Il concetto della "durata fissa" dal farmacologo all'ematologo

Nel paziente in prima linea

Chiarenza MD, PhD

Div. Ematologia con TMO
A.O.U. Policlinico G.Rodolico-San Marco
Catania

REVOLUTIONARY ROAD IN CLL

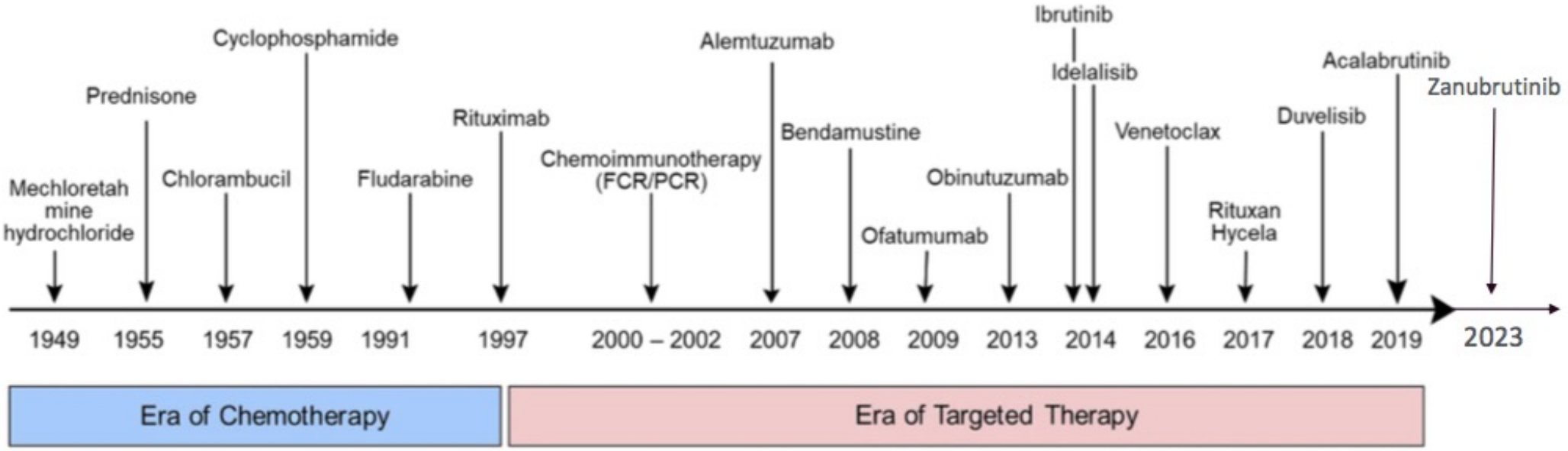
Innovazione rivoluzionaria nella terapia della leucemia linfatica cronica

Catania, 28 maggio 2024
Palace Catania UNA Esperienze

Annalisa Chiarenza Disclosure

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Roche			X		X	X	X
Janssen					X	X	X
Abbvie					X	X	X
Gilead						X	
AstraZeneca					X	X	X
Takeda						X	X
Lilly					X		X
Beigene					X		X

Evolution of Chronic Lymphocytic Leukemia Therapy



FCR fludarabine, cyclophosphamide, and rituximab, PCR pentostatin, cyclophosphamide, and rituximab.

Modif. Parikh et al., Nature 2020

Target Therapy: FDA Approvals and Current Status in CLL

Agent	Target	Status in CLL/SLL
Ibrutinib[1]	BTK (covalent)	Approved
Acalabrutinib[2]		Approved
Zanubrutinib[3]		Approved
Pirtobrutinib	BTK (non-covalent)	Phase 3 BRUIN CLL-321 Phase 3 BRUIN CLL-313
Nemtabrutinib		Phase 2
Venetoclax[4]	BCL-2	Approved
Idelalisib[5]	PI3K	Approved
Duvelisib[6]		Approved

Clinical note: In January 2023, pirtobrutinib was approved for the treatment of adult patients with R/R MCL after ≥2 lines of systemic therapy, including a BTK inhibitor[7]

1. Imbruvica (ibrutinib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205552s002lbl.pdf. 2. Calquence (acalabrutinib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/210259s000lbl.pdf. 3.Zanubrutinib prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/213217s007lbl.pdf. 4. Venclexta (venetoclax) Prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208573s009lbl.pdf. 5. Zydelig (idelalisib) Prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206545lbl.pdf. 6. Copiktra (duvelisib) Prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/211155s000lbl.pdf. 7. Jaypirca (pirtobrutinib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/216059s000lbl.pdf.

Modif. Lamanna, 2023

Target Therapy: FDA Approvals and Current Status in CLL

- **Fixed-duration:** a therapy given for a set period of time in all patients and then stopping

- **Continous:** a therapy given for unlimited period of time until acceptable toxicity or disease progression

