Update on Treatments for Patients with CLL

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WILLIAM G. WIERDA MD,PHD

PROFESSOR OF MEDICINE

SECTION HEAD, CLL

DEPARTMENT OF LEUKEMIA

U.T. M.D. ANDERSON CANCER CENTER

HOUSTON, TX USA

BTKi- *vs.* BCL-2i-based Treatment

BTK Inhibitor[1-4]

- Easy initiation
- Continuous and indefinite therapy
- Very low TLS risk
- More cardiac risk
- Some favor in del(17p)/ mutated-*TP53*
- Activity in nodal disease

BCL-2 Inhibitor[4,5]

- Risk for TLS requires monitoring for initiation
- Includes CD20 mAb – immunosuppression
- Fixed duration
- GFR sensitivity
- Concern for del(17p)/mutated-*TP53*
- Activity in BM and blood

1. Acalabrutinib PI. 2. Ibrutinib PI. 3. Zanubrutinib PI. 4. Awan. Am Soc Clin Oncol Educ Book. 2020;40:1. 5. Venetoclax PI.

Important for Selecting Treatment in CLL

- IGHV mutation status (for first line): **does not change**[1]
- del(17p) status by FISH: **can change**[2]
  - Know % of cells with deletion
- *TP53* mutation status: **can change**[2]

- Age and comorbidities (cardiac and renal)

- *BTK* and *PLCG2* mutation status (in BTKi treated): **can change**[3]

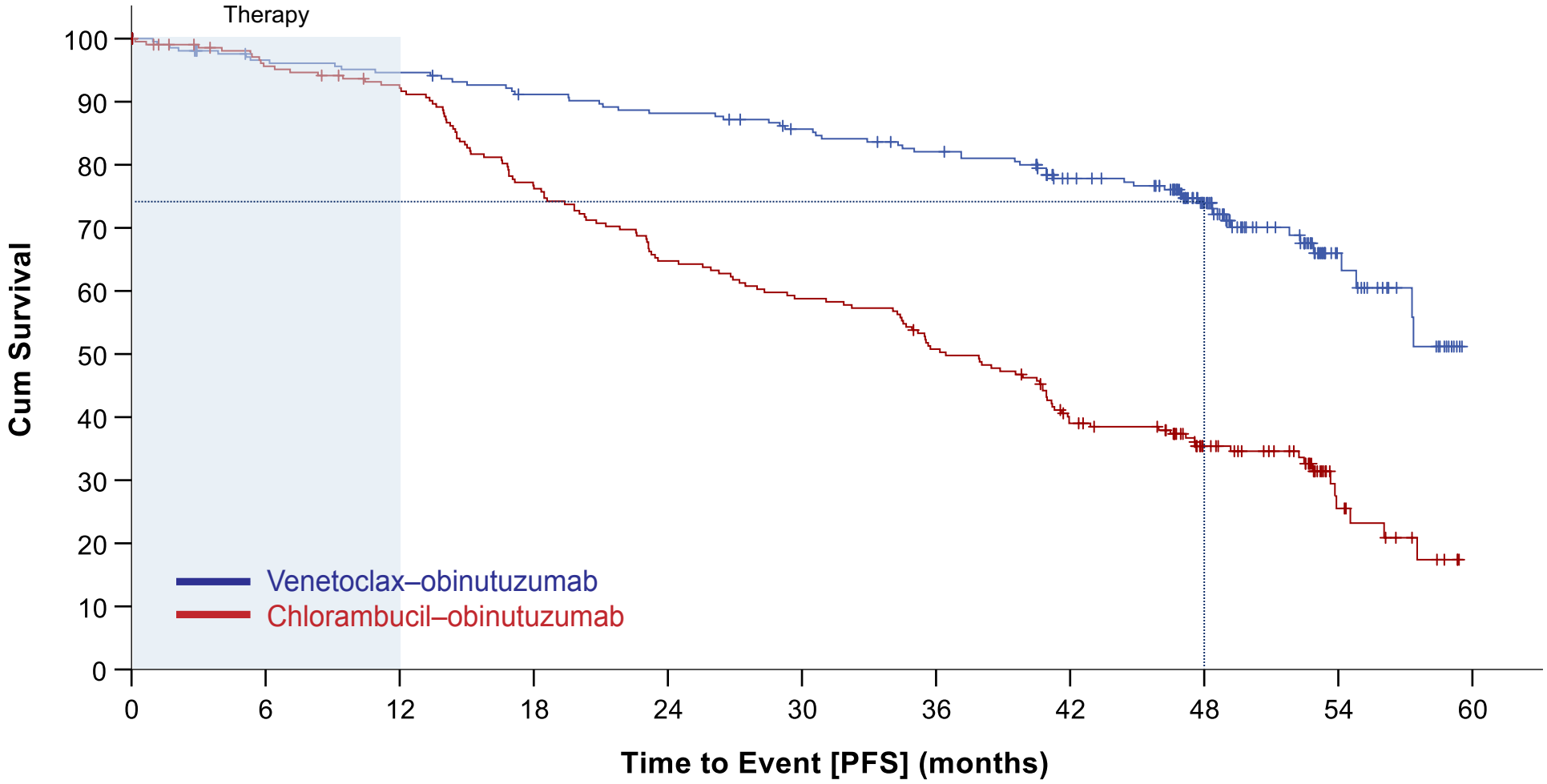
1. Crombie. Am J Hematol. 2017;92:1393. 2. Chauffaille. Hematol Transfus Cell Ther. 2020;42:261. 3. Hallek. Am J Hematol. 2019;94:1266.

First-line Phase III Randomized Trials

- **CLL14** (CIRS >6; CrCl <70 mL/min)
  - **Venetoclax + Obinutuzumab** *vs.*
  - **Chlorambucil + Obinutuzumab**
- **GLOW** (>65yo or ≤65yo with comorbidities)
  - **Ibrutinib + Venetoclax** *vs.*
  - **Chlorambucil + Obinutuzumab**
- **CLL13 / GAIA** [CIRS ≤ 6; non-del(17p)]
  - **Venetoclax + Obinutuzumab** *vs.*
  - **Venetoclax + Ibruitnib + Obinutuzumab** *vs.*
  - **Venetoclax + Rituximab** *vs.*
  - **FCR / BR**
- **RESONATE-2**
  - **Ibrutinib** *vs.*
  - **Chlorambucil**
- **iLLUMINATE** (PCYC-1130) (>65yo or ≤65yo with comorbidities)
  - **Ibrutinib + Obinutuzumab** *vs.*
  - **Chlorambucil + Obinutuzumab**
- **ECOG E1912** [<70yo; non-del(17p)]
  - **Ibrutinib + Rituximab** *vs.*
  - **FCR**
- **Alliance** (A041202) (>65yo)
  - **Ibrutinib** *vs.*
  - **Ibrutinib + Rituximab** *vs.*
  - **BR**
- **ELEVATE-TN** (>65yo or younger with CIRS score >6, or CrCl <70 mL/min)
  - **Acalabrutinib** *vs.*
  - **Acalabrutinib + Obinutuzumab**
  - **Chlorambucil + Obinutuzumab**
- **SEQUOIA** [≥65 yo OR unsuitable for FCR; non-del(17p)]
  - **Zanubrutinib** *vs.*
  - **BR**

CLL 14: Progression-free Survival

Median observation time 52.4 months



Median PFS

Ven-Obi: not reached

Clb-Obi: 36.4 months

4-year PFS rate

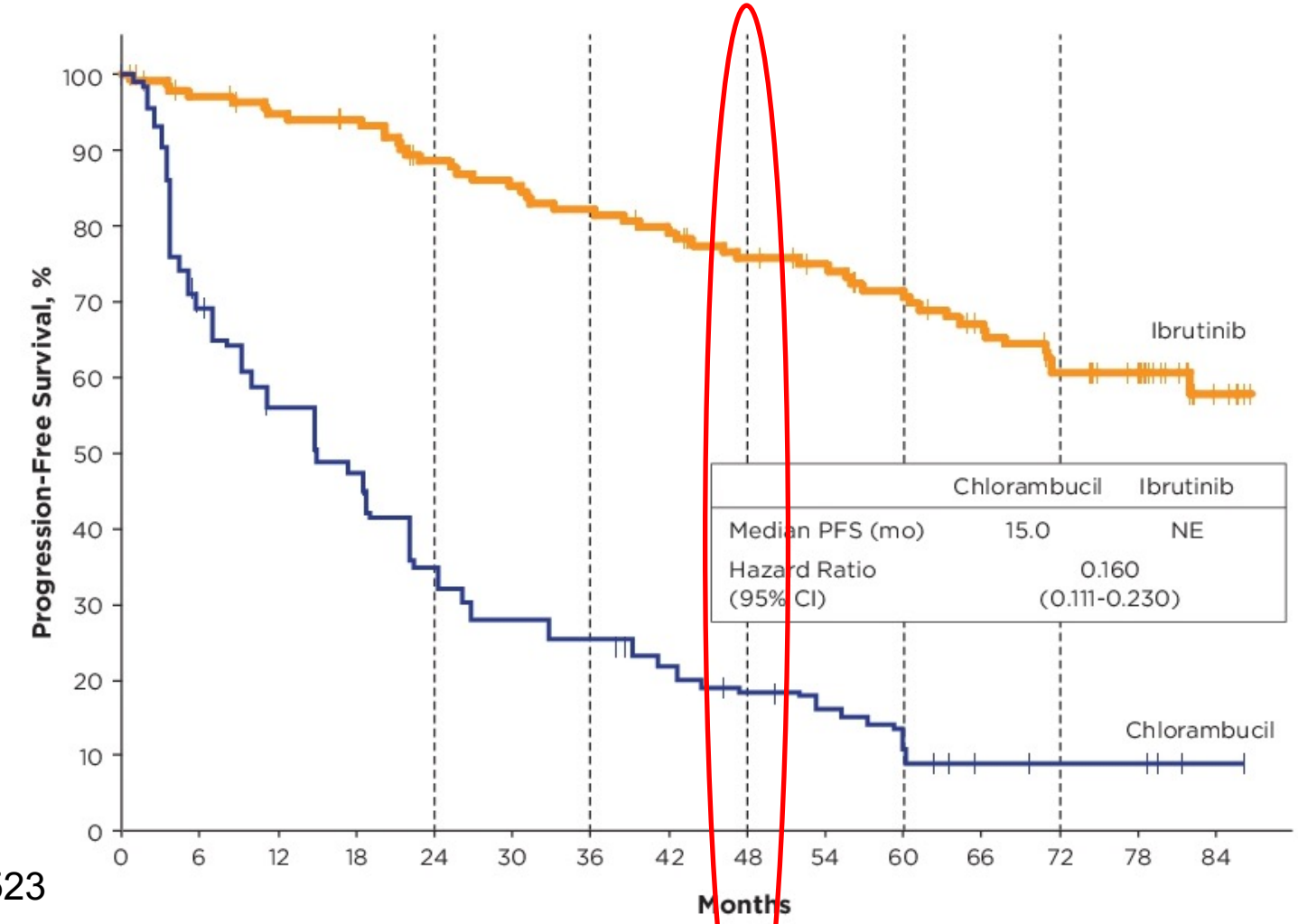
Ven-Obi: 74.0%

Clb-Obi: 35.4%

HR 0.33, 95% CI [0.25-0.45]
P<0.0001

Al-Sawaf et al. EHA 2021, Abstract S146

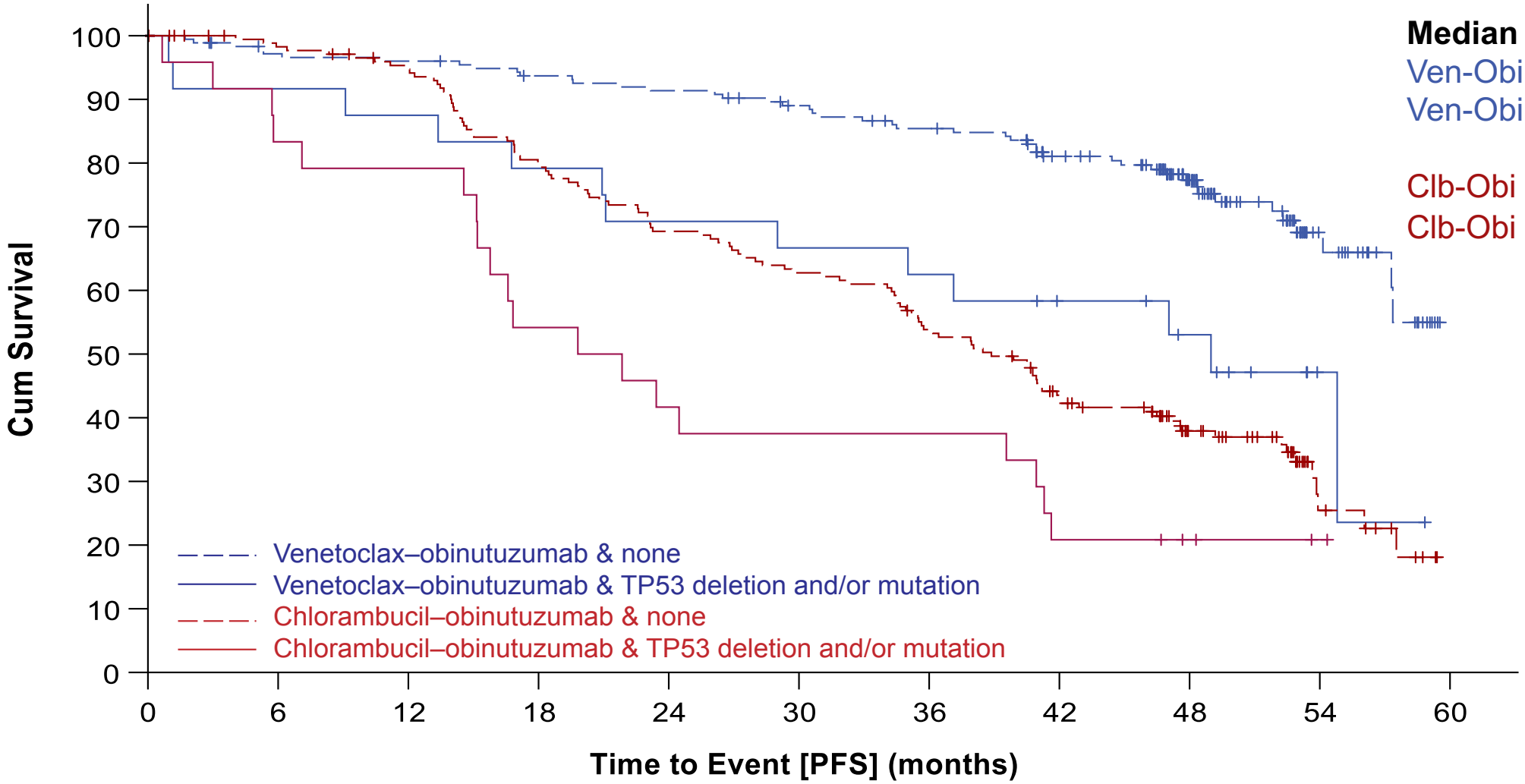
RESONATE-2: First-line, Age >65yrs
Ibrutinib Prolonged PFS Over Chlorambucil



Barr et al. ASCO 2021, Poster 7523

Progression-free Survival – *TP53* Status

Median observation time 52.4 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: 20.8 m

Al-Sawaf et al. EHA 2021, Abstract S146

Predictors of Outcomes with VEN-based Combinations (CLL13/GAIA) – ASH 2022

- **Response (ORR and uMRD) for all subgroups; independent association of U-IGHV, *NOTCH1, BRAF/NRAS/KRAS* mutations, hCKT (≥5 abberations), and chromosome translocations with shorter PFS**

