

# FD vs Indefinite Therapy in CLL

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## REVOLUTIONARY ROAD IN CLL

Innovazione rivoluzionaria nella terapia  
della leucemia linfatica cronica

Padova, 22 maggio 2024  
Hotel NH Padova



# Disclosures

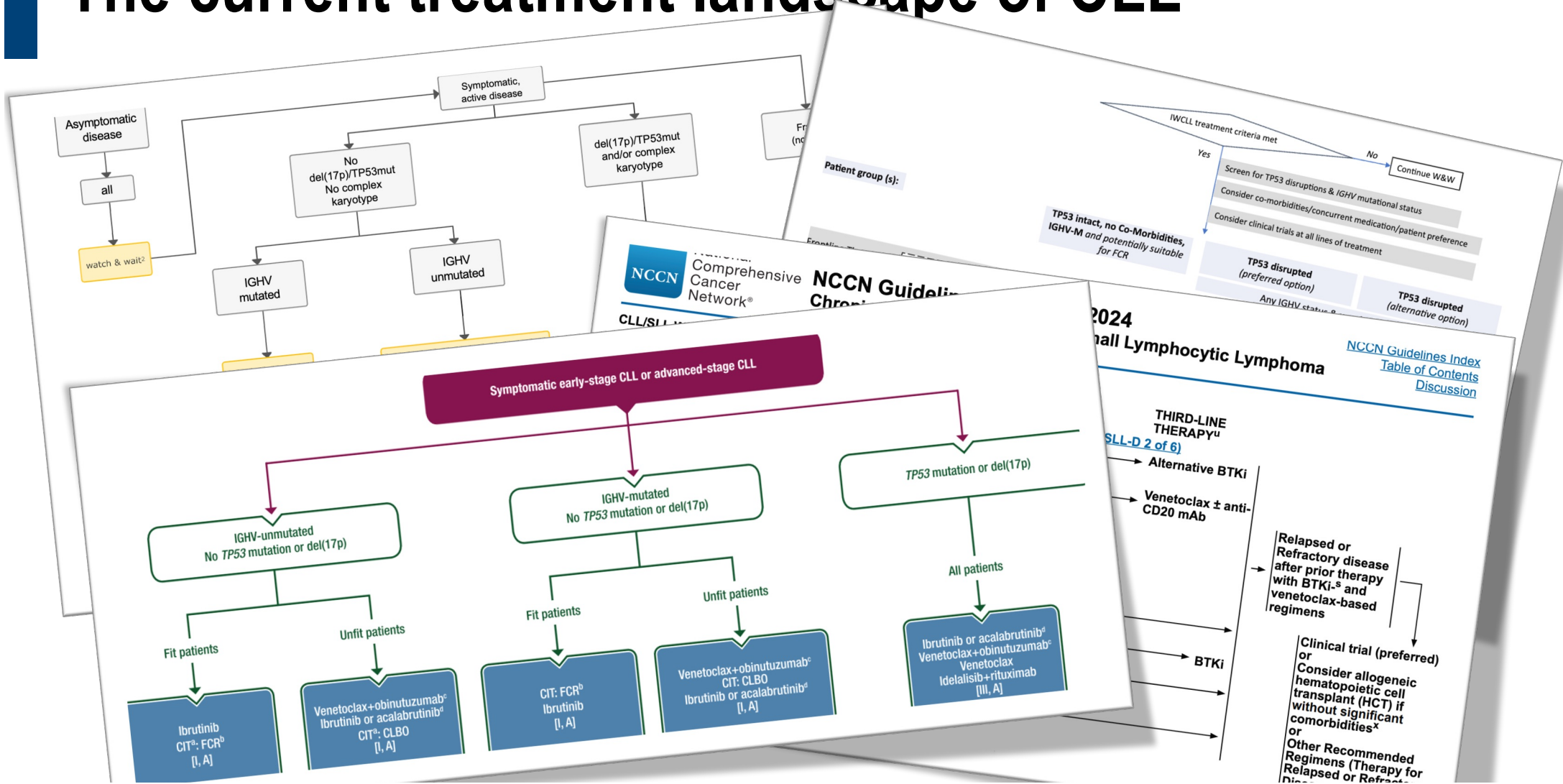
**Honoraria:** Roche, Janssen, Gilead, AbbVie, Lilly, AstraZeneca, Adaptive, BeiGene

**Advisory boards:** AstraZeneca, Roche, Janssen, Gilead, AbbVie

**Personal fees:** Roche, Janssen, Gilead, AbbVie, AstraZeneca

**Research grants:** Beigene, Roche, Janssen, AbbVie

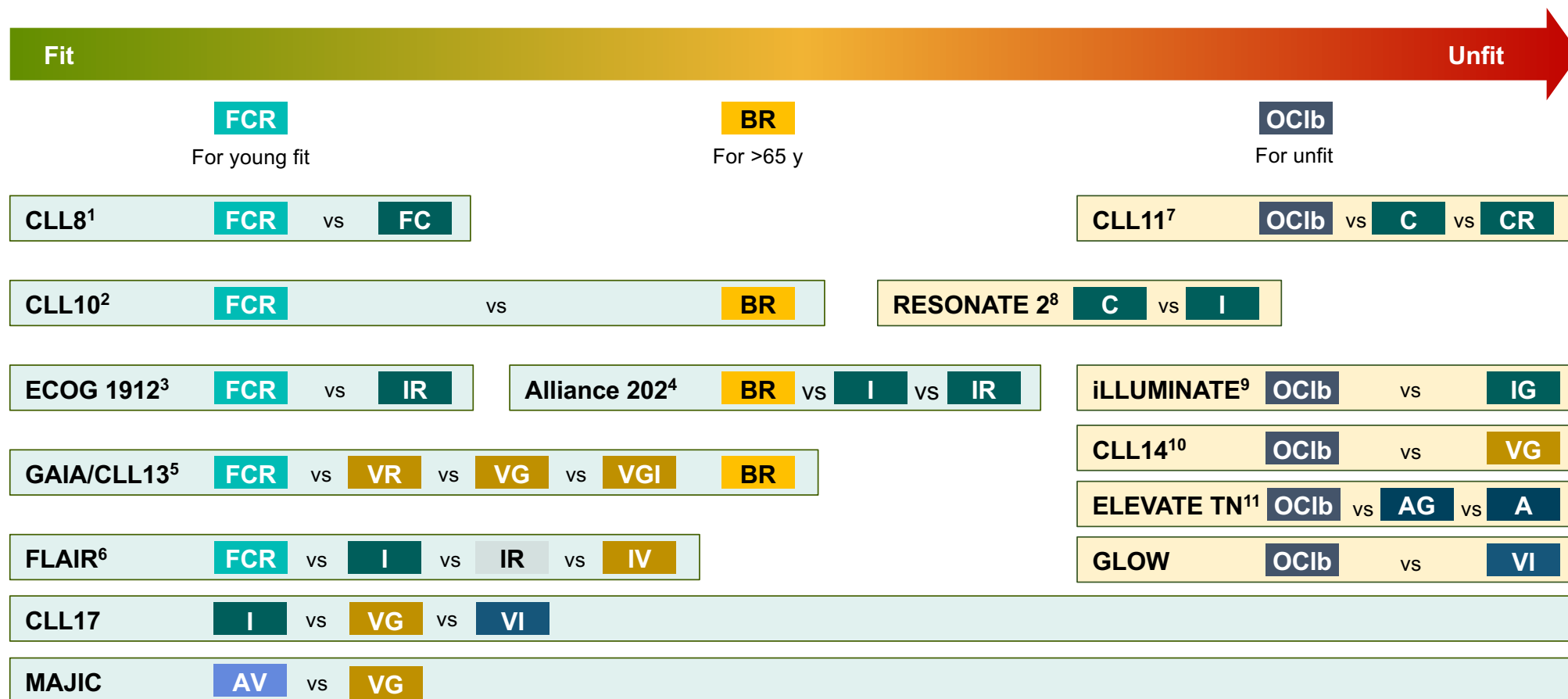
# The current treatment landscape of CLL





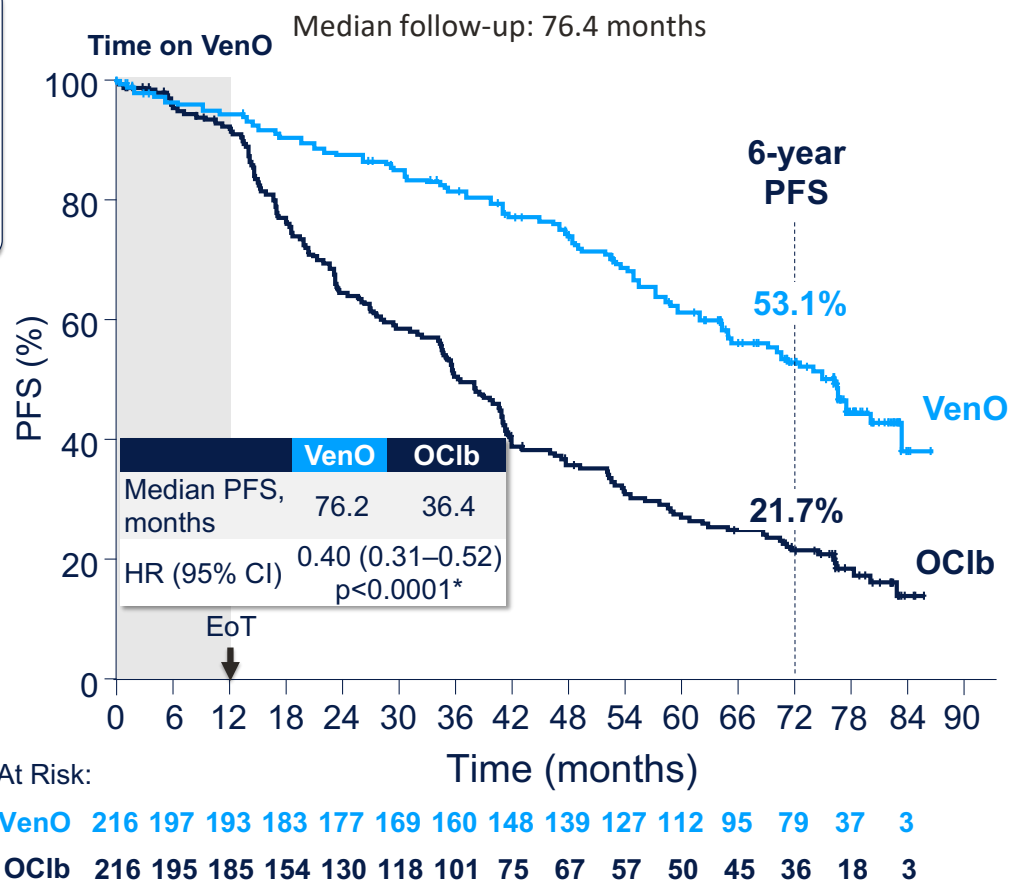
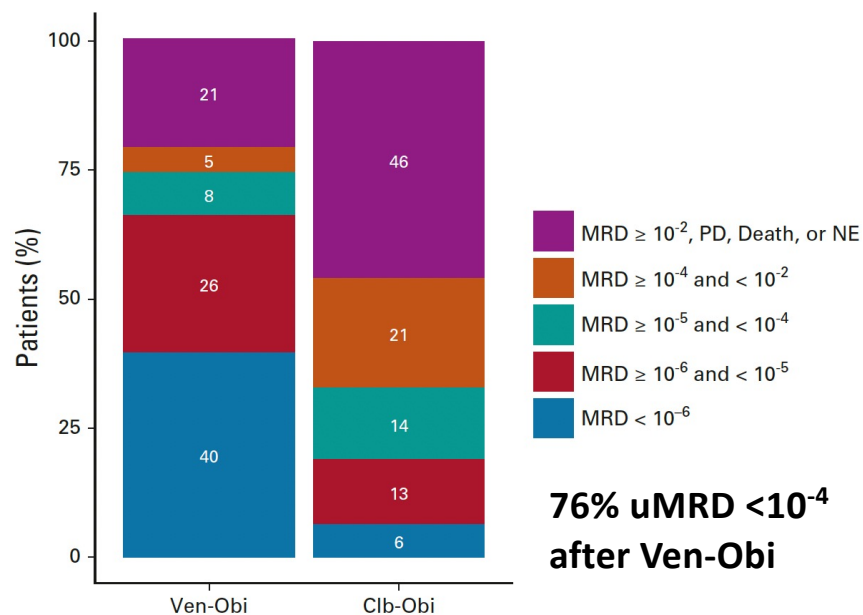
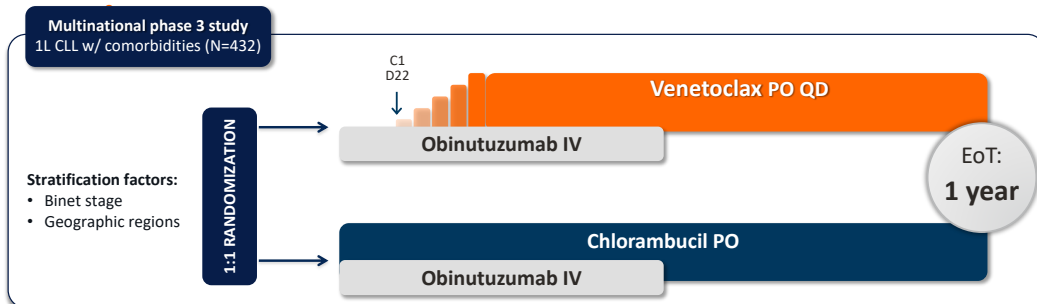


