MEET THE
EXPERT *in CLL*

POTENZA, 2 LUGLIO 2025
Ospedale San Carlo – Aula B

Terapia a durata fissa: fitness e stato mutazionale

FRANCESCA R MAURO
DISCLOSURES

	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Janssen					**x**	**x**	
AstraZeneca					**x**	**x**	
Abbvie	**x**				**x**	**x**	
BeOne					**x**	**x**	
Lilly					**x**		

Clinical characteristics of Patients with CLL

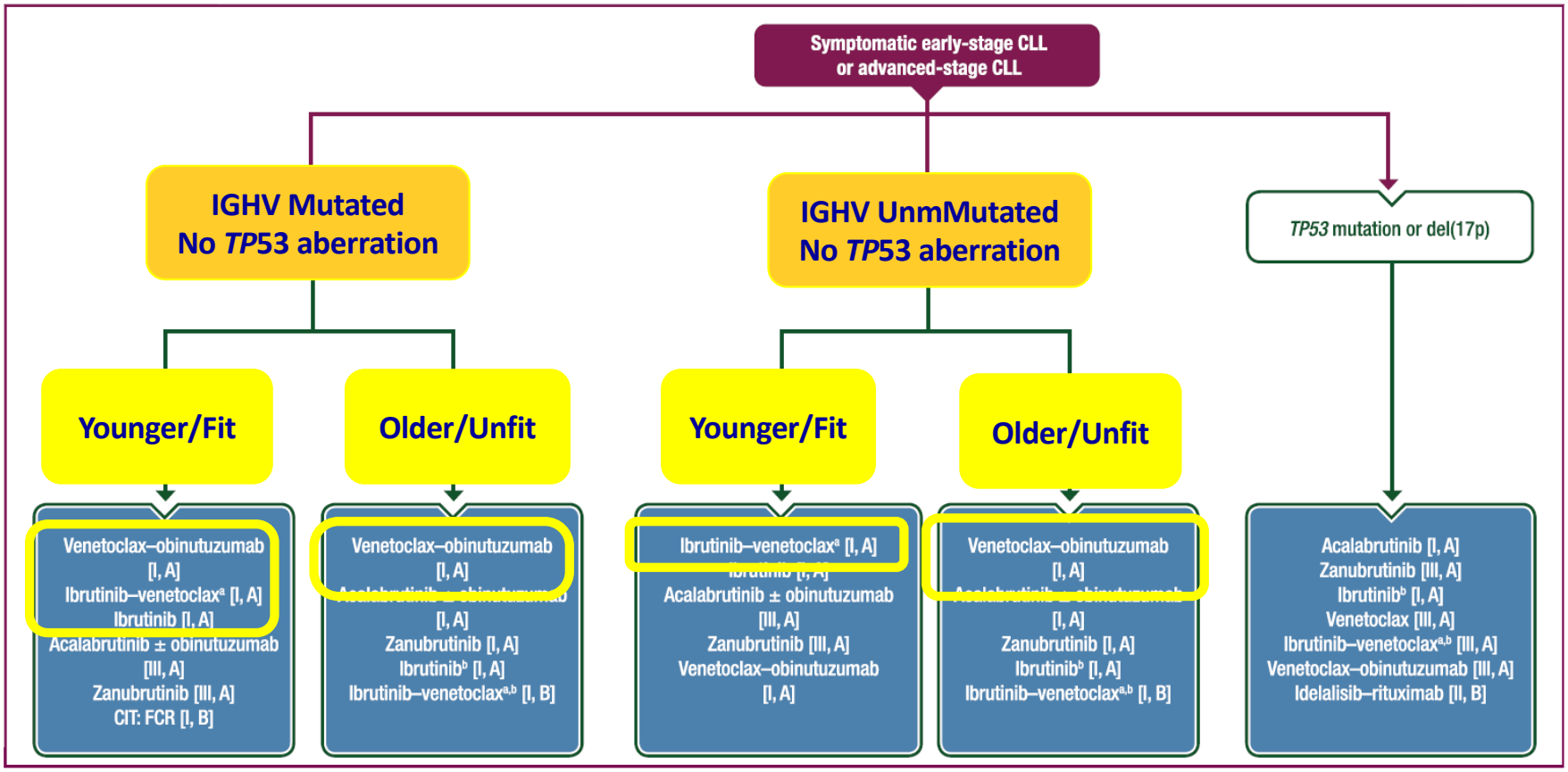
Genetic characteristics of CLL cells

Patients characteristics (age/fitness)

