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4–5 maggio 2026

Come la nuova combo BTKi+BCL2 cambia l'approccio terapeutico di prima linea

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Why Acalabrutinib + Venetoclax in first line CLL treatment?

- Patients with TN CLL needing therapy have several treatment options:
  - Continuous BTKi therapy; fixed-duration venetoclax regimens[1,2]
- While fixed-duration venetoclax + ibrutinib can result in deep, durable responses, cardiac toxicity remains a concern, particularly in older patients[3-5]
- Acalabrutinib is a highly selective BTKi with improved safety and tolerability vs ibrutinib[6]
- The phase 3 AMPLIFY trial
  - Efficacy and safety of fixed-duration acalabrutinib-venetoclax (±obinutuzumab) versus investigator's choice of chemoimmunotherapy in fit patients with TN CLL

1. Eichhorst B, et al. *Ann Oncol*. 2024;35:762-68. **2.** Hallek M, Al-Sawaf O. *Am J Hematol*. 2021;96:1679-1705. **3.** Kater AP, et al. *NEJM Evid*. 2022;1(7). **4.** Niemann CU, et al. *Lancet Oncol*. 2023;24:1423-33. **5.** Brown JR, et al. *Haematologica*. 2017;102:1796-1805. **6.** Byrd JC, et al. *J Clin Oncol*. 2021;39:3441-52.

How Acalabrutinib synergize with Venetoclax[1]

- **Lymphocytosis***
- **CLL cells priming for apoptosis**
- **pro-apoptotic protein BIM expression**
- **survival in CLL mouse models alone and at higher level with venetoclax**

- **CLL cells migration towards SDF-1 (CXCL12)**
- **anti-apoptotic protein Mcl-1 expression**

* In one study[6] Acalabrutinib exhibited lower ALC from Month 6 to Month 12 compared to ibrutinib especially in IGHV mutated pts. Kinetics of BTKi-induced lymphocytosis vary according to +12 presence and CD49d expression[6,7].

When acalabrutinib and ibrutinib were tested in the same e*x vivo* experiment at same conditions they similarly Increased[1,2]:

- **BCL-2 dependence in CLL cells**
- **CLL cell sensitivity to BCL-2 inhibition**
- **Expression of the BH3-only protein BIM**
- **CLL cell death when combined with venetoclax**

1. Patel et al. Leukemia. 2018 April ; 32(4): 920–930. doi:10.1038/leu.2017.321; 2. Deng Leukemia. 2017 October ; 31(10): 2075–2084. doi:10.1038/leu.2017.32; 3. Byrd 2016 N Engl J Med 2016;374:323-32; 4. Furman Leukemia 2021 Nov, 35(11):3201-3211.; 5 Alsadhan Clin Cancer Res. 2023 September 15; 29(18): 3612–3621; 6. Innocenti 2024 HemaSphere. 2024;8:e144; 7. Laurenti Poster iwCLL 2025

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

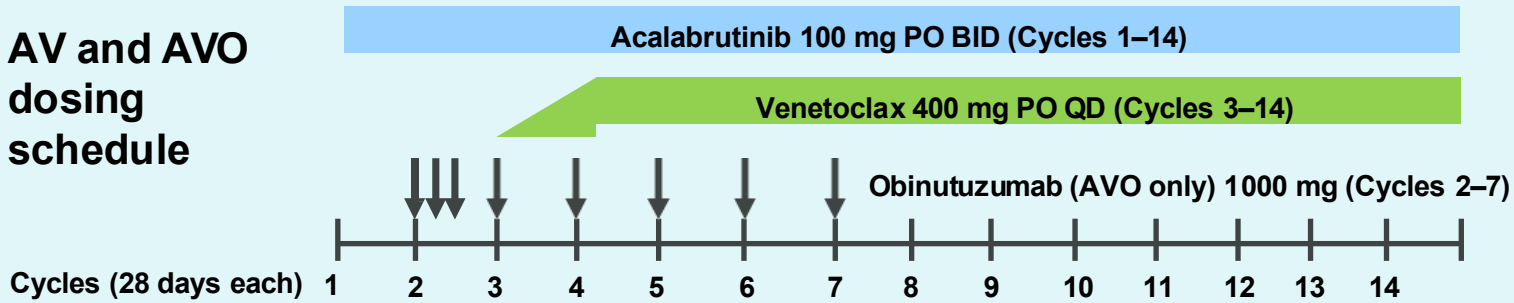
- AV (14 cycles)
- AVO (14 cycles)
- FCR/BR (6 cycles)

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



Hallek M, et al. *Blood*. 2018;131:2745-60.
Brown JR NEJM 20205
NCT03836261. Data cutoff: April 30, 2024.[a]Assayed by central lab.

Demographics and Baseline Characteristics

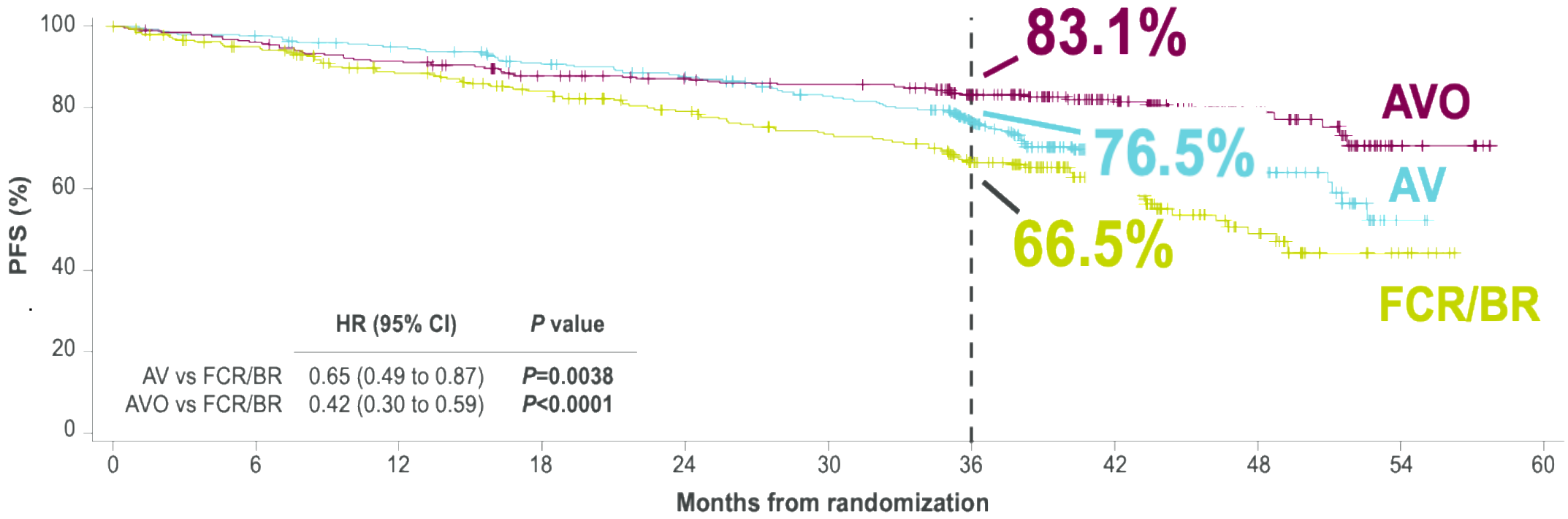
Characteristic	AV (n=291)	AVO (n=286)	FCR/BR (n=290)
Age, median (range), yr	61 (31–84)	61 (29–81)	61 (26–86)
≤65 yr	212 (72.9)	210 (73.4)	213 (73.4)
>65 yr	79 (27.1)	76 (26.6)	77 (26.6)
Male sex	178 (61.2)	198 (69.2)	183 (63.1)
ECOG PS score			
0–1	262 (90.0)	272 (95.1)	262 (90.3)
2	28 (9.6)	14 (4.9)	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)

