Current standard of therapies in CLL

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MOFFITT CANCER CENTER

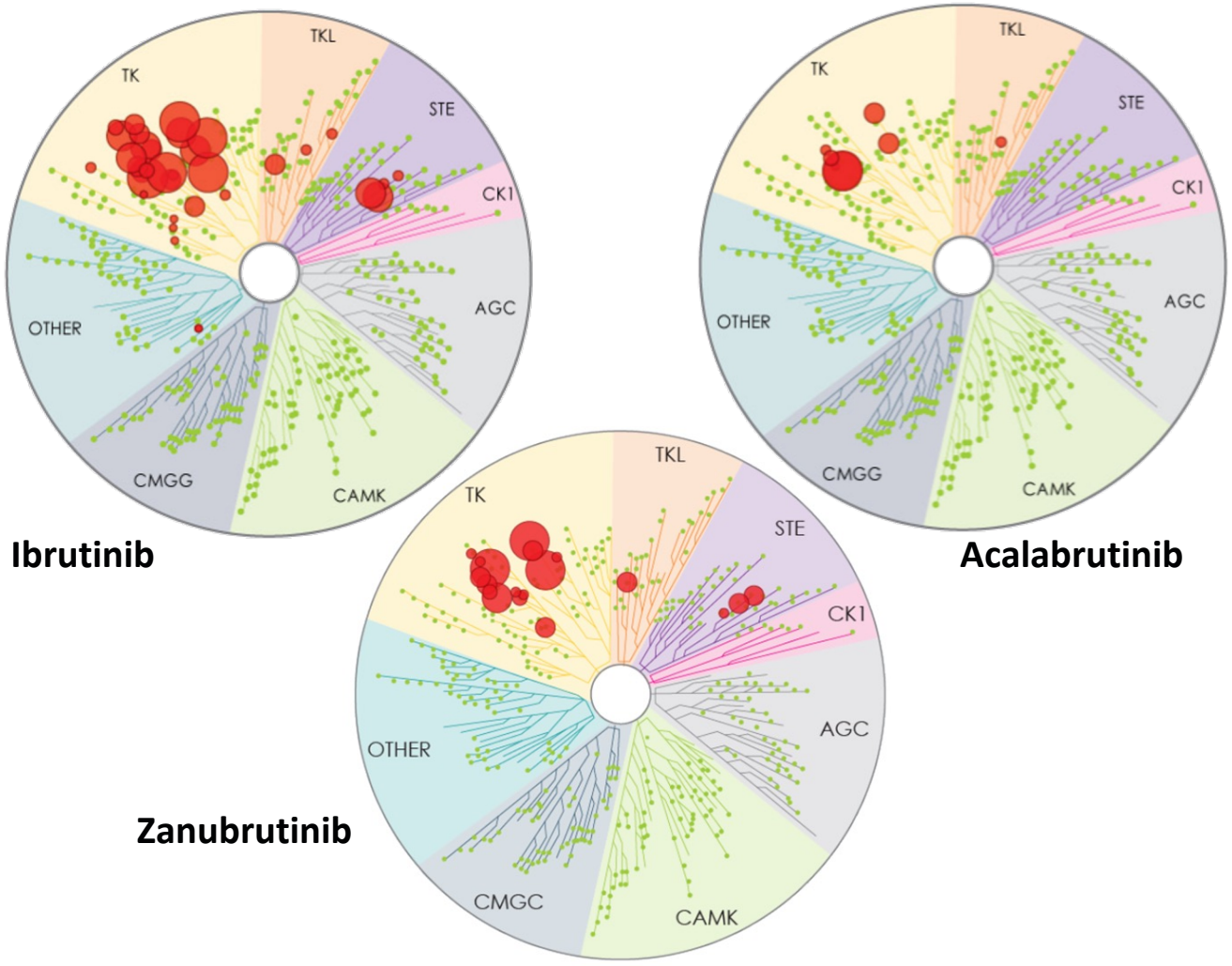
The dilemma continue between long term therapy vs fixed duration

The new era of BTK Inhibitors in CLL

Kinase	Ibrutinib	Acalabrutinib	Zanubrutinib
	IC_{50}/EC_{50} (nM)		
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

Kinase Selectivity Profiling at 1 μmol/L (in vitro)

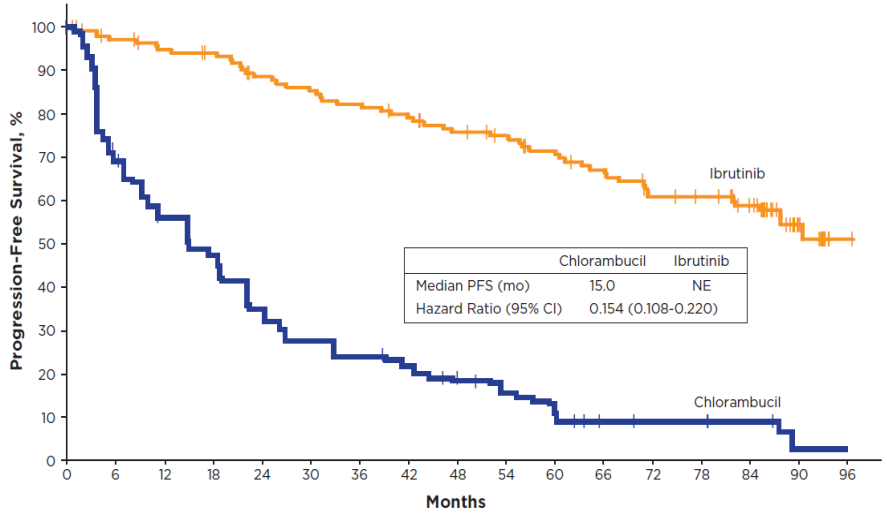
Larger red circles represent stronger inhibition

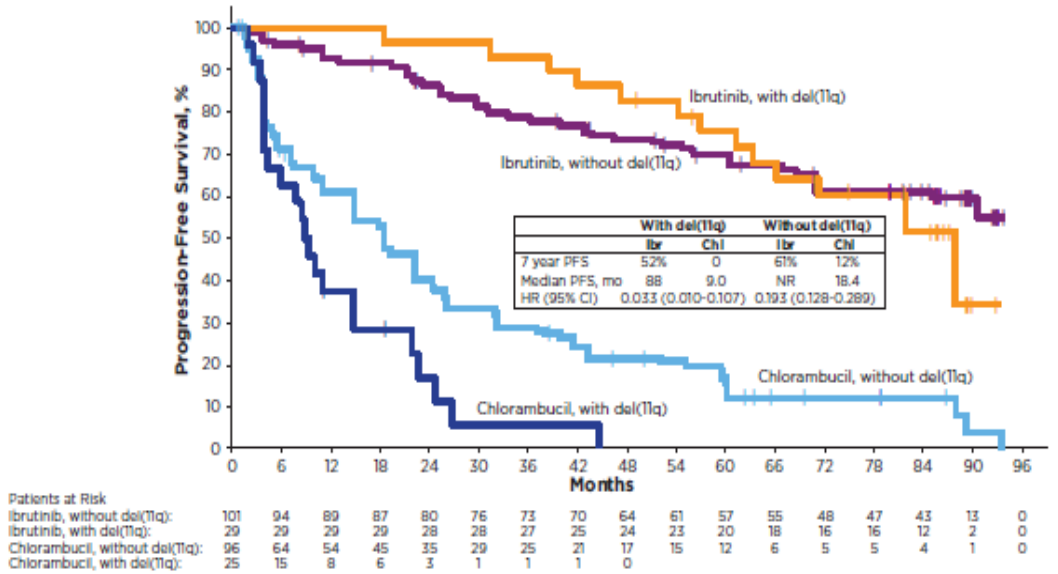


Kaptein. ASH 2018.

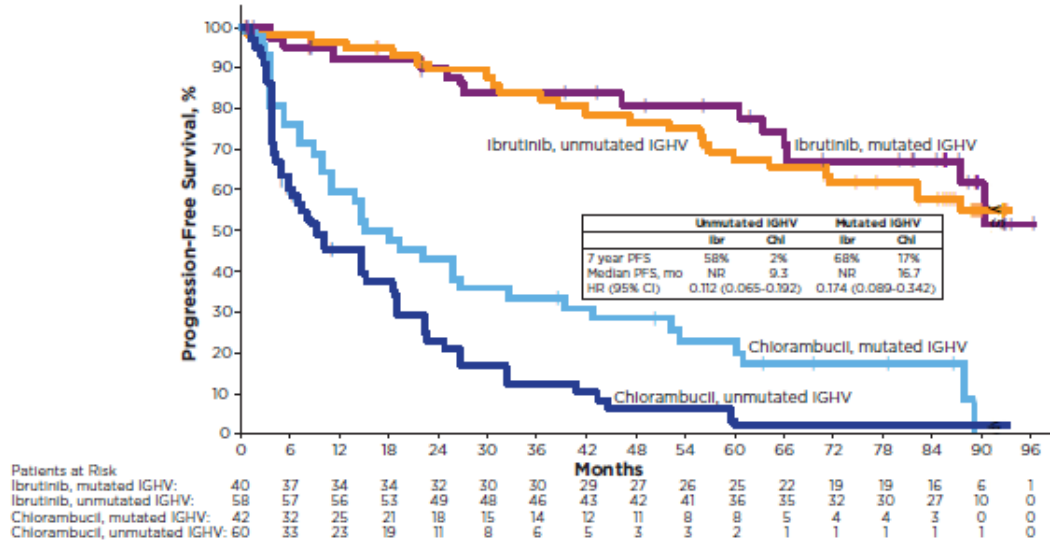
BTKi long term data
Ibrutinib

RESONATE-2: 8-Year Follow-Up - PFS





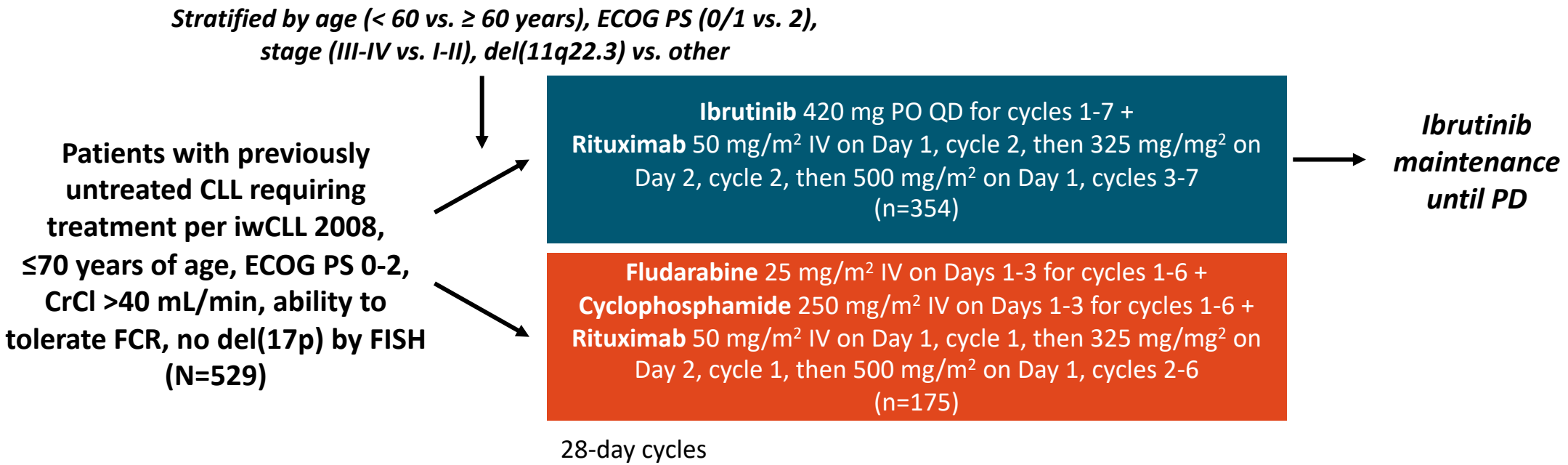
	Ibrutinib n=136
Median duration of ibrutinib treatment, years	6.2
Continuing ibrutinib on study, n (%)	57 (42)
Discontinued ibrutinib, n (%)	
AE	**32 (24)**
PD	**18 (13)**
Death	12 (9)
Withdrawal by patient	9 (7)
Investigator decision	7 (5)



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).



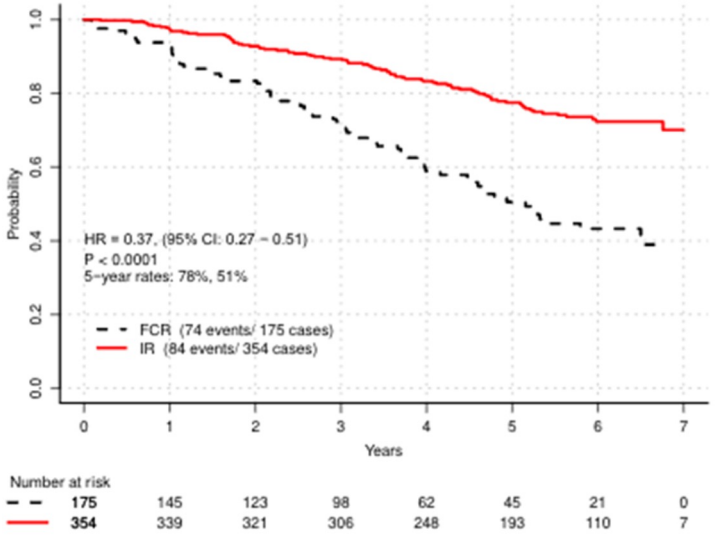
- Primary endpoint: PFS.
  - Study has 80% power to detect PFS HR for IR vs. FCR of 0.67 using stratified log-rank test, with prespecified boundary of 2.87 for first PFS interim analysis corresponding to 1-sided *P*=0.0025.
- Secondary endpoints: OS, safety.

Shanafelt et al *Blood 2022*.

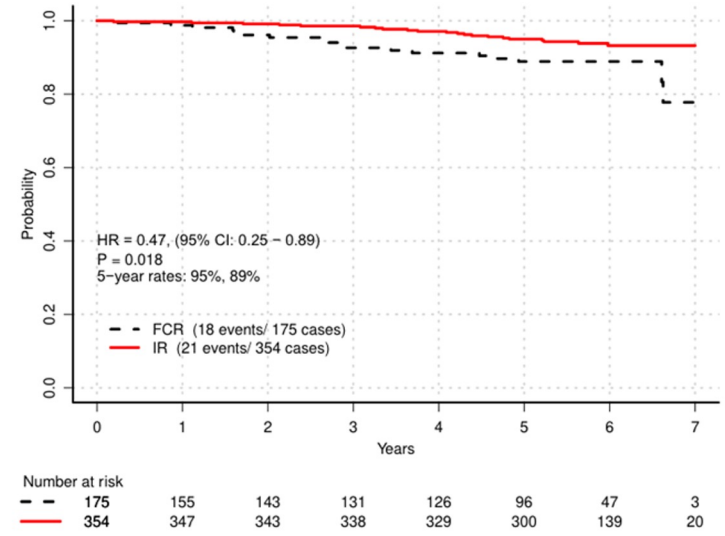
E1912: 5 years Updated PFS, OS by IGHV Status

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%)

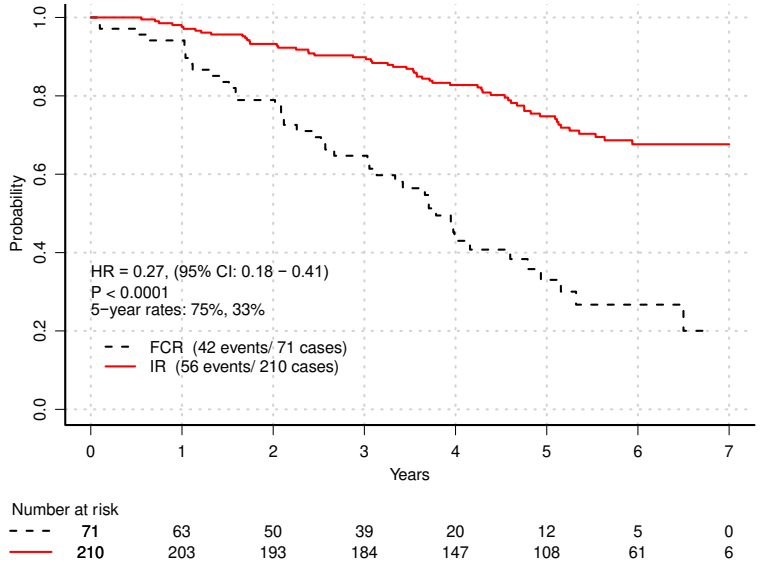
Progression Free Survival



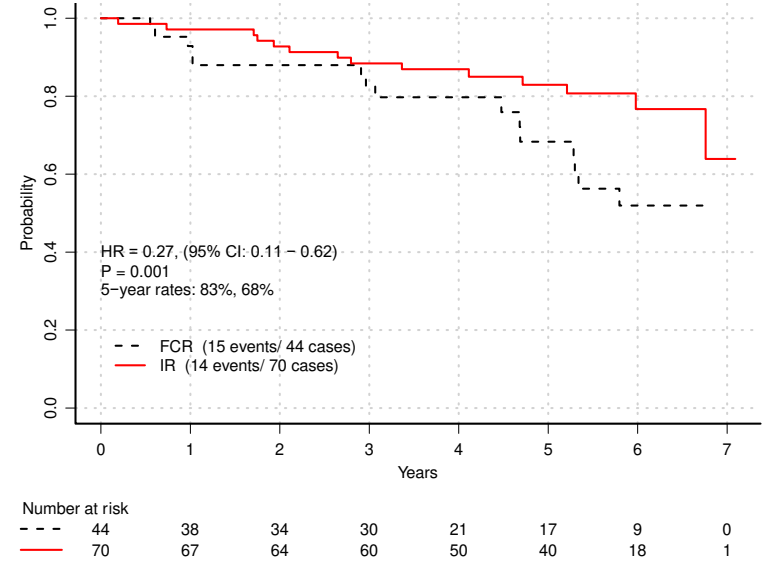
Overall Survival



IgHV unmutated



IgHV mutated

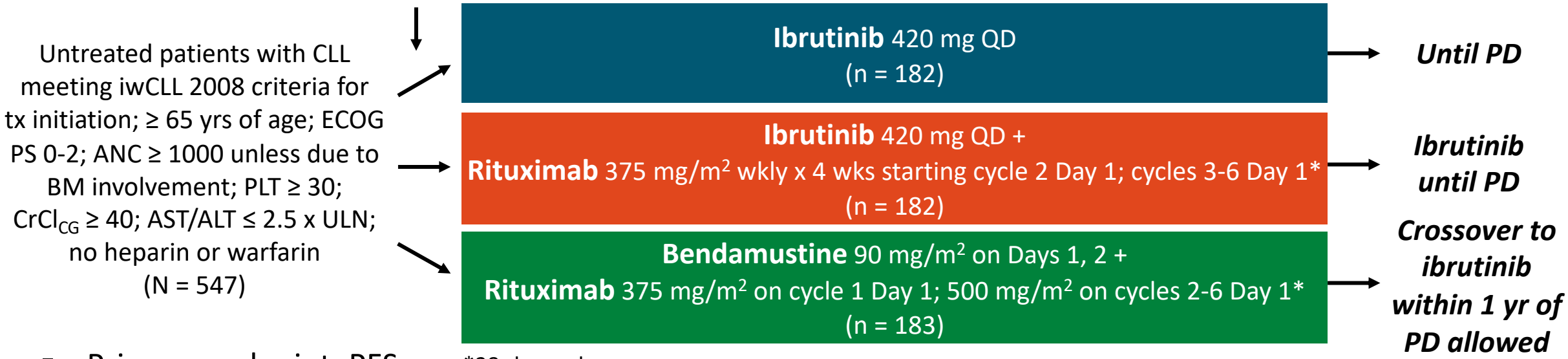


Shanafelt et al *Blood 2022*.

