Leucemia linfocítica crónica: ¿cómo tomamos las decisiones terapéuticas?

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Disclosures

	Research funding	Consultancy
BMS	√	√
Gilead	√	√
AstraZeneca	√	√
AbbVie	√	√
Roche	√	√
Janssen	√	√
Novartis	√	√
Takeda	√	√
TG Therapeutics		√
Kite	√	√
Lilly		√
BeiGene	√	√
Advantage		√
Allogene		√

No share ownership, patents or board membership

Case study

- ❒ 73-year-old male
- ❒ Fit, engages in regular exercise (hiking, skiing)
- ❒ Medical history: Hypertension, well-controlled with valsartan
- ❒ Lives 1 hour from the hospital, prefers time-limited treatment

2020

- ❒ CLL, Stage A(I), UM-IGHV, high ZAP70, no symptoms → **W&W**

2023

- ❒ Fatigue
- ❒ Enlarged lymph nodes in the neck, axillary, and groin regions (< 3 cm)
- ❒ Splenomegaly (enlarged spleen by 6 cm BCM)
- ❒ Lymphocytes 34 x 10^9/L, Hb 103 g/L, Platelets 10^5 x 10^9/L. Morphology: 12% prolymphocytes
- ❒ Normal serum LDH, β2-m, and renal function
- ❒ Biological profile: UM-IGHV, normal FISH, Karyotype < 3 abnormalities, $TP53^{wt}$ (NGS)

CLL, Stage C(III), UM-IGHV, normal FISH, $TP53^{wt}$

Therapeutic options in CLL (2025)

mAbs
- Rituximab
- Obinutuzumab
- Alemtuzumab

CIT
- FCR
- BR
- Clb + O

cBTKi
- Ibrutinib
- Acalabrutinib
- Zanubrutinib

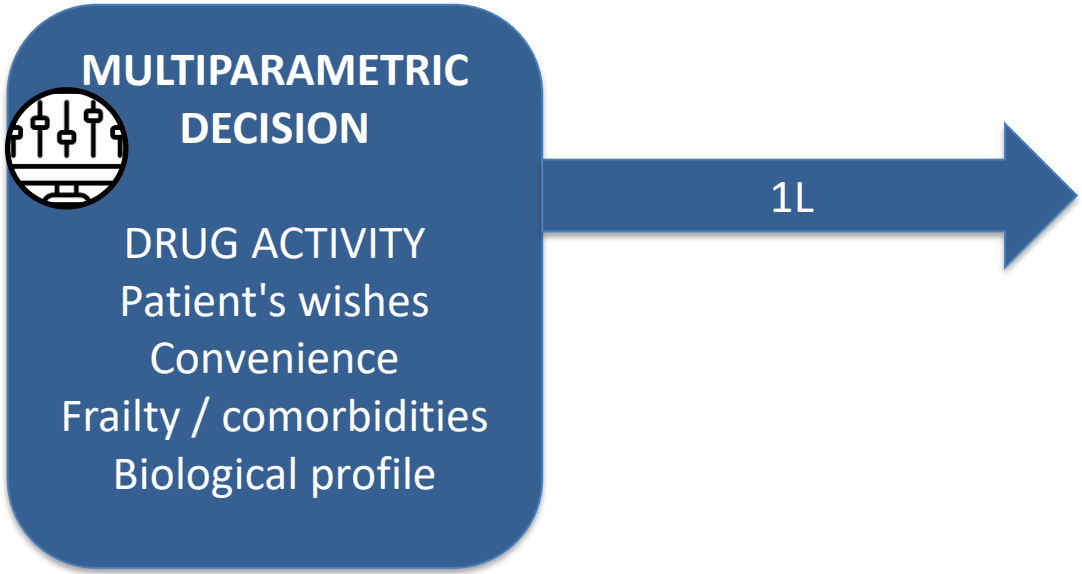
Nc-BTKi
- Pirtobrutinib

BCL2i Mono - Combo
- Venetoclax
- Venetoclax + Anti-CD20
- Venetoclax + Ibrutinib
- Venetoclax + Acalabrutinib

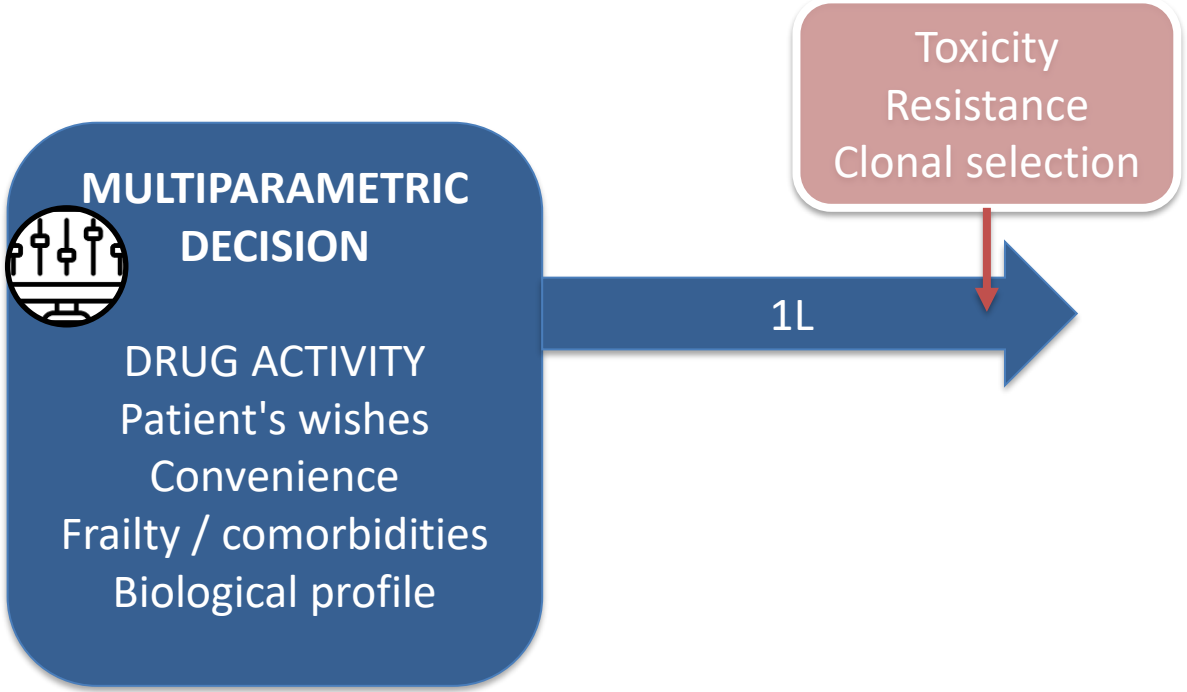
- Idelalisib
- Allo HSCT

- Non-covalent BTKi
- BTK degraders
- CAR-T
- Bispecific antibodies
- Immunotherapies
- New BCL2i

