Novel Strategies Combining BTK and Bcl-2 Inhibitors in CLL

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BTK inhibition increases CLL cell dependence on Bcl-2

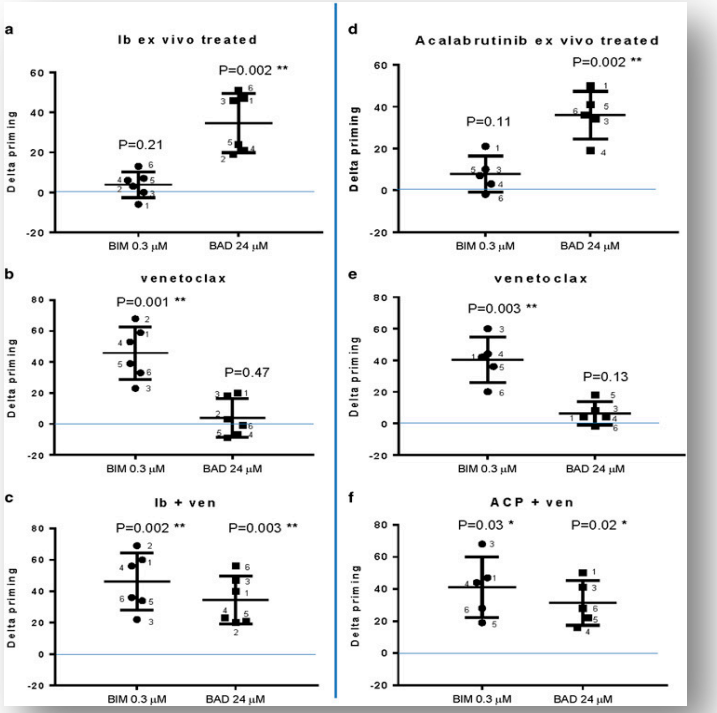
Leukemia (2017), 1–10

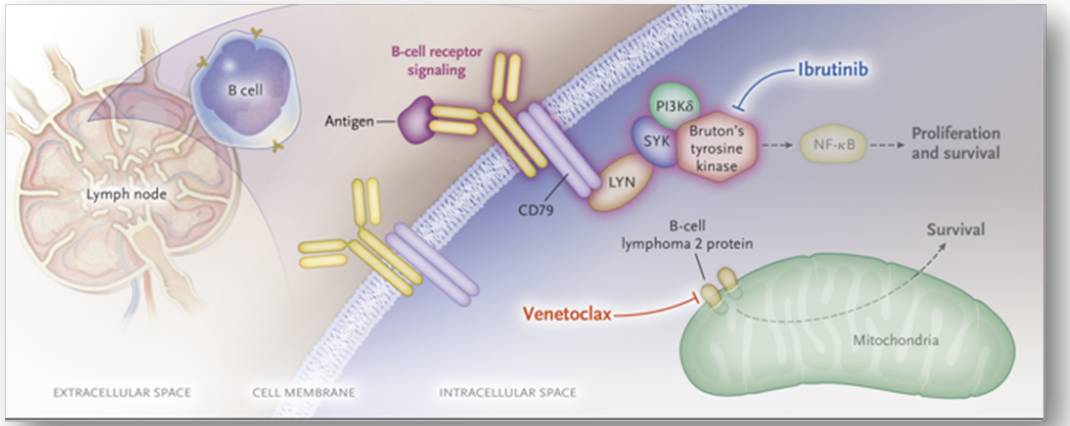
www.nature.com/leu

ORIGINAL ARTICLE

Bruton's tyrosine kinase inhibition increases BCL-2 dependence and enhances sensitivity to venetoclax in chronic lymphocytic leukemia

J Deng, E Isik, SM Fernandes, JR Brown, A Letai[1] and MS Davids[1]