Data are n (%) unless otherwise specified.

Brown JR NEJM 20205

EFFICACY

Significantly improved PFS with fixed-duration AV and AVO vs FCR/BR

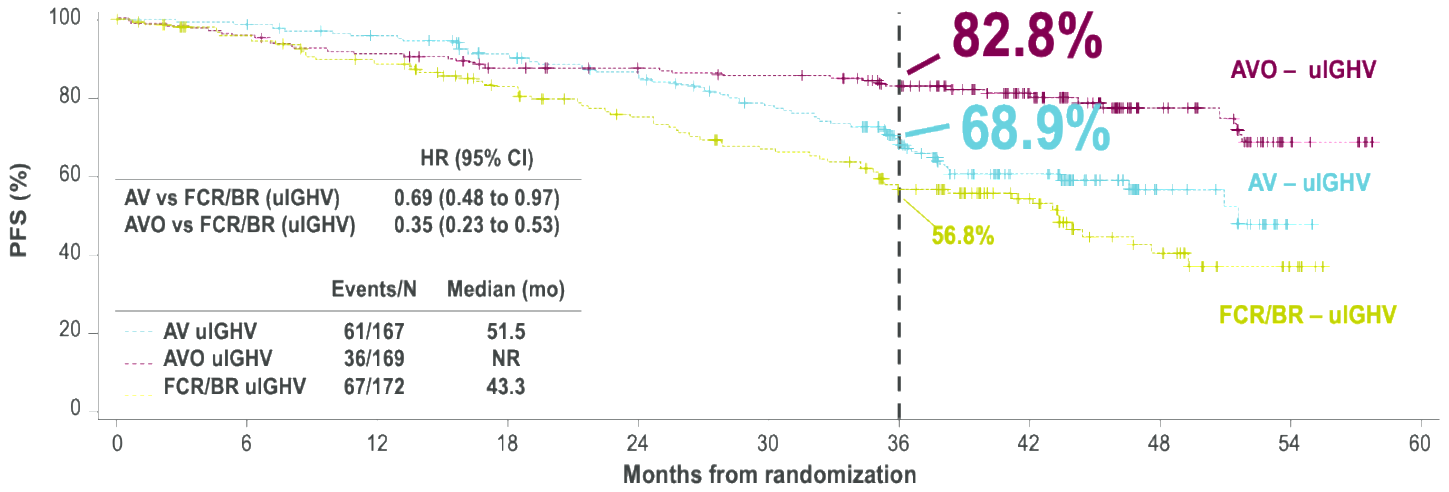


Median PFS was NR for AV and AVO, and was 47.6 mo for FCR/BR

Brown JR NEJM 20205

PFS evaluated by IGHV mutational status in a prespecified analysis

uIGHV



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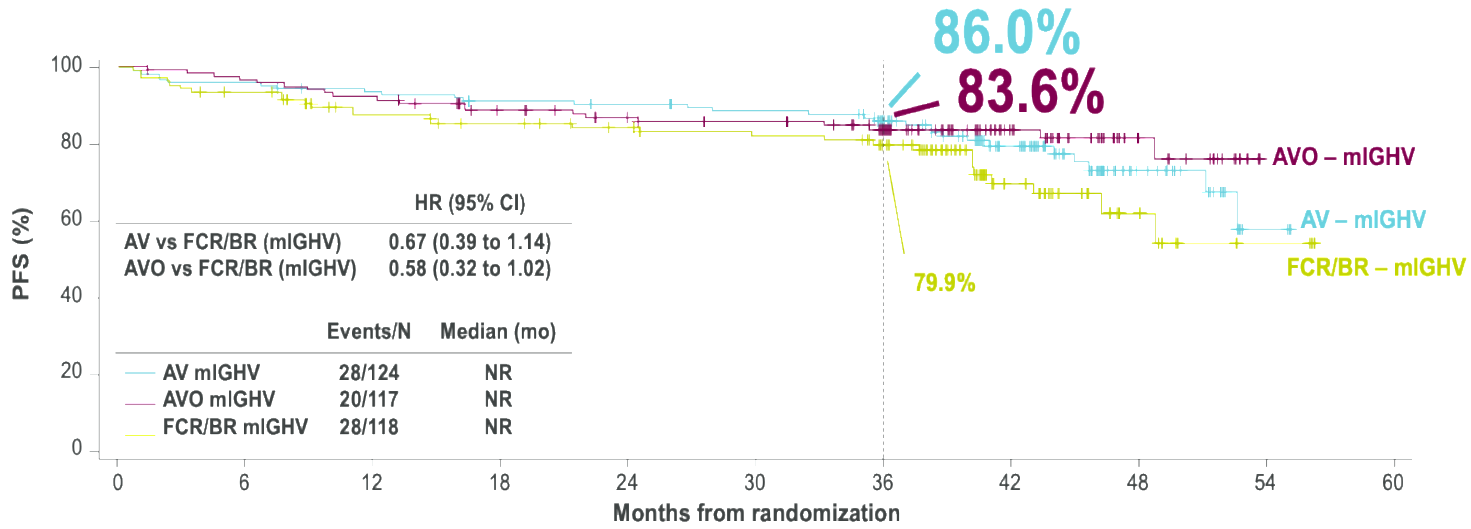
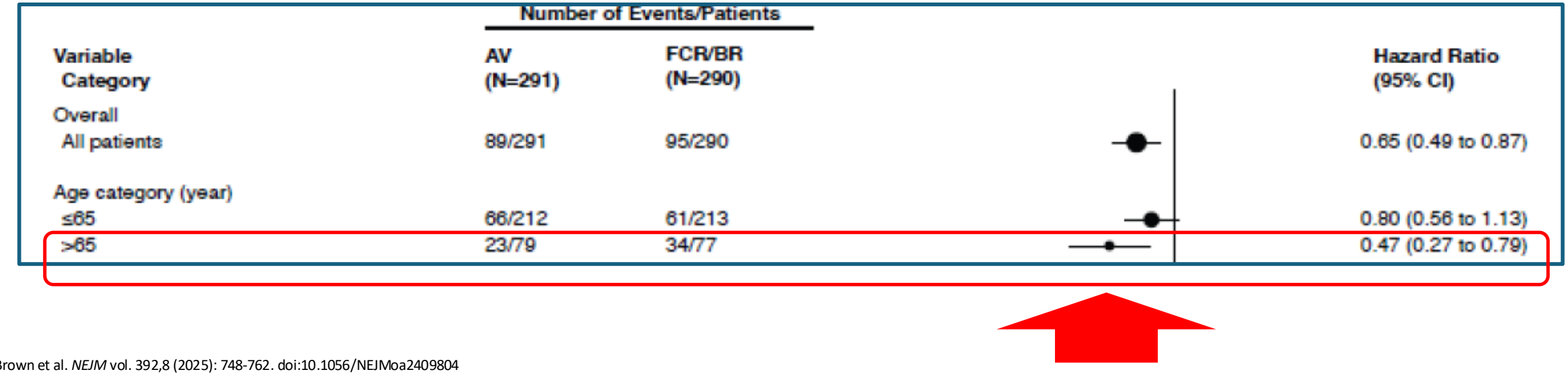
mIGHV