IGHV mutational status

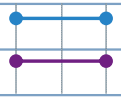
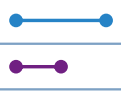
TP53 disruption

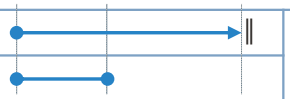
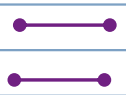
2024 ESMO Treatment guidelines: 1L treatment for CLL



Eichhorst B & Ghia P Annals of Oncology, 2024

FIXED-DURATION REGIMENS FOR FRONT-LINE TREATMENT OF CLL PATIENTS

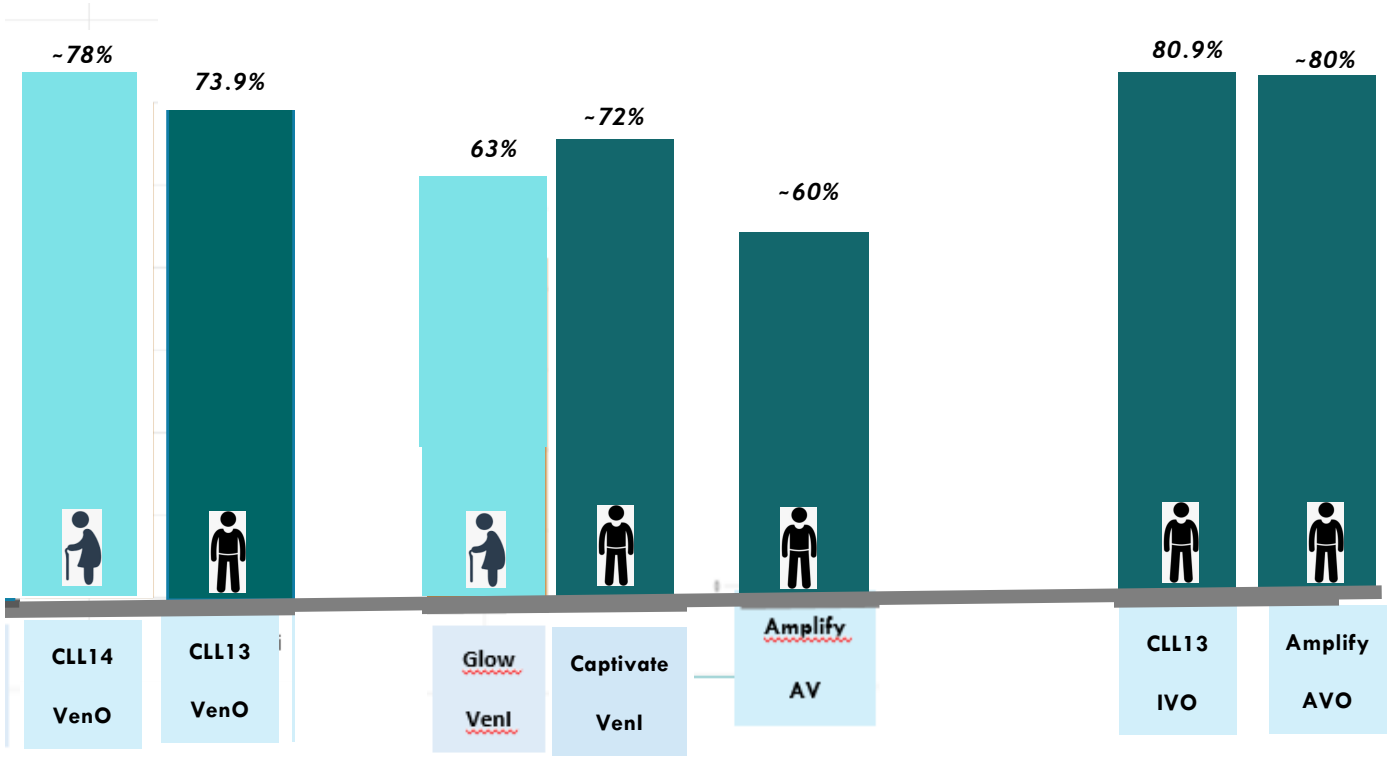
Study		Treatment duration (6m 1y to PD)	Key eligibility criteria (Age: Years; CrCl: mL/min)	Key patient demographics			
				Median age	Median CIRS	Unmutated IGHV	del(17p)/*TP53*^{mut}
CLL14[1,2]	VenO		Age ≥18, CIRS >6 or CrCl <70	72 years	9	61%	9%/11%
	OClb			71 years	8	59%	7%/8%
GLOW[5–7]	IVen		Age ≥65 or <65 with CIRS >6 or CrCl <70; no del(17p) or known *TP53*^{mut}	71 years	9	63.2%	–/6.6%
	OClb			71 years	8	54.3%	–/1.9%

