Ibrutinib + Venetoclax

Constantine (Con) Tam

Head of Lymphoma Service, Alfred Hospital
Professor of Haematology, Monash University

Disclosure of Constantine TAM

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Janssen	x					x	
AbbVie	x					x	
BeiGene	x					x	
LOXO						x	
AstraZeneca						x	

The NEW ENGLAND JOURNAL of MEDICINE

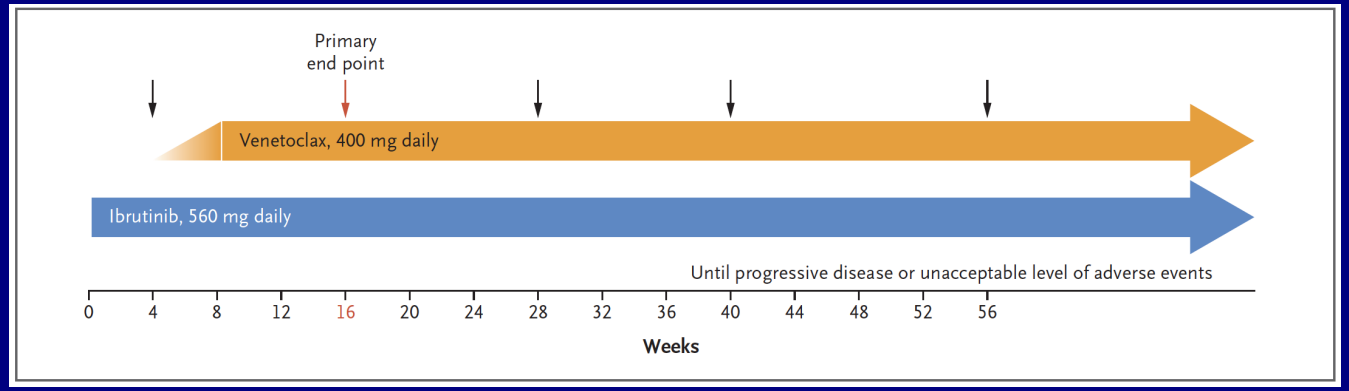
ORIGINAL ARTICLE

Ibrutinib plus Venetoclax for the Treatment of Mantle-Cell Lymphoma

Constantine S. Tam, M.B., B.S., M.D., Mary Ann Anderson, M.B., B.S., Ph.D., Christiane Pott, M.D., Ph.D., Rishu Agarwal, M.B., B.S., Sasanka Handunnetti, M.B., B.S., Rodney J. Hicks, M.B., B.S., Kate Burbury, M.B., B.S., Gillian Turner, B.N., M.I.P.H., Juliana Di Iulio, Ph.D., Mathias Bressel, M.Sc., David Westerman, M.B., B.S., Stephen Lade, M.B., B.S., Martin Dreyling, M.D., Sarah-Jane Dawson, M.B., B.S., Ph.D., Mark A. Dawson, M.B., B.S., Ph.D., John F. Seymour, M.B., B.S., Ph.D., and Andrew W. Roberts, M.B., B.S., Ph.D.

- **Study conceived at IWCLL Cologne 2013 (in a pub!)**
- **Published NEJM March 2018**

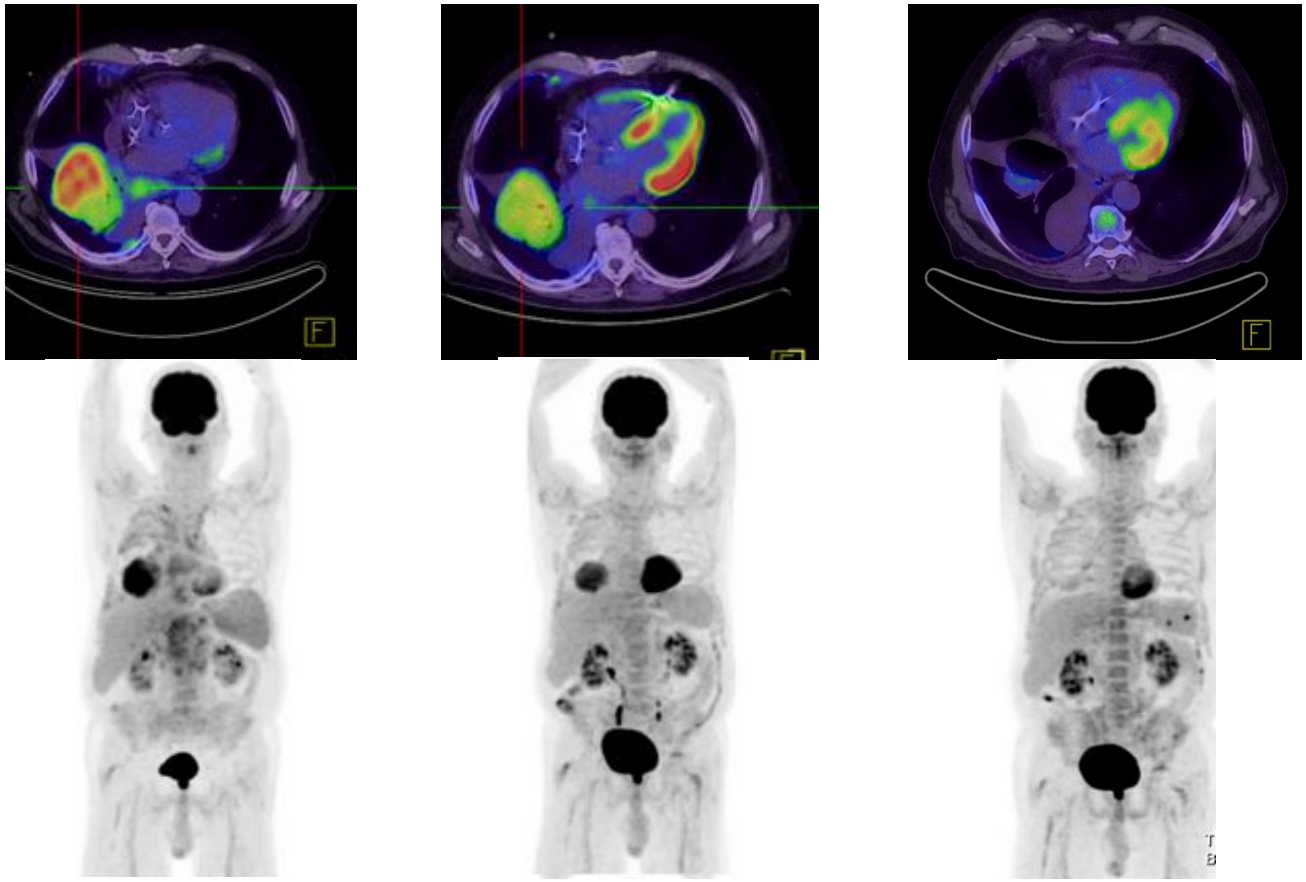
AIM (ABT-199 & Ibrutinib in MCL): Phase 2, Single-Arm Study



- CT, BMAT and MRD at Weeks 0, 4, 16, 28, 40 and 56 (PET at 0, 16 and 56).
- Double endoscopy + random biopsies at week 16 (if baseline gastrointestinal tract involvement)

