First-line treatment for CLL: An evolving landscape

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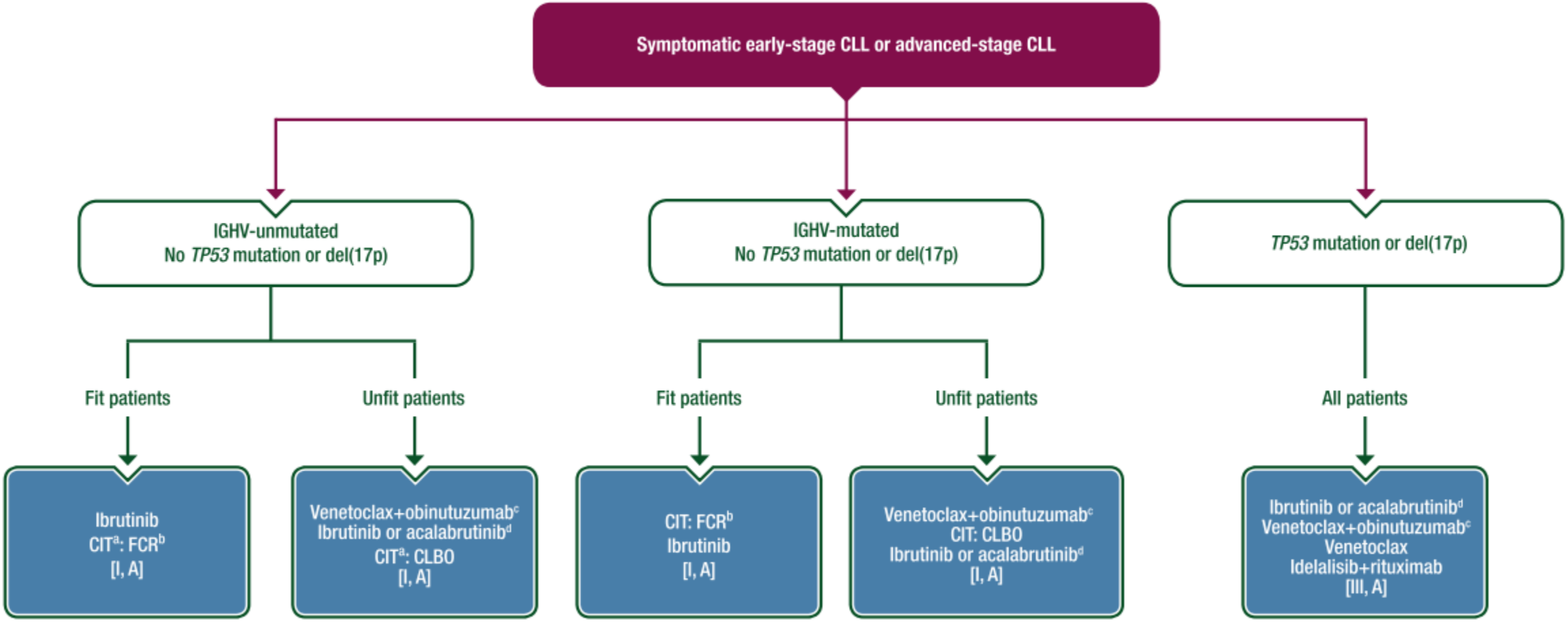
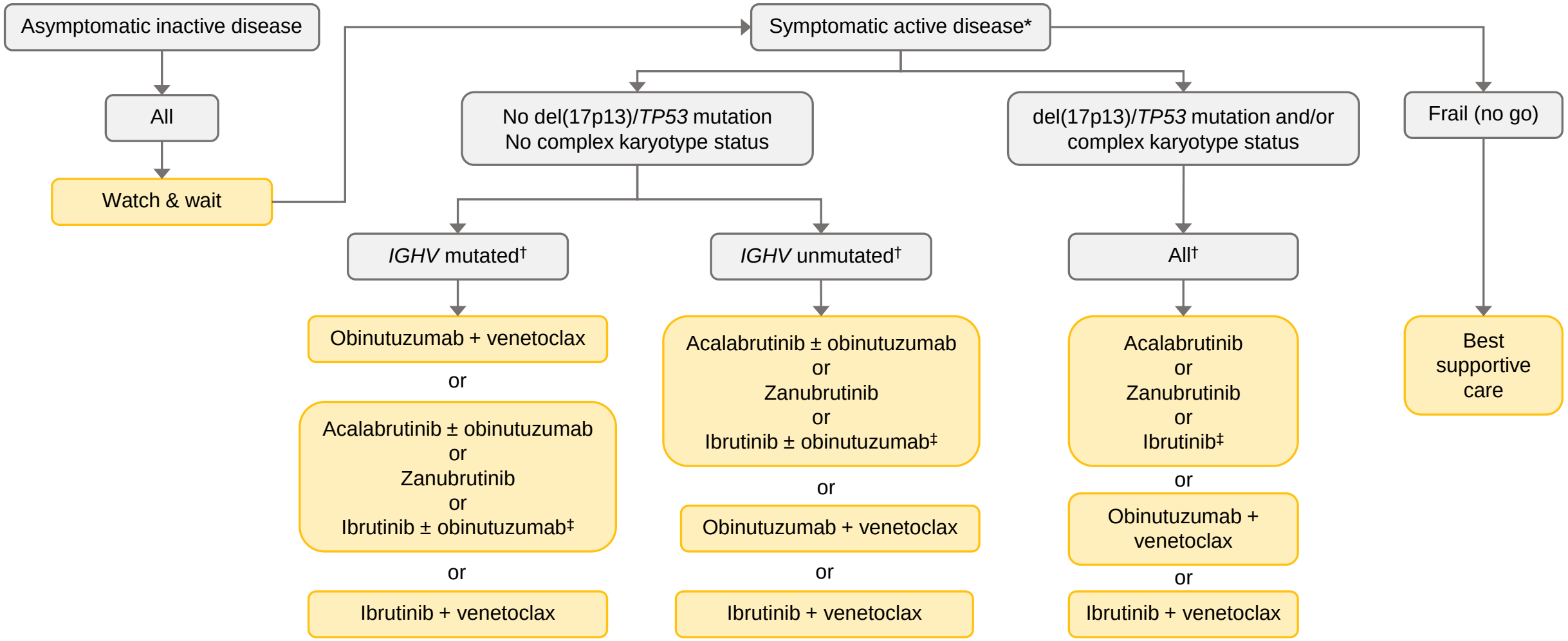
First-line CLL: ESMO guidelines are already personalized



[a]CIT as alternative treatment, only if reasons against treatment with targeted therapies or non-availability. [b]BR might be considered alternatively in patients >65 years. [c]If available. [d]If approved and available. BR, bendamustine and rituximab; CIT, chemoimmunotherapy; CLBO, chlorambucil plus obinutuzumab; CLL, chronic lymphocytic leukemia; ESMO, European Society for Medical Oncology; FCR, fludarabine, cyclophosphamide and rituximab; IGHV, immunoglobulin heavy chain variable. Eichhorst B *et al*. *Ann Oncol* 2021; 32 (1): 23–33.

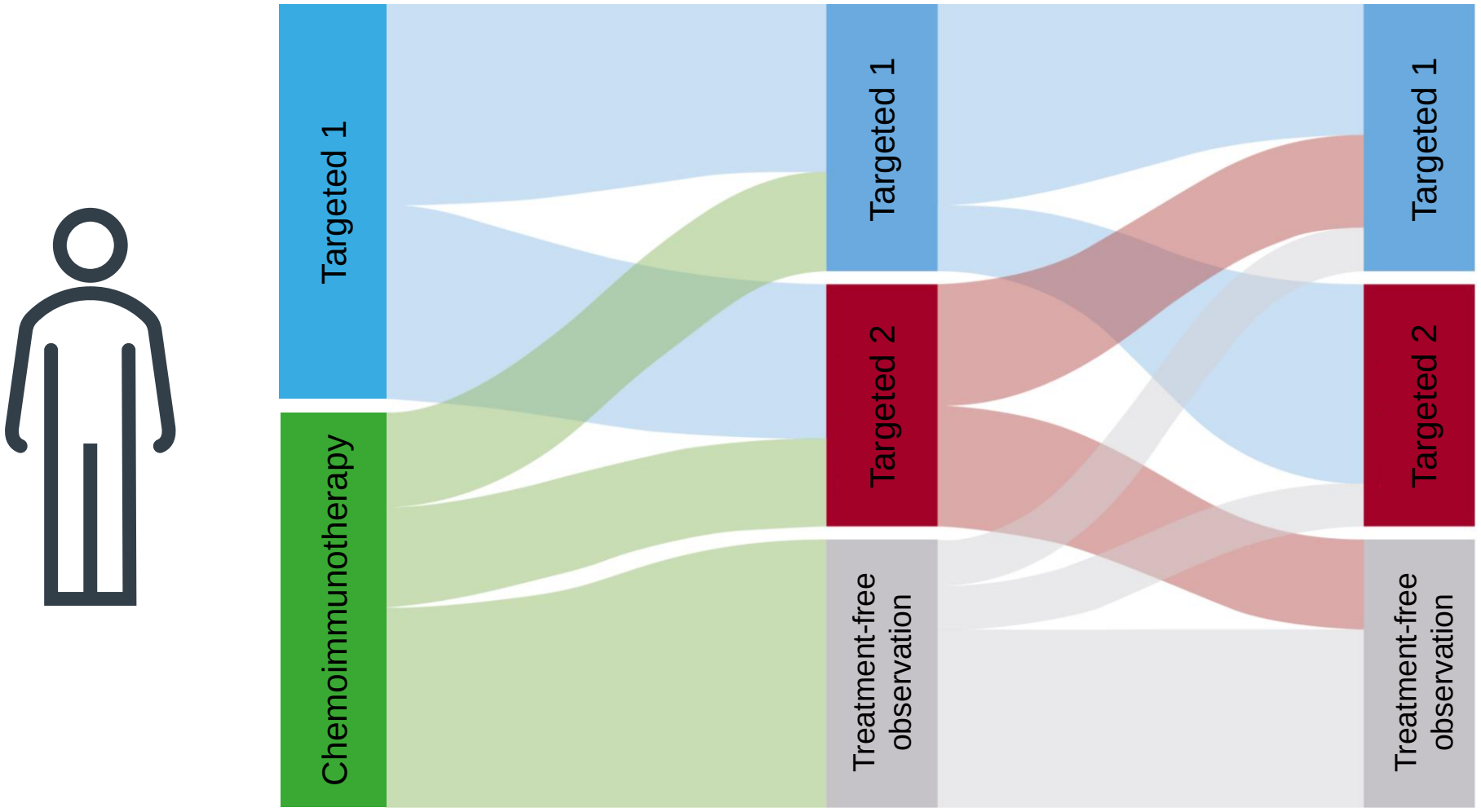
First-line CLL: Onkopedia 2023 guidelines



*Active disease according to the iwCLL 2018 criteria; †The sequence of therapies represents one possibility. ‡If acalabrutinib or zanubrutinib are contraindicated or not available, ibrutinib (± obinutuzumab) remains a therapy option, taking into account an increased risk of cardiac side effects. Acalabrutinib and zanubrutinib have not been systematically evaluated in younger/fit patients as first-line therapy.

Onkopedia guidelines: Chronic Lymphocytic Leukemia (CLL), 2023. Available at: https://www.onkopedia.com/de/onkopedia/guidelines/chronische-lymphatische-leukaemie-cll. Accessed March 2023.

Treatment trajectories in CLL: Sequencing?



CLL, chronic lymphocytic leukemia.
Adapted from Niemann CU. *Blood* 2020; 136 (17): 1896–1898.

State of the art diagnostic work-up in CLL!

