Venetoclax and Obinutuzuamb in CLL patient and *(a lot)* coexisting conditions

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REVOLUTIONARY ROAD IN CLL

Innovazione rivoluzionaria nella terapia della leucemia linfatica cronica

Bologna, 20 maggio 2024
Royal Hotel Carlton

No disclosures

Caso clinico 3: A. G., 78 anni

Diagnosi di CLL nel 2021
Stadio 0 sec. Rai/A sec. Binet

Anamnesi patologica remota
- Gennaio 2015: tachi-FA + scompenso cardiaco (EF% 35) trattato con CVE a Marzo 2015, in NAO da allora
- Cardiopatia ipertensiva e insufficienza cardiaca (NYHA II-III)
- Endocardite batterica da S. salivarus con sepsi associata ad IRA (07/2015) con sostituzione valvolare mitralica con protesi biologica (07/2015)
- IRC secondaria ad AKI (da shock settico)
- Diabete mellito tipo II in terapia con ipoglicemizzanti orali
- Litiasi biliare con pancreatite acuta su base litiasica che ha richiesto ricovero (02/2023)
- LST del colon ascendente sottoposto a resezione endoscopica (17/03/2023)
- Lombosciatalgia da compressione (ernia espulsa L4-L5)

Settembre 2023
- Emocromo (13/09/2023): Hb 9.3, GB 101670 (Ly 98500), PLTs 84.000

Caso clinico 3: A. G., 78 anni

Dovevamo stadiare il paziente, tuttavia, è stato ricoverato per complicanza…

Ottobre 2023: durante RSCS di monitoraggio per LST (noto in anamnesi) riscontro di polipo: sanguinamento colico in corso di polipectomia con anemizzazione grave e ricovero in Medicina di Urgenza, necessità di supporto trasfusionale con ripresa dei valori di Hb > 11g/dL.

Dimesso ad Ottobre 2023.

Gli endoscopisti ci riprovano!, eseguono la polipectomia a Novembre 2023 (adenoma tubulo-villoso con displasia di basso grado), tuttavia il paziente riferisce melena dopo alcuni giorni.

Agli esami eseguiti in PS riscontro di Hb 5.6g/dL e IRA su IRC (Crea 2.9mg/dL)

Ricovero in Medicina di Urgenza per supporto trasfusionale ed osservazione.

Caso clinico 3: A. G., 78 anni; stadiazione

- **BOM (27/12/2024):** popolazione midollare è estesamente sostituita da linfociti di piccole dimensioni, monomorfi con nuclei ipercromici positivi per CD20, CD79a, CD5 e CD23 e negativi per CD3 e Ciclina D1. Tale popolazione **occupa circa il 90% delle lacune midollari.** Il reperto morfologico è coerente con la diagnosi di leucemia linfatica cronica/linfoma a piccoli linfociti B.

- **TC collo-torace-addome senza mdc (04/01/2024):** Collo-Torace: linfoadenopatie in sede latero-cervicale sottomentoniera con **dimensioni massime di circa 23 mm** in sede latero-cervicale sinistra **16 mm** in sede latero-cervicale destra e **15 mm** in sede sottomentoniera. Non formazioni espansive o nodulari a carico di entrambi i polmoni. Non versamento pleurico. A livello mediastinico si evidenziano alcune formazioni linfonodali delle dimensioni massime a livello della loggia di Barety di circa **22 mm**; difficile la valutazione in assenza di MdC di linfoadenopatie a livello ilare. Addome: appaiono lievemente incrementate dal punto di vista numerico e dimensionale le note linfoadenopatie segnalate in particolare in prossimità dell'ilo epatico (**massimo 40 mm**) e in sede interaorto-cavale superiore (**massimo 35 mm**) dove si osserva anche la comparsa di imbibizione tessuto adiposo mesenteriale-periviscerale. Stabili le linfoadenopatie lungo gli assi iliaci e in sede inguinale bilateralmente.

- **Valutazione cardiologica (08/01/2024):** Conclusioni: nota cardiopatia ipertensiva e valvolare ad evoluzione ipocinetico-dilatativa. Fibrillazione atriale permanente in nao. Portatore di bioprotesi mitralica con residua lieve insufficienza. Pregressa endocardite batterica. IRC. Ecocardiogramma: Ventricolo sinistro lievemente ipertrofico e dilatato con moderata riduzione degli indici di funzione sistolica globale (FE 42%) Bioprotesi valvolare mitralica con residua insufficienza lieve. Aortosclerosi. Dilatazione biatriale. Sezioni destre nella norma con pressioni polmonari aumentate. Vena cava inferiore non dilatata. Pericardio indenne.

Caso clinico 3: A. G., 78 anni; fattori prognostici

- IgVH (14/12/2022): **non mutato (U-CLL)**
- FISH (20/12/2023): del 13q14.3
- TP53 (20/12/2023): negativa

Quale miglior terapia in I linea per questo paziente?

- **Paziente anziano (≥75 anni), fragile**
  Esami ematochimici (27/12/2023): Hb 8.8, GB 164600 (N 3400 L 158450), PLTs 84000. Crea 1.65. Funzione epatica nella norma. Urato 4.5. Elettroliti nella norma. LDH 340. B2M 5.6.

- **CIRS 13**
  a. NYHA II-III
  b. Flutter atriale
  c. Endocardite batterica (con sostituzione valvolare mitralica)
  d. Ipertensione arteriosa (cardiopatia ipertensiva)
  e. IRC
  f. Pancreatite litiasica

- **IGvH unmutated**

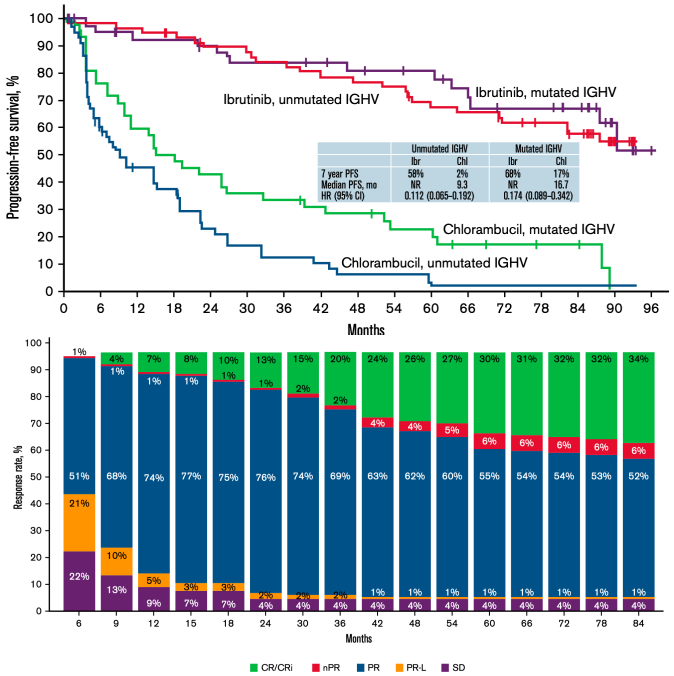
1) Non abbiamo necessità di programmare un terapia sequenziale per un lungo periodo (≥ 10 anni)
2) Dobbiamo prendere in considerazione le notevoli comorbidità **cardiache** (di questo paziente)
3) Dobbiamo adattare la terapia di I linea sul profilo citogenetico e molecolare della malattia e sui probabili eventi avversi

