MEET THE

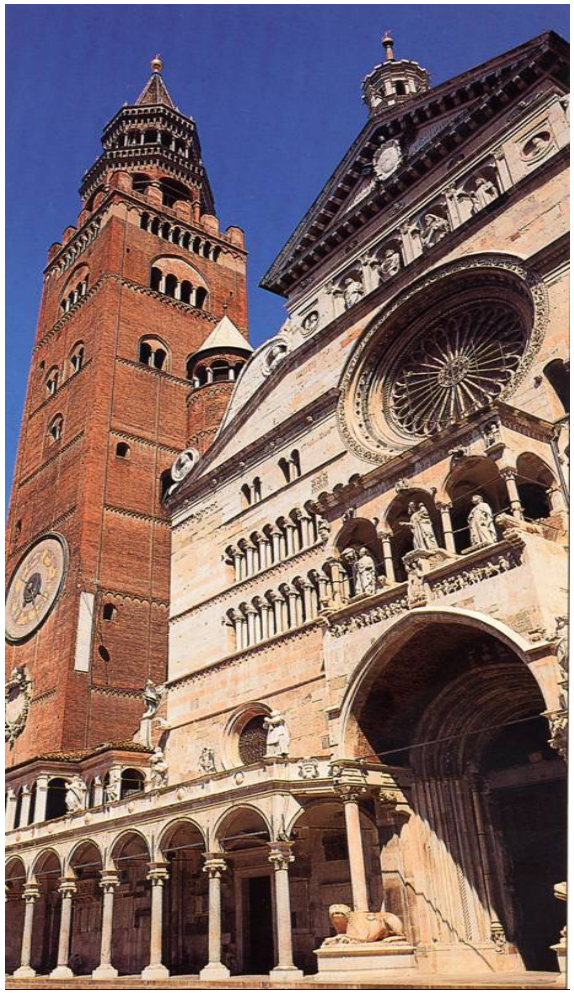
EXPERT *in CLL*

CREMONA, 30 GIUGNO 2025

Ospedale di Cremona

Disclosures dott. Monica Tajana

No disclosures



CLL-B

CASO CLINICO 1

dott. Monica Tajana

Caso clinico

S.R.1959, M , anni 62

Comorbidità

Prostatectomia nel 2014 per K seguita da RTE e ormonoterapia
Ipertiroidismo circa nel 2000 trattato con Tapazole e poi con terapia radiometabolica esitata in ipotiroidismo

Anamnesi fisiologica

Normopeso, abitudini di vita regolari, non fumo, non alcool

APP

A Luglio 2021 giunge all'attenzione per linfocitosi assoluta , già presente da qualche anno secondo quanto riferito, ma senza documentazione.

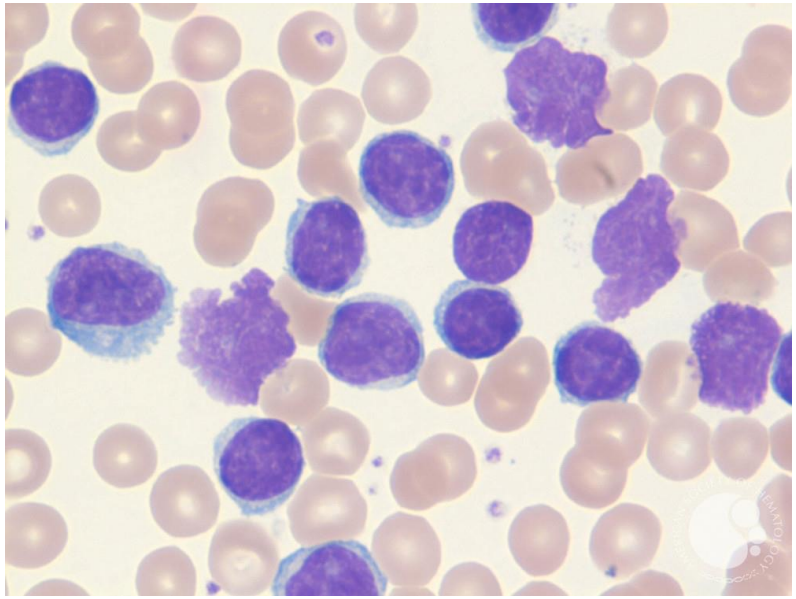
Diagnosi

Esami ematochimici: GB 18,390/mmc (L14,250), Hb 14,5 g/dl, PLT 267,000/mmc.

LDH e beta2micro sierica nella norma.

Foresi proteica con ipogamma 10%.

Immunofenotipo SP: CD5, CD19, C20 low, CD23, CD79b , basso livello di immunoglobuline di superficie con restrizione monotipica



CLL-B

Staging

Stage		Definition
Binet system		
Binet A		Hb ≥100 g/l (6.21 mmol/l), platelets ≥100 × 10^9/l <3 involved lymphoid sites[a]
Binet B		Hb ≥100 g/l (6.21 mmol/l), platelets ≥100 × 10^9/l ≥3 involved lymphoid sites[a]
Binet C		Hb <100 g/l (6.21 mmol/l), platelets <100 × 10^9/l
Rai system		
Low-risk	Rai 0	Lymphocytosis >5 × 10^9/l
Intermediate-risk	Rai I	Lymphocytosis and lymphadenopathy
	Rai II	Lymphocytosis and hepatomegaly and/or splenomegaly with/without lymphadenopathy
High-risk	Rai III	Lymphocytosis and Hb <110 g/l (6.83 mmol/l) with/without lymphadenopathy/organomegaly
	Rai IV	Lymphocytosis and platelets <100 × 10^9/l with/without lymphadenopathy/organomegaly

E.O. negativo per adenopatie palpabili o epatosplenomegalia

RX torace ed eco addome: nella norma

CLL-B stadio A Binet e 0 RAI

Criteri di inizio terapia sulla base delle linee guida ESMO 2020

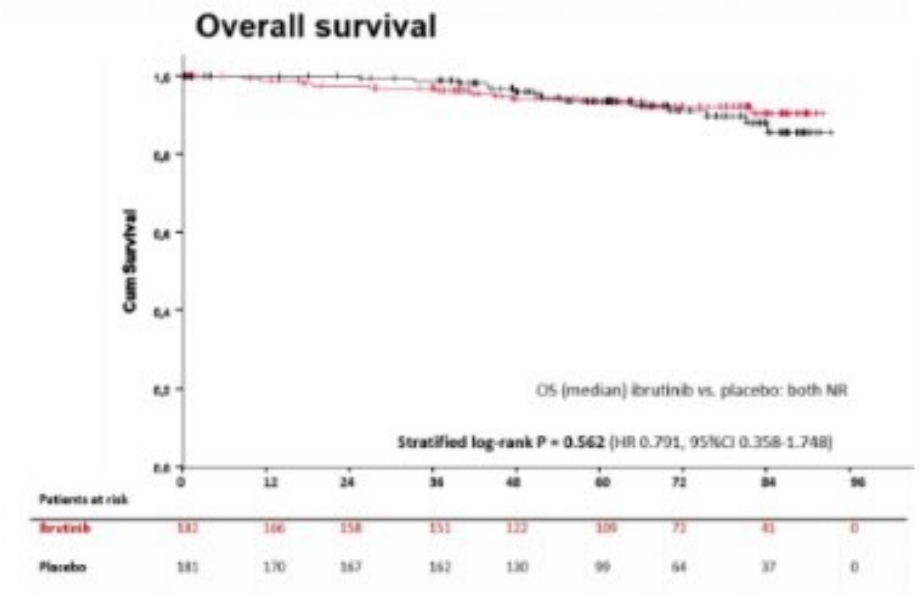
.

- presenza di anemia o piastrinopenia da infiltrazione midollare
- splenomegalia massiva (i.e. 6 cm sotto il margine costale) o progressiva o sintomatica
- massiva (i.e. 10 cm) o progressiva o sintomatica linfoadenopatia
- progressiva linfocitosi con un incremento della conta linfocitaria almeno del 50% in 2 mesi o raddoppiamento della conta linfocitaria (LDT) in 6 mesi.
- complicanze autoimmuni quali anemia e piastrinopenia non responsive agli steroidi
- interessamento extranodale (es cute, reni, polmoni, vertebre)sintomatico o funzionale
- sintomi costituzionali quali perdita di peso > 10% nei 6 mesi precedenti, astenia, febbre 38° C per 2 settimane senza segni di infezione in atto, sudorazioni per un mese

watch and wait

Annals of Oncology 2020 Volume 32 - Issue 1 - 20
B. Eichhorst et al. Oncology

Ibrutinib versus placebo in patients with asymptomatic, treatment-naïve early stage chronic lymphocytic leukemia (CLL): final results of the phase 3, doubleblind, placebo-controlled CLL12 trial.
Hematol Oncol. 2023;41(S2): 56-58.