Study		Treatment duration	Key eligibility criteria (Age: Years; CrCl: mL/min)	Key patient demographics			
				Median age	Median CIRS	Unmutated IGHV	del(17p)/*TP53*^{mut}
CAPTIVATE FD Cohort[29-31]	IVen	 PD re-treated with I until PD or unacceptable toxicity	Age ≤70; ECOG PS 0–1, adequate hepatic, renal, and hematologic function	60 years	–	56%	17%‡
CLL13[28]	IVO		Total CIRS score <6, CrCl ≥70 mL/min, no del(17p)/*TP53*^{mut}	60 years	2	53%	–
	VenO			62 years	2	57%	–
	VenR			62 years	2	57%	–
	CIT			61 years	2	57%	–
AMPLIFY	AVO		no del(17p) or *TP53* mutation ECOG PS 0-2 no CIRS-Geriatric >6 no significant CVD	61 years	3	58%	–
	AV			61 years	2	58%	–
	CIT			61 years	2	59%	–

I è inserito all'interno dell'RCP di Ibrutinib.

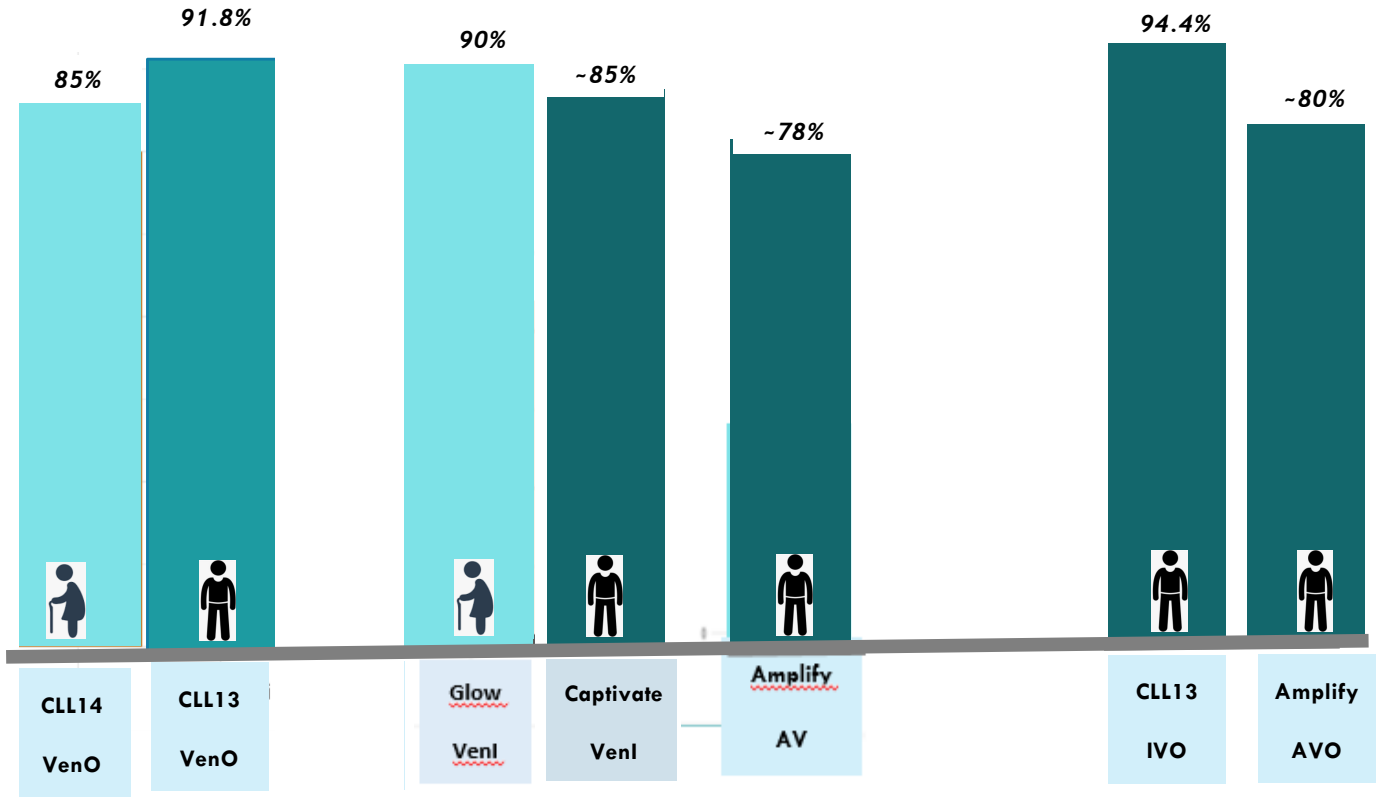
Age & Fitness, IGHV and outcomes with FD therapy for CLL

