LEUCEMIA LINFATICA CRONICA, OGGI... ED OLTRE

Il profilo di tossicità: non può che giocare un ruolo nella scelta

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Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other

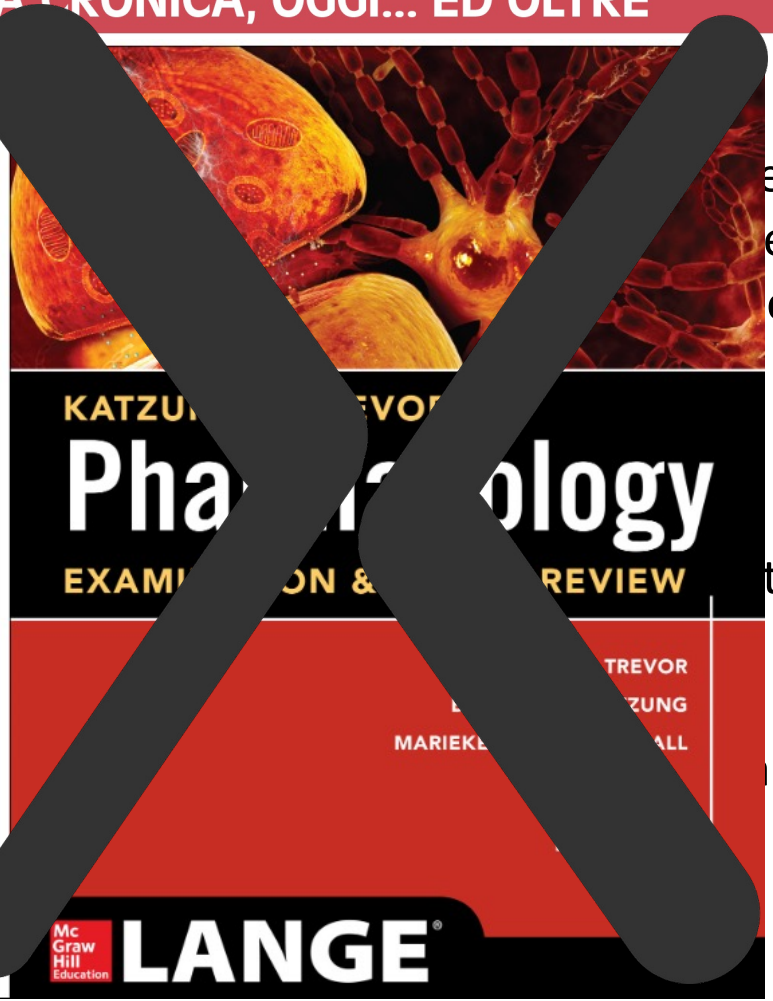
1 Per tossicità si inter
eventi avversi di una s
(farmaco, xenobiotico
sugli organismi viventi

e dei farmaci, a
e concentrazioni, si
edicamenti mentre a
comportano da tossico

3 L'Indice Terapeutico
confronto tra dosi tera
efficaci e dosi tossiche
esso è un indice della s
(maneggevolezza) dell

tossici possono

sostanza
i metaboliti



Fattori che influenzano la Tossicità

1) **Dose**
2) **Struttura molecolare** → mimetismo
3) **Meccanismo d'azione**
4) **Fattori relativi all'individuo**

Biodisponibilità
Metabolismo
Escrezione

tossicocinetica s'intende l'evolversi temporale delle concentrazioni tissutali del tossico dovuto all'equilibrio tra cinetiche di assorbimento, distribuzione ed eliminazione

1) I fattori genetici
2) La specie
3) Il sesso
4) L'età
5) Le condizioni patologiche
6) L'induzione degli enzimi microsomiali epatici

LA VERA SFIDA è PREVENIRE EFFETTI TOSSICI

Giocare d'Anticipo

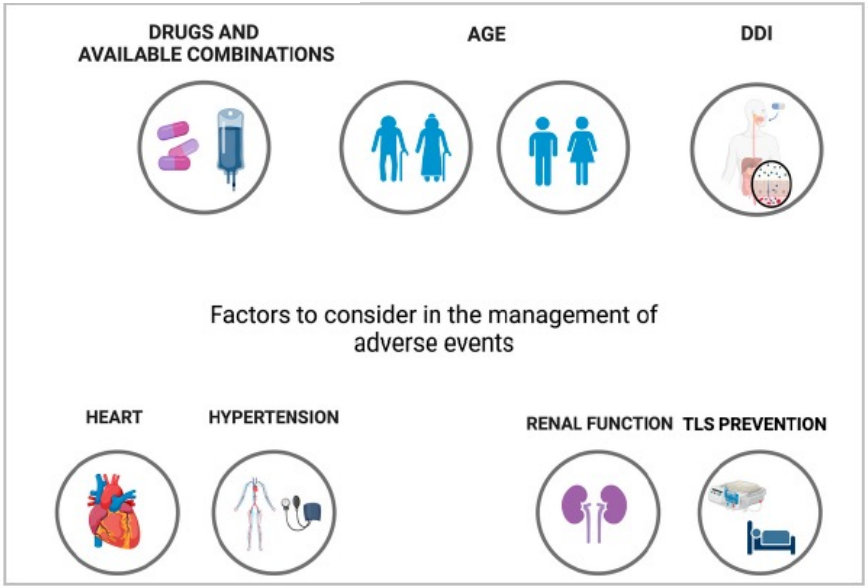
cancers MDPI

Review

Chronic Lymphocytic Leukemia: Management of Adverse Events in the Era of Targeted Agents

Andrea Galitzia [1,†], Monica Maccaferri [2,†], Francesca Romana Mauro [3], Roberta Murru [4,*,‡] and Roberto Marasca [2,5,‡]

Main factors influencing treatment selections and toxicity development and management.



Management of AEs extends beyond dose adjustments or treatment discontinuation and includes vigilant monitoring and targeted interventions for specific complications. In this context, perfect collaboration between specialists, employing a multidisciplinary approach,
leads to achieving better outcomes.

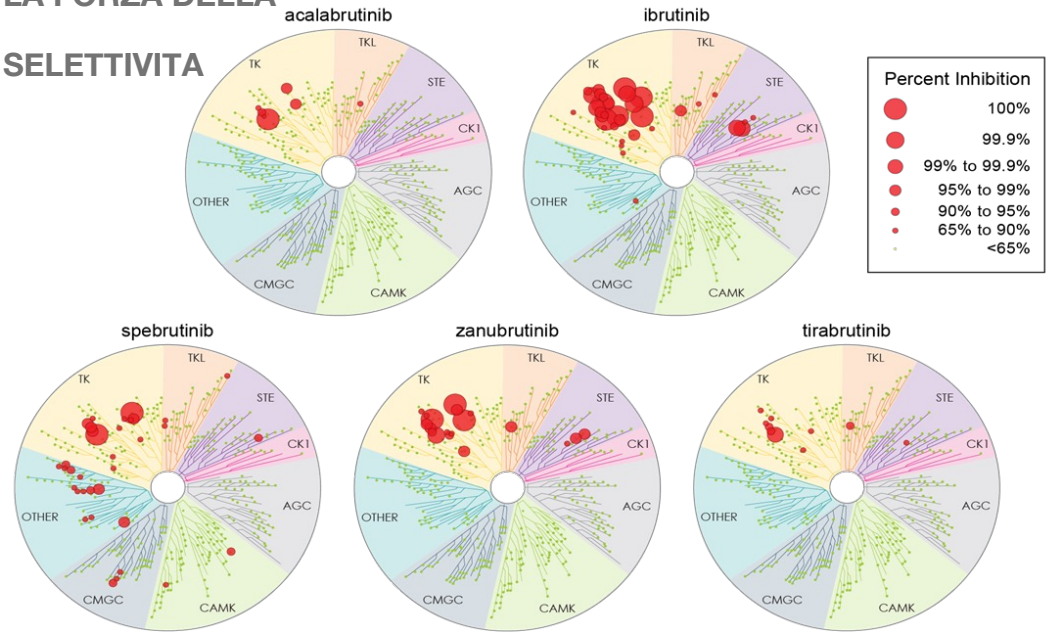
Cancers **2024**, 16, 1996. https://doi.org/10.3390/cancers16111996

Selectivity: Kinome Profiling of BTK Inhibitors Using DiscoverX KINOMEscan at a Single Dose (1 µM)

