Caso Clinico: Leucemia Linfatica Cronica

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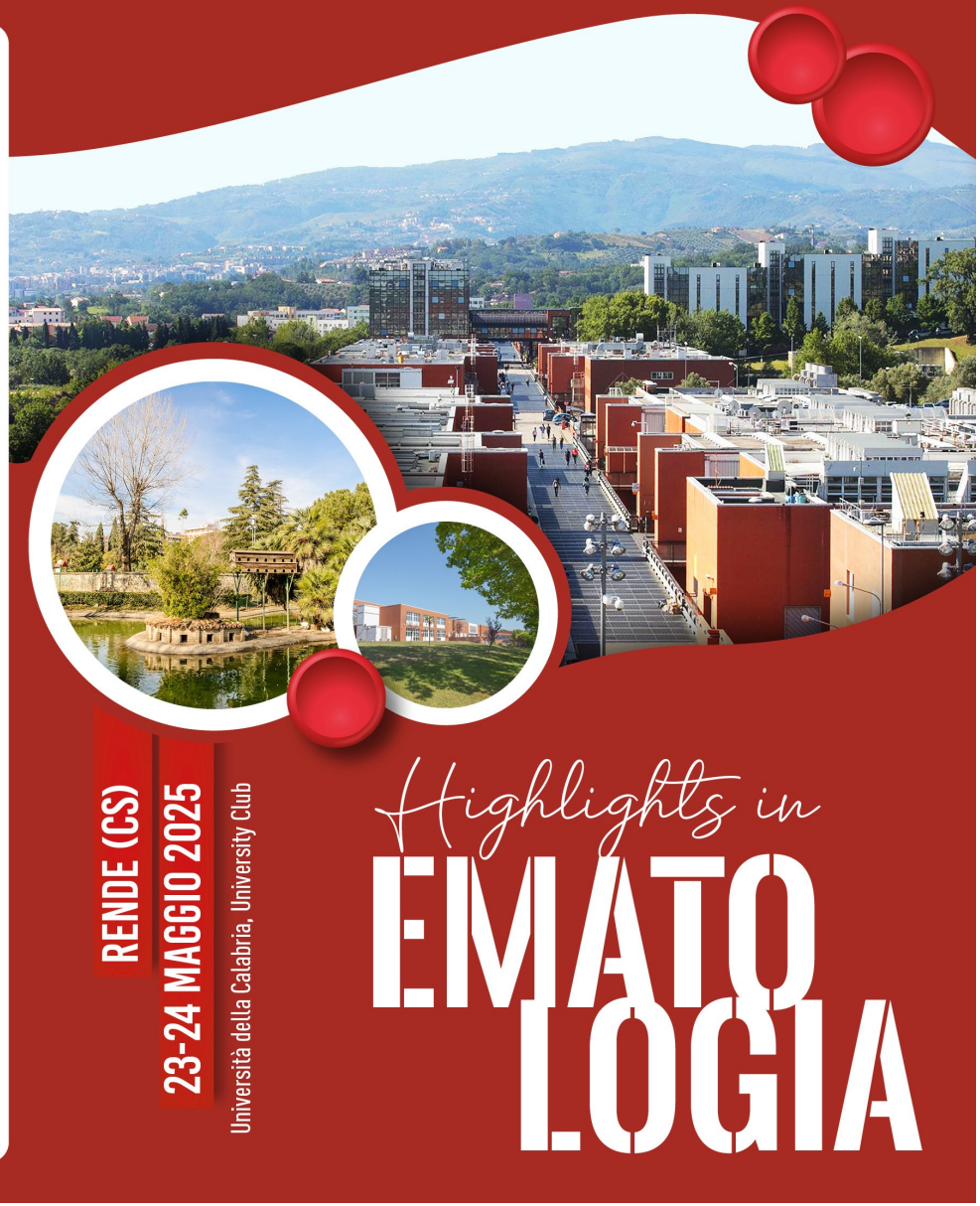


Anamnesi

- Pz maschio di 66 anni
- Forte fumatore (1 pacchetto /die)
- Sportivo , padre di 3 figli
- Madre deceduta di K colon, padre deceduto di infarto a 50 anni
- Appendicectomia a 14 anni, intervento per varicocele nel 2018
- Anamnesi: Diabete mellito di tipo II

Presentazione malattia all'esordio

- **Novembre 2019** :riscontro occasionale di linfocitosi assoluta in pieno benessere
- **Emocromo** : GB 57.5; Lymph 82.3 %; Hgb 13; PLT 153.000
- **EO**: linfoadenopatia di circa 2 cm collo/ascella/inguine.
- Non organomegalie addominali apprezzabili

Presentazione malattia all'esordio

Novembre 2019:

Diagnosi occasionale di Leucemia Linfatica Cronica (Matutes 5)
Stadio RAI I / Binet A

Novembre 2019 ⟶ **Dicembre 2021** :

FUP osservazionale con cadenza trimestrale ; mantenendo buone condizioni generali

Decorso Clinico

Dicembre 2021: progressione sintomatica della malattia,sudorazioni notturne e febbricola serotina (68 Anni)

***Emocromo*:** Hb 10.1 g/dl ; PLT 88.000/mmc ; GB 288.000/mmc L 92%

***TAC*:** linfoadenopatie fino a 4 cm in sede latero cervicale ed ascellare, fino a 6 cm in sede iliaca esterna bilaterale e fino a 4,5 cm in sede inguinale . Modesta epato-splenomegalia.