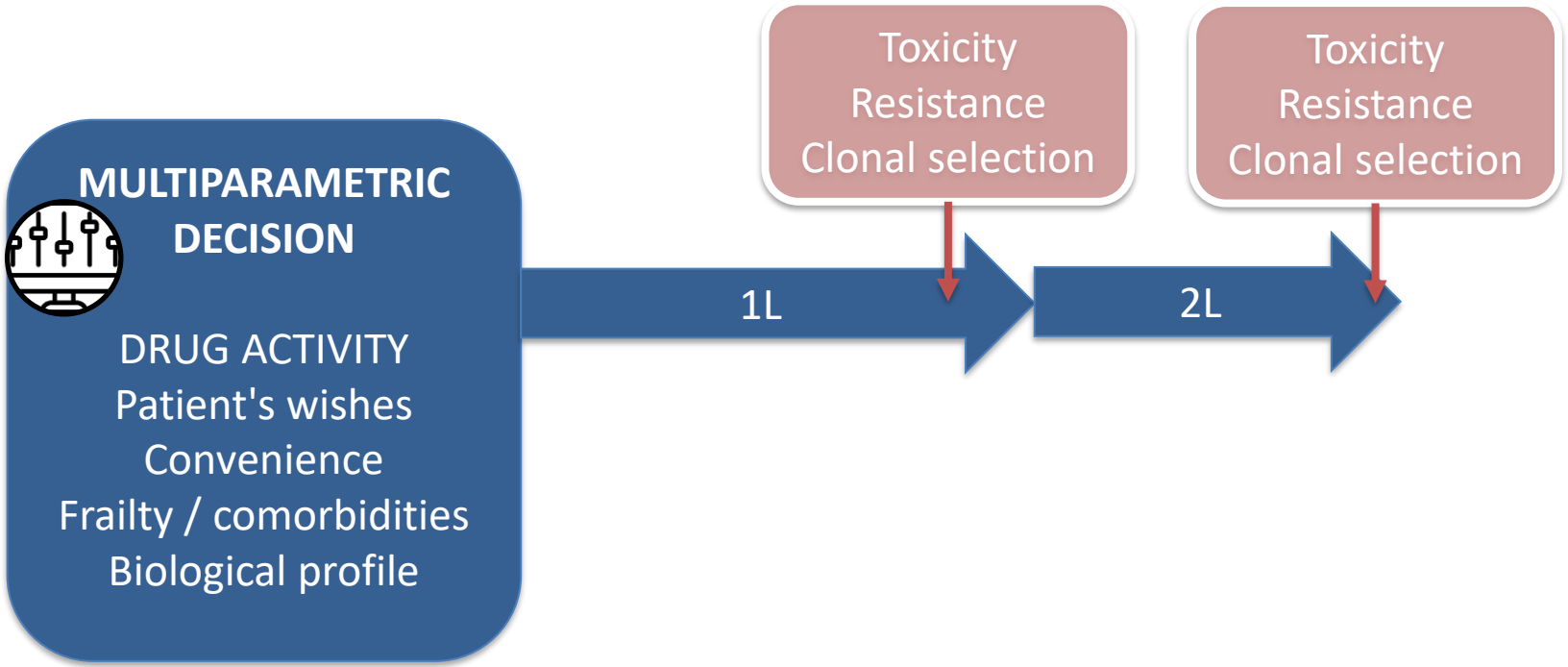
Treatment selection



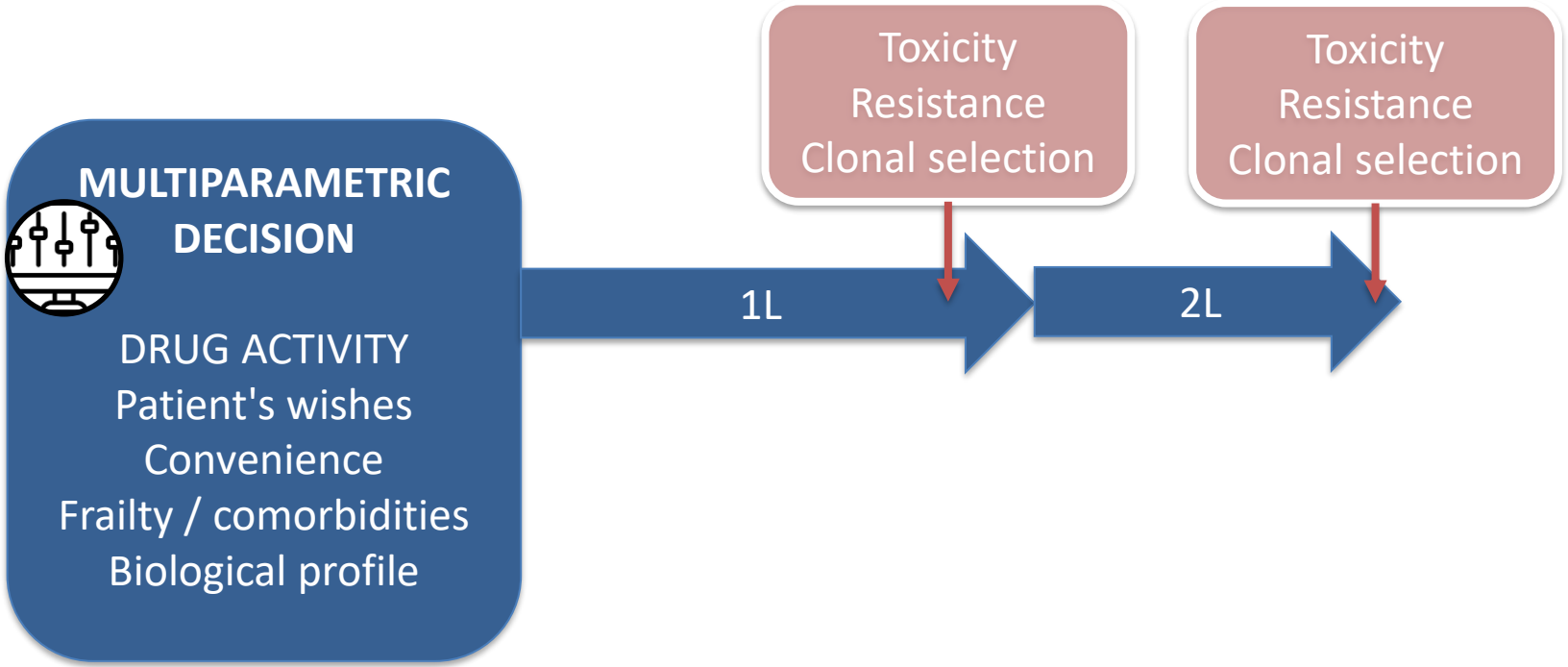
Treatment selection



Treatment selection



Treatment selection



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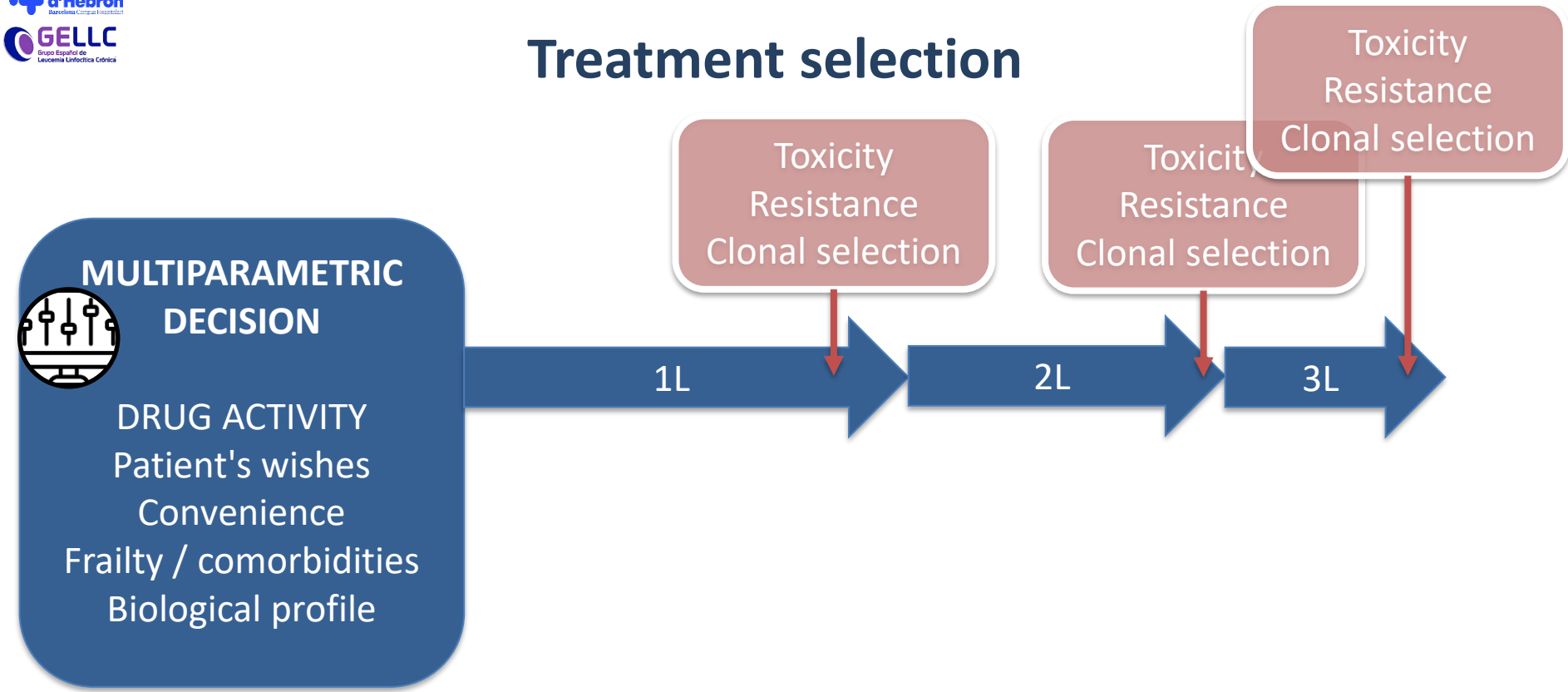
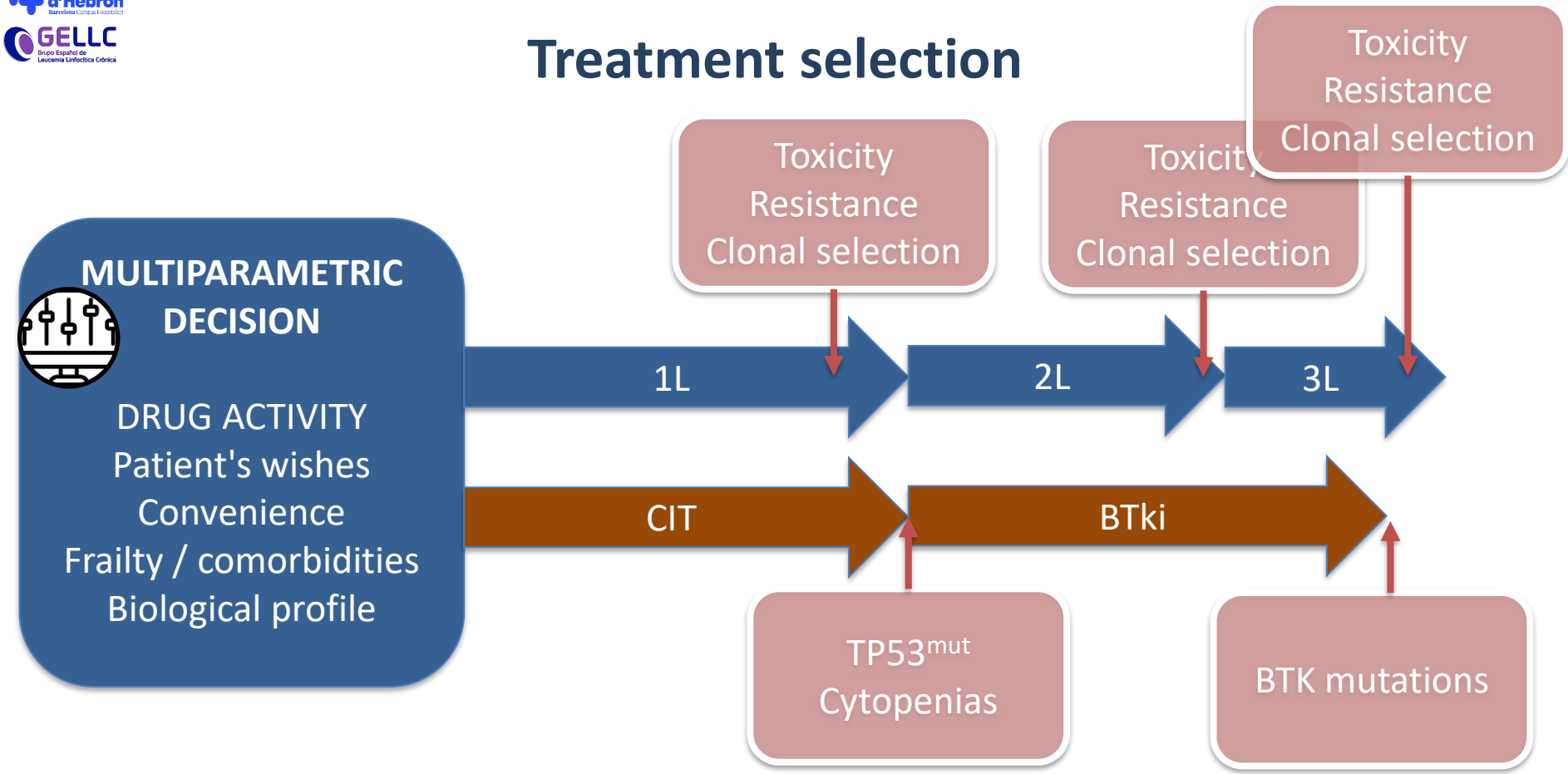


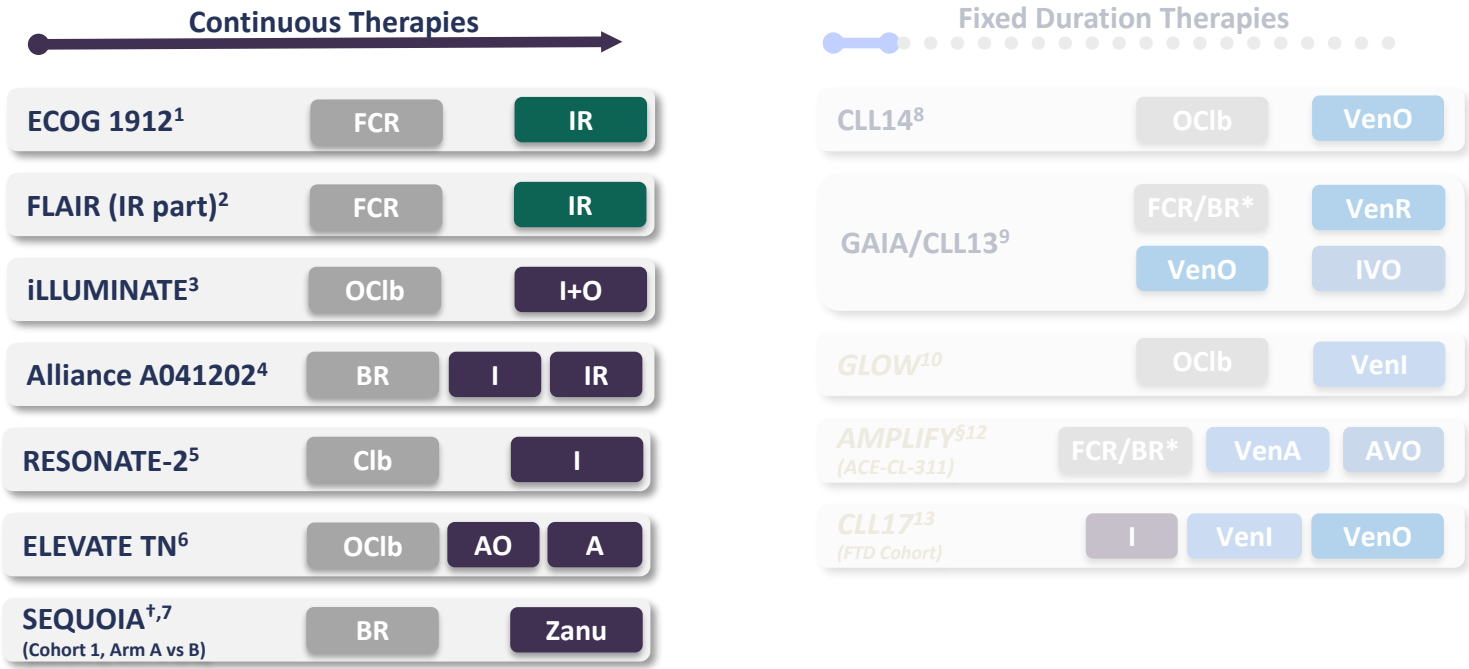
Treatment selection



Selecting 1L treatment in CLL (2025)

		Comorbidities			Logistics	Biology (efficacy & toxicity)				Cost
		Impaired Renal Function	Cardiovasc risk	Bleeding risk		mIGHV	uIGHV	Del(17p) TP53^{mut}	CK $\geq$ 5	
Continuous	Ibrutinib									
	Acalabrutinib									
	Zanubrutinib									
Fixed Duration	Venetoclax + Obinutuzumab									
	Venetoclax + Ibrutinib									
	Venetoclax + Acalabrutinib									

Select phase 2/3 1L CLL clinical trials
Continuous Therapies

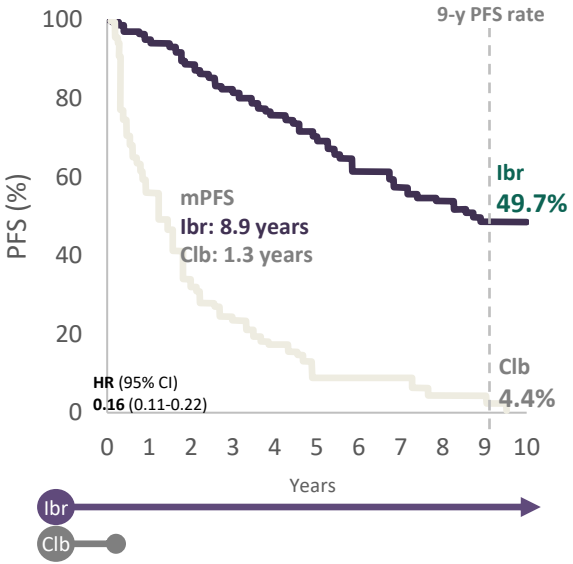


1. Shanafelt TD et al, *N Engl J Med.* 2019;**381**(5):432-443. 2. Hillmen P, et al. *Lancet Oncol*. 2023;**24**(5):535-552.
3. Moreno C. et al, *Lancet Oncol.* 2019;**20**:43-56. 4. Woyach JA, et al, *Blood* 2021;**138**:639.
5. Barr PM, et al. *Blood Adv.* 2022;**6**(11):3400-3450. 6. Sharman JP, et al, *Leukemia* 2022; **36**(4):1171-1175.
7. Tam CS, et al, *Lancet Oncol.* 2022;**23**(8):1031-1043. 8. Al Sawaf O, et al. *Nat Commun.* 2023;**14**:2147
9. Eichhorst B, et al. *N Engl J Med.* 2023;**388**(19):1739-54. 10. Kater AP, et al, *NEJM Evid.* 2022;**1**(7).
11. Tam CS, et al. Blood.2022;139(22):3278-3289.
12. Clinicaltrials.gov. NCT03836261. Accessed May 2024. 13. Clinicaltrials.gov. NCT04608318. Accessed May 2024.

Progression-free survival in pivotal BTKi trials

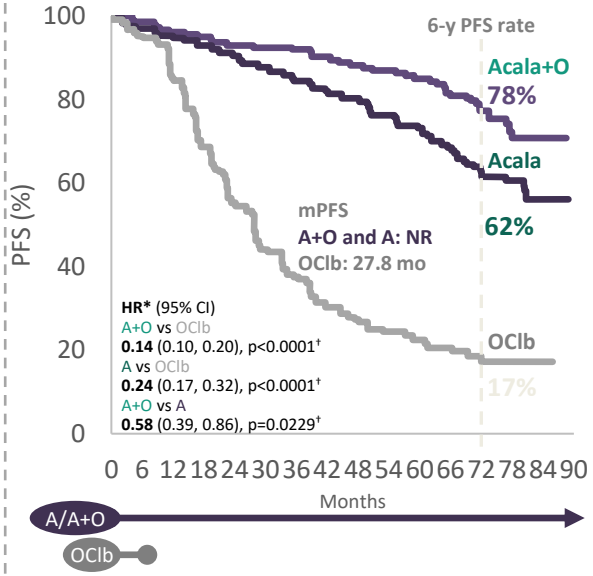
RESONATE-2[1]

median F/U: 9.6 years (5.6y for Clb)



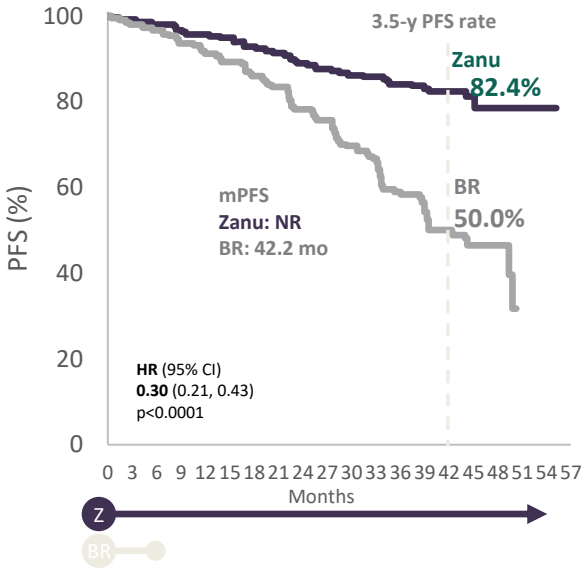
ELEVATE TN[2]

median F/U: 6.2 years



SEQUOIA[3] (Cohort 1, Arm A vs B)

median F/U: 3.6 years

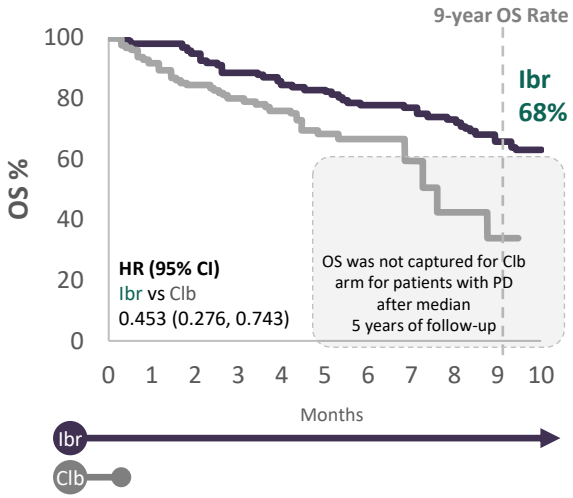


1. Burger J, et al. EHA 2024. Abstract P670 (Poster). 2. Sharman JP, et al. ASH 2023. Abstract 636 (Oral). 3. Munir T, et al. EHA 2023. Abstract P639 (Poster). .

