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Show of the powerful: are we already curing CLL?

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Disclosures

AstraZeneca – Research funding, advisory board participation, speaking engagements

Abbvie – Advisory board participation

BeiGene – Research funding

BMS – Consulting

Eli Lilly – Advisory board participation, speaking engagements

Janssen – Speaking engagements

Galapagos – Advisory board participation

Agenda

Cure vs. Functional Cure

Cure – Have we done it?

Functional Cure – Have we done it?



Cure vs. Functional Cure – What matters?

ChatGPT Definitions:

Cure - In cancer care, a "**cure**" is typically defined as the **complete eradication of cancer from the body**, with **no signs of the disease returning for a prolonged period**—often five years or more after treatment ends.

Functional Cure - Cancer is still technically present in the body, but it is controlled so effectively that it causes **no symptoms, doesn't grow or spread**, and **doesn't affect the patient's lifespan**.

So let's talk about "Cure"

1) Complete eradication of cancer from the body:

- iwCLL – Complete Response

+

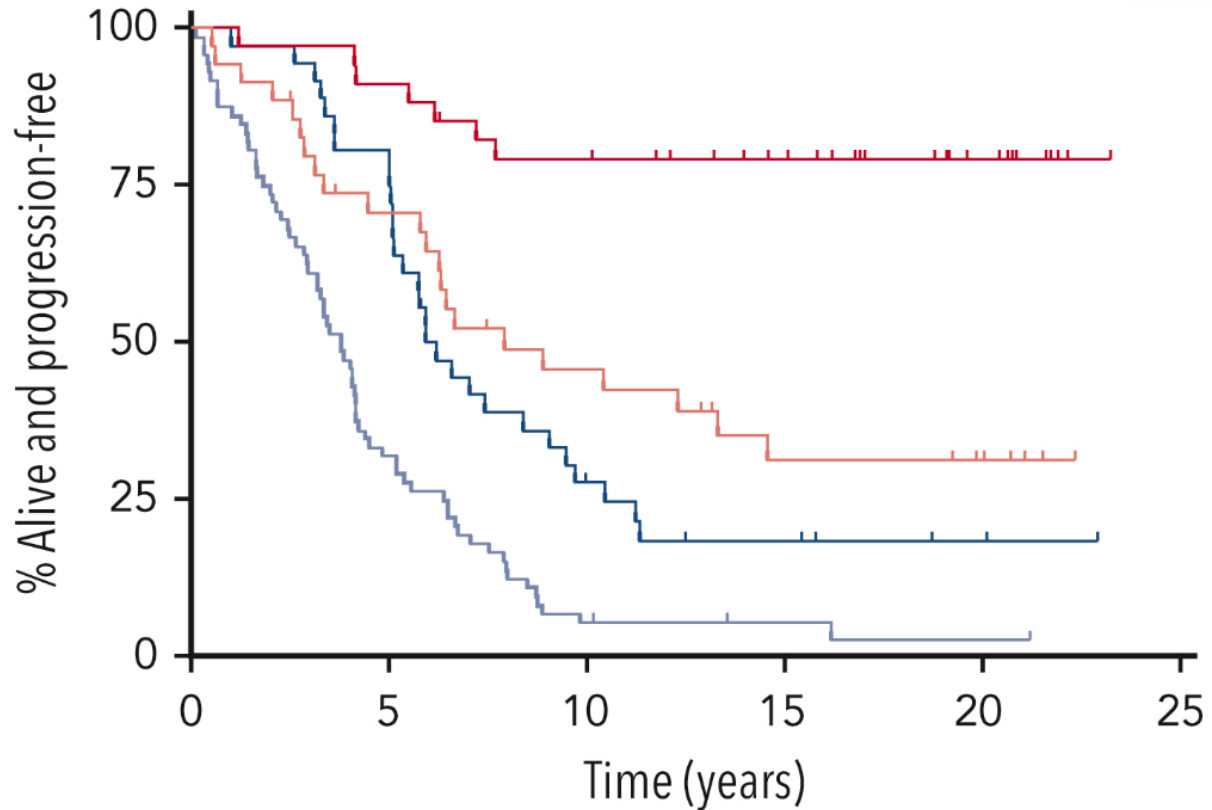
- undetectable MRD - Defined as 10^{-6} via modern day testing

2) No signs of the disease returning for a prolonged period:

- >5 years of follow-up

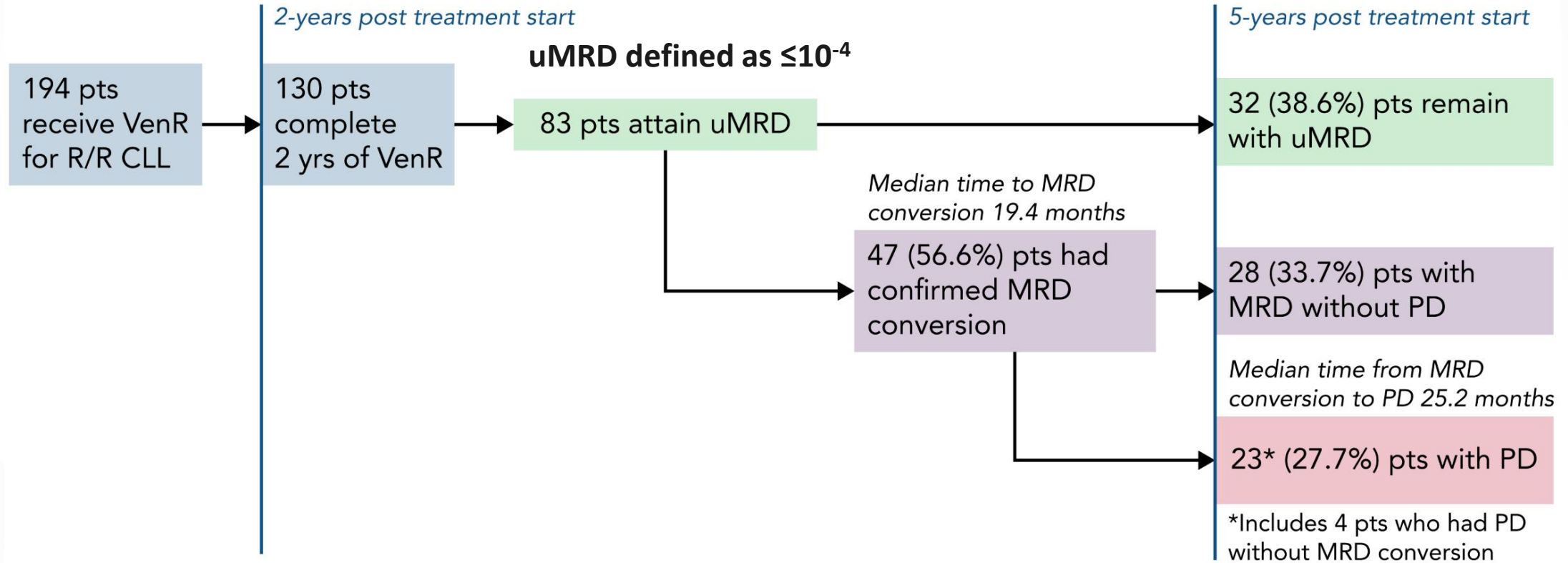
Long term FCR Data - MRD

. Minimal residual disease (MRD) was assessed posttreatment by a polymerase chain reaction-based ligase chain reaction assay (**sensitivity 0.01%**). **MRD2**