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%)

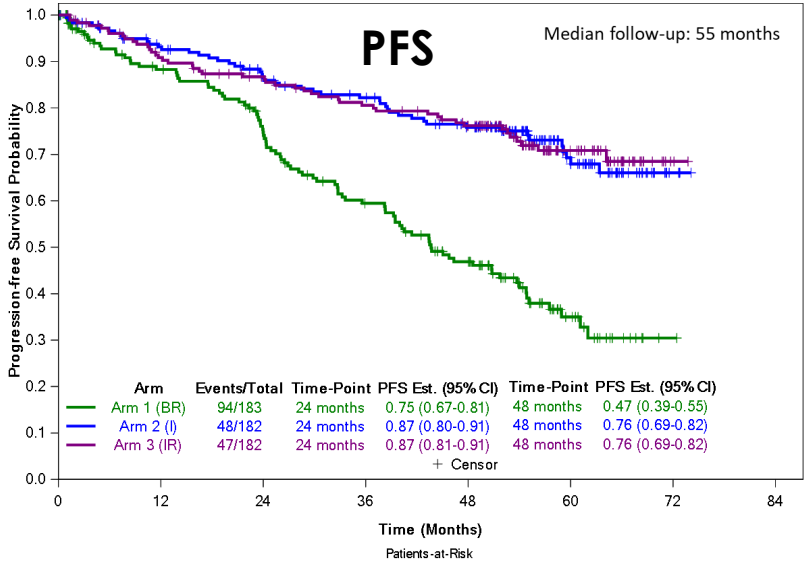


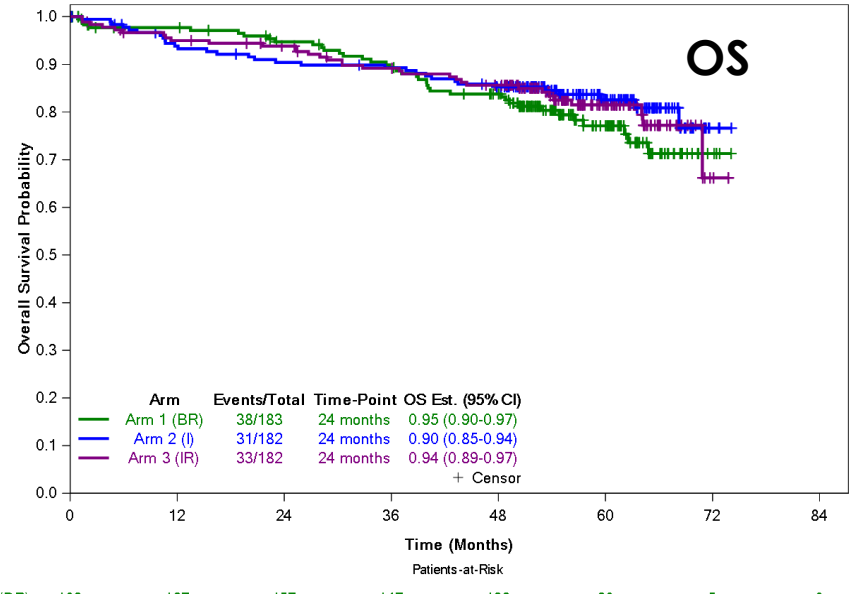
*28-day cycles.

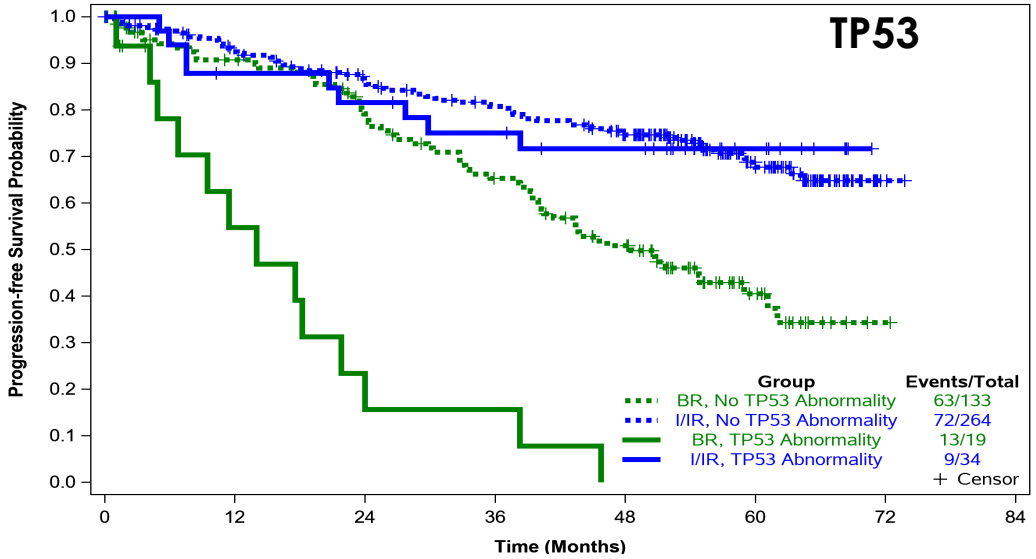
- Primary endpoint: PFS
  - 2 primary comparisons of ibrutinib vs BR and ibrutinib + R vs BR with 90% power to detect HR of 0.586 (estimated 2-yr PFS rates: ibrutinib, 75%; BR, 61%) and overall 1-sided α = 0.025 for each comparison
  - If both primary comparisons significant, third planned comparison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

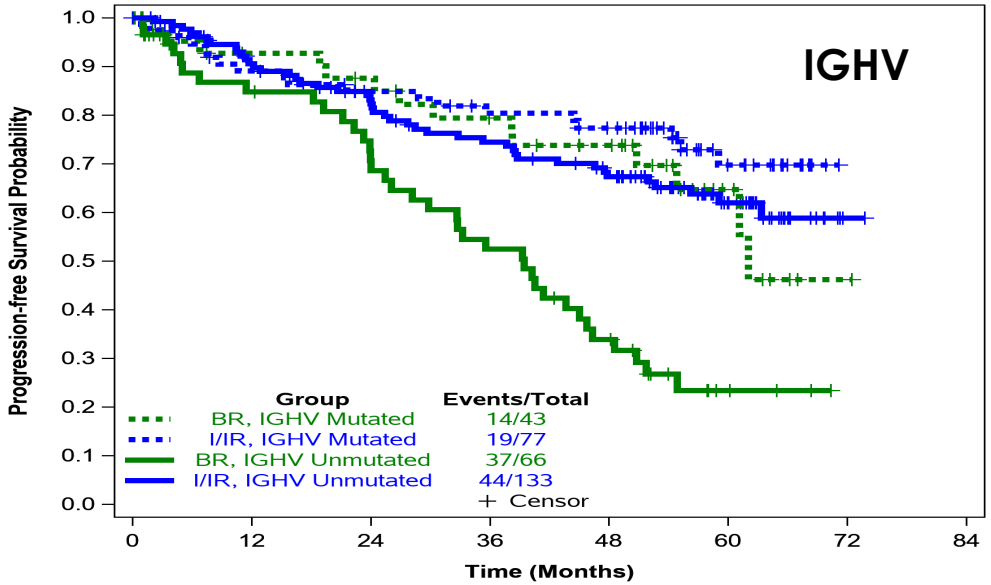
Woyach. ASH 2018. Abstr 6. Woyach. NEJM. 2018;379:2517. NCT01886872.

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





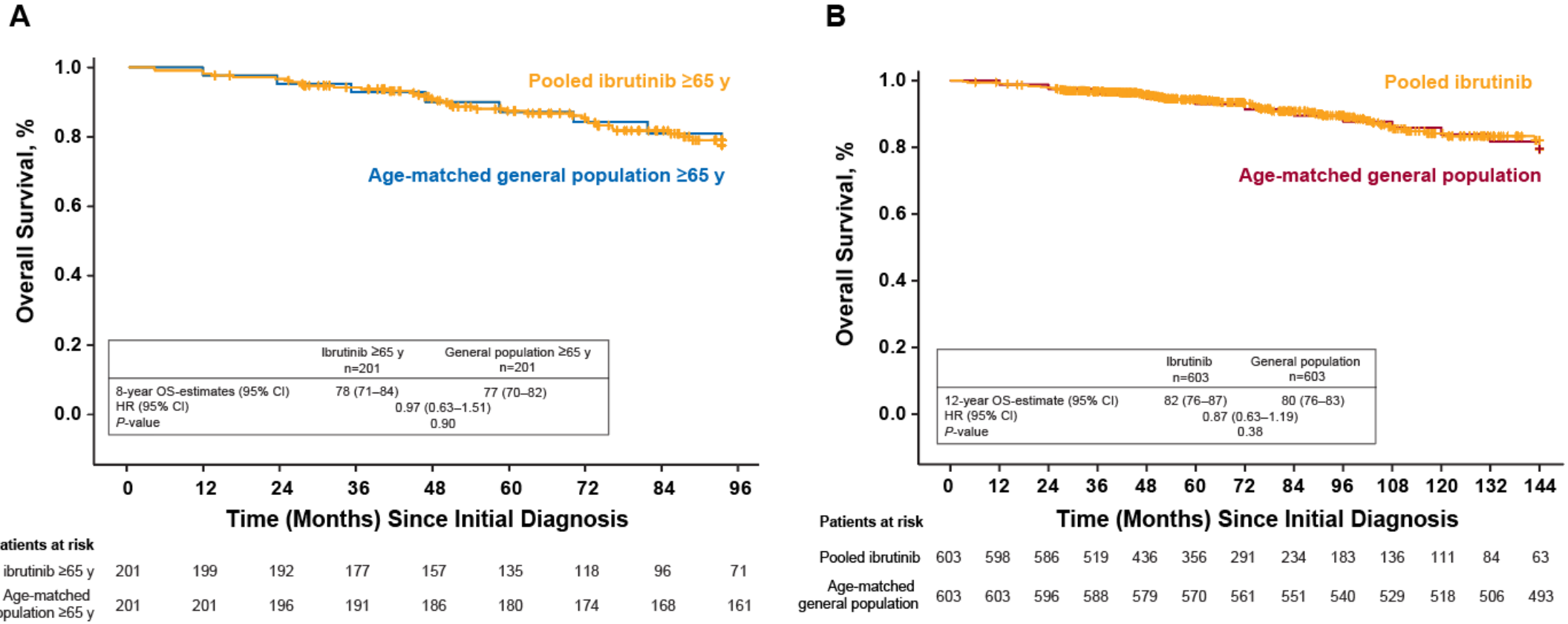




Woyach. ASH 2021.

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



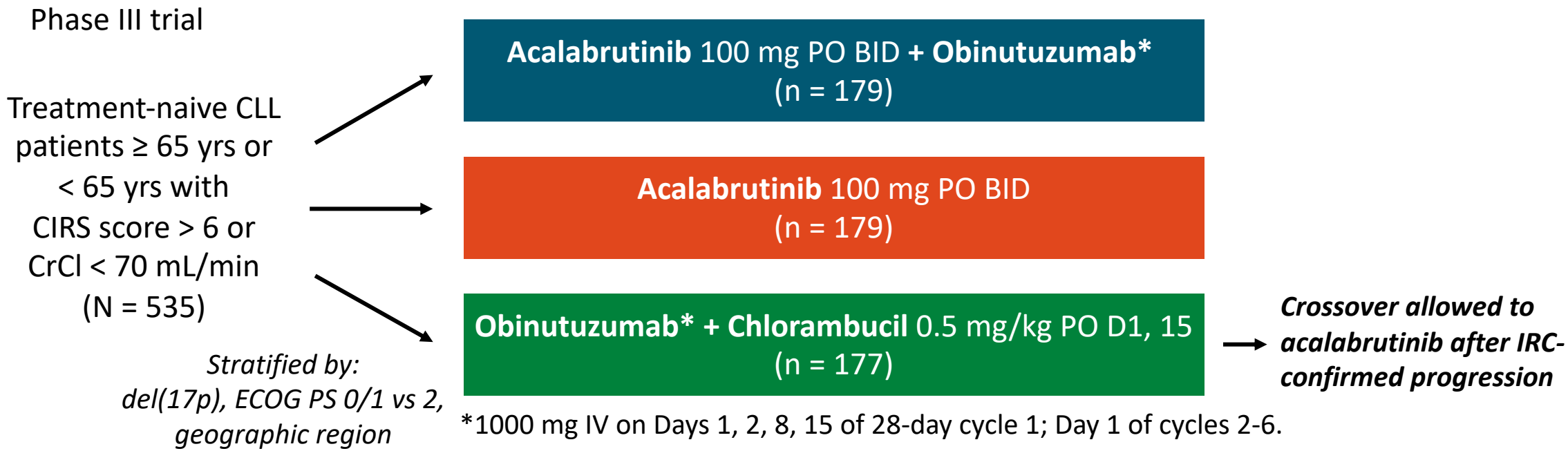
[a]*Data after 96 months is not represented in the KM curve;* [b]*Data after 144 months is not represented in the KM curve*

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

2nd generation BTKi

Acalabrutinib

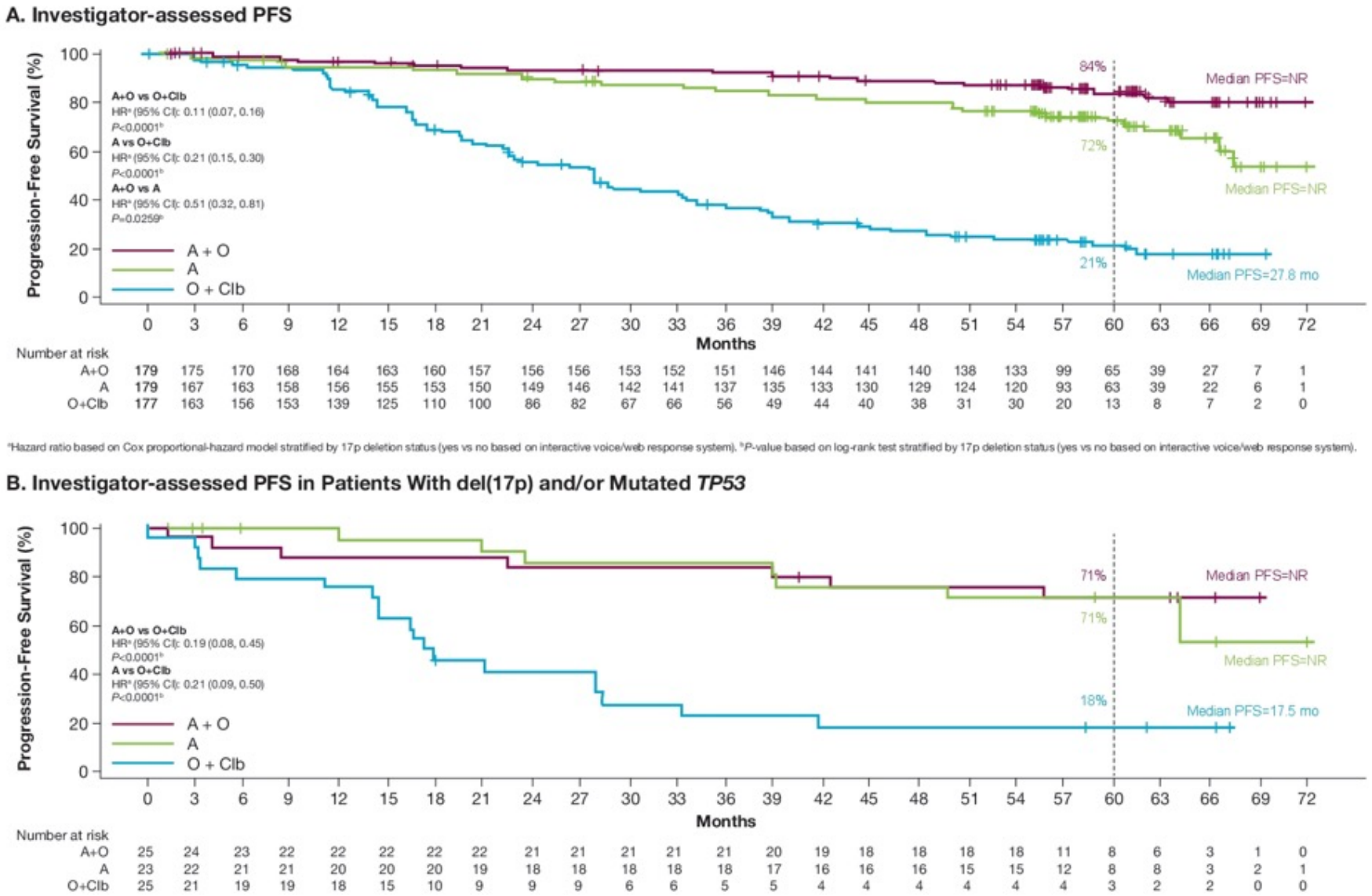
ELEVATE-TN: Acalabrutinib ± Obinutuzumab vs Chlorambucil + Obinutuzumab in Previously Untreated CLL



