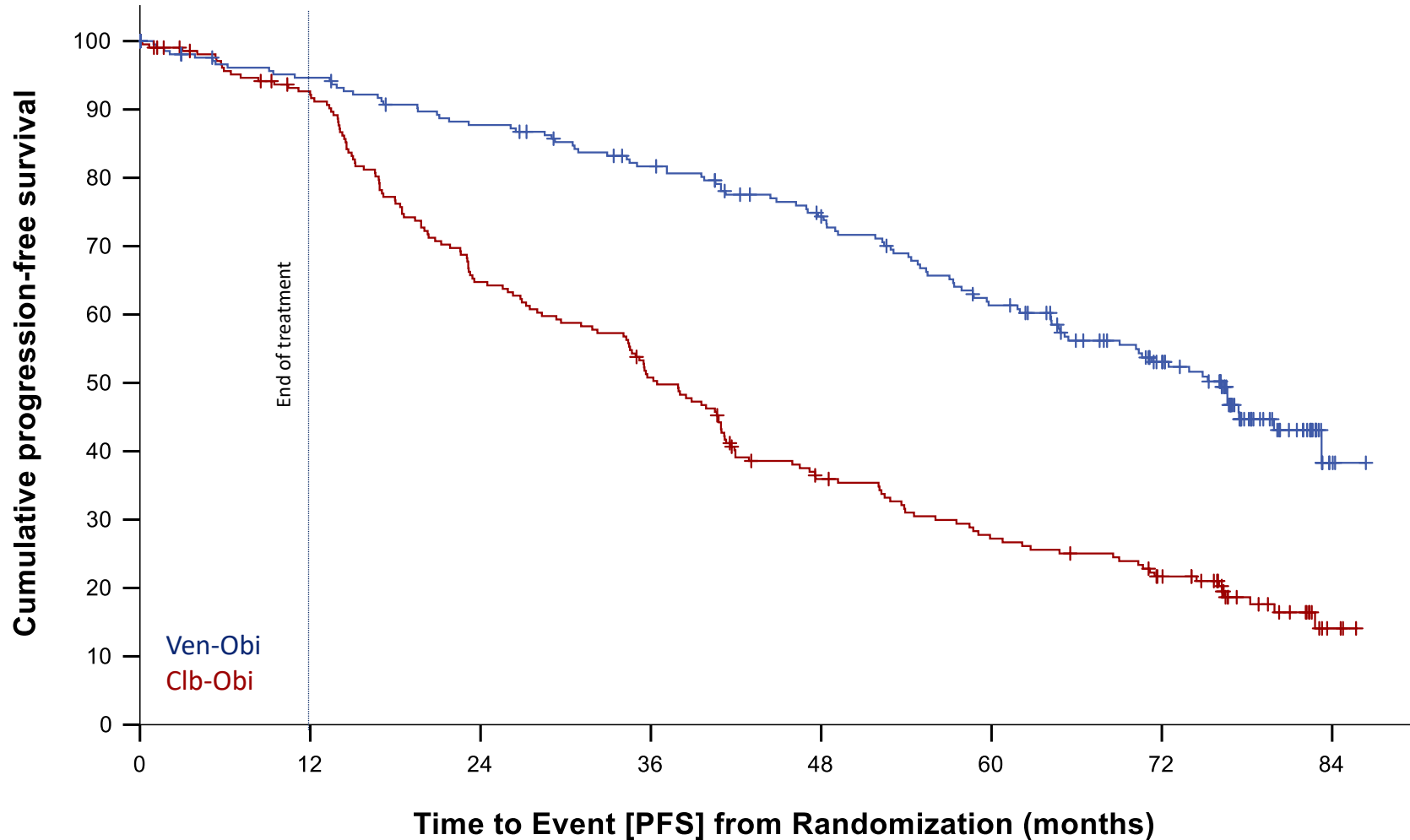
# CLL14 – venetoclax/obinutuzumab vs chlorambucil/obin