Modif. Lamanna, 2023

Modern therapy is very effective but can achieve different goal

Continuous tx

- Disease control
- Prolonged PFS
- Independent from response/MRD

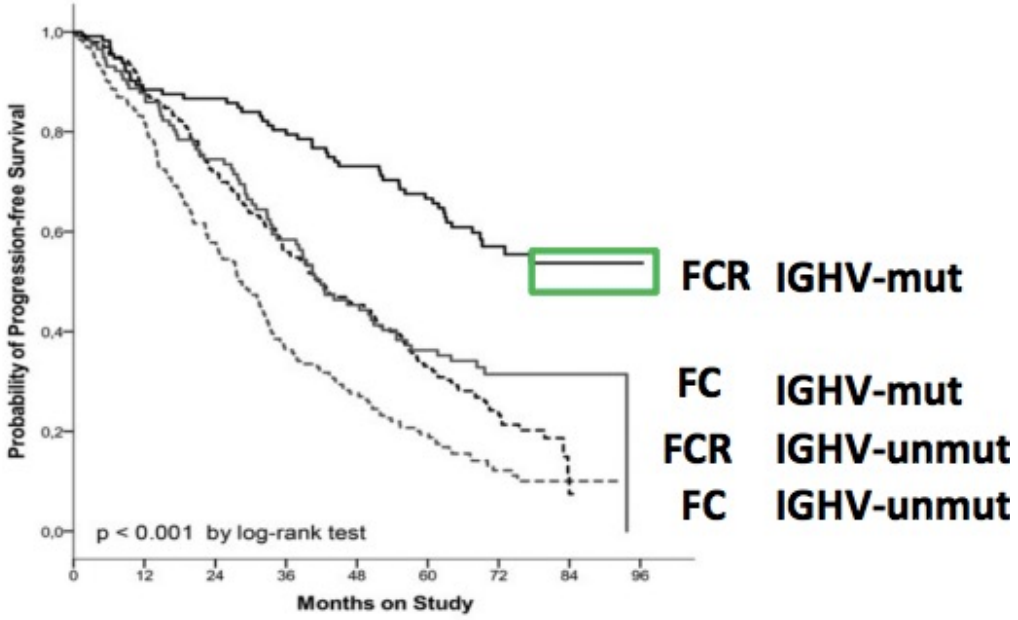
Fixed-duration

- Disease eradication
- Prolonged PFS
- Undetectable MRD

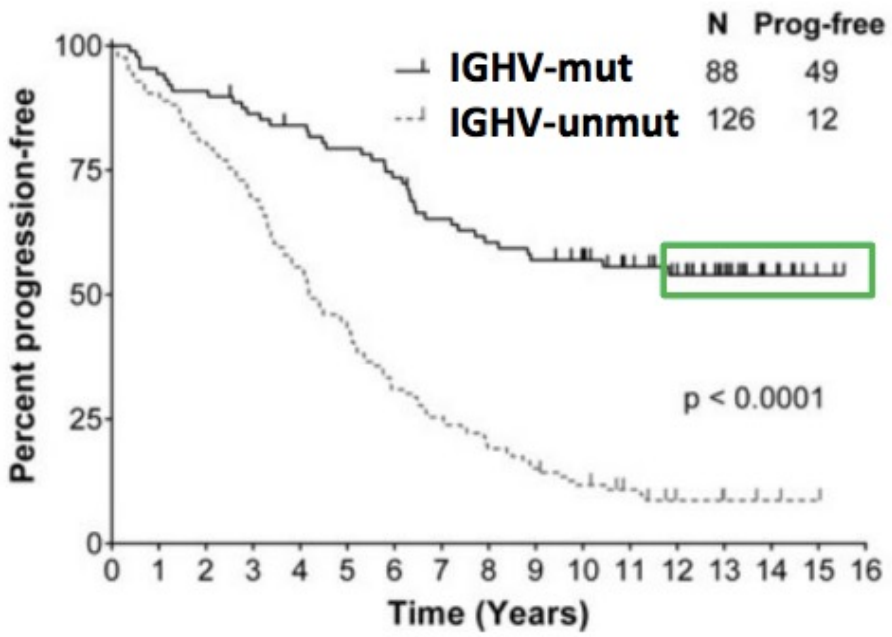
Modif. Lamanna, 2023

ChemoImmunoTherapy (CIT) is the original Fixed-Duration therapy

GCLLSG – CLL8

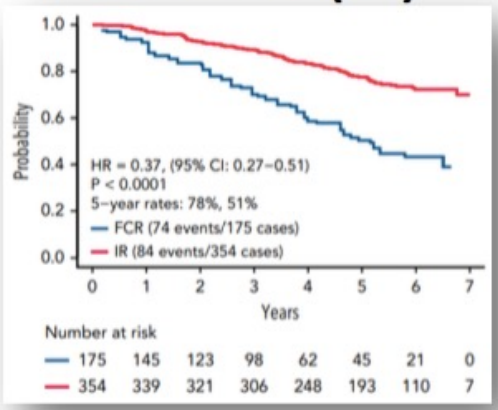
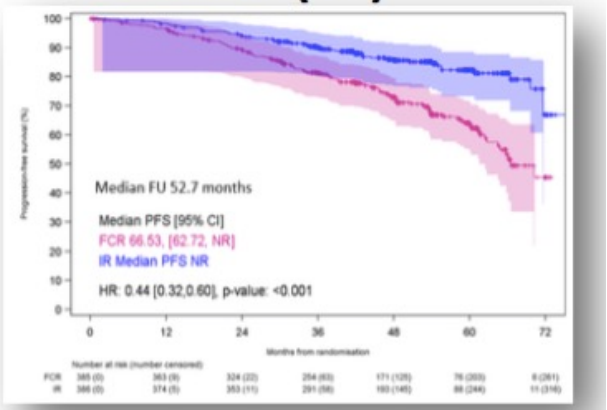
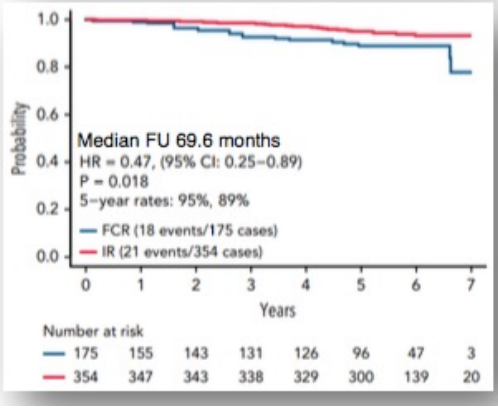
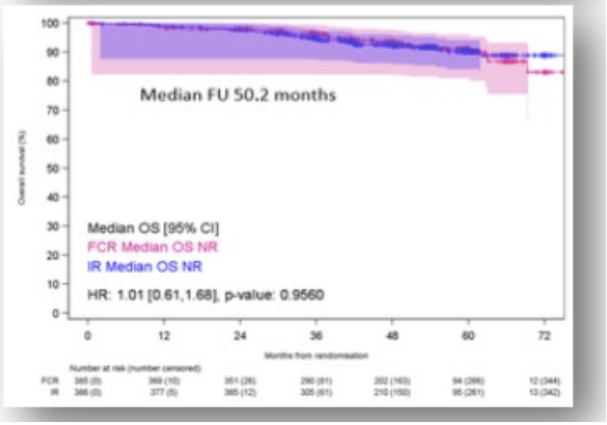


MDACC – FCR 300



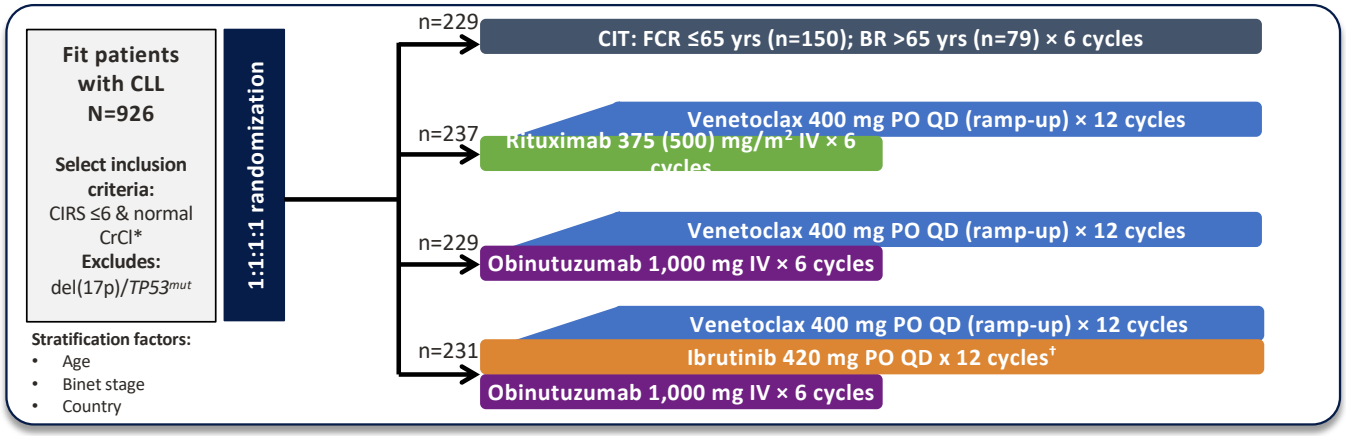
Thompson et al., *Blood*, 2016. Fischer et al., Blood 2016

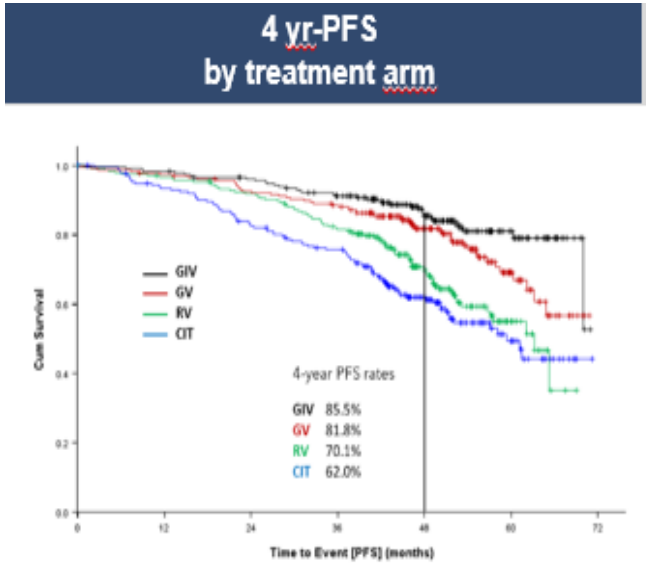
Survival benefit of continuous ibrutinib-based therapy

	ECOG 1912 (US)	FLAIR (UK)
PFS		
OS		

Shanafelt et al., *Blood*, 2022. Hillmen et al., ASH, 2021

Survival benefit of continuous venetoclax-based therapy





GV superior to CIT independent of IGHV

GIV superior to GV in terms of TTNT, not in OS

GIV: higher rates of infections and cardiac disorder

GIV *vs* CIT: HR 0.30, 97.5%CI: 0.19-0.47, ***p<0.001***
GIV *vs* RV: HR 0.38, 97.5%CI: 0.24-0.59, ***p<0.001***
GIV *vs* GV: HR 0.63, 97.5%CI: 0.39-1.02, p=0.03

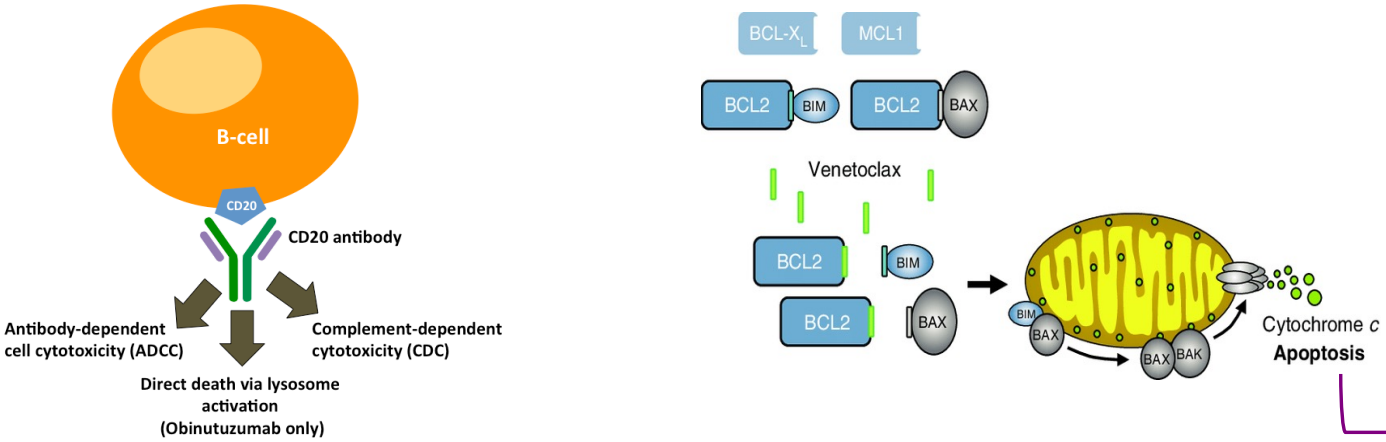
GV *vs* CIT: HR 0.47, 97.5%CI: 0.32-0.69, ***p<0.001***
GV *vs* RV: HR 0.57, 97.5%CI: 0.38-0.84, ***p=0.001***

