# Updates in Chronic Lymphocytic Leukemia

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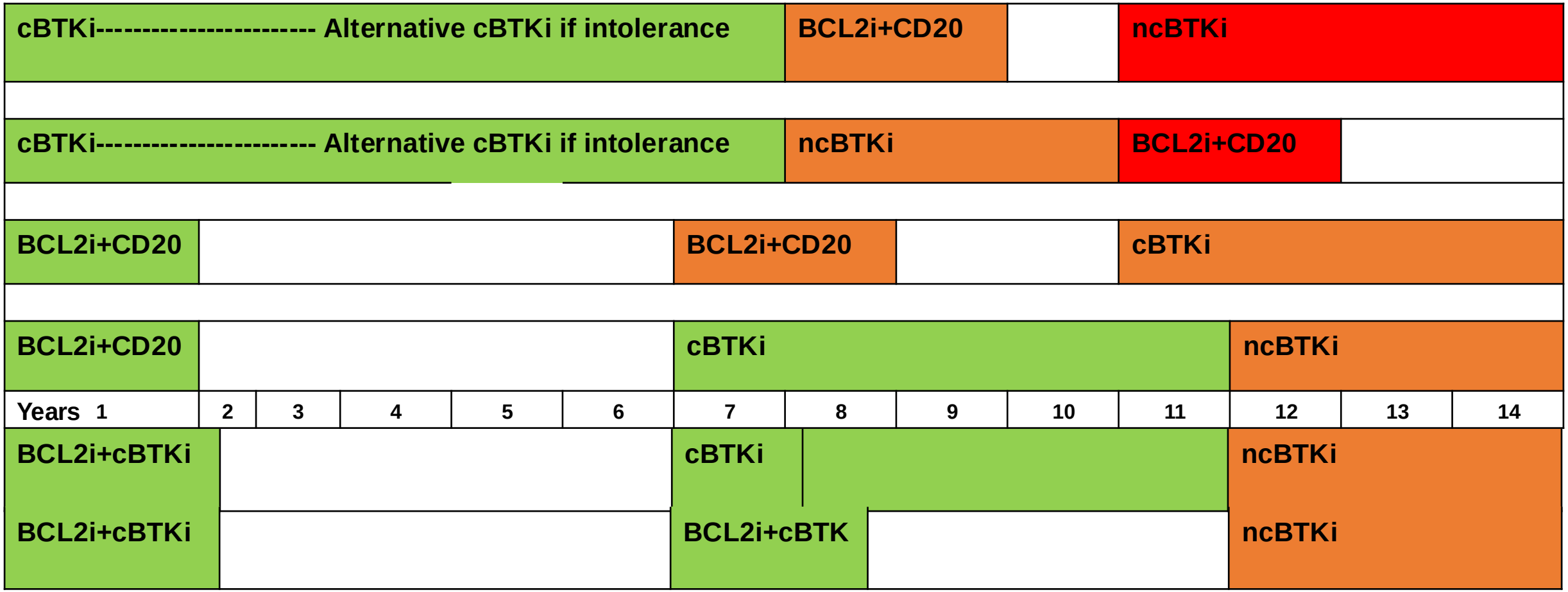
MOFFITT CANCER CENTER

# Sequencing Targeted CLL Therapies



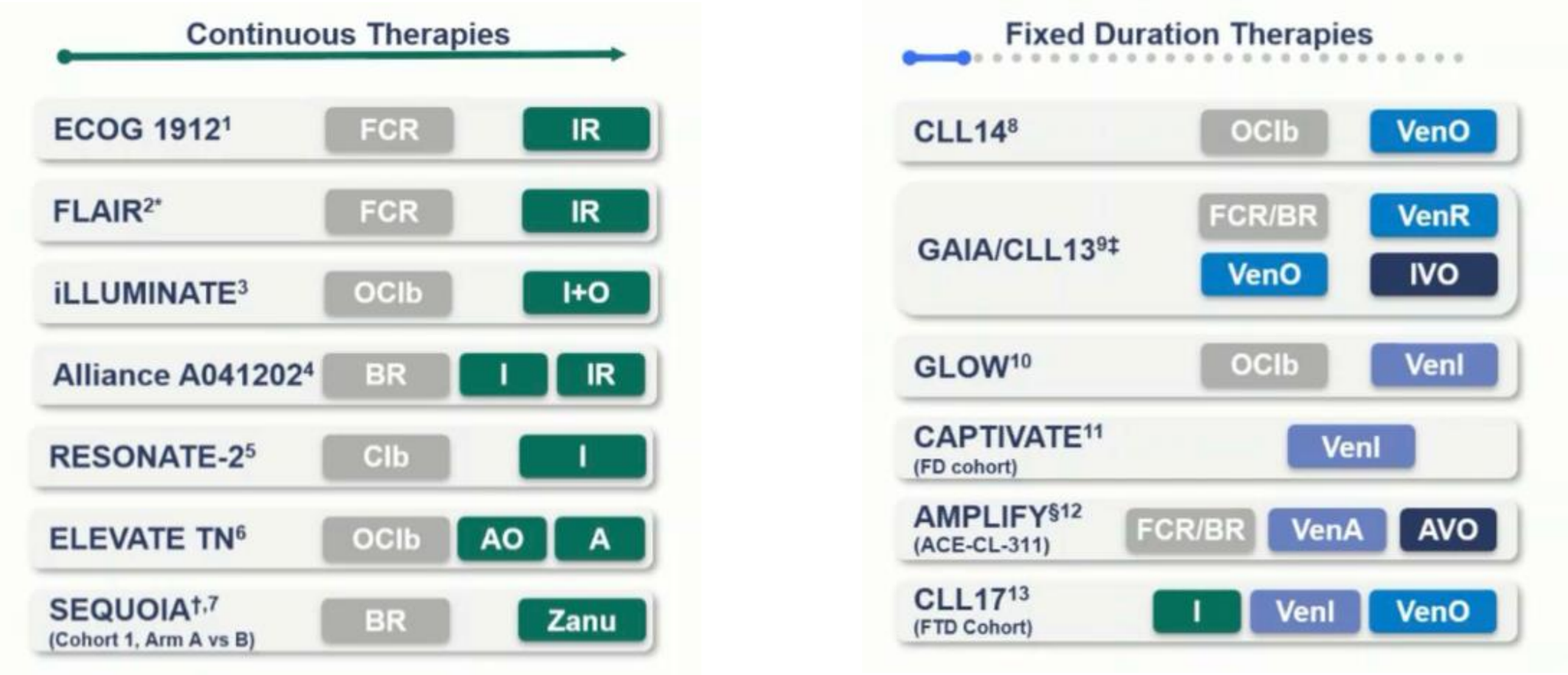

cBTKi = covalent BTKi
ncBTKi = non-covalent

**<u>Double exposed *vs* double refractory</u>**

- Exposed ≠ refractory
- Refractory= progression on treatment

**Faculty's opinion.**

# Continuous Therapy vs Fixed Duration

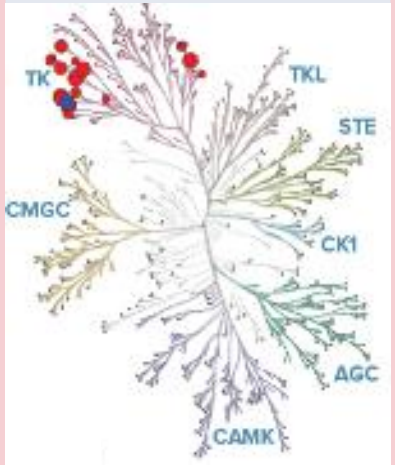



Shanafelt TD, et al. *New Engl J Med.* 2019; 381:435-443. Hillman P, et al. *Lancet Oncol,* 2023,24:535-552. Moreno C, et al. *Lancet Oncol.* 2019,20:43-56. Woyach JA, et al. *Blood,* 2021;138:639. Barr PM, et al. *Blood Adv.* 2022;6:3400-3450. Sharman JP, et al. *Leukemia.* 2022;36:1171-1175. Tam CS, et al. *Lancet Oncol.* 2022;23:1031-1043. AlSawaf O, et al. *Nat Commun.* 2023;14:2147. Eichhorst B, et al. *N Eng J Med.* 2023;338:1739-1754. Kater AP, et al. *NEJM Evid.* 2022;1:711. Tam CS, et al. *Blood*. 2022;139:3278-3289. National Institute of Health (NIH). Accessed Sept 25, 2024. https://clinicaltrials.gov/study/NCT04608318; NCT03836261

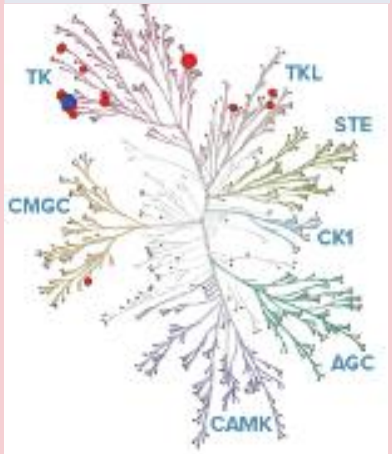
# Several Covalent BTKi to Consider with Differences in BTKi Specificity, MOA, and Potential for Off-Target Effects

## Covalent

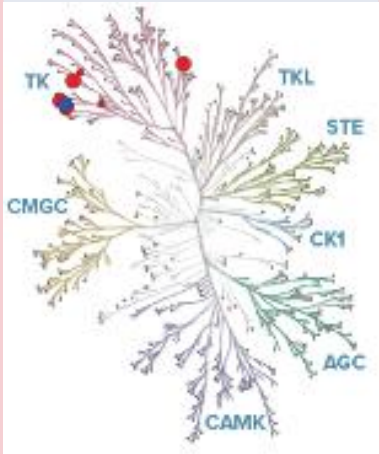
### Ibrutinib




### Acalabrutinib




### Zanubrutinib

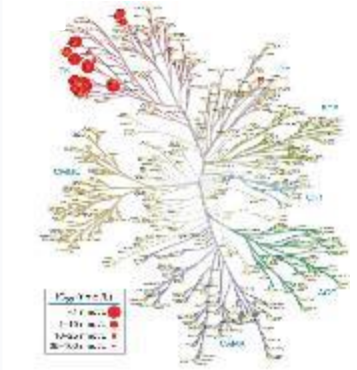



- BTK
- Off target kinases

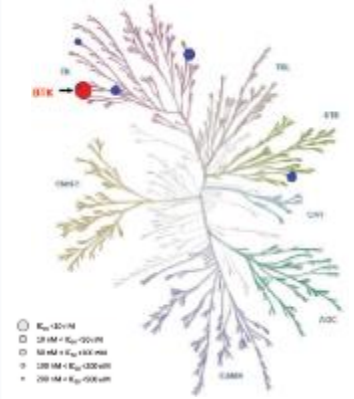
- 95-100% inhibition
- 90-95% inhibition
- 75-90% inhibition
- 50-75% inhibition

## Noncovalent

### Nemtabrutinib



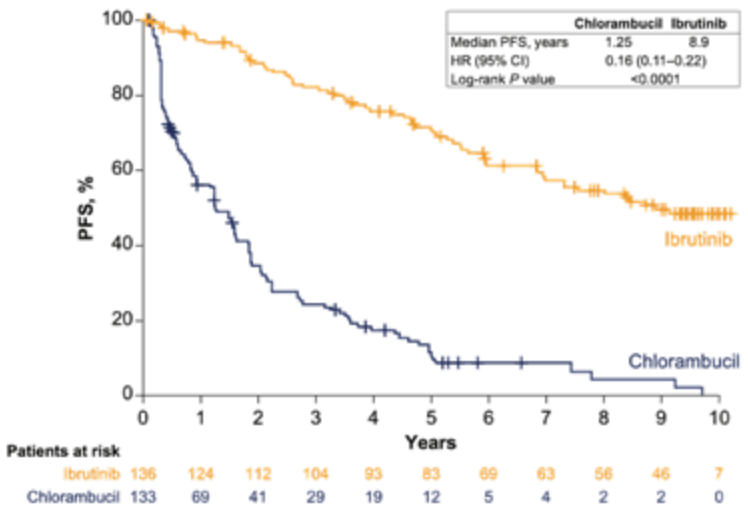
### Pirtobrutinib

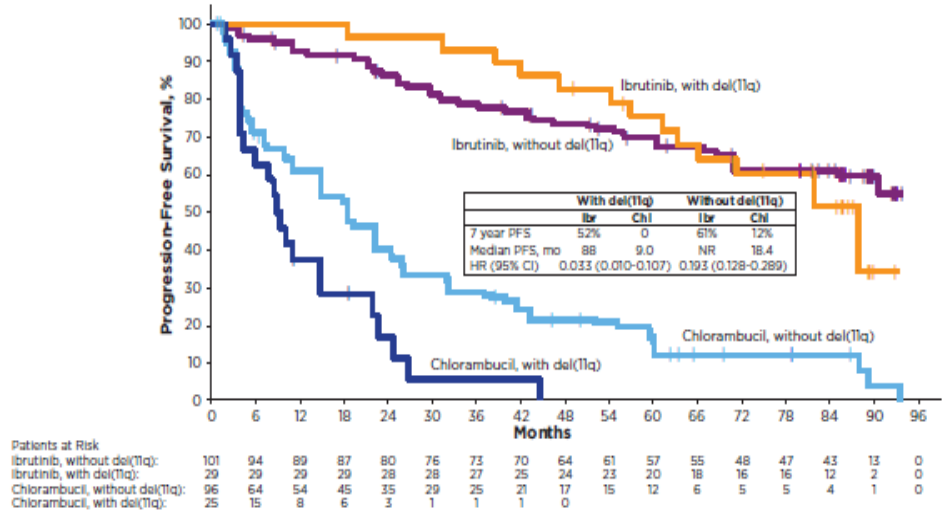


MOA = mechanism of action.

Shadman M, et al. *Lancet Haematol*. 2023;10(1):e35-e45. Reiff SD, et al. *Cancer Discov*. 2018;8(10):1300-1315. Brandhuber B, et al. Presented at: Society of Hematologic Oncology (SOHO) Sixth Annual Meeting; Sep 12-25, 2018; Houston, TX. CLL-200.

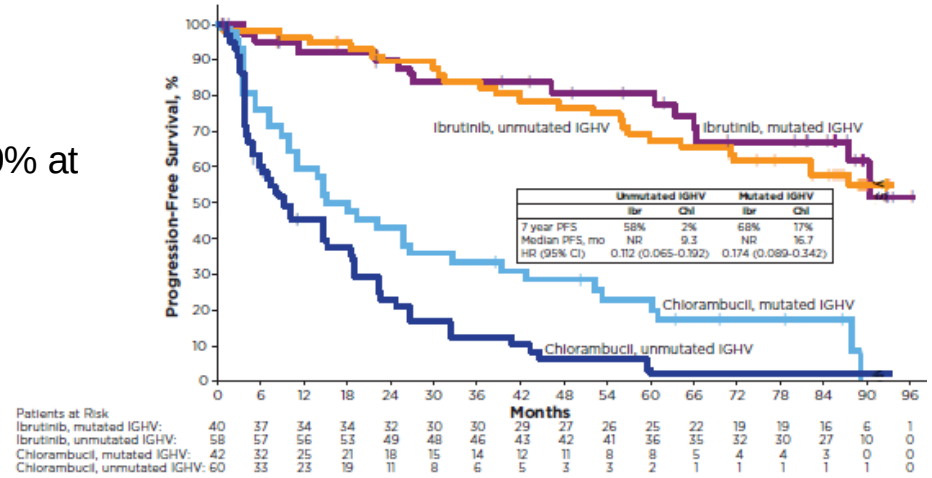
# RESONATE-2: Median PFS Reached at 8.9 Years




| | 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) |

PFS with ibrutinib: 59% at 84 mo



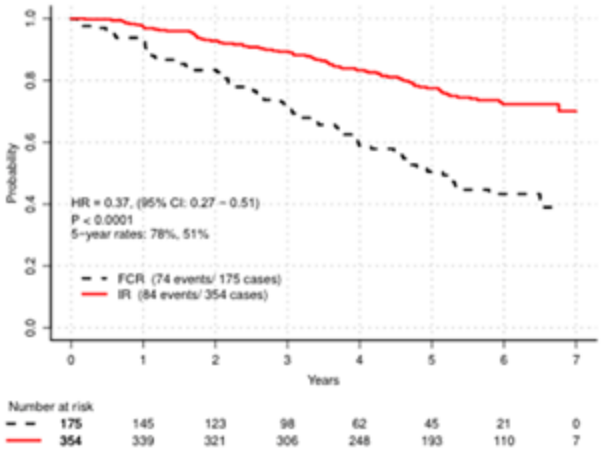

**PFS = progression free survival; AE = adverse event; PD = progressive disease.**

**Barr PM, et al. *Blood Adv*. 2022;6(11):3440-3450. Burger J, et al. Presented at: European Hematology Association (EHA); June 13, 2024; Madrid, Spain. P1841.**

