

**HOT
NEWS**

**NELLE SINDROMI
LINFOPROLIFERATIVE:**

La storia continua

LA LEUCEMIA LINFATICA CRONICA

PROGRAMMA

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CLL TN

CONTINUOUS THERAPY

Ibrutinib monotherapy

Acalabrutinib monotherapy

Acalabrutinib Obinutuzumab *AIFA NOT REIMBURSED*

Zanubrutinib Monotherapy AIFA PENDING

FIXED DURATION THERAPY

Venetoclax Obinutuzumab

Venetoclax Ibrutinib AIFA PENDING

CLL R/R

CONTINUOUS THERAPY

Ibrutinib monotherapy

Acalabrutinib monotherapy (not if previously venetoclax)

Zanubrutinib Monotherapy AIFA PENDING

Pirtobrutinib Monotherapy EMA PENDING

FIXED DURATION THERAPY

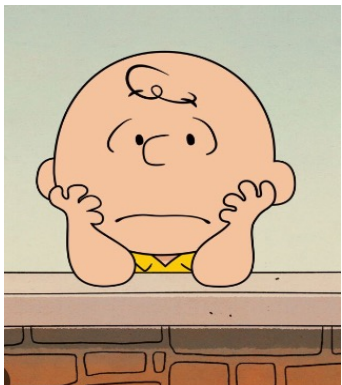
Venetoclax Rituximab

CLL BTKi INTOLLERANT

Zanubrutinib Monotherapy (?) AIFA PENDING

Pirtobrutinib Monotherapy (?) EMA PENDING

CLL DOUBLE REFRACTORY



1

**VENETOCLAX OBINUTUZUMAB
or
BTKi**

No randomized study

2

If BTKi: WICH BTKi

No randomized study

➤ **Ibrutinib:**

Chlorambucil vs Ibrutinib (Resonate 2)

Chlorambucil Obinutuzumab vs Ibrutinib Obinutuzumab (Illuminate)

Bendamustine Rituximab vs Ibrutinib Rituximab vs Ibrutinib (Alliance)

FCR vs IR (ECOG)

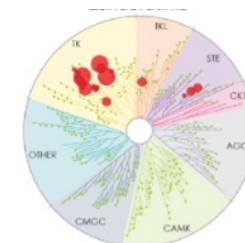
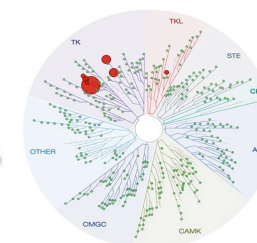
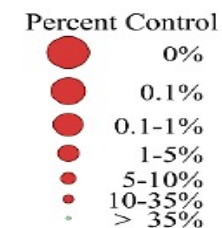
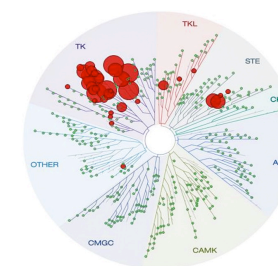
FCR vs IR (Flair)

➤ **Acalabrutinib:**

Chlorambucil Obinutuzumab vs Acalabrutinib Obinutuzumab vs Acalabrutinib

➤ **Zanubrutinib:**

Bendamustine Rituximab vs Zanubrutinib (Sequoia)

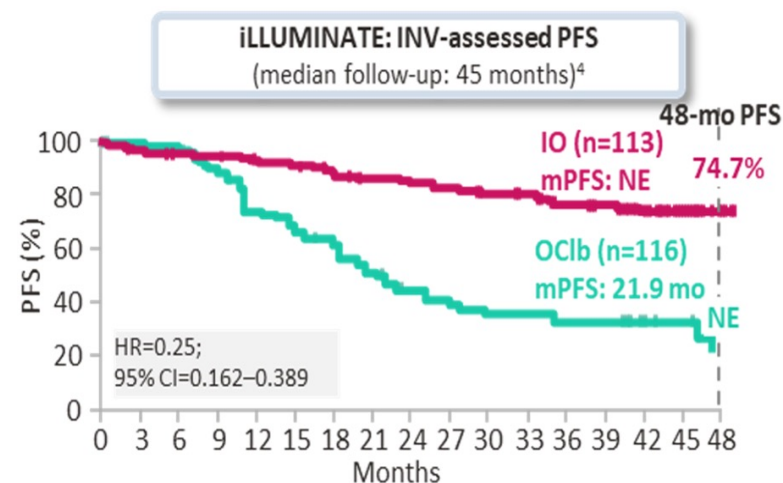
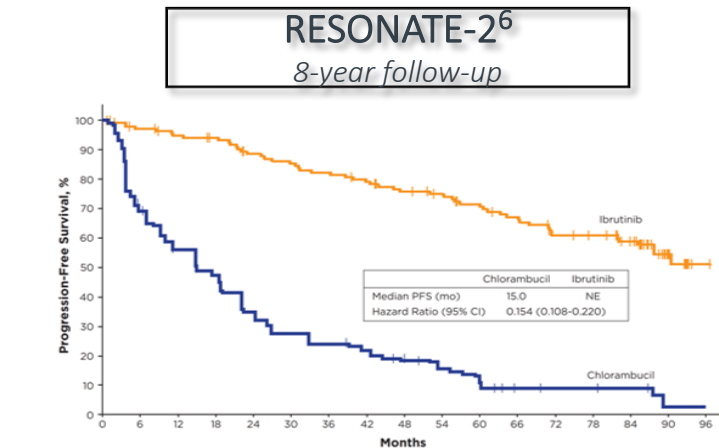
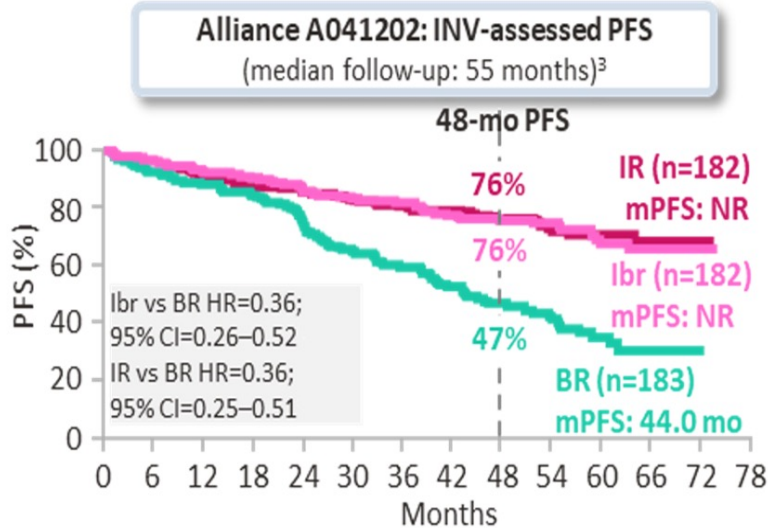
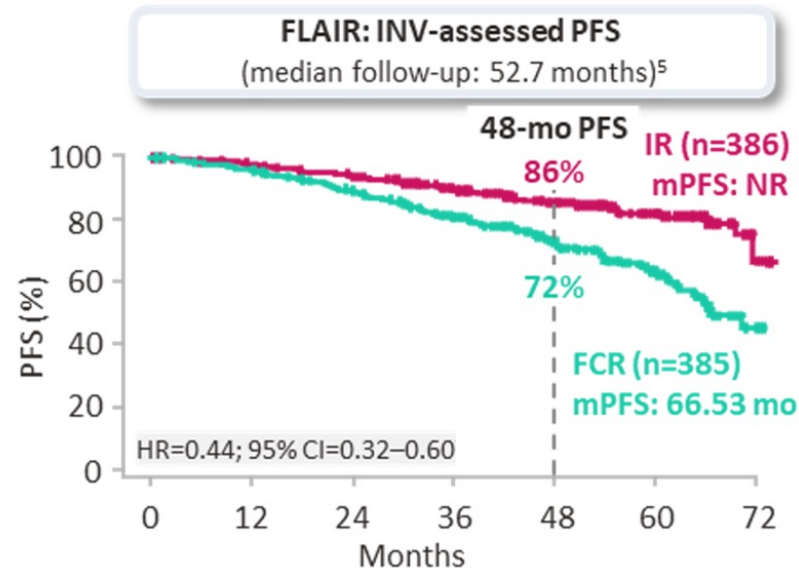
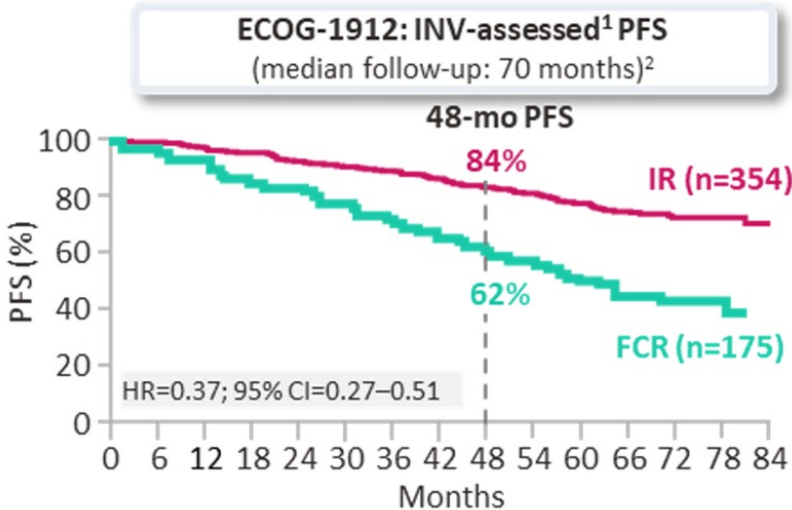


Ibrutinib in TN pts

Young FIT



Elderly/Unfit



1. Shanafelt TD et al. *N Engl J Med* 2019; 381 (5): 432-443. 2. Shanafelt TD et al. *Blood* 2022; 140 (2): 112-120. 3. Woyach J et al. *Blood* 2021; 138 (Suppl_1): 639. 4. Moreno C et al. *Haematologica* 2022; 107 (9): 2108-2120. 5. Hillmen P et al. Oral presentation at ASH 2021; Georgia, USA, December 11-14, 2021 (Session 642). 6. Barr PM et al. *Blood Adv* 2022; 6 (11): 3440-3450.

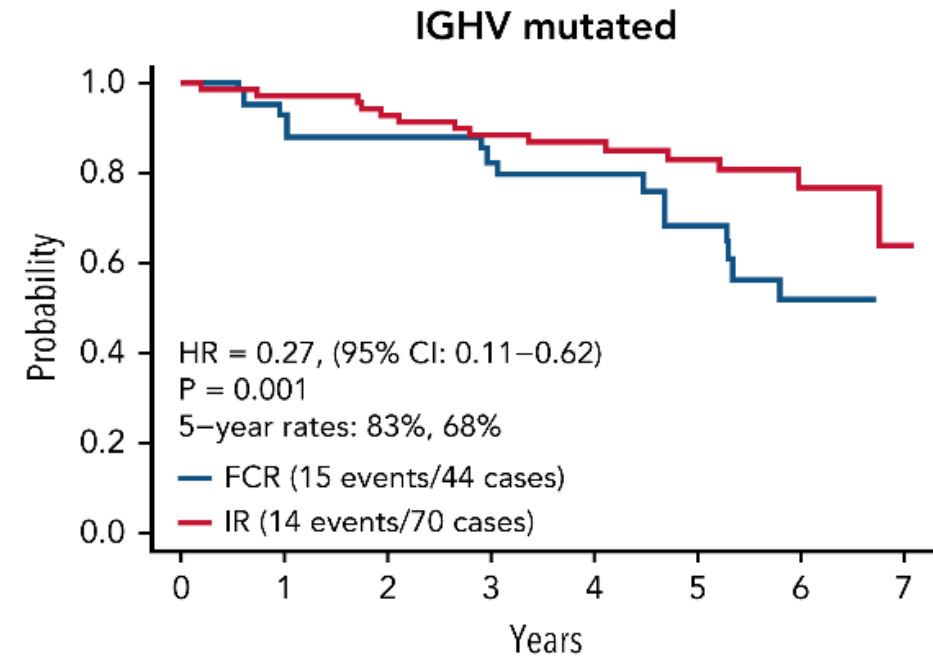
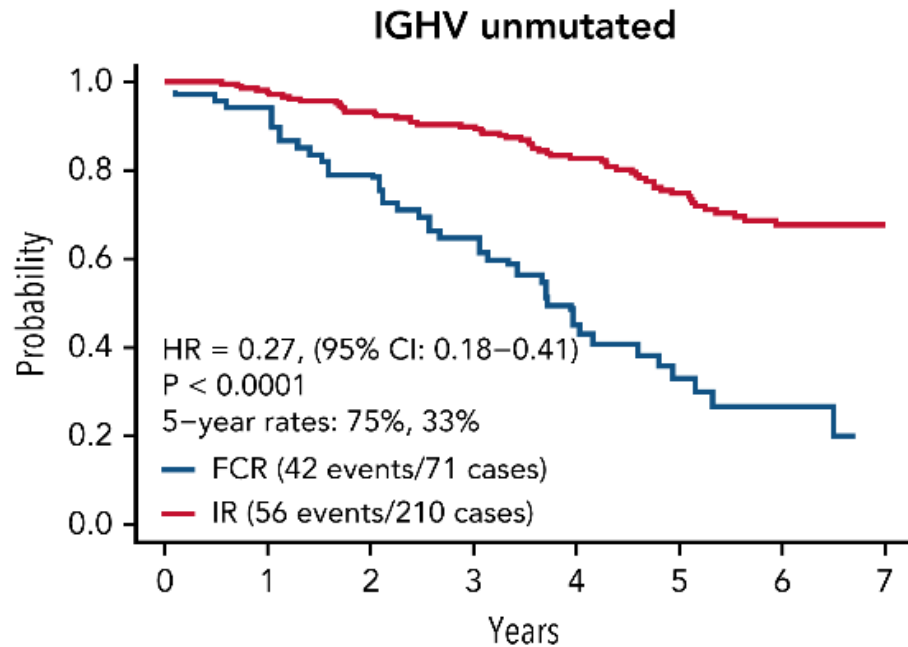
ECOG study (IR vs FCR): PFS by IGHV mutation status

ECOG 1912

IR vs. FCR

70-month follow-up

- ≤70 years old
- Ability to tolerate FCR



IGHV unmutated: PFS significantly different in all the studies at the first FU

IGHV mutated: PFS significantly different ECOG1912, Resonate 2 (in all other studies only a trend)

Acalabrutinib in TN CLL (Elevate TN study)

✓ PFS Benefit With Acalabrutinib Containing Regimens

Age ≥ 65 y or
 < 65 y with coexisting conditions:

- CIRS score > 6, or
- CrCl < 70 mL/min

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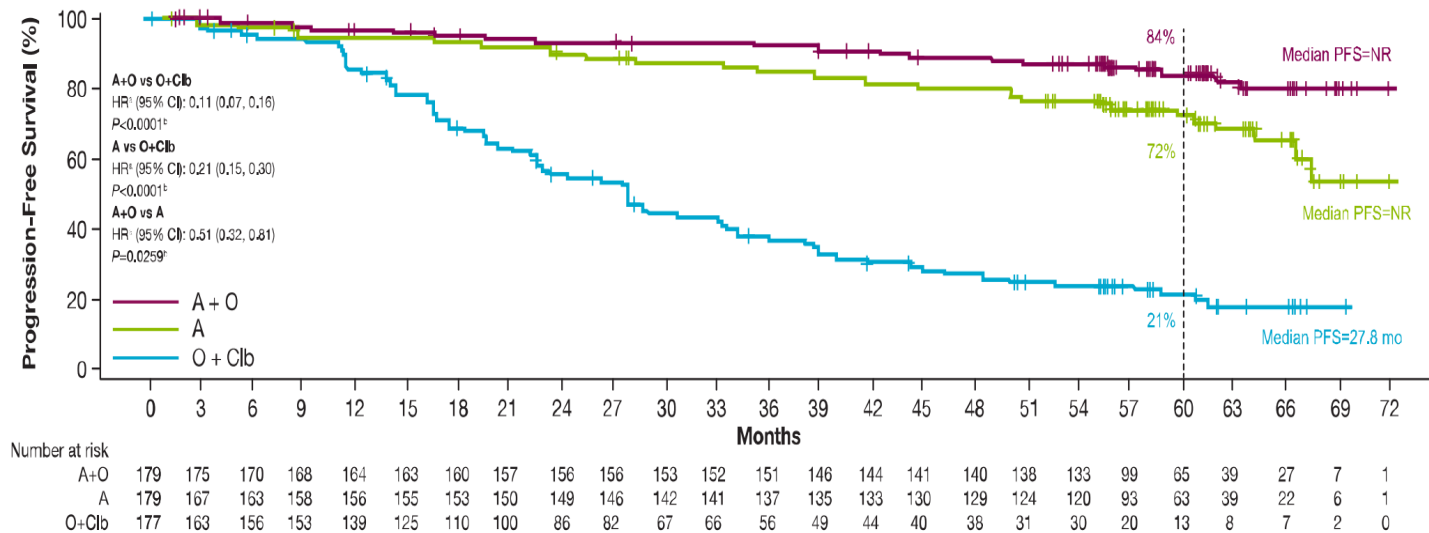
Acalabrutinib

Acalabrutinib + obinutuzumab*

Chlorambucil* + obinutuzumab*

* 6 cycles

Median follow-up 58.2 months



CIRS, Cumulative Illness Rating Scale; CrCl, creatinine clearance.

