UCI 趙 Chao Family Comprehensive Cancer Center

Updates in CLL from #ASH24

Has SOC changed?

Elizabeth Brem, MD
Associate Clinical Professor

Disclosures

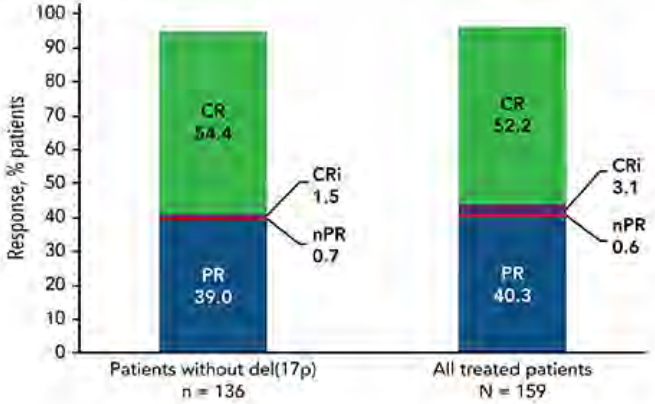
- **Speakers Bureau:** AstraZeneca, AbbVie/Genmab, BMS
- **Advisory Boards:** BeiGene, AstraZeneca, ADC Therapeutics, Caribou Biosciences, Poseida
- **Consulting:** Caribou Biosciences, Regeneron, Genetech, Incyte
- **Promotional Services Provided:** AstraZeneca

Ibrutinib + Venetoclax

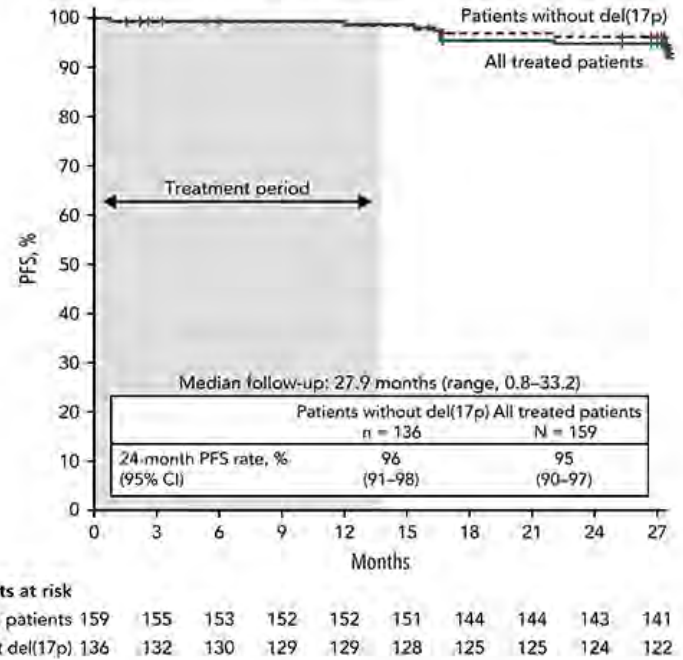
2021-2023: CAPTIVATE (fixed-duration)

Best overall response rates with fixed-duration ibrutinib + venetoclax as assessed by investigators

Best response, % (95% CI)	Patients without del(17p) n = 136	All treated patients N = 159
CR/CRi	56 (48–64)	55 (48–63)
ORR	96 (92–99)	96 (93–99)
Duration of CR ≥12 cycles, n/N (%)	66/76 (87)	78/88 (89)



PFS with fixed-duration ibrutinib + venetoclax as assessed by investigators



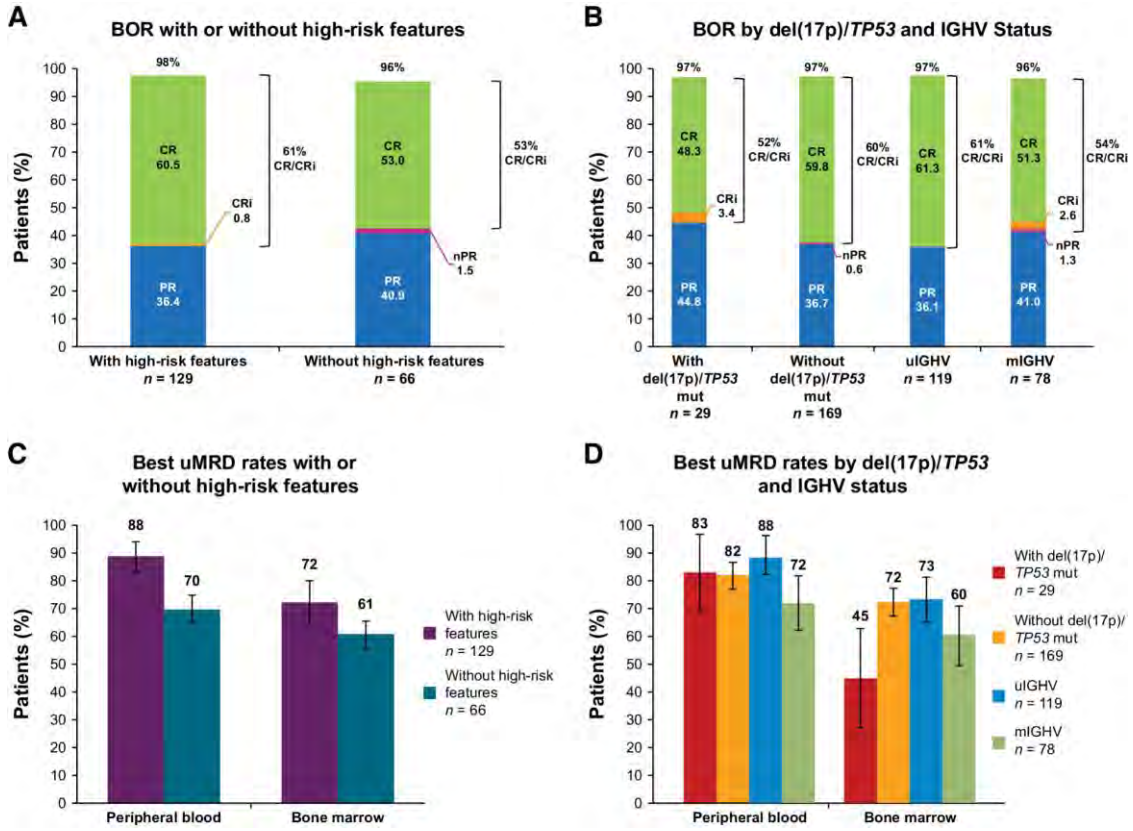
Key safety outcomes

- **Completed all planned treatment:** 92%
- **Median treatment duration:** 13.8 months (range, 0.5–24.9)
- **Most common AEs (any grade):** diarrhea (62%), nausea (43%), neutropenia (42%), and arthralgia (33%)
- **Most common grade 3/4 AEs:** neutropenia (33%), hypertension (6%), and neutrophil count decreased (5%)

AE, adverse event; CR, complete response; CRi, complete response with incomplete bone marrow recovery; nPR, nodular partial response; ORR, objective response rate; PFS, progression-free survival; PR, partial response.

Tam CS et al, Blood, 2023.

CAPTIVATE: High Risk



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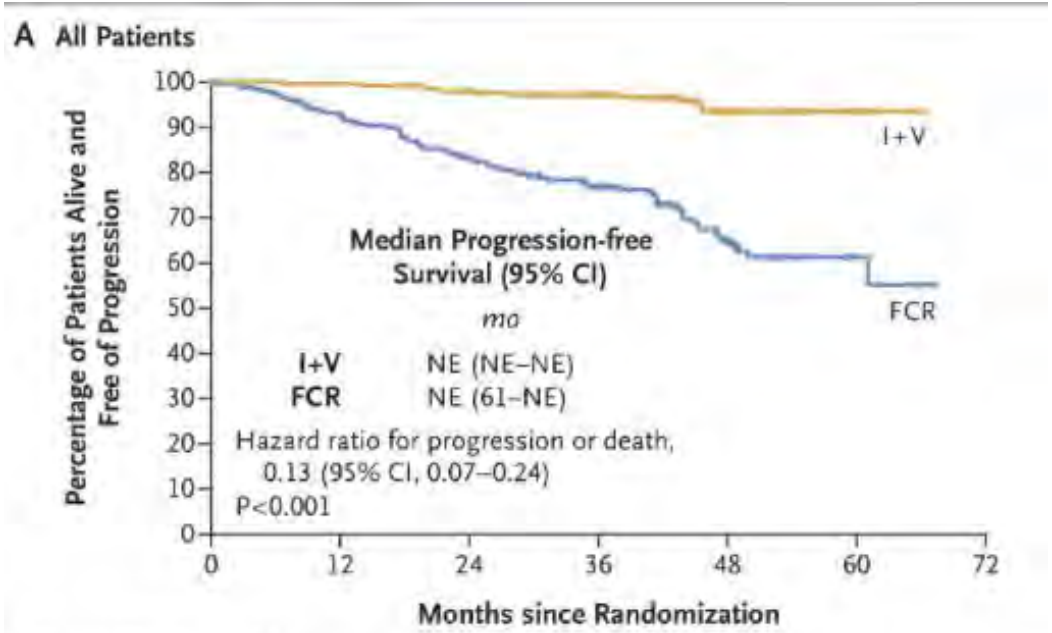
Allan JN et al, Cancer Res, 2023.

