

Some specific comorbidities are drivers of choice

Clinical condition	BTKi-based	BCL2-based	Obinu
 Severe/uncontrolled arrhythmias	✗	✓	✓
 Acute/subacute cardiac failure	✗	✓	✗
 Recent acute coronary syndrome	✗	✓	⚠
 Severe renal impairment	✓	✗	⚠
 History/high risk of bleeding	✗	✓	⚠
 Relevant DDI	✗	✗	✓
 High infection risk	⚠	⚠	✗
 Unfavorable logistic	✓	⚠	✗

- ✗ Contraindicated
- ⚠ Use with caution
- ✓ No treatment-specific considerations

Adverse events

Selected adverse events of interest, all CTC grades

	VO	VI	I
Safety population – No. (%)	295	303	298
Blood and lymphatic system disorders	174 (59.0)	130 (42.9)	85 (28.5)
Febrile neutropenia	14 (4.7)	7 (2.3)	0 (0)
Neutropenia	155 (52.5)	110 (36.3)	49 (16.4)
Cardiac disorders	41 (13.9)	72 (23.8)	103 (34.6)
Atrial fibrillation	11 (3.7)	38 (12.5)	50 (16.8)
Gastrointestinal disorders	176 (59.7)	225 (74.3)	189 (63.4)
Diarrhea	80 (27.1)	143 (47.2)	104 (34.9)
Infections and infestations	225 (76.3)	243 (80.2)	238 (79.9)
COVID-19	113 (38.3)	128 (42.2)	117 (39.3)
Pneumonia	41 (13.9)	28 (9.2)	40 (13.4)
Metabolism and nutrition disorders	90 (30.5)	75 (24.8)	72 (24.2)
Tumor lysis syndrome	12 (4.1)	4 (1.3)	1 (0.3)
Neoplasms benign, malignant and unspecified	35 (11.9)	35 (11.6)	55 (18.5)
Richter Transformation	4 (1.4)	1 (0.3)	4 (1.3)
Vascular disorders	60 (20.3)	102 (33.7)	124 (41.6)
Hypertension	34 (11.5)	51 (16.8)	72 (24.2)

Adverse events

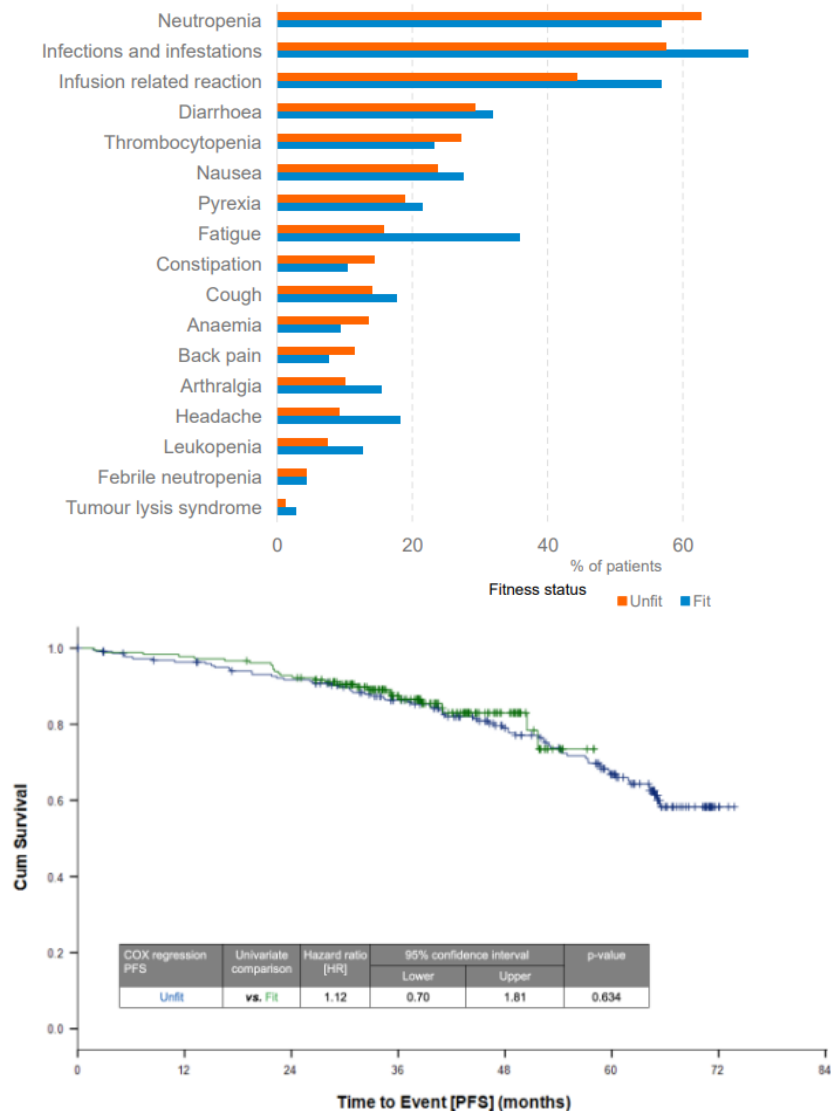
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Grade 3-5 Infections	VO	VI	I
	295	303	298
Infections and infestations	103 (34.9)	76 (25.1)	74 (24.8)
COVID-19	47 (15.9)	26 (8.6)	20 (6.7)
Pneumonia	29 (9.8)	22 (7.3)	22 (7.4)