RV *vs* CIT: HR 0.78, 97.5%CI: 0.55-1.10, p=0.1

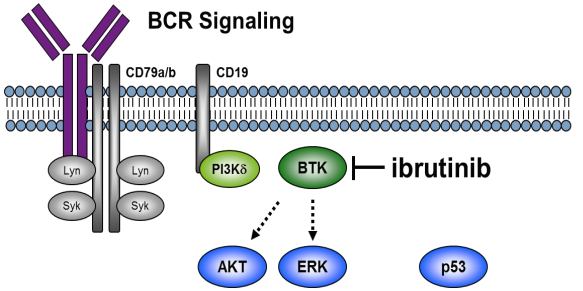
Eichhorst B, *et al.* EHA 2022. Abstract LB2365 (Oral). Furstenau et al., ASH 2023

Modern fixed-duration therapy

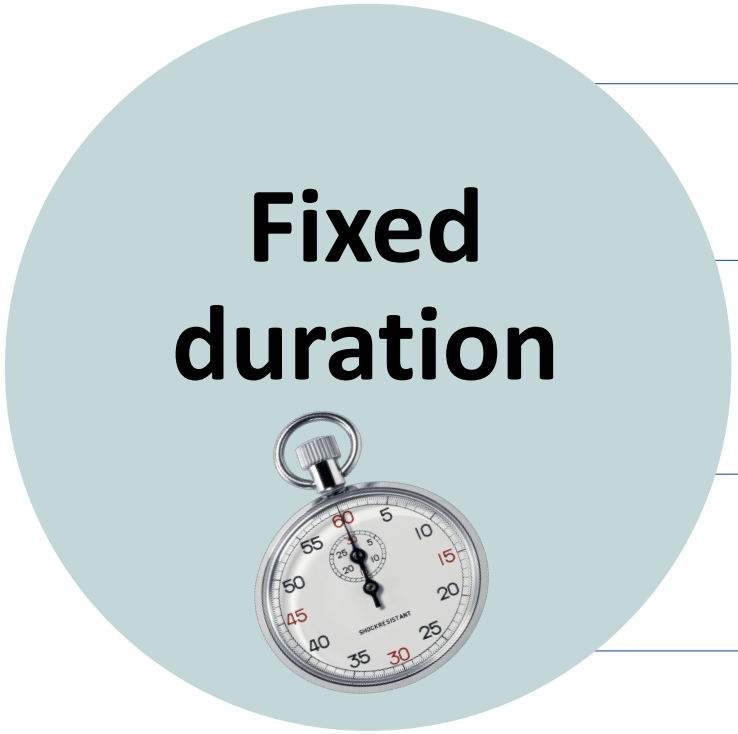
Ven-Obino



Ven-Ibr

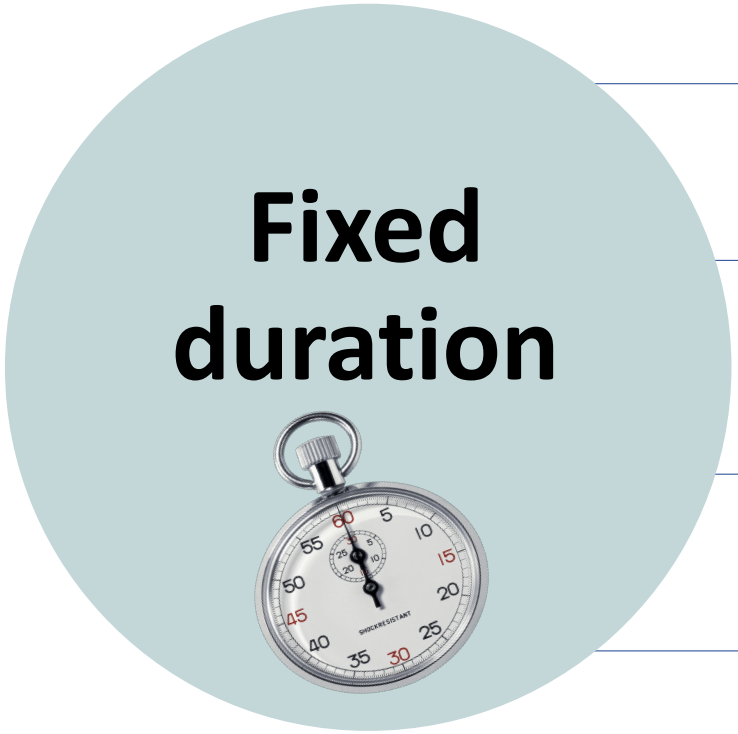


Key Goals of Fixed-Duration Treatment Regimens



- Efficacy
- Resistance mutations
- Tollerability
- QoL

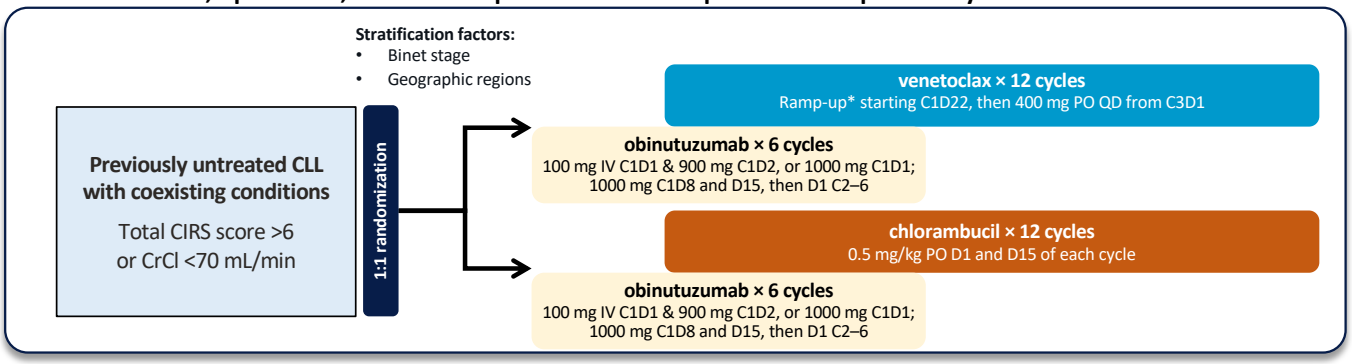
Key Goals of Fixed-Duration Treatment Regimens



- Efficacy
- Resistance mutations
- Tollerability
- QoL

CLL14: 6-Year Follow-Up Shows Efficacy of Frontline Venetoclax/Obinutuzumab vs Chlorambucil/Obinutuzumab

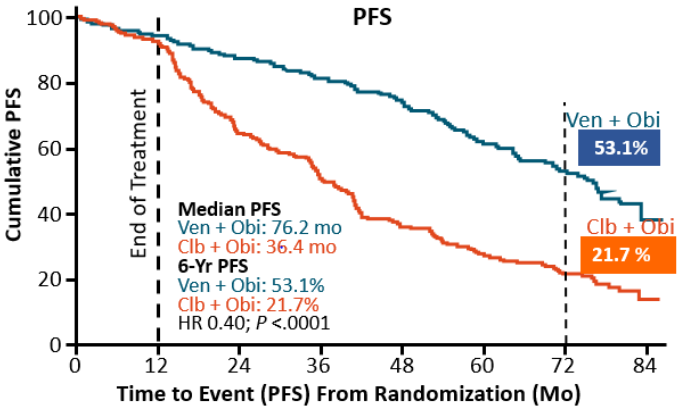
International, open-label, randomized phase III trial: 432 patients with previously untreated CLL

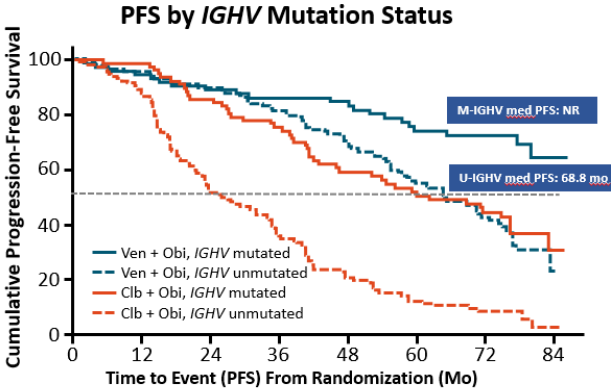


Median Observation time: 76.4 months

Primary Endpoint: inv-PFS

Secondary Endpoint: IRC-PFS, ORR, CR 3 months after EoT, MRD negativity (PB and BM) 3 months after EoT, OS