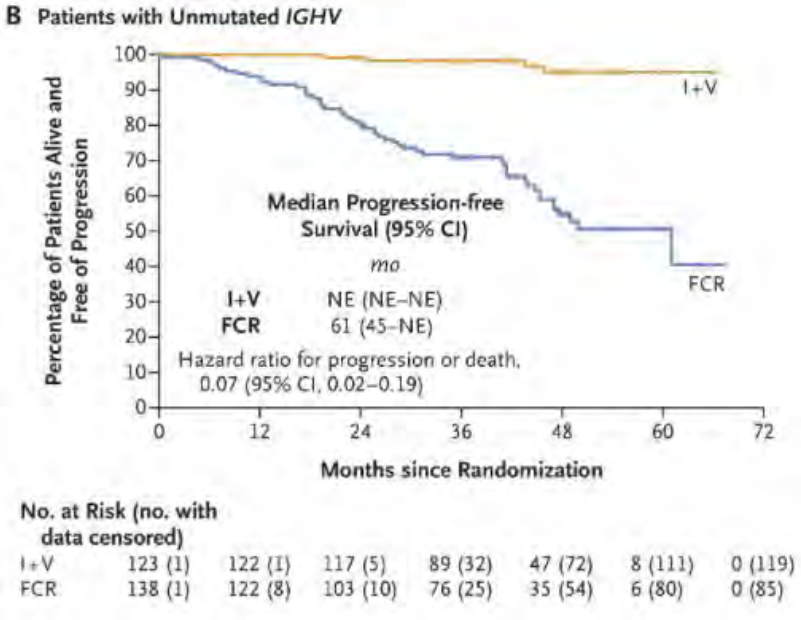
2021-2023: FLAIR

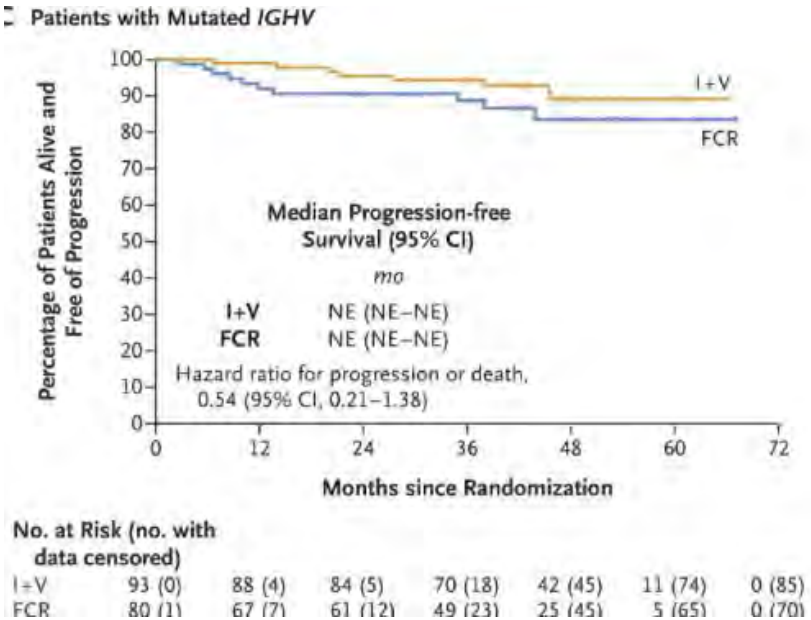
*updated at ASH: abstract 585



Munir T et al, NEJM, 2023

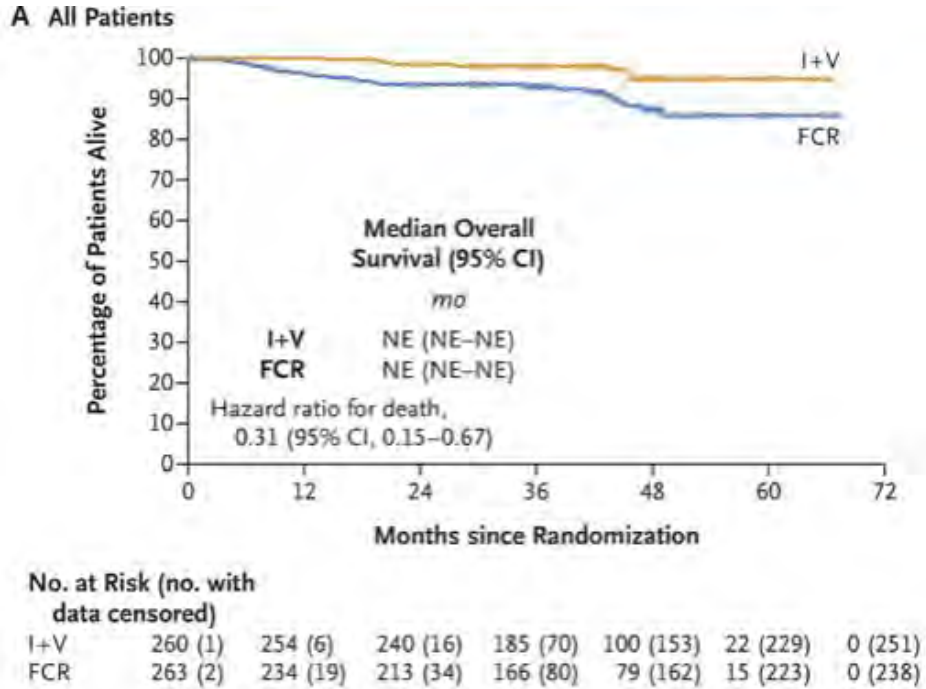
2021-2023: FLAIR (PFS)





Munir T et al, NEJM, 2023

2021-2023: FLAIR (OS)



Munir T et al, NEJM, 2023

NCCN v1.2025

SUGGESTED TREATMENT REGIMENS[a,b,c,d]
CLL/SLL Without del(17p)/*TP53* Mutation
(alphabetical by category)

FIRST-LINE THERAPY[e]		
Preferred Regimens	**Other Recommended Regimens**	**Useful in Certain Circumstances**
• cBTKi ▸ Acalabrutinib[f,g,*] ± obinutuzumab (category 1) ▸ Zanubrutinib[f,g,*] (category 1) • Venetoclax[f,h] + obinutuzumab (category 1)	• cBTKi ▸ Ibrutinib [f,g,i,*](category 1) • Ibrutinib[f,g,*] + venetoclax[f,h]	• Consider for IGHV-mutated CLL in patients aged <65 y without significant comorbidities ▸ FCR (fludarabine, cyclophosphamide, rituximab)[j,k] • Ibrutinib[f,g,*] + anti-CD20 mAb (category 2B)[l] • Consider when cBTKi and venetoclax are not available or contraindicated or rapid disease debulking needed ▸ Bendamustine[m] + anti-CD20 mAb[l,n] ▸ Obinutuzumab ± chlorambucil[o] ▸ High-dose methylprednisolone (HDMP) + anti-CD20 mAb[l] (category 2B; category 3 for patients <65 y without significant comorbidities)

* Covalent BTKi (cBTKi).

NCCN v1.2025

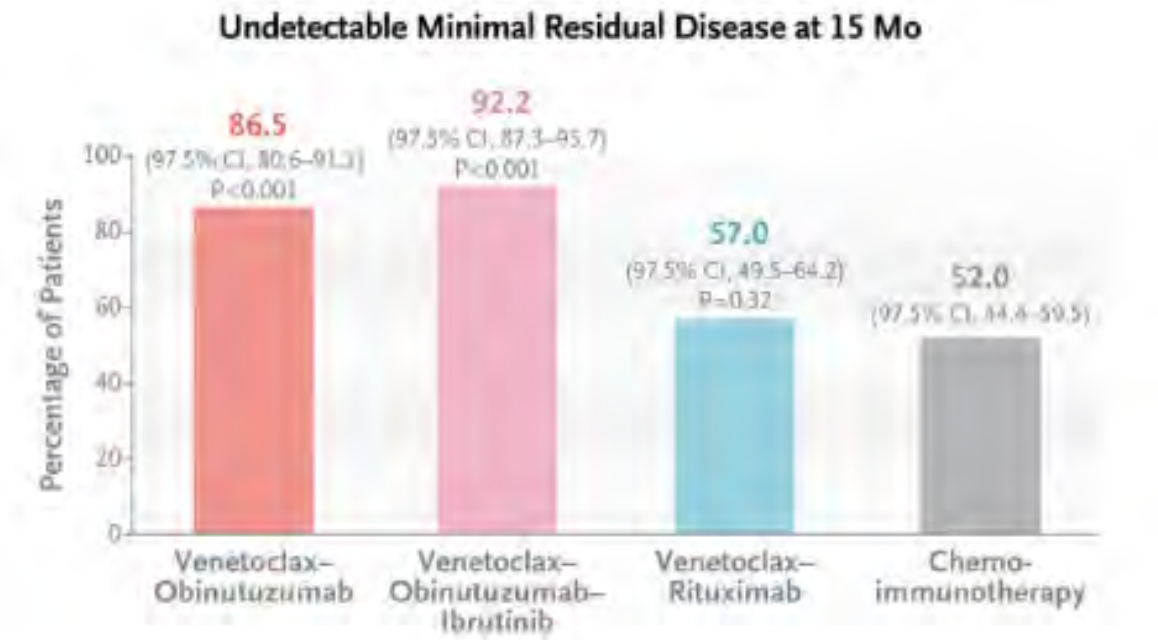
SUGGESTED TREATMENT REGIMENS[a,b,c,d]
CLL/SLL With del(17p)/*TP53* Mutation
(alphabetical by category)
CIT is not recommended since del(17p)/*TP53* mutation is associated with low response rates.

FIRST-LINE THERAPY[e]		
Preferred Regimens	**Other Recommended Regimens**	**Useful in Certain Circumstances**
• cBTKi ▸ Acalabrutinib[f,g] ± obinutuzumab ▸ Zanubrutinib[f,g] • Venetoclax[f,h] + obinutuzumab	• cBTKi ▸ Ibrutinib[f,g,i] • Ibrutinib[f,g,*] + venetoclax[f,h]	• Consider when cBTKi and venetoclax are not available or contraindicated or rapid disease debulking needed ▸ HDMP + anti-CD20 mAb[l] ▸ Obinutuzumab

Why didn’t I+V become widely adopted?

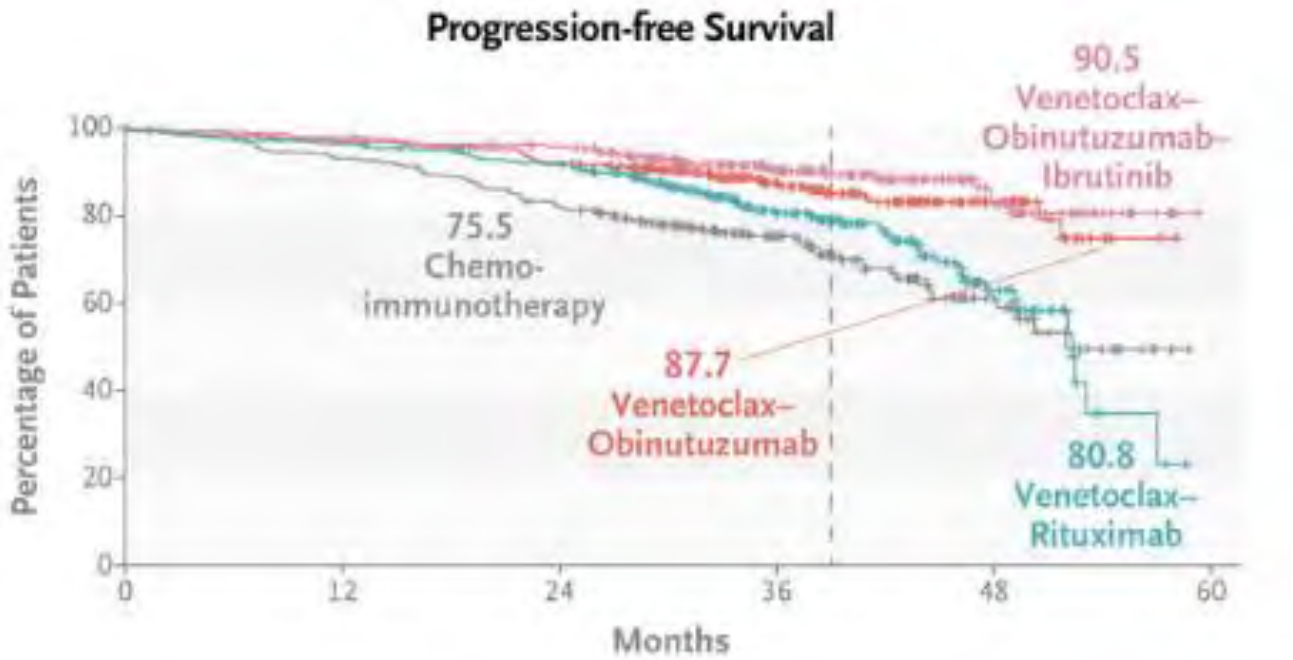
- **no FDA approval
- General movement away from ibrutinib
- Comfort with ongoing cBTKi
  - Especially for high risk features
  - Fear of ven?
- Confusion — studies varied in terms of duration of therapy, MRD assays used, etc

Triple vs Doublet



Eichhorst B et al, NEJM, 2023

Does MRD negativity translate to PFS?