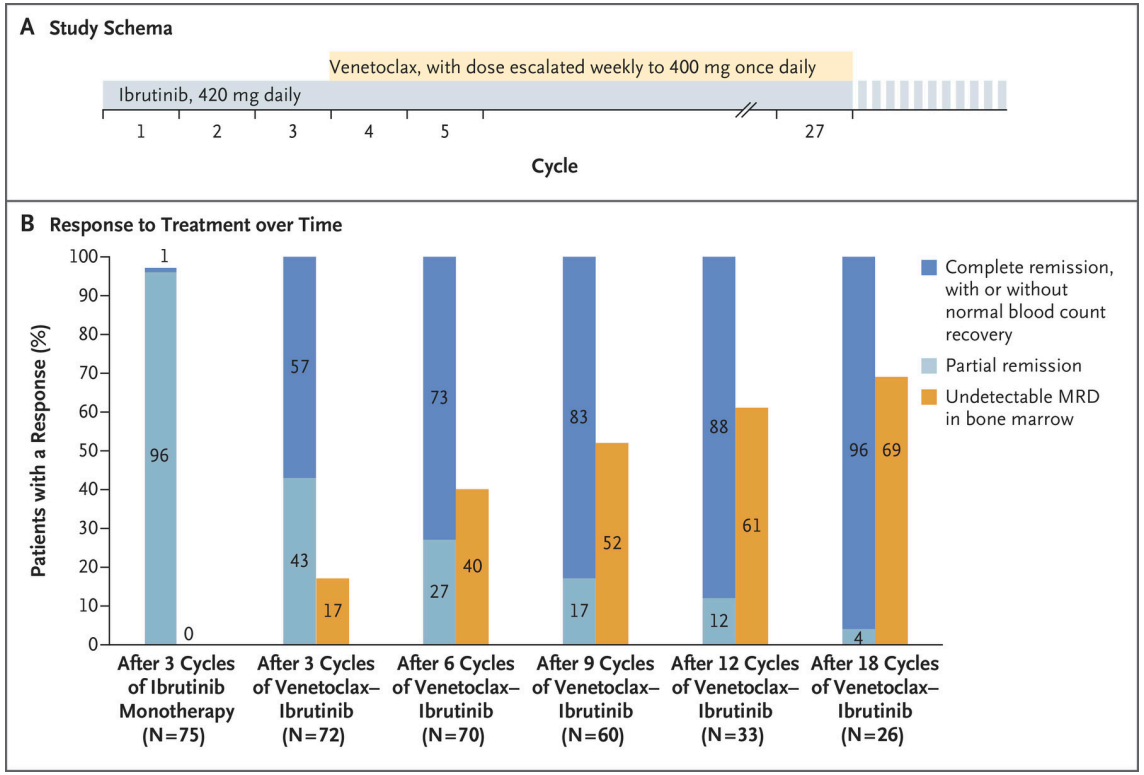


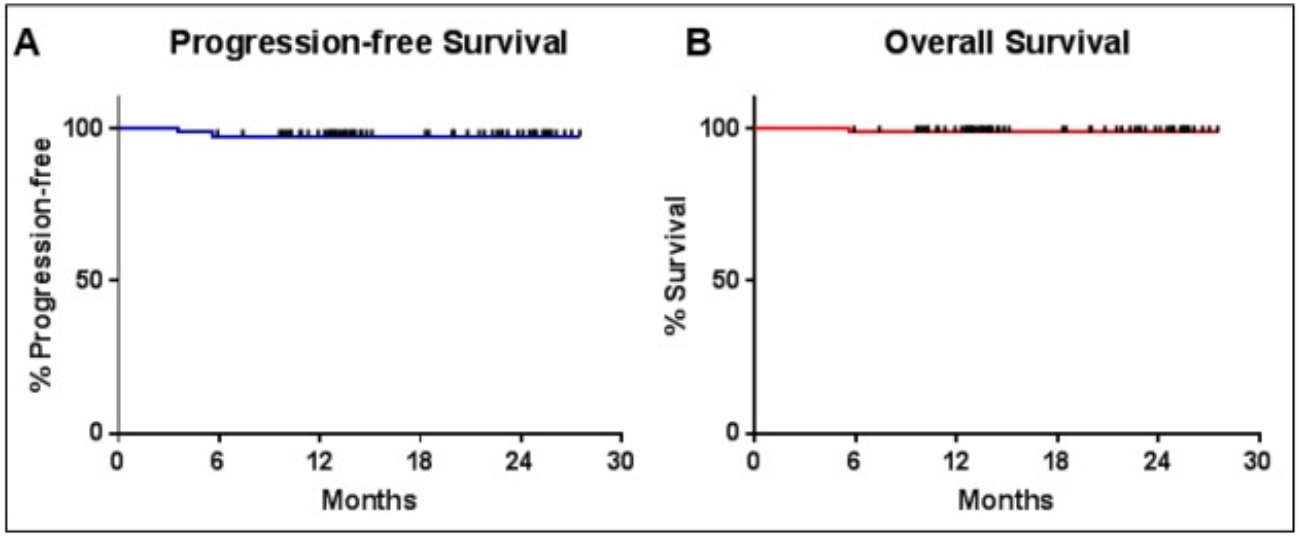
Deng et al., *Leukemia*, 2017

Wiestner et al., *NEJM*, 2019

Frontline Ibrutinib + Venetoclax rapidly induces deep responses

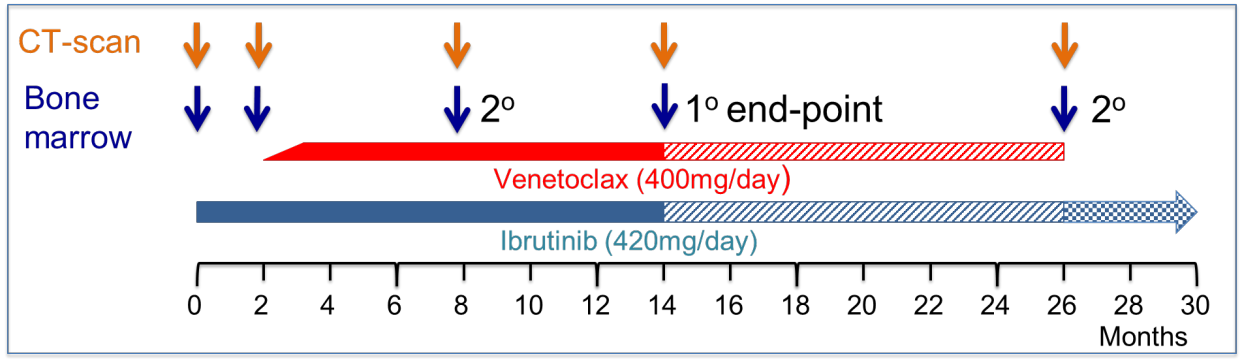
MDACC IST

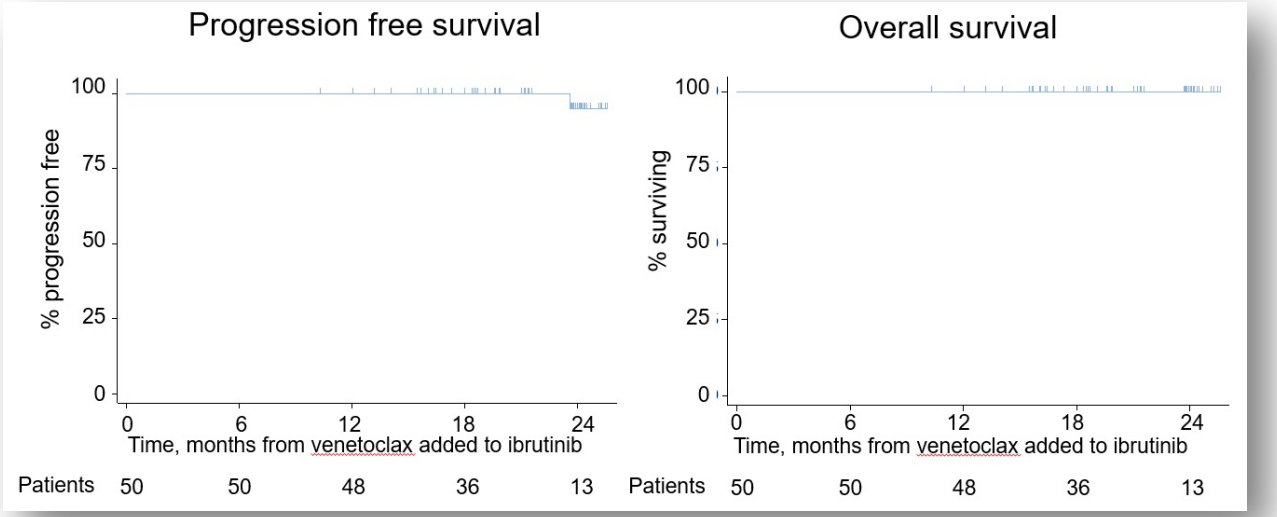


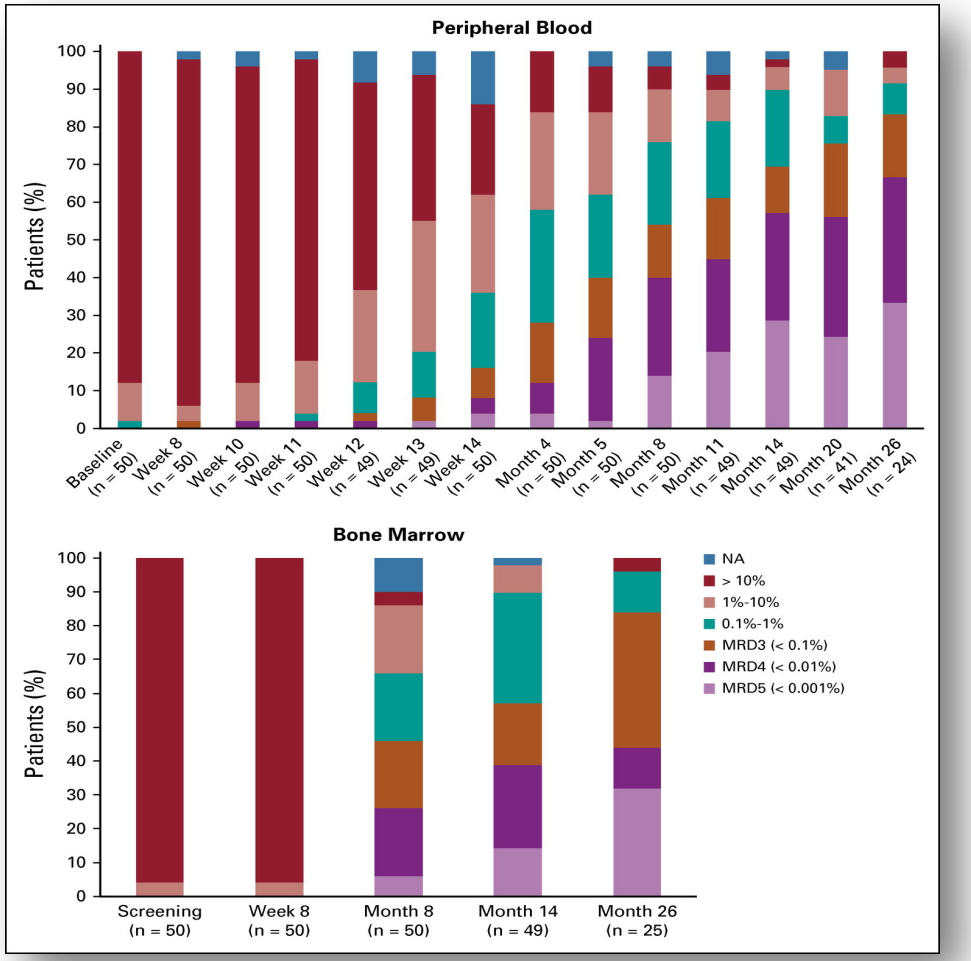


Jain et al., *NEJM*, 2019

UK CLARITY: Ibrutinib + Venetoclax also leads to high rates of undetectable MRD in R/R CLL, which are translating into durable response



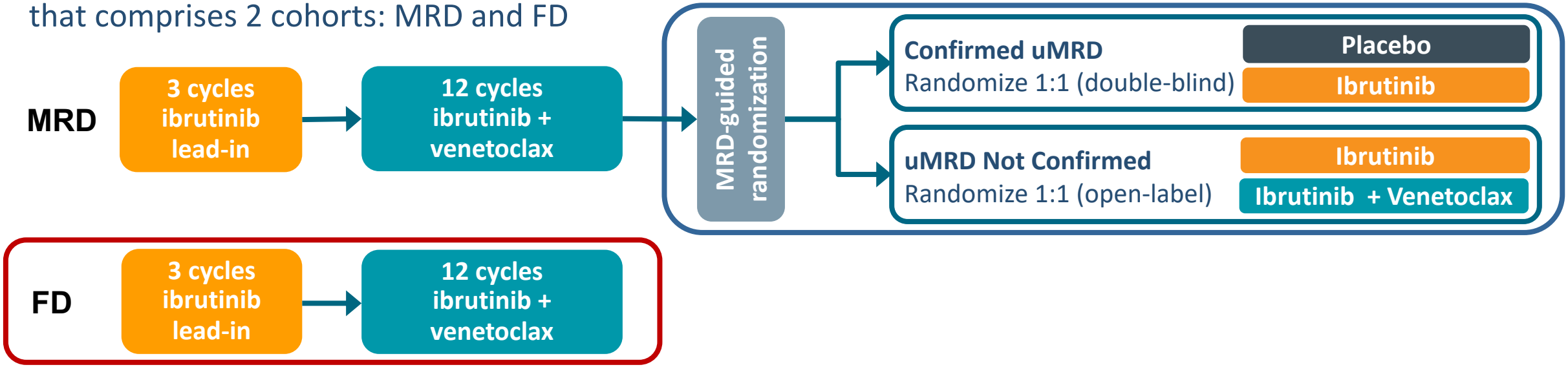




Hillmen et al., *J Clin Oncol*, 2019

Phase 2 CAPTIVATE Study

- CAPTIVATE (PCYC-1142) is an international, multicenter phase 2 study evaluating first-line treatment with 3 cycles of ibrutinib followed by 12 cycles of combined ibrutinib + venetoclax that comprises 2 cohorts: MRD and FD



- Results from the MRD cohort demonstrated uMRD in more than two-thirds of patients treated with 12 cycles of ibrutinib + venetoclax (PB, 75%; BM, 68%), and 30-month PFS rates of ≥95% irrespective of subsequent MRD-guided randomized treatment[1]