Venetoclax + Obinutuzumab TN CLL

CLL13 and CLL14 phase 3 randomized trials: Safety

CLL14: Most frequent ≥ grade 3 adverse events



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



Pts Resilience Equal Across All Treatments?

	Young/Fit Elderly/Fit Elderly/Unfit				
	ECOG1912 ¹ IBR R	RESONATE-2 ² IBR	ALLIANCE ³ IBR	SEQUOIA ⁴ ZANU	ELEVATE TN ⁵ ACALA
Median age	58	70	71	70	70
Tox-related discontinuation at ~5 yrs	22%	21%	18%	20%	18%
Median age	BRUIN CLL322 PIRTO				
Tox-related discontinuation at 32 m	65 4.3%				

	Young/Fit Elderly/Unfit	
	CLL13	CLL14
Median age	62	72
Tox-related discontinuation	4%	15%

Venetoclax dose reductions more common in unfit patients (CIRS CrCL)
only reduced dose intensities of < 70% associated with shorter PFS

	Young/Fit Elderly/Unfit			
	CAPTIVATE IV	AMPLIFY AV	AMPLIFY AVO	GLOW IV
Median age	60	61	61	71
Tox-related discontinuation	5%	< 65y 5.7%; ≥65 y 12.4%	< 65y 14.6%; ≥65 y 32.6%	11%

¹Shanafelt et al, Blood 2023; ²Barr et al, Blood Adv 2022; ³Wojach et al, Blood 2023; ⁴Shadman et al, ICML 2023; ⁵Allan et al, ASH 2022; ⁶Eichhorst et al, NEJM 2023; ⁷Fisher et al, NEJM 2019; Brown et al, NEJM 2025; Tam et al, Blood 2022; Kater et al, NEJM evidence 2022; al eswaf O et al, Blood 2025