Eichhorst B et al, NEJM, 2023

2024-2025: AMPLIFY

Abstract 1009

AMPLIFY Study Design

TN CLL (N=867)

Key inclusion criteria
- Age ≥18 years
- TN CLL requiring treatment per iwCLL 2018 criteria[1]
- Without del(17p) or *TP53*[a]
- ECOG PS ≤2

Key exclusion criteria
- CIRS-Geriatric >6
- Significant cardiovascular disease

Stratification
- Age (>65 vs ≤65 years)
- IGHV mutational status
- Rai stage (≥3 vs <3)
- Geographic region

AMPLIFY: randomized, multicenter, open-label, Ph 3 trial

RANDOMIZE 1:1:1

- AV (14 cycles)
- AVO (14 cycles)
- FCR/BR (6 cycles)

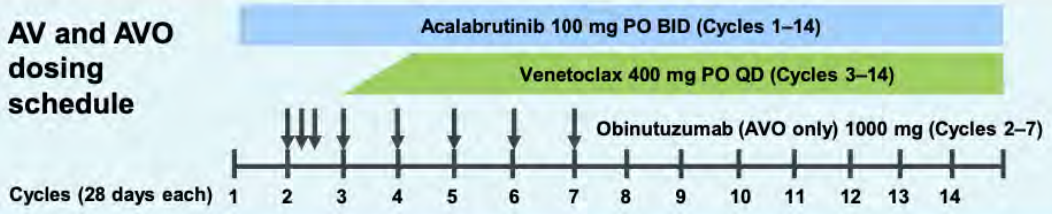
Crossover not built into protocol

Primary endpoint: IRC-assessed PFS (AV vs FCR/BR)

If primary endpoint met, secondary endpoints tested in fixed sequential hierarchy:

1) IRC-PFS (AVO vs FCR/BR)
2) uMRD (AV vs FCR/BR)
3) uMRD (AVO vs FCR/BR)
4) OS (AV vs FCR/BR)
5) OS (AVO vs FCR/BR)

AV and AVO dosing schedule



NCT03836261. Data cutoff: April 30, 2024.

[a]Assayed by central lab.

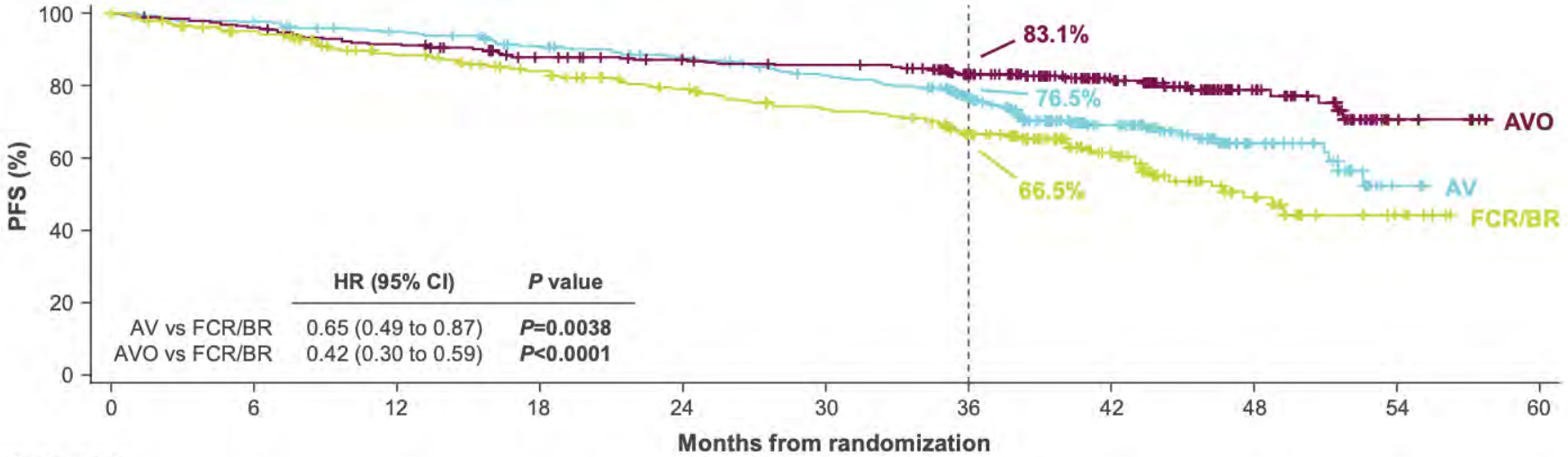
AV, acalabrutinib-venetoclax; AVO, acalabrutinib-venetoclax-obinutuzumab; BR, bendamustine-rituximab; CIRS-Geriatric, Cumulative Illness Rating Scale-Geriatric; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; FCR, fludarabine-cyclophosphamide-rituximab; IGHV, immunoglobulin heavy-chain variable region gene; iwCLL, International Working Group on CLL; OS, overall survival; PFS, progression-free survival; TN, treatment-naive; uMRD, undetectable measurable residual disease.

1. Hallek M, et al. *Blood*. 2018;131:2745-60.

Demographics and Baseline Characteristics

Characteristic	AV (n=291)	AVO (n=286)	FCR/BR (n=290)
Age, median (range), yr	61 (31–84)	61 (29–81)	61 (26–86)
≤65 yr	212 (72.9)	210 (73.4)	213 (73.4)
>65 yr	79 (27.1)	76 (26.6)	77 (26.6)
Male sex	178 (61.2)	198 (69.2)	183 (63.1)
ECOG PS score			
0–1	262 (90.0)	272 (95.1)	262 (90.3)
2	28 (9.6)	14 (4.9)	26 (9.0)
Geographic region*			
Europe	184 (63.2)	179 (62.6)	183 (63.1)
North America	50 (17.2)	51 (17.8)	50 (17.2)
Other	57 (19.6)	56 (19.6)	57 (19.7)
Rai stage			
0–II	154 (52.9)	170 (59.4)	163 (56.2)
III–IV	137 (47.1)	116 (40.6)	127 (43.8)
del(11q) present	51 (17.5)	56 (19.6)	46 (15.9)
Unmutated IGHV	167 (57.4)	169 (59.1)	172 (59.3)
Complex karyotype (≥3 aberrations)	45 (15.5)	46 (16.1)	42 (14.5)

IRC-assessed PFS

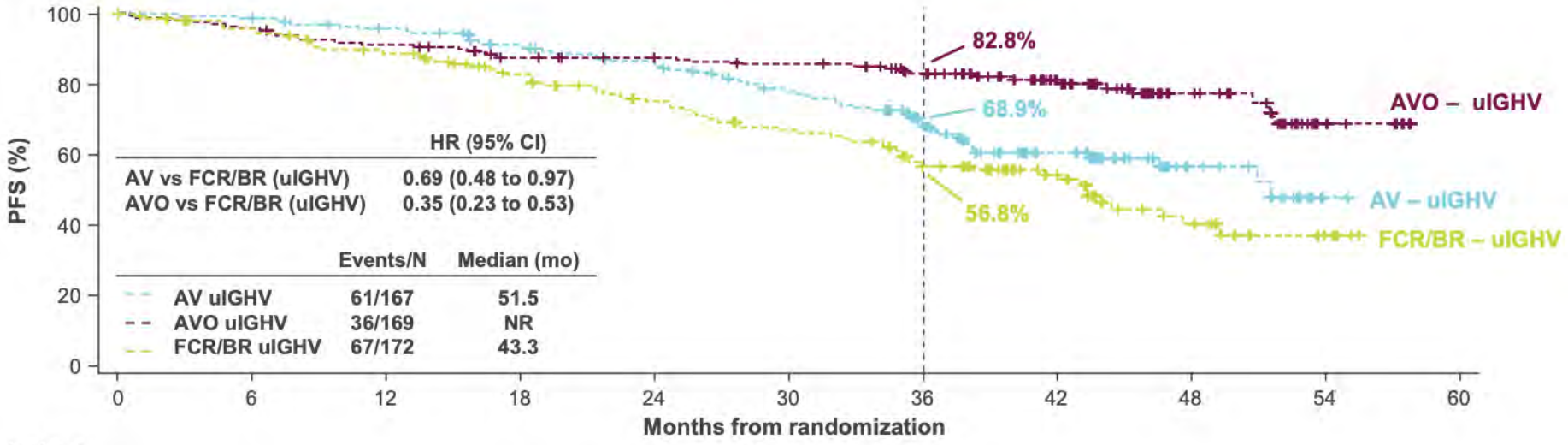


Patients at risk

AV	291	282	269	251	237	219	177	102	35	3	0
AVO	286	272	258	237	225	219	191	116	51	7	0
FCR/BR	290	236	208	189	170	154	127	66	28	6	0