4-year PFS rates with 1L FD therapy for IGHV unmmutated patients



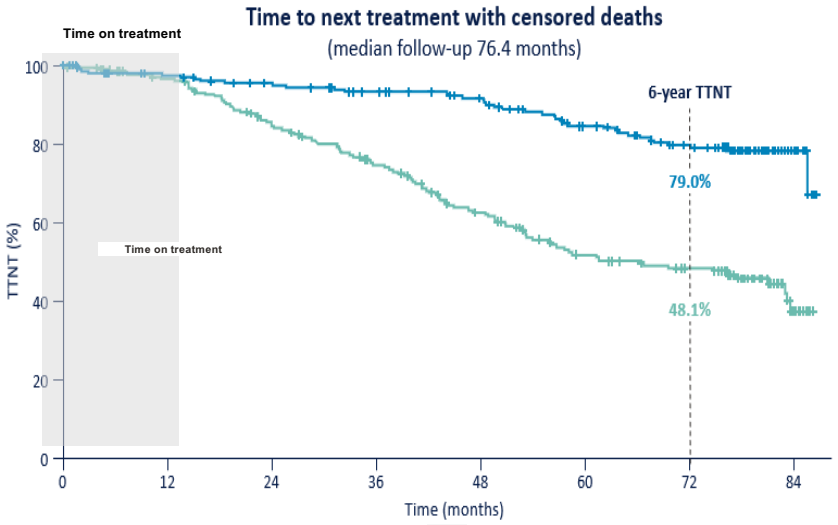
Al-Sawaf O, et al. Lancet Oncol 2020; Eichhorst B, et al. NEJM 2023; Munir et al.N Engl J Med. 2024 Sharman et al., 2024 ASH- Brown et al., 2024 ASH , abstract #1009

4-year PFS rates with 1L FD therapy for IGHV mutated patients



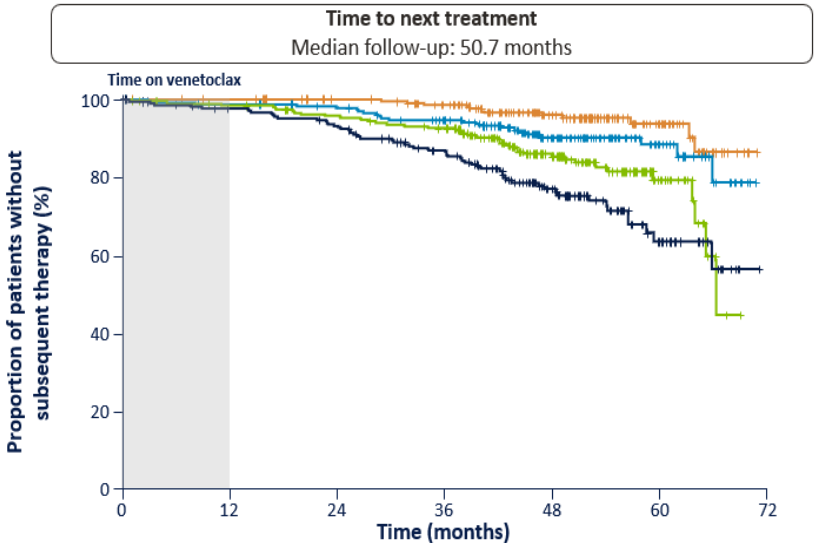
1L FIXED-DURATION TREATMENT FOR CLL: TTNT

