New developments in CLL

Javier Pinilla-Ibarz, MD, PhD.

Senior Member

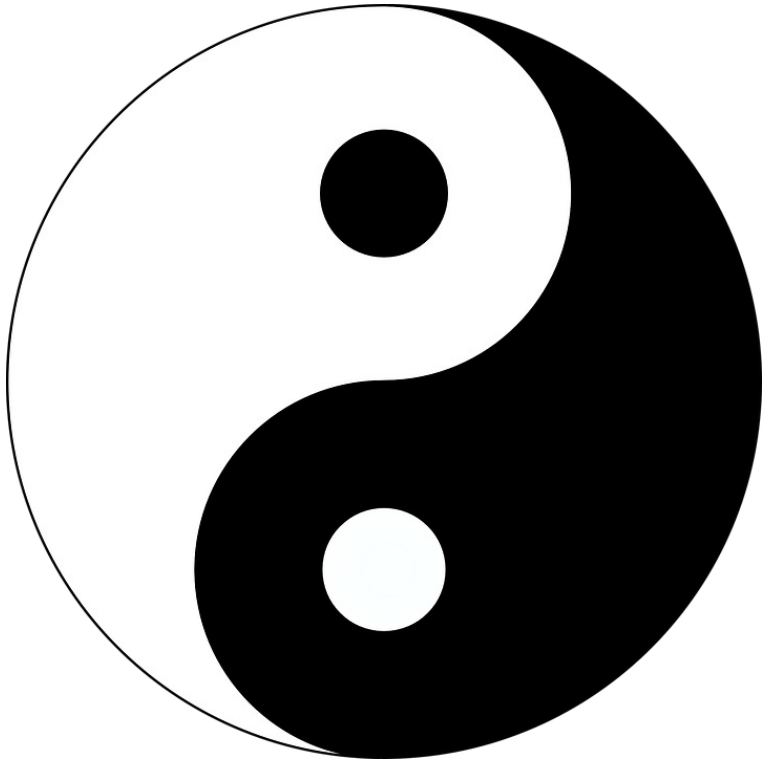
Head of Lymphoma section and

Director of Immunotherapy

Malignant Hematology Department

MOFFITT CANCER CENTER

The dilemma continue between long term therapy vs fixed duration

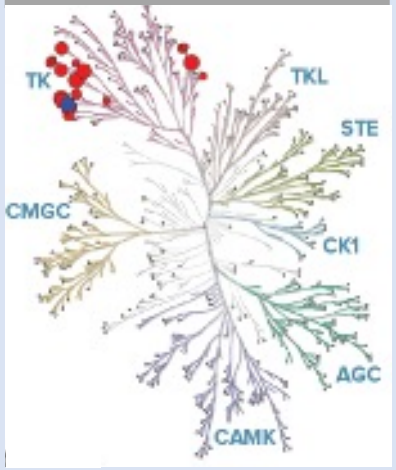


Author’slide

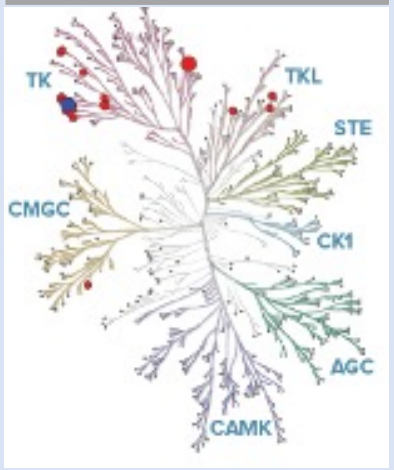
Several Covalent BTKi to Consider With Differences in BTKi Specificity, MOA, and Potential for Off-Target Effects

Covalent

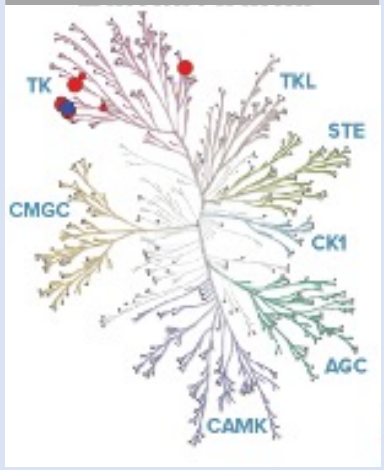
Ibrutinib[1]

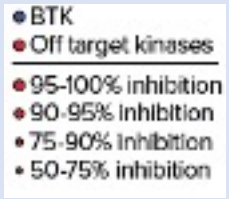


Acalabrutinib[1]



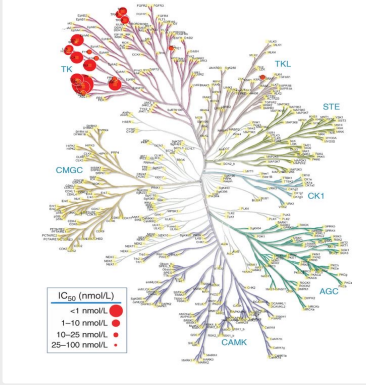
Zanubrutinib[1]



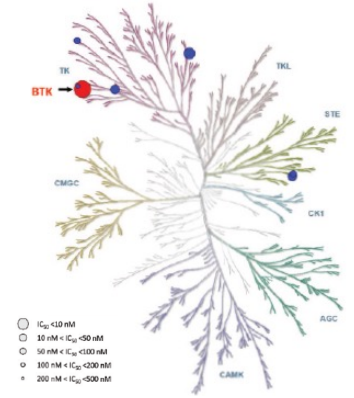


Noncovalent

Nemtabrutinib[2]



Pirtobrutinib[3]



1. Shadman M, et al. *Lancet Haematol*. 2023;10(1):e35-e45. 2. Reiff SD, et al. *Cancer Discov*. 2018;8(10):1300-1315.
3. Brandhuber B, et al. SOHO 2018. Abstract CLL-200.

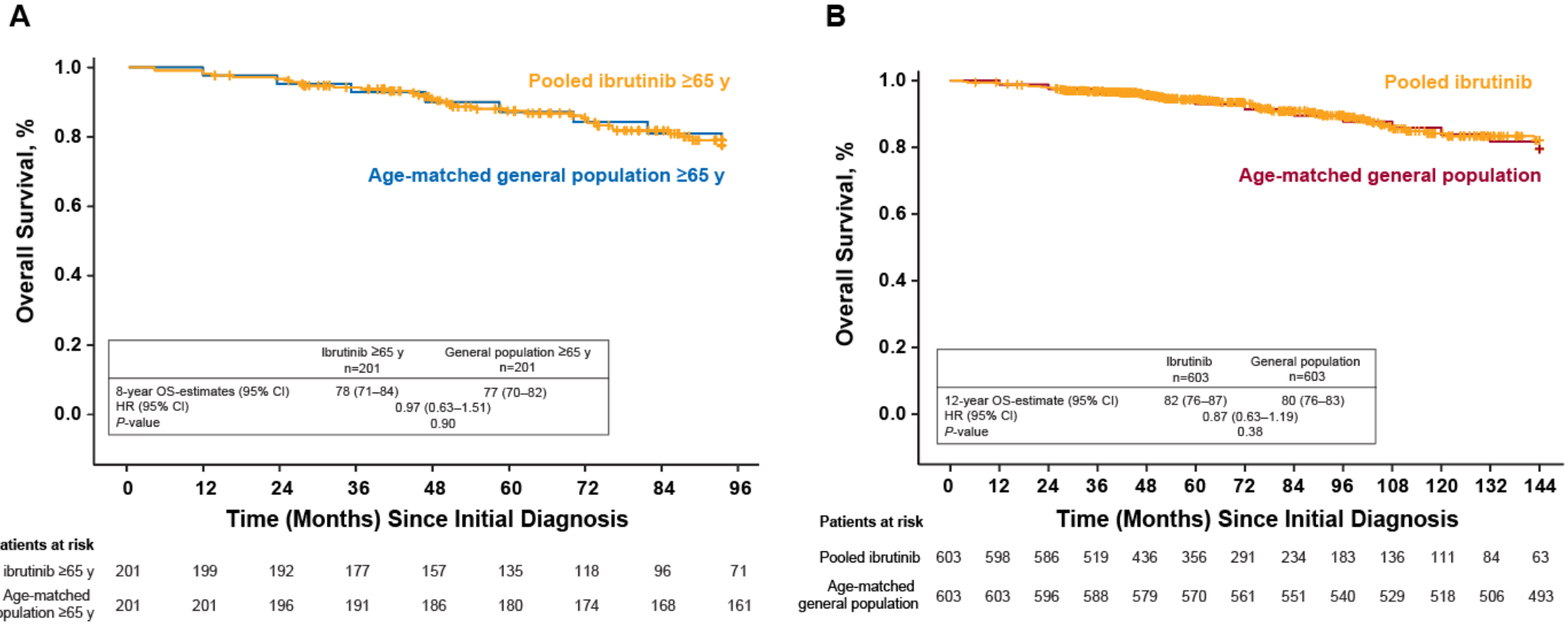
Key Clinical Trials of 1st-Generation BTKi Ibrutinib in TN CLL

RESONATE-2[1]	iLLUMINATE[2]	ECOG E1912[3-4]	Alliance (A041202)[5]
• Aged ≥65 years • Non-del(17p) • **Ibrutinib vs Clb** • With up to 7 years of follow-up, median PFS was not reached vs 15.0 months • 6.5-year PFS: 61% vs 9% • 6.5-year PFS by *IGHV* status – Mut: 67% vs 18% – Unmut: 62% vs 2% • 6.5-year PFS by del(11q) status – With: 60% vs 0% – Without: 67% vs 13%	• Aged >65 years or ≤65 years with comorbidities • **Ibrutinib + G vs Clb + G** • With a median follow-up of 31.3 months, median PFS was significantly longer with Ibr+G vs Clb+G (NR vs 19.0 months; HR 0.23; *P*<0.0001) • 30-month PFS was 79% vs 31%	• Aged >70 years • Non-del(17p) • **Ibrutinib + R (IR) vs FCR** • With a median follow-up of 70 months, 5-year PFS was 78% vs 51%, respectively (*P*<0.0001) • PFS with IR vs FCR was statistically significant in *IGHV*mut (HR 0.27, *P*=0.001) and -unmut (HR 0.27, *P*<0.001) patients • 5-year OS was 95% vs 89%, respectively (*P*=0.018)	• Aged ≥65 years • **BR (Arm 1) vs Ibr (Arm 2) vs Ibr + R (Arm 3)** • With a median follow-up of 55 months, median PFS was 44 months with Arm 1 and not reached with the others – Arm 2 vs 1: HR 0.36, 95% CI 0.26-0.52, *P*<0.0001 – Arm 3 vs 1: HR 0.36, 95% CI 0.25-0.51, *P*<0.0001 – Arm 3 vs 2: HR 0.99, 95% CI 0.66-1.48, *P*=0.96 • There were no significant differences in OS among the arms (*P*=0.49)

1. Barr PB, et al. ASCO 2021. Abstract 7523. 2. Moreno C, et al. *Lancet Oncol.* 2018;20(1):P43-56. 3. Shanafelt TD, et al. ASH 2019. Abstract 33. 4. Shanafelt TD, et al. *Blood*. 2022;140(2):112-120. 5. Woyach JA, et al. ASH 2021. Abstract 639.

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., ASH 2022; No. #1809

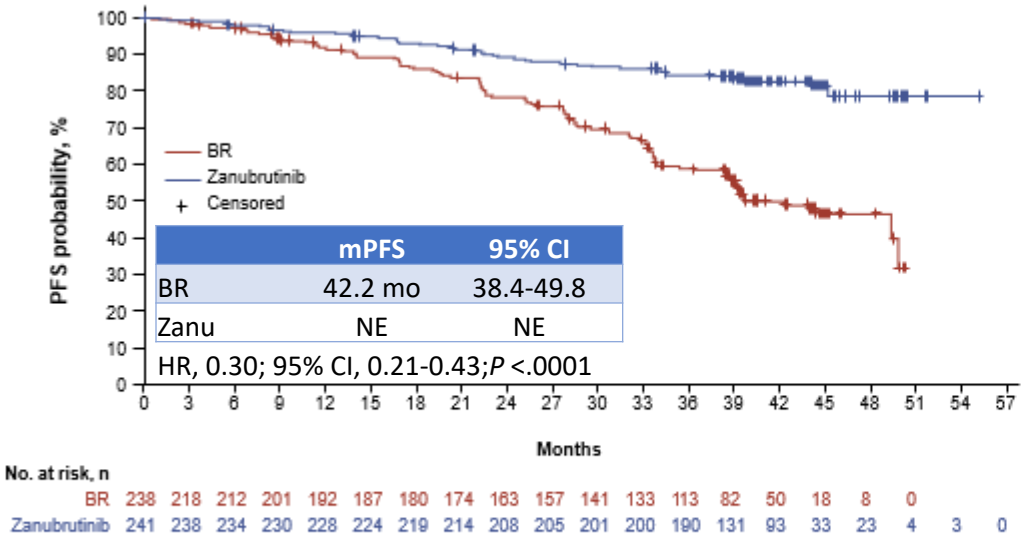
Key Phase 3 Clinical Trials of 2nd-Generation BTKi in TN CLL

Acalabrutinib: ELEVATE-TN[1,2]	Zanubrutinib: SEQUOIA[3,4]
• Aged ≥65 years, or younger with CIRS score >6 or CrCl <70 mL/min; del(17p) included • Arms – **Acalabrutinib vs** – **Acalabrutinib + Obin vs** – **Clb + O** • Improved PFS with acalabrutinib ± O – Median PFS (median follow-up: 58.2 months) was significantly longer for A-arms vs Clb+O (NR vs 27.8 months) • A+O vs Clb+O: HR 0.11 (95% CI, 0.07-0.16) • A vs Clb+O: HR: 0.21 (95% CI, 0.15-0.30) – Estimated 60-month PFS: 84% and 72% for A+O and A	• Aged ≥65 years or unsuitable for FCR • Non-del(17p) arms – **Zanubrutinib vs** – **BR** • Del(17p) arms – **Zanubrutinib** • Improved PFS with zanubrutinib – Median PFS (median follow-up: 43.7 months) was significantly longer for zanubrutinib vs BR (NR vs 42.2 months; HR 0.30 [95% CI, 0.21-0.43]; *P*<.0001) – Estimated 42-month PFS: 82.4% vs 50.0% for zanubrutinib vs BR

1. Sharman JP, et al. ASCO 2022. Abstract 7539. 2. Sharman JP, et al. *Leukemia.* 2022;36(4):1171-1175.
3. Tam CS, et al. *Lancet Oncol.* 2022;23(8):1031-1043. 4. Munir T, et al. EHA 2023. Abstract P639.

SEQUOIA: PFS

Overall Population



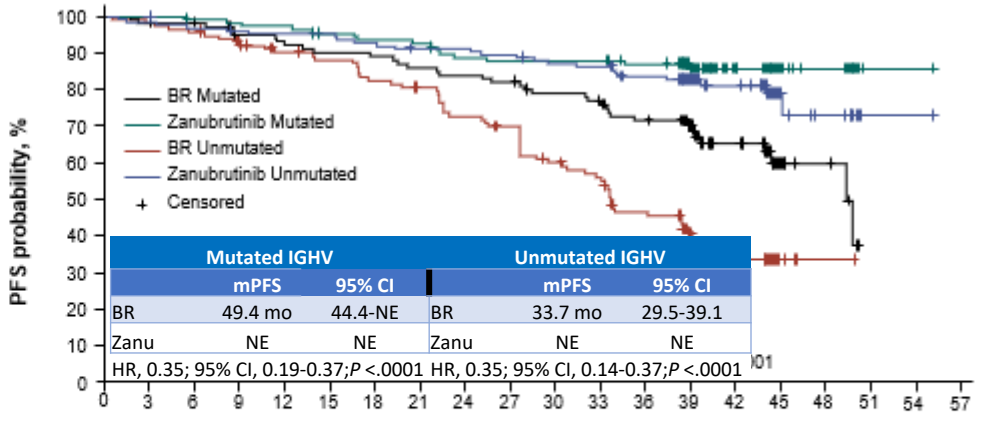
	mPFS	95% CI
BR	42.2 mo	38.4-49.8
Zanu	NE	NE

HR, 0.30; 95% CI, 0.21-0.43;*P* <.0001

No. at risk, n

BR	238	218	212	201	192	187	180	174	163	157	141	133	113	82	50	18	8	0	
Zanubrutinib	241	238	234	230	228	224	219	214	208	205	201	200	190	131	93	33	23	4	3	0

Overall Population: Mutated and Unmutated IGHV



Mutated IGHV			Unmutated IGHV		
	mPFS	95% CI		mPFS	95% CI
BR	49.4 mo	44.4-NE	BR	33.7 mo	29.5-39.1
Zanu	NE	NE	Zanu	NE	NE

HR, 0.35; 95% CI, 0.19-0.37;*P* <.0001 HR, 0.35; 95% CI, 0.14-0.37;*P* <.0001

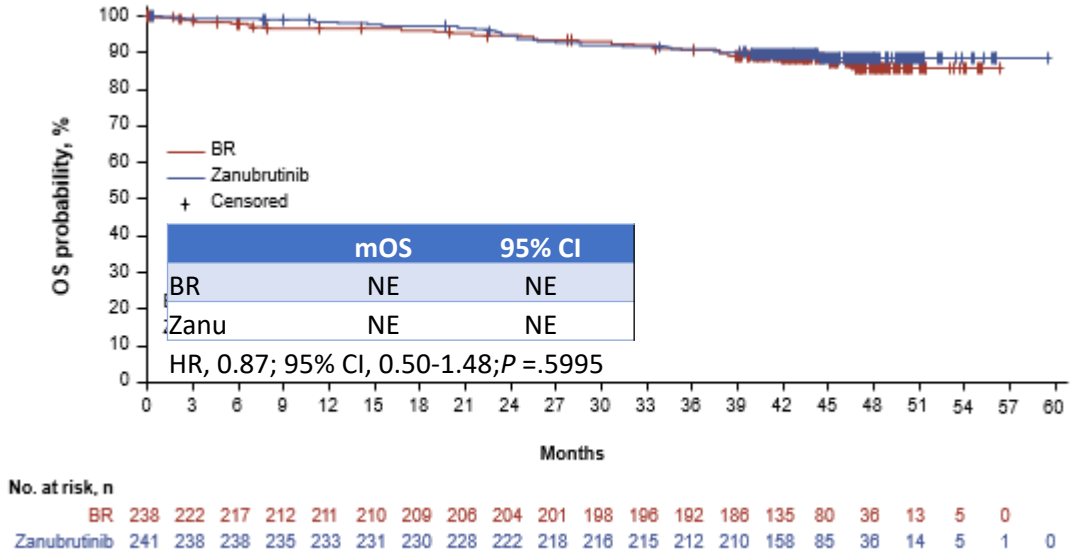
No. at risk, n

BR Mutated	110	101	99	94	91	89	88	85	83	81	76	73	67	53	31	14	7	0	
Zanubrutinib Mutated	109	109	107	106	105	101	99	98	93	92	92	92	89	63	43	18	13	1	1	0
BR Unmutated	121	110	107	101	95	92	86	83	75	71	60	55	43	26	17	4	1	0	
Zanubrutinib Unmutated	125	122	120	118	117	117	114	111	111	109	105	104	97	65	47	14	9	2	2	0

Munir, et al. Presented at EHA 2023

SEQUOIA: Survival Outcomes

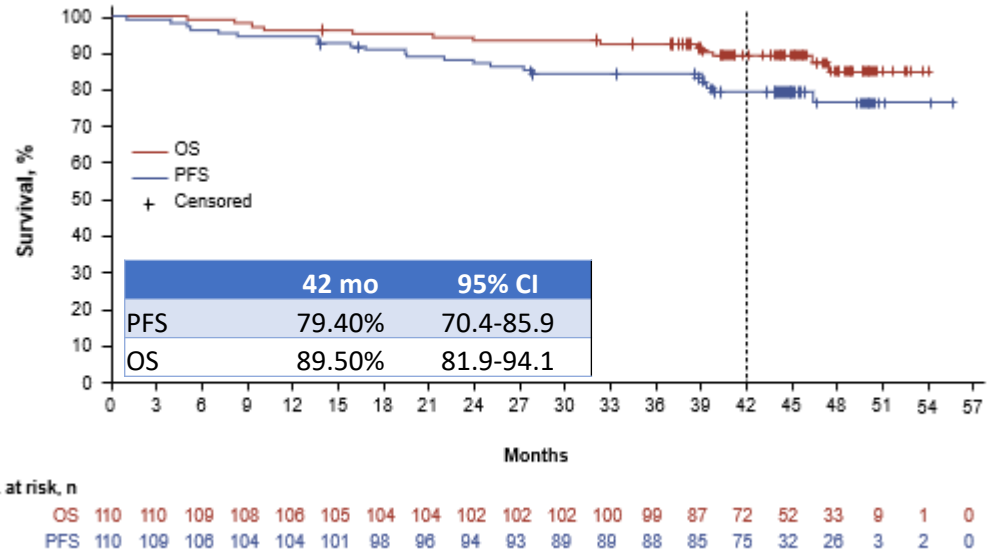
Overall Population



	mOS	95% CI
BR	NE	NE
Zanu	NE	NE

HR, 0.87; 95% CI, 0.50-1.48;*P* =.5995

PFS and OS: With del(17p)



	42 mo	95% CI
PFS	79.40%	70.4-85.9
OS	89.50%	81.9-94.1

Munir, et al. Presented at EHA 2023.

