Outcomes in High-risk Subgroups After Fixed-Duration Ibrutinib + Venetoclax for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: Up To 5.5 years of Follow-up in the Phase 2 CAPTIVATE Study

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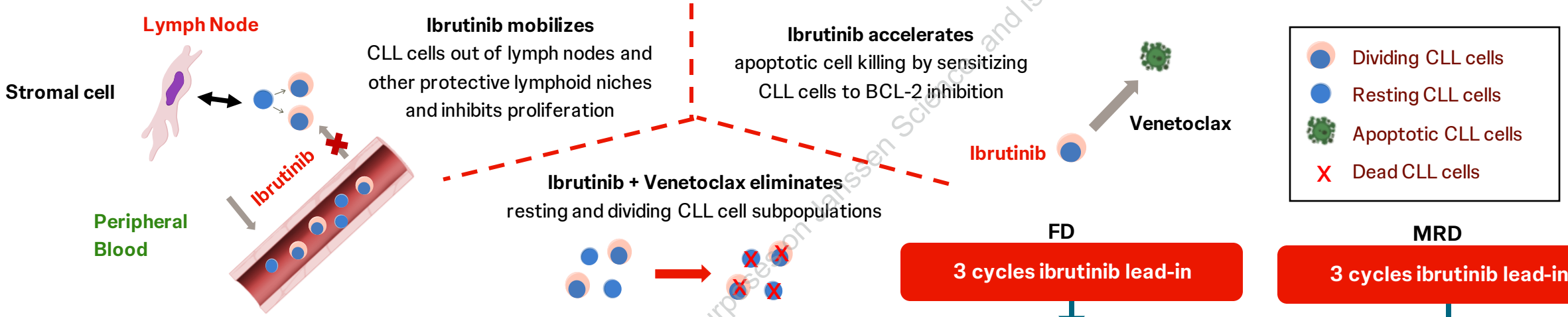
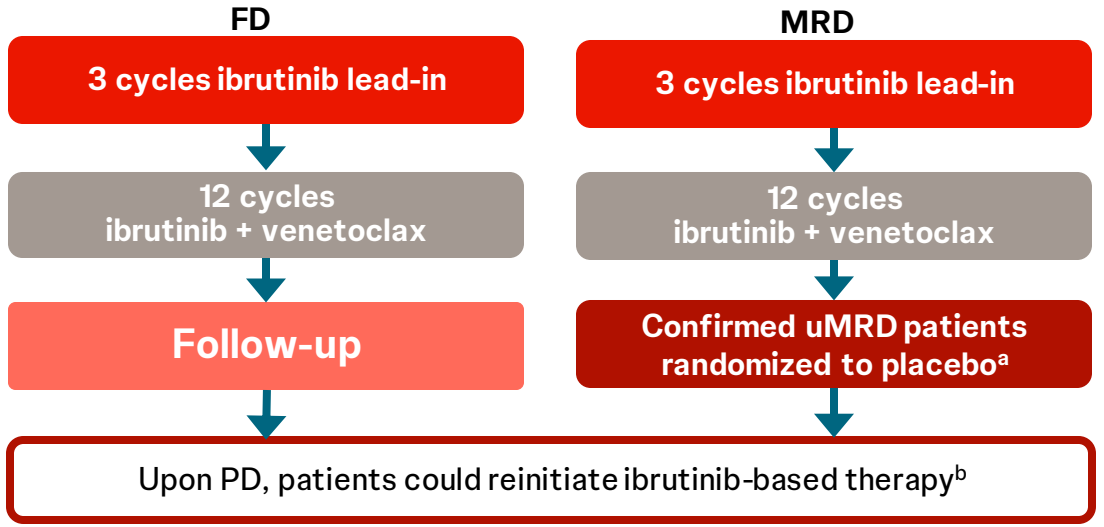
CAPTIVATE Study: Ibrutinib and Venetoclax Work Synergistically Through Distinct and Complementary Modes of Action[1-3]

- Ibrutinib + venetoclax is approved for first-line treatment of CLL/SLL in 78 countries across Asia, Europe, the Middle East, and South America, as well as Canada, Australia, and New Zealand



- This presentation reports outcomes after fixed-duration treatment with ibrutinib + venetoclax in the phase 2 CAPTIVATE study demonstrating:
  - Patients with high-risk genomic features (FD cohort [N=159]) derive meaningful survival benefits from fixed-duration ibrutinib + venetoclax
  - Ibrutinib-based retreatment (FD cohort [N=159] and MRD cohort placebo arm [n=43]) appear to have a positive benefit-risk profile



