Session II – Current initial treatment
Is there still a role for the conventional chemoimmunotherapy?

Clemens Wendtner

Professor of Medicine & Director
Munich Clinic
Academic Teaching Hospital
Ludwig Maximilian University (LMU)
Munich

3rd Postgraduate CLL Conference, Bologna, Nov 14th, 2022

Potential Conflicts of Interest

Research Support/P.I.	Hoffmann-La Roche, GSK, Cilag-Janssen, Gilead, Genentech, Morphosys, AbbVie, AstraZeneca, BeiGene
Employee	NA
Consultant	Hoffmann-La Roche, GSK, Cilag-Janssen, Gilead, Genentech, Morphosys, AbbVie, Amgen, AstraZeneca, BioNTech, Lilly, BeiGene
Major Stockholder	NA
Speakers Bureau	NA
Honoraria	Hoffmann-La Roche, GSK, Cilag-Janssen, Gilead, Genentech, Morphosys, AbbVie, Amgen, AstraZeneca, BioNTech, Lilly, BeiGene
Scientific Advisory Board	Hoffmann-La Roche, GSK, Cilag-Janssen, Gilead, Genentech, Morphosys, AbbVie, AstraZeneca, BioNTech, Lilly, BeiGene

How many of your CLL patients did you treat in the last 6 months with conventional chemoimmunotherapy?

1) none
2) 1-5 pts
3) 6-10 pts
4) >10 pts

Case:

68 year-old man

chronic kidney failure (creatinine clearance 15 ml/min)

history of ventricular arrhythmias (Brugada syndrome) → ICD

diagnosis of CLL in 9/2022, stage Binet C with massive lymphadenopathy and B symptoms

- **IGHV mutated**
- **13q-**
- **no TP53 mutation**
- **no complex karyotype**

How would you treat this patient in your daily practice?

1) **ibrutinib**

2) **acalabrutinib plus obinutuzumab**

3) **venetoclax plus obinutuzumab**

4) **bendamustine plus rituximab**

REVIEW ARTICLE

blood advances

International consensus statement on the management of cardiovascular risk of Bruton's tyrosine kinase inhibitors in CLL

Farrukh T. Awan,[1] Daniel Addison,[2] Feras Alfraih,[3] Sergio J. Baratta,[4] Rodrigo Noronha Campos,[5] María Silvana Cugliari,[6] Yeow Tee Goh,[7] Valery Alexandrovich Ionin,[8] Stefanie Mundnich,[9] Aaron L. Sverdlov,[10] Constantine Tam,[11] and Loïc Ysebaert[12]

[1]Harold C. Simmons Comprehensive Cancer Center, University of Texas Southwestern Medical Center, Dallas, TX; [2]Cardio–Oncology Program, Division of Cardiology, The Ohio State University Medical Center, Columbus, OH; [3]Oncology Center, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia; [4]Hospital Universitario Austral, Buenos Aires, Argentina; [5]Benefieciencia Portuguesa Hospital, São Paulo, Brazil; [6]Hematology Department, Angel Roffo Institute of Oncology University of Buenos Aires, Buenos Aires, Argentina; [7]Singapore General Hospital, Duke–National University of Singapore Graduate Medical School, Singapore, Singapore; [8]Almazov National Medical Research Centre and Pavlov University, St. Petersburg, Russia; [9]Clínica Red Salud Vitacura y Providencia, Santiago, Chile; [10]Cardiovascular Department, John Hunter Hospital, Hunter New England Local Health District and University of Newcastle, Callaghan, NSW, Australia; [11]Alfred Health and Monash University, Melbourne, Australia; and [12]Institut Universitaire du Cancer de Toulouse Oncopole, Toulouse, France

Table 3. Recommendations for patients with CV risk

Atrial fibrillation
Determine whether the patient is high or low risk
Low-risk cases may be safely treated with BTKis
Favor more second-generation BTKis (acalabrutinib or zanubrutinib) or alternative treatments
BTKi treatment may be continued in consultation with MDT for patients with:
Permanent/persistent AF
HTN
History of myocardial infarction
BTKis **NOT** recommended for patients with:
History of ventricular arrhythmia
Family history of sudden cardiac death
Severe, uncontrolled HTN
Severe or uncontrolled congestive heart failure (LVEF <30%)
Hypertension
If HTN is well-controlled, BTKi therapy may be used
Monitor blood pressure at least biweekly for the first 3-6 mo of BTKi therapy
Maintain early threshold for treatment during BTKi therapy
CHF
Examine with echocardiogram
Restrict to <2 g daily sodium intake
Monitor weight daily
Monitor blood pressure twice weekly
Manage care with MDT (preferred) or in collaboration with a cardio-oncologist
Ventricular arrhythmias
Ibrutinib should be avoided
The risk of second-generation BTKis (acalabrutinib or zanubrutinib) is not currently known

LVEF, left ventricular ejection fraction; MDT, multidisciplinary team.

