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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

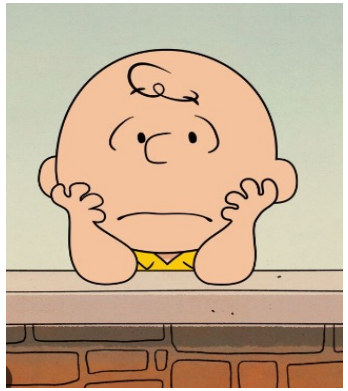
Venetoclax Rituximab

CLL BTKi INTOLLERANT

Zanubrutinib Monotherapy (?) AIFA PENDING

Pirtobrutinib Monotherapy (?) EMA PENDING

CLL DOUBLE REFRACTORY



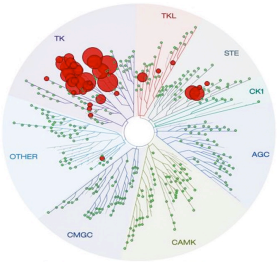
1

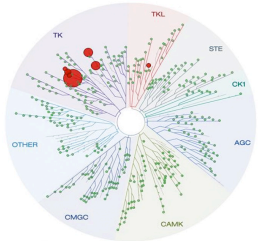
VENETOCLAX OBINUTUZUMAB
or
BTKi → No randomized study

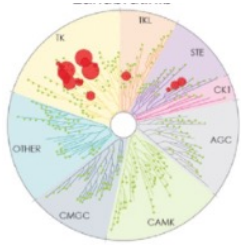
2

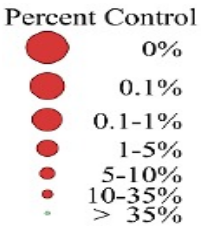
If BTKi: WICH BTKi → No randomized study

- ***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)







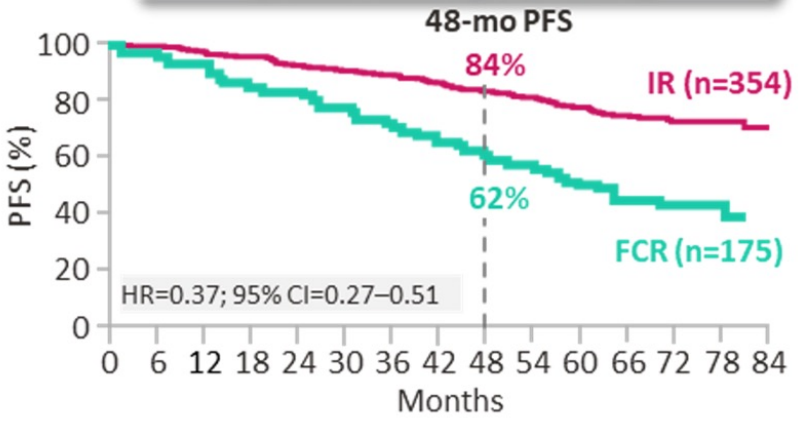


BTKi

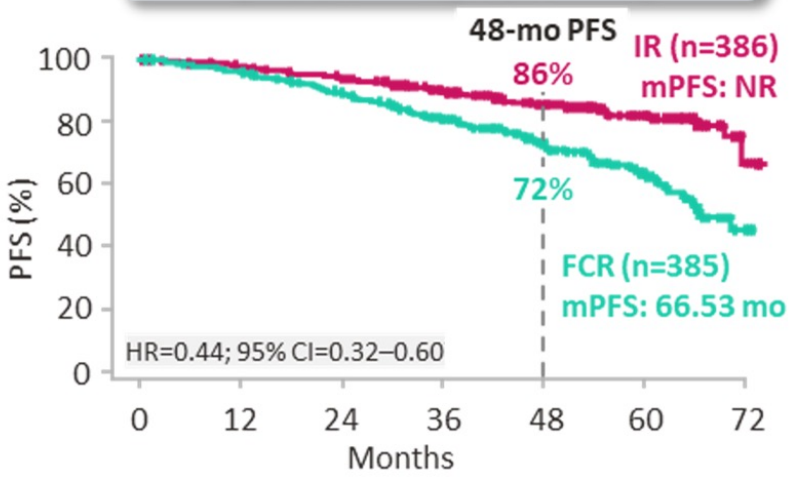
Ibrutinib in TN pts

Young FIT → **Elderly/Unfit**

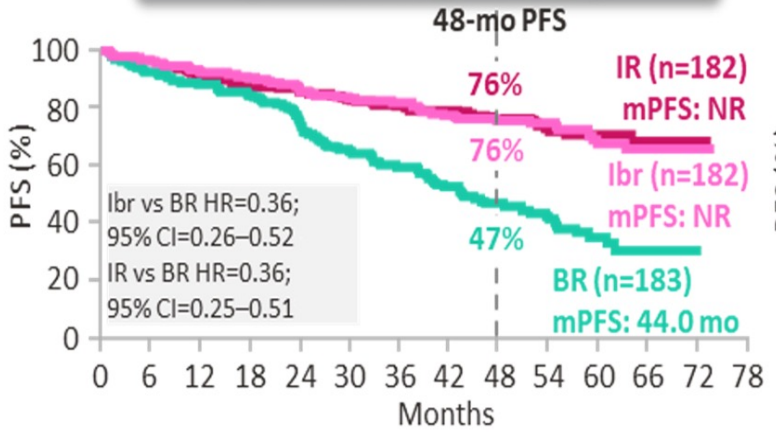
ECOG-1912: INV-assessed[1] PFS
(median follow-up: 70 months)[2]



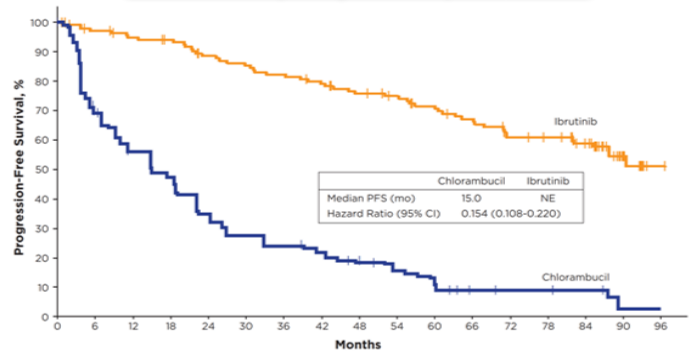
FLAIR: INV-assessed PFS
(median follow-up: 52.7 months)[5]



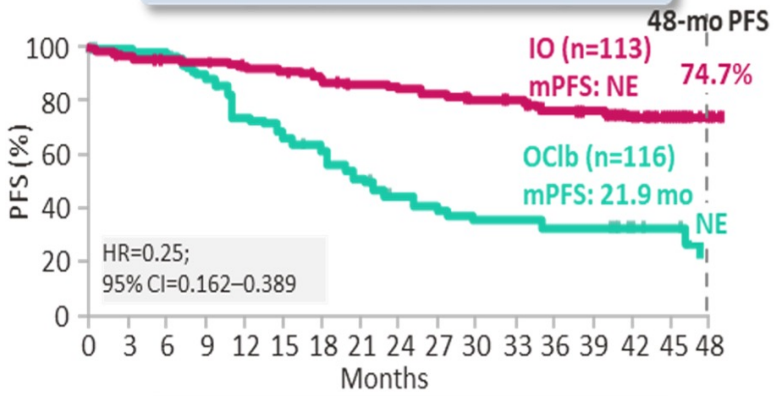
Alliance A041202: INV-assessed PFS
(median follow-up: 55 months)[3]



RESONATE-2[6]
8-year follow-up



iLLUMINATE: INV-assessed PFS
(median follow-up: 45 months)[4]



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.

BTKi

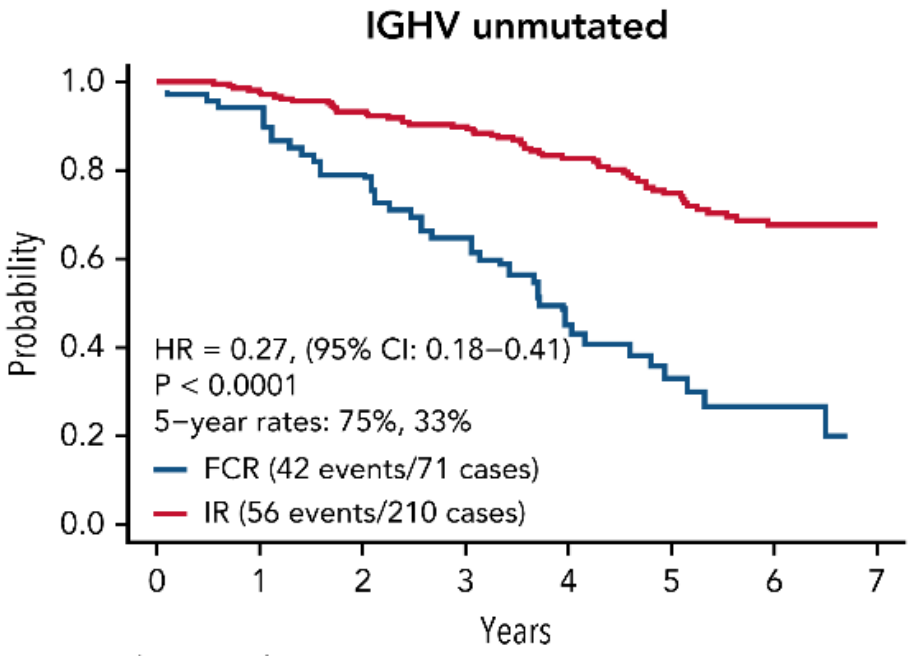
ECOG study (IR vs FCR): PFS by IGHV mutation status

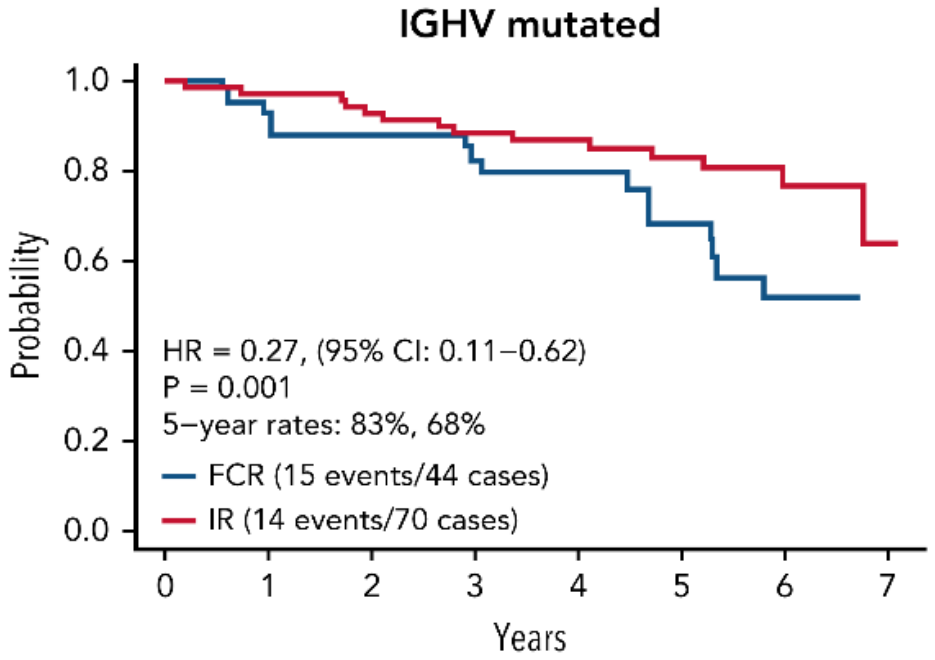
ECOG 1912

IR vs. FCR

70-month follow-up

- ≤70 years old
- Ability to tolerate FCR





IGHVunmutated: PFS significantly different in all the sudies at the first FU

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

Shanafelt TD *et al*. *Blood* 2022; 140 (2): 112–120

BTKi

Acalabrutinib in TN CLL (Elevate TN study)

✓ PFS Benefit With Acalabrutinib Containing Regimens

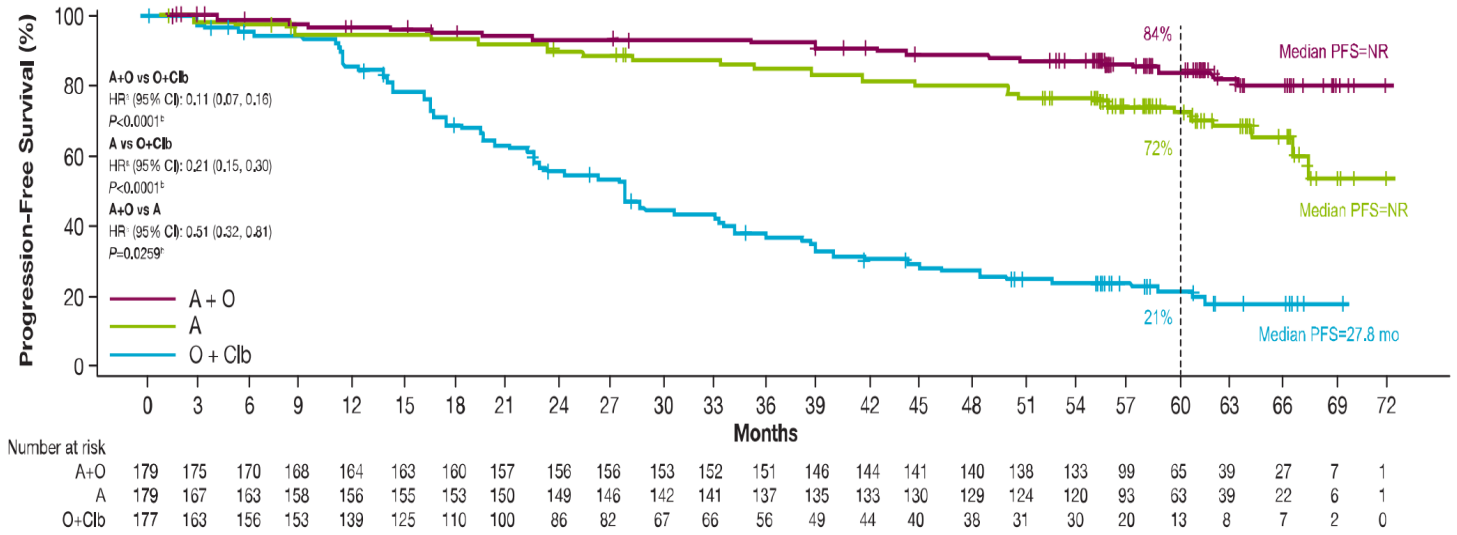
Age ≥ 65 y or
< 65 y with coexisting conditions:
- CIRS score > 6, or
- CrCl < 70 mL/min

randomize

- **Acalabrutinib**
- **Acalabrutinib + obinutuzumab***
- **Chlorambucil* + obinutuzumab***

