CLL: ASH Update

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Disclosures

- Research funding (includes institutional funding) from BMS/Celgene, Acerta, Janssen, Genentech, BeiGene, Morphosys/Incyte, Genmab, ADC Therapeutics, Schrodinger

- Consulting for Genentech, Pharmacyclics, Janssen

OHSU KNIGHT CANCER Institute

Case

- 70-year-old F with untreated CLL
- Worsening fatigue, progressive lymphocytosis, and cytopenia (hemoglobin 9 g/dL, platelet 110×10^9/L)
- Deletion 11q and Unmutated-IGHV
- No evidence of deletion 17p by FISH or *TP53* mutation by targeted sequencing

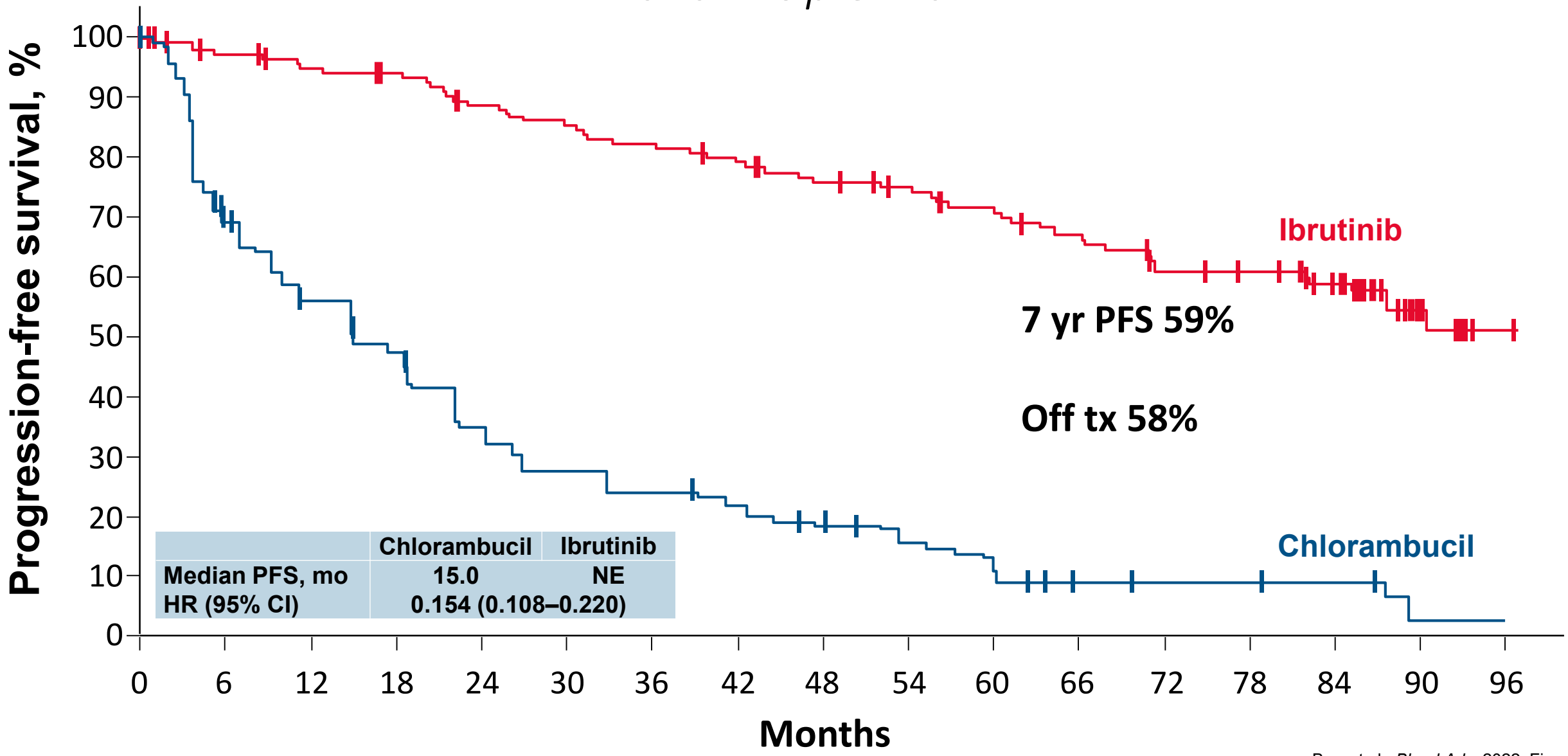
- PMH notable for:
  - Myocardial infarction requiring CABG 10 years ago
  - Paroxysmal atrial fibrillation
  - Medications include aspirin and carvedilol (P-gp inhibitor)

CLL Therapy: What are the Options?

- **Targeted Agents:**
  - **Continuous therapy: BTKi (+/- anti-CD20 antibody)**
  - **Time-limited therapy: BCL2i (Venetoclax) + anti-CD20 antibody**
  - ***Approximately 75% 4 yr PFS with either regimen in RCT***
- **Choice depends on:** patient preference, comorbidities and concomitant medications, safety profile, and *TP53* aberration, IGHV?
- **What about patients with del17p / *TP53* aberrant CLL? IGHV?**
- What about BTKi-BCL-2i combinations?

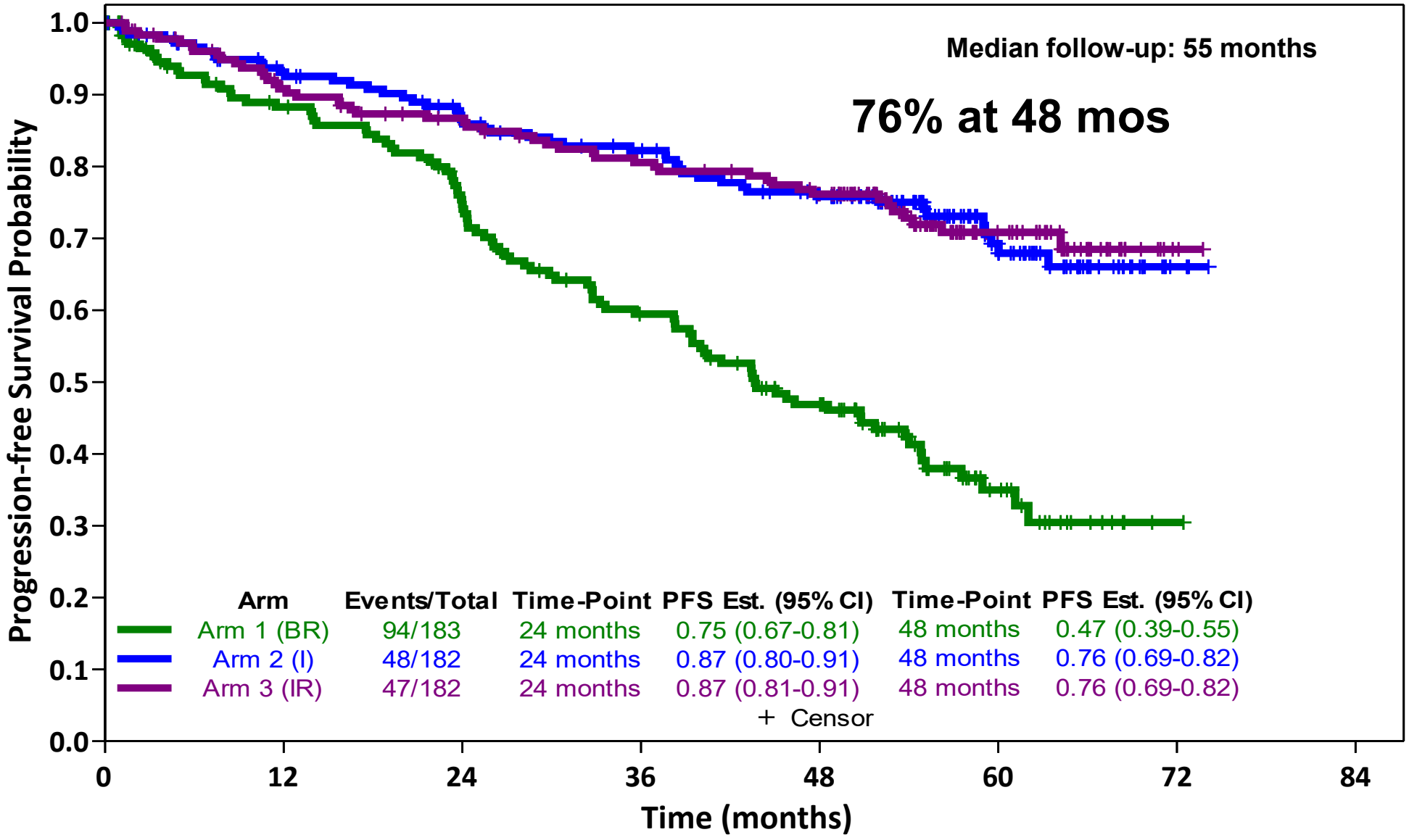
IBRUTINIB: Long-Term Follow-Up of RESONATE-2

Median Follow-Up 8 Yrs



Barr et al., *Blood Adv*, 2022, Figure 1

ALLIANCE: Updated Progression-Free Survival



Pairwise Comparisons

I vs BR:
Hazard Ratio 0.36
95% CI: 0.26-0.52
P <0.0001

IR vs BR:
Hazard Ratio 0.36
95% CI: 0.25-0.51
P <0.0001

IR vs I:
Hazard Ratio 0.99
95% CI: 0.66-1.48
P = 0.96

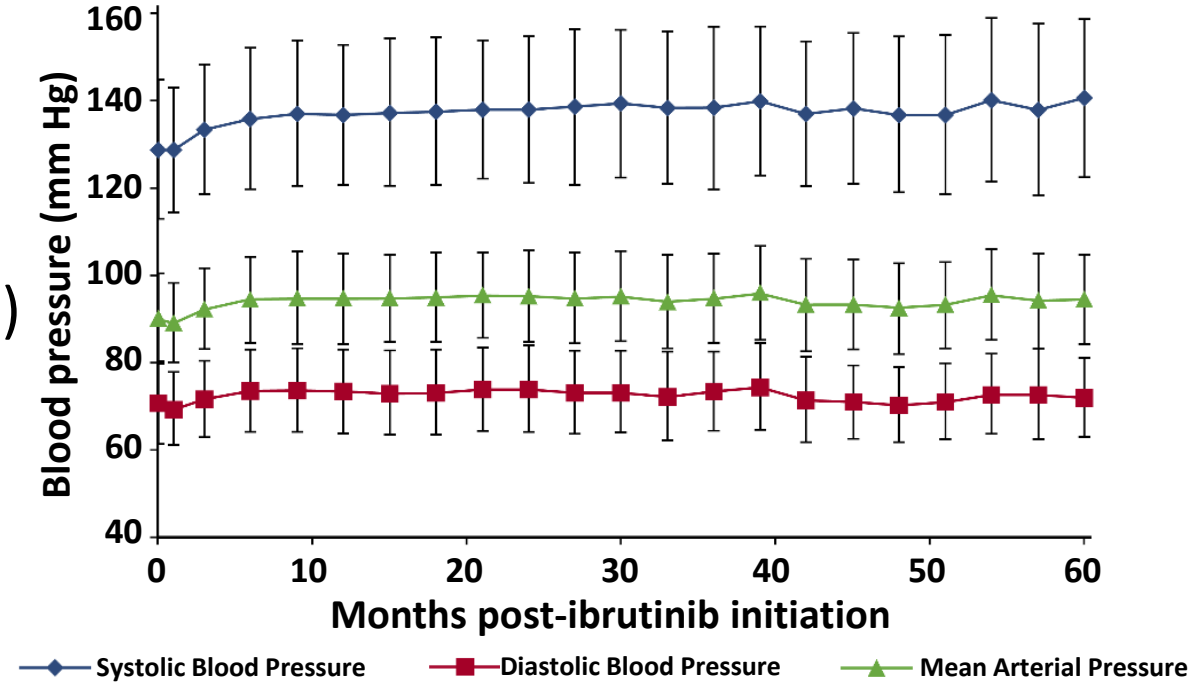
Woyach et al, *ASH* 2021

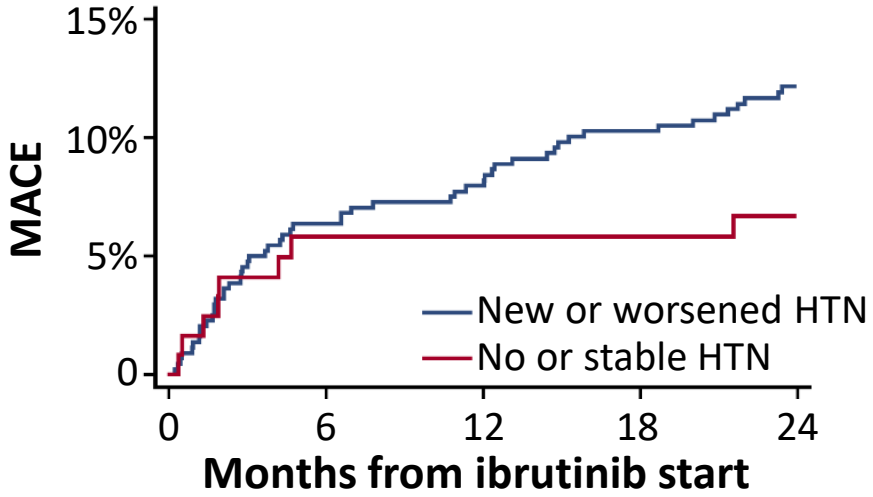
CV Adverse Effects of Ibrutinib: Hypertension

In 562 consecutive patients on ibrutinib (2009-16) w median F/U 30 months

- 72% new HTN (SBP >130)
- 18% high-grade (SBP>160)
- HTN~MACE, HR 2.17, 95% CI 1.08-4.38
- Use of antihypertensives (37%) associated with lower MACE

MACE = Major Cardiovascular Events

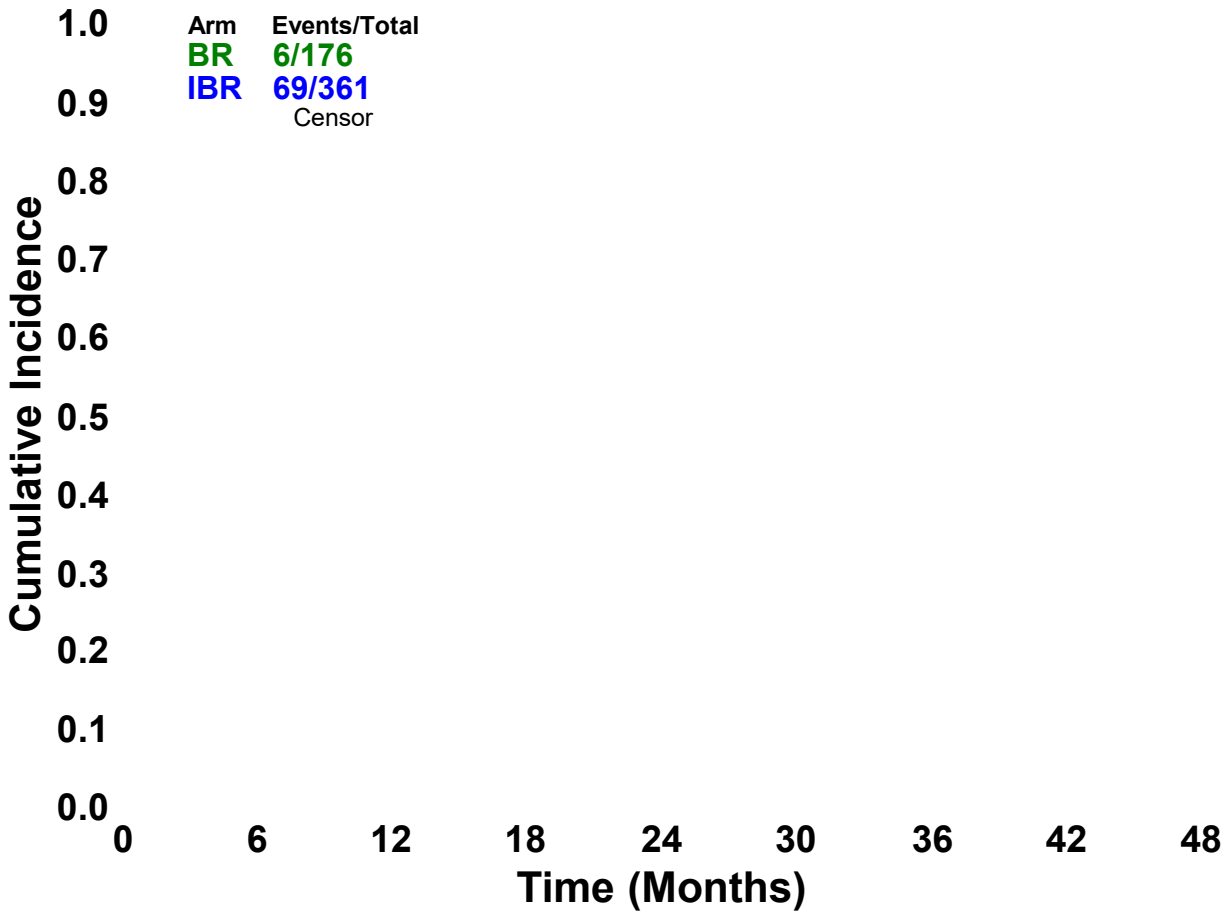




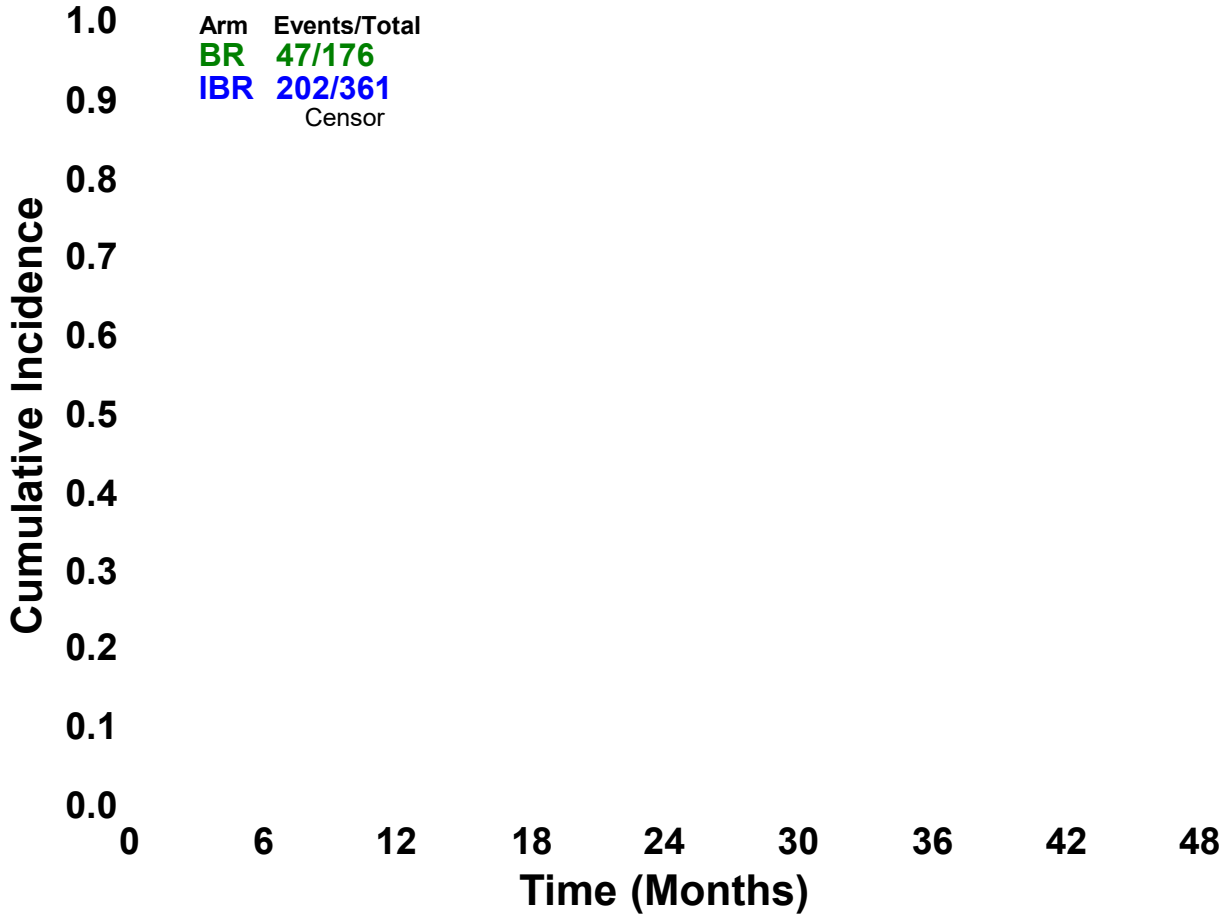
Dickerson T. *Blood* 2019; 134(22): 1919

ALLIANCE Long-Term Follow-Up: Notable Adverse Events

Atrial Fibrillation/Flutter
(All Grades)



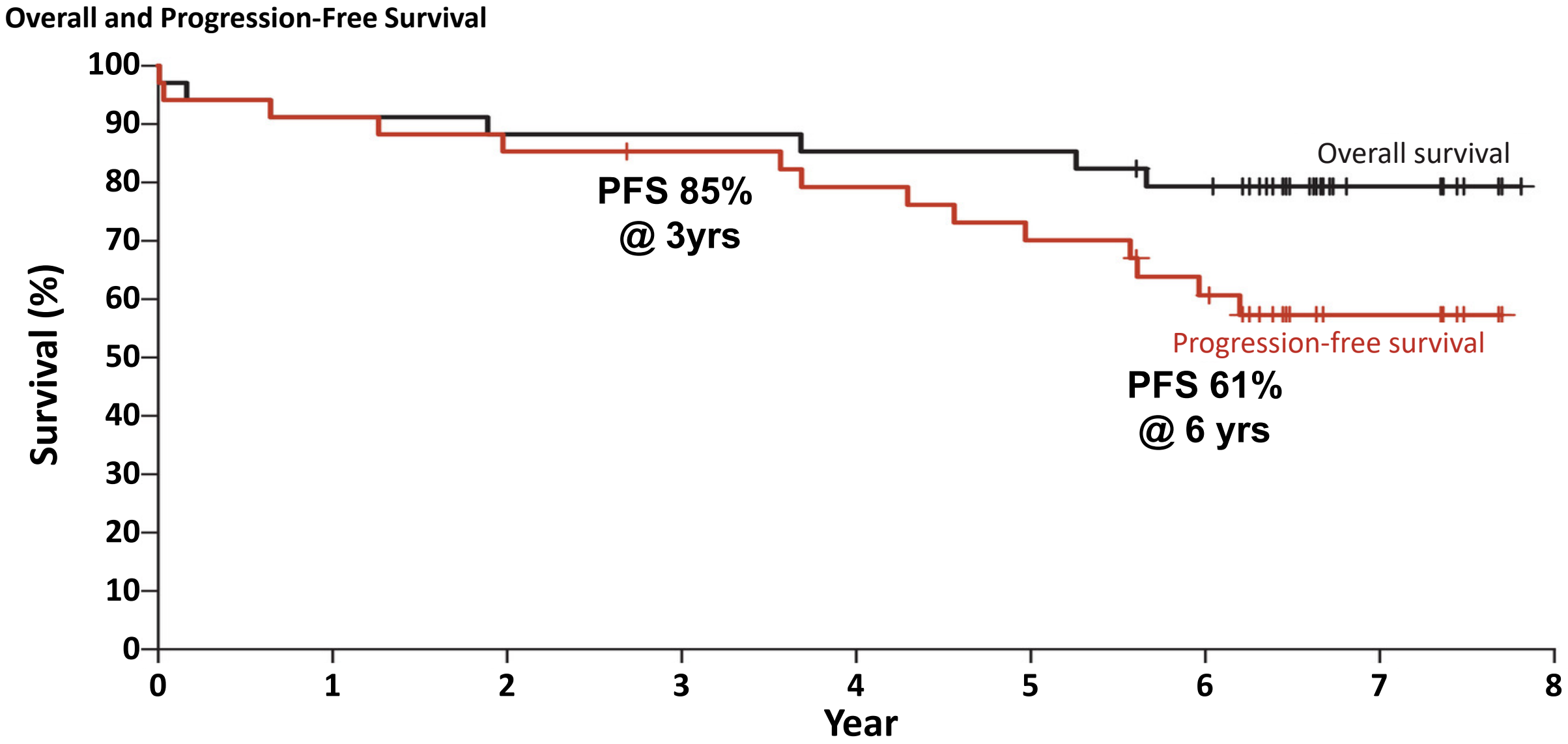
Hypertension
(All Grades)



Woyach JA *et al*, *ASH* 2021, Abstract 639

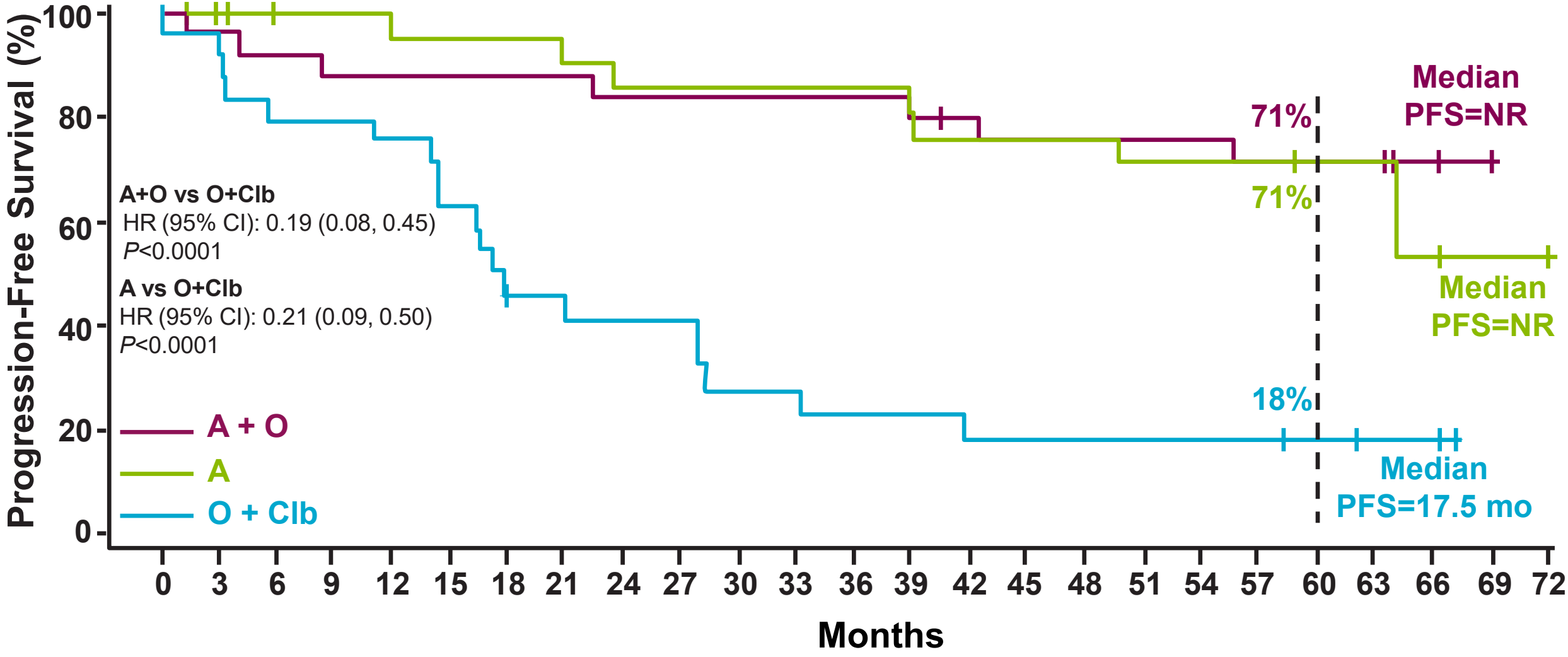
What is the Preferred Frontline Regimen in Del17p CLL?