Tam NEJM 2018; 378:1211-1223

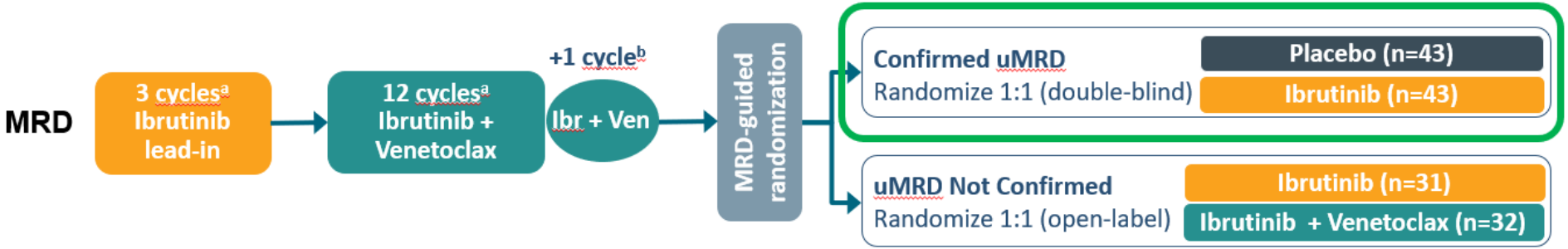
AIM Patient #1: Response Kinetics (PET)



Baseline | 1 month (Ibrutinib) | 4 months (both drugs)

CAPTIVATE MRD Cohort Study Design

- CAPTIVATE (NCT02910583) is an international, multicenter phase 2 study evaluating first-line treatment with the Ibr + Ven combination
- The CAPTIVATE study comprises 2 cohorts: FD[1] and MRD[2]
- In this MRD cohort, after completion of Ibr + Ven, patients with Confirmed uMRD* were randomly assigned to double-blind treatment with placebo (ie, a fixed-duration regimen), or continued ibrutinib



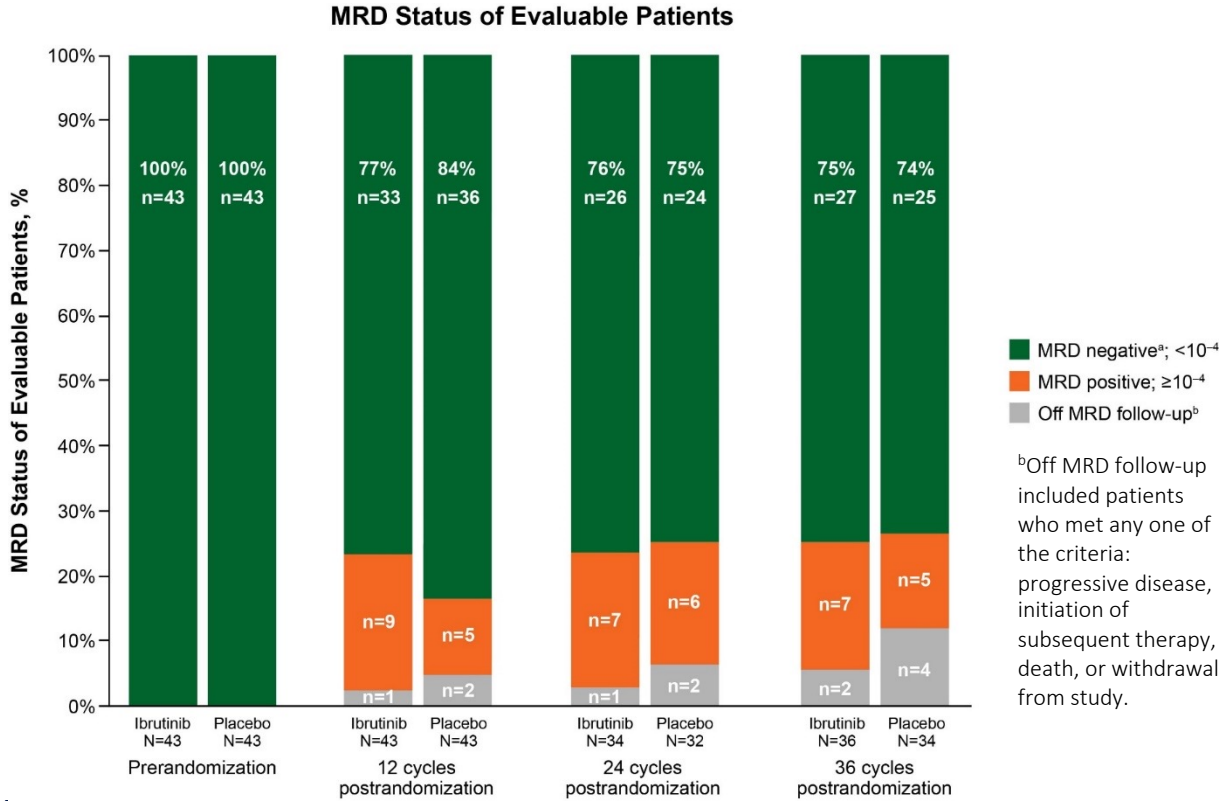
*Confirmed uMRD was defined as uMRD serially over at least 3 cycles in both peripheral blood and bone marrow. Patients who achieved Confirmed uMRD with Ibr + Ven were randomly assigned 1:1 to double-blinded treatment with placebo or single-agent ibrutinib.

[a]One cycle = 28 days; [b]During MRD status confirmation and tumor response assessment; FD, fixed duration; MRD, minimal residual disease.

1. *Tam CS et al. Blood. 2022;139:3278-3289.* 2. Wierda, WG. *J Clin Oncol*, 2021;39:3853-3865.

ASH 2022; Allan JN et al.

MRD Negativity Rates Were Sustained 3-years Post-randomization and Similar in Patients Randomized to Placebo vs Continued Ibrutinib



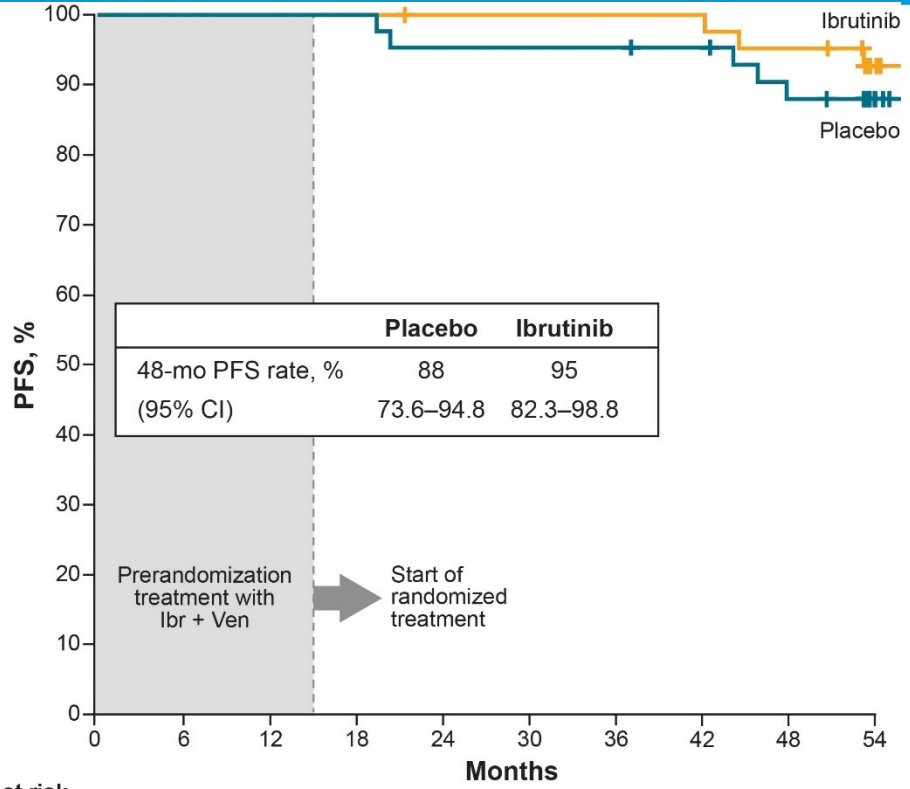
[b]Off MRD follow-up included patients who met any one of the criteria: progressive disease, initiation of subsequent therapy, death, or withdrawal from study.

