The art of medicine in treating CLL

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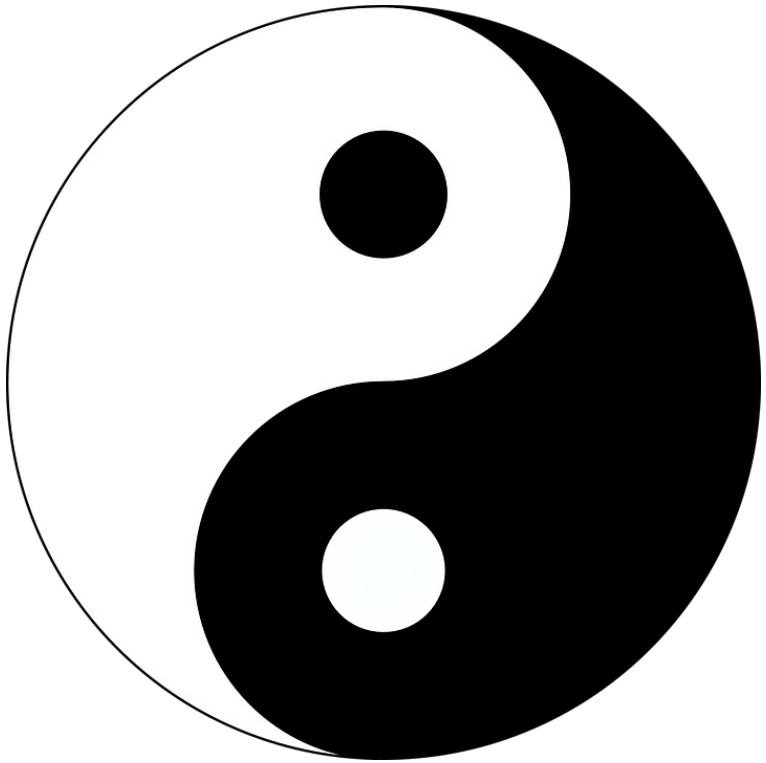
The dilemma continue between long term therapy vs fixed duration

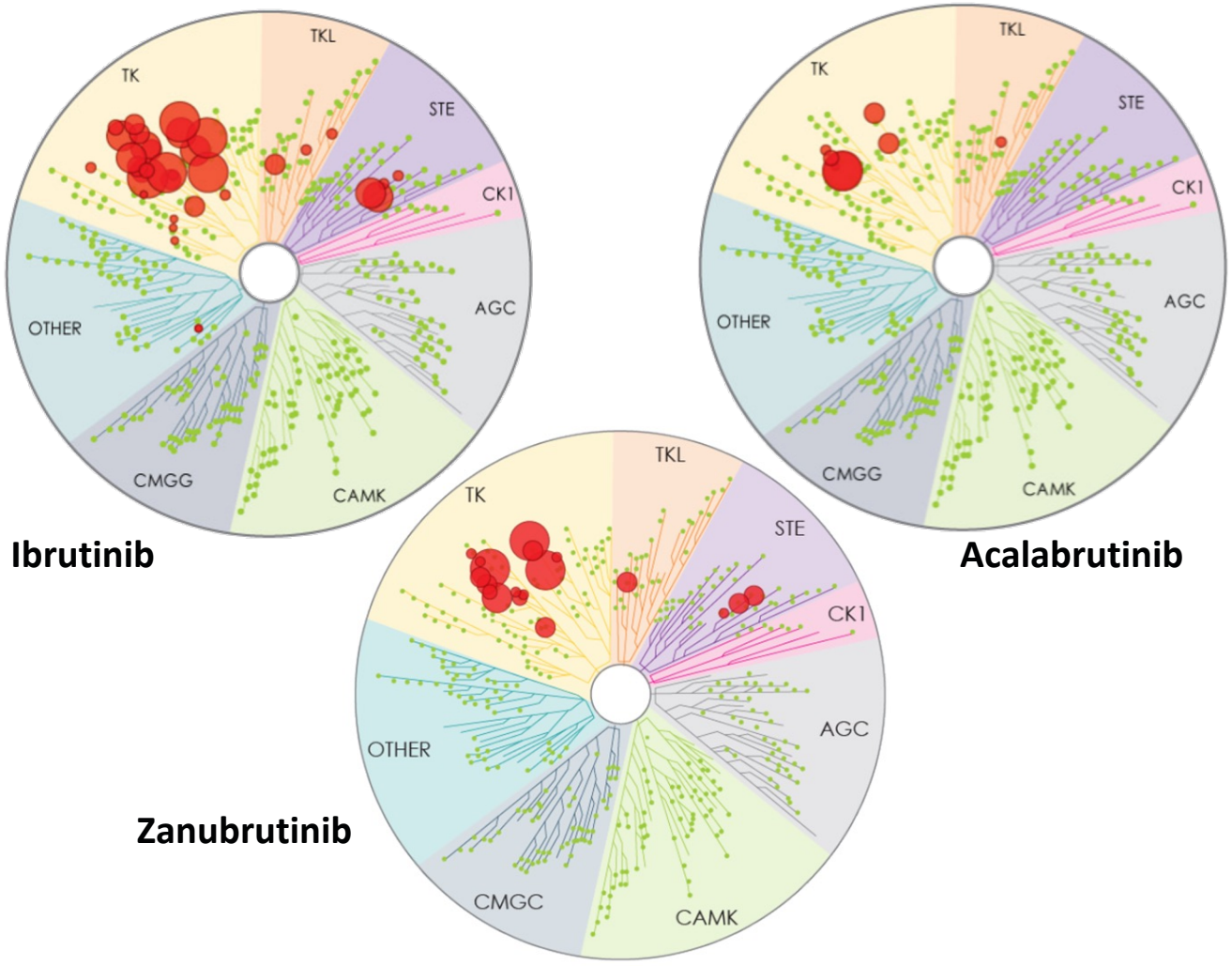


The new era of BTK Inhibitors in CLL

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

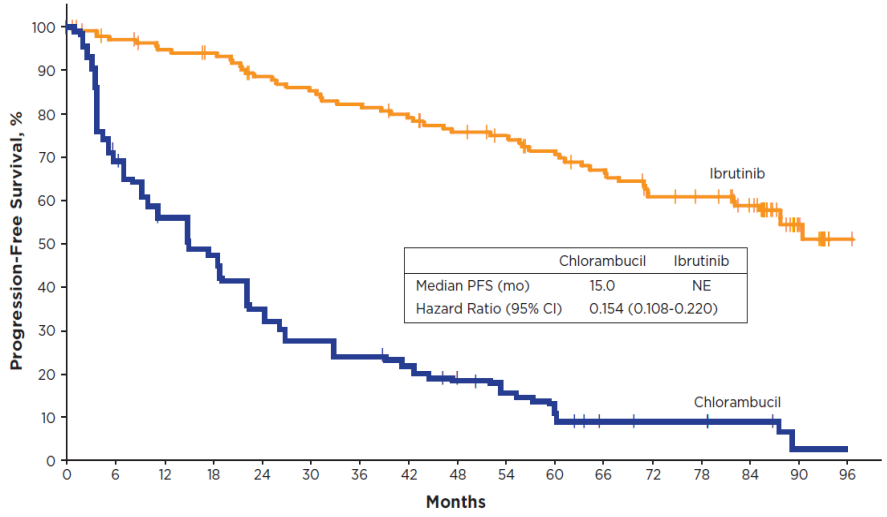
Kinase Selectivity Profiling at 1 μmol/L (in vitro)

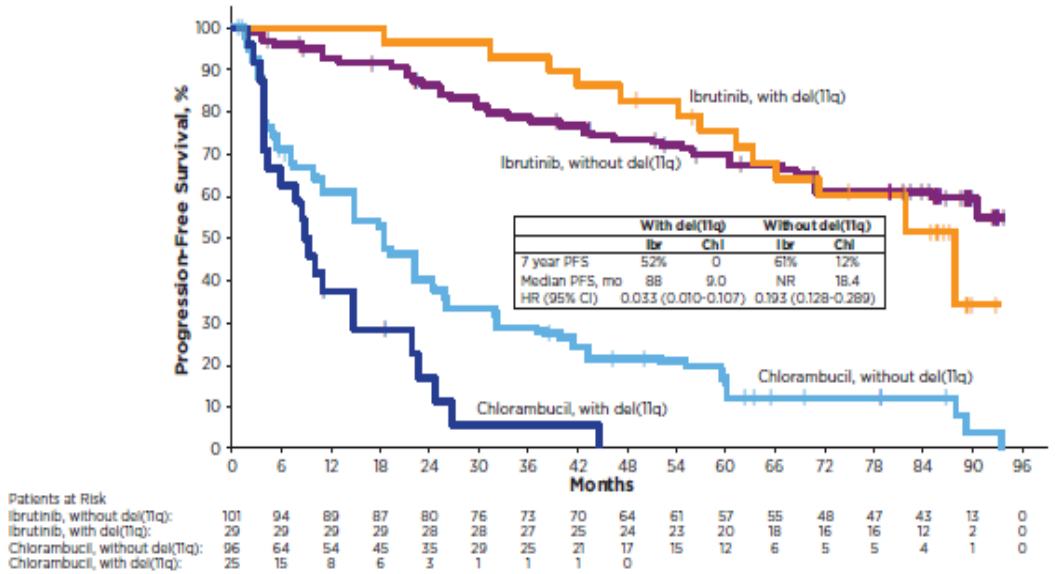
Larger red circles represent stronger inhibition



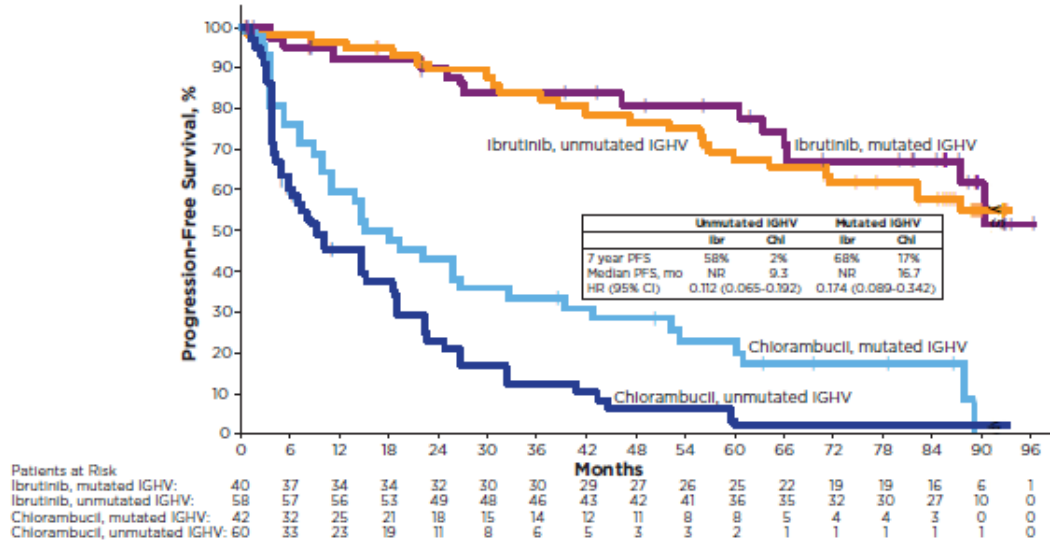
Kaptein. ASH 2018.

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



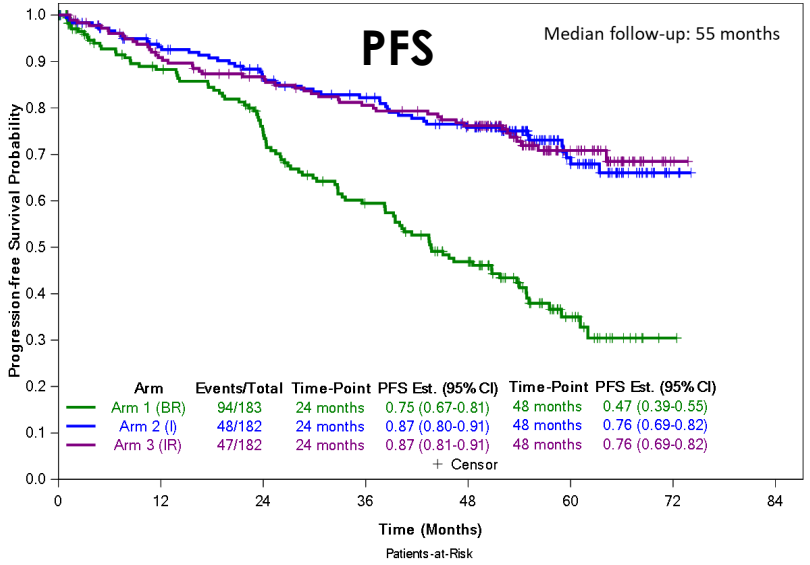


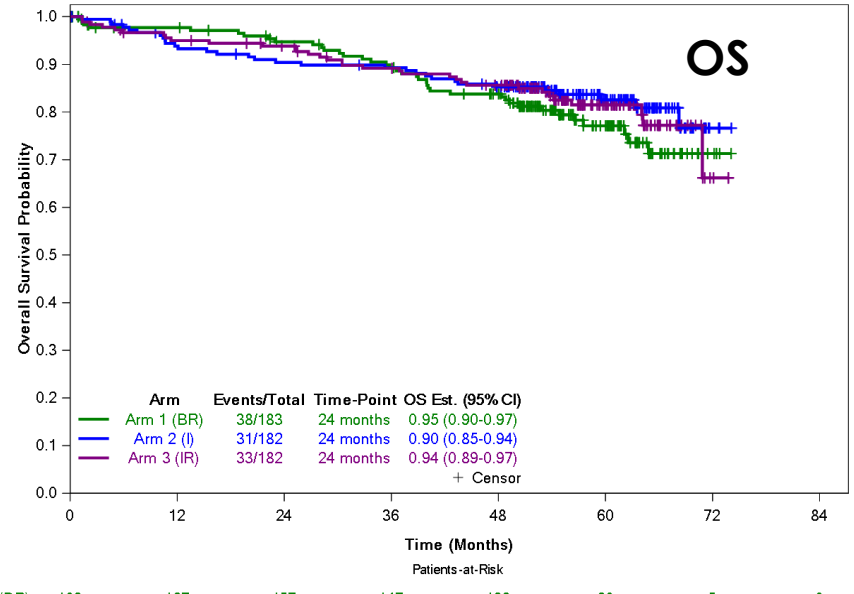
	Ibrutinib n=136
Median duration of ibrutinib treatment, years	6.2
Continuing ibrutinib on study, n (%)	57 (42)
Discontinued ibrutinib, n (%)	
AE	**32 (24)**
PD	**18 (13)**
Death	12 (9)
Withdrawal by patient	9 (7)
Investigator decision	7 (5)

