3rd POSTGRADUATE

CLL Conference

Bologna
November 14-15
2022

Royal Hotel Carlton

President:
Pier Luigi Zinzani

What is the primary role of fixed-duration therapy?

Should it be the main approach for (all) next-generation combination approaches or only for venetoclax-based combinations?

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15 November, 2022

Disclosures of Matthew S. Davids, MD, MMSc

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
AbbVie	✓		✓			✓	
Adaptive Biotechnologies			✓			✓	
Ascentage Pharma	✓		✓				
AstraZeneca	✓		✓			✓	
BeiGene			✓			✓	
Bristol-Myers Squibb			✓			✓	
Eli Lilly			✓			✓	
Genentech	✓		✓			✓	
Janssen			✓			✓	
Merck			✓			✓	
Novartis	✓						
Ono Pharmaceuticals			✓				
Research to Practice							✓ (Honoraria)
Secura Bio	✓		✓				
Takeda			✓			✓	
TG Therapeutics	✓		✓			✓	

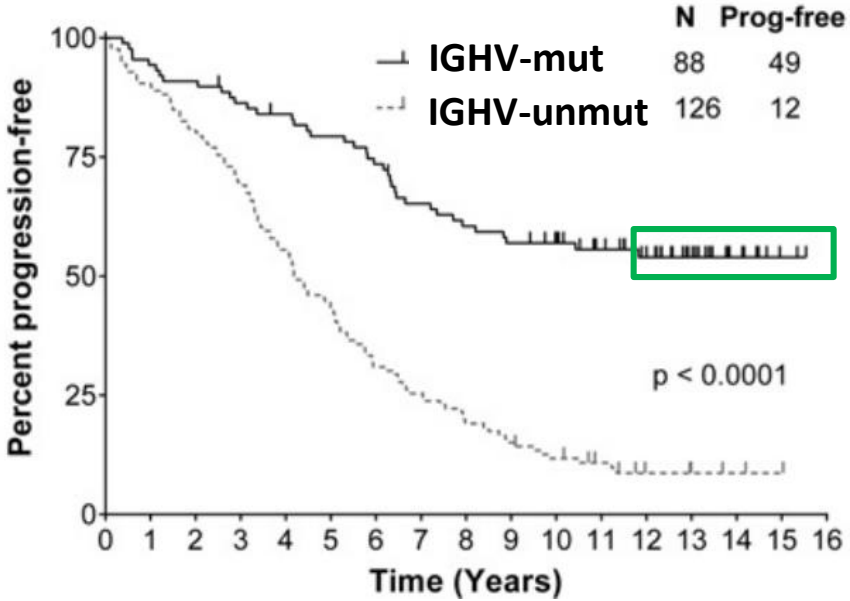
Definitions

- **Fixed-duration:** a therapy given for the same defined period of time in all patients on the regimen (e.g. VenG for 1 year)

- **Time-limited:** a therapy given for a limited period of time but the amount of time can either be the same or vary for different patients (e.g. VenG for 1 year *or* MRD-guided I + V)

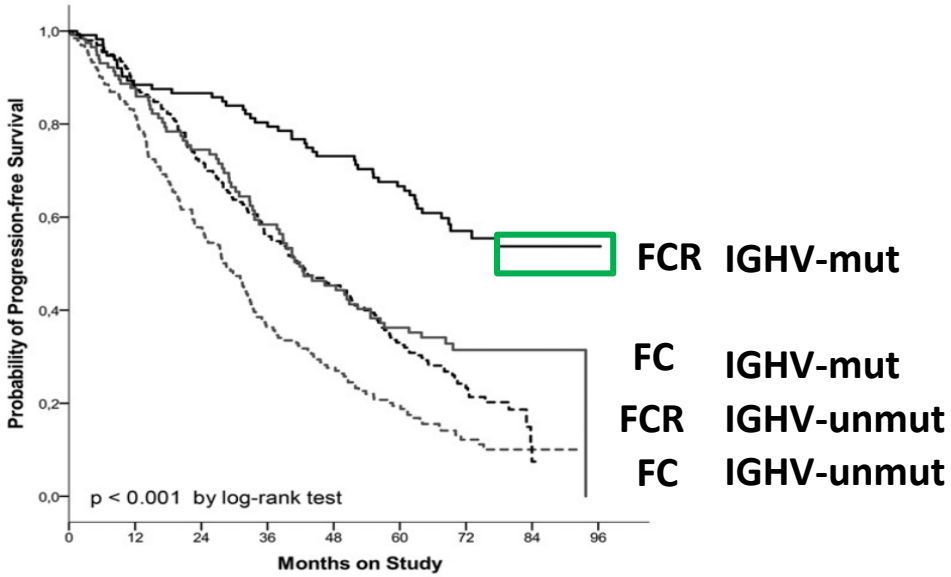
CIT is the original fixed-duration therapy, and can provide functional cure in mutated IGHV CLL

MDACC – FCR 300



Thompson et al., *Blood*, 2016

GCLLSG – CLL8



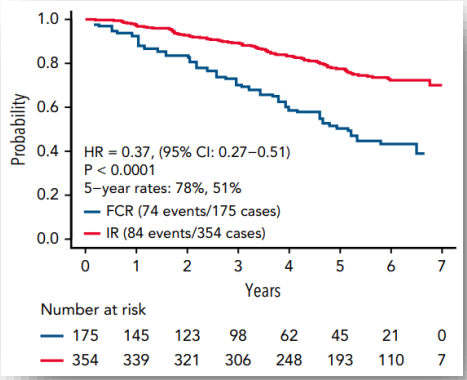
Fischer et al., *Blood*, 2016

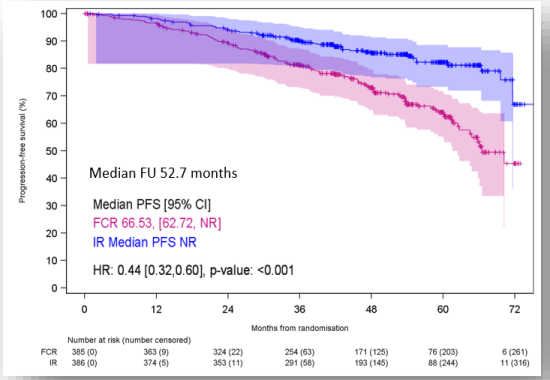
Phase 3 data of IR vs. FCR: PFS and possibly also OS benefit of continuous ibrutinib-based therapy

ECOG 1912 (US)

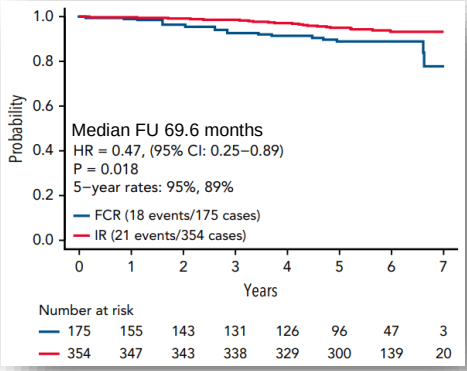
FLAIR (UK)

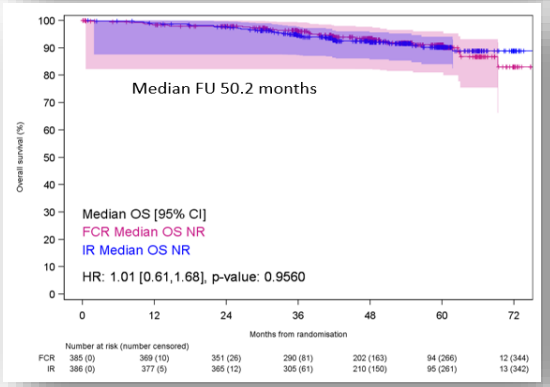
PFS





OS

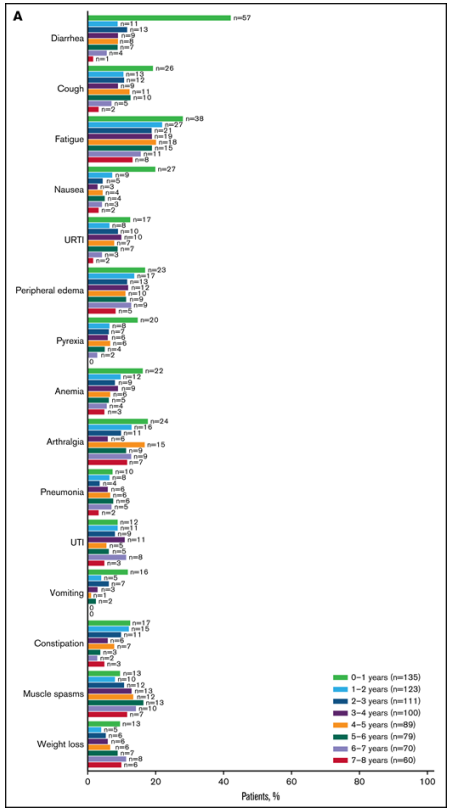


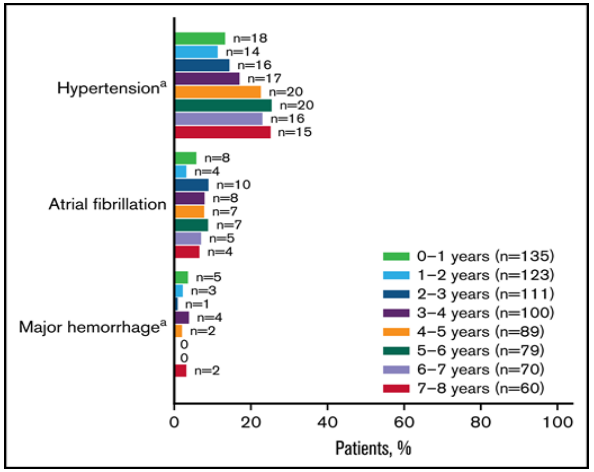


Shanafelt et al., *Blood*, 2022

Hillmen et al., ASH, 2021

But discontinuation rates with ibrutinib are high, and are due mostly to AEs





- 42% of patients still on ibrutinib at 8 years
- Most common reason for discontinuation was AEs (24%)

