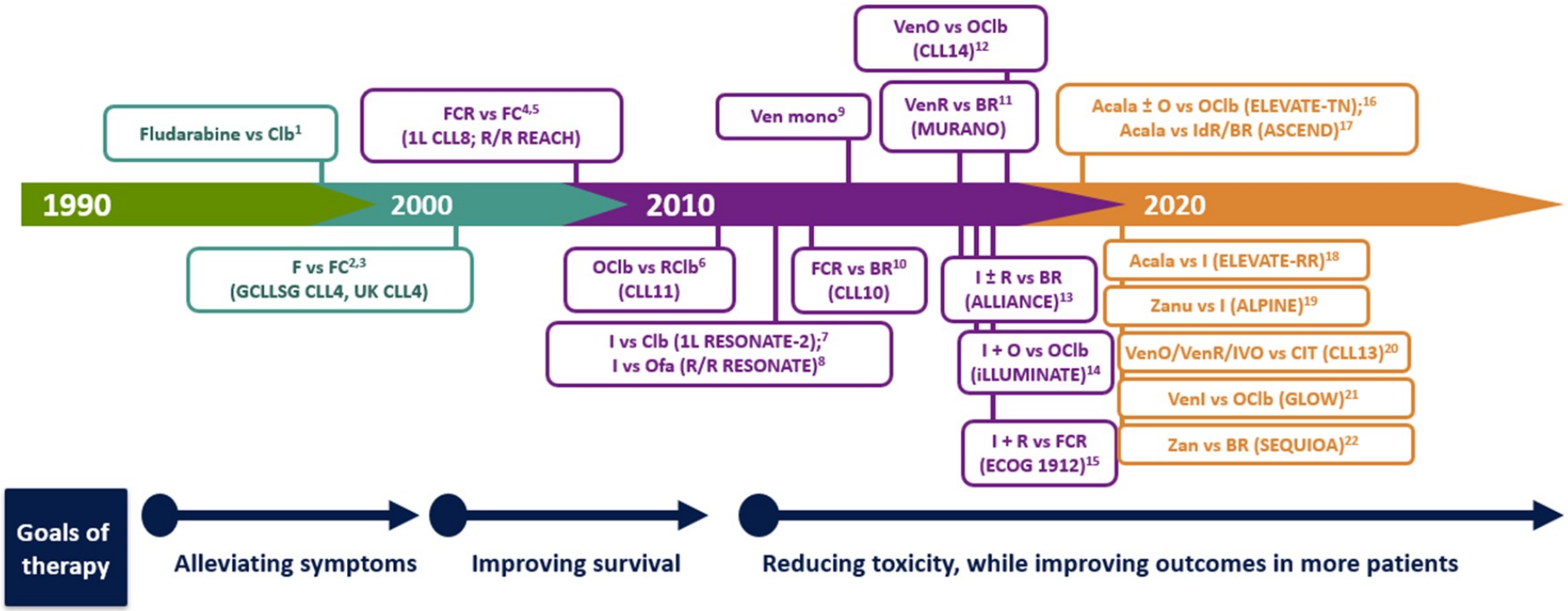
Il tramonto scritto della chemioterapia

Dott. Mariano Lucignano
Ospedale A. Tortora Pagani

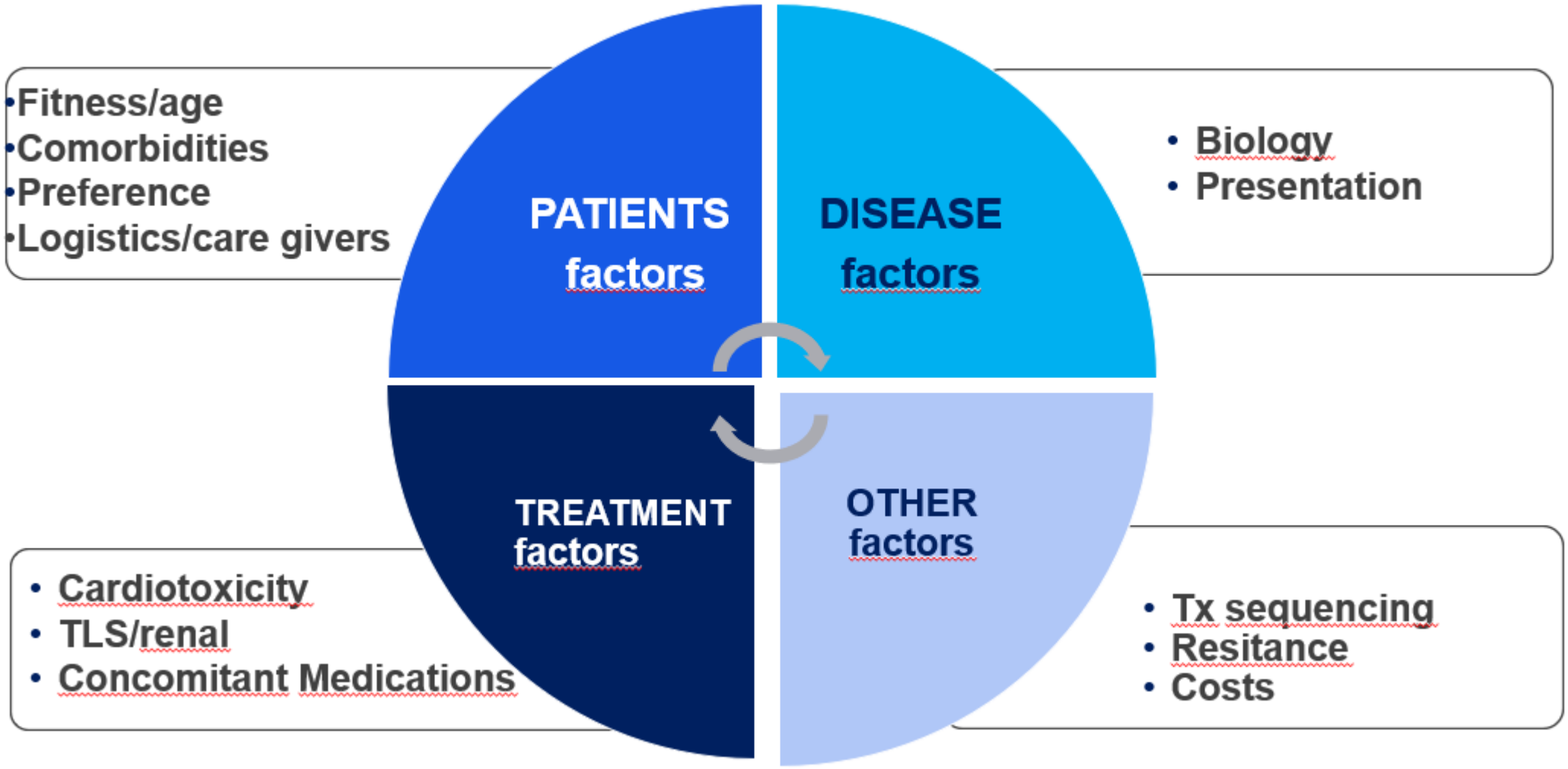
STORIA DELLA TERAPIA



A, acalabrutinib; B, bendamustine; C, cyclophosphamide; Clb, chlorambucil; F, fludarabine; Id, idelalisib; Ibr, ibrutinib; O, obinutuzumab; R, rituximab; Ven, venetoclax.