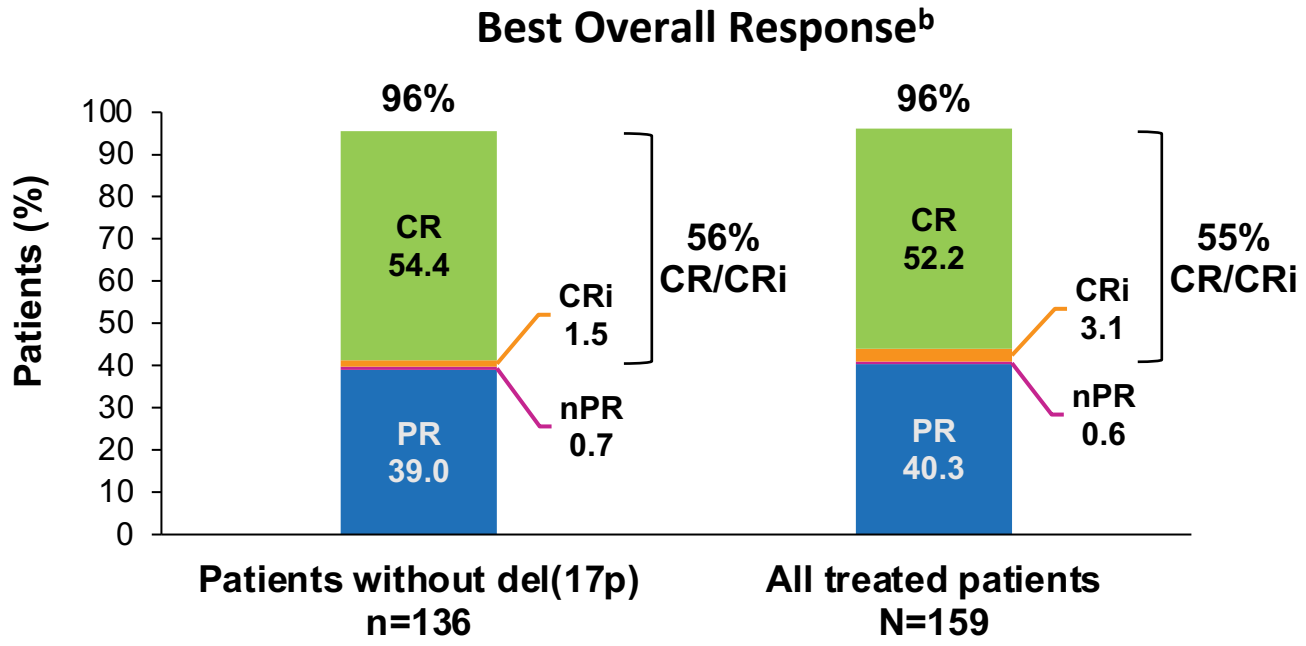
- Primary analysis of results from the FD cohort of CAPTIVATE are presented

BM, bone marrow; MRD, minimal residual disease; FD, fixed-duration; PB, peripheral blood; PFS, progression-free survival.

1. Wierda WG et al. ASH 2020, Abstract #123.

ASCO 2021, CAPTIVATE-FD; Ghia et al.

CAPTIVATE: Primary Endpoint of CR Rate[a]: Fixed-Duration Treatment with Ibrutinib + Venetoclax Provides Deep, Durable Responses



DOCR ≥12 cycles n/N (%)	66/76 (87)	78/88 (89)*

- Median age: 60 (range 33-71)
- *TP53* aberrance in 17%
- Primary endpoint was met: 56% (95% CI, 48–64) CR rate[a] in patients without del(17p)
  - Significantly excludes 37% minimum rate (P<0.0001)
  - Meaningful improvement over 40% rate of historical comparator of FCR in CLL10[1]

*After achieving CR[a], 9 patients with <1 year of follow-up were not evaluable; 1 patient died 7 months after CR and completion of therapy.