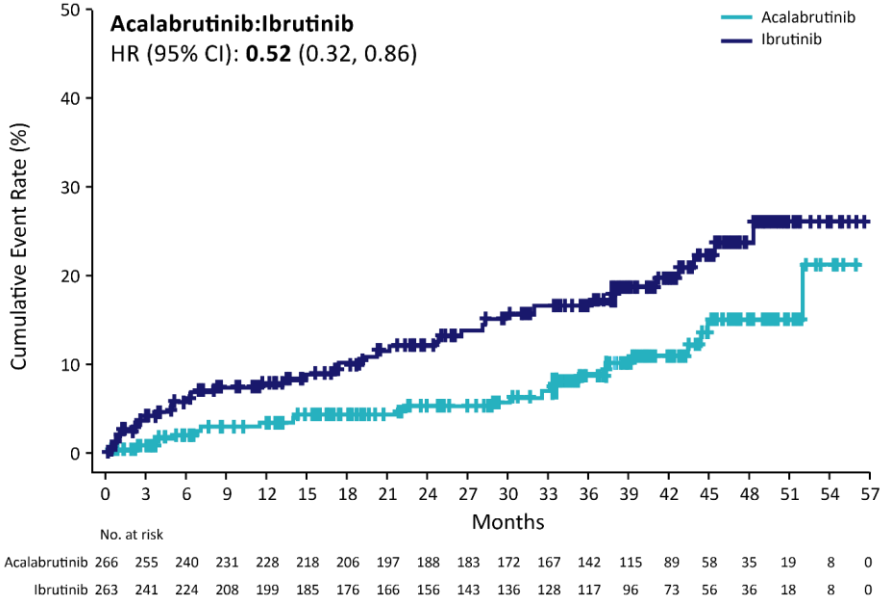
Barr et al., *Blood Advances*, 2022

- Discontinuation due to AEs may be even more common in the real-world setting (41% discontinuation at median of 17 mo.)

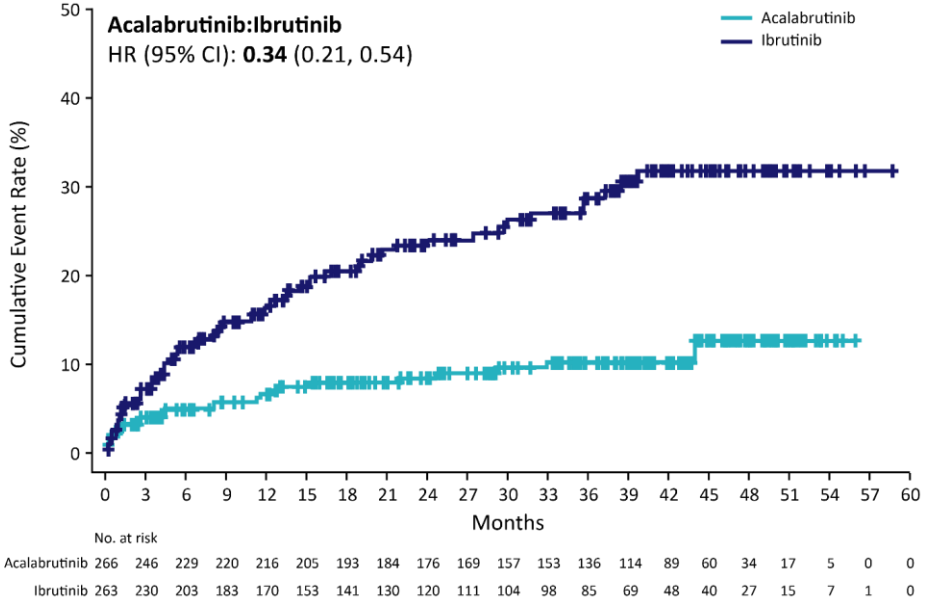
Mato et al., *Haematologica*, 2018

The more specific BTKi have improved AE profiles, buttoxicities are still common (I)

Afib/Flutter



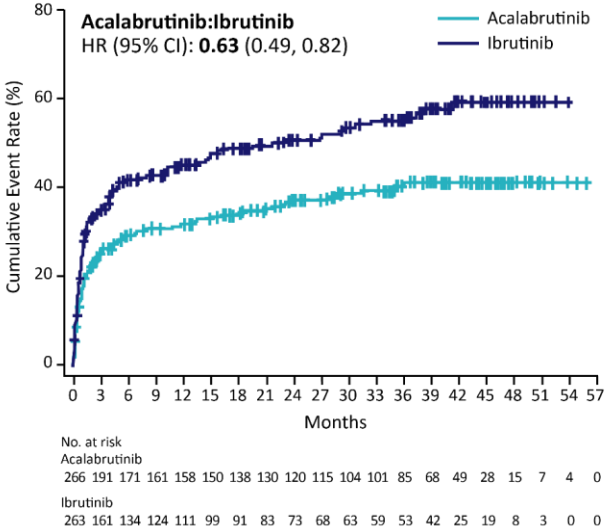
Hypertension



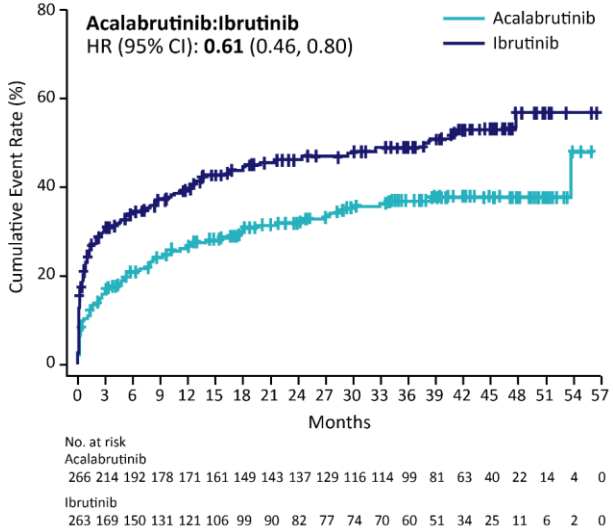
Byrd et al, JCO, 2021

The more specific BTKi have improved AE profiles, but toxicities are still common (II)

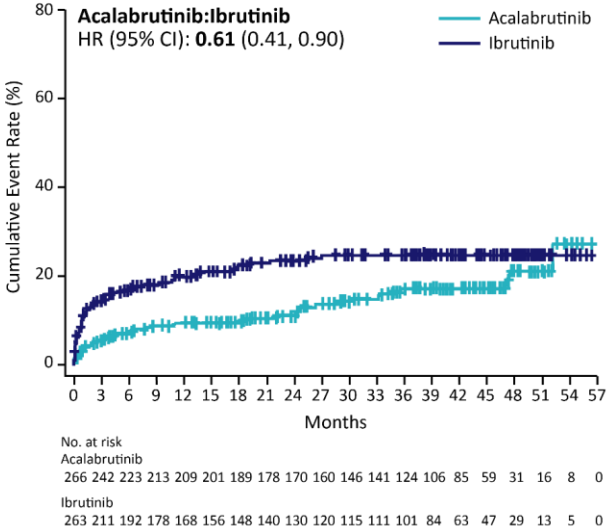
Bleeding Events



Diarrhea



Arthralgia



Byrd et al, JCO, 2021

Ibrutinib: Risk of Drug Interactions

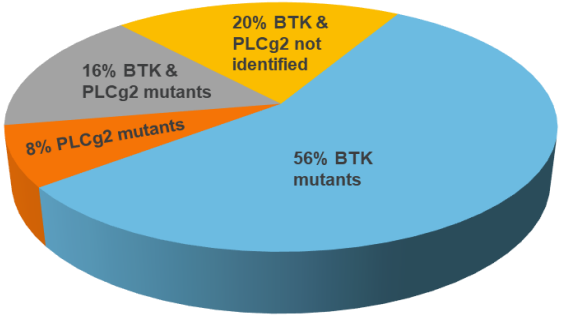
Medication	Level of Interaction	Effect	Mechanism of Interaction
Diltiazem/verapamil	**Major**	↑↑ ibrutinib level	CYP450 3A4 inhibition by diltiazem/verapamil
Digoxin	Moderate	↑ digoxin level	P-glycoprotein inhibition by ibrutinib
Amiodarone/dronedarone	**Major**	↑↑ ibrutinib level	CYP450 3A4 inhibition amiodarone/dronedarone
Factor Xa inhibitors (rivaroxaban, apixaban, edoxaban)	Moderate	↑ factor Xa inhibitor level	CYP450 3A4 inhibition and P-glycoprotein inhibition by ibrutinib
Direct thrombin inhibitor (dabigatran)	**Major**	↑ dabigatran level	P-glycoprotein inhibition by ibrutinib

The risk of clinically relevant drug interactions increases, the longer patients stay on treatment. This is particularly relevant in elderly or comorbid patients.