1. Rai KR, *et al. N Engl J Med* 2000; **343**:1750–1757; 2. Eichhorst BF, *et al. Blood* 2006; **114**:3382–3391; 3. Catovsky D, *et al. Lancet* 2007; **370**:230–239; 4. Hallek M, *et al. Lancet* 2010; **376**:1164–1174; 5. Robak T, *et al. J Clin Oncol* 2010; **8**:1756–1765; 6. Goede V, *et al. N Engl J Med* 2014; **370**:1101–1110; 7. Burger JA, *et al. N Engl J Med* 2015; **373**:2425–2437; 8. Byrd JC, *et al. N Engl J Med* 2014; **372**:213–223; 9. Roberts AW, *et al. N Engl J Med* 2016; 10. Eichhorst B, *et al. Lancet Oncol* 2016; **17**:928–942; 11. Seymour JF, *et al. N Engl J Med* 2018; **378**:1107–1120; 12. Fischer K, *et al. N Engl J Med* 2019; **380**:2225–2236; 13. Woyach JA, *et al. N Engl J Med* 2018; **379**:2517–2528 (incl. suppl.); 14. Moreno C, *et al. Lancet Oncol* 2019; **20**:43–56; 15. Shanafelt TD, *et al. N Engl J Med* 2019; **381**:432–443; 16. Sharman JP, *et al. Lancet* 2020; **379**:1278–1291; 17. Ghia P, *et al. J Clin Oncol* 2020; **38**:2849–2861.

Treatment decision in CLL 1L



Author opinion

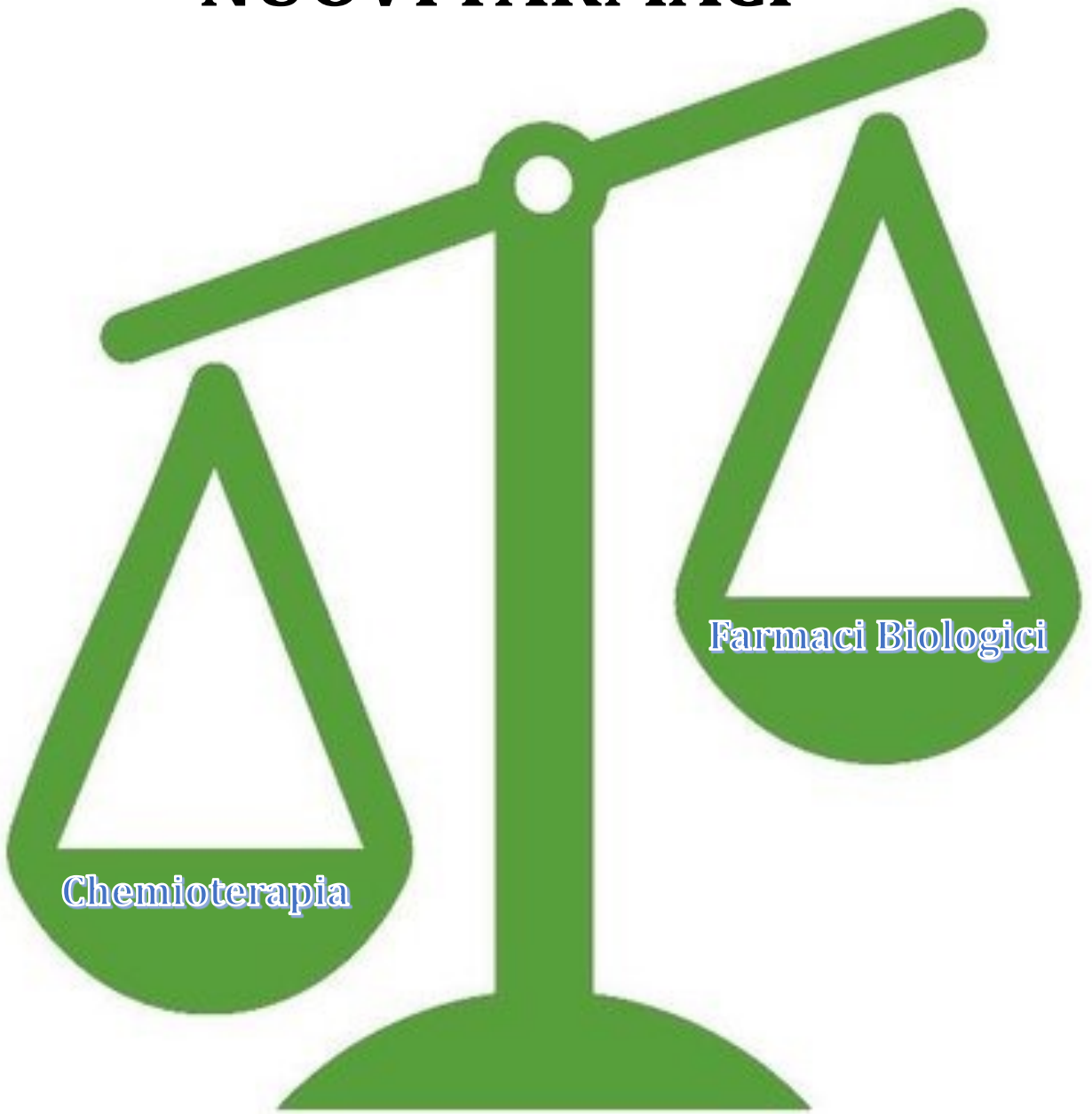
CLASSIFICAZIONE DEL PAZIENTE SECONDO IL FITNESS STATUS

‘Go-go’ o fit	‘Slow-go’ o unfit	‘No-go’ o frail
•Completamente indipendente •Nessuna comorbidità •Normale aspettativa di vita •Habitus psicologico ottimale	•Qualche comorbidità •Ridotte funzionalità d’organo •Ridotto performance status •Habitus psicologico buono	•Gravi handicap •Gravi comorbidità •Ridotta aspettativa di vita •Habitus psicologico compromesso

QUALE È L'OBIETTIVO TERAPEUTICO?

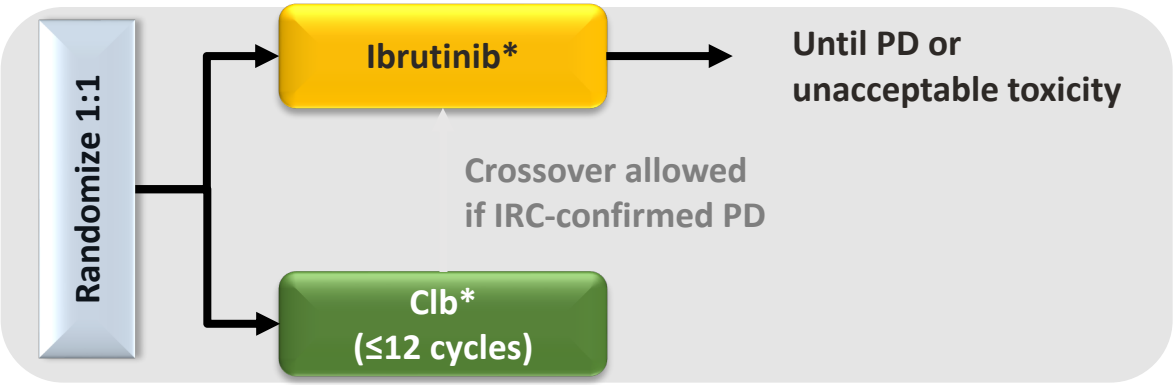
1. Prolungamento della OS
2. MRD -
3. Palliazione dei sintomi
4. Prolungamento della PFS

NUOVI FARMACI



RESONATE-2: Study design

Open-label, multicenter, randomized, Phase 3 study assessing the efficacy and safety of ibrutinib vs chlorambucil[1]



Key endpoints:

- **IRC-assessed PFS (Primary endpoint)**
- OS
- ORR
- Improvement in hematologic variables (hemoglobin and platelets)‡
- Safety

Key inclusion criteria[1]

- Age ≥65 years†
- ECOG PS 0–2
- ANC ≥1000 cells/mm^3
- Platelet count ≥50,000 cells/mm^3
- Adequate liver and kidney function
- No del(17p)