- **The sustainability of MRD negativity in the ITT population was comparable to that observed in the evaluable population**
  - Ibrutinib arm (ITT): 77% (33/43), 60% (26/43) and 63% (27/43) at 12, 24, and 36 cycles postrandomization, respectively
  - Placebo arm (ITT): 84% (36/43), 56% (24/43), and 58% (25/43) at 12, 24, and 36 cycles postrandomization, respectively

[a]MRD negative status $<10^{-4}$ by 8-color flow cytometry.

ASH 2022; Allan JN et al.

Progression-Free Survival Rates Continue to Be High and Durable Across Study Arms



- At 48 months, PFS was 88% (95% CI, 74–95) with placebo and 95% (95% CI, 82–99) with continued ibrutinib

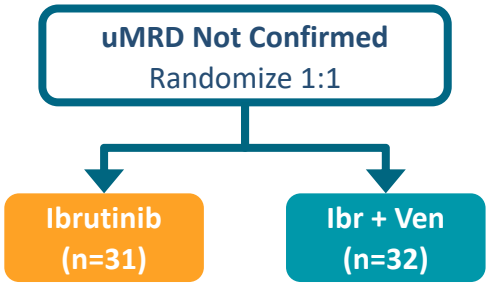
PD and Retreatment Outcomes

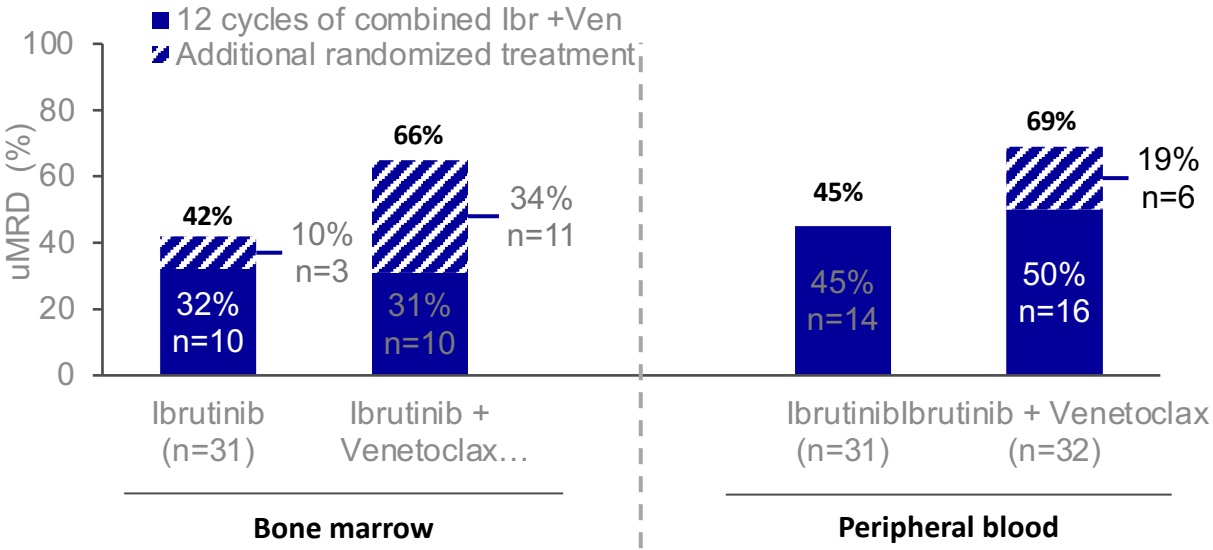
- 3 of 7 patients with PD in the placebo arm have initiated retreatment with ibrutinib; all 3 patients had PR
- 2 patients in the ibrutinib arm had PD; none have initiated retreatment

PFS, progression-free survival.

ASH 2022; Allan JN et al.

For MRD-Positive Patients, a Second Year of Venetoclax Deepens MRD





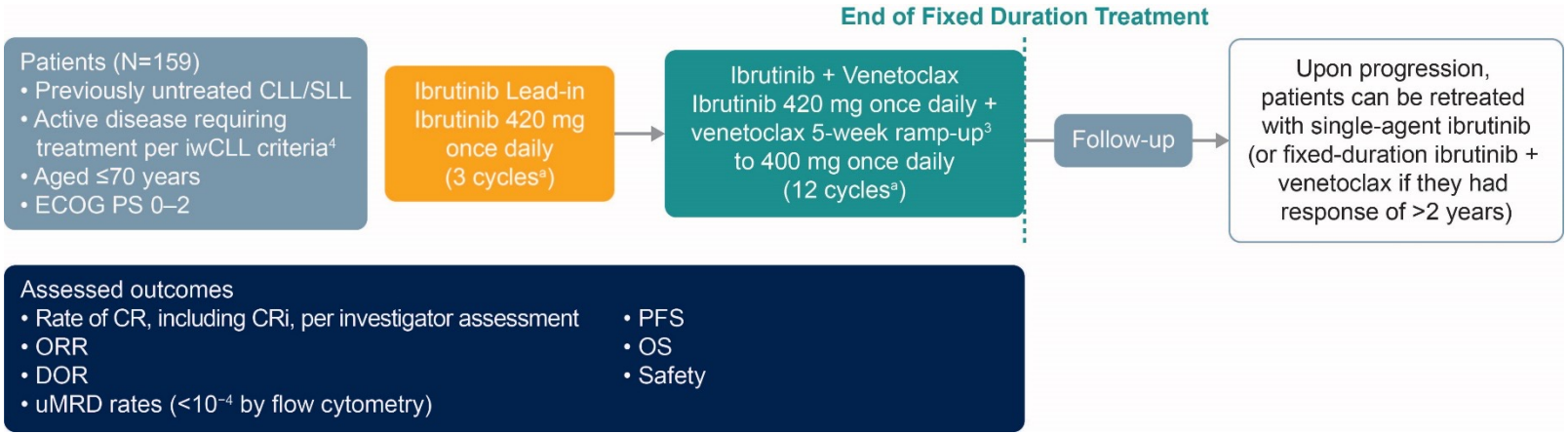
- In patients without confirmed uMRD[a] after 12 cycles of combined ibrutinib + venetoclax, increases in uMRD were greater with continued ibrutinib + venetoclax versus ibrutinib alone

[a]Confirmed uMRD defined as having uMRD ($<10^{-4}$ by 8-color flow cytometry) serially over at least 3 cycles, and undetectable MRD in both PB and BM.