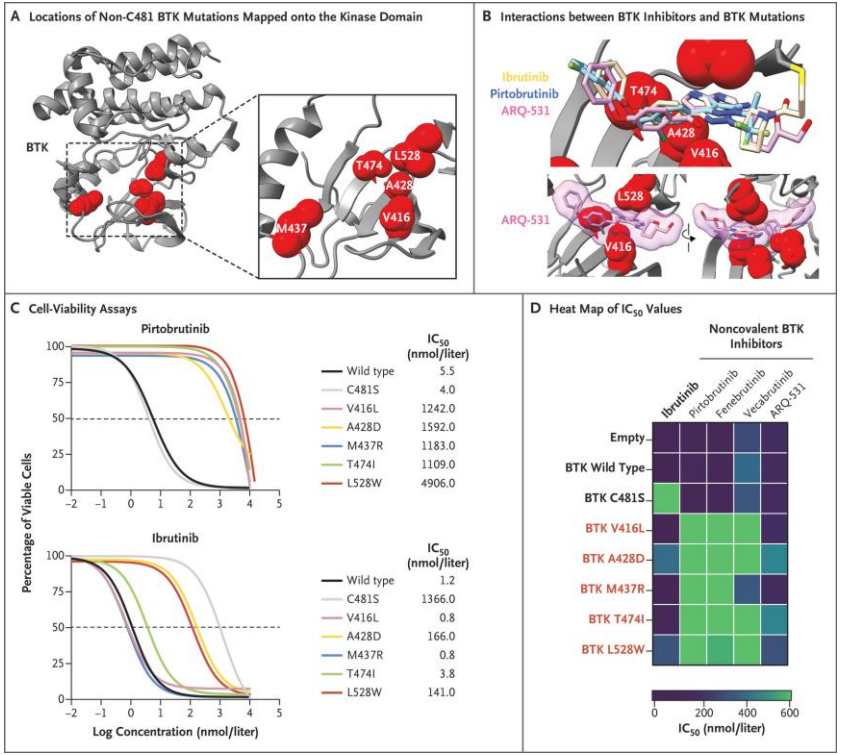
Ganatra et al, JACC, 2018

BTKi resistance mutations arise, raising the question of the optimal sequence of administration

Ibrutinib acquired resistance in patients with progressive CLL



Lampson et al., Expert Rev Hematol, 2018



Wang E et al., N Engl J Med, 2022

Cost Effectiveness of Frontline CLL Therapies

Treatment	Total costs ($)	Life-years gained	QALYs gained	Incremental costs ($)	Incremental life-years gained	Incremental QALYs gained	ICER ($/QALY)
VenG	$291,012	13.01	6.521	–	–	–	–
GClb	$491,040	13.01	6.188	$200,028	0	−0.333	VenG is dominant
BR	$595,771	12.31	5.815	$304,759	−0.70	−0.706	VenG is dominant
Ibr	$1,045,472	12.31	6.004	$754,460	−0.70	−0.517	VenG is dominant
Ibr + G	$1,779,412	13.02	6.543	$1,488,400	0.01	0.022	$67,856,575
Ibr + R	$1,040,860	12.22	5.946	$749,848	−0.79	−0.576	VenG is dominant
Acala	$1,870,749	13.55	7.194	$1,579,737	0.54	0.672	$2,349,304
Acala + G	$1,947,166	13.56	7.482	$1,656,154	0.55	0.961	$1,724,052

TABLE 2 Cost-Effectiveness of VenG Compared With Other Treatments
Acala = acalabrutinib; B = bendamustine; Clb = chlorambucil; G = obinutuzumab; Ibr = ibrutinib; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; R = rituximab; Ven = venetoclax.

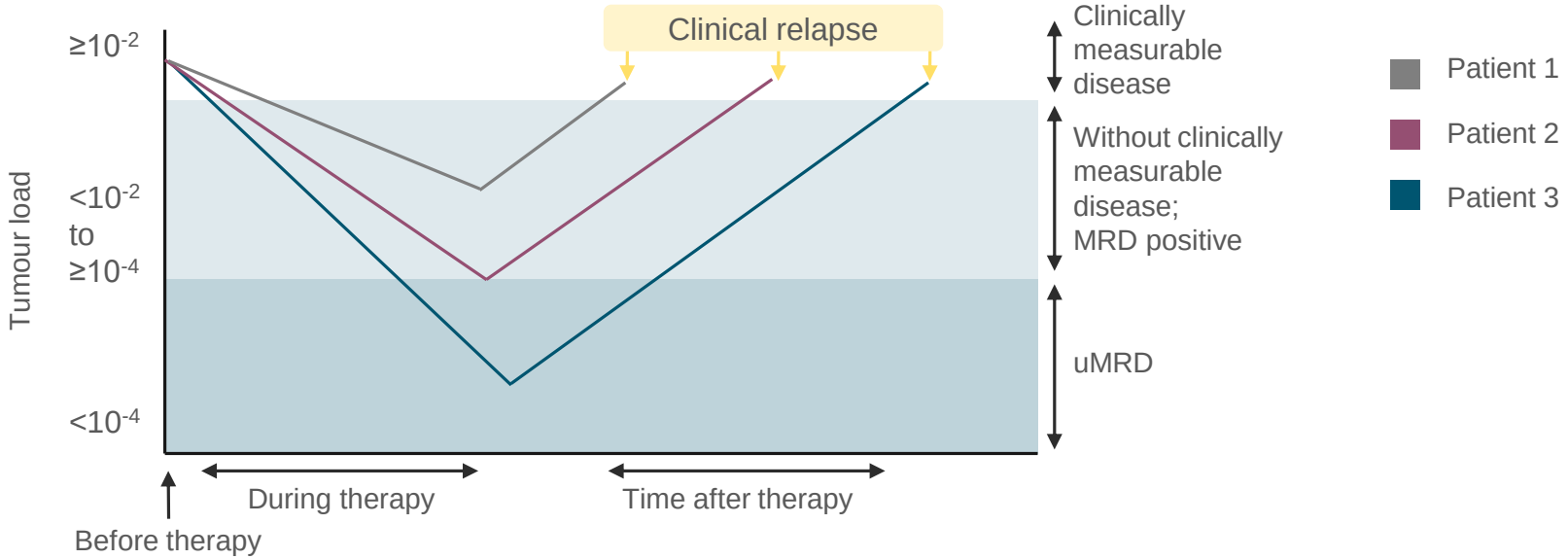
Chatterjee et al, 2021

What are some limitations of novel agent monotherapy?

- Achievement of CR and uMRD is rare
- Resistance mutations already described
- Optimal sequence of BTKi remains undefined
- Ongoing drug-drug interaction risk
- Ongoing toxicities
- Long term adherence issues
- Co$t

Achieving uMRD is associated with longer PFS

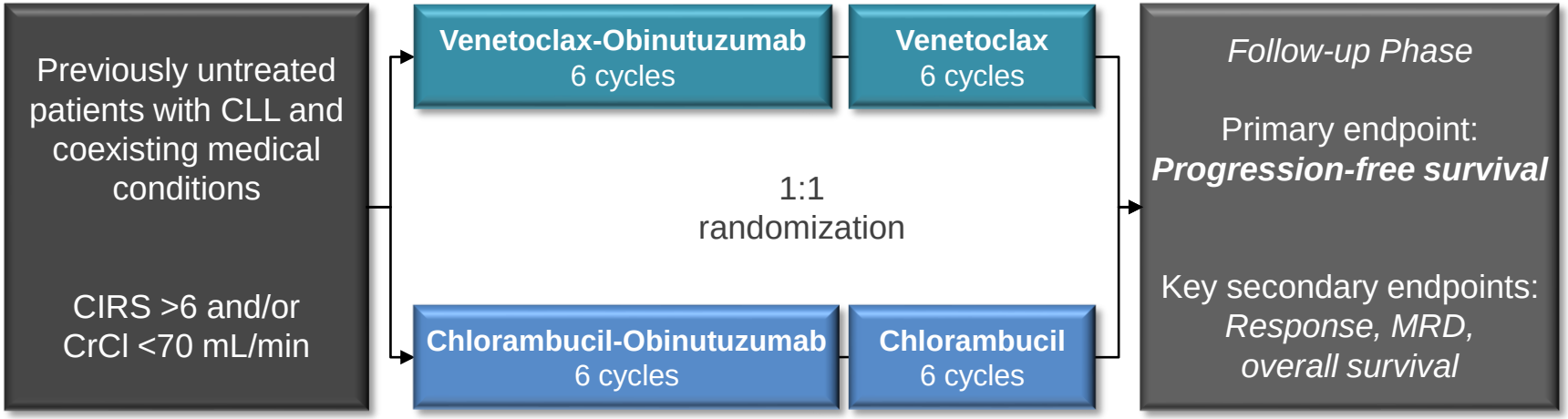
uMRD IS A KEY GOAL OF FIXED-DURATION TREATMENT REGIMENS



Adapted from Böttcher et al. 2013

What are the data supporting the use of venetoclax-based fixed duration therapy in CLL?