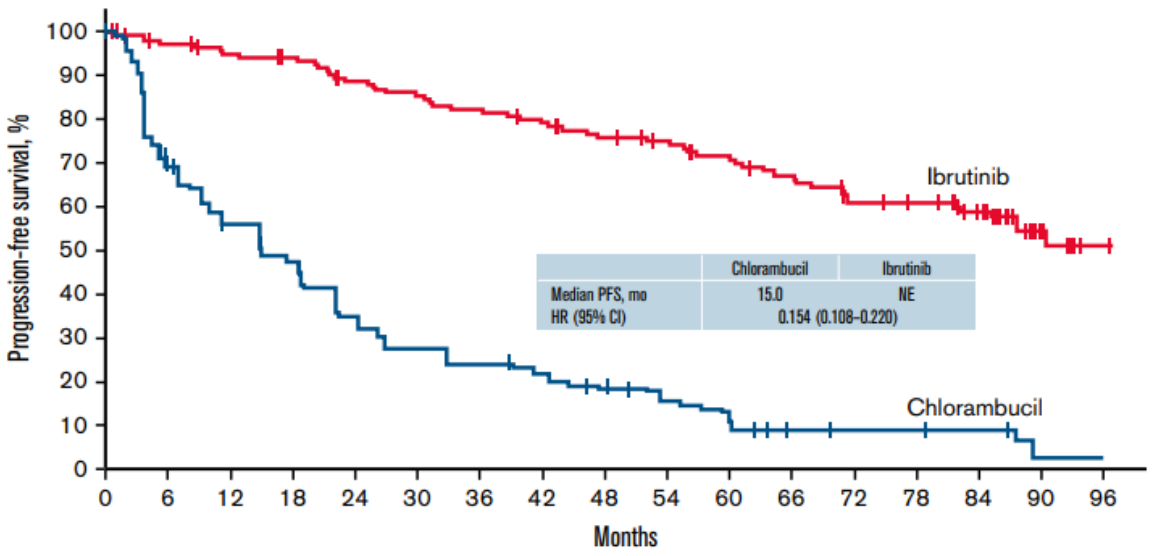
Baseline characteristic	Ibrutinib (n=136)	Clb (n=133)
Median age, years (range)[2,3]	73 (65–89)	72 (65–90)
≥70 years, n (%)[3]	96 (71)	93 (70)
Total CIRS >6, n (%)[2,3]	42 (31)	44 (33)
CrCl <60 mL/min, n (%)[2,3]	60 (44)	67 (50)
del(11q), n/N (%)[2,3]	29/130 (22)	25/121 (21)
IGHV unmutated, n/N (%)[3]	58/101 (57)	60/103 (58)
***TP53*^{mut}, n/N (%)**[3]	12/124 (10)	3/94 (3)

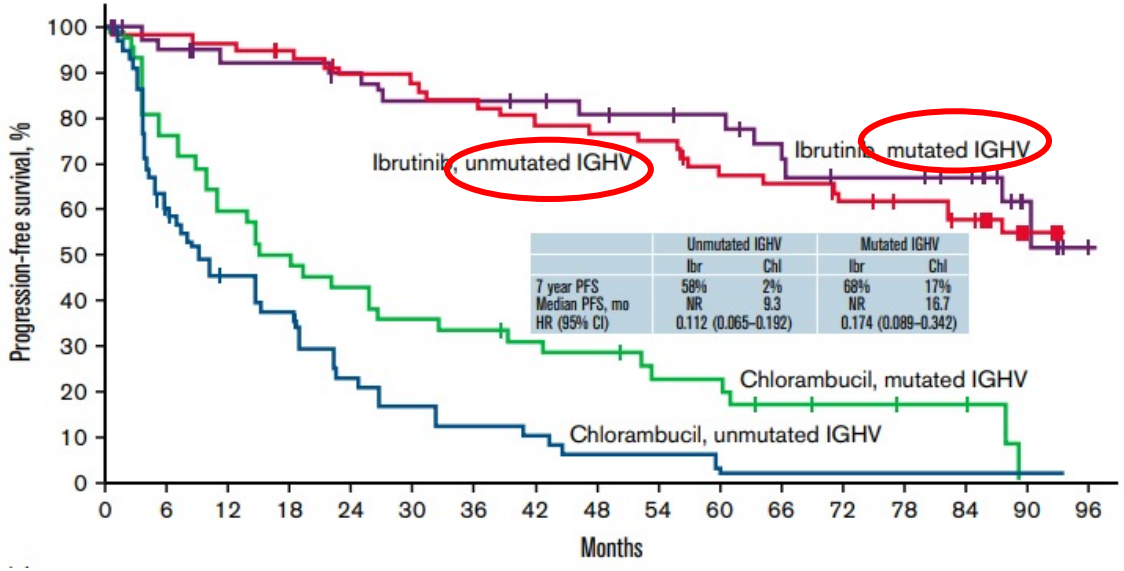
* Ibrutinib PO, 420 mg daily; Clb PO 0.5 mg/kg on day 1 and 15, increased up to 0.8 mg/kg based on tolerability for 12 cycles (in absence of PD or unacceptable toxicity);
† Patients aged 65–70 years must have a comorbidity that precludes treatment with FCR; ‡ Hemoglobin: >11 g/dL or increase ≥2 g/dL over baseline, platelets: >100×10^9/L or increase ≥50% over baseline and persisted continuously for ≥56 days without blood transfusion or growth factors.

1. ClinicalTrials.gov: https://www.clinicaltrials.gov/ct2/show/NCT01722487 (accessed February 2022);
2. Burger JA, *et al. N Engl J Med* 2015; **373:**2425–2437;
3. Burger JA, *et al. Leukemia* 2020; **34:**787–798.

RESONATE-2: Long-term follow-up (up to 8 years)

INV-assessed PFS

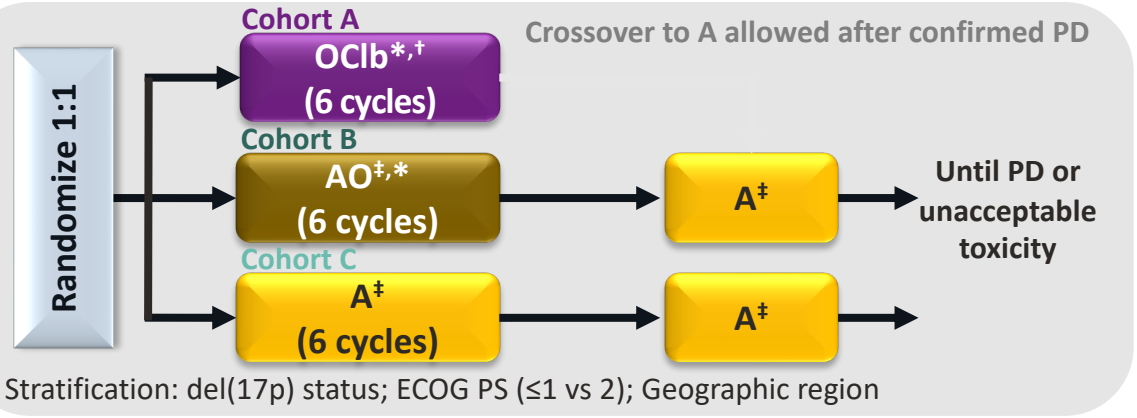




Sharman JP, Egyed M, Jurczak W, et al. Acalabrutinib ± Obinutuzumab vs Obinutuzumab + Chlorambucil in Treatment-Naïve Chronic Lymphocytic Leukemia: 5-Year Follow-up of ELEVATE-TN [ ]. Presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; June 3-7, 2022; Chicago, Illinois.