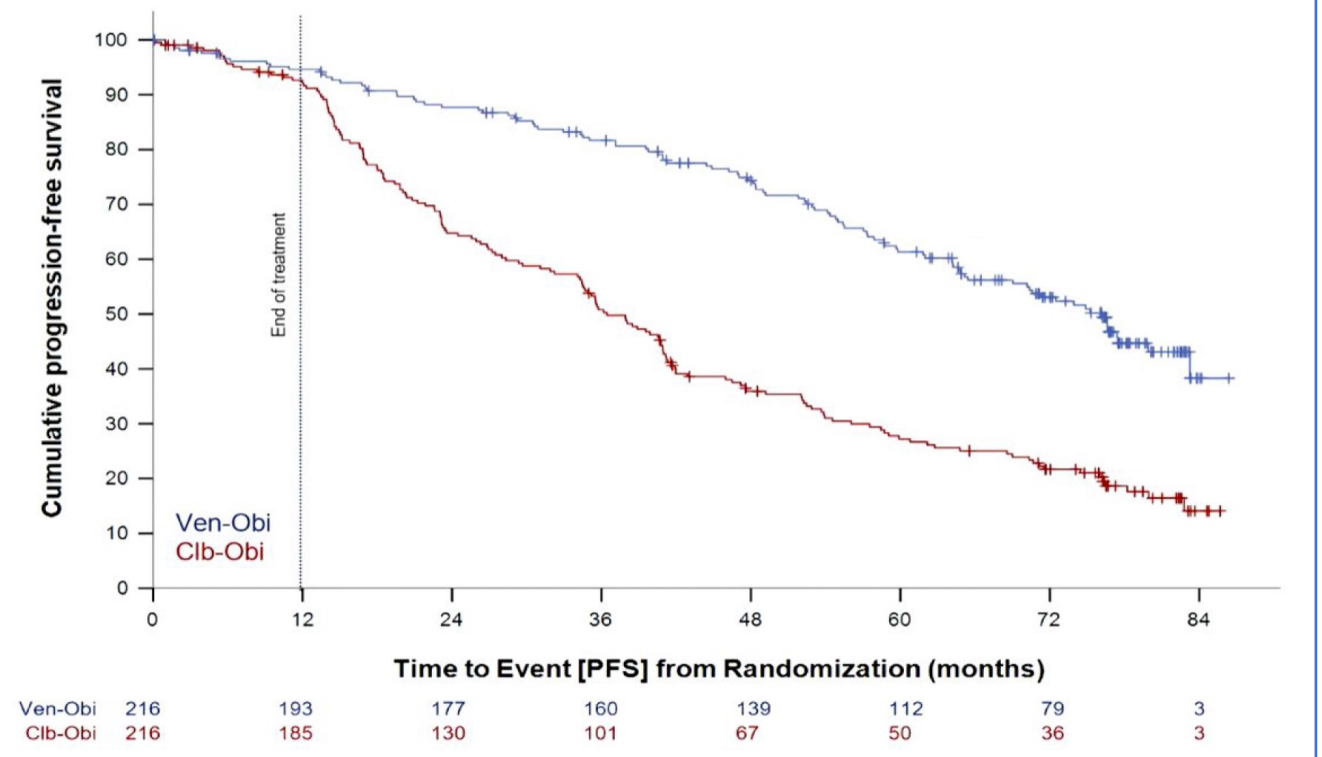
Fixed duration, doublets and triplets combinations

CLL14: Venetoclax. +Obinutuzumab in TN CLL

CLL14

- CIRS score >6 and/or CrCl <70 mL/min
- *TP53*mut/del(17p) included
- Arms
  - VenG vs
  - Clb + G
- **Median follow-up reached: 76.4 months**
- Median PFS: 76.2 vs 36.4 months
  - **6-year PFS: 53.1% vs 21.7%**
  - HR 0.40 (95% CI, 0.31-0.52); *P*<0.0001
- Median OS not reached
  - 6-year OS: 78.7% vs 69.2%
  - HR 0.69 (95% CI, 0.48-1.01); *P*=0.05

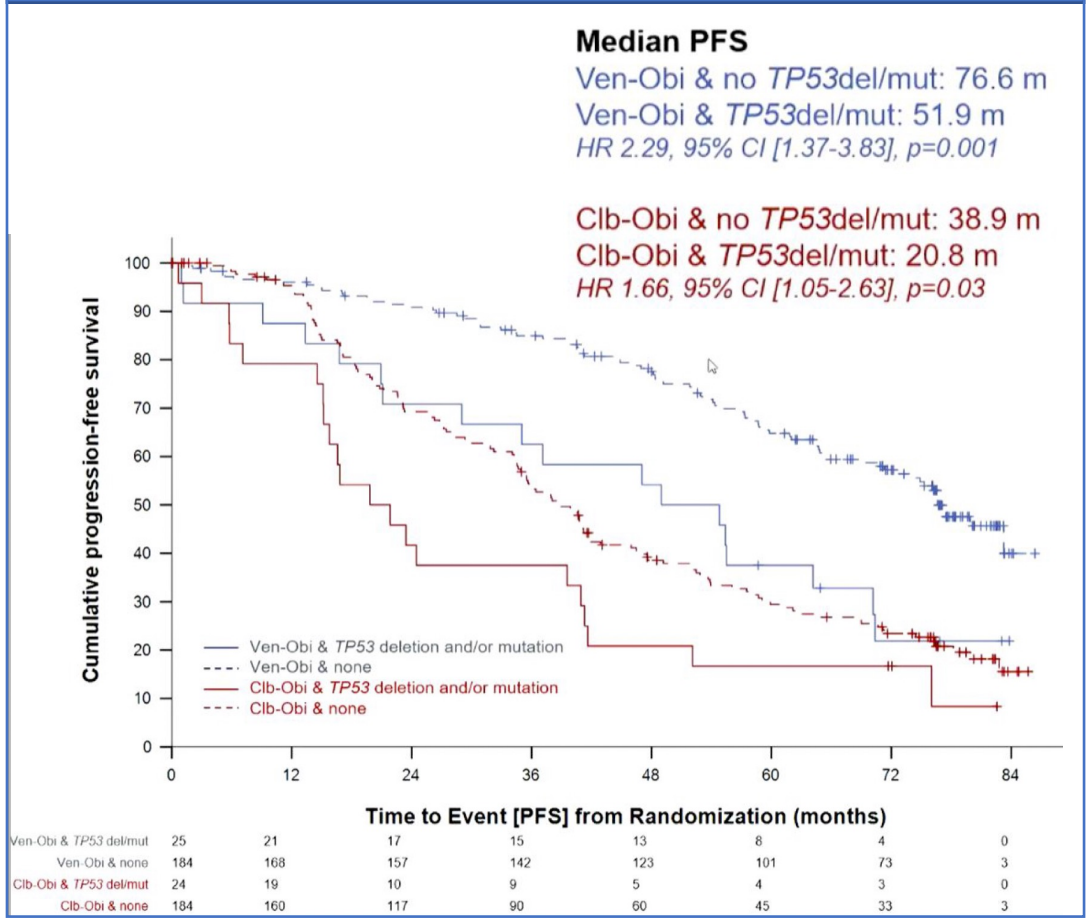
PFS



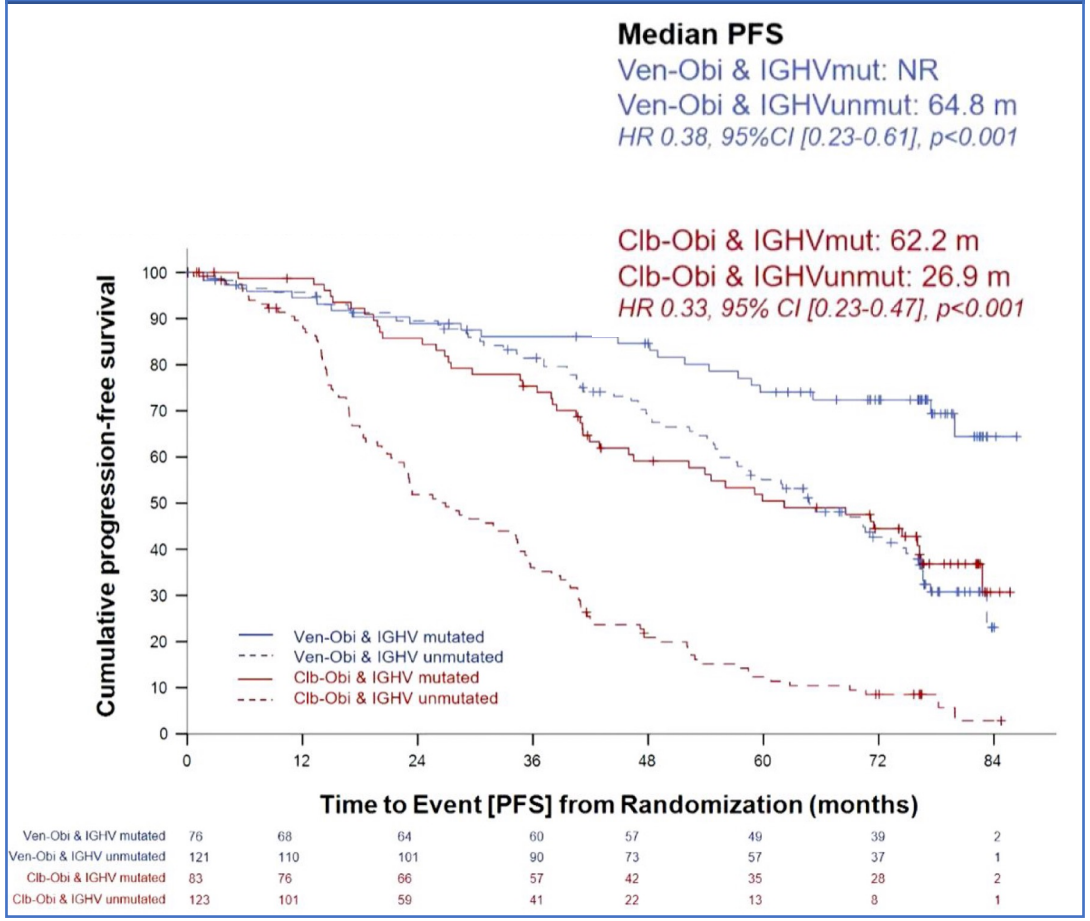
Al-Sawaf O, et al. EHA 2023. Abstract S145.

CLL14: PFS

PFS by *TP53* Status



PFS by *IGHV* Status



Al-Sawaf O, et al. EHA 2023. Abstract S145.

Ongoing Phase 2/3 Studies With BTKi Doublets for TN CLL

Ibrutinib + venetoclax (IV)

- IV in TN CLL (cohort 2) with high-risk features (phase 2, reported)[1-3]
- IV vs FCR in TN CLL without del(17p) or *TP53*mut (phase 2, ongoing)[4]
- **CAPTIVATE:** IV in TN CLL (FD and MRD-guided cohorts) (phase 2, reported)[5-7]
- **CLL17:** I vs IV vs VO in TN CLL[8] (ongoing)
- **GLOW:** IV vs G-Clb in TN CLL without del(17p) or *TP53*mut[9] (reported)

Acalabrutinib + venetoclax (AV)

- AO vs AV in TN CLL without del(17p), *TP53*mut, or complex karyotype (phase 2, ongoing)[10]
- AV in TN CLL in patients at high risk of infection (phase 2, ongoing)[11]
- **MAJIC:** AV vs VO in TN CLL (all-comers, ongoing)[12]

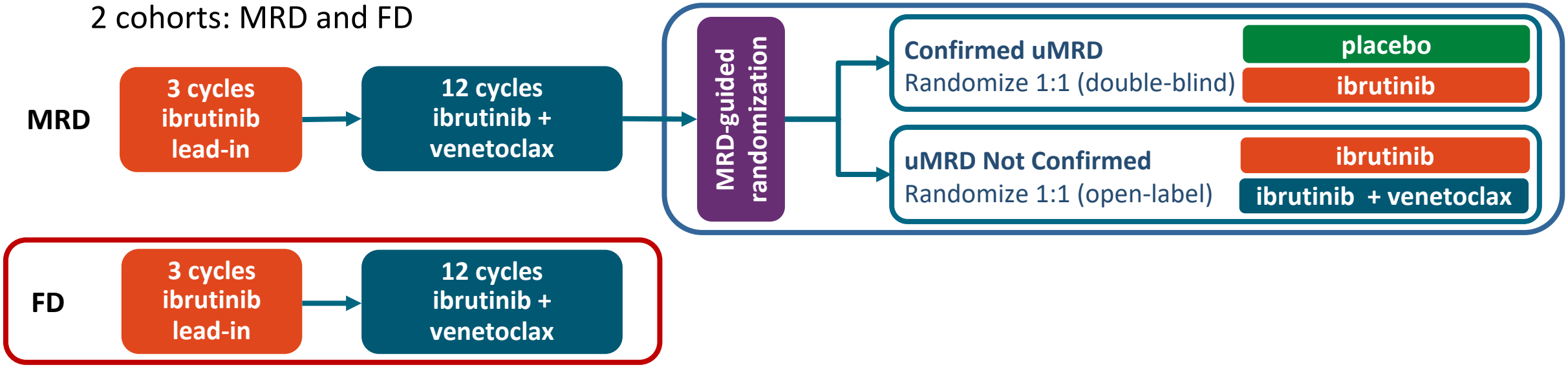
Zanubrutinib + venetoclax (ZV)

- **SEQUOIA:** Zanubrutinib + venetoclax (Arm D) vs zanubrutinib (Arm C) in TN CLL with del(17p) or *TP53*mut[13] (reported)

1. NCT02756897. 2. Jain N, et al. *N Engl J Med*. 2019;380(22):2095-2103. 3. Jain N, et al. *JAMA Oncol*. 2021;7(8):1213-1219. 4. NCT04010968.
5. NCT02910583. 6. Wierda WG, et al. *J Clin Oncol*. 2021;39(34):3853-3865. 7. Tam CS, et al. *Blood*. 2022;139(22):3278-3289. 8. NCT04608318.
9. NCT03462719. 10. NCT05336812. 11. NCT03868722. 12. NCT05057494. 13. NCT03336333.

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

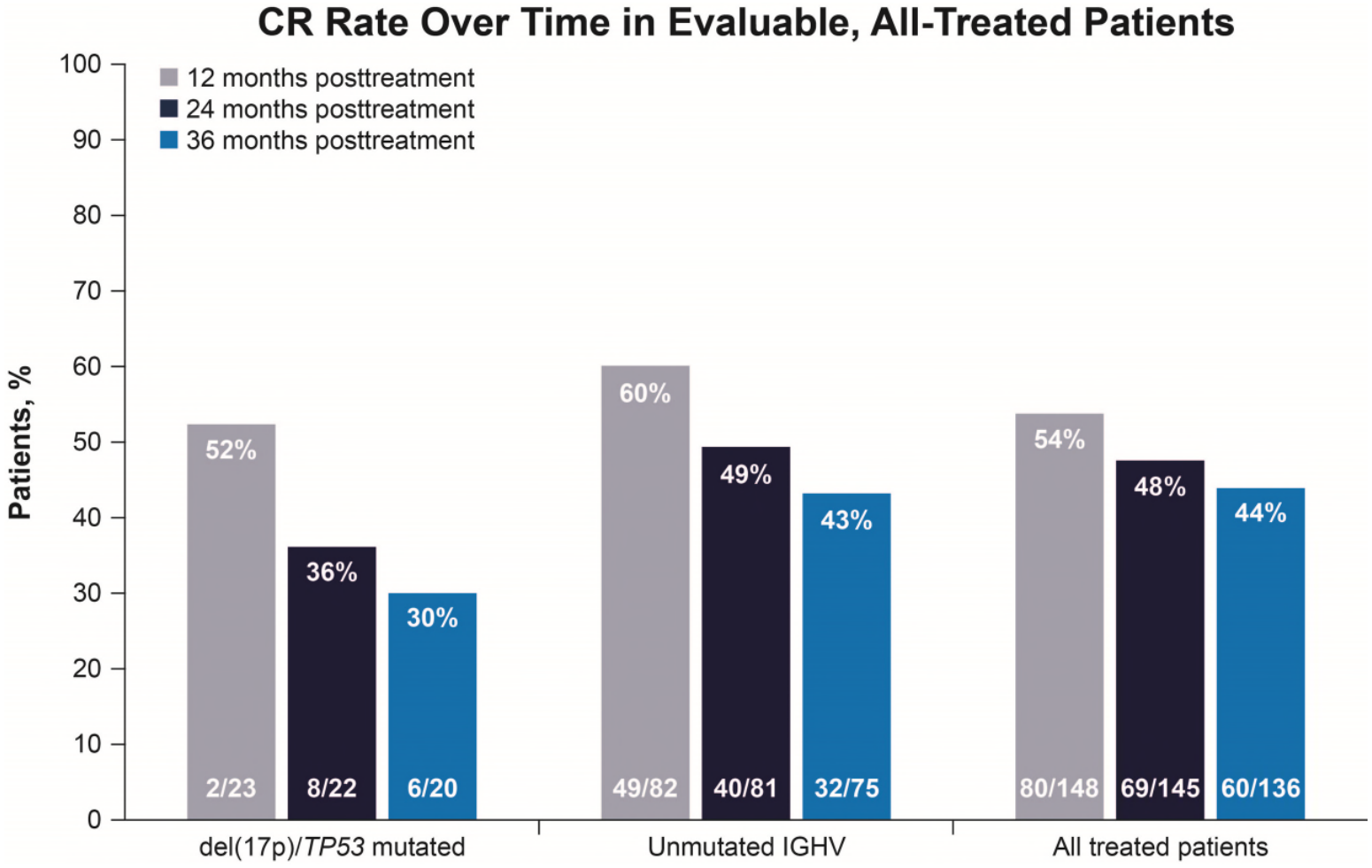


- Results from the MRD cohort demonstrated uMRD in more than two-thirds of patients treated with 12 cycles of ibrutinib + venetoclax (PB, 75%; BM, 68%), and 30-month PFS rates of ≥95% irrespective of subsequent MRD-guided randomized treatment[1]

Ghia, ASCO 2021. Allen, EHA 2021.