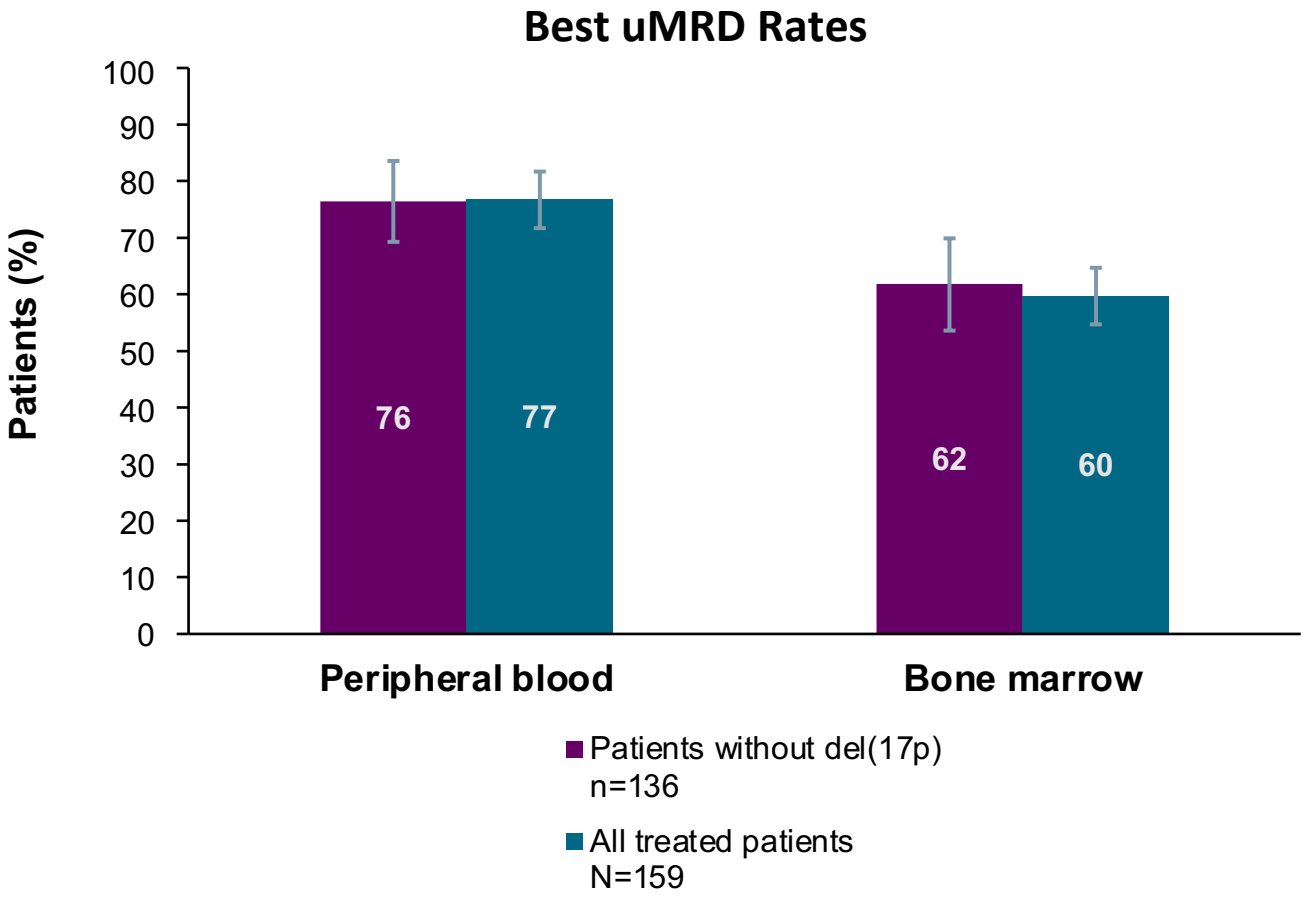
nPR, nodular partial response; PR, partial response; DOCR, duration of complete response.

[a]Proportion of patients with CR or CRi. [b]Overall response was assessed at the end of Cycle 3, on Day 1 of Cycles 7, 10, 13, 19, 25, 28, and 31, and every 6 months thereafter.

1. Eichhorst B et al. *Lancet Oncol.* 2016;17:928-942.

ASCO 2021, CAPTIVATE-FD; Ghia et al.

CAPTIVATE: FD Cohort: High Rates of Undetectable MRD[a] in BM and PB



- High rates of uMRD were observed in both BM and PB, including in patients with high-risk disease features
- uMRD rates were similar between patients with and without bulky disease in BM (63% vs 59%) and PB (both 77%)
- uMRD rates were higher in patients with unmutated IGHV versus mutated IGHV in BM (64% vs 53%) and PB (84% vs 67%)

[a]By 8-color flow cytometry (sensitivity, 10^{-4}).

ASCO 2021, CAPTIVATE-FD; Ghia et al.

CAPTIVATE: Majority of AEs with Ibrutinib + Venetoclax Were Low Grade

AEs, n (%)	All treated patients N=159	
Most frequent AEs (≥30%)	**Grade 1/2**	**Any grade**
Diarrhea	94 (59)	99 (62)
Nausea	66 (42)	68 (43)
Neutropenia	14 (9)	66 (42)
Arthralgia	51 (32)	53 (33)
Grade 3/4 AEs (≥5%)	98 (62)	
Neutropenia	52 (33)	
Infections[a]	13 (8)	
Hypertension	9 (6)	
Neutrophil count decreased	8 (5)	
AEs of clinical interest (any grade)		
Atrial fibrillation	7 (4)	
Major hemorrhage[a]	3 (2)	
Any serious AE	36 (23)	
Fatal AEs	1 (1)[b]	

Dose reduction in 21%, discontinuation due to AE in 5%

[a]Combined terms. [b]Sudden death in 1 patient during ibrutinib lead-in.

ASCO 2021, CAPTIVATE-FD; Ghia et al.

Phase 3 GLOW Study

Subjects N=211

Key inclusion criteria
- ≥65 years or
- 18–64 with CIRS score >6 or creatinine clearance <70 mL/min

Stratification
- IGHV mutation and del(11q) status

1:1

I+V (n=106)