BCL-2, B cell lymphoma 2; CLL, chronic lymphocytic leukemia; FD, fixed duration; MRD, minimal residual disease; PD, progressive disease; SLL, small lymphocytic lymphoma; uMRD, undetectable MRD.
[a]Patients with confirmed uMRD (defined as uMRD [<10^{-4} by 8-color flow cytometry] serially over ≥3 cycles in both peripheral blood and bone marrow) after 12 cycles of ibrutinib + venetoclax were randomly assigned 1:1 to receive placebo or ibrutinib; only the placebo arm was included in the current analysis. [b]Patients with PD after completion of fixed-duration ibrutinib + venetoclax could reinitiate single-agent ibrutinib (FD cohort or MRD cohort placebo arm); patients with PD >2 years after treatment completion could reinitiate fixed-duration ibrutinib + venetoclax (FD cohort).
[1]Lu P et al. *Blood Cancer J.* 2021;11:39. [2]Deng J et al. *Leukemia.* 2017;31:2075-2084. [3]Herman ES et al. *Clin Cancer Res.* 2015;21:4642-4651.

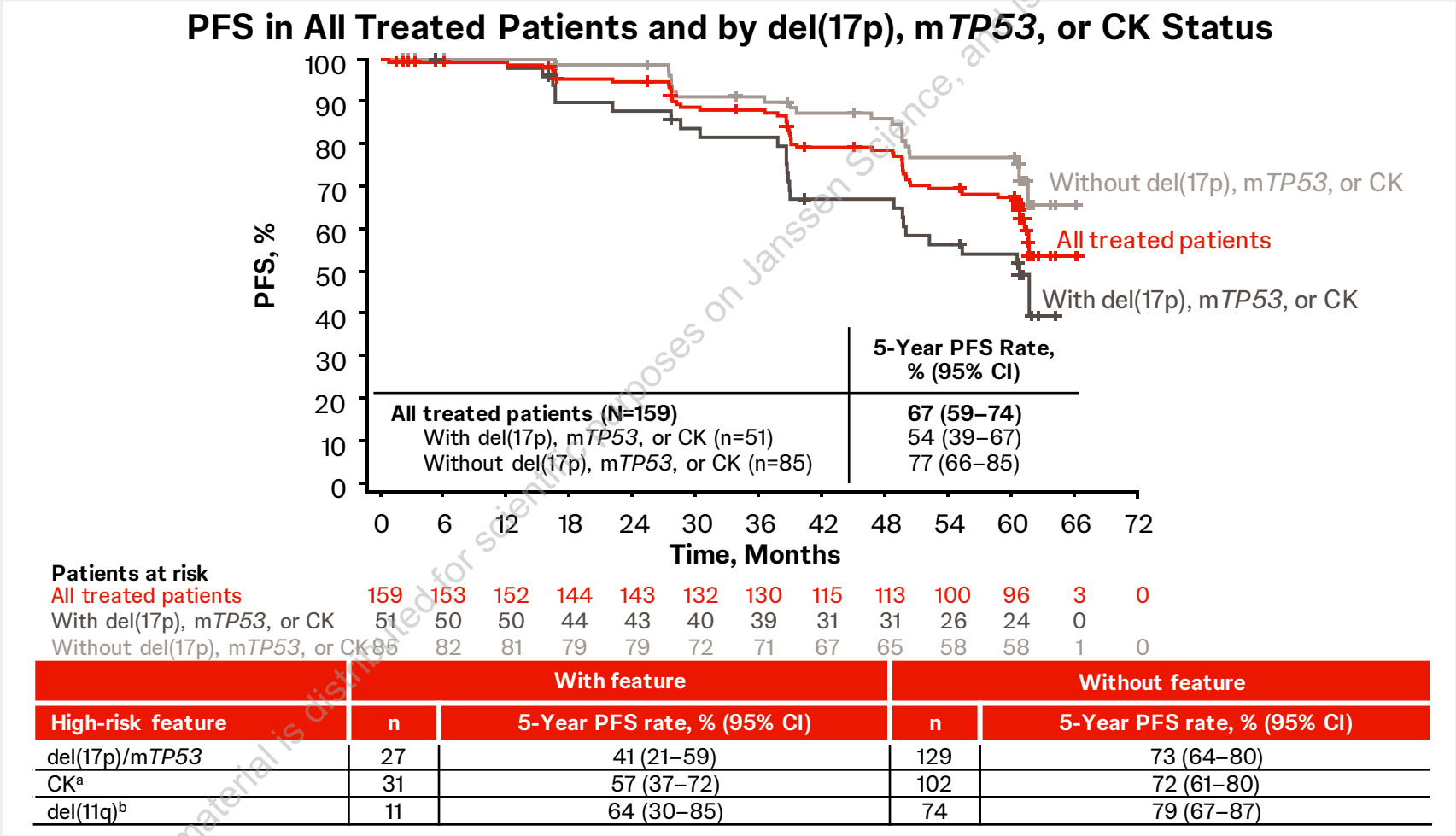
FD Cohort: Baseline Characteristics (N=159)