# The role of fitness

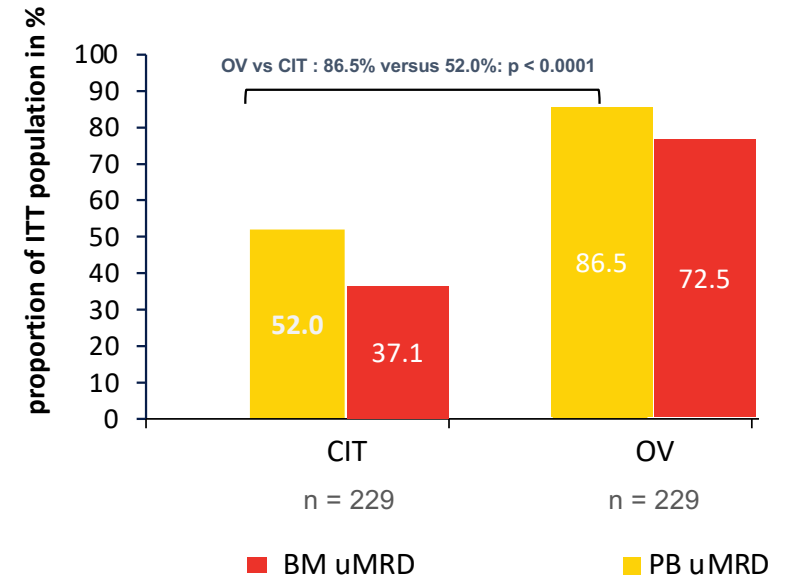
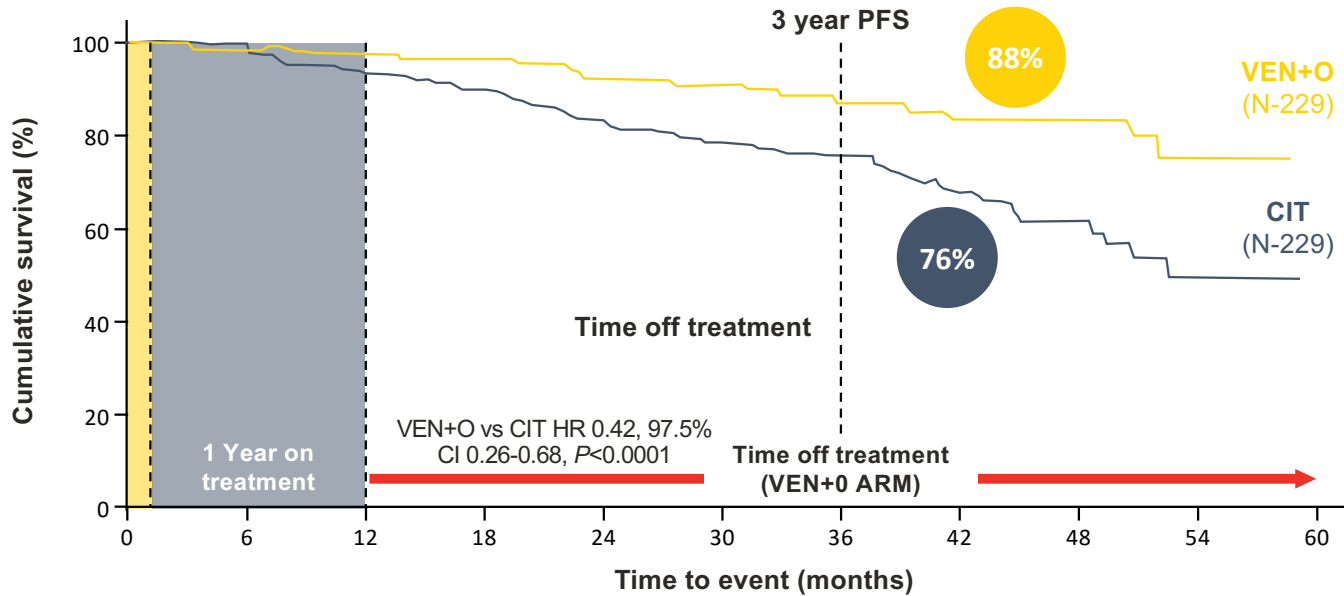
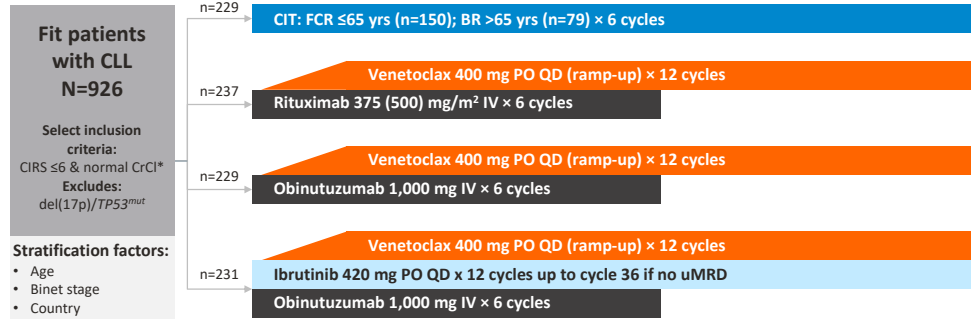


Clinicaltrials.gov: 1. NCT00281918; 2. NCT00769522; 3. NCT02048813; 4. NCT01886872 5. NCT02950051; 6. EudraCT number 2013-001944-76. 7. NCT01010061; 8. NCT01722487; 9.; NCT02264574 10. NCT02242942; 11. NCT02475681.

# CLL14 – Ven-Obi in unfit patients

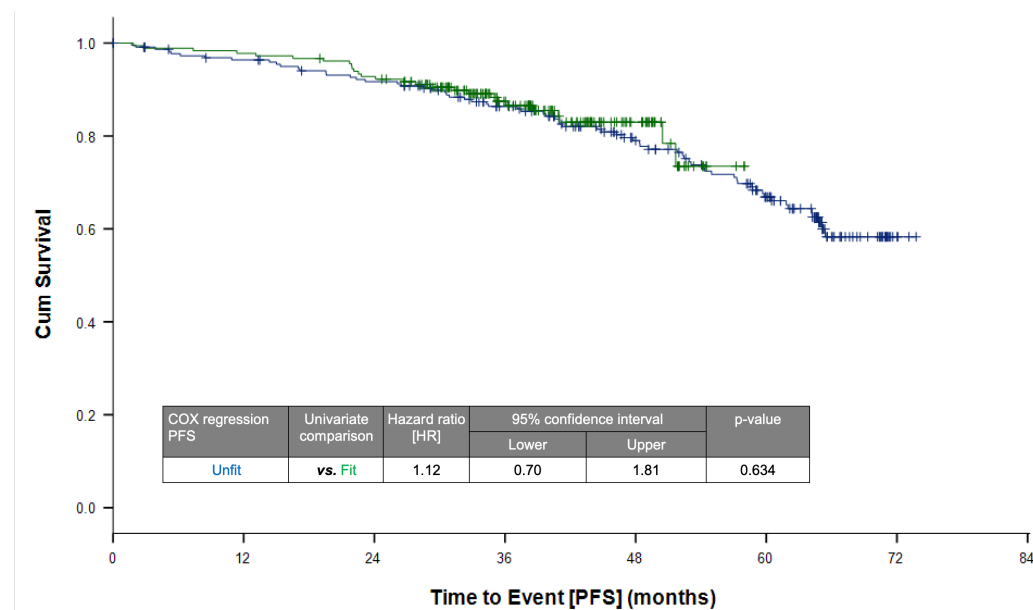
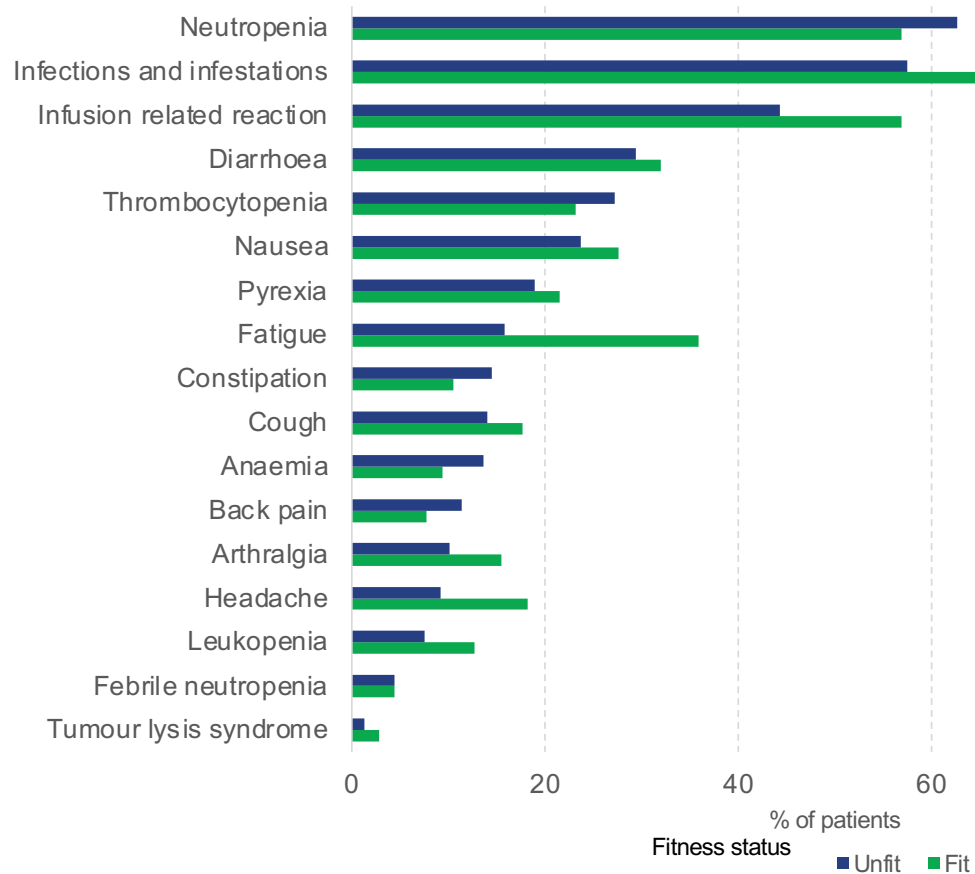


# CLL13 – Ven-Obi in fit patients



**High efficacy in unfit and fit patients.**

# Does fitness matter with Ven-Obi?

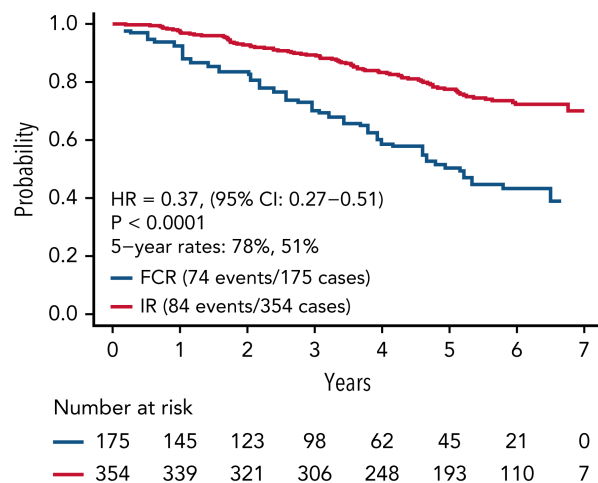


Unfit	228	210	197	167	125	89	4	0
Fit	181	177	167	99	35	0	0	0

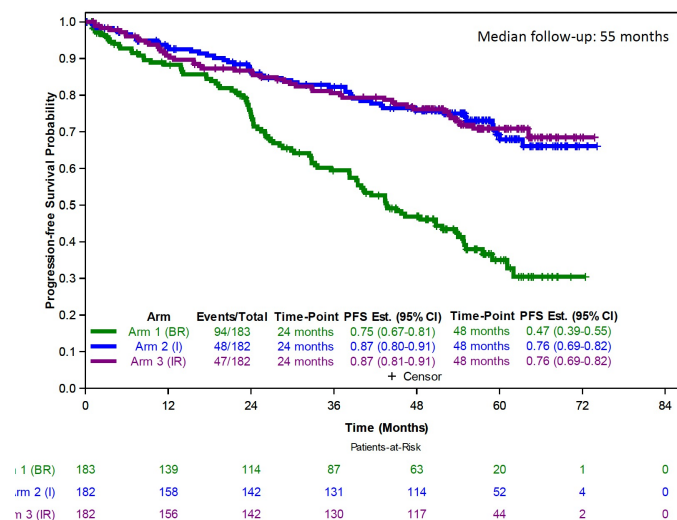
Unpublished data

# Does fitness matter with BTKi?

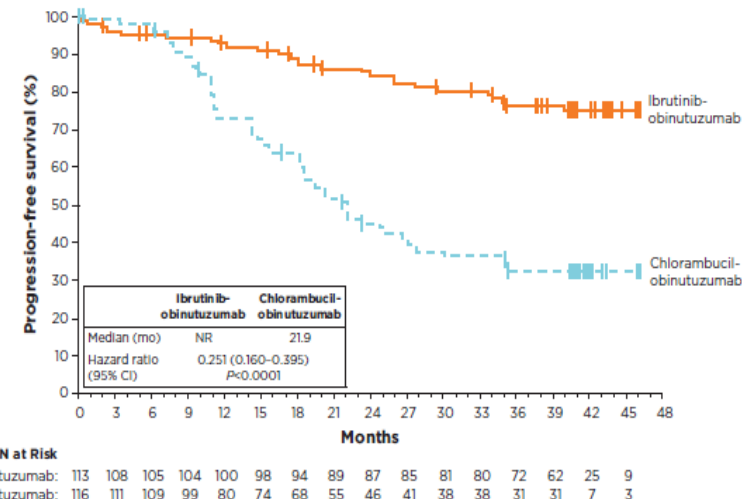
ECOG1912: Young/fit patients



A041202: Elderly/fit patients



iLLUMINATE: Elderly/unfit patients

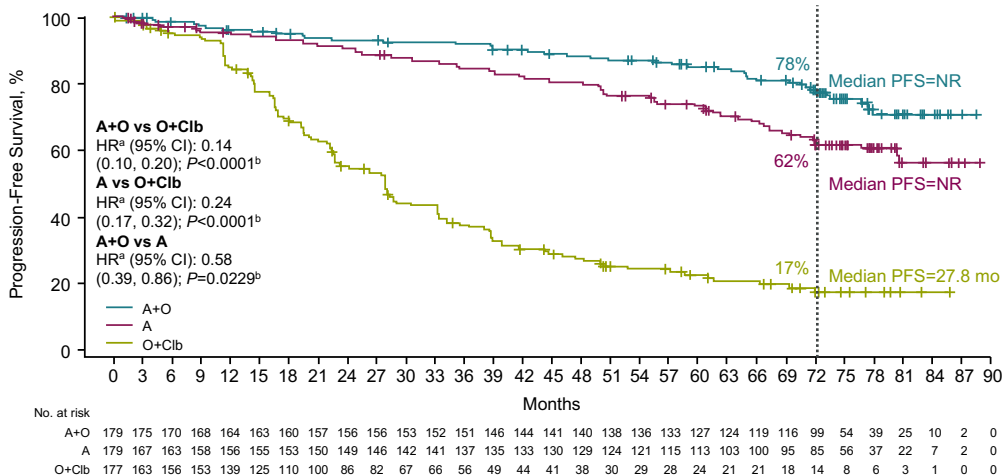


High efficacy of ibrutinib confirmed in randomized studies with fit and unfit patients.