Giugno 2024: progressione clinica

- EE : GB 30.93/mmc, L 27.370, Hb 11.2 g/dl, plt 136.000/mmc, crea 0.93, ALT 20, AST 14, LDH 258 U/l, beta 2 micro sierica 2,8 mg/dl.

- eco addome (13/6/24): milza 167 mm, disomogenea per la presenza di multiple sparse micro-focalità. Adenopatie in sede para ilo splenico di 19 mm. Multiple adenopatie mesenteriche e retroperitoneali fino a 24 mm.

- comparsa di adenopatie laterocervicali e ascellari bilaterali fino a 3 cm di diametro

Indicazione a trattamento

Annals of Oncology 2020 Volume 32 - Issue 1 - 20
B. Eichhorst et al.

Valutazione pre trattamento secondo linee guida ESMO

PARAMETRI PAZIENTE RELATI

Fitness

Terapia farmacologica, comorbidità, (in particolare studio della funzionalità cardiaca se proponibile un BTKi)

Valutazione aderenza attesa alla terapia

Paziente FIT

In terapia con EUTIROX

Buona aderenza ma insofferenza alle terapia croniche ed ai controlli

Valutazione pre trattamento secondo linee guida ESMO

PARAMETRI MALATTIA RELATI

stato mutazionale IGHV

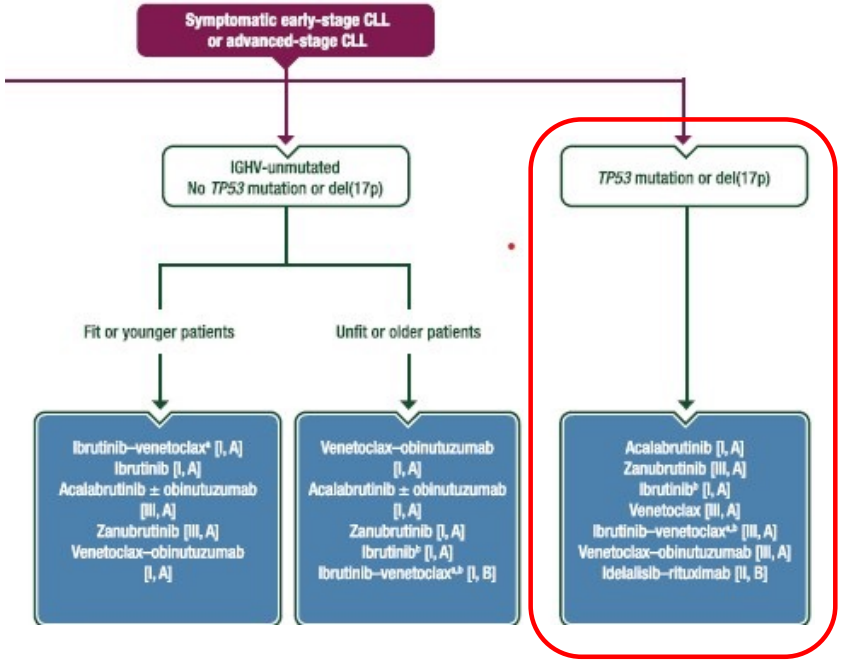
mutazione di TP53

delezione 17p

IGHV MUTATO

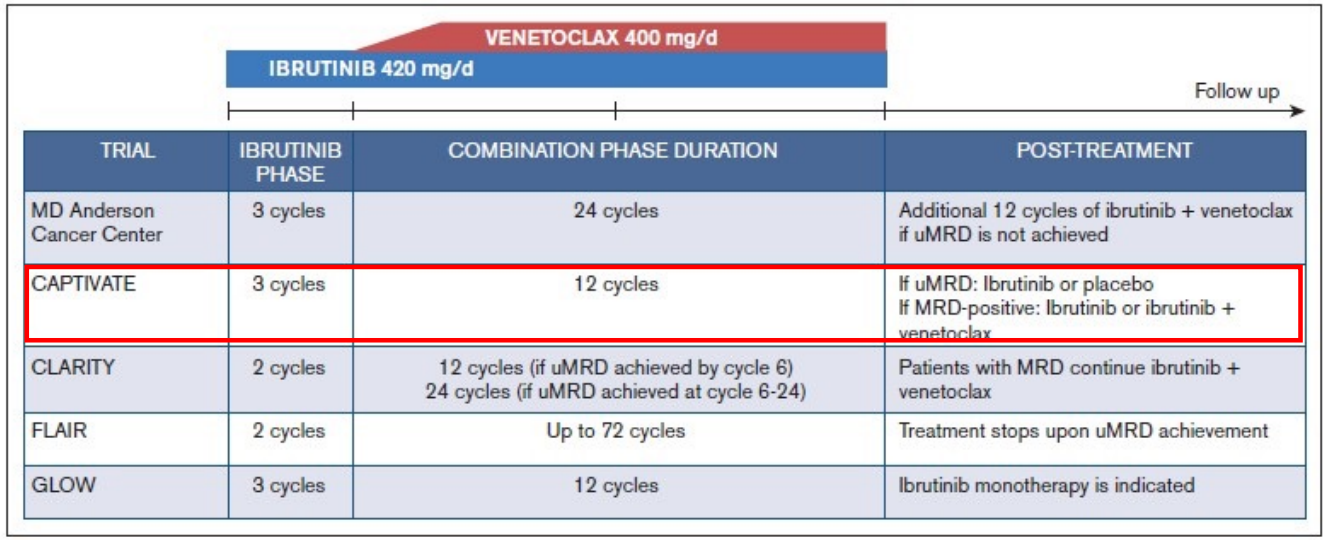
Del17p e TP53 mu

ESMO Clinical Practice Guideline interim update on new targeted therapies in the first line and at relapse of chronic lymphocytic leukaemia



B. Eichhorst et al.2024

Studi di combinazione IBRUTINIB VENETOCLAX

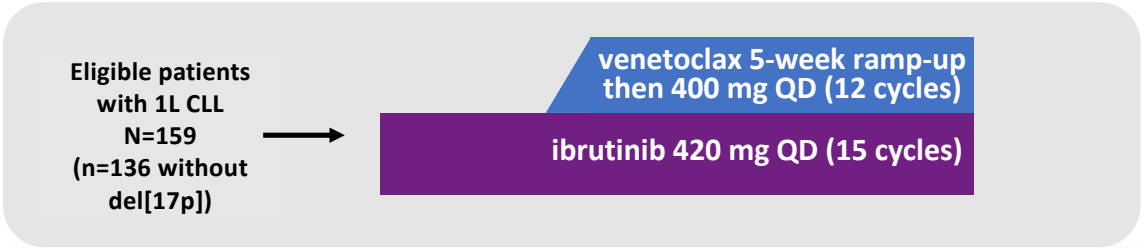


TRIAL	IBRUTINIB PHASE	COMBINATION PHASE DURATION	POST-TREATMENT
MD Anderson Cancer Center	3 cycles	24 cycles	Additional 12 cycles of ibrutinib + venetoclax if uMRD is not achieved
CAPTIVATE	3 cycles	12 cycles	If uMRD: Ibrutinib or placebo If MRD-positive: Ibrutinib or ibrutinib + venetoclax
CLARITY	2 cycles	12 cycles (if uMRD achieved by cycle 6) 24 cycles (if uMRD achieved at cycle 6-24)	Patients with MRD continue ibrutinib + venetoclax
FLAIR	2 cycles	Up to 72 cycles	Treatment stops upon uMRD achievement
GLOW	3 cycles	12 cycles	Ibrutinib monotherapy is indicated

Figure 2. **Ibrutinib plus venetoclax combination trial designs.** Ibrutinib was administered for 2 to 3 cycles, each lasting for 28 days, to induce a debulking effect, disrupt the protective microenvironment of CLL cells in the lymph node, and complementarily reduce MCL-1 levels to enhance sensitivity to venetoclax. Venetoclax was then added. Following venetoclax dose ramp-up, the combination of ibrutinib and venetoclax was given for 12 or 24 cycles or until uMRD was achieved.

