“Treatment-Naive”: quali spunti e suggerimenti dai trial clinici di fase II e III»

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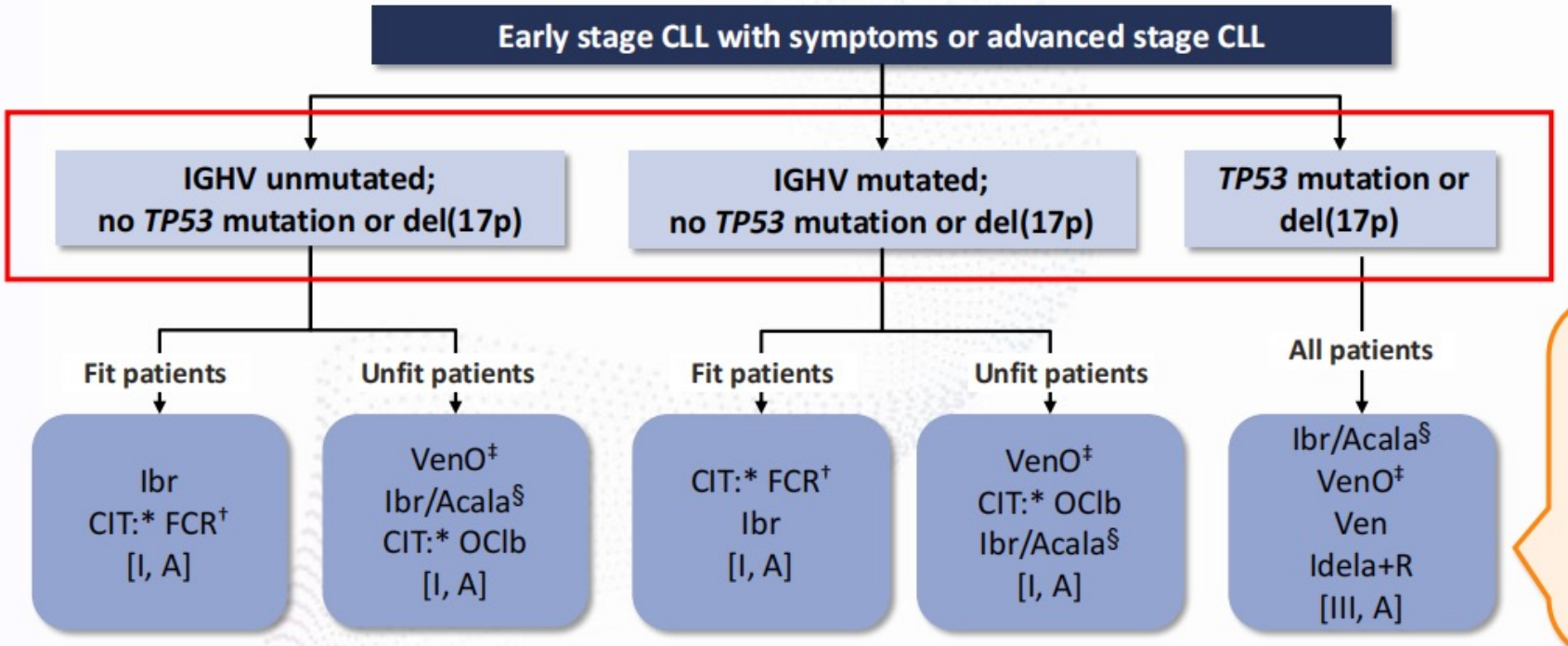
L’OTTIMIZZAZIONE DELLA
TERAPIA LEUCEMIA LINFATICA CRONICA:
UNA CONDIZIONE DINAMICA
ED INNOVATIVA

12-13 APRILE 2022 **BOLOGNA** ROYAL HOTEL CARLTON

ESMO 2021 guidelines for 1L CLL[1]



- Order of treatment for each subgroup based on expert opinion
- When evidence is equal for treatment options, time-limited therapies considered more valuable

I: Evidence from ≥1 large randomized, controlled trial of good methodological quality (low potential of bias) or meta-analyses of well-conducted randomized trials without heterogeneity; III: Prospective cohort studies; A: Strong evidence for efficacy with a substantial clinical benefit, strongly recommended.[2]

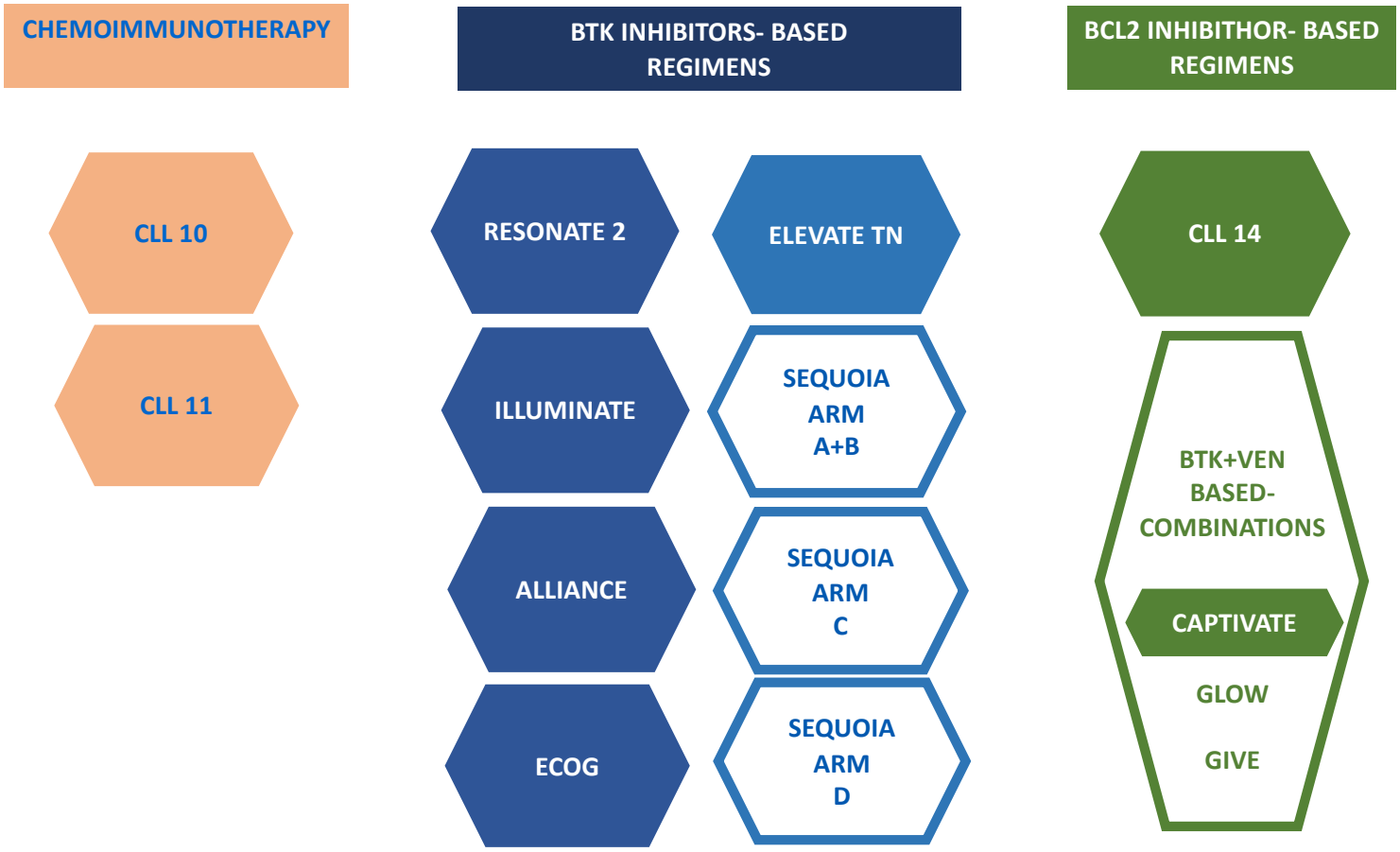
* CIT as alternative treatment, only if reasons against treatment with targeted therapies or non-availability;

† BR might be considered alternatively in patients >65 years; ‡ If available; § If approved and available.

Acala, acalabrutinib; CIT, chemoimmunotherapy; FCR, fludarabine + cyclophosphamide + rituximab; Ibr, ibrutinib; Idela+R, idelalisib + rituximab; OClb, obinutuzumab + chlorambucil; VenO, venetoclax + obinutuzumab; Ven, venetoclax.

1. Eichhorst B, *et al. Ann Oncol* 2021; **32**:23–33; 2. ESMO. Standard Operating Procedures. Available at: https://www.esmo.org/content/download/77789/1426712/file/ESMO-Clinical-Practice-Guidelines-Standard-Operating-Procedures.pdf (accessed August 2021).

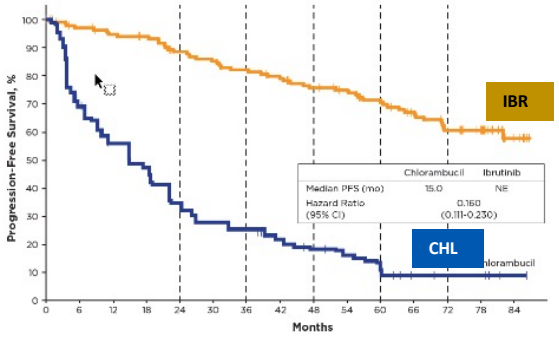
FRONT-LINE TREATMENT TRIALS IN CLL



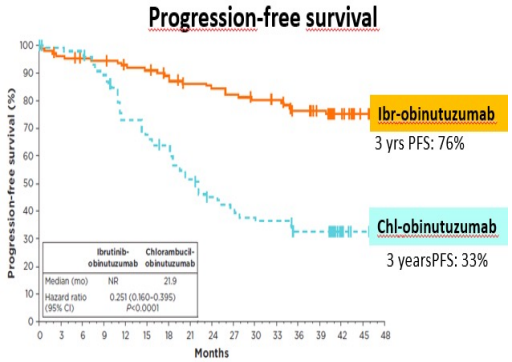
FRONT-LINE THERAPY WITH BTK INHIBITORS

FRONT-LINE TREATMENT WITH BTK INHIBITORS SUPERIOR TO CIT

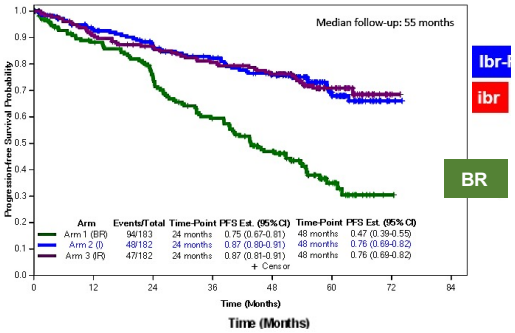
RESONATE 2 trial
Ghia et al.
2021 EHA



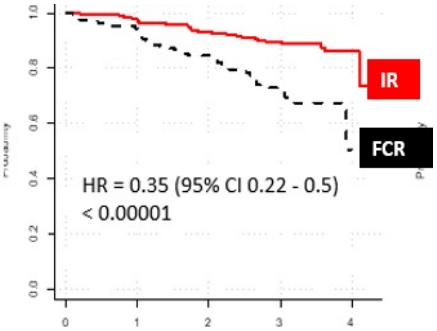
ILLUMINATE trial
Moreno et al.
Lancet Oncol. 2019