Overall Survival in pivotal BTKi trials

RESONATE-2[1]

median F/U: 9.6 years (5.6y for Clb)



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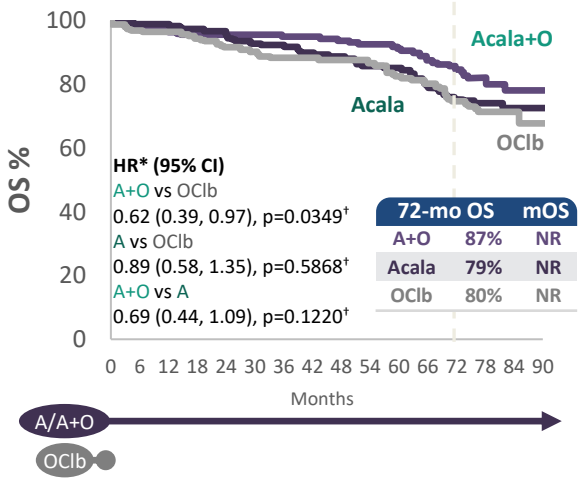

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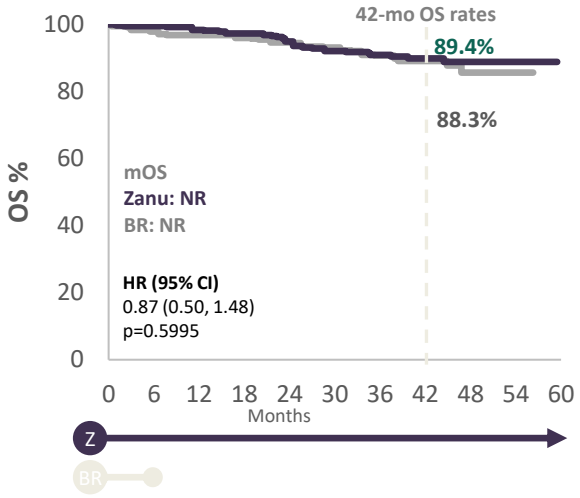
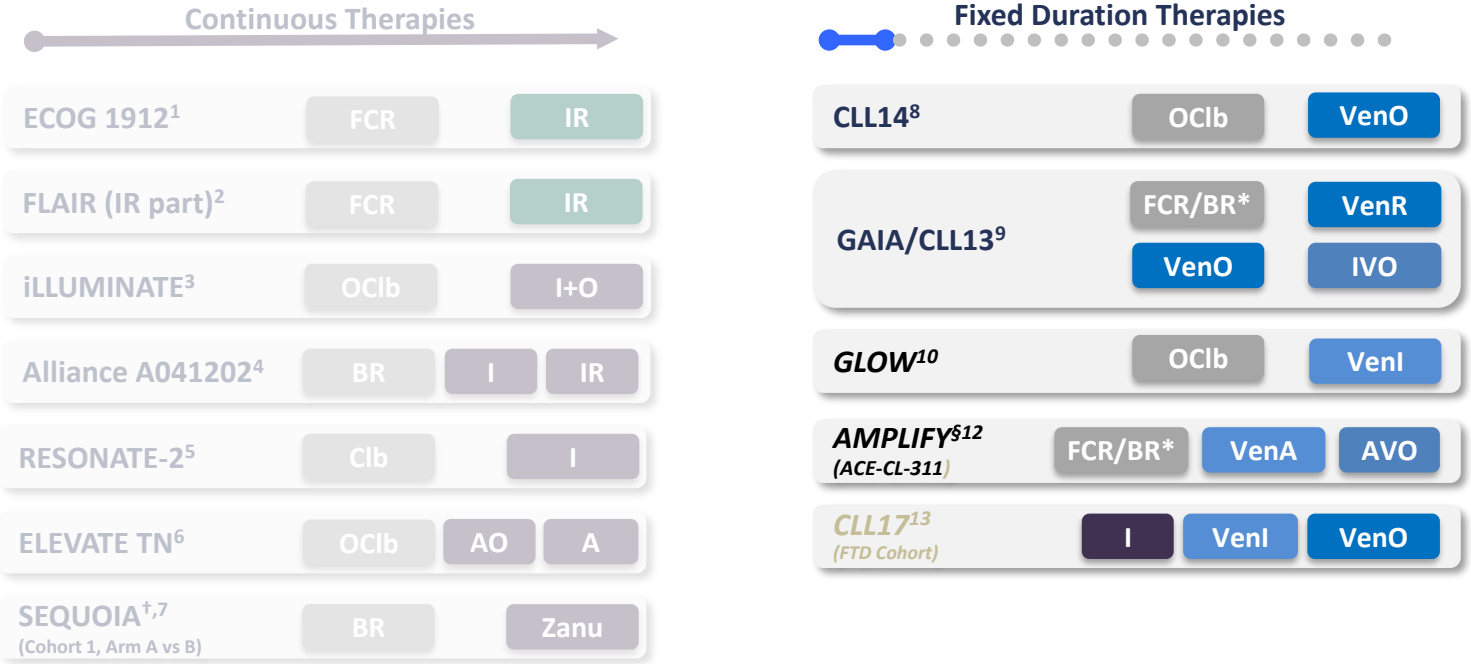


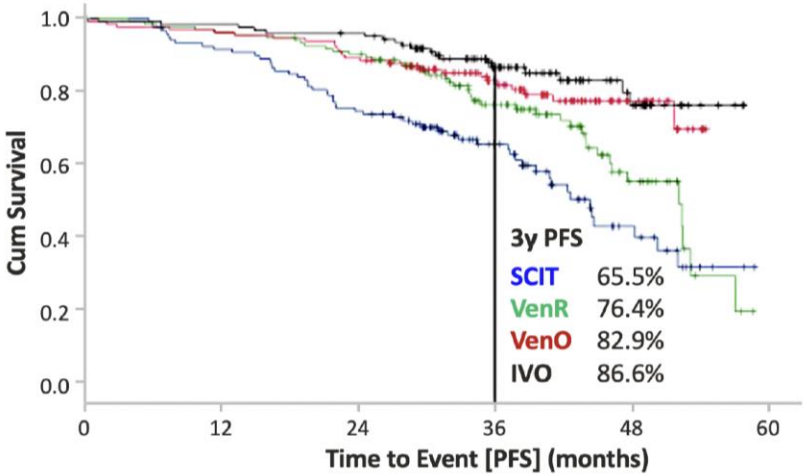
1. Barr PM, et al. *Blood Adv.* 2022;**6**(11): 3440-3450. 2. Sharman JP, et al. ASH 2023. Abstract 636 (Oral). 3. Munir T, et al. EHA 2023. Abstract P639 (Poster).

Select phase 2/3 1L CLL clinical trials
Fixed Duration Therapies



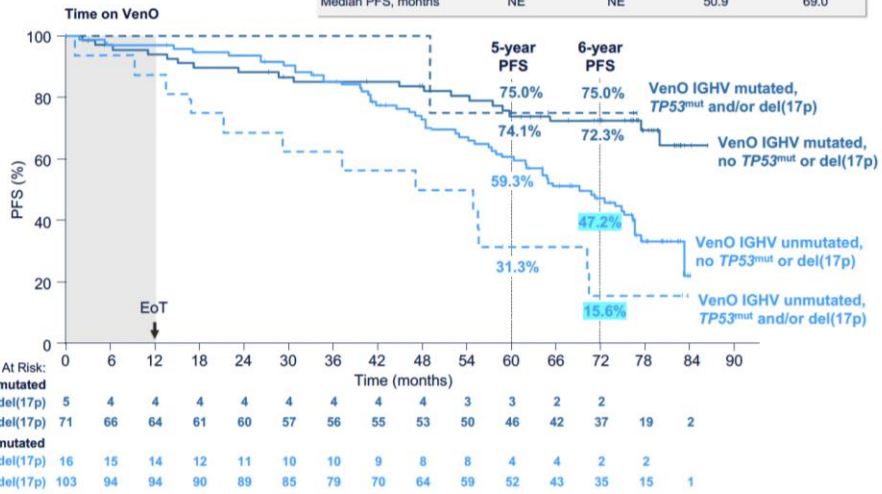
1. Shanafelt TD et al, *N Engl J Med.* 2019;**381**(5):432-443. 2. Hillmen P, et al. *Lancet Oncol*. 2023;**24**(5):535-552.
3. Moreno C. et al, *Lancet Oncol.* 2019;**20**:43-56. 4. Woyach JA, et al, *Blood* 2021;**138**:639.
5. Barr PM, et al. *Blood Adv.* 2022;**6**(11):3400-3450. 6. Sharman JP, et al, *Leukemia* 2022; **36**(4):1171-1175.
7. Tam CS, et al, *Lancet Oncol.* 2022;**23**(8):1031-1043. 8. Al Sawaf O, et al. *Nat Commun.* 2023;**14**:2147
9. Eichhorst B, et al. *N Engl J Med.* 2023;**388**(19):1739-54. 10. Kater AP, et al, *NEJM Evid.* 2022;**1**(7).
11. Tam CS, et al. Blood.2022;139(22):3278-3289.
12. Clinicaltrials.gov. NCT03836261. Accessed May 2024. 13. Clinicaltrials.gov. NCT04608318. Accessed May 2024.

Outcomes with Ven + Obi



Eichhorst B et al., NEJM 2023

	VenO			
	IGHV mutated		IGHV unmutated	
	With *TP53*^{mut} and/or del(17p)	No *TP53*^{mut} or del(17p)	With *TP53*^{mut} and/or del(17p)	No *TP53*^{mut} or del(17p)
Median PFS, months	NE	NE	50.9	69.0



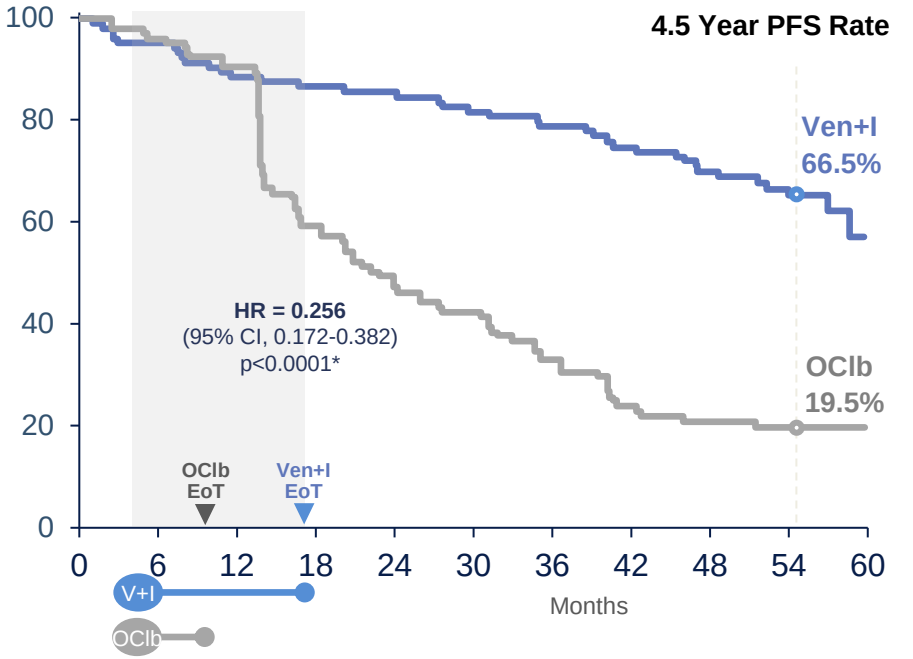
Al-Sawaf ICML 2023

V+I in fit and unfit patients with 1L CLL

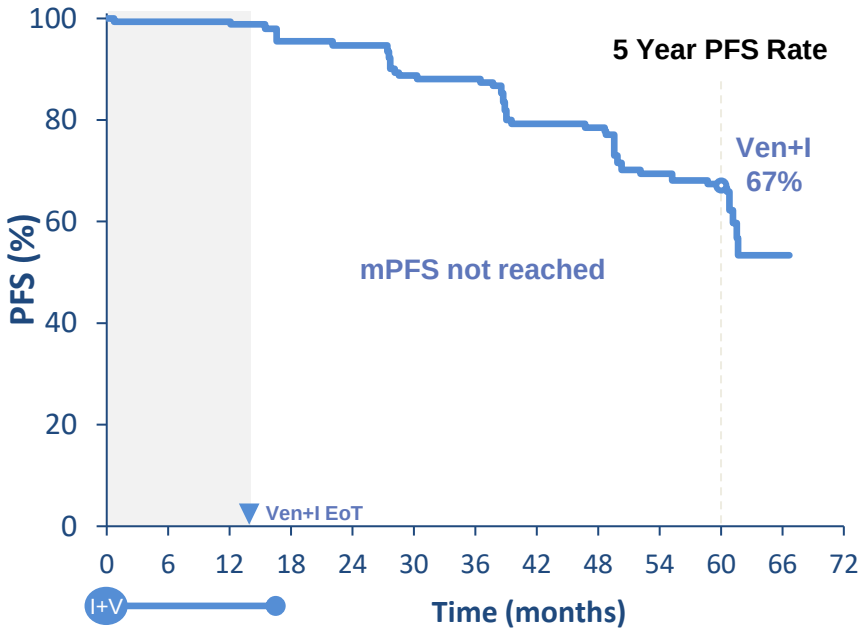
GLOW OClb IVen

CAPTIVATE (FD cohort) IVen

GLOW PFS by IRC (median follow-up 57 months)[1]



