



SINTOMA'25

8 A 10 DE MAIO

HOTEL INTERCONTINENTAL | SÃO PAULO

PARCERIA



APOIO
INSTITUCIONAL



Educação
e Pesquisa



Is finite duration therapy becoming infinite?

*A terapia finita na LLC está
se tornando infinita?*

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BP – A Beneficência Portuguesa de SP

CROMA Oncologia

DISCLOSURES - DECLARAÇÃO DE CONFLITOS DE INTERESSE

<u>Patrocínio para esse evento</u>	Sem patrocínio
<u>Instituição</u>	BP - Beneficencia Portuguesa de Sao Paulo e CROMA Oncologia
<u>Participação em estudos clínicos</u> <u>(Indústria farmacêutica)</u>	Roche, Novartis, GSK, Janssen, Millenium Takeda, ABBVIE, Daichii Sankyo, Pfizer, Celltrion, BMS, AstraZeneca, Viracta, Sandoz, AGIOS, Astellas, MEDAC, Onconova, MSD, Sanofi, Regeneron, Lilly, ADC Therapeutics, Libbs, Beigene
<u>Participação em estudos clínicos</u> <u>(ITT, RWE ou registros)</u>	T-Cell Project, HOLA registry, MMyBrave registry, REALITY WW, , Brazilian Group of CLL, Brazilian Group of Multiple myeloma, AML-Brazil, Coalizão COVID Brazil,
<u>Palestrante</u>	Janssen, AstraZeneca, Zodiac, Roche, Novartis, Takeda, AMGEN, Roche, Libbs, BMS, Celgene, Pfizer, ABBVIE, Sanofi, Pintfarma, Knight Therapeutics/United Medical
<u>Membro de Advisory Board</u>	Kite/Gilead, Knight Therapeutics/United Medical, Janssen, Novartis, AMGEM, Takeda, Roche, BMS, ABBVIE, Libbs, Celgene, Eurofarma,
<u>Membro de Steering Committee</u>	Janssen
<u>Membro de Independent Data Monitoring Committee</u>	Libbs /Mabxscience
<u>Afiliação</u>	ASH, EHA, ESO, IMS, CDCN (Castleman disease), ABHH (Associação Brasileira de Hematologia), Coordinator of Clinical Research Committee at ABHH, Myeloma Committee (ABHH), CLL Committee (ABHH), Lymphoma Committee (ABHH)

CLL TREATMENT



TRENDS IN CLL TREATMENT – 1L and RR

- New therapeutic combinations
- More fixed duration therapies
- MRD as a key endpoint
- Advances in targeted therapies
- CAR-T cell therapy and bispecific antibodies for R/R CLL

KEY FACTORS IN SELECTING CLL TREATMENT

Age and
comorbidities

Treatment goal

Line of treatment

Prognostic
stratification

R/R CLL:
Previous results
and toxicity

Risk of short,
medium, and long-
term toxicity

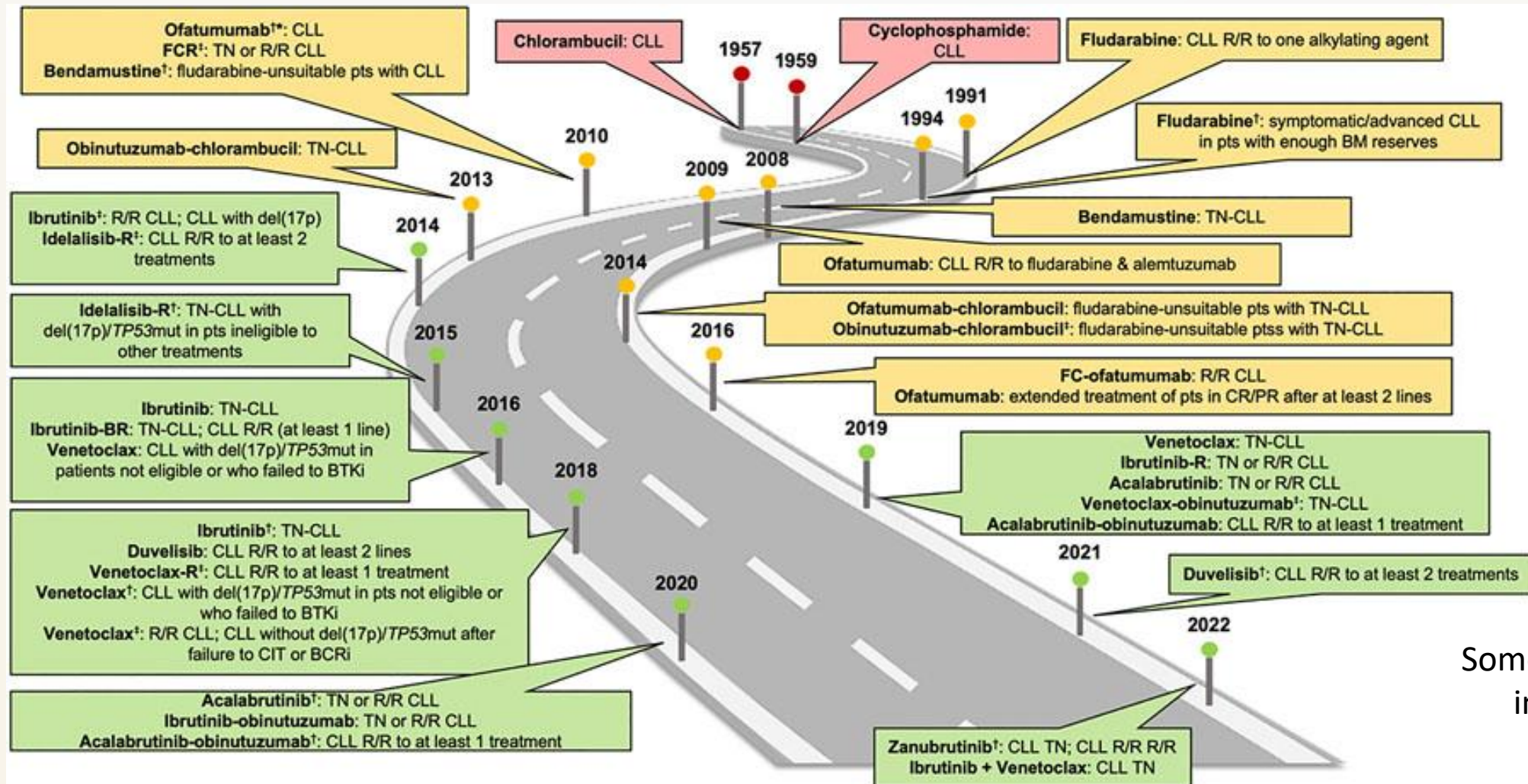
Patient's socio-
cultural profile
(adherence, etc.)

Patient
expectations

Access

“The long and winding road”

Frontline Therapy in CLL



TREATMENT OPTIONS FOR 1L CLL

- APPROVED IN BRAZIL -

FIXED DURATION

CHEMOFREE

- I + V = Ibrutinibe + venetoclax
- VenG = obinutuzumabe + venetoclax

IMMUNOCHEMOTHERAPY

- FCR
- G-clorambucil
- R- clorambucil

CONTINUOUS

BTKi

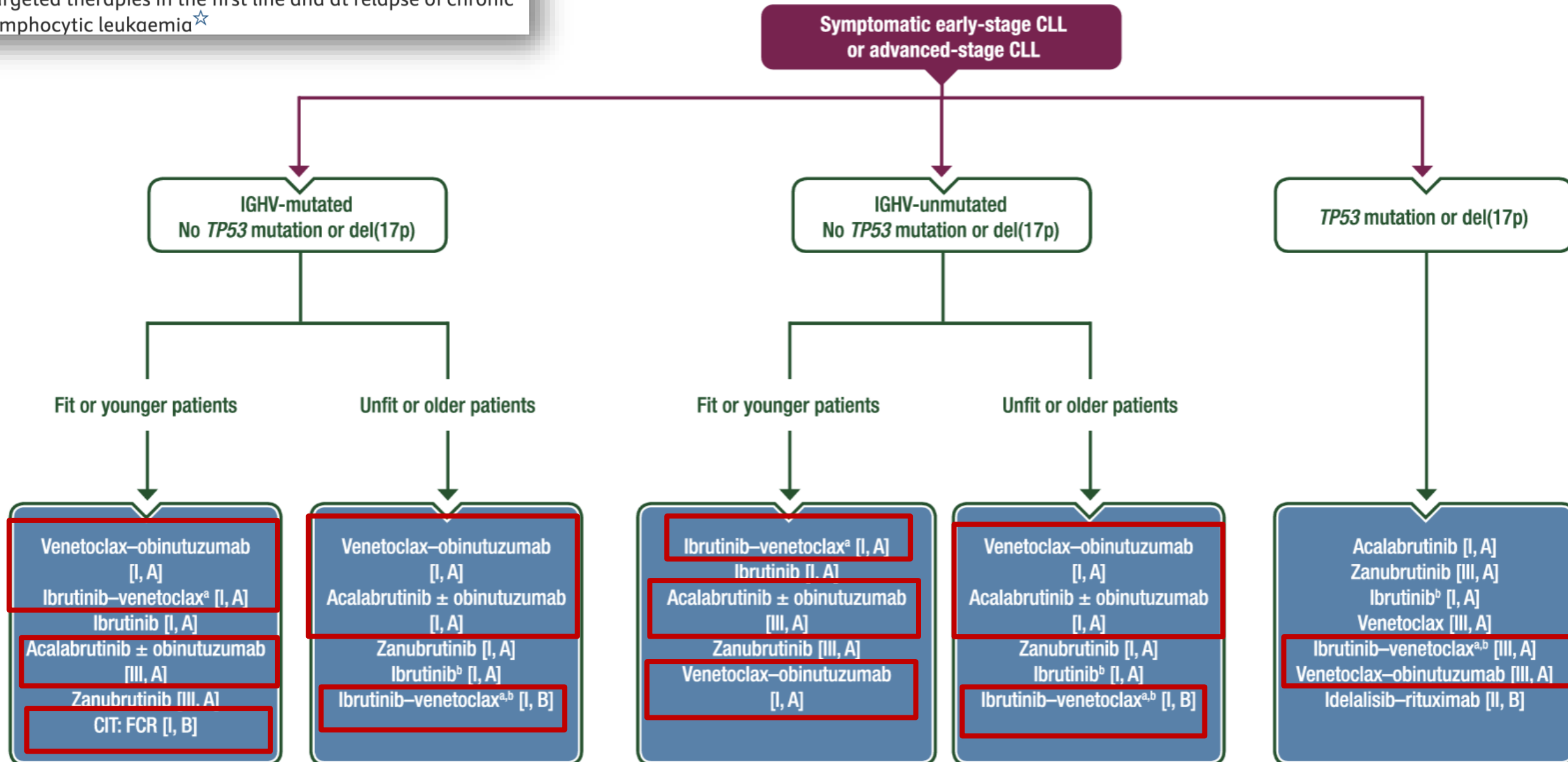
- Ibrutinibe
- Acalabrutinibe (+-G)
- Zanubrutinibe

(ESMO Guideline- for del17p/TP53 mut:

- Venetoclax)

ESMO Clinical Practice Guideline interim update on new targeted therapies in the first line and at relapse of chronic lymphocytic leukaemia[☆]

Ann Oncol. 2024 Sep;35(9):762-768.