…proviamo a dare un punteggio alla nostra decisione…

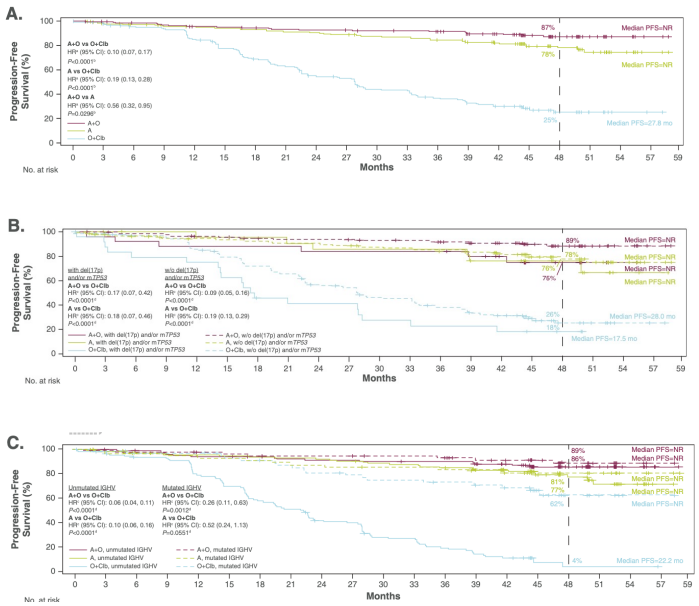
BTKi in prima linea

PFS in I linea in pazienti con IgVH unmutated

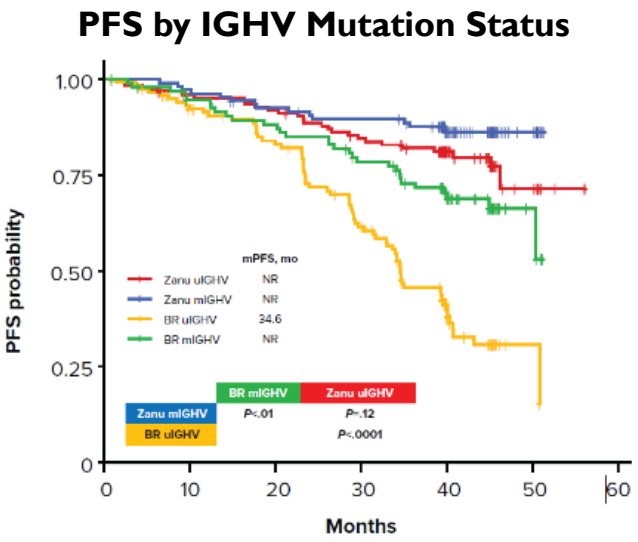
RESONATE-2



ELEVATE-TN



SEQUOIA



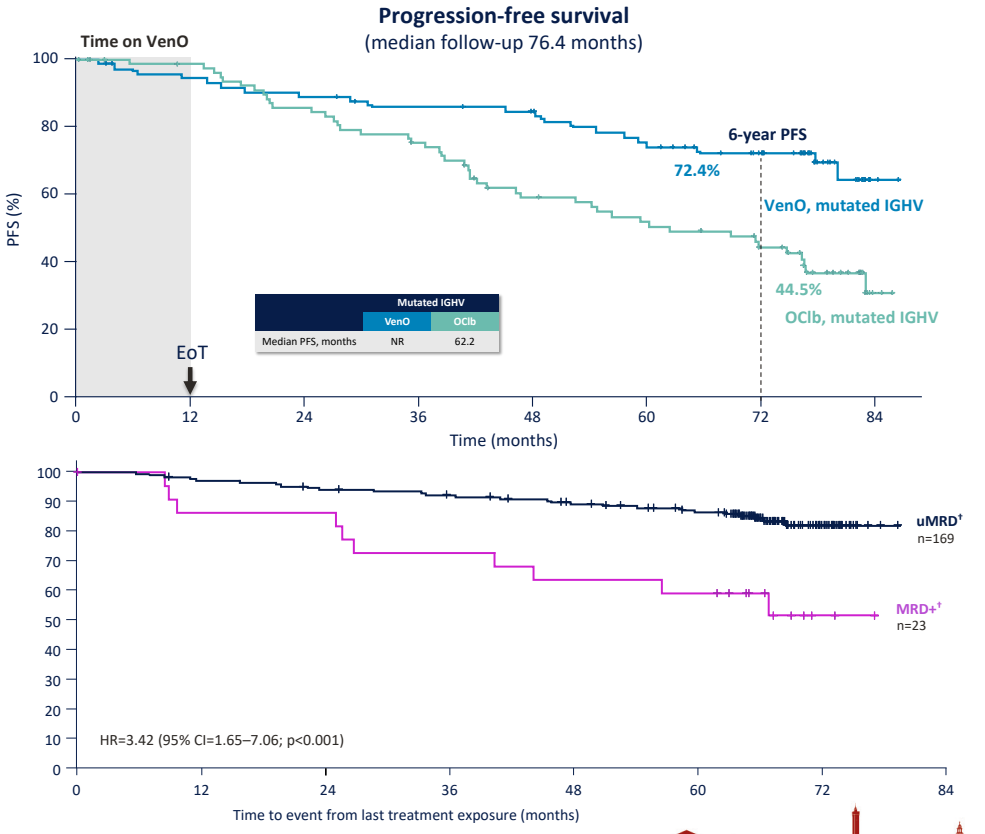
P.M. Barr et al. Blood Adv 2022
J. P. Sherman et al. Leukemia 2022
Xu L et al. ASH 2023; poster number: 1902

Ven-O in I linea

PFS in I linea in pazienti con IgVH unmutated

Table 1. Selected Patient Demographic and Disease Characteristics at Baseline (Intention-to-Treat Population).*

Characteristic	Venetoclax–Obinutuzumab (N=216)	Chlorambucil–Obinutuzumab (N=216)
Age ≥75 yr — no. (%)	72 (33.3)	78 (36.1)
Male sex — no. (%)	146 (67.6)	143 (66.2)
Binet stage — no. (%)†		
A	46 (21.3)	44 (20.4)
B	77 (35.6)	80 (37.0)
C	93 (43.1)	92 (42.6)
Tumor lysis syndrome risk category — no. (%)		
Low	29 (13.4)	26 (12.0)
Intermediate	139 (64.4)	147 (68.1)
High	48 (22.2)	43 (19.9)
Total CIRS score >6 — no. (%)‡	186 (86.1)	177 (81.9)
Calculated creatinine clearance <70 ml/min — no./total no. (%)	128/215 (59.5)	118/213 (55.4)
Cytogenetic subgroup — no./total no. (%)§		
Deletion in 17p	17/200 (8.5)	14/193 (7.3)
Deletion in 11q	36/200 (18.0)	38/193 (19.7)
Trisomy 12	36/200 (18.0)	40/193 (20.7)
No abnormalities	50/200 (25.0)	42/193 (21.8)
Deletion in 13q alone	61/200 (30.5)	59/193 (30.6)
IGHV mutational status — no./total no. (%)		
Mutated	76/200 (38.0)	83/208 (39.9)
Unmutated	121/200 (60.5)	123/208 (59.1)
Could not be evaluated	3/200 (1.5)	2/208 (1.0)
TP53 mutational status — no./total no. (%)		
Mutated	19/171 (11.1)	13/157 (8.3)
Unmutated	152/171 (88.9)	144/157 (91.7)

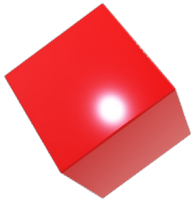


K. Fisher et al. NEJM, 2019
Al-Sawaf O, *et al.* EHA 2023. Abstract S145 (Oral).

…Filini!, segni!