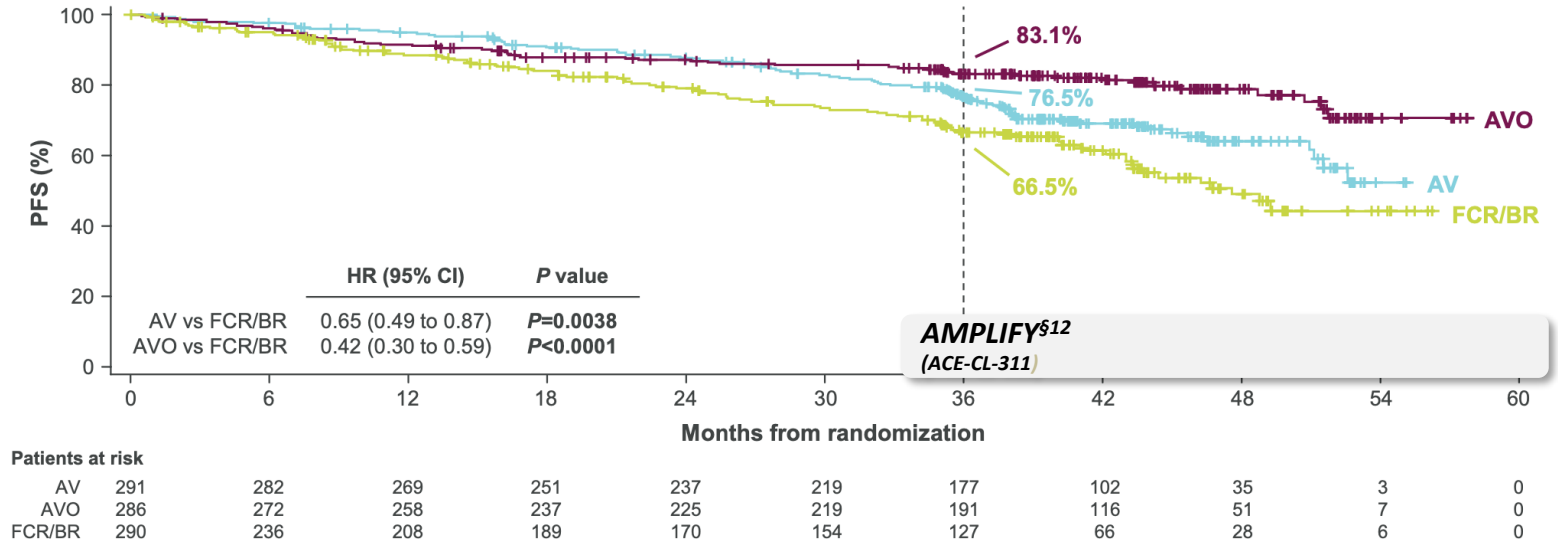
CAPTIVATE PFS by INV (median follow-up 61.2 mo)[2]



Kater et al, NEJM Evidence 2023; Tam CS et al., Blood 2022

AMPLIFY Study: IRC-assessed PFS

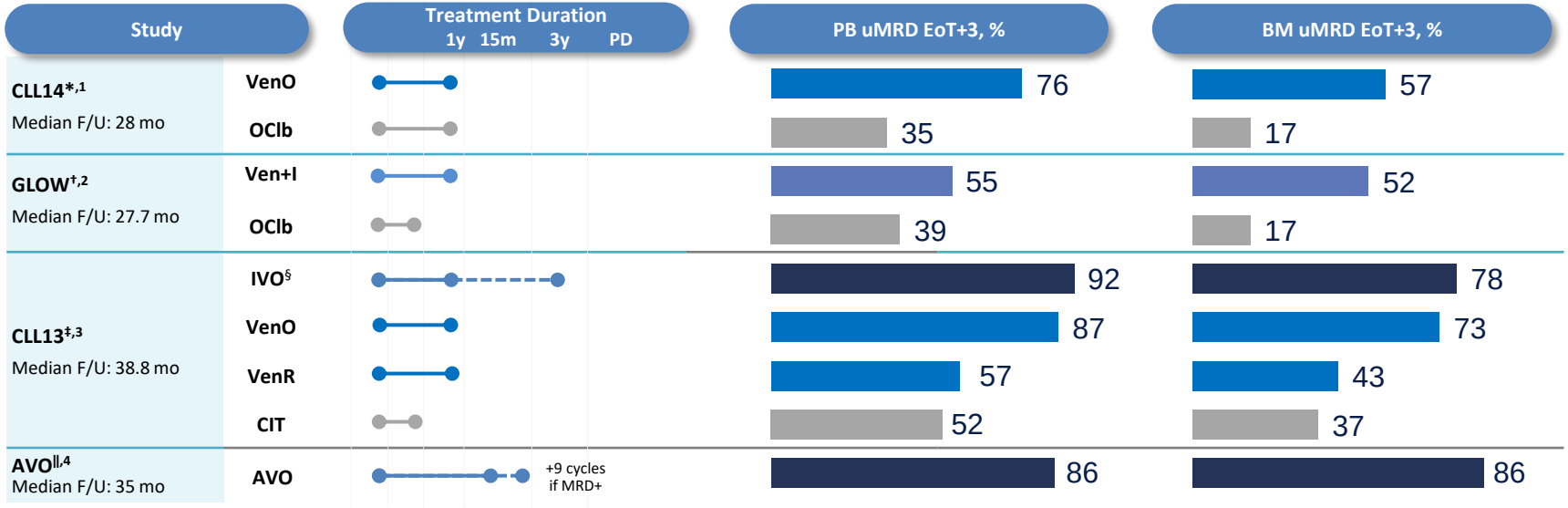
AMPLIFY | FCR/BR* | VenA | AVO



Median PFS was NR for AV and AVO, and was 47.6 mo for FCR/BR

Brown J et al, #1009, *ASH 2024, NEJM 2025*

MRD: Venetoclax-based fixed-duration



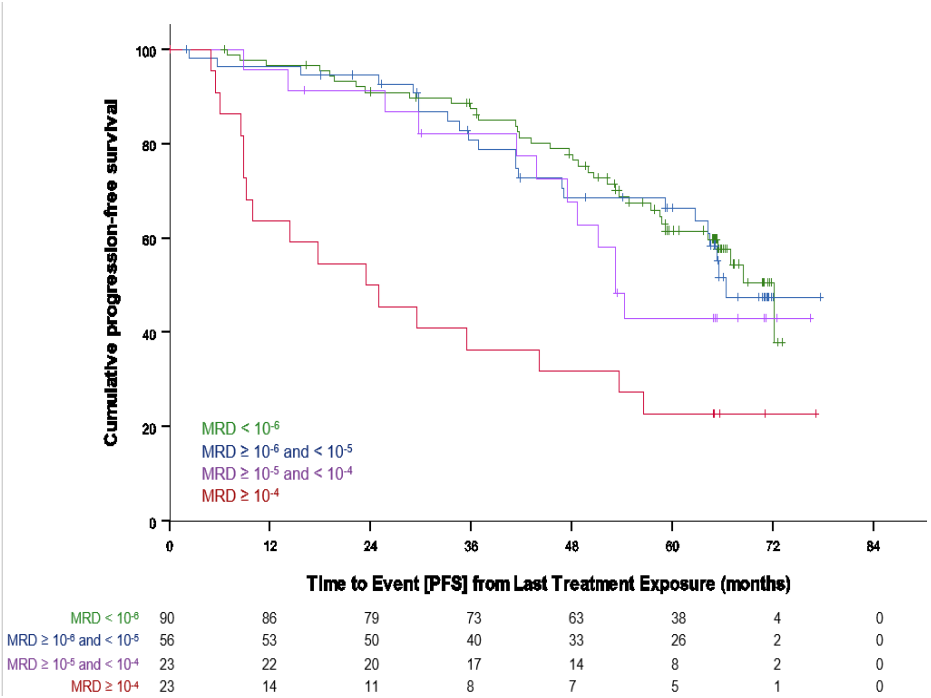
* uMRD (<10-4) by ASO-PCR, confirmed by FCM; † uMRD (<10-4) by NGS; ‡ uMRD at month 15 in PB (all arms) and final restaging in BM; § Ibrutinib continued up to cycle 36 if MRD still detectable; ǁ uMRD rates at EoT, C16 D1.

1. Fischer K, et al. N Engl J Med 2019; 380:2225–2236; 2. Kater AP, et al, NEJM Evid. 2022;1(7); 3. Eichhorst B, et al. N Engl J Med. 2023; 388(19):1739-54; 4. Tam CS, et al. Blood 2022; 139:3278–3289 (incl. suppl.); 5. Ryan CE, et al. Blood 2022; 140(Suppl 1):837–838 (Oral).

Frontline BCL2i-based Therapy: Outcome by MRD

CLL14

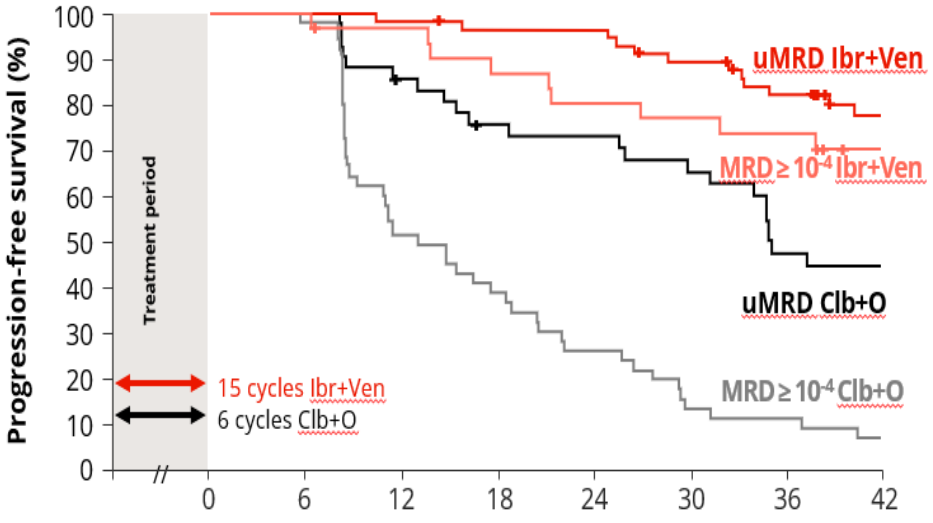
PFS for Obi-Ven from End of Treatment



MRD < 10^{-6}	90	86	79	73	63	38	4	0
MRD ≥ 10^{-6} and < 10^{-5}	56	53	50	40	33	26	2	0
MRD ≥ 10^{-5} and < 10^{-4}	23	22	20	17	14	8	2	0
MRD ≥ 10^{-4}	23	14	11	8	7	5	1	0

GLOW

PFS Landmark Analysis from End of Treatment

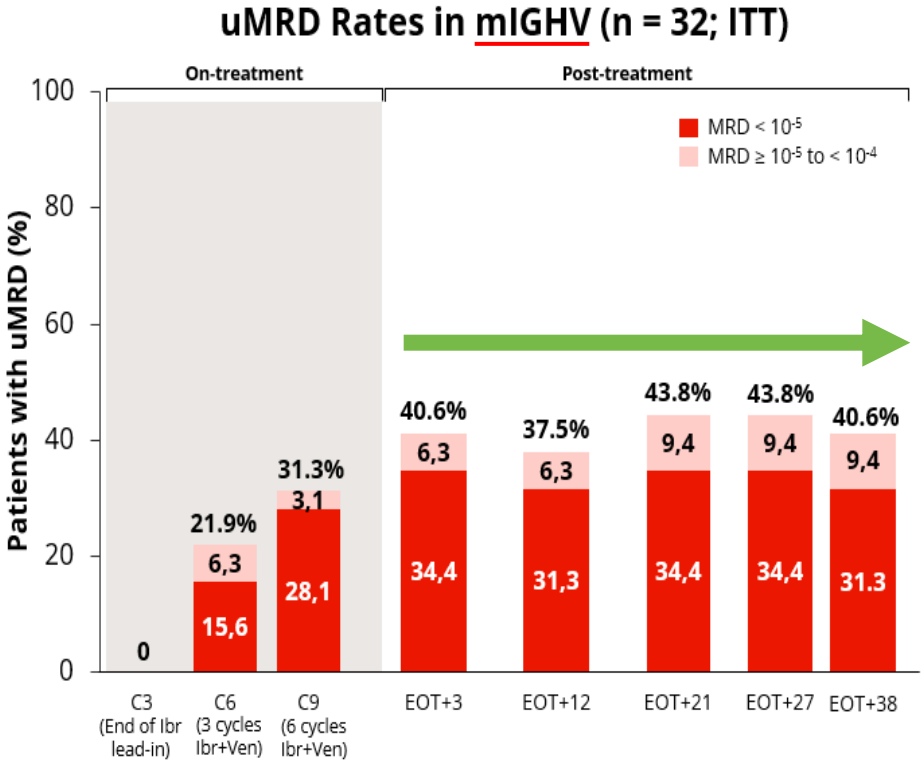


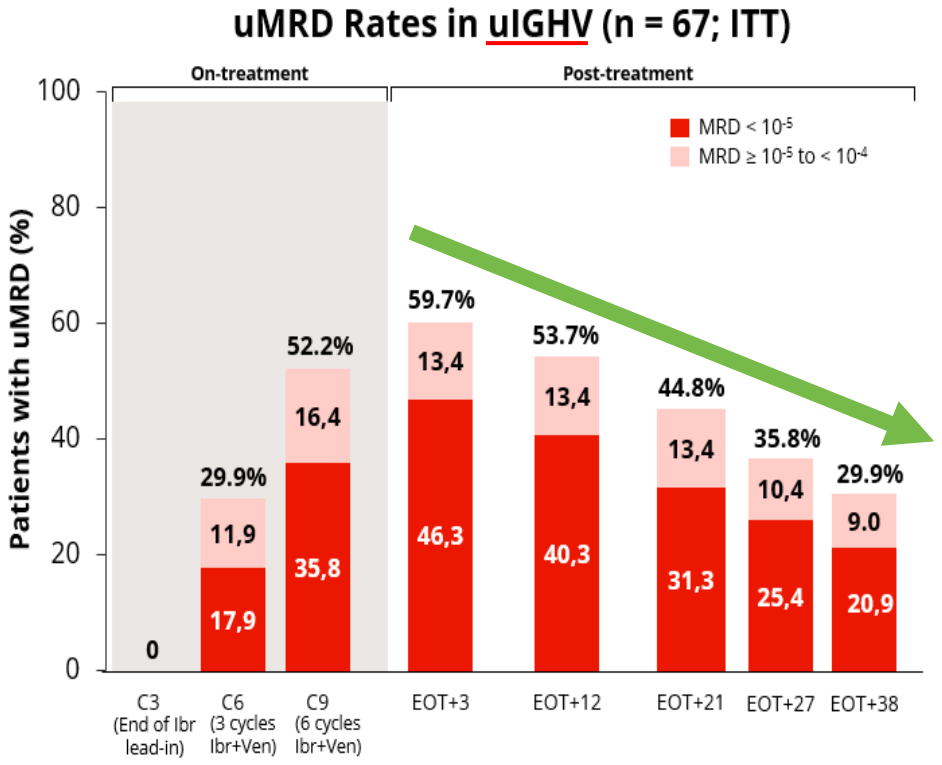
Patients at risk								
MRD ≥ 10^{-4} Ibr+Ven	31	31	29	26	24	23	22	18
MRD ≥ 10^{-4} Clb+O	47	46	24	18	12	6	5	3
uMRD Ibr+Ven	58	58	57	55	55	50	44	35
uMRD Clb+O	41	41	34	29	28	25	18	17