Phase 3 CLL14 Study of Ven-G vs Chl-G in Patients With TN CLL With Coexisting Medical Conditions

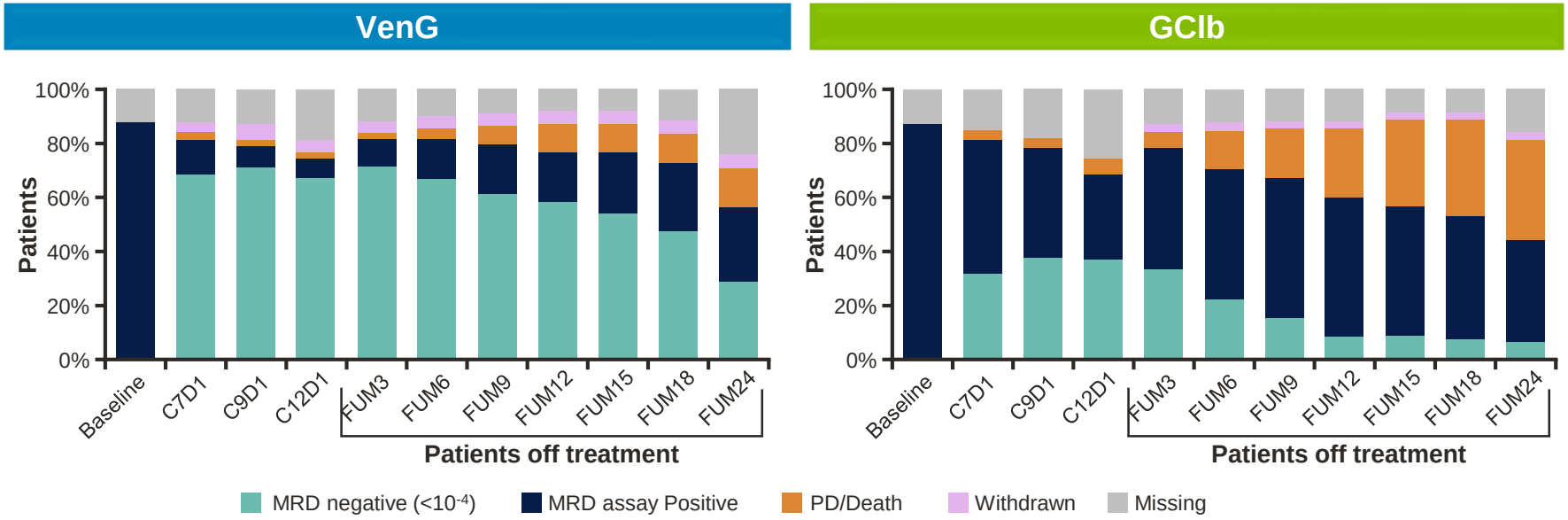


CIRS, Cumulative Illness Rating Scale; Clb-G, chlorambucil, obinutuzumab; CLL, chronic lymphocytic leukemia; CrCl, creatinine clearance; MRD, minimal residual disease; PB, peripheral blood; TN, treatment-naive, Ven-G, venetoclax, obinutuzumab.

Al-Sawaf, et al. *Blood.* 2020;136(supplement 1): 22-23.

VenG achieves uMRD for most patients

PB MRD by ASO-PCR

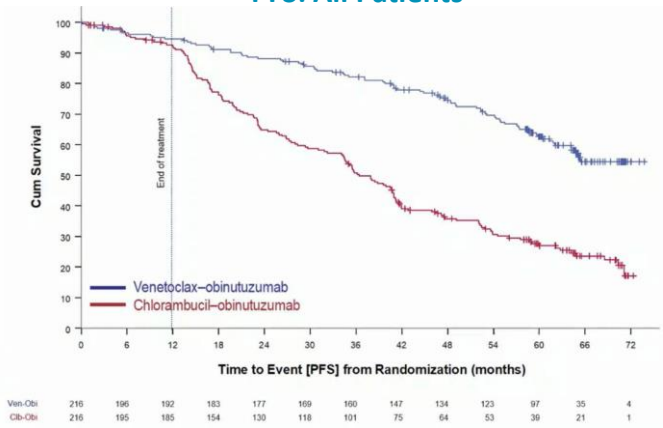


MRD-negativity rates were more sustainable after completion of therapy with VenG than with GClb as assessed by ASO-PCR

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

5-year follow-up of Ven-Obin in CLL14 in frontline CLL

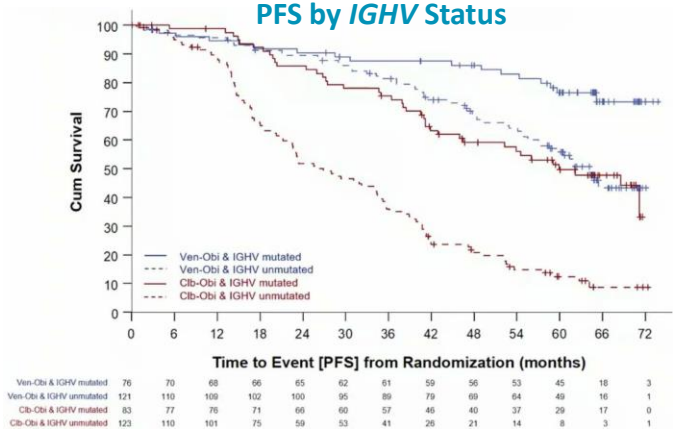
PFS: All Patients



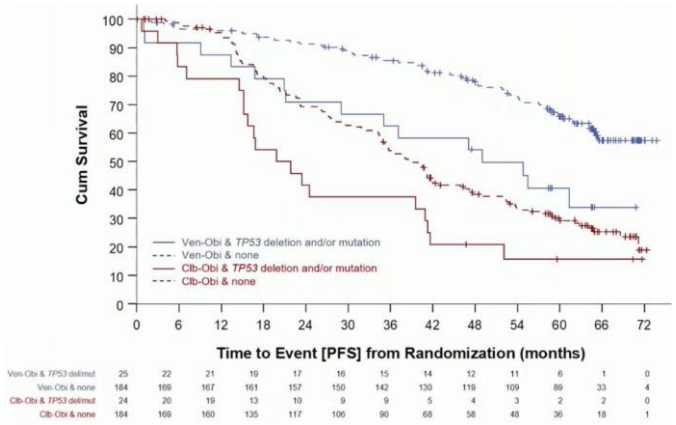
PFS by Subgroup		Ven-Obi (n=216)	Clb-Obi (n=216)
All patients	Median, months	NR	36.4
	5-year rate, %	62.6	27.0
	HR (95% CI); *P* value	0.35 (0.26-0.46); <0.0001	
Median, months			
TP53 del/mut	No	NR (n=184)	38.9 (n=184)
	Yes	49.0 (n=25)	19.8 (n=24)
IGHV status	Mut	NR (n=76)	59.9 (n=83)
	Unmut	64.2 (n=121)	26.9 (n=123)

Median observation time: 65.4 months

PFS by *IGHV* Status



PFS by *TP53* Status



Al-Sawaf O, et al. EHA 2022. Abstract S148.

