FD vs Indefinite Therapy in CLL

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REVOLUTIONARY ROAD IN CLL

Innovazione rivoluzionaria nella terapia della leucemia linfatica cronica

Milano, 10 luglio 2024
Starhotels E.c.ho.

Disclosures

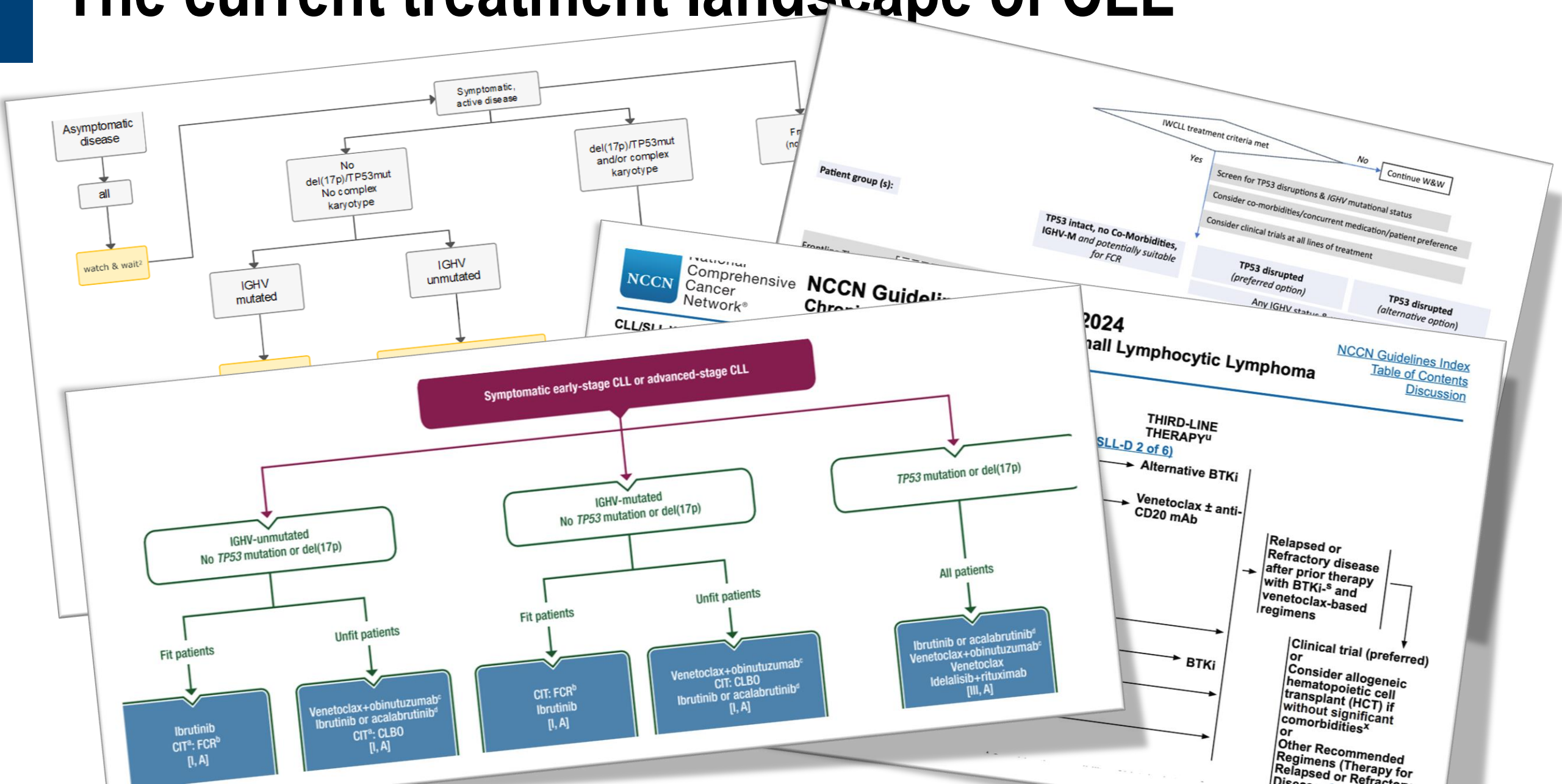
Honoraria: Roche, Janssen, Gilead, AbbVie, Lilly, AstraZeneca, Adaptive, BeiGene

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



Which factors should we use for stratification?

CIRS

AGE

SEX

BINET STAGE

B-SYMPTOMS

ZAP70

LACTATE DEHYDROGENASE

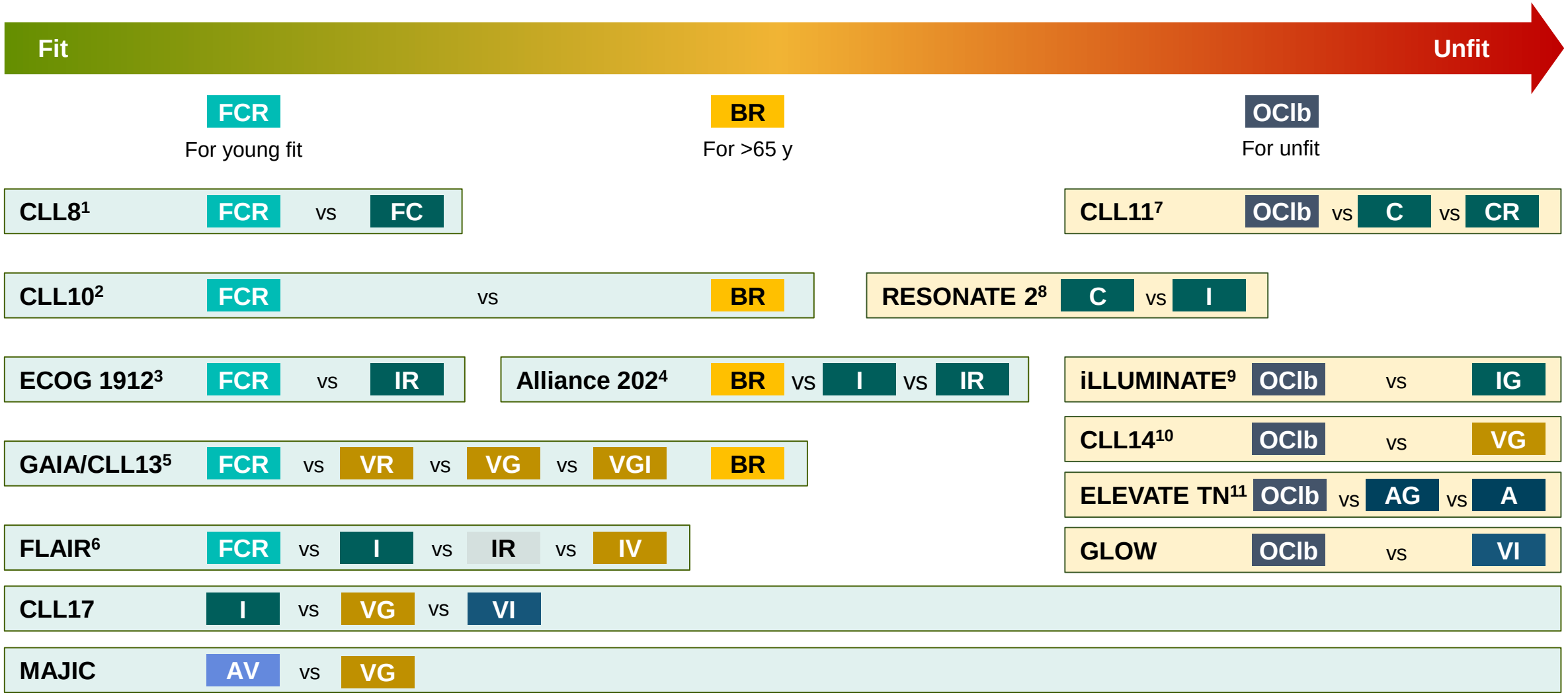
ß2 MICROGLOBULIN

THYMIDINE KINASE

RAI STAGE

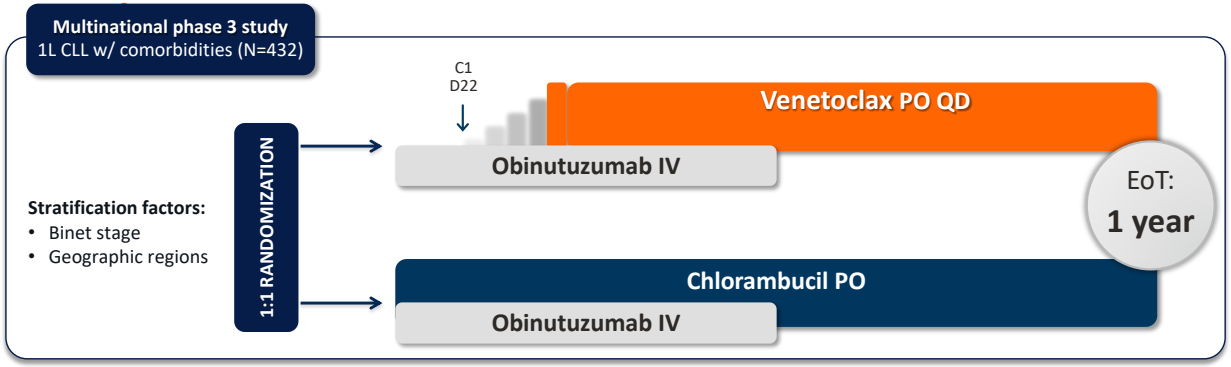
ECOG STATUS

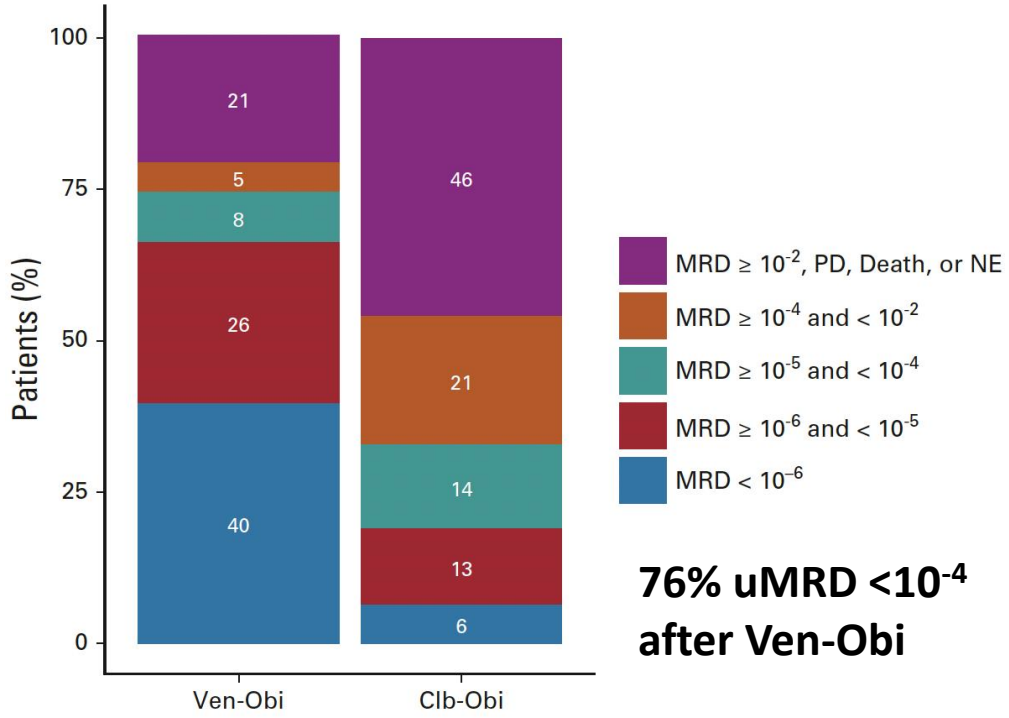
The role of fitness



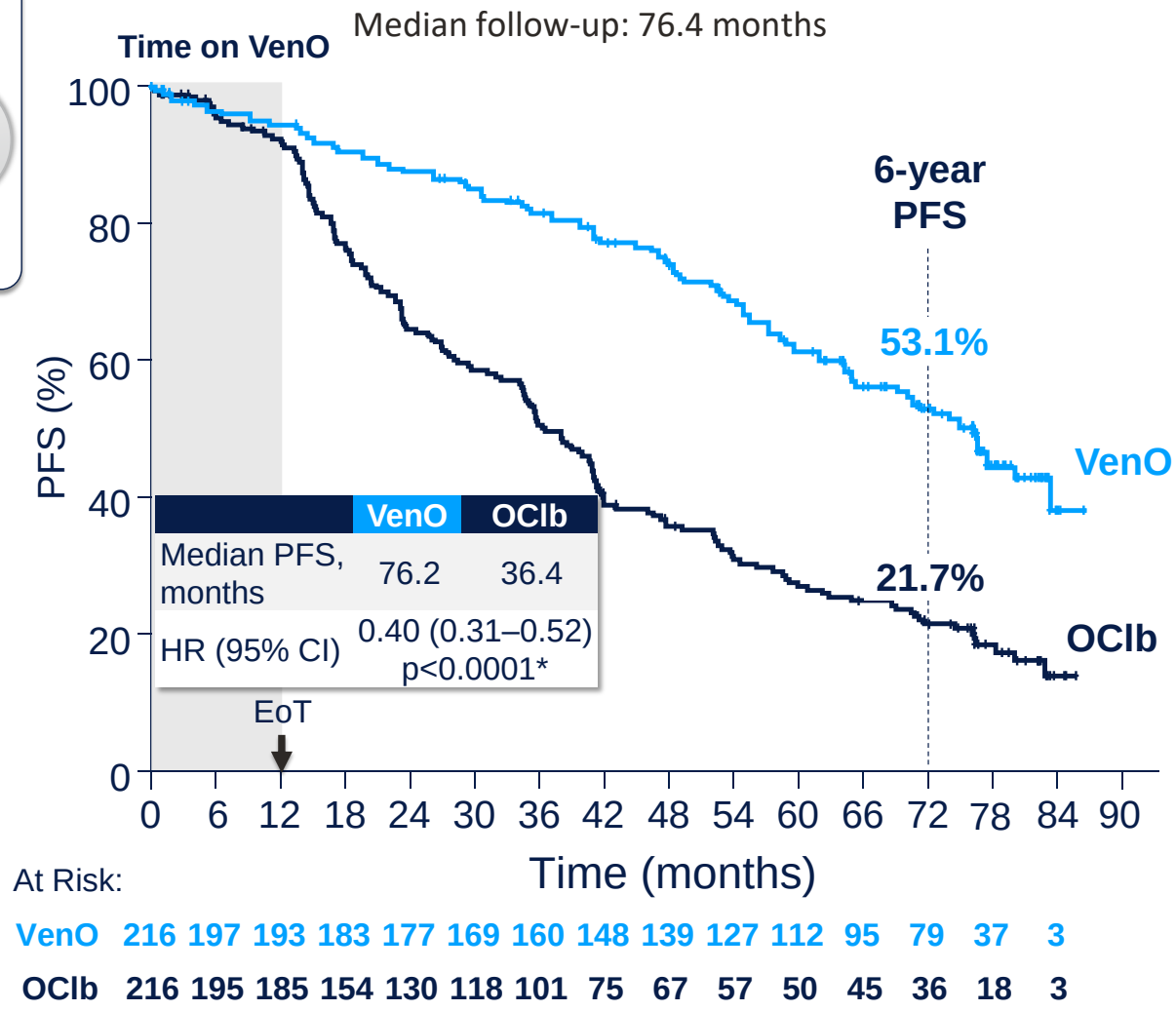
Clinicaltirals.gov: 1. NCT00281918; 2. NCT00769522; 3. NCT02048813; 4. NCT01886872 5. NCT02950051; 6. EudraCT number 2013-001944-76. 7. NCT01010061; 8. NCT01722487; 9.; NCT02264574 10. NCT02242942; 11. NCT02475681.