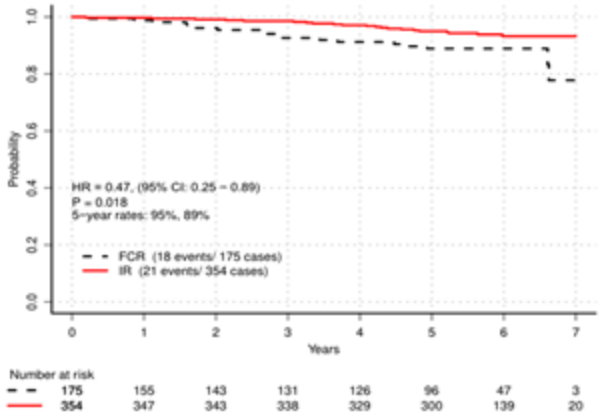
# E1912: 5 Years Updated PFS, OS by IGHV Status

| 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%) |

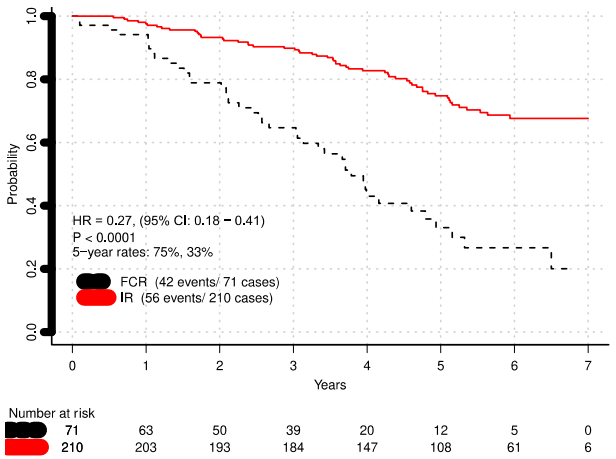
PFS



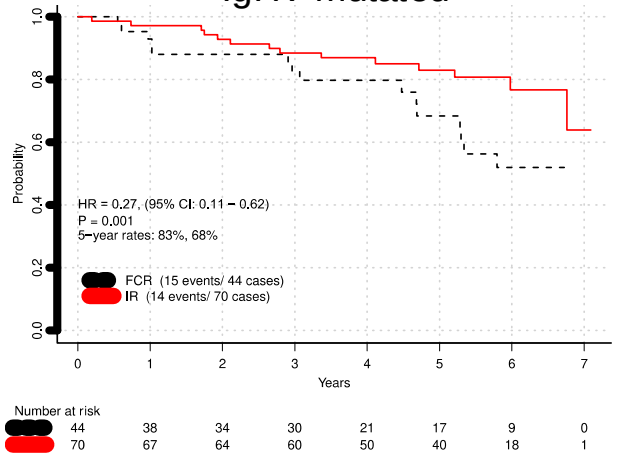

OS




IgHV unmutated




IgHV mutated

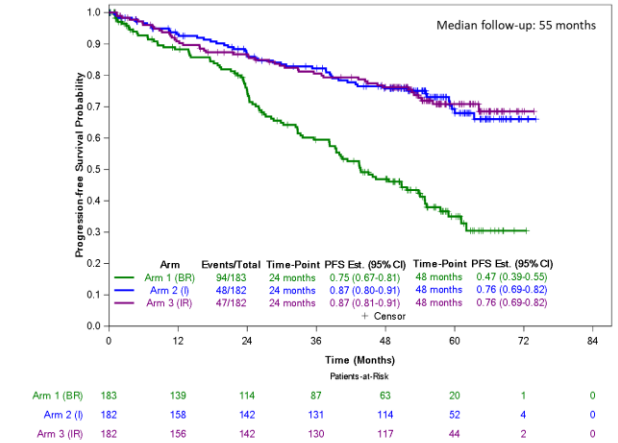



OS = overall survival; FCR = fludarabine, cyclophosphamide, rituximab; IR = ibrutinib, rituximab.

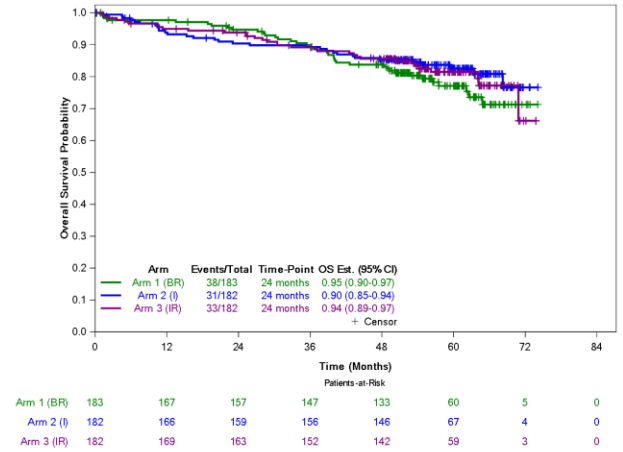
Shanafelt TD, et al. *Blood*. 2022;140(2):112-120.

# A041202: First-Line Ibrutinib ± Rituximab vs Bendamustine + Rituximab in Older Patients with CLL/SLL

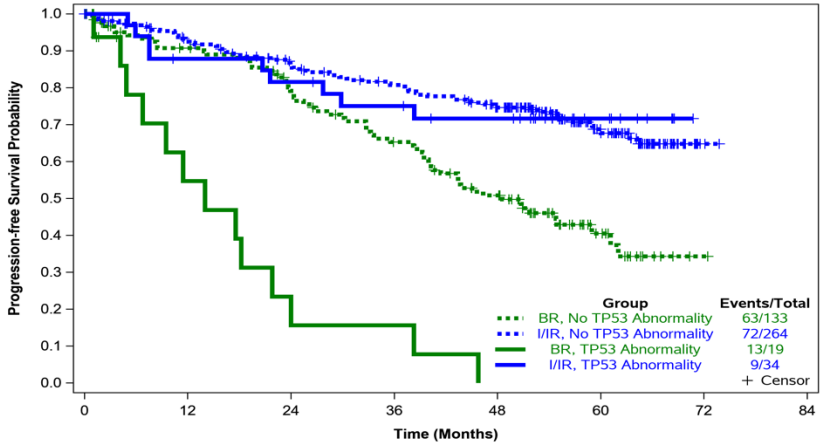
**PFS**



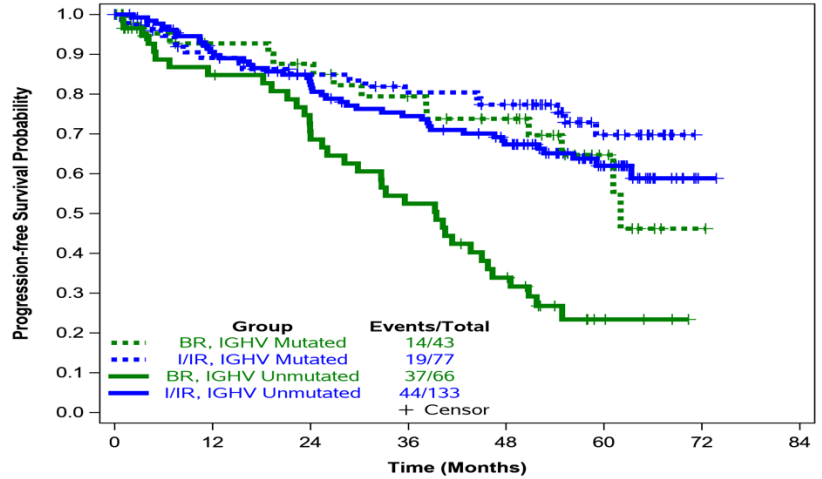

**OS**




**TP53**



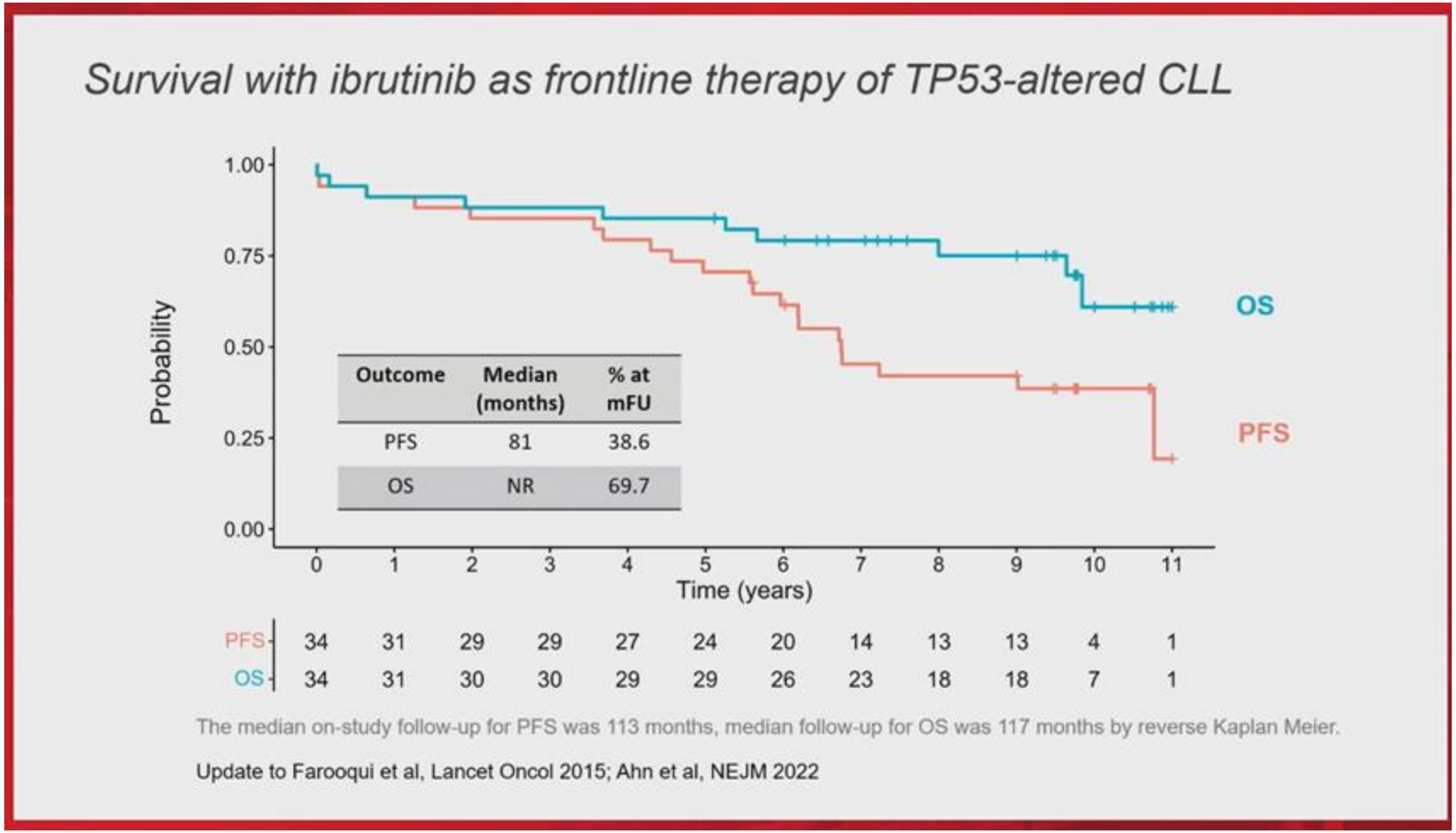

**IGHV**




Woyach JA, et al. *Blood.* 2021;138(Suppl 1):639.

# PFS and OS in TP53 Altered, Treatment-Naïve CLL

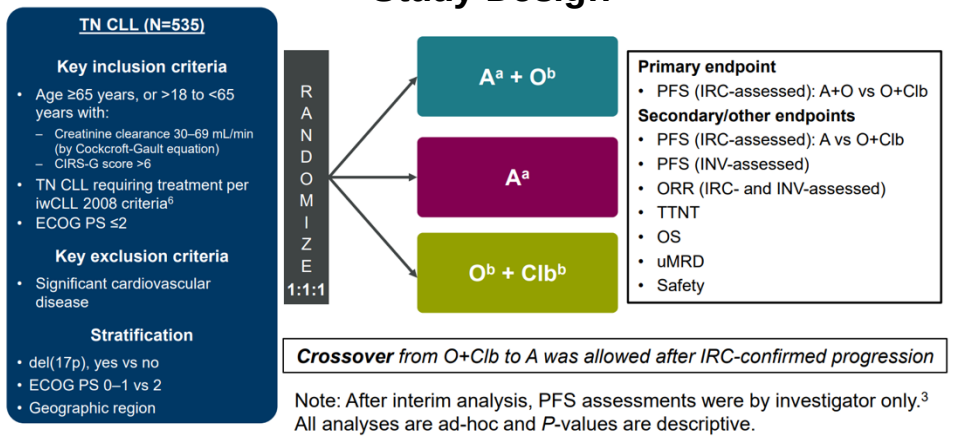
- OS at 117 months (~10 years) was 69.7%
- mPFS was 81 months (~7 years)




**Itsara A, et al. Presented at: American Society of Hematology (ASH) 2023; December 9, 2023; San Diego, CA. 201.**

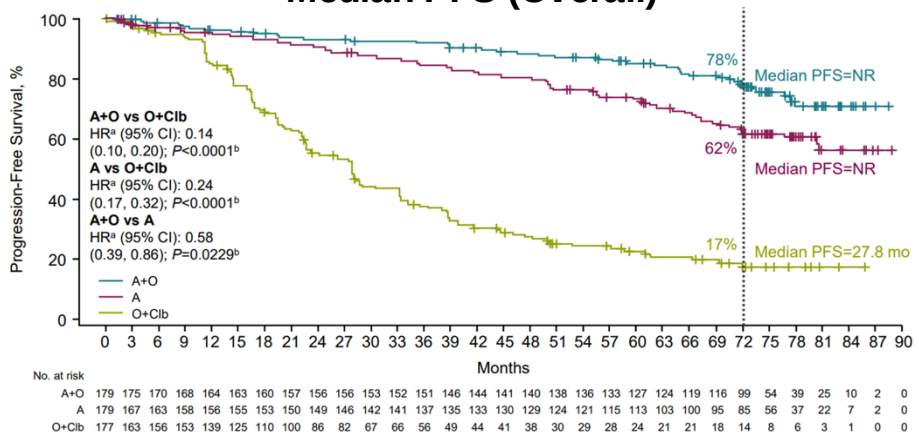
# ELEVATE-TN: 6-Year Follow-Up Results

## Study Design

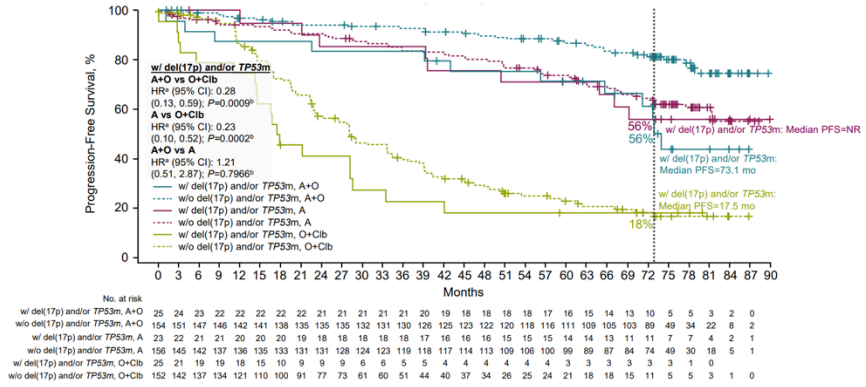



Note: After interim analysis, PFS assessments were by investigator only.[3] All analyses are ad-hoc and *P*-values are descriptive.