ELEVATE TN: Study design

Open-label, randomized, multicenter, Phase 3 study to assess efficacy and safety of AO vs A alone vs OClb[1–3]



Key endpoints:

- **IRC-assessed PFS (arm A vs arm B) (Primary endpoint)**
- IRC-assessed PFS (arm A vs arm C only)

Arm A vs arm B and arm A vs arm C:

- IRC- and INV-assessed ORR
- Time to next treatment
- Safety
- Overall survival

Key inclusion criteria

- Age ≥65 years OR age <65 years with CrCl 30–69 mL/min or CIRS >6
- CD20+ CLL

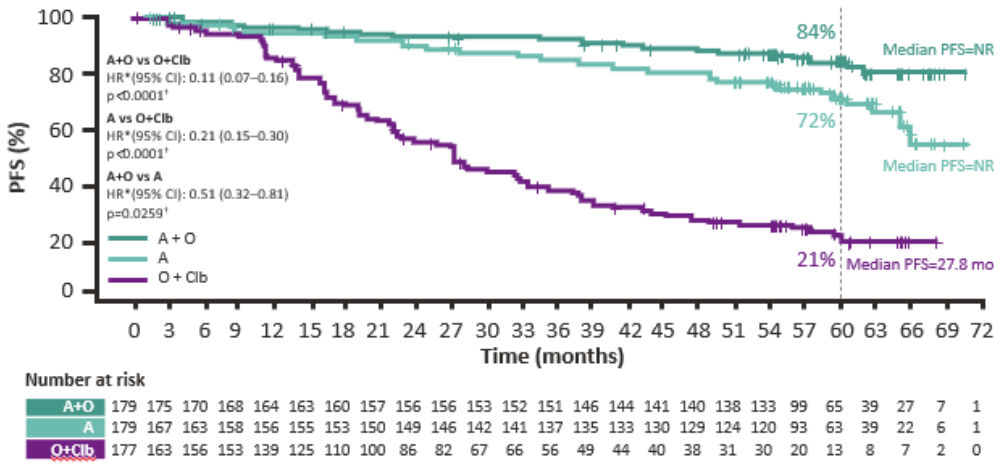
Baseline characteristic		AO (n=179)	A (n=179)	OClb (n=177)
Age	Median (range), years	**70 (41–88)**	**70 (44–87)**	**71 (46–91)**
Rai stage				
III	n (%)	47 (26.3)§	51 (28.5)§	40 (22.6)
IV		38 (21.2)	37 (20.7)	38 (21.5)
Cytogenetic subgroup				
del(17p)(p13.1)	n (%)	17 (9.5)	16 (8.9)	16 (9.0)
del(17p)(p13.1) and/or mutated *TP53*		25 (14.0)	23 (12.8)	25 (14.1)
del(11q)		31 (17.3)	31 (17.3)	33 (18.6)
Complex karyotype¶		29 (16.2)	31 (17.3)	32 (18.1)
Mutated *TP53*	n (%)	21 (11.7)	19 (10.6)	21 (11.9)
Unmutated IGHV	n (%)	103 (57.5)	119 (66.5)	116 (65.5)

* Obinutuzumab: 1,000 mg IV on days 1, 2 (split 100/900), 8, and 15 of cycle 2 and day 1 of subsequent 28-day cycles for 6 cycles; † Chlorambucil: 0.5 mg/kg PO on days 1 and 15 of each 28-day cycle for 6 cycles; ‡ Acalabrutinib: 100 mg PO BID; § Proportion of patients with Rai stage III in the AO and A arms differed from that reported in the primary publication (48 [26.8%] and 50 [27.9%], respectively) because of lack of database lock at interim analysis and the potential site-level changes post-interim analysis; ¶ Patients with ≥3 cytogenetic abnormalities. See slide notes for abbreviations.

1. ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT02475681 (accessed March 2022);
2. Sharman JP, *et al. Lancet* 2020; **395:**1278–1291;
3. Sharman JP, *et al. Leukemia* 2022; **36:**1171–1175 (inc. suppl.).

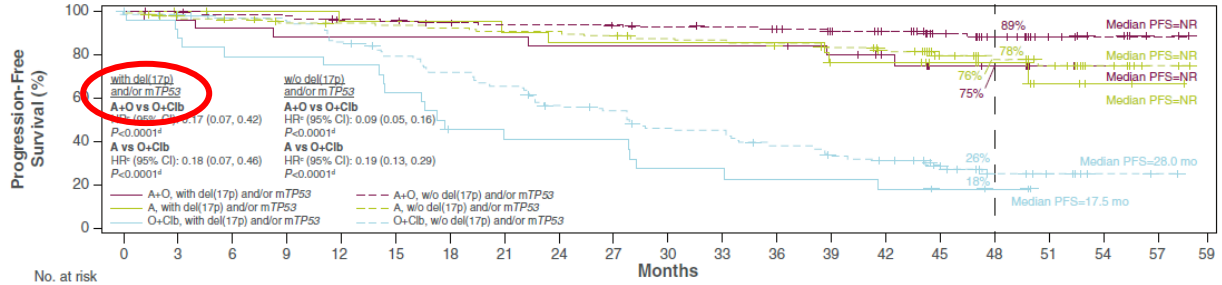
ELEVATE TN: Survival data

Investigator-assessed PFS
(Median follow-up: 58.2 months)



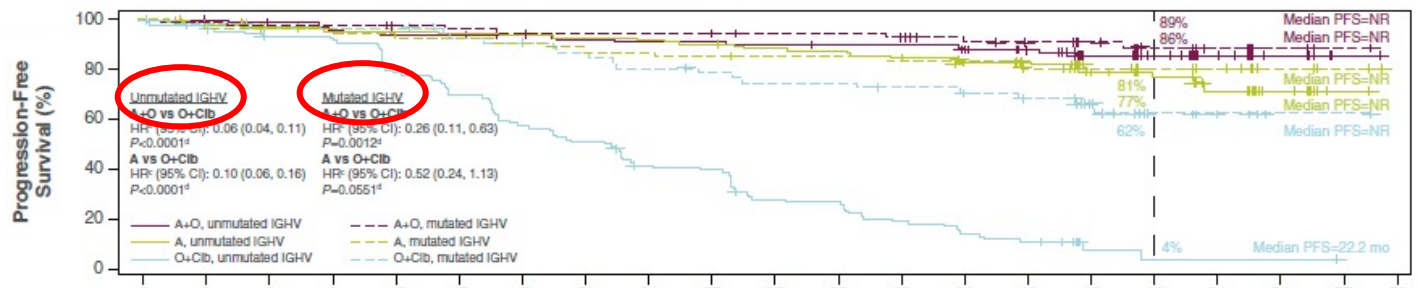
Number at risk

A+O	179	175	170	168	164	163	160	157	156	156	153	152	151	146	144	141	140	138	133	99	65	39	27	7	1
A	179	167	163	158	156	155	153	150	149	146	142	141	137	135	133	130	129	124	120	93	63	39	22	6	1
O+Clb	177	163	156	153	139	125	110	100	86	82	67	66	56	49	44	40	38	31	30	20	13	8	7	2	0