- 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*

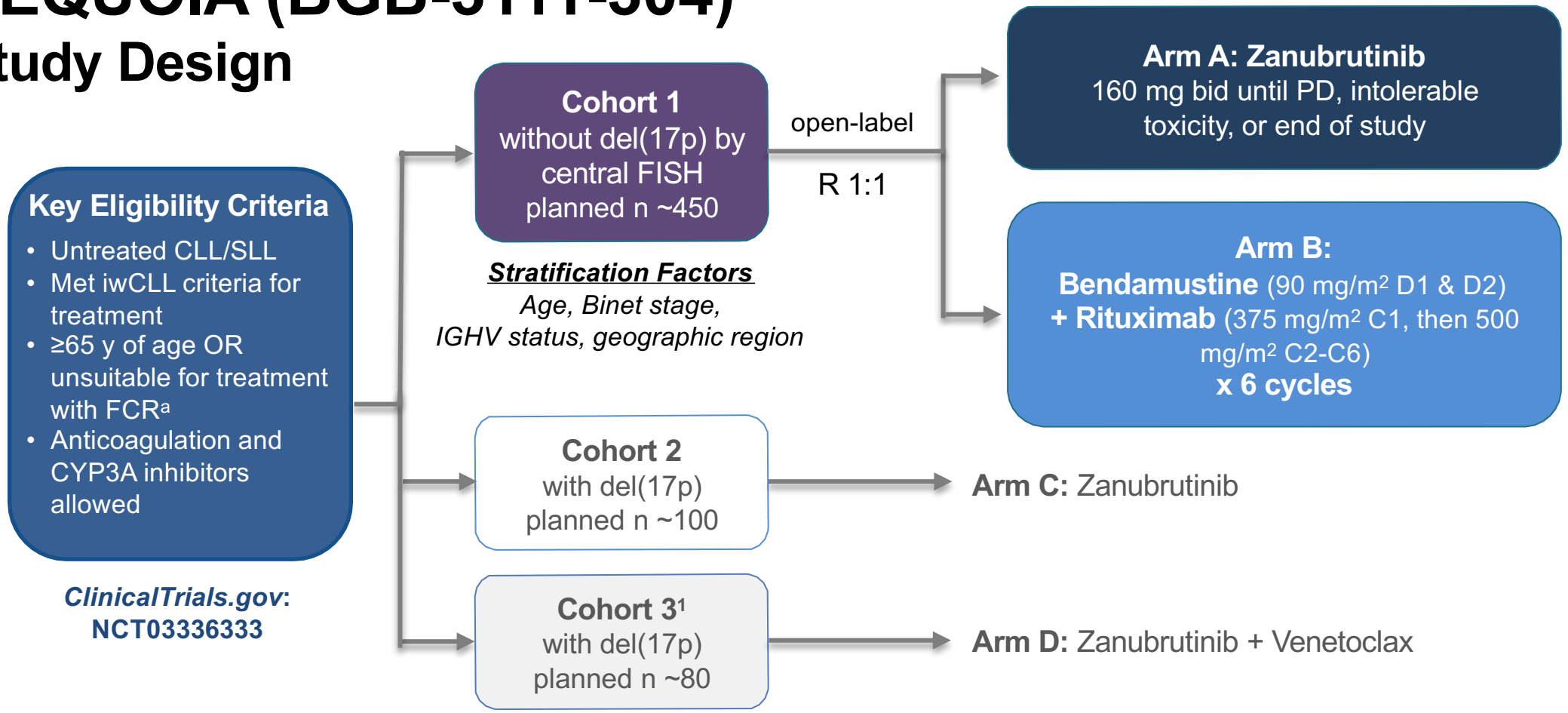


Sharman et al ASCO 2022

2nd generation BTKi

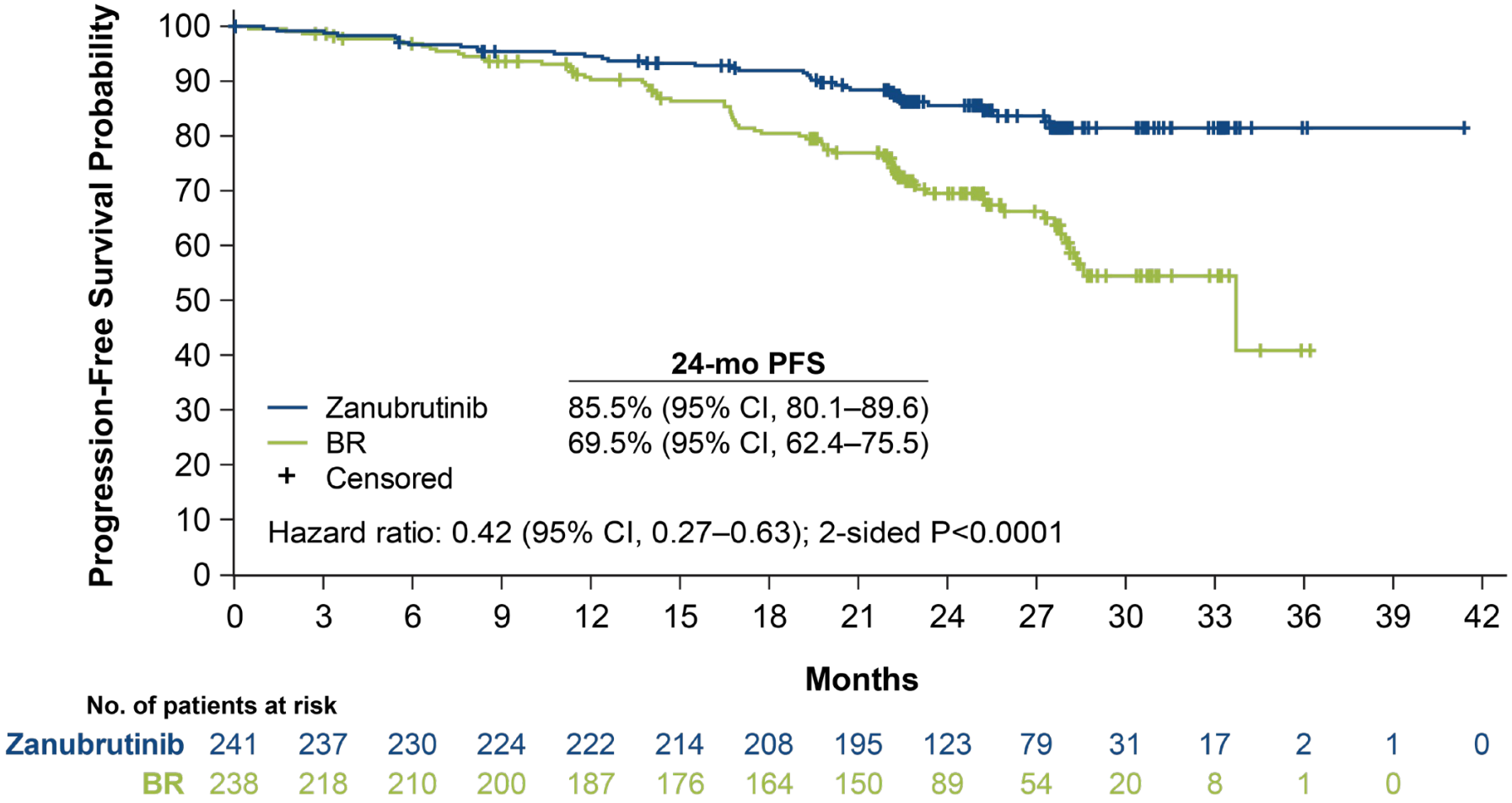
Zanubrutinib

SEQUOIA (BGB-3111-304)
Study Design



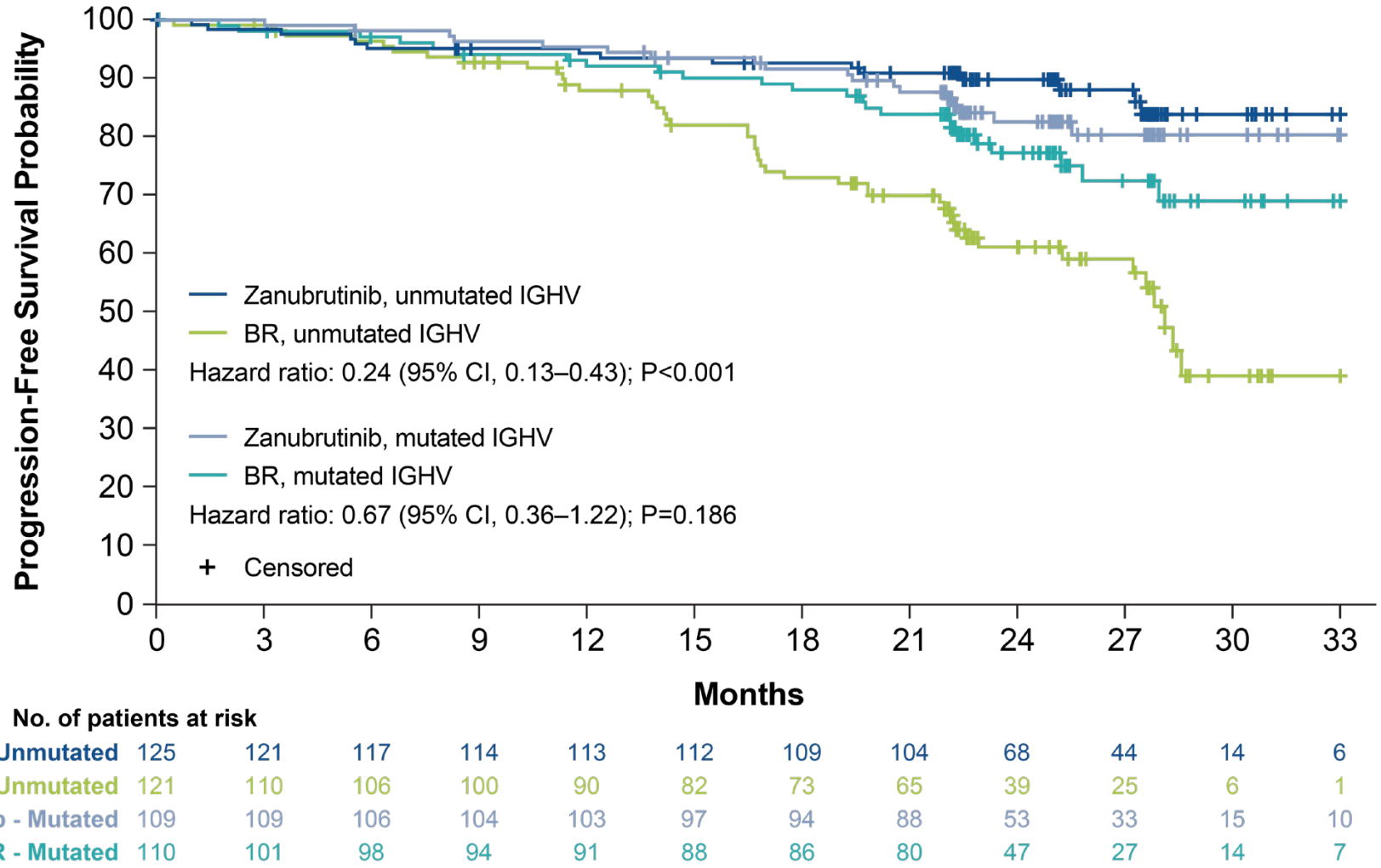
Tan, et al. ASH 2021

SEQUOIA Cohort 1:PFS per IRC Assessment



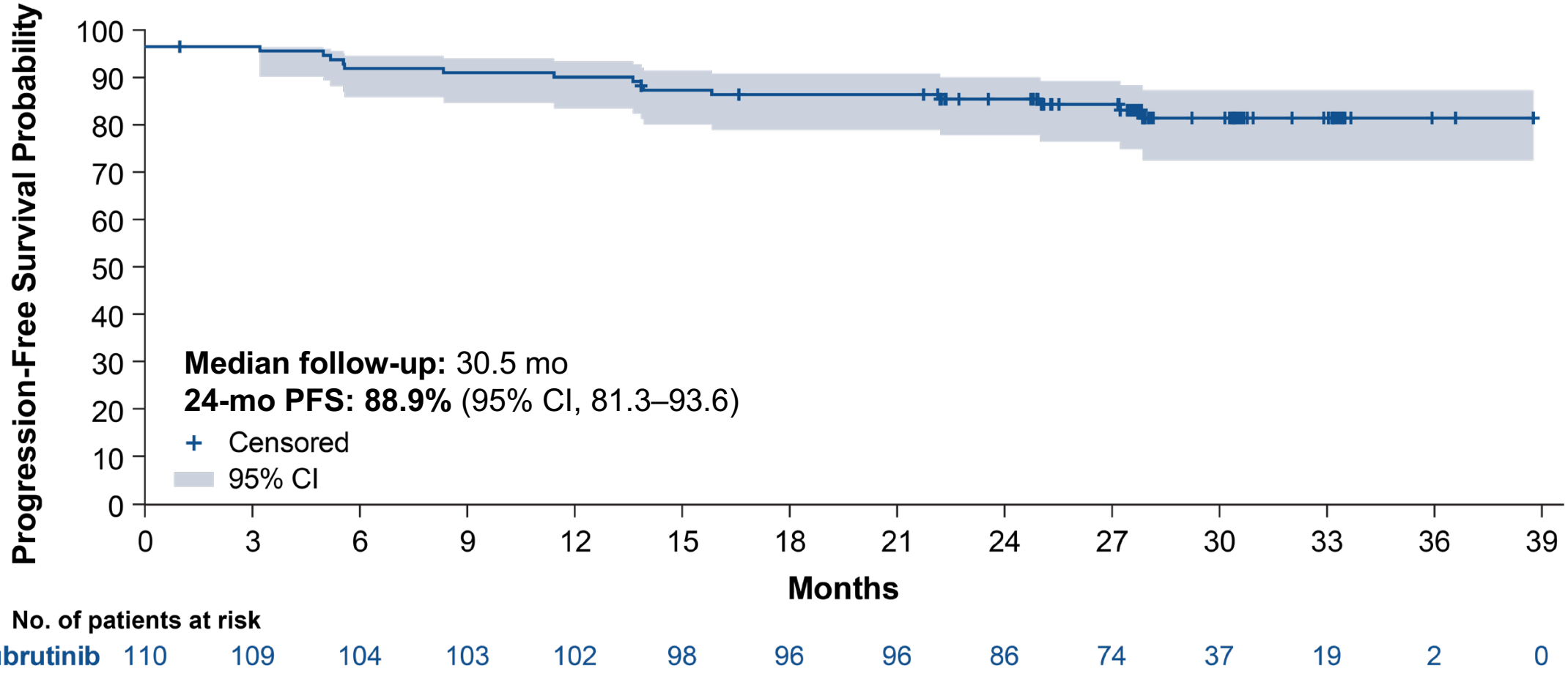
Tan, et al. ASH 2021

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)



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

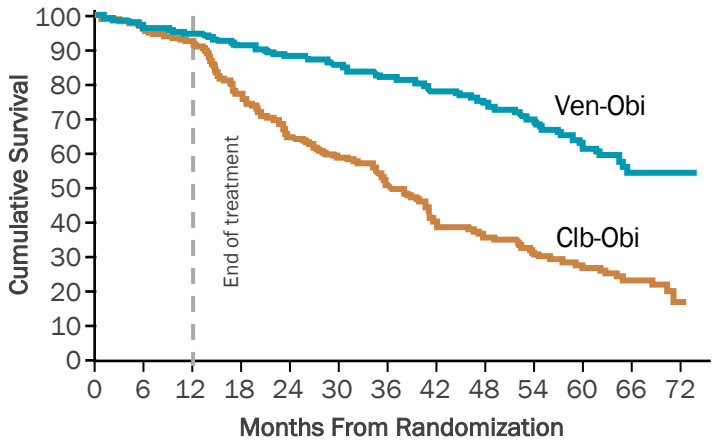
- Primary endpoint: investigator-assessed PFS
- Secondary endpoints: IRC-assessed PFS, ORR, MRD negativity, OS, safety

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

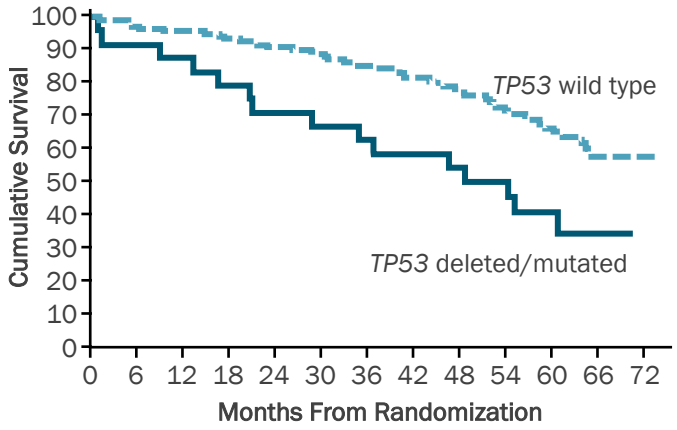
CLL14: Phase 3 Study of Venetoclax-Obinutuzumab vs Chlorambucil-Obinutuzumab in Unfit Patients

5-Year Progression-Free and Overall Survival

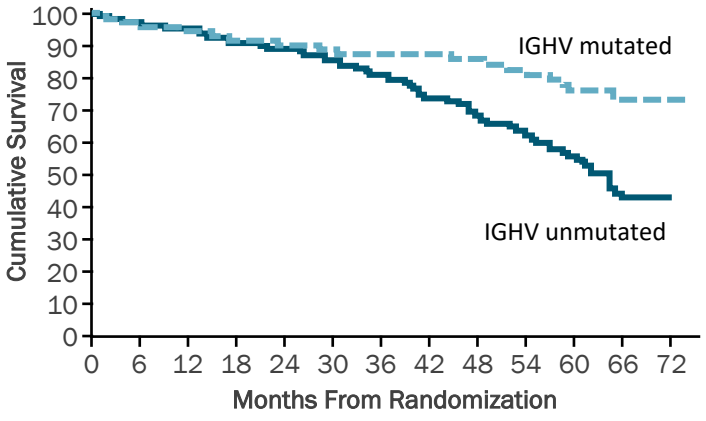
PFS Overall



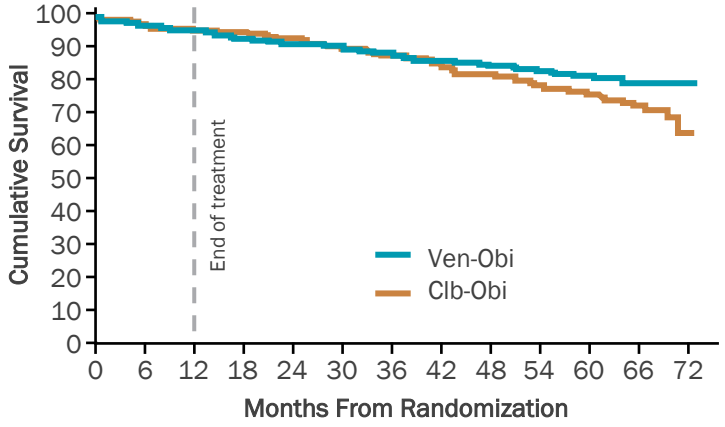
PFS With Ven-Obi by *TP53* Status



PFS With Ven-Obi by IGHV Status



Overall Survival



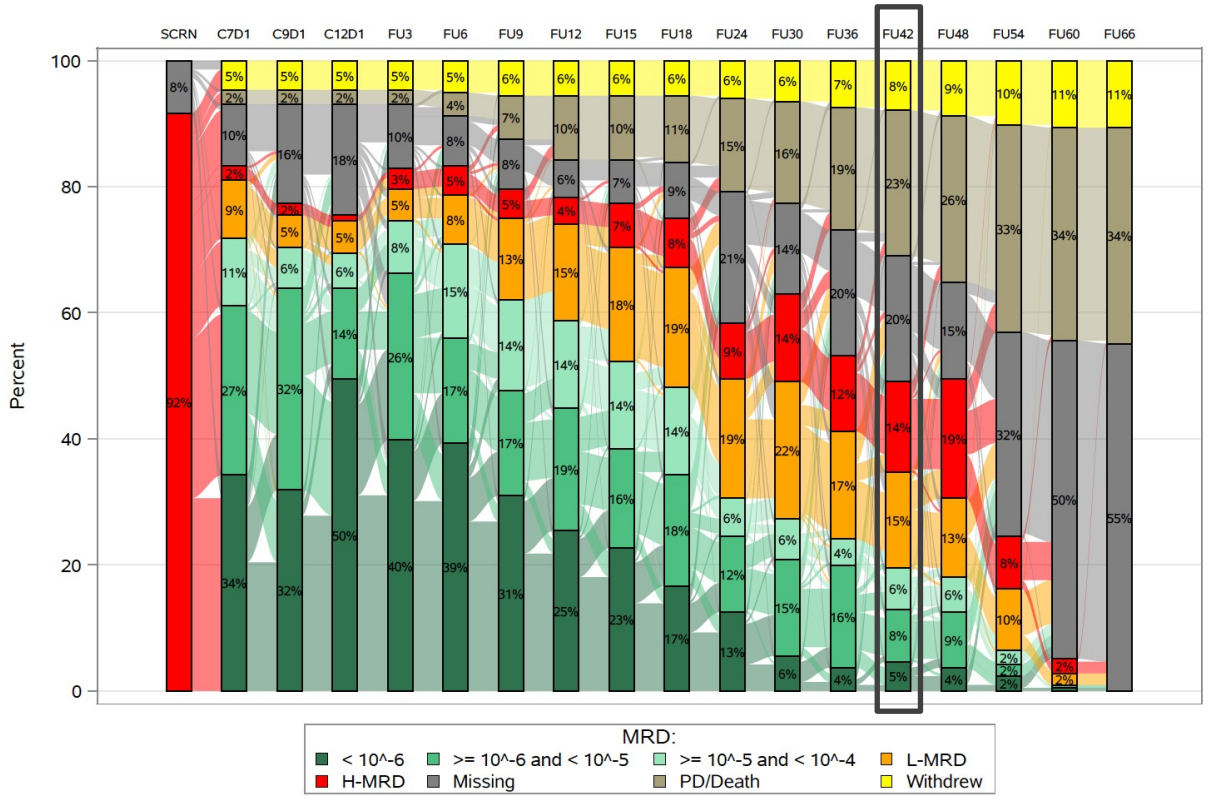
PFS by Subgroup		Ven-Obi (n=216)	Clb-Obi (n=216)
All patients	Median, months	NR	36.4
	5-year rate, %	62.6	27.0
	HR (95% CI); *P* value	0.35 (0.26-0.46); <0.0001	
Median PFS, months			
TP53 del/mut	No	NR (n=184)	38.9 (n=184)
	Yes	49.0 (n=25)	19.8 (n=24)
IGHV status	Mutated	NR (n=76)	59.9 (n=83)
	Unmutated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