PrVENCLEXTA®

Dose Modifications for Patients with Renal Impairment

No dose adjustment is recommended for patients with mild or moderate renal impairment (CrCl ≥ 30 mL/min). While severe renal impairment (CrCl ≥ 15 mL/min and < 30 mL/min) did not affect venetoclax pharmacokinetics in 6 patients with AML, clinical experience is limited and a recommended dose has not been determined for patients with severe renal impairment (CrCl < 30 mL/min) or patients on dialysis (see **7 WARNINGS AND PRECAUTIONS** and **10 CLINICAL PHARMACOLOGY**).

Renal Insufficiency

Based on a population pharmacokinetic analysis that included 321 subjects with mild renal impairment (CrCl ≥ 60 and < 90 mL/min, calculated by Cockcroft-Gault equation), 219 subjects with moderate renal impairment (CrCl ≥ 30 and < 60 mL/min), 6 subjects with severe renal impairment (CrCl ≥ 15 and < 30 mL/min) and 224 subjects with normal renal function (CrCl ≥ 90 mL/min), venetoclax exposures in subjects with mild, moderate or severe renal impairment are similar to those with normal renal function. The pharmacokinetics of venetoclax has not been studied in subjects with end-stage renal disease (CrCl < 15 mL/min) or subjects on dialysis (see **7 WARNINGS AND PRECAUTIONS** and **4 DOSAGE AND ADMINISTRATION**).

Successful treatment of relapsed chronic lymphocytic leukemia with venetoclax in a patient with severe chronic kidney disease

Hiroyuki Sugiura[1] | Nobuo Sezaki[1] | Tatsunori Ishikawa[1] | Taiga Kuroi[1] | Sachiyo Okamoto[1] | Naho Nomura[1] | Taro Masunari[1] | Yukio Nakasako[2] | Toru Kiguchi[3] | Mitsune Tanimoto[1]