CAPTIVATE FD cohort: Patient baseline characteristics

CAPTIVATE is a multicenter phase 2 study investigating combined ibrutinib plus venetoclax in 1L treatment of CLL and SLL in 2 separate cohorts: MRD-guided randomized treatment discontinuation (MRD) and fixed duration (FD)[1–3]



Primary endpoint:
Complete response rate for patients without del(17p)

Key secondary endpoints:
- uMRD rates, PFS, OS
- Duration of response, ORR
- Safety, including TLS risk reduction after 3 cycles of ibrutinib

Key inclusion criteria
- Aged >17 and ≤70 years with previously untreated CLL requiring treatment (iwCLL)
- ECOG PS 0–2
- Adequate hepatic, renal, and hematologic function

After completion of the FD regimen, patients who subsequently had confirmed PD by iwCLL criteria could be retreated with single-agent ibrutinib until PD or unacceptable toxicity. For patients who had PD 2 years after completion of the FD regimen, retreatment with the FD ibrutinib plus venetoclax regimen could be considered.

Baseline characteristics – FD cohort	IVen (N=159)
Median age, years (range)	60 (33–71)
Male sex, n (%)	106 (67)
Rai Stage III/IV disease, n (%)	44 (28)
Any cytopenia at baseline, n (%)	54 (34)
ANC ≤1.5×10^9/L	13 (8)
Hemoglobin ≤11 g/dL	37 (23)
Platelets ≤100×10^9/L	21 (13)
Lymph node diameter, n (%)	
≥5 cm	48 (30)
≥10 cm	5 (3)
High-risk features, n (%)	
del(17p)/*TP53* mutation	27 (17)
del(17p)*	20 (13)
del(11q)†	28 (18)
Complex karyotype‡	31 (19)
IGHV unmutated, n (%)	89 (56)

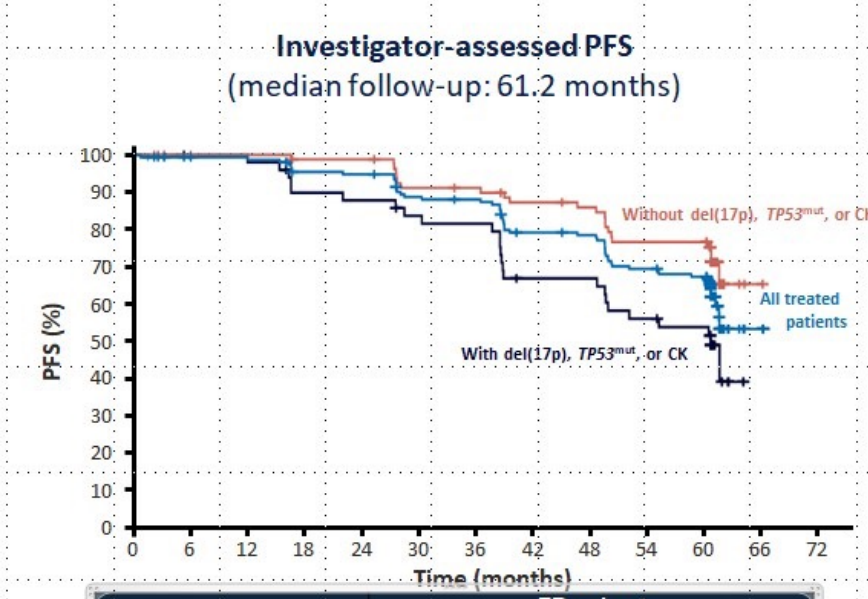
Outcomes in high-risk subgroups: Up to 5.5 years of follow-up in the phase 2 CAPTIVATE study.

FD cohort	With high-risk genomic feature[a]		Without high-risk genomic feature[a]	
	n	5-y PFS rate, % (95% CI)	n	5-y PFS rate, % (95% CI)
del(17p)/mutated *TP53*	27	41 (21–59)	129	73 (64–80)
CK[b]	31	57 (37–72)	102	72 (61–80)
Unmutated IGHV[c]	40	68 (50–80)	44	85 (69–93)
del(11q)[c]	11	64 (30–85)	74	79 (67–87)

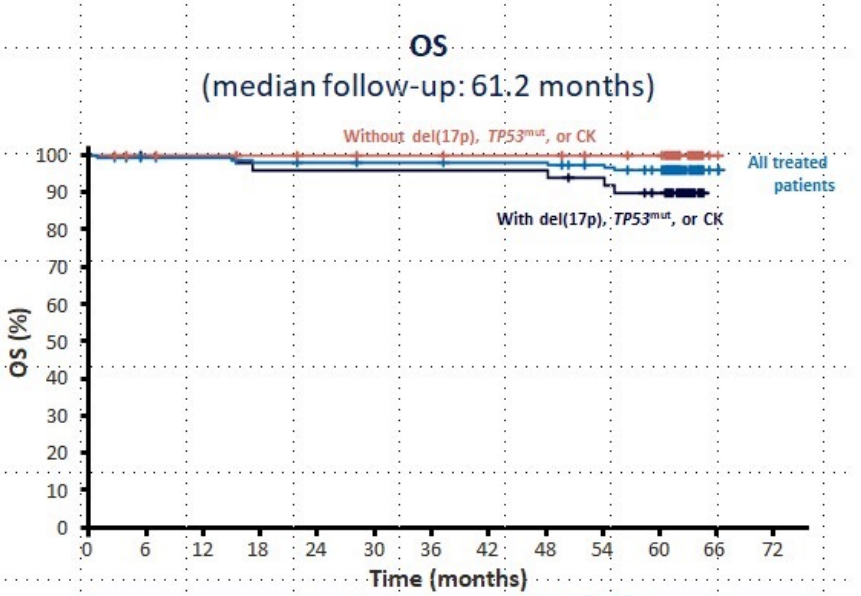
[a]Among pts with known baseline status. [b]Defined as ≥3 chromosomal abnormalities. [c]Excluding pts with del(17p)/mutated *TP53* or CK.

After 5.5 y of follow-up, FD Ibr+Ven continues to provide clinically meaningful PFS in pts with high risk genomic features, as well as in the overall population.
Ibr-based retreatment provides promising responses in pts needing subsequent therapy after the all-oral FD regimen of Ibr+Ven.

CAPTIVATE FD cohort: PFS and OS



	FD cohort		
	With del(17p), *TP53*^{mut}, or CK (n=51)	Without del(17p), *TP53*^{mut}, or CK (n=85)	All (N=159)
60-month PFS rate, % (95% CI)	54 (39–67)	77 (66–85)	67 (59–74)

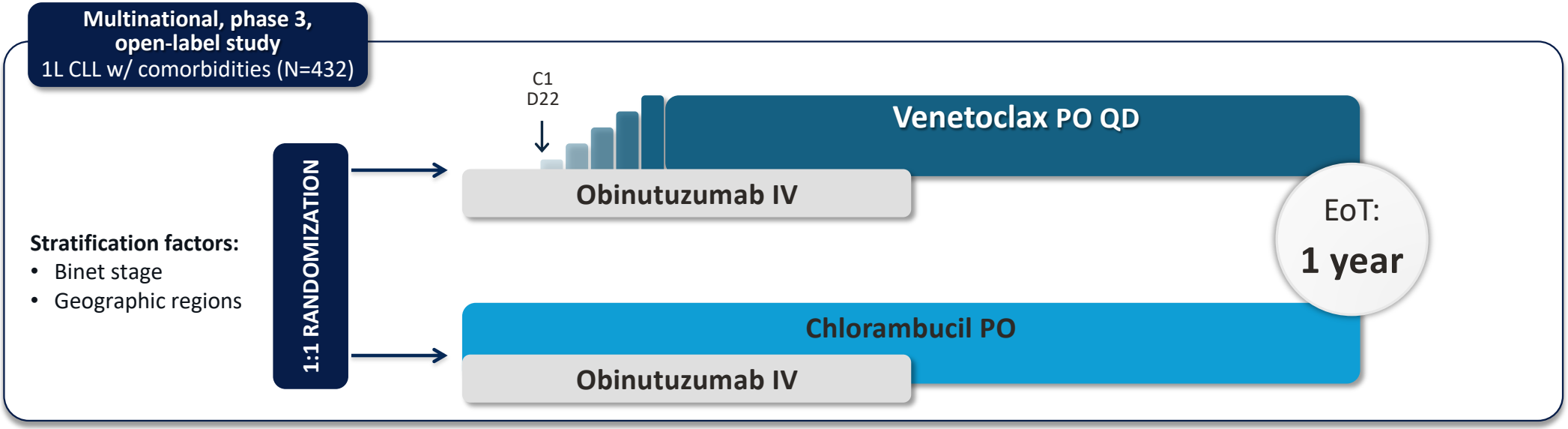


	FD cohort		
	With del(17p), *TP53*^{mut}, or CK (n=51)	Without del(17p), *TP53*^{mut}, or CK (n=85)	All (N=159)
60-month OS rate, % (95% CI)	90 (77–96)	100 (100–100)	96 (91–98)

CK, complex karyotype; FD, fixed duration.