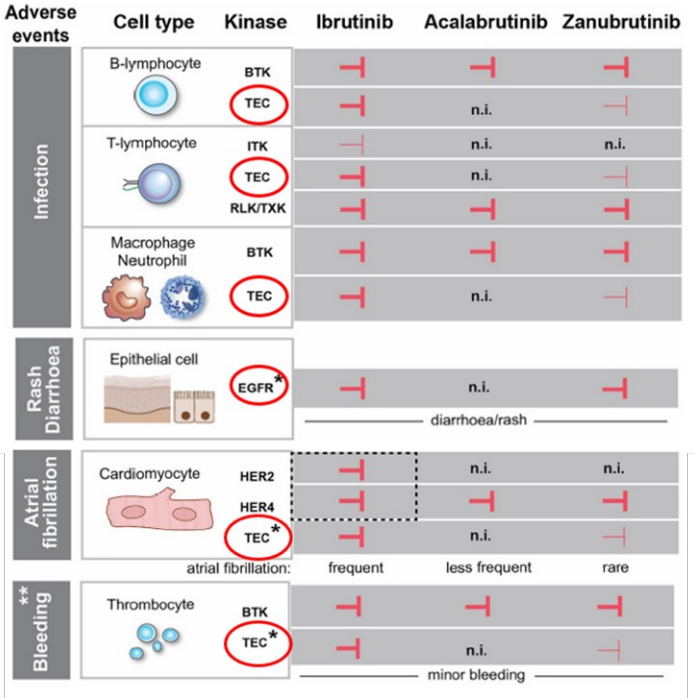
Acalabrutinib is a Potent and Selective BTK Inhibitor That Minimizes Off-Target Activity

LA FORZA DELLA

SELETTIVITA



Herman SEM, et al.. ClinCancer Res. 2017



Estupinan et al. Frontiers in Cell and Dev Biology 2021

Dati aggregati provenienti da tutti gli studi registrativi in vari contesti di malattia indicano che, in termini di **fibrillazione atriale di ogni grado**, l'incidenza diminuisce da ibrutinib ad acalabrutinib e da questo a zanubrutinib, in accordo con la crescente selettività chinasica dei tre BTKi misurata in condizioni farmacologicamente plausibili.

In termini di **sanguinamenti maggiori** non sembrano esserci grandi differenze tra i tre BTKi, probabilmente a causa dell' alta omologia esistente tra BTK

Un discorso a parte merita l'**ipertensione di ogni grado**, rispetto alla quale i dati in aggregato sembrano ribaltare l'ordine della selettività chinasica dei tre BTKi e indicano una eguale maggiore incidenza con ibrutinib e zanubrutinib, e una minore incidenza con acalabrutinib.

Zanubrutinib	Irreversible, covalent binding to Cysteine-481	CLL/SLL Mantle cell lymphoma* Relapsed/refractory marginal zone lymphoma** Waldenstrom's macroglobulinemia	SEQUOIA ASPEN ALPINE	Arrhytmia	*AF* *VA*	2–5% 0.2–0.8%
				Hypertension		10–23.5%
				Major bleeding		2.9–5.9%

**After at least one previous anti-CD20–based therapy*
***Who have received at least one anti-CD20–based therapy but it did not work or is no longer working*

AF: atrial fibrillation; VA: cardiac arrest, unexplained/unwitnessed death, or cardiac death

Mod. da Ng J. et al. American College of Cardiology 2023. Expert Analysis

Slide adattata da Prof. Minotti

ELEVATE-TN – 6 years follow up

- **Median study follow-up was 74.5 months (range, 0.0–89.0 months).**
- **54% (A+O; n=96) and 47% (A; n=84) of patients continue to receive treatment.**

Parameter	A+O (n=179)	A (n=179)	O+Clb (n=177)
Treated with ≥1 dose of study drug	179 (100.0)	178 (99.4)	169 (95.5)
Randomized but not treated	0	1 (0.6)	8 (4.5)
Treatment status[a]			
Ongoing	96 (53.6)	84 (46.9)	0
Completed regimen	NA	NA	136 (76.8)
Discontinued regimen	83 (46.4)	95 (53.1)	41 (23.2)
Death	5 (2.8)	16 (8.9)	3 (1.7)
Adverse event	38 (21.2)	[illegible]	25 (14.1)
Acalabrutinib-related AE	9 (5.0)	13 (7.3)	NA
Lost to follow-up	2 (1.1)	[illegible]	1 (0.6)
CLL progressive disease	10 (5.6)	25 (14.0)	4 (2.3)
Withdrawal of consent	5 (2.8)	3 (1.7)	6 (3.4)
Investigator's discretion	13 (7.3)	13 (7.3)	0
Other	10 (5.6)	5 (2.8)	2 (1.1)

- **Data are n (%) unless otherwise specified.**
- [a]Treatment status refers to the period on treatment. For A-containing arms, patients are treated to progression or unacceptable toxicity; treatment period is 6 months fixed duration for O+Clb.

A = acalabrutinib; AE = adverse events; Clb = chlorambucil; CLL = chronic lymphocytic leukemia; DCO = data cutoff; NA = not applicable; O = Obinutuzumab.

- Sharman JP et al. Oral Presentation Presented at: ASH; December 9-12, 2023; San Diego.

ELEVATE-TN – 6 years follow up
Safety: Most Common AEs in ≥5% of Patients

- Most common AEs reported were **diarrhea** (43.8% [A+O] and 42.5% [A]), **headache** (40.4% [A+O] and 39.1% [A]), and **arthralgia** (36.0% [A+O] and 27.4% [A])
- The most common AE profile was consistent with the earlier analyses as summarized in the table below.

AEs[a]	A+O (n=178)		A (n=179)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Diarrhea	78 (43.8)	11 (6.2)	76 (42.5)	1 (0.6)
Headache	72 (40.4)	2 (1.1)	70 (39.1)	2 (1.1)
Arthralgia	64 (36.0)	4 (2.2)	49 (27.4)	2 (1.1)
Neutropenia	61 (34.3)	55 (30.9)	23 (12.8)	21 (11.7)
Fatigue	55 (30.9)	4 (2.2)	43 (24.0)	2 (1.1)
Cough	50 (28.1)	1 (0.6)	45 (25.1)	1 (0.6)
COVID-19	44 (24.7)	16 (9.0)	38 (21.2)	13 (7.3)
Thrombocytopenia	26 (14.6)	15 (8.4)	16 (8.9)	6 (3.4)
Pneumonia	25 (14.0)	13 (7.3)	27 (15.1)	11 (6.1)
Hypertension	17 (9.6)	8 (4.5)	19 (10.6)	9 (5.0)
Syncope[b]	12 (6.7)	9 (5.1)	5 (2.8)	4 (2.2)

Data are n (%) unless otherwise specified.

AEs in ≥30% of acalabrutinib-treated patients or grade ≥3 in ≥5% of acalabrutinib-treated patients. [b]Cardiac-related syncope events were reported separately. A = acalabrutinib; AEs = adverse events; Clb = chlorambucil; O = Obinutuzumab.

ELEVATE-TN – 6 years follow up
Safety: Events of Clinical Interest

- The median duration of treatment was 74.4 months for A in A+O, and 72 months for A monotherapy, and 5.5 and 5.6 months for O in the A+O and O+Clb arms respectively, and 5.5 months for Clb in O+Clb arm.

	A+O (n=178)		A (n=179)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Cardiac events	49 (27.5)	22 (12.4)	42 (23.5)	21 (11.7)
Atrial fibrillation	13 (7.3)	3 (1.7)	16 (8.9)	3 (1.7)
Bleeding	95 (53.4)	12 (6.7)	81 (45.3)	8 (4.5)
Major bleeding	16 (9.0)	12 (6.7)	10 (5.6)	8 (4.5)
Hypertension[a]	20 (11.2)	8 (4.5)	20 (11.2)	9 (5.0)
Infections	147 (82.6)	63 (35.4)	144 (80.4)	50 (27.9)
SPMs	36 (20.2)	18 (10.1)	35 (19.6)	9 (5.0)
SPMs excluding non-melanoma skin	24 (13.5)	13 (7.3)	22 (12.3)	7 (3.9)

Data are n (%) unless otherwise specified.

[a]Hypertension events were based on Standardized MedDRA query (SMQ) Hypertension (narrow).

A = acalabrutinib; Clb = chlorambucil; O = obinutuzumab; SPM = secondary primary malignancies.