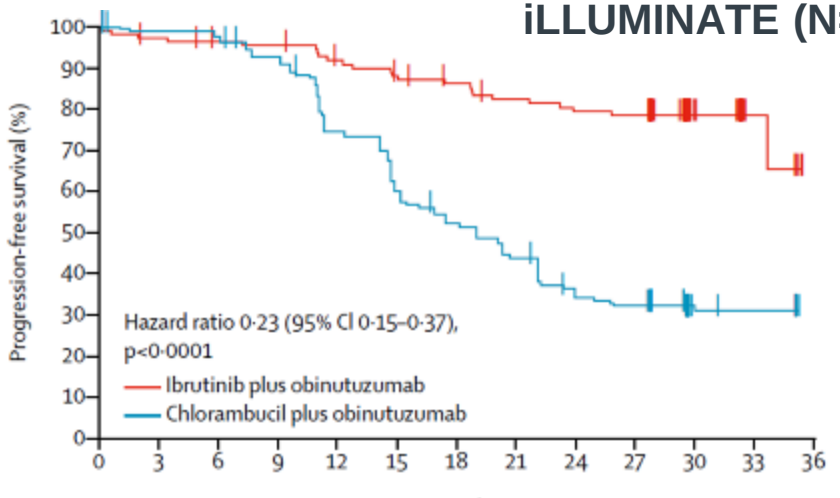
iwCLL guidelines: Baseline evaluation of patients

Diagnostic test	General practice	Clinical trial
Tests to establish the diagnosis		
CBC and differential count	Always	Always
Immunophenotyping of peripheral blood lymphocytes	Always	Always
Assessment before treatment		
History and physical, performance status	Always	Always
CBC and differential count	Always	Always
Marrow aspirate and biopsy	When clinically indicated (unclear cytopenia)	Desirable
Serum chemistry, serum immunoglobulin, and direct antiglobulin test	Always	Always
Chest radiograph	Always	Always
Infectious disease status	Always	Always
Additional tests before treatment		
Molecular cytogenetics (FISH) for del(13q), del(11q), del(17p), add(12) in peripheral blood lymphocytes	Always	Always
Conventional karyotyping in peripheral blood lymphocytes (with specific stimulation)	NGI*	Desirable
TP53 mutation	Always	Always
IGHV mutational status	Always	Always
Serum β_2-microglobulin	Desirable	Always
CT scan of chest, abdomen, and pelvis	NGI	Desirable
MRI, PET scans	NGI	NGI
Abdominal ultrasound†	Possible	NGI

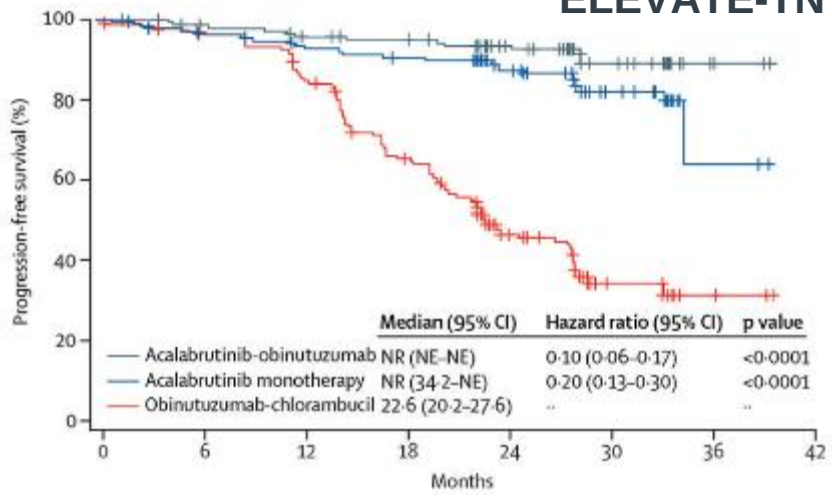
*Conventional karyotyping in peripheral blood lymphocytes (with specific stimulation) may be useful before therapy, if established methodology is available.
†Used in some countries to monitor lymphadenopathy and organomegaly.
CBC, complete blood count; CLL, chronic lymphocytic leukemia; CT, computerized tomography; FISH, fluorescence in situ hybridization; IGHV, immunoglobulin heavy chain variable; iwCLL, international workshop on CLL; MRI, magnetic resonance imaging; NGI, not generally indicated; PET, positron emission tomography. Hallek M *et al*. *Blood* 2018; 131 (25): 2745–2760.

First-line treatment with BTK inhibitors
Progression-free survival

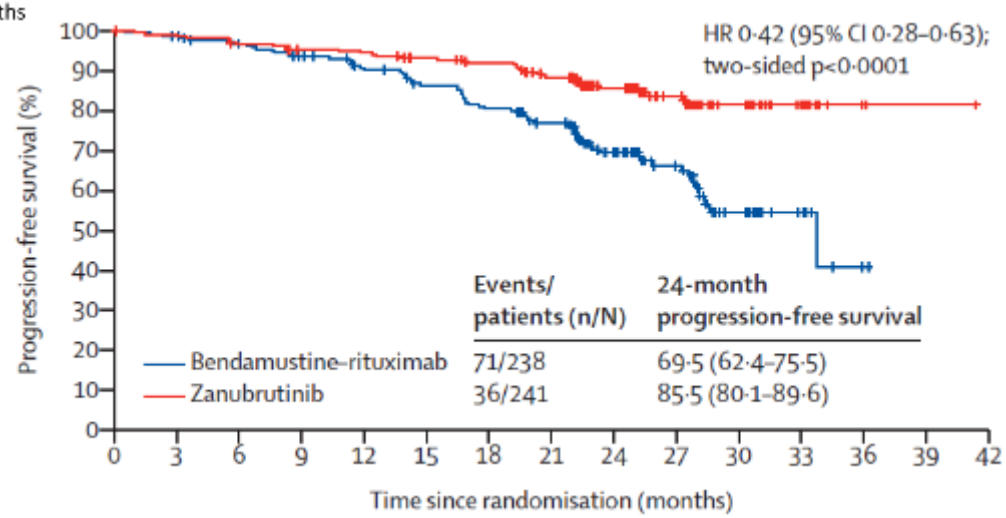
iLLUMINATE (N=229)[1]



ELEVATE-TN (N=535)[2]



SEQUOIA (N=479)[3]

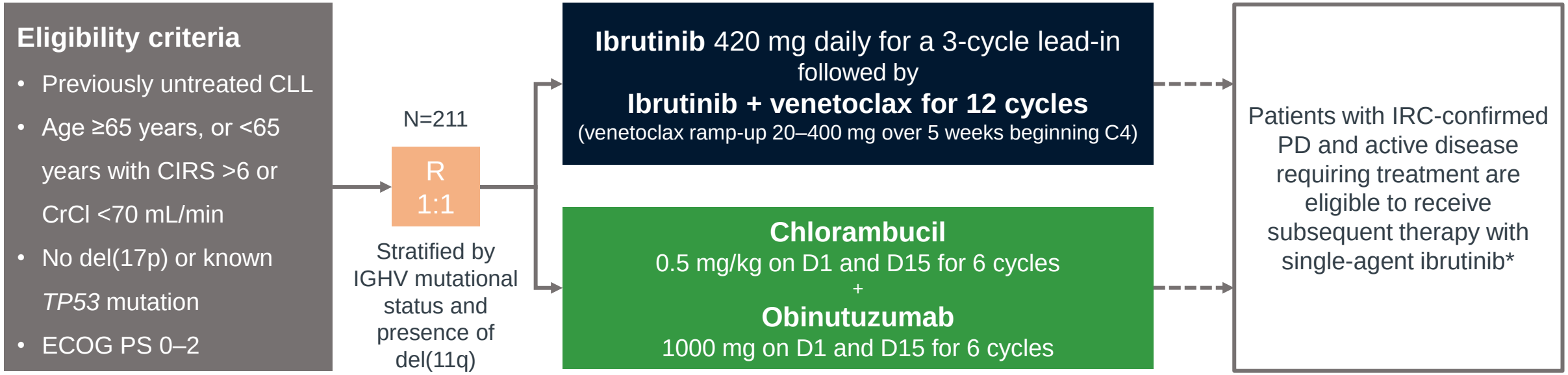


This slide includes data from different clinical trials. These data are meant for demonstration purposes only and are not meant for cross-trial comparison purposes.

CI, confidence interval; NE, not estimable; NR, not reached. 1. Moreno C *et al. Lancet Oncol*. 2019; 20 (1): 43–56. 2. Sharman JP *et al. Lancet*. 2020; 395 (10232): 1278–1291. 3. Tam CS *et al. Lancet Oncol.* 2022; 23 (8): 1031–104.

GLOW Phase 3 study (NCT03462719)

First-line ibrutinib plus venetoclax vs. chlorambucil plus obinutuzumab



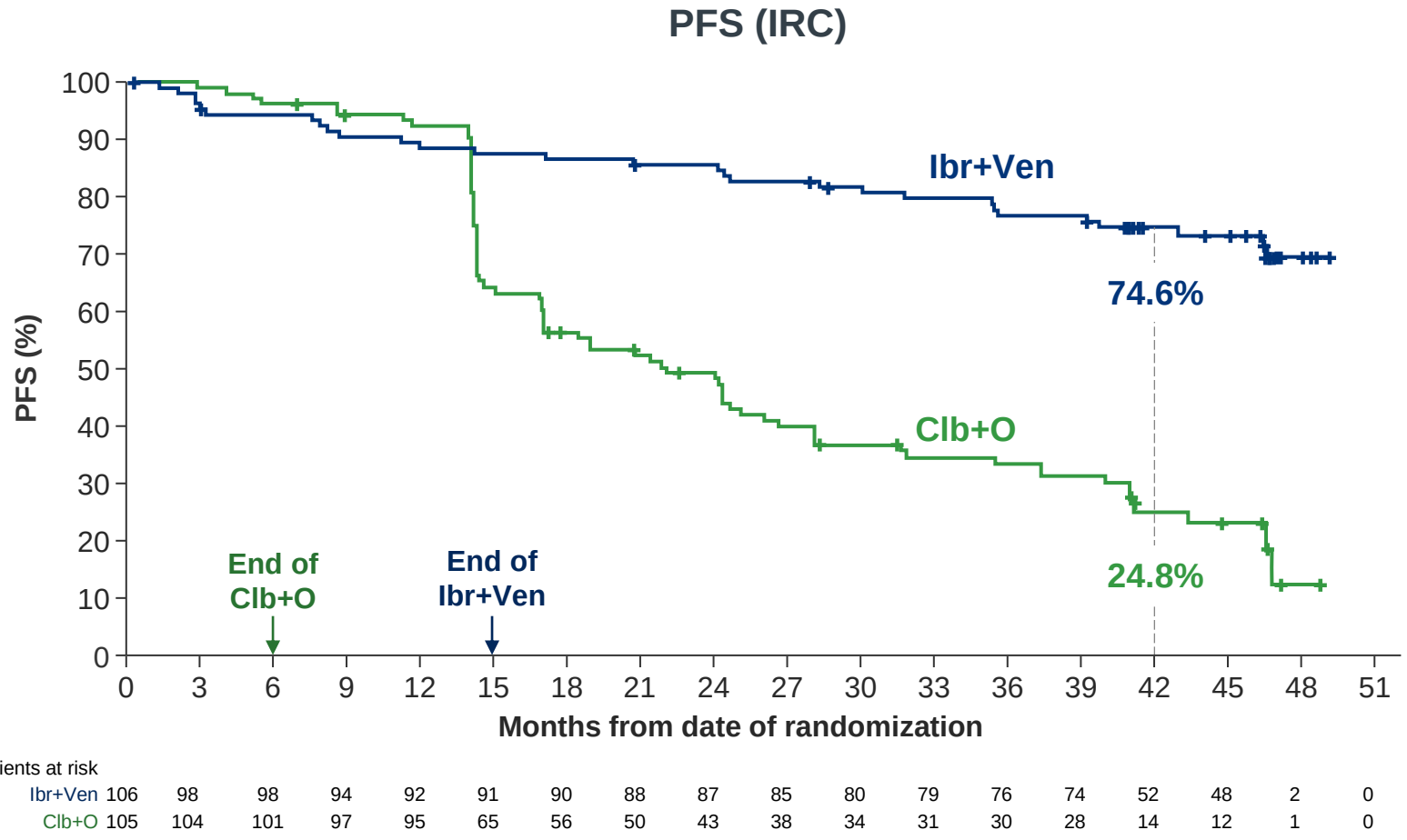
Primary end point: IRC-assessed PFS

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

*Ibrutinib was 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; CLL, chronic lymphocytic leukemia; CrCl, creatinine clearance; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; IGHV, immunoglobulin heavy chain variable; IRC, independent review committee; MRD, minimal residual disease; NGS, next-generation sequencing; PD, progressive disease; R, randomization; uMRD, undetectable MRD.
Niemann CU *et al*. Oral presentation at ASH 2022; New Orleans, LA, USA, December 10–13, 2022 (Abstract 93).