Zanubrutinib in TN CLL (Sequoia study)

✓ PFS Benefit With Zanubrutinib monotherapy

Cohort 1

- Untreated CLL/SLL
- ≥ 65 y of age OR unsuitable for treatment with FCR[^]
- Without del(17p) by central FISH

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Zanubrutinib

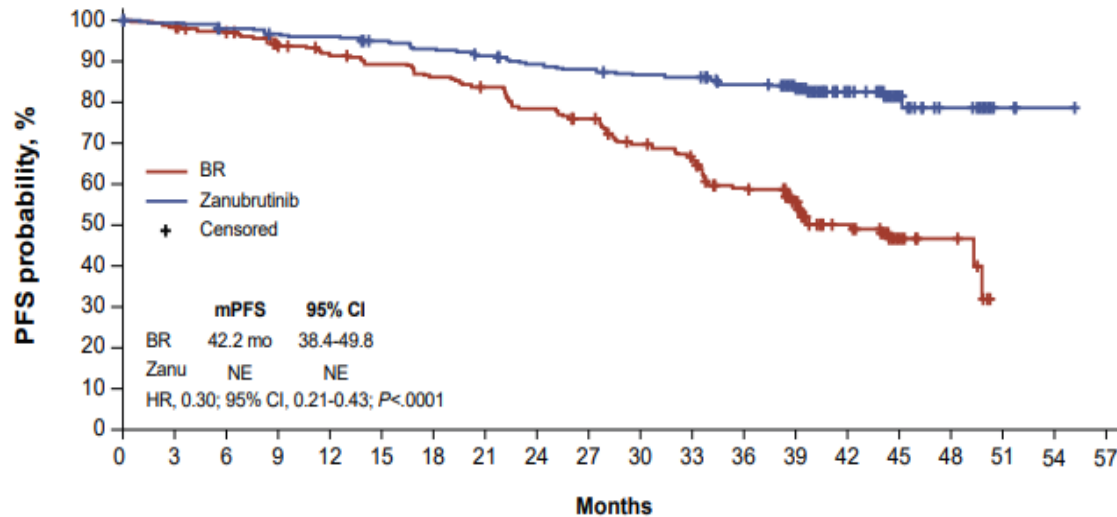
Bendamustine* + rituximab*

* 6 cycles

[^]Defined as Cumulative illness rating score > 6, CrCl < 70 mL/min, or a history of previous severe infection or multiple infections within the last 2 years; †6 cycles. FISH, fluorescence in situ hybridization.

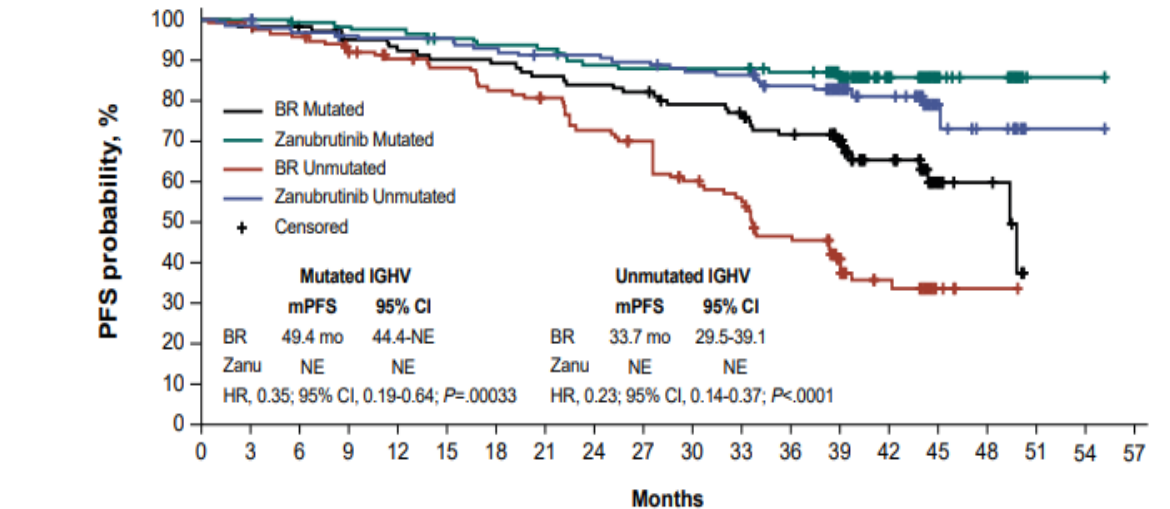
Median Follow-up 43.7 m

PFS, cohort 1, overall population



No. at risk, n	BR	238	218	212	201	192	187	180	174	163	157	141	133	113	82	50	18	8	0	
Zanubrutinib	241	238	234	230	228	224	219	214	208	205	201	200	190	131	93	33	23	4	3	0

PFS, cohort 1, mutated and unmutated IGHV, overall population



No. at risk, n	BR Mutated	110	101	99	94	91	89	88	85	83	81	76	73	67	53	31	14	7	0	
Zanubrutinib Mutated	109	109	107	106	105	101	99	98	93	92	92	92	89	63	43	18	13	1	1	0

Zanubrutinib in TN CLL (Sequoia study)

Cohort 1

- Untreated CLL/SLL
- ≥ 65 y of age OR unsuitable for treatment with FCR[^]
- Without del(17p) by central FISH

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Zanubrutinib

Bendamustine* + rituximab*

Median Follow-up 43.7 m

	Patients without del(17p)				Patients with del(17p)	
	Arm A: zanubrutinib (n=240) ^a		Arm B: BR (n=217) ^b		Arm C: zanubrutinib (n=111)	
AEIs, n (%)	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Infections	175 (72.9)	57 (23.8)	142 (62.6)	50 (22.0)	89 (80.2)	30 (27.0)
Bleeding	117 (48.8)	14 (5.8)	28 (12.3)	4 (1.8)	64 (57.7)	6 (5.4)
Other malignancies	45 (18.8)	22 (9.2)	28 (12.3)	11 (4.8)	27 (24.3)	8 (7.2)
Hypertension	42 (17.5)	22 (9.2)	31 (13.7)	15 (6.6)	15 (13.5)	7 (6.3)
Diarrhea	41 (17.1)	4 (1.7)	32 (14.1)	5 (2.2)	22 (19.8)	1 (0.9)
Neutropenia	40 (16.7)	30 (12.5)	129 (56.8)	116 (51.1)	21 (18.9)	18 (16.2)
Arthralgia	37 (15.4)	2 (0.8)	23 (10.1)	1 (0.4)	26 (23.4)	1 (0.9)
Anemia	17 (7.1)	1 (0.4)	47 (20.7)	5 (2.2)	7 (6.3)	0 (0)
Thrombocytopenia	15 (6.3)	5 (2.1)	41 (18.1)	18 (7.9)	9 (8.1)	2 (1.8)
Atrial fibrillation/flutter	12 (5.0)	3 (1.3)	6 (2.6)	3 (1.3)	7 (6.3)	5 (4.5)
Myalgia	9 (3.8)	0 (0)	4 (1.8)	0 (0)	8 (7.2)	1 (0.9)
Opportunistic infection	6 (2.5)	1 (0.4)	4 (1.8)	3 (1.3)	1 (0.9)	1 (0.9)

* 6 cycles

BTKi AEs in first line tx

	Ibrutinib ¹ (N=136)	Acalabrutinib ² (N=179)	Zanubrutinib ³ (N=240)
Median age	73 (65-89)	70 (44-87)	70 (66-75)
Median treatment duration, months	48	46.9	43.7
Ongoing Treatment	65%	69.3%	75%
Discontinuations due to AE	19%	12.3%	15%
Atrial fibrillation			
All grades	13%	6%	5%
Hypertension			
All grades	21%	7.3%	17.5%
Grade ≥3	7%	2.8%	9.2%
Bleeding			
All grades	nr	41.9%	49%
Major	10%	2.8%	6%

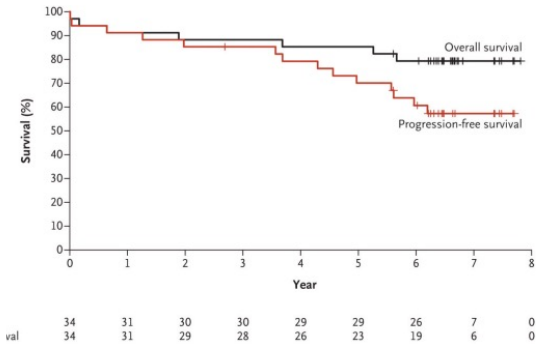
This slide includes data from different clinical trials. These data are meant for demonstration purposes only and are not meant for cross-trial comparison purposes.

AE, adverse event; BTKi, Bruton's tyrosine kinase inhibitor; NR, not reported.

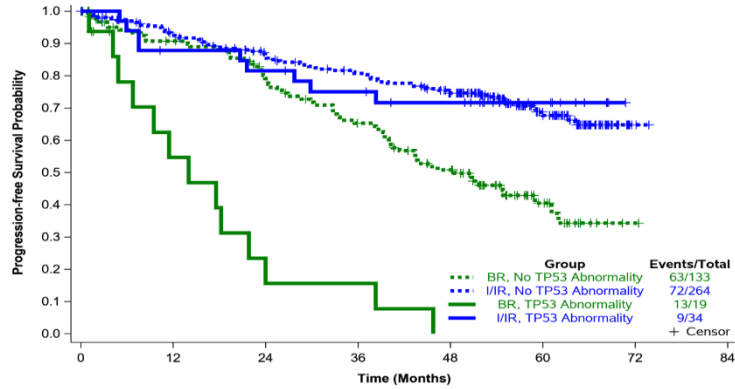
1. Burger et al EHA 2018., Sharman JP *et al. Hemasphere* 2022. 3. Munhir T et al EHA 2023

BTKi Covalent BTKi in del(17p)/TP53^{mut} CLL

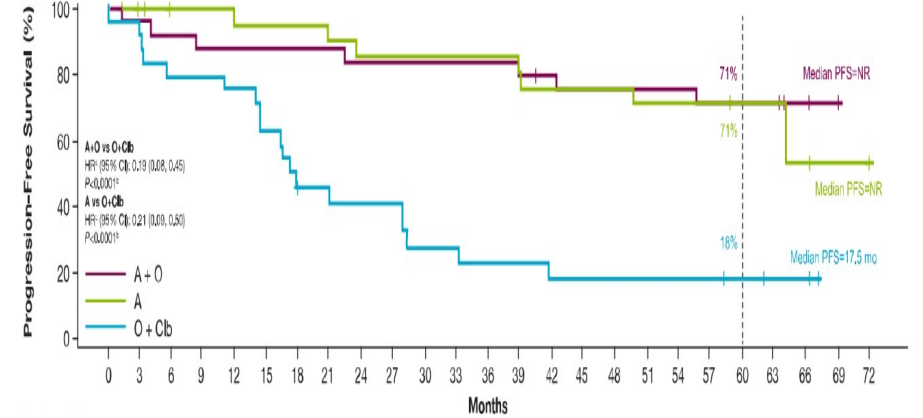
Phase II trial:
Ibrutinib monotherapy¹
Median FU: 6.5 years



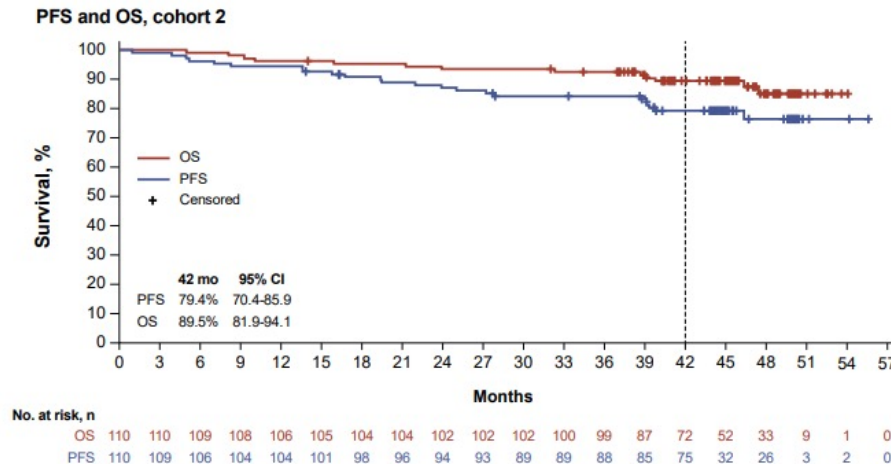
ALLIANCE:
Ibrutinib vs. IR vs. BR²
Median FU: 55 months



ELEVATE TN:
Acalabrutinib vs. AO vs. O + Clb³
Median FU: 58.2 months



SEQUOIA arm C:
Zanubrutinib monotherapy⁴
Median FU: 47.9 months



1. Ahn IE *et al.* *N Engl J Med* 2020; 383 (5): 498–500.
2. Woyach J *et al.* Oral presentation at ASH 2021
3. Sharman JP *et al.* Oral presentation at ASCO 2022
4. Munhhir *et al.* *EHA 2023*

CLL first Line: venetoclax obinutuzumab

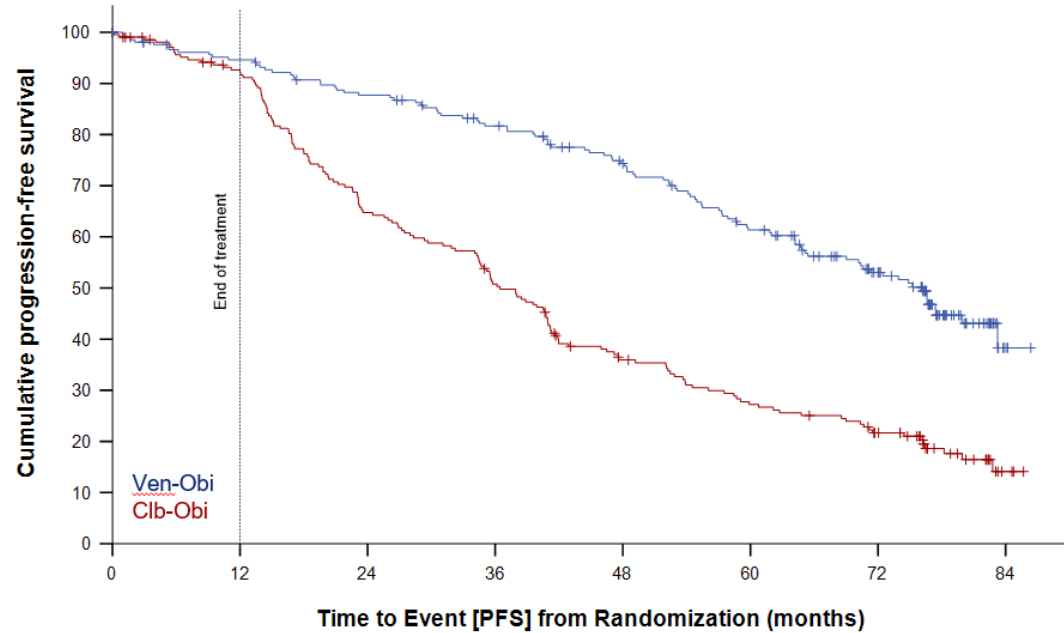
CLL 14

Venetoclax Obinutuzumab versus Chlorambucil Obinutuzumab

Median follow-up 76.4 months

CIRS score >6
CrCl <70 mL/min

PROGRESSION-FREE SURVIVAL



Ven-Obi 216
Clb-Obi 216

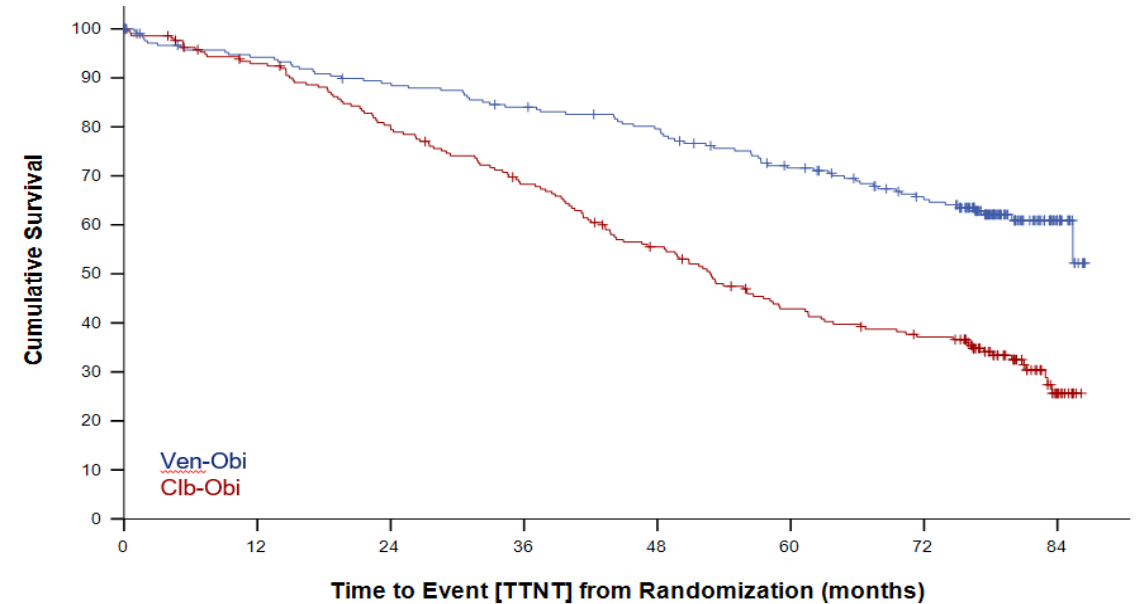
Median PFS
Ven-Obi: 76.2 months
Clb-Obi: 36.4 months