Wierda et al. ASH 2020 Abstract #123

CAPTIVATE FIXED-DURATION COHORT

- CAPTIVATE (NCT02910583) is an international, multicenter phase 2 study evaluating first-line treatment with the ibrutinib + venetoclax combination, comprising 2 cohorts: MRD[1] and FD[2]

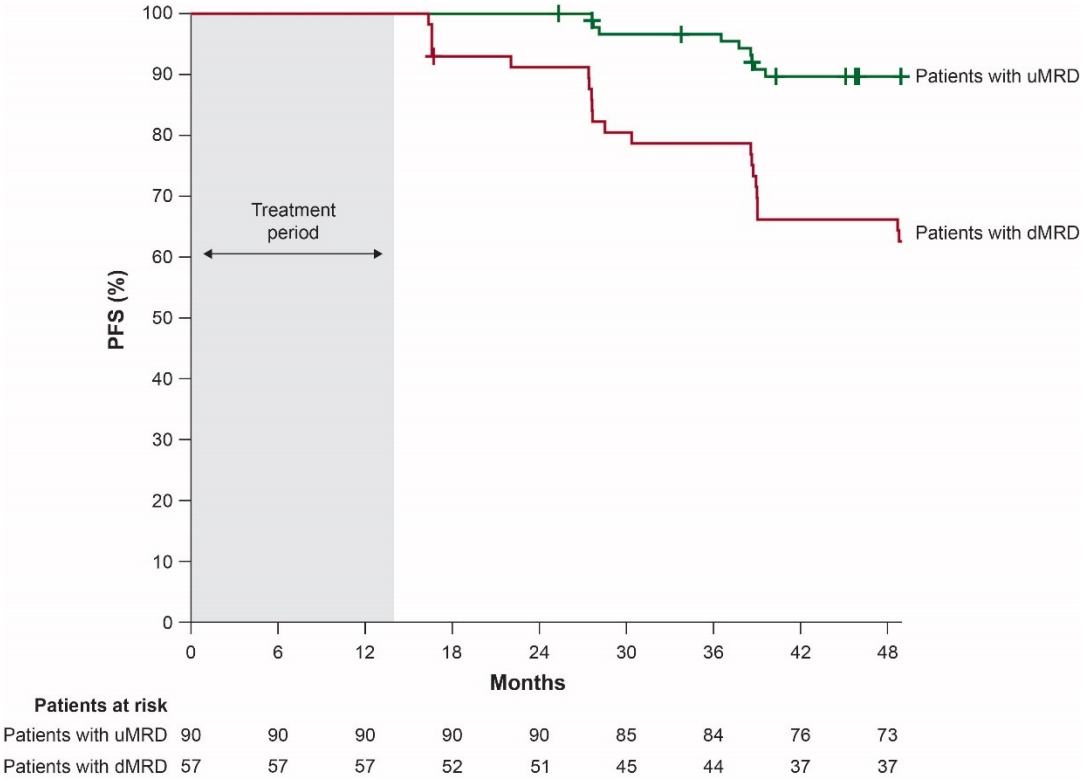


The Primary Analysis reported an ORR of 96%, a best uMRD rate of 77% in PB, and 24-mo PFS of 95%

[a]One cycle = 28 days; CR, complete response; CRi, complete response with incomplete bone marrow recovery; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FD, fixed duration; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; MRD, minimal residual disease. ORR, overall response rate; PFS, progression-free survival.

1. Wierda, WG. *J Clin Oncol*, 2021;39:3853-3865 2. Tam CS et al. *Blood.* 2022;139:3278-3289. 3. Venclexta [package insert]. South San Francisco, CA: Genentech USA Inc; 2021. 4. Lu P et al. *Blood Cancer J*. 2021;11:39.

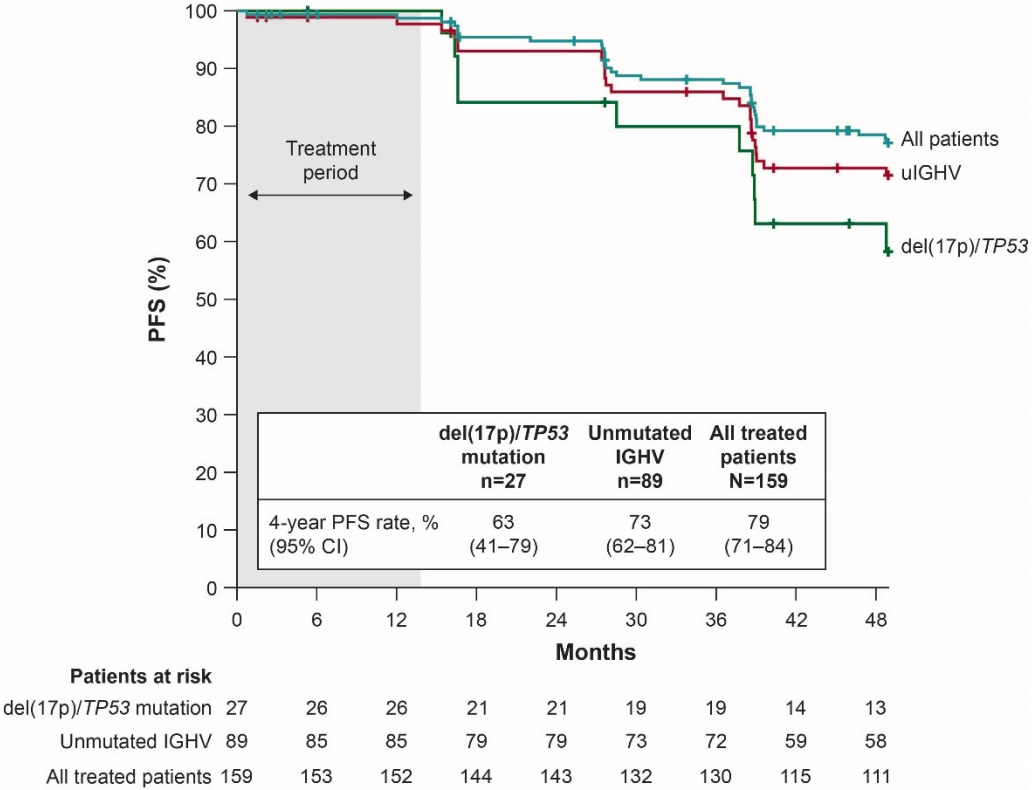
4-Year PFS Rates by MRD Status 3 Months After Stopping Treatment Were Significantly Higher in Patients With Undetectable Versus Detectable MRD in PB



- Landmark PFS rates at 48 months in patients who had uMRD in PB 3 months posttreatment were higher (90%) than those with detectable MRD in PB 3 months posttreatment (66%)

dMRD, detectable minimal residual disease; PB, peripheral blood; PFS, progression-free survival; uMRD, undetectable minimal residual disease.