CLL14 – Ven-Obi in unfit patients



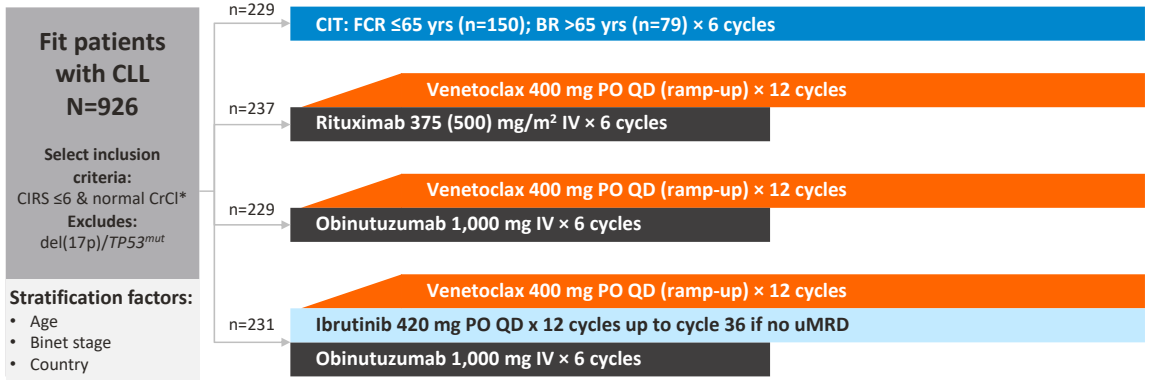


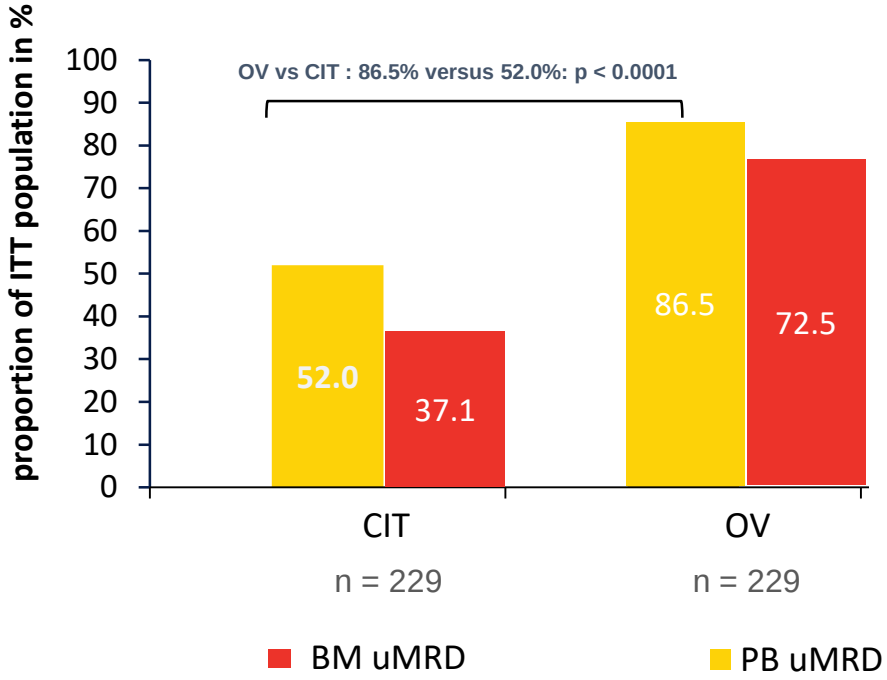
76% uMRD <10^{-4} after Ven-Obi

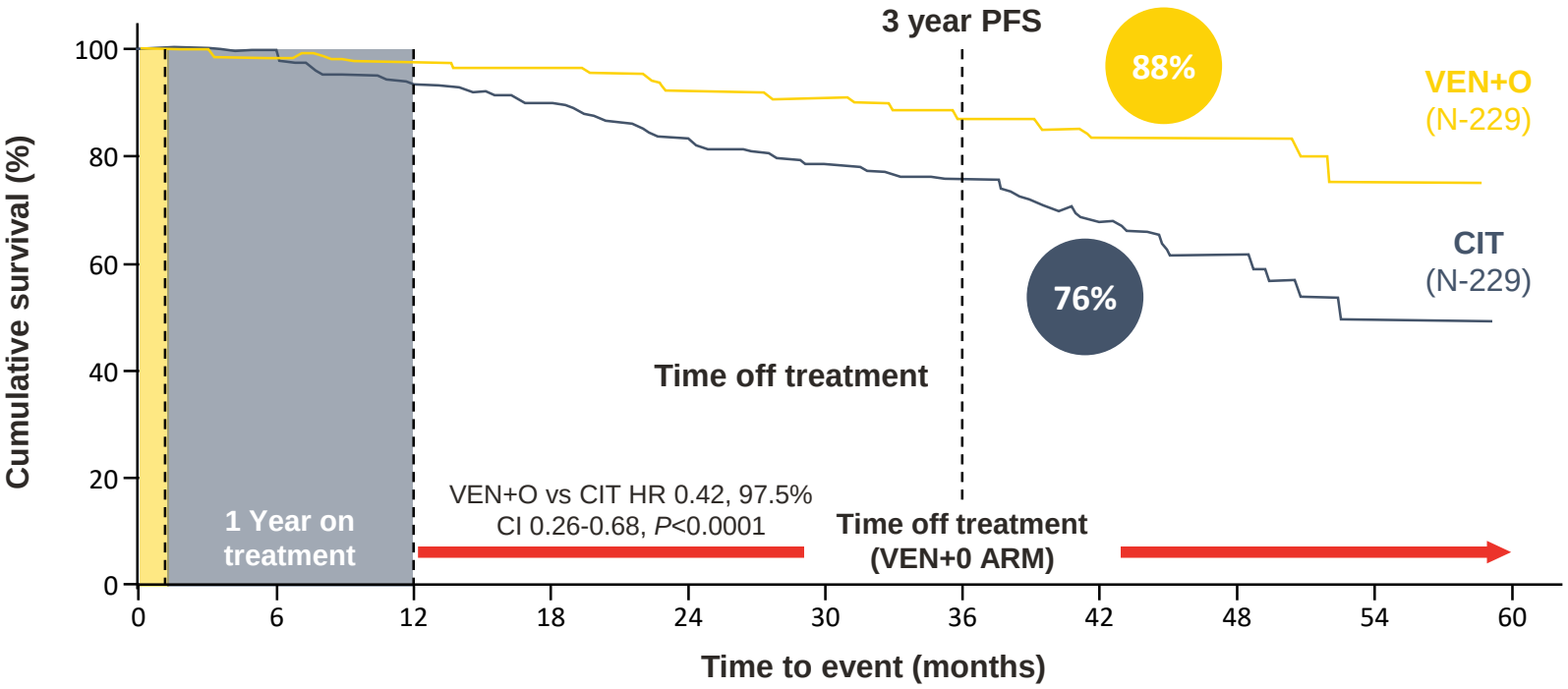


Al-Sawaf et al, *Blood* 2024 (accepted)

CLL13 – Ven-Obi in fit patients



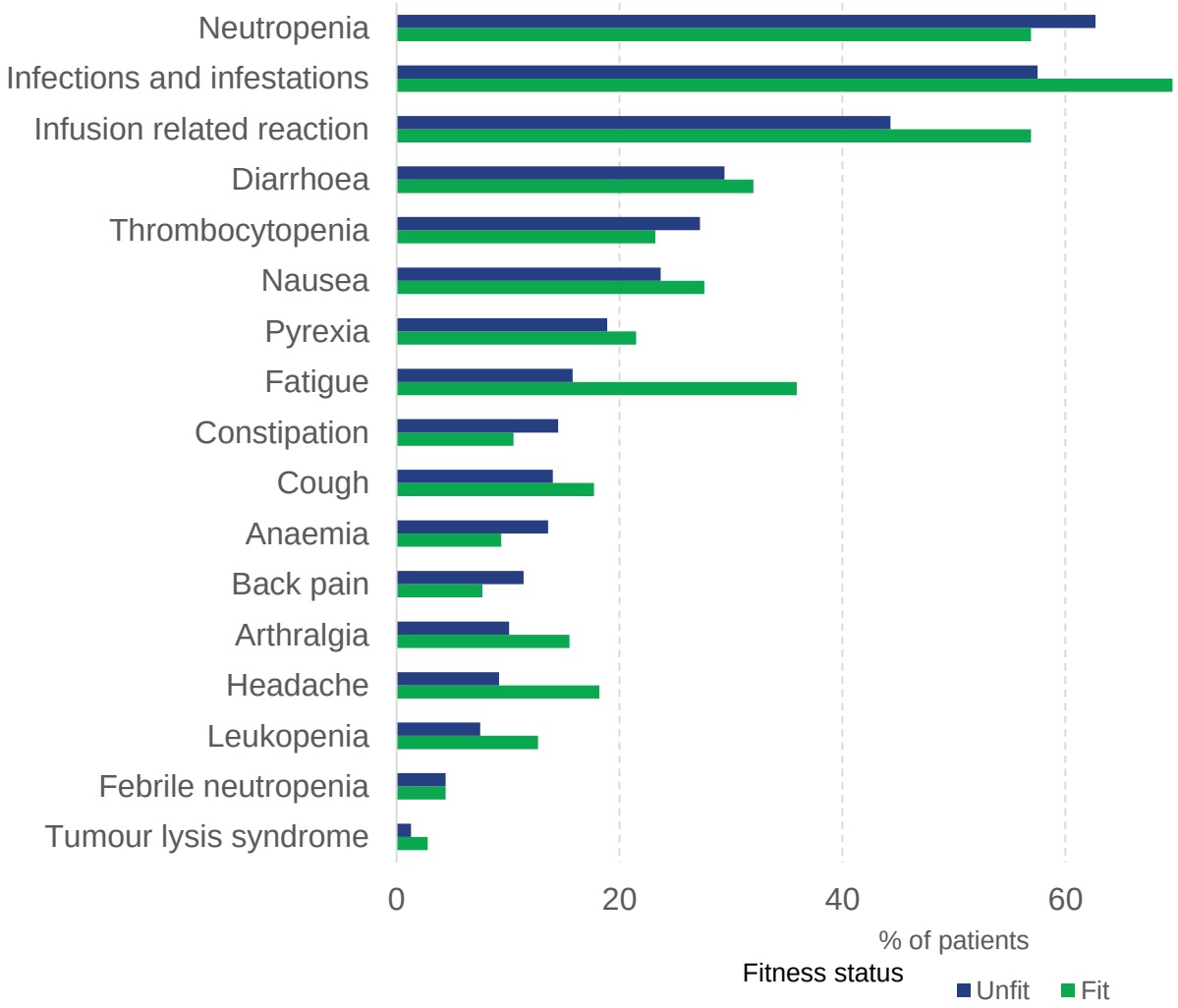


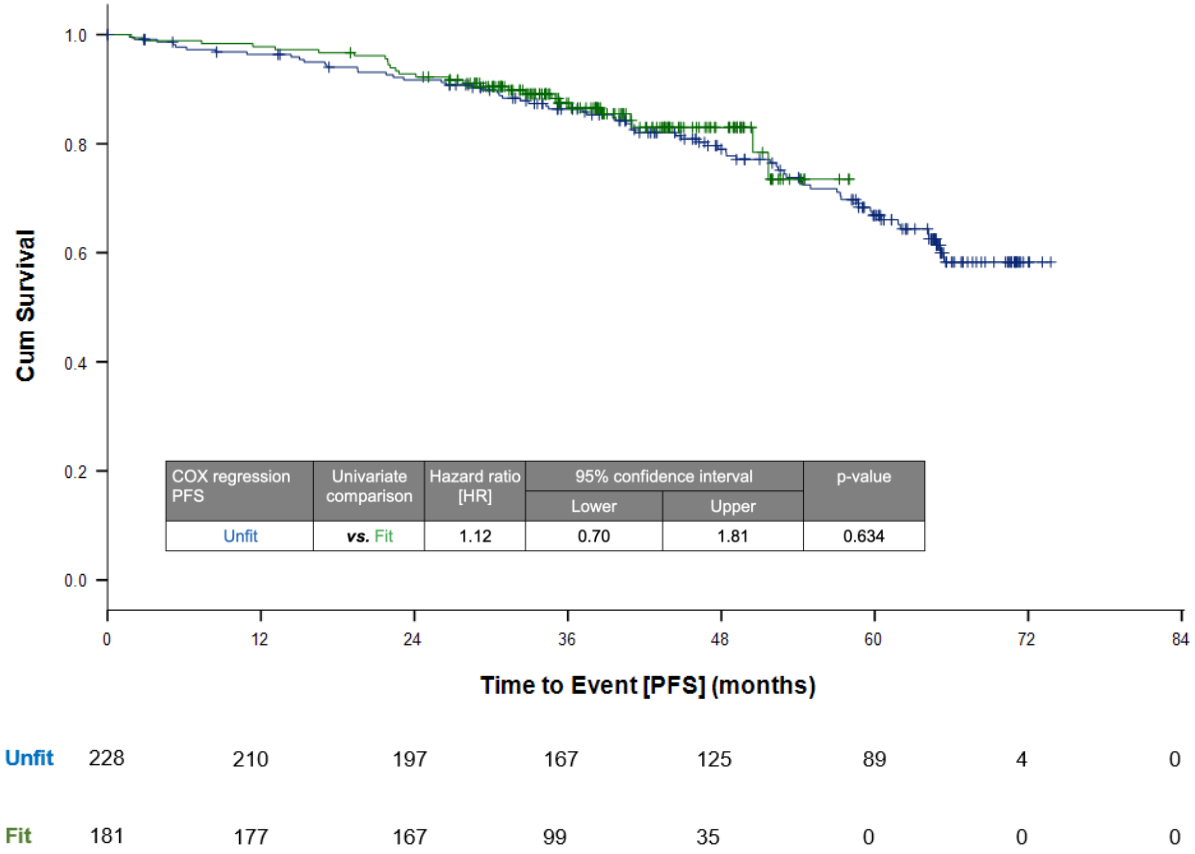


High efficacy in unfit and fit patients.

Eichhorst et al, *NEJM* 2023

Does fitness matter with Ven-Obi?





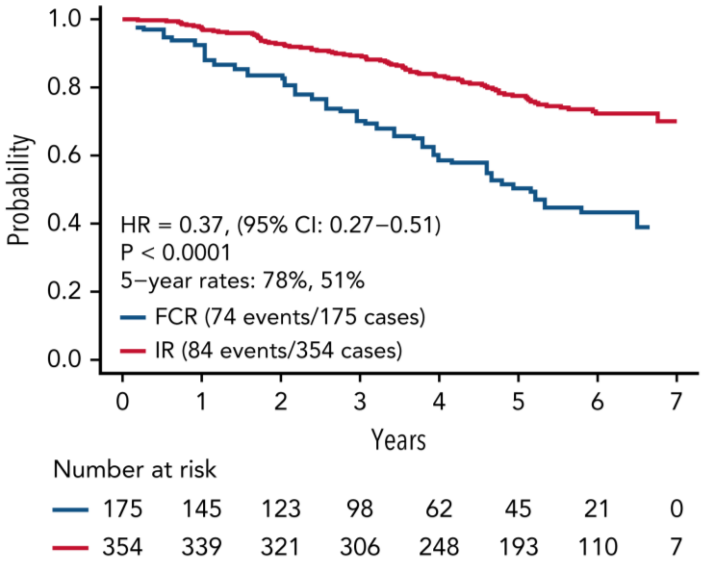
COX regression PFS	Univariate comparison	Hazard ratio [HR]	95% confidence interval		p-value
			Lower	Upper	
Unfit	*vs.* Fit	1.12	0.70	1.81	0.634

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

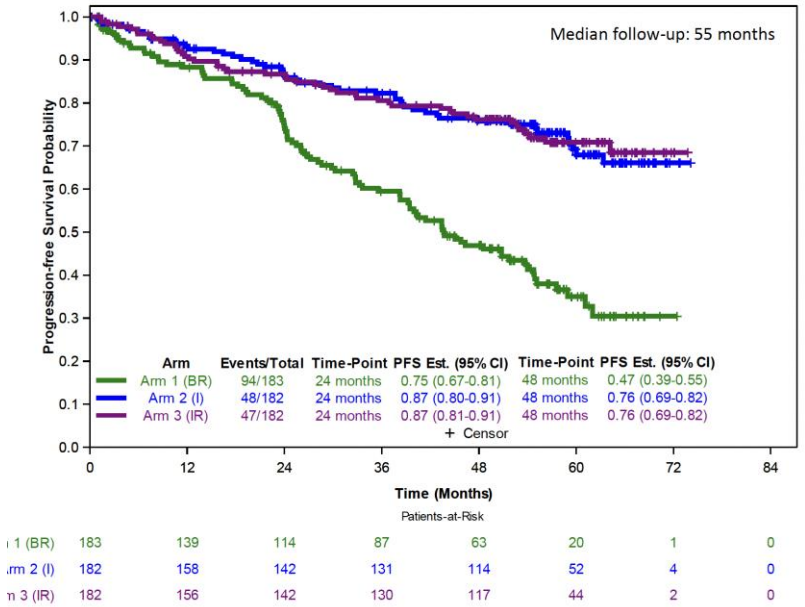
Unpublished data

Does fitness matter with BTKi?