NHLBI Phase 2 Study of Frontline Ibrutinib in Del17p CLL



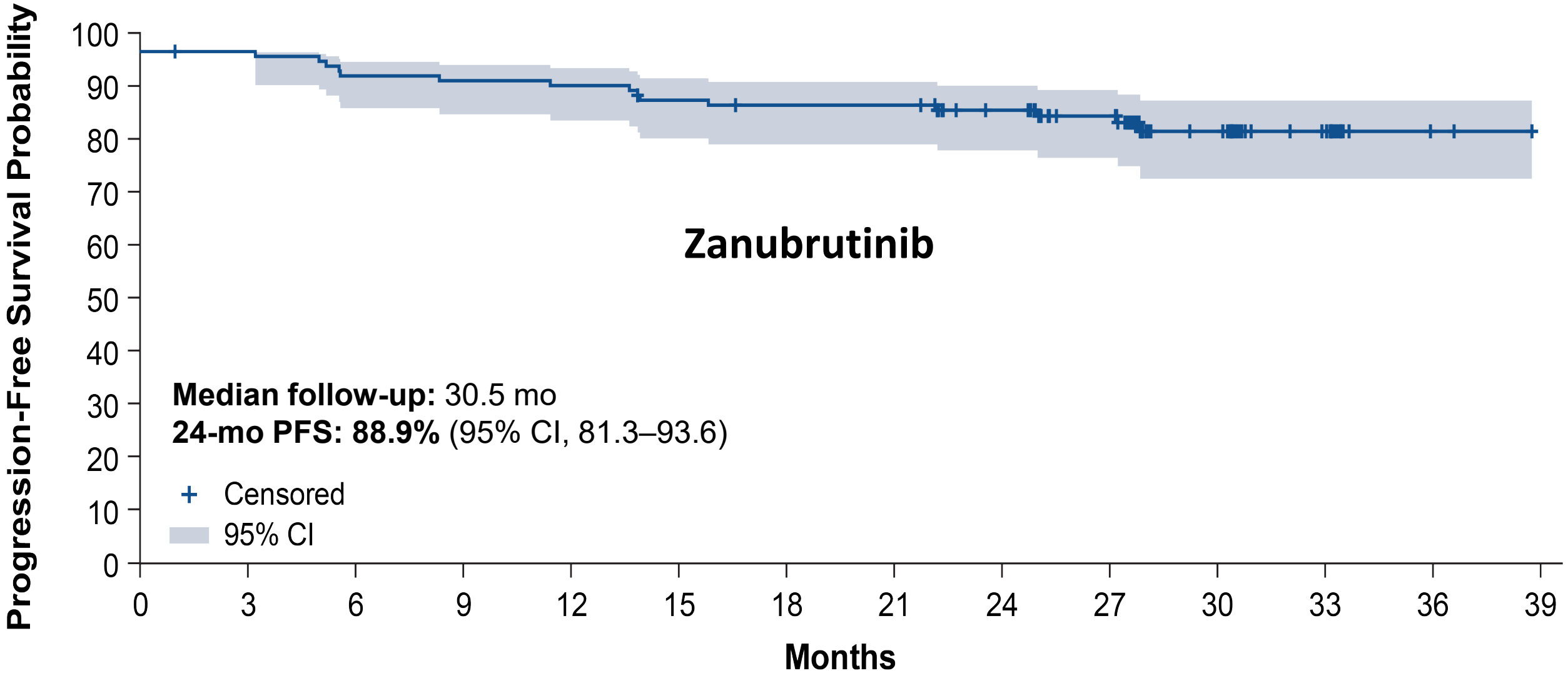
Ahn et al. *NEJM* 383: 498

ELEVATE-TN Acalabrutinib: 5 Yr PFS in Patients With del(17p) and/or Mutated *TP53*



Sharman et. al. *ASCO 2022*, Poster 7539

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

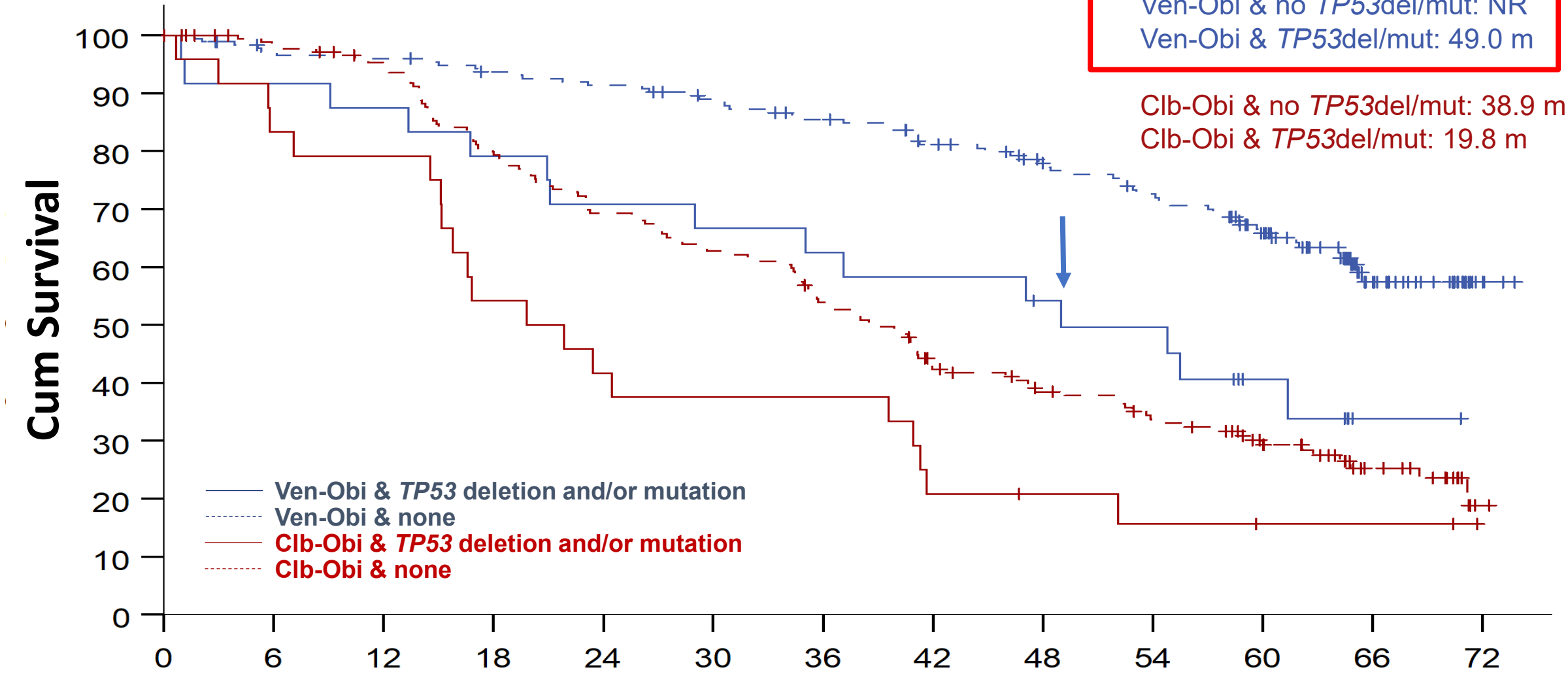


CLL14 PFS by *TP53* Status

Median observation time 65.4 months

Median PFS
Ven-Obi & no *TP53*del/mut: NR
Ven-Obi & *TP53*del/mut: 49.0 m

Clb-Obi & no *TP53*del/mut: 38.9 m
Clb-Obi & *TP53*del/mut: 19.8 m

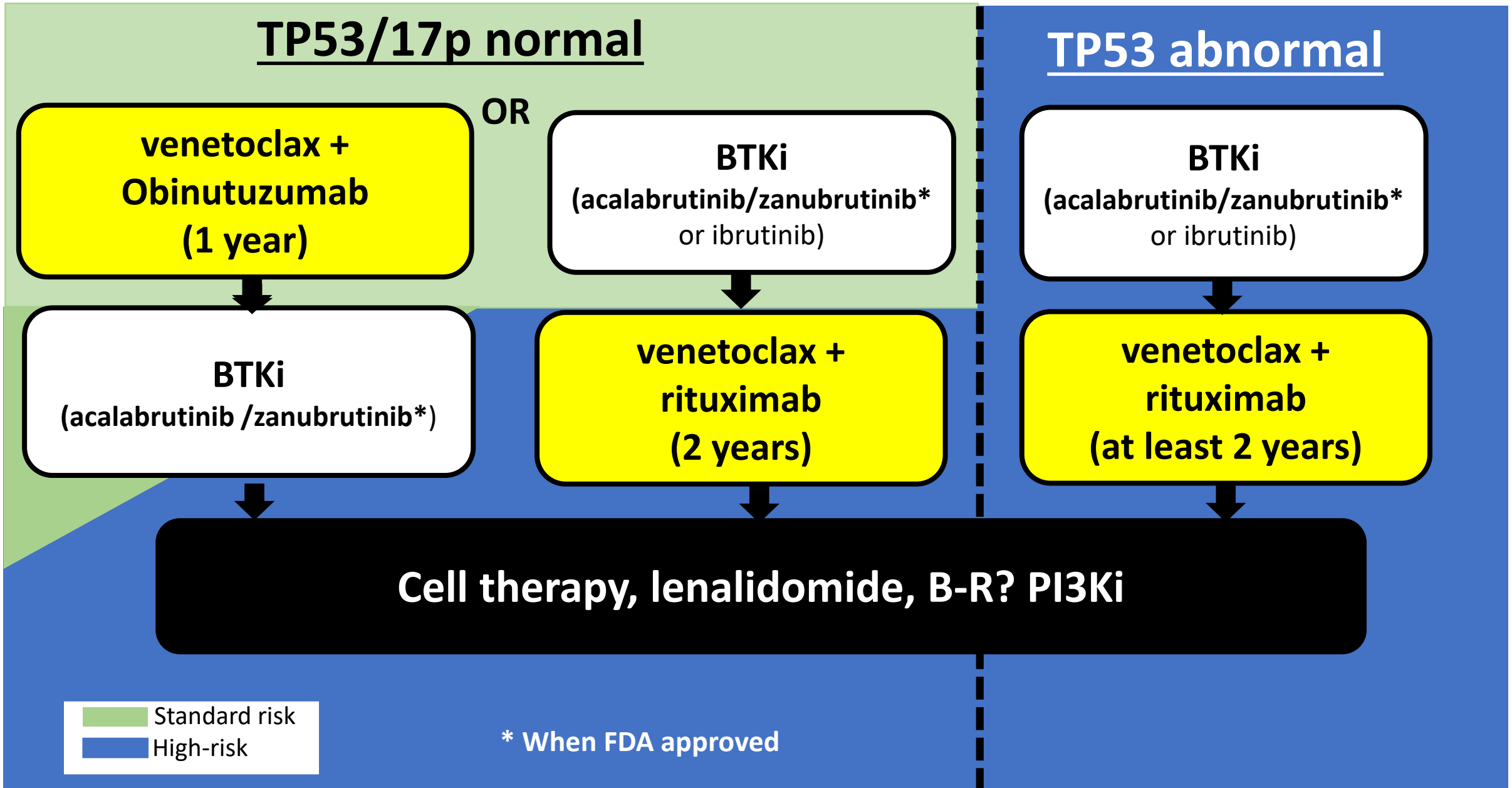


Choice Between BTKi and Ven-Based Therapy?

- *Favors BTKi:*
  - Easy to initiate vs intense early monitoring with ven
  - Longer follow-up data (only with ibrutinib)
  - *TP53* aberrancy

- *Favors Ven-Based Therapy:*
  - High CR and undetectable MRD (What about IGHV status?)
  - Time-limited therapy
    - Avoids selection pressure for resistance
    - Reduces long term side effects
    - Lower cost
  - Potential to repeat the same therapy again in the future

CLL: Current State Upfront Treatment



Important ASH abstracts

- **Upfront treatment including prognostication**
  - DFCI AVO
  - CLL13
  - GLOW

ROLE OF MRD?
Should we be incorporating other prognostic factors?

- **Relapsed Disease**
  - ALPINE
  - BRUIN CLL cohort
  - BRUIN RT cohort

OHSU KNIGHT CANCER Institute

Updated Results from a Multicenter, Phase 2 Study of Acalabrutinib, Venetoclax, Obinutuzumab (AVO) in a Population of Previously Untreated Patients with CLL Enriched for High-Risk Disease

Christine E. Ryan, MD[1], Benjamin L. Lampson, MD, PhD[1], Svitlana Tyekucheva, PhD[2], Liam R. Hackett, AB[1], Yue Ren, MS[2], Samantha J. Shupe, BS[1], Stacey M. Fernandes, BS[1], Jennifer L. Crombie, MD[1], Samuel Ng, MD, PhD[1], Austin I. Kim, MD[1], Inhye E. Ahn, MD[1], Matthew Weinstock, MD[3], Samantha Pazienza, BS[1], Josie Montegaard, NP[1], Victoria Patterson, RN[1], Caron A. Jacobson, MD[1], Ann S. LaCasce, MD, MMSc[1], Philippe Armand, MD, PhD[1], David C. Fisher, MD[1], Jon E. Arnason, MD[3], Steve Lo, MD,[4] Adam Olszewski, MD,[5] Jennifer R. Brown, MD, PhD[1], Matthew S. Davids, MD, MMSc[1]

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[2]Department of Data Science, Dana-Farber Cancer Institute, Boston, MA
[3]Department of Hematology/Oncology, Beth Israel Deaconess Medical Center, Boston, MA
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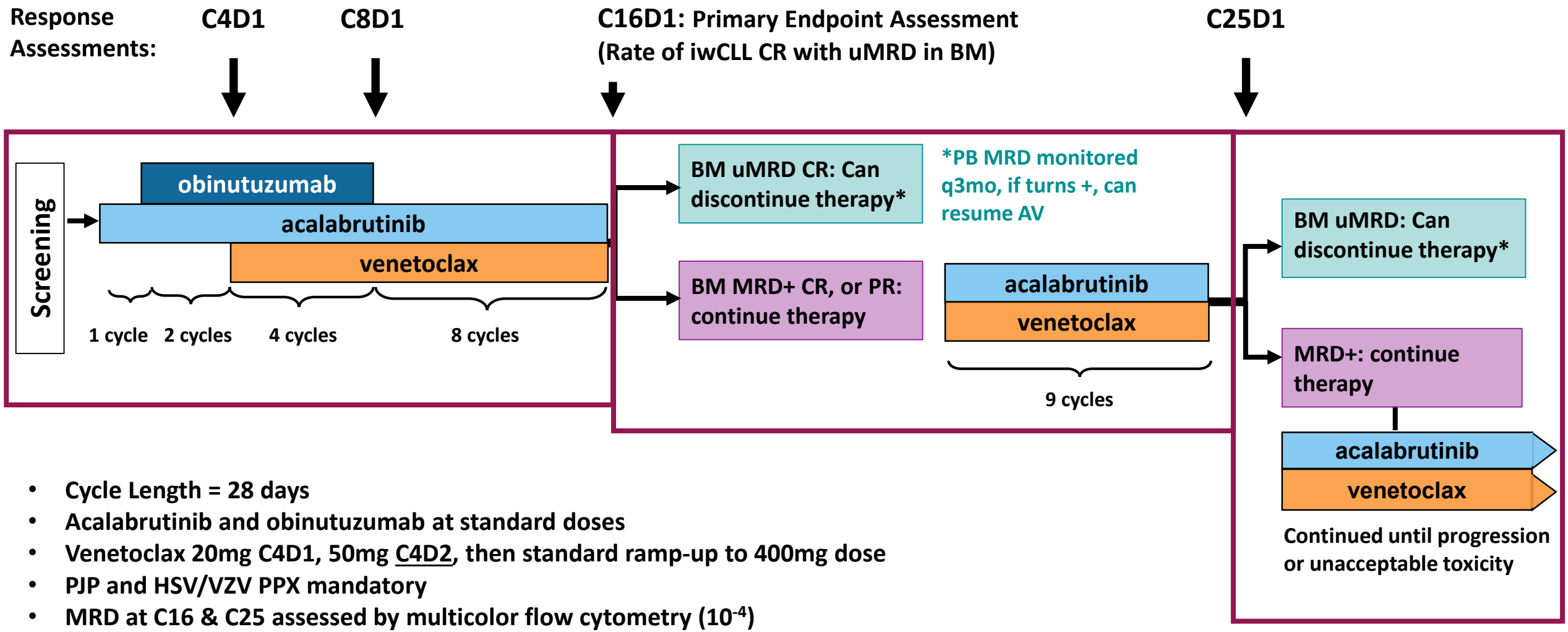
[5]Lifespan / Rhode Island Hospital, Providence, RI

December 10, 2022
ASH Annual Meeting
New Orleans, LA

Study Schema



- Cycle Length = 28 days
- Acalabrutinib and obinutuzumab at standard doses
- Venetoclax 20mg C4D1, 50mg C4D2, then standard ramp-up to 400mg dose
- PJP and HSV/VZV PPX mandatory
- MRD at C16 & C25 assessed by multicolor flow cytometry (10^{-4})

Dana-Farber Cancer Institute

Baseline Patient Characteristics

Total number of patients: 68
- **Initial all-comer cohort:** 37
- **Expansion high-risk cohort:** 31

Characteristic (n=68) [median (range) or n (%)]	
Age, years	63 (36-80)
Male	45 (66.2%)
Rai Stage 3-4	32 (47.1%)
Bulky lymphadenopathy	23 (34.3%)
White blood cell count, $x10^9$ per L	99 (2-602)
Hemoglobin, g/dL	11.3 (7.4-16.4)
Platelets, $x10^9$ per L	146 (38-339)

Characteristic (n=68)	**n**	**%**
***TP53* Status**		
del(17p) and/or *TP53* mutation	41	60.3%
del(17p) and *TP53* mutation	28	41.2%
***TP53* mutation only**	10	14.7%
del(17p) only	3	4.4%
IGHV Status		
Unmutated	50	73.5%
Mutated	15	22.1%
Unknown	3	4.4%
Other Cytogenetics		
del(11q)	17/65	26.2%
Trisomy 12	11/66	16.7%
Complex karyotype (≥3 cytogenetic abnormalities)	16/61	26.2%
***NOTCH1* Mutation**	10/52	19.2%

Data Cutoff: 07/26/2022

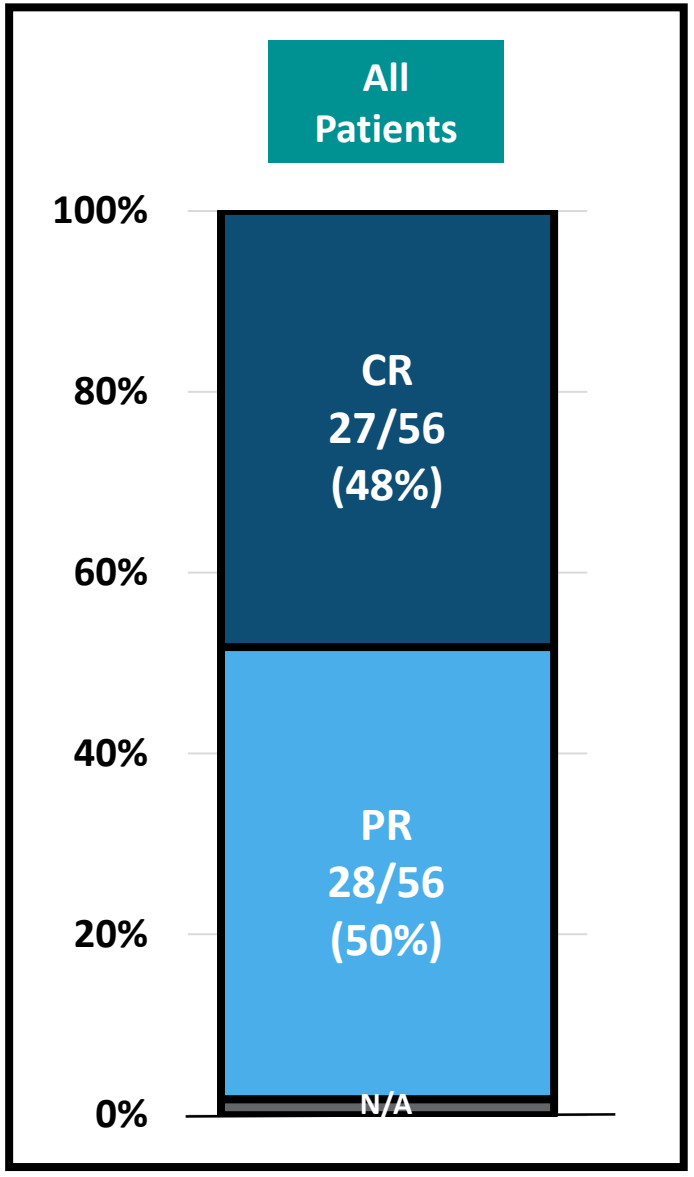
Efficacy: AVO Achieves High Clinical Response Rates by iwCLL Criteria at Cycle 16

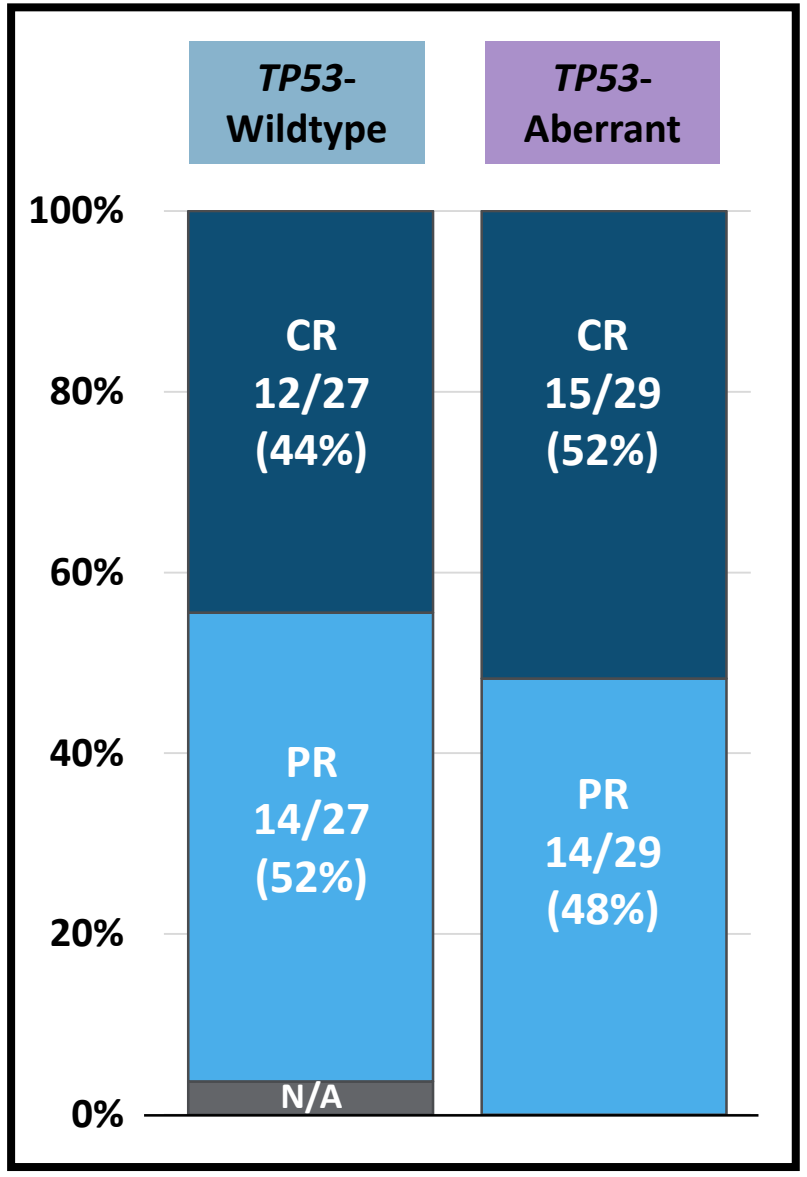
Primary Endpoint:
BM-uMRD CR Rate at Cycle 16

All Patients: 43%
(24/56*)

***TP53*-aberrant: 45%**
(13/29)

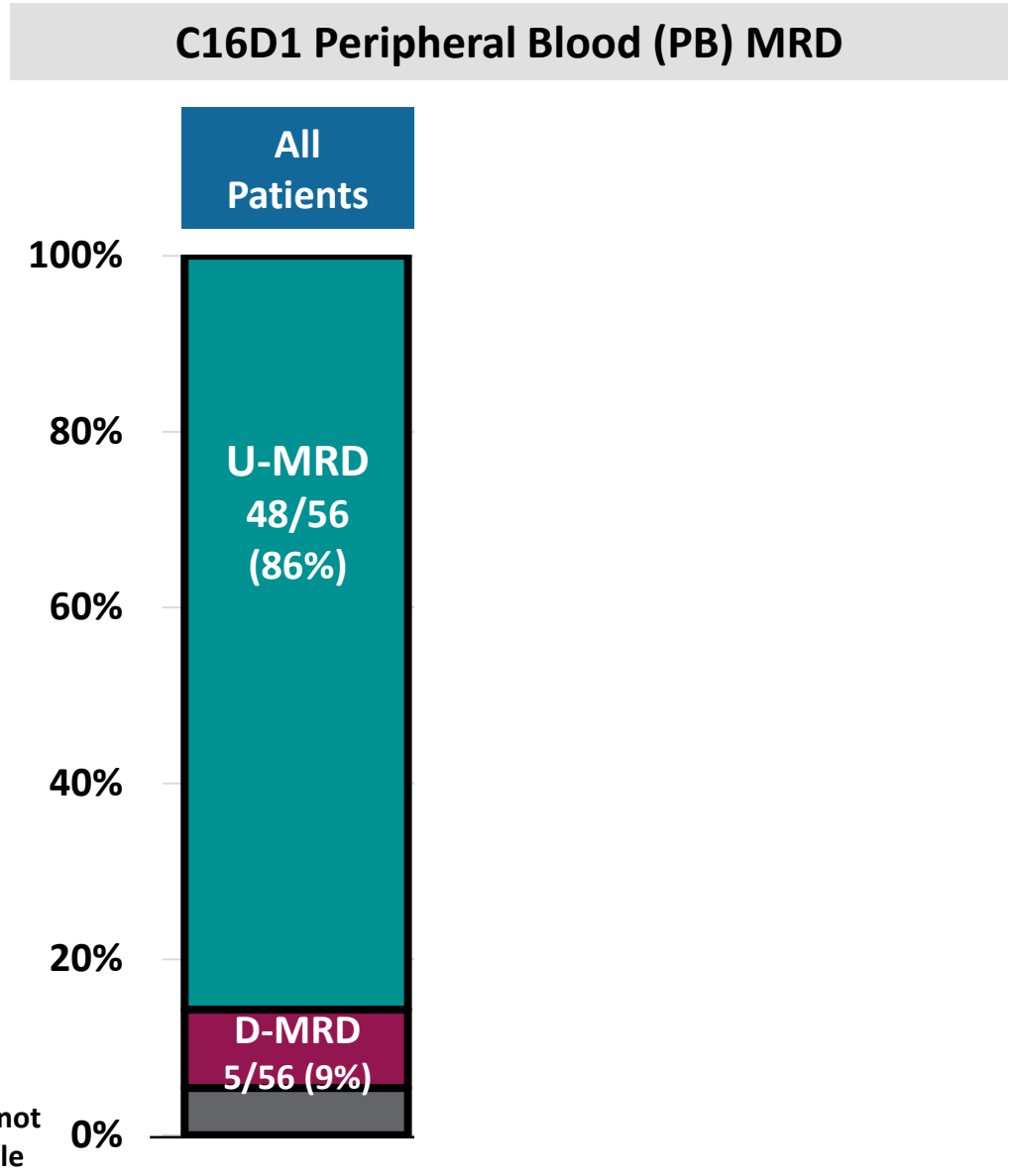
***n=12 patients currently on treatment who have not reached C16 are not yet included in efficacy analysis**

