AMPLIANDO opciones para el tratamiento de la LLC

Dr. Miguel A. Pavlovsky

Director Médico-Científico

Fundaleu

45 años varón sin antec patológicos

- Derivado a la consulta por leucocitosis en análisis de rutina
- Laboratorio inicial febrero 2019: GB 23.500/uL , Linfos 68%, Hb 16.9 g/dl, Plaq 147.000/uL, LDH normal.
- Examen fisico: Linfadenopatias y esplenomegalia
- TC (03/2019): Linfadenopatias cervicales, supraclaviculares y axilares de 24 y 20mm. Esplenomegalia con adenopatías en hilio hepático, tronco celiaco y precava.
- **Citometria de Flujo: linfos clonales CD19+,CD5+, CD20 +, CD200 +, CD23+, CD38 -**
  IGHV status: Unmutated IGVH

- **Cytogenetico:** Cariotipo complejo:
- 43-46 XY, del11(q21q23), add(15)(p11.2), -18,-22, i(22)(p10)
- **FISH:** 17 Deleción Negativa**. Del 11q positiva.**

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LLC (04/2019) IGVH no mutado. RAI II. Binet B. Cariotipo complejo. Del 11q.

Estudios diagnósticos - pronósticos

CELULAS PATOLOGICAS

91,7 % células de tamaño pequeño a mediano (de acuerdo con los parámetros de dispersión de luz) , CD45++, CD1-++, CD20-/+v, CD38-/+d, CD10(-), CD5++, CD23+, CD200++, CD43+d, CD79b-/+d, con restricción de cadena liviana KAPPA+d, vinculable a linfocitos B clonales.

CONCLUSIONES:

Se detecta una población(91,7 %) de linfocitos B clonales fenotípicamente compatible con linfoma de pequeños linfocitos/leucemia linfática crónica B .

Specimen: Peripheral Blood
Collected: 08/19/2020
Received: 08/21/2020
Reported: 08/30/2020
Clinical Hx: Screening

Client Address: 2200 Bridge Pkwy, Ste 202
Redwood City, CA 94065
Telephone: 650-591-2800

IGHV HYPERMUTATION ANALYSIS REPORT

Results:	**IGHV Family:**	V3-9
	Functionality:	Productive
	Mutation Frequency:	0%
Interpretation:	***Unmutated***	

Description: The mutation status of the unique immunoglobulin gene (IGHV) rearrangement in the monoclonal proliferation of B-cells in chronic lymphocytic leukemia (CLL) is considered to have prognostic value. If mutations are detected at a level of 2% or higher in the sequenced V region of the clonal rearrangement, then the result is interpreted as "Mutated". If mutations are detected at a level below 2% in the sequenced V region of the clonal rearrangement, then the result is interpreted as "Unmutated". Those patients with a mutated IGHV gene usually have a less aggressive and more indolent disease, with longer overall survival. Those patients with an unmutated IGHV gene usually have a more aggressive disease and shorter overall survival.

This assay utilizes PCR to detect a monoclonal IGHV rearrangement followed by sequence analysis to determine the specific IGHV family and mutation frequency. The sensitivity of the assay is 10%. Samples in which the monoclonal B-cells are present at less than 10%, a specific IGHV rearrangement will not be

Received: 08/21/2020
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CYTOGENETICS REPORT

Procedure: GTG-banding
Chromosome band-resolution: 350-450
Culture: 24 Hr. Unstimulated, 72 Hr. Stimulated w/ DSP30/IL-2 and 72 Hr. Stimulated w/ PHA/IL-2

Metaphases analyzed and cells counted: 20/20
Metaphases Karyotyped: 5
Metaphases Captured: 7

Karyotype:	**43~46,XY,del(11)(q21q23),add(15)(p11.2),-18,-22,i(22)(p10)[cp20]**
Summary:	**Complex Karyotype**
Interpretation:	Cytogenetic analysis showed complex clonal abnormalities in all the cells analyzed. Complex karyotypes are found in approximately 16% of CLL. These cases form an independent group associated with less favorable prognosis.

The results of this analysis do not exclude the possibility of genetic alterations below the band-resolution of this test or abnormalities due to other etiologies.

Criterios de Inicio de tratamiento

Duplicación linfocitaria entre diciembre 2019 - abril 2020

- Linfadenopatias y esplenomegalia progresiva en evaluación clínica y por TC (3/2019 – 8/2020)

	Dec 2019	April 2020
GB	62.200/ul	109.500/ul
Linfocitos	50.076/ul	102.930/ul

- 8/20 BMO 99% de infiltración por LLC

Material: MEDULA OSEA
Biopsia con aguja

MACROSCOPÍA
Se recibe cilindro óseo que mide 1 x 0.3 cm
Metodología: Estudio seriado.
Técnicas especiales: 1.- Fibras de reticulina (Gomori)
2.- Depósitos de colágeno y osteoide (Tricrómico de Masson)
3.- Hierro (Perls - Ferrocianuro de potasio)
Inmunomarcación

MICROSCOPÍA
Las secciones histológicas muestran cilindro óseo con caracteres adecuados para evaluación.
La celularidad global representa el 90% del volumen de los espacios medulares en relación al componente adiposo, distribuido en forma regular.
Destaca infiltración intersticial difusa por células linfoides B (CD20+ débil/heterogéneo) pequeños, monomorfos, con escaso citoplasma y membrana nuclear regular, representando el 99% de la celularidad global. Muestran coexpresión para Bcl2, CD5 y CD23, resultando negativos para Ciclina D1.
El tejido hematopoyético remanente está representado por aislados nidos de precursores eritroides, granulocitos maduros y megacariocitos típicos.
Con técnica de Gomori la trama de reticulina está preservada.
No se observa incremento del hierro de depósito con técnica de Perls.

DIAGNÓSTICO
Biopsia con aguja. Médula Ósea
INFILTRACION DE MEDULA OSEA POR LEUCEMIA LINFOCITICA CRONICA/LINFOMA DE LINFOCITOS PEQUEÑOS (LLC/LLP, OMS 2017).
NOTA: Se sugiere correlacionar estos hallazgos con estudio por citometría de flujo.

Dra. Marina I. Narbaitz

Terapias target para LLC primera linea

Continuas

- Ibrutinib
- Acalabrutinib +/- obinutuzumab
- Zanubrutinib

Tiempo limitado

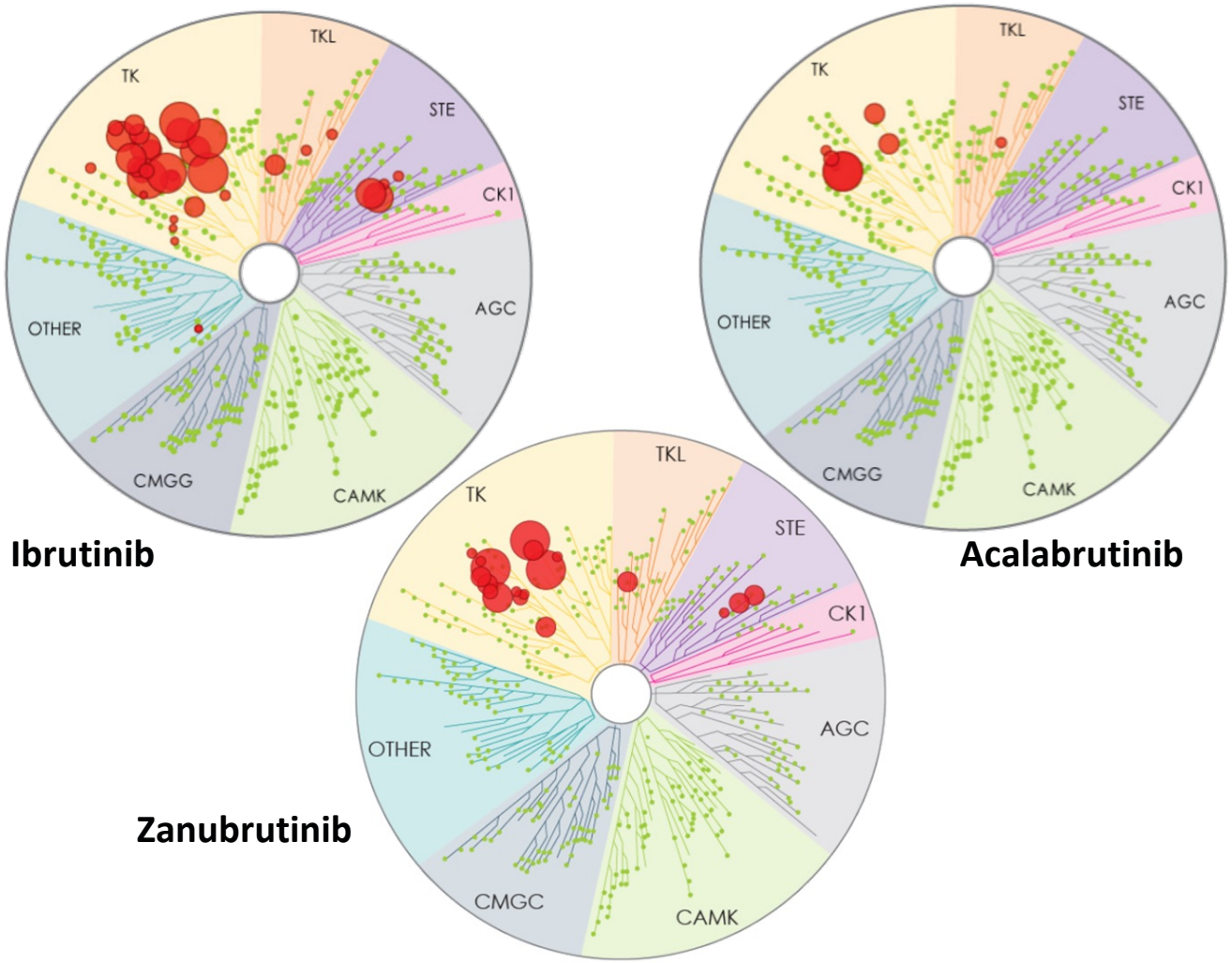
- 1 yr Ven + obinutuzumab
- 1 yr Ven + ibrutinib (aprobado fuera de USA)
- 1 yr Ven + acalabrutinib +/- obinutuzumab (proximo a aprobarse)

Kinase Selectivity of BTK Inhibitors

Adverse events	Cell type	Kinase	Ibrutinib	Acalabrutinib	Zanubrutinib
Infection	B-lymphocyte	BTK	⊣	⊣	⊣
		TEC	⊣	n.i.	⊣
	T-lymphocyte	ITK	⊣	n.i.	n.i.
		TEC	⊣	n.i.	⊣
		RLK/TXK	⊣	⊣	⊣
	Macrophage Neutrophil	BTK	⊣	⊣	⊣
		TEC	⊣	n.i.	⊣
** Bleeding	Thrombocyte	BTK	⊣	⊣	⊣
		TEC*	⊣	n.i.	⊣
			minor bleeding		
Atrial fibrillation	Cardiomyocyte	HER2	⊣	n.i.	n.i.
		HER4	⊣	⊣	⊣
		TEC*	⊣	n.i.	⊣
			atrial fibrillation: frequent	less frequent	rare
Rash Diarrhoea	Epithelial cell	EGFR*	⊣	n.i.	⊣
			diarrhoea/rash		
Unclear	Endothelial cell	BMX	⊣	⊣	⊣
	Lymphoid tissue	JAK3	⊣	n.i.	⊣

Kinase Selectivity Profiling at 1 µmol/L (in vitro)

Larger red circles represent stronger inhibition



Kaptein. ASH 2018. Abstr 1871.