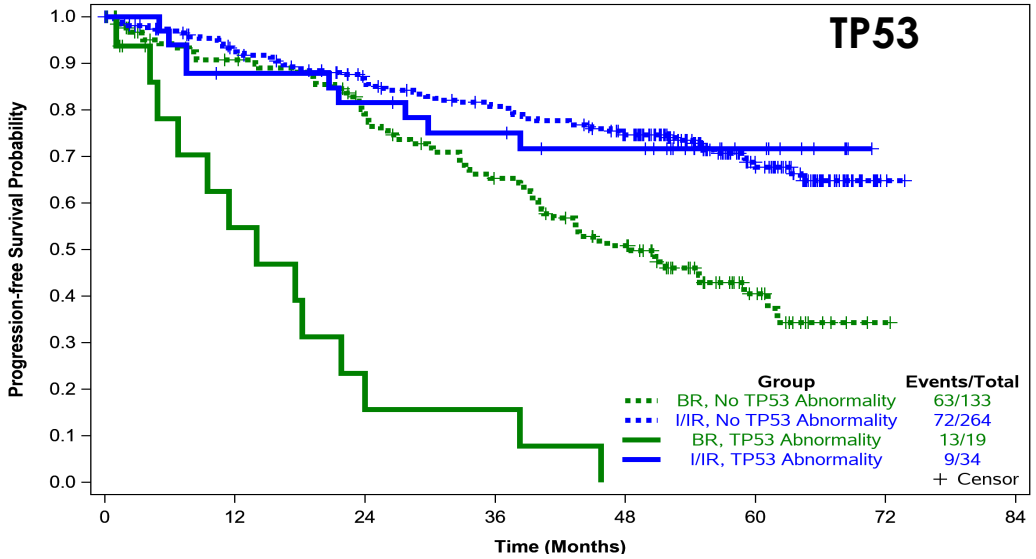


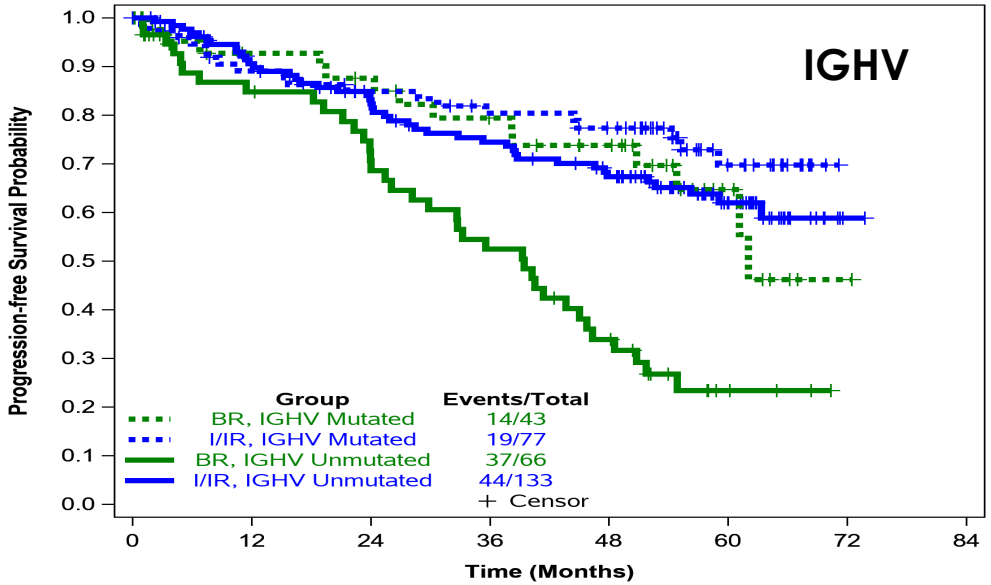
Barr et al Blood Advances 2022

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





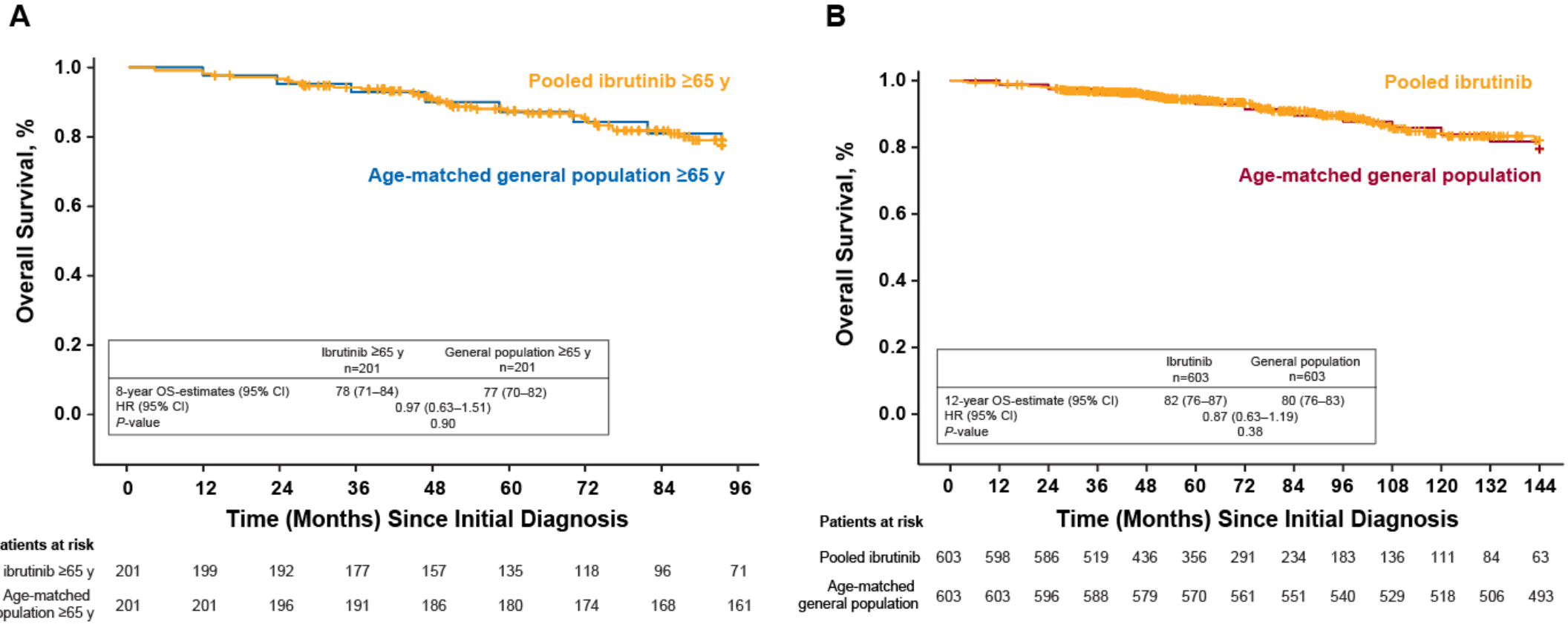




Woyach. ASH 2021.

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

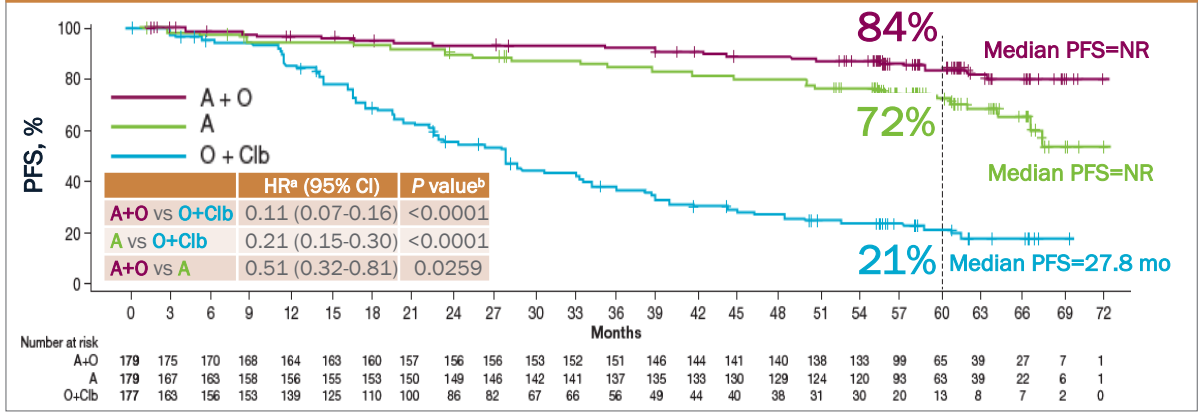


[a]*Data after 96 months is not represented in the KM curve;* [b]*Data after 144 months is not represented in the KM curve*

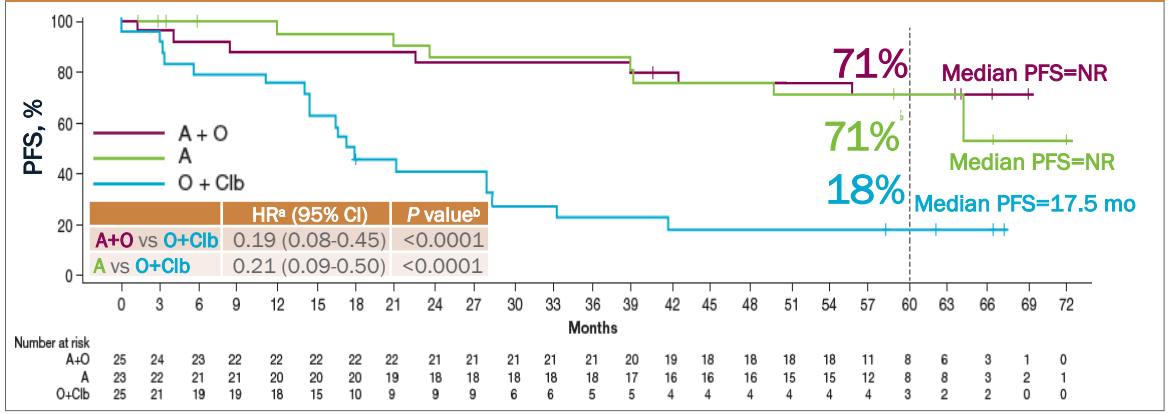
Paolo Ghia et al.,
Presented at ASH 2022; No. #1809

5-Year Follow-Up of ELEVATE-TN: Acalabrutinib ± Obinutuzumab vs Obinutuzumab + Chlorambucil in TN CLL – PFS and OS[1,2]

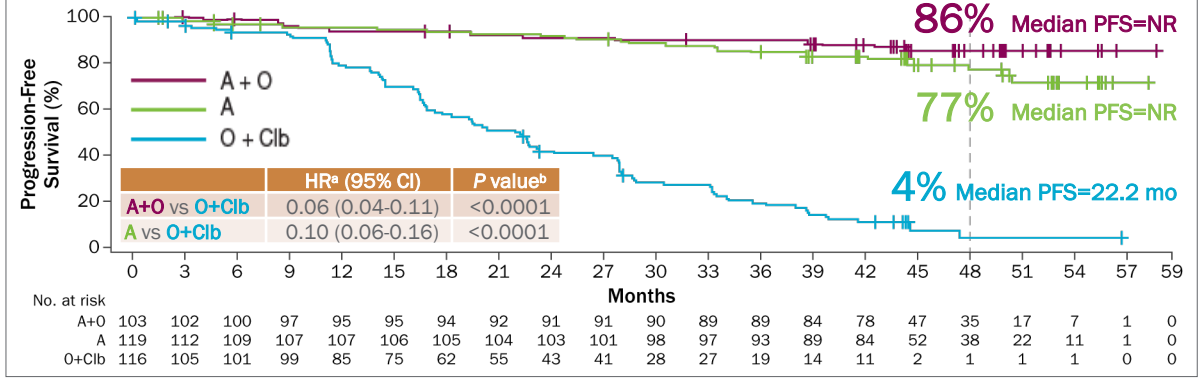
INV-Assessed PFS (Median Follow-Up: 58.2 Months)[1]



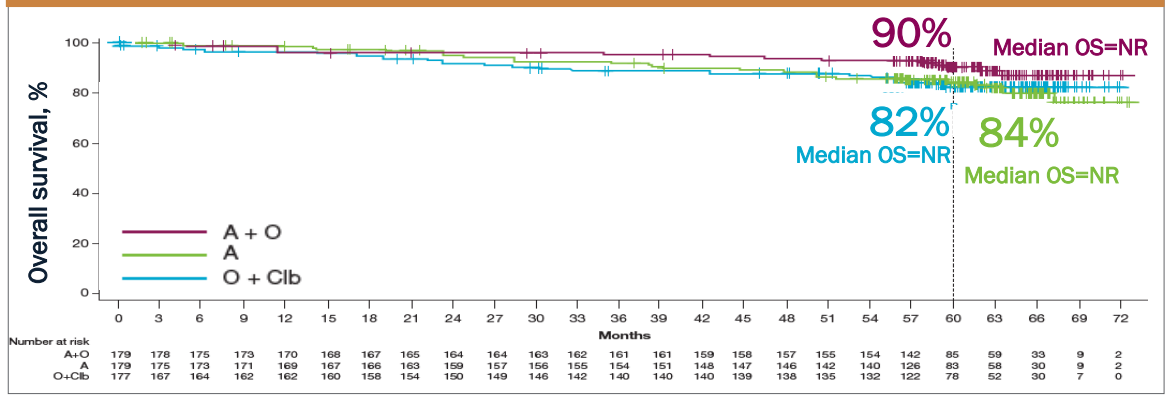
INV-Assessed PFS in del(17p) and/or *TP53*-mut (Median Follow-Up: 58.2 Months)[1]



INV-Assessed PFS in Unmutated *IGHV* (Median Follow-Up: 46.9 Months)[2]



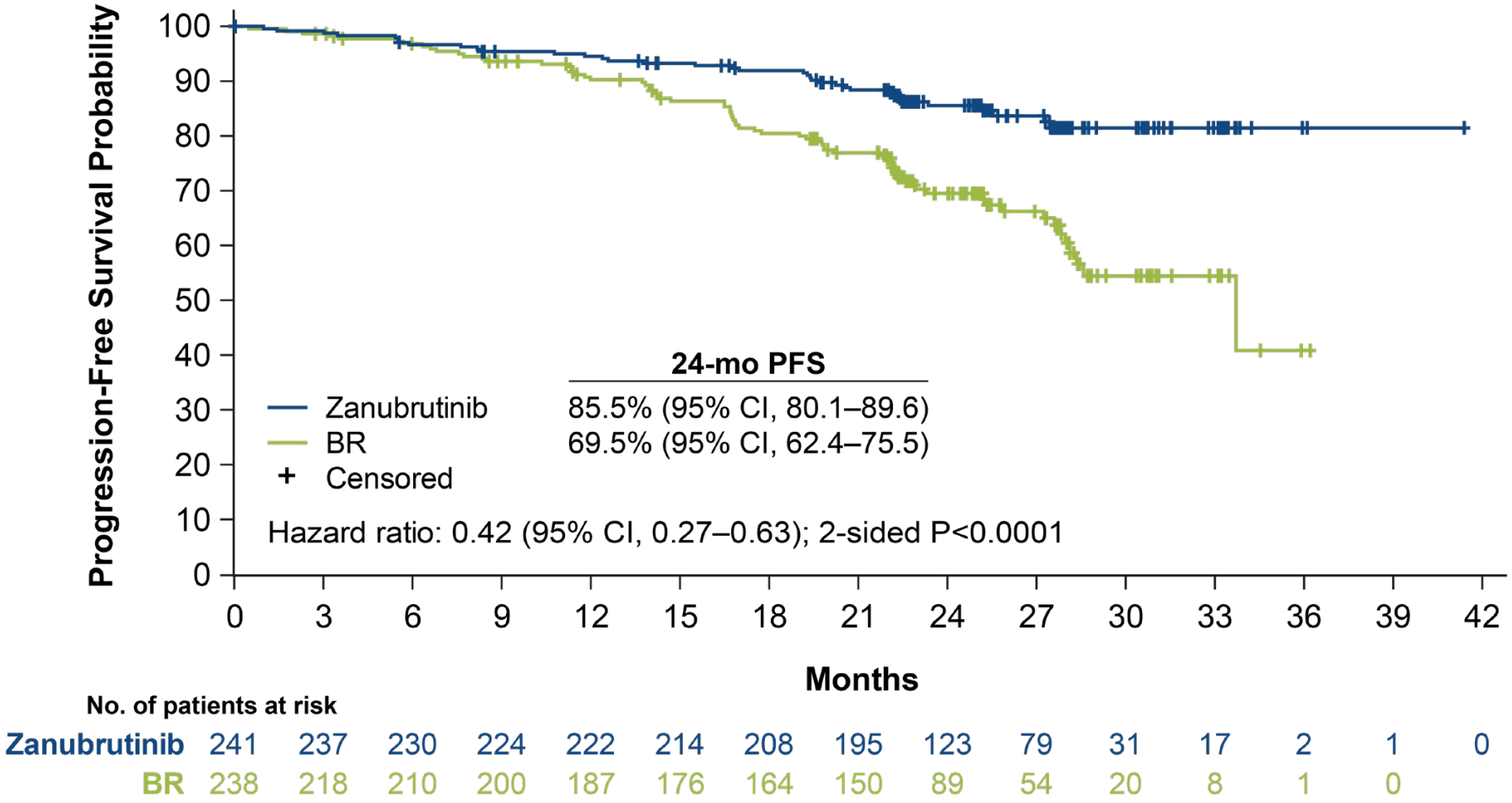
Overall Survival (Median Follow-Up: 58.2 Months)[1]



- At a median follow-up of 58.2 months (range, 0.0-72.0), OS data were immature, and medians were not reached in any treatment arm
- Relative risk for death was lower in the A+O vs O+Clb arm (HR=0.55, 95% CI: 0.30-0.99)
  - Crossover from O+Clb to A occurred after disease progression in 72 patients (41%)
- All analyses are based on descriptive statistics

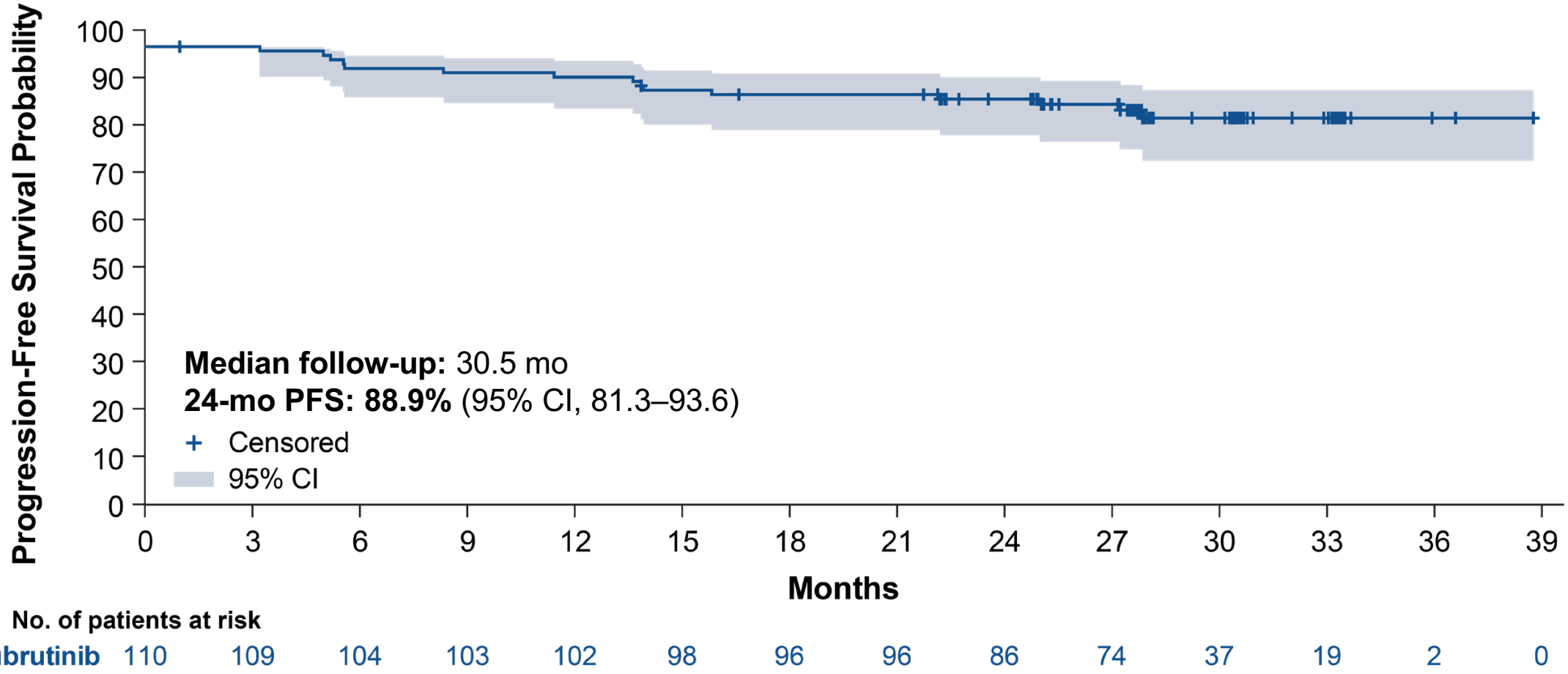
1. Sharman JP, et al. ASCO 2022. Abstract 7539. **2.** Sharman JP, et al. *Leukemia*. 2022;36(4):1171-1175.