Crea Cl: 18ml/min

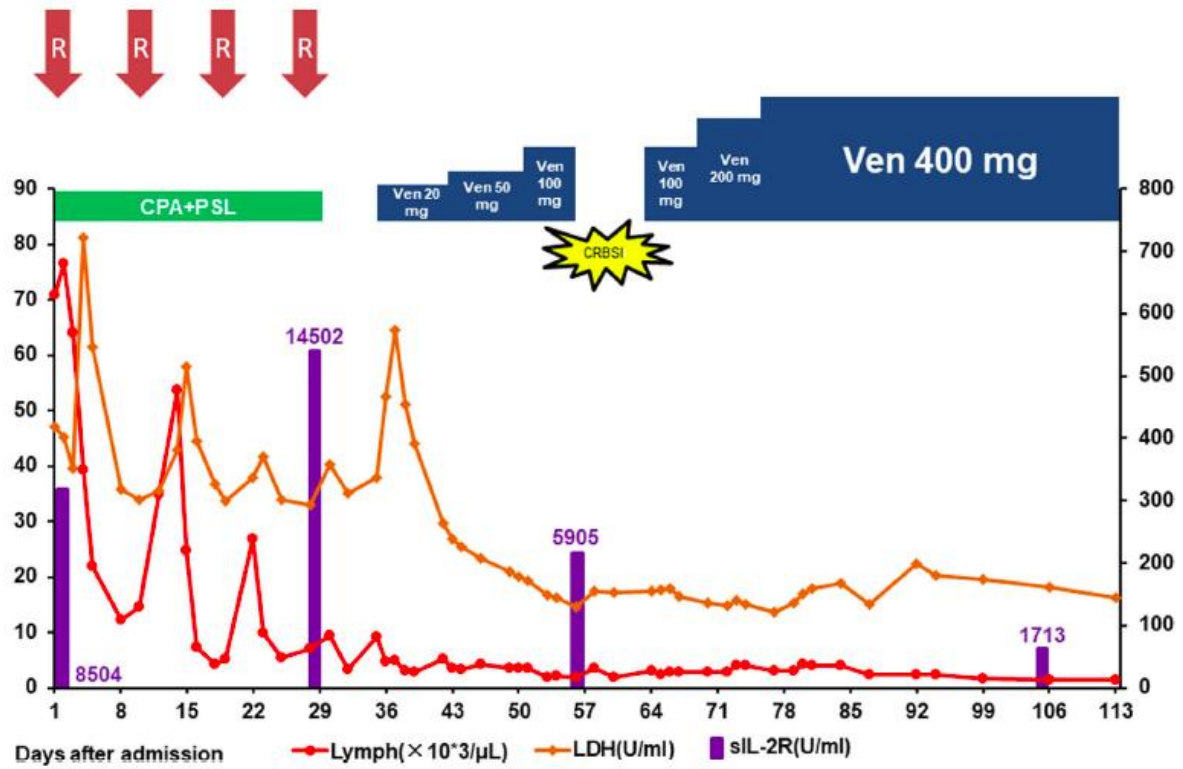
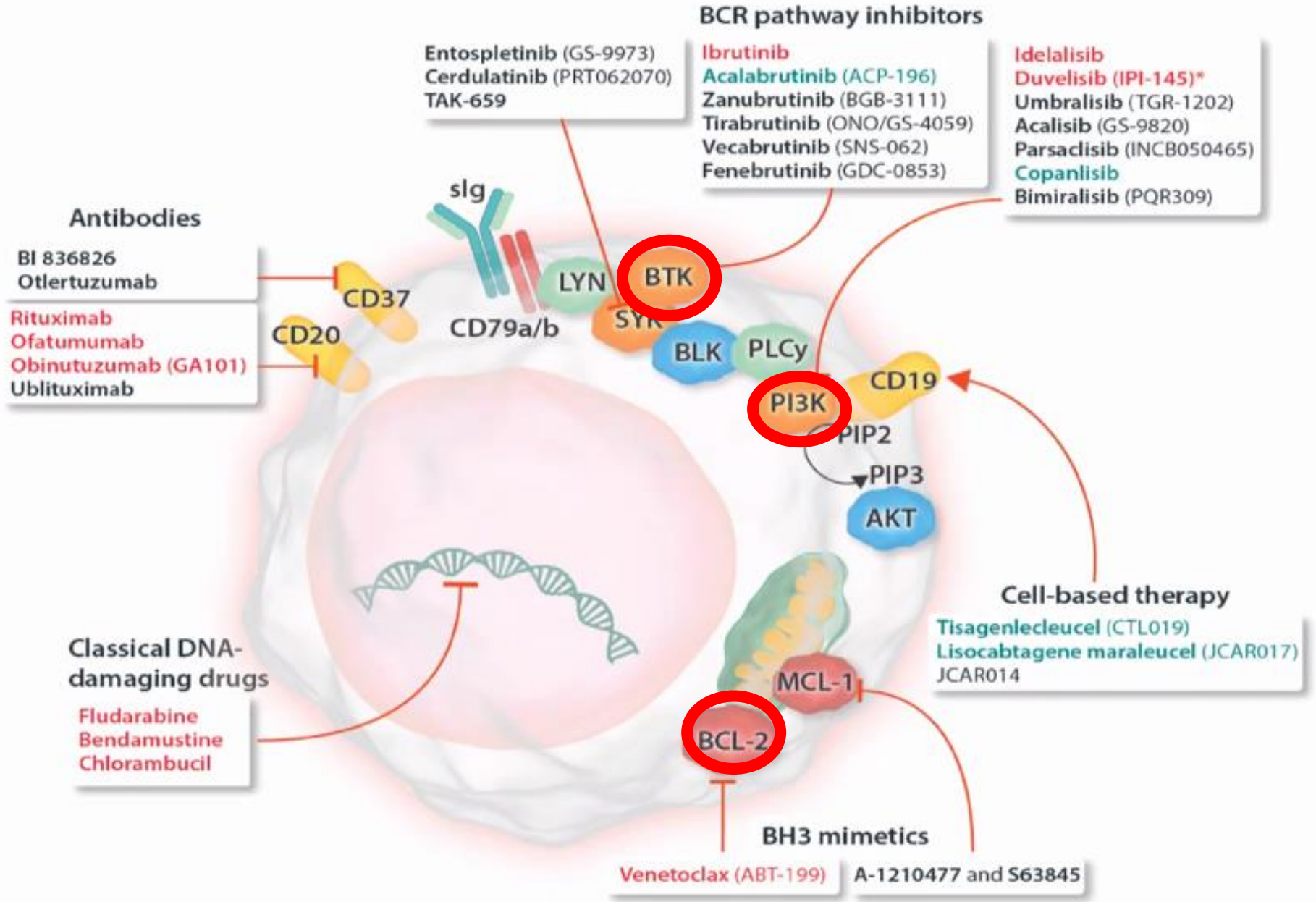


FIGURE 2 Clinical course of the patient from the admission day to the discharge day (Day 113). Lymphocyte follows left axis and LDH follows right axis. After debulking by CPA + PSL + Rituximab, venetoclax was started, and the dose was increased gradually; the treatment response was good. Because of the complications of CRBSI, venetoclax treatment was stopped. After the exchange of the catheter and antibiotic therapy, venetoclax was restarted safely. CPA, cyclophosphamide; CRBSI, catheter-related bloodstream infection; PSL, prednisolone; R, rituximab; Ven, venetoclax

