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First line therapy in CLL: what are the best options?

Is two better than one?

Is three better than two?

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Conflict of Interest Disclosure

I hereby declare the following potential conflicts of interest concerning my presentation:

- Consultancy: None
- Research Funding: Pharmacyclics, BeiGene, AstraZeneca
- Honoraria: Janssen
- Patents and Royalties: None
- Membership on an Entity's Board of Directors or Advisory Committees:
None
- Discussion of off-label drug use: None

Novel agents in CLL: Flexible Options

**Continuous
therapy**

**Time-limited
therapy**



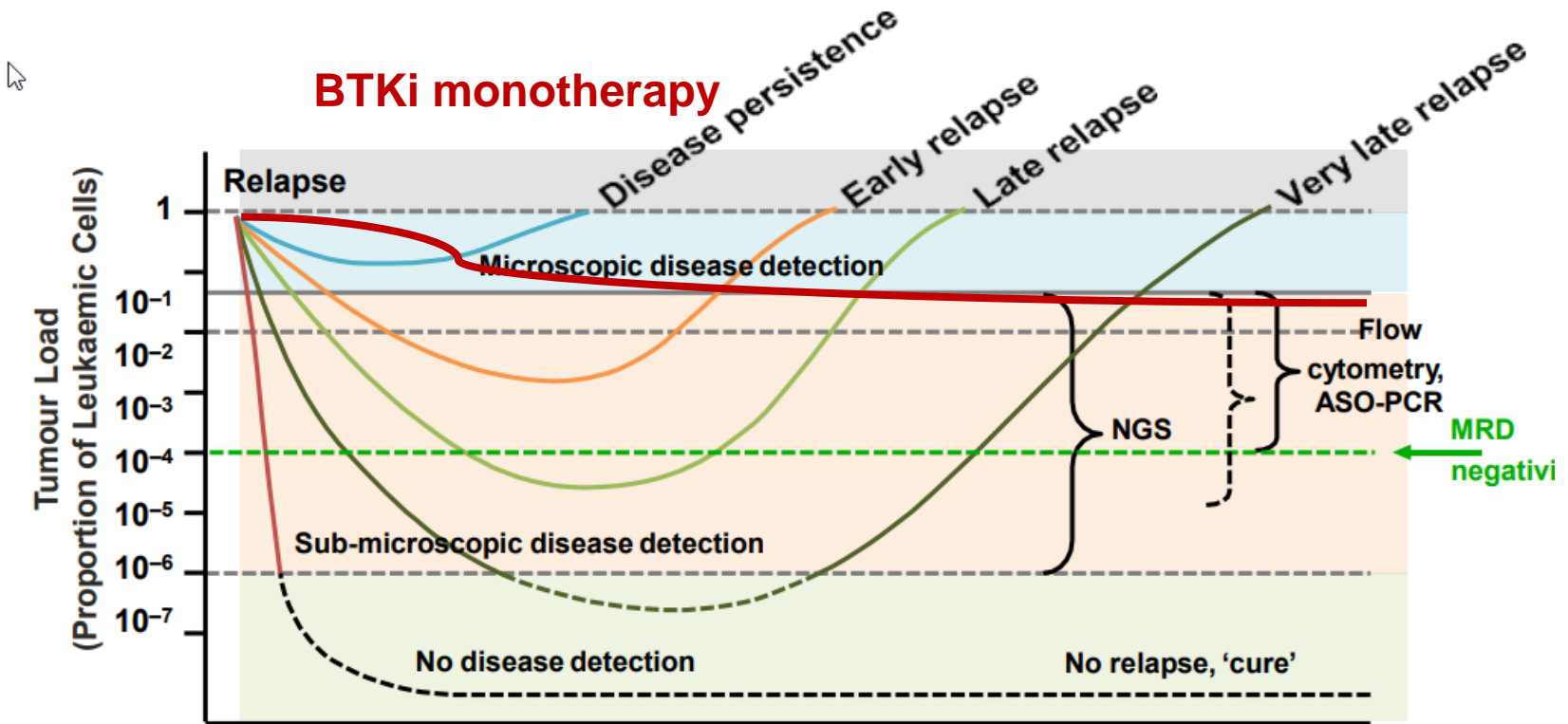
BTKi
(ibrutinib,
acalabrutinib,
zanubrutinib)

Venetoclax +
anti-CD20

BTKi + venetoclax +/-
anti-CD20

**BTKi +
anti-CD20**

Rationale for Combination Therapy – Correlation of uMRD and Relapse



Lower level of residual disease, generally associated with longer time to progression (i.e. less likely to relapse)

Up to 8-year follow-up from RESONATE-2: first-line ibrutinib treatment for patients with chronic lymphocytic leukemia

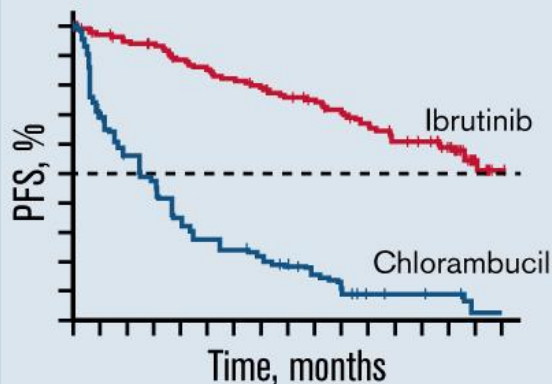
Up to 8 years of follow-up for ibrutinib treatment of CLL

Safety



- No new safety signals
- Active dose management allowed continued ibrutinib benefit

Efficacy



- Median PFS not reached up to 8 years

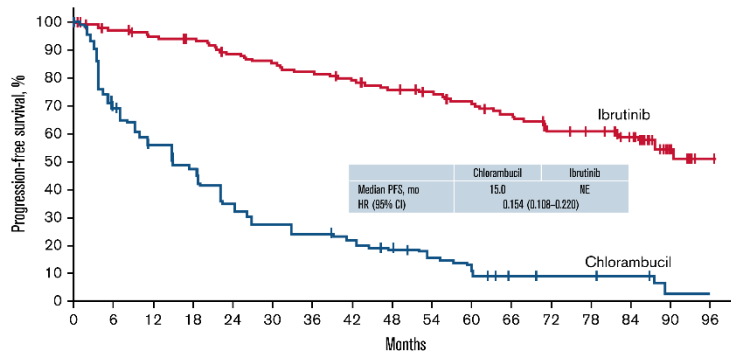
Patient disposition



- 42% of patients continue on ibrutinib at 8 years

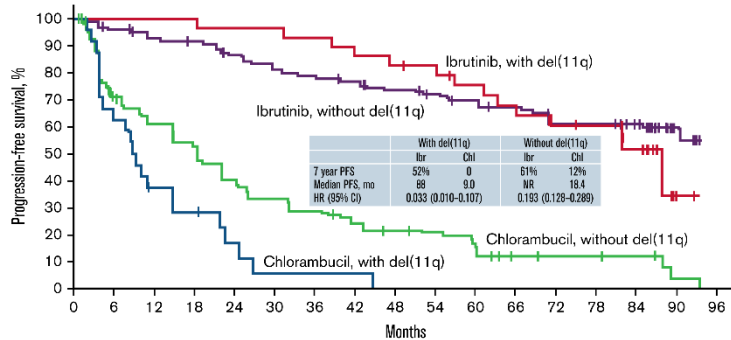
Paul M. Barr et al. Up to 8-year follow-up from RESONATE-2: first-line ibrutinib treatment for patients with CLL, *Blood Adv*, 2022

Up to 8-year follow-up from RESONATE-2: first-line ibrutinib treatment for patients with chronic lymphocytic leukemia



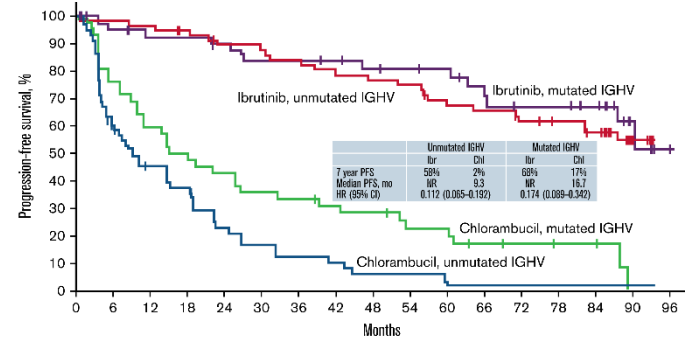
Patients at risk

	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90	96
Ibrutinib:	136	129	124	121	112	108	104	99	92	88	81	76	67	65	57	17	1
Chlorambucil:	133	88	69	57	41	33	30	25	19	16	12	6	5	5	4	1	0



Patients at risk

	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90	96
Ibrutinib, without del(11q):	101	94	89	87	80	76	73	70	64	61	57	55	48	47	43	13	0
Ibrutinib, with del(11q):	29	29	29	29	28	28	27	25	24	23	20	18	16	16	12	2	0
Chlorambucil, without del(11q):	96	64	54	45	35	29	25	21	17	15	12	6	5	5	4	1	0
Chlorambucil, with del(11q):	25	15	8	6	3	1	1	1	1	0							