Characteristic	FD Cohort All Treated Patients N=159
Median age (range), years	60 (33–71)
Male, n (%)	106 (67)
Rai stage III/IV, n (%)	44 (28)
High-risk genomic features, n (%)	
Unmutated IGHV	89 (56)
del(17p)/mutated *TP53*[a]	27 (17)
del(17p)	20 (13)
del(11q)[b]	28 (18)
Complex karyotype[c]	31 (23)
Any cytopenia, n (%)	54 (34)
ANC ≤1.5 × 10^9/L	13 (8)
Hemoglobin ≤11 g/dL	37 (23)
Platelet count ≤100 × 10^9/L	21 (13)
Bulky LN disease ≥5 cm, n (%)	48 (30)
Median ALC × 10^9/L (range)	70 (1–503)
ALC ≥25 × 10^9/L, n (%)	120 (75)

ALC, absolute lymphocyte count; ANC, absolute neutrophil count; LN, lymph node.
[a]del(17p)/*TP53* status was missing for 3 patients. [b]Without del(17p) per Döhner hierarchy. [c]Defined as ≥3 abnormalities by conventional CpG-stimulated cytogenetics; complex karyotype status was missing for 26 patients.

FD Cohort: Overall Median PFS Was Not Reached With Up to 5.5 Years of Follow-Up

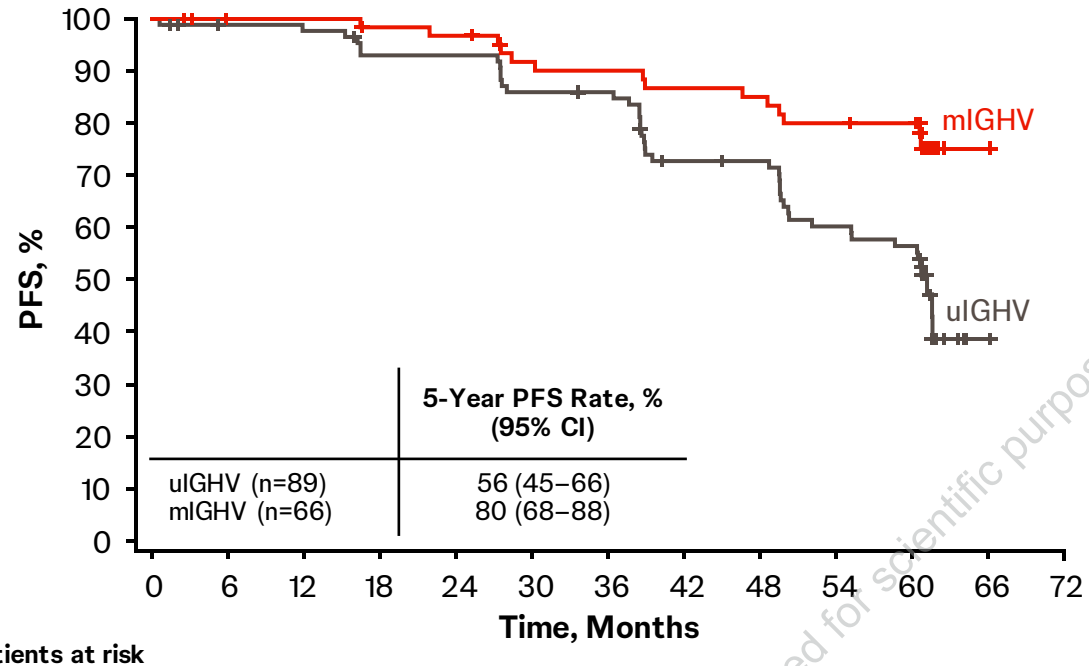
- Median time on study: 61.2 months (range, 0.8–66.3)