CAPTIVATE FD Cohort:
4y Follow up – Deep And Durable Responses

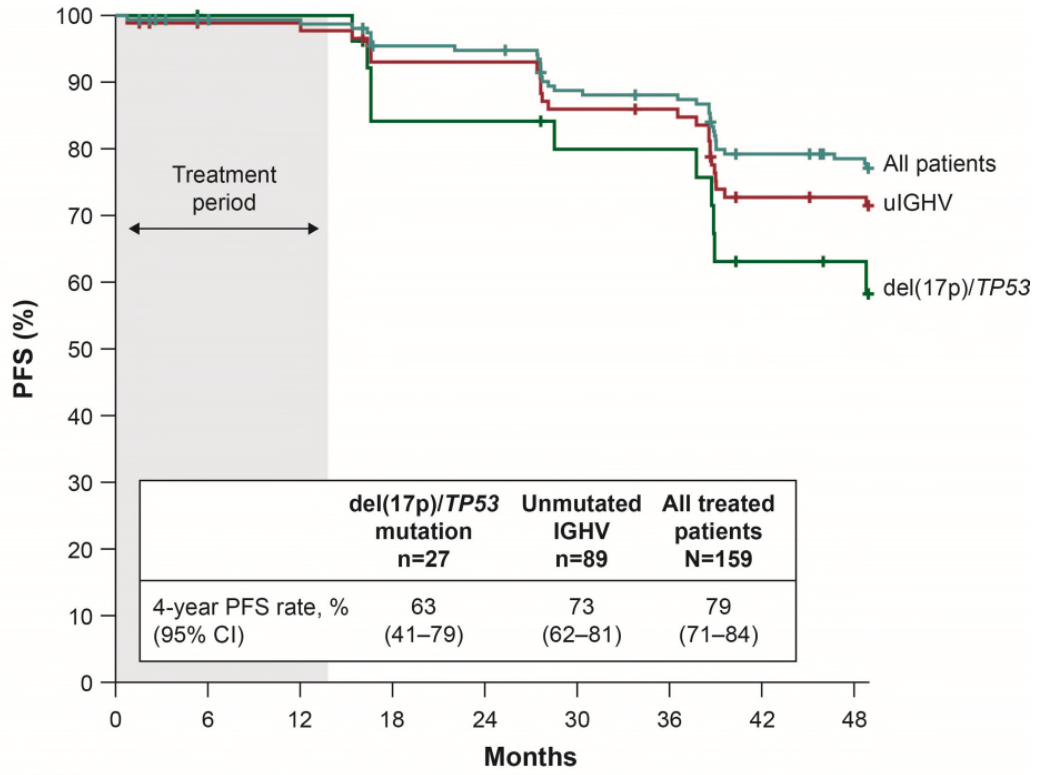
- Best ORR was 96%
- Median DOR was not reached for responding patients (n=153)
- Median duration of CR was not reached (n=93); the 36-month landmark estimate for durable CR was 80% (95% CI 69–87)



Ghia, Lugano 2023

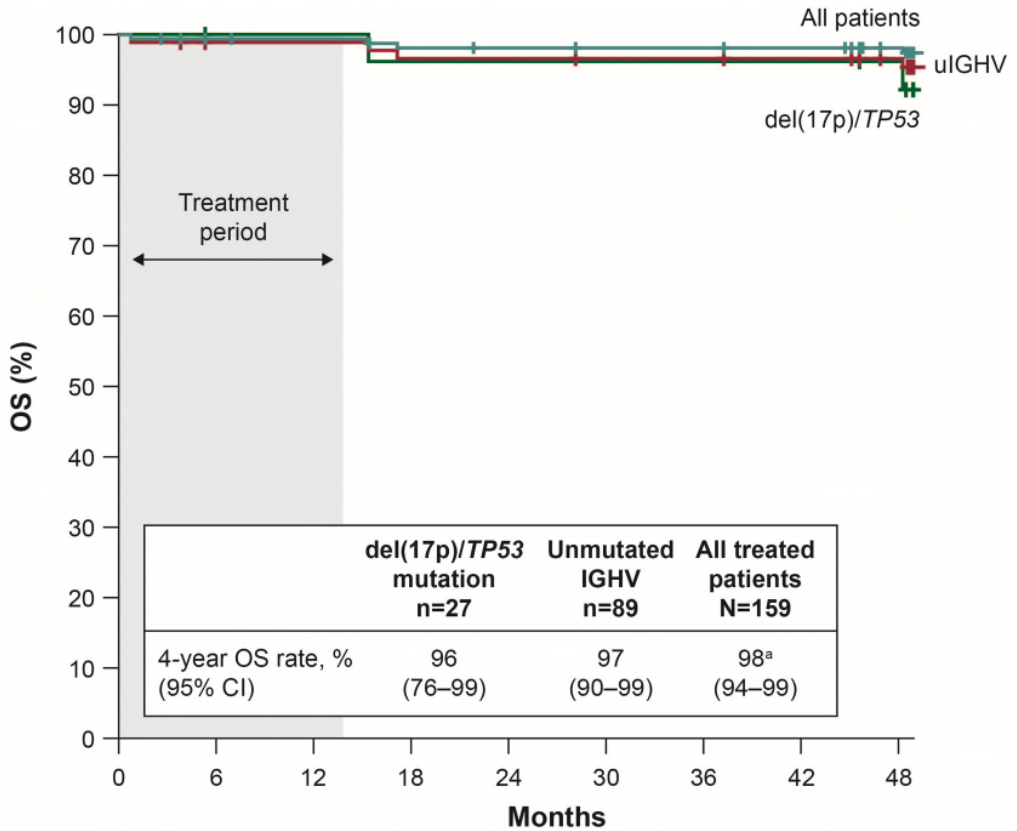
CAPTIVATE FD Cohort: 4y follow up

Progression-Free and Overall Survival[1,2]



	del(17p)/*TP53* mutation n=27	Unmutated IGHV n=89	All treated patients N=159
4-year PFS rate, % (95% CI)	63 (41–79)	73 (62–81)	79 (71–84)

Patients at risk									
del(17p)/*TP53* mutation	27	26	26	21	21	19	19	14	13
Unmutated IGHV	89	85	85	79	79	73	72	59	58
All treated patients	159	153	152	144	143	132	130	115	111

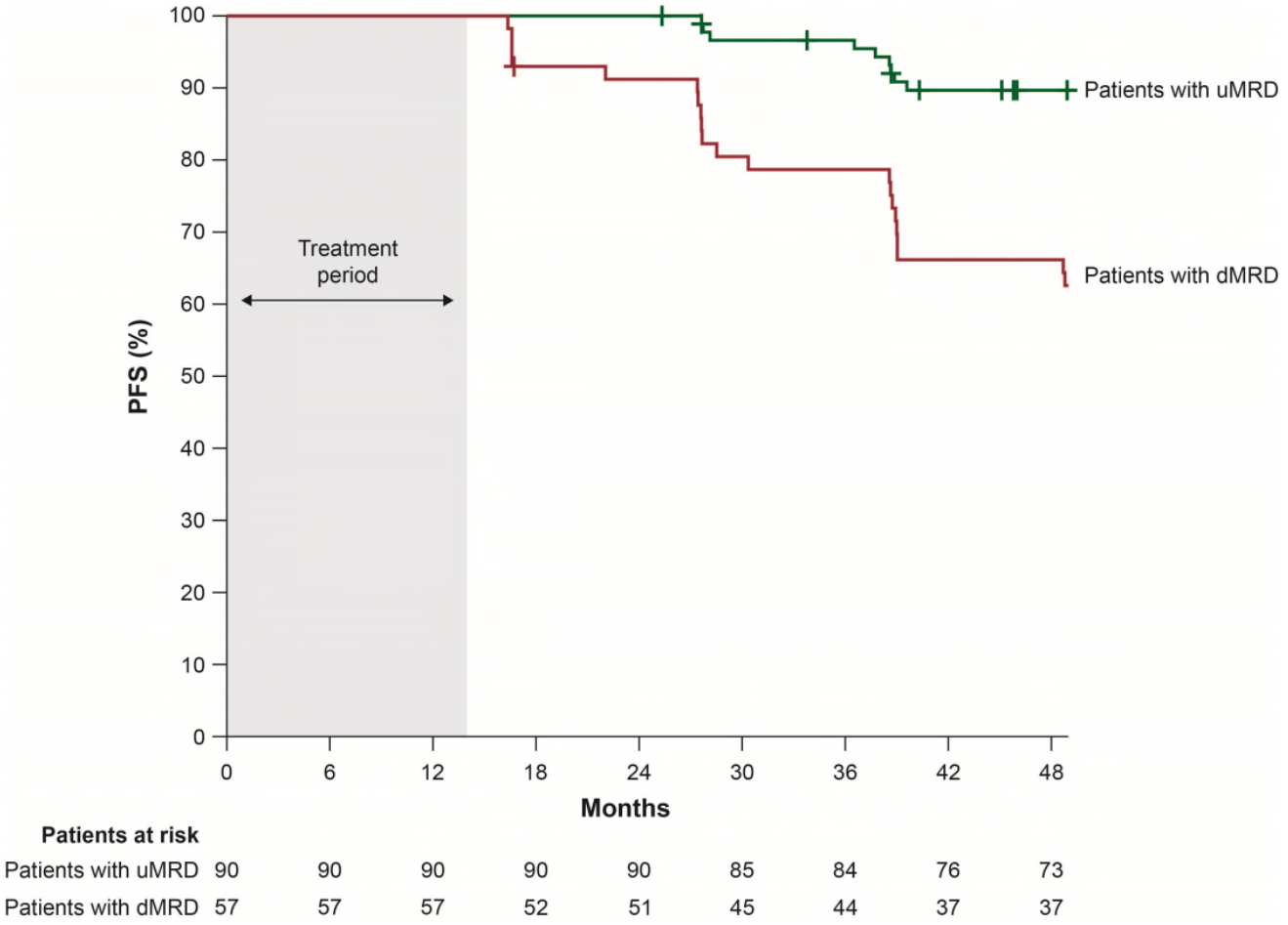


	del(17p)/*TP53* mutation n=27	Unmutated IGHV n=89	All treated patients N=159
4-year OS rate, % (95% CI)	96 (76–99)	97 (90–99)	98[a] (94–99)

Patients at risk									
del(17p)/*TP53* mutation	27	26	26	25	25	25	25	25	24
Unmutated IGHV	89	86	86	84	84	83	83	82	79
All treated patients	159	155	154	151	150	149	149	148	143

Ghia, Lugano 2023

CAPTIVATE Fixed-Dose Cohort 4-yr Update: PFS by MRD in PB



Landmark PFS rates at 48 months in patients who had uMRD in PB 3 months posttreatment were higher (90% than those with detectable MRD in PB 3 months posttreatment (66%)

Ghia, Lugano 2023

Retreatment Data From CAPTIVATE: 4-yr Update

To date, 19 patients who have progressed after completing fixed-duration ibrutinib + venetoclax (in either the FD or MRD cohort placebo arm) have initiated retreatment with ibrutinib; the median (range) retreatment duration is 11.1 (0–38.6) months

Patient	Baseline high risk features[a]				Response to FD ibrutinib + venetoclax[a]		Response to retreatment with ibrutinib
	del(17p)	TP53 mutated	ulGHV	Complex karyotype	PFS (months)	Best response	Best Response
1	No	No	Yes	Unknown	38.6	CR	CR
2	No	No	Yes	No	20.3	PR	PR
3	No	No	Yes	No	19.4	PR	PR
4	No	No	Yes	No	44.2	CR	PR
5	No	No	Yes	Yes	38.6	CR	PR
6	No	No	Yes	No	27.4	PR	PR
7	No	No	Yes	Yes	38.6	PR	PR
8	No	No	Yes	Yes	27.6	CR	PR
9	Yes	No	No	No	28.5	CRi	PR
10	Yes	No	Yes	Yes	16.6	PR	PR
11	No	No	Yes	No	36.5	CR	PR
12	No	No	No	No	27.4	PR	PR
13	No	No	No	Yes	22.0	PR	PR
14	No	No	No	Yes	30.4	PR	PR
15	No	No	Yes	Yes	38.6	CR	PRL
16	No	No	Yes	No	39.6	PR	SD
17	Yes	Yes	Yes	Yes	48.8	PR	PD[b]

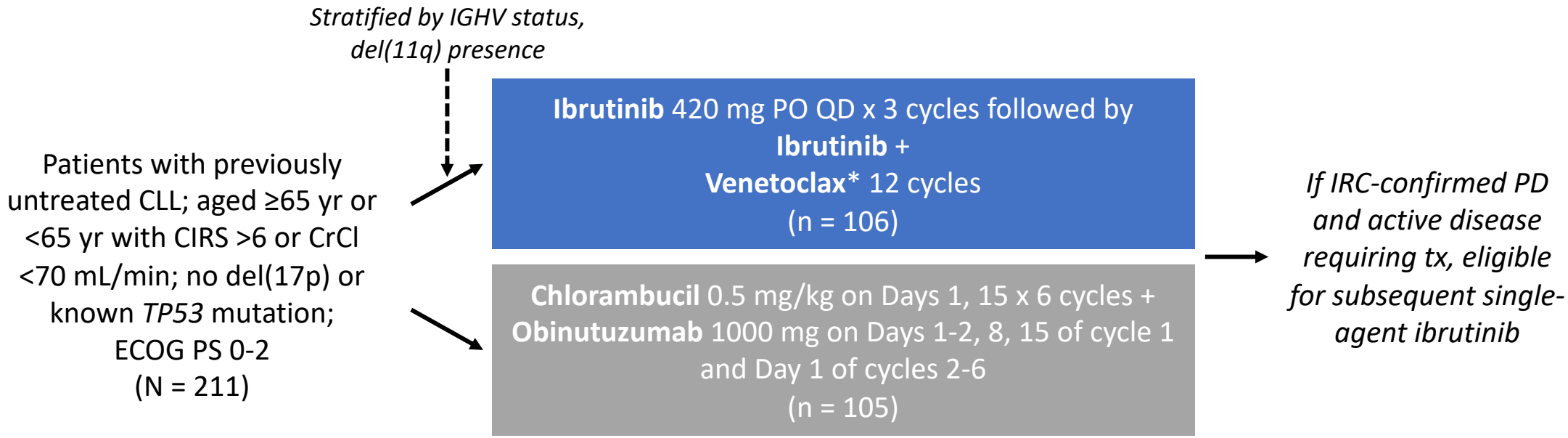
Response data are available for 17 of these patients:

- CR, n=1
- PR, n=13
- PR with lymphocytosis, n=1
- Stable disease, n=1
- PD, n=1[b]

Ghia, iCML 2023

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

International, open-label, randomized phase III trial

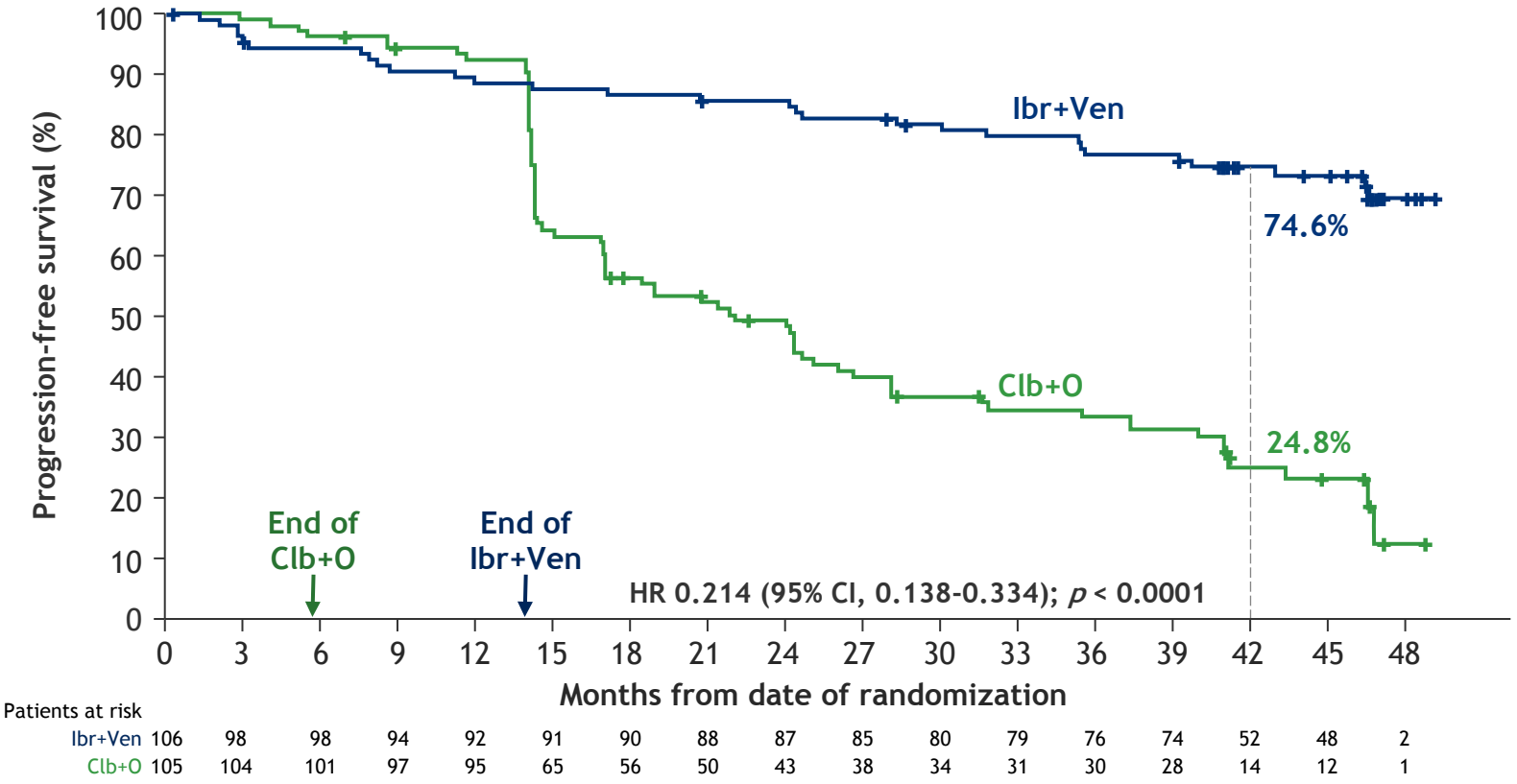


*Ramp-up from 20 to 400 mg over 5 wk starting in cycle 4.

- **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

Superior PFS (by IRC) With I+V Versus Clb+O Was Maintained With Median 46 Months of F/u

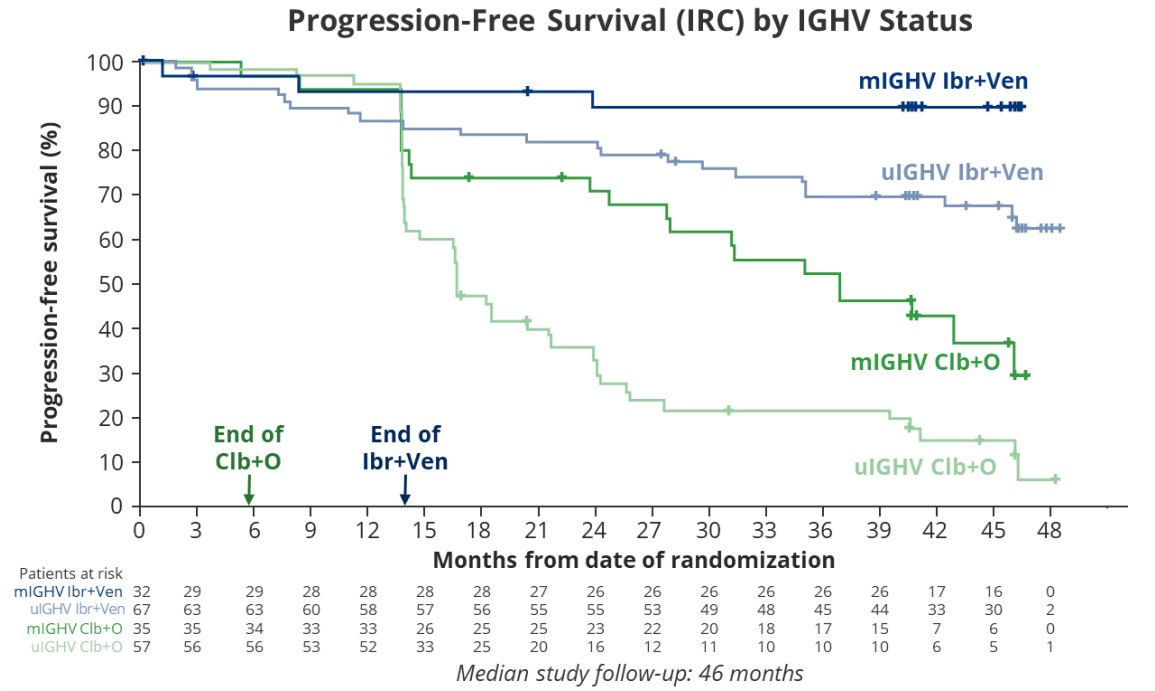


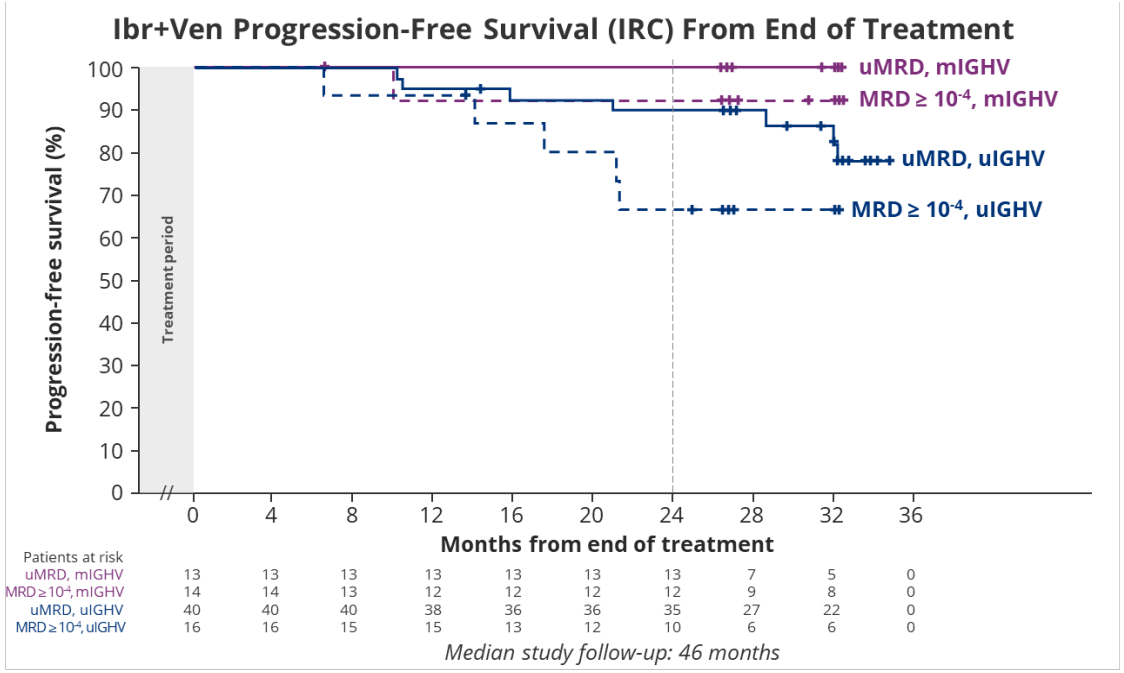
- I+V reduced the risk of progression or death by 79% versus Clb+O
- Estimated 3.5-year PFS rates:
  - 74.6% for I+V
  - 24.8% for Clb+O

Niemann, et al., ASH 2022;

GLOW: PFS by IGHV Mutational Status

(Elderly/Unfit, 12-mo Fixed Duration)