GLOW: PFS 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 (95% CI): **0.214** (0.13–0.334); ***P*<0.0001**

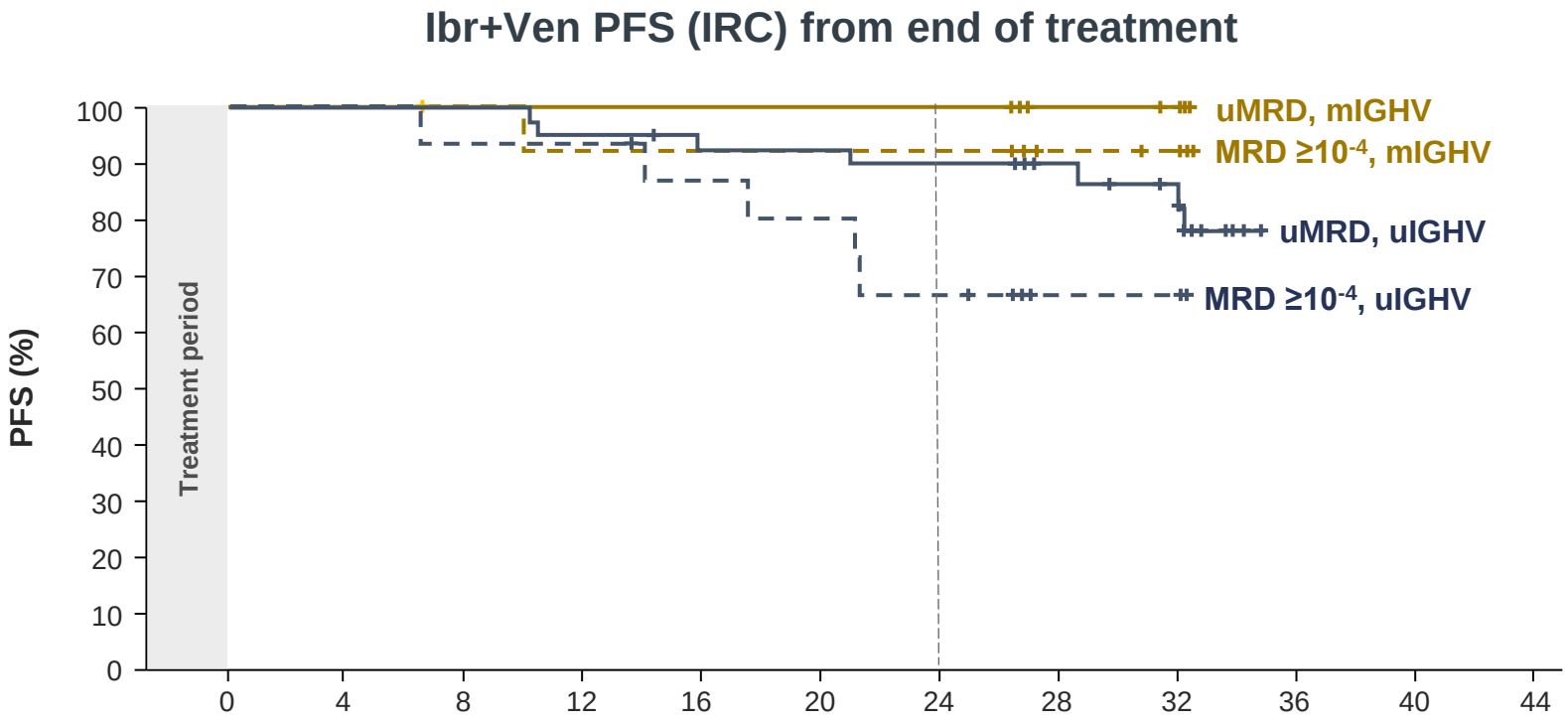
Estimated 3.5-year PFS rates:

- **74.6%** for Ibr+Ven
- **24.8%** for Clb+O

Clb, chlorambucil; CI, confidence interval; HR, hazard ratio; Ibr, ibutinib; IRC, independent review committee; O, Obinutuzumab; PFS, progression-free survival; Ven, venetoclax.

Niemann CU *et al*. Oral presentation at ASH 2022; New Orleans, LA, USA, December 10–13, 2022 (Abstract 93).

GLOW: Ibr+Ven PFS was ≥90% at two years post-treatment for patients with uMRD at EOT+3, regardless of IGHV status



Patients at risk

uMRD, mIGHV	13	13	13	13	13	13	13	7	5	0	0	0
MRD ≥10^{-4}, mIGHV	14	14	13	12	12	12	12	9	8	0	0	0
uMRD, uIGHV	40	40	40	38	36	36	35	27	22	0	0	0
MRD ≥10^{-4}, uIGHV	16	16	15	15	13	12	10	6	6	0	0	0

Estimated PFS at 2 years post-treatment for **uIGHV** CLL:

- 90% for uMRD at EOT+3 versus 67% for MRD ≥10^{-4}

Estimated PFS at 2 years post-treatment for **mIGHV** CLL:

- >90% regardless of MRD status at EOT+3

Median study follow-up: 46 months

EOT+3, EOT plus 3 months; Ibr, ibutinib; IGHV, immunoglobulin heavy chain variable; IRC, independent review committee; mIGHV, mutated IGHV; MRD, minimal residual disease; PFS, progression-free survival; uIGHV, unmutated IGHV; uMRD, undetectable minimal residual disease; Ven, venetoclax.

Niemann CU *et al*. Oral presentation at ASH 2022; New Orleans, LA, USA, December 10–13, 2022 (Abstract 93).

First-line Ibr+Ven in frail patients:
Early ibrutinib toxicity? Infections still occur

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†	-	-	-	2
General disorders (sudden death)	-	2	-	1‡	-
Neoplasm	1	-	-	-	-

	I+V (n=106)		Clb+O (n=105)	
Median treatment exposure – months (range)	13.8 (0.7–19.5)		5.1 (1.8–7.9)	
Adverse events (AE) – n (%)	**Grade 3/4**	**Grade 5**	**Grade 3/4**	**Grade 5**
Patients with 1 or more AE	73 (68.9)	7 (6.6)	71 (67.6)	2 (1.9)
Neutropenia§	37 (34.9)	0	52 (49.5)	0
Infections and infestations‖	16 (15.1)	2 (1.9)¶	11 (10.5)	1 (1.0)

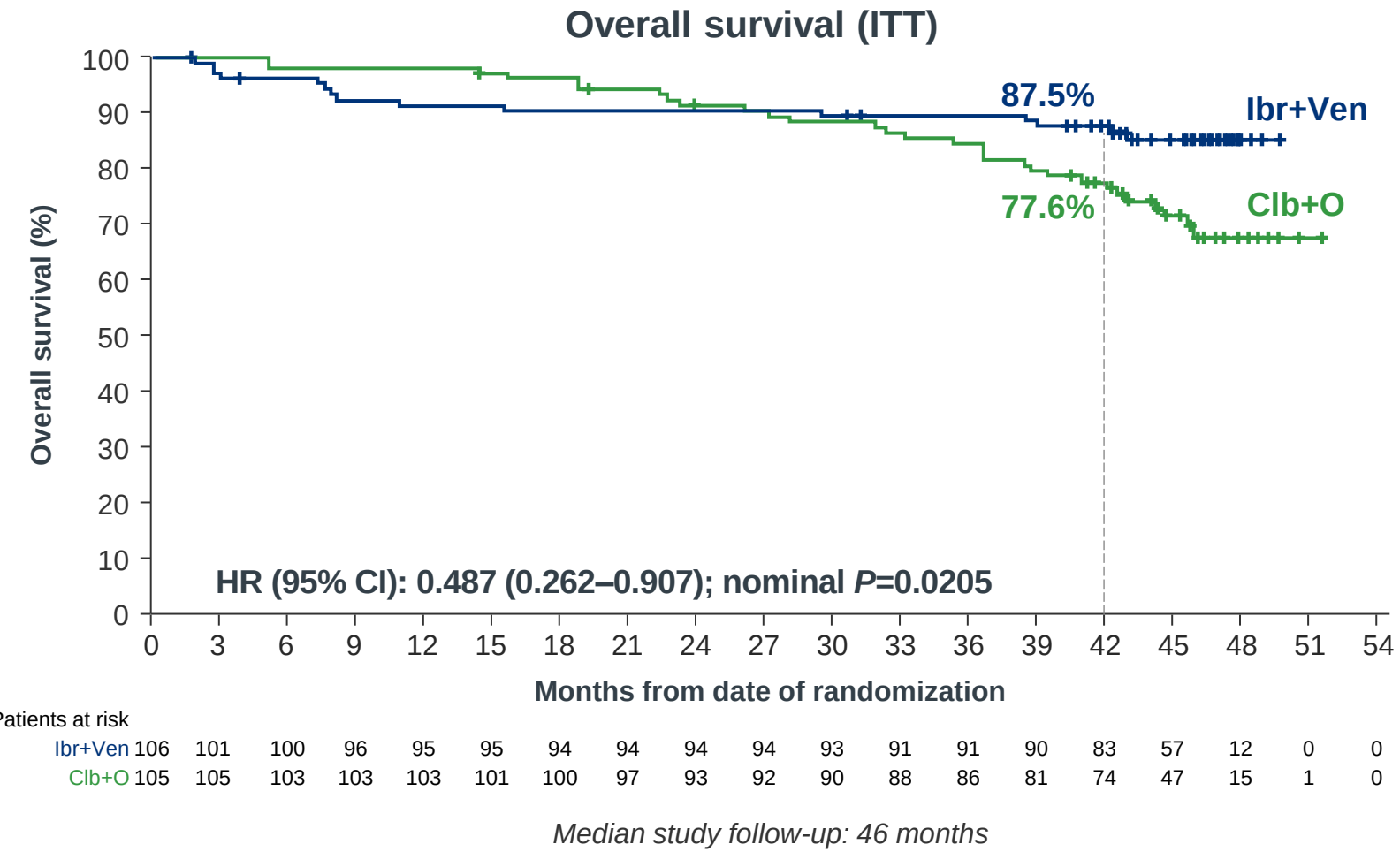
Please note that these data are a selection of outcomes and are not representative of the overall safety profile of the study treatments.

*Includes 5 COVID-19–related deaths: 1 in the I+V arm, 4 in the Clb+O arm. †1 patient listed as cardiac event had 3 causes of death: sinus node dysfunction, cardiac failure, pneumonia. ‡An additional sudden death occurred in the ibrutinib-venetoclax arm more than 30 days after last dose of study medication. §Includes "neutrophil count decreased." Rates of febrile neutropenia (grade ≥3): 1.9% for I+V versus 2.9% for Clb+O. ‖Includes multiple preferred terms. Only pneumonia (grade ≥3) occurred in 5% or more of patients in the ibrutinib-venetoclax (7 [6.6%]) and chlorambucil-obinutuzumab (6 [5.7%]) arms. ¶Both Grade 5 AEs were pneumonia.

AE, adverse event; Clb, chlorambucil, I, ibrutinib; Ibr, ibrutinib; O, obinutuzumab; Ven, venetoxlax; V, venetoclax.

Kater AP *et al. NEJM Evidence.* 2022; 1 (7): EVIDoa2200006.