NCCN Guidelines Version 3.2025**Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma****SUGGESTED TREATMENT REGIMENS^{a,b,c,d}****** WITHOUT DEL17P/ TP53 MUTATION**

FIRST-LINE THERAPY ^e	
<u>Preferred Regimens</u>	<u>Other Recommended Regimens</u>
• BCL2i-containing regimens ▶ Venetoclax^{f,h} + obinutuzumab (category 1) ▶ Venetoclax^{f,h} + acalabrutinib ± obinutuzumab (category 1) • cBTKi-based regimens ▶ Acalabrutinib^{f,g} ± obinutuzumab (category 1) ▶ Zanubrutinib^{f,g} (category 1)	• BCL2i-containing regimen ▶ Venetoclax^{f,h} + ibrutinib^{f,g} • cBTKi-based regimen ▶ Ibrutinib^{f,g,i} (category 1)

**** WITH DEL17P/ TP53 MUTATION**

Similar, but without
any category

NEW DRUGS X IMMUNOCHEMOTHERAPY

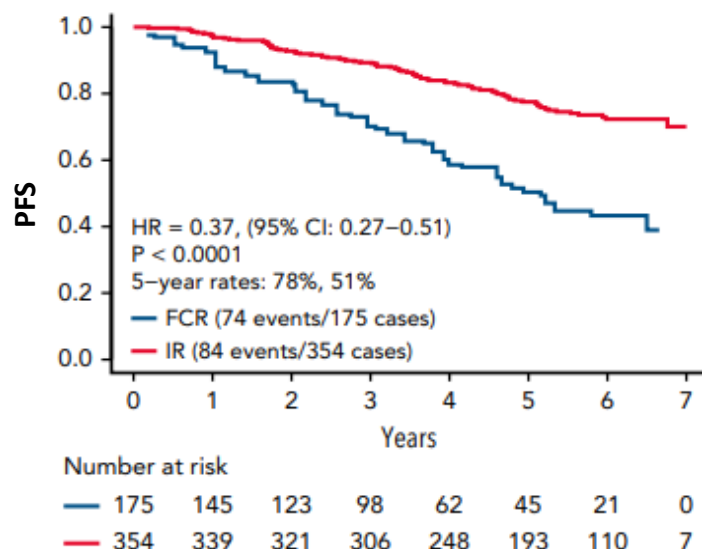
Young
Fit

Elderly
Unfit

ECOG1912¹

IR vs. FCR

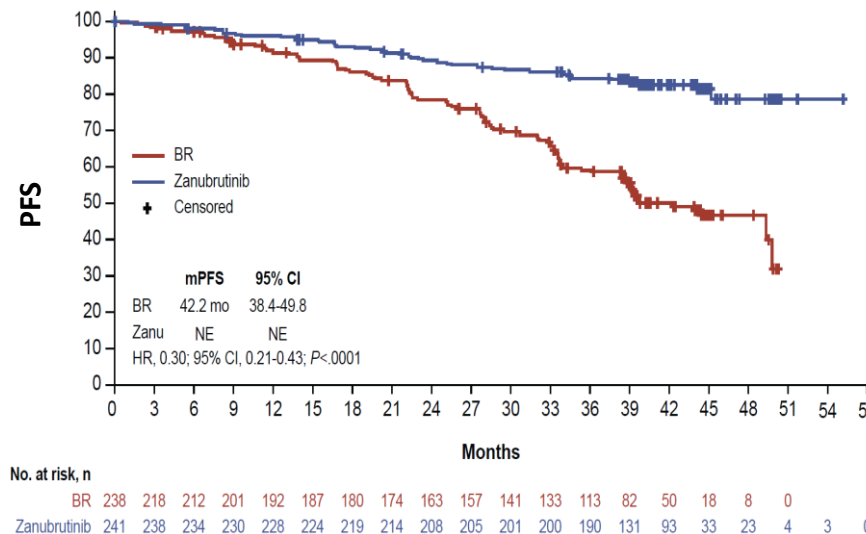
Median FU: 70 months



SEQUOIA²

Zanubrutinib vs. BR

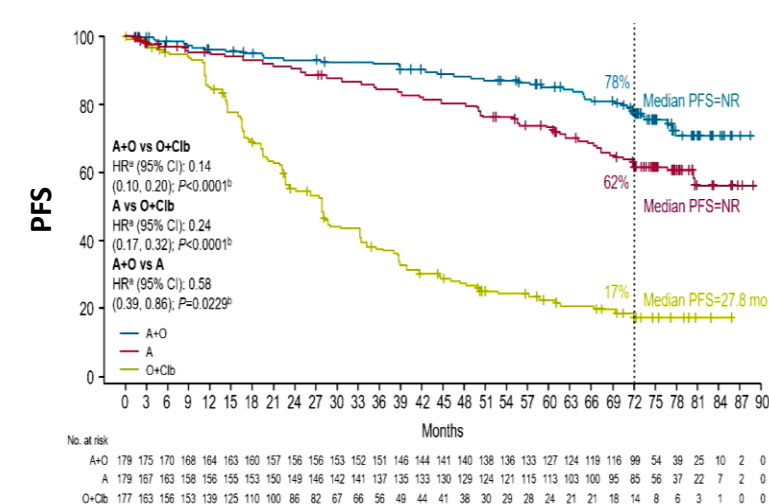
Median FU: 43.7 months



ELEVATE TN³

Acala vs. Acala-Obi vs. Clb-Obi

Median FU: 74.5 months

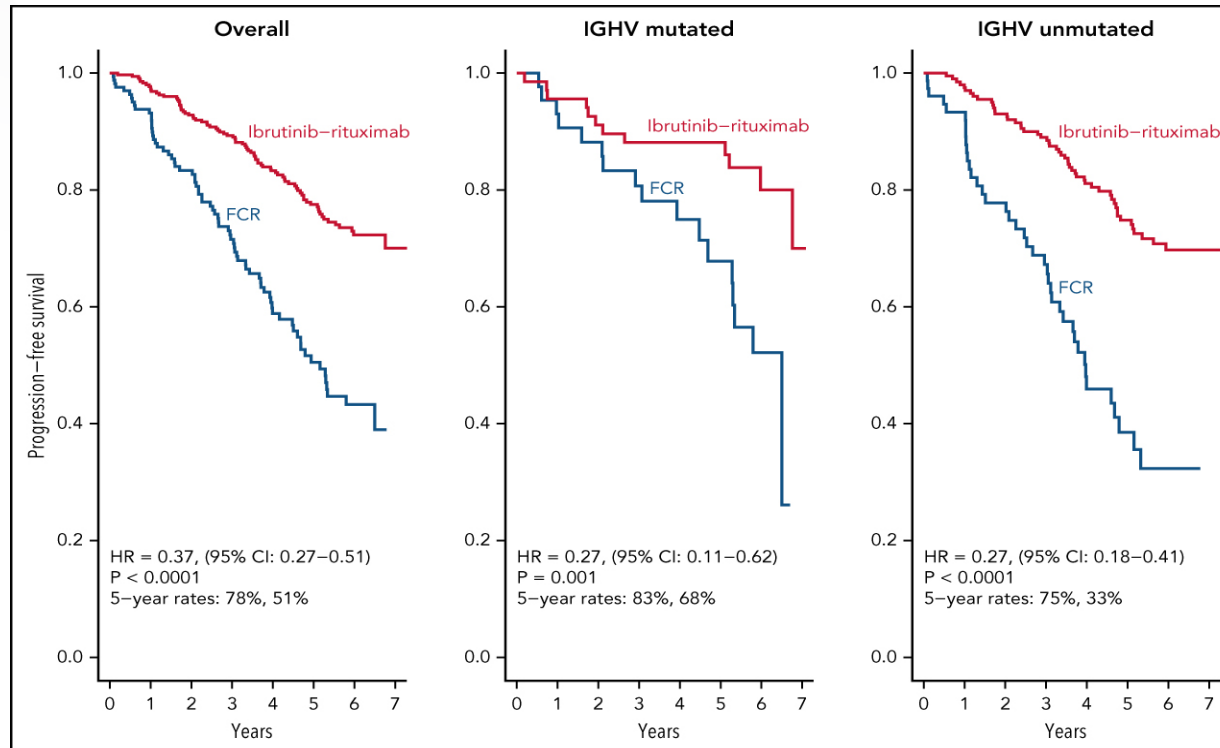


This slide includes data from different clinical trials. These data are meant for demonstration purposes only and are not meant for cross-trial comparison purposes.

A/Acala, acalabrutinib; BR, bendamustine-rituximab; cBTKi, covalent Bruton's tyrosine kinase inhibitor; CI, confidence interval; Clb, chlorambucil; ECOG, Eastern Cooperative Oncology Group; FCR, fludarabine-cyclophosphamide-rituximab; FU, follow-up; HR, hazard ratio; IR, ibrutinib-rituximab; (m)PFS, (median) progression-free survival; NE, not evaluable; NR, not reached; O/Obi, Obinutuzumab; Zanu, zanubrutinib.

1. Shanafelt TD *et al.* *Blood* 2022; 140 (2): 112–120. 2. Opat S *et al.* Poster presented at EHA2023; Frankfurt, Germany, June 8–11, 2023 (Abstract P265). 3. Sharman JP *et al.* Oral presentation 636 at ASH 2023; San Diego, CA, USA, December 9–12, 2023.

ECOG 1912 – FUP 6y - FCR X Chemofree treatment



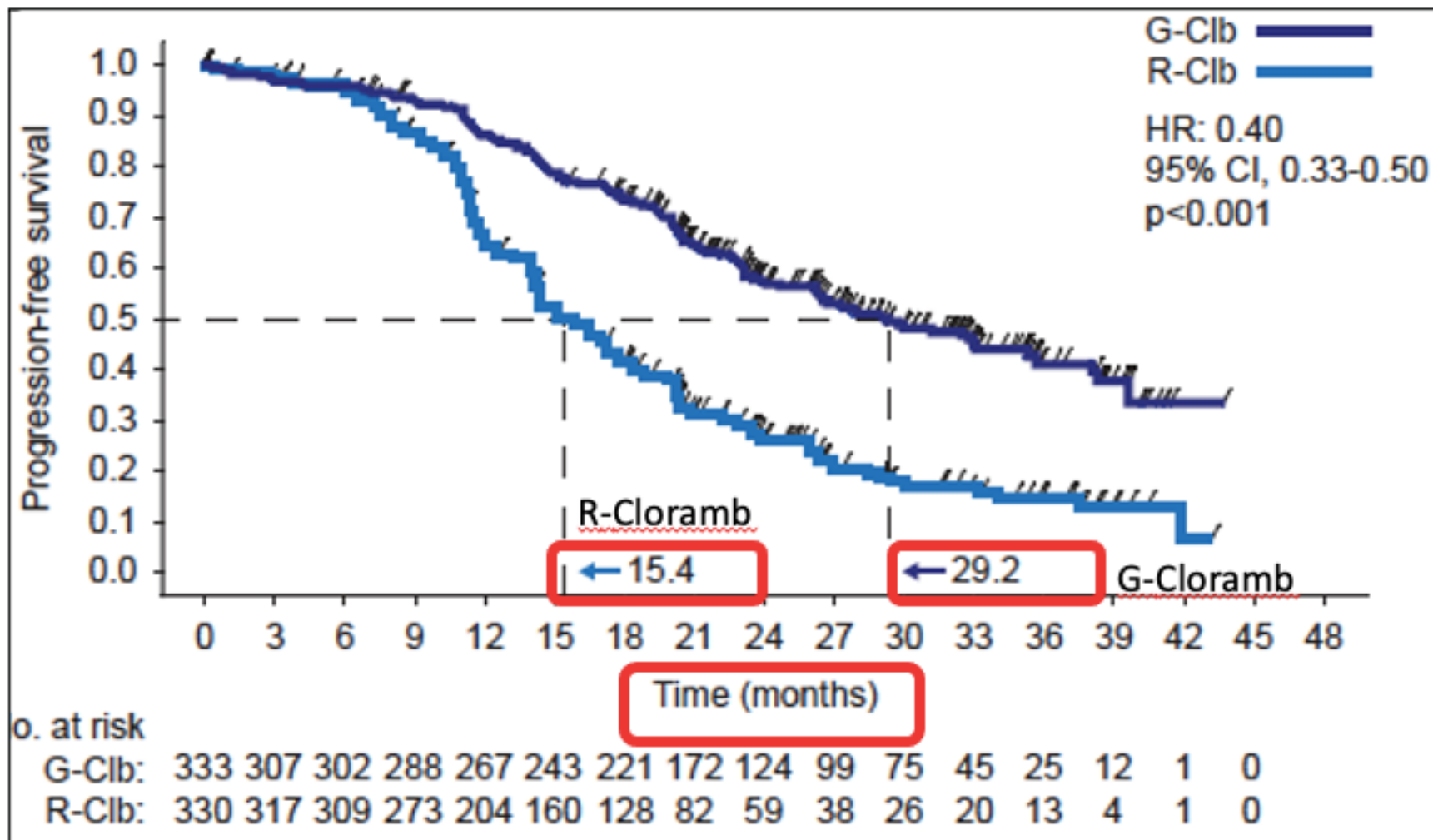
Fludarabine:

- Acute and long-term toxicity
- Infections
- Cytopenias
- Bone marrow hypocellularity, risk of MDS and AML of 6–10%*

Awan & Byrd. Clin Cancer Res. 2014;20(23):5869

Overall	IGHV mutated	IGHV unmutated
HR = 0.37, (95% CI: 0.27–0.51) P < 0.0001 5-year rates: 78%, 51%	HR = 0.27, (95% CI: 0.11–0.62) P = 0.001 5-year rates: 83%, 68%	HR = 0.27, (95% CI: 0.18–0.41) P < 0.0001 5-year rates: 75%, 33%