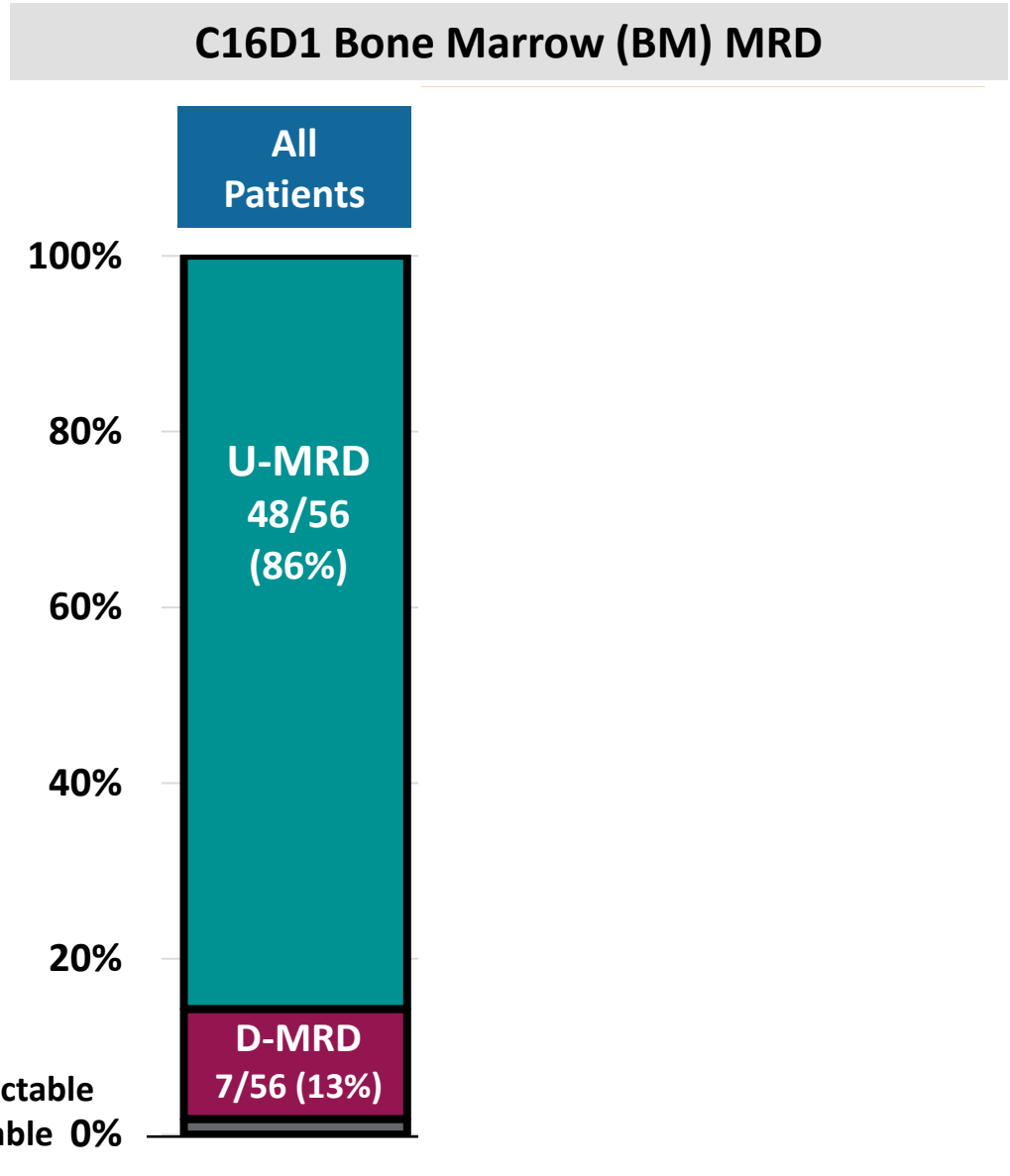




Dana-Farber Cancer Institute

Efficacy: AVO Achieves High Rates of Undetectable MRD by Multicolor Flow Cytometry (10^{-4}) at Cycle 16

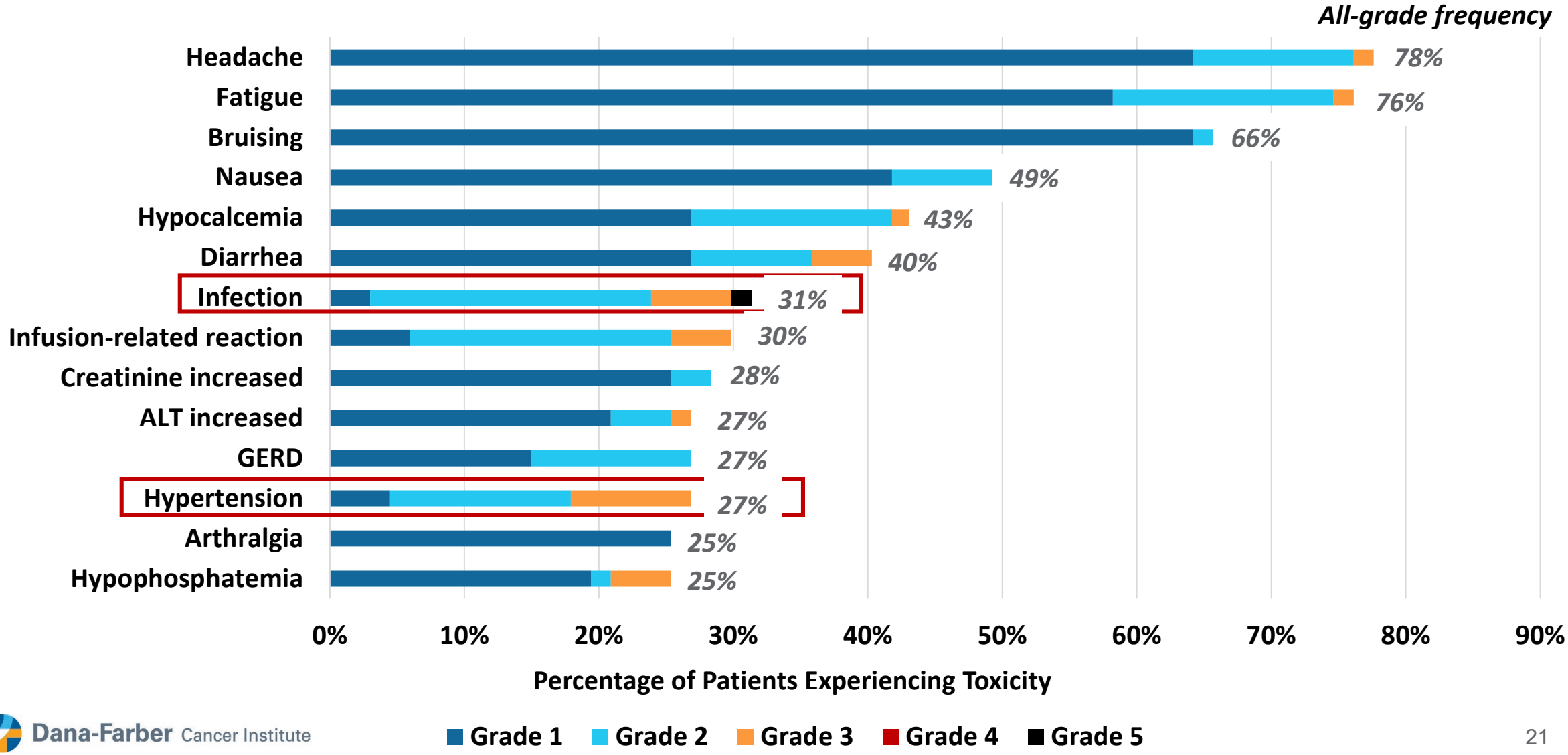




Safety Analysis

Median Follow-Up: 35 months (range: 2-45)

Non-Hematologic Toxicities Occurring in ≥ 25% of Patients



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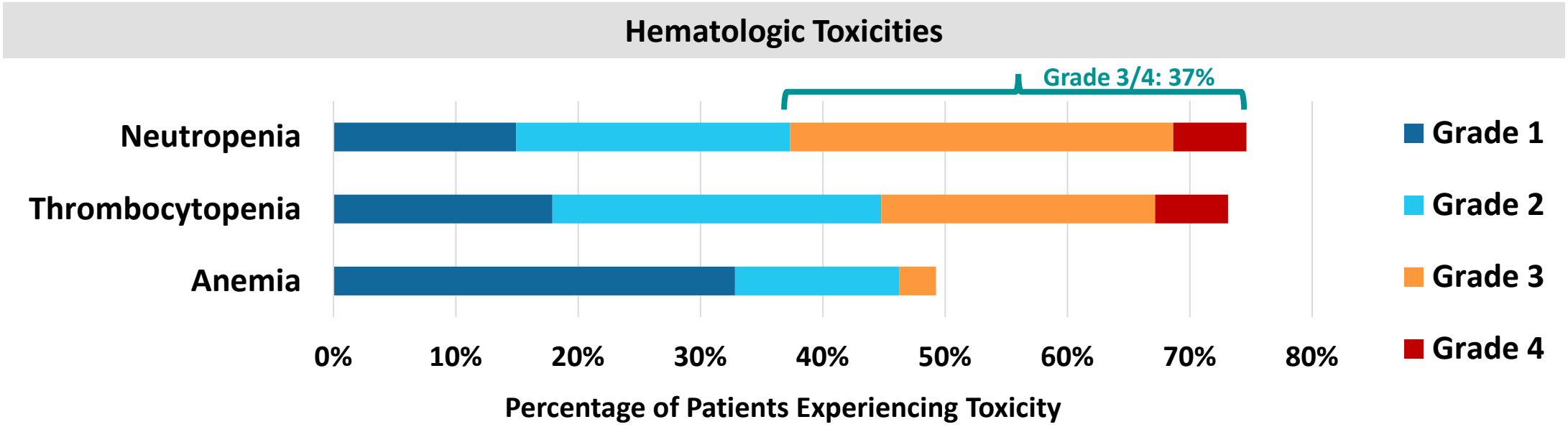


Adverse Events of Special Interest

- Grade 3 non-COVID infections: 5.8% [pneumonia (n=3), colitis (n=1)]
- COVID-19 Infections: 9.0% (Gr 2 (n=4), Gr 3 (n=1), Gr 5 (n=1)
- AFib: 3.0% (n=1 Gr 2, n=1 Gr 3); no ventricular arrhythmias
- No febrile neutropenia or opportunistic infections
- No major bleeding events

Dose Reductions

14 patients (21%) with any dose reduction

- Acalabrutinib only: n=3
- Venetoclax only: n=6
- Both drugs: n=5

Progression & Overall Survival

4 progression events:

- 1 patient with CLL disease progression (del(17p) & *TP53* mutation)
- 3 patients had transformation events
  - 1 with Hodgkin transformation 13 months after completing study treatment (*NOTCH1* mutation)
  - 1 with Hodgkin transformation 12 months into study treatment (del(17p) & *TP53* mutation)
  - 1 with DLBCL after 15 months on study (del(17p), *TP53* mutation, & complex karyotype)

1 death: Due to COVID-19 pneumonia

At a median follow-up of 35 months:

- **92.6% of all patients (63/68) are progression-free and alive**
- **98.5% of all patients (67/68) are alive**

Conclusions

- AVO is a highly active, well-tolerated triplet in a frontline CLL population enriched for high-risk disease
- 83% of *TP53*-a 16
- At a median fo with a 93% PFS rate (1 CLL disease
- Low rates of ca
- AVO is current 311 / AMPLIFY trial (AVO vs AV vs
- Our results pro imited AVO triplet, particularly in

Kinetics of Response?

Responses at 9 and 12 months – can we stop earlier?

MRD positive at the end of treatment?

Longer follow up (after additional 9 months may inform this) but only 7 patient

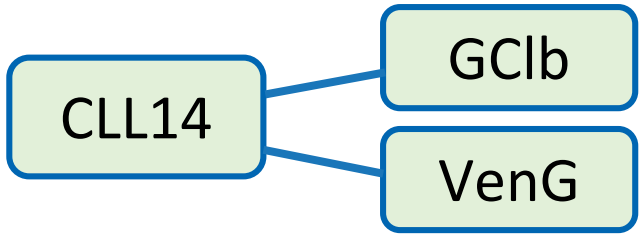
Not clear if any better than other fixed duration regimens

Genetic markers and front line FCR/BR vs. RVe, GVe and GIVe treatment – outcome results from the CLL13/GAIA trial.

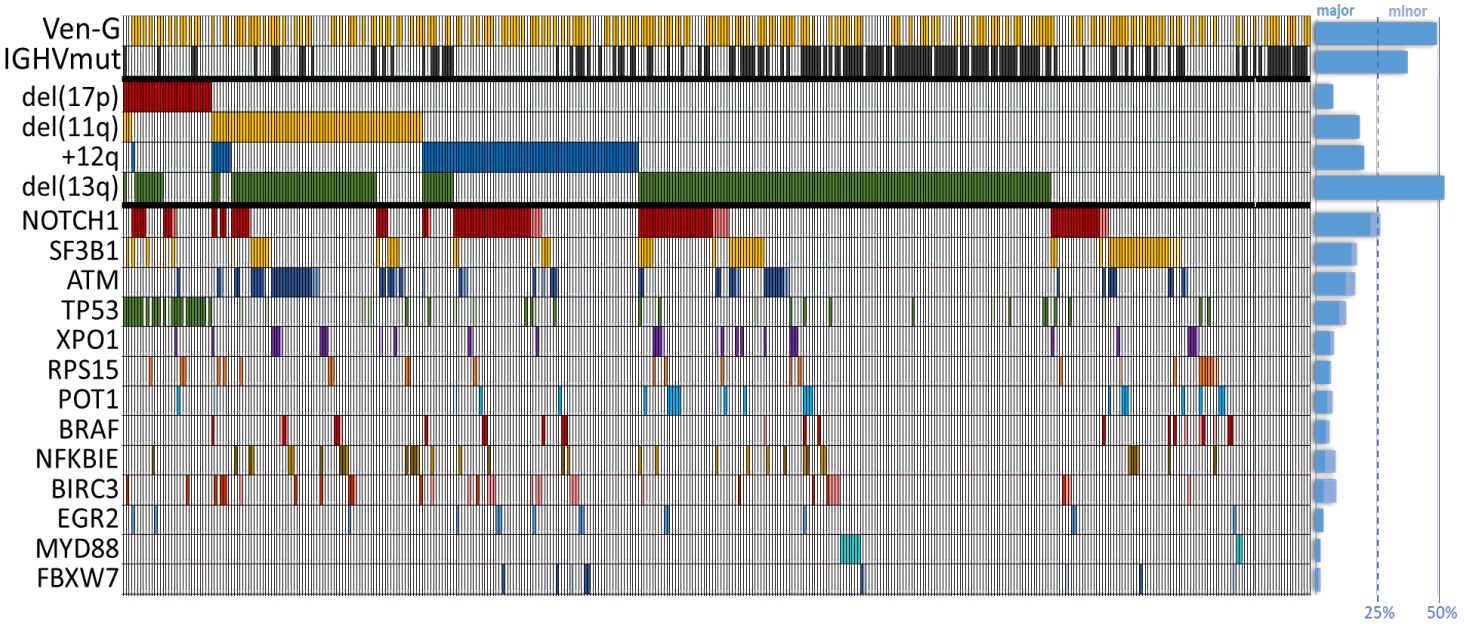
American Society of Hematology Annual Meeting - December 10th, 2022

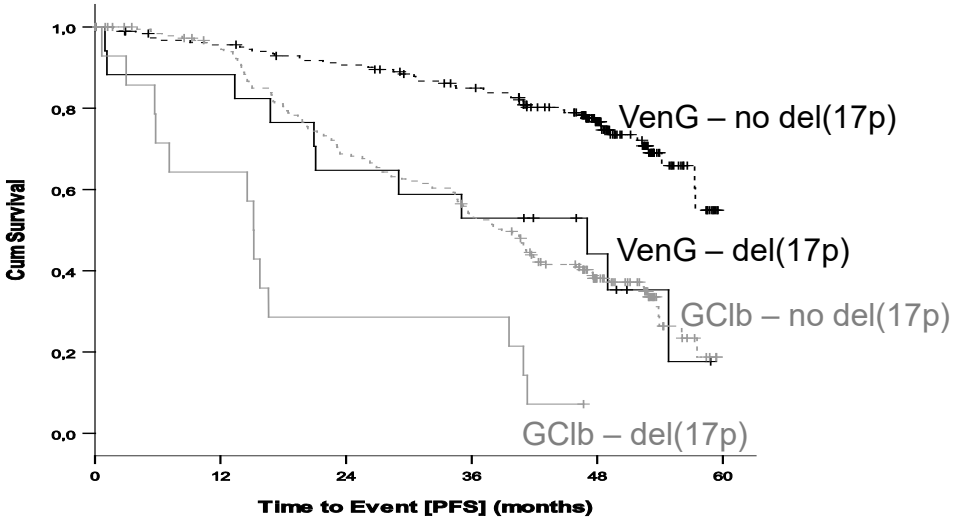
Eugen Tausch, Christof Schneider, Moritz Fürstenau, Sandra Robrecht, Deyan Yosifov, Daniel Mertens, Michael Gregor, Patrick Thornton, Philipp B. Staber, Tamar Tadmor, Mark-David Levin, Caspar da Cunha-Bang, Christian Bjoern Poulsen, Thomas Illmer, Björn Schöttker, Ann Janssens, Ilse Christiansen, Thomas Nösslinger, Michael Baumann, Clemens Martin Wendtner, Eric Eldering, Karl-Anton Kreuzer, Matthias Ritgen, Anna-Maria Fink, Kirsten Fischer, Arnon P Kater, Carsten Niemann, Michael Hallek, Barbara Eichhorst, Stephan Stilgenbauer

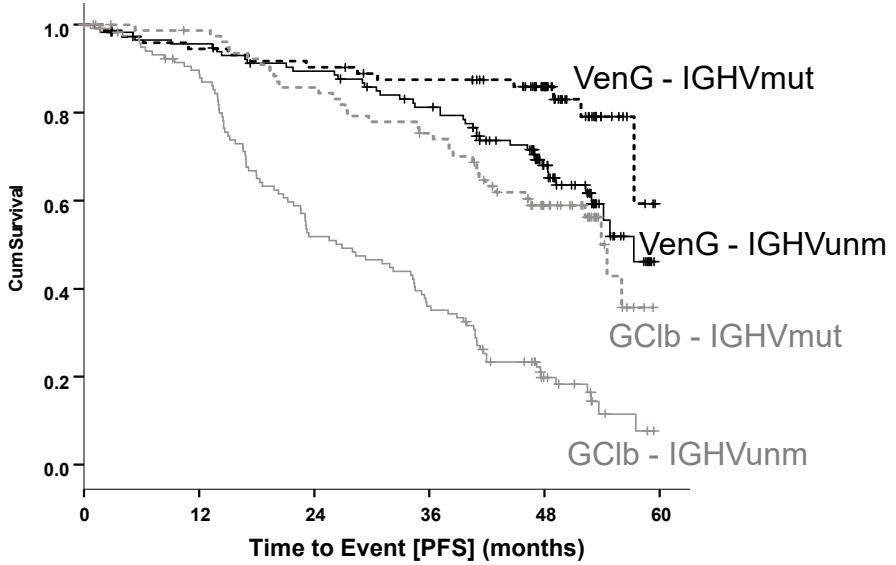
Background: del(17p) and U-IGHV of prognostic impact for VenG in the CLL14 trial



- Untreated CLL n=432 with “active disease”
- Median Age 72 years, CIRS score 8, Creat Clear 66.4m
- 12 cycles treatment in each arm







1. Fischer et al, NEJM 2019; 2. Tausch et al, Blood 2020; 3. Al-Sawaf et al, 2021; 4. Tausch et al, EHA2022;

CLL13/GAIA: venetoclax-based treatments vs. CIT in younger/fit patients

Fit patients with untreated CLL:
CIRS ≤ 6 & normal CrCl

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

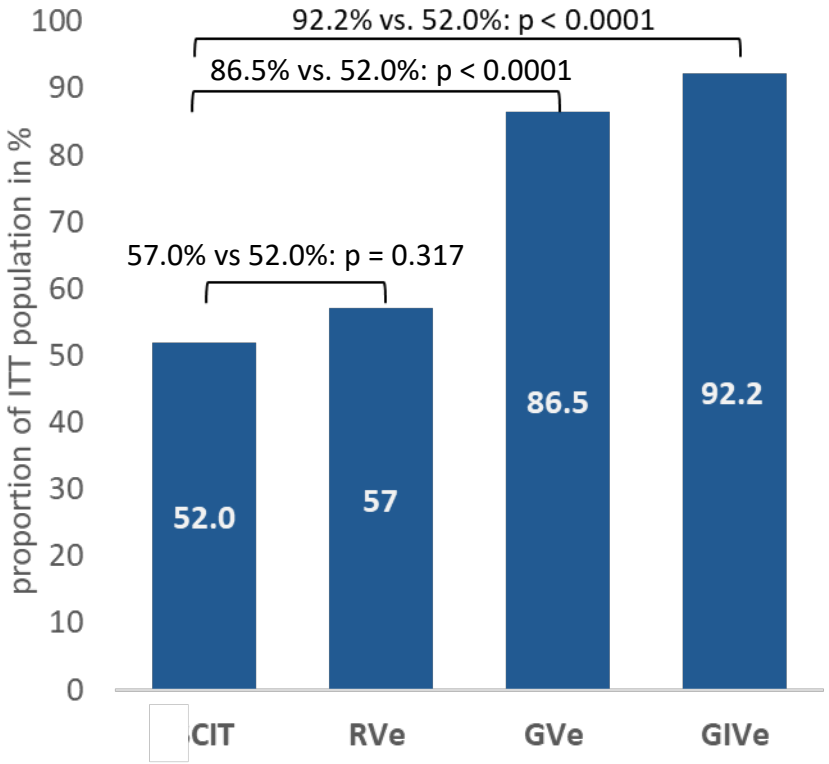
CIT: FCR/BR*
6 cycles,n=230

RVe
12 cycles, n=230

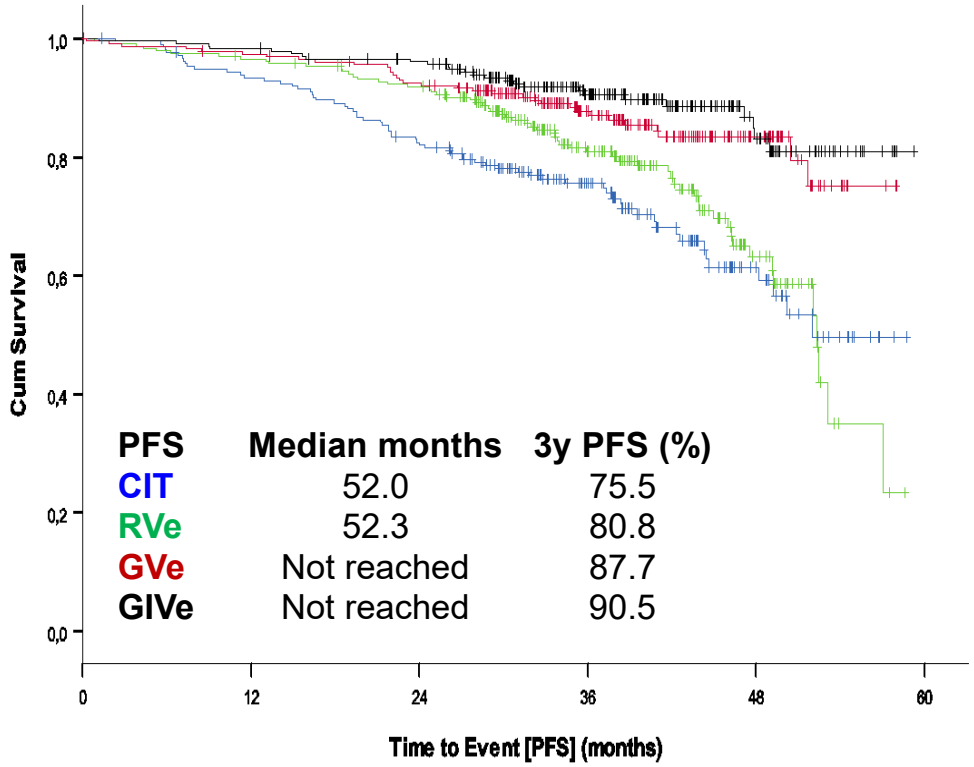
GVe
12 cycles, n=230

GIVe
15# cycles, n=230

uMRD (< 10^{-4})
at month 15 in PB by 4-colour-flow



PFS
at median FU of 38.8 months



PFS	Median months	3y PFS (%)
CIT	52.0	75.5
RVe	52.3	80.8
GVe	Not reached	87.7
GIVe	Not reached	90.5

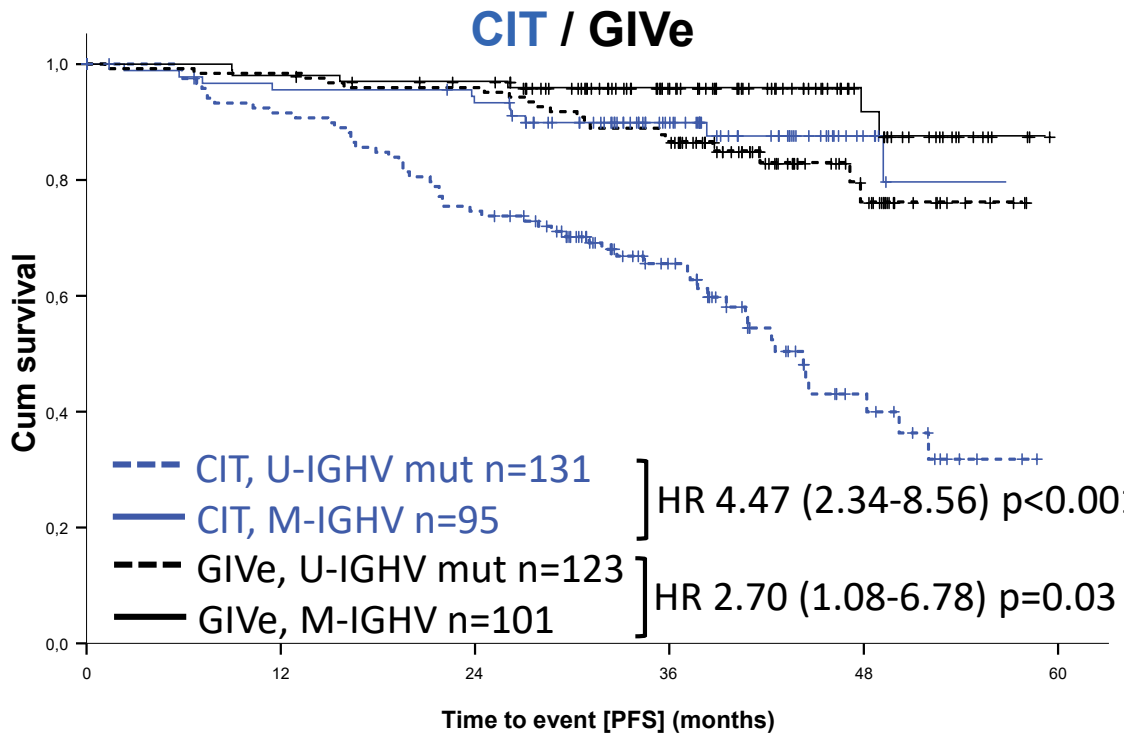
* ≤ 65 years: FCR, > 65 years: BR; [50% FCR / 50% BR]
# continuation of ibrutinib up to cycle 36 if MRD detectable

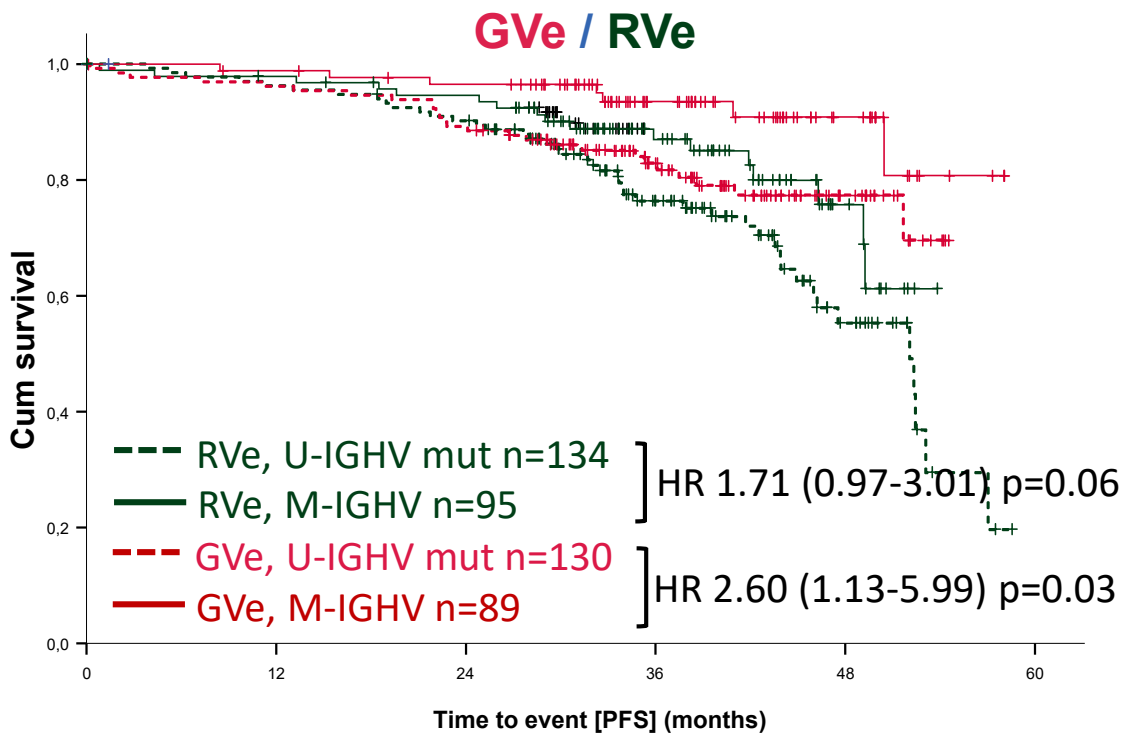
NO PFS DIFFERENCE FOR VEN-G based regimens

Eichhorst et al, ASH2021 and EHA2022

U-IGHV associated with shorter PFS with CIT, GVe, GIVe (and RVe)

IGHV associated with shorter PFS for all treatment arms with highest difference between U-IGHV and M-IGHV with CIT.