6-year PFS rate
Ven-Obi: 53.1%
Clb-Obi: 21.7%

HR 0.40, 95% CI [0.31-0.52] P<0.0001

TIME TO NEXT TREATMENT

Defined as time to death or next-antileukemic treatment

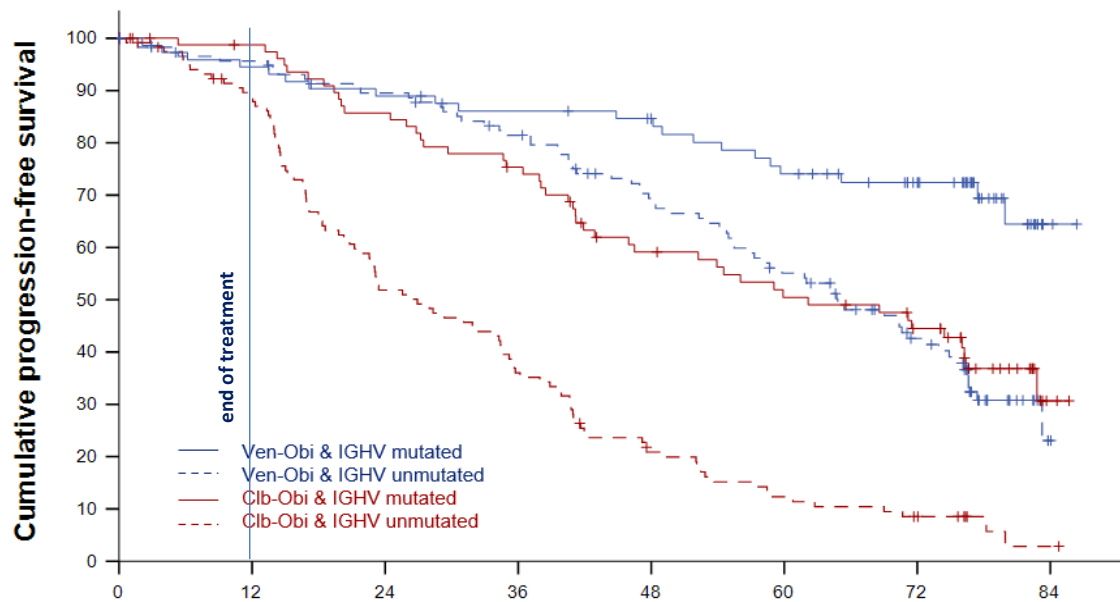


Ven-Obi 216
Clb-Obi 216

Median TTNT
Ven-Obi: not reached
Clb-Obi: 52.9 m

6-year TTNT rate
Ven-Obi: 65.2%
Clb-Obi: 37.1%

PROGRESSION-FREE SURVIVAL – IGHV status



Time to Event [PFS] from Randomization (months)

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

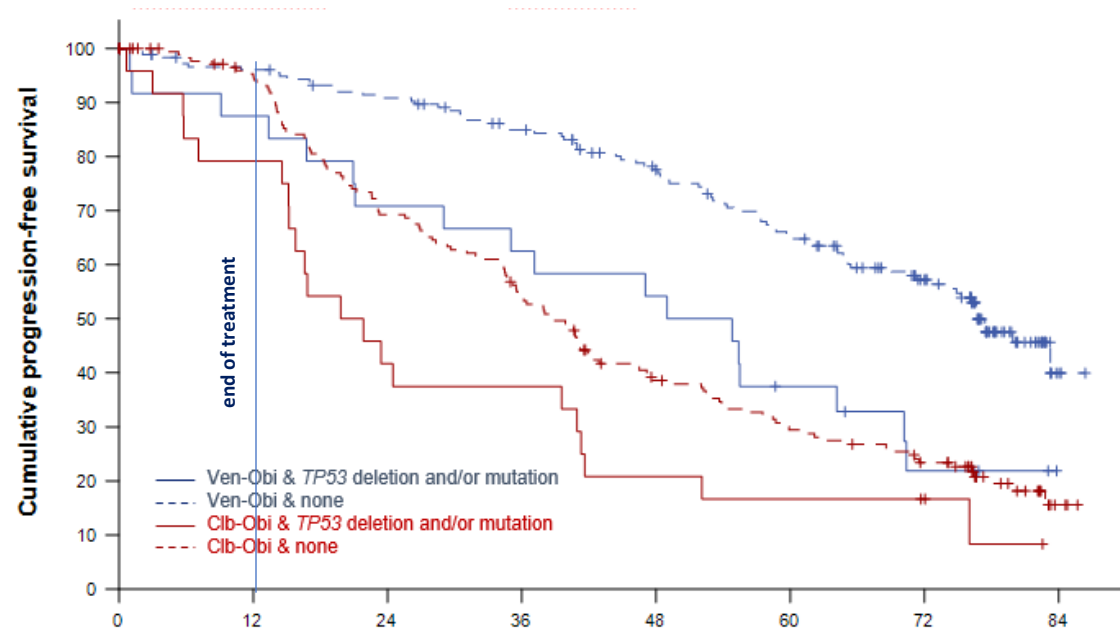
Median PFS

Ven-Obi & IGHVmut: NR
 Ven-Obi & IGHVunmut: 64.8 m
 HR 0.38, 95%CI [0.23-0.61], p<0.001

Median PFS

Clb-Obi & IGHVmut: 62.2 m
 Clb-Obi & IGHVunmut: 26.9 m
 HR 0.33, 95% CI [0.23-0.47], p<0.001

PROGRESSION-FREE SURVIVAL – TP53



Time to Event [PFS] from Randomization (months)

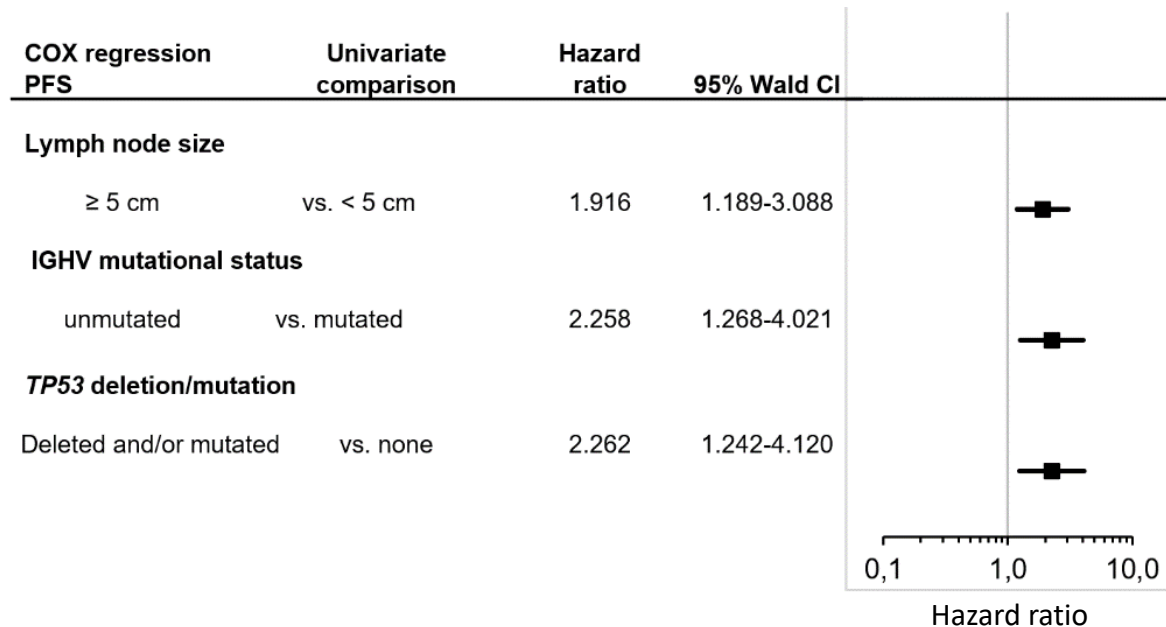
Ven-Obi & TP53 del/mut	25	21	17	15	13	8	4	0
Ven-Obi & none	184	168	157	142	123	101	73	3
Clb-Obi & TP53 del/mut	24	19	10	9	5	4	3	0
Clb-Obi & none	184	160	117	90	60	45	33	3

Median PFS

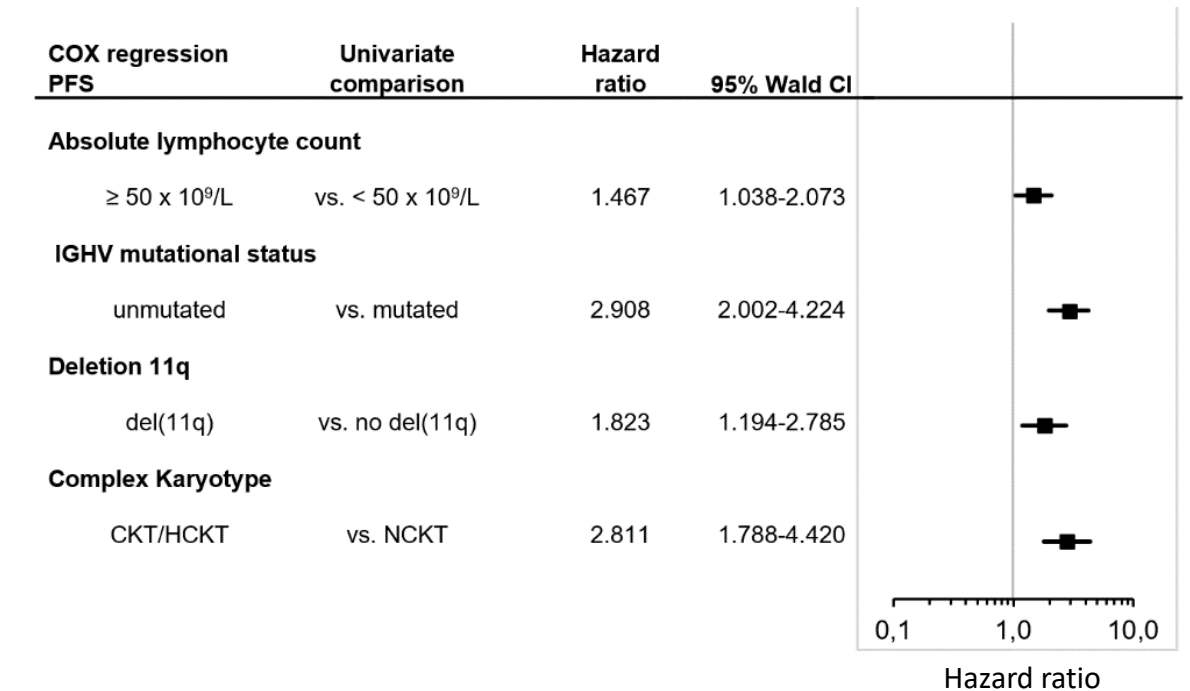
Ven-Obi & no TP53del/mut: 76.6 m
 Ven-Obi & TP53del/mut: 51.9 m
 HR 2.29, 95% CI [1.37-3.83], p=0.001

Clb-Obi & no TP53del/mut: 38.9 m
 Clb-Obi & TP53del/mut: 20.8 m
 HR 1.66, 95% CI [1.05-2.63], p=0.03

Ven-Obi



Clb-Obi



In the context of Ven-Obi, max. lymph node size ≥ 5 cm, unmutated IGHV and TP53 deletion/mutation are independent negative prognostic factors for PFS.

Dose modifications and discontinuations due to adverse events

Most frequent ≥ grade 3 adverse events

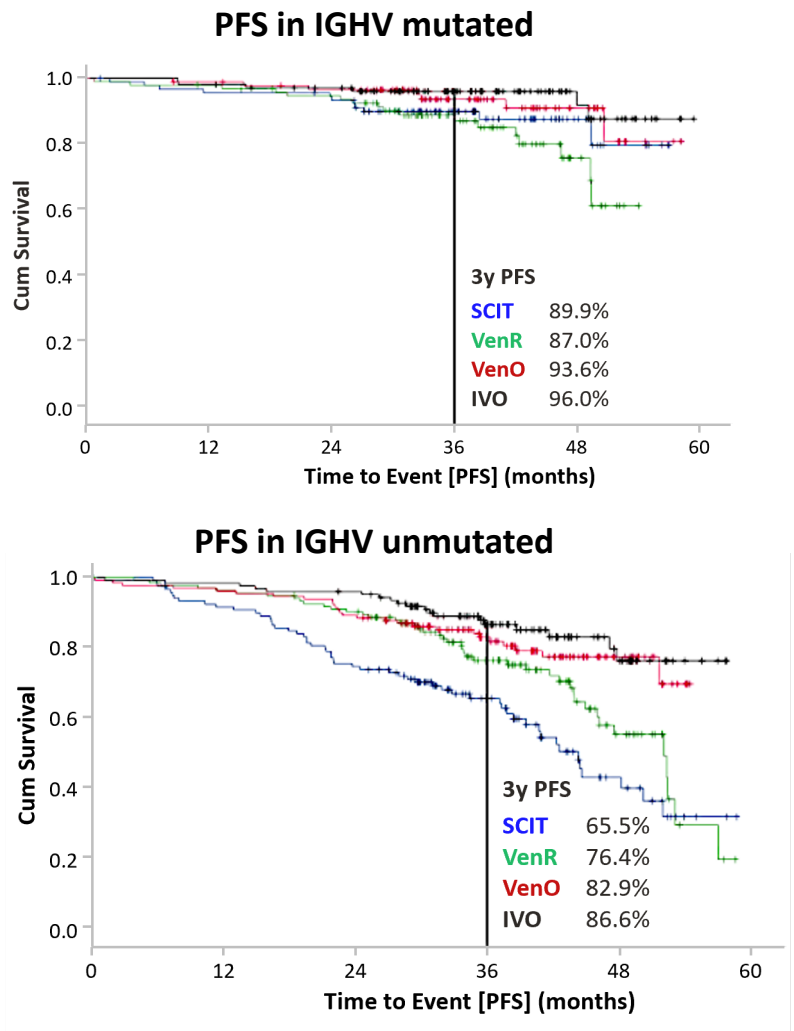
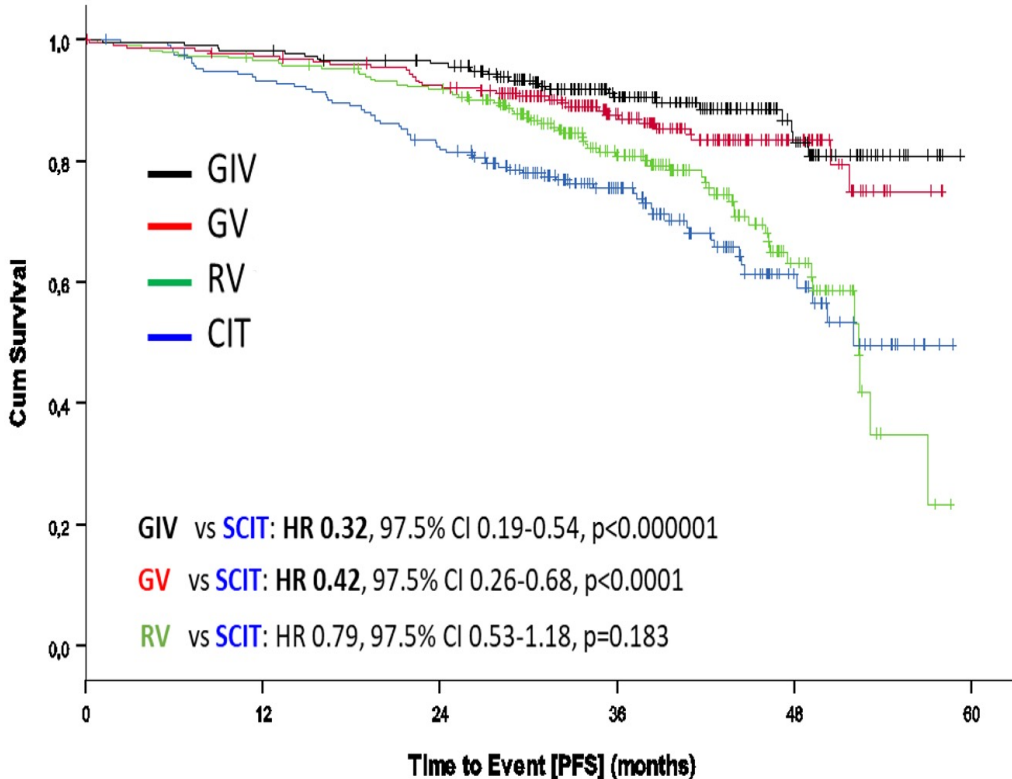
Patients	VenO arm (venetoclax) n=212	OC1b arm (chlorambucil) n=214
Dose reduction due to AE, n (%)¹	43 (20)	17 (8)
Due to neutropenia [most common cause]	28 (13)	13 (6)
Treatment-emergent (VenO or OC1b) AE leading to treatment discontinuation, n (%)¹	33 (16)	35 (16)
Treatment discontinuation due to any AE, n (%)¹	27 (13)	31 (15)
Due to neutropenia [most common cause]	5 (2)	5 (2)
Median dose intensity, % (range)^{*.2}	95.1 (21–100)	95.4 (4–111)

	Venetoclax-obinutuzumab (N=212)	
	During Treatment	After Treatment
Neutropenia	51.9%	3.8%
Thrombocytopenia	14.2%	0.5%
Anemia	7.5%	1.9%
Febrile neutropenia	4.2%	0.9%
Leukopenia	2.4%	0.0%
Pneumonia	3.8%	3.3%
Infusion-related reaction	9.0%	0.0%
Tumour lysis syndrome	1.4%	0.0%

GAIA/CLL13 evaluated 3 time-limited Ven-based 1L regimens vs. CIT in fit pts with CLL