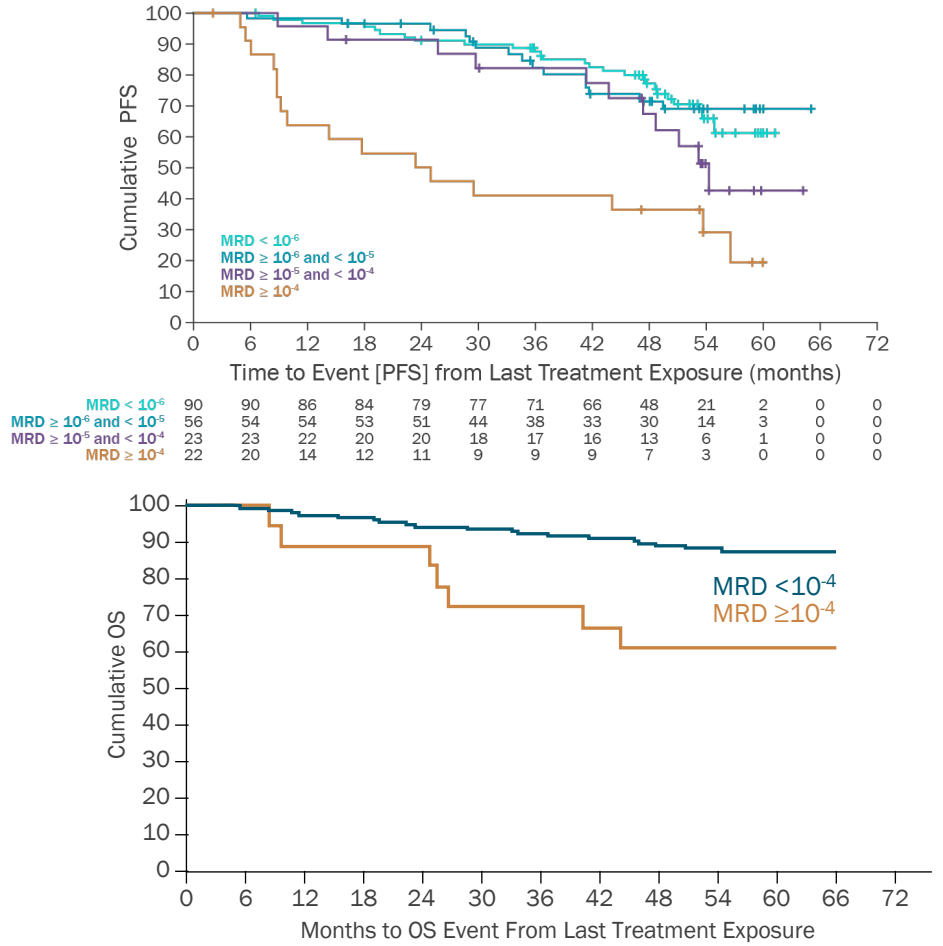
MRD Assessments

Longitudinal MRD Assessment by NGS in PB: Ven-Obi



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

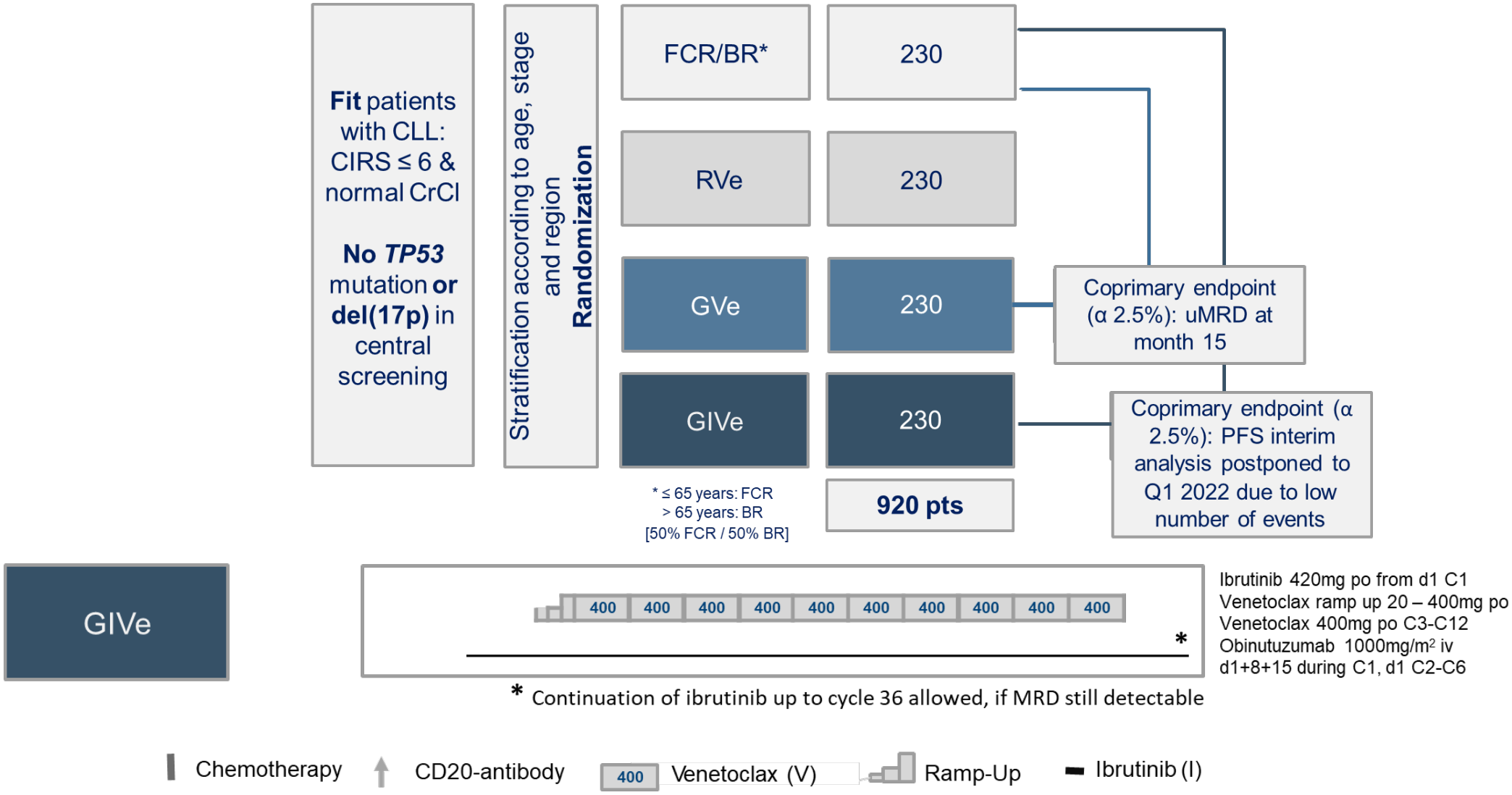
PFS and OS After Ven-Obi According to MRD Status



End of treatment MRD status in peripheral blood by next-generation sequencing.

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

GAIA (CLL13) trial



Treatment exposure

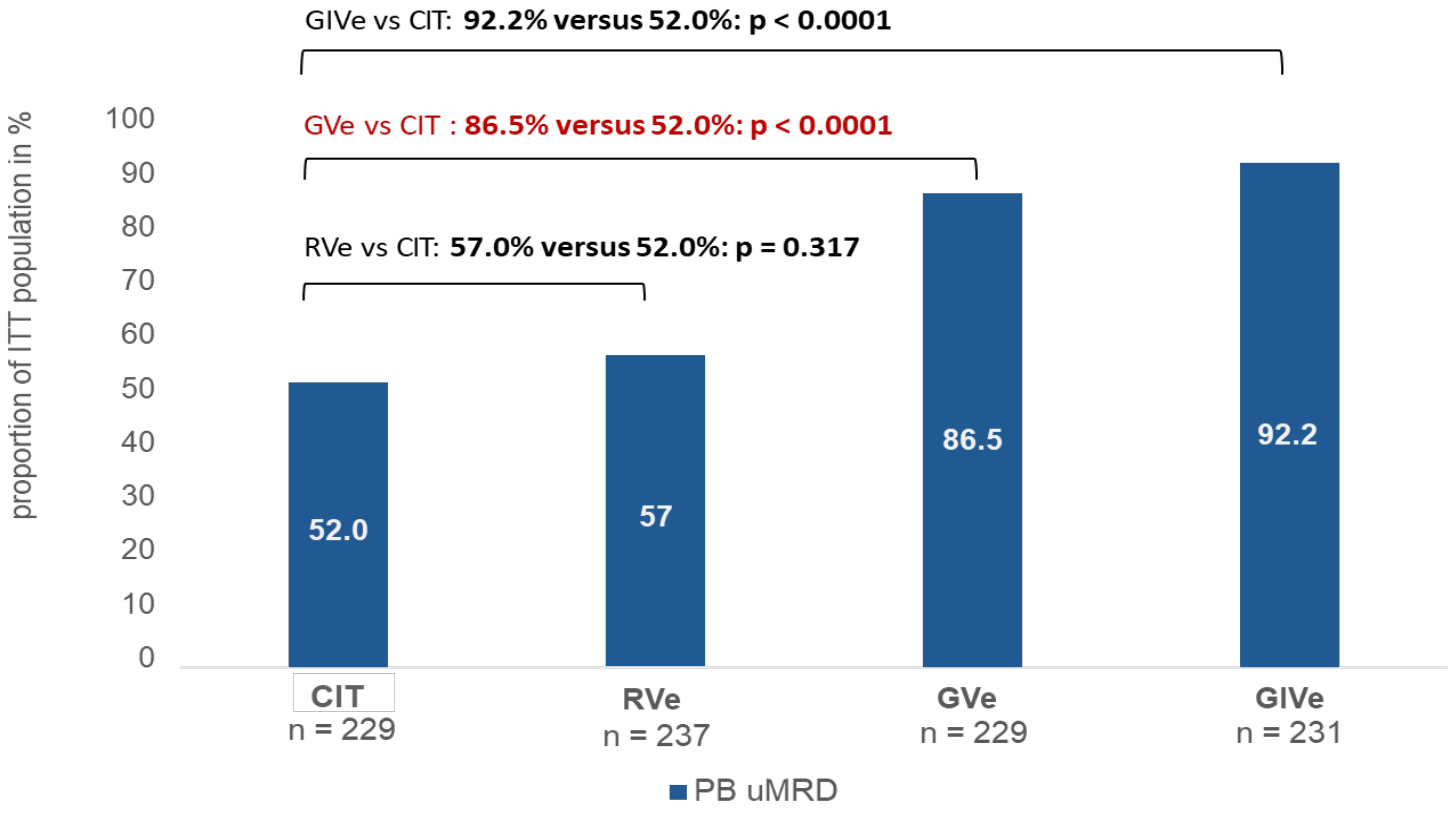
Median FU 27.9 months (range: 0.0 – 49.0)

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



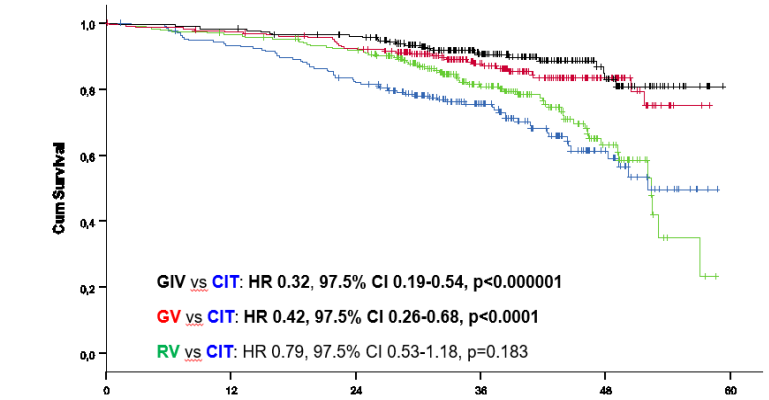
	uMRD%	97.5% CI
GIVe	92.2	87.3 – 95.7
GVe	86.5	80.6 – 91.1
RVe	57.0	49.5 – 64.2
SCIT	52.0	44.4 – 59.5

Eichhorst, et al., ASH 2021

GAIA (CLL13) trial
PFS and PFS by IgHV

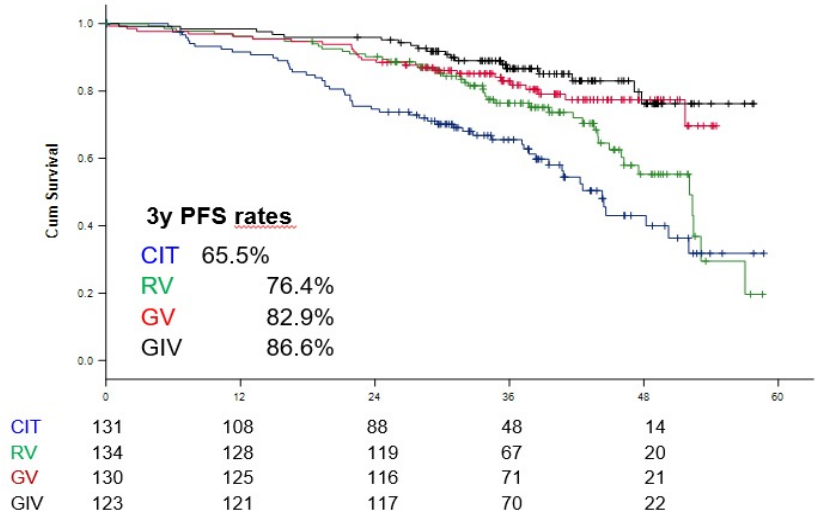
Results of the coprimary endpoint progression-free survival (PFS)

Median FU 38.8 months (range: 0.0 – 59.2)

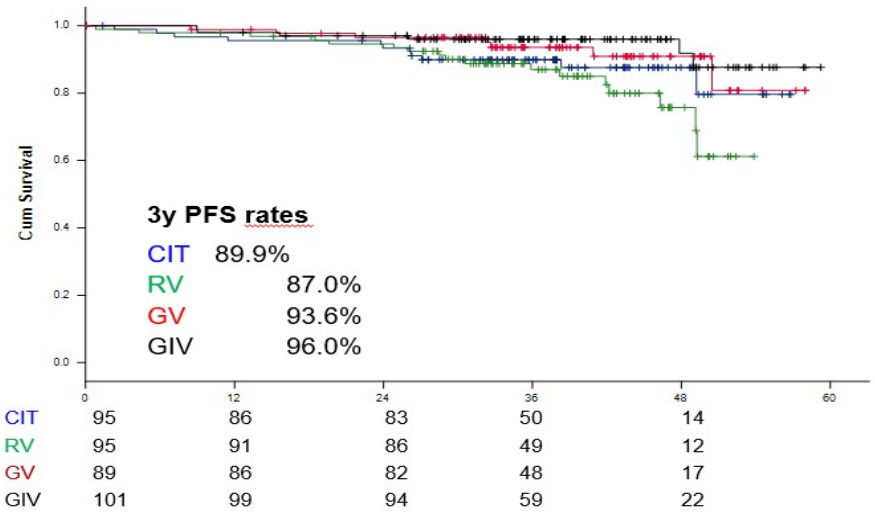


PFS	Median months	3y PFS (%)
CIT	52.0	75.5
RV	52.3	80.8
GV	NR	87.7
GIV	NR	90.5

Unmutated IGHV



Mutated IGHV



Eichhorst, et al., EHa 2022

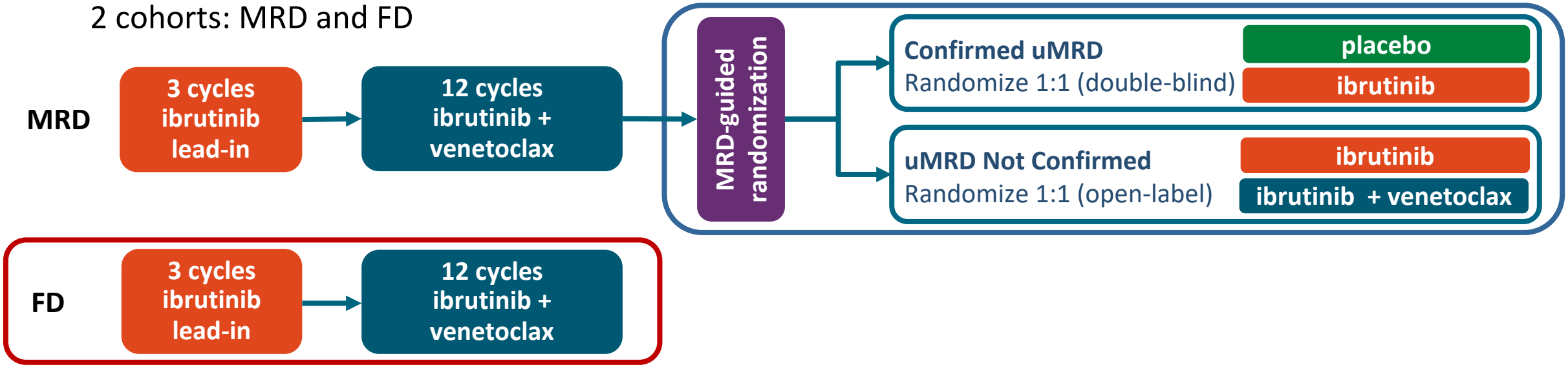
fixed duration novel agent combinations

BTKi + BCL2i

(i.e. Ibrutinib+Venetoclax)

Phase 2 CAPTIVATE Study

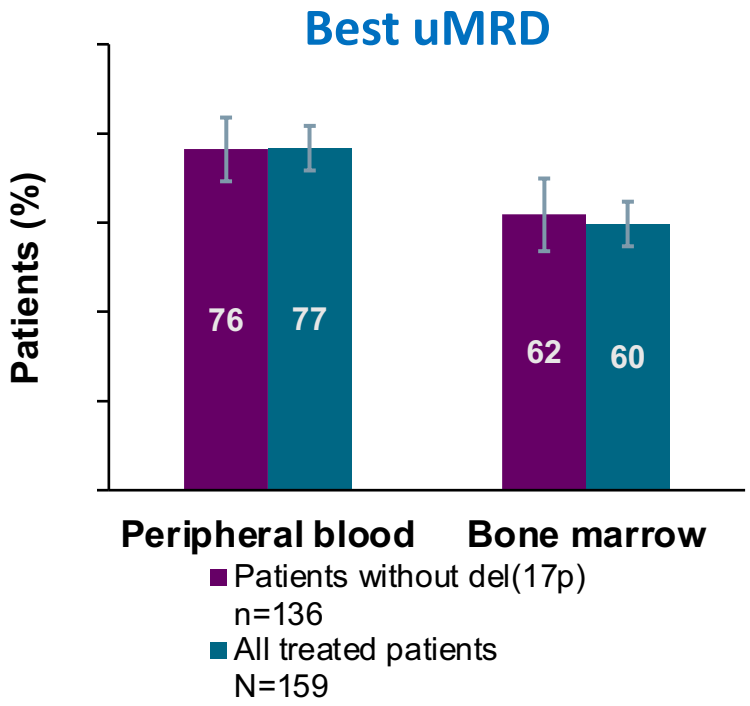
- CAPTIVATE (PCYC-1142) is an international, multicenter phase 2 study evaluating first-line treatment with 3 cycles of ibrutinib followed by 12 cycles of combined ibrutinib + venetoclax that comprises 2 cohorts: MRD and FD



- 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]

Ghia, ASCO 2021. Allen, EHA 2021.