Jacobs R, *et al*. EHA 2024. Abstract P675 (Poster).

Venetoclax-obinutuzumab for previously untreated chronic lymphocytic leukemia: 6-year results of the randomized phase 3 CLL14 study



Primary endpoint (ITT population):
- PFS – investigator assessed

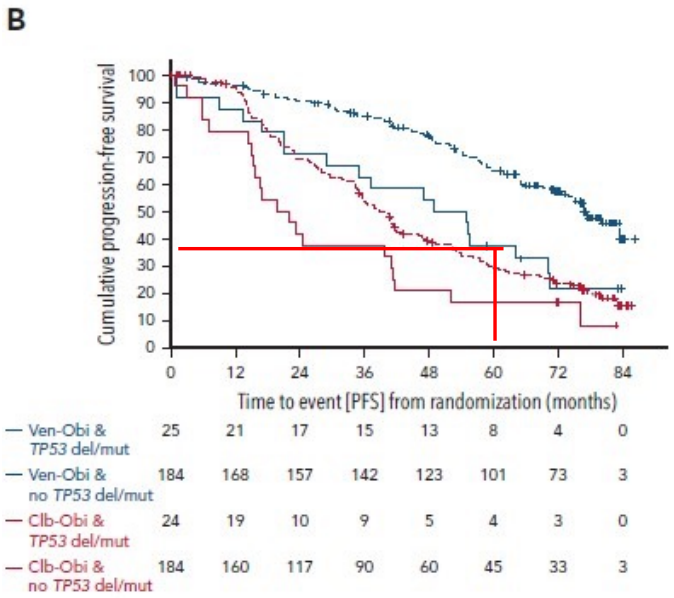
Key secondary endpoints (ITT population):
- PFS – IRC assessed
- ORR and CR 3 months after EoT
- uMRD rate (PB and BM) 3 months after EoT
- OS

Key inclusion criteria
- Previously untreated CLL according to iwCLL criteria
- CIRS >6 and/or CrCl <70 mL/min

MRD was a secondary efficacy endpoint, not a determinant of treatment duration

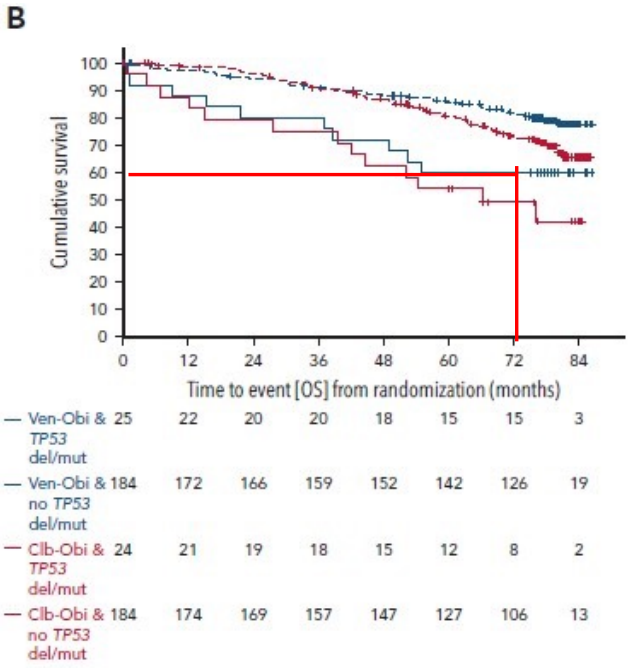
BM, bone marrow; C, cycle; CIRS, cumulative illness rating scale; CrCl, creatinine clearance; D, day; EoT, end of treatment; FTD, fixed treatment duration; IRC, independent review committee; ITT, intent to treat; iwCLL, International Workshop on CLL; PB, peripheral blood; VenO, venetoclax + obinutuzumab.

Venetoclax-obinutuzumab : 6-year DFS per CLL alto rischio



Characteristic	VenO (n=216)	OClb (n=216)
TLS risk category, n (%)		
Low	29 (13.4)	26 (12.0)
Intermediate	139 (64.4)	147 (68.1)
High	48 (22.2)	43 (19.9)
IGHV mutational status, n (%)		
Unmutated	121/200 (60.5)	123/208 (59.1)
Mutated	76/200 (38.0)	83/208 (39.9)
Not evaluable	3/200 (1.5)	2/208 (1.0)
***TP53*^{mut} and/or del(17p), n (%)**	25/209 (12.0)	24/208 (11.5)
Cytogenetic subgroups as per hierarchy,* n (%)		
del(17p)	17/210 (8.1)	14/208 (6.7)
del(11q)	36/210 (17.1)	38/208 (18.3)
Trisomy in 12	36/210 (17.1)	40/208 (19.2)
No abnormalities	50/210 (23.8)	42/208 (20.2)
del(13q) alone	71/210 (33.8)	74/208 (35.6)
Complex karyotype group, n (%)		
NCKT	166/200 (83.0)	167/197 (84.8)
CKT/HCKT, n (%)	34/200 (17.0)	30/197 (15.2)

Venetoclax-obinutuzumab : 6-year OS per CLL alto rischio



TERAPIA

Inizio della terapia il 02/10/2024
EE del 19/9/24: GB 60.700, L 6070, linfociti 48.560, Hb 9.9 g/dl, MCV 105, plt 174.000/mmc

IBRUTINIB 420 mg/die

EE del 24/12/24: GB 48.550, L 45.180, Hb 11.9, MCV 104, plt 181.000
Sogg. bene. Riduzione delle adenopatie palpabili.

Ad IBRUTINIB 420 mg/die
si associa ramp up di VENETOCLAX

EE del 25/01/25: GB 9520, N 1580, L 7660, Hb 13.6, MCV 99, plt 193.000, crea 0.88, sodio 138, potassio 4.4, calcio 9.3, Mg 2.11, ALT 17, AST 14.

IBRUTINIB 420 mg/die
VENETOCLAX 400 mg/die

EVENTI AVVERSI

12/3/25 6° ciclo giorno 12° : NEUTROPENIA GRADO 4
EE del 7/3/25 : GB 1860, **N 260**, Hb 13.1, MCV 95, plt 181.000

Continua IBRUTINIB 420 mg/die
STOP VENETOCLAX

EE del 29/3/25 : 7° ciclo giorno 1°:
GB 3630, N 1920, Hb 13.8, plt 159.000

Continua IBRUTINIB 420 mg/die
Riprende VENETOCLAX 300 mg/die

CAPTIVATE safety

AE summary, n (%)[1]	All patients (N=159)
Most common AEs (any grade, ≥30%)	
Diarrhea	99 (62)
Nausea	68 (43)
Neutropenia	66 (42)
Arthralgia	53 (33)
Most common Grade 3/4 AEs (≥5%)	
Neutropenia	52 (33)
Hypertension	9 (6)
Neutrophil count decreased	8 (5)
AEs of clinical interest (any grade)	
Atrial fibrillation	7 (4)
Major hemorrhage*	3 (2)
Any SAE	36 (23)
Fatal AEs	1 (1)†

1. Tam CS, *et al. Blood* 2022; **139:**3278–3289;
2. Moreno C, *et al.* EHA 2022. Abstract P669 (Poster);
3. Jacobs R, *et al.* EHA 2024. Abstract P675 (Poster).