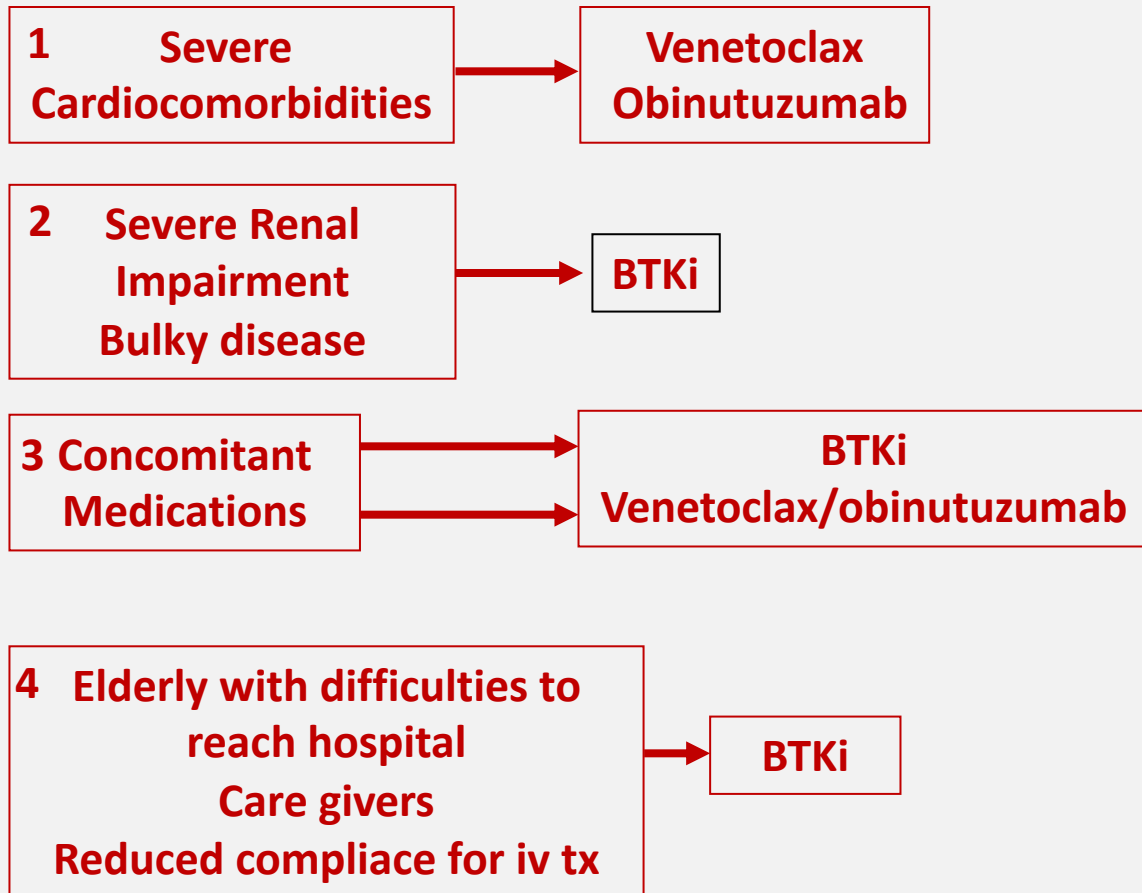
FIT pts
No del17p/TP53mut

- FCR ≤65 yrs or BR >65 yrs
- Ibruinib Venetoclax Obinutuzumab 12 cycles
- Venetoclac Obinutuzumab 12 cycles
- Venetoclax Rituximab 12 cycles



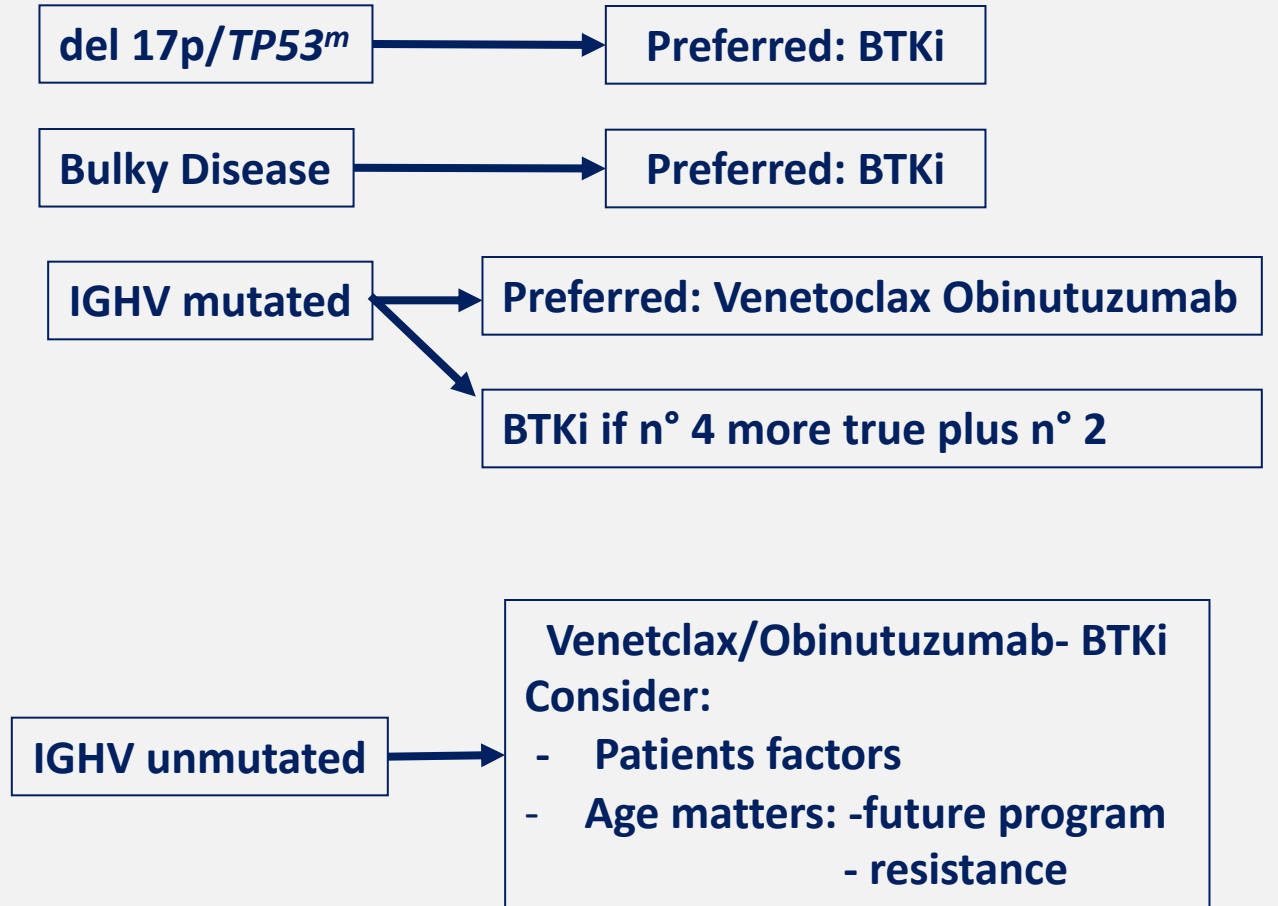
PERSONAL CONSIDERATION (WHILE WAITING CLL17)

PATIENTS FACTORS



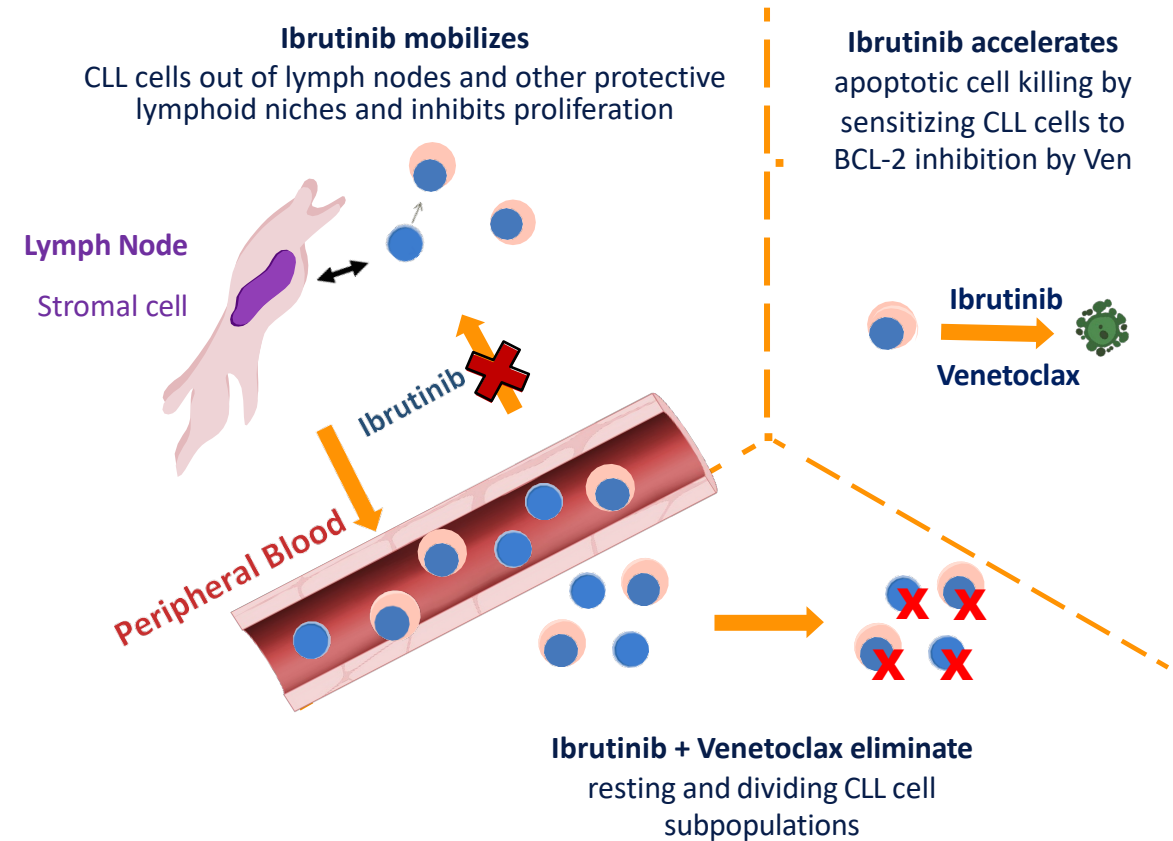
DISEASE FACTORS

Consider patients factors



FIXED DURATION IBRUTINIB VENETOCLAX COMBINATION

- Ibr + Ven preferentially target complementary cell compartments and CLL subpopulations to eliminate both dividing and resting CLL cells¹⁻³
 - Ibrutinib, a once-daily oral Bruton tyrosine kinase inhibitor, is the only targeted therapy to demonstrate significant OS benefit in randomized phase 3 studies in first-line CLL/SLL^{4,5}
 - Venetoclax, an oral BCL-2 inhibitor approved for the treatment of CLL as a single agent or in combination with anti-CD20 monoclonal antibodies, achieves high rates of uMRD⁶
 - This combination regimen was recently approved in the EU for patients with previously untreated CLL⁷



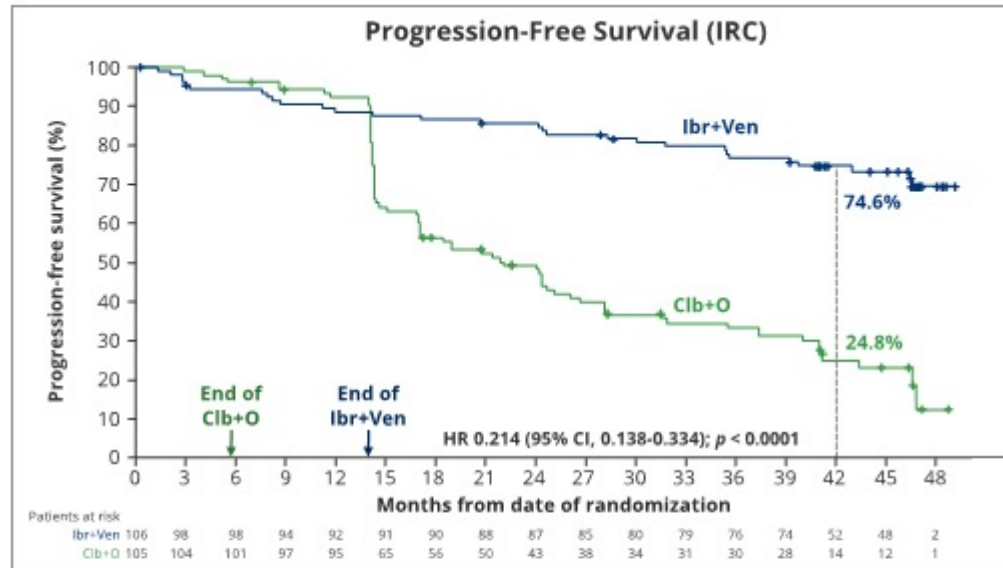
Ibrutinib Venetoclax Fixed Duration

Glow FD: Ibr+Ven vs Chl O

106 pts ≥65 y or unfit (no del17p)

CR 38.7%

uMRD PB: 54.7%



GLOW TRIAL: 46 months follow-up

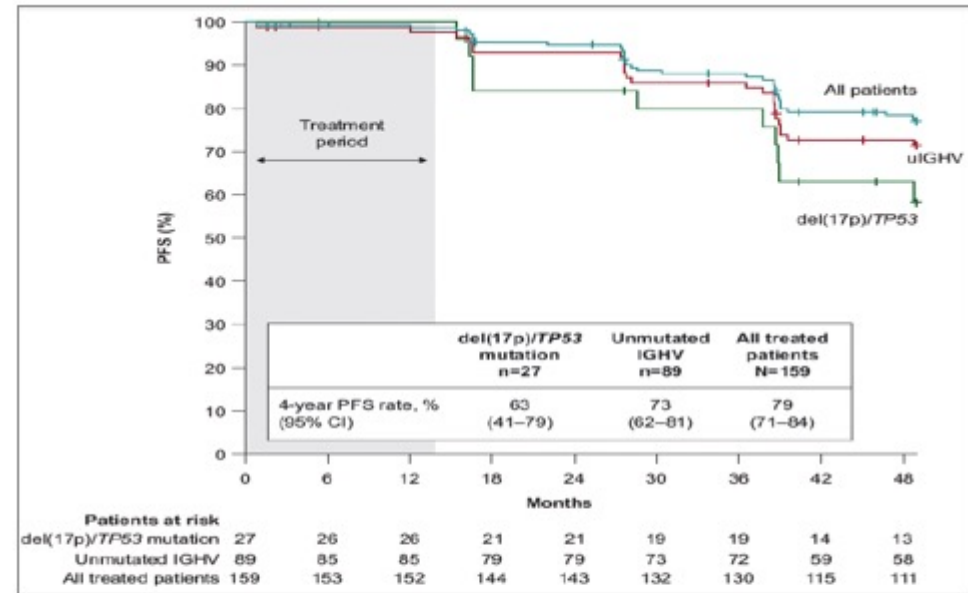
4-yr estimated PFS: 74.6% vs 24.8%

Captivate FD: Ibr+Ven

159 pts ≤ 70 y

CR 58%

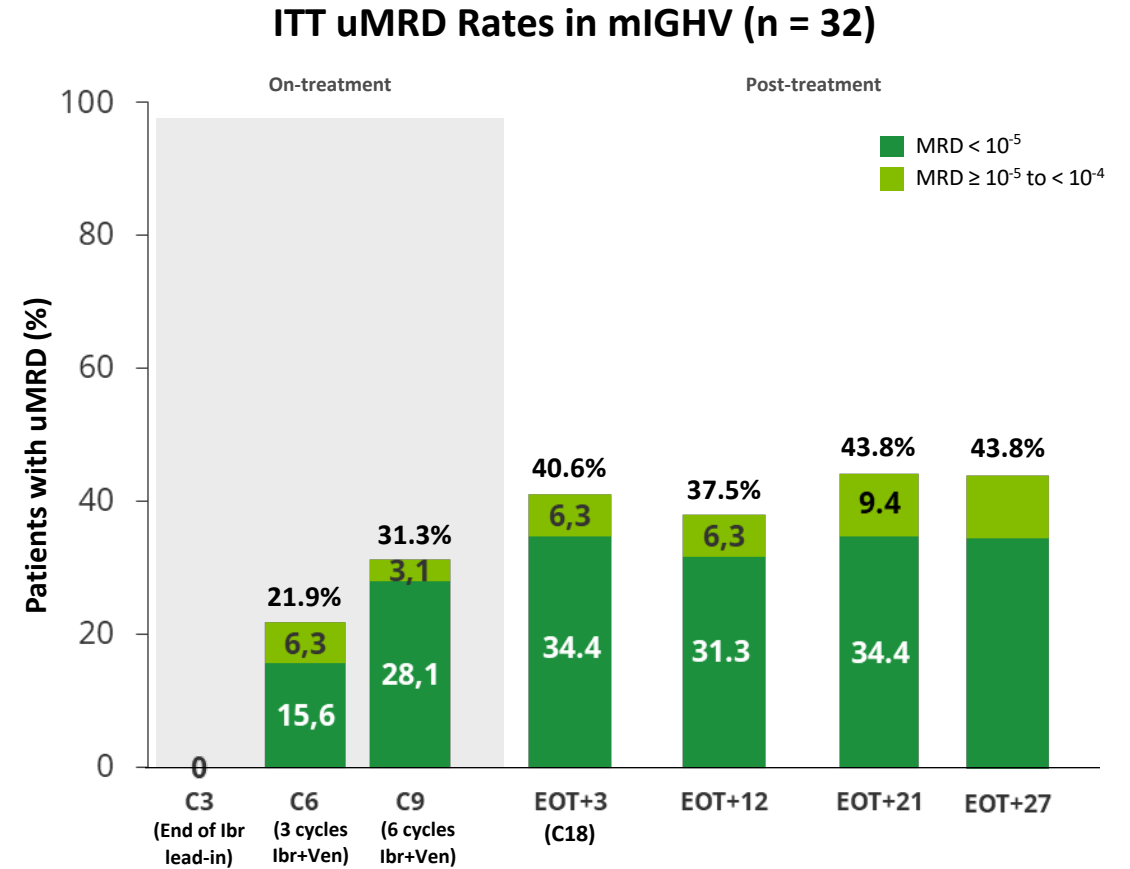
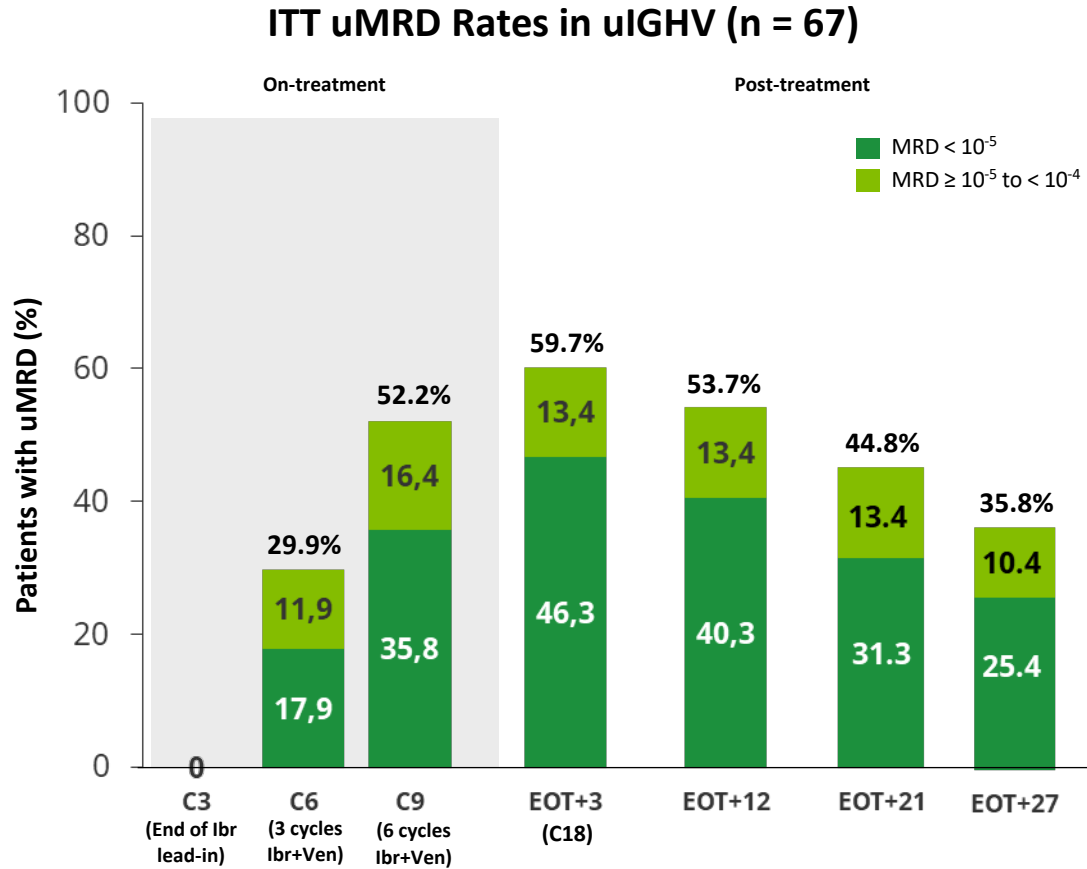
uMRD PB: 57%