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

# CLL14 – venetoclax/obinutuzumab vs chlorambucil/obin

## 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],  $P < 0.0001$

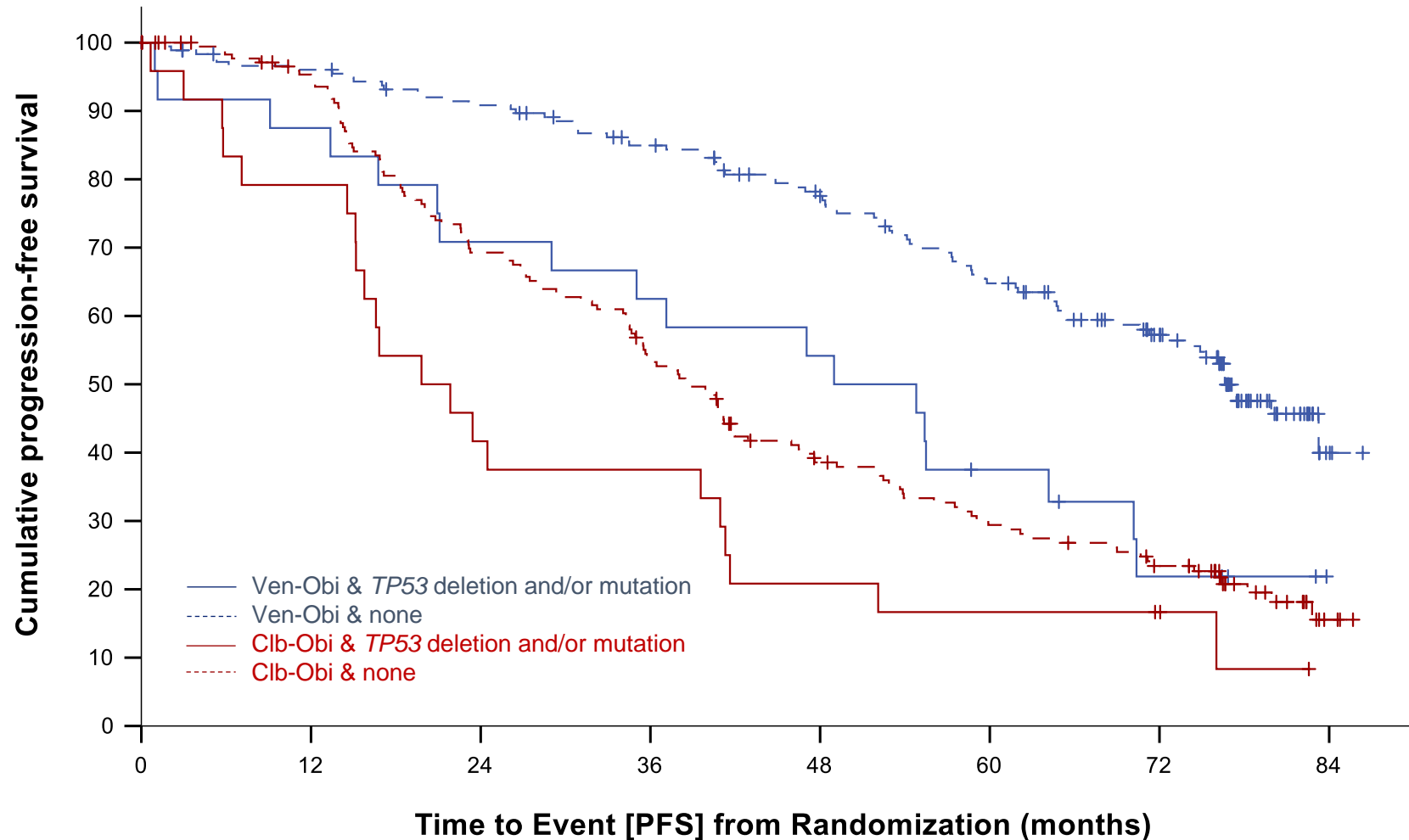
### 6-year PFS rate

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

Ven-Obi	216	193	177	160	139	112	79	3
Clb-Obi	216	185	130	101	67	50	36	3

# CLL14 – venetoclax/obinutuzumab vs chlorambucil/obi

## Progression-Free Survival by *TP53* Status

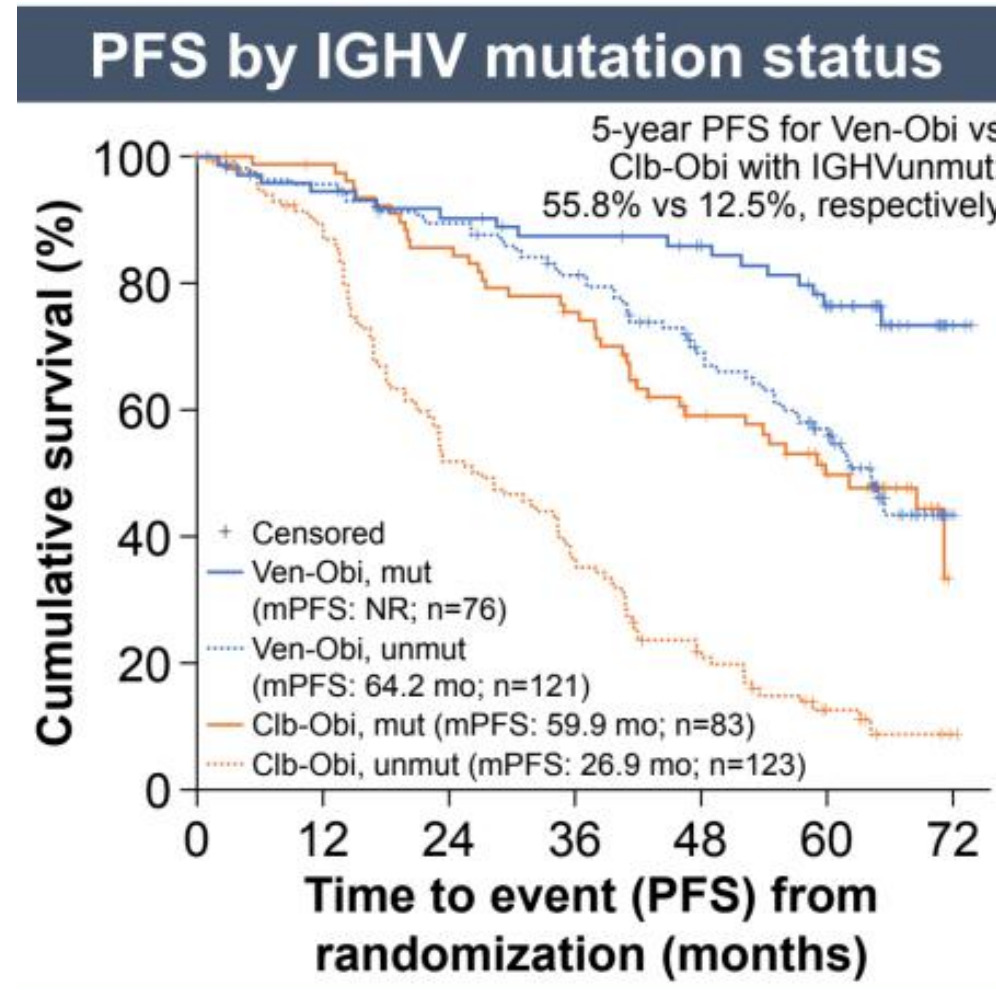


### Median PFS

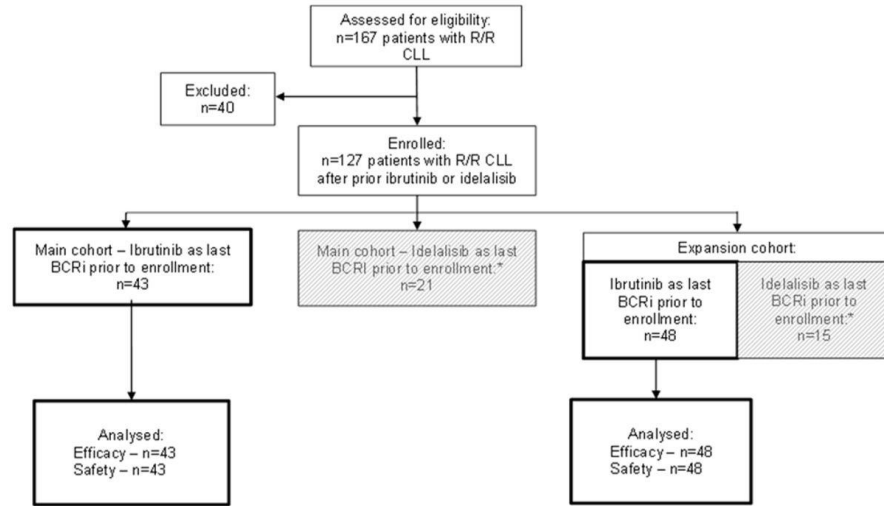
- Ven-Obi & no *TP53*del/mut: 76.6 mo
- Ven-Obi & *TP53*del/mut: 51.9 mo
  - HR 2.29 (95% CI 1.37-3.83);  $P=0.001$
- Clb-Obi & no *TP53*del/mut: 38.9 mo
- Clb-Obi & *TP53*del/mut: 20.8 mo
  - HR 1.66 (95% CI 1.05-2.63),  $P=0.03$

# CLL14 – venetoclax/obinutuzumab vs chlorambucil/obin

## Progression-Free Survival by *IGHV mut* Status



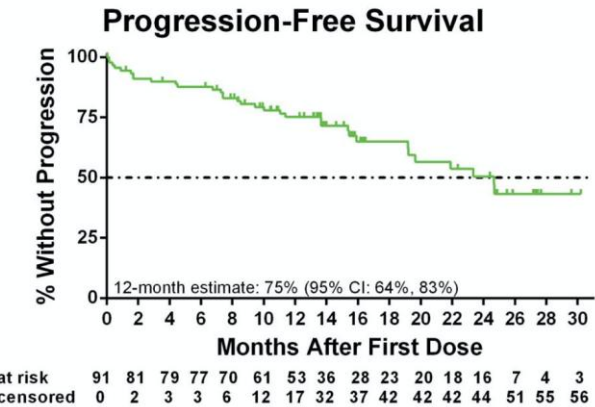
# Venetoclax post Ibrutinib



	Patients who received ibrutinib as the last prior BCRi		
	Main cohort n=43	Expansion cohort n=48	All patients N=91
