State of the art on therapies in CLL 2023

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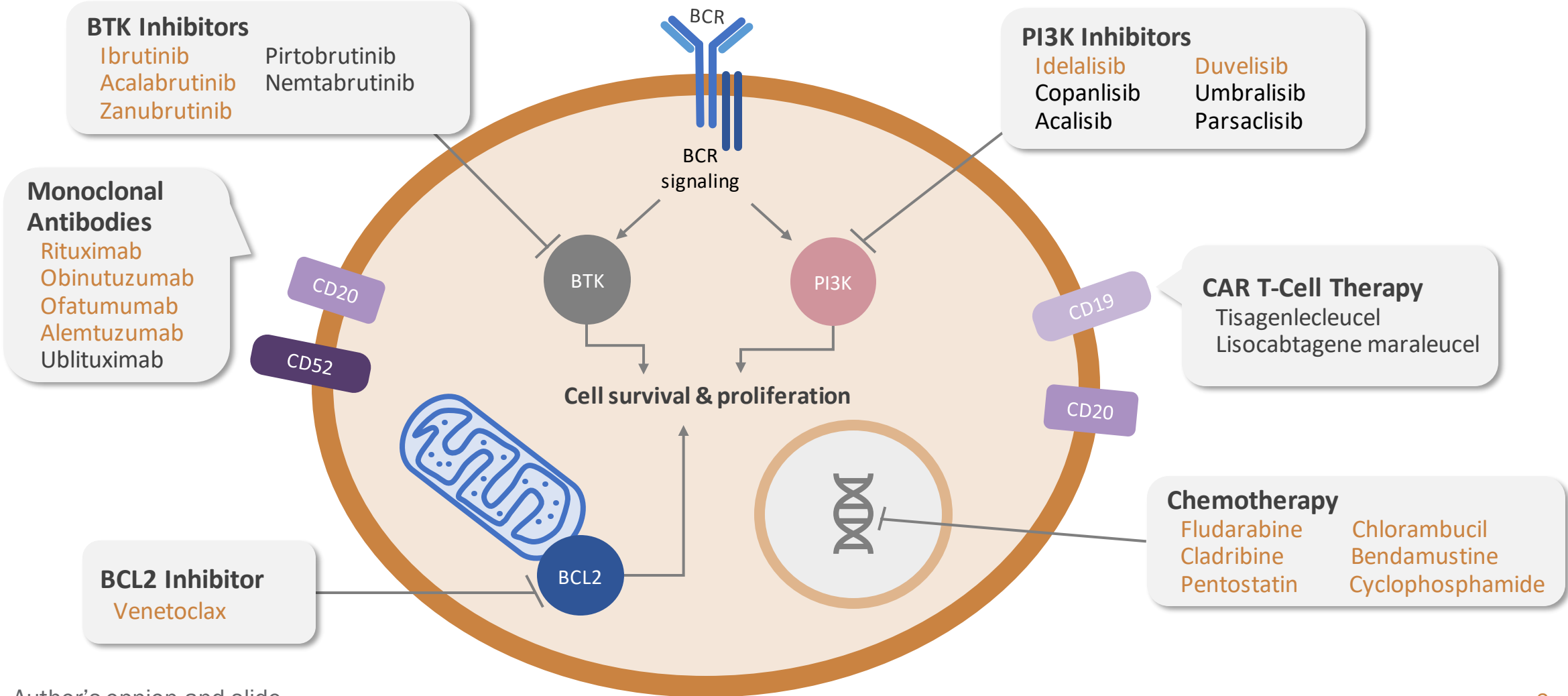*Malignant Hematology Department*

MOFFITT
CANCER CENTER

COI

- Janssen/Pharmacyclics, Abbvie, Genentech, AstraZeneca, Pfizer, Beigene and Takeda : Consulting and speaker bureau.

- Novartis, Lilly, BMS and Merck: Consulting.

# Established and Experimental Therapies in CLL

BTK Inhibitors
Ibrutinib   Pirtobrutinib
Acalabrutinib   Nemtabrutinib
Zanubrutinib

PI3K Inhibitors
Idelalisib   Duvelisib
Copanlisib   Umbralisib
Acalisib   Parsaclisib

Monoclonal Antibodies
Rituximab
Obinutuzumab
Ofatumumab
Alemtuzumab
Ublituximab

CAR T-Cell Therapy
Tisagenlecleucel
Lisocabtagene maraleucel

BCL2 Inhibitor
Venetoclax

Chemotherapy
Fludarabine   Chlorambucil
Cladribine   Bendamustine
Pentostatin   Cyclophosphamide

BCR

BCR signaling

CD20

CD52

BTK

PI3K

CD19

CD20

Cell survival & proliferation

BCL2

The dilemma continue between long term therapy vs fixed duration

# The new era of BTK Inhibitors in CLL

IC_{50}/EC_{50} (nM)

Kinase	Ibrutinib	Acalabrutinib	Zanubrutinib
BTK	1.5	5.1	0.5
TEC	10	126	44
ITK	4.9	> 1000	50
BMX	0.8	46	1.4
EGFR	5.3	> 1000	21
ERBB4	3.4	16	6.9
JAK3	32	> 1000	1377
BLK	0.1	> 1000	2.5

Kaptein. ASH 2018.

Kinase Selectivity Profiling at 1 µmol/L (in vitro)
Larger red circles represent stronger inhibition

Ibrutinib

Acalabrutinib

Zanubrutinib
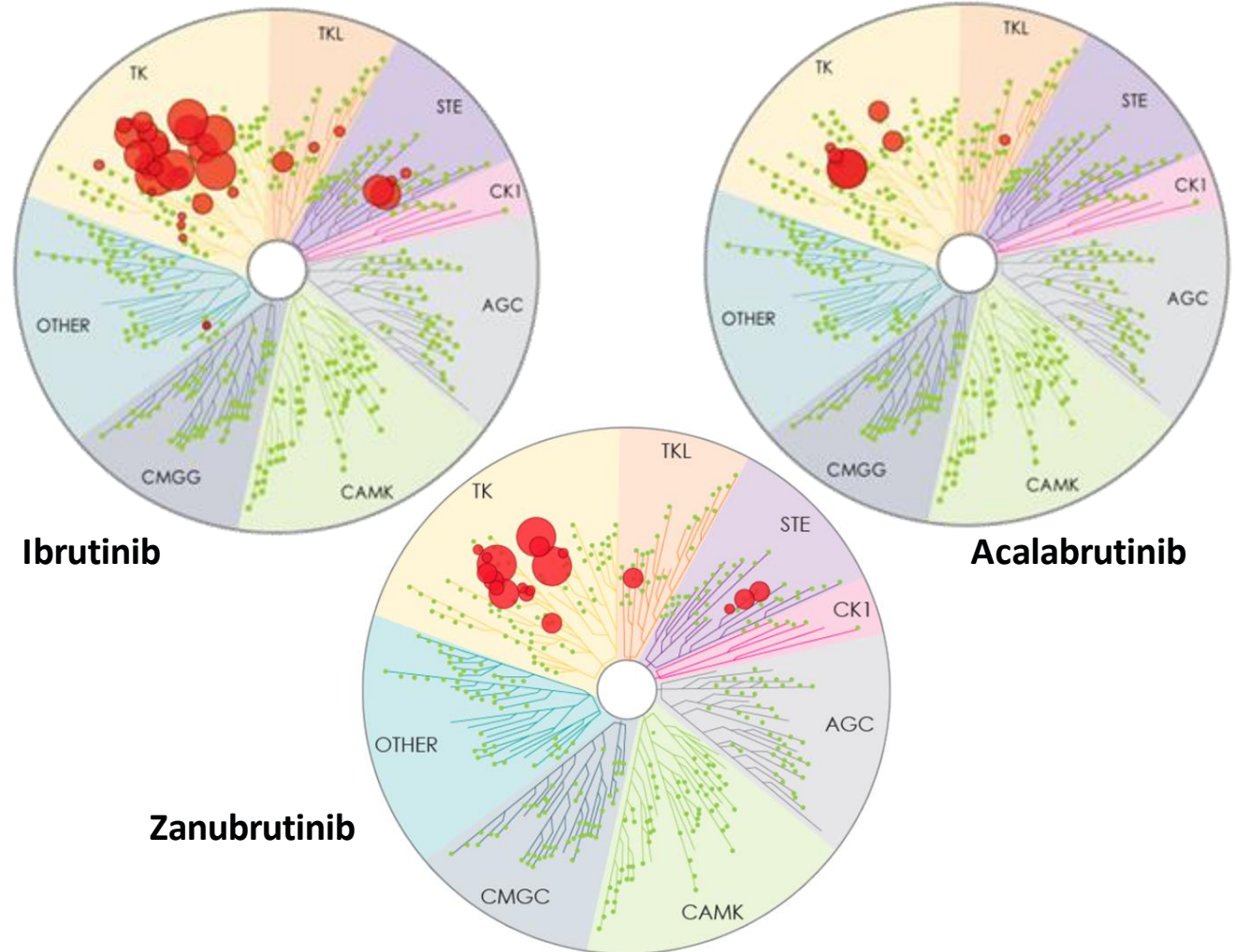
BTKi long term data
Ibrutinib

RESONATE-2: 8-Year Follow-Up - PFS
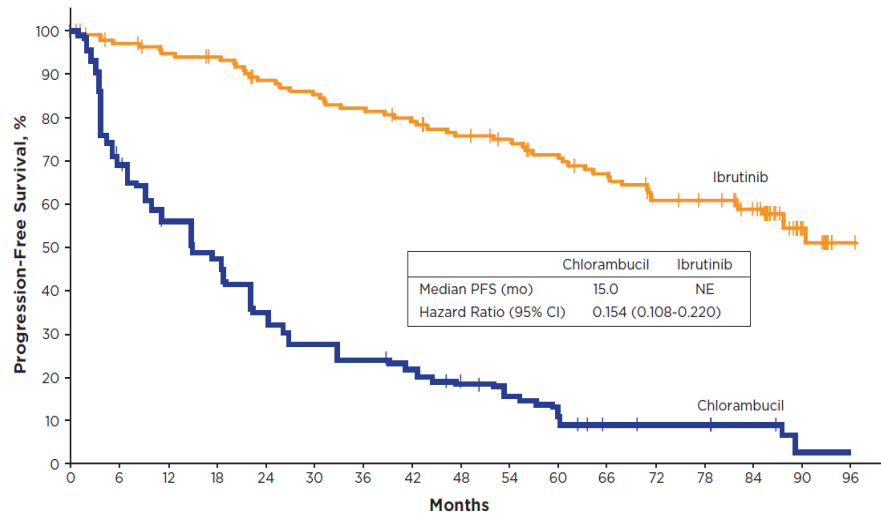
	Chlorambucil	Ibrutinib
Median PFS (mo)	15.0	NE
Hazard Ratio (95% CI)	0.154 (0.108-0.220)	

Patients at Risk

Ibrutinib:	136	129	124	121	112	108	104	99	92	88	81	76	67	65	57	17	1
Chlorambucil:	133	88	69	57	41	33	30	25	19	16	12	6	5	5	4	1	0

	Ibrutinib n=136
Median duration of ibrutinib treatment, years	6.2
Continuing ibrutinib on study, n (%)	57 (42)
Discontinued ibrutinib, n (%)	
AE	**32 (24)**
PD	**18 (13)**
Death	12 (9)
Withdrawal by patient	9 (7)
Investigator decision	7 (5)

	With del(11q)		Without del(11q)	
	Ibr	Chl	Ibr	Chl
7 year PFS	52%	0	61%	12%
Median PFS, mo	88	9.0	NR	18.4
HR (95% CI)	0.033 (0.010-0.107)		0.193 (0.128-0.289)	

Patients at Risk

Ibrutinib, without del(11q):	101	94	89	87	80	76	73	70	64	61	57	55	48	47	43	13	0
Ibrutinib, with del(11q):	29	29	29	28	28	27	25	24	23	20	18	16	16	12	2	0
Chlorambucil, without del(11q):	96	64	54	45	35	29	25	21	17	15	12	6	5	5	4	1	0
Chlorambucil, with del(11q):	25	15	8	6	3	1	1	1	0

	Unmutated IGHV		Mutated IGHV	
	Ibr	Chl	Ibr	Chl
7 year PFS	58%	2%	68%	17%
Median PFS, mo	NR	9.3	NR	16.7
HR (95% CI)	0.112 (0.065-0.192)		0.174 (0.089-0.342)	

Patients at Risk

Ibrutinib, mutated IGHV:	40	37	34	34	32	30	30	29	27	26	25	22	19	19	16	6	1
Ibrutinib, unmutated IGHV:	58	57	56	53	49	48	46	43	42	41	36	35	32	30	27	10	0
Chlorambucil, mutated IGHV:	42	32	25	21	18	15	14	12	11	8	8	5	4	4	3	0	0
Chlorambucil, unmutated IGHV:	60	33	23	19	11	8	6	5	3	3	2	1	1	1	1	0	0

Barr et al Blood Advances 2022

Phase III E1912 Trial of Ibrutinib + Rituximab vs. FCR in Patients ≤70 Years of Age With Previously Untreated CLL

- Primary analysis of randomized, open-label phase III trial (data cutoff: October 24, 2018).

Stratified by age (< 60 vs. ≥ 60 years), ECOG PS (0/1 vs. 2),
stage (III-IV vs. I-II), del(11q22.3) vs. other

Patients with previously untreated CLL requiring treatment per iwCLL 2008, ≤70 years of age, ECOG PS 0-2, CrCl >40 mL/min, ability to tolerate FCR, no del(17p) by FISH (N=529)

Ibrutinib 420 mg PO QD for cycles 1-7 + **Rituximab** 50 mg/m^2 IV on Day 1, cycle 2, then 325 mg/mg^2 on Day 2, cycle 2, then 500 mg/m^2 on Day 1, cycles 3-7 (n=354)

Fludarabine 25 mg/m^2 IV on Days 1-3 for cycles 1-6 + **Cyclophosphamide** 250 mg/m^2 IV on Days 1-3 for cycles 1-6 + **Rituximab** 50 mg/m^2 IV on Day 1, cycle 1, then 325 mg/mg^2 on Day 2, cycle 1, then 500 mg/m^2 on Day 1, cycles 2-6 (n=175)

Ibrutinib maintenance until PD

28-day cycles

- Primary endpoint: PFS.
  - Study has 80% power to detect PFS HR for IR vs. FCR of 0.67 using stratified log-rank test, with prespecified boundary of 2.87 for first PFS interim analysis corresponding to 1-sided *P*=0.0025.

- Secondary endpoints: OS, safety.

Shanafelt et al *Blood 2022*.

E1912: 5 years Updated PFS, OS by IGHV Status

Progression Free Survival

HR = 0.37, (95% CI: 0.27 − 0.51)
P < 0.0001
5−year rates: 78%, 51%

FCR (74 events/ 175 cases)
IR (84 events/ 354 cases)

Number at risk
175 145 123 98   62   45   21   0
354 339 321 306 248 193 110 7

Overall Survival

HR = 0.47, (95% CI: 0.25 − 0.89)
P = 0.018
5−year rates: 95%, 89%

FCR (18 events/ 175 cases)
IR (21 events/ 354 cases)

Number at risk
175 155 143 131 126 96   47   3
354 347 343 338 329 300 139 20

IgHV unmutated

HR = 0.27, (95% CI: 0.18 − 0.41)
P < 0.0001
5−year rates: 75%, 33%

FCR (42 events/ 71 cases)
IR (56 events/ 210 cases)

Number at risk
71   63   50   39   20   12   5   0
210 203 193 184 147 108 61   6

IgHV mutated

HR = 0.27, (95% CI: 0.11 − 0.62)
P = 0.001
5−year rates: 83%, 68%

FCR (15 events/ 44 cases)
IR (14 events/ 70 cases)

Number at risk
44   38   34   30   21   17   9   0
70   67   64   60   50   40   18   1

Reason for Discontinuation	All Patients Who Started IR N=352
Progression or death	37 (10.5%)
Adverse event or complication	77 (21.9%)
Other reason*	24 (6.8%)
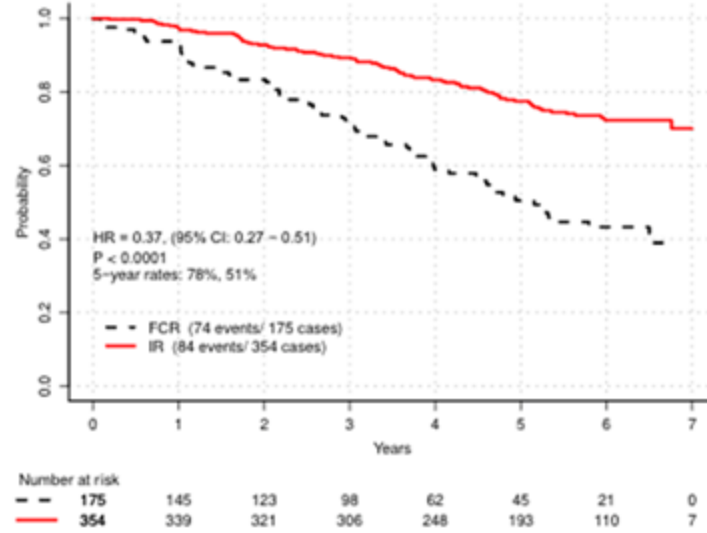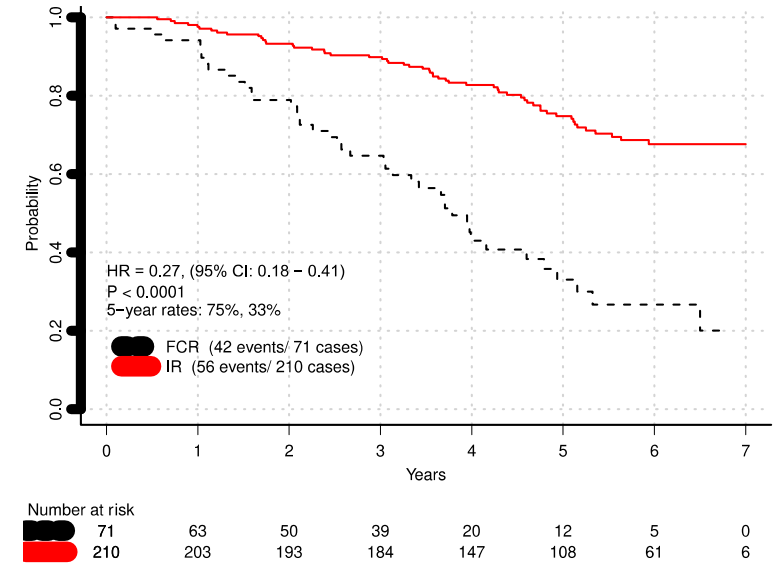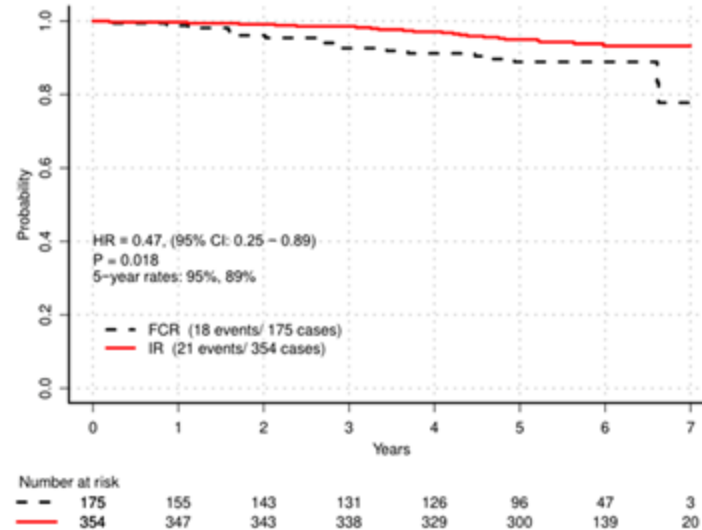
Shanafelt et al *Blood 2022*.
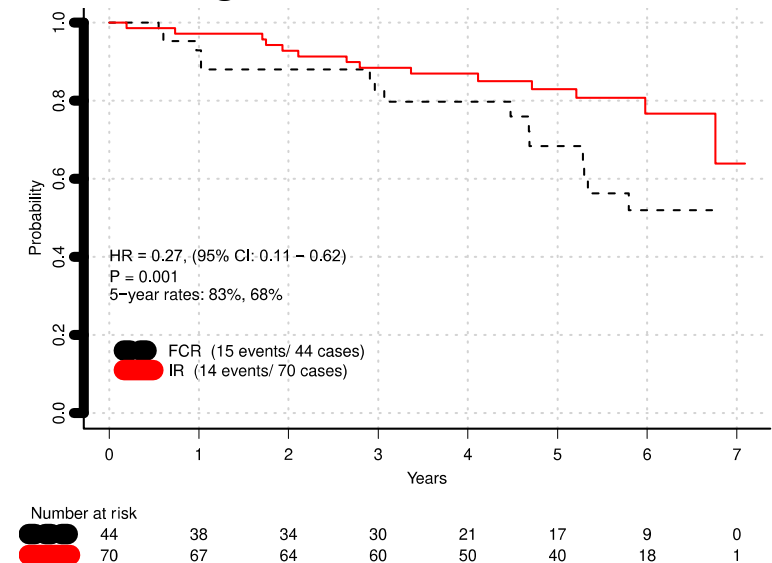
A041202: First-line Ibrutinib ± Rituximab vs Bendamustine + Rituximab in Older Patients With CLL/SLL

- Multicenter, randomized, double-blind phase III study (data cutoff: October 4, 2018)

Stratified by Rai stage (high vs intermediate risk), del(11q22.3) or del(17p13.1) (presence vs absence), ZAP-70 methylation (< vs ≥ 20%)

Untreated patients with CLL meeting iwCLL 2008 criteria for tx initiation; ≥ 65 yrs of age; ECOG PS 0-2; ANC ≥ 1000 unless due to BM involvement; PLT ≥ 30; $CrCl_{CG}$ ≥ 40; AST/ALT ≤ 2.5 x ULN; no heparin or warfarin
(N = 547)

Ibrutinib 420 mg QD (n = 182)
Ibrutinib 420 mg QD + **Rituximab** 375 mg/m^2 wkly x 4 wks starting cycle 2 Day 1; cycles 3-6 Day 1* (n = 182)
Bendamustine 90 mg/m^2 on Days 1, 2 + **Rituximab** 375 mg/m^2 on cycle 1 Day 1; 500 mg/m^2 on cycles 2-6 Day 1* (n = 183)

→ *Until PD*

→ *Ibrutinib until PD*

→ *Crossover to ibrutinib within 1 yr of PD allowed*

- Primary endpoint: PFS   *28-day cycles.

  - 2 primary comparisons of ibrutinib vs BR and ibrutinib + R vs BR with 90% power to detect HR of 0.586 (estimated 2-yr PFS rates: ibrutinib, 75%; BR, 61%) and overall 1-sided α = 0.025 for each comparison

  - If both primary comparisons significant, third planned comparison of ibrutinib + R vs ibrutinib

Woyach. ASH 2018. Abstr 6. Woyach. NEJM. 2018;379:2517. NCT01886872.