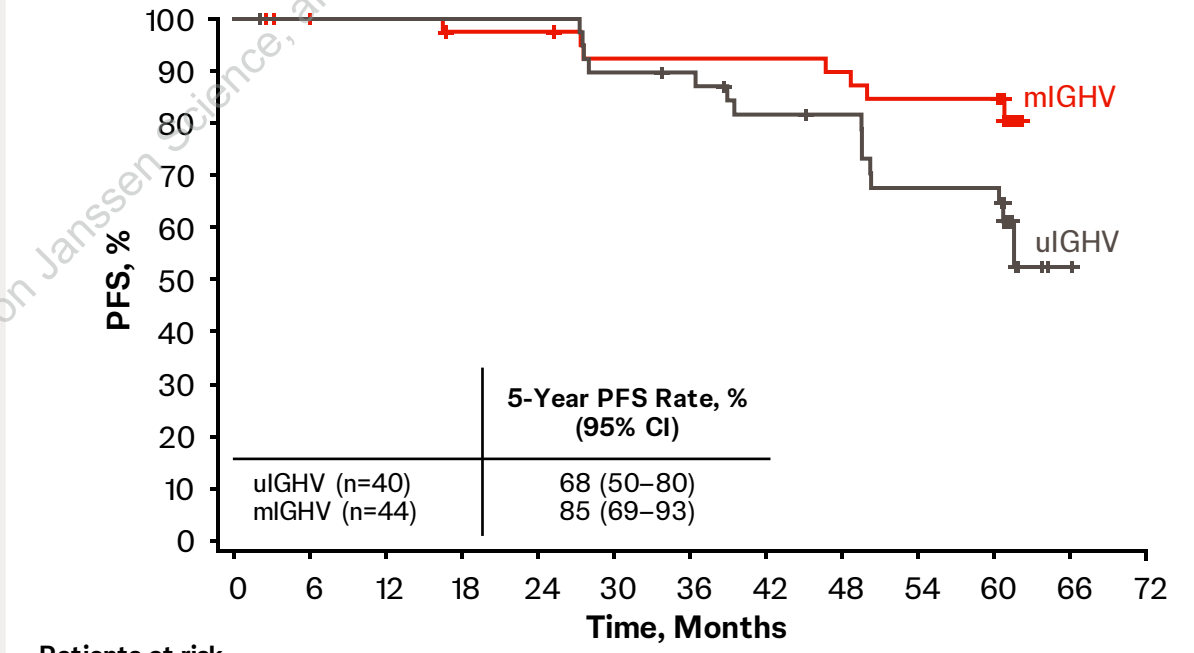


	With feature		Without feature	
High-risk feature	n	5-Year PFS rate, % (95% CI)	n	5-Year PFS rate, % (95% CI)
del(17p)/m*TP53*	27	41 (21–59)	129	73 (64–80)
CK[a]	31	57 (37–72)	102	72 (61–80)
del(11q)[b]	11	64 (30–85)	74	79 (67–87)

CK, complex karyotype; m*TP53*, mutated *TP53*; PFS, progression-free survival. [a]Defined as ≥3 chromosomal abnormalities by conventional CpG-stimulated cytogenetics; [b]Excluding patients with del(17p)/mutated *TP53* or CK.

FD Cohort: 5-Year PFS Rates by IGHV Mutation Status (N=159)



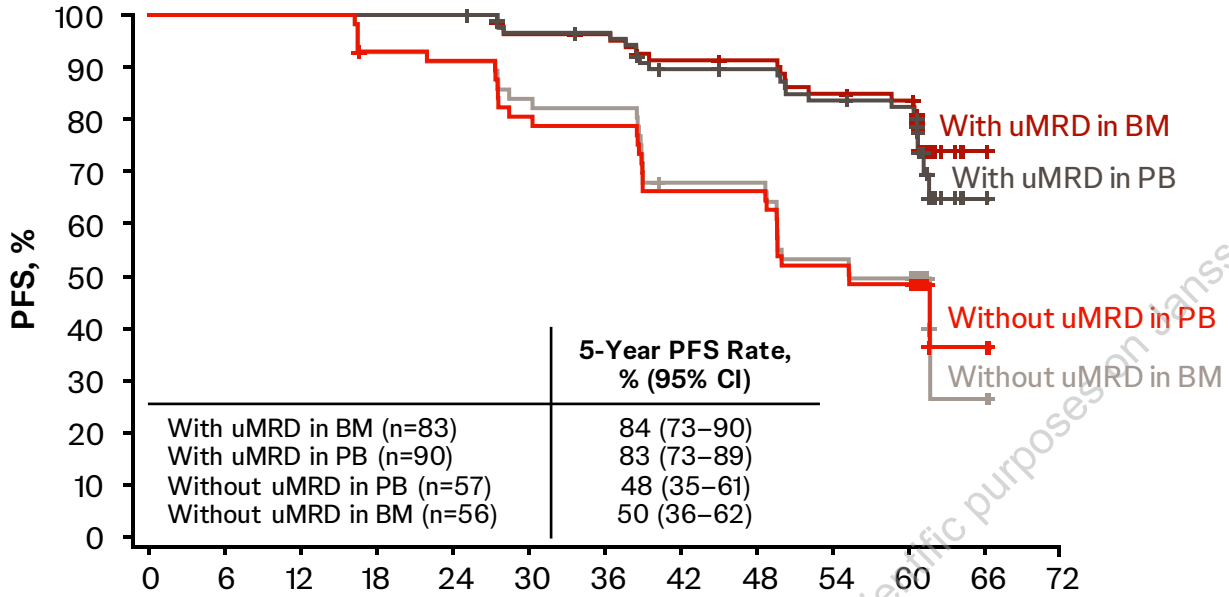


- Co-existing del(17p), m*TP53*, or CK had a substantial impact on PFS in patients with uIGHV and mIGHV

mIGHV, mutated IGHV; uIGHV, unmutated IGHV.