SEQUOIA Cohort 1:PFS per IRC Assessment



Tan, et al. ASH 2021

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

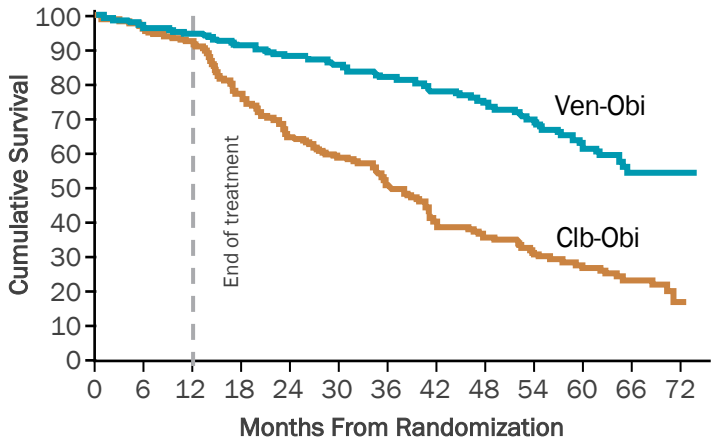


Tan, et al. ASH 2021

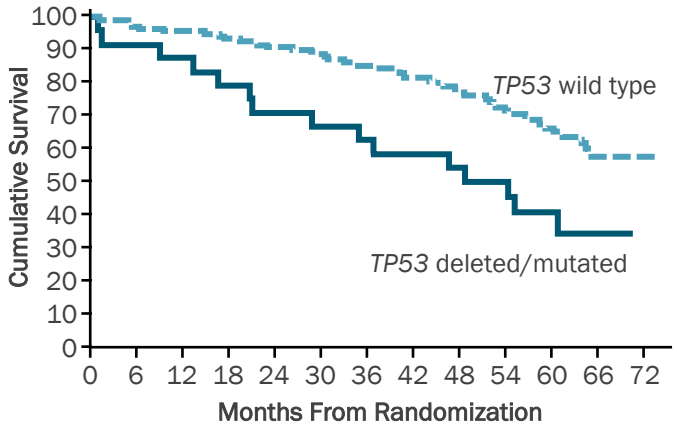
CLL14: Phase 3 Study of Venetoclax-Obinutuzumab vs Chlorambucil-Obinutuzumab in Unfit Patients

5-Year Progression-Free and Overall Survival

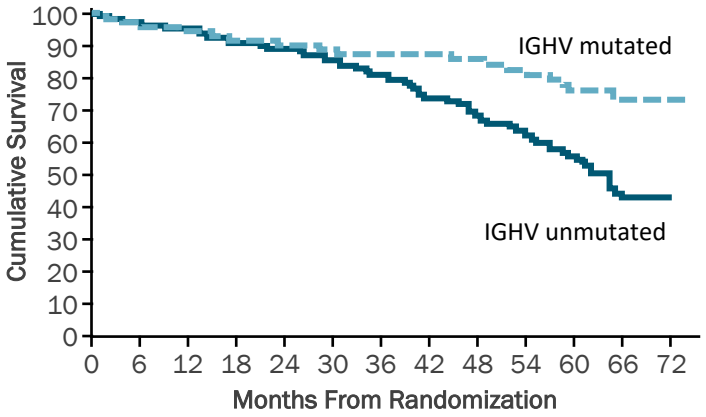
PFS Overall



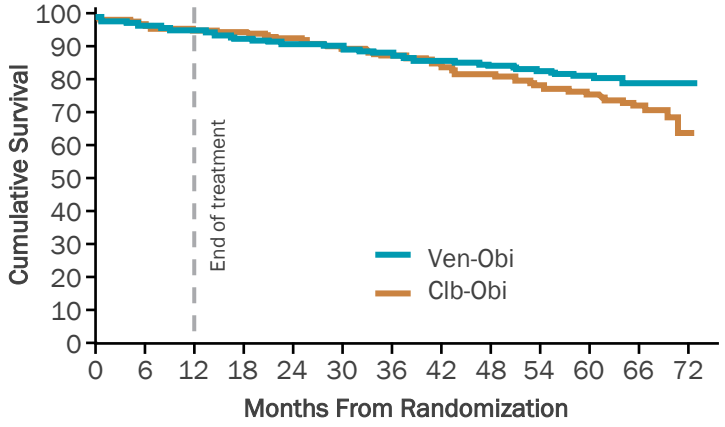
PFS With Ven-Obi by *TP53* Status



PFS With Ven-Obi by IGHV Status



Overall Survival



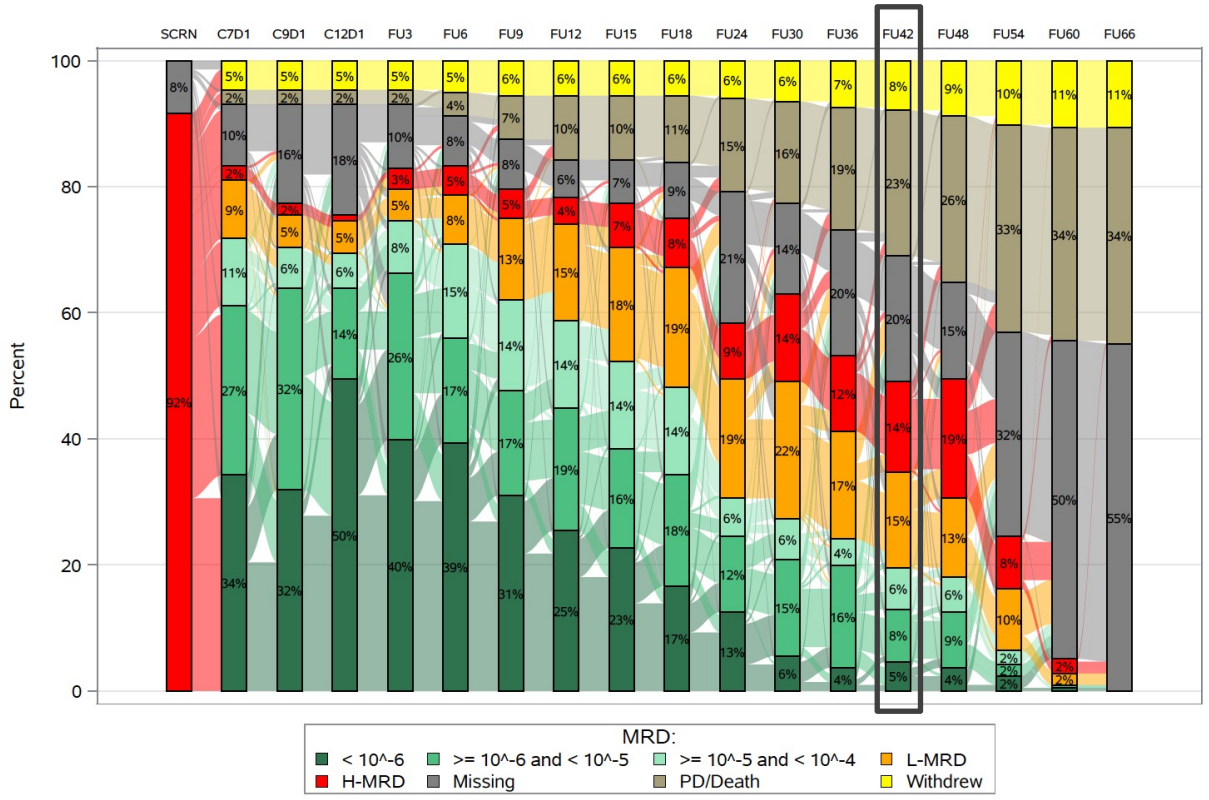
PFS by Subgroup		Ven-Obi (n=216)	Clb-Obi (n=216)
All patients	Median, months	NR	36.4
	5-year rate, %	62.6	27.0
	HR (95% CI); *P* value	0.35 (0.26-0.46); <0.0001	
Median PFS, months			
TP53 del/mut	No	NR (n=184)	38.9 (n=184)
	Yes	49.0 (n=25)	19.8 (n=24)
IGHV status	Mutated	NR (n=76)	59.9 (n=83)
	Unmutated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

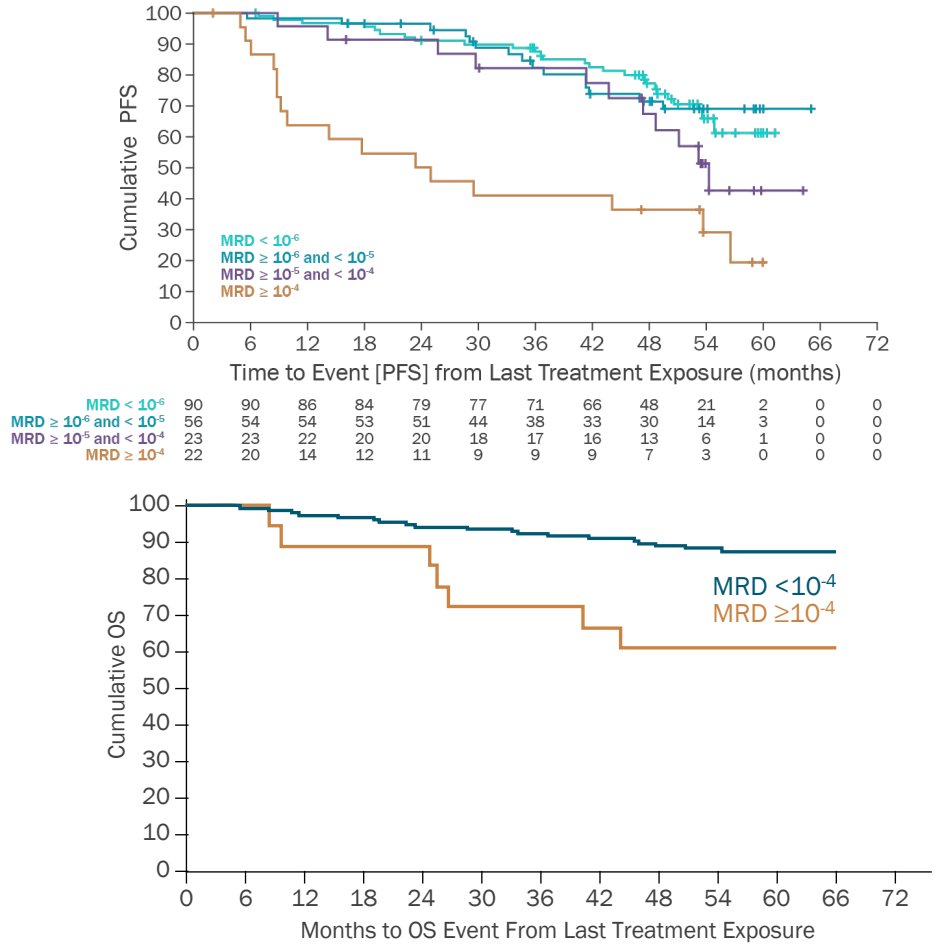
MRD Assessments

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



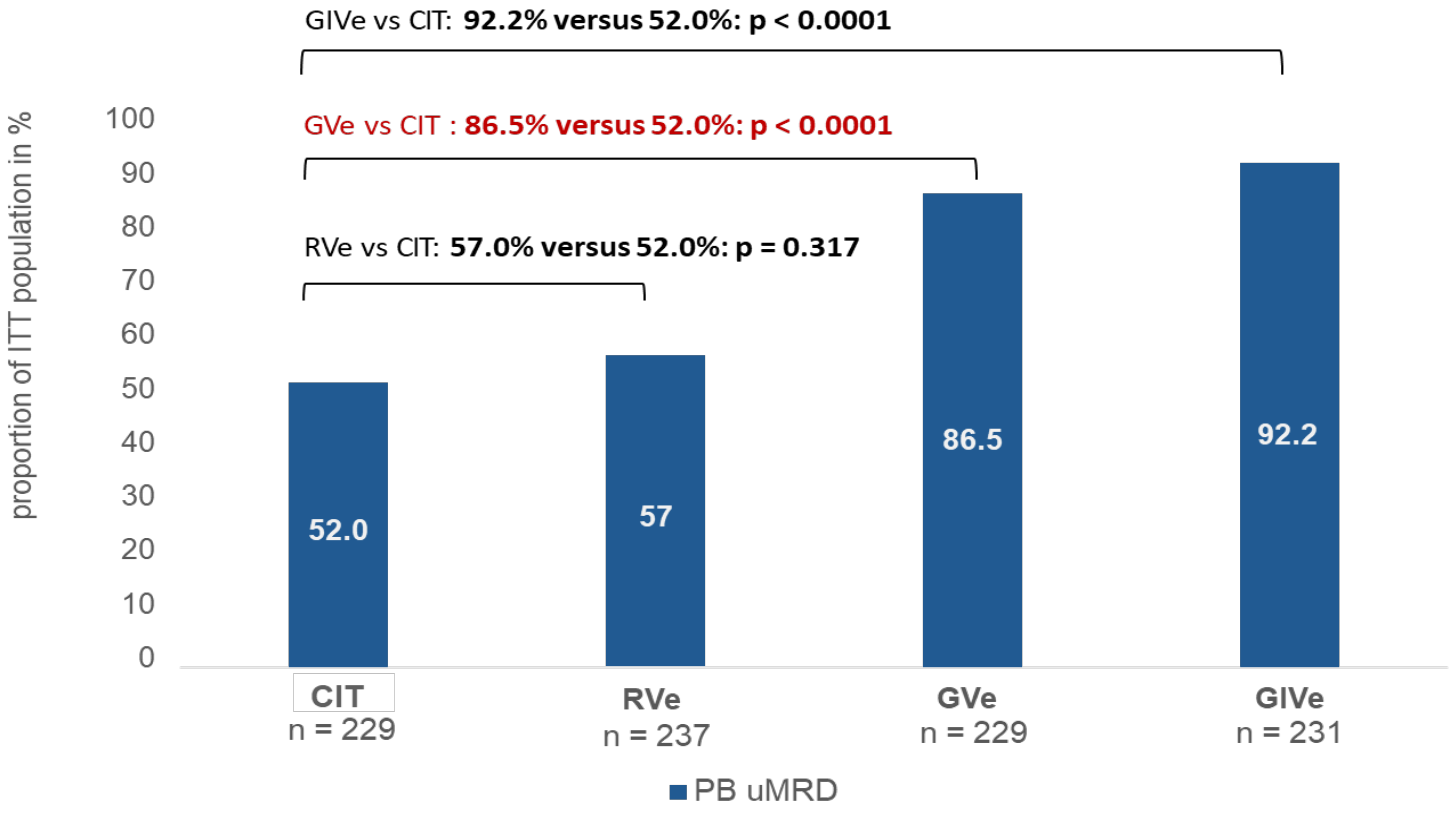
End of treatment MRD status in peripheral blood by next-generation sequencing.