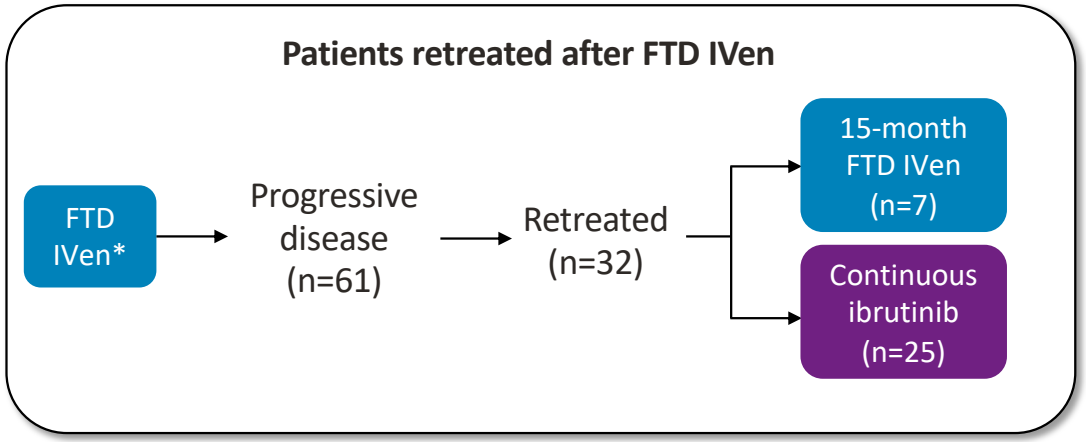
RISPOSTA CLINICA a 6 mesi

- EE del 12/04/2025: GB 2860, N 1370, Hb 14.3, MCV 96, plt 175.000.

- eco addome (13/04/25): milza 13.5 mmm; adenopatie in sede para ilo splenico di 12 mm; multiple adenopatie mesenteriche e retroperitoneali fino a 16 mm.

- scomparsa delle adenopatie laterocervicali e ascellari bilaterali

CAPTIVATE FD and MRD retreatment outcomes



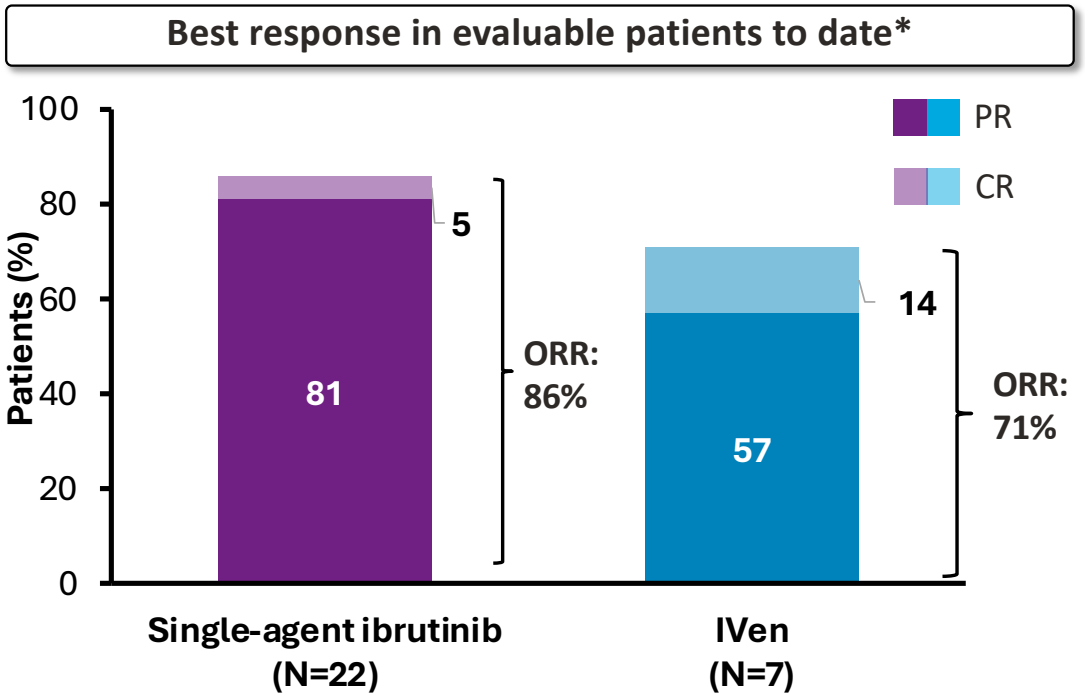
Baseline characteristics	Ibrutinib (N=25)	IVen* (N=7)	All retreated patients (N=32)
Median time on retreatment, months (range)	21.9 (0.0–50.4)	13.8 (3.7–15.1)	
Median age, years (range)	56 (39–71)	63 (49–69)	59 (39–71)
Male sex, n (%)	15 (60)	6 (86)	21 (66)
Rai Stage III/IV disease, n (%)	4 (16)	2 (29)	6 (19)
High-risk features, n (%)			
uIGHV	20 (80)	5 (71)	25 (78)
del(17p)/*TP53* mutation	5 (20)	5 (71)	10 (31)
del(11q)†	6 (24)	1 (14)	7 (22)
Complex karyotype‡	9 (36)	2 (29)	11 (34)

* Per protocol, only patients with PD >2 years after completion of treatment were eligible to reinitiate ibrutinib + venetoclax. Four patients exited the study during ibrutinib + venetoclax treatment and completed retreatment off study; † Without del(17p) per Döhner hierarchy; ‡ Defined as ≥3 abnormalities by conventional CpG-stimulated cytogenesis.

FTD, fixed treatment duration.

Jacobs R, *et al.* EHA 2024. Abstract P675 (Poster).

CAPTIVATE Retreatment outcomes: Efficacy and safety



AE summary, n (%)	Ibrutinib (N=25)	IVen (N=7)
Any AE	18 (72)	7 (100)
Most common AEs†		
COVID-19‡	5 (20)	2 (29)
Diarrhea	5 (20)	3 (43)
Hypertension	4 (16)	4 (57)
Pyrexia	3 (12)	0
Upper respiratory tract infection	3 (12)	0
Nausea	1 (4)	2 (29)
Grade 3/4 AEs	6 (24)	2 (29)
Serious AEs	5 (20)	0
AEs leading to discontinuation	1 (4)	0
AEs leading to dose reduction	0	0

* 3 patients who initiated single-arm ibrutinib treatment had not yet undergone assessment;
† Occurring in ≥10% of patients with single-agent ibrutinib or ≥2 patients with IVen; ‡ All events were grade 1/2.

CR, complete response; PR, partial response.

Jacobs R, *et al.* EHA 2024. Abstract P675 (Poster).

CHRONIC LYMPHOCYTIC LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL

Prevalence of Resistance-Associated Bruton Tyrosine Kinase (BTK) C481 Mutations By Prior Treatment Status Among Patients with Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL): A Real-World Observational Study

130 patients with clinical and BTK C481 mutation data available grouped by treatment status at the time of blood collection:
-treatment naive (group 1)
-treated with therapies other than a BTKi (group 2)
-previously treated with or currently receiving a covalent BTKi (group 3).

BTK C481 mutations were only detected among the 16 pts with cumulative exposure to a covalent BTKi of >36 mo (21%)

Blood 2 NOVEMBER 2023 | VOLUME 142, NUMBER Supplement 1

Caso Clinico 2

M.L .P,1948, anni 50

Comorbidità

Ipertiroidismo in terapia con Tapazole

BPCO in terapia con broncodilatatori e PFR con deficit ostruttivo medio

Anamnesi fisiologica

Sovrappeso, abitudini di vita regolari, non fumo, non alcool

APP

A Luglio 1998 giunge all'attenzione per linfocitosi assoluta lieve preceduta da tempo da inversione della formula

Diagnosi

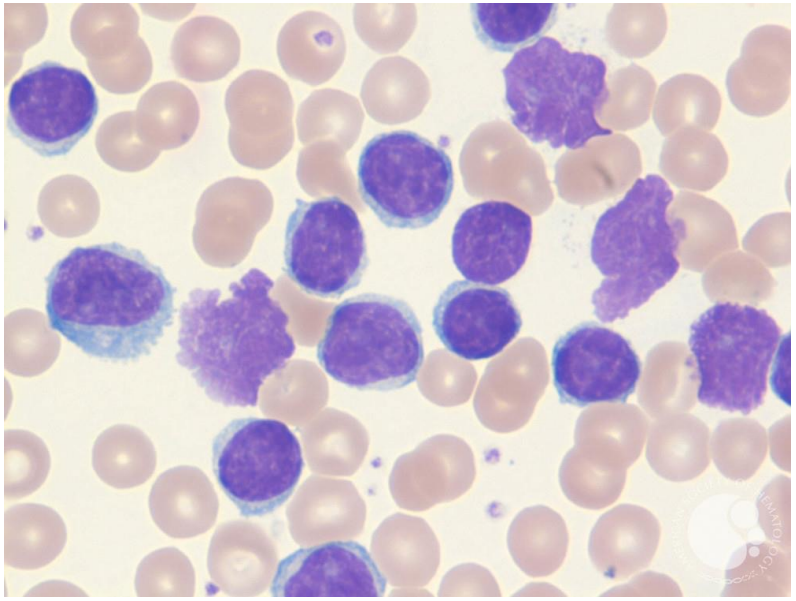
Esami ematochimici: GB 25,390/mmc (L19,250), Hb 13,5 g/dl, PLT 245,000/mmc.