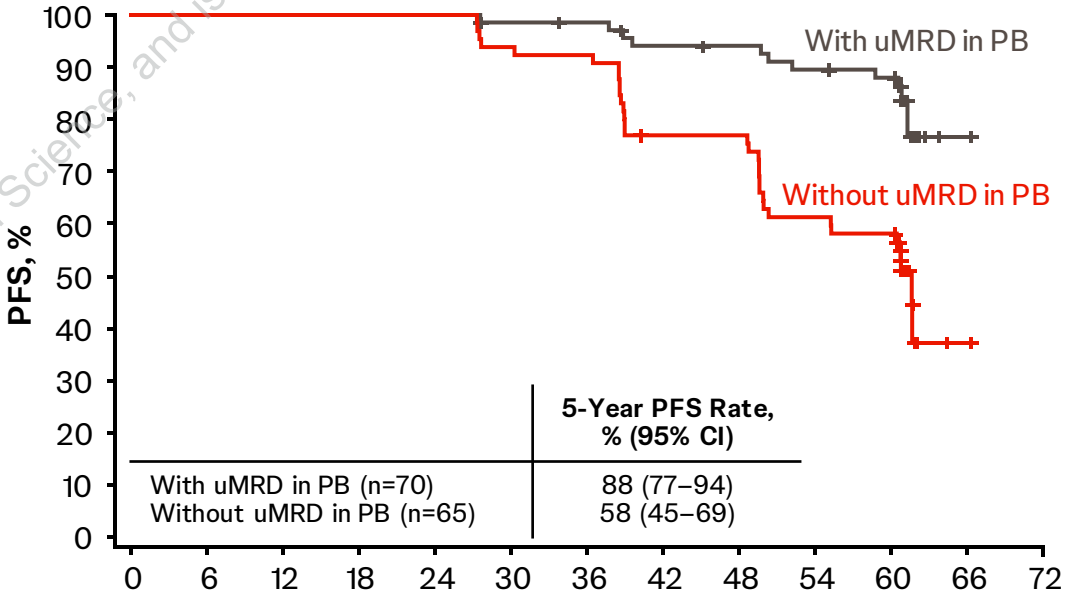
FD Cohort: Improved 5-Year PFS Rates With uMRD in BM and PB (N=159)

PFS by MRD Status at 3 Months After EOT[a]



Patients at risk													
With uMRD in BM	83	83	83	83	83	78	77	72	71	66	64	1	0
With uMRD in PB	90	90	90	90	90	85	84	76	75	70	68	1	0
Without uMRD in PB	57	57	57	52	51	45	44	37	37	29	27	2	0
Without uMRD in BM	56	56	56	52	51	47	46	37	37	29	27	2	0

PFS by MRD Status at 12 Months After EOT[a]



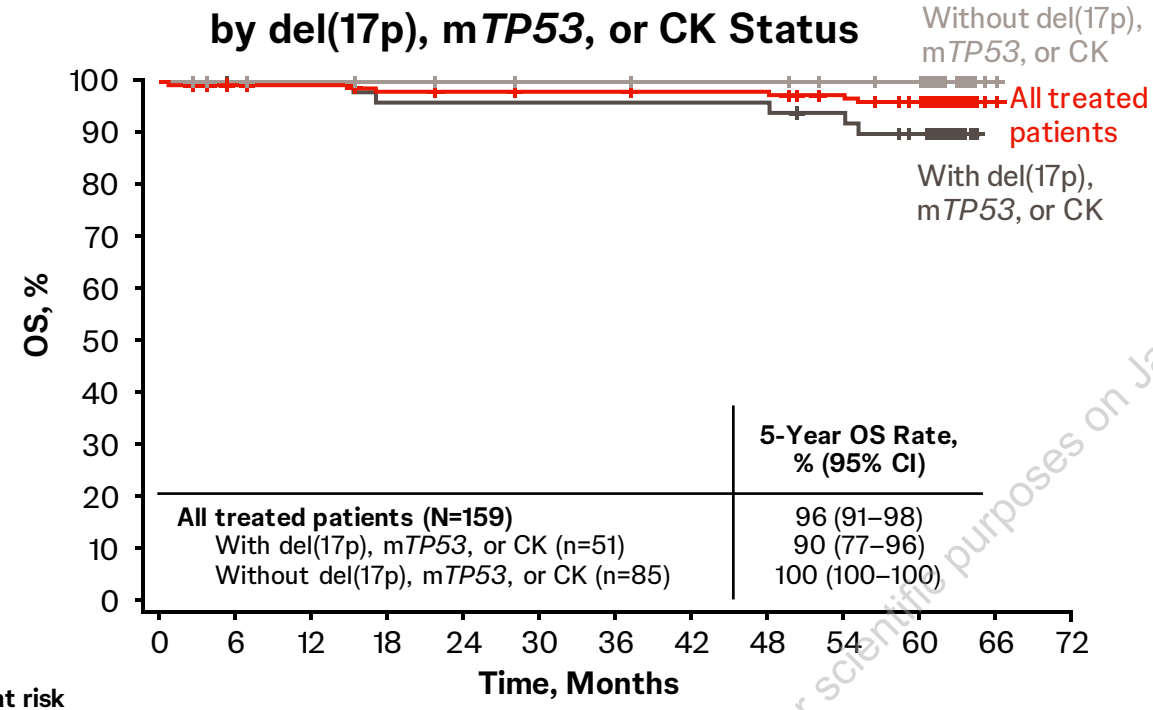
Patients at risk													
With uMRD in PB	70	70	70	70	70	68	67	63	62	59	57	1	0
Without uMRD in PB	65	65	65	65	65	61	60	49	49	39	37	2	0