Clin Case Rep. 2022;10:e05735.
https://doi.org/10.1002/ccr3.5735

From Biology to Therapy: Model System CLL

Yosifov, et al. Hemashere 2019



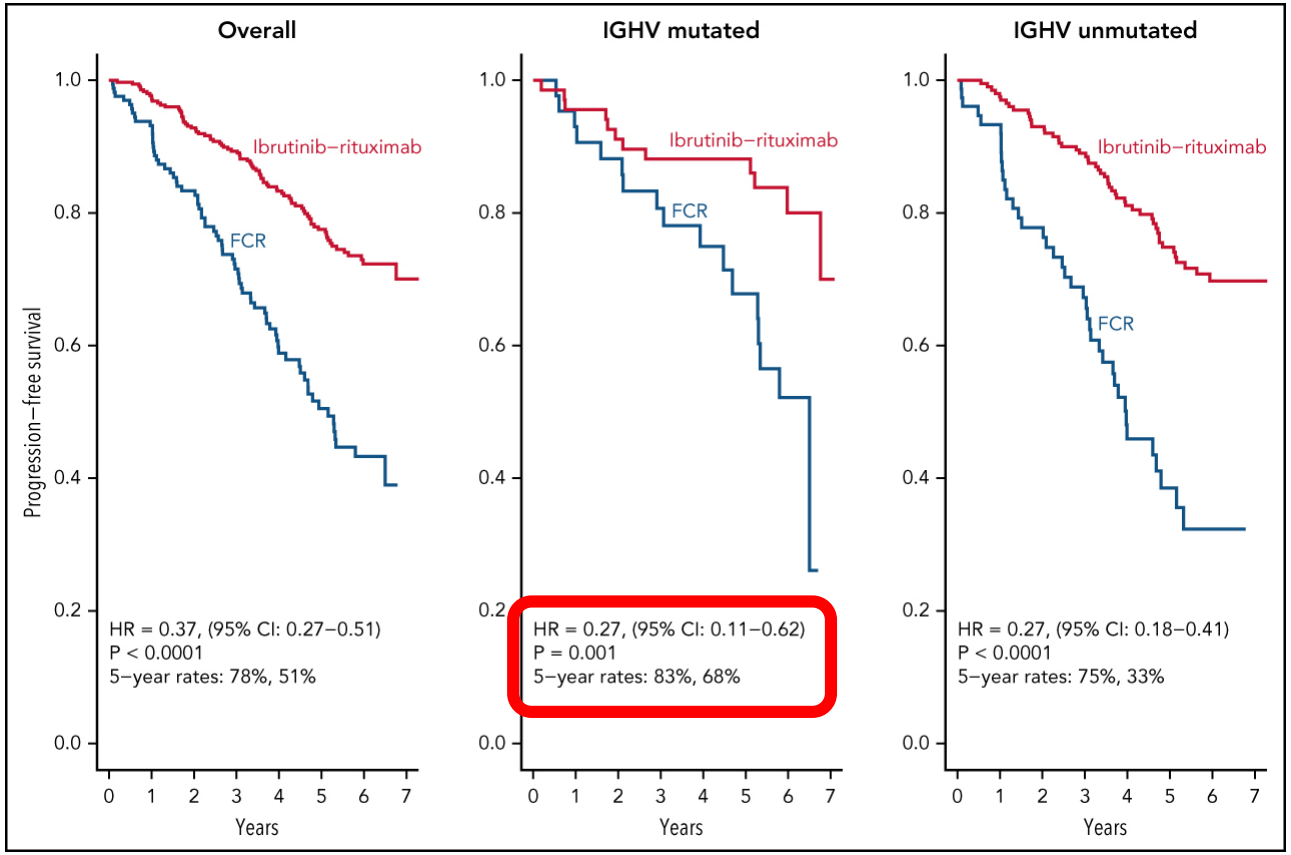
ECOG 1912: Ibrutinib/Rituximab (IR) vs FCR

Based on ECOG1912 (IR vs FCR), which statement is wrong?

1) **median PFS is superior for ibrutinib/rituximab (IR) compared to FCR**
2) **PFS benefits for IR were only seen in the $IGHV_{unmut}$ subgroup**
3) **after a median follow-up of 5.8 yrs only 60.5% of pts remain on IR**
4) **OS was significantly superior for pts being treated with IR (vs. FCR)**

Long-term outcomes for ibrutinib–rituximab and chemoimmunotherapy in CLL: updated results of the E1912 trial

Tait D. Shanafelt,[1] Xin Victoria Wang,[2] Curtis A. Hanson,[3] Elisabeth M. Paietta,[4] Susan O'Brien,[5] Jacqueline Barrientos,[6] Diane F. Jelinek,[3] Esteban Braggio,[3] Jose F. Leis,[3] Cong Christine Zhang,[7] Steven E. Coutre,[1] Paul M. Barr,[8] Amanda F. Cashen,[9] Anthony R. Mato,[10] Avina K. Singh,[11] Michael P. Mullane,[12] Richard F. Little,[13] Harry Erba,[14] Richard M. Stone,[2] Mark Litzow,[3] Martin Tallman,[10] and Neil E. Kay[3]