Estupiñán et al Cell Dev. Biol., 11 March 2021

Tratamientos continuos: Menos eventos adversos con iBTK 2G (EA grado 3)

Trial	Median Follow-Up (Months)	AFib (*)	Hypertension	Bleeding	Infections ^	Arthralgia
Resonate-2	18.4	IBRU *6%/1.5%; CHLOR 0.7%	IBRU 4%; CHLOR 0%	IBRU 4% CHLOR 2%	8% 4%	IBRU 16% **; CHLOR 7%;
Alliance	38	IBR *17%/9%; IBR + R *14%/6% BR 3%/3%	IBR 29%; IBR + R 34%; BR 15%	IBR 2% IBR + R 4% BR 0%	20% 20% 15%	NR
iLLUMINATE	31.3	IBRU + O *12%/5%; CHLOR + O 0%	IBRU + O 4%; CHLOR + O 4%	NR	11% 5%	IBRU + O 1% CHLOR + O 0%
ACAL + O, ACAL, Chlor + O	28.3	A *4%; A + O *3%; CHLOR + O: *1%	A 2%; A + O 3%	A 2%; A + O 2%	11% 3.9% 2.4%	A 0.6%; A + O 1.1%
SEQUOIA	26.2	ZANU *3%; BR *3%	ZANU 6%; BR 5%	ZANU 3.5% BR 1.5%	3% 5%	ZANU 1%; BR 0.5%

(*) all grades/grade $\geq$ 3; ** all grades; ^ infections including pneumonia.

Urso A. et al. Cancers 2023, 15, 3859.

Tratamientos finitos: CLL14 y GLOW toxicidad

Table 3. Percentage of grade ≥ 3 adverse events of clinical interest with venetoclax-containing regimes at the time of primary analyses in phase 3 clinical trials in previously untreated older patients.

Trial	Median Follow-Up (Months)	Infusion Related Reactions	Tumor Lysis Syndrome	Neutropenia	Infections	AFib *	Reference
CLL14	28.1	V + O 9%; Chlor + O 10.3%	V + O 0.5%; Chlor + O 1.9%	V + O 52.8%; Chlor + O 48.1%	V + O 17.5%; Chlor + O 15.0%	NA	[20]
GLOW	27.7	NA	Ibr + V 0%; Chlor + O 5.7%	Ibr + V 34.9%; Chlor + O 49.5%	Ibr + V 12.3%; Chlor + O 8.6%	Ibr + V ^ 14%/6%; Chlor + O 1.9%/0%	[23]

(*) all grades/grade ≥ 3; IBR: ibrutinib; Chlor: chlorambucil; O: obinutuzumab; V: Venetoclax; AFib: atrial fibrillation; NA: not applicable; ^ four sudden deaths, all in patients with high comorbidities and an ECOG PS

Urso A. et al. Cancers 2023, 15, 3859.

ELEVATE-TN study design

TN CLL (N=535)

Key inclusion criteria

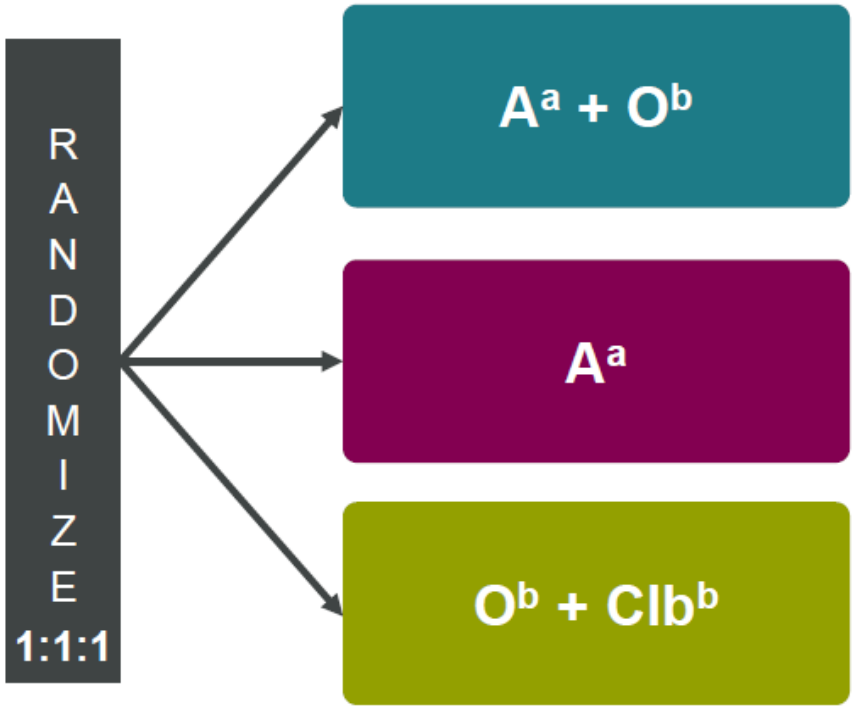
- Age ≥65 years, or >18 to <65 years with:
  - Creatinine clearance 30–69 mL/min (by Cockcroft-Gault equation)
  - CIRS-G score >6
- TN CLL requiring treatment per iwCLL 2008 criteria[6]
- ECOG PS ≤2

Key exclusion criteria

- Significant cardiovascular disease

Stratification

- del(17p), yes vs no
- ECOG PS 0–1 vs 2
- Geographic region



Primary endpoint

- PFS (IRC-assessed): A+O vs O+Clb

Secondary/other endpoints

- PFS (IRC-assessed): A vs O+Clb
- PFS (INV-assessed)
- ORR (IRC- and INV-assessed)
- TTNT
- OS
- uMRD
- Safety

***Crossover** from O+Clb to A was allowed after IRC-confirmed progression*

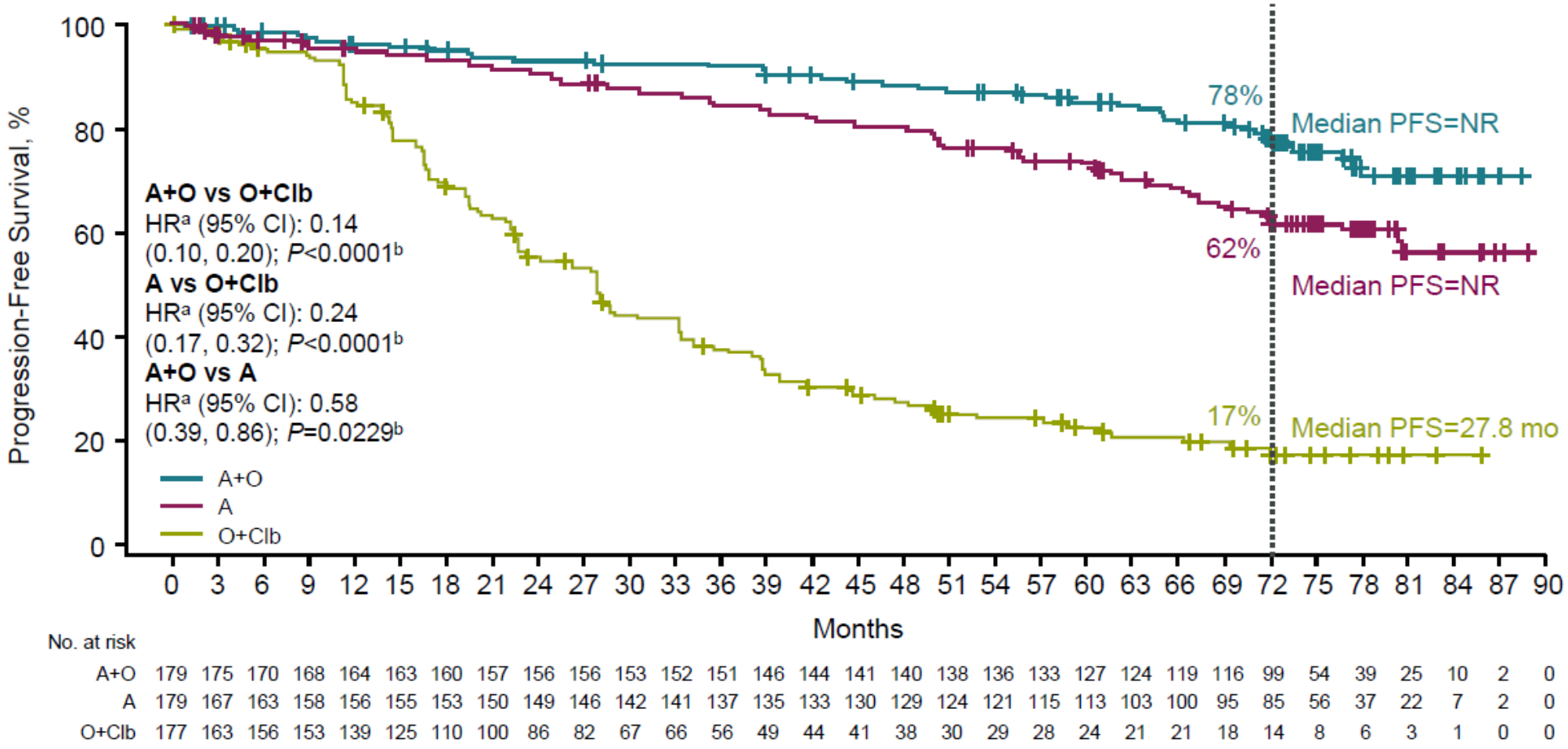
Note: After interim analysis, PFS assessments were by investigator only.[3] All analyses are ad-hoc and *P*-values are descriptive.

NCT02475681. Data cutoff: March 3, 2023. Patients were enrolled between September 2015 and February 2017.

[a]Continued until disease progression or unacceptable toxicity at 100 mg PO BID.

[b]Treatments were fixed duration and administered for 6 cycles.