BTKi single agent

V+O durata fissa



BTKi in I linea

TTD e TTNT in paziente con comorbidità cardiovascolare

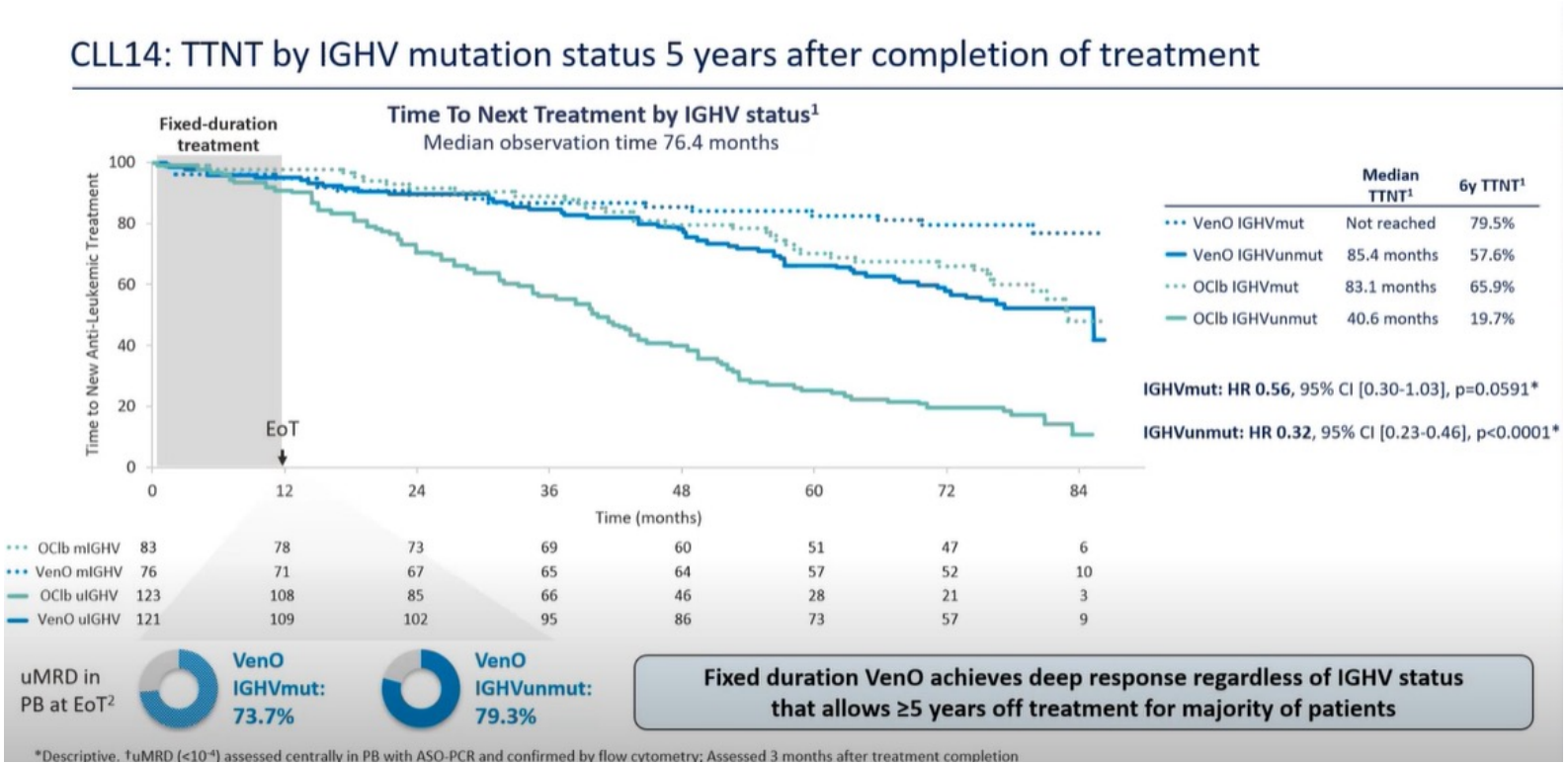
	All Patients	CHARGE-AF High Risk	CHA_2DS_2-VASc High Rsk
		1L	
	N = 2190	N = 438	N = 1080
Time to discontinuation (in months), mean ± SD [median]	20.0 ± 17.3 [15.7]	16.1 ± 15 [11.7]	18.0 ± 16.4 [13.7]
Patients with ≥12 mo of follow-up	N = 1699	N = 320	N=808
Persistent on treatment for ≥12 mo, n (%)	1294 (76.2)	217 (67.8)	577 (71.4)
Patients with ≥24 mo of follow-up	N = 1045	N = 177	N = 478
Persistent on treatment for ≥24 mo, n (%)	730 (69.9)	110 (62.1)	319 (66.7)
Patients with ≥36 mo of follow-up	N = 625	N = 86	N = 262
Persistent on treatment for ≥36 mo, n (%)	386 (61.8)	49 (57.0)	156 (59.5)
		2L+	
	N = 1851	**N = 324**	**N = 824**
Time to discontinuation (in months), mean ± SD [median]	19.3 ± 19.0 [12.5]	15.4 ± 15.9 [9.5]	17.2 ± 17.6 [10.6]
Patients with ≥12 mo of follow-up	N = 1319	N = 212	N = 563
Persistent on treatment for ≥12 mo, n (%)	950 (72.0)	149 (70.3)	391 (69.4)
Patients with ≥24 mo of follow-up	N = 873	N = 113	N = 340
Persistent on treatment for ≥24 mo, n (%)	566 (64.8)	69 (61.1)	208 (61.2)
Patients with ≥36 mo of follow-up	N = 589	N = 64	N = 216
Persistent on treatment for ≥36 mo, n (%)	343 (58.2)	39 (60.9)	123 (56.9)

Abbreviations: 1L = first line; 2L+ = second or later line; CHARGE-AF = Cohorts for Aging and Research in Genomic Epidemiology–Atrial Fibrillation; SD: standard deviation.

A. Narezkina et al. Clinical Lymphoma, Myeloma and Leukemia. 2022

Ven-O in I linea

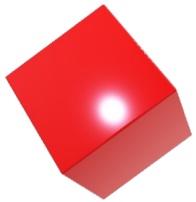
TNTT



Al-Sawaf O, *et al.* EHA 2023. Abstract S145 (Oral).

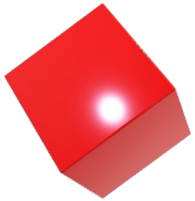
…Filini!, segni!

BTKi single agent



PFS

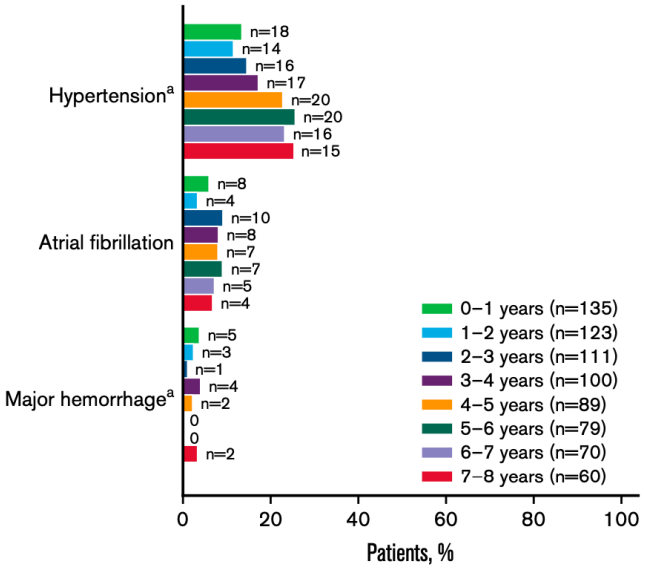
V+O durata fissa



BTKi in prima linea

Eventi avversi CV rilevanti

RESONATE-2



ELEVATE-TN

	A + O (*n* = 178)		A (*n* = 179)
Treatment exposure, median (range), months	46.6 (2.3–58.6)		45.7 (0.3–59.3)
Common AEs (in ≥ 25% of patients [any grade] in any group), *n* (%)			
	Any grade	Grade ≥3	Any grade
Diarrhea	73 (41.0)	9 (5.1)	72 (40.2)
Headache	71 (39.9)	2 (1.1)	68 (38.0)
Neutropenia	60 (33.7)	55 (30.9)	22 (12.3)
Fatigue	50 (28.1)	4 (2.2)	39 (21.8)
Arthralgia	47 (26.4)	2 (1.1)	35 (19.6)
Cough	46 (25.8)	1 (0.6)	40 (22.3)
URTI	44 (24.7)	4 (2.2)	46 (25.7)
Nausea	41 (23.0)	0	41 (22.9)
IRR	25 (14.0)	5 (2.8)	0
Selected events of clinical interest, *n* (%)			
Cardiac events[a]	37 (20.8)	14 (7.9)[b]	34 (19.0)
Atrial fibrillation/flutter	7 (3.9)	1 (0.6)	11 (6.1)
Bleeding	84 (47.2)	5 (2.8)	75 (41.9)
Major bleeding[d]	7 (3.9)	5 (2.8)	7 (3.9)
Hypertension	14 (7.9)	6 (3.4)	13 (7.3)
Infections	134 (75.3)	42 (23.6)	132 (73.7)
SPMs	28 (15.7)	13 (7.3)	24 (13.4)
Excluding NMS	15 (8.4)	10 (5.6)	11 (6.1)

a Cardiac events that occurred in >1 patient (any grade; other than atrial fibrillation) in any group include angina pectoris, palpitations, atrioventricular block complete, myocardial ischemia, tachycardia, bradycardia, cardiac failure, left ventricular failure, myocardial infarction, pericardial effusion, acute myocardial infarction, and supraventricular tachycardia.