Fixed-Duration Ibr + Ven Continues to Provide Durable, High PFS Rates

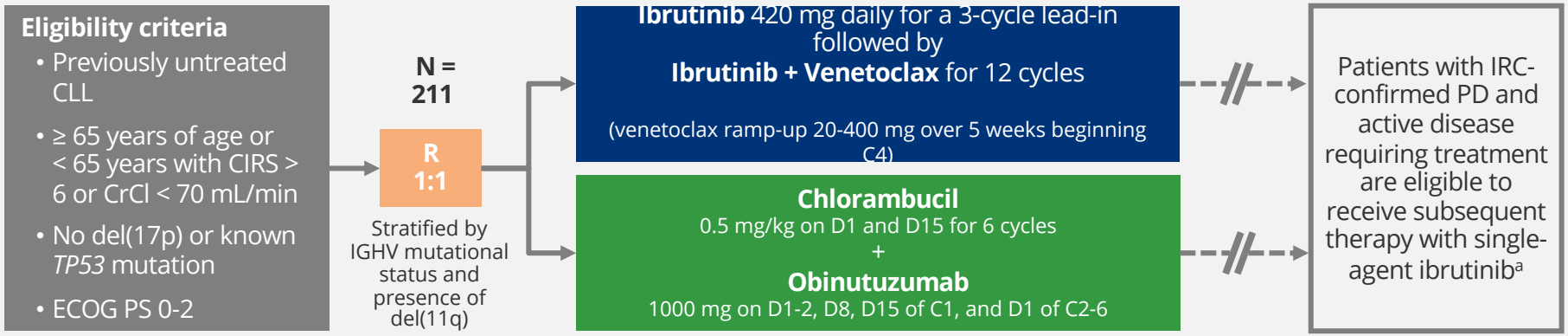


Time to Next Treatment

- Median TTNT was not reached (n=28; range 1–53 months)
- Landmark estimate of the proportion of patients who had not started a next treatment at 4 years was 84% (95% CI 77–89)

IGHV, immunoglobulin heavy chain variable region gene; PFS, progression-free survival; uMRD, undetectable minimal residual disease.

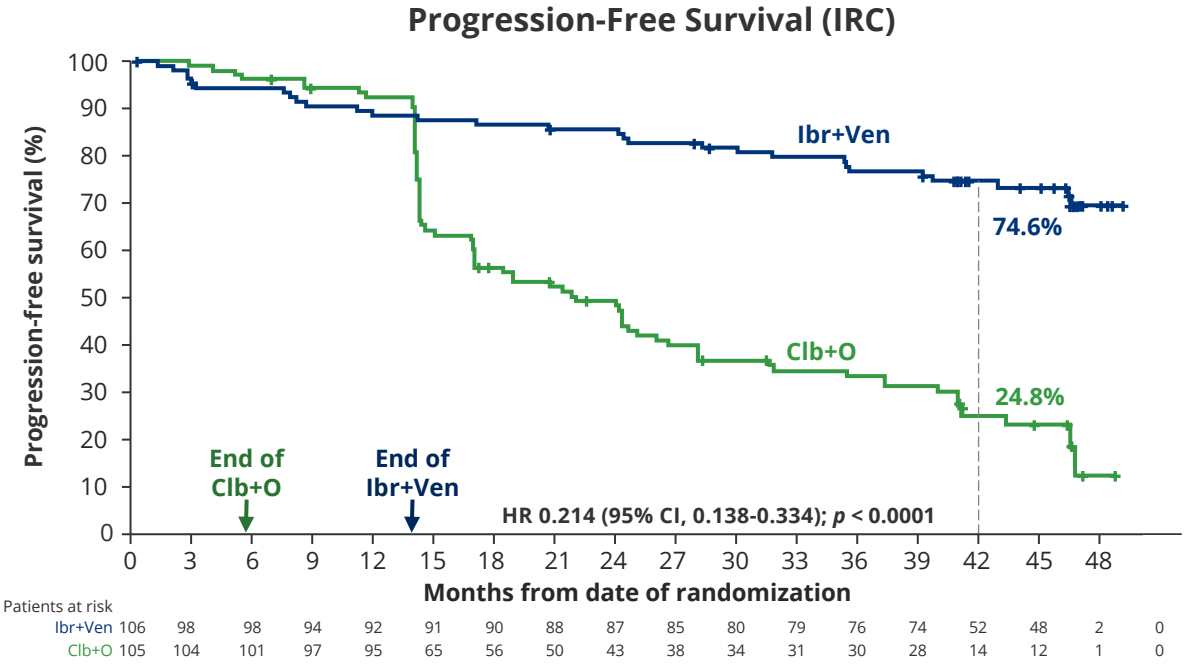
Phase 3 GLOW Study (NCT03462719)



- **Primary end point: IRC-assessed PFS**
- Key secondary end points: uMRD rates, response rates, overall survival, time to next treatment, and safety
- Current analysis
  - Median study follow-up of 46 months (range, 1.7-51.7)
  - MRD assessed in peripheral blood in responders by NGS

[a]Ibrutinib provided by the Sponsor to patients from both arms who were eligible to participate in the Subsequent Therapy Phase of the study.
C, cycle (28 days); CIRS, Cumulative Illness Rating Scale score; CrCl, creatinine clearance; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent review committee; PD, progressive disease; R, randomization; uMRD, undetectable minimal residual disease; NGS, next-generation sequencing.

GLOW: Progression-Free Survival by IRC Remained Superior For Ibr+Ven Versus Clb+O With 4 Years of Study Follow-up



Median study follow-up: 46 months

- **Ibr+Ven reduced the risk of progression or death by 79%** versus Clb+O
  - HR 0.214 (95% CI, 0.138-0.334); $p < 0.0001$
- Estimated 3.5-year PFS rates:
  - **74.6%** for Ibr+Ven
  - **24.8%** for Clb+O

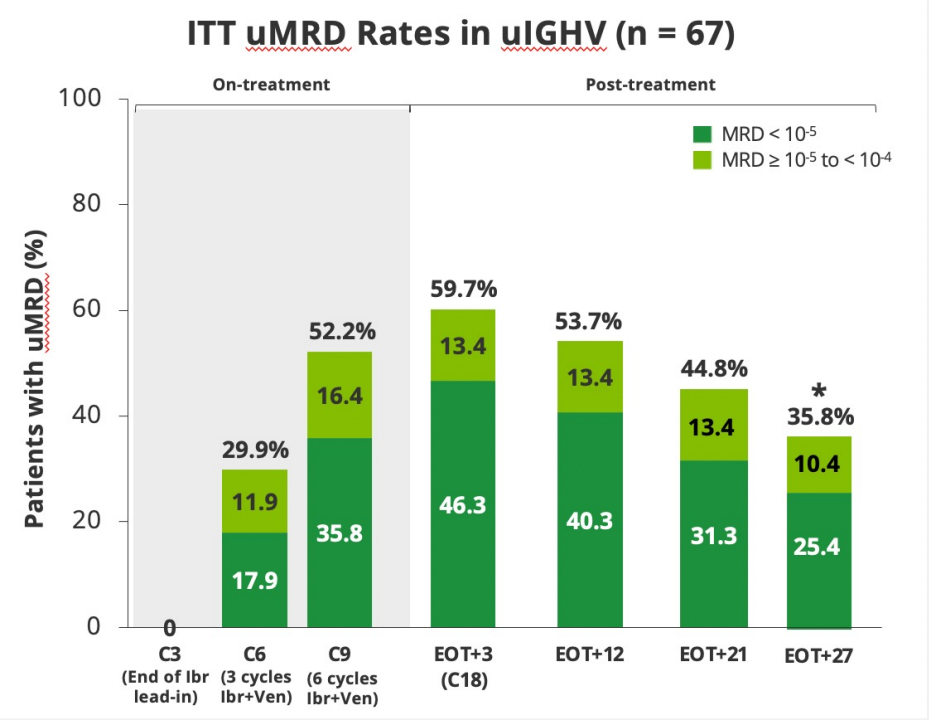
IRC, independent review committee; CI, confidence interval; HR, hazard ratio.