Brown JR NEJM 20205

AMPLIFY shows significant PFS benefit in elderly patients

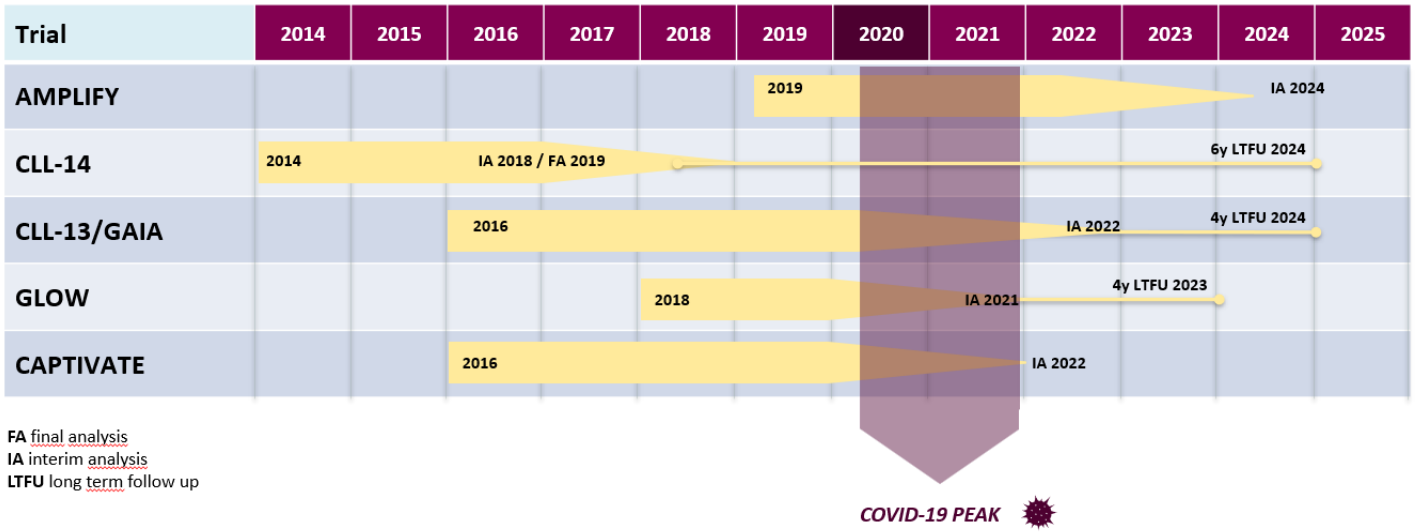
	AV N=291	AVO N=286	FCR/BR N=290
Median age	61 years	61 years	61 years
Age range	31–84	29–81	26-86
N° pts > 65 years	79 (27.1%)	76 (26.6%)	77 (26.6%)



Brown et al. *NEJM* vol. 392,8 (2025): 748-762. doi:10.1056/NEJMoa2409804

Brown et al. *NEJM* vol. 392,8 (2025): 748-762. doi:10.1056/NEJMoa2409804; Supplementary

AMPLIFY was deeply impacted the COVID-19 pandemic during the treatment phase



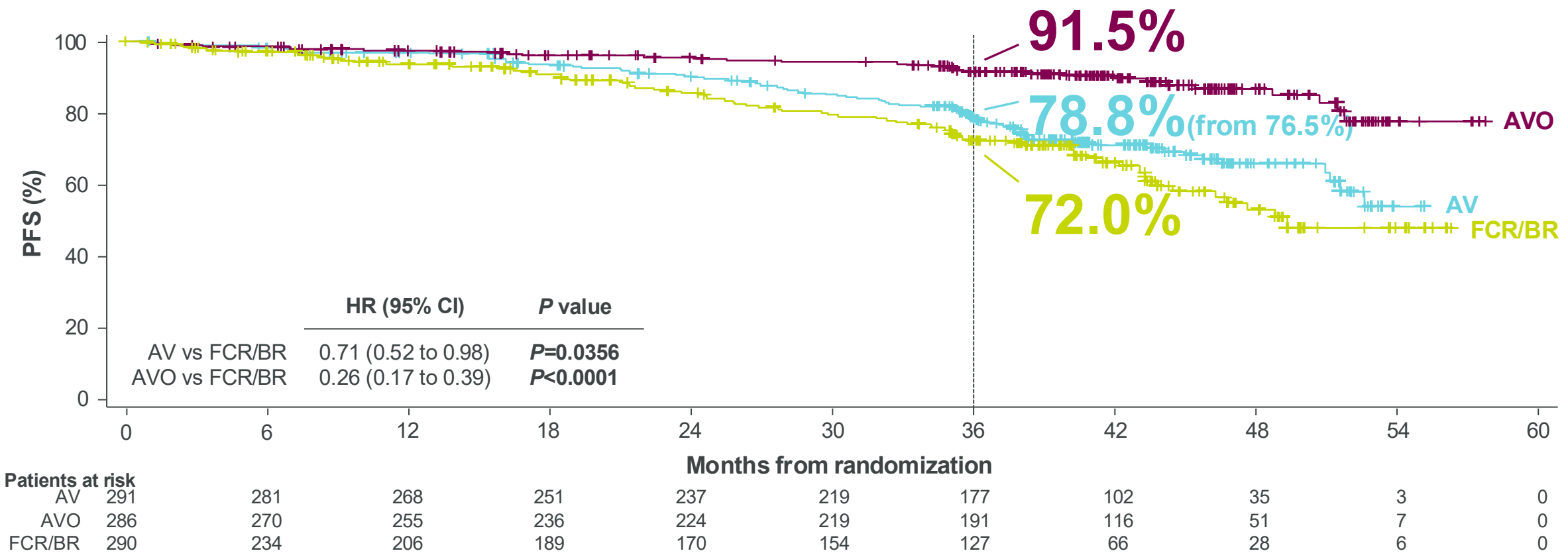
FA final analysis
IA interim analysis
LTFU long term follow up