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

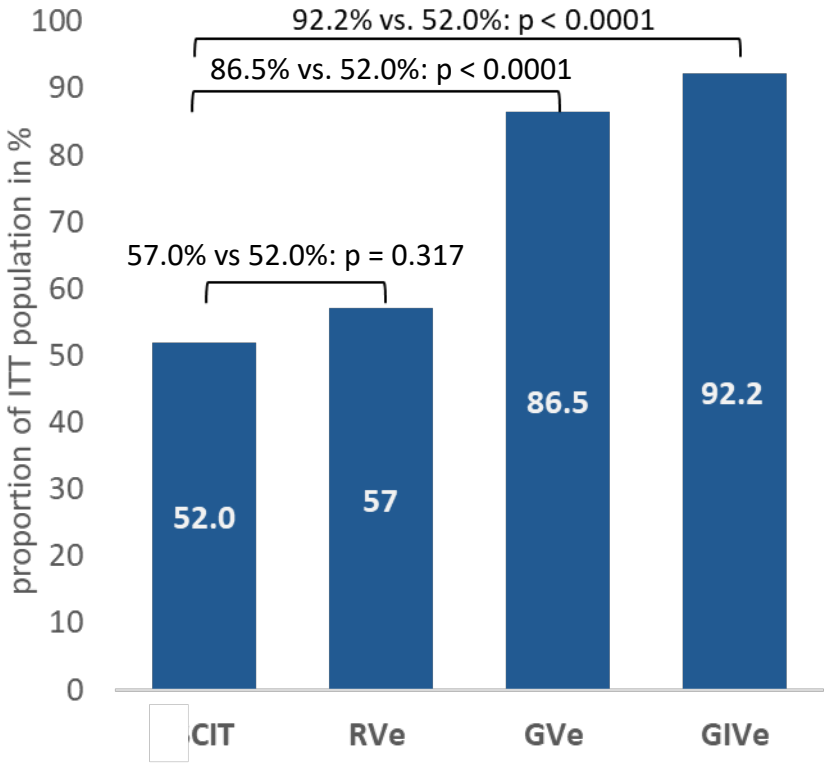
RVe
12 cycles, n=230

GVe
12 cycles, n=230

GIVe
15# cycles, n=230

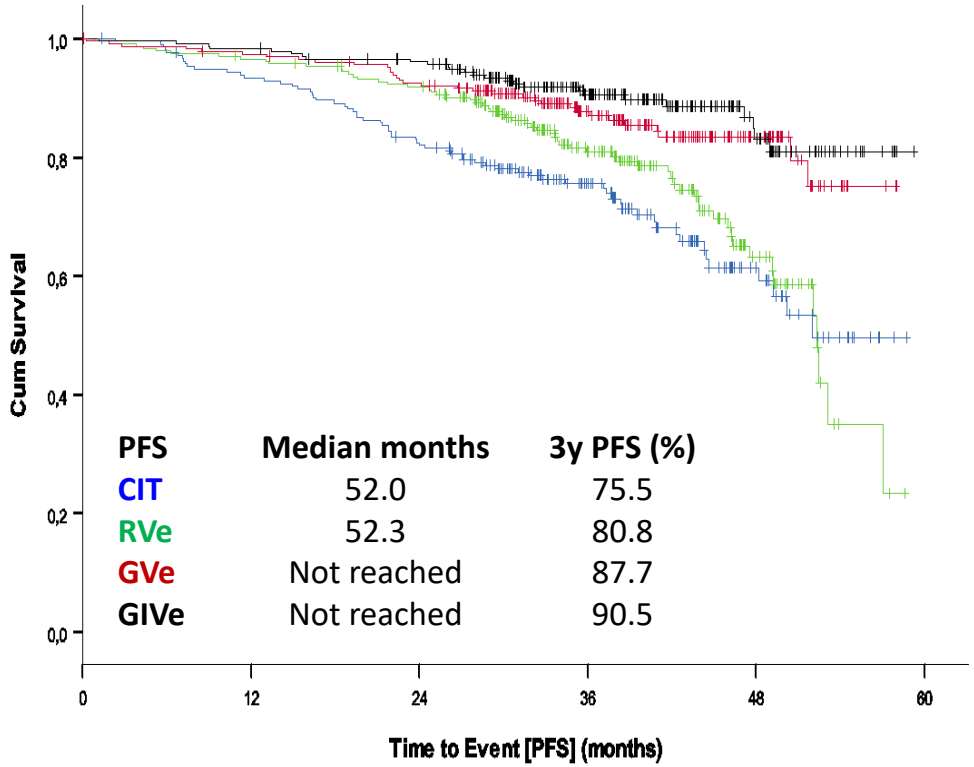
uMRD (< 10^{-4})

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

Eichhorst et al, ASH2021 and EHA2022

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

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

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

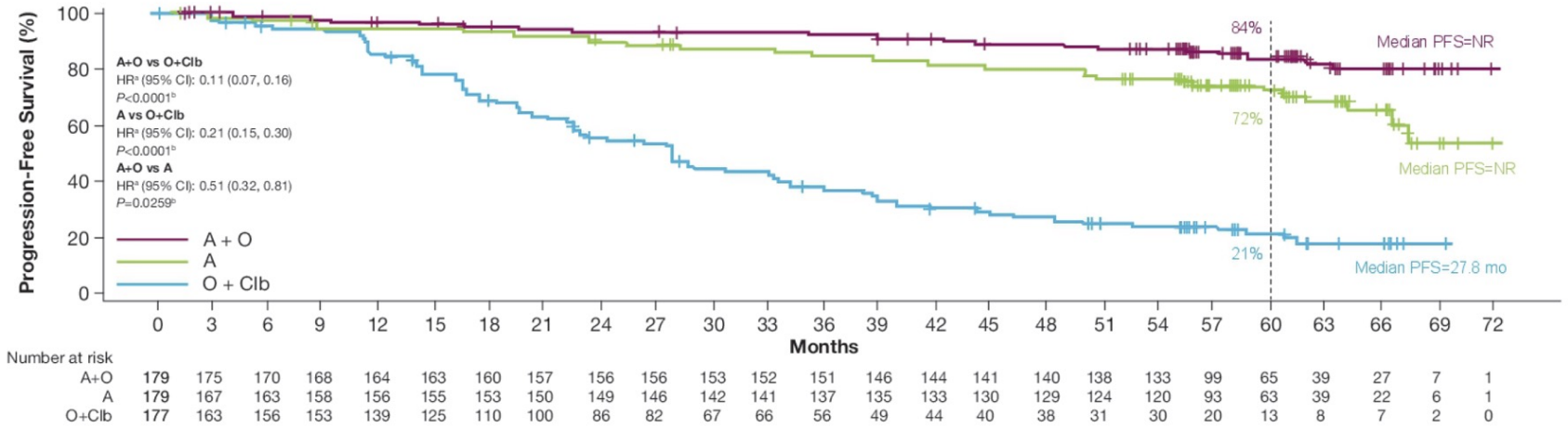
	HR	95%CI	p
U-IGHV	3.08	1.55-6.12	0.001
>65 years	2.26	1.34-3.83	0.002
NOTCH1mut	2.12	1.16-3.88	0.01
del(11q)	1.89	1.06-3.36	0.03
CKT	1.87	1.06-3.27	0.03

RVe/GVe/GIVe for PFS

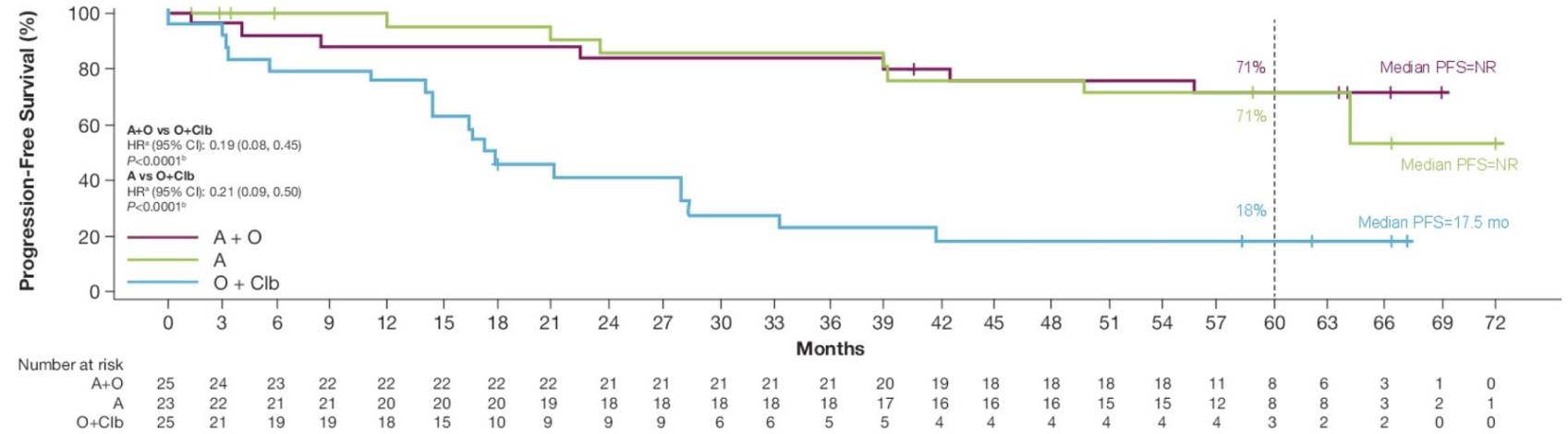
	HR	95%CI	p
U-IGHV	1.85	1.20-2.84	0.005
RAS/RAFmut	1.87	1.14-3.06	0.01
CKT	1.66	1.07-2.56	0.02
b2MG>3.5mg/L	1.56	1.03-2.36	0.04
NOTCH1mut	1.54	1.02-2.33	0.04

5-Year Follow-Up of the ELEVATE-TN Phase 3 Study: PFS Acalabrutinib

INV-Assessed PFS



INV-Assessed PFS in Patients With del(17p) and/or Mutated *TP53*

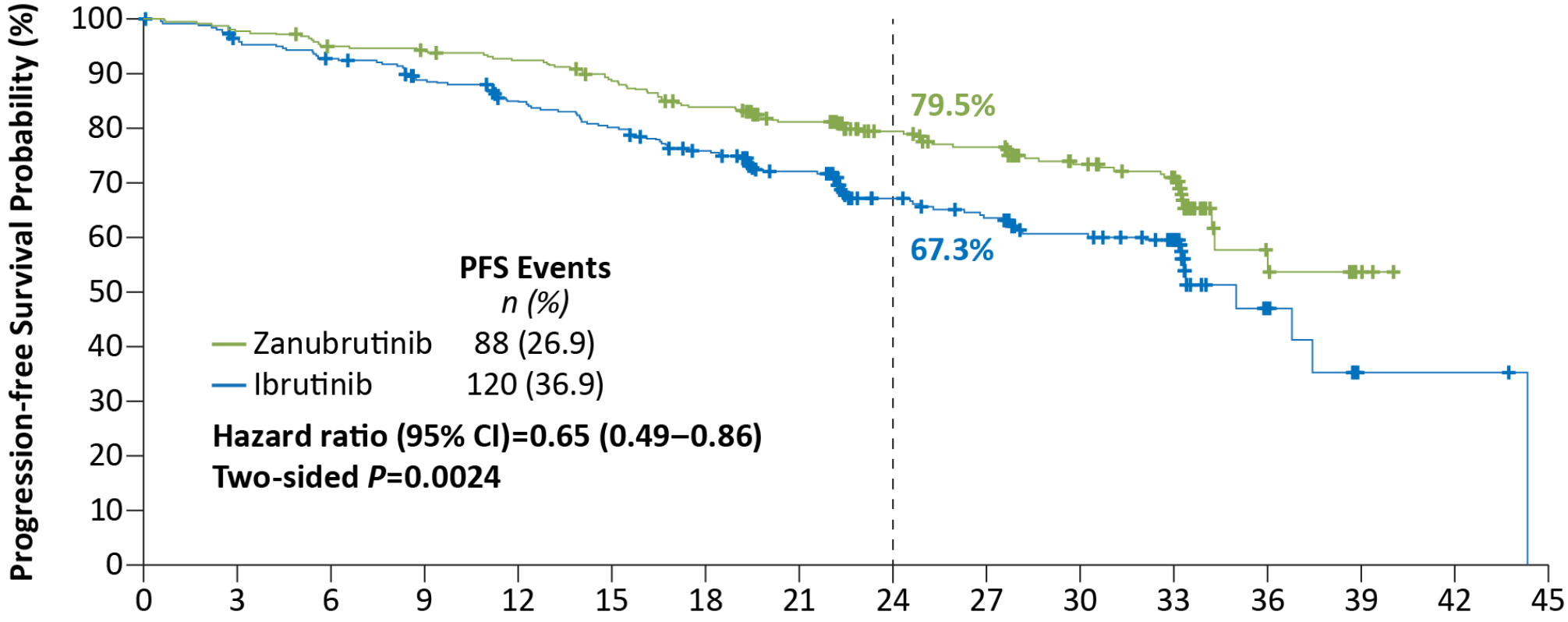


Median follow-up: 58.2 months (range, 0.0-72.0)

Sharman JP, et al. ASCO 2022. Abstract 7539. Sharman JP, et al. EHA 2022. Abstract P666.

ALPINE: Zanubrutinib PFS by IRC Superior to Ibrutinib

Median study follow-up of 29.6 months

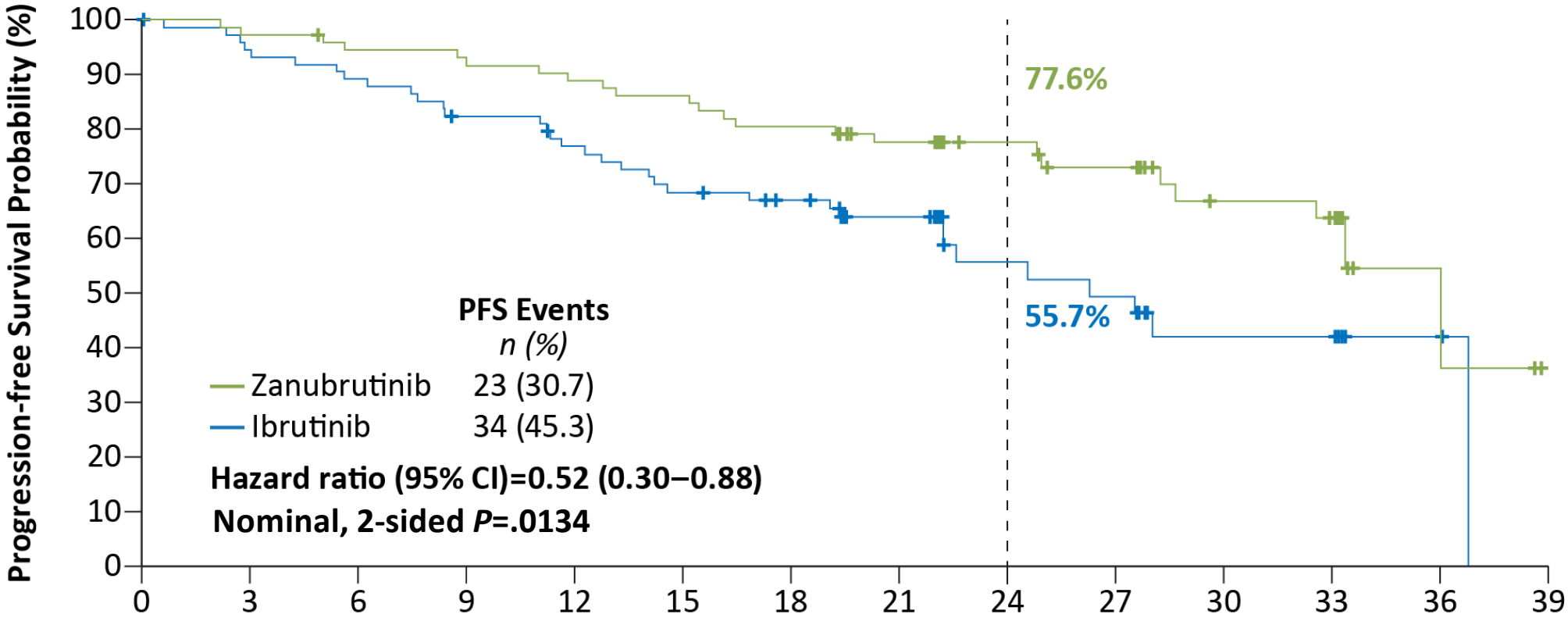


No. at Risk																
Zanubrutinib	327	315	304	301	294	280	263	226	172	161	125	113	14	2	0	
Ibrutinib	325	305	293	277	260	246	228	191	133	123	98	87	9	2	2	0