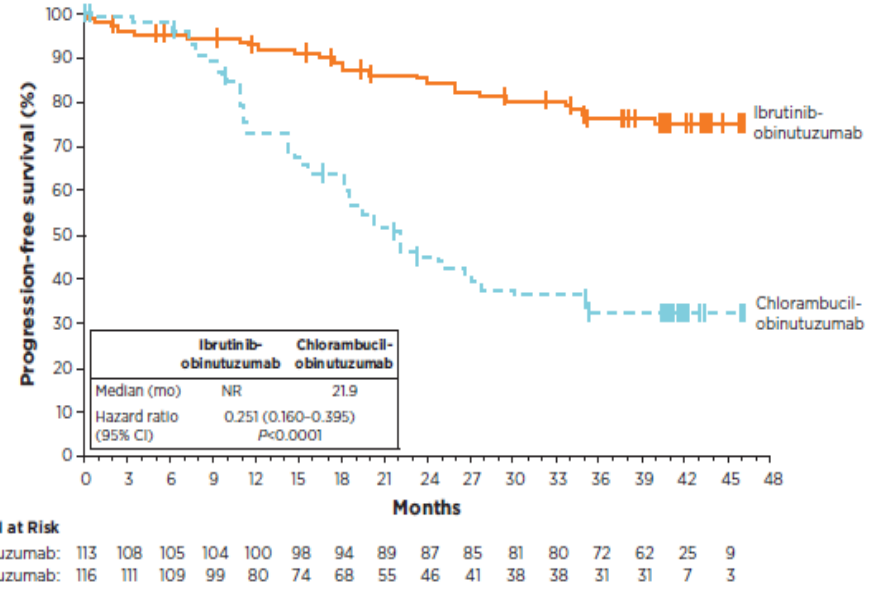
ECOG1912: Young/fit patients



A041202: Elderly/fit patients



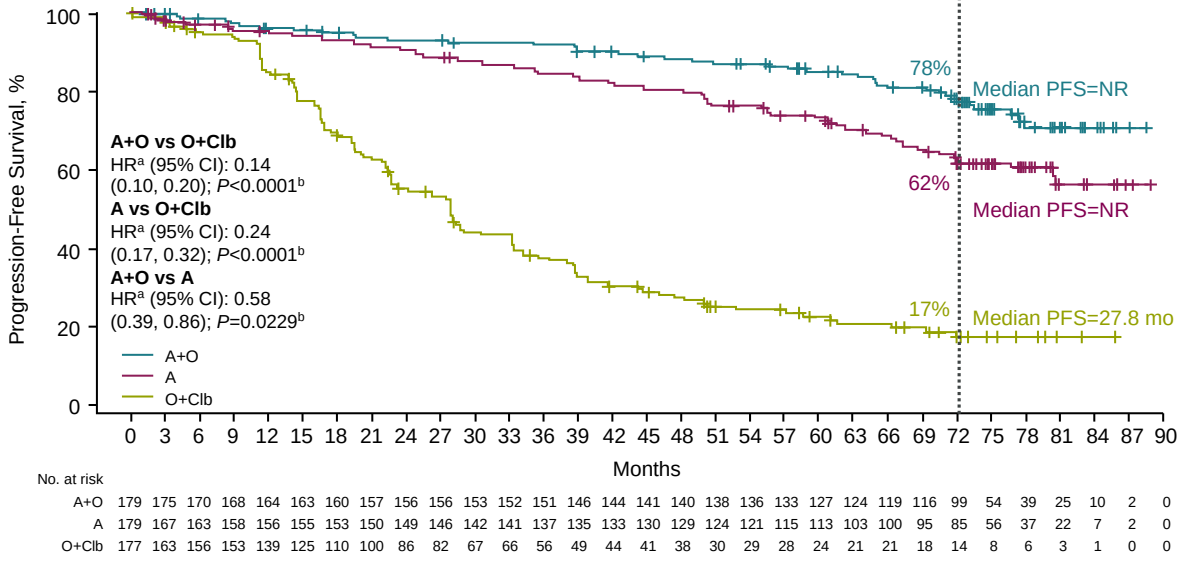
iLLUMINATE: Elderly/unfit patients



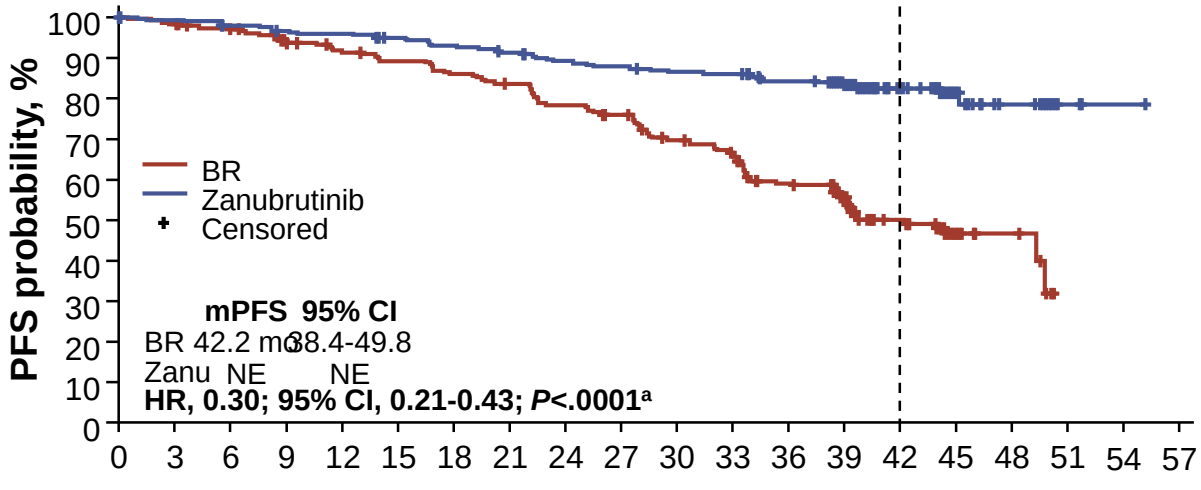
High efficacy of ibrutinib confirmed in randomized studies with fit and unfit patients.

Does fitness matter with BTKi?

ELEVATE-TN: Elderly/unfit patients



SEQUOIA: Elderly/fit patients



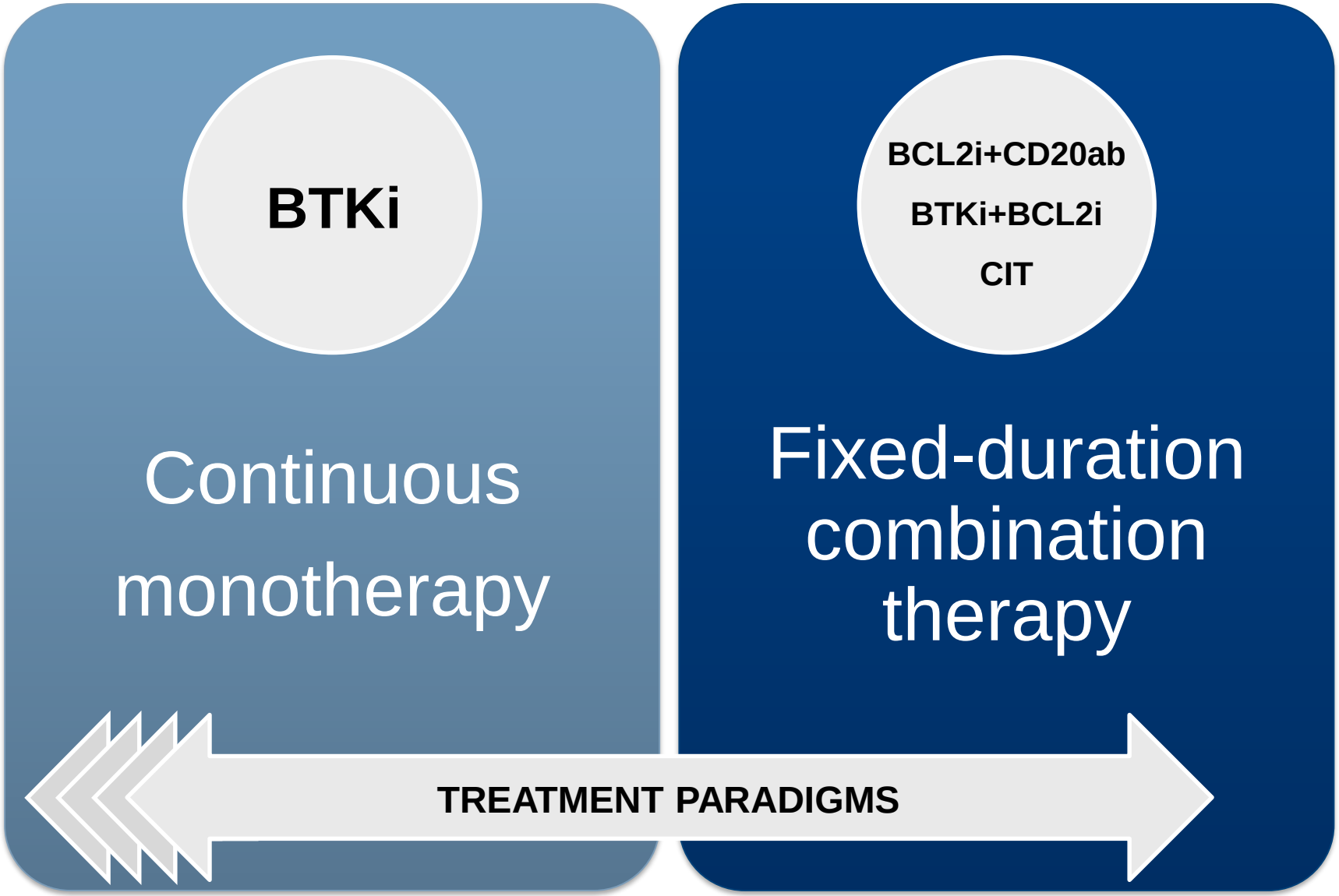
No randomized first-line data have been generated so far on Acalabrutinib or Zanubrutinib in *fit* patients

Summary I

With currently available evidence, we can assume:

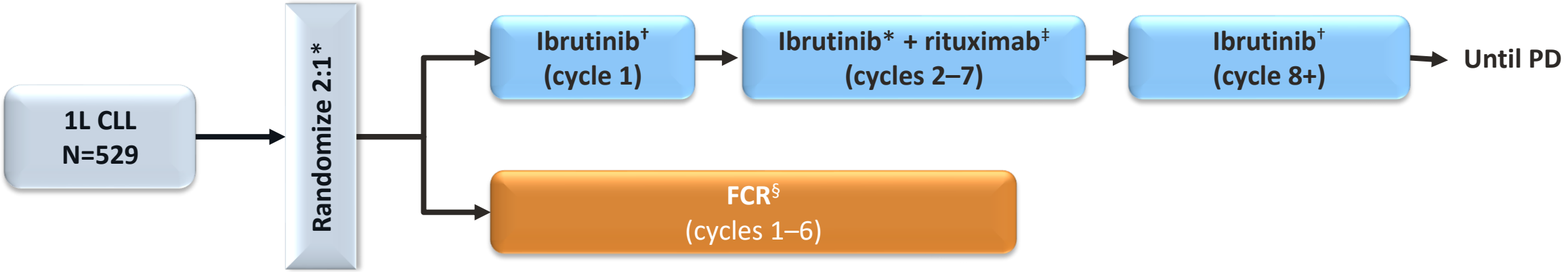
- ‚quantitative' fitness, as measured by CIRS, ECOG, Karnofsky etc. is **not a major determinant of outcome**

- rather, **the type of coexisiting 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¶

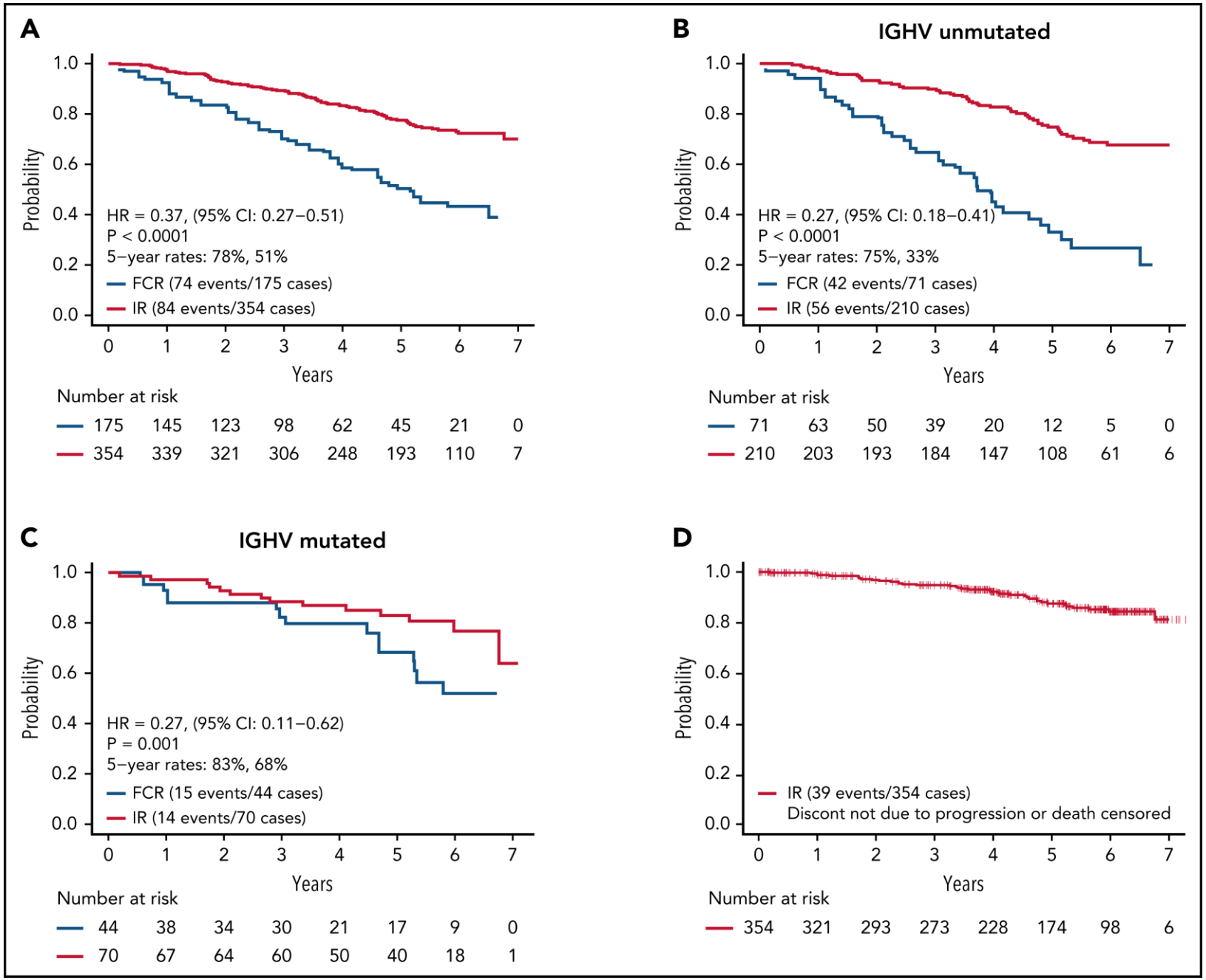
Primary endpoints

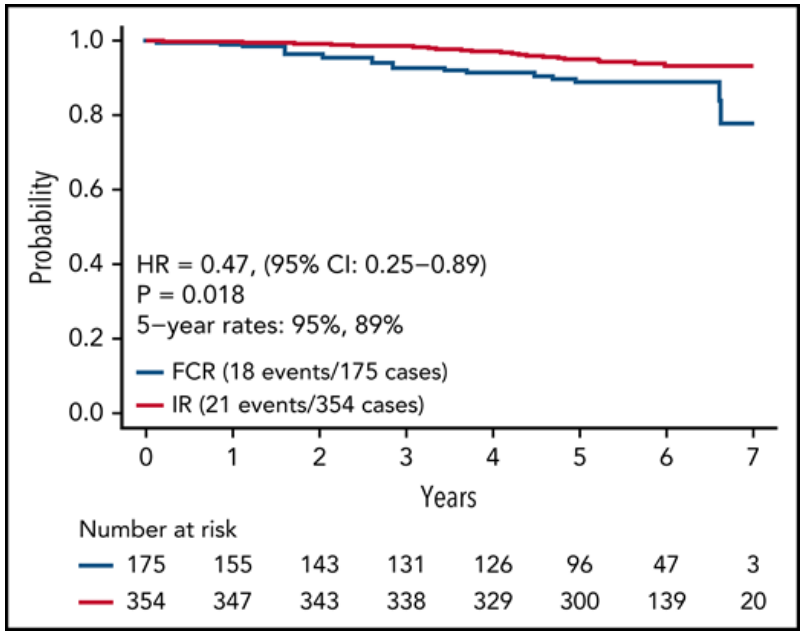
- PFS
- QoL (FACT-Leu TOI)

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^2 C2D1, 325 mg/m^2 C2D2, then 500 mg/m^2 day 1 of C3–7;
§ Fludarabine 25 mg/m^2 days 1–3, cyclophosphamide 250 mg/m^2 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.).