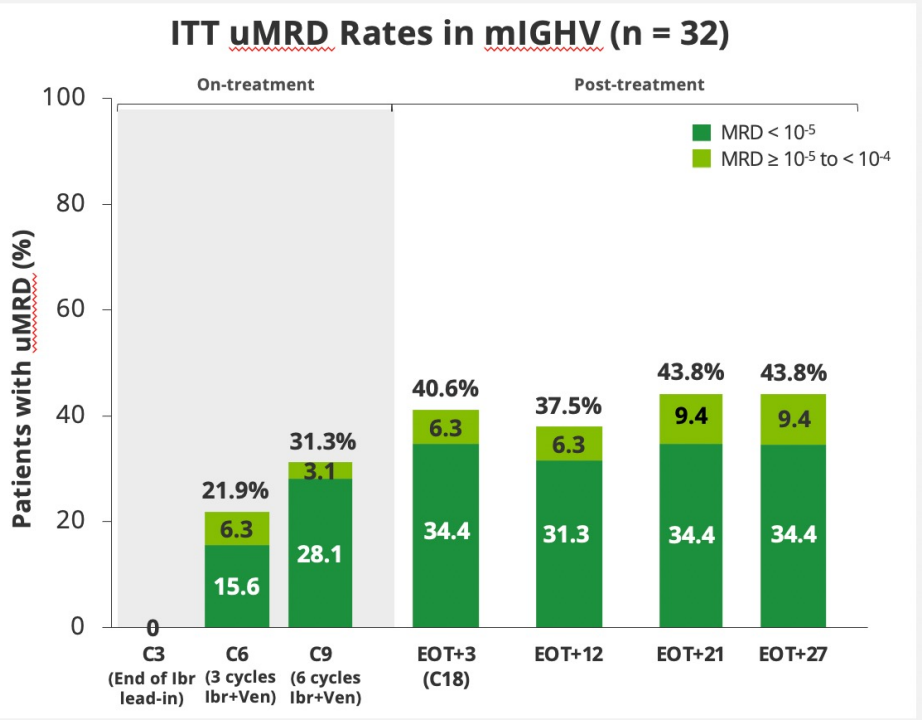
Treatment Disposition

	I+V (N=106)	Clb+O (N=105)
Median treatment exposure,[a] mos (range)	13.8 (0.7-19.5)	5.1 (1.8-7.9)
Discontinued all study treatment, n (%)	24 (22.6)	5 (4.8)
Reason for treatment discontinuation, n (%)		
Adverse event	11 (10.4)	2 (1.9)
Patient refused treatment	4 (3.8)	1 (1.0)
Death	4 (3.8)	0
Disease progression[b]	3 (2.8)	1 (1.0)
Physician decision	2 (1.9)	1 (1.0)

- In the I+V arm, 78.3% of patients received at least 12 months of treatment
- COVID-19 had no impact on treatment disposition; all but 6 patients had completed treatment prior to the pandemic

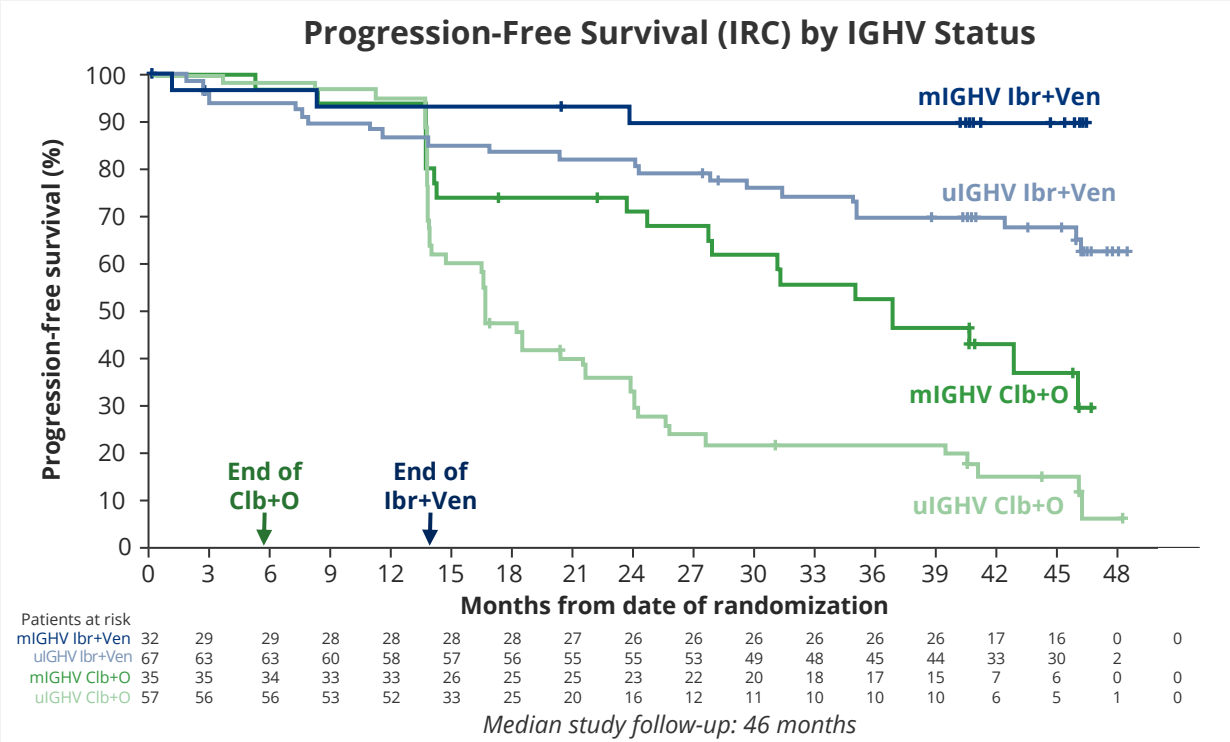
GLOW: Ibr+Ven On-treatment and Post-treatment uMRD Dynamics According to IGHV Status





- uMRD rates (including < 10^{-5}) were higher and uMRD was achieved faster in patients with uIGHV versus mIGHV CLL
- uMRD was better sustained post-treatment in patients with mIGHV CLL

GLOW: Ibr+Ven Improved PFS Versus Clb+O Regardless of IGHV Status



- PFS at 3.5 years was higher for Ibr+Ven versus Clb+O for both uIGHV and mIGHV CLL
- Impact of IGHV status on PFS was more pronounced with Clb+O
- > 90% of patients in the Ibr+Ven arm did not require subsequent treatment at 3.5 years:
  - 91.5% for uIGHV
  - 93.5% for mIGHV

Results based on updated IGHV reclassifications; 6 of 7 on-treatment deaths in Ibr+Ven arm were in uIGHV.
IRC, independent review committee; mIGHV, mutated IGHV; uIGHV, unmutated IGHV.