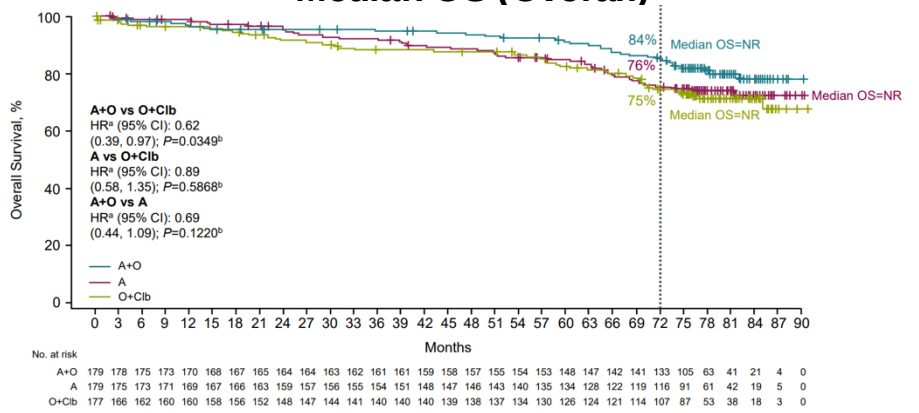
## Median PFS (Overall)




## Median PFS (del[17p]) and/or TP53 Mutation)




## Median OS (Overall)

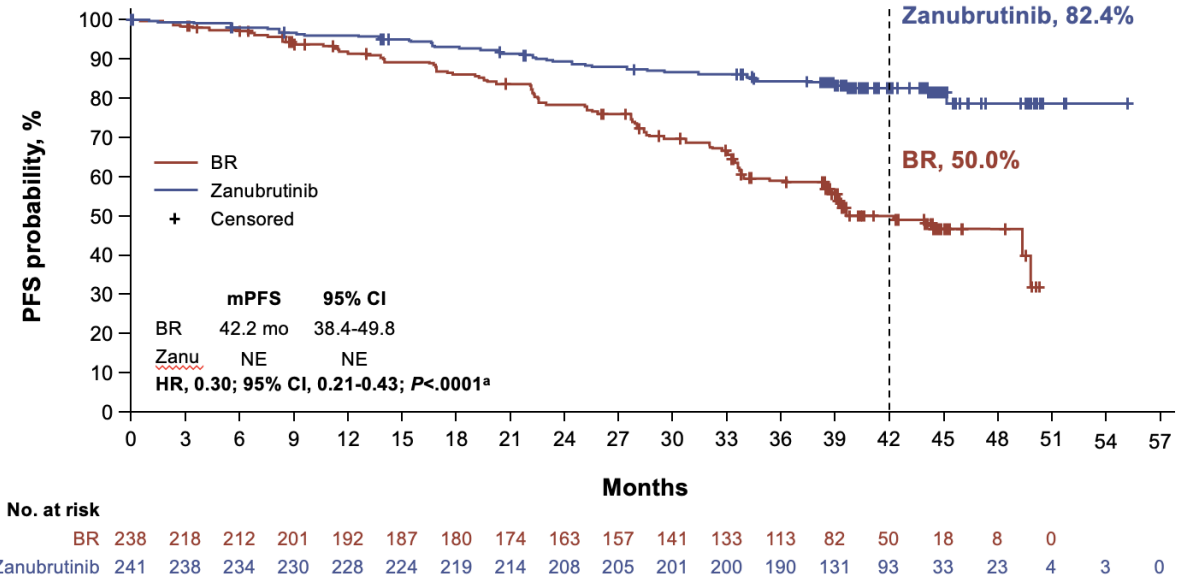



**ECOG = Eastern Cooperative Oncology Group; IRC = independent review committee; INV = investigator; ORR = objective response rate; TTNT = time to next treatment; uMRD = undetectable minimal residual disease.**

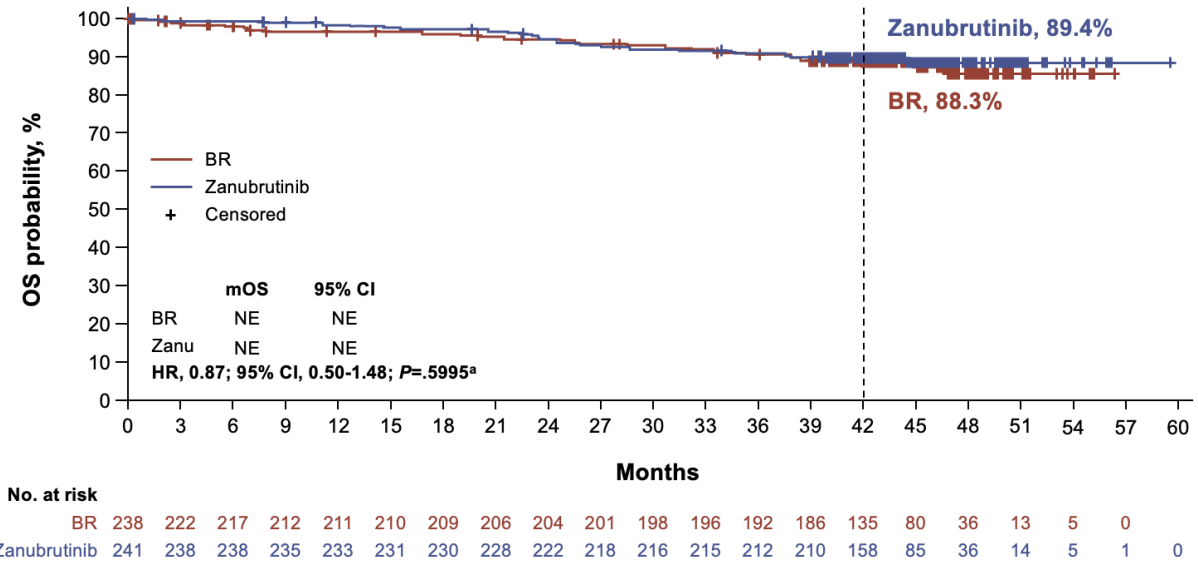
**Sharman JP, et al. Presented at: ASH; December 10, 2023; San Diego, CA. 636. Itsara A, et al. Presented at ASH; December 9, 2023; San Diego, CA. 201.**

# SEQUOIA Cohort 1: PFS and OS in Patients without del(17p)

## Progression Free Survival




## Overall Survival

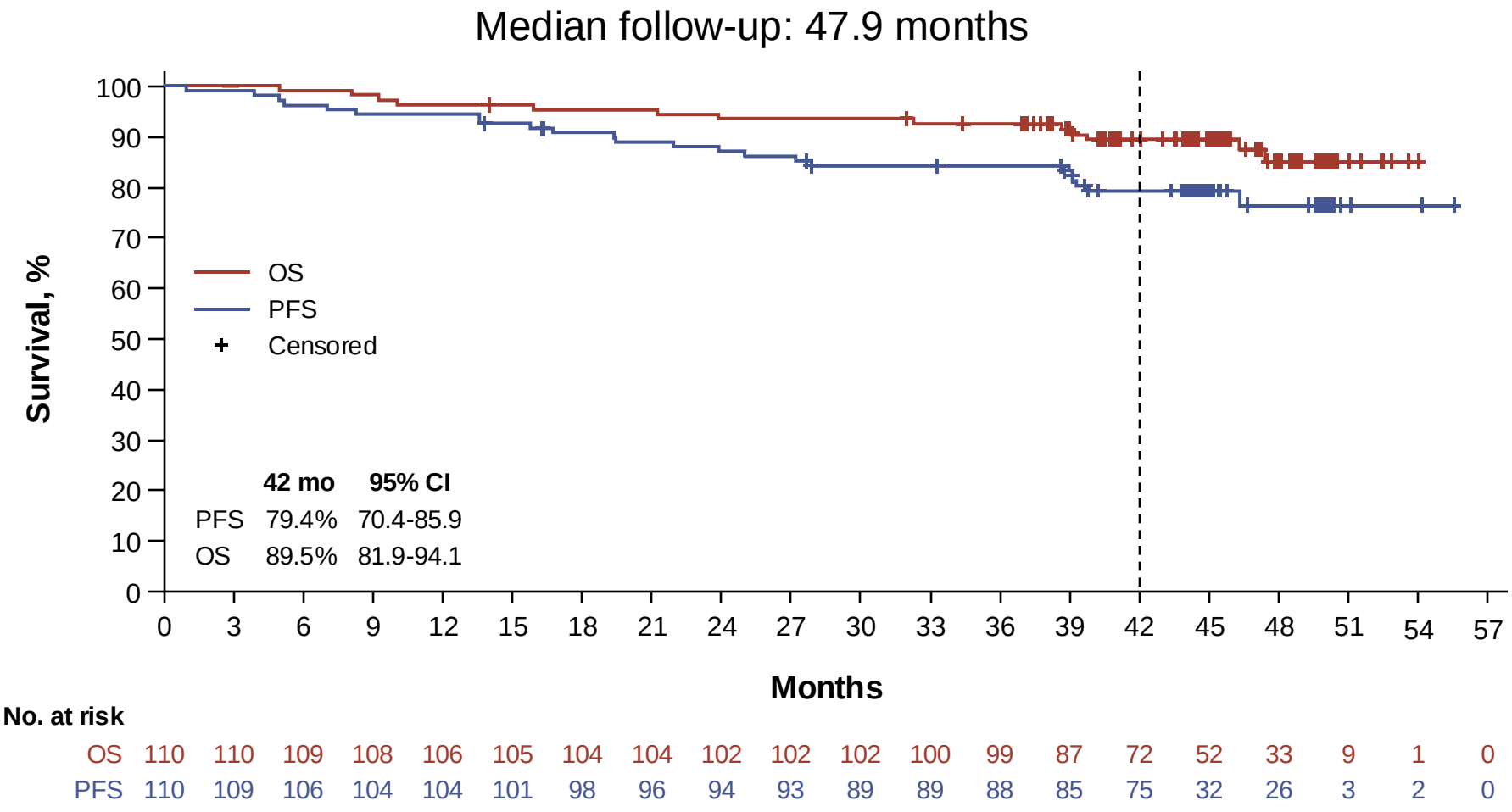



## Median follow-up: 43.7 months

BR = bendamustine, rituximab; NE = not evaluated.

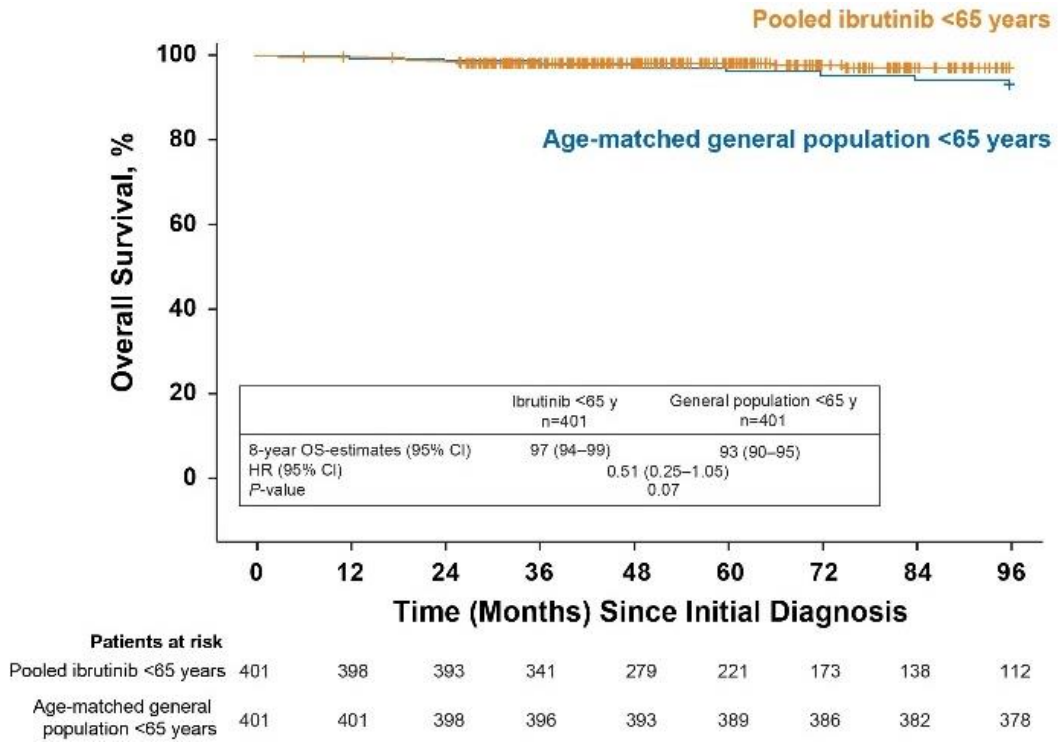
Shadman JP, et al. Presented at: 17th International Conference on Malignant Lymphoma (ICML); June 13-17, 2023; Lugano, Switzerland. 154.

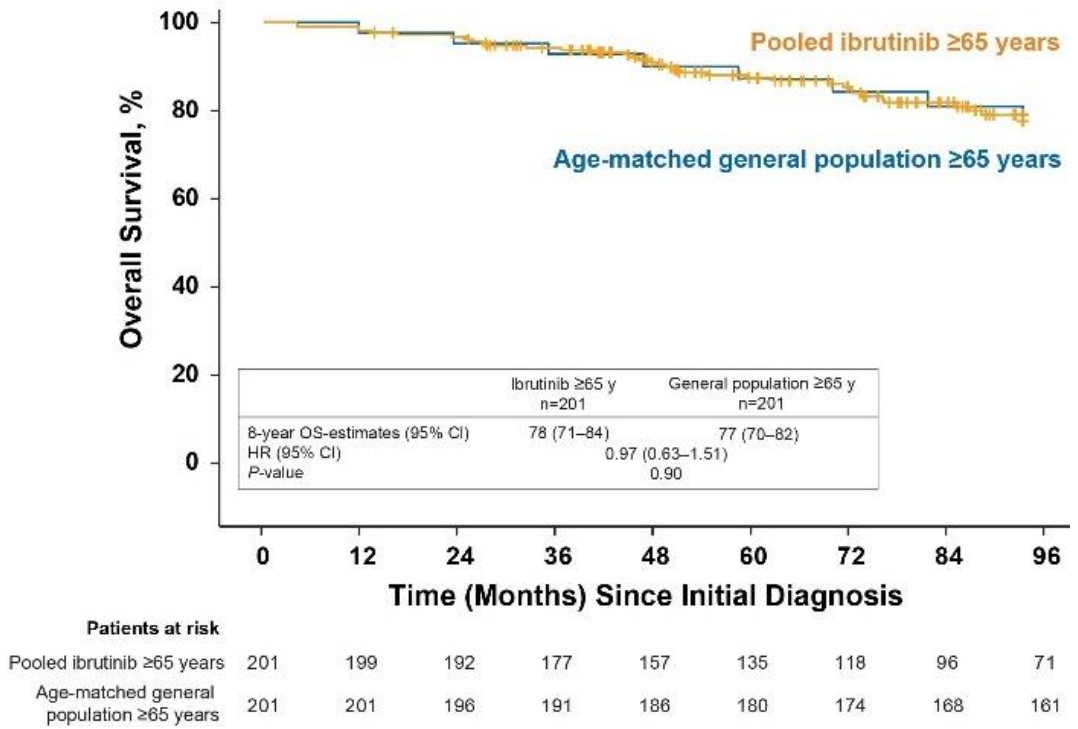
# SEQUOIA Cohort 1: PFS and OS in Patients with del(17p)




Shadman JP, et al. Presented at: ICML 2023; June 13-17, 2023; Lugano, Switzerland. 154.

# Patients with CLL Treated with Continuous BTKi Are Living Longer, therefore QoL Becomes Paramount when Selecting Treatment

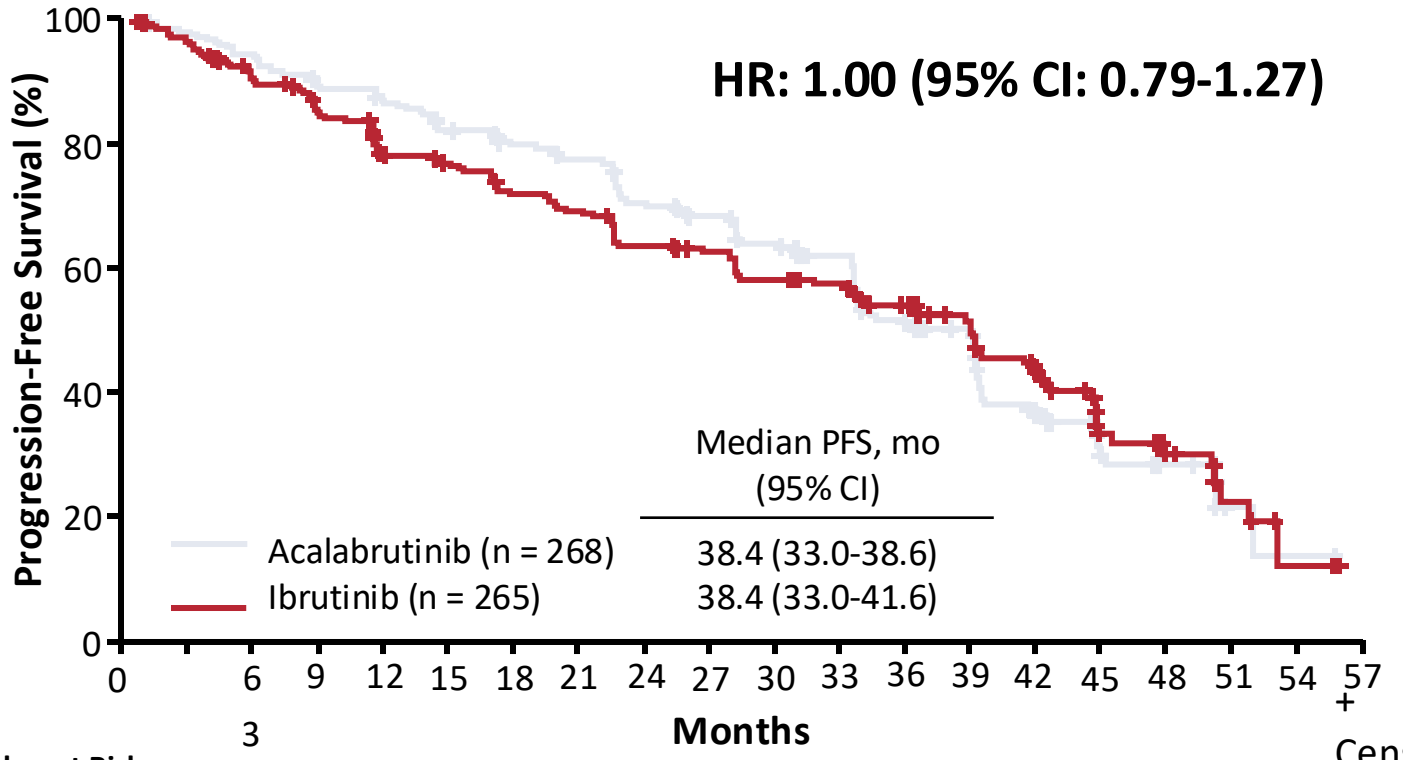



Ghia P, et al. *Hemasphere*. 2024;8(5):e74.