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

GAIA (CLL13) trial

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



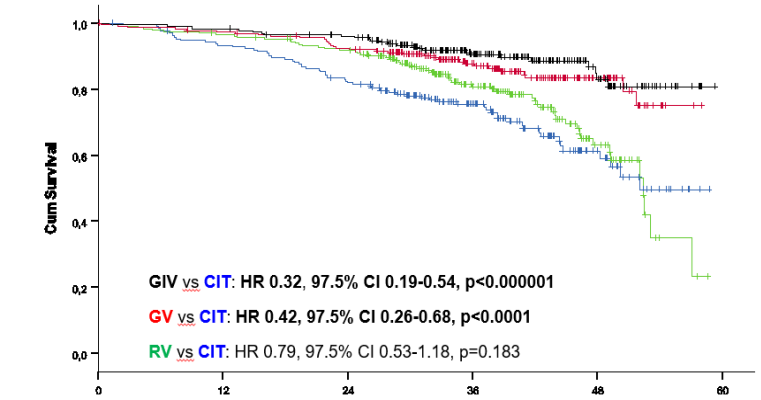
	uMRD%	97.5% CI
GIVe	92.2	87.3 – 95.7
GVe	86.5	80.6 – 91.1
RVe	57.0	49.5 – 64.2
SCIT	52.0	44.4 – 59.5

Eichhorst, et al., ASH 2021

GAIA (CLL13) trial
PFS and PFS by IgHV

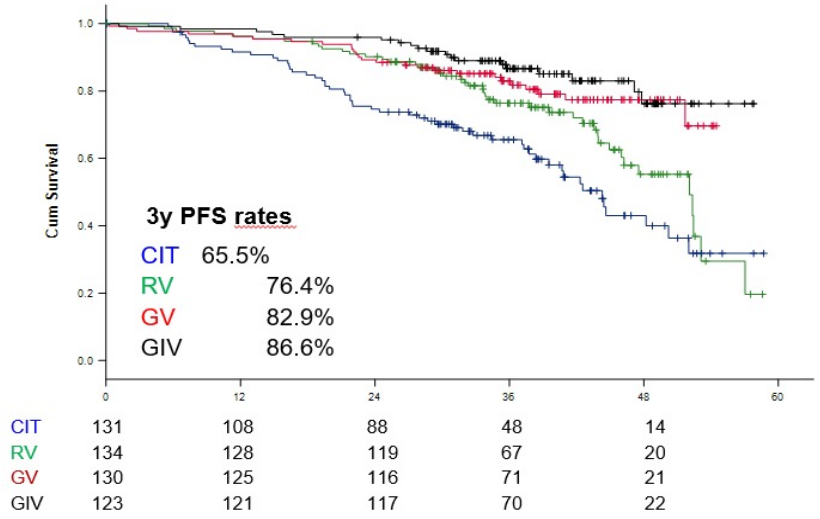
Results of the coprimary endpoint progression-free survival (PFS)

Median FU 38.8 months (range: 0.0 – 59.2)

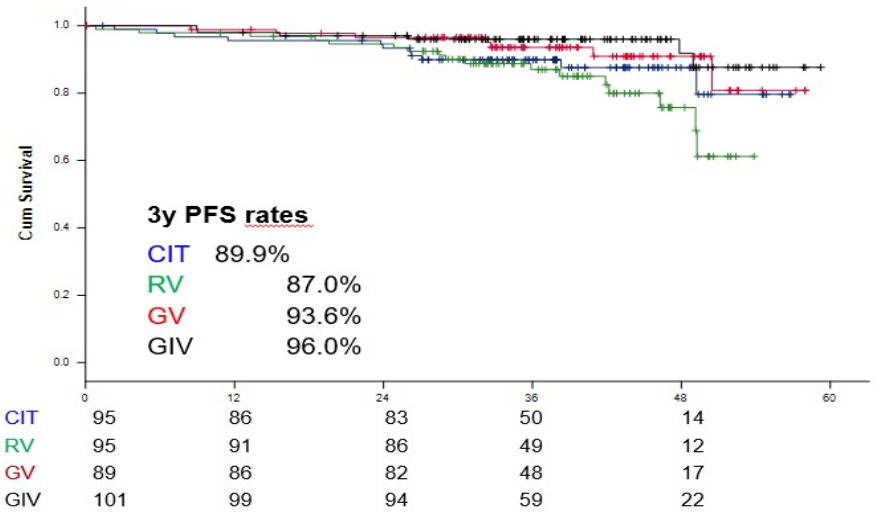


PFS	Median months	3y PFS (%)
CIT	52.0	75.5
RV	52.3	80.8
GV	NR	87.7
GIV	NR	90.5

Unmutated IGHV



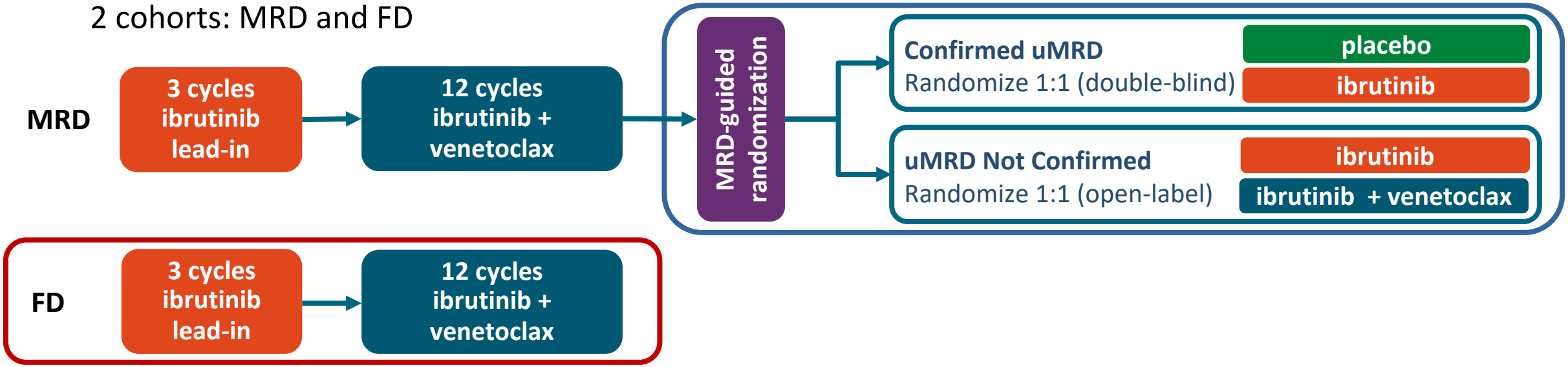
Mutated IGHV



Eichhorst, et al., EHa 2022

Phase 2 CAPTIVATE Study

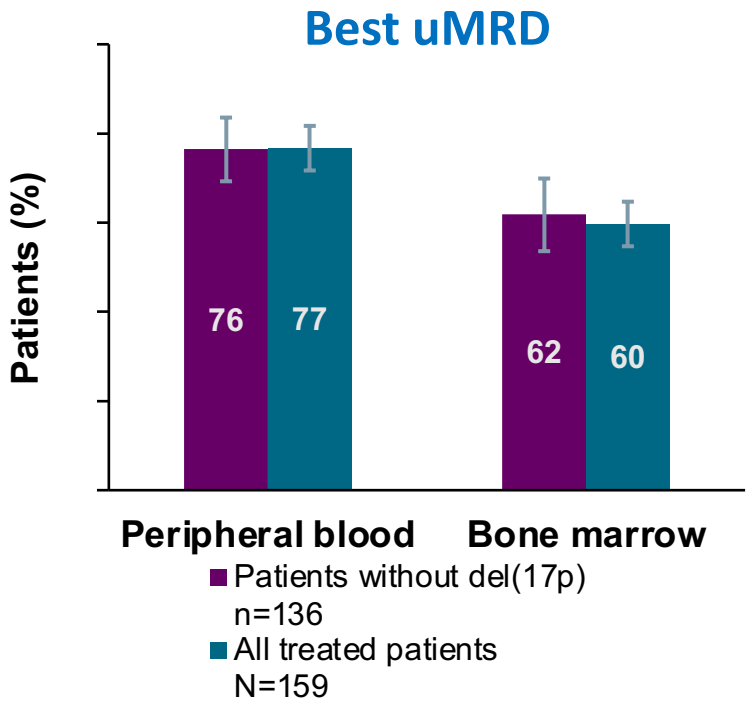
- CAPTIVATE (PCYC-1142) is an international, multicenter phase 2 study evaluating first-line treatment with 3 cycles of ibrutinib followed by 12 cycles of combined ibrutinib + venetoclax that comprises 2 cohorts: MRD and FD



- 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



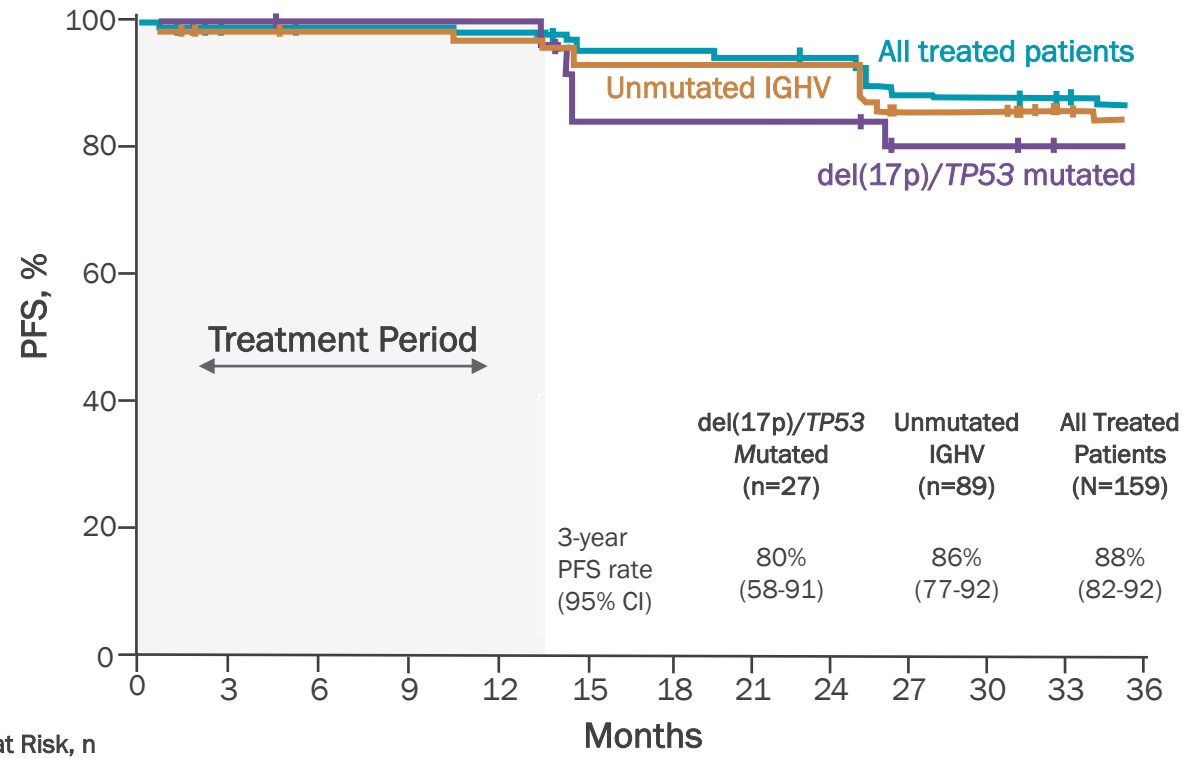
uMRD rate	PB	BM
Bulky Disease		
Yes	77%	63%
No	77%	59%
IGHV status		
uIGHV	84%	64%
mIGHV	67%	53%

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]

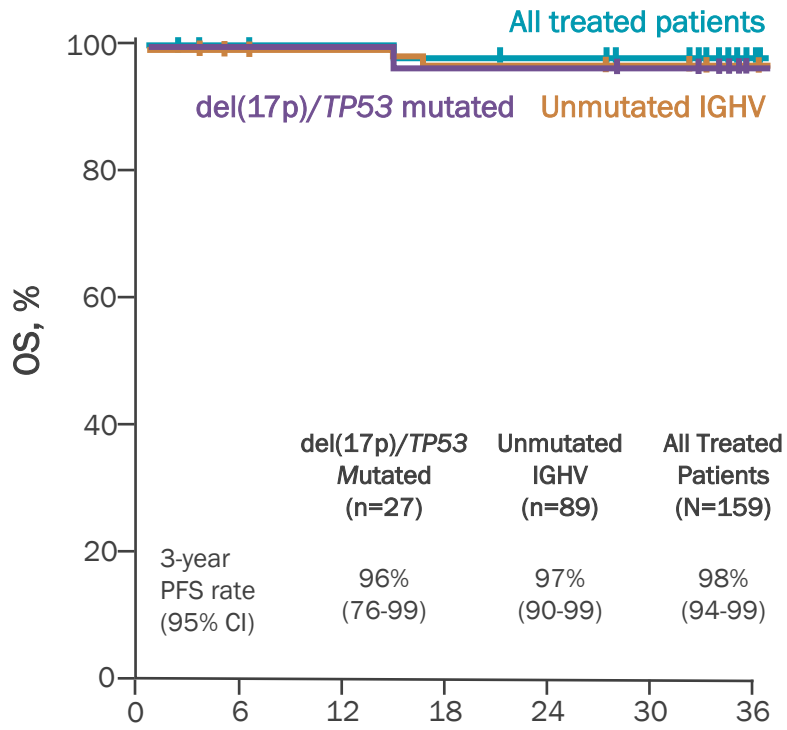
Progression-Free Survival[a]



	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

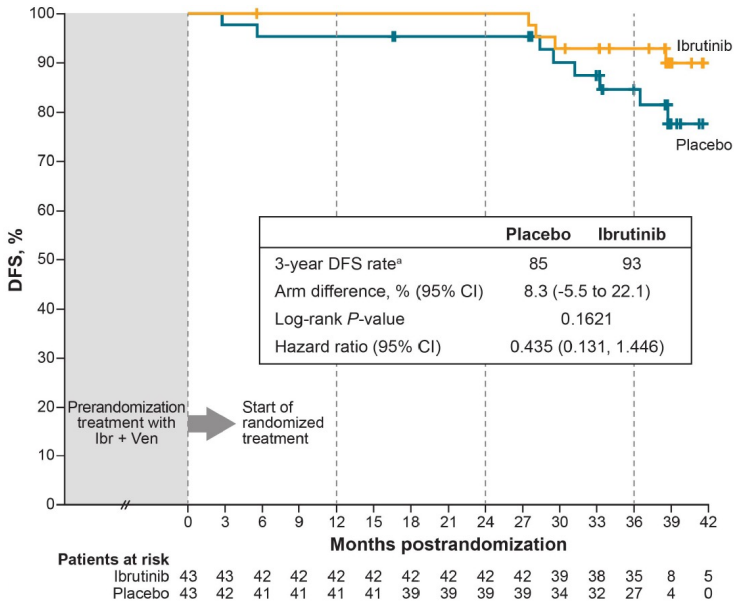
[a] Due to rapid enrollment in the study, the number of patients at risk drops substantially between 36 and 39 months. The Kaplan-Meier curves have therefore been truncated at 38 months due to instability of the curves.

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

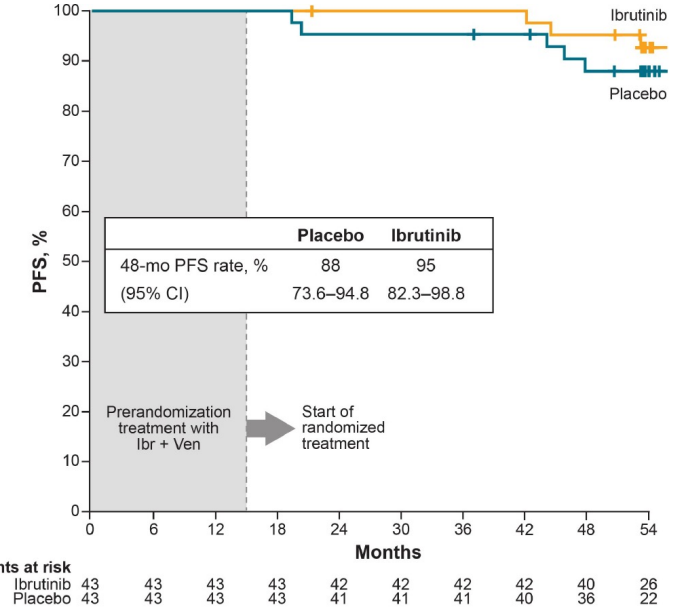
CAPTIVATE MRD Cohort: Phase 2 Study of Ibrutinib-Venetoclax

Disease-Free and Progression-Free Survival

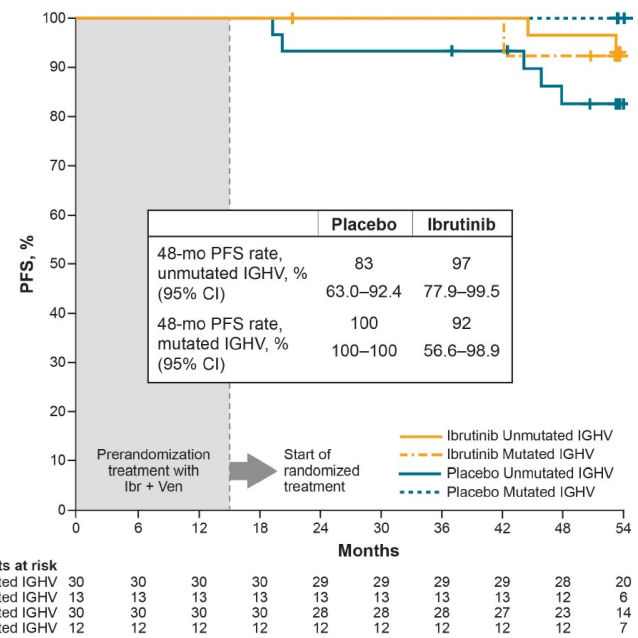
Disease-Free Survival



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.