CLL11 – Chloramb x R-Chl x G-Chl



Chemofree fixed duration therapies – 1L CLL

(off label)*

1. **CLL14** : Venetoclax + obinutuzumab (VenG) vs obinutuzumab + chlorambucil (G-Chl)
2. **CAPTIVATE**: Ibrutinib + venetoclax (I+V)
3. **GLOW** (Ph2): Ibrutinib + venetoclax (I+V) vs obinutuzumab + chlorambucil (G-Chl)
4. **AMPLIFY***: Acalabrutinib + venetoclax + obinutuzumab (AVO) vs

Acala-venetoclax (AV) vs FCR/BR

1. **BGB-11417-204***(Ph2): Zanubrutinib + sonrotoclax (15 Cycles) vs Zanubrutinib (cont)

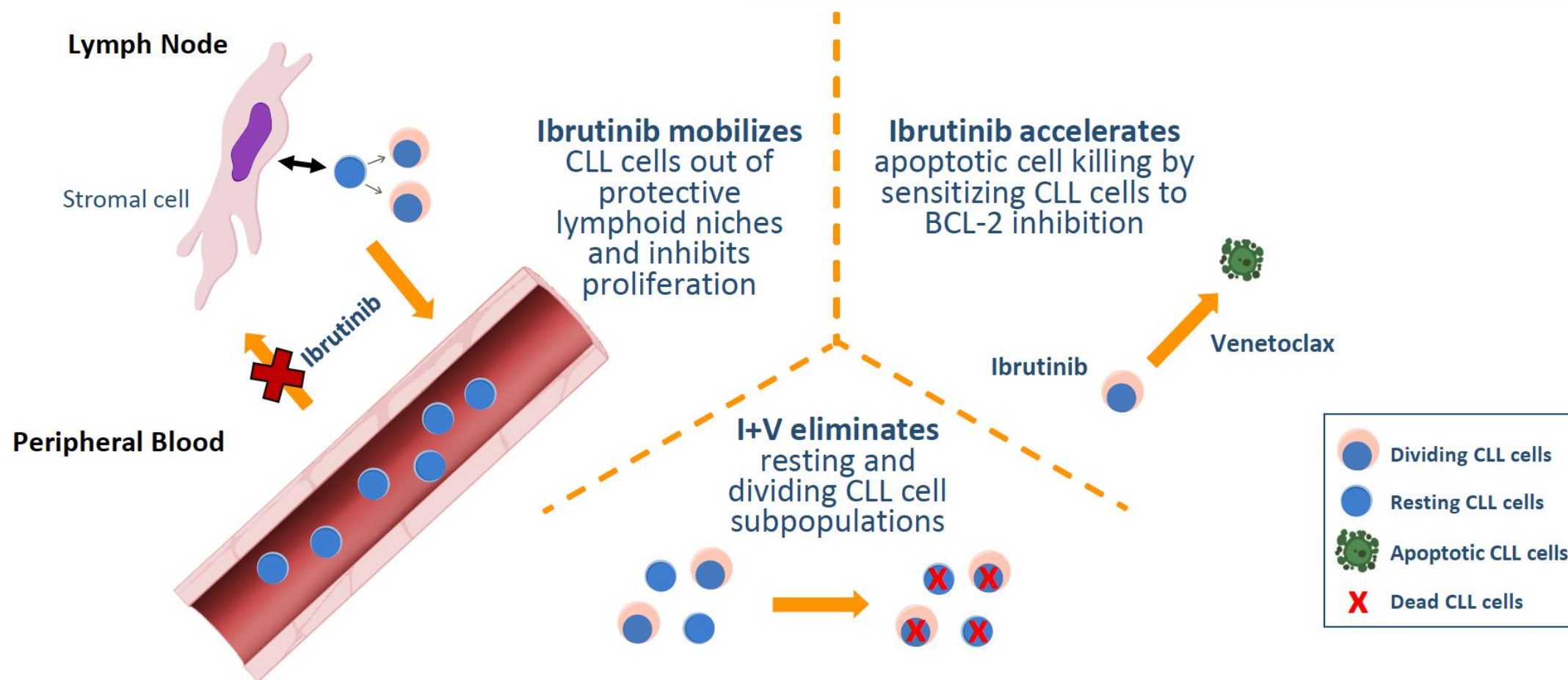
AMPLIFY: Acalabrutinib-venetoclax +/- obinutuzumab



EMA: 25 APR 2025 – recommendation of approval by the Committee for Medicinal Products for Human Use (CHMP)

<https://www.ema.europa.eu/en/medicines/human/variation/calquence-1>, access 01 MAY 2025

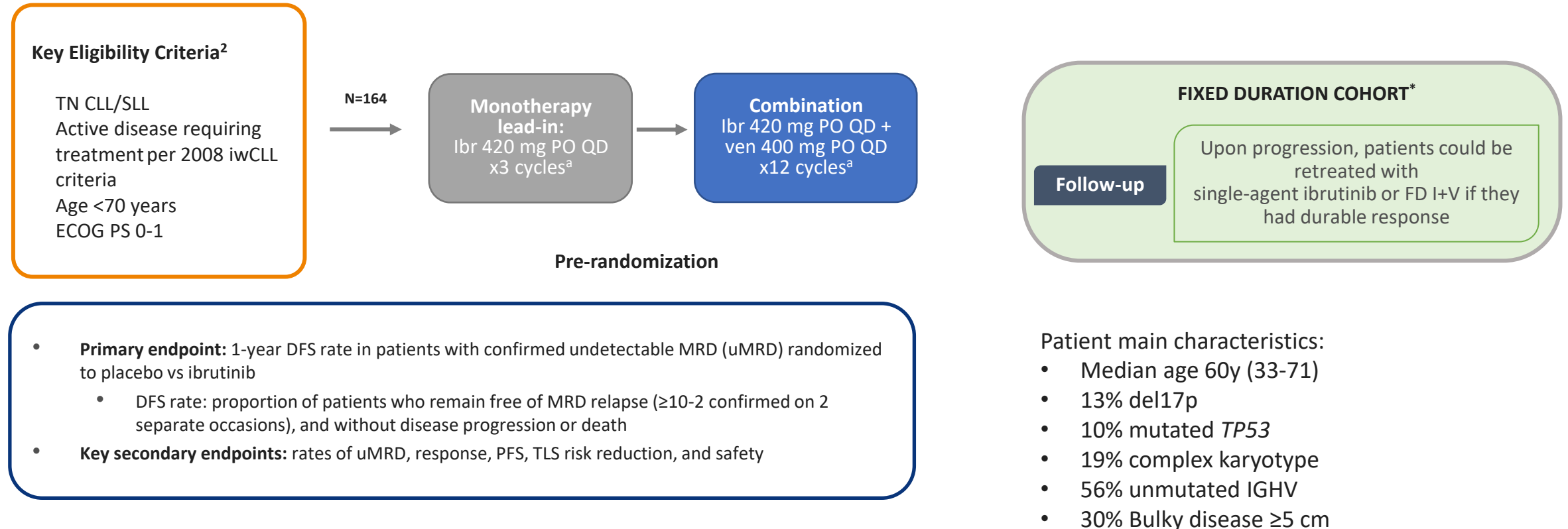
Ibrutinib + Venetoclax: Distinct and Complementary Modes of Action That Work Synergistically¹⁻⁹



CAPTIVATE: Fixed duration cohort¹

Phase 2 trial in TN CLL

Double-blind, placebo-controlled trial of ibrutinib vs placebo



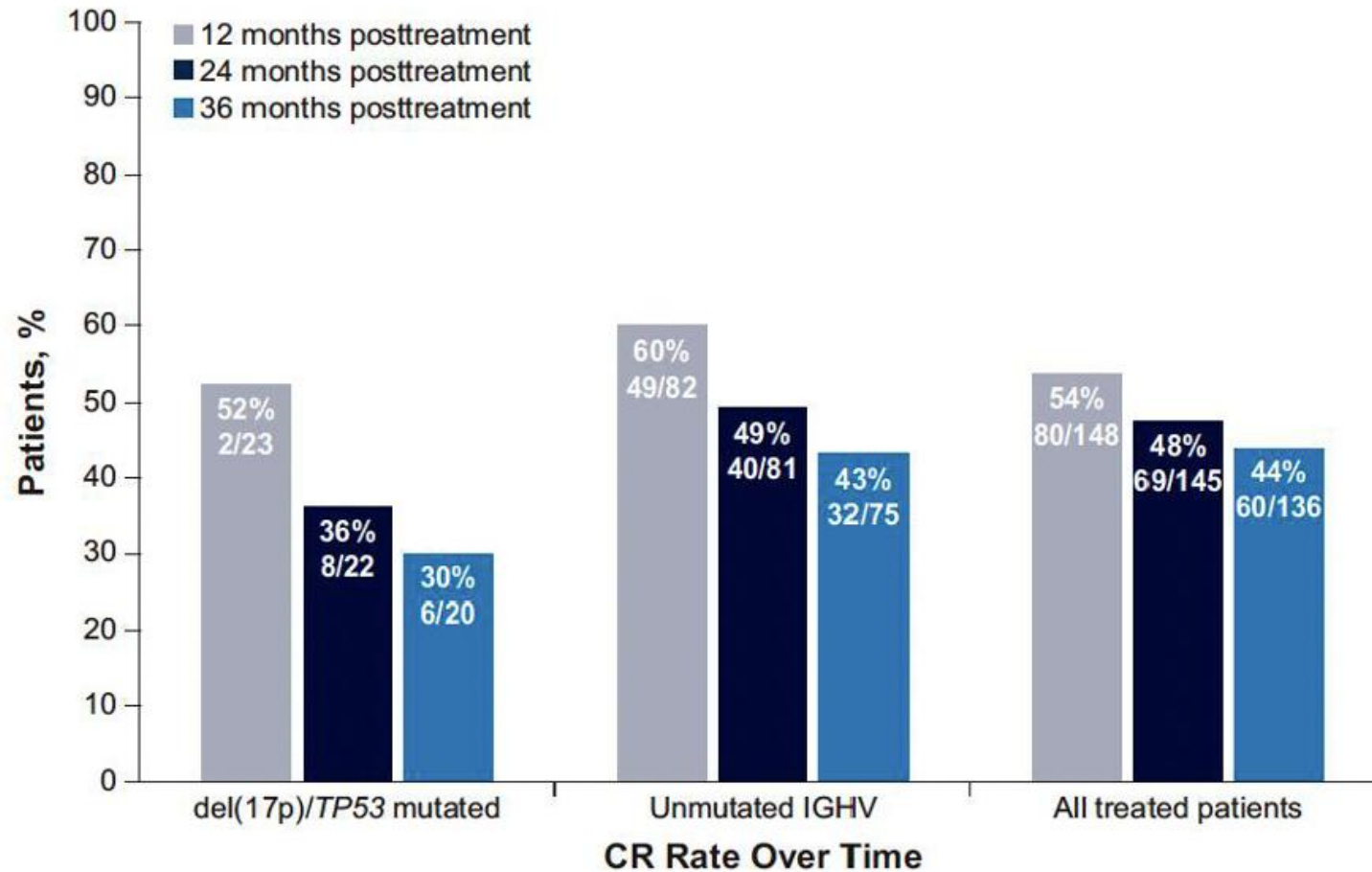
^a1 cycle = 28 days; patients may have received 1 additional cycle while awaiting confirmation of undetectable MRD for randomization. ^bStratified by IGHV mutation status.

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

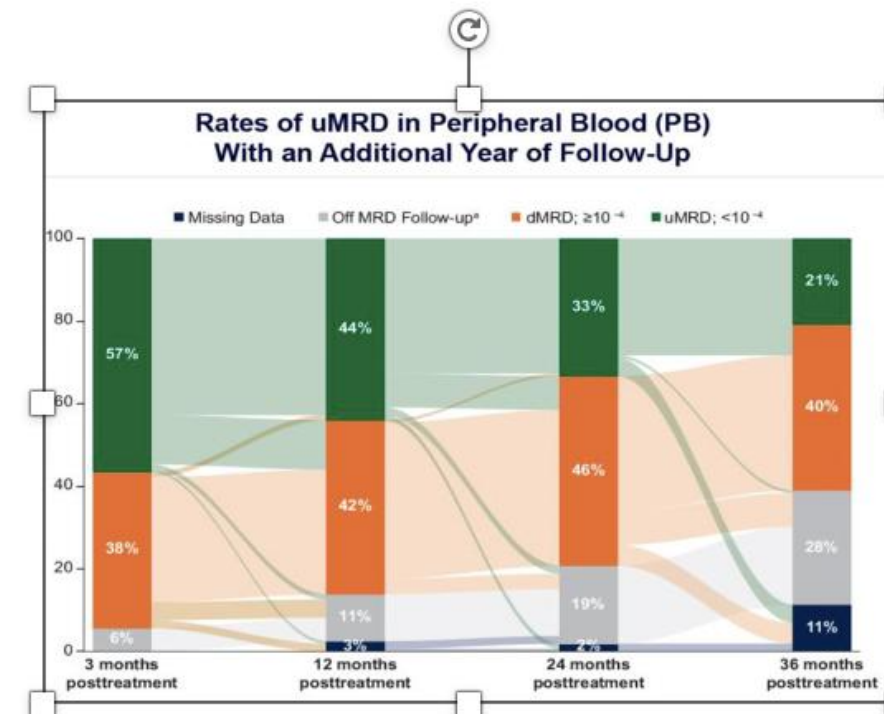
^dDefined as having detectable MRD or undetectable MRD not confirmed serially or not confirmed in both PB and BM.