***PET*:** captazione in tutte le sedi linfonodali con SUV medio pari a 3,7 vs SUV medio epatico di 2,2

LDH 320 (ULN 280 U/L); *Beta2* 3,1 mg/L

ECOG/PS : 0

Studio biologico:

FISH Non Del 17p Non evidenza di mutazioni TP53 , IGHV Non mutato

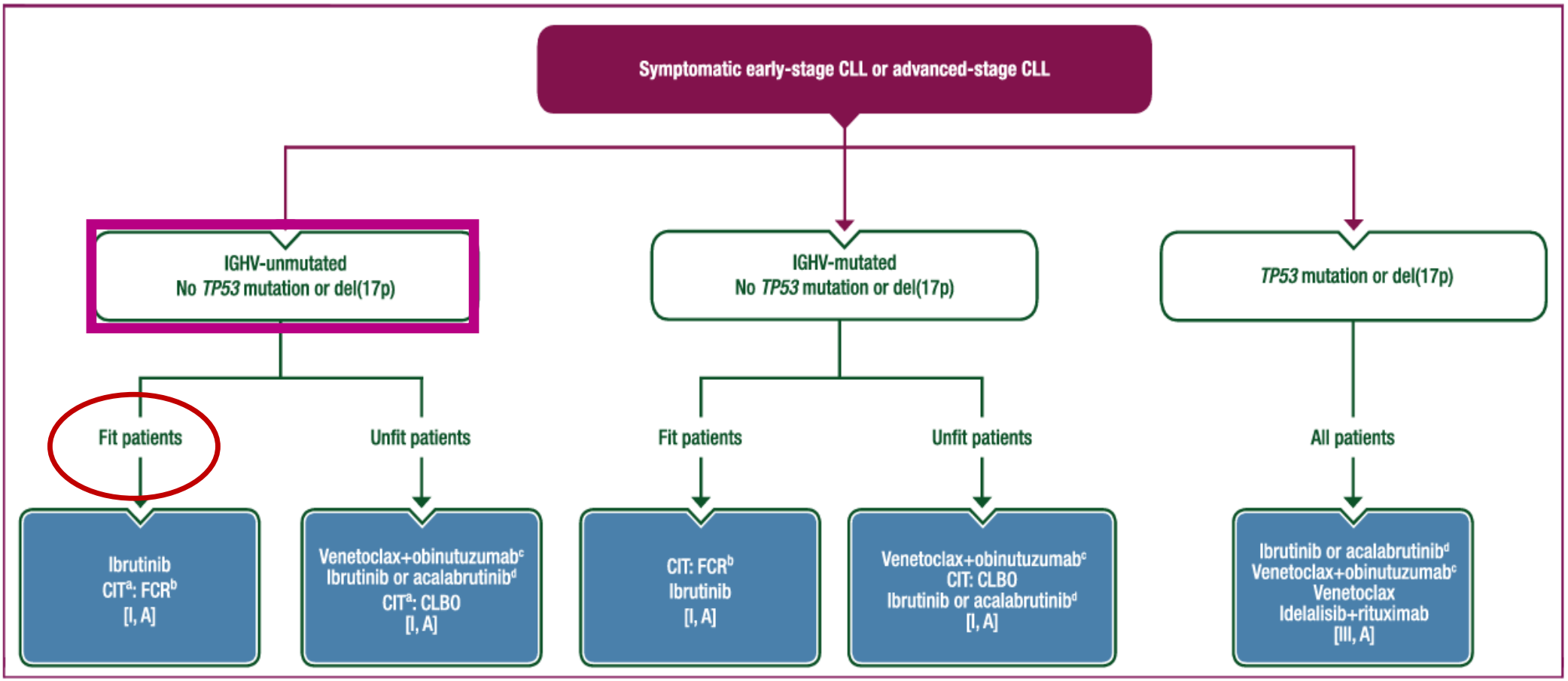
PAZIENTE
IGHV NON MUTATO

1-QUALE MIGLIORE TERAPIA PER IL PAZIENTE?

- **BTKi**
- Obinotuzumab/Venetoclax
- Chemio-immunoterapia

Evidence

Linee guida ESMO – *Front-line therapy*



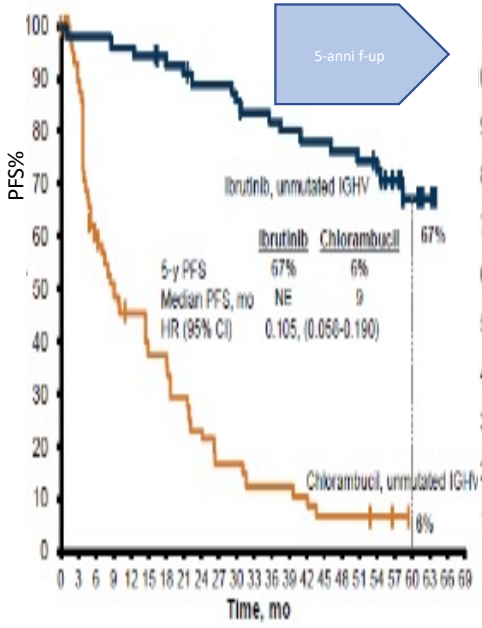
ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Eichhorst B. et al. Annals of Oncology, 19 October 2020.

Pazienti unfit con IGHV non mutato

RESONATE 2[1]

≥70 y
65-70 y and unfit for FCR

5-anni f-up

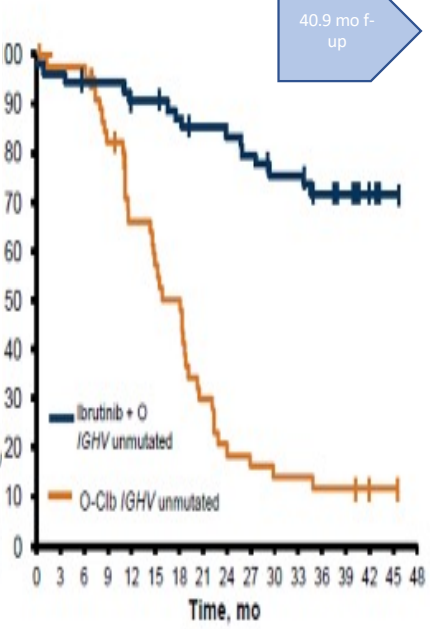


	Ibrutinib	Chlorambucil
5-y PFS	67%	6%
Median PFS, mo	NE	9
HR (95% CI)	0.105, (0.050-0.190)	

ILLUMINATE[2]

≥65 y
<65 y and comorbidities

40.9 mo f-up



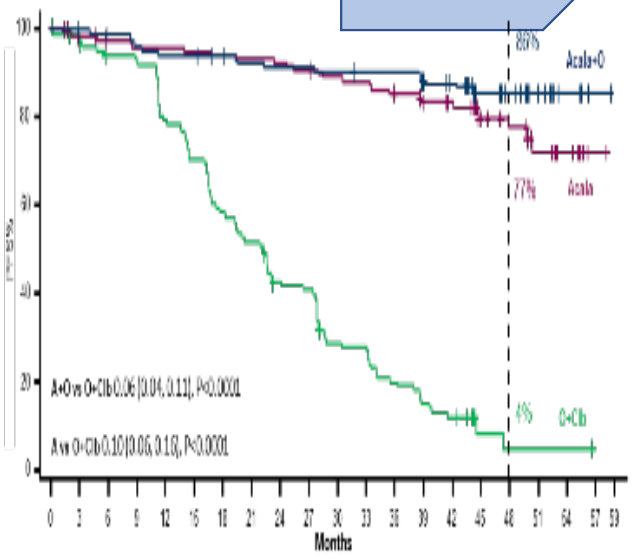
	Unmutated IGHV		Mutated IGHV	
	Ibr	Chl	Ibr	Chl
6.5 year PFS	62%	2%	67%	18%
Median PFS, mo	NR	9.3	NR	16.7
HR (95% CI)	0.109 (0.063-0.189)		0.197 (0.098-0.394)	