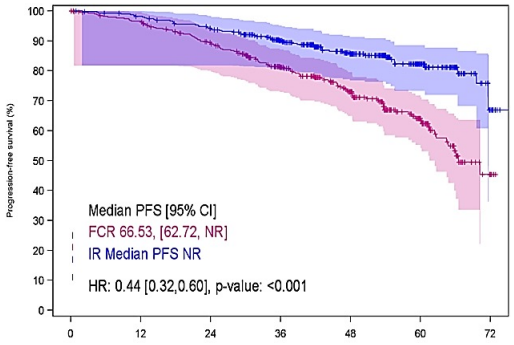
ALLIANCE trial
Woyach et al.
2021 ASH 2021



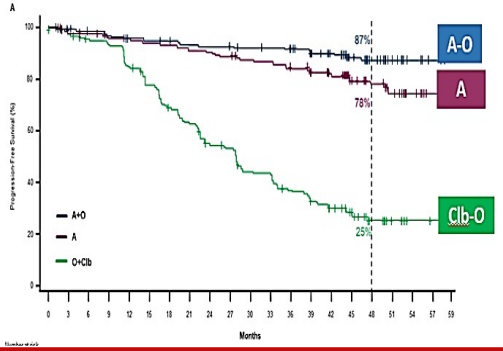
ECOG-E1912 trial
Shanafelt et al.
NEJM 2019



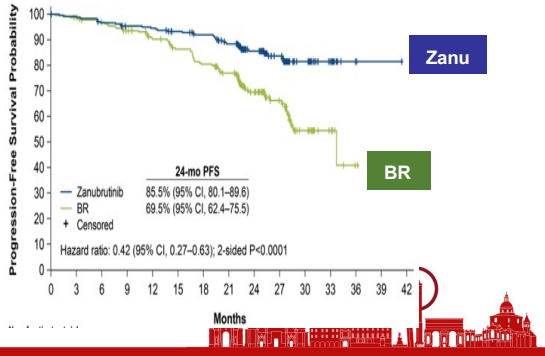
FLAIR TRIAL.
Hillmen et al.
2021 ASH



ELEVATE TN trial
Sharman et al.,
Lancet. 2020

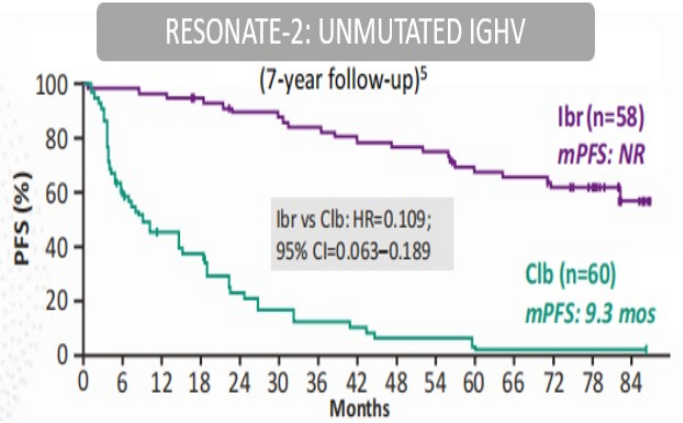


SEQUOIA Cohort 1
Tam et al.
2021 ASH

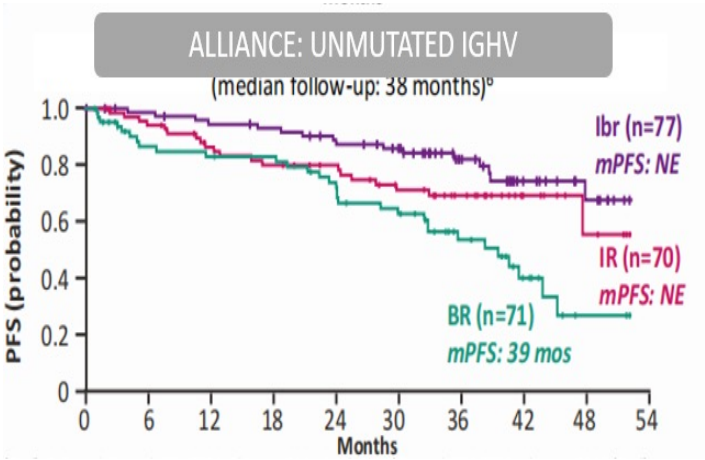


FRONT-LINE BTK INHIBITORS SUPERIOR TO CIT IN UM-IGHV PATIENTS

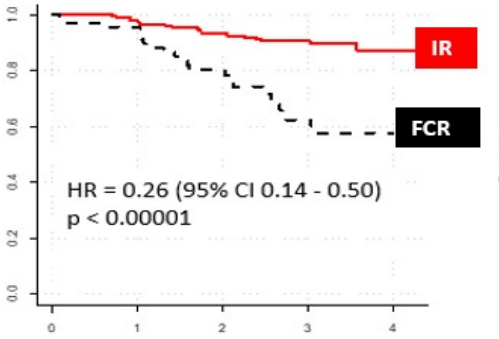
RESONATE-2: UNMUTATED IGHV



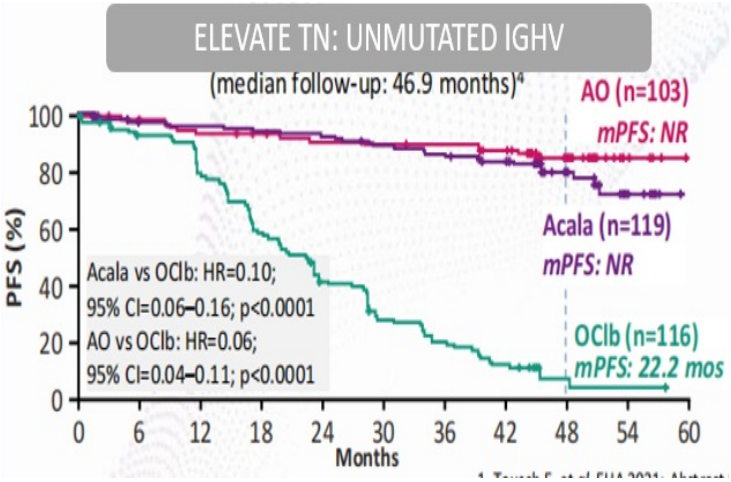
ALLIANCE: UNMUTATED IGHV



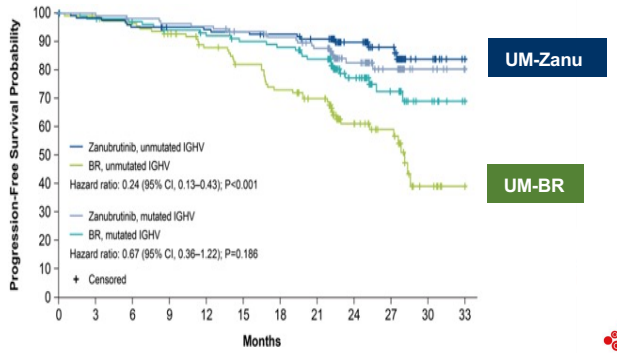
ECOG: UNMUTATED IGHV



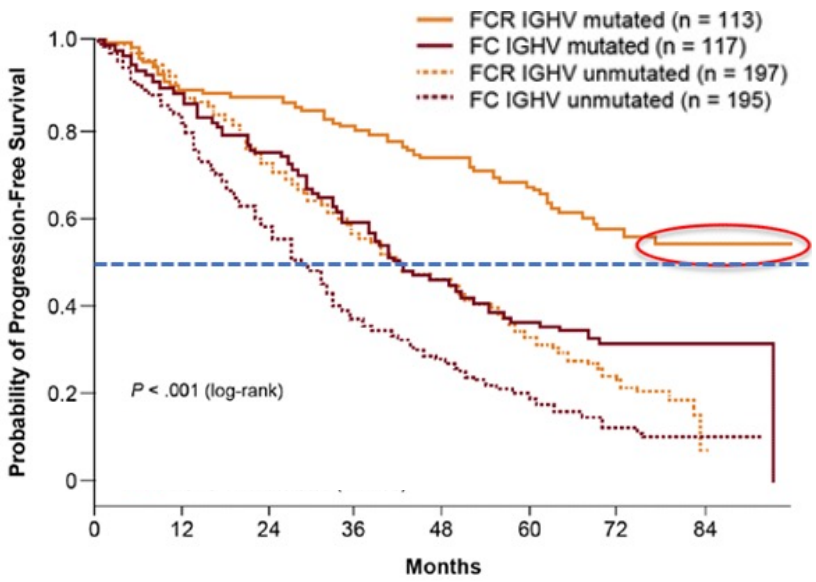
ELEVATE TN: UNMUTATED IGHV

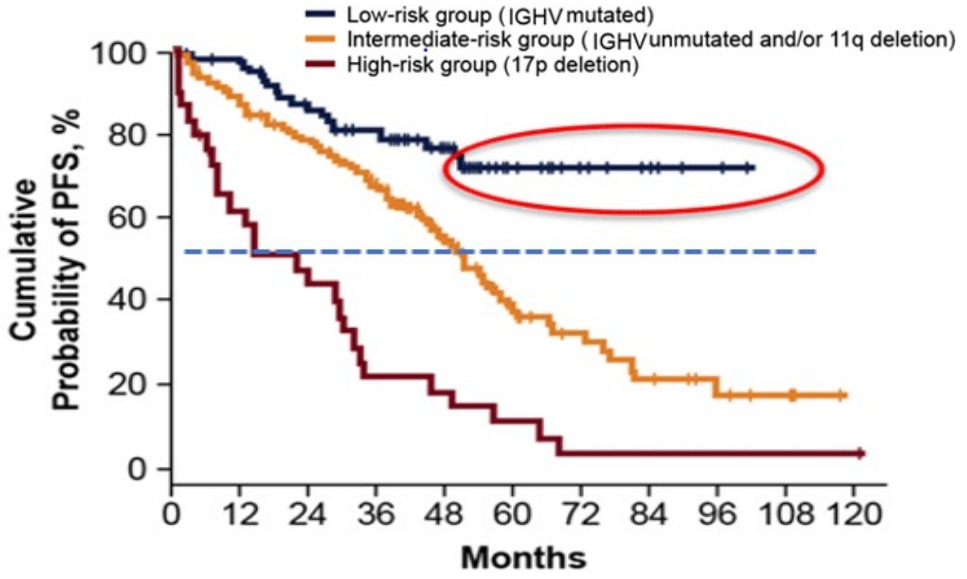


SEQUOIA: UNMUTATED IGHV



Favorable outcomes for IGHV-mutated patients treated with FCR in multiple studies

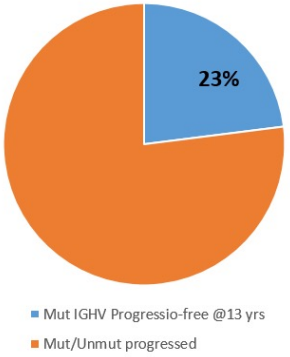




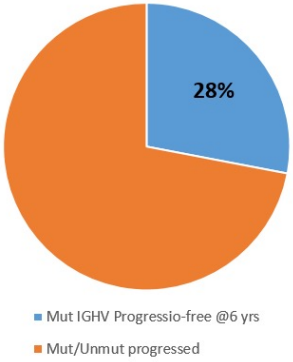
1. Fischer K et al. *Blood*. 2016;127:208-215. 2. Rossi D et al. *Blood*. 2015;126:1921-1924.

How many fit patients are IGHV mutated with a long lasting response with FCR ?