1. Siddiqi T, et al. EHA 2020. Oral Presentation. Abstract S158. 2. Wierda W, et al. ASH 2020. Oral Presentation 133.

CAPTIVATE – FD COHORT – FUP 4 years

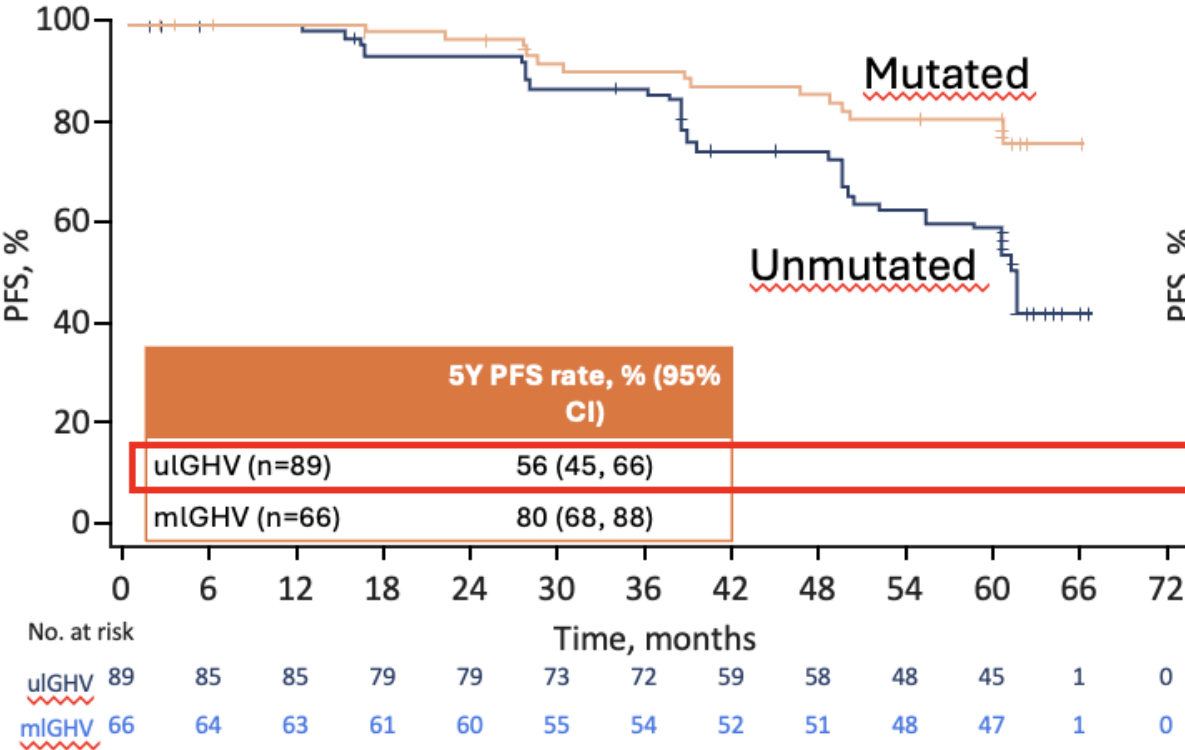


EHA 2023 Ghia P. et al. P617

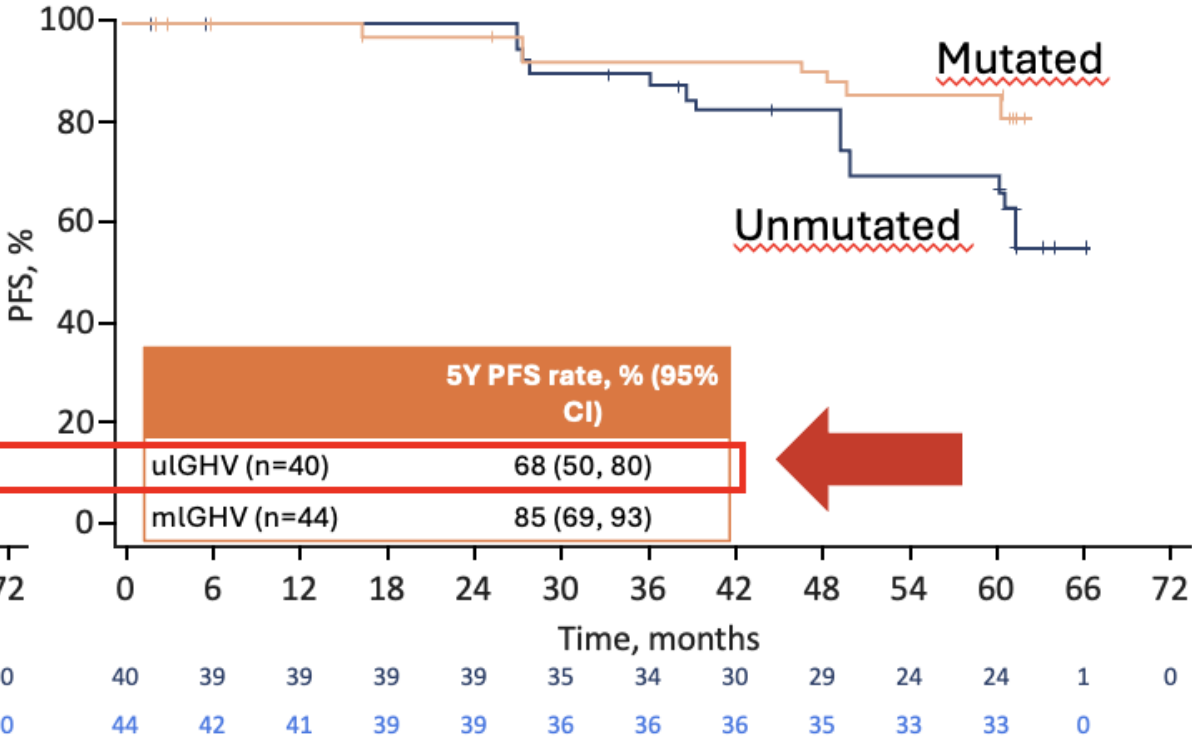


CAPTIVATE: Outcomes in high-risk subgroups – 5.5 years Follow up

PFS by IGHV mutation status
(All patients)



PFS by IGHV mutation status
(excluding patients with del(17p), TP53m, or CK)



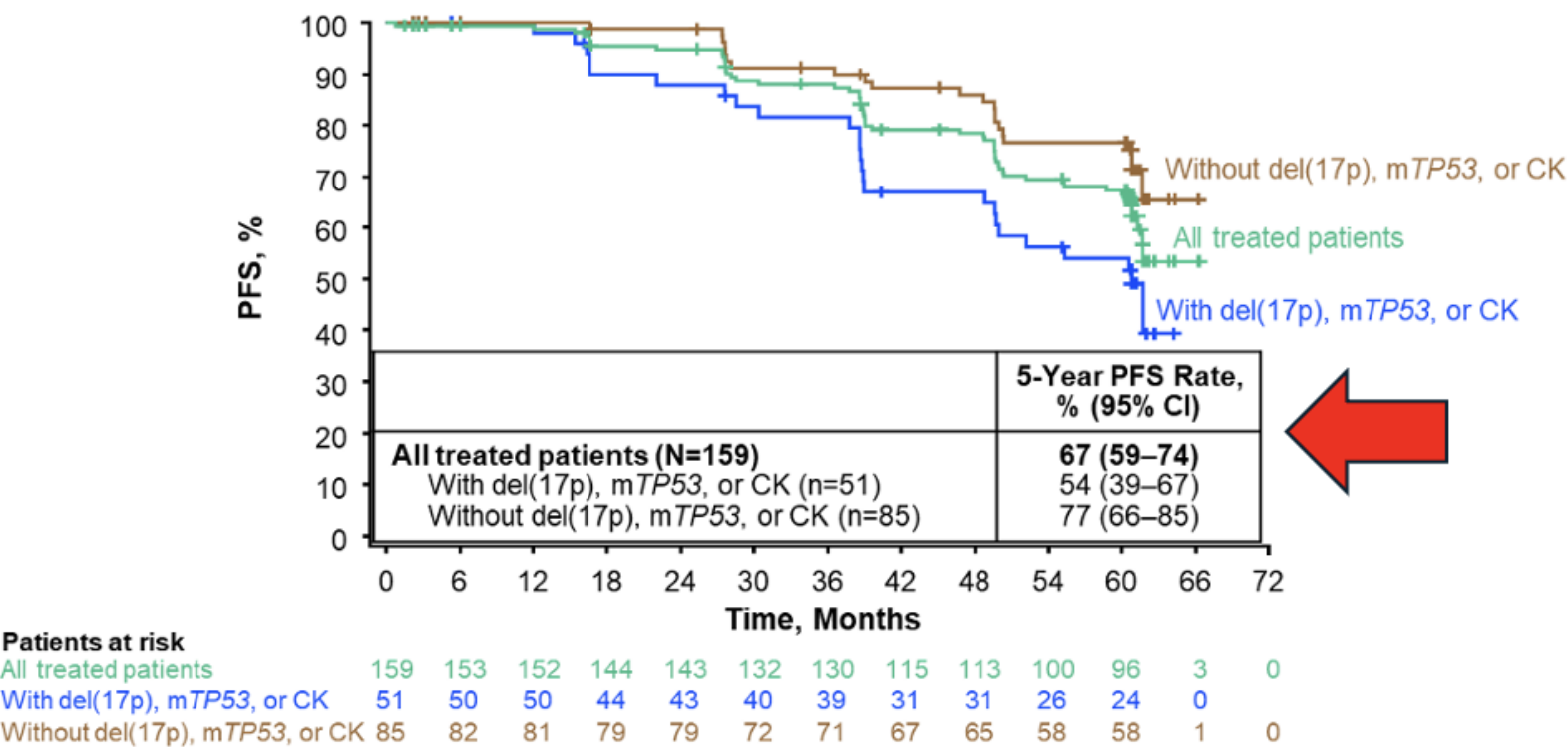
CAPTIVATE:

Outcomes in high-risk subgroups – 5.5 years Follow up

Results: FD Cohort: PFS Rates

Median time on study: 61.2 months (range, 0.8–66.3)
Overall median PFS was not reached with up to 5.5 years of follow-up

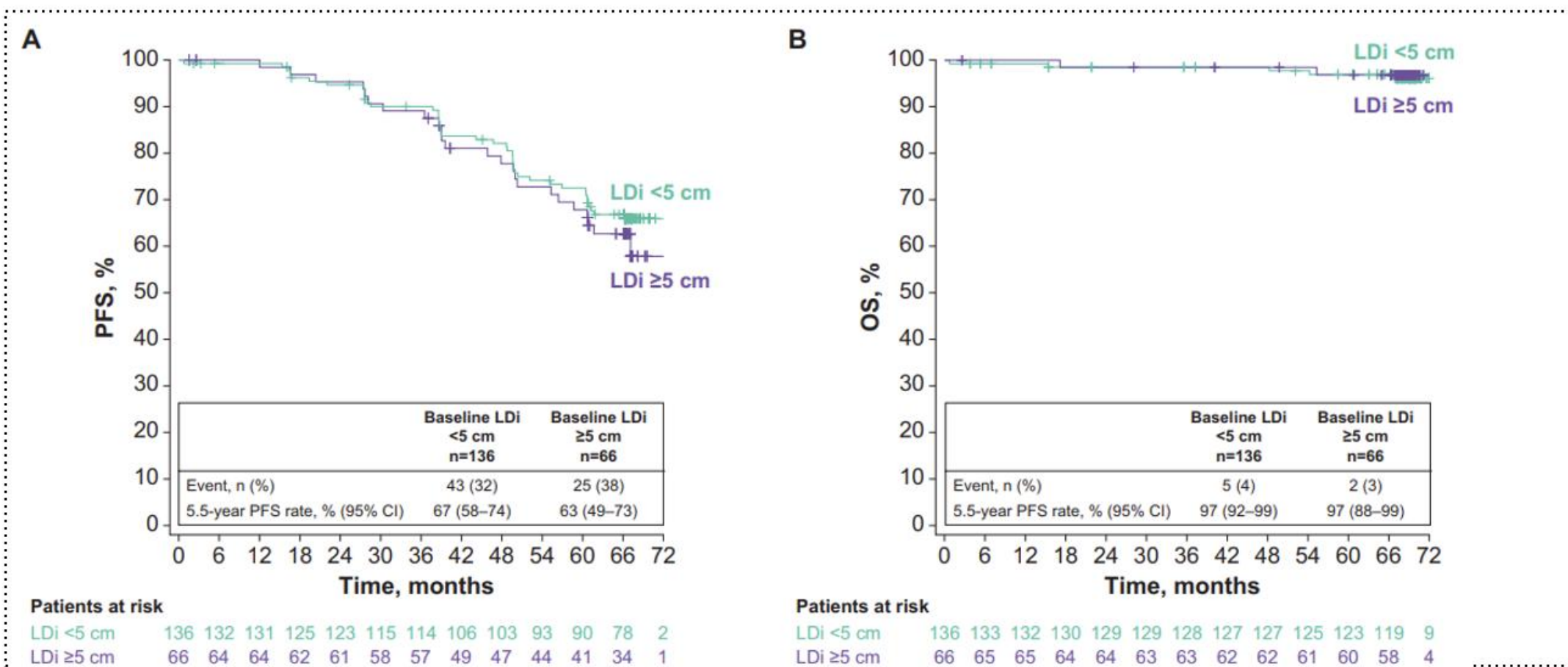
PFS in All Treated Patients and by del(17p), mTP53, or CK Status



