

FD vs Indefinite Therapy in CLL

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REVOLUTIONARY ROAD IN CLL

Innovazione rivoluzionaria nella terapia
della leucemia linfatica cronica

Bologna, 20 maggio 2024

Royal Hotel Carlton



Disclosures

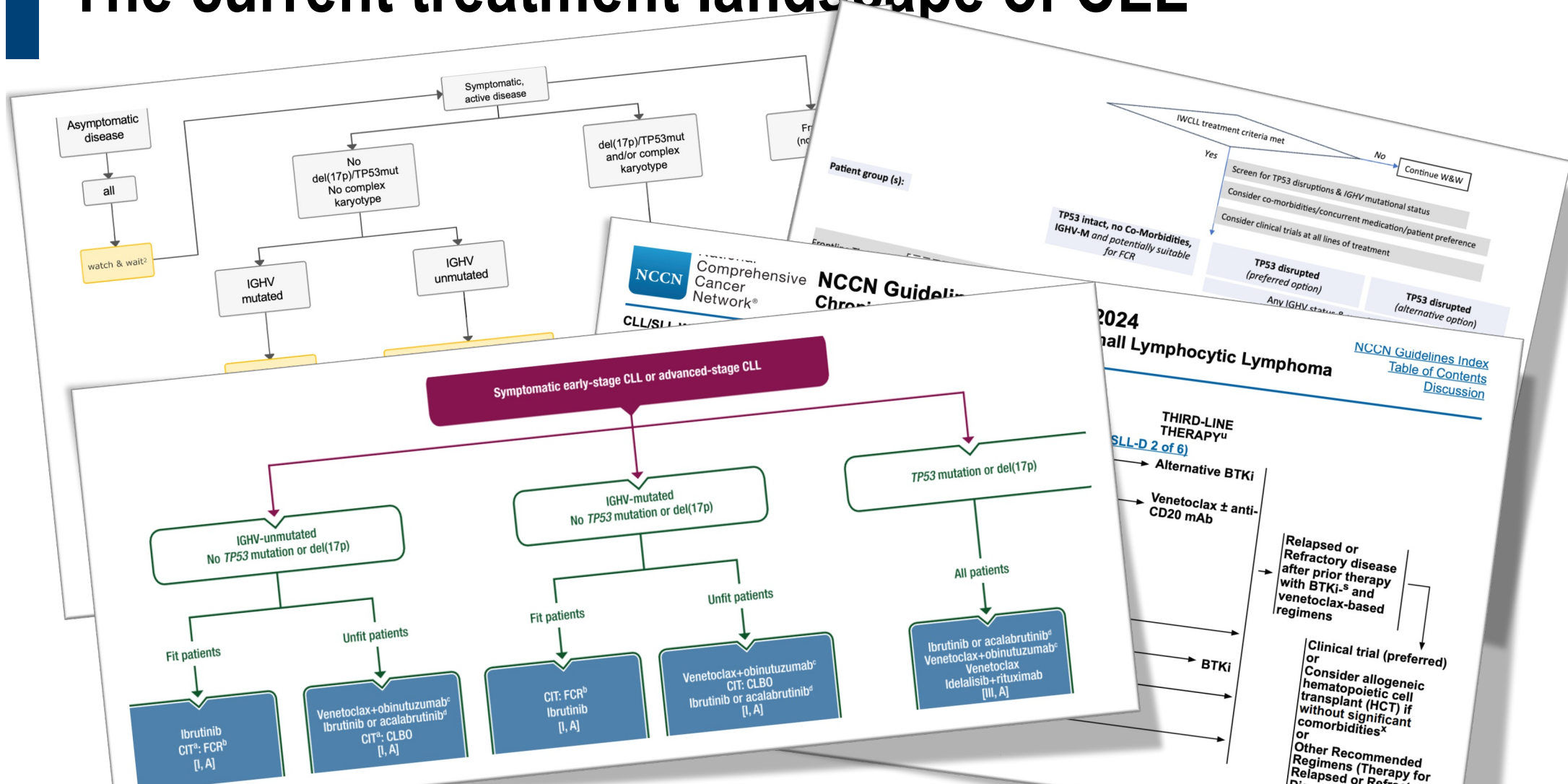
Honoraria: Roche, Janssen, Gilead, AbbVie, Lilly, AstraZeneca, Adaptive, BeiGene

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

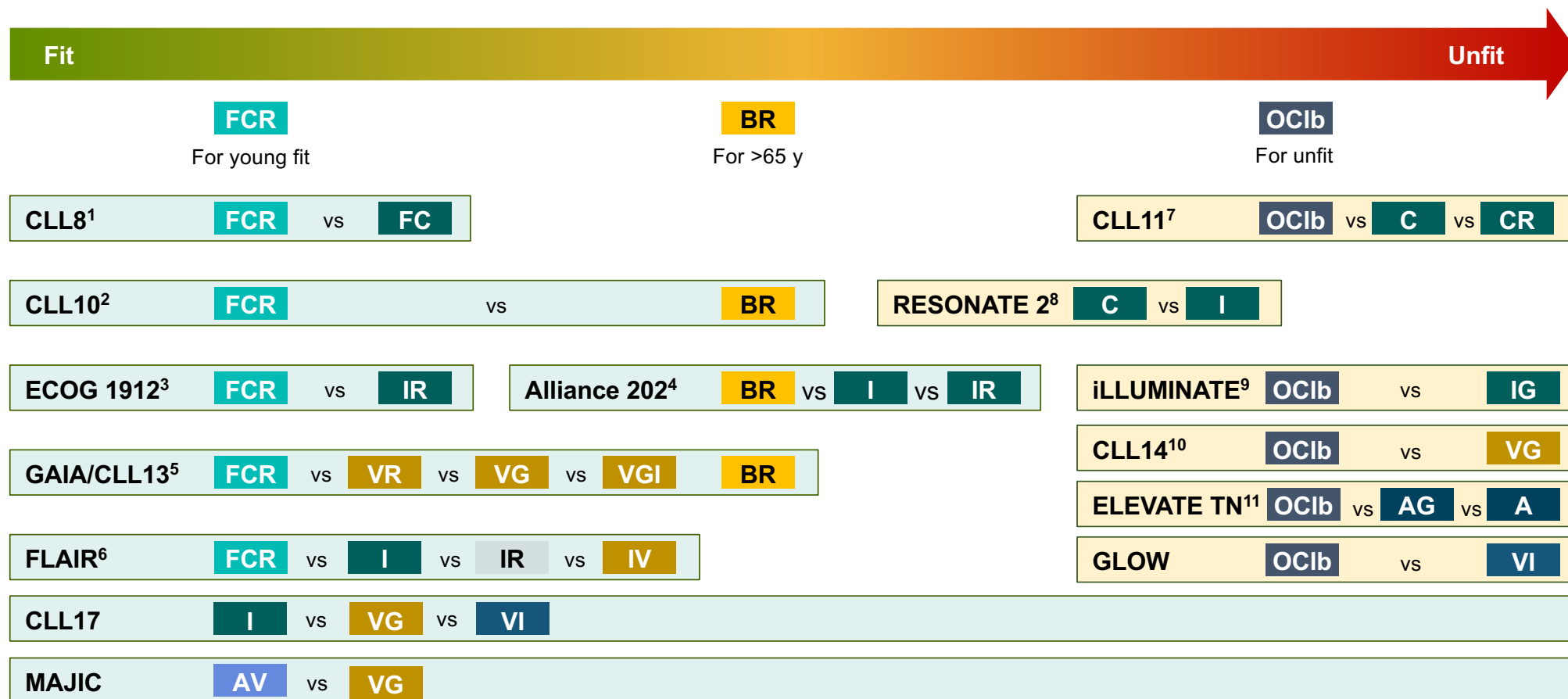
Personal fees: Roche, Janssen, Gilead, AbbVie, AstraZeneca

Research grants: Beigene, Roche, Janssen, AbbVie

The current treatment landscape of CLL

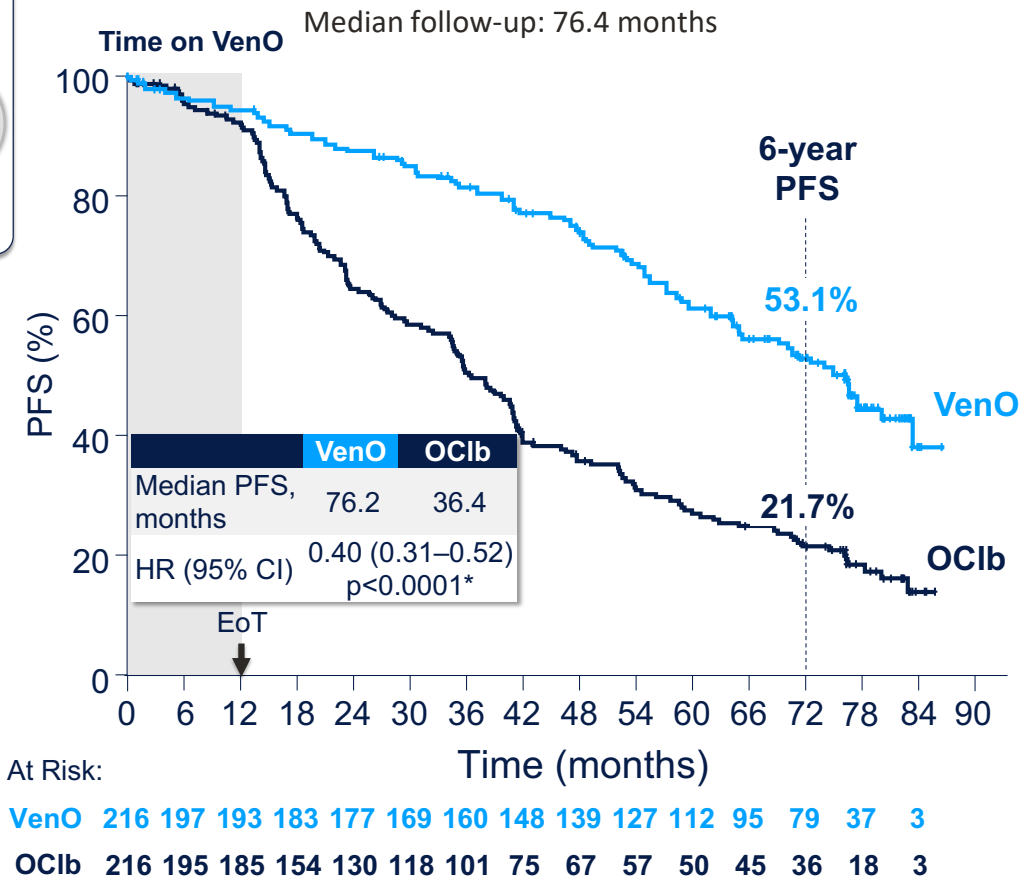
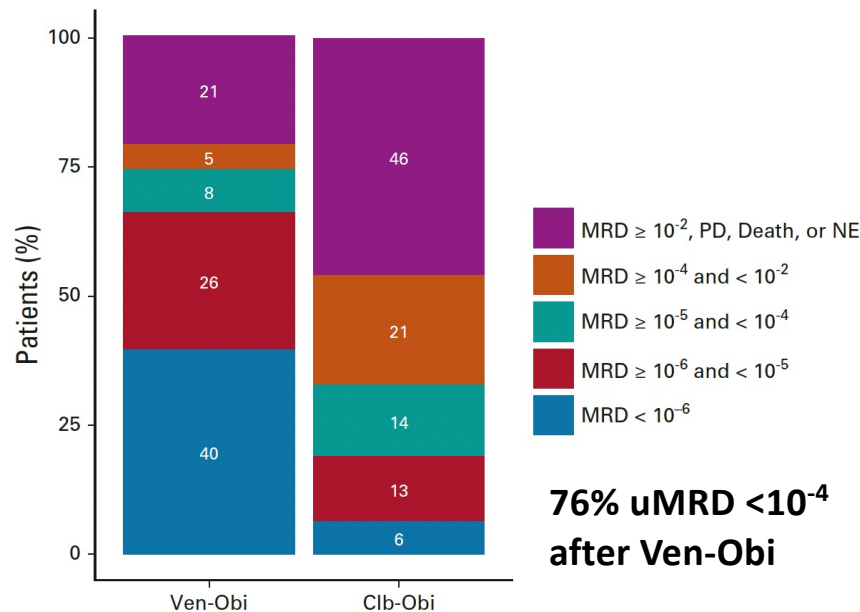
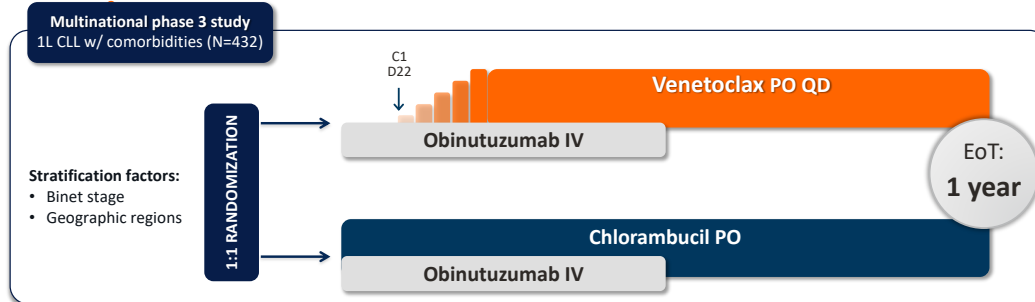


