AMPLIFY study design

TN CLL (N=867)

Key inclusion criteria
- Age ≥18 years
- TN CLL requiring treatment per iwCLL 2018 criteria[3]
- 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, Phase III trial

RANDOMIZE 1:1:1

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

***Crossover** not built into protocol*

Primary endpoint

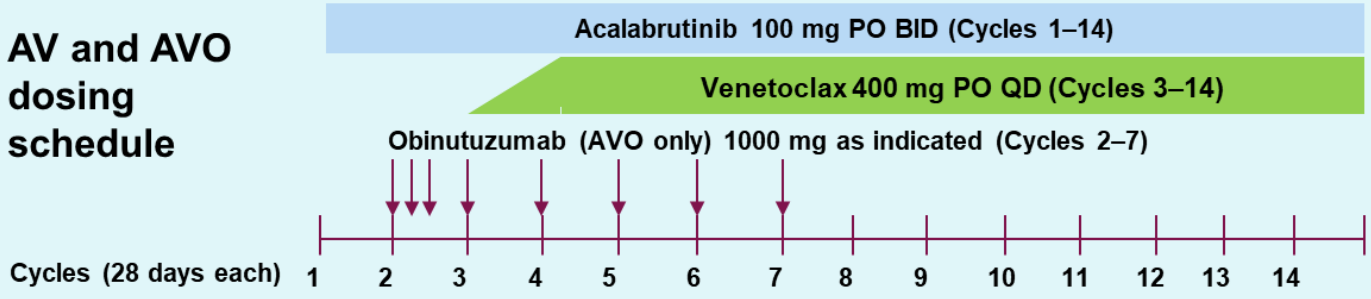
IRC-assessed PFS (AV vs FCR/BR)

If primary endpoint met, the following were

Secondary endpoints (tested in fixed sequential hierarchy)

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

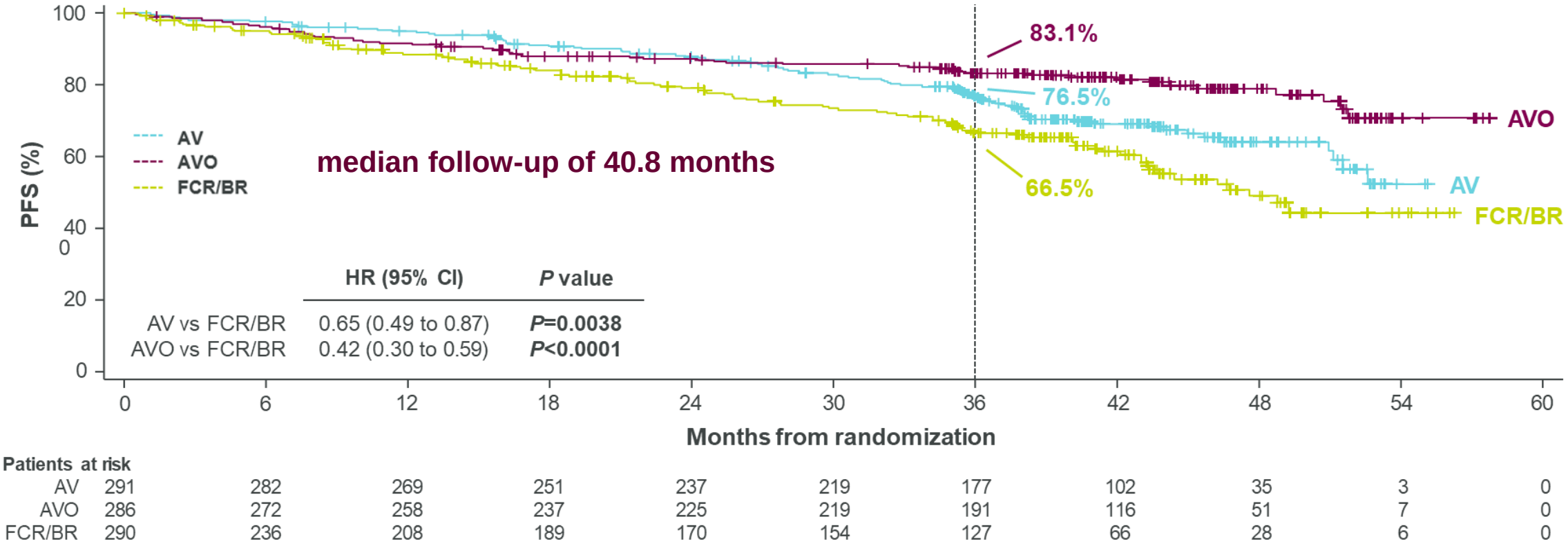
AV and AVO dosing schedule



Median age 61 years BUT >25% of patients in both AV and AVO arms (27.1% and 26.6%, respectevely) are older than 65