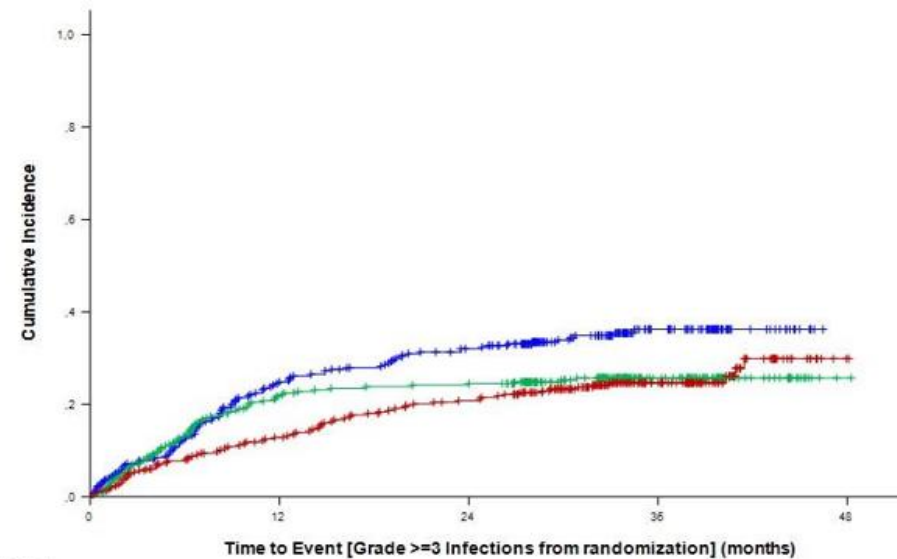
ADVERSE EVENTS: INFECTIONS

CLL EHA guidelines 2026

	Infection risk
Venetoclax - Obinutuzumab	C
Venetoclax + Ibrutinib ¹	B
Venetoclax + Acalabrutinib	B
Venetoclax + Acalabrutinib + obinutuzumab	C
Acalabrutinib	A
Zanubrutinib	A
Ibrutinib	A

A= Strongly recommended
B= Recommended;
C= consider alternatives.

CLL17: Time to occurrence of severe infections



No. at Risk					
VO	295	221	195	69	0
VI	303	231	223	90	2
I	298	251	225	109	2

Impact of FD I+V on other immune cells

- Treatment with I+V led to normalisation of T-cell subsets to healthy donor levels
- I+V also favoured the recovery of classical monocytes and dendritic cells

continuous BTK

Ibru

Acala

Zanu

Pirtobrutinib

TREATMENT LOGISTICS



- ☐ **EASY ADMINISTRATION**
- ☐ **REDUCED HOSPITAL VISITS**
- ☐ **EASY LOGISTICS (care givers/distance)**

EFFICACY



- ☐ **PROLONGED PFS**
*irrespective if IGHV status
even in del17p/TP53^m*
- ☐ **BETTER OS:** *ECOG 1912 6y: Ibr vs FCR*
ELEVATE TN 6 y: Acala O vs Chl O

- ☐ **FAVOURABLE PFS2:** *SEQUOIA: zanubrutinib 6 y*



Continuos Drug Exposition:

- ✓ **DISCONTINUATIONS DUE TO AE/AE**
- ✓ **DEVELOPMENT OF RESISTANCE**
- ✓ **COSTS**

PIRTOBRUTINIB

- ✓ **LOW DISCONTINUATIONS RATE DUE TO AE**
- ✓ **LOWER RATES OF AES**

continuous BTK

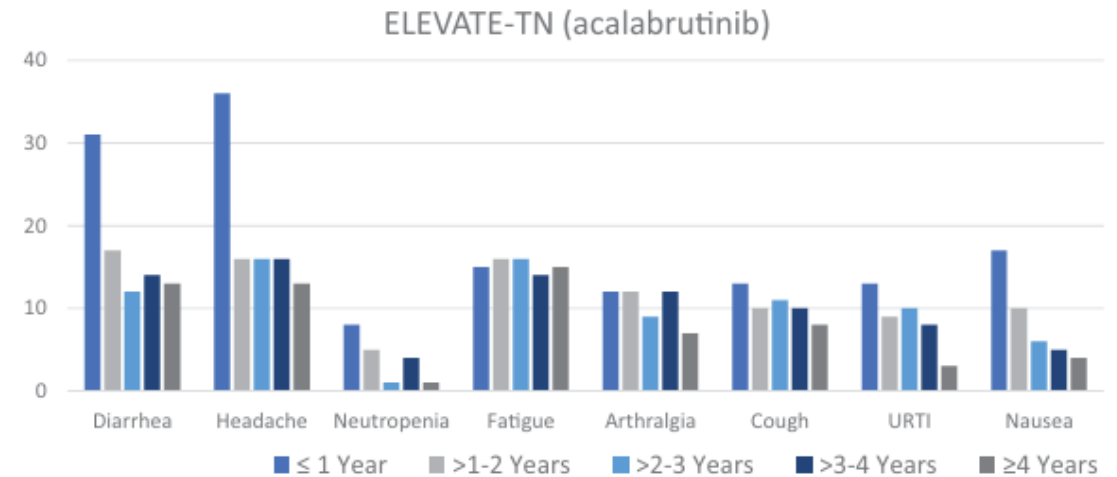
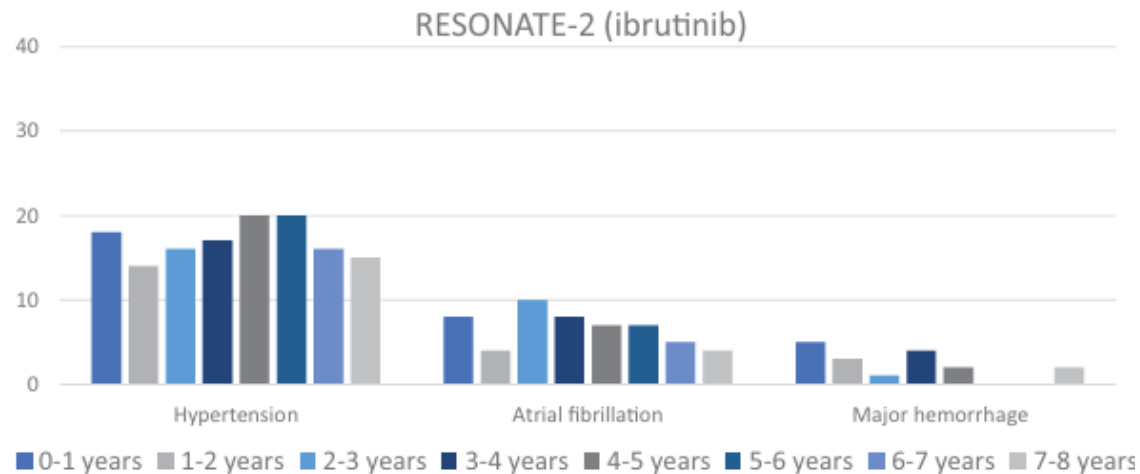
Ibru

Acala

Zanu

Pirtobrutinib

- BTKi-related AEs tend to **decrease** over time
- **Cumulative tox** may lead to tox-related discontinuations





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Tox-related discontinuation at 32 m		4.3%			

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FD treatment

Ven Obi

Ven Ibr

Ven Acala

Ven Acala Obi

TREATMENT LOGISTICS



- **MORE HOSPITAL ADMISSIONS**
- **DIFFICULT PTS LOGISTICS** (care givers/distance)

- VEN O □ **IV THERAPY**
- Ven ACALA O □ **HOSPITAL LOGISTICS**

EFFICACY



- **PROLONGED PFS**
Ven Obi CLL14: MEDIAN 8.7 y;
I plus V CAPTIVATE: 60% at 5,5 y
- **BETTER PFS IGHV MUTATED**
Ven Obi
MEDIAN 104.9m mIGHV vs 64.7m uIGHV
I plus V CAPTIVATE
at 5.5y: 80% mIGHV vs 53% uIGHV
- **BETTER OS:** GLOW I plus V versus Chl O
Amplify A plus V versus FCR/BR

- **PROLONGED TTNT**
Ven Obi CLL14
median: 91.9 m (better IGHV mutated)
- **RATE RETREATMENT**
I plus V GLOW similar mIGHV uIGHV
~20% at 66 m



- Limited Drug Exposition:**
- ✓ **AE LIMITED TO TREATMENT PERIOD**
- ✓ **NO RESISTANCE DEVELOPMENT**

- VEN O □ **INFECTIONS**
- Ven ACALA O



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