V+O - CLL14



6yTTNT
(censored deaths)
79,0%

V+O - CLL13

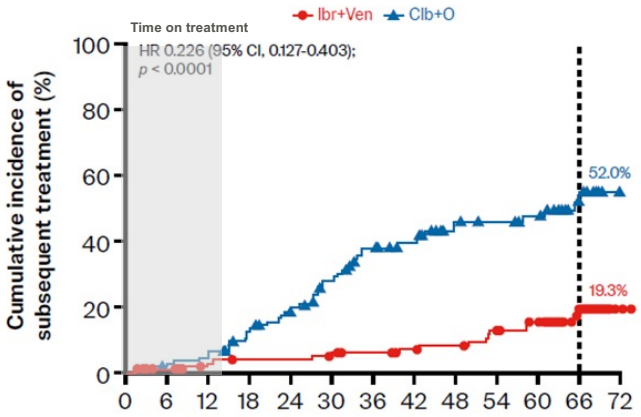


4y TTNT
90,4%

Al-Sawaf *et al.* Blood 2024 : Fürstenau *et al. Lancet Oncol* 2024

1L Fixed-Duration treatment for CLL: TTNT

V+I - GLOW



5.5y TTNT

80,7%*

*calculated as 100 - 19.3

V+I – FD- CAPTIVATELOW

At 5.5 years, 73% of patients required no additional treatment

5.5y TTNT

73.3%

Niemann et al. ASH 2024

Age & Fitness and Safety profile of CLL patients receiving FD therapy

VENETOCLAX-BASED TRIALS: SAFETY

	CLL14	CLL13
% AEs of clinical interest	V+O	V+O
Median age, yrs	72	62
Gr≥3 ganulocytopenia	52.8	56
Gr≥3 infections	17.4	18.5
Gr≥3 bleeding	-	-
Gr≥3 hypertension	-	1.8
All grades AF	0.5	<1
Cardiac failure	2	<1
Sudden death	-	-
Infusion reaction	9	11

Eichhorst B. et al. Oral #71 -63rd ASH. 2021 ; Al-Sawaf O. et al. Oral S145. 28th EHA. June 8-11. 2023;

VENETOCLAX-BASED TRIALS: SAFETY

	GLOW	CAPIVATE	CLL13
% AEs of clinical interest	V+I°	V+I°	V+I+O*
Median age, yrs	71	60	60
Gr≥3 ganulocytopenia	35	38	48
Gr≥3 infections	29	8	27.7
Gr≥3 bleeding	1.9	2	<1
Gr≥3 hypertension	7.5	6	5.6
All grades AF	14.2	4	9
Cardiac failure	3.8	-	-
Sudden death	1.9	<1	-
Infusion reaction	-	-	4.3

. Moreno C, et al. EHA 2022. Abstract P669 (Poster), . Niemann CU, et al. Oral #93 64th ASH 2022,

VENETOCLAX-BASED TRIALS: SAFETY

Follow-up:

	AMPLIFY	AMPLIFY
% AEs of clinical interest	V+A	V+A+O
Median age, yrs	61	61
Gr≥3 ganulocytopenia	33.3	46.1
Gr≥3 infections	12.4	23.6
Gr≥3 bleeding	2	2.1
Gr≥3 hypertension	2.7	2.1
All grades AF	0.7	2.1
Cardiac failure	0.3	0
Sudden death	-	-
Infusion reaction	-	-

Brown J et al. ASH 2024

VENETOCLAX-BASED TRIALS: SAFETY

	CLL14[3]	CLL13[1]	GLOW[4]	CAPIVATE[2]	CLL13[1]	AMPLIFY	AMPLIFY
% AEs of clinical interest	V+O	V+O	V+I°	V+I°	V+I+O*	V+A	V+A+O
Median age, yrs	72	62	71	60	60	61	61
Gr≥3 ganulocytopenia	52.8	56	35	38	48	33.3	46.1
Gr≥3 infections	17.4	18.5	29	8	27.7	12.4	23.6
Gr≥3 bleeding	-	-	1.9	2	<1	2	2.1
Gr≥3 hypertension	-	1.8	7.5	6	5.6	2.7	2.1
All grades AF	0.5	<1	14.2	4	9	0.7	2.1
Cardiac failure	2	<1	3.8	-	-	0.3	0
Sudden death	-	-	1.9	<1	-	-	-
Infusion reaction	9	11	-	-	4.3	-	-

Eichhorst B, et al. Oral #71 -63rd ASH, 2021.; Moreno C, et al. EHA 2022. Abstract P669 (Poster); Al-Sawaf O, et al. Oral S145. 28th EHA, June 8-11, 2023; Niemann CU, et al. Oral #93 64th ASH 2022Brown J et al. ASH 2024

CAPTIVATE- Safety analysis:

Median time on study 27.9 months

Median Age: 60 yrs
Median time on study 27.9 months

AF: 3-6%
Hypertension: 3-9%.