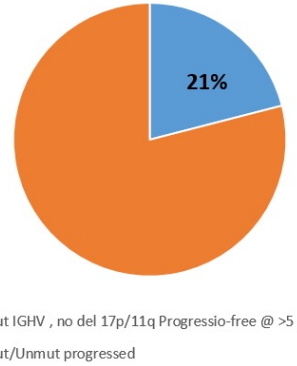
Thompson et al., Blood 2016

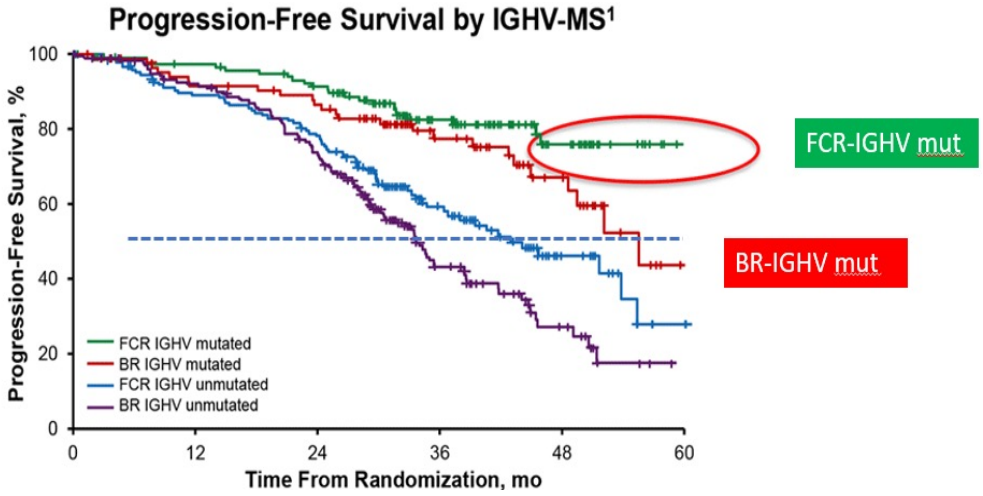


CLL8 Fisher et al. Blood 2015



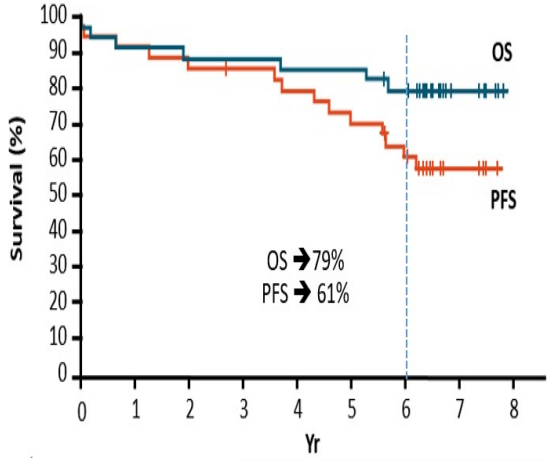
Rossi et al., Blood 2015



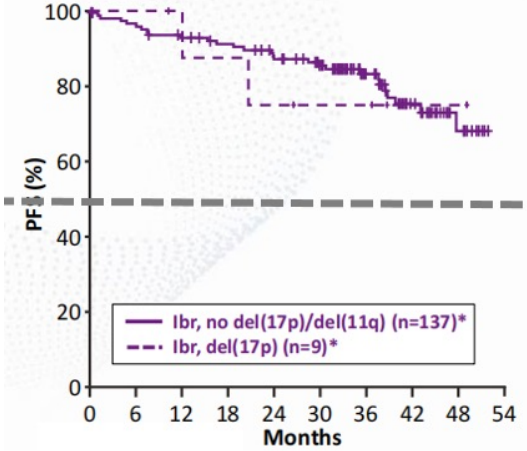


FRONT-LINE BTK INHIBITORS IN *TP*53 DISRUPTED PATIENTS

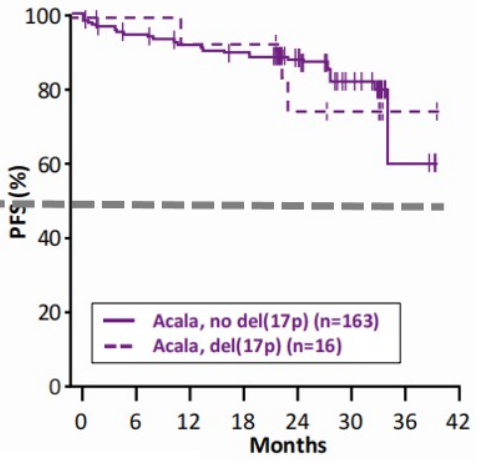
AHN et al. study



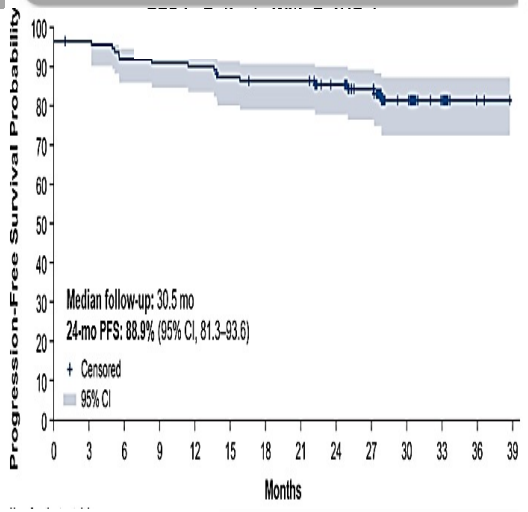
ALLIANCE



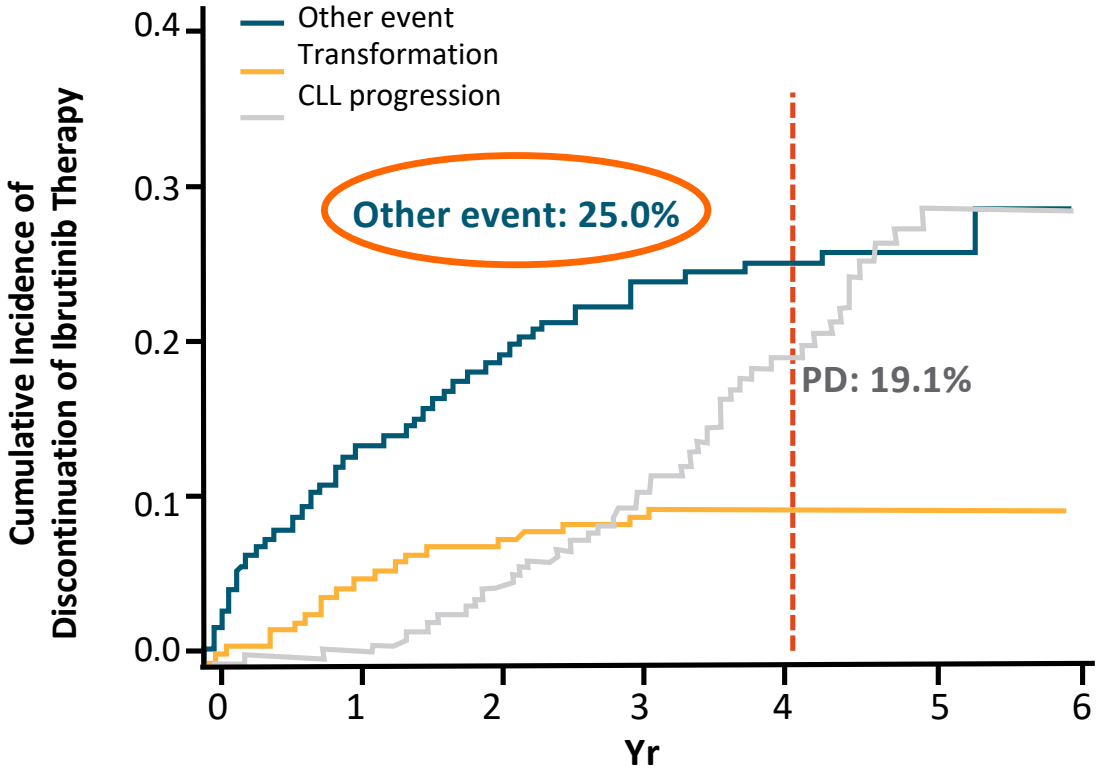
ELEVATE TN



SEQUOIA Cohort 2

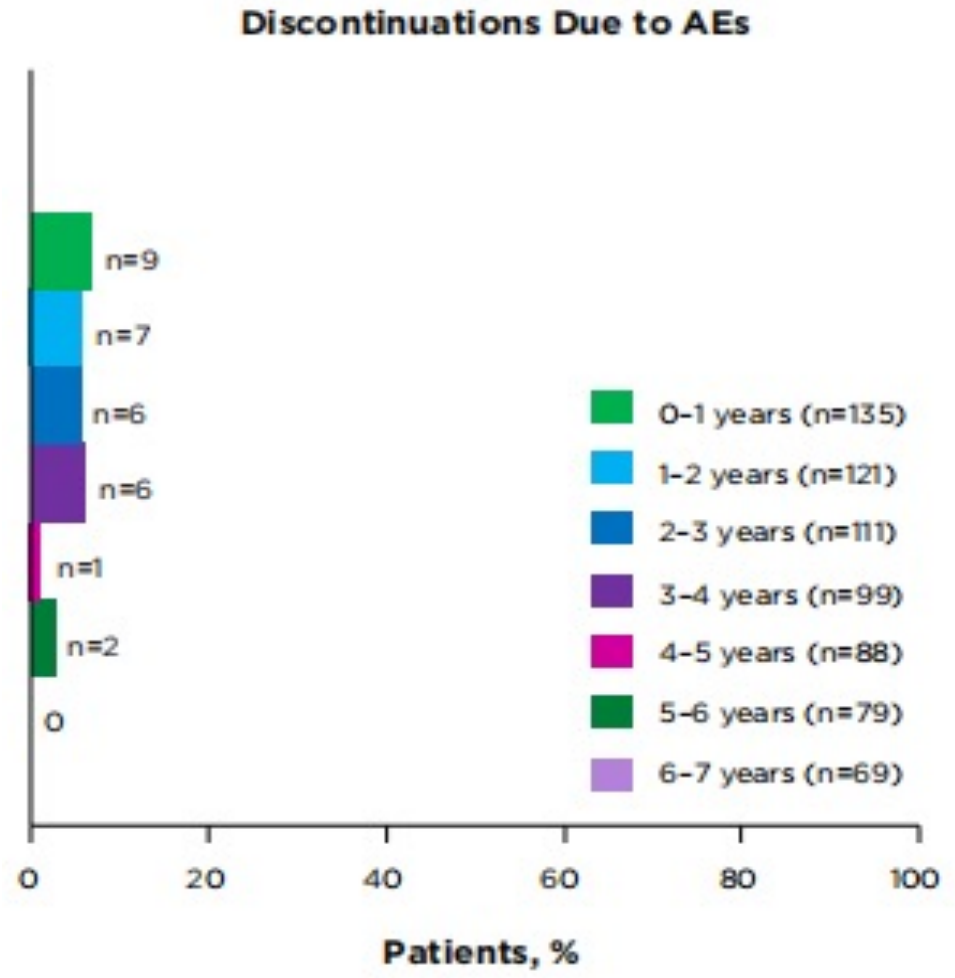


Ibrutinib Discontinuation Across 4 Clinical Trials



Woyach. JCO. 2017;35:1437. 2. Lampson. Expert Rev Hematol. 2018;11:185. 3. Mato. ASH 2019. Abstr 501. 4. Burger. Leukemia. 2020;34:787.