	AV (n=291)	AVO (n=284)	FCR/BR (n=259)
Any confirmed / suspected COVID-19 AE	64 (22.0%)	69 (24.3%)	10 (3.9%)
Any COVID-19 AE leading to dose withholding of any tx	(13.1%)	(14.4%)	(0.4%)
Any COVID-19 AE leading to discontinuation of any tx	7 (2.4%)	23 (8.1%)	3 (1.2%)
Deaths due to COVID-19* → COVID-19 deaths predominantly occurred early in the pandemic, with **48 of the 56 deaths total (86%) occurring in 2020 and 2021**	10 (3.4%)	25 (8.7%)	21 (7.2%)

*based on the ITT population (AV, n=291; AVO, n=286; FCR/BR, n=290)

Brown et al., poster presentation EHA 2025

PFS Censoring COVID-19 Deaths (Prespecified Analysis)



Patients at risk

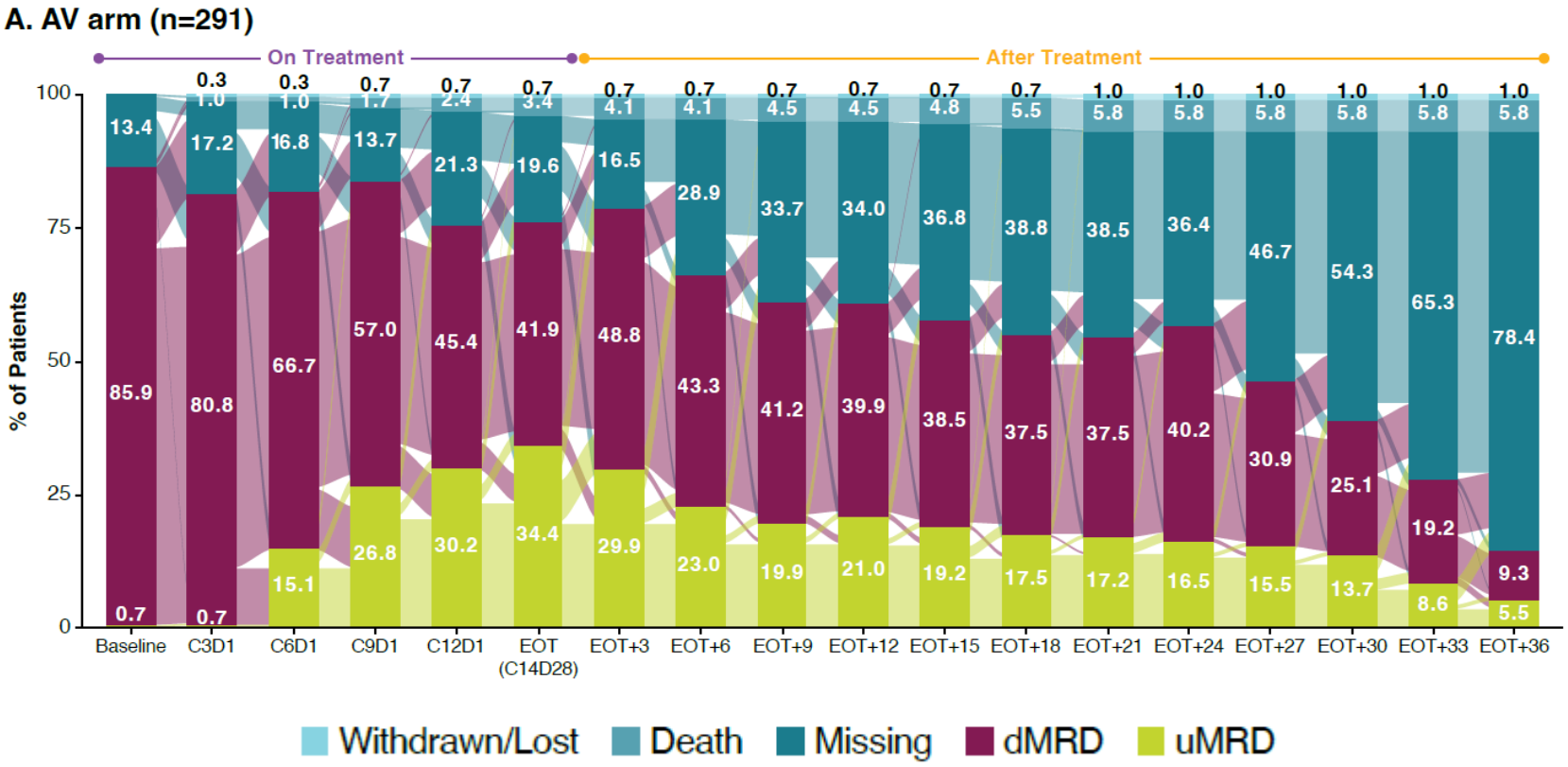
AV	291	281	268	251	237	219	177	102	35	3	0
AVO	286	270	255	236	224	219	191	116	51	7	0
FCR/BR	290	234	206	189	170	154	127	66	28	6	0