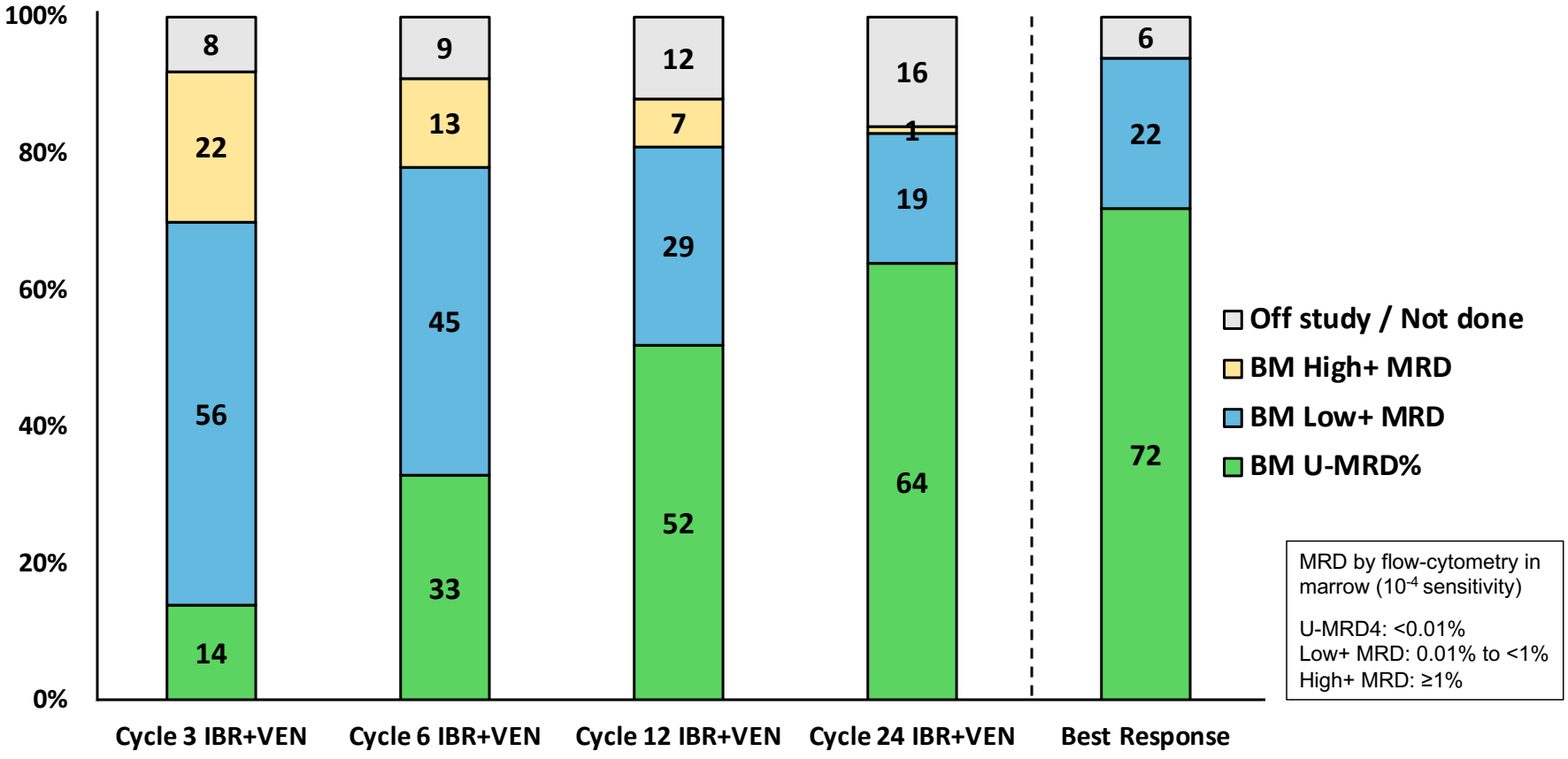
Ibrutinib and Venetoclax Trial

- Investigator-initiated Phase II trial (NCT02756897)

- Patients with treatment-naïve CLL/SLL meeting 2008 iwCLL treatment criteria with at least one of the following feature:
  - Del(17p) or mutated *TP53*
  - Del(11q)
  - Unmutated *IGHV*
  - Age ≥65 years

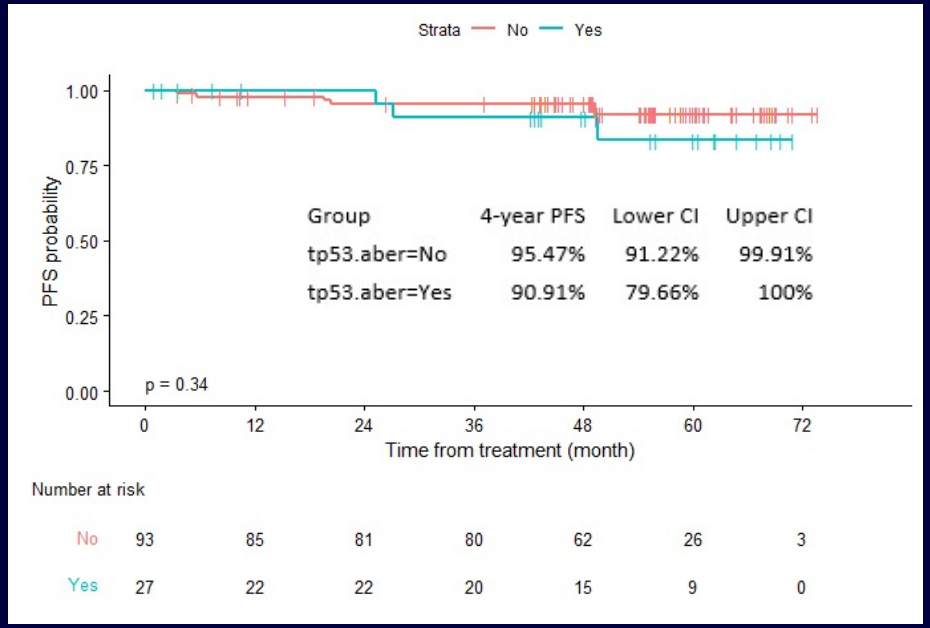
Jain, IBR + VEN in CLL, ASH 2022, Abs 95

Marrow MRD Response at Serial Time-Points
Intent-to-Treat (N=120)