*** 6 cycles**

Median follow-up 58.2 months



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

Sharman JP, et al. EHA 2022

BTKi

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

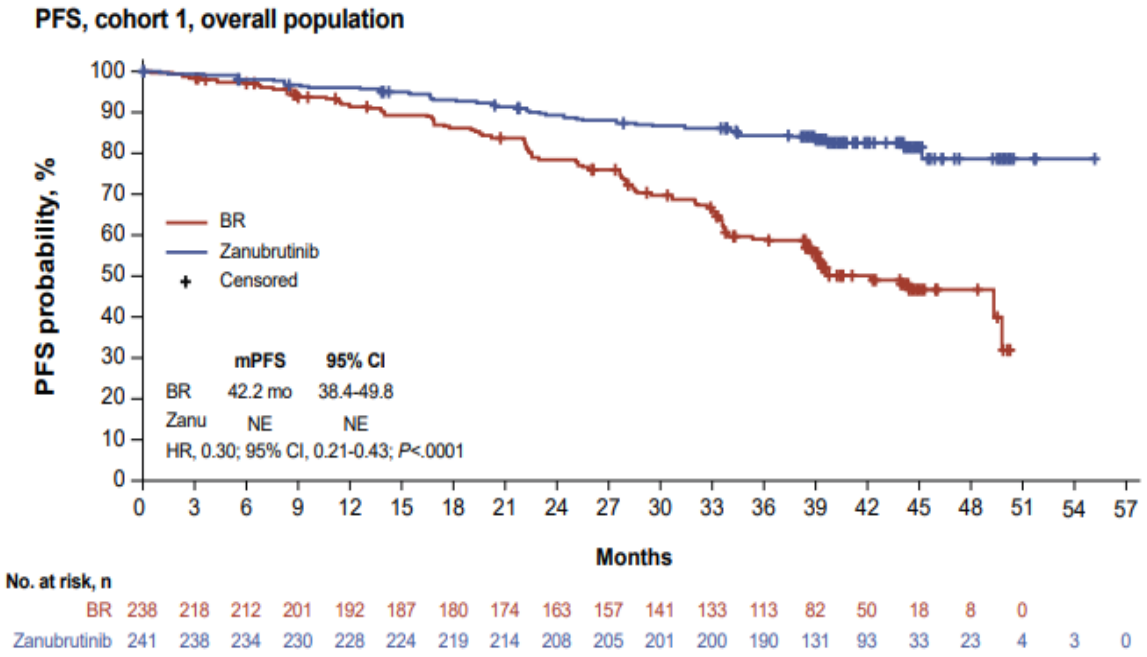
randomize

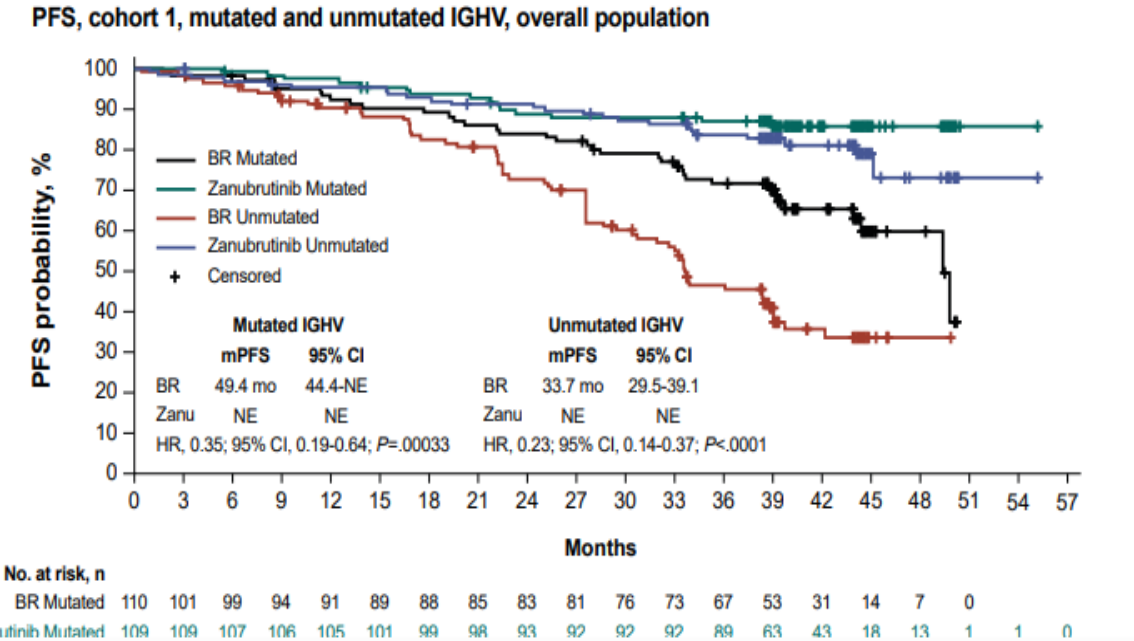
- Zanubrutinib
- Bendamustine* + rituximab*

* 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





Munhir T, et al. EHA 2023

BTKi

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

randomize

- 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

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.

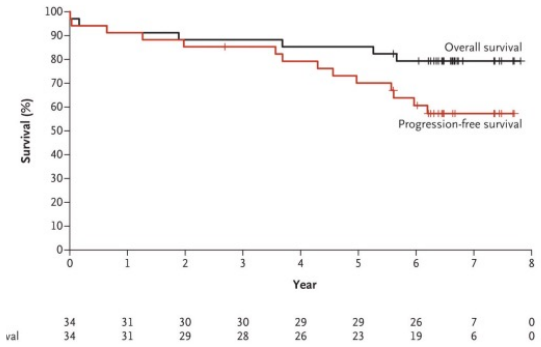
AE, adverse event; BTKi, Bruton's tyrosine kinase inhibitor; NR, not reported.

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

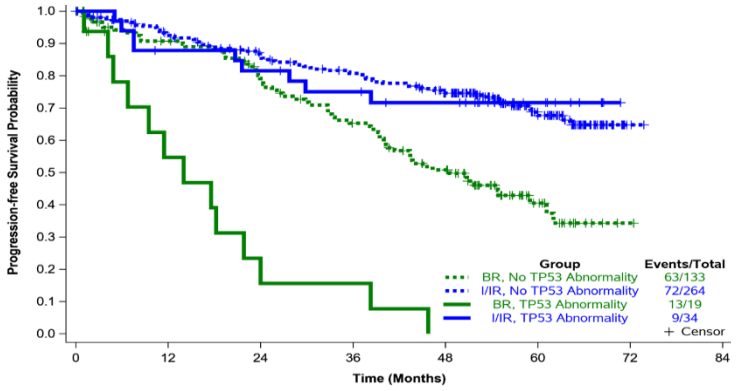
BTKi

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

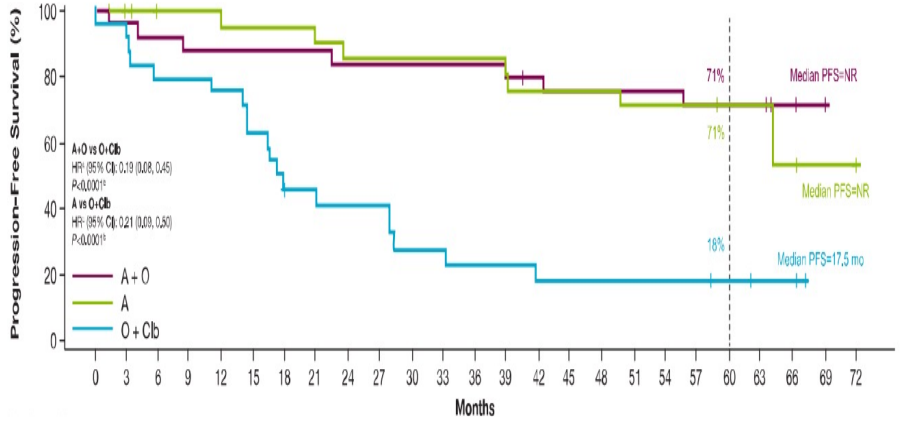
Phase II trial:
Ibrutinib monotherapy[1]
Median FU: 6.5 years



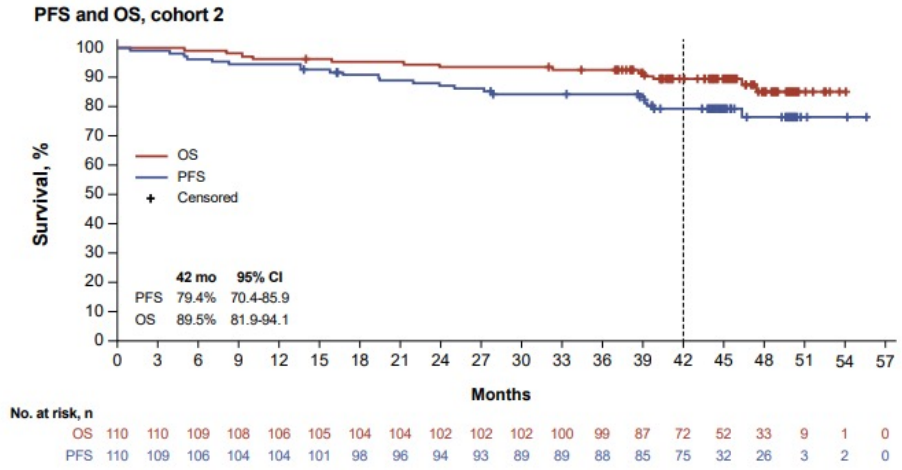
ALLIANCE:
Ibrutinib vs. IR vs. BR[2]
Median FU: 55 months



ELEVATE TN:
Acalabrutinib vs. AO vs. O + Clb[3]
Median FU: 58.2 months



SEQUOIA arm C:
Zanubruitnib monotherapy[4]
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*

Venetoclax O

CLL first Line: venetoclax obinutuzumab

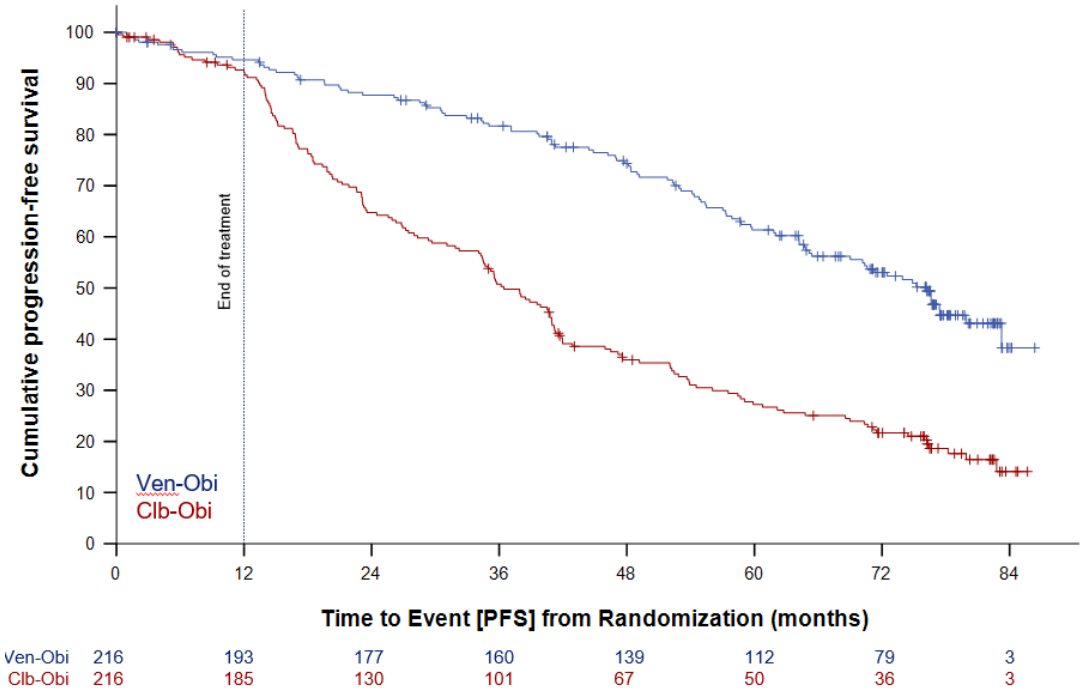
CLL 14

Venetoclax Obinutuzumab versus Chlorambucil Obinutuzumab

Median follow-up 76.4 months

CIRS score >6
CrCl <70 mL/min

PROGRESSION-FREE SURVIVAL



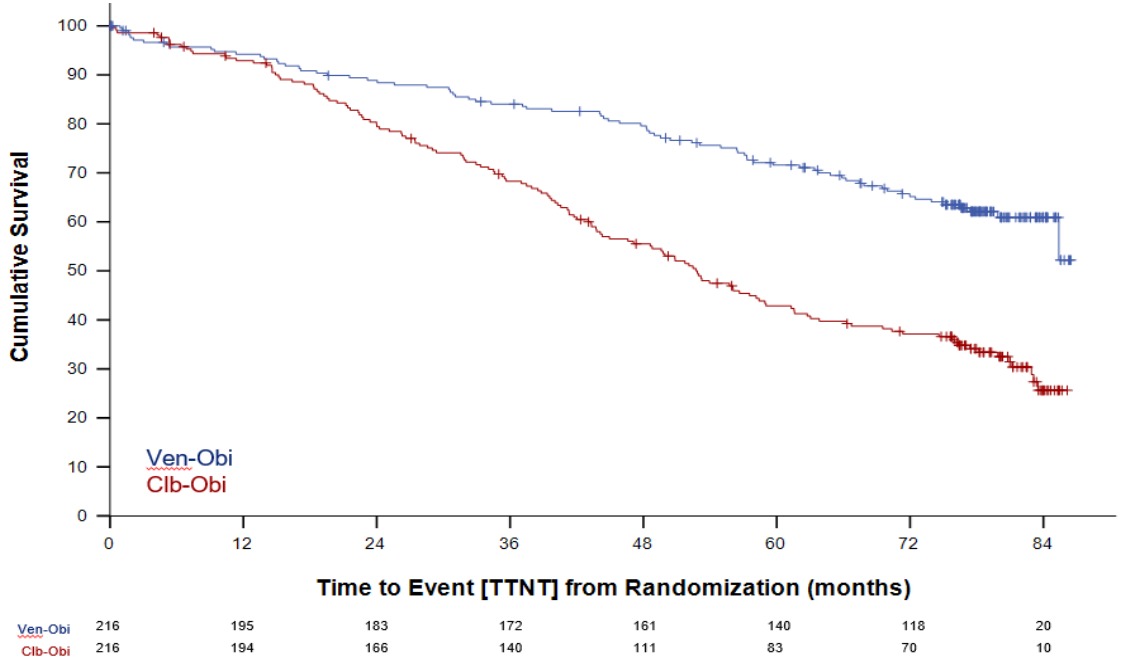
Median PFS
Ven-Obi: 76.2 months
Clb-Obi: 36.4 months