Data cutoff: 8 Aug 2022

Brown et al. ASH 2022, LBA-6

ALPINE: 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

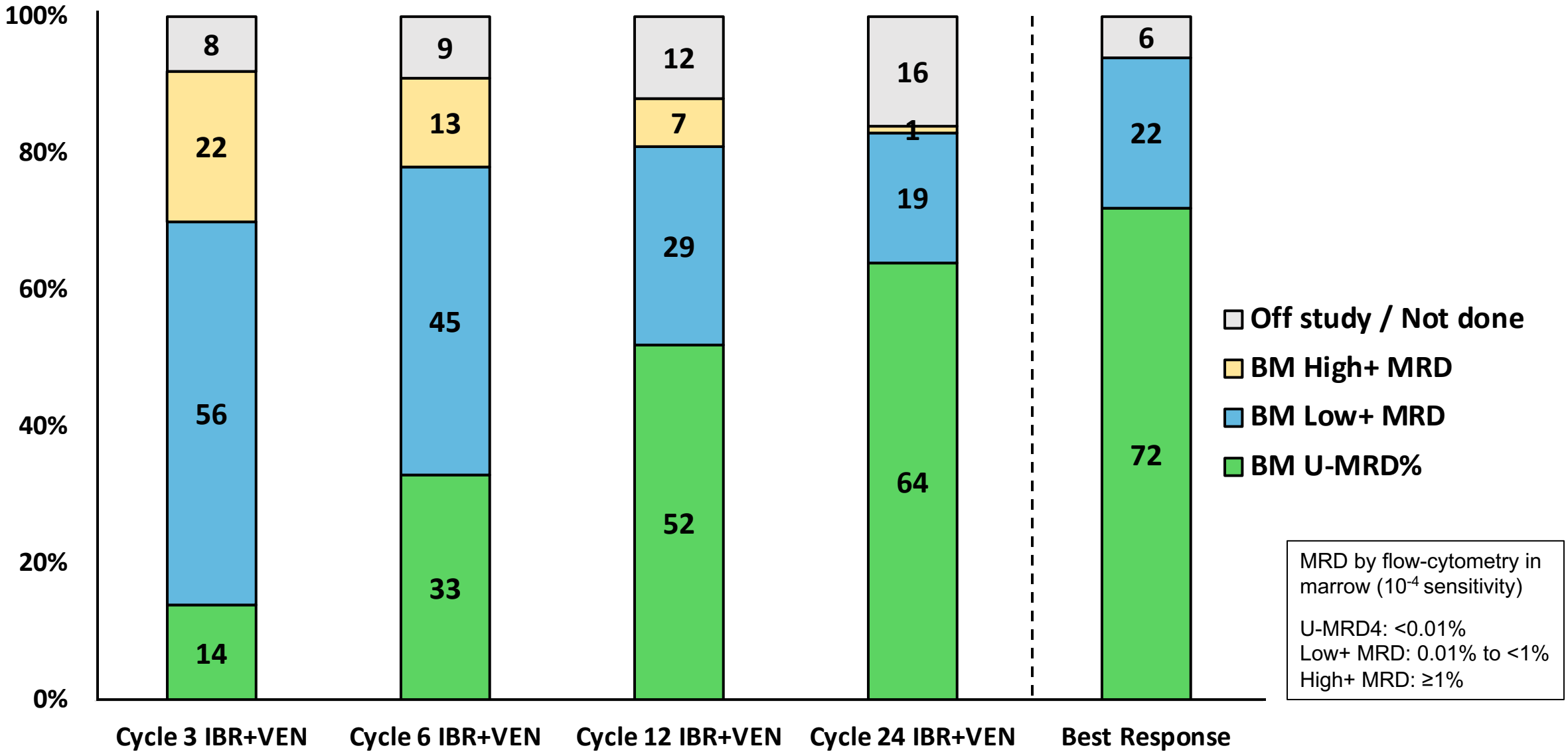
PFS data assessed by IRC

Data cutoff: 8 Aug 2022

First-line Ibrutinib + Venetoclax (MDACC / CAPTIVATE / GLOW / FLAIR) ASH2022

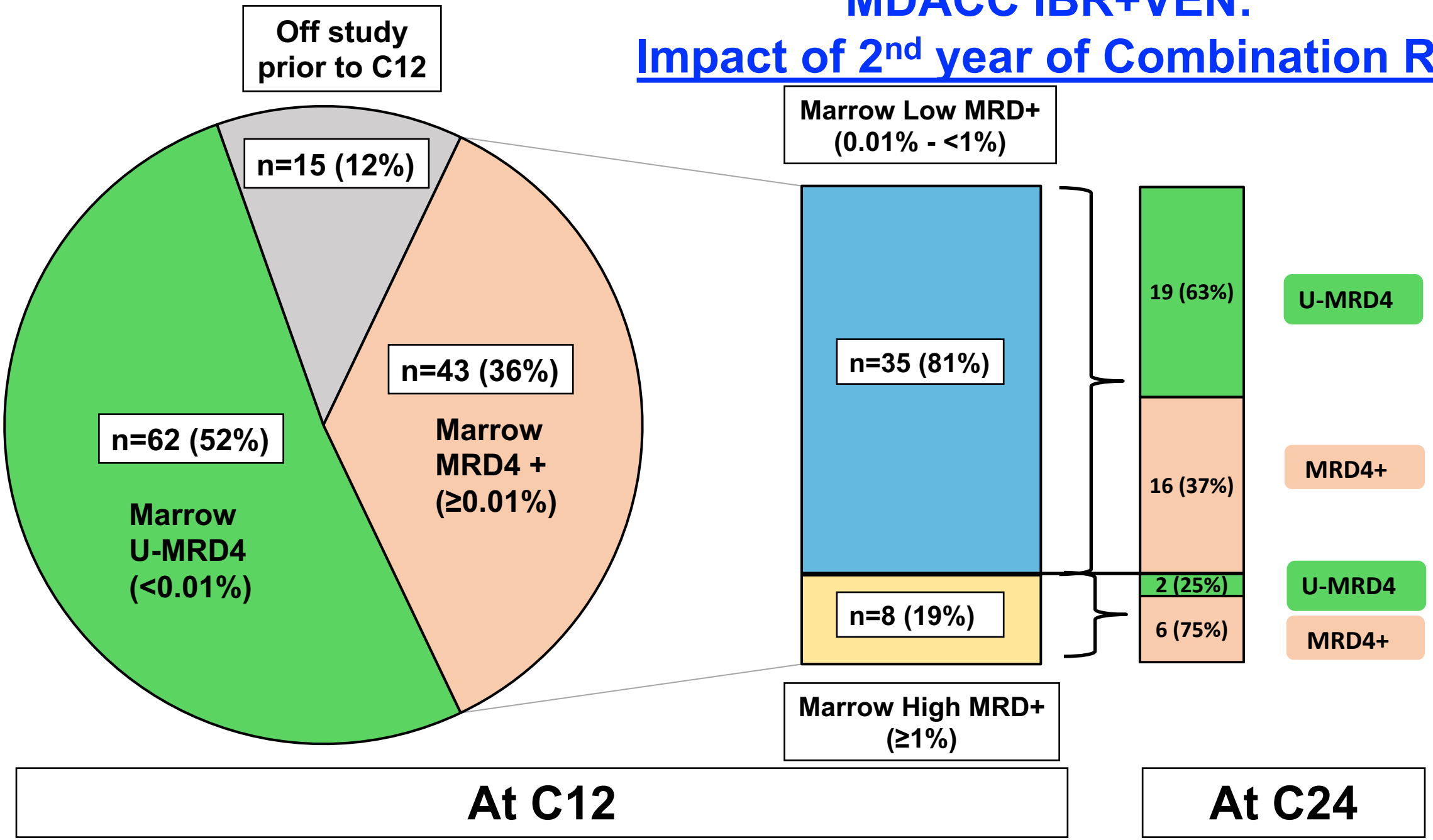
- Deep remissions with IBR+VEN for most, long remissions for all uMRD (All studies)
- Higher uMRD rate for IGHV-unmutated (MDACC, GLOW, FLAIR)
- Shorter PFS for IGHV-unmutated (GLOW)
- Optimal duration of treatment still unclear (longer treatment for slower responders?)

MDACC IBR+VEN: Marrow MRD Response at Serial Time-Points
Intent-to-Treat (N=120)



Jain et al. ASH 2022, Abstract #95

MDACC IBR+VEN:
Impact of 2nd year of Combination Rx



Jain et al. ASH 2022, Abstract #95

MDACC IBR+VEN: Baseline Variables and U-MRD4 Over Time

	U-MRD at 6 mo IBR+VEN		U-MRD at 12 mo IBR+VEN		U-MRD as best response	
Variables	**Odds ratio**	**P-value**	**Odds ratio**	**P-value**	**Odds ratio**	**P-value**
Age	1	0.91	0.98	0.25	0.98	0.25
IGHV-M	0.41	0.19	0.37	0.09	0.25	0.01
FISH [del(17p) vs others)	0.46	0.29	1.17	0.81	0.65	0.42
Cyto (CK vs others)	0.68	0.53	1.38	0.56	0.97	0.96
Del(17p) / *TP53*-m	0.39	0.08	0.83	0.68	0.56	0.21
SF3B1-m	1.7	0.24	0.77	0.56	1.36	0.55
NOTCH1-m	0.76	0.53	0.62	0.24	1.16	0.75

Jain et al. ASH 2022, Abstract #95

MDACC IBR+VEN: Factors Predicting for Blood MRD Recurrence

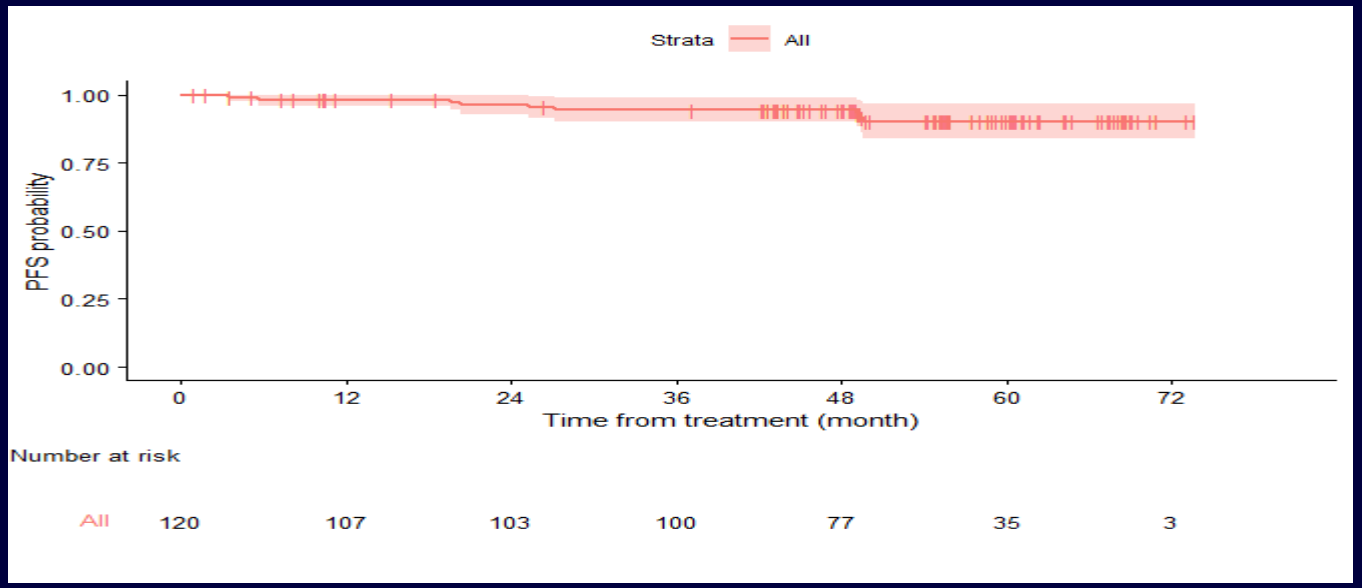
Univariate Logistic regression for odds of MRD recurrence in patients who were UMRD4 at C24 (n=77)

Variables	Odds ratio	95% CI	P-value
Age	1	0.96-1.04	0.96
IGHV-M	1.36	0.24-7.78	0.73
FISH (Del17p vs others)	0.61	0.09-2.65	0.55
Cyto (CK vs others)	0.83	0.16-4.32	0.83
Del(17p) / *TP53*-m	0.78	0.19-3.15	0.73
SF3B1-m	0.9	0.26-3.15	0.87
NOTCH1-m	1.43	0.46-4.47	0.54
Early MRD negative*	**0.2**	**0.04-0.68**	**0.02**

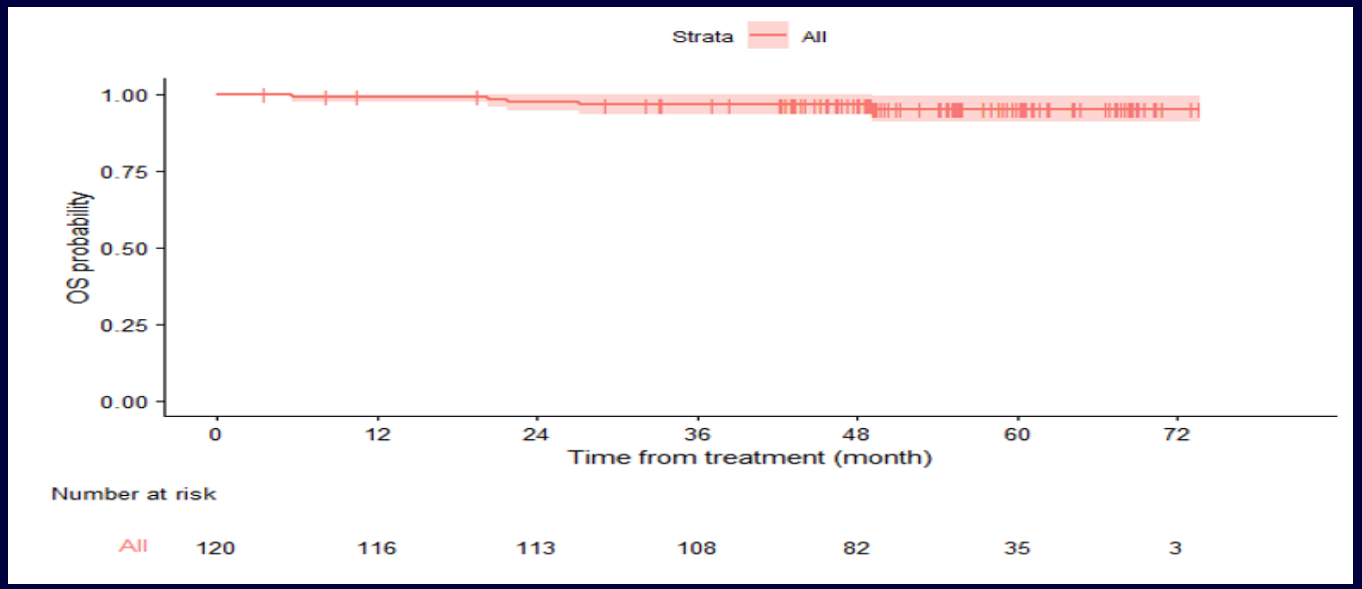
* U-MRD4 in marrow by 6 months of combination therapy

Jain et al. ASH 2022, Abstract #95

MDACC IBR+VEN: PFS and OS (N=120)



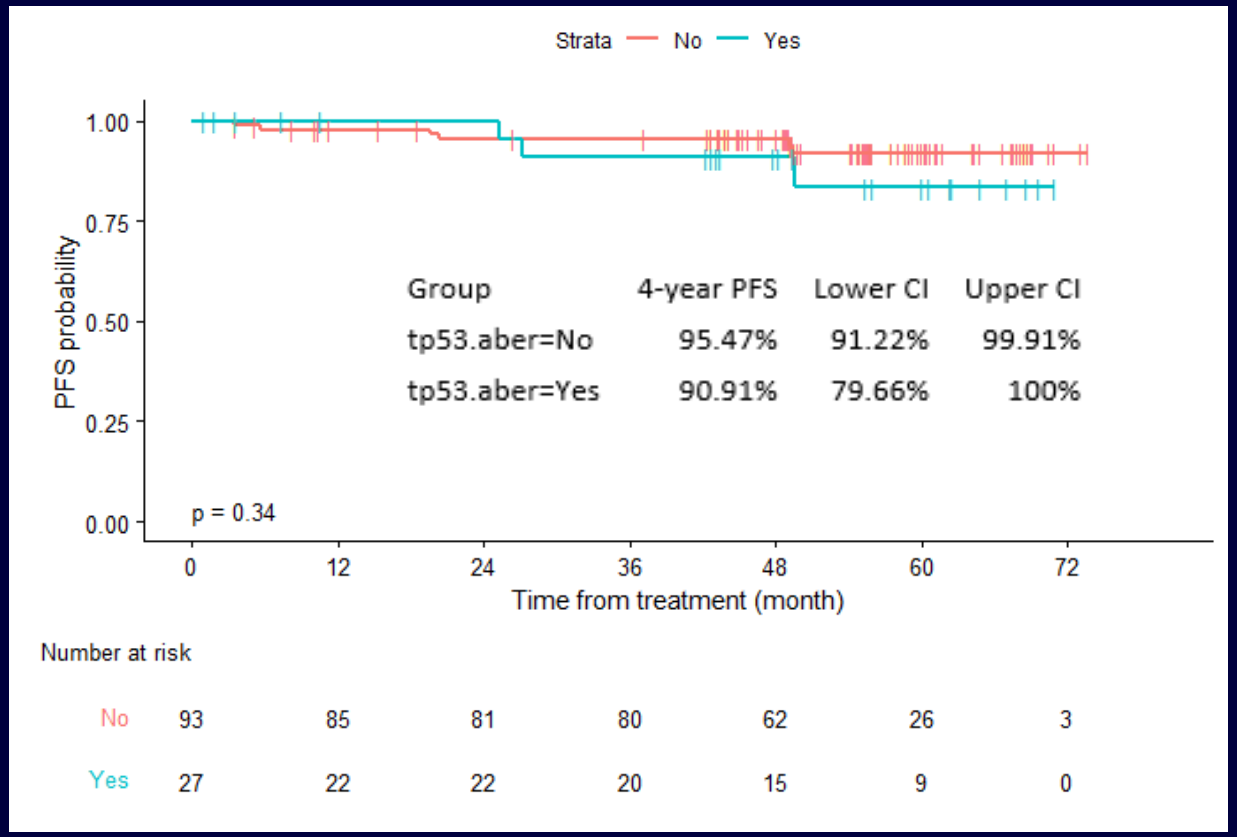
4-year PFS = 94.5%
(95% CI, 90.3-98.9%)