LDH e beta2micro sierica nella norma.

Foresi proteica con ipogamma 10%.

Immunofenotipo SP: CD5, CD19, C20 low, CD23, CD79b , basso livello di immunoglobuline di superficie con restrizione monotipica

Rx torace ed eco addome negativi



CLL-B stadio A Binet e 0 RAI

Giugno 2003: progressione clinica

- EE : GB 50.93/mmc, L 42.370, Hb 12.2 g/dl, plt 120.000/mmc, crea 0.93, ALT 20, AST 14, LDH 258 U/l, beta2micro sierica 2,8mg/dl.
- eco addome (13/6/24): milza 15 mmm e adenopatie in sede iliaca e mesenterica fino a 36 mm
- comparsa di adenopatie laterocervicali e inguinali bilaterali fino a 3 cm di diametro

Indicazione a terapia

Annals of Oncology 2020 Volume 32 - Issue 1 - 20
B. Eichhorst et al. Oncology

Valutazione pre trattamento secondo linee guida ESMO

PARAMETRI PAZIENTE RELATI

Fitness

Terapia farmacologica, comorbidità, (in particolare studio della funzionalità cardiaca se proponibile un BTKi)

Valutazione aderenza attesa alla terapia

Paziente FIT

In terapia con TAPAZOLE

La paziente accetta malissimo l'idea di essere sottoposta ad una chemioterapia

Valutazione pre trattamento secondo linee guida ESMO

PARAMETRI MALATTIA RELATI

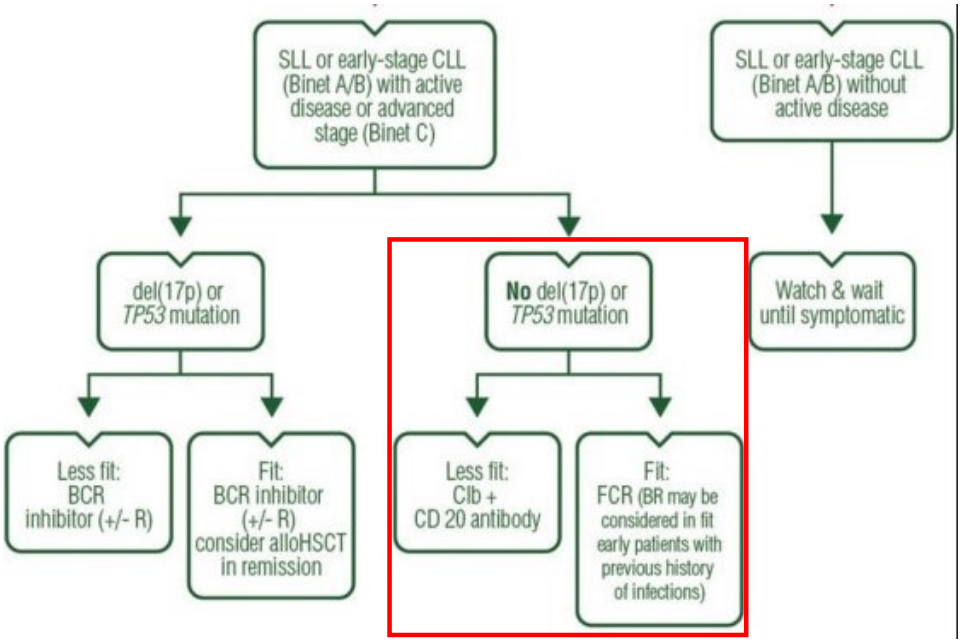
Mutazione TP53

Delezione 17p

TP53 wt

assenza di del17p

Valutazione pre trattamento secondo linee guida ESMO



FCR

Annals of Oncology 2020 Volume 32 - Issue 1 - 20
B. Eichhorst et al.

TERAPIA

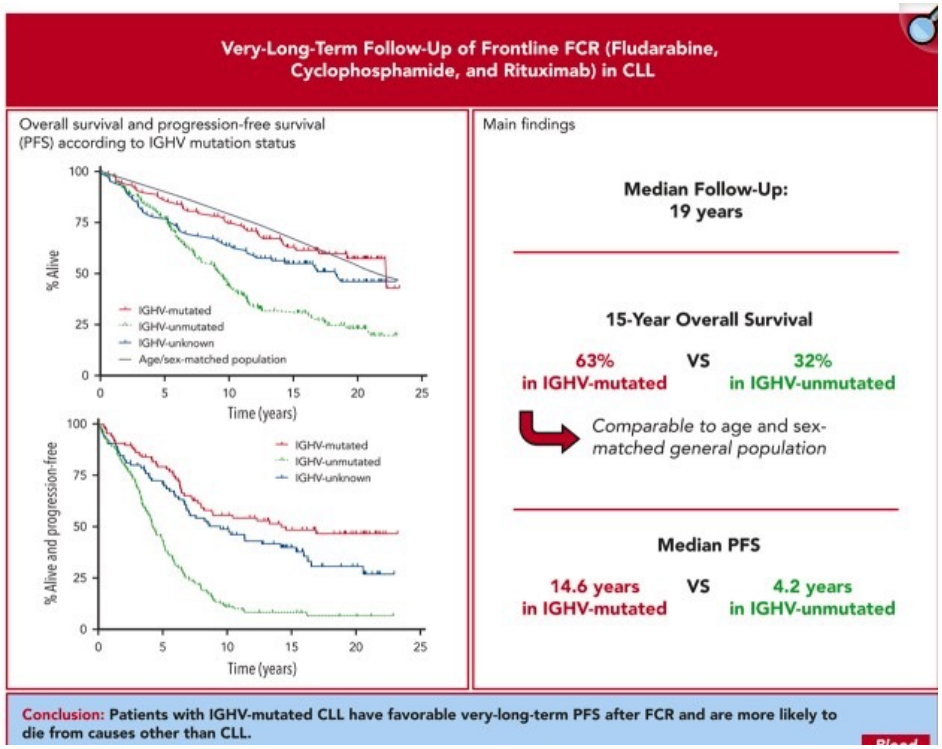
La paziente viene sottoposta a 6 cicli FCR dal 24 Luglio 2003

- Dopo il 4° ciclo, a Novembre 2004 si verifica ricovero per neutropenia febbrile da urosepsi con isolamento di Klebsiella pn. multisensibile complicato da piccolo focolaio bpn.
- Il 5° ciclo viene quindi rimandato, la terapia viene ripresa a fine Novembre e conclusa a fine Gennaio 2005 con il 6° ciclo.