Long-term outcomes for ibrutinib–rituximab and chemoimmunotherapy in CLL: updated results of the E1912 trial

Tait D. Shanafelt,[1] Xin Victoria Wang,[2] Curtis A. Hanson,[3] Elisabeth M. Paietta,[4] Susan O'Brien,[5] Jacqueline Barrientos,[6] Diane F. Jelinek,[3] Esteban Braggio,[3] Jose F. Leis,[3] Cong Christine Zhang,[7] Steven E. Coutre,[1] Paul M. Barr,[8] Amanda F. Cashen,[9] Anthony R. Mato,[10] Avina K. Singh,[11] Michael P. Mullane,[12] Richard F. Little,[13] Harry Erba,[14] Richard M. Stone,[2] Mark Litzow,[3] Martin Tallman,[10] and Neil E. Kay[3]

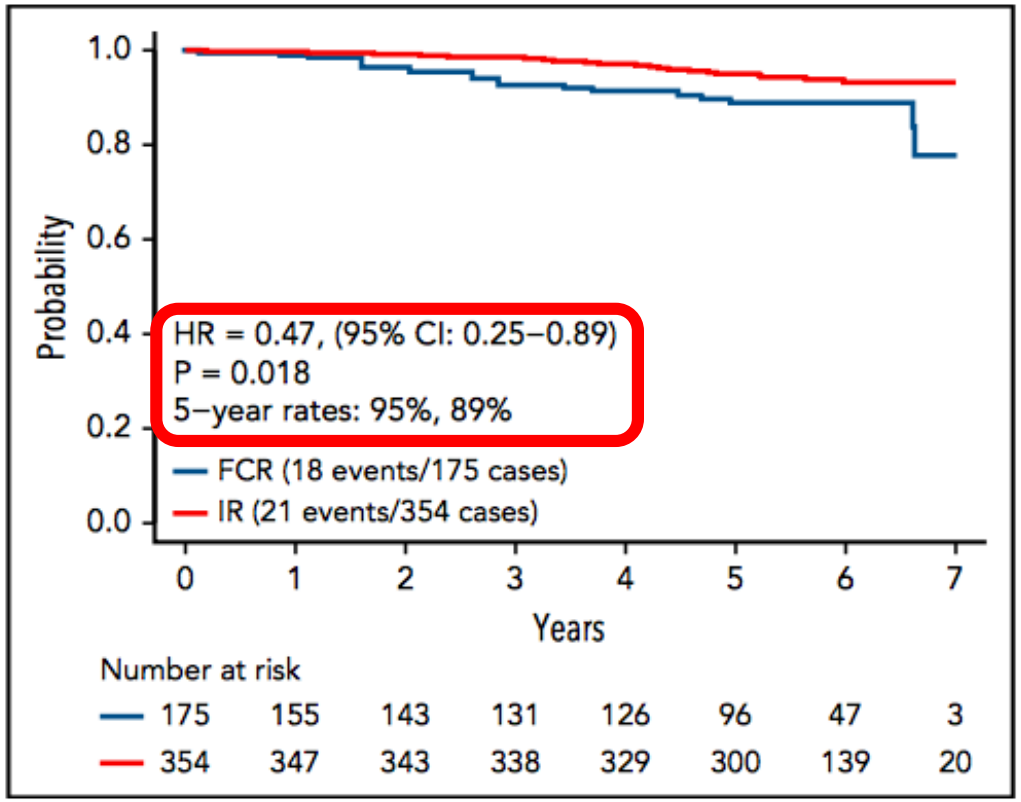
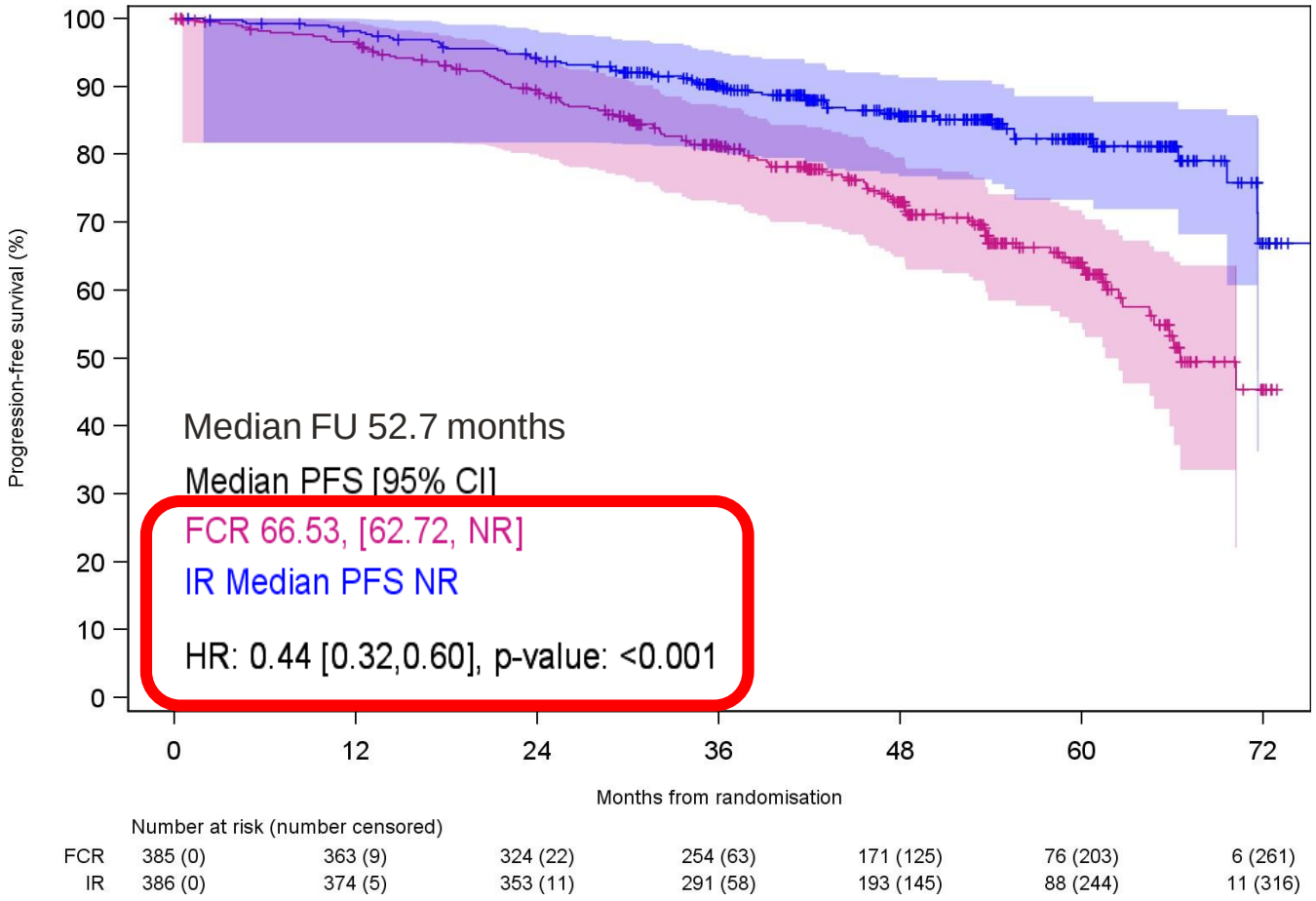