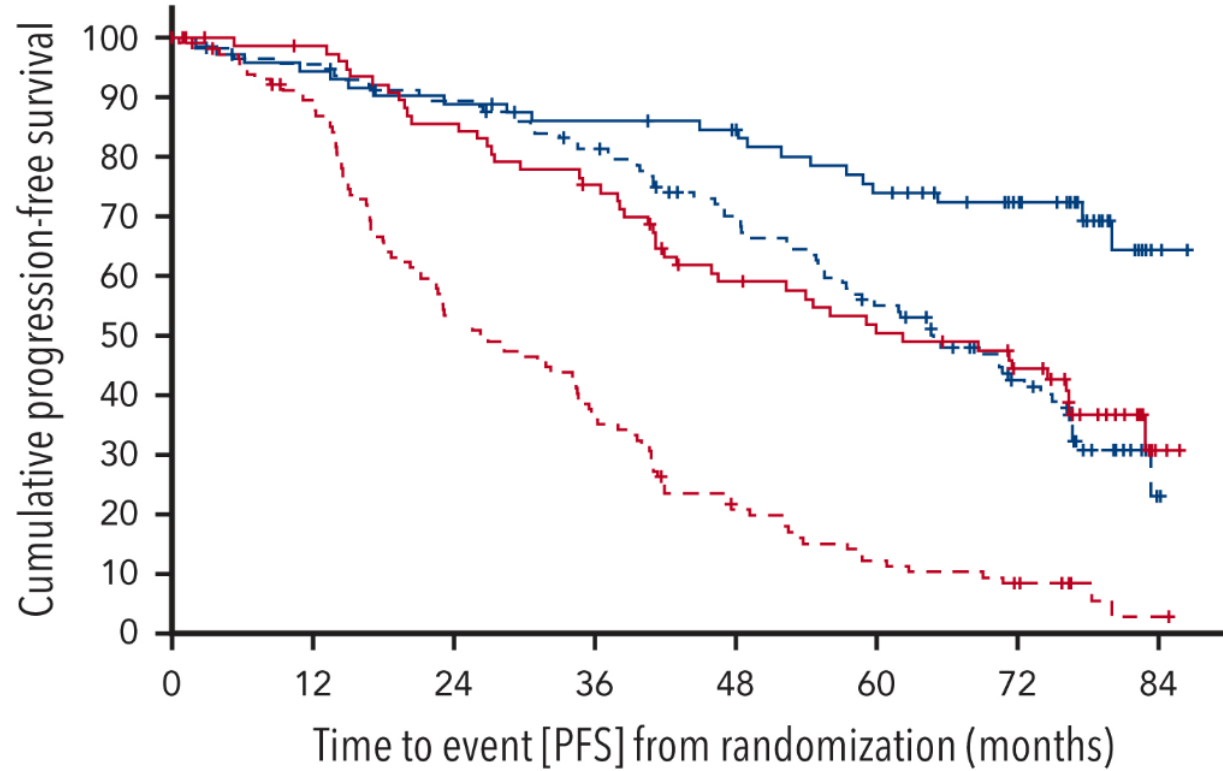


	No at risk	0	5	10	15	20	25
IGHV-M MRD-neg	34	31	26	20	9	0	0
IGHV-M MRD-pos	35	23	14	8	6	0	0
IGHV-UM MRD-neg	36	27	9	5	2	0	0
IGHV-UM MRD-pos	72	23	4	2	1	0	0

MRD Follow up of MURANO



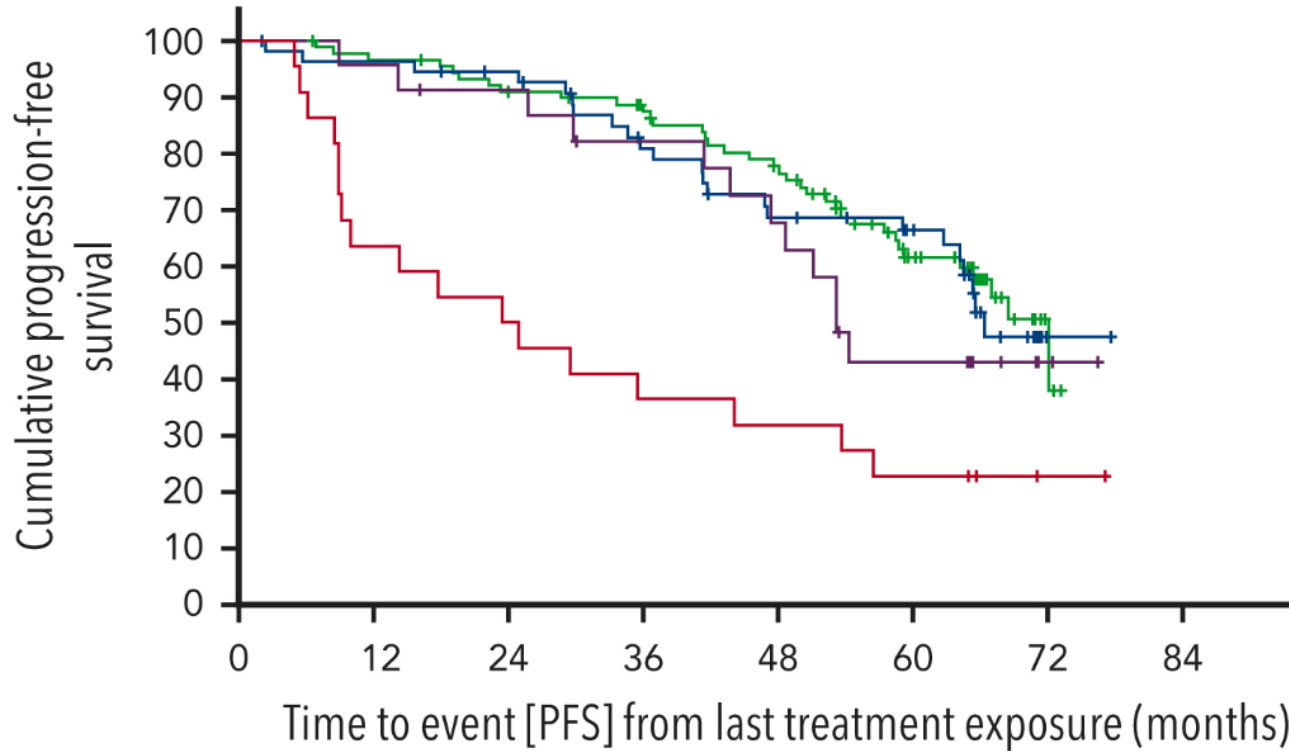
PFS 5-year Follow up of CLL14



— Ven-Obi & mIGHV	76	68	64	60	57	49	39	2
--- Ven-Obi & uIGHV	121	110	101	90	73	57	37	1
— Clb-Obi & mIGHV	83	76	66	57	42	35	28	2
--- Clb-Obi & uIGHV	123	101	59	41	22	13	8	1

5-year Follow up by MRD of CLL14

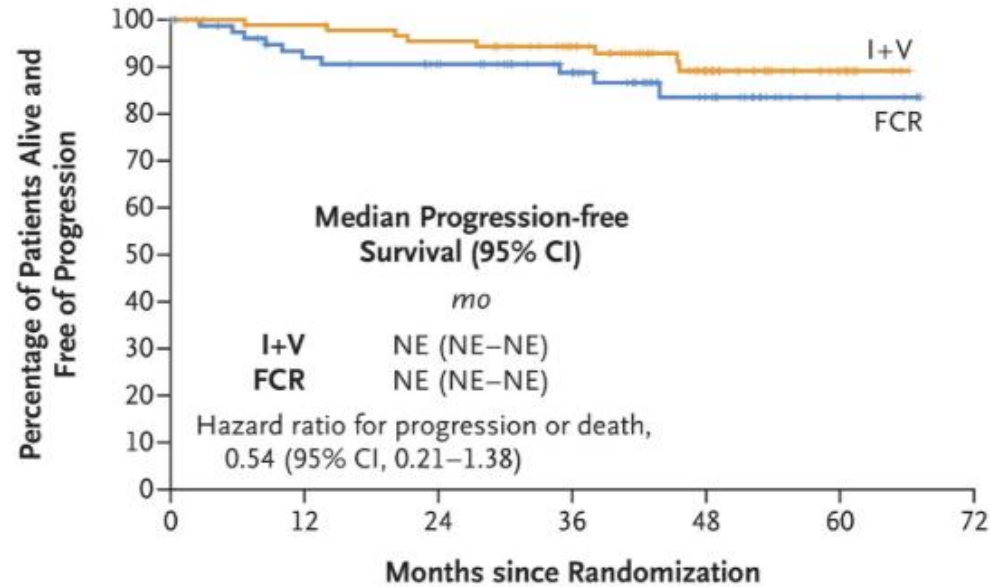
Ven-Obi



$< 10^{-6}$	90	86	79	73	63	38	4	0
$\geq 10^{-6}$ and $< 10^{-5}$	56	53	50	40	33	26	2	0
$\geq 10^{-5}$ and $< 10^{-4}$	23	22	20	17	14	8	2	0
$\geq 10^{-4}$	23	14	11	8	7	5	1	0