The role of fitness

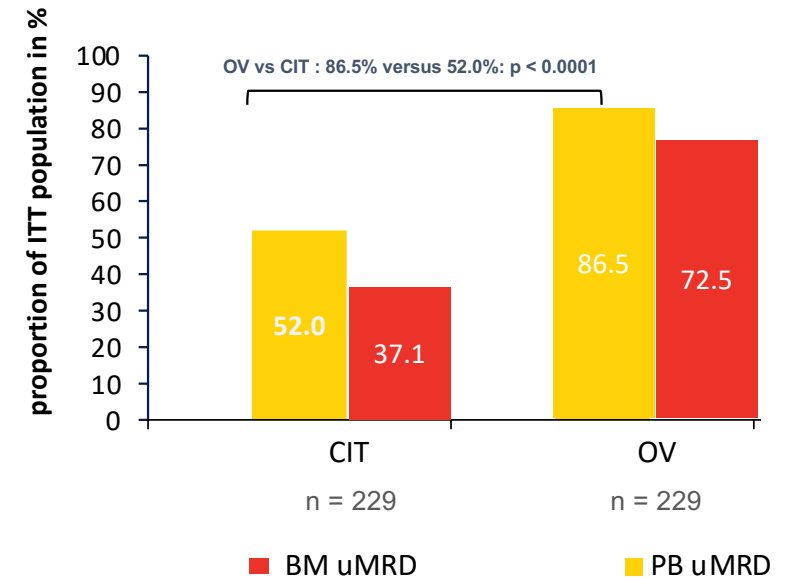
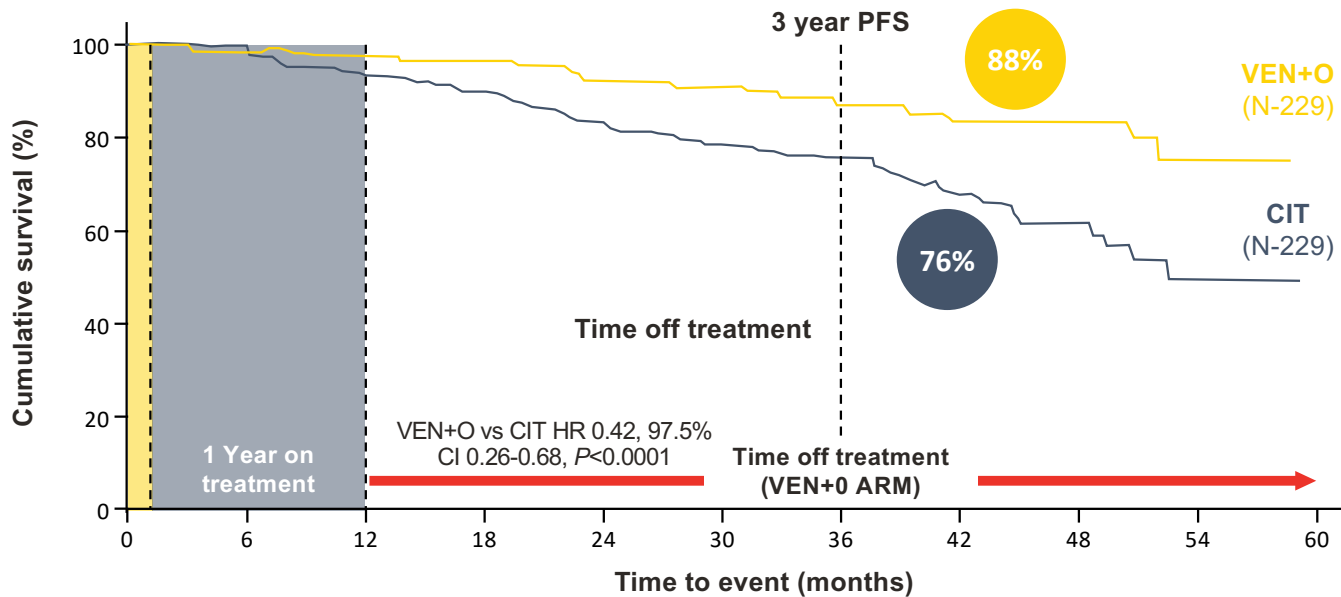
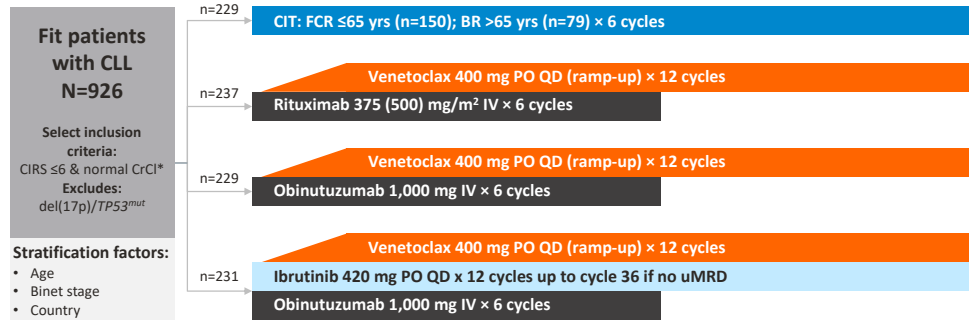


Clinicaltrials.gov: 1. NCT00281918; 2. NCT00769522; 3. NCT02048813; 4. NCT01886872 5. NCT02950051; 6. EudraCT number 2013-001944-76. 7. NCT01010061; 8. NCT01722487; 9.; NCT02264574 10. NCT02242942; 11. NCT02475681.

CLL14 – Ven-Obi in unfit patients



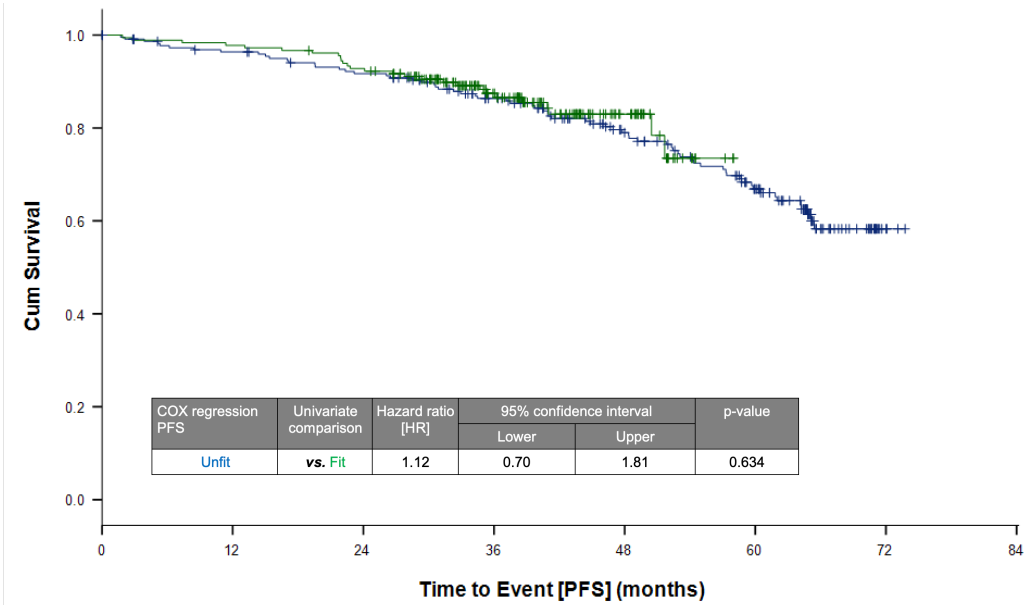
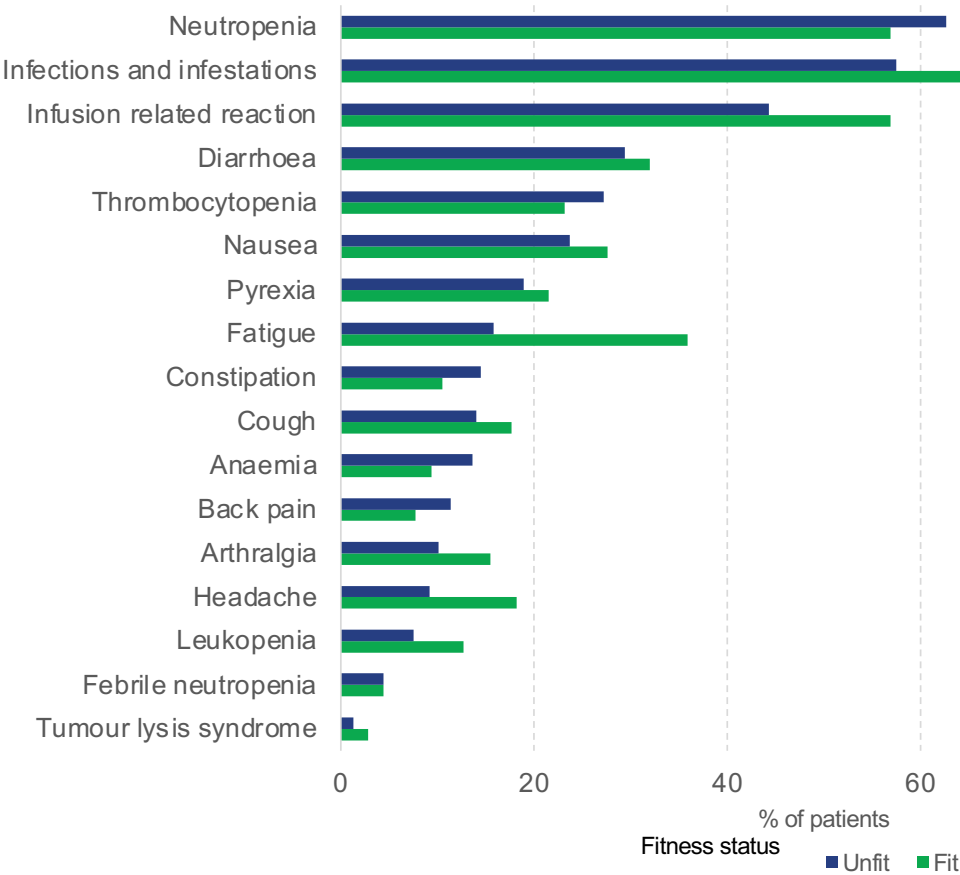
CLL13 – Ven-Obi in fit patients



High efficacy in unfit and fit patients.

Eichhorst et al, NEJM 2023

Does fitness matter with Ven-Obi?

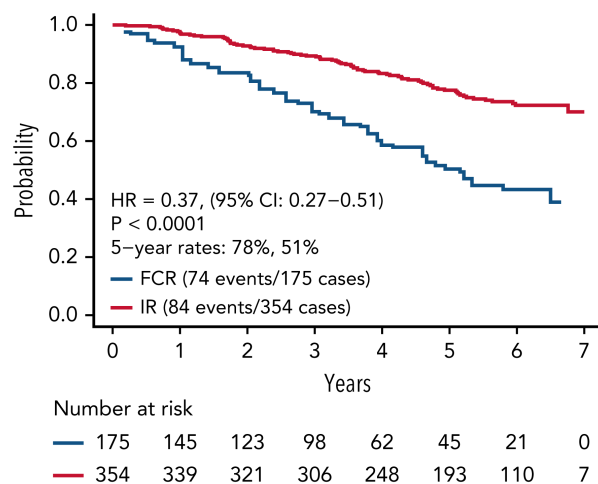


Unfit	228	210	197	167	125	89	4	0
Fit	181	177	167	99	35	0	0	0

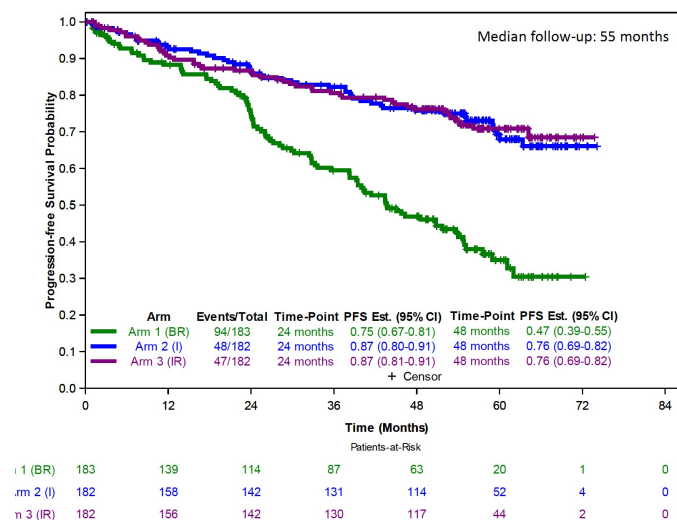
Unpublished data

Does fitness matter with BTKi?