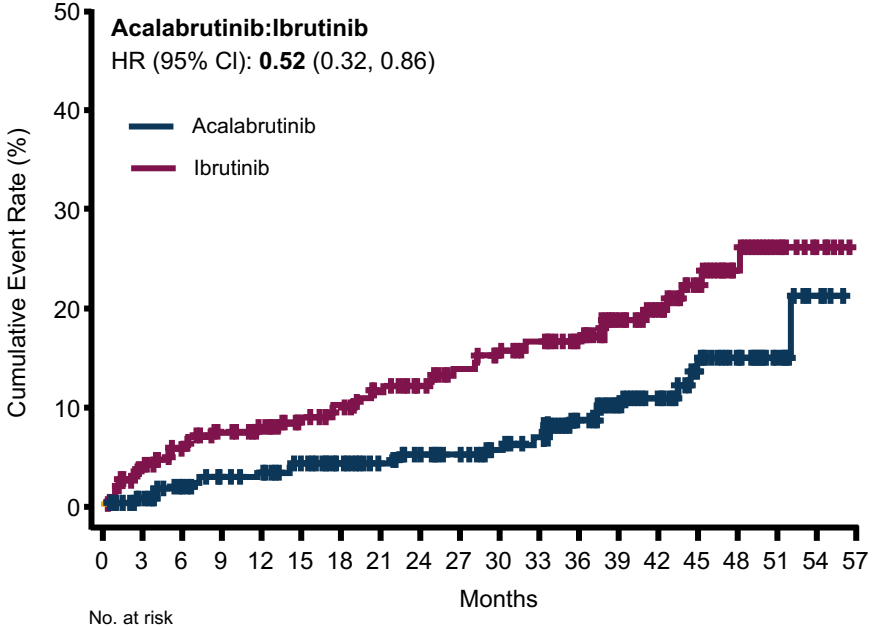
Sharman JP et al. Oral Presentation Presented at: ASH; December 9-12, 2023; San Diego.

ELEVATE RR – Safety

Safety: Atrial fibrillation/flutter and Hypertension

- **Lower cumulative incidences of any grade atrial fibrillation/flutter and hypertension with acalabrutinib**

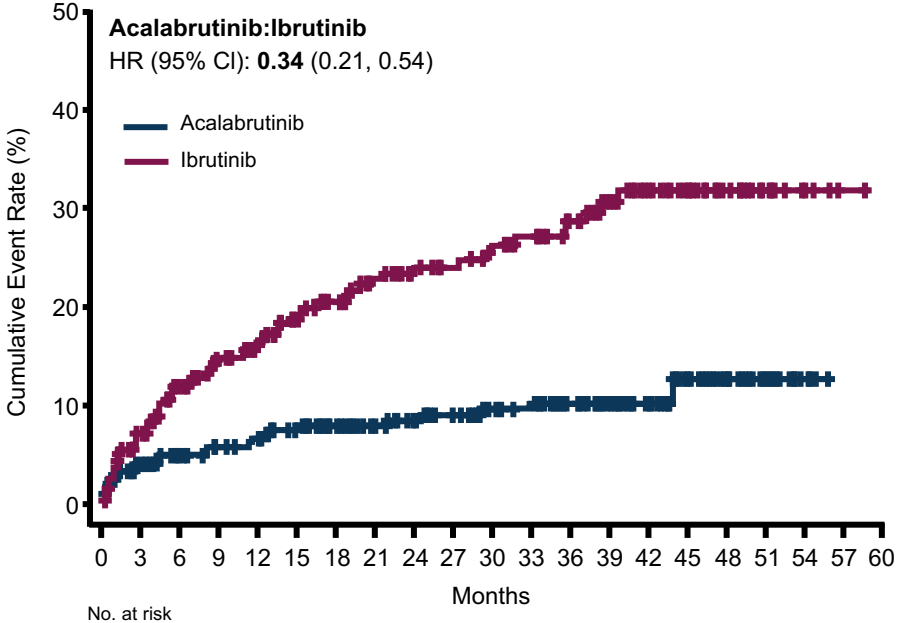
Atrial fibrillation/flutter



No. at risk

Acalabrutinib	266	255	240	231	228	218	206	197	188	183	172	167	142	115	89	58	35	19	8	0
Ibrutinib	263	241	224	208	199	185	176	166	156	143	136	128	117	96	73	56	36	18	8	0

Hypertension



No. at risk

Acalabrutinib	266	246	229	220	216	205	193	184	176	169	157	153	136	114	89	60	34	17	5	0	0
Ibrutinib	263	230	203	183	170	153	141	130	120	111	104	98	85	69	48	40	27	15	7	1	0

CI = confidence interval; HR = hazard ratio.

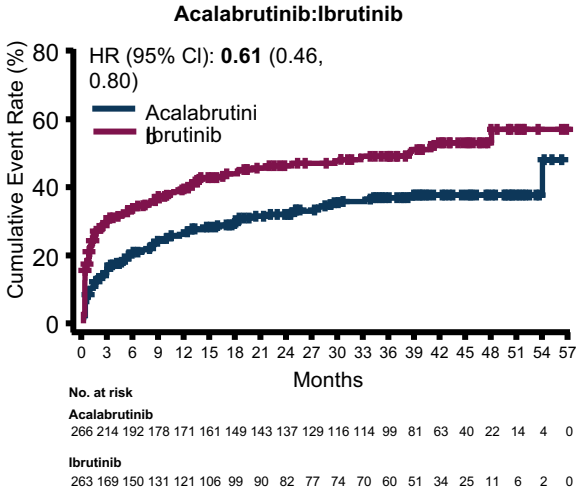
Byrd JC et al. JCO 2021

ELEVATE RR – Safety

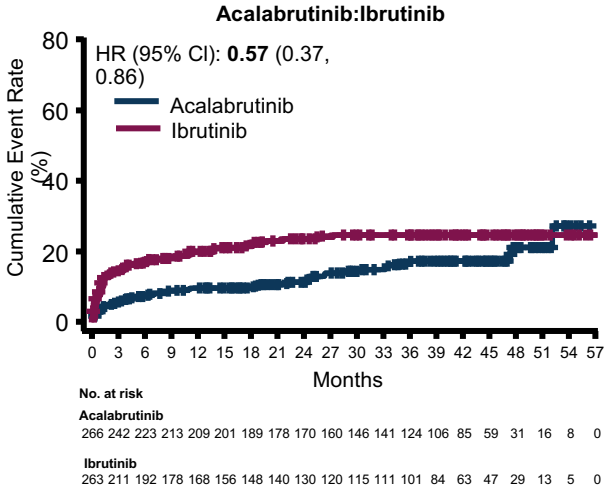
Safety: Diarrhea and Arthralgia

- Lower cumulative incidences of any grade diarrhea, arthralgia and bleeding events with acalabrutinib

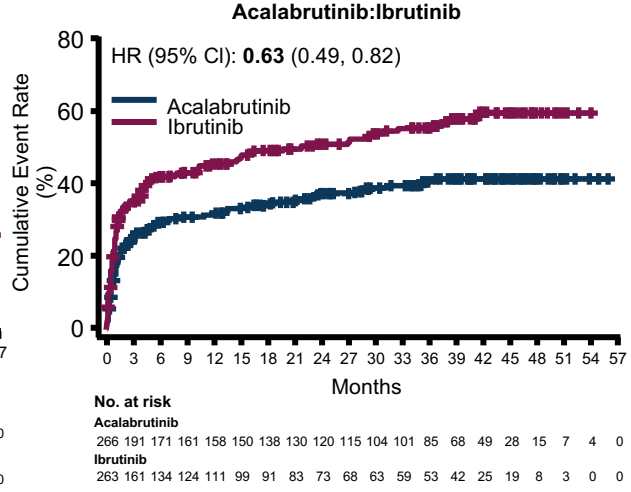
Diarrhea



Arthralgia



Bleeding events



CI = confidence interval; HR = hazard ratio.
Byrd JC et al. JCO 2021

SEQUOIA – Extended Follow-Up

Study Design[1-3]

PHASE 3

Study Identifier: BGB-3111-304, NCT03336333

Primary Endpoint: PFS by IRC in Cohort 1

Key Secondary Endpoints: Cohort 1: ORR, DOR, safety; Cohort 2: ORR, PFS, DOR; Cohort 3: ORR, PFS, DOR, rate of undetectable MRD at $<10^{-4}$ sensitivity, safety

KEY ELIGIBILITY CRITERIA

- Treatment-naïve CLL/SLL
- Met iwCLL criteria for treatment
- ≥65 years of age or <65 years of age and unsuitable for FCR treatment[a]
- Measurable disease by CT/MRI
- No current or past history of Richter's transformation

STRATIFICATION FACTORS

- Age (<65 vs. ≥65 years)
- Binet stage (C vs. A or B)
- *IGHV* mutational status (mutated vs. unmutated)
- Geographic region (NA vs. EU vs. APAC)

TREATMENT

del(17p) FISH test

- **Cohort 1** without del(17p) → R 1:1
  - **Arm A: Zanubrutinib 160 mg PO BID until PD (n=241)**
  - **Arm B: Bendamustine + rituximab × 6 (n=238)**
- **Cohort 2** with del(17p) → **Arm C: Zanubrutinib 160 mg PO BID until PD (n=111)[b]**
- **Cohort 3** with del(17p) → **Arm D: Zanubrutinib 160 mg PO BID + venetoclax (n= ~80)**