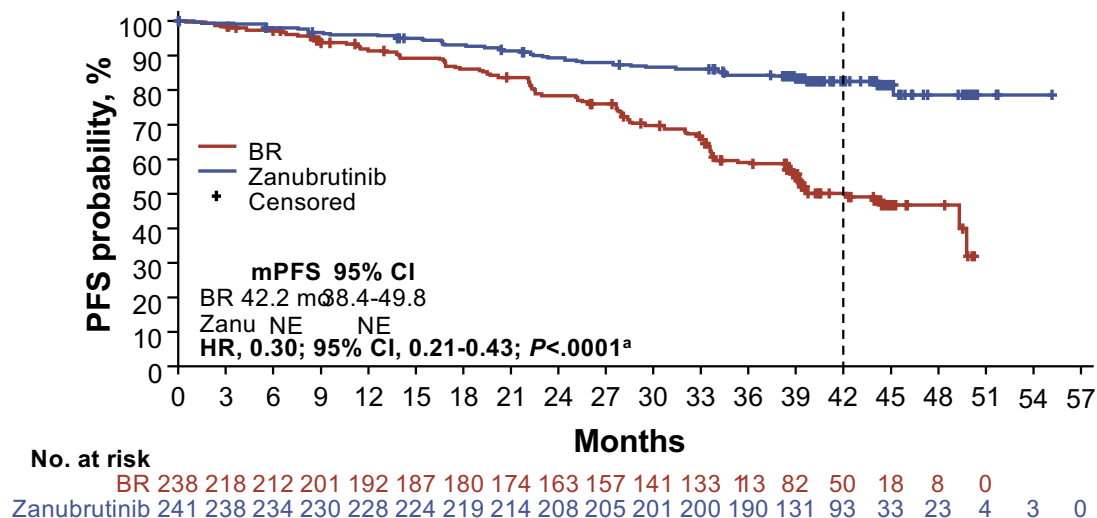


# Does fitness matter with BTKi?

**ELEVATE-TN: Elderly/unfit patients**



**SEQUOIA: Elderly/fit patients**



**No randomized first-line data have been generated so far on Acalabrutinib or Zanutrutinib in *fit* patients**



# Summary I

With currently available evidence, we can assume:

- ,quantitative' fitness, as measured by CIRS, ECOG, Karnofsky etc. is **not a major determinant of outcome**
- rather, **the type of coexisting conditions** should be considered in light of distinct toxicity profiles of targeted agents

**BTKi**

Continuous  
monotherapy

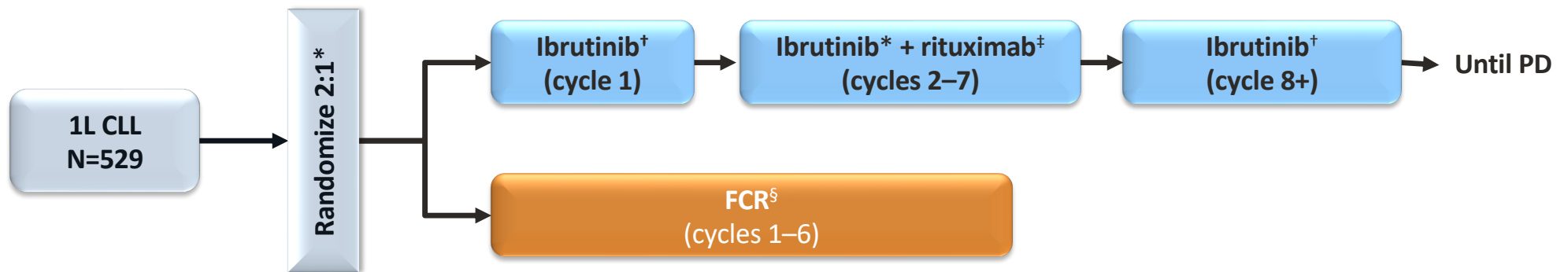
BCL2i+CD20ab  
BTKi+BCL2i  
CIT

Fixed-duration  
combination  
therapy

TREATMENT PARADIGMS

# ECOG 1912: Study design

Open-label, multicenter, randomized, phase 3 study assessing the efficacy and safety of IR vs FCR in younger patients



## Key inclusion criteria

- Age ≤70 years
- ECOG PS 0–2
- Life expectancy ≥12 months
- Ability to tolerate FCR-based therapy
- No del(17p)
- Glomerular filtration rate >40 mL/min<sup>¶</sup>

## Primary endpoints

- PFS
- QoL (FACT-Leu TOI)

## Secondary endpoints

- Overall survival
- Safety
- Change in QoL
- Adherence (ibrutinib arm only)

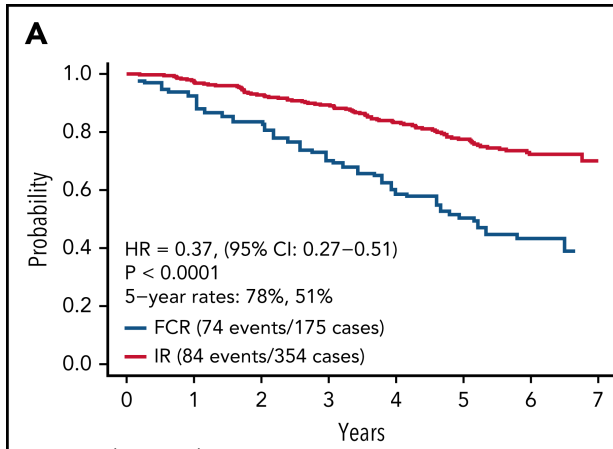
\* Stratification according to age, ECOG PS, Rai stage, and del(11q);

† Ibrutinib PO 420 mg daily, D1–28; ‡ rituximab IV 50 mg/m<sup>2</sup> C2D1, 325 mg/m<sup>2</sup> C2D2, then 500 mg/m<sup>2</sup> day 1 of C3–7;

§ Fludarabine 25 mg/m<sup>2</sup> days 1–3, cyclophosphamide 250 mg/m<sup>2</sup> days 1–3, rituximab as per ibrutinib arm but starting on cycle 1; q28 cycles 1–6.

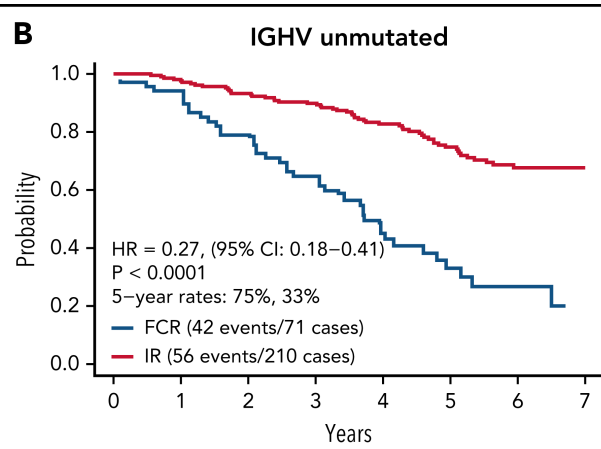
¶ By Cockcroft-Gault formula.

1. ClinicalTrials.gov. NCT02048813 (accessed February 2020); 2. Shanafelt TD, *et al.* *N Engl J Med* 2019; **381**:432–443 (incl. suppl.).



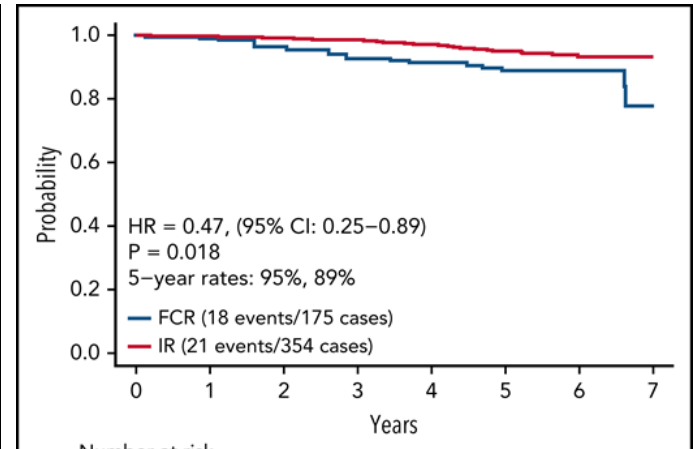
Number at risk

—	175	145	123	98	62	45	21	0
—	354	339	321	306	248	193	110	7



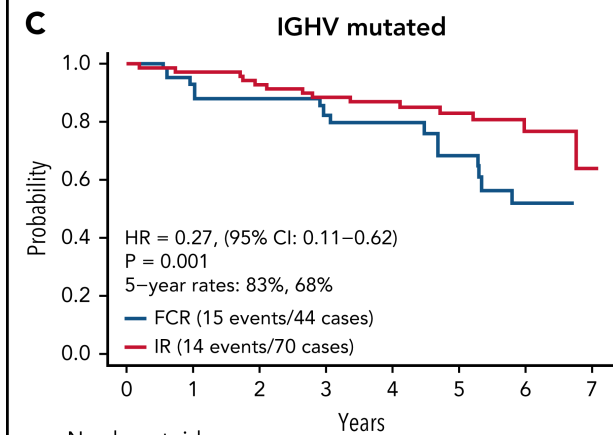
Number at risk

—	71	63	50	39	20	12	5	0
—	210	203	193	184	147	108	61	6



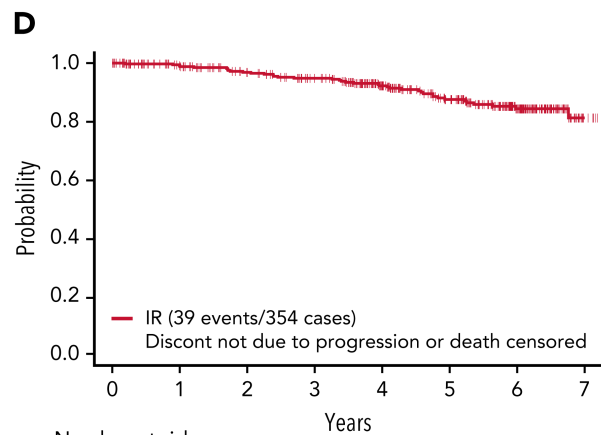
Number at risk

—	175	155	143	131	126	96	47	3
—	354	347	343	338	329	300	139	20



Number at risk

—	44	38	34	30	21	17	9	0
—	70	67	64	60	50	40	18	1



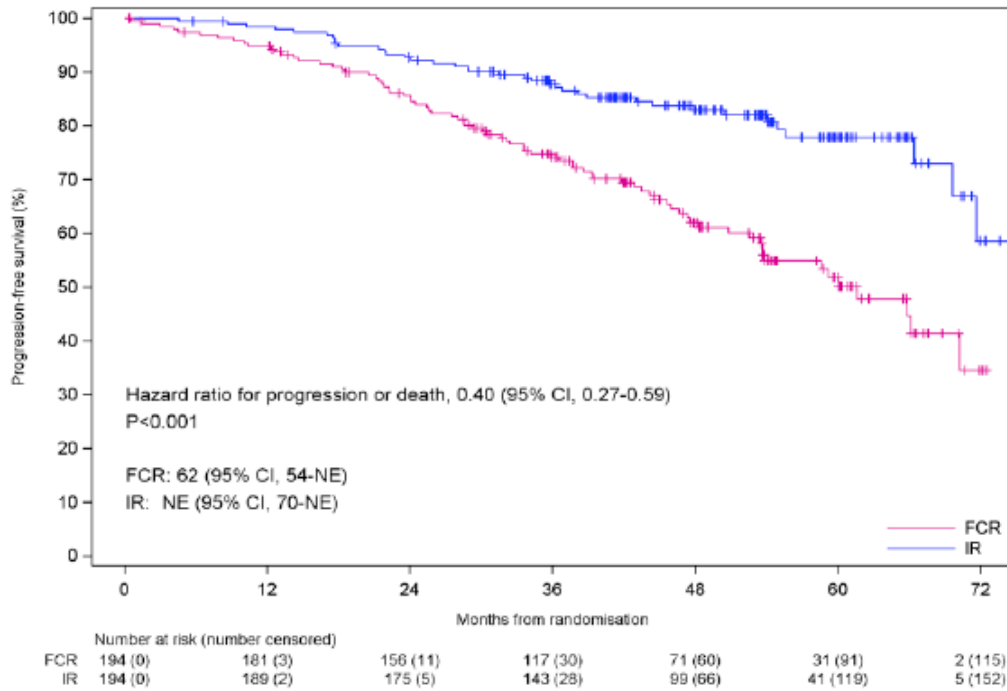
Number at risk

—	354	321	293	273	228	174	98	6
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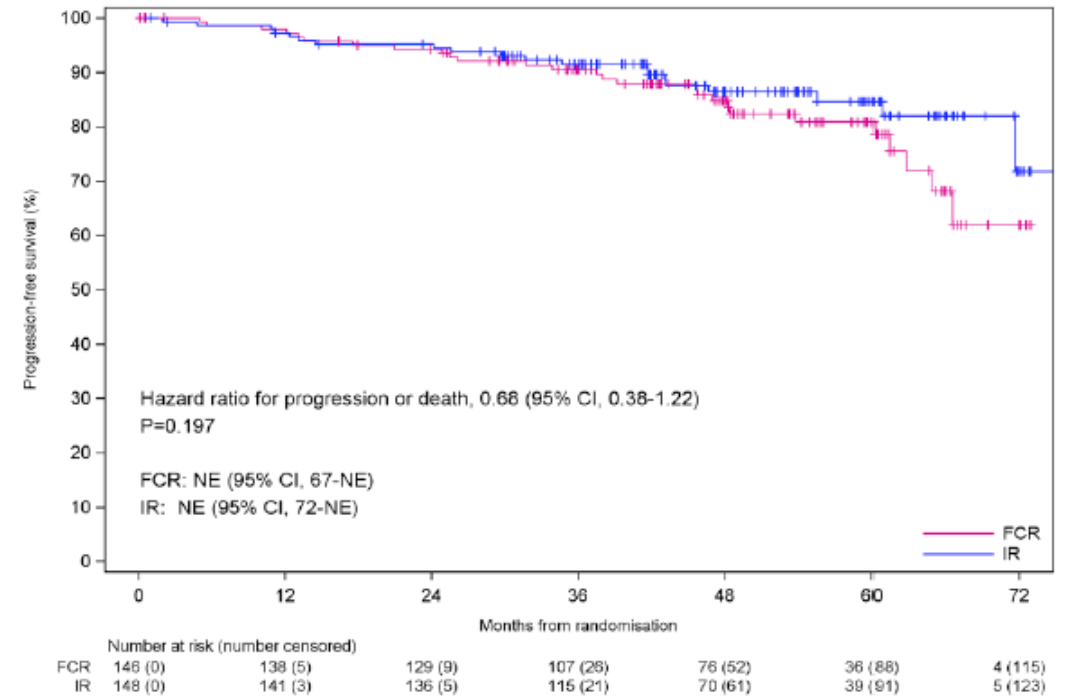


# Flair PFS by IGHV mutation status

IGHV unmutated excl. Subset 2 CLL (n=388)