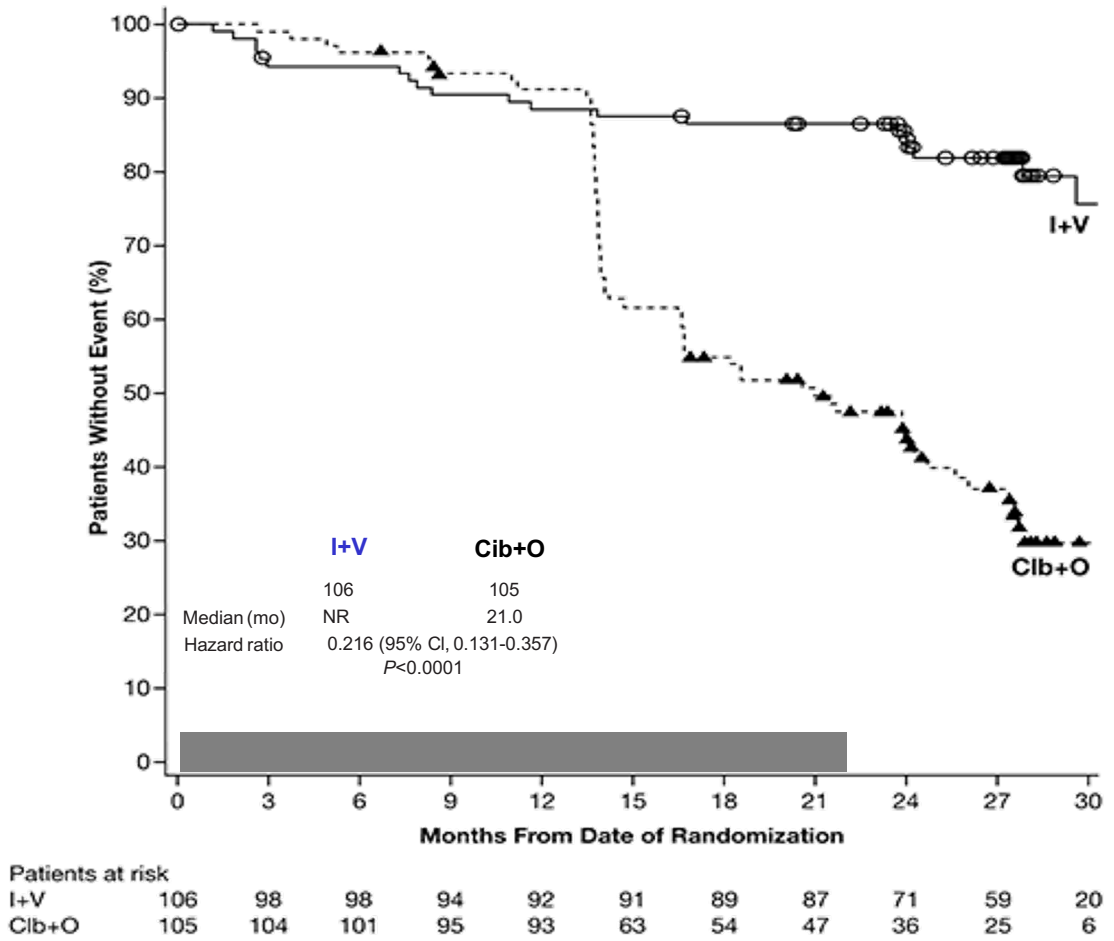
Clb+O (n=105)

Primary endpoint:
- PFS (assessed by IRC)

Median age: 71 (range 47-93)

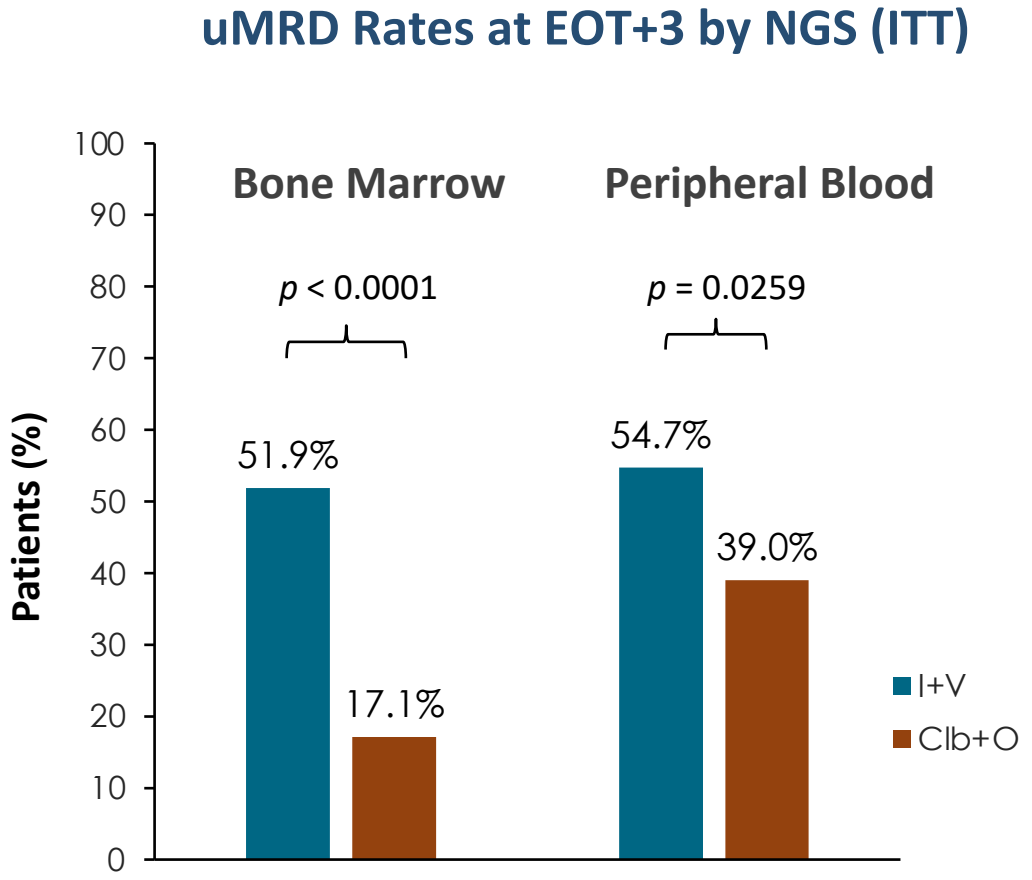
CIRS = cumulative illness rating scale; CLL = chronic lymphocytic leukemia; PFS = progression-free survival; R/R = relapsed/refractory;
I = ibrutinib; V = Venetoclax; O = Obinutuzumab; Clb = Chlorambucil.

I+V was superior to Clb+O in PFS and consistent across predefined subgroups



Kater A, et al. EHA2021 Abstract LB1902 (Oral Presentation), June 12, 2021.

GLOW: Undetectable MRD[a] Rate with I+V was Significantly Higher



- Rate of uMRD at EOT+3 was significantly higher for I+V vs Clb+O, irrespective of compartment
- With I+V, PB/BM uMRD concordance[b] was 92.9% (52/56)
  - Versus 43.6% (17/39) for Clb+O
- Best uMRD rates were higher for I+V (by flow cytometry)
  - I+V: 67.9% (BM) and 80.2% (PB)
  - Clb+O: 22.9% (BM) and 46.7% (PB)

[a] All rates are reported with a cutoff of 10^{-4}
[b] PB/BM uMRD concordance calculated for patients with uMRD in PB and a paired BM sample at 3 months after end of treatment (EOT+3);
uMRD, undetectable minimal residual disease; EOT+3, 3 months post end of treatment; NGS, next-generation sequencing; ITT, intent to treat; BM, bone marrow; PB, peripheral blood

EHA 2021, Kater AP, et al.