- EE del 20/02/2005: GB 1860, N 970,L 890, Hb 11,2, MCV 96, plt 115.000.
- eco addome (13/02/2005): milza 9 cm; assenza di adenopatie
- scomparsa delle adenopatie laterocervicali e ascellari bilaterali
- BOM negativa
- IF SP negativo

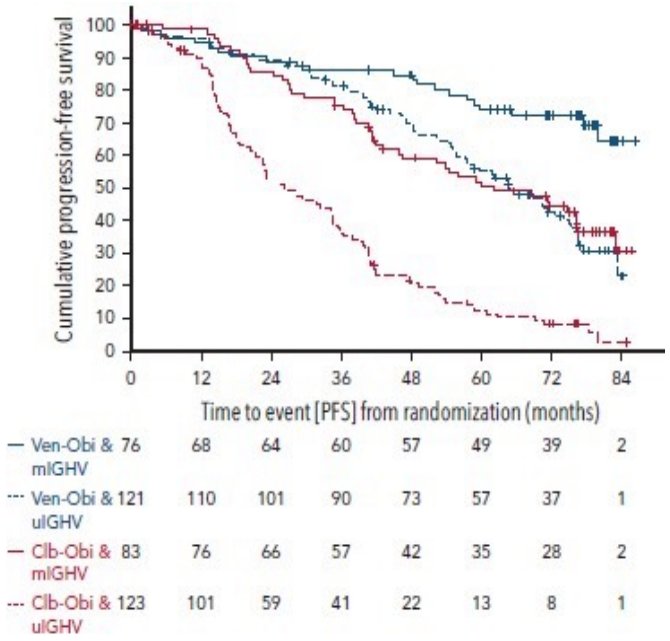
Sustained remissions in CLL after frontline FCR treatment with very-long-term follow-up

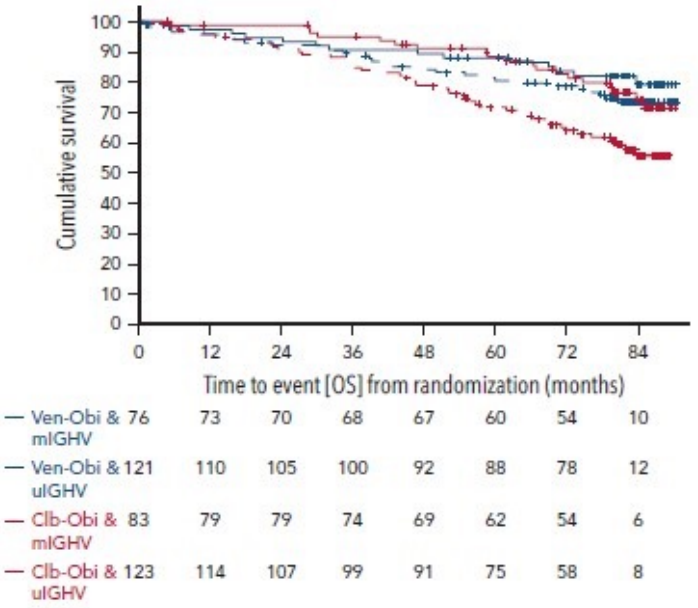
.

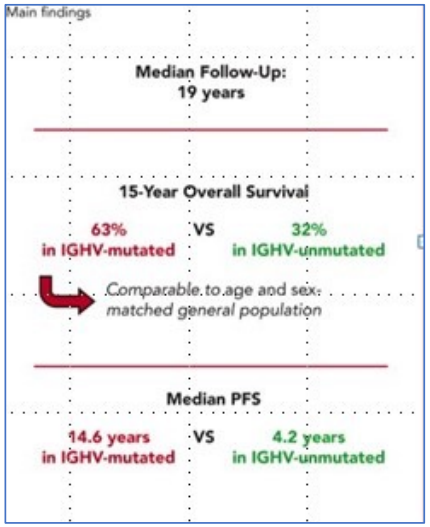


Blood 2023 Aug 22;142(21):1784–1788

Sustained remissions in CLL after frontline FCR treatment with very-long-term follow-up: PFS e OS in IGVH mutati e non mutati







Blood 2023 Aug 22;142(21):1784–1788

FCR cumulative toxicity

Total deaths	169 of 300 (56%)
CLL	69 (23/41)
Richter transformation	24 (8/14)
Solid tumor	18 (6/11)
Other hematologic neoplasm	15 (5/9)

Follow-up

A Gennaio 2018 perdita di peso , iperpiressia senza apparente causa infettiva e grave astenia.

Agli esami ematochimici l'emocromo è nella norma e mantiene la formula leucocitaria normale , ma emerge LDH 850 U/l.

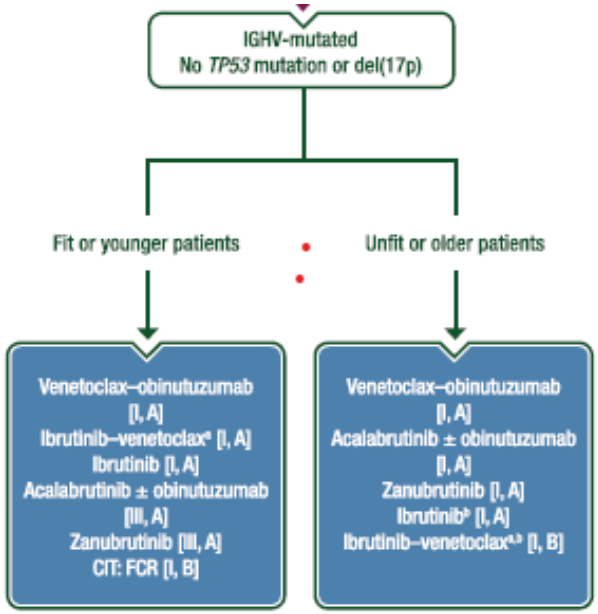
Tc collo-torace -addome -pelvi: massa addominale di 13

BOM negativa

Evoluzione in sindrome di Richter

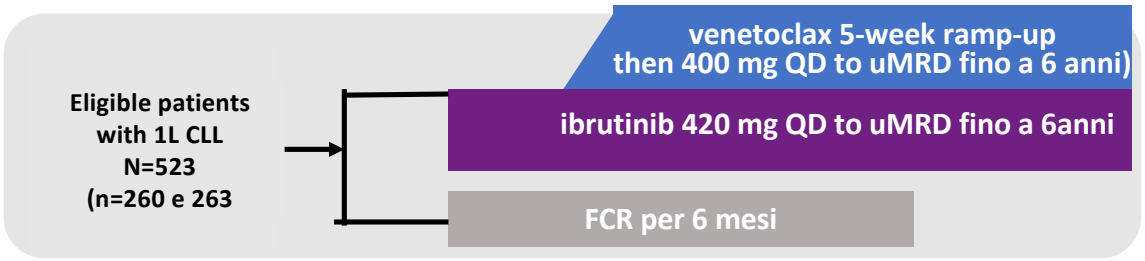
Riscriviamo la storia nel 2025: faremmo la stessa scelta ?

Opzioni per l'esordio



Studio FLAIR

FLAIR is a phase 3, multicenter, randomized, controlled, trial involving patients with untreated CLL investigating ibrutinib - venetoclax and ibrutinib monotherapy with FCR.
In the ibrutinib - venetoclax group, after 2 months of ibrutinib, venetoclax was added for up to 6 years of therapy



Primary endpoint:

- PFS

Key secondary endpoints:

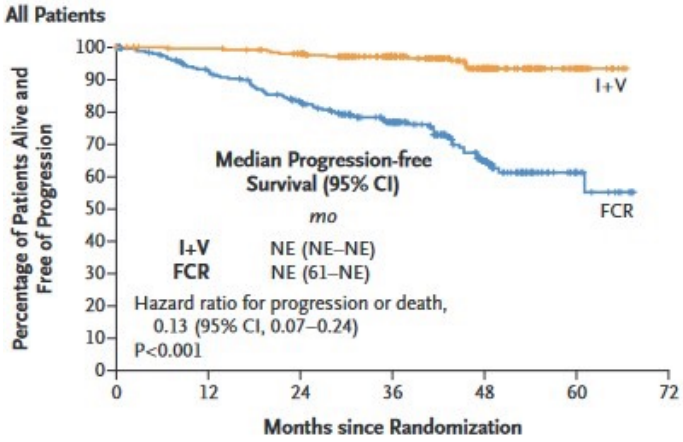
- ORR, uMRD rates,
- Duration of response and retreatment
- Toxic effects, QoL
- Cost-effectiveness

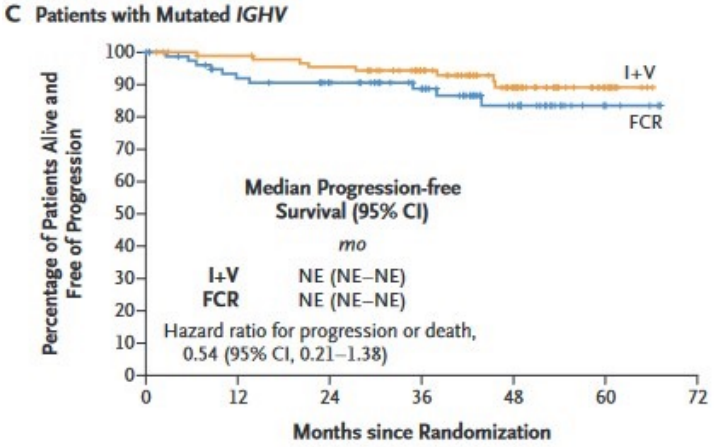
Key inclusion criteria

- Patients FIT with previously untreated CLL requiring treatment (iwCLL)