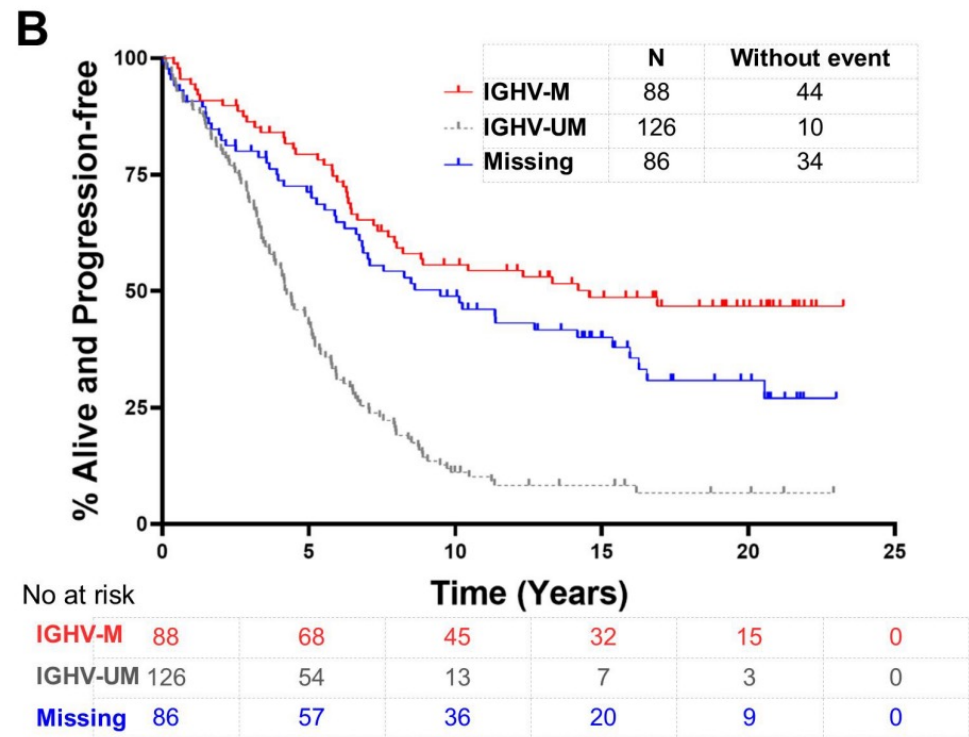
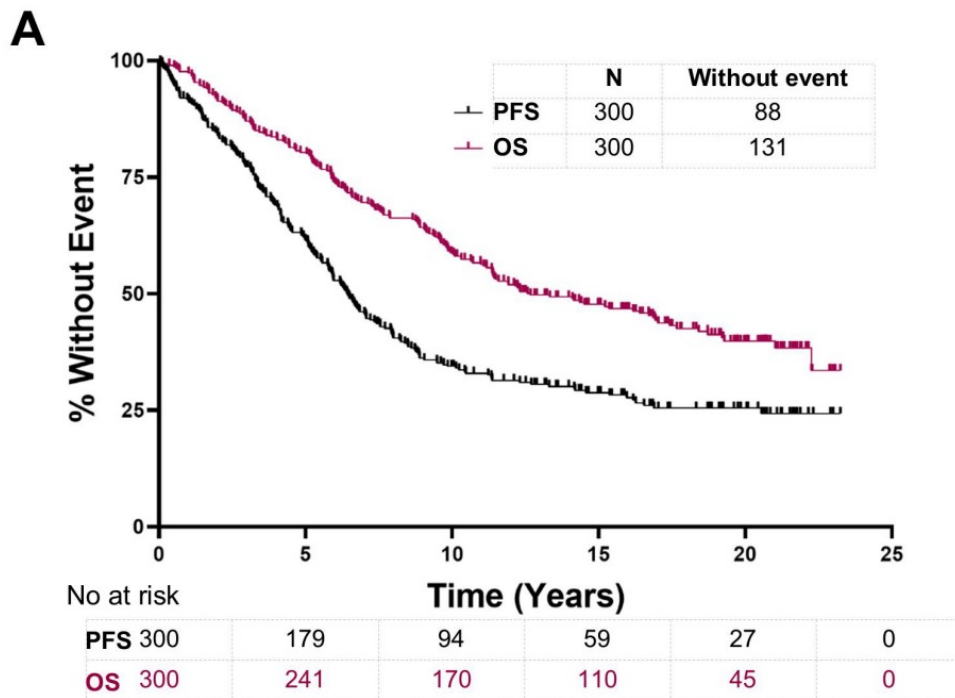


IGHV mutated CLL excl. Subset 2 (n=294)



Stereotype Subset 2: n=46 (FCR 20; IR 26) → HR for PD or death 0.32 (95% CI, 0.06-1.76), p=0.191

# Long-term remission post-FCR in IGHVmut setting



# Issues with chemoimmunotherapy

Long-term safety	Total	
	Cases N (%)	Patients N (%)
Total patients (safety population), N		800
Total cases [N (%)] and patients [N (%)] with ≥1 SPM	136 (100)	122 (15)
<b>Secondary malignancies</b>		
<b>Richter's transformation</b>	38 (28)	38 (5)
<b>Solid tumors</b>	55 (40)	52 (7)
Lung	18/55 (33)	18 (2)
Prostate	8/55 (15)	8 (1)
Renal/bladder	7/55 (13)	6 (1)
Colorectal	2/55 (4)	2 (<1)
Melanoma	8/55 (15)	8 (1)
Breast	3/55 (6)	3 (<1)
Pancreatic	2/55 (4)	2 (<1)
Ovarian/uterine/cervical	1/55 (2)	1 (<1)
Liver/gall bladder	1/55 (2)	1 (<1)
Thyroid	2/55 (4)	2 (<1)
Pharyngeal/laryngeal	1/55 (2)	1 (<1)
Other	2/55 (4)	2 (<1)
<b>Hematologic neoplasia</b>	24 (18)	23 (3)
AML/MDS	14/24 (58)	13 (2)
Indolent B-non-Hodgkin lymphoma	3/24 (13)	3 (<1)
Aggressive B-non-Hodgkin lymphoma	2/24 (8)	2 (<1)
ALL	1/24 (4)	1 (<1)
CML	1/24 (4)	1 (<1)
Other	3/24 (13)	3 (<1)
<b>Basalioma, squamous cell</b>	19 (14)	17 (2)
<b>Prolonged neutropenia</b>		
2 months after end of treatment		101 (13)
12 months after end of treatment		30 (4)

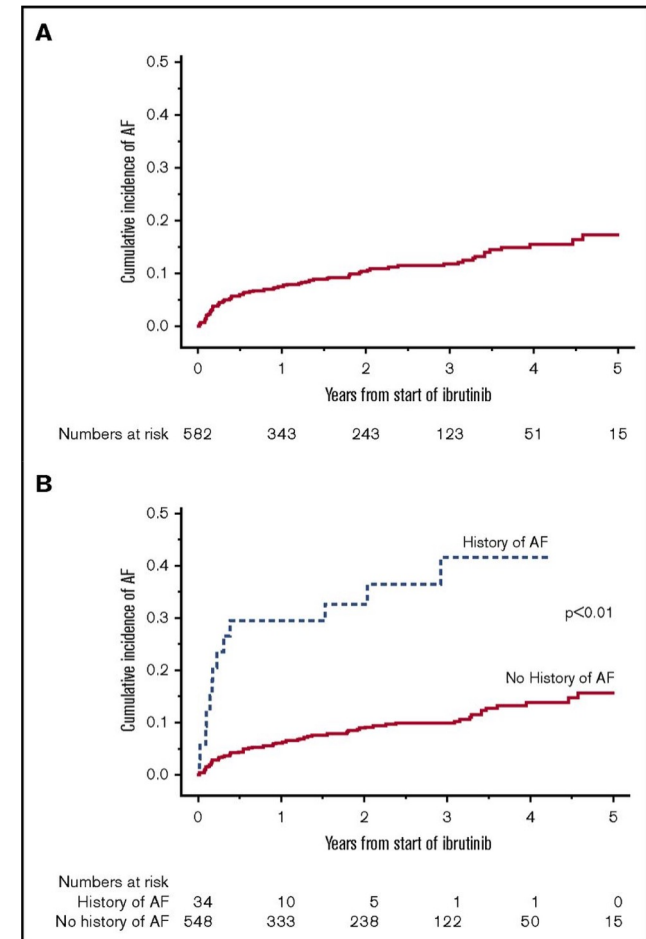
Increased risk of secondary malignancies

# CLL13: Second primary malignancies

<b>Cases of second cancers</b>	<b>CIT</b>	<b>RV</b>	<b>GV</b>	<b>GIV</b>	<b>Total</b>
Hematological malignancies	4	2	0	8	14
Solid tumors	19	13	15	18	65
Non-melanoma skin cancer	33	15	16	11	75
Richter's transformations	6	5	7	3	21
<b>Incidence rates</b> (per 1000 pt-months)					
All SPM (excl. NMSC and Richter's)	2.21	1.21	1.16	2.36	1.71

# Issues with 1<sup>st</sup> generation BTKi

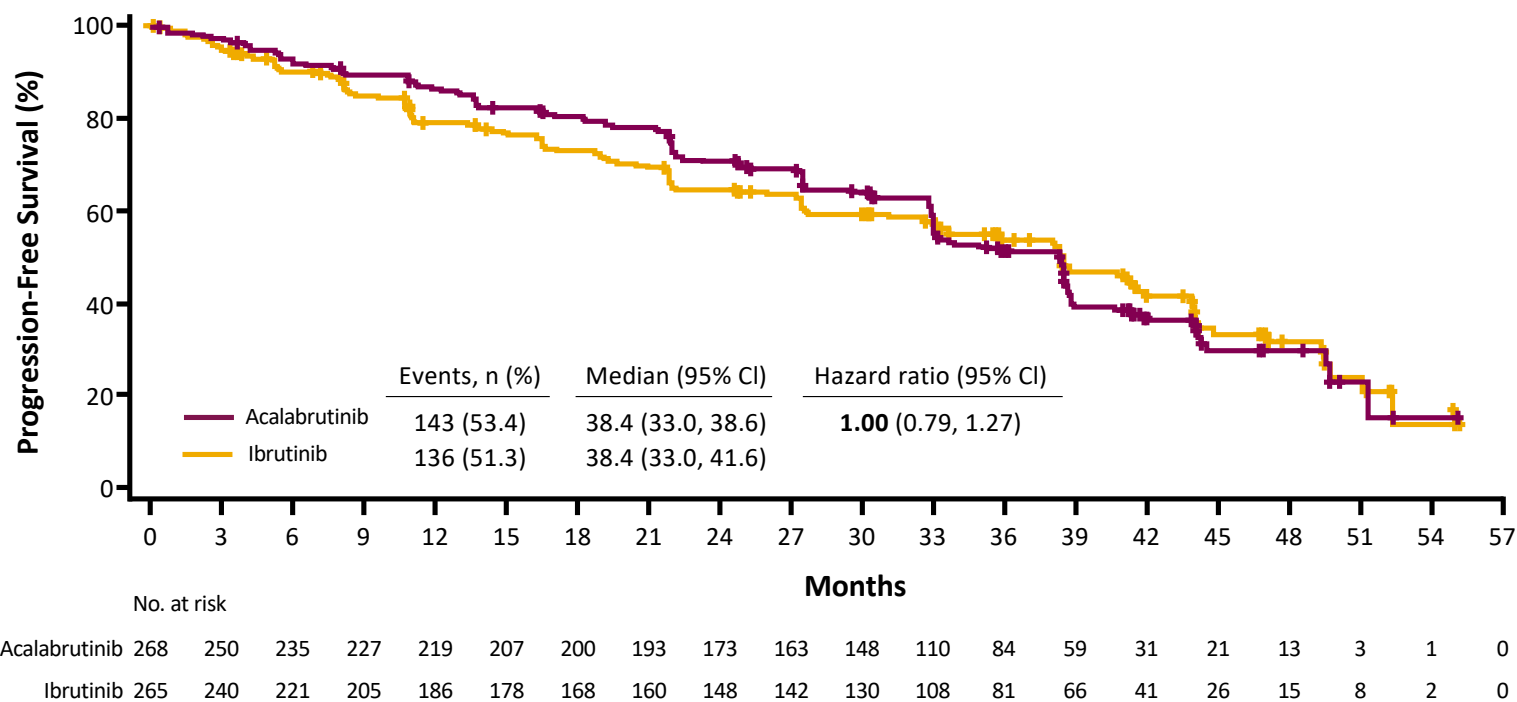
- Distinct toxicity profile
  - Cardiovascular toxicity
    - Atrial fibrillation
    - Ventricular fibrillation/arrhythmia
    - Cardiac arrests / sudden death
    - Congestive heart failure
  - Bleeding disorders
  - Hypertension
- High discontinuation rates (up to 40% in the first 24 months)





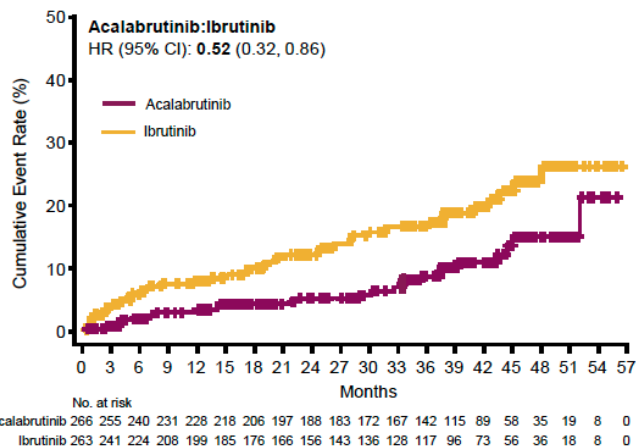
# Can next-generation BTKi improve this?