Figure 4. OS comparison for IR vs FCR arms.

Phase III NCRI FLAIR Trial: Ibrutinib plus rituximab vs FCR

Primary endpoint: PFS



IWCLL Response 3-months post-treatment with FCR/R

	FCR (n=385)	IR (n=386)
CR	233 (60.5%)	81 (21.0%)
PR	106 (27.6%)	271 (70.2%)
SD/PD/NR	46 (11.9%)	34 (8.8%)

Proportion of participants with MRD negativity* in the bone marrow at 3-months post-treatment with FCR/R

	FCR (n=385)	IR (n=386)
MRD Negative	213 (55.3%)	15 (3.9%)
MRD Positive	140 (36.4%)	357 (92.5%)
N/A	32 (8.3%)	14 (3.6%)

*, MRD flow cytometry <1 CLL cell/10,000 (IWCLL criteria)

A greater percentage of participants in the FCR arm became MRD negative in the bone marrow 3-months post-treatment compared to the IR arm (55.3% vs 3.9%)

Hillmen et al., ASH 2021; abstract 642

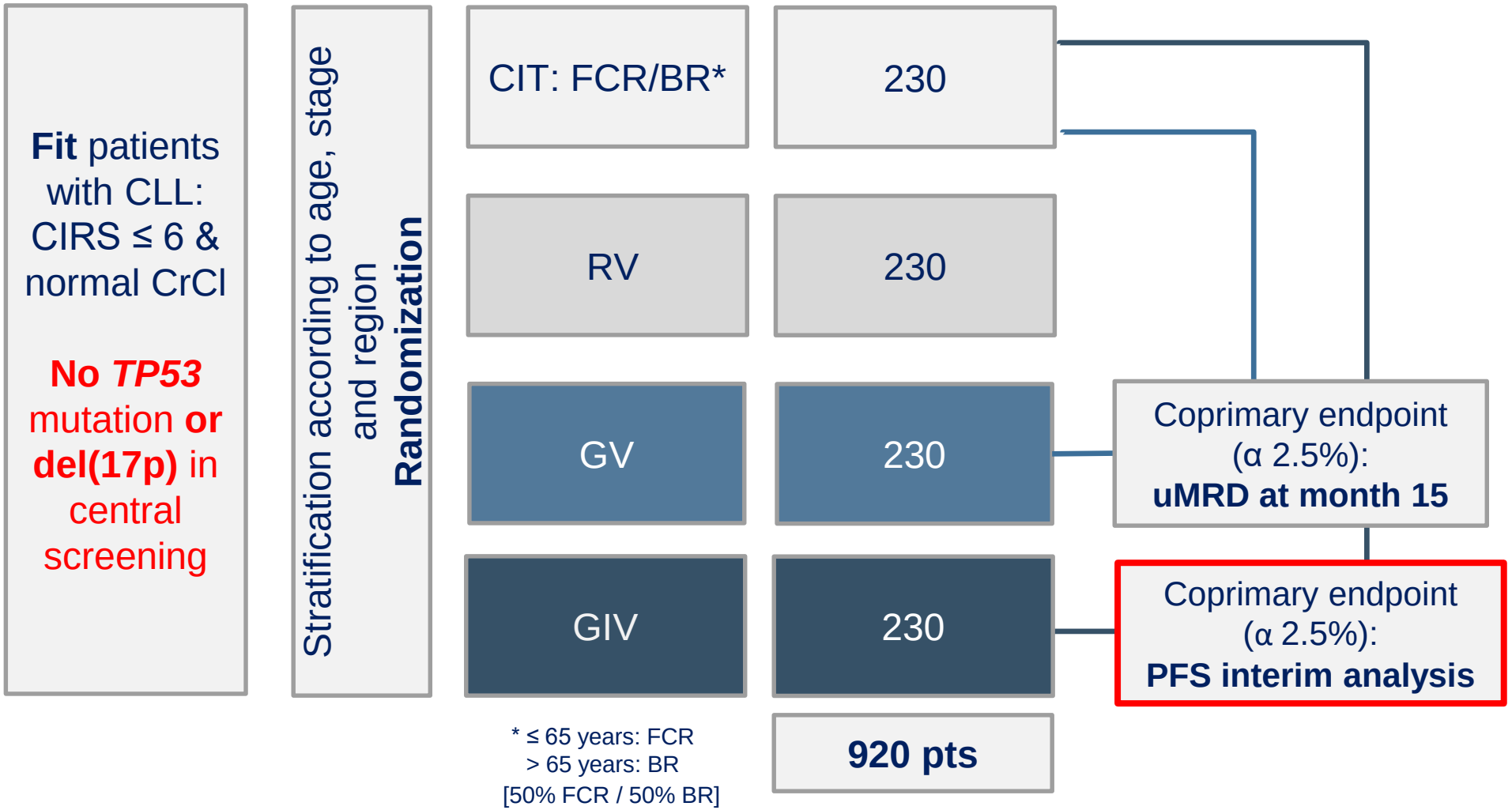
TIME-LIMITED VENETOCLAX-OBINUTUZUMAB +/- IBRUTINIB IS SUPERIOR TO CHEMOIMMUNOTHERAPY IN FRONTLINE CHRONIC LYMPHOCYTIC LEUKEMIA (CLL): PFS CO-PRIMARY ENDPOINT OF THE RANDOMIZED PHASE 3 GAIA/CLL13 TRIAL

Barbara Eichhorst, Carsten U Niemann, Arnon P Kater, Moritz Fürstenau, Julia von Tresckow, Can Zhang, Sandra Robrecht, Michael Gregor, Gunnar Juliusson, Patrick Thornton, Philipp B. Staber, Tamar Tadmor, Vesa Lindström, Caspar da Cunha-Bang, Christoph Schneider, Christian Poulsen, Thomas Illmer, Björn Schöttker, Ann Janssens, Ilse Christiansen, Thomas Nösslinger, Michael Baumann, Marjolein van der Klift, Ulrich Jäger, Henrik Frederiksen, Maria BL Leys, Mels Hoogendoorn, Kourosh Lotfi, Holger Hebart, Tobias Gaska, Harry Koene, Florian Simon, Nisha De Silva, Anna Fink, Kirsten Fischer, Clemens Wendtner, Karl A Kreuzer, Matthias Ritgen, Monika Brüggemann, Eugen Tausch, Mark-David Levin, Marinus van Oers, Christian Geisler, Stephan Stilgenbauer, Michael Hallek

GAIA/CLL13 study design for **fit** patients with CLL

Chemoimmunotherapy (**FCR/BR**) versus **R**ituximab + **V**enetoclax versus Obinutuzumab (**G**) + **V** versus **G** + **I**brutinib + **V**

Recruitment in 10 countries (DE, AT, CH, NL, BE, DK, SE, FI, IE, IL)



Based on CLL13, which statement is wrong?