Al-Sawaf et al. EHA 2023; Follows et al. ASH 2023

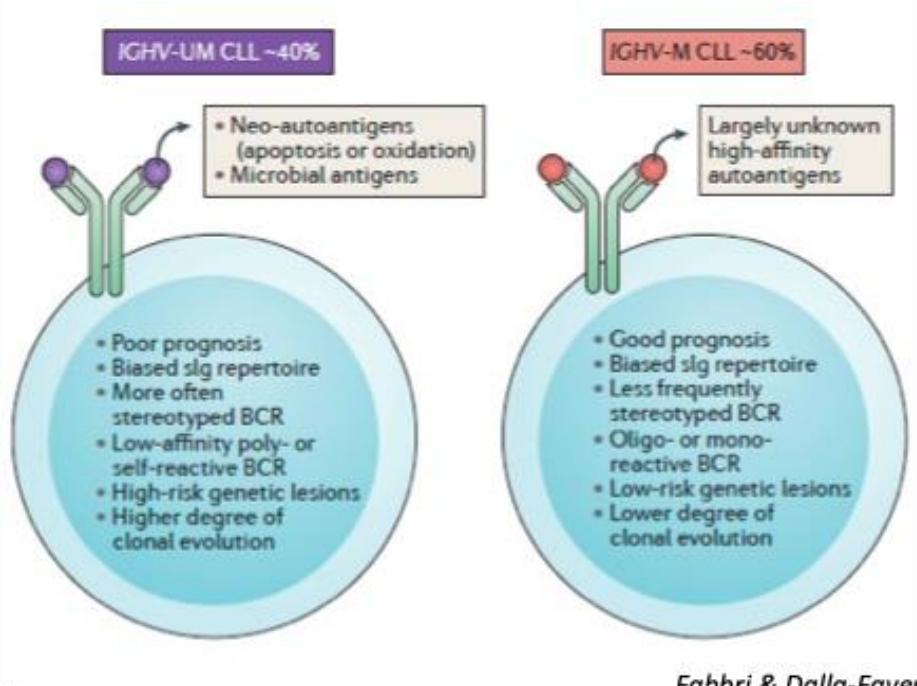
Frontline BTKi + BCL2i: MRD Depth and Dynamics - GLOW

MRD Levels with Ibrutinib + Venetoclax over Time by IGHV Status





G. Follows et al. ASH 2023

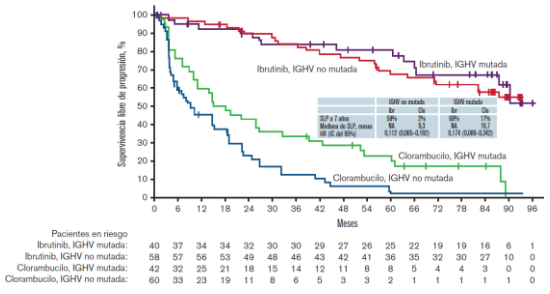


Fabbri & Dalla-Favera, Nature 2016

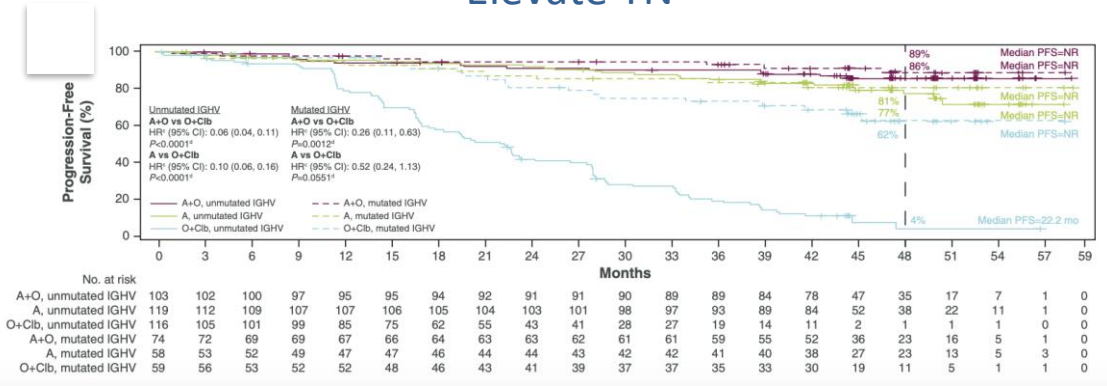
WHAT ABOUT UM-IGHV?

High efficacy of cBTKi in UM-IGHV

Ibrutinib
Resonate-2



Acalabrutinib
Elevate TN

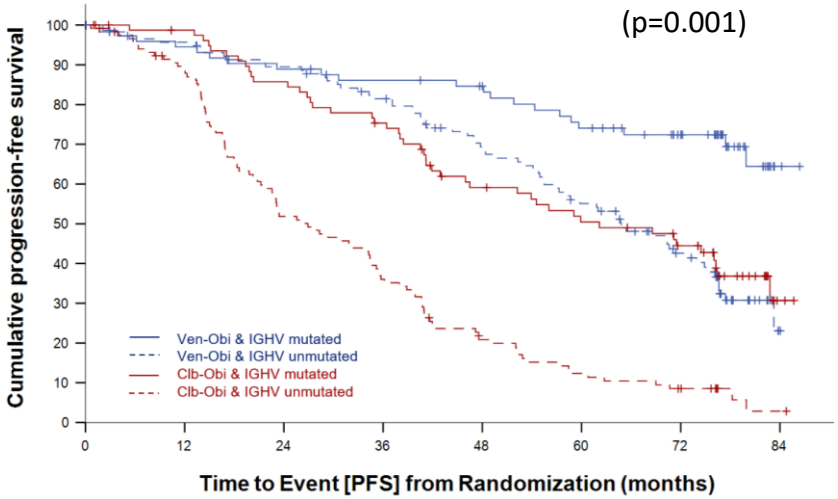


Barr et al, Blood Adv, 2022
Sharman et al. Leukemia 2022

BCL2i + antiCD20: lower activity in UM-IGHV

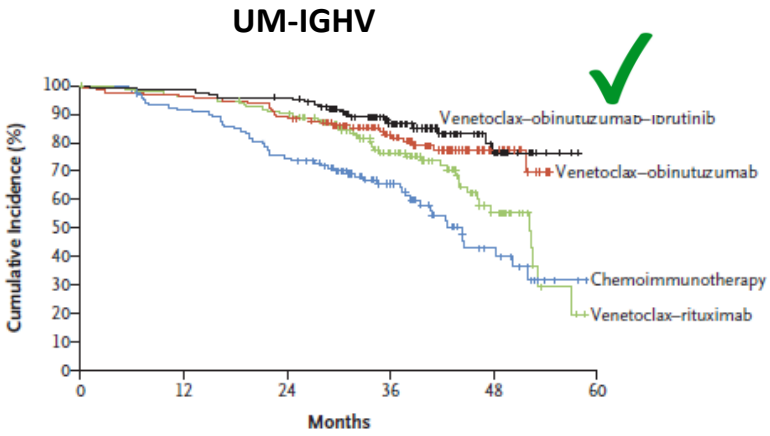
CLL14 (6y)

Median PFS:
-UM-IGHV 64.8m
-M-IGHV NR
(p=0.001)



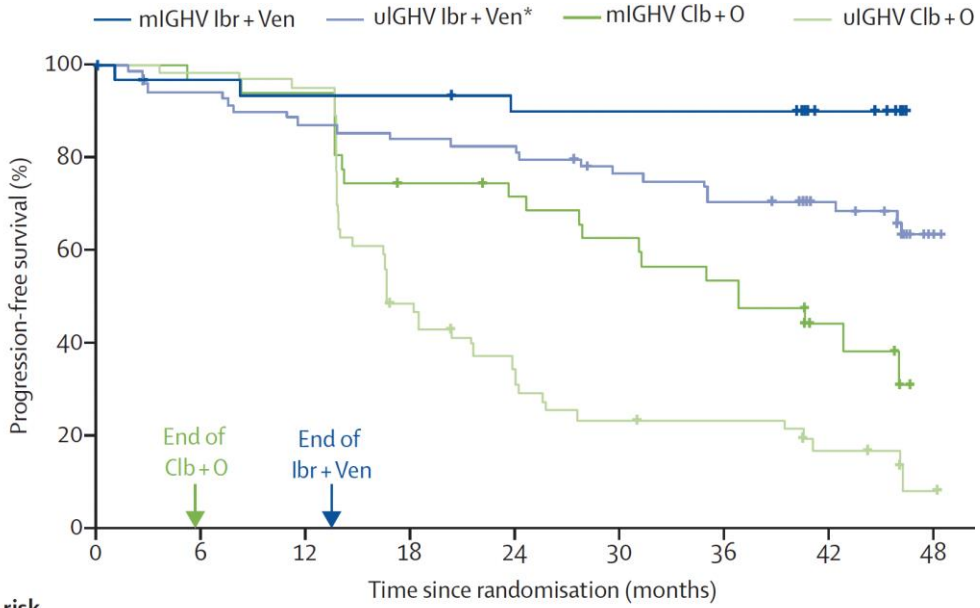
CLL13 (3y)

PFS @ 3 ys con VO:
-UM-IGHV 82.9 m
-M-IGHV 93.6 m



Al-Sawaf O, Blood October 2024
Eichhorst B, NEJM 2023

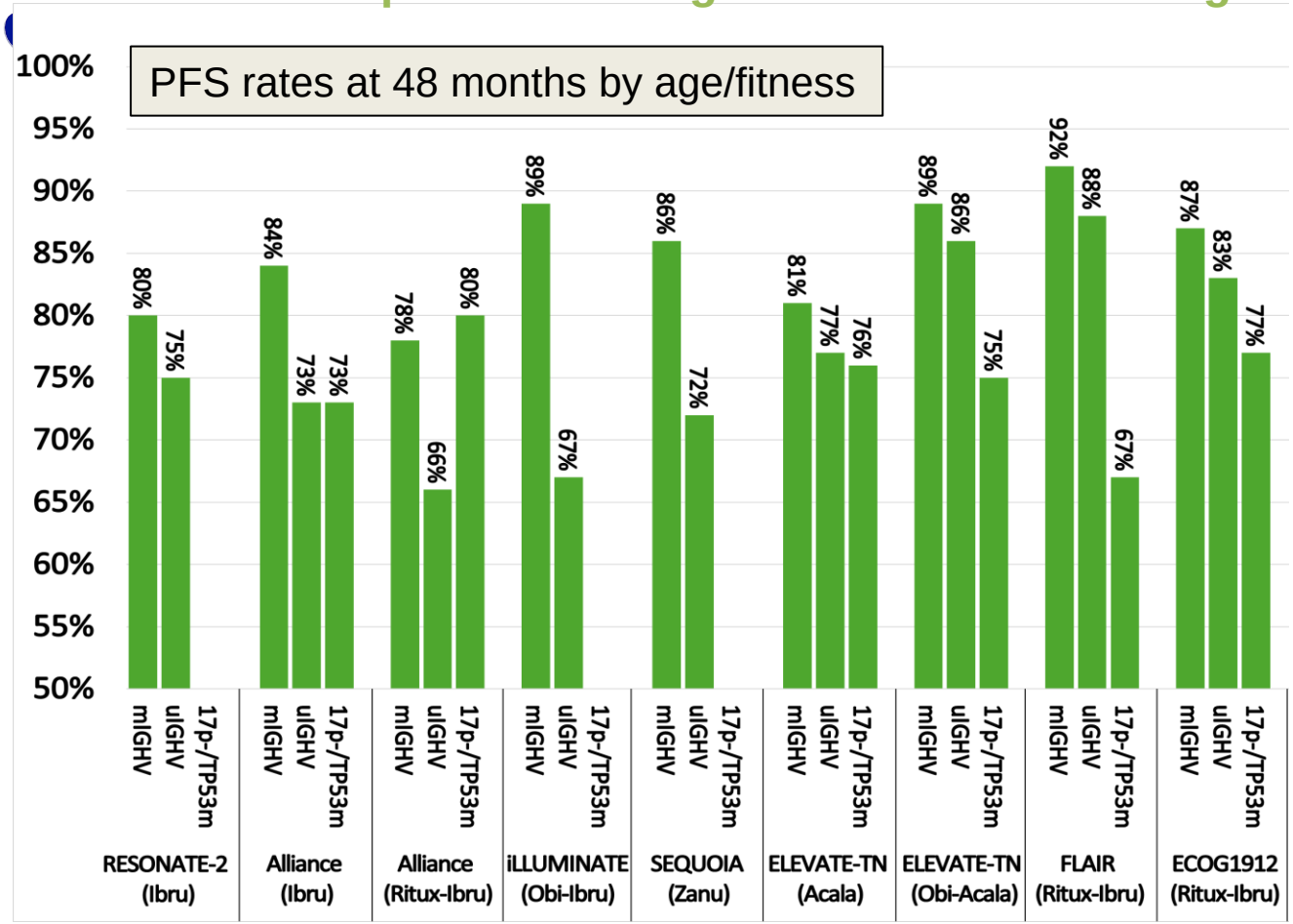
Venetoclax + Ibrutinib: Glow Study
IGHV mutational status



Number at risk (number censored)									
mIGHV Ibr + Ven	32 (0)	29 (2)	28 (2)	28 (2)	26 (3)	26 (3)	26 (3)	17 (12)	0 (29)
uIGHV Ibr + Ven	67 (0)	63 (0)	58 (0)	56 (0)	55 (0)	49 (2)	45 (2)	33 (14)	2 (42)
mIGHV Clb + O	35 (0)	34 (0)	33 (0)	25 (1)	23 (2)	20 (2)	17 (2)	7 (9)	0 (14)
uIGHV Clb + O	57 (0)	56 (0)	52 (2)	25 (3)	16 (4)	11 (4)	10 (5)	6 (6)	1 (9)