SEQUOIA

	Patients without del(17)(p13·1)			
	Group A, zanubrutinib (n=240*)			
	Grade 1–2	Grade 3	Grade 4	Grade 5
Any	98 (41%)	87 (36%)	28 (12%)	11 (5%)
Serious	16 (7%)	49 (20%)	12 (5%)	11 (5%)
Common adverse events				
Contusion	46 (19%)	0	0	0
Upper respiratory tract infection	39 (16%)	2 (1%)	0	0
Diarrhoea	32 (13%)	2 (1%)	0	0
Arthralgia	30 (13%)	2 (1%)	0	0
Neutropenia	10 (4%)	11 (5%)	16 (7%)	0
Hypertension	14 (6%)	15 (6%)	0	0
Fatigue	25 (10%)	3 (1%)	0	0
Cough	27 (11%)	0	0	0
Headache	26 (11%)	0	0	0
Rash	26 (11%)	0	0	0
Constipation	23 (10%)	1 (<1%)	0	0
Nausea	24 (10%)	0	0	0
Back pain	21 (9%)	0	0	0
Pyrexia	17 (7%)	0	0	0
Vomiting	17 (7%)	0	0	0
Pneumonia	8 (3%)	4 (2%)	0	0
Anaemia	10 (4%)	1 (<1%)	0	0
Basal cell carcinoma	10 (4%)	1 (<1%)	0	0
Thrombocytopenia	5 (2%)	3 (1%)	1 (<1%)	0
Infusion-related reaction	1 (<1%)§	0	0	0
All bleeding adverse events¶	99 (41%)	8 (3%)	0	1 (<1%)
All cardiac adverse events¶	24 (10%)	10 (4%)	0	2 (1%)

P.M. Barr et al. Blood Adv 2022
J. P. Sherman et al. Leukemia 2022
C. Tam et al. Lancet, 2023

Ven-O in I linea

Eventi avversi CV rilevanti

5.7% con eventi vascolari G≥3
- Ipertensione
- Ipotensione

7.5% con reazione infusionale G≥3

14.6% hanno avuto una complicanza infettiva di G≥3

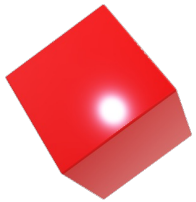
24.5% hanno sperimentato una neutropenia G≥3

Adverse Event	Venetoclax–Obinutuzumab (N=212)†			Chlorambucil–Obinutuzumab (N=214)		
	Maximum Grade 3	Maximum Grade 4	Maximum Grade 3 or 4	Maximum Grade 3	Maximum Grade 4	Maximum Grade 3 or 4
	number of patients (percent)					
Adverse event of grade 3 or 4	81 (38.2)	86 (40.6)	167 (78.8)	93 (43.5)	71 (33.2)	164 (76.6)
Adverse events of grade 3 or 4 that occurred in ≥3% of the patients in either treatment group‡						
Blood and lymphatic system disorders	59 (27.8)	69 (32.5)	128 (60.4)	61 (28.5)	57 (26.6)	118 (55.1)
→ Neutropenia	52 (24.5)	60 (28.3)	112 (52.8)	56 (26.2)	47 (22.0)	103 (48.1)
Thrombocytopenia	20 (9.4)	9 (4.2)	29 (13.7)	19 (8.9)	13 (6.1)	32 (15.0)
Anemia	16 (7.5)	1 (0.5)	17 (8.0)	13 (6.1)	1 (0.5)	14 (6.5)
Febrile neutropenia	7 (3.3)	4 (1.9)	11 (5.2)	4 (1.9)	4 (1.9)	8 (3.7)
Leukopenia	5 (2.4)	0	5 (2.4)	9 (4.2)	1 (0.5)	10 (4.7)
→ Infections and infestations	31 (14.6)	6 (2.8)	37 (17.5)	31 (14.5)	1 (0.5)	32 (15.0)
Pneumonia	8 (3.8)	1 (0.5)	9 (4.2)	8 (3.7)	0	8 (3.7)
Injury, poisoning, and procedural complications	21 (9.9)	5 (2.4)	26 (12.3)	29 (13.6)	1 (0.5)	30 (14.0)
→ Infusion-related reaction	16 (7.5)	3 (1.4)	19 (9.0)	21 (9.8)	1 (0.5)	22 (10.3)
Investigations	26 (12.3)	6 (2.8)	32 (15.1)	16 (7.5)	7 (3.3)	23 (10.7)
Neutrophil count decreased	7 (3.3)	2 (0.9)	9 (4.2)	4 (1.9)	6 (2.8)	10 (4.7)
Aspartate aminotransferase increased	5 (2.4)	0	5 (2.4)	7 (3.3)	0	7 (3.3)
Alanine aminotransferase increased	4 (1.9)	0	4 (1.9)	7 (3.3)	0	7 (3.3)
Metabolism and nutrition disorders§	19 (9.0)	6 (2.8)	25 (11.8)	11 (5.1)	1 (0.5)	12 (5.6)
Hyperglycemia	6 (2.8)	2 (0.9)	8 (3.8)	2 (0.9)	1 (0.5)	3 (1.4)
Gastrointestinal disorders ¶	16 (7.5)	1 (0.5)	17 (8.0)	6 (2.8)	1 (0.5)	7 (3.3)
Diarrhea‖	9 (4.2)	0	9 (4.2)	1 (0.5)	0	1 (0.5)
→ Cardiac disorders	9 (4.2)	1 (0.5)	10 (4.7)	10 (4.7)	2 (0.9)	12 (5.6)
Neoplasms benign, malignant, and unspecified, including cysts and polyps	10 (4.7)	3 (1.4)	13 (6.1)	7 (3.3)	1 (0.5)	8 (3.7)
→ Vascular disorders**	12 (5.7)	2 (0.9)	14 (6.6)	7 (3.3)	0	7 (3.3)
General disorders and administration-site conditions ††	14 (6.6)	0	14 (6.6)	6 (2.8)	0	6 (2.8)

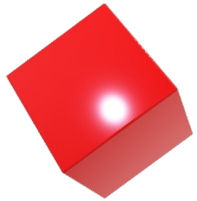
K. Fisher et al. NEJM, 2019

…Filini!, segni!

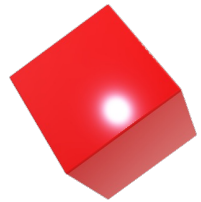
BTKi single agent



PFS



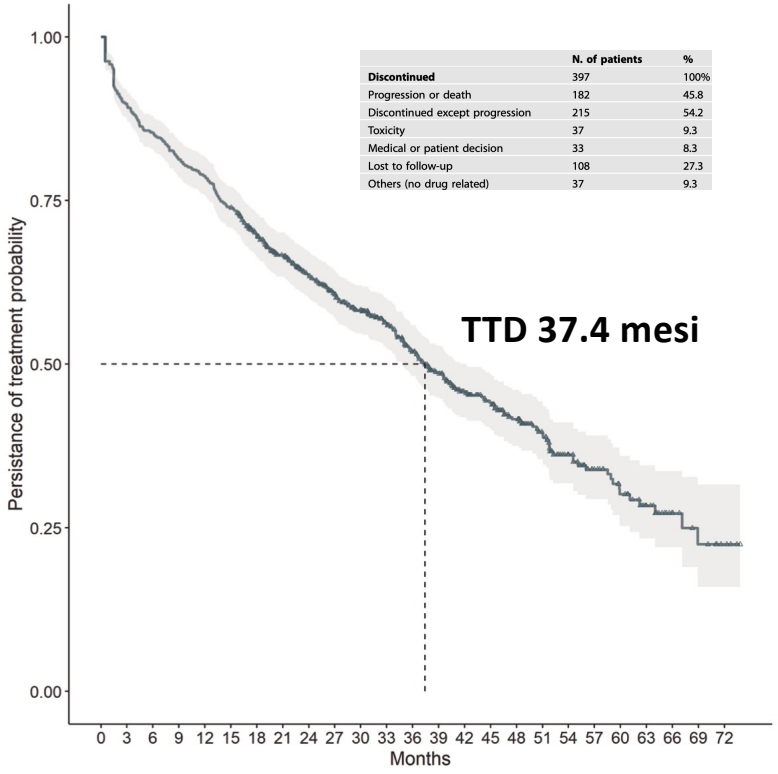
V+O durata fissa



TNTT

Ibrutinib in I linea

Aderenza al trattamento



	N. of patients	%
Discontinued	397	100%
Progression or death	182	45.8
Discontinued except progression	215	54.2
Toxicity	37	9.3
Medical or patient decision	33	8.3
Lost to follow-up	108	27.3
Others (no drug related)	37	9.3