Table 2. Treatment-emergent AEs

AEs	All treated patients (n = 159), n (%)	
	Any grade	Grade 3/4
Most common AEs*		
Diarrhea	99 (62)	5 (3)
Nausea	68 (43)	2 (1)
Neutropenia	66 (42)	52 (33)
Arthralgia	53 (33)	2 (1)
Hypertension	25 (16)	9 (6)
Neutrophil count decreased	16 (10)	8 (5)
Other AEs of clinical interest		
Atrial fibrillation	7 (4)	2 (1)
Major hemorrhage†	3 (2)	2 (1)
Laboratory safety parameters		
Hematology		
Neutrophils decreased	115 (72)	60 (38)
Platelets decreased	94 (59)	20 (13)
Hemoglobin decreased	31 (19)	0
Chemistry		
Corrected calcium decreased	61 (38)	1 (1)
Potassium increased	39 (25)	4 (3)
Uric acid increased	34 (21)	34 (21)
Creatinine increased	27 (17)	0

Tam et al. Blood, 2022

Table 2. Treatment-emergent AEs[a] in patients with versus without high-risk features.

AEs, *n* (%)	With high-risk features *n* = 129	Without high-risk features *n* = 66
Most common AEs of any grade (occurring in ≥20% of patients)		
Diarrhea	80 (62)	39 (59)
Neutropenia[b]	59 (46)	36 (55)
Nausea	54 (42)	29 (44)
Arthralgia	43 (33)	21 (32)
Headache	33 (26)	19 (29)
Upper respiratory tract infection	32 (25)	20 (30)
Fatigue	30 (23)	22 (33)
Muscle spasms	29 (22)	21 (32)
Vomiting	23 (18)	15 (23)
Increased tendency to bruise	23 (18)	17 (26)
Most common grade 3/4 AEs (occurring in ≥5% of patients)		
Neutropenia[b]	47 (36)	24 (36)
Hypertension	12 (9)	2 (3)
AEs of clinical interest (any grade)		
Atrial fibrillation	8 (6)	2 (3)
Major hemorrhage[c]	2 (2)	1 (2)
Serious AEs	28 (22)	14 (21)
Related to study treatment	15 (12)	10 (15)
Fatal AEs	1 (1)[d]	0
AEs leading to discontinuation		
Ibrutinib only	3 (2)	2 (3)
Venetoclax only	0	0
Both ibrutinib and venetoclax	1 (1)	2 (3)
AEs leading to dose reduction		
Ibrutinib only	9 (7)	3 (5)
Venetoclax only	14 (11)	7 (11)
Both ibrutinib and venetoclax	3 (2)	4 (6)

Allan et al. Clin Cancer Res 2023

GLOW: Safety analysis

Table S11: **Grade 3 or higher treatment-emergent adverse events by preferred term and toxicity grade**

	Ibr+Ven Toxicity Grade			Clb+Ob Toxicity Grade		
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
Analysis set: Safety	106			105		
Patients with 1 or more AEs	46 (43·4%)	27 (25·5%)	7 (6·6%)	33 (31·4%)	38 (36·2%)	2 (1·9%)
Preferred term						
Neutropenia*	17 (16·0%)	20 (18·9%)	0	23 (21·9%)	29 (27·6%)	0
Diarrhoea	11 (10·4%)	0	0	1 (1·0%)	0	0
Hypertension	8 (7·5%)	0	0	2 (1·9%)	0	0
Atrial fibrillation	7 (6·6%)	0	0	0	0	0
[illegible]	[illegible]	[illegible]	[illegible]	5 (4·8%)	0	1 (1·0%)
Hyponatraemia	6 (5·7%)	0	0	0	0	0
Thrombocytopenia	6 (5·7%)	0	0	16 (15·2%)	5 (4·8%)	0
[illegible]	[illegible]	[illegible]	[illegible]	0	0	0
Cardiac failure	3 (2·8%)	0	1 (0·9%)	0	0	0
Hyperuricaemia	0	4 (3·8%)	0	0	2 (1·9%)	0
Rash	4 (3·8%)	0	0	0	0	0
Anaemia	3 (2·8%)	0	0	2 (1·9%)	0	0
Alanine aminotransferase increased	2 (1·9%)	0	0	3 (2·9%)	0	0
Bronchitis	2 (1·9%)	0	0	2 (1·9%)	0	0
Cholecystitis acute	2 (1·9%)	0	0	0	0	0
Chronic kidney disease	2 (1·9%)	0	0	0	0	0
Febrile neutropenia	1 (0·9%)	1 (0·9%)	0	3 (2·9%)	0	0
Haematuria	2 (1·9%)	0	0	0	0	0
Hypokalaemia	2 (1·9%)	0	0	0	0	0
Hypophosphataemia	2 (1·9%)	0	0	0	0	0
Infection	2 (1·9%)	0	0	0	0	0
Osteoarthritis	2 (1·9%)	0	0	0	0	0
Sudden death	0	0	2 (1·9%)	0	0	0
Syncope	2 (1·9%)	0	0	1 (1·0%)	0	0
Urinary tract infection	2 (1·9%)	0	0	2 (1·9%)	0	0
Aspartate aminotransferase increased	1 (0·9%)	0	0	3 (2·9%)	0	0
Herpes zoster	0	0	0	2 (1·9%)	0	0
Infusion related reaction	0	0	0	3 (2·9%)	0	0
Leukopenia	0	0	0	3 (2·9%)	0	0
Lymphopenia	0	0	0	2 (1·9%)	0	0
Tumour lysis syndrome	0	0	0	6 (5·7%)	0	0