Retreatment Data From CAPTIVATE: 3-yr Update

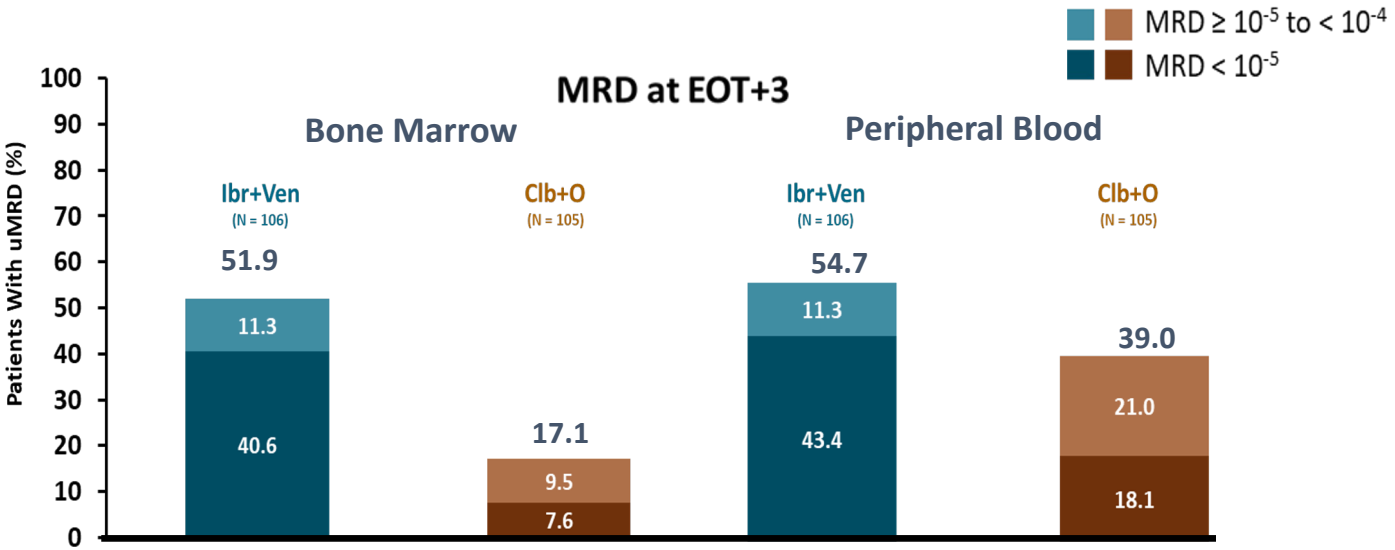
Patient	Baseline High-Risk Features[a]				Response to FD Ibr + Ven[a]		Response to Retreatment with Ibr as of April 2022
	del(17p)	*TP53* mutated	uIGHV	Complex karotype	PFS (months)	Best response	
1	No	No	Yes	No	36.5	CR	PR
2	No	No	Yes	Yes	27.6	CR	PR
3	Yes	No	No	No	28.5	CRi	PR
4	No	No	No	Yes	30.4	PR	PR
5	No	No	No	No	27.4	PR	PR
6	No	No	No	Yes	22.0	PR	PR
7	No	No	Yes	Yes	38.6	CR	PR-L
8	No	No	Yes	Yes	38.6	PR	PR
9	Yes	No	Yes	Yes	16.6	PR	PR
10	No	No	Yes	No	39.6	PR	SD
11	No	No	Yes	Unknown	38.6	CR	PR
12	No	No	Yes	Yes	38.6	CR	Unavailable

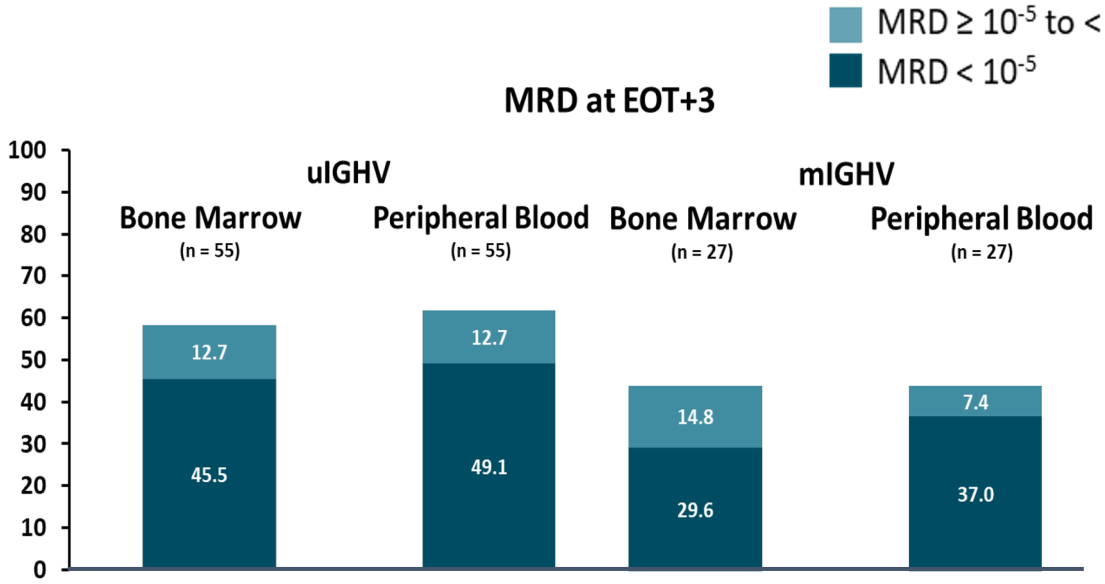
[a]*Data per 04 Aug 2021 data cut.*

- As of April 2022, 12 patients with PD after FD ibrutinib + venetoclax were retreated with ibrutinib monotherapy
  - Best response to FD ibrutinib + venetoclax ranged from PR to CR
  - Duration of single-agent ibrutinib retreatment ranged from 6 to 32 mo
  - 11 of 12 patients were evaluable for response
    - PR (n = 9);
    - PR-L (n = 1);
    - SD (n = 1)

Wierda et al, ASCO 2022

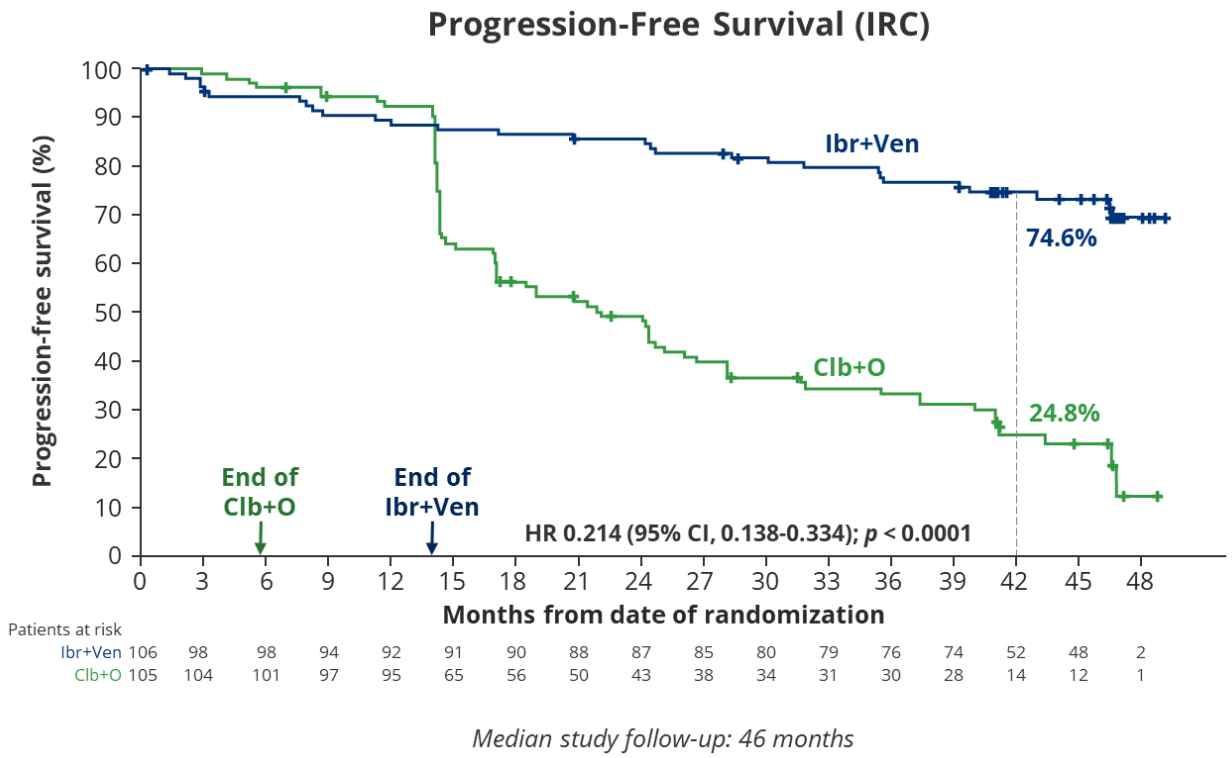
GLOW: MRD at EOT+3 by IgHV status



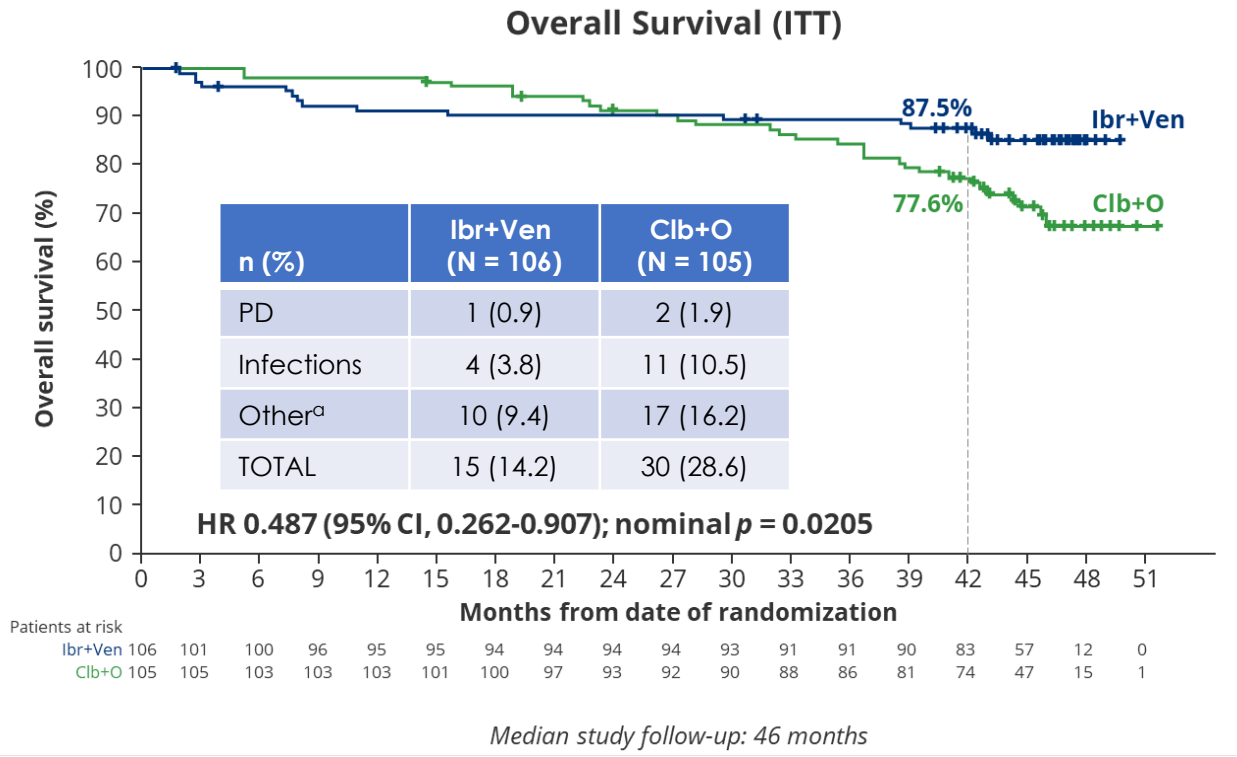


Munir, ASH 2021.

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

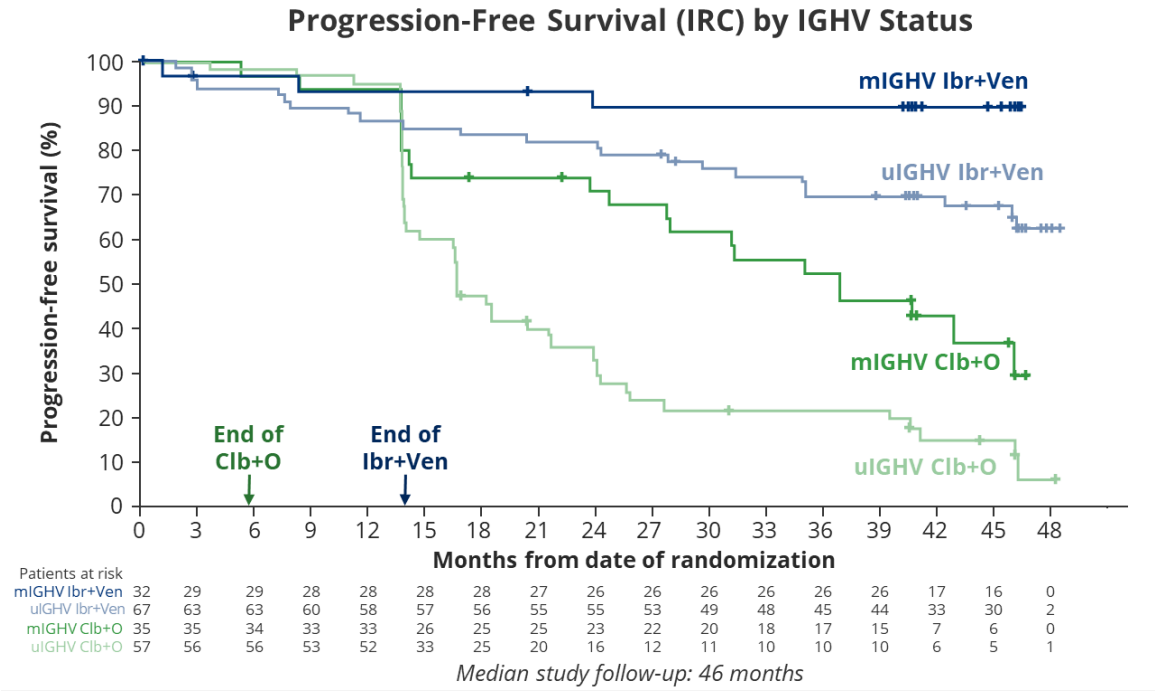
Overall Survival:

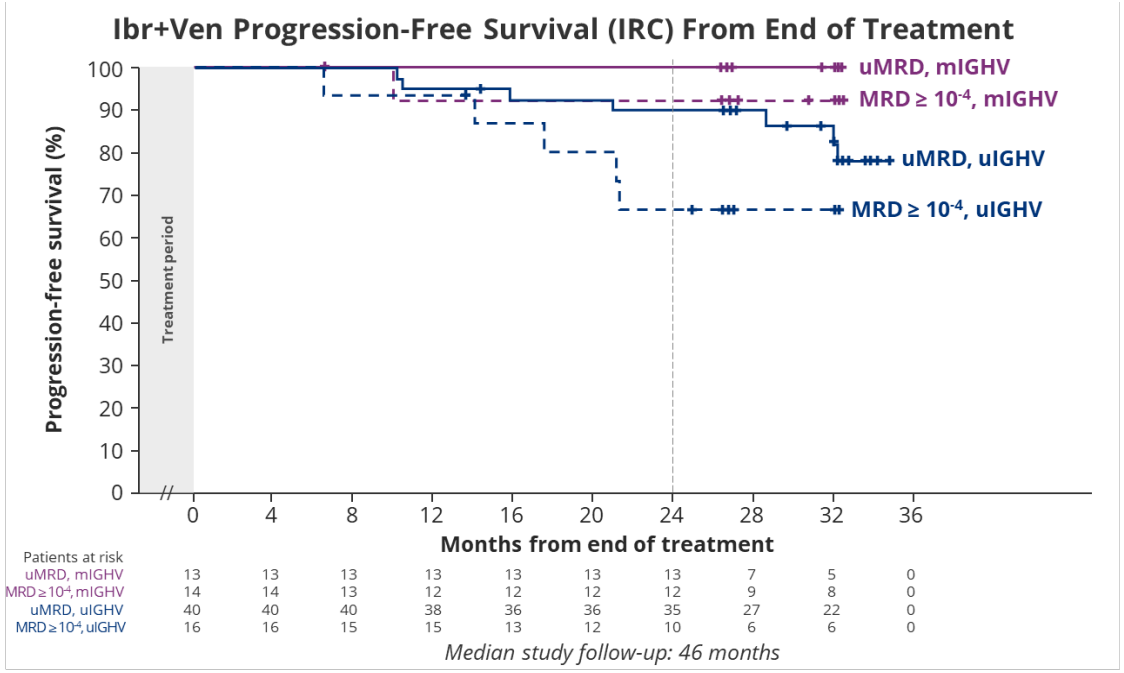
- In the Clb+O arm, 39/41 patients requiring subsequent treatment received a BTKi or venetoclax
- The majority of deaths in the Clb+O arm occurred while off any treatment
- More infection-related deaths were seen in the Clb+O arm