Variable	**Total *N* = 747 (%)**
Sex M/F	456 (61.0)/291 (39.0)
Age	
median	71 years (range 32–95)
<65/65–69/≥70 years	215 (28.8)/132 (17.7)/400 (53.5)
Median time from diagnosis months (IQ range)	11 (2–39)
ECOG performance status 0/1/≥2	421 (56.4) / 275 (36.8)/51 (6.8)
Rai stage 0/I/II/III/IV	45 (6.0)/159 (21.3)/206 (27.6)/195 (26.1)/142 (19.0)
Bulky and/or elevated lymphocytosis and/or severe splenomegaly yes/no	546 (73.1)/201 (26.9)
del 17p absent/present/not available	134 (18.0)/568 (76.0)/45 (6.0)
TP53 WT/mutated /not available	112 (15.0)/429 (57.4)/206 (27.6)
del 17p only / TP53 mut only /del 17p & TP53 mut[a]	112 (15.0)/134 (17.9)/250 (33.4)
History of atrial fibrillation yes/no	25 (3.4)/722 (96.6)
Pre-existing severe heart disease yes/no	21 (2.8)/726 (97.2)
Renal impairment (Creatine clearance < 70 ml/min) yes/no	68 (9.1)/679 (90.9)
Concomitant use of anticoagulant yes/no	30 (4.0)/717 (96.0)
Number of experienced/less experienced centers[b]	24 (15.3)/133 (84.7)
Patients treated at experienced/less experienced centers	312 (41.8)/435 (58.2)

	HR (95% CI)
TTD variable	
Age years <65/65–69/≥70	
65–69 vs <65 years	1.16 (0.83–1.61)
≥70 vs <65 years	1.82 (1.41–2.35)
ECOG performance status 0/1/≥2	
1 vs 0	1.32 (1.07–1.63)
2+ vs 1	1.94 (1.35–2.77)
History of atrial fibrillation yes/no	1.80 (1.14–2.85)
Pre-existing severe heart disease yes/no	1.69 (1.03–2.77)
Renal impairment[a] no vs yes	0.72 (0.52–0.99)
OS variable	
Gender M vs F	1.38 (1.01–1.87)
Age years <65/65–69/>70	
65-69 vs <65 years	1.30 (0.81–2.09)
≥70 vs <65 years	1.68 (1.15–2.45)
ECOG performance status 0/1/≥2	
1 vs 0	1.43 (1.05–1.95)
2+ vs 1	2.59 (1.63–4.12)
Pre-existing severe heart disease yes/no	1.77 (0.89–3.50)
Renal impairment[a] no vs yes	0.72 (0.46–1.13)

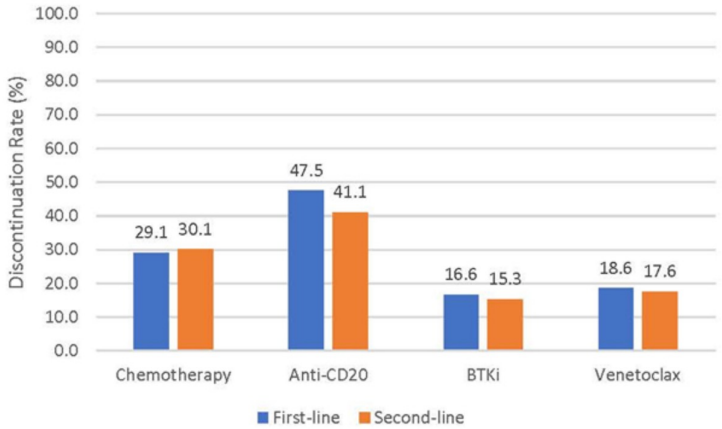
[a]Creatine clearance < 70 ml/min.

GM Rigolin et al. Blood Can Jour 2023

BTKi in I linea

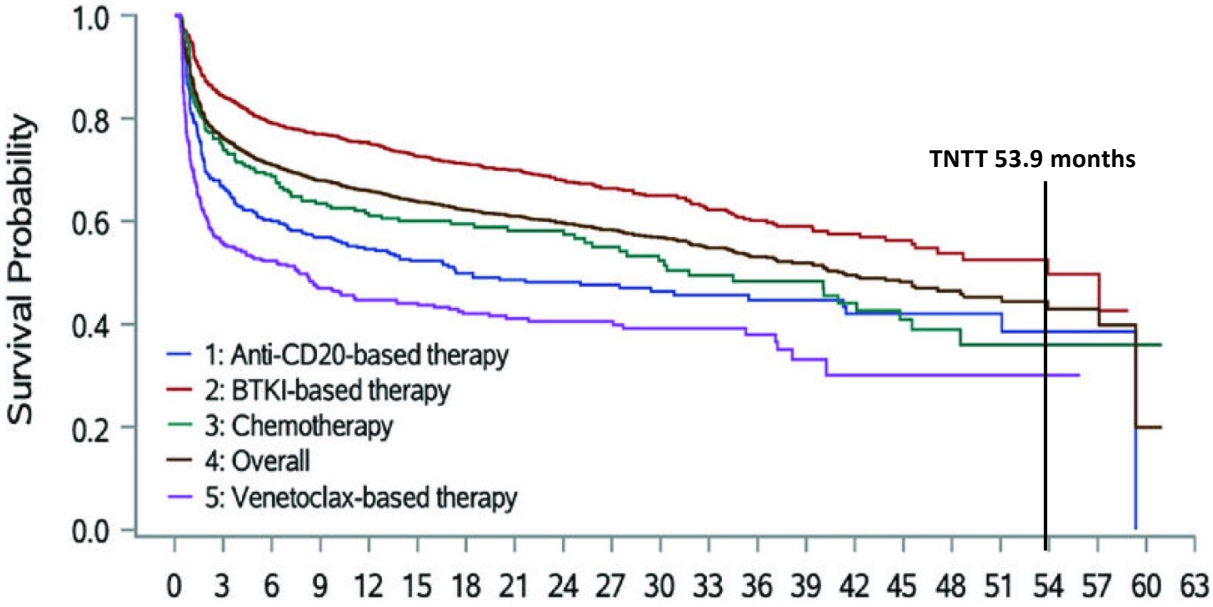
Aderenza al trattamento

N = 3431	
Age (yrs; median)	69
Males	63.8%
Frontline BTKi	60.1%
Frontline Ven	16%
Frontline antiCD20 regimens	15.4%
TTNT (median; BTKi)	53.9 months



AA Chanan-Khan et al. ASH 2023

Figure 1: Kaplan-Meier Curve of Time to Next Treatment for First-Line Regimens by Treatment Category

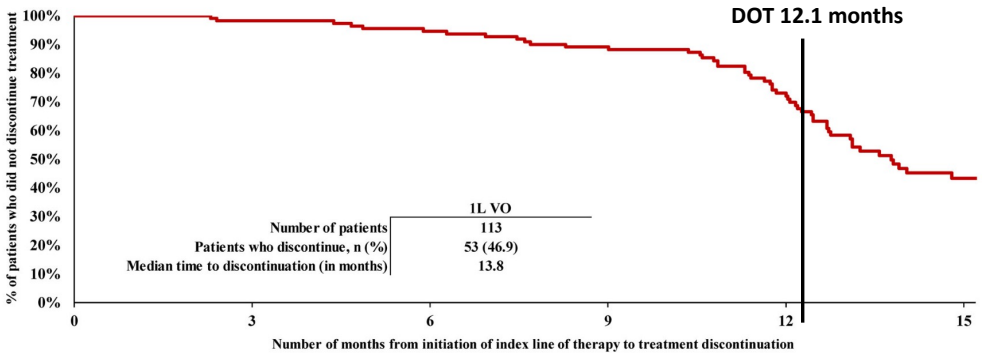


Ven-O in I linea

Aderenza al trattamento

Table 3. Treatment discontinuation characteristics for patients treated with 1L VO.