# 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**

**NI = noninferiority.**

**Byrd JC, et al. *J Clin Oncol*. 2021;39(31):3441-3452.**

# ELEVATE-RR: AEs of Clinical Interest

| AE, n (%) | Acalabrutinib (n = 266) | | Ibrutinib (n = 263) | |
|---|---|---|---|---|
| | Any Grade | Grade ≥3 | Any Grade | Grade ≥3 |
| Cardiac events<br>▪ Atrial fibrillation/flutter<br>▪ Ventricular arrhythmias | 64 (24.1)<br>**25 (9.4)**<br>0 | 23 (8.6)<br>13 (4.9)<br>0 | 79 (30.0)<br>**42 (16.0)**<br>3 (1.1) | 25 (9.5)<br>10 (3.8)<br>1 (0.4) |
| Bleeding events<br>▪ Major bleeding events | **101 (38.0)**<br>12 (4.5) | 10 (3.8)<br>10 (3.8) | **135 (51.3)**<br>14 (5.3) | 12 (4.6)<br>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) |

**SPM = second primary malignancy; NMSC = non-melanoma skin cancer; ILD = interstitial lung disease.**

**Byrd JC, et al. *J Clin Oncol*. 2021;39(31):3441-3452.**

# ALPINE: Zanubrutinib Sustains PFS Benefit at 36 Mo


Brown JR, et al. Presented at: ASH 2023; December 9, 2023; San Diego, CA. 202.

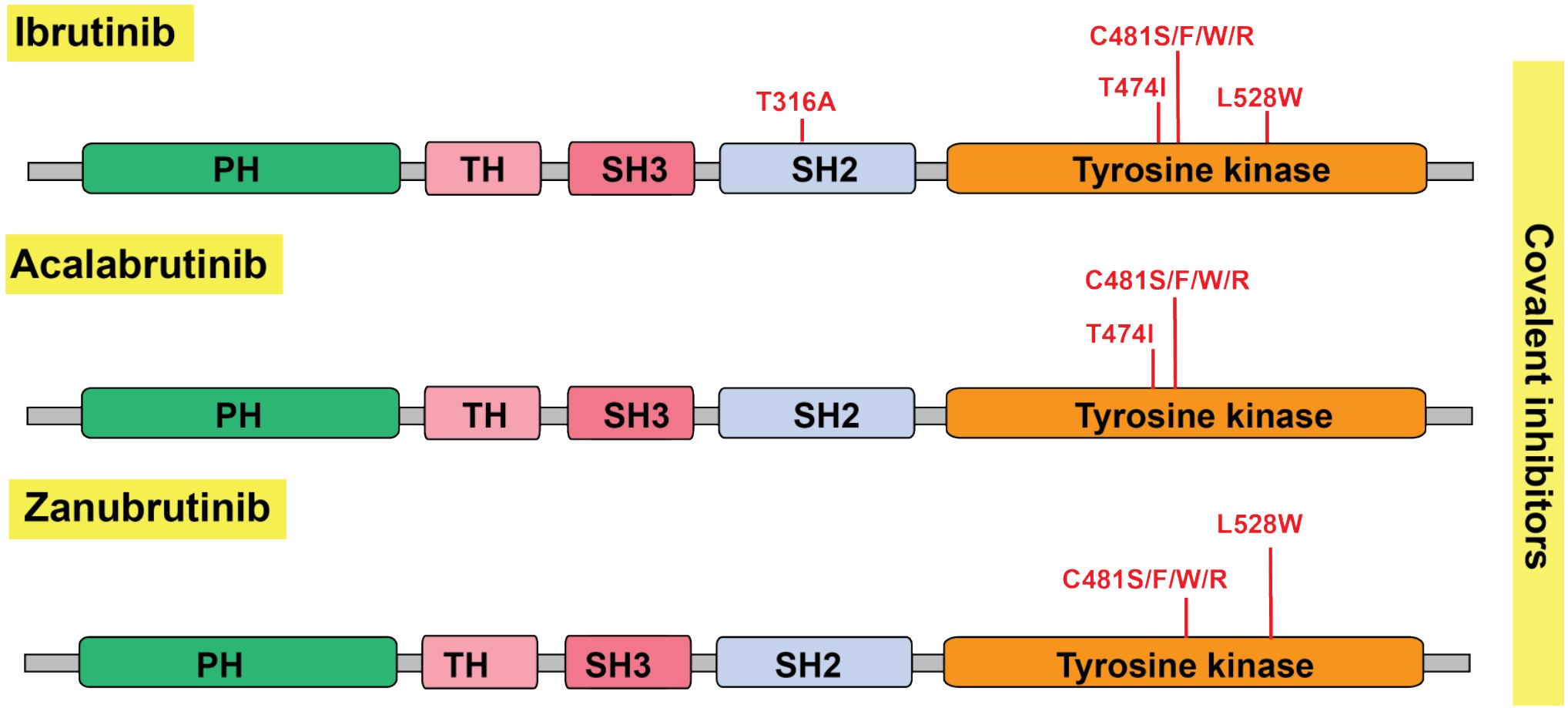
# AEs of Special Interest Occurring in ≥ 2 Patients

| | Zanubrutinib (n=324) | | Ibrutinib (n=324) | |
|---|---|---|---|---|
| | **Any Grade** | **Grade ≥3** | **Any Grade** | **Grade ≥3** |
| Infection | 264 (81.5) | 115 (35.5) | 260 (80.2) | 111 (34.3) |
| *Opportunistic Infections* | 8 (2.5) | 6 (1.9) | 13 (4.0) | 5 (1.5) |
| ***COVID-19 Related[b]*** | **145 (44.8)** | **56 (17.3)** | **105 (32.4)** | **38 (11.7)** |
| Bleeding | 142 (43.8) | 12 (3.7) | 144 (44.4) | 13 (4.0) |
| *Major Hemorrhage* | 13 (4.0) | 12 (3.7) | 16 (4.9) | 13 (4.0) |
| **Hypertension** | **86 (26.5)** | **53 (16.4)** | **80 (24.7)** | **47 (14.5)** |
| **Atrial fibrillation/flutter** | **22 (6.8)** | **10 (3.1)** | **53 (16.4)** | **16 (4.9)** |
| Anemia | 53 (16.4) | 7 (2.2) | 59 (18.2) | 11 (3.4) |
| **Neutropenia** | **100 (30.9)** | **72 (22.2)** | **94 (29.0)** | **72 (22.2)** |
| Thrombocytopenia | 43 (13.3) | 12 (3.7) | 53 (16.4) | 19 (5.9) |
| Second primary malignancies | 46 (14.2) | 26 (8.0) | 52 (16.0) | 19 (5.9) |

[a]Pooled MedDRA preferred terms.
[b]Includes preferred terms of COVID-19, COVID-19 pneumonia, and suspected COVID-19.

**The rate of any grade atrial fibrillation/flutter was significantly lower with zanubrutinib vs ibrutinib (6.8% vs 16.4%, $p<0.0001$).**
**Brown JR, et al. Presented at: ASH 2023; December 9, 2023; San Diego, CA. 202.**

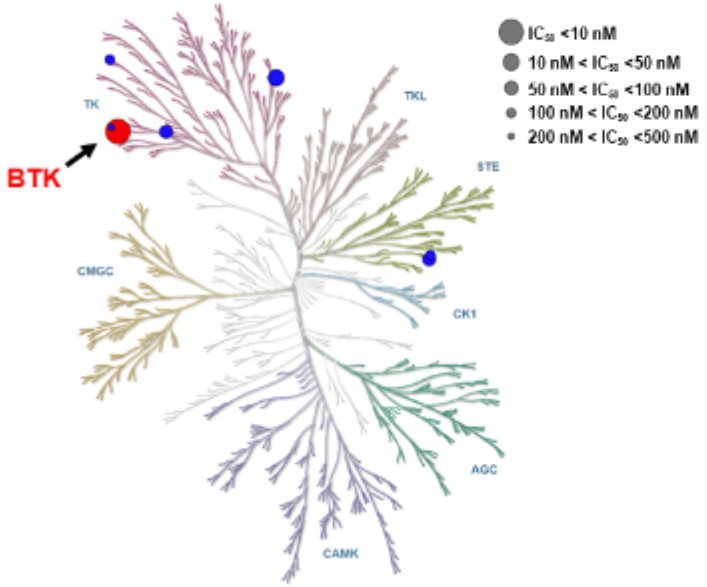
# Diverse BTK mutations cause resistance to covalent BTK inhibitors



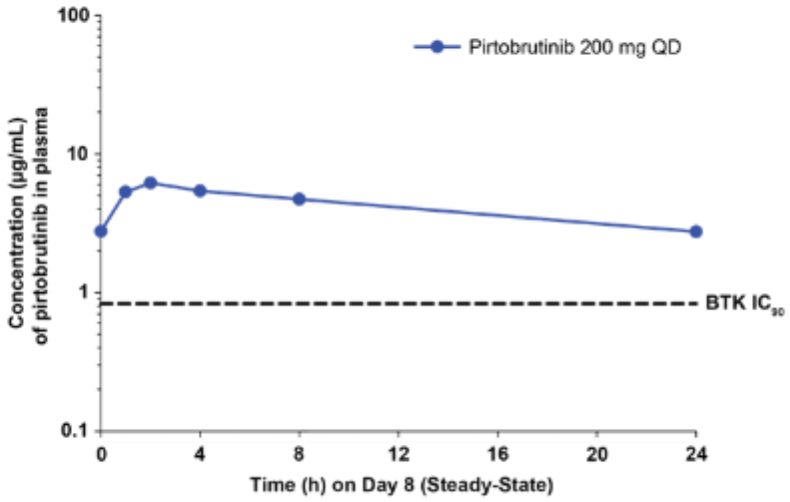

Montoya et al ASH 2022

# Pirtobrutinib Is a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor

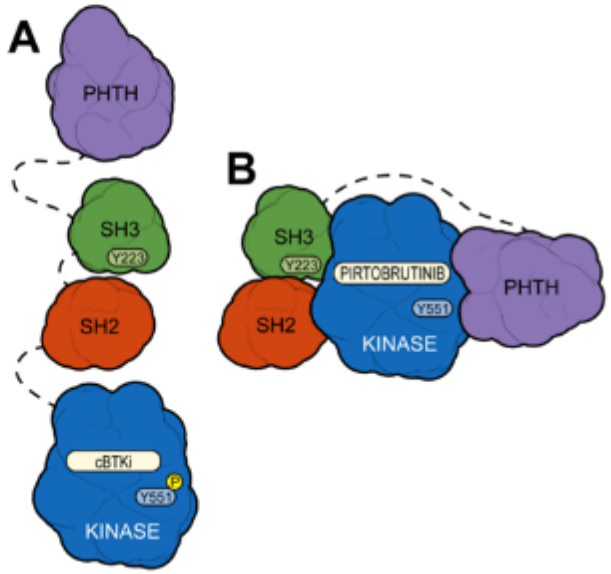
**Highly selective for BTK**[5,6]




**Plasma exposures exceeded BTK $IC_{90}$ throughout dosing interval**



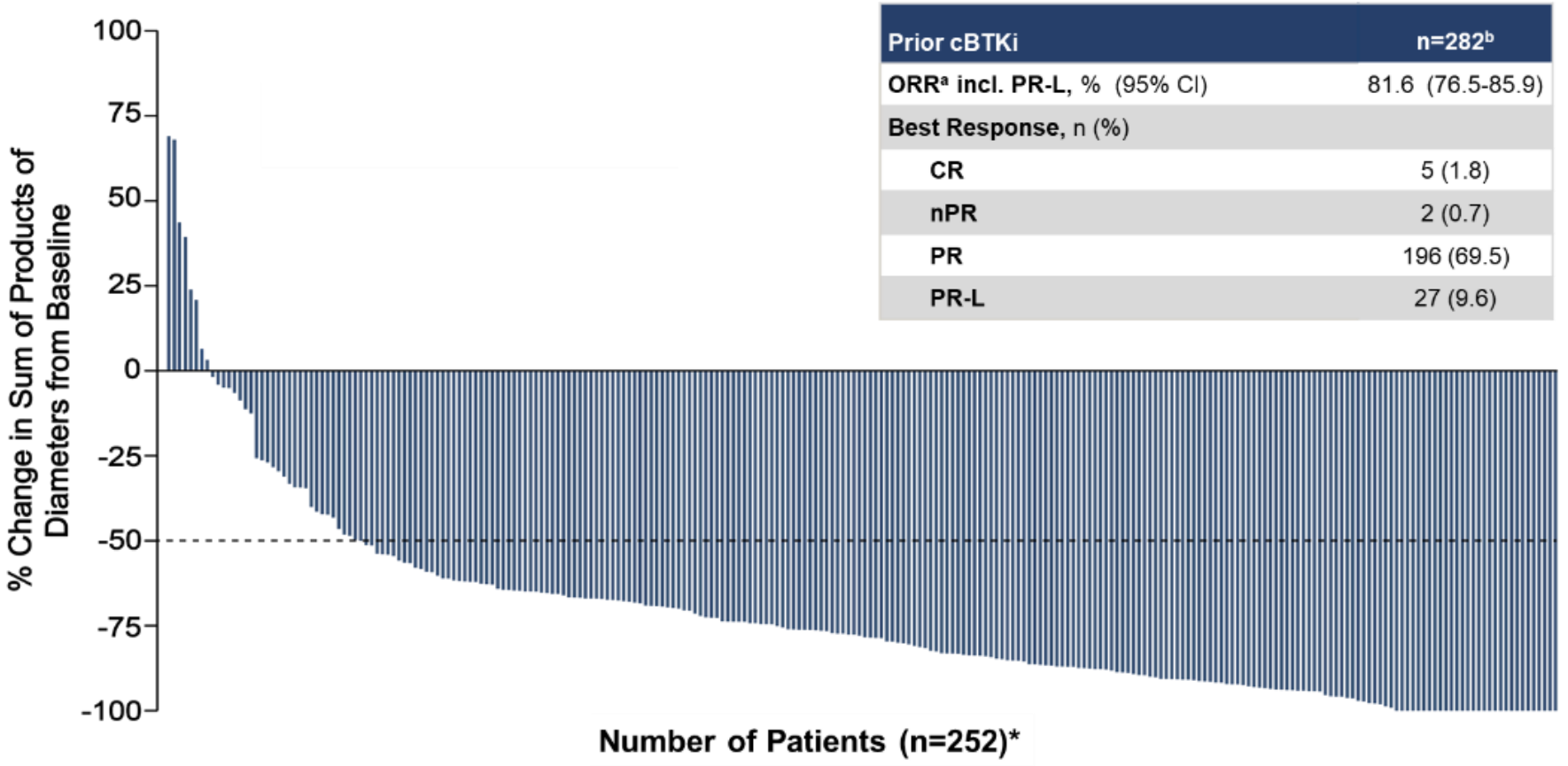

**Pirtobrutinib may stabilize/maintain BTK in a closed inactive conformation**[7]




- Inhibits both WT and C481-mutant BTK with equal low nM potency
- Steady state plasma exposure corresponding to 96% BTK target inhibition and a half-life of about 20 hours
- In contrast to cBTKi (A), pirtobrutinib (B) appears to stabilize BTK in a closed, inactive conformation, blocking access to upstream kinases and phosphorylation of Y551, thus inhibiting scaffolding interactions that support kinase-independent BTK signaling