No. at risk

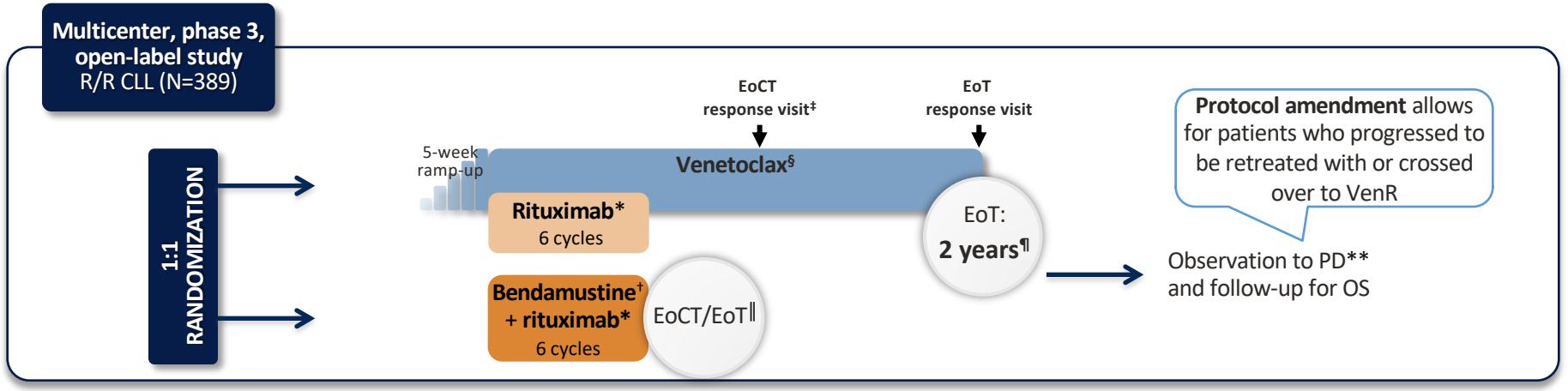
A+O, with del(17p) and/or m*TP53*	25	24	23	22	22	22	22	22	21	21	21	21	21	19	16	9	8	3	1	0	0
A, with del(17p) and/or m*TP53*	23	22	21	21	20	20	20	19	18	18	18	18	18	15	15	11	9	5	2	1	0
O+Clb, with del(17p) and/or m*TP53*	25	21	19	19	18	15	10	9	9	9	6	6	5	5	4	3	2	0	0	0	0
A+O, w/o del(17p) and/or m*TP53*	154	152	148	146	142	141	138	135	135	134	132	131	129	122	116	76	51	30	11	2	0
A, w/o del(17p) and/or m*TP53*	156	145	142	137	136	135	133	131	131	128	124	123	118	115	108	68	52	30	14	3	0
O+Clb, w/o del(17p) and/or m*TP53*	152	142	137	134	121	110	100	91	77	73	61	60	50	43	38	19	11	6	2	1	0



No. at risk

A+O, unmutated IGHV	103	102	100	97	95	95	94	92	91	91	90	89	89	84	78	47	35	17	7	1	0
A, unmutated IGHV	119	112	109	107	107	106	105	104	103	101	98	97	93	89	84	52	38	22	11	1	0
O+Clb, unmutated IGHV	116	105	101	99	85	75	62	55	43	41	28	27	19	14	11	2	1	1	1	0	0
A+O, mutated IGHV	74	72	69	69	67	66	64	63	63	62	61	61	59	55	52	36	23	16	5	1	0
A, mutated IGHV	58	53	52	49	47	47	46	44	44	43	42	42	41	40	38	27	23	13	5	3	0
O+Clb, mutated IGHV	59	56	53	52	52	48	46	43	41	39	37	37	35	33	30	19	11	5	1	1	0

VenR was studied as 2-year fixed treatment duration in R/R CLL



Primary endpoint:
- INV-assessed PFS

Key secondary endpoints:
- IRC-assessed PFS
- PFS in patients with del(17p)
- ORR (IRC- and INV-assessed) at EoCT
- OS, uMRD at EoCT, DoR, EFS, TTNT

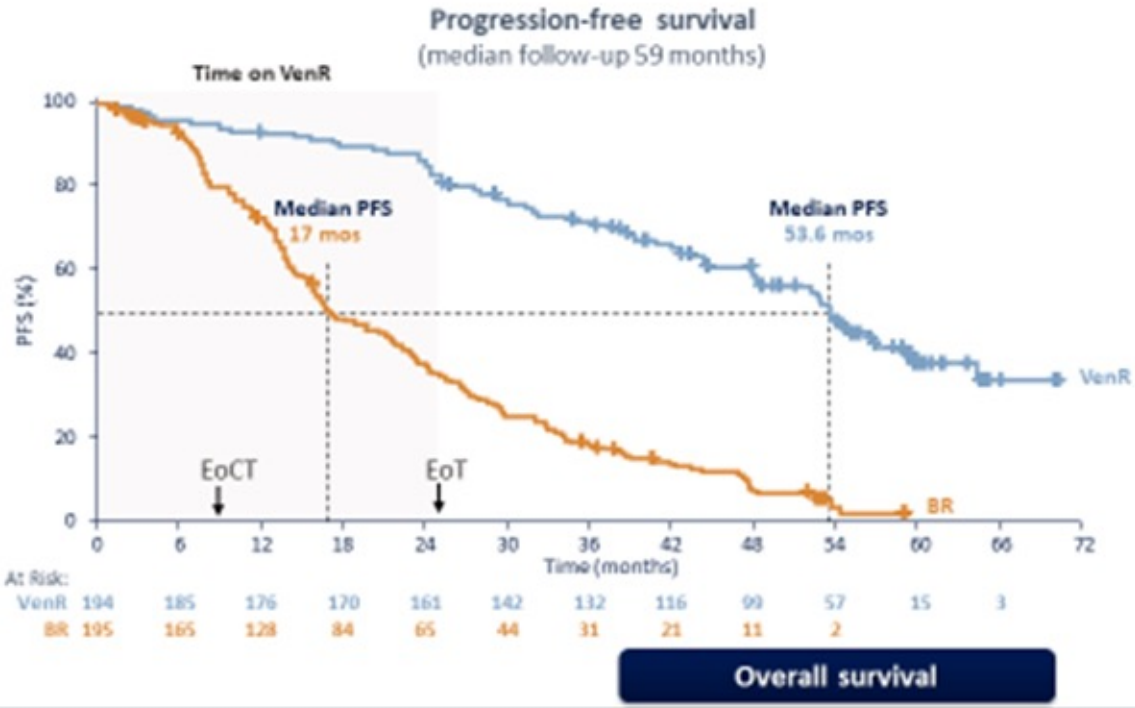
Key inclusion criteria
- 1–3 lines of prior therapy††
- Prior bendamustine if DoR was ≥2 years
  ECOG PS ≤1

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

* Rituximab: 375 mg/m² C1D1 and 500 mg/m² D1C2–6; † Bendamustine: 70 mg/m² days 1 and 2 of each cycle; ‡ 8 to 12 weeks after C6D1; § Venetoclax 400 mg PO daily; ‖ EoCT corresponds to EoT in BR arm; patients received a total treatment of 6 cycles; ¶ From C1D1; ** Or unacceptable toxicity; †† Including ≥1 chemotherapy-containing regimen. EoCT, end of combination therapy; EoT, end of treatment; INV, investigator; IRC, independent review committee; TTNT, time to next treatment.

Kater AP, *et al. J Clin Oncol* 2020; **38:**4042–4054; ClinicalTrials.gov. NCT02005471 (accessed January 2022).