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

AMPLIFY primary endpoint: 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

AMPLIFY was **deeply impacted by the peak of the COVID-19 pandemic during the treatment phase**

Major COVID-19 impact on AV/AVO arms vs FCR/BR is due to the AV/AVO longer duration of treatment

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

AMPLIFY: events of clinical interest

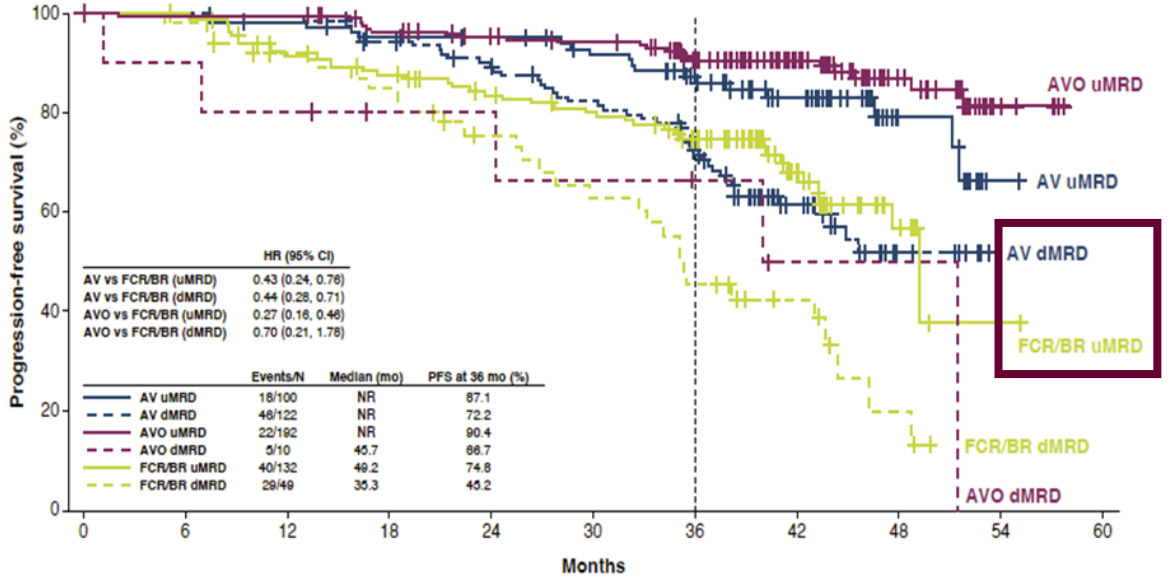
	AV (n=291)		AVO (n=284)		FCR/BR (n=259)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any ECI	222 (76.3)	136 (46.7)	242 (85.2)	188 (66.2)	185 (71.4)	141 (54.4)
Cardiac events	27 (9.3)	5 (1.7)	34 (12.0)	7 (2.5)	9 (3.5)	3 (1.2)
Atrial fibrillation/flutter	**2 (0.7)**	**1 (0.3)**	**6 (2.1)**	**2 (0.7)**	**2 (0.8)**	**2 (0.8)**
Ventricular tachyarrhythmia	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)