**Mato AR, et al. *Lancet*. 2021;397(10277):892-901. Brandhuber B, et al. *Clin Lymphoma Myeloma Leuk.* 2018;18(Suppl.1):S216. Gomez EB, et al. *Blood*. 2023;142(1):62-72. Woyach JA, et al. Presented at: ASH 2023; December 9, 2023; San Diego, CA. 325.**

# Pirtobrutinib Efficacy in All Patients with CLL/SLL Who Received Prior cBTKi

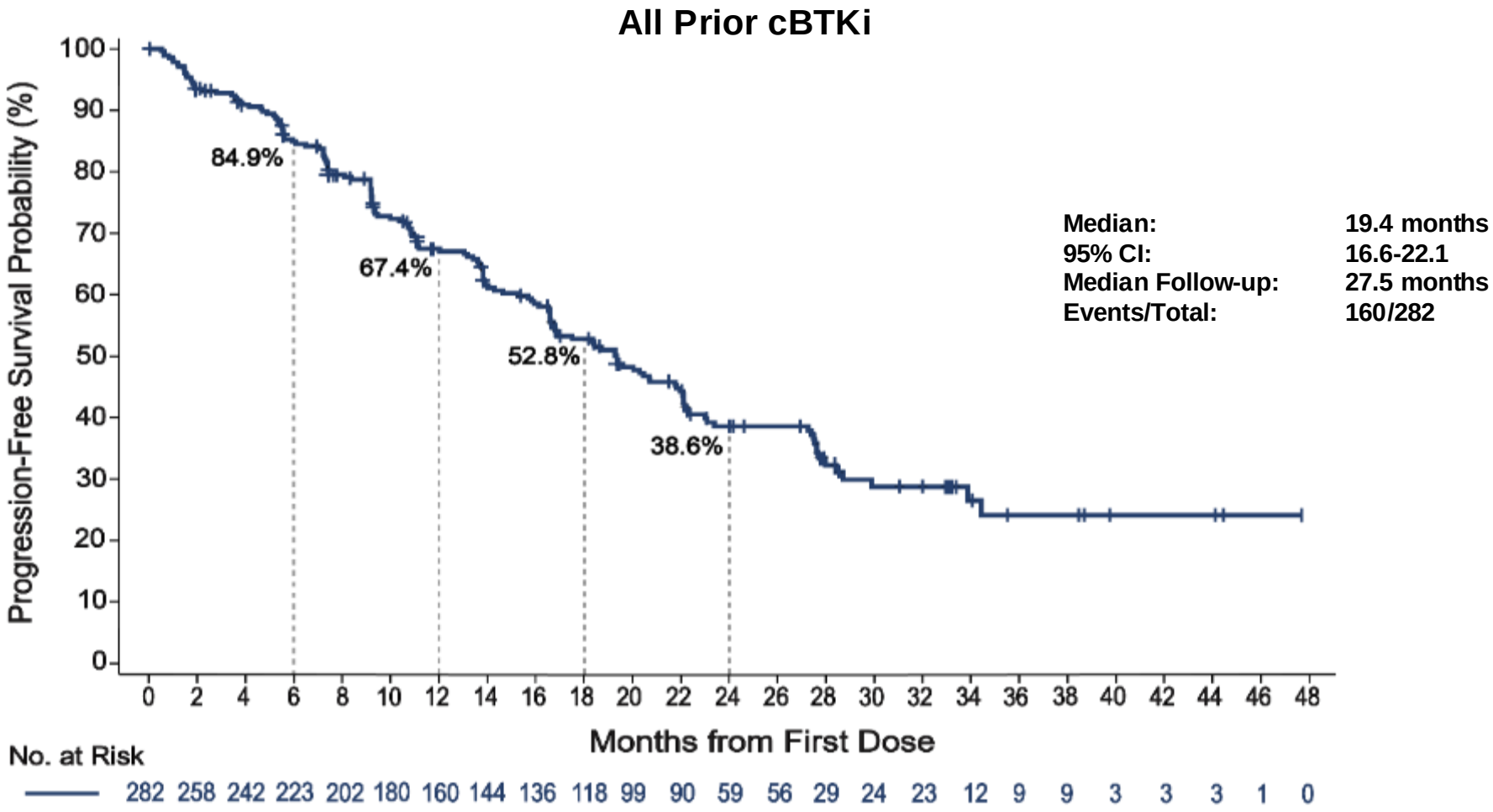



| Prior cBTKi | n=282[b] |
|---|---|
| ORR[a] incl. PR-L, % (95% CI) | 81.6 (76.5-85.9) |
| Best Response, n (%) | |
| CR | 5 (1.8) |
| nPR | 2 (0.7) |
| PR | 196 (69.5) |
| PR-L | 27 (9.6) |

Data of patients with baseline and at least one evaluable post baseline tumor measurement. *Data for 30/282 patients are not shown in the waterfall plot due to no measurable target lesions identified by CT at baseline, discontinuation prior to first response assessment, or lack of adequate imaging in follow-up. [a]ORR including PR-L is the number of patients with best response of PR-L or better divided by the total number of patients; 14 patients with a best response of not evaluable (NE) are included in the denominator. [b]Post-cBTKi patients included a subgroup of 19 patients with one prior line of cBTKi-containing therapy and second line therapy of pirtobrutinib, who had an ORR including PR-L of 89.5% (95% CI: 66.9-98.7). Response status per iwCLL 2018 based on IRC assessment.

Woyach JA, et al. Presented at: ASH 2023; December 9, 2023; San Diego, CA. 325.

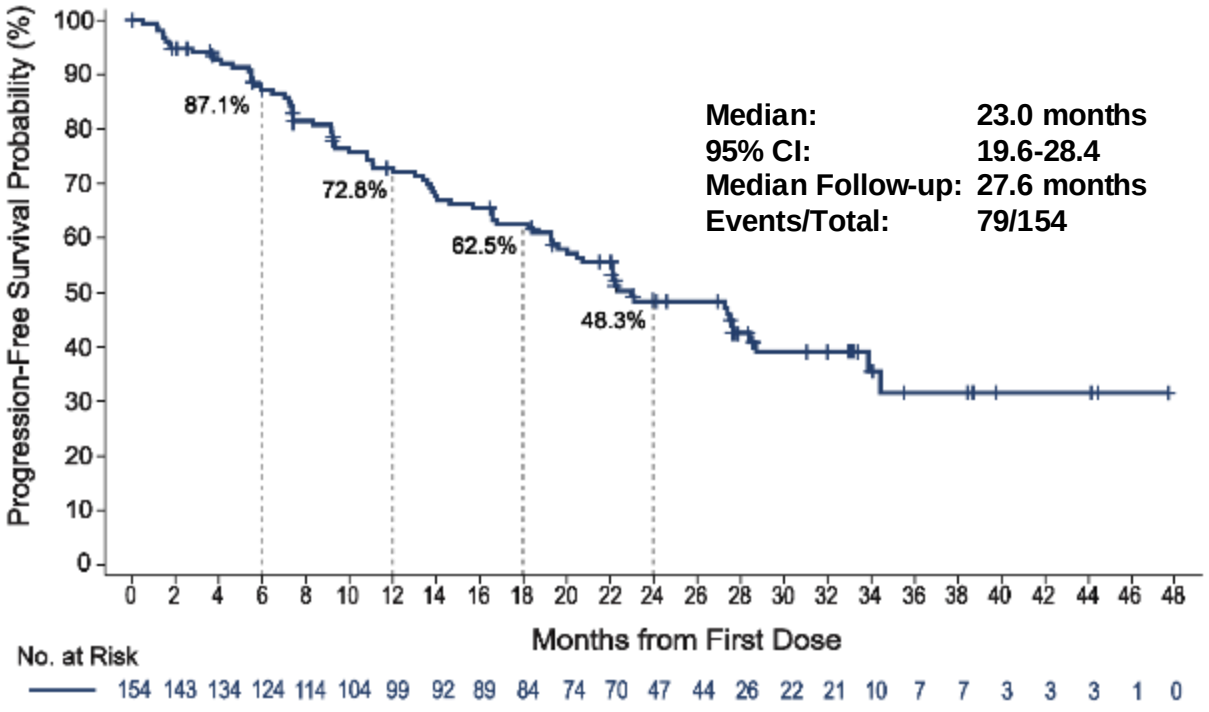
# Pirtobrutinib PFS in Patients with Prior cBTKi




Woyach JA, et al. Presented at: ASH 2023; December 9, 2023; San Diego, CA. 325.

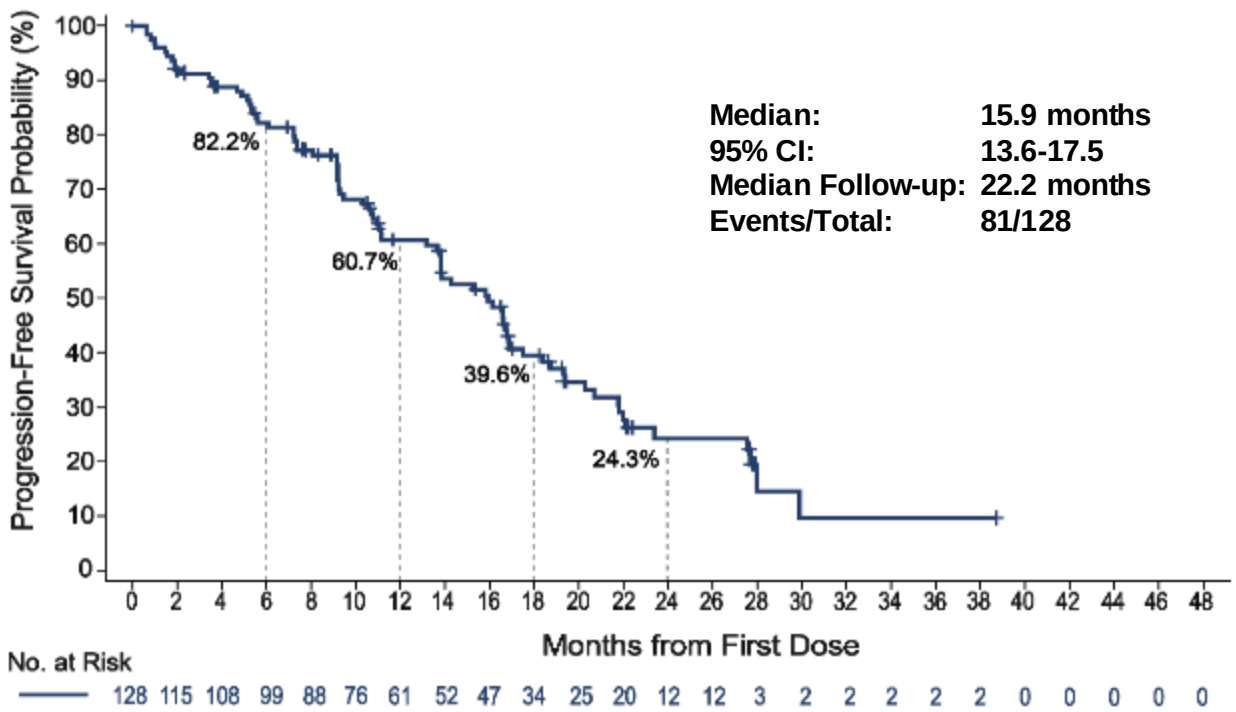
# Pirtobrutinib PFS with Prior cBTKi, with or without Prior BCL2i

**BCL2i-N**




| | |
|---|---|
| **Median:** | **23.0 months** |
| **95% CI:** | **19.6-28.4** |
| **Median Follow-up:** | **27.6 months** |
| **Events/Total:** | **79/154** |

**BCL2i-E**




| | |
|---|---|
| **Median:** | **15.9 months** |
| **95% CI:** | **13.6-17.5** |
| **Median Follow-up:** | **22.2 months** |
| **Events/Total:** | **81/128** |

**Woyach JA, et al. Presented at: ASH 2023; December 9, 2023; San Diego, CA. 325.**

# Pirtobrutinib Safety Profile of Patients Who Received Prior cBTKi

| | Treatment-Emergent AEs in Patients with CLL/SLL (n=282) | | | |
|---|---|---|---|---|
| | All Cause AEs, (≥20%), % | | Treatment-Related AEs, % | |
| **Adverse Event** | **Any Grade** | **Grade ≥3** | **Any Grade** | **Grade ≥3** |
| Fatigue | 36.9 | 1.8 | 3.5 | 0.0 |
| Neutropenia[b,c] | 34.4 | 28.4 | 19.5 | 15.2 |
| Diarrhea | 28.4 | 0.4 | 7.8 | 0.0 |
| Cough | 27.3 | 0.0 | 1.8 | 0.0 |
| Contusion | 26.2 | 0.0 | 17.4 | 0.0 |
| Covid-19 | 25.9 | 4.6 | 0.7 | 0.0 |
| Dyspnea | 22.3 | 2.1 | 0.7 | 0.4 |
| Nausea | 22.0 | 0.0 | 3.5 | 0.0 |
| Abdominal pain | 21.3 | 1.8 | 2.1 | 0.4 |
| **AEs of Interest[a]** | **Any Grade** | **Grade ≥3** | **Any Grade** | **Grade ≥3** |
| Infections[d] | 74.1 | 30.9 | 12.8 | 4.3 |
| Bruising[e] | 30.1 | 0.0 | 19.1 | 0.0 |
| Rash[f] | 24.5 | 1.1 | 5.7 | 0.4 |
| Arthralgia | 22.7 | 1.4 | 4.3 | 0.0 |
| Hemorrhage[g] | 13.5 | 2.1 | 4.6 | 1.1 |
| Hypertension | 14.2 | 4.3 | 3.5 | 0.4 |
| Atrial Fibrillation/Flutter[h,i] | 4.6 | 1.8 | 1.4 | 0.7 |

**Median time on treatment was 18.7 months (prior cBTKi), 24.3 months (BCL2i-N) and 15.3 months (BCL2i-E)**

**11 (3.9%; 9 BCL2i-N, 2 BCL2i-E) patients had treatment-related AEs leading to pirtobrutinib dose reduction**

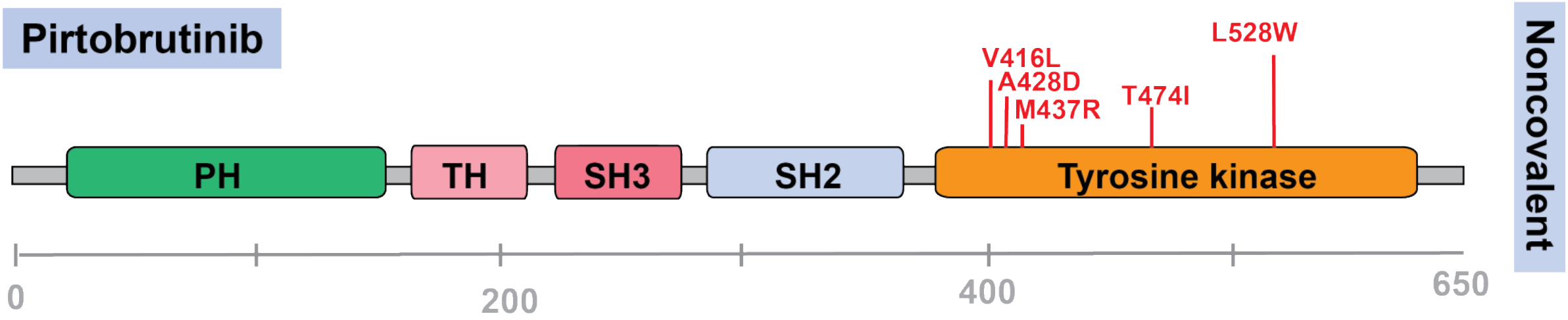
**7 (2.5%; 4 BCL2i-N, 3 BCL2i-E) patients had treatment-related AEs leading to pirtobrutinib discontinuation**

**Safety profiles of BCL2i-N and BCL2i-E subgroups were similar**

[a]AEs of interest are those that were previously associated with covalent BTK inhibitors; [b]Neutropenia at baseline for prior BTKi (n=282) was 18.4, BCL2i-N (n=154) was 11.0 and BCL2i-E (n=128) was 27.3; [c]Aggregate of neutropenia and neutrophil count decreased; [d]Aggregate of all preferred terms including infection and COVID-19; [e]Aggregate of contusion, ecchymosis, increased tendency to bruise and oral contusion; [f]Aggregate of all preferred terms including rash; [g]Aggregate of all preferred terms including hemorrhage or hematoma; [h]Aggregate of atrial fibrillation and atrial flutter; [i]Of the 13 total afib/aflutter TEAEs in the prior BTKi safety population (n=282), 6 occurred in patients with a prior medical history of atrial fibrillation.