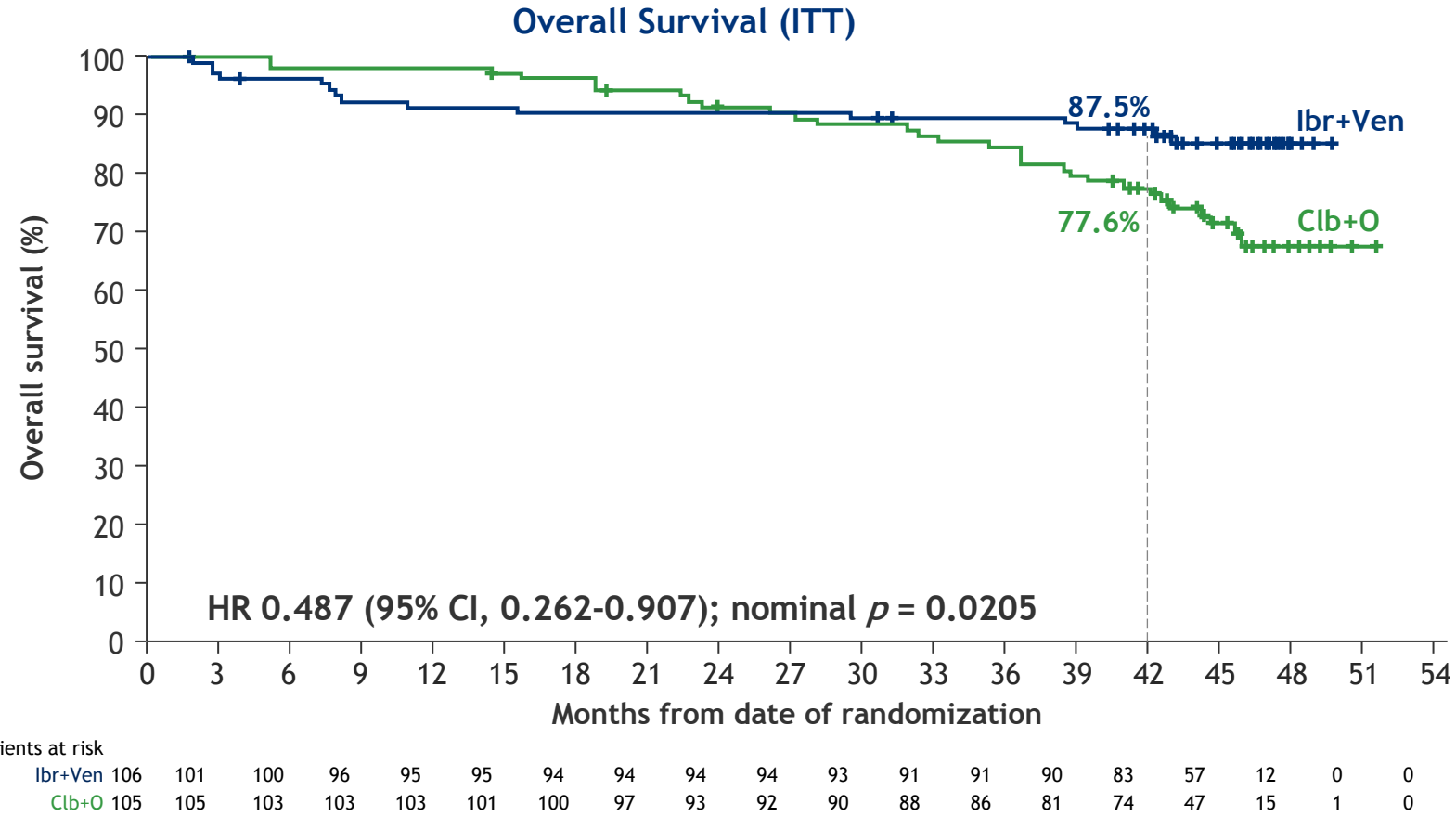
- Impact of IGHV status on PFS was more pronounced with Clb+O
- > 90% of patients in the I+V arm did not require subsequent treatment at 3.5 years:
  - 91.5% for uIGHV
  - 93.5% for mIGHV

- 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

I+V Improved OS Versus Clb+O With 4 Years of Study Follow-up

Median F/u 46 Months



Causes of Death

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)**

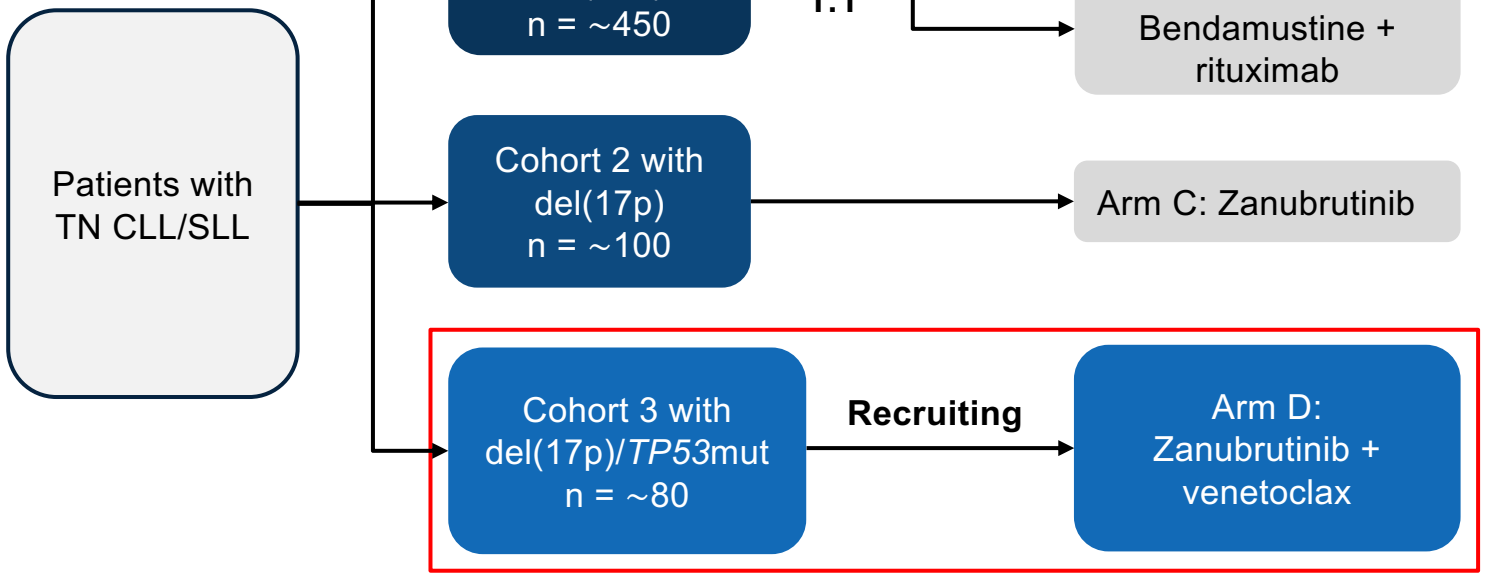
[a]Cause and number (I+V arm, Clb+O arm) of "other" deaths: general/unknown (4, 5), cardiac (2, 4), CNS (2, 3), neoplasm (1, 3), euthanasia (1, 0), hepatobiliary (0, 1), respiratory (0, 1).

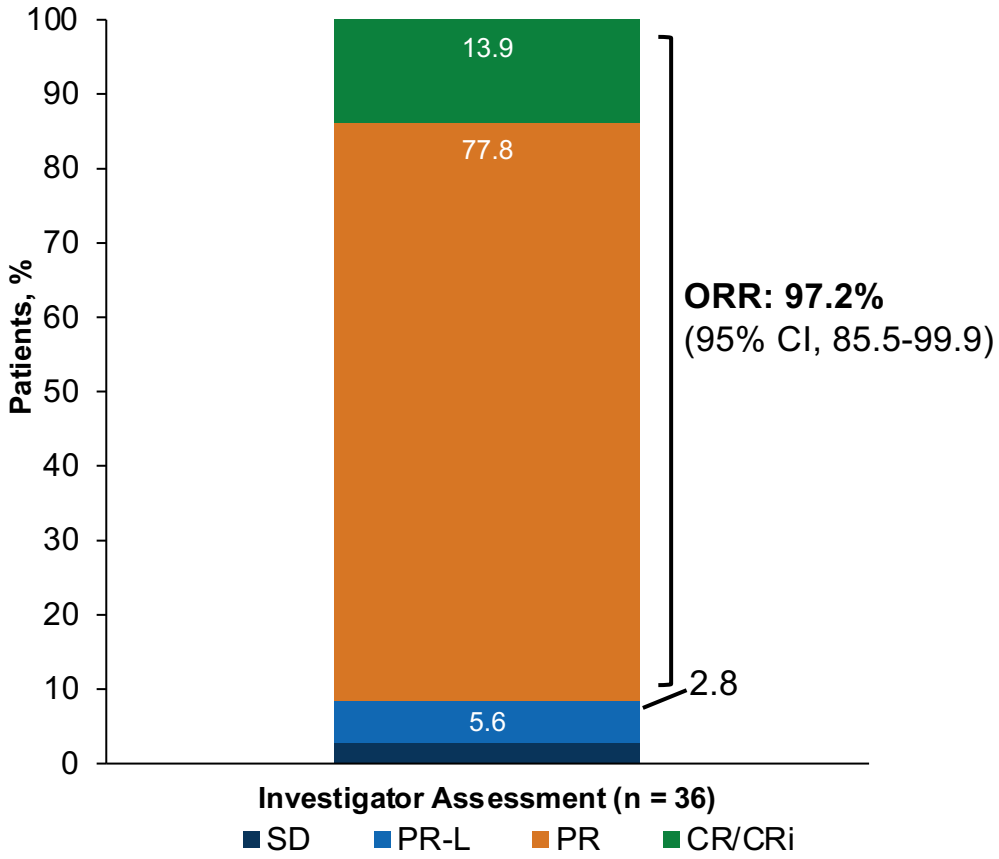
Niemann et al. ASH 2022

Zanubrutinib-Venetoclax Combination Is Active in Del(17p)/*TP53* CLL

SEQUOIA Arm D Tested Zanubrutinib-Venetoclax in High-Risk CLL[1]

Of 36 evaluable patients, 14 were treated with the combination therapy for at least 12 months





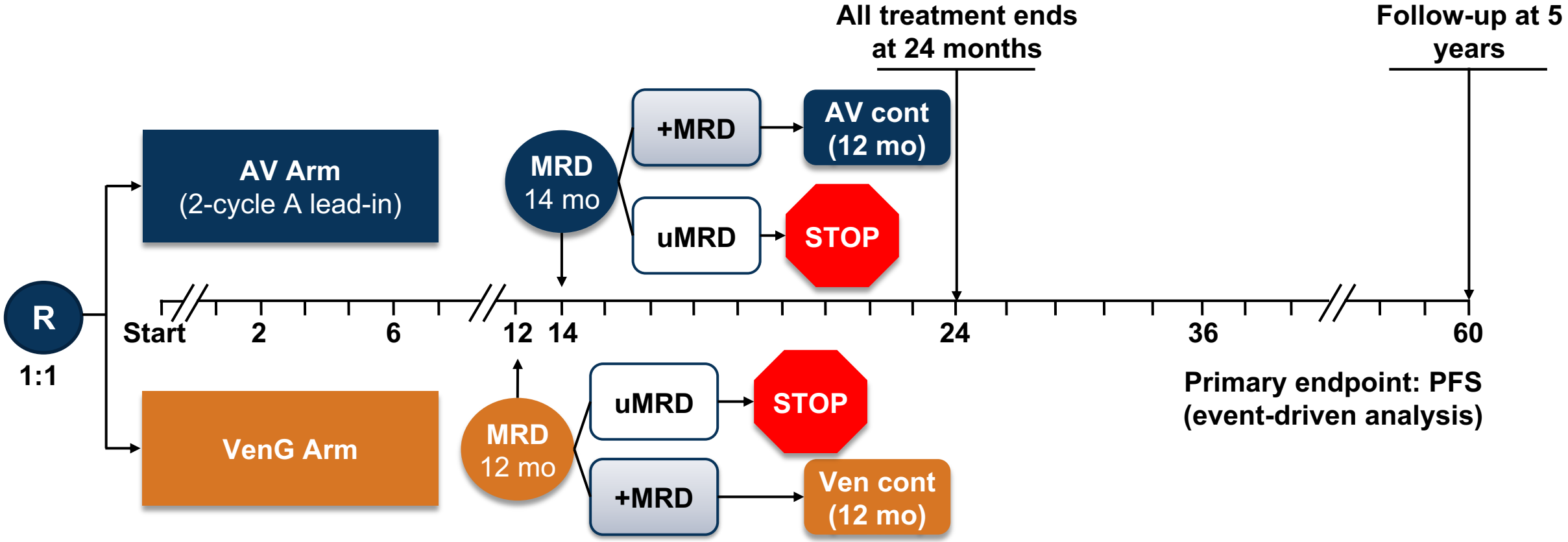
1. Tedeschi A et al. ASH 2021. Abstract 67.

MAJIC Phase 3 Study Will Test Acalabrutinib-Venetoclax Combination in Patients With CLL/SLL[1]

- ~750 patients to be recruited
- 40 sites around the world

Key Eligibility Criteria

- TN CLL/SLL requiring treatment per 2018 iwCLL guidelines
- ECOG PS 0-2
- Antithrombotic agents permitted except for warfarin or equivalent vitamin K antagonists



1. Davids MS et al. ASH 2021. Abstract 1553.

Ongoing Phase 2/3 Studies With BTKi Triplets for TN CLL

Ibrutinib + venetoclax + obinutuzumab (IVO)

- IVO in TN CLL with del(17p) or *TP53*mut (phase 2, ongoing)[1]
- IO±V in patients with TN CLL <70 years of age without del(17p)[2] (ongoing)
- IO±V in patients with TN CLL ≥65 years of age[3] (ongoing)
- **Alliance A041702**: IO±V in patients with TN CLL ≥70 years of age[4,5] (reported)
- **GAIA-CLL13**: IVO vs VO vs VR vs CIT in TN CLL without *TP53* aberrations[6,7] (reported)

Acalabrutinib + venetoclax ± obinutuzumab (AVO)

- AVO in TN CLL (cohort 2: with del[17p] or *TP53*mut) (phase 2, reported)[8,9]
- AVO vs VO in TN CLL with del(17p), TP53mut, or complex karyotype[10] (ongoing)
- AV±O vs FCR/BR in TN CLL without del(17p) or *TP53*mut[11] (ongoing)

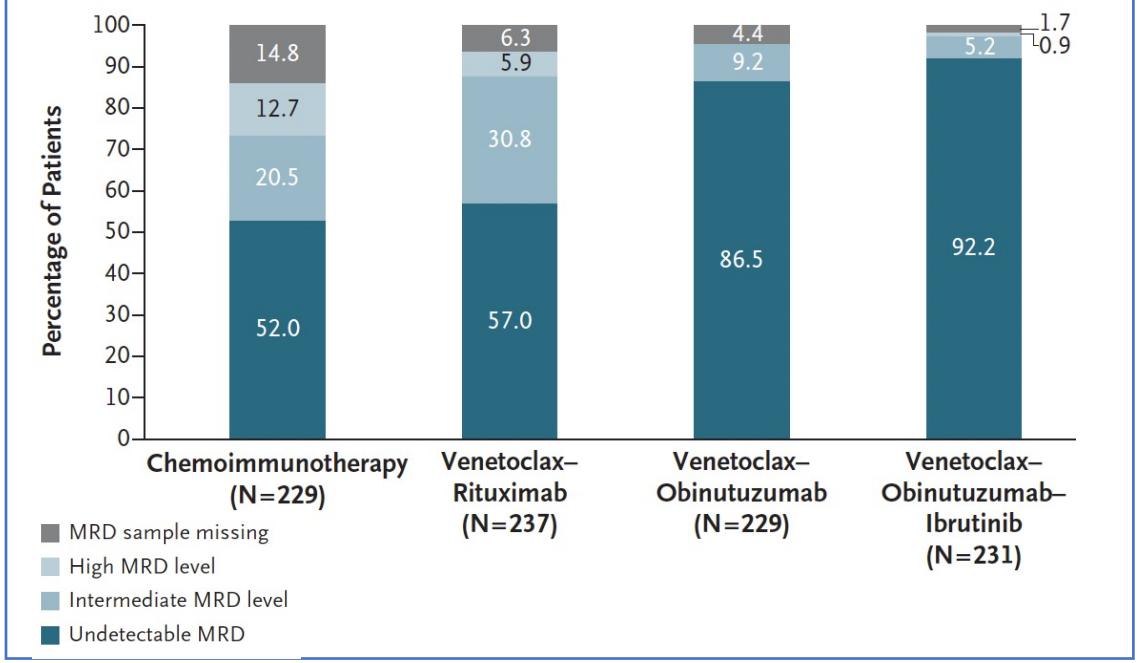
Zanubrutinib + venetoclax + obinutuzumab (ZVO)

- **BOVen:** ZVO in TN CLL (phase 2, reported)[12,13]
- **BruVenG:** ZV with response-based obinutuzumab in TN CLL (phase 2, ongoing)[14]

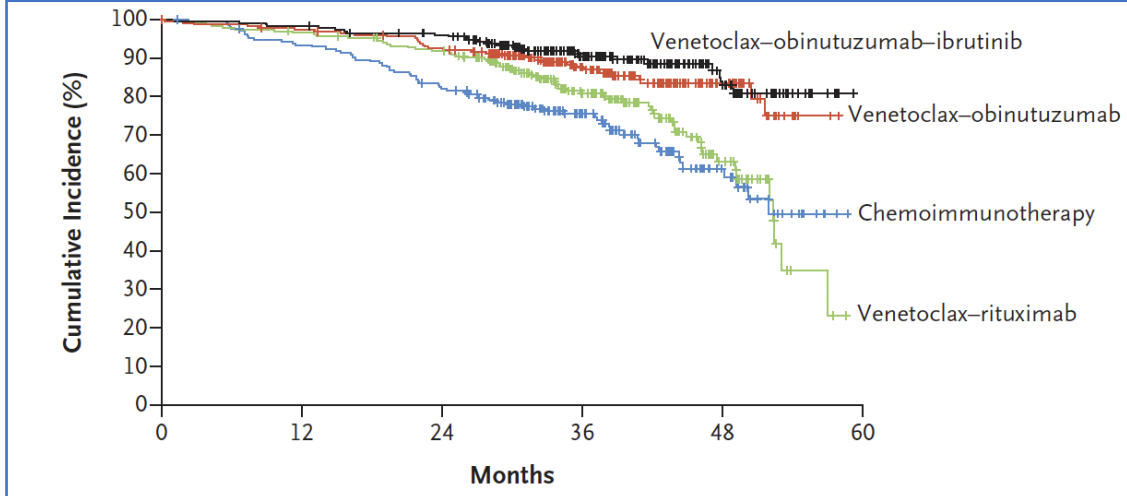
1. NCT02758665. 2. NCT03701282. 3. NCT03737981. 4. NCT03737981. 5. Woyach JA, et al. ASCO 2023. Abstract 7500. 6. NCT02950051. 7. Eichhorst B, et al. *N Engl J Med*. 2023;388:1739-1754. 8. NCT03580928. 9. Davids MS, et al. *Lancet Oncol*. 2021;22(10):1391-1402. 10. NCT05197192. 11. NCT03836261. 12. NCT03824483. 13. Soumerai JD, et al. *Lancet Haematol*. 2021;8(12):e879-e890. 14. NCT05650723.