FLAIR – Ibrutinib + Venetoclax

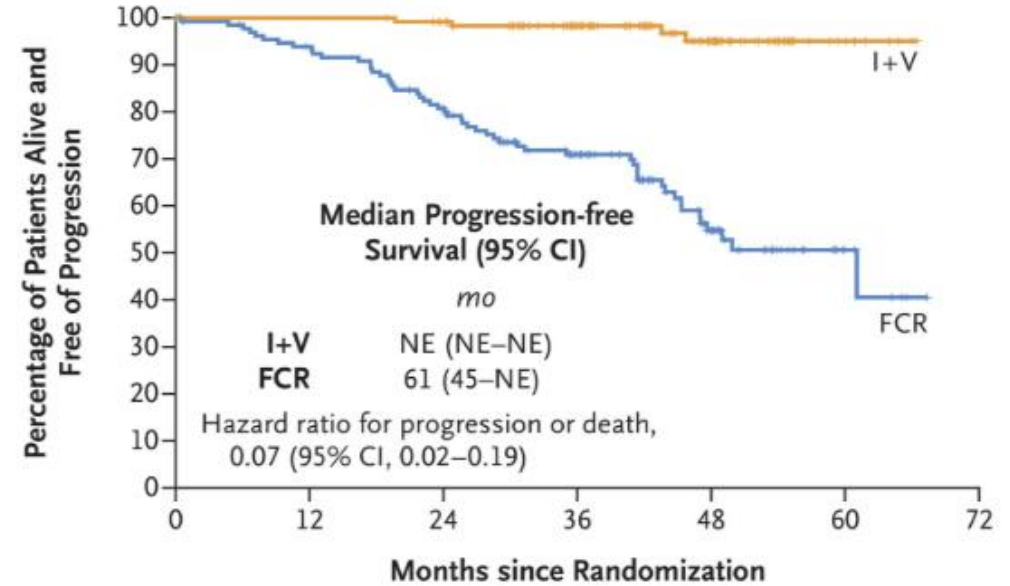
C Patients with Mutated *IGHV*



No. at Risk (no. with data censored)

I+V	93 (0)	88 (4)	84 (5)	70 (18)	42 (45)	11 (74)	0 (85)
FCR	80 (1)	67 (7)	61 (12)	49 (23)	25 (45)	5 (65)	0 (70)

B Patients with Unmutated *IGHV*

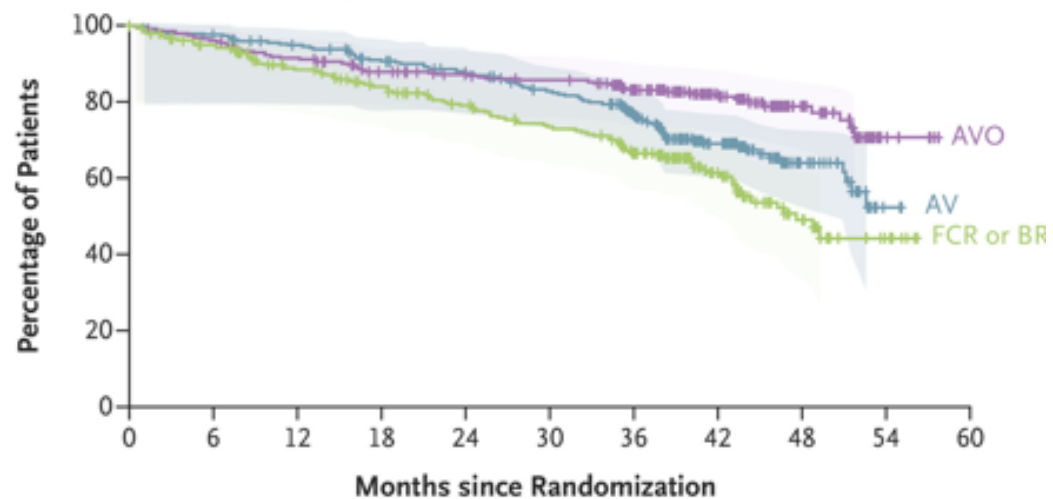


No. at Risk (no. with data censored)

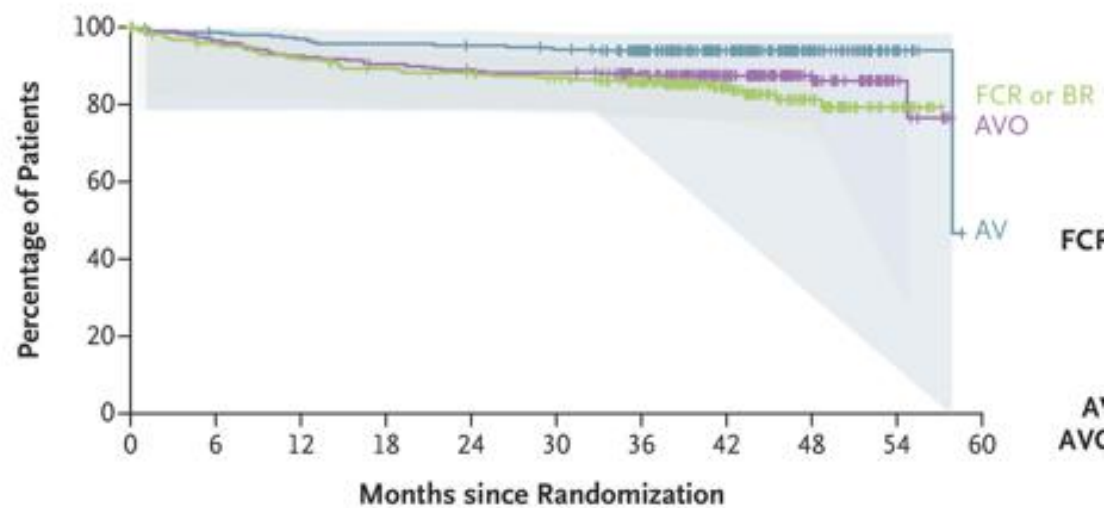
I+V	123 (1)	122 (1)	117 (5)	89 (32)	47 (72)	8 (111)	0 (119)
FCR	138 (1)	122 (8)	103 (10)	76 (25)	35 (54)	6 (80)	0 (85)