Ibr-O NON ammessa alla rimborsabilità AIFA

ELEVATE-TN[3]

≥65 y
<65 y and comorbidities

46.9 mo f-up

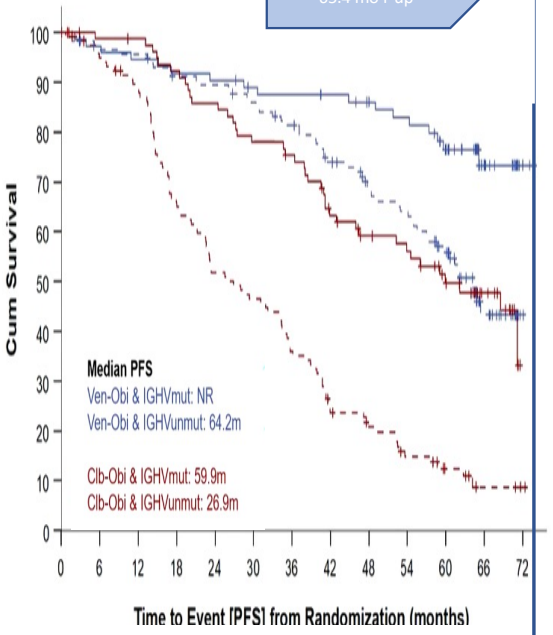


F-up 60 mo: estimated PFS
82% (A+O), 72% (A), 6% (O+Clb)[5]

CLL14[4]

≥18 y
CIRS >6 and/or CrCL <70 mL/min

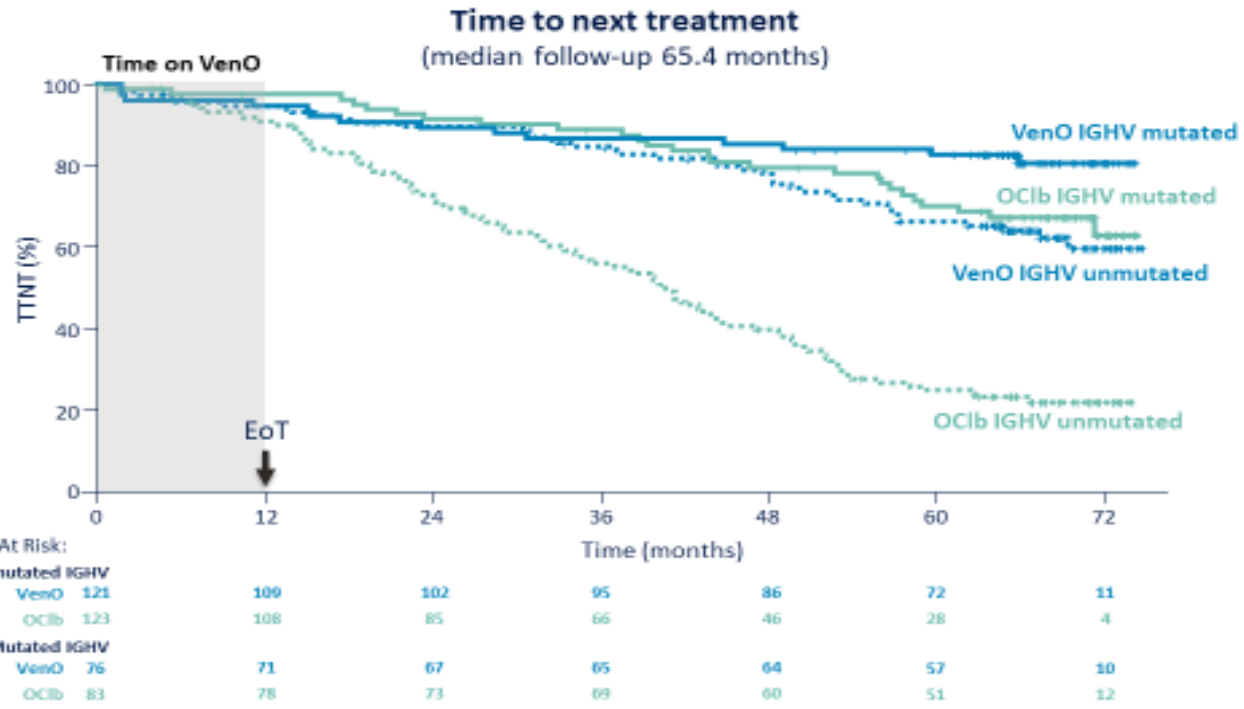
65.4 mo f-up



1 Burger JA et al. Leukemia 2020; 2. Moreno C et al. HWCLL 2019; 3. Ghia P presented at ASCO 2021; 4. Al-Sawaf presented at EHA 2022. 5. Data presented at EHA 2022

5-y analysis

Time to next treatment in patients by IGHV status: 5 years post-randomization



	IGHV unmutated		IGHV mutated	
	VenO	OClb	VenO	OClb
5-year TTNT, %	66.2	25.1	NA	NA