Niemann, et al., ASH 2022;

GLOW: PFS by IGHV Mutational Status/MRD

(Elderly/Unfit, 12-mo Fixed Duration)





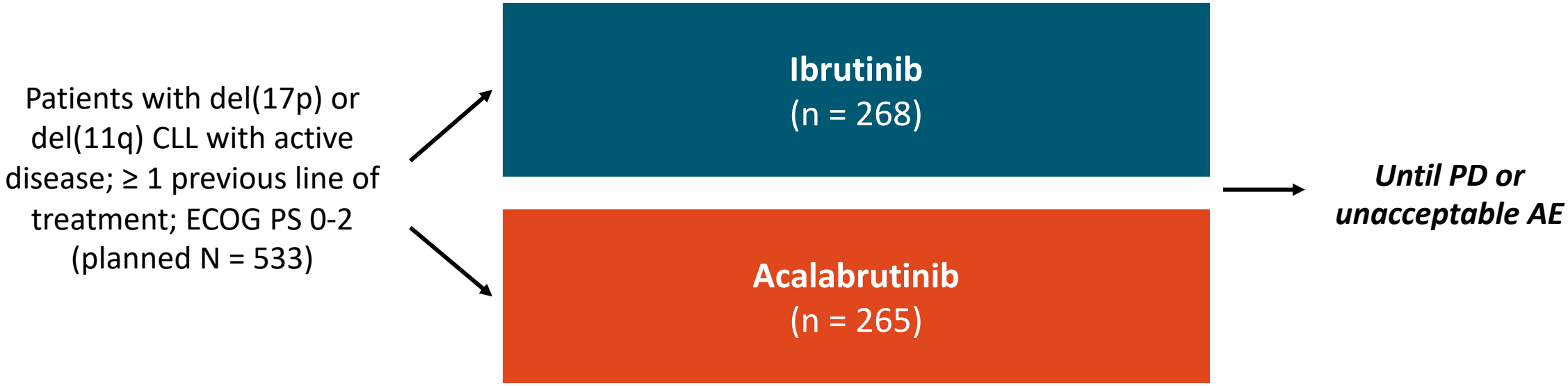
- Impact of IGHV status on PFS was more pronounced with Clb+O
- > 90% of patients in the I+V arm did not require subsequent treatment at 3.5 years:
  - 91.5% for uIGHV
  - 93.5% for mIGHV

- 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

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

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

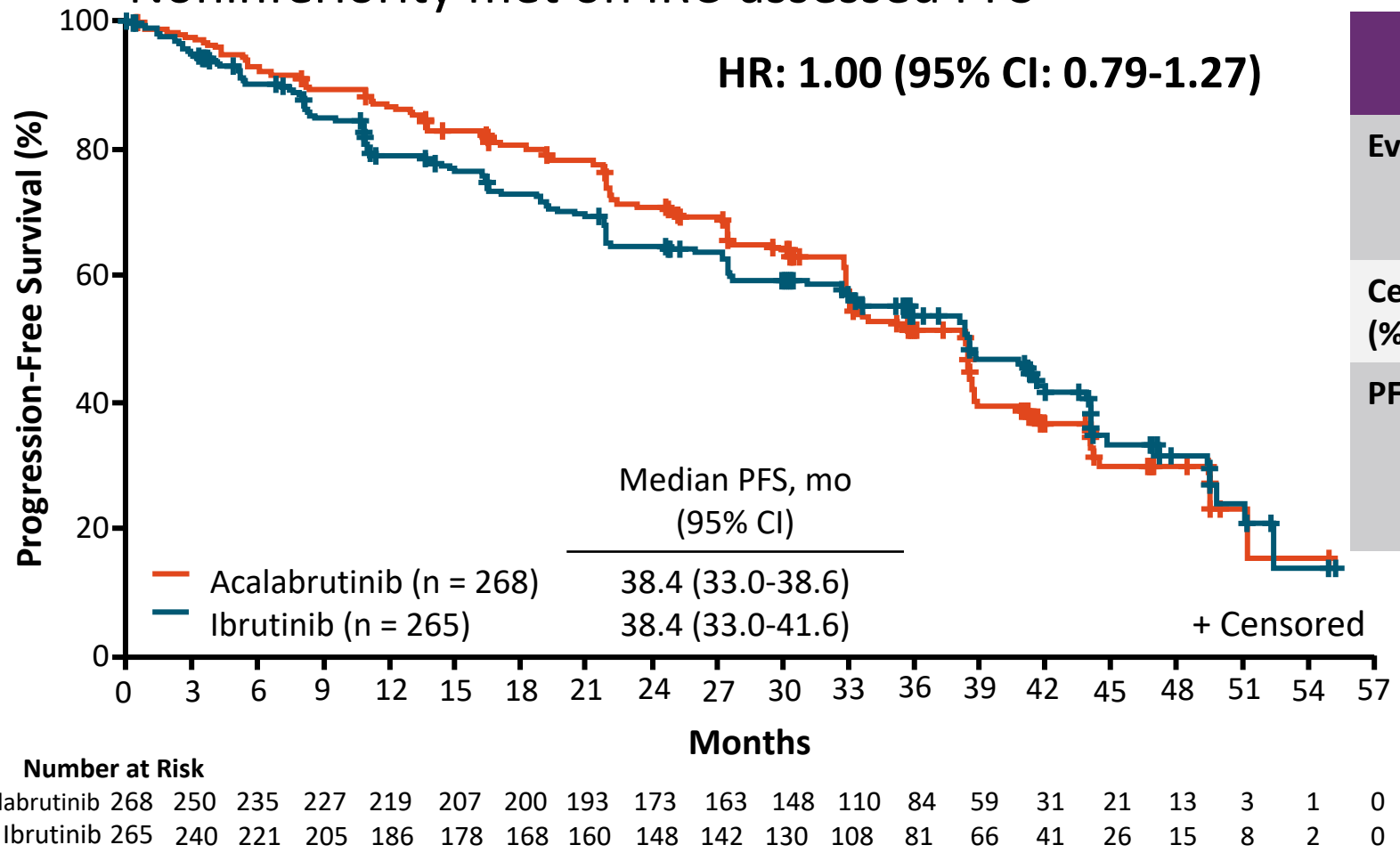


- Primary endpoint: PFS
- Secondary endpoints: OS; incidence of treatment-emergent AEs, atrial fibrillation; Richter's transformation; grade ≥3 infections
- FPI October 2015 – LPI November 2017 (25 mo)
- Final analysis: 279 IRC PFS events, data cutoff 9/2020

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

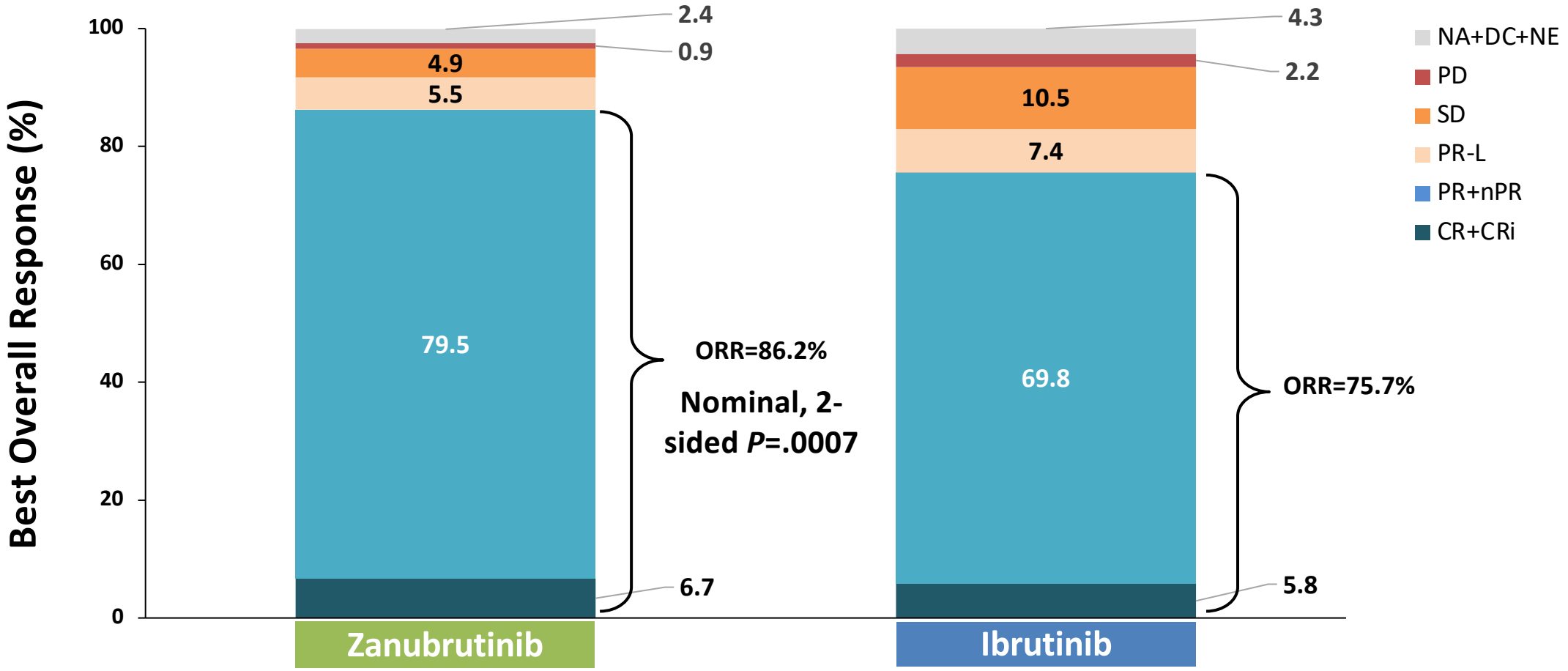
Byrd. ASCO 2021.

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.

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.

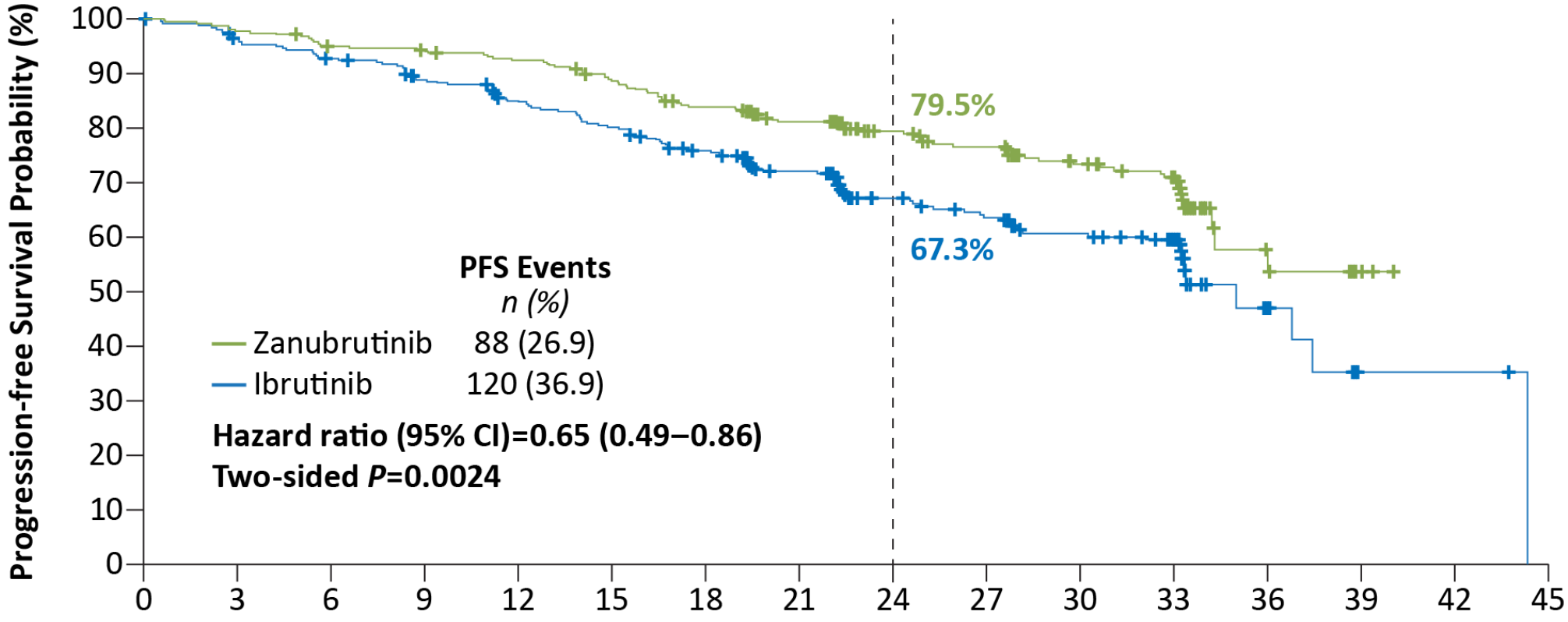
Data cutoff: 8 Aug 2022

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



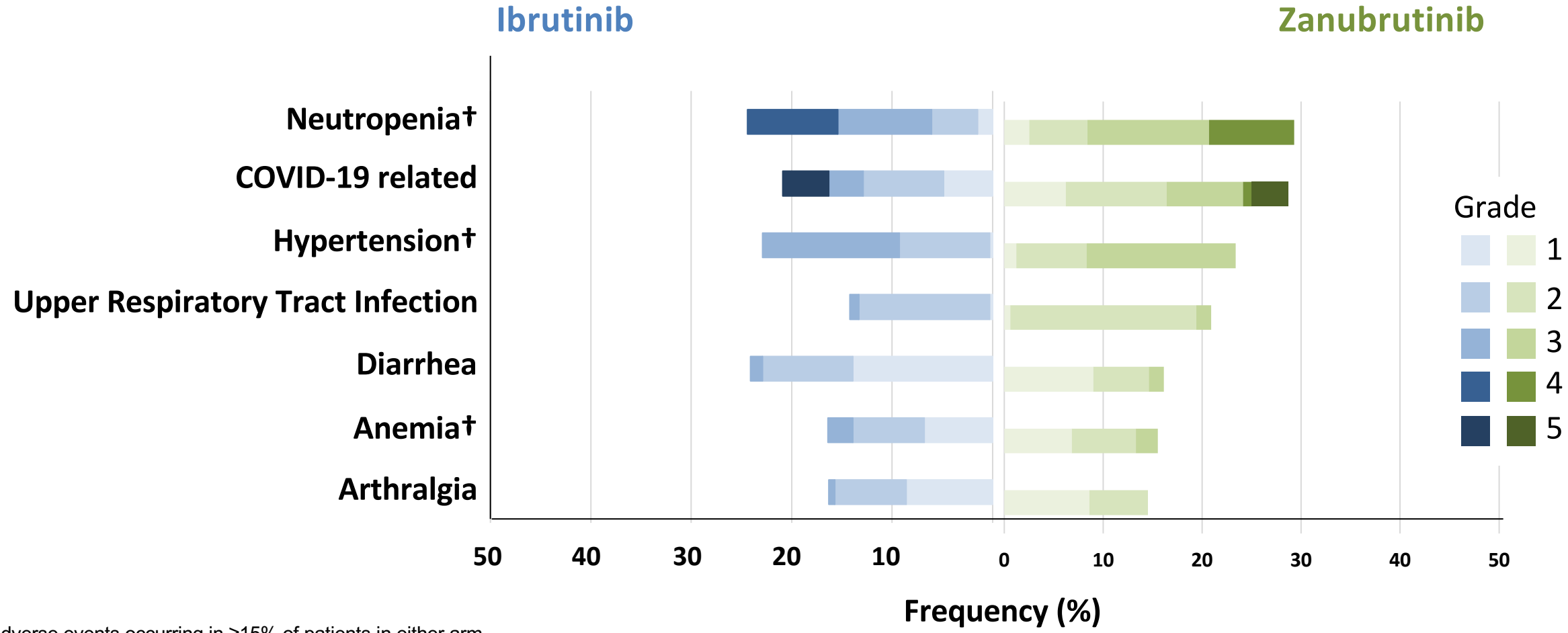
No. at Risk																
Zanubrutinib	327	315	304	301	294	280	263	226	172	161	125	113	14	2	0	
Ibrutinib	325	305	293	277	260	246	228	191	133	123	98	87	9	2	2	0

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)