Woyach JA, et al. Presented at: ASH 2023; December 9, 2023; San Diego, CA. 325.

# Diverse BTK mutations cause resistance to non-covalent BTKi




Montoya et al ASH 2022

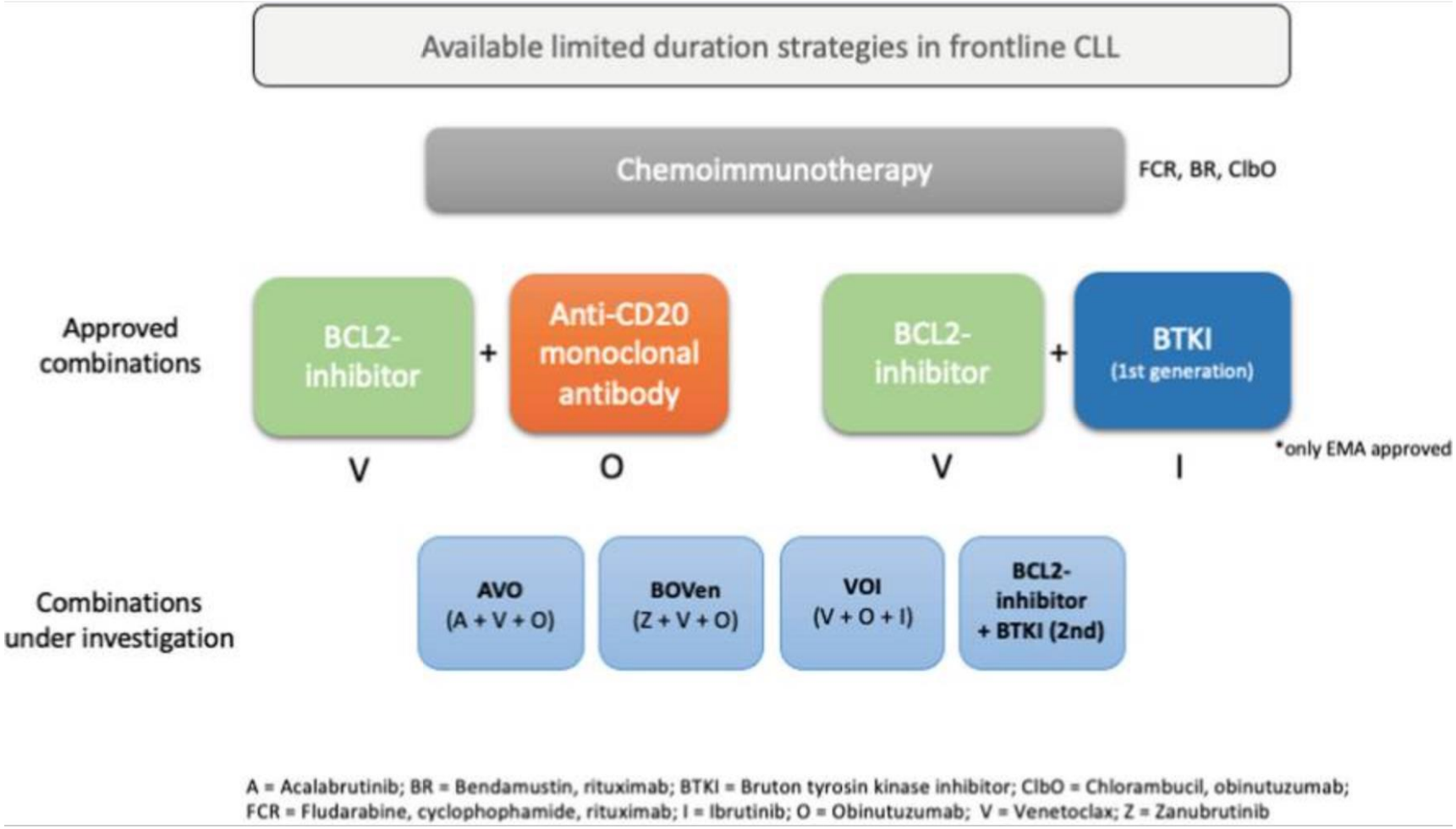
# Long term treatment: Key Points

- BTKi treatment is superior to any form of CIT
- Very long-term efficacy data up to 10 years even in high risk
  - For patients treated with ibrutinib, mPFS at 7 years with OS of 70% at 10 years
- Most discontinuations are secondary to intolerance
- Low rates of progression even in high-risk disease in front line
- BTKi has a class effect AEs but second generation are better tolerated
- Cardiovascular toxicities should be taken into consideration in high-risk patients
- Non-covalent inhibitors can keep patients on BTKi after covalent failures

# Continuous Therapy vs Fixed Duration



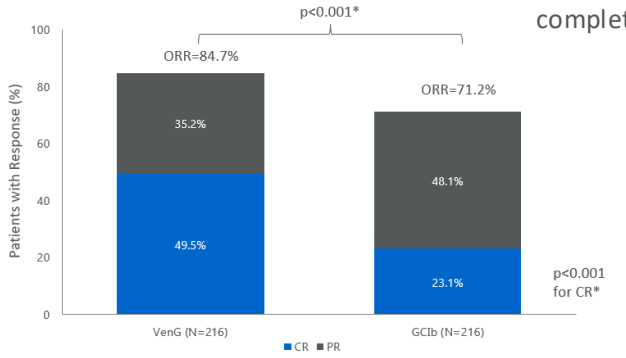
Shanafelt TD, et al. *New Engl J Med.* 2019; 381:435-443. Hillman P, et al. *Lancet Oncol,* 2023,24:535-552. Moreno C, et al. *Lancet Oncol.* 2019,20:43-56. Woyach JA, et al. *Blood,* 2021;138:639. Barr PM, et al. *Blood Adv.* 2022;6:3400-3450. Sharman JP, et al. *Leukemia.* 2022;36:1171-1175. Tam CS, et al. *Lancet Oncol.* 2022;23:1031-1043. AlSawaf O, et al. *Nat Commun.* 2023;14:2147. Eichhorst B, et al. *N Eng J Med.* 2023;338:1739-1754. Kater AP, et al. *NEJM Evid.* 2022;1:711. Tam CS, et al. *Blood*. 2022;139:3278-3289. National Institute of Health (NIH). Accessed Sept 25, 2024. https://clinicaltrials.gov/study/NCT04608318; NCT03836261.




**Stumpf J, et al. *Curr Oncol Rep*. 2024;26(2):136-146.**

# CLL14: Venetoclax + Obinutuzumab in TN CLL

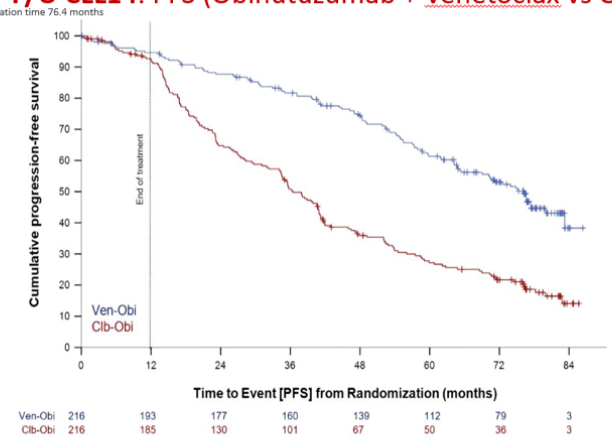
OVERALL AND COMPLETE RESPONSE RATES AT EOT+3




*EOT+3, 3 months after treatment completion.

p<0.001 for CR*

**6 Year F/U CLL14**: PFS (Obinutuzumab + Venetoclax vs Obinutuzumab + Chlorambucil)



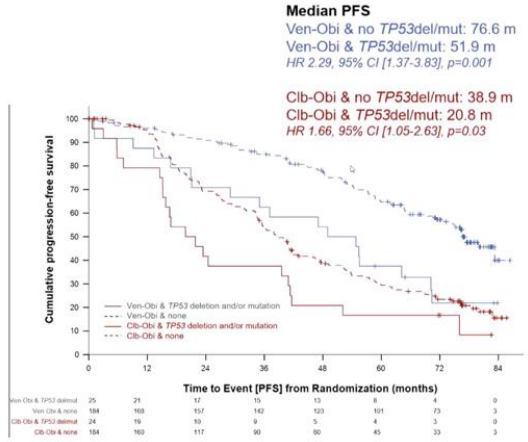

**Median PFS**
Ven-Obi: 76.2 months
Clb-Obi: 36.4 months

**6-year PFS rate**
Ven-Obi: 53.1%
Clb-Obi: 21.7%

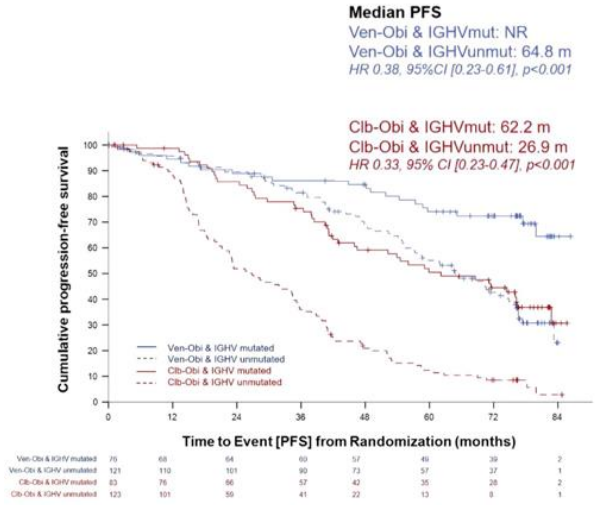
HR 0.40, 95% CI [0.31-0.52]
P<0.0001

**Key Takeaway:** Obinutuzumab + Venetoclax improved PFS over Obinutuzumab + Chlorambucil
**[53% of patients are still in remission 5 years after completing fixed-duration therapy]**

PFS by TP53

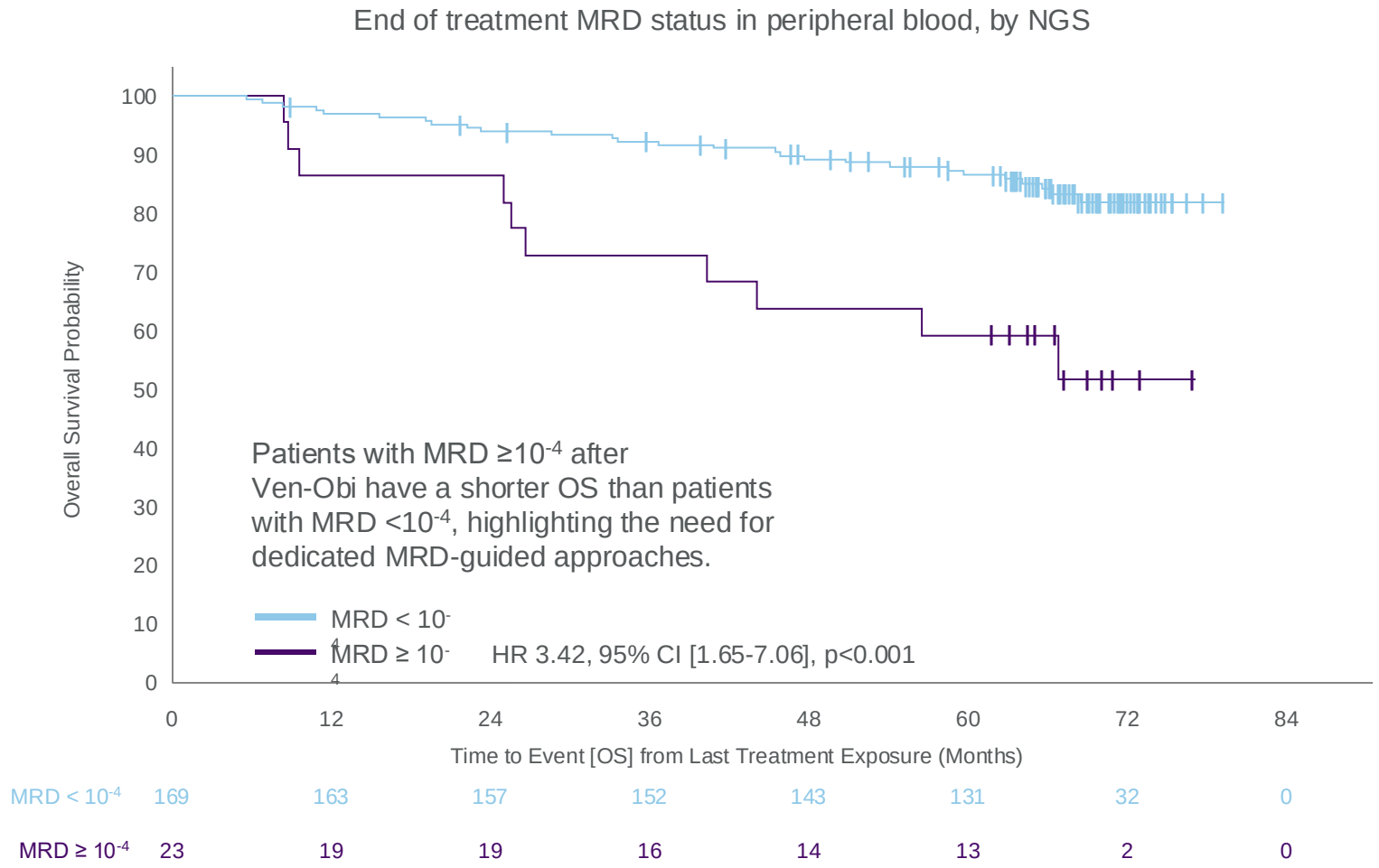



PFS by IGHV




Fischer K, et al. *N Engl J Med.* 2019;380:2225-2236. al-Sawaf O, et al. Presented at: EHA 2023; June 8, 2023; Madrid, Spain. S145.

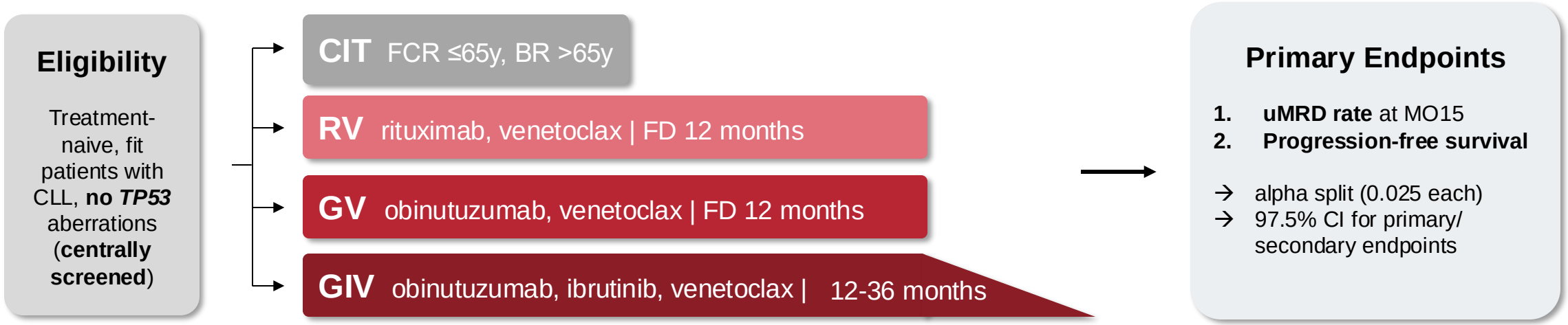
# Landmark OS after Ven-Obi According to MRD Status




- 53.1% treated with ven+obi remain without PFS event five years after tx
- Over 60% have not required a second-line treatment
- EOT MRD status significantly correlates with PFS and OS
- Benefit observed across all subgroups, including TP53del/mut and uIGHV
- No new safety signals or 2ry malignancies

**Median observation time 76.4 months.**
**al-Sawaf O, et al. Presented at: EHA 2023; June 8, 2023; Madrid, Spain. S145.**

# 4-Year Follow-Up from the Phase 3 GAIA/CLL13 Trial




Key patient characteristics

Randomized patients (=ITT population): **n= 926**

| | |
|---|---|
| Median age: | **61 years** (range: 27-84) |
| Median CIRS score: | **2** (range: 0-7) |
| Unmutated IGHV: | **56%** of all patients |
| Complex karyotype: | **17%** of all patients |