Median PFS was NR for AV and AVO, and was 47.6 mo for FCR/BR

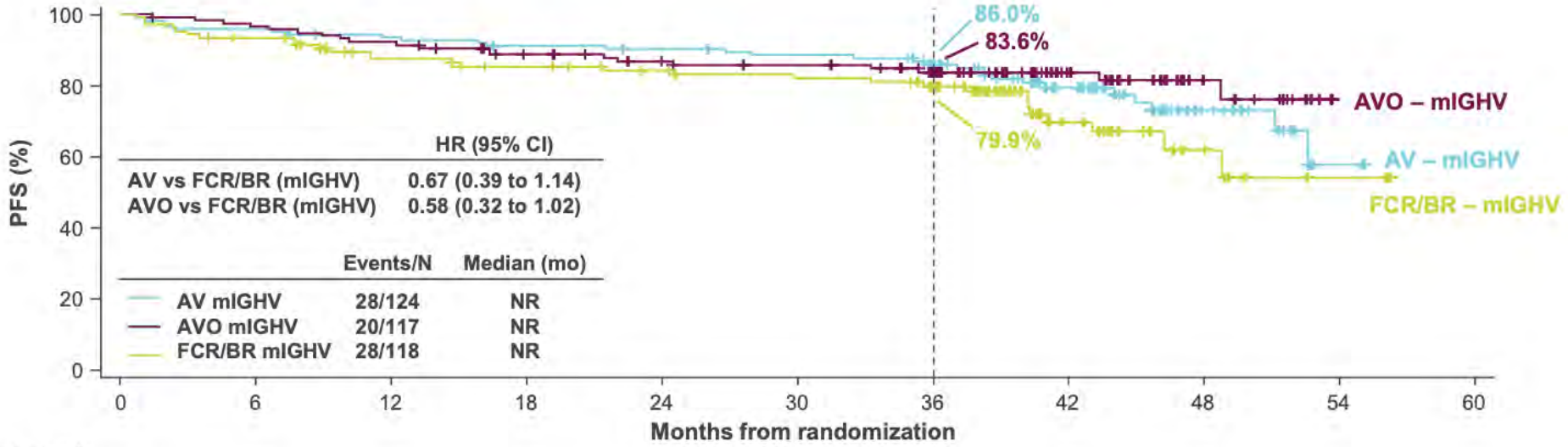
PFS in the uIGHV Subgroup



Patients at risk

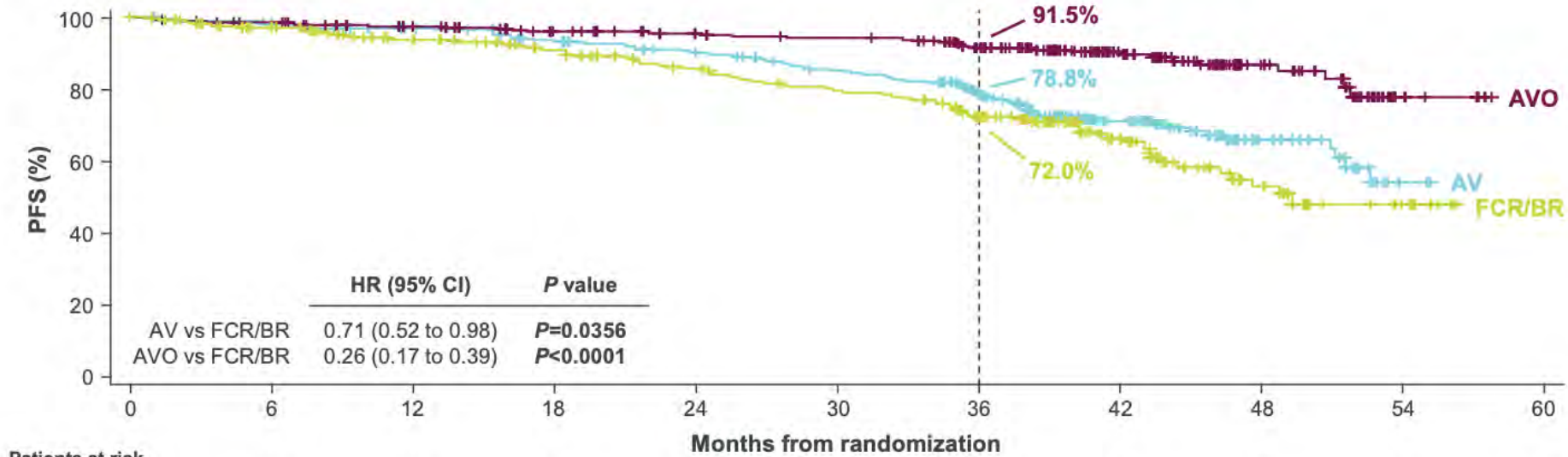
AV uIGHV	167	163	155	141	129	114	86	48	17	1	0
AVO uIGHV	169	161	152	141	136	133	118	75	36	7	0
FCR/BR uIGHV	172	137	122	108	94	82	62	38	19	4	0

PFS in the mIGHV Subgroup



Patients at risk											
AV mIGHV	124	119	114	110	108	105	91	54	18	2	0
AVO mIGHV	117	111	106	96	89	86	73	41	15	0	
FCR/BR mIGHV	118	99	86	81	76	72	65	28	9	2	0

PFS Censoring COVID-19 Deaths (Prespecified Analysis)

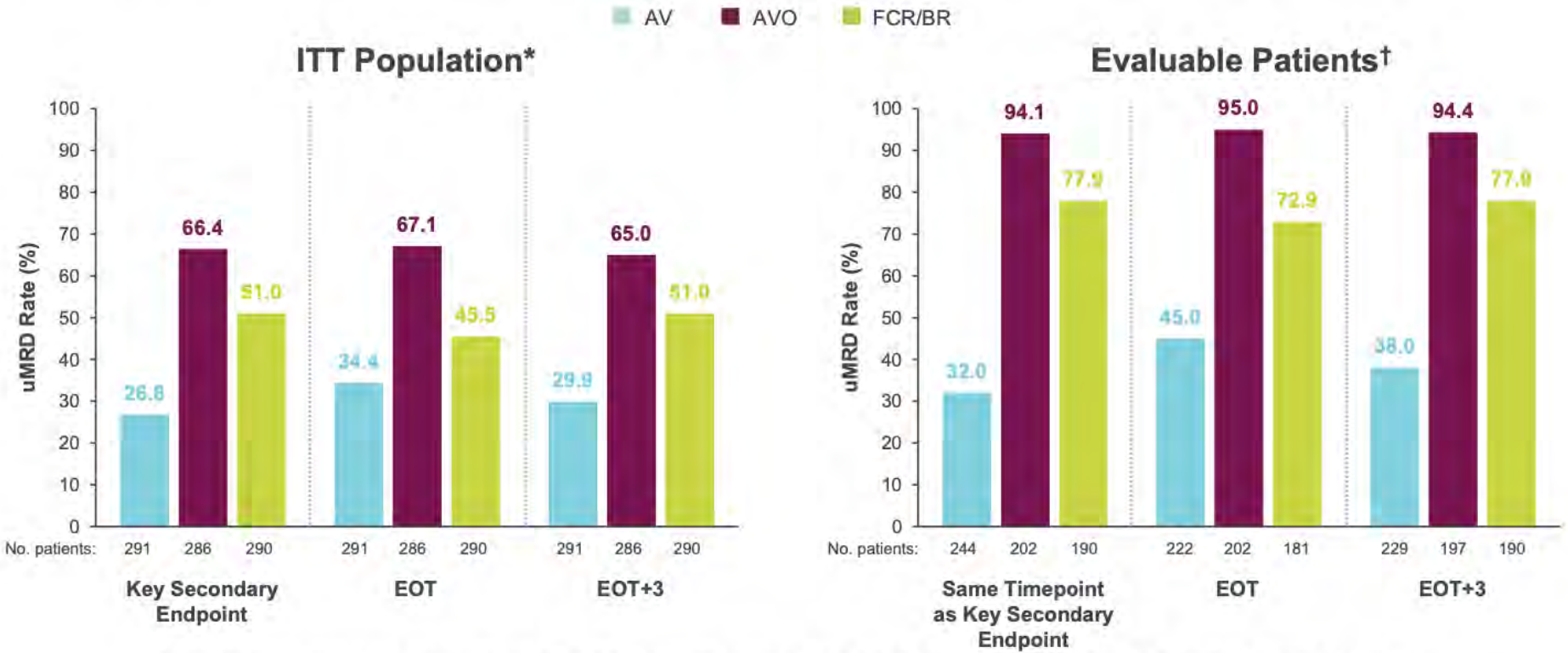


Patients at risk

AV	291	281	268	251	237	219	177	102	35	3	0
AVO	286	270	255	236	224	219	191	116	51	7	0
FCR/BR	290	234	206	189	170	154	127	66	28	6	0

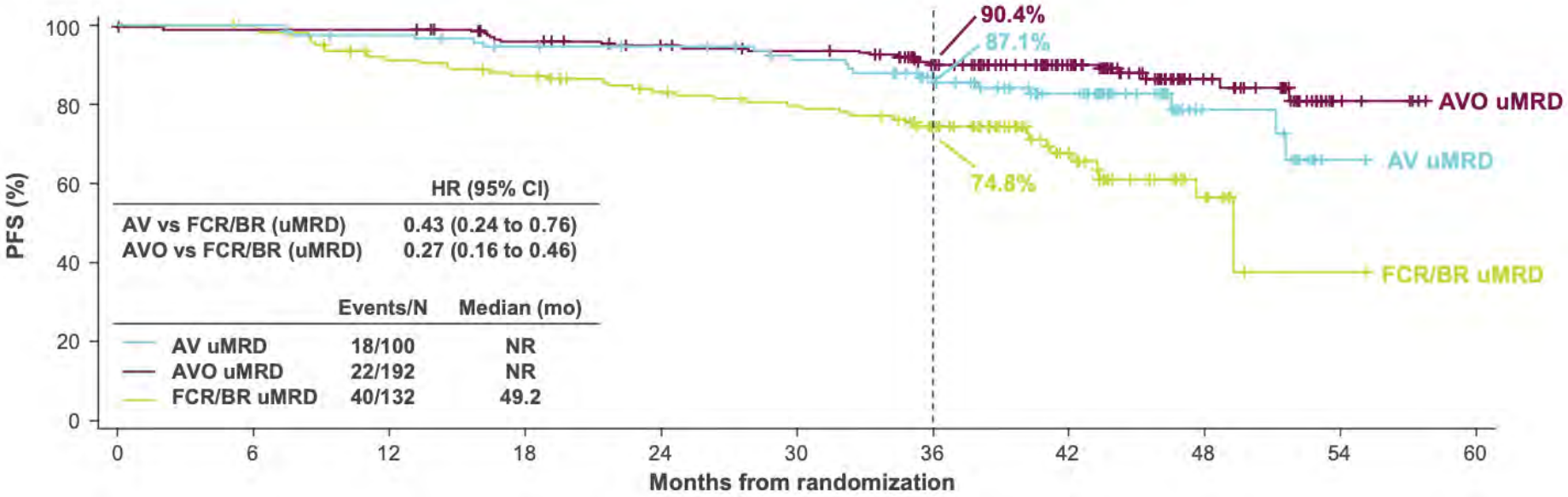
Median PFS: NR (AV and AVO) and 49.2 mo (FCR/BR)

uMRD Rates (Flow Cytometry [<10^{-4}] in PB)

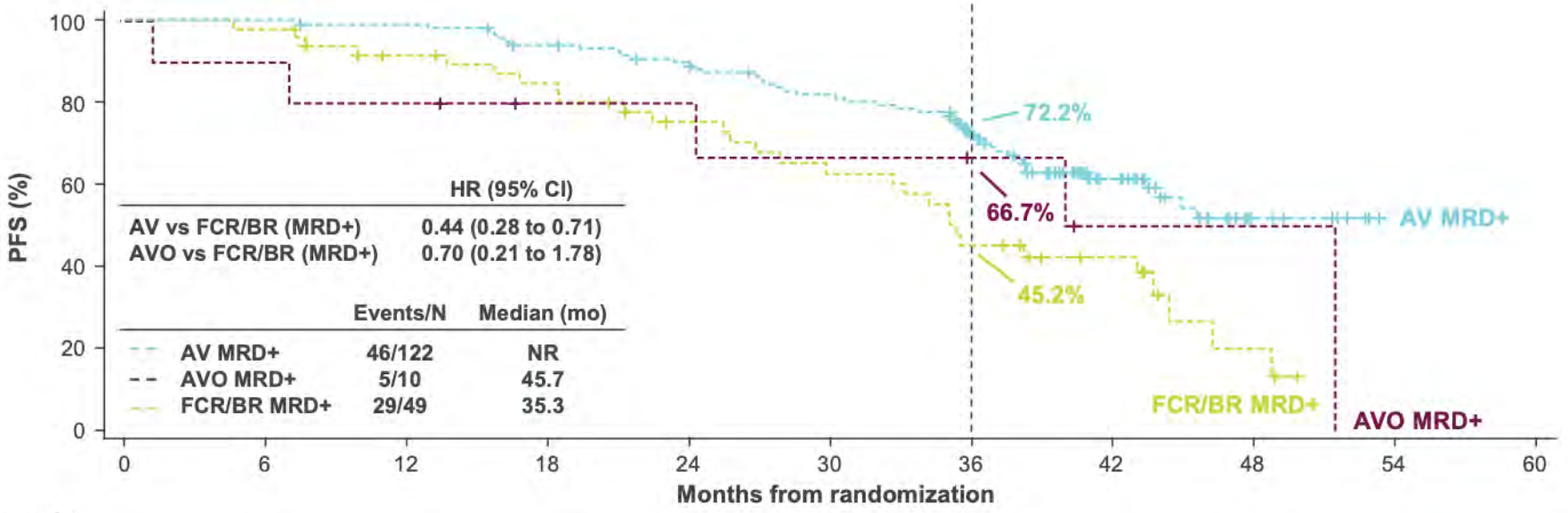


Key secondary endpoint timing: cycle 9, day 1 (AV arm), cycle 10, day 1 (AVO arm), and cycle 6, day 1 plus 12 weeks (FCR/BR)