Median PFS was significantly higher for A-containing arms vs O+Clb

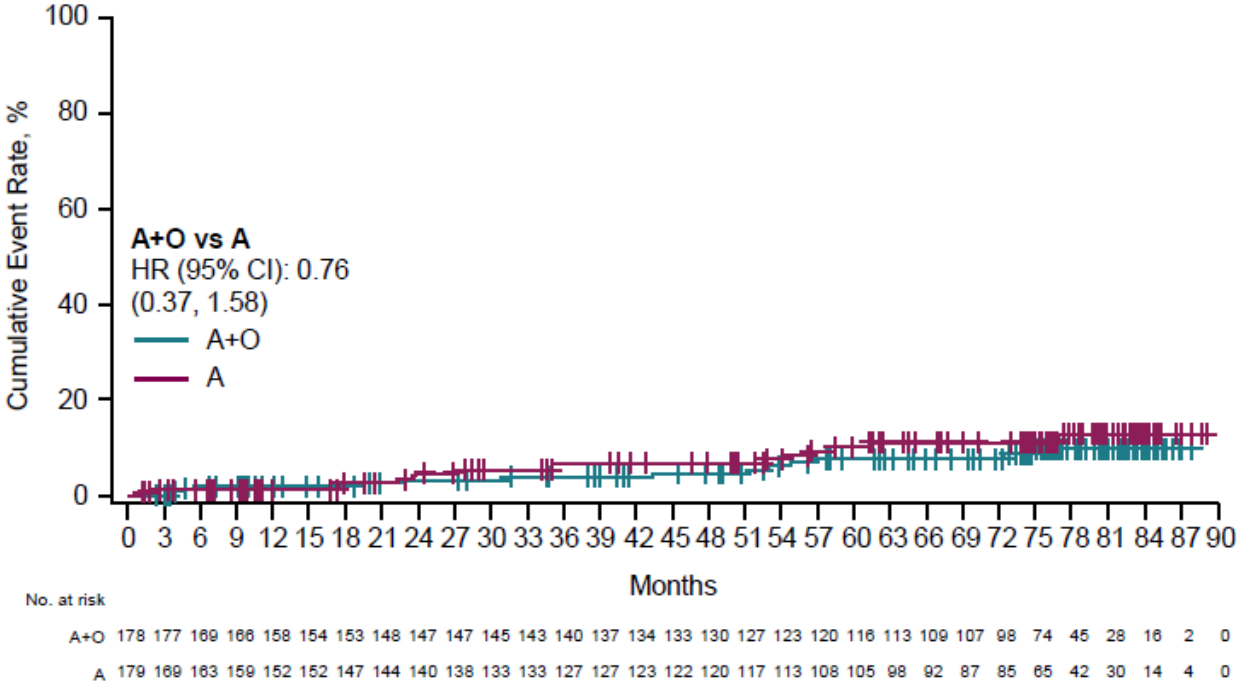


- Median PFS was significantly higher for A+O vs A

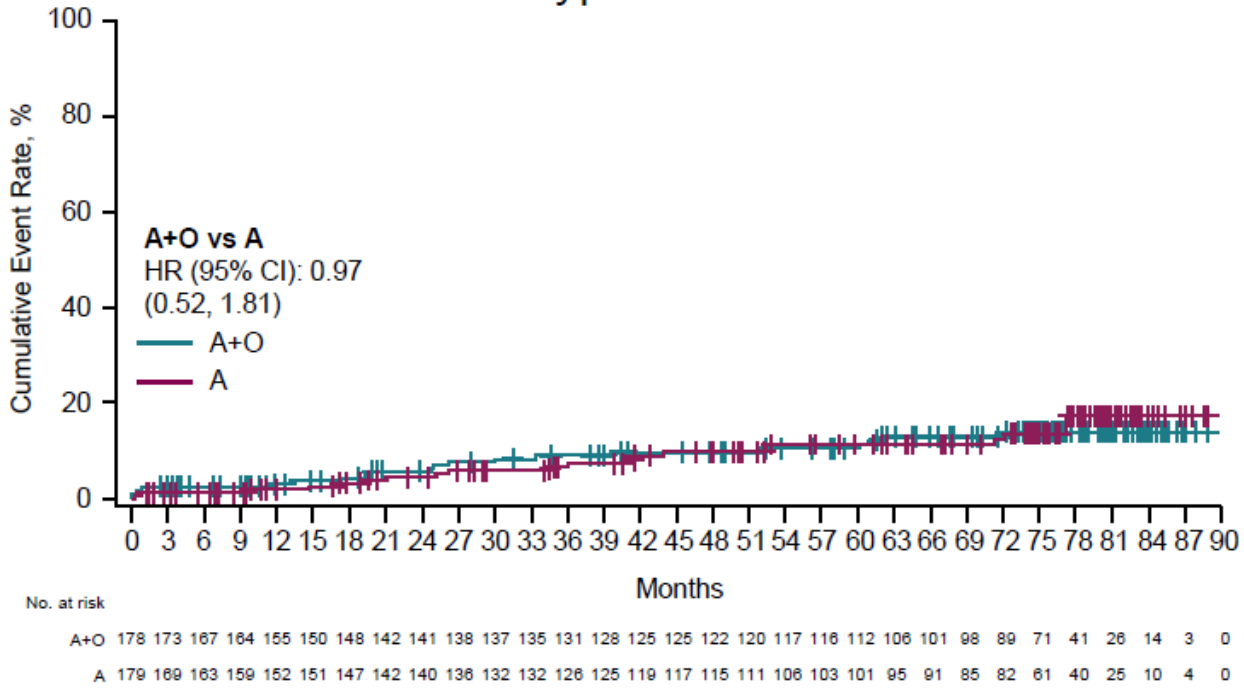
[a]Hazard ratio based on stratified Cox proportional-hazards model.
[b]*P*-value based on stratified log-rank test.

Incidence of cardiac-related AEs remains low

Cumulative incidence of any-grade atrial fibrillation/flutter



Cumulative incidence of any-grade hypertension



ELEVATE-RR: Phase 3 Randomized Non-inferiority Open-Label Trial

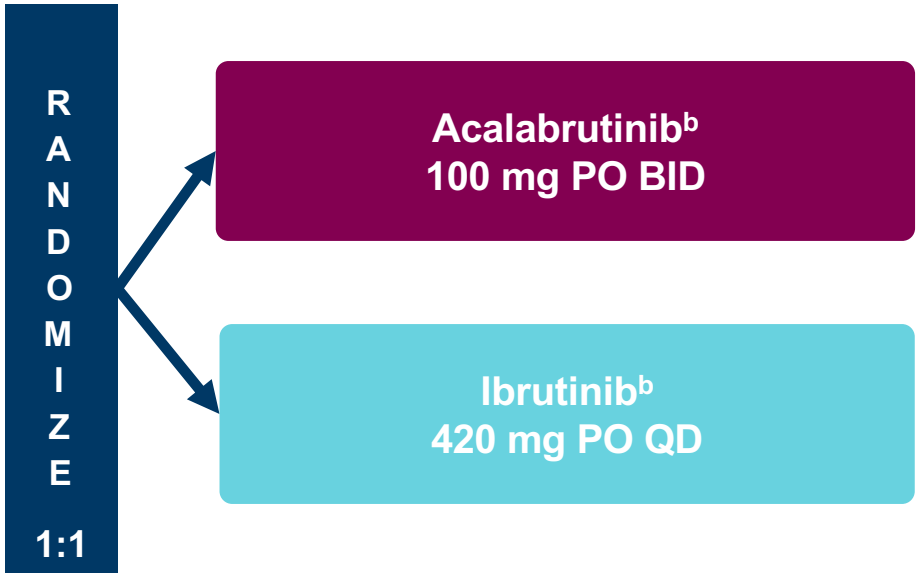
Patients (N=533)

Key Inclusion Criteria

- Adults with previously treated CLL requiring therapy (iwCLL 2008 criteria[1])
- Presence of del(17p) or del(11q)[a]
- ECOG PS of ≤2

Stratification

- del(17p) status (yes or no)
- ECOG PS (2 vs ≤1)
- No. prior therapies (1–3 vs ≥4)



Primary endpoint

- Non-inferiority on IRC-assessed PFS[c]

Secondary endpoints (hierarchical order):

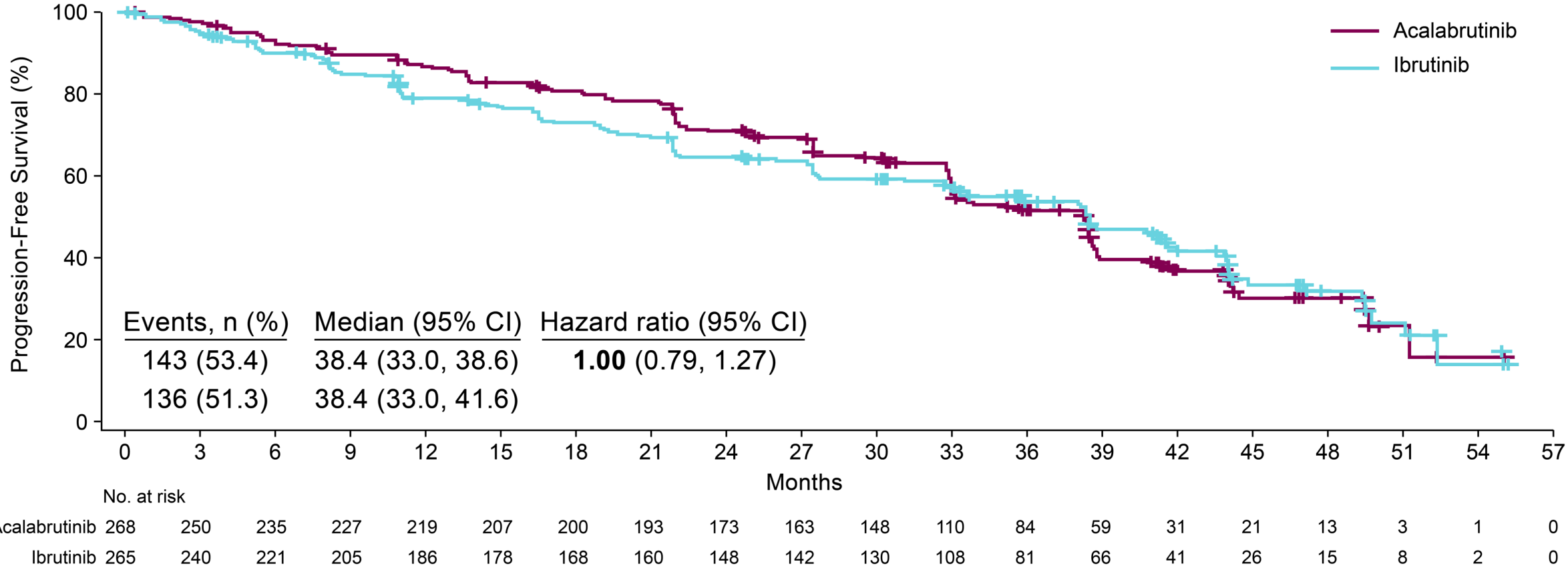
- Incidence of any grade atrial fibrillation/flutter
- Incidence of grade ≥3 infection
- Incidence of Richter transformation
- Overall survival

Key exclusion criteria: Significant CV disease; concomitant treatment with warfarin or equivalent vitamin K antagonist; prior treatment with ibrutinib, a BCR inhibitor, (eg, BTK , PI3K, or Syk inhibitors) or a BCL-2 inhibitor (eg, venetoclax)

NCT02477696 (ACE-CL-006).
[a]By central laboratory testing; [b]Continued until disease progression or unacceptable toxicity; [c]Conducted after enrollment completion and accrual of ~250 IRC-assessed PFS events.
Afib/flutter, atrial fibrillation/flutter; BCL-2, B-cell leukemia/lymphoma-2; BCR, B-cell receptor; BID, twice daily; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CV, cardiovascular; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent review committee; iwCLL, International Workshop on CLL; PFS, progression-free survival; PI3K, phosphatidylinositol 3-kinase; PO, orally; QD, once daily.
1. Hallek M, et al. *Blood*. 2008;111:5446-56.

Byrd John, etal. ASCO 2021. Oral presentation

Primary Endpoint: Non-inferiority Met on IRC-Assessed PFS



Median follow-up: 40.9 months (range, 0.0–59.1).

CI, confidence interval; IRC, independent review committee; PFS, progression-free survival.

Byrd John, etal. ASCO 2021. Oral presentation

Safety Summary

Event	Acalabrutinib (n=266)	Ibrutinib (n=263)
Duration of treatment exposure, median (range), months	38.3 (0.3–55.9)	35.5 (0.2–57.7)
Any grade AEs	260 (97.7)	256 (97.3)
Grade ≥3 AEs	183 (68.8)	197 (74.9)
AEs leading to treatment discontinuation	39 (14.7)	56 (21.3)
Serious AEs	143 (53.8)	154 (58.6)
Deaths due to AEs[a]	17 (6.4)	25 (9.5)

Values are reported as n (%) unless stated otherwise.
[a]Includes deaths occurring within 30 days of last dose; deaths occurring after the start of subsequent anticancer therapy were not included in the assessment of deaths within 30 days of last dose, regardless of time after last dose.
AE, adverse event.