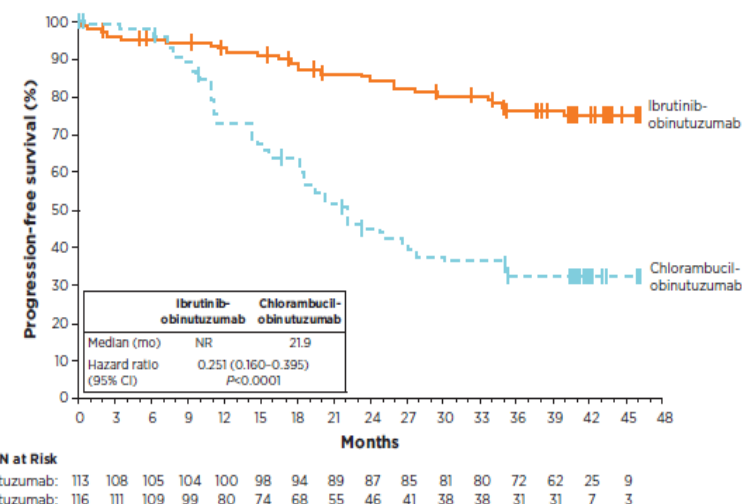
ECOG1912: Young/fit patients



A041202: Elderly/fit patients



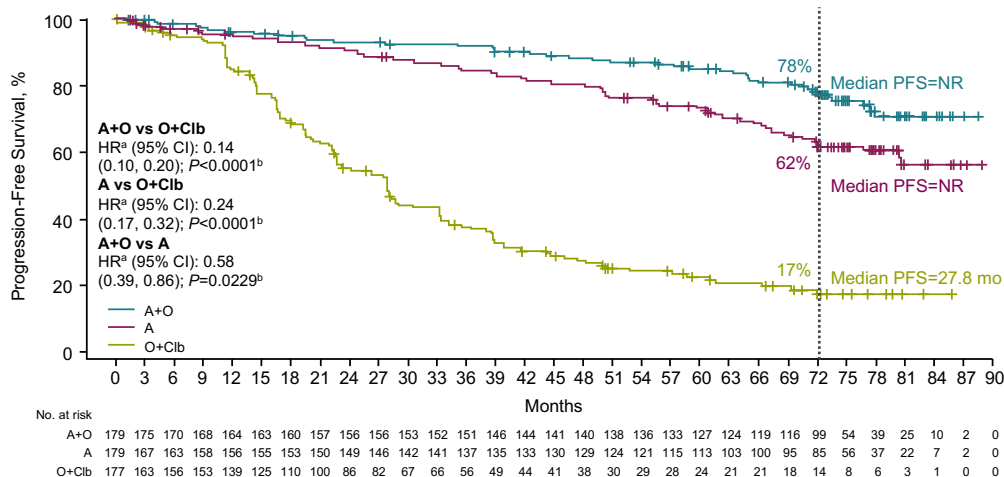
iLLUMINATE: Elderly/unfit patients



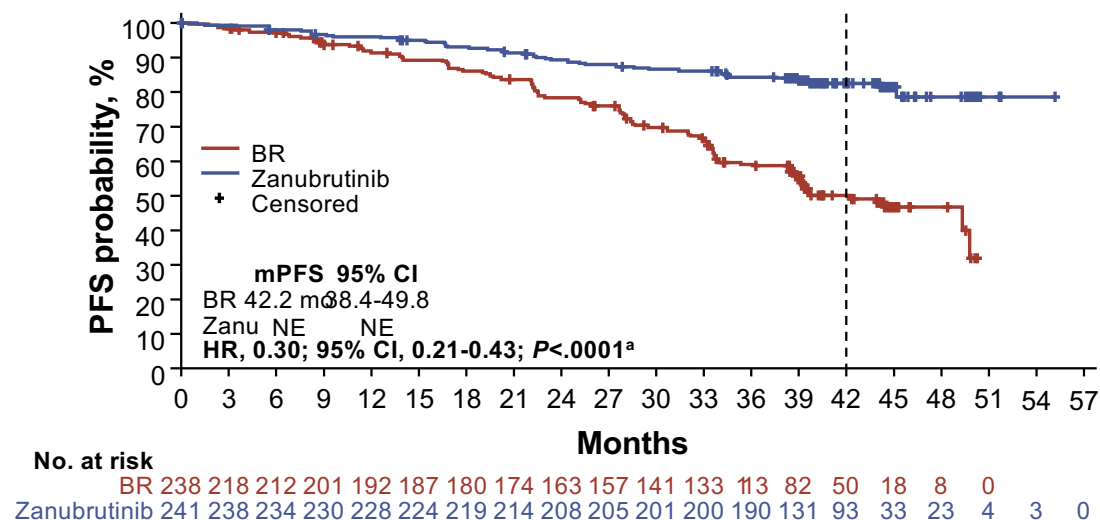
High efficacy of ibrutinib confirmed in randomized studies with fit and unfit patients.

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

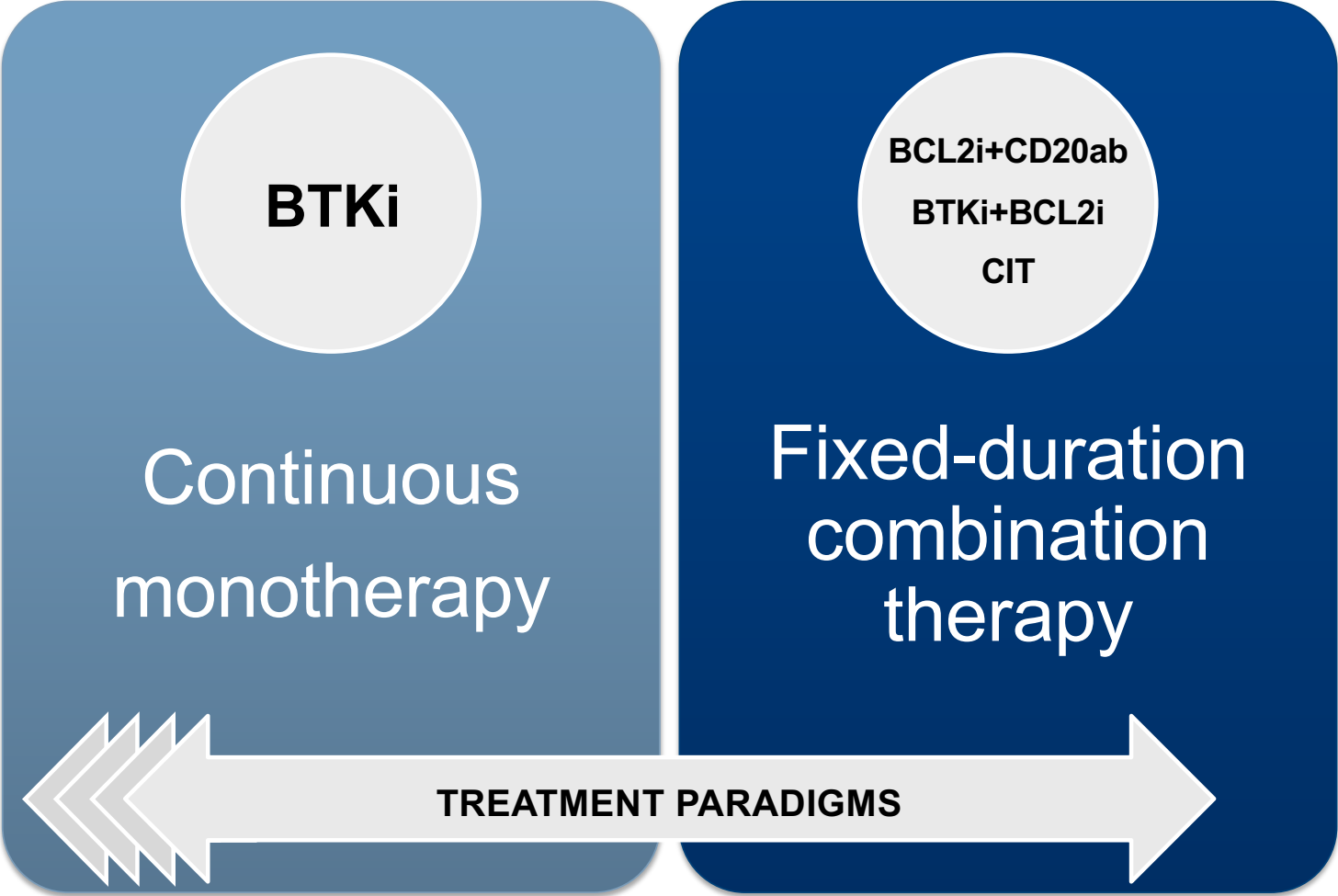
BTKi

Continuous
monotherapy

BCL2i+CD20ab
BTKi+BCL2i
CIT

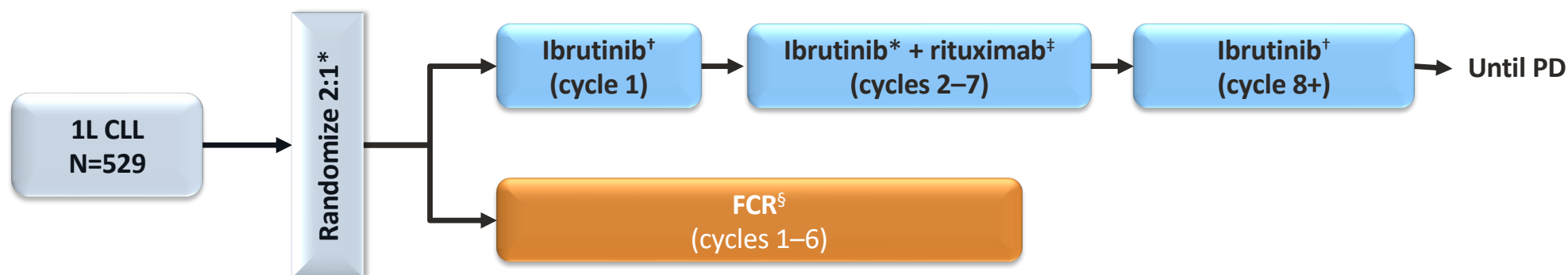
Fixed-duration
combination
therapy

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[¶]

Primary endpoints

- PFS
- QoL (FACT-Leu TOI)

Secondary endpoints

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

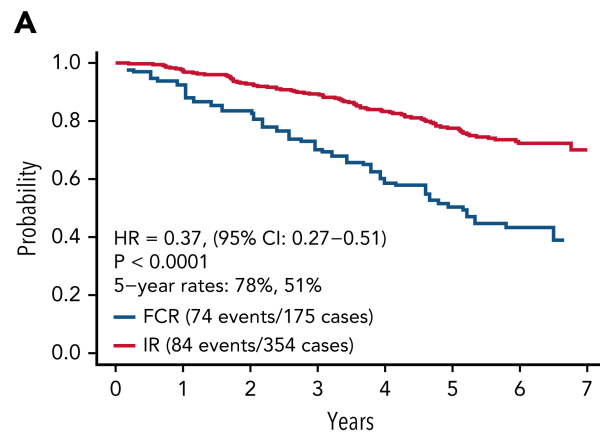
* Stratification according to age, ECOG PS, Rai stage, and del(11q);

[†] Ibrutinib PO 420 mg daily, D1–28; [‡] rituximab IV 50 mg/m² C2D1, 325 mg/m² C2D2, then 500 mg/m² day 1 of C3–7;

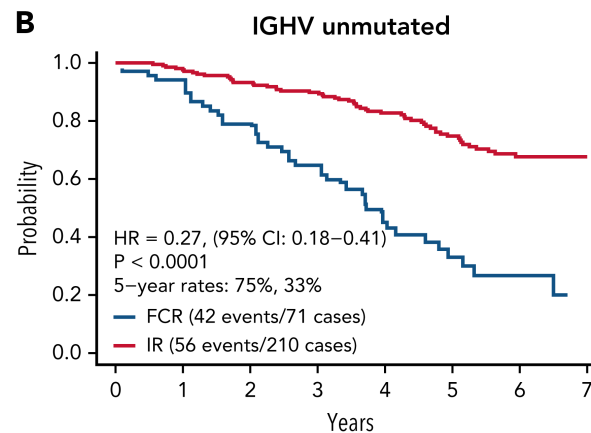
[§] Fludarabine 25 mg/m² days 1–3, cyclophosphamide 250 mg/m² days 1–3, rituximab as per ibrutinib arm but starting on cycle 1; q28 cycles 1–6.

[¶] By Cockcroft-Gault formula.

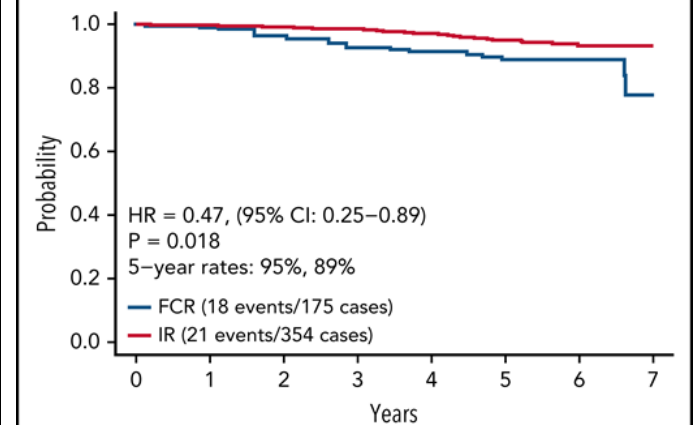
1. ClinicalTrials.gov. NCT02048813 (accessed February 2020); 2. Shanafelt TD, *et al.* *N Engl J Med* 2019; **381**:432–443 (incl. suppl.).



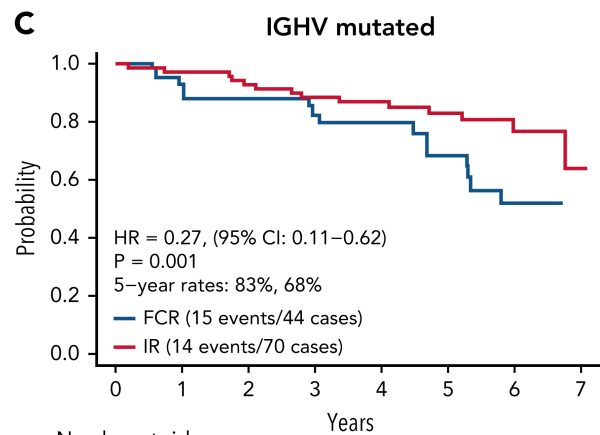
Number at risk							
—	175	145	123	98	62	45	21
—	354	339	321	306	248	193	110



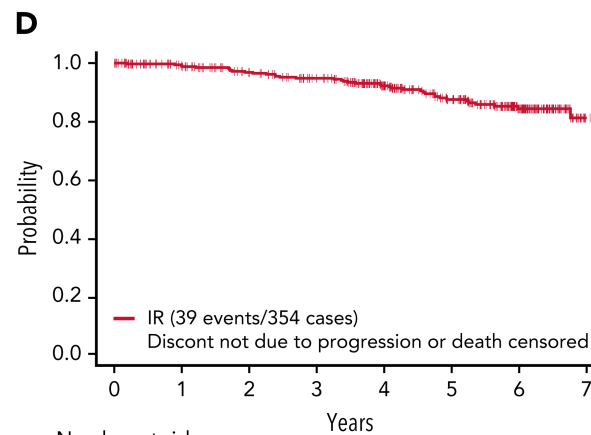
Number at risk							
—	71	63	50	39	20	12	5
—	210	203	193	184	147	108	61