GLOW: Ibr+Ven improved overall survival versus Clb+O with 4 years of study follow-up



Median study follow-up: 46 months

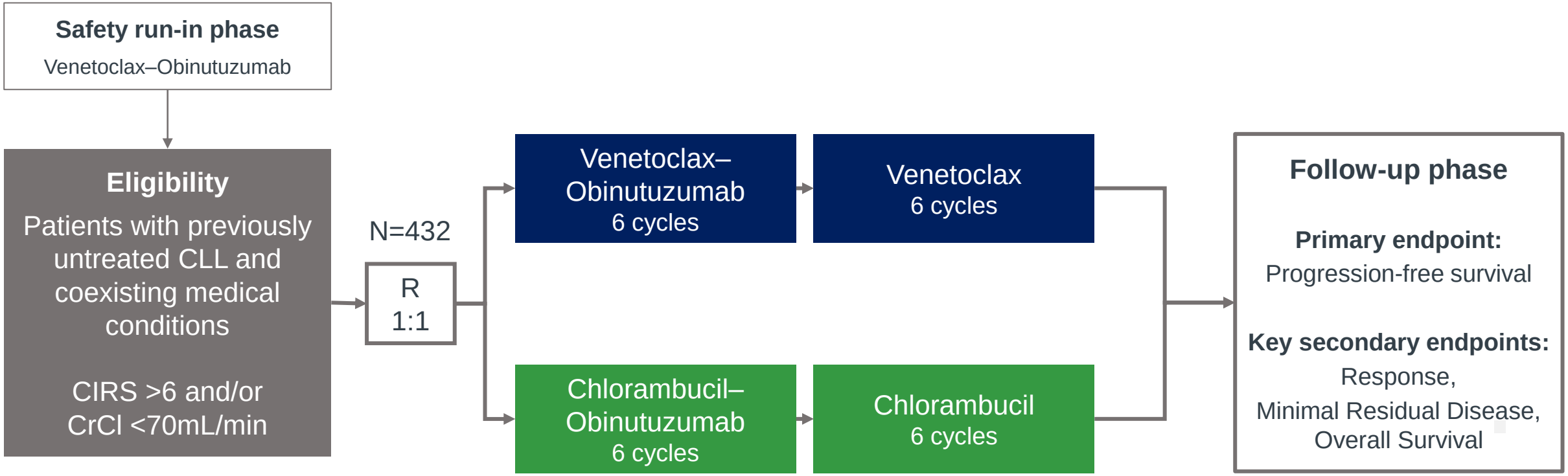
- In the Clb+O arm, 39/41 patients requiring subsequent treatment received a BTKi or venetoclax
- The majority of deaths in the Clb+O arm occurred while off any treatment
- More infection-related deaths were seen in the Clb+O arm

Causes of death

n (%)	Ibr+Ven (N = 106)	Clb+O (N = 105)
PD	1 (0.9)	2 (1.9)
Infections	4 (3.8)	11 (10.5)
Other*	10 (9.4)	17 (16.2)
TOTAL	15 (14.2)	30 (28.6)

*Cause and number (Ibr+Ven arm, Clb+O arm) of "other" deaths: general/unknown (4, 5), cardiac (2, 4), central nervous system (2, 3), neoplasm (1, 3), euthanasia (1, 0), hepatobiliary (0, 1), respiratory (0, 1).
BTKi, Bruton's tyrosine kinase inhibitor; CI, confidence interval; Clb; chlorambucilHR, hazard ratio; Ibr, ibrutinib; ITT, intention-to-treat; O, obinutuzumab; PD, progressive disease.
Niemann CU *et al*. Oral presentation at ASH 2022; New Orleans, LA, USA, December 10–13, 2022 (Abstract 93)

CLL14 trial: First-line Ven-Obi versus Clb-Obi in frail CLL patients

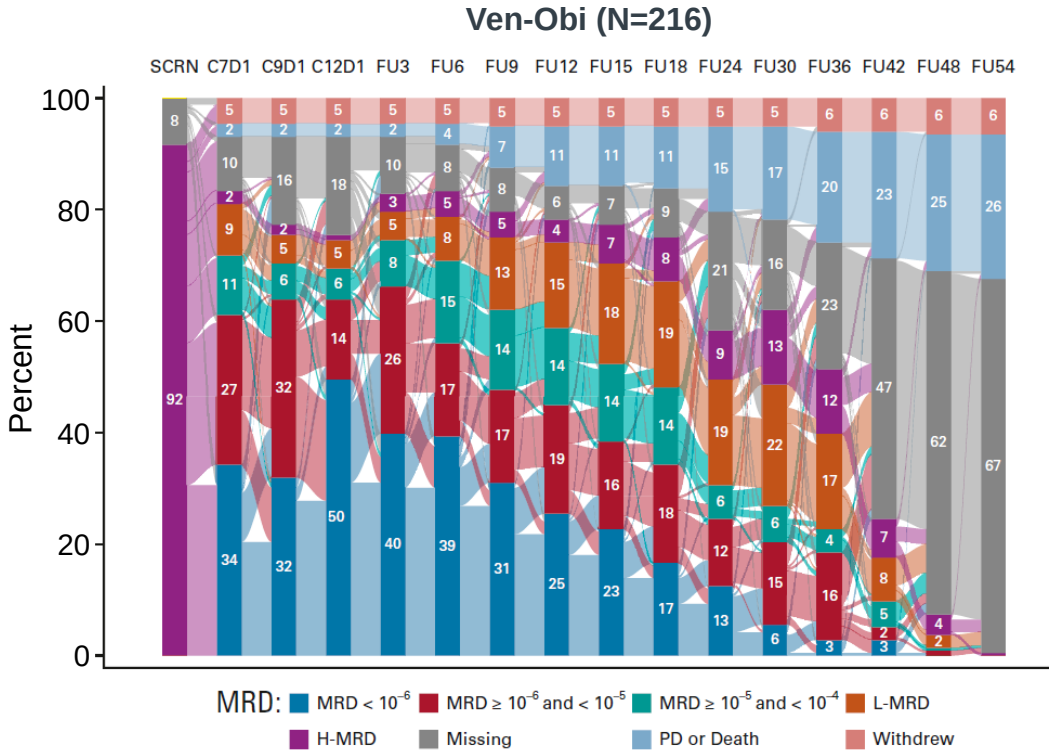


Clb, chlorambucil; CIRS; cumulative illness rating scale; CLL, chronic lymphocytic leukemia; CrCl, creatinine clearance; Obi obinutuzumab; Ven, venetoclax.
Fischer K *et al*. *N Engl J Med* 2019; 380 (23): 2225–2236.

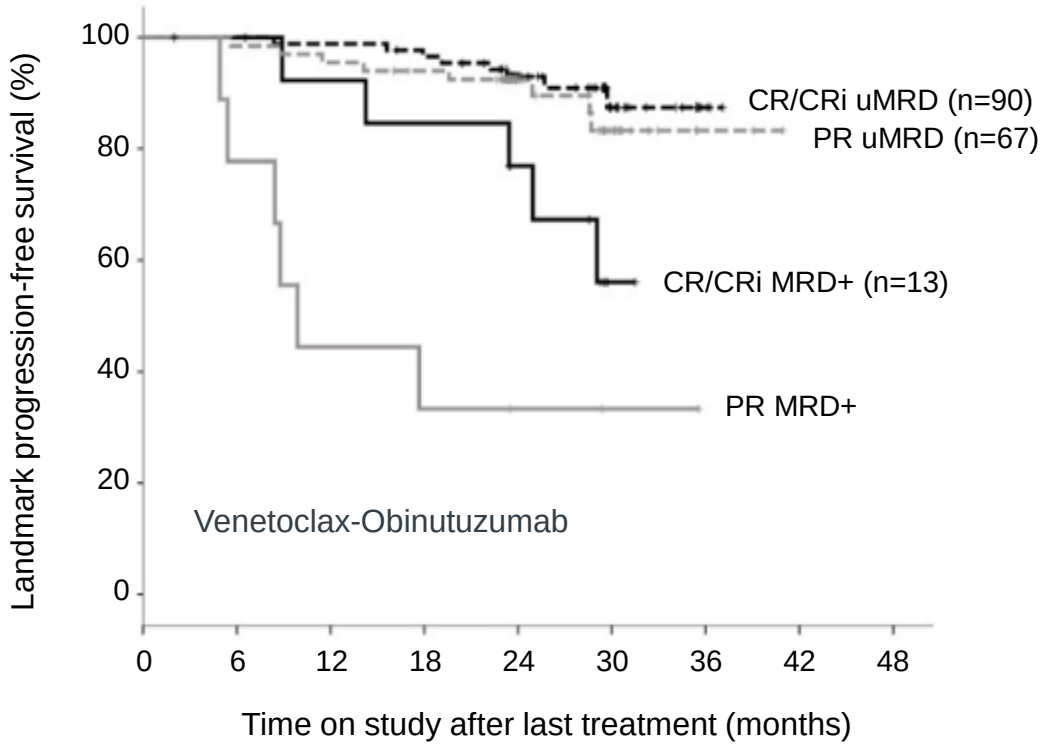
CLL14 trial: First-line Ven-Obi in CLL

uMRD decreases over time but correlates with PFS

MRD levels from baseline to latest follow up[1]



PFS by MRD status and clinical response at EOT[2]



C, cycle; CLL, chronic lymphocytic leukemia; CR, complete response; CRi, complete remission with incomplete bone marrow recovery; D, day; EOT, end of treatment; FU, follow up; H-MRD, high MRD; L-MRD, low MRD; MRD, minimal residual disease; Obi obinutuzumab; PFS, progression-free survival; PD, progressive disease; PR, partial response; SCRN, screening; uMRD, undetectable MRD; Ven, venetoclax.

1. Al-Sawaf O *et al. J Clin Oncol* 2021; 39 (36): 4049–4060. 2. Fischer K *et al*. Oral presentation at ASH; Orlando, FL, USA, December 7–10, 2019.

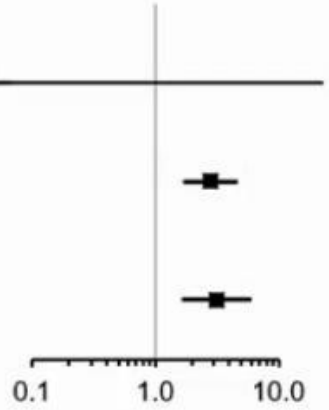
CLL14 trial: First-line Ven-Obi versus Clb-Obi in frail CLL patients

Progression-free survival

Multivariable models

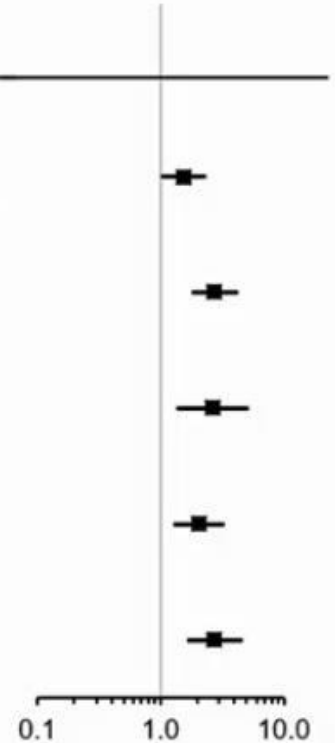
Ven-Obi

COX regression PFS	Univariate comparison	Hazard ratio	95% Wald CI
Disease burden category (TLS risk category)			
High	Vs. intermediate/low	2.815	1.773-4.469
Deletion 17p			
del(17p)	vs. no del(17p)	3.150	1.727-5.745



Clb-Obi

COX regression PFS	Univariate comparison	Hazard ratio	95% Wald CI
Serum β2 microglobulin			
> 3.5	vs. <= 3.5	1.534	1.037-2.269
IGHV mutational status			
unmutated	Vs. mutated	2.765	1.847-4.141
Deletion 17p			
del(17p)	vs. no del(17p)	2.667	1.413-5.036
Deletion 11q			
del(11q)	vs. no del(11q)	2.056	1.331-3.177
Complex Karyotype			
CKT/HCKT	vs. NCKT	2.761	1.720-4.433



CI, confidence interval; CKT, complex karyotype; CLL, chronic lymphocytic leukemia; HCKT, high-CKT; IGHV, immunoglobulin heavy chain variable; MRD, minimal residual disease; NCKT, no CKT; Obi, obinutuzumab; PFS, progression-free survival; uMRD, undetectable MRD: Ven, venetoclax.

Al-Sawaf O *et al*. Oral presentation at EHA 2022; Vienna, Austria, June 9–12, 2022 (Abstract S148).