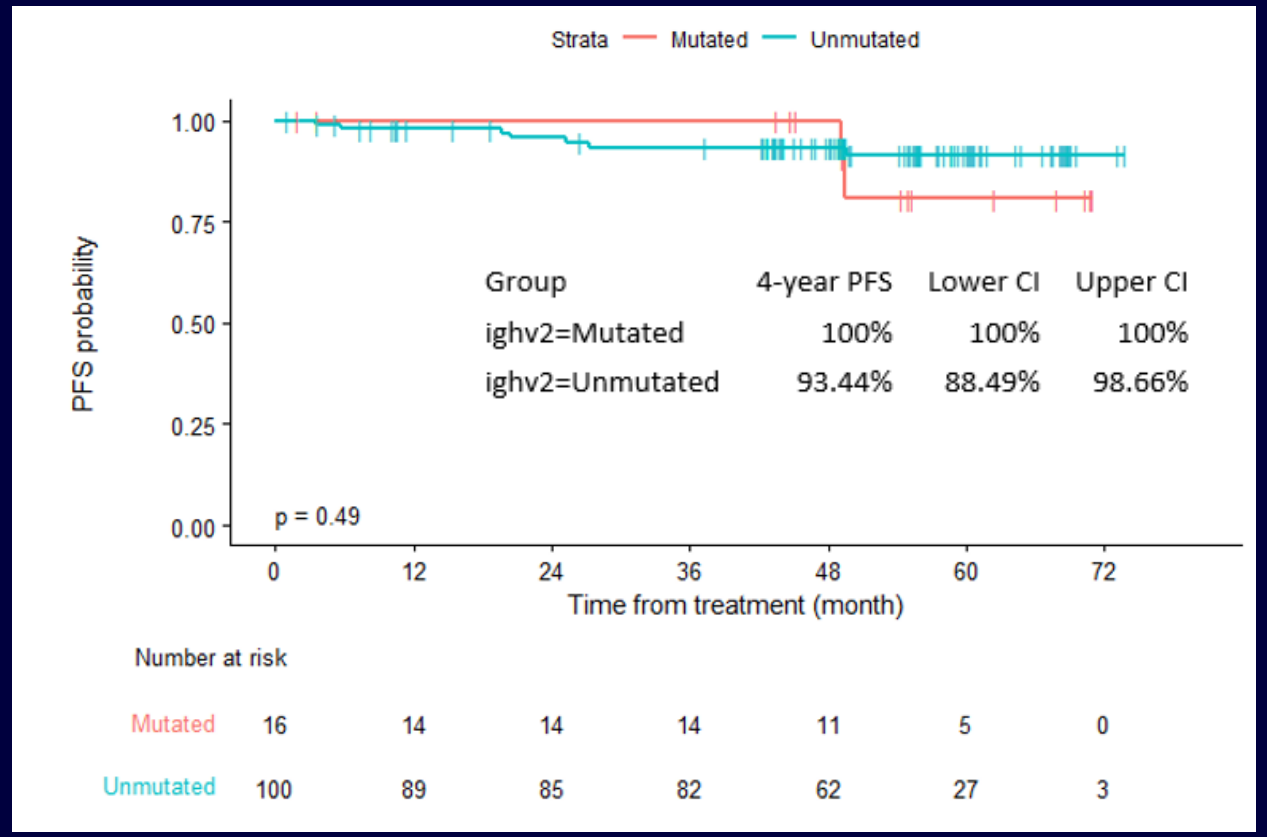
4-year OS = 96.6%
(95% CI, 93.3-99.9%)

Jain et al. ASH 2022, Abstract #95

MDACC IBR+VEN: PFS by Genomic Subgroups



TP53 aberrant status



IGHV mutation status

Jain et al. ASH 2022, Abstract #95

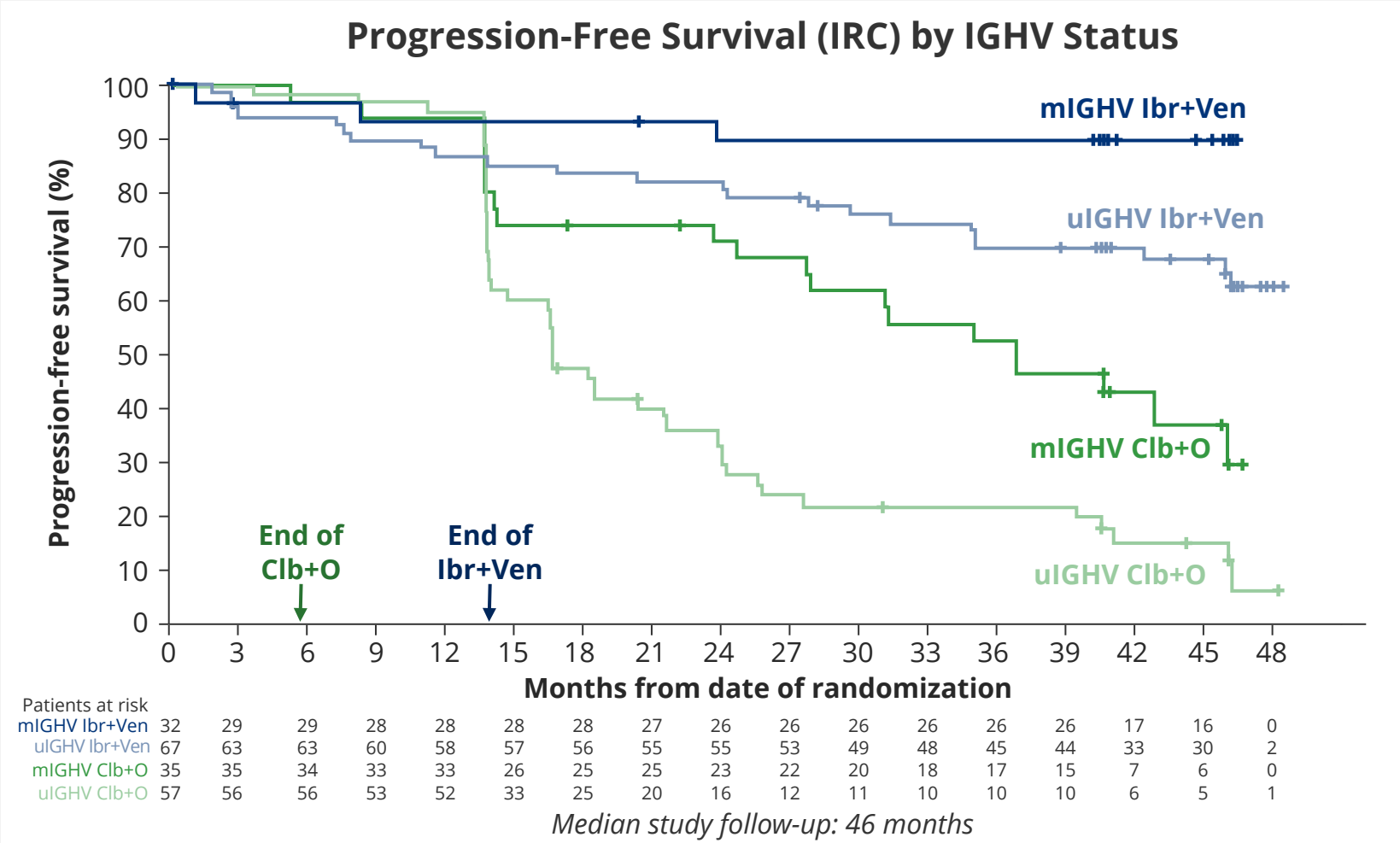
MDACC IBR+VEN: Factors Associated with PFS

Univariate Cox regression analysis for hazards of progression/death

Variables	HR	95% CI	P-value
Age	1.05	0.97-1.13	0.22
IGHV-M	1.72	0.36-8.29	0.50
Cyto (CK vs. others)	3.04	0.76-12.18	0.12
Del(17p) / *TP53*-m	1.95	0.49-7.8	0.35
NOTCH1 mut	2.11	0.57-7.87	0.27
SF3B1 mut	1.7	0.42-6.78	0.46

Jain et al. ASH 2022, Abstract #95

GLOW: Ibr+Ven Improved PFS Versus Clb+O Regardless of IGHV Status

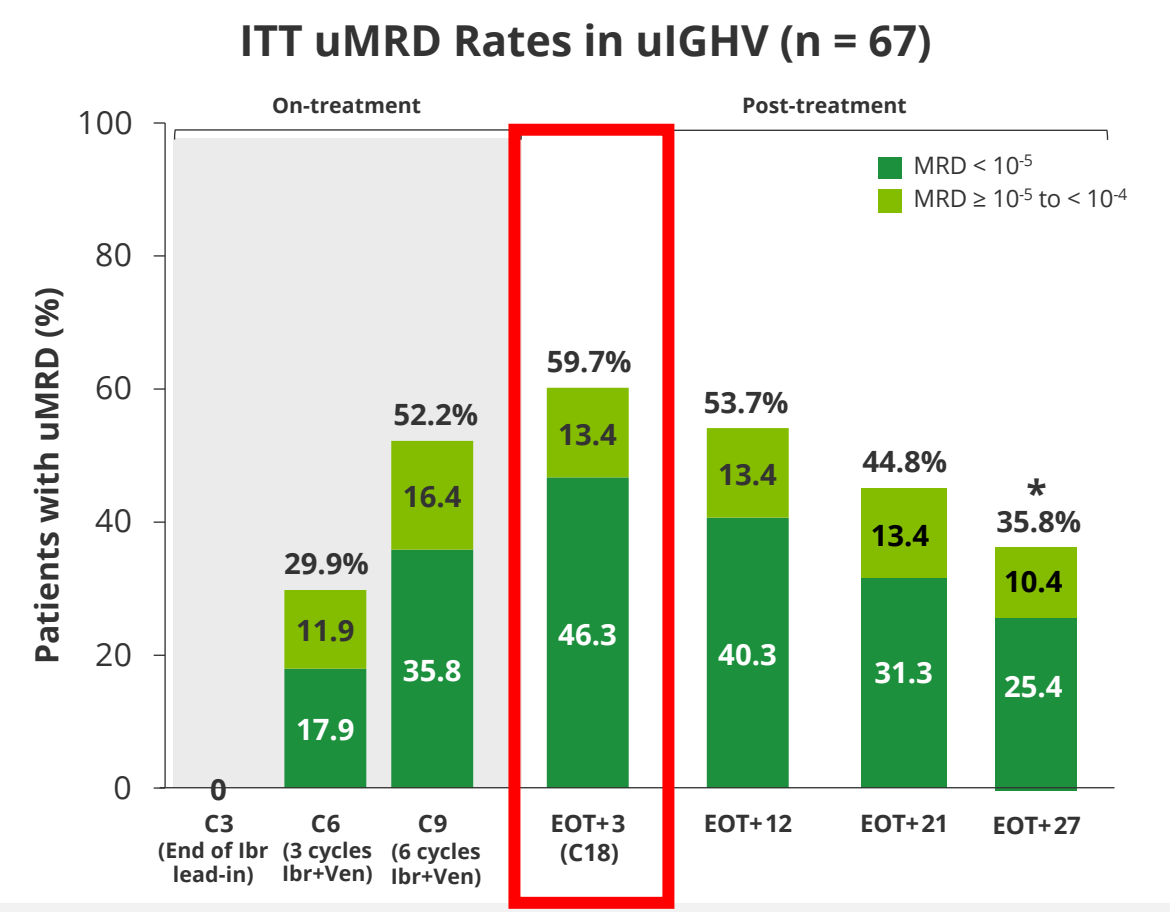


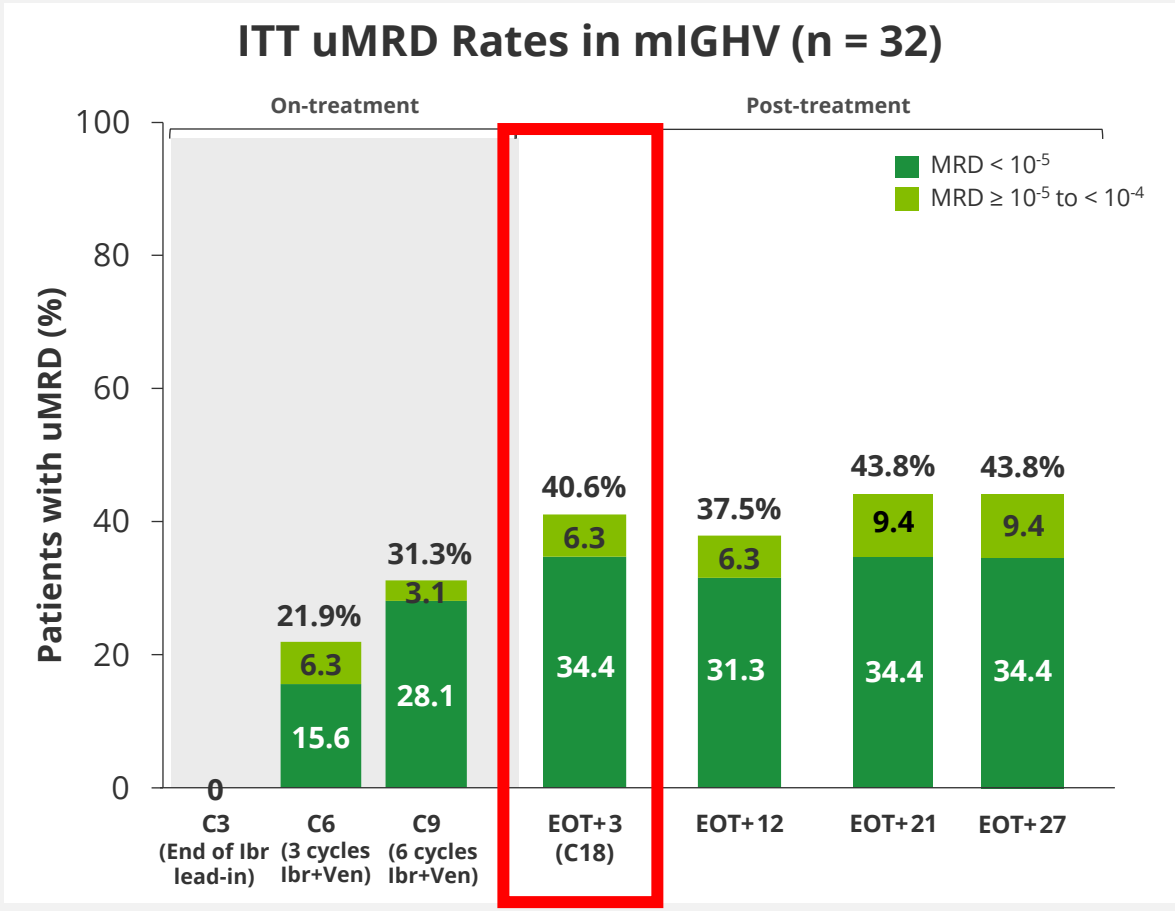
- PFS at 3.5 years was higher for Ibr+Ven versus Clb+O for both uIGHV and mIGHV CLL
- Impact of IGHV status on PFS was more pronounced with Clb+O
- > 90% of patients in the Ibr+Ven arm did not require subsequent treatment at 3.5 years:
  - 91.5% for uIGHV
  - 93.5% for mIGHV

Results based on updated IGHV reclassifications; 6 of 7 on-treatment deaths in Ibr+Ven arm were in uIGHV.
IRC, independent review committee; mIGHV, mutated IGHV; uIGHV, unmutated IGHV.

Niemann et al. ASH 2022, Abstract #93

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



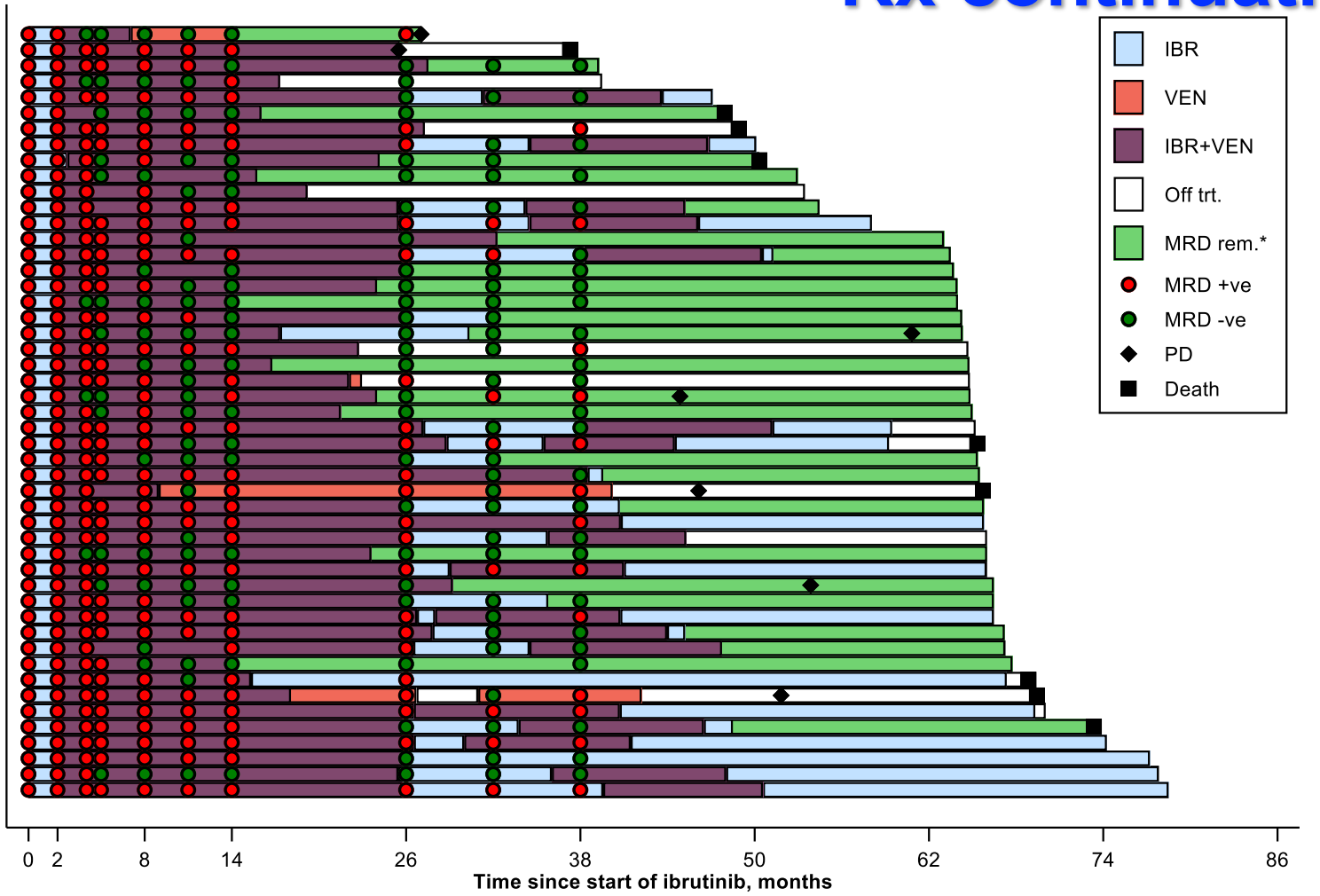


- uMRD rates (including < 10^{-5}) were higher and uMRD was achieved faster in patients with uIGHV versus mIGHV CLL
- uMRD was better sustained post-treatment in patients with mIGHV CLL

*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.