Number at risk							
—	175	155	143	131	126	96	47
—	354	347	343	338	329	300	139



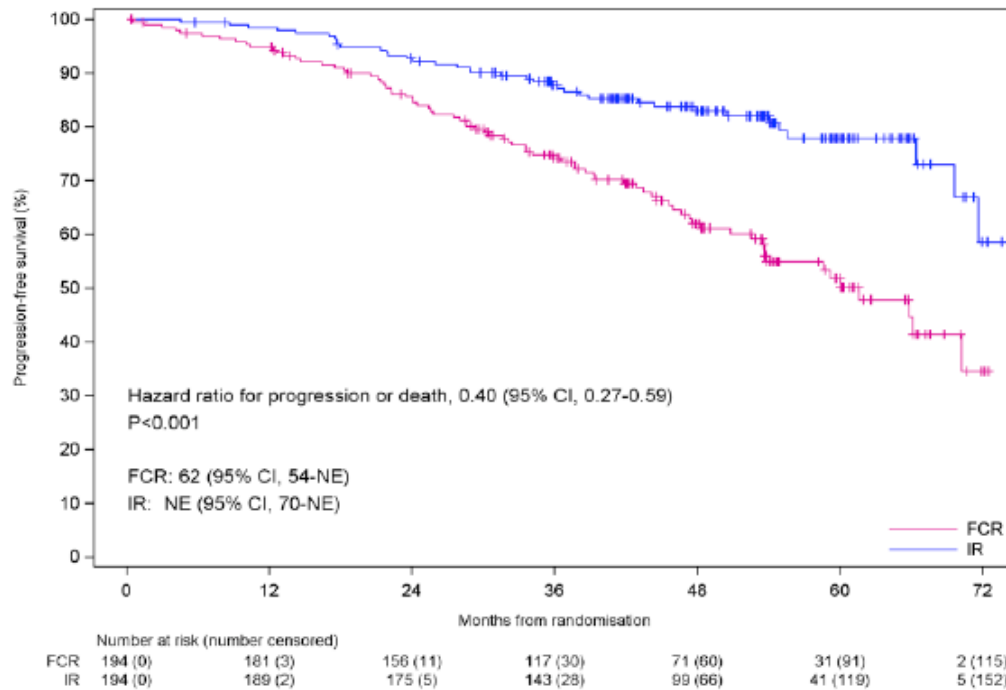
Number at risk							
—	44	38	34	30	21	17	9
—	70	67	64	60	50	40	18



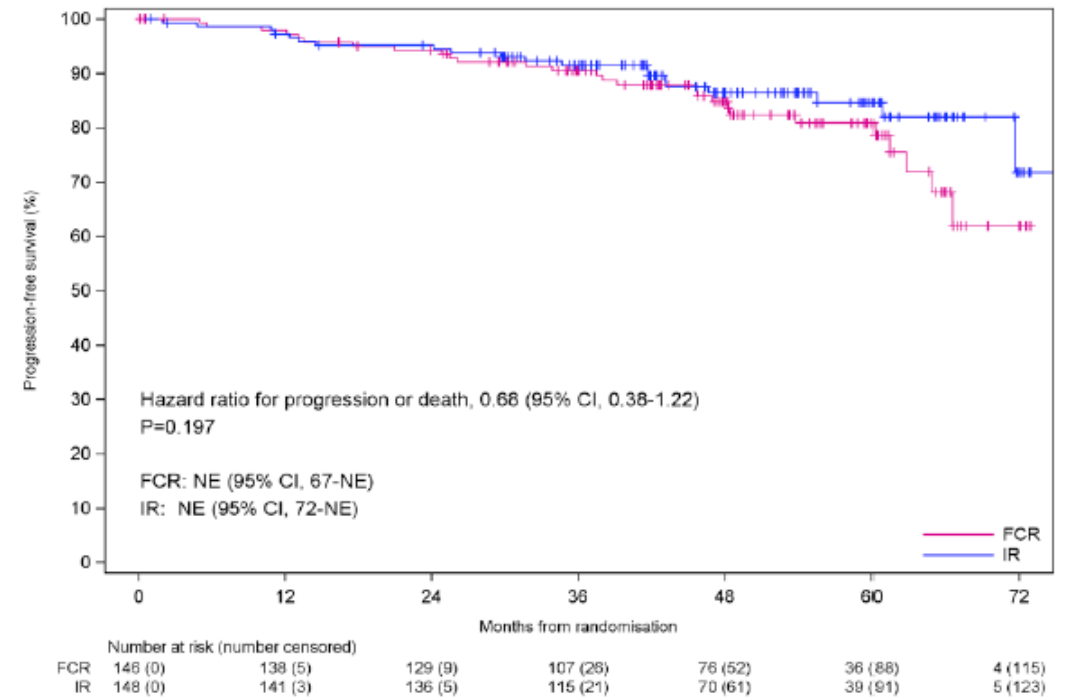
Number at risk							
—	354	321	293	273	228	174	98

Flair PFS by IGHV mutation status

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



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

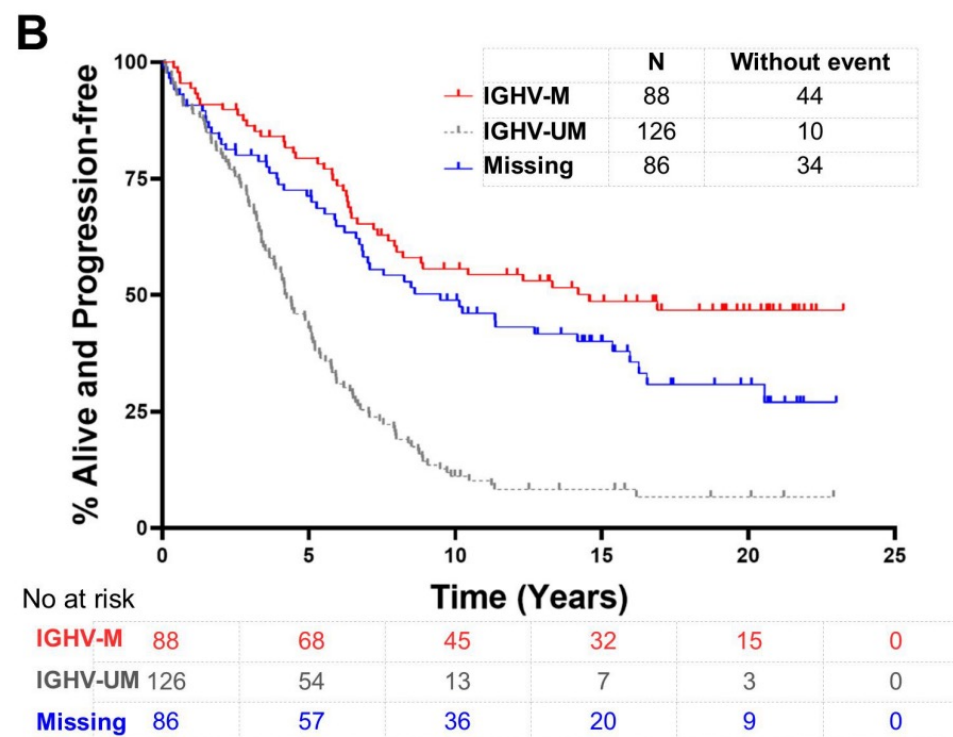
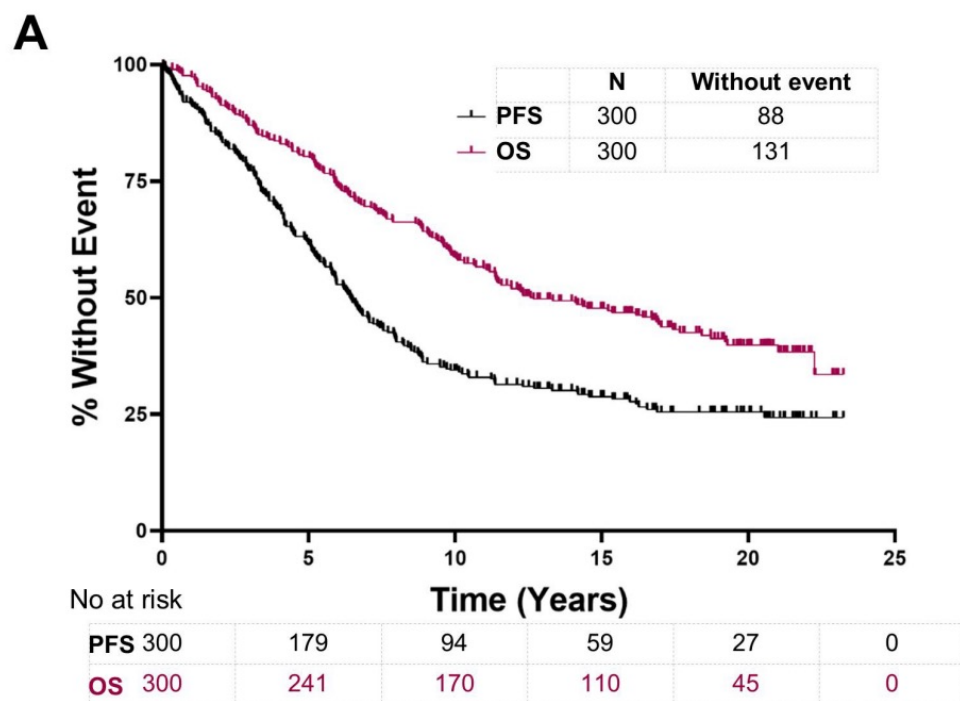


Stereotype Subset 2: n=46 (FCR 20; IR 26) → HR for PD or death 0.32 (95% CI, 0.06-1.76), p=0.191

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

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)
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)

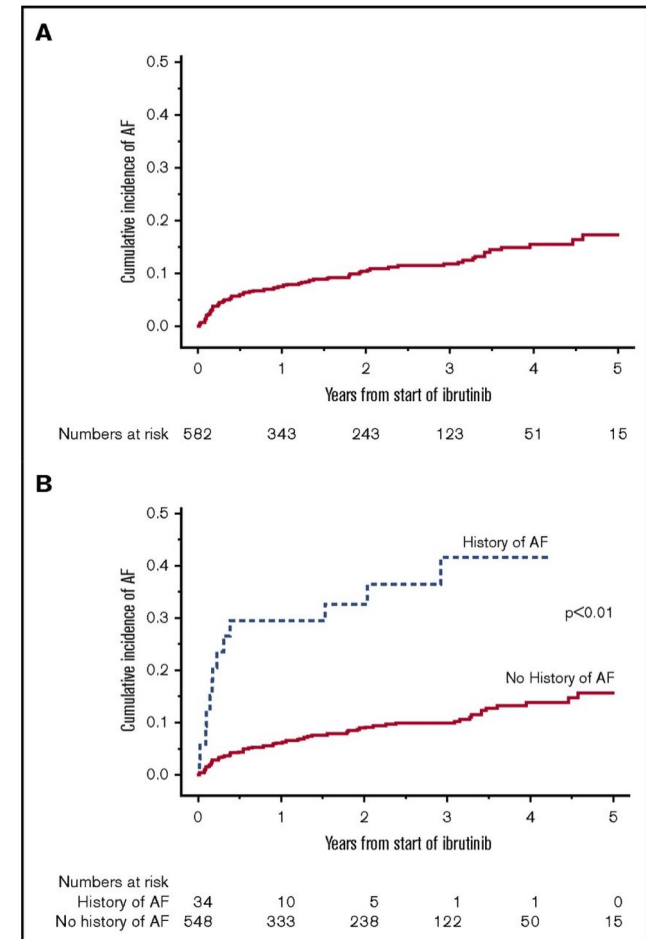
Increased risk of secondary malignancies

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

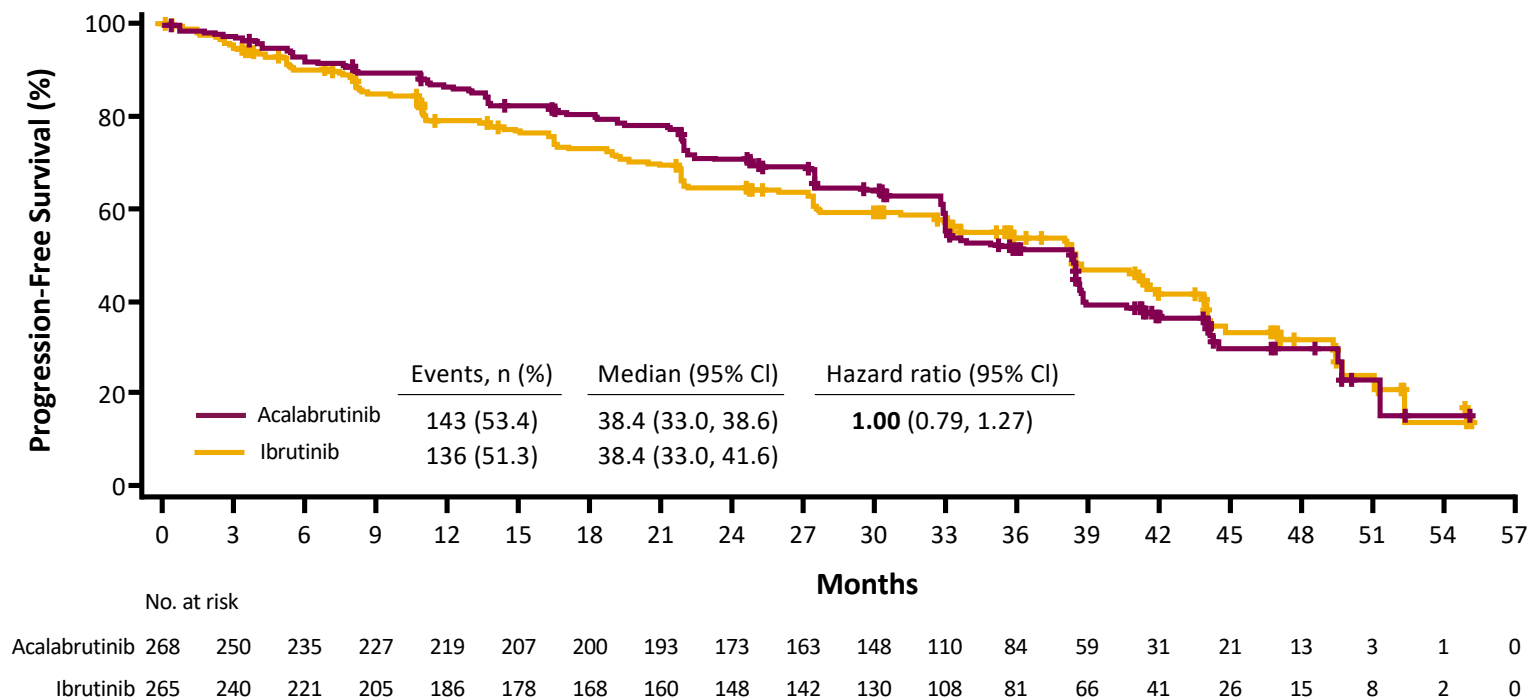
Issues with 1st generation BTKi

- 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)