CLL 14: First-line Ven-Obi in frail CLL patients
Infections still occur

Fatal (Grade 5) AEs*

n (%)	Venetoclax-Obinutuzumab (N=212)†	Chlorambucil-Obinutuzumab (N=214)
Grade 5 event during treatment	5 (2.4)‡	4 (1.9)
Infections and infestations	4 (1.9)	3 (1.4)
Grade 5 event after completion of treatment	11 (5.2)	4 (1.9)
Cardiac disorders	3 (1.4)	1 (0.5)
Infections and infestations	4 (1.9)	0

Non-fatal (Max. Grade 3 or 4) AEs*

n (%)	Venetoclax-Obinutuzumab (N=212)†		Chlorambucil-Obinutuzumab (N=214)	
	Max. Grade 3	Max. Grade 4	Max. Grade 3	Max. Grade 4
Grade 3 or 4 event occurring in ≥3% of the patients in either treatment group‡				
Infections and infestations	31 (14.6)	6 (2.8)	31 (14.5)	1 (0.5)
Pneumonia	8 (3.8)	1 (0.5)	8 (3.7)	0

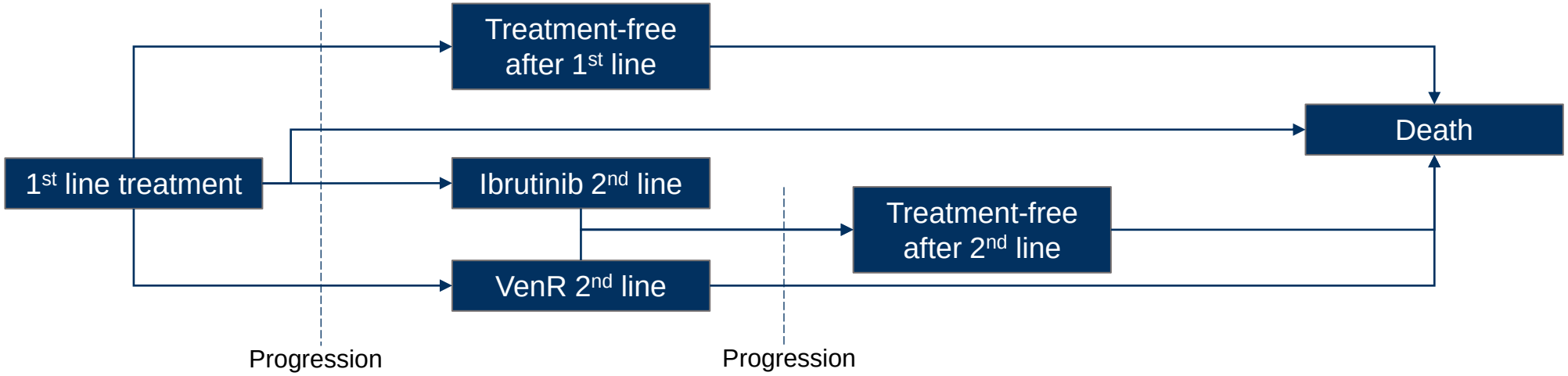
Please note that these data are a selection of outcomes and are not representative of the overall safety profile of Venetoclax-Obinutuzumab.

*Safety population; † Nine patients received obinutuzumab only. ‡Two patients received obinutuzumab only.

Fischer K *et al*. *N Engl J Med* 2019; 380 (23): 2225–2236.

First-line CLL: Health economics

Taking the next line of treatment into account



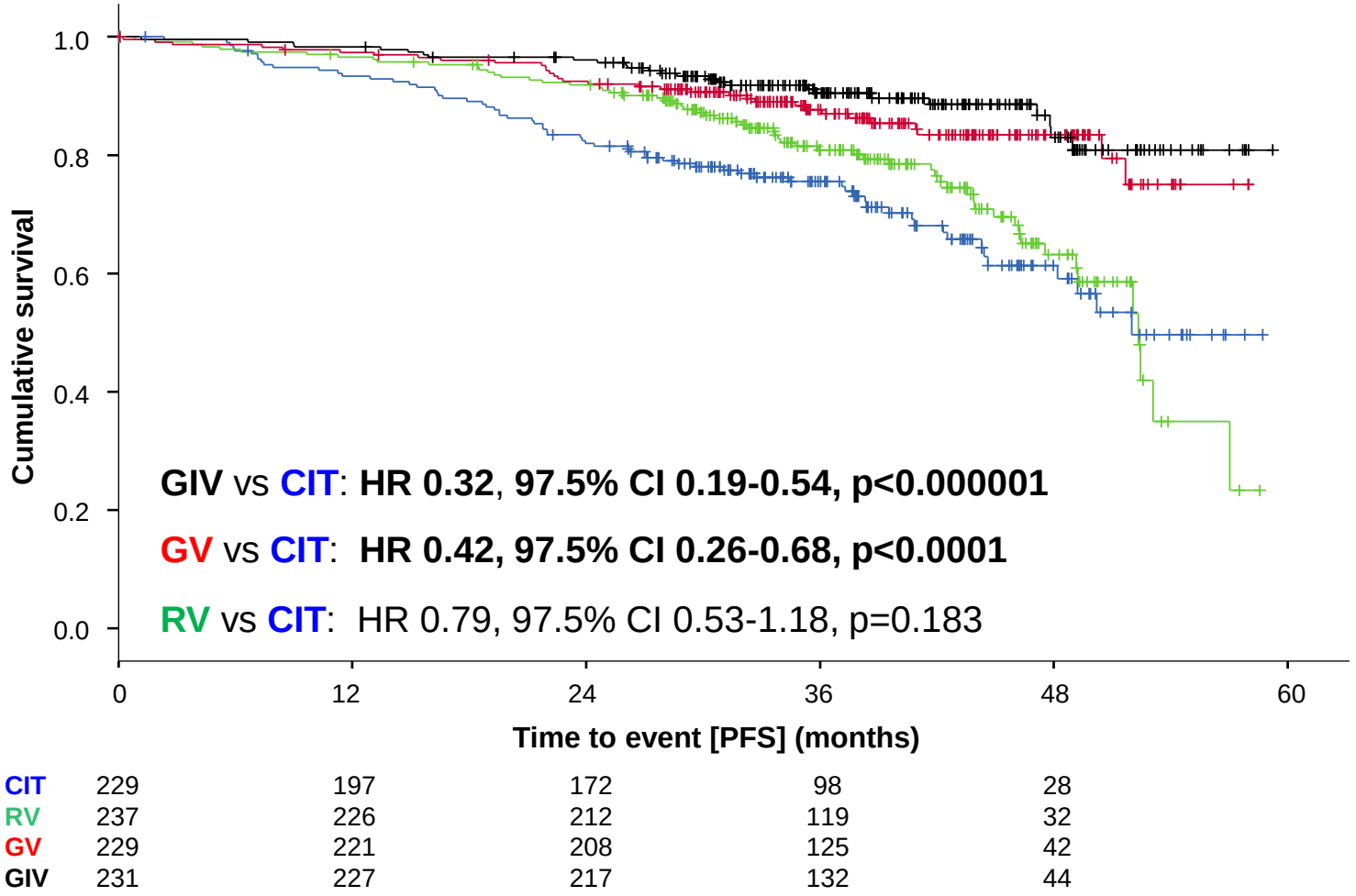
	VenO			ClbO			ICER
	Cost (EUR)	QALY	Life-years	Cost (EUR)	QALY	Life-years	(EUR/QALY)
Base case	205,590	5.11	7.54	199,305	3.80	6.12	4,808
Only 1st line	110,606	4.43	6.04	54,453	2.88	4.02	36,213
Ibrutinib in 2nd line	235,272	5.03	7.18	244,550	3.68	5.58	VenO dominates
VenR in 2nd line	175,907	5.18	7.89	154,060	3.92	6.66	17,261
15% discount on Ven	194,907	5.11	7.54	194,944	3.80	6.12	VenO dominates

ClbO, chlorambucil plus obinutuzumab; CLL, chronic lymphocytic leukemia; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; Ven, venetoclax; VenO, venetoclax plus obinutuzumab; VenR, venetoclax plus rituximab.

Slot M *et al*. Oral presentation at ASH 2022; New Orleans, LA, USA, December 10–13, 2022 (Abstract 893).

GAIA/CLL13 trial co-primary endpoint: Progression-free survival

Median FU 38.8 months (range: 0.0–59.2)

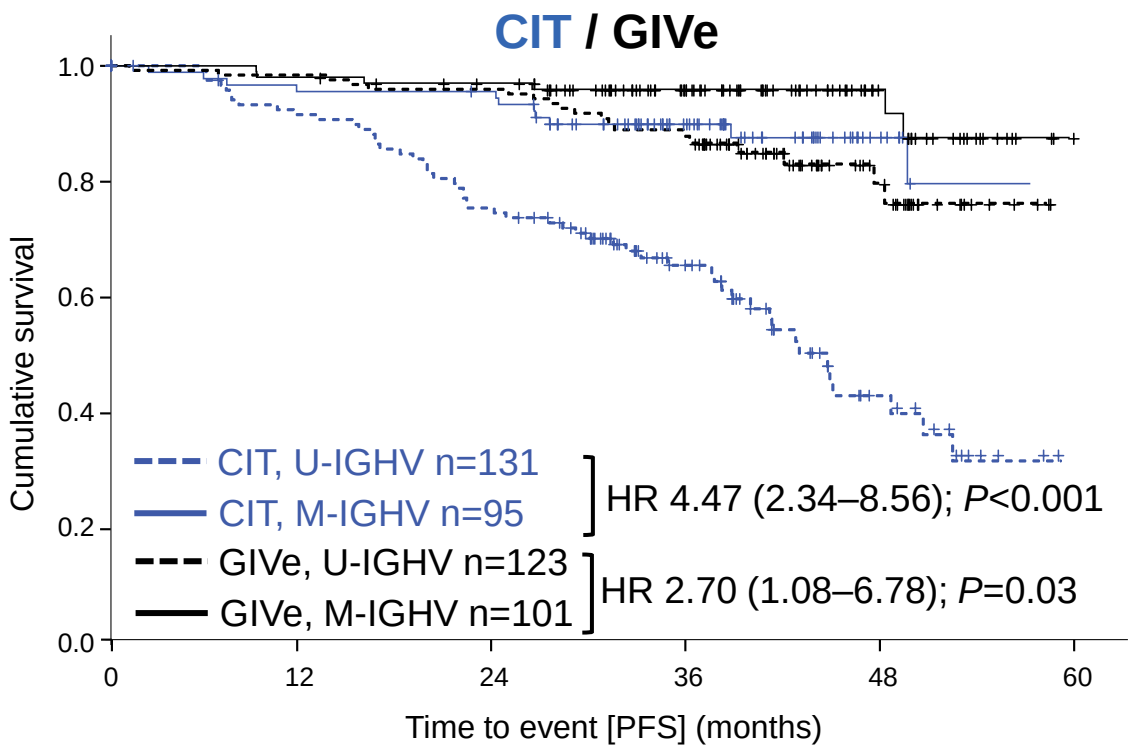


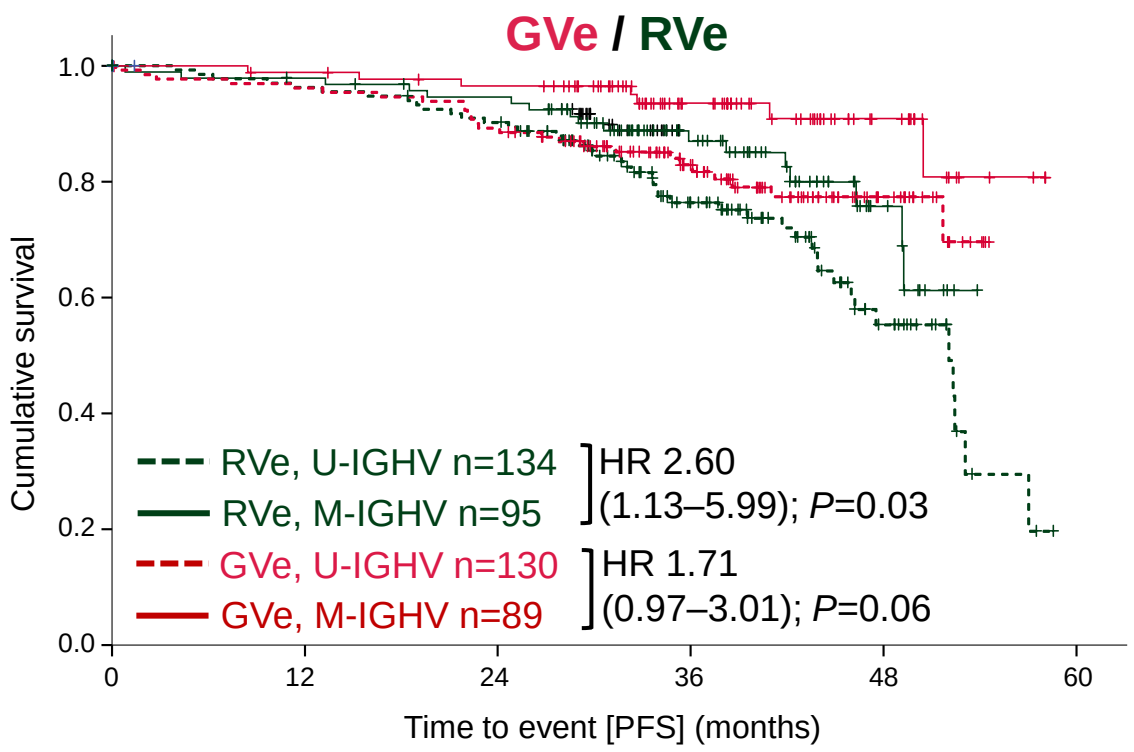
PFS	Median months	3y PFS (%)
CIT	52.0	75.5
RV	52.3	80.8
GV	Not reached	87.7
GIV	Not reached	90.5

CIT, chemoimmunotherapy; GIV, obinutuzumab plus ibrutinib plus venetoclax; GV, obinutuzumab plus venetoclax; HR, hazard ratio; PFS, progression-free survival; RV, rituximab plus venetoclax.