Niemann et al. ASH 2022, Abstract #93

IBR + VEN for R/R CLL
Change in MRD after Rx discontinuation and Rx continuation



* Stopped treatment due to MRD negative remission

- 9 patients continued on ibrutinib after 60 months
- 11 disease progression
- 9 Deaths
- 17 patients continue in uMRD ($<10^{-4}$) after discontinuation at any time point

Date of data lock: 6-Nov-2020

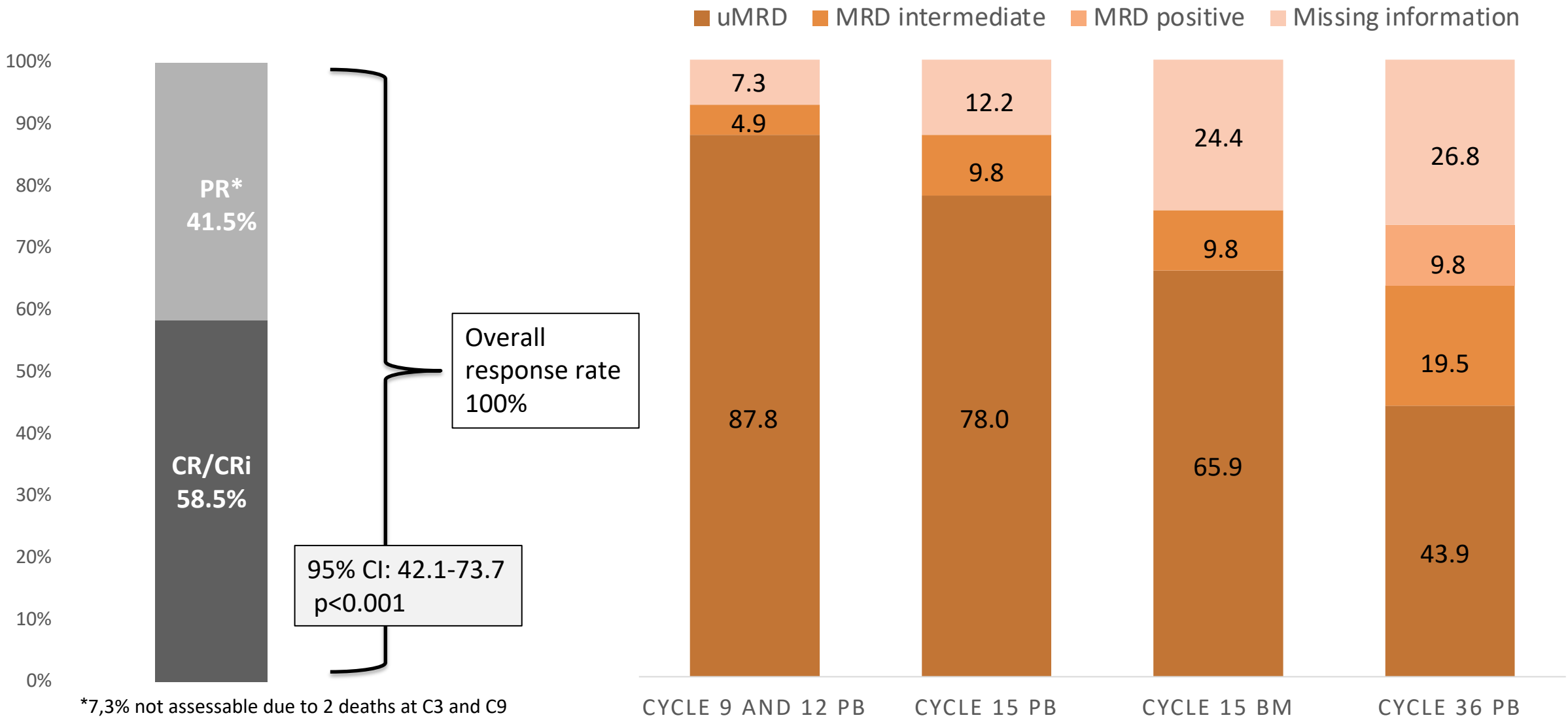
Munir et al. ASH 2022, Abstract #91

Date of data lock: 01-Nov-2022

First-line BTKi + Venetoclax + Obinutuzumab (GiVe and AVO)

- **High uMRD rate, tolerable toxicity (individual contributions?)**

CLL2 GiVe Results: Efficacy
CR rate at final restaging and MRD results



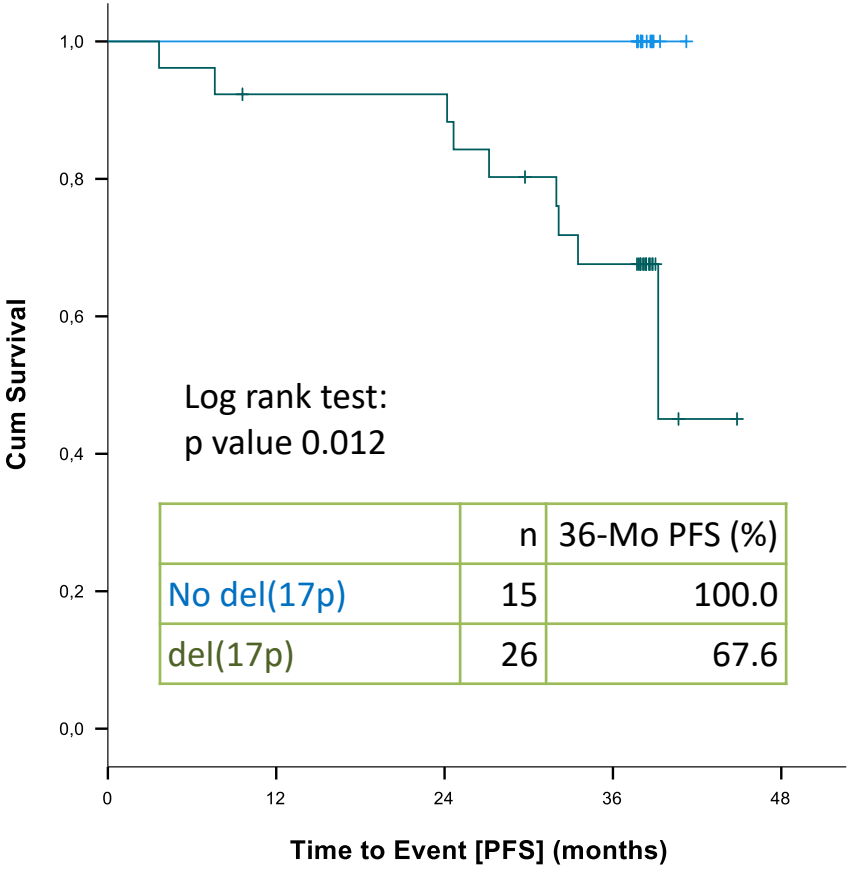
*7,3% not assessable due to 2 deaths at C3 and C9 and 1 withdrawal of informed consent at C9

uMRD: $<10^{-4}$
MRD intermediate: $\geq 10^{-4}$, $<10^{-2}$
MRD positive $\geq 10^{-2}$

Huber et al. ASH 2022, Abstract #343

Results: Efficacy
Correlation between PFS and genetics

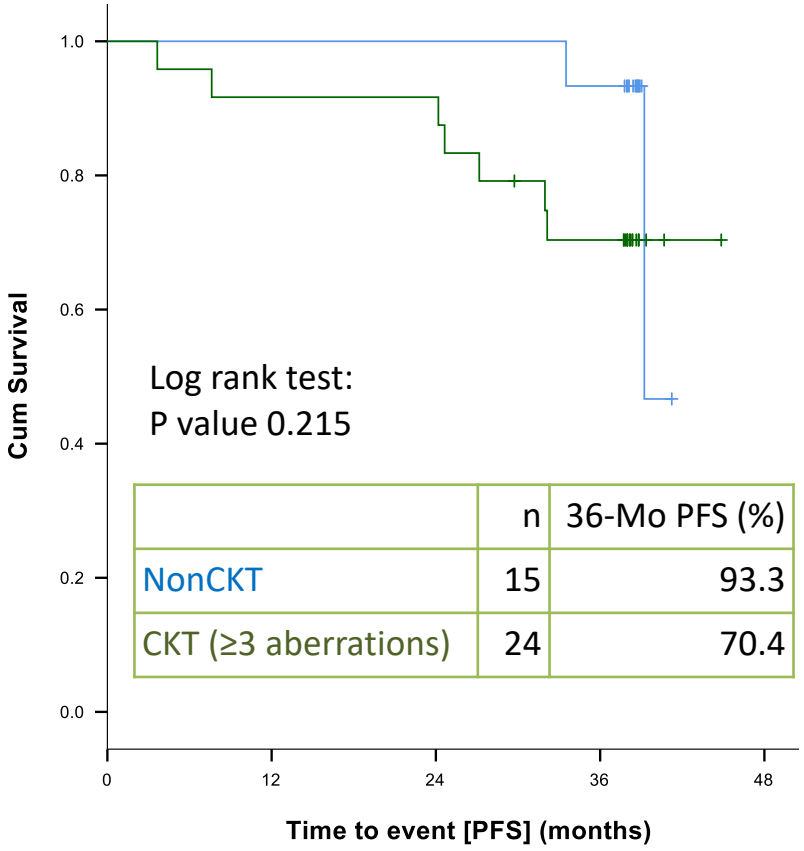
PFS and del(17p)



Log rank test:
p value 0.012

	n	36-Mo PFS (%)
No del(17p)	15	100.0
del(17p)	26	67.6

PFS and complex karyotype*

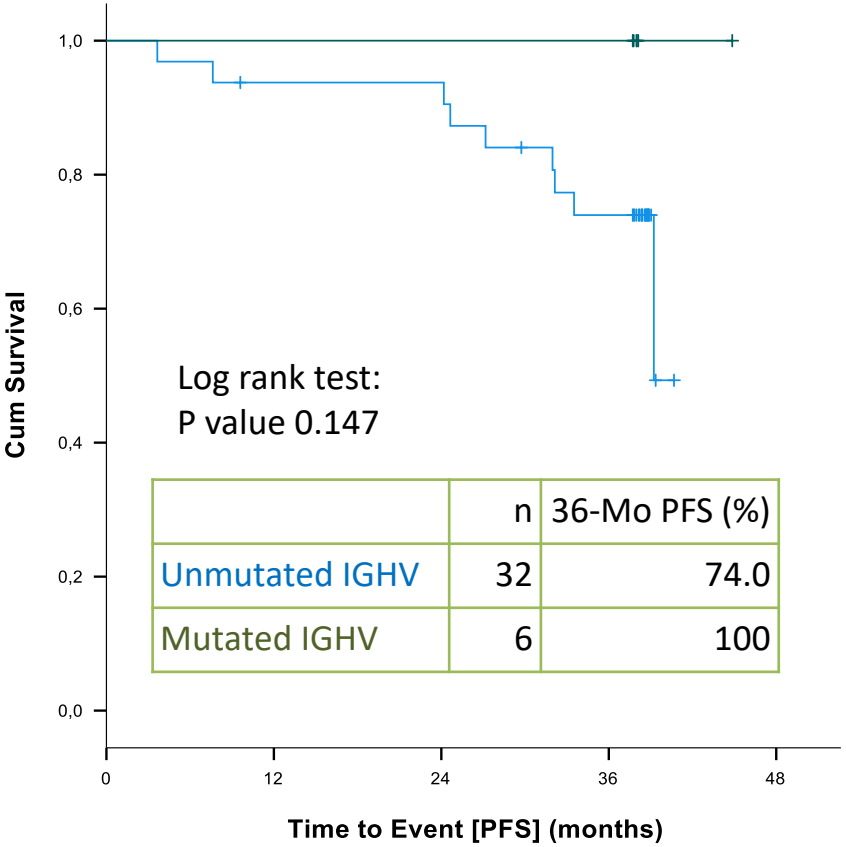


Log rank test:
P value 0.215

	n	36-Mo PFS (%)
NonCKT	15	93.3
CKT (≥3 aberrations)	24	70.4

*Karyotype: 2 patients were not evaluable

PFS and IGHV mutational status

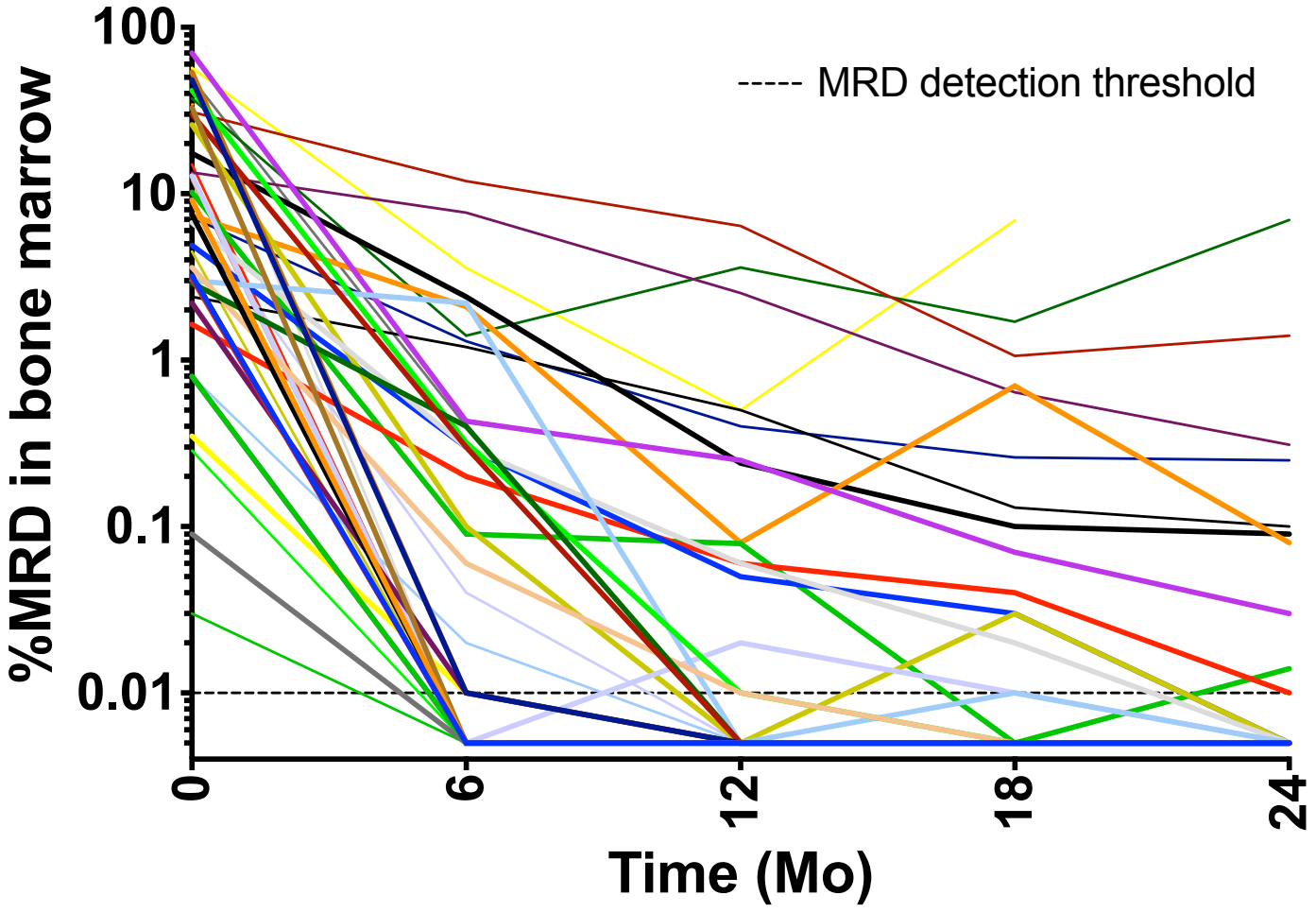


Log rank test:
P value 0.147

	n	36-Mo PFS (%)
Unmutated IGHV	32	74.0
Mutated IGHV	6	100

Venetoclax added to ibrutinib in high-risk CLL

MRD Results



- **CLL/SLL on IBR ≥12 mo with measurable MRD, no PD, ≥1 high-risk feature:**
  - Del(17p) and/or TP53-m
  - Del(11q)
  - Complex karyotype
  - Elevated B2M

- 17/45 pts (38%) post-C6 and 26/45 (57%) post-C12 achieved U-MRD4.