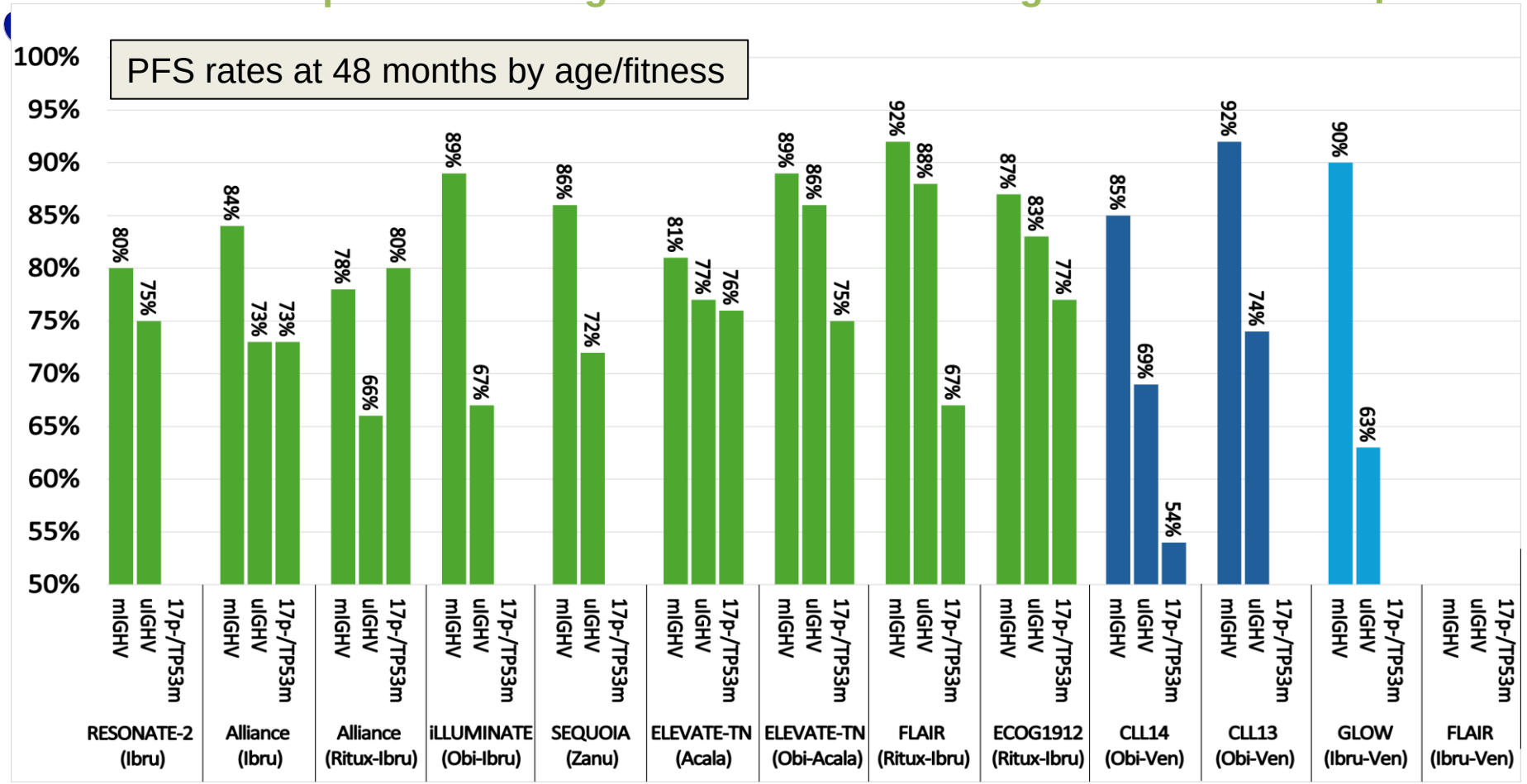
Niemann et al, 2024

Cross Trial Comparison of Targeted Frontline CLL Regimens: IGHV & 17p/*TP53*



Barr et al. Blood Adv 2022; Woyach et al. Blood 2024; Moreno et al. Haematologica 2022; Ramakrishnan et al. ASH 2023; Sharman et al. ASH 2023; Hillmen Lancet Onc 2023; Shanafelt et al. Blood 2022; Al-Sawaf et al. Blood 2024; Fürstenau et al. Lancet Onc 2024; Moreno et al. ASH 2023; Munir et al. NEJM 2023 *(missing columns: no data)*

Cross Trial Comparison of Targeted Frontline CLL Regimens: IGHV & 17p/*TP53*



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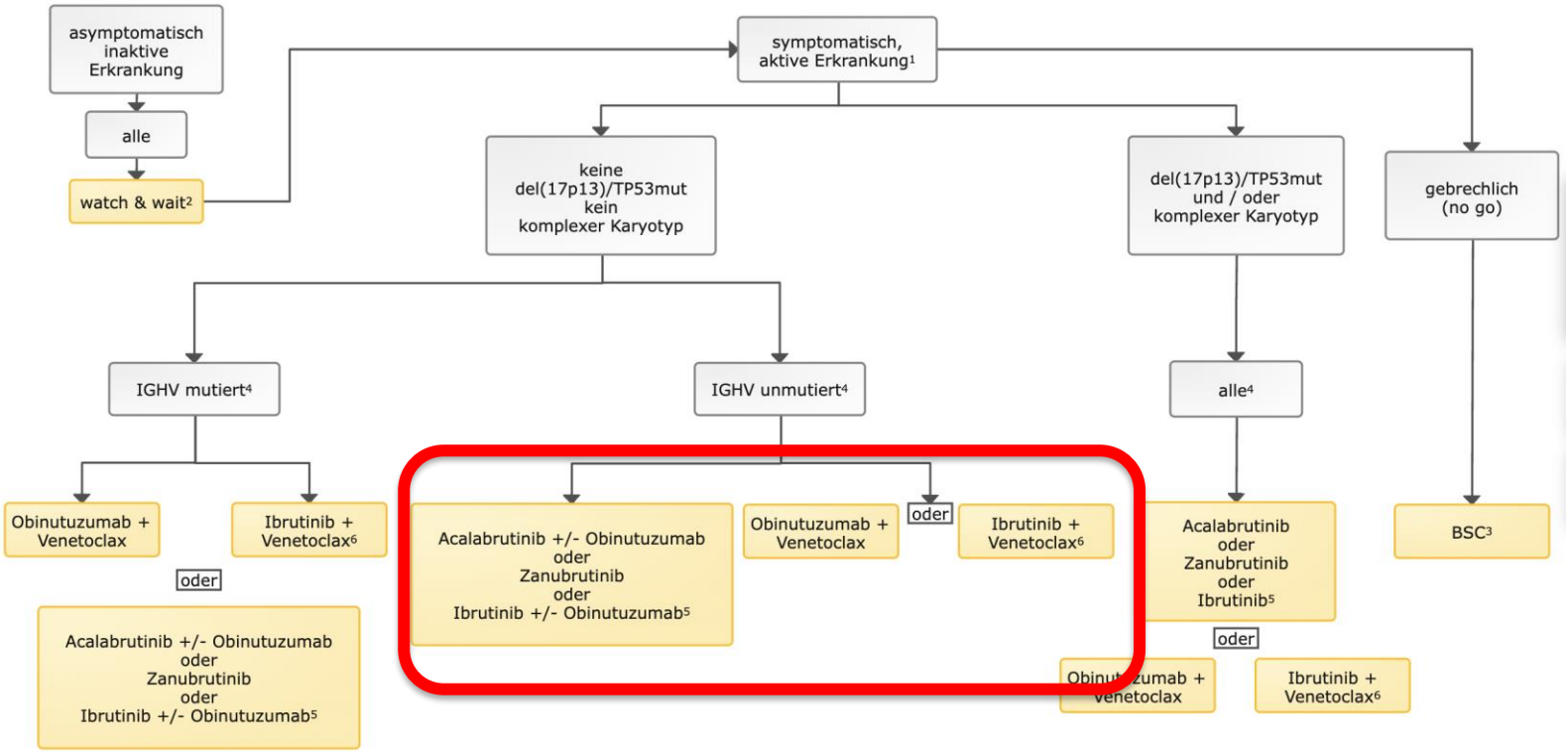
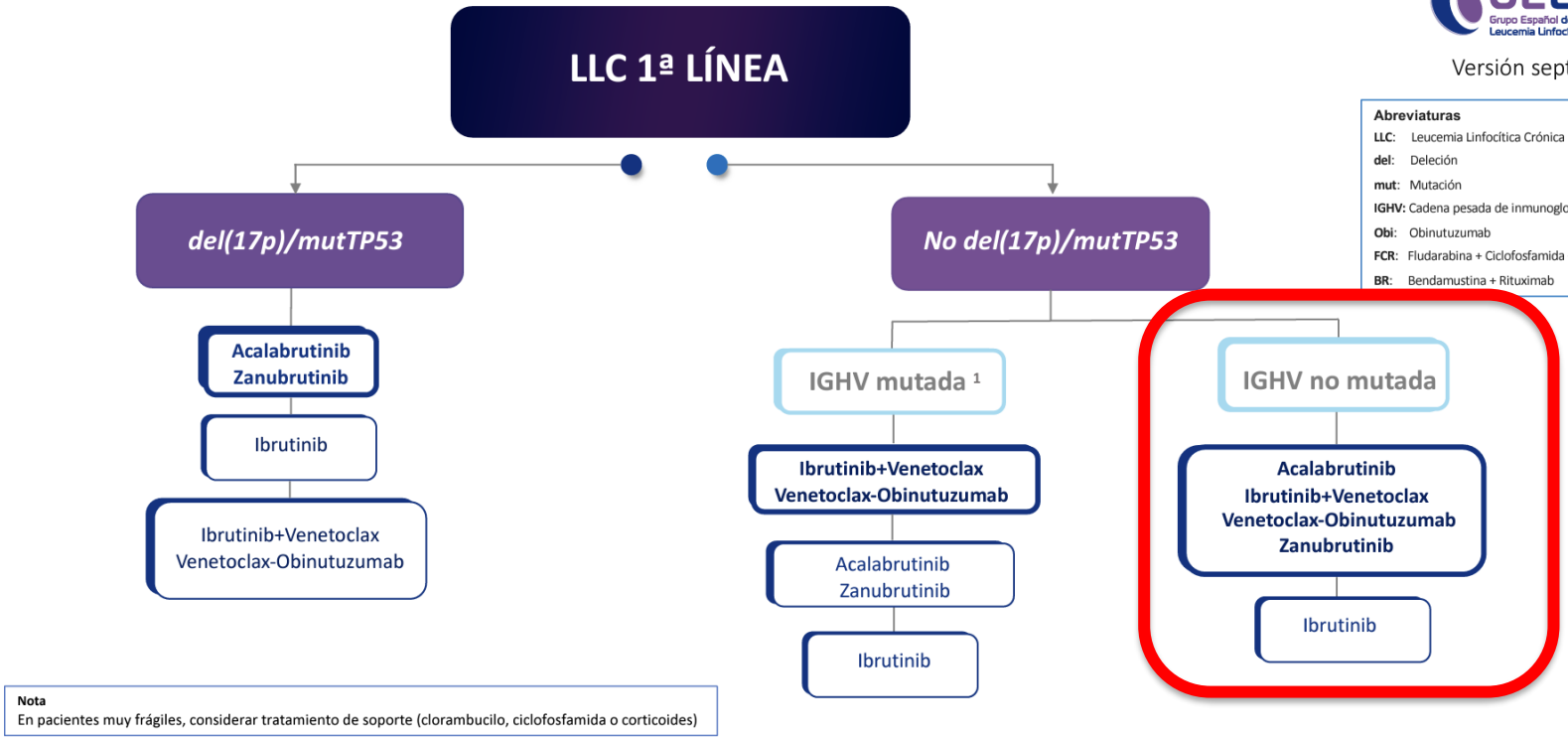
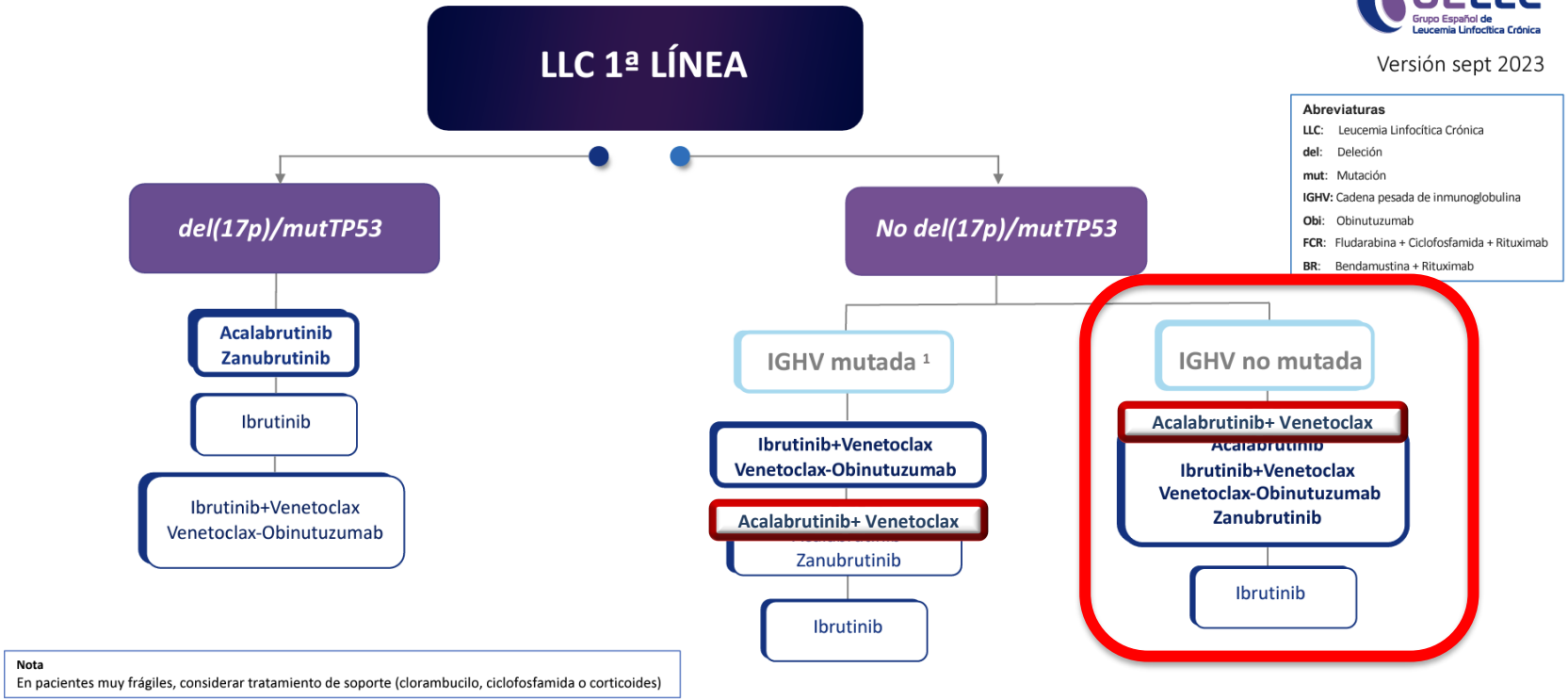
German Guidelines