CIT,U-IGHV	131	108	88	48	14
CIT,M-IGHV	95	86	83	50	14
GIVe,U-IGHV	123	121	117	70	22
GIVe,M-IGHV	101	99	94	59	22

RVe,U-IGHV	134	128	119	67	20
RVe,M-IGHV	95	91	86	49	12
GVe,U-IGHV	130	125	116	71	21
GVe,M-IGHV	89	86	82	48	17

Results: GAIA/CLL13: Multivariate analysis for the full trial

Full trial analysis for PFS

	HR	95%CI	p
GVe vs. CIT	0.42	0.27-0.65	<0.001
GIVe vs. CIT	0.33	0.21-0.52	<0.001
U-IGHV	2.43	1.70-3.47	<0.001
CKT	1.98	1.42-2.77	<0.001
Binet B/C vs. A	1.55	1.06-2.27	0.03
NOTCH1mut	1.46	1.05-2.05	0.03

Excluded 17p del or p53 patients

All factors with a significant impact on outcome in univariate analysis were included in the MVA model.

Multivariate analysis of the full trial confirmed a PFS benefit of GVe and GIVe independent of the genetic risk factors.

Results: GAIA/CLL13: Multivariate analysis for CIT and RVe/GVe/GIVe

Full trial analysis for PFS

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U-IGHV, CKT and *NOTCH1* mutations were independent prognostic factors for CIT and RVe/GVe/GIVe.

RAS/RAF mutations were only prognostic with venetoclax therapy.

CIT for PFS

	HR	95%CI	p
U-IGHV	3.08	1.55-6.12	0.001
>65 years	2.26	1.34-3.83	0.002
NOTCH1mut	2.12	1.16-3.88	0.01
del(11q)	1.89	1.06-3.36	0.03
CKT	1.87	1.06-3.27	0.03

RVe/GVe/GIVe for PFS

	HR	95%CI	p
U-IGHV	1.85	1.20-2.84	0.005
RAS/RAFmut	1.87	1.14-3.06	0.01
CKT	1.66	1.07-2.56	0.02
b2MG>3.5mg/L	1.56	1.03-2.36	0.04
NOTCH1mut	1.54	1.02-2.33	0.04

GAIA/CLL13 genetics summary

ORR and MRD

U-IGHV patients had e.

No genetic factor had st del(11q) and
U-IGHV had lower u

PFS

Del(11q) associated v /GVe/GIVe.

Mutated *BRAF/NRAS* e/GIVe, but not CIT.

U-IGHV and *NOTCH* endent of the treatment.

Multivariate analysis *RAS* as independent
prognostic factors for

UM-IGHV matters but outcomes still good

Depth of response not affected but how does this directly impact remission on an individual basis

Landmark analysis based on MRD status at the end of treatment?

IMO

Favor BTKi in IGHV UM, notch 1, Complex karyotype patients

NEED RANDOMIZED DATA
A14702 and EA9161

Residual Disease Kinetics Among Patients With High-Risk Factors Treated With First-Line Fixed-Duration Ibrutinib Plus Venetoclax (Ibr+Ven) Versus Chlorambucil Plus Obinutuzumab (Clb+O): the GLOW Study

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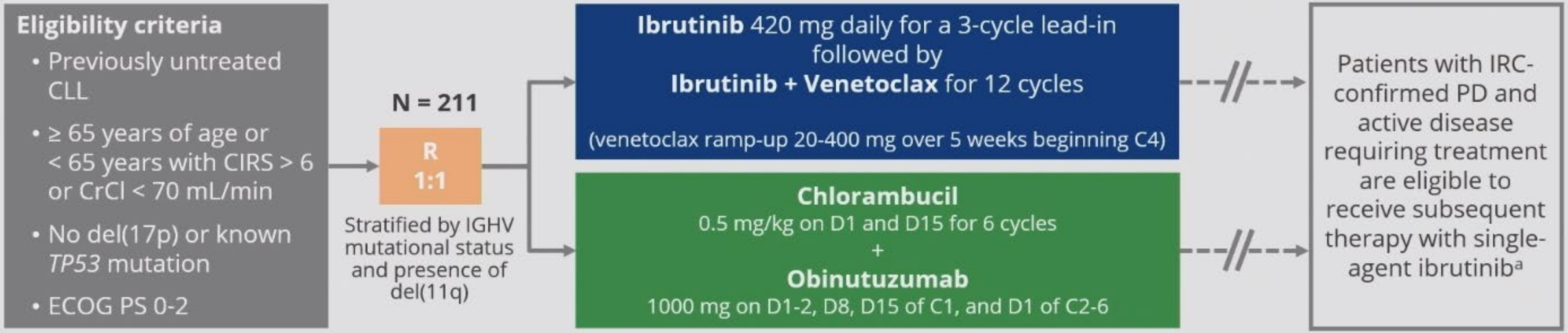
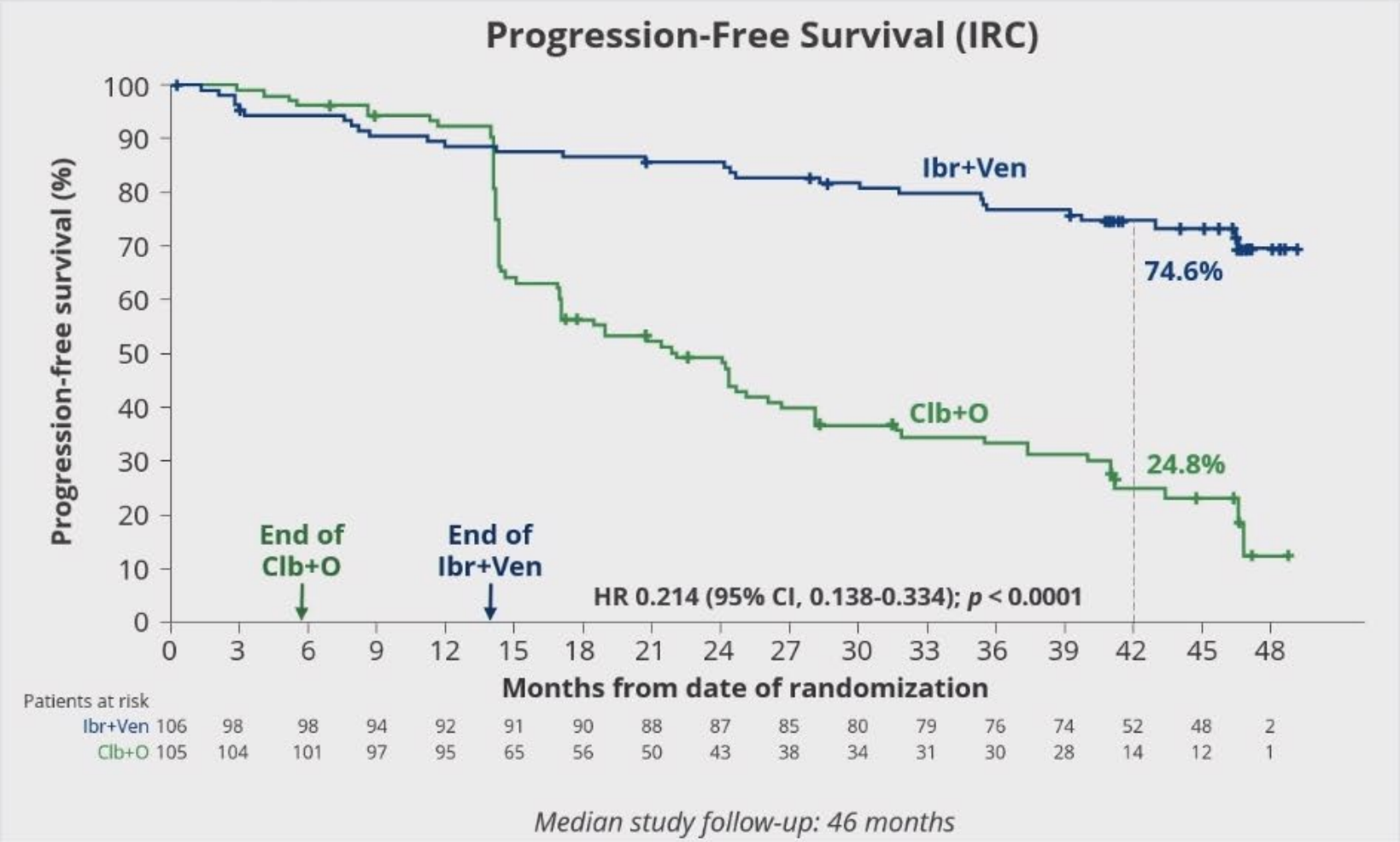
Phase 3 GLOW Study (NCT03462719)



- **Primary end point: IRC-assessed PFS**
- Key secondary end points: uMRD rates, response rates, overall survival, time to next treatment, and safety
- Current analysis
  - Median study follow-up of 46 months (range, 1.7-51.7)
  - MRD assessed in peripheral blood in responders by NGS

[a]Ibrutinib provided by the Sponsor to patients from both arms who were eligible to participate in the Subsequent Therapy Phase of the study.
C, cycle (28 days); CIRS, Cumulative Illness Rating Scale score; CrCl, creatinine clearance; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent review committee; PD, progressive disease; R, randomization; uMRD, undetectable minimal residual disease; NGS, next-generation sequencing.

GLOW: Progression-Free Survival by IRC Remained Superior For Ibr+Ven Versus Clb+O With 4 Years of Study Follow-up

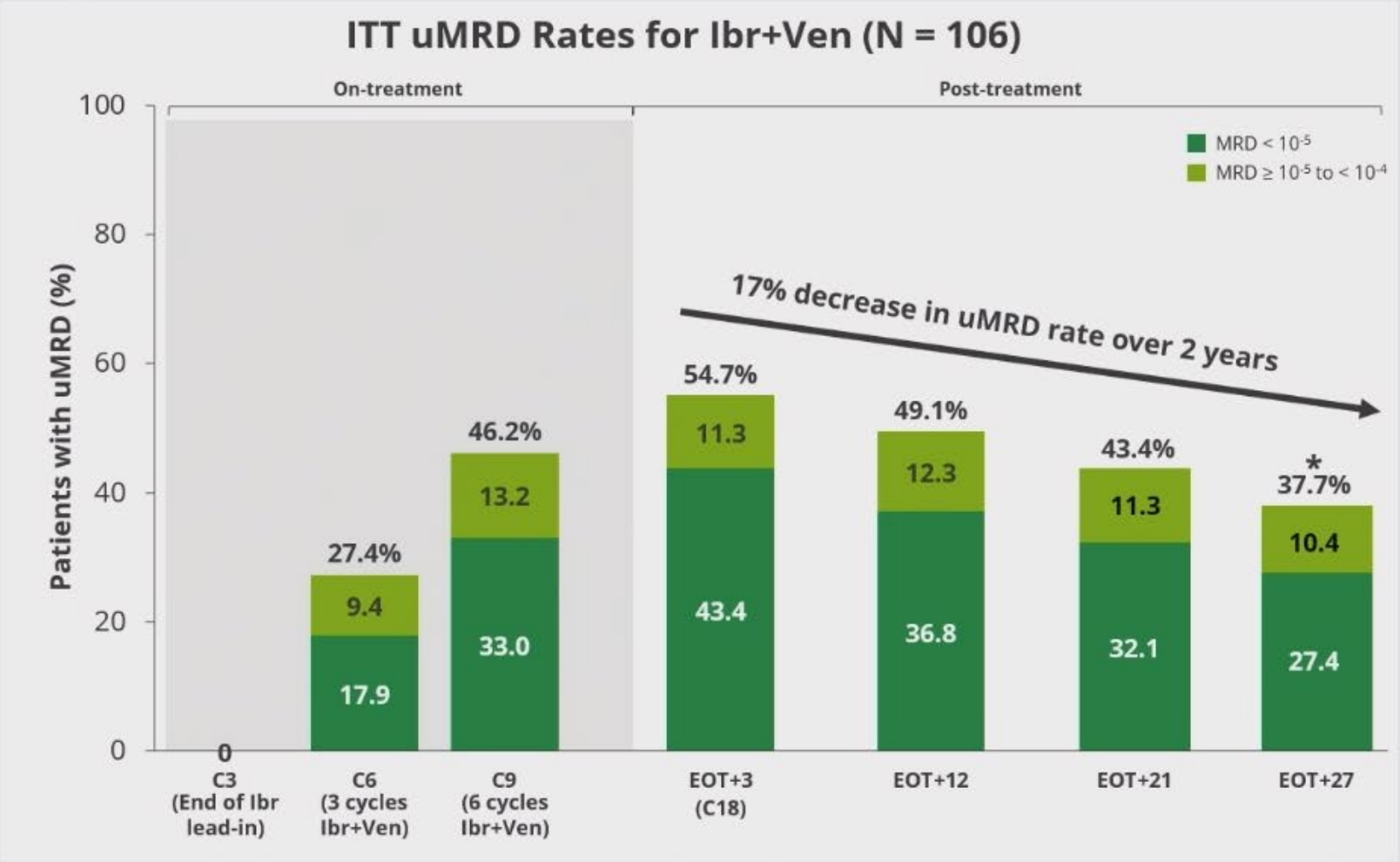


Median study follow-up: 46 months

- **Ibr+Ven reduced the risk of progression or death by 79%** versus Clb+O
  - HR 0.214 (95% CI, 0.138-0.334); $p < 0.0001$
- Estimated 3.5-year PFS rates:
  - **74.6%** for Ibr+Ven
  - **24.8%** for Clb+O

IRC, independent review committee; CI, confidence interval; HR, hazard ratio.

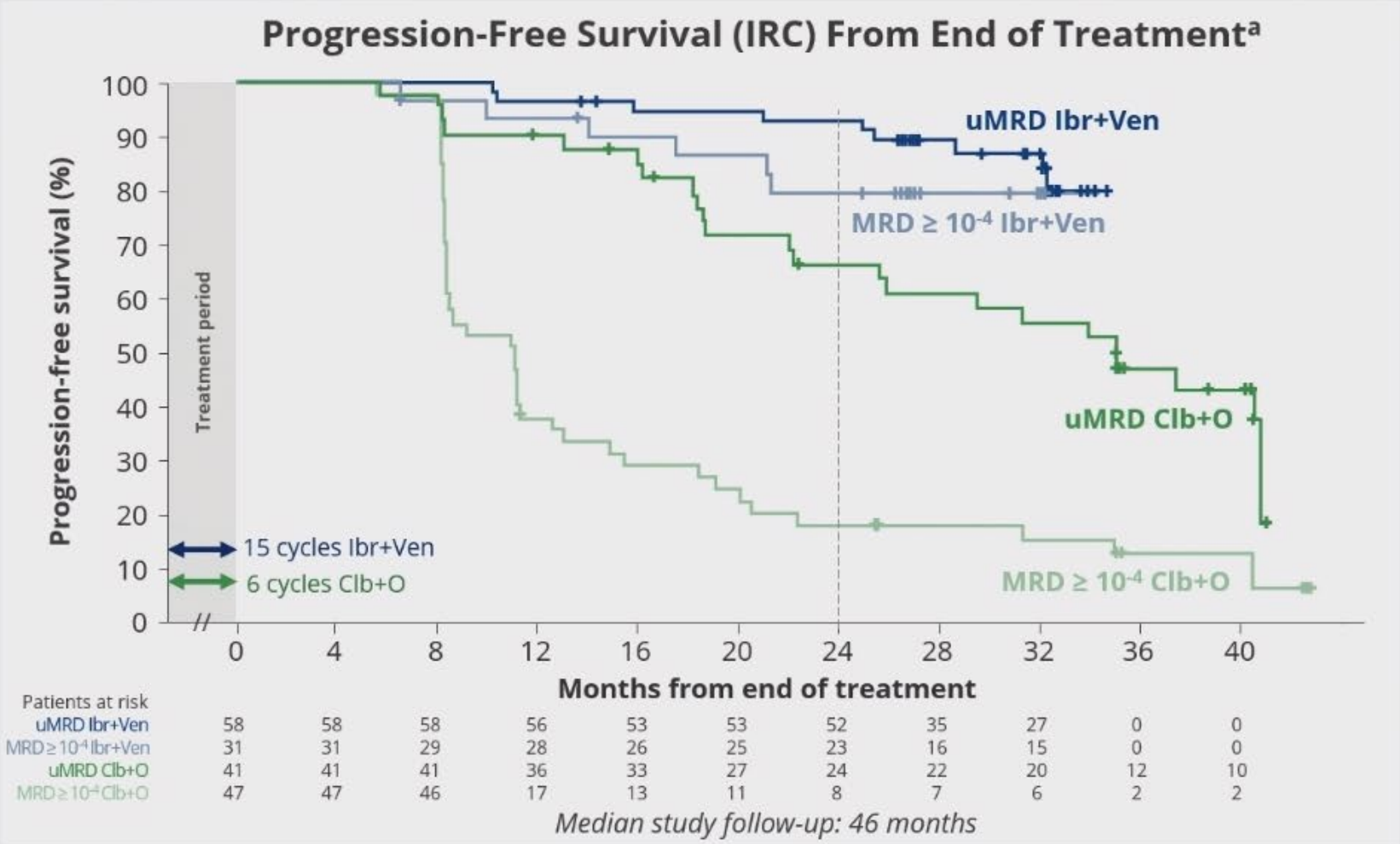
GLOW: PB uMRD Was Attained Early During Treatment With Ibr+Ven and Declined < 10% Per Year Post-treatment



- On-treatment:
  - Most patients who achieved uMRD by EOT+3 did so by C9, after 6 cycles of combined Ibr+Ven
- 2 years post-treatment:
  - Nearly 40% of patients had uMRD, including > 25% with deeper uMRD responses of < 10^{-5}

*8 (7.5%) patients with uMRD (including 6 with uMRD < 10^{-5}) at EOT+21 had missing samples at EOT+27 and were considered not uMRD.
Numbers may not add up to exact total due to rounding.
PB, peripheral blood; ITT, intent to treat; uMRD, undetectable minimal residual disease; C, cycle; EOT+3, end of treatment plus 3 months.

GLOW: Ibr+Ven Improved PFS Versus Clb+O Regardless of MRD Status at EOT+3

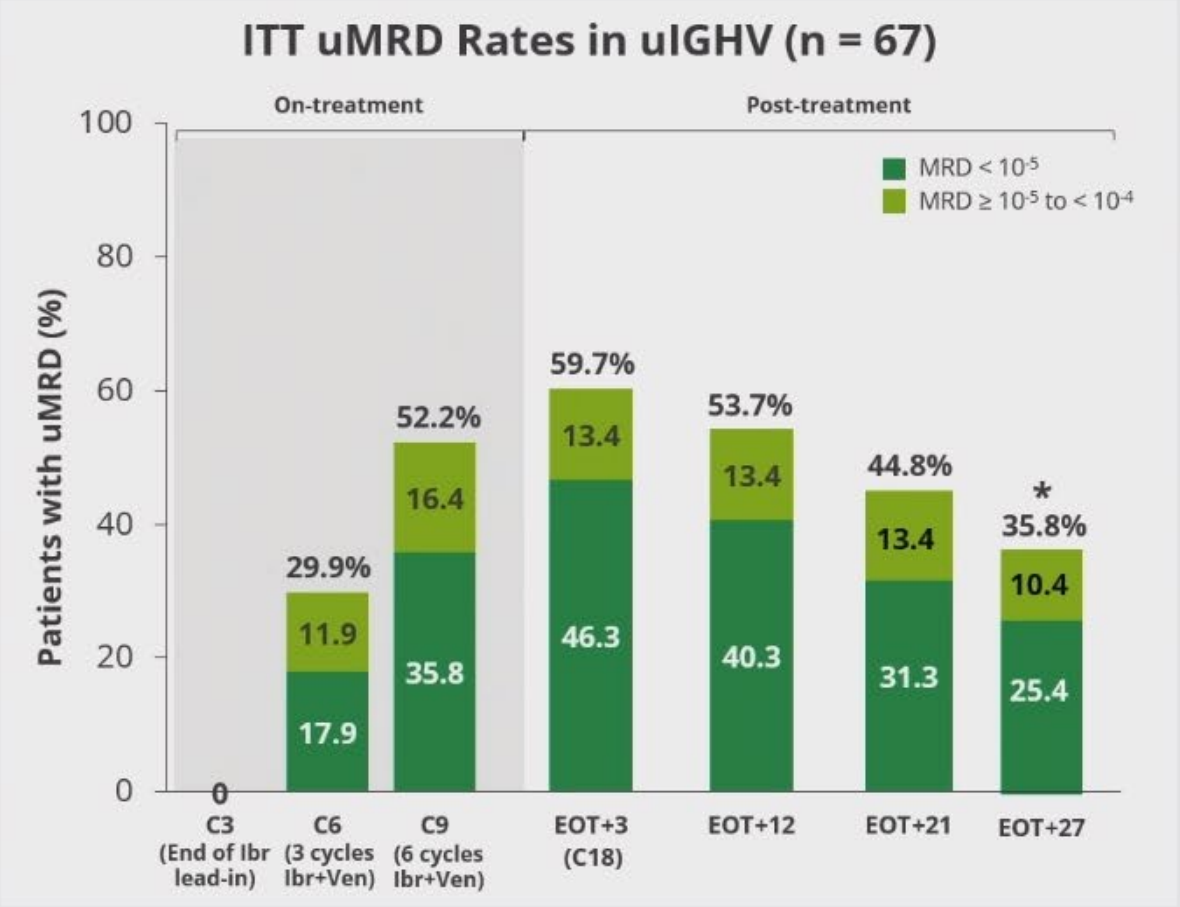


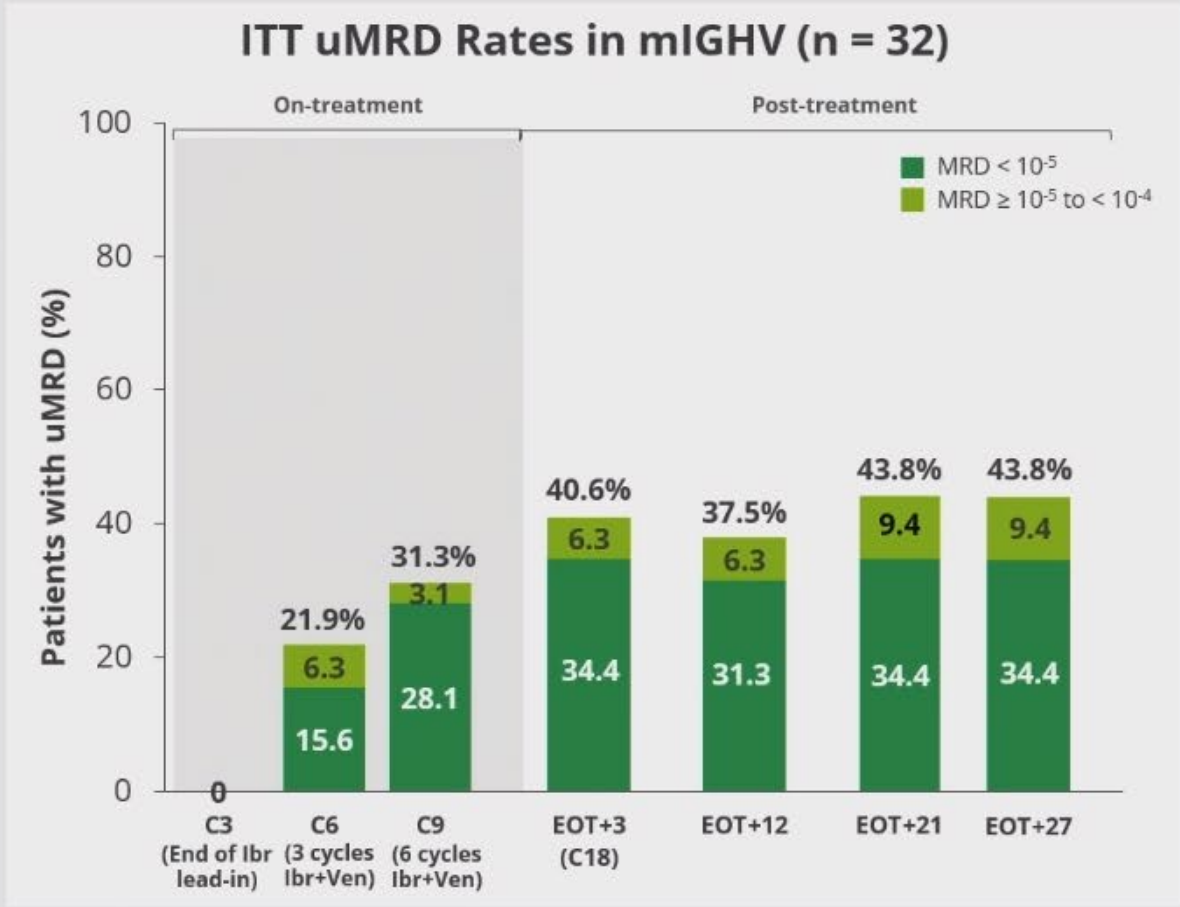
- PFS was better sustained with Ibr+Ven versus Clb+O, regardless of MRD status at EOT+3

- With Ibr+Ven:
  - Low impact of EOT+3 MRD status on PFS post-treatment
  - PFS rate at 2 years post-treatment remained ≥ 80% regardless of MRD status

[a]Curves generated from end of treatment (Cycle 15 for Ibr+Ven, Cycle 6 for Clb+O), resulting in different durations of post-treatment follow-up.
IRC, independent review committee; uMRD, undetectable minimal residual disease; EOT+3, end of treatment plus 3 months.