- 6/16 patients MRD+ at C12 converted to U-MRD4 at C24

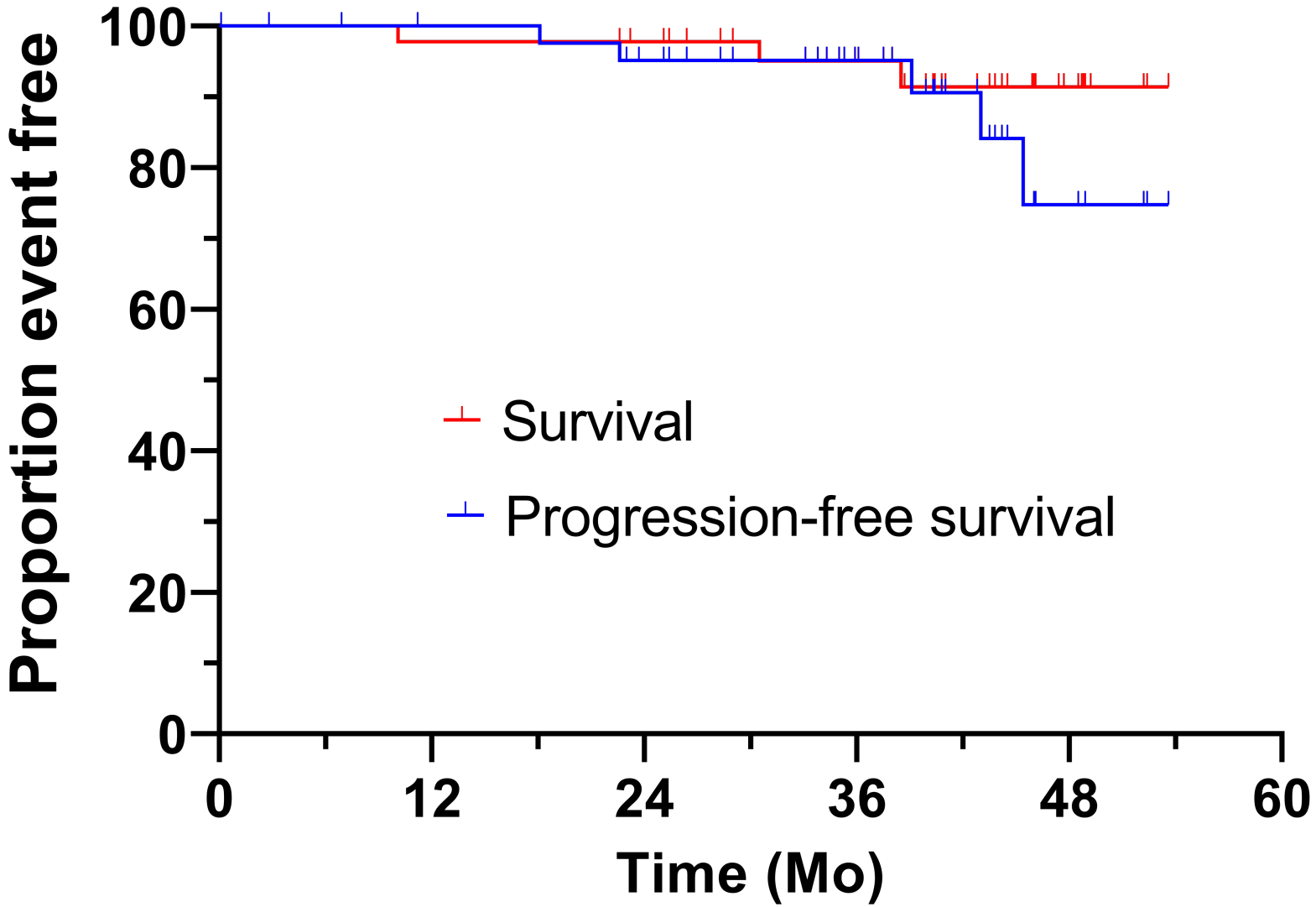
- Best cumulative rate of U-MRD4 in bone marrow was 33/45 (73%)

- **32/45 (71%) had U-MRD4 at the completion of venetoclax**

Thompson et al. ASH 2022, Abstract #96

Venetoclax added to ibrutinib in high-risk CLL

PFS and OS

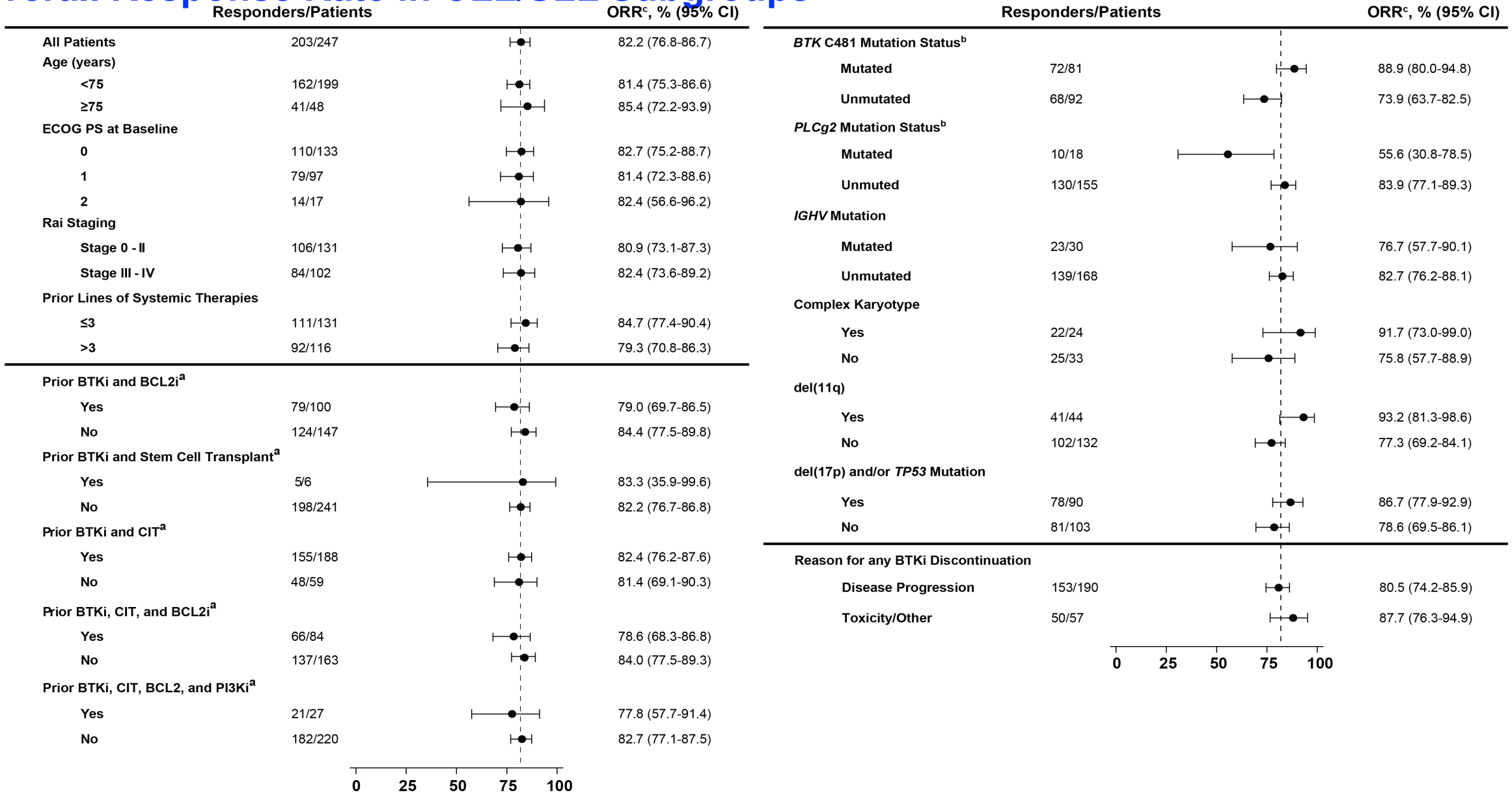


Causes of death:

1. Metastatic melanoma
2. AML
3. Unknown in a patient who was lost to follow-up

Thompson et al. ASH 2022, Abstract #96

Pirtobrutinib:
Overall Response Rate in CLL/SLL Subgroups



Data cutoff date of 29 July 2022. [a]Prior therapy labels indicate that patients received at least the prior therapy, rows are not mutually exclusive. [b]Patients with available mutation data who progressed on any prior BTKi. [c]Response includes partial response with lymphocytosis. Response status per iwCLL 2018 according to independent review committee assessment.

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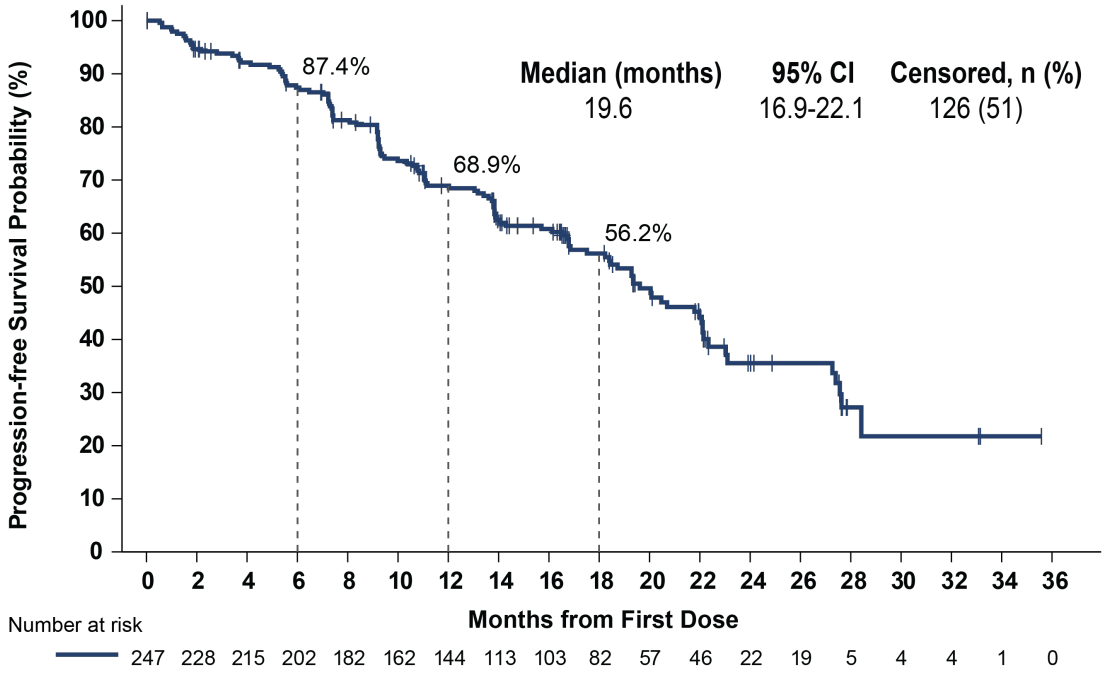
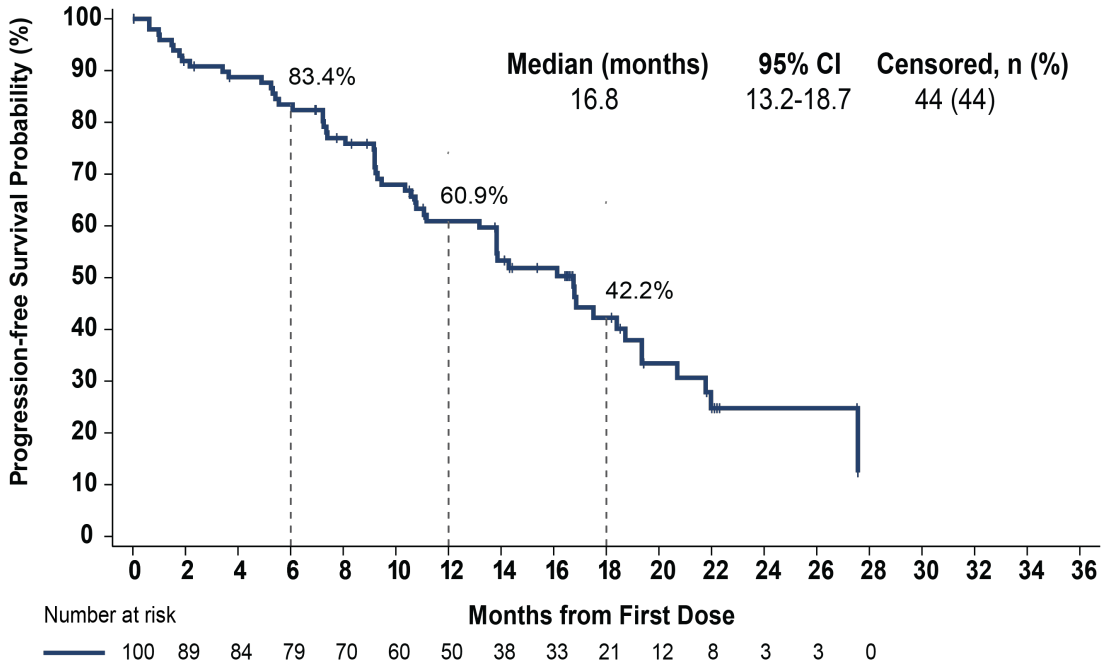
Pirtobrutinib:
Progression-Free Survival in CLL/SLL Patients who Received Prior BTKi Treatment

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.

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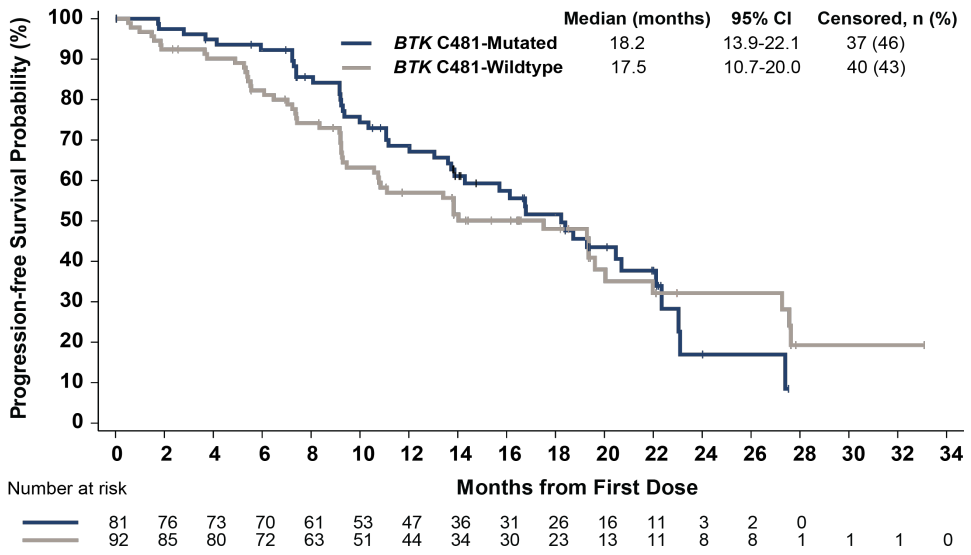
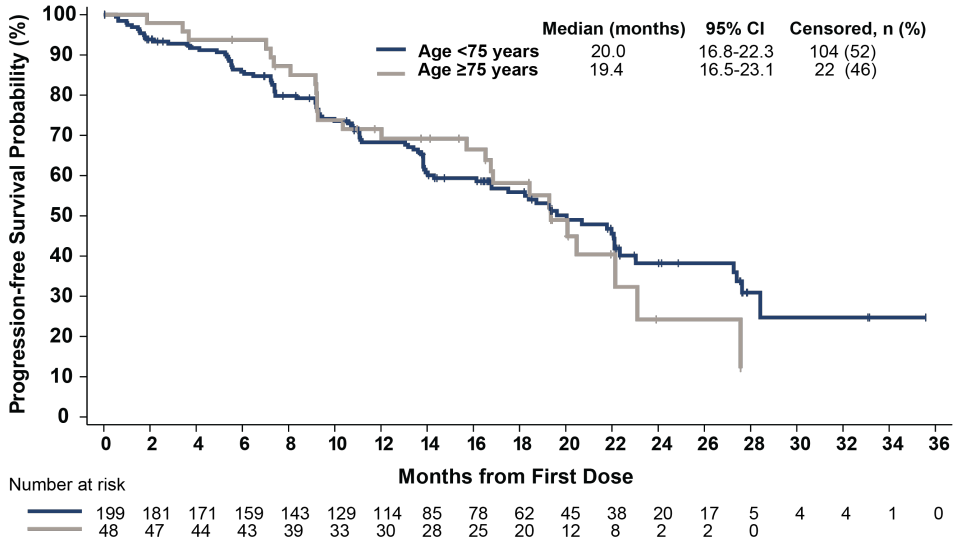
Pirtobrutinib: Progression-Free Survival in CLL/SLL Subgroups

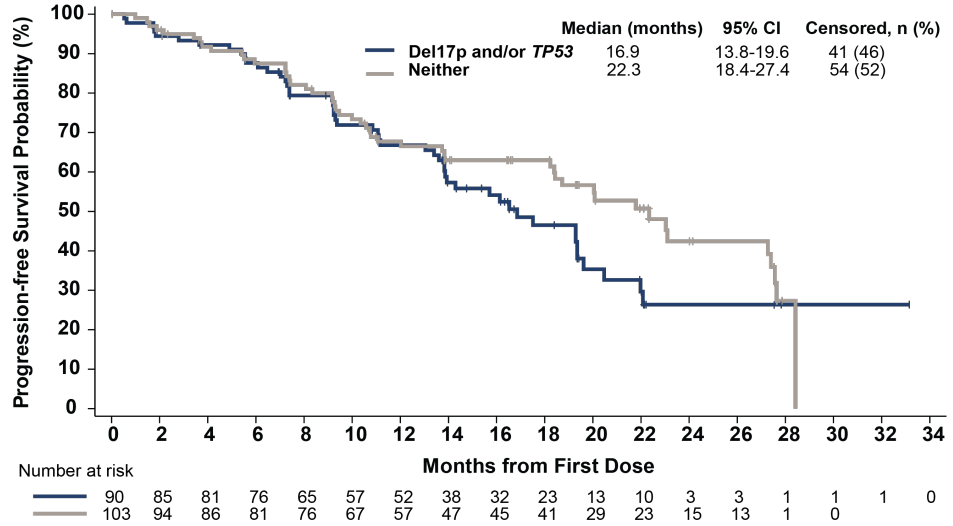
BTK C481 mutation status[a,b]



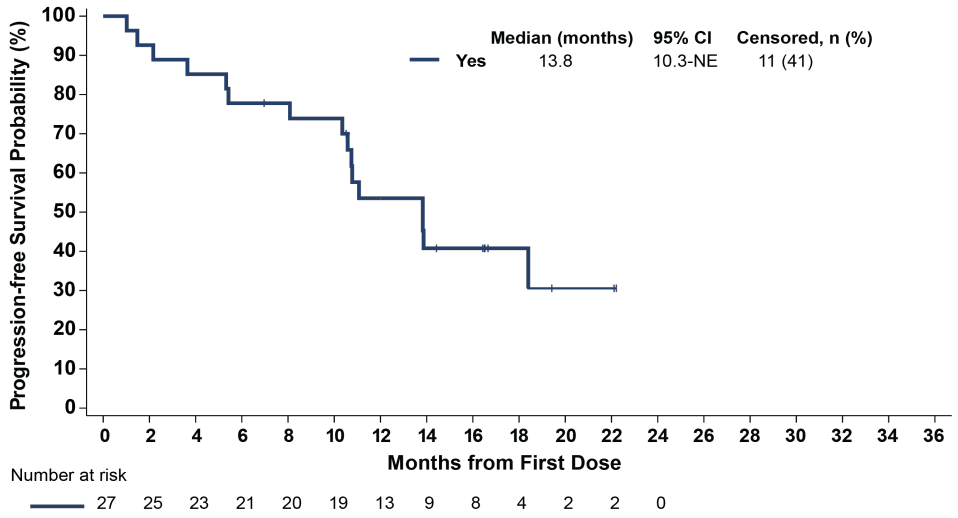
Age



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



Prior BTKi, CIT, BCL2i, and PI3Ki therapy



Data cutoff date of 29 July 2022. Response status per iwCLL 2018 according to independent review committee assessment. [a]*BTK* C481 mutation status, del(17p), and *TP53* mutation status were centrally determined and based on pre-treatment samples. [b]Patients with available mutation data who progressed on any prior BTKi.