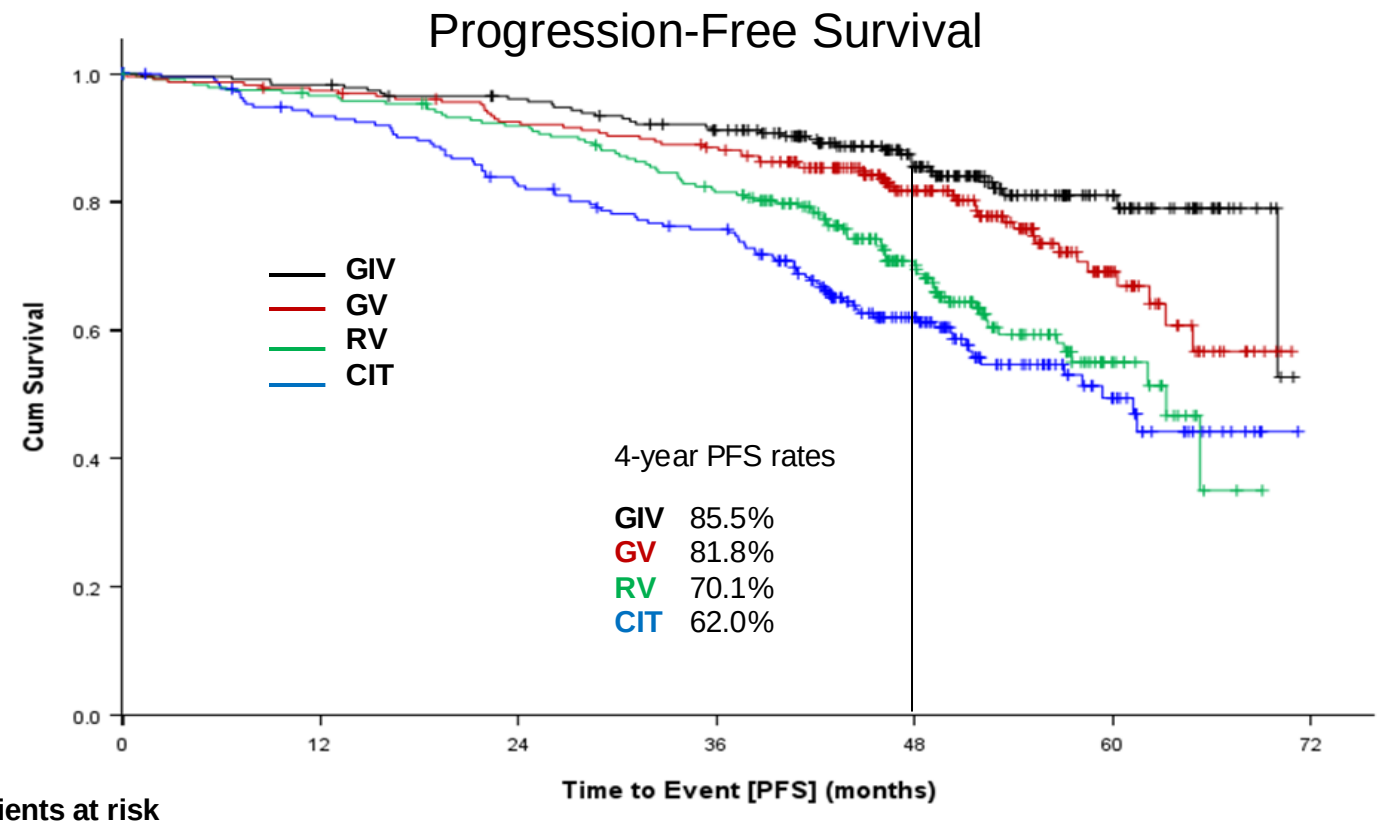
Follow-up analysis (data cut-off: 01/2023)

Median observation time
**50.7 months** (IQR: 44.6-57.9)

Median observation time after end of treatment
**40.7 months** (IQR: 34.5-47.9)

**Fürstenau M, et al. Presented at: ASH 2023; December 10, 2023; San Diego, CA. 635.**

# Efficacy: PFS




| Patients at risk | | | | | | |
|---|---|---|---|---|---|---|
| CIT | 229 | 197 | 173 | 156 | 84 | 24 |
| RV | 237 | 227 | 214 | 188 | 106 | 21 |
| GV | 229 | 222 | 209 | 198 | 121 | 32 |
| GIV | 231 | 227 | 218 | 201 | 130 | 44 |

PFS comparisons

**GIV** *vs* **CIT**: HR 0.30, 97.5%CI: 0.19-0.47, ***p<0.001***
**GIV** *vs* **RV**: HR 0.38, 97.5%CI: 0.24-0.59, ***p<0.001***
**GIV** *vs* **GV**: HR 0.63, 97.5%CI: 0.39-1.02, *p*=0.03

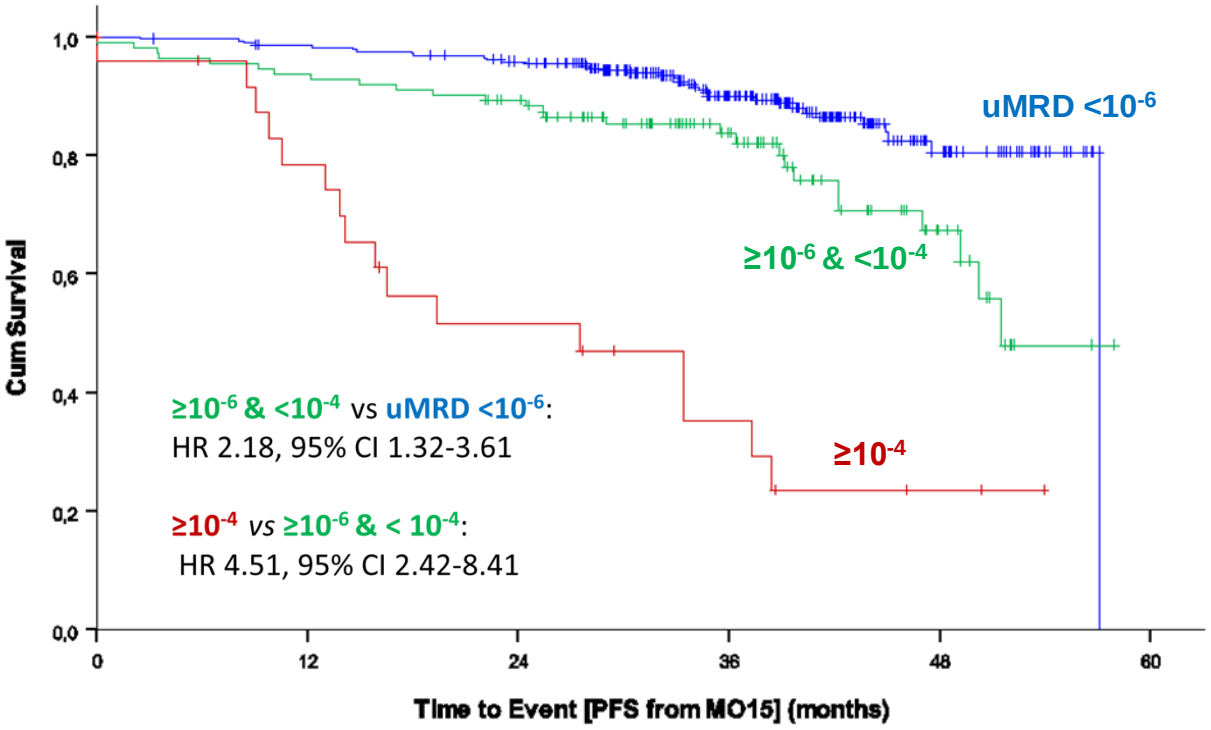
**GV** *vs* **CIT**: HR 0.47, 97.5%CI: 0.32-0.69, ***p<0.001***
**GV** *vs* **RV**: HR 0.57, 97.5%CI: 0.38-0.84, ***p=0.001***

**RV** *vs* **CIT**: HR 0.78, 97.5%CI: 0.55-1.10, *p*=0.1

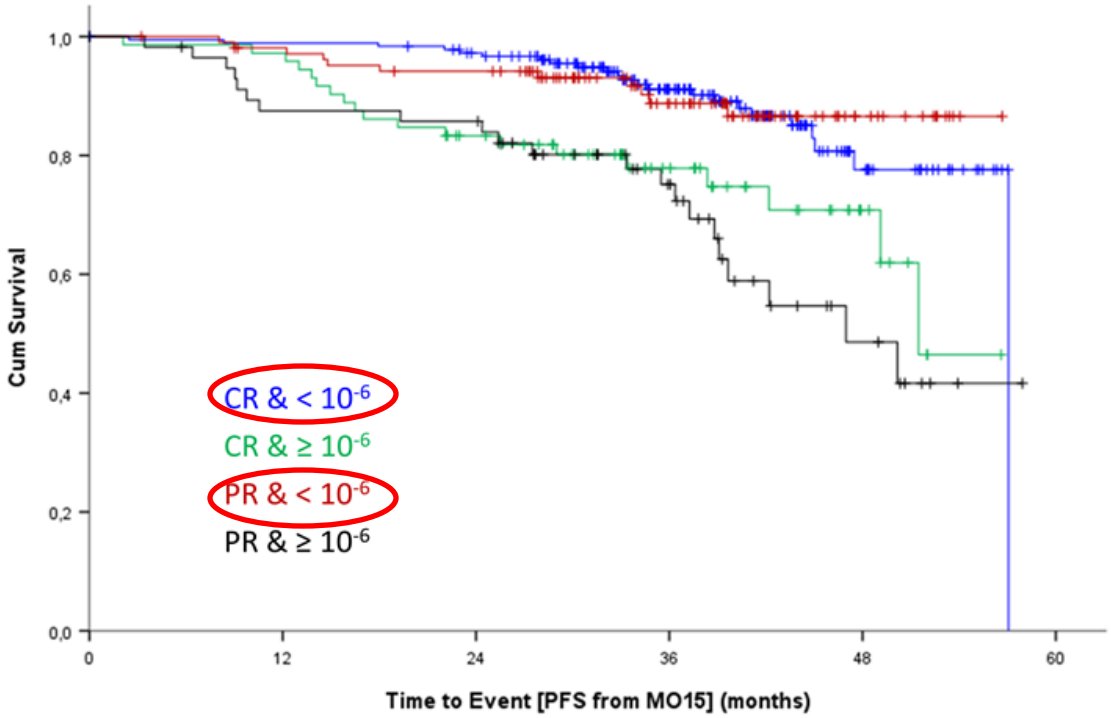
**Fürstenau M, et al. Presented at: ASH 2023; December 10, 2023; San Diego, CA. 635.**

# Correlation PB MRD/PFS

PFS by MRD level at MO15, GV/GIV




PFS by MRD level & response at MO15, GV/GIV

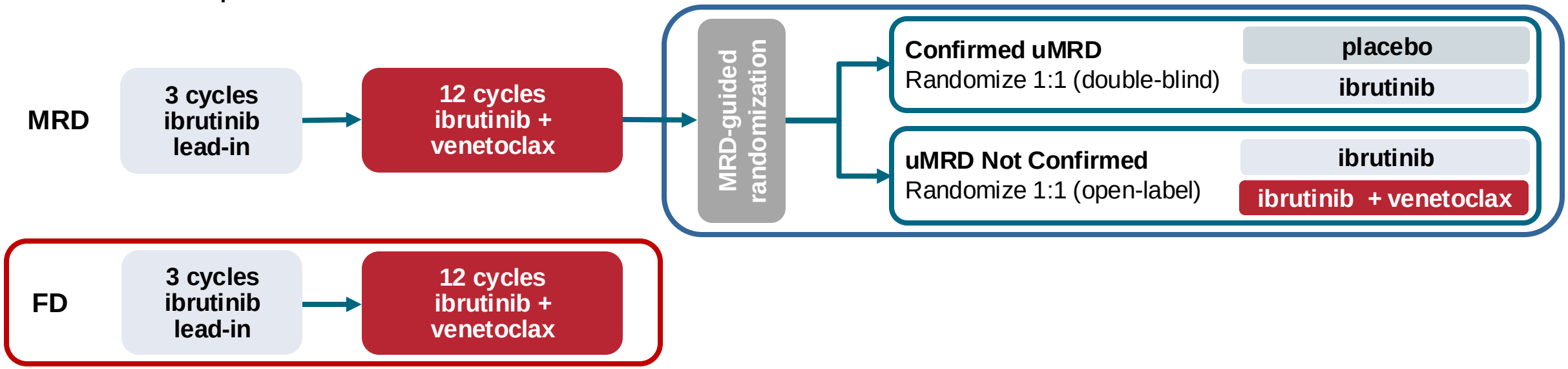



| Pts at risk | | | | | |
|---|---|---|---|---|---|
| CR & <10$^{-6}$ | 183 | 180 | 172 | 105 | 25 |
| CR & ≥10$^{-6}$ | 72 | 70 | 56 | 29 | 9 |
| PR & <10$^{-6}$ | 105 | 100 | 95 | 56 | 13 |
| PR & ≥10$^{-6}$ | 58 | 49 | 48 | 28 | 8 |

**Fürstenau M, et al. Presented at: ASH 2023; December 10, 2023; San Diego, CA. 635.**

# 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

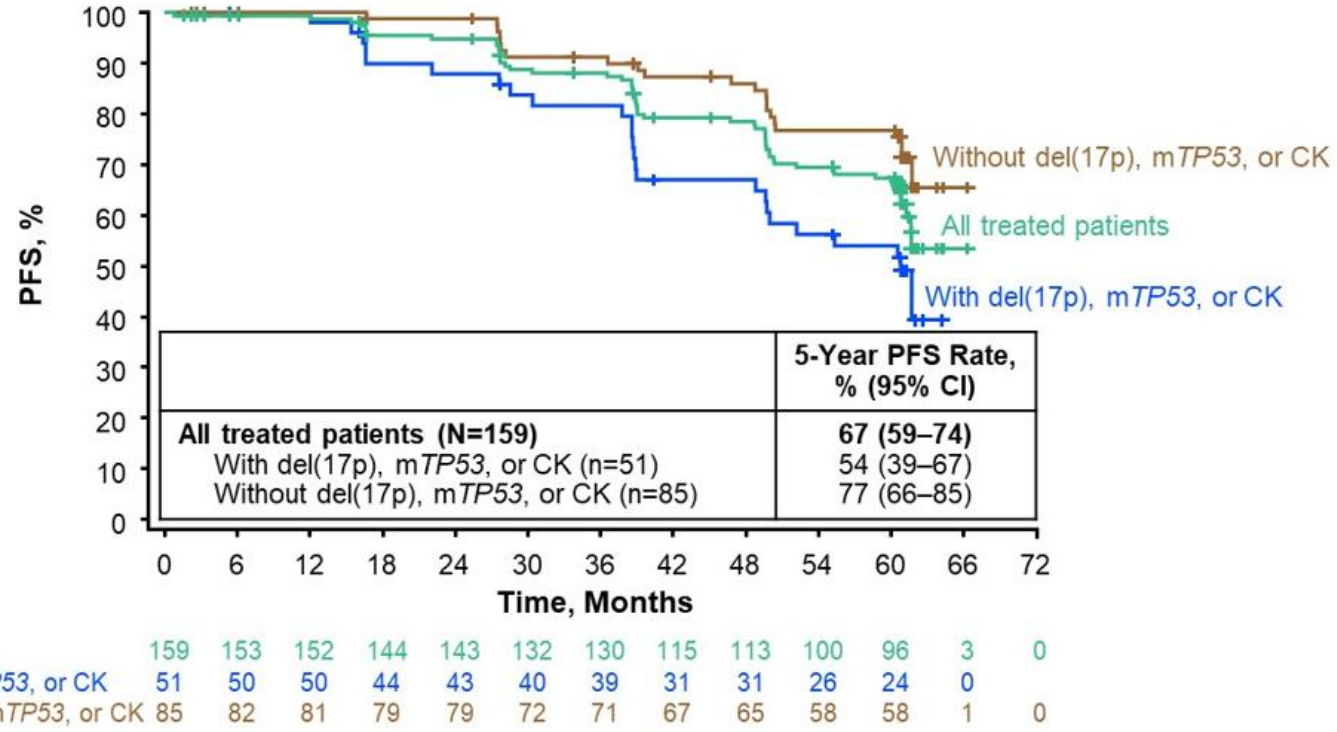
**BM = bone marrow; FD = fixed-duration; PB = peripheral blood.**

**Ghia P, et al. *JCO.* 2021;39:7501-7501.**

# PFS in the FD Cohort

**PFS in All Treated Patients and by del(17p), m*TP53,* or CK**

Median time on study: 61.2 months (range, 0.8-66.3)