ORR, n (%); [95% CI]	30 (70); [54%; 83%]	29 (60); [43%, 72%]	59 (65); [53%, 74%]
CR/CRi, n (%)	4 (9)	4 (8)	8 (9)
nPR, n (%)	2 (5)	1 (2)	3 (3)
PR, n (%)	24 (56)	24 (48)	48 (52)
SD, n (%)	8 (19)	14 (29)	22 (24)
PD, n (%)	1* (2)	4* (8)	5 (6)
Discontinued prior to response assessment	4 (9)	2 (4)	6 (7)

mF/U 19 mo      mF/U 12 mo      mF/U 14 mo

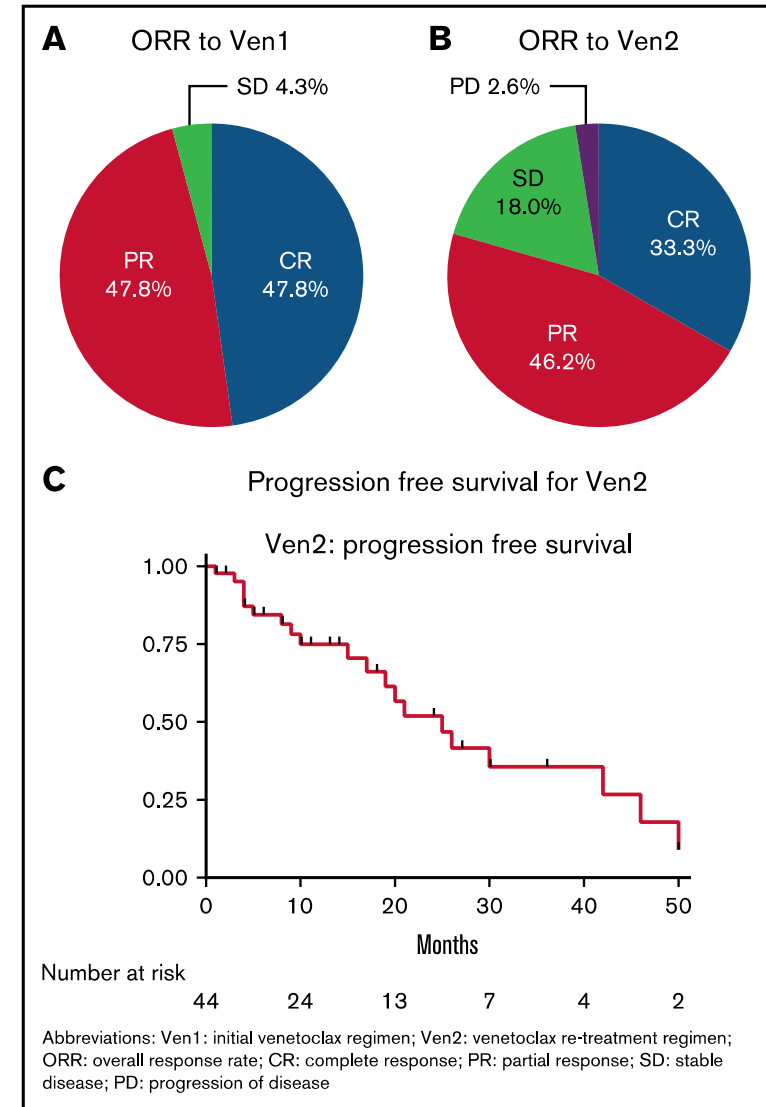
Characteristic	Patients who received ibrutinib as the last prior BCRi		
	Main cohort n=43	Expansion cohort n=48	Total N=91
Age, median (range), years	66 (48 – 80)	65 (28 – 81)	66 (28 – 81)
Unmutated <i>IGHV</i>	25/29 (86)	25/38 (66)	50/67 (75)
del(17)(p13:1)	21/43 (49)	21/47 (40)	42/90 (47)
del(11)(q22:3)	13/43 (30)	17/48 (33)	30/91 (33)
<i>TP53</i> mutation	15/41 (37)	14/46 (30)	29/87 (33)
No. of prior therapies, median (range)	5 (1 – 12)	4 (1 – 15)	4 (1 – 15)
Prior ibrutinib use, n (%)	43 (100)	48 (100)	91 (100)
Time on prior ibrutinib, median (range), months	18 (1 – 56)	21 (1 – 61)	20 (1 – 61)
Relapsed during or after ibrutinib, <sup>§</sup> n (%)	11 (26)	17 (35)	28 (31)
Refractory to ibrutinib, <sup>§</sup> n (%)	32 (74)	30 (63)	62 (68)