A041202: First-line Ibrutinib ± Rituximab vs Bendamustine + Rituximab in Older Patients With CLL/SLL
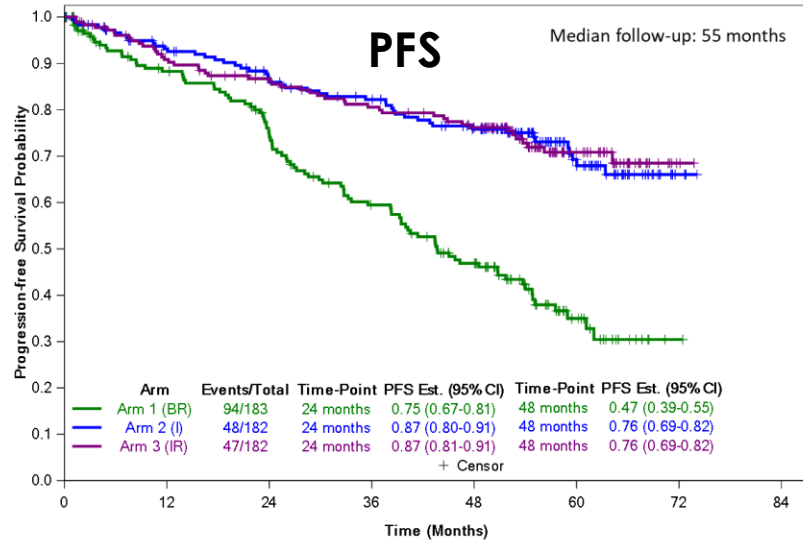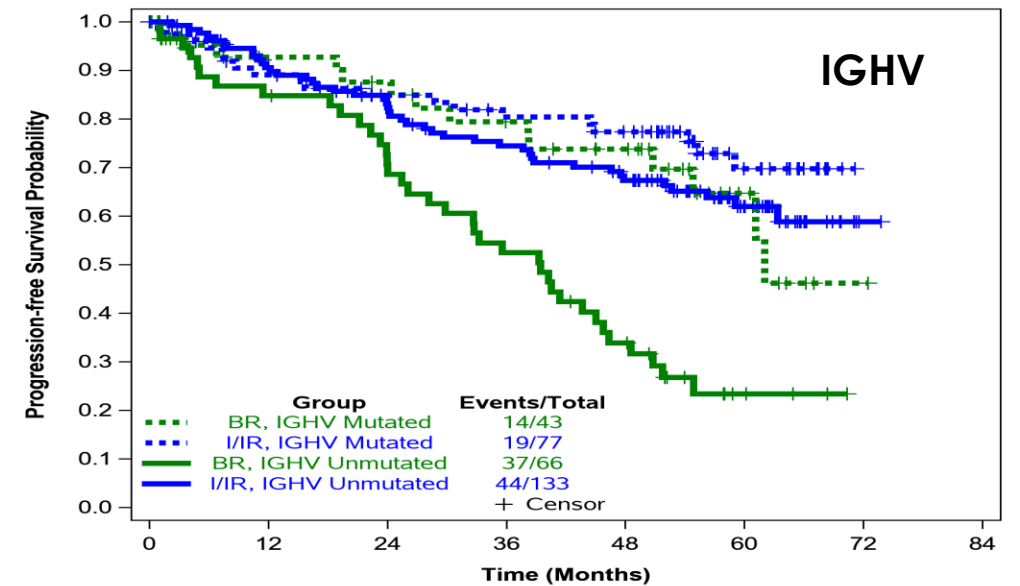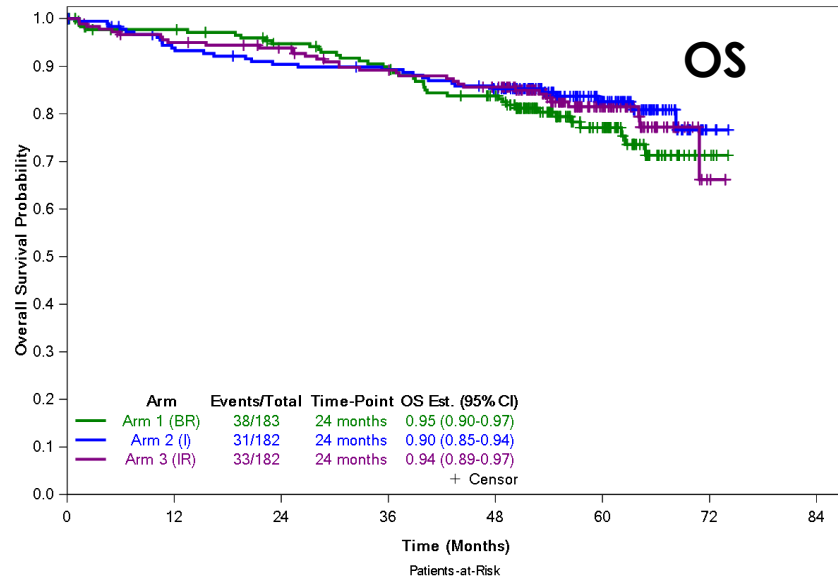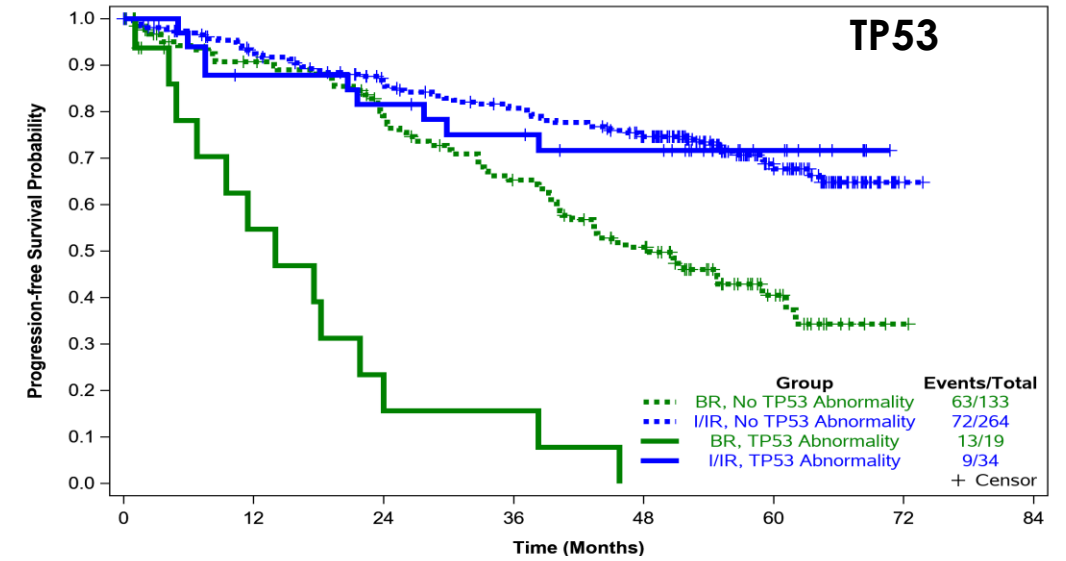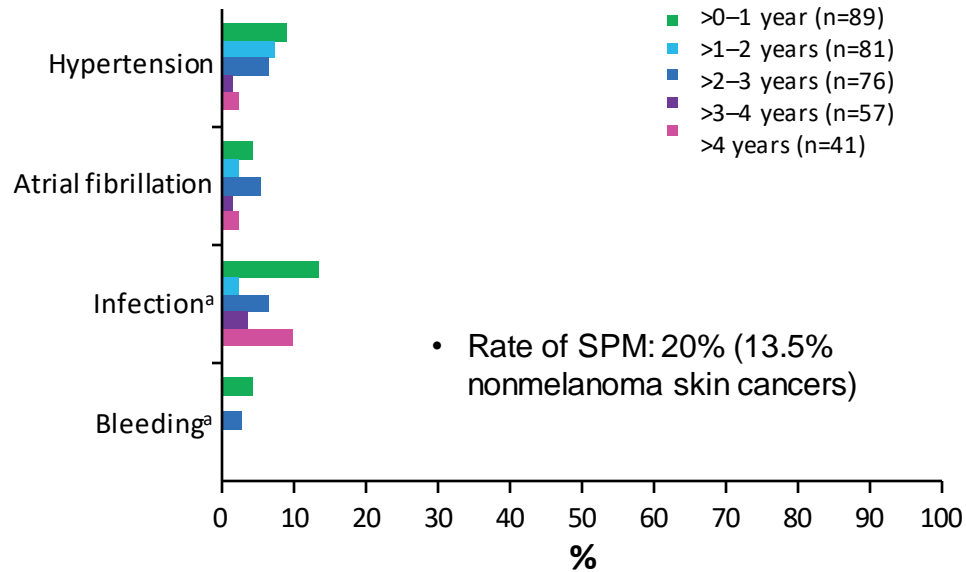

Woyach. ASH 2021.

Long-Term Efficacy of First-Line Ibrutinib for CLL With 4 Years of Follow-Up in Patients With TP53 Aberrations: Pooled Analysis From 4 Clinical Trials

	PCYC-1122e (NIH study)	RESONATE-2	iLLUMINATE	ECOG1912
N	34	11	18	26
Regimen	Ibr	Ibr	Ibr + Obinu	Ibr + Ritux
Patients	del(17p)/ *TP53*mut	*TP53*mut	del(17p)/ *TP53*mut	*TP53*mut

Progression-free Survival

79% at 4 yrs

Overall Survival

88% at 4 yrs

Grade ≥3 AEs

- >0–1 year (n=89)
- >1–2 years (n=81)
- >2–3 years (n=76)
- >3–4 years (n=57)
- >4 years (n=41)

Hypertension

Atrial fibrillation

Infection[a]

Bleeding[a]
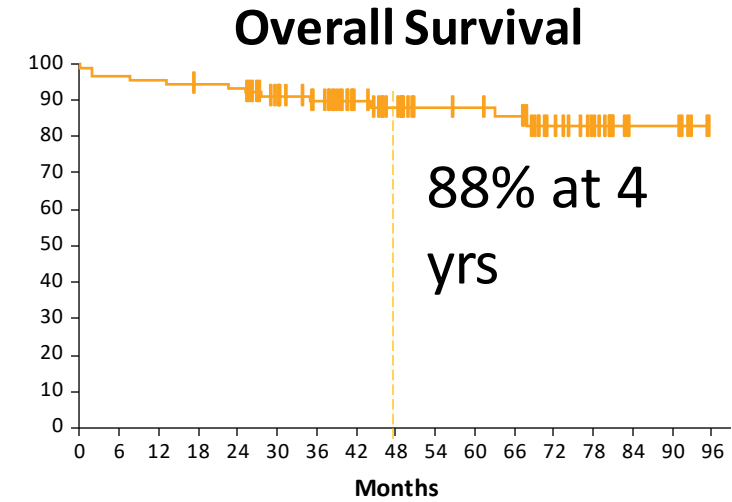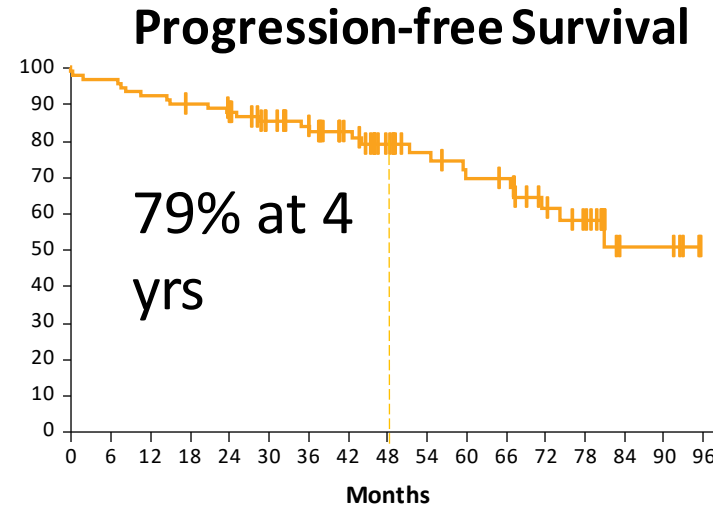
- Rate of SPM: 20% (13.5% nonmelanoma skin cancers)

- 2 Richter transformations among 63 evaluable pts (none in RES-2, iLLUMINATE)

- 9 pts d/c due to AEs: 2 deaths and one PD (at 36 mos post-dc)

CONCLUSIONS:
- With a median follow-up of 4 years (max. 8 years), first line ibrutinib-based treatment results in sustained efficacy in patients with *TP53* aberrations:
  - 4-year PFS 79%
  - 4-year OS 88%
  - ORR 94% and CR 39%
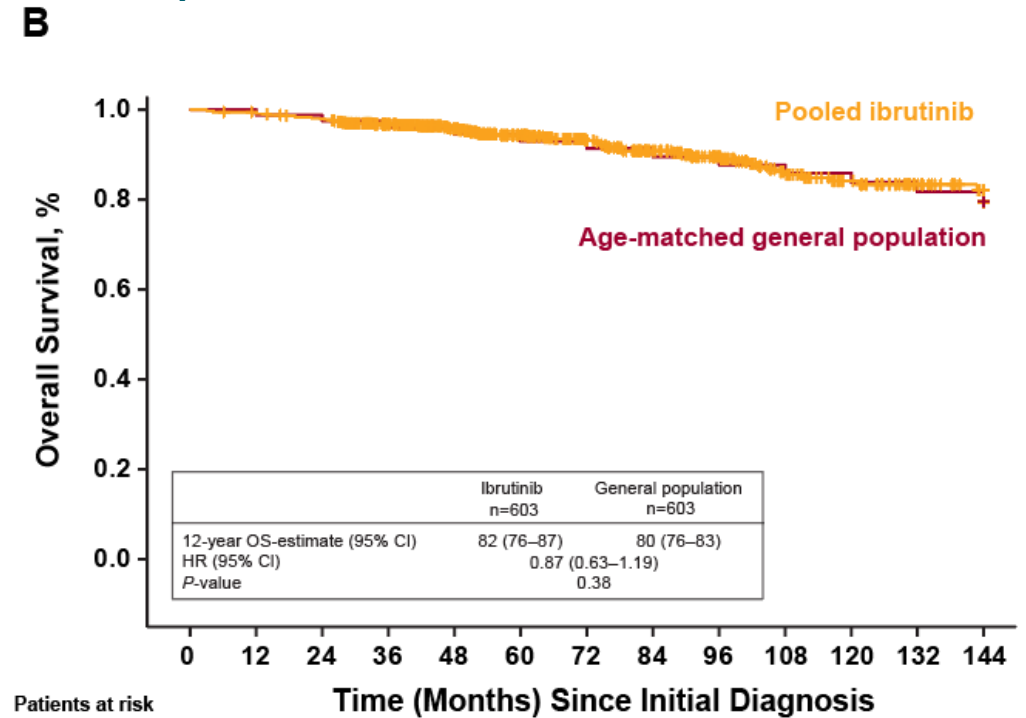- First line treatment with ibrutinib has meaningfully improved the poor prognosis in this high-risk population

Allan J, et al., BJH 2022

Initiating 1L Ibrutinib in Patients with CLL Improves Overall Survival Outcomes to Rates Approximating an Age-Matched Population of ≥65

Similar OS for Pooled Ibrutinib-Treated Patients ≥65 years[a] and (A) All Pooled Ibrutinib-Treated Patients[b], (B) Age-Matched General US Population

[a]Data after 96 months is not represented in the KM curve; [b]Data after 144 months is not represented in the KM curve

Paolo Ghia et al.,
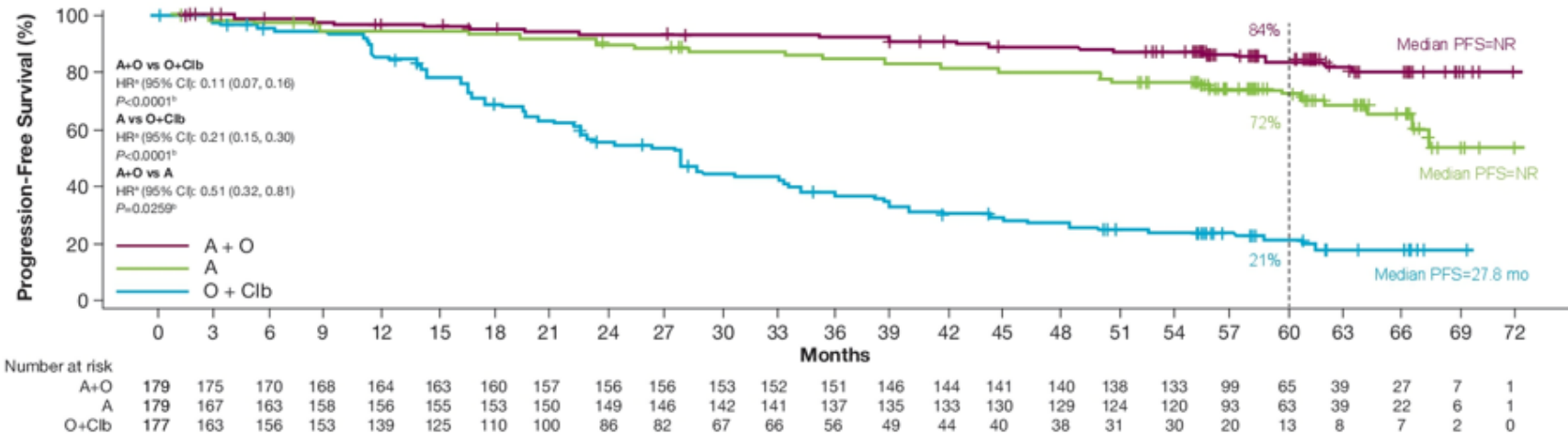*Presented at ASH 2022; No. #1809*

13

2nd generation BTKi
Acalabrutinib

ELEVATE-TN: Acalabrutinib ± Obinutuzumab vs Chlorambucil + Obinutuzumab in Previously Untreated CLL

Phase III trial

Treatment-naive CLL patients ≥ 65 yrs or < 65 yrs with CIRS score > 6 or CrCl < 70 mL/min (N = 535)

Stratified by: del(17p), ECOG PS 0/1 vs 2, geographic region

Acalabrutinib 100 mg PO BID **+ Obinutuzumab***
(n = 179)

Acalabrutinib 100 mg PO BID
(n = 179)

Obinutuzumab* + Chlorambucil 0.5 mg/kg PO D1, 15
(n = 177)

Crossover allowed to acalabrutinib after IRC-confirmed progression

*1000 mg IV on Days 1, 2, 8, 15 of 28-day cycle 1; Day 1 of cycles 2-6.

- Primary endpoint: PFS by IRC of acalabrutinib + obinutuzumab vs obinutuzumab + chlorambucil

- Key secondary endpoints: PFS of acalabrutinib vs obinutuzumab + chlorambucil, ORR by IRC and investigators, time to next treatment, OS, safety
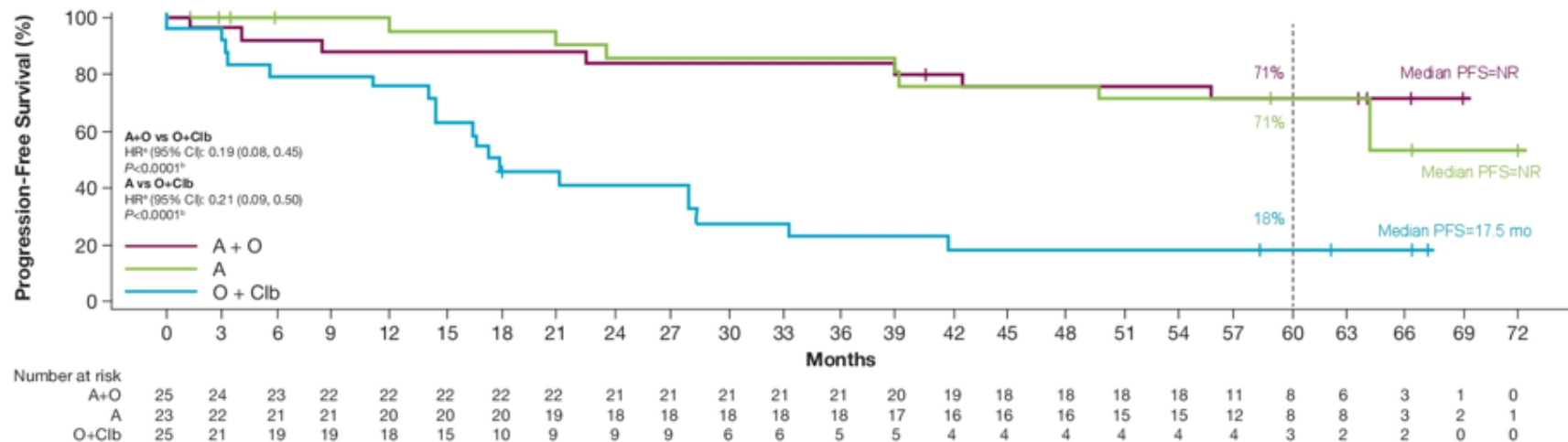
Sharman. Lancet. 2020;395:1278. NCT02475681. Sharman ASCO 2022

ELEVATE TN, 5y: Investigator-assessed PFS and del(17p)/*TP53*

A. Investigator-assessed PFS

A+O vs O+Clb
HR[a] (95% CI): 0.11 (0.07, 0.16)
P<0.0001[b]
A vs O+Clb
HR[a] (95% CI): 0.21 (0.15, 0.30)
P<0.0001[b]
A+O vs A
HR[a] (95% CI): 0.51 (0.32, 0.81)
P=0.0259[b]

[a]Hazard ratio based on Cox proportional-hazard model stratified by 17p deletion status (yes vs no based on interactive voice/web response system). [b]P-value based on log-rank test stratified by 17p deletion status (yes vs no based on interactive voice/web response system).