The Resonate2 Trial: treatment discontinuations due to AEs

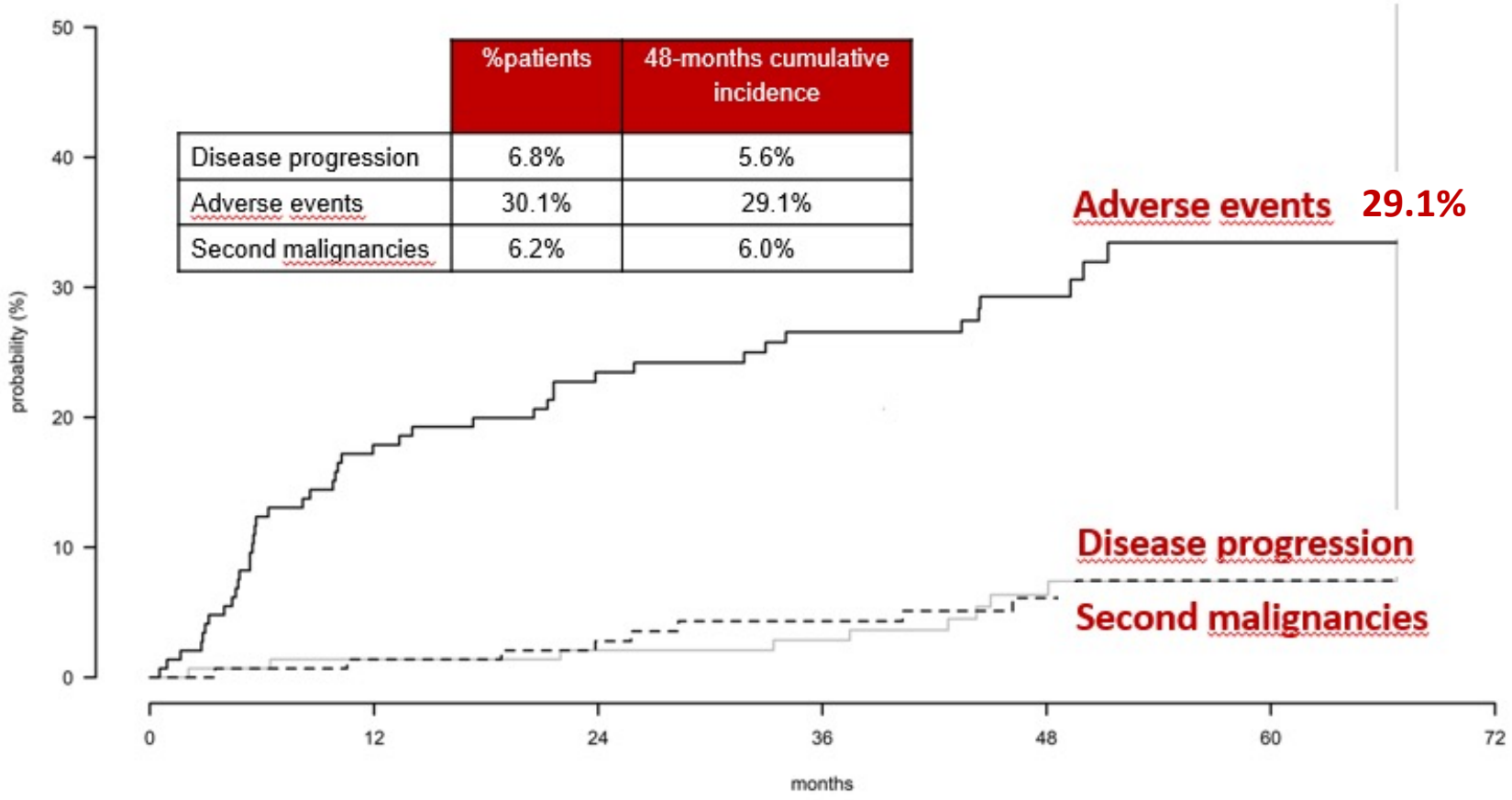


At follow-up up to 7 years
23% of patients experienced AEs
as the primary cause of ibrutinib discontinuation

Ghia et al., 2021 EHA

Ibrutinib dicontinuations: the GIMEMA LLC1114 trial

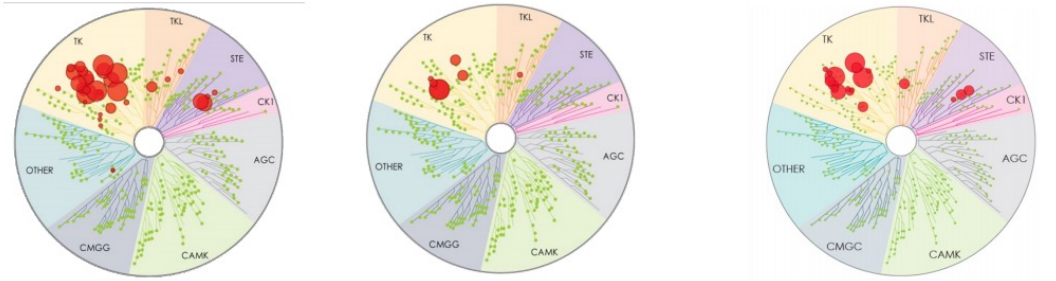
	%patients	48-months cumulative incidence
Disease progression	6.8%	5.6%
Adverse events	30.1%	29.1%
Second malignancies	6.2%	6.0%



SECOND GENERATION BTK INHIBITORS:EFFECTIVE WITH MORE FAVORABLE TOXICITY PROFILE

Second generation BTK inhibitors

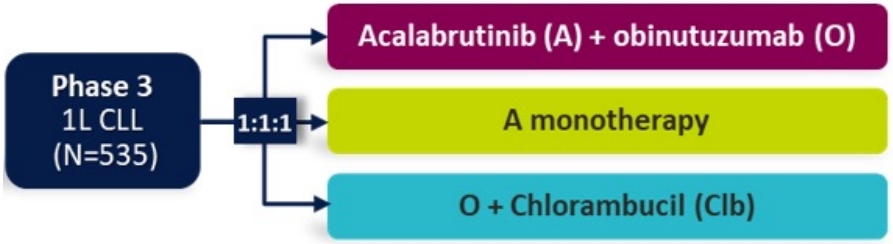
Ibrutinib | **Acalabrutinib** | **Zanubrutinib**

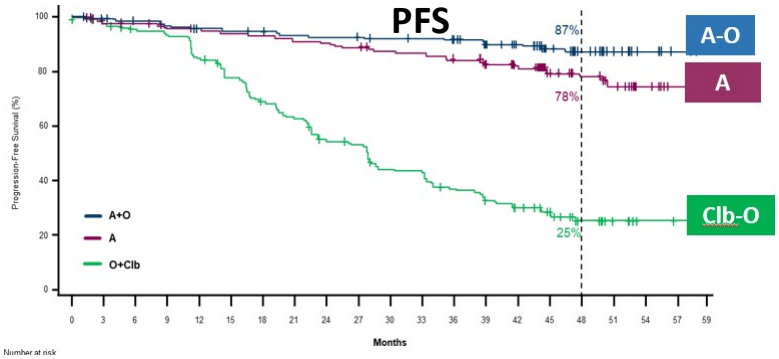


IC_{50}/EC_{50} (nM)

Kinase	Ibrutinib	Acalabrutinib	Zanubrutinib
BTK	1.5	5.1	0.5
TEC	10	126	44
ITK	4.9	> 1000	50
BMX	0.8	46	1.4
EGFR	5.3	> 1000	21
ERBB4	3.4	16	6.9
JAK3	32	> 1000	1377
BLK	0.1	> 1000	2.5

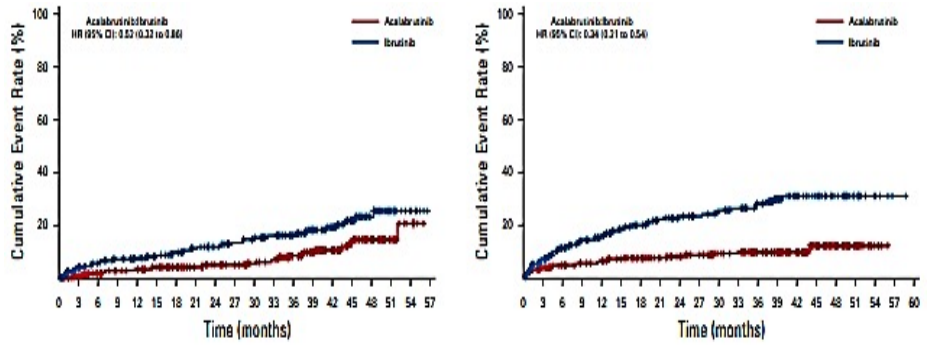
ELEVATE TN trial: Acalabrutinib with + Obinutuzumab vs Acalabrutinib vs. Obinutuzumab+ Chlorambucil in TN Patients With CLL





Events of Clinical Interest						
	A+O (n=178)		A (n=179)		O+Clb (n=169)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Cardiac events[a]	37 (20.8)	14 (7.9)[b]	34 (19.0)	15 (8.4)[c]	13 (7.7)	3 (1.8)
Atrial fibrillation	7 (3.9)	**1 (0.6)**	11 (6.1)	**2 (1.1)**	1 (0.6)	0
Bleeding	84 (47.2)	5 (2.8)	75 (41.9)	5 (2.8)	20 (11.8)	0
Major bleeding[d]	7 (3.9)	**5 (2.8)**	7 (3.9)	**5 (2.8)**	2 (1.2)	0
Hypertension	14 (7.9)	**6 (3.4)**	13 (7.3)	**5 (2.8)**	7 (4.1)	6 (3.6)
Infections	134 (75.3)	42 (23.6)	132 (73.7)	29 (16.2)	75 (44.4)	14 (8.3)
SPMs	28 (15.7)	13 (7.3)	24 (13.4)	5 (2.8)	7 (4.1)	3 (1.8)
SPMs excluding non-melanoma skin	15 (8.4)	10 (5.6)	11 (6.1)	4 (2.2)	3 (1.8)	2 (1.2)

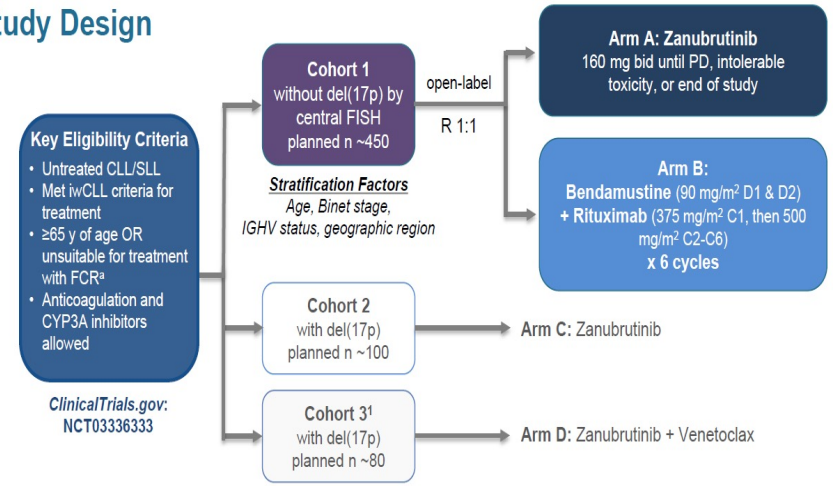
ELEVATE-RR: Ibrutinib vs Acalabrutinib in Patients With High-Risk R/R CLL