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

Brown JR ASH 2024

COVID-19 also affected the MRD analysis rate

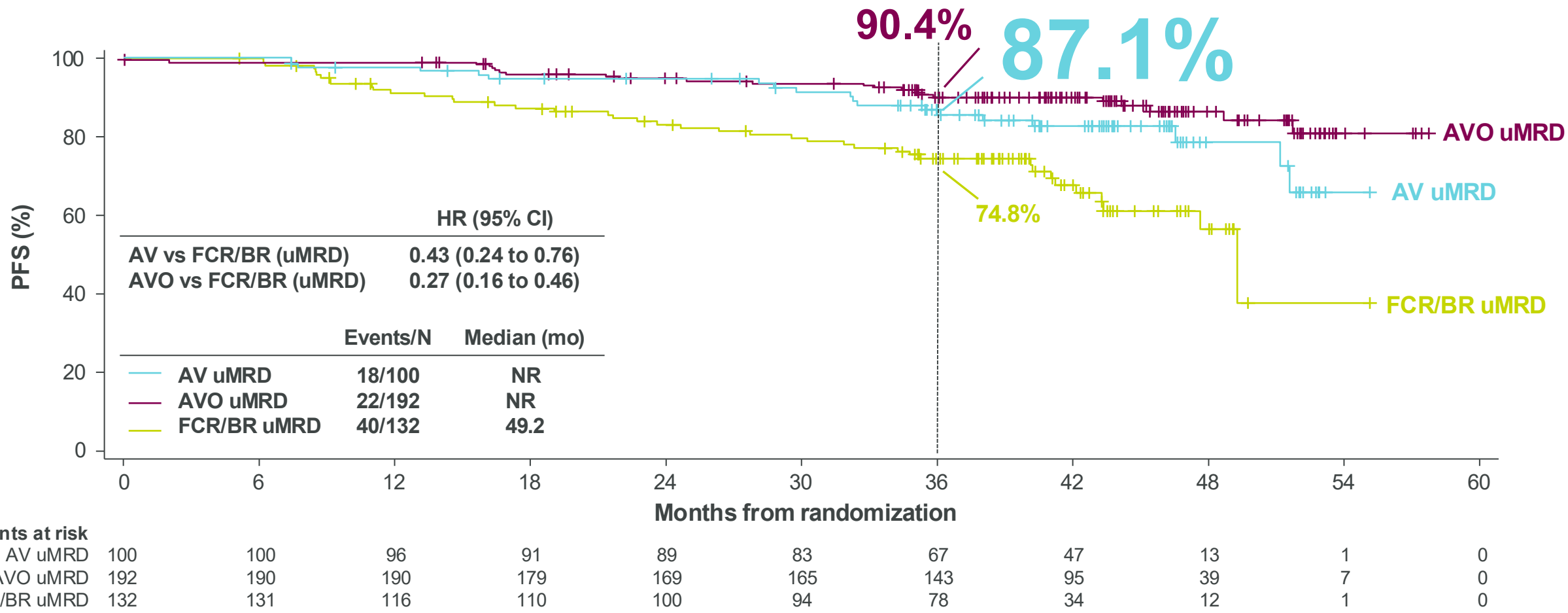
Figure 1. MRD Rates (PB by Flow Cytometry; 10^{-4}) up to EOT+36 (ITT Population) in the AV (A), AVO (B), and FCR/BR (C) Arms



- a EOT, circa il 20% pazienti non valutabili su braccio AV
- a EOT+36, circa l'80% pazienti non valutabili su braccio AV

Ghia et al. Poster presentation EHA 2025

PFS in the uMRD Subgroup at EOT



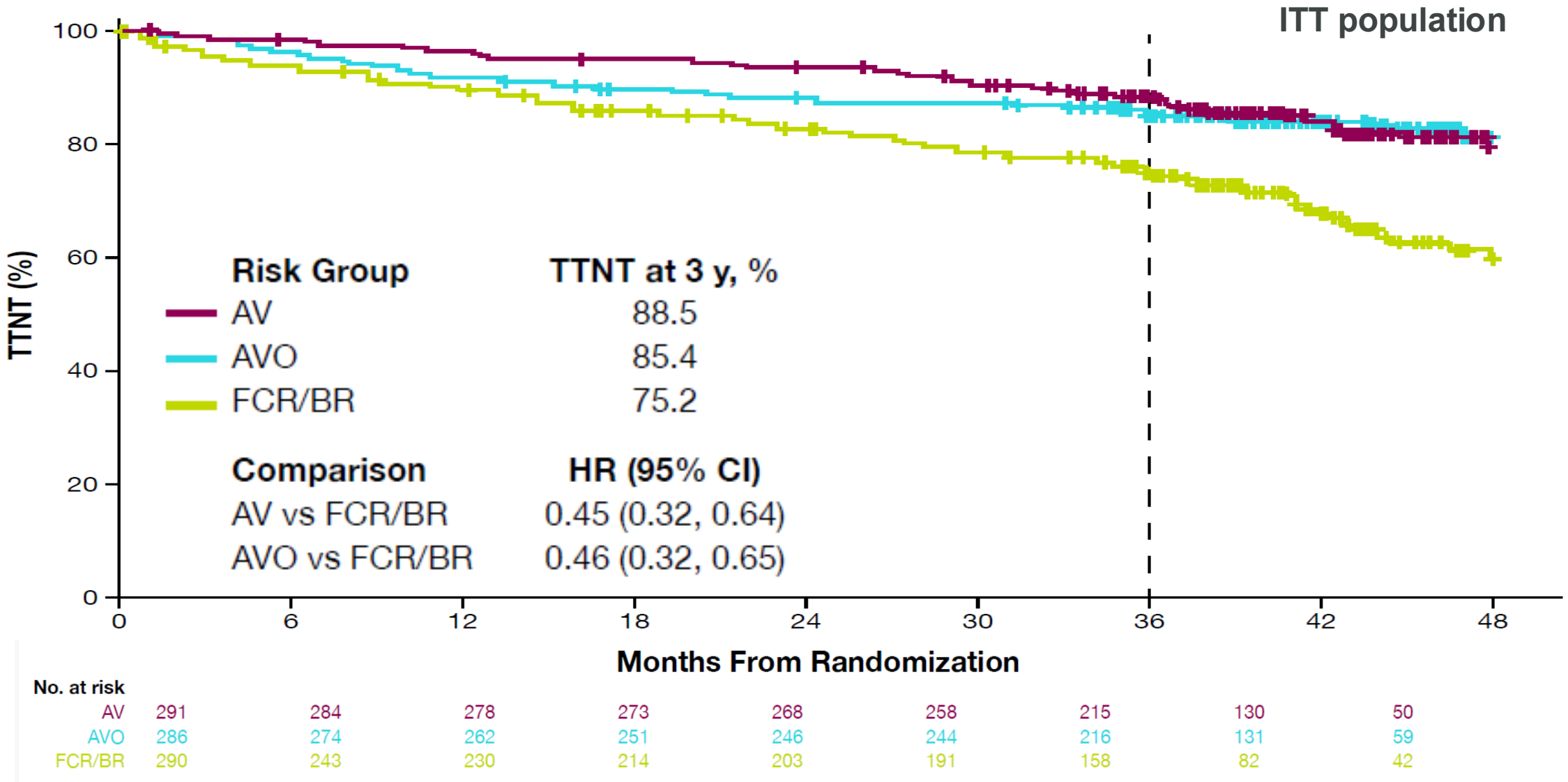
Patients at risk

AV uMRD	100	100	96	91	89	83	67	47	13	1	0
AVO uMRD	192	190	190	179	169	165	143	95	39	7	0
FCR/BR uMRD	132	131	116	110	100	94	78	34	12	1	0