5Y PFS rate, % (95% CI)	Present	Absent
del17p/ <u>mut</u> TP53	41 (21, 59)	73 (64, 80)
Complex karyotype	57 (37, 72)	73 (61, 80)

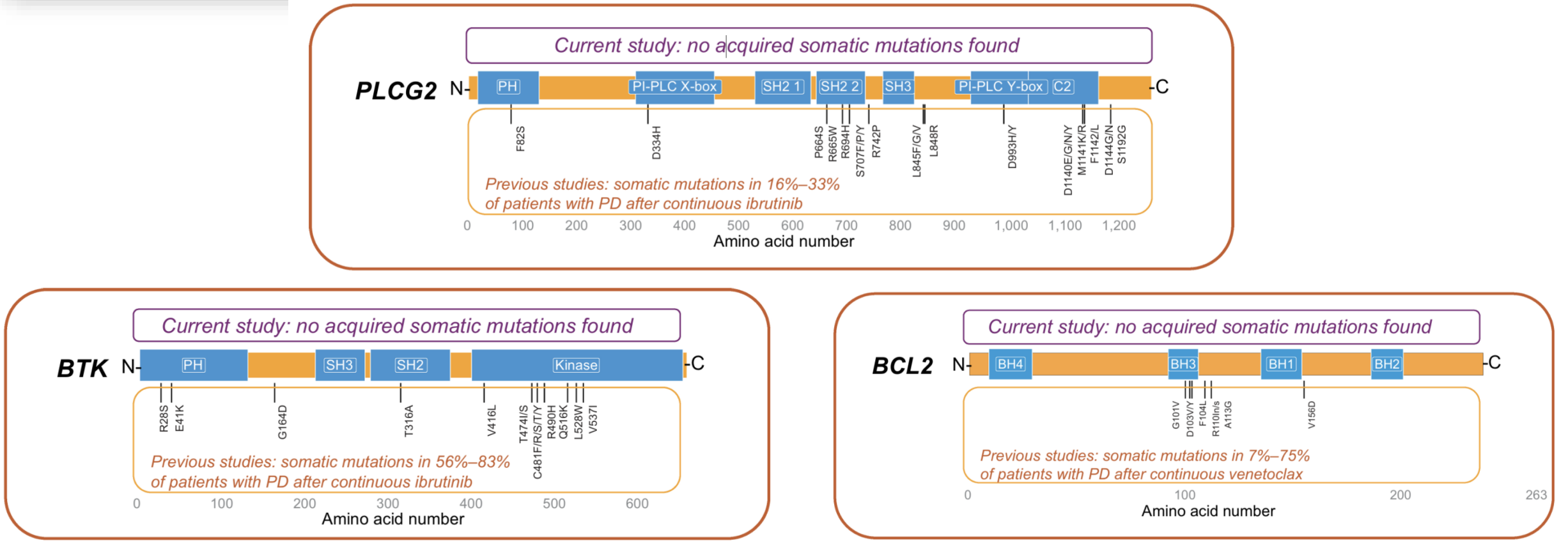
CAPTIVATE:

PFS and OS in Bulky Lymphadenopathy at baseline



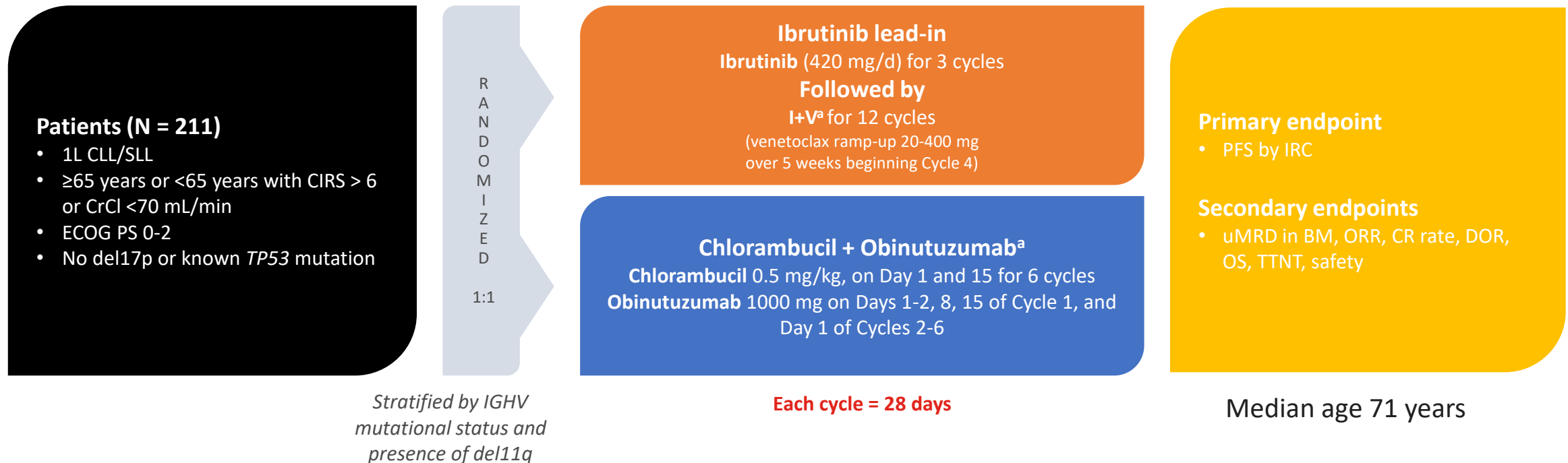
Absence of *BTK*, *BCL2*, and *PLCG2* Mutations in Chronic Lymphocytic Leukemia Relapsing after First-Line Treatment with Fixed-Duration Ibrutinib plus Venetoclax

Nitin Jain¹, Lisa J. Croner^{2,3}, John N. Allan⁴, Tanya Siddiqi⁵, Alessandra Tedeschi⁶, Xavier C. Badoux⁷, Karl Eckert³, Leo W.K. Cheung^{2,3}, Anwesha Mukherjee³, James P. Dean³, Edith Szafer-Glusman^{2,3}, and John F. Seymour^{8,9}



GLOW/CLL3011: Phase 3 study design

- I+V vs chlorambucil + obinutuzumab for elderly/unfit patients with previously untreated CLL/SLL



Objective: To evaluate 1L, FD I+V vs Clb+O in elderly/unfit patients without del17p mutation

GLOW: Study Population Was Unfit, Median Age 71 Years

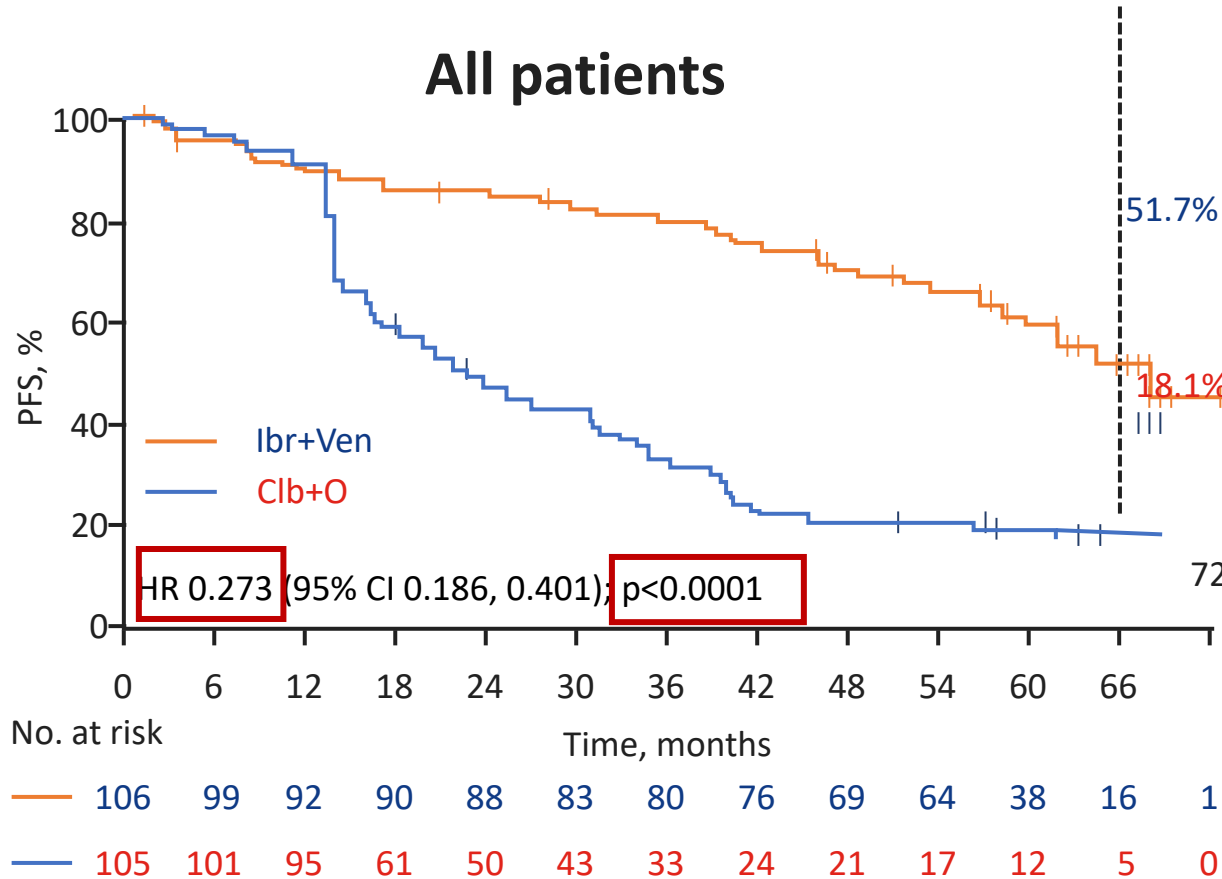
CHARACTERISTIC	I+V (N = 106)	Clb+O (N = 105)
Age, median (range), years	71.0 (47-93)	71.0 (57-88)
≥ 75 years, %	33.0	35.2
Male, %	55.7	60.0
ECOG PS 1-2, %	67.0	62.9
CIRS score, median (IQR)	9 (6-12)	8 (5-10)
> 6, %	69.8	58.1
CrCl, median (range) mL/min	66.5 (34.0-168.1)	63.2 (32.3-180.9)
Rai stage III-IV, %	57.3	52.5
Bulky disease ≥ 5 cm, %	39.0	36.2
Elevated LDH, %	33.0	48.6
Mutated IGHV, ^a %	25.5	25.7
Unmutated IGHV, ^a %	51.9	51.4
Del11q, %	18.9	17.1
TP53 mutation, %	6.6	1.9