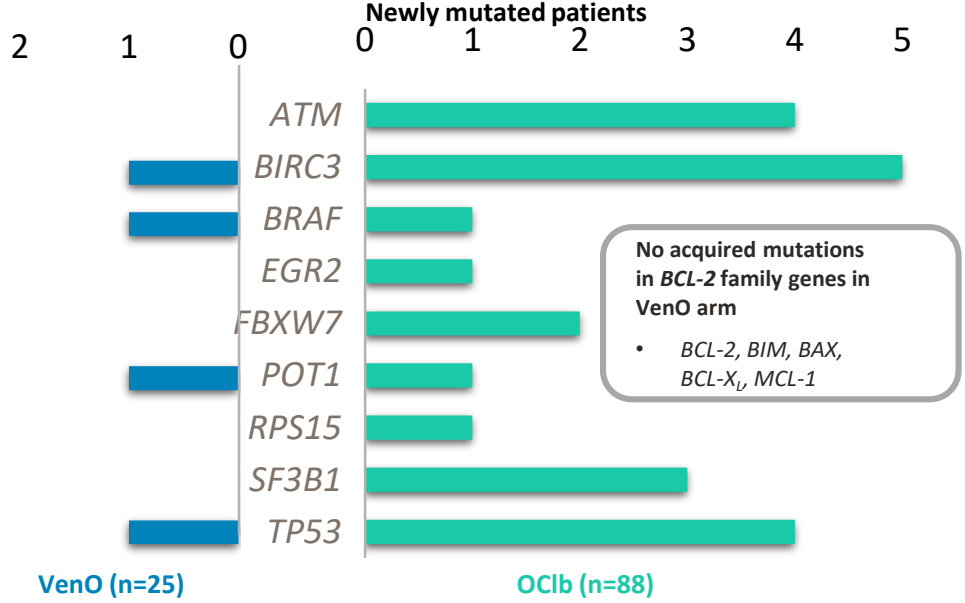
Less drug exposure = less toxicity

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%

Al-Sawaf et al, EHA 2020

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

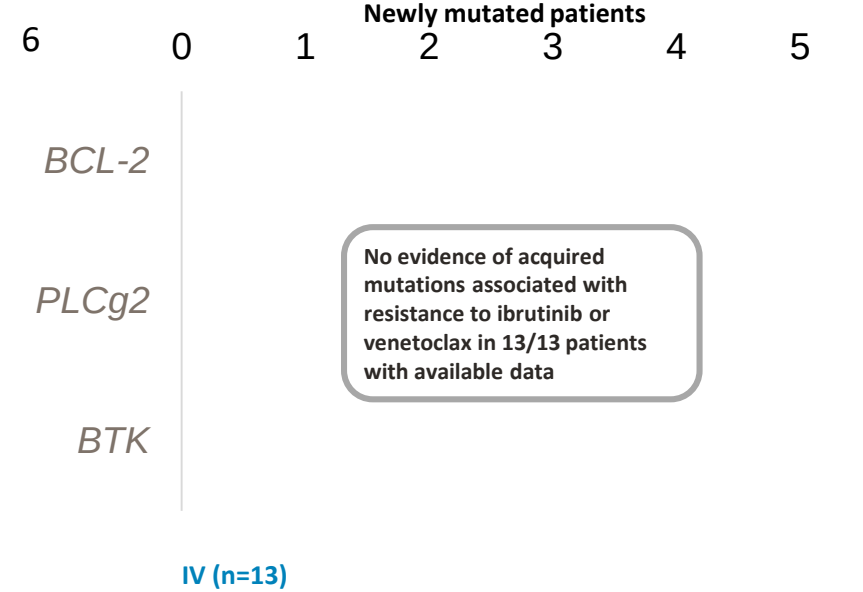
CLL14: Acquired mutations in previously untreated patients with CLL after 12 cycles of VenO or OClb[1]



No acquired mutations in *BCL-2* family genes in VenO arm

- *BCL-2, BIM, BAX, BCL-X_L, MCL-1*

CAPTIVATE FD: Acquired mutations in previously untreated patients with CLL after 3 cycles of ibrutinib followed by 12 cycles of IV[2]

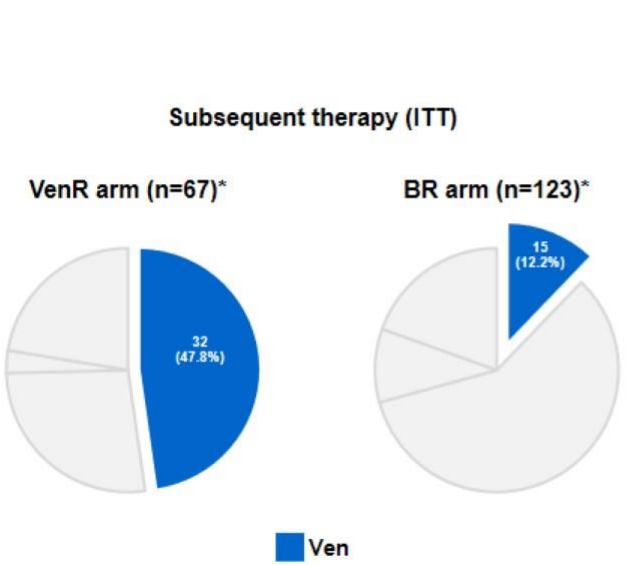


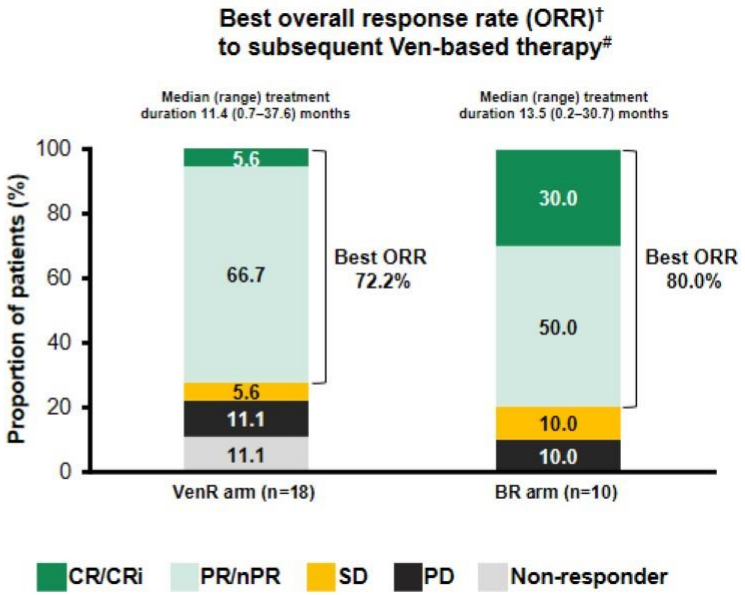
No evidence of acquired mutations associated with resistance to ibrutinib or venetoclax in 13/13 patients with available data

Clb, chlorambucil; I, ibrutinib; O, obinutuzumab; Ven, venetoclax.

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

Fixed duration = potential for re-treatment



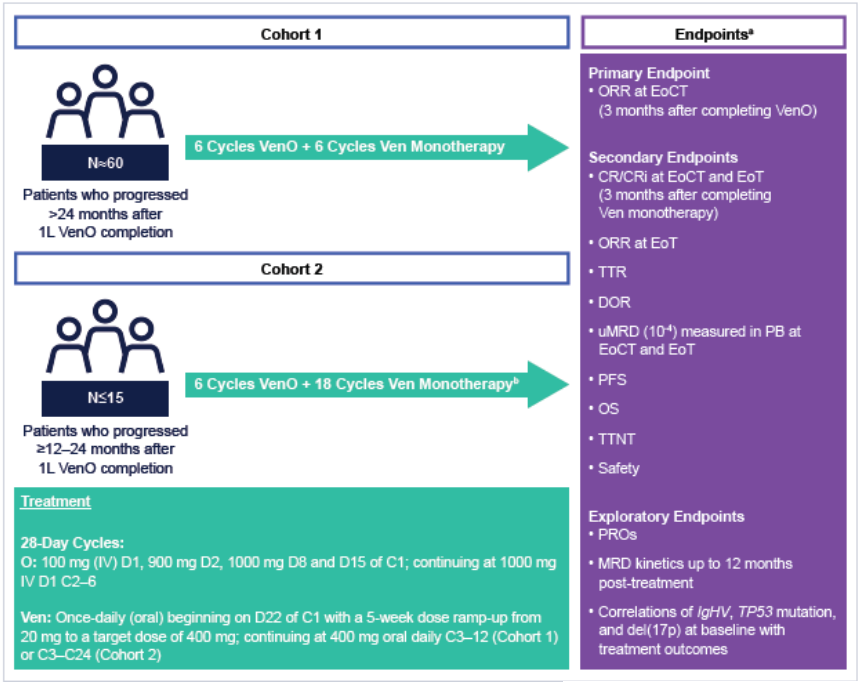


Limited drug exposure avoids drug resistance → re-treatment remains an option

Harrup et al, ASH 2020

A phase 2 study of venetoclax plus obinutuzumab retreatment in patients with relapsed CLL

Study Design



OBJECTIVES

The ReVenG study will assess whether patients with chronic lymphocytic leukemia who completed first-line venetoclax + obinutuzumab (VenO) can derive clinical benefit with VenO retreatment following disease progression

1. The primary objective is to evaluate the overall response rate of VenO retreatment in patients who progressed >24 months after first-line VenO
2. The secondary objective is to quantify time-to-event efficacy endpoints and to assess the safety of VenO retreatment in patients who progressed >24 months after first-line VenO

STUDY OVERVIEW

Multicenter	International	Open-Label	Phase 2	Up to 75 Patients Are Planned for Enrollment	NCT04895436 Planned Initiation in December 2021

DEUTSCHE CLL STUDIENGRUPPE

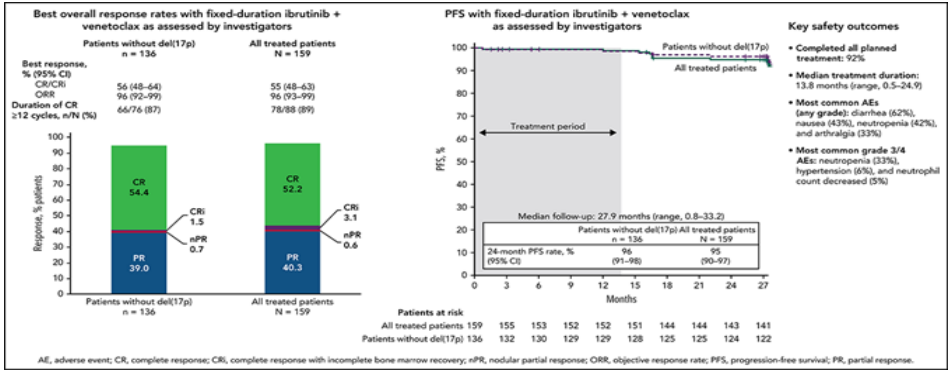
Dana-Farber Cancer Institute

Now accruing!