B. Investigator-assessed PFS in Patients With del(17p) and/or Mutated *TP53*

A+O vs O+Clb
HR[a] (95% CI): 0.19 (0.08, 0.45)
P<0.0001[b]
A vs O+Clb
HR[a] (95% CI): 0.21 (0.09, 0.50)
P<0.0001[b]

Sharman et al ASCO 2022

2nd generation BTKi
Zanubrutinib

SEQUOIA (BGB-3111-304)
Study Design

Key Eligibility Criteria
- Untreated CLL/SLL
- Met iwCLL criteria for treatment
- ≥65 y of age OR unsuitable for treatment with FCR[a]
- Anticoagulation and CYP3A inhibitors allowed

ClinicalTrials.gov: **NCT03336333**

Cohort 1
without del(17p) by central FISH
planned n ~450

Stratification Factors
Age, Binet stage, IGHV status, geographic region

open-label

R 1:1

Arm A: Zanubrutinib
160 mg bid until PD, intolerable toxicity, or end of study

Arm B:
Bendamustine (90 mg/m^2 D1 & D2)
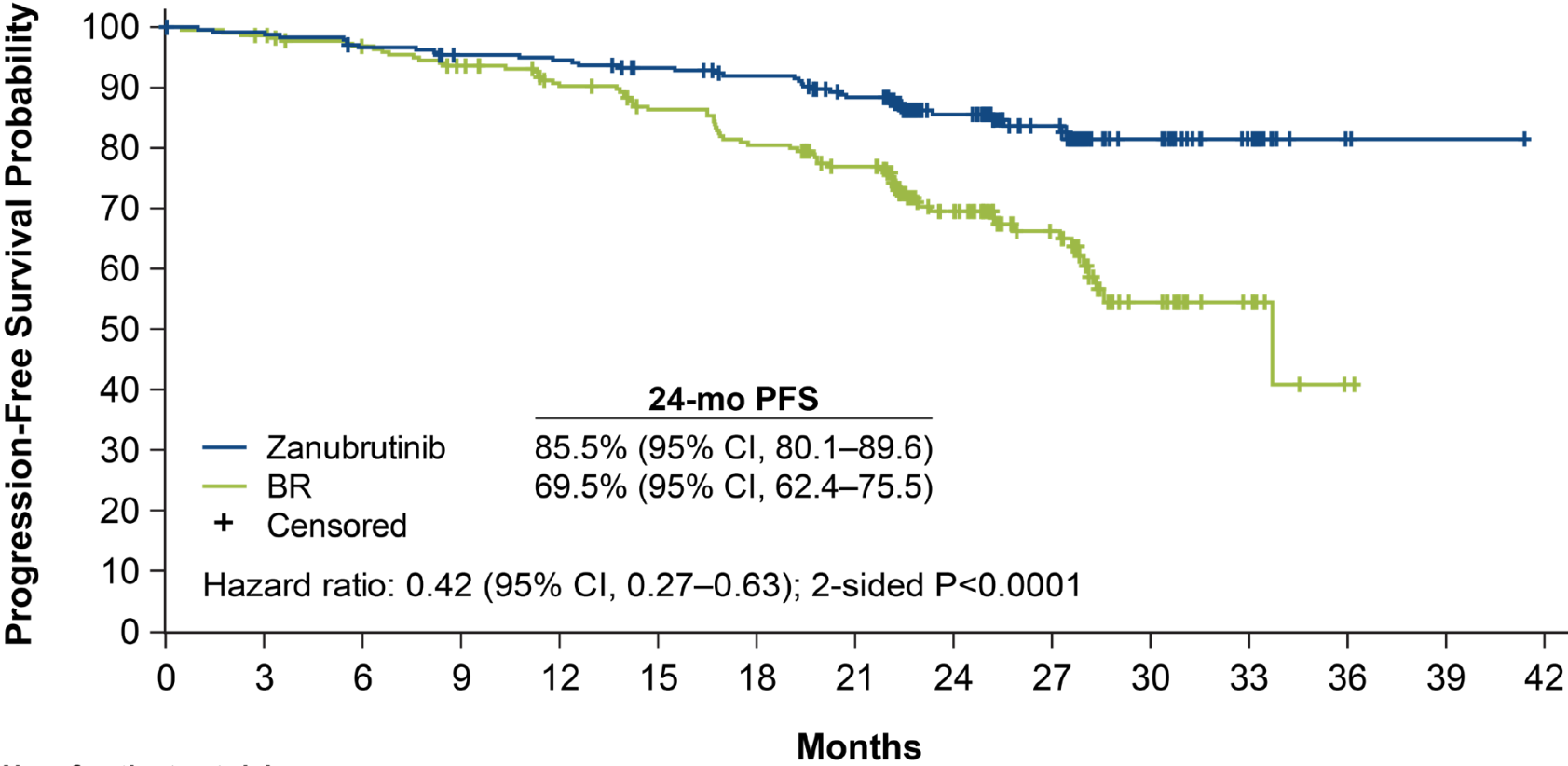**+ Rituximab** (375 mg/m^2 C1, then 500 mg/m^2 C2-C6)
x 6 cycles

Cohort 2
with del(17p)
planned n ~100

Arm C: Zanubrutinib
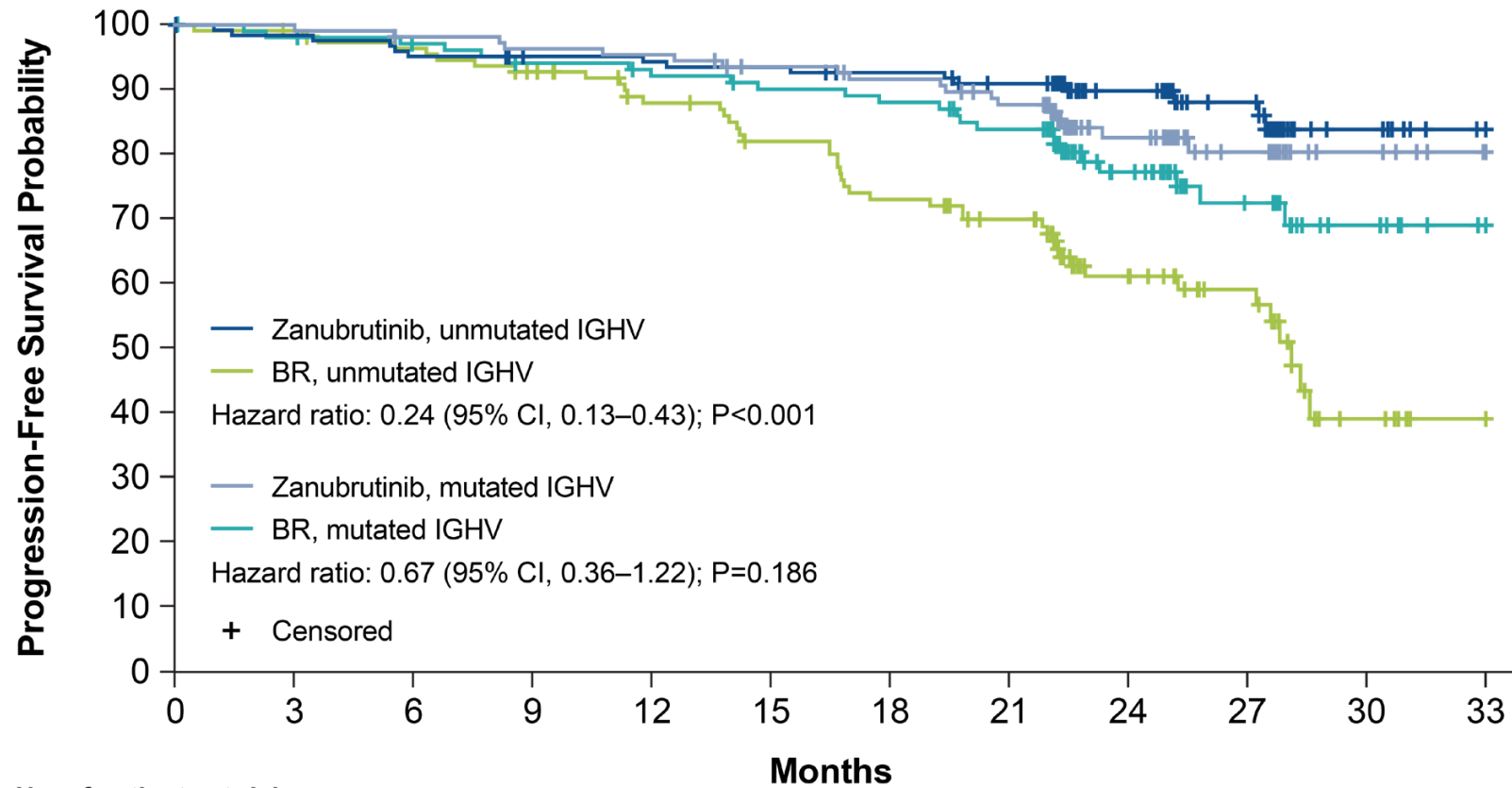
Cohort 3[1]
with del(17p)
planned n ~80

Arm D: Zanubrutinib + Venetoclax

Tan, et al. ASH 2021

SEQUOIA Cohort 1:PFS per IRC Assessment

Tan, et al. ASH 2021

SEQUOIA Cohort 1: PFS per IRC Assessment by IGHV

Tan, et al. ASH 2021

Cohort 2: PFS Per IRC Assessment in Patients With Del(17p)

Median follow-up: 30.5 mo
24-mo PFS: 88.9% (95% CI, 81.3–93.6)
+ Censored
▪ 95% CI

X-axis: Months (0, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39)
Y-axis: Progression-Free Survival Probability (0–100)

No. of patients at risk

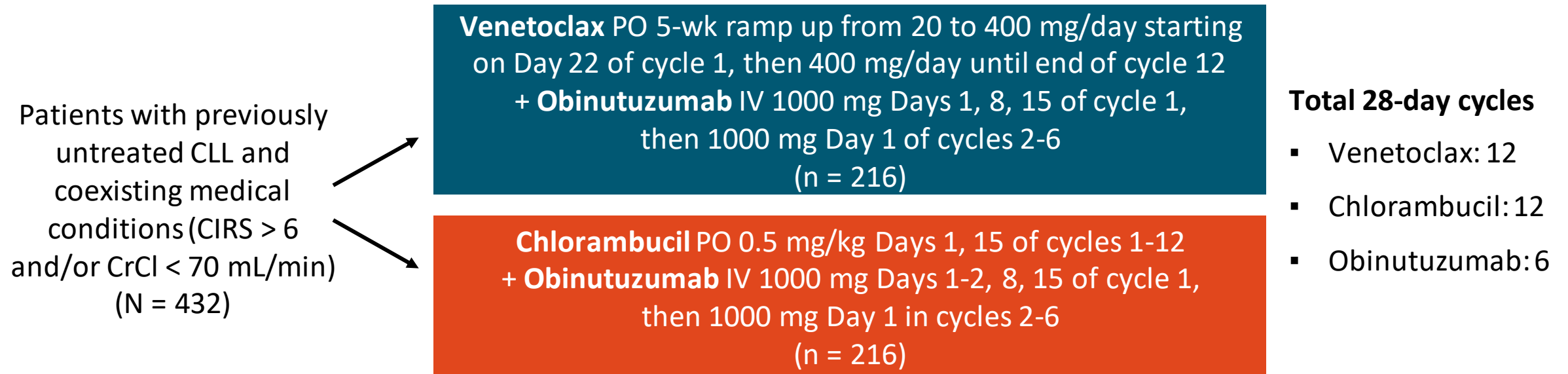| Zanubrutinib	110	109	104	103	102	98	96	96	86	74	37	19	2	0

Tan, et al. ASH 2021
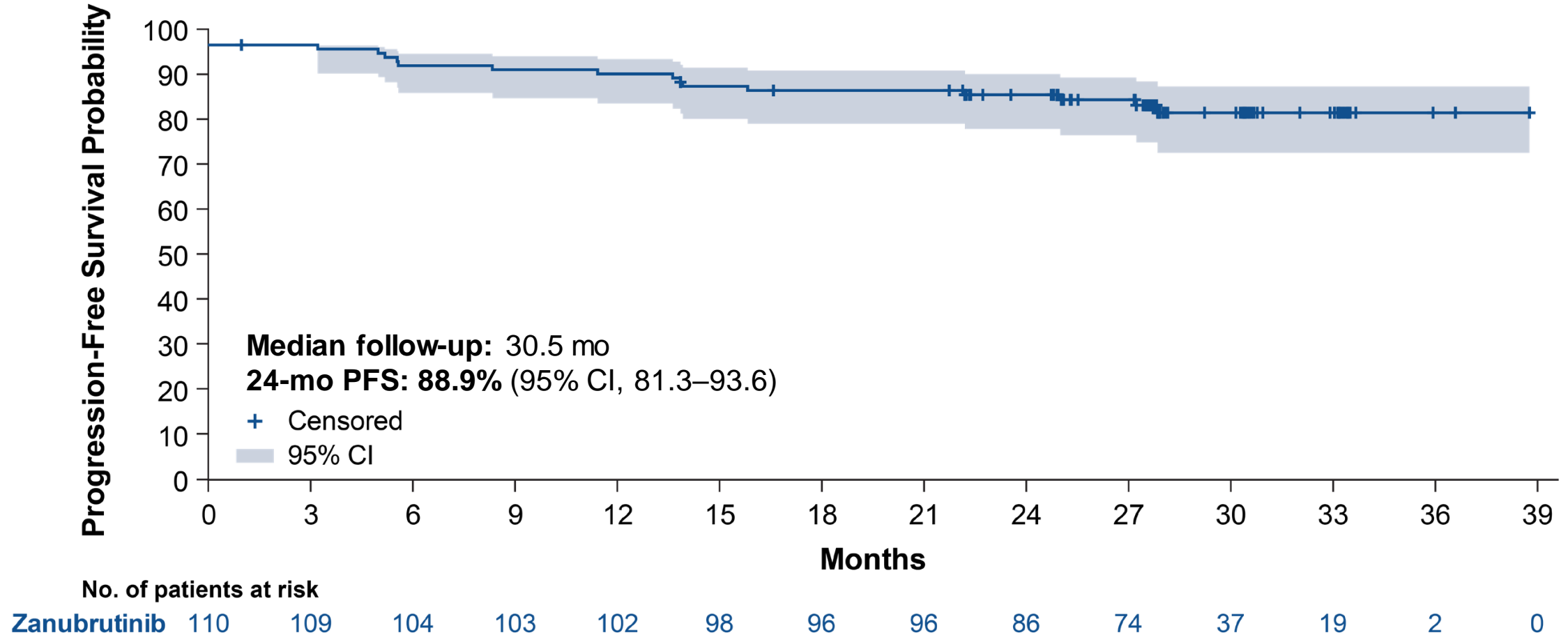
Fixed duration combination:

Obinutuzumab+Venetoclax in 1L CLL

CLL14: First-line Obinutuzumab + Venetoclax or Chlorambucil in CLL With Coexisting Medical Conditions

- Open-label, multicenter, randomized phase III trial

Patients with previously untreated CLL and coexisting medical conditions (CIRS > 6 and/or CrCl < 70 mL/min) (N = 432)

Venetoclax PO 5-wk ramp up from 20 to 400 mg/day starting on Day 22 of cycle 1, then 400 mg/day until end of cycle 12 + **Obinutuzumab** IV 1000 mg Days 1, 8, 15 of cycle 1, then 1000 mg Day 1 of cycles 2-6
(n = 216)

Chlorambucil PO 0.5 mg/kg Days 1, 15 of cycles 1-12 + **Obinutuzumab** IV 1000 mg Days 1-2, 8, 15 of cycle 1, then 1000 mg Day 1 in cycles 2-6
(n = 216)

Total 28-day cycles

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

- Primary endpoint: investigator-assessed PFS

- Secondary endpoints: IRC-assessed PFS, ORR, MRD negativity, OS, safety

Fischer, NEJM 2019. Al-Sawaf, Lancet Oncol 2020. Al-Sawaf, EHA 2021.

CLL14: Phase 3 Study of Venetoclax-Obinutuzumab vs Chlorambucil-Obinutuzumab in Unfit Patients

5-Year Progression-Free and Overall Survival

PFS Overall

PFS With Ven-Obi by *TP53* Status

PFS With Ven-Obi by IGHV Status

Overall Survival
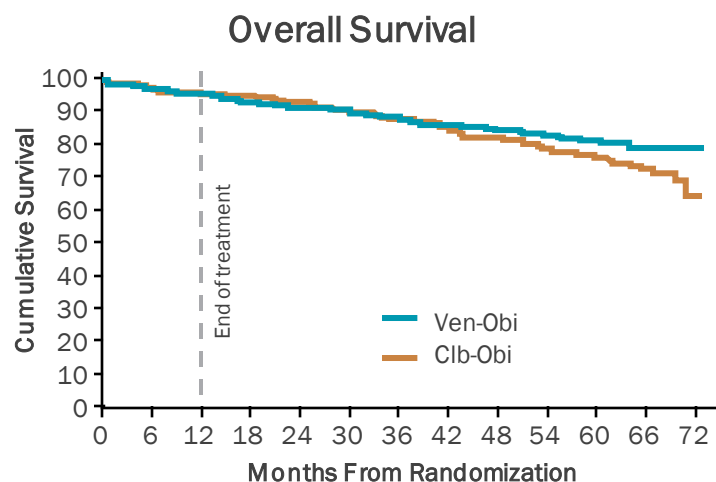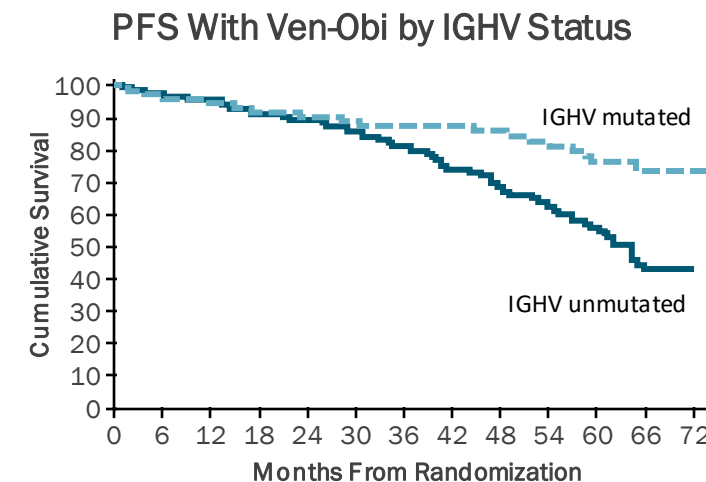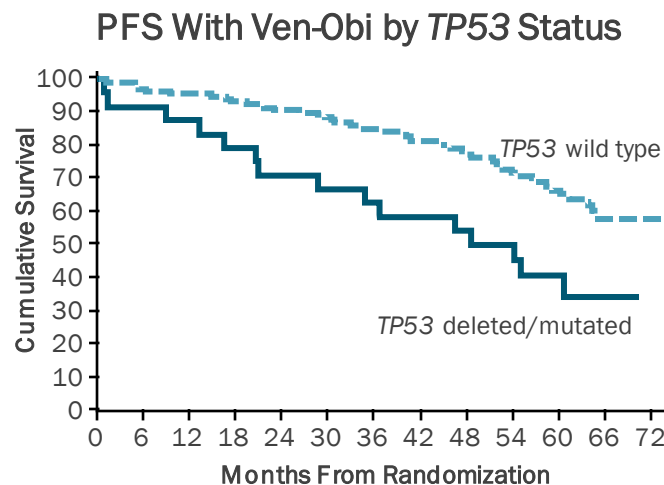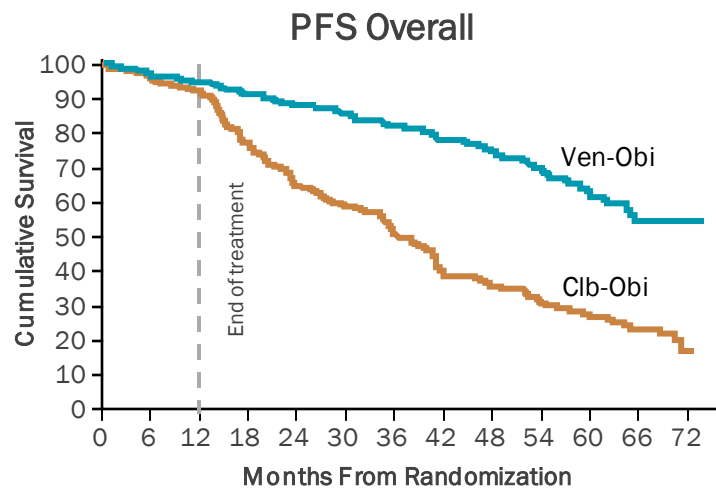
PFS by Subgroup		Ven-Obi (n=216)	Clb-Obi (n=216)
All patients	Median, months	NR	36.4
	5-year rate, %	62.6	27.0
	HR (95% CI); *P* value	0.35 (0.26-0.46); <0.0001	
Median PFS, months			
TP53 del/mut	No	NR (n=184)	38.9 (n=184)
	Yes	49.0 (n=25)	19.8 (n=24)
IGHV status	Mutated	NR (n=76)	59.9 (n=83)
	Unmutated	64.2 (n=121)	26.9 (n=123)

Al-Sawaf O, et al. EHA 2022. Abstract S148.

CLL14: Phase 3 Study of Venetoclax-Obinutuzumab vs Chlorambucil-Obinutuzumab in Unfit Patients

MRD Assessments

Longitudinal MRD Assessment by NGS in PB: Ven-Obi
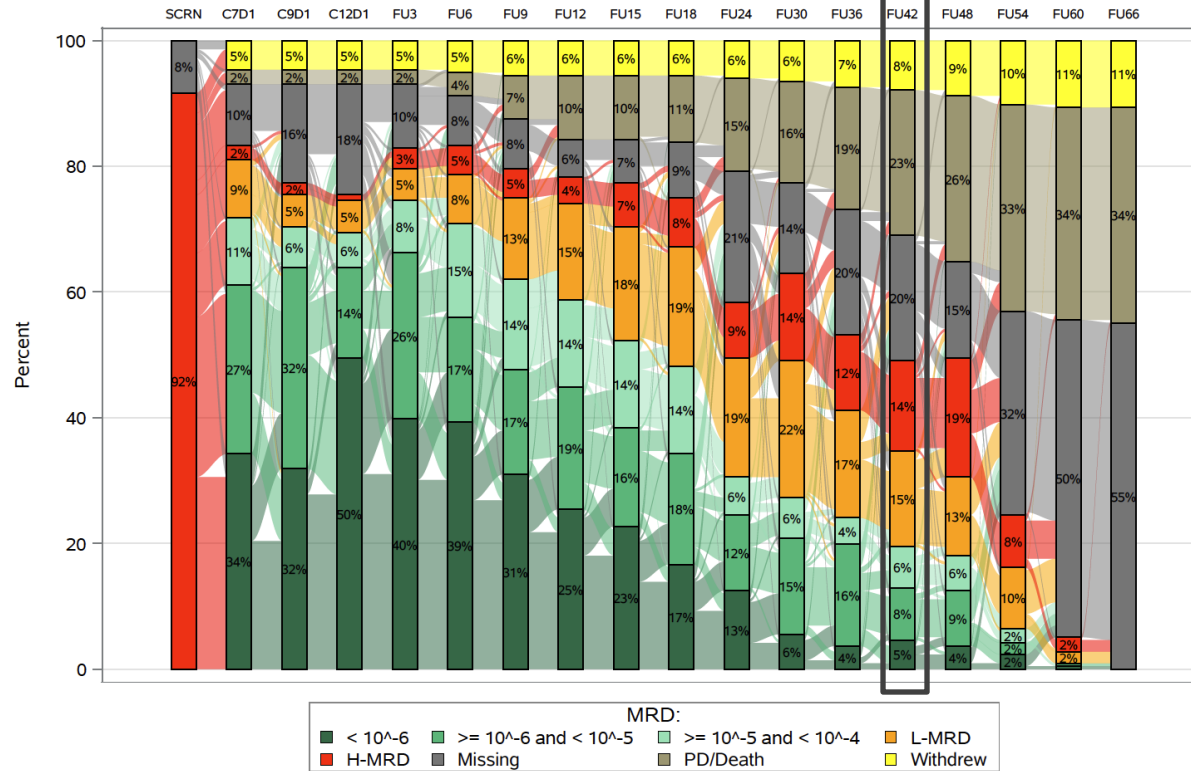
PFS and OS After Ven-Obi According to MRD Status

- 4 years after Ven-Obi, 39 patients (18.1%) had sustained MRD <10^{-4}

End of treatment MRD status in peripheral blood by next-generation sequencing.
Al-Sawaf O, et al. EHA 2022. Abstract S148.