GLOW: Ibr+Ven On-treatment and Post-treatment uMRD Dynamics According to IGHV Status

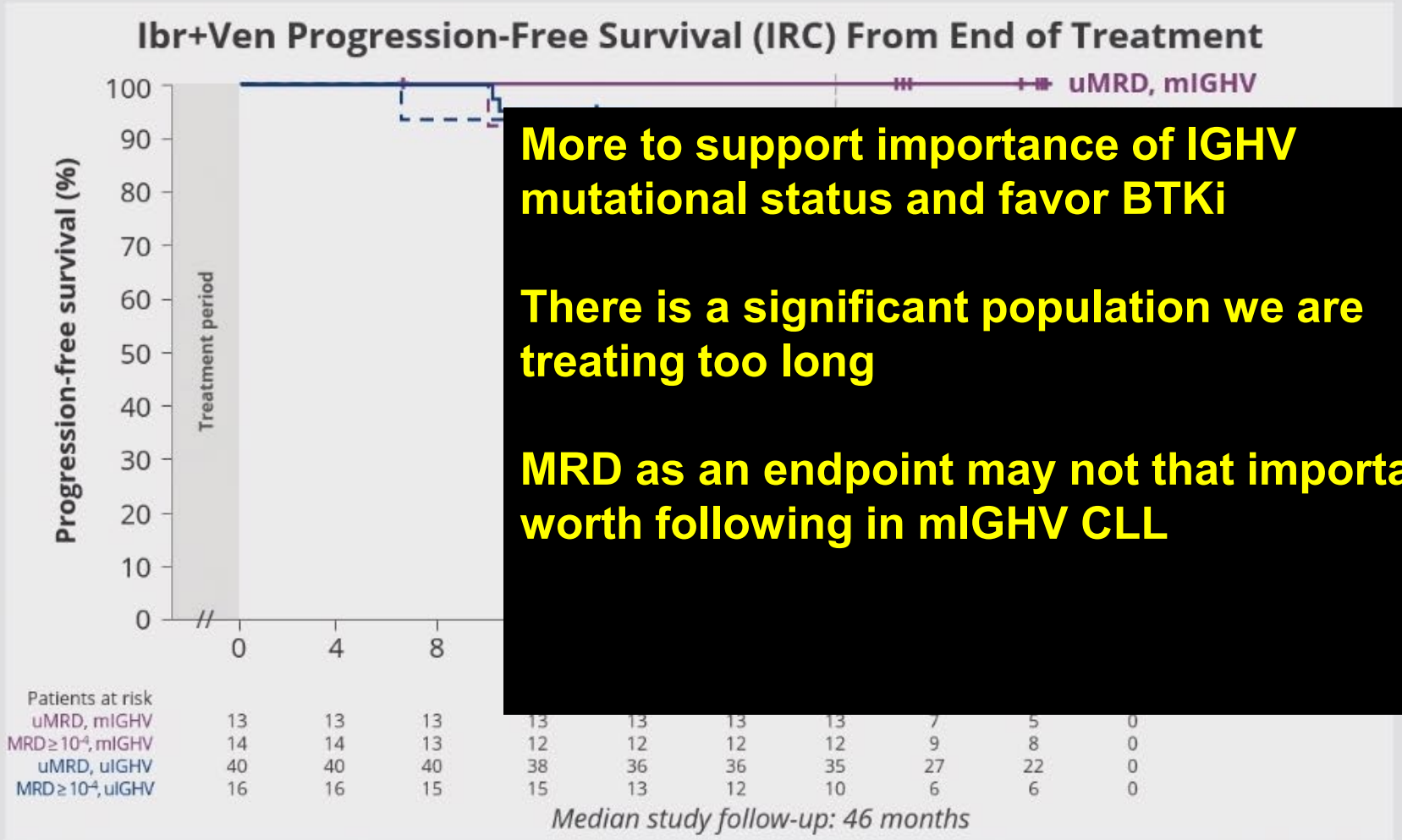




- uMRD rates (including < 10^{-5}) were higher and uMRD was achieved faster in patients with uIGHV versus mIGHV CLL
- uMRD was better sustained post-treatment in patients with mIGHV CLL

*7 (10.4%) patients with uMRD (including 5 with uMRD < 10^{-5}) at EOT+21 had missing samples at EOT+27 and were considered not uMRD.
Numbers may not add up to exact total due to rounding. ITT, intent to treat; uMRD, undetectable minimal residual disease; mIGHV, mutated IGHV; uIGHV, unmutated IGHV; C, cycle.

GLOW: Ibr +Ven PFS was ≥90% at Two years Post-treatment for Patients with uMRD at EOT+3, Regardless of IGHV Status



More to support importance of IGHV mutational status and favor BTKi

There is a significant population we are treating too long

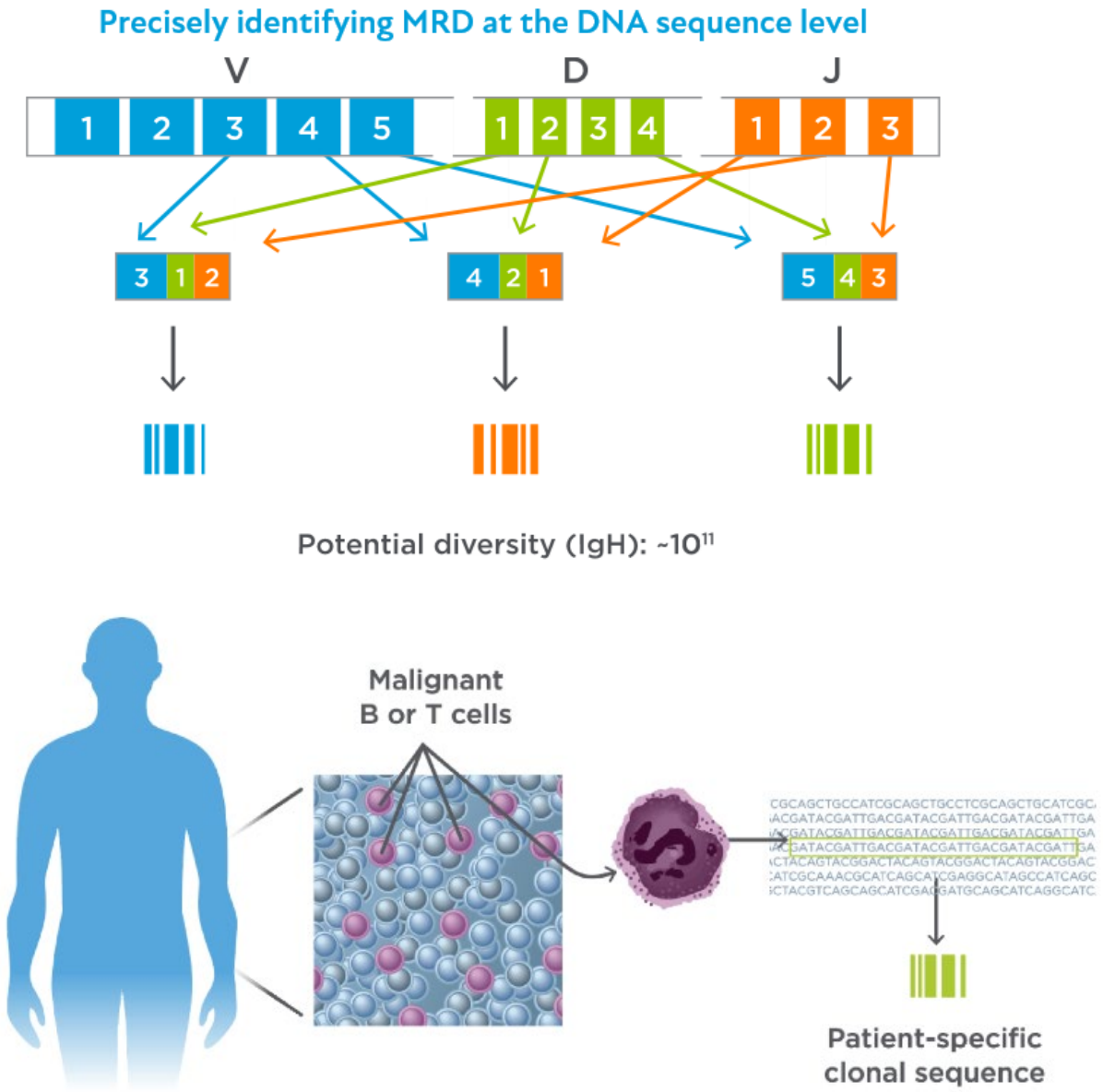
MRD as an endpoint may not that important/ worth following in mIGHV CLL

imated PFS at 2 years post-
atment for **uIGHV** CLL:
0% for uMRD at EOT+3
ersus 67% for MRD ≥ 10^{-4}

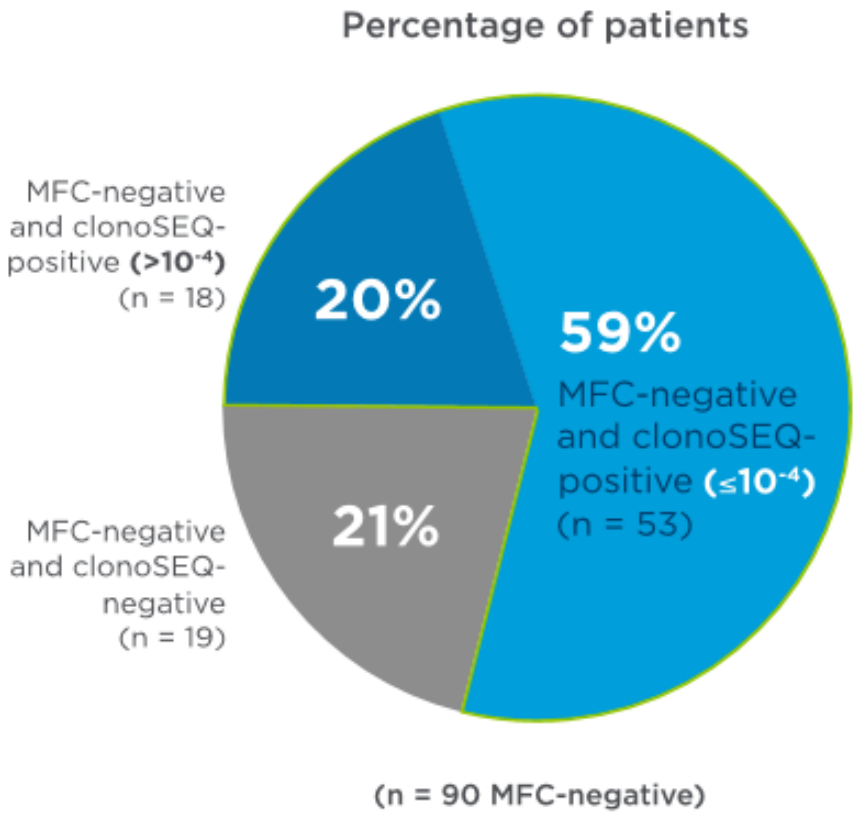
imated PFS at 2 years post-
atment for **mIGHV** CLL:
90% regardless of MRD
tatus at EOT+3

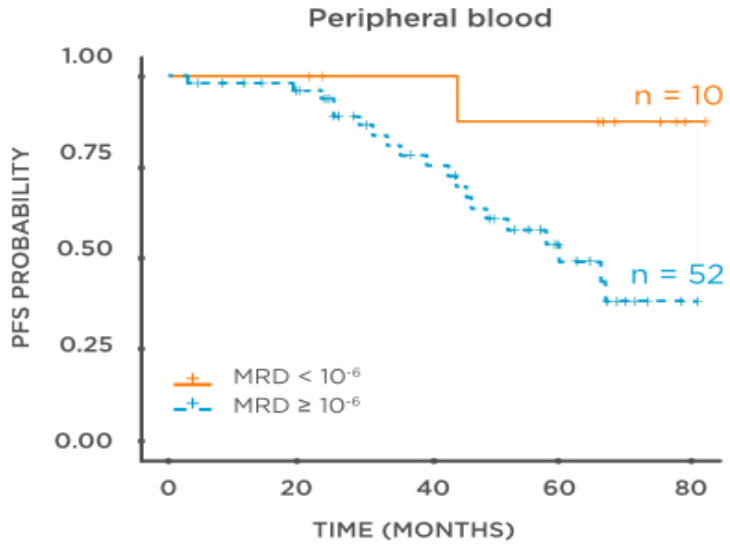
IRC, independent review committee; uMRD, undetectable minimal residual disease; EOT+3, end of treatment plus 3 months.

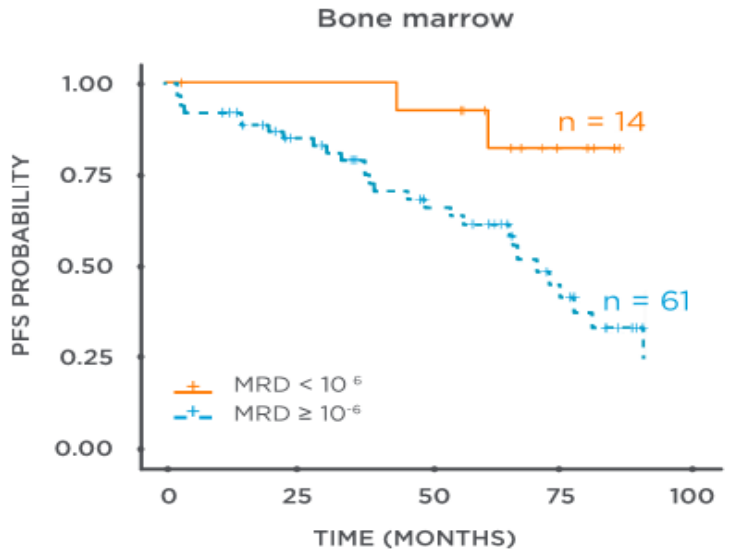

clonoSEQ
By Adaptive


Precisely identifying MRD at the DNA sequence level
V
D
J
1 2 3 4 5
1 2 3 4
1 2 3
3 1 2
4 2 1
5 4 3
Potential diversity (IgH): ~10^11
Malignant
B or T cells
Patient-specific
clonal sequence

NGS more sensitive than multi-color flow cytometry (MCF)







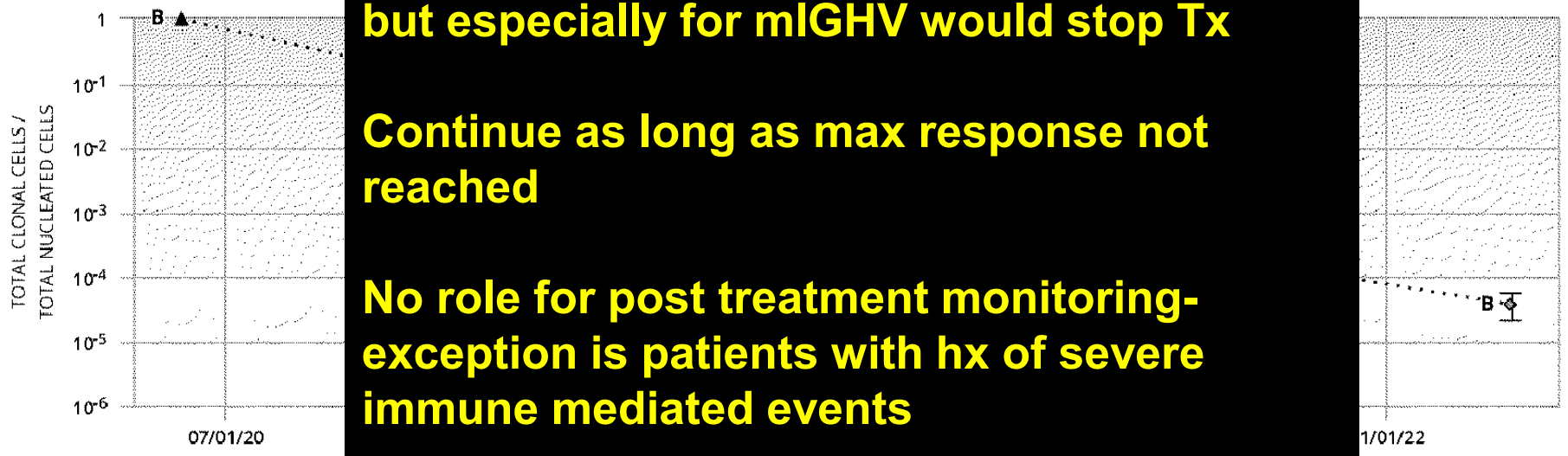
RESULTS SUMMARY

- Genomic DNA was extracted
- 6 of the 6 dominant sequen
- 121 copies of the dominant
  evaluated from this sample.
- **The results obtained from**
  and other findings.

nucleated cells

medical history,

SAMPLE-LEVEL MRD TRACKING



Can use NGS without need for bone marrow

Can use to stop treatment early
-baseline, 3 months, 6 months, 9 months, etc.

No idea what to do if MRD + post treatment but especially for mIGHV would stop Tx

Continue as long as max response not reached

No role for post treatment monitoring- exception is patients with hx of severe immune mediated events

American Society of Hematology
Helping hematologists conquer blood diseases worldwide

Zanubrutinib Demonstrates Superior Progression-Free Survival Compared with Ibrutinib for Treatment of Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma: Results from Final Analysis of ALPINE Randomized Phase 3 Study

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Bruton Tyrosine Kinase Inhibition in CLL: Background

- B-cell antigen receptor (BCR) signaling is required for tumor expansion and proliferation in CLL and B-cell lymphomas[1]
  - BCR signaling is dependent on BTK (Bruton's Tyrosine Kinase)
- Ibrutinib, a first-in-class, covalent BTK inhibitor, has transformed CLL therapy; however, it has properties that limit use
  - Treatment discontinuation from toxicities has been reported in 16%-23% of patients[3-6]
  - Exposure coverage between dosing intervals falls below IC_{50} and variable BTK occupancy at trough has been observed

Ibrutinib concentration-time profile

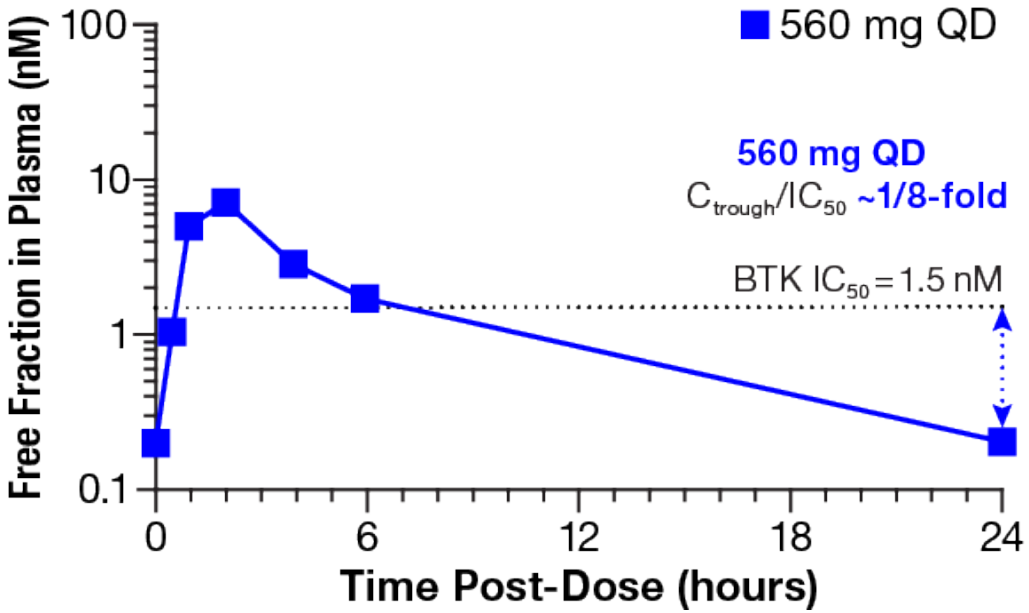


Figure adapted from Tam CS et al. *Expert Rev Clin Pharmacol*. 2021;14:11, 1329-1344

1. Singh SP, Dammeijer F and Hendriks RW. *Molecular Cancer.* 2018; 17:57.; 2. Molis S, Matures E, Tam C, Polliack A. *Hematol Oncol*. 2020; 38: 129-136; 3. Sharman JP, Black-Shinn JL, Clark J, et al. *Blood*. 2017;130(suppl 1):4060; 4. Mato AR, Nabhan C, Thompson MC, et al. *Haematologica*. 2018;103(5):874-879; 5. Munir T, Brown JR, O'Brien S, et al. *Am J Hematol*. 2019;94(12):1353-1363; 6. Ghia P, Owen C, Robak T, et al. EHA Abstract EP636 2021.

Zanubrutinib: Differentiating Features and Background

- Zanubrutinib is a second-generation Bruton tyrosine kinase inhibitor (BTKi)
  - Zanubrutinib was designed to have greater BTK specificity than ibrutinib
  - Zanubrutinib has exposure coverage above its IC_{50}
  - Higher drug-concentration/IC_{50} ratios would be expected to lead to more sustained and complete BTK inhibition to improve efficacy
- Zanubrutinib has demonstrated superior PFS by IRC over chemoimmunotherapy in treatment-naive CLL/SLL patients without del(17p)[1]

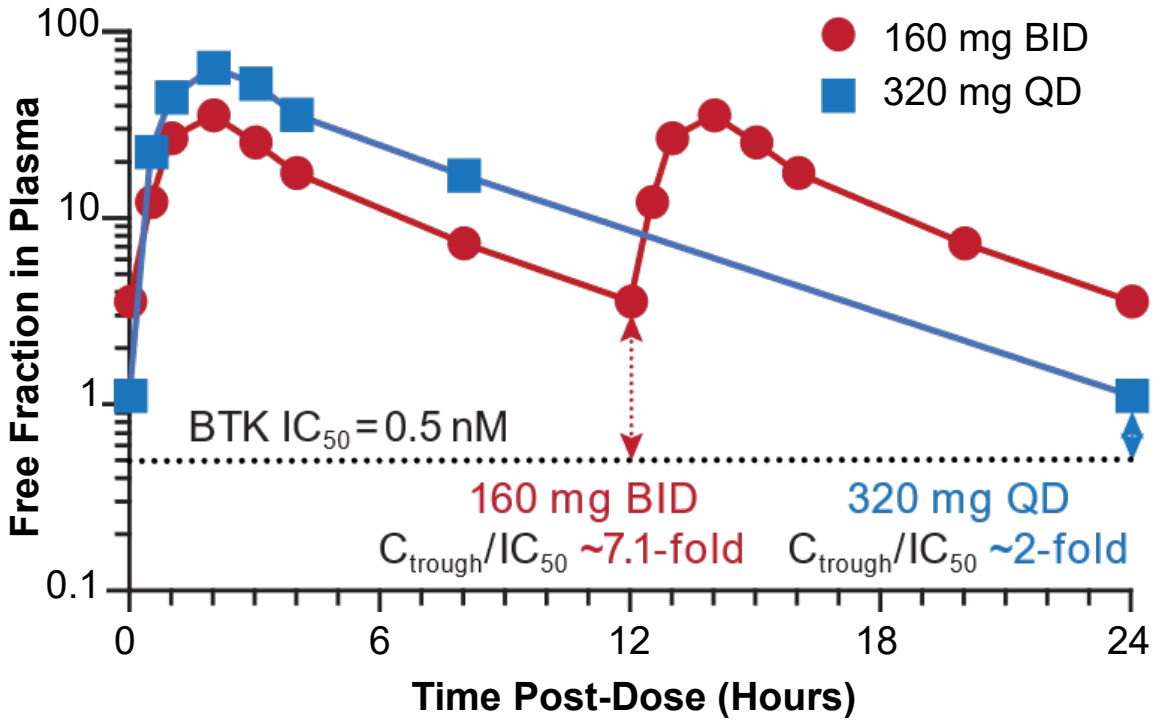


Figure modified from Ou YC, Tang Z, Novotny W, et al *Leukemia & Lymphoma.* 2021; 62(11):2612-2624.

[1]Tam CS, Brown JB, Kahl BS, et al. *Lancet Oncol*. 2022. https://doi.org/10.1016/S1470-2045(22)00293-5

ALPINE Study Design

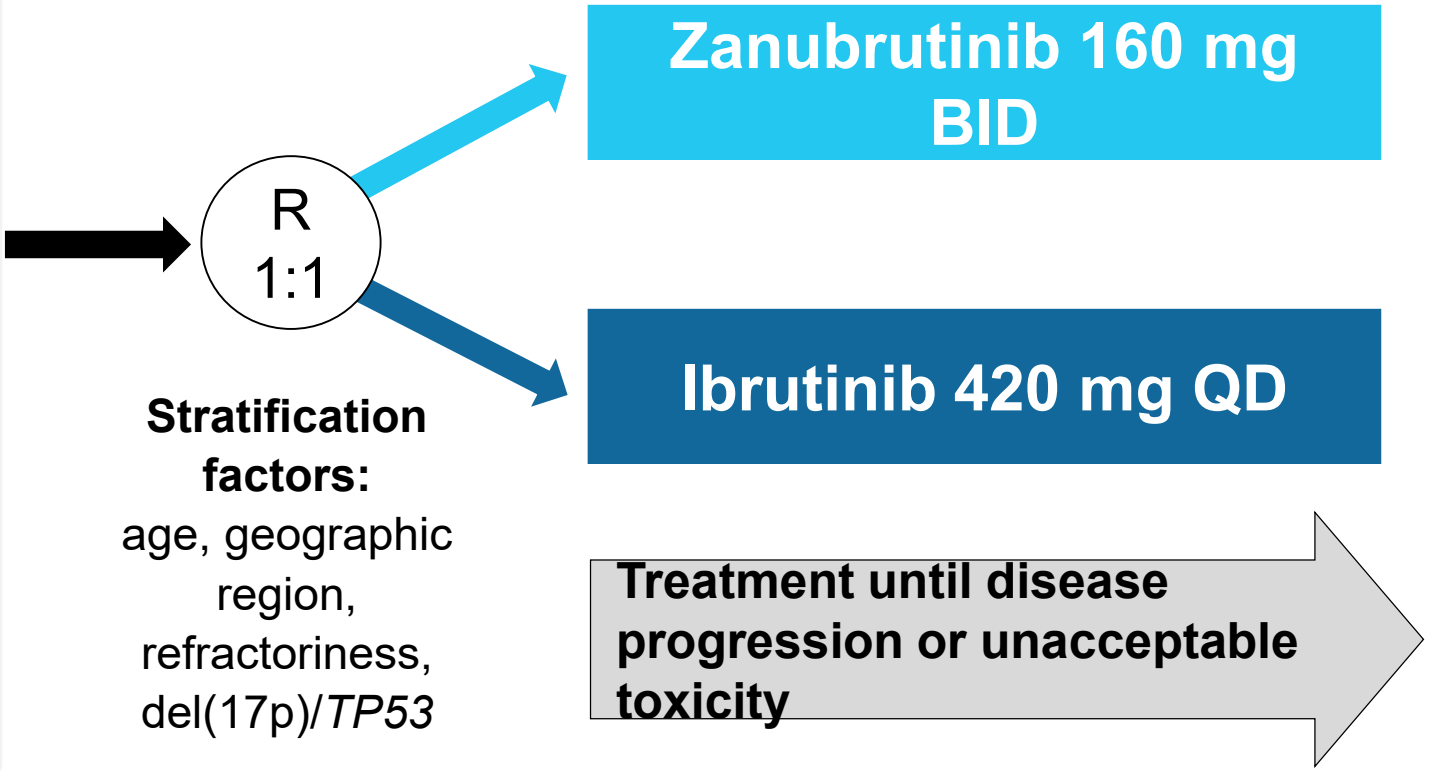
R/R CLL/SLL with ≥ 1 prior treatment
(Planned N=600, Actual N=652)

Key Inclusion Criteria

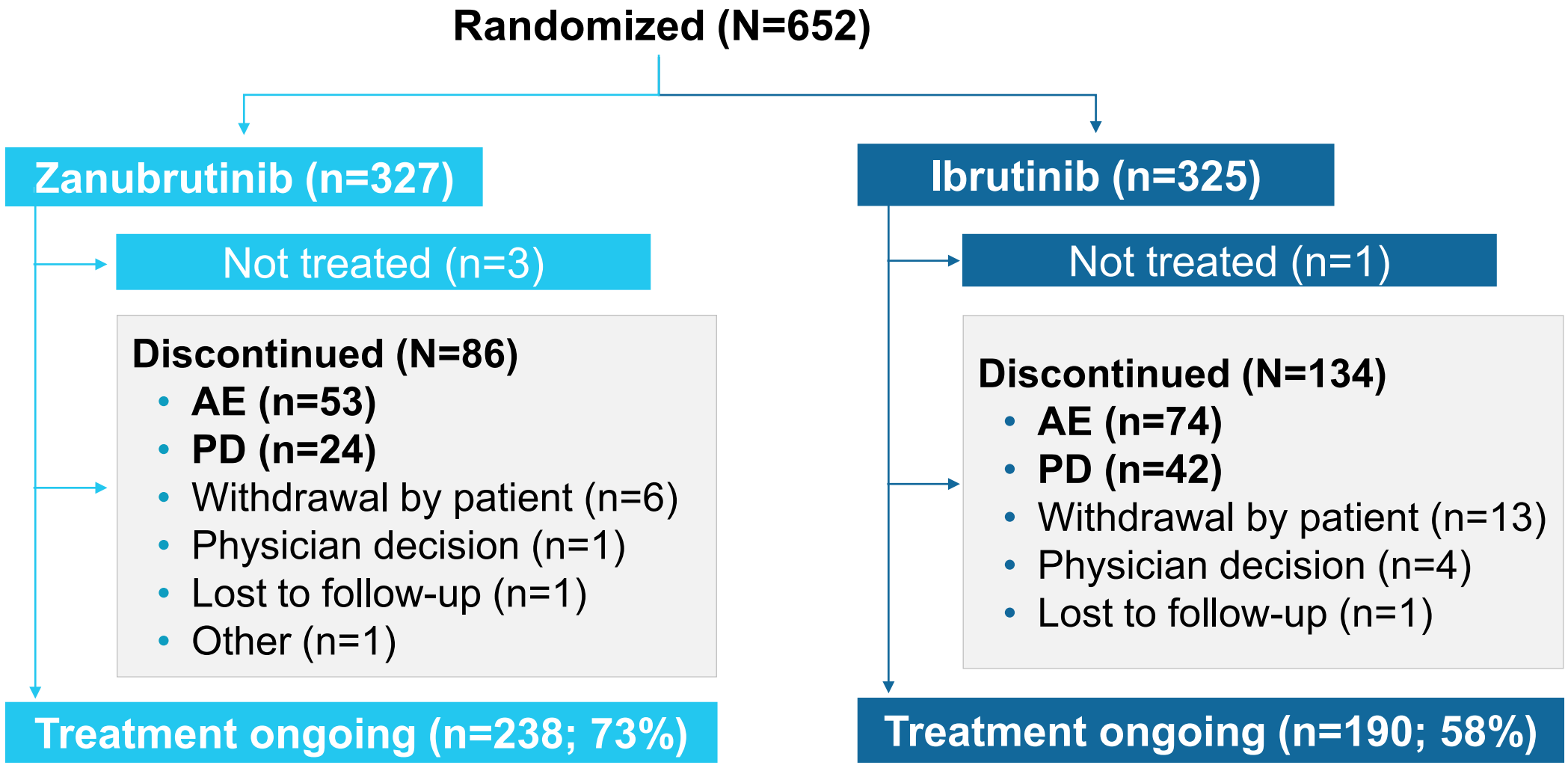
- R/R to ≥1 prior systemic therapy for CLL/SLL
- Measurable lymphadenopathy by CT or MRI

Key Exclusion Criteria

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



Patient Disposition



AE, adverse event; PD, progressive disease.