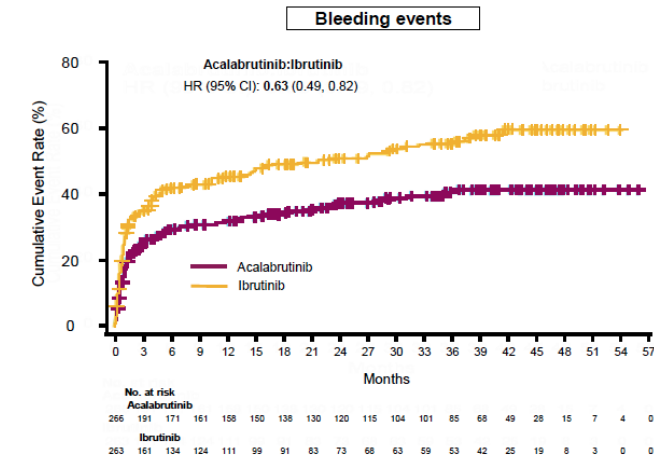
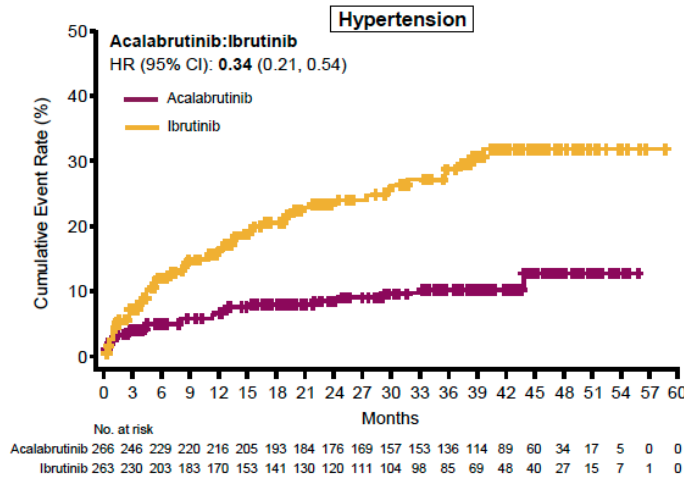
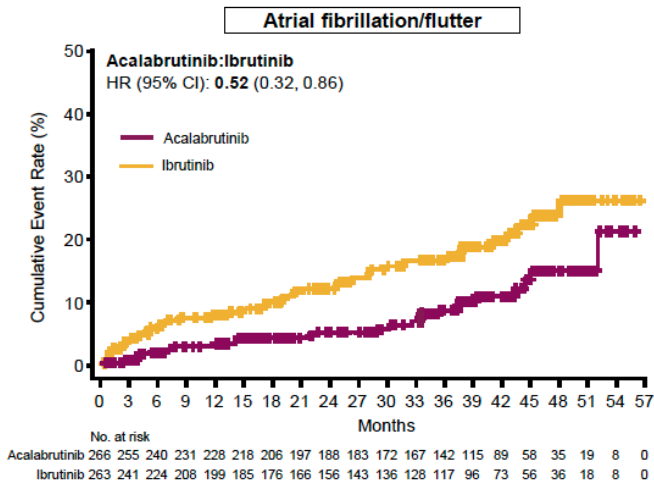


Can next-generation BTKi improve this?

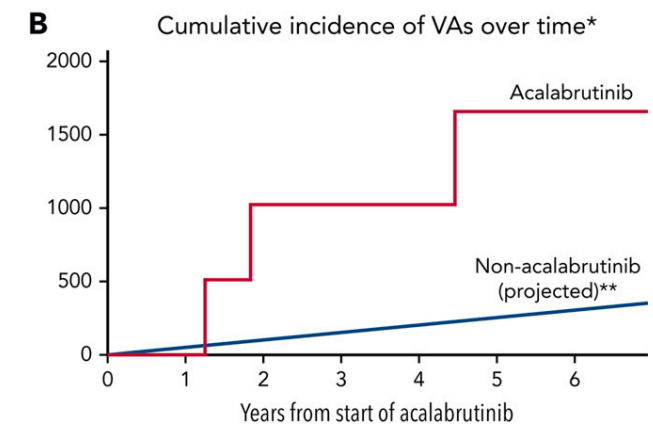
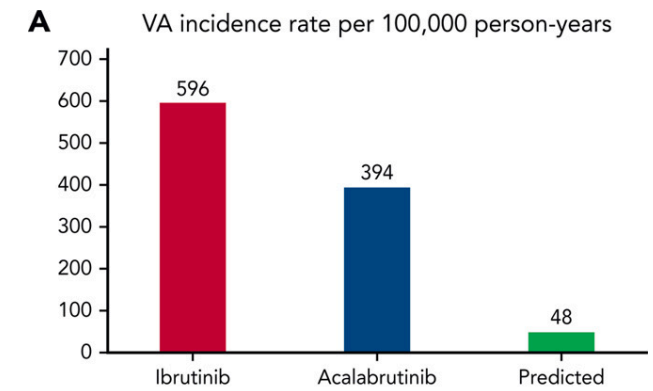
PFS Acalabrutinib = Ibrutinib



Cardiovascular toxicity under Acalabrutinib vs Ibrutinib



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



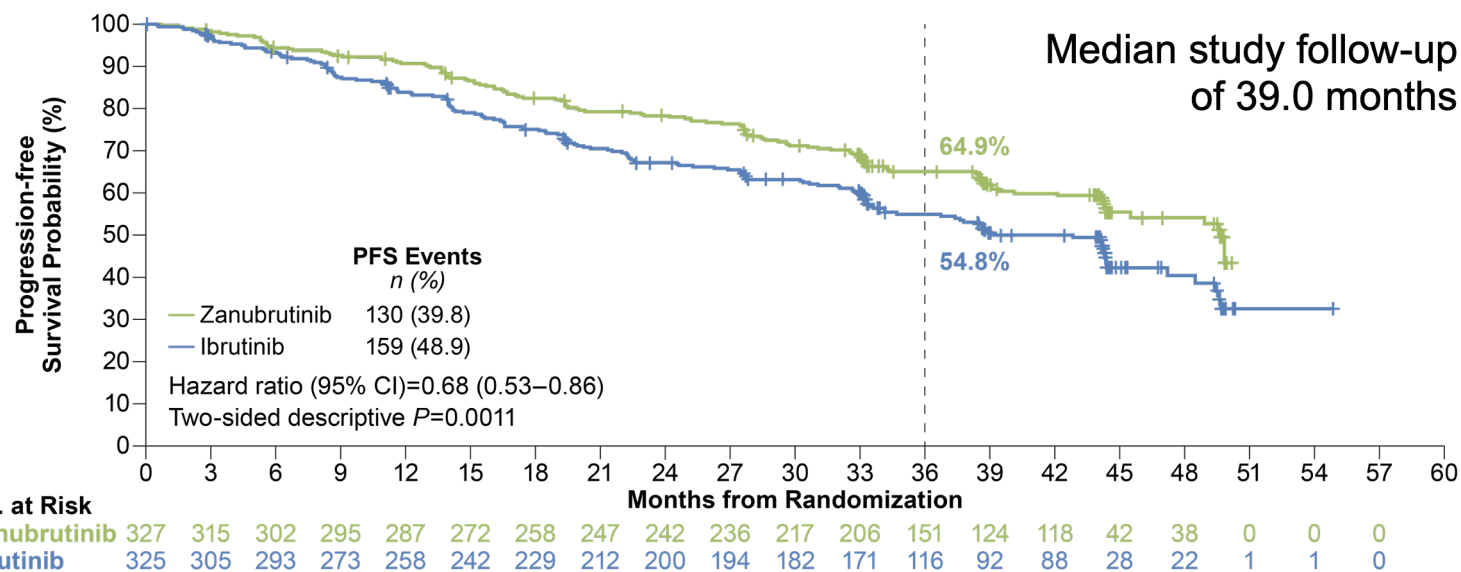
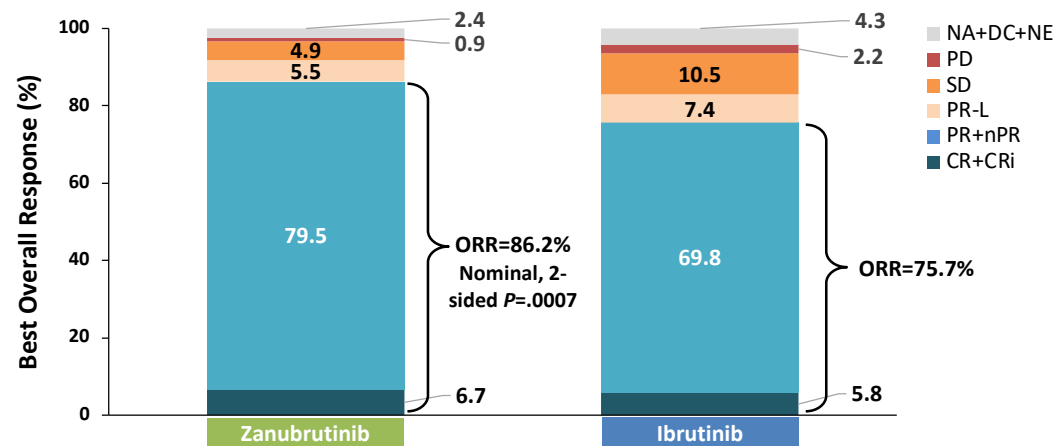
What about Zanubrutinib?

AEI, n (%)	Any Grade		Grade ≥3	
	Zanubrutinib (n=324)	Ibrutinib (n=324)	Zanubrutinib (n=324)	Ibrutinib (n=324)
≥1 AEI	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 fibrillation is less common with Zanubrutinib than with Ibrutinib, but rates of bleeding and hypertension and other toxicities similar.

Brown et al, NEJM 2021

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
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%
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)

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)

^aAEs are reported by Medical Dictionary for Regulatory Activities (MedDRA) superclass and preferred terms and National Cancer Institute Common Terminology Criteria for Adverse Events grade.

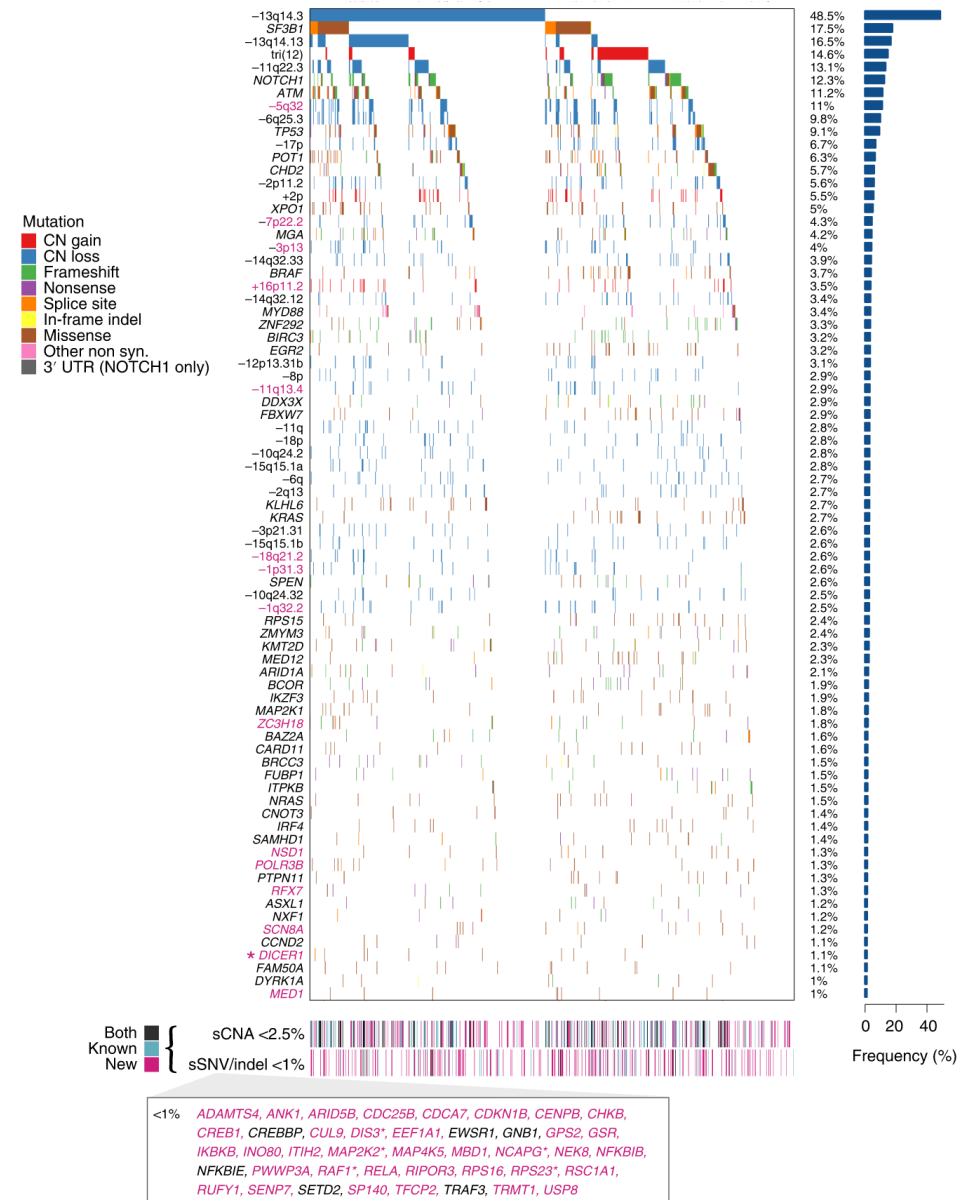
^bIncludes both “Neutropenia” and “Neutrophil count decreased.”