Davids MS et al., ASH 2021, Abstract 2634

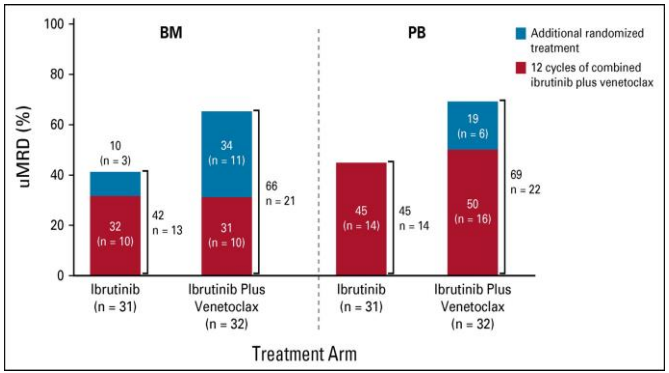
Doublets: BTKi/BCL-2i combos are active, though follow-up is still relatively short

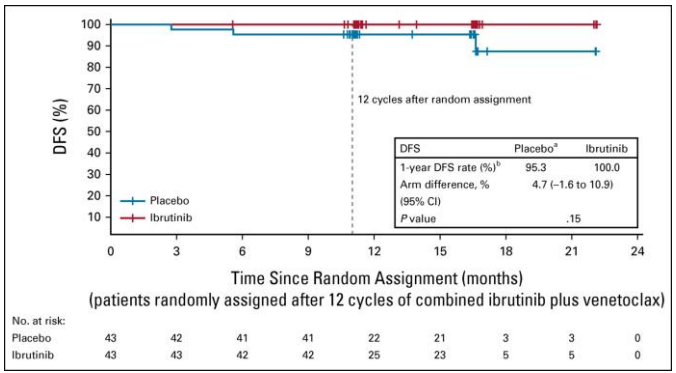
CAPTIVATE FD Cohort



Tam et al., *Blood*, 2022

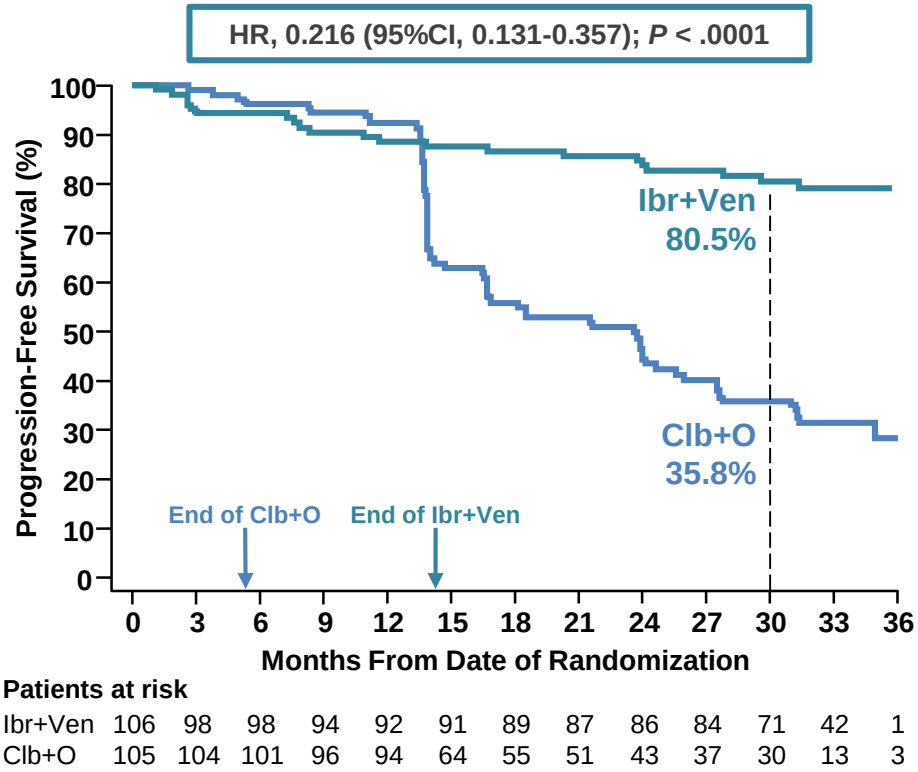
CAPTIVATE MRD Cohort





Wierda et al., J Clin Oncol, 2021

Phase 3 GLOW Study: superior PFS with Ibr+Ven vs Clb+O in older patients

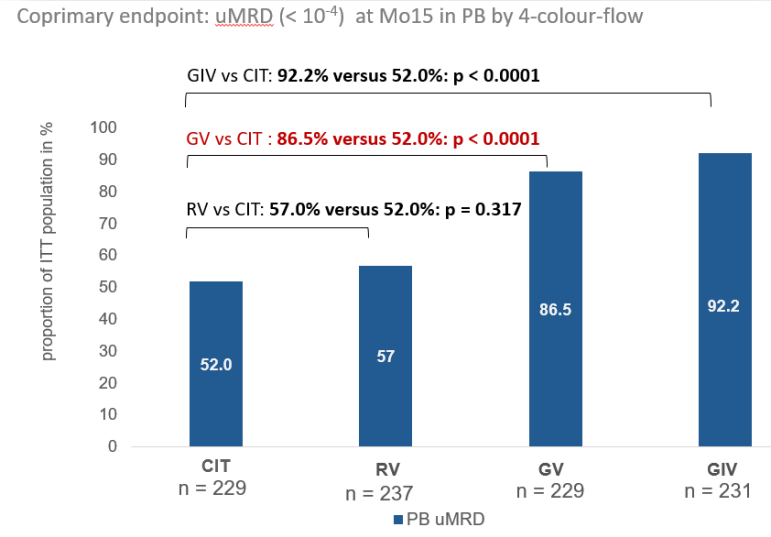


- **With median follow-up of 34.1 months:**
  - Overall survival HR 0.76 (95% CI, 0.35-1.64)
    - 11 deaths for Ibr+Ven vs 16 for Clb+O
    - 4 on treatment deaths due to CV complications in IV arm[24]

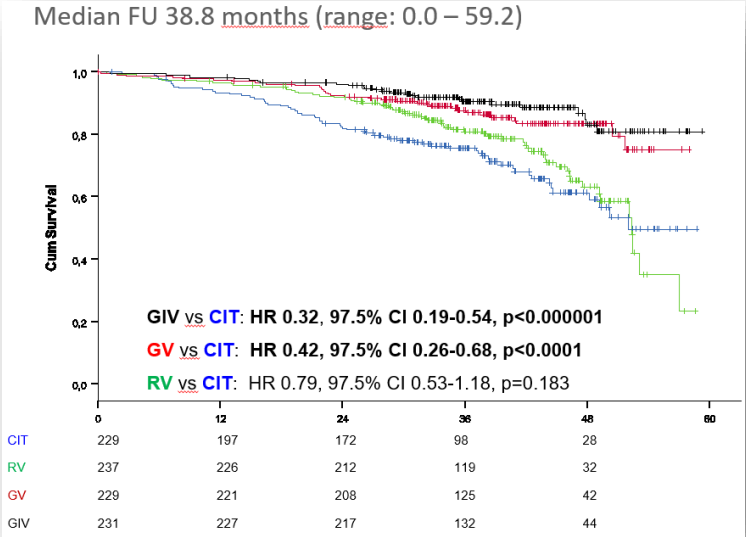
Munir T. et al. Presented at: 2021 ASH Annual Meeting and Exposition; December 11-14, 2021; Atlanta, GA. Abstract 70.

CLL13: R vs. G, triplet vs. doublets

MRD



PFS



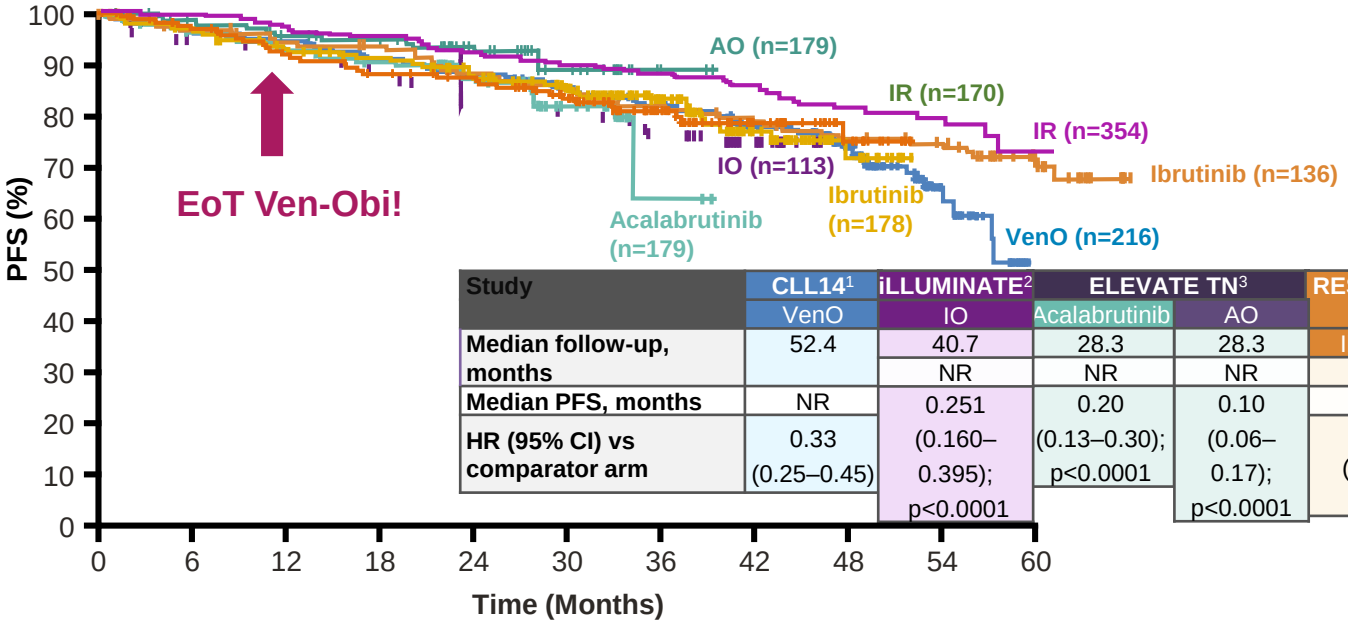
PFS	Median months	3y PFS (%)
CIT	52.0	75.5
RV	52.3	80.8
GV	Not reached	87.7
GIV	Not reached	90.5