GAIA-CLL13 Phase 3 Trial of First-Line Venetoclax Combinations in Fit Patients With CLL Without *TP53* Aberrations

MRD in PB at Month 15 (Primary Endpoint)



PFS



CIT	229	197	172	98	28	0
VenR	237	226	212	119	32	0
VenG	229	221	208	125	42	0
Ibrutinib	231	227	217	132	44	0

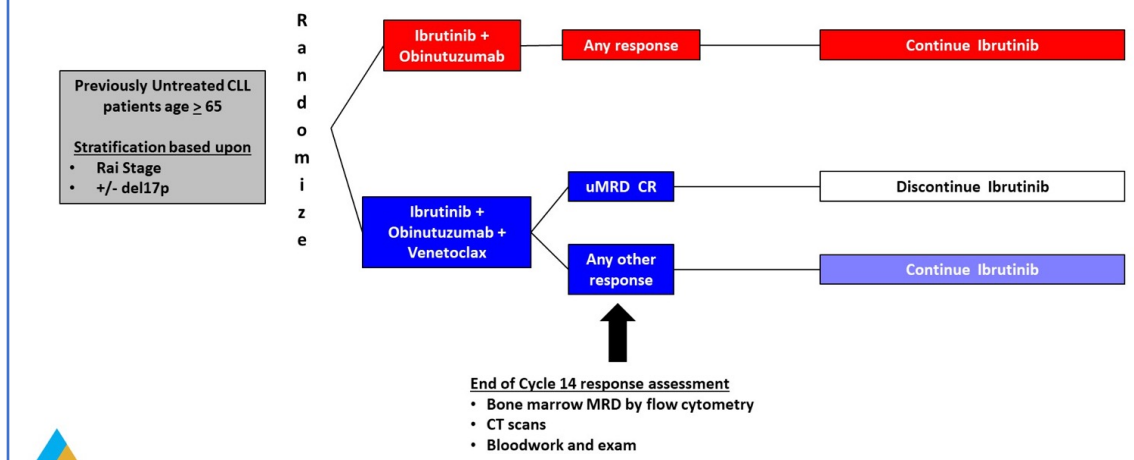
- uMRD in PB at month 15
  - VO was superior to CIT (86.5% [97.5% CI, 80.6-91.1] vs 52.0% [97.5% CI, 44.4-59.5]; *P*<0.001)
  - VOI was superior to CIT (92.2% [97.5% CI, 87.3-95.7); *P*<0.001)
  - No significant difference between VR and CIT (57.0% [97.5% CI, 49.5-64.2]; *P*=0.32)

- PFS after a median follow-up of 38.8 months (IQR, 32.7-46.1)
  - VOI was superior to CIT (HR 0.32 [97.5% CI, 0.19-0.54]; *P*<0.001)
  - VO was superior to CIT (HR 0.42 [97.5% CI, 0.26-0.68]; *P*<0.001)
  - No significant difference between VR and CIT (HR 0.79 [97.5% CI, 0.53-1.18]; *P*=0.18)

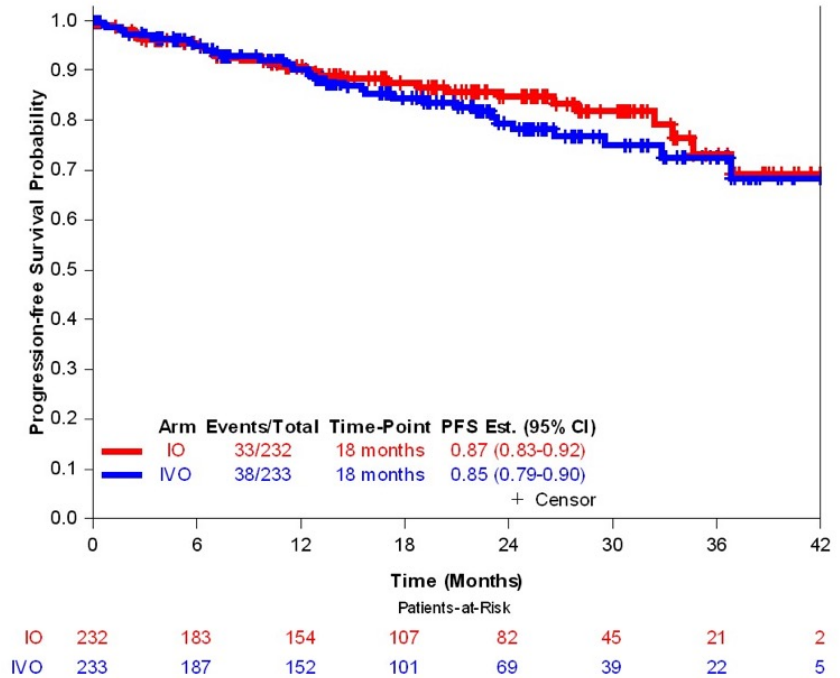
Eichhorst B, et al. N Engl J Med. 2023;388:1739-1754.

Alliance A041702 Phase 3 Trial of IO±V in Patients With TN CLL (≥70 years of age)

Study Schema



PFS



IVO vs IO:
Hazard Ratio 1.12
95% CI: 0.70-1.79

9

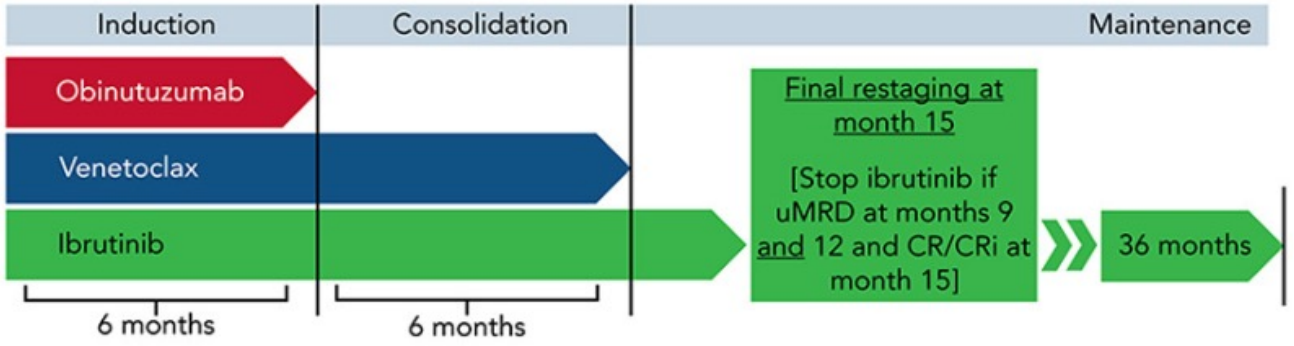
Conclusions

- In this study, IVO is not superior to IO for the initial treatment of older patients with CLL
- COVID 19 may have significantly altered these results, with data suggesting a death imbalance for patients treated with venetoclax
- At this follow-up, PFS with IVO is not impacted by MRD or response status at end of 14 cycles
- Long-term follow-up of this study will be critical to determine whether some patients benefit from IVO

Woyach JA, et al. ASCO 2023. Abstract 75

CLL2-GIVe: An Induction/Maintenance Approach Appears Feasible in High-Risk TN CLL[1]

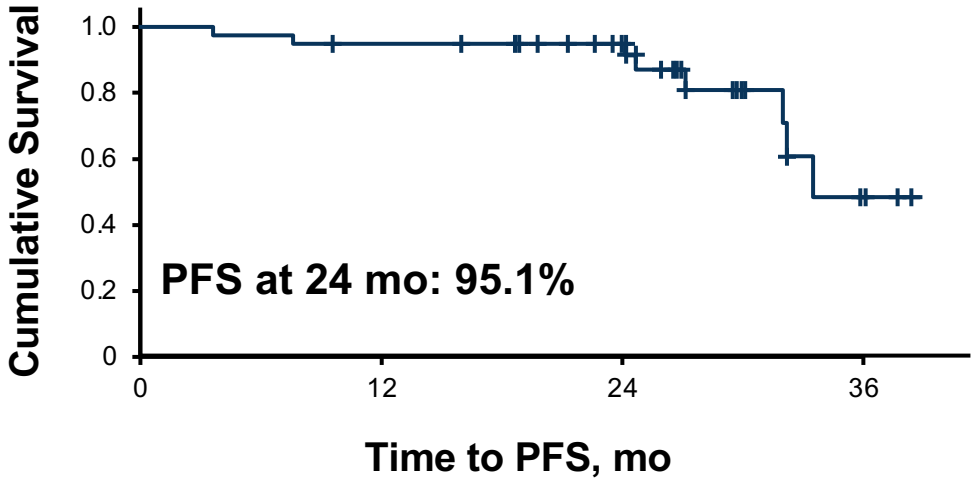
CLL2-GIVe study: Time limited first-line therapy in CLL with del(17p)/*TP53*mut

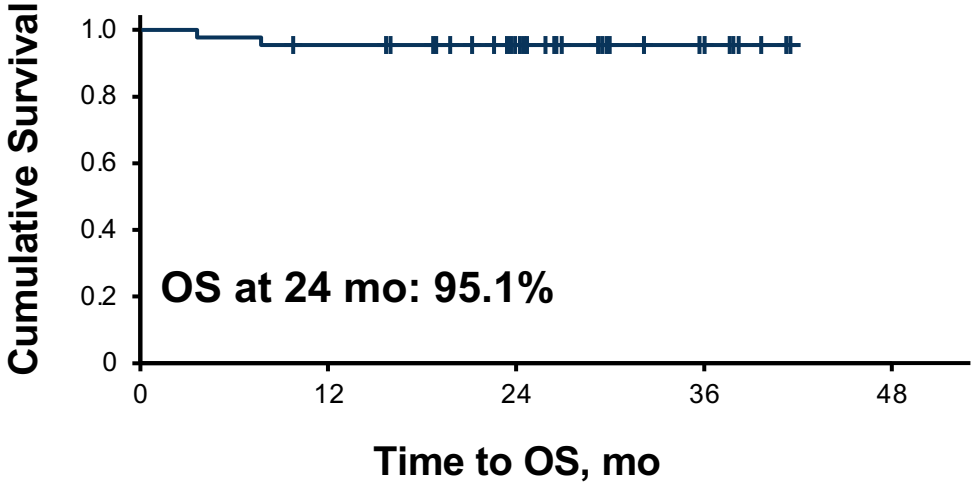


Time-limited therapy with ibrutinib, venetoclax, and obinutuzumab followed by maintenance ibrutinib

N = 41 patients, all with del(17p) and/or *TP53*-mutated CLL

	Efficacy Outcome
CR at cycle 15	58.5% (primary endpoint met)
uMRD at final restaging	PB: 78.0% BM: 65.9%

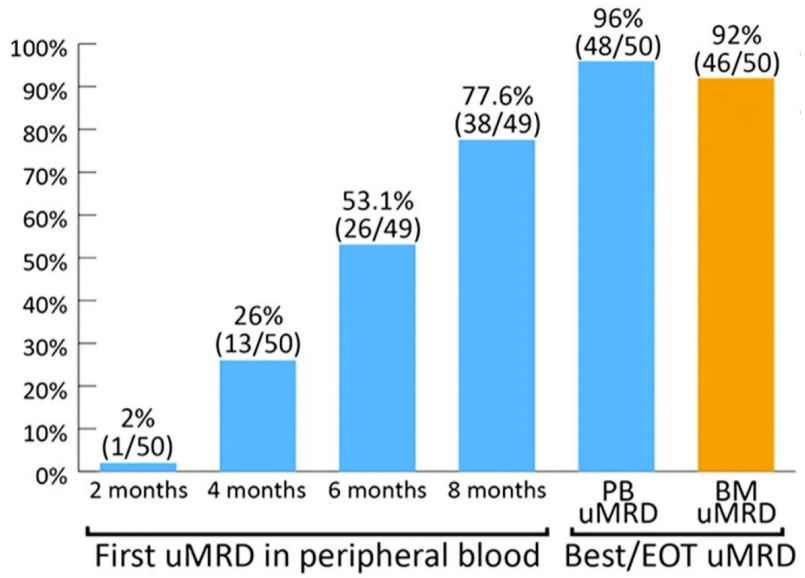




1. Huber H et al. *Blood*. 2022;139:1318-1329.

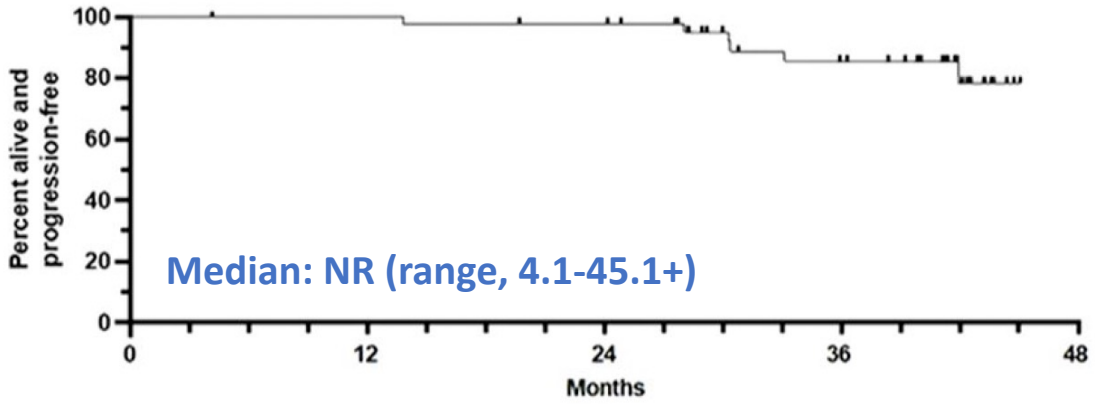
40-Month Follow-Up From the Phase 2 Trial of BOVen (Zanubrutinib, Obinutuzumab, and Venetoclax) in TN CLL/SLL

MRD Outcomes

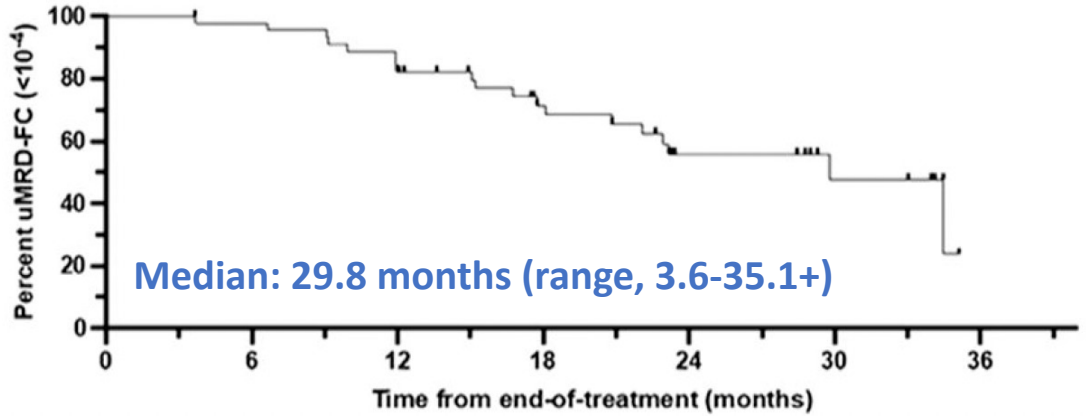


- 96% (48/50) uMRD ($<10^{-4}$) in PB
- 92% (46/50) uMRD in both PB and BM
  - All met prespecified MRD endpoint/treatment discontinuation criterion and stopped therapy after median of 10 months (IQR 8-12 months)
- 400-fold MRD reduction at C5D1 associated with 100% MRD-neg at 8 months

PFS in All Patients (n=50)



MRD-Free Survival in BM uMRD Patients (n=46)

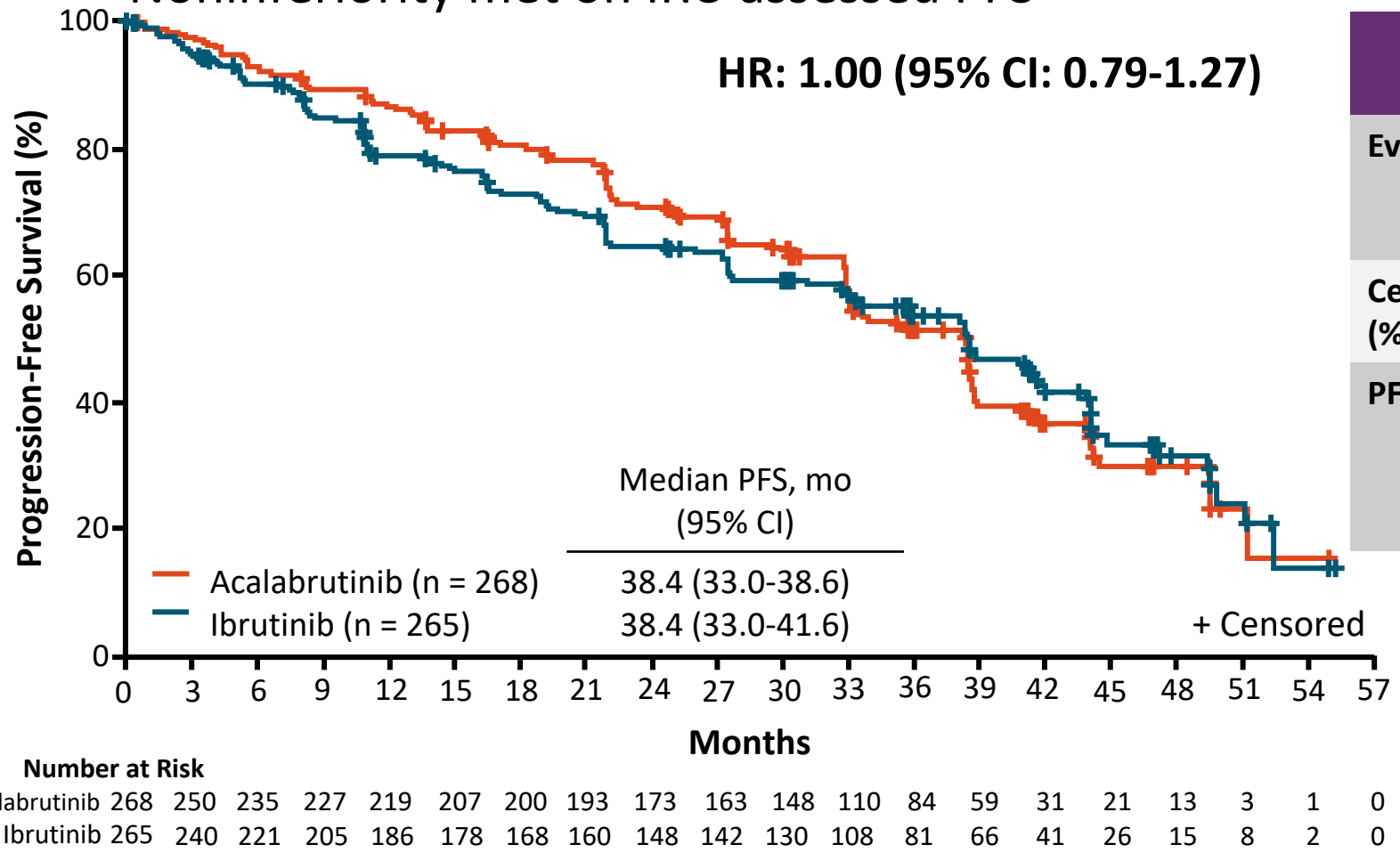


Soumerai J, et al. ICML 2023. Abstract 153.

Relapsed/Refractory and BTK mutational profile

ELEVATE-RR: IRC-Assessed PFS

- Noninferiority met on IRC-assessed PFS



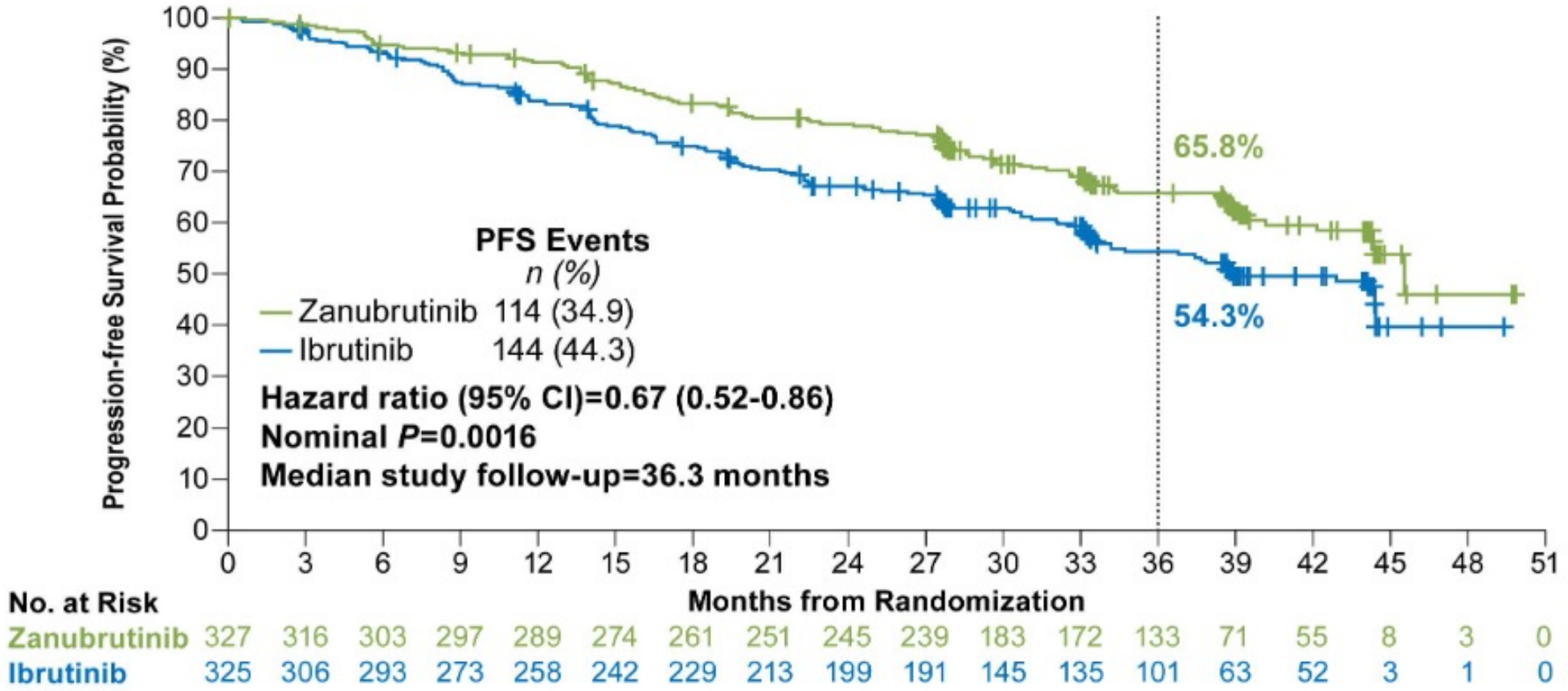
Median follow-up: 41 months

	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

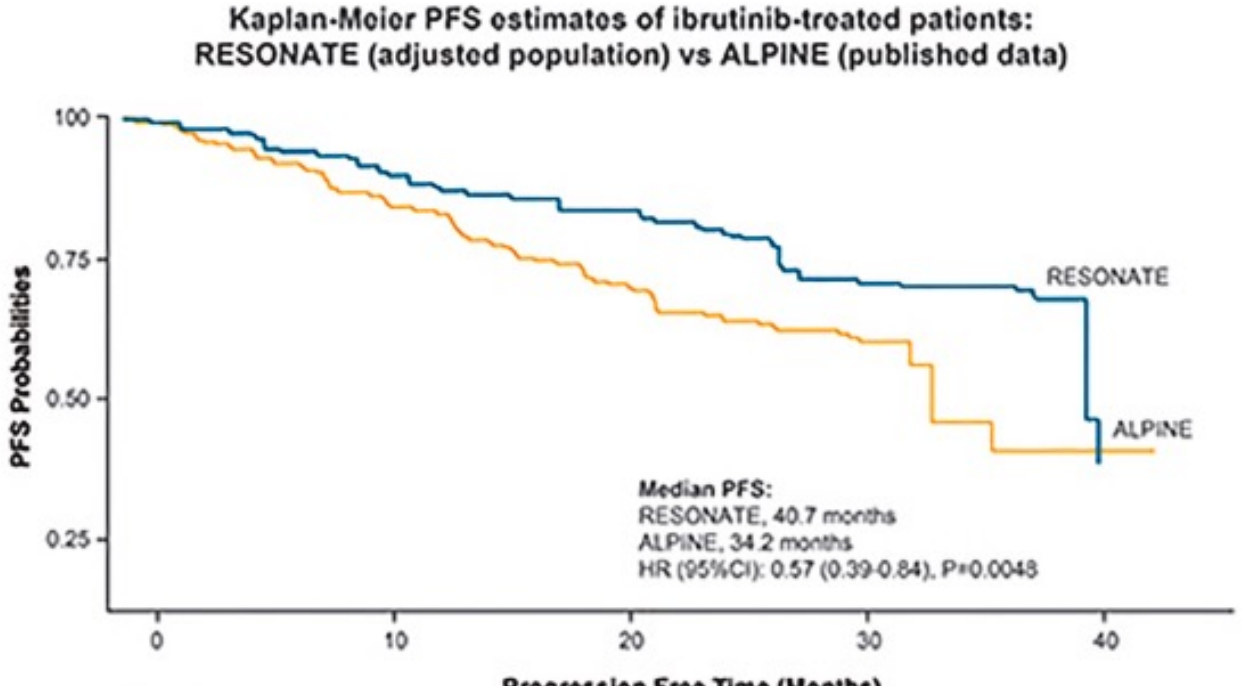
Byrd. ASCO 2021.