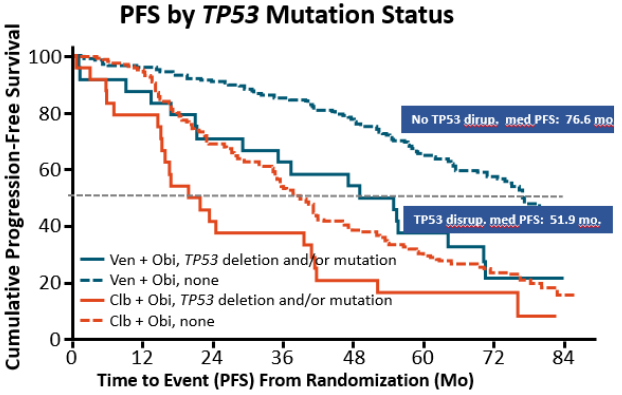
Median PFS, Mo

Ven + Obi, *IGHV* mut: NR

Ven + Obi, *IGHV* unmut: 64.8

Clb + Obi, *IGHV* mut: 62.2

Clb + Obi, *IGHV* unmut: 26.9



Median PFS, Mo

Ven + Obi, no *TP53* del/mut: 76.6

Ven + Obi, *TP53* del/mut: 51.9

HR: 2.29; *P* = .001

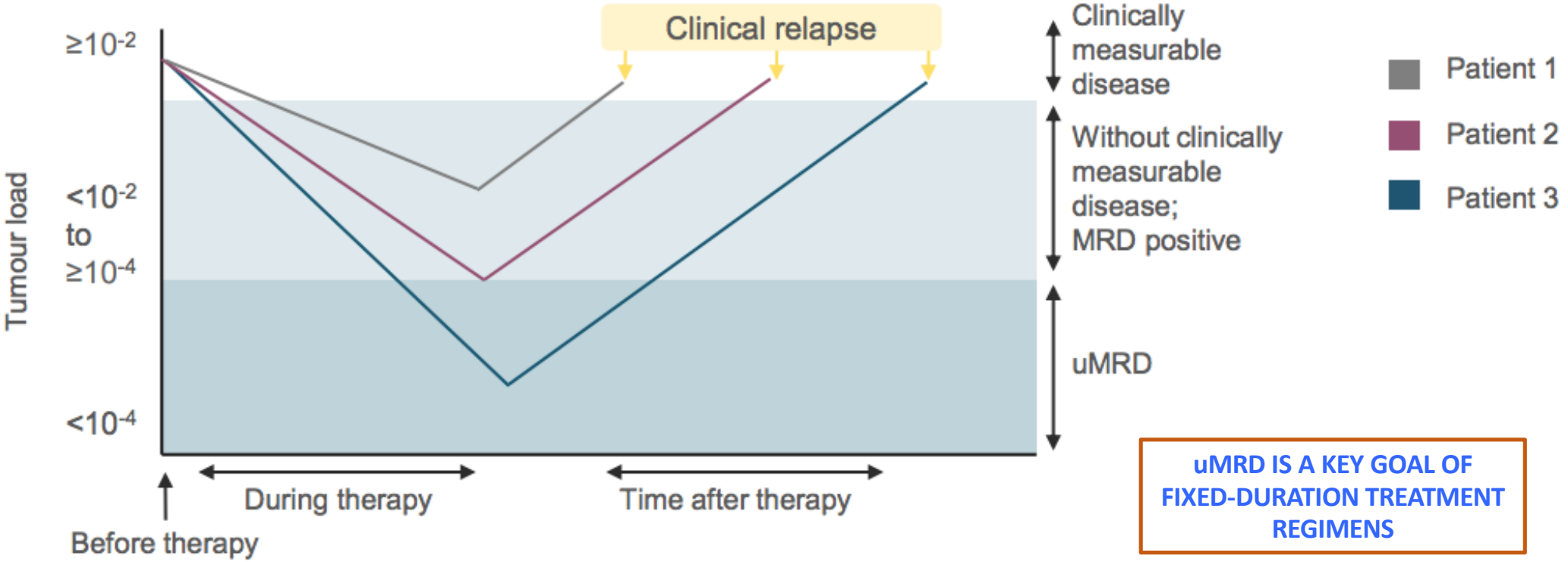
Clb + Obi, no *TP53* del/mut: 38.9

Clb + Obi, *TP53* del/mut: 20.8

HR: 1.66; *P* = .03

Al-Sawaf et al. Lancet Oncol. 2020;21:1188. Al-Sawaf EHA 2023

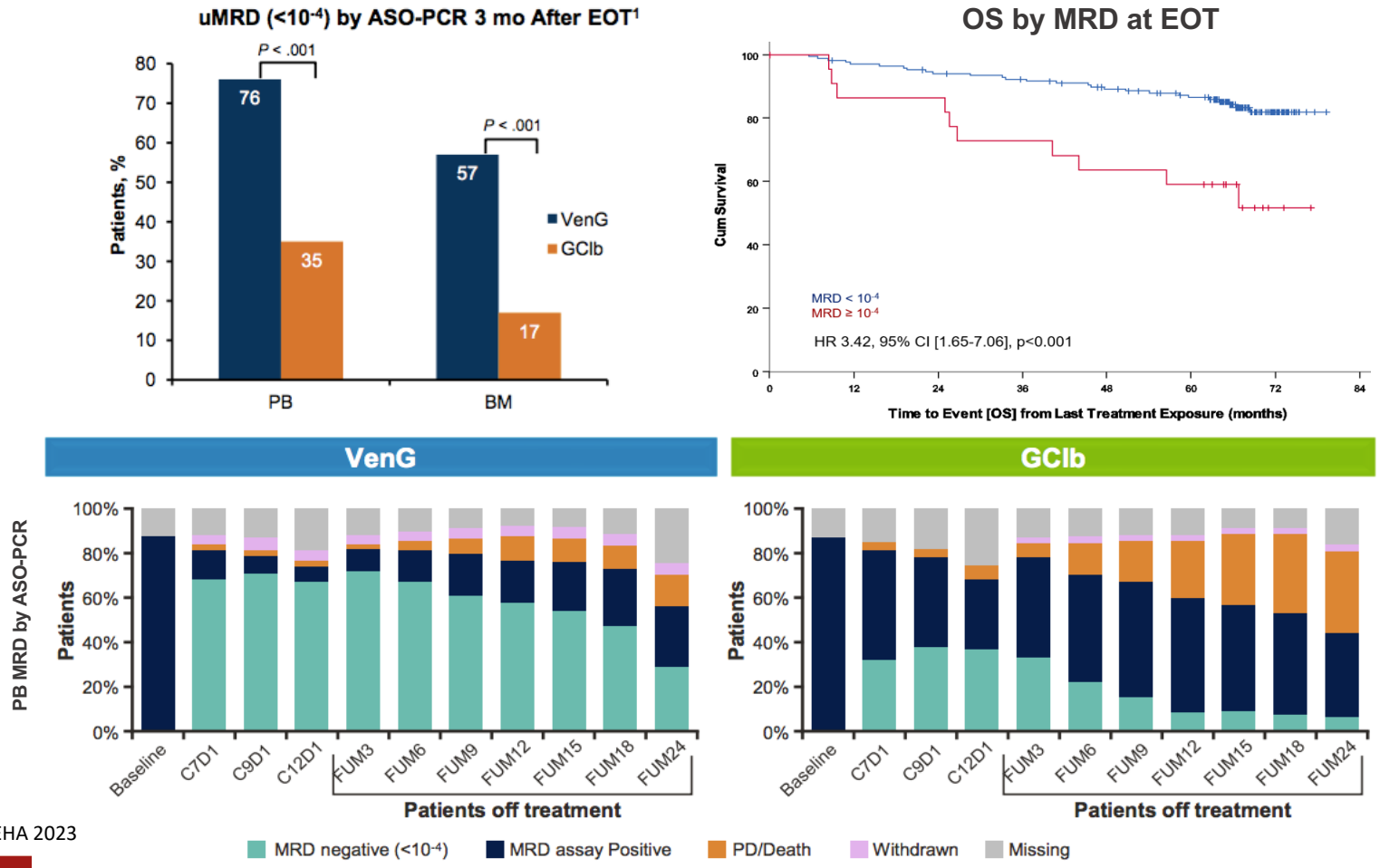
Achieving uMRD is associated with longer PFS