- In high-risk genomic subgroups with del(17p)/m*TP53*, CK, or uIGHV, 5-year PFS rates were also consistently higher in patients with uMRD4 in PB or BM at 3 months after EOT than in those without uMRD4[b]

BM, bone marrow; EOT, end of treatment; NE, not estimable; PB, peripheral blood.
[a]Analyzed in patients who completed FD treatment with ibrutinib + venetoclax and had valid MRD results at the specified time point. [b]uMRD <10^{-4} by 8-color flow cytometry.

FD Cohort: 5-Year OS Rates Were ≥90% Regardless of Genomic Risk Features

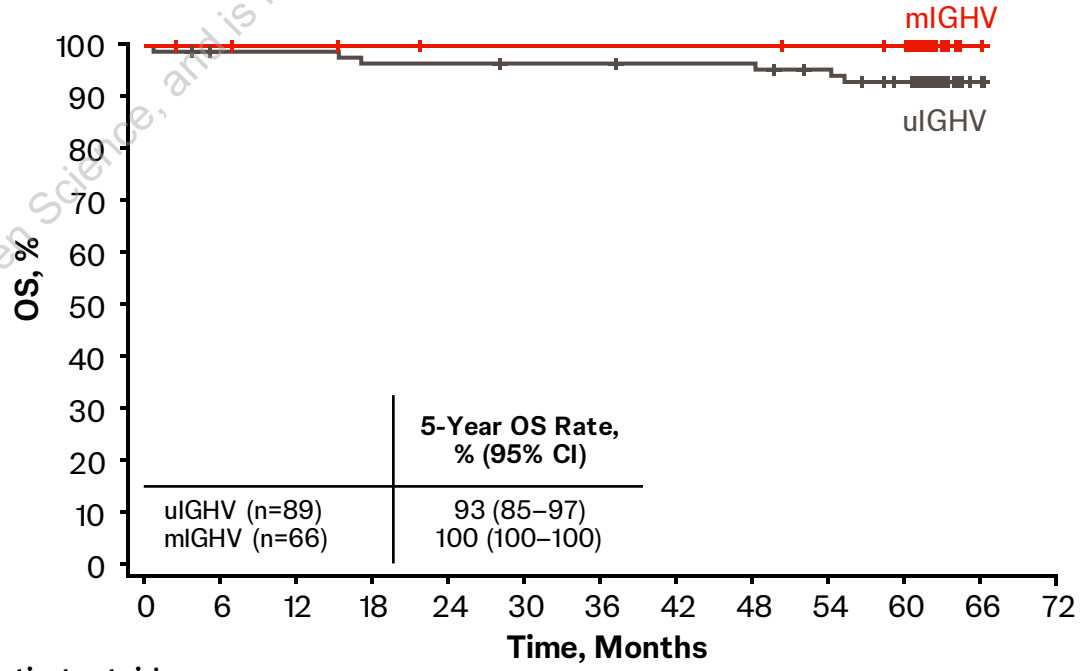
OS in All Treated Patients and by del(17p), m*TP53*, or CK Status



Patients at risk

All treated patients	159	155	154	151	150	149	149	148	148	144	138	4	0
With del(17p), m*TP53*, or CK	51	50	50	48	48	48	48	48	48	46	42	0	
Without del(17p), m*TP53*, or CK	85	83	82	81	80	79	79	78	78	76	75	1	0

OS by IGHV Mutation Status



Patients at risk

uIGHV	89	86	86	84	84	83	83	82	82	79	74	2	0
mIGHV	66	65	64	63	62	62	62	62	62	61	60	1	0

- 5-year OS rates were ≥95% regardless of MRD status in PB or BM at 3 months after EOT or in PB at 12 months after EOT

OS, overall survival.