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



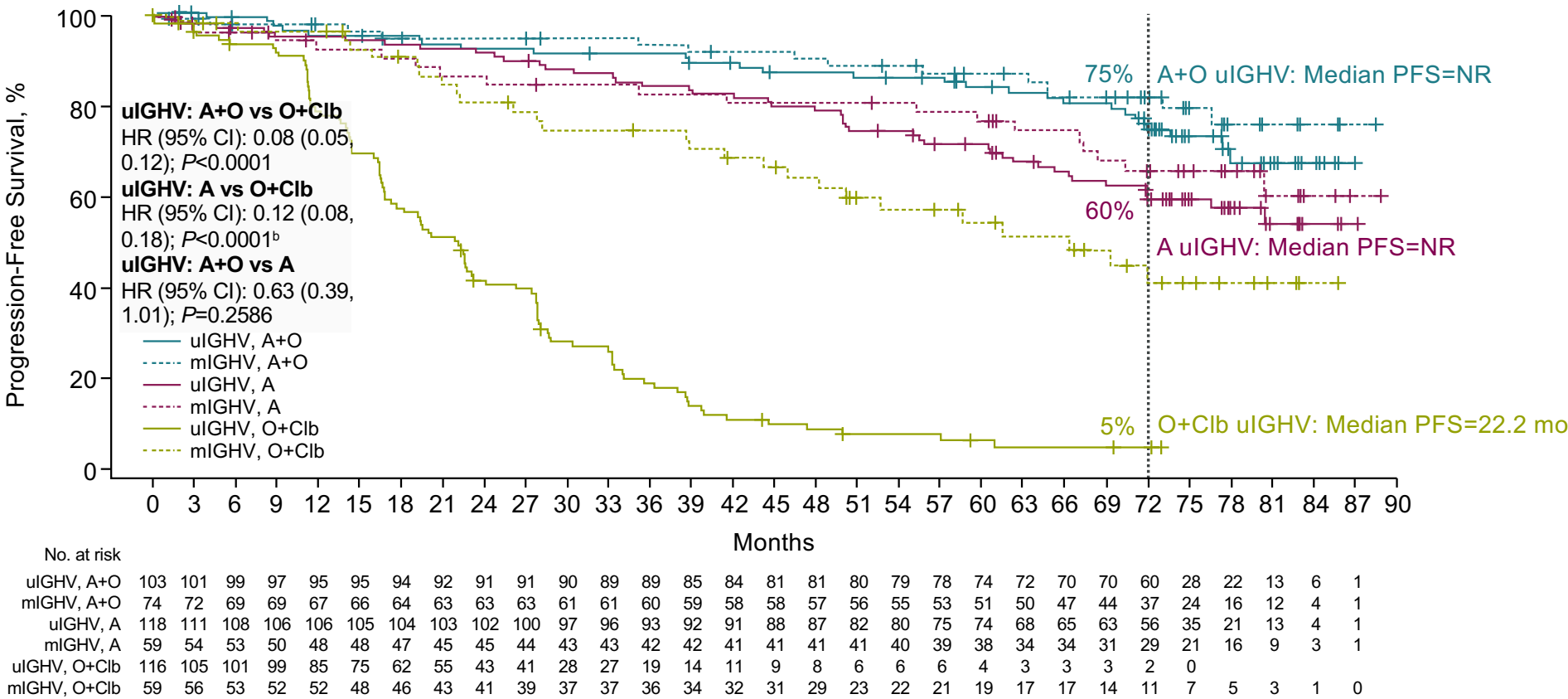


(Only) two clinically relevant genomic features

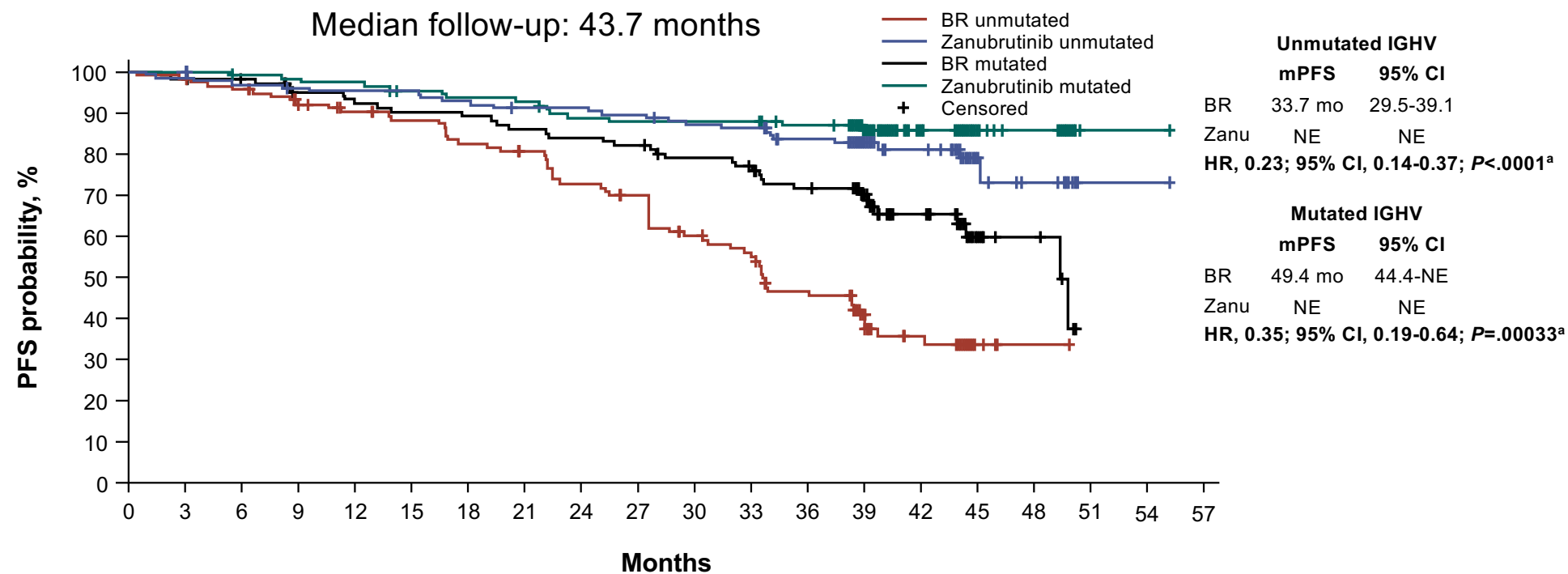
IGHV

TP53

PFS according IGHV status with Acalabrutinib



PFS according IGHV status with Zanubrutinib

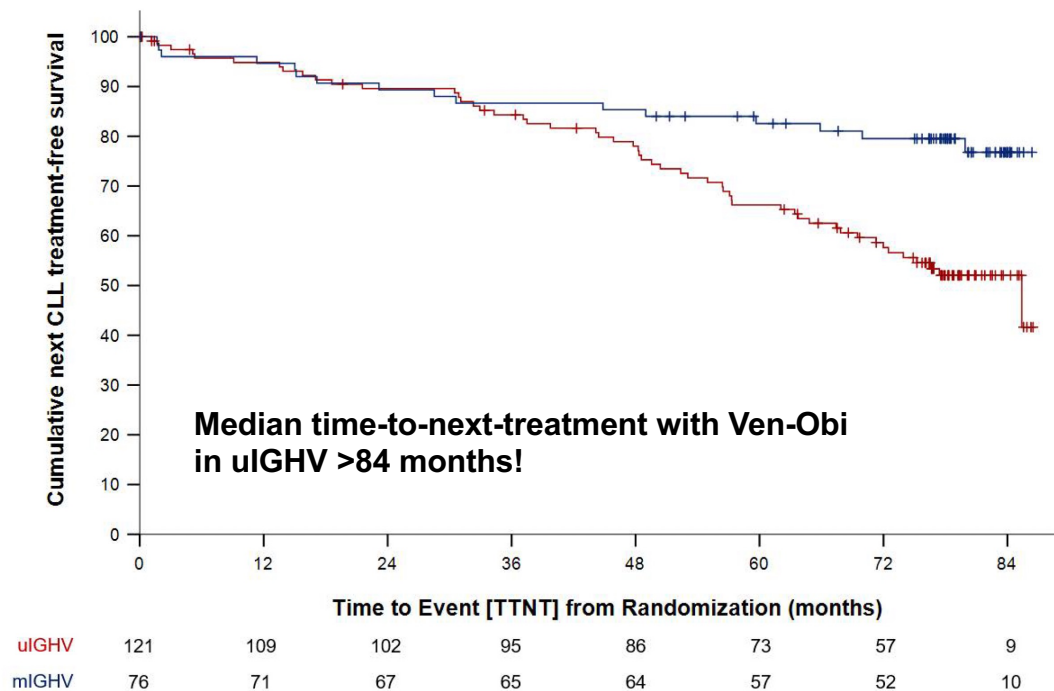


	No. at risk																			
	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57
BR unmutated	121	110	107	101	95	92	86	83	75	71	60	55	43	26	17	4	1	0		
Zanubrutinib unmutated	125	122	120	118	117	117	114	111	111	109	105	104	97	65	47	14	9	2	2	0
BR mutated	110	101	99	94	91	89	88	85	83	81	76	73	67	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

Shadman et al, ICML 2023

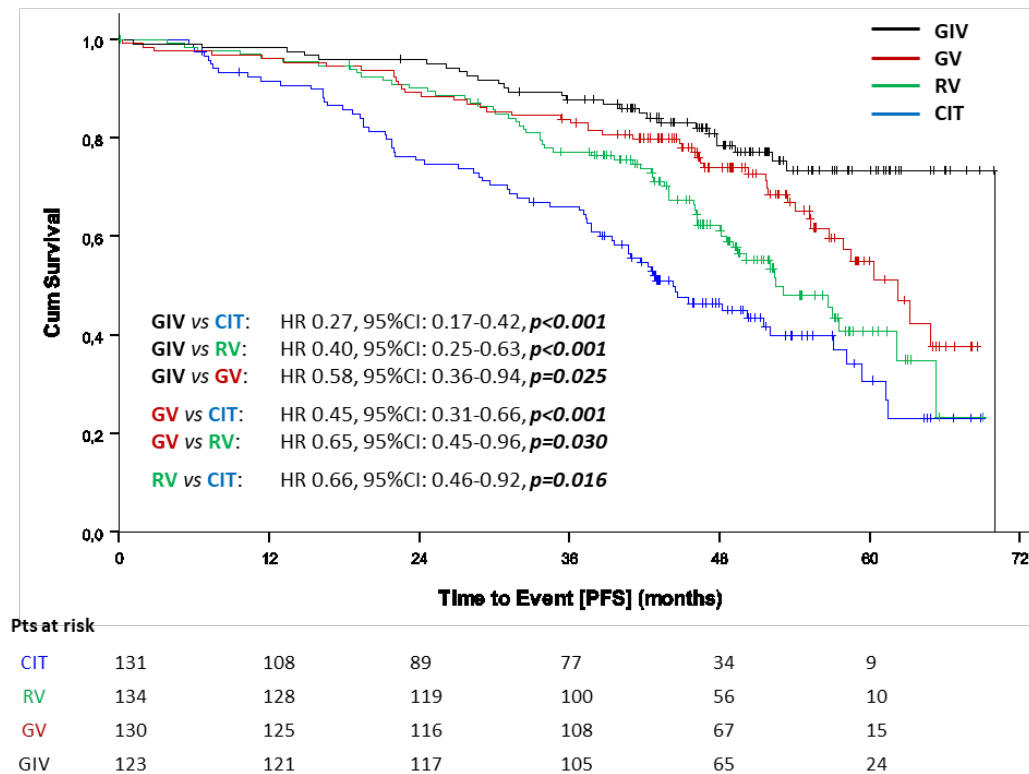
PFS according toIGHV status with Ven-Obi