ELEVATE-RR: Lower Incidence of Key AEs With Acalabrutinib vs Ibrutinib[1]

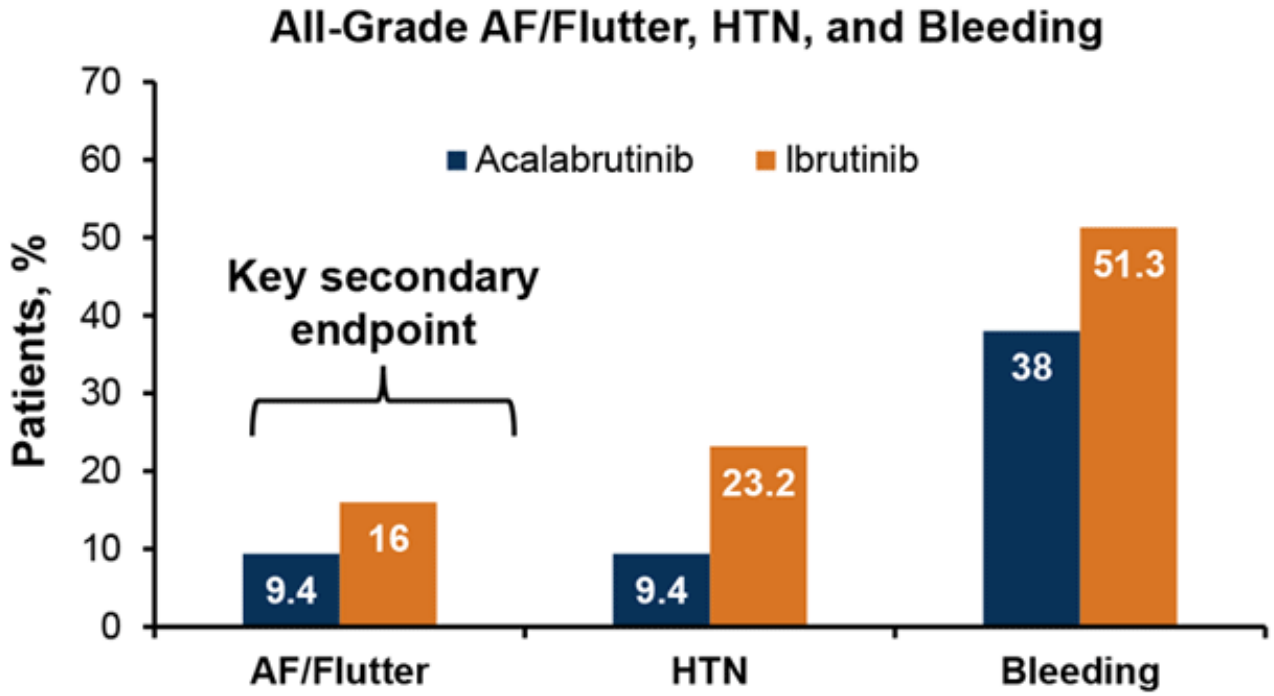
After Median Follow-Up of 40.9 Months

Non-inferior PFS (primary endpoint)

- Median PFS of 38.4 mo in both arms (HR = 1.00)

Lower cumulative incidences of

- AF/flutter (HR = 0.52)
- Hypertension (HR = 0.34)
- Bleeding (HR = 0.63)
- Diarrhea (HR = 0.61)
- Arthralgia (HR = 0.61)



Byrd JC et al. J Clin Oncol. 2021;39:3441-3452.

Varón 46 años LLC (04/2019) IGVH no mutado. RAI 2. Binet B. Cariotipo complejo. Rai II. Del 17p (-) / Del 11q (+)

Varón 46 años LLC (04/2019) IGVH no mutado. RAI 2. Binet B. Cariotipo complejo. Rai II. Del 17p (-) / Del 11q (+)

Key eligibility criteria

- Previously untreated CLL
- Without del(17p) or *TP53* mutations
- ECOG PS ≤2

RANDOMIZE 1:1:1

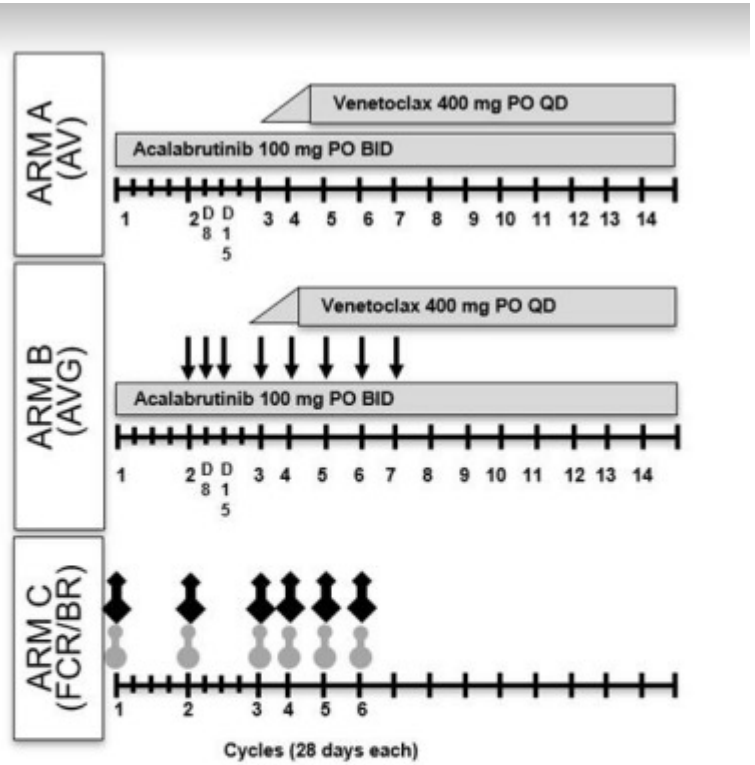
- **Acalabrutinib + venetoclax (AV)** Up to 1 year
- **Acalabrutinib + venetoclax + obinutuzumab (AVO)** Up to 1 year
- **FCR or BR** Up to 6 cycles

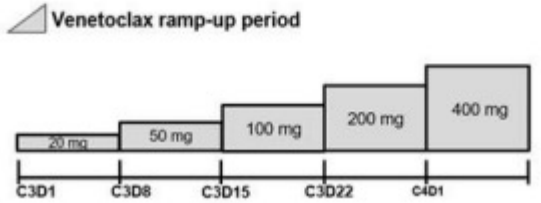
Primary endpoint

- PFS (IRC assessed) of AV vs FCR/BR

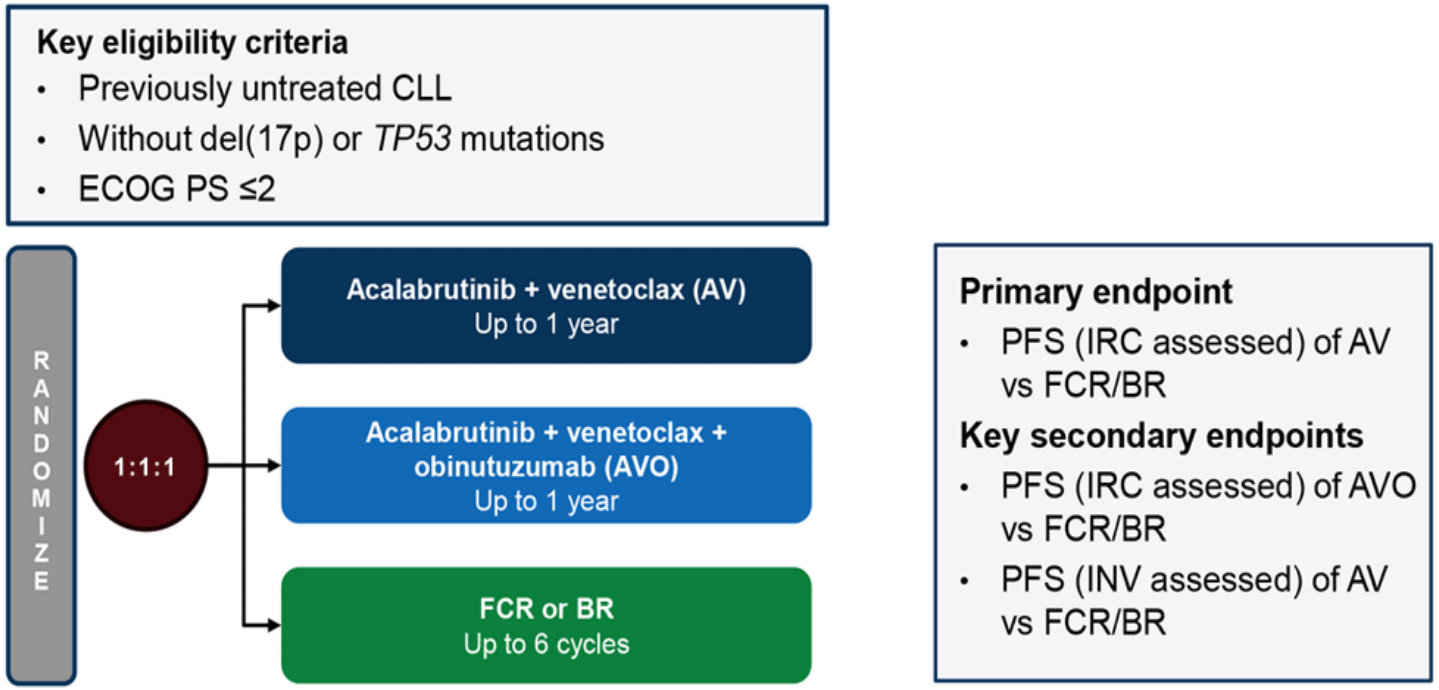
Key secondary endpoints

- PFS (IRC assessed) of AVO vs FCR/BR
- PFS (INV assessed) of AV vs FCR/BR





Varón 46 años LLC (04/2019) IGVH no mutado. RAI 2. Binet B. Cariotipo complejo. Rai II. Del 17p (-) / Del 11q (+)

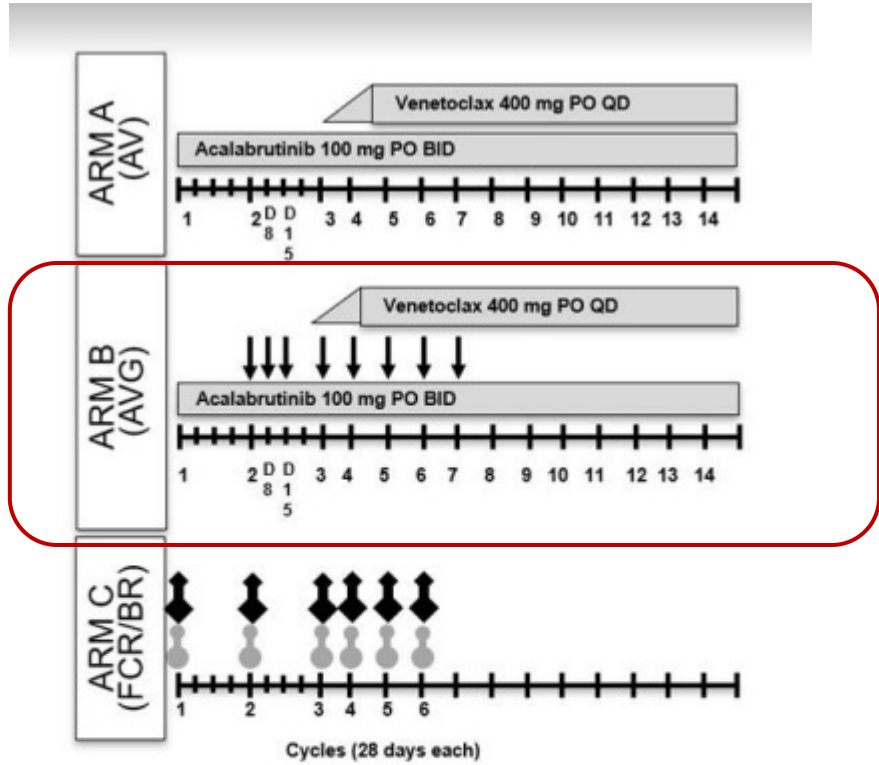


Primary endpoint

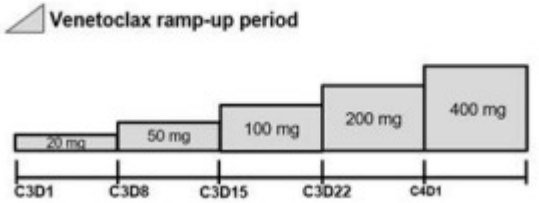
- PFS (IRC assessed) of AV vs FCR/BR

Key secondary endpoints

- PFS (IRC assessed) of AVO vs FCR/BR
- PFS (INV assessed) of AV vs FCR/BR



Randomizado a rama B:
AVG (Acalabrutinib+ Venetoclax + Obinutuzumab.
Alto riego de Lisis tumoral. ECOG 0.