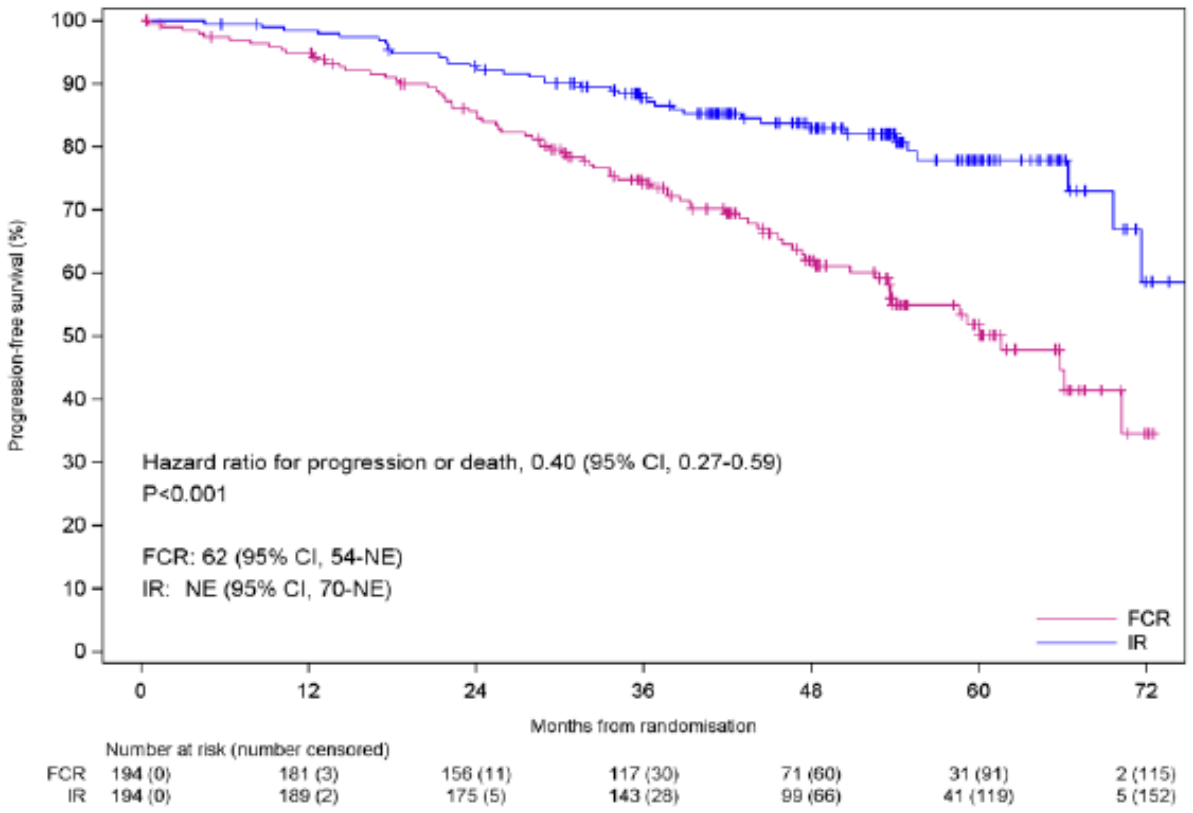




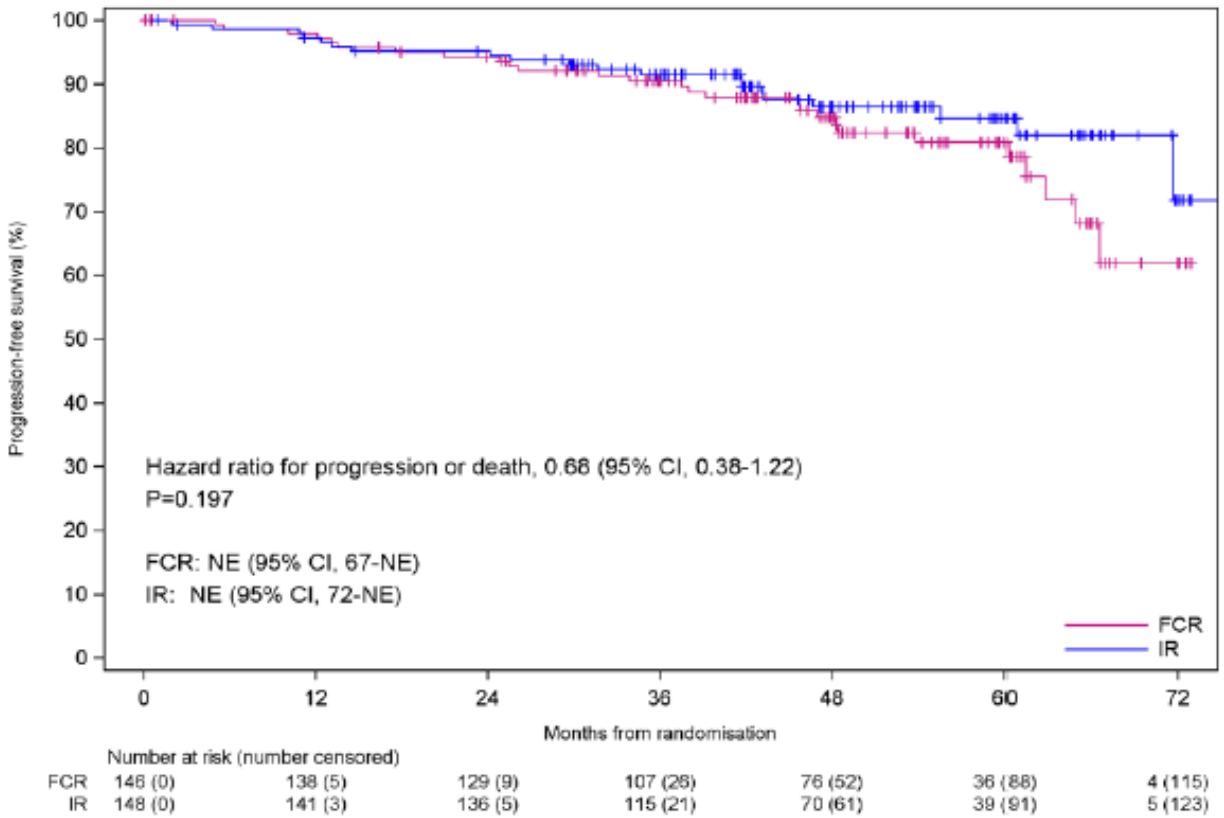
Shanafelt et al, Blood 2022

Flair PFS by IGHV mutation status

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



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

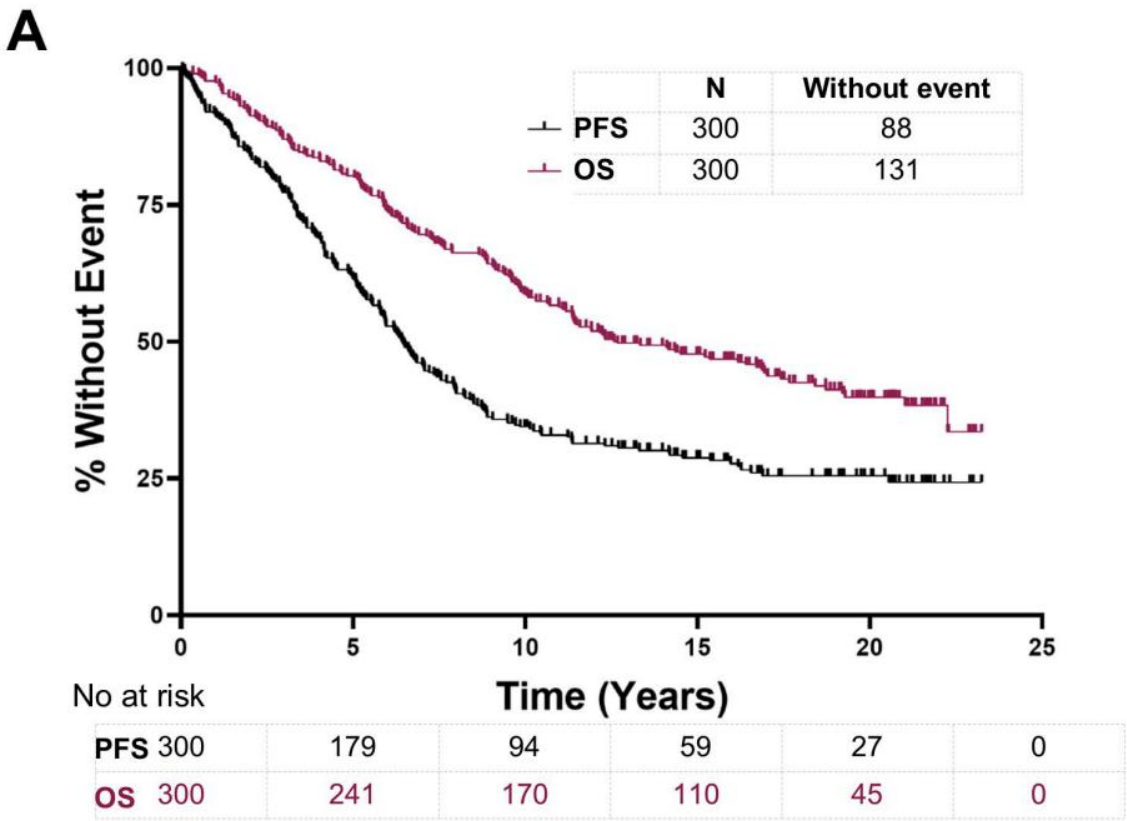


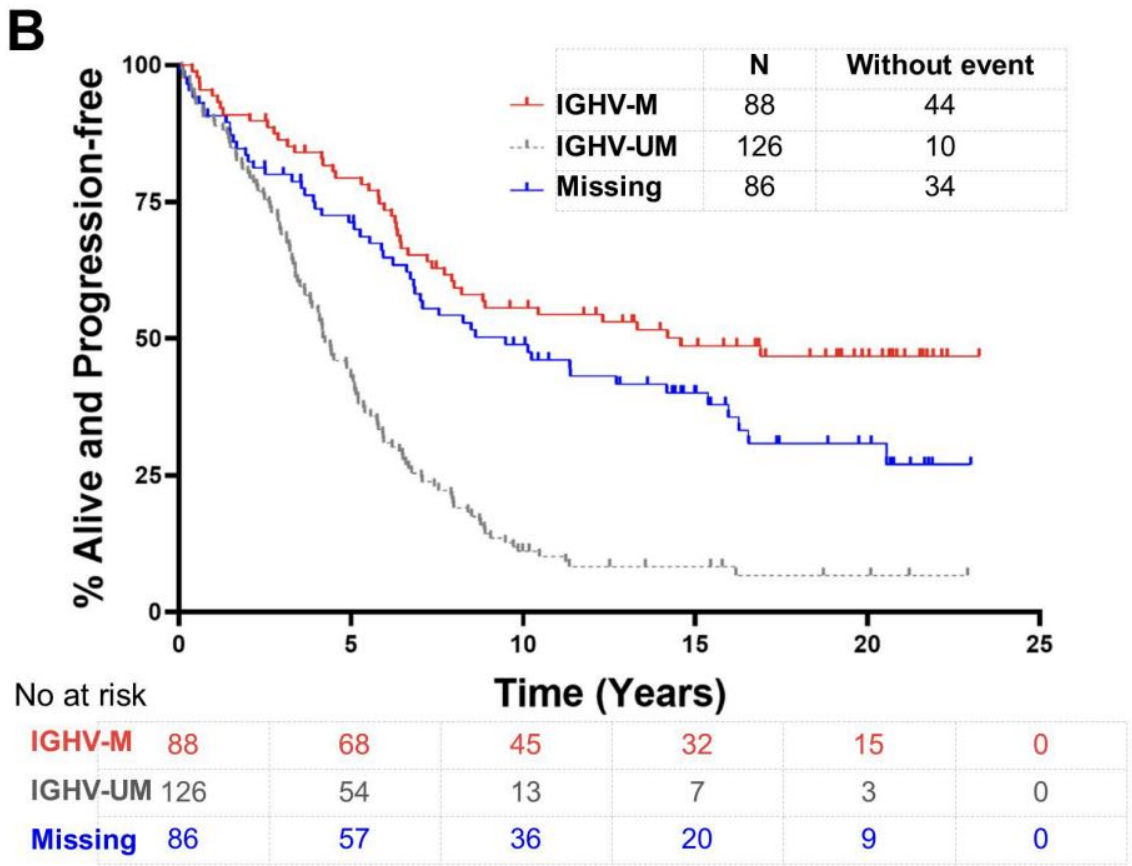
Stereotype Subset 2: n=46 (FCR 20; IR 26) → HR for PD or death 0.32 (95% CI, 0.06-1.76), p=0.191

Data-lock: 24th May 2021

Hillmen *et al.*, Abstract 642, ASH 2021

Long-term remission post-FCR in IGHVmut setting





Thompson et al, Blood, 2023

Issues with chemoimmunotherapy

	Total	
Long-term safety	**Cases N (%)**	**Patients N (%)**
Total patients (safety population), N		800
Total cases [N (%)] and patients [N (%)] with ≥1 SPM	136 (100)	122 (15)
Secondary malignancies		
Richter's transformation	38 (28)	38 (5)
Solid tumors	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)
Hematologic neoplasia	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)
Basalioma, squamous cell	19 (14)	17 (2)
Prolonged neutropenia		
2 months after end of treatment		101 (13)
12 months after end of treatment		30 (4)

Increased risk of secondary malignancies

Fischer et al, Blood 2016

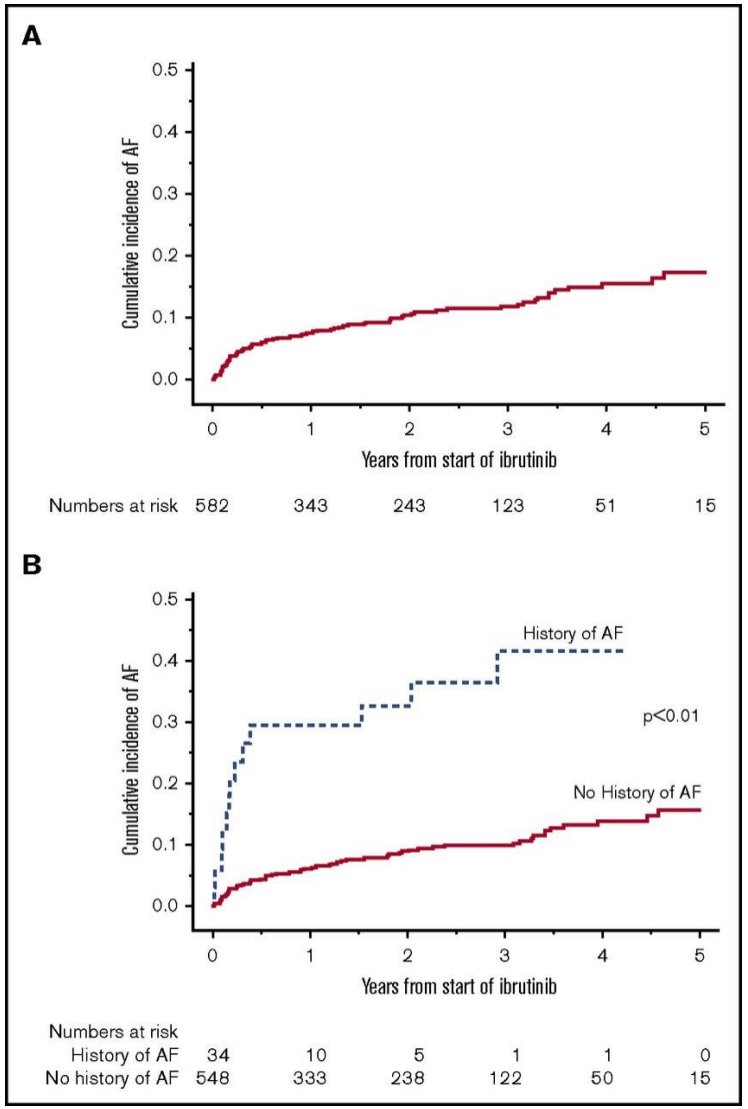
CLL13: Second primary malignancies

Cases of second cancers	**CIT**	**RV**	**GV**	**GIV**	**Total**
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
Incidence rates (per 1000 pt-months)					
All SPM (excl. NMSC and Richter‘s)	2.21	1.21	1.16	2.36	1.71

Fürstenau et al, ASH 2023

Issues with 1st generation BTKi

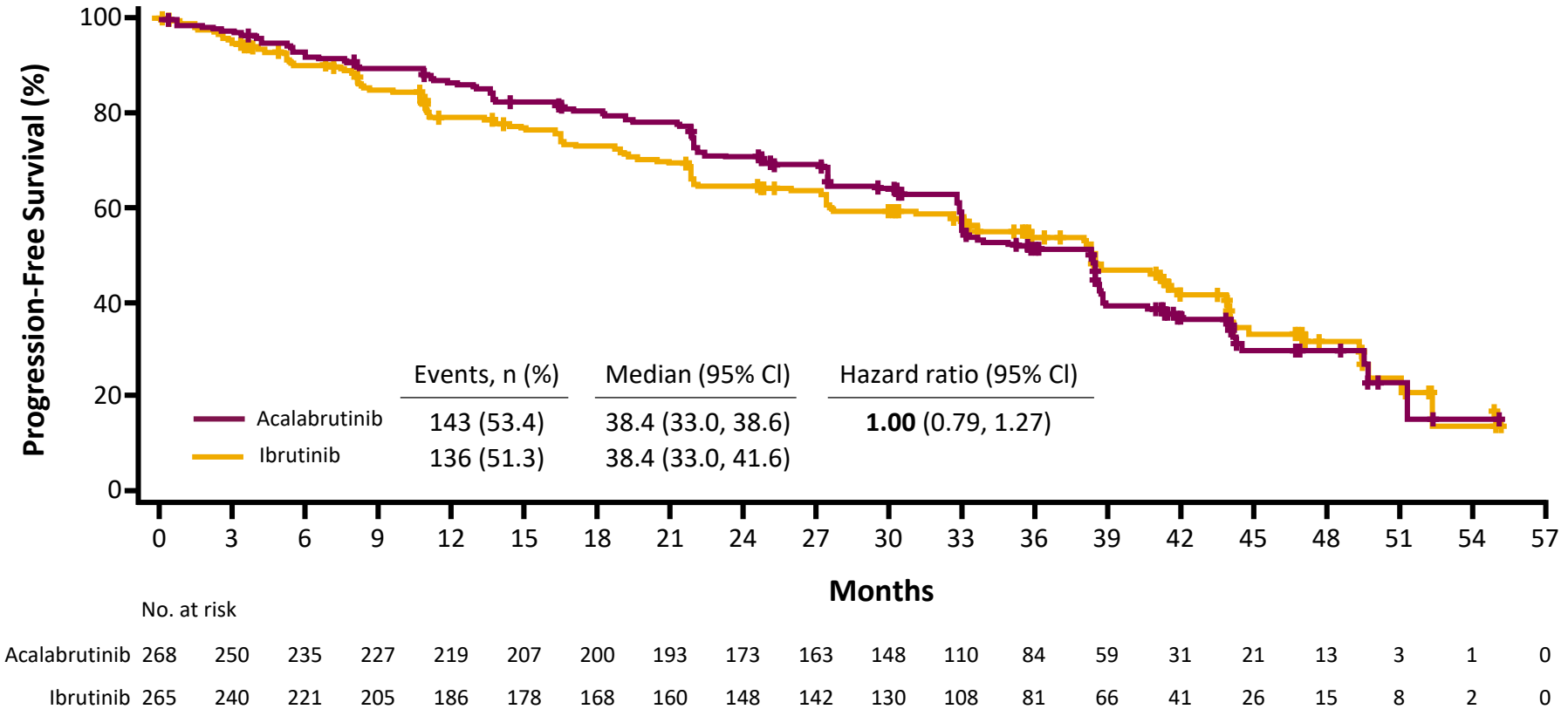
- Distinct toxicity profile
  - Cardiovascular toxicity
    - Atrial fibrillation
    - Ventricular fibrillation/arrythmia
    - Cardiac arrests / sudden death
    - Congestive heart failure
  - Bleeding disorders
  - Hypertension
- High discontinuation rates (up to 40% in the first 24 months)