Eichhorst B *et al*. Oral presentation at EHA 2022; Vienna, Austria, June 9–12, 2022 (Abstract LB2365).

GAIA/CLL13: Unmutated IGHV associated with shorter PFS for all treatment arms

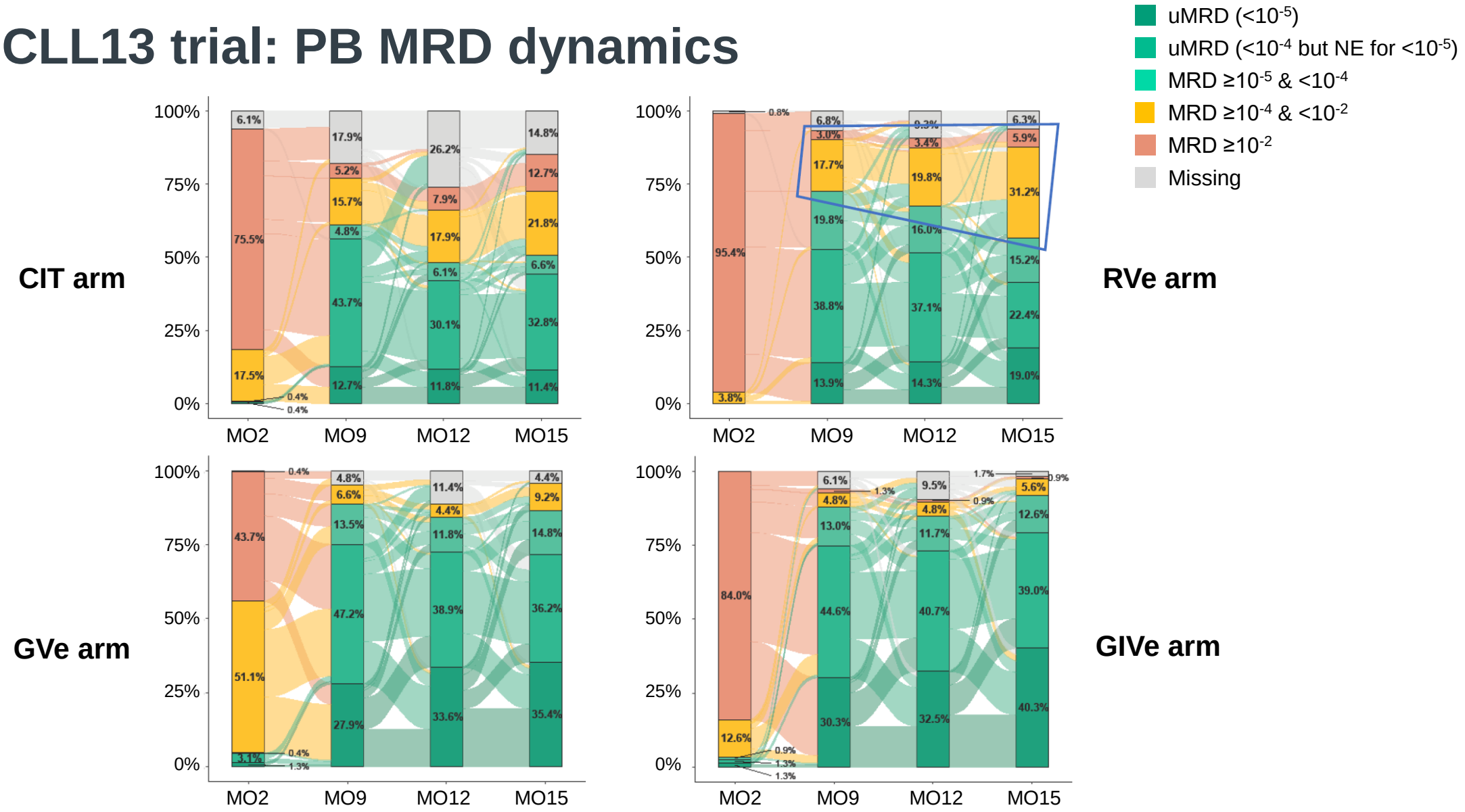




CIT, chemoimmunotherapy; GIVe, obinutuzumab plus ibrutinib plus venetoclax; GVe, obinutuzumab plus venetoclax; HR, hazard ratio; IGHV, immunoglobulin heavy chain variable; M-IGHV, mutated IGHV; PFS, progression-free survival; RV, rituximab plus venetoclax; U-IGHV, unmutated IGHV.

Eichhorst B *et al*. Oral presentation at EHA 2022; Vienna, Austria, June 9–12, 2022 (Abstract LB2365).

GAIA CLL13 trial: PB MRD dynamics



CIT, chemoimmunotherapy; GIVe, obinutuzumab plus ibrutinib plus venetoclax; GVe, obinutuzumab plus venetoclax; MO, month; MRD, minimal residual disease; NE, not evaluable; PB, peripheral blood; RV, rituximab plus venetoclax; uMRD, undetectable MRD. Fürstenau M *et al*. Oral presentation at ASH 2021; Atlanta, GA, USA, December 11–14, 2021.

GAIA/CLL13 trial: Infections with first-line triplet therapy

AEs, Grade ≥3	CIT (n=216)	RV (n=237)	GV (n=228)	GIV (n=231)
Anemia	16 (7.4)	9 (3.8)	11 (4.8)	9 (3.9)
Neutropenia	113 (52.3)	109 (46.0)	127 (55.7)	112 (48.5)
Thrombocytopenia	22 (10.2)	10 (4.2)	42 (18.4)	37 (16.0)
Febrile neutropenia	**24 (11.1)**	**10 (4.2)**	**7 (3.1)**	**18 (7.8)**
Infections	**43 (19.9)**	**27 (11.4)**	**32 (14.0)**	**51 (22.1)**
Tumor lysis syndrome	**9 (4.2)**	**24 (10.1)**	**20 (8.8)**	**15 (6.5)**
Bleeding events	1 (0.5)	1 (0.4)	1 (0.4)	4 (1.7)
Atrial fibrillation	1 (0.5)	1 (0.4)	0 (0.0)	6 (2.6)

CIT, chemoimmunotherapy; CLL, chronic lymphocytic leukemia; GIV, obinutuzumab plus ibrutinib plus venetoclax; GV, obinutuzumab plus venetoclax; RV, rituximab plus venetoclax.

Eichhorst B *et al*. Oral presentation at ASH 2021; Atlanta, Georgia, USA, December 11–14, 2021 (Abstract 71)

CLL2GIVe: Study design and treatment disposition

Phase 2 trial, N=41

Eligibility:

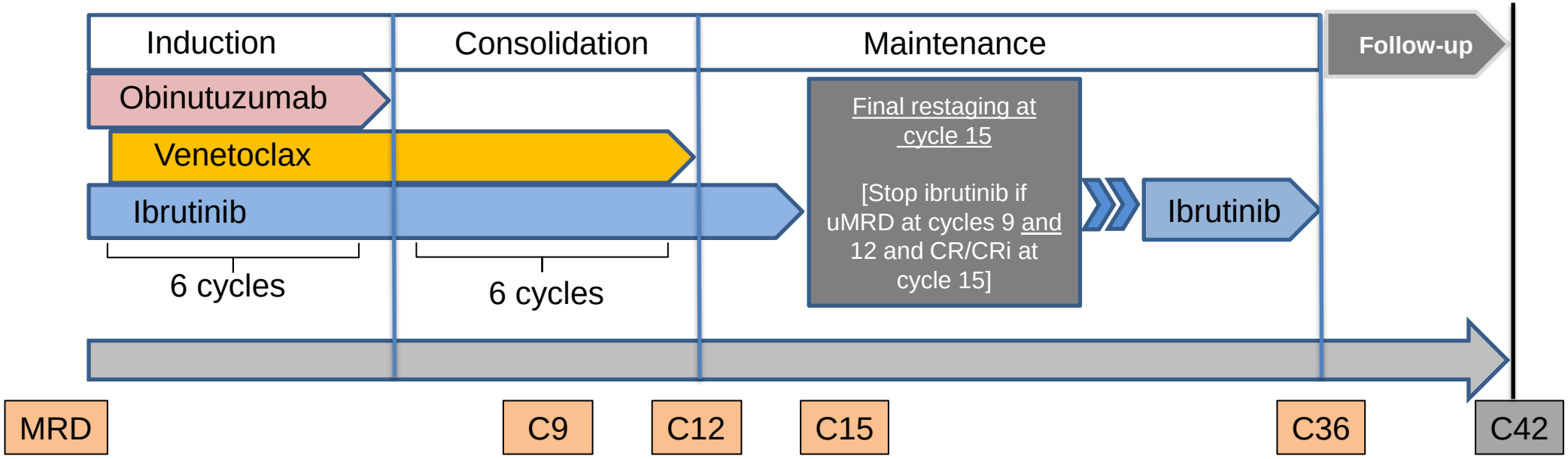
- Previously untreated CLL
- Del(17p) and/or *TP53*^{mut}
- Adequate renal function (CrCl >50 mL/min)

Primary endpoint:

- CR rate at C15

Secondary endpoints:

- PFS, OS, EFS
- Safety
- MRD levels



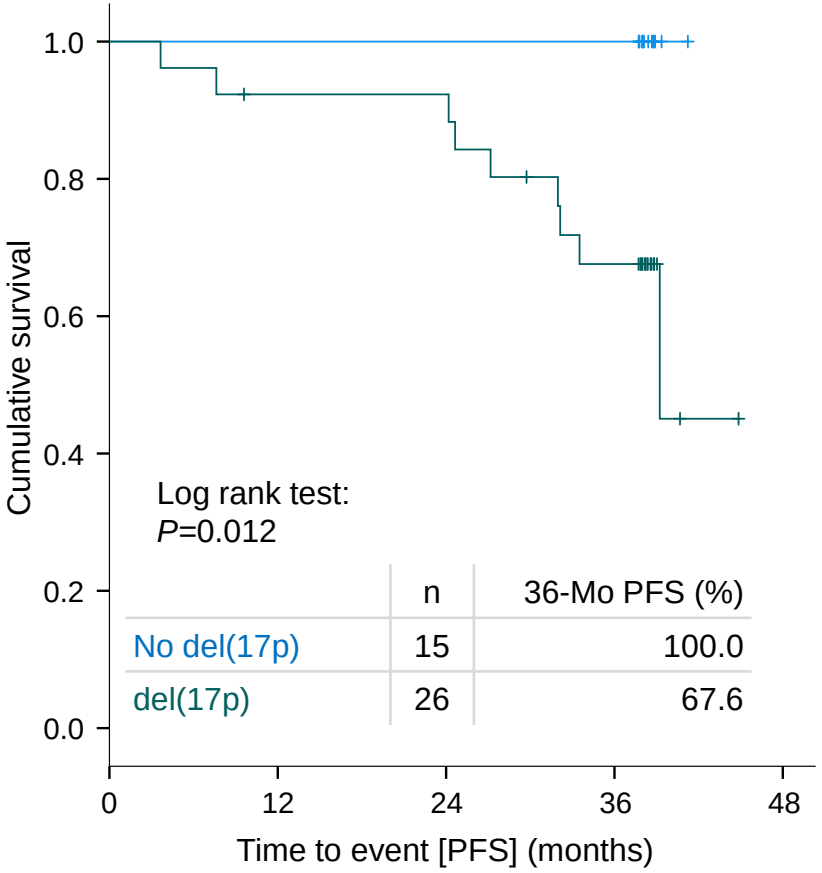
C, cycle; CLL, chronic lymphocytic leukemia; CRi, complete response with incomplete hematological recovery; CR, complete response; CrCl, creatinine clearance; EFS, event-free survival; MRD, minimal residual disease; OS, overall survival; PFS, progression-free survival; uMRD, undetectable minimal residual disease.

Huber H *et al*. Oral presentation at ASH 2022; New Orleans, LA, USA, December 10–13, 2022 (Abstract 343).