-Tratamiento desde el 14/09/2020 hasta 10/2021.

Eventos adversos de tratamiento con AVO

- Inicia tratamiento en 2020
- **GB 188.700/uL** , Linfos 79%, Hb 15 g%, Plaq 124.000/uL, LDH 422 (< 240). Prot gamma 1.35 gr/dl, **comp M 1gr/dl, IEF: IgM 1087**, IgG 428 e IgA 28. Adenomegalias y esplenomegalia progresiva

Eventos Adversos:

- Durante 1ra infusion de Obinutuzumab 100 mg presenta reaccion infusional con escalofríos, subfebril, taquicardia, se suspende infusion por 4 horas y reanuda luego de medicar con Solumedrol **(grado 3)**
- Trombocitopenia **grado 2**

Plaq	10/20	11/20	12/20	01/21	02/21	03/21	04/21	05/21	06/21	07/22
	94.000	102.000	88.000	124.000	103.000	90.000	114.000	121.000	119.000	153.000

Evaluacion post-tratamiento

- ***Respuesta global basada en lab:*** linfocitos normales (4.420 /uL), Hb >11 g/dl (15,7 g%) y plaquetas >100.000 (132.000 /uL) con examen físico normal. Sin comp M

Remisión Completa Hematologica

- ***Respuesta basada en TC***: por presentar ganglio residual axilar izquierdo de 21x16 mm

Resto de las imágenes normales

Remisión Parcial x imágenes

- Al finalizar tratamiento (fuera de protocolo)→ Citometria de sangre periférica (09/2021): Linfocitos B clonales no detectables con sensibilidad de 0,00098% (10<5).

Apéndice 2. Criterios para la evaluación de respuesta (modificado de Hallek et al. 2018)

Definición de respuesta después del tratamiento de pacientes con LLC

Grupo	Parámetro	RC	RP	EP	EE
A	Ganglios linfáticos	Ninguno ≥1,5 cm	Disminución ≥50% (desde inicial)[a]	Aumento ≥50% desde inicial o desde respuesta	Cambio de -49% a +49%
	Tamaño de hígado y/o bazo[b]	Tamaño de bazo <13 cm; tamaño normal de hígado	Disminución ≥50% (desde inicial)	Aumento ≥50% desde inicial o desde respuesta	Cambio de -49% a +49%
	Síntomas constitucionales	Ninguno	Alguno	Alguno	Alguno
	Recuento linfocitario circulante	Normal	Disminución ≥50% desde inicial	Aumento ≥50% desde inicial	Cambio de -49% a +49%
B	Recuento de plaquetas	≥100 000/µl	≥100-000/µl o aumento ≥50% desde inicial	Disminución de ≥50% desde inicial conse-cuencia de LLC	Cambio de -49% a +49%
	Hemoglobina	≥11,0 g/dl (no trans-fundidos y sin eritro-poyetina)	≥11 g/dl o aumento ≥50% desde inicial	Disminución de ≥2 g/dl desde inicial conse-cuencia de LLC	Aumento <11,0 g/dl o <50% desde inicial, o disminución >2 g/dl
	Médula	Normocelular sin células de LLC, sin ganglios linfáticos B	Presencia de células de LLC, o de ganglios lin-fáticos B, o no realizado	Aumento de células de LLC en ≥50% en biopsias sucesivas	Sin cambio en infiltrado de médula

P1009

Fixed-Duration Acalabrutinib plus Venetoclax With or Without Obinutuzumab versus Chemoimmunotherapy for First-Line Treatment of Chronic Lymphocytic Leukemia: Interim Analysis of the Multicenter, Open-Label, Randomized, Phase 3 AMPLIFY Trial

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Brown J, et al. ASH 2024. Oral presentation

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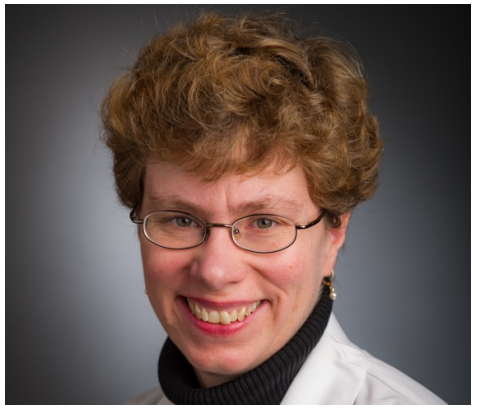

ORIGINAL ARTICLE

Fixed-Duration Acalabrutinib Combinations in Untreated Chronic Lymphocytic Leukemia

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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)

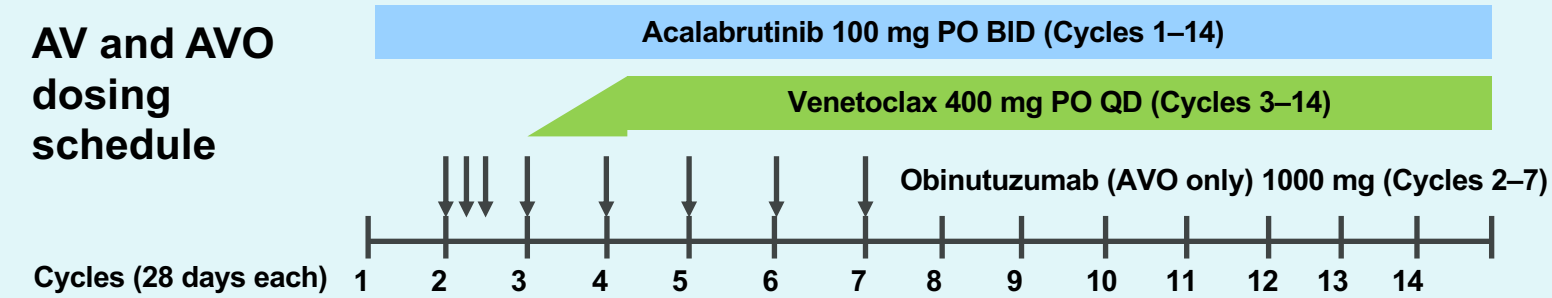
***Crossover** not built into protocol*

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



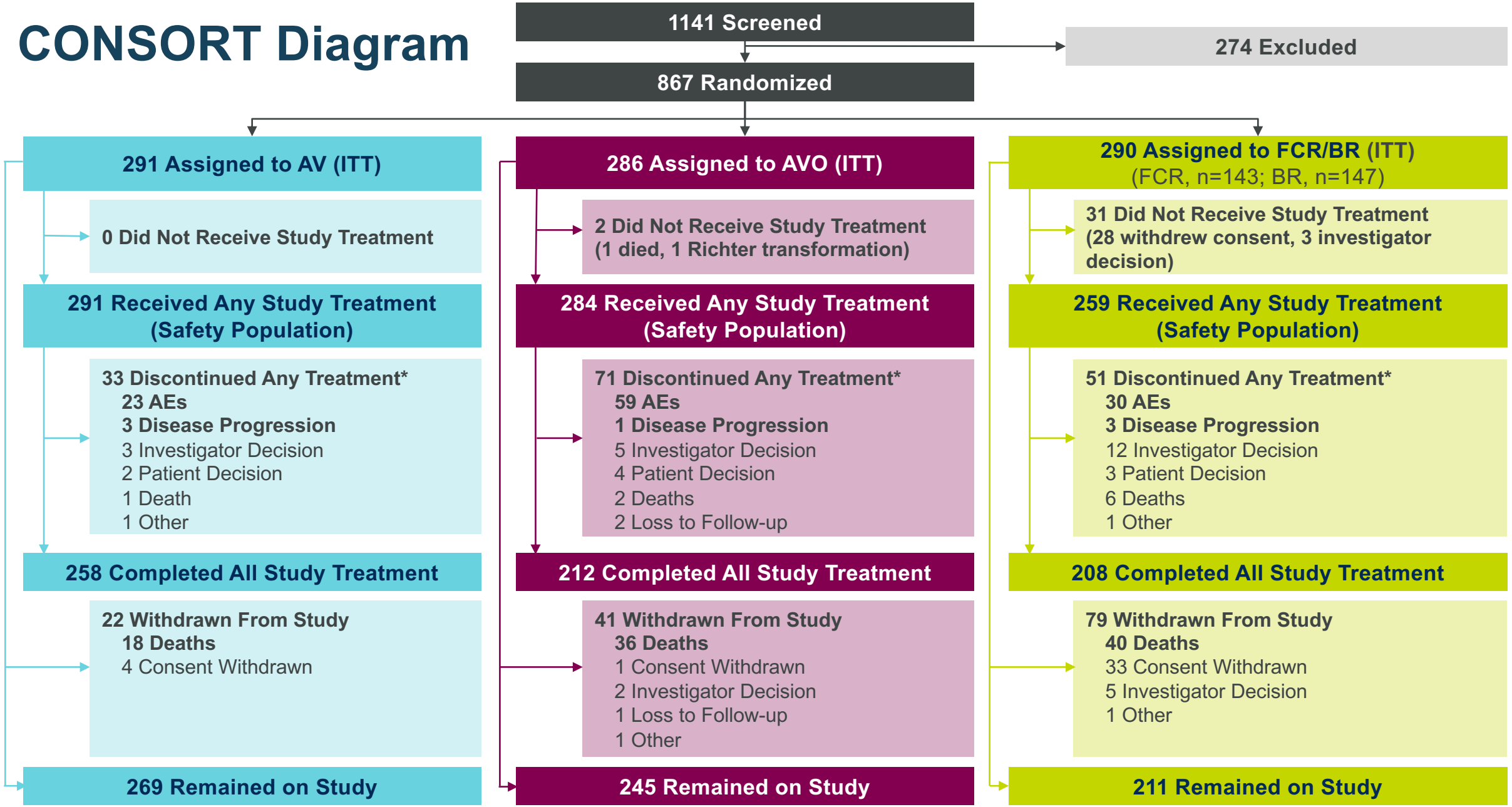
NCT03836261. Data cutoff: April 30, 2024.

[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; ORR, overall response rate; 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.

CONSORT Diagram



*A reason for discontinuation was reported for each drug discontinued, and subjects are counted a maximum of once per discontinuation reason and may be counted under multiple discontinuation reasons.
AE, adverse event; AV, acalabrutinib-venetoclax; AVO, acalabrutinib-venetoclax-obinutuzumab; BR, bendamustine-rituximab; FCR, fludarabine-cyclophosphamide-rituximab; ITT, intent-to-treat.