NEJ 390;4 January 25, 2024

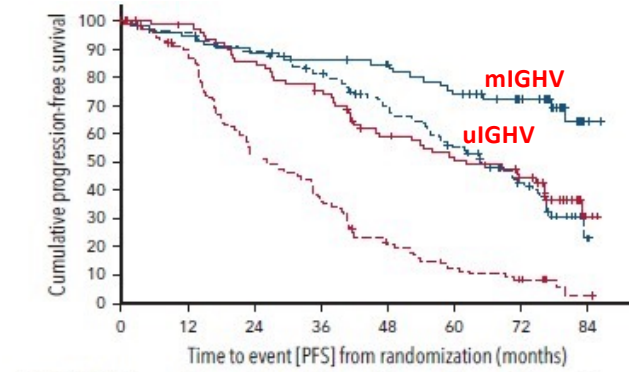
DFS results



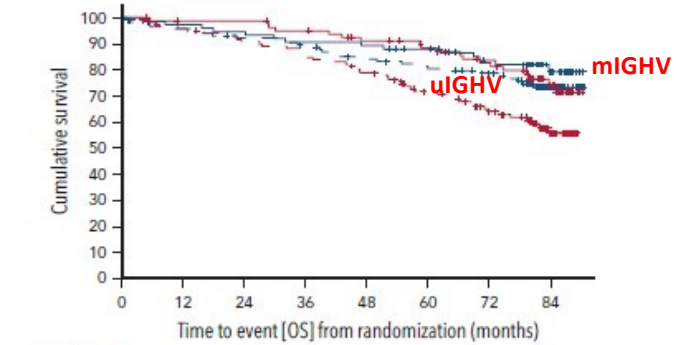


Ibrutinib - venetoclax (I+V) è risultato superiore a FCR per DFS nella popolazione totale ma sovrapponibile nella popolazione mIGVH.

Venetoclax - obinutuzumab for previously untreated chronic lymphocytic leukemia : 6-year results of the randomized phase 3 CLL14 study

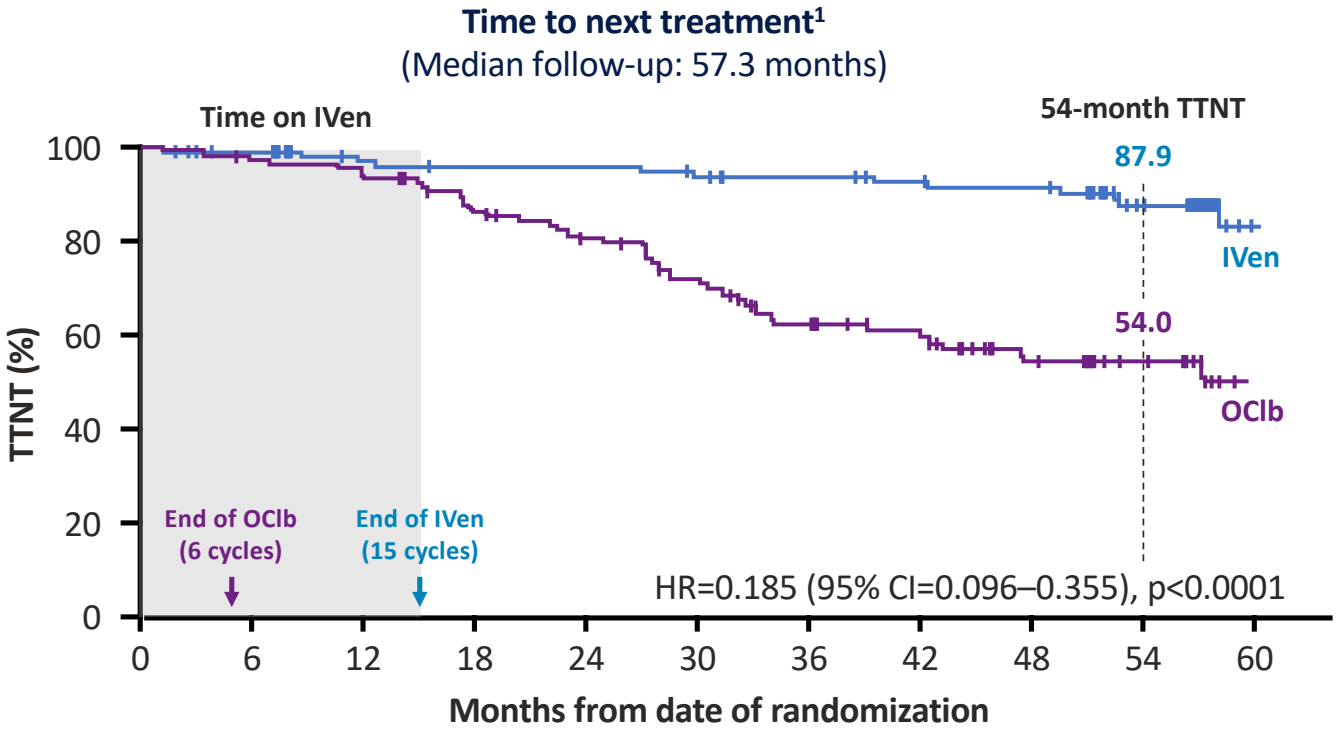


— Ven-Obi & mIGHV	76	68	64	60	57	49	39	2
--- Ven-Obi & uIGHV	121	110	101	90	73	57	37	1
— Clb-Obi & mIGHV	83	76	66	57	42	35	28	2
--- Clb-Obi & uIGHV	123	101	59	41	22	13	8	1



— Ven-Obi & mIGHV	76	73	70	68	67	60	54	10
— Ven-Obi & uIGHV	121	110	105	100	92	88	78	12
— Clb-Obi & mIGHV	83	79	79	74	69	62	54	6
— Clb-Obi & uIGHV	123	114	107	99	91	75	58	8

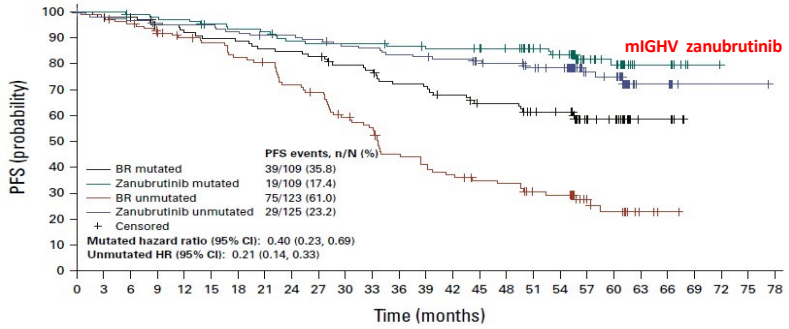
GLOW: Time to next treatment

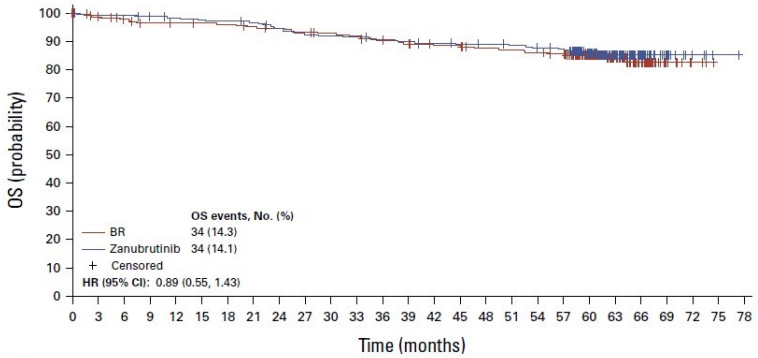


15 cycles×28 days=11.8 months for IVen and 6 cycles×28 days=5.5 months for OClb.[3]
* Not presented to 57.3 months median follow-up.
IVen, ibrutinib + venetoclax; OClb, obinutuzumab + chlorambucil; TTNT, time to next treatment.

2. Munir T, *et al. J Clin Oncol* 2023; 41:3689–3699.
3. Kater AP, *et al. NEJM Evid* 2022; 1:EVIDoa2200139.

Zanubrutinib Versus Bendamustine and Rituximab in Patients With Treatment-Naïve Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: Median 5-Year Follow-Up of SEQUOIA





JCO 780 | Volume 43, Issue 7 |

Grazie per l’attenzione