FOLLOW-UP

Safety and survival

Assessments

- Response assessments were conducted every 12 weeks from start of cycle 1 for 96 weeks and then every 24 weeks until PD
- CR/CRi confirmed via bone marrow biopsy
- AEs documented until PD or start of next CLL therapy

Statistical Analysis

- Efficacy endpoints analyzed using ITT analysis and the per-protocol analysis set
- Safety was assessed in all pts who received ≥1 dose of treatment

[a]Defined as Cumulative Illness Rating Scale >6, creatinine clearance <70 mL/min, or a history of previous severe infection or multiple infections within the last 2 years; [b]One patient without del(17p) was misassigned to the nonrandomly assigned cohort of patients with del(17p). The patient is excluded from the efficacy analysis in this cohort

1L=first line, AE=adverse event, APAC=Asia/Pacific, BID=twice daily, CLL=chronic lymphocytic leukemia, CR=complete response, CRi=complete response with incomplete hematologic recovery, CT=computed tomography, DOR=duration of response, EU=Europe, FCR=fludarabine, cyclophosphamide, and rituximab (chemotherapy regimen), FISH=fluorescence in situ hybridization, IGHV=immunoglobulin heavy-chain variable region gene, IRC=independent review committee, ITT=intention-to-treat, iwCLL=International Workshop on Chronic Lymphocytic Leukemia, MRD=minimal residual disease, MRI=magnetic resonance imaging, NA=North America, ORR=overall response rate, OS=overall survival, PD=progression disease, PFS=progression-free survival, PO=per oral, R=randomized, SLL=small lymphocytic lymphomae.

1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03336333. Accessed January 2021. 2. Tam et al. Lancet Oncology. 2022. 22;S1460-2045. 3. Munir T et al. Poster presented at EHA 2023; Abstract number: P639

Summary of EAIRs[a] for Select AEIs

Cohorts 1 and 2 (Any Grade and Grade ≥3)[b]

SEQUOIA – Extended Follow-Up

	Patients without del(17p)		Patients with del(17p)
	Arm A: zanubrutinib (n=240)[b]	Arm B: BR (n=227)[c]	Arm C: zanubrutinib (n=111)
Atrial fibrillation and flutter	0.13	0.08	0.15
Hemorrhage	2.02	0.40	2.73
Major hemorrhage	0.20	0.05	0.20
Hypertension	0.49	0.45	0.35

- Exposure-adjusted incidence rates for hypertension were similar between arms and lower than previously reported

Data cutoff: 31 October 2022.

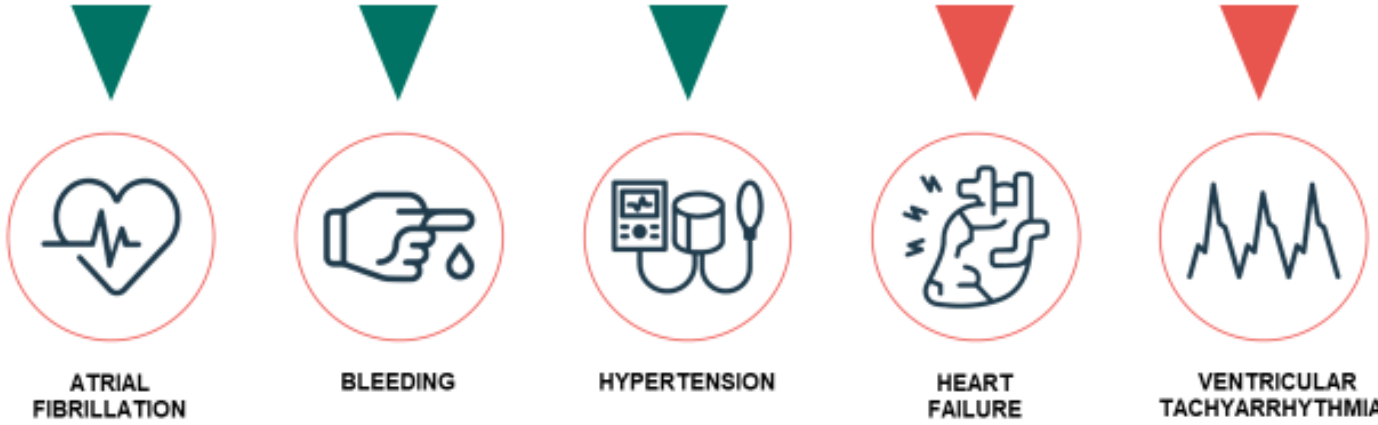
[a]EAIR was calculated as the number of patients with an event in each TEAE category divided by the total time from the first dose date to the first event date, or the exposure time if no event occurred; [b]Patients who did not receive zanubrutinib are not included in the safety analysis; [c]Patients who did not receive BR are not included in the safety analysis..

AEI=adverse event of interest, BR=bendamustine plus rituximab, EAIR=exposure-adjusted incidence rate,

Munir T et al. Poster presented at EHA 2023; Abstract number: P639

La lezione MD Anderson: la FA è un evento atteso nel paziente con CLL. Il ruolo del/dei BTKi è probabilmente quello di *trigger* di un evento atteso.... con qualche differenza tra i tre

Sia ibrutinib sia gli inibitori di BTK (BTKi) di seconda generazione (acalabrutinib, zanubrutinib) sono caratterizzati da una tossicità cardiovascolare che si manifesta con **fibrillazione atriale, sanguinamento e ipertensione arteriosa** (livello di evidenza alto). Sono segnalati anche scompenso cardiaco e tachiaritmie ventricolari (livello di evidenza più basso)



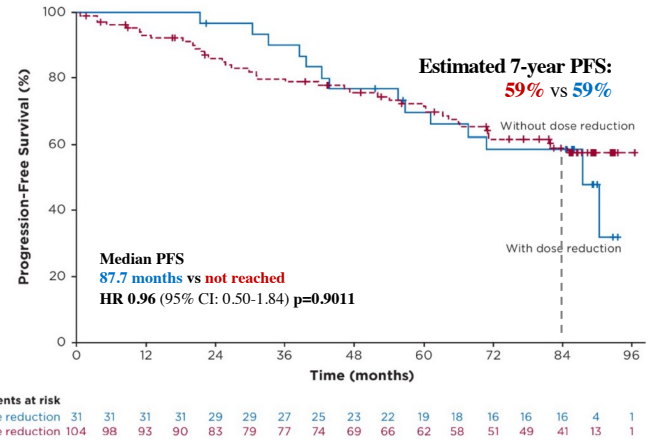
LEUKEMIA & LYMPHOMA, 2016
http://dx.doi.org/10.1080/10428194.2016.1257795
Taylor & Francis

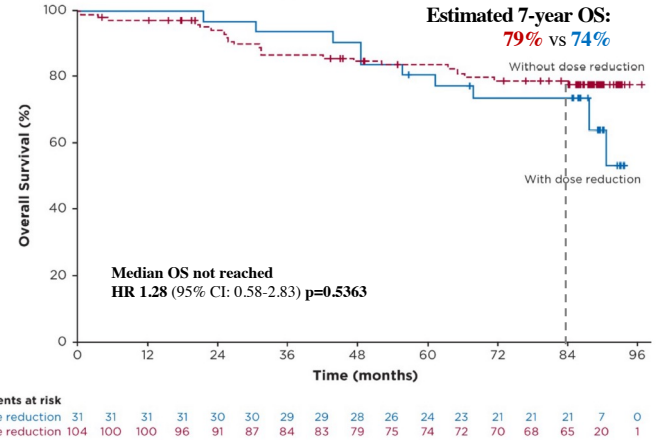
Slide adattata da Prof. Minotti

Ibrutinib dose modifications due to AEs did not impact efficacy outcomes and resolved AEs for most patients[1]

RESONATE-2: Post-hoc analysis in patients with dose reductions

Up to 8 years follow-up[1]





RESONATE-2 ibrutinib-treated patients n=135	Dose reductions per protocol	Dose reductions per recent US/EU label update*	Dose holds ≥7 day
AEs leading to dose reduction or hold	31 (23%)	11 (8%)	79 (59%)
Initial AE **resolved**	28/31 (**90%**)	10/11 (**91%**)	75/79 (**95%**)
No recurrence or recurred at lower level	19/31 (**61%**)	7/11 (**64%**)	Not reported

*AEs for which dose reductions are recommended in the ibrutinib USPI & EU SmPC (grade 2 cardiac failure, grade 3 cardiac arrhythmia, grade 3 or 4 nonhematologic AEs [excluding cardiac failure and cardiac arrhythmia], grade 3 or 4 neutropenia with infection or fever, and grade 4 hematologic AEs).[2,3]

1. Woyach, J.A et al. Cancers 2023, 15, 507. https://doi.org/10.3390/cancers15020507

cancers MDPI

Review

Chronic Lymphocytic Leukemia: Management of Adverse Events in the Era of Targeted Agents

Andrea Galitzia [1,†], Monica Maccaferri [2,†], Francesca Romana Mauro [3], Roberta Murru [4,*,‡] and Roberto Marasca [2,5,‡]

Table 3. Management recommendations for BTKis with CYP3A modulators and selected interactors.

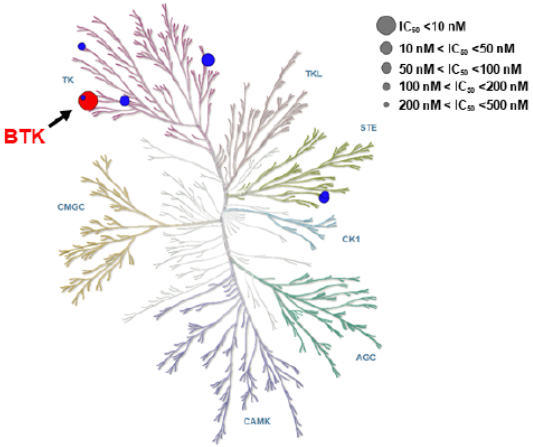
Interacting Agents	Ibrutinib	Acalabrutinib	Zanubrutinib
Strong CYP3A inhibitors	avoid	avoid	80 mg OD
Moderate CYP3A inhibitors	280 mg OD 140 mg OD with voriconazole 70 mg OD with posaconazole	100 mg OD	80 mg BID
Strong CYP3A inducers	avoid	avoid	avoid
PPI	-	avoid	-
Grapefruit, St John's wort, Seville Oranges	avoid	avoid	80 mg BID
Warfarin/ Vit K antagonists	avoid	avoid	avoid

OD: once daily; BID: bis in die; PPI: proton pump inhibitors.

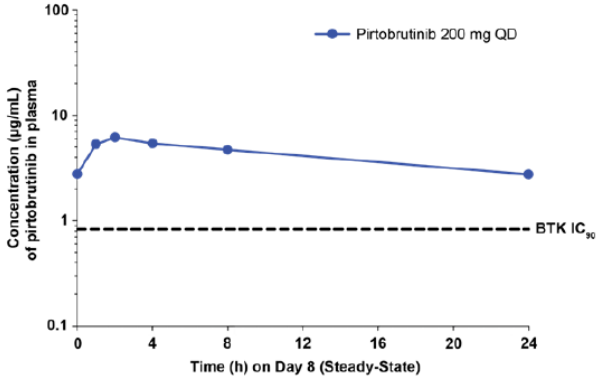
Cancers **2024**, 16, 1996. https://doi.org/10.3390/cancers16111996

Pirtobrutinib is a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor

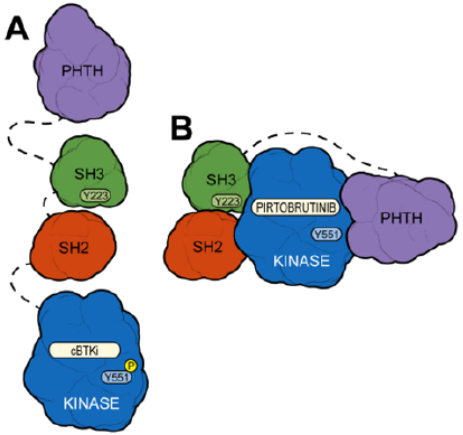
Highly selective for BTK[5,6]



Plasma exposures exceeded BTK IC_{90} throughout dosing interval



Pirtobrutinib may stabilize/maintain BTK in a closed inactive conformation[7]



- Inhibits both WT and C481-mutant BTK with equal low nM potency[7]
- Steady state plasma exposure corresponding to 96% BTK target inhibition and a half-life of about 20 hours[7]
- In contrast to cBTKi (A), pirtobrutinib (B) appears to stabilize BTK in a closed, inactive conformation, blocking access to upstream kinases and phosphorylation of Y551, thus inhibiting scaffolding interactions that support kinase-independent BTK signaling[7]

[5]Mato et al, *Lancet* 2021; 397: 892–901. [6]Brandhuber et al. *Clin Lymphoma Myeloma Leuk* 2018; 18(Suppl.1):S216. [7]Gomez et al. *Blood*.2023; 142(1):62-72.

Pirtobrutinib Safety Profile of Patients who Received Prior cBTKi

	Treatment-Emergent AEs in Patients with CLL/SLL (n=282)			
	All Cause AEs, (≥20%), %		Treatment-Related AEs, %	
Adverse Event	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Fatigue	36.9	1.8	3.5	0.0
Neutropenia[b,c]	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[d]	74.1	30.9	12.8	4.3
Bruising[e]	30.1	0.0	19.1	0.0
Rash[f]	24.5	1.1	5.7	0.4
Arthralgia	22.7	1.4	4.3	0.0
Hemorrhage[g]	13.5	2.1	4.6	1.1
Hypertension	14.2	4.3	3.5	0.4
Atrial Fibrillation/Flutter[h,i]	4.6	1.8	1.4	0.7

Median time on treatment was 18.7 months (prior cBTKi), 24.3 months (BCL2i-N) and 15.3 months (BCL2i-E)
11 (3.9%; 9 BCL2i-N, 2 BCL2i-E) patients had Treatment-Related AEs leading to pirtobrutinib dose reduction
7 (2.5%; 4 BCL2i-N, 3 BCL2i-E) patients had Treatment-Related AEs leading to pirtobrutinib discontinuation
Safety profiles of BCL2i-N and BCL2i-E subgroups were similar

[a]AEs of interest are those that were previously associated with covalent BTK inhibitors. [b]Neutropenia at baseline for prior BTKi (n=282) was 18.4, BCL2i-N (n=154) was 11.0 and BCL2i-E (n=128) was 27.3. [c]Aggregate of neutropenia and neutrophil count decreased. [d]Aggregate of all preferred terms including infection and COVID-19. [e]Aggregate of contusion, ecchymosis, increased tendency to bruise and oral contusion. [f]Aggregate of all preferred terms including rash. [g]Aggregate of all preferred terms including hemorrhage or hematoma. [h]Aggregate of atrial fibrillation and atrial flutter. [i]Of the 13 total afib/aflutter TEAEs in the prior BTKi safety population (n=282), 6 occurred in patients with a prior medical history of atrial fibrillation.

Woyach et al.; ASH 2023

Pirtobrutinib Safety Profile in Prior cBTKi Patients, with or without Prior BCL2i

	Treatment-Emergent AEs in Patients with CLL/SLL							
	BCL2i-N (n=154)				BCL2i-E (n=128)			
	All Cause AEs, (≥20%)		Treatment-Related AEs		All Cause AEs, (≥20%)		Treatment-Related AEs	
Adverse Event (AE), %	**Any Grade**	**Grade ≥ 3**	**Any Grade**	**Grade ≥ 3**	**Any Grade**	**Grade ≥ 3**	**Any Grade**	**Grade ≥ 3**
Fatigue	32.5	0.6	2.6	0.0	42.2	3.1	4.7	0.0
Neutropenia[b,c]	27.9	21.4	16.9	13.0	42.2	36.7	22.7	18.0
Diarrhea	29.9	0.6	6.5	0.0	26.6	0.0	9.4	0.0
Cough	29.9	0.0	1.3	0.0	24.2	0.0	2.3	0.0
Contusion	22.1	0.0	16.2	0.0	31.3	0.0	18.8	0.0
Covid-19	29.2	5.8	0.0	0.0	21.9	3.1	1.6	0.0
Dyspnea	20.1	1.9	0.6	0.0	25.0	2.3	0.8	0.8
Nausea	20.1	0.0	3.9	0.0	24.2	0.0	3.1	0.0
Abdominal pain	18.8	1.3	1.9	0.6	24.2	2.3	2.3	0.0
Adverse Event (AE) of interest[a], %	**Any Grade**	**Grade ≥ 3**	**Any Grade**	**Grade ≥ 3**	**Any Grade**	**Grade ≥ 3**	**Any Grade**	**Grade ≥ 3**
Infections[d]	72.7	26.6	12.3	2.6	75.8	35.9	13.3	6.3
Bruising[e]	26.0	0.0	18.2	0.0	35.2	0.0	20.3	0.0
Rash[f]	28.6	1.3	7.1	0.6	19.5	0.8	3.9	0.0
Arthralgia	23.4	1.3	2.6	0.0	21.9	1.6	6.3	0.0
Hypertension	16.9	3.2	3.9	0.0	10.9	5.5	3.1	0.8
Hemorrhage[g]	11.7	1.3	2.6	0.0	15.6	3.1	7.0	2.3
Atrial fibrillation / flutter[h,i]	5.2	1.3	1.3	0.6	3.9	2.3	1.6	0.8

Median time on treatment was 18.7 months (prior BTKi), 24.3 months (BCL2i-N) and 15.3 months (BCL2i-E)
11 (3.9%; 9 BCL2i-N, 2 BCL2i-E) patients had Treatment-Related AEs leading to pirtobrutinib dose reduction
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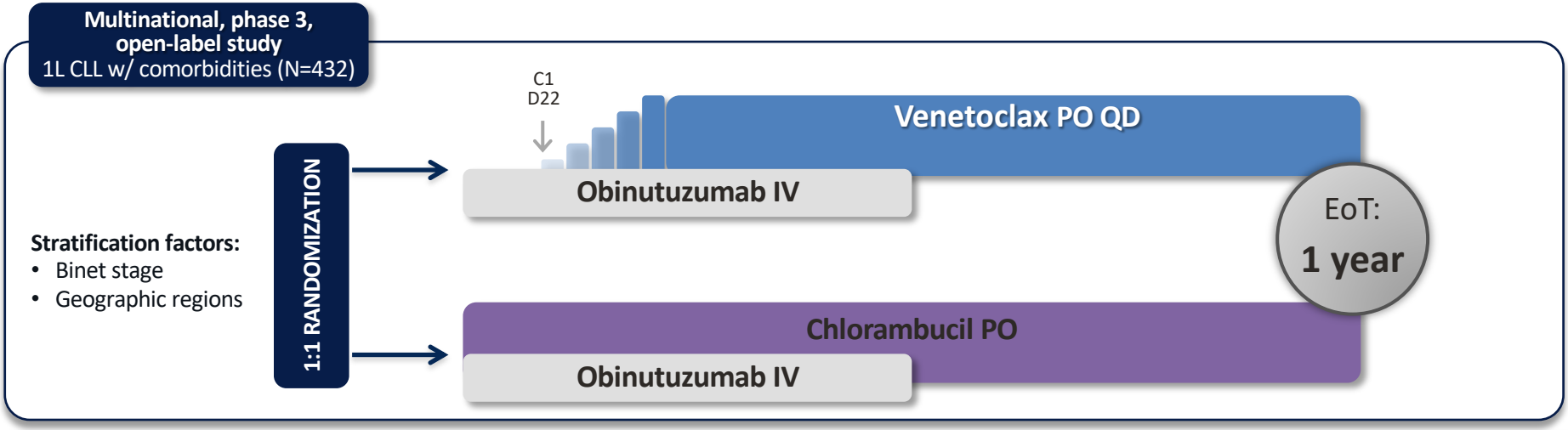
[a]AEs of interest are those that were previously associated with covalent BTK inhibitors. [b]Aggregate of neutropenia and neutrophil count decreased. [c]Neutropenia at baseline for prior BTKi (n=282) was 18.4, BCL2i-E (n=128) was 27.3 and BCL2i-N (n=154) was 11.0. [d]Aggregate of all preferred terms including infection and COVID-19. [e]Aggregate of contusion, ecchymosis, increased tendency to bruise and oral contusion. [f]Aggregate of all preferred terms including rash. [g]Aggregate of all preferred terms including hemorrhage or hematoma. [h]Aggregate of atrial fibrillation and atrial flutter. [i]Of the 13 total afib/aflutter TEAEs in the prior BTKi safety population (n=282), 6 occurred in patients with a prior medical history of atrial fibrillation.

Woyach et al.; ASH 2023

Fixed Therapy

VenO was studied as a 1-year FTD regimen in 1L CLL - CLL14 study design



Primary endpoint (ITT population):
- PFS – investigator assessed

Key secondary endpoints (ITT population):
- PFS – IRC assessed
- ORR and CR 3 months after EoT
- uMRD rate (PB and BM) 3 months after EoT
- OS

Key inclusion criteria
- Previously untreated CLL according to iwCLL criteria
- CIRS >6 and/or CrCl <70 mL/min

MRD was a secondary efficacy endpoint, not a determinant of treatment duration

See notes for dosing regimens.
BM, bone marrow; C, cycle; CIRS, cumulative illness rating scale; CrCl, creatinine clearance; D, day; EoT, end of treatment; FTD, fixed treatment duration; IRC, independent review committee; ITT, intent to treat; iwCLL, International Workshop on CLL; PB, peripheral blood; VenO, venetoclax + obinutuzumab.

Fischer K, *et al. N Engl J Med* 2019; **380:**2225–2236 (incl. appendix).

Consistent safety profile for VenO, with no new safety signals identified with longer follow-up

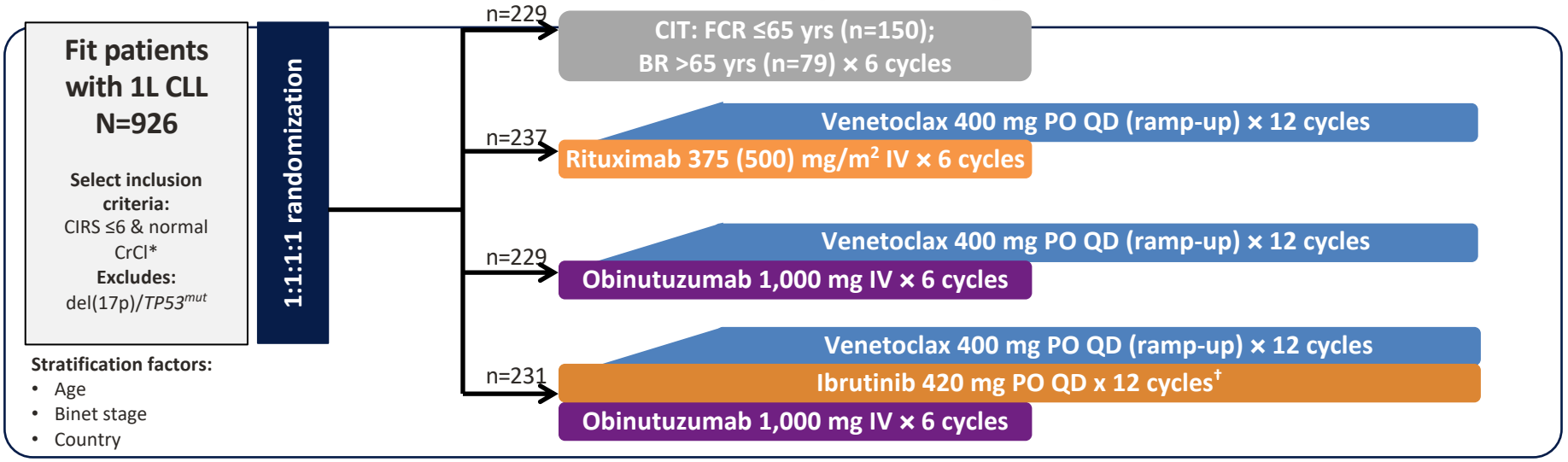
Rates of select Grade ≥3 AEs over time,* %[1]	VenO (N=212)	
	During treatment (months 1–12)†	After treatment*
Neutropenia	**51.9**	**3.8**
Thrombocytopenia	14.2	0.5
Anemia	7.5	1.9
Febrile neutropenia	4.2	0.9
Leukopenia	2.4	0.0
Pneumonia	3.8	3.3
Infusion-related reaction	9.0	0.0
TLS	1.4	0.0

- No new safety signals identified with **longer follow-up (76.4 months)**[1]
- SPMs reported in 30 (14.2%) and 18 (8.4%) patients in VenO and OClb arms, respectively[1]
- No statistical difference in cumulative incidence of SPMs between VenO and OClb arms[1]
- SPM incidence rate was 2.3% with VenO vs 1.4% with OClb[2]

* Grade 3/4 AEs were reported for up to 6 months after EoT; Grade ≥3 infections were reported for 2 years after EoT or until disease progression or NLT; after disease progression, only treatment-related SAEs and SPMs were reported[3]; † Nine patients received obinutuzumab only.[3]
EoT, end of treatment; NLT, next line of therapy; NMSC, non-melanoma skin cancer; SPM, second primary malignancy; TLS, tumor lysis syndrome.

1. Al-Sawaf O, *et al.* EHA 2023. Abstract S145 (Oral).
2. Al-Sawaf O, *et al.* ICML 2023. Abstract 025 (Oral);
3. Al-Sawaf O, *et al. Lancet Oncol* 2020; **21:**1188–1200 (incl. appendix).

CLL13 study design



Co-Primary Endpoints:
- uMRD ($<10^{-4}$) in PB at month 15 (VenO vs CIT)
- PFS (IVO vs CIT)

Key Secondary Endpoints:
- MRD in PB at month 15 (all other comparisons)
- MRD in BM at final restaging
- PFS (all other comparisons)
- ORR
- CR/CRi rate
- Overall survival

Analyses: at the fixed time point of month 61 for interim analysis of PFS, an independent data monitoring committee recommended full analysis

28-day cycles; * Normal CrCl defined as ≥70 mL/min; † Continuation of ibrutinib up to cycle 36 allowed if MRD still detectable (80% received 12–15 cycles); Data cut for first co-primary endpoint analysis (uMRD): February 28, 2021; data cut for second co-primary endpoint analysis (PFS): January 20, 2022.
BM, bone marrow; BR, bendamustine + rituximab; CIRS, cumulative illness rating scale; CIT, chemoimmunotherapy; CrCl, creatinine clearance; EFS, event-free survival; FCR, fludarabine + cyclophosphamide + rituximab; IVO, ibrutinib + venetoclax + obinutuzumab; O, obinutuzumab; PB, peripheral blood; Ven, venetoclax.

ClinicalTrials.gov: http://clinicaltrials.gov/ct2/show/NCT02950051 (accessed December 2021);
Eichhorst B, *et al.* ASH 2021. Abstract 71 (Oral);
Eichhorst B, *et al.* EHA 2022. Abstract LB2365 (Oral).

Most common Grade ≥3 TEAEs and AEs of interest

The most common Grade ≥3 TEAEs reported overall were neutropenia (42.8%), infections (15.8%), thrombocytopenia (9.4%), TLS (7.3%), infusion-related reactions (7.3%), and febrile neutropenia (6.5%)

CTC Grade ≥3 AEs (≥5%) and AEs of interest	CIT (n=216)	VenR (n=237)	VenO (n=228)	IVO (n=231)	Total (N=912)
Anemia*	16 (7.4)	9 (3.8)	11 (4.8)	9 (3.9)	45 (4.9)
Neutropenia*	98 (45.4)	94 (39.7)	103 (45.2)	95 (41.1)	390 (42.8)
Thrombocytopenia*	18 (8.3)	8 (3.4)	34 (14.9)	26 (11.3)	86 (9.4)
Febrile neutropenia*	24 (11.1)	10 (4.2)	7 (3.1)	18 (7.8)	59 (6.5)
Infections†	40 (18.5)	25 (10.5)	30 (13.2)	49 (21.2)	144 (15.8)
TLS*,‡	9 (4.2)	24 (10.1)	19 (8.3)	15 (6.5)	67 (7.3)
Atrial fibrillation*	1 (0.5)	1 (0.4)	0 (0.0)	6 (2.6)	8 (0.9)
Infusion-related reaction*	12 (5.6)	19 (8.0)	26 (11.4)	10 (4.3)	67 (7.3)
Hypertension*	3 (1.4)	5 (2.1)	4 (1.8)	13 (5.6)	25 (2.7)
Pneumonia*	12 (5.6)	4 (1.7)	12 (5.3)	15 (6.5)	43 (4.7)

No major differences observed in hematologic AEs among all four arms.
Grade ≥3 infections were more common with IVO and CIT vs VenO or VenR

Median follow-up: 38.8 months; * Adverse events reported as single term; † Adverse event reported as high-level term; ‡ Including clinical and laboratory TLS according to Cairo–Bishop as per protocol; no fatal TLS occurred. CIT, chemoimmunotherapy; CTC, Common Terminology Criteria; IRR, infusion-related reactions; IVO, ibrutinib + venetoclax + obinutuzumab; O, obinutuzumab; R, rituximab; TEAE, treatment-emergent adverse event; TLS, tumor lysis syndrome; Ven, venetoclax.

Eichhorst B, *et al. N Engl J Med* 2023; **388**:1739–1754.

Glow

Studio di Fase 3 IBrutinib+Venetoclax vs Clorambucil+Obinotuzumab

- Pazienti Over 65 o tra i 18 e 64 Anni con CIRSS > 6 (0-56) e Clearence Creatinina <70 ml/min
- 3 Cicli Lead In IBR poi 12 Cicli IBR + Venetoclax Vs 6 Cicli Clorambucil Obinotuzumab
- Primary End point : PFS by IRC
- Secondary End point : uMRD, RR (response Rate), Safety
- Esclusi i pz TP53 mutati

(Kater 2022) New England JM (27.7 Mesi FU)
(Niemann 2023) Lancet Oncology (46 mesi FU)
(Moreno 2023) Oral Abstract ASH (55 mesi FU)

Table 2. Grade 3 or 4 Adverse Events Occurring in 5% or More of Either Arm and Grade 5 Adverse Events Occurring in Any Patient (Safety Population).*

	Ibrutinib-Venetoclax (n=106)		Chlorambucil-Obinutuzumab (n=105)	
Treatment exposure — mo, median (range)	13.8 (0.7–19.5)		5.1 (1.8–7.9)	
Adverse events — n (%)	**Grade 3/4**	**Grade 5**	**Grade 3/4**	**Grade 5**
Patients with ≥1 adverse events	73 (68.9)	7 (6.6)	71 (67.6)	2 (1.9)
Neutropenia†	37 (34.9)	0	52 (49.5)	0
Infections and infestations‡	16 (15.1)	2 (1.9)§	11 (10.5)	1 (1.0)
Diarrhea¶	11 (10.4)	0	1 (1.0)	0
Hypertension	8 (7.5)	0	2 (1.9)	0
Atrial fibrillation	7 (6.6)	0	0	0
Thrombocytopenia	6 (5.7)	0	21 (20.0)	0
Hyponatremia	6 (5.7)	0	0	0
Cardiac failure	3 (2.8)	1 (0.9)§		
Sinus node dysfunction	1 (0.9)	1 (0.9)§		
Cholestasis	1 (0.9)	0		
Sudden death	0	2 (1.9)		
Ischemic stroke	0	1 (0.9)		
Malignant neoplasm	0	1 (0.9)		
Cardiac arrest	0	1 (0.9)	0	0
Tumor lysis syndrome	0	0	6 (5.7)	0

* Fifteen 28-day cycles are equivalent to 13.8 months for ibrutinib-venetoclax, and six 28-day cycles are equivalent to 5.5 months for chlorambucil-obinutuzumab. Patients may have treatment exposure times exceeding these limits due to cycle holds.

† Includes "neutrophil count decreased." Rates of febrile neutropenia (grade ≥3): 1.9% for ibrutinib-venetoclax versus 2.9% for chlorambucil-obinutuzumab.

‡ Includes multiple preferred terms. Only pneumonia (grade ≥3) occurred in 5% or more of patients in the ibrutinib-venetoclax (7 [6.6%]) and chlorambucil-obinutuzumab (6 [5.7%]) arms.

§ Both grade 5 adverse events were pneumonia (one patient experienced three grade 5 adverse events: pneumonia, cardiac failure, and sinus node dysfunction).

¶ In the ibrutinib-venetoclax arm, 3 diarrhea (grade ≥3) resolved or improved after a median of 9.0 days.

Tra i decessi improvvisi per cause cardiache, l'elemento commune era rappresentato da un punteggio della CIRS ≥10 e/o un ECOG PS di 2, suggerendo che i pazienti nello studio GLOW con un significativo carico di comorbidità fossero potenzialmente a maggior rischio per tali eventi[Kat]

Fixed-duration ibrutinib plus venetoclax for first-line treatment of CLL: primary analysis of the CAPTIVATE FD cohort

blood® 2 JUNE 2022 | VOLUME 139, NUMBER 22

Constantine S. Tam,[1-3] John N. Allan,[4] Tanya Siddiqi,[5] Thomas J. Kipps,[6] Ryan Jacobs,[7] Stephen Opat,[8] Paul M. Barr,[9] Alessandra Tedeschi,[10] Livio Trentin,[11] Rajat Bannerji,[12] Sharon Jackson,[13] Bryone J. Kuss,[14] Carol Moreno,[15] Edith Szafer-Glusman,[16] Kristin Russell,[16] Cathy Zhou,[16] Joi Ninomoto,[16] James P. Dean,[16] William G. Wierda,[17,*] and Paolo Ghia[18,19,*]

STUDIO di FASE 2 (senza braccio di controllo)
Pazienti Inferiori a 70 anni Età mediana 60 (33-71)
Primary End Point **CR**
Secondary End Point **uMRD, PFS, OS, Safety**

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

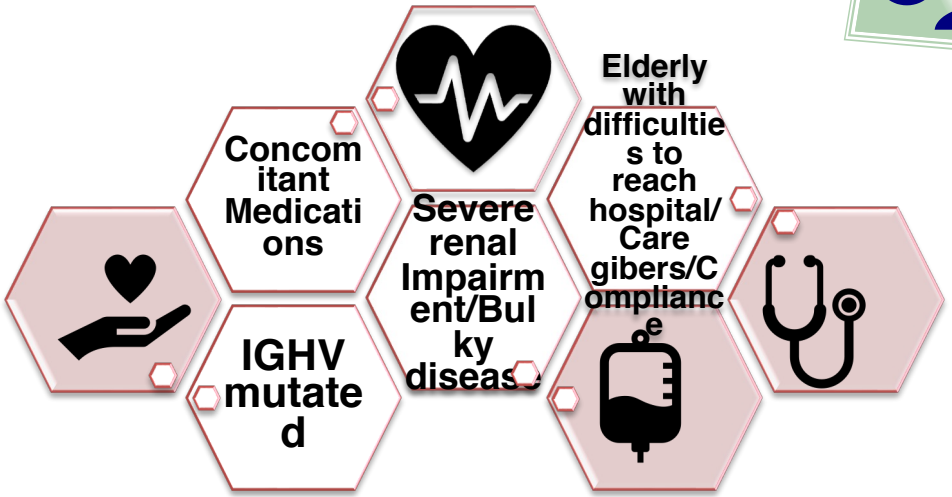
CAPTIVATE

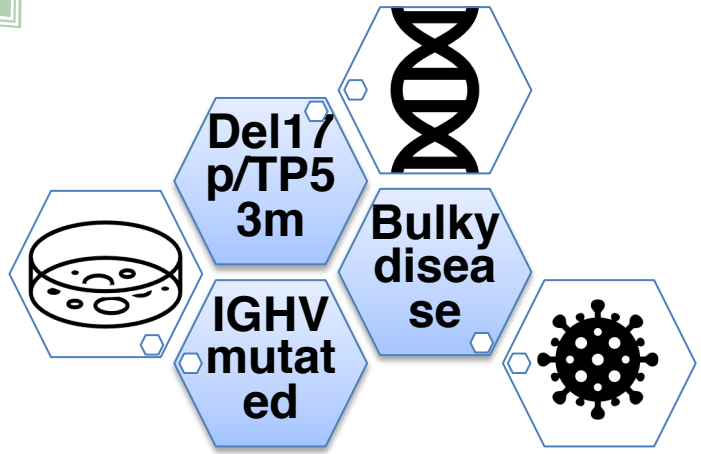
*AEs of any grade occurring in ≥30% of patients or grade 3/4 occurring in ≥5% of patients.

†Major hemorrhage was identified using the Standardized MedDRA Query for Hemorrhage, excluding laboratory terms.

Patients factors

Disease factors





Valutazione dinamica dei fattori di rischio

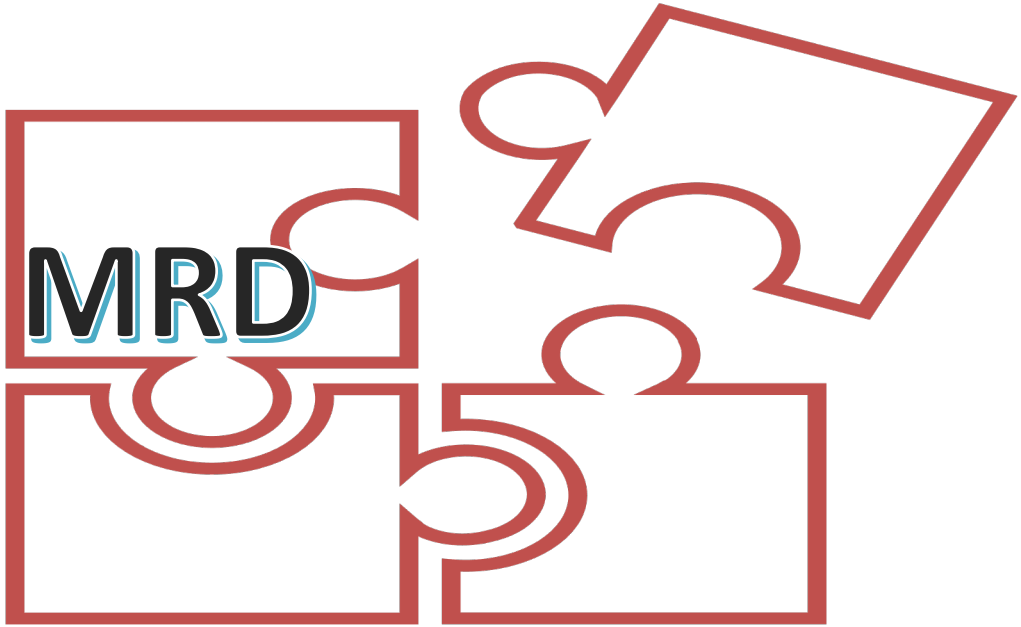
Team multidisciplinare

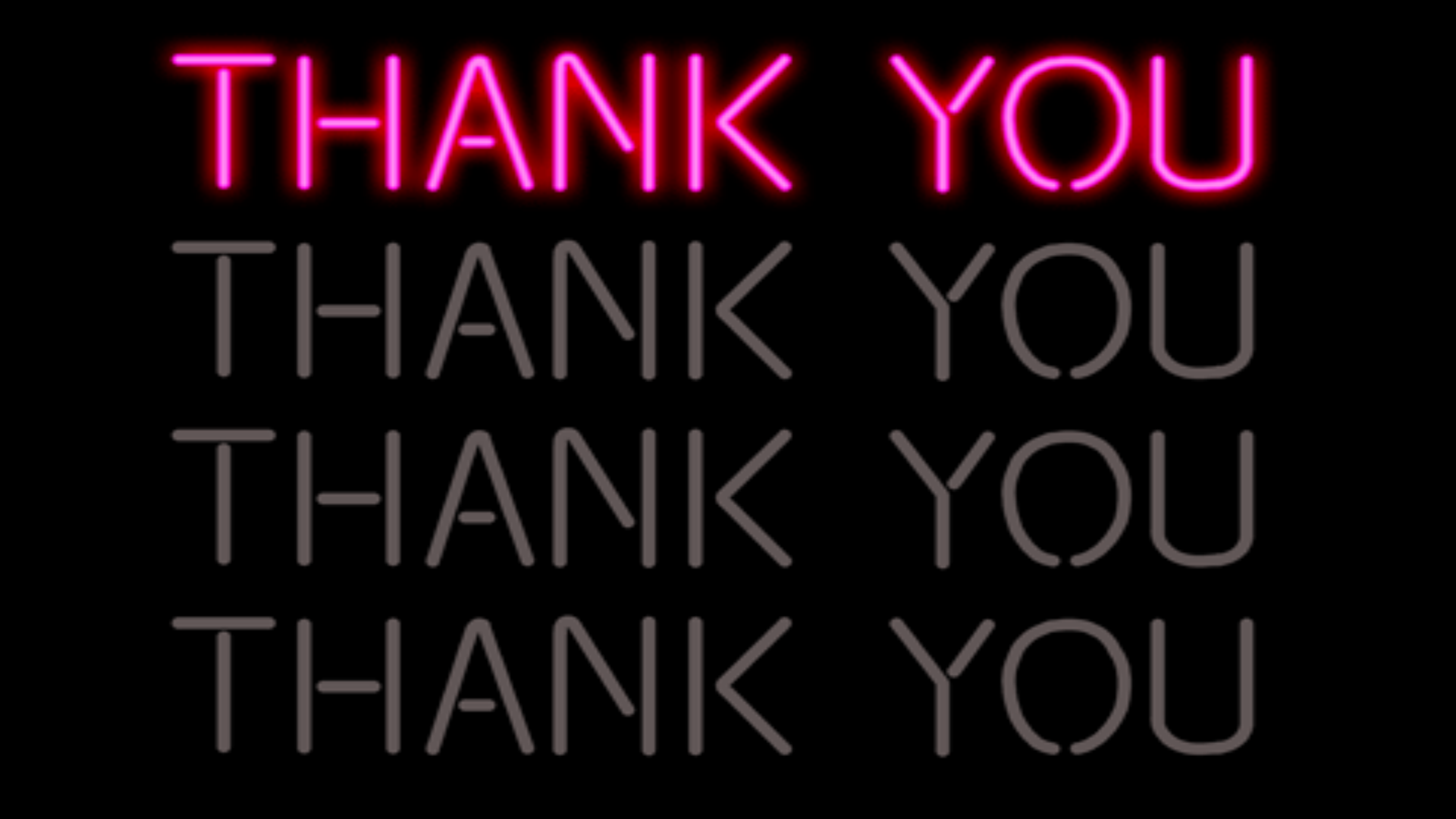
CONTINOUS TREATMENT

- Descalation dose
- Cumulative toxicities,
- impaired quality of life,
- considerable health-economic burden

FIXED THERAPY

- ✓ Less treatment- related toxicity
- ✓ Less side effects
- ✓ lower rate of clonal evolution and resistance mutation

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