Median fol

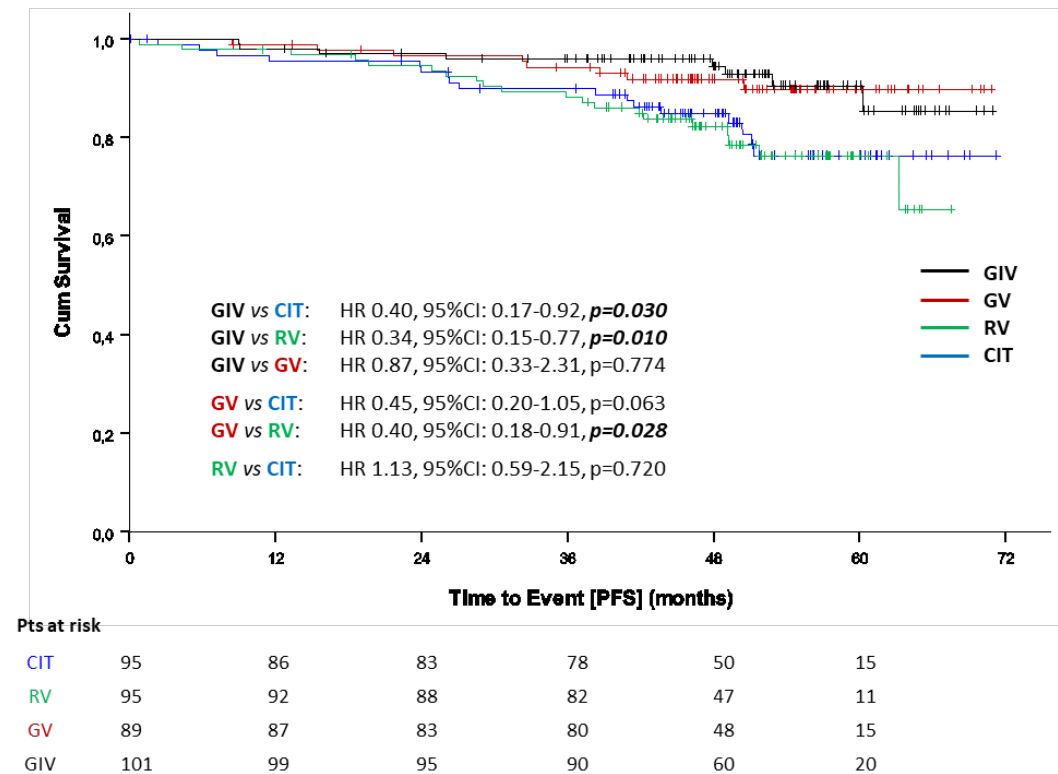


PFS according to IGHV status with Ven-Obi

PFS, patients with unmutated IGHV

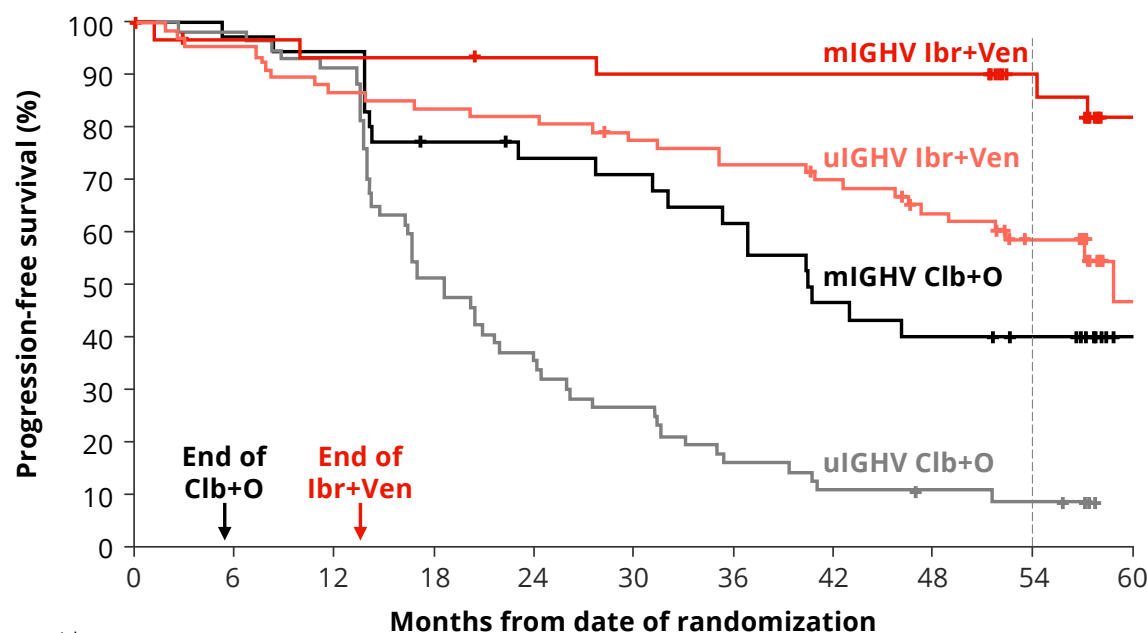


PFS, patients with mutated IGHV



PFS according to IGHV status with Ven-Ibru

Progression-Free Survival (ITT) by IGHV Status



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

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

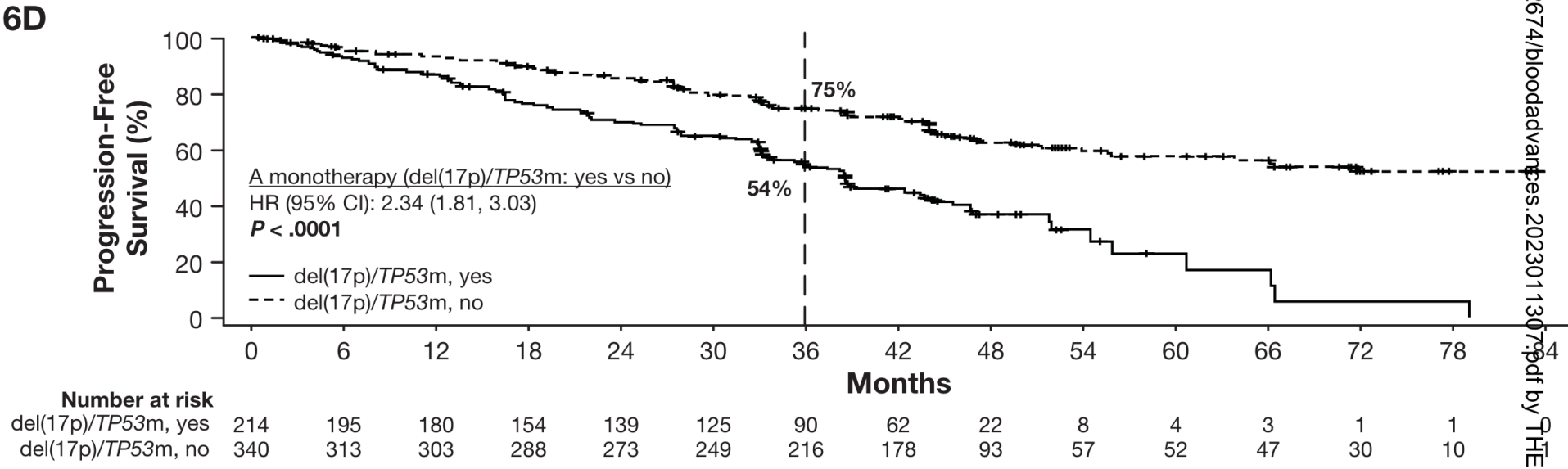


(Only) two clinically relevant genomic features

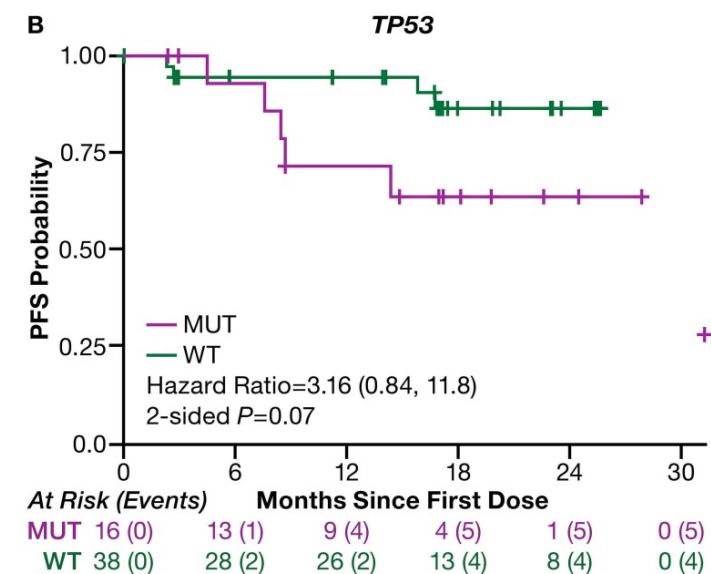
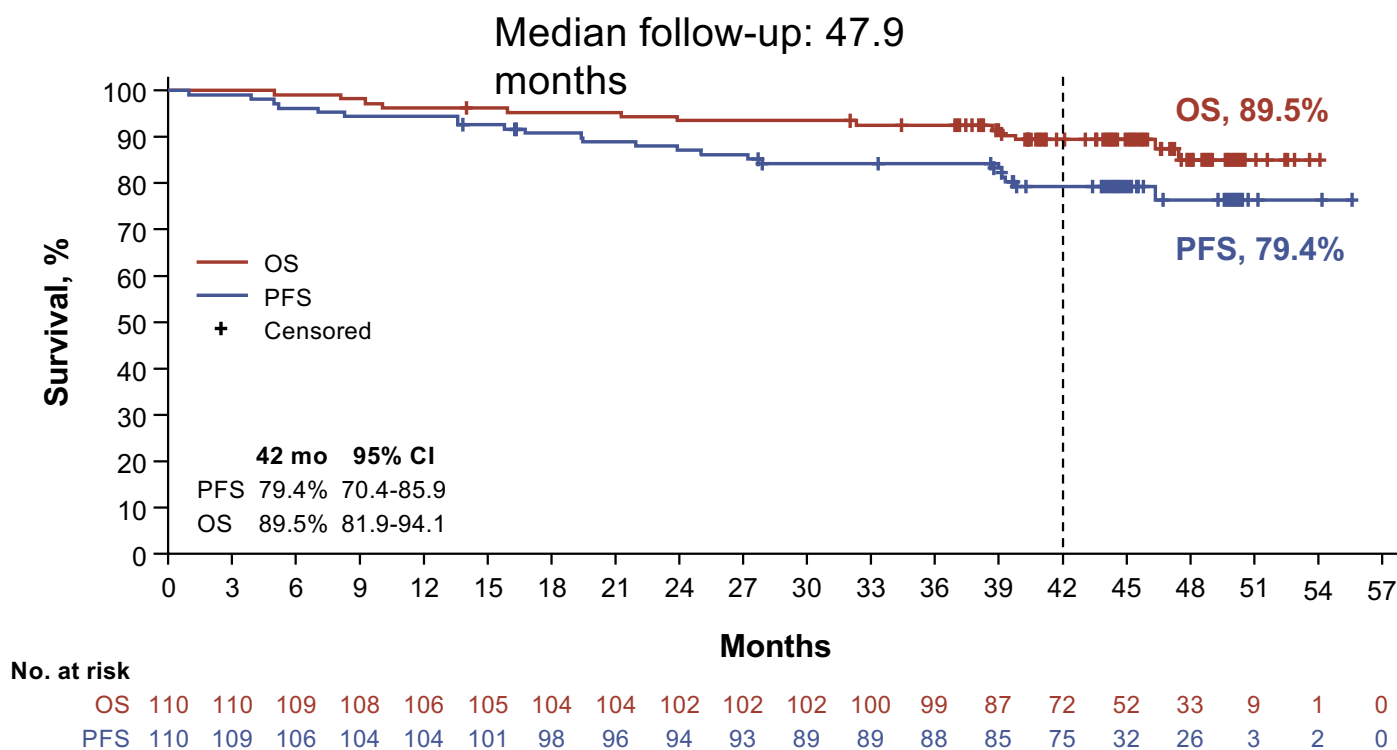
IGHV

TP53

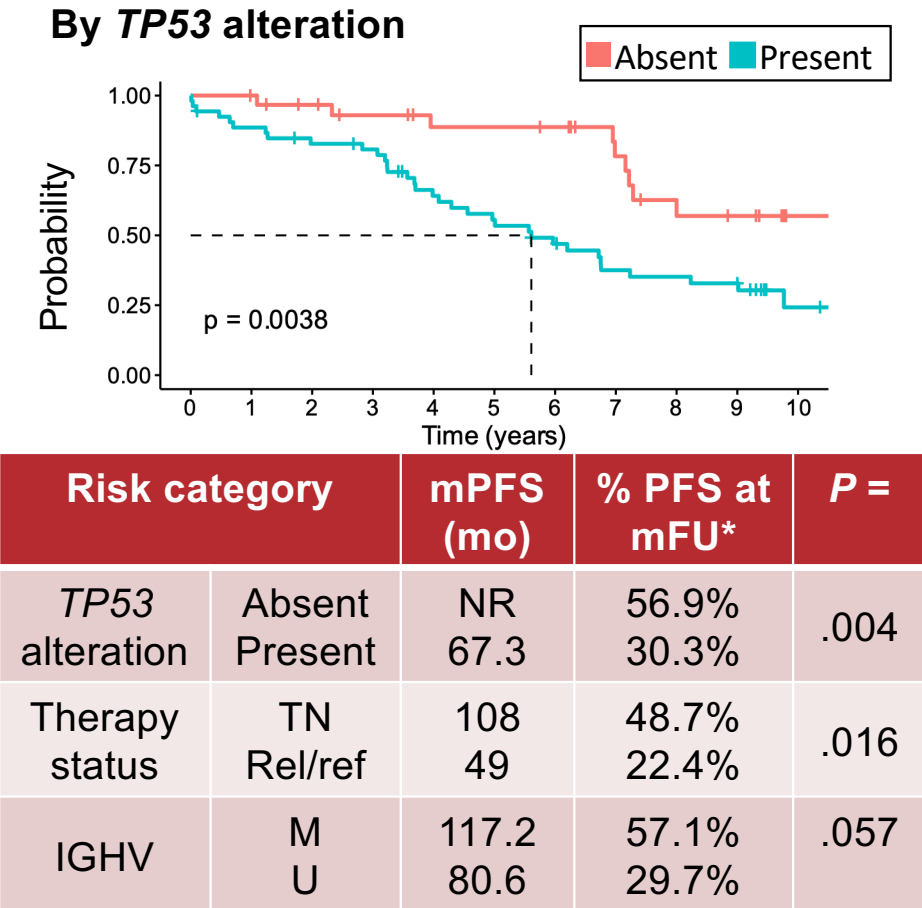
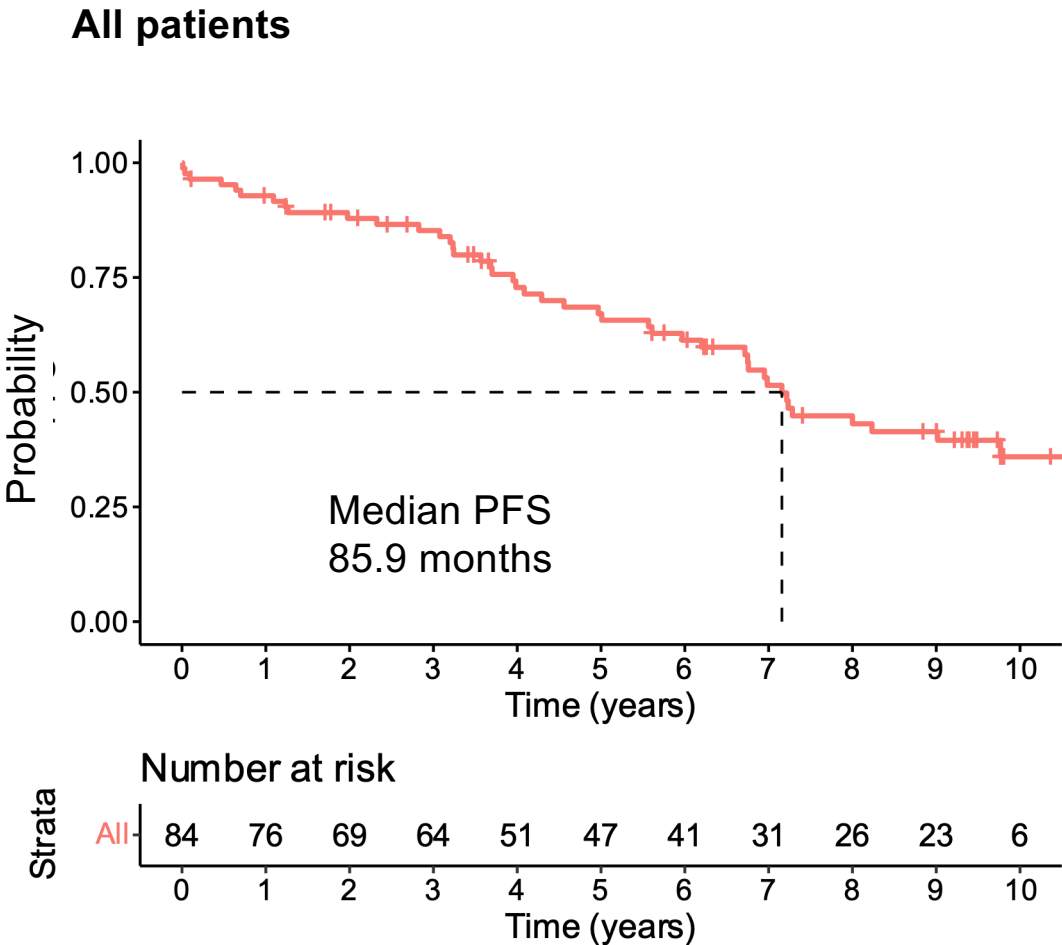
PFS according to *TP53* status with Acalabrutinib