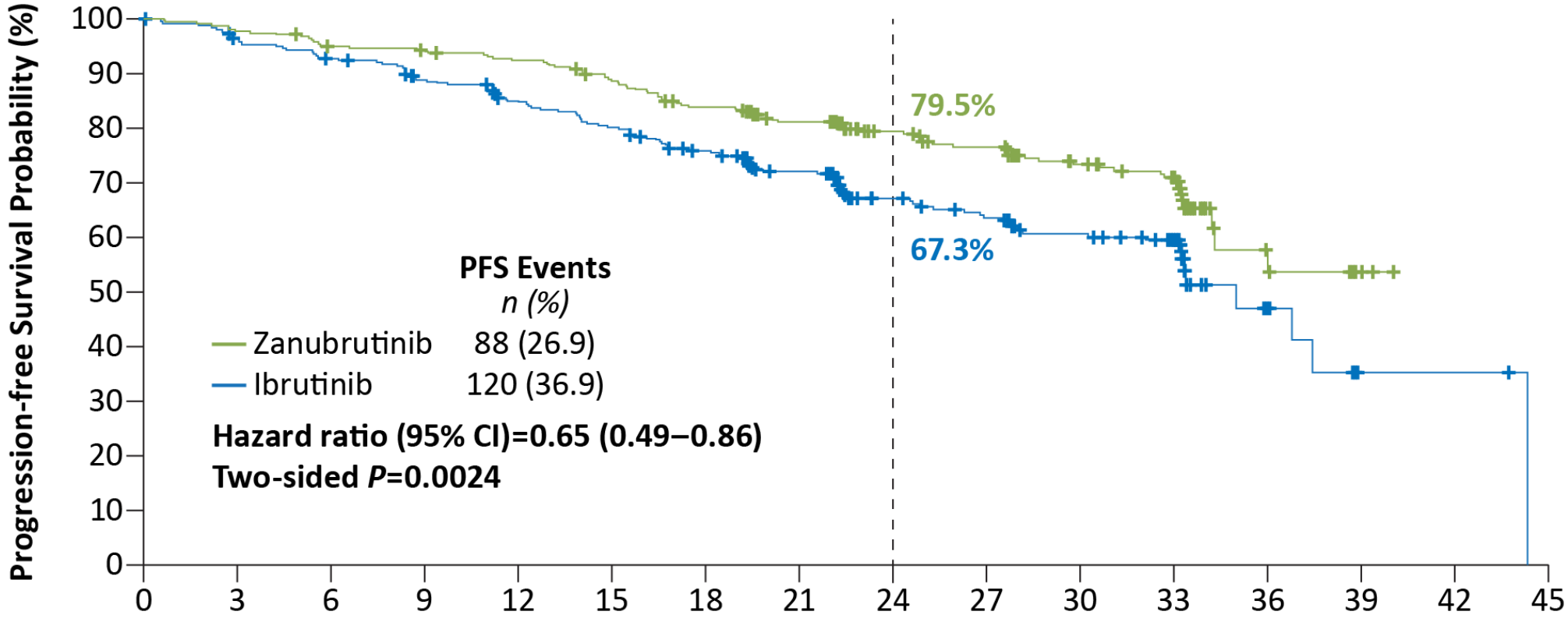
Balanced Demographics and Disease Characteristics

	Zanubrutinib (n=327)	Ibrutinib (n=325)
Age, median (range)	**67 (35-90)**	**68 (35-89)**
≥65 years, n (%)	201 (61.5)	200 (61.5)
Male, n (%)	**213 (65.1)**	**232 (71.4)**
ECOG PS ≥1, n (%)	**198 (60.6)**	**203 (62.5)**
Prior lines of systemic therapy, median (range)	**1 (1-6)**	**1 (1-12)**
>3 prior lines, n (%)	24 (7.3)	30 (9.2)
del(17p) and/or *TP53*^{mut}, n (%)	**75 (22.9)**	**75 (23.1)**
del(17p)	45 (13.8)	50 (15.4)
TP53^{mut} without del(17p)	30 (9.2)	25 (7.7)
del(11q), n (%)	**91 (27.8)**	**88 (27.1)**
IGHV mutational status, n (%)		
Mutated	79 (24.2)	70 (21.5)
Unmutated	**239 (73.1)**	**239 (73.5)**
Complex karyotype*	**56 (17.1)**	**70 (21.5)**
Bulky disease (≥5 cm), n (%)	**145 (44.3)**	**149 (45.8)**

*Complex karyotype is defined as having ≥3 abnormalities.

Zanubrutinib PFS by IRC Significantly Superior to Ibrutinib

Median study follow-up of 29.6 months

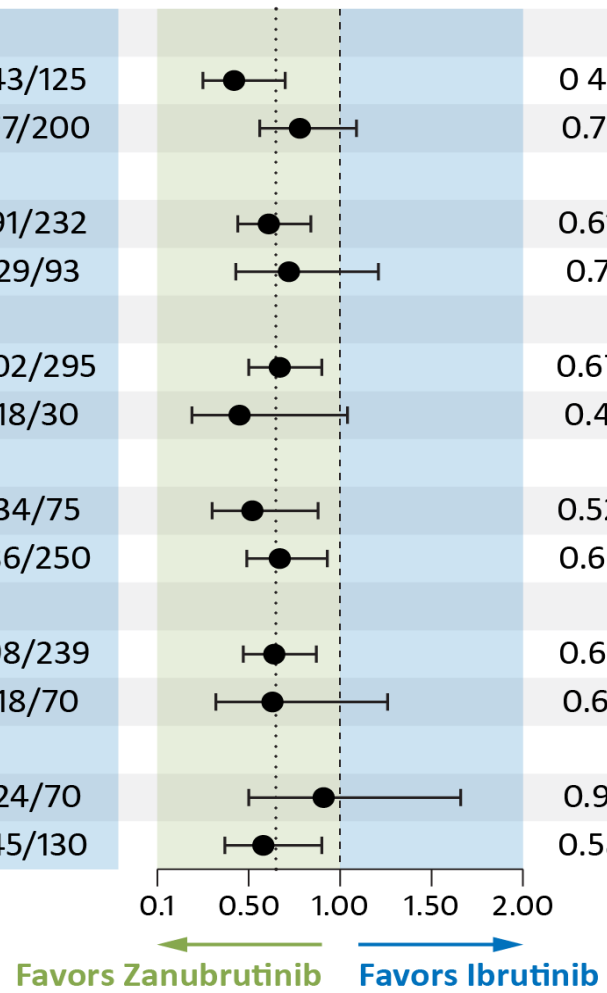


No. at Risk															
Zanubrutinib	327	315	304	301	294	280	263	226	172	161	125	113	14	2	0
Ibrutinib	325	305	293	277	260	246	228	191	133	123	98	87	9	2	2	0

Data cutoff: 8 Aug 2022

PFS Favored Zanubrutinib Across Subgroups

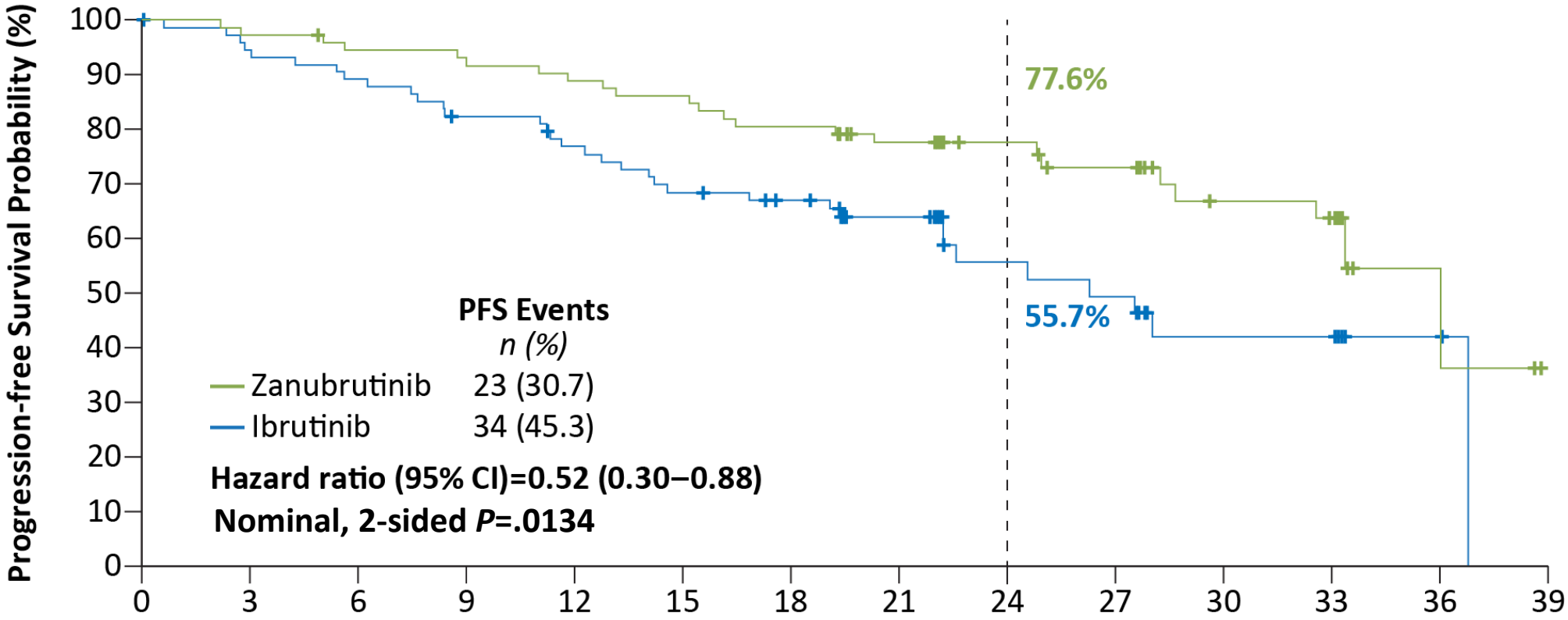
Subgroup	Zanubrutinib Response/Patients	Ibrutinib Response/Patients	Hazard Ratio (95% CI)[a]
Age group			
<65 years	23/126	43/125	0 42 (0.25, 0.70)
≥65 years	65/201	77/200	0.78 (0.56, 1.09)
Sex			
Male	59/213	91/232	0.61 (0.44, 0.84)
Female	29/114	29/93	0.72 (0.43, 1.21)
Prior lines of therapy			
1–3	80/303	102/295	0.67 (0.50, 0.90)
>3	8/24	18/30	0.45 (0.19, 1.04)
Baseline *del*(17p)/*TP53* mutation status			
Present	23/75	34/75	0.52 (0.30, 0.88)
Absent	65/251	86/250	0.67 (0.49, 0.93)
Baseline IGHV mutation status			
Unmutated	72/239	98/239	0.64 (0.47, 0.87)
Mutated	15/79	18/70	0.63 (0.32, 1.26)
Complex karyotype			
Yes	20/56	24/70	0.91 (0.50, 1.66)
No	37/153	45/130	0.58 (0.37, 0.90)



Data cutoff: 8 Aug 2022

[a]Hazard ratio and 95% CI were unstratified for subgroups.

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

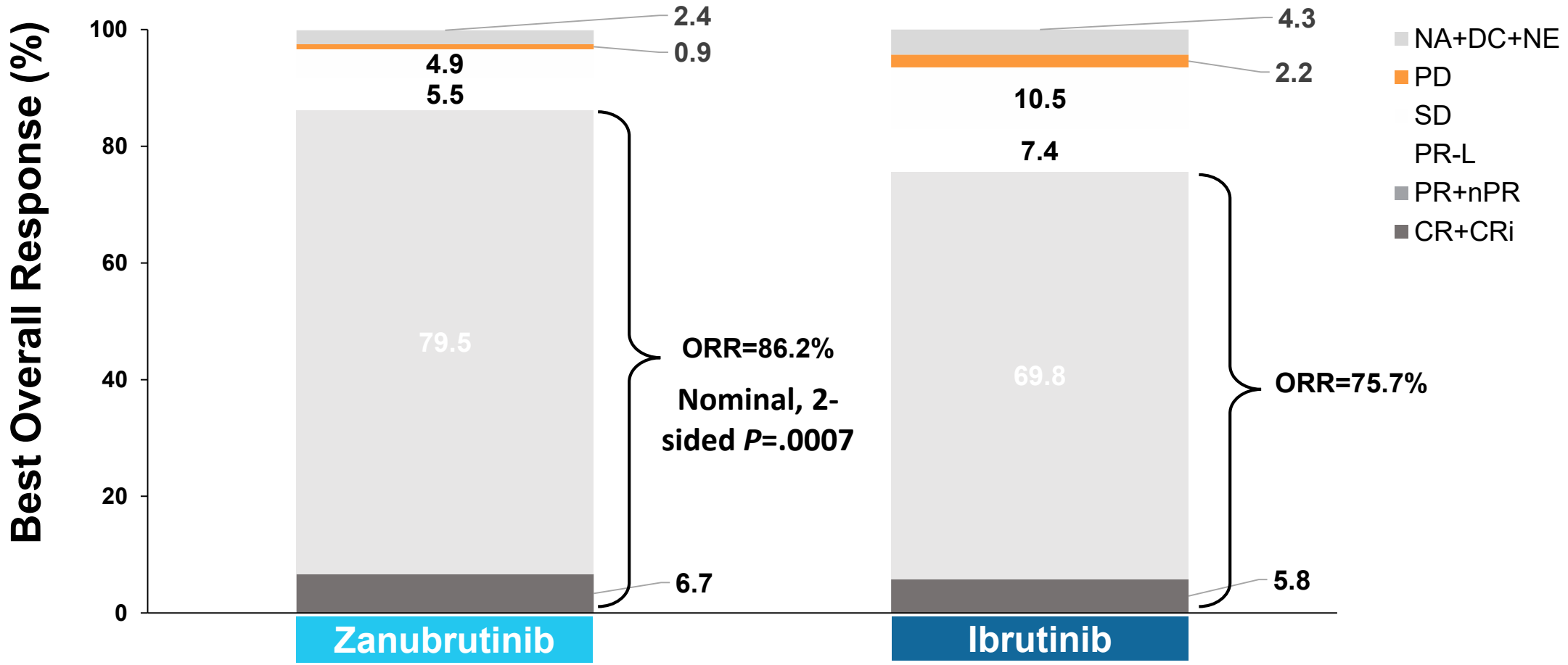


No. at Risk														
Zanubrutinib	75	71	68	67	64	62	58	49	35	30	21	19	3	0
Ibrutinib	75	70	66	60	55	49	45	34	18	16	10	10	2	0

PFS data assessed by IRC

Data cutoff: 8 Aug 2022

Zanubrutinib Showed Higher ORR Assessed by IRC

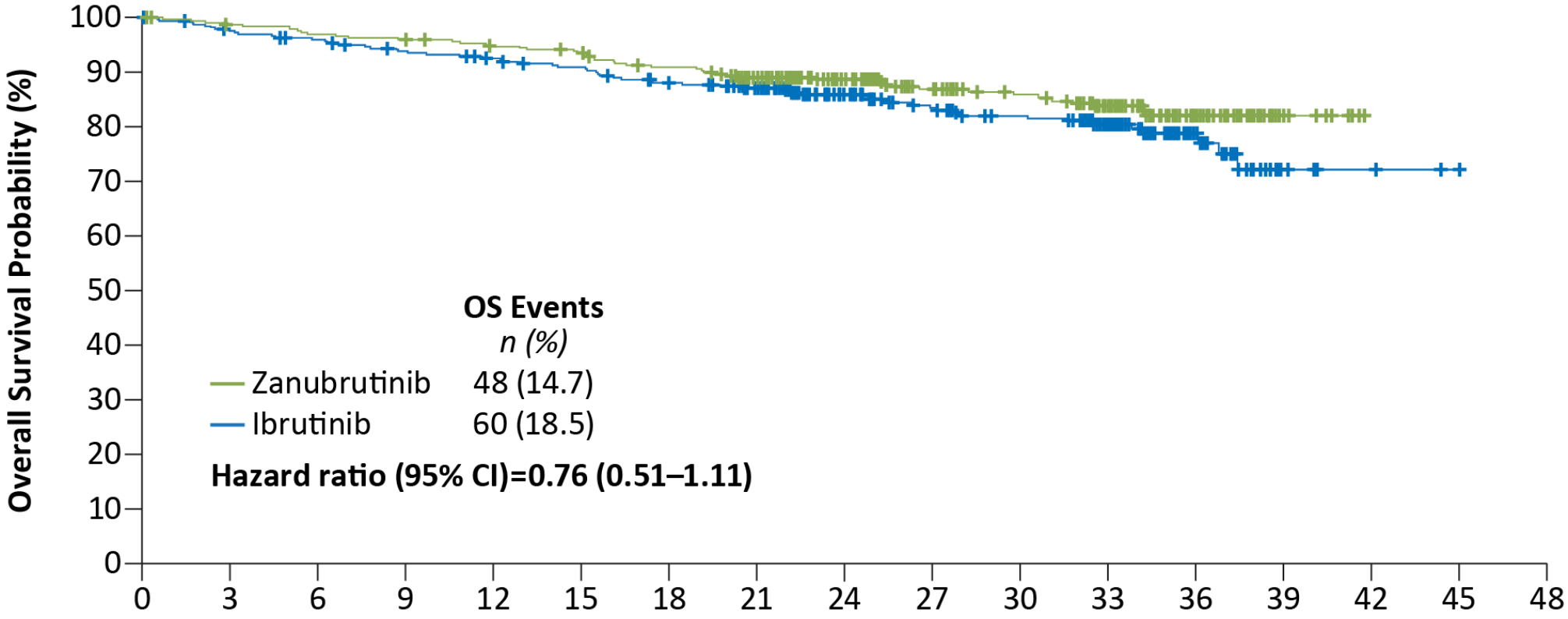


CR, complete response; CRi, complete response with incomplete bone marrow recovery; nPR, nodular partial response; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable response; PD, progressive disease; NA, not assessed; DC, discontinued prior to first assessment; NE, not evaluable.

Data cutoff: 8 Aug 2022

Overall Survival

Fewer deaths with zanubrutinib compared with ibrutinib



No. at Risk																	
Zanubrutinib	327	319	313	310	303	298	287	268	224	185	169	134	56	8	0		
Ibrutinib	325	314	307	297	290	283	271	255	200	171	156	124	50	7	3	1	0

Data cutoff: 8 Aug 2022

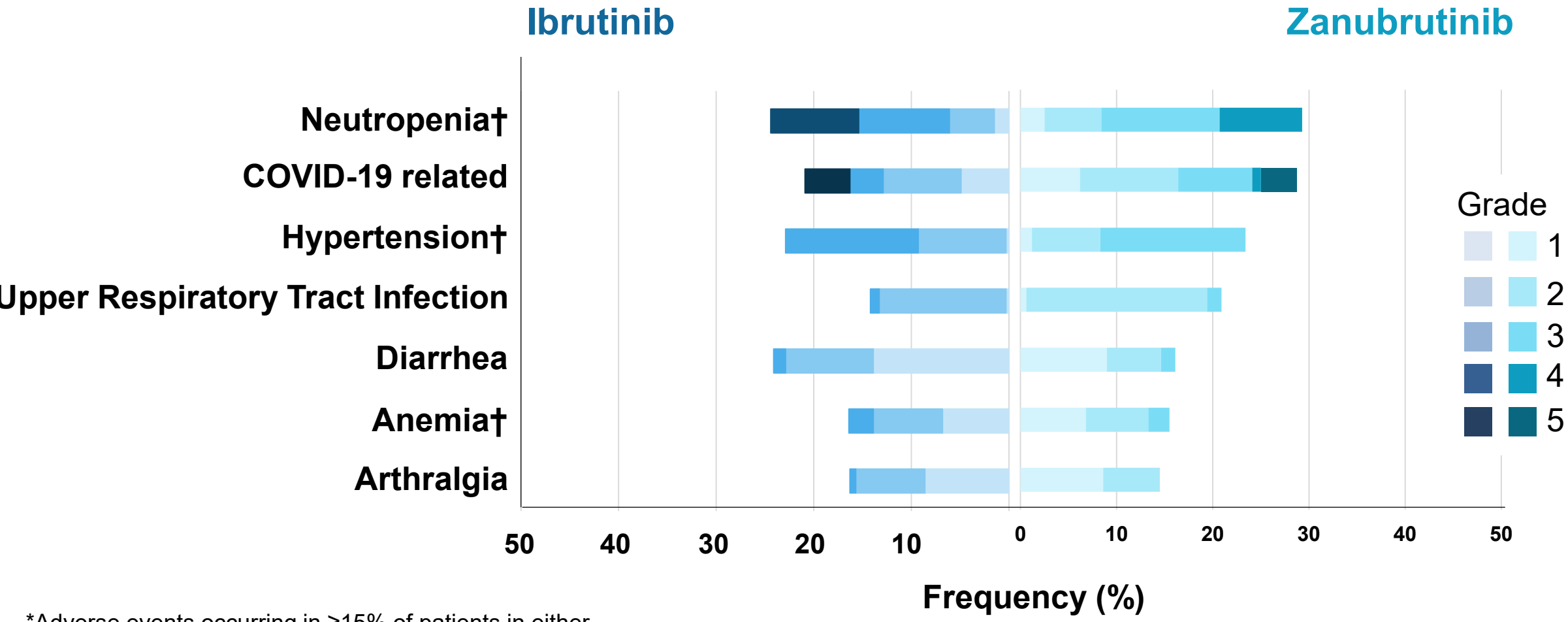
Overall Safety/Tolerability Summary

Zanubrutinib safety profile was favorable to ibrutinib

	Zanubrutinib (n=324)	Ibrutinib (n=324)
Median treatment duration, months	**28.4**	**24.3**
Any grade adverse event	**318 (98.1)**	**321 (99.1)**
Grade 3 to 5	218 (67.3)	228 (70.4)
Grade 5	33 (10.2)	36 (11.1)
Serious adverse event	**136 (42.0)**	**162 (50.0)**
Adverse events leading to		
Dose reduction	**40 (12.3)**	**55 (17.0)**
Dose interruption	**162 (50.0)**	**184 (56.8)**
Treatment discontinuation	**50 (15.4)**	**72 (22.2)**

Data cutoff: 8 Aug 2022

Most Common Adverse Events*



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

Data cutoff: 8 Aug 2022

Zanubrutinib Had A Favorable Cardiac Profile

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

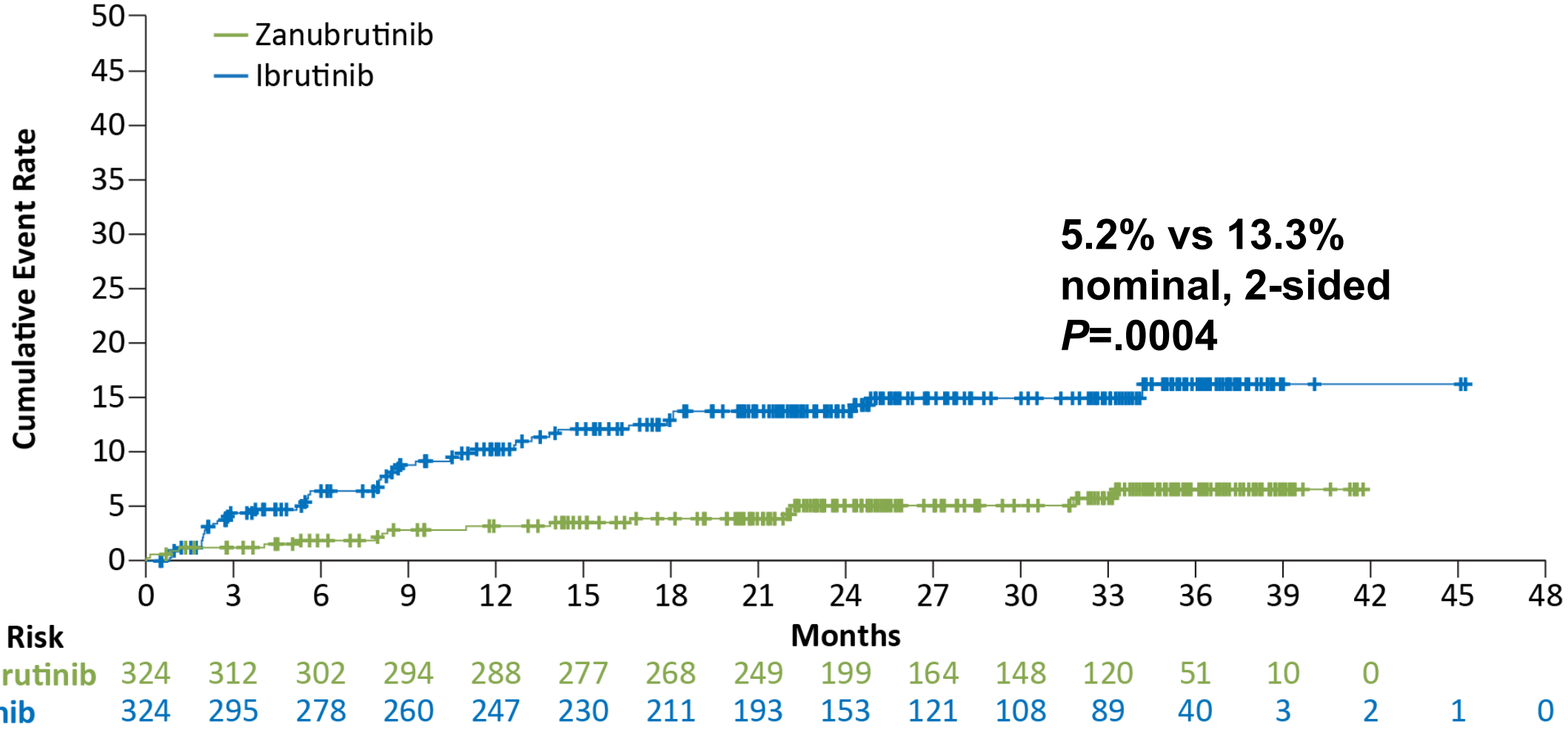
- Lower rate of serious cardiac adverse events reported with zanubrutinib
  - A fib/flutter (n=2)
  - MI/ACS (n=2)
  - CHF (n=2)
- **Fatal cardiac events:**
  - **Zanubrutinib, n=0 (0%)**
  - **Ibrutinib, n=6 (1.9%)**

	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.