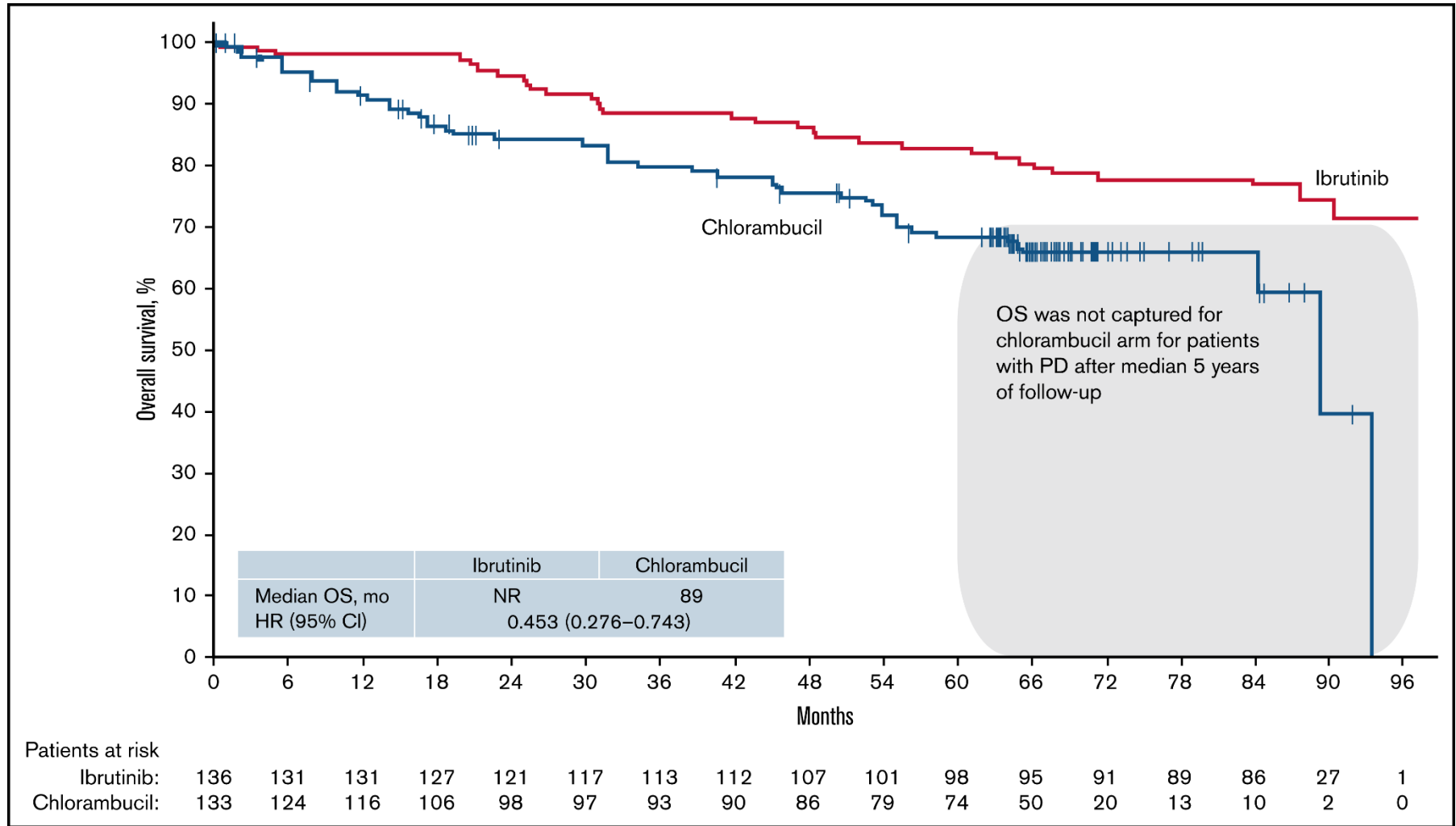
Patients at risk

	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90	96
Ibrutinib, mutated IGHV:	40	37	34	34	32	30	30	29	27	26	25	22	19	19	16	6	1
Ibrutinib, unmutated IGHV:	58	57	56	53	49	48	46	43	42	41	36	35	32	30	27	10	0
Chlorambucil, mutated IGHV:	42	32	25	21	18	15	14	12	11	8	8	5	4	4	3	0	0
Chlorambucil, unmutated IGHV:	60	33	23	19	11	8	6	5	3	3	2	1	1	1	1	1	0

Paul M. Barr et al. Up to 8-year follow-up from RESONATE-2: first-line ibrutinib treatment for patients with CLL, Blood Adv, 2022



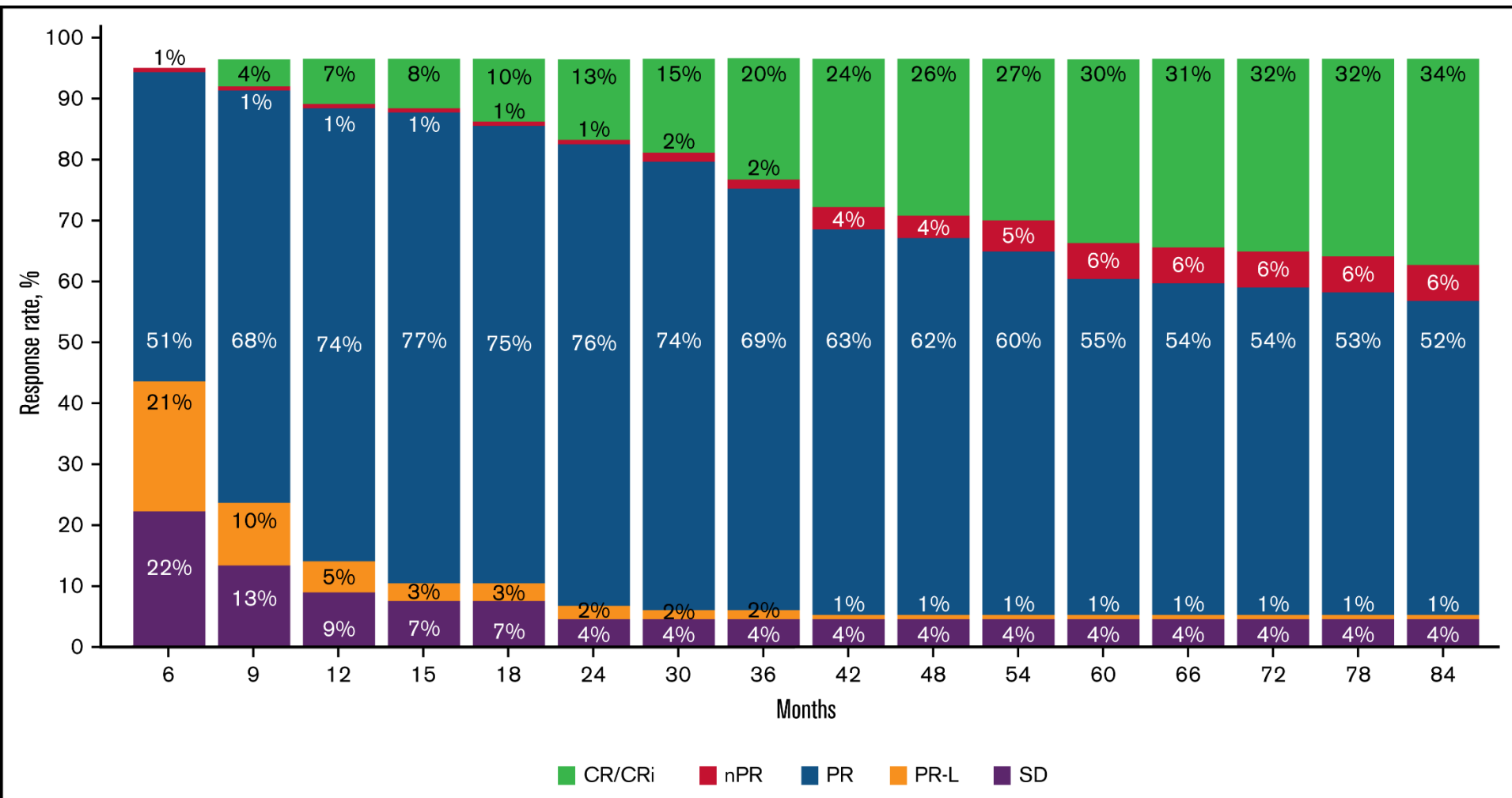
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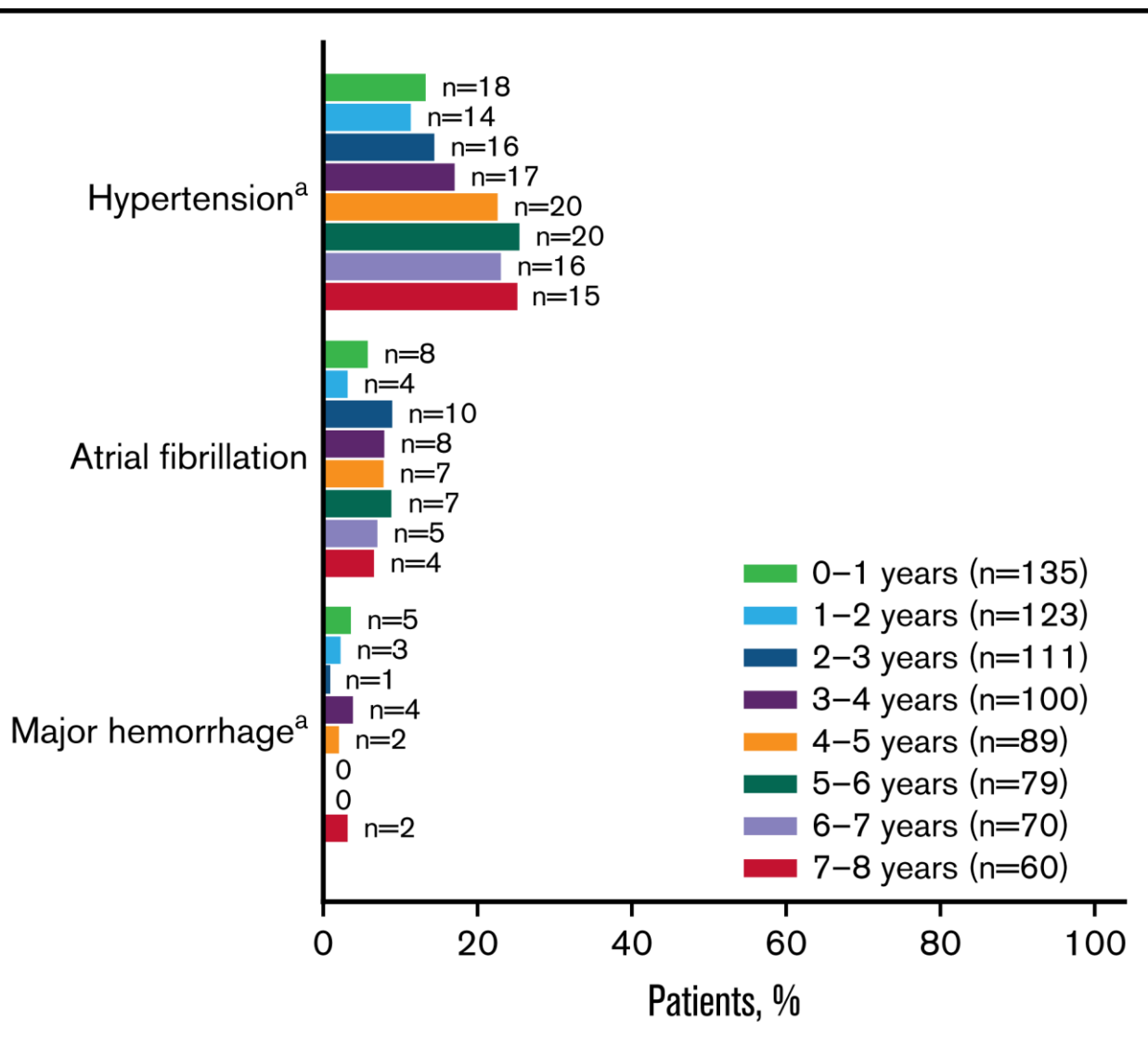
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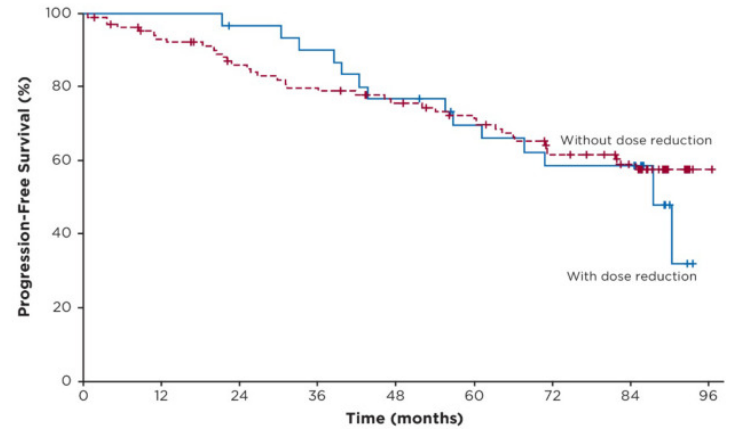
Up to 8-year follow-up from RESONATE-2: first-line ibrutinib treatment for patients with chronic lymphocytic leukemia