PFS in the uMRD Subgroup at EOT (Flow Cytometry [<10^{-4}] in PB)

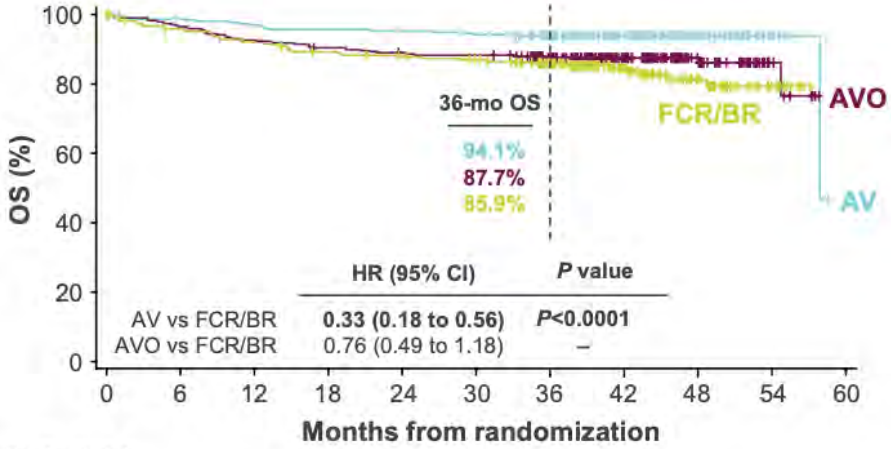


PFS in the MRD+ Subgroup at EOT (Flow Cytometry [<10^{-4}] in PB)



Overall Survival

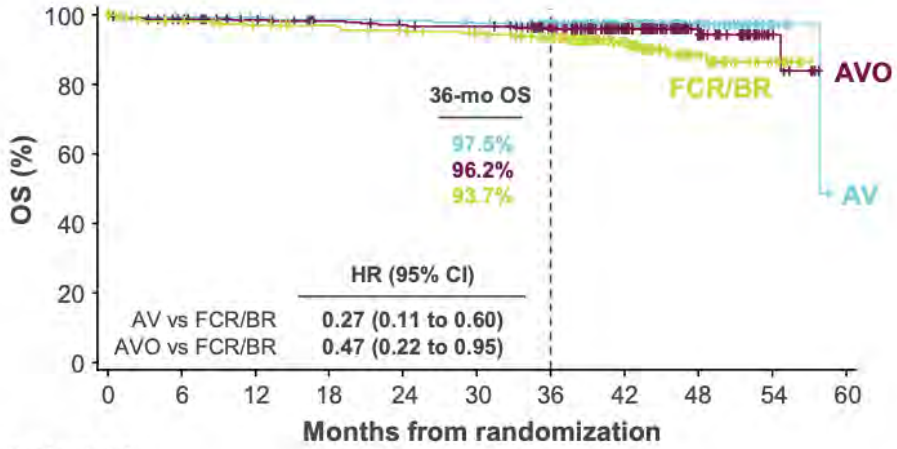
OS Prolonged With AV vs FCR/BR



Patients at risk

AV	291	286	281	277	275	270	233	142	58	10	0
AVO	286	276	265	257	252	250	223	143	64	10	0
FCR/BR	290	247	236	228	223	217	182	98	45	13	0

OS Prolonged With AV and AVO vs FCR/BR (COVID-19 Deaths Censored)



Patients at risk

AV	291	286	281	277	275	270	233	142	58	10	0
AVO	286	276	265	257	252	250	223	143	64	10	0
FCR/BR	290	247	236	228	223	217	182	98	45	13	0

COVID-19 deaths: 10 (AV), 25 (AVO), 21 (FCR/BR)

Safety Summary

	AV (n=291)	AVO (n=284)	FCR/BR (n=259)
Duration of exposure, median (range), mo	12.9 (1–18)	12.9 (0–18)	5.6 (1–11)
Summary of AEs			
Any AE	270 (92.8)	269 (94.7)	236 (91.1)
Any AE grade ≥3	156 (53.6)	197 (69.4)	157 (60.6)
Any serious AE	72 (24.7)	109 (38.4)	71 (27.4)
Serious AEs leading to death	10 (3.4)	17 (6.0)	9 (3.5)
AE leading to treatment discontinuation	23 (7.9)	57 (20.1)	28 (10.8)

When might we chose AVO over AV?

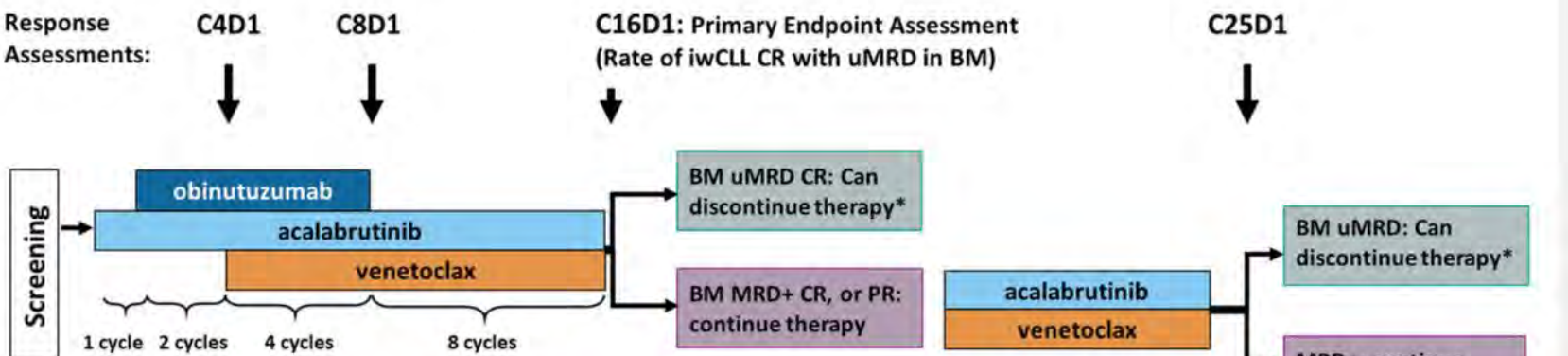
- Patient willing to risk more viral infections in exchange for higher likelihood of MRD negativity?

- uIGVH?

What about AVO in higher risk groups?

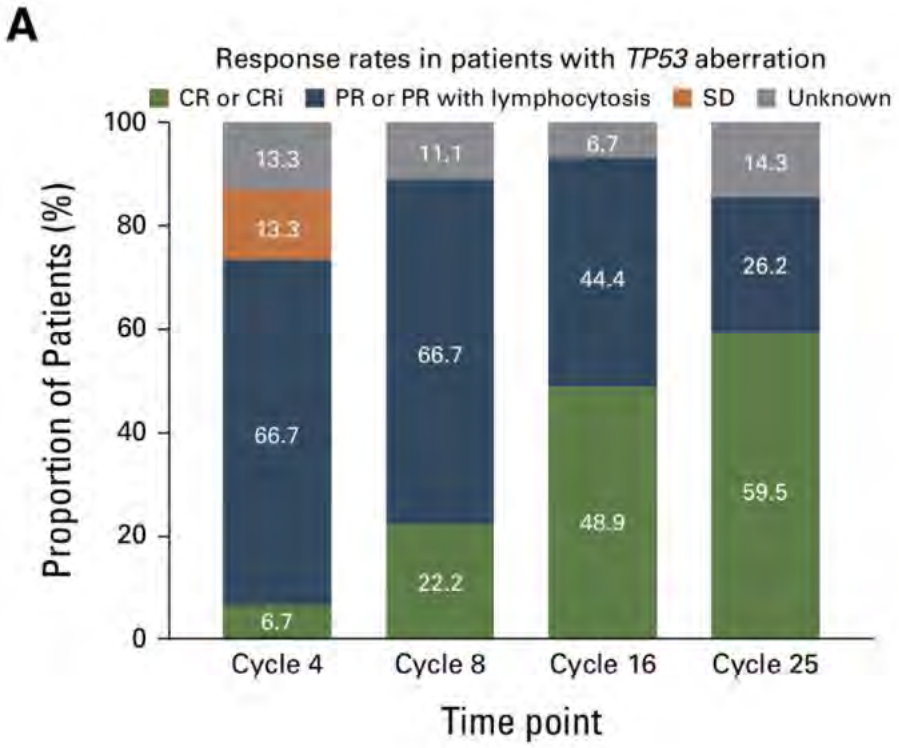
Phase 2: AVO in pts with TP53 aberration