CAPTIVATE FD: 48 months follow-up

4-yr PFS: 79%

GLOW: Ibr+Ven On-treatment and Post-treatment uMRD Dynamics According to IGHV Status



- uMRD rates (including < 10⁻⁵) were higher and uMRD was achieved faster in patients with uIGHV versus mIGHV CLL
- uMRD was better sustained post-treatment in patients with mIGHV CLL

Phase 3 Clinical Trials in R/R CLL

Study	Arm	Treatment duration			Key eligibility criteria				Key patient demographics		
		6 m	2 y	PD	Prior Tx, n	ECOG PS, score	CrCl, mL/min	Median age, years	Median prior Tx, n (range)	del(17p), %	
RESONATE ^{1,2}	Ibr	●	→	→	≥1 (unsuitable for purine analogs)	0-1	NS	67	3 (1-12)	32	
	Ofa	●	→	→							
ASCEND ³	Acala	●	→	→	≥1 systemic (no prior BCL-2 Tx)	0-2	≥30	68	1 (1-8)	17	
	IdR/BR	●	→	→							
ELEVATE-RR ⁴	Acala	●	→	→	≥1 (no prior BTKi, PI3Ki, or BCL-2i)	0-2	≥30	66	2 (1-9)	45.1 [†]	
	Ibr	●	→	→							
ALPINE ⁵	Zanu	●	→	→	≥1 (no prior BTKi)	0-2	NS	67	1 (1-6)	13.8 [‡]	
	Ibr	●	→	→							
MURANO ⁶⁻⁹	VenR	●	→	→	1-→3 (≥1 CIT); prior B if DoR ≥24 months (not BR refractory/resistant)	0-1	NS	64.5	1 (1-5)*	26.6	
	BR	●	→	→							

BCRi
 Venetoclax

Acala, acalabrutinib **Ofa**, ofatumumab
B, bendamustine **R**, rituximab
I, ibrutinib **Ven**, venetoclax
Id, idelalisib **Zanu**, zanubrutinib

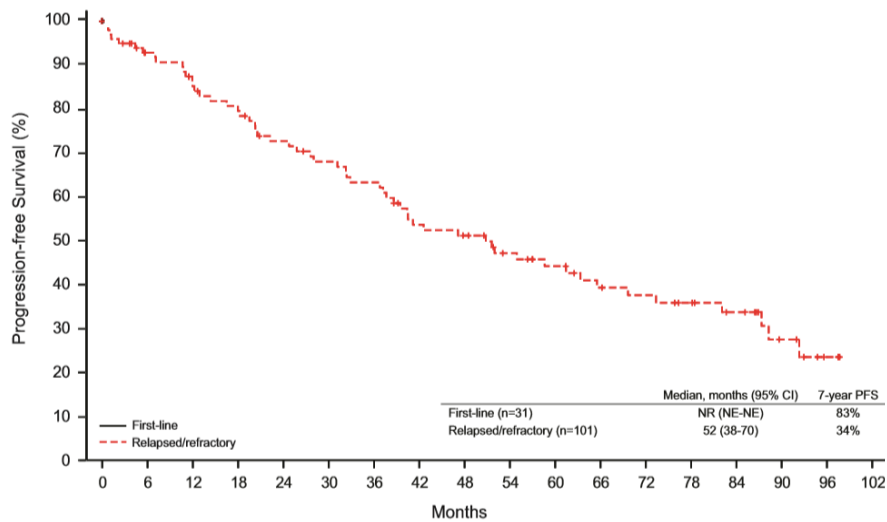
1. Byrd JC, et al. *N Engl J Med* 2014; **372**:213-223; 2. Byrd JC, et al. *Blood* 2019; **133**:2031-2042;
 3. Ghia P, et al. EHA 2022. Abstract 668 (Poster); 4. Byrd JC, et al. *J Clin Oncol* 2021; **39**:3441-3452 (incl. suppl.);
 5. Brown JR, et al. *N Engl J Med* 2022; doi: 10.1056/NEJMoa2211582.
 6. Seymour JF, et al. *N Engl J Med* 2018; **378**:1107-1120 (incl. suppl.); 7. Seymour JF, et al. *Blood* 2022; **140**:839-850;
 8. Venclyxto® (venetoclax). EMA SmPC (May 2020 update); 9. Kater AP, et al. ASH 2020. Abstract 125 (Oral);

* Data from SmPC; † By central laboratory testing was an inclusion criterion for this study;
 ‡ del(17p) with or without TP53 mutation.

Ibrutinib in relapsed refractory patients

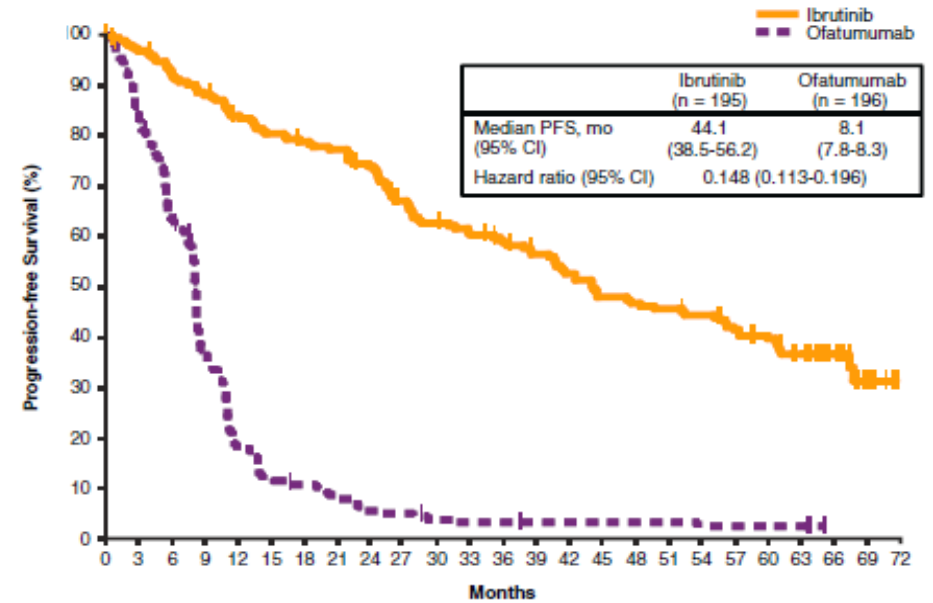
Pivotal Phase Ib/II PCYC-1102 Study in R/R CLL Up to 8 years of Follow-up

	Ibrutinib n=101
Prior Tx ≥ 4	59%
IGHV unmutated	78%
del(17p)	34%



Final analysis from RESONATE Trial in R/R CLL Up to 6 years follow-up Ibrutinib vs Ofatumumab

	Ibrutinib n=195
Prior Tx ≥ 3	53%
IGHV unmutated	73%
del(17p)	34%
TP53 ^{mut}	51%

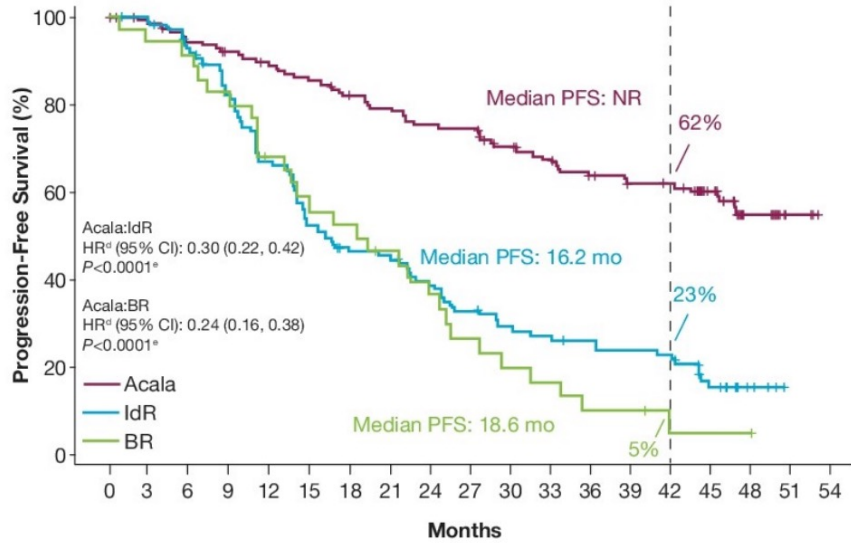




Acalabrutinib in relapsed refractory patients

Phase III ASCEND Trial in RR CLL
Acalabrutinib vs Idelalisib + Rituximab or BR
4 years Follow-up

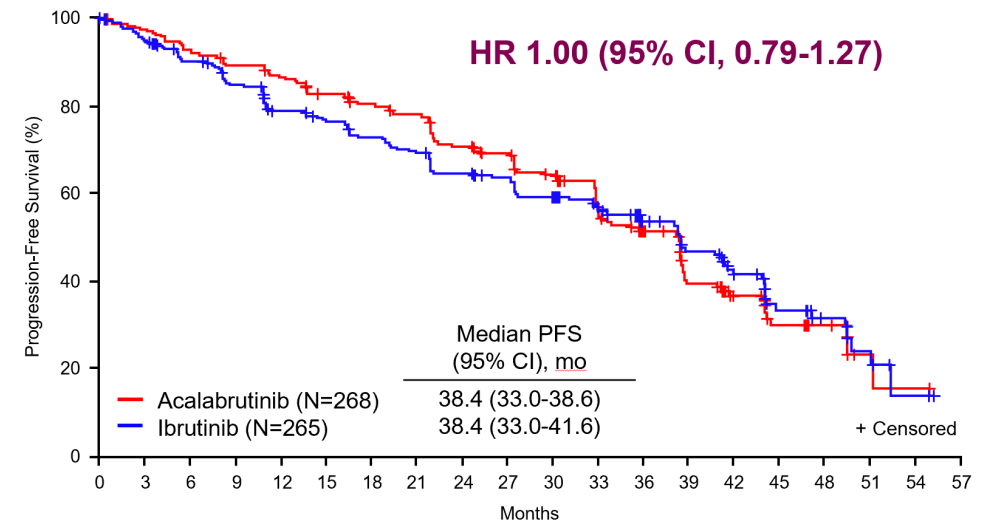
	Acalabrutinib n=101
Median Prior Tx	1 (1-8)
IGHV unmutated	70.3%
del(17p)	17.4%



Number at risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
Acala	155	151	143	139	133	128	121	117	111	110	100	94	85	80	79	52	21	4	0
IdR	119	114	106	90	73	57	49	48	40	34	29	27	25	23	22	11	4	0	0
BR	36	33	32	28	22	19	17	14	12	8	6	5	3	3	1	1	1	0	0

Phase III Elevate RR CLL
Acalabrutinib vs Ibrutinib only del17p del11q
40.9m median Follow-up

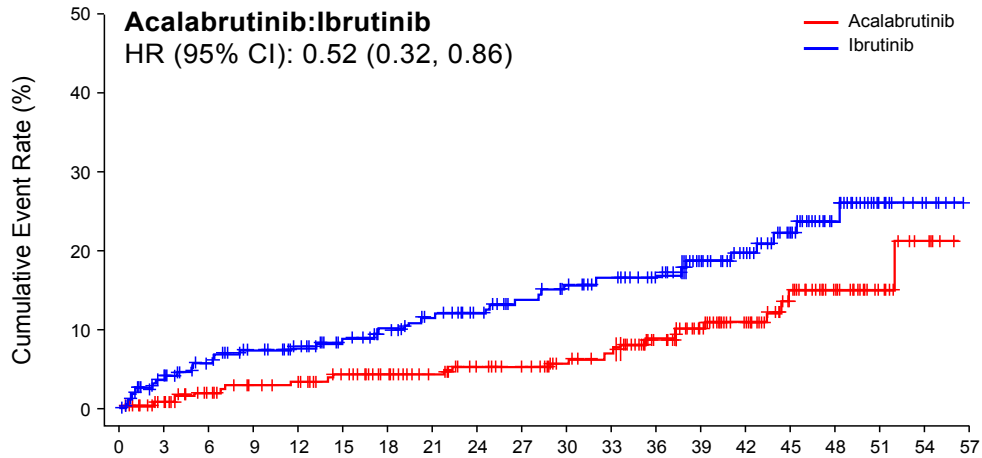
	Acalabrutinib n=268	Ibrutinib N=265
Median Prior Tx	2 (1-9)	2 (1-12)
IGHV unmutated	82%	83%
del(17p)	45.1%	45.3%



Number at risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57
Acalabrutinib	268	250	235	227	219	207	200	193	173	163	148	110	84	59	31	21	13	3	1	0
Ibrutinib	265	240	221	205	186	178	168	160	148	142	130	108	81	66	41	26	15	8	2	0

ELEVATE RR: Secondary Endpoints

ITT Population	Acalabrutinib (N=266)	Ibrutinib (N=263)	Difference in TEAE Incidence Rates [A-I], %	P-value
Atrial fibrillation/flutter, all grades, n (%) 95% CI ^a	25 (9.4) (6.4, 13.5)	42 (16.0) (12.0, 20.9)	-6.6 (-12.2, -0.9)	0.0228
Subgroup analysis				
			Acalabrutinib	Ibrutinib
			15/243 (6.2)	37/249 (14.9)
Infections, grade ≥3, n (%) 95% CI ^a	82 (30.8) (25.6, 36.6)	79 (30.0) (24.8, 35.8)	+0.8 (-7.1, +8.6)	0.8777
Richter's transformation, n (%) 95% CI ^a	10 (3.8) (2.1, 6.8)	13 (4.9) (2.9, 8.3)	-1.2 (-4.7, +2.3)	0.5131

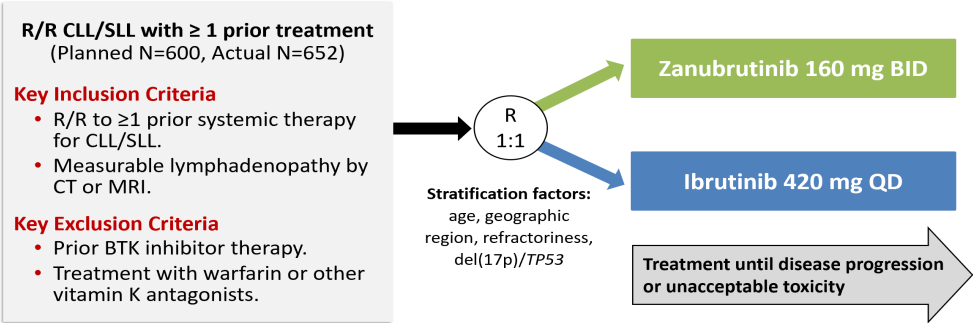


^a≥5% difference between arms are highlighted; **green** favors acalabrutinib, **red** favors ibrutinib.
^b95% confidence interval based on Normal approximation (with use of Wilson's score). ^cBased on Cochran-Mantel-Haenszel test stratified by del(17p) status (yes vs no) and number of prior therapies (1-3 vs ≥4).