TTNT longer with VenO irrespective of IGHV mutational status

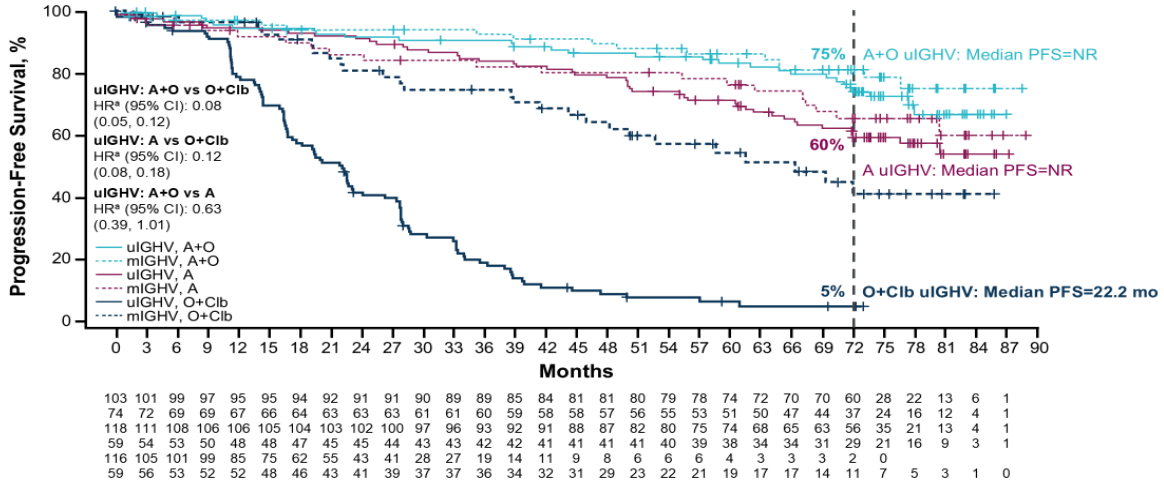
EoT, end of treatment; NA, not available; TTNT, time to next treatment.

Al-Sawaf O, *et al.* EHA 2022. Abstract S148 (Oral).

Investigator-Assessed PFS in Patients with uIGHV

Investigator-Assessed PFS in Patients with uIGHV

- PFS result in A-treated patients with uIGHV was consistent with overall result
- Median PFS was NR in patients with uIGHV treated with A+O and A vs. 22.2 months in O+Clb arm



[a]Hazard ratio was based on unstratified Cox-Proportional-Hazards model.

A = acalabrutinib; CI = confidence interval; Clb = chlorambucil; HR = hazard ratio; IGHV = immunoglobulin heavy chain variable; mIGHV = mutated IGHV; NR = not reached; O = Obinutuzumab; PFS = progression free survival; uIGHV = unmutated IGHV; vs = versus.

Sharman JP et al. Oral Presentation Presented at: ASH; December 9-12, 2023; San Diego.

Safety: Most Common AEs in ≥5% of Patients

- Most common AEs reported were diarrhea (43.8% [A+O] and 42.5% [A]), headache (40.4% [A+O] and 39.1% [A]), and arthralgia (36.0% [A+O] and 27.4% [A])
- The most common AE profile was consistent with the earlier analyses as summarized in the table below.

AEs[a]	A+O (n=178)		A (n=179)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Diarrhea	78 (43.8)	11 (6.2)	76 (42.5)	1 (0.6)
Headache	72 (40.4)	2 (1.1)	70 (39.1)	2 (1.1)
Arthralgia	64 (36.0)	4 (2.2)	49 (27.4)	2 (1.1)
Neutropenia	61 (34.3)	55 (30.9)	23 (12.8)	21 (11.7)
Fatigue	55 (30.9)	4 (2.2)	43 (24.0)	2 (1.1)
Cough	50 (28.1)	1 (0.6)	45 (25.1)	1 (0.6)
COVID-19	44 (24.7)	16 (9.0)	38 (21.2)	13 (7.3)
Thrombocytopenia	26 (14.6)	15 (8.4)	16 (8.9)	6 (3.4)
Pneumonia	25 (14.0)	13 (7.3)	27 (15.1)	11 (6.1)
Hypertension	17 (9.6)	8 (4.5)	19 (10.6)	9 (5.0)
Syncope[b]	12 (6.7)	9 (5.1)	5 (2.8)	4 (2.2)

Data are n (%) unless otherwise specified.

[a]Any-grade AEs in ≥30% of acalabrutinib-treated patients or grade ≥3 in ≥5% of acalabrutinib-treated patients. [b]Cardiac-related syncope events were reported separately.

A = acalabrutinib; AEs = adverse events; Clb = chlorambucil; O = Obinutuzumab.

Sharman JP et al. Oral Presentation Presented at: ASH; December 9-12, 2023; San Diego.

SCELTA TERAPIA DI I linea

- Profilo di Tollerabiità migliore di Ibrutinib
- Compliance
- Effetti collaterali lievi cefalea transitoria ,nessuna tossicità cardiovascolare

Decorso Clinico

Dicembre 2021: Inizia terapia con Acalabrutinib 100 mg BID

Emocromo (Marzo 22)Gb 332.3 di cui Neu 7.4, Ly 417.7, PLT 181, Hb 9.4

Emocromo (Maggio 22)Gb 300.2 di cui Neu 4.1, Ly 287, PLT 123, Hb 10

Emocromo (Agosto 22)Gb 164.2 di cui Neu 3.8, Ly 156.2, PLT 146, Hb 12

- Settembre 2023 : Gb 12,540, N 4500, PLT 188.000, Hb 13

Recidiva ed evoluzione genetica

Dicembre 2023 (70 anni):