Demographics and Baseline Characteristics

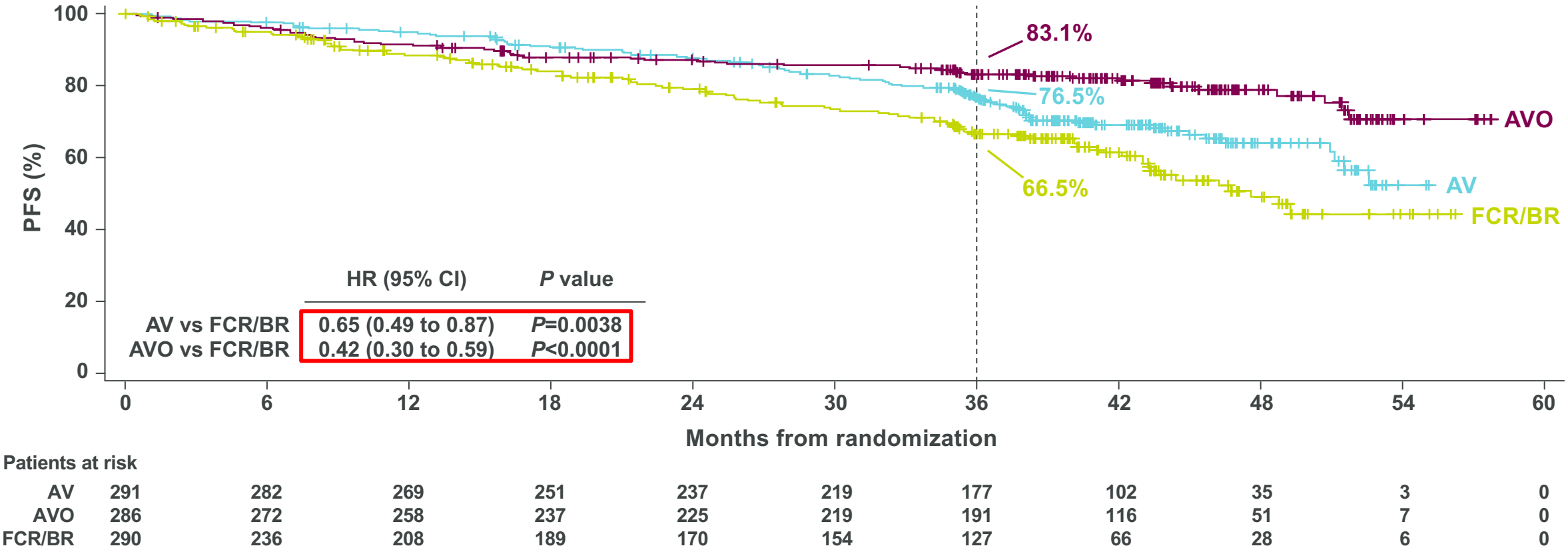
Characteristic	AV (n=291)	AVO (n=286)	FCR/BR (n=290)
Age, median (range), yr	61 (31–84)	61 (29–81)	61 (26–86)
≤65 yr	212 (72.9)	210 (73.4)	213 (73.4)
>65 yr	79 (27.1)	76 (26.6)	77 (26.6)
Male sex	178 (61.2)	198 (69.2)	183 (63.1)
ECOG PS score			
0–1	262 (90.0)	272 (95.1)	262 (90.3)
2	28 (9.6)	14 (4.9)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

*Europe includes Eastern and Western Europe; Other includes Argentina, Australia, Brazil, China, Korea, Saudi Arabia, South Africa, and Taiwan.

AV, acalabrutinib-venetoclax; AVO, acalabrutinib-venetoclax-obinutuzumab; BR, bendamustine-rituximab; ECOG PS, Eastern Cooperative Oncology Group performance status; FCR, fludarabine-cyclophosphamide-rituximab; IGHV, immunoglobulin heavy-chain variable region gene.

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

ITT population. Median follow-up from randomization: 40.8 months (range, 0–59 months).
Hazard ratio (95% CI) computed using a Cox proportional-hazards model stratified by the randomization strata. *P*-value based on stratified log-rank test.
AV, acalabrutinib-venetoclax; AVO, acalabrutinib-venetoclax-obinutuzumab; BR, bendamustine-rituximab; CI, confidence interval; FCR, fludarabine-cyclophosphamide-rituximab; HR, hazard ratio; IRC, independent review committee; ITT, intent-to-treat; NR, not reached; PFS, progression-free survival.

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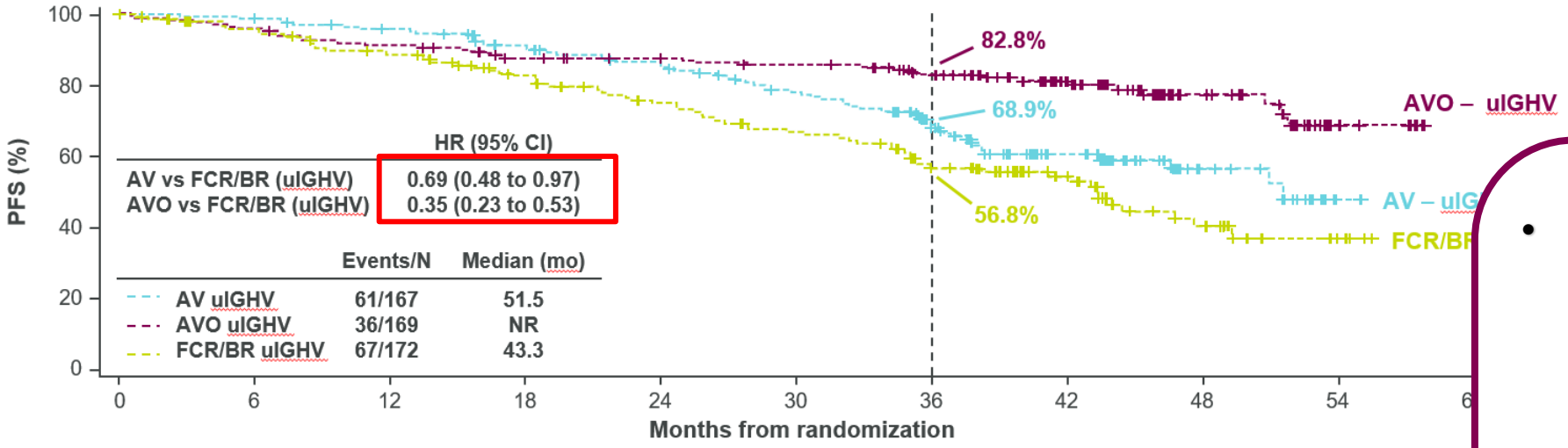
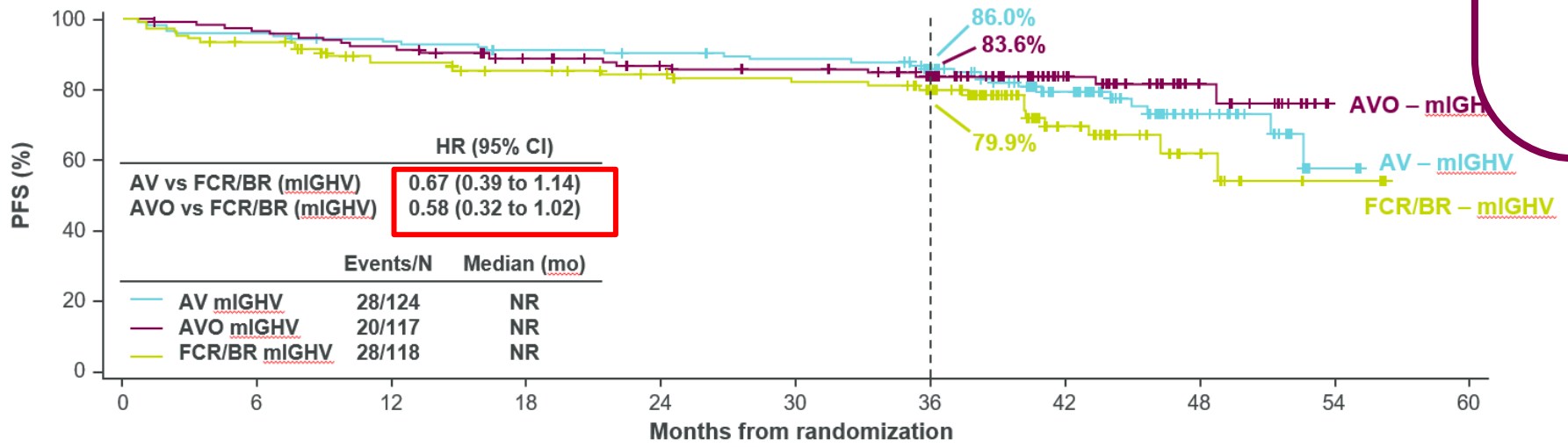
PFS in the uIGHV Subgroup



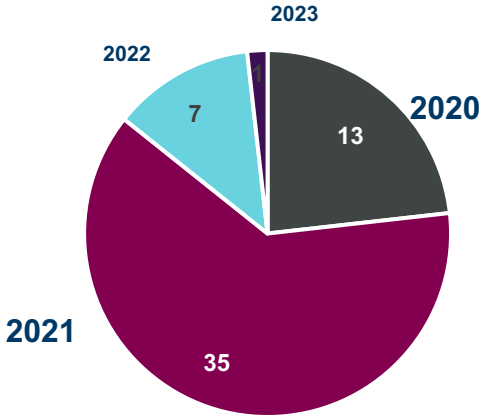
PFS in the mIGHV Subgroup



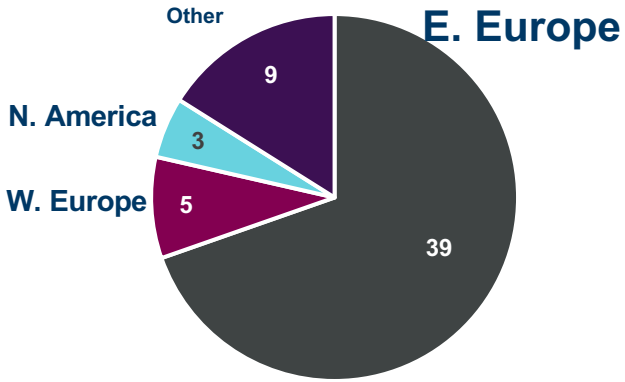
- En el subgrupo no mutado las diferencias en SLP fueron significativas a favor de AVO.
- La SLP en pacientes que recibieron AVO fue similar en mutados vs no mutados.

COVID-19 AEs, Treatment Discontinuations, and Deaths

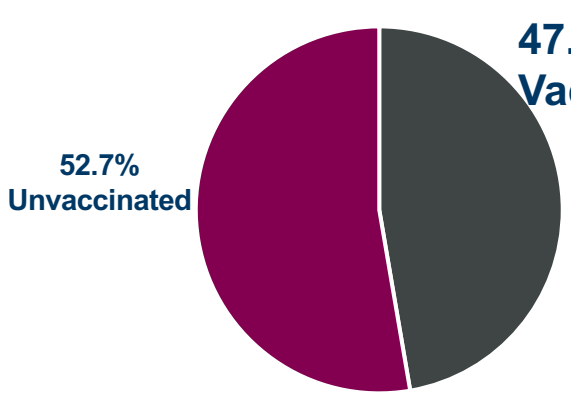
	AV (n=291)	AVO (n=284)	FCR/BR (n=259)
Any confirmed/suspected COVID-19 AE	64 (22.0)	69 (24.3)	10 (3.9)
Any confirmed/suspected COVID-19 AE leading to discontinuation of any treatment	7 (2.4)	23 (8.1)	3 (1.2)
Deaths due to COVID-19*	10 (3.4)	25 (8.7)	21 (7.2)