Wiczer et al, Blood Advances 2021

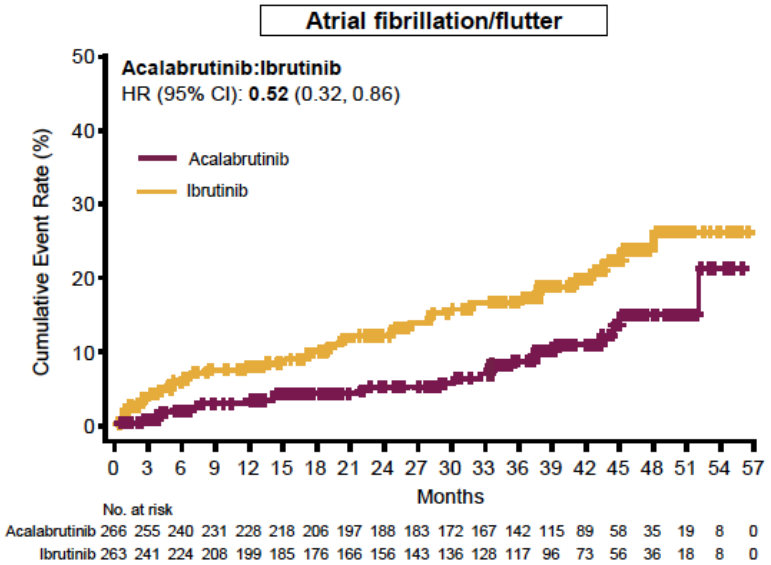
Can next-generation BTKi improve this?

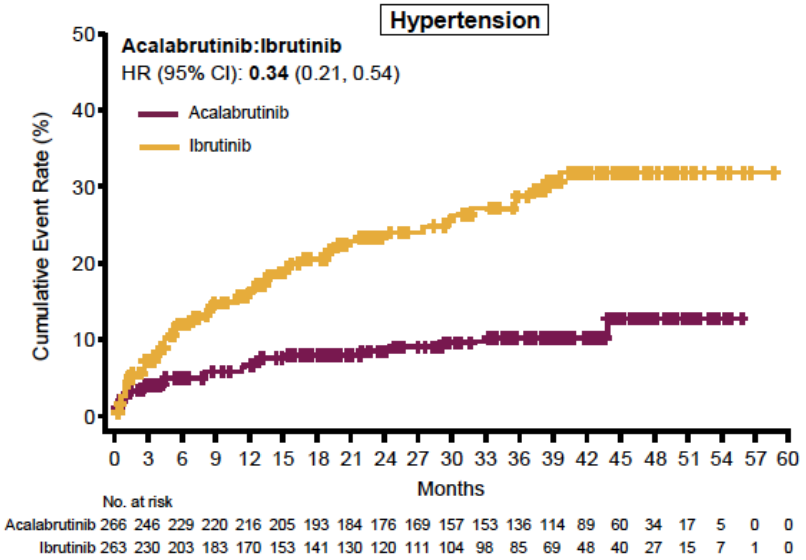
PFS Acalabrutinib = Ibrutinib

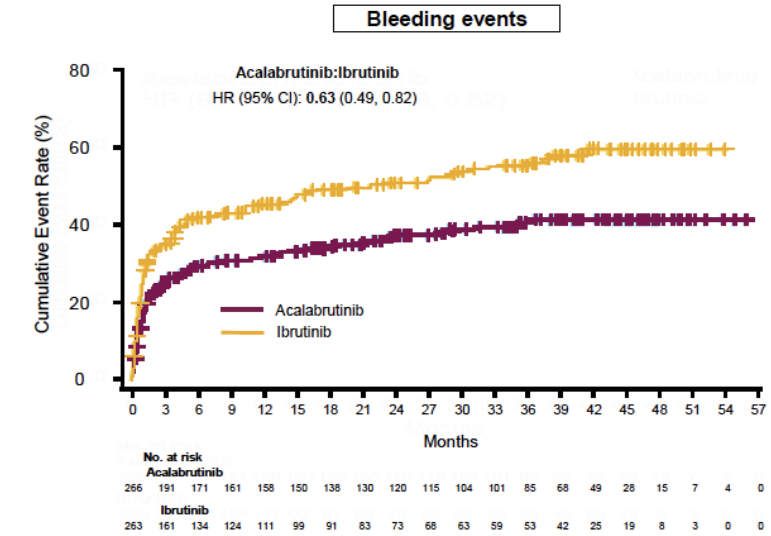


Byrd et al, JCO, 2021

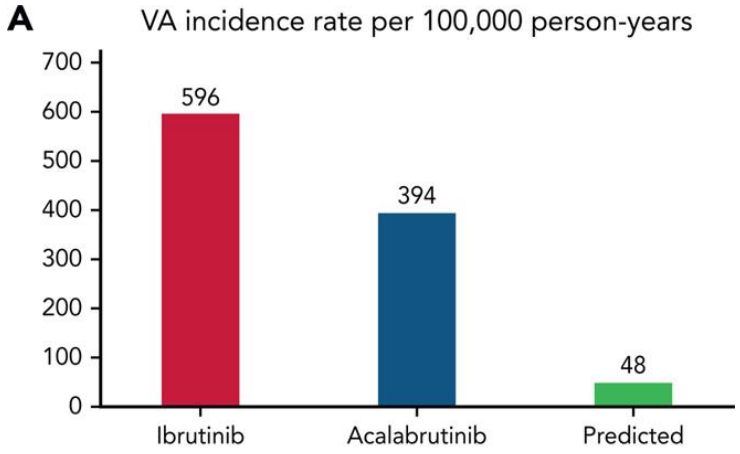
Cardiovascular toxicity under Acalabrutinib vs Ibrutinib

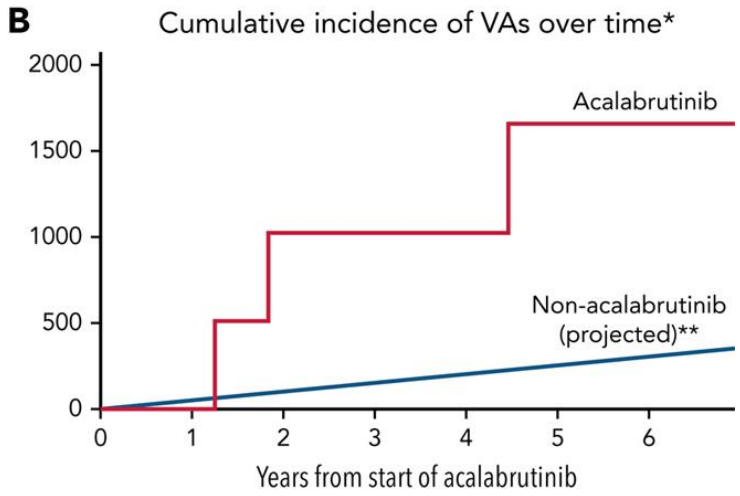






AF, hypertension, bleeding less Communon with acalabrutinib than with ibrutinib, but <u>only relative risk reduction</u>





Byrd et al, JCO, 2021

Bhat et al, 2022

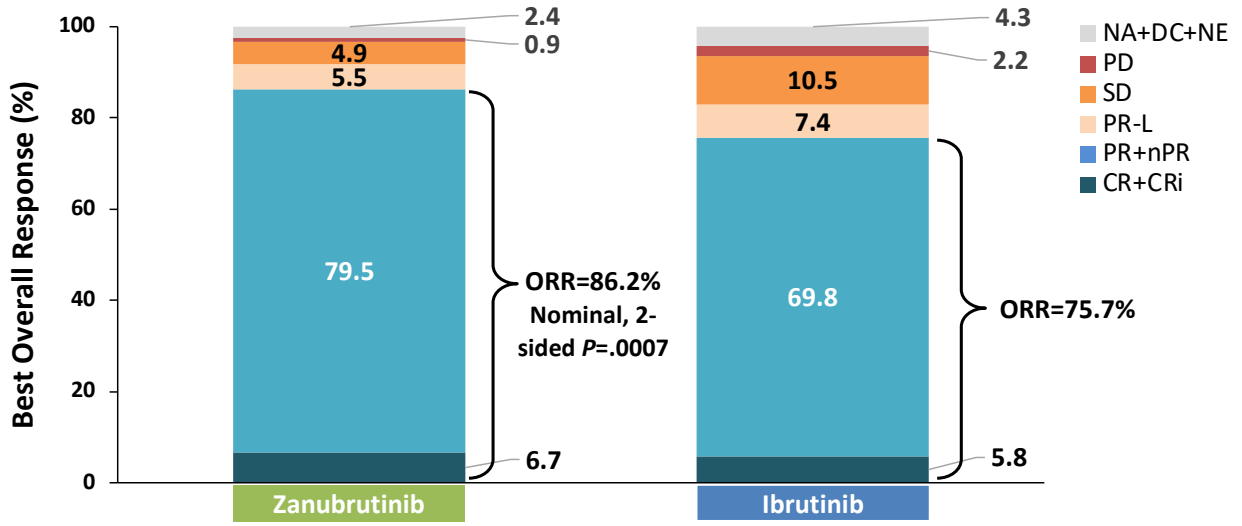
What about Zanubrutinib?

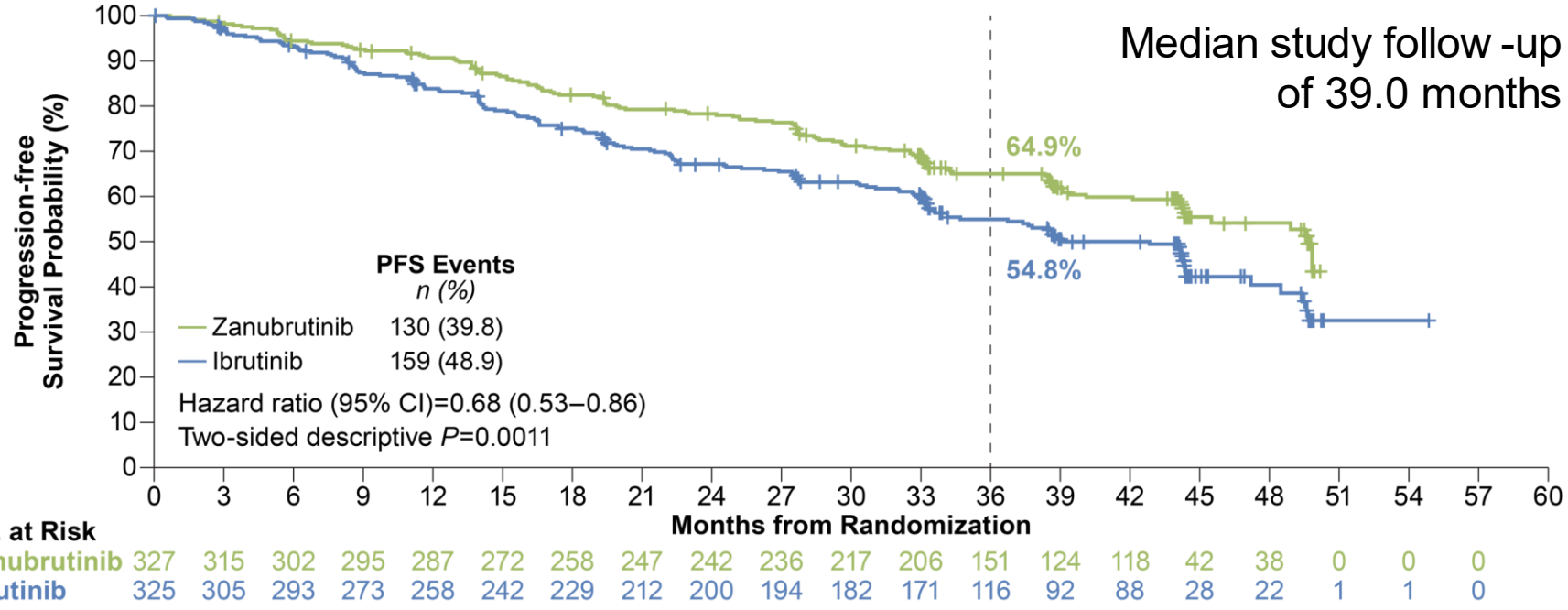
AESI, n (%)	Any Grade		Grade ≥3	
	Zanubrutinib (n=324)	Ibrutinib (n=324)	Zanubrutinib (n=324)	Ibrutinib (n=324)
≥1 AESI	**294 (90.7)**	**300 (92.6)**	**186 (57.4)**	**184 (56.8)**
Anemia	50 (15.4)	53 (16.4)	7 (2.2)	8 (2.5)
Atrial fibrillation and flutter	17 (5.2)	43 (13.3)	8 (2.5)	13 (4.0)
Hemorrhage	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

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

Brown et al, NEJM 202

What about Zanubrutinib?





Median study follow -up of 39.0 months

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

Brown et al, ASH 2023

What about Pirtobrutinib?

	Treatment-Emergent AEs in Patients with CLL/SLL (n=282)			
	All Cause AEs, (≥20%), %		Treatment-Related AEs, %	
Adverse Event	**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
Contusion	26.2	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[a]	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Infections	74.1	30.9	12.8	4.3
Bruising	30.1	0.0	19.1	0.0
Rash	24.5	1.1	5.7	0.4
Arthralgia	22.7	1.4	4.3	0.0
Hemorrhage	13.5	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.

Woyach et al, ASH 2023

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%
Pneunomia	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)

1. Al-Sawaf O, et al. EHA 2023. Abstract S145; 2. Al-Sawaf O, et al. *Lancet Oncol* 2020; 21:1188–1200 (incl. appendix).

Toxities with Ven-Ibru

Adverse Events,[a] n (%)	Ibrutinib-Venetoclax (n = 106)	Chlorambucil-Obinutuzumab (n = 105)
Diarrhea	54 (50.9)	13 (12.4)
Neutropenia[b]	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,[a] 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)

[a]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.

[b]Includes both “Neutropenia” and “Neutrophil count decreased.”