CAPTIVATE Fixed-Dose Cohort: MRD



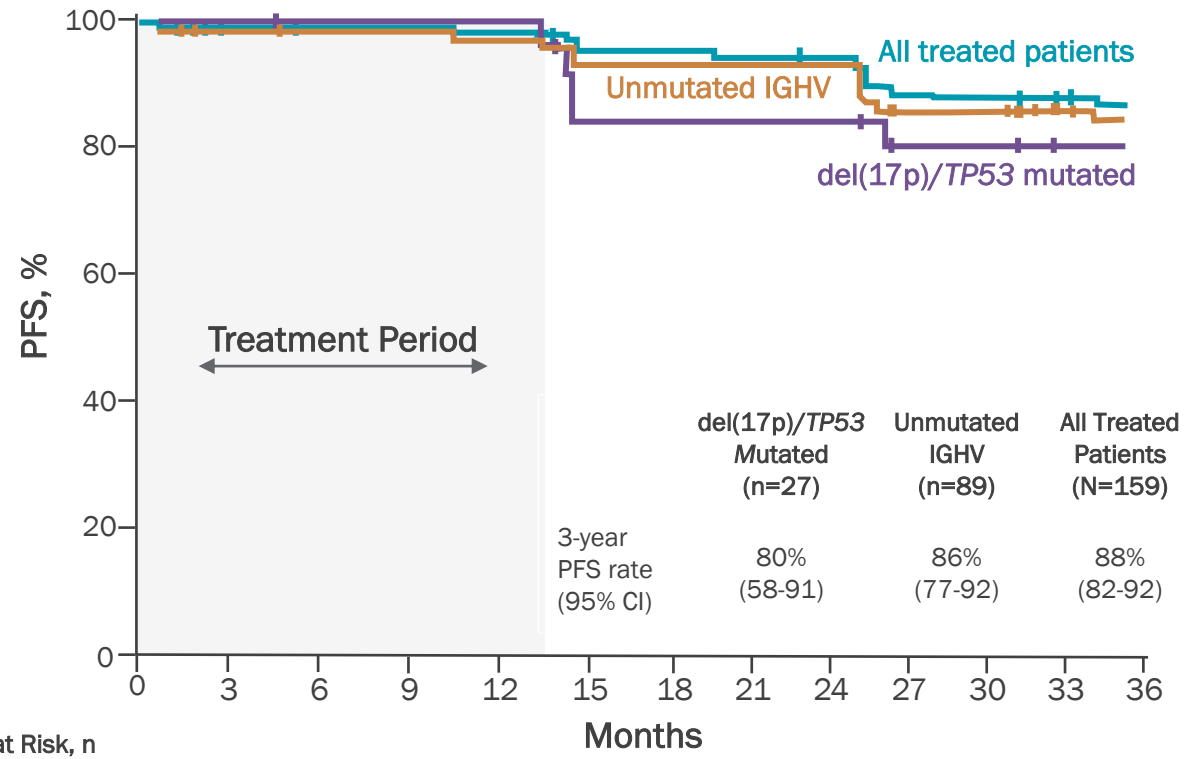
uMRD rate	PB	BM
Bulky Disease		
Yes	77%	63%
No	77%	59%
IGHV status		
uIGHV	84%	64%
mIGHV	67%	53%

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]

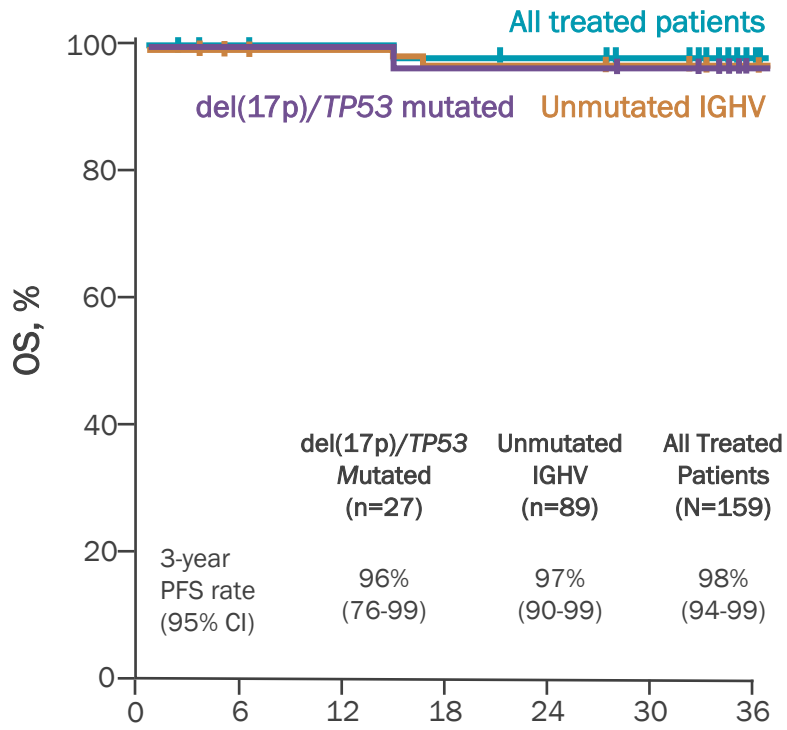
Progression-Free Survival[a]



	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)

Pts at Risk, n													
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]



	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)

Pts at Risk, n							
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

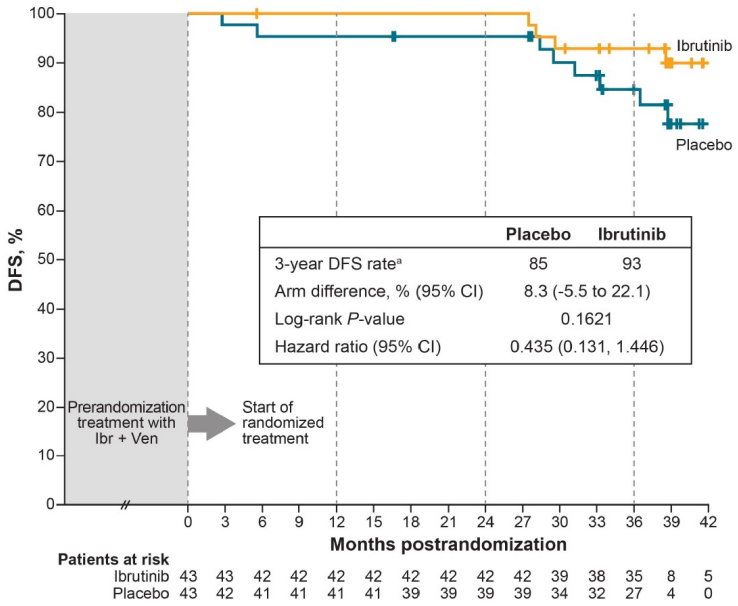
[a] Due to rapid enrollment in the study, the number of patients at risk drops substantially between 36 and 39 months. The Kaplan-Meier curves have therefore been truncated at 38 months due to instability of the curves.

1. Moreno C, et al. EHA 2022. Abstract P669. 2. Weirda WG, et al. ASCO 2022. Abstract 7519.

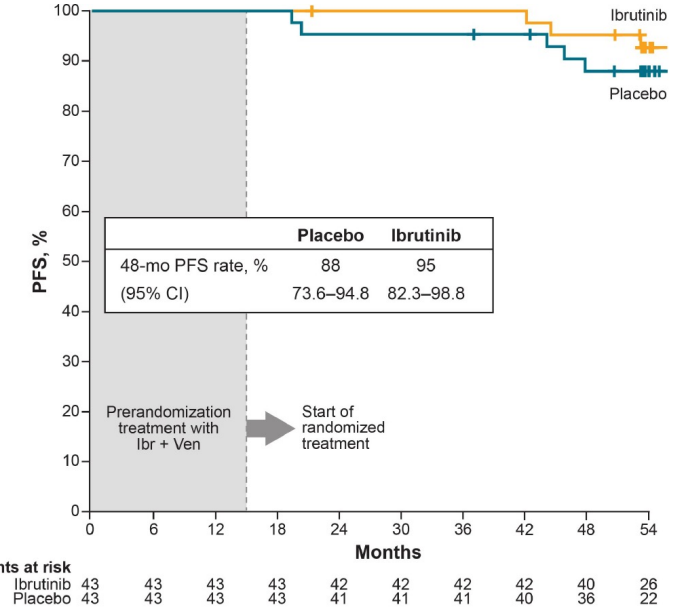
CAPTIVATE MRD Cohort: Phase 2 Study of Ibrutinib-Venetoclax

Disease-Free and Progression-Free Survival

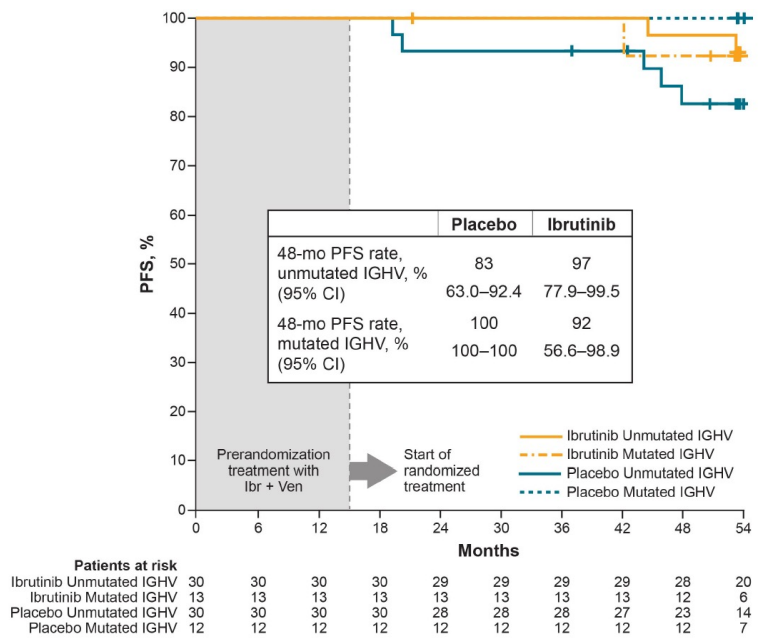
Disease-Free Survival



PFS Overall



PFS by IGHV Status

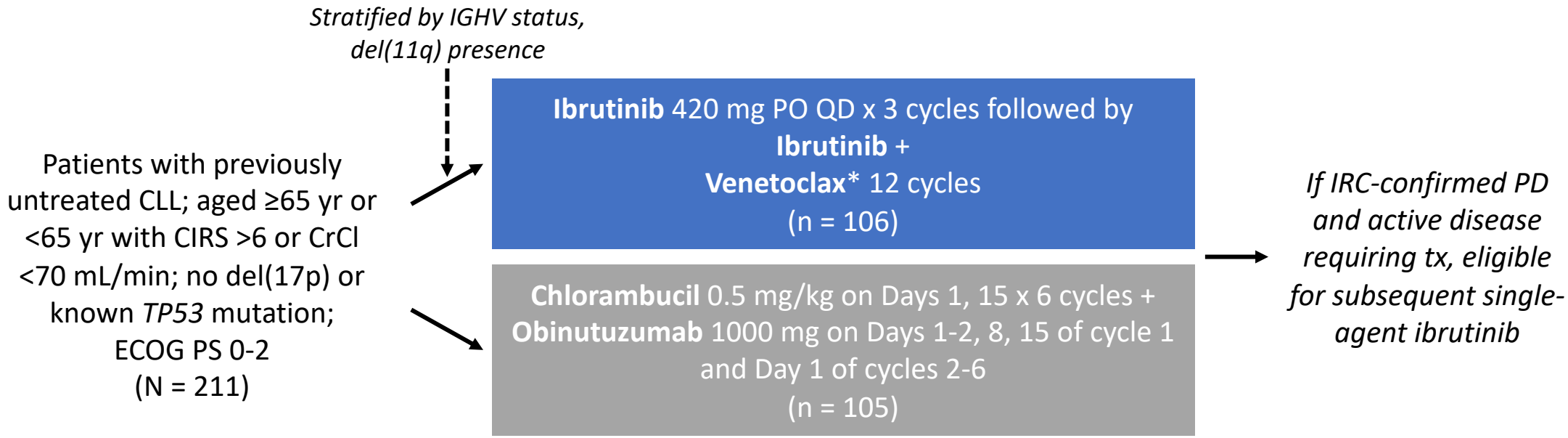


- **Median time on study (patients with confirmed uMRD):** 56 months
- **Median follow-up postrandomization:** 41.2 months in placebo arm; 41.5 months in ibrutinib arm
- **4-year overall survival rate:** 100% in placebo arm; 98% in ibrutinib arm

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

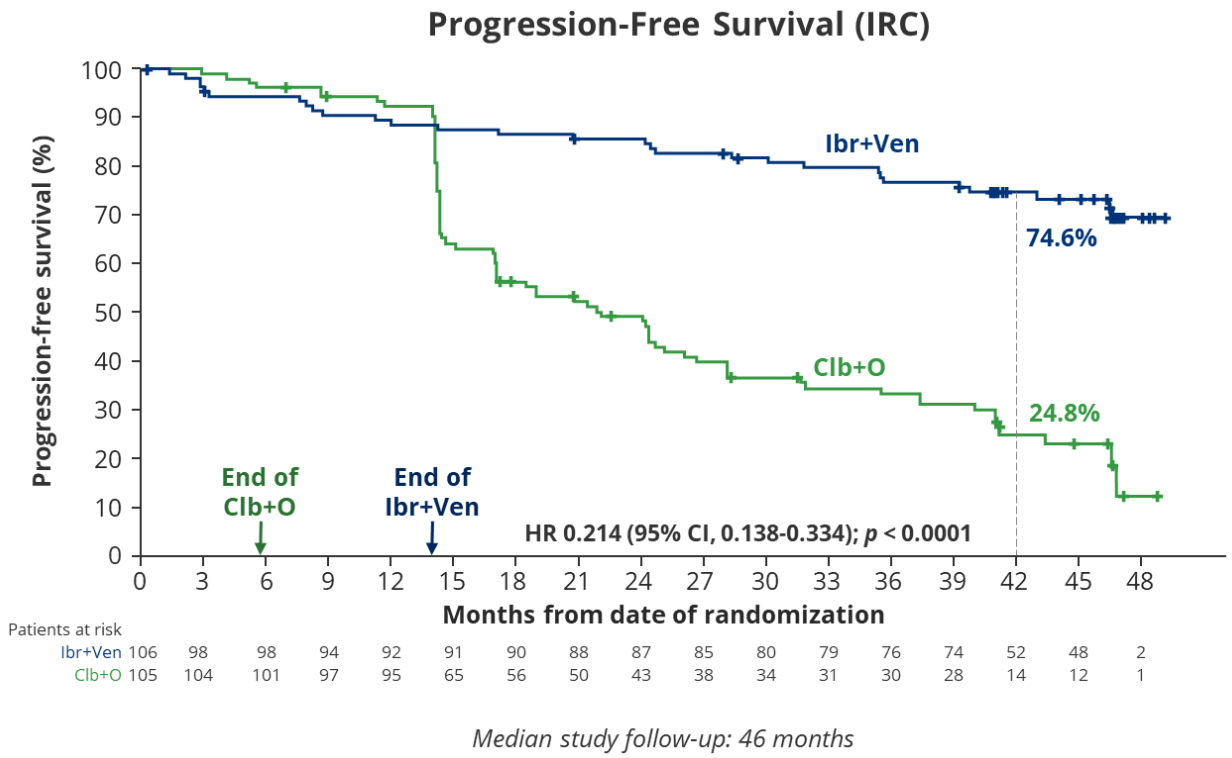


*Ramp-up from 20 to 400 mg over 5 wk starting in cycle 4.

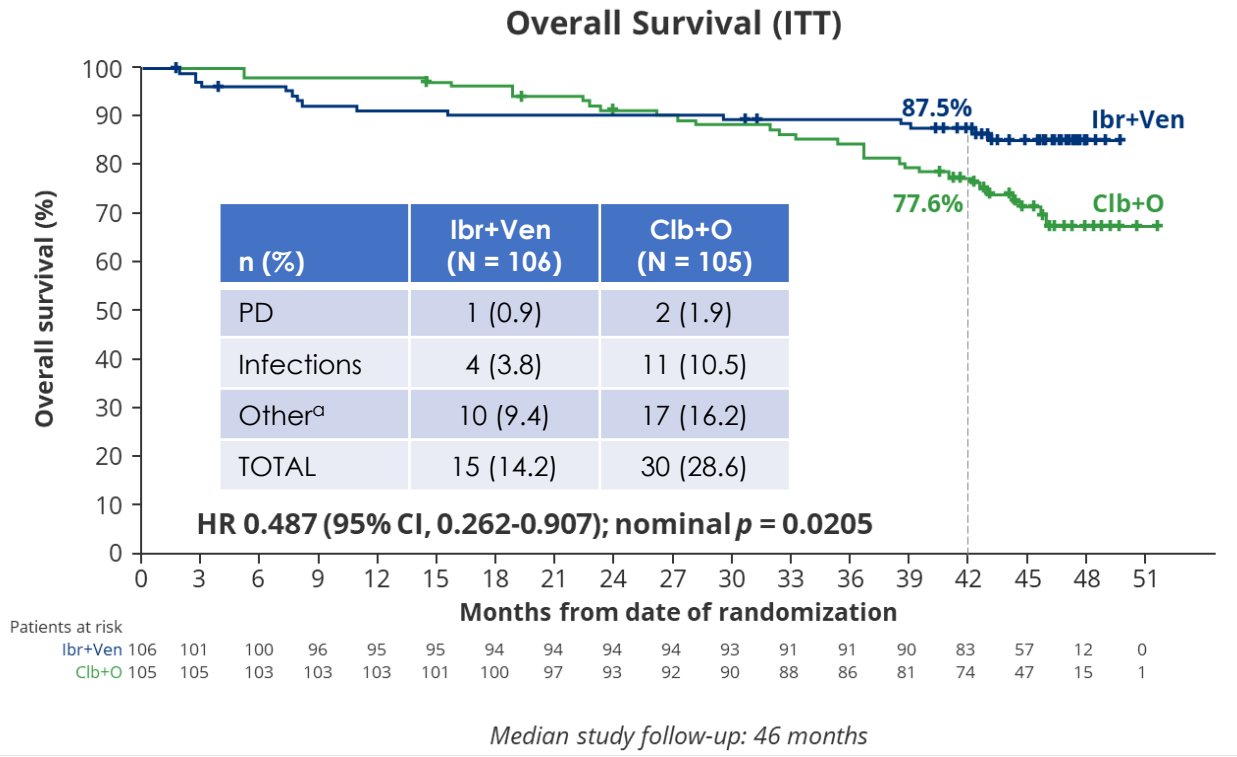
- **Primary endpoint:** PFS per IRC
  - 71 PFS events to detect effect size with HR of 0.5 (80% power, 2-sided α = 0.05)
- **Key secondary endpoints:** uMRD in BM, CR rate per IRC, ORR per IRC, OS, safety
- 46 months median follow up

Nieman et al. ASH 2022

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



Median study follow-up: 46 months



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)

Median study follow-up: 46 months

Progression free survival:

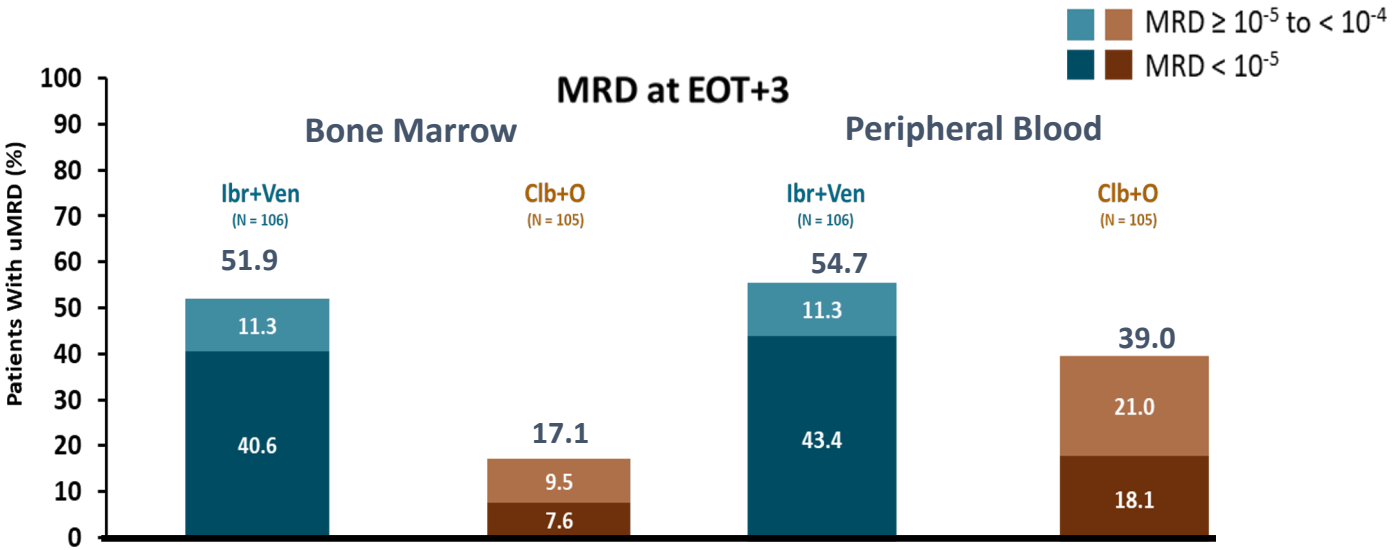
- Ibr + Ven reduced risk of progression or death by 79%
- Estimated 3.5 year PFS:
  74.6% for Ibr+Ven
  24.8% for Clb + O