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



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

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

Al Sawaf et al, EHA 2023

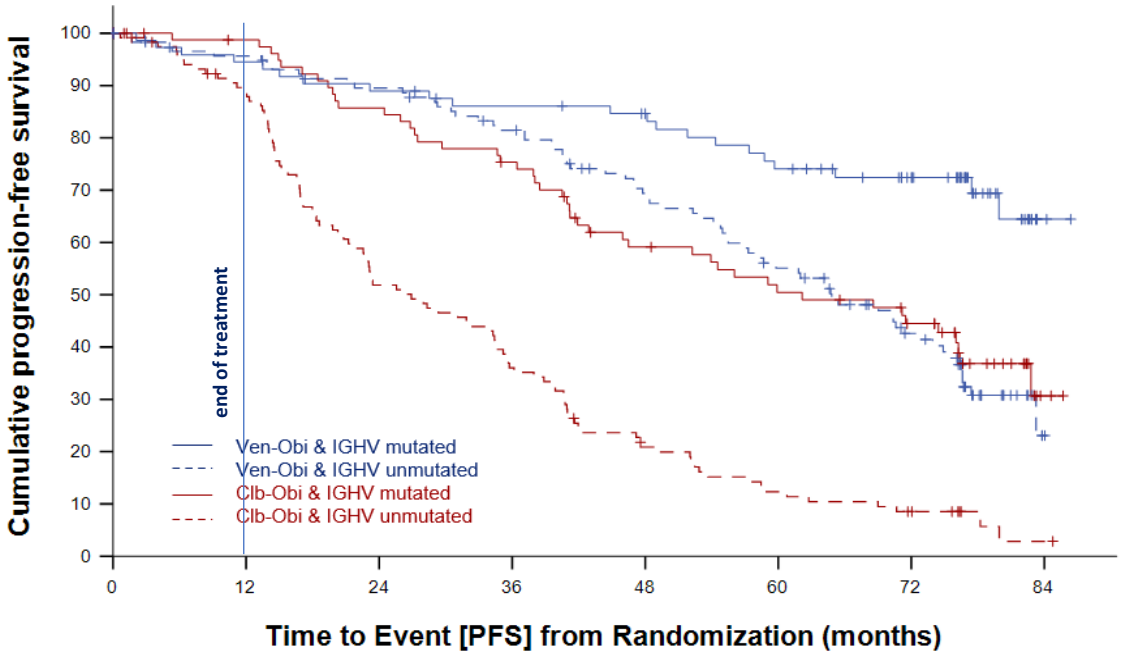
Venetoclax O

CLL first Line: CLL 14

Venetoclax Obinutuzumab versus Chlorambucil Obinutuzumab

Median follow-up 76.4 months

PROGRESSION-FREE SURVIVAL – IGHV status



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

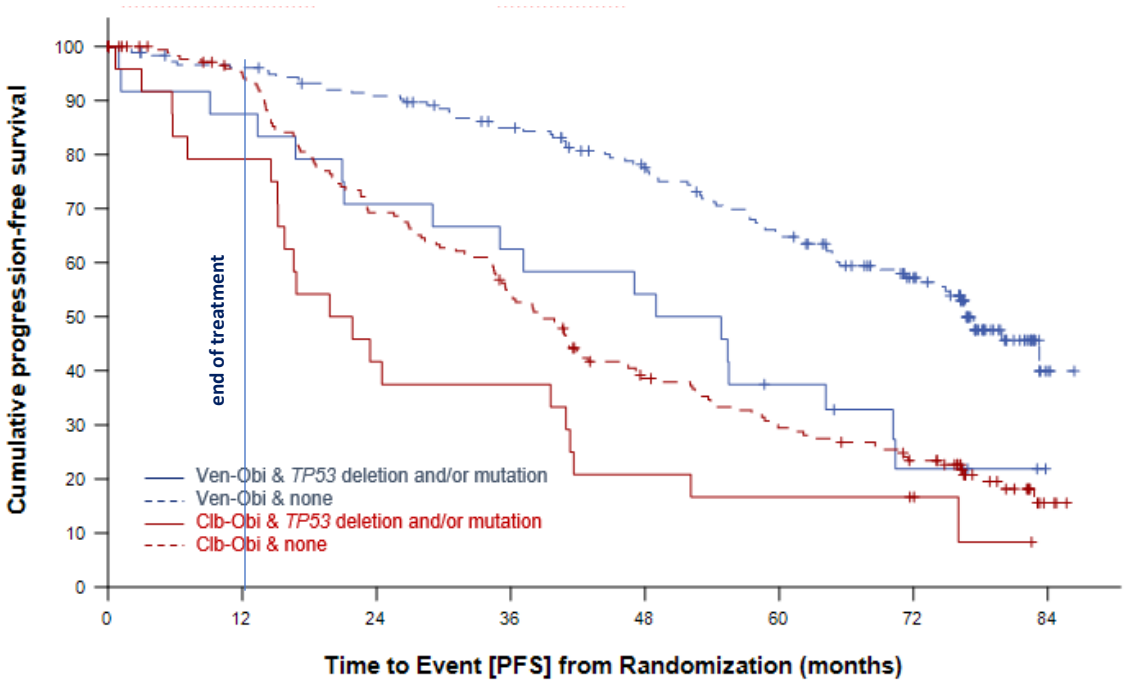
Median PFS

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



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 *TP53*del/mut: 76.6 m

Ven-Obi & *TP53*del/mut: 51.9 m

HR 2.29, 95% CI [1.37-3.83], p=0.001

Clb-Obi & no *TP53*del/mut: 38.9 m

Clb-Obi & *TP53*del/mut: 20.8 m

HR 1.66, 95% CI [1.05-2.63], p=0.03

Al Sawaf et al, EHA 2023

Venetoclax O

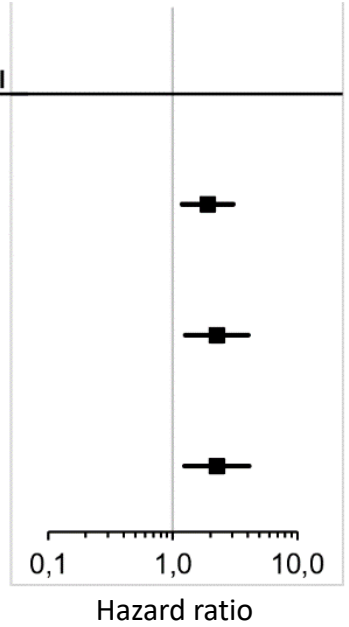
CLL first Line: CLL 14

Venetoclax Obinutuzumab versus Chlorambucil Obinutuzumab

Median follow-up 76.4 months

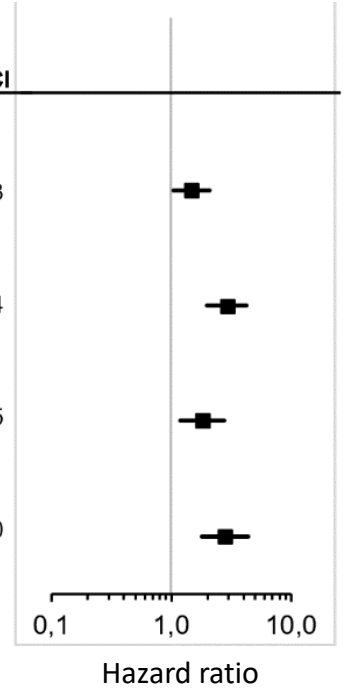
Ven-Obi

COX regression PFS	Univariate comparison	Hazard ratio	95% Wald CI
Lymph node size			
≥ 5 cm	vs. < 5 cm	1.916	1.189-3.088
IGHV mutational status			
unmutated	vs. mutated	2.258	1.268-4.021
***TP53* deletion/mutation**			
Deleted and/or mutated	vs. none	2.262	1.242-4.120



Clb-Obi

COX regression PFS	Univariate comparison	Hazard ratio	95% Wald CI
Absolute lymphocyte count			
≥ 50 x 10^9/L	vs. < 50 x 10^9/L	1.467	1.038-2.073
IGHV mutational status			
unmutated	vs. mutated	2.908	2.002-4.224
Deletion 11q			
del(11q)	vs. no del(11q)	1.823	1.194-2.785
Complex Karyotype			
CKT/HCKT	vs. NCKT	2.811	1.788-4.420



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.

Al Sawaf et al, EHA 2023

Venetoclax O

CLL first Line: CLL 14

Venetoclax Obinutuzumab versus Chlorambucil Obinutuzumab

Median follow-up 76.4 months

Dose modifications and discontinuations due to adverse events

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

Most frequent ≥ grade 3 adverse events

	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%
Pneunomia	3.8%	3.3%
Infusion-related reaction	9.0%	0.0%
Tumour lysis syndrome	1.4%	0.0%

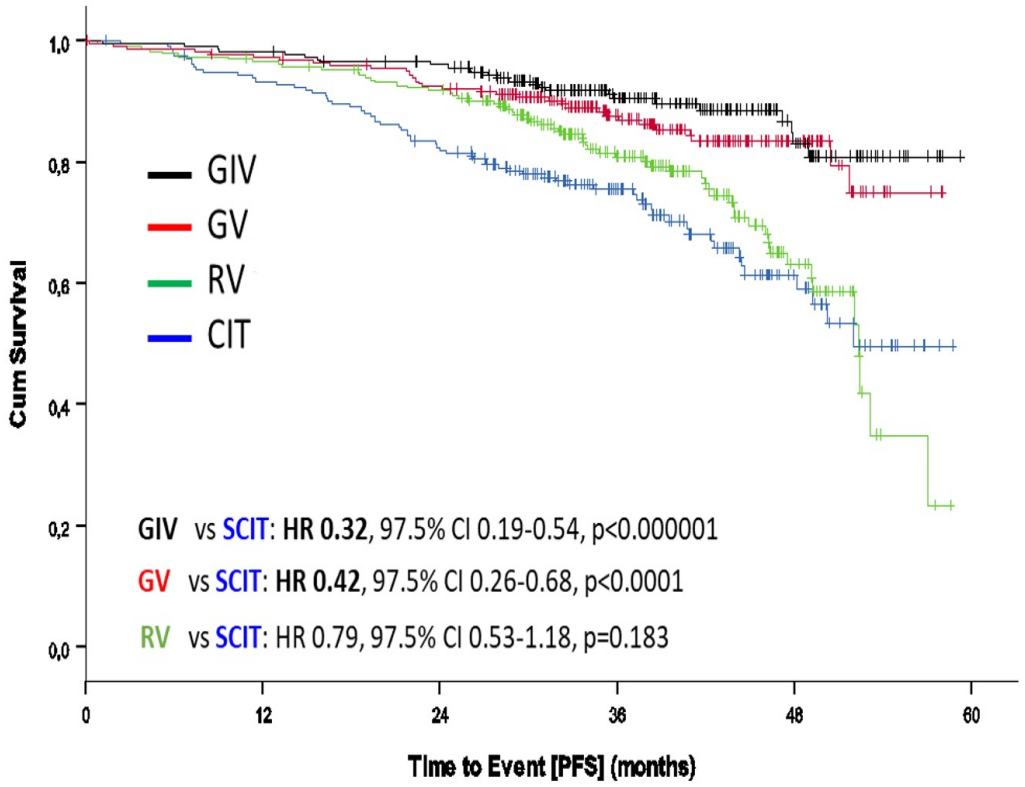
Al Sawaf et al, EHA 2023

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

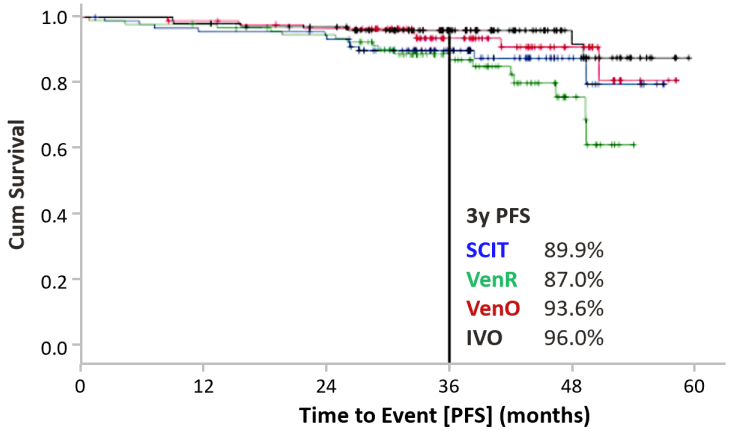
FIT pts

No del17p/TP53mut

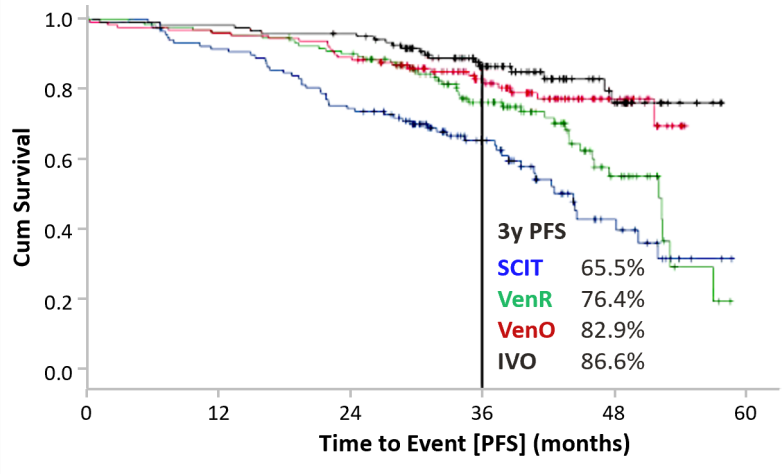
- FCR ≤65 yrs or BR >65 yrs
- Ibruinib Venetoclax Obinutuzumab 12 cycles
- Venetoclac Obinutuzumab 12 cycles
- Venetoclax Rituximab 12 cycles



PFS in IGHV mutated



PFS in IGHV unmutated



Eichorst B et al, EHA 2022

PERSONAL CONSIDERATION (WHILE WAITING CLL17)