CLL2GIVe: Efficacy results

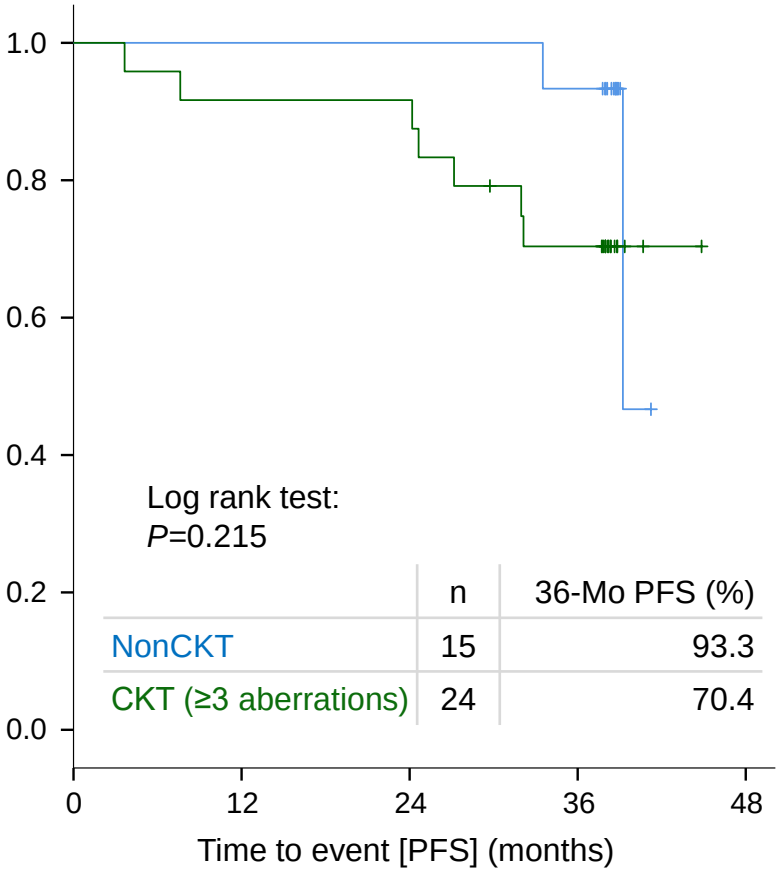
Correlation between PFS and genetics

PFS and del(17p)



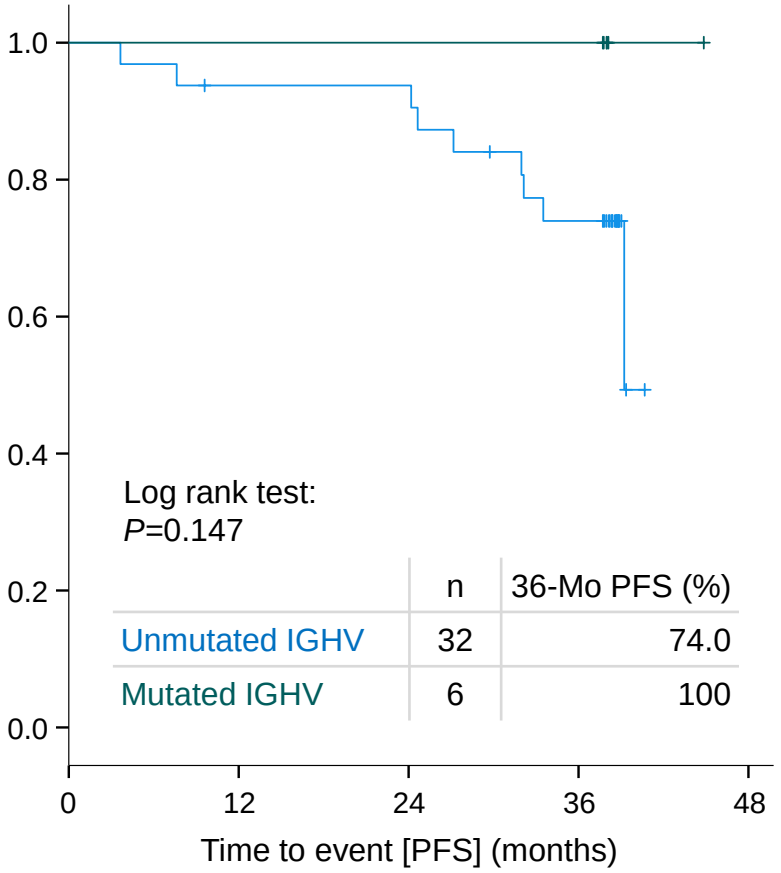
	n	36-Mo PFS (%)
No del(17p)	15	100.0
del(17p)	26	67.6

PFS and complex karyotype*



	n	36-Mo PFS (%)
NonCKT	15	93.3
CKT (≥3 aberrations)	24	70.4

PFS and IGHV mutation status

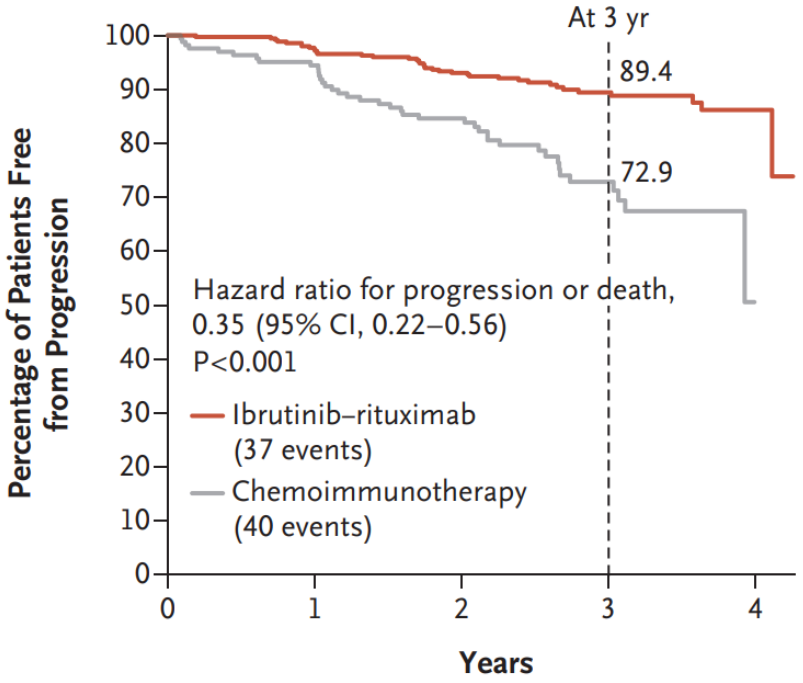


	n	36-Mo PFS (%)
Unmutated IGHV	32	74.0
Mutated IGHV	6	100

*Two patients were not evaluable.
CKT, complex karyotype; IGHV, immunoglobulin heavy chain variable; Mo, months; PFS, progression-free survival.
Huber H *et al*. Oral presentation at ASH 2022; New Orleans, LA, USA, December 10–13, 2022 (Abstract 343).

First-line ibrutinib in fit patients with CLL: Rtx-Ibr vs. FCR

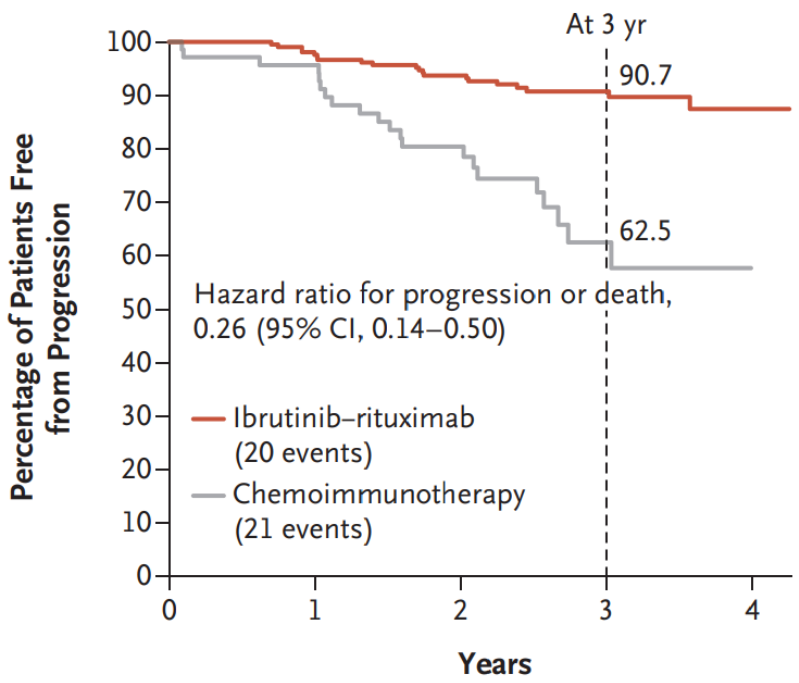
PFS among all patients



No. at Risk

Ibrutinib–rituximab	354	339	298	148	16
Chemoimmunotherapy	175	147	112	50	0

PFS among patients with unmutated IGHV



No. at Risk

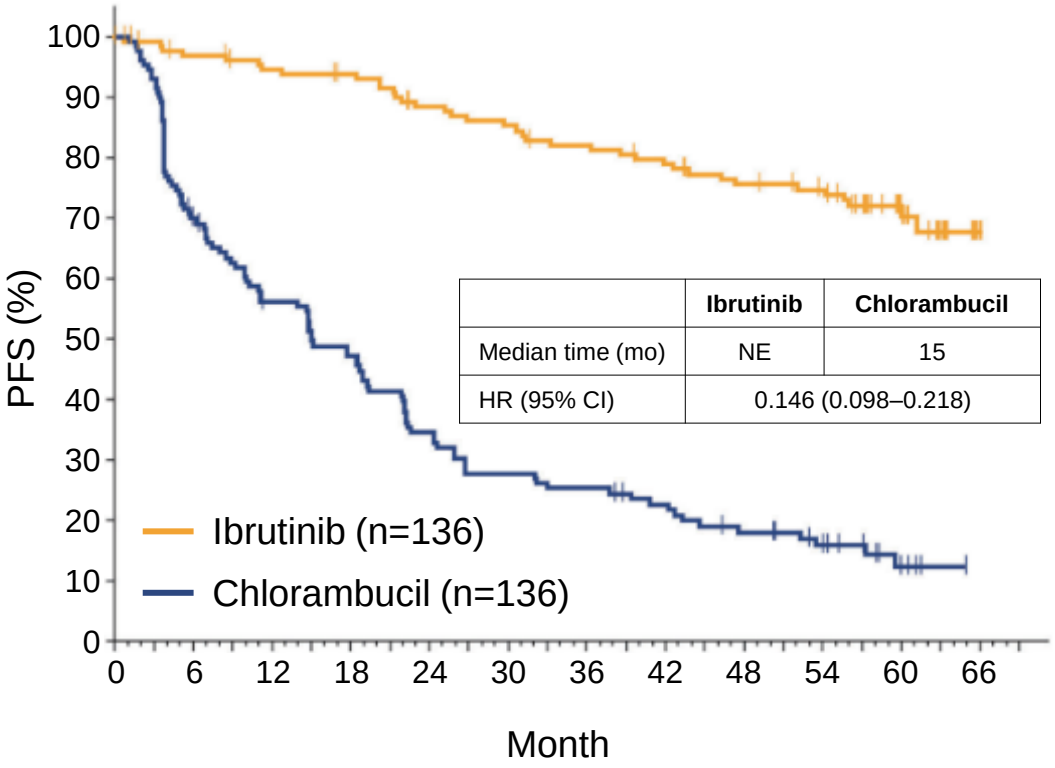
Ibrutinib–rituximab	210	203	177	90	12
Chemoimmunotherapy	71	64	43	14	0

CI, confidence interval; CLL, chronic lymphocytic leukemia; FCR, fludarabine, cyclophosphamide and rituximab; Ibr, ibrutinib; IGHV, immunoglobulin heavy chain variable; Rtx, rituximab.

Shanafelt TD *et al*. *N Engl J Med* 2019; 381 (5): 432–443.