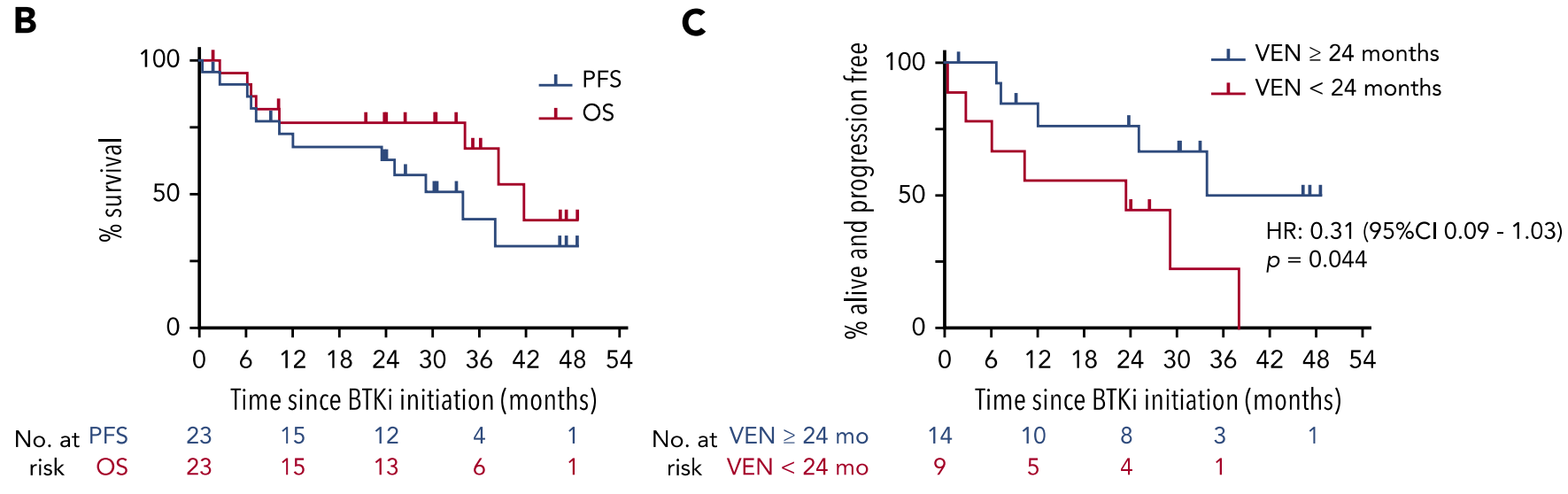
# Venetoclax post Venetoclax

Baseline Characteristics	Results	N (pts w avail data)
Median age at diagnosis (range), years	55.5 (24-75)	46
Median age at Ven1 start (range), years	64 (31-75)	46
Ven1 as monotherapy	37%	46
Ven1 as first line	8.7%	46
Median prior lines of therapy (range)	2 (0-10)	46
Prior BTKi	40%	45
del(17p)	25%	44
TP53 mut	15.6%	32
Complex karyotype	20.5%	39
Unmutated IGHV	82.1%	39
Ven1 regimen	Monotherapy 37% Ven-R 47.8% Ven-G 4.3% Ven-Ibr 2.2% Other 8.7%	46
Ven2 regimen	Monotherapy 45.7% Ven-R 28.2% Ven-G 10.9% Ven-Ibr 4.4% Other 10.9%	46

- median 16 mos completion Ven1 - start Ven2 (3-52)
  - 84.8% of patients with 6+-month interval
  - 58.7% 12+-month interval
  - 84.8% no tx between Ven1-Ven2