PATIENTS FACTORS

1 Severe Cardiocomorbidities → Venetoclax Obinutuzumab

2 Severe Renal Impairment Bulky disease → BTKi

3 Concomitant Medications → BTKi Venetoclax/obinutuzumab

4 Elderly with difficulties to reach hospital Care givers Reduced compliace for iv tx → BTKi

DISEASE FACTORS

Consider patients factors

del 17p/*TP53*^{m} → Preferred: BTKi

Bulky Disease → Preferred: BTKi

IGHV mutated → Preferred: Venetoclax Obinutuzumab

IGHV mutated → BTKi if n° 4 more true plus n° 2

IGHV unmutated → Venetclax/Obinutuzumab- BTKi

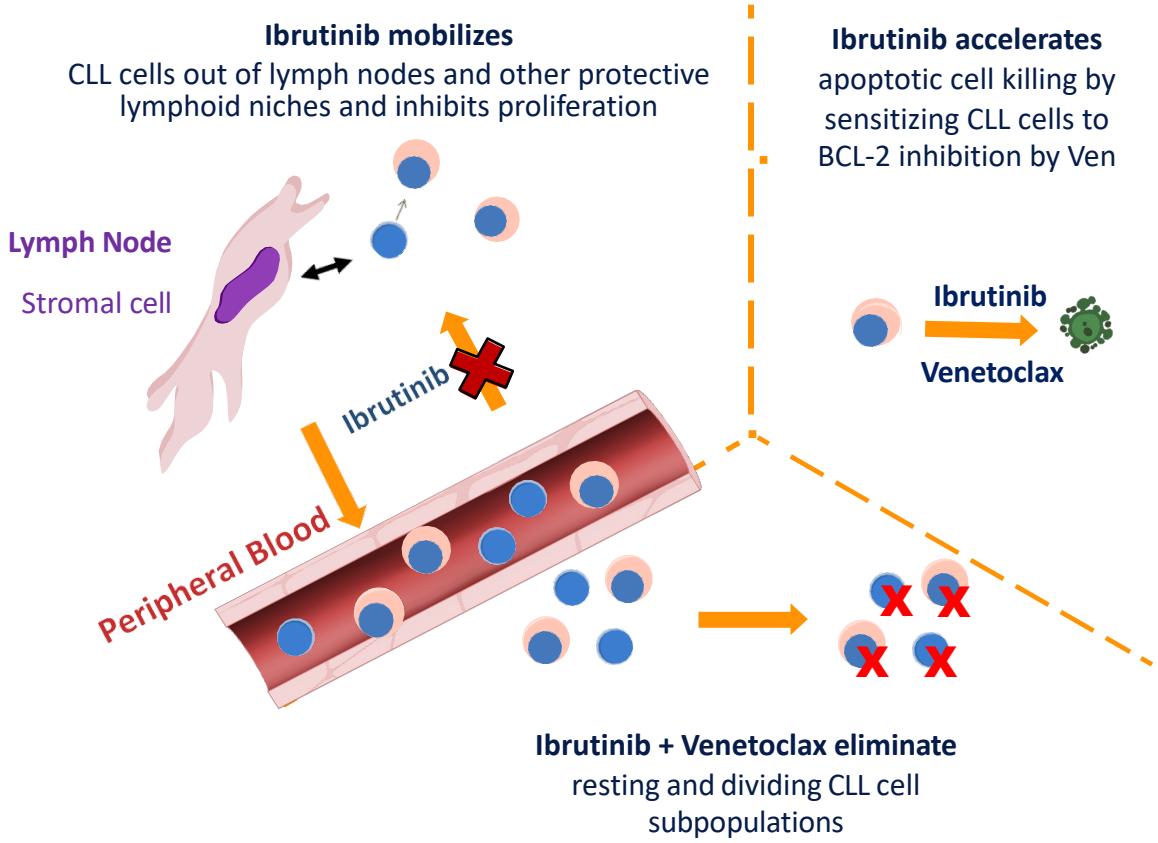
Consider:

- Patients factors
- Age matters: -future program
  - resistance

Venetoclax
Ibrutinib

FIXED DURATION IBRUTINIB VENETOCLAX COMBINATION

- Ibr + Ven preferentially target complementary cell compartments and CLL subpopulations to eliminate both dividing and resting CLL cells[1-3]
  - 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 uMRD[6]
  - This combination regimen was recently approved in the EU for patients with previously untreated CLL[7]

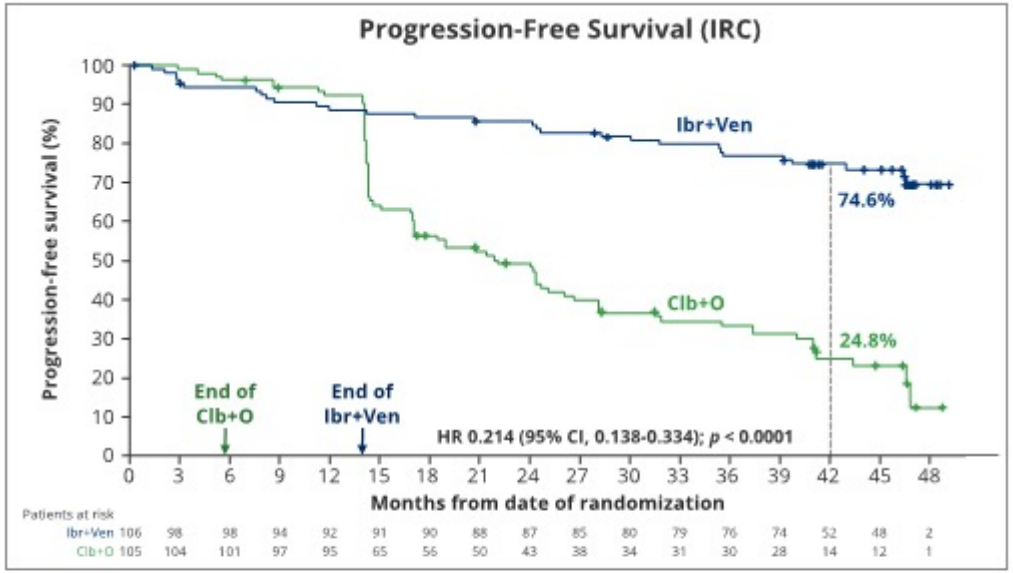


Venetoclax
Ibrutinib

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%



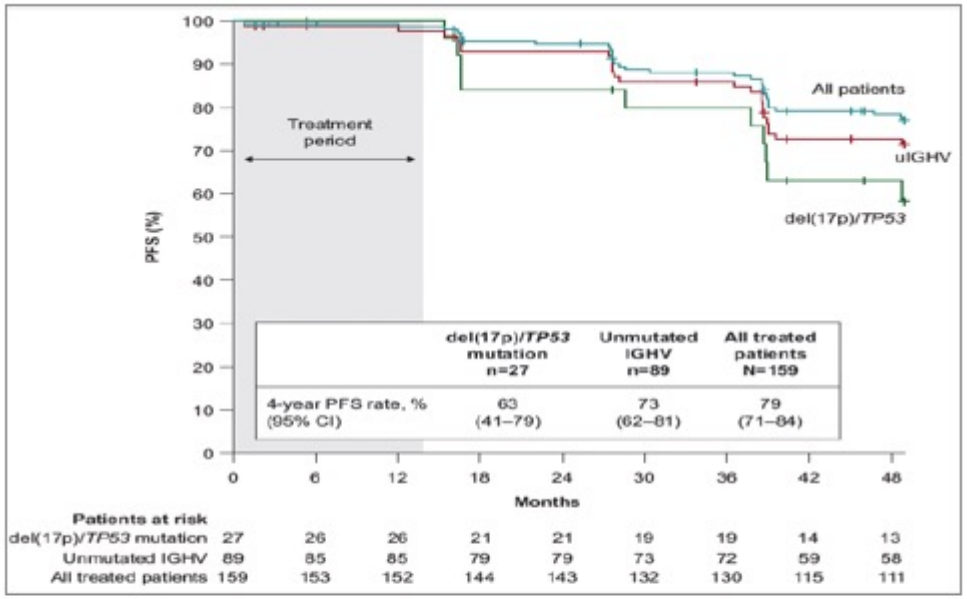
GLOW TRIAL: 46 months follow-up

4-yr estimated PFS: 74.6% *vs* 24.8%

Niemman et al , ASH 2022

Captivate FD: Ibr+Ven

159 pts ≤ 70 y
CR 58%
uMRD PB: 57%



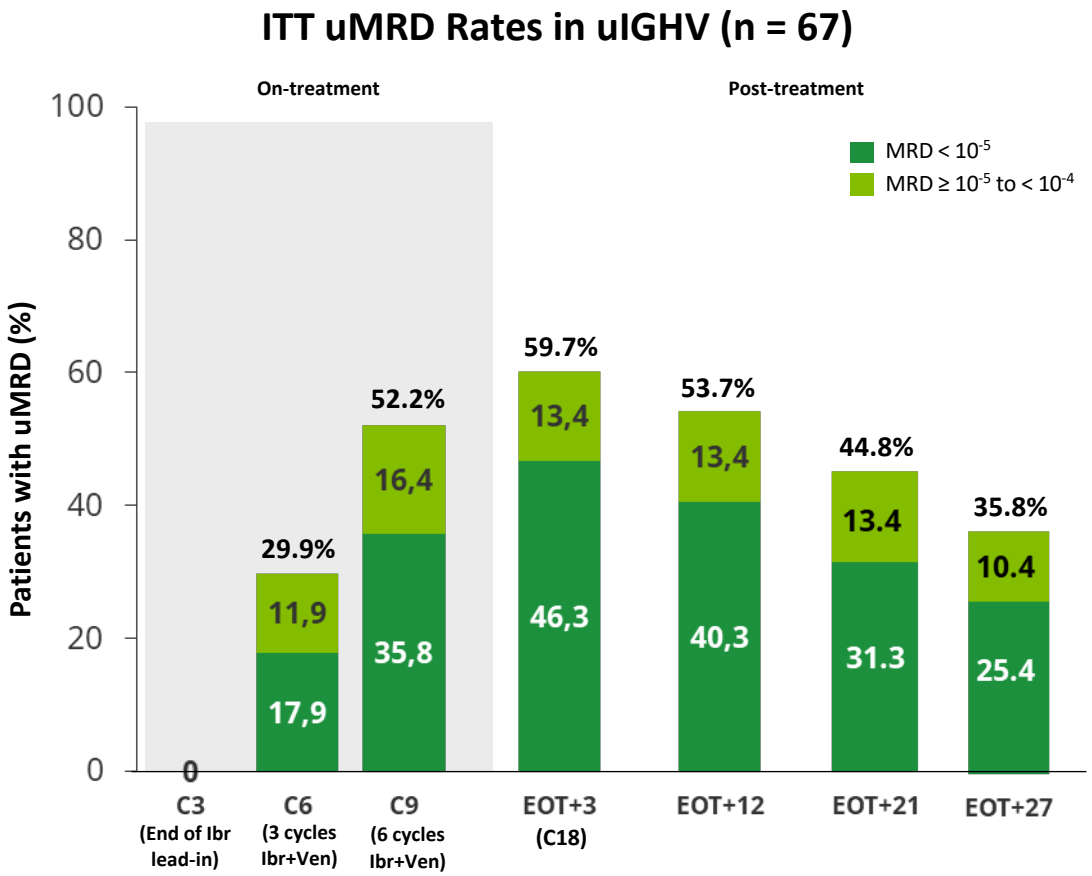
CAPTIVATE FD: 48 months follow-up

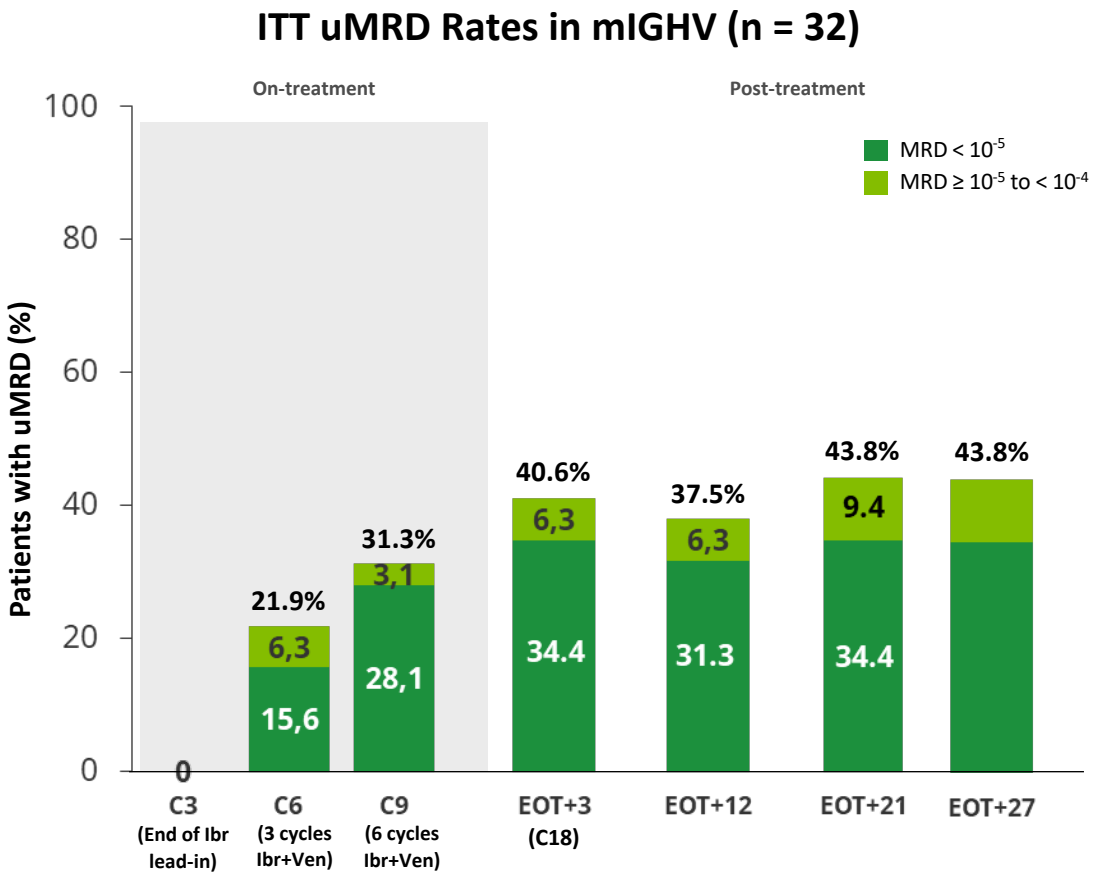
4-yr PFS: 79%

Tedeschi et al , EHA 2023

Venetoclax
Ibrutinib

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

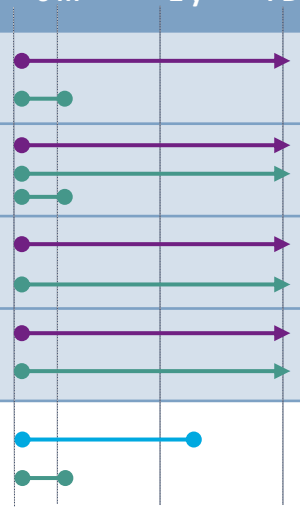




- uMRD rates (including < 10^{-5}) were higher and uMRD was achieved faster in patients with uIGHV versus mIGHV CLL
- uMRD was better sustained post-treatment in patients with mIGHV CLL