GAIA (CLL13) trial

Fit patients with CLL: CIRS ≤ 6 & normal CrCl

No *TP53* mutation or del(17p) in central screening

Stratification according to age, stage and region
Randomization
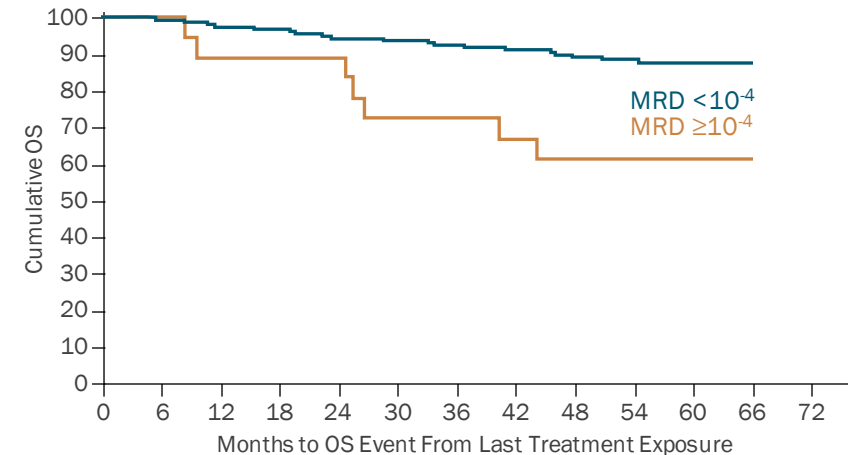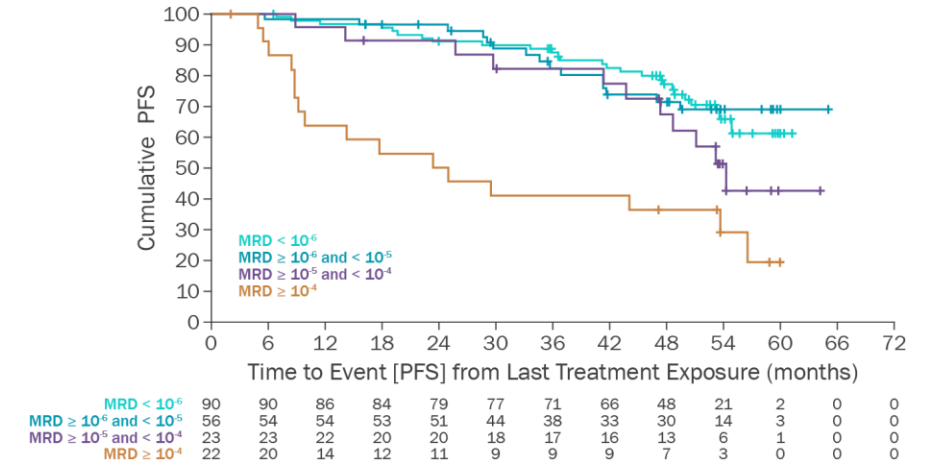
FCR/BR*	230
RVe	230
GVe	230
GIVe	230

* ≤ 65 years: FCR
> 65 years: BR
[50% FCR / 50% BR]

920 pts

Coprimary endpoint (α 2.5%): uMRD at month 15

Coprimary endpoint (α 2.5%): PFS interim analysis postponed to Q1 2022 due to low number of events

GIVe

400 | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400

*

Ibrutinib 420mg po from d1 C1
Venetoclax ramp up 20 – 400mg po
Venetoclax 400mg po C3-C12
Obinutuzumab 1000mg/m^2 iv
d1+8+15 during C1, d1 C2-C6

* Continuation of ibrutinib up to cycle 36 allowed, if MRD still detectable

| Chemotherapy | CD20-antibody | 400 Venetoclax (V) | Ramp-Up | Ibrutinib (I) |

Treatment exposure
Median FU 27.9 months (range: 0.0 – 49.0)

Eichhorst, et al., ASH 2021

GAIA (CLL13) trial

uMRD (< 10-4) at Mo15 in PB by 4-colour-flow

ITT analysis: 63 pts (34 CIT, 15 RVe, 10 GVe, 4 GIVe) with missing samples (6.8%) were counted as MRD positive

GIVe vs CIT: **92.2% versus 52.0%: p < 0.0001**

GVe vs CIT : **86.5% versus 52.0%: p < 0.0001**

RVe vs CIT: **57.0% versus 52.0%: p = 0.317**

proportion of ITT population in %

CIT n = 229	RVe n = 237	GVe n = 229	GIVe n = 231
52.0	57	86.5	92.2

■ PB uMRD

	uMRD%	97.5% CI
GIVe	92.2	87.3 − 95.7
GVe	86.5	80.6 − 91.1
RVe	57.0	49.5 − 64.2
SCIT	52.0	44.4 − 59.5

Eichhorst, et al., ASH 2021
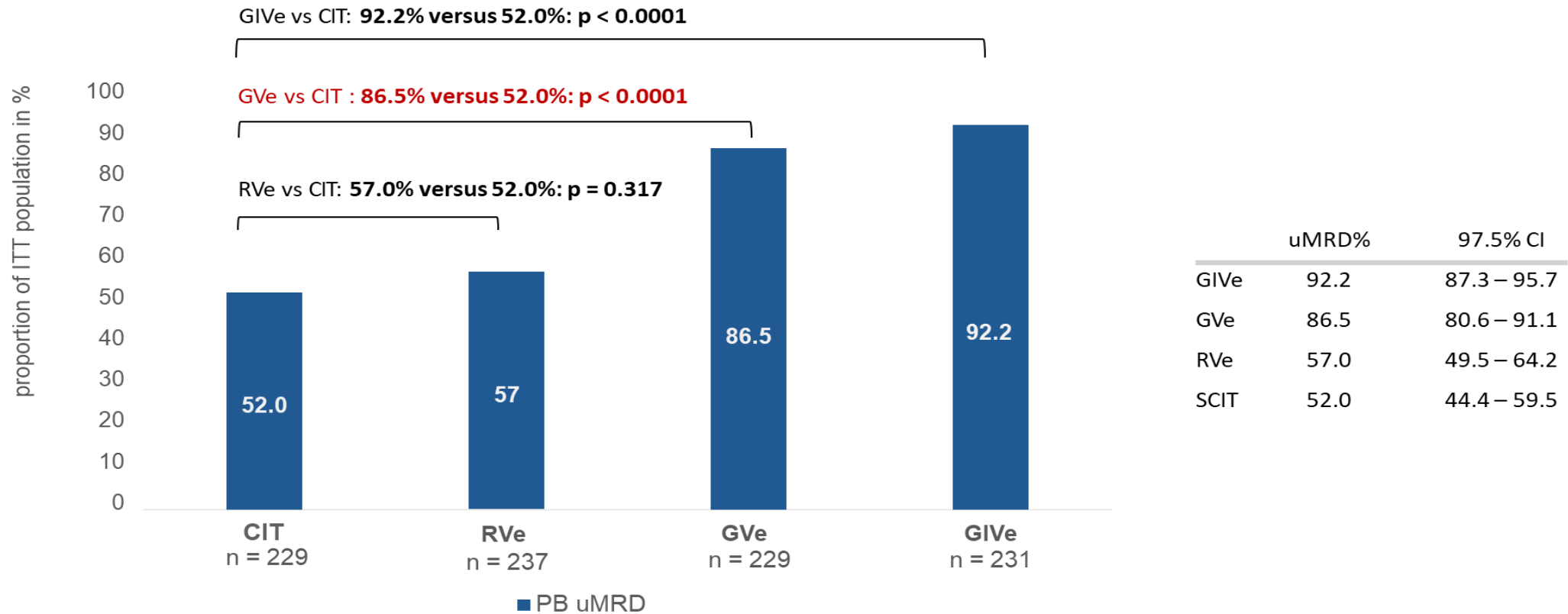
GAIA (CLL13) trial PFS and PFS by IgHV

Median FU 38.8 months (range: 0.0 – 59.2)

GIV vs CIT: **HR 0.32, 97.5% CI 0.19-0.54, p<0.000001**

GV vs CIT: **HR 0.42, 97.5% CI 0.26-0.68, p<0.0001**

RV vs CIT: HR 0.79, 97.5% CI 0.53-1.18, p=0.183

PFS	Median months	3y PFS (%)
CIT	52.0	75.5
RV	52.3	80.8
GV	NR	87.7
GIV	NR	90.5

CIT	229	197	172	98	28
RV	237	226	212	119	32
GV	229	221	208	125	42
GIV	231	227	217	132	44

Unmutated IGHV

3y PFS rates

CIT 65.5%
RV 76.4%
GV 82.9%
GIV 86.6%

CIT	131	108	88	48	14
RV	134	128	119	67	20
GV	130	125	116	71	21
GIV	123	121	117	70	22

Mutated IGHV

3y PFS rates

CIT 89.9%
RV 87.0%
GV 93.6%
GIV 96.0%

CIT	95	86	83	50	14
RV	95	91	86	49	12
GV	89	86	82	48	17
GIV	101	99	94	59	22

Eichhorst, et al., EHa 2022

fixed duration novel agent combinations

BTKi + BCL2i
(i.e. Ibrutinib+Venetoclax)

Phase 2 CAPTIVATE Study

- CAPTIVATE (PCYC-1142) is an international, multicenter phase 2 study evaluating first-line treatment with 3 cycles of ibrutinib followed by 12 cycles of combined ibrutinib + venetoclax that comprises 2 cohorts: MRD and FD

MRD

| 3 cycles ibrutinib lead-in | → | 12 cycles ibrutinib + venetoclax | → | MRD-guided randomization |

Confirmed uMRD
Randomize 1:1 (double-blind)
- placebo
- ibrutinib

uMRD Not Confirmed
Randomize 1:1 (open-label)
- ibrutinib
- ibrutinib + venetoclax

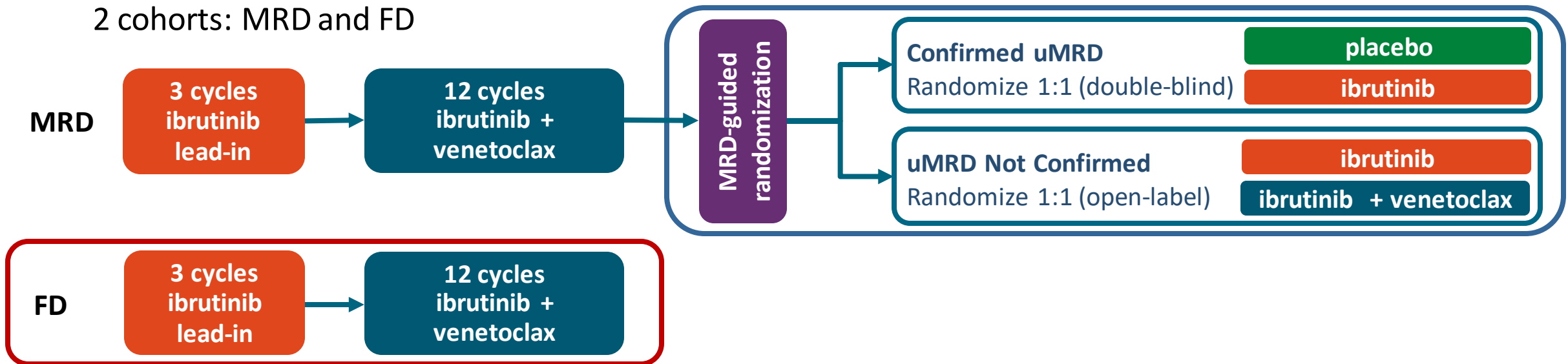**FD**

| 3 cycles ibrutinib lead-in | → | 12 cycles ibrutinib + venetoclax |

- Results from the MRD cohort demonstrated uMRD in more than two-thirds of patients treated with 12 cycles of ibrutinib + venetoclax (PB, 75%; BM, 68%), and 30-month PFS rates of ≥95% irrespective of subsequent MRD-guided randomized treatment[1]

CAPTIVATE Fixed-Dose Cohort 3-yr Update: Best Overall response
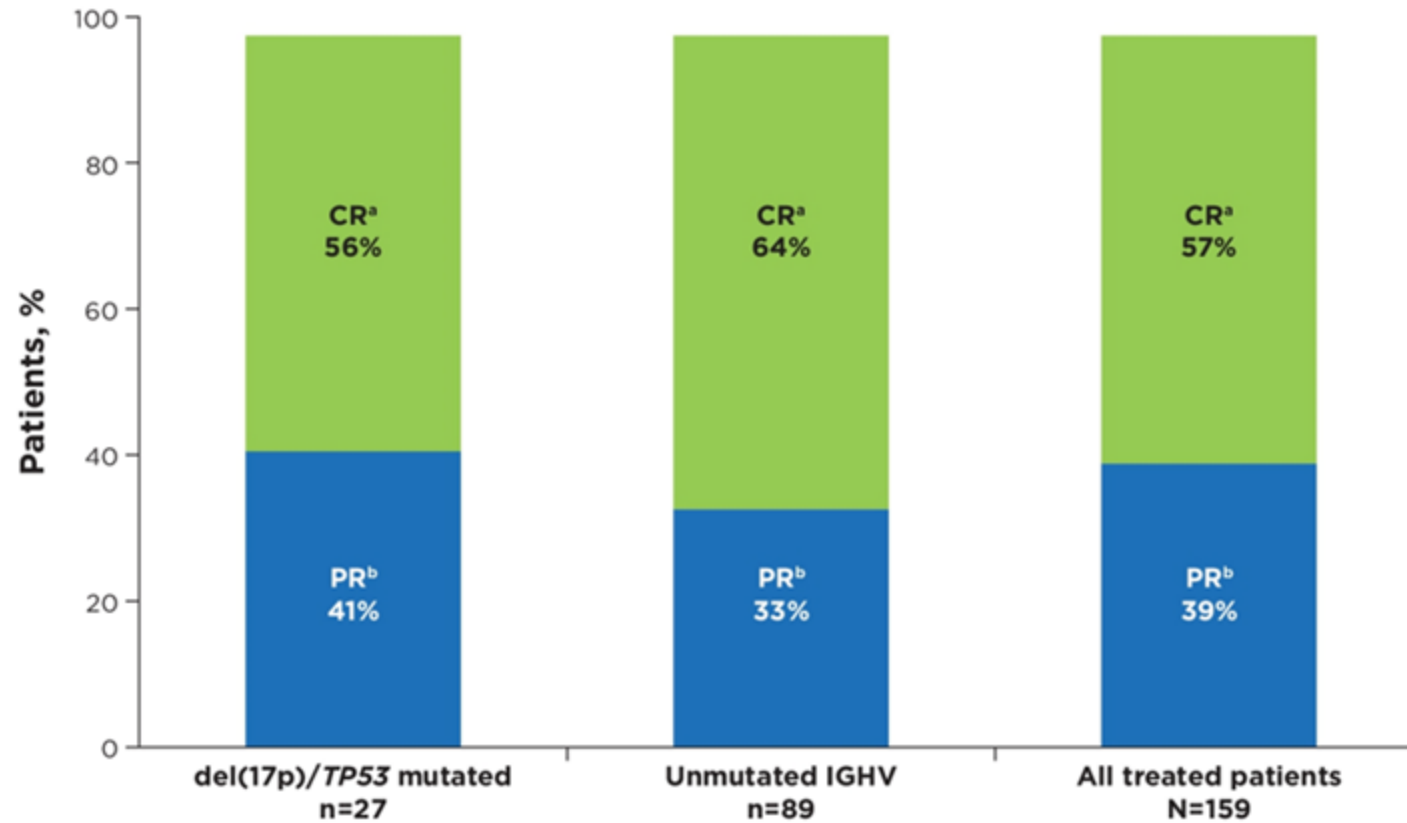
- The CR rate in all treated patients increased from 55% (95% CI, 48–63) at primary analysis to 57% (95% CI, 50–65) with an additional year of follow-up off treatment
- 79% of patients (125/159) had a best response of uMRD in PB and/or BM

Wierda et al, ASCO 2022

CAPTIVATE Fixed-Dose Cohort: MRD

Best uMRD

Patients (%)

	76	77		62	60

Peripheral blood **Bone marrow**

■ Patients without del(17p)
n=136
■ All treated patients
N=159
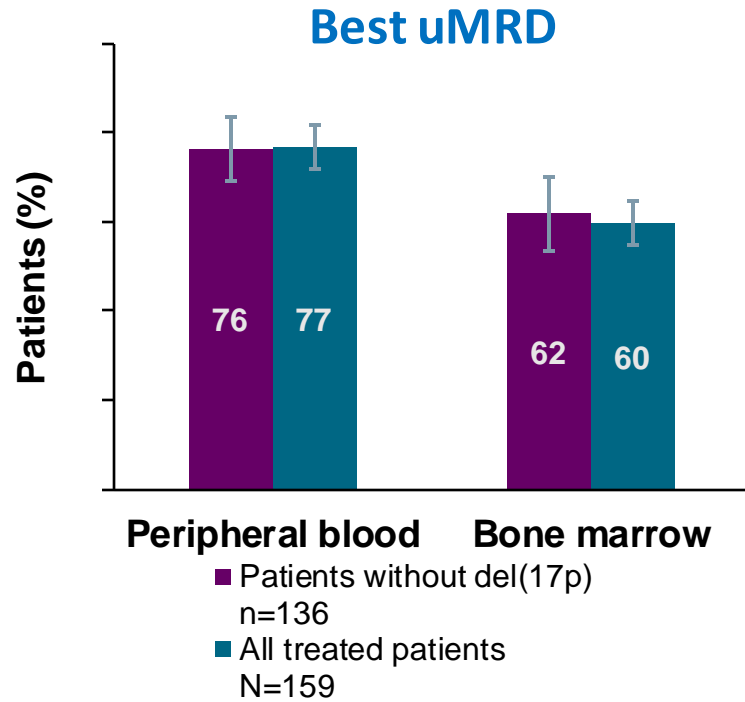
uMRD rate	PB	BM
Bulky Disease		
Yes	77%	63%
No	77%	59%
IGHV status		
uIGHV	84%	64%
mIGHV	67%	53%

Ghia et al . ASCO 2021. Allen et al EHA21

CAPTIVATE FD Cohort: Phase 2 Study of Ibrutinib-Venetoclax
Progression-Free and Overall Survival[1,2]

Progression-Free Survival[a]

PFS, %

Treatment Period

All treated patients
Unmutated IGHV
del(17p)/TP53 mutated

	del(17p)/TP53 Mutated (n=27)	Unmutated IGHV (n=89)	All Treated Patients (N=159)
3-year PFS rate (95% CI)	80% (58-91)	86% (77-92)	88% (82-92)
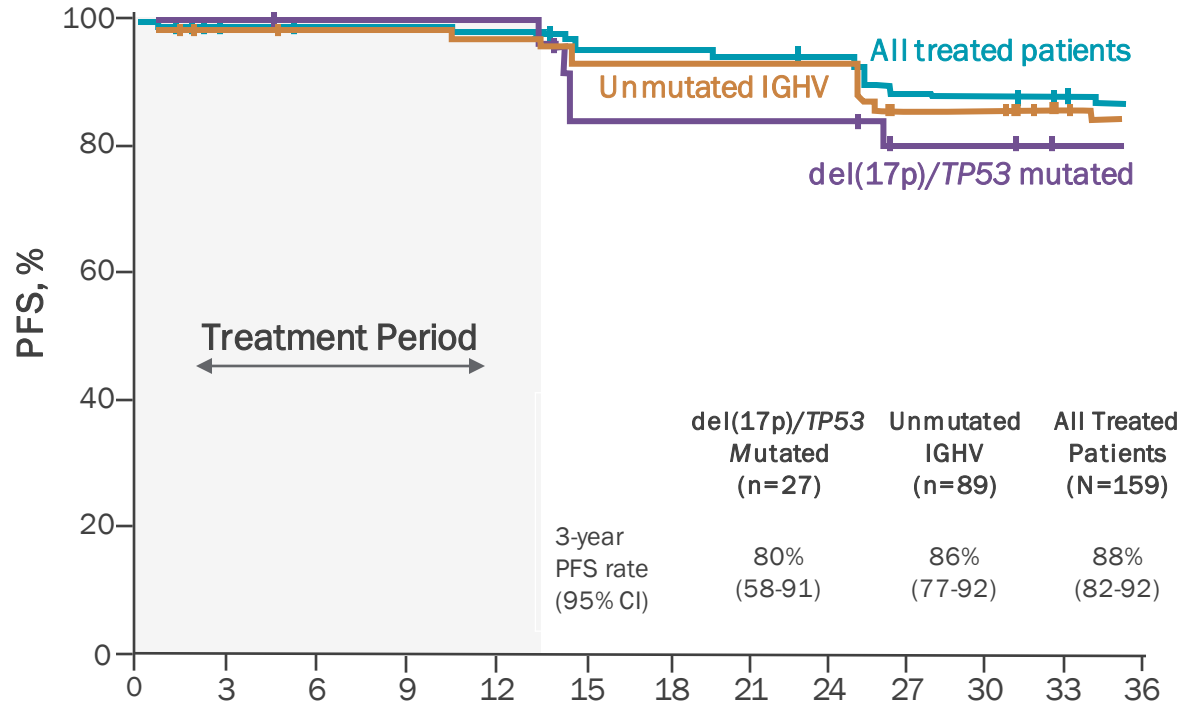
Months

Pts at Risk, n													
	0	3	6	9	12	15	18	21	24	27	30	33	36
All treated	159	155	153	152	152	151	144	144	143	142	131	130	117
Unmut IGHV	89	86	85	85	85	84	79	79	79	79	72	72	63
del(17p)/TP53 mut	27	27	26	26	26	26	21	21	21	21	18	18	15

Overall Survival[a]

OS, %

All treated patients
del(17p)/TP53 mutated   Unmutated IGHV

	del(17p)/TP53 Mutated (n=27)	Unmutated IGHV (n=89)	All Treated Patients (N=159)
3-year PFS rate (95% CI)	96% (76-99)	97% (90-99)	98% (94-99)
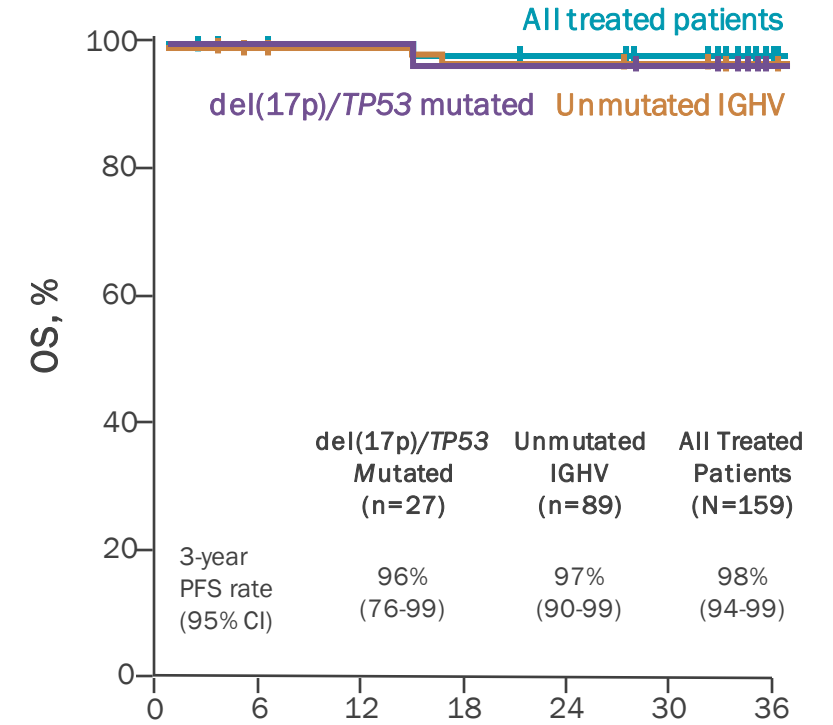
Months

Pts at Risk, n							
	0	6	12	18	24	30	36
All treated	159	155	154	151	150	148	139
Unmut IGHV	89	86	85	84	84	82	75
del(17p)/TP53 mut	27	26	26	25	25	24	20

[a] Due to rapid enrollment in the study, the number of patients at risk drops substantially between 36 and 39 months. The Kaplan-Meier curves have therefore been truncated at 38 months due to instability of the curves.
1. Moreno C, et al. EHA 2022. Abstract P669. 2. Weirda WG, et al. ASCO 2022. Abstract 7519.