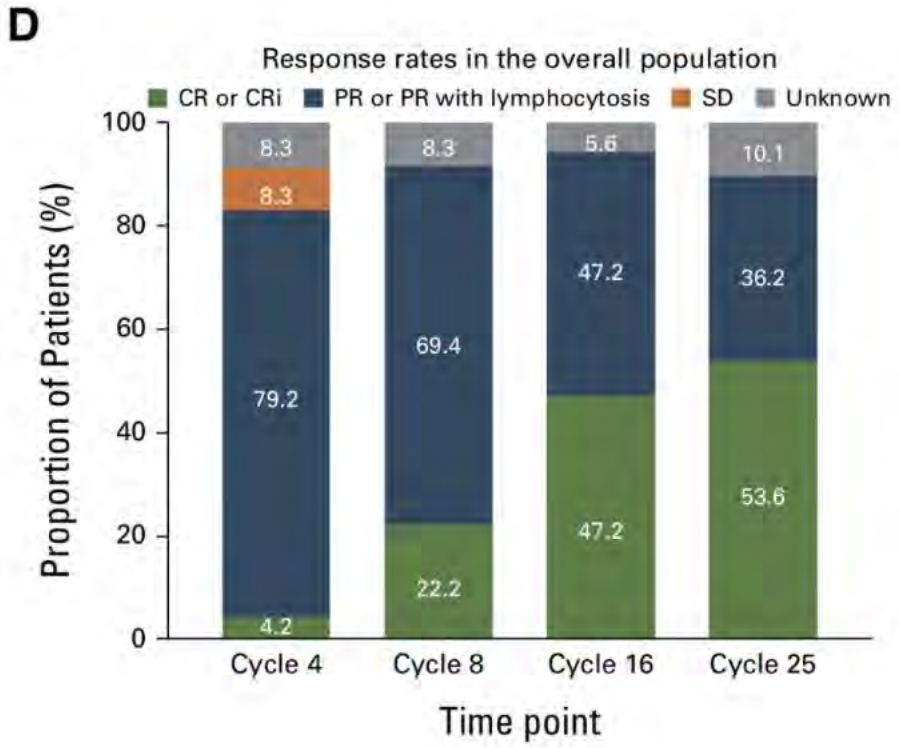
Figure 1. Study schema



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

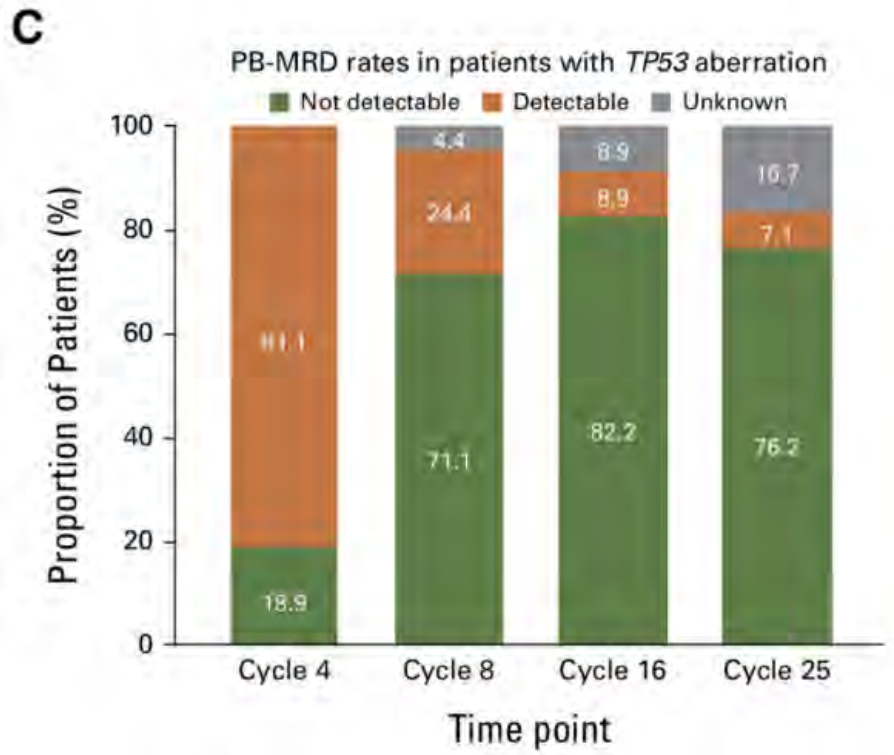
Phase 2: AVO in pts with TP53 aberration

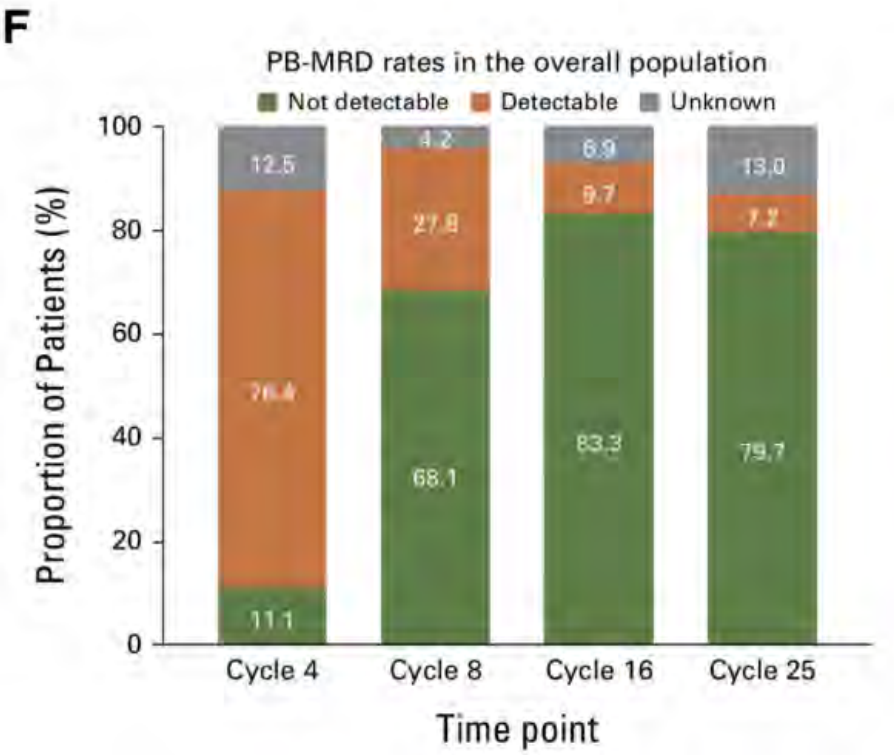




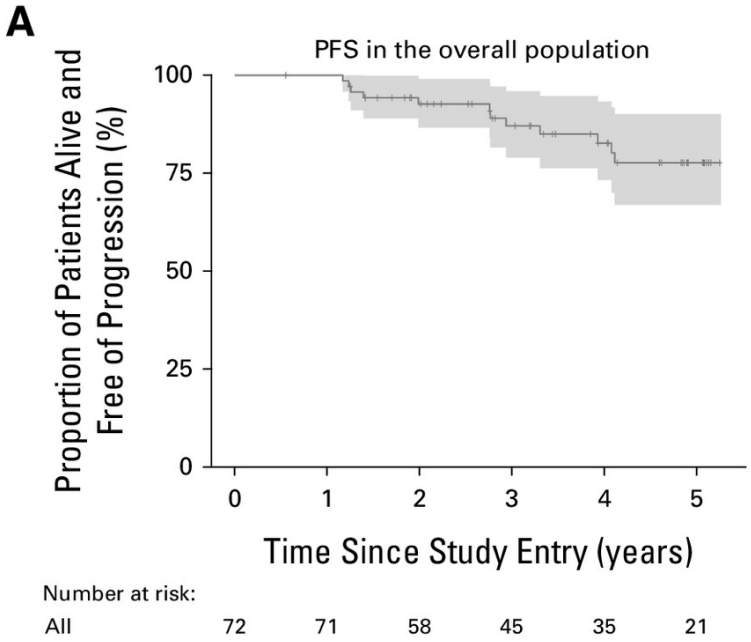
Davids MS et al, JCO, 2024

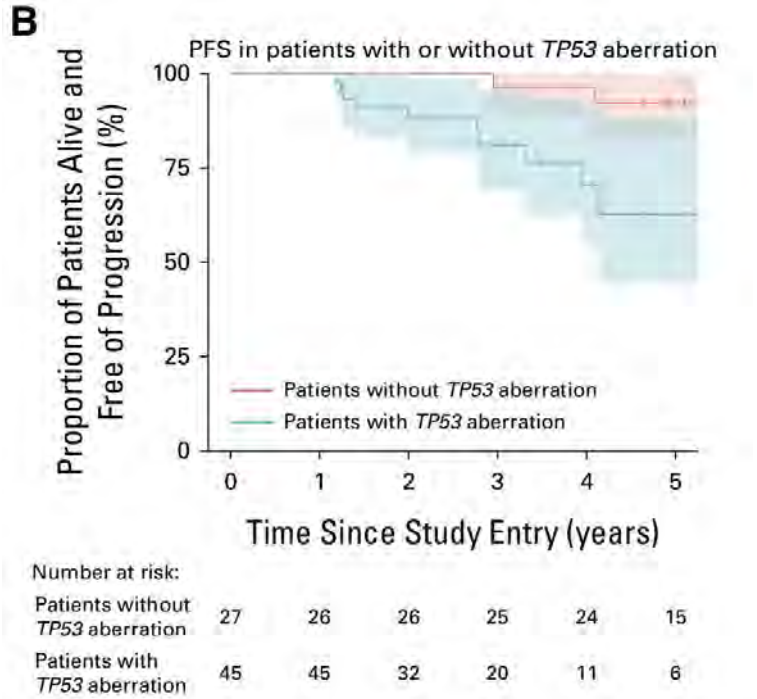
Phase 2: AVO in pts with TP53 aberration





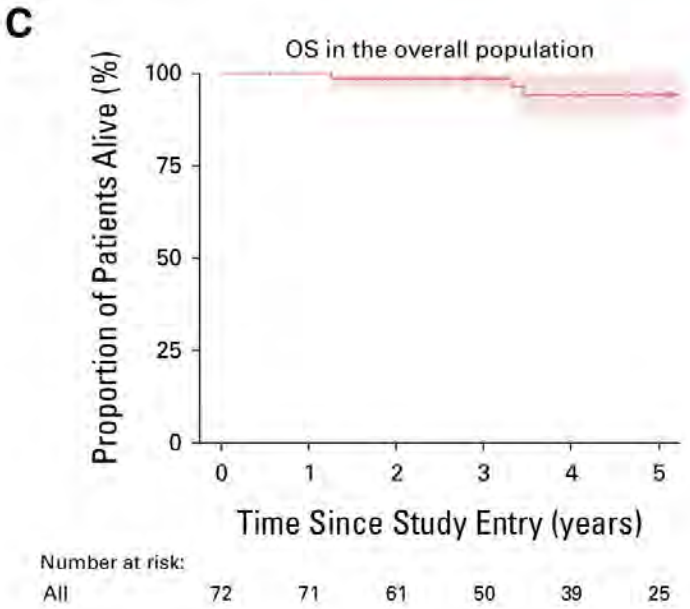
PFS: AVO in pts with TP53 aberration

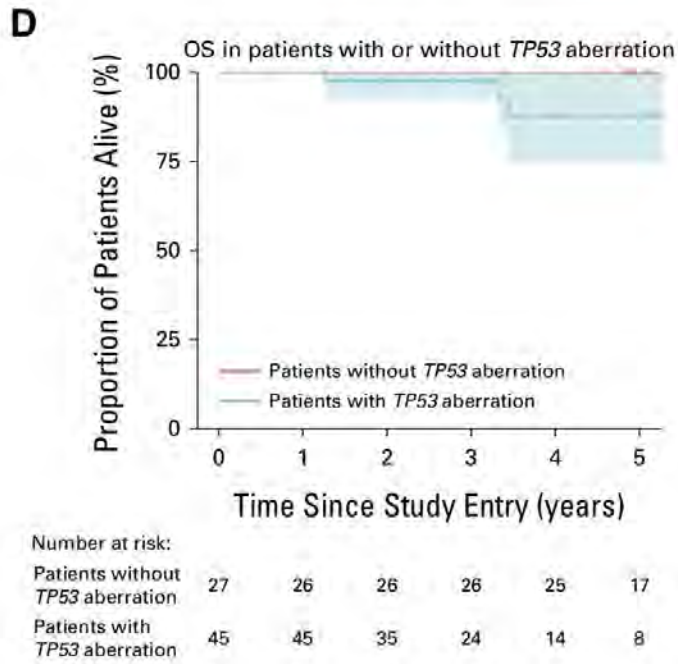




Davids MS et al, JCO, 2024

OS: AVO in pts with TP53 aberration





Davids MS et al, JCO, 2024

Safety

AE	Any Grade, No. of Patients (%)	Grade ≥3, No. of Patients (%)
Any AE	71 (99)	40 (56)
Any SAE	19 (26)	17 (24)
Common AEs (≥25% of patients)		
Fatigue	59 (82)	2 (3)
Headache	54 (75)	1 (1)
Neutropenia	52 (72)	26 (36)
Thrombocytopenia	51 (71)	20 (28)
Bruising	47 (65)	0
Anemia	37 (51)	3 (4)
Nausea	37 (51)	0
Diarrhea	34 (47)	4 (6)
Hypocalcemia	31 (43)	1 (1)