Niemann C U et al, 2022

Phase 3 Clinical Trials in R/R CLL

Study	Arm	Treatment duration (6 m, 2 y, PD)	Key eligibility criteria: Prior Tx, n	Key eligibility criteria: ECOG PS, score	Key eligibility criteria: CrCl, mL/min	Key patient demographics: Median age, years	Key patient demographics: Median prior Tx, n (range)	Key patient demographics: del(17p), %
RESONATE[1,2]	Ibr Ofa		≥1 (unsuitable for purine analogs)	0–1	NS	67 67	3 (1–12) 2 (1–13)	32 33
ASCEND[3]	Acala IdR/BR		≥1 systemic (no prior BCL-2 Tx)	0–2	≥30	68 67	1 (1–8) 2 (1–10)	17 14
ELEVATE-RR[4]	Acala Ibr		≥1 (no prior BTKi, PI3Ki, or BCL-2i)	0–2	≥30	66 65	2 (1–9) 2 (1–12)	45.1† 45.3†
ALPINE[5]	Zanu Ibr		≥1 (no prior BTKi)	0–2	NS	67 68	1 (1–6) 1 (1–12)	13.8‡ 15.4‡
MURANO[6–9]	VenR BR		1–>3 (≥1 CIT); prior B if DoR ≥24 months (not BR refractory/resistant)	0–1	NS	64.5 66.0	1 (1–5)* 1 (1–5)*	26.6 27.2

BCRi

Venetoclax

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

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

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);

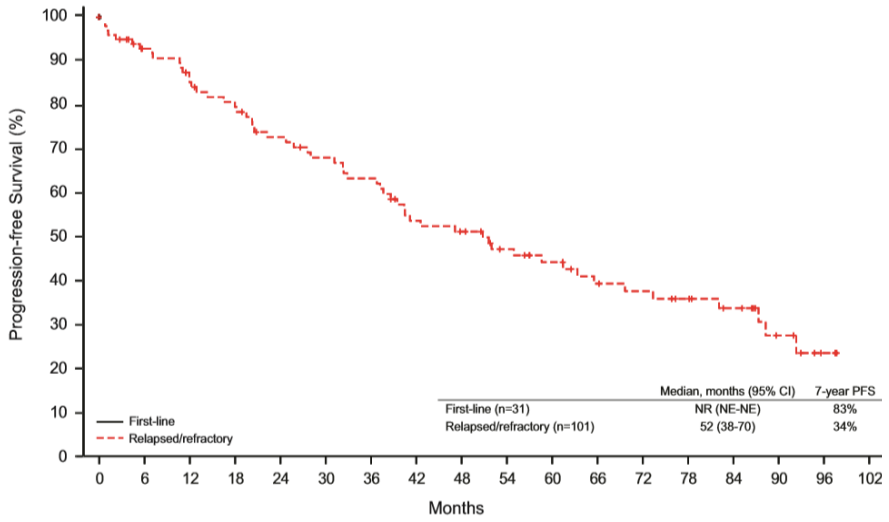
BTKi

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 unm	78%
del(17p)	34%



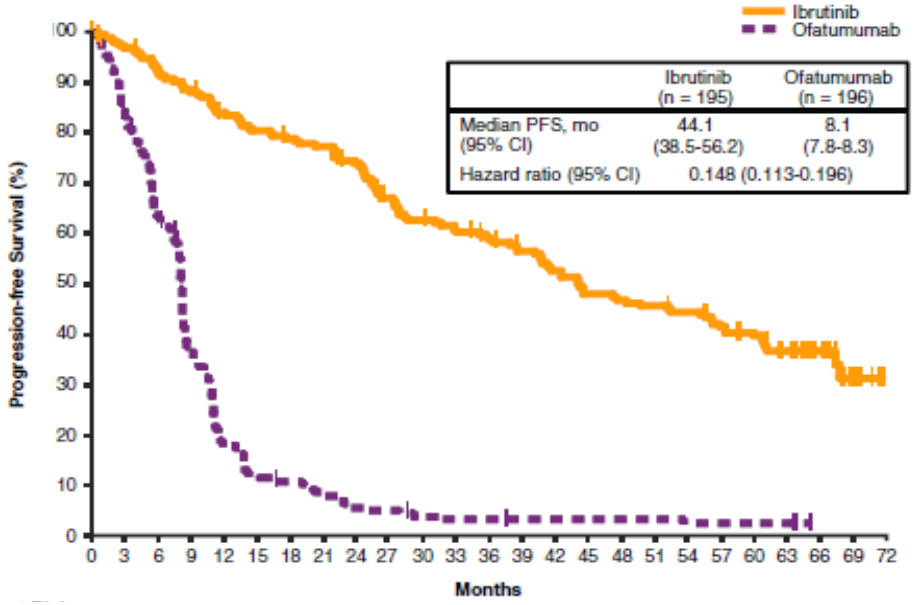
Byrd et al., 2103; Byrd et al., 2020

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 unm	73%
del(17p)	34%
TP53^{mut}	51%

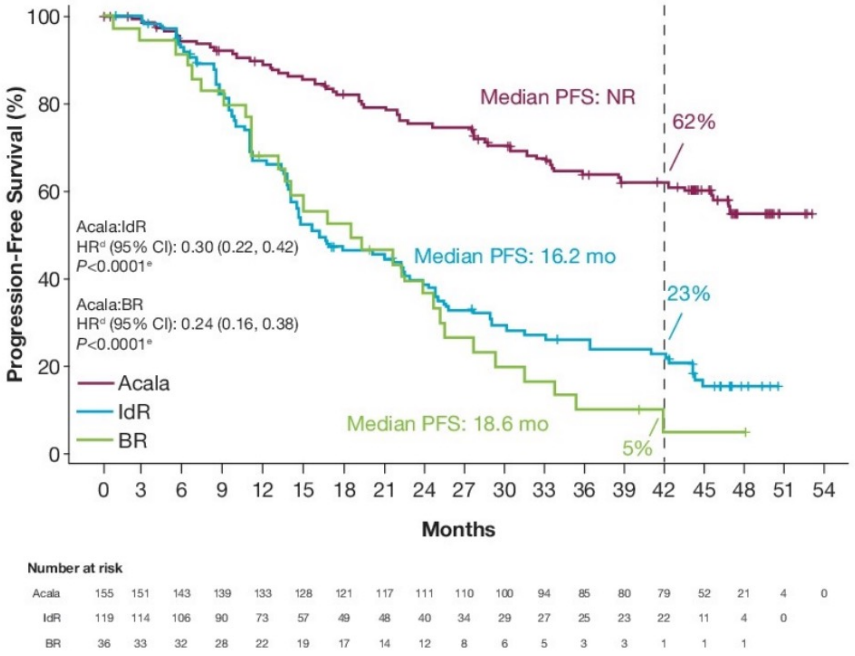


Byrd et al., 2014; Munir et al., 2019

BTKi Acalabrutinib in relapsed refractory patients

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

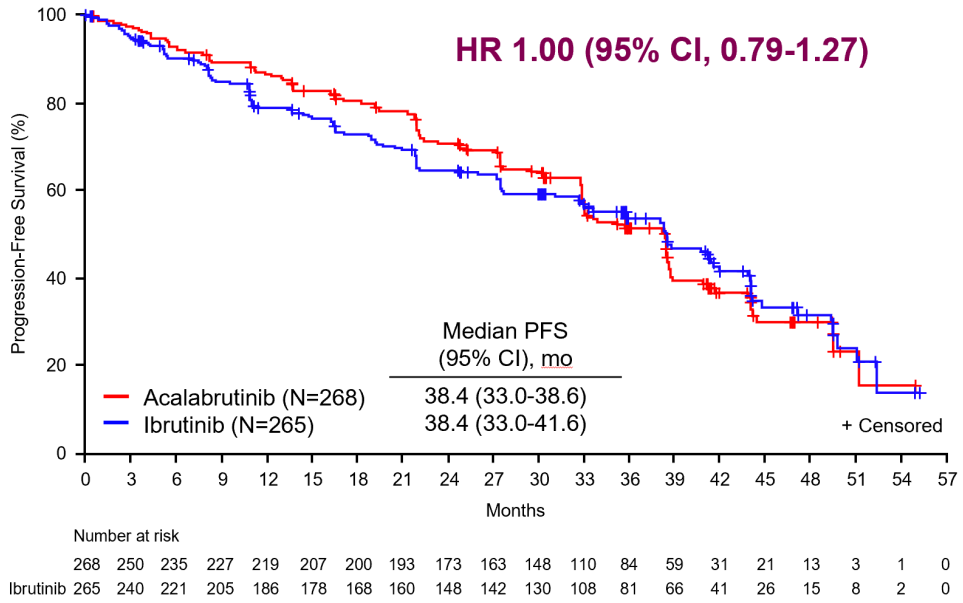
	Acalbruitnib n=101
Median Prior Tx	1 (1-8)
IGHV unm	70.3%
del(17p)	17.4%



Jurczac et al 2022

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

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



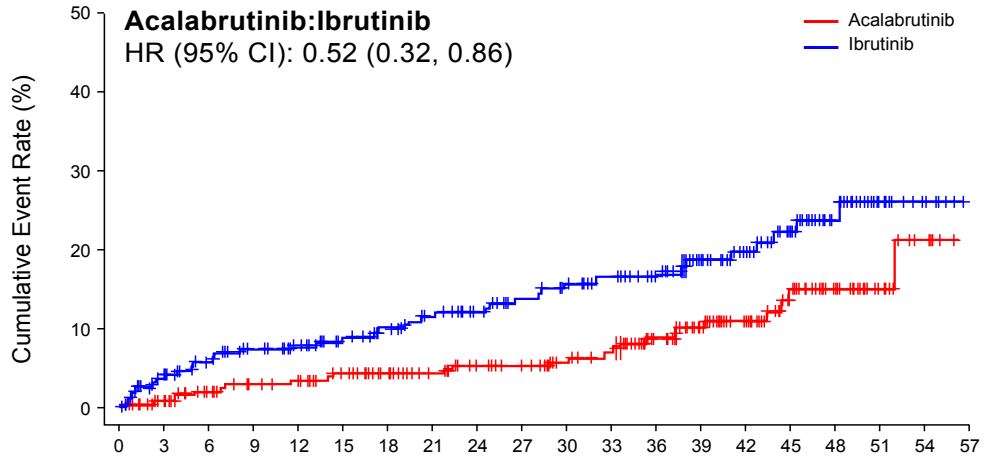
Byrd et al 2021

BTKi

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 (%)	25 (9.4)	42 (16.0)	−6.6	**0.0228**
95% CI[a]	(6.4, 13.5)	(12.0, 20.9)	(−12.2, −0.9)	
Infections, grade ≥3, n (%)	82 (30.8)	79 (30.0)	+0.8	0.8777
95% CI[a]	(25.6, 36.6)	(24.8, 35.8)	(−7.1, +8.6)	
Richter's transformation, n (%)	10 (3.8)	13 (4.9)	−1.2	0.5131
95% CI[a]	(2.1, 6.8)	(2.9, 8.3)	(−4.7, +2.3)	

Subgroup analysis	Acalabrutinib	Ibrutinib
Pts without prior history of AF/flutter	15/243 (6.2)	37/249 (14.9)

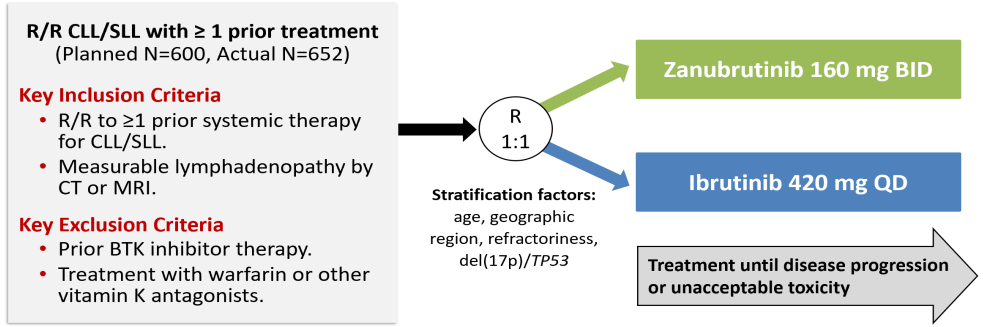


≥5% difference between arms are highlighted; **green** favors acalabrutinib, **red** favors ibrutinib.

[a]95% confidence interval based on Normal approximation (with use of Wilson's score). [b]Based on Cochran-Mantel-Haenzel test stratified by del(17p) status (yes vs no) and number of prior therapies (1-3 vs ≥4).