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CAPTIVATE MRD Cohort: Phase 2 Study of Ibrutinib-Venetoclax
Disease-Free and Progression-Free Survival

Disease-Free Survival

	Placebo	Ibrutinib
3-year DFS rate[a]	85	93
Arm difference, % (95% CI)	8.3 (-5.5 to 22.1)	
Log-rank *P*-value	0.1621	
Hazard ratio (95% CI)	0.435 (0.131, 1.446)	

PFS Overall

	Placebo	Ibrutinib
48-mo PFS rate, %	88	95
(95% CI)	73.6–94.8	82.3–98.8

PFS by IGHV Status

	Placebo	Ibrutinib
48-mo PFS rate, unmutated IGHV, % (95% CI)	83	97
	63.0–92.4	77.9–99.5
48-mo PFS rate, mutated IGHV, % (95% CI)	100	92
	100–100	56.6–98.9
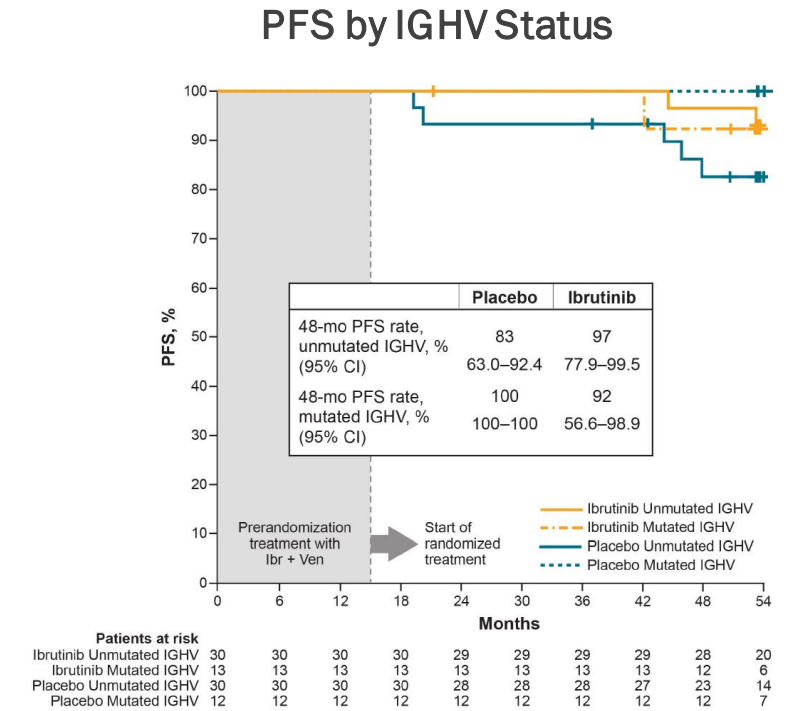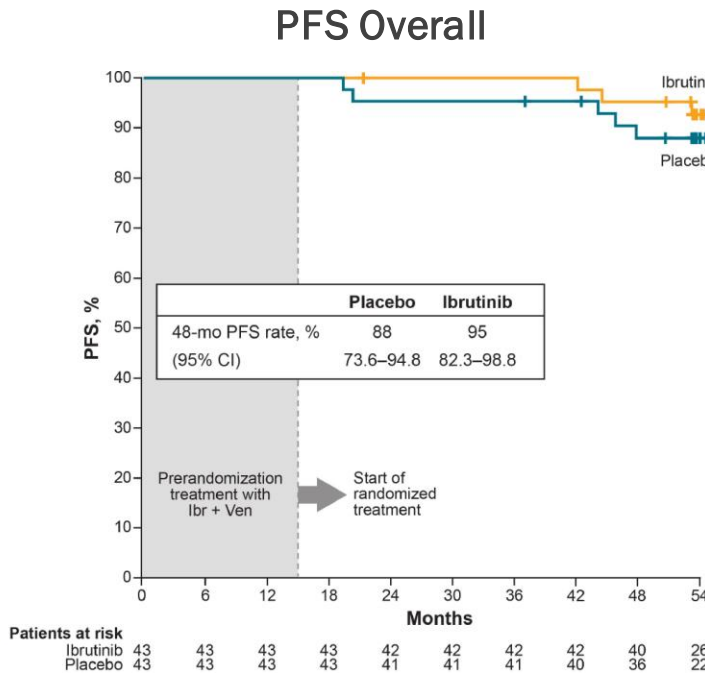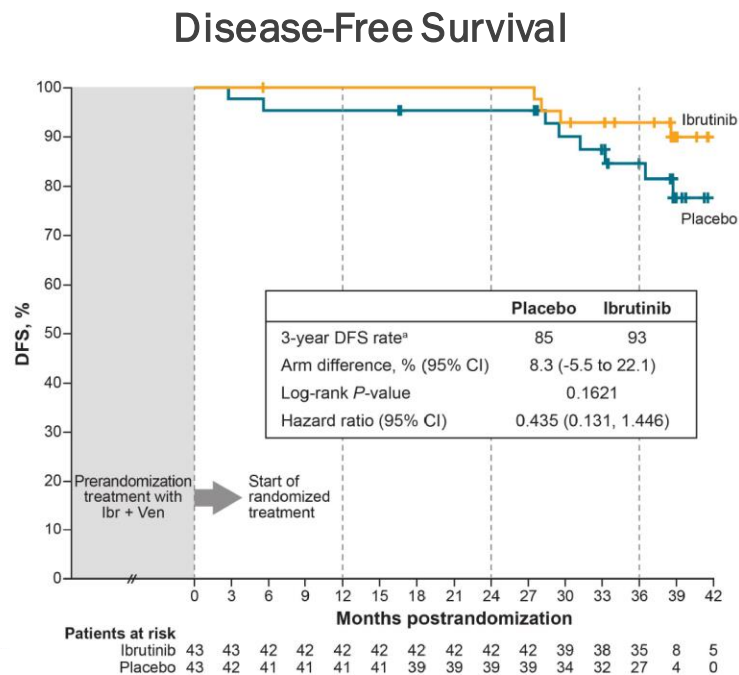
- **Median time on study (patients with confirmed uMRD):** 56 months

- **Median follow-up postrandomization:** 41.2 months in placebo arm; 41.5 months in ibrutinib arm

- **4-year overall survival rate:** 100% in placebo arm; 98% in ibrutinib arm

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

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

International, open-label, randomized phase III trial

Stratified by IGHV status, del(11q) presence

Patients with previously untreated CLL; aged ≥65 yr or <65 yr with CIRS >6 or CrCl <70 mL/min; no del(17p) or known *TP53* mutation; ECOG PS 0-2
(N = 211)

Ibrutinib 420 mg PO QD x 3 cycles followed by
**Ibrutinib +
Venetoclax*** 12 cycles
(n = 106)

Chlorambucil 0.5 mg/kg on Days 1, 15 x 6 cycles +
Obinutuzumab 1000 mg on Days 1-2, 8, 15 of cycle 1 and Day 1 of cycles 2-6
(n = 105)

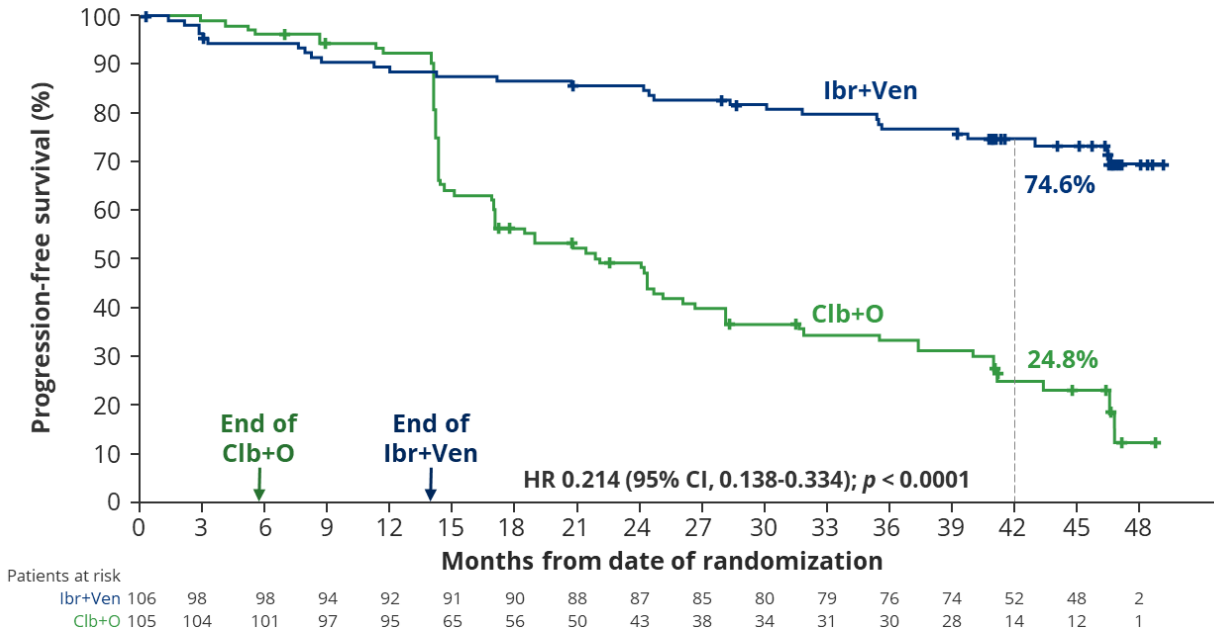*If IRC-confirmed PD and active disease requiring tx, eligible for subsequent single-agent ibrutinib*

*Ramp-up from 20 to 400 mg over 5 wk starting in cycle 4.

- **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

- 46 months median follow up

Nieman et al. ASH 2022

GLOW: I+V vs Clb+O in Elderly or Unfit 1L CLL: *4-year Update*

Progression-Free Survival (IRC)

Median study follow-up: 46 months

Overall Survival (ITT)

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)

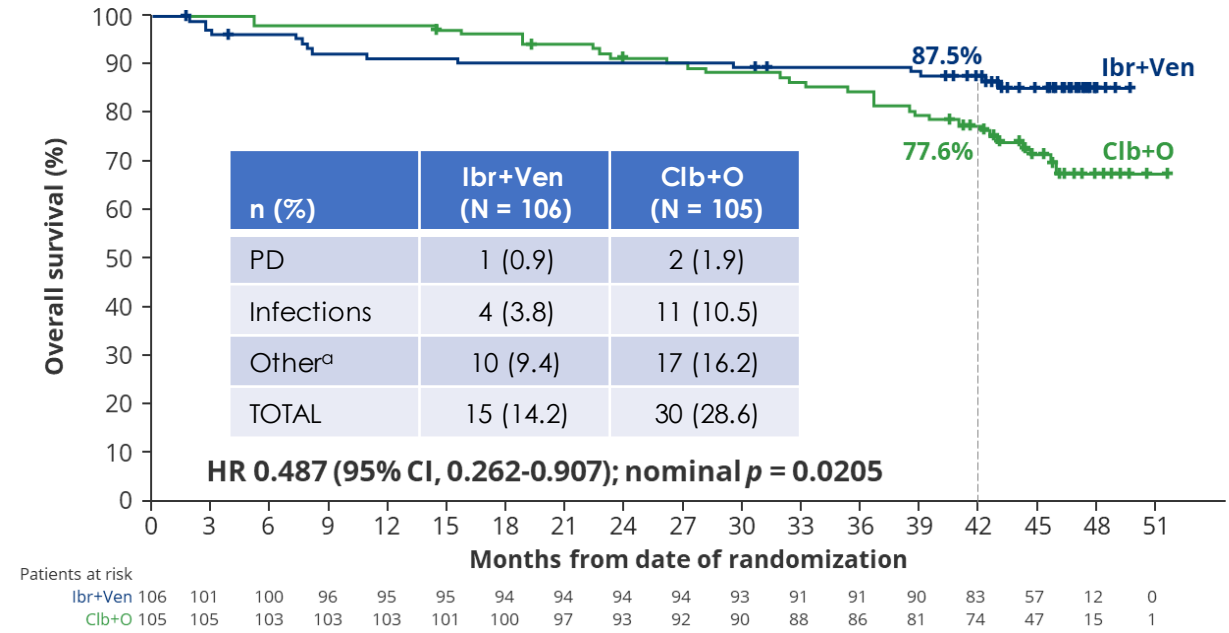**HR 0.487 (95% CI, 0.262-0.907); nominal *p* = 0.0205**

Median study follow-up: 46 months

Progression free survival:

- Ibr + Ven reduced risk of progression or death by 79%
- Estimated 3.5 year PFS:
  74.6% for Ibr+Ven
  24.8% for Clb + O
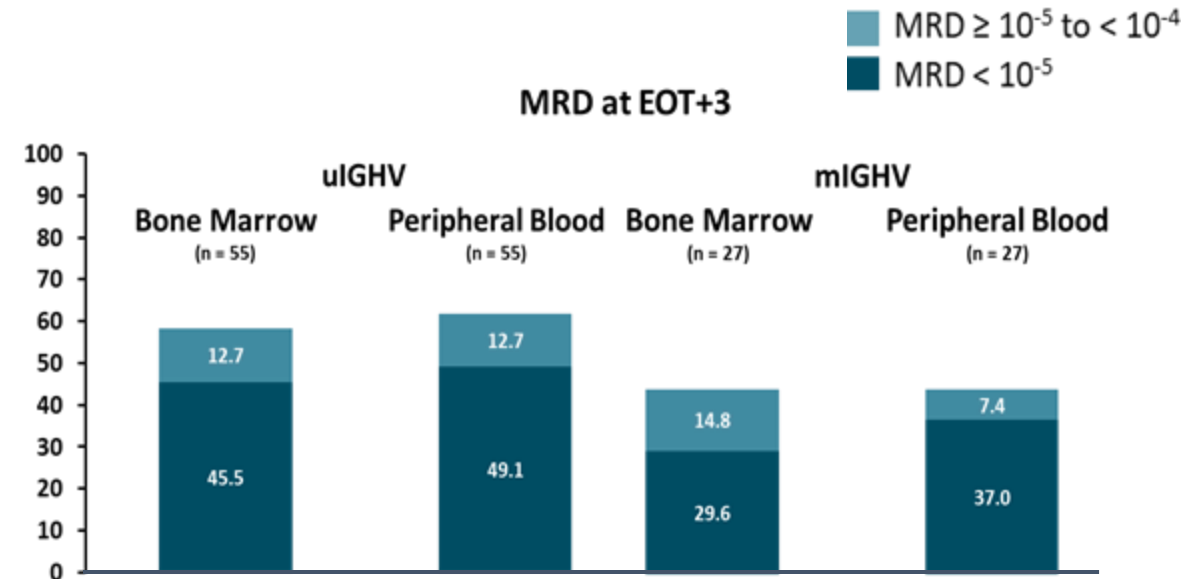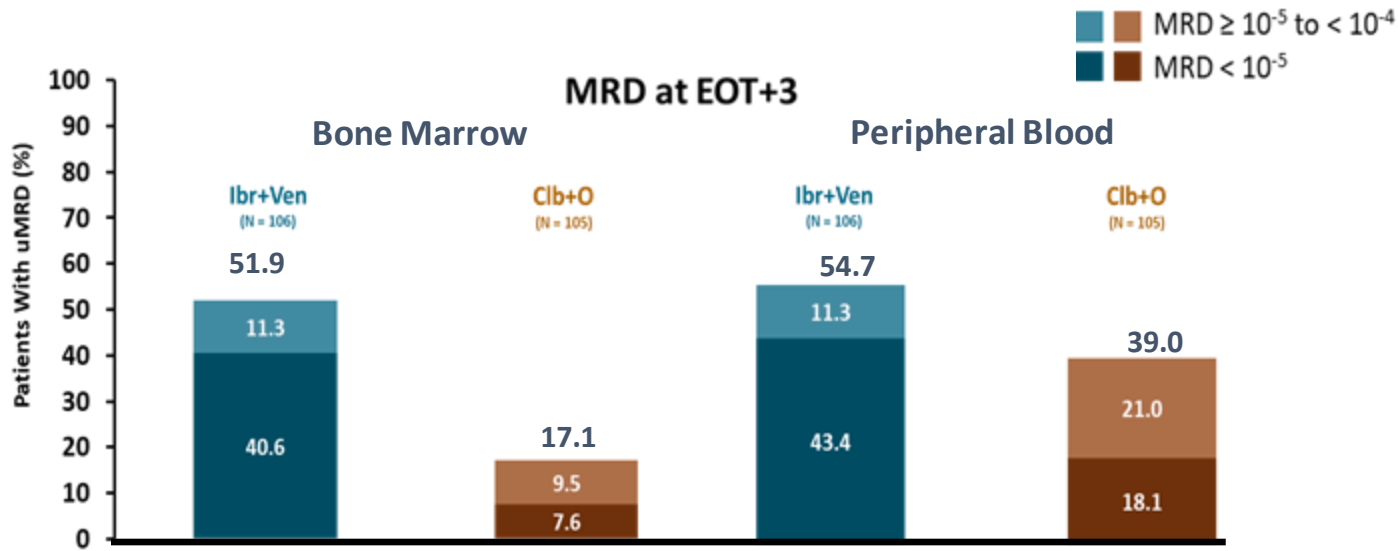
Overall Survival:

- 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
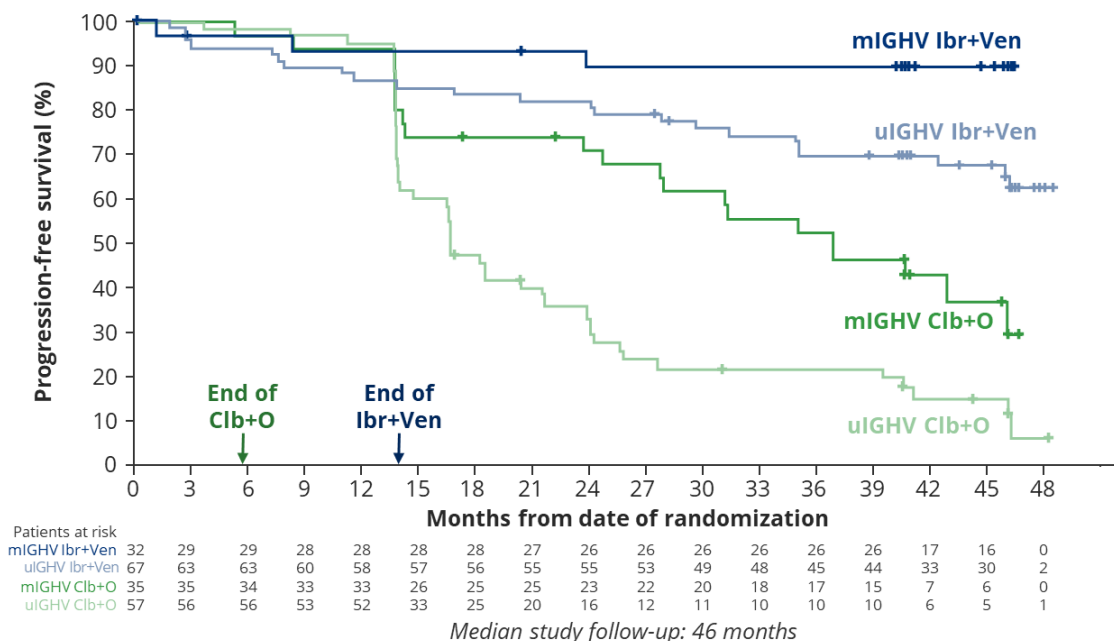- More infection-related deaths were seen in the Clb+O arm

Niemann, et al., ASH 2022;
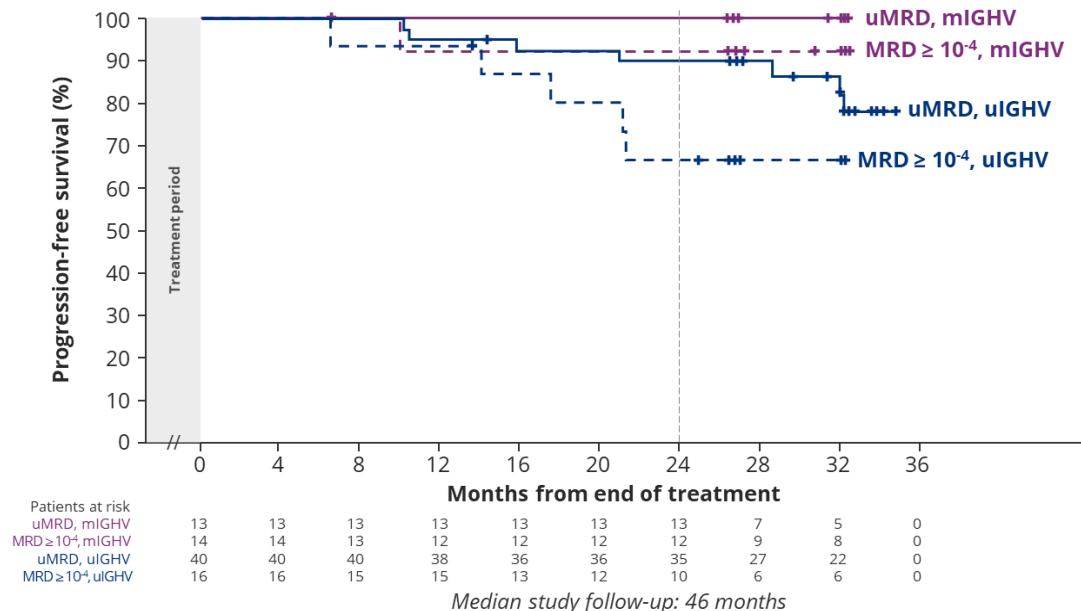
GLOW: MRD at EOT+3 by IgHV status

Munir, ASH 2021.