GLOW: Summary of Safety and TLS Risk Reduction

Grade 3 or Higher AEs in ≥5% of Patients

	I+V (N = 106)	Clb+O (N = 105)
Median exposure, mos (range)	13.8 (0.7-19.5)	5.1 (1.8-7.9)
Any, %	75.5	69.5
Neutropenia[a]	34.9	49.5
Infections[b]	17.0	11.4
Thrombocytopenia	5.7	20.0
Diarrhea	10.4	1.0
Hypertension	7.5	1.9
Atrial fibrillation	6.6	0
Hyponatremia	5.7	0
TLS	0	5.7

[a]Includes 'neutrophil count decreased'; grade ≥3 febrile neutropenia: 1.9% for I+V vs 2.9% for Clb+O
[b]Includes multiple preferred terms

- After 3 cycles of ibrutinib lead-in, <2% of patients remained at risk for TLS based on high tumor burden
- 2 (1.9%) patients in I+V arm discontinued ibrutinib due to atrial fibrillation
- SAEs in ≥5% of patients for I+V vs Clb+O: Infections (12.3% vs 8.6%) and atrial fibrillation (6.6% vs 0%)
- Rate of secondary malignancies at time of analysis: 8.5% for I+V vs 10.5% for Clb+O
  - NMSC: 3.8% vs 1.9%
  - Other: 4.7% vs 8.6%

--Discontinuation due to AE in 10%--

EHA 2021, Kater AP, et al.

TLS, tumor lysis syndrome; AE, adverse event; SAE, serious AE; NMSC, non-melanoma skin cancer

GLOW: Overall Survival

- HR (95% CI) for overall survival: 1.048 (0.454, 2.419), with 11 deaths in I+V arm and 12 in Clb+O arm (Table)
- Causes of death were generally similar in nature for both study arms, with infections (including COVID-19-related pneumonia) and cardiac events most common

Death from Any Cause	During Treatment			During Follow-up	
	I+V (N=106)		Clb+O (N=105)	I+V (N=106)	Clb+O (N=105)
	Ibr lead-in	I+V			
Total, n	**4**	**3**	**2**	**4**	**10**
Infections and Infestations	1	-	1	2	6
Cardiac Disorders	2[a]	-	-	-	2
General Disorders (Sudden Death)	-	2	-	1	-
Neoplasm	1	-	-	-	-
Nervous System Disorders	-	1	-	-	1
Hepatobiliary Disorders	-	-	1	-	-
Respiratory, Thoracic, Mediastinal Dis.	-	-	-	-	1
Progressive Disease/Richter's Transform.	-	-	-	1	-

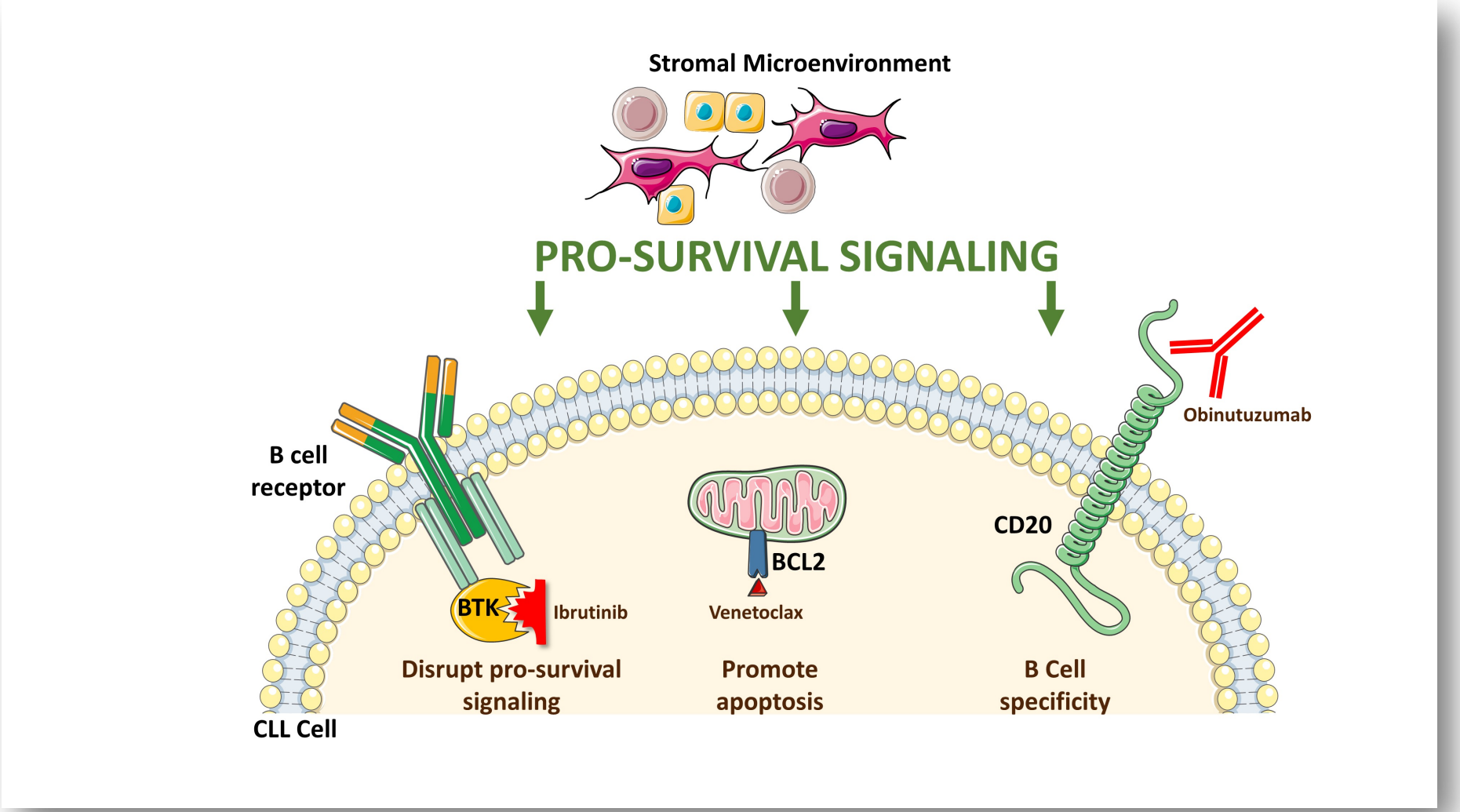
Median treatment exposure 13.8 mos for I+V and 5.1 mos for Clb+O; overall median study follow up 27.7 months

[a] 1 patent listed as cardiac disorder had 3 causes of death: Tachy-brady syndrome, cardiac failure, pneumonia

EHA 2021, Kater AP, et al.