PFS Acalabrutinib = Ibrutinib

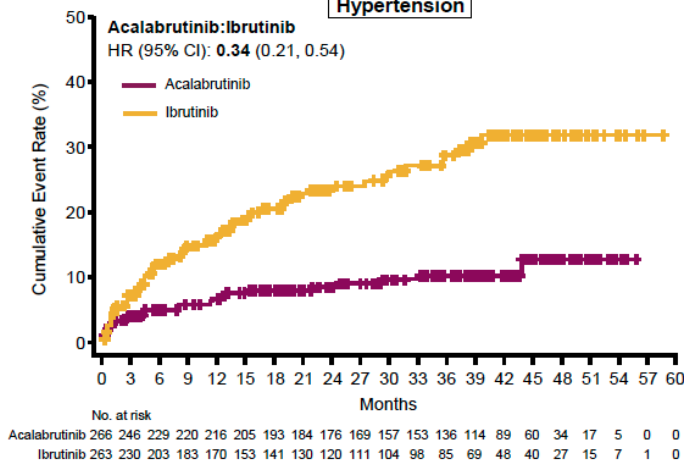


# Cardiovascular toxicity under Acalabrutinib vs Ibrutinib

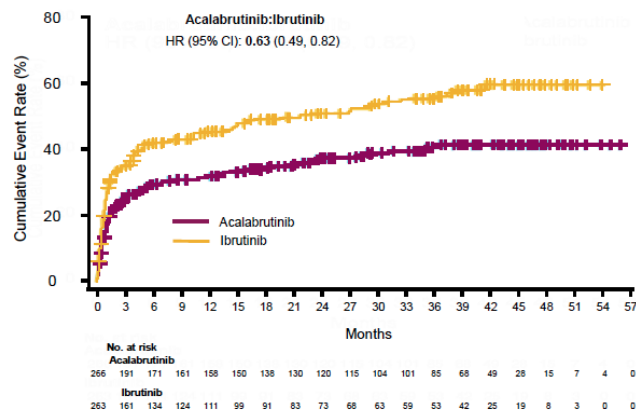
Atrial fibrillation/flutter



Hypertension

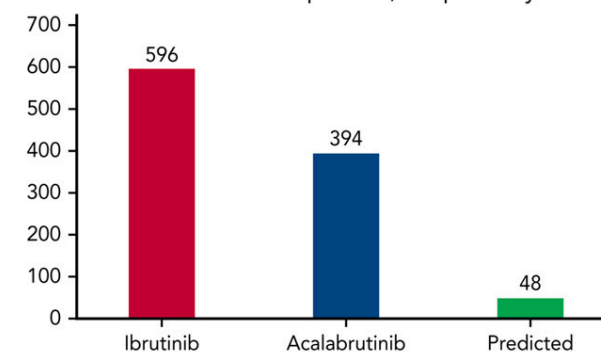


Bleeding events

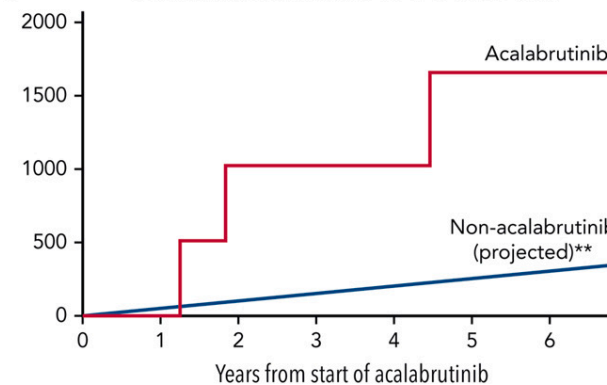


AF, hypertension, bleeding less Common with acalabrutinib than with ibrutinib, but only relative risk reduction

A VA incidence rate per 100,000 person-years



B Cumulative incidence of VAs over time\*

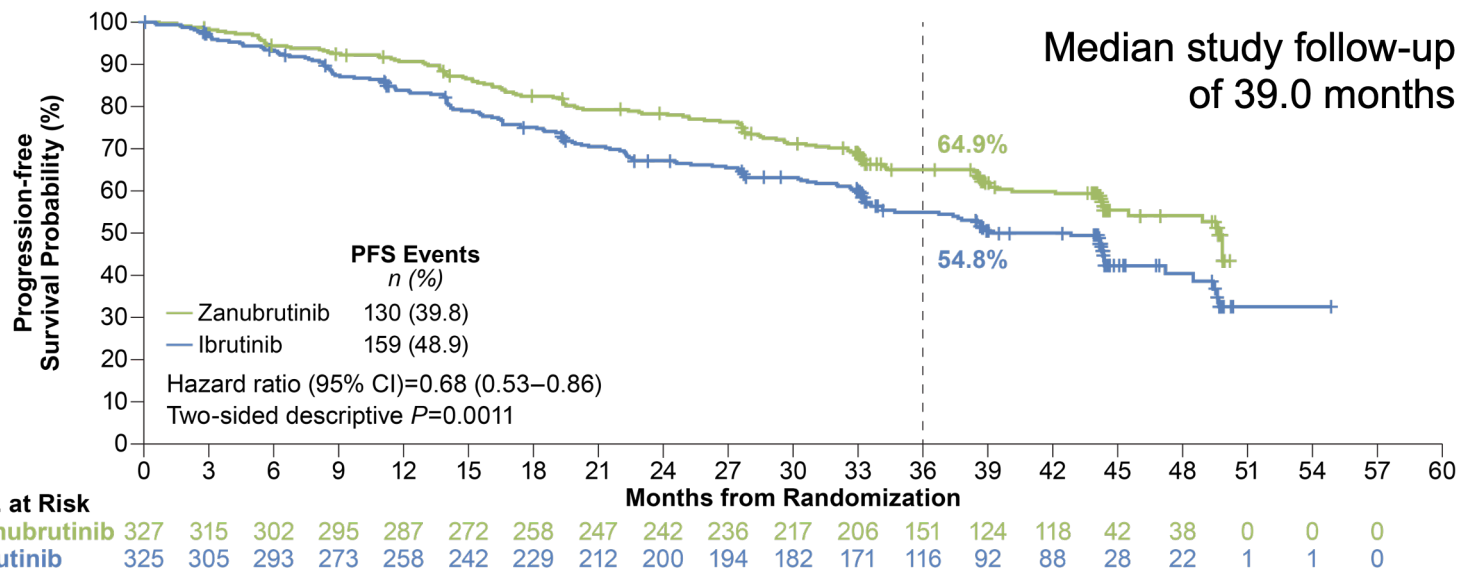
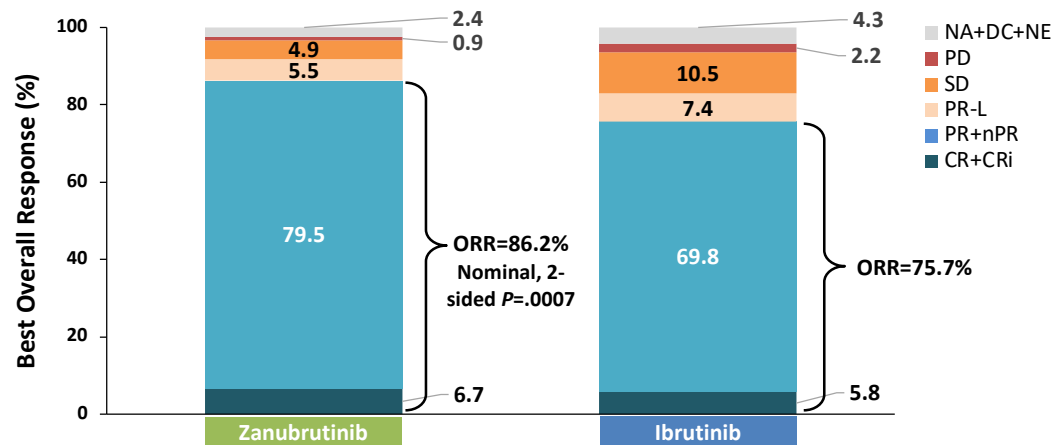


# What about Zanubrutinib?

AEI, n (%)	Any Grade		Grade ≥3	
	Zanubrutinib (n=324)	Ibrutinib (n=324)	Zanubrutinib (n=324)	Ibrutinib (n=324)
≥1 AEI	<b>294 (90.7)</b>	<b>300 (92.6)</b>	<b>186 (57.4)</b>	<b>184 (56.8)</b>
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 <sup>†</sup>	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

**Atrial fibrillation is less common with Zanubrutinib than with Ibrutinib, but rates of bleeding and hypertension and other toxicities similar.**

# What about Zanubrutinib?



PFS possibly longer with Zanubrutinib in ALPINE, but some limitations in interpretability due to study design

# What about Pirtobrutinib?

Adverse Event	Treatment-Emergent AEs in Patients with CLL/SLL (n=282)			
	All Cause AEs, (≥20%), %		Treatment-Related AEs, %	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Fatigue	36.9	1.8	3.5	0.0
Neutropenia	34.4	28.4	19.5	15.2
Diarrhea	28.4	0.4	7.8	0.0
Cough	27.3	0.0	1.8	0.0
<b>Contusion</b>	<b>26.2</b>	0.0	17.4	0.0
Covid-19	25.9	4.6	0.7	0.0
Dyspnea	22.3	2.1	0.7	0.4
Nausea	22.0	0.0	3.5	0.0
Abdominal pain	21.3	1.8	2.1	0.4
AEs of Interest <sup>a</sup>	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Infections	74.1	30.9	12.8	4.3
<b>Bruising</b>	<b>30.1</b>	0.0	19.1	0.0
Rash	24.5	1.1	5.7	0.4
Arthralgia	22.7	1.4	4.3	0.0
<b>Hemorrhage</b>	<b>13.5</b>	2.1	4.6	1.1
Hypertension	14.2	4.3	3.5	0.4
Atrial Fibrillation/Flutter	4.6	1.8	1.4	0.7

No randomized Pirtobrutinib data available yet.



# Toxicities with Ven-Obi

	Venetoclax-obinutuzumab (N=212)		Chlorambucil-obinutuzumab (N=214)	
	During Treatment	After Treatment	During Treatment	After Treatment
Neutropenia	51.9%	3.8%	47.2%	1.9%
Thrombocytopenia	14.2%	0.5%	15.0%	0.0%
Anemia	7.5%	1.9%	6.1%	0.5%
Febrile neutropenia	4.2%	0.9%	3.3%	0.5%
Leukopenia	2.4%	0.0%	4.7%	0.0%
Pneumonia	3.8%	3.3%	3.7%	1.4%
Infusion-related reaction	9.0%	0.0%	9.8%	0.5%
Tumour lysis syndrome	1.4%	0.0%	3.3%	0.0%

No new safety signals identified with longer follow-up (76.4 months)

# Toxicities with Ven-Ibru

Adverse Events, <sup>a</sup> n (%)	Ibrutinib-Venetoclax (n = 106)	Chlorambucil- Obinutuzumab (n = 105)
Diarrhea	54 (50.9)	13 (12.4)
Neutropenia <sup>b</sup>	44 (41.5)	61 (58.1)
Nausea	28 (26.4)	27 (25.7)
Anemia	19 (17.9)	19 (18.1)
Rash	18 (17.0)	7 (6.7)
Urinary tract infection	17 (16.0)	5 (4.8)
Fatigue	16 (15.1)	10 (9.5)
Edema peripheral	16 (15.1)	3 (2.9)
Vomiting	15 (14.2)	14 (13.3)
Atrial fibrillation	15 (14.2)	2 (1.9)
Decreased appetite	14 (13.2)	6 (5.7)
Hypertension	14 (13.2)	5 (4.8)

Adverse Events, <sup>a</sup> n (%)	Ibrutinib-Venetoclax (n = 106)	Chlorambucil- Obinutuzumab (n = 105)
Upper respiratory tract infection	13 (12.3)	14 (13.3)
Thrombocytopenia	12 (11.3)	28 (26.7)
Arthralgia	12 (11.3)	7 (6.7)
Epistaxis	12 (11.3)	3 (2.9)
Pneumonia	11 (10.4)	10 (9.5)
Constipation	11 (10.4)	7 (6.7)
Hyperphosphatemia	11 (10.4)	0
Cough	9 (8.5)	11 (10.5)
Pyrexia	7 (6.6)	20 (19.0)
Chills	2 (1.9)	12 (11.4)
Infusion-related reaction	0	31 (29.5)

<sup>a</sup>AEs are reported by Medical Dictionary for Regulatory Activities (MedDRA) superclass and preferred terms and National Cancer Institute Common Terminology Criteria for Adverse Events grade.

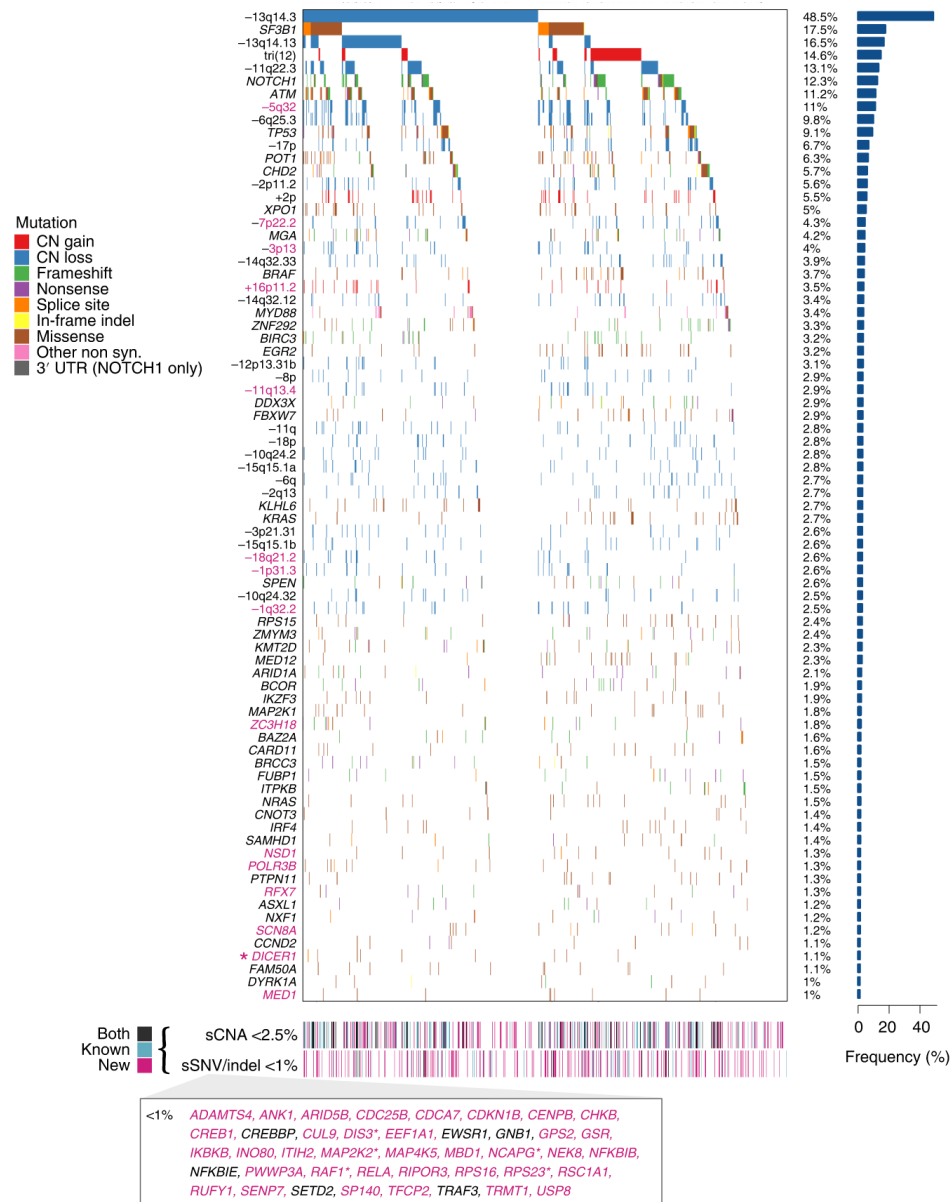
<sup>b</sup>Includes both “Neutropenia” and “Neutrophil count decreased.”