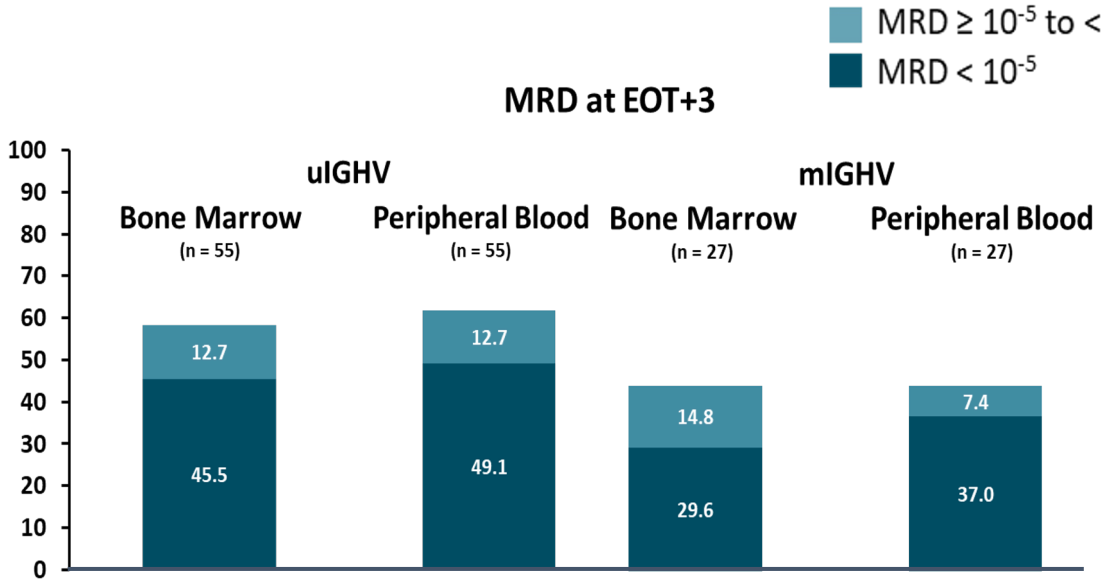
Overall Survival:

- 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

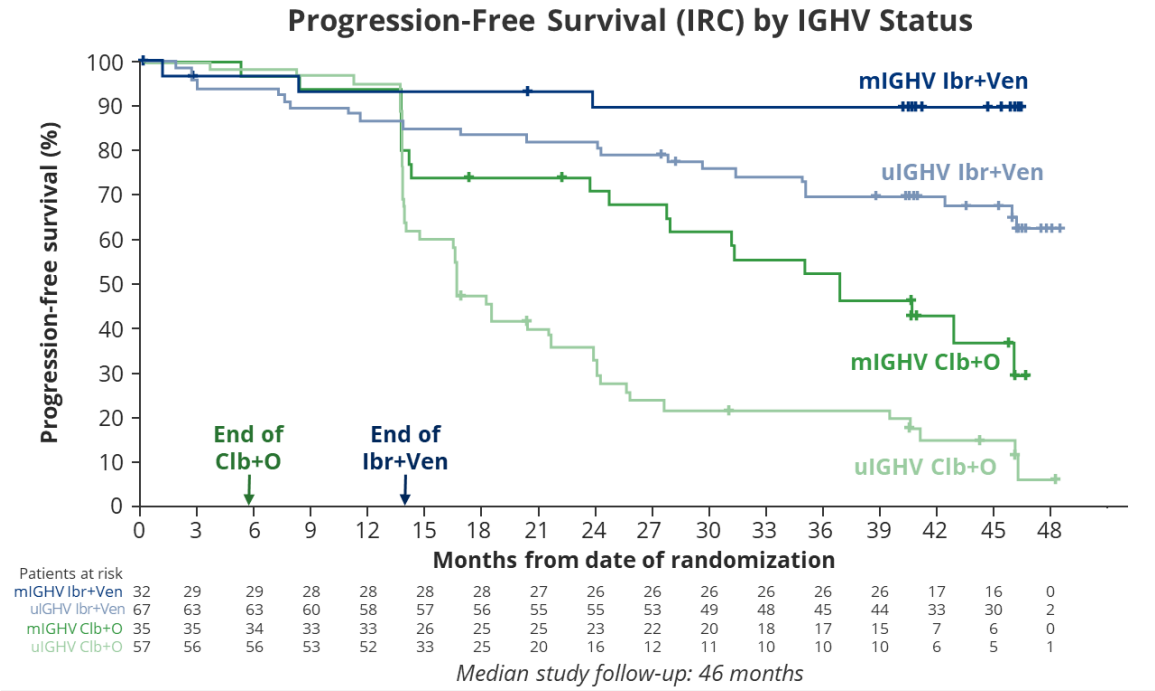


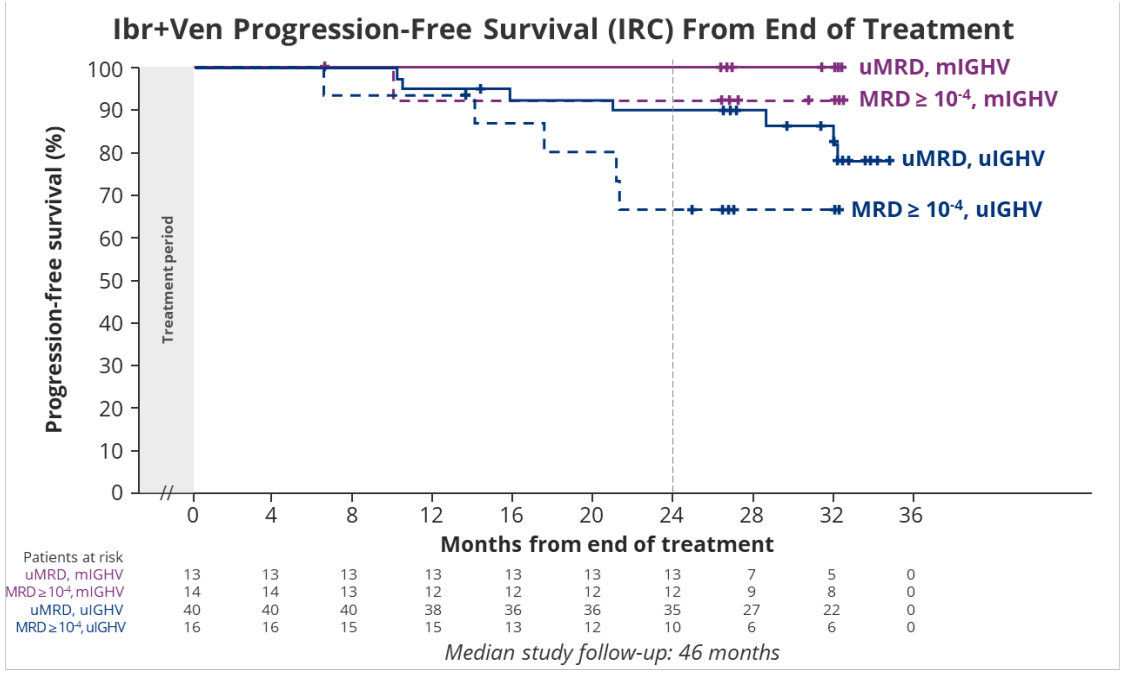


Munir, ASH 2021.

GLOW: PFS by IGHV Mutational Status/MRD

(Elderly/Unfit, 12-mo Fixed Duration)



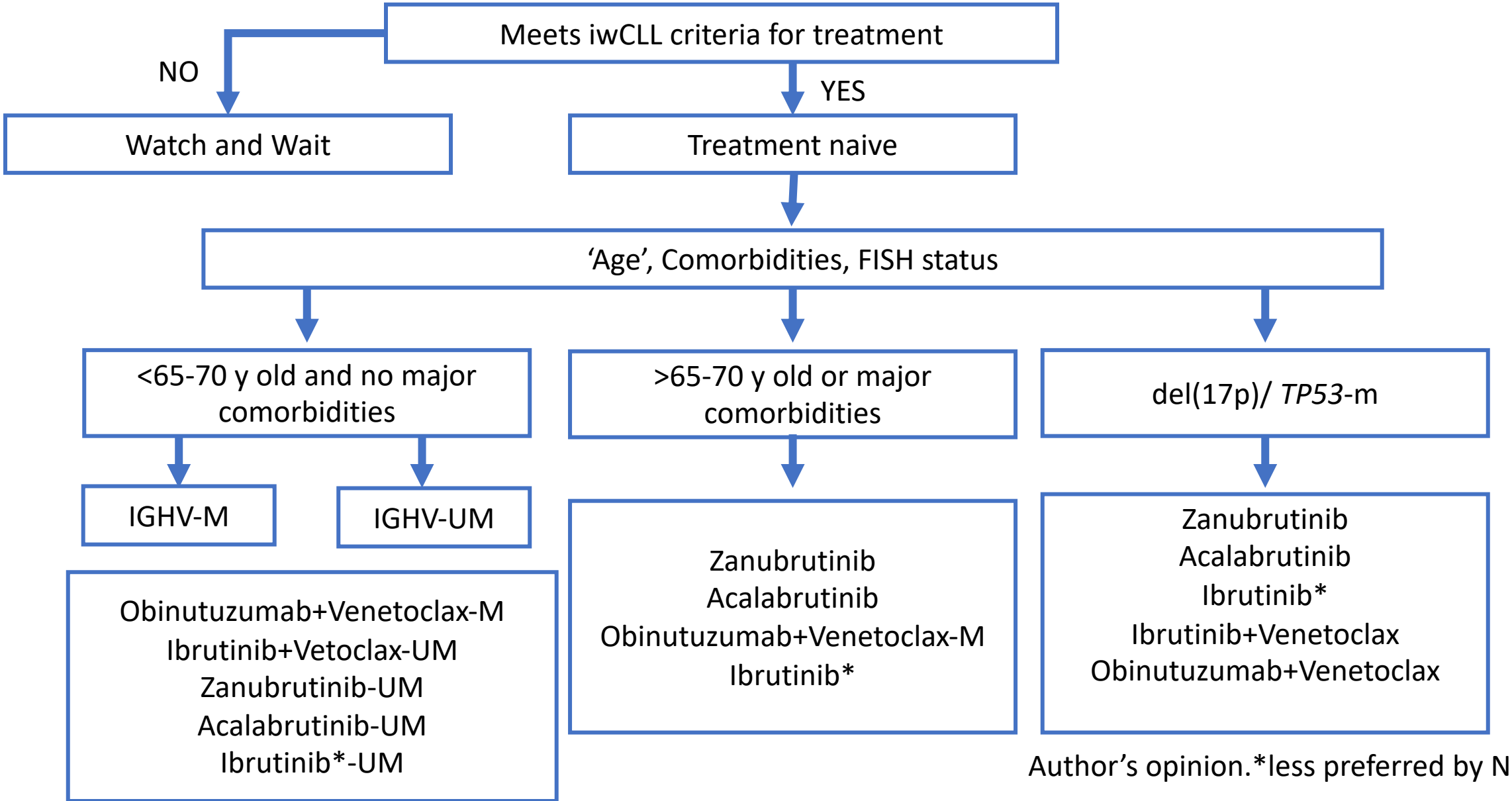


- Impact of IGHV status on PFS was more pronounced with Clb+O
- > 90% of patients in the I+V arm did not require subsequent treatment at 3.5 years:
  - 91.5% for uIGHV
  - 93.5% for mIGHV

- 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

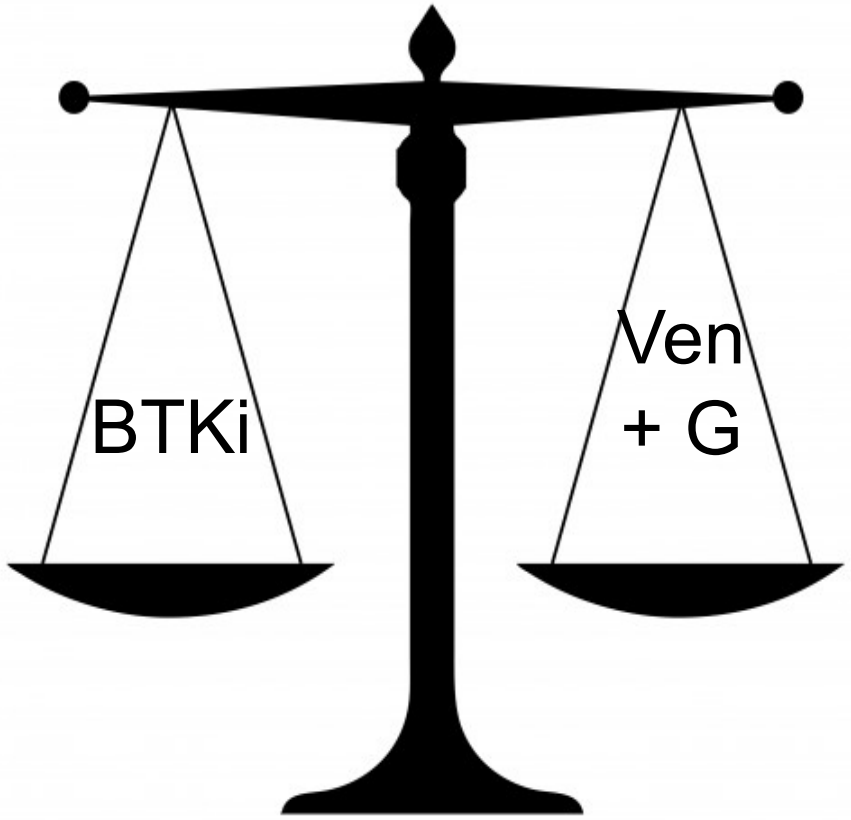
CLL Front Line Treatment Algorithm 2023



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**



Author's opinion.

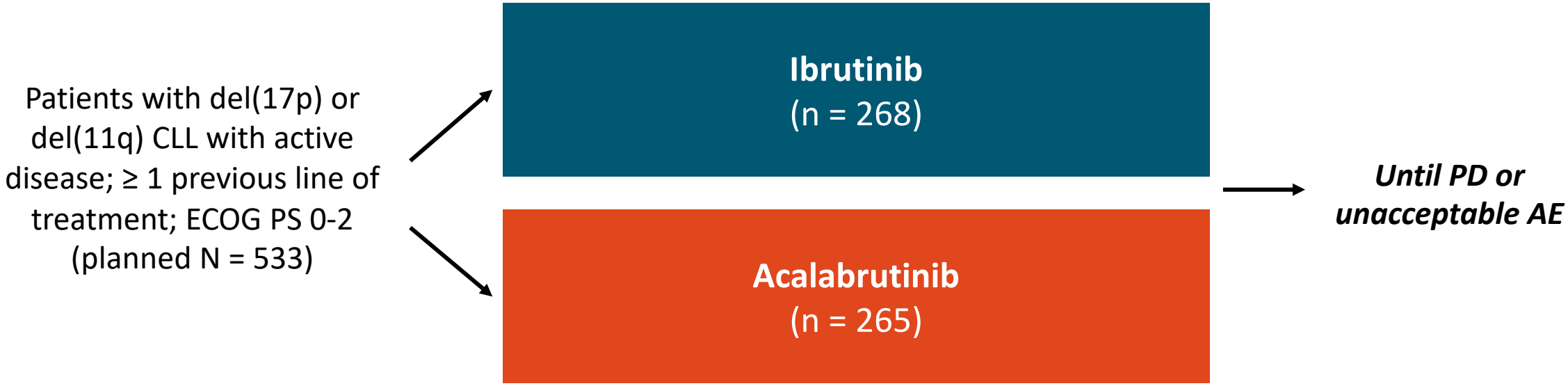
- Potential for 1-year time-limited therapy
- No known cardiac or bleeding risks
- Less concern with long-term adherence
- Potential for cost-savings if 1 year of therapy is durable
- Less financial toxicity
- Low risk dx
- BM based disease: cytopenias.
- Younger age
- Possibility of retreatment

- **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

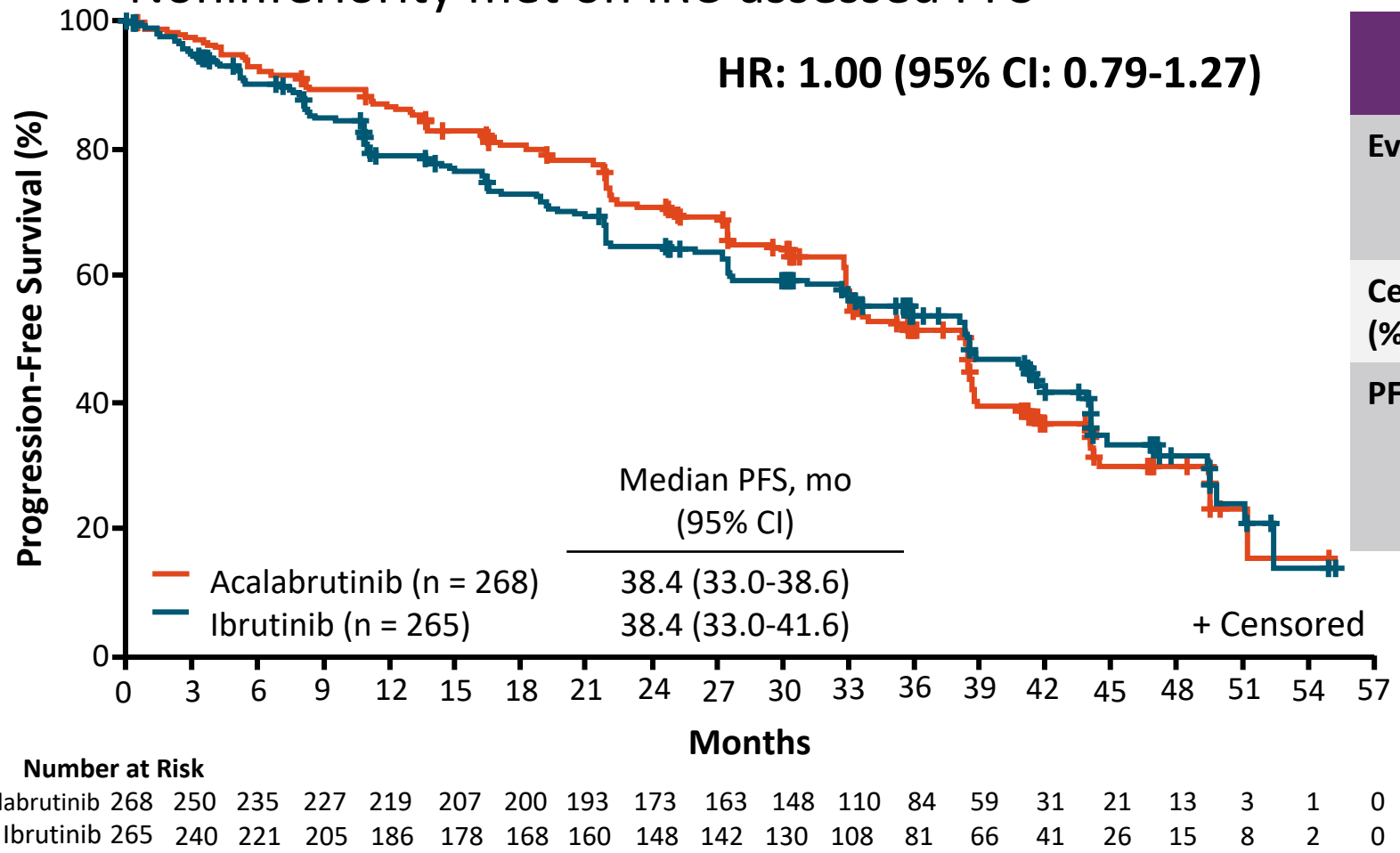


- Primary endpoint: PFS
- Secondary endpoints: OS; incidence of treatment-emergent AEs, atrial fibrillation; Richter's transformation; grade ≥3 infections
- FPI October 2015 – LPI November 2017 (25 mo)
- Final analysis: 279 IRC PFS events, data cutoff 9/2020

Byrd. ASCO 2021.

ELEVATE-RR: Noninferiority Met on IRC-Assessed PFS

- Noninferiority met on IRC-assessed PFS



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

Byrd. ASCO 2021.