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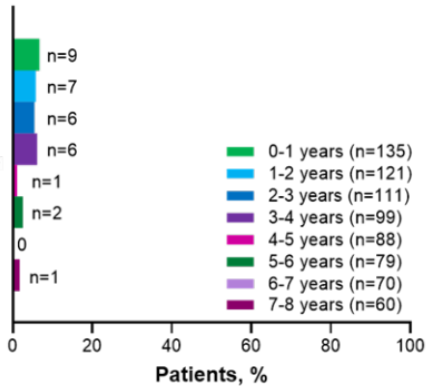
RESONATE-2: 31 patients with dose reduction had no difference in PFS/OS

	Ibrutinib n=136
Median duration of ibrutinib treatment, years	6.2
Continuing ibrutinib on study, n (%)	57 (42)
Discontinued ibrutinib, n (%)	
AE	32 (24)
PD ^b	18 (13)
Death	12 (9)
Withdrawal by patient	9 (7)
Investigator decision	7 (5)

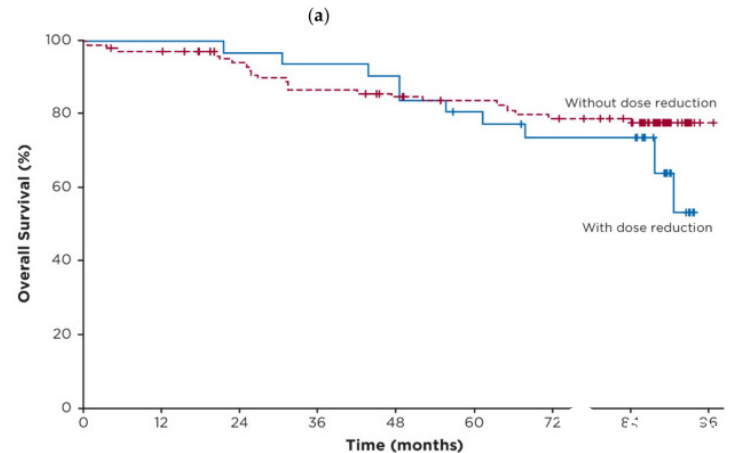
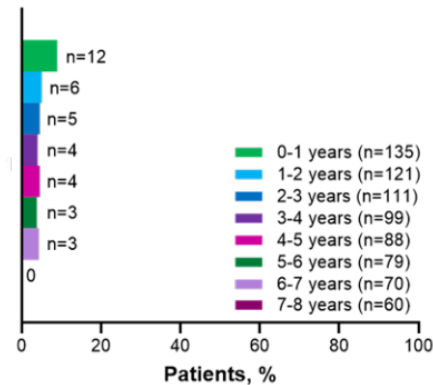


	0	12	24	36	48	60	72	84	96								
With dose reduction	31	31	31	31	29	29	27	25	23	22	19	18	16	16	16	4	1
Without dose reduction	104	98	93	90	83	79	77	74	69	66	62	58	51	49	41	13	1

Discontinuations Due to AEs



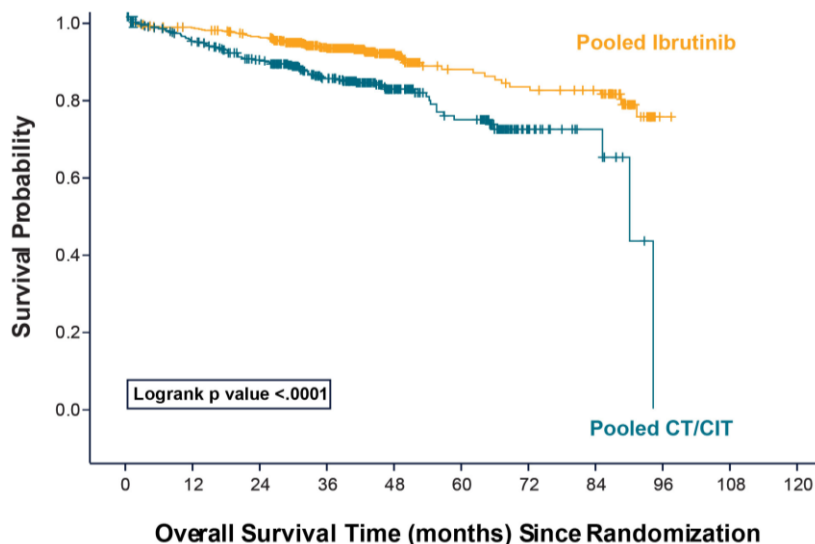
Dose Reductions Due to AEs^a



	0	12	24	36	48	60	72	84	96								
With dose reduction	31	31	31	31	30	30	29	29	28	26	24	23	21	21	21	7	0
Without dose reduction	104	100	100	96	91	87	84	83	79	75	74	72	70	68	65	20	1

First-line ibrutinib treatment in CLL: survival is similar to an age-matched general population: a pooled post hoc analysis

Figure 2. Improved OS for pooled 1L Ibr (603 pts) vs CT/CIT (424 pts) across the 3 ibr studies



With Number of Patients at Risk

Pooled Ibrutinib	603	583	559	396	164	98	91	86	1	0
Pooled CT/CIT	424	379	339	253	108	74	20	10	0	0

^aData after 96 months is not represented in the KM curve;

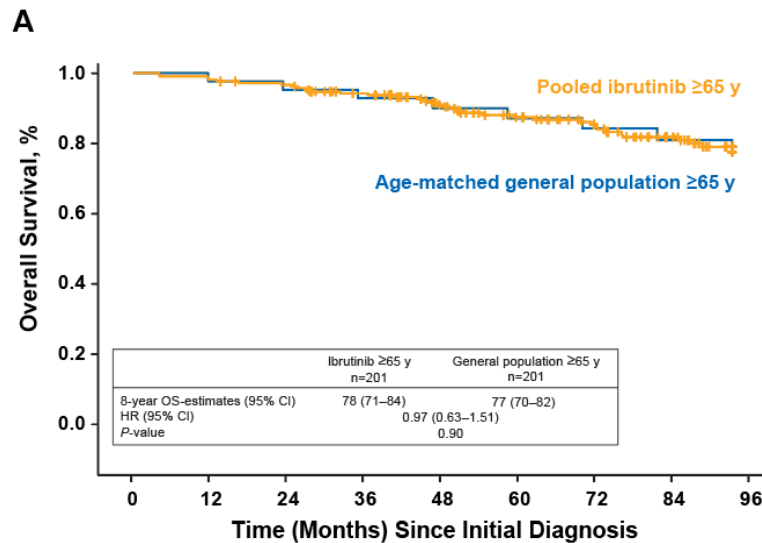
^bData after 144 months is not represented in the KM curve

- Pooled from **RESONATE-2, ECOG-1912, and iLLUMINATE** evaluating ibrutinib monotherapy and in combination in **treatment naïve CLL**
- 603 treatment naïve patients were received ibrutinib across the three studies. Median age was 63 years.
 - 58.7% Ibr + Ritux
 - 22.6% Ibr monotherapy
 - 18.7% Ibr + Obi
- **Initiation of ibrutinib in the frontline improved overall survival compared to chemoimmunotherapy**

Similar OS for Pooled Ibrutinib-Treated CLL Patients

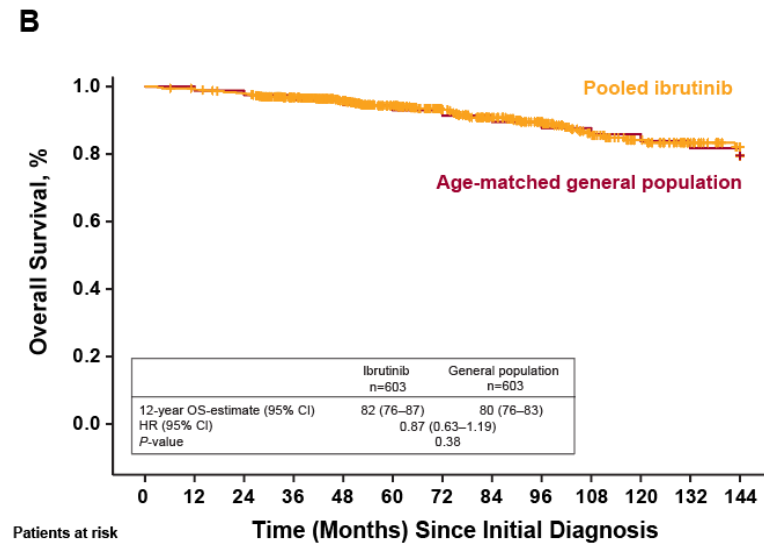
(A) All Pooled Ibrutinib-Treated Patients

(B) Age-Matched General US Population



Patients at risk

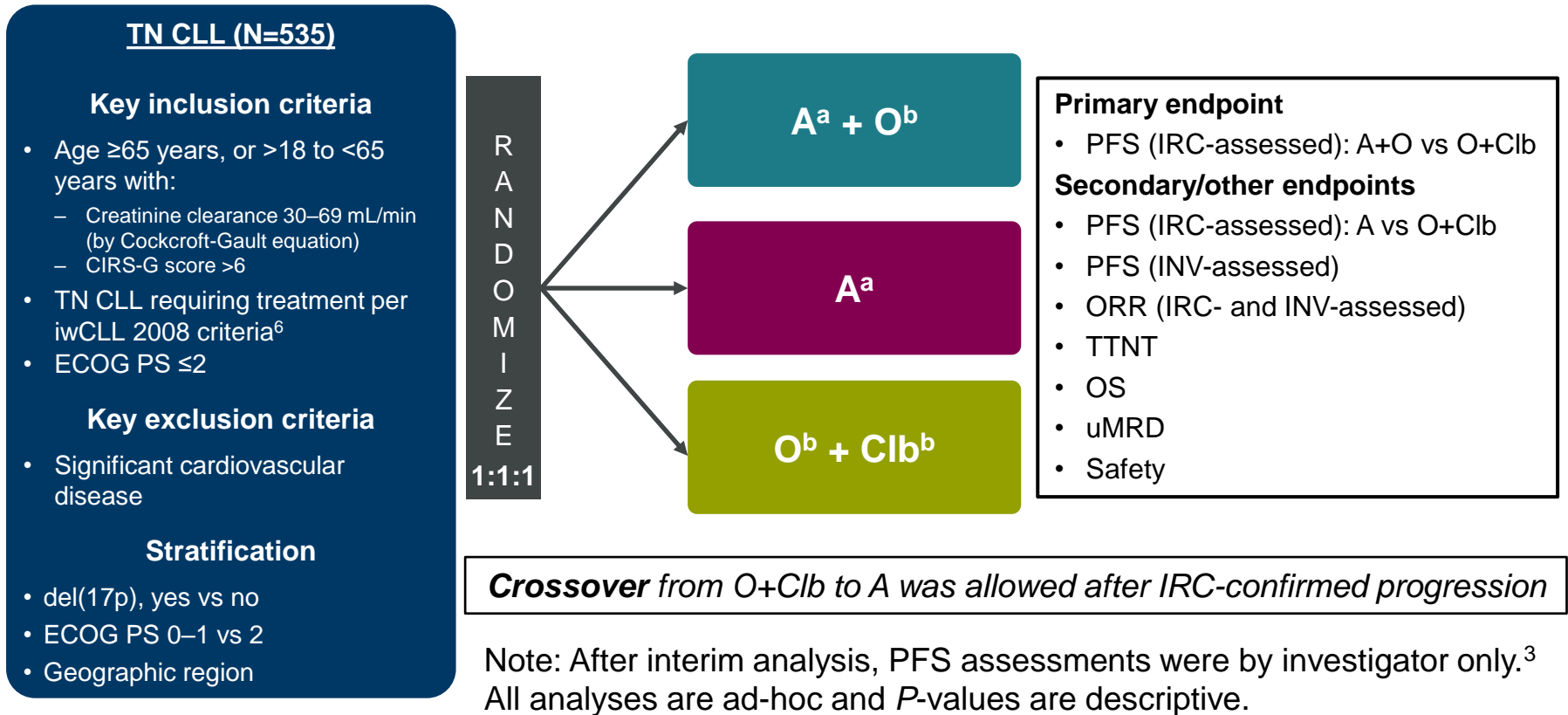
	0	12	24	36	48	60	72	84	96
Pooled ibrutinib ≥65 y	201	199	192	177	157	135	118	96	71
Age-matched general population ≥65 y	201	201	196	191	186	180	174	168	161