ZANUBRUTINIB IN RELAPSED REFRACTORY PATIENTS

Alpine Phase III Trial In R/R CLL

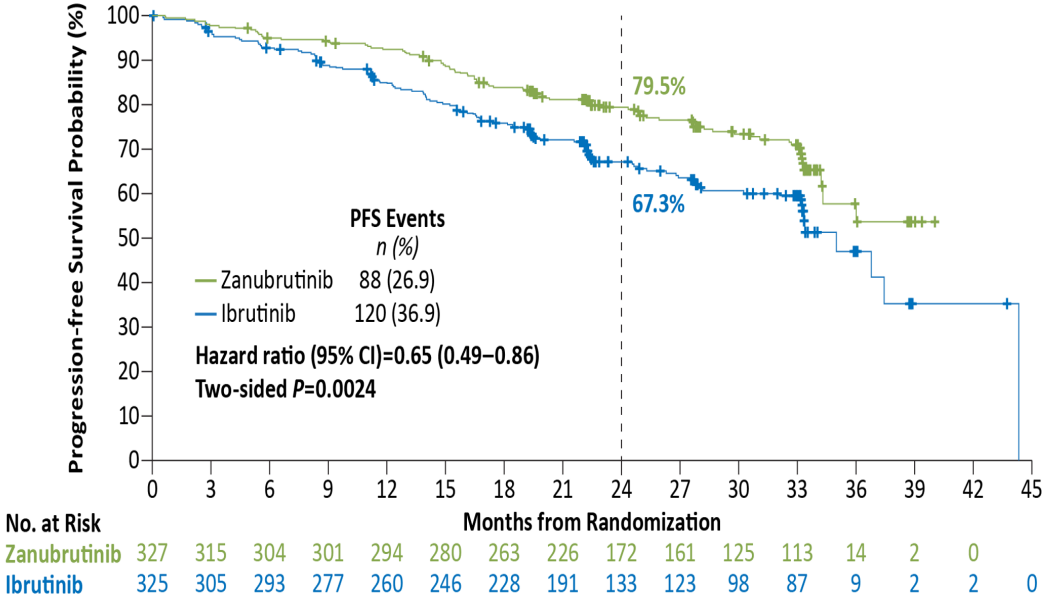


Median FU: 29.6 m

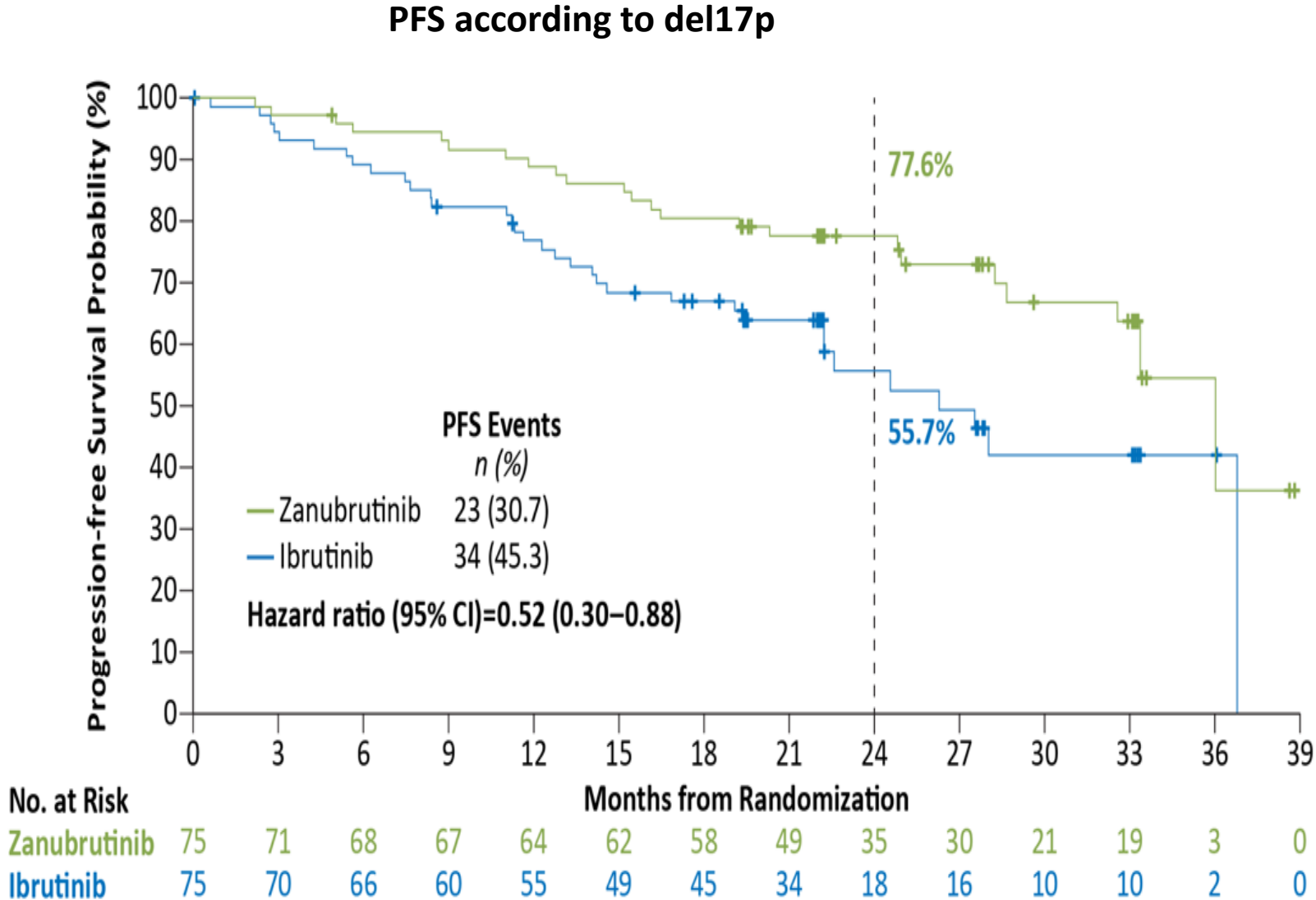
	Zanubrutinib (n=327)	Ibrutinib (n=325)
Age, median (range)	67 (35-90)	68 (35-89)
≥65 years, n (%)	201 (61.5)	200 (61.5)
Male, n (%)	213 (65.1)	232 (71.4)
ECOG PS ≥1, n (%)	198 (60.6)	203 (62.5)
Prior lines of systemic therapy, median (range)	1 (1-6)	1 (1-12)
>3 prior lines, n (%)	24 (7.3)	30 (9.2)
del(17p) and/or TP53^{mut}, n (%)	75 (22.9)	75 (23.1)
del(17p)	45 (13.8)	50 (15.4)
TP53 ^{mut} without del(17p)	30 (9.2)	25 (7.7)
del(11q), n (%)	91 (27.8)	88 (27.1)
IGHV mutational status, n (%)		
Mutated	79 (24.2)	70 (21.5)
Unmutated	239 (73.1)	239 (73.5)
Complex karyotype*	56 (17.1)	70 (21.5)
Bulky disease (≥5 cm), n (%)	145 (44.3)	149 (45.8)

*Complex karyotype is defined as having ≥3 abnormalities.

Progression Free Survival

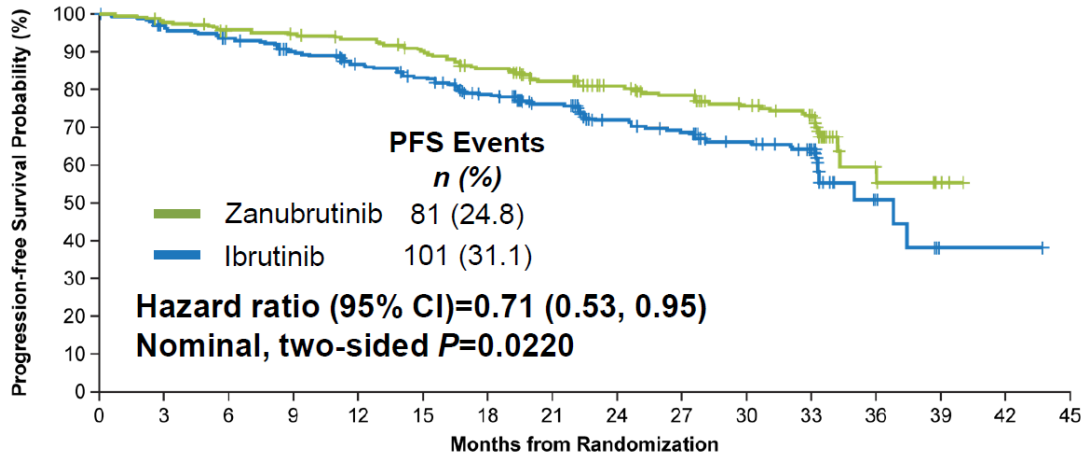


ALPINE: PFS according to del17p



ALPINE: PFS according to del17p

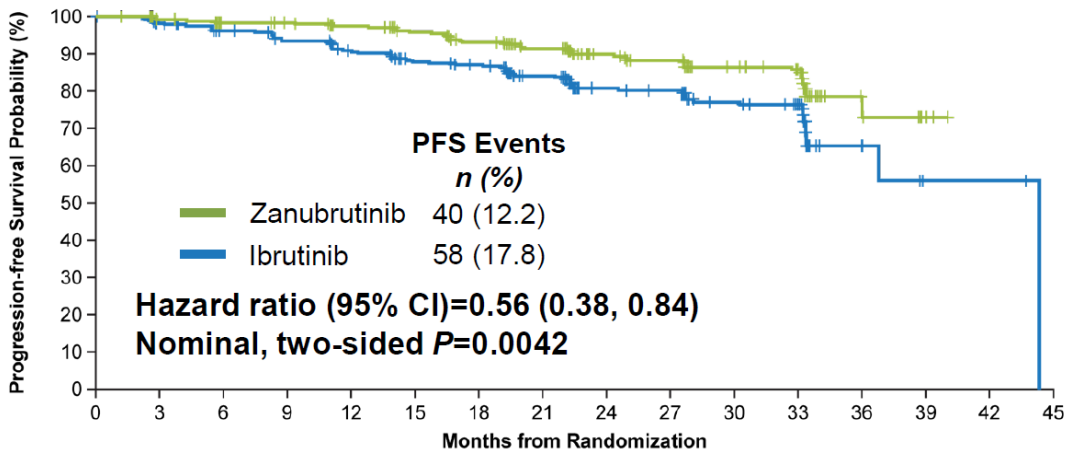
Drug Interruptions



No. of Patients at Risk

Zanubrutinib	327	313	303	299	292	279	264	224	169	159	124	113	14	2	0	
Ibrutinib	325	301	289	273	256	244	223	190	132	124	99	88	9	1	1	0

Treatment Discontinuation



No. of Patients at Risk

Zanubrutinib	327	308	298	294	283	271	258	222	164	156	119	111	14	2	0	
Ibrutinib	325	293	275	263	245	225	217	182	122	119	93	85	8	2	2	0

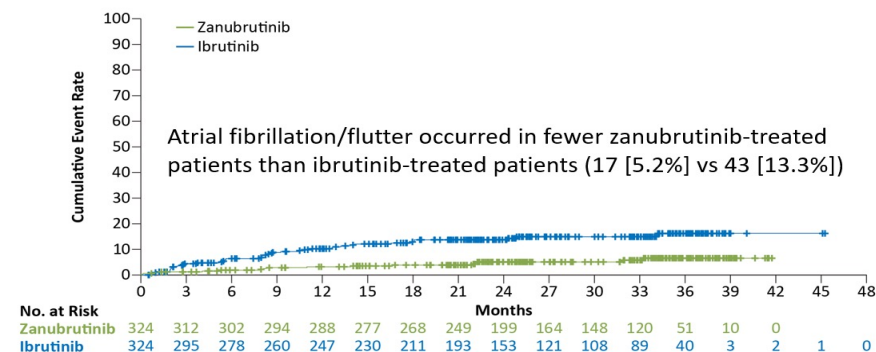
BTKi ALPINE: Safety data – Events of special interest

Adverse Events of special interest

AESI, n (%)	Any Grade		Grade ≥3	
	Zanubrutinib (n=324)	Ibrutinib (n=324)	Zanubrutinib (n=324)	Ibrutinib (n=324)
≥1 AESI	294 (90.7)	300 (92.6)	186 (57.4)	184 (56.8)
Anemia	50 (15.4)	53 (16.4)	7 (2.2)	8 (2.5)
Atrial fibrillation and flutter	17 (5.2)	43 (13.3)	8 (2.5)	13 (4.0)
Hemorrhage	137 (42.3)	134 (41.4)	11 (3.4)	12 (3.7)
Major hemorrhage	12 (3.7)	14 (4.3)	11 (3.4)	12 (3.7)
Hypertension	76 (23.5)	74 (22.8)	49 (15.1)	44 (13.6)
Infections	231 (71.3)	237 (73.1)	86 (26.5)	91 (28.1)
Opportunistic infection	7 (2.2)	10 (3.1)	5 (1.5)	5 (1.5)
Neutropenia†	95 (29.3)	79 (24.4)	68 (21.0)	59 (18.2)
Secondary primary malignancies	40 (12.3)	43 (13.3)	22 (6.8)	17 (5.2)
Skin cancers	21 (6.5)	28 (8.6)	7 (2.2)	4 (1.2)
Thrombocytopenia	42 (13.0)	50 (15.4)	11 (3.4)	17 (5.2)
Tumor lysis syndrome	1 (0.3)	0	1 (0.3)	0

Cardiovascular Events

	Zanubrutinib (n=324)	Ibrutinib (n=324)
Cardiac adverse events	69 (21.3%)	96 (29.6%)
Serious cardiac adverse events	6 (1.9%)	25 (7.7%)
Cardiac adverse events leading to treatment discontinuation	1 (0.3)	14 (4.3)
Ventricular extrasystoles	1 (0.3)	0
Atrial fibrillation	0	5 (1.5)
Cardiac arrest	0	2 (0.6)*
Cardiac failure	0	2 (0.6)
Cardiac failure acute	0	1 (0.3)*
Congestive cardiomyopathy	0	1 (0.3)*
Myocardial infarction	0	1 (0.3)*
Palpitations	0	1 (0.3)
Ventricular fibrillation	0	1 (0.3)

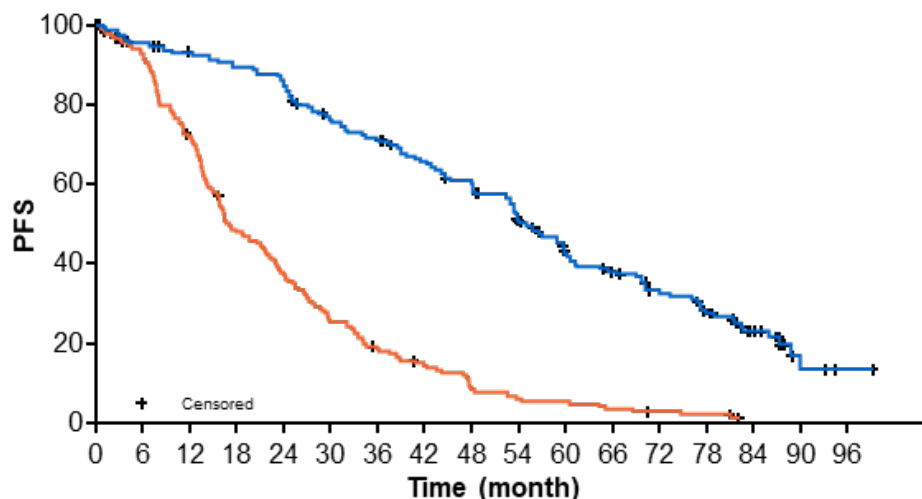


VENETOCLAX RITUXIMAB SALVAGE REGIMEN Phase III Murano study RR CLL: Venetoclax R versus Benda R

Characteristics		VenR (n=194)	BR (n=195)
del(17p) – central	Deleted	46/173 (26.6)	46/169 (27.2)
TP53 mutational	Mutated TP53	48/192 (25.0)	51/184 (27.7)
Number of prior therapies, n (%) ²	1	111 (57.2)	117 (60)
	2	58 (29.9)	43 (22.1)
	3 or >3	25 (12.0)	35 (17.9)

7 y follow-up

Progression Free Survival

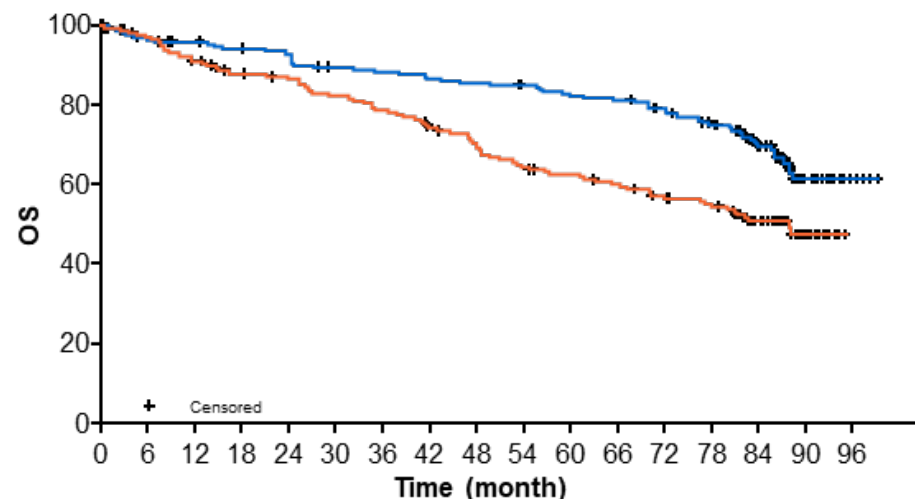


No. of Patients at Risk

— 194 190 185 179 176 174 170 167 161 150 142 136 133 125 119 111 107 102 88 79 68 63 57 54 46 45 37 34 19 14 4 4 1
— 195 178 166 144 129 104 85 80 68 56 45 40 32 27 24 21 14 13 10 9 9 8 6 5 4 3 3 2