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

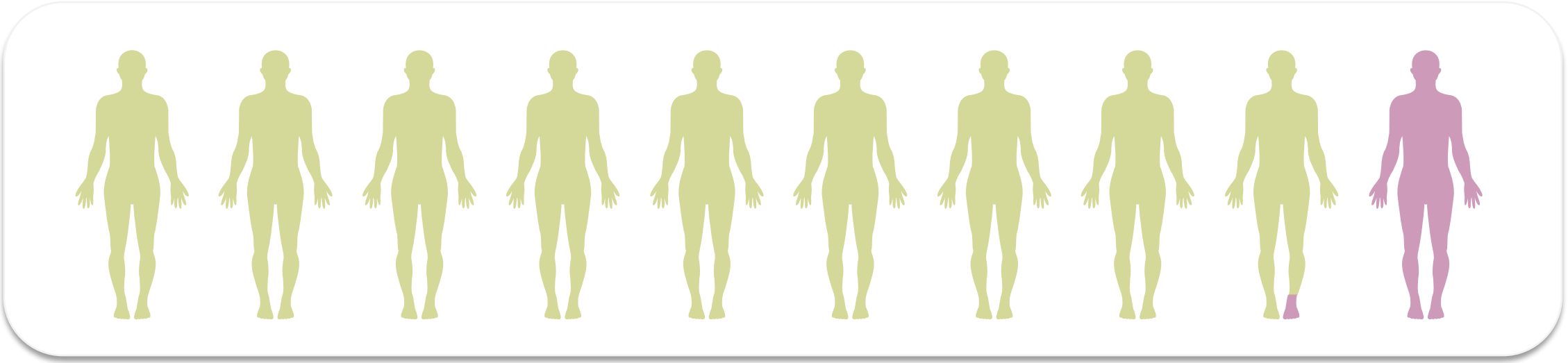
Brown JR NEJM 20205

Significant TTNT improvement with AV/AVO vs FCR/BR



Poster 3898_Ghia et al_Impact of Mutations with AV vs CIT Exploratory Analysis from AMPLIFY_ASH2025

TTNT: 9 out of 10 patients do not require subsequent treatment at 36 months



*The 36-mo TTNT (ITT) was **88.5% (AV),** 85.4% (AVO), and 75.2% (FCR/BR).*

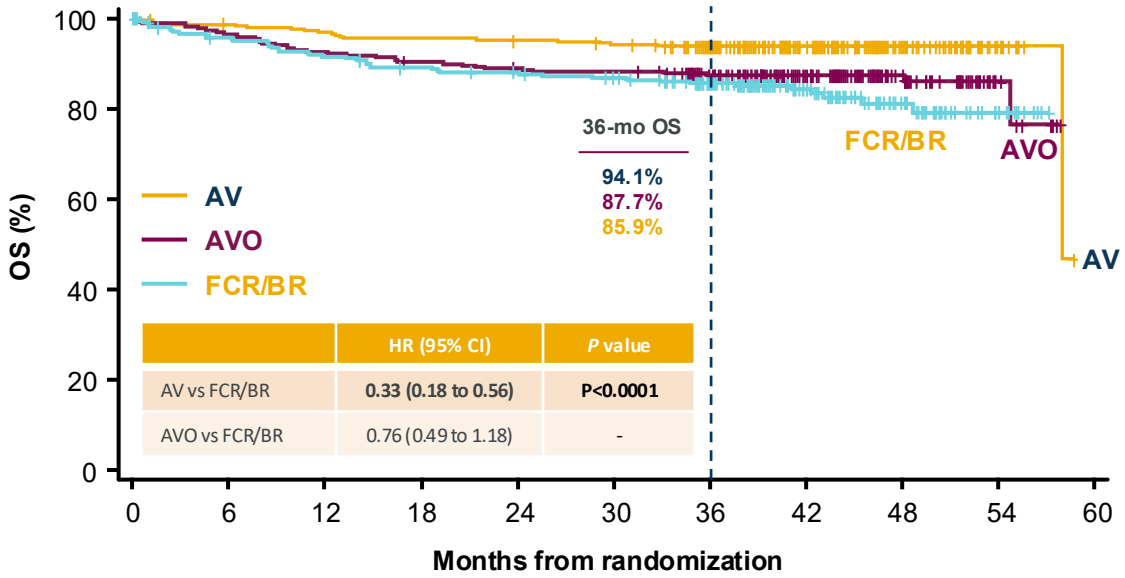
Abstract Number : abs25-8313

Abstract Title : Impact of prognostic mutations on outcomes with fixed-duration acalabrutinib-venetoclax combinations versus chemoimmunotherapy: An exploratory analysis from AMPLIFY

Authors Paolo Ghia1, et al.

AMPLIFY Overall Survival[a]

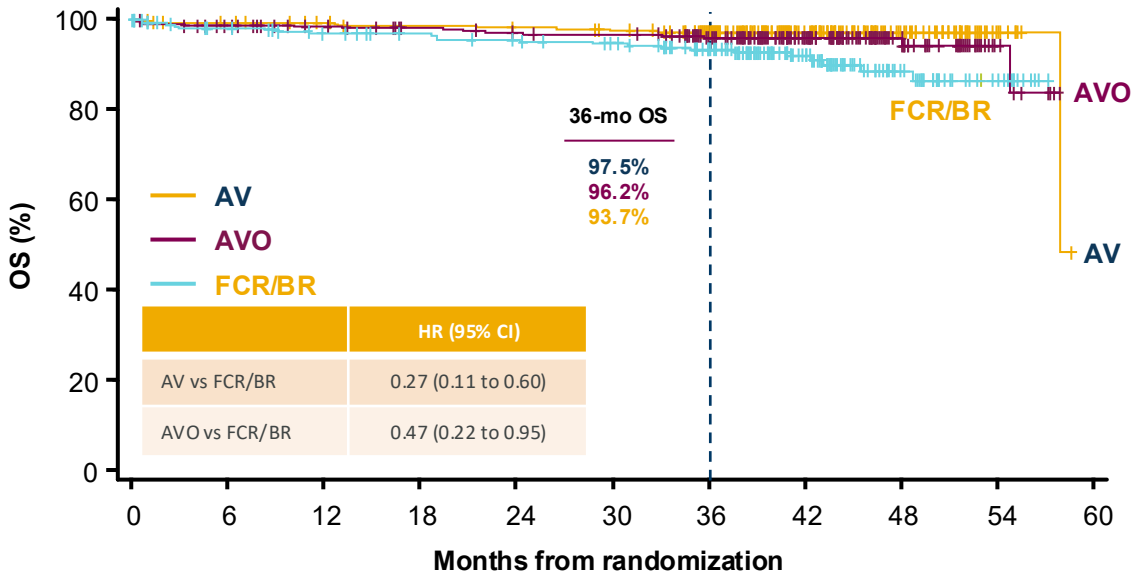
OS Prolonged With AV vs FCR/BR



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)

ITT population.

Hazard ratio (95% CI) computed using a Cox proportional-hazards model stratified by the randomization strata. P-value based on stratified log-rank test.

aOS results were immature at the time of this analysis.
AV, acalabrutinib-venetoclax; AVO, acalabrutinib-venetoclax-obinutuzumab; BR, bendamustine-rituximab; CI, confidence interval; FCR, fludarabine-cyclophosphamide-rituximab; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival.

Brown JR, et al. N Engl J Med. 2025 Feb 20;392(8):748-762

Can we compare AMPLIFY with other BTKi+BCL2i clinical trials ?