Modificado de A. Medina et al., *Medicina Clínica 2025* (en prensa)



Versión sept 2023

Modificado de A. Medina et al., *Medicina Clínica 2025* (en prensa)

Selecting 1L treatment in CLL (2025)

		Comorbidities			Logistics	Biology (efficacy & toxicity)				Cost
		Impaired Renal Function	Cardiovasc risk	Bleeding risk		mIGHV	uIGHV	Del(17p) TP53^{mut}	CK $\geq$ 5	
Continuous	Ibrutinib									
	Acalabrutinib									
	Zanubrutinib									
Fixed Duration	Venetoclax + Obinutuzumab									
	Venetoclax + Ibrutinib									
	Venetoclax + Acalabrutinib									

Excellent — Bad

Case study

- ❒ 73-year-old male
- ❒ Fit, engages in regular exercise (hiking, skiing)
- ❒ Medical history: Hypertension, well-controlled with valsartan
- ❒ Lives 1 hour from the hospital

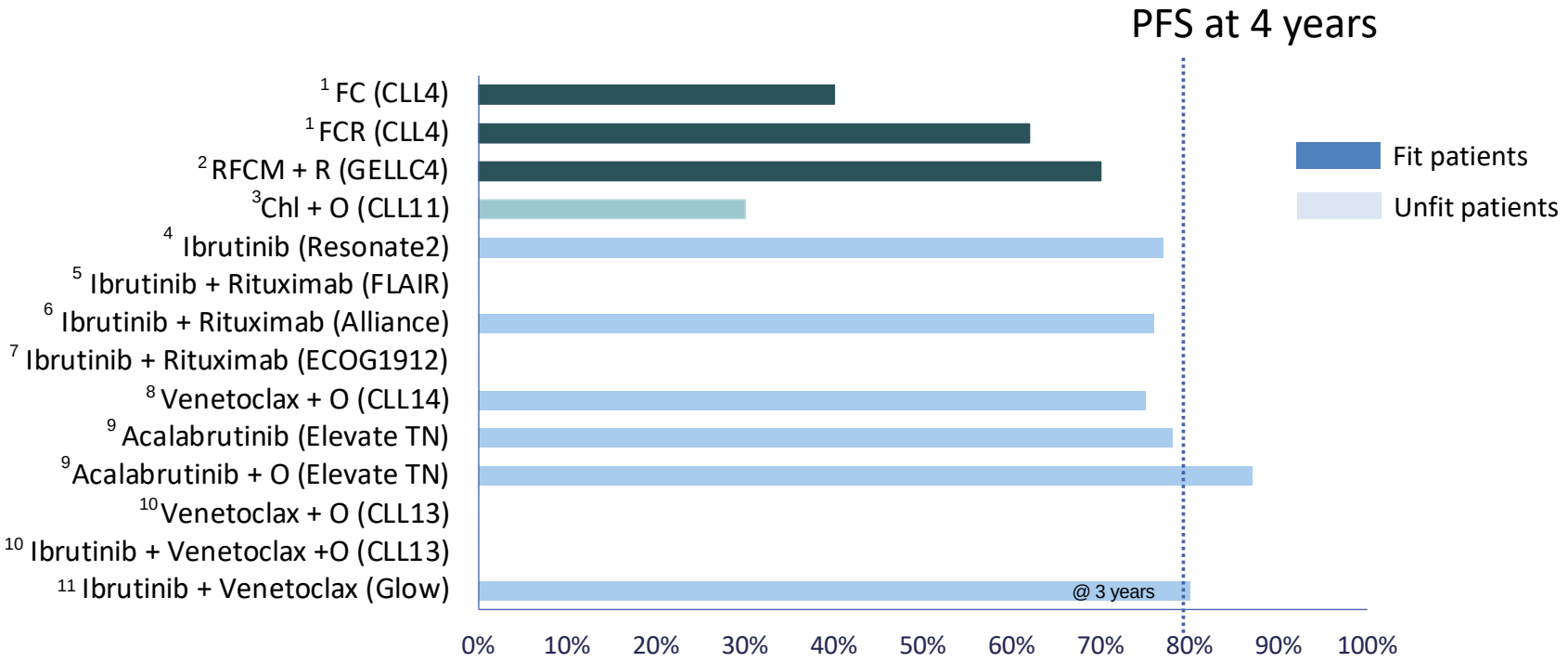
CLL, Stage C(III), UM-IGHV, normal FISH, TP53^{wt}

<u>Ibrutinib + Venetoclax</u>

Neutropenia grade 3, no infections

CR with U-MRD (3 months)

Historical evolution of PFS in CLL

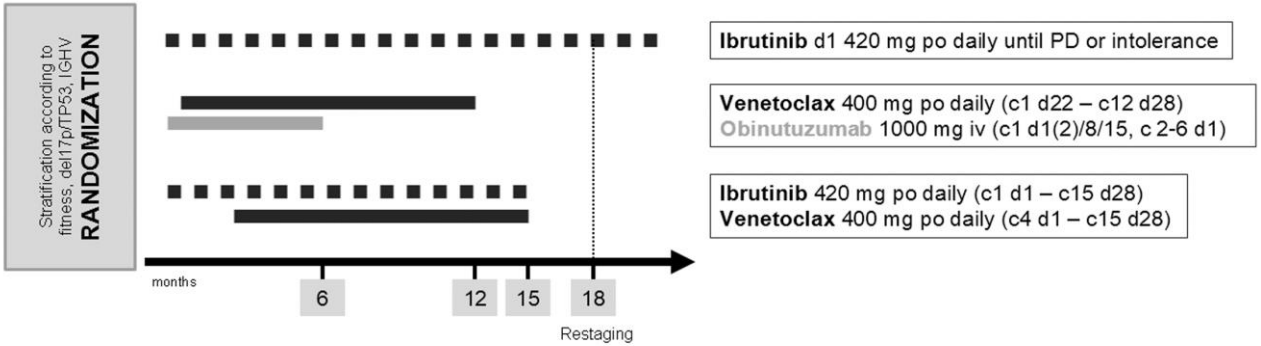


Chl, chlorambucil; FCR, Fludarabine, cyclophosphamide and rituximab; O, obinituzumab; PFS, progression-free survival; R, rituximab; R-FCM, rituximab, fludarabine, cyclophosphamide and mitoxantrone

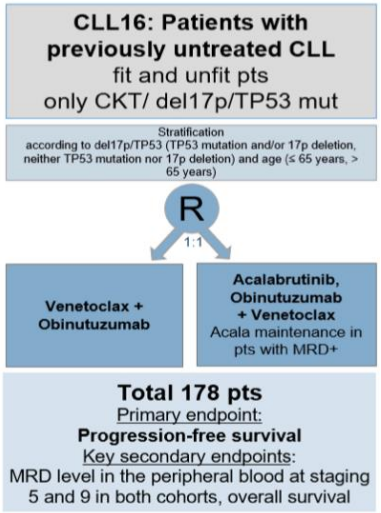
1. Fischer K, et al. Blood.2016;127:208-215; 2. Bosch F. et al. JCO 2011; 3. Goede, et al. Presented at EHA 2018; abstract S151; 4. Burger JA, et al. Leukemia.2020;34:787-798; 5. Hillmen et al; ASH 2021; 6. Woyack, et al.Presented at ASH 2021; abstract 639; 7. Shanafeld et al. Blood 2022, 140:112-20; 8. Al-Sawaf, et al. Presented at EHA 2021; abstract S146; 9. Sharman, et al. Presented at ASCO 2022: 10. Eichhorst B. et al, EHA 2022; 11. Kater et al, NEJM evid 2022

Treatment schedule:

CLL17



CLL16

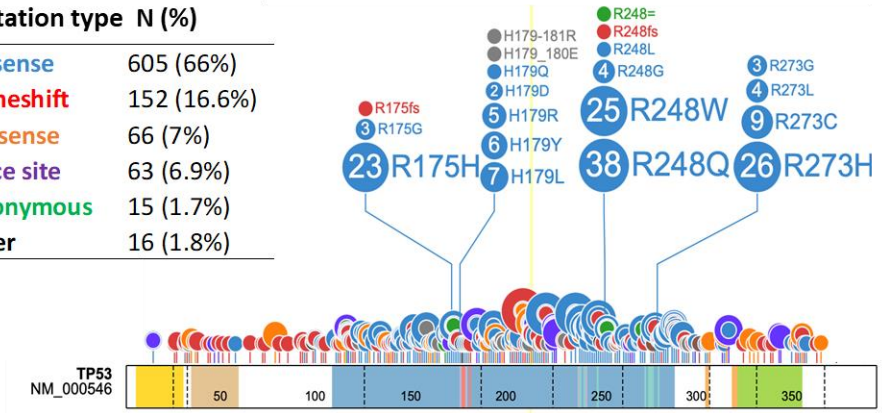


WHAT ABOUT TP53 ABERRATIONS?

TP53 mutation landscape by del(17p)

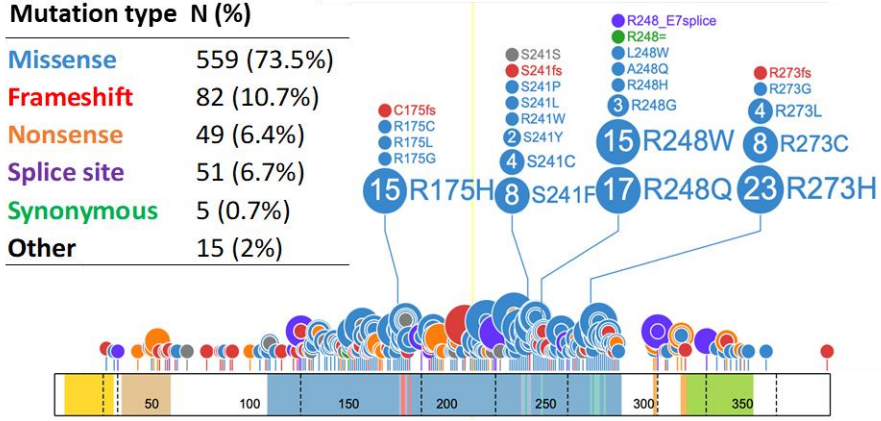
Del(17p): n=917/1824*

Mutation type	N (%)
Missense	605 (66%)
Frameshift	152 (16.6%)
Nonsense	66 (7%)
Splice site	63 (6.9%)
Synonymous	15 (1.7%)
Other	16 (1.8%)



No del(17p): n=761/1824*

Mutation type	N (%)
Missense	559 (73.5%)
Frameshift	82 (10.7%)
Nonsense	49 (6.4%)
Splice site	51 (6.7%)
Synonymous	5 (0.7%)
Other	15 (2%)



Visualisation via https://pecan.stjude.cloud

- Same distribution of mutations and number of mutations per patient with/without del(17p)
- Del(17p) associated with higher VAF (44% vs. 20%, p<0.001)

*del(17p) NA: 146/1824

Bertossi et al, EHA 2024

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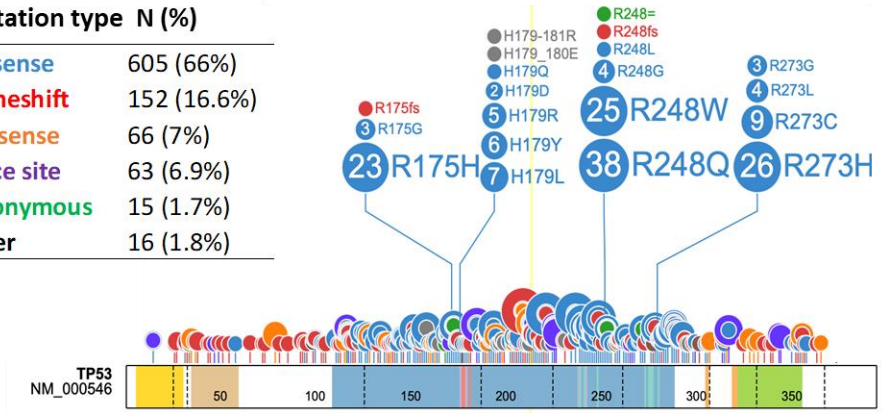

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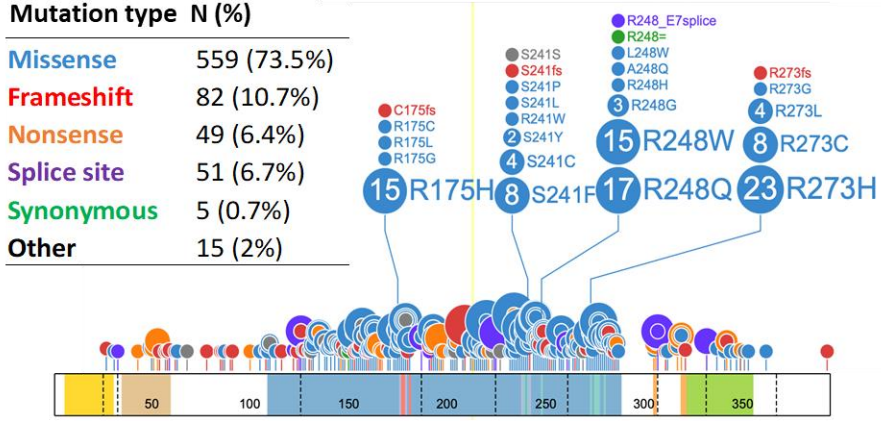