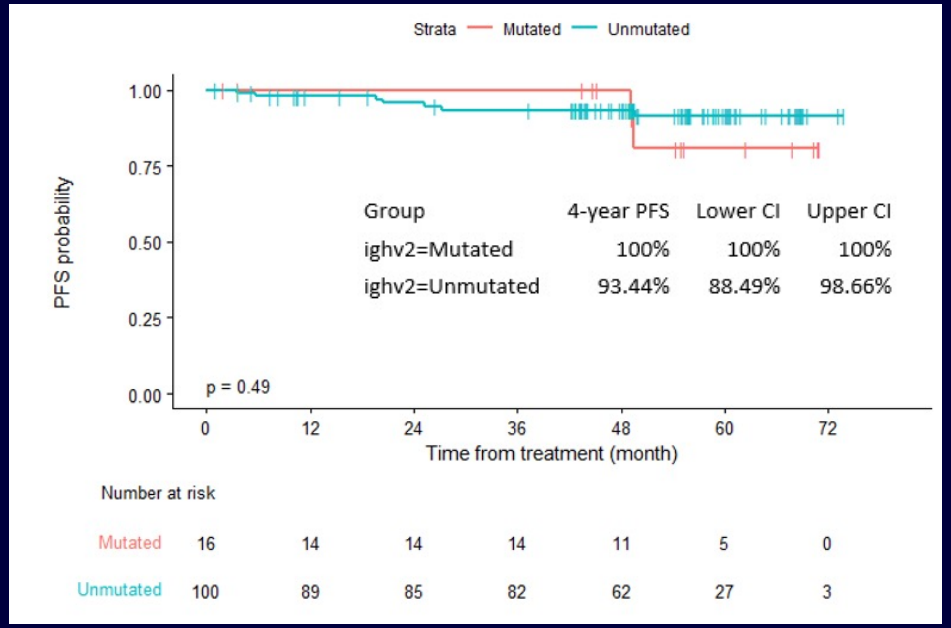


Jain, IBR + VEN in CLL, ASH 2022, Abs 95

PFS by Genomic Subgroups



TP53 aberrant status



IGHV mutation status

Jain, IBR + VEN in CLL, ASH 2022, Abs 95

CLL13/GAIA: venetoclax-based treatments vs. CIT in younger/fit patients

Fit patients with untreated CLL:
CIRS ≤ 6 & normal CrCl

No *TP53* mutation or del(17p) in central screening

CIT:
FCR/BR*
6 cycles,n=230

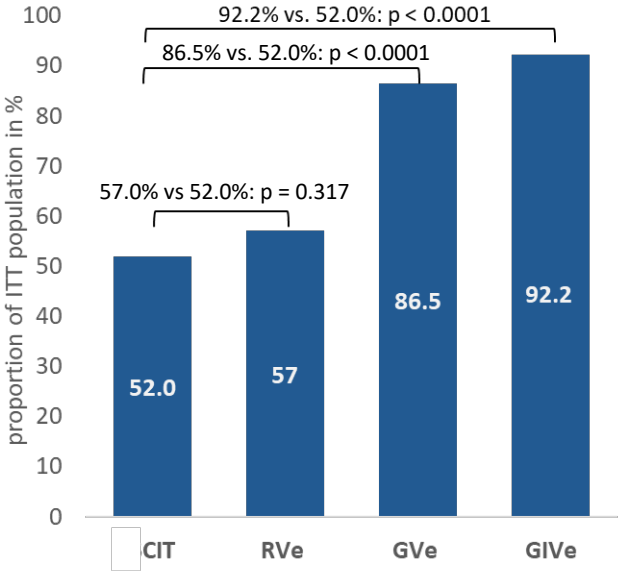
RVe
12 cycles, n=230

GVe
12 cycles, n=230

GIVe
15# cycles, n=230

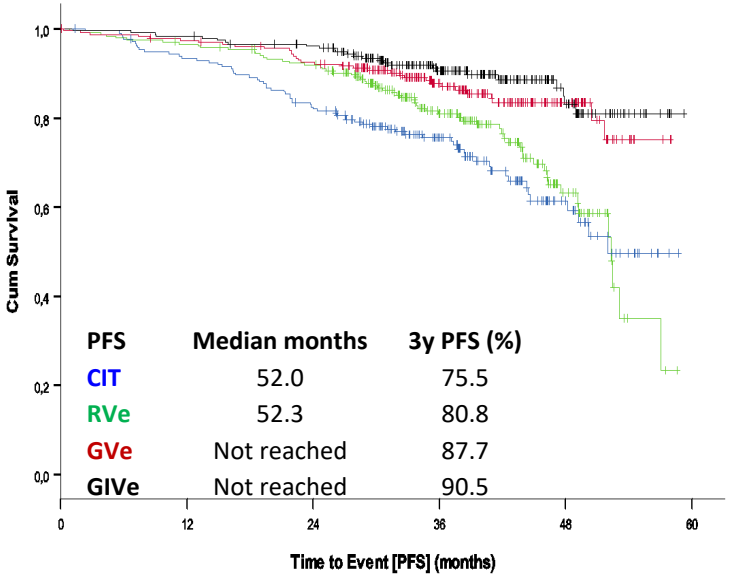
uMRD (< 10^{-4})

at month 15 in PB by 4-colour-flow



PFS

at median FU of 38.8 months

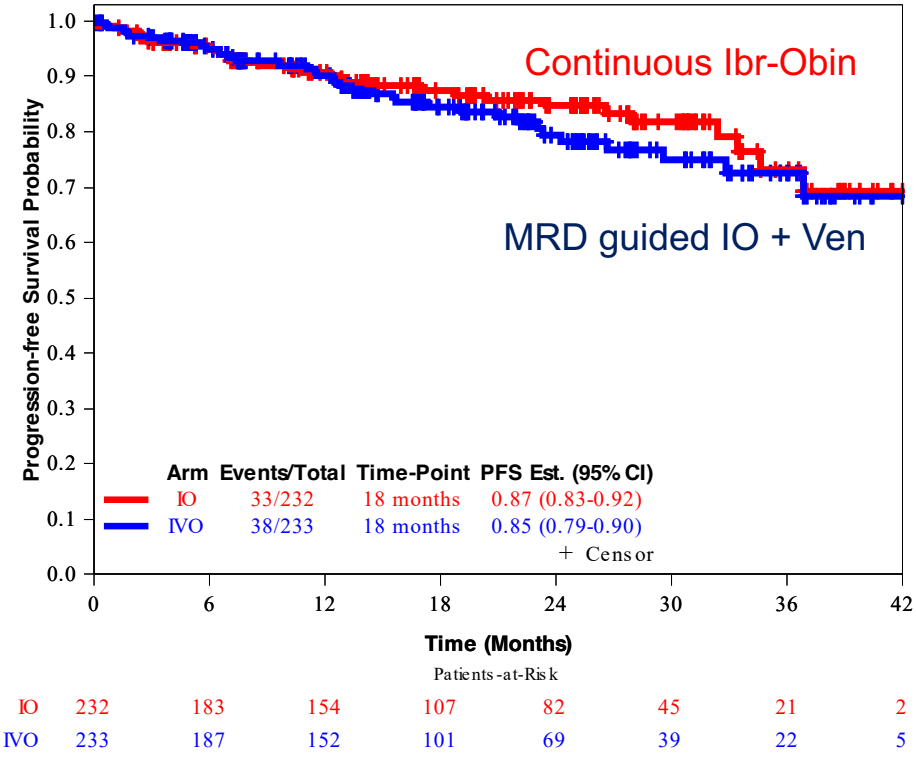


PFS	Median months	3y PFS (%)
CIT	52.0	75.5
RVe	52.3	80.8
GVe	Not reached	87.7
GIVe	Not reached	90.5

* ≤ 65 years: FCR, > 65 years: BR; [50% FCR / 50% BR]
# continuation of ibrutinib up to cycle 36 if MRD detectable

Eichhorst et al, ASH2021 and EHA2022

A041702: No Benefit to Triplet Combo



IVO vs I0:
Hazard Ratio 1.12
95% CI: 0.70-1.79

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

CONCLUSIONS

- Ibrutinib + Venetoclax results in ~75% MRD clearance and favorable outcomes in all prognostic categories of CLL
- Advantages: all oral, fixed duration, likely reduced mutations
- “Triplet” combos are looking similar to doublets
- May have reduced tolerance in elderly (GLOW vs CAPTIVATE) – argument for 2nd Gen BTKi combos