With FTD VenR, PFS benefits are sustained beyond completion of treatment



	VenR	BR
HR (95% CI)	0.19 (0.15–0.26) p<0.0001*	
5-year PFS estimate, %	38	NE

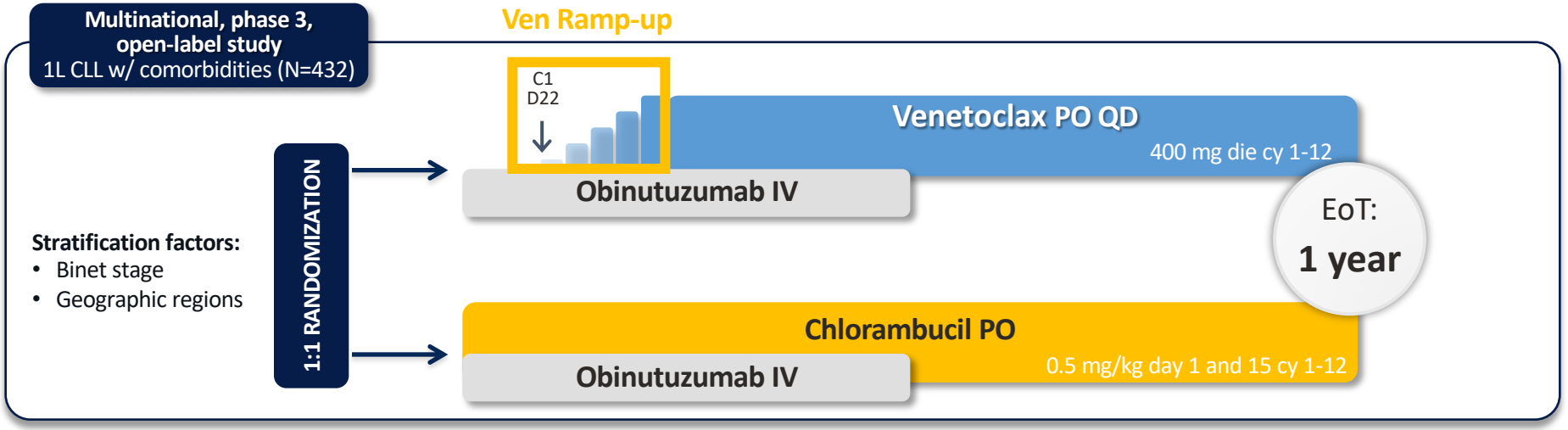
Overall survival

PFS benefits were sustained 3 years after completing VenR, with an 81% reduction in the risk of progression or death

* Descriptive. EoCT, end of combination treatment; EoT, end of treatment; FTD, fixed-treatment duration; mos, months; NE, not estimable.

Kater AP, *et al.* ASH 2020. Abstract 125 (Oral).

CLL14 - *VenO was studied as a 1-year FTD regimen in 1L CLL*



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

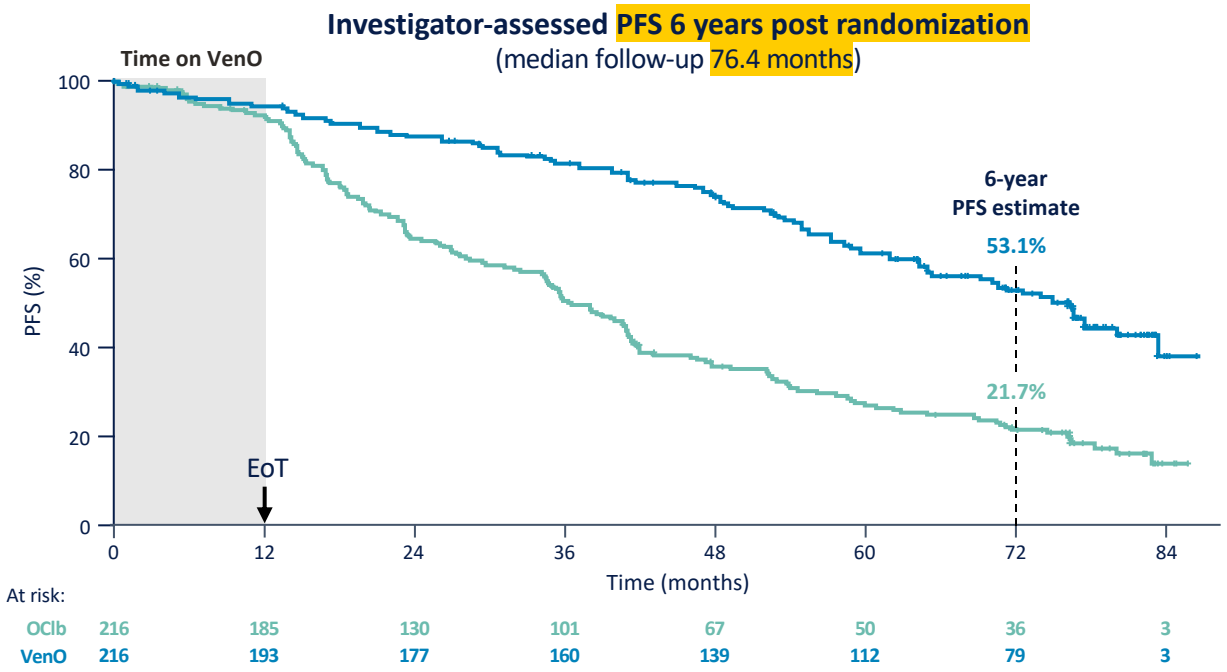
Key secondary endpoints (ITT population):
- PFS – IRC assessed
- ORR and CR 3 months after EoT
- uMRD rate (PB and BM) 3 months after EoT
- OS

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

See notes for dosing regimens.
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.

Fischer K, *et al. N Engl J Med* 2019; **380:**2225–2236 (incl. appendix).

CLL14 - *PFS benefits are sustained beyond completion of treatment*



	VenO	OClb
Median PFS, months	76.2	36.4
HR (95% CI)	0.40 (0.31–0.52) p<0.0001*	

VenO IGHV mut : NR

VenO IGHV unmut : 64.8 months

VenO TP53mut : 51.9 months

PFS benefit was sustained 5 years after completing VenO, with a 60% reduction in risk of PD or death

* Descriptive. EoT, end of treatment; FTD, fixed treatment duration; NR, not reached.

Al-Sawaf O, *et al.* EHA 2023. Abstract S145 (Oral).

Progressive replacement (residual role) of the CIT in 1L and especially after the 1L