ALPINE: PFS - ITT Population



Brown, JR., et al. *ASH Meeting*. 2023;Poster 202.

MAIC: Is Ibrutinib Performing Historically?



ALPINE								
Number at risk	325	292	259	227	128	97	9	1
Cumulative Observed Events	0	22	49	78	101	107	118	119
RESONATE								
Number at risk	179	170	158	149	139	119	64	0
Cumulative Observed Events	0	8	18	26	33	49	52	58

Due to variations inherent to manual data collection, there was a discrepancy (<1%) between the numbers of identified and published censoring events. This discrepancy is not likely to affect the conclusions.

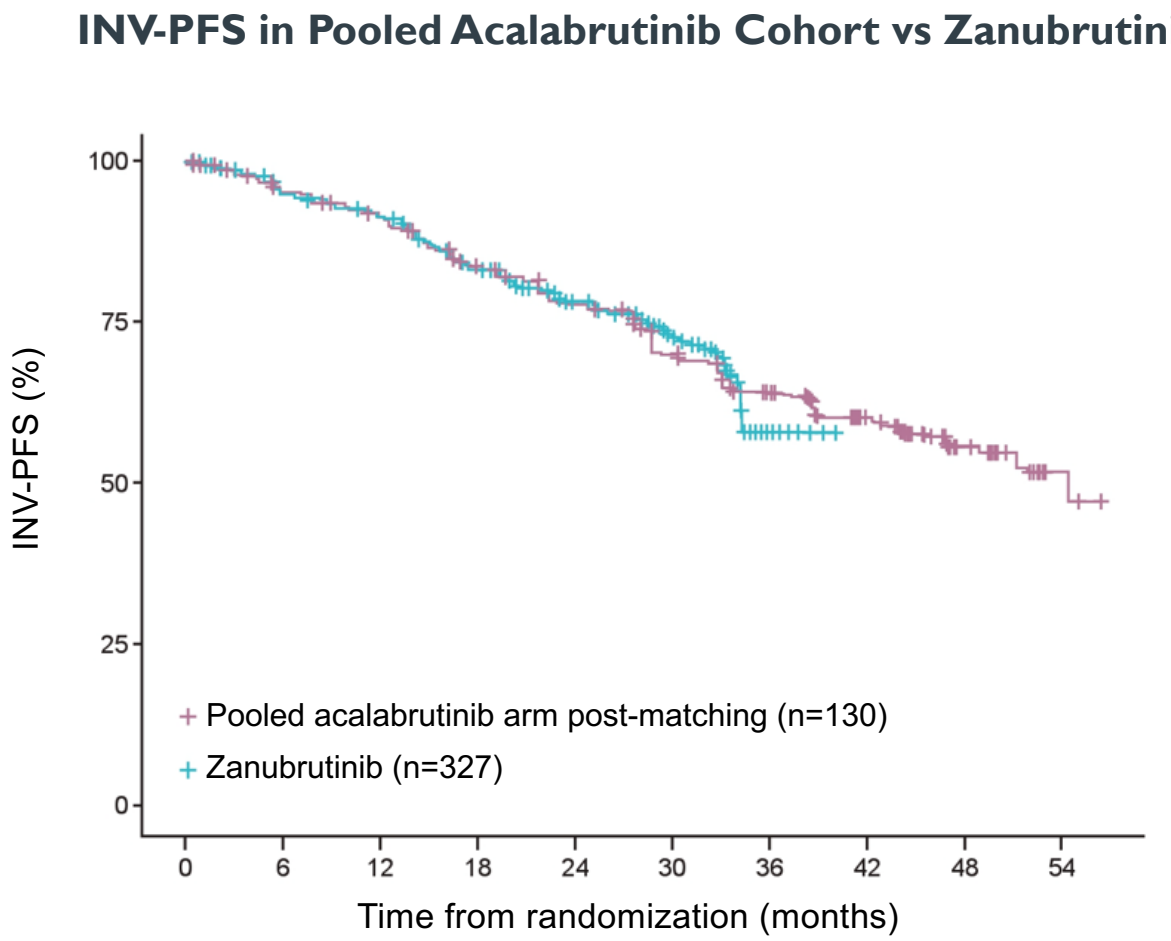
mPFS:

RESONATE (adjusted) vs **ALPINE**
40.7 months vs 34.2 months
HR 0.57 (CI 0.39-0.84)

RESONATE (adjusted) vs **ELEVATE-RR**
41.2 months vs 44 months
HR: 1.15 (CI 0.46-1.31)

Ghia et al ICML 2023.

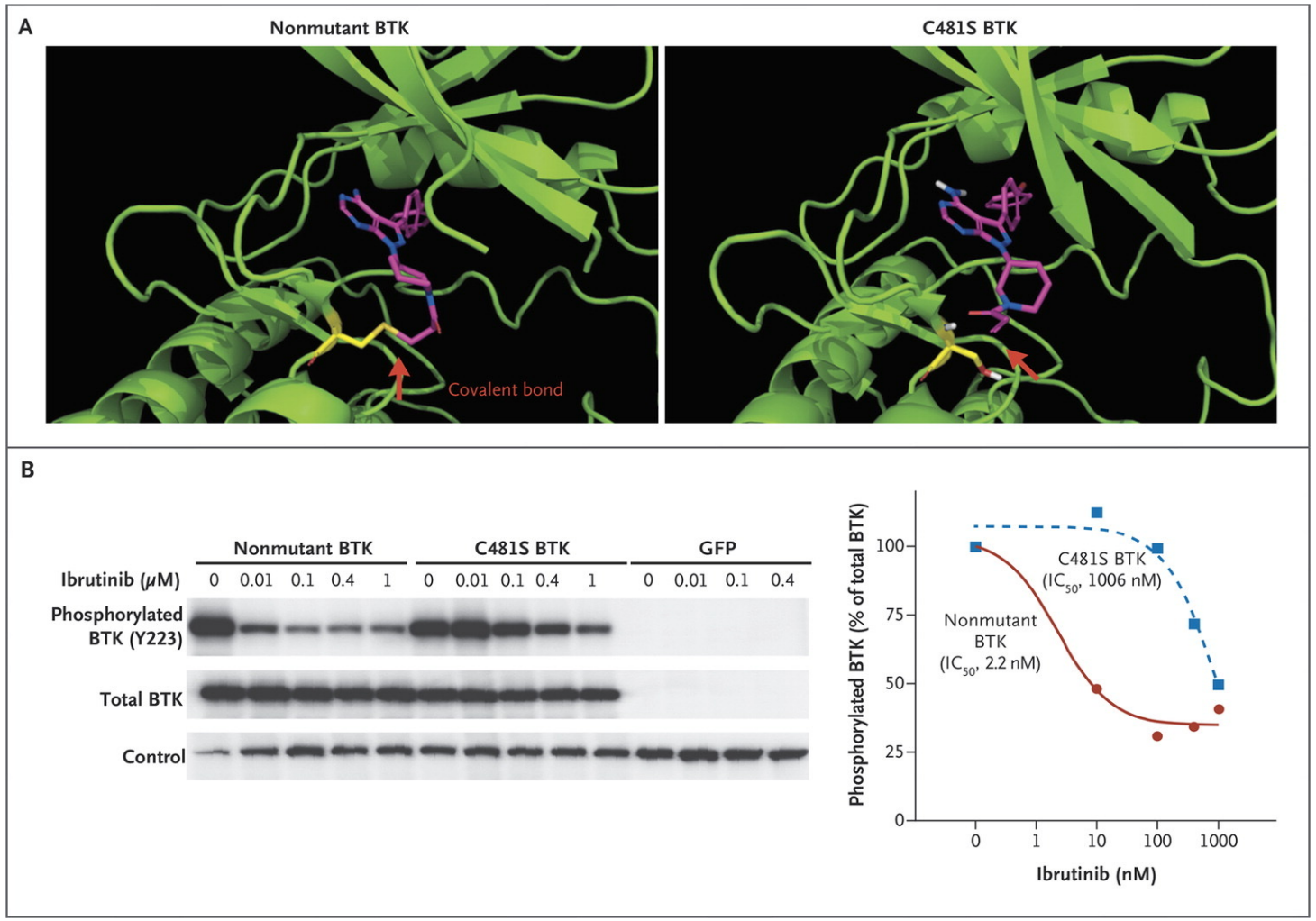
MAIC: PFS by Investigator assessment in pooled acalabrutinib cohort compared with zanubrutinib



- Post-matching ESS of the pooled acalabrutinib arm from ASCEND and ELEVATE-RR was 130 (32% of the original pooled arm)
- There was no difference in INV-PFS between the pooled acalabrutinib cohort and zanubrutinib (HR 0.92; 95% CI 0.64–1.34)

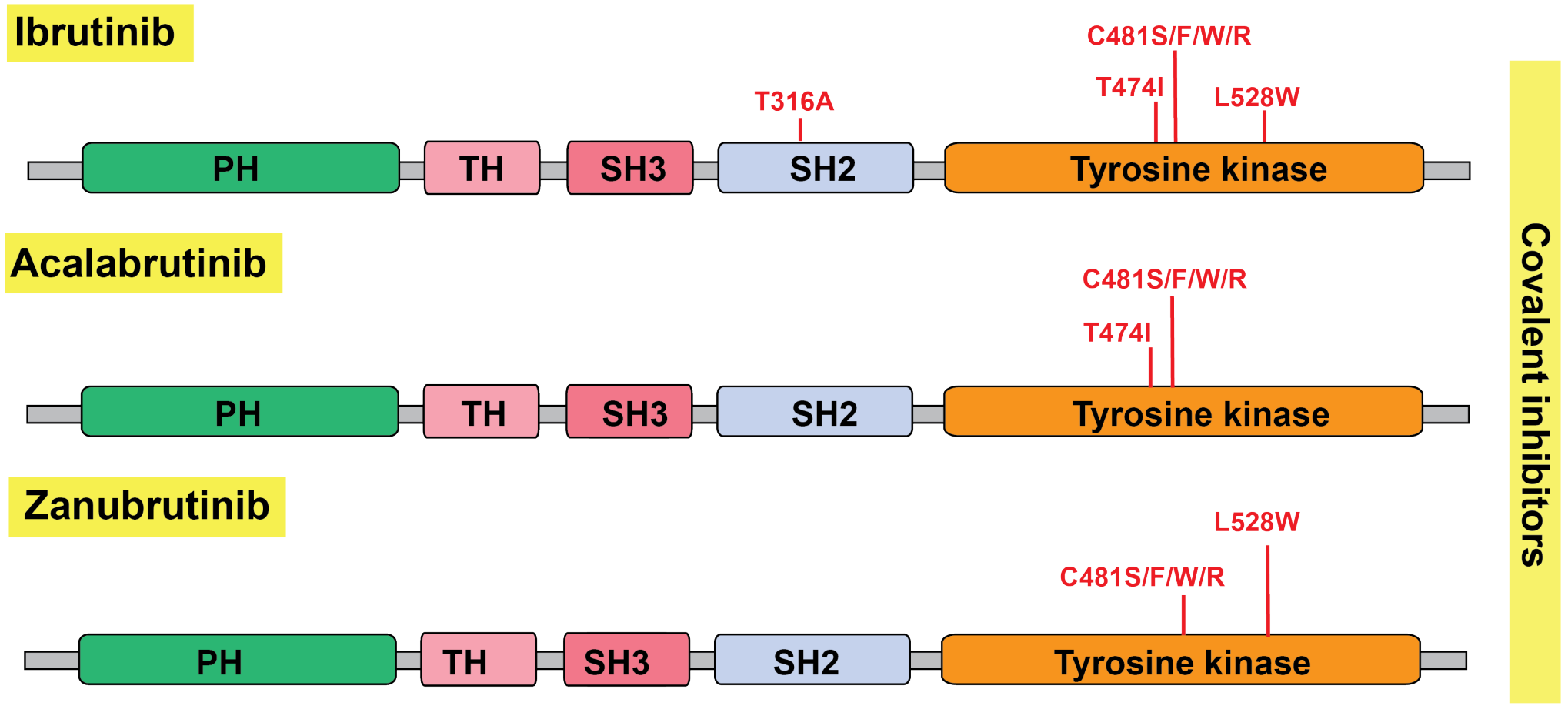
CI, confidence interval; ESS, effective sample size; HR, hazard-ratio; INV-PFS, investigator-assessed progression-free survival.
Source: Kittai et al. Abstract 7540, ASCO 2023.

Effect of C481S Mutation of BTK on BTKi Binding



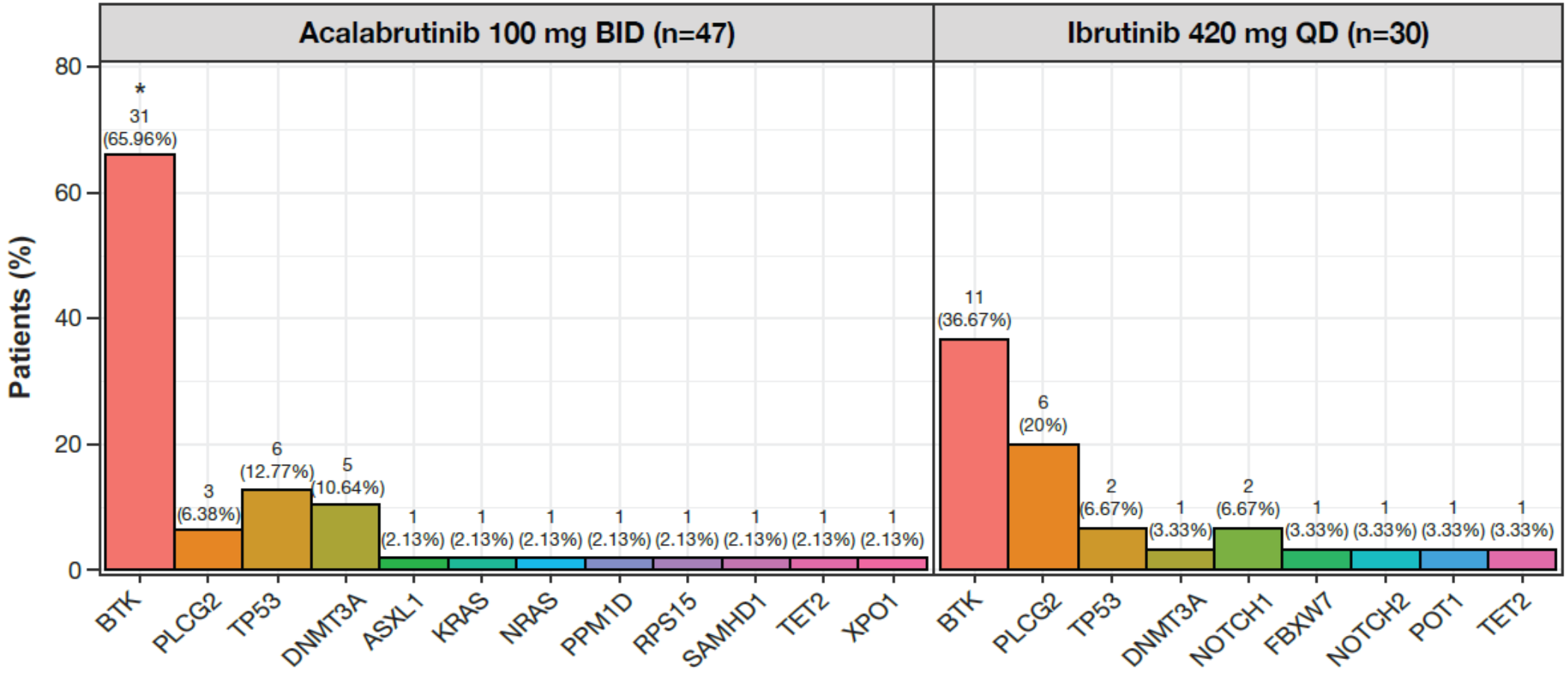
Furman RR et al. N Engl J Med 2014;370:2352-2354.

Diverse BTK mutations cause resistance to covalent BTK inhibitors



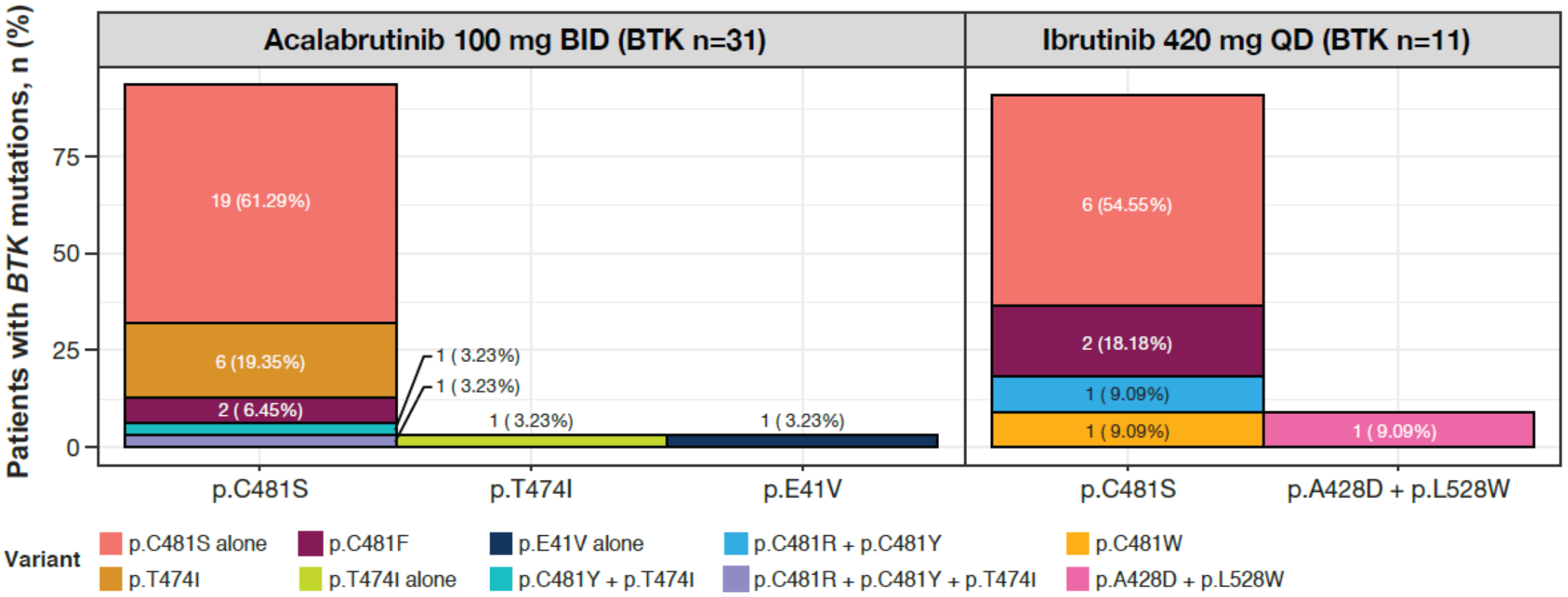
Montoya et al ASH 2022

EMERGENT MUTATIONS AT THE TIME OF PROGRESSION IN PATIENTS TREATED WITH ACALABRUTINIB OR IBRUTINIB



BID, twice a day; QD, once a day.
*$P<0.05$ per Fisher's Exact Test.
Patients could have been included in >1 mutation category but were counted only once in a given single mutation category.
Source: Woyach et al. Abstract 163, ICML 2023.