Davids MS et al, JCO, 2024

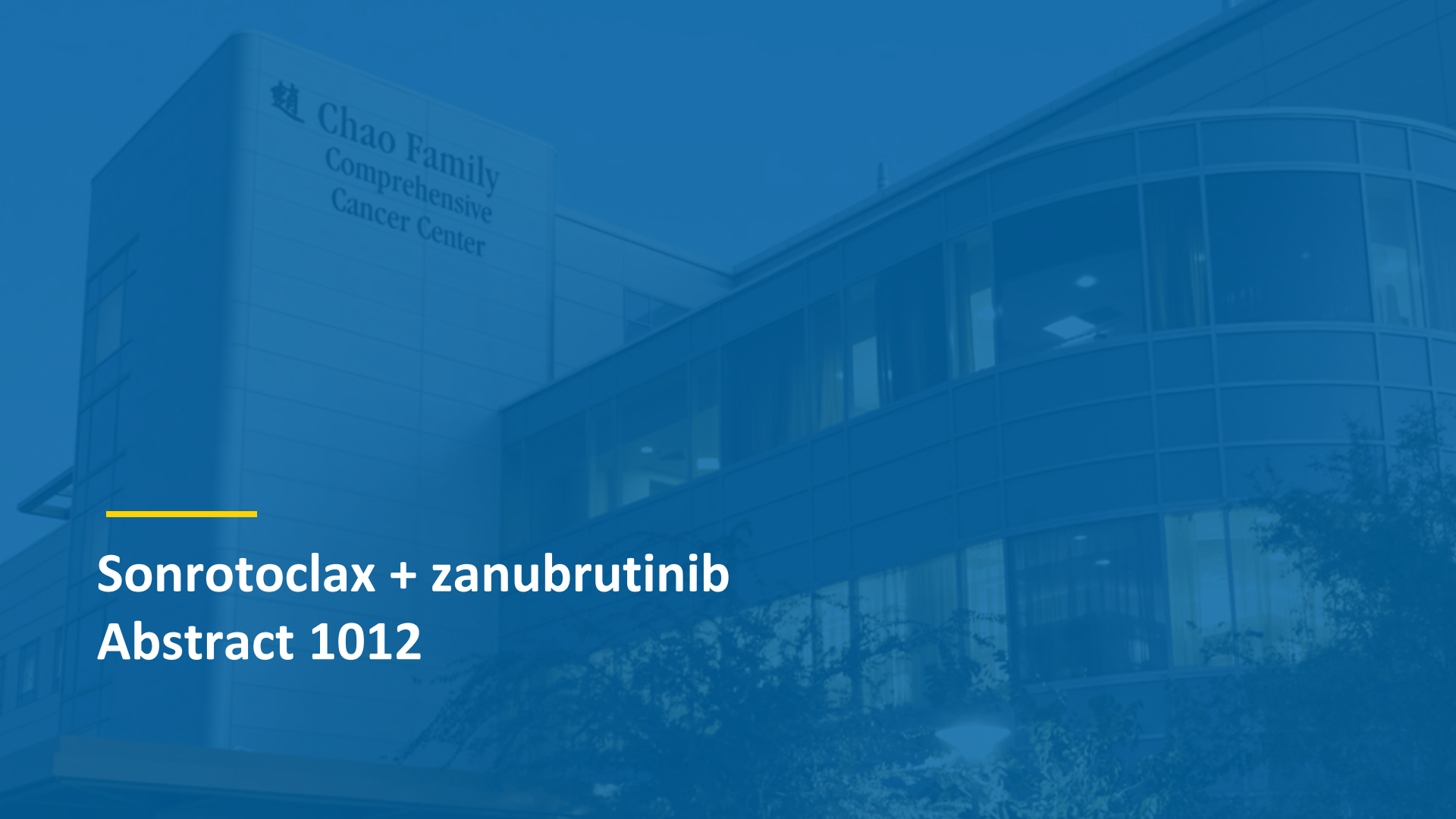
Safety

AE	Any Grade, No. of Patients (%)	Grade ≥3, No. of Patients (%)
Rash maculopapular	18 (25)	0
AEs of special interest		
Infection[a]	33 (46)	7 (10)
Hypertension	8 (11)	7 (10)
Infusion-related reactions	20 (28)	3 (4)
Bleeding events	8 (11)	0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	8 (11)	4 (6)
Atrial fibrillation	4 (6)	2 (3)
Tumor lysis syndrome	3 (4)	3 (4)
Ventricular arrhythmias	0 (0)	0 (0)

Davids MS et al, JCO, 2024

What questions remain?

- How much does the O add in the population with TP53 aberration?
  - This study had fewer COVID deaths than AMPLIFY
- What about other high risk features?
  - Complex karyotype?
- Role for re-treatment?
  - Looking to balance PFS with toxicity for higher-risk patients

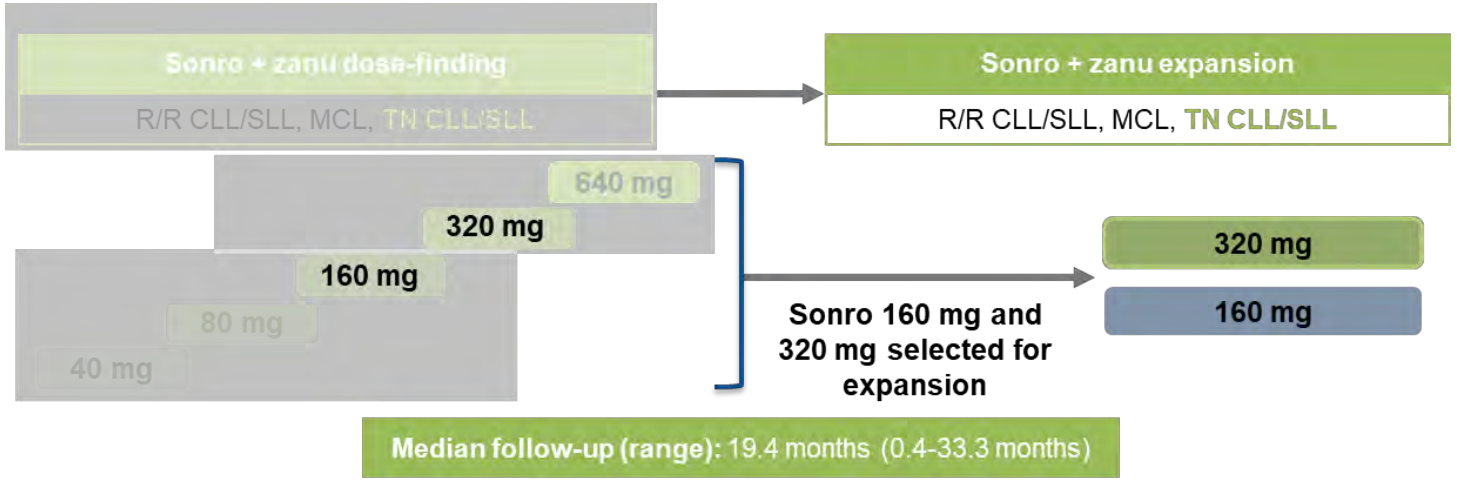


Sonrotoclax + zanubrutinib
Abstract 1012

BGB-11417-101 (NCT04277637) Study Design

BGB-11417-101: TN CLL

- BGB-11417-101 is a global phase 1/1b study evaluating sonrotoclax as monotherapy, or in combination with zanubrutinib and/or obinutuzumab in patients with B-cell malignancies
- The study endpoints included safety per CTCAE v5.0, RP2D, and efficacy
- Treatment consisted of 8-12 weeks of zanubrutinib lead-in (320 mg QD or 160 mg BID), then zanubrutinib + sonrotoclax until disease progression or intolerance



BID=twice daily, CLL=chronic lymphocytic leukemia, CTCAE=Common Terminology Criteria for Adverse Events, MCL=mantle cell lymphoma, QD=once daily, RP2D=recommended phase 2 dose, R/R=relapsed/refractory, SLL=small lymphocytic lymphoma, TN=treatment naïve.

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Baseline Characteristics

BGB-11417-101: TN CLL

Characteristics	Sonro 160 mg + zanu (n=51)	Sonro 320 mg + zanu (n=86)	All Patients (N=137)
Study follow-up, median (range), months	19.5 (12.6-33.3)	19.3 (0.4-29.7)	19.4 (0.4-33.3)
Age, median (range), years	63 (38-82)	61 (32-84)	62 (32-84)
≥65 years, n (%)	20 (39.2)	35 (40.7)	55 (40.1)
Male sex, n (%)	37 (72.5)	61 (70.9)	98 (71.5)
Disease type, n (%)			
CLL	48 (94.1)	82 (95.3)	130 (94.9)
SLL	3 (5.9)	4 (4.7)	7 (5.1)
Risk status, n/tested (%)			
del(17p)	5/45 (11.1)	6/77 (7.8)	11/122 (9.0)
TP53 mutation[a]	11/47 (23.4)	13/62 (21.0)	24/109 (22.0)
del(11q)	10/45 (22.2)	11/77 (14.3)	21/122 (17.2)
IGHV status, n/tested (%)			
Unmutated IGHV	32/47 (68.1)	32/60 (53.3)	64/107 (59.8)
High tumor bulk[b] at baseline, n/tested (%)	22/51 (43.1)	17/82 (20.7)	39/133 (29.3)

Data cutoff: August 23, 2024.
[a]TP53 mutations defined as >0.1% VAF. [b]Nodes ≥10 cm or nodes >5 cm and ALC >25×10^9/L.
ALC=absolute lymphocyte count, CLL=chronic lymphocytic leukemia, IGHV=immunoglobulin heavy chain variable region, SLL=small lymphocytic lymphoma, VAF=variant allele frequency.

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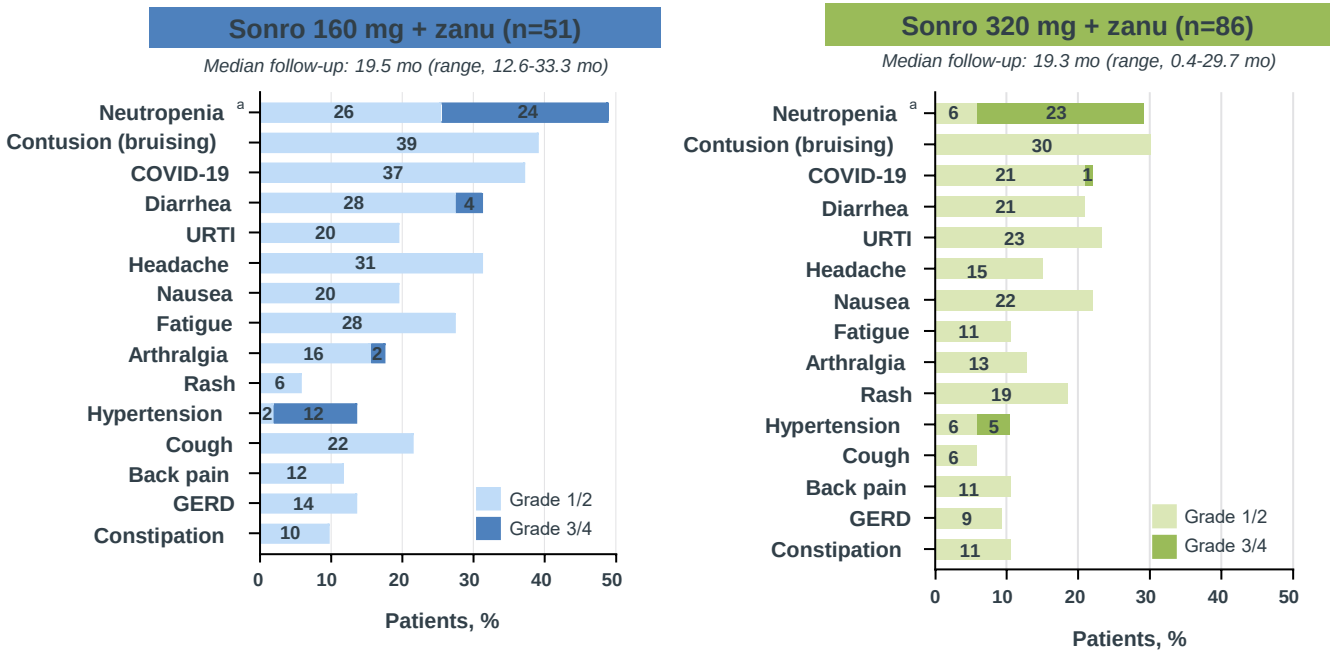
TEAEs Observed With Sonrotoclax + Zanubrutinib Were Mostly Low Grade and Transient

BGB-11417-101: TN CLL

- No TLS
- Neutropenia was transient and did not lead to higher rates of grade ≥3 infections

TEAEs in ≥10% of all patients



[a]Includes the combined preferred terms neutrophil count decreased and neutropenia.
GERD=gastroesophageal reflux disease, TEAE=treatment-emergent adverse event, URTI=upper respiratory tract infection.