Progressive Disease and Richter Transformation

- In total, 202 patients completed fixed-duration ibrutinib + venetoclax (FD cohort, N=159; MRD cohort placebo arm, n=43)
  - Only 63 patients have had PD to date
    - 61 patients had CLL PD, including 2 patients who subsequently experienced RT during retreatment
    - 2 patients had RT
  - PD occurred >2 years after EOT in most patients (43/63; 68%)

- In the 4 patients with RT, time from first dose to RT was
  - Patient 1: 12.7 months (0.2 months before EOT)
  - Patient 2: 28.1 months (14.3 months after EOT)
  - Patient 3: 50.9 months (after 1.0 months of single-agent ibrutinib retreatment)
  - Patient 4: 55.3 months (after 27 months of single-agent ibrutinib retreatment)

Study Entry Baseline Characteristics: Patients With RT

Characteristic	Patient 1 (DLBCL)	Patient 2 (HD)	Patient 3 (DLBCL)	Patient 4 (DLBCL)
Age, years	68	58	48	55
Sex	Male	Male	Male	Female
Rai stage	I	II	IV	I
Time from CLL diagnosis to study enrollment, months	46.5	13.3	6.3	9.4
Bulky LN disease ≥5 cm	Y	Y	N	N
High-risk genomic features				
Unmutated IGHV	Y	Y	Y	Y
del(17p)/mutated *TP53*	N	N	Y	N
del(11q)[a]	N	Y	N	N
Complex karyotype[b]	Y	N	Y	Y

DLBCL, diffuse large B cell lymphoma; HD, Hodgkin disease; RT, Richter transformation.
[a]Without del(17p) per Döhner hierarchy. [b]Defined as ≥3 abnormalities by conventional CpG-stimulated cytogenetics.

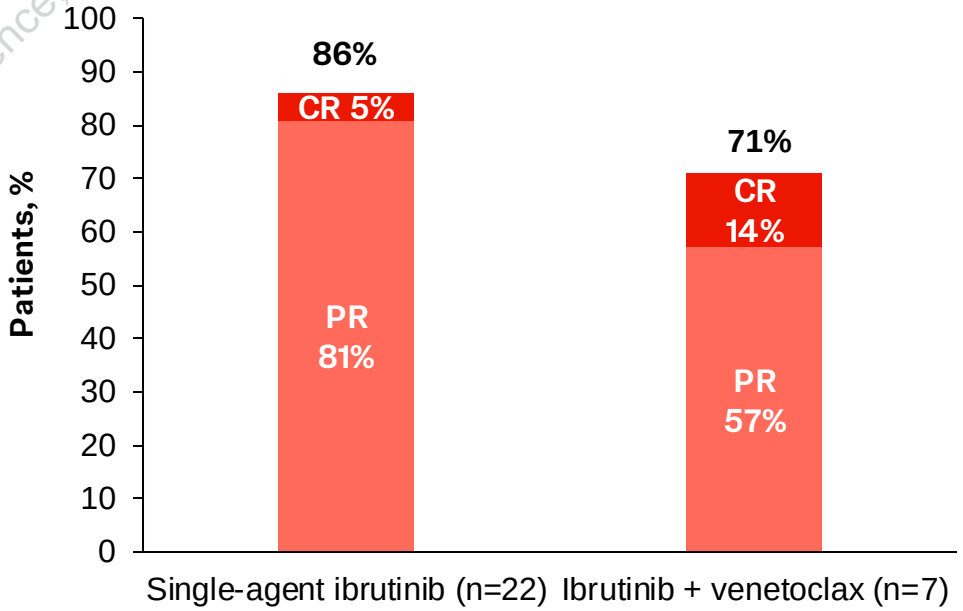
Responses Observed With Ibrutinib-Based Retreatment

- Of 61 patients with CLL PD after completion of fixed-duration ibrutinib + venetoclax, 32 (52%) initiated retreatment with single-agent ibrutinib (n=25) or ibrutinib + venetoclax (n=7)[a]
- Median time on retreatment on study:
  - 21.9 months (range, 0.0–50.4) for single-agent continuous ibrutinib
  - 13.8 months (range, 3.7–15.1) for 15-month fixed-duration ibrutinib + venetoclax[a,b]

Study Entry Baseline Characteristics: Retreated Patients

Characteristic	Single-agent ibrutinib (n=25)	Ibrutinib + venetoclax (n=7)	All Retreated Patients (n=32)
Median age (range), years	56 (39–71)	63 (49–69)	59 (39–71)
Male, n (%)	15 (60)	6 (86)	21 (66)
Rai stage III/IV, n (%)	4 (16)	2 (29)	6 (19)
High-risk genomic features, n (%)			
Unmutated IGHV	20 (80)	5 (71)	25 (78)
del(17p)/mutated *TP53*	5 (20)	5 (71)	10 (31)
del(11q)[d]	6 (24)	1 (14)	7 (22)
Complex karyotype[e]	9 (36)	2 (29)	11 (34)
Bulky LN disease ≥5 cm, n (%)	10 (40)	1 (14)	11 (34)