GLOW: PFS by IGHV Mutational Status

(Elderly/Unfit, 12-mo Fixed Duration)

Progression-Free Survival (IRC) by IGHV Status

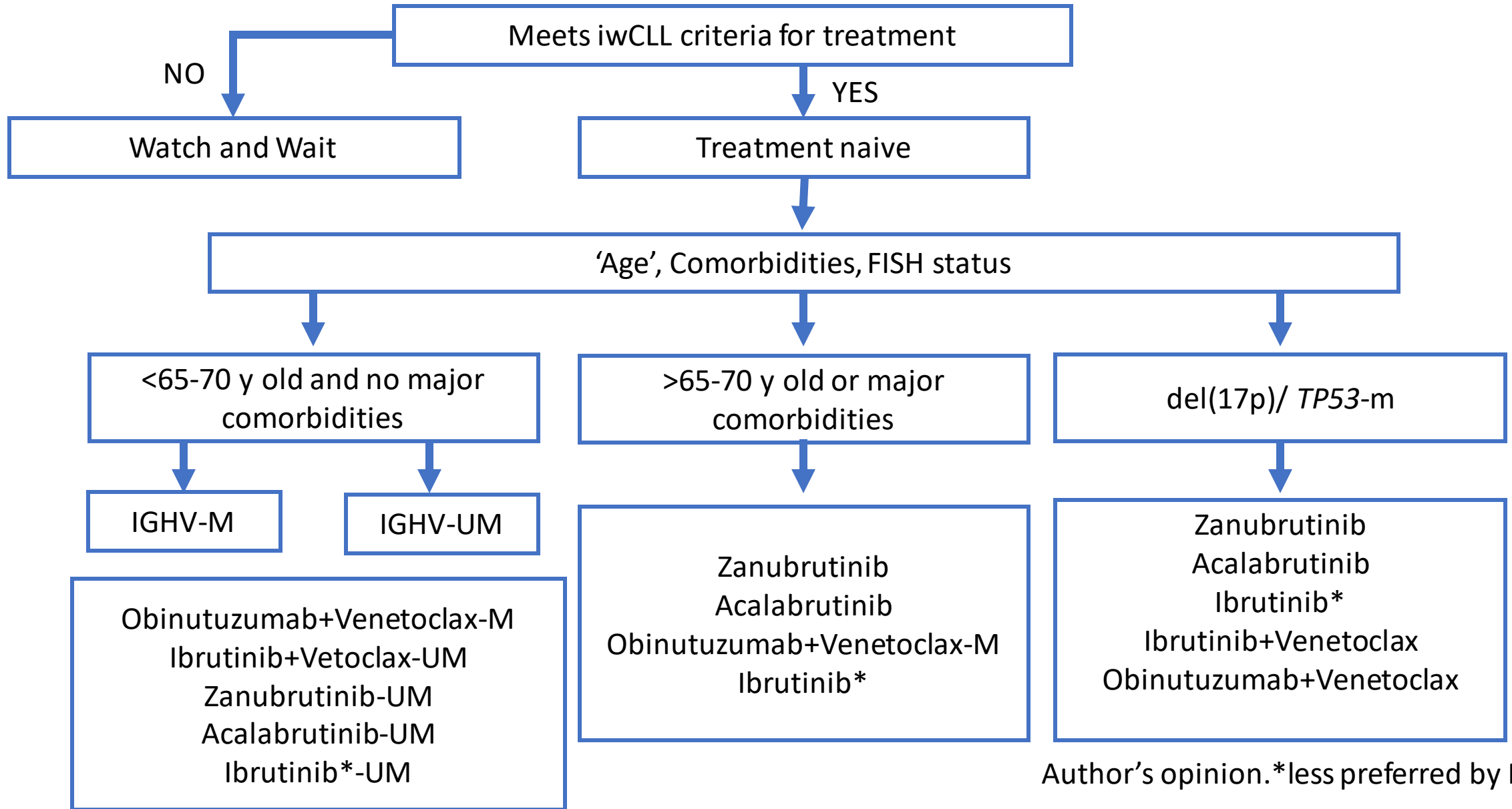Patients at risk

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48
mIGHV Ibr+Ven	32	29	29	28	28	28	28	27	26	26	26	26	26	26	17	16	0
uIGHV Ibr+Ven	67	63	63	60	58	57	56	55	55	53	49	48	45	44	33	30	2
mIGHV Clb+O	35	35	34	33	33	26	25	25	23	22	20	18	17	15	7	6	0
uIGHV Clb+O	57	56	56	53	52	33	25	20	16	12	11	10	10	10	6	5	1

Median study follow-up: 46 months

Ibr+Ven Progression-Free Survival (IRC) From End of Treatment

Patients at risk

	0	4	8	12	16	20	24	28	32	36
uMRD, mIGHV	13	13	13	13	13	13	13	7	5	0
MRD ≥ 10^{-4}, mIGHV	14	14	13	12	12	12	12	9	8	0
uMRD, uIGHV	40	40	40	38	36	36	35	27	22	0
MRD ≥ 10^{-4}, uIGHV	16	16	15	15	13	12	10	6	6	0

Median study follow-up: 46 months

- Impact of IGHV status on PFS was more pronounced with Clb+O

- > 90% of patients in the I+V arm did not require subsequent treatment at 3.5 years:
  - 91.5% for uIGHV
  - 93.5% for mIGHV

- Estimated PFS at 2 years post-treatment for **uIGHV** CLL:
  - 90% for uMRD at EOT+3 vs 67% for MRD ≥ 10^{-4}

- Estimated PFS at 2 years post-treatment for **mIGHV** CLL:
 - > 90% regardless of MRD status at EOT+3

Nieman et al. ASH 2022

CLL Front Line Treatment Algorithm 2023

Meets iwCLL criteria for treatment

NO → Watch and Wait

YES → Treatment naive

↓

'Age', Comorbidities, FISH status

↓ ↓ ↓

<65-70 y old and no major comorbidities

>65-70 y old or major comorbidities

del(17p)/ *TP53*-m

↓ ↓

IGHV-M | IGHV-UM

↓

Obinutuzumab+Venetoclax-M
Ibrutinib+Vetoclax-UM
Zanubrutinib-UM
Acalabrutinib-UM
Ibrutinib*-UM

Zanubrutinib
Acalabrutinib
Obinutuzumab+Venetoclax-M
Ibrutinib*

Zanubrutinib
Acalabrutinib
Ibrutinib*
Ibrutinib+Venetoclax
Obinutuzumab+Venetoclax

Author's opinion.*less preferred by NCCN

The alternatives Treatment Paradigm in CLL:
Factors to Consider

- Convenience (no infusions, TLS monitoring)
- Long-term efficacy data
- Multiple Phase 3 data
- Data for efficacy of venetoclax at time of ibrutinib progression
- Low progression while on continue therapy.
- Older age.
- Good data on High risk factors.
- LN based disease.
- High financial toxicity
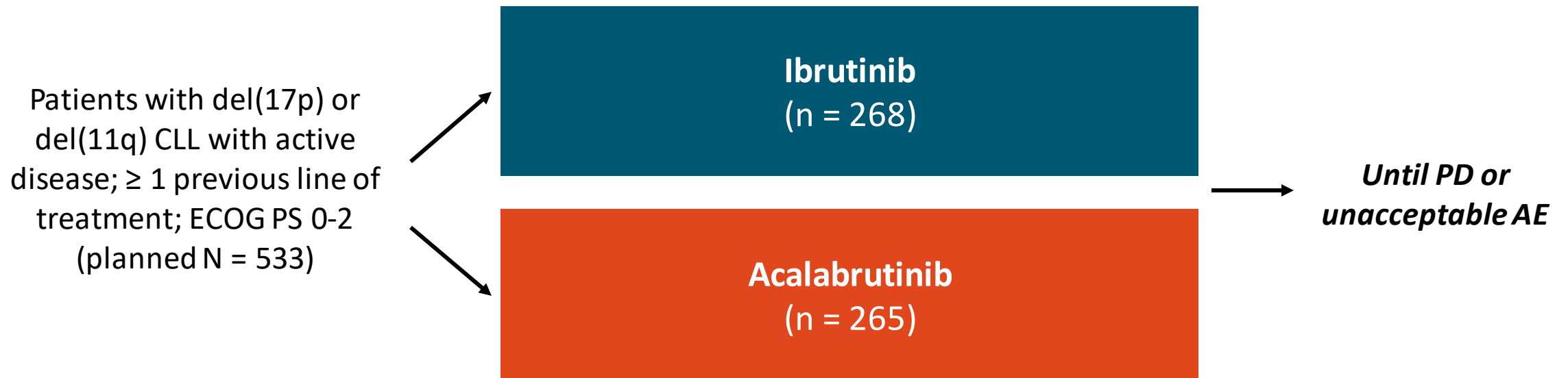- **Prolong PFS while on therapy**

BTKi

Ven + G
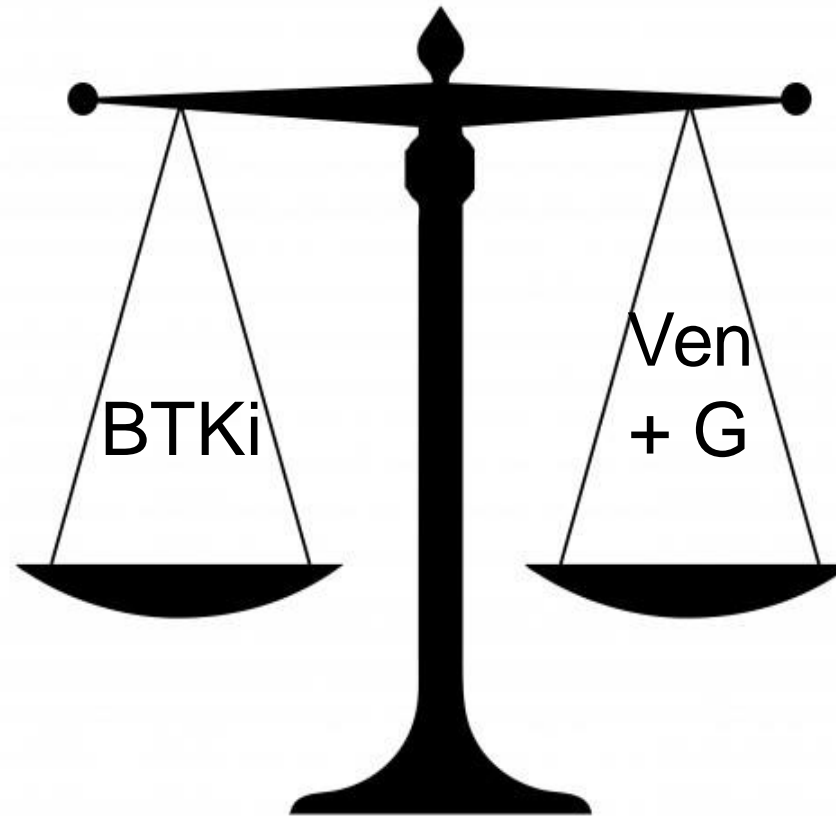
Author's opinion.

- Potential for 1-year time-limited therapy
- No known cardiac or bleeding risks
- Less concern with long-term adherence
- Potential for cost-savings if 1 year of therapy is durable
- Less financial toxicity
- Low risk dx
- BM based disease: cytopenias.
- Younger age
- Possibility of retreatment
- **Prolong PFS after MRD negative**
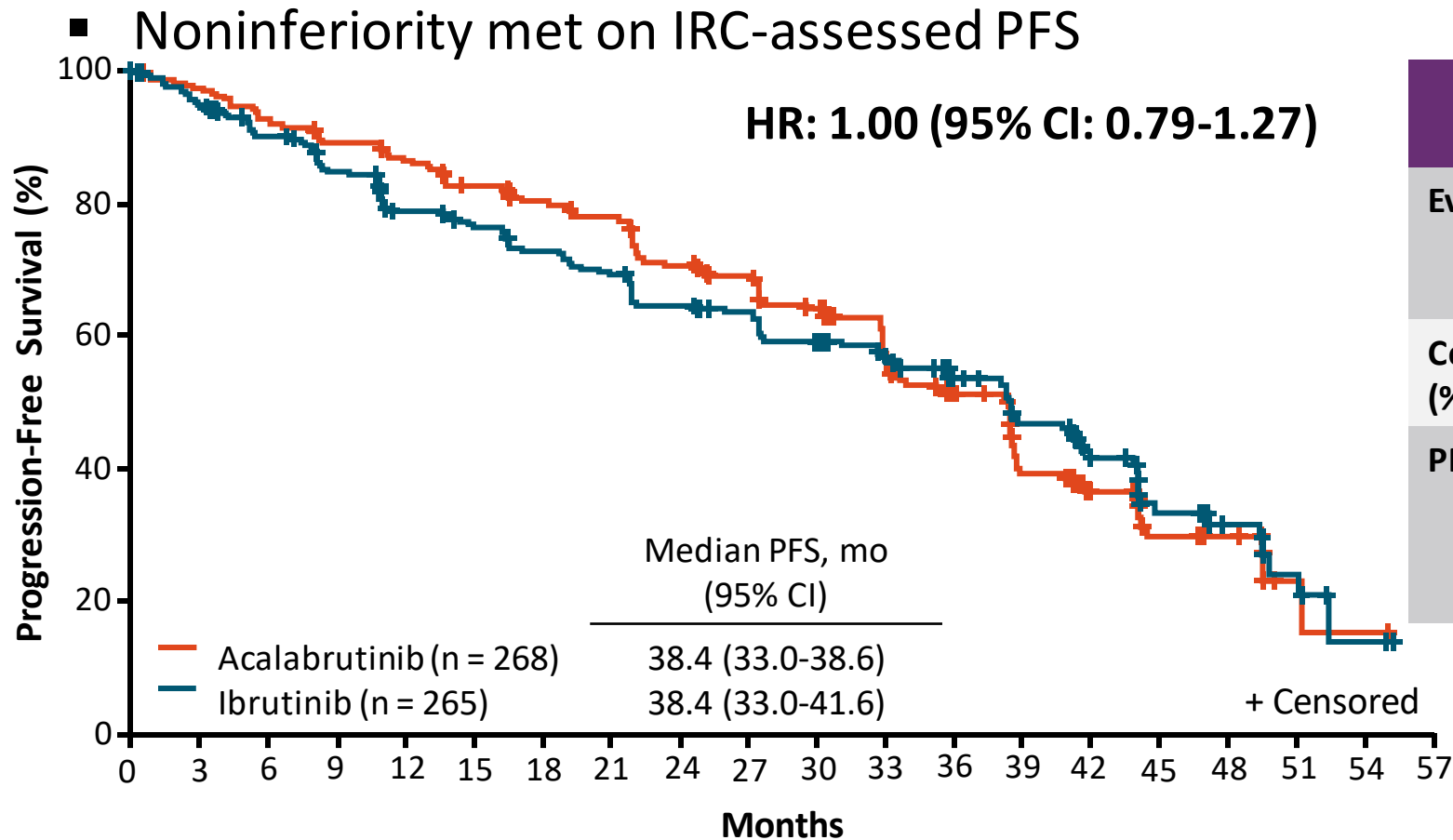
Head to Head BTKi trials

ELEVATE-RR: Ibrutinib vs Acalabrutinib in Patients With High-Risk Relapsed/Refractory CLL

- Final analysis of randomized, multicenter, open-label, noninferiority phase III trial

Patients with del(17p) or del(11q) CLL with active disease; ≥ 1 previous line of treatment; ECOG PS 0-2 (planned N = 533)

Ibrutinib
(n = 268)

Acalabrutinib
(n = 265)

Until PD or unacceptable AE

- Primary endpoint: PFS

- Secondary endpoints: OS; incidence of treatment-emergent AEs, atrial fibrillation; Richter's transformation; grade ≥3 infections

- FPI October 2015 – LPI November 2017 (25 mo)

- Final analysis: 279 IRC PFS events, data cutoff 9/2020

Byrd. ASCO 2021.

ELEVATE-RR: Noninferiority Met on IRC-Assessed PFS

- Noninferiority met on IRC-assessed PFS

HR: 1.00 (95% CI: 0.79-1.27)

Median PFS, mo (95% CI)

Acalabrutinib (n = 268)   38.4 (33.0-38.6)
Ibrutinib (n = 265)   38.4 (33.0-41.6)

+ Censored

Number at Risk

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57
Acalabrutinib	268	250	235	227	219	207	200	193	173	163	148	110	84	59	31	21	13	3	1	0
Ibrutinib	265	240	221	205	186	178	168	160	148	142	130	108	81	66	41	26	15	8	2	0

Median follow-up: 41 months

	Acalabrutinib (n = 268)	Ibrutinib (n = 265)
Events, n (%)	143 (53.4)	136 (51.3)
Death	22 (8.2)	28 (10.6)
PD	121 (45.1)	108 (40.8)
Censored, n (%)	125 (46.6)	129 (48.7)
PFS (95% CI), %		
12 months	86.7 (81.8-90.3)	78.8 (73.1-83.4)
24 months	70.9 (64.8-76.1)	64.5 (58.1-70.2)
36 months	51.4 (44.7-57.8)	53.8 (47.0-60.1)

Noninferiority achieved if upper bound of the 95% CI of HR is less than the prespecified NI margin of 1.429

Byrd. ASCO 2021.

ELEVATE-RR: AEs of clinical interest

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)**	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)

Byrd. ASCO 2021.

ELEVATE-RR: Summary Adverse events

- *Initial safety results*

  - **Atrial fibrillation significantly less common with acalabrutinib (P = .023)**

    - Acalabrutinib: 9.4%

    - Ibrutinib: 16.0%

  - Grade ≥3 infection and Richter transformation comparable between arms (~30% and ~4.5%, respectively)

- Any-grade AEs in ≥20%

  - Less common with acalabrutinib: hypertension, arthralgia, diarrhea, cardiac, hypertension, bleeding

  - More common with acalabrutinib: headache, cough

- Fewer discontinuations with acalabrutinib: 14.7% vs 21.3% with ibrutinib
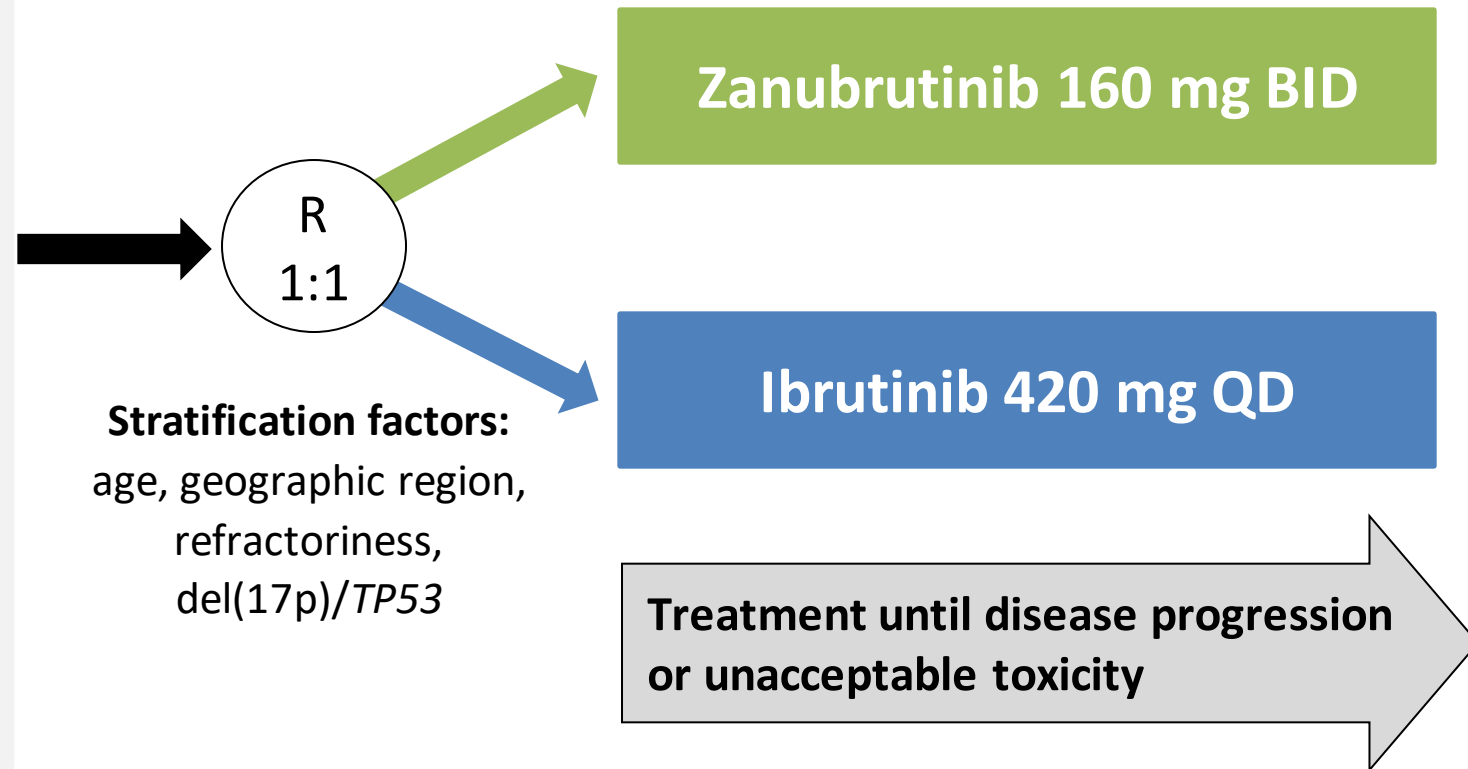
ALPINE Study Design

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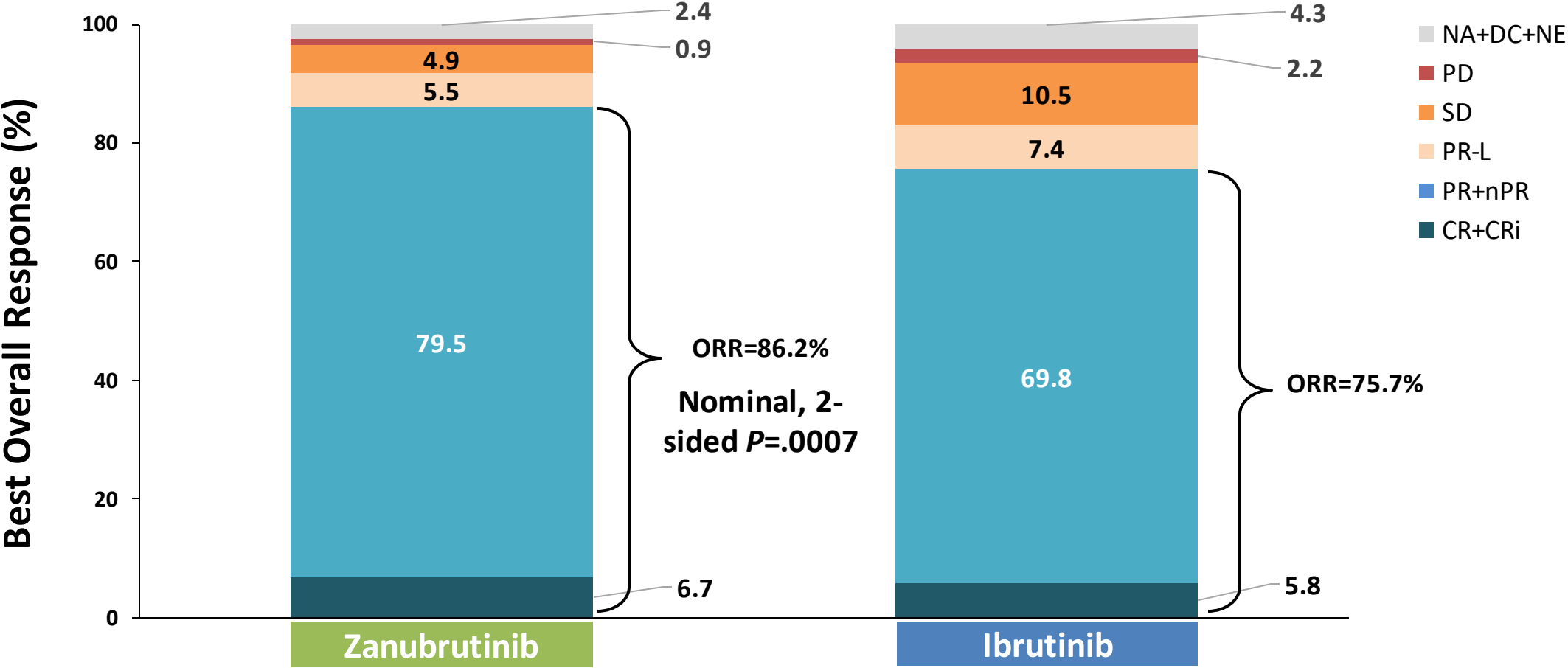(Planned N=600, Actual N=652)