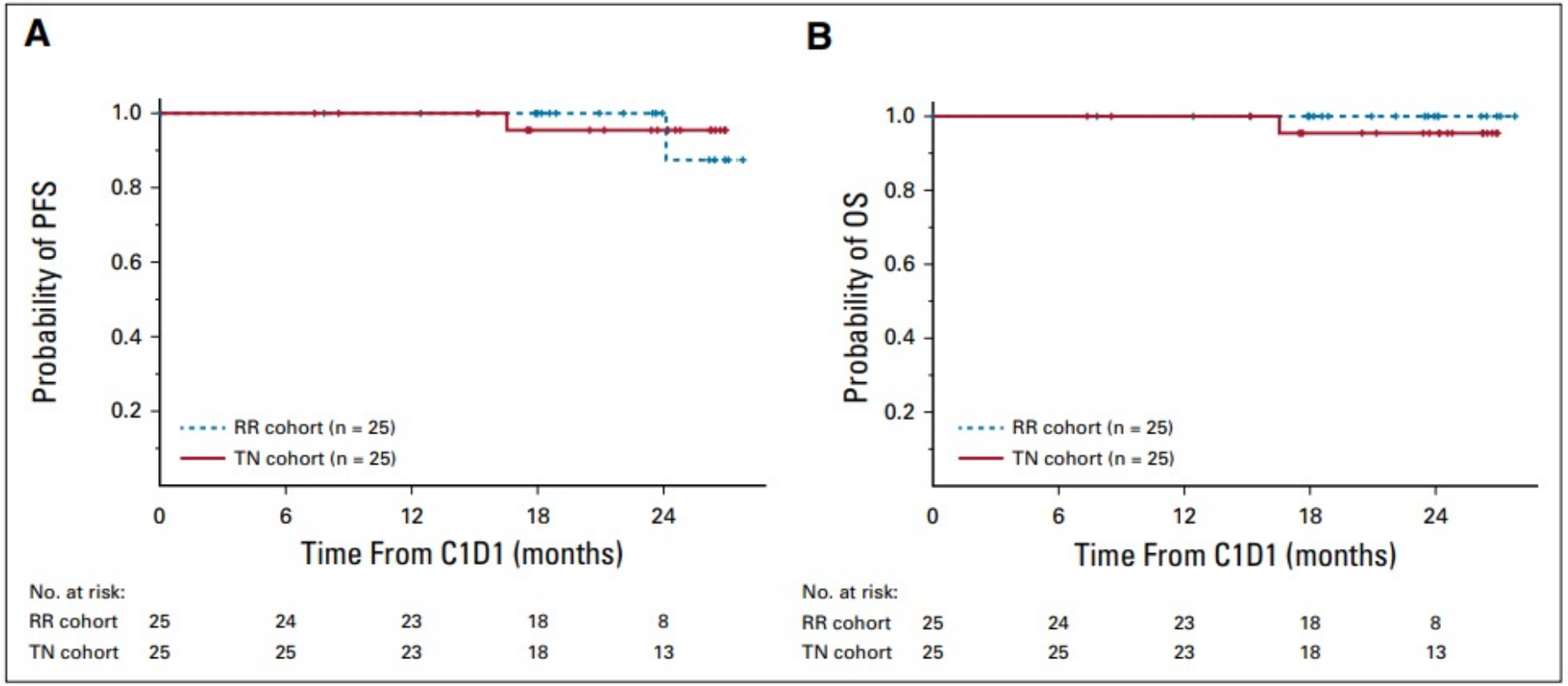
HR, hazard ratio; CI, confidence interval

Inhibiting 3 distinct targets may result in even greater efficacy



Lampson and Davids, *Blood*, 2018

I+V+O (IVO) is highly active in 1L CLL, though tolerability is variable



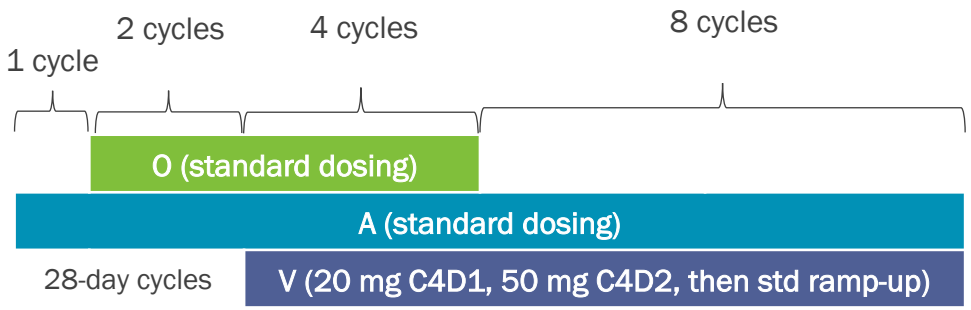
Safety:

- **Hypertension: 82%**
- **Infusion-related reactions: 74%**
- **Gr 3/4 neutropenia in 66%**
- **Arthralgias: 56%**
- **Headache: 52%**
- **Atrial fibrillation 10%**

Rogers et al., *J Clin Oncol*., 2020

Triplets with newer BTKis are also active and well-tolerated: AVO Study

Study schema (n=44)



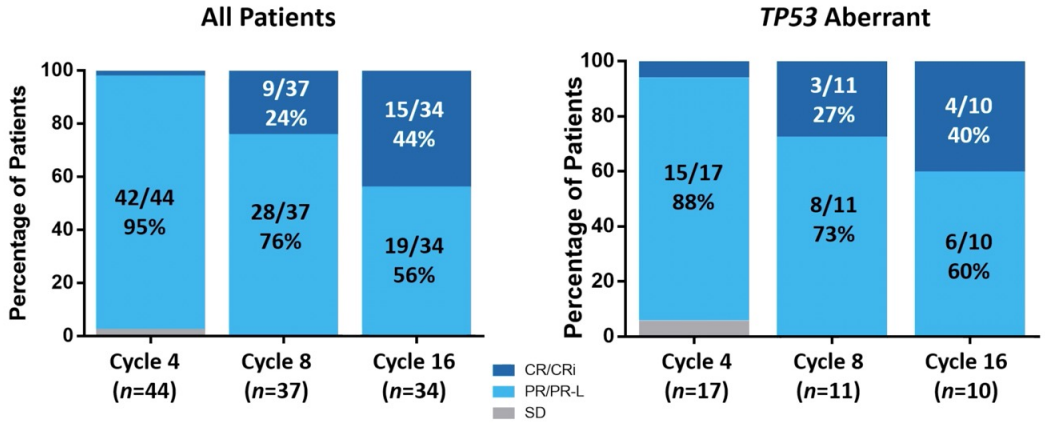
Primary endpoint: BM-uMRD CR at C16D1

Safety

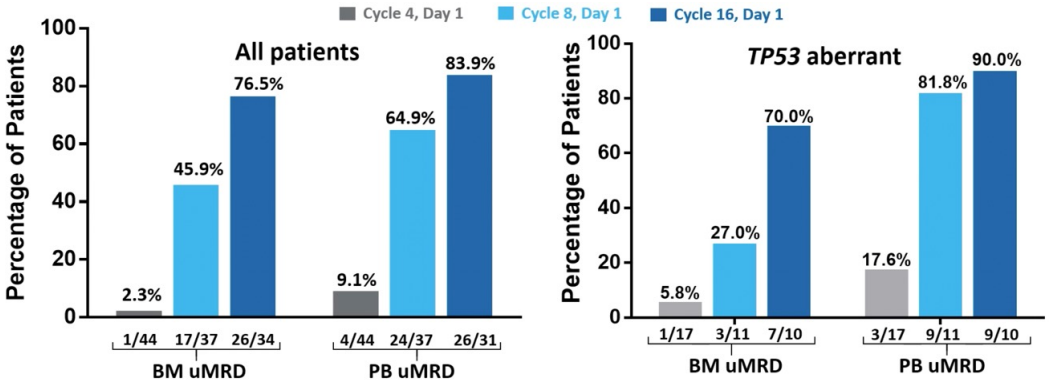
- 80% headache (2% Gr ≥3)
- 33% Gr ≥3 neutropenia
- 25% Infusion-related reactions
- 11% hypertension
- 2% Gr ≥3 infection, Afib, and infusion-related reactions (2% each)
- No major bleeding or febrile neutropenia