BTKi ZANUBRUTINIB IN RELAPSED REFRACTORY PATIENTS

Alpine Phase III Trial In R/R CLL

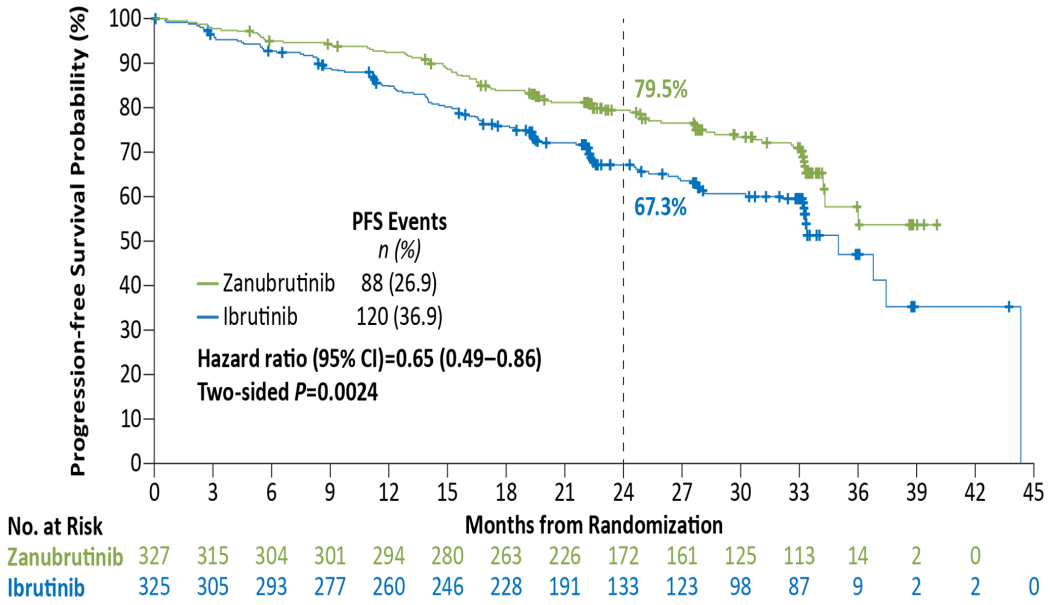


Median FU: 29.6 m

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

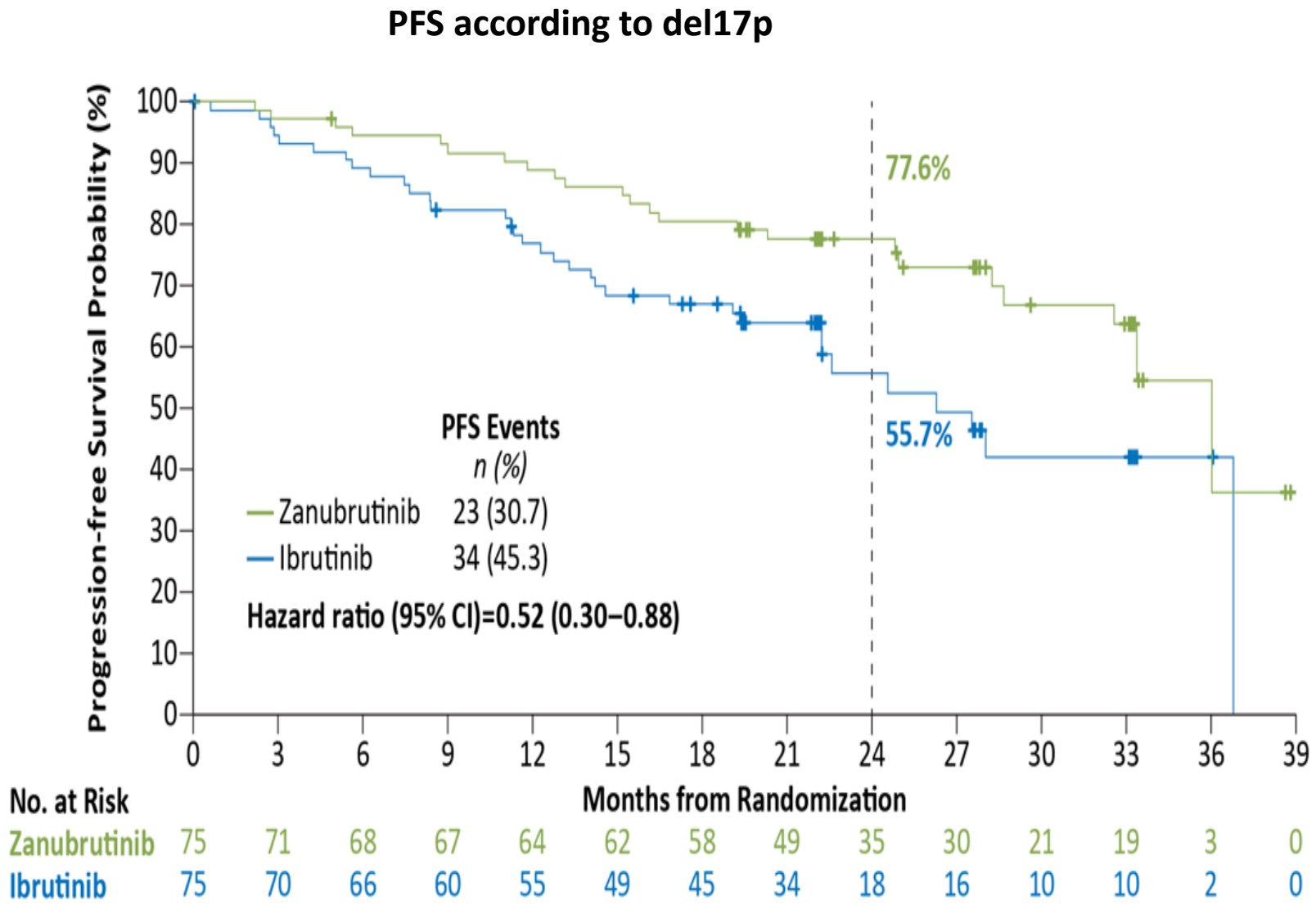
*Complex karyotype is defined as having ≥3 abnormalities.

Progression Free Survival



Brown et al, 2022

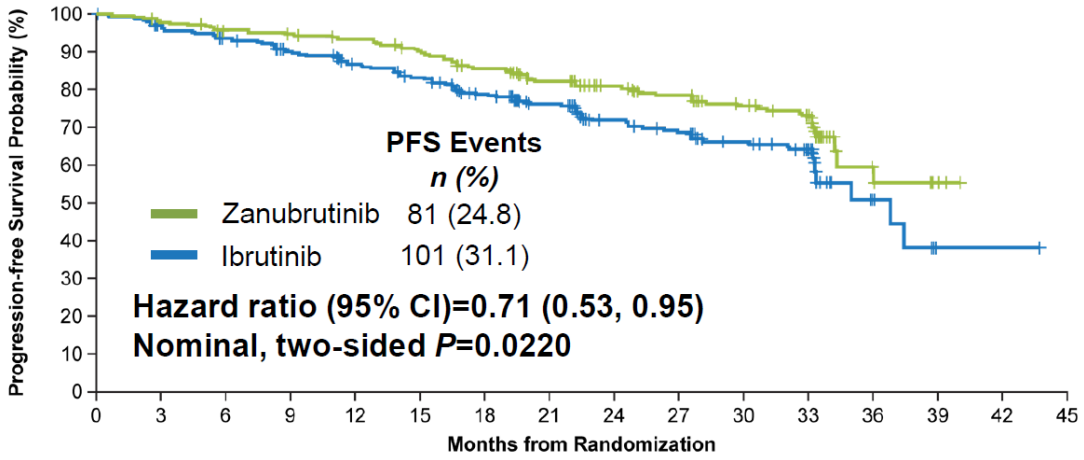
BTKi ALPINE: PFS according to del17p



Brown JR, et al. 2022

BTKi ALPINE: PFS according to del17p

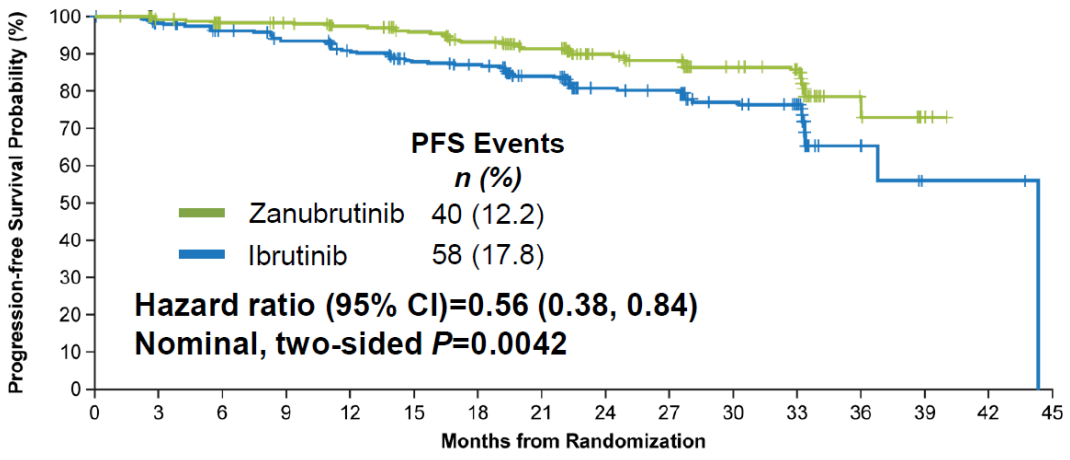
Drug Interruptions



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

Brown JR, et al. 2022

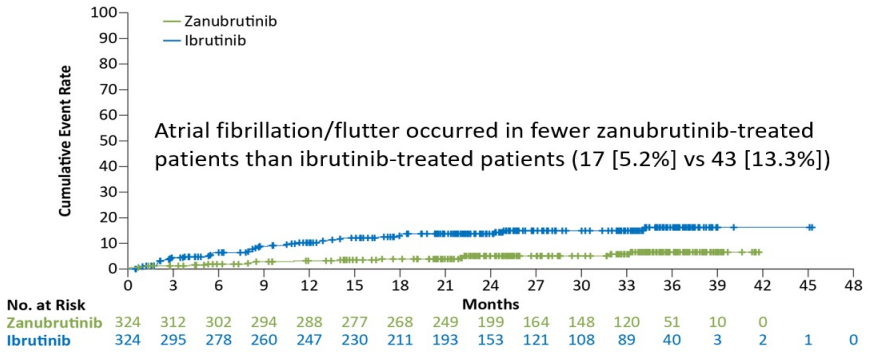
BTKi ALPINE: Safety data – Events of special interest

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)



Brown JR, et al. 2022

Venetoclax Rituximab

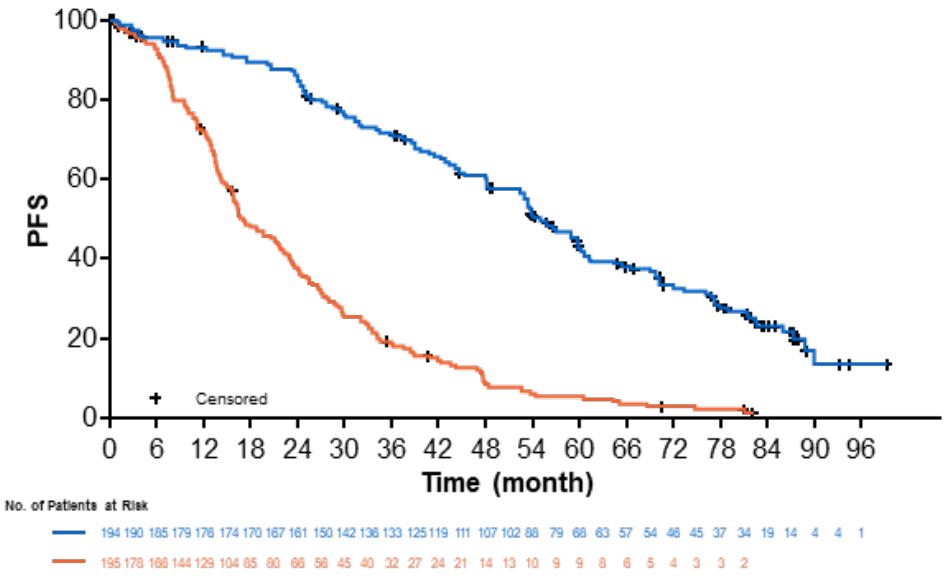
VENETOCLAX RITUXIMAB SALVAGE REGIMEN

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 2 3 or >3	111 (57.2) 58 (29.9) 25 (12.0)	117 (60) 43 (22.1) 35 (17.9)

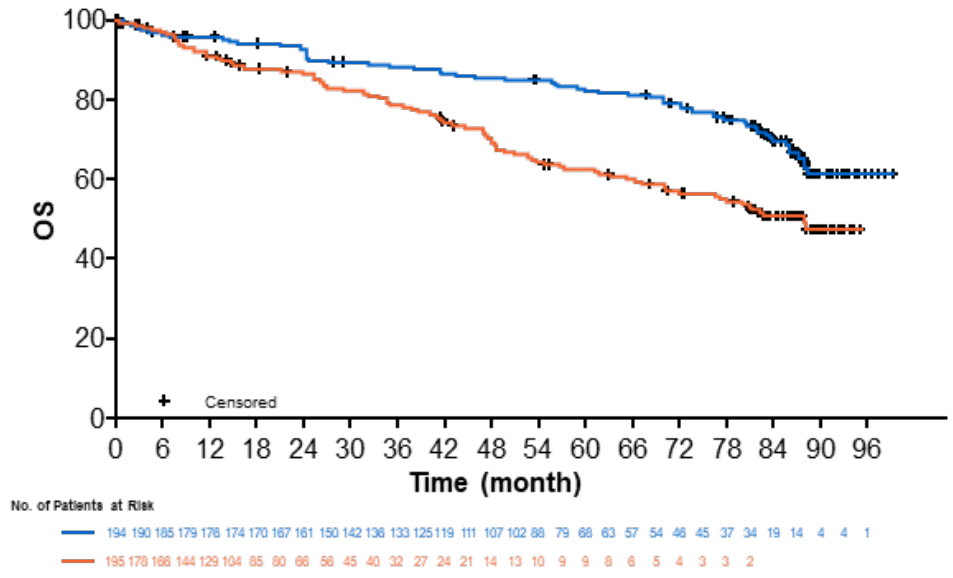
7 y follow-up

Progression Free Survival



	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



	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

Kater et al EHA 2023

Venetoclax Rituximab

VENETOCLAX RITUXIMAB SALVAGE REGIMEN

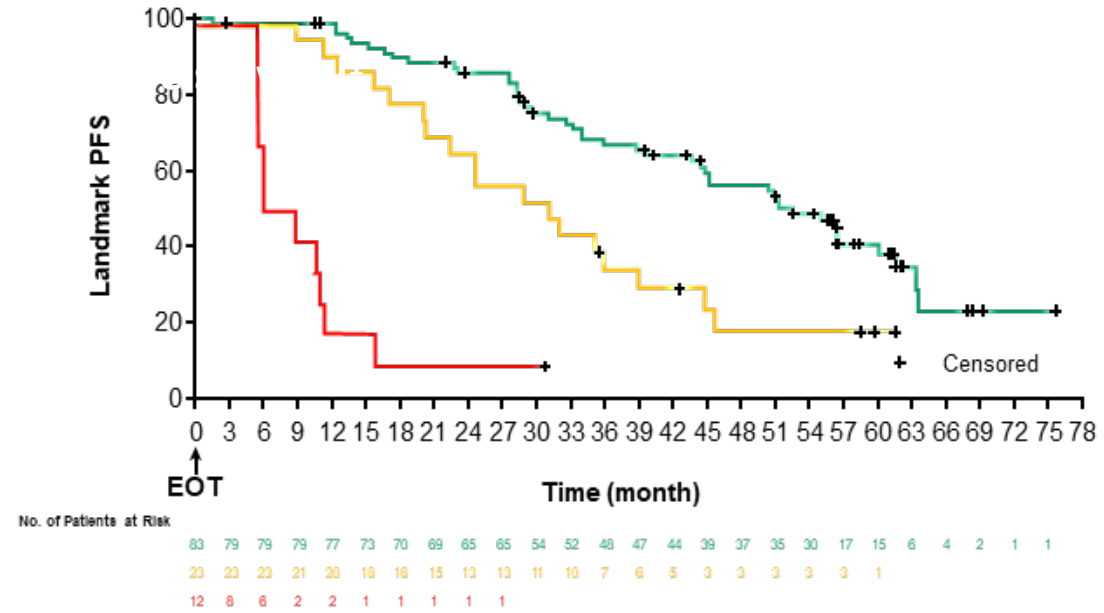
Phase III Murano study RR CLL: Venetoclax R versus Benda R