# BTKi post Venetoclax

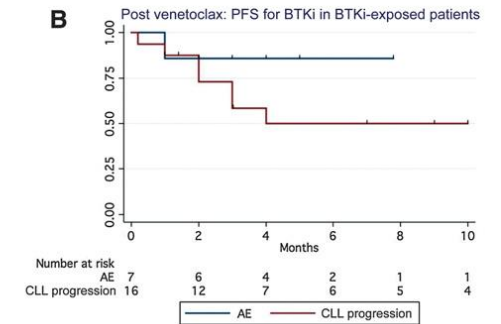
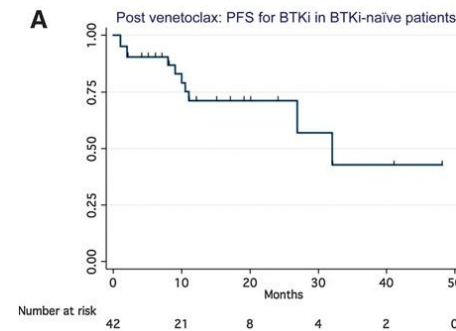


- N=23 (ibrutinib, n=21; zanubrutinib, n=2)
- mF/U 33 months (range, 2-53)
  - 11 pts remained on BTKi
  - 12 pts stopped therapy (PD, n=8; toxicity, n=4)
- mPFS 34 months (range, <1 to 49)
- mOS 42 months (range, 2-49)

# BTKi post Venetoclax

Characteristic	Result (range)	Number with available data
Median age at CLL diagnosis	58 years (32-88)	326
Median age at venetoclax start	66 years (38-91)	324
Median number therapies prior to venetoclax	3 (0-11)	326
Male	69%	326
White	87%	325
Rai stage $\geq 3$	64%	318
Del(17p) positive	47%	312
TP53 mutation present	45%	221
TP53 disruption (del17p or TP53 mutation)	56%	312
Del(11q) positive	27%	311
Complex karyotype present	39%	279
NOTCH1 mutation present	18%	103
IGHV unmutated	82%	171
Ibrutinib prior to venetoclax	60%	324
Any BTKi prior to venetoclax	61%	324
Idelalisib prior to venetoclax	19%	324

Subsequent therapy	BTKi	BTKi
Agents	Ibrutinib Acalabrutinib	Ibrutinib Acalabrutinib Noncovalent BTKi
Pre-ven exposure	BTKi-naïve	BTKi exposed 33% BTKi intolerant 66% BTKi resistant
Patient number	44	30
Lines of therapy pre-ven, median (range)	2 (0-8)	4 (1-11)
ORR	83.9%	53.4%
CR	9.0%	10.0%
PR	56.8%	26.7%
PR-L	18.1%	16.7%
SD	11.6%	23.3%
PD	4.5%	23.3%
Median PFS (months)	32	12
Median follow-up (months)	10.5	3.5
DC rate	38%	38%
Reasons for DC (% discontinuations)		
CLL progression	21.4%	66.6%
Adverse event	14.3%	8.3%
Transformation	14.3%	—
Planned cellular Tx	14.2%	—
Unrelated death	7.1%	8.3%
Sudden death on Tx	7.1%	16.6%
Patient preference	7.1%	—
Other	14.2%	—



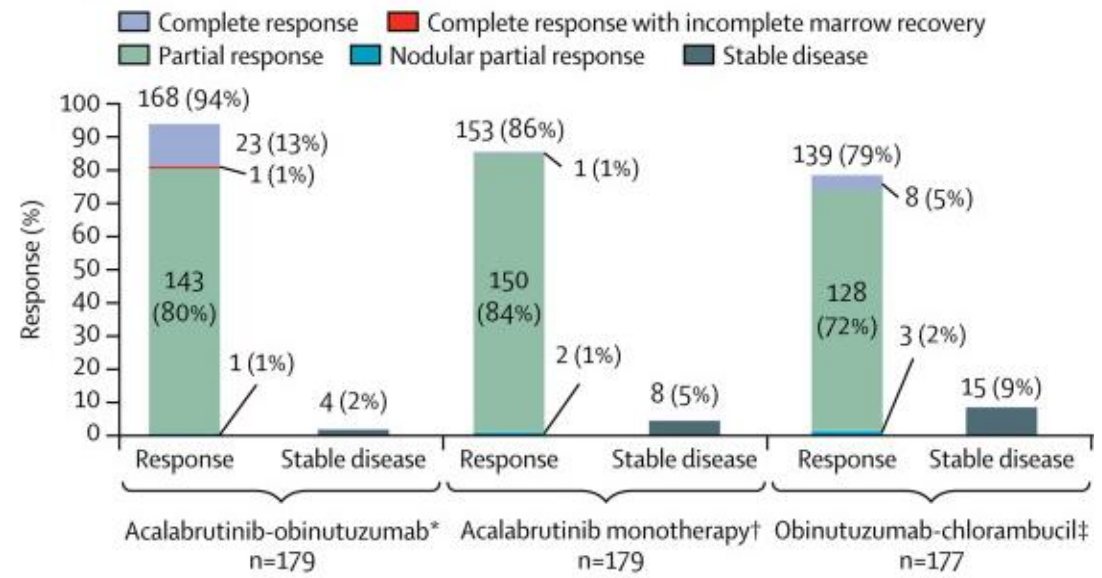
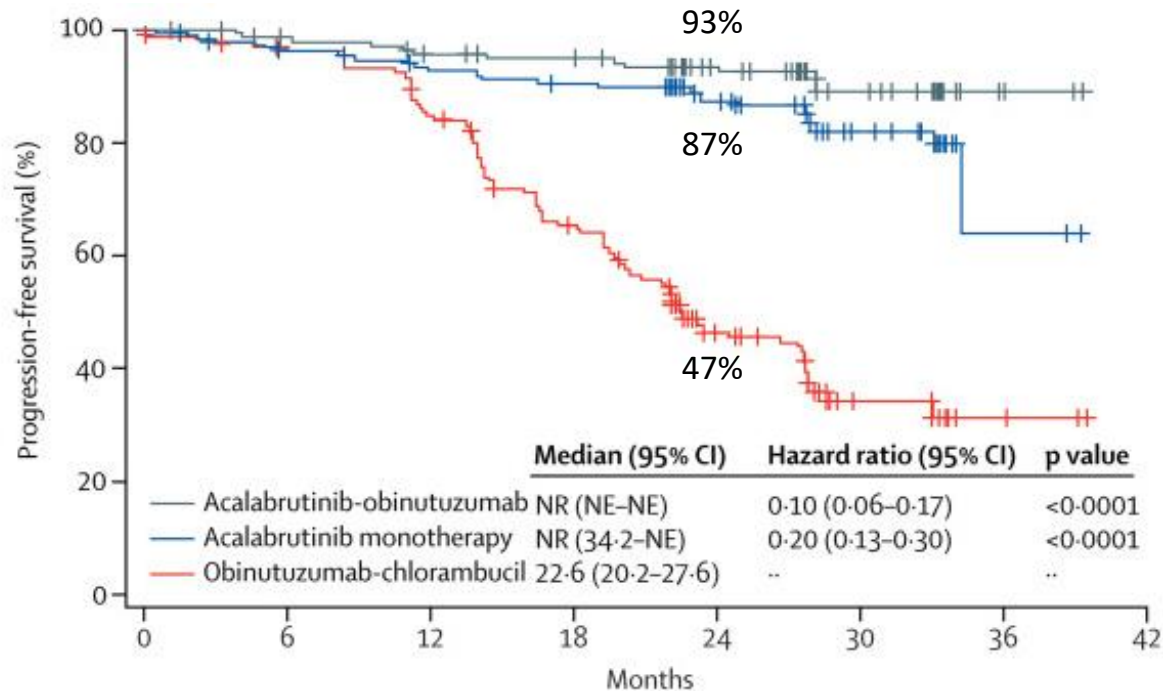
# New combinations