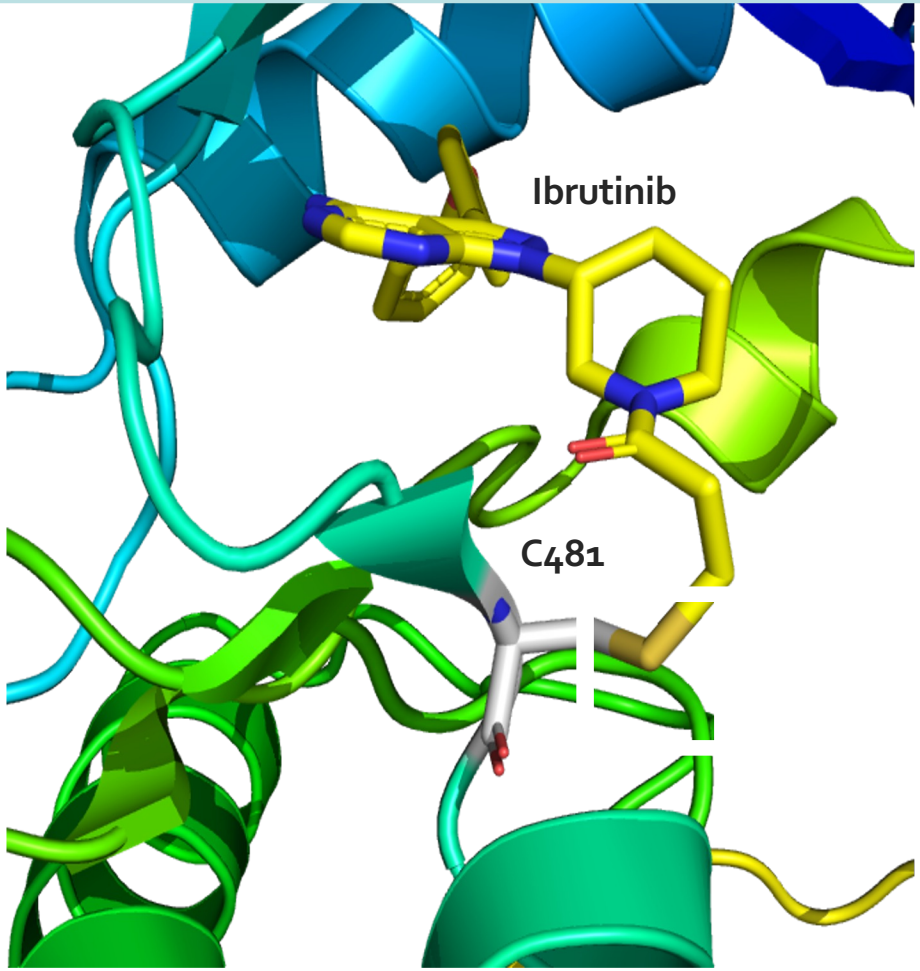
Data cutoff: 8 Aug 2022

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

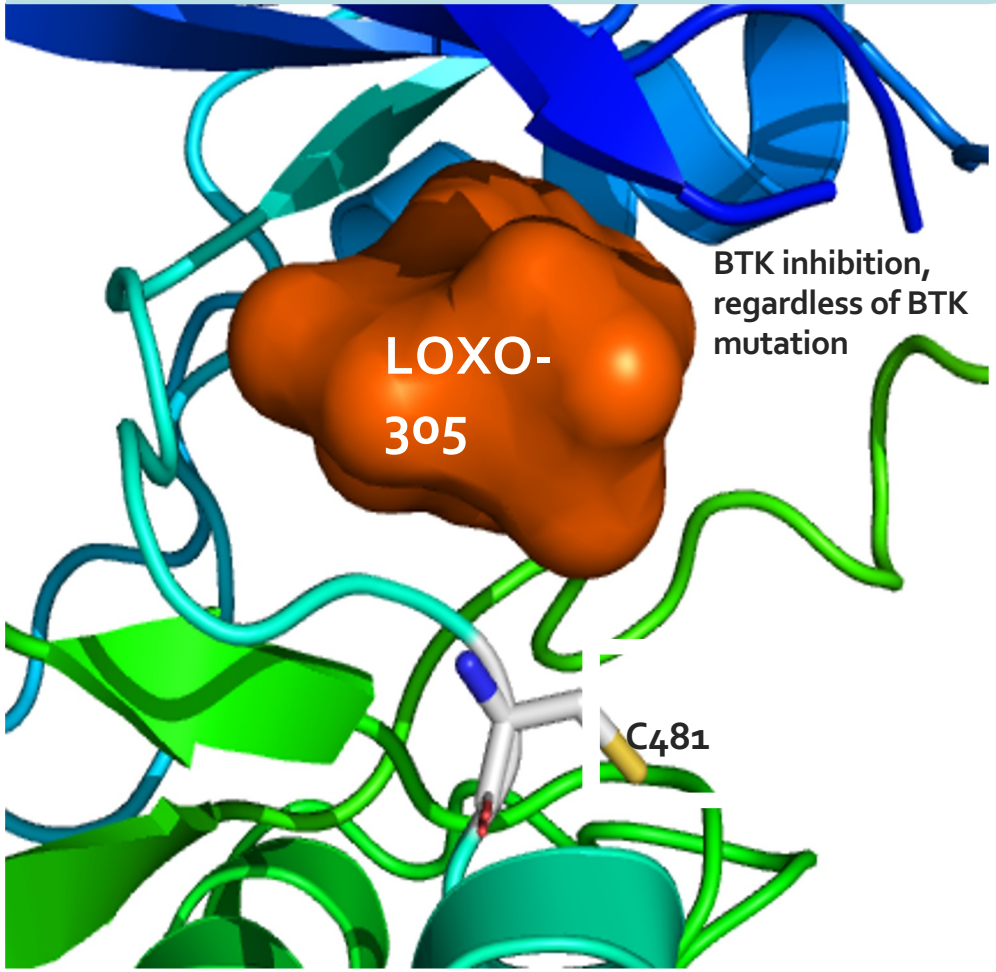
Brown et al. NEJM, December 2022

Brown et al. ALPINE ASH 2022

Covalent BTK inhibitors (ibrutinib, acalabrutinib, zanubrutinib) require WT BTK for activity

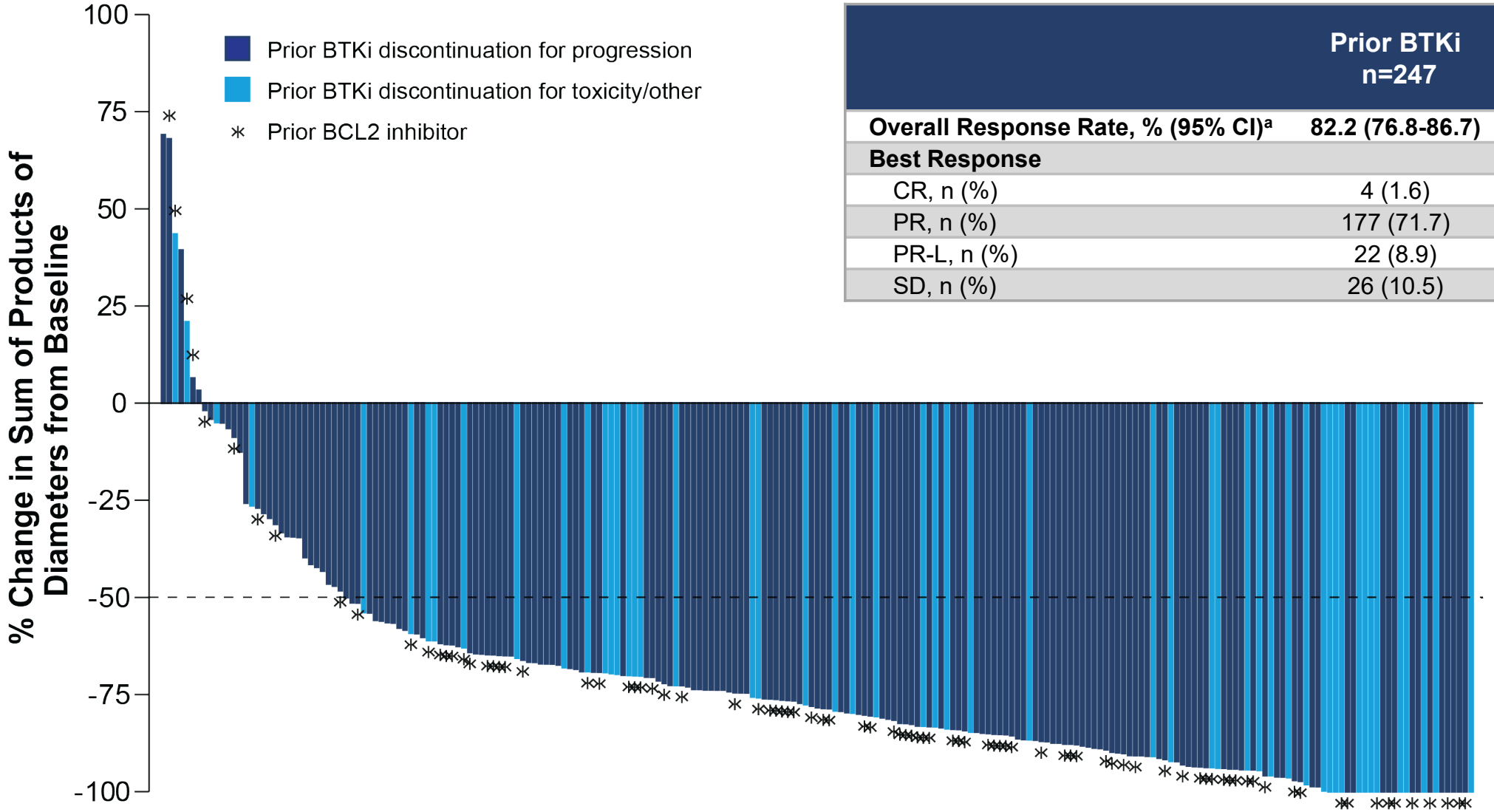


LOXO-305 is a non-covalent BTK inhibitor that is potent against both WT and C481-mutant BTK



Mato et al ASH 2022

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

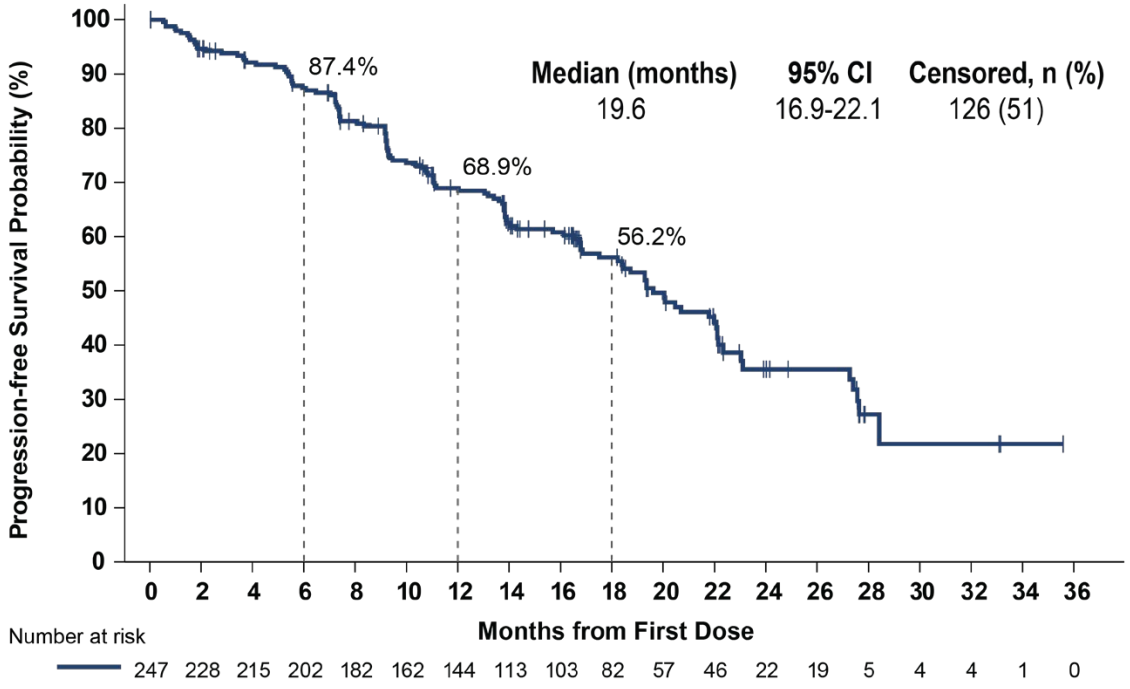


	Prior BTKi n=247	Prior BTKi+BCL2i n=100
Overall Response Rate, % (95% CI)[a]	**82.2 (76.8-86.7)**	**79.0 (69.7-86.5)**
Best Response		
CR, n (%)	4 (1.6)	0 (0.0)
PR, n (%)	177 (71.7)	70 (70.0)
PR-L, n (%)	22 (8.9)	9 (9.0)
SD, n (%)	26 (10.5)	11 (11.0)

Mato et al ASH 2022

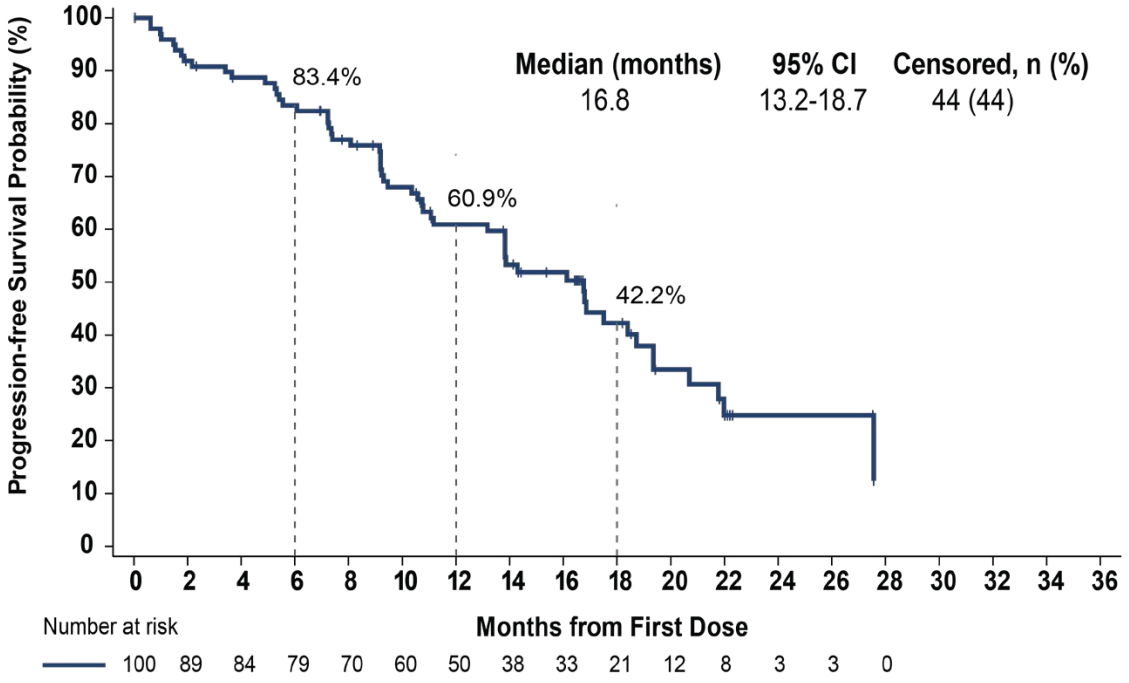
Progression-Free Survival in CLL/SLL Patients who Received Prior BTKi Treatment