uMRD IS A KEY GOAL OF FIXED-DURATION TREATMENT REGIMENS

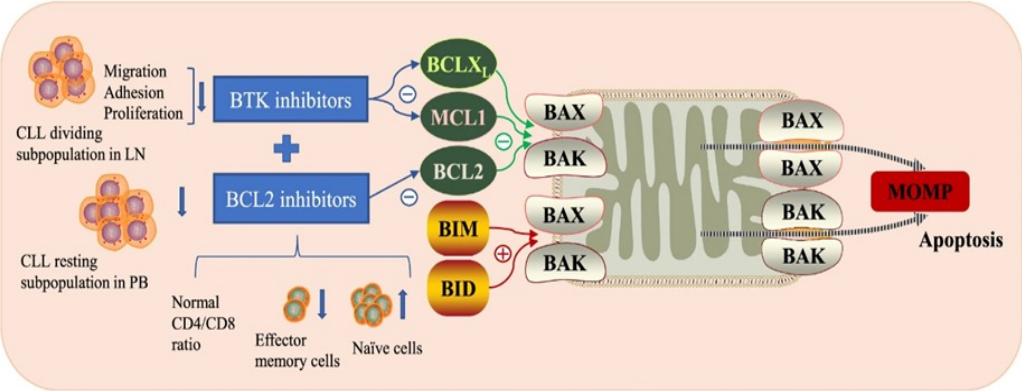
Adapted from Böttcher et al. 2013

CLL14 study: VenG achieves uMRD for most patients



Al-Sawaf O, et al. Lancet Onc, 2020. EHA 2023

Ibrutinib and Venetoclax Combination

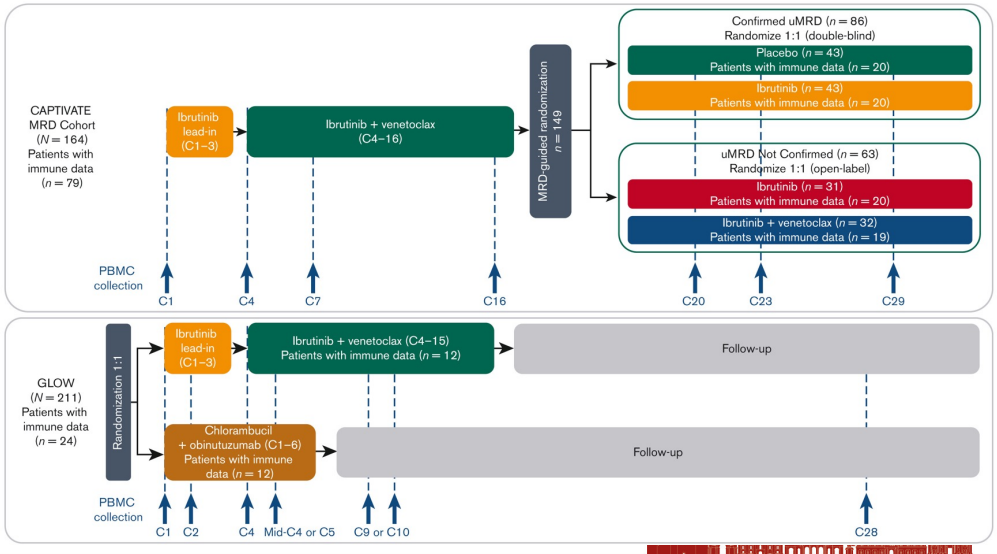


- Both BTKi and BCL2i are associated with superior PFS compared with CIT as first therapy for CLL patients
- Complementary mechanisms of action

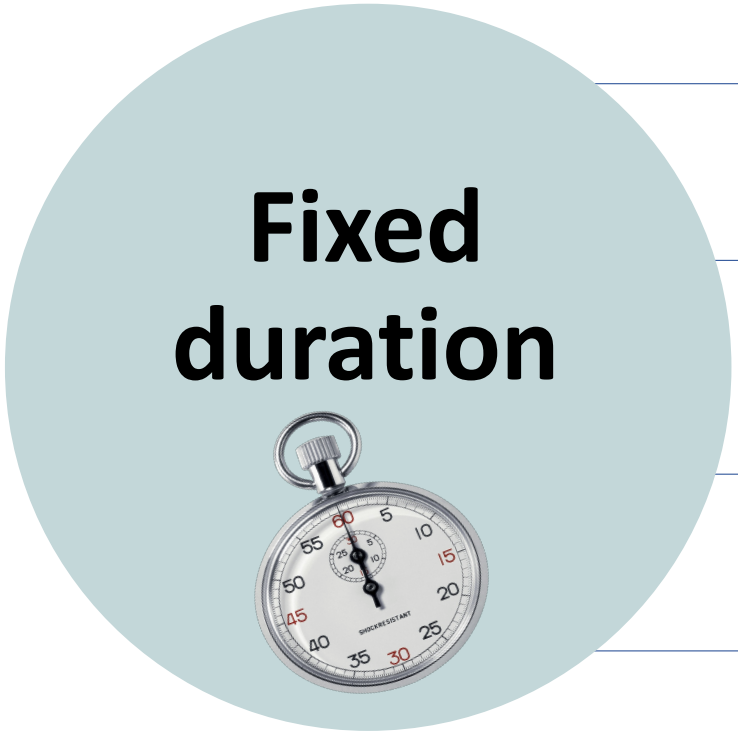
Superior depth and durability of responses

Theoretical concern for BTKi-BCL2i combination:

- Potential for augmented adverse events
- Low efficacy in re-treatment option
- Acquisition of resistance