AMPLIFY – AV or AVO v.s CIT

A Progression-free Survival, Assessed by Blinded Independent Central Review



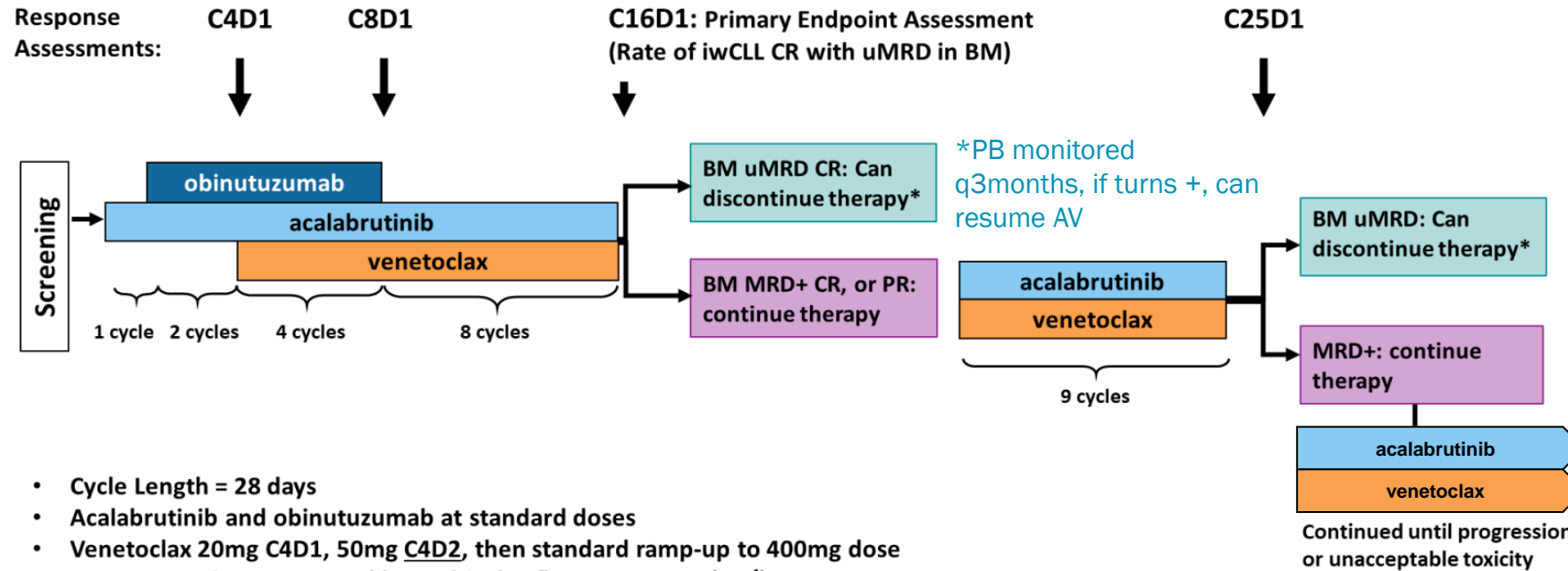
C Overall Survival



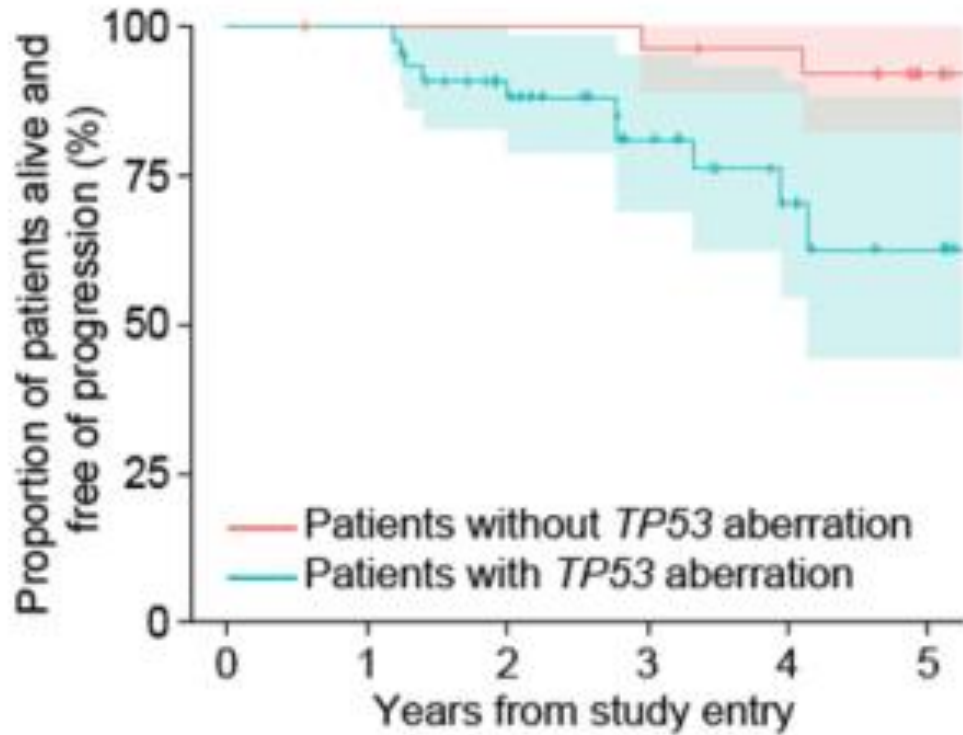
AVO in High-Risk Patients

Key Eligibility Criteria

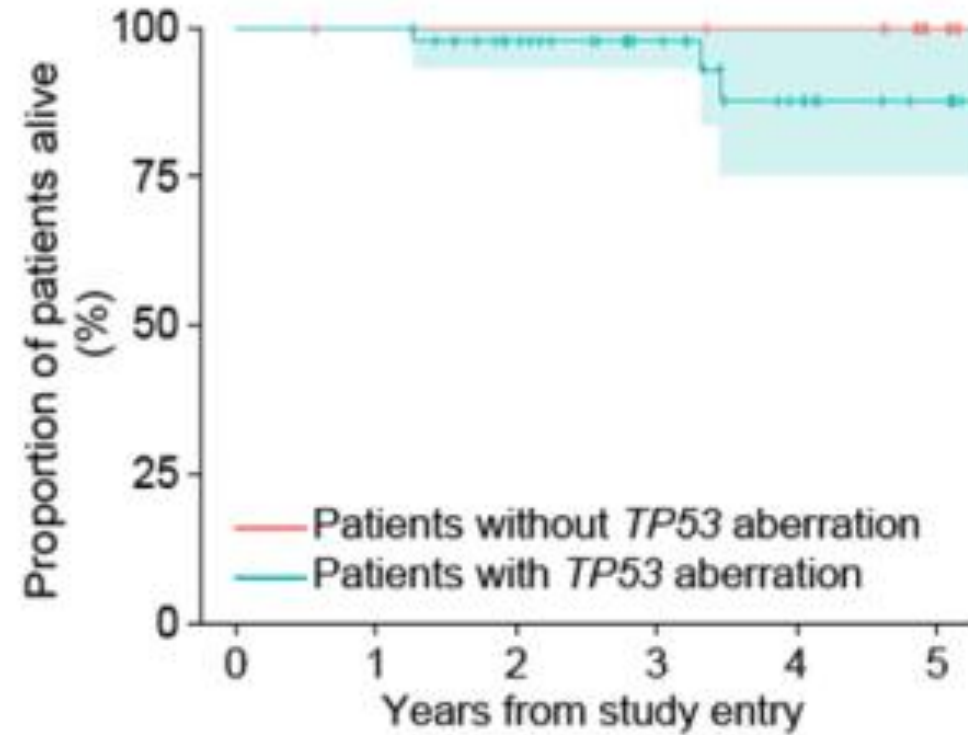
- Aged ≥ 18 years and ECOG PS ≤ 2
- Expansion cohort: *TP53*-aberrant disease (del[17p] or *TP53*mut [any VAF eligible])
- No Richter transformation or CNS involvement