# Summary II

- BTK inhibitors (covalent and non-covalent) have **class-specific side effects** (e.g. bleeding), but **risk of atrial fibrillation** is substantially lower with next-generation BTKi compared with ibrutinib
- Fixed-duration regimens have high rate of **hematotoxicity (neutropenia)** during treatment (~1 year), but **very little to no post-treatment toxicity**

# Updated genomic landscape

Over 100 new genetic drivers, but clinical utility and prognostic value unclear and limited



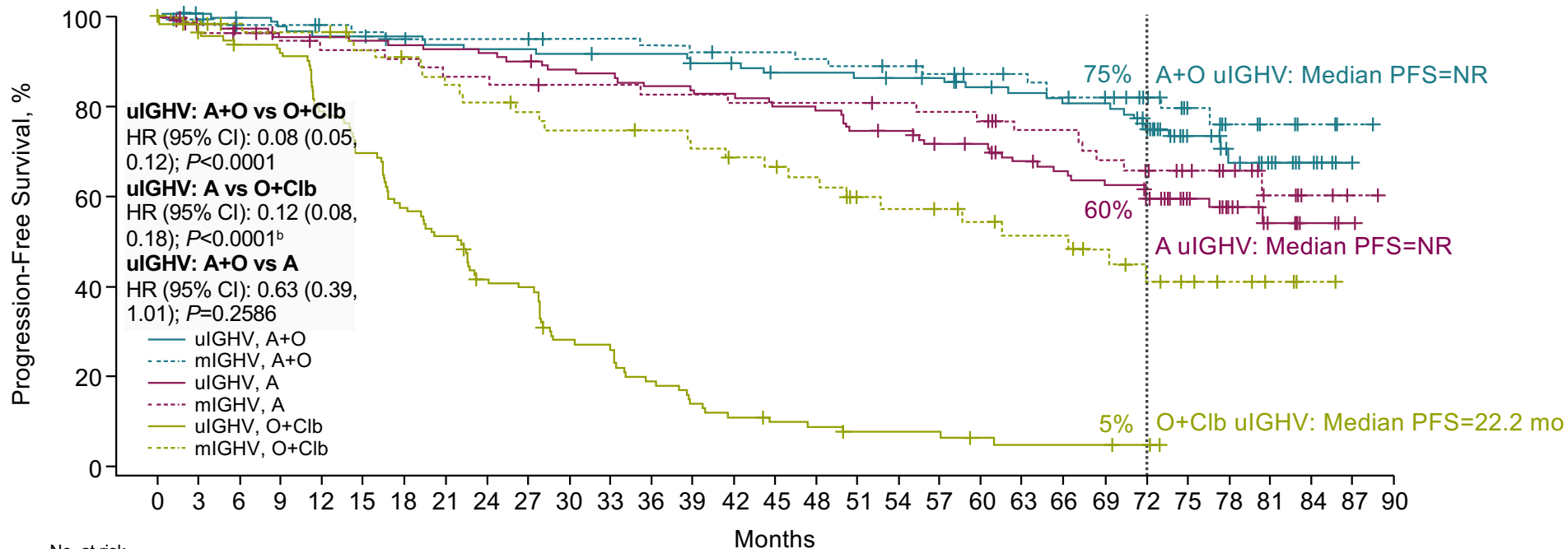


**(Only) two clinically relevant genomic features**

IGHV

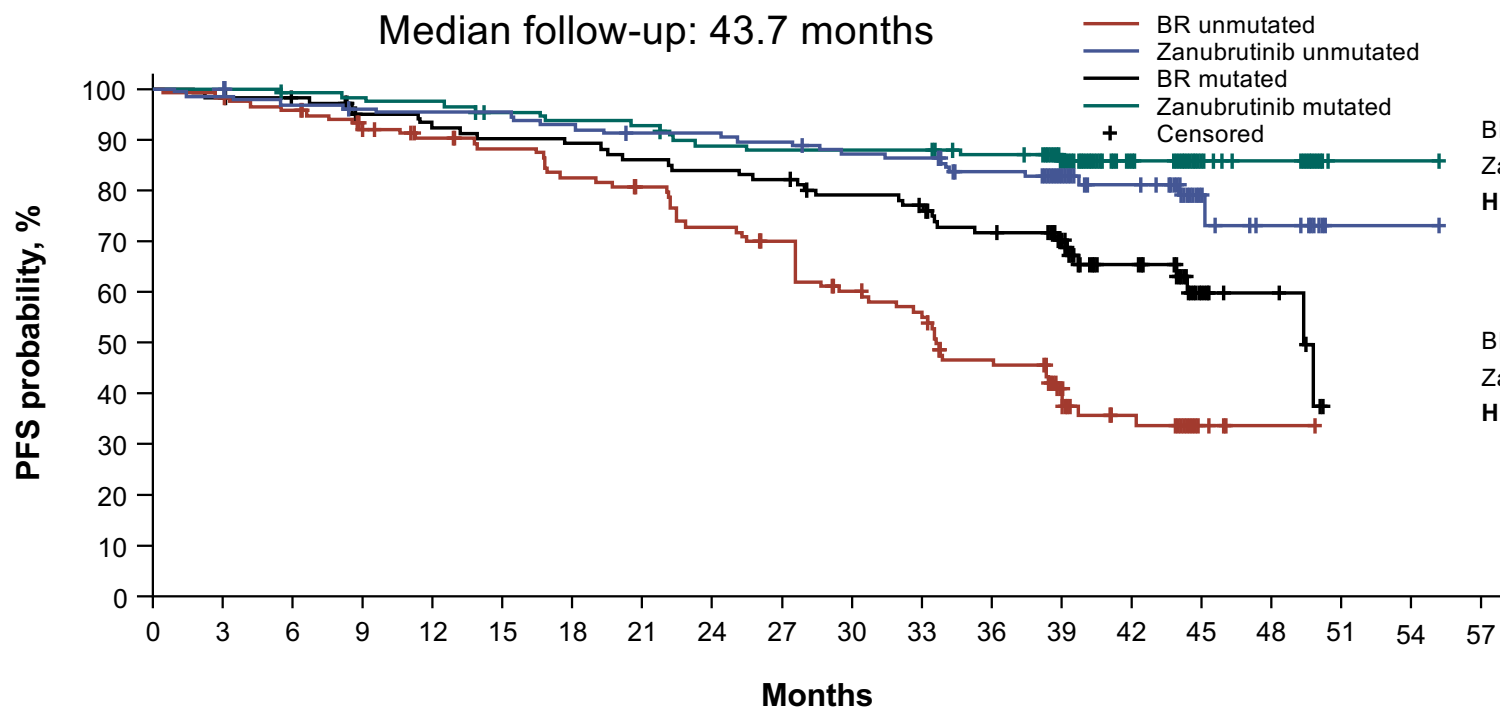
*TP53*

# PFS according IGHV status with Acalabrutinib



	No. at risk																														
	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66	69	72	75	78	81	84	87	90
ulIGHV, A+O	103	101	99	97	95	95	94	92	91	91	90	89	89	85	84	81	81	80	79	78	74	72	70	70	60	28	22	13	6	1	
mIGHV, A+O	74	72	69	69	67	66	64	63	63	63	61	61	60	59	58	58	57	56	55	53	51	50	47	44	37	24	16	12	4	1	
ulIGHV, A	118	111	108	106	106	105	104	103	102	100	97	96	93	92	91	88	87	82	80	75	74	68	65	63	56	35	21	13	4	1	
mIGHV, A	59	54	53	50	48	48	47	45	45	44	43	43	42	42	41	41	41	41	40	39	38	34	34	31	29	21	16	9	3	1	
ulIGHV, O+Clb	116	105	101	99	85	75	62	55	43	41	28	27	19	14	11	9	8	6	6	6	4	3	3	3	2	0					
mIGHV, O+Clb	59	56	53	52	52	48	46	43	41	39	37	37	36	34	32	31	29	23	22	21	19	17	17	14	11	7	5	3	1	0	

# PFS according IGHV status with Zanubrutinib



**Unmutated IGHV**

	mPFS	95% CI
BR	33.7 mo	29.5-39.1
Zanu	NE	NE
<b>HR, 0.23; 95% CI, 0.14-0.37; P&lt;.0001<sup>a</sup></b>		

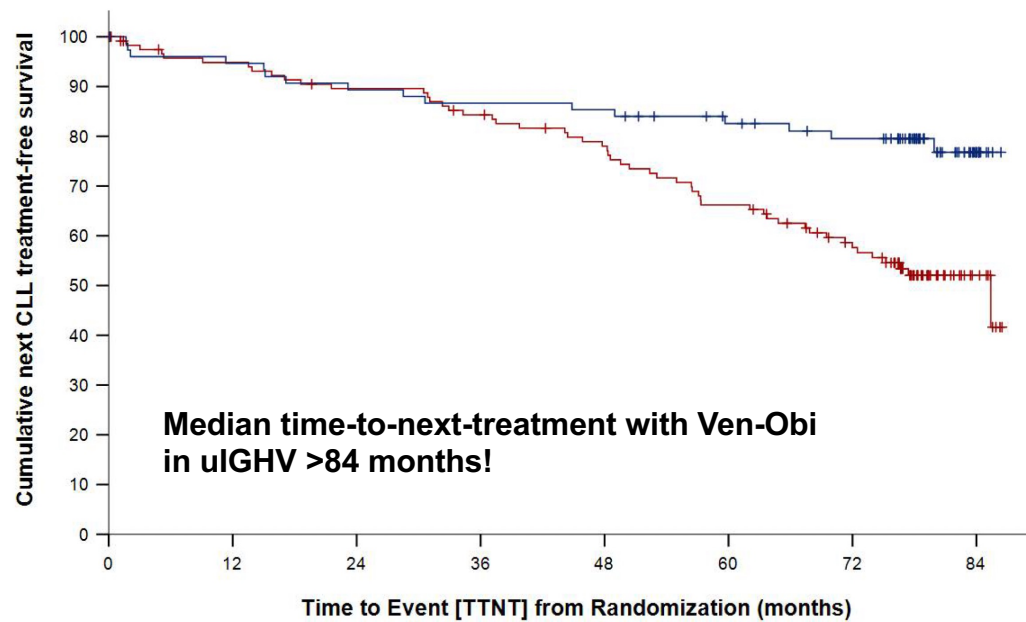
**Mutated IGHV**

	mPFS	95% CI
BR	49.4 mo	44.4-NE
Zanu	NE	NE
<b>HR, 0.35; 95% CI, 0.19-0.64; P=.00033<sup>a</sup></b>		

	Months																			
No. at risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57
BR unmutated	121	110	107	101	95	92	86	83	75	71	60	55	43	26	17	4	1	0		
Zanubrutinib unmutated	125	122	120	118	117	117	114	111	111	109	105	104	97	65	47	14	9	2	2	0
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

# PFS according to IGHV status with Ven-Obi

Median fol

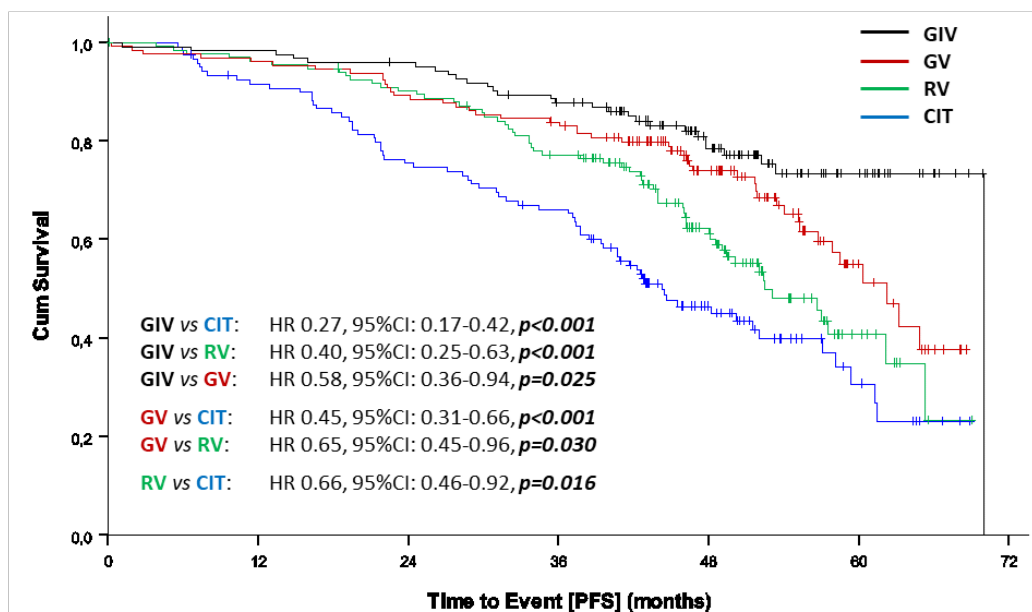


	0	12	24	36	48	60	72	84
uIGHV	121	109	102	95	86	73	57	9
mIGHV	76	71	67	65	64	57	52	10



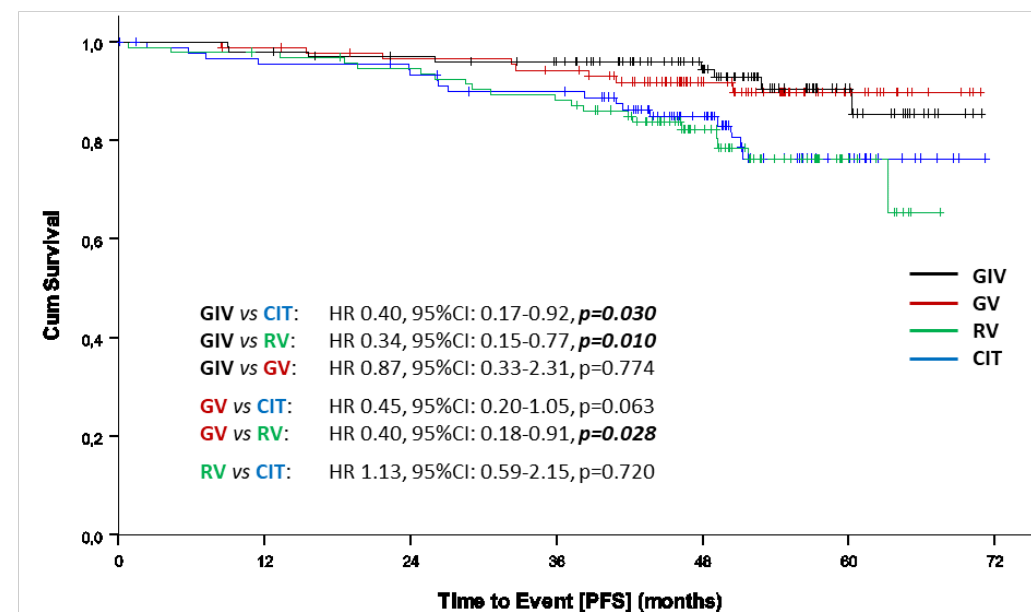
# PFS according to IGHV status with Ven-Obi