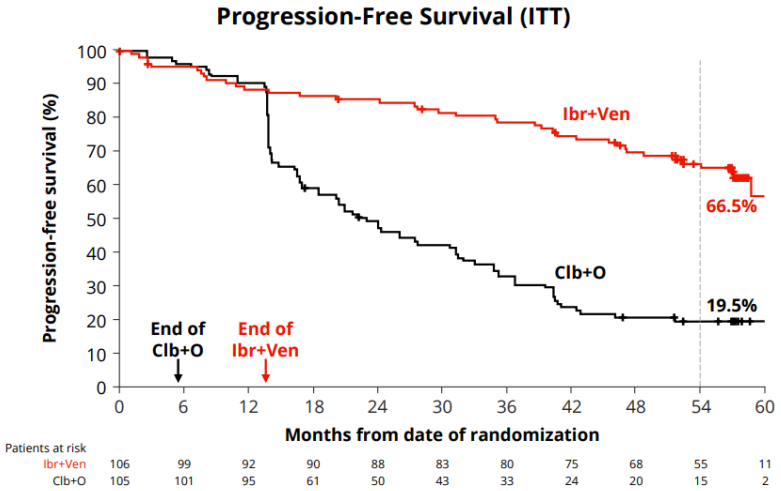



| High-risk feature | n | 5-year PFS rate, % (95% CI) |
|---|---|---|
| With del(17p)/m*TP53* | 27 | 41 (21-59) |
| Without del(17p)/m*TP53* | 129 | 73 (64-80) |
| With CK[a] | 31 | 57 (37-72) |
| Without CK[a] | 102 | 72 (61-80) |
| With del(11q)[b] | 11 | 64 (30-85) |
| Without del(11q)[b] | 74 | 79 (67-87) |

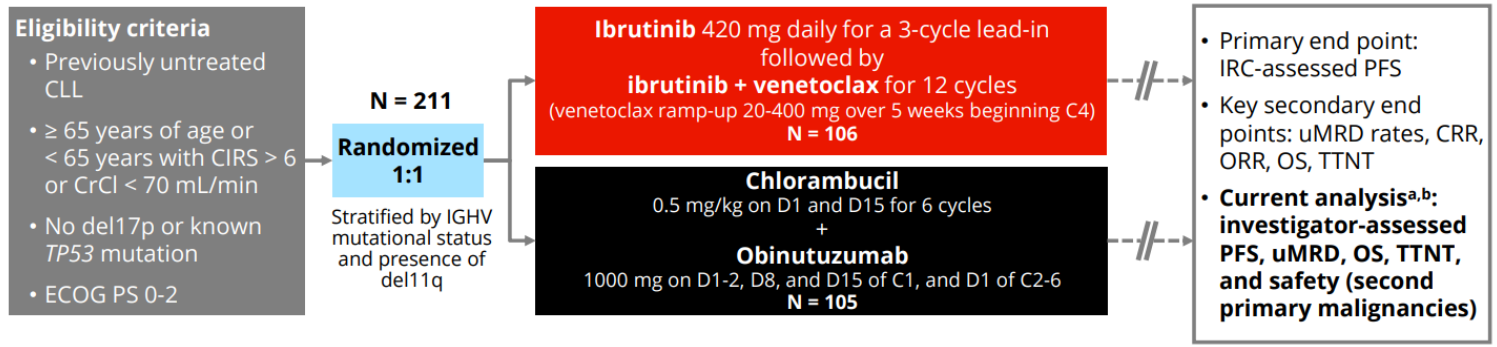
- Overall median PFS was not reached with up to 5.5 years of follow-up

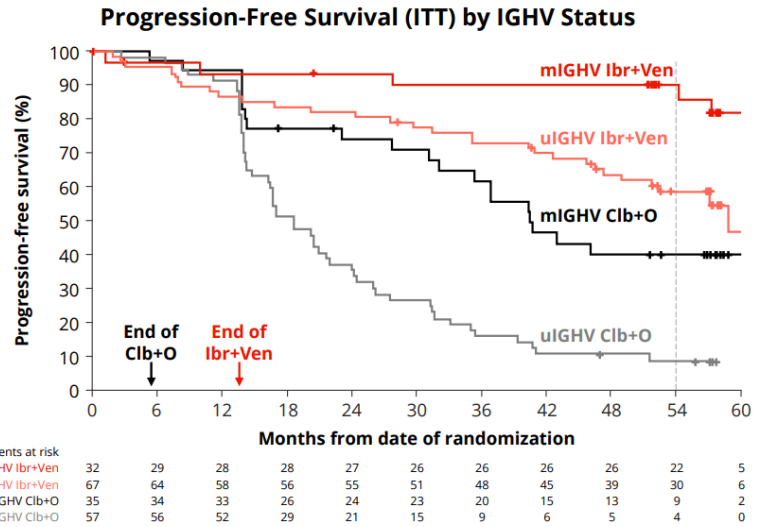
**[a]Defined as ≥3 chromosomal abnormalities by conventional CpG-stimulated cytogenetic; [b]Excluding patients with del(17p)/mTP53 or CK.**
**CK = complex karyotype.**
**Wierda WG, et al. *JCO*. 42:7009-7009.**

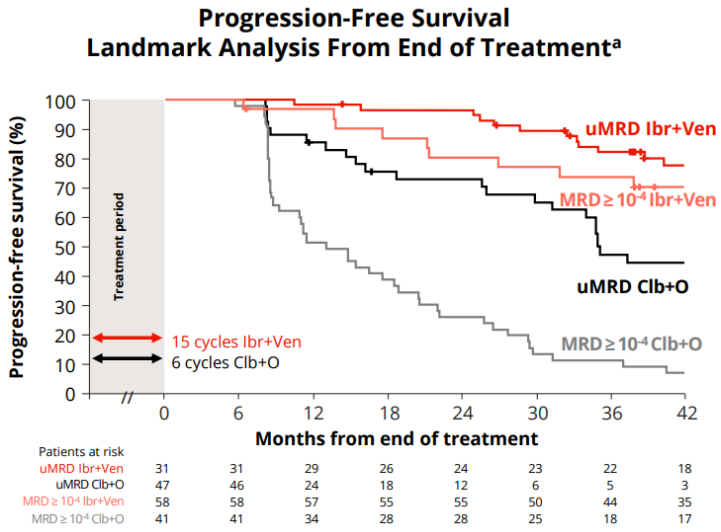
# Phase III GLOW Ibrutinib+Venetoclax: Median PFS Was Not Reached with up to 57mo of Follow-Up




- Estimated PFS rates at 42 months post tx
  - mIGHV CLL: 91% for uMRD at EOT+3, 92% for patients with MRD ≥ 10 -4 at EOT+3
  - uIGHV CLL: 78% for patients with uMRD at EOT+3, 50% for patients with MRD ≥ 10-4 at EOT+3

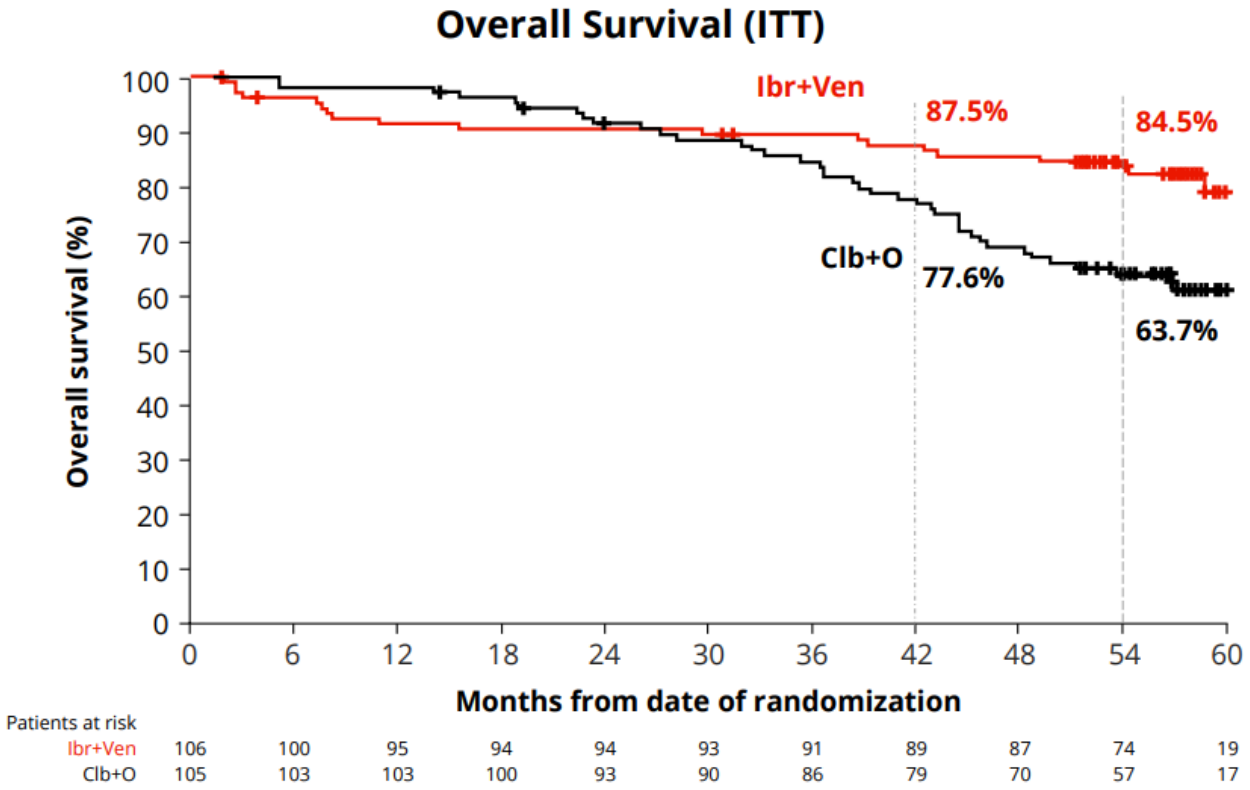



**Moreno C, et al. Presented at: ASH 2023; December 10, 2023; San Diego, CA. 634.**

# Phase III GLOW Ibr +Ven Remained Associated with Improved OS at 57 Months of Study Follow-Up




- **Ibr+Ven reduced the risk of death by 55%** versus Clb+O
  - HR 0.453 (95% CI, 0.261-0.785); $p = 0.0038$
- Estimated 54-month OS rates:
  - **84.5%** for patients treated with Ibr+Ven
  - **63.7%** for patients treated with Clb+O

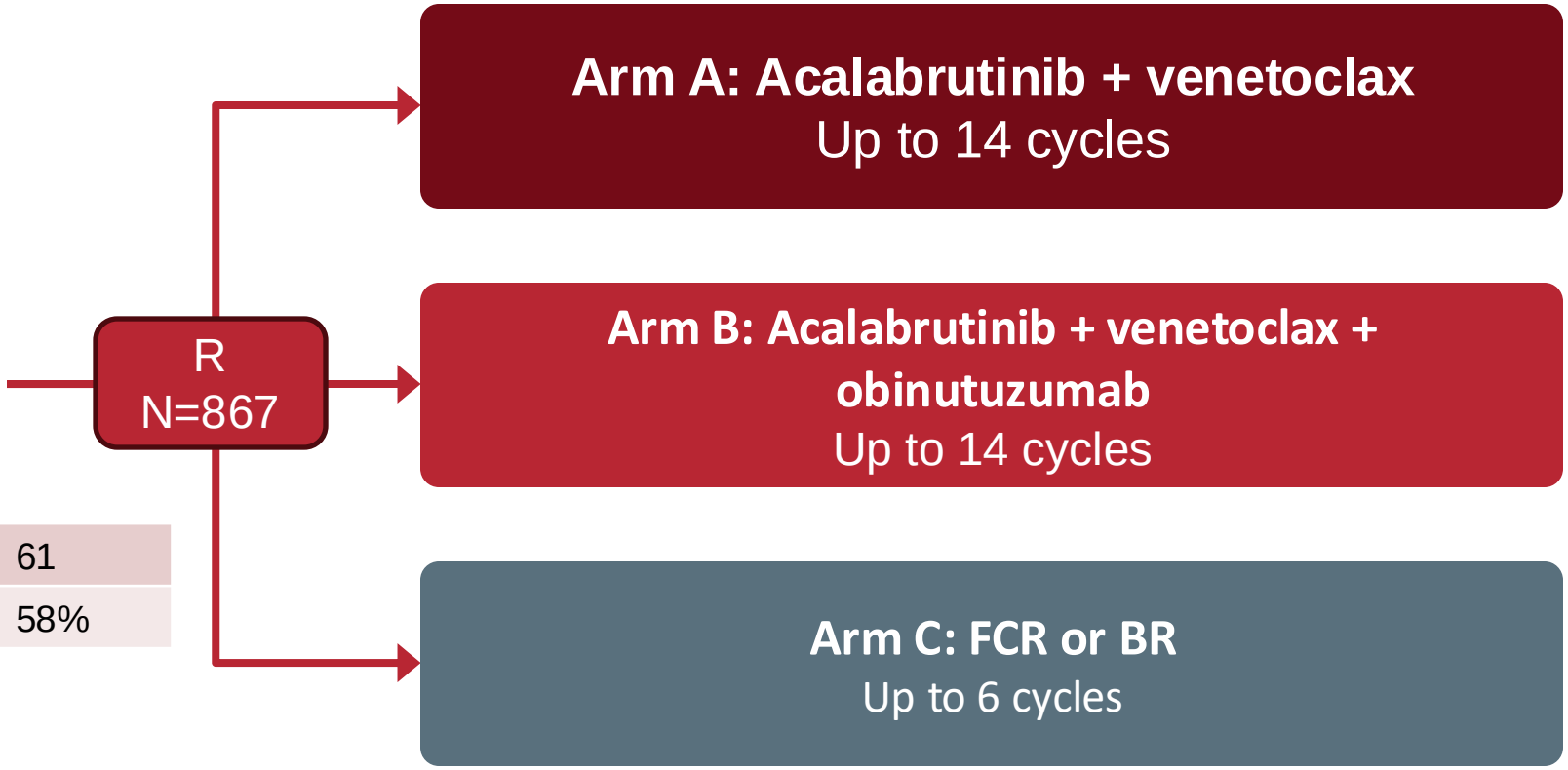
**Moreno C, et al. Presented at: ASH 2023; December 10, 2023; San Diego, CA. 634.**

# AMPLIFY Trial: Fixed-Duration Acalabrutinib + Venetoclax ± Obinutuzumab

**Untreated CLL**

- No del(17p) or *TP53* mutation

| | |
|---|---|
| **Median age** | 61 |
| **IGHV unmutated** | 58% |




**Median follow-up: 41 mo**

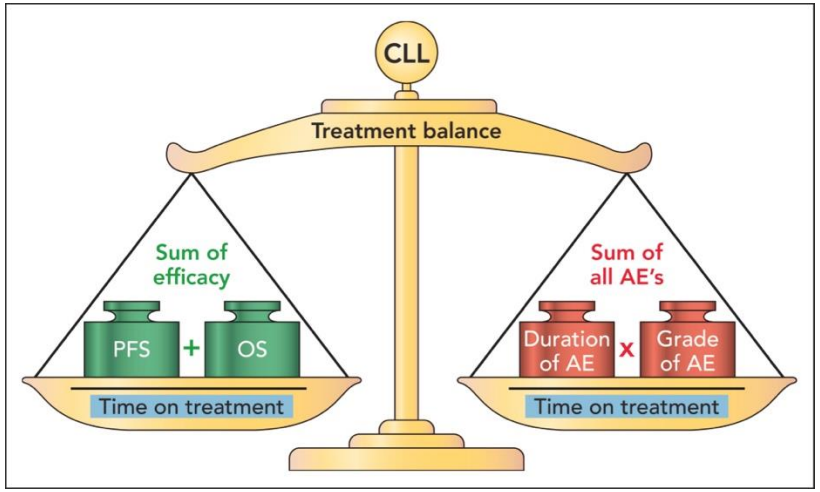
Primary endpoint: Estimated PFS at 36m AV:76.5%, AVO 83.1%, and 66.5%
Secondary endpoints included: OS, uMRD, ORR, EFS, DOR, TNT

Brown et al ASH 2024

# Fixed duration treatment: Key Points

- Fixed duration with venetoclax and obinutuzumab results in high levels of MRD- that translate in better PFS and OS compare with MRD+
  - CLL14 trial shows long-term PFS benefits for patients with high-risk CLL
- Double oral combination will offer another convenience fix duration strategy
  - In Phase 3 GLOW trial, ibrutinib + venetoclax showed a 57-month PFS of 66.5% in first-line treatment in older or unfit patients
  - Phase 3 Amplify release at ASH 2024
- Fixed duration combinations may lead to lower rates of cumulative toxicity/ongoing risks as well as less financial toxicity

# Summary




Modern therapy is very effective but can achieve different goals

| Continuous Therapy | Goals of Therapy |
| --- | --- |
| • BTK inhibitors | • Disease control<br>• Prolonged PFS<br>• Independent from response, MRD |

Be prepared to review goals of care with patients and empower their decision-making

| Fixed Duration | Goals of Therapy |
| --- | --- |
| • Venetoclax + obinutuzumab | • Disease eradication<br>• Prolonged PFS<br>• Undetectable MRD |