Patients at risk

	0	12	24	36	48	60	72	84	96	108	120	132	144
Pooled ibrutinib	603	598	586	519	436	356	291	234	183	136	111	84	63
Age-matched general population	603	603	596	588	579	570	561	551	540	529	518	506	493

ELEVATE-TN study design

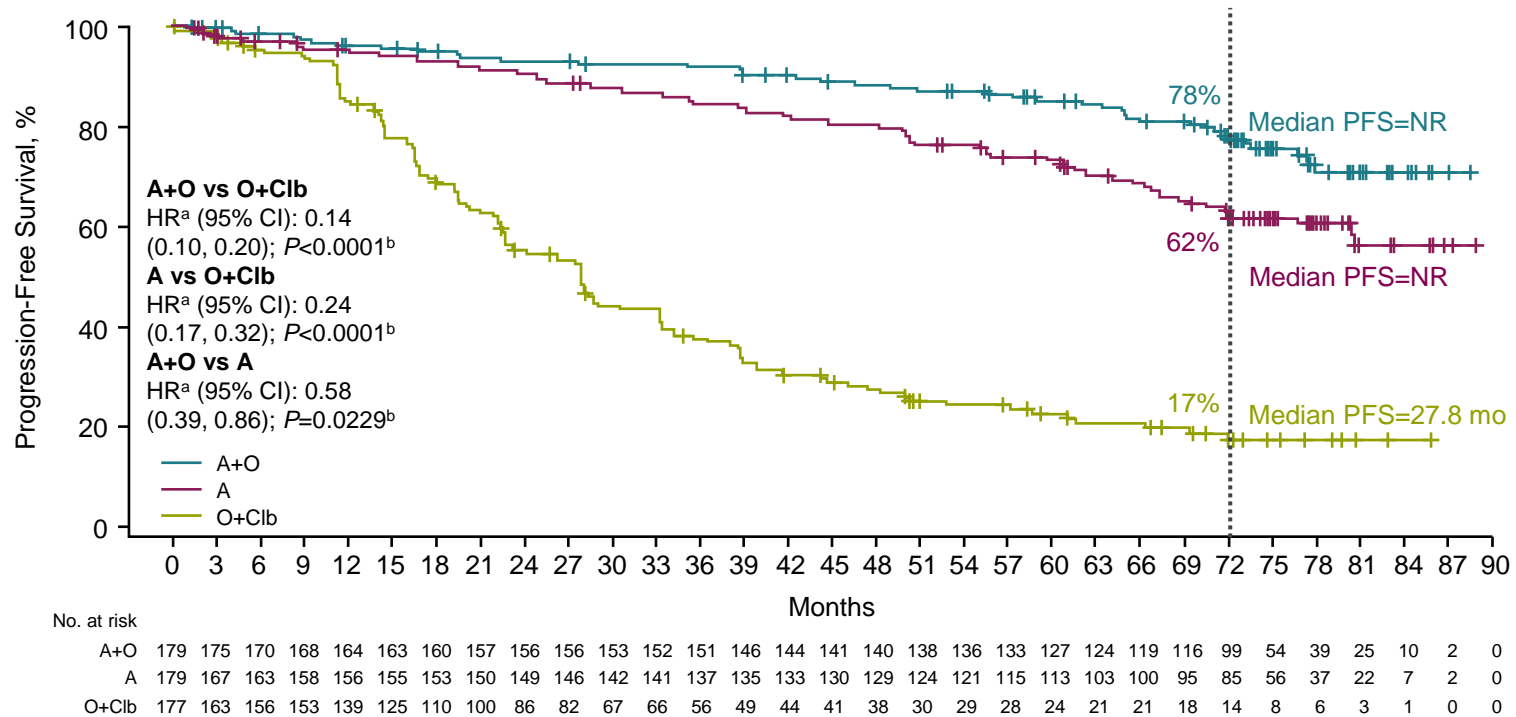


NCT02475681. Data cutoff: March 3, 2023. Patients were enrolled between September 2015 and February 2017.

^aContinued until disease progression or unacceptable toxicity at 100 mg PO BID.

^bTreatments were fixed duration and administered for 6 cycles.

Median PFS was significantly higher for A-containing arms vs O+Clb



- Median PFS was significantly higher for A+O vs A

^aHazard ratio based on stratified Cox proportional-hazards model.

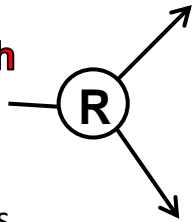
15 ^bP-value based on stratified log-rank test.

Flair

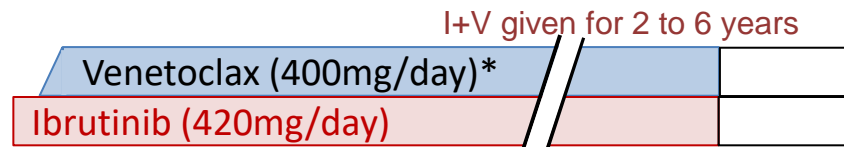
FCR vs I+V: Trial design

**Patients with
CLL
(n=523)**

96 UK Centres
July 2017-March
2021



F Oral Fludarabine (24mg/m²/day x 5 days; C1-6)
C Oral Cyclophosphamide (150mg/m²/days x 5 days; C1-6)
R Intravenous Rituximab (375mg/m² C1; 500mg/m²; C2-6)



*, weekly escalation 20mg → 50mg → 100mg → 200mg → 400mg

Primary end-point:
To assess whether I+V
is superior to FCR in
terms of PFS

**Key secondary end-
points:**
Overall survival
Response incl. MRD
Safety and toxicity

Key Inclusion Criteria:

- Previously untreated CLL requiring therapy by IWCLL criteria
- Considered fit for FCR
- ≤75 years old

Key Exclusion Criteria:

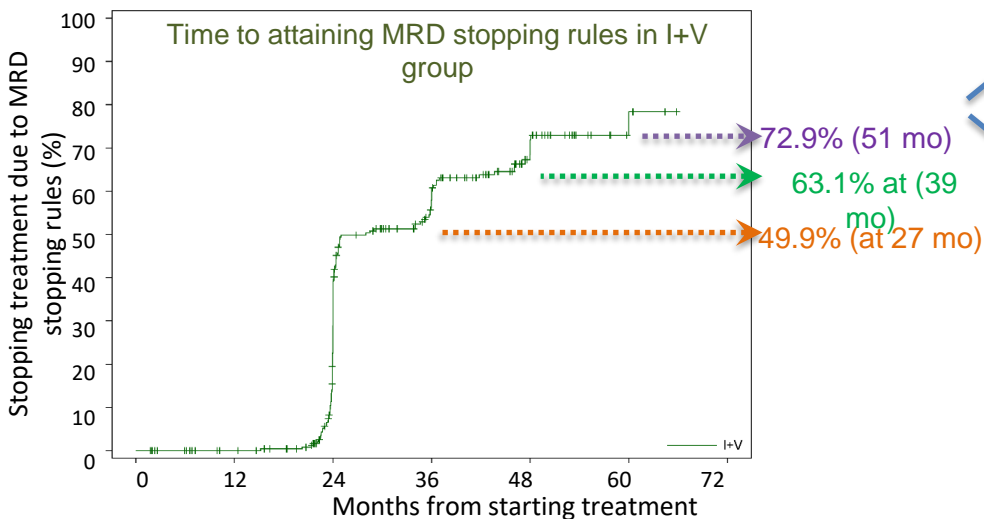
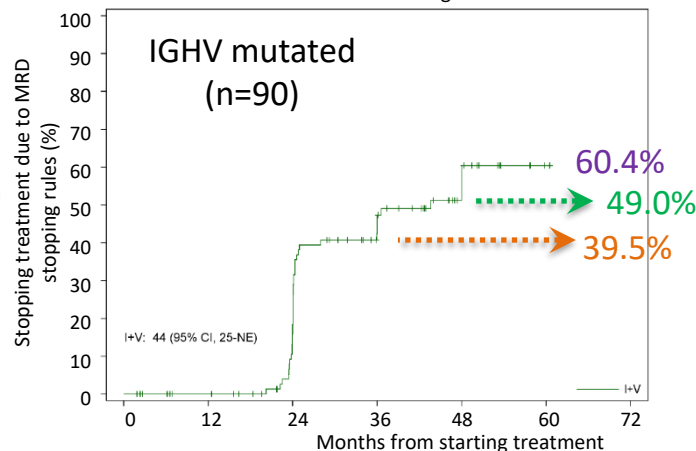
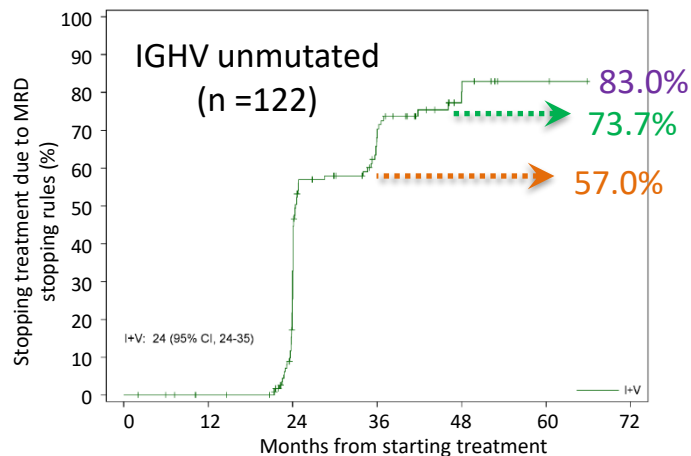
- Prior therapy for CLL; History of Richter's transformation;
- >20% TP53 deletion by FISH; Concomitant warfarin (or equivalent)
- Symptomatic cardiac failure or angina

iwCLL Responses

	Complete Response/CRi		Overall Response		BM uMRD
	9 months	Anytime	9 months	Anytime	Anytime
FCR	49%	71.5%	76.4%	83.7%	40.3%
I+V	59.2%	92.3%	86.5%	95.4%	61.9%