COVID-19 Deaths by Year



COVID-19 Deaths by Region



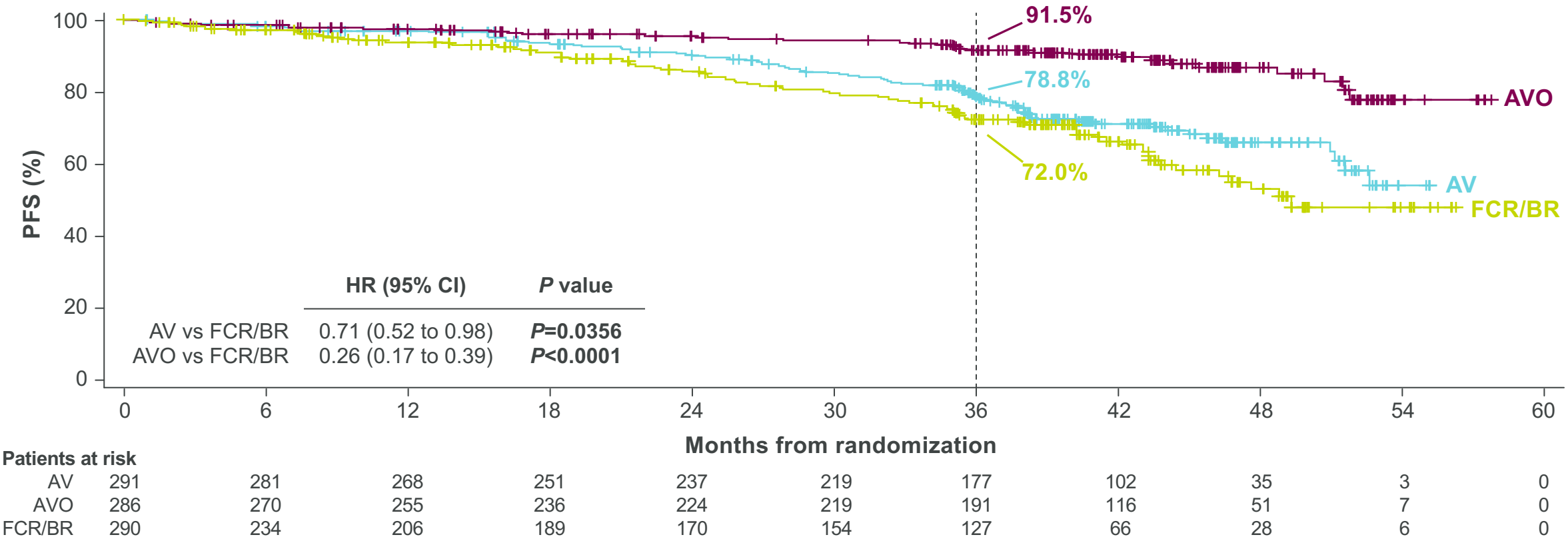
% COVID-19 Vaccinated

82% in 2020 or 1H2021

- Vaccination timing did not seem to differ by region

Data are n (%).
*Deaths due to COVID-19 are based on the ITT population (AV, n=291; AVO, n=286; FCR/BR, n=290).
AE, adverse event; AV, acalabrutinib-venetoclax; AVO, acalabrutinib-venetoclax-obinutuzumab; BR, bendamustine-rituximab; FCR, fludarabine-cyclophosphamide-rituximab.
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. Deaths included all deaths reported throughout the study.

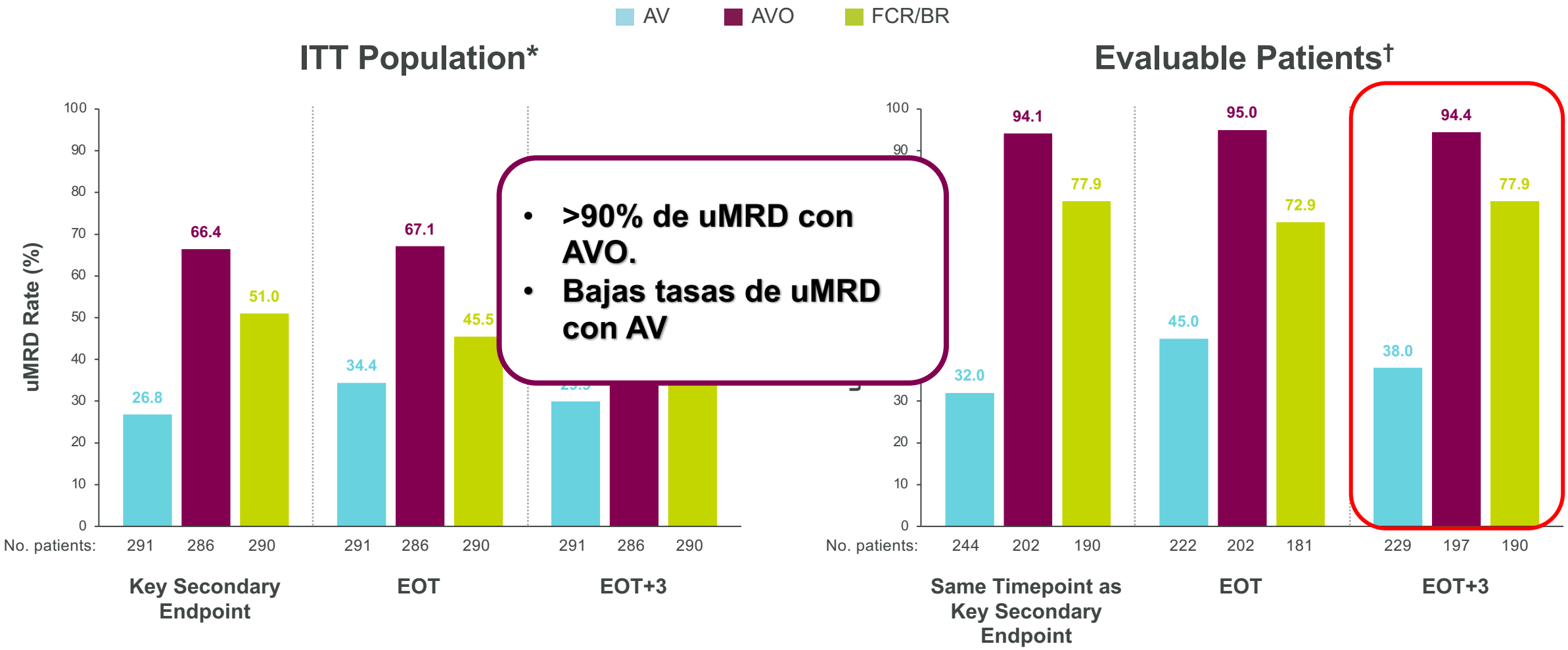
PFS Censoring COVID-19 Deaths (Prespecified Analysis)



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

Total COVID-19 deaths (censored for PFS sensitivity): AV, 10 (**8**), AVO, 25 (**25**), FCR/BR, 21 (**18**); patients with PD event prior to COVID-19 death were not censored for PFS.
PFS was assessed by IRC; median follow-up from randomization: 40.8 months (range, 0–59 months).
Hazard ratio (95% CI) computed using a Cox proportional-hazards model stratified by the randomization strata. *P*-value based on stratified log-rank test.
AV, acalabrutinib-venetoclax; AVO, acalabrutinib-venetoclax-obinutuzumab; BR, bendamustine-rituximab; CI, confidence interval; FCR, fludarabine-cyclophosphamide-rituximab; HR, hazard ratio; IRC, independent review committee; NR, not reached; PD, progressive disease; PFS, progression-free survival.

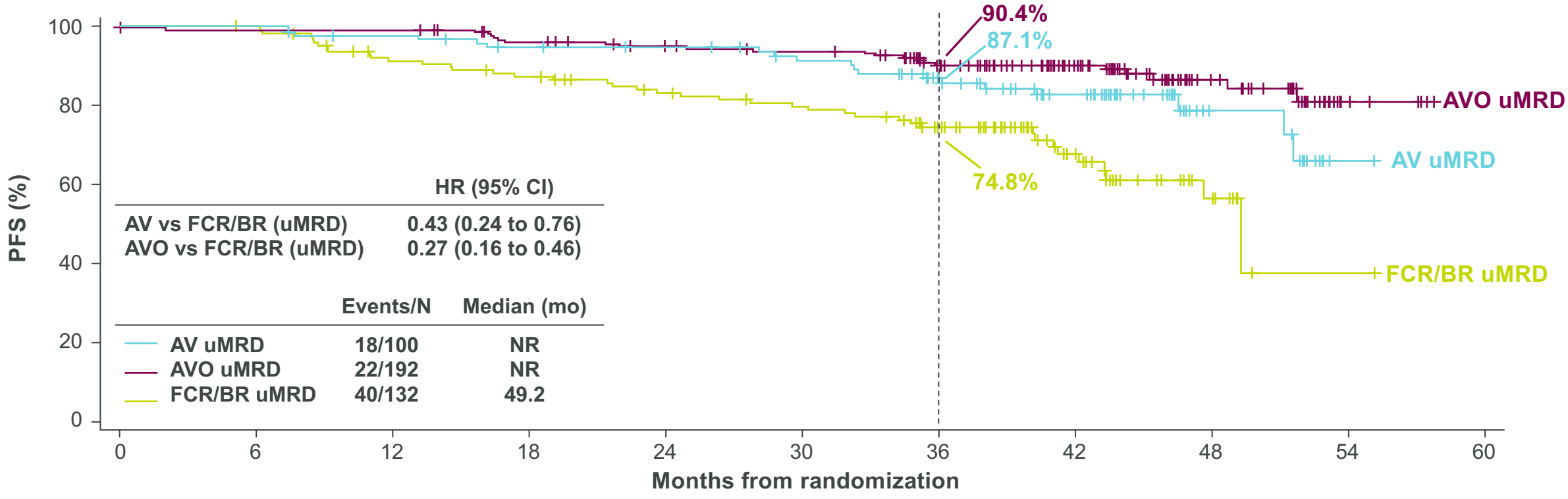
uMRD Rates (Flow Cytometry [<10^{-4}] in PB)



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)

Key secondary endpoint (ITT population): AV vs FCR/BR: *P*<0.0001 (favoring FCR/BR); AVO vs FCR/BR: *P*=0.0003 (favoring AVO; not adjusted for multiplicity).
*ITT population: all randomized patients regardless of whether MRD assessment was performed at the specified time point (missing assessments considered MRD+).
†Evaluable patients: those with MRD assessment at the specified timepoint.
EOT: cycle 14 day 28 for AV (± obinutuzumab); cycle 6 day 1 (±28-day window) (FCR/BR).
AV, acalabrutinib-venetoclax; AVO, acalabrutinib-venetoclax-obinutuzumab; BR, bendamustine-rituximab; EOT, end of therapy; EOT+3, end of therapy plus 12 weeks; FCR, fludarabine-cyclophosphamide-rituximab; ITT, intent-to-treat; MRD+, detectable measurable residual disease; PB, peripheral blood; uMRD, undetectable measurable residual disease.

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



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

PFS assessed by IRC among MRD-evaluable patients; uMRD assessed by flow cytometry (10^{-4}) in peripheral blood.
Hazard ratio (95% CI) computed using an unstratified Cox proportional-hazards model.
AV, acalabrutinib-venetoclax; AVO, acalabrutinib-venetoclax-obinutuzumab; BR, bendamustine-rituximab; CI, confidence interval; EOT, end of therapy; FCR, fludarabine-cyclophosphamide-rituximab; HR, hazard ratio; IRC, independent review committee; MRD, measurable residual disease; NR, not reached; PB, peripheral blood; PFS, progression-free survival; uMRD, undetectable measurable residual disease.