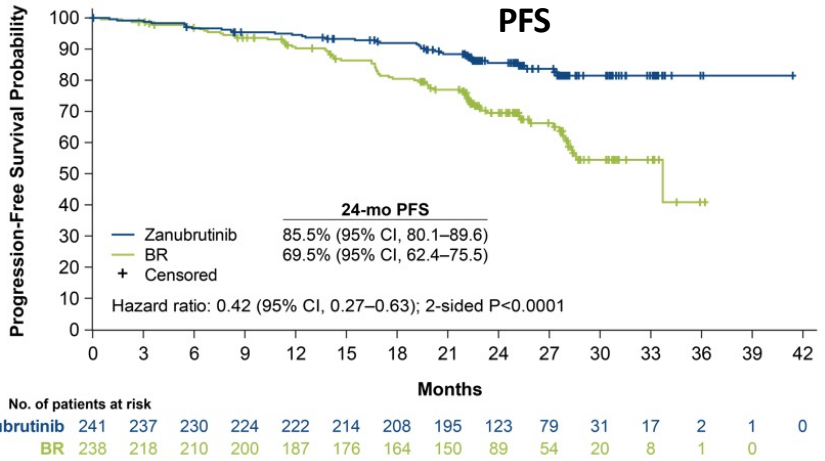
Sharman et al., ASCO 2021

SEQUOIA (BGB-3111-304): 1L Zanubrutinib vs BR

Study Design

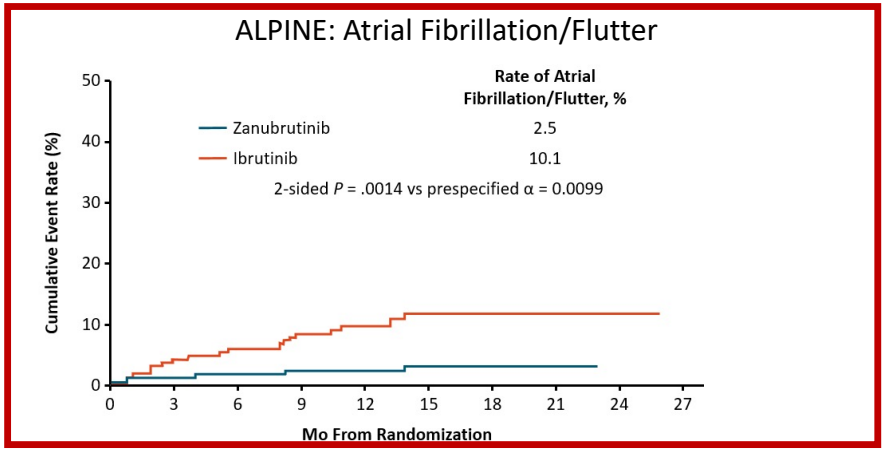


Median follow-up: 26.2 months



Common Adverse Events (≥12% of Patients in Any Arm)

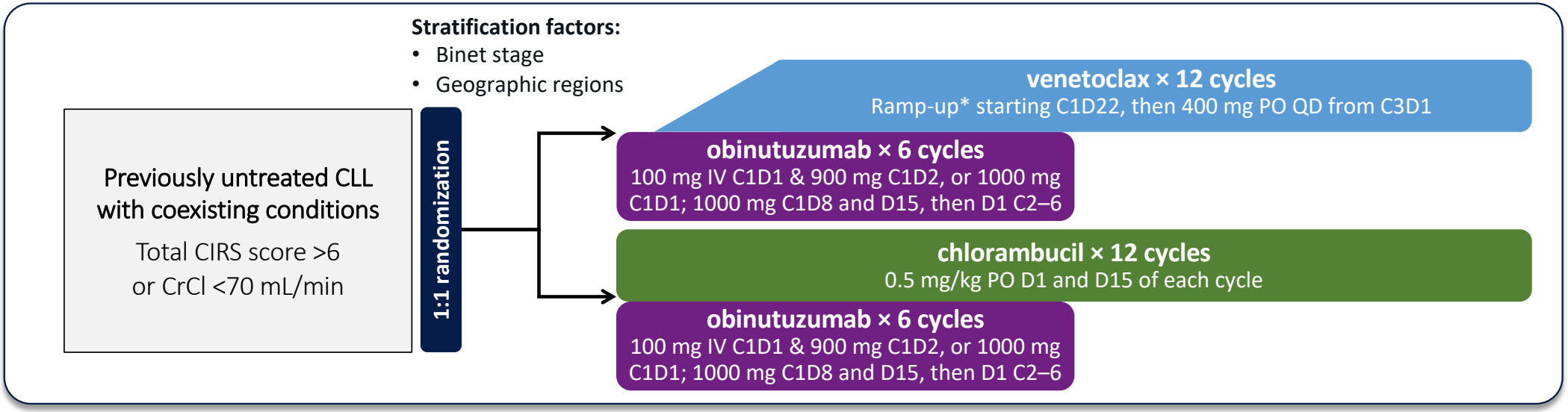
	Arm A Zanubrutinib (n=240[a])		Arm B Bendamustine + Rituximab (n=227[a])	
AE, n (%)	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Contusion	46 (19.2)	0 (0.0)	8 (3.5)	0 (0.0)
Upper respiratory tract infection	41 (17.1)	2 (0.8)	27 (11.9)	2 (0.9)
Neutropenia[b]	37 (15.4)	27 (11.3)	129 (56.8)	116 (51.1)
Diarrhea	33 (13.8)	0 (0.0)	30 (13.2)	4 (1.8)
Arthralgia	32 (13.3)	2 (0.8)	20 (8.8)	1 (0.4)
Fatigue	28 (11.7)	3 (1.3)	36 (15.9)	2 (0.9)
Rash	26 (10.8)	0 (0.0)	44 (19.4)	6 (2.6)
Constipation	24 (10.0)	1 (0.4)	43 (18.9)	0 (0.0)
Nausea	24 (10.0)	0 (0.0)	74 (32.6)	3 (1.3)
Pyrexia	17 (7.1)	0 (0.0)	60 (26.4)	8 (3.5)
Vomiting	17 (7.1)	0 (0.0)	33 (14.5)	3 (1.3)
Anemia	11 (4.6)	1 (0.4)	43 (18.9)	4 (1.8)
Thrombocytopenia	9 (3.8)	4 (1.7)	31 (13.7)	16 (7.0)
Infusion-related reaction[c]	1 (0.4)	0 (0.0)	43 (18.9)	6 (2.6)



Tam et al., ASH 2021

FRONT-LINE THERAPY WITH BCL2 INHIBITORS

Venetoclax-obinutuzumab for TN patients with CLL: 4-year follow.up of the randomized CLL14 Trial



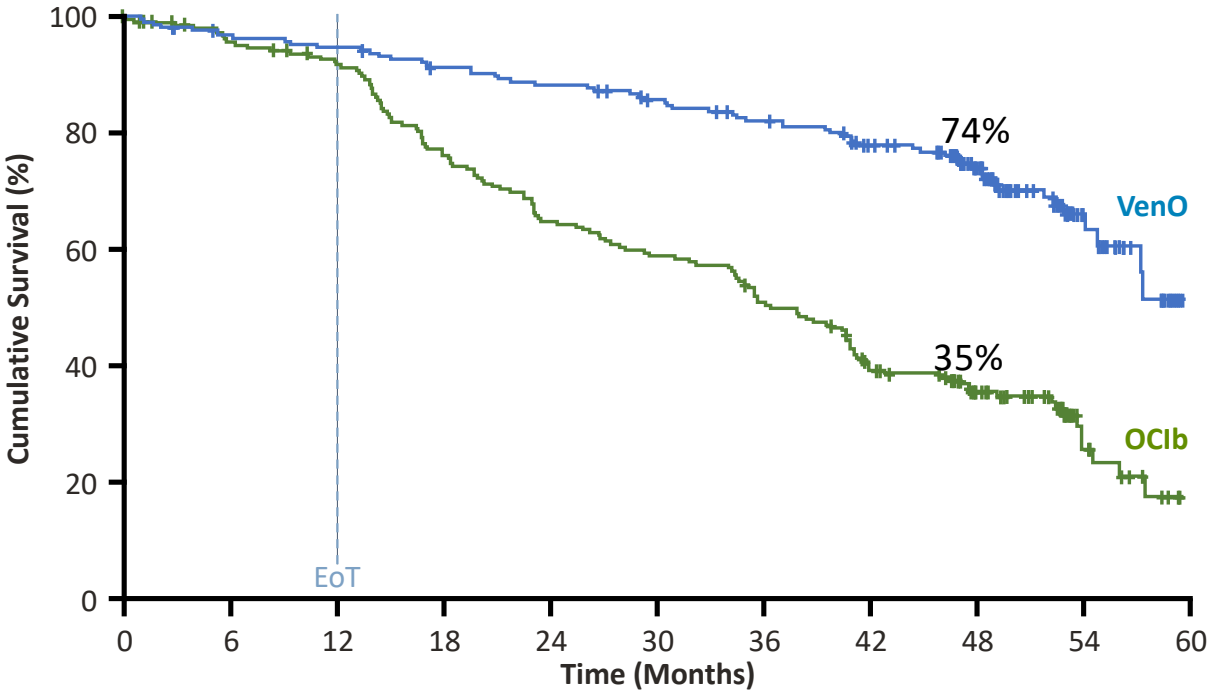
Primary Endpoint (ITT Population):
- PFS – investigator-assessed

Key Secondary Endpoints (ITT Population):
- PFS – IRC-assessed
- ORR and CR 3 months after EoT
- MRD– rate (PB and BM) 3 months after EoT
- OS

Characteristic		VenO (n=216)	OClb (n=216)
Age	Median, years (IQR)	72 (67–77)	71 (66–77)
TLS risk category, n (%)	Intermediate High	139 (64) 48 (22)	147 (68) 43 (20)
Total CIRS score	>6, n (%)	186 (86)	177 (82)
Estimated CrCl*	<70 mL/min, n/N (%)	129/215 (60)	119/213 (56)
***IGHV* mutation status, n/N (%)**	Unmutated	121/200 (61)	123/208 (59)
TP53* deleted and/or mutated, n/N (%)		25/209 (12)	24/208 (12)

Fisher et al., NEJM 2019; Al-Sawaf O, *et al.* EHA 2021;