	Median PFS (95% CI), months	HR* (95% CI)	7-year PFS (%)
VenR (n=194)	54.7 (52.3–59.9)	0.23 (0.18–0.29) Stratified P-value <0.0001†	23.0
BR (n=195)	17.0 (15.5–21.7)		NE

Overall Survival



No. of Patients at Risk

— 194 190 185 179 176 174 170 167 161 150 142 136 133 125 119 111 107 102 88 79 68 63 57 54 46 45 37 34 19 14 4 4 1
— 195 178 166 144 129 104 85 80 68 56 45 40 32 27 24 21 14 13 10 9 9 8 6 5 4 3 3 2

	Median OS (95% CI), months	HR† (95% CI)	7-year OS (%)
VenR (n=194)	NE	0.53 (0.37–0.74) Stratified P-value <0.0002†	69.6
BR (n=195)	87.8 (70.1–NE)		51.0

VENETOCLAX RITUXIMAB SALVAGE REGIMEN

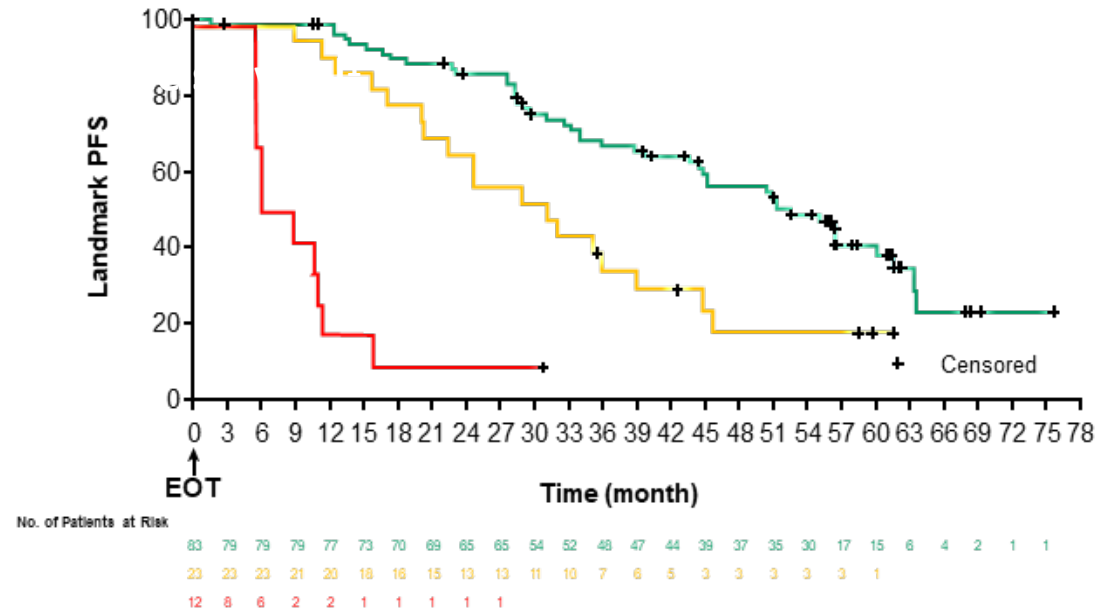
Phase III Murano study RR CLL: Venetoclax R versus Benda R

PFS according to MRD status

Time To Next anti-leukaemic Treatment (TTNT)

	Median TTNT (95% CI), months	HR* (95% CI)
VenR	63.0 (56.1–73.6)¹	0.30 (0.23–0.39) Stratified P-value
BR	24.0 (20.7–29.5)¹	<0.0001^{1†}

VenR-treated patients who completed 2 years of Ven without PD	Median PFS since EOT (95% CI), months	HR* (95% CI)
uMRD (n=83)	52.5 (44.5–61.5)	4.47 (2.39–8.36)
MRD+ (n=35)	18.0 (8.5–29.3)	Stratified P-value <0.0001[†]

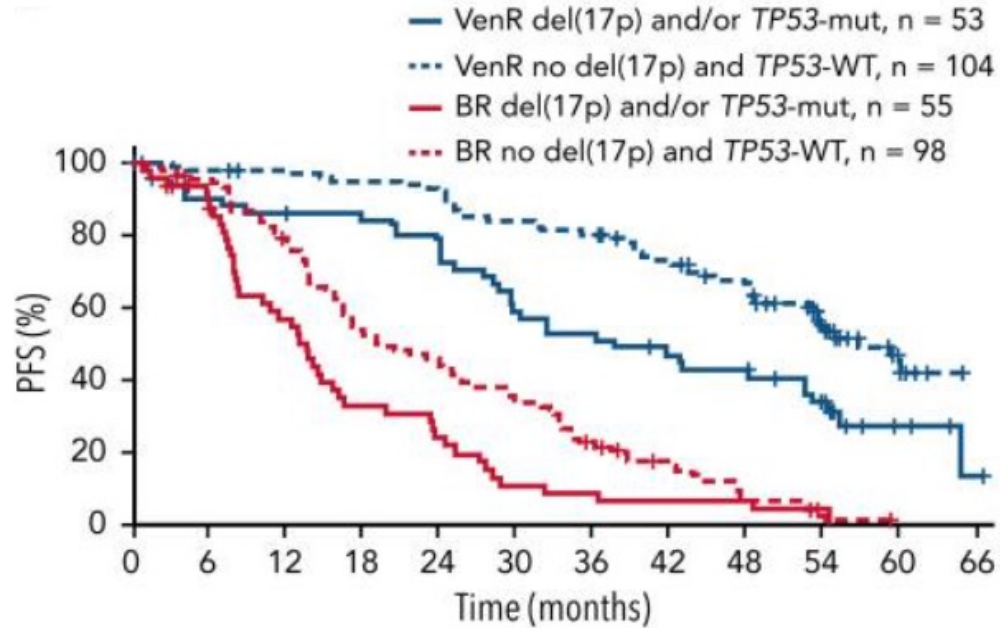


Favorable baseline characteristics were over-represented among patients with enduring uMRD

Phase III Murano study RR CLL: Venetoclax R versus Benda R

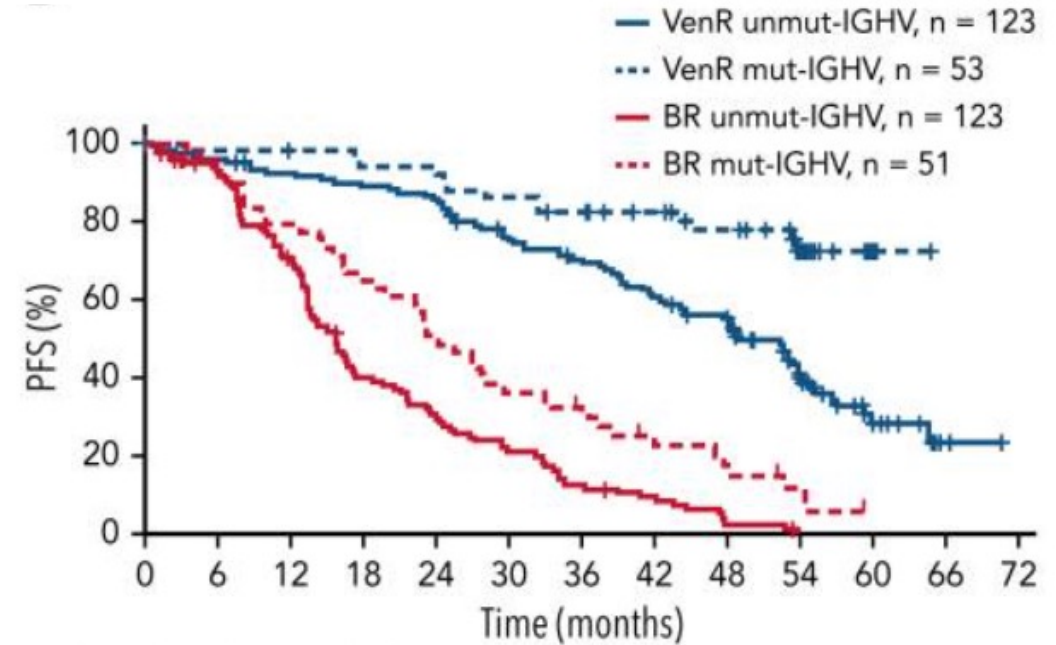
Median study follow-up 59.2 m

PFS del17p

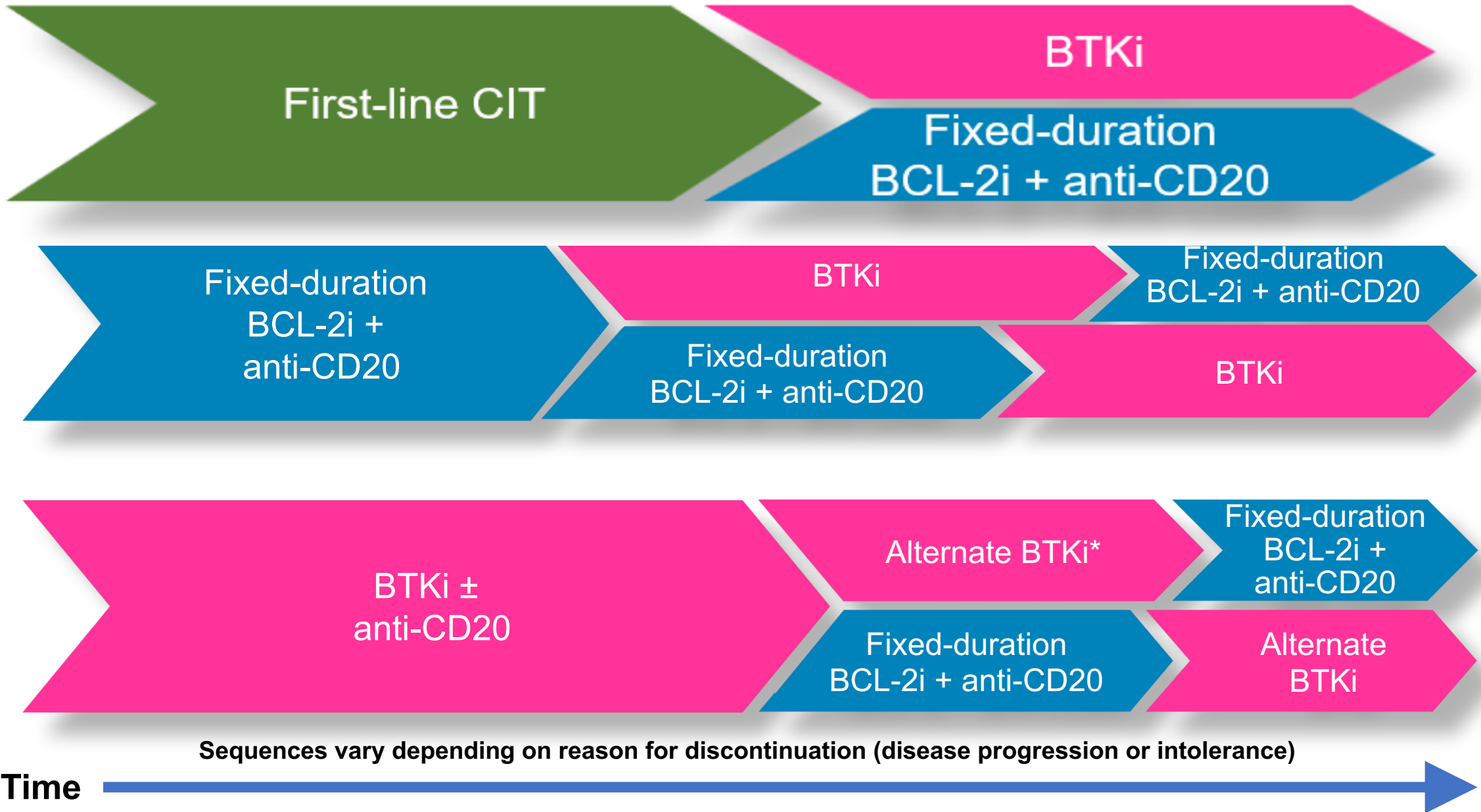


Category		Median PFS, months (95% CI)	HR (95% CI); P value [†]	5-year PFS, % (95% CI)
VenR	del(17p) and/or TP53-mut	37.4 (29.4, 52.3)	2.04 (1.32, 3.15);	27.3 (13.6, 41.0)
	No del(17p) and TP53-WT	56.6 (53.0, NE)	.0010	42.5 (28.9, 56.0)
BR	del(17p) and/or TP53-mut	13.4 (8.0, 15.8)	1.67 (1.15, 2.40);	NE
	No del(17p) and TP53-WT	19.6 (16.4, 25.4)	.0059	NE

PFS according to IGHV



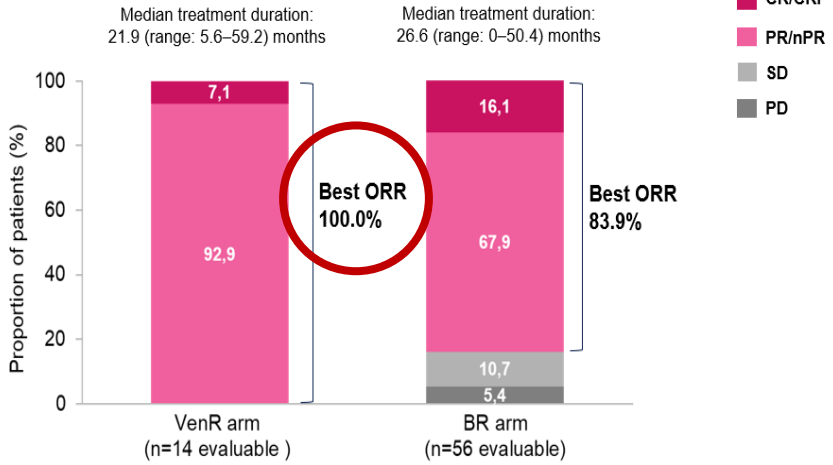
Category		Median PFS, months (95% CI)	HR (95% CI); P value [†]	5-year PFS, % (95% CI)
VenR	unmut-IGHV	52.2 (44.1, 53.8)	2.96 (1.64, 5.34);	28.7 (18.5, 38.9)
	mut-IGHV	NE	.0002	72.7 (59.7, 85.6)
BR	unmut-IGHV	15.7 (13.4, 17.3)	1.79 (1.24, 2.58);	NE
	mut-IGHV	24.2 (18.6, 32.8)	.0015	NE



Alternate BTKi*: if intolerance

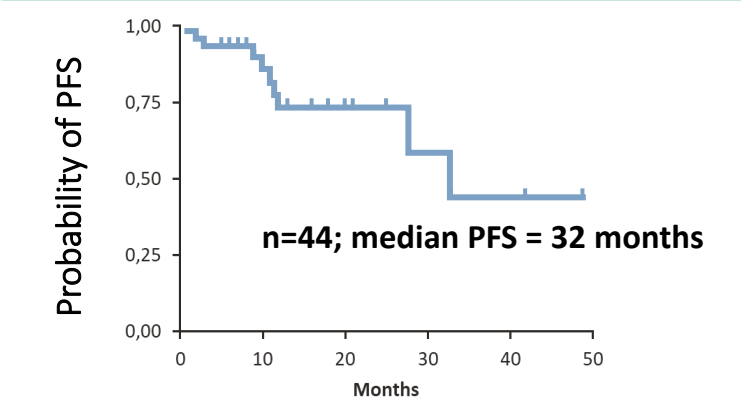
BCRi Treatment after Venetoclax: Clinical Trial Murano

MURANO: Best ORR to subsequent BTKi therapy*
(median follow-up: 59 months)



BCRi Treatment after Venetoclax: Real-World Experience – Summary

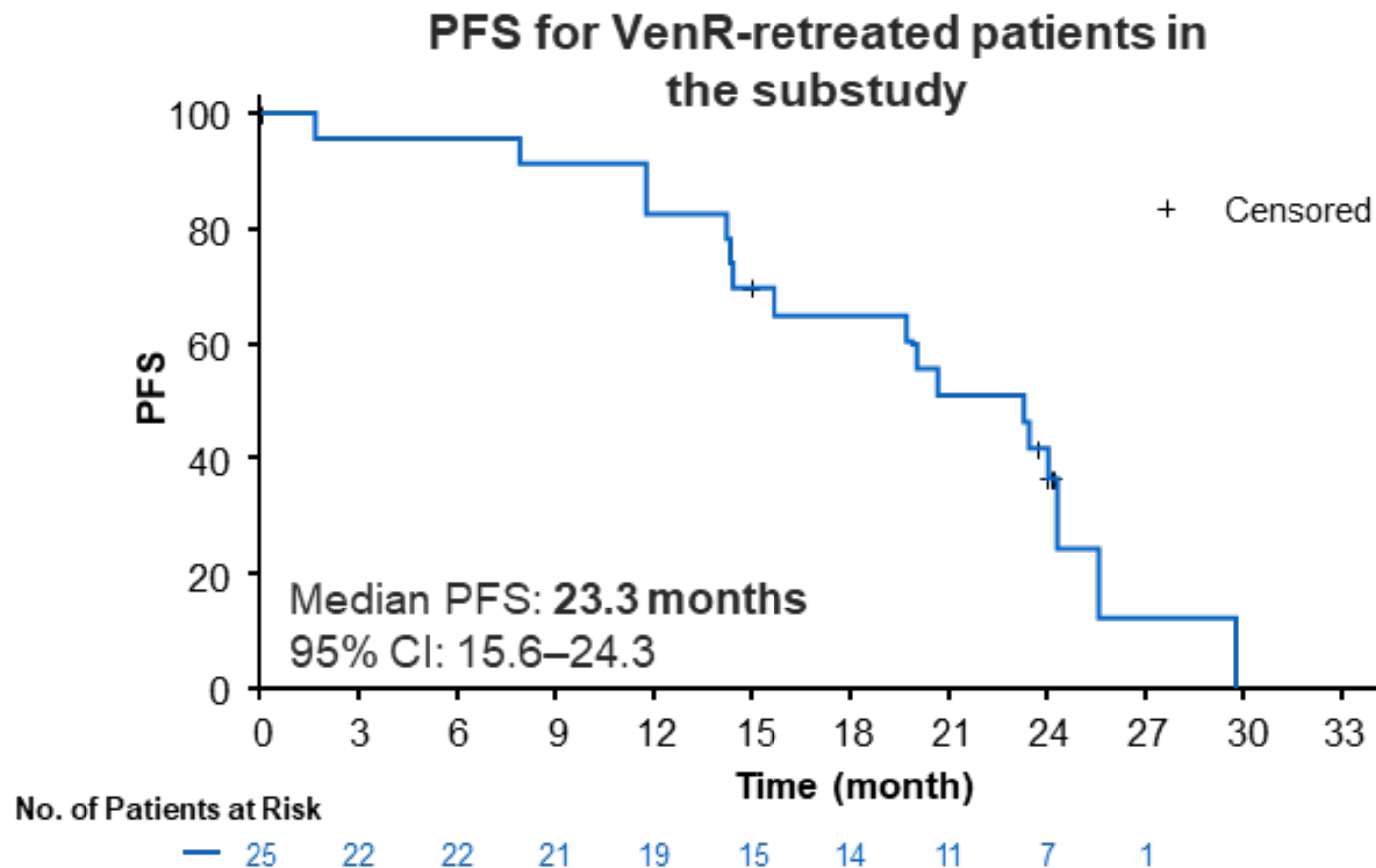
Analyses of ibrutinib regimens post-venetoclax regimen	Treatment	ORR
Ibr post-Ven, in 4 US centers¹	Ibr post-Ven (n=25)* All patients were Ibr-naive	14 (56%)
BTKi post-Ven/VenR, in 2 Australian centers³	Ibr (n=21) or zanubrutinib (n=2) post-Ven [†] All patients were BCRi-naive	91%
BCRi⁵ post-Ven regimen (CORE Registry, US centers, EU/UK centers)⁴ (67% treated in real-world setting)	BTKi post-Ven in BTKi-naive (n=44)	83.9%



Harrup R, et al. ASH 2020. Abstract 3139 (Poster).