A = Acalabrutinib; V = Venetoclax; O = Obinutuzumab

iwCLL Response

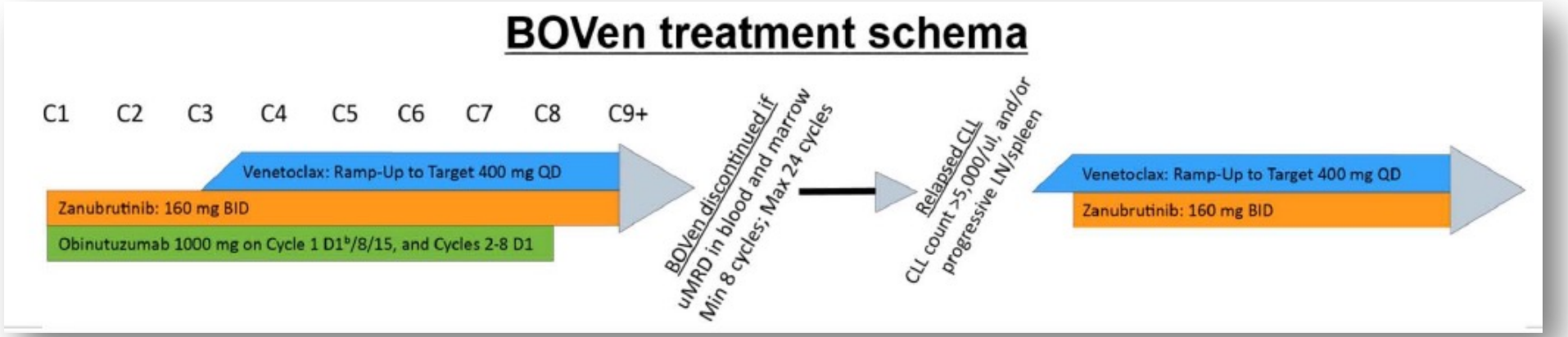


MRD by ITT

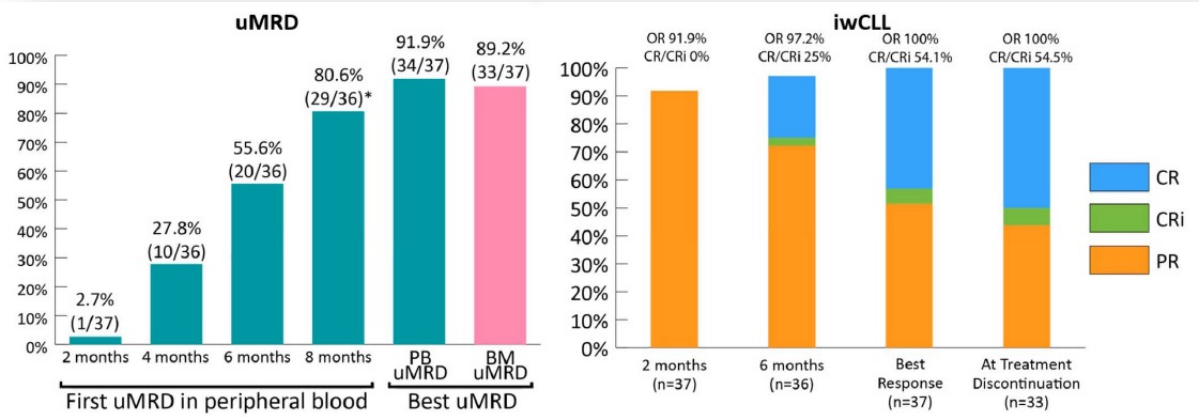


Davids MS, et al., ASH 2020, Abstract 2216

Triplets with newer BTKis are also active and well-tolerated: BOVen Study

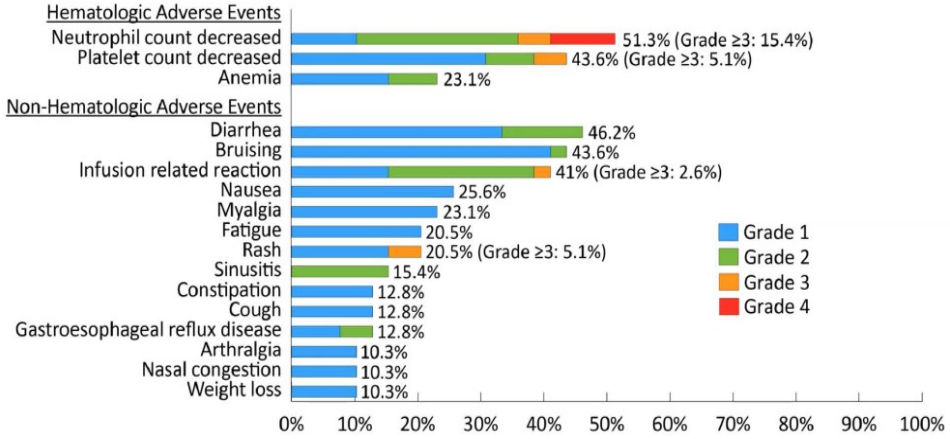


Efficacy



- 89.2% (33/37) have achieved uMRD in peripheral blood and bone marrow and stopped therapy after a median of 10 mo (8 mo of triplet)

Safety



- One grade 5 ICH on cycle 1 day after initiating intravenous heparin for pulmonary emboli
- Atrial fibrillation occurred in 1 patient who had a history of prior paroxysmal atrial fibrillation

BOVen Treatment = Zanubrutinib (Z), Obinutuzumab and Venetoclax

Soumerai, JD, et al. ASH 2020

Where are we heading in 1L CLL?

Selected phase 3 trials:

- **UK NCRI FLAIR**: FCR vs. I vs. IV (vs. IR) (n=1,522)
- **CLL13/GAIA**: FCR/BR vs. VR, vs. VO, vs. IVO (n=920)
- **Alliance A041702**: IO vs. IVO (older pts, n=454)
- **ECOG EA9161**: IO vs. IVO (younger pts, n=720)
- **ACE-CL-311**: AVO vs. AV vs. CIT (non-*TP53* aberrant, n=780)
- **CLL17**: I vs. IV vs. VO (all comers, n=882)
- **MAJIC**: AV vs. VO (all comers, n=600)

Conclusions: BTKi/BCL-2i in CLL

- Strong scientific rationale for combining BTKi/BCL-2i in CLL
- Early studies of Ibr/Ven showed excellent efficacy in 1L and R/R
- More mature studies of Ibr/Ven continue to show excellent efficacy but suggest better tolerability in younger patients
- Promising triplet therapies now in development with IVO, AVO, ZVO
- Active participation in clinical trials remains critical

Case 1

- A 78 y.o. man with distant h/o prostate cancer and appendiceal carcinoid both cured with surgical resection, 20-year history of SVT managed with diltiazem, as well as trisomy 12, unmutated IGHV CLL observed with his local oncologist since 2012. Gradual progression for the first few years, but by 2018 had more steady progression of CLL and saw me in 10/2018 for initial consultation.
- I repeated prognostic markers and he had acquired del(17p) and TP53 mutation. WBC count up to 233, Hgb 11.6, Plts 283. Lymph nodes 3-4 cm in max dimension, and developing progressive fatigue that was interfering with his daily activities.
- Patient enrolls in the AVO trial (Acala x 1 month, Acala/Obinu x 2 months, Acala/Ven/Obinu x 6 months, then Acala/Ven x 6 or 18 months depending on response). Tolerated therapy well and by C4D1, he achieved a PR, WBC count 3.6, Hgb 13.7, Plts 242. Underwent 4-week outpatient V ramp-up without TLS. At C16D1 had achieved CR with uMRD in the marrow by flow (10^{-4}) and discontinued Acala/Ven.
- Pt has been back on observation since that time and is now still in CR with uMRD about 20 months after completing all therapy.