Investigator-Assessed PFS (ITT Population): 4 Years Post-Randomization

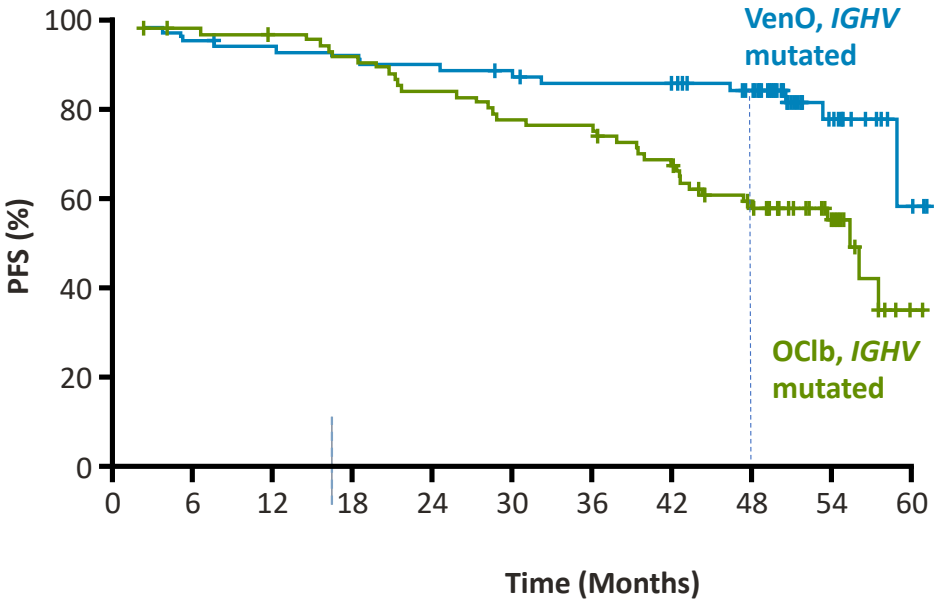


- Median observation time: 52 months
- All patients off treatment for ≥3 years

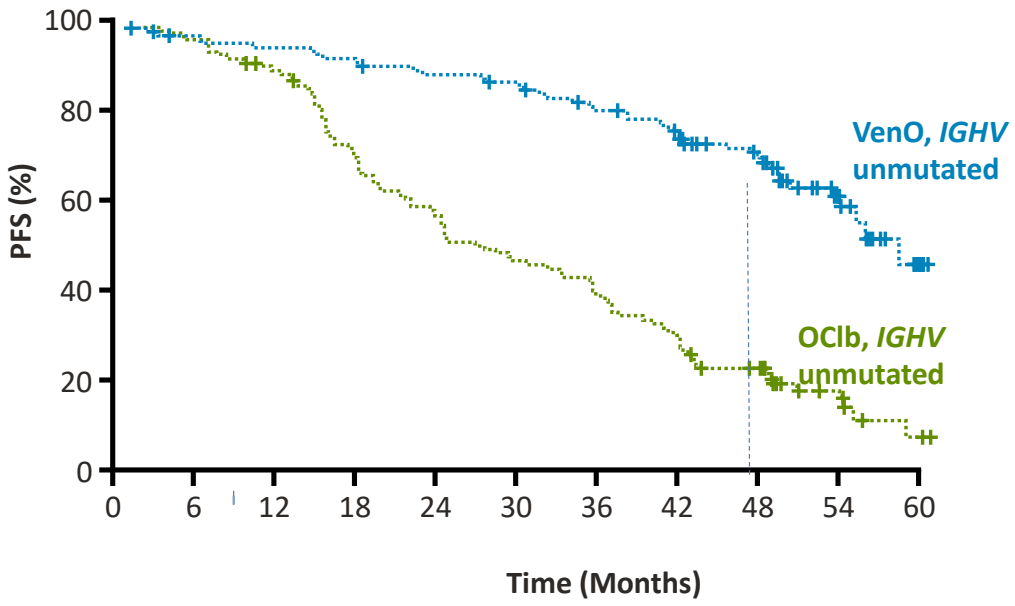
	VenO (n=216)	OCIb (n=216)
HR (95% CI) p-value	0.33 (0.25–0.45) p<0.0001, descriptive	
48-month PFS estimate, %	74.0	35.4
Median PFS, months	NR	36.4

Al-Sawaf O et al. EHA 2021

Investigator-Assessed PFS by IGHV mutational status: 4 Years Post-Randomization



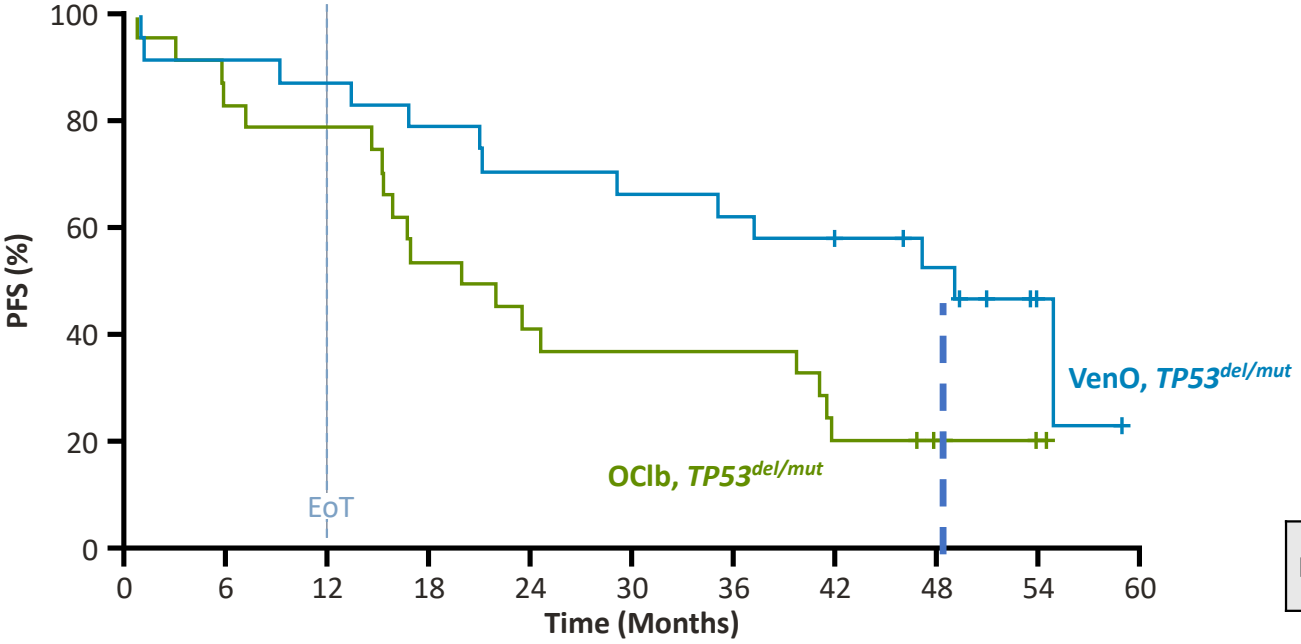
	IGHV mutated	
	VenO	OClb
Median PFS, months	NR	54.5
HR (95% CI)[2]	0.36 (0.19–0.68)	



	IGHV unmutated	
	VenO	OClb
Median PFS, months	57.3	26.9
HR (95% CI)[2]	0.25 (0.17–0.37)	

Al-Sawaf O et al. EHA 2021

Investigator-Assessed PFS in Patients with Aberrant *TP53*: 4 Years Post-Randomization

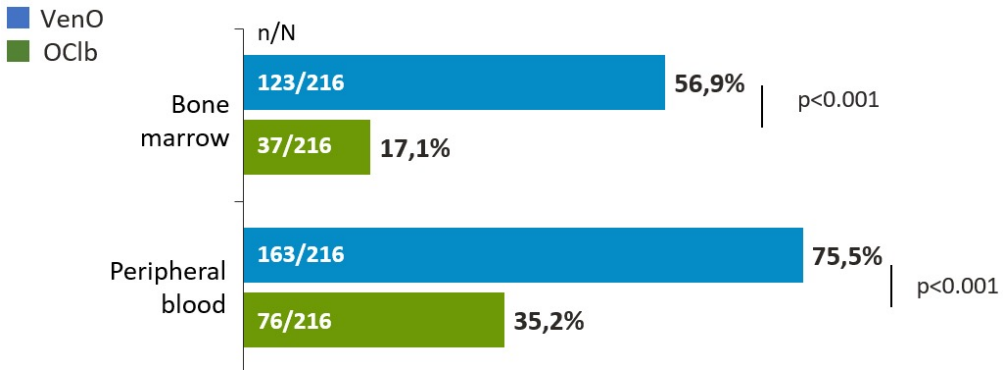


	TP53 del and/or mut	
	VenO	OClb
Median PFS, months	49.0	20.8

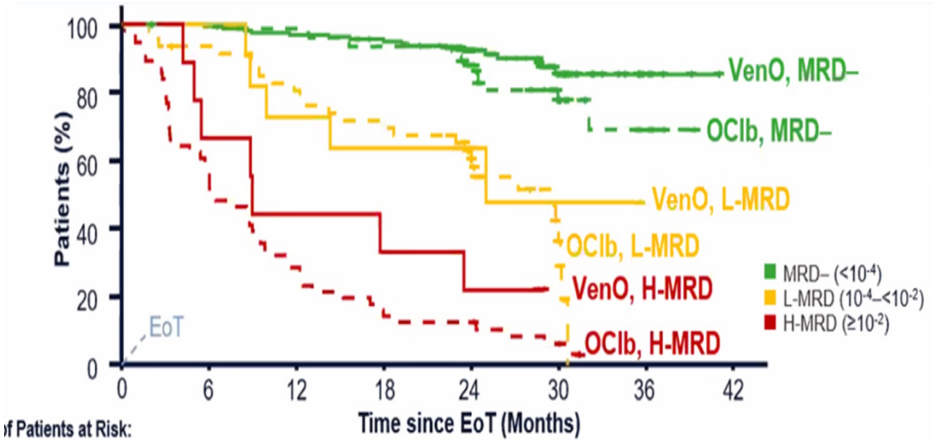
Al-Sawaf O et al. EHA 2021

Venetoclax-obinutuzumab for TN patients with CLL: 4-year follow-up of the CLL14 Trial

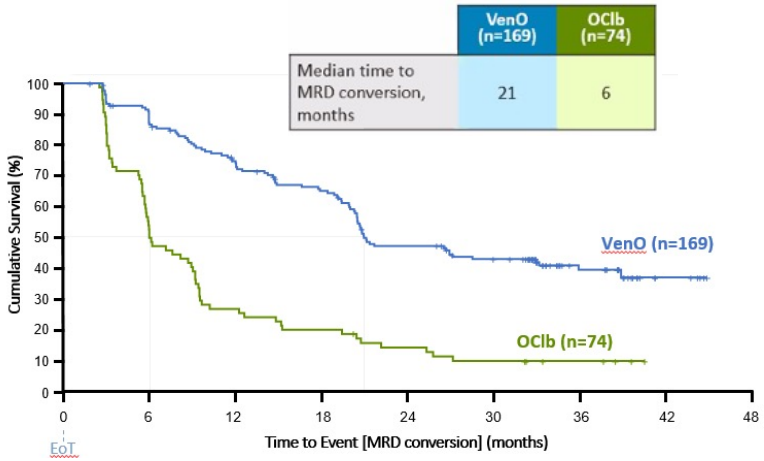
MRD negativity (>10^{-4}) at EOT by ASO PCR