AVO in High-Risk Patients



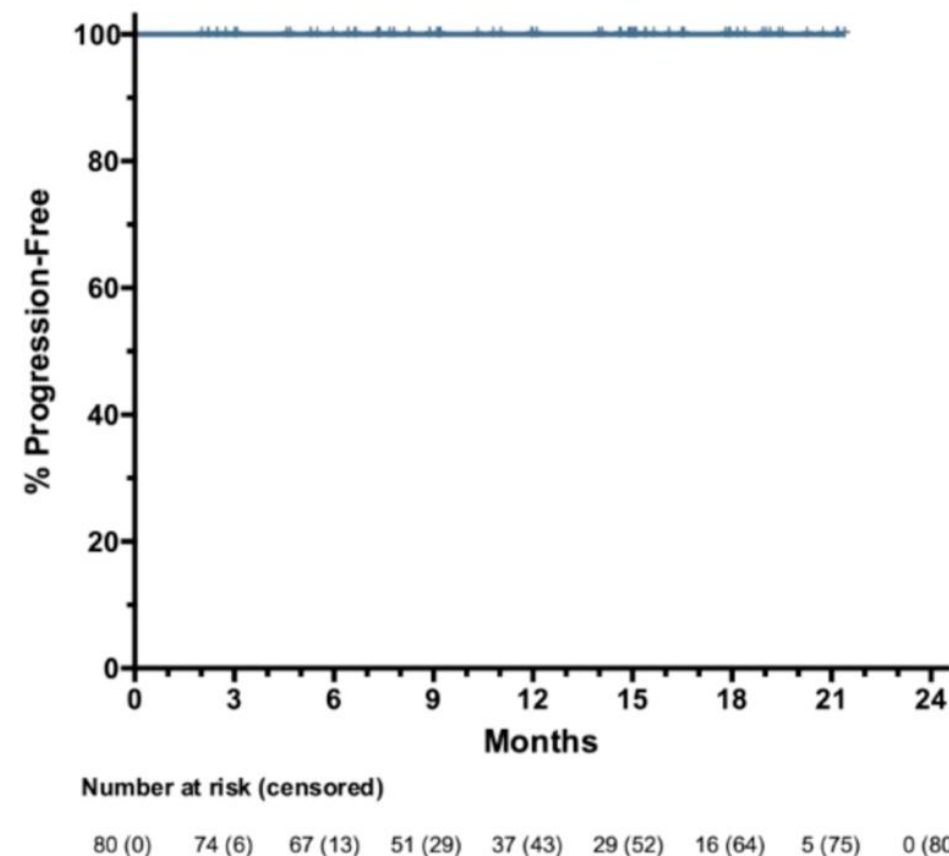
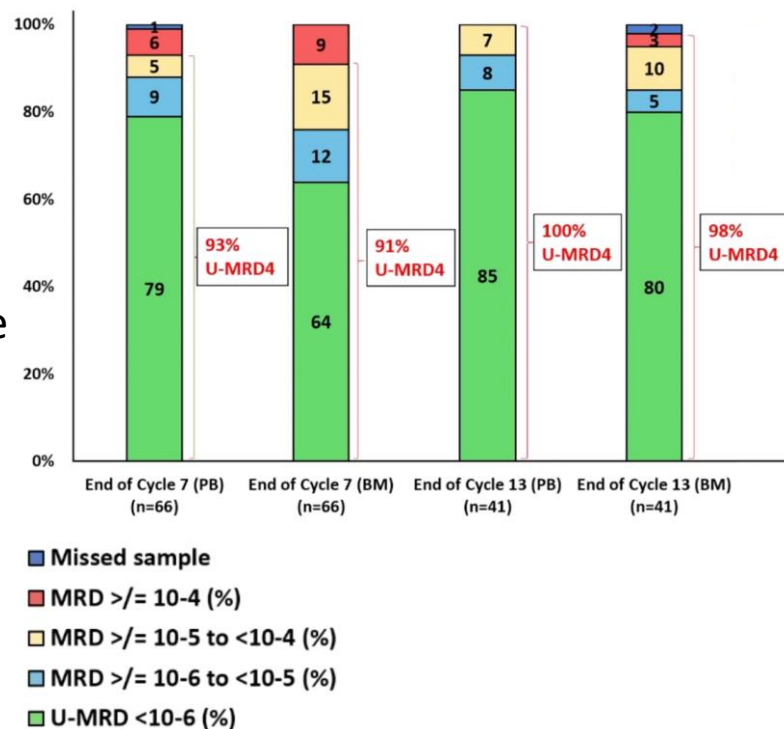
	Number at risk					
	0	1	2	3	4	5
Patients without <i>TP53</i> aberration	27	26	26	25	24	15
Patients with <i>TP53</i> aberration	45	45	32	20	11	6



	Number at risk					
	0	1	2	3	4	5
Patients without <i>TP53</i> aberration	27	26	26	26	25	17
Patients with <i>TP53</i> aberration	45	45	35	24	14	8

Pirto + Ven + Obin

- Each cycle is 28 days
- Patients typically stopped after C13
- But... For patients who are MRD+ at $\geq 10^{-5}$ in either PB or BM at end of C13 can continue PV for an additional 12 cycles



Are we curing patients?

1) Complete eradication of cancer from the body:

- iwCLL – Complete Response

+

- undetectable MRD - Defined as 10^{-6} via modern day testing



2) No signs of the disease returning for a prolonged period:

- >5 years of follow-up



But....

Is 5 years long enough for CLL? Patients are recurring despite meeting these criteria.



So let's talk about "Functional Cure"