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cBTKi, ncBTKi, obin, ven alphabet soup

# Acalabrutinib in CLL – ELEVATE-TN

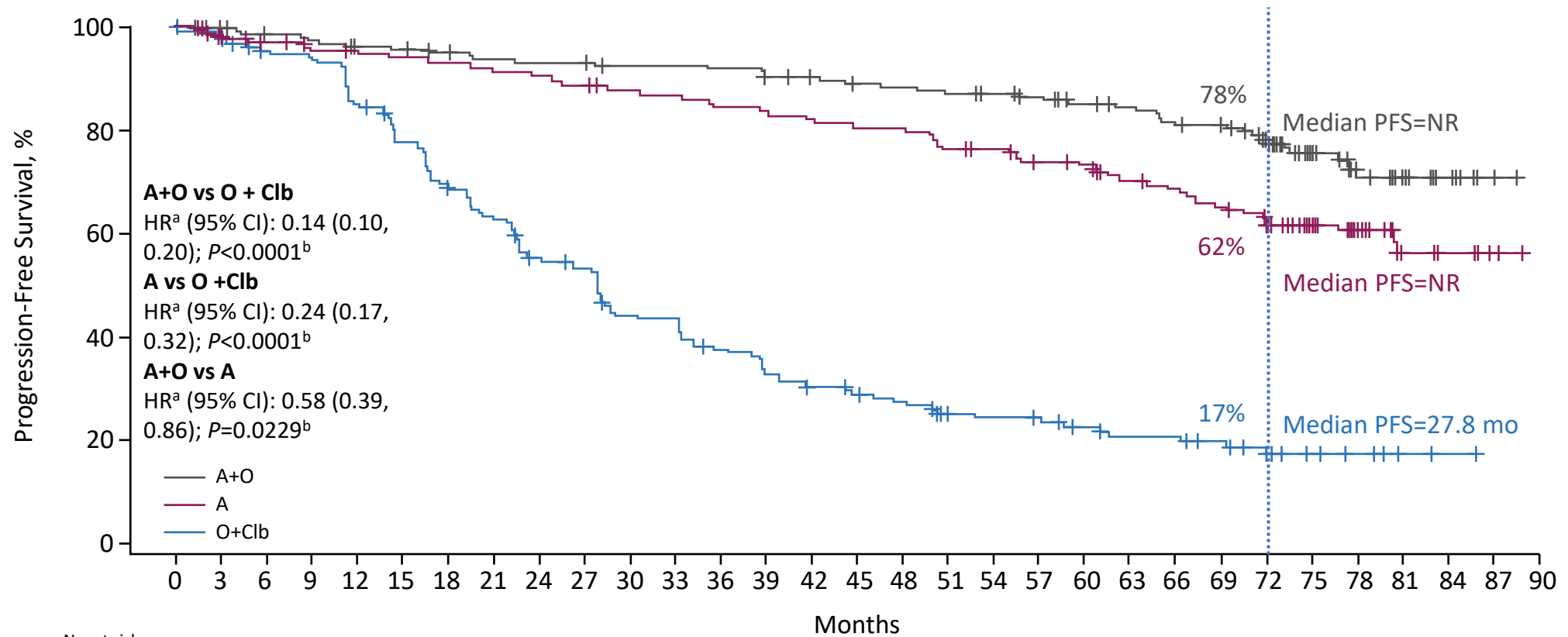
- Phase 3, elderly patients/comorbidities-frail, primary endpoint PFS
  - n=535, median age 70