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

Key Exclusion Criteria
- Prior BTK inhibitor therapy
- Treatment with warfarin or other vitamin K antagonists

R 1:1

Stratification factors:
age, geographic region, refractoriness, del(17p)/*TP53*

Zanubrutinib 160 mg BID

Ibrutinib 420 mg QD

Treatment until disease progression or unacceptable toxicity

Brown et al. NEJM, December 2022

Brown et al. ALPINE ASH 2022

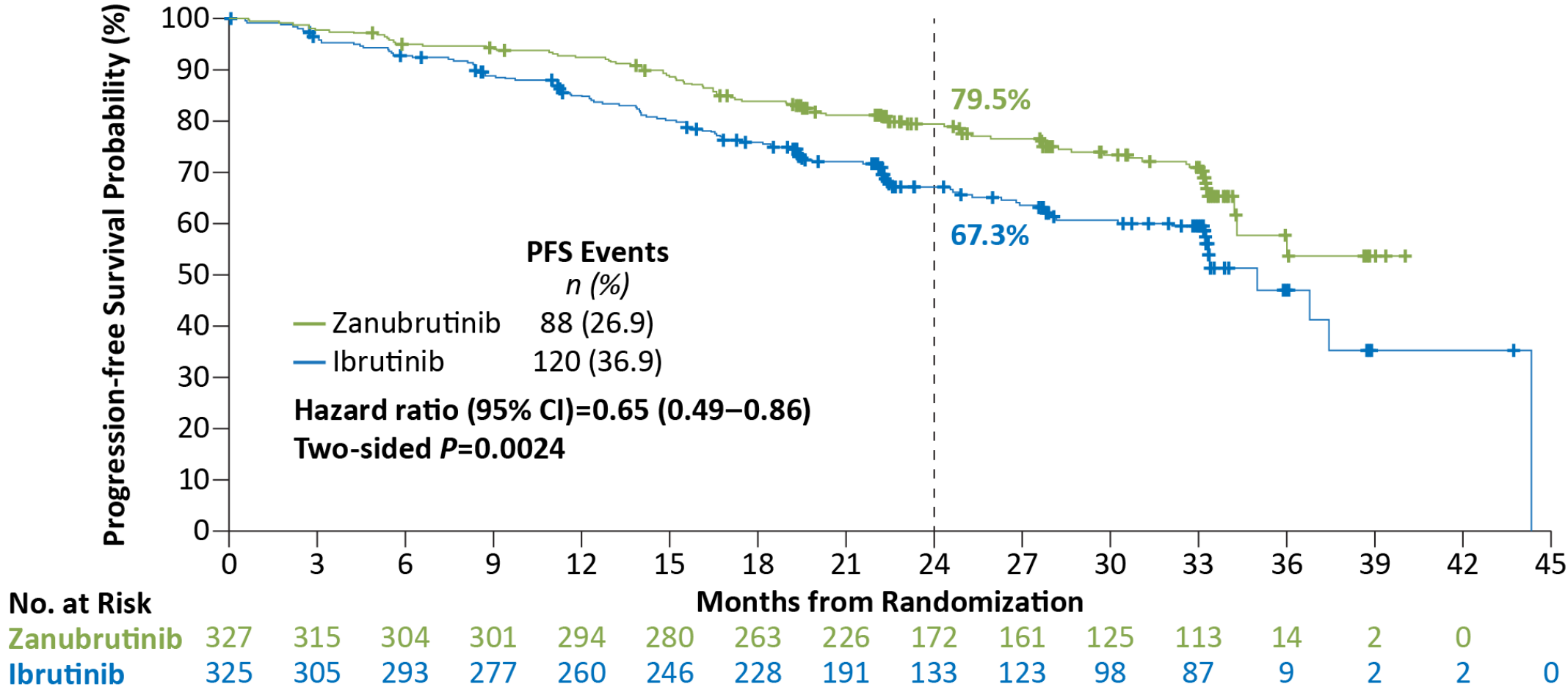# Zanubrutinib Showed Higher ORR Assessed by IRC

CR, complete response; CRi, complete response with incomplete bone marrow recovery; nPR, nodular partial response; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable response; PD, progressive disease; NA, not assessed; DC, discontinued prior to first assessment; NE, not evaluable.

Data cutoff: 8 Aug 2022

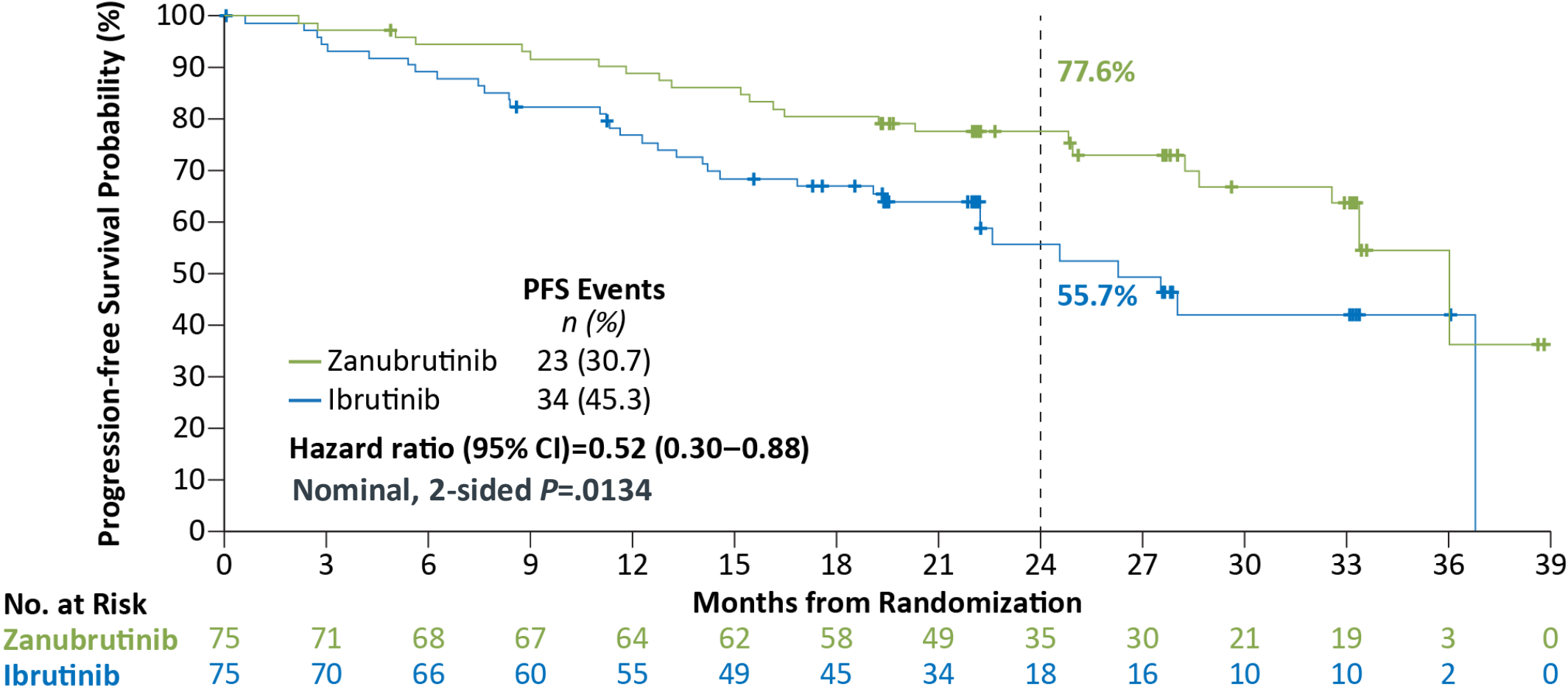# Zanubrutinib PFS by IRC Significantly Superior to Ibrutinib

Median study follow-up of 29.6 months

PFS Events
n (%)

— Zanubrutinib   88 (26.9)
— Ibrutinib   120 (36.9)

Hazard ratio (95% CI)=0.65 (0.49−0.86)
Two-sided *P*=0.0024

79.5%

67.3%

No. at Risk															
Zanubrutinib	327	315	304	301	294	280	263	226	172	161	125	113	14	2	0
Ibrutinib	325	305	293	277	260	246	228	191	133	123	98	87	9	2	2	0

Data cutoff: 8 Aug 2022

Brown et al. NEJM, December 2022

Brown et al. ALPINE ASH 2022

Zanubrutinib Improved PFS in Patients with del(17p)/*TP53^mut*

PFS Events
n (%)
— Zanubrutinib 23 (30.7)
— Ibrutinib 34 (45.3)
Hazard ratio (95% CI)=0.52 (0.30−0.88)
Nominal, 2-sided *P*=.0134

77.6%

55.7%

Progression-free Survival Probability (%)

Months from Randomization

No. at Risk

	0	3	6	9	12	15	18	21	24	27	30	33	36	39
Zanubrutinib	75	71	68	67	64	62	58	49	35	30	21	19	3	0
Ibrutinib	75	70	66	60	55	49	45	34	18	16	10	10	2	0

PFS data assessed by IRC

Data cutoff: 8 Aug 2022

Brown et al. NEJM, December 2022

Brown et al. ALPINE ASH 2022

Most Common Adverse Events*

Ibrutinib | Zanubrutinib

Grade
1
2
3
4
5

Neutropenia†
COVID-19 related
Hypertension†
Upper Respiratory Tract Infection
Diarrhea
Anemia†
Arthralgia

50 40 30 20 10 0 0 10 20 30 40 50

Frequency (%)
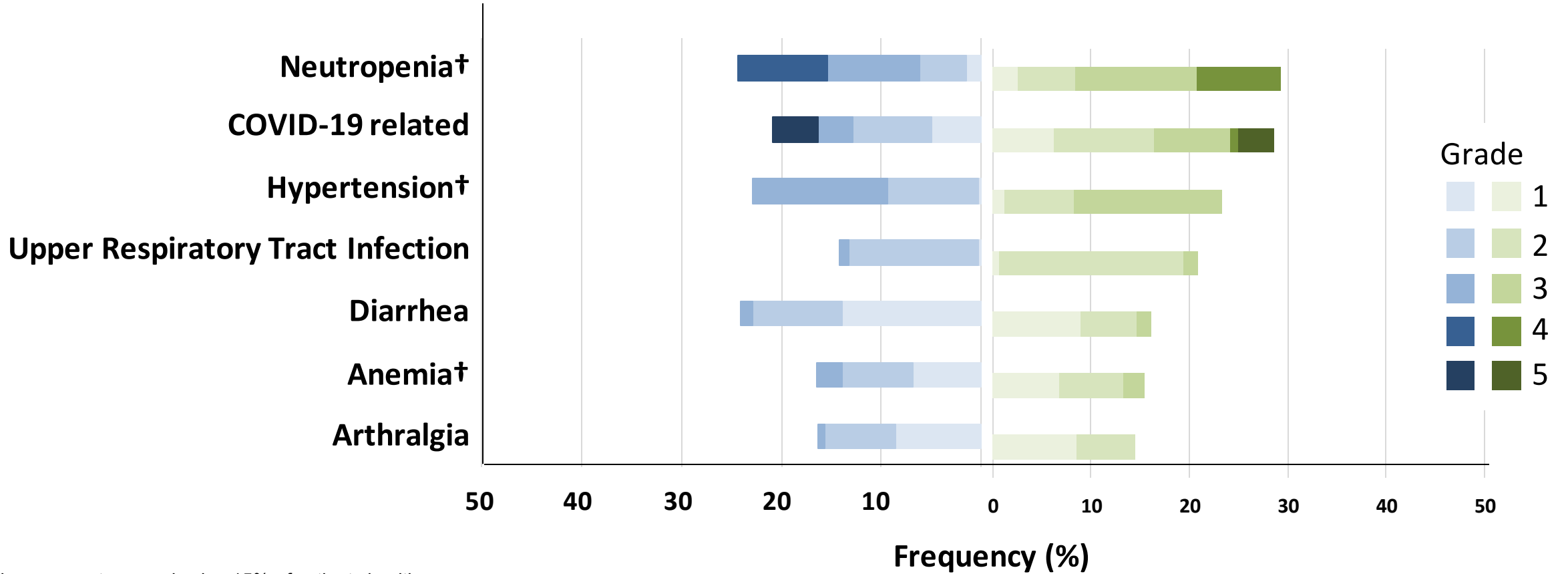
*Adverse events occurring in ≥15% of patients in either arm.
†Pooled terms.

Data cutoff: 8 Aug 2022

Brown et al. NEJM, December 2022

Brown et al. ALPINE ASH 2022

Zanubrutinib: Cardiac Profile

Lower rate of cardiac events, serious cardiac events, treatment discontinuation, and deaths

- Lower rate of serious cardiac adverse events reported with zanubrutinib
  - A fib/flutter (n=2)
  - MI/ACS (n=2)
  - CHF (n=2)

- **Fatal cardiac events:**
  - **Zanubrutinib, n=0 (0%)**
  - **Ibrutinib, n=6 (1.9%)**

	Zanubrutinib (n=324)	Ibrutinib (n=324)
Cardiac adverse events	**69 (21.3%)**	**96 (29.6%)**
Serious cardiac adverse events	**6 (1.9%)**	**25 (7.7%)**
Cardiac adverse events leading to treatment discontinuation	**1 (0.3)**	**14 (4.3)**
Ventricular extrasystoles	1 (0.3)	0
Atrial fibrillation	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)
Ventricular fibrillation	0	1 (0.3)

Data cutoff: 8 Aug 2022

*Cardiac deaths. One death not listed due to myocardial infarction with ibrutinib discontinuation due to diarrhea 14 days prior to the fatal event.
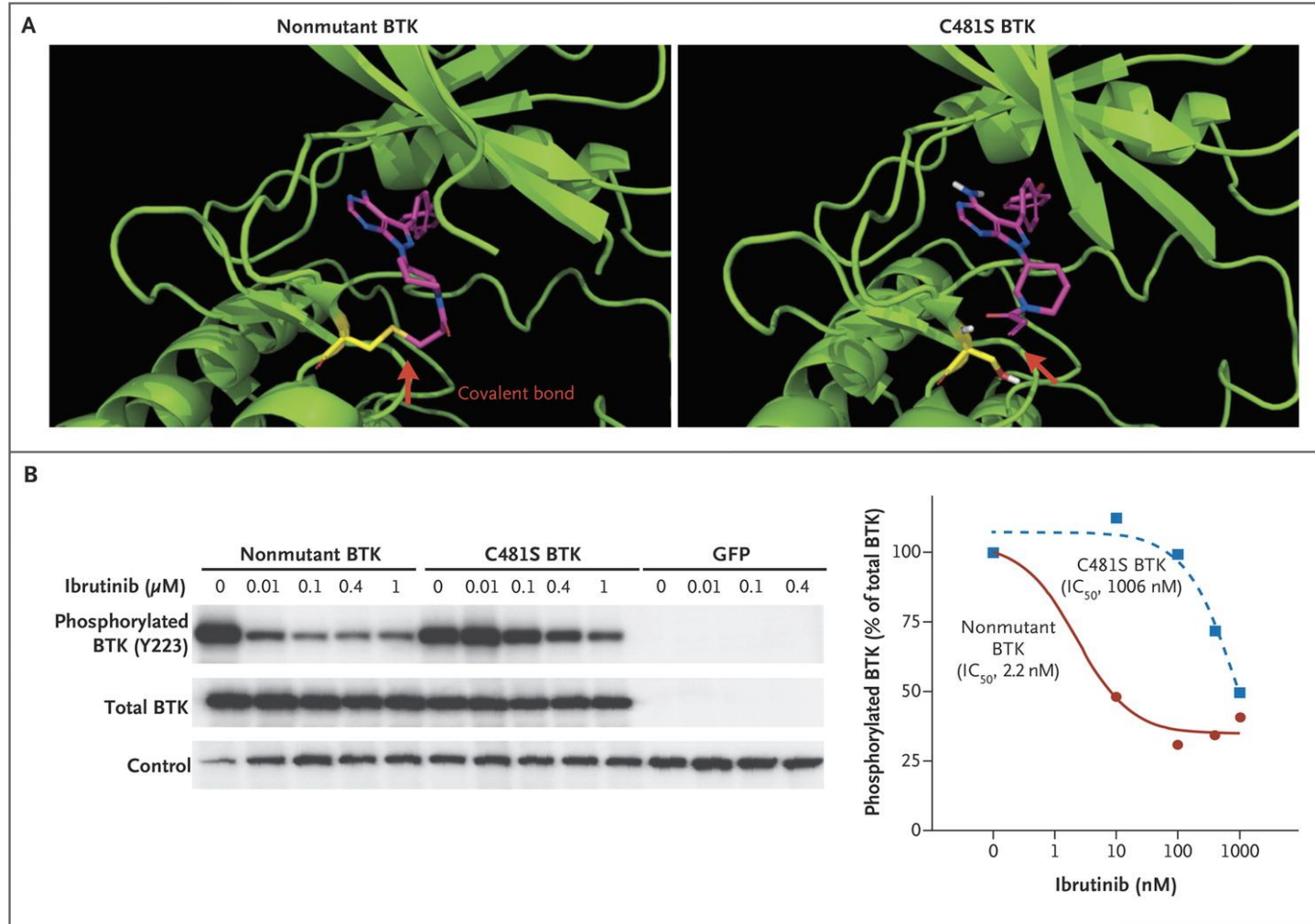
Atrial Fibrillation/Flutter Events With Zanubrutinib
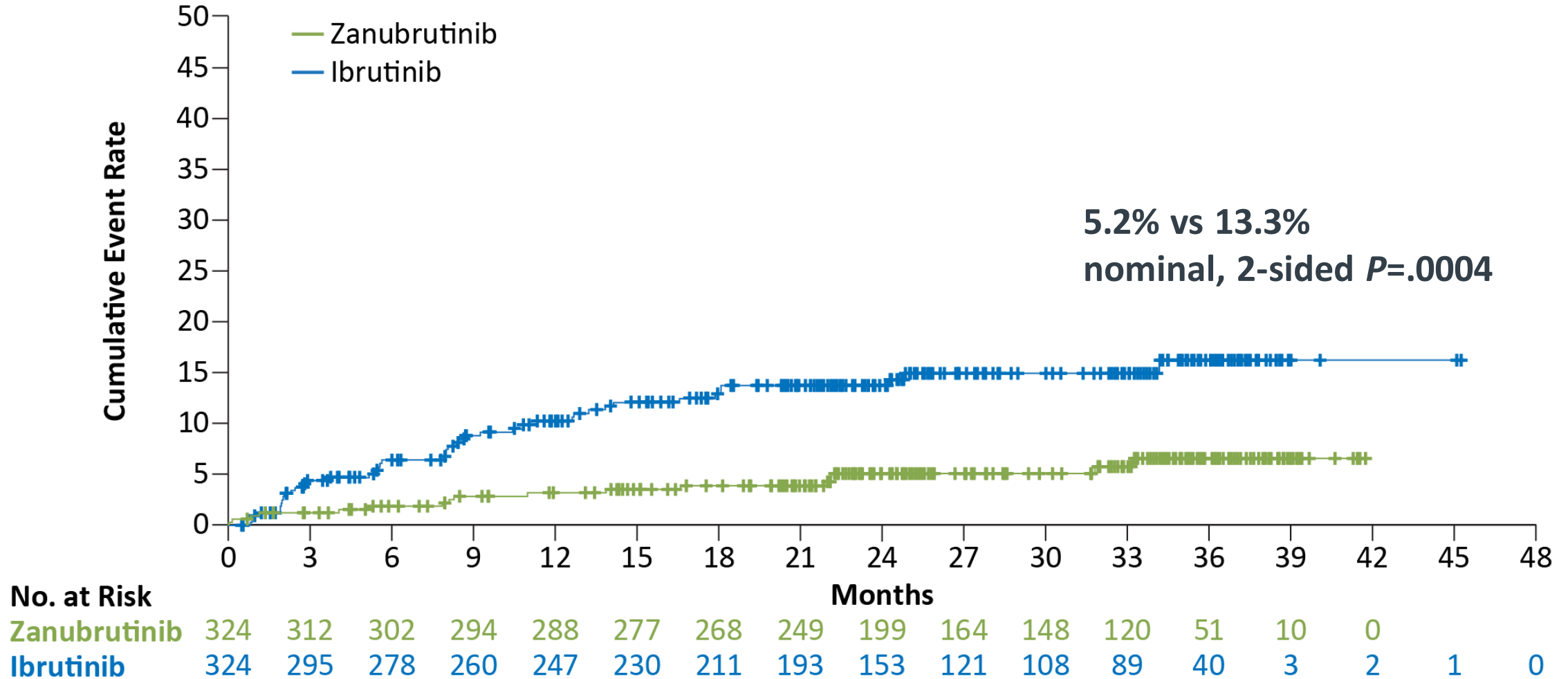
Data cutoff: 8 Aug 2022

ELEVATE-RR vs ALPINE: AEs of clinical interest, D/C and PD

	Alpine 29.6m		Elevate RR 41m	
	Zanubrutinib	**Ibrutinib**	**Acalabrutinib**	**Ibrutinib**
▪ ORR (IRC) ▪ ORR + PRL ▪ 24 m PFS	86.6% 91.7% 79.5%	75.7% 81.3% 67.3%	81% 83% 70%	77% 80% 65%
Median PFS	NR	35m	38.4m	38.4m
Discontinuation total	**26.3%**	**41.2%**	**52.6%**	**58.5%**
D/C AEs	16.2%	22.8%	14.9%	22.3%
D/C PD	7.3%	12.9%	30.6%	25.7%
Atrial fibrillation/flutter	5.3%	13.3%	9.4%	16%

Byrd et al. ASCO 2021, Brown et al ASH 2022.

Effect of C481S Mutation of BTK on BTKi Binding

Furman RR et al. N Engl J Med 2014;370:2352-2354.