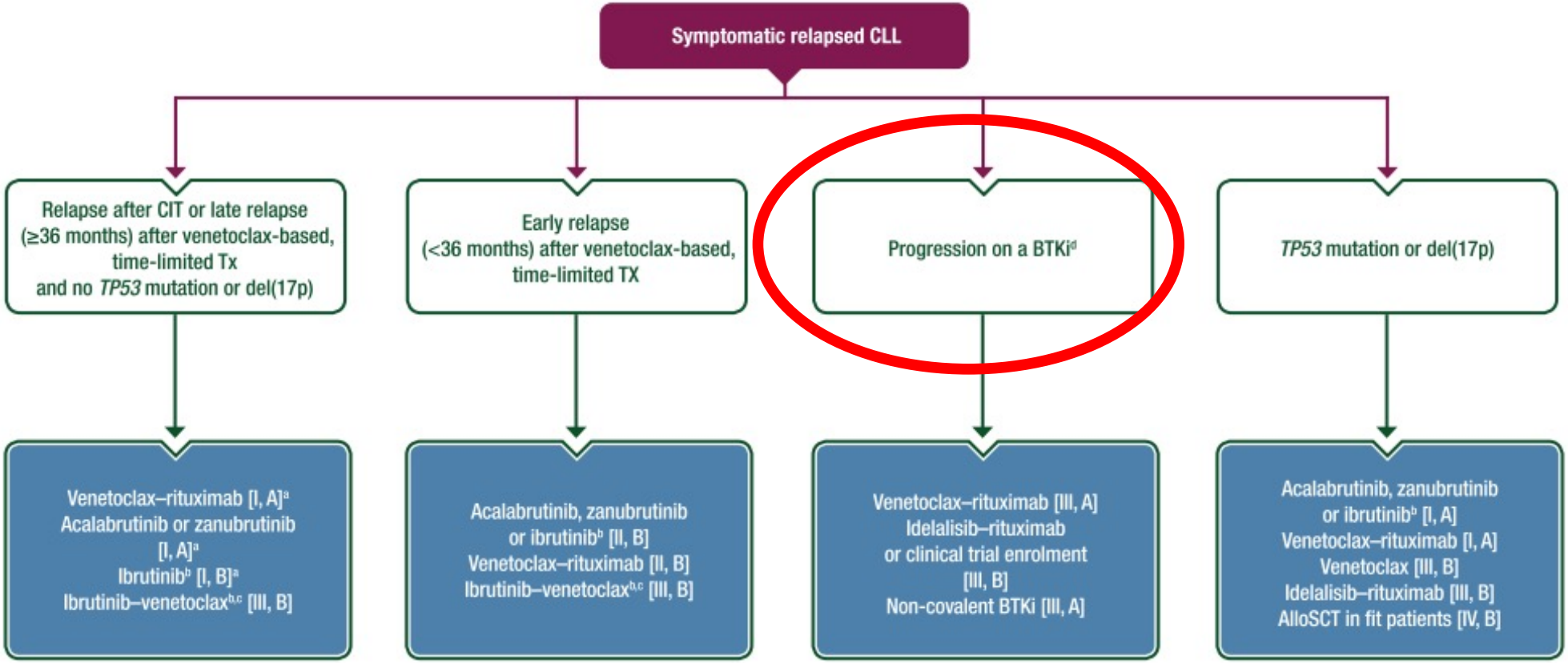
Ripresa della linfocitosi e astenia marcata

Emocromo : Gb 88.2 di cui Neu 3.8, Ly 83.2, PLT 76, Hb 10

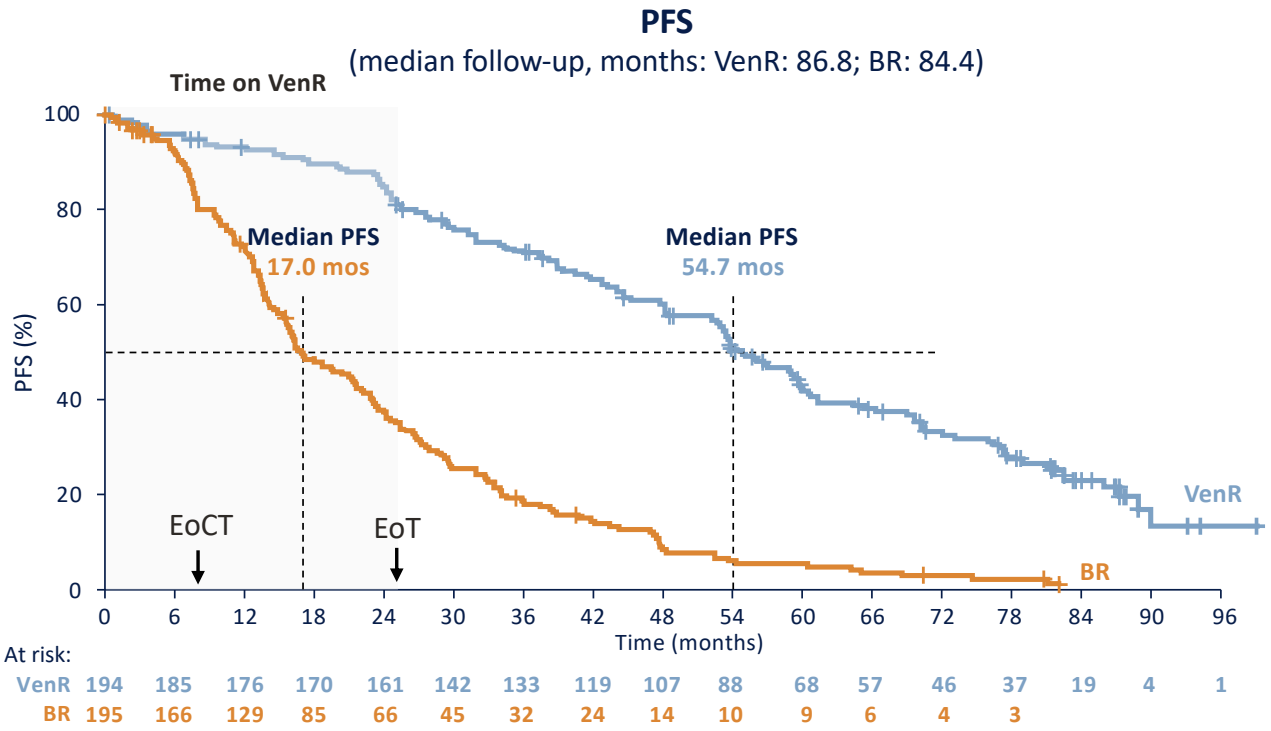
Rivalutazione molecolare : TP53 Mut.

Rivalutazione citogenetica: del17p

PAZIENTE
IGHV NON MUTATO, TP53 MUTATO


Symptomatic relapsed CLL
Relapse after CIT or late relapse (≥36 months) after venetoclax-based, time-limited Tx and no *TP53* mutation or del(17p)
Early relapse (<36 months) after venetoclax-based, time-limited TX
Progression on a BTKi[d]
TP53 mutation or del(17p)
Venetoclax–rituximab [I, A][a]
Acalabrutinib or zanubrutinib [I, A][a]
Ibrutinib[b] [I, B][a]
Ibrutinib–venetoclax[b,c] [III, B]
Acalabrutinib, zanubrutinib or ibrutinib[b] [II, B]
Venetoclax–rituximab [II, B]
Ibrutinib–venetoclax[b,c] [III, B]
Venetoclax–rituximab [III, A]
Idelalisib–rituximab or clinical trial enrolment [III, B]
Non-covalent BTKi [III, A]
Acalabrutinib, zanubrutinib or ibrutinib[b] [I, A]
Venetoclax–rituximab [I, A]
Venetoclax [III, B]
Idelalisib–rituximab [III, B]
AlloSCT in fit patients [IV, B]