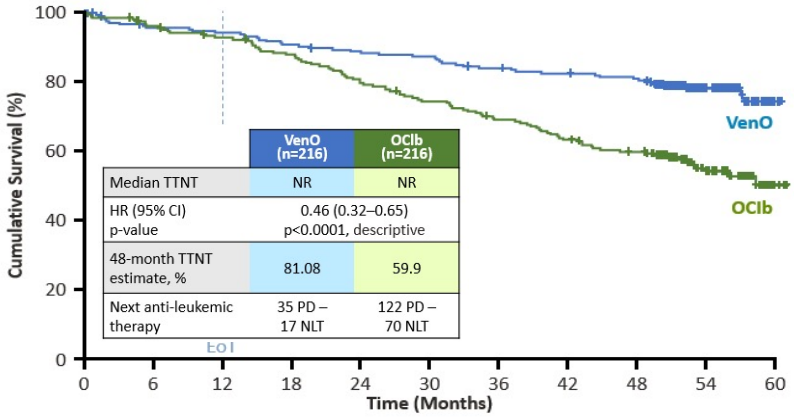
PFS by MRD status by ASO-PCR at EOT



MRD negativity at EOT: MRD conversion

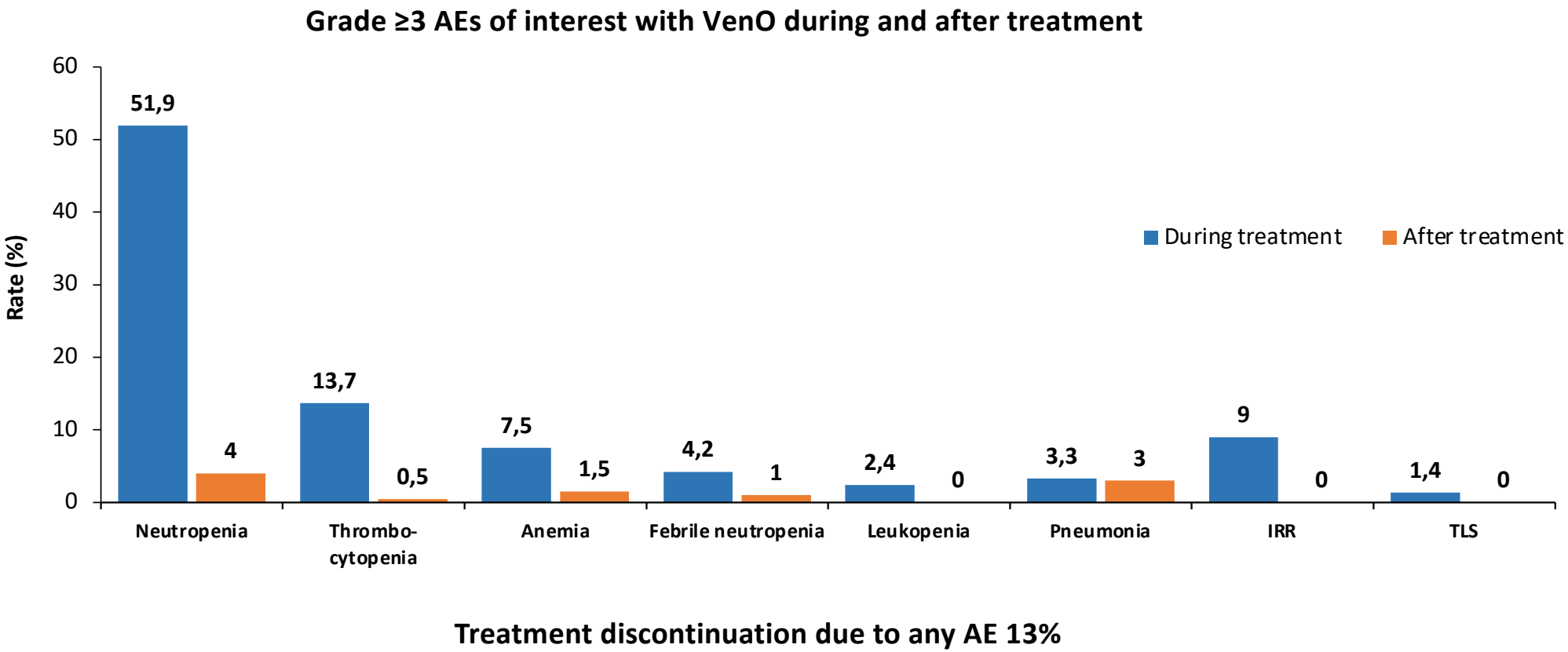


Time to Next Treatment: 4 Years Post-Randomization



Al-Sawaf O et al. EHA 2021

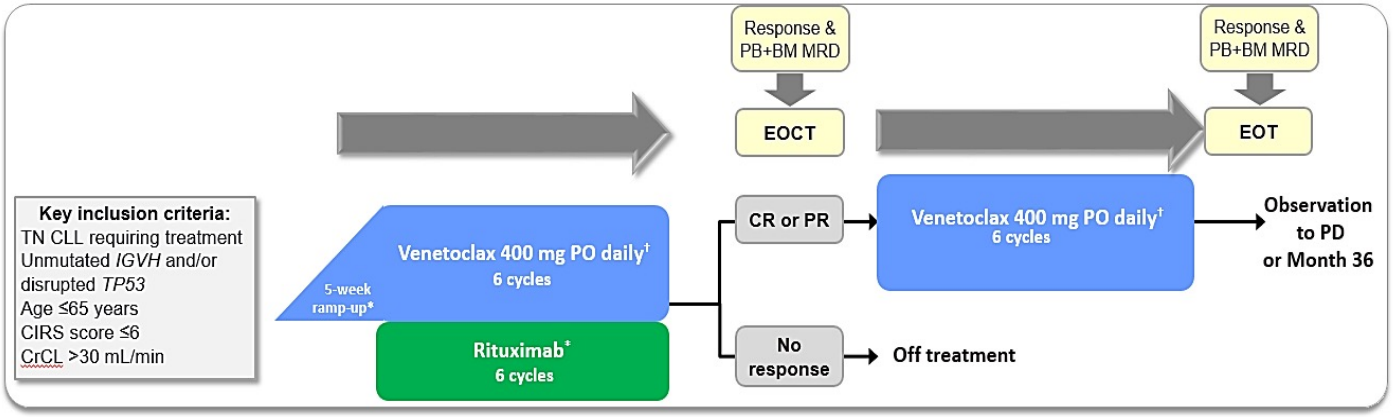
Rates of Select Grade ≥3 Adverse Events over Time



Treatment discontinuation due to any AE 13%

Al-Sawaf O et al. EHA 2021

Front-Line Venetoclax and Rituximab for the Treatment of Young Patients with CLL and Unfavorable Biologic Profile. The GIMEMA Study 'Veritas'



* Venetoclax, PO daily: 20 mg week 1, 50 mg week 2, 100 mg week 3, 200 mg week 4, 400 mg week 5 onwards;
† Venetoclax 400 mg PO daily, day 1–28 of each cycle;
‡ Rituximab IV: 375 mg/m2 on day 1 month 1, 500 mg/m2 on day 1 months 2–6.
EOCT, end of combination therapy; EOT, end of treatment ; ORR, overall response rate.

Primary endpoint:

CR rate at EOT

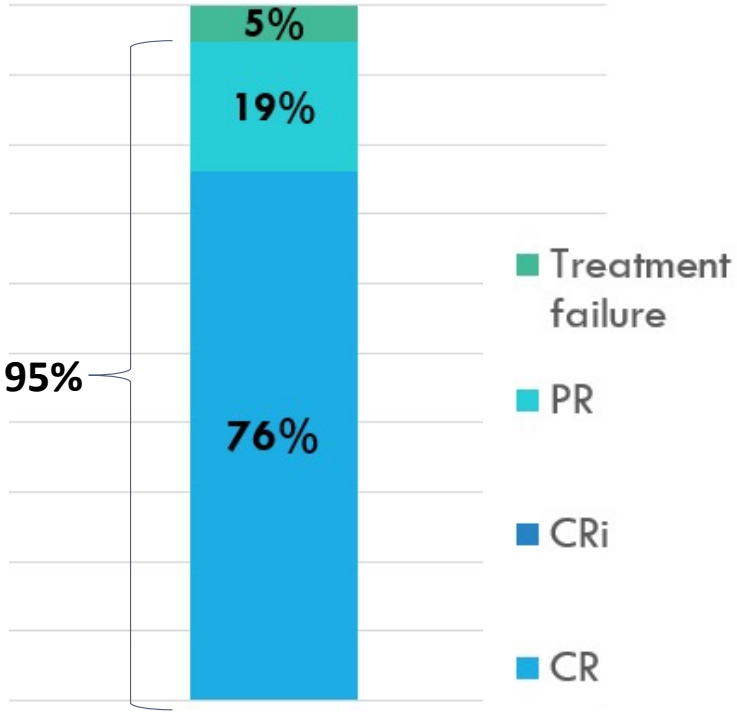
Key Secondary endpoints:

- ORR at EOT
- uMRD response rate at EOT
- PFS
- OS
- Safety

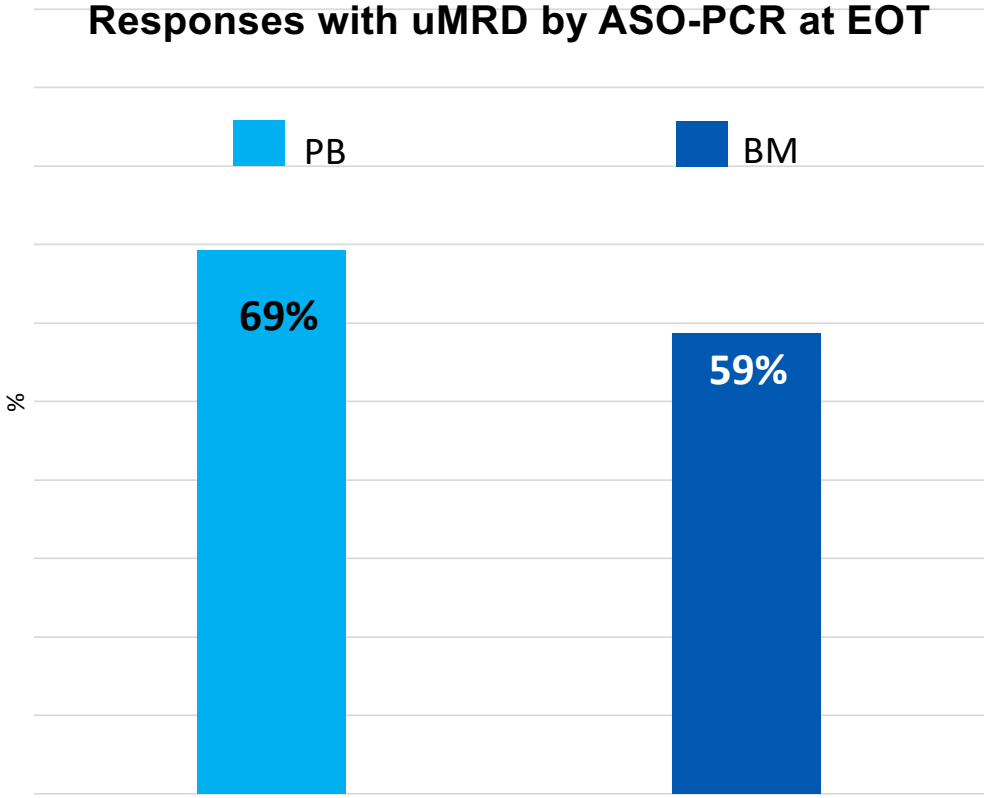
Baseline characteristics, n (%)	N=75*
Median age, years (range)	53.45 (38–65)
Lymphocyte count x 10^9/L (range)	96.2 (5.3–556.5)
Bulky nodes (lymph nodes size ≥5 cm) (%)	18 (25)
Binet stage B/C (%)	37 (49) - 26 (35)
TLS risk: high (%)	33 (44)
Beta-2 microglobulin ≥ 3.5 mg/L	27 (41)
Increased LDH	26 (35)
CD38 ≥30%	38 (51)
*TP*53 mutation	9 (12)
Unmutated *IGHV*	71 (96)