	CAPTIVATE phase II	GLOW phase III	AMPLIFY phase III	CLL17 phase III
	I + V	I + V	A + V	I + V
Number of Patients	159	106	**291**	**305**
Median age(range)	60 (33-71)	71 (47-93)	61 (31–84)	66 (59-73)
Patients with ≥65yrs	28%	84,9%	27,1%	51,8%
Stage Rai III/IV	28%	57.3%	**47,1%**	**48,9%**
Bulky disease ≥5 cm	30%	39%	38,8%	-
IGHV unmutated	56%	51.9%	**57,4%**	**56,4%**
Deletion(17p)	13%	0%	0%	6.3%
TP53 mutation	10%	6.6%	-	-
Del(17p) or TP53mut	17%	-	-	7.6%
Complex Karyotype ≥3	19%	-	15,5%	14,7%

Brown et al. *N Engl J Med*. 2025;392(8):748-762.; Ghia et al ASH 2025 abstract 3898; Paul M. Barr et al. *J Clin Oncol 41*, 7535-7535(2023); Barr et al. *J Clin Oncol 41*, 7535-7535(2023) extrapolated from KM curves; Tam et al. *Blood* vol. 139,22 (2022): 3278-3289 supplementary material; Niemann et al *The Lancet. Oncology* vol. 24,12 (2023): 1423-1433 extrapolated from KM curves; Kater et al. *NEJM evidence* vol. 1,7 (2022): EVIDoa2200006; Al-Sawaf, Othman et al *The New England journal of medicine*, 10.1056/NEJMoa2515458; Al-Sawaf, Othman et al *The New England journal of medicine*, .1056/NEJMoa2515458 supplementary material

Acalabrutinib + Venetoclax achieves 3-year TTNT comparable to Ibrutinib + Venetoclax

	uMRD EOT+3	3 years PFS	3 years TTNT
A+V ***Amplify***	38%	76,5%	88,5%
I+V ***Captivate***	57%	88%	89%
I+V ***Glow***	55%	77%	92%
I+V **CLL17**	47%	*79%*	88%

1 Tam et al. *Blood* vol. 139,22 (2022): 3278-3289. doi:10.1182/blood.2021014488**; 2** Kater et al. *NEJM evidence* vol. 1,7 (2022): EVIDoa2200006. doi:10.1056/EVIDoa2200006**; 3** Brown et al. *NEJM* vol. 392,8 (2025): 748-762. doi:10.1056/NEJMoa2409804**; 4** Davids et al. *Journal of clinical oncology* vol. 43,7 (2025): 788-799. doi:10.1200/JCO-24-02503**; 5** Fürstenau et al. *The Lancet. Oncology* vol. 25,6 (2024): 744-759. doi:10.1016/S1470-2045(24)00196-7**; 6** Al-Sawaf et al. *Blood* vol. 144,18 (2024): 1924-1935. doi:10.1182/blood.2024024631 **7.** Ryan et al., Future Oncol. 2022 Oct;18(33):3689-3699. doi: 10.2217/fon-2022-0456. Epub 2022 Sep 14

SAFETY

AMPLIFY 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)

Data are n (%) unless otherwise noted.

AEs with an onset date or that worsened on or after the date of first dose and up to and including 30 days following the date of last dose of treatment or up to the day prior to start of subsequent anti-CLL therapy, whichever came first.

1. Brown JR, et al. *N Engl J Med*. 2025.

Most Common AEs (Any Grade: ≥15%; Grade ≥3: ≥5%, Any Arm)

	AV (n=291)		AVO (n=284)		FCR/BR (n=259)	
Preferred Term	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Neutropenia	90 (30.9)	78 (26.8)	114 (40.1)	100 (35.2)	99 (38.2)	84 (32.4)
Diarrhea	95 (32.6)	5 (1.7)	103 (36.3)	4 (1.4)	28 (10.8)	1 (0.4)
Headache	102 (35.1)	4 (1.4)	80 (28.2)	1 (0.4)	20 (7.7)	1 (0.4)
Nausea	43 (14.8)	0	62 (21.8)	2 (0.7)	93 (35.9)	0
Infusion-related reaction	0	0	56 (19.7)	6 (2.1)	85 (32.8)	9 (3.5)
COVID-19	55 (18.9)	8 (2.7)	58 (20.4)	19 (6.7)	6 (2.3)	4 (1.5)
Pyrexia	17 (5.8)	1 (0.3)	44 (15.5)	5 (1.8)	47 (18.1)	6 (2.3)
Contusion	40 (13.7)	0	44 (15.5)	0	4 (1.5)	0
Neutrophil count decreased	18 (6.2)	16 (5.5)	29 (10.2)	29 (10.2)	27 (10.4)	22 (8.5)
Thrombocytopenia	13 (4.5)	4 (1.4)	24 (8.5)	17 (6.0)	33 (12.7)	22 (8.5)
COVID-19 pneumonia	21 (7.2)	16 (5.5)	35 (12.3)	33 (11.6)	7 (2.7)	7 (2.7)
Febrile neutropenia	5 (1.7)	5 (1.7)	7 (2.5)	7 (2.5)	24 (9.3)	24 (9.3)
Anemia	20 (6.9)	11 (3.8)	13 (4.6)	6 (2.1)	25 (9.7)	17 (6.6)

Data are n (%).
Table includes AEs occurring in ≥15% (any grade) or ≥5% (grade ≥3) of any treatment arm. AEs with an onset date or that worsened on or after the date of first dose and up to and including 30 days following the date of last dose of treatment or up to the day prior to start of subsequent anti-CLL therapy, whichever came first.
AE, adverse event; AV, acalabrutinib-venetoclax; AVO, acalabrutinib-venetoclax-obinutuzumab; BR, bendamustine-rituximab; FCR, fludarabine-cyclophosphamide-rituximab.

Events of Clinical Interest: Acalabrutinib + Venetoclax is generally well tolerated

	AV (n=291)		AVO (n=284)		FCR/BR (n=259)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any ECI	222 (76.3)	136 (46.7)	242 (85.2)	188 (66.2)	185 (71.4)	141 (54.4)
Cardiac events	27 (9.3)	5 (1.7)	34 (12.0)	7 (2.5)	9 (3.5)	3 (1.2)
Atrial fibrillation	2 (0.7)	1 (0.3)	6 (2.1)	2 (0.7)	2 (0.8)	2 (0.8)
Ventricular tachyarrhythmias[a]	2 (0.7)	0	3 (1.1)	0	0	0
Hypertension	12 (4.1)	8 (2.7)	11 (3.9)	6 (2.1)	7 (2.7)	2 (0.8)
Hemorrhage	94 (32.3)	3 (1.0)	86 (30.3)	6 (2.1)	11 (4.2)	1 (0.4)
Major hemorrhage	3 (1.0)	3 (1.0)	8 (2.8)	6 (2.1)	2 (0.8)	1 (0.4)
Neutropenia (any)[b]	108 (37.1)	94 (32.3)	143 (50.4)	131 (46.1)	132 (51.0)	112 (43.2)
Infections (any)	148 (50.9)	36 (12.4)	153 (53.9)	67 (23.6)	82 (31.7)	26 (10.0)
Second primary malignancies	15 (5.2)	5 (1.7)	12 (4.2)	5 (1.8)	2 (0.8)	0