# Acalabrutinib in CLL – ELEVATE-TN - long-term

	A+O (n=178)		A (n=179)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Diarrhea	78 (43.8)	11 (6.2)	76 (42.5)	1 (0.6)
Headache	72 (40.4)	2 (1.1)	70 (39.1)	2 (1.1)
Arthralgia	64 (36.0)	4 (2.2)	49 (27.4)	2 (1.1)
Neutropenia	61 (34.3)	55 (30.9)	23 (12.8)	21 (11.7)
Fatigue	55 (30.9)	4 (2.2)	43 (24.0)	2 (1.1)
Cough	50 (28.1)	1 (0.6)	45 (25.1)	1 (0.6)
COVID-19	44 (24.7)	16 (9.0)	38 (21.2)	13 (7.3)
Thrombocytopenia	26 (14.6)	15 (8.4)	16 (8.9)	6 (3.4)
Pneumonia	25 (14.0)	13 (7.3)	27 (15.1)	11 (6.1)
Hypertension	17 (9.6)	8 (4.5)	19 (10.6)	9 (5.0)
Syncope	12 (6.7)	9 (5.1)	5 (2.8)	4 (2.2)

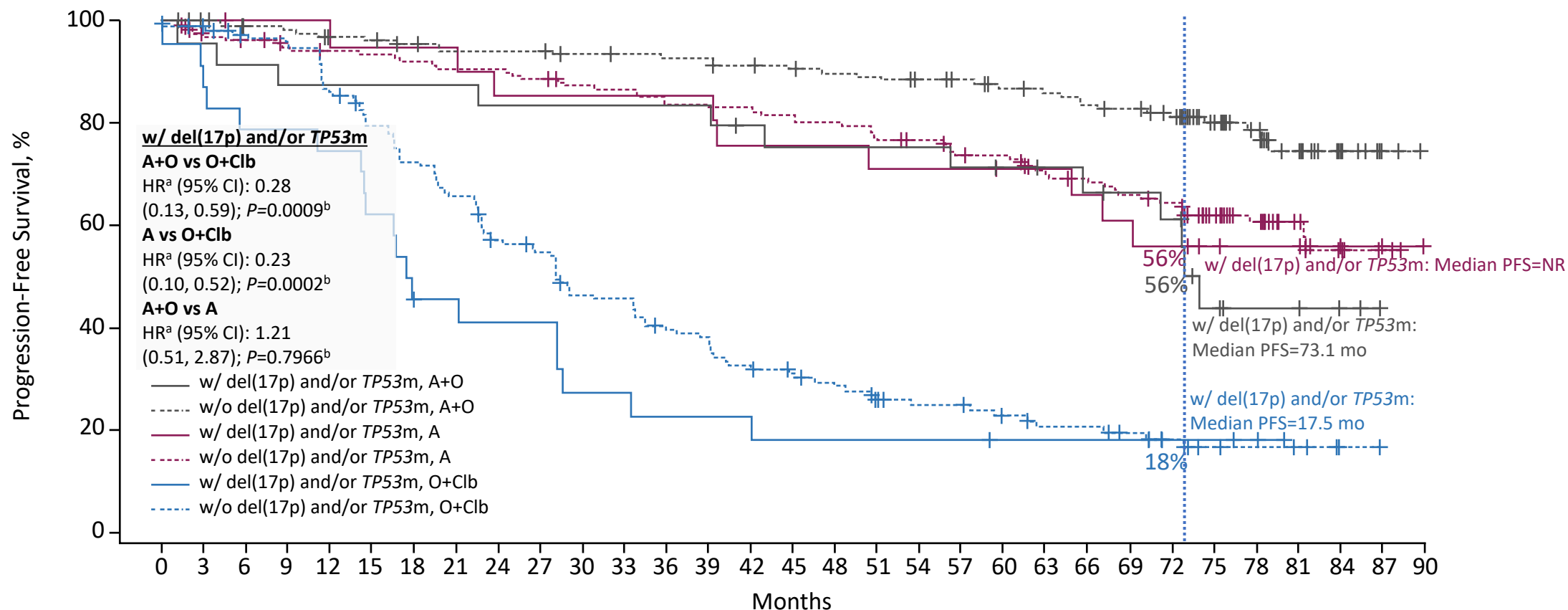
# Acalabrutinib in CLL – ELEVATE-TN - long-term



No. at risk

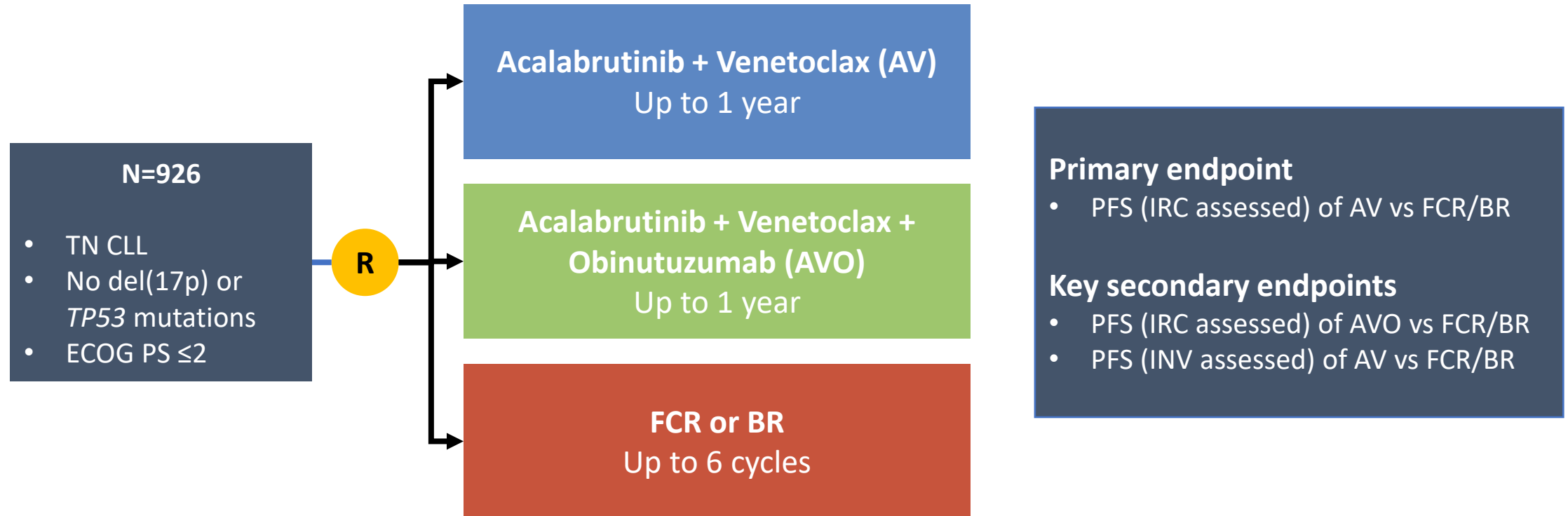
A+O	179	175	170	168	164	163	160	157	156	156	153	152	151	146	144	141	140	138	136	133	127	124	119	116	99	54	39	25	10	2	0
A	179	167	163	158	156	155	153	150	149	146	142	141	137	135	133	130	129	124	121	115	113	103	100	95	85	56	37	22	7	2	0
O+Clb	177	163	156	153	139	125	110	100	86	82	67	66	56	49	44	41	38	30	29	28	24	21	21	18	14	8	6	3	1	0	0