	1L VO $N=113$
Length of follow-up (in months), mean ± SD [median]	16.3 ± 5.0 [16.2]
Duration of active treatment (in months), mean ± SD [median]	11.6 ± 3.6 [12.1]
Duration < 12 cycles[a,b], ***n*** (%)	36 (31.9)
Duration ≥ 12 cycles[a], ***n*** (%)	77 (68.1)
Duration ≥ 15 cycles[c], ***n*** (%)	23 (29.9)
Patients with a next line of therapy, *n* (%)	2 (1.8)
Patients who discontinued treatment before completing 12 cycles with VO[a], *n* (%)	19 (16.8)
Patients who stopped treatment for >120 days	17 (15.0)
Patients who switched to another therapy (without stopping treatment for >120 days)	2 (1.8)

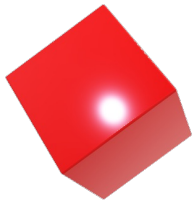


	Patients who completed ≥12 treatment cycles[a] $N=77$	Patients discontinuing treatment before completing 12 treatment cycles[a] $N=19$	Patients censored before completing 12 treatment cycles[a] $N=17$
Duration of the baseline period (in months), mean ± SD [median]	8.8 ± 4.4 [12.0]	9.6 ± 4.4 [12.0]	6.8 ± 5.1 [8.0]
Age, mean ± SD [median]	65.1 ± 10.4 [66.0]	70.4 ± 9.4 [72.0]	64.4 ± 9.5 [67.0]
Women, *n* (%)	25 (32.5)	6 (31.6)	5 (29.4)
Year of index date, *n* (%)			
2018	2 (2.6)	0 (0.0)	0 (0.0)
2019	33 (42.9)	11 (57.9)	0 (0.0)
2020	42 (54.5)	8 (42.1)	17 (100.0)
Practice type, *n* (%)			
Community	68 (88.3)	17 (89.5)	16 (94.1)
Academic	9 (11.7)	2 (10.5)	1 (5.9)
Quan-CCI, mean ± SD [median]	2.4 ± 1.0 [2.0]	2.4 ± 0.8 [2.0]	2.4 ± 1.2 [2.0]
Time from CLL/SLL diagnosis confirmation to the initiation of 1L therapy (in months), mean ± SD [median]	42.2 ± 51.5 [21.7]	35.1 ± 38.4 [23.5]	27.9 ± 41.4 [3.1]
Baseline medication use, *n* (%)			
Corticosteroids	12 (15.6)	4 (21.1)	1 (5.9)
Anti-hyperuricemics	50 (64.9)	13 (68.4)	9 (52.9)
Anti-emetics	34 (44.2)	9 (47.4)	4 (23.5)
Anti-infectives	23 (29.9)	1 (5.3)	4 (23.5)
Risk factors associated with TLS, *n* (%)			
Chronic kidney disease	1 (1.3)	2 (10.5)	0 (0.0)
Renal failure	2 (2.6)	0 (0.0)	0 (0.0)
Creatinine clearance (mL/min), mean ± SD [median]	89.9 ± 29.9 [84.8]	71.4 ± 23.9 [70.2]	90.6 ± 34.3 [82.7]
Creatine clearance <60 mL/min	10 (13.0)	7 (36.8)	3 (17.6)
Clinical characteristics, *n* (%)			
Rai stage at initial CLL/SLL diagnosis			
0	26 (33.8)	5 (26.3)	3 (17.6)
I	13 (16.9)	3 (15.8)	4 (23.5)
II	2 (2.6)	1 (5.3)	2 (11.8)
III	1 (1.3)	2 (10.5)	2 (11.8)
IV	12 (15.6)	2 (10.5)	1 (5.9)
Not documented	23 (29.9)	6 (31.6)	5 (29.4)
Most recent ECOG performance status			
0	37 (48.1)	9 (47.4)	7 (41.2)
1	20 (26.0)	2 (10.5)	7 (41.2)
2	1 (1.3)	2 (10.5)	1 (5.9)
3	2 (2.6)	0 (0.0)	0 (0.0)
4	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	17 (22.1)	6 (31.6)	2 (11.8)

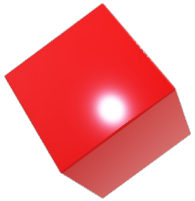
X. Lu et al. Curr Medical Res and Opinion 2023

…Filini!, segni!

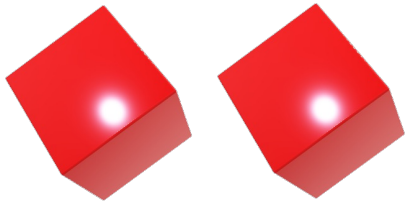
BTKi single agent



PFS



V+O durata fissa

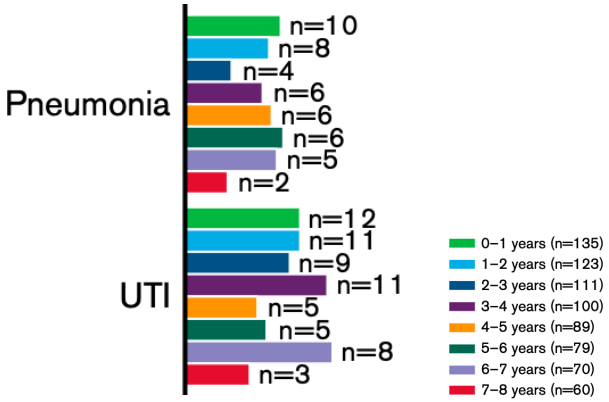


AEs TNTT

BTKi in prima linea

Infezioni

RESONATE-2



ELEVATE-TN

	A + O (*n* = 178)		A (*n* = 179)
Treatment exposure, median (range), months	46.6 (2.3–58.6)		45.7 (0.3–59.3)
Common AEs (in ≥ 25% of patients [any grade] in any group), *n* (%)			
	Any grade	Grade ≥3	Any grade
Diarrhea	73 (41.0)	9 (5.1)	72 (40.2)
Headache	71 (39.9)	2 (1.1)	68 (38.0)
Neutropenia	60 (33.7)	55 (30.9)	22 (12.3)
Fatigue	50 (28.1)	4 (2.2)	39 (21.8)
Arthralgia	47 (26.4)	2 (1.1)	35 (19.6)
Cough	46 (25.8)	1 (0.6)	40 (22.3)
URTI	44 (24.7)	4 (2.2)	46 (25.7)
Nausea	41 (23.0)	0	41 (22.9)
IRR	25 (14.0)	5 (2.8)	0
Selected events of clinical interest, *n* (%)			
Cardiac events[a]	37 (20.8)	14 (7.9)[b]	34 (19.0)
Atrial fibrillation/flutter	7 (3.9)	1 (0.6)	11 (6.1)
Bleeding	84 (47.2)	5 (2.8)	75 (41.9)
Major bleeding[d]	7 (3.9)	5 (2.8)	7 (3.9)
Hypertension	14 (7.9)	6 (3.4)	13 (7.3)
Infections	134 (75.3)	42 (23.6)	132 (73.7)
SPMs	28 (15.7)	13 (7.3)	24 (13.4)
Excluding NMS	15 (8.4)	10 (5.6)	11 (6.1)