PFS at the final analysis



	VenR	BR
HR (95% CI) p value	0.23 (0.18–0.29)* Stratified p<0.0001†	
Estimated 7-year PFS, %	23.0	NE

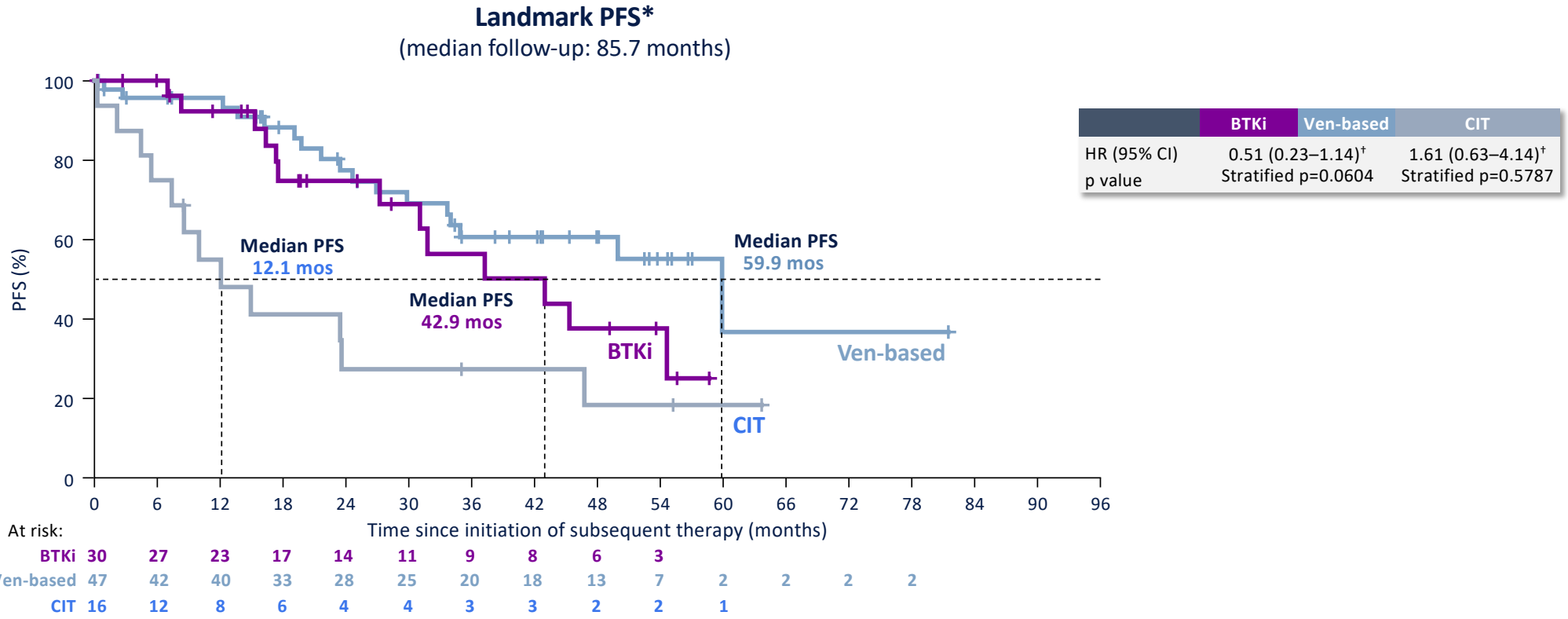
PFS benefits were sustained 5 years after completing VenR, with a 77% reduction in the risk of progression or death vs BR; 50% of VenR patients were without progression approximately 2.5 years after completion of treatment

* Stratified HR presented, unstratified HR=0.25; † p values are descriptive only.
EoCT, end of combination treatment; EoT, end of treatment; FTD, fixed-treatment duration; mos, months; NE, not estimable.

Kater A, *et al.* EHA 2023. Abstract S201 (Oral).

7-y analysis

PFS for patients in the VenR arm who received a subsequent therapy by treatment type



	BTKi	Ven-based	CIT
HR (95% CI)	0.51 (0.23–1.14)†		1.61 (0.63–4.14)†
p value	Stratified p=0.0604		Stratified p=0.5787

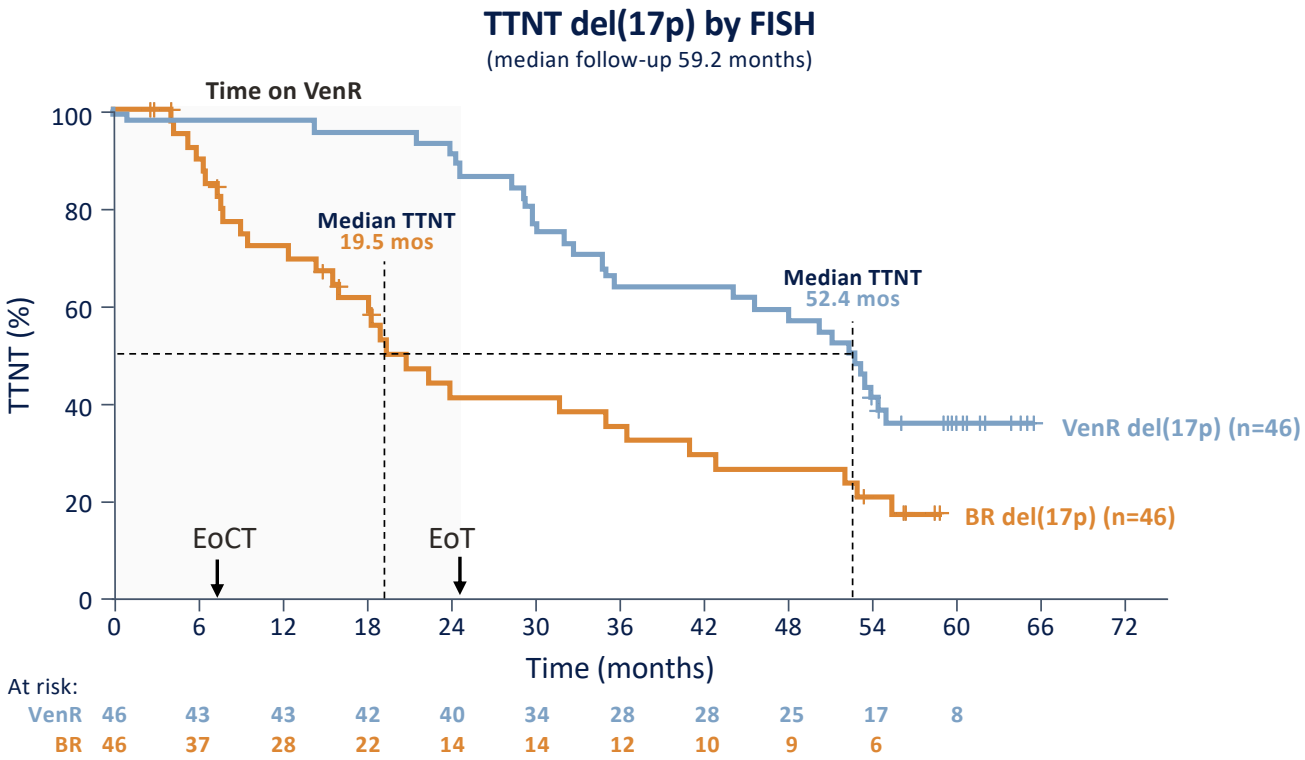
In patients initially treated with VenR, re-treatment with Ven-based regimens prolonged PFS vs those who received subsequent BTKi or CIT