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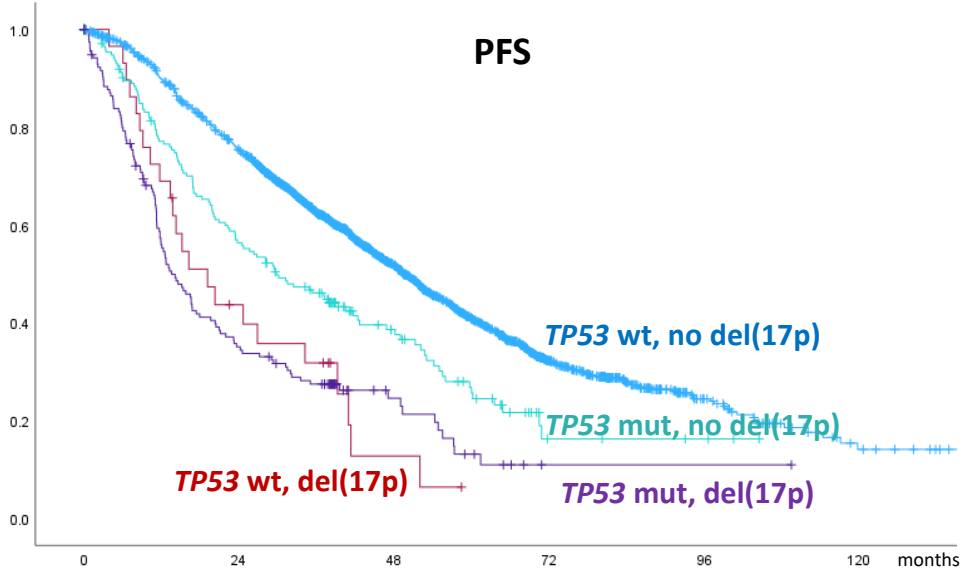
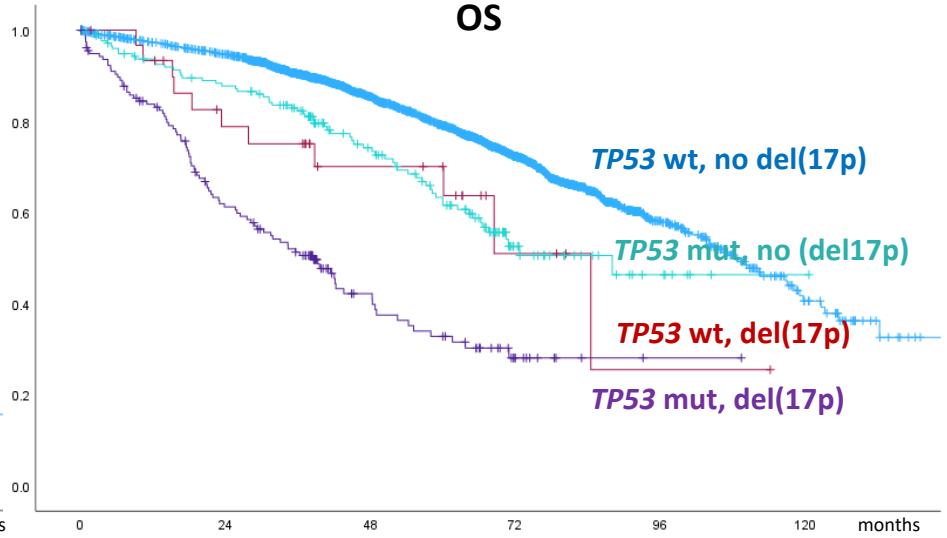
Bertossi et al, EHA 2024

Prognostic impact by TP53mut and del(17p)





- No del(17p) – *TP53* mut (n=177)
- No del(17p) – *TP53* wt (n=3276)

HR 1.609, p<0.001

- Del(17p) – *TP53* mut (n=157)
- Del17p – *TP53* wt (n=31)

HR 1.010 , p=0.96

- No del(17p) – *TP53* mut (n=177)
- No del(17p) – *TP53* wt (n=3276)

HR 1.82, p<0.001

- Del(17p) – *TP53* mut (n=157)
- Del17p – *TP53* wt (n=31)

HR 2.51 , p=0.004

Bertossi et al, EHA 2024

Predictive value of common genetic lesions in CLL: Targeted therapies

Study	Drug	Line	UM-IGHV	TP53	SF3B1	NOTCH1	XPO-1	BIRC3	CKT ≥ 3	ATM	BRAF
Pooled (2 trials)[1]	Ibrutinib	1L									
Resonate[2]	Ibrutinib	2L									
ELEVATE[3]	Acalabrutinib	1L									
CLL14[4]	VEN + G	1L									
	CLB + G										
Glow[5]	Ven + I	1L									
Captivate[6] (FD&MRD)	Ven + I	1L									
Pooled pts[7]	Venetoclax mono	>1L									

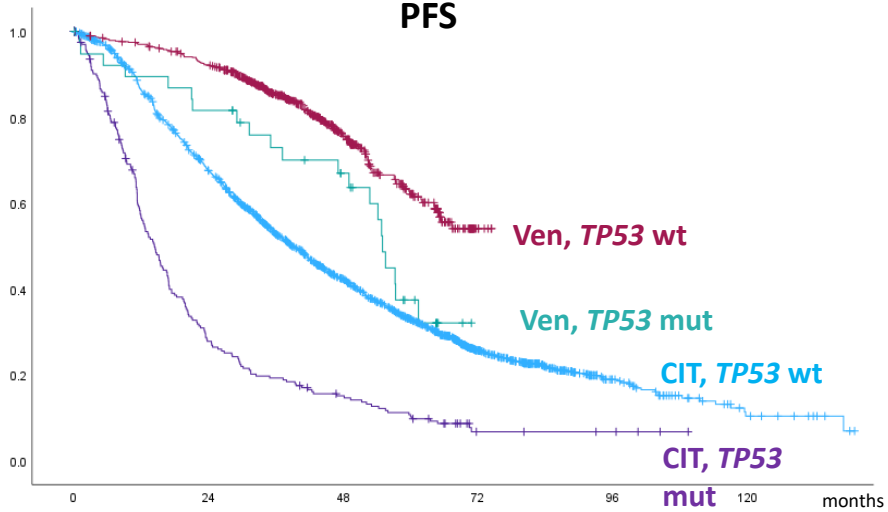
Not Significant Significant

[1]Burger J, et al Leuk, Lymphoma (2022); [2]John C. et al, Blood, 2019,[3] Sharman et al., ASH 2023; [4]*Tausch et al, Blood* (2020) 135 (26): 2402–2412; [5]Kater et al, EHA 2023; [6]Jain N et a., CCR 2024; [7]Roberts AW et al., Blood 2019

Prognostic impact by type of therapy: CIT vs Venetoclax

Bertossi et al, EHA 2024

PFS



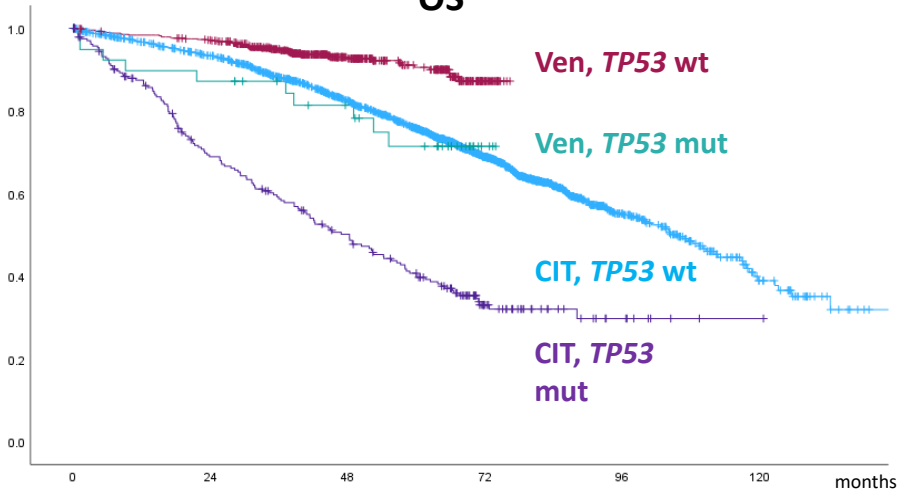
- CIT – *TP53* mut (n=237)
- CIT – *TP53* wt (n=2403)

HR 2.55, p<0.001

- Ven – *TP53* mut (n=39)
- Ven – *TP53* wt (n=673)

HR 2.12, p<0.001

OS



- CIT – *TP53* mut (n=237)
- CIT – *TP53* wt (n=2403)

HR 3.00, p<0.001

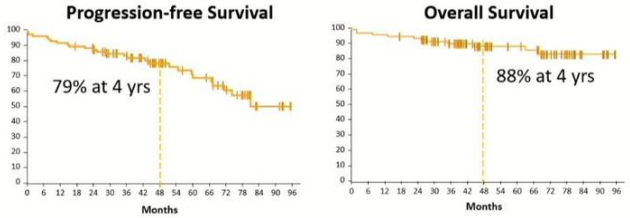
- Ven – *TP53* mut (n=39)
- Ven – *TP53* wt (n=673)

HR 2.84, p=0.003

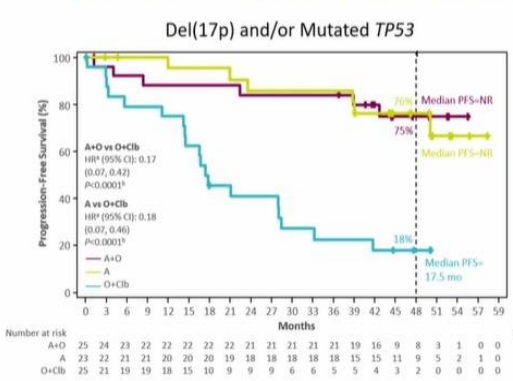
High efficacy of cBTKi in aberrant TP53 gene

Ibrutinib
Pooled-analysis

	PCYC-1122e (NIH study)	RESONATE-2	iLLUMINATE	ECOG1912
N	34	11	18	26
Regimen	Ibr	Ibr	Ibr + Obinu	Ibr + Ritux
Patients	del(17p)/ *TP53*mut	*TP53*mut	del(17p)/ *TP53*mut	*TP53*mut



Acalabrutinib
Elevate TN

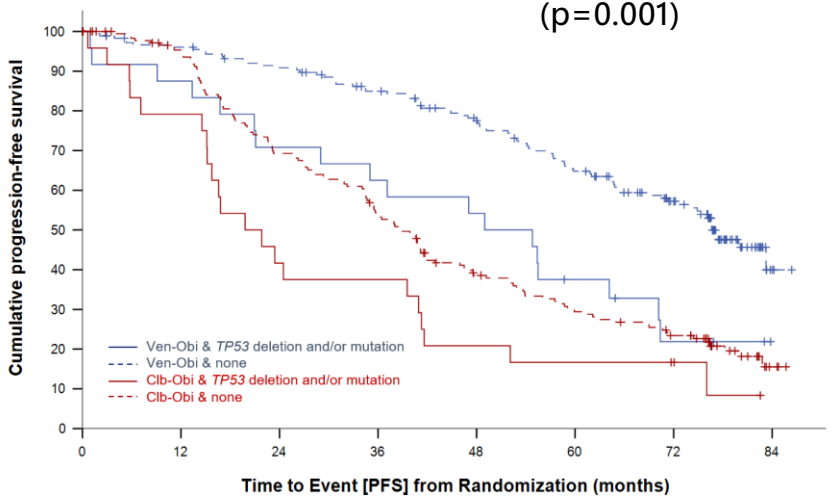


Ahn et al. 2020. NEJM; Allan et al. ASH 2020
Sharman J, EHA 2022

BCL2i + antiCD20: lower activity in del17p/mutTP53

CLL14 (6y)

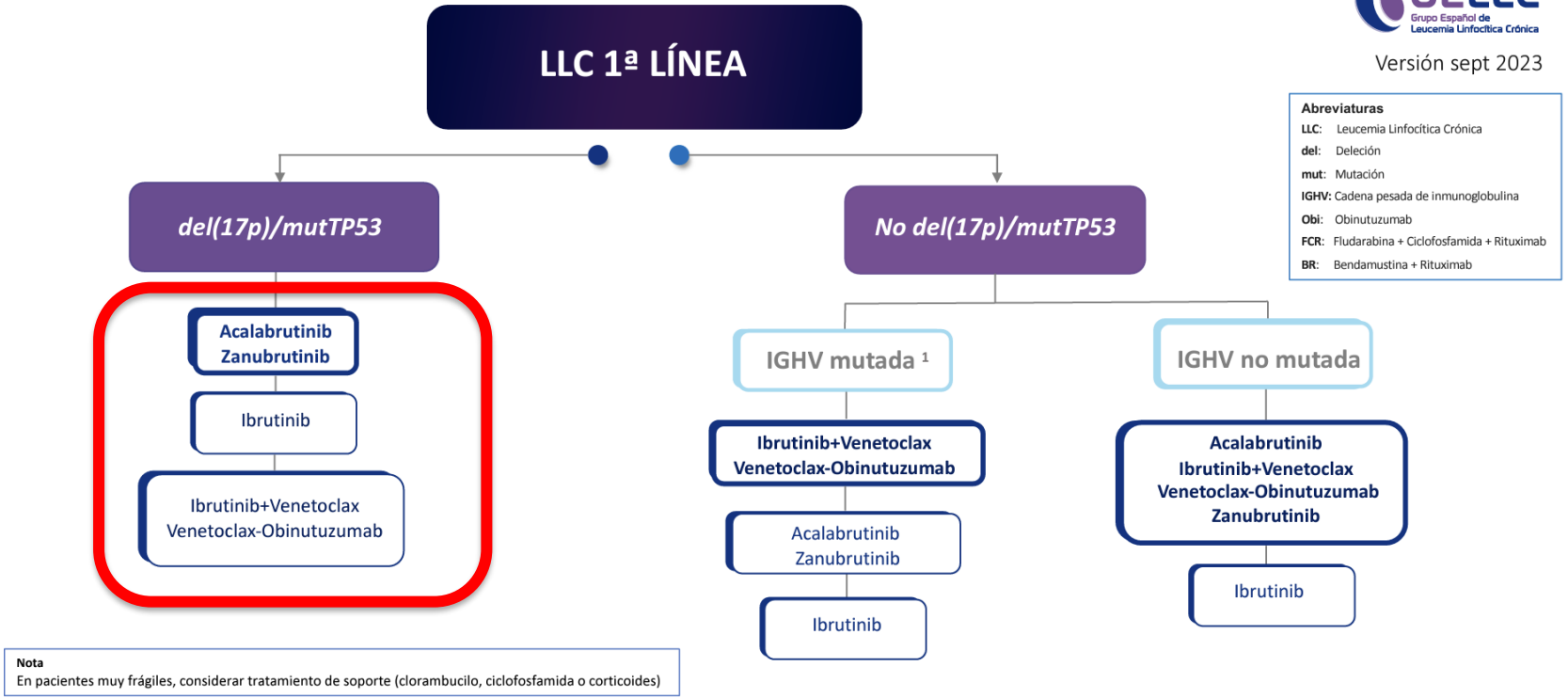
Median PFS:
-del17p/TP53 51.9m
-No del17p/TP53 76.6m
(p=0.001)



CLL13

Excluded del17p & mut *TP53*

Al-Sawaf O. et al. , Blood et al 2024



Modificado de A. Medina et al., *Medicina Clínica 2025* (en prensa)

CONCLUSIONS

Treatment strategy: a multiparametric approach

CLL Therapy Trends: Shift toward fixed-duration treatment strategies

High-Risk Genetic CLL: Still a challenge in effective management

Future Directions: Focused research on addressing and eliminating residual persistent cells