PFS, patients with unmutated IGHV



Pts at risk	0	12	24	36	48	60	72
CIT	131	108	89	77	34	9	
RV	134	128	119	100	56	10	
GV	130	125	116	108	67	15	
GIV	123	121	117	105	65	24	

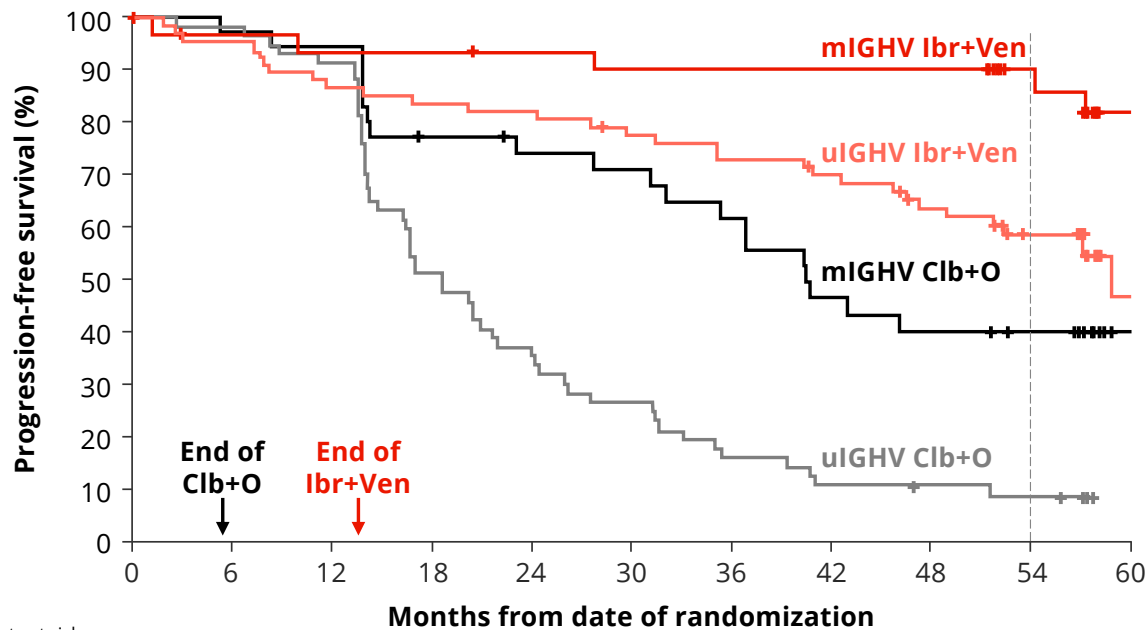
PFS, patients with mutated IGHV



Pts at risk	0	12	24	36	48	60	72
CIT	95	86	83	78	50	15	
RV	95	92	88	82	47	11	
GV	89	87	83	80	48	15	
GIV	101	99	95	90	60	20	

# PFS according to IGHV status with Ven-Ibru

Progression-Free Survival (ITT) by IGHV Status



- Estimated 54-month PFS rates:
  - **Ibr+Ven:**
    - 90% for patients with mIGHV
    - 59% for patients with uIGHV
  - **Clb+O:**
    - 40% for patients with mIGHV
    - 8% for patients with uIGHV

Patients at risk	0	6	12	18	24	30	36	42	48	54	60
mIGHV Ibr+Ven	32	29	28	28	27	26	26	26	26	22	5
uIGHV Ibr+Ven	67	64	58	56	55	51	48	45	39	30	6
mIGHV Clb+O	35	34	33	26	24	23	20	15	13	9	2
uIGHV Clb+O	57	56	52	29	21	15	9	6	5	4	0

# Summary III

- IGHV status is an (independent) **prognostic factor for PFS with fixed-duration therapies**, but not continuous therapies
- Given the long treatment-free window (>6 years), fixed-duration options **can still be considered in the context of uIGHV**, depending on patients' preferences



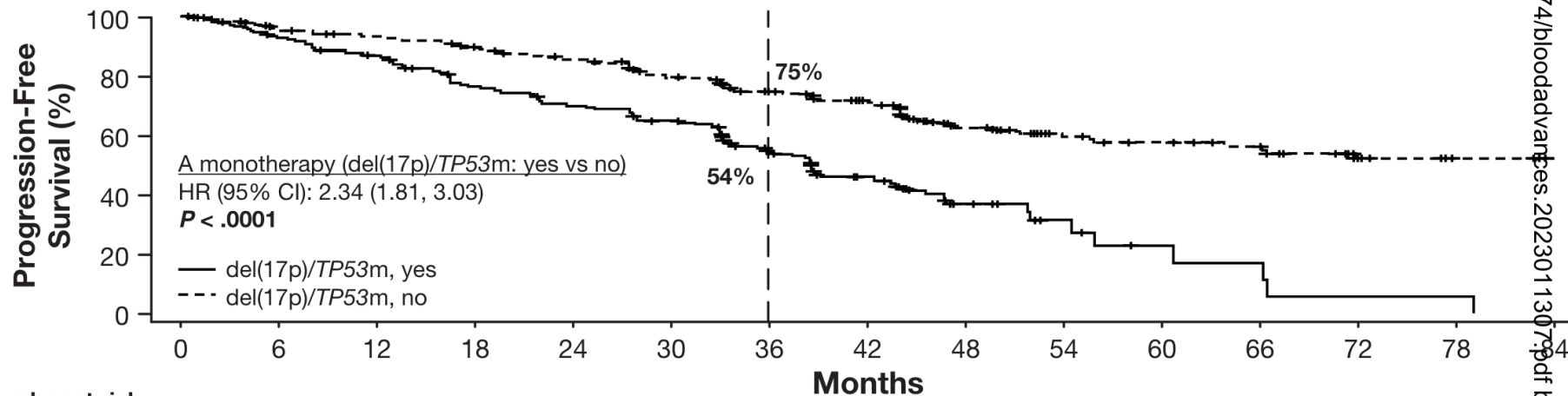
**(Only) two clinically relevant genomic features**

IGHV

TP53

# PFS according to *TP53* status with Acalabrutinib

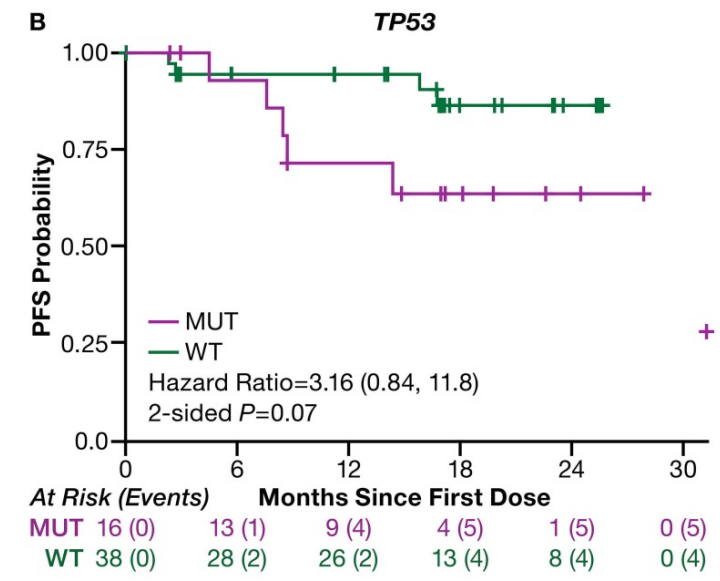
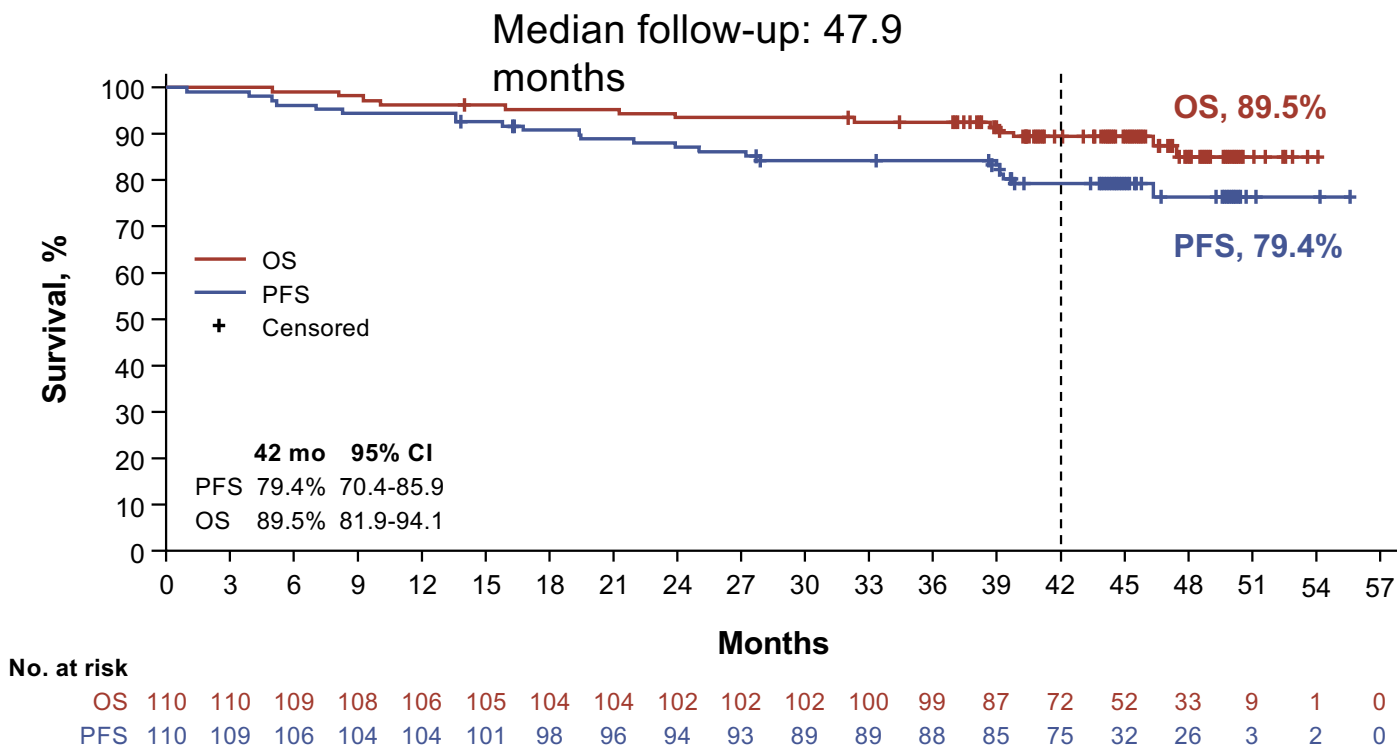
6D



Number at risk	
del(17p)/TP53m, yes	214    195    180    154    139    125    90    62    22    8    4    3    1    1
del(17p)/TP53m, no	340    313    303    288    273    249    216    178    93    57    52    47    30    10

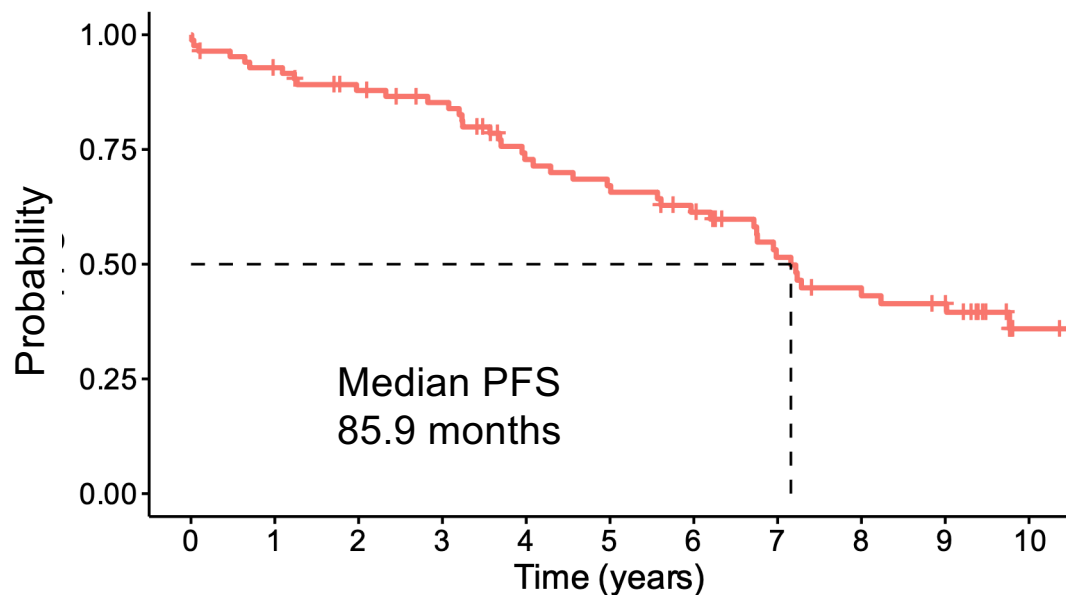
12674/bloodadvances.2023011307.pdf by THE