Ongoing US ECOG and ALLIANCE studies are comparing IVO to IO

Eichhorst B, et al. ASH 2021

Eichhorst B, et al. EHA 2022

PFS outcomes with fixed vs. continuous therapy



Study	CLL14[1]	iLLUMINATE[2]	ELEVATE TN[3]		RESONATE-2[4]	Alliance 202[5]		ECOG 1912[6]
	VenO	IO	Acalabrutinib	AO	Ibrutinib	Ibrutinib	IR	IR
Median follow-up, months	52.4	40.7	28.3	28.3	Ibrutinib	38.0	38.0	IR
		NR	NR	NR	60.0	NR	NR	48.0
Median PFS, months	NR	0.251 (0.160–0.395); p<0.0001	0.20 (0.13–0.30); p<0.0001	0.10 (0.06–0.17); p<0.0001	NE	0.39	0.38	-
HR (95% CI) vs comparator arm	0.33 (0.25–0.45)				0.146 (0.098–0.218)	(0.26–0.58); p<0.001	(0.25–0.59); p<0.001	0.39 (0.26–0.57); p<0.0001

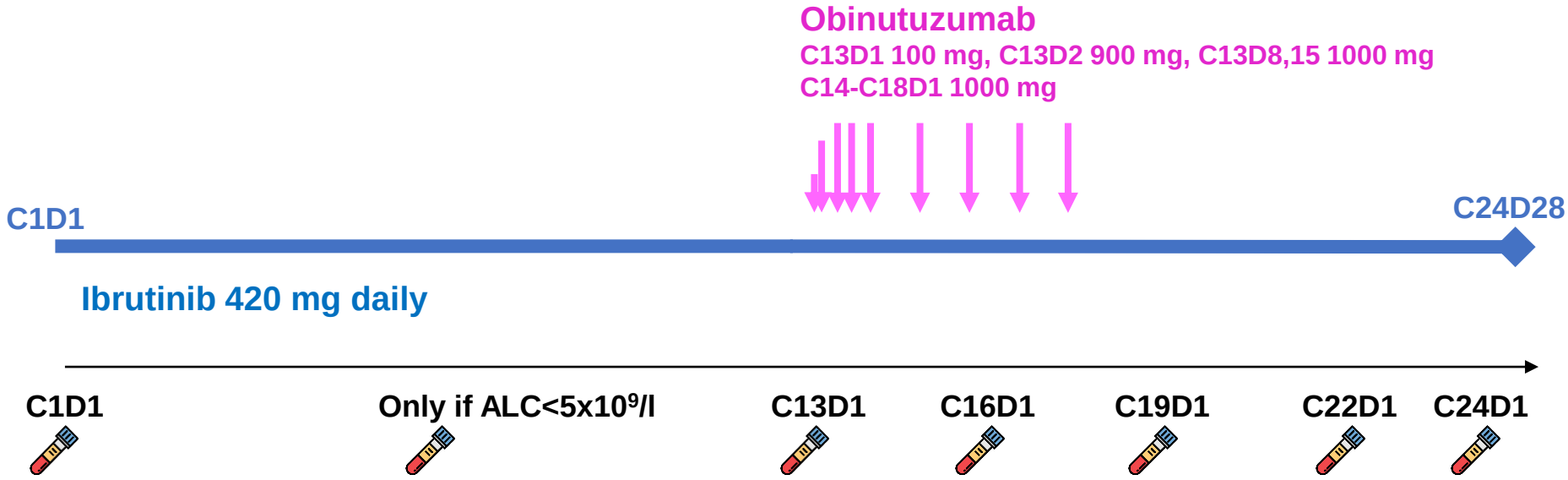
1. Al-Sawaf O, *et al.* ASH 2020; oral presentation 127; 2. Moreno C, *et al.* iwCLL 2019; poster presentation 2069;
3. Sharman JP, *et al. Lancet* 2020; **396:**1278–1291; 4. Burger JA, *et al. Leukemia* 2020; **34:**787–798;
5. Woyach JA, *et al. N Engl J Med* 2018; **379:**2517–2528; 6. Shanafelt TD, *et al.* ASH 2019; oral presentation 33.

(Slide adapted from O. Al-Sawaf)

Is it possible to achieve durable remission with a time-limited regimen *without* venetoclax?

Fixed-duration therapy with ibrutinib and obinutuzumab in treatment-naïve patients with CLL (FIGHT-CLL)

- **Phase 2 single-arm** interventional study
- **Treatment-naïve** patients with CLL, **without TP53 aberrations**
- **Primary objective: BM MRD <10^{-4} at +30 Days after ibrutinib** and **obinutuzumab**

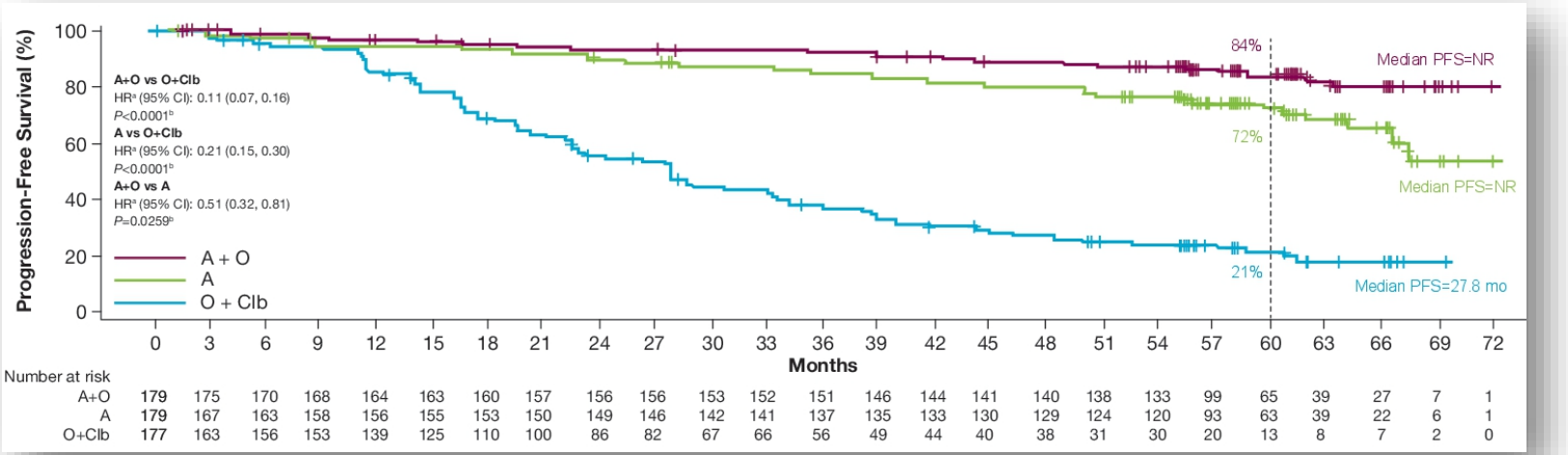


6-color flow cytometry ERIC panel including CD5/CD81/CD43/CD19/CD20/CD79b

(slide courtesy of P. Ghia)

5-year follow-up from ELEVATE-TN demonstrated a particularly impressive PFS in the A + O arm