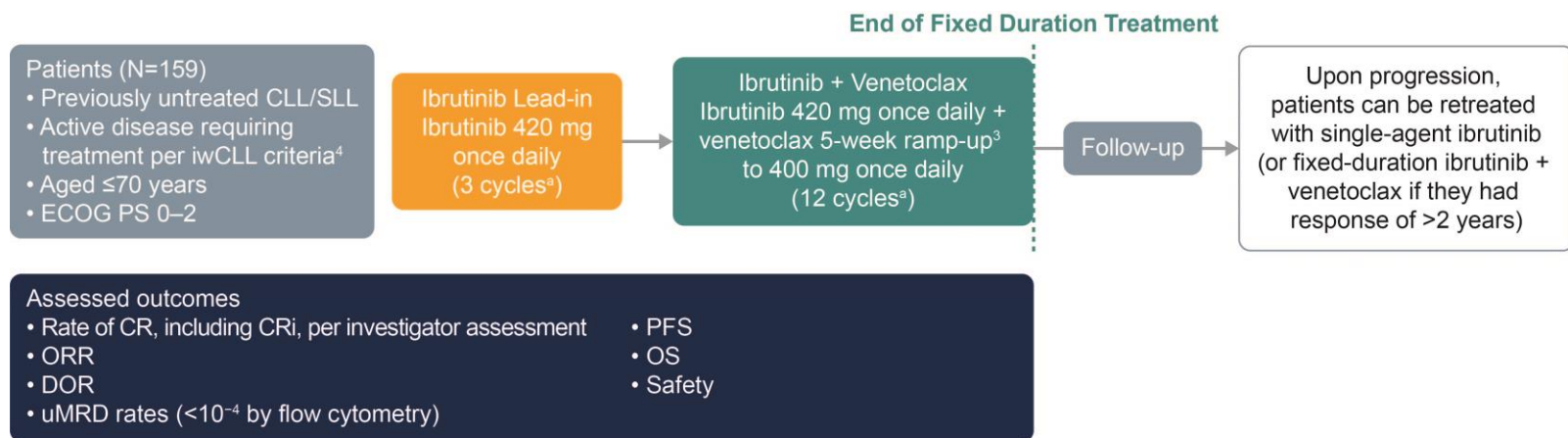
Odds ratio:
1.51

Odds ratio:
2.0



4-yr follow up data from the CAPTIVATE FD Cohort

- CAPTIVATE (NCT02910583) is an international, multicenter phase 2 study evaluating first-line treatment with the ibrutinib + venetoclax combination, comprising 2 cohorts: MRD¹ and FD²



The Primary Analysis reported an ORR of 96%, a best uMRD rate of 77% in PB, and 24-mo PFS of 95%

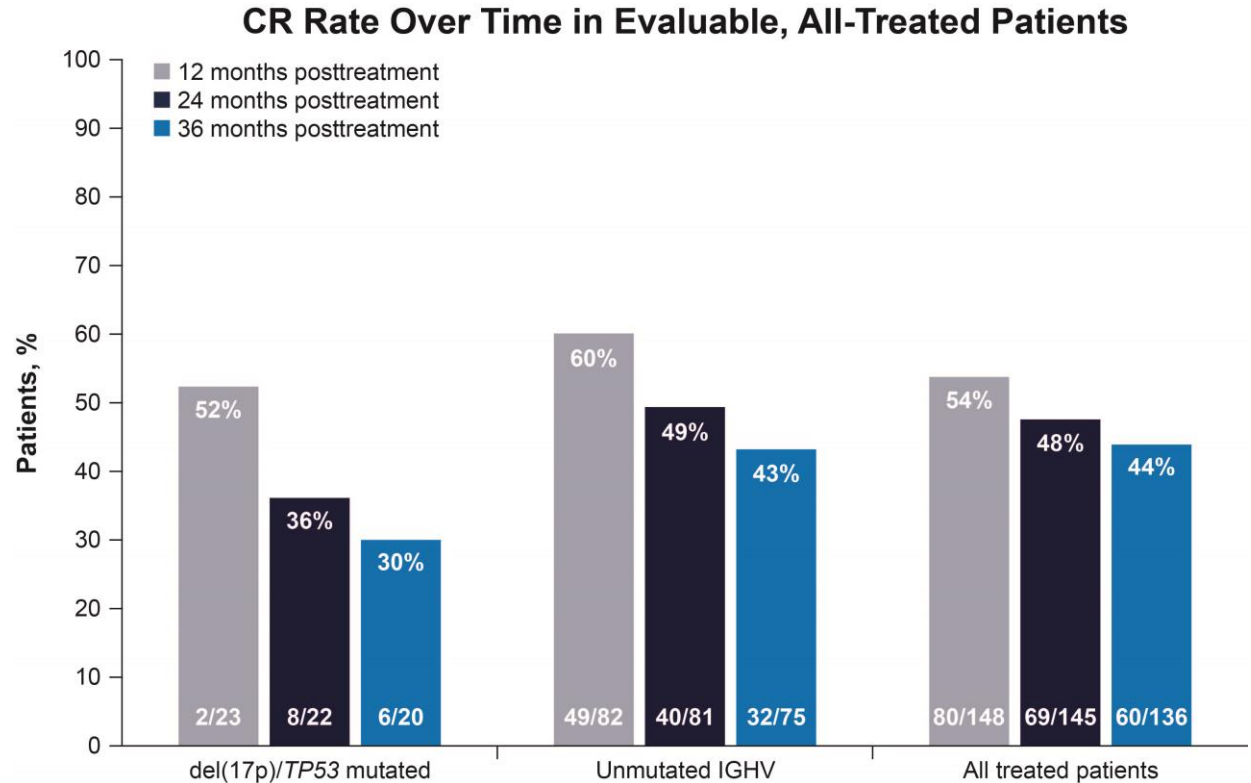
^aOne cycle = 28 days; CR, complete response; CRi, complete response with incomplete bone marrow recovery; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FD, fixed duration; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; MRD, minimal residual disease. ORR, overall response rate; PFS, progression-free survival.

1. Wierda, WG. *J Clin Oncol*, 2021;39:3853-3865 2. Tam CS et al. *Blood*. 2022;139:3278-3289. 3. Venclexta [package insert]. South San Francisco, CA: Genentech USA Inc; 2021. 4. Lu P et al. *Blood Cancer J*. 2021;11:39.



CR Rates Off-Treatment

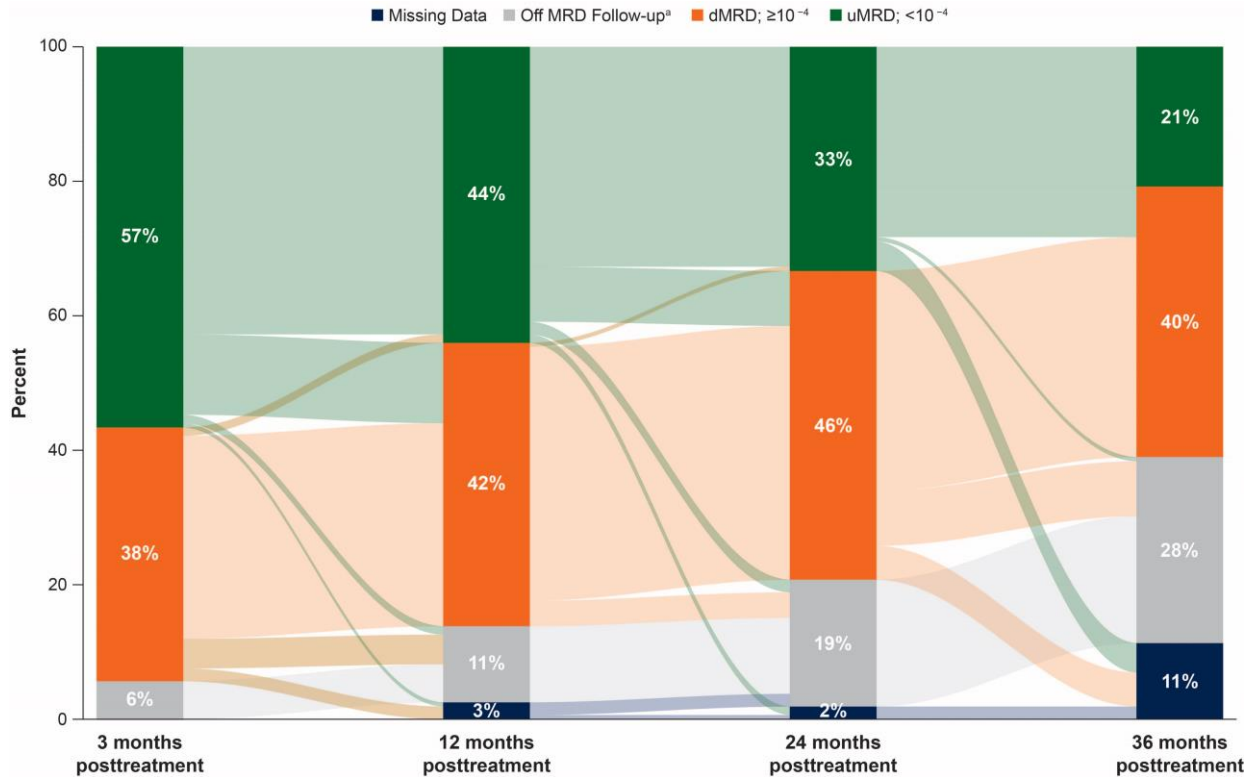
- Best ORR was 96%
- Median DOR was not reached for responding patients (n=153)
- Median duration of CR was not reached (n=93); the 36-month landmark estimate for durable CR was 80% (95% CI 69–87)



CR, complete response; DOR, duration of response; IGHV, immunoglobulin heavy chain variable region gene; ORR, overall response rate.



Rates of uMRD in Peripheral Blood With an Additional Year of Follow-Up (ITT)



- In the overall population, 21% of patients had uMRD in PB at 36 months posttreatment

dMRD, detectable minimal residual disease; ITT, intent to treat; uMRD, undetectable minimal residual disease; PB, peripheral blood.

^aOff MRD follow-up included patients who met any one of the criteria: progressive disease (PD), initiation of subsequent therapy, death, or withdrawal from study.