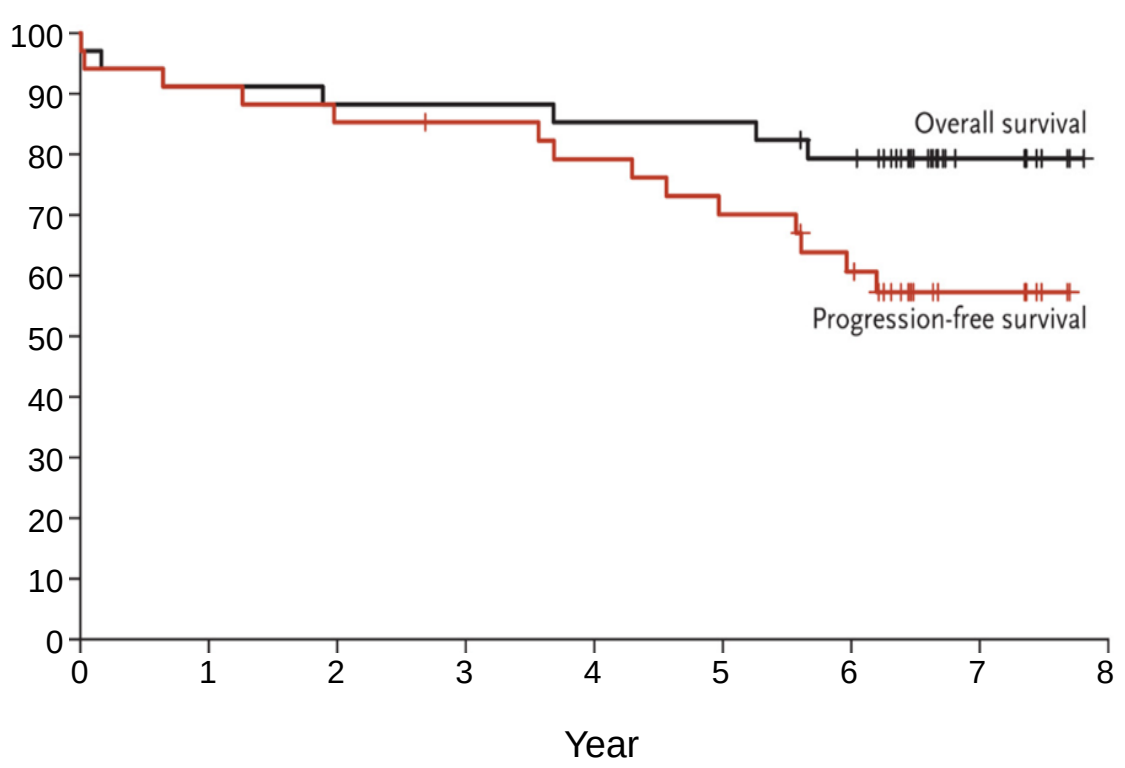
First-line ibrutinib treatment: Long-term outcomes

PFS with single-agent ibrutinib vs. chlorambucil in first-line treatment for CLL/SLL[1]



	Ibrutinib	Chlorambucil
Median time (mo)	NE	15
HR (95% CI)	0.146 (0.098–0.218)	

OS and PFS with ibrutinib in first-line treatment for CLL with *TP53* alterations (N=34)[2]

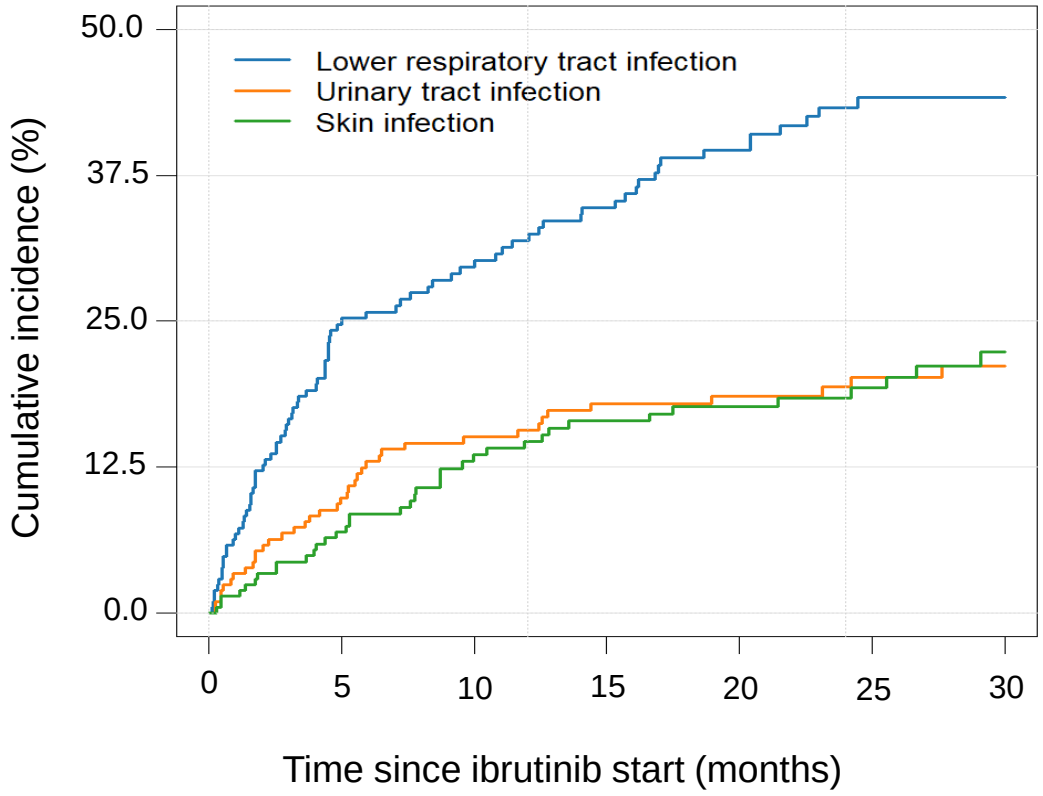


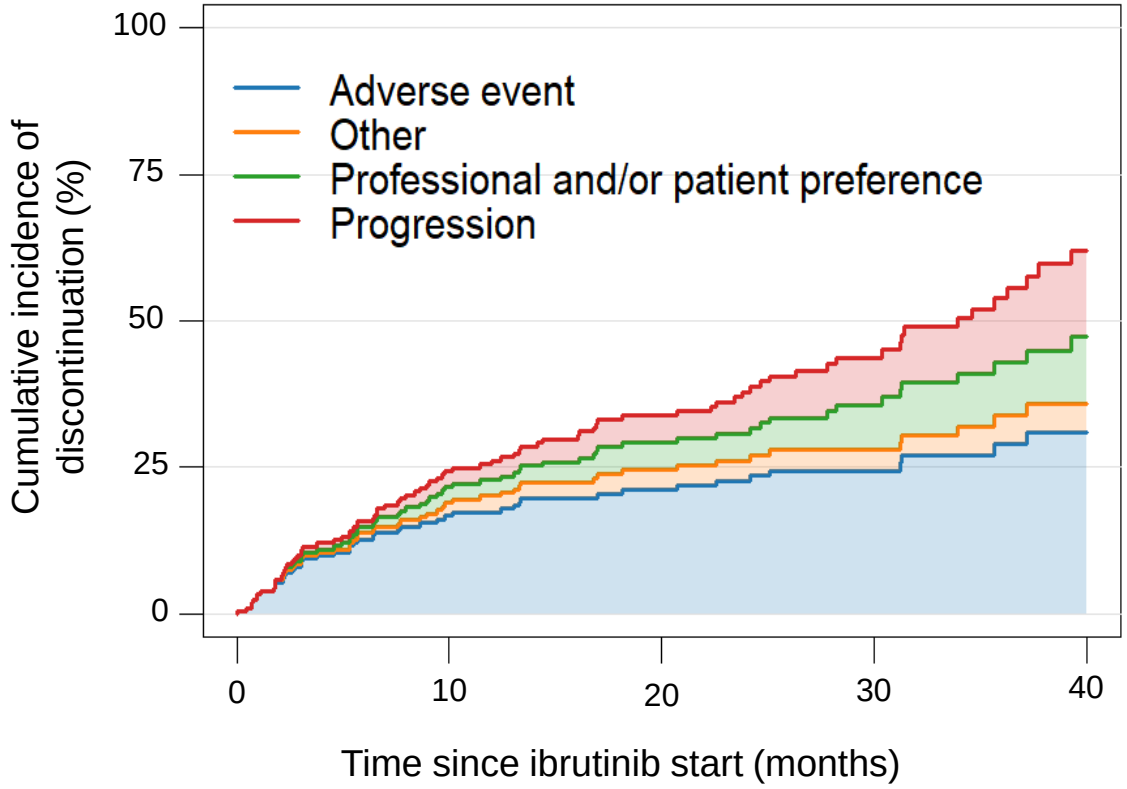
CI, confidence interval; CLL, chronic lymphocytic leukemia; mo, months; NE, not estimable; SLL, small lymphocytic leukemia.

1. Burger JA *et al*. *Leukemia* 2020; 34 (3): 787–798; 2. Ahn IE *et al*. *N Engl J Med* 2020; 383: 498–500.

Ibrutinib: Danish real-world data

Infections, adverse events, discontinuations





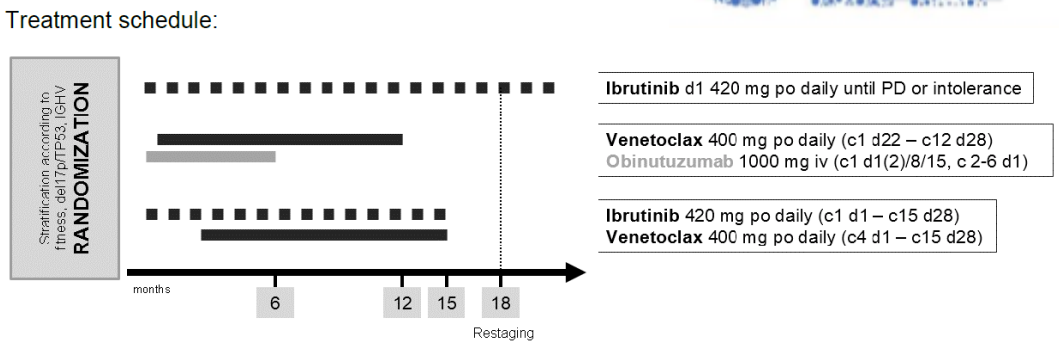
Data are for 205 patients with CLL treated with ibrutinib, including 39 (19%) who were previously treatment-naïve.
Aarup K *et al*. *Eur J Haematol* 2020; 105 (5): 646–654.

Personalized CLL: Treatment patterns and future perspectives

First-line CLL

- Patients with CLL and mutated IGHV have excellent outcomes on CIT
- Patients with CLL and unmutated IGHV should receive BCL2i- or BTKi-based therapy
- *TP53*: maybe a BTKi is better; >1 aberration: consider a clinical trial
- FISH and IGHV testing should be performed before treatment
- ~~Continuous treatment~~
- Head-to-head comparison of fixed-duration versus continuous regimens in the CLL17 trial is awaited[1]

CLL17



BCL2i, B-cell lymphoma 2 inhibitor; BTKi, Bruton's tyrosine kinase inhibitor; c, cycle; CIT, chemoimmunotherapy; CLL, chronic lymphocytic leukemia; d, day; FISH, fluorescence in situ hybridization; IGHV, immunoglobulin heavy chain variable; IV, intravenous; PD, progressive disease; PO, per os.

1. ClinicalTrials.gov. NCT04608318. Available at: https://clinicaltrials.gov/ct2/show/NCT04608318. Accessed February 2023.

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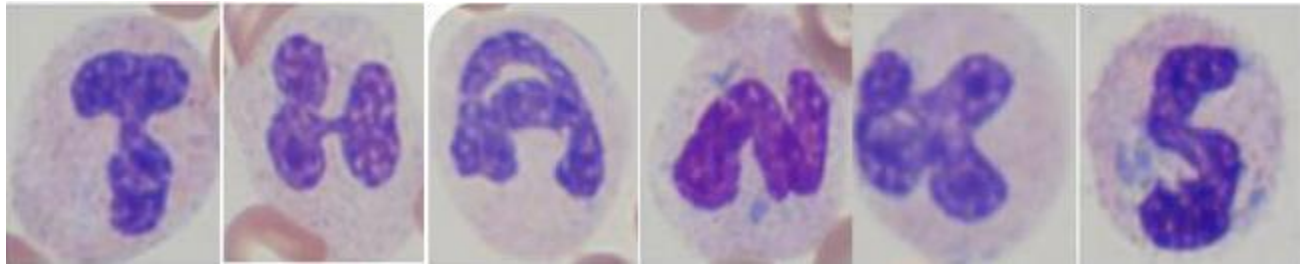

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Combining translational, epidemiological and clinical research to develop individually tailored supportive care and CLL specific treatment

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