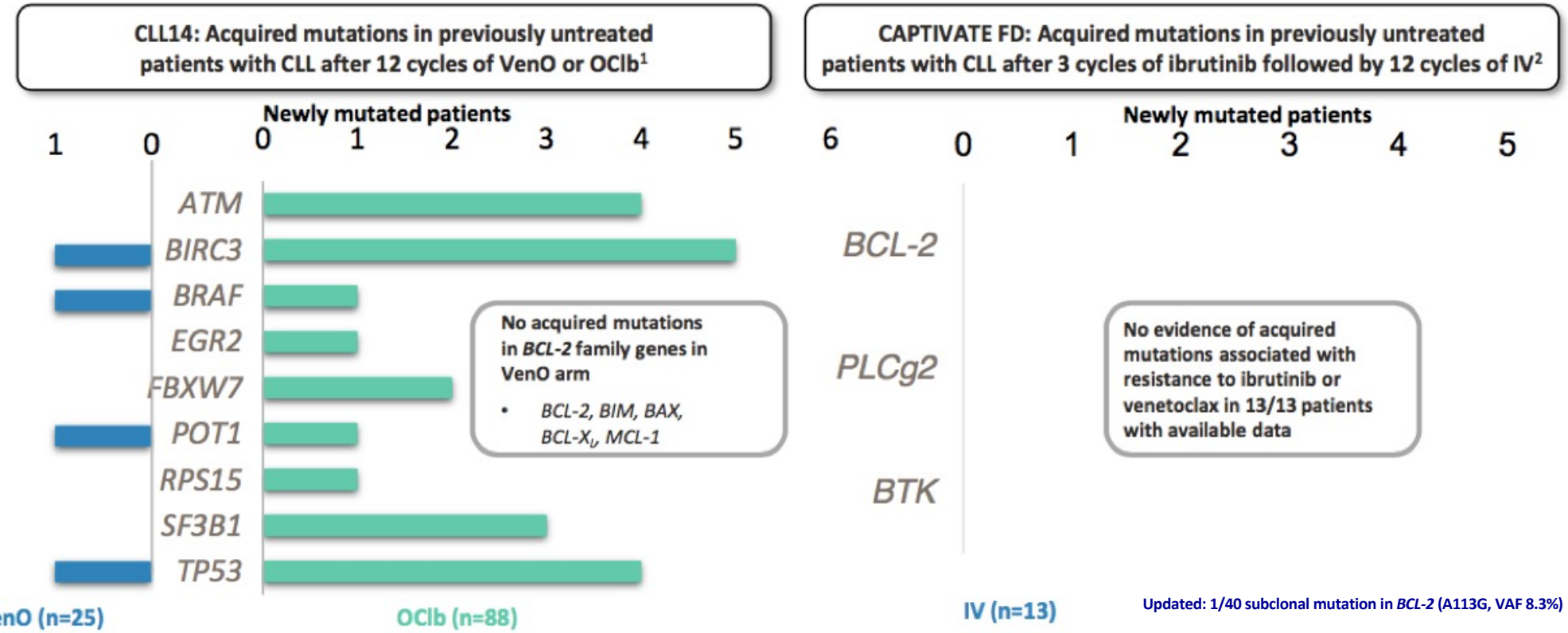


Key Goals of Fixed-Duration Treatment Regimens



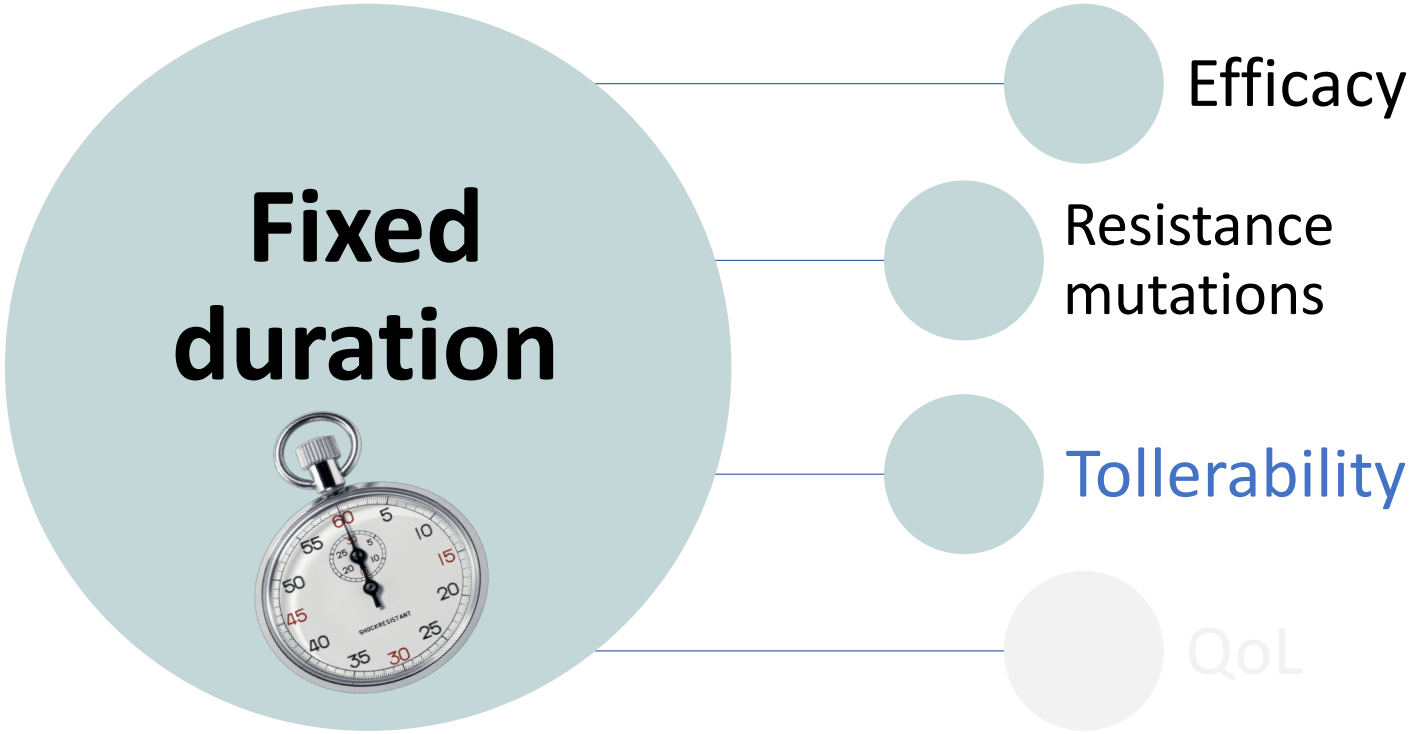
- Efficacy
- Resistance mutations
- Tollerability
- QoL

Acquired mutations rare in CLL treated with fixed-duration venetoclax-based therapy



Tausch E, *et al.* EHA 2021. Abstract S144 (Oral); 2. Tam CS, *et al. Blood* 2022; 139:3278–3289.

Key Goals of Fixed-Duration Treatment Regimens



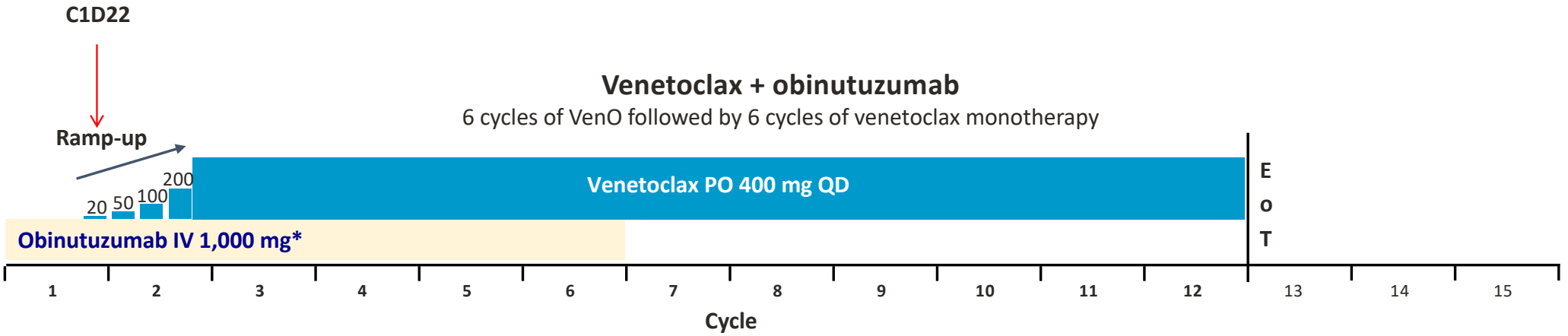
Obinutuzumab plus Venetoclax Safety Profile

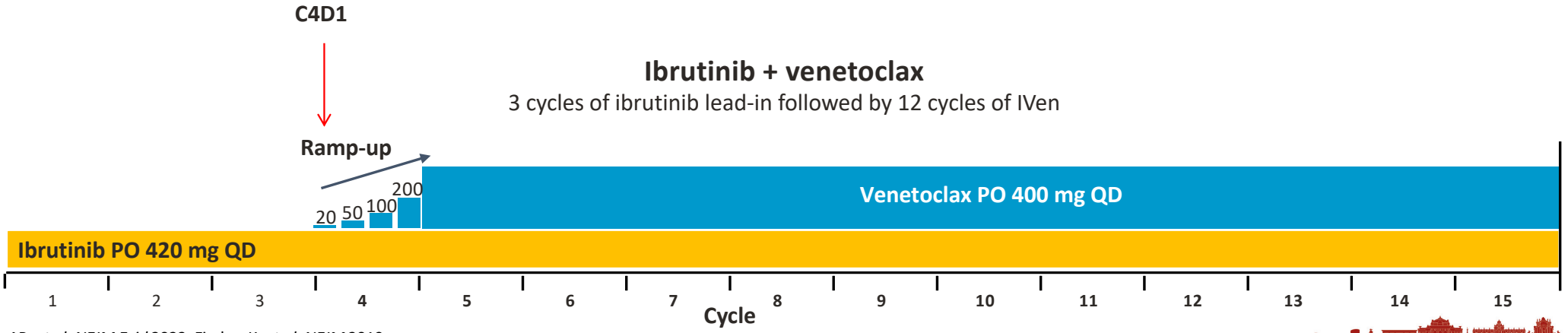
Most frequent ≥ grade 3 adverse events	Venetoclax-obinutuzumab (N=212)		Chlorambucil-obinutuzumab (N=214)	
	During Treatment	After Treatment	During Treatment	After Treatment
Neutropenia	51.9%	4.0%	47.2%	1.9%
Thrombocytopenia	13.7%	0.5%	15.0%	0.0%
Anemia	7.5%	1.5%	6.1%	0.5%
Febrile neutropenia	4.2%	1.0%	3.3%	0.5%
Infusion-related reaction	9.0%	0.0%	9.8%	0.5%
Tumour lysis syndrome	1.4%	0.0%	3.3%	0.0%
Neoplasms	1.4%	6.4%	1.4%	1.9%

Anti-CD20 MoAb Infusion Related Reaction (IRR)

IRR	G-CHL	FCR/BR	RVe	GVe	GIVe
CLL11 any grade G3 or higher	 221 (66%) **67 (20%)**	-	-	-	-
CLL14 any grade G3 or higher	 107 (55%) 22 (11%)	-	-	 96 (44%) **19 (9%)**	-
CLL13 any grade G3 or higher	-	 70 (32.4%) 12 (5.6%)	 82 (34.6%) 18 (7.6%)	 119 (52.2%) **10 (4.3%)**	 53 (22.9%) 10 (4.3%)

Lead-in time and Ramp up Phase

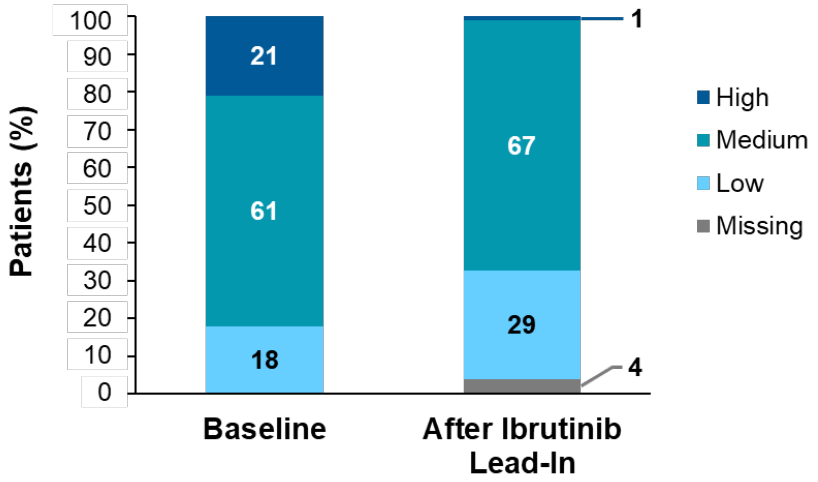




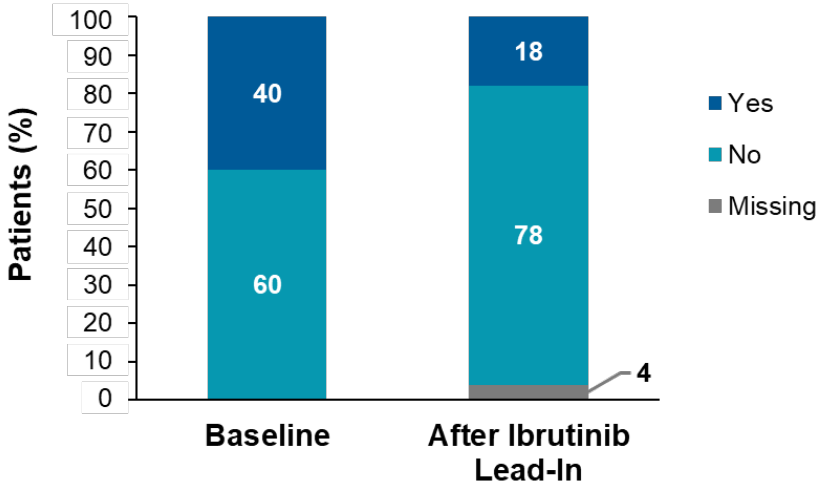
Kater AP, *et al. NEJM Evid* 2022. Fischer K, *et al. NEJM* 2019.