Kater et al. EHA 2021, Oral LB1902

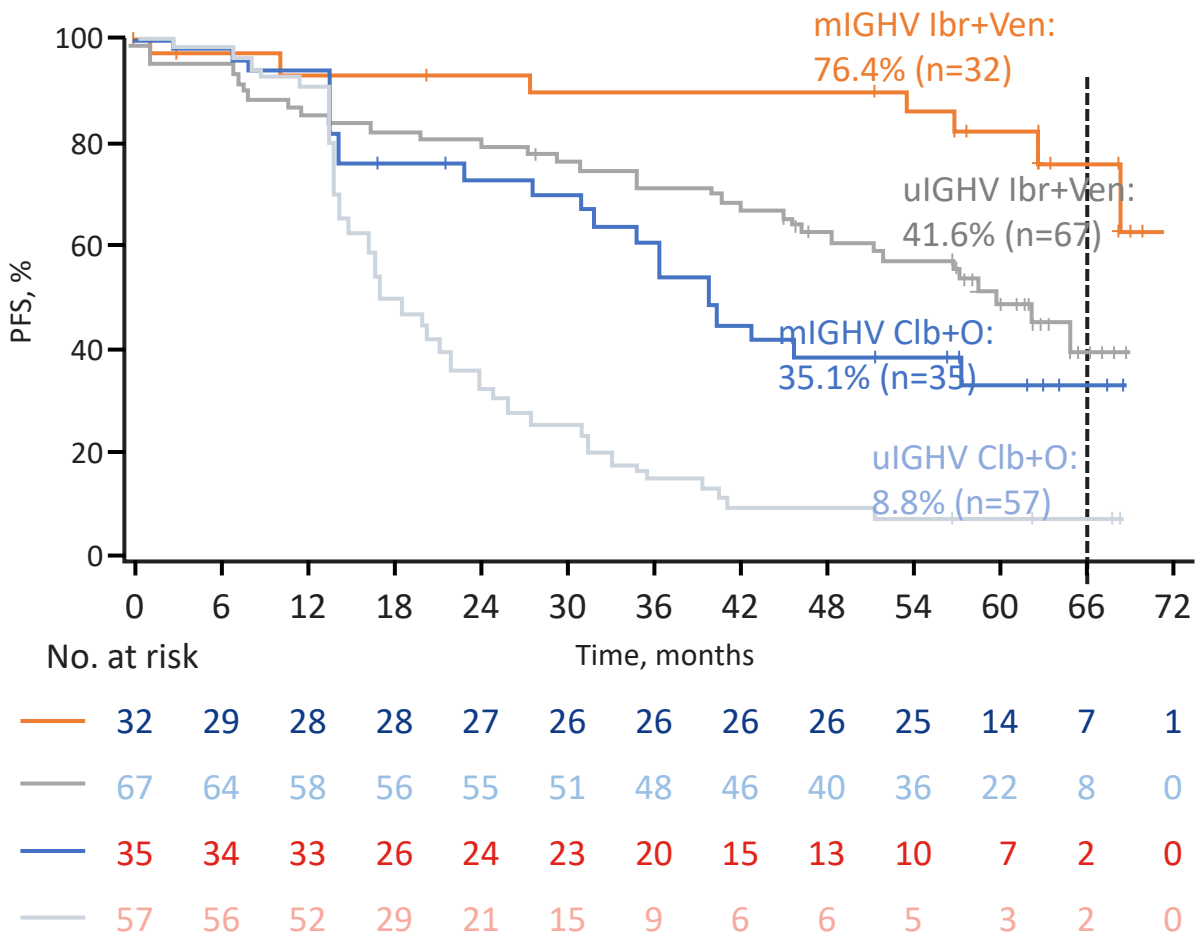
Kater AP, et al. *NEJM Evid* 2022; 1 (7)

GLOW : Progression-free survival

All patients



According to IGHV status

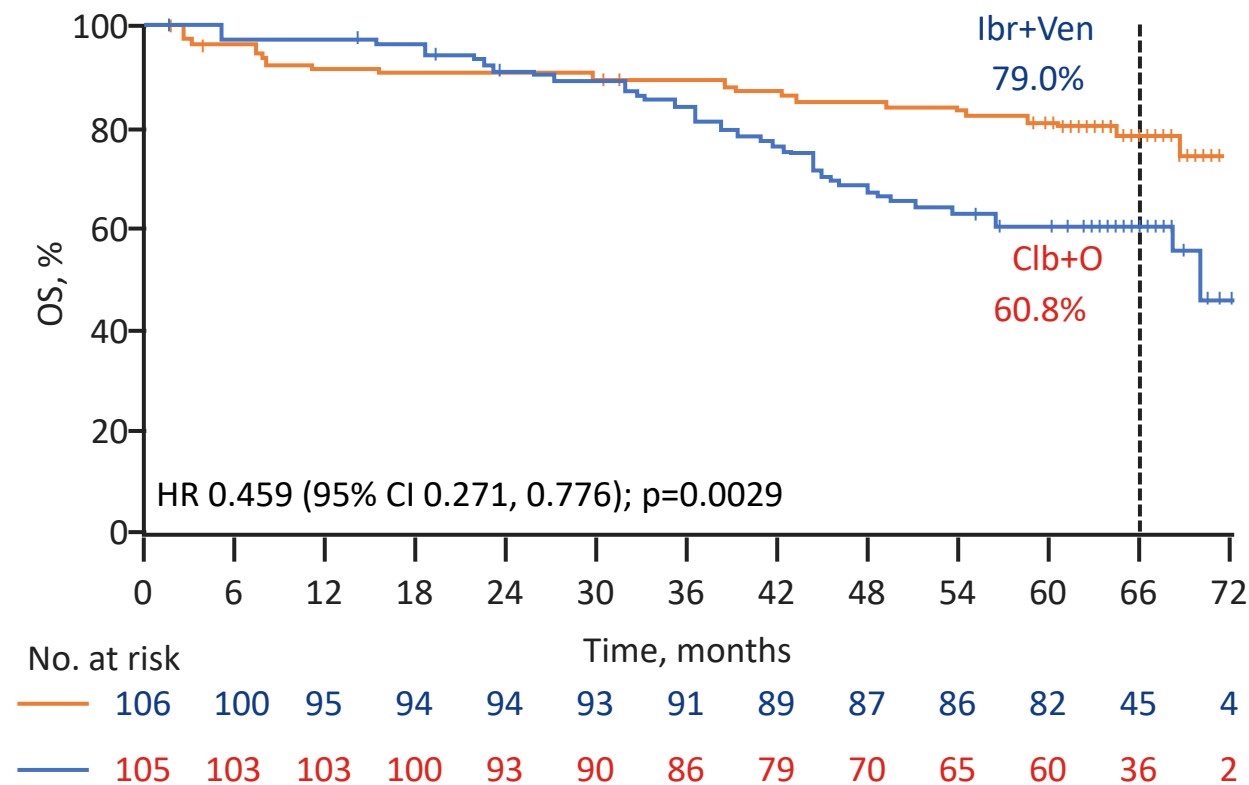


I+V vs G-Clb

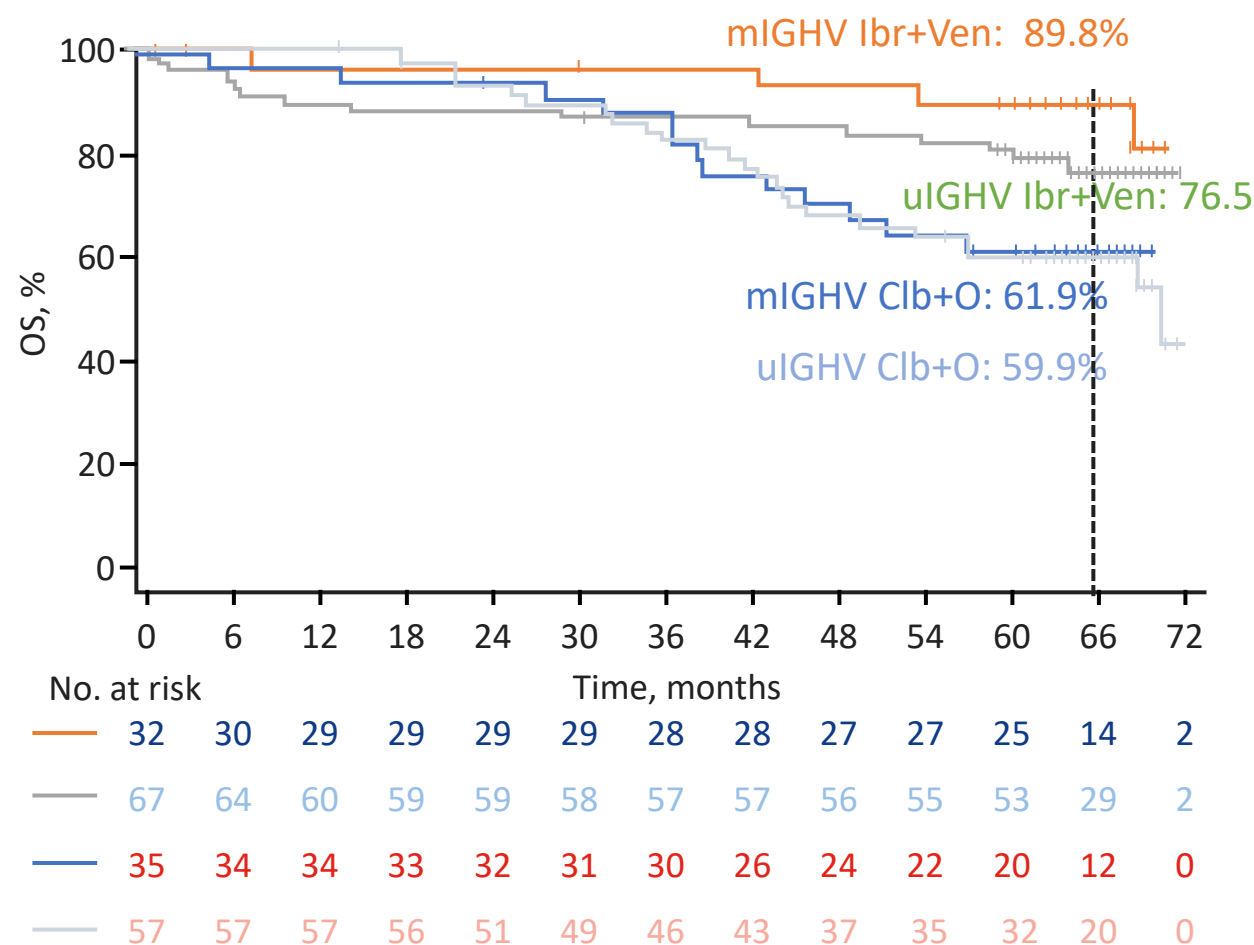
uIGHV: HR: 0.273 (95% CI 0.171, 0.434); p<0.0001
mIGHV: HR: 0.246 (95% CI 0.097, 0.619); p=0.0014