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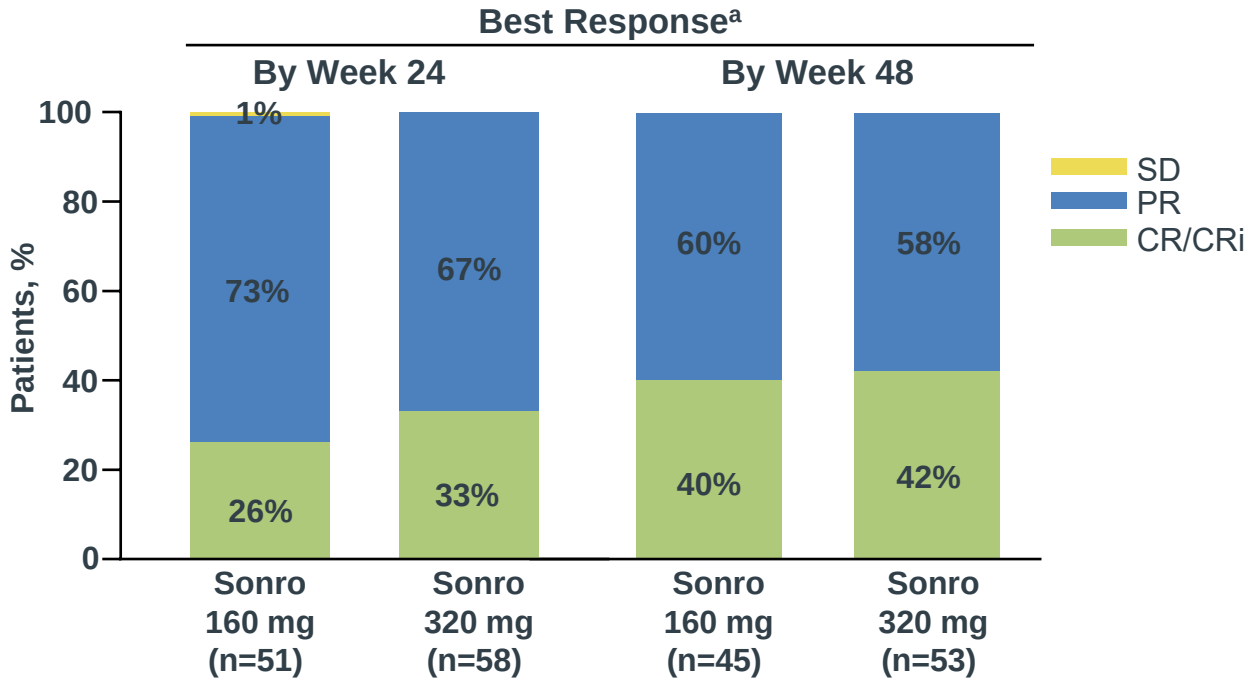
Sonrotoclax + Zanubrutinib Demonstrates Antitumor Activity in TN CLL

BGB-11417-101: TN CLL



[a]Percentages based on the number of patients who reached assessment at 24 or 48 weeks after completion of ramp-up, following zanu monotherapy and sonro ramp-up to target dose.
CR=complete response, CRi=complete response with incomplete count recovery, PR, partial response, SD=stable disease.

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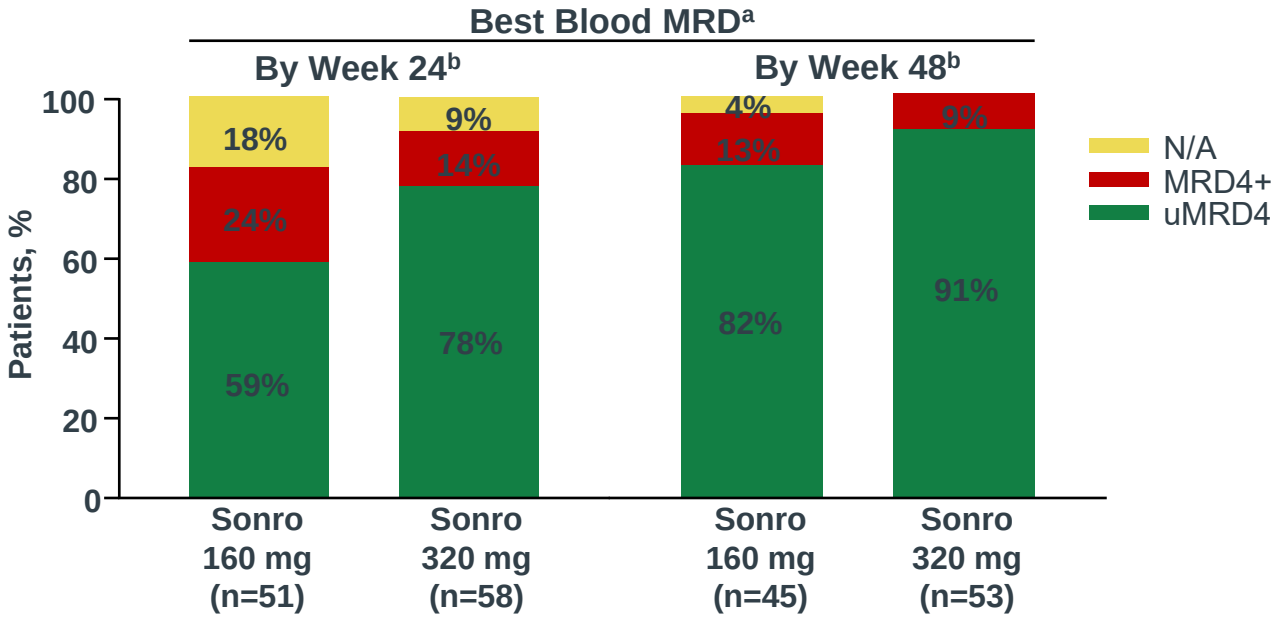
High Blood uMRD4 Rates Occurred Early and All Patients Remain in uMRD

BGB-11417-101: TN CLL

- As of the data cutoff date, no patients had switched from uMRD to MRD4+



[a]As measured by ERIC flow cytometry panel; uMRD4 is defined as less than 1 CLL cell per 10,000 leukocytes ($<10^{-4}$). [b]Number of weeks at target dose, following zanu monotherapy and sonro ramp-up to target dose.
CLL=chronic lymphocytic leukemia, ERIC=European Research Initiative in CLL, MRD=minimal residual disease, uMRD=undetectable minimal residual disease.

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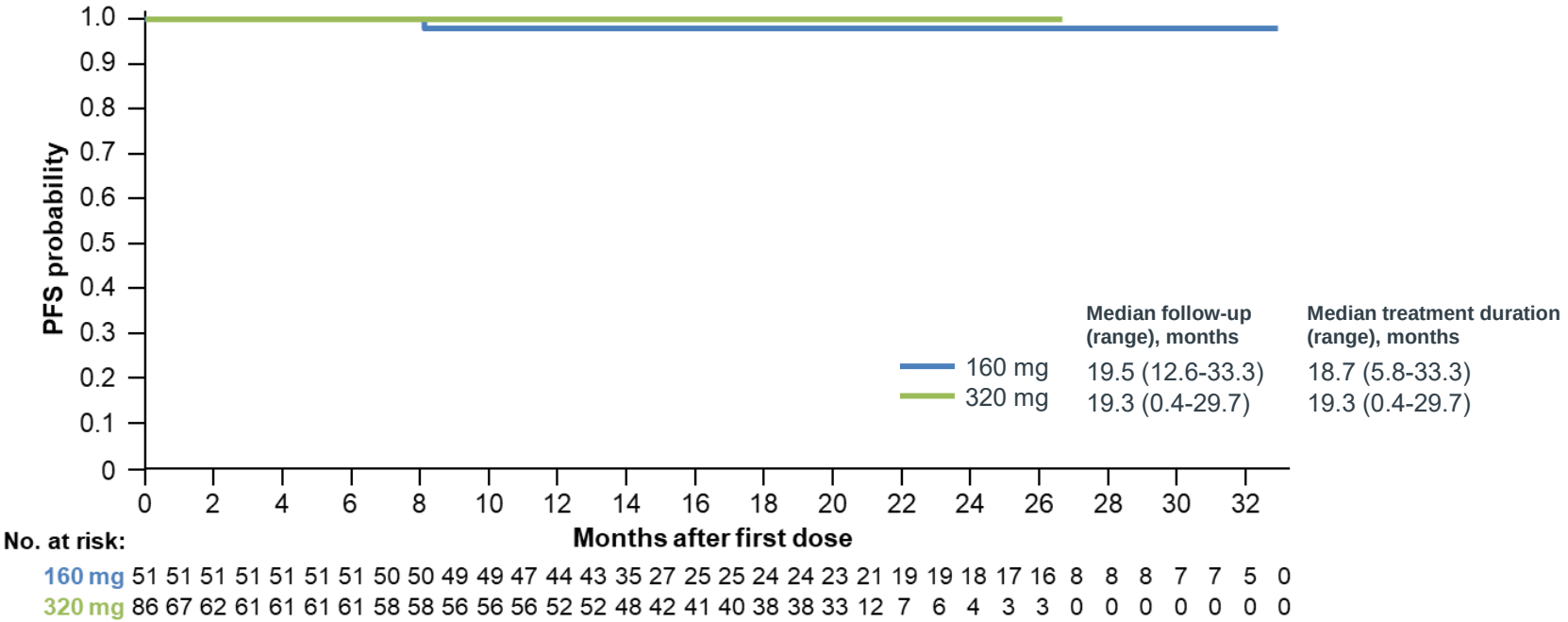
At Median Study Follow-Up of 19.4 Months, No Progression Was Observed With Sonrotoclax 320 mg

BGB-11417-101: TN CLL

- 1 PFS event in sonrotoclax 160-mg cohort (Richter transformation)



PFS=progression-free survival.

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What else happened at ASH in CLL?

Not yet ready for prime time…

- Ibrutinib + liso-cel (abstract 887)
  - CR better than lisp-cel alone (45% vs 20%), but CART use likely to remain rare in CLL
- BRUIN CLL-321: pirto vs ideal/BR (abstract 886)
  - Not a useful comparator arm
- BTK degraders looking good
  - Mostly PRs, but durable

Questions?

ebrem@hs.uci.edu

@DrLizBrem