Primary Analysis of the FD Cohort Phase 2 CAPTIVATE Study

Tumor Burden Category for TLS Prophylaxis (N=159)



Indication for Hospitalization[a] (N=159)

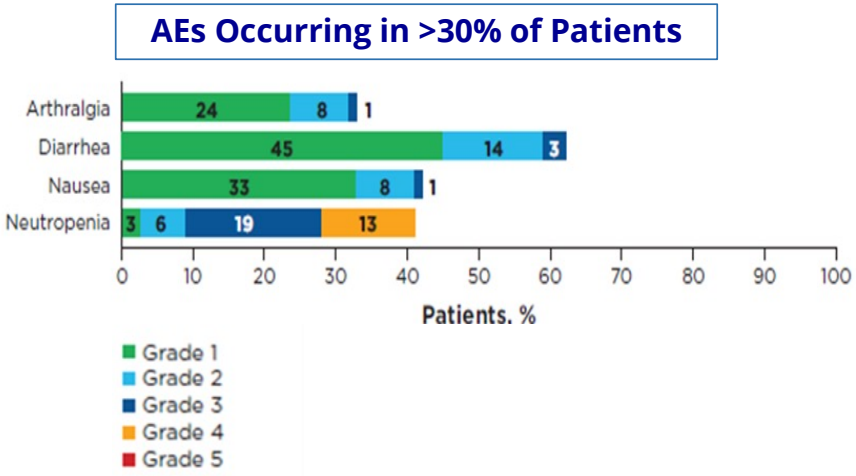


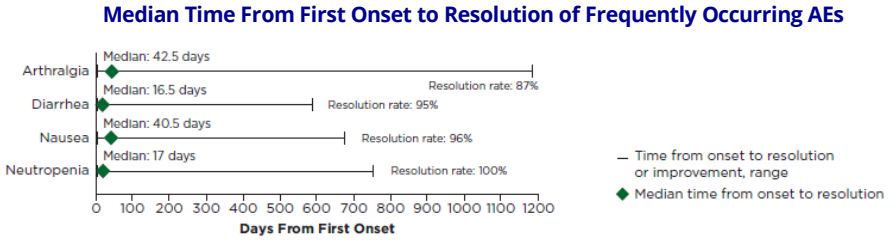
Debulking With 3 Cycles of Ibrutinib Lead-In Reduces Tumor Burden Category for TLS

No clinical TLS occurred, and no patient had laboratory TLS per Howard criteria

Ghia P et al. ASCO 2021. Oral Presentation. Abstract 7501; Tam CS et al. Blood 2022; 139(22): 3278-89.

Ibrutinib plus Venetoclax Safety Profile



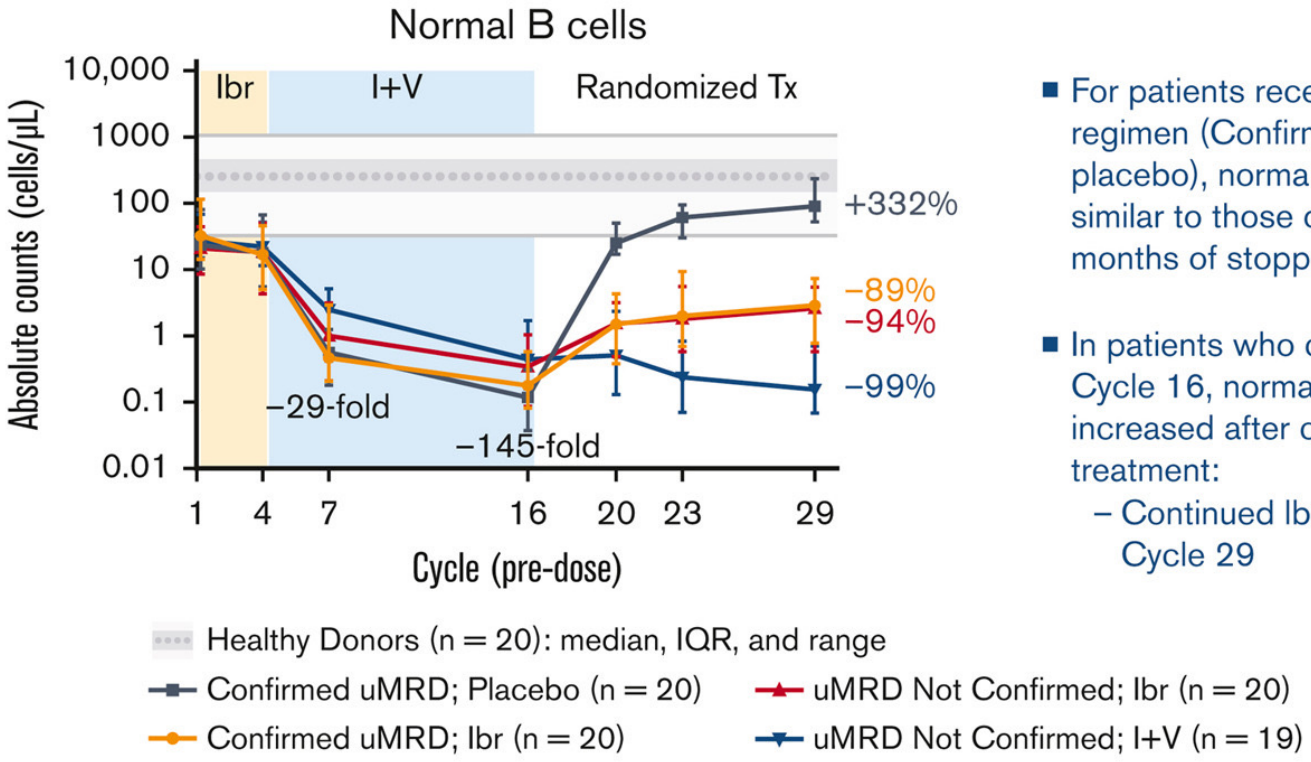


selected grade ≥ adverse events

	CAPTIVATE FD N=159	GLOW N=106
Median follow-up, months	27.9	46
Median age, years	60	71
Grade ≥3 granulocytopenia	38	34.9
Grade ≥3 infections	9	10.4
Atrial fibrillation/Flutter	2	**6.6**
Hypertension	16	7.5 (Gr 3-4)
Other severe CV events	1	**2.8**
Sudden deaths	-	**1.9** (+1.9)*
Clinical TLS	0	0

Moreno C, et al. Blood Adv. 2023

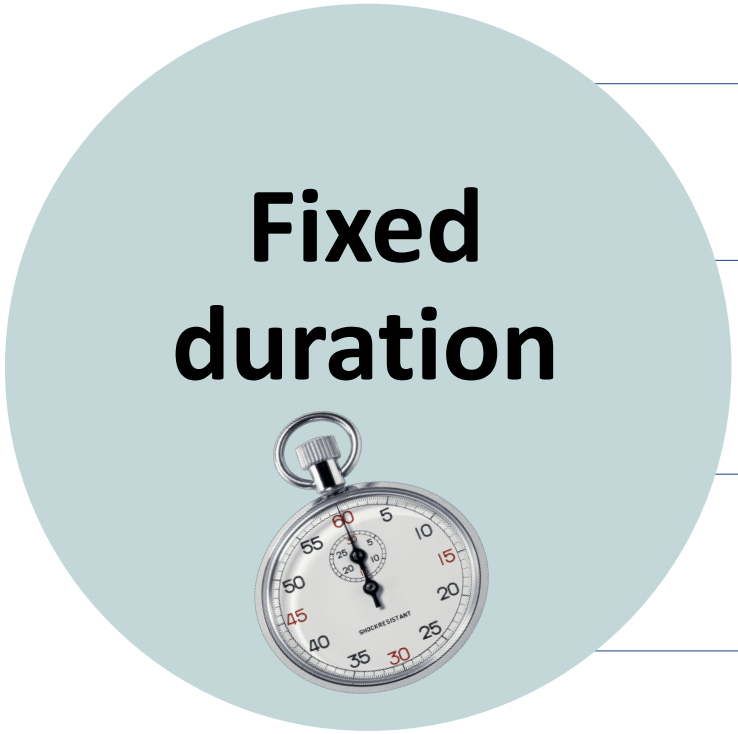
Normal B cells Increased to Healthy Donor Levels After Fixed-Duration Ibrutinib plus Venetoclax