1) no symptoms

-From both the CLL and the treatment

2) doesn't grow or spread

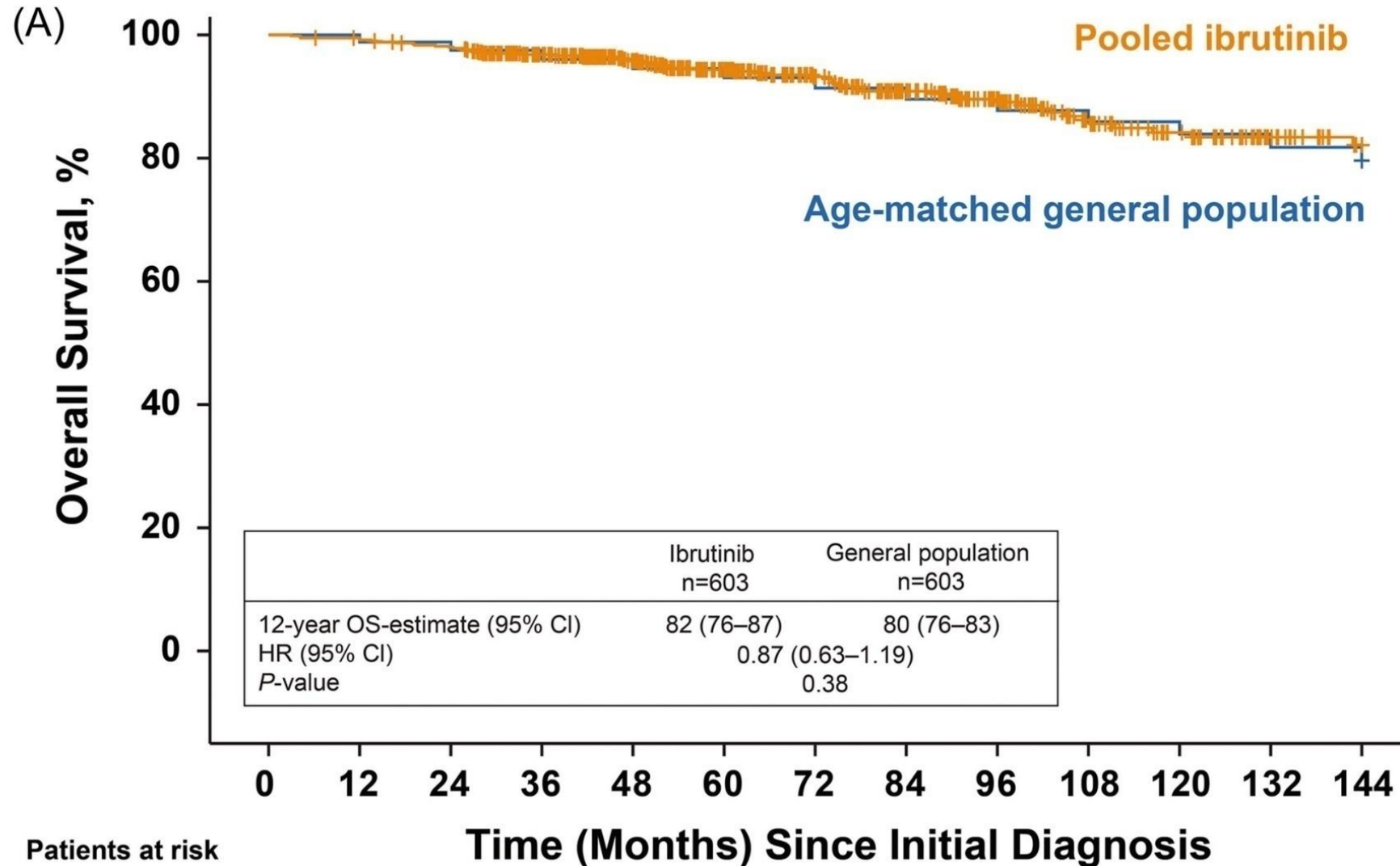
-Stable disease via iwCLL

-Able to detect CLL via MRD testing

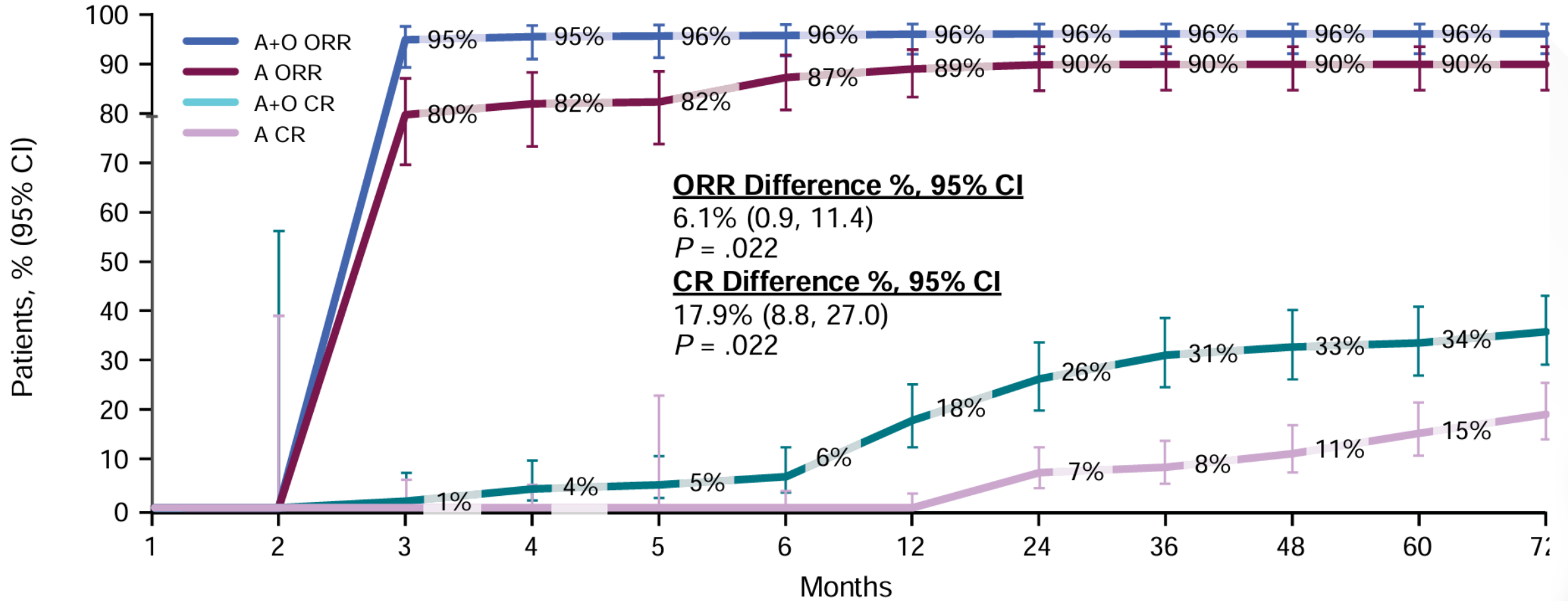
3) doesn't affect the patient's lifespan

-Are patients living as long as aged matched controls

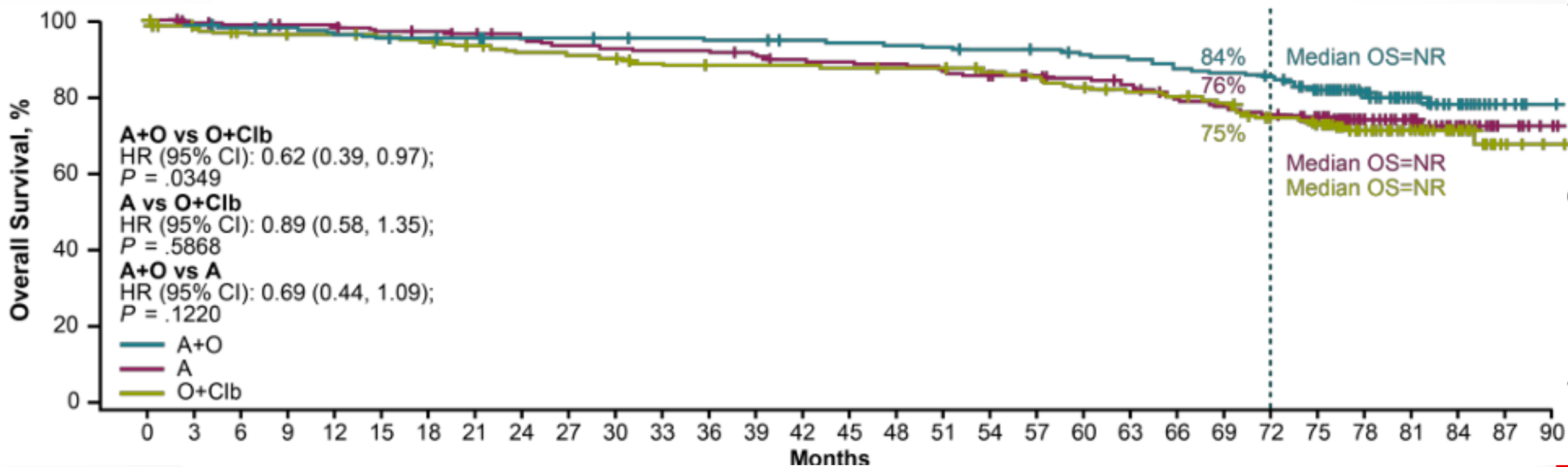
Pts on Ibrutinib trials live as long as age-matched controls