GLOW: Overall survival

All patients

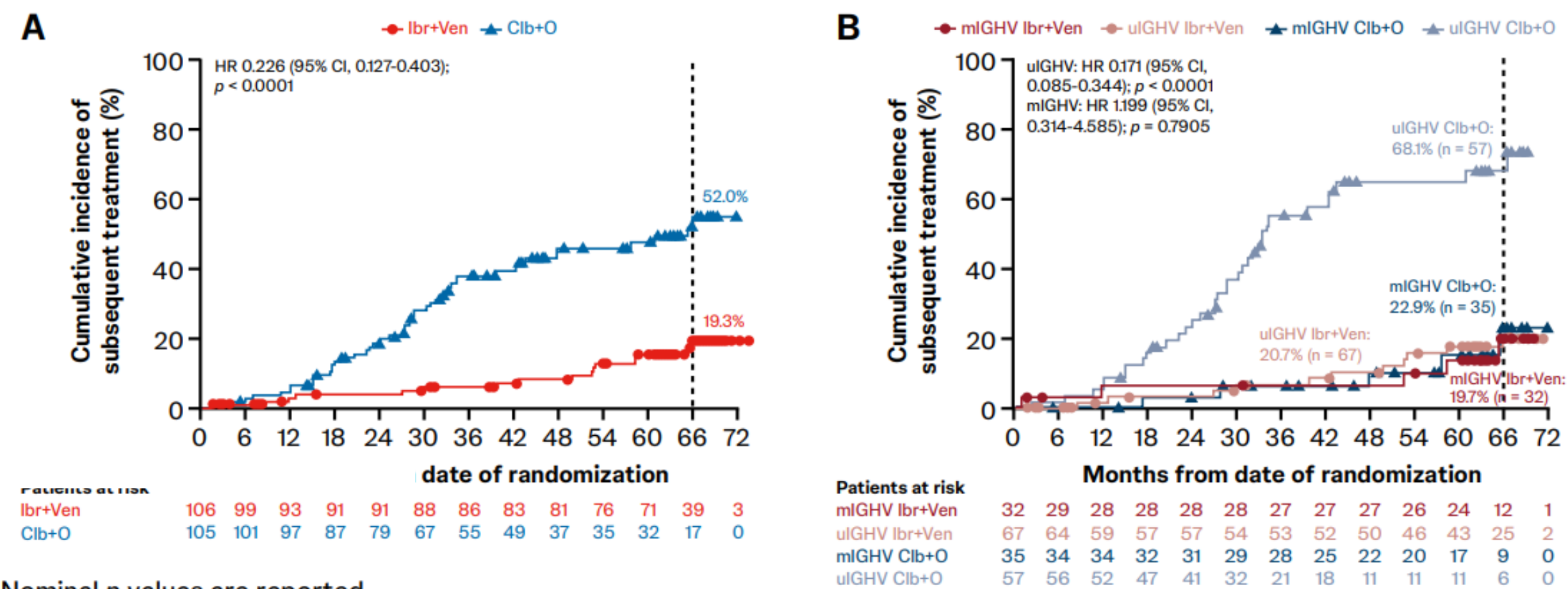


According to IGHV status



GLOW : Time to next treatment

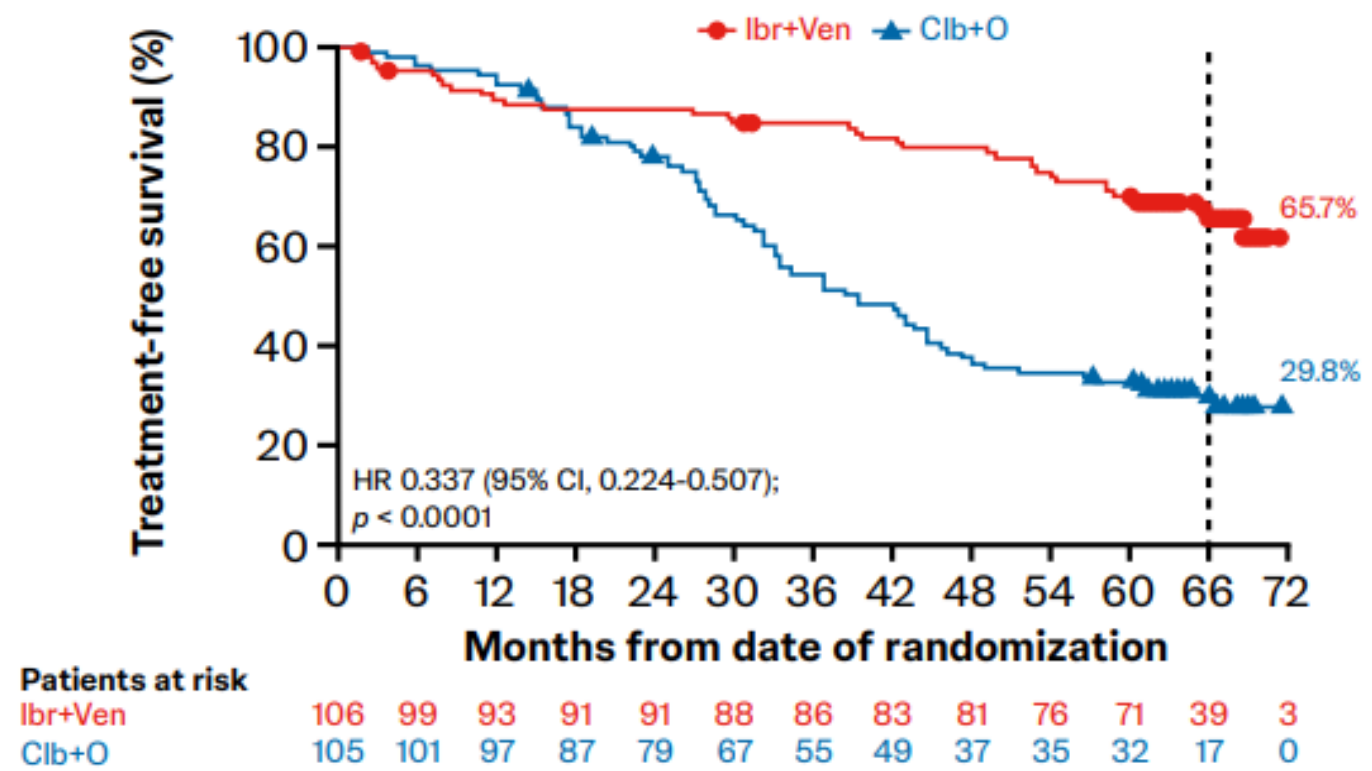
Figure 3: TTNT for all patients (A) and patients by IGHV status (B)



Nominal p values are reported.

GLOW : Treatment free survival

Figure 4: Treatment-free survival for all patients



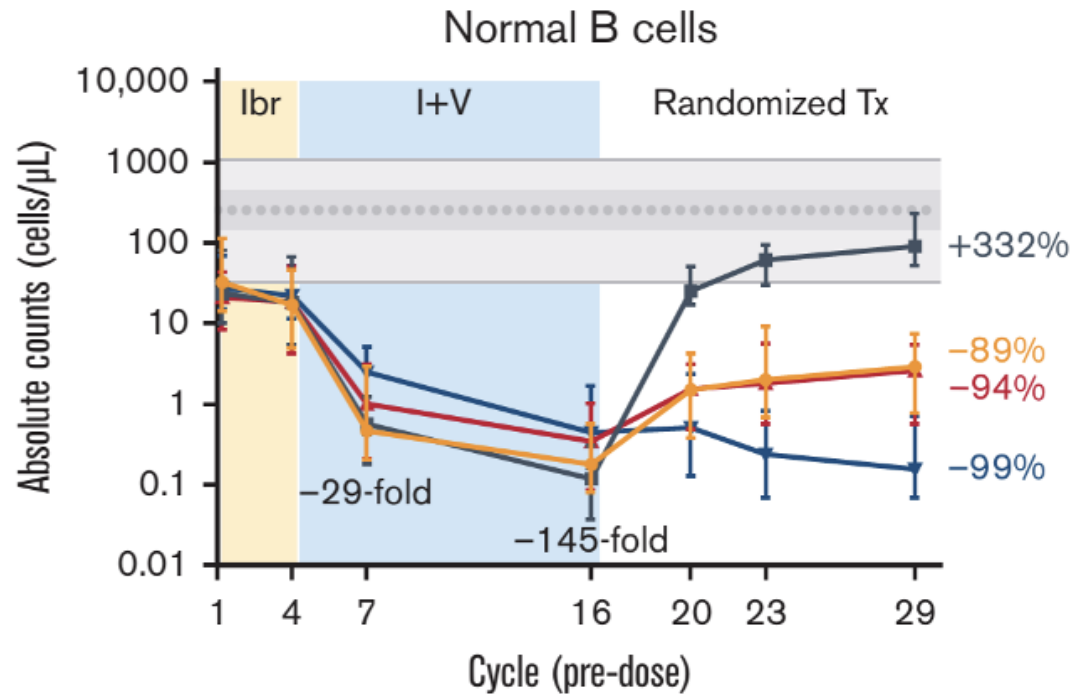
GLOW: Summary of safety and TLS risk reduction

Grade ≥3 AEs occurring in ≥5% of patients	I+V (N=106)	Clb+O (N=105)
Median exposure, mo (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

- 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 the 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%

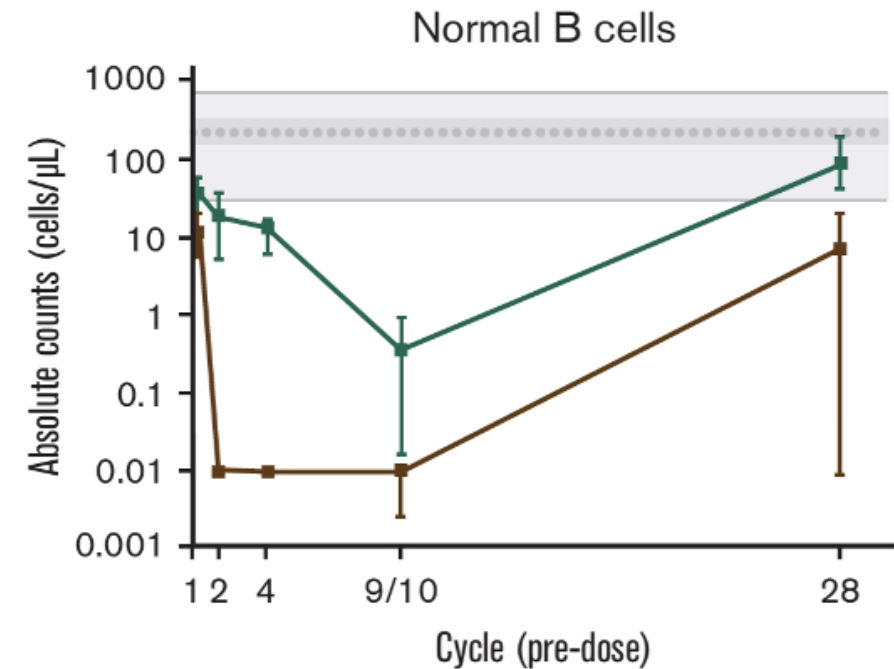
Immune restoration and I+V

CAPTIVATE TRIAL



- Healthy Donors ($n = 20$): median, IQR, and range
- Confirmed uMRD; Placebo ($n = 20$)
- Confirmed uMRD; lbr ($n = 20$)
- uMRD Not Confirmed; lbr ($n = 20$)
- uMRD Not Confirmed; I+V ($n = 19$)

GLOW TRIAL



- Healthy Donors ($n = 20$):
- GLOW; I+V ($n = 12$)
- GLOW; C+O ($n = 12$)

Janssen Research & Development*

Non-interventional Study Protocol

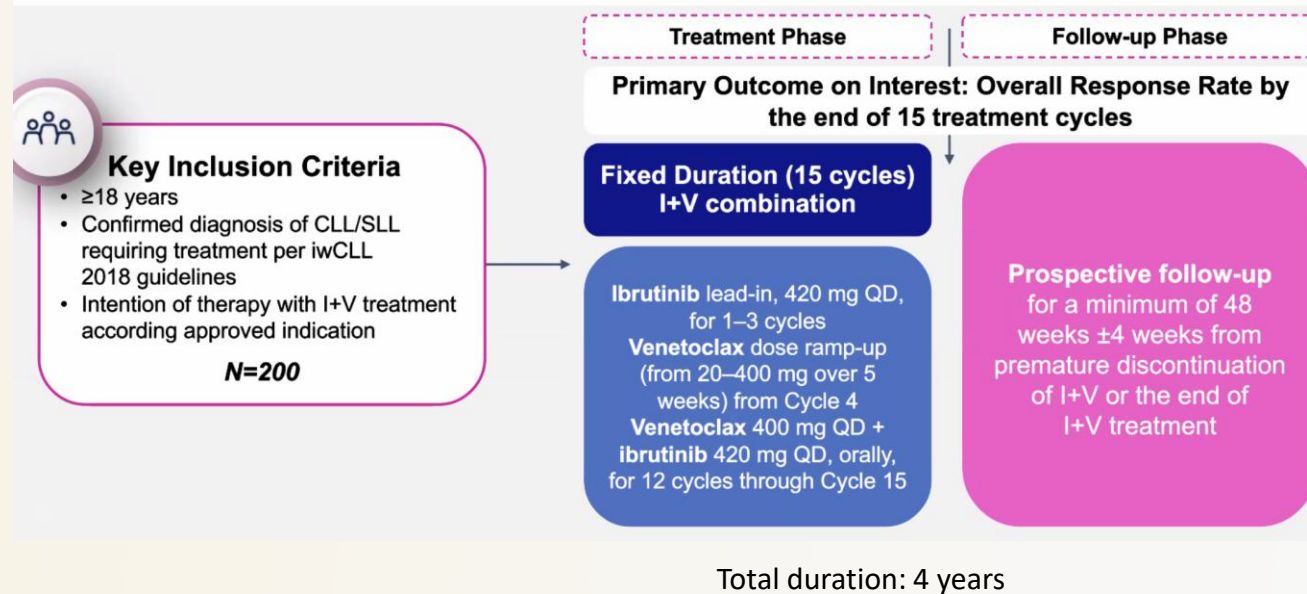
Prospective Cohort Study With Fixed-Duration Ibrutinib + Venetoclax (I+V) First-Line Treatment in Patients with Chronic Lymphocytic Leukemia in a Real-World Setting

REALITY-WW

Protocol 54179060CLL4032

REALITY WW: Prospective Cohort Study With FD I+V First-Line Treatment in Patients with CLL in a Real-World Setting