Tam et al. Blood 2022
Brown et al. N Engl J Med 2025

Cumulative incidence vs exposure-adjusted incidence of cardiac events

❖ Incidence rates of **any-grade cardiac events** were higher with AV (9.3%) and AVO (12.0%) vs FCR/BR (3.5%)

❖ EAERs of **cardiac events** were similar across arms: 0.83 (AV), 1.11 (AVO) and 0.86 (FCR/BR)

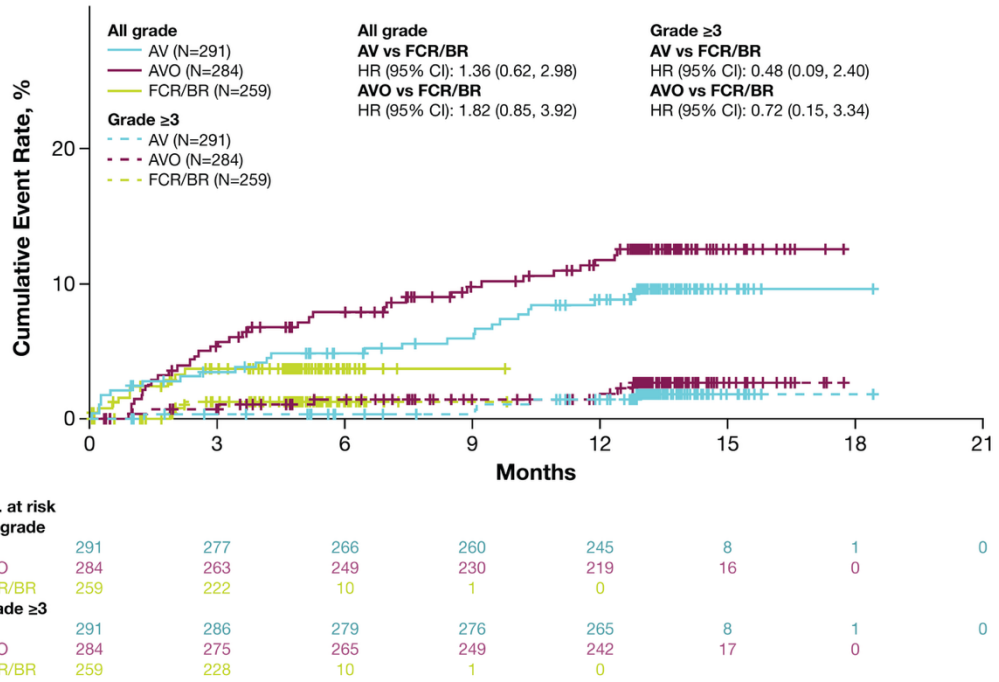


Table 1. Exposure-Adjusted Event Rates of ECIs

Events per 100 Person-Months	AV (N=291) Any Grade	AV (N=291) Grade ≥3	AVO (N=284) Any Grade	AVO (N=284) Grade ≥3	FCR/BR (N=259) Any Grade	FCR/BR (N=259) Grade ≥3
Any TEAE of clinical interest	25.275	11.706	36.098	18.895	57.791	38.123
Cardiac events	0.831	0.126	1.110	0.211	0.855	0.285
Atrial fibrillation	0.050	0.025	0.159	0.053	0.143	0.143
Ventricular tachyarrhythmias	0.050	0	0.079	0	0	0

Seymour et al. Presented at the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) Biennial Meeting; September 12–15, 2025; Kraków, Poland P1424

Grade ≥3 Events of Clinical Interest

Atrial fibrillation: 0.3% AV, 0.7% AVO.
Hypertension: 2.7% AV, 2.1% AVO.

Major bleeding: 1% AV, 2.1% AVO.

Infections: 12.4% AV, 23.6% AVO.

Secondary primary malignancy excluding NMSC: 1.7% AV, 1.4% AVO.

Summary of Adverse Events of BTKi+BCL-2i clinical trials

	CAPTIVATE Fase II		GLOW Fase III		AMPLIFY Fase III		CLL17 Fase III	
	I + V		I + V		A + V		I + V	
Number of Patients	159		106		291		305	
Median age(range)	60 (33-71)		71 (47-93)		61 (31–84)		66 (59-73)	
Patients with ≥65aa	28%		84,9%		27,1%		51,8%	
Adverse Events	All Grade (%)	**Grade ≥3 (%)**	All Grade (%)	**Grade ≥3 (%)**	All Grade (%)	**Grade ≥3 (%)**	All Grade (%)	**Grade ≥3 (%)**
Atrial Fibrillation	4	**1**	14.2	**6.6**	0.7	**0,3**	12.5	**3.6**
Hypertension	16	**6**	13.2	**7.5**	4.1	**2.7**	16.8	**7.6**
Bleeding	60	**2**	-	**-**	32.3	**1**	-	**-**
Neutropenia	43	**33**	41.5	**34.9**	30.9	**26.8**	28	**22.1**
Infections	67	**8**	-	**17**	50.9	**12.4**	80.2	**25.1**
Diarrhea	62	**3**	50.9	**10.4**	32.6	**1.7**	47.2	**1.3**
Nausea	43	**1**	26.4	**-**	14.8	**0**	-	**-**

Brown et al. *N Engl J Med*. 2025;392(8):748-762.; Ghia et al ASH 2025 abstract 3898; Paul M. Barr et al. *J Clin Oncol 41*, 7535-7535(2023); Barr et al. *J Clin Oncol 41*, 7535-7535(2023) extrapolated from KM curves; Tam et al. *Blood* vol. 139,22 (2022): 3278-3289 supplementary material; Niemann et al *The Lancet. Oncology* vol. 24,12 (2023): 1423-1433 extrapolated from KM curves; Kater et al. *NEJM evidence* vol. 1,7 (2022): EVIDoa2200006; Al-Sawaf, Othman et al *The New England journal of medicine*, 10.1056/NEJMoa2515458; Al-Sawaf, Othman et al *The New England journal of medicine*, .1056/NEJMoa2515458 supplementary material

Summary

- AMPLIFY provides the first phase 3 evidence of efficacy in fixed-duration therapy combining a 2G BTKi with venetoclax in TN CLL
- Conclusions on the relative efficacy of A +V vs I + V are limited by a lack of head-to-head data
- TTNT results should be considered when making treatment decisions as an important patient-orientated outcome

- Incidence of cardiac AEs remained low in both the AV and AVO regimens
- Safety analyses should be considered when selecting treatments

Treatment decisions should be taken on a case-by-case basis, and should account for individual patient and disease characteristics, as well as the patient's preferences