1. Brown J, et al. ASH 2019: Abstract 4320; poster; 2. Mato AR, et al. Haematologica 2018; **103**:1511–1517; 3. Lin VS, et al. Blood 2020; **135**:2266–2270; 4. Mato AR, et al. Clin Cancer Res 2020; **26**:3589–3596; 5. Mato AR, et al. ASH 2019; Abstract 1756; poster; 6. Seymour JF, et al. ASH 2019: Abstract 355; oral.

Patient Outcomes With Venetoclax Retreatment Murano Study



	Patients retreated with VenR (n=25)
Median age, years (range)	66 (49–82)
No. of prior therapies*, n (%)	
2	20 (80.0)
3	4 (16.0)
≥4	1 (4.0)
del(17p) [†] and/or TP53 mutation [‡] ,	
yes	8 (32.0)
no	5 (20.0)
unknown/not assessed	12 (48.0)
IGHV [§] , n (%)	
mutated	1 (4.0)
unmutated	22 (88.0)
unknown/not assessed	2 (8.0)
GC [†] , n (%)	
0–2	9 (36.0)
3–4	3 (12.0)
≥5	8 (32.0)
unknown/not assessed	5 (20.0)

BTKi

BCL-2i +
anti-CD20

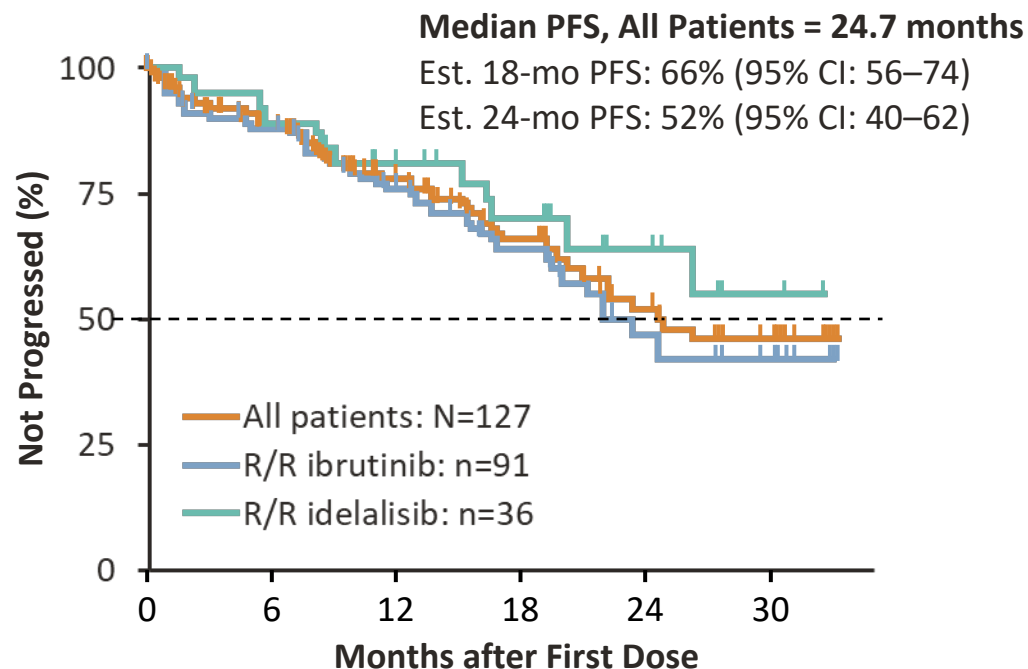
VENETOCLAX IN R/R CLL AFTER IBRUTINIB OR IDELALISIB (M14-032)

Phase 2
R/R CLL after
ibrutinib or
idelalisib (N=127)¹⁻³

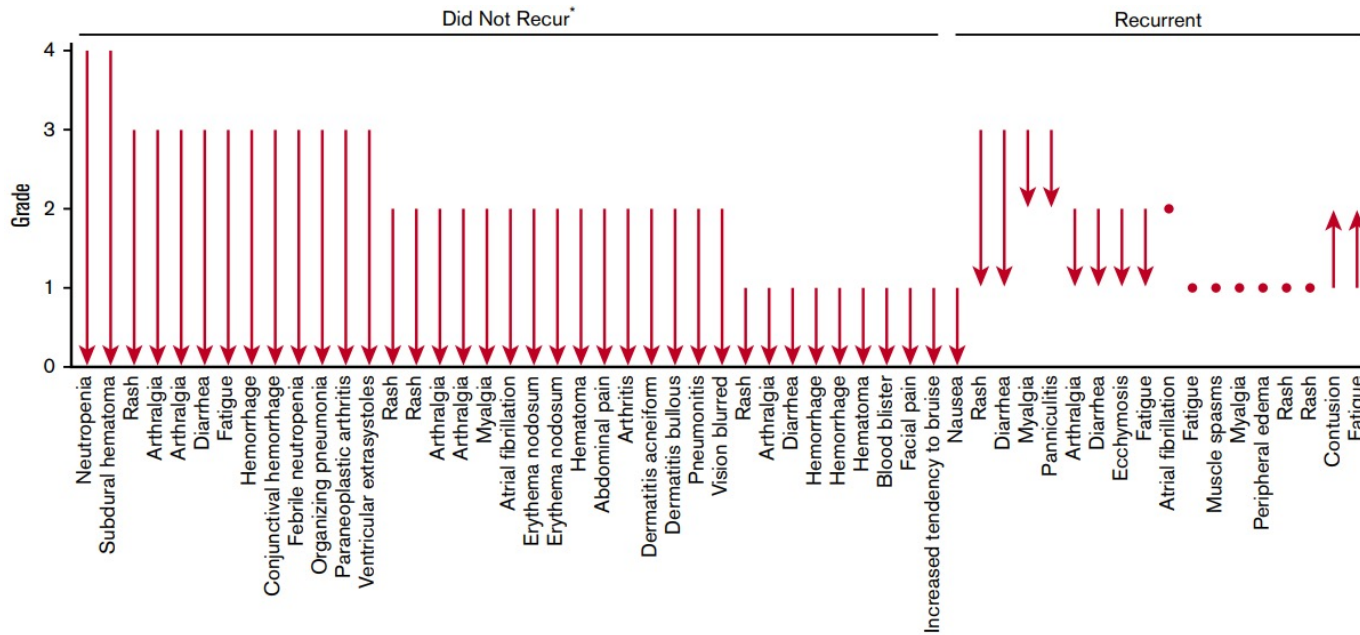
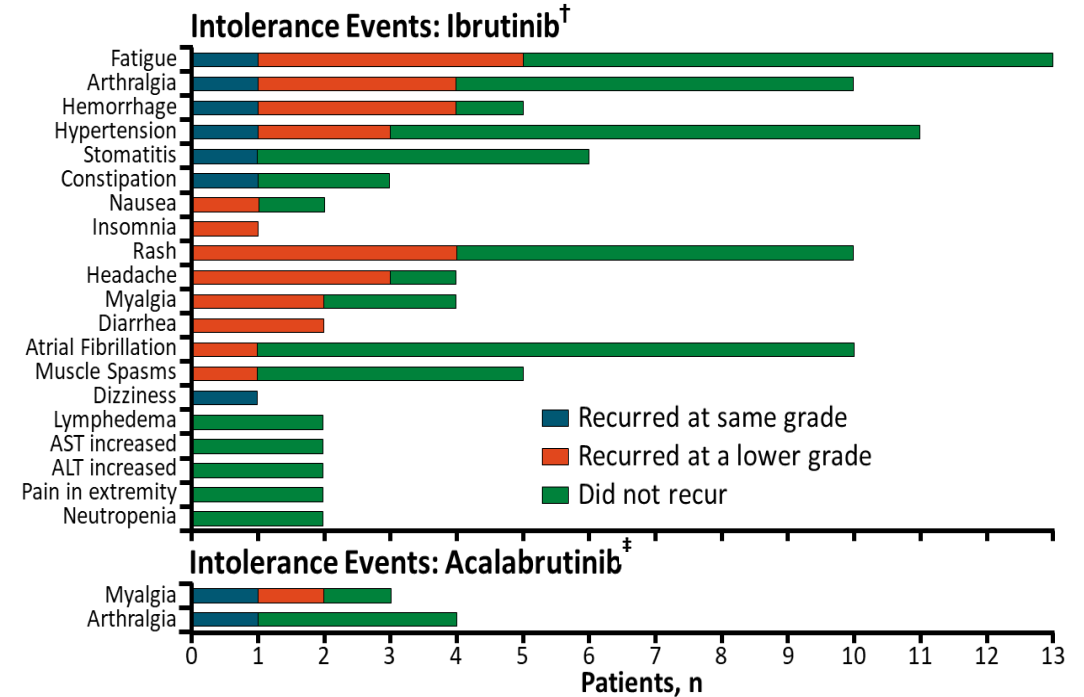
Venetoclax PO QD
to progression or
unacceptable toxicity

Primary Endpoint: **ORR**
Secondary Endpoints:
DoR, TTP, PFS, OS, MRD

PFS with Venetoclax Treatment



- Median time on venetoclax: 17.3 months (range, 0.1–35.5)

Acalabrutinib in patients intolerant to ibrutinib¹Zanubrutinib in patients intolerant to acalabrutinib or ibrutinib²

*An additional 6 events of unknown grade (rash, diarrhea, hemorrhage, decreased appetite, dyspnea, and weight decreased) did not recur. †18 additional ibrutinib-related intolerance events (arthritis, bone pain, bronchitis, embolism, irregular heart rate, malaise, pericardial effusion, pleural effusion, pneumonia, psoriasis, pyrexia, sinusitis, subcutaneous abscess, supraventricular tachycardia, aminotransferases increased, ventricular extrasystoles, vertigo, and vomiting) occurred in one patient and did not recur on zanubrutinib. ‡ 11 additional acalabrutinib-related intolerance events (abdominal pain, asthenia, atrial fibrillation, dyspepsia, fatigue, groin pain, headache, insomnia, malaise, pain in extremity, and rash) occurred in one patient and did not recur on zanubrutinib.

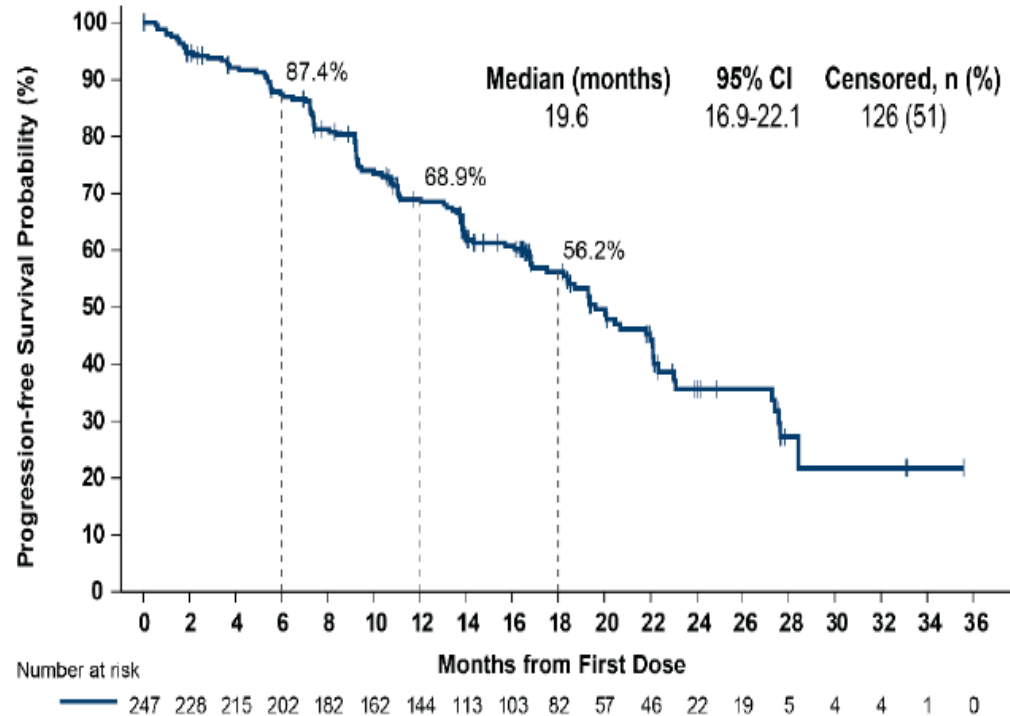
ALT, alanine aminotransferase; AST, aspartate aminotransferase BTK, Bruton's tyrosine kinase.

1. Awan FT *et al. Blood Adv* 2019; 3 (9): 1553–1562. 2. Shadman M *et al. Lancet Haematol* 2023; 10 (1): 35–45.

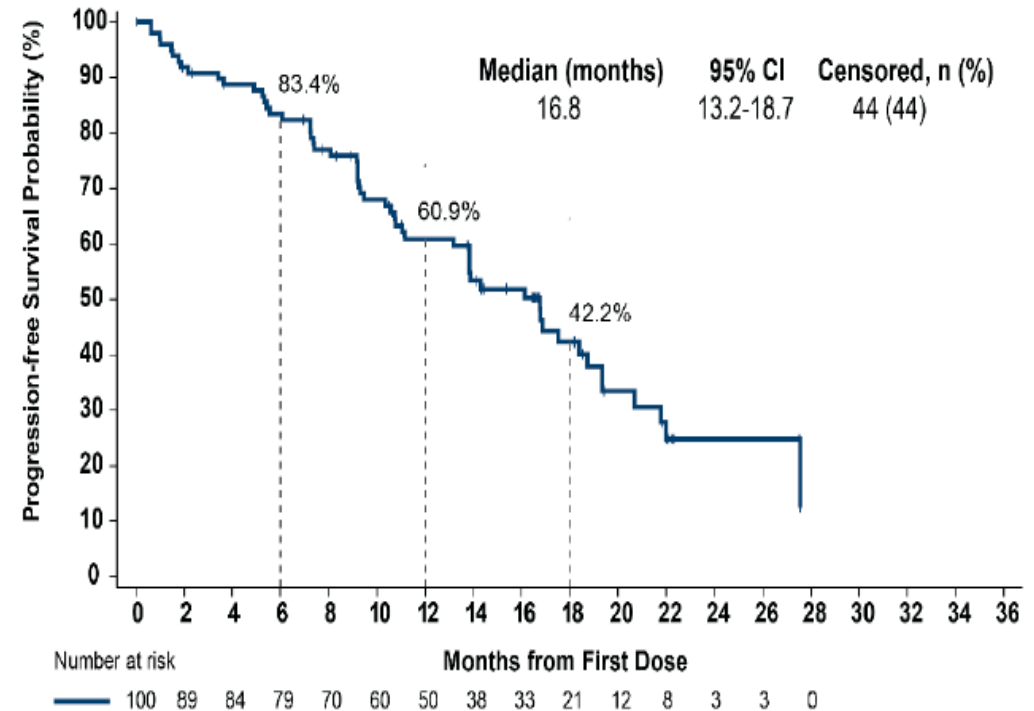
NON Covalent BTKi

PFS with pirtobrutinib in patients with CLL/SLN and prior BTKi treatment

All prior BTKi patients
Median prior lines = 3



Prior BTKi and BCL2i patients
Median prior lines = 5



Conclusions

No current place for immuno-CHT in CLL treatment

Covalent BTKi: **consistent data of their efficacy in first line**
zanubrutinib more effective better tolerated compared to ibrutinib in R/R disease
acalabrutinib better tolerated compared to ibrutinib in R/R disease

No trials comparing fixed duration target therapy vs continuous therapy

Treatment program should be planned from first line therapy:

- age (different goals)** **elderly: life expectancy**
logistics care givers
younger: consider future cellular therapy
- low risk (IGHVmutated)** **favourable outcomes with FD or continuous tx**
- High Risk/genetic instability** **..... cellular therapy**