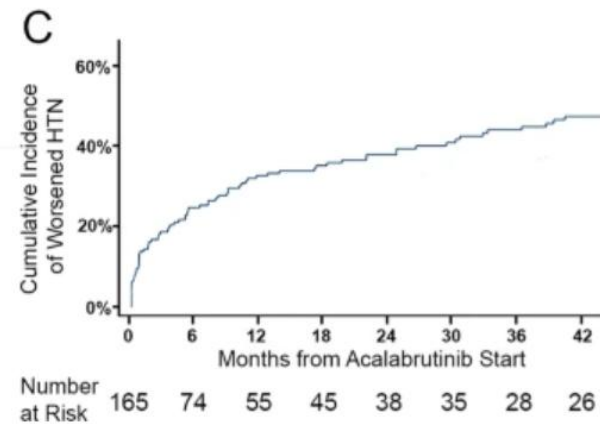
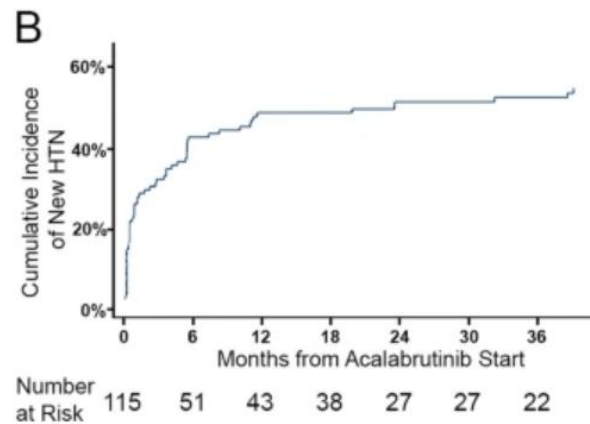
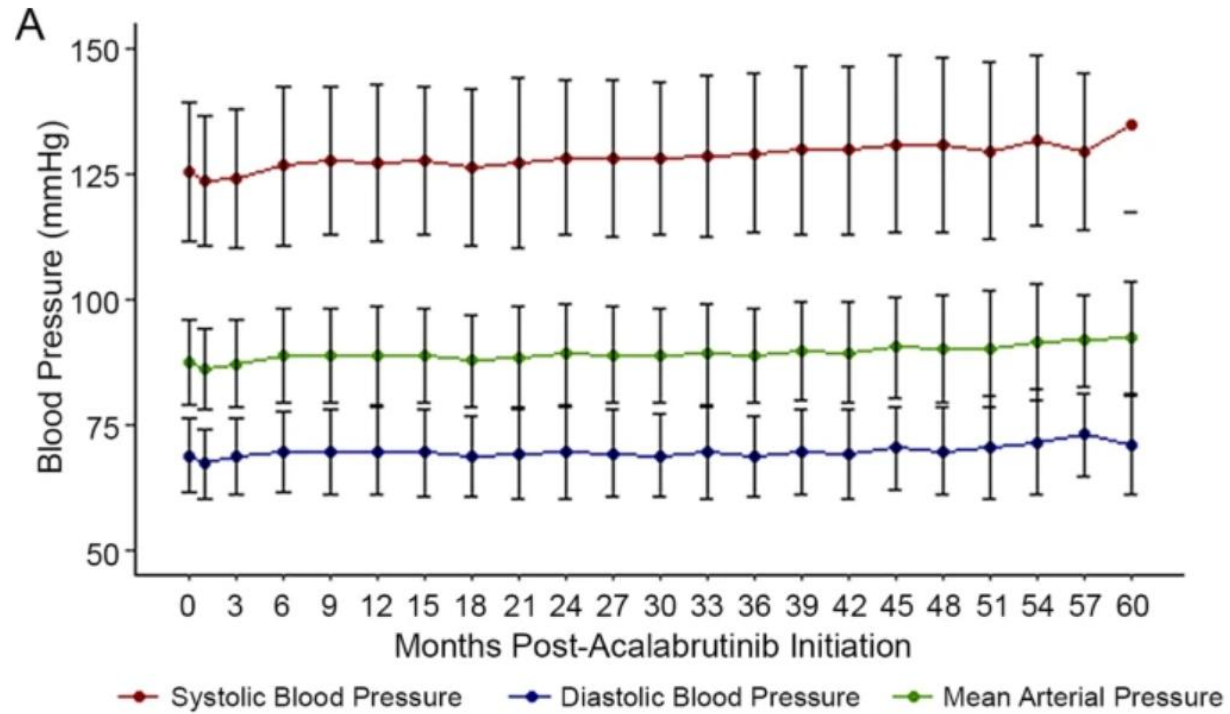
Long term follow up ELEVATE-TN – By responses