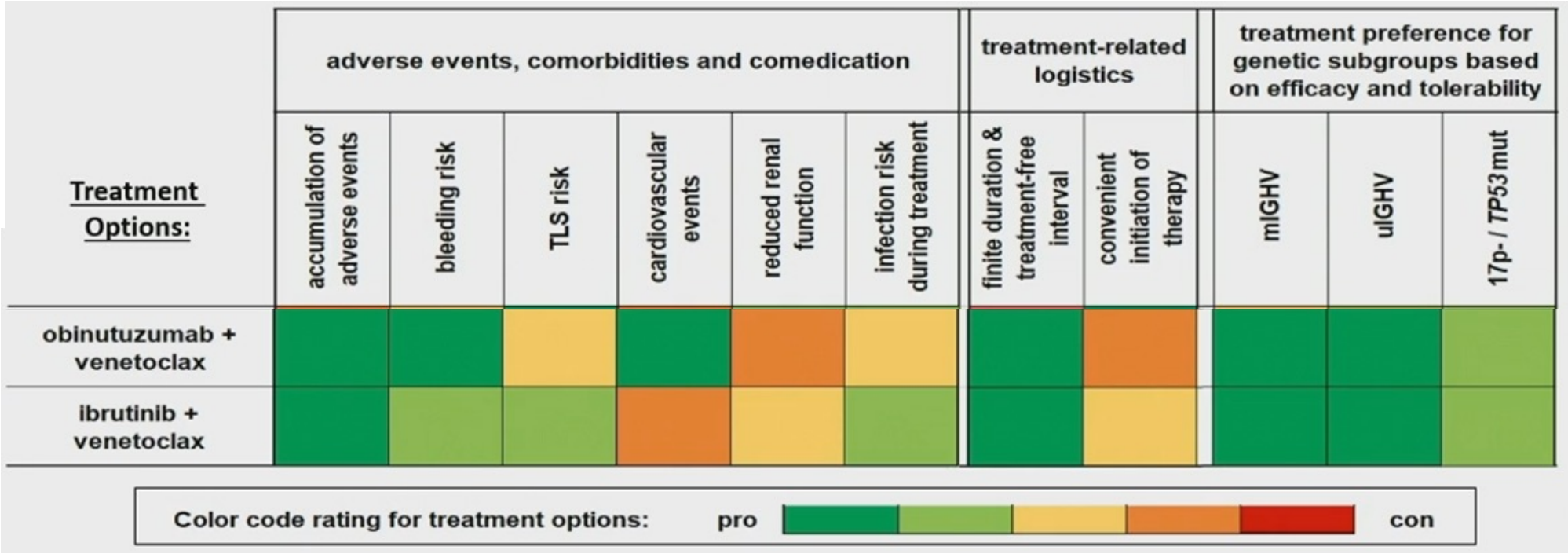
AE=adverse event.
Shown are grade 3, 4, and 5 events with frequency 1% or higher.
Adverse events are coded using MedDRA version 23.0.
*Includes both "Neutropenia" and "Neutrophil count decreased."