URTI, *upper respiratory tract infections*

SEQUOIA

	Patients without del(17)(p13·1)			
	Group A, zanubrutinib (n=240*)			
	Grade 1–2	Grade 3	Grade 4	Grade 5
Any	98 (41%)	87 (36%)	28 (12%)	11 (5%)
Serious	16 (7%)	49 (20%)	12 (5%)	11 (5%)
Common adverse events				
Contusion	46 (19%)	0	0	0
Upper respiratory tract infection	39 (16%)	2 (1%)	0	0
Diarrhoea	32 (13%)	2 (1%)	0	0
Arthralgia	30 (13%)	2 (1%)	0	0
Neutropenia	10 (4%)	11 (5%)	16 (7%)	0
Hypertension	14 (6%)	15 (6%)	0	0
Fatigue	25 (10%)	3 (1%)	0	0
Cough	27 (11%)	0	0	0
Headache	26 (11%)	0	0	0
Rash	26 (11%)	0	0	0
Constipation	23 (10%)	1 (<1%)	0	0
Nausea	24 (10%)	0	0	0
Back pain	21 (9%)	0	0	0
Pyrexia	17 (7%)	0	0	0
Vomiting	17 (7%)	0	0	0
Pneumonia	8 (3%)	4 (2%)	0	0
Anaemia	10 (4%)	1 (<1%)	0	0
Basal cell carcinoma	10 (4%)	1 (<1%)	0	0
Thrombocytopenia	5 (2%)	3 (1%)	1 (<1%)	0
Infusion-related reaction	1 (<1%)§	0	0	0
All bleeding adverse events¶	99 (41%)	8 (3%)	0	1 (<1%)
All cardiac adverse events¶	24 (10%)	10 (4%)	0	2 (1%)

P.M. Barr et al. Blood Adv 2022
J. P. Sherman et al. Leukemia 2022
C. Tam et al. Lancet, 2023

BTKi in prima linea

Infezioni

	Alliance Woyach JA et al. 2018 [25]	Ascend Ghia P et al. 2020 [42]	Elevate-TN Sharman JP et al. 2020 [30]	Sequoia Tam CS et al. 2022 [45]
Study design	Phase III, MC, OL	Phase III, MC, OL	Phase III, MC, OL	Phase III, MC, OL
Enrolled period	December 2013–May 2016	February 2017–January 2018	September 2015–February 2017	October 2017–July 2019
ClinicalTrials.gov ID	NCT01886872	NCT02970318	NCT02475681	NCT03336333
Method of analysis	ITT	ITT	ITT	ITT
Response definition	iwCLL 2008 criteria	iwCLL 2008 criteria	iwCLL 2008 criteria	iwCLL 2008 criteria (CLL) or Lugano classification (SLL)
Safety assessment	NR	CTCAE v4.03	CTCAE v4.03	CTCAE v4.03
Inclusion criteria	Treatment-naive patients	Relapsed or refractory patients	Treatment-naive patients	Treatment-naive patients
Randomization	1:1	1:1	1:1	1:1
Masking	No	No	No	No
Randomization stratification	Risk factors for CLL	Presence or absence of del[17p] status, ECOG PS score, and lines of prior therapy received	Presence or absence of del[17p], ECOG PS score, and geographic region	Based on age, Binet stage, IGHV mutational status, and geographical region
Primary outcome	PFS	PFS	PFS	PFS
Secondary outcome	OS, ORR, CR, safety, etc	ORR, OS, DOR, safety, etc	ORR, OS, CR, safety, etc	ORR, OS, safety, etc
Definition PFS	The interval time from randomization until disease progression or death from any cause	The time from randomization until disease progression or death	The time from randomization until disease progression or death	The time from randomization until disease progression or death
Intervention arm	Ibrutinib 420 mg/day	Acalabrutinib 200 mg/day	Acalabrutinib 200 mg/day	Zanubrutinib 320 mg/day
Standard of care arm	Bendamustine 90 mg/m^2 + Rituximab (375 mg/m^2)	Bendamustine 70 mg/m^2 or Idelalisib 300 mg/day + Rituximab (500 mg/m^2)	Chlorambucil (0.5 mg/kg on day 1 and day 15) + Obinutuzumab (1000 mg)	Bendamustine 90 mg/m^2 + Rituximab (500 mg/m^2)
Sample size	365	310	356	479
Time of initial response assessment	NR	NR	Week 12	Week 12
Crossover design	Yes	Yes	Yes	Yes

T. T. Nguyen et al. Cancers, 2023

BTKi in prima linea

Infezioni

Adverse Events	BTK Inhibitor		Combination Therapy		Risk Ratio	95% Confident Interval	I^2 (%)	p-Value
	Events	Total	Event	Total				
AE any grade	543	573	530	549	0.98	0.91–1.06	51	0.13
AE of grade 3 or higher	452	753	535	725	0.82	0.55–1.23	92	<0.01
AE of grade 3 or higher subgroup	319	573	424	549	0.73	0.54–0.98	64	0.06
Anemia	54	753	49	725	1.06	0.45–2.49	30	0.23
Arthralgia	7	753	3	725	1.79	0.58–5.57	0	0.81
Diarrhea	11	753	42	725	1.58	0.22–11.56	43	0.15
Fatigue	16	753	12	725	1.29	0.92–1.82	0	0.97
Hemorrhage	21	753	8	752	2.01	0.54–7.44	0	0.40
Infection	150	753	127	725	1.18	0.68–2.03	52	0.10
Neutropenia	103	753	315	725	0.32	0.18–0.58	70	0.02
Neutropenia subgroup	74	599	257	572	0.28	0.14–0.55	44	0.17
Pneumonia	23	573	26	549	0.85	0.18–4.05	30	0.24
Sepsis	14	753	25	725	0.55	0.32–0.93	0	0.86
SPM	45	753	20	725	2.09	1.01–4.36	0	0.53
Thrombocytopenia	27	753	73	725	0.37	0.20–0.70	0	0.48
URTI	17	753	22	725	0.77	0.51–1.16	0	0.91
UTI	14	753	13	725	1.03	0.21–4.95	22	0.28
Cardiac adverse events	35	573	23	549	1.50	0.17–13.49	62	0.07
Atrial fibrillation	22	753	10	725	1.74	0.30–9.96	32	0.22
Ventricular tachycardia	2	753	0	725	-	-	-	-
Sudden death	7	420	2	403	-	-	-	-
Hypertension	80	753	43	725	1.64	0.60–4.51	36	0.19

T. T. Nguyen et al. Cancers, 2023

Ven-O in I linea

Eventi avversi CV rilevanti

5.7% con eventi vascolari G≥3
- Ipertensione
- Ipotensione

7.5% con reazione infusionale G≥3

14.6% hanno avuto una complicanza infettiva di G≥3

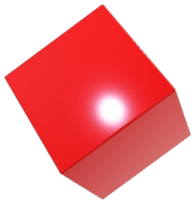
24.5% hanno sperimentato una neutropenia G≥3