# PFS according to *TP53* status with Zanubrutinib



# PFS according to *TP53* status with Ibrutinib

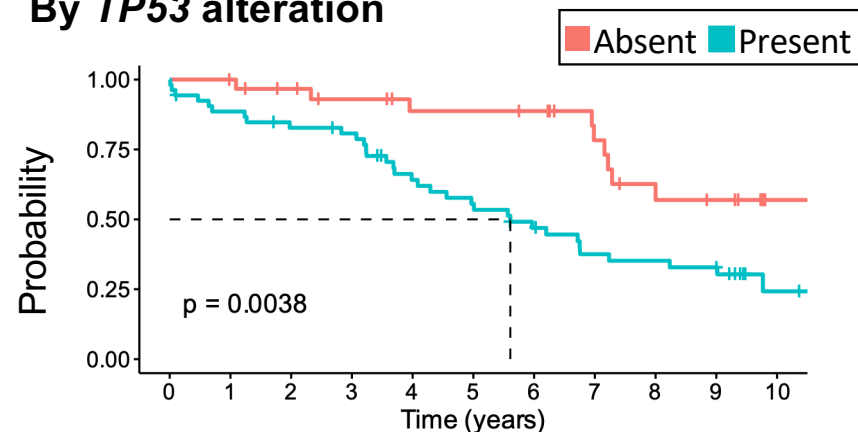
All patients



Number at risk

Strata	0	1	2	3	4	5	6	7	8	9	10
All	84	76	69	64	51	47	41	31	26	23	6

By *TP53* alteration

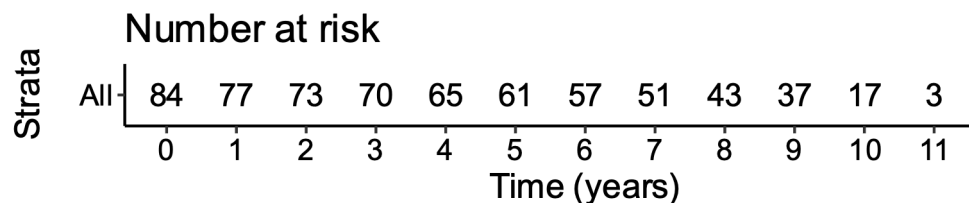
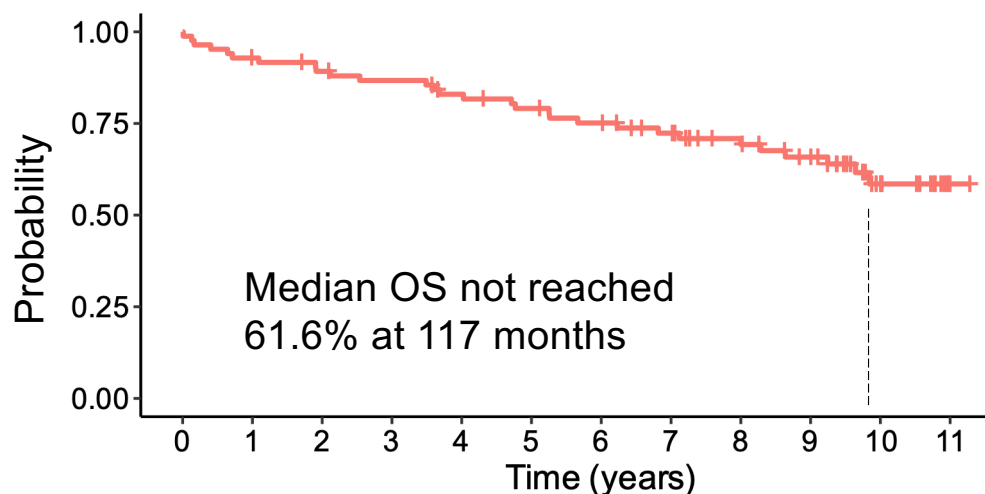


Risk category		mPFS (mo)	% PFS at mFU*	P =
<i>TP53</i> alteration	Absent	NR	56.9%	.004
	Present	67.3	30.3%	
Therapy status	TN	108	48.7%	.016
	Rel/ref	49	22.4%	
IGHV	M	117.2	57.1%	.057
	U	80.6	29.7%	

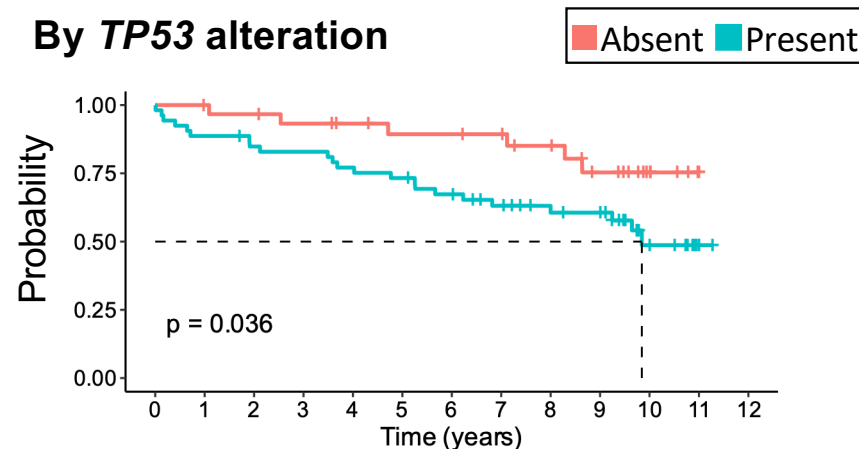
TN; treatment-naïve; rel/ref – relapsed/refractory; IGHV, M, mutated; U, unmutated

# OS according to *TP53* status with Ibrutinib

All patients



By *TP53* alteration



Risk category		mOS (m0)	% OS at mFU*	P =
<i>TP53</i> alteration	Absent	NR	75.3	.036
	Present	118	54.1	
Therapy status	TN	NR	73.8	.004
	Rel/ref	104	41.6	
IGHV	M	NR	77	.036
	U	118	52.7	

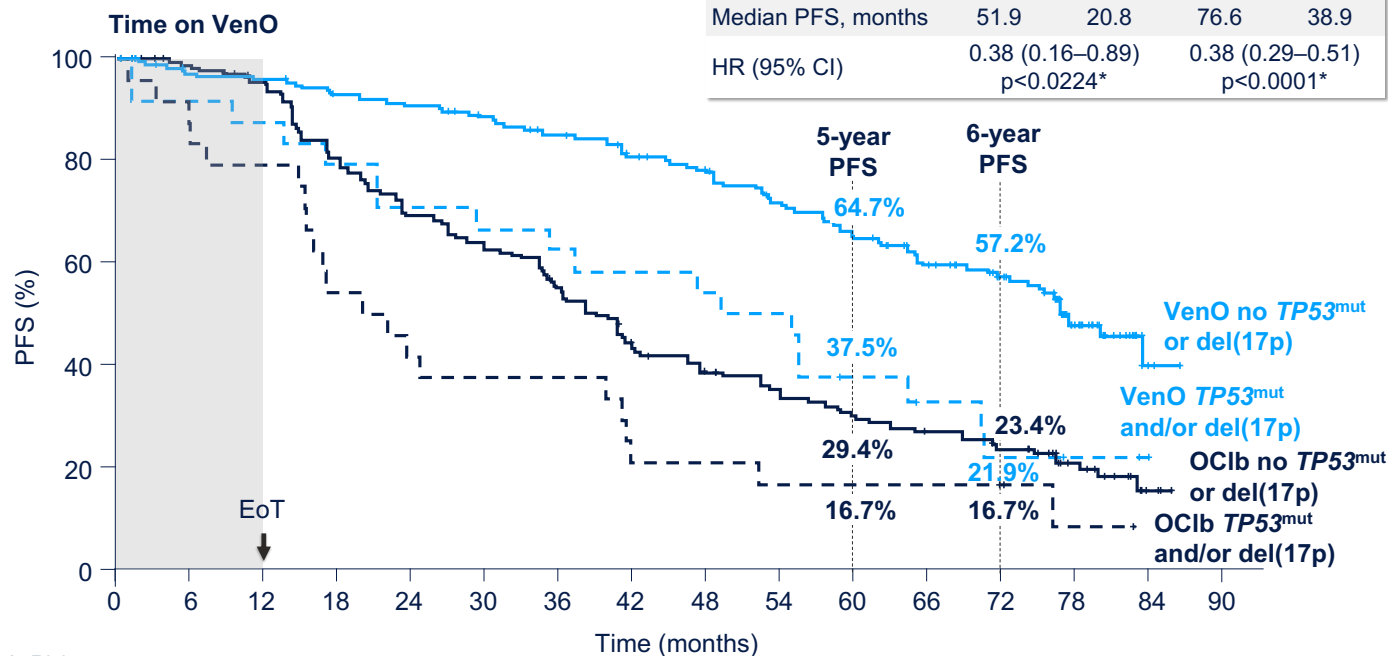
TN; treatment-naïve; rel/ref – relapsed/refractory;  
IGHV, M, mutated; U, unmutated



# PFS according to *TP53* status with Ven-Obi

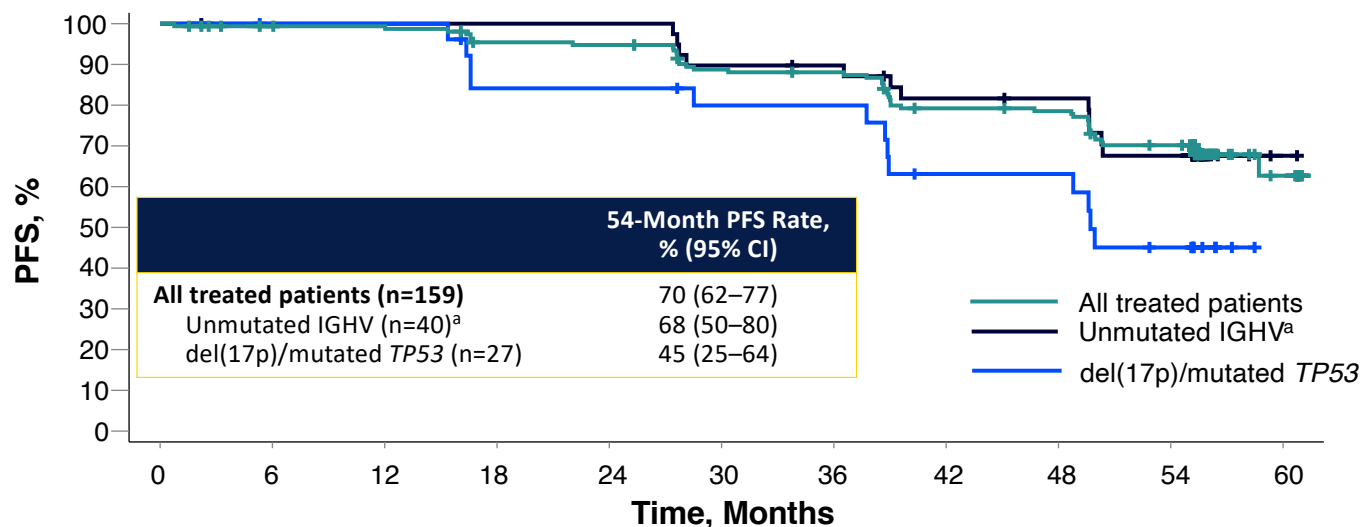
Median follow-up: 76.4 months

	<i>TP53</i> <sup>mut</sup> and/or del(17p)		No <i>TP53</i> <sup>mut</sup> or del(17p)	
	VenO	OC1b	VenO	OC1b
Median PFS, months	51.9	20.8	76.6	38.9
HR (95% CI)	0.38 (0.16–0.89) p<0.0224*		0.38 (0.29–0.51) p<0.0001*	



At Risk:	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90
OC1b <i>TP53</i> <sup>mut</sup> and/or del(17p)	24	20	19	13	10	9	9	5	5	4	4	4	3	1		
VenO <i>TP53</i> <sup>mut</sup> and/or del(17p)	25	22	21	19	17	16	15	14	13	12	8	6	4	2		
OC1b no <i>TP53</i> <sup>mut</sup> or del(17p)	184	169	160	135	117	106	90	68	60	51	45	40	33	17	3	
VenO no <i>TP53</i> <sup>mut</sup> or del(17p)	184	170	168	161	157	150	142	131	123	112	101	87	73	34	3	

# PFS according to *TP53* status with Ven-Ibru



Patients at risk	0	6	12	18	24	30	36	42	48	54	60
All treated patients	159	153	152	144	143	132	130	115	113	99	11
Unmutated IGHV <sup>a</sup>	40	39	39	39	39	35	34	30	29	24	1
del(17p)/mutated <i>TP53</i>	27	26	26	21	21	19	19	14	14	9	0

# Summary IV

- Randomized data on *TP53* with **fixed-duration therapies are still limited** (25 pts for Ven-Obi, 0 pts for Ven-lbru)
- Long-term outcomes with ***TP53* del/mut under continuous BTKi are more favorable** than with fixed-duration therapies (cross-trial comparison), however, ***TP53* status remains a prognostic factor with continuous BTKi**
- Given the long treatment-free window (>6 years), fixed-duration options **can still be considered in the context of uIGHV**, depending on patients' preferences



A PROSPECTIVE, RANDOMIZED, OPEN-LABEL, MULTICENTRE PHASE-III TRIAL OF  
**IBRUTINIB** VERSUS **VENETOCLAX PLUS OBINUTUZUMAB** VERSUS **IBRUTINIB PLUS VENETOCLAX** FOR PATIENTS WITH PREVIOUSLY UNTREATED CHRONIC LYMPHOCYTIC LEUKAEMIA

**Patients with previously untreated CLL**

Incl. fit and unfit patients  
 Incl. patients with del17p/TP53 mut

**1:1:1 Randomization**

Stratification according to  
 fitness, del17p/TP53,IGHV



**Ibrutinib**



**Venetoclax  
 Obinutuzumab**

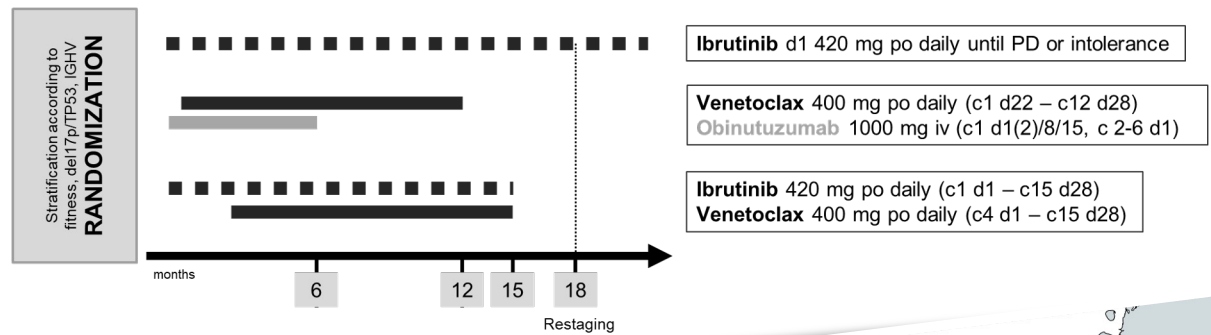


**Venetoclax  
 Ibrutinib**

**909 patients**

Primary endpoint:  
**Progression-free survival**

**TREATMENT SCHEDULE**



**TIMELINES**

Start of recruitment Q1/2021  
 End of recruitment Q4/2022  
 End of study Q1/2027

**Participating countries**



# Conclusion

- **Targeted therapies** have shown higher efficacy than chemotherapy in all settings of CLL
- The current first-line toolbox of **BTKi, Bcl2-i and CD20-ab** is able to provide long-term disease control for most patients with CLL
- The decision between **continuous and fixed-duration therapy**, given pending prospective comparisons, should be made with consideration of **high-risk features, comorbidities and patients' preferences**