Kater A, et al. *NEJM Evidence.* 2022

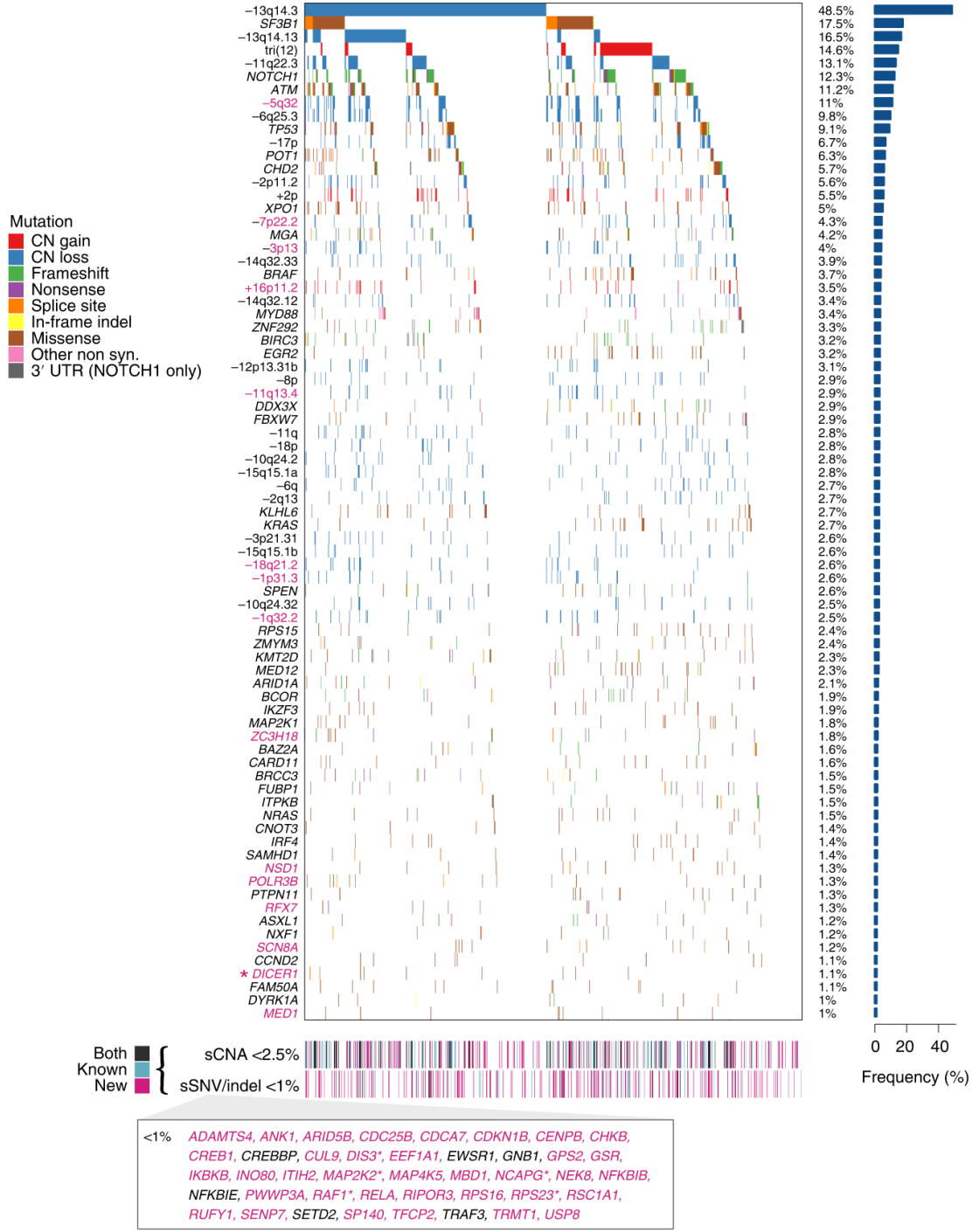
Summary II

- 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



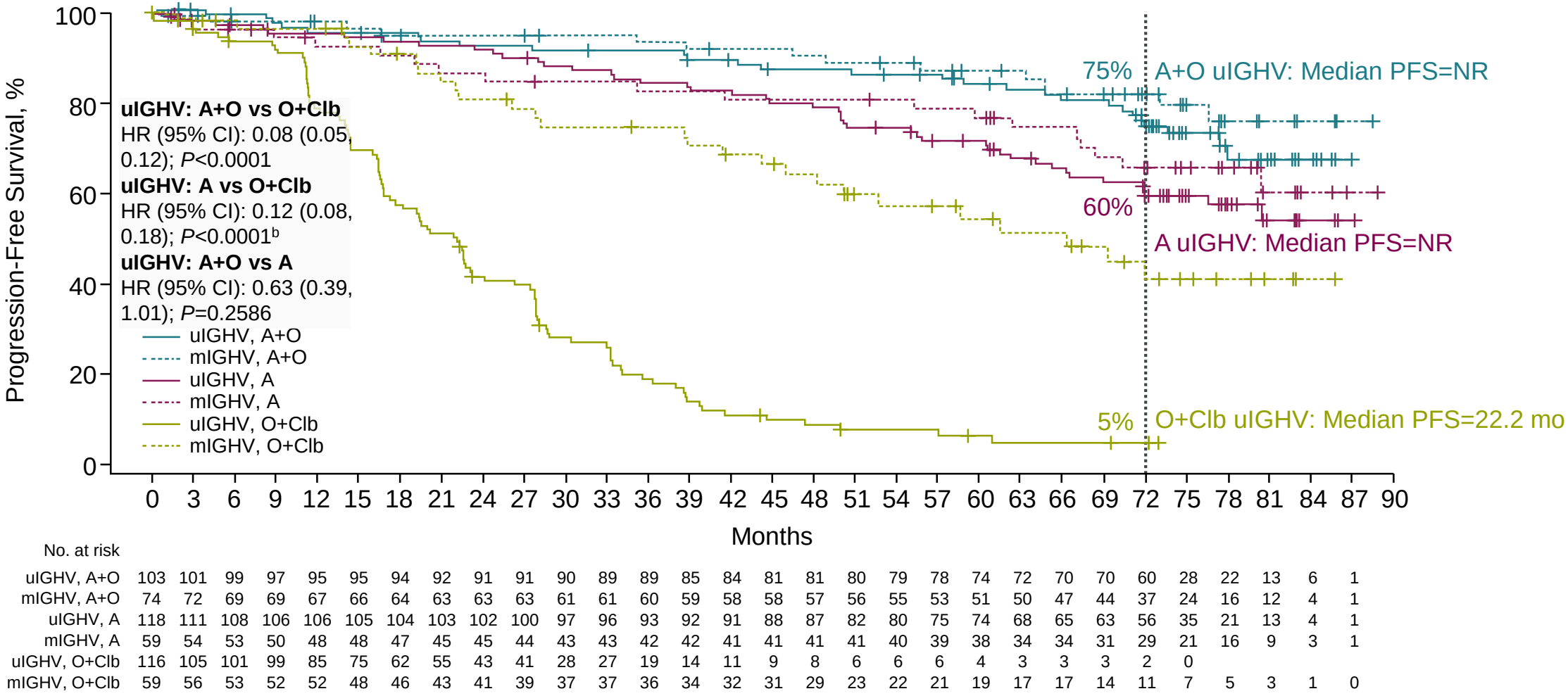
Knisbacher et al, 2022

(Only) two clinically relevant genomic features

IGHV

TP53

PFS according IGHV status with Acalabrutinib

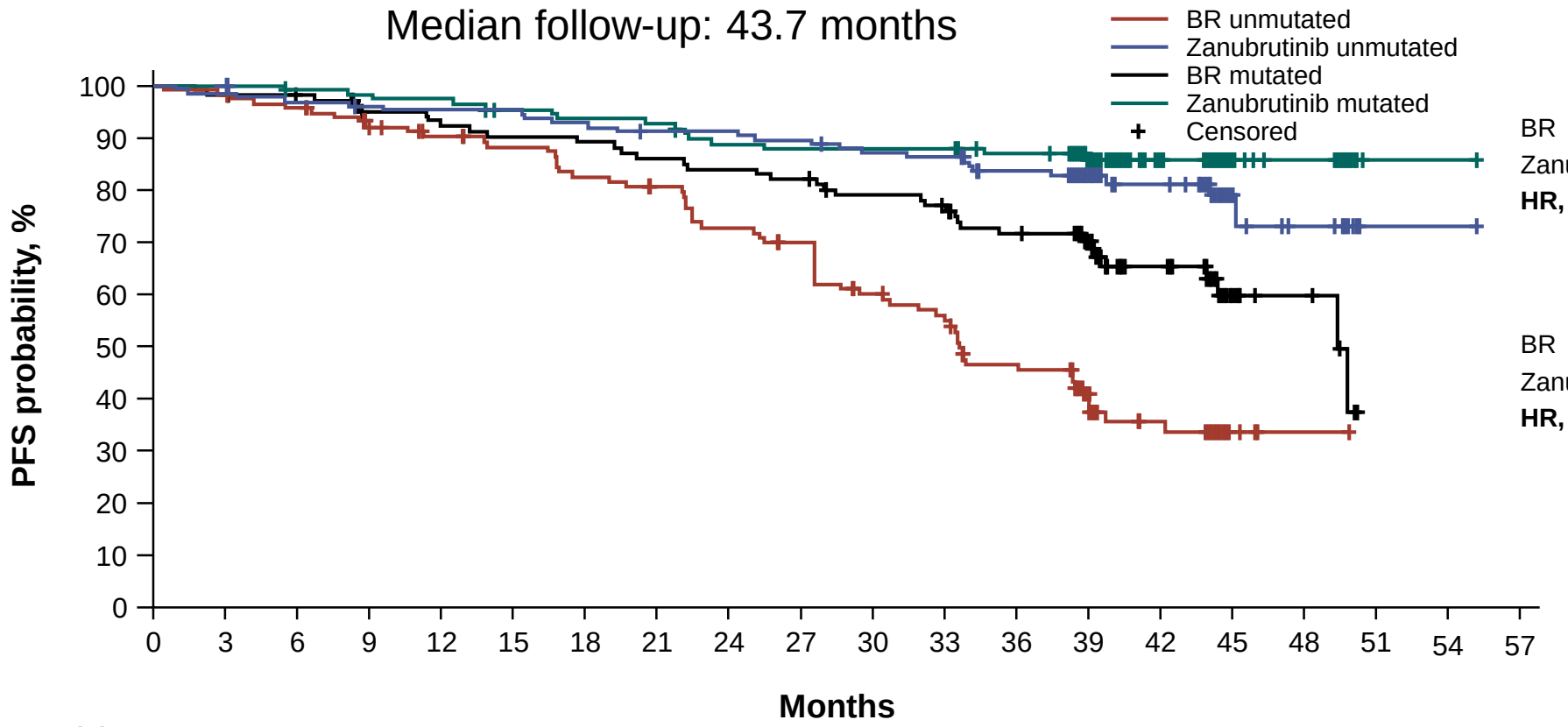


No. at risk

uIGHV, 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
uIGHV, 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
uIGHV, 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

Sharman et al, ASH 2023

PFS according IGHV status with Zanubrutinib



Unmutated IGHV

	mPFS	95% CI
BR	33.7 mo	29.5-39.1
Zanu	NE	NE

HR, 0.23; 95% CI, 0.14-0.37; *P*<.0001[a]

Mutated IGHV

	mPFS	95% CI
BR	49.4 mo	44.4-NE
Zanu	NE	NE

HR, 0.35; 95% CI, 0.19-0.64; *P*=.00033[a]

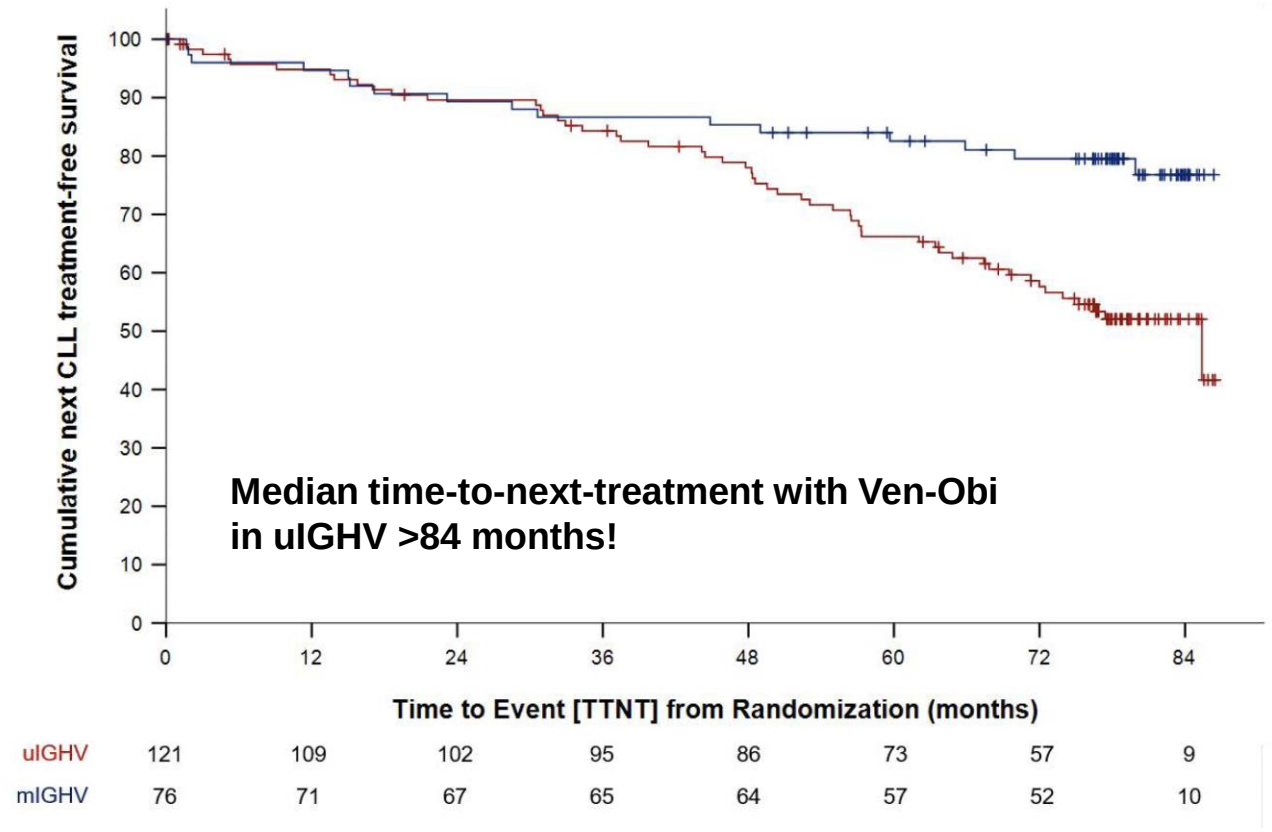
No. at risk

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

Shadman et al, ICML 2023

PFS according to IGHV status with Ven-Obi

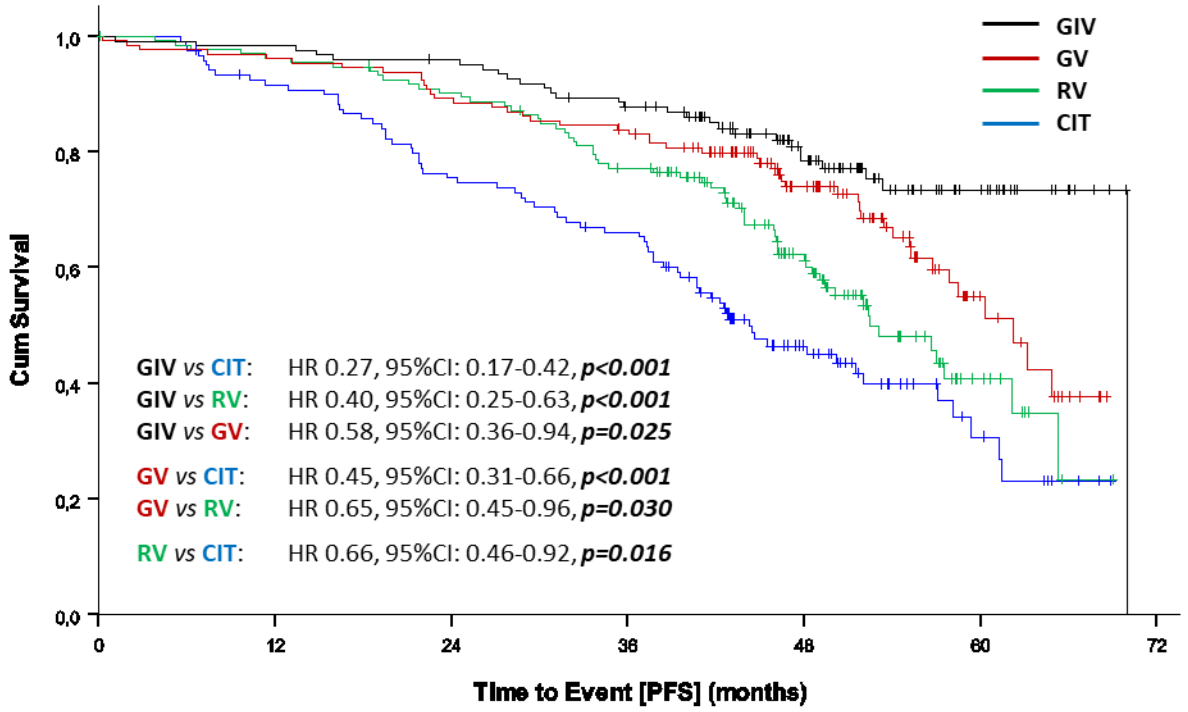
Median fol



Al-Sawaf et al, *Blood* 2024 (accepted)