ELEVATE RR: *BTK* MUTATION VARIANT DISTRIBUTION BY TREATMENT ARM



BID, twice a day; QD, once a day.
Source: Woyach et al. Abstract 163, ICML 2023.

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

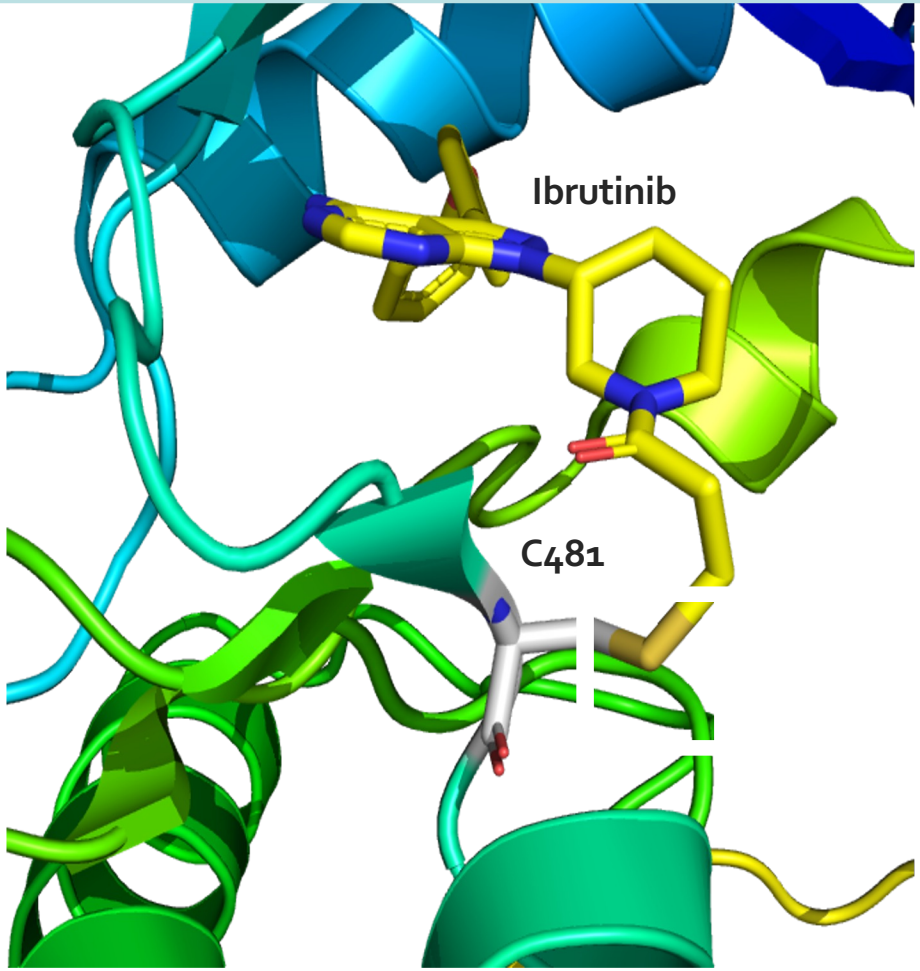
	Number of patients carrying the mutations			
	Ibrutinib-treated patients (n = 24)	Zanubrutinib-treated patients (n =13)	Total	*P*
Cys481 codon mutations	24	10	34	.03
Leu528Trp	1	7	8	.001

Both patients with Leu528Trp mutations treated with pirtobrutinib had poor responses

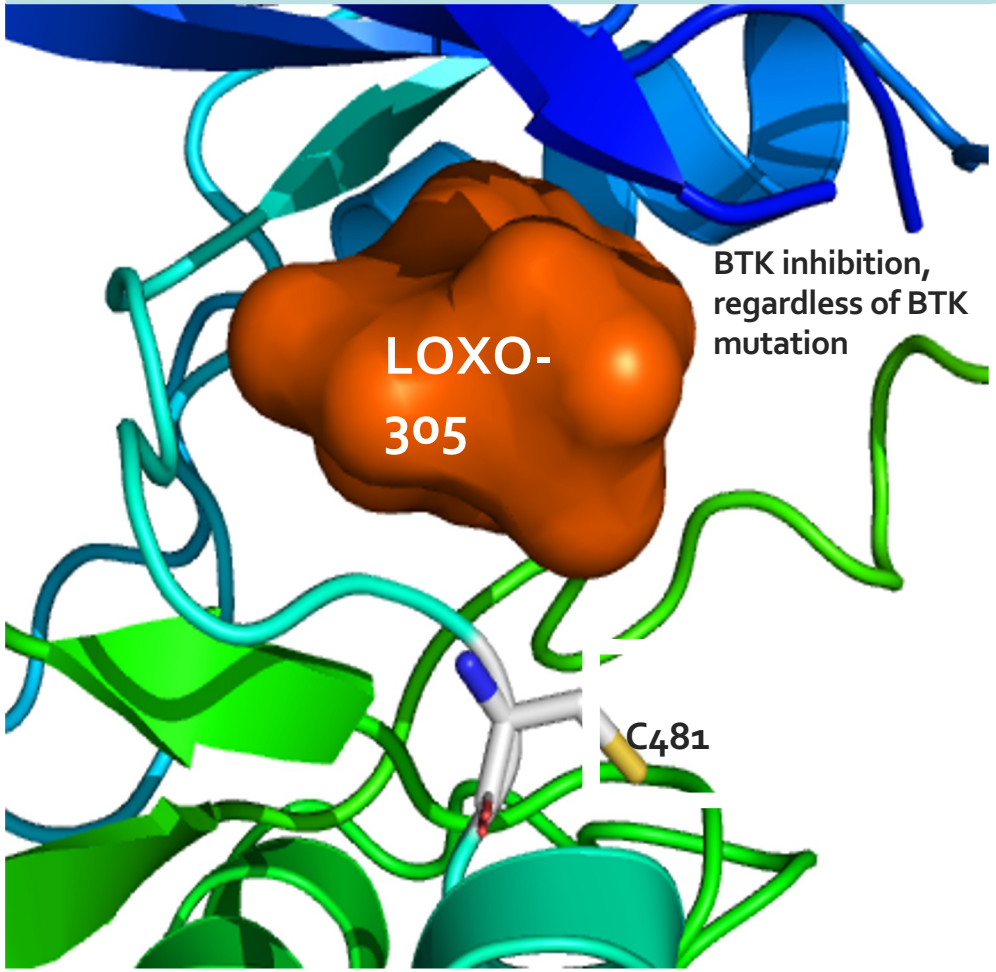
Kinase-dead BTK Leu528Trp mutation is enriched in patients with CLL progressing on zanubrutinib versus ibrutinib, which has potential implications for choice of BTK inhibitor and subsequent therapies, like pirtobrutinib, where this mutation is suspected to confer resistance

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.

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

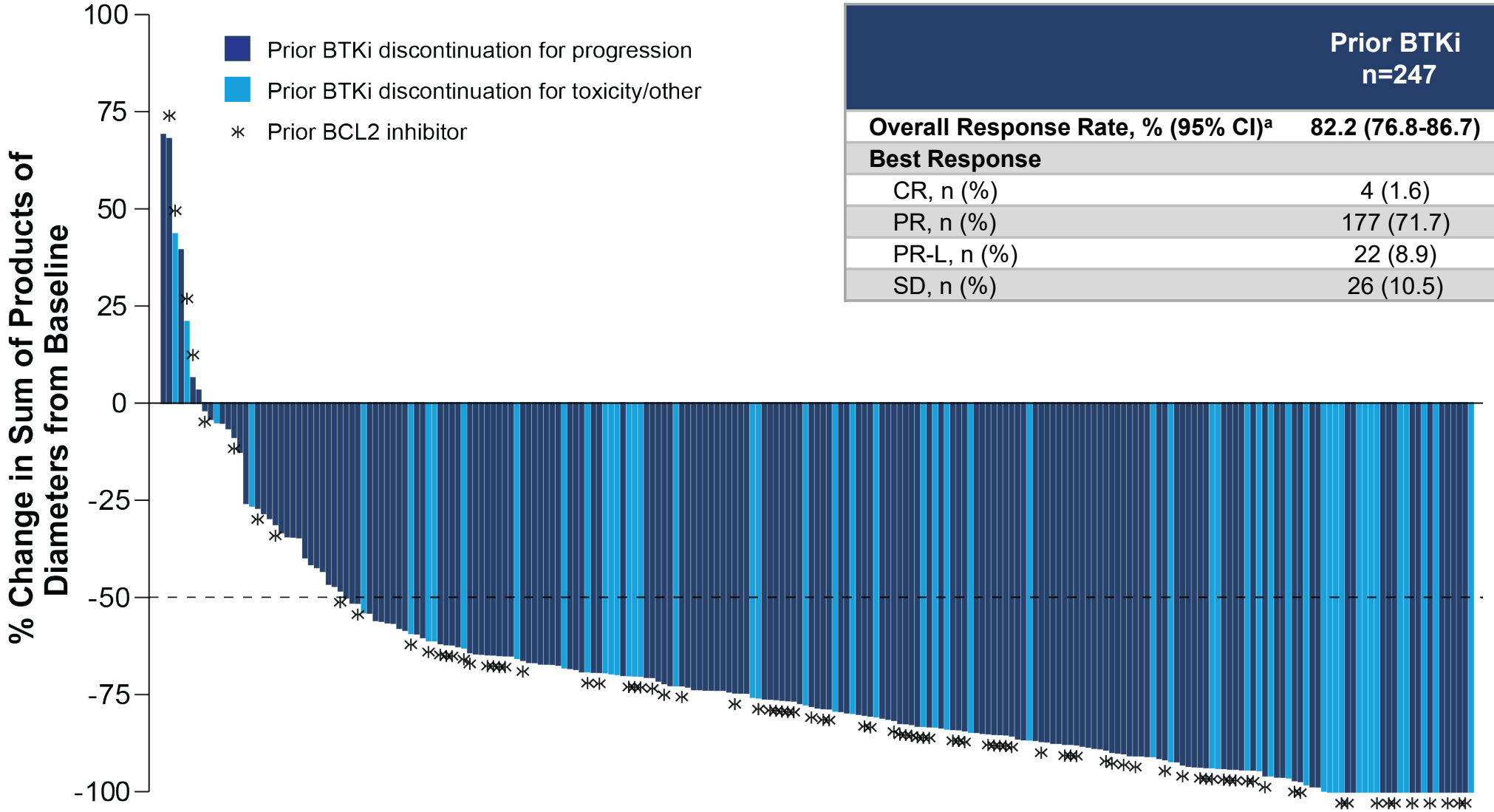


LOXO-305 is a non-covalent BTK inhibitor that is potent against both WT and C481-mutant BTK



Mato et al ASH 2022

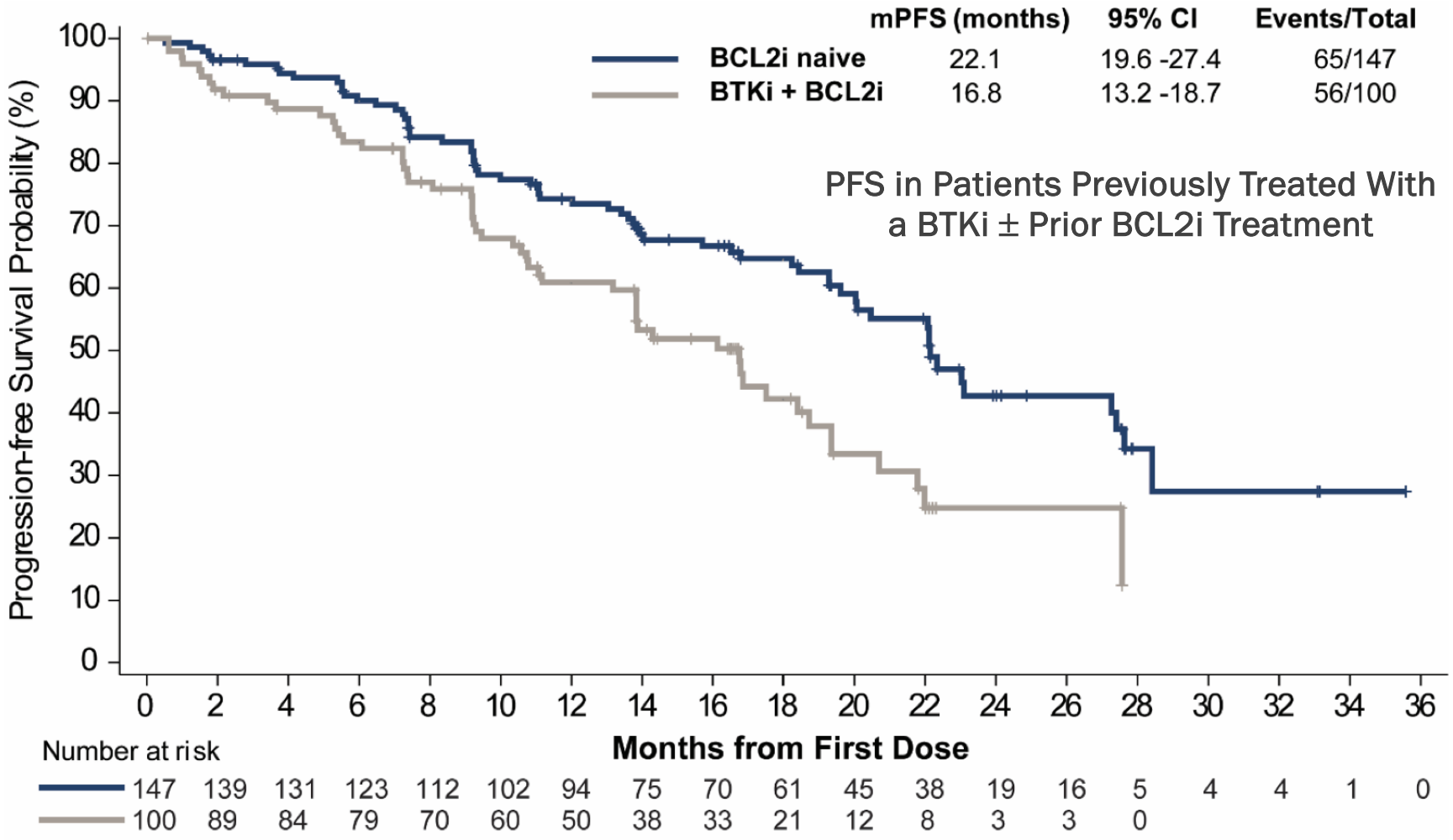
Pirtobrutinib Efficacy in CLL/SLL Patients who Received Prior BTKi Treatment



	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

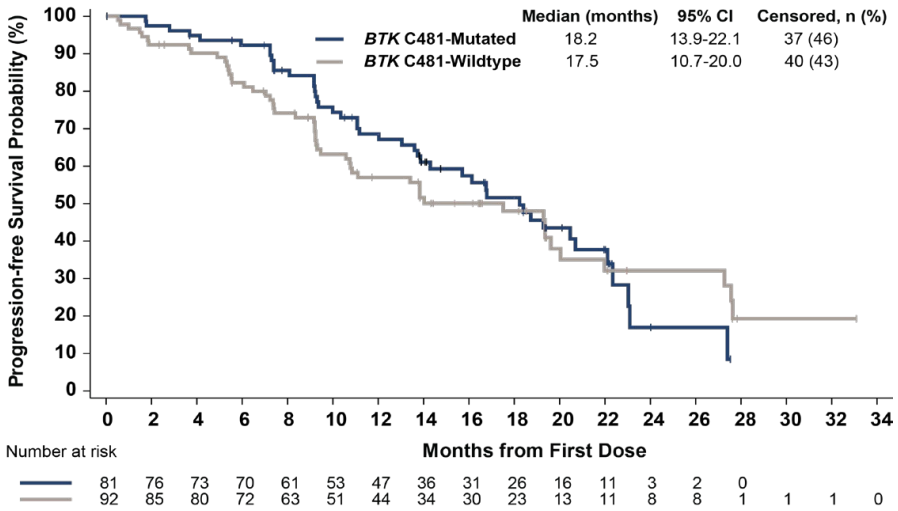
BRUIN 1/2: PFS



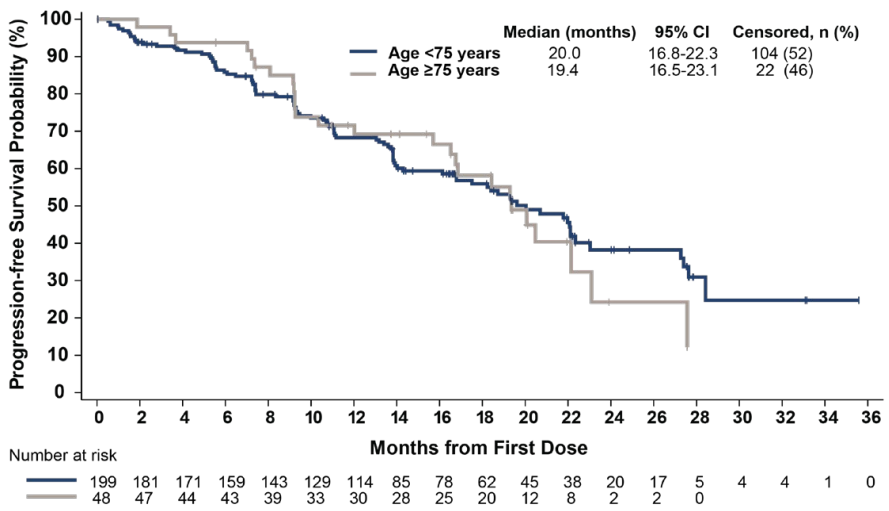
Mato et al. *N Engl J Med*. 2023.

Progression-Free Survival in CLL/SLL Subgroups

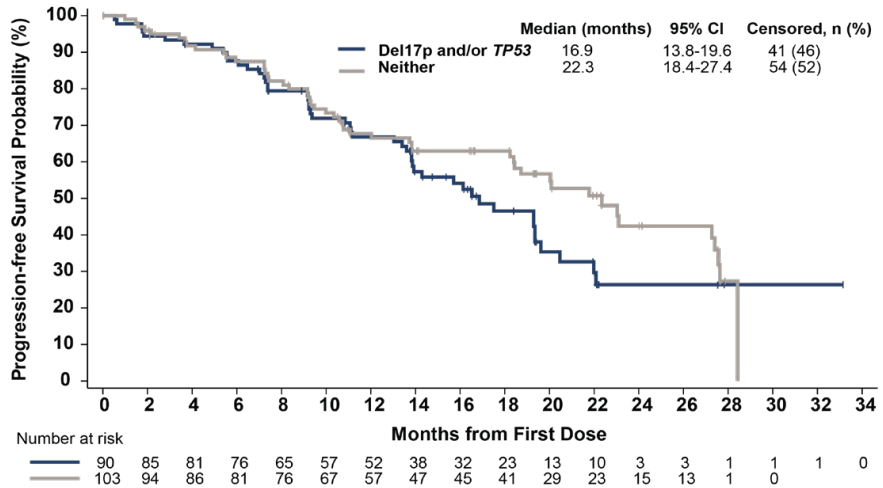
BTK C481 mutation status[a,b]