1) **triple combo obinutuzumab/ibrutinib/venetoclax (GIV) induces uMRD ($<10^{-4}$) in 92% of treated pts**

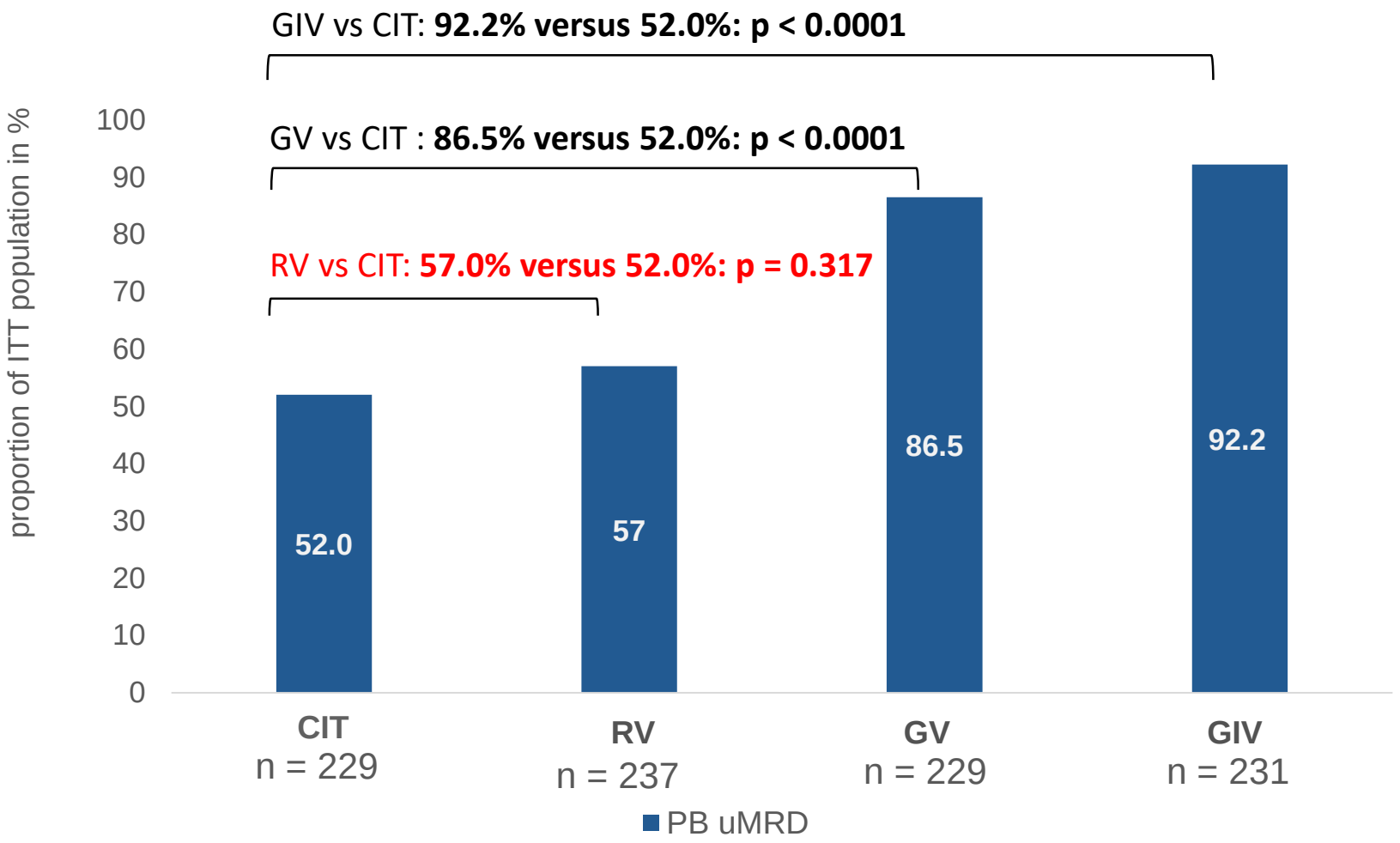
2) **venetoclax/rituximab is equally effective with respect to uMRD compared to CIT (FCR, BR)**

3) **3-yr PFS rate is 80% for GIV-treated pts**

4) **more than 20% of pts suffered from severe infections (III/IV) under GIV treatment**

Results of coprimary endpoint rate of undetectable minimal residual disease (uMRD)

Coprimary endpoint: uMRD (< 10^{-4}) at Mo15 in PB by 4-colour-flow