PFS according to IGHV status with Ven-Obi

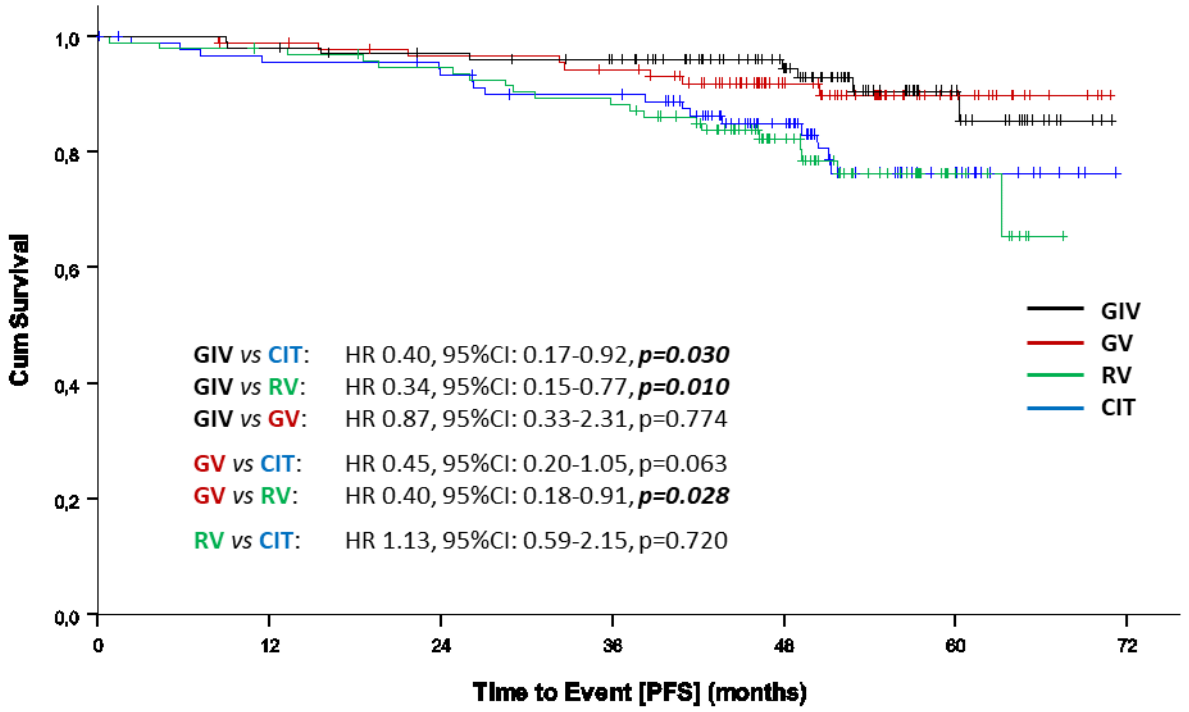
PFS, patients with unmutated IGHV



Pts at risk

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

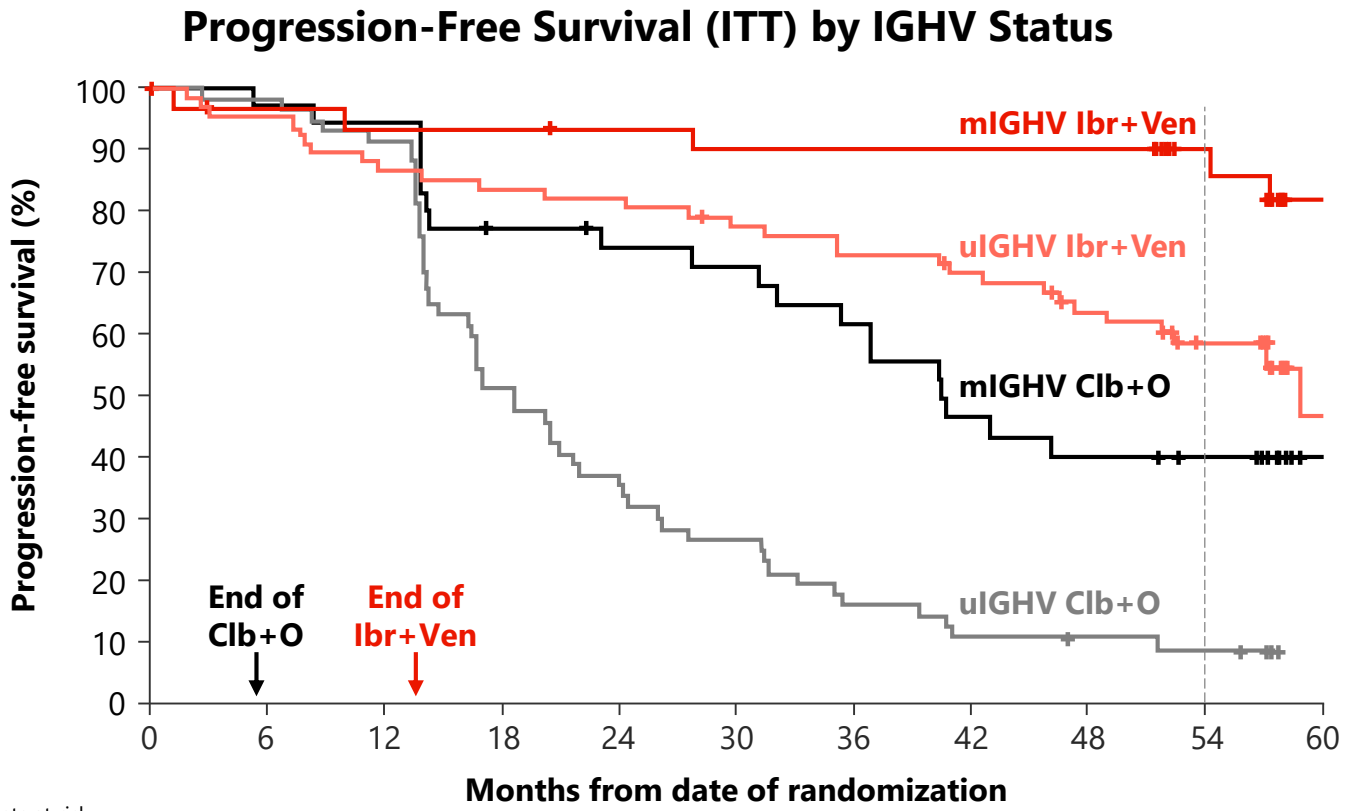


Pts at risk

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

Fürstenau et al, ASH 2023

PFS according to IGHV status with Ven-Ibru



Patients at risk											
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

- 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

Follows et al, ASH 2023

Summary III

- IGHV status is an (independent) **prognostic factor for PFS with fixed-duration therapies**, but not continuous therapies

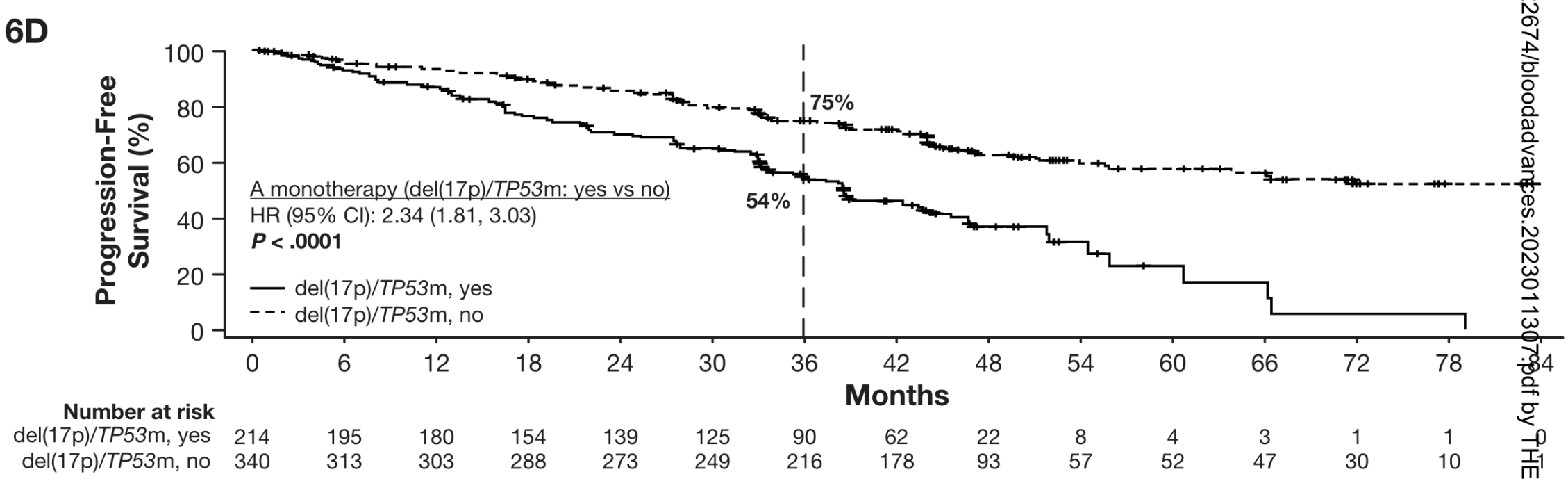
- Given the long treatment-free window (>6 years), fixed-duration options **can still be considered in the context of uIGHV**, depending on patients‘ preferences

(Only) two clinically relevant genomic features

IGHV

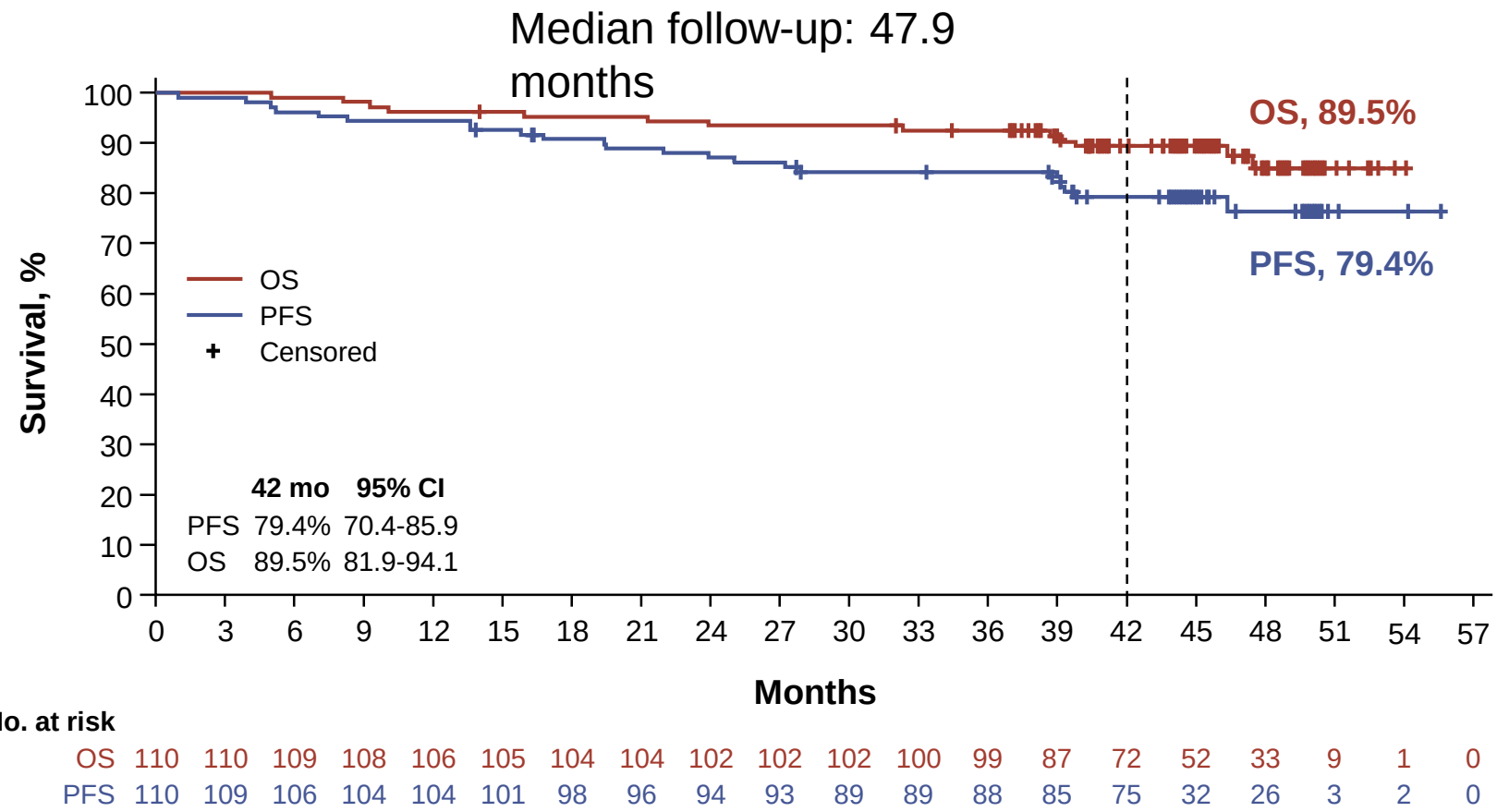
TP53

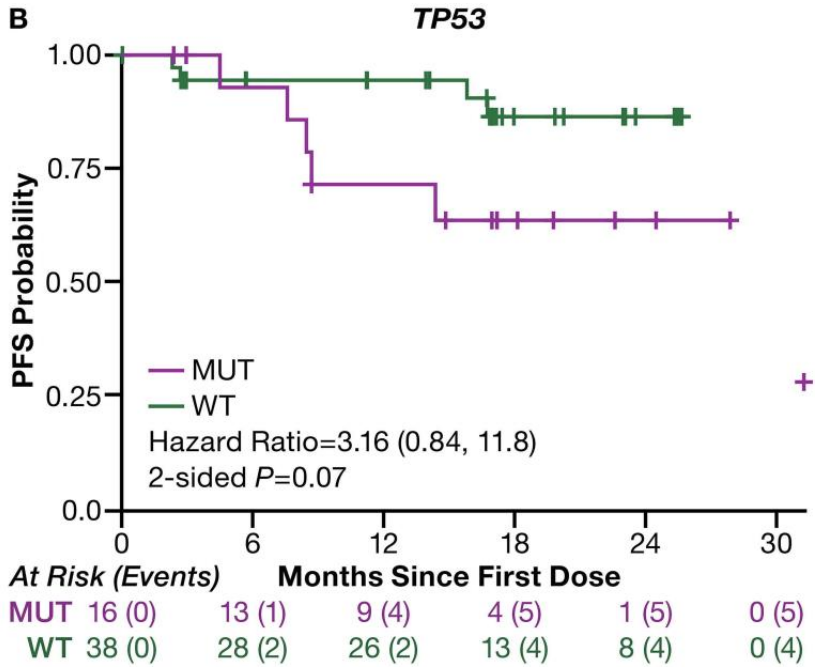
PFS according to *TP53* status with Acalabrutinib