15th HAIMATUS 32



REALITY-WW Steering Committee

15th HAIMATUS 32



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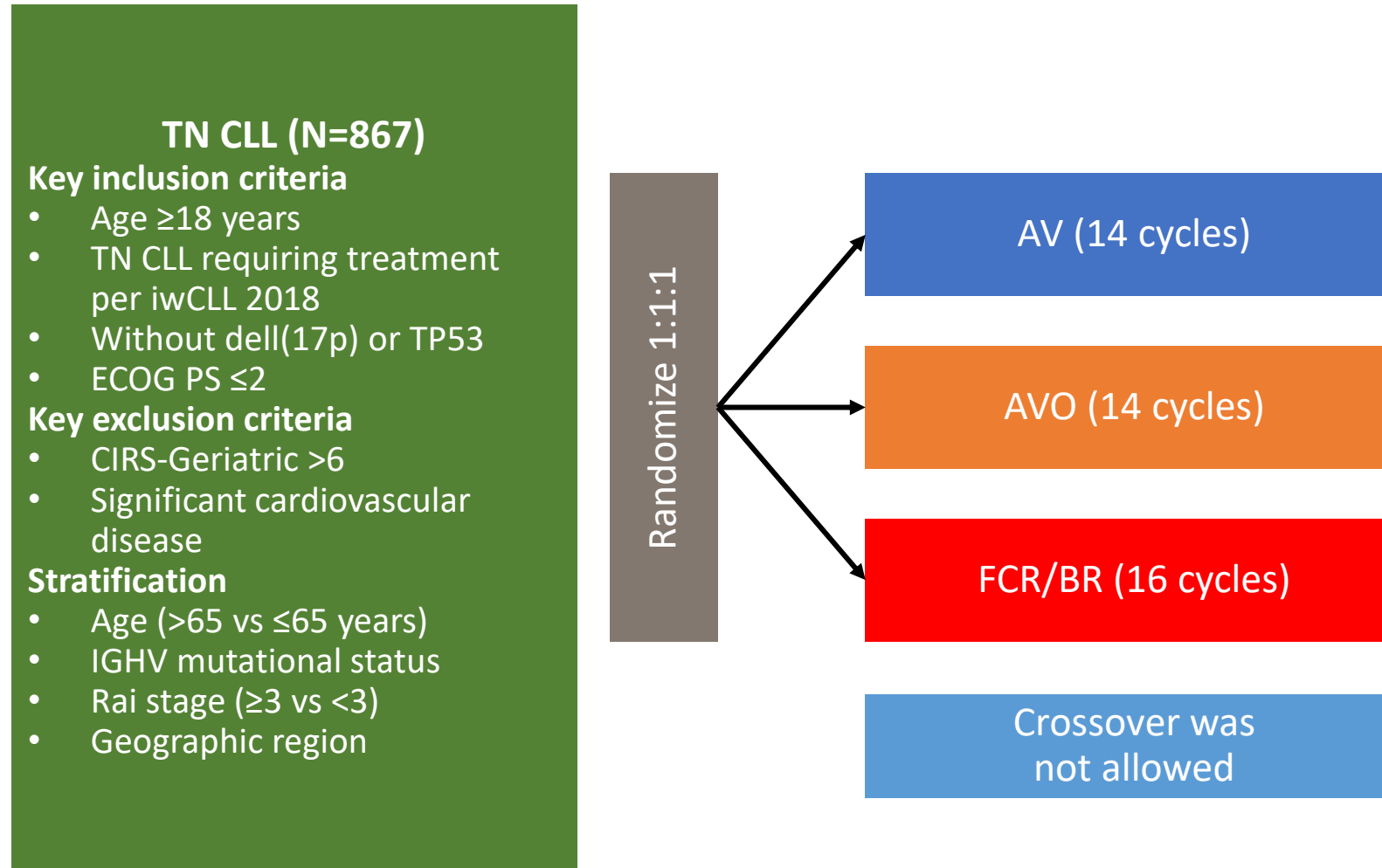
Paolo Ghia,
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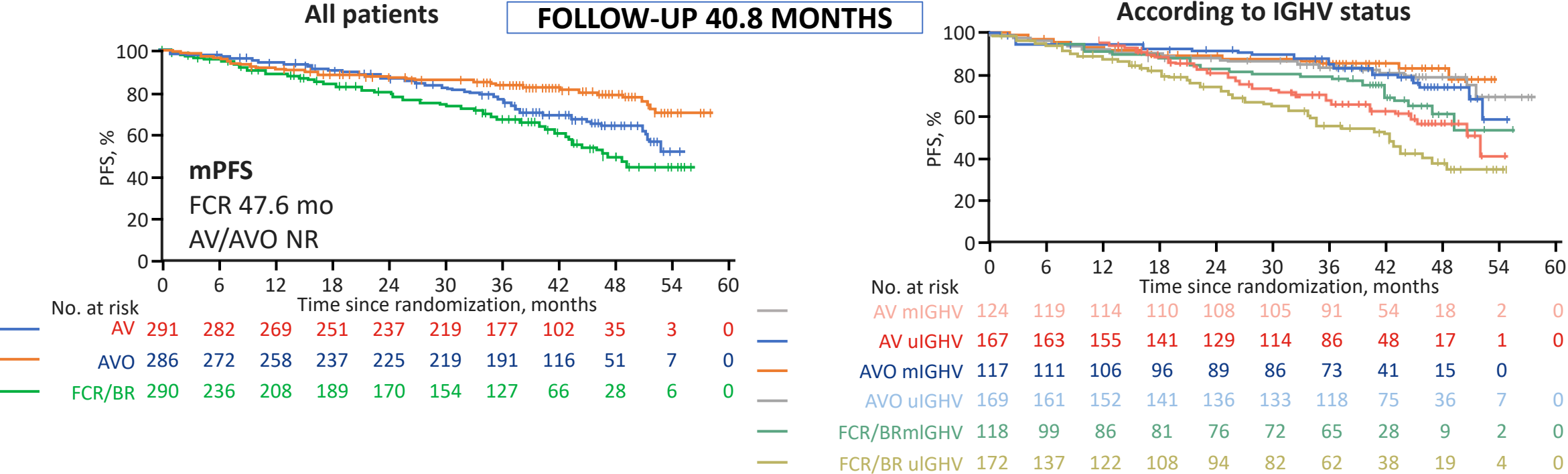
Ahmad Absi,
MD
National Guard Health
Affairs,
Saudi Arabia



AMPLIFY: Fixed-duration acalabrutinib combinations in TN CLL



AMPLIFY: PFS by blinded independent central review



	PFS -HR for PD or death (95% CI)	p-value
AV vs FCR/BR	0.65 (0.49, 0.87)	0.004
AVO vs FCR/BR	-	<0.001

	N	Events, n	mPFS, mo	36-mo PFS rate, %
AV mIGHV	124	28	NC	86.0
AV uIGHV	167	61	51.5	68.9
AVO mIGHV	117	20	NC	83.6
AVO uIGHV	169	36	NC	82.8
FCR/BR mIGHV	118	28	NC	79.9
FCR/BR uIGHV	172	67	43.3	56.8

	HR for PD or death (95% CI)	p-value
AV vs FCR/BR mIGHV	0.67 (0.39, 1.14)	
AV vs FCR/BR uIGHV	0.69 (0.48, 0.97)	
AVO vs FCR/BR mIGHV	0.58 (0.32, 1.02)	
AVO vs FCR/BR uIGHV	-	<0.001

AMPLIFY: Adverse events

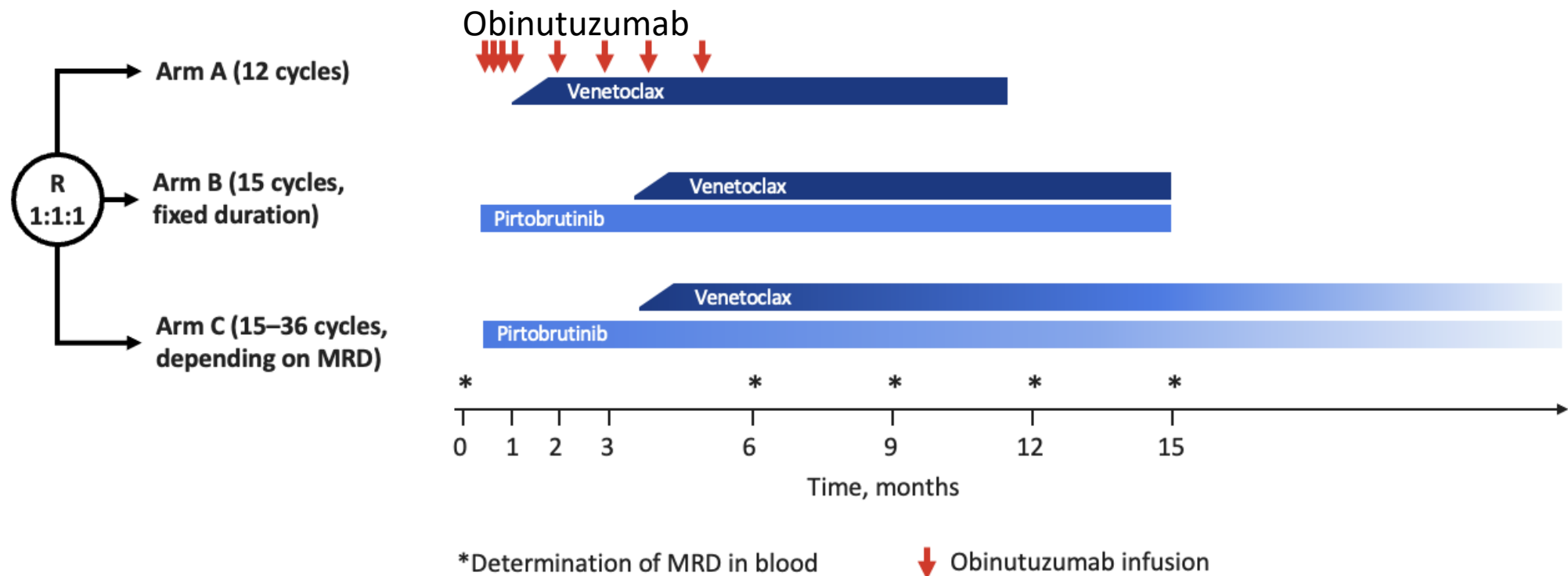
AEs, n (%)	AV (n=291)		AVO (n=284)		Chemoimmunotherapy (n=259)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Hypertension	12 (4.1)	8 (2.7)	11 (3.9)	6 (2.1)	7 (2.7)	2 (0.8)
Hemorrhage						
Any	94 (32.3)	3 (1.0)	86 (30.3)	6 (2.1)	11 (4.2)	1 (0.4)
Major	3 (1.0)	3 (1.0)	8 (2.8)	6 (2.1)	2 (0.8)	1 (0.4)
Neutropenia	108 (37.1)	94 (32.3)	143 (50.4)	131 (46.1)	132 (51.0)	112 (43.2)
Infection	148 (50.9)	36 (12.4)	153 (53.9)	67 (23.6)	82 (31.7)	26 (10.0)
Second primary cancer						
Any	15 (5.2)	5 (1.7)	12 (4.2)	5 (1.8)	2 (0.8)	0
Excluding nonmelanoma skin cancer	8 (2.7)	5 (1.7)	7 (2.5)	4 (1.4)	1 (0.4)	0
Tumor lysis syndrome	1 (0.3)	1 (0.3)	1 (0.4)	1 (0.4)	8 (3.1)	8 (3.1)
Cardiac event						
Any	27 (9.3)	5 (1.7)	34 (12.0)	7 (2.5)	9 (3.5)	3 (1.2)
Atrial fibrillation or flutter	2 (0.7)	1 (0.3)	6 (2.1)	2 (0.7)	2 (0.8)	2 (0.8)
Ventricular tachyarrhythmia	2 (0.7)	0	3 (1.1)	0	0	0

Chemofree fixed duration therapies guided by MRD– 1L CLL

1. **Ibrutinib + Venetoclax** (up to 6y...) vs **FCR**
2. **PVO** - Pirtobrutinib + Venetoclax + Obinutuzumab (Phase 2; 13-25 cycles)
3. **BOVen**: Zanubrutinib + venetoclax (8-24 cycles)
4. **FLAIR**: Venetoclax + ibrutinib
5. **HOVON 158/ NEXT STEP** - Ibrut+Ven --> if MRD+: Ibr + G

CLL18: Phase 3 - TN CLL/SLL

- Time-limited VenG vs
- Time-limited Ven + Pirto vs
- MRD-guided Ven + Pirto



Vision for the future

- Better understanding of drug resistance
- Fixed duration treatments associating drugs and guided by MRD
- Other targets
- Better control for high risk CLL
- Better salvage therapies for double-refractory CLL and Richter's transformation
- Cure? - we hope so! Until there, at least, functional cure!

Obrigada! Gracias! Thank you!



CONFIRA O CONTEÚDO ATUALIZADO
MOC-Hemato 2024



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