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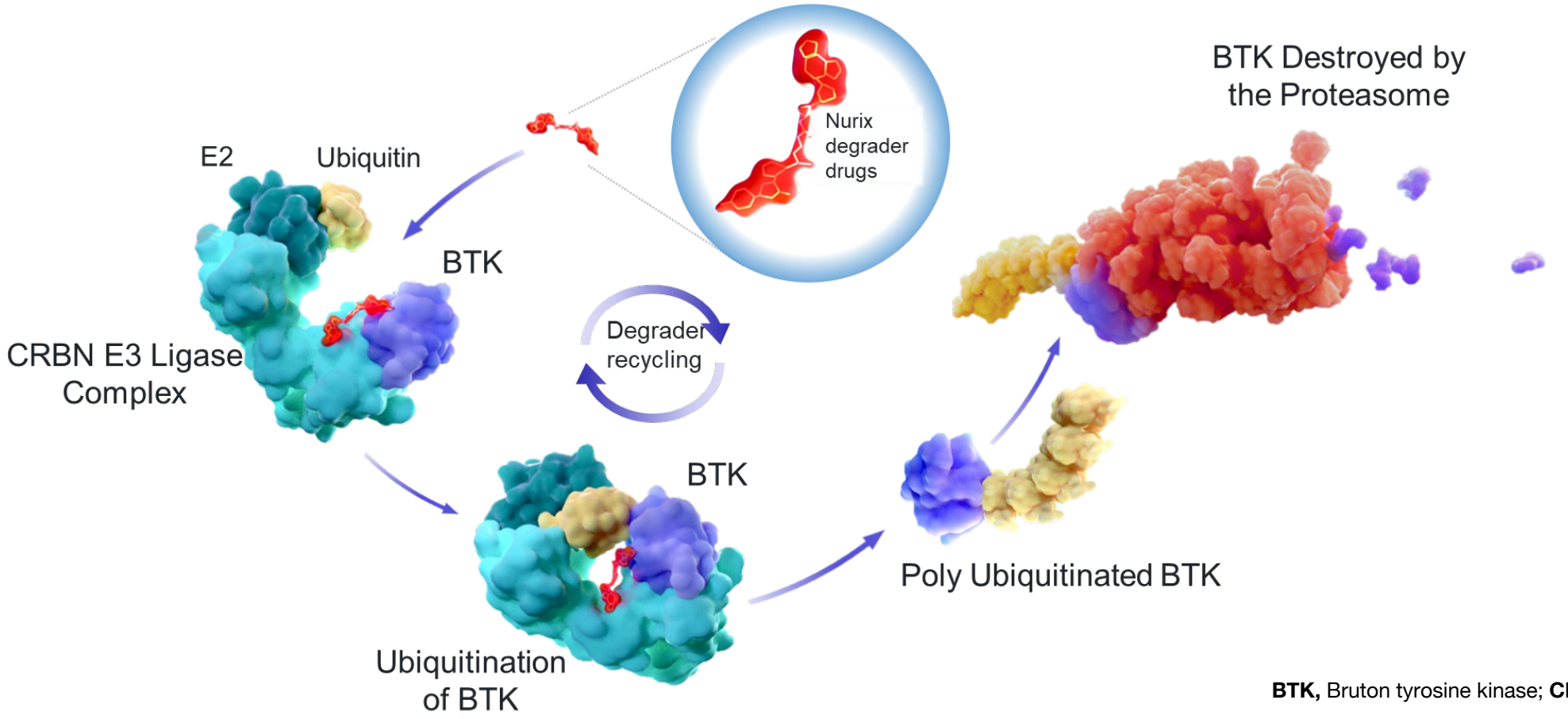
NX-2127: first-in-class targeted protein degrader of BTK

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



BTK, Bruton tyrosine kinase; **CRBN,** cereblon

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NX-2127 safety summary (all participants) by dose

AEs: all grades, n (%)	All doses (n=36)	100 mg* (n=22)	200 mg (n=8)	300 mg (n=6)
Fatigue	19 (53)	13 (59)	5 (63)	1 (17)
Neutropenia[a]	14 (39)	5 (23)	5 (63)	4 (67)
Contusion[b]	10 (28)	4 (18)	3 (38)	3 (50)
Thrombocytopenia[c]	9 (25)	5 (23)	2 (25)	2 (33)
Hypertension	9 (25)	5 (23)	2 (25)	2 (33)
Anemia	8 (22)	6 (27)	2 (25)	0
Constipation	7 (19)	7 (32)	0	0
Dyspnea	7 (19)	4 (18)	3 (38)	0
Pruritis	7 (19)	5 (23)	1 (13)	1 (17)
Atrial fibrillation/Atrial flutter[d]	6 (17)	3 (14)	2 (25)	1 (17)
Diarrhea	6 (17)	5 (23)	1 (13)	0
Petechiae	6 (17)	4 (18)	1 (13)	1 (17)
Rash	6 (17)	5 (23)	1 (13)	0

[a]Aggregate of "neutropenia" and "neutrophil count decreased" [b] Includes episodes of bruising and other similar verbatim terms [c]Aggregate of "thrombocytopenia" and "platelet count decreased" [d]Cases were confounded by risk factors such as: age >80 years (4 cases), history of hypertension (4 cases), male sex (3 cases), and history of prior AF on ibrutinib (2 cases)
*18 of the 22 patients treated at the 100 mg qd dose had CLL

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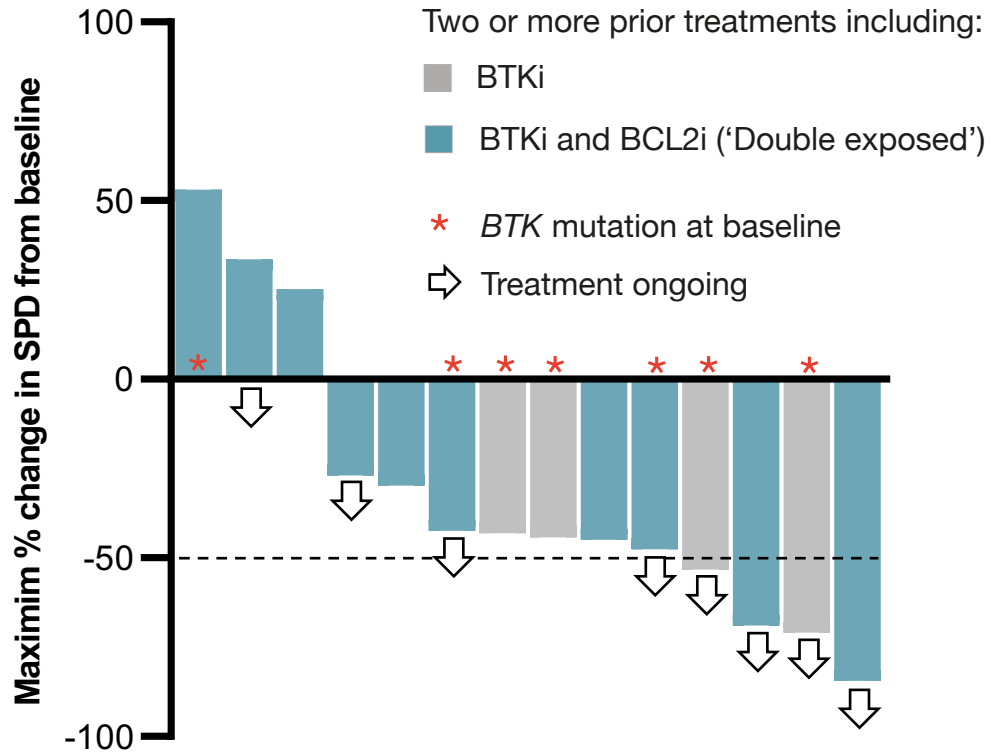
Data cutoff: September 21, 2022

NX-2127 preliminary efficacy (patients with CLL)

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

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



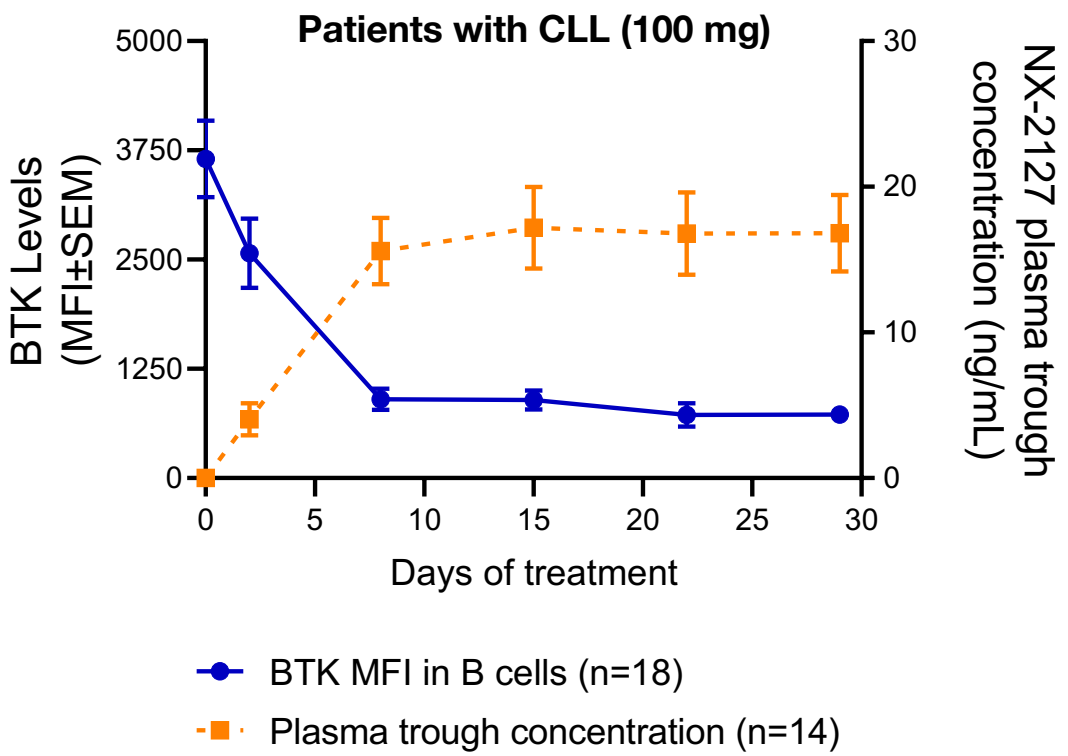
***One patient, not shown above, with prior BTKi and BCL2i treatment and with a *BTK* mutation detected at baseline, had no nodal disease at baseline. Their treatment is ongoing with a PR**

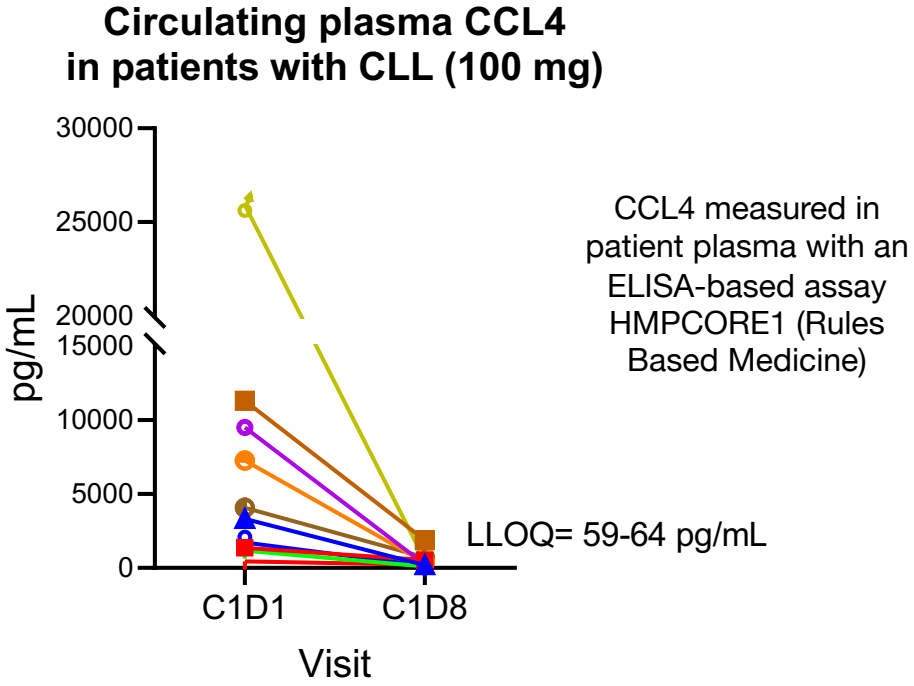
BCL2i, B-cell lymphoma-2 inhibitor; **BTK**, Bruton's tyrosine kinase; **BTKi**, BTK inhibitor; **CR**, complete response; **CRi**, complete response with incomplete count recovery; **NE**, not evaluable; **PD**, progressive disease; **PR**, partial response; **SD**, stable disease

Mato et al. ASH 2022, Abstract #965

Data cutoff: September 21, 2022

NX-2127 leads to robust BTK degradation and decrease in B-cell activation





- Daily treatment with NX-2127 resulted in a fast and sustained suppression of BTK (CD19+) as measured in patient whole blood using a flow cytometry assay. BTK suppression target of 80% reached consistently (data not shown here)
- Robust decrease of plasma CCL4 by Cycle 1 Day 8 and suppression was maintained through Cycle 2 Day 1, consistent with clinically observed lymphocytosis occurring in majority of patients with nodal disease by Cycle 1 Day 8
- NX-2127 treatment also resulted in degradation of cereblon neo-substrate Ikaros

BTK, Bruton's tyrosine kinase; **CCL4**, C–C motif ligand 4; **LLOQ**, lower limit of quantification