Nuovi agenti vs CIT in 1L

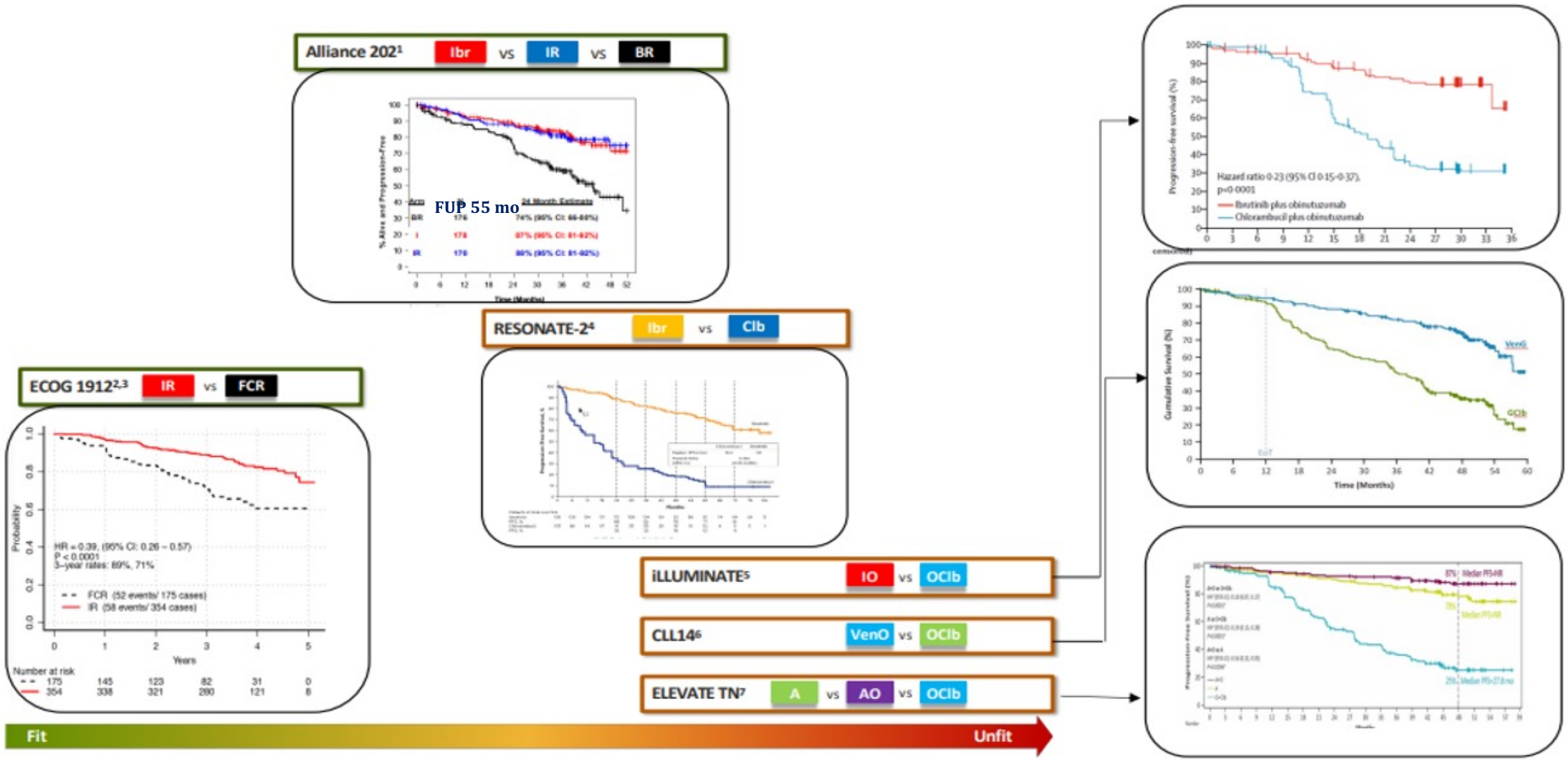
↓

Risultati sempre a sfavore della CIT

Study	Population	Design	PFS Benefit for Experimental Arm?
E1912[1]	"Fit," no del(17p)	FCR x 6 vs IR x 6 then ibrutinib maintenance	Yes
ALLIANCE[2]	"Fit," older, del(17p) allowed	3 arm: BR vs IR vs I	Yes
iLLUMINATE[3]	Unfit (CIRS >6 or CrCl <70) or *TP53* del/mut	G + Cbl vs G + ibrutinib	Yes
ELEVATE-TN[4]	Unfit (CIRS >6 or CrCl <70)	G + Cbl vs acalabrutinib vs G + acalabrutinib	Yes
SEQUOIA[5]	Older, no del(17p)	BR vs zanubrutinib	Yes
CLL14[6]	Unfit (CIRS >6 or CrCl <70)	G + Cbl vs VenG	Yes

1. Shanafelt TD et al. *N Engl J Med.* 2019;381:432-443. 2. Woyach JA et al. *N Engl J Med.* 2018;379:2517-2528. 3. Moreno C et al. *Lancet Oncol.* 2019;20:43-56.
4. Sharman JP et al. *Lancet.* 2020;395:1278-1291. 5. Tam C et al. ASH 2021. Abstract 396. 6. Fischer K et al. *N Engl J Med.* 2019;380:2225-2236.

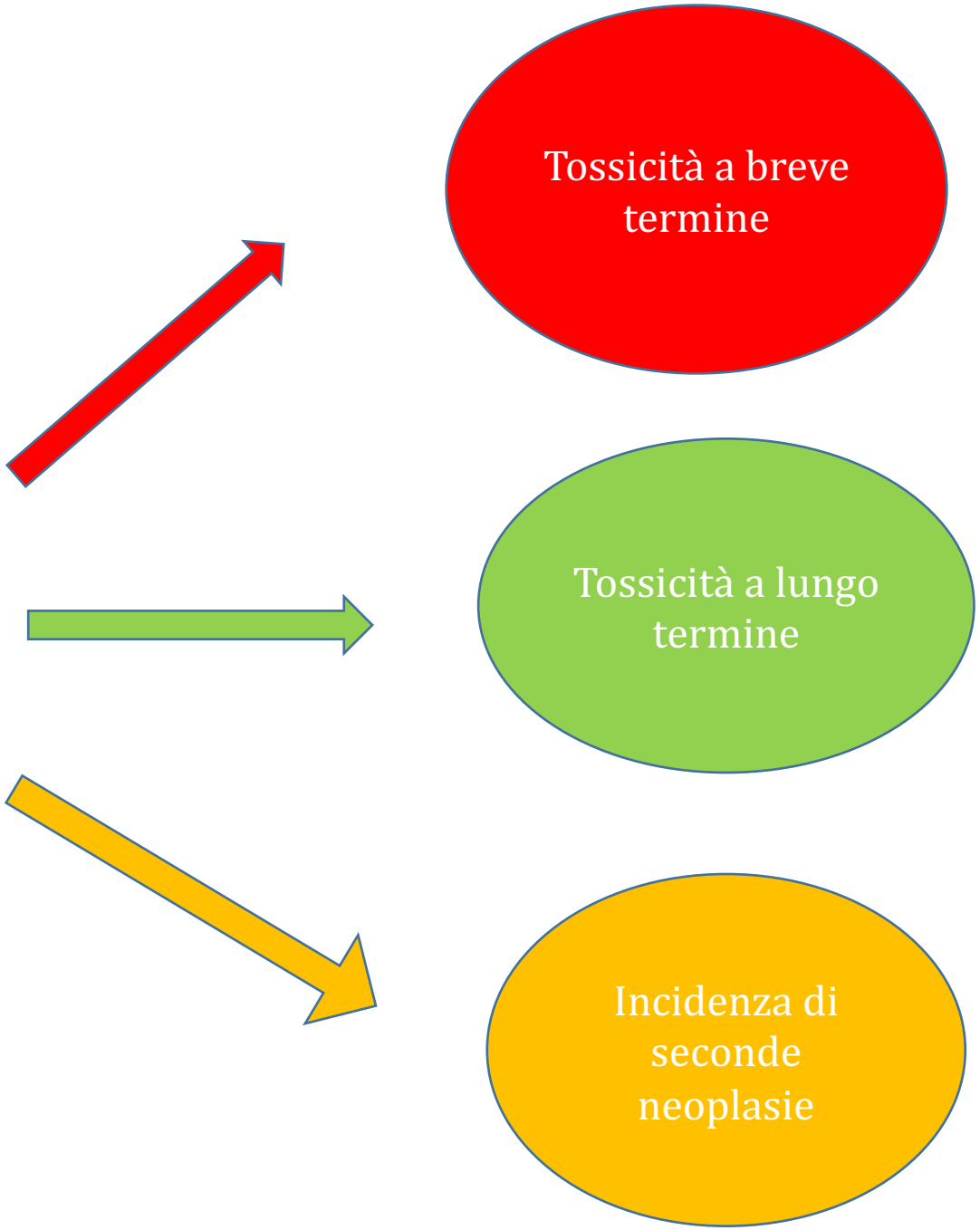
Targeted therapy outperform CIT in Key phase 3 trials in first line CLL