Fewer Atrial Fibrillation/Flutter Events With Zanubrutinib



Data cutoff: 8 Aug 2022

Conclusions

- Zanubrutinib de patients with relapsed/refract
  - PFS benefit del(17p)/*TP53*^{mut} population
- Zanubrutinib ha ibrutinib
  - Lower rate o to treatment discontinuat
  - Zanubrutinib lower rates of atrial fibrillation, s o treatment discontinuation, and fatal car
- ALPINE is the f in a head-to-head comparison of I fractory CLL/SLL; **zanubrutinib has now proven superiority to ibrutinib in both PFS and ORR.**

PFS for ibrutinib in poor risk patients wasn't as good as prior studies

Is not blinided

Due to toxicity alone, Second Generation BTKi should replace ibrutinib

Unclear if zanubrutinib any better than acalabrutinib

If on ibrutinib and responding/tolerating well, generally do not switch therapy

Efficacy of Pirtobrutinib in Covalent BTK-Inhibitor Pre-Treated Relapsed / Refractory CLL/SLL: Additional Patients and Extended Follow-up from the Phase 1/2 BRUIN Study

Anthony R. Mato[1], Jennifer A. Woyach[2], Jennifer R. Brown[3], Paolo Ghia[4], Krish Patel [5], Toby A. Eyre[6], Talha Munir[7], Ewa Lech-Maranda[8], Nicole Lamanna[9], Constantine S. Tam[10], Nirav N. Shah[11], Catherine C. Coombs[12], Chaitra S. Ujjani[13], Manish R. Patel[14], Bita Fakhri[15], Chan Y. Cheah[16], Alvaro J. Alencar[17], Jonathon B. Cohen[18], James N. Gerson[19], Ian W. Flinn[20], Shuo Ma[21], Deepa Jagadeesh[22], Joanna M. Rhodes[23], Francisco Hernandez-Ilizaliturri[24], John F. Seymour[10], Pier Luigi Zinzani[25], Minna Balbas[26], Binoj Nair[26], Paolo Abada[26], Chunxiao Wang[27], Amy S. Ruppert[27], Denise Wang[26], Donald E. Tsai[26], William G. Wierda[28], Wojciech Jurczak[29]

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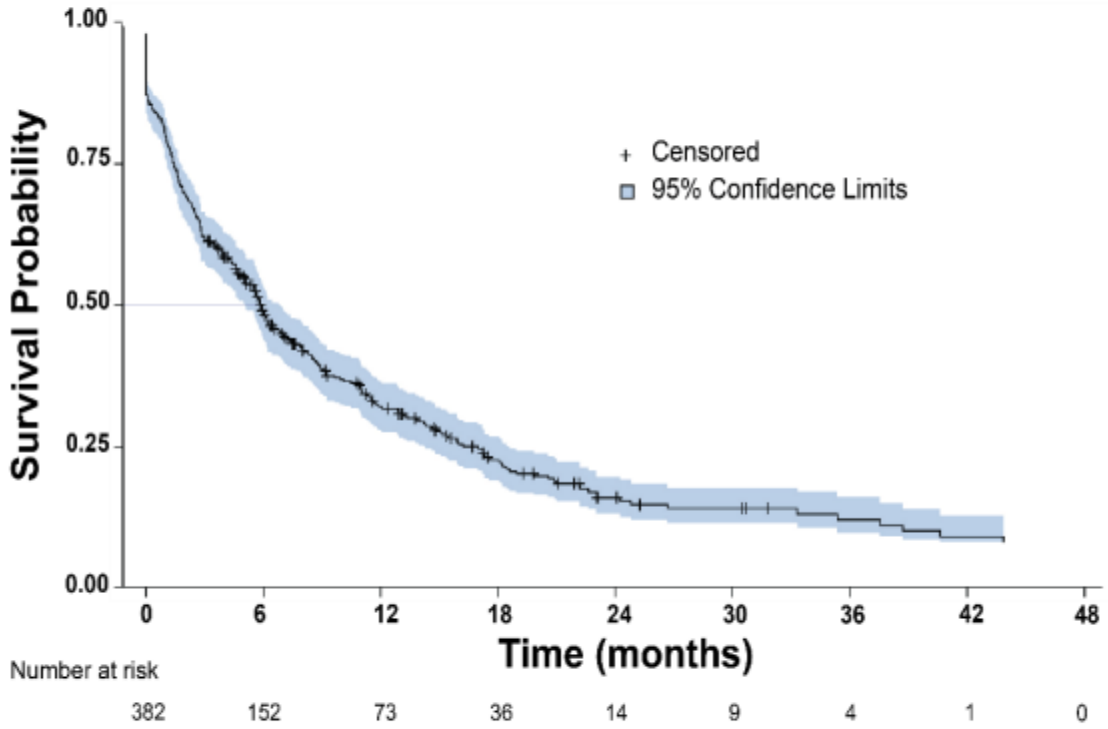
Limited Therapeutic Options and Poor Outcomes after cBTKi Treatment Represent a Major Unmet Medical Need in CLL/SLL

- With prolonged follow-up from the initial clinical trials of the cBTK inhibitors, a substantial proportion of patients discontinue these drugs for either progression or intolerance[1,2,3]
- Limited prospective data exist on the efficacy and safety of available or investigational therapy in the post-cBTK setting
- With 9 years since the initial ibrutinib approval, an increasing number of patients are now seeking therapy after their cBTK regimen
- An increasing number of these patients have also discontinued venetoclax (BCL2i), where outcomes are particularly poor[4]

Time from cBTKi/BCL2i discontinuation to subsequent treatment failure or death[5]

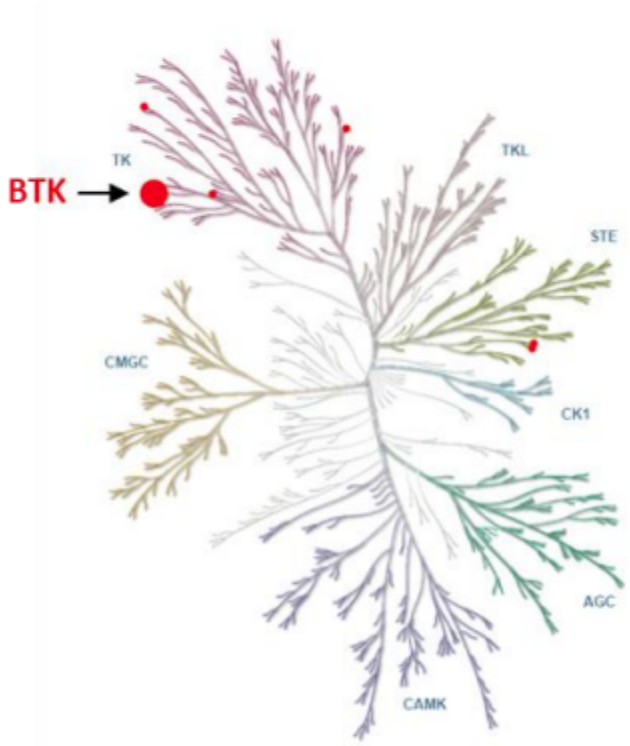


- Median OS: 5.5 months (95% CI: 4.3-6.0)

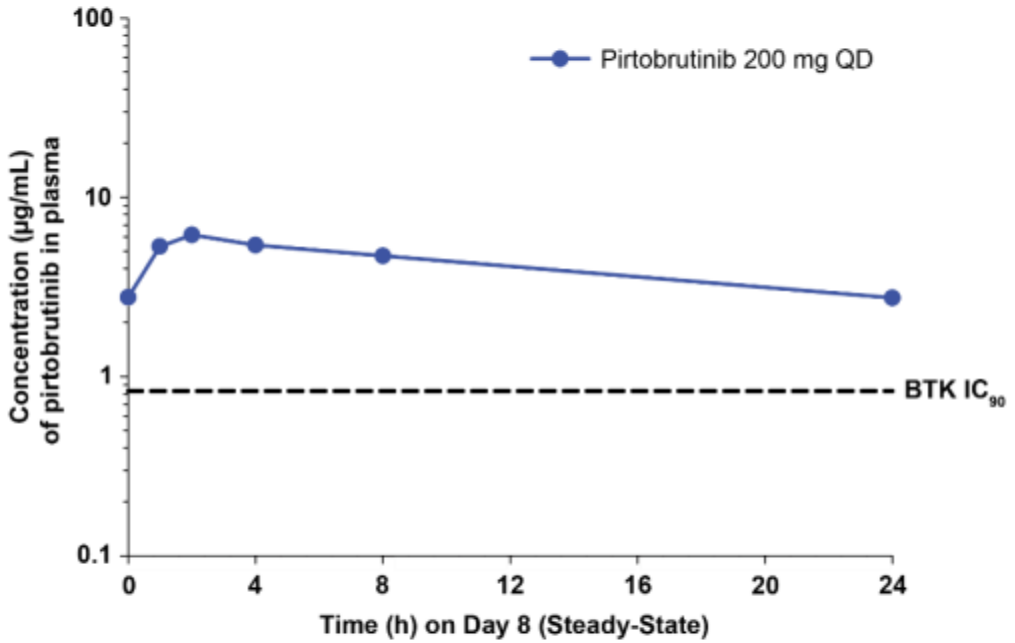
cBTKi, covalent bruton tyrosine kinase; BCL2i, B-cell lymphoma 2 inhibitor; CLL, chronic lymphocytic leukemia; CI, confidence interval; [1]Woyach et al. *J Clin Oncol*. 2017; 35:1437–43. [2]Barr et al. Blood Adv. 2022;6:3440-50;[3]Byrd et al. Ash 2022; [4]Mato et al. *Clinical Lymphoma Myeloma and Leukemia. 2022;* S2152-2650(22)01691-3; [5]Mato et al. Ash 2021

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

Highly Selective for BTK[6,7]



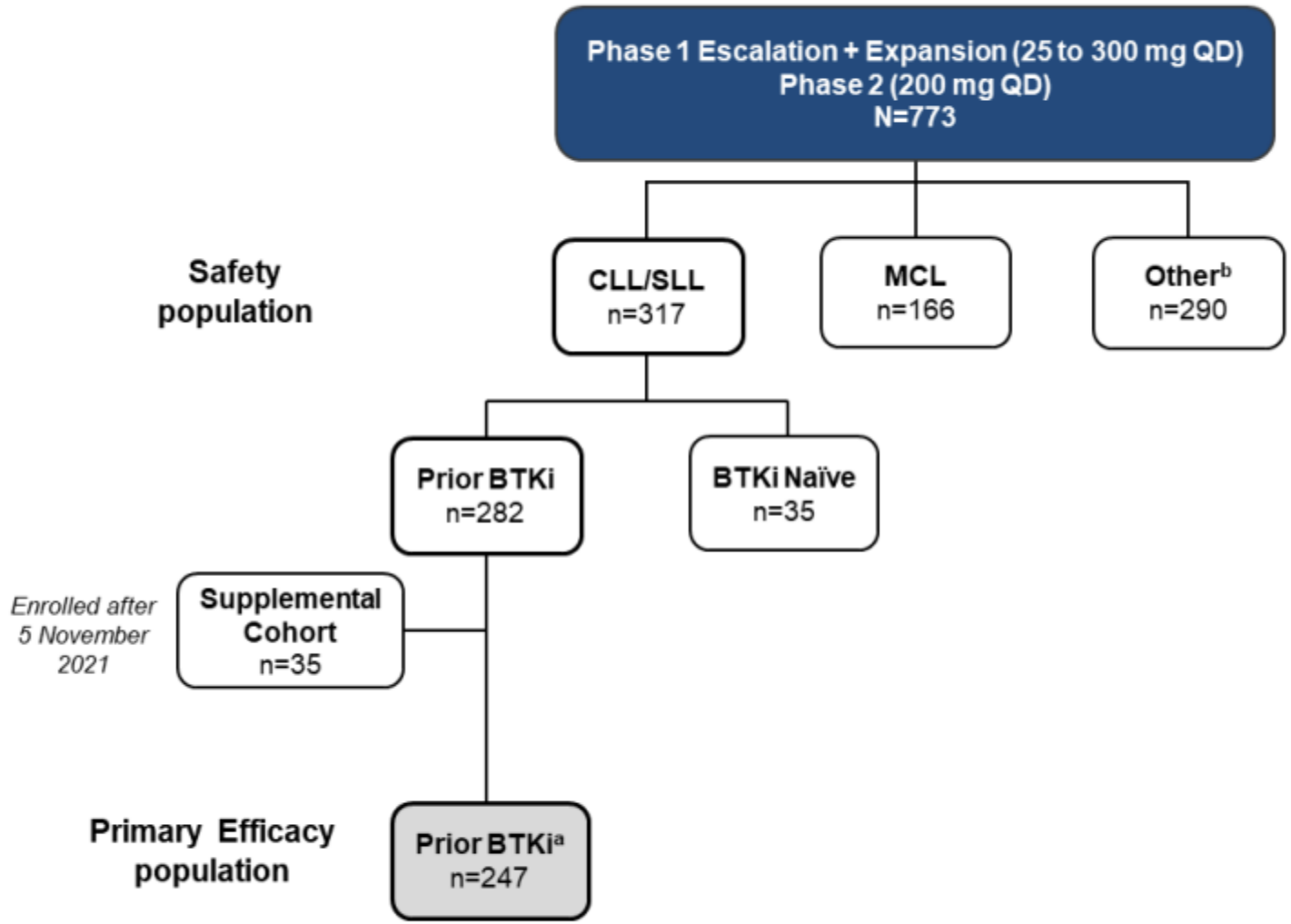
Plasma Exposures Exceeded BTK IC_{90} Throughout Dosing Interval



- Inhibits both wildtype and C481-mutant BTK with equal low nM potency, and has favorable oral pharmacology that enables continuous BTK inhibition throughout the dosing interval regardless of intrinsic rate of BTK turnover
- Pirtobrutinib is well tolerated and demonstrates promising efficacy in poor-prognosis B-cell malignancy patients following prior therapy, including prior cBTKi[1]

cBTKi, covalent Bruton tyrosine kinase inhibitor. [6]Mato et al, *Lancet*, 2021:397:892-901. [7]Brandhuber et al. *Clin. Lymphoma Myeloma Leuk*. 2018.18:S216. Illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com).

Phase 1/2 BRUIN Study: Design, Eligibility and Enrollment



Phase 1 3+3 design

- 28-day cycles
- Intra-patient dose escalation allowed
- Cohort expansion permitted at doses deemed safe

Eligibility

- Age ≥18
- ECOG PS 0-2
- Active disease and in need of treatment
- Previously treated

Key endpoints

- Safety/tolerability
- Determine MTD and recommended phase 2 dose
- Pharmacokinetics
- Efficacy according to ORR and DOR (iwCLL) as assessed by IRC

Primary efficacy population[a]

- Enrolled in phase 1 or 2
- Treated with prior BTK inhibitor containing regimen
- Received one or more doses of pirtobrutinib monotherapy

DOR, duration of response: ORR, overall response rate; ECOG PS, Eastern Cooperative Oncology Group Performance Score; MTD, maximum tolerated dose; IRC, independent review committee; QD, daily;
Data cutoff date of 29 July 2022. [a]To ensure adequate follow-up, the primary efficacy population included all CLL/SLL patients who enrolled prior to 5 November 2021. [b]Other includes DLBCL, WM, FL, MZL, Richter transformation, B-PLL, Hairy Cell Leukemia, PCNSL, and other transformation.

CLL/SLL Patient Characteristics

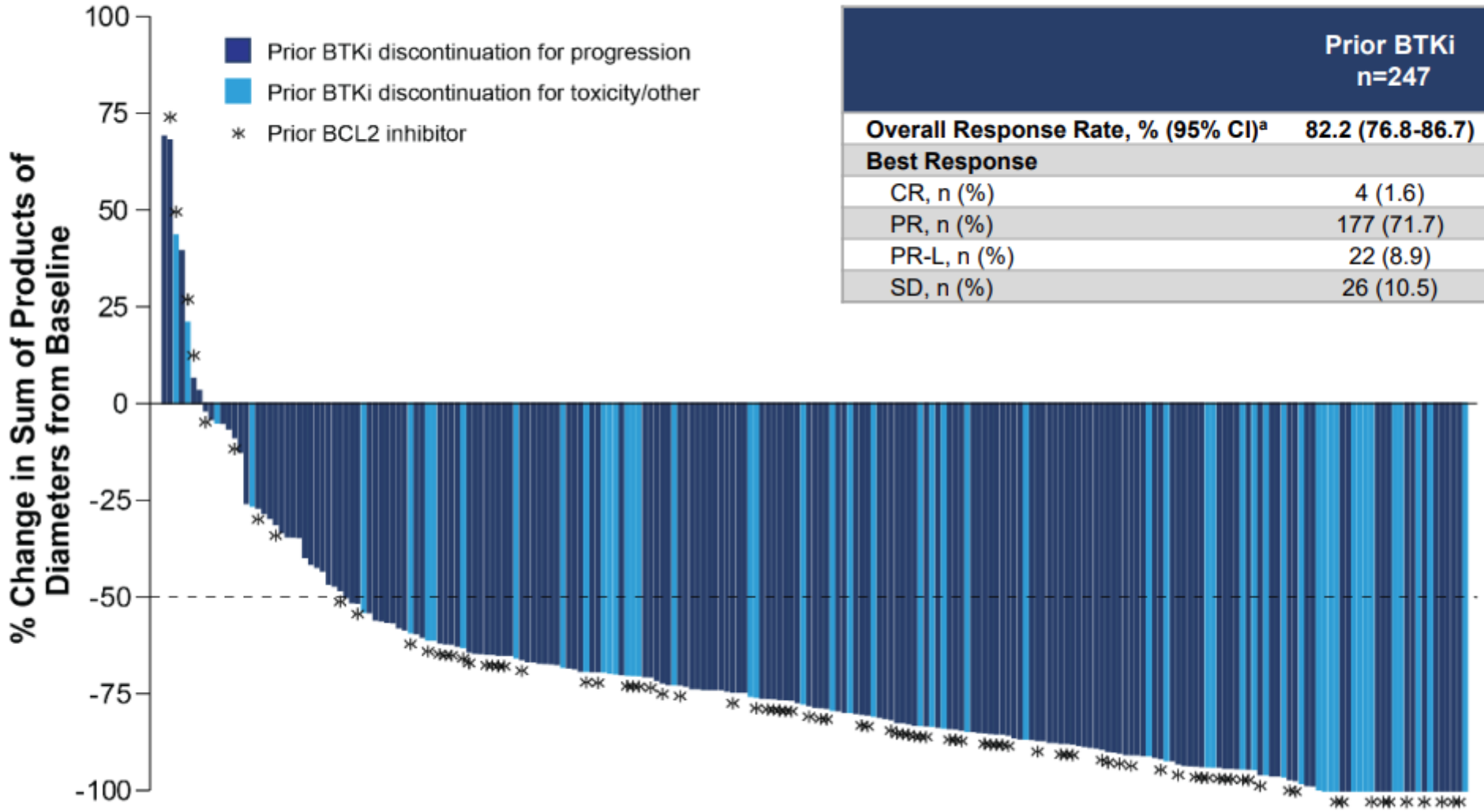
Characteristics	n=247
Median age, years (range)	69 (36-88)
Male, n (%)	168 (68)
Histology	
CLL	246 (>99)
SLL	1 (<1)
Rai staging[a]	
0-II	131 (53)
III-IV	102 (41)
Bulky Disease ≥5 cm, n (%)	78 (32)
ECOG PS, n (%)	
0	133 (54)
1	97 (39)
2	17 (7)
Median number of prior lines of systemic therapy, n (range)	3 (1-11)
Prior therapy, n (%)	
BTK inhibitor	247 (100)
Anti-CD20 antibody	217 (88)
Chemotherapy	195 (79)
BCL2 inhibitor	100 (41)
PI3K inhibitor	45 (18)
CAR-T	14 (6)
Allogeneic stem cell transplant	6 (2)
Median time from diagnosis to first dose, years (IQR)	11 (8-15)

Baseline Molecular Characteristics[b]	
Mutation status, n/n available (%)	
BTK C481-mutant	84/222 (38)
BTK C481-wildtype	138/222 (62)
PLCG2-mutant	18/222 (8)
PLCG2-wildtype	204/222 (92)
High Risk Molecular Features, n/n available (%)	
17p deletion	51/176 (29)
TP53 mutation	87/222 (39)
17p deletion and/or *TP53* mutation	90/193 (47)
Both 17p deletion and *TP53* mutation	48/170 (28)
IGHV unmutated	168/198 (85)
Complex Karyotype	24/57 (42)
11q deletion	44/176 (25)

Reason for prior BTKi discontinuation[c], n (%)	
Progressive disease	190 (77)
Toxicity/Other	57 (23)

ECOG PS, Eastern Cooperative Oncology Group Performance Score; Data cutoff date of 29 July 2022. [a]14 patients had missing data for Rai staging data. [b]Molecular characteristics were determined centrally and are presented based on data availability, in those patients with sufficient sample to pass assay quality control. [c]In the event more than one reason was noted for discontinuation, disease progression took priority.

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

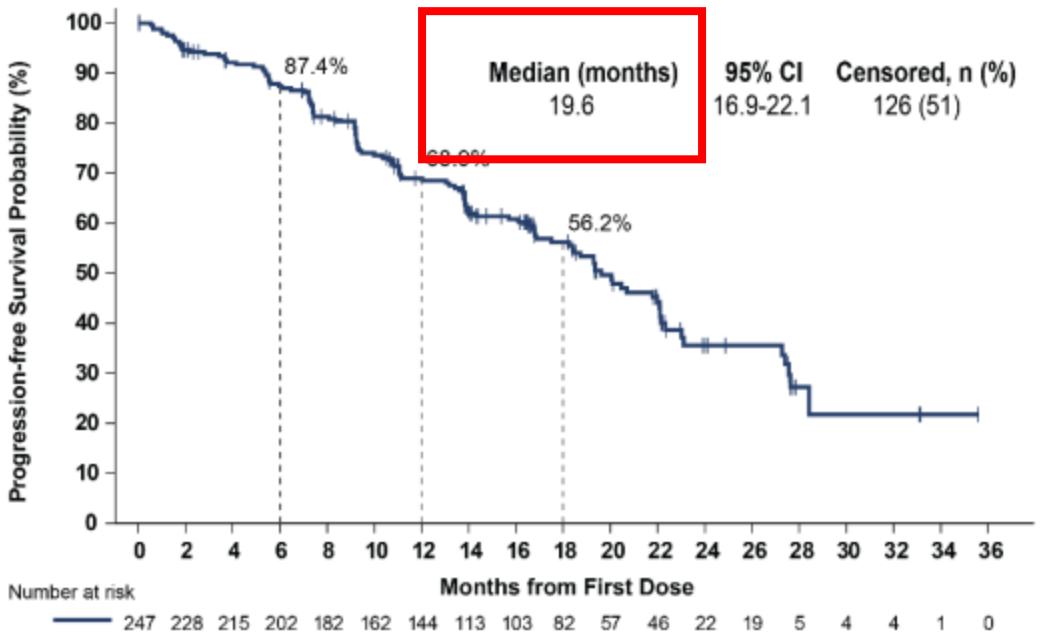


	Prior BTKi n=247	Prior BTKi+BCL2i n=100
Overall Response Rate, % (95% CI)[a]	**82.2 (76.8-86.7)**	**79.0 (69.7-86.5)**
Best Response		
CR, n (%)	4 (1.6)	0 (0.0)
PR, n (%)	177 (71.7)	70 (70.0)
PR-L, n (%)	22 (8.9)	9 (9.0)
SD, n (%)	26 (10.5)	11 (11.0)

Data cutoff date of 29 July 2022. Data for 24 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 includes patients with a best response of CR, PR, and PR-L. Response status per iwCLL 2018 according to independent review committee assessment.

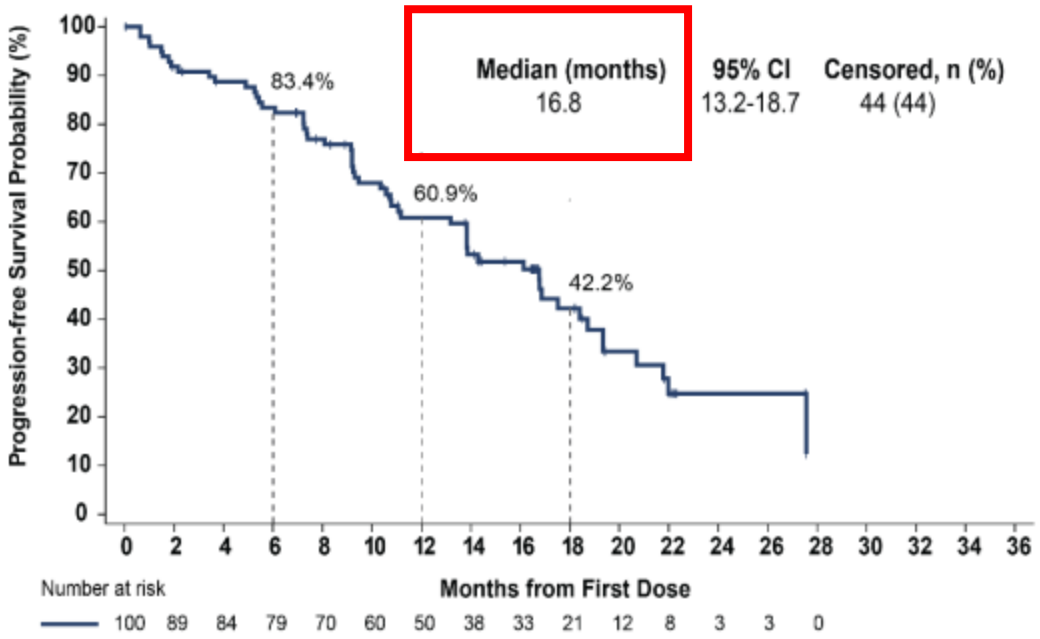
Progression-Free Survival in CLL/SLL Patients who Received Prior BTKi Treatment

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

Data cutoff date of 29 July 2022. Response status per iwCLL 2018 according to independent review committee assessment.

Pirtobrutinib Safety Profile

	All Doses and Patients (N=773)			
	Treatment-Emergent AEs, (≥15%), %		Treatment-Related AEs, %	
Adverse Event (AEs)	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Fatigue	28.7%	2.1%	9.3%	0.8%
Diarrhea	24.2%	0.9%	9.3%	0.4%
Neutropenia[a]	24.2%	20.4%	14.7%	11.5%
Contusion	19.4%	0.0%	12.8%	0.0%
Cough	17.5%	0.1%	2.3%	0.0%
Covid-19	16.7%	2.7%	1.3%	0.0%
Nausea	16.2%	0.1%	4.7%	0.1%
Dyspnea	15.5%	1.0%	3.0%	0.1%
Anemia	15.4%	8.8%	5.2%	2.1%
AEs of Special Interest[b]	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Bruising[c]	23.7%	0.0%	15.1%	0.0%
Rash[d]	12.7%	0.5%	6.0%	0.4%
Arthralgia	14.4%	0.6%	3.5%	0.0%
Hemorrhage/Hematoma[e]	11.4%	1.8%	4.0%	0.6%
Hypertension	9.2%	2.3%	3.4%	0.6%
Atrial fibrillation/flutter[f,g]	2.8%	1.2%	0.8%	0.1%

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

Data cutoff date of 29 July 2022.. [a]Aggregate of neutropenia and neutrophil count decreased. [b]AEs of special interest are those that were previously associated with covalent BTK inhibitors. [c]Aggregate of contusion, petechiae, ecchymosis, and increased tendency to bruise. [d]Aggregate of all preferred terms including rash. [e]Aggregate of all preferred terms including hematoma or hemorrhage. [f]Aggregate of atrial fibrillation and atrial flutter. [g]Of the 22 total afib/aflutter TEAEs in the overall safety population, 7 occurred in patients with a prior medical history of atrial fibrillation. [h]CLL/SLL safety population data can be found via QR code.