PFS according to *TP53* status with Zanubrutinib



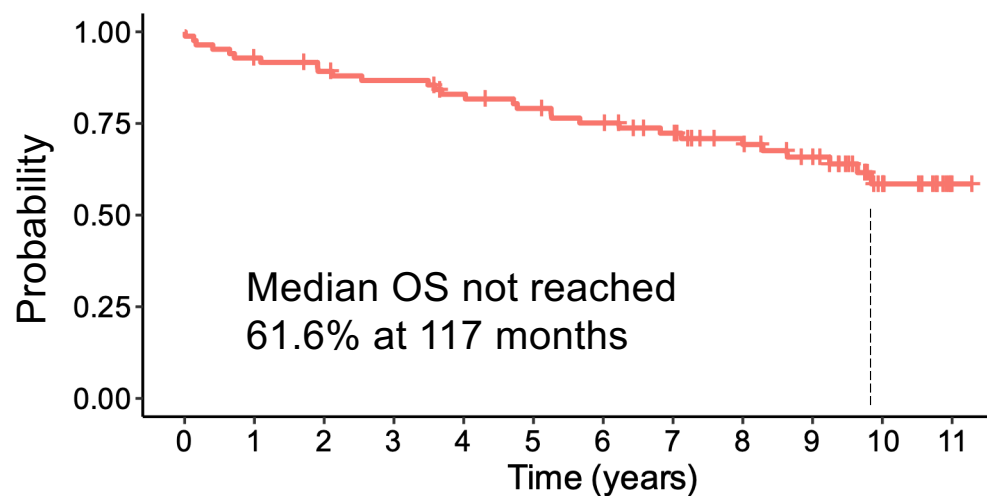
PFS according to *TP53* status with Ibrutinib



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

OS according to *TP53* status with Ibrutinib

All patients

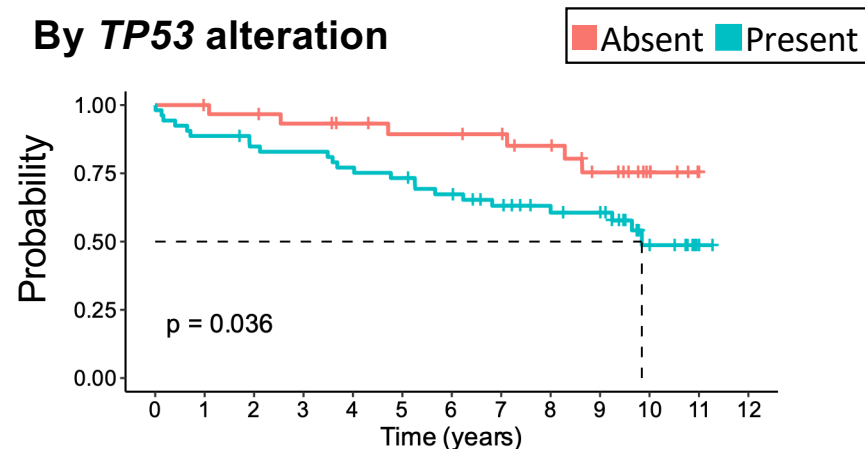


Number at risk

Strata	0	1	2	3	4	5	6	7	8	9	10	11
All	84	77	73	70	65	61	57	51	43	37	17	3

Time (years)

By *TP53* alteration

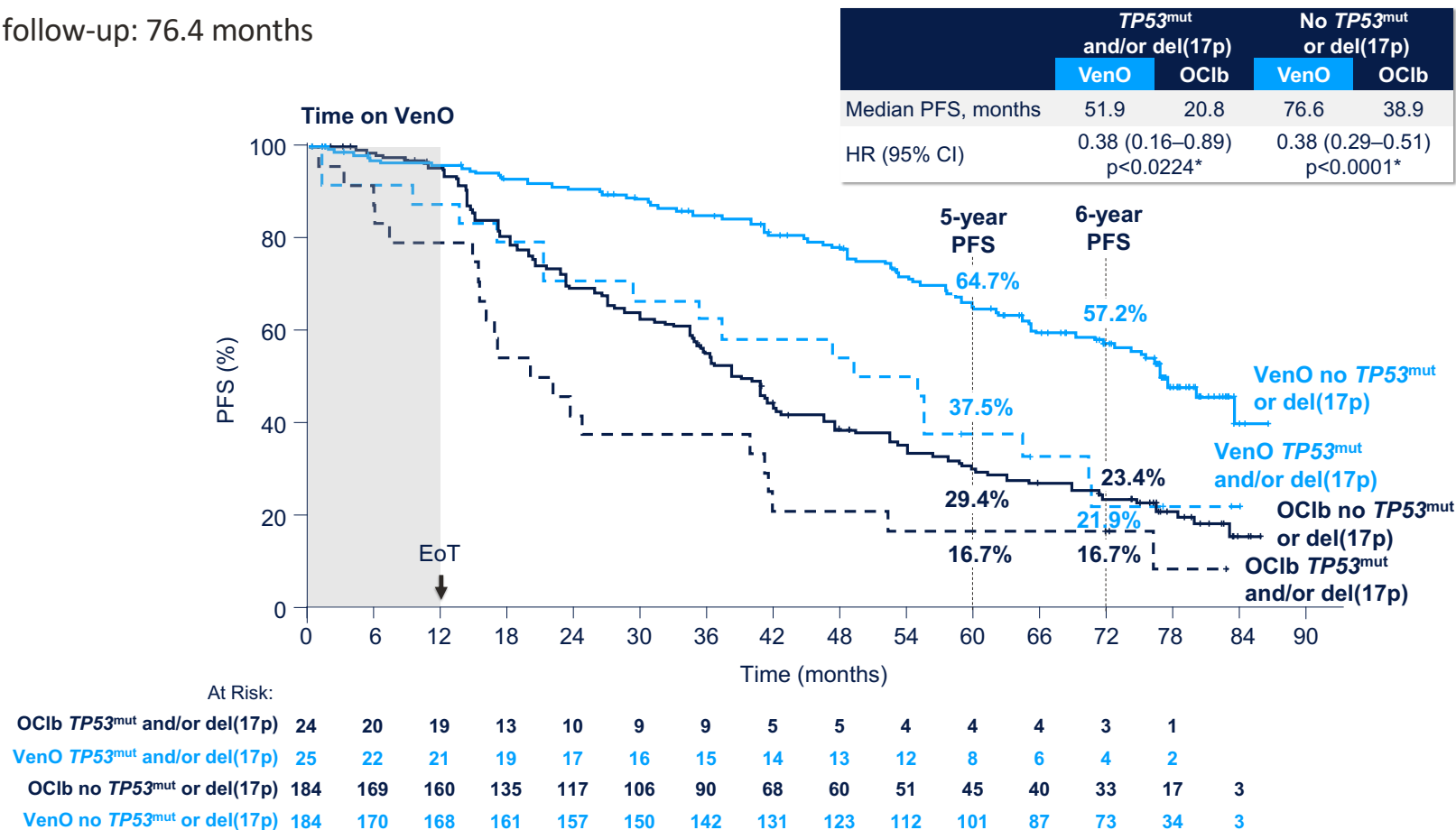


Risk category		mOS (m0)	% OS at mFU*	P =
TP53 alteration	Absent	NR	75.3	.036
	Present	118	54.1	
Therapy status	TN	NR	73.8	.004
	Rel/ref	104	41.6	
IGHV	M	NR	77	.036
	U	118	52.7	

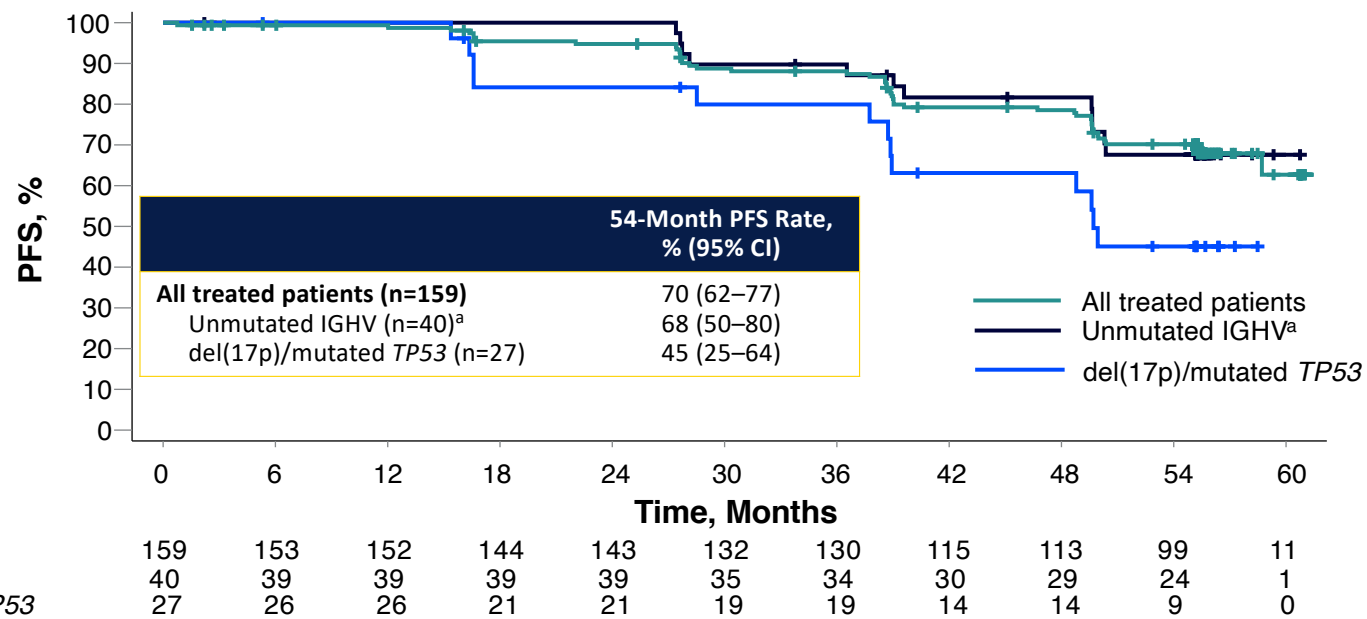
TN; treatment-naïve; rel/ref – relapsed/refractory;
IGHV, M, mutated; U, unmutated

PFS according to *TP53* status with Ven-Obi

Median follow-up: 76.4 months



PFS according to *TP53* status with Ven-Ibru



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



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**

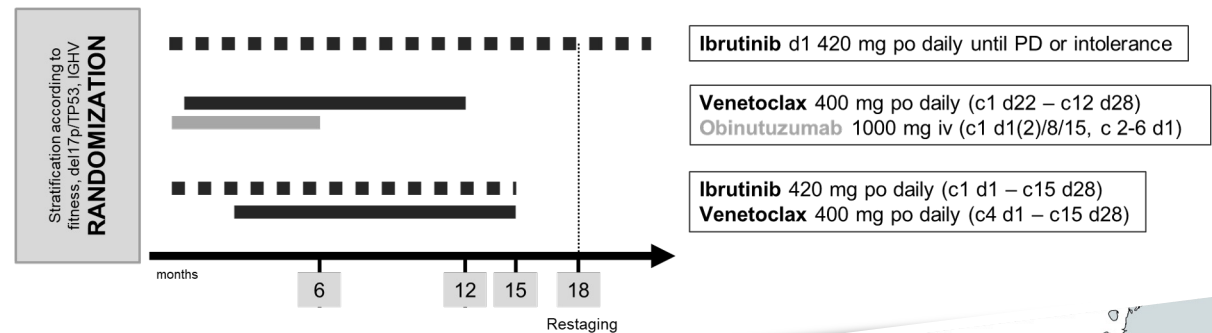


**Venetoclax
Ibrutinib**

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

DEUTSCHE
STUDIENGRUPPE



The Israeli CLL Association (ICLLA)



The Israeli CLL Study Group (ICLSG)



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**