BTK Leu528Trp Mutations in Patients with CLL on Zanubrutinib

- Consecutive samples at Peter MacCallum (AUS); N=37
- BTK Leu528Trp mutations were significantly enriched at time of PD for zanubrutinib versus ibrutinib:
  - **54%** [7/13] vs **4%** [1/24] (p=0.001)
- Other studies have shown that Leu528Trp mutations are rarely seen with ibrutinib

BTKi mutations detected in a cohort of patients with disease progression during BTKi treatment

| | Number of patients carrying the mutations | | | |
	Ibrutinib-treated patients (n = 24)	Zanubrutinib-treated patients (n =13)	Total	P
Cys481 codon mutations	24	10	34	.03
Leu528Trp	1	7	8	.001

Both patients with Leu528Trp mutations treated with pirtobrutinib had poor responses

Kinase-dead BTK Leu528Trp mutation is enriched in patients with CLL progressing on zanubrutinib versus ibrutinib, which has potential implications for choice of BTK inhibitor and subsequent therapies, like pirtobrutinib, where this mutation is suspected to confer resistance

Piers Blombery, e.t al *Blood Adv* 2022;

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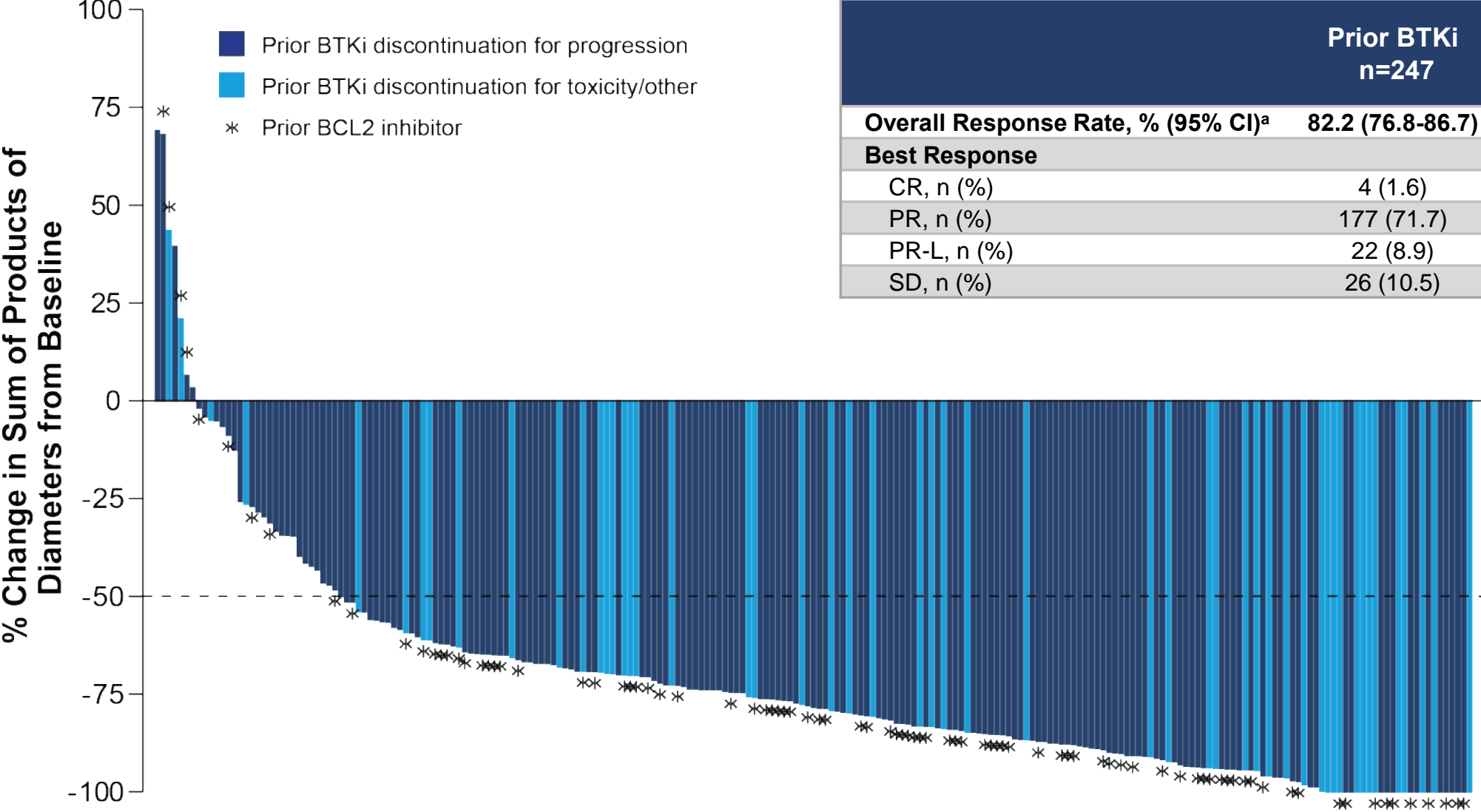
	Prior BTKi n=247	Prior BTKi+BCL2i n=100
Overall Response Rate, % (95% CI)[a]	**82.2 (76.8-86.7)**	**79.0 (69.7-86.5)**
Best Response		
CR, n (%)	4 (1.6)	0 (0.0)
PR, n (%)	177 (71.7)	70 (70.0)
PR-L, n (%)	22 (8.9)	9 (9.0)
SD, n (%)	26 (10.5)	11 (11.0)

Legend:
- Prior BTKi discontinuation for progression
- Prior BTKi discontinuation for toxicity/other
- * Prior BCL2 inhibitor

Y-axis: % Change in Sum of Products of Diameters from Baseline
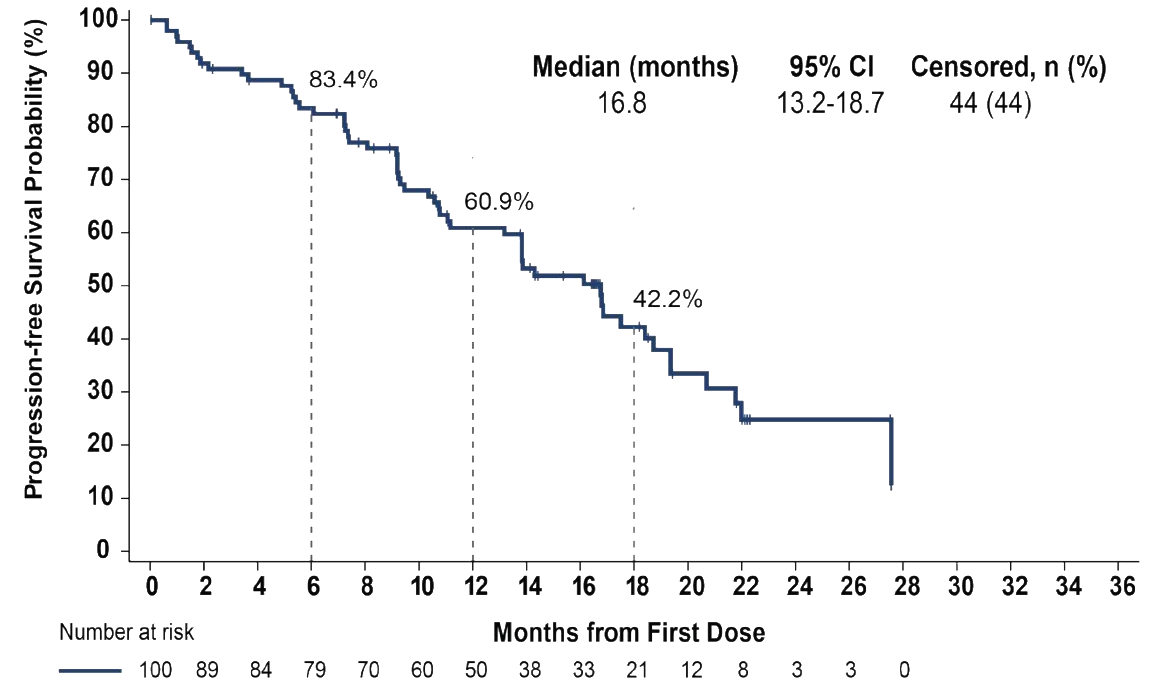
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Progression-Free Survival in CLL/SLL Patients who Received Prior BTKi Treatment
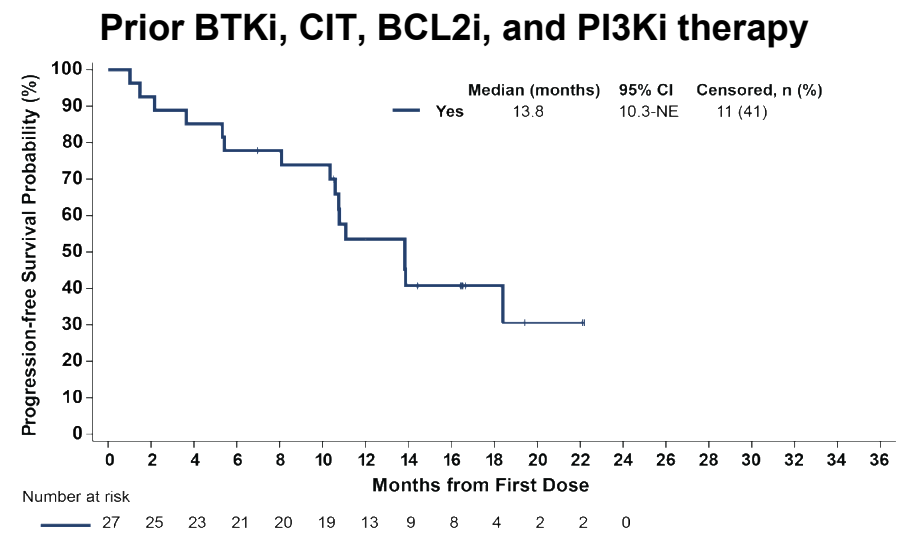

All prior BTKi patients
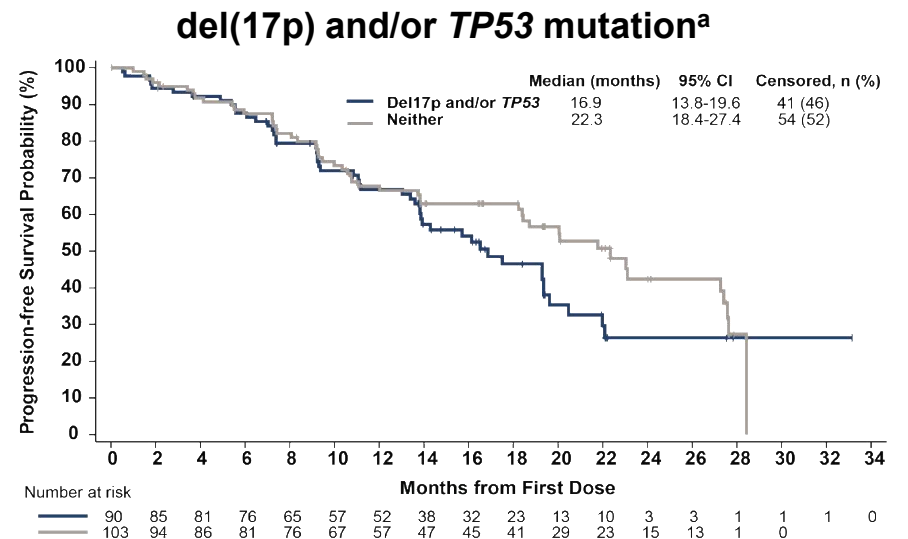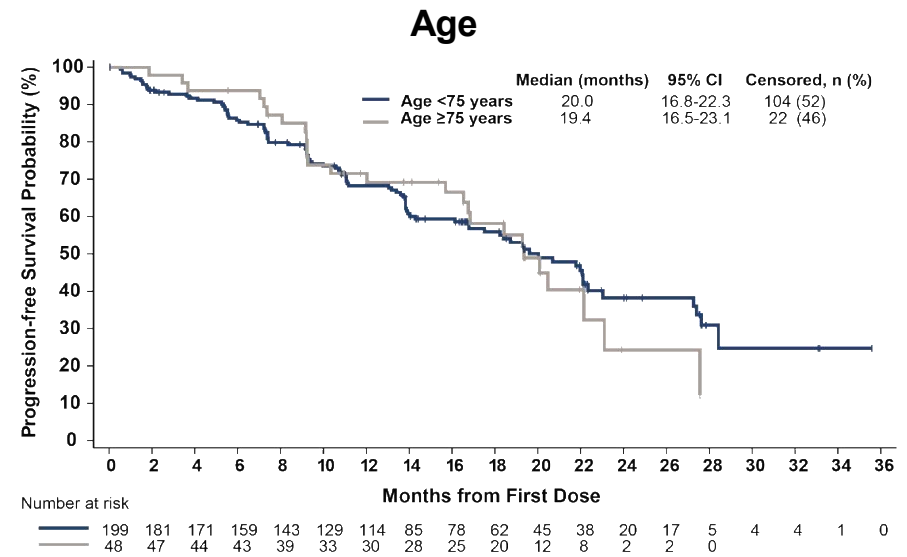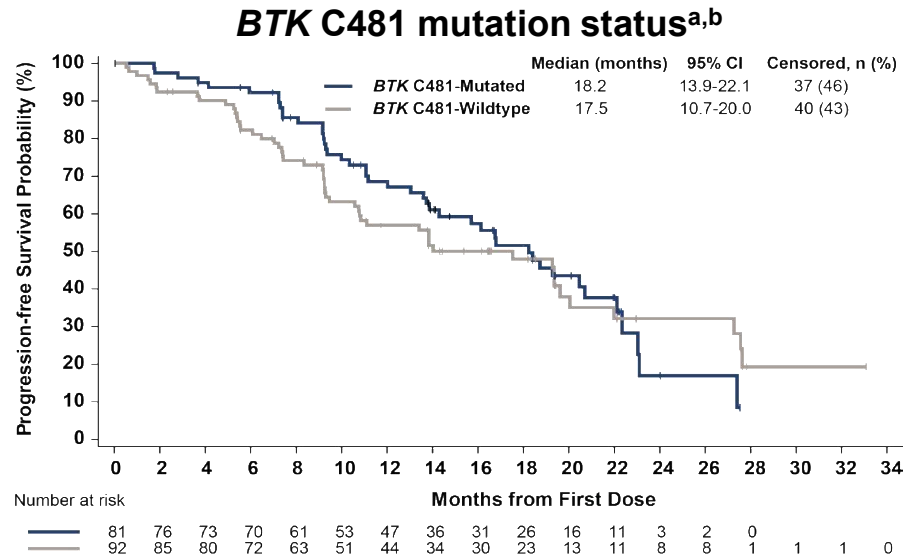**Median prior lines = 3**
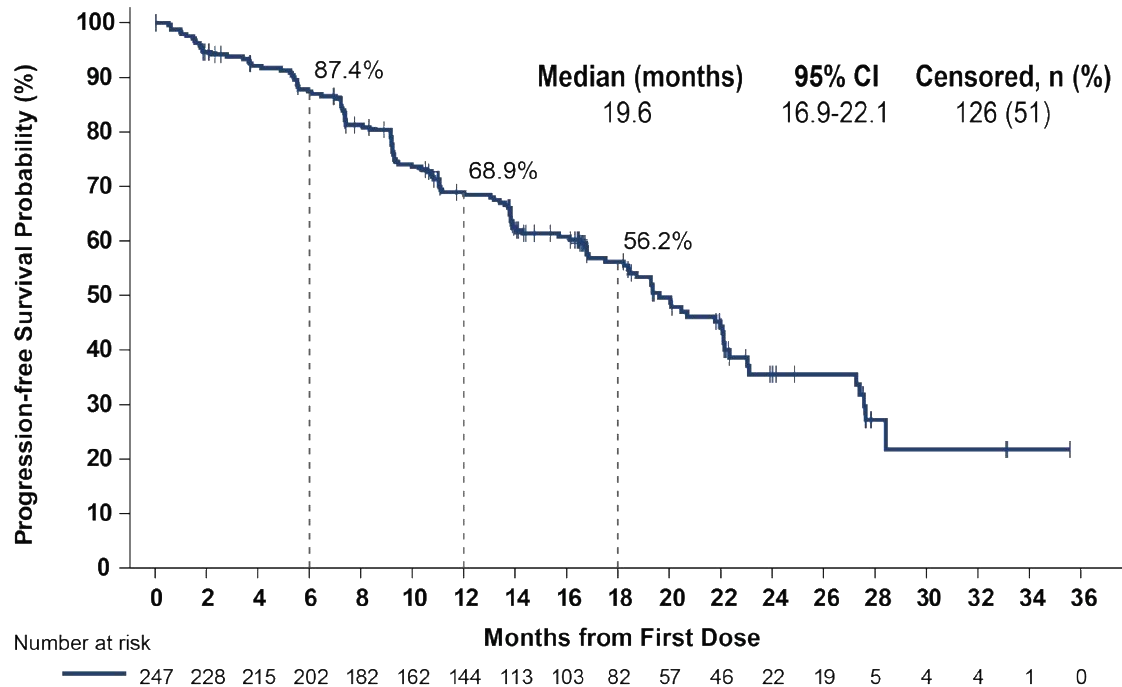
Prior BTKi and BCL2i patients
Median prior lines = 5

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

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

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Progression-Free Survival in CLL/SLL Subgroups

BTK C481 mutation status[a,b]

	Median (months)	95% CI	Censored, n (%)
BTK C481-Mutated	18.2	13.9-22.1	37 (46)
BTK C481-Wildtype	17.5	10.7-20.0	40 (43)

Number at risk

| 81 | 76 | 73 | 70 | 61 | 53 | 47 | 36 | 31 | 26 | 16 | 11 | 3 | 2 | 0 |
| 92 | 85 | 80 | 72 | 63 | 51 | 44 | 34 | 30 | 23 | 13 | 11 | 8 | 8 | 1 | 1 | 1 | 0 |

del(17p) and/or *TP53* mutation[a]

	Median (months)	95% CI	Censored, n (%)
Del17p and/or *TP53*	16.9	13.8-19.6	41 (46)
Neither	22.3	18.4-27.4	54 (52)

Number at risk

| 90 | 85 | 81 | 76 | 65 | 57 | 52 | 38 | 32 | 23 | 13 | 10 | 3 | 3 | 1 | 1 | 1 | 0 |
| 103 | 94 | 86 | 81 | 76 | 67 | 57 | 47 | 45 | 41 | 29 | 23 | 15 | 13 | 1 | 0 |

Age

	Median (months)	95% CI	Censored, n (%)
Age <75 years	20.0	16.8-22.3	104 (52)
Age ≥75 years	19.4	16.5-23.1	22 (46)

Number at risk

| 199 | 181 | 171 | 159 | 143 | 129 | 114 | 85 | 78 | 62 | 45 | 38 | 20 | 17 | 5 | 4 | 4 | 1 | 0 |
| 48 | 47 | 44 | 43 | 39 | 33 | 30 | 28 | 25 | 20 | 12 | 8 | 2 | 2 | 0 |

Prior BTKi, CIT, BCL2i, and PI3Ki therapy

	Median (months)	95% CI	Censored, n (%)
Yes	13.8	10.3-NE	11 (41)

Number at risk

| 27 | 25 | 23 | 21 | 20 | 19 | 13 | 9 | 8 | 4 | 2 | 2 | 0 |

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Pirtobrutinib Safety Profile

Adverse Event (AEs)	All Doses and Patients (N=773)			
	Treatment-Emergent AEs, %		Treatment-Related AEs, %	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Fatigue	28.7%	2.1%	9.3%	0.8%
Diarrhea	24.2%	0.9%	9.3%	0.4%
Neutropenia[a]	24.2%	20.4%	14.7%	11.5%
Contusion	19.4%	0.0%	12.8%	0.0%
Cough	17.5%	0.1%	2.3%	0.0%
Covid-19	16.7%	2.7%	1.3%	0.0%
Nausea	16.2%	0.1%	4.7%	0.1%
Dyspnea	15.5%	1.0%	3.0%	0.1%
Anemia	15.4%	8.8%	5.2%	2.1%
AEs of Special Interest[b]	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Bruising[c]	23.7%	0.0%	15.1%	0.0%
Rash[d]	12.7%	0.5%	6.0%	0.4%
Arthralgia	14.4%	0.6%	3.5%	0.0%
Hemorrhage/Hematoma[e]	11.4%	1.8%	4.0%	0.6%
Hypertension	9.2%	2.3%	3.4%	0.6%
Atrial fibrillation/flutter[f,g]	2.8%	1.2%	0.8%	0.1%

Median time on treatment for the overall safety population was 9.6 months
Discontinuations due to treatment-related AEs occurred in 2.6% (n=20) of all patients
Dose reductions due to treatment-related AEs occurred in 4.5% (n=35) of all patients
Overall and CLL/SLL safety profiles are consistent[h]

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Mutations conferring Resistance to non covalent BTKis
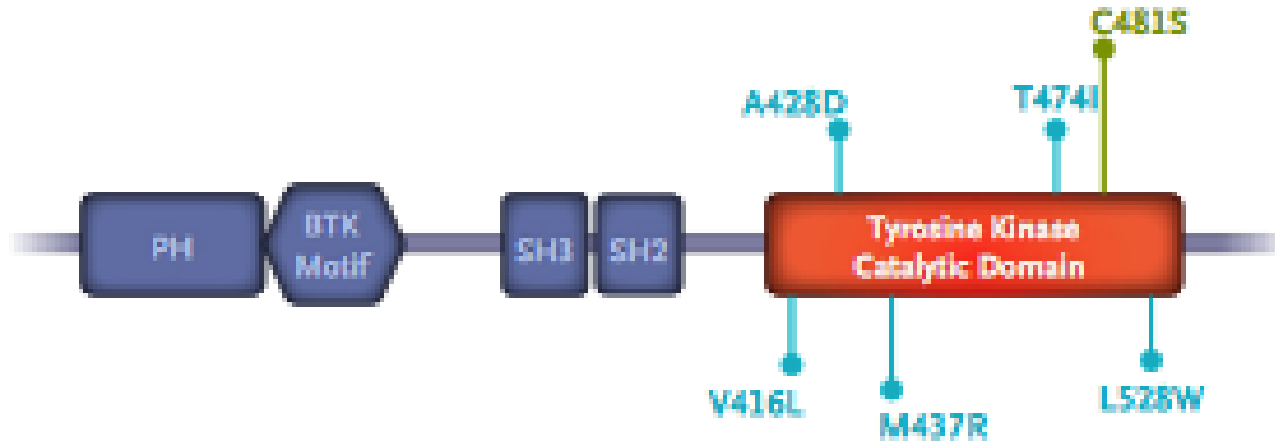
- Novel, acquired mutations in *BTK* identified in patients with CLL at the time of disease progression:
  - *BTK L528W*
  - *BTK V416L*
  - *BTK M437R*
  - *BTK T474I*
  - *BTK A428D*

- These mutations cluster around the tyrosine kinase catalytic domain of BTK

- Several patients with progressive disease additionally had preexisting *PLCG2* mutations

Wang et al NEJM 2022

Binding Affinities of BTK Inhibitors

	Noncovalent				Covalent
	Pirtobrutinib	ARQ-531	Vecabrutinib	Fenebrutinib	Ibrutinib
Wild type	Normal	Normal	Normal	Normal	Normal
A428D	None	Decreased	None	None	None
M437R	Decreased	Normal	Decreased	Decreased	Normal
T474I	Decreased	Decreased	Decreased	Normal	Normal
L528W	None	None	Decreased	Normal	None
C481S	Normal	Normal	Normal	Normal	Decreased

Conclusions

- Patients preferences and Individualized therapy should be take into consideration.
- Great options for front line CLL: **Long term therapy**
  - First generation **ibrutinib** show great long term efficacy supported by multiple Phase III trials as well data for del17p/TP53 more discontinuation for AEs.
  - Second gen BTKi, **acalabrutini**b also showing excellent data with better tolerability.
  - **Zanubrutinib** now approved with great data in front line and good tolerability.
  - **Pirtobrutinib** soon to be an alternative for BTK resistance (approved in MCL).
- Great options for front line CLL: **Fixed duration**
  - **Obinutuzumab+venetoclax**: great efficacy with deep MRD responses.
  - **Ibrutinib+venetoclax**: approved in EU.
  - Triple therapies trials ongoing but unclear benefits.