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 <0.0001[1†]
BR	**24.0** (20.7–29.5)[1]	

PFSaccording to MRD status

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) Stratified P-value <0.0001[†]
MRD+ (n=35)	**18.0** (8.5–29.3)	



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

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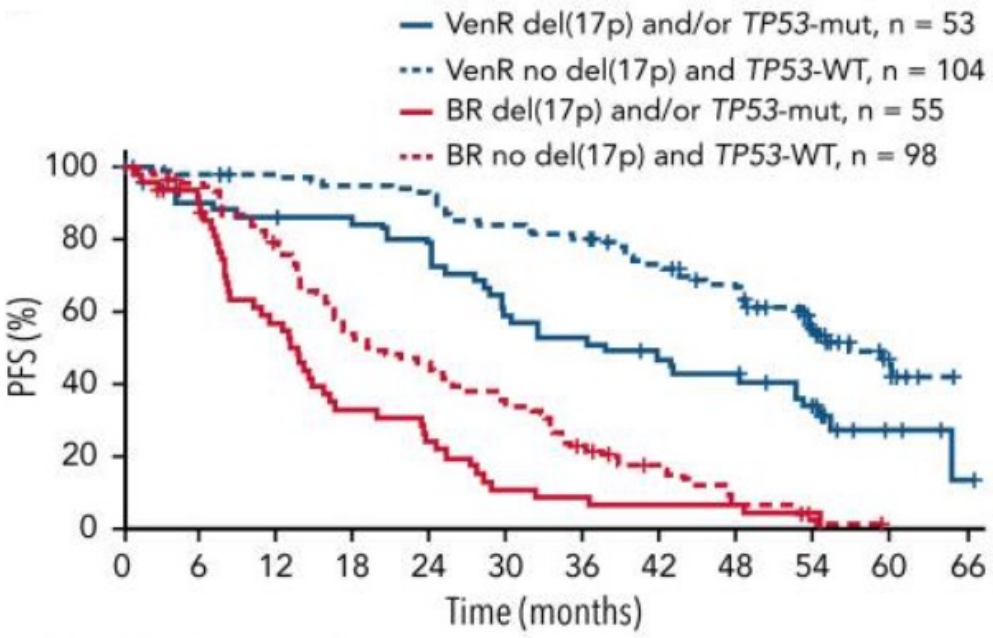
Venetoclax Rituximab

VENETOCLAX RITUXIMAB SALVAGE REGIMEN

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

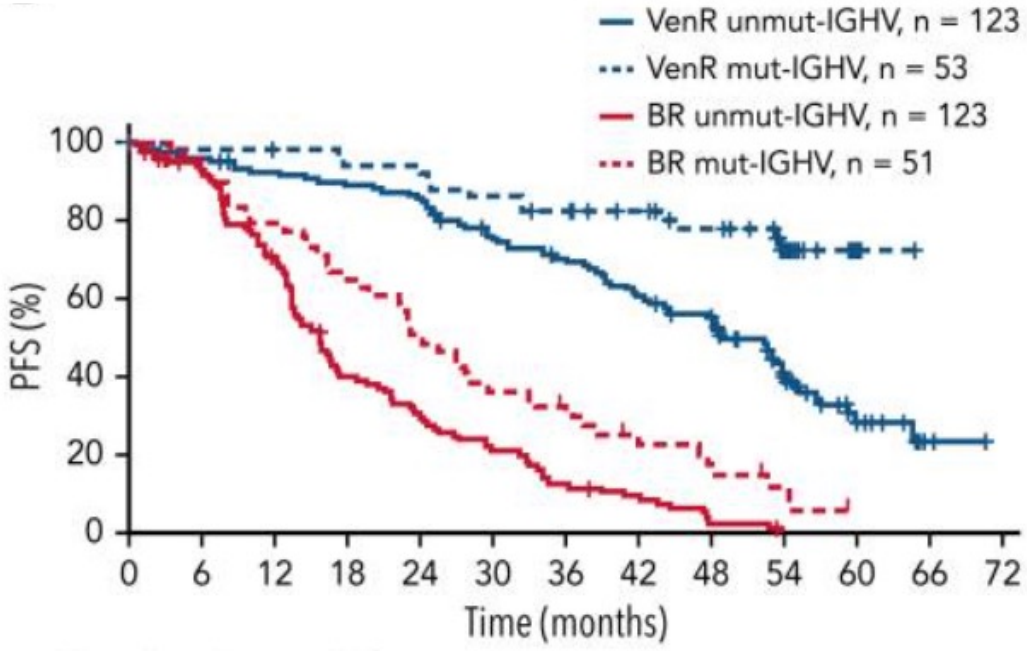
Median study follow-up 59.2 m

PFS del17p



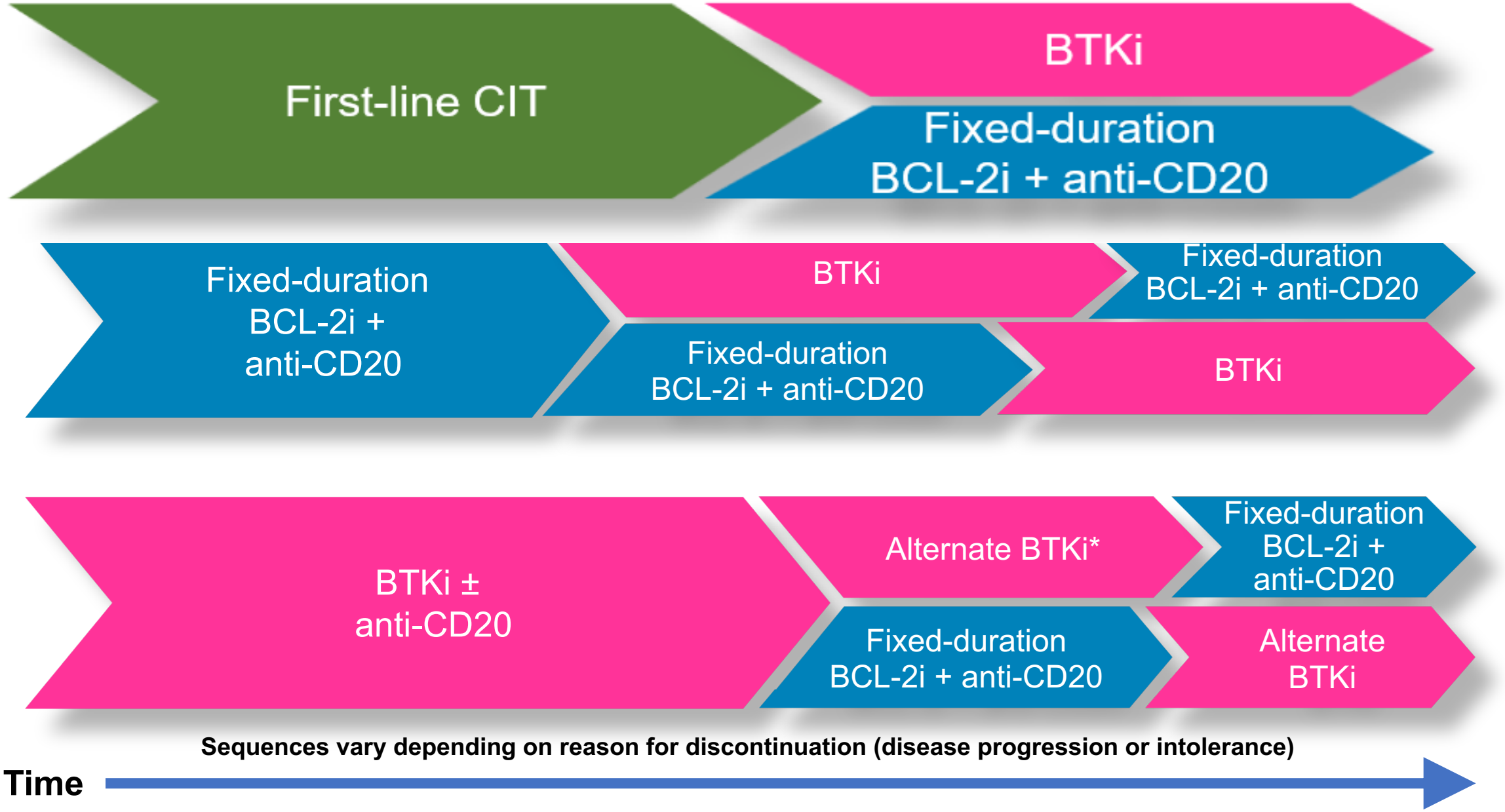
Category		Median PFS, months (95% CI)	HR (95% CI); *P* value†	5-year PFS, % (95% CI)
VenR	del(17p) and/or *TP53*-mut	37.4 (29.4, 52.3)	2.04 (1.32, 3.15);	27.3 (13.6, 41.0)
	No del(17p) and *TP53*-WT	56.6 (53.0, NE)	.0010	42.5 (28.9, 56.0)
BR	del(17p) and/or *TP53*-mut	13.4 (8.0, 15.8)	1.67 (1.15, 2.40);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

Seymour et al 2022

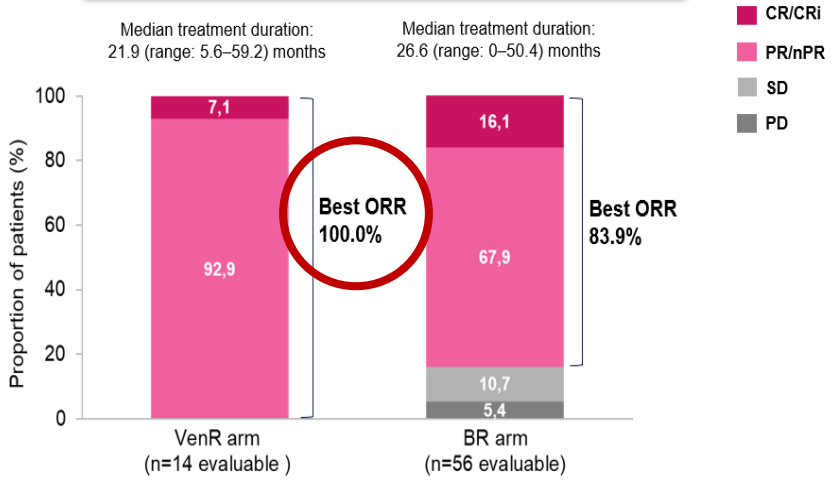


Alternate BTKi*: if intollerance

BCL-2i + anti-CD20 → BTKi

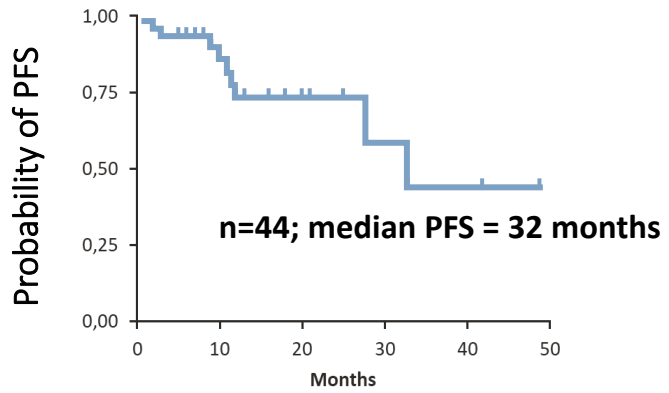
BCRi Treatment after Venetoclax: Clinical Trial Murano

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 centers[1]	Ibr post-Ven (n=25)* All patients were Ibr-naive	14 (56%)
BTKi post-Ven/VenR, in 2 Australian centers[3]	Ibr (n=21) or zanubrutinib (n=2) post-Ven† All patients were BCRi-naive	91%
BCRi[§] 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%



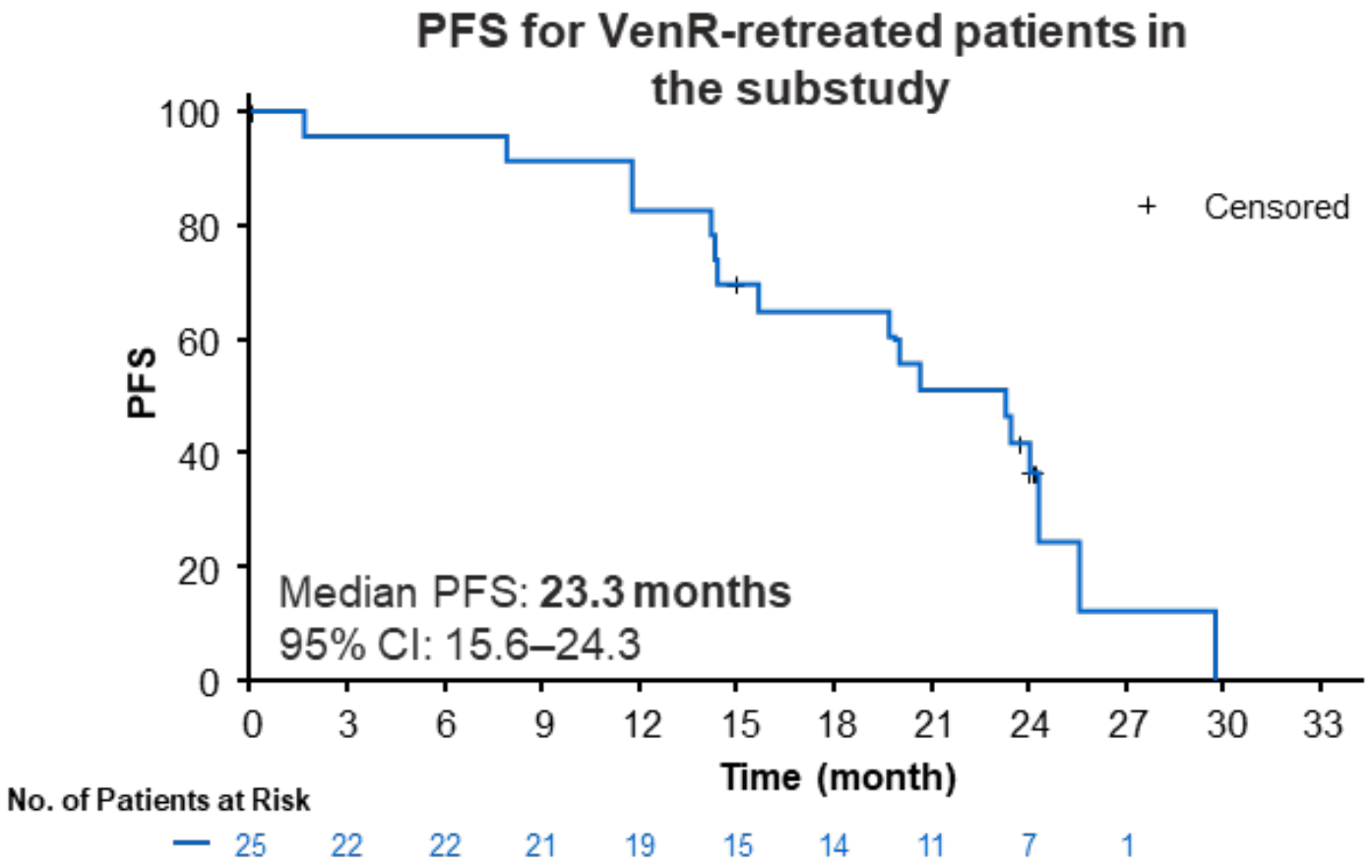
Harrup R, *et al*. ASH 2020. Abstract 3139 (Poster).