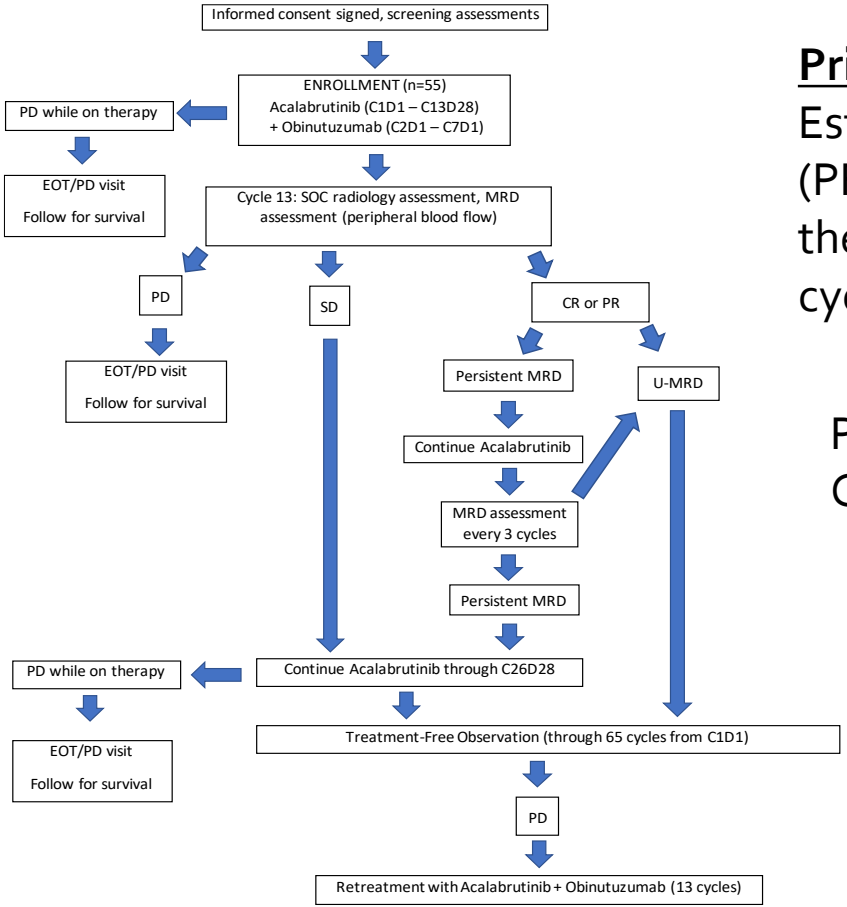
Investigator-assessed PFS



…but what would have happened if A + O patients discontinued therapy?

Sharman et al., EHA 2021

MED20-167: A phase 2 study of MRD-guided A + O



Primary Objective

Estimate 36-month progression-free survival (PFS) to acalabrutinib plus obinutuzumab in the front-line setting administered for 13-26 cycles (based on depth of response).

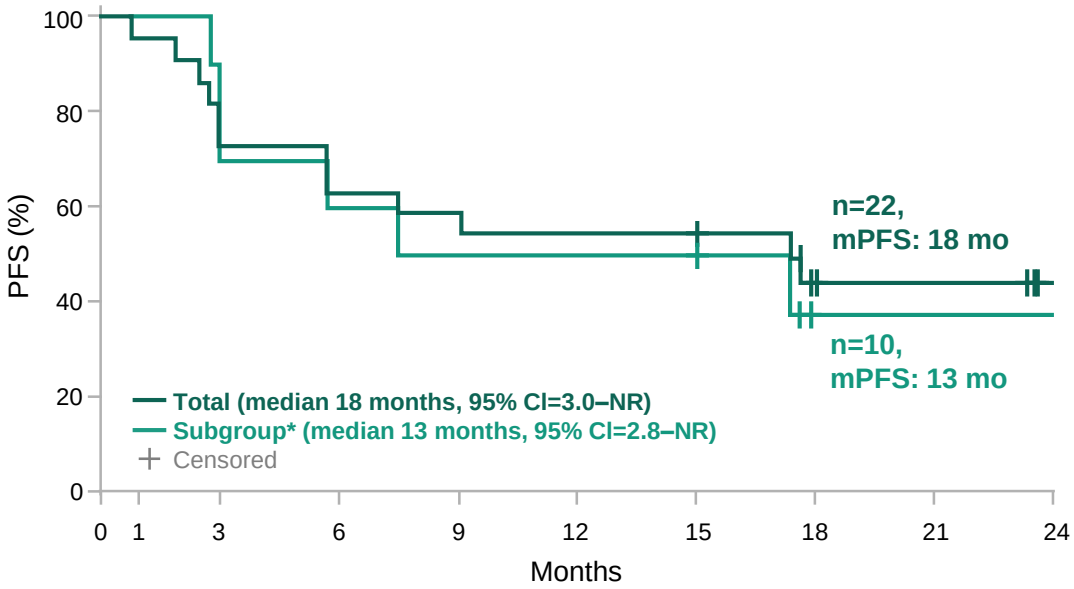
PI: Anthony Mato, MD
Co-PI: Lia Palomba, MD

(slide courtesy of A. Mato)

Memorial Sloan Kettering Cancer Center

Anti-CD19 CAR T-cell therapy has activity in CLL, but also significant toxicity and challenging logistics

TRANSCEND-CLL-004: PFS with liso-cel ± ibrutinib (N=23)
(median follow-up: 24 months)

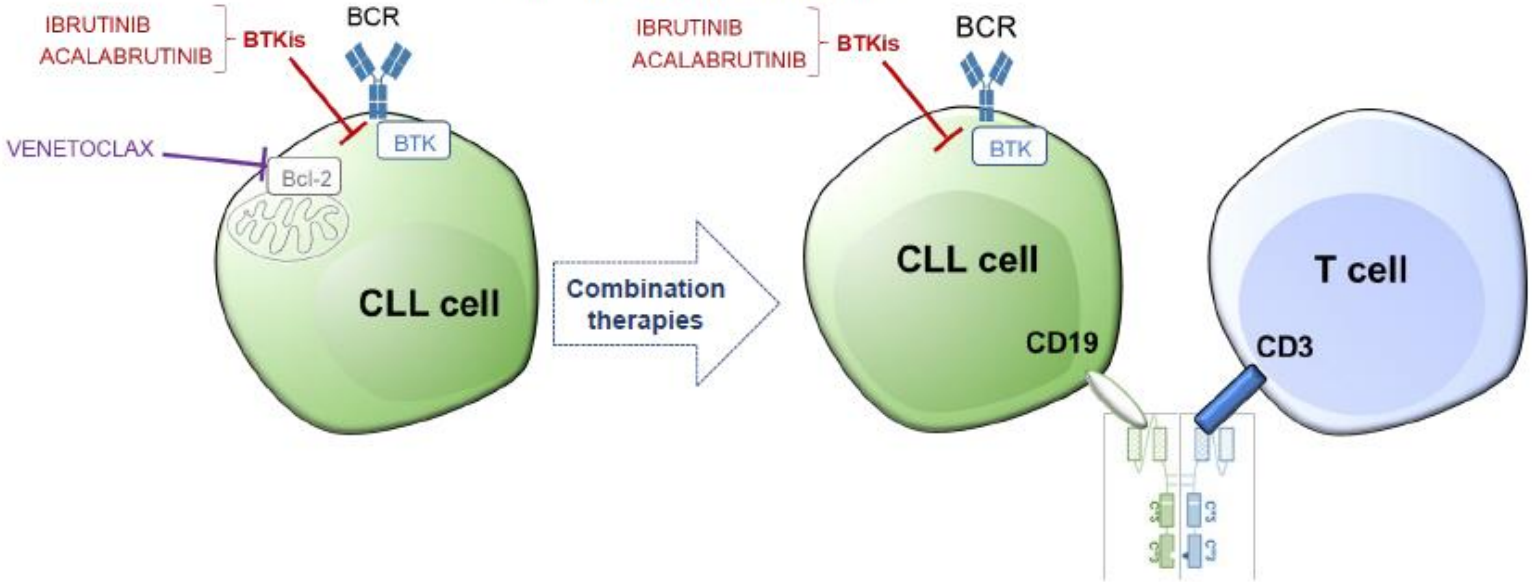


Notable toxicities include:
-Cytokine Release Syndrome
-Neurologic Events

Siddiqi T, *et al.* Blood 2022; 139:1794–1806.

Bi-specific antibodies may eventually play a role in CLL treatment

Successful treatment modalities for CLL but variable patient responses and drug resistance
-> Call for adjunct therapies



Anti-CD19/CD3

Combining BTKis with a CD19/CD3 bispecific antibody

- Enhanced T-cytotoxicity activity against CLL cells

Mhibik et al., Blood 2021

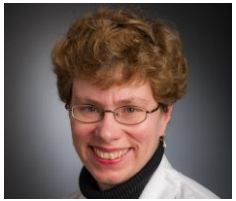
Conclusioni

- Intermittent time-limited combo therapy will ultimately win over continuous BTKi mono, as the PFS will likely be similar, but the costs and toxicities will be less with combos
- The majority of patients will be treated with ven-based time-limited therapies, but there may also be a place for time-limited BTKi plus anti-CD20 regimens
- There may remain a place for continuous BTKi monotherapy for certain patients (e.g. older patients seeking simplicity), particularly once generic BTKi eventually become available
- Immune-based approaches may be integrated into the treatment paradigm (e.g. bispecific Abs, CAR-T, at least for younger fit patients, especially those with high-risk disease)
- Much work still to be done, and we need to continue to accrue well to our studies, as there are still many aspects of CLL care that remain to be optimized

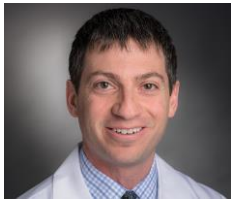
Dana-Farber Cancer Institute

Harvard Medical School

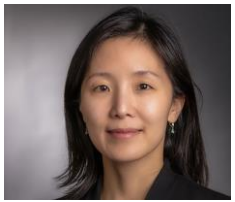
DFCI CLL Center



Jennifer Brown, MD, PhD



Matthew Davids, MD, MMSc



Inhye Ahn, MD

Catherine Wu, MD

We hope to welcome you to Boston next fall!