- **Study deaths**

Reasons for Death	I + V (n = 106)				GClb (n =105)			
	On Treatment		Post Randomized Treatment		On Treatment		Post Randomized Treatment	
Infection-related	1		3		1		13	
Second primary malignancy	1		1		0		7	
Cardiac	2		0		0		4	
Sudden/unknown	2	5	3	6	0	0	4	13
Progressive disease	0		1		0		2	
Vascular disorders	1		2		0		3	
Other	0		2		1		4	
Total	**7**		**12**		**2**		**37**	
Total per arm	**19**				**39**			

Niemann et al, Lancet Oncol 2023

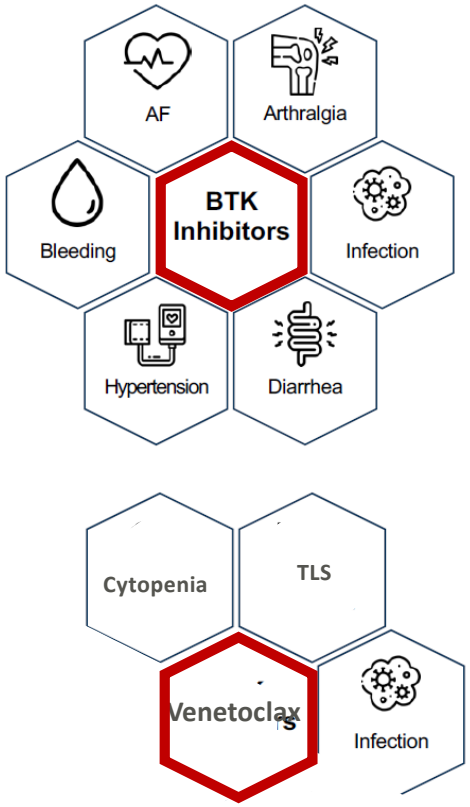
Safety profile of Venetoclax-based regimens and treatment-related logistics



Less prolonged drug exposure = less toxicity

Tausch E. Schneider C. Stilgenbauer S. Risk-stratification in frontline CLL: standard of care; ASH Education Program 2024

Screening of patients candidate to treatment



Geriatric assessment
- Physical
- Cognitive
- Emotional

OR **PGA**

- Comorbidities
- Polypharmacy
- Nutrition
- Social support

Disease biology
- *TP*53 status
- FISH
- Mutational status of IGHV

Patient´s and caregivers preferences

Comorbidities of interest
- *Cardiovascular disorder*
- *Renal function*
- *Anticoagulant/anti.PLTS agent*
- *Infections history*
- *Disease-related cytopenia*

Evaluation and Monitoring of Cardiovascular safety

• ESC guidelines for baseline risk assessment and monitoring during BTKi therapy[1]

- **BTKi are commonly used in elderly patients in whom frequent comorbidities coexist at diagnosis that increase the risk of CTR-CVT.**
- **Caution should be exercised with first and second-generation BTK inhibitors [2 especially in] patients ≥ 75 years old or with previous AF[1]**
- **Antihypertensive initiation has been associated with a lower risk of a major adverse CV events (MACE).**
- **Opportunistic screening for AF by pulse-taking or ECG rhythm strip is recommended at every clinical visit during BTKi therapy.**

Recommendations	Class[a]	Level[b]
BP monitoring and management		
BP measurement **is recommended for patients treated with BTK inhibitors at every clinical visit.**	I	B
Weekly home monitoring of BP during the first 3 months and every month thereafter should be considered for patients treated with BTK inhibitors.	IIa	C
Echocardiography		
Baseline echocardiography is recommended in high-risk patients[c] scheduled to receive BTK inhibitors: Male, age ≥ 65 years, previous history of hypertension,	I	C
TTE is recommended in all patients who develop AF during BTK inhibitor therapy.	I	C
AF		
Opportunistic screening for AF by pulse-taking or ECG rhythm strip is recommended at every clinical visit during BTK inhibitor therapy.	I	C

AF: Atrial fibrillation; BP: Blood pressure; BTK: Bruton's tyrosine kinase; CLL: Chronic lymphocytic leukemia; CTR-CVT: Cancer treatment-related cardiovascular toxicity; CV: Cardiovascular; CVD: Cardiovascular disease; CVRD: Cardiovascular renal disease; DM: Diabetes mellitus; ECG: Electrocardiogram; ESC: European society of cardiology?; HF: Heart failure; MACE: Major adverse CV events; QTc: Corrected QT interval; TTE: Transthoracic echocardiography; VHD: Valvular heart disease

[a] Class of recommendation. [b] Level of evidence. [c] Male, age ≥ 65 years, previous history of hypertension, DM, QTc ≥ 480 ms, AF, HF, cardiomyopathy or severe VHD.

1. Lyon A, et al. European Heart Journal 2022; 43: 4229–4361; 2. Boriani G, et al. Chemotherapy 2022; doi: 10.1159/000528019.