Davids et al, Blood Adv, 2024

PFS according to *TP53* status with Zanubrutinib



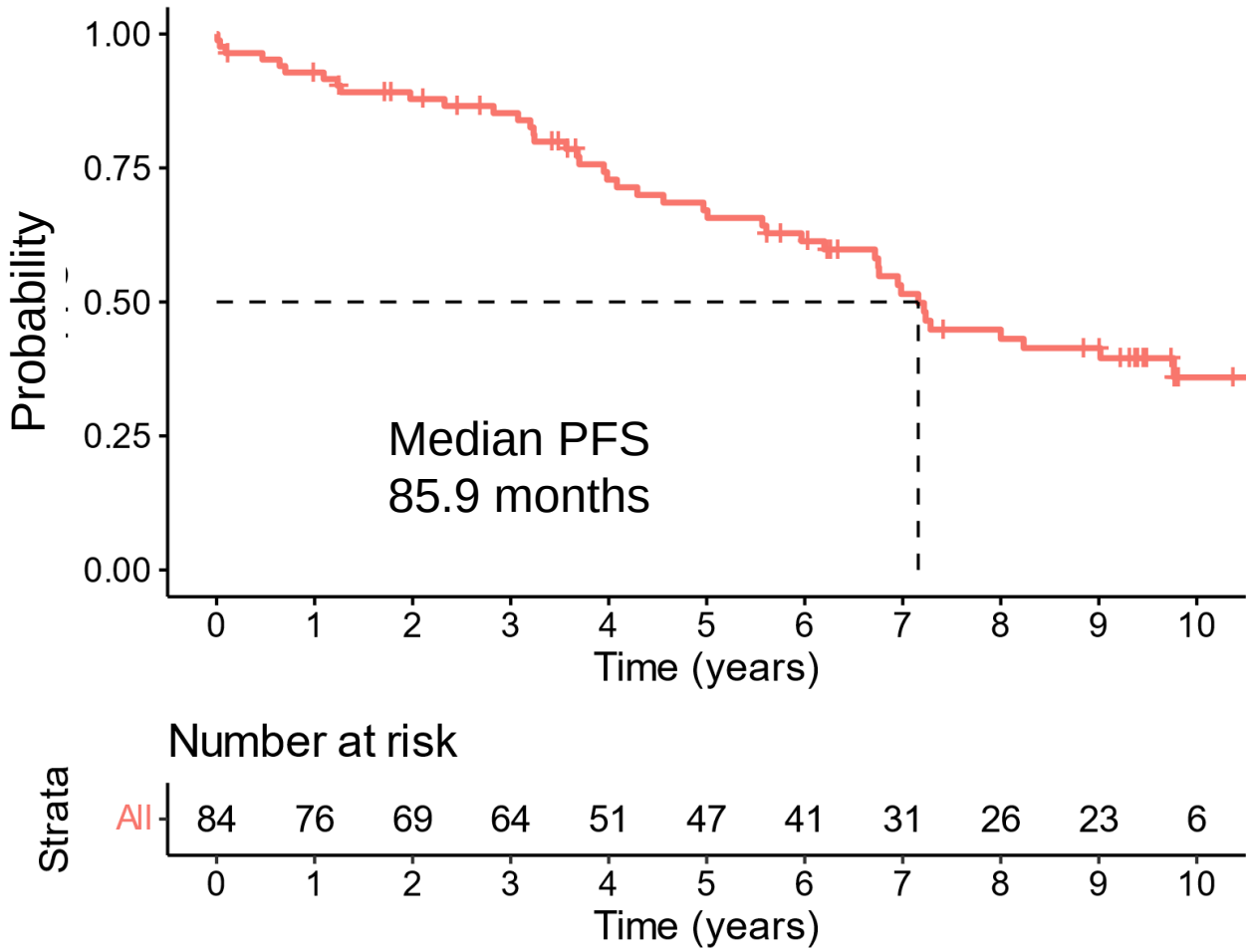


Shadman et al, ICML 2023

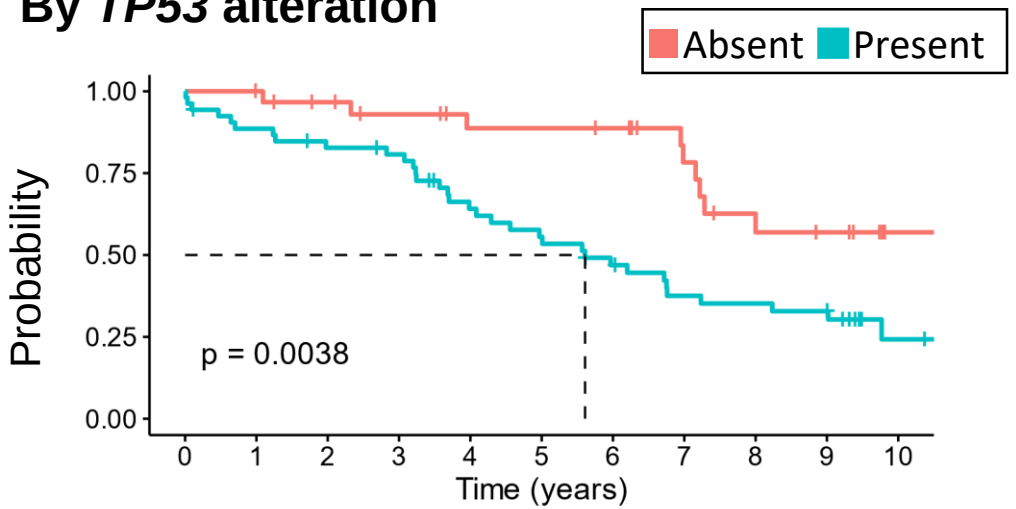
Xu et al, Haematologica, 2024

PFS according to *TP53* status with Ibrutinib

All patients



By *TP53* alteration



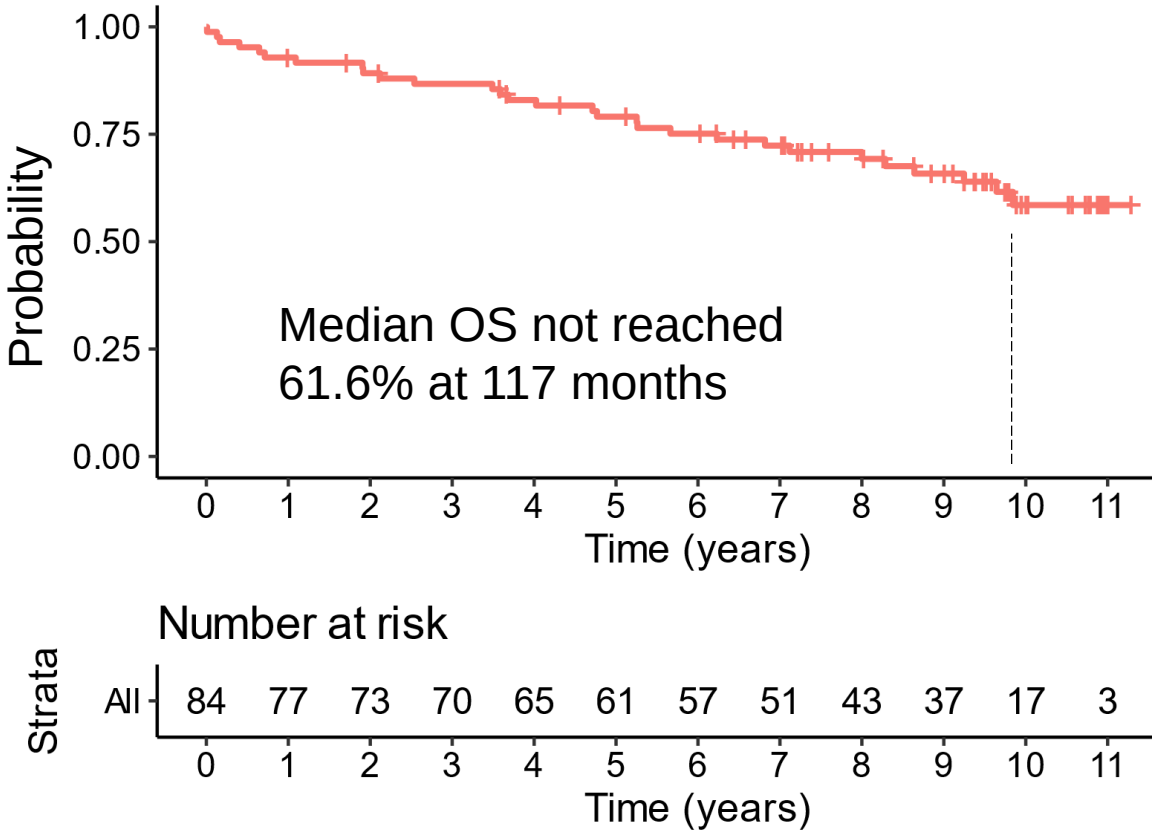
Risk category		mPFS (mo)	% PFS at mFU*	*P* =
TP53 alteration	Absent Present	NR 67.3	56.9% 30.3%	.004
Therapy status	TN Rel/ref	108 49	48.7% 22.4%	.016
IGHV	M U	117.2 80.6	57.1% 29.7%	.057

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

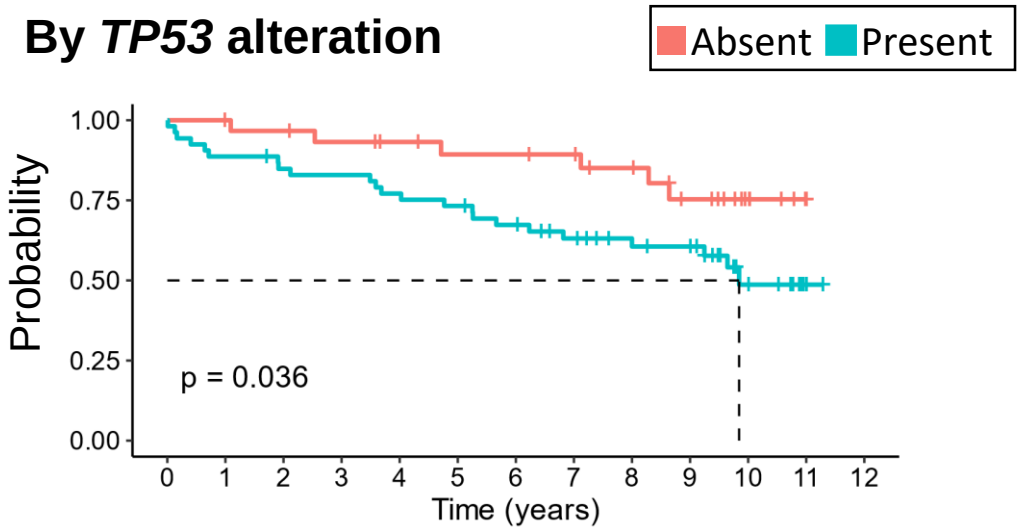
Itsara et al, ASH 2023

OS according to *TP53* status with Ibrutinib

All patients



By *TP53* alteration



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

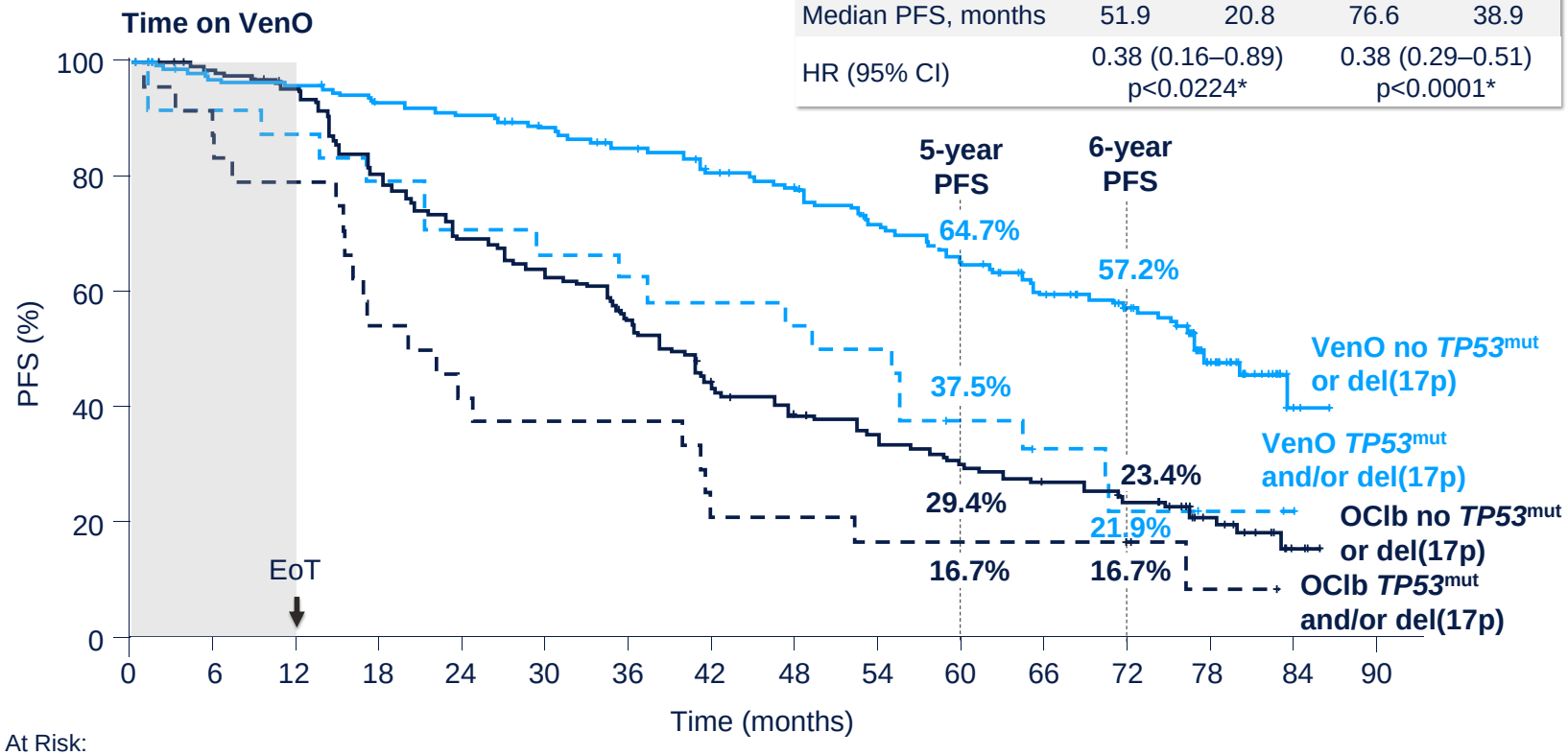
TN; treatment-naïve; rel/ref – relapsed/refractory;
IGHV, M, mutated; U, unmutated

Itsara et al, ASH 2023

PFS according to *TP53* status with Ven-Obi

Median follow-up: 76.4 months

	TP53^{mut} and/or del(17p)		No *TP53*^{mut} or del(17p)	
	VenO	OClb	VenO	OClb
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*	

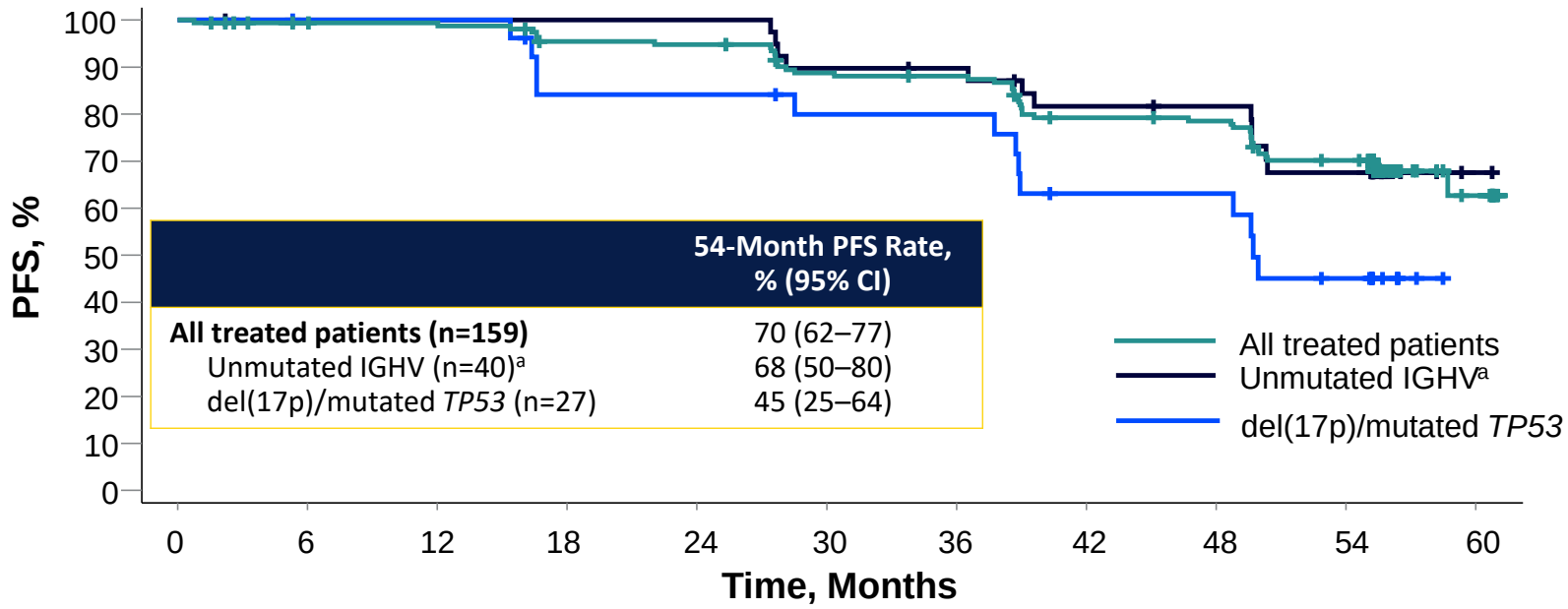


At Risk:

OClb *TP53*^{mut} and/or del(17p)	24	20	19	13	10	9	9	5	5	4	4	4	3	1	
VenO *TP53*^{mut} and/or del(17p)	25	22	21	19	17	16	15	14	13	12	8	6	4	2	
OClb no *TP53*^{mut} or del(17p)	184	169	160	135	117	106	90	68	60	51	45	40	33	17	3
VenO no *TP53*^{mut} or del(17p)	184	170	168	161	157	150	142	131	123	112	101	87	73	34	3

Al-Sawaf et al, *Blood* 2024 (accepted)

PFS according to *TP53* status with Ven-Ibru



Patients at risk

All treated patients	159	153	152	144	143	132	130	115	113	99	11
Unmutated IGHV[a]	40	39	39	39	39	35	34	30	29	24	1
del(17p)/mutated *TP53*	27	26	26	21	21	19	19	14	14	9	0

Ghia et al, ASH 2023

Summary IV

- Randomized data on *TP53* with **fixed-duration therapies are still limited** (25 pts for Ven-Obi, 0 pts for Ven-Ibru)

- 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

CLL17

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

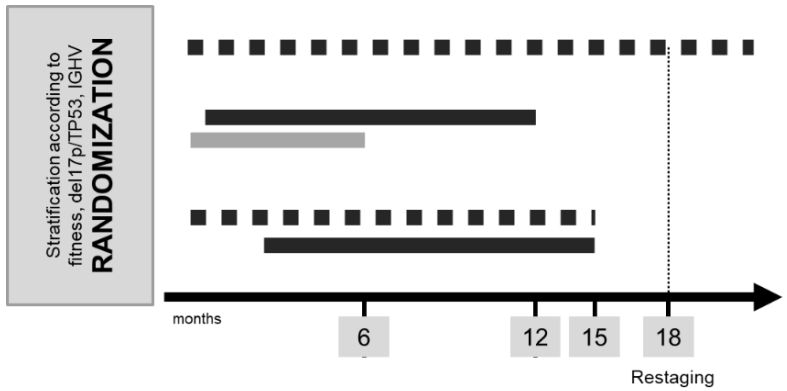
Stratification according to fitness, del17p/TP53, IGHV

Ibrutinib	Venetoclax Obinutuzumab	Venetoclax Ibrutinib

909 patients

Primary endpoint:
Progression-free survival

TREATMENT SCHEDULE



Ibrutinib d1 420 mg po daily until PD or intolerance

Venetoclax 400 mg po daily (c1 d22 – c12 d28)
Obinutuzumab 1000 mg iv (c1 d1(2)/8/15, c 2-6 d1)

Ibrutinib 420 mg po daily (c1 d1 – c15 d28)
Venetoclax 400 mg po daily (c4 d1 – c15 d28)

TIMELINES

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

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**