ALPINE Study Design

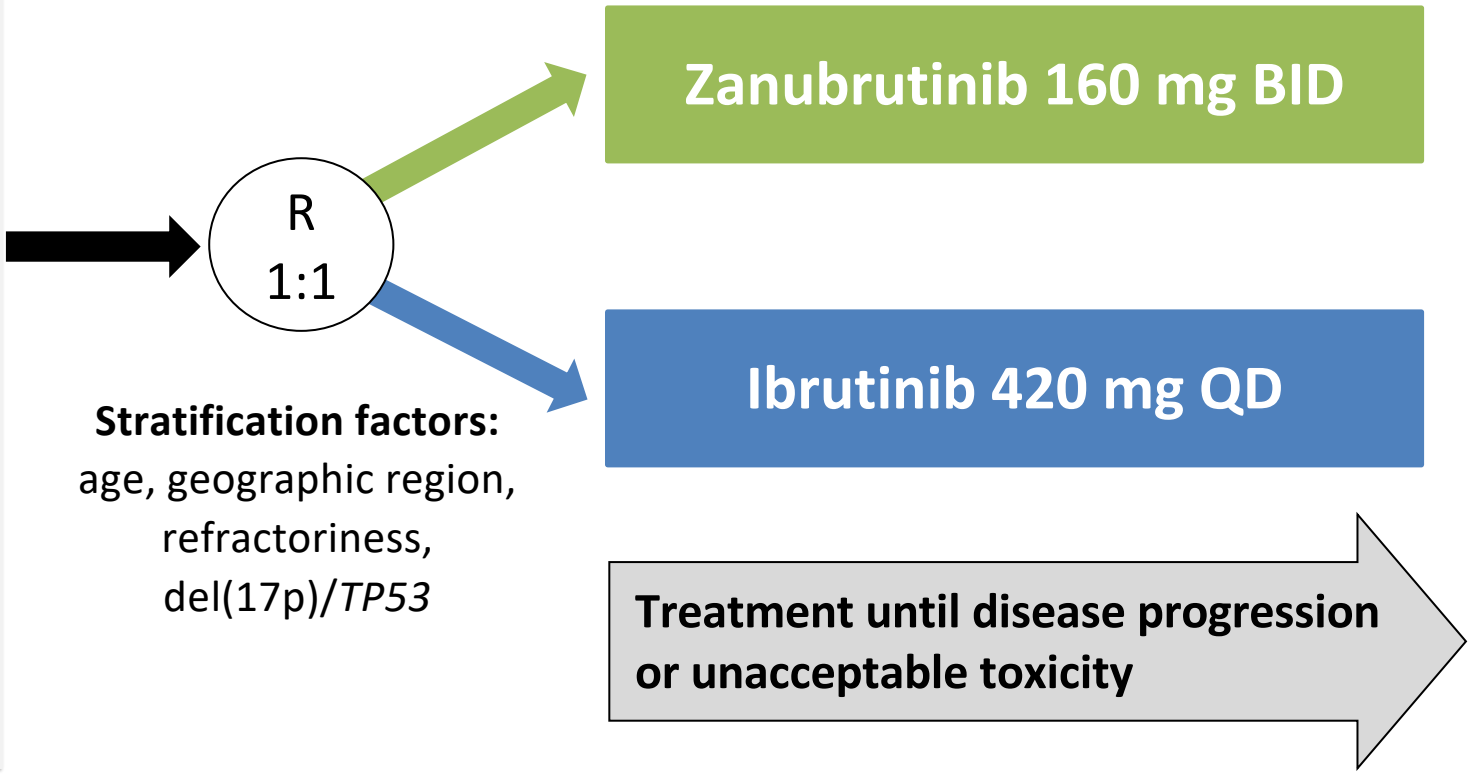
R/R CLL/SLL with ≥ 1 prior treatment
(Planned N=600, Actual N=652)

Key Inclusion Criteria

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

Key Exclusion Criteria

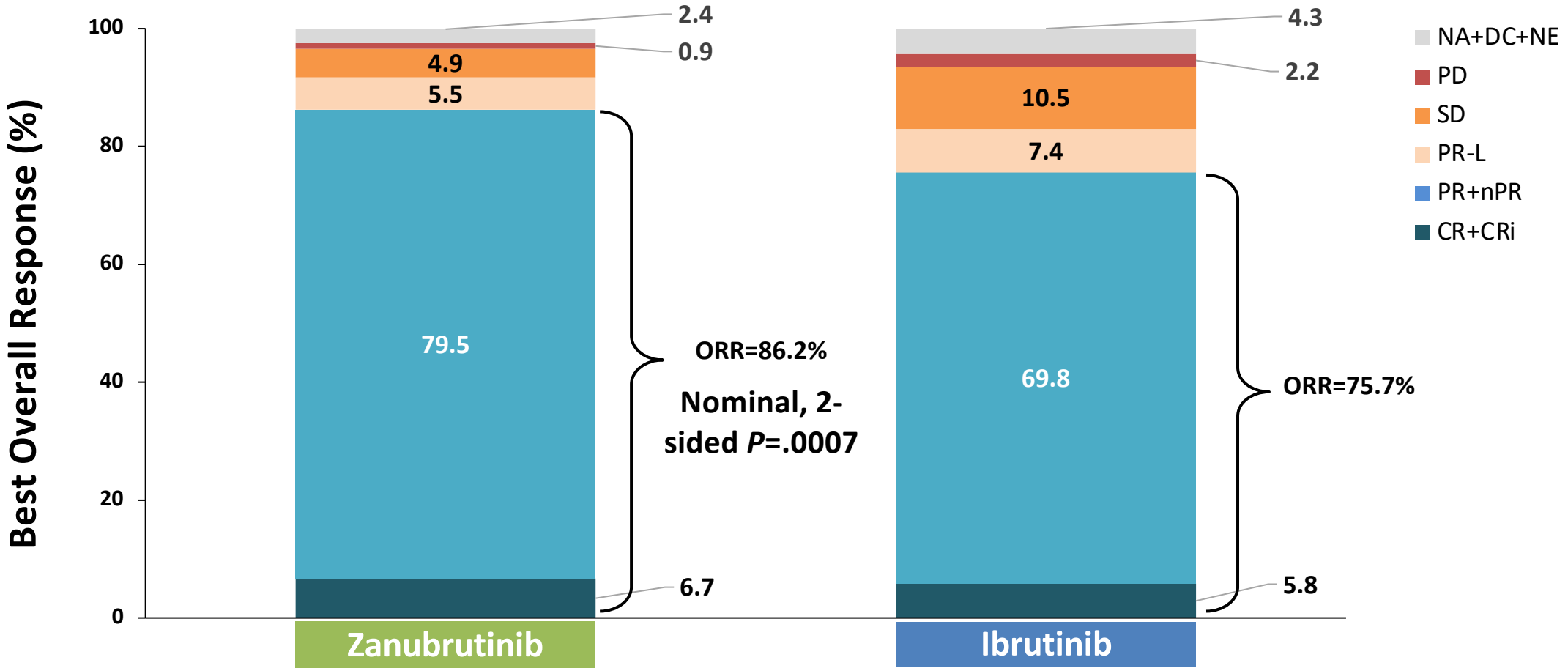
- Prior BTK inhibitor therapy
- Treatment with warfarin or other vitamin K antagonists



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.

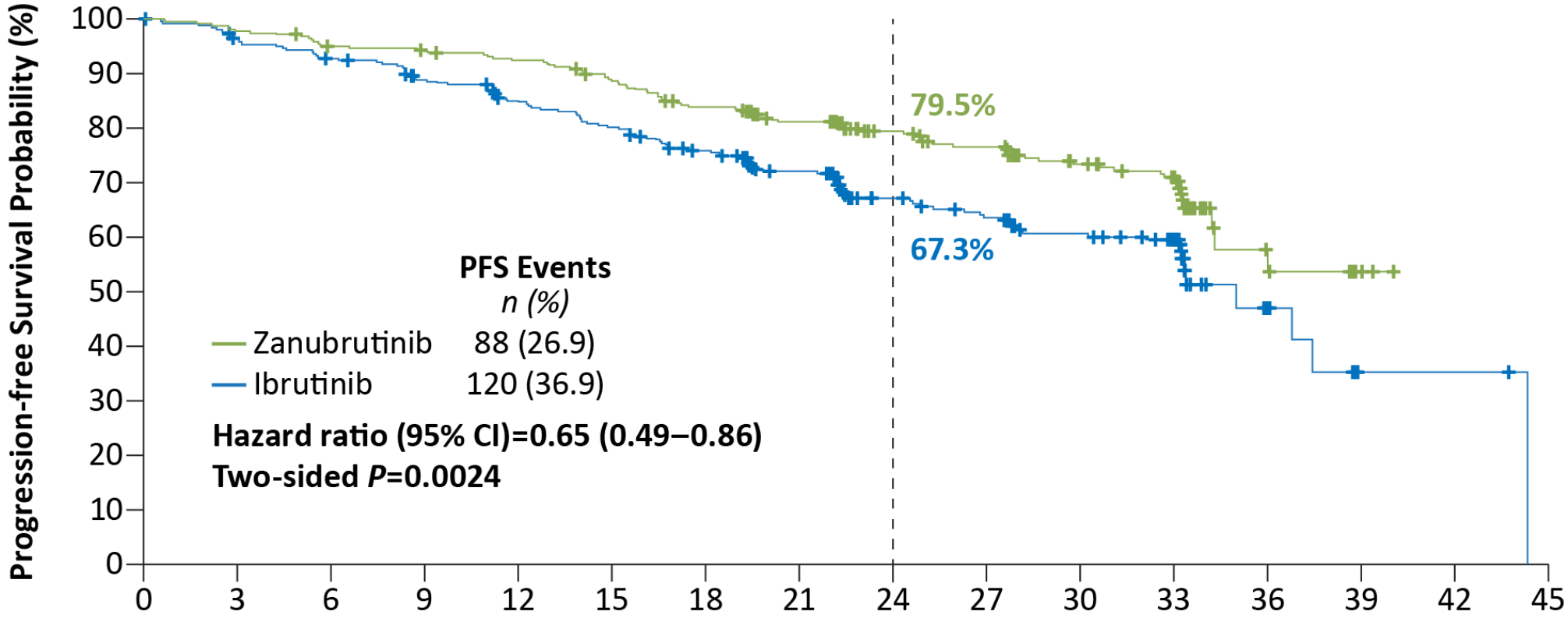
Data cutoff: 8 Aug 2022

Brown et al. NEJM, December 2022

Brown et al. ALPINE ASH 2022

Zanubrutinib PFS by IRC Significantly Superior to Ibrutinib

Median study follow-up of 29.6 months



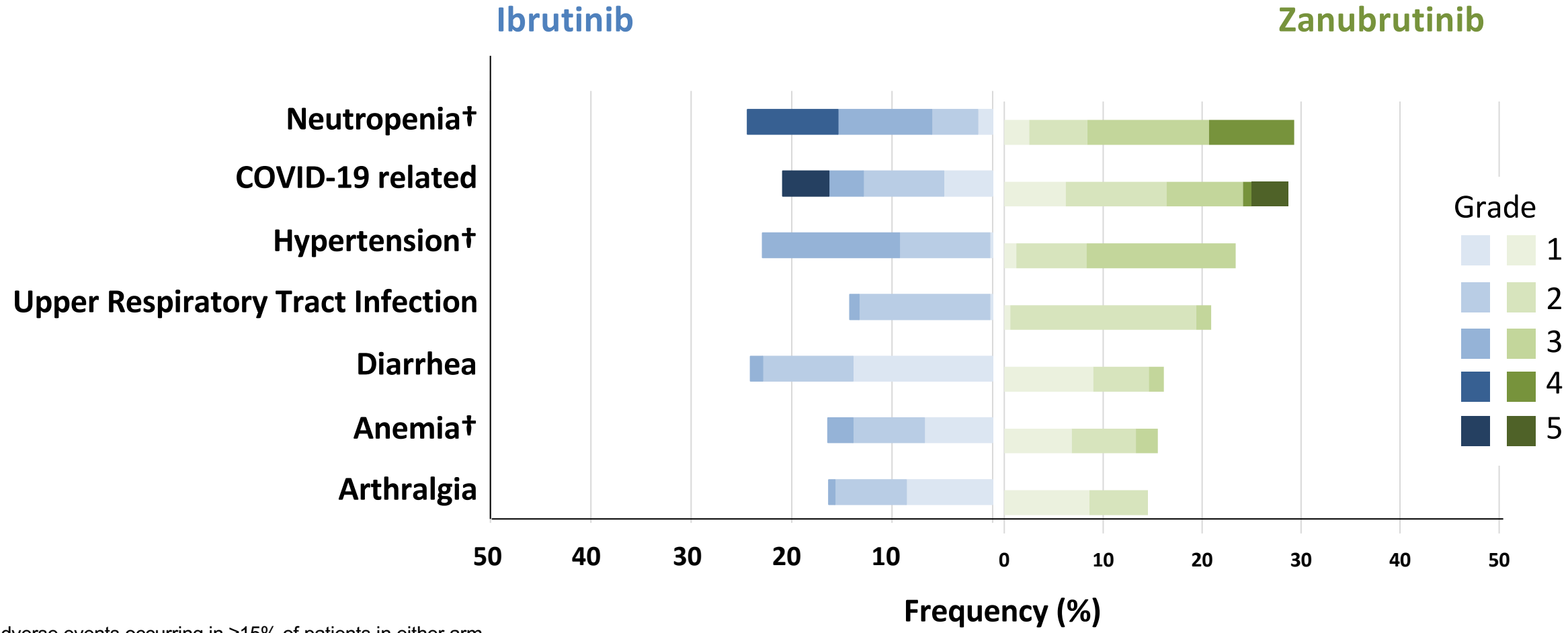
No. at Risk																
Zanubrutinib	327	315	304	301	294	280	263	226	172	161	125	113	14	2	0	
Ibrutinib	325	305	293	277	260	246	228	191	133	123	98	87	9	2	2	0

Data cutoff: 8 Aug 2022

Brown et al. NEJM, December 2022

Brown et al. ALPINE ASH 2022

Most Common Adverse Events*



*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)

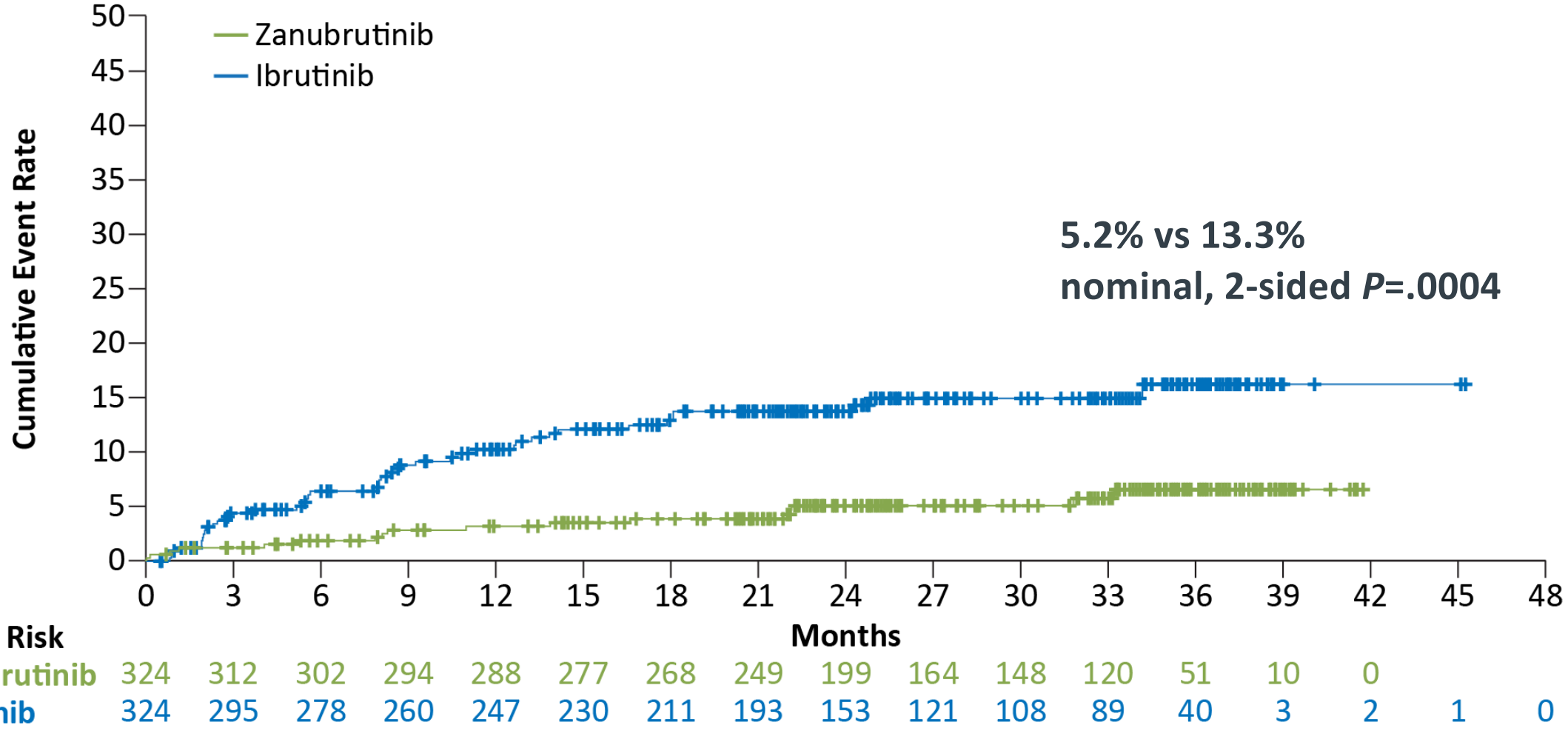
Data cutoff: 8 Aug 2022

*Cardiac deaths. One death not listed due to myocardial infarction with ibrutinib discontinuation due to diarrhea 14 days prior to the fatal event.

Brown et al. NEJM, December 2022

Brown et al. ALPINE ASH 2022

Atrial Fibrillation/Flutter Events With Zanubrutinib



Data cutoff: 8 Aug 2022

Brown et al. NEJM, December 2022

Brown et al. ALPINE ASH 2022

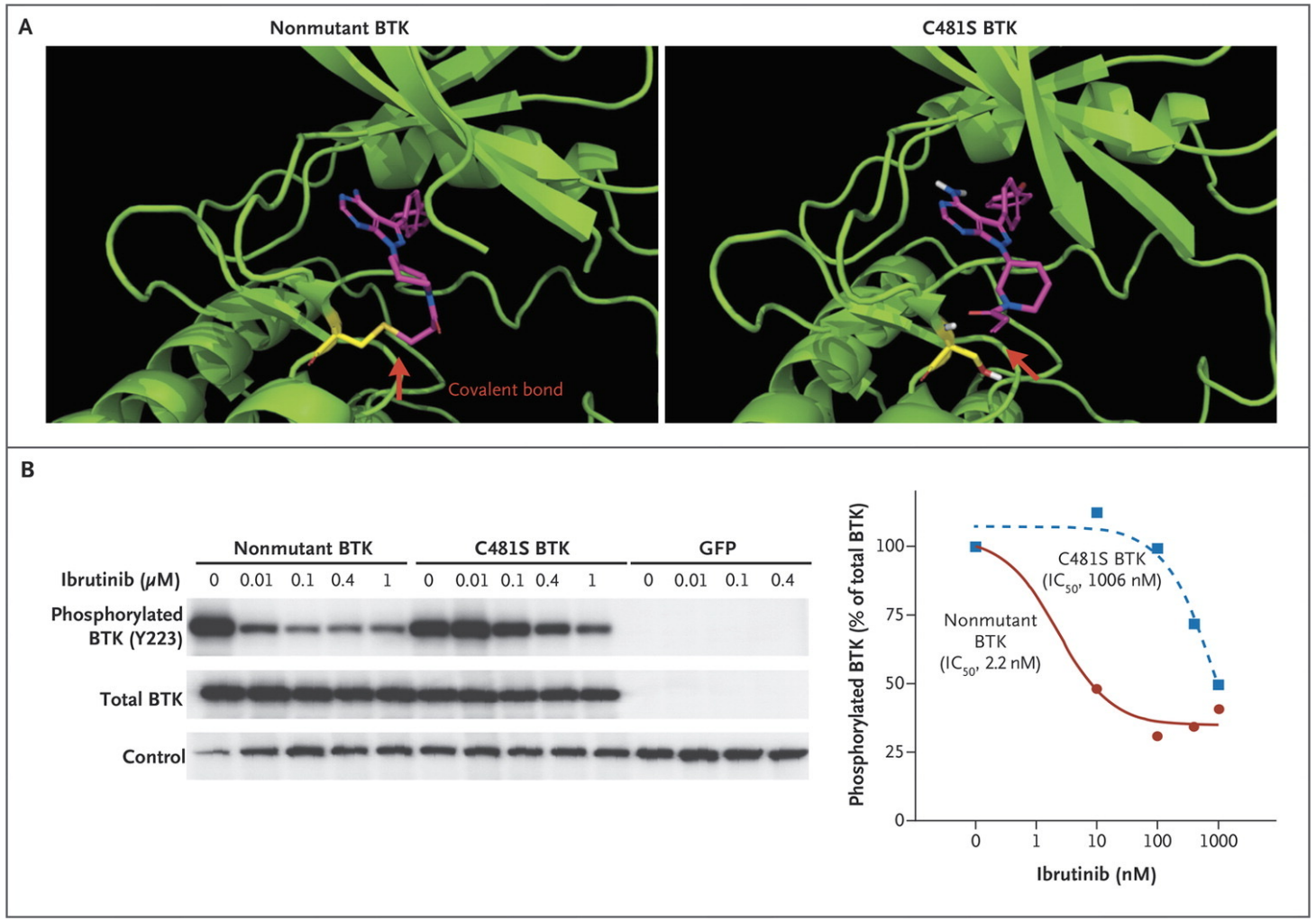
ELEVATE-RR vs ALPINE: AEs of clinical interest, D/C and PD

	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.