Conclusions

- With more than 2 years of additional data, pirtobrutinib continues to demonstrate clinically meaningful and durable efficacy in CLL/SLL patients previously treated with BTK inhibitors
- Favorable efficacy was observed regardless of BTK C481 mutation status, age, TP53 and/or del(17p) mutation status, and in those with additional lines of therapy
  - Notably, this was observed in patients with relapsed / refractory disease after prior treatment with BTKi and BCL2i
- Consistently high overall response rates were observed across all subgroups
- Pirtobrutinib continues to be well-tolerated with low-rates of Grade ≥3 AEs and discontinuation due to drug-related toxicity
- Four global, randomized, Phase 3 trials evaluating pirtobrutinib in CLL/SLL are ongoing:

BRUIN-CLL-313	BRUIN-CLL-314	BRUIN-CLL-321	BRUIN-CLL-322
Monotherapy vs. bendamustine + rituximab in treatment naïve CLL/SLL	Head-to-head vs. ibrutinib in CLL/SLL	Monotherapy vs. investigator's choice (IdelaR or BR) in post-BTKi CLL/SLL	Combo with venetoclax + rituximab vs. venetoclax + rituximab in CLL/SLL
NCT05023980	NCT05254743	NCT04666038	NCT04965493

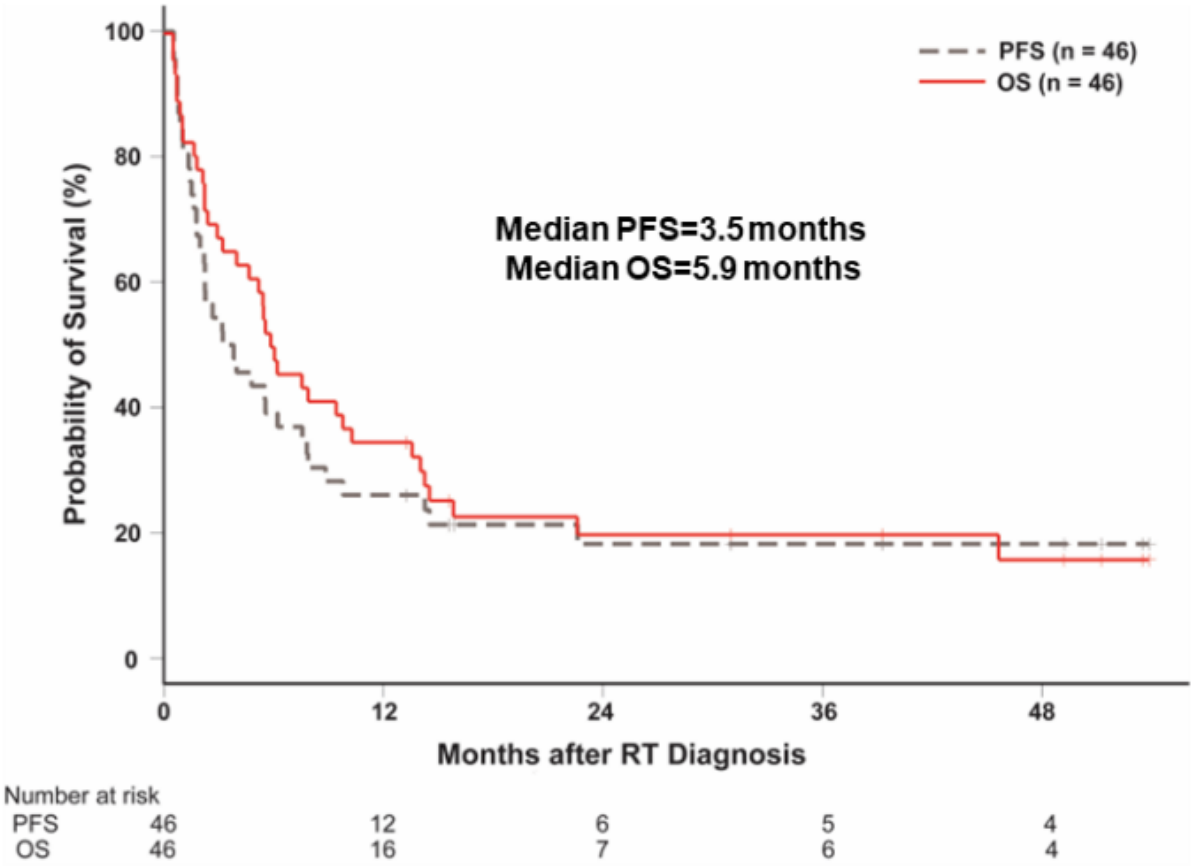
Efficacy of Pirtobrutinib, a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor in Richter Transformation: Results From the Phase 1/2 BRUIN Study

William G. Wierda[1], David Lewis[2], Paolo Ghia[3], Nirav N. Shah[4], Catherine C. Coombs[5], Chan Y. Cheah[6], Jennifer Woyach[7], Nicole Lamanna[8], Joanna M. Rhodes[9], Marc S. Hoffmann[10], Shuo Ma[11], Toby A. Eyre[12], Talha Munir[13], Manish R. Patel[14], Alvaro J. Alencar[15], Constantine S. Tam[16], Wojciech Jurczak[17], Ewa Lech-Maranda[18], John F. Seymour[16], Lindsey E. Roeker[19], Philip A. Thompson[1], Paolo B. Abada[20], Chunxiao Wang[21], Amy S. Ruppert[21], Binoj Nair[20], Hui Liu[20], Donald E. Tsai[20], Anthony R. Mato[19]

[1]The University of Texas, MD Anderson Cancer Center, Houston, USA; [2]Plymouth Hospitals NHS Trust – Derriford Hospital, Plymouth, UK; [3]Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milan, Italy; [4]Medical College of Wisconsin, Brookfield, USA; [5]University of North Carolina at Chapel Hill, Chapel Hill, USA; [6]Linear Clinical Research and Sir Charles Gairdner Hospital, Perth, Australia; [7]The Ohio State University Comprehensive Cancer Center, Columbus, USA; [8]Herbert Irving Comprehensive Cancer Center, New York-Presbyterian/Columbia University Medical Center, New York, USA; [9]Northwell Health Cancer Institute, New Hyde Park, USA; [10]The University of Kansas Cancer Center, Kansas City, USA; [11]Robert H. Lurie Comprehensive Cancer Center, Feinberg School of Medicine, Northwestern University, Chicago, USA; [12]Oxford University Hospitals NHS Foundation Trust, Churchill Cancer Center, Oxford, UK; [13]Department of Haematology, St. James's University Hospital, Leeds, UK; [14]Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, USA; [15]Sylvester Comprehensive Cancer Center, University of Miami, Miller School of Medicine, Miami, USA; [16]Peter MacCallum Cancer Center, Royal Melbourne Hospital, University of Melbourne, Melbourne, Australia; [17]Maria Sklodowska-Curie National Research Institute of Oncology, Krakow, Poland; [18]Institute of Hematology and Transfusion Medicine, Warsaw, Poland; [19]Memorial Sloan Kettering Cancer Center, New York, USA; [20]Loxo@Lilly, Indianapolis, USA; [21]Eli Lilly and Company, Indianapolis, USA

Richter Transformation is a Complication of CLL With Poor Prognosis

Progression-Free and Overall Survival after RT Diagnosis[a]

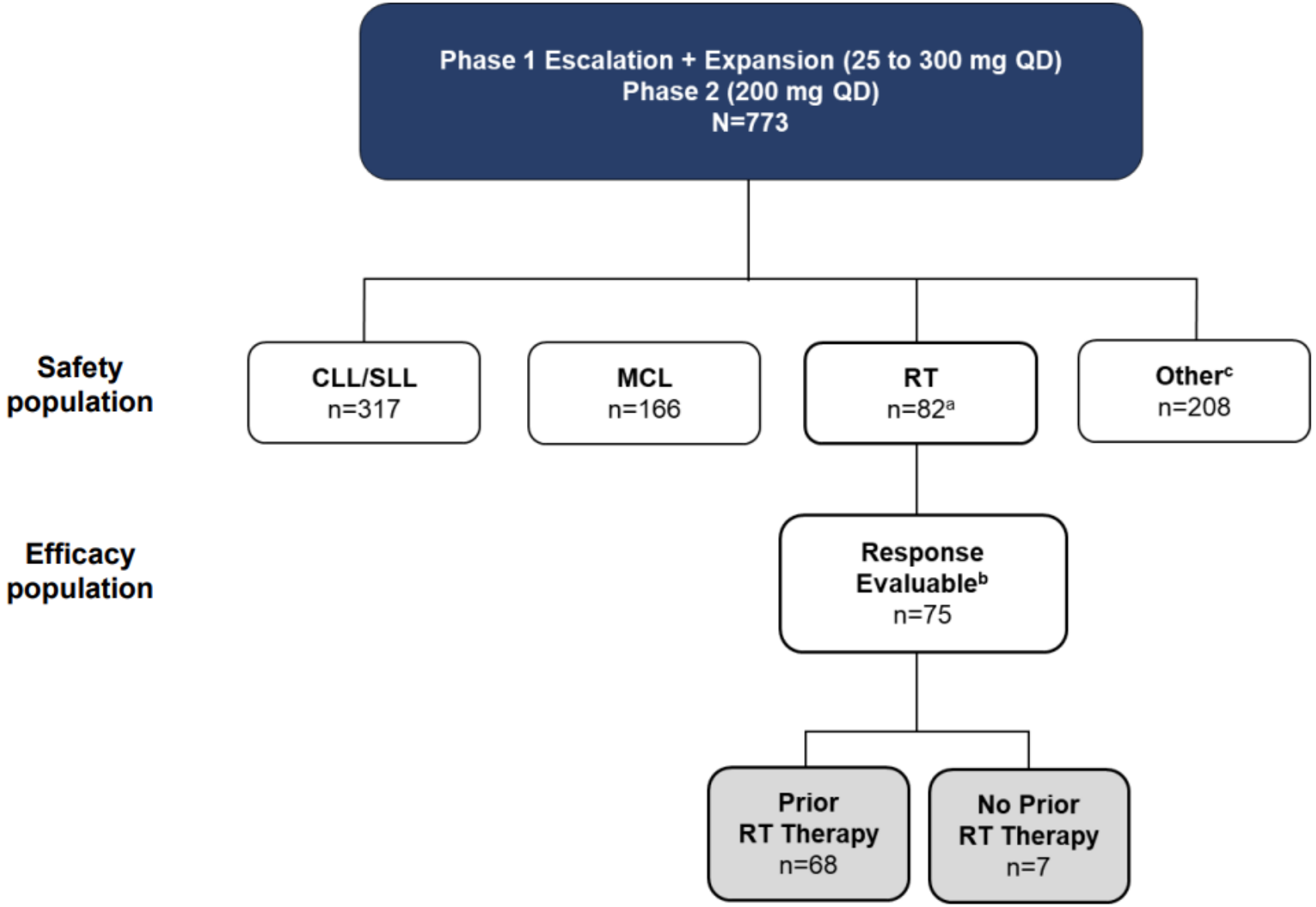


Data from Figure 1, Rogers KA, et al.[5]

- **RT occurs in up to 10% of patients with CLL[1,2]**
  - Estimated median OS of 3-12 months[1,3-5]
  - No approved therapies, clinical trial preferred as standard of care
  - cBTKi clinical trials have reported
    - Median OS of 4 months (95% CI, 0.9-5) for patients on ibrutinib monotherapy[6]
    - ORR of 40% (95% CI, 21.1-61.3) for patients on acalabrutinib monotherapy[7]

CLL, chronic lymphocytic leukemia. RT, Richter transformation. [1]Al-Sawaf et al. *Leukemia* 2021;35:169-76. [2]Tadmor and Levy *Cancers (Basel)* 2021;13:5141. [3]Ding *Hematology Am Soc Hematol Educ Program* 2018;30:256-63. [4]Wang et al. *Haematologica* 2020;105:765-73. [5]Rogers et al, *Br J Haematol* 2018;180:259-66. [6]Byrd et al, *Clin Cancer Res* 2020;26:3918-27. [7]Eyre et al, *Lancet Haematol* 2021;8:e912-21. [a]Patients receiving R-EPOCH.

Phase 1/2 BRUIN Study: Design, Eligibility, and Enrollment



Phase 1 3+3 design

- 28-day cycles
- Intra-patient dose escalation allowed
- Cohort expansion permitted at doses deemed safe

RT eligibility

- Age ≥18
- ECOG PS 0-2
- Previously treated
- Histologically confirmed active RT (all DLBCL)
- No limit on prior lines of therapy
- Prior cBTKi permitted
- With Amendment 10, frontline RT patients were eligible[d]

Key endpoints

- Safety/tolerability
- Determine MTD and RP2D
- Pharmacokinetics
- Efficacy according to ORR and DoR based on Lugano criteria

Data cutoff date of 29 July 2022. [a]n=74 received prior RT therapy and n=8 did not. [b]Response evaluable patients are those who had ≥1 post-baseline response assessment or discontinued treatment prior to first post-baseline response assessment. [c]Other includes DLBCL, WM, FL, MZL, B-PLL, Hairy Cell Leukemia, PCNSL, and other transformation. [d]Prior to Amendment 10 (21 Jan 2022), patients required to be previously treated for RT.

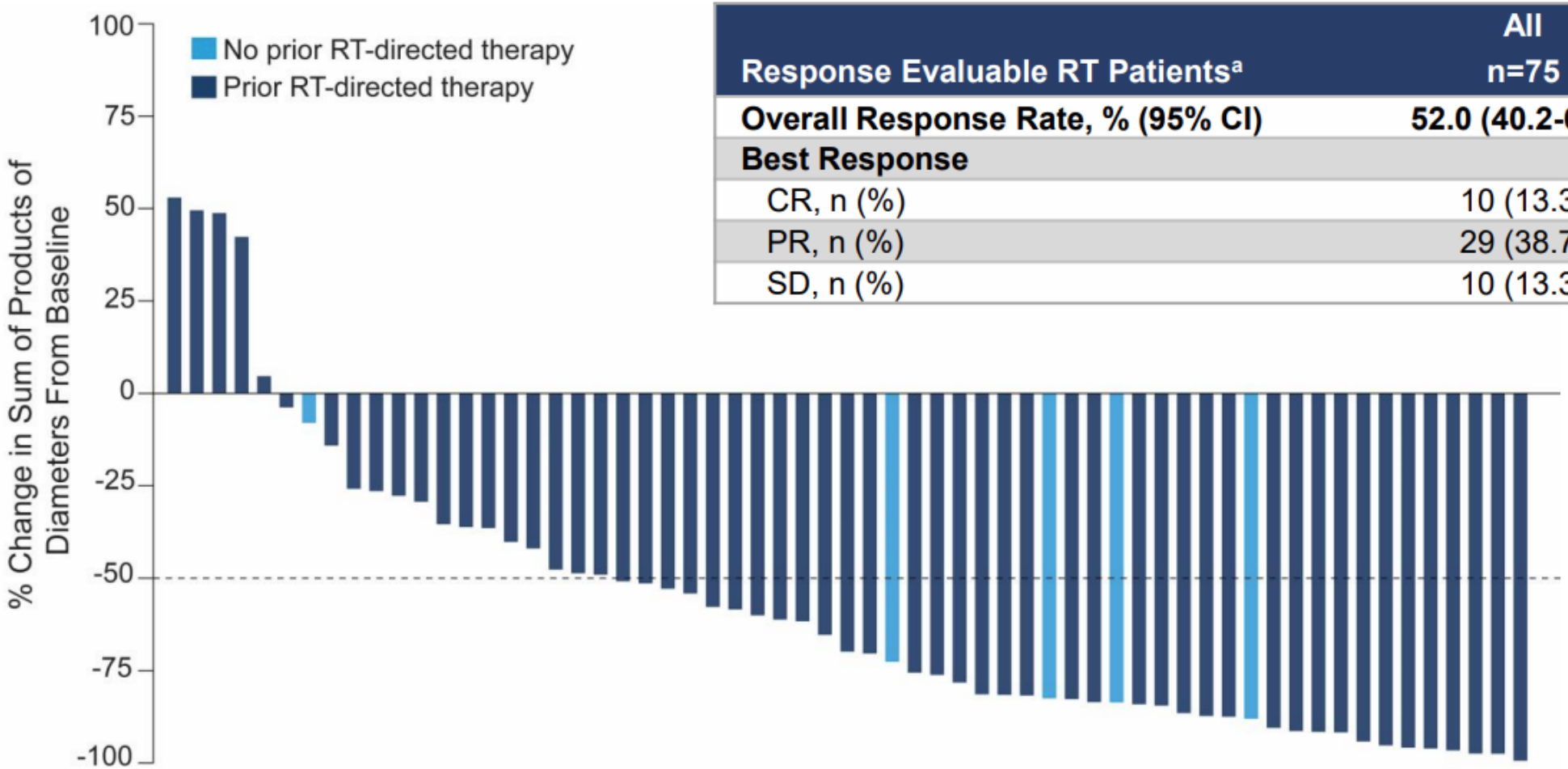
RT Patient Characteristics

Characteristics	All n=82	Prior RT Therapy n=74
Median age, years (range)	67 (26-95)	66 (26-95)
Male, n (%)	55 (67)	53 (72)
ECOG PS, n (%)		
0	32 (39)	29 (39)
1	38 (46)	34 (46)
2	12 (15)	11 (15)
Ann Arbor Stage		
Stage I-II	8 (10)	8 (11)
Stage III	15 (18)	13 (18)
Stage IV	42 (51)	38 (51)
Missing	17 (21)	15 (20)
Tumor bulk, cm, n (%)		
<5 cm	41 (50)	35 (47)
≥5 cm	31 (38)	31 (42)
Missing	10 (12)	8 (11)
Elevated LDH, n (%)		
Yes	66 (81)	60 (81)
No	16 (20)	14 (19)
Median time from initial CLL diagnosis to RT presentation (months, IQR)	60.8 (17.4-101.5)	60.8 (18.8-98.6)
Median time from transformation to first pirtobrutinib dose (months, IQR)	4.6 (1.8-13.1)	5.5 (2.2-15.6)

Characteristics	All n=82	Prior RT Therapy n=74
Median number of prior lines of CLL therapy (range)[a]	2 (0-13)	2 (0-11)
Median number of prior lines of RT therapy (range)	2 (0-8)	2 (1-8)
Median number of prior lines of CLL and RT therapy (range)	4 (0-13)	4 (1-12)
Prior RT therapies, n (%)		
Anti-CD20 antibody	64 (78)	64 (87)
Chemotherapy	62 (76)	62 (84)
BCL2 inhibitor	31 (38)	31 (42)
BTK inhibitor	28 (34)	28 (38)
CAR-T cell therapy	9 (11)	9 (12)
PI3K inhibitor	8 (10)	8 (11)
Stem cell transplant	5 (6)	5 (7)
Allogeneic	4 (5)	4 (5)
Autologous	1 (1)	1 (1)
Immunomodulator[b]	3 (4)	3 (4)
Other systemic therapy	25 (31)	25 (34)

Data cutoff date of 29 July 2022. [a]17 patients were CLL therapy naïve. [b]Includes IMID and lenalidomide.

Pirtobrutinib Efficacy in RT Patients

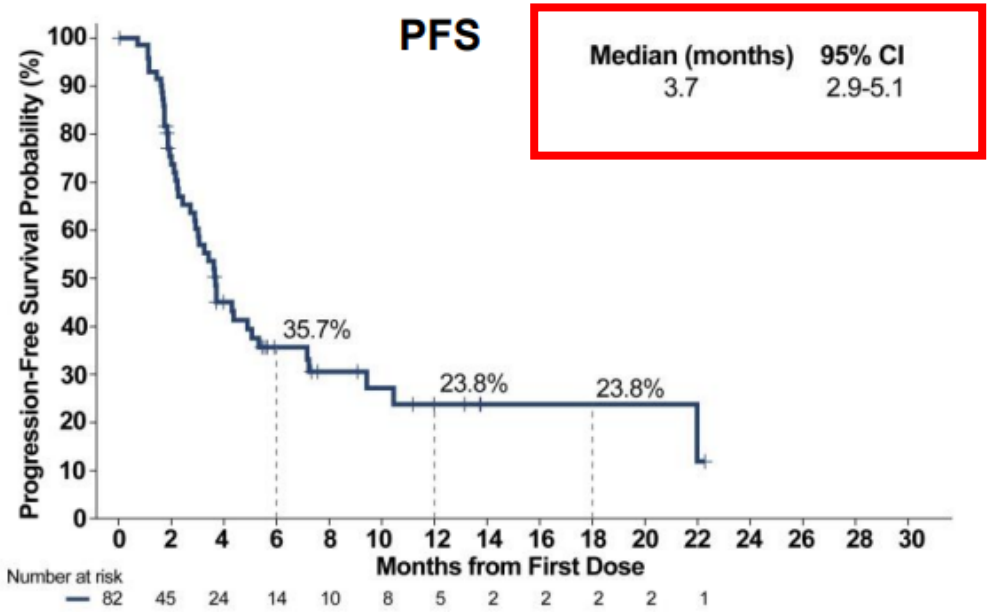


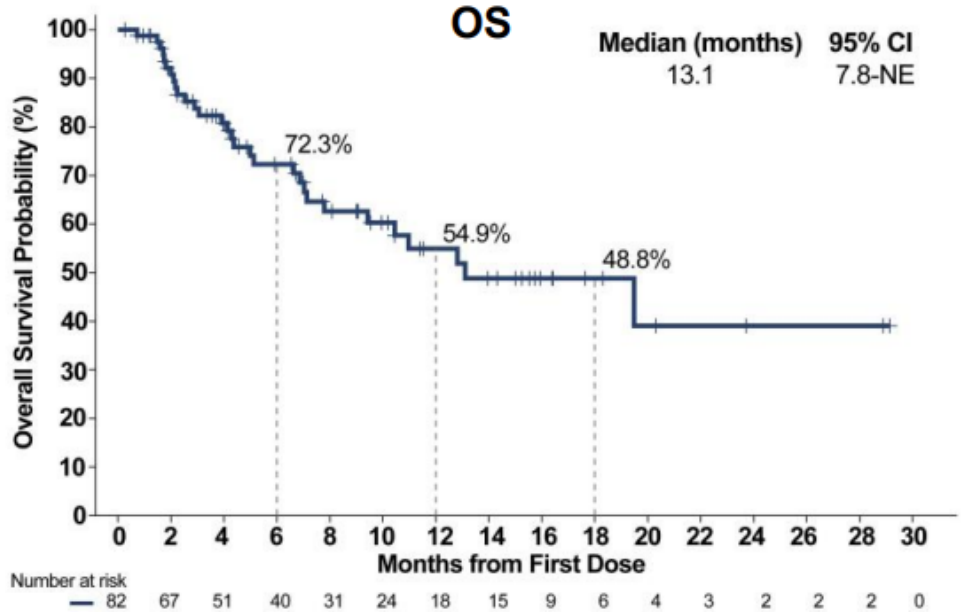
Response Evaluable RT Patients[a]	All n=75	Prior RT Therapy n=68
Overall Response Rate, % (95% CI)	**52.0 (40.2-63.7)**	**50.0 (37.6-62.4)**
Best Response		
CR, n (%)	10 (13.3)	9 (13.2)
PR, n (%)	29 (38.7)	25 (36.8)
SD, n (%)	10 (13.3)	10 (14.7)

- Among 75 response-evaluable patients, the median time-to-response was 1.8 months (range, 0.9-9.2), median time on study was 6.7 months (range, 0.7-29.1), and median time on treatment was 3.4 months (range, 0.2-26.7)

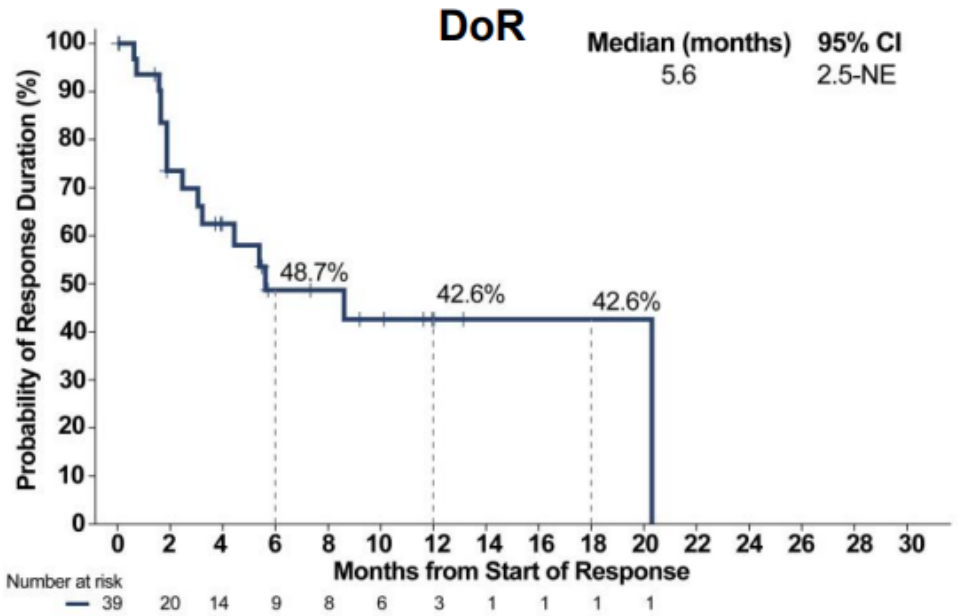
Data cutoff date of 29 July 2022. Data for 14 patients are not shown in the waterfall plot due to no baseline or post-baseline assessment. [a]Response evaluable patients are those who had at least 1 post-baseline response assessment or had discontinued treatment prior to first post-baseline response assessment. Response as assessed by investigator based on Lugano criteria.

PFS, OS, and DoR in All RT Patients





- 6 responding patients were censored for curative intent transplant therapy



Data cutoff date of 29 July 2022. Response as assessed by investigator based on Lugano criteria.

Conclusions

- This trial represents one of the largest prospective RT populations ever studied, comprised predominantly of heavily pretreated RT patients with an extremely poor expected overall survival
- Pirtobrutinib demonstrated promising efficacy, including among patients who received prior RT chemoimmunotherapy and cBTKi
  - Notably, pirtobrutinib demonstrated an ORR of 52% overall and 50% among patients who received prior RT therapy
  - Median OS was 13.1 months, regardless of prior RT therapy
  - DoR was 5.6 months, regardless of prior RT therapy
  - 6 responding patients discontinued in ongoing response to pursue curative intent transplant therapy
- Pirtobrutinib continues to be well-tolerated with low rates of Grade ≥3 AEs and discontinuation due to drug-related toxicity
  - Low rates of cBTKi-associated AEs were observed with pirtobrutinib

Important ASH abstracts: Take Home points

- **Upfront treatment including prognostication**
  - DFCI AVO - active, high rates of uMRD: most achieve at 9 months, increased toxicities
  - CLL13 – IGHV status matters, Gve Rx superior.
  - GLOW – IGHV status matters, MRD negativity may not be as important as we thought especially in lower risk patients

- **Relapsed Disease**
  - ALPINE - Zanubrutinib has superior PFS and better cardiac safety profile compared to ibrutinib in relapsed CLL setting including in patients with del17p.
  - BRUIN CLL cohort
  - BRUIN RT cohort

} Pirtobrutinib is safe and effective

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