Best Response in Evaluable Patients to Date[c]



CR, complete response; PR, partial response.
[a]Per protocol, only patients with PD >2 years after completion of treatment were eligible to reinitiate ibrutinib + venetoclax. [b]Four patients exited the study during ibrutinib + venetoclax retreatment and completed retreatment off study. [c]Three patients who initiated single-agent ibrutinib retreatment had not yet undergone response assessment. [d]Without del(17p) per Döhner hierarchy. [e]Defined as ≥3 abnormalities by conventional CpG-stimulated cytogenetics.

Safety With FD Cohort Treatment and Ibrutinib-Based Retreatment

FD Cohort

- Serious AEs considered related to study treatment and second malignancies continued to be collected after completion of fixed-duration treatment
- No new related serious AEs were reported since the previous analysis[1]
- In total, 18 second malignancies occurred in 13 patients
  - 10 events in 8 patients during the TEAE period[a] for fixed-duration ibrutinib + venetoclax
  - 6 events in 4 patients after the TEAE period[a] and before retreatment
  - 2 events in 2 patients during the TEAE period[a] for ibrutinib-based retreatment

Ibrutinib-Based Retreatment

- AEs during retreatment were consistent with known safety profiles for single-agent ibrutinib and ibrutinib + venetoclax

AEs, n (%)	Single-agent ibrutinib (n=25)	Ibrutinib + venetoclax (n=7)
Any AE	18 (72)	7 (100)
Most frequent AEs[b]		
COVID-19[c]	5 (20)	2 (29)
Diarrhea	5 (20)	3 (43)
Hypertension	4 (16)	4 (57)
Pyrexia	3 (12)	0
Upper respiratory tract infection	3 (12)	0
Nausea	1 (4)	2 (29)
Grade 3/4 AEs	6 (24)	2 (29)
Serious AEs	5 (20)	0
AEs leading to discontinuation	1 (4)	0
AEs leading to dose reduction	0	0

AE, adverse event; TEAE, treatment-emergent adverse event.
[a]TEAEs were collected until 30 days after last dose of study treatment or start of subsequent therapy, whichever occurred first. [b]Occurring in ≥10% of patients with single-agent ibrutinib or ≥2 patients with ibrutinib + venetoclax.
[c]All events were grade 1/2.
[1]Ghia P et al. Presented at: 65th ASH Annual Meeting and Exposition; December 9–12, 2023; San Diego, CA, USA.

Conclusions

- Ibrutinib + venetoclax is an all-oral, once-daily, chemotherapy-free fixed-duration regimen for first-line treatment of CLL/SLL
- With up to 5.5 years of follow-up, median PFS is still not reached with fixed-duration ibrutinib + venetoclax and achievement of uMRD4 correlates with improved PFS
- Patients with high-risk genomic features, including del(17p)/mutated *TP53*, complex karyotype, and unmutated IGHV, derive meaningful survival benefits from fixed-duration ibrutinib + venetoclax
- In patients relapsing after fixed-duration ibrutinib + venetoclax, retreatment with ibrutinib-based regimens yields durable responses with acceptable safety, including in patients with high-risk genomic features
- Based on the safety profiles of fixed-duration ibrutinib + venetoclax and ibrutinib-based retreatment, this treatment approach appears to have a positive benefit-risk profile

https://www.congresshub.com/Oncology/AM2024/Ibrutinib/Wierda

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Supplementary Information

PFS by MRD Status at 3 Months After EOT in High-Risk Subgroups

Outcome	With uMRD in PB	Without uMRD in PB	With uMRD in BM	Without uMRD in BM
del(17p)/mutated *TP53* (n=27)				
Evaluable patients, n	16	8	11	12
5-year PFS rate, % (95% CI)	65 (35–84)	0 (NE–NE)	60 (25–83)	21 (4–48)
Complex karyotype (n=31)				
Evaluable patients, n	19	10	17	12
5-year PFS rate, % (95% CI)	79 (53–92)	20 (3–48)	82 (55–94)	25 (6–51)
Unmutated IGHV (n=89)[a]				
Evaluable patients, n	56	25	49	26
5-year PFS rate, % (95% CI)	74 (60–84)	24 (10–42)	72 (57–83)	33 (16–51)

BM, bone marrow; EOT, end of treatment; NE, not estimable; PB, peripheral blood.
[a]Irrespective of other genomic risk features.