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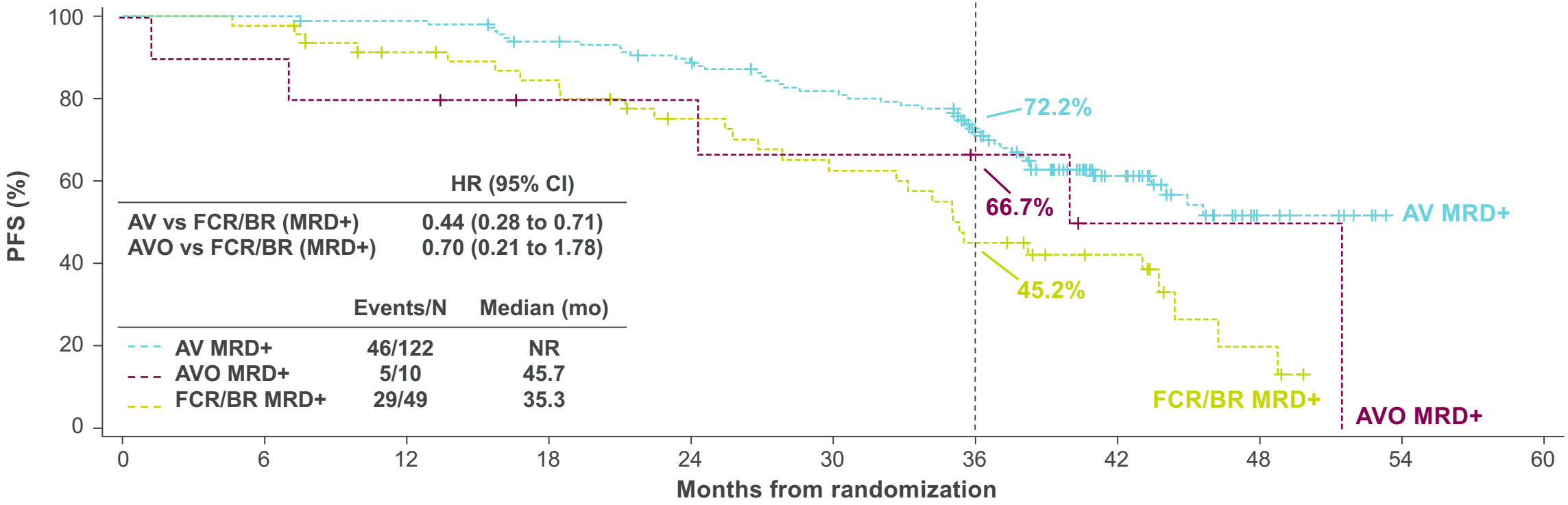
PFS in the MRD+ Subgroup at EOT (Flow Cytometry [<10^{-4}] in PB)



Patients at risk

AV MRD+	122	122	120	112	103	94	75	35	9	0
AVO MRD+	10	9	8	6	6	5	4	1	1	0
FCR/BR MRD+	49	48	41	37	30	25	18	12	3	0

PFS assessed by IRC among MRD-evaluable patients; uMRD assessed by flow cytometry (10^{-4}) in peripheral blood.
Hazard ratio (95% CI) computed using an unstratified Cox proportional-hazards model.
AV, acalabrutinib-venetoclax; AVO, acalabrutinib-venetoclax-obinutuzumab; BR, bendamustine-rituximab; CI, confidence interval; EOT, end of therapy; FCR, fludarabine-cyclophosphamide-rituximab; HR, hazard ratio; IRC, independent review committee; MRD, measurable residual disease; NR, not reached; PB, peripheral blood; PFS, progression-free survival.

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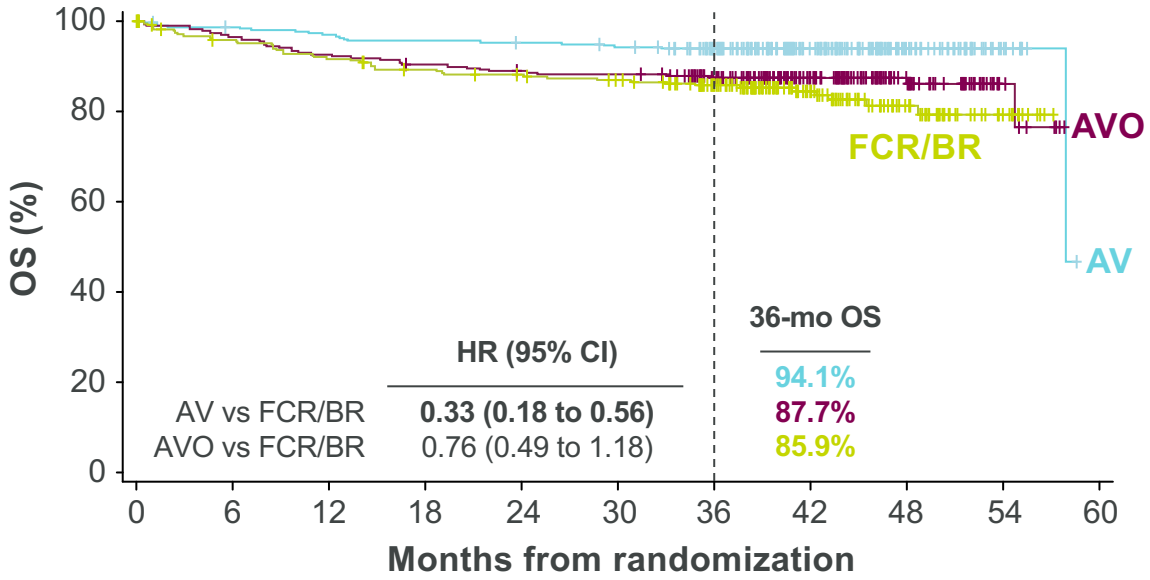
Overall Survival

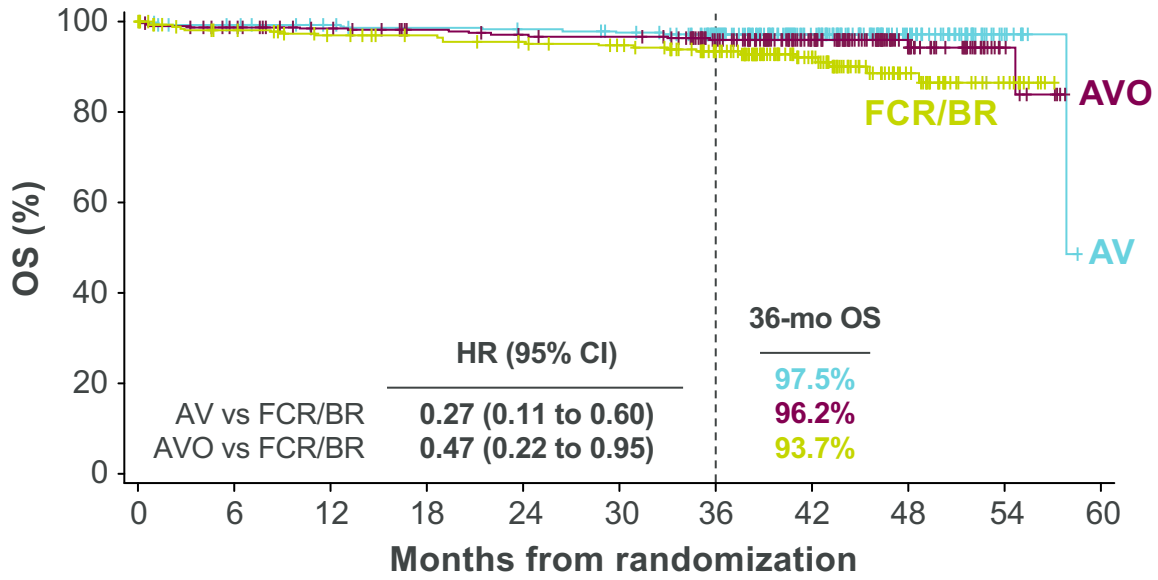
With AV vs FCR/BR



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

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.
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.

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.
AE, adverse event; AV, acalabrutinib-venetoclax; AVO, acalabrutinib-venetoclax-obinutuzumab; BR, bendamustine-rituximab; FCR, fludarabine-cyclophosphamide-rituximab.

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

	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
Excl. non-melanoma skin	8 (2.7)	5 (1.7)	7 (2.5)	4 (1.4)	1 (0.4)	0
Tumor lysis syndrome	1 (0.3)	1 (0.3)	1 (0.4)	1 (0.4)	8 (3.1)	8 (3.1)

Data are n (%). ECIs listed by category and sub-category.
[a]Ventricular tachyarrhythmias consisted of ventricular extrasystoles (n=1 in AV arm; n=2 in AVO arm) and ventricular tachycardia (n=1 each in AV and AVO arms).
[b]Includes neutropenia, neutrophil count decreased, and febrile neutropenia.
AEs with an onset date or that worsen 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 comes first.
AE, adverse event; AV, acalabrutinib-venetoclax; AVO, acalabrutinib-venetoclax-obinutuzumab; BR, bendamustine-rituximab; ECI, event of clinical interest; FCR, fludarabine-cyclophosphamide-rituximab.

The authors would like to thank the patients and their families, investigators, and personnel who participated in the AMPLIFY trial from 133 sites in 27 countries.

This study was sponsored by AstraZeneca.

The authors directed development of the presentation and are fully responsible for all content and editorial decisions.
Medical writing and editorial support was provided by Marco Cicero, PhD, and Cindy Gobbel, PhD, of Peloton Advantage, LLC (Parsippany, NJ, USA), an OPEN Health company, and funded by AstraZeneca.

Conclusions

- **AMPLIFY provides the first phase 3 evidence of fixed-duration therapy combining a 2G BTKi with venetoclax (with or without anti-CD20) in TN CLL**
- **This interim analysis of AMPLIFY (median follow-up: 40.8 months) in fit patients with TN CLL demonstrated:**
  - **Significantly improved PFS with fixed-duration AV and AVO vs FCR/BR**
    - **Including in the uIGHV subgroup**
  - **Longer OS with AV versus FCR/BR (primary analysis) and with both AV and AVO vs FCR/BR (censoring COVID-19 deaths)**
  - **Highest uMRD rates in the AVO arm (ITT and evaluable populations)**
    - **Longer PFS in those with uMRD at EOT (all 3 treatment arms)**
- **Incidence of cardiac AEs remained low in both the AV and AVO regimens**

2G, second generation; AE, adverse event; AV, acalabrutinib-venetoclax; AVO, acalabrutinib-venetoclax-obinutuzumab; BCL2i, B cell lymphoma 2 inhibitor; BR, bendamustine-rituximab; BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; EOT, end of therapy; FCR, fludarabine-cyclophosphamide-rituximab; ITT, intent-to-treat; OS, overall survival; PFS, progression-free survival; TN, treatment-naive; uIGHV, unmutated immunoglobulin heavy-chain variable region gene; uMRD, undetectable measurable residual disease.

NCCN guidelines 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**
• BCL2i-containing regimens ▸ Venetoclax[f,h] + obinutuzumab (category 1) ▸ Venetoclax[f,h] + acalabrutinib ± obinutuzumab (category 1) • cBTKi-based regimens ▸ Acalabrutinib[f,g] ± obinutuzumab (category 1) ▸ Zanubrutinib[f,g] (category 1)	• BCL2i-containing regimen ▸ Venetoclax[f,h] + ibrutinib[f,g] • cBTKi-based regimen ▸ Ibrutinib[f,g,i] (category 1)	• Consider for IGHV-mutated CLL in patients aged <65 y without significant comorbidities ▸ FCR (fludarabine, cyclophosphamide, rituximab)[j,k] • cBTKi-based regimen ▸ Ibrutinib[f,g] + anti-CD20 mAb (category 2B)[l] • Consider when cBTKi and BCL2i 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)

Major Phase 3 Trials Support the Use of Targeted Agents in TN CLL

Ibrutinib

- ✓ **RESONATE-2**:superior PFS and OS vs Clb
- ✓ **iLLUMINATE**: superior PFS vs GClb
- ✓ **ALLIANCE:** superior PFS vs BR in older patients
- ✓ **ECOG 1912:** superior PFS and OS vs FCR in younger patients
- ✓ **FLAIR:** superior PFS and OS vs FCR in younger patients

Acalabrutinib

- ✓ **ELEVATE-TN**: superior PFS for acalabrutinib regimens vs GClb

Zanubrutinib

- ✓ **SEQUOIA**: superior PFS vs BR

Venetoclax

- ✓ **CLL14**: VenG superior to GClb in unfit patients
- ✓ **CLL13**: VenG superior to FCR/BR in fit patients

Ibru + Ven

- ✓ **GLOW:** I+V superior PFS vs GClb
- ✓ FLAIR: I+V superior PFS vs FCR

Acala + Ven

- ✓ **AMPLIFY:** AV or AVO superior PFS vs FCR/BR

Authors slide

- Continuous BTKi
- FD BCL-2 inh combination
- FD Ibrutinib and BCL-2 inh
- FD Acala and BCL-2 inh

6TH LAG-CLL 2026

Latin American Group on Chronic Lymphoctic Leukemia

ARGENTINA

Mendoza, 16-17 **April** 2026.

President of honor
Guillermo Dighiero

Gracias