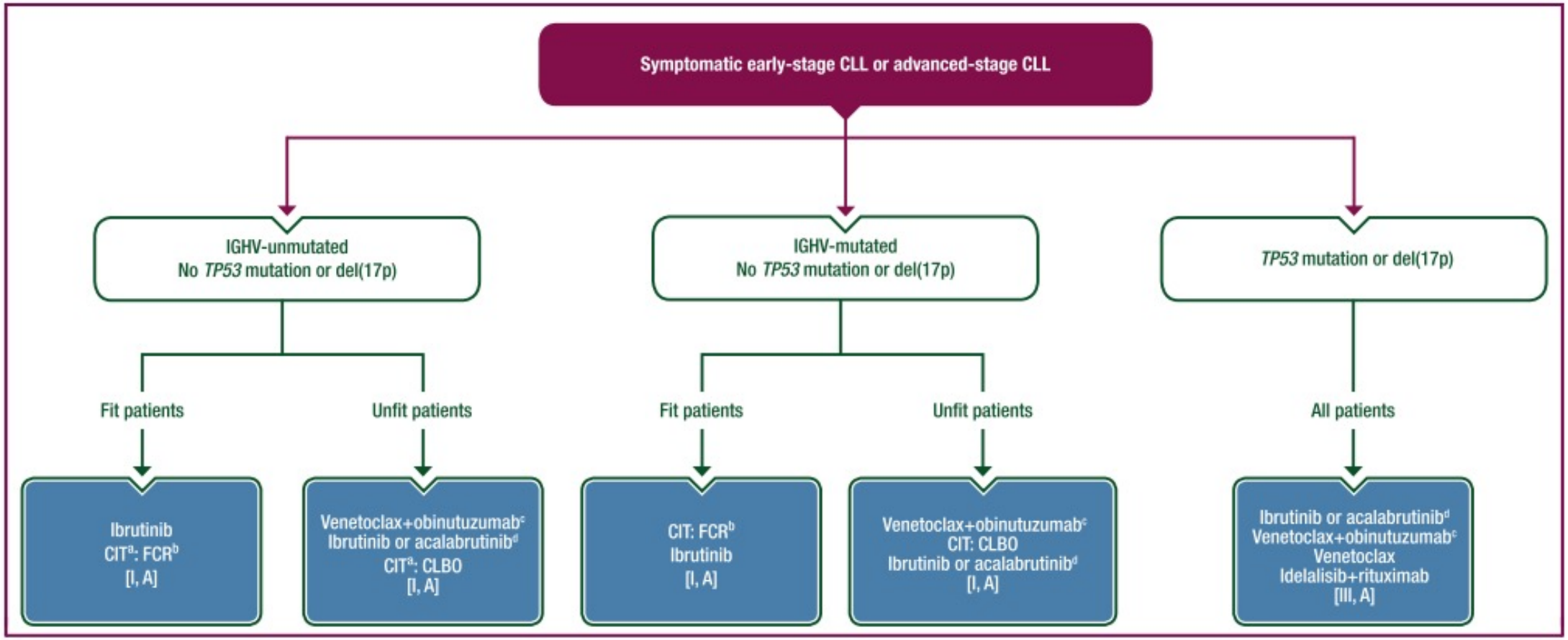
A, acalabrutinib; AO, acalabrutinib + obinutuzumab; BR, bendamustine + rituximab; Clb, chlorambucil; IO, ibrutinib + obinutuzumab; IR, ibrutinib + rituximab.

1. Woyach JA, *et al. N Engl J Med* 2018; **379**:2517–2528 (incl. suppl.); 2. Shanafelt TD, *et al. N Engl J Med* 2019; **381**:432–443 (incl. suppl); 3. Shanafelt TD, *et al.* ASH 2019; Abstract 33 (Oral); 4. Burger JA, *et al. N Engl J Med* 2015; **373**:2425–2437; 5. Moreno C, *et al. Lancet Oncol* 2019; **20**:43–56; 6. Fischer K, *et al. N Engl J Med* 2019; **380**:2225–2236 (incl. suppl); 7. Sharman JP, *et al. Lancet* 2020; **396**:1278–1291.

SVANTAGGI DELLA CHT

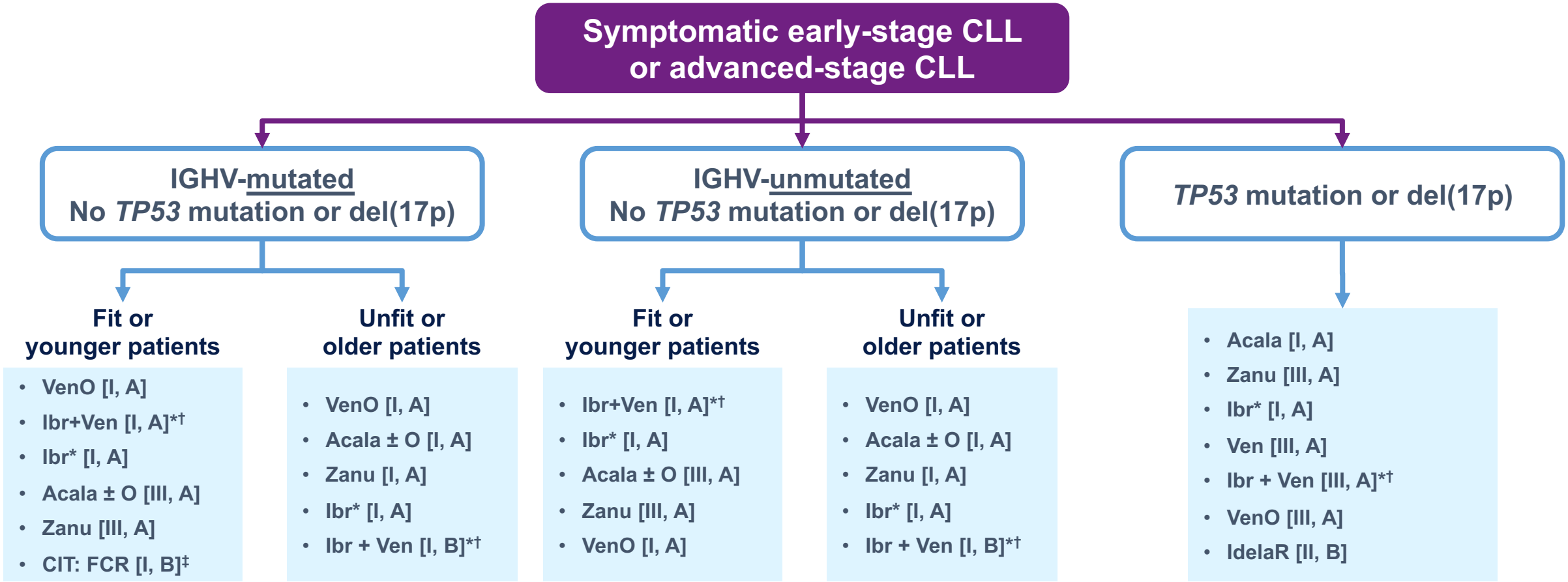


ESMO 1L CLL Treatment Guidelines



Eichhorst B,et Al. Ann Oncol. 2021 Jan;32(1):23-33.

ESMO 2024 Guidelines for 1L CLL



*Ibr or Ibr+Ven should be considered carefully in older patients with cardiac comorbidities.
†Ibr+Ven with a 15-month fixed duration or an MRD-guided duration.
‡Should only be considered for patients with a good genetic risk profile and if targeted therapies are not reimbursed.
Acala=Acalabrutinib. CIT=Chemoimmunotherapy. CLL=Chronic Lymphocytic Leukemia.
del(17p)=Deletion in the Chromosome 17p. FCR=Fludarabine+cyclophosphamide+Rituximab. Ibr=Ibrutinib.
Idela=Idelalisib. IGHV=Immunoglobulin Heavy Chain Variable Region Genes. O=Obinutuzumab. R=Rituximab. Ven=Venetoclax. Zanu=Zanubrutinib.

Eichhorst B & Ghia P, Annals of Oncology, 2024

ESMO 2024 Guidelines for 1L CLL

- La **CIT** dovrebbe essere considerata **solo** in pazienti con profilo genetico particolamente positivo e **solo se non disponibili le target therapy**
- **La terapia a durata fissa (V+O e V+I) è raccomandata rispetto alla terapia continuativa** grazie alla ridotta tossicità, possibilità di retreatment, ridotta selezione di cloni resistenti e assenza di eventi avversi a lungo termine
- Nei pazienti con LLC **indipendentemente dallo stato IGHV**, ma senza mutazione TP53 o del(17p), **si deve dare la preferenza a terapie limitate nel tempo** e a terapie e/o combinazioni con dati di follow-up più lunghi, se l'efficacia è simile

Eichhorst B & Ghia P, Annals of Oncology, 2024

WHAT'S NEXT?

La chemioterapia non ha più spazio nella CLL sia in termini di efficacia che di sicurezza terapeutica