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

MRD persistency and impact on PFS

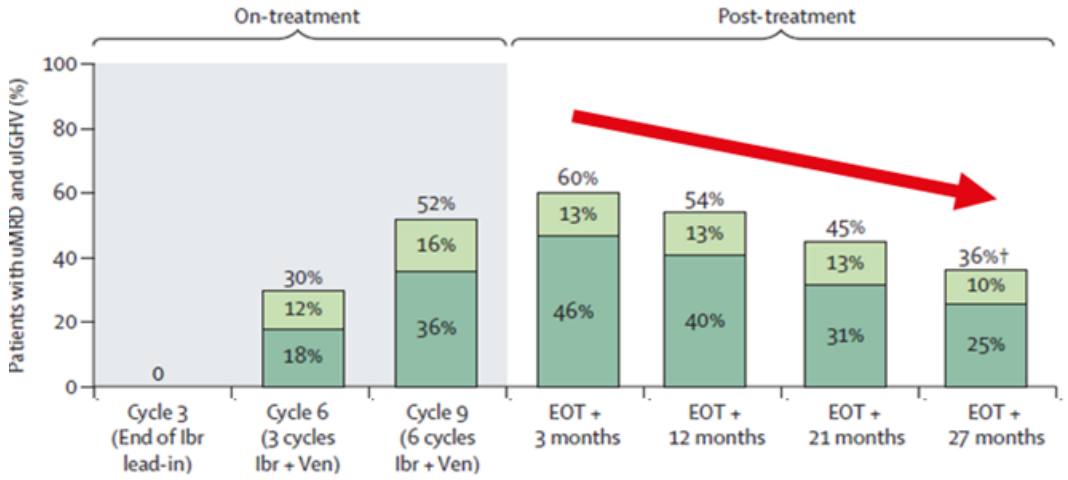
AMPLIFY (AV)

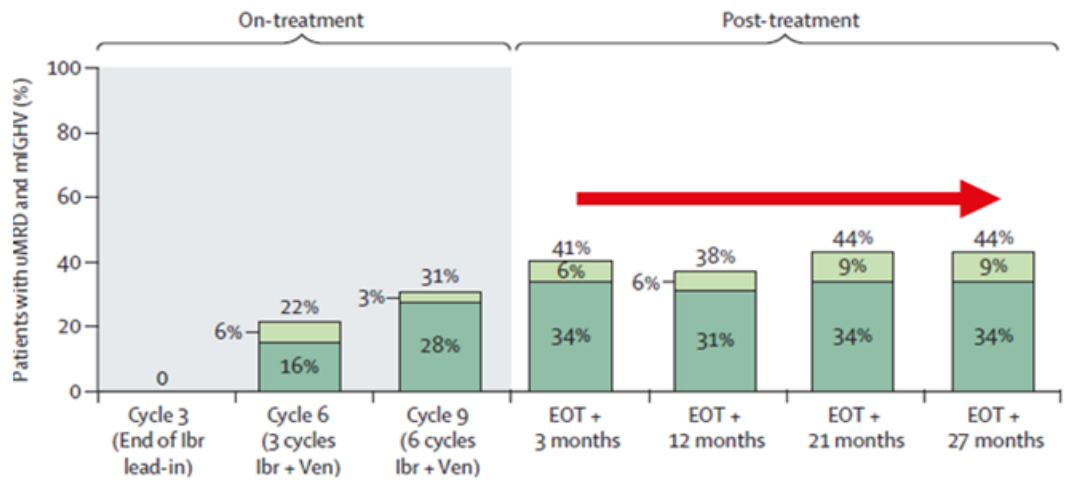
- Globalmente, il 38% dei pz valutabili raggiunge la uMRD @EOT+3
- La uMRD si mantiene nel tempo, indipendente dallo stato IGHV



AV treated patients show durable PFS even when not achieving EOT uMRD

GLOW (IV)





Niemann CU et al. Lancet Oncolol 2023; Ghia et al., Poster Presentation EHA 2025

PFS and TTNT comparison for FD regimens

	3-year PFS	3-year TTNT	UMRD rate @EOT+3
CAPTIVATE	88%[3]	**89%**[4]	57%[5]
GLOW	77%[6]	**92%**[6]	55%[7]
CLL17	79%[8]	N/A	47%[8]
AMPLIFY	76.5%[1]	**88.5%**[2]	30%[1]

1 Brown et al. *N Engl J Med*. 2025; 2 Ghia et al ASH 2025 abstract 3898; 3 Barr PM et al. *J Clin Oncol. 2*023; 4 Barr PM et al. *J Clin Oncol.* 2023 (extrapolated from KM curves); 5 Tam C et al. *Blood* 2022, supplementary material; 6 Niemann C et al *Lancet Oncol* 2023, extrapolated from KM curves; 7 Kater A et al. *NEJM evidence* 2022; 8 Al-Sawaf O et al ASH 2025 abstract 2071.

Quale parametro giudicate più rilevante nel valutare l'efficacia di una terapia di prima linea

1) Percentuale di remissioni complete (CRR)
2) Percentuale di pazienti che ottengono una malattia minima residua non misurabile (uMRD)
3) Durata della progression free survival (PFS)
4) Tempo al successivo trattamento (TTNT)