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

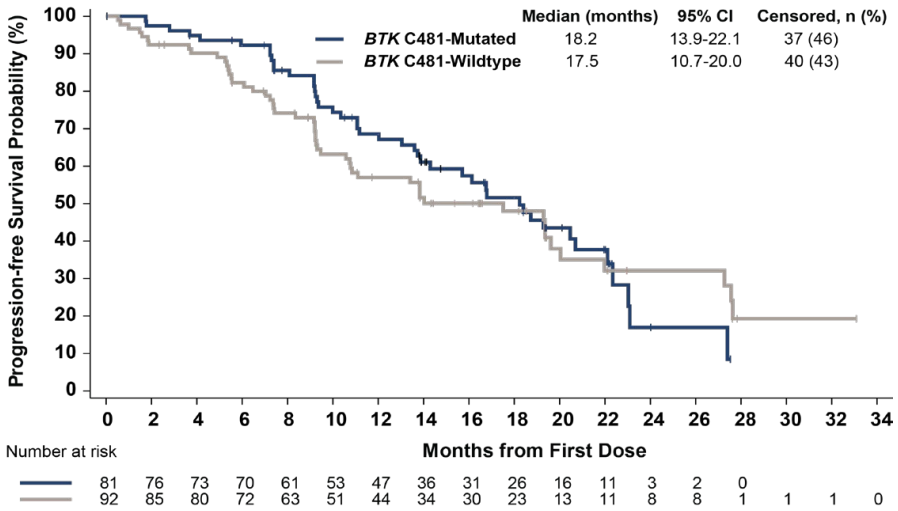


- Median follow-up of 18.2 months for patients who received prior BTKi and BCL2i

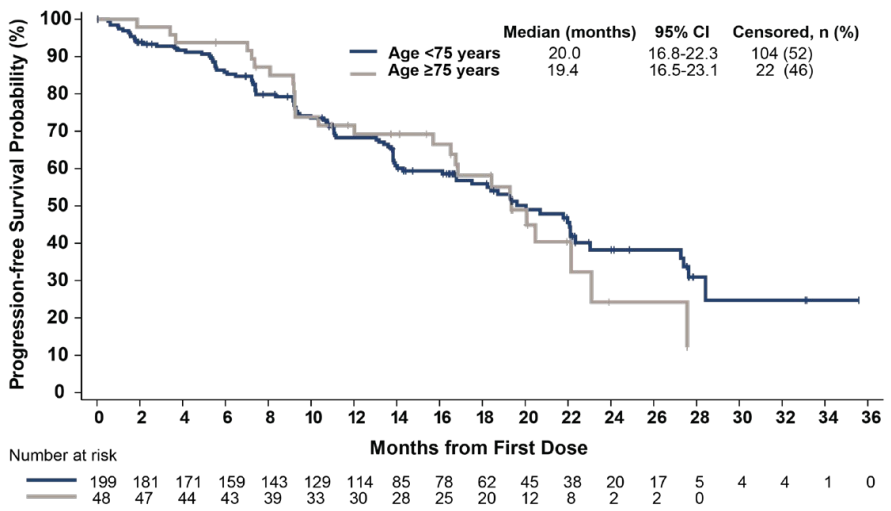
Mato et al ASH 2022

Progression-Free Survival in CLL/SLL Subgroups

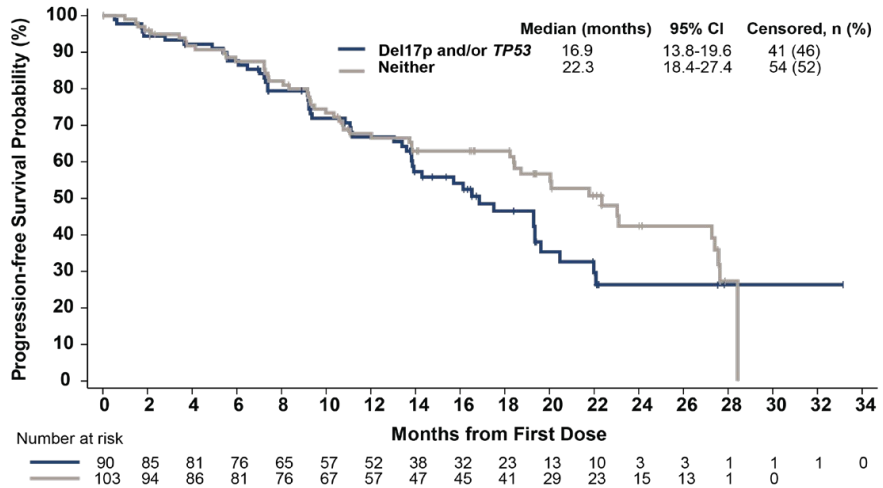
BTK C481 mutation status[a,b]



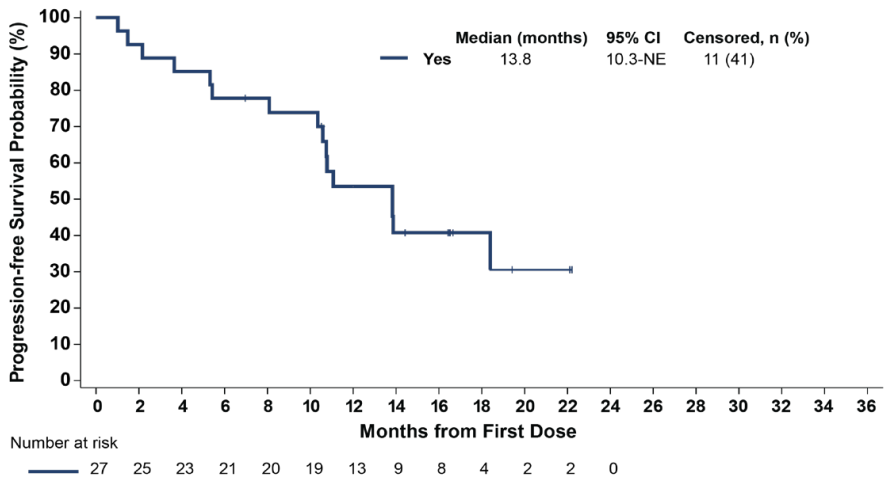
Age



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

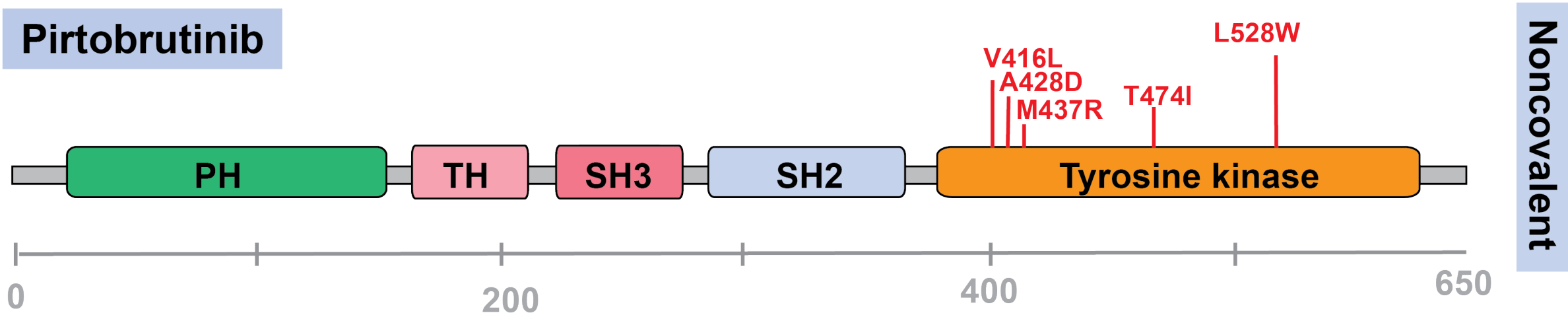


Prior BTKi, CIT, BCL2i, and PI3Ki therapy



Mato et al ASH 2022

Diverse BTK mutations cause resistance to non- covalent BTKi



Montoya et al ASH 2022

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

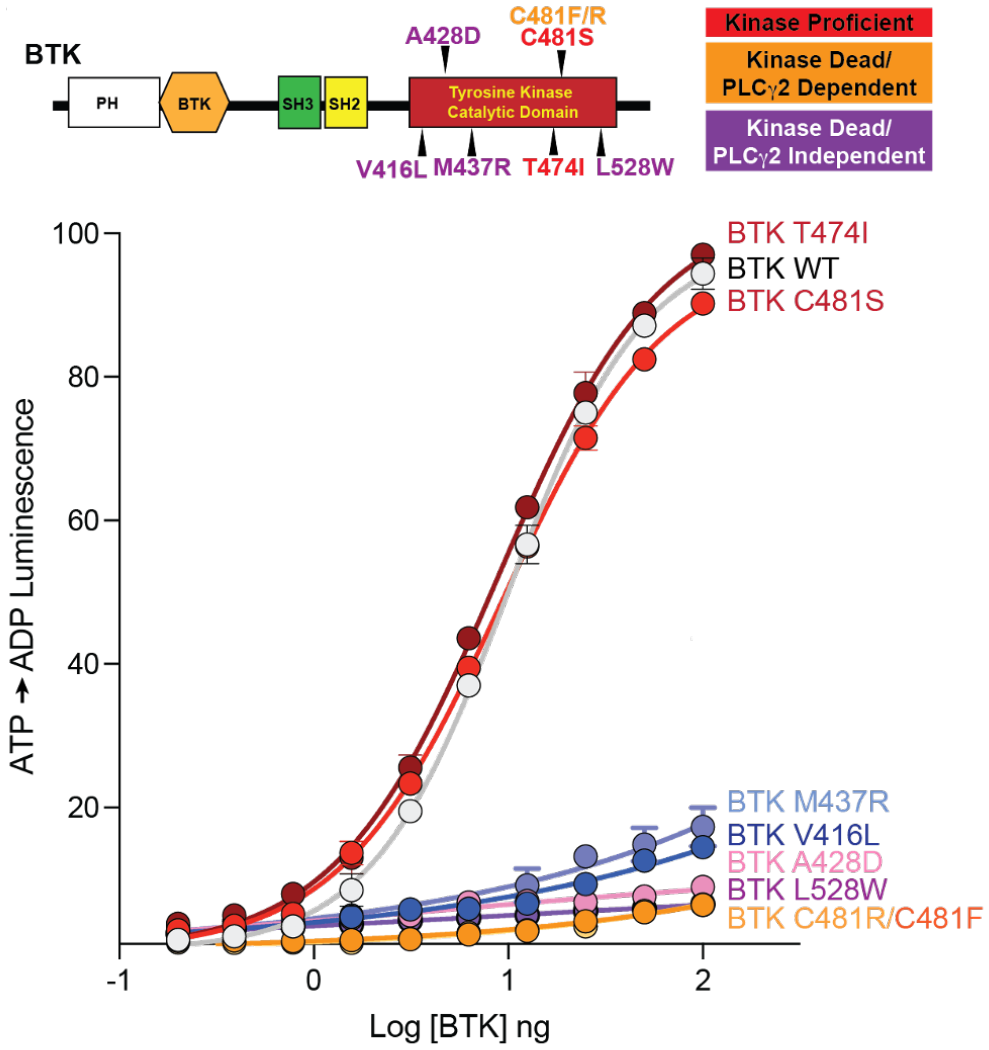
	Number of patients carrying the mutations			
	Ibrutinib-treated patients (n = 24)	Zanubrutinib-treated patients (n =13)	Total	*P*
Cys481 codon mutations	24	10	34	.03
Leu528Trp	1	7	8	.001

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.

Not All BTK Mutations Are Equal: Concept of Kinase-Dead Mutations



Montoya et al ASH 2022

- C481S mutations retain the kinase activity of BTK and can be successfully targeted with non-covalent BTK inhibitors like pirtobrutinib
- On the other hand, mutations such as L528W will lead to a kinase dead (or PLCγ2 independent) BTK that acts as a scaffold protein for other components of the BCR pathway.
- Both covalent and non-covalent BTKi that target the kinase domain will be ineffective in this setting.

A First-in-Human Trial of NX-2127, a BTK Degrader, in R/R CLL and B-Cell Malignancies

R/R CLL (N=17)
≥ 2 prior line of therapy (median 6),
100% post BTKi, 77% post Ven

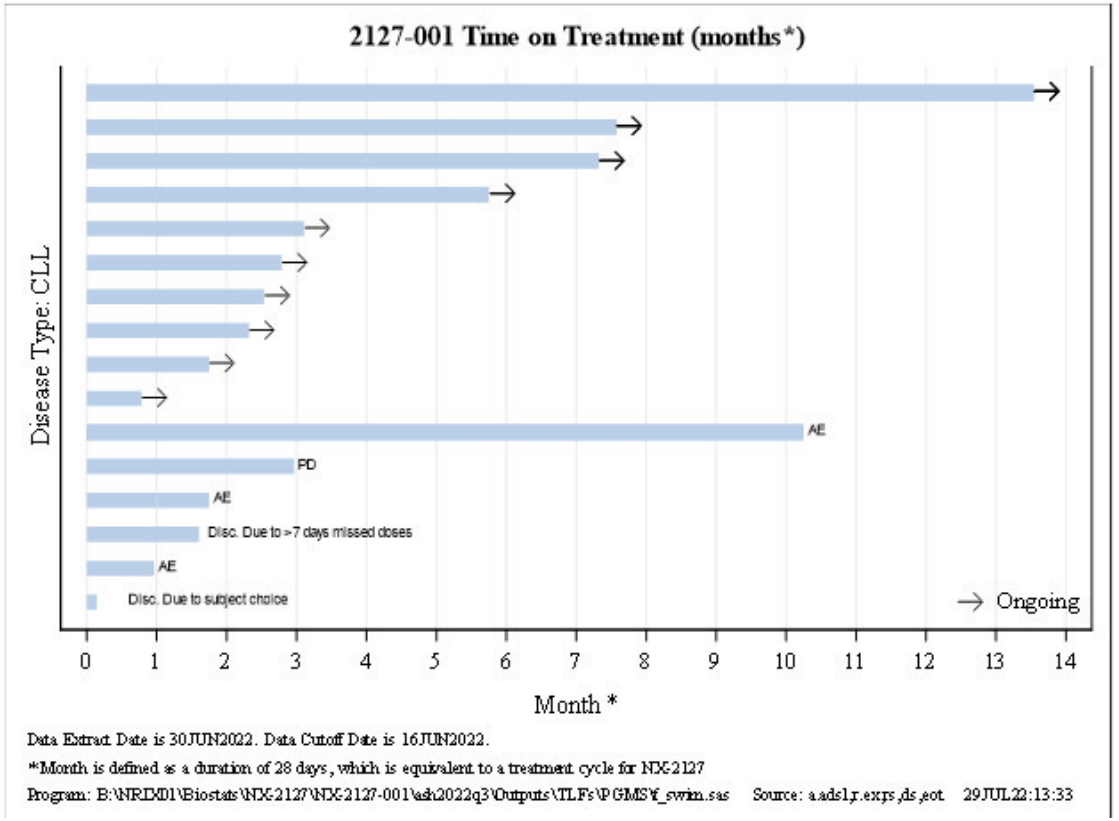
NX-2127
Dose escalation: 100, 200, 300 mg orally daily

Tolerability, Safety, Preliminary Efficacy

Table 1. Summary of treatment-emergent adverse events (TEAEs) occurring in >15% of all patients (including patients with CLL and NHL)

Preferred Term	All Grades (N=26)	Grade ≥ 3 (N=26)	Grade ≥ 3 Related (N=26)
Any AE	25 (96%)	15 (58%)	12 (46%)
Fatigue	16 (62%)	0 (0%)	0 (0%)
Neutrophil Count Decrease	10 (39%)	9 (35%)	9 (35%)
Anemia	7 (27%)	4 (15%)	2 (8%)
Contusion	7 (27%)	0 (0%)	0 (0%)
Hypertension	7 (27%)	1 (4%)	1 (4%)
Dyspnoea	5 (19%)	1 (4%)	0 (0%)
Pruritis	5 (19%)	0 (0%)	0 (0%)
Rash maculo-papular	5 (19%)	0 (0%)	0 (0%)
Blood creatinine increased	4 (15%)	0 (0%)	0 (0%)
COVID-19	4 (15%)	1 (4%)	0 (0%)
Diarrhea	4 (15%)	0 (0%)	0 (0%)
Petechiae	4 (15%)	0 (0%)	0 (0%)
Platelet count decreased	4 (15%)	1 (4%)	0 (0%)

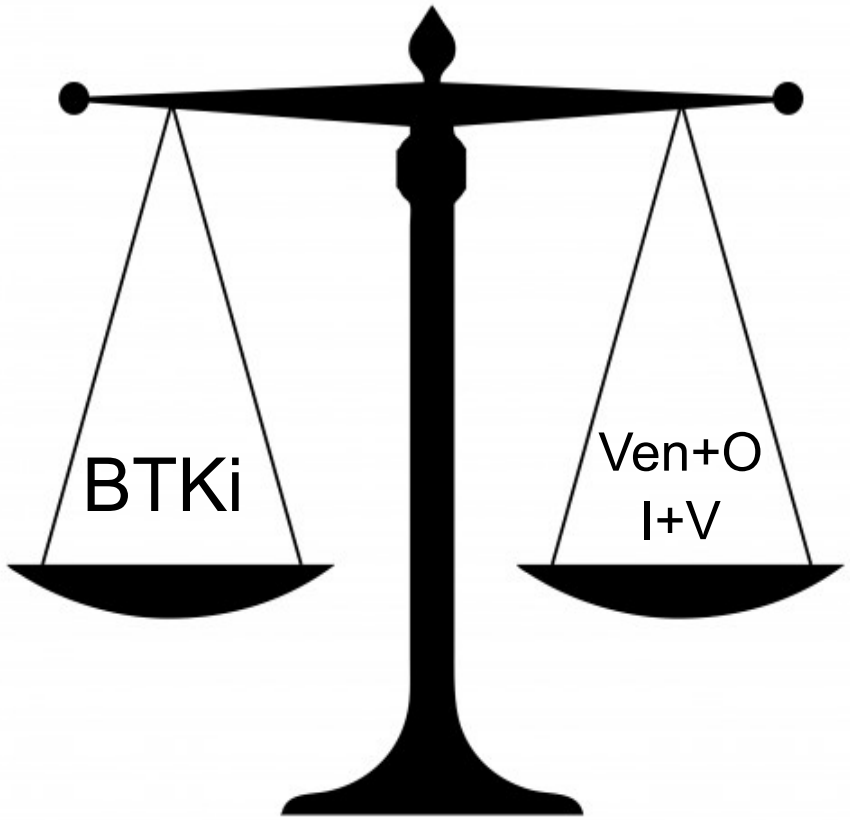
Figure 1. CLL patient disposition



Mato et al. ASH 2022, A#965

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 time-limited therapy
- Less concern with long-term adherence
- Potential for cost-savings if 1 year of therapy is durable
- Less financial toxicity
- Low risk dx/high risk
- BM and LN based disease: cytopenias.
- Younger age
- Possibility of retreatment

- **Prolong PFS after MRD negative**

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.