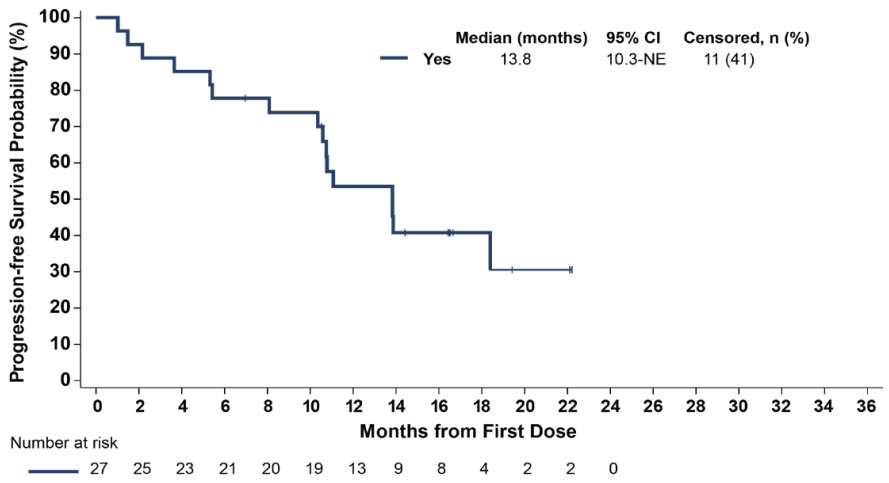
Age



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

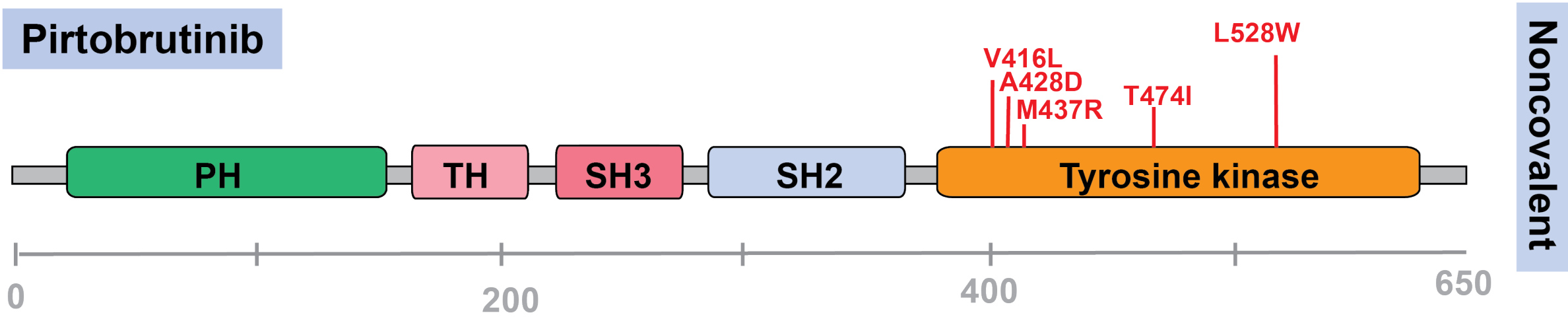


Prior BTKi, CIT, BCL2i, and PI3Ki therapy



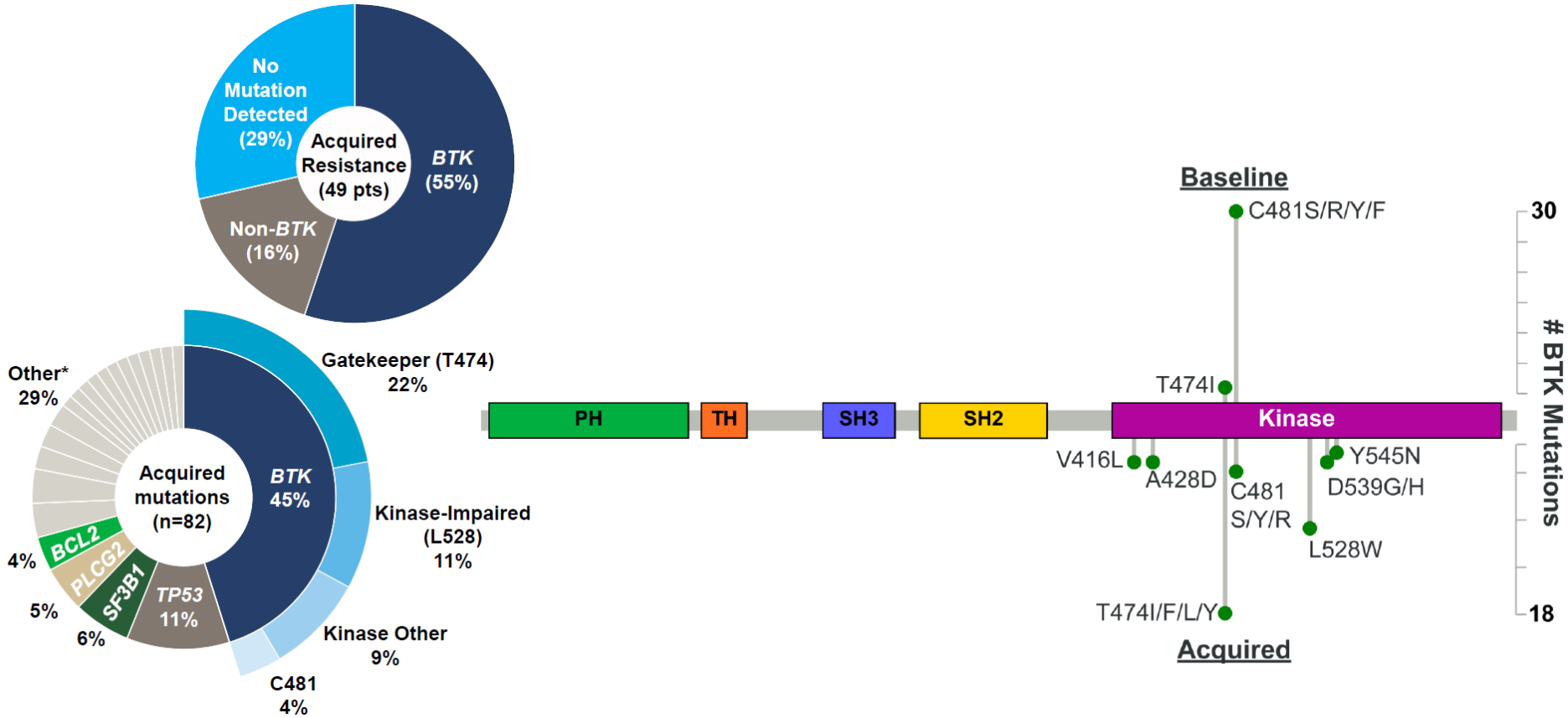
Mato et al ASH 2022

Diverse BTK mutations cause resistance to non- covalent BTKi



Montoya et al ASH 2022

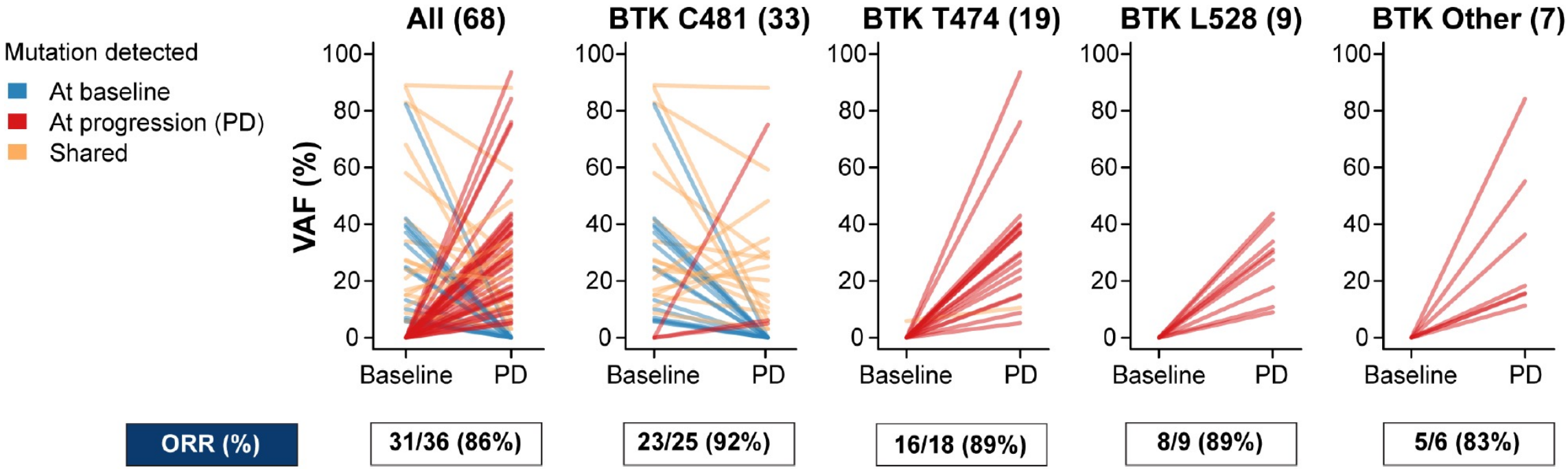
ACQUIRED RESISTANCE TO PIRTOBRUTINIB MOSTLY CONVERGES AROUND ON-TARGET *BTK* MUTATIONS



- Most (71% [35/49]) patients had at least 1 acquired mutation at progression
- There were a total of 82 acquired mutations in 3 patients

*Others: *APC, ATM, CDKN2A, CDKN2B, EP300, ERBB3, IRF4, KIT, KMT2C, NOTCH1, NRAS, NTRK1, PIK3CG, RB1, SMARCA4, TNFAIP3, XPO1*.
Source: Brown et al. Abstract S146, EHA 2023.

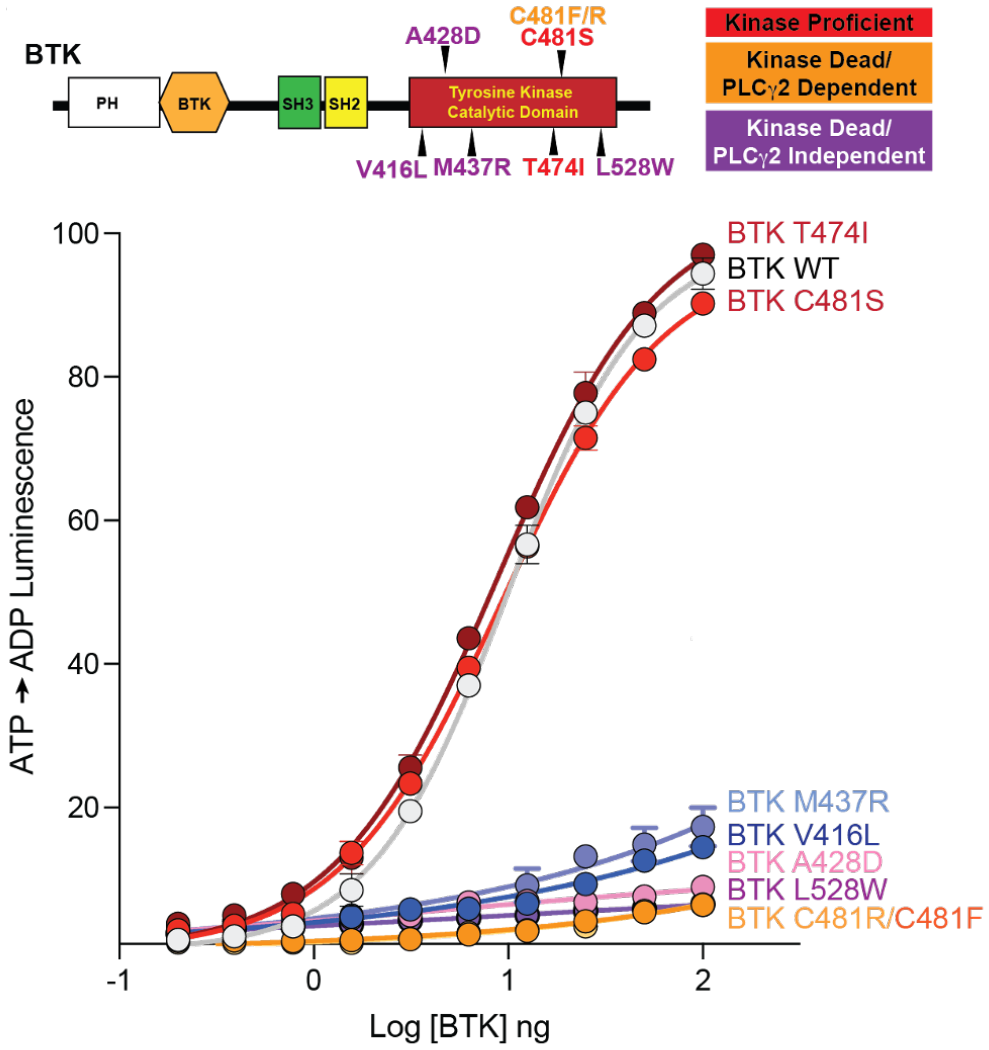
PIRTOBRUTINIB: BTKi ACQUIRED MUTATIONS



- Decrease/clearance of C481 clones observed at progression on pirtobrutinib in 92% (22/24) of patients
- BTK C481R/S/Y, T474, L528, other kinase mutations arose at/near progression (n=27 patients)
- ORRs were similar across groups regardless of the acquired *BTK* mutation

BTKi, Bruton tyrosine kinase inhibitor; ORR, overall response rate; PD, progressive disease; VAF, variant allele frequency.
Source: Brown et al. Abstract S146, EHA 2023.

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

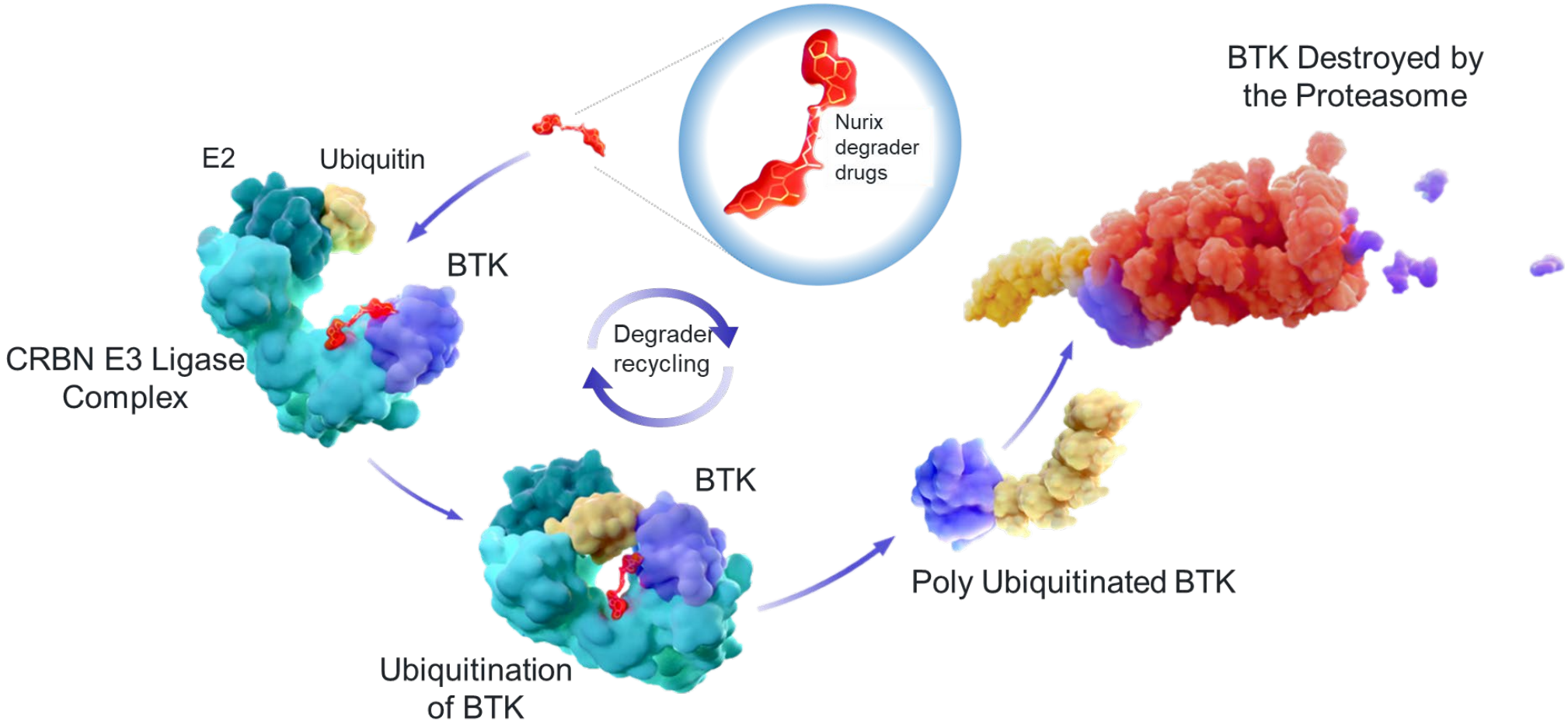


Montoya et al ASH 2022

- 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.

NX-2127: first-in-class targeted protein degrader of BTK

Utilizing the ubiquitin-proteasome pathway to degrade BTK, a well-validated target in B-cell malignancies



Montoya et al ASH 2022

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

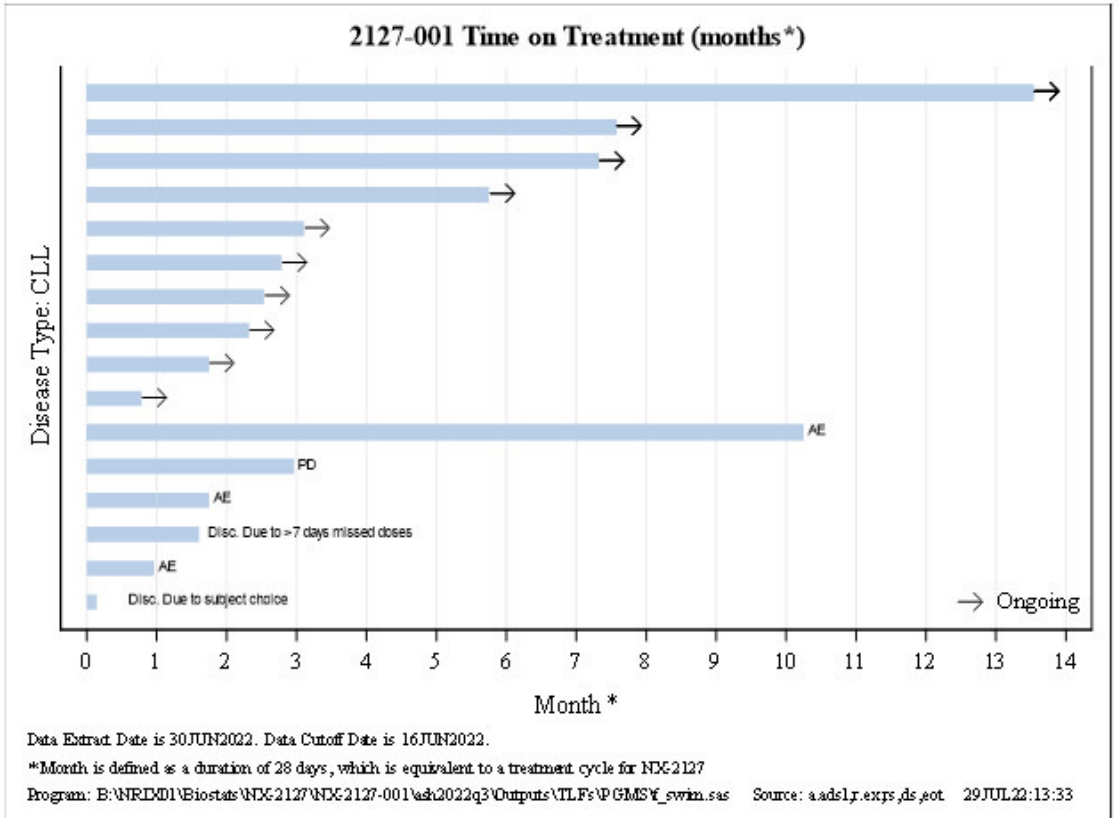
NX-2127
Dose escalation: 100, 200, 300 mg orally daily

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

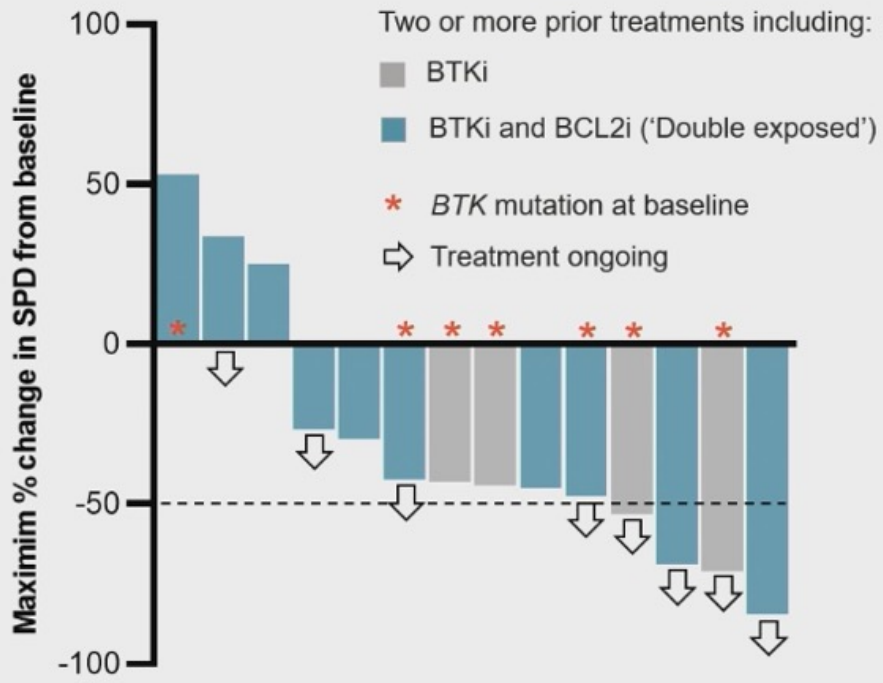


Mato et al. ASH 2022, A#965

NX-2127: Response in BTKi Exposed Patients

Disease-evaluable patients	n=15
Objective response rate,[a] % (95% CI)	33 (12–62)
Best response, n (%)	
CR	0 (0)
PR	5 (33.3)
SD	5 (33.3)
PD	2 (13.3)
NE[b]	3 (20)

[a]Objective response rate includes CR + CRi + nPR + PR-L + PR
[b]Patients who discontinued after a single assessment of SD are considered as NE



***One patient, not shown above, with prior BTKi and BCL2i treatment and with a *BTK* mutation detected at baseline, had no nodal disease at baseline. Their treatment is ongoing with a PR**

Mato et al ASH 2022

Conclusions

- Patient preferences and Individualized therapy should be taken into consideration to choose between fixed duration or tx until progression.
- 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, **acalabrutinib** also showing excellent data with better tolerability.
  - **Zanubrutinib** now approved with great data in front line and good tolerability.
- 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.
- **Relapsed/Refractory CLL**
  - **BTK mutational profile** is an important tool to define BTKi sequencing
  - **Pirtobrutinib** soon to be an option in CLL but already approved in MCL
  - Others non covalent inhibitors on their way.
  - Protein degraders entering Phase I/II
  - CART pending evaluation in a Phase III