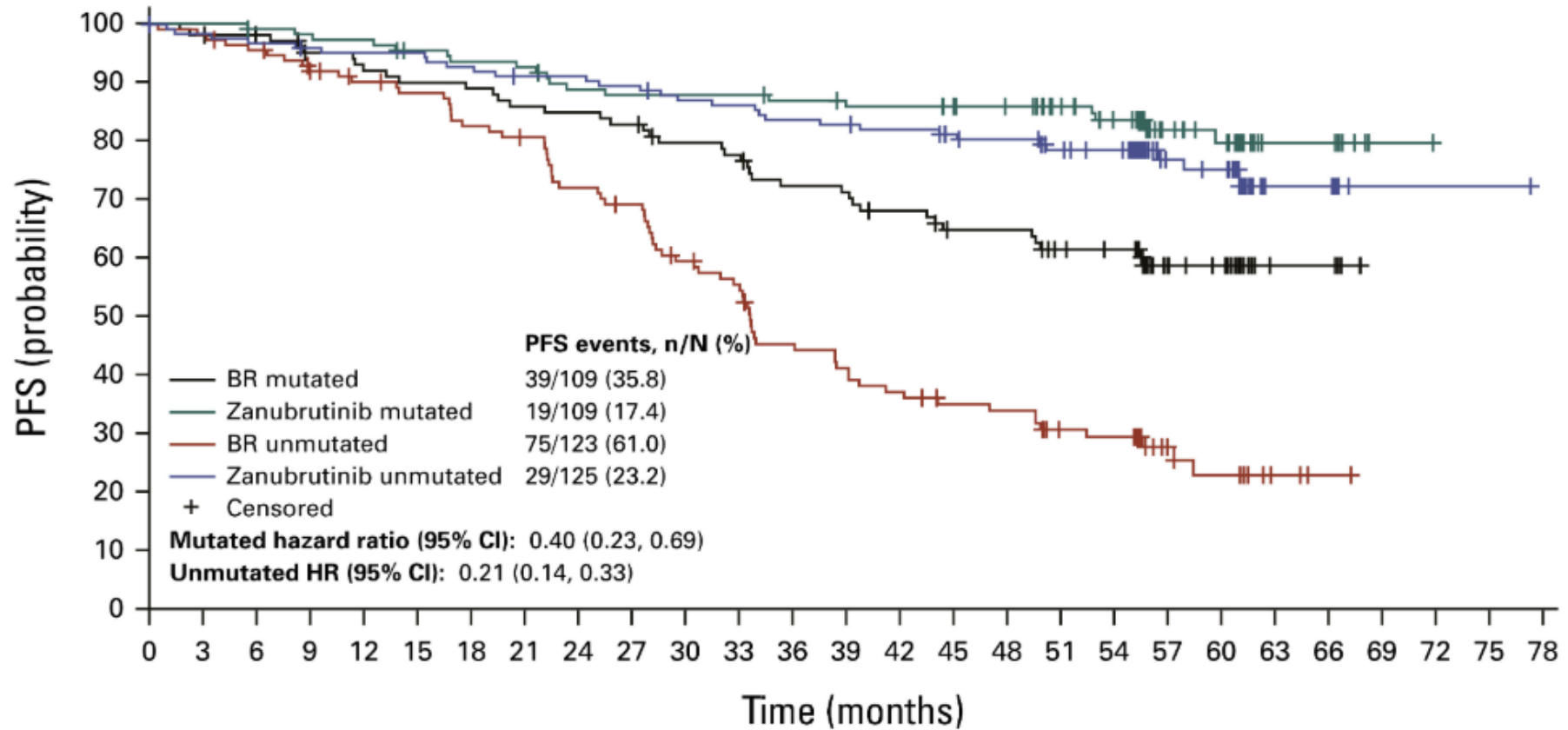
Long term follow of up ELEVATE-TN – OS



HTN increases over time cBTKi



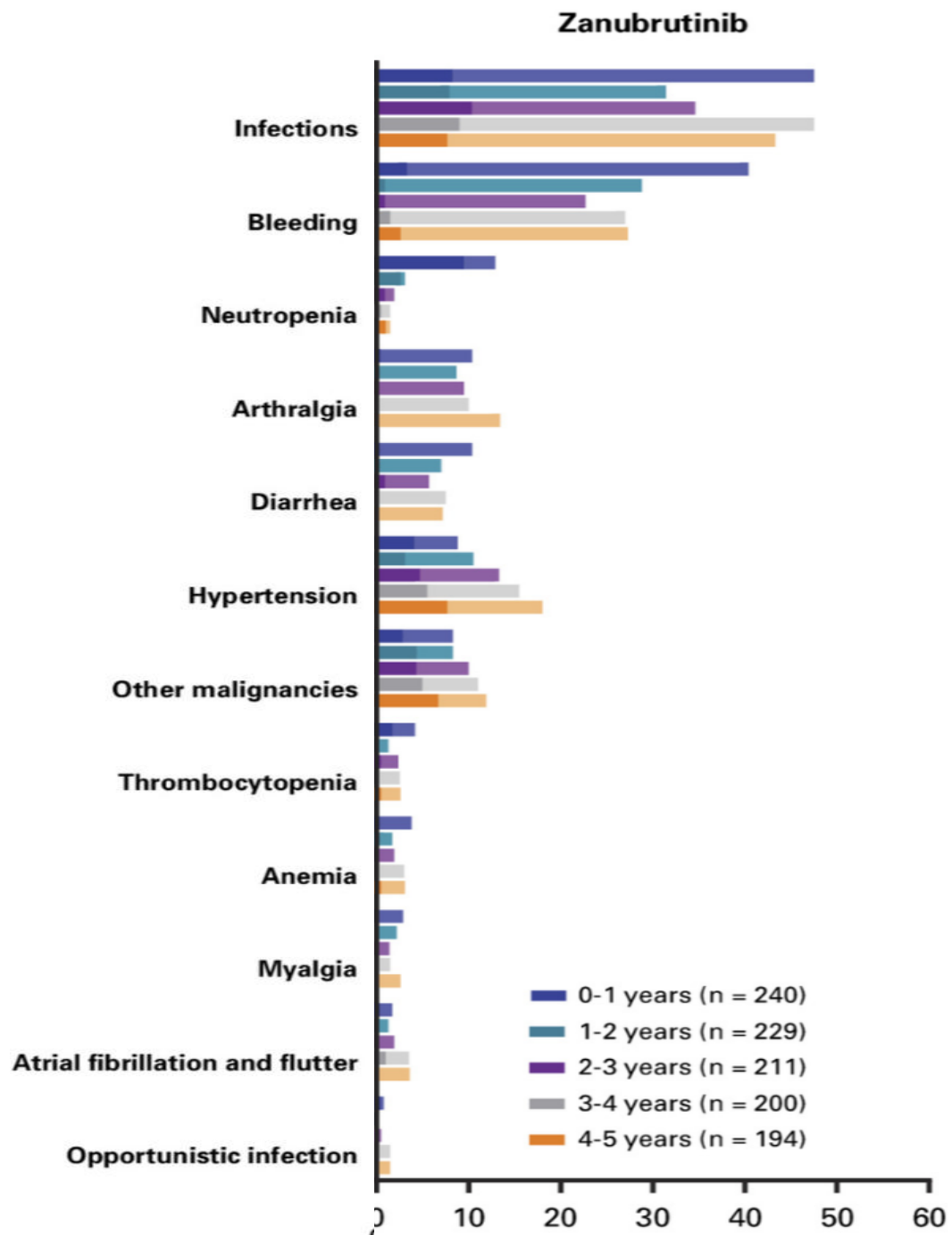
Long term follow up of Sequoia



No. at risk:

BR mutated	109	100	98	93	90	88	87	84	83	81	76	74	68	67	63	58	58	52	50	25	22	5	5	0			
Zanubrutinib mutated	109	109	107	106	105	101	99	98	93	92	92	92	90	88	88	86	83	77	69	41	36	11	11	1	0		
BR unmutated	123	112	108	102	96	93	87	84	75	71	60	55	44	40	36	32	31	24	23	12	9	3	1	0			
Zanubrutinib unmutated	125	122	120	118	117	117	114	111	111	109	105	104	101	100	98	93	91	84	81	45	43	8	8	1	1	1	0

Toxicity over time



Are we achieving “Functional Cure”?

1) no symptoms

-From both the CLL and the treatment



2) doesn't grow or spread

-Stable disease via iwCLL

-Able to detect CLL via MRD testing



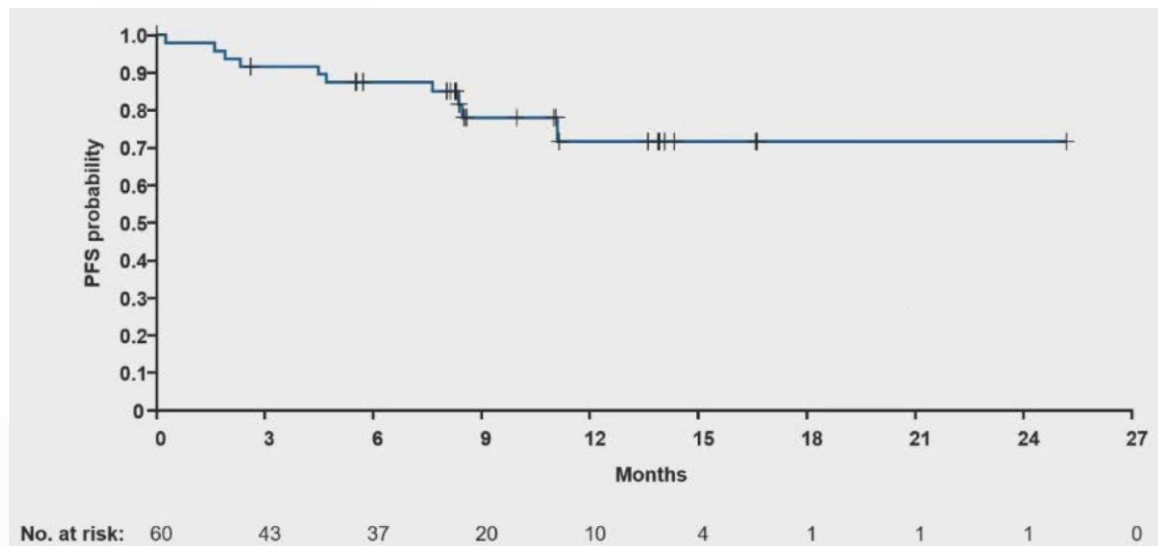
3) doesn't affect the patient's lifespan

-Are patients living as long as aged matched controls

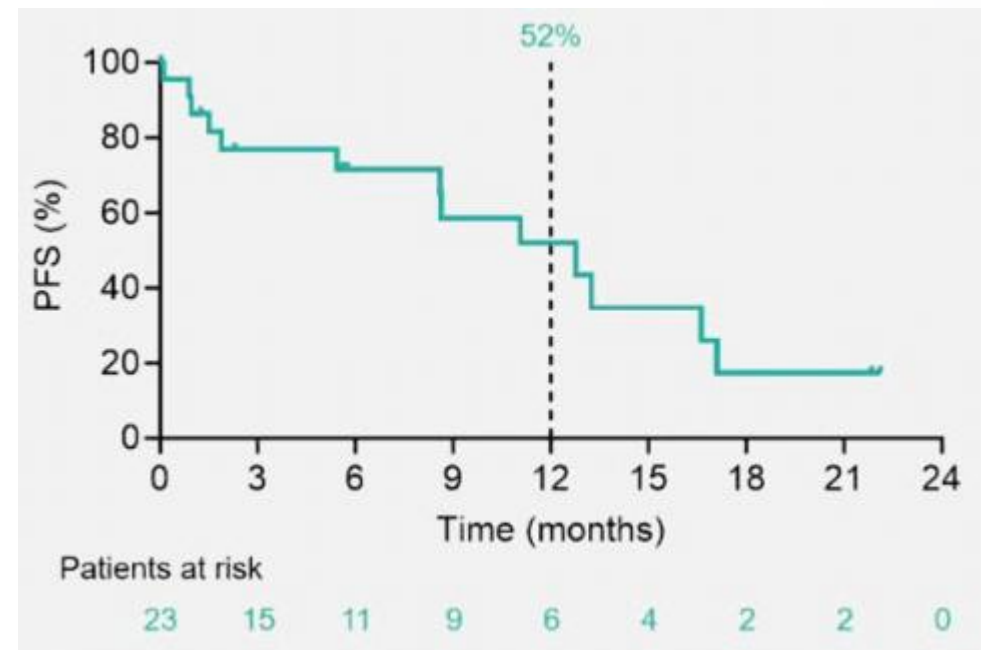


What's on the horizon – BTK degraders and Bispecific Antibodies

BGB-16674



Epcoritamab



Conclusions

By definition - we are not curing, or functionally curing patients with CLL

We are getting close, especially towards functional cure

New treatments are currently being developed that appear safer and possibly more effective than what we currently have available



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