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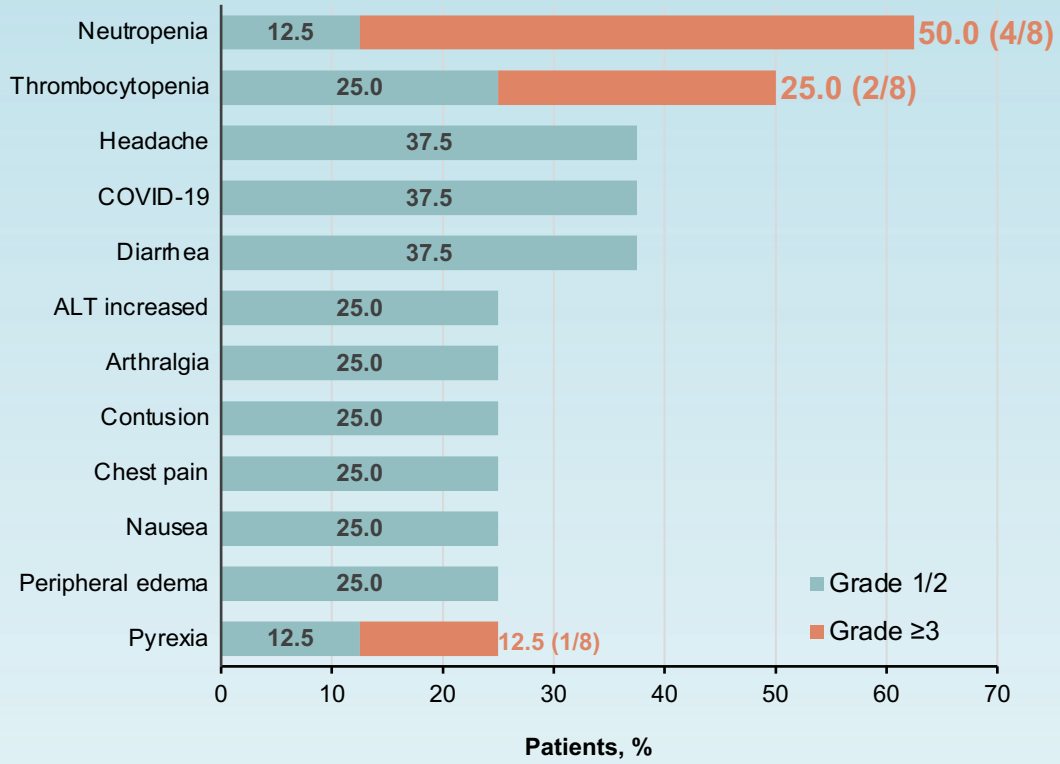
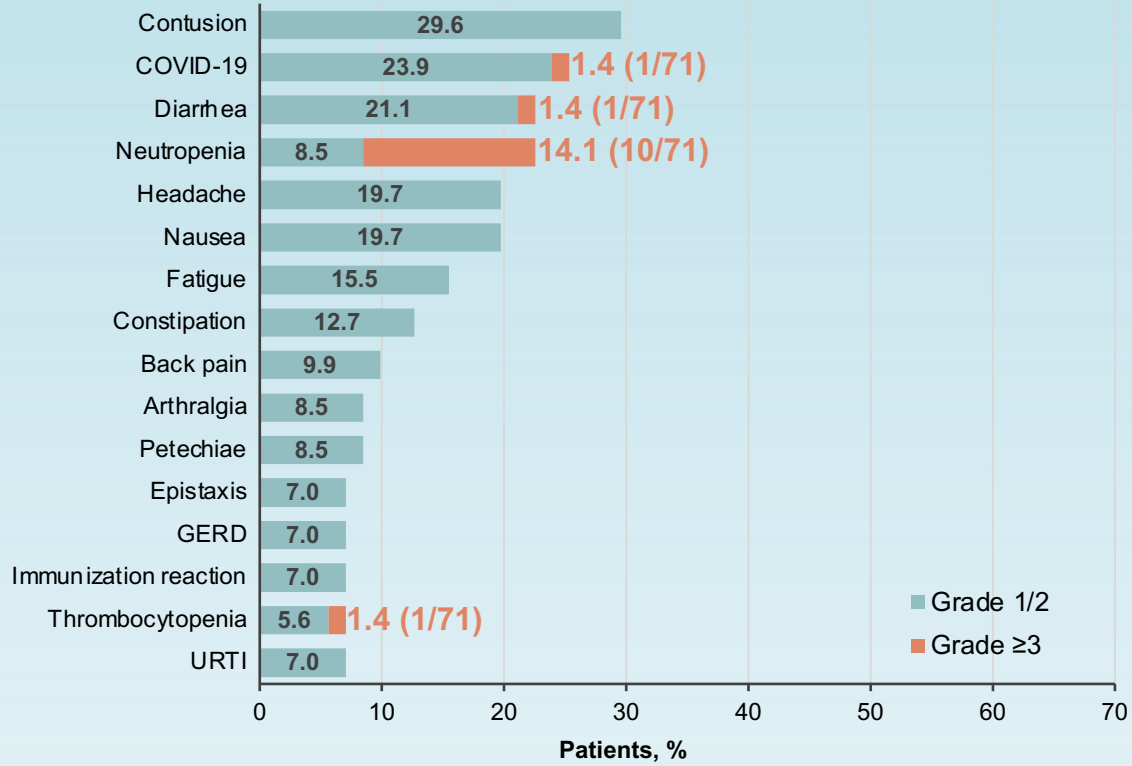
Data cutoff: September 21, 2022

BGB-11417 (BCL2i) ± Zanubrutinib
Most Frequent Adverse Events

BGB-11417 Monotherapy, n=8
(Events in ≥2 Patients)



BGB-11417 + Zanubrutinib, n=71[a,b]
(Events in ≥5 Patients)



[a]Includes 21 patients who are still in zanubrutinib pretreatment phase and have not yet received BGB-11417. [b]Includes 46 patients who are TN.

Cheah et al. ASH 2022, Abstract #962

BGB-11417 (BCL2i) ± Zanubrutinib
Overall Response Rate

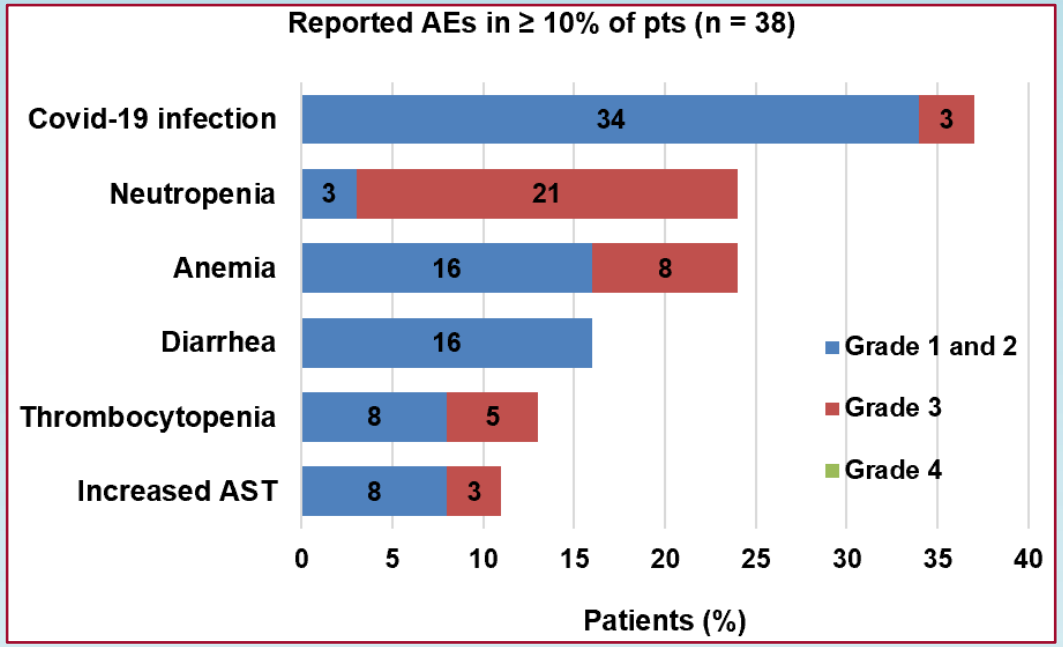
Response, n (%)	R/R BGB-11417 (n=8)	R/R BGB-11417 + zanubrutinib (n=25)	TN BGB-11417 + zanubrutinib (n=46)
Treated with BGB-11417	**8**	**24**	**26**
Efficacy evaluable	**6**	**20[a]**	**11[a]**
ORR, n (%)	4 (67)	19 (95)	11 (100)
CR	2 (33)[b]	6 (30)[c]	2 (18)[d]
PR	2 (33)[e]	13 (65)[f]	9 (82)[g]
SD	2 (33)	1 (5)	0
PD	0	0	0
Median follow-up, months (range)	13.4 (1.4-21.9)	11.1 (2.2-18.6)	3.5 (0.4-9.7)

[a]n=2 (R/R) and n=11 (TN) have responded after zanubrutinib pretreatment but have not yet had response assessment on combination treatment: they are not included here. [b]40 mg: n=1; 80 mg: n=1. [c] 40 mg: n=1; 80 mg: n=2; 160 mg: n=3. [d] 160 mg: n=2. [e]40 mg: n=1; 80 mg: n=1. [f] 40 mg: n=2; 80 mg: n=3; 160 mg: n=3 ; 320 mg: n=5. [g]160 mg: n=9.
CR, complete response; ORR, overall response rate; PR, partial response; SD, stable disease.

Cheah et al. ASH 2022, Abstract #962

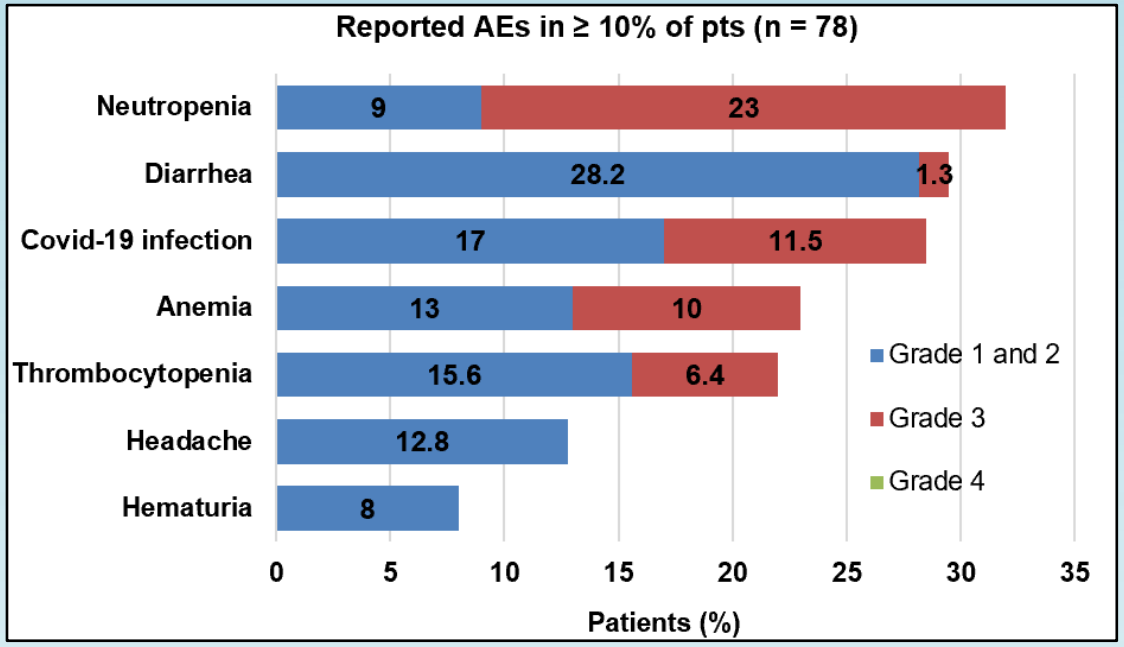
Lisaftoclax Safety: Combinations

Rituximab + Lisaftoclax



Grade 3/4 AEs in ≥ 2% of pts, no. (%)	
Neutropenia	8 (21)
Clinical TLS	1 (2.7)

Acalabrutinib + Lisaftoclax



Grade 3/4 AEs in ≥ 2% of pts, no. (%)	
Neutropenia	18 (23)
Covid-19 infection	9 (11.5)
Atrial fibrillation	3 (3.8)
Abscess	2 (3)

AST, aspartate aminotransferase
TLS, tumor lysis syndrome

Davids et al. ASH 2022, Abstract #964

Lisaftoclax: Efficacy Summary

	Monotherapy	Combined with rituximab	Combined with acalabrutinib	
Response Evaluable	**R/R n=43**	**R/R n=34**	**R/R n=57**	**TN n=16**
Median (range) treatment duration	16.5 (1-36)	11 (1-21)	12 (1-24)	7 (5-11)
Overall Response Rate n, (%)	29/43 (67)	27/34 (79)	56/57 (98)	16/16 (100)
Biological Characteristics, no. (%)				
TP53-mutated and/or del(17p)	N/A	5/6 (83)	11/12 (92)	4/4 (100)
Complex karyotype (≥ 3 abnormities)	N/A	5/5 (100)	15/16 (94)	7/7 (100)
Unmutated IGHV	N/A	N/A	23/25 (92)	9/9 (100)
Mutated IGHV	N/A	N/A	13/13 (100)	3/3 (100)
BTKi resistant or intolerant	4/6 (67)	0/4 (0)	7/8 (88)	N/A

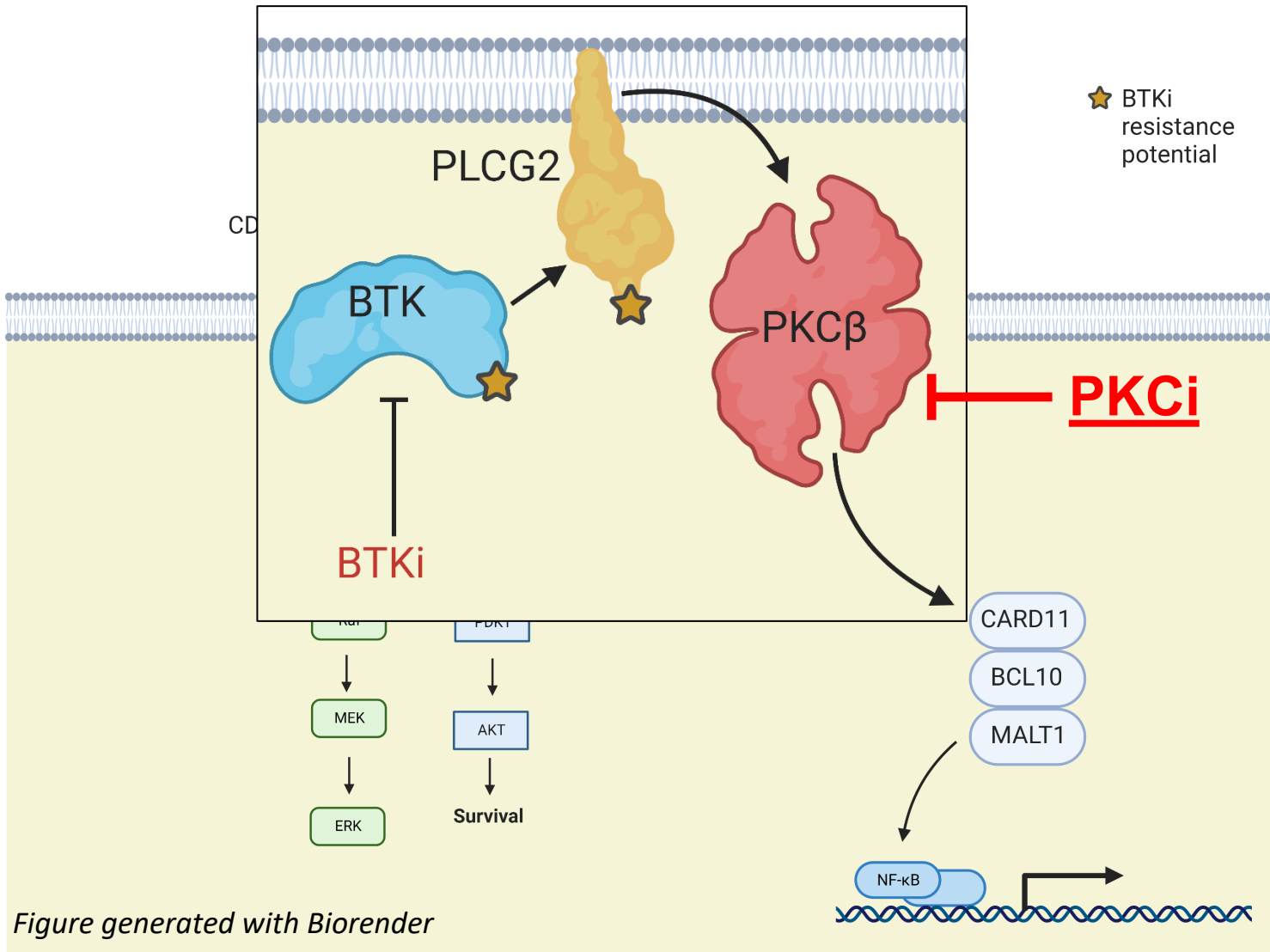
Data on iwCLL CR and MRD rates not yet available

Davids et al. ASH 2022, Abstract #964

Protein Kinase C-beta Background

Resistance mutations are upstream of PKCβ

Inhibition of PKCβ has potential to overcome mutation-driven resistance



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PKCβi (MS-553)

Safety Profile in Depth

- 14 pts (33%) had Gr 3-4 TR-AE
- One Grade 4 related AE: Neutropenia
- One DLT occurred at 350 mg BID
- MTD was not reached
- RP2D of 250 mg BID was selected
- Six patients were dosed at above RP2D with drug withdrawn on 3 patients

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PKCβi (MS-553)
Efficacy

	R/R Mono	
Efficacy evaluable patients*	CLL/SLL N=23	Richter's N=3
Best Response	n(%)	
CR	0	0
PR	6 (26)	1 (33)
PRL	5 (22)	0
SD	11 (48)	0

48

* Efficacy evaluable patients are patients who have completed at least one cycle of study drug treatment or had at least one response assessment with data cutoff as of June 20, 2022

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Conclusions

- Combined targeted therapy highly active in first-line and R/R CLL, not standard of care
- First-line VEN-based treatment is active (ORR and uMRD) across all subgroups; independent association of U-IGHV, *NOTCH1, BRAF/NRAS/KRAS* mutations, hCKT (≥5 abberations), and chromosome translocations with shorter PFS
- Consolidation with venetoclax feasible in patients on IBR ≥12 months with potential clinical benefit
- Pirtobrutinib efficacy in prior BTKi-treated CLL
- BTK-degrader (NX-2127) tolerated with activity
- New BCL2 inhibitors (BCL2i) (BGB-11417 and Lisaftoclax) have activity and being combined with BTKi and CD20 mAb
- Protein kinase C-beta inhibitor (PKCβi) - MS-553 tolerated with activity in BTKi-treated CLL