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.

BCL-2i + anti-CD20

BCL-2i + anti-CD20

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)

Kater et al EHA 2023

BTKi

BCL-2i + anti-CD20

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

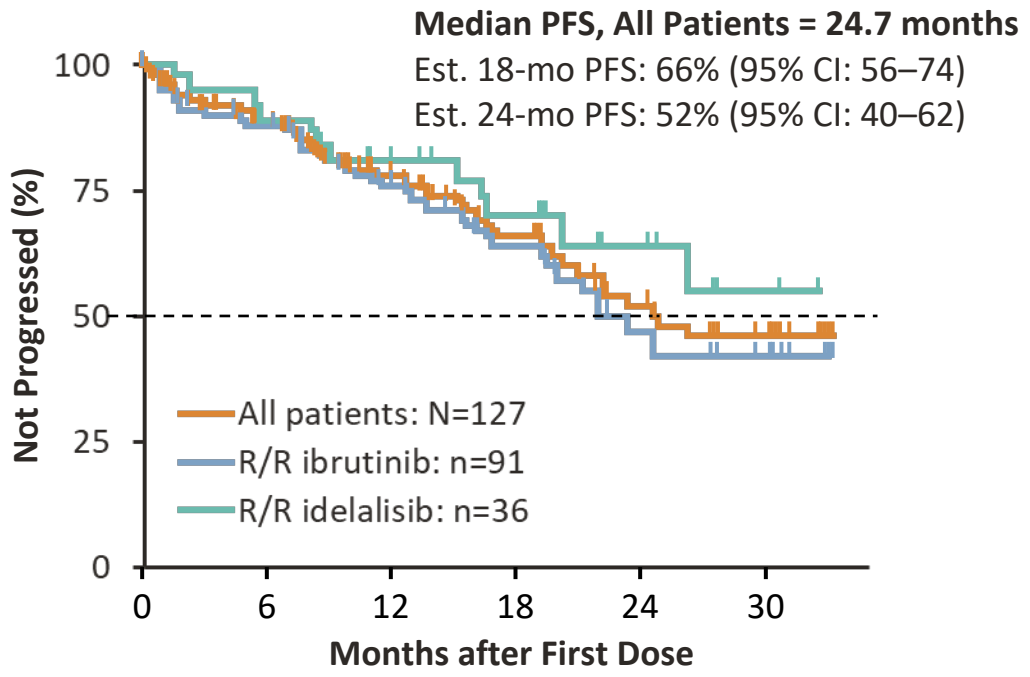
Phase 2
R/R CLL after ibrutinib or idelalisib (N=127)[1–3]

↓

Venetoclax PO QD to progression or unacceptable toxicity

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

PFS with Venetoclax Treatment



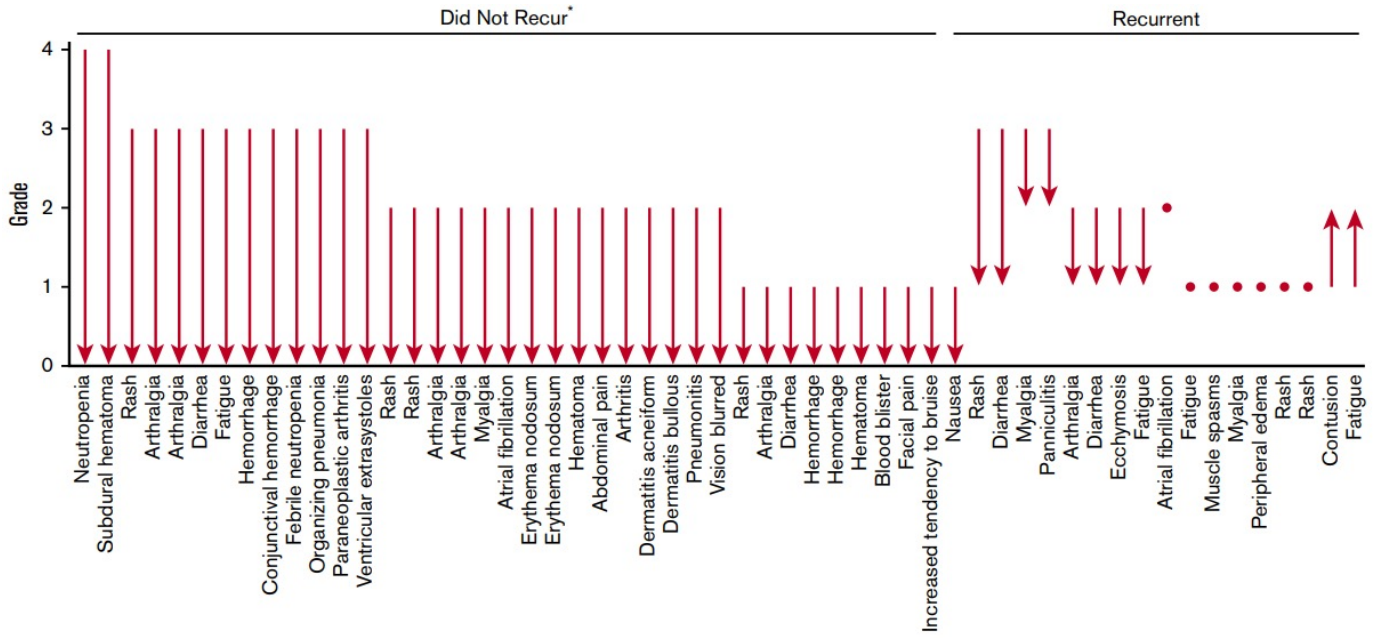
- **Median time on venetoclax: 17.3 months (range, 0.1–35.5)**

TTP, time to progression.

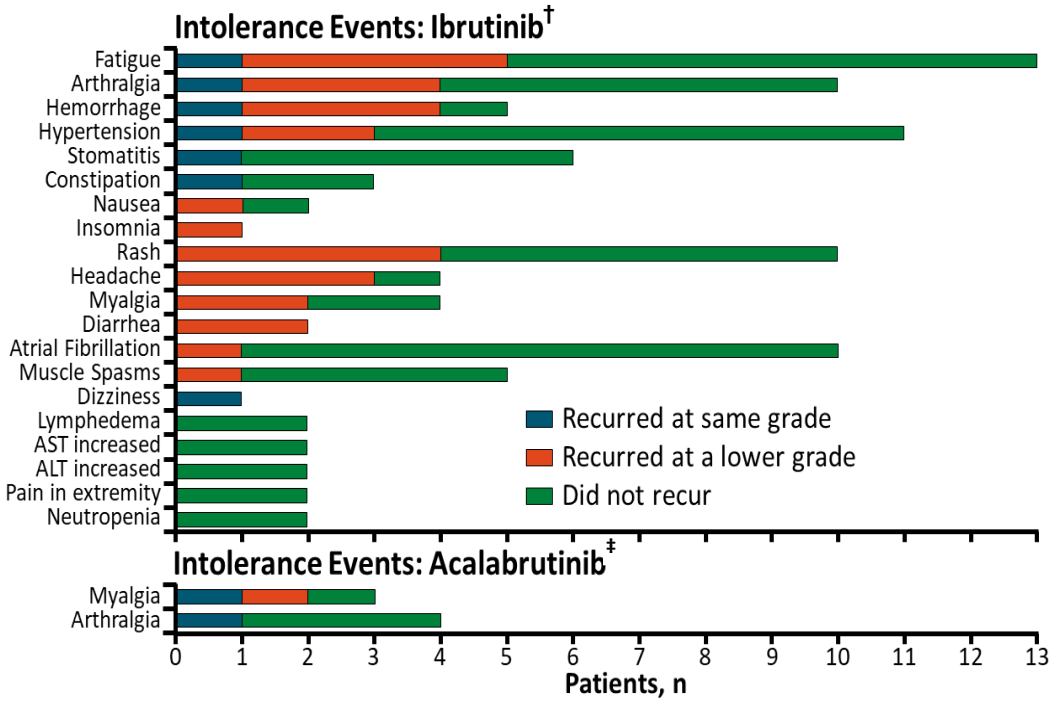
1. Jones JA, *et al. Lancet Oncol* 2018; **19:**65–75; 2. Coutre S, *et al. Blood* 2018; **131:**1704–1711; 3. Byrd JC, *et al.* ASCO 2018: Abstract 7512; poster presentation.

NEXT-GENERATION BTK INHIBITORS IN INTOLERANT PATIENTS

Acalabrutinib in patients intolerant to ibrutinib[1]



Zanubrutinib in patients intolerant to acalabrutinib or ibrutinib[2]



*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.

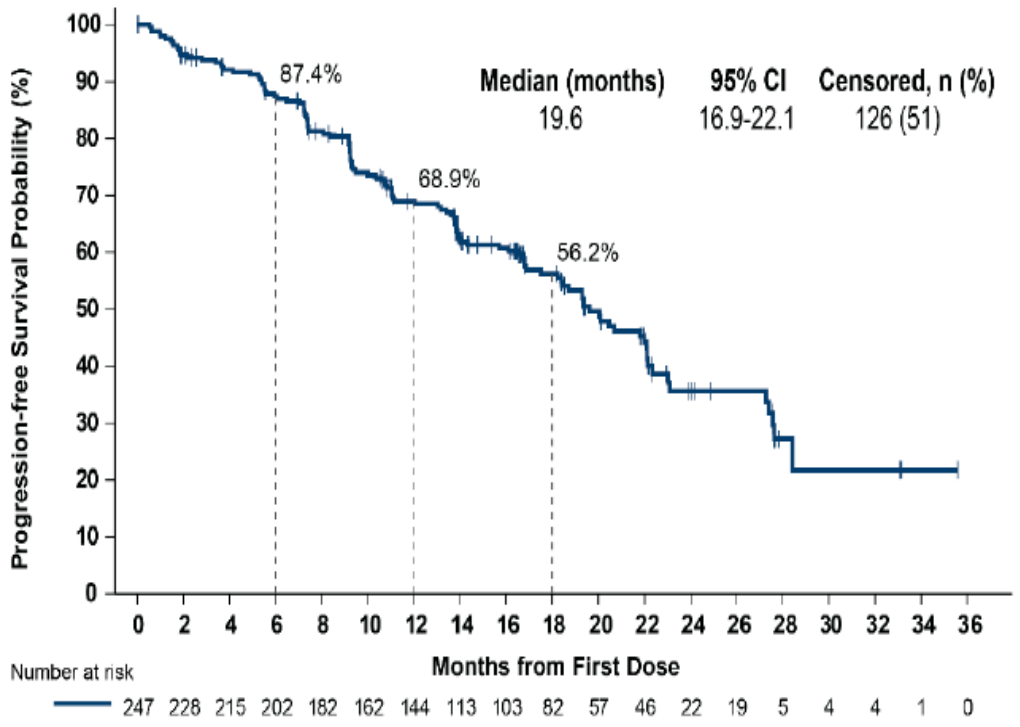
ALT, alanine aminotransferase; AST, aspartate aminotransferase BTK, Bruton's tyrosine kinase.

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

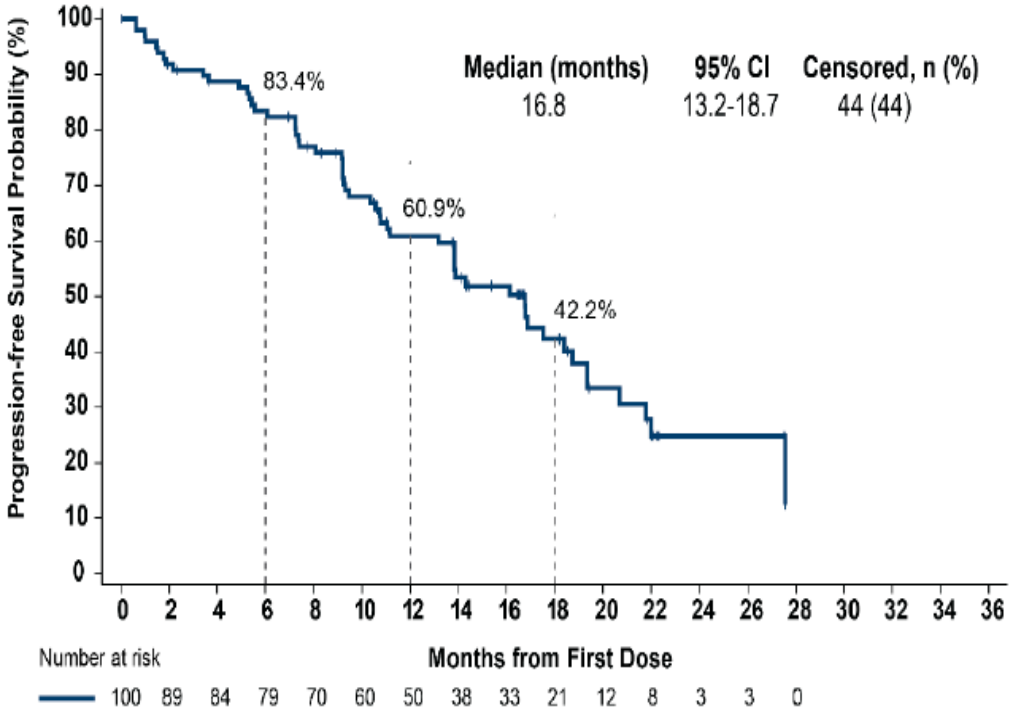
NON Covalent BTKi

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

All prior BTKi patients
Median prior lines = 3



Prior BTKi and BCL2i patients
Median prior lines = 5



- *Mato AR et al. Oral presentation at ASH 2022; New Orleans, LA, USA, December 10–13, 2022*

Conclusions

No current place for immuno-CHT in CLL treatment

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

No trials comparing fixed duration target therapy vs continuos 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 continuo tx**

-High Risk/genetic instability **….. cellular therapy**