# Acalabrutinib in CLL – ELEVATE-TN - long-term

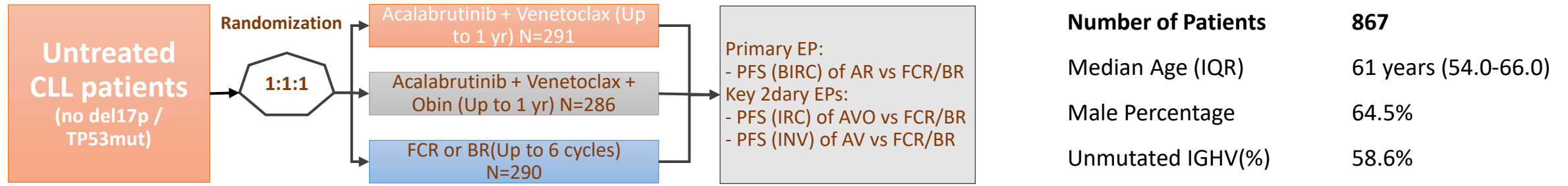


No. at risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66	69	72	75	78	81	84	87	90
w/ del(17p) and/or TP53m, A+O	25	24	23	22	22	22	22	22	21	21	21	21	21	20	19	18	18	18	18	17	16	15	14	13	10	5	5	3	2	0	
w/o del(17p) and/or TP53m, A+O	154	151	147	146	142	141	138	135	135	135	132	131	130	126	125	123	122	120	118	116	111	109	105	103	89	49	34	22	8	2	
w/ del(17p) and/or TP53m, A	23	22	21	21	20	20	20	19	18	18	18	18	18	17	16	16	16	15	15	15	14	14	13	11	11	7	7	4	2	1	
w/o del(17p) and/or TP53m, A	156	145	142	137	136	135	133	131	131	128	124	123	119	118	117	114	113	109	106	100	99	89	87	84	74	49	30	18	5	1	
w/ del(17p) and/or TP53m, O+Clb	25	21	19	19	18	15	10	9	9	9	6	6	5	5	4	4	4	4	4	4	3	3	3	3	3	3	1	0			
w/o del(17p) and/or TP53m, O+Clb	152	142	137	134	121	110	100	91	77	73	61	60	51	44	40	37	34	26	25	24	21	18	18	15	11	5	5	3	1	0	

# AMPLIFY – acalabrutinib + ven +/- obin (no TP53/del17p)



# AMPLIFY – acalabrutinib + ven +/- obin (no TP53/del17p)



	<b>AV</b>	<b>AVO</b>	<b>FCR/BR</b>
Median Follow-Up		41 months	
Median PFS (BIRC)	Not reached	Not reached	47.6 months
<b>36-Month PFS Rate</b>	<b>76.5%</b>	<b>83.1%</b>	<b>66.5%</b>
BICR-Assessed ORR	92.8% (95% CI 89.4-95.4)	92.7% (95% CI 89.2-95.3)	75.2% (95% CI 70.0-79.9)

# AMPLIFY – acalabrutinib + ven +/- obin (no TP53/del17p)

	<b>AV</b>	<b>AVO</b>	<b>FCR/BR</b>
Deaths Prior to April 30, 2024	18 (10 COVID-related)	37 (25 COVID-related)	42 (21 COVID-related)

<b>Event</b>	<b>AV</b>	<b>AVO</b>	<b>FCR/BR</b>
Most Common Grade ≥3 AE (Neutropenia)	26.8%	35.2%	32.4%
Serious AEs	24.7%	38.4%	27.4%
Tumor Lysis Syndrome	0.3%	0.4%	3.1%
Atrial Fibrillation (any grade)	0.7%	2.1%	0.8%
Hypertension (Grade ≥3)	2.7%	2.1%	0.8%

Then what?

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What do you do?

# Current practice

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- Consider mainly single agent BTKi or ven/obin
  - Take all features beyond disease into consideration
  - Preferably BTKi for del17p/TP53
  - Discuss potential inferiority for ven in del17p/TP53, unmut IgVH but may still do it
  - "Finite" therapy for TP53/del17p with BTKi+ven
- Preferably use Zanubrutinib
  - AEs are very mild, may avoid in very select cases
- Obinutuzumab in select situations
  - Sluggish response, hemolytic anemia
- Venetoclax ramp up hardly ever a problem
  - Neutropenias generally mild and controlled with gcsf
  - Anemia, thrombocytopenia more frequently from CLL itself
- Never switch between cBTKi if progression
  - Reason that led to cBTKi may be the same that will lead to ncBTKi

# Thank you

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