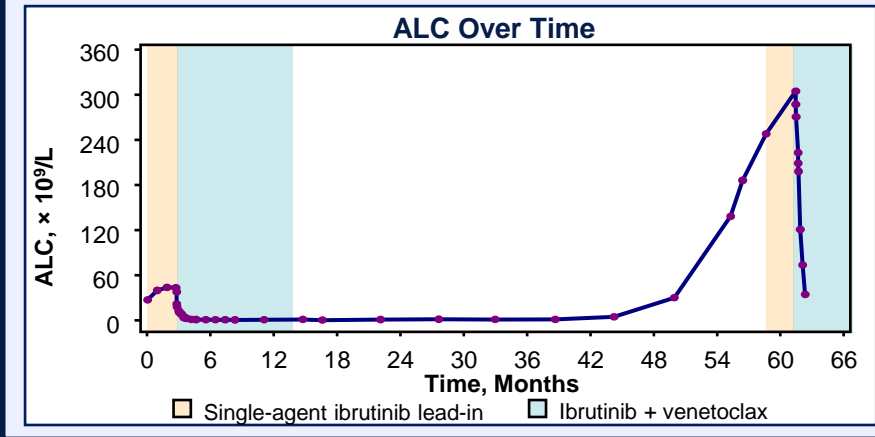


CAPTIVATE: Evaluation of *BTK*, *PLCG2*, and *BCL-2* Mutations in Patients with PD

- Samples collected at PD after fixed-duration treatment from 40 patients were evaluated for mutations in *BTK/PLCG2* or *BCL-2* associated with resistance to ibrutinib or venetoclax^a
 - Median time from start of treatment to PD for these patients was 3.2 years (range, 1.4–4.2)
- **No *BTK* or *PLCG2* mutations were identified in the 40 patients evaluated**
- In 1 of 40 patients, an acquired subclonal mutation in *BCL-2* (A113G, VAF 8.3%) was identified
 - *BCL-2* A113G identified previously in patients with PD on venetoclax, usually in combination with *BCL-2* G101V (66-100% of cases), the most common venetoclax resistance mutation¹⁻³
 - Emergence of subclonal *BCL-2* A113G in the absence of co-occurring *BCL-2* mutations has unclear clinical significance

Patient With *BCL-2* (A113G) at PD

- With initial fixed-duration ibrutinib + venetoclax:
 - uMRD (<0.01%) achieved in both PB and BM by C13 and maintained in PB until C31
 - CR achieved at C10 and maintained through C49
- PD occurred 3 years after EOT
- After PD, reinitiated fixed-duration ibrutinib + venetoclax
 - To date, the patient has PR-L after 4 months of retreatment (3 months of ibrutinib and 1 month of ibrutinib + venetoclax)



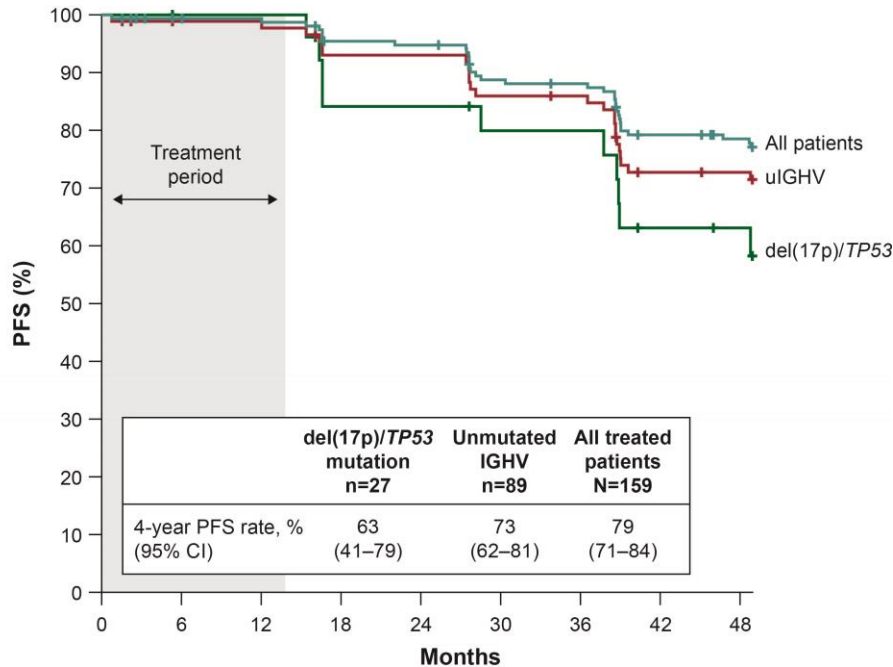
BM, bone marrow; C, cycle; PB, peripheral blood; PLCG2, phospholipase C gamma 2; PR-L, partial response with lymphocytosis; VAF, variant allele frequency.

^aResistance-associated variants in *BTK*, *PLCG2*, or *BCL-2* were assessed by next-generation sequencing using a custom panel with a limit of detection of 1% VAF.

¹Popovic R et al, *Am J Hematol*. 2022;97(2):e47-e51. ²Kotmayer L et al, *Int J Mol Sci*. 2023;24:5802. ³Lucas F et al, *Blood*. 2020;135:2192-2195.



Fixed-Duration Ibr + Ven Continues to Provide Durable and High PFS Rates



Time to Next Treatment

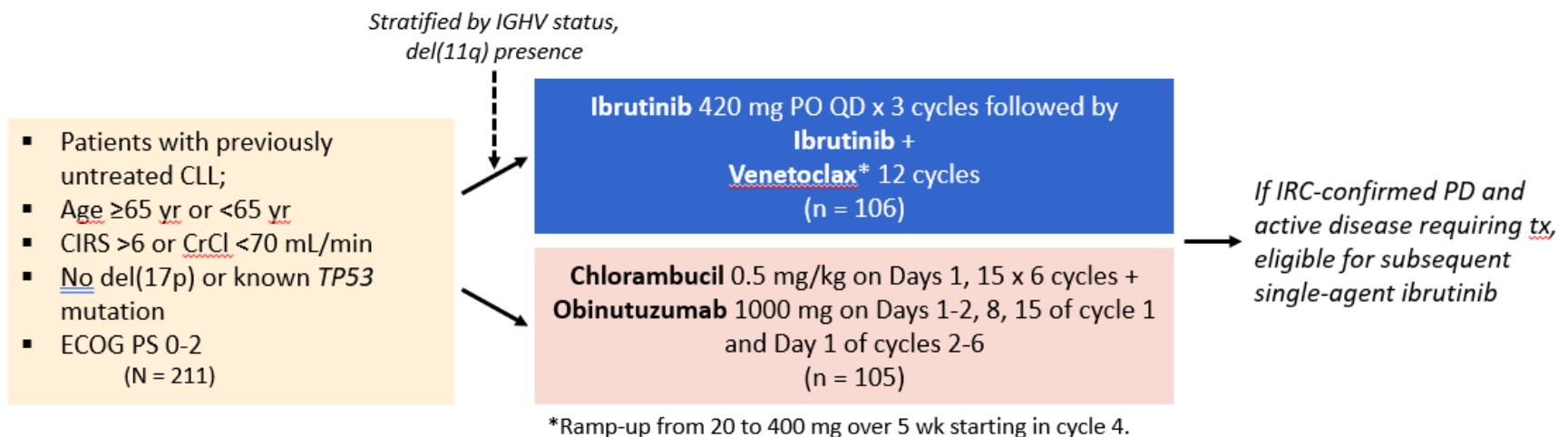
- Median TTNT was not reached (n=28; range 1–53 months)
- Landmark estimate of the proportion of patients who had not started a next treatment at 4 years was 84% (95% CI 77–89)

Patients at risk	Months								
	0	6	12	18	24	30	36	42	48
del(17p)/TP53 mutation	27	26	26	21	21	19	19	14	13
Unmutated IGHV	89	85	85	79	79	73	72	59	58
All treated patients	159	153	152	144	143	132	130	115	111

IGHV, immunoglobulin heavy chain variable region gene; PFS, progression-free survival; uMRD, undetectable minimal residual disease.

GLOW: *Fixed-Duration Ibrutinib + Venetoclax vs Chlorambucil + Obinutuzumab in 1L CLL*

- International, open-label, randomized phase III trial

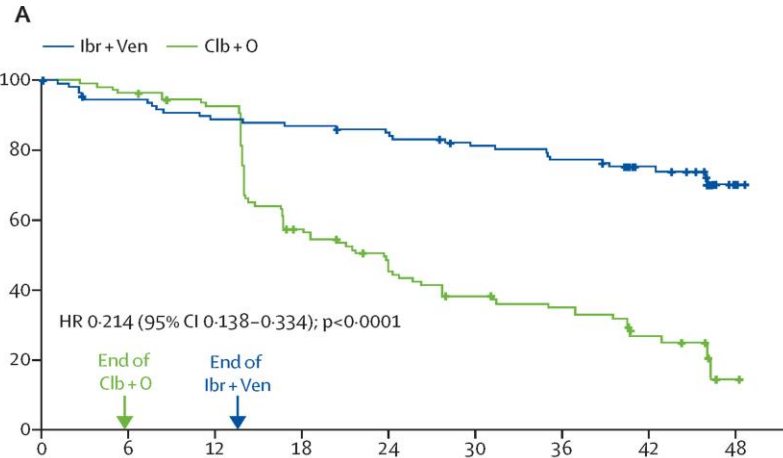


- Primary endpoint:** PFS per IRC

– 71 PFS events to detect effect size with HR of 0.5 (80% power, 2-sided $\alpha = 0.05$)

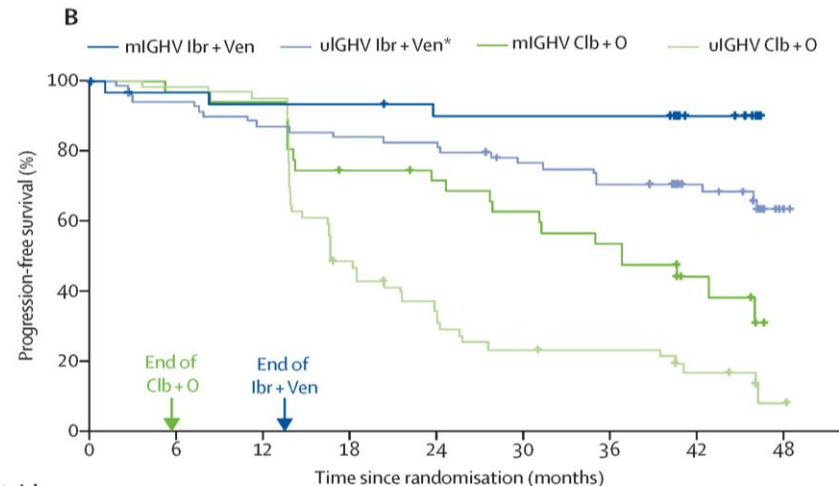
- Key secondary endpoints:** uMRD in BM, CR rate per IRC, ORR per IRC, OS, safety

GLOW: Progression Free Survival



Number at risk (number censored)