* Landmark (time zero) taken at initiation of next-line therapy; † Stratified HR presented.
BTKi, Bruton's tyrosine kinase inhibitor; CIT, chemoimmunotherapy.

Harrup R, *et al.* ASH 2023; Abstract P1898 (Poster).

5-y analysis

TTNT in patients with del(17p)



	VenR	BR
HR (95% CI)	NA	

In the VenR arm, patients with del(17p) had a median TTNT of 52.4 months (~2.5 year treatment-free period) vs 19.5 months (~6 months prior to EoT) in the BR arm

B, bendamustine; EoCT, end of combination treatment; EoT, end of treatment; FISH, fluorescent in situ hybridization; mos, months; NA, not available; R, rituximab; TTNT, time to next treatment; Ven, venetoclax.

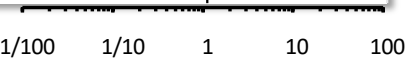
AbbVie. Data on file. ABVRRTI71439.

5-y analysis

PFS by subgroup 3 years after completion of treatment

EMA Summary of Product Characteristics

Subgroup PFS 5-year analysis		Total N	VenR (n=194) n	VenR (n=194) Median (months)	BR (n=195) n	BR (n=195) Median (months)	Hazard ratio*	95% CI	VenR favored	BR favored
All patients		**389**	**194**	**53.6**	**195**	**17.0**	**0.21**	**(0.16–0.27)**		
Age group	<65	186	97	49.0	89	15.4	0.20	(0.14–0.29)		
	≥65	203	97	57.0	106	21.7	0.20	(0.14–0.30)		
No. of prior regimens	1	228	111	54.0	117	16.4	0.18	(0.13–0.26)		
	>1	161	83	53.1	78	18.6	0.25	(0.17–0.38)		
Bulky disease (LN with the largest diameter)	<5 cm	197	100	53.8	97	16.6	0.21	(0.14–0.30)		
	≥5 cm	172	84	48.4	88	15.8	0.19	(0.13–0.29)		
del(17p) by FISH	Normal	250	127	55.1	123	21.6	0.19	(0.13–0.27)		
	Abnormal	**92**	**46**	**47.9**	**46**	**14.6**	0.27	(0.16–0.45)		
del(11q)	Normal	217	112	53.7	105	22.1	0.24	(0.17–0.34)		
	Abnormal	125	61	53.8	64	15.7	0.16	(0.10–0.26)		
IGHV	Mutated	104	53	NE	51	24.2	0.14	(0.07–0.26)		
	Unmutated	246	123	52.2	123	15.7	0.19	(0.13–0.26)		
***TP53* mutation and/or del(17p) by FISH**	Unmutated	201	106	56.6	95	22.9	0.18	(0.12–0.26)		
	Mutated	147	**72**	**45.3**	**75**	**14.2**	0.26	(0.17–0.38)		



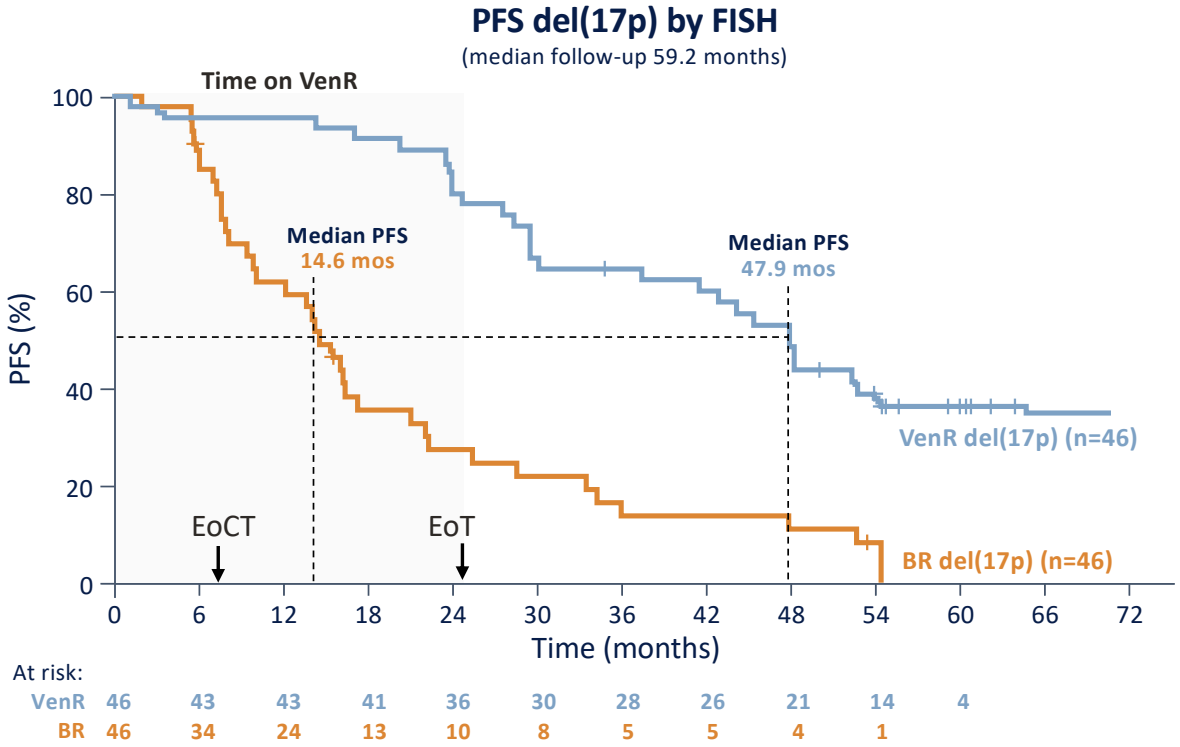
With FTD VenR, a consistent PFS benefit vs BR was observed across all prespecified subgroups, including patients with *TP53* aberrations

* Unstratified HR. B, bendamustine; FISH, fluorescent *in situ* hybridization; FTD, fixed treatment duration; IGHV, immunoglobulin heavy chain variable region; LN, lymph node; R, rituximab; Ven, venetoclax.