Front-Line Venetoclax and Rituximab for the Treatment of Young Patients with CLL and Unfavorable Biologic Profile. The GIMEMA Study 'Veritas'

iwCLL response rates at EOT

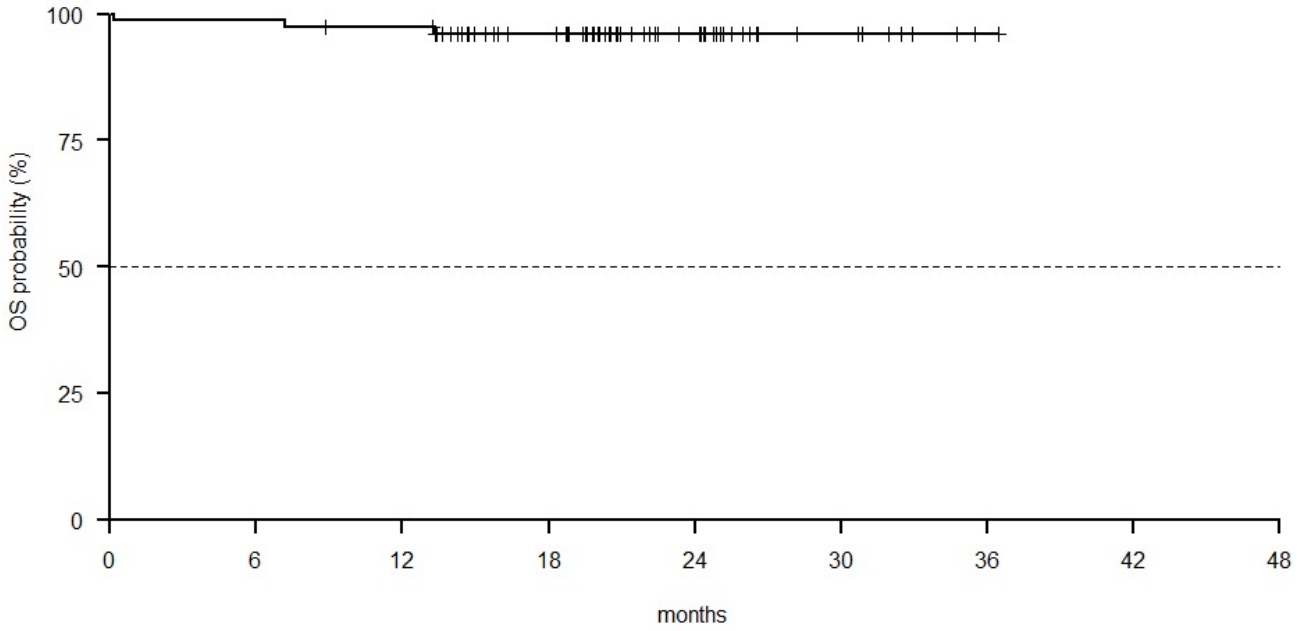


Responses with uMRD by ASO-PCR at EOT



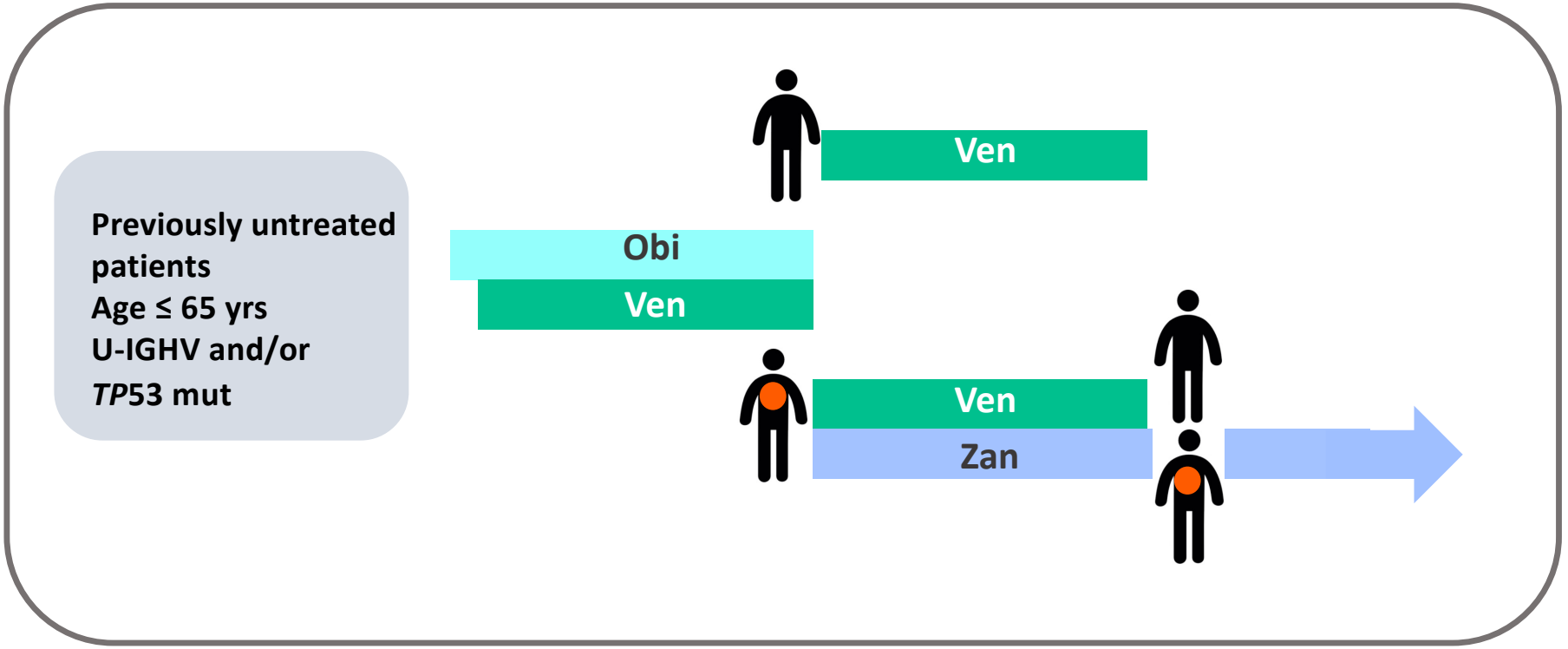
OVERALL SURVIVAL

24 months OS: 96%



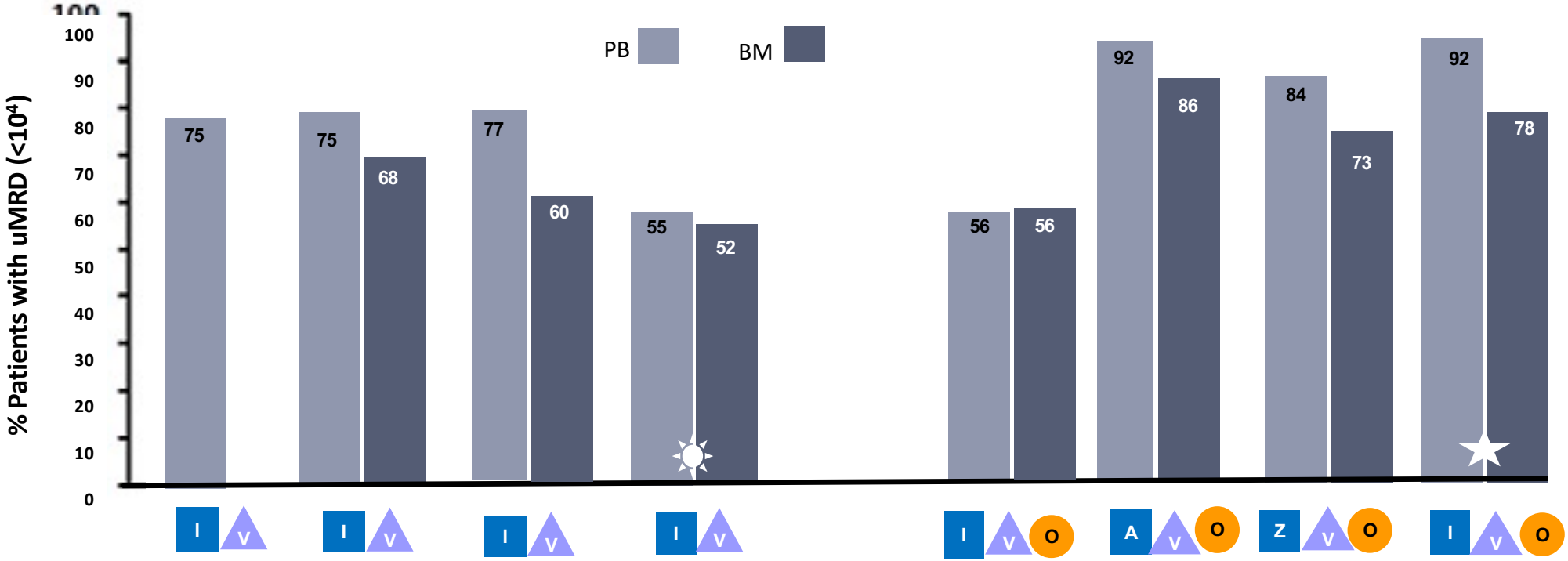
- No progression

THE GIMEMA VIS TRIAL: STUDY DESIGN



FRONT-LINE THERAPY WITH BTK+BCL2 INHIBITORS

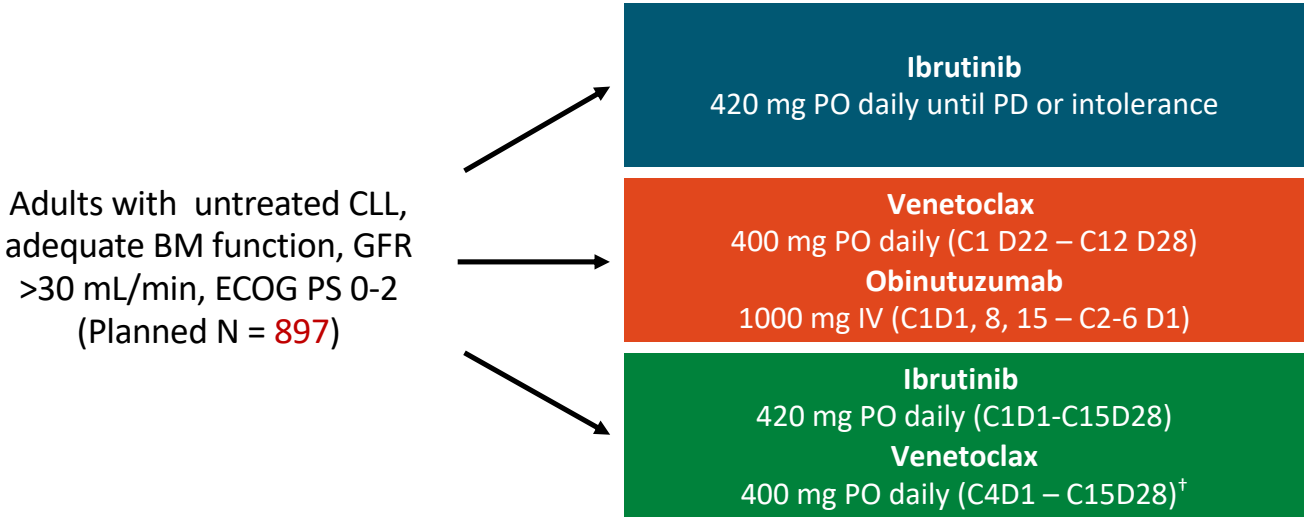
Front-line Ibrutinib-Venetoclax-based combinations



	Jain et al. NEJM 2019	CAPTIVATE MRD Wierda etal. JCO 2021	CAPTIVATE FD	GLOW Munir et al. ASH 2021	IVO Rogers et al, ASH 2020	AVO Davids et al. Lancet Oncol 2021	BOVEN Soumerai et al . ASCO 2020	GAIA-GIVE Eichhorst et al., ASH 2021
N	80	164	159	106 unfit	25	37	39	231 unfit
Treatment duration	27 >	15± mant	15	15>	14	16>25	8>24	12 >36
Median FU, months	24	31	28	34	41	28	11	28

CLL17: Ibrutinib + Venetoclax vs Venetoclax + Obinutuzumab vs Ibrutinib in Treatment-Naive CLL

- Randomized, open-label, multicenter phase III trial



- Primary endpoint: Investigator-assessed PFS
- Secondary endpoints: uMRD, MRD in PB, ORR, CR/CRi rate, safety

Grazie!