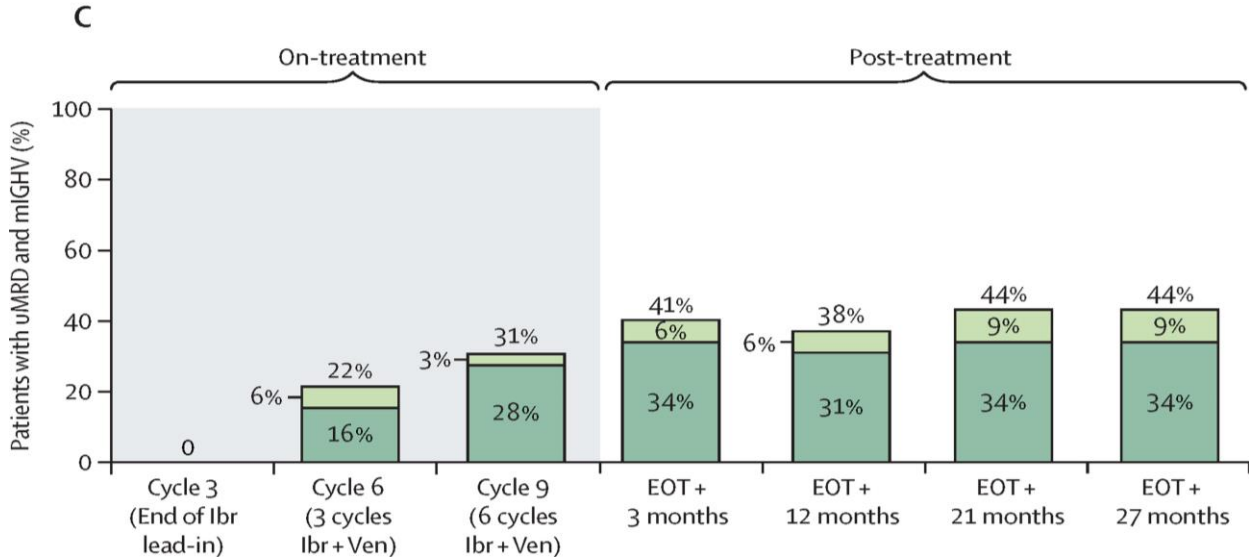
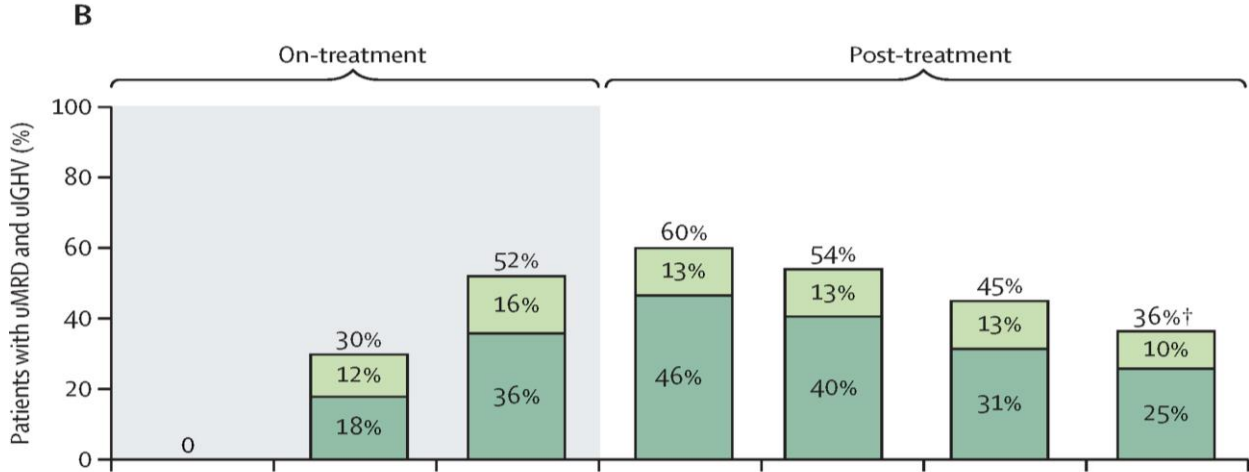
	0	6	12	18	24	30	36	42	48
Ibr+Ven	106 (0)	98 (2)	92 (2)	90 (2)	87 (3)	80 (6)	76 (6)	52 (28)	2 (75)
Clb+O	105 (0)	101 (0)	95 (2)	56 (4)	43 (6)	34 (7)	30 (8)	14 (17)	1 (26)



Number at risk (number censored)

	0	6	12	18	24	30	36	42	48
mIGHV Ibr+Ven	32 (0)	29 (2)	28 (2)	28 (2)	26 (3)	26 (3)	26 (3)	17 (12)	0 (29)
uIGHV Ibr+Ven	67 (0)	63 (0)	58 (0)	56 (0)	55 (0)	49 (2)	45 (2)	33 (14)	2 (42)
mIGHV Clb+O	35 (0)	34 (0)	33 (0)	25 (1)	23 (2)	20 (2)	17 (2)	7 (9)	0 (14)
uIGHV Clb+O	57 (0)	56 (0)	52 (2)	25 (3)	16 (4)	11 (4)	10 (5)	6 (6)	1 (9)

GLOW: uMRD Dynamics According to IGHV Status

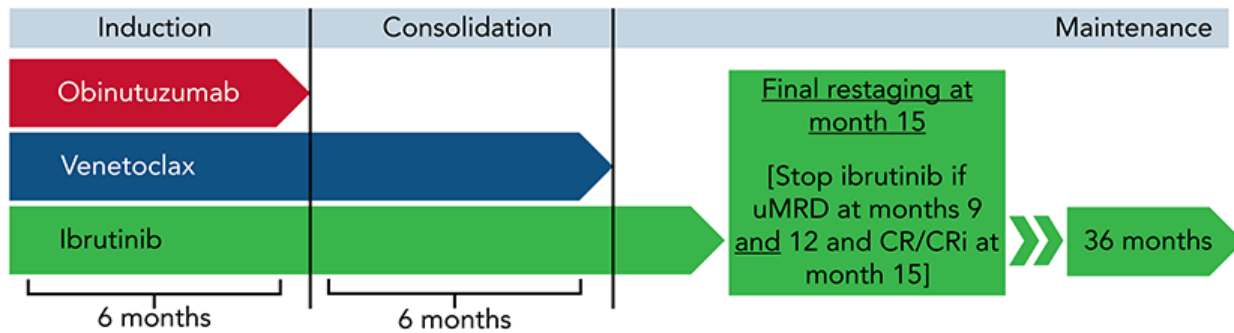


Triple combinations in CLL frontline therapy

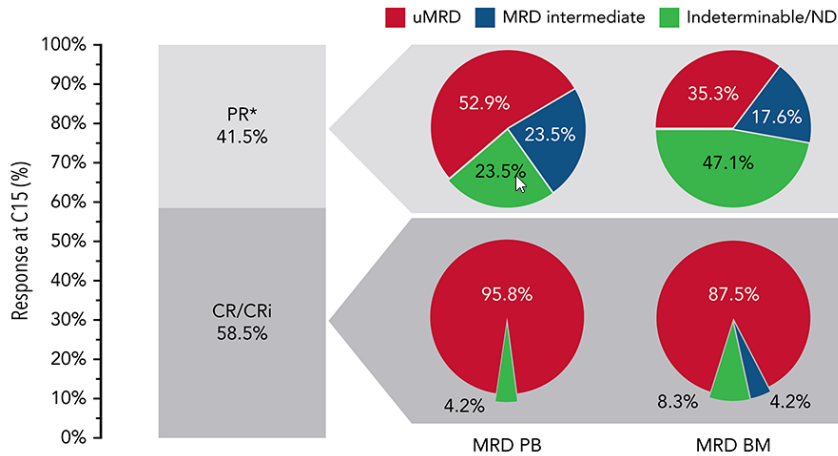
Treatment	N	Age	TP53 ab	ORR/CR	PFS	OS	uMRD (10^{-4})	uMRD (10^{-5})	Median FU
IBRU + VEN + OBINU (vs. FCR/BR) [GAIA/CLL13]	231	61	Excluded	94.4%/61.9%	3-yr 90.5%	3-yr 95.3%	92.2%/77.9% (PB/BM) at 15 months	NR	38.8 months
IBRU + VEN + OBINU	25	59	12%	84%/32%	4-yr 96%	4-yr 85%	67% (PB + BM) at EOT	NR	57 months
IBRU + VEN + OBINU [CLL2-GIVe]	41	62	100%	100%/58.5%	3-yr 79.7%	3-yr 92.6%	78%/65.9% (PB/BM) at cycle 15	NR	36 months
ACALA + VEN + OBINU (AVO)	68	63	45.6%	98%/48%	3-yr 93%	NR	86% (PB and BM) at 16 months (+1 mo EoT)	59% (PB)	35 months
ZANU + VEN [SEQUOIA D]	35	NR	100%	96.8%/12.9%	NR	NR	NR	NR	9.7 months
ZANU + VEN + OBINU (ZVO)	39	62	13%	100%/57%	NR	NR	92%/84% (PB/BM) at best	40% (PB)	25.8 months

uIGHV, unmutated IGHV; ORR, overall response rate; CR, complete response; PFS, progression-free survival; OS, overall survival; FU, follow-up; mo, months; uMRD, undetectable measurable residual disease; PB, peripheral blood; BM, bone marrow; c/ncMRD, confirmed MRD; FCR, fludarabine plus cyclophosphamide plus rituximab; BR, bendamustine plus rituximab; IBRU, ibrutinib; VEN, venetoclax; OBINU, obinutuzumab; ACALA, acalabrutinib; ZANU, zanubrutinib; NR, not reported; TP53 ab, TP53 aberrations.

CLL2-GIVe trial (ibrutinib, venetoclax, and obinutuzumab) in TN CLL with del(17p) and/or TP53 mutation

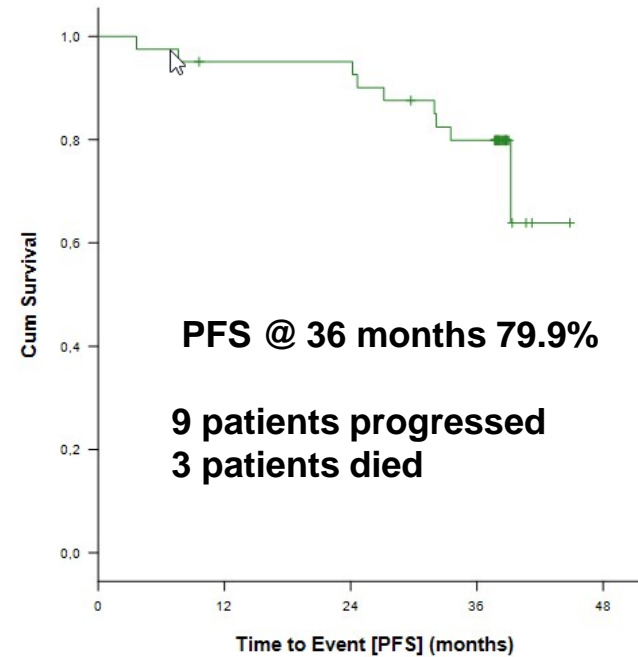
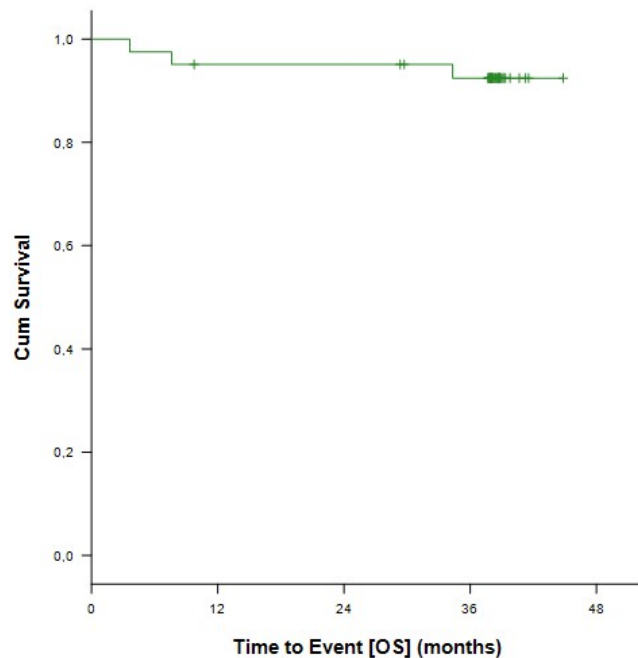