Adverse Event	Venetoclax–Obinutuzumab (N=212)†			Chlorambucil–Obinutuzumab (N=214)		
	Maximum Grade 3	Maximum Grade 4	Maximum Grade 3 or 4	Maximum Grade 3	Maximum Grade 4	Maximum Grade 3 or 4
	number of patients (percent)					
Adverse event of grade 3 or 4	81 (38.2)	86 (40.6)	167 (78.8)	93 (43.5)	71 (33.2)	164 (76.6)
Adverse events of grade 3 or 4 that occurred in ≥3% of the patients in either treatment group‡						
Blood and lymphatic system disorders	59 (27.8)	69 (32.5)	128 (60.4)	61 (28.5)	57 (26.6)	118 (55.1)
Neutropenia	52 (24.5)	60 (28.3)	112 (52.8)	56 (26.2)	47 (22.0)	103 (48.1)
Thrombocytopenia	20 (9.4)	9 (4.2)	29 (13.7)	19 (8.9)	13 (6.1)	32 (15.0)
Anemia	16 (7.5)	1 (0.5)	17 (8.0)	13 (6.1)	1 (0.5)	14 (6.5)
Febrile neutropenia	7 (3.3)	4 (1.9)	11 (5.2)	4 (1.9)	4 (1.9)	8 (3.7)
Leukopenia	5 (2.4)	0	5 (2.4)	9 (4.2)	1 (0.5)	10 (4.7)
Infections and infestations	31 (14.6)	6 (2.8)	37 (17.5)	31 (14.5)	1 (0.5)	32 (15.0)
Pneumonia	8 (3.8)	1 (0.5)	9 (4.2)	8 (3.7)	0	8 (3.7)
Injury, poisoning, and procedural complications	21 (9.9)	5 (2.4)	26 (12.3)	29 (13.6)	1 (0.5)	30 (14.0)
Infusion-related reaction	16 (7.5)	3 (1.4)	19 (9.0)	21 (9.8)	1 (0.5)	22 (10.3)
Investigations	26 (12.3)	6 (2.8)	32 (15.1)	16 (7.5)	7 (3.3)	23 (10.7)
Neutrophil count decreased	7 (3.3)	2 (0.9)	9 (4.2)	4 (1.9)	6 (2.8)	10 (4.7)
Aspartate aminotransferase increased	5 (2.4)	0	5 (2.4)	7 (3.3)	0	7 (3.3)
Alanine aminotransferase increased	4 (1.9)	0	4 (1.9)	7 (3.3)	0	7 (3.3)
Metabolism and nutrition disorders§	19 (9.0)	6 (2.8)	25 (11.8)	11 (5.1)	1 (0.5)	12 (5.6)
Hyperglycemia	6 (2.8)	2 (0.9)	8 (3.8)	2 (0.9)	1 (0.5)	3 (1.4)
Gastrointestinal disorders ¶	16 (7.5)	1 (0.5)	17 (8.0)	6 (2.8)	1 (0.5)	7 (3.3)
Diarrhea‖	9 (4.2)	0	9 (4.2)	1 (0.5)	0	1 (0.5)
Cardiac disorders	9 (4.2)	1 (0.5)	10 (4.7)	10 (4.7)	2 (0.9)	12 (5.6)
Neoplasms benign, malignant, and unspecified, including cysts and polyps	10 (4.7)	3 (1.4)	13 (6.1)	7 (3.3)	1 (0.5)	8 (3.7)
Vascular disorders**	12 (5.7)	2 (0.9)	14 (6.6)	7 (3.3)	0	7 (3.3)
General disorders and administration-site conditions ††	14 (6.6)	0	14 (6.6)	6 (2.8)	0	6 (2.8)

K. Fisher et al. NEJM, 2019

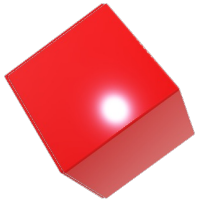
…Filini!, segni!

BTKi single agent

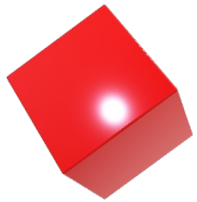


PFS

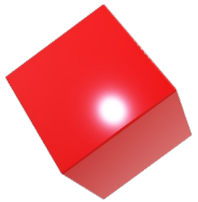
Infezioni



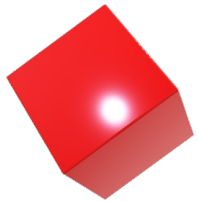
V+O durata fissa



Aderenza



AEs

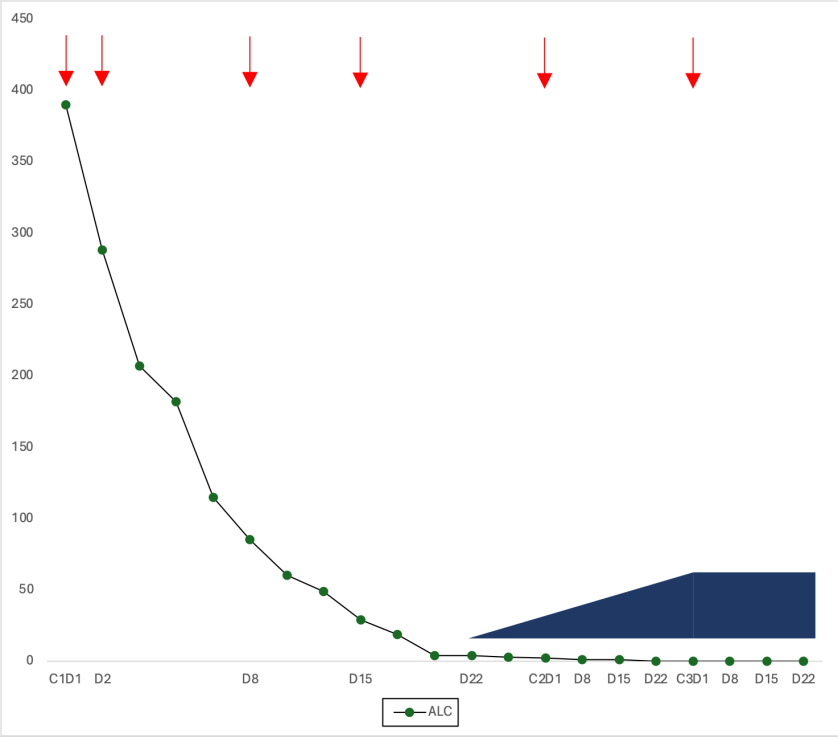


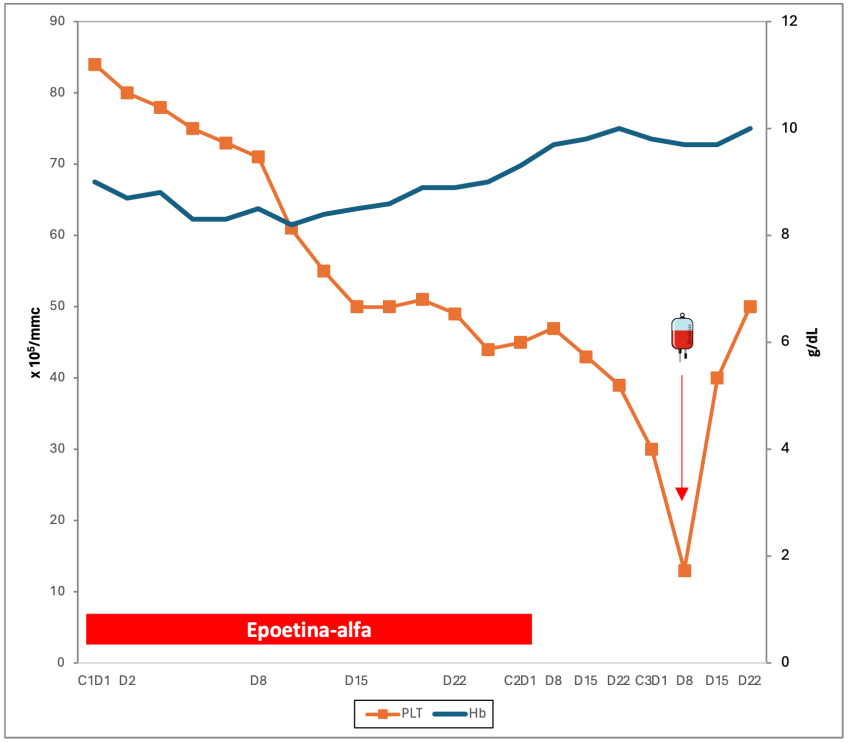
TNTT

Infezioni

…torniamo ad A.G., 78 anni

I linea Ven-O; paziente ricoverato a Gennaio 2024; dimesso dopo il C1D15





A.G., 78 anni, + 4 mesi dall'inizio della terapia

- Paziente in buone condizioni generali con aumento ponderale +4Kg
- Sospeso supporto con epoetina-alfa
- Iniziato ramp-up del Venetoclax in regime DH
- **No TLS (clinica/laboratoristica)**
- **No reazioni infusionali**
- Singolo caso di trombocitopenia G4 (C2D8) che ha richiesto trasfusione e sospensione per 5 giorni del venetoclax (400mg)
- No eventi di neutropenia di G > 2
- Rivalutazione di malattia dopo il C6
- **Es ematochimici (Maggio 2024):** Hb 11.3, GB 3080 (N 1900 L 880), PLTs 114000. Crea 1.4.

GRAZIE PER L'ATTENZIONE