VENCLYXTO® (venetoclax). EMA SmPC (accessed August 2022).

5-y analysis

PFS in patients with del (17p) 3 years after completion of treatment



	del(17p) by FISH
	VenR / BR
HR (95% CI)	0.27 (0.15–0.46)

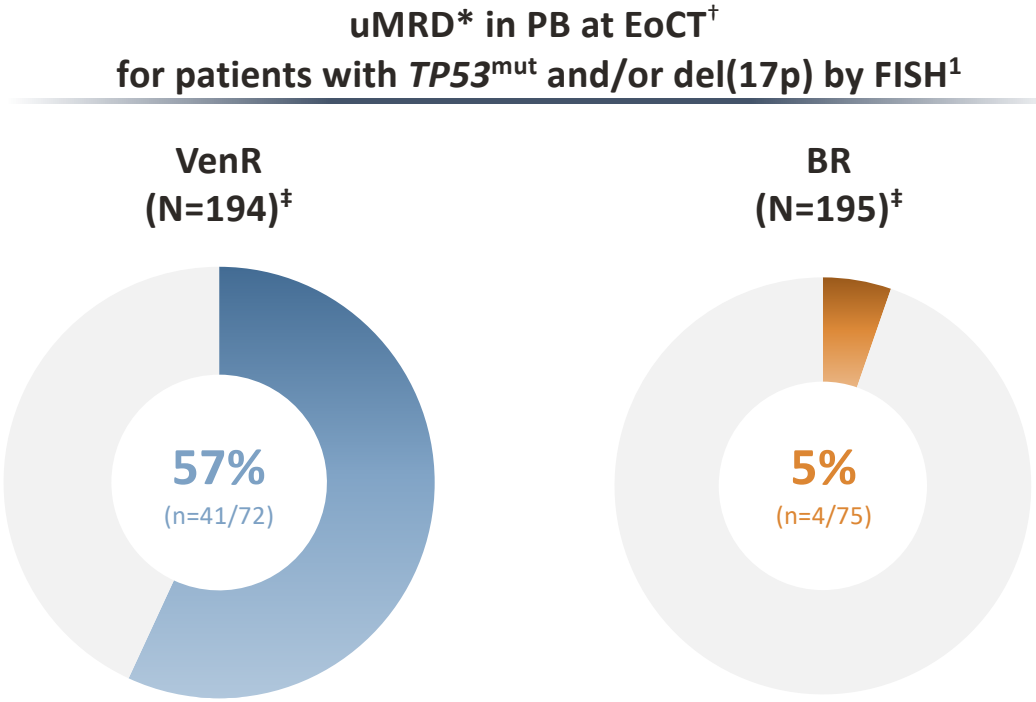
PFS benefits were sustained 3 years after completing VenR in patients with del(17p) by FISH, with a 73% reduction in the risk of progression or death vs BR; 50% of VenR patients with del(17p) by FISH were without progression approximately 2 years after completion of treatment

B, bendamustine; EoCT, end of combination treatment; EoT, end of treatment; FISH, fluorescent *in situ* hybridization; FTD, fixed treatment duration; mos, months; R, rituximab; Ven, venetoclax.

AbbVie. Data on File. ABVRRTI71439; Seymour JF, *et al. N Engl J Med* 2018; **378**:1107–1120 (incl. suppl.); VENCLYXTO® (venetoclax). EMA SmPC (accessed August 2022).

3-y analysis

PB uMRD rates at EoCT in patients with *TP53*^{mut} and/or del(17p) by FISH



Higher rates of uMRD were achieved with VenR vs BR at EoCT in patients with *TP53*^{mut} and/or del(17p)

* uMRD ($<10^{-4}$) assessed centrally in PB with ASO-PCR or flow cytometry; † 3 mos after combination treatment completion[1,2];
‡ ITT population, n=72 and n=75 of whom had *TP53*^{mut} and/or del(17p) by FISH at baseline in the VenR arm and BR arm, respectively.
B, bendamustine; EoCT, end of combination treatment; FISH, fluorescent *in situ* hybridization; ITT, intent-to-treat; PB, peripheral blood; R, rituximab; Ven, venetoclax.

1. Kater AP, *et al. J Clin Oncol* 2019; **37**:269–277;
2. Seymour JF, *et al. N Engl J Med* 2018; **378**:1107–1120.

Terapia di II linea

Dicembre 2023 :

Inizia rump up di Venetoclax

No TLS, no eventi avversi

Gennaio 2024: I Rituximab c 2+1

- Emocromo: Hb 11,4; WBC 6760, L 45%, PLT 110.000

Terapia di II linea

Maggio 2025 :

No sintomi B, TC total body: Risposta Completa al Trattamento

Emocromo : Hb 13,4 gr/dl, PLT 187.000, WBC 4560 N 2450

MRD su sp Negativo

Discussione clinica: Paziente ad alto rischio

- TP53 mutato = elevato rischio di progressione futura
- Risposta attuale ottima, ma monitoraggio stretto necessario
- Pazienti doppio refrattari: Unmet Need

Prospettive future

- CAR-T: studi promettenti in LLC refrattaria, ma ancora in fase sperimentale

- Pirtobrutinib (LOXO-305): BTKi di nuova generazione, attivo anche in TP53

- Altri agenti in sviluppo: bispecifici

- Necessario approccio personalizzato

Conclusioni

Venetoclax-Rituximab è opzione valida post-BTKi anche con TP53

La gestione del rischio a lungo termine richiede visione proattiva

Nuove terapie come CAR-T e pirtobrutinib aprono scenari futuri concreti

Grazie per l’attenzione

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