Response and MRD at final restaging

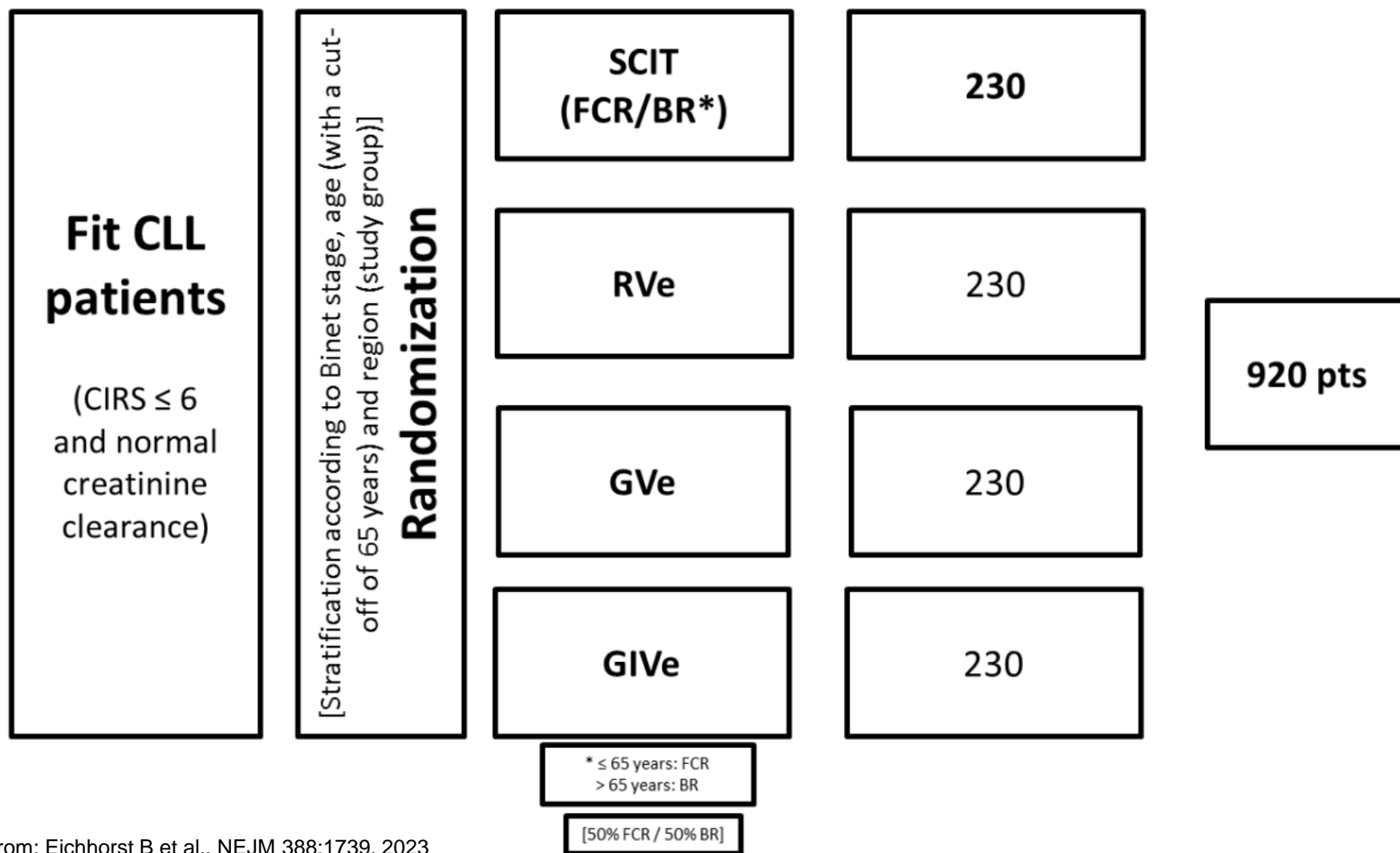


Huber H et al., Blood 139:1318-1329, 2022

CLL2-GIVe trial: OS and PFS in 41 pt

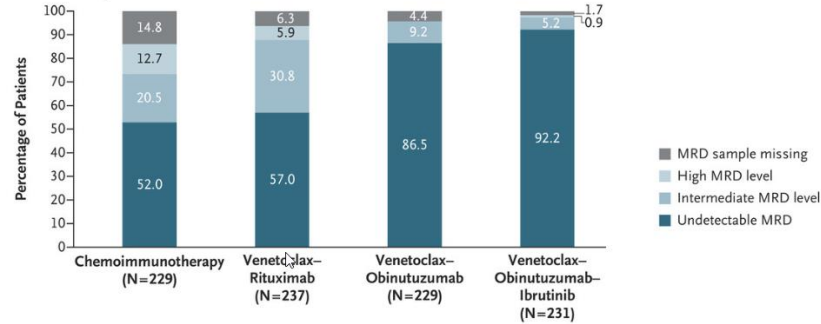


Phase III GAIA/CLL13 trial (NCT02950051)

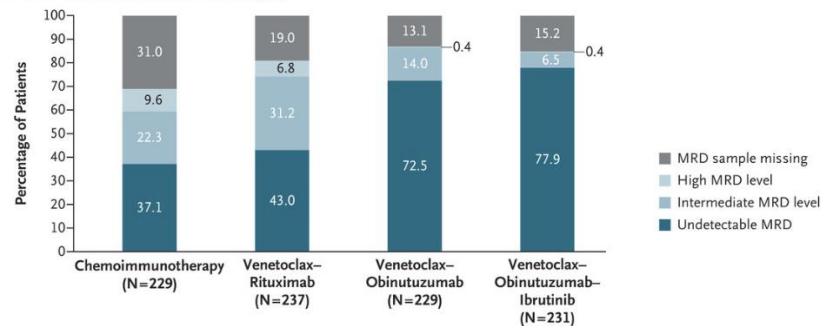


Phase III GAIA/CLL13 trial (NCT02950051)

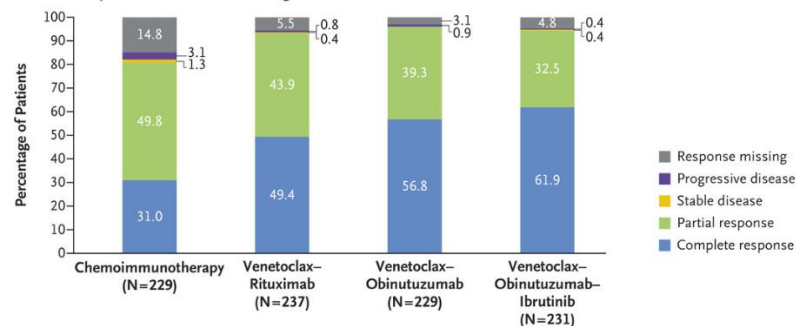
A MRD in Peripheral Blood at Month 15



B MRD in Bone Marrow at Final Restaging



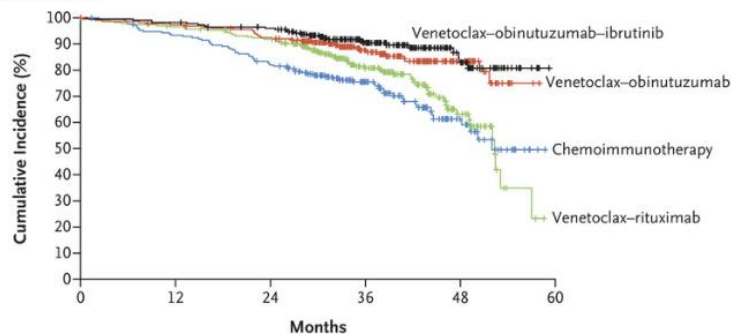
C Clinical Response at Month 15 According to IWCLL Criteria



Conclusion: Venetoclax–obinutuzumab with or without ibrutinib was superior to chemoimmunotherapy

Phase III GAIA/CLL13 trial (NCT02950051)

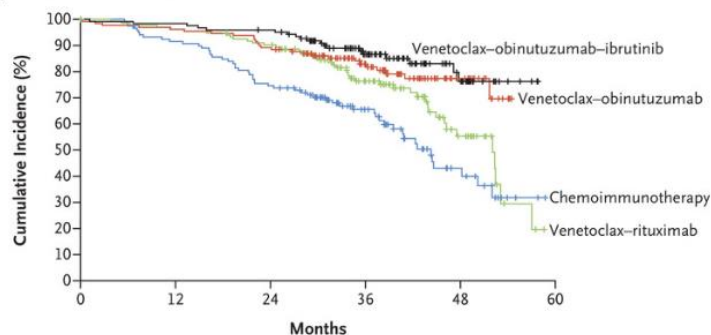
A Progression-free Survival, All Patients



No. at Risk

Chemoimmunotherapy	229	197	172	98	28	0
Venetoclax-rituximab	237	226	212	119	32	0
Venetoclax-obinutuzumab	229	221	208	125	42	0
Venetoclax-obinutuzumab-ibrutinib	231	227	217	132	44	0

B Progression-free Survival, Patients with Unmutated IGHV



No. at Risk

Chemoimmunotherapy	131	108	88	48	14	0
Venetoclax-rituximab	134	128	119	67	20	0
Venetoclax-obinutuzumab	130	125	116	71	21	0
Venetoclax-obinutuzumab-ibrutinib	123	121	117	70	22	0

Current status of triple combinations

- IVO demonstrated higher response rates over venetoclax-rituximab or chemoimmunotherapy in the GAIA-CLL13 trial
- Difference in MRD-negative rates between IVO and venetoclax-obinutuzumab was not apparent
- In older patients, the Alliance A041702 trial failed to demonstrate PFS benefit of IVO over IO/ibrutinib-obinutuzumab (14 month PFS 87.5% in the IO arm compared to 85% with IVO)¹
- Therefore: triplet combinations for CLL remain investigational

Conclusions

- Current standard therapy: BTK inhibitor monotherapy or Venetoclax + CD20 mAbs or BTKi + venetoclax (ibrutinib+ven)
- Venetoclax + CD20 mAbs or BTKi + venetoclax time-limited therapy: deeper remissions, but no demonstrated PFS/OS benefit vs. BTKi monotherapy
- Low-risk patients have longer remissions after time-limited therapy, i.e. venetoclax +/- CD20 mAbs or BTKi + venetoclax
- Preliminary data suggest triple therapy does not provide PFS benefit over double therapy
- Choice of Tx ultimately depends on patient and physician goals and preferences (younger patients prefer time-limited Tx, elderly frail patients prefer Tx with “simple” logistics)



Thank you!

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