Brown et al. ALPINE 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

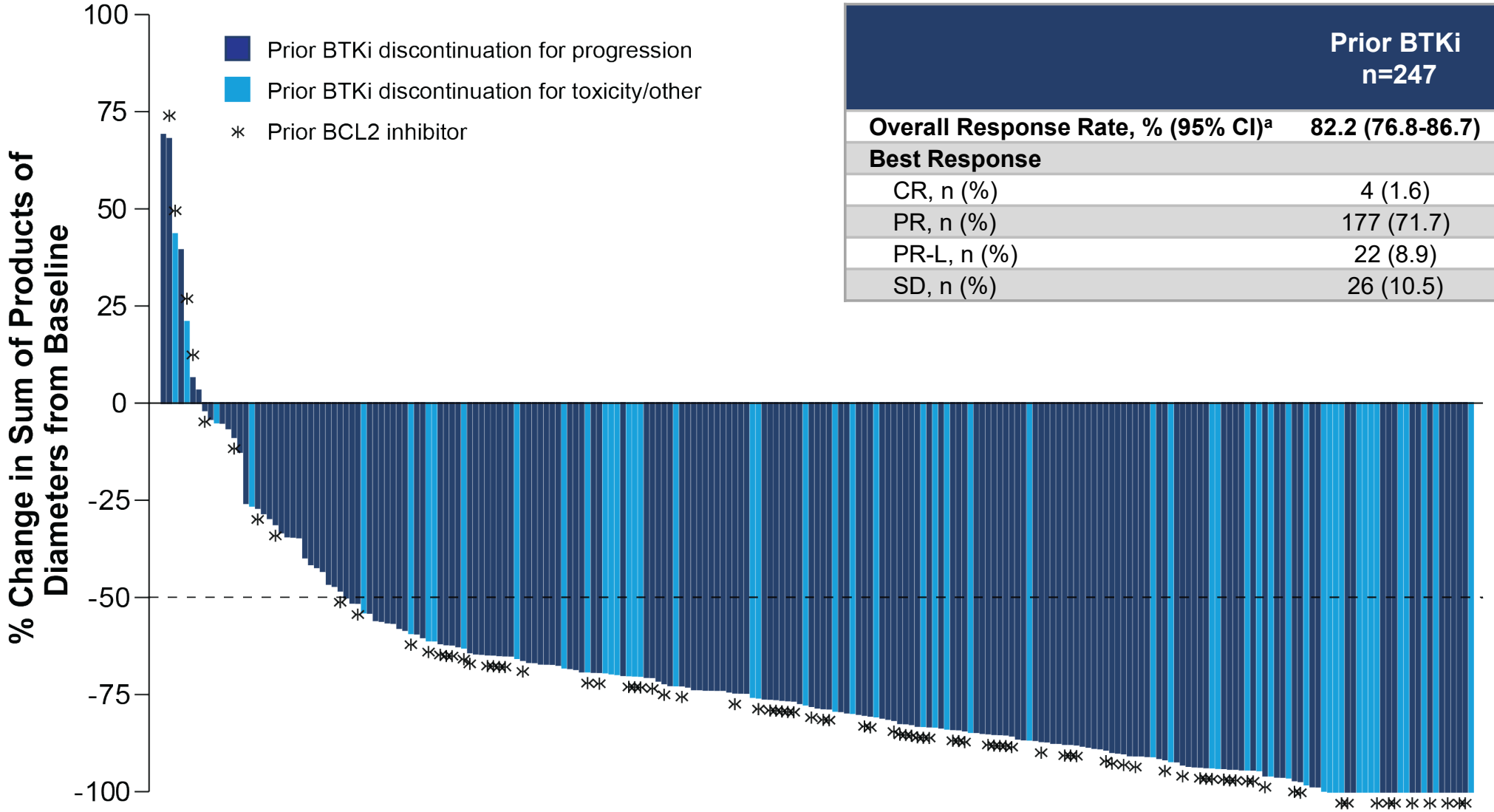
	Number of patients carrying the mutations			
	Ibrutinib-treated patients (n = 24)	Zanubrutinib-treated patients (n =13)	Total	*P*
Cys481 codon mutations	24	10	34	.03
Leu528Trp	1	7	8	.001

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, Ella R. Thompson, Thomas E. Lew, Ing Soo Tiong, Rory Bennett, Chan Y. Cheah, Katharine Louise Lewis, Sasanka M. Handunnetti, Chloe Pek Sang Tang, Andrew Roberts, John F. Seymour, Constantine S. Tam; Enrichment of BTK Leu528Trp mutations in patients with CLL on zanubrutinib: potential for pirtobrutinib cross-resistance. *Blood Adv* 2022; 6 (20): 5589–5592.

Pirtobrutinib Efficacy in CLL/SLL Patients who Received Prior BTKi Treatment

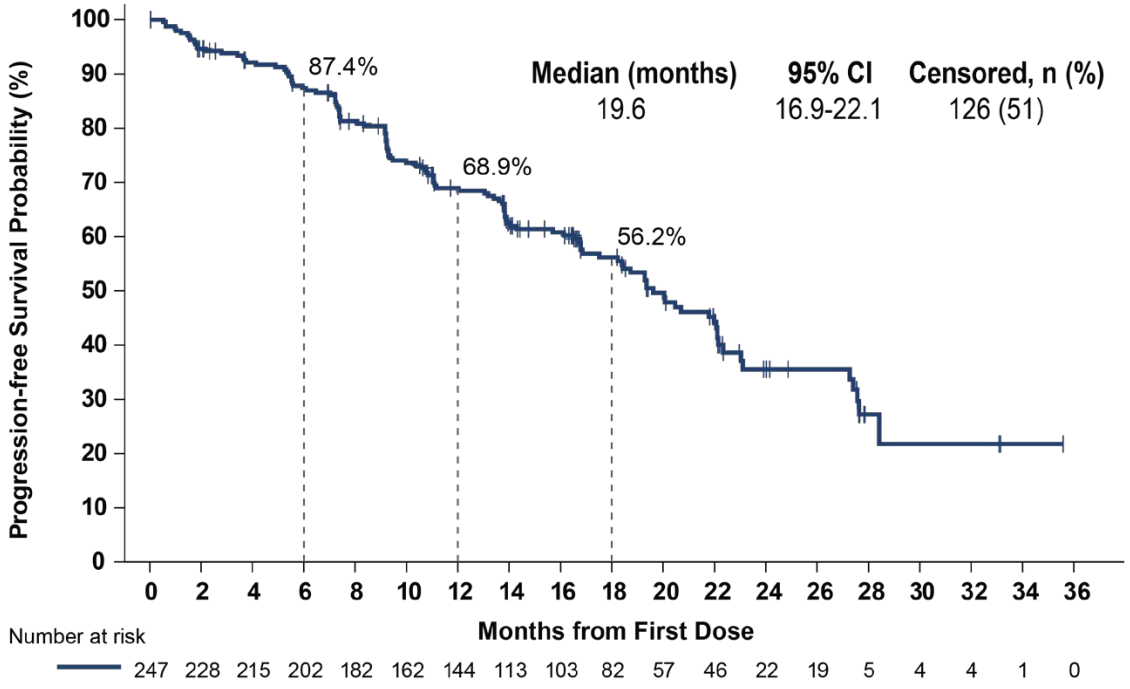


	Prior BTKi n=247	Prior BTKi+BCL2i n=100
Overall Response Rate, % (95% CI)[a]	**82.2 (76.8-86.7)**	**79.0 (69.7-86.5)**
Best Response		
CR, n (%)	4 (1.6)	0 (0.0)
PR, n (%)	177 (71.7)	70 (70.0)
PR-L, n (%)	22 (8.9)	9 (9.0)
SD, n (%)	26 (10.5)	11 (11.0)

Mato et al ASH 2022

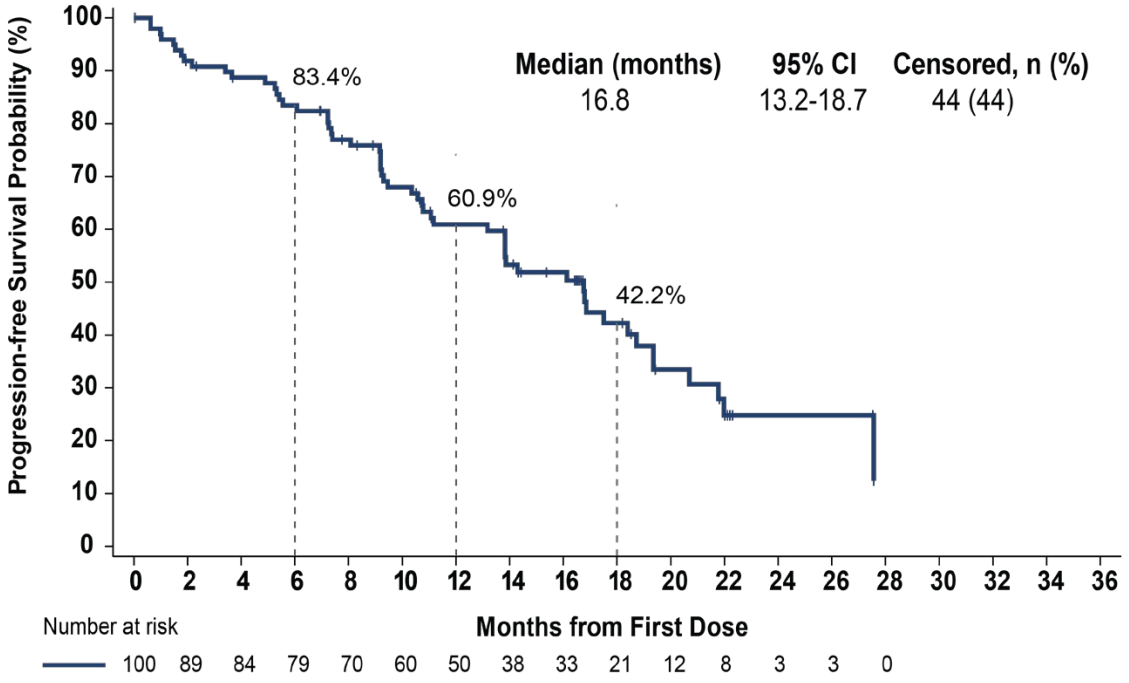
Progression-Free Survival in CLL/SLL Patients who Received Prior BTKi Treatment

All prior BTKi patients
Median prior lines = 3



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

Prior BTKi and BCL2i patients
Median prior lines = 5

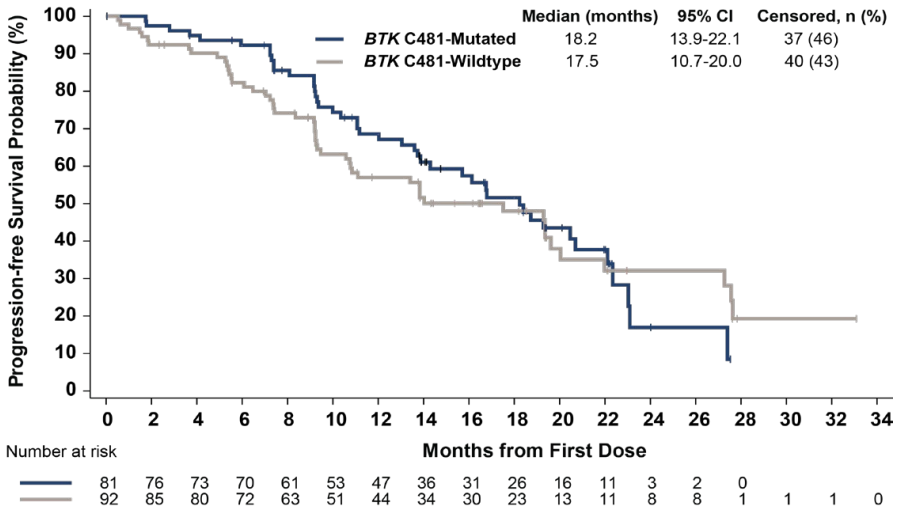


- Median follow-up of 18.2 months for patients who received prior BTKi and BCL2i

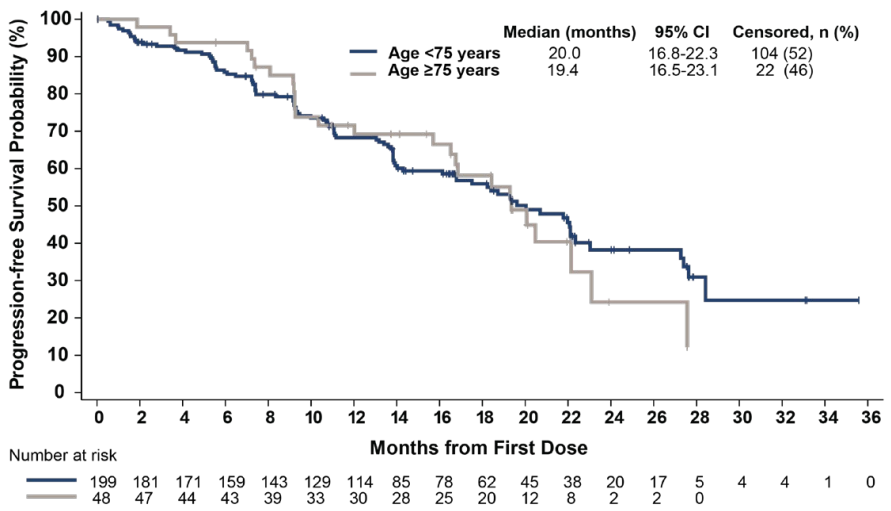
Mato et al ASH 2022

Progression-Free Survival in CLL/SLL Subgroups

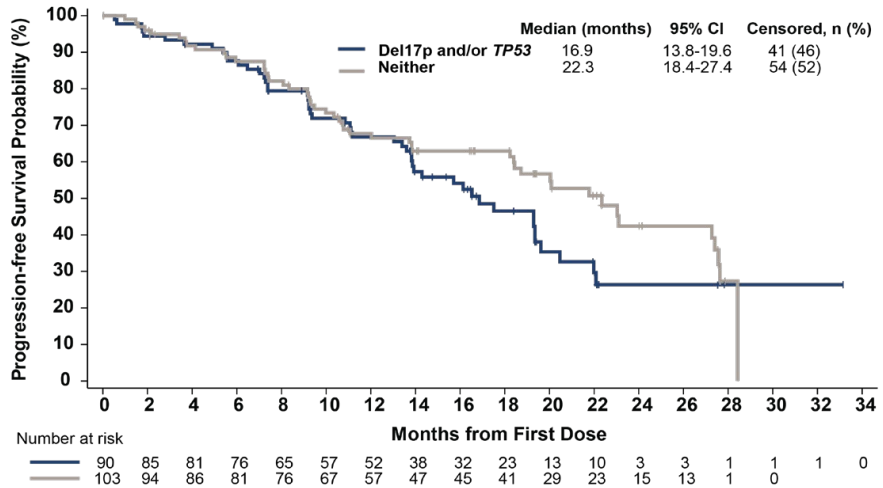
BTK C481 mutation status[a,b]



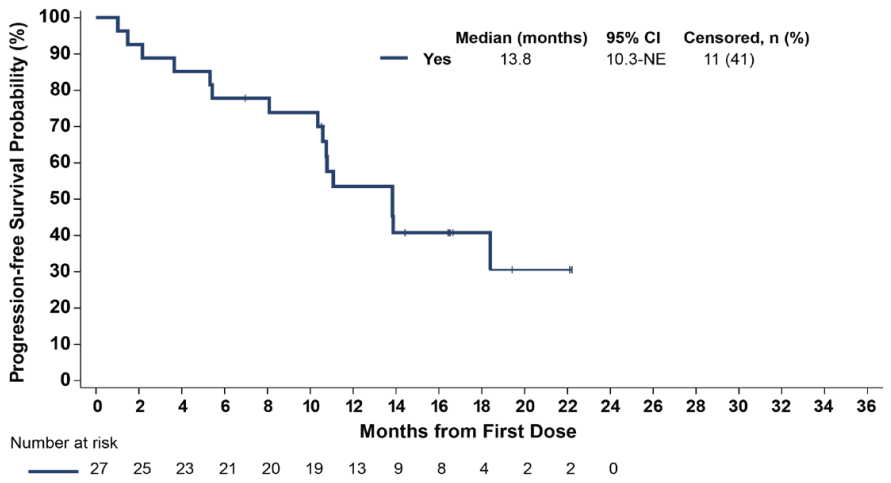
Age



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



Prior BTKi, CIT, BCL2i, and PI3Ki therapy



Mato et al ASH 2022

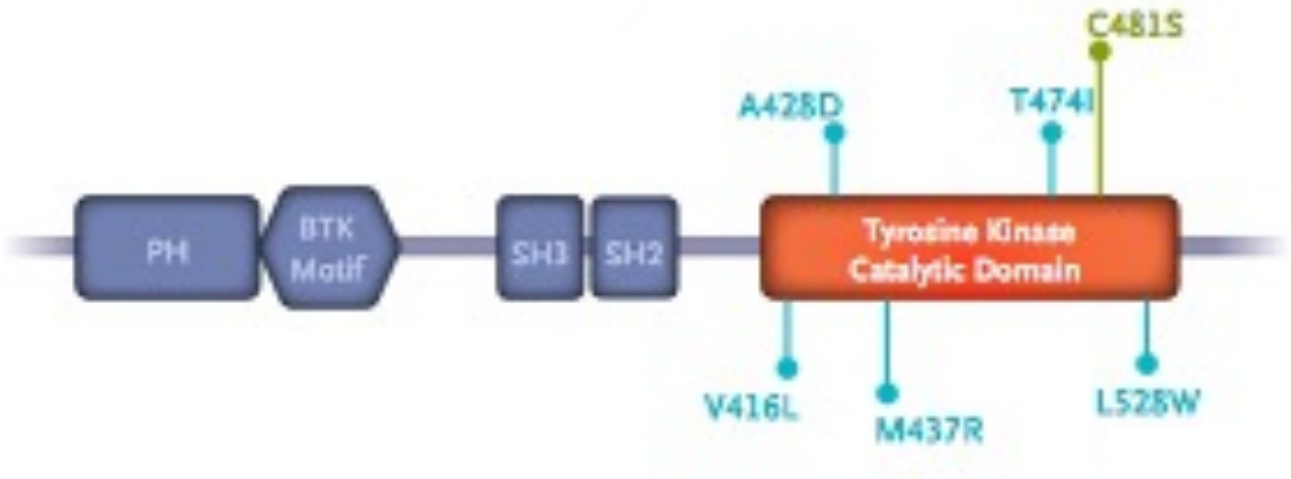
Pirtobrutinib Safety Profile

	All Doses and Patients (N=773)			
	Treatment-Emergent AEs, (≥15%), %		Treatment-Related AEs, %	
Adverse Event (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]

Mato et al ASH 2022

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.