- For patients receiving the fixed duration regimen (Confirmed uMRD randomized to placebo), normal B cells recovered to levels similar to those of healthy donors within 4 months of stopping treatment
- In patients who continued treatment after Cycle 16, normal B cell counts significantly increased after completion of venetoclax treatment:
  - Continued Ibr vs Ibr + Ven: $P = .0001$ at Cycle 29

Moreno C, et al. Blood Adv. 2023

Key Goals of Fixed-Duration Treatment Regimens



- Efficacy
- Resistance mutations
- Tollerability
- QoL

Table 1. Participant-Reported Perceived Benefits and Drawbacks of Fixed-Duration Versus Treat-to-Progression Therapies

	Benefits	Drawbacks
Fixed duration	▪ Budgeting and anticipating expenses (i.e., being able to plan for medical expenses and not having to pay for treatment repeatedly over an indefinite period of time) ▪ Convenience (i.e., not having to take a treatment [freedom from medication]) ▪ Being more in control ▪ Not having to refill prescription ▪ Not having to travel for treatment ▪ No short-term side effects when off treatment ▪ Reduced risk of long-term side effects ▪ Getting back to "normal" life	▪ Concentrated costs (the cost can be very high over a short period of time) ▪ Side effects might be worse if treatment duration is shorter ▪ Their CLL might worsen or spread if they are not taking a medication
Treat-to-progression	▪ Doing something (i.e., the feeling of comfort gained by taking action and treating their cancer)	▪ Worry that the medicine may become less effective over time ▪ Cost of treatment ▪ Taking a medicine continuously is a constant reminder of the cancer ▪ Inconvenience (i.e., always taking a medicine) ▪ Getting refills ▪ Following up with nurse or pharmacy ▪ Continual risk of short- and long-term side effects

Non è possibile visualizzare l'immagine.

The Power of the Patient Perspective

Oncologists and CLL patients in the US, UK, Germany, France, and Australia were recruited into the study (259 oncologists, 192 patients) → online survey including a discrete choice experiment (DCE)

In contrast to oncologists, patients preferred FD oral therapy over TTP regimens.

Una terapia a durata fissa ha delle implicazioni importanti dal punto di vista emotivo e psicologico

Is Fixed-Duration Therapy the New Standard of Care in Frontline Chronic Lymphocytic Leukemia?

Is Fixed-Duration Therapy the New Standard of Care in Frontline Chronic Lymphocytic Leukemia?

Grazie per l'attenzione

CIRS score and Performance Status significantly impact on tolerability in the phase 3 GLOW study

Table 1. Baseline Patient Demographics and Disease Characteristics (Intent-to-Treat Population).*

Characteristic	Ibrutinib-Venetoclax (n=106)	Chlorambucil-Obinutuzumab (n=105)
Age, yr	71.0 (47–93)	71.0 (57–88)
≥75	35 (33.0)	37 (35.2)
Men	59 (55.7)	63 (60.0)
ECOG PS 1 to 2	71 (67.0)	66 (62.9)
CIRS score	9 (1–20)	8 (0–22)
>6†	74 (69.8)	61 (58.1)
CrCl, ml/min‡	66.5 (34.0–168.1)	63.2 (32.3–180.9)
Rai stage III to IV§	55 (57.3)	53 (52.5)
Binet stage (CLL only)	96	101
A	7 (7.3)	8 (7.9)
B	46 (47.9)	53 (52.5)
C	43 (44.8)	40 (39.6)
Ann Arbor stage (SLL only)	10	4
IV	10 (100)	4 (100)
Bulky disease ≥5 cm	41 (39.0)	38 (36.2)
Elevated LDH¶	35 (33.0)	51 (48.6)
IGHV status		
Mutated	27 (25.5)	27 (25.7)
Unmutated	55 (51.9)	54 (51.4)
Unknown	24 (22.6)	24 (22.9)
Del(11q)	20 (18.9)	18 (17.1)
TP53 mutation	7 (6.6)	2 (1.9)

Seven (6.6%) treatment-emergent deaths, including four sudden cardiac deaths, occurred during Ibrutinib-Venetoclax treatment.

All patients who suffered sudden cardiac death had CIRS ≥ 10 and/or ECOG performance status score of 2.

Cumulative Illness Rating Scale

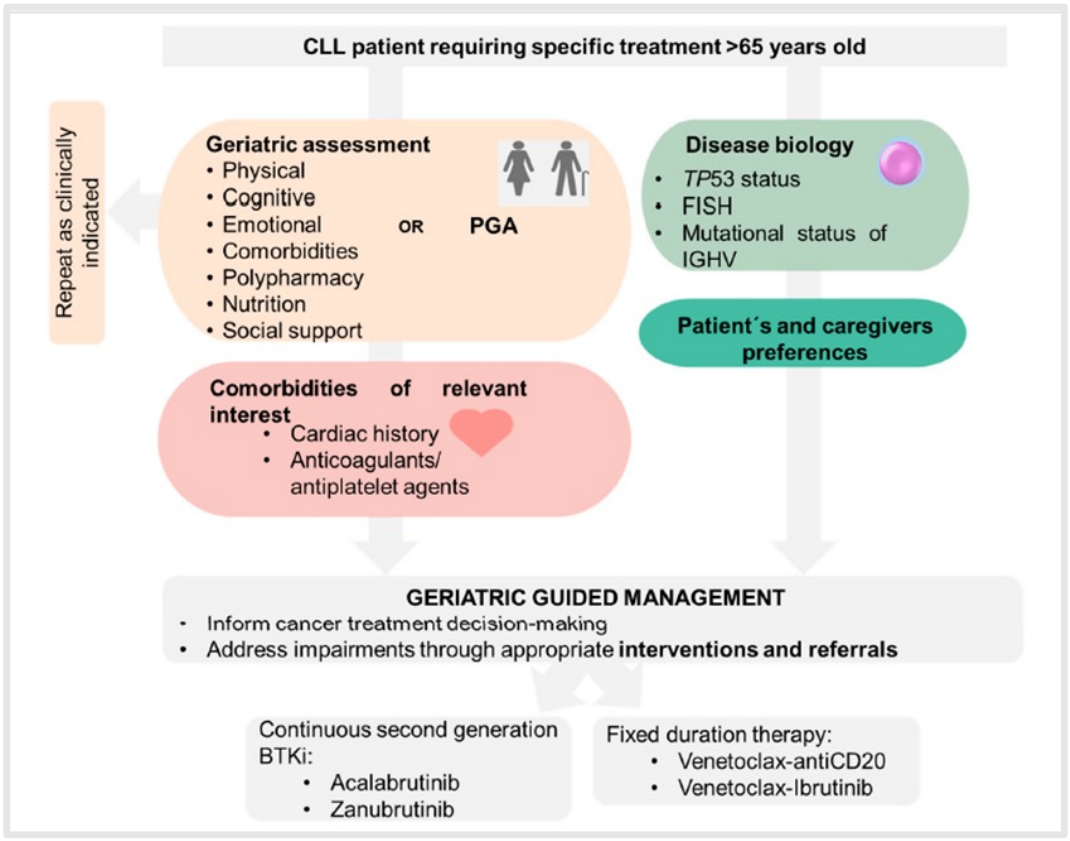
Score	Description
0	No problem affecting that system
1	Current mild problem/past significant problem
2	Moderate disability/morbidity and/or requires first-line therapy
3	Severe problem and/or constant and significant disability and/or hard-to-control chronic problems
4	Extremely severe problem and/or immediate treatment required and/or organ failure and/or severe functional impairment

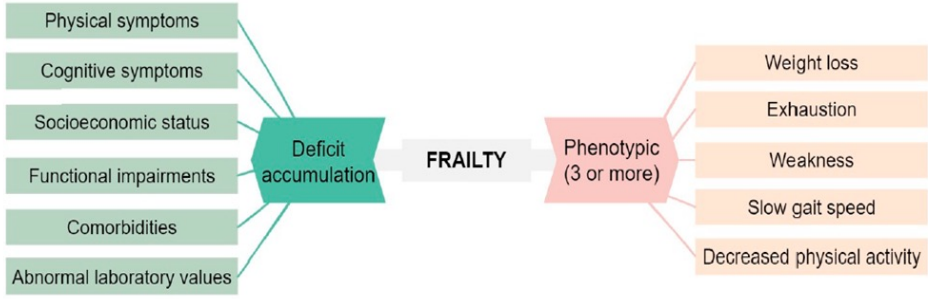
Total score: 0-56

System scored: cardiac, vascular, hematological, respiratory, EENT, upper lower GI, hepatic and pancreatic, renal, genitourinary, musculoskeletal, neurological, endocrine-metabolic, psychiatric

Kater et al. NEJM Evid 2022; 1(7)

Role of comorbidities as a prognostic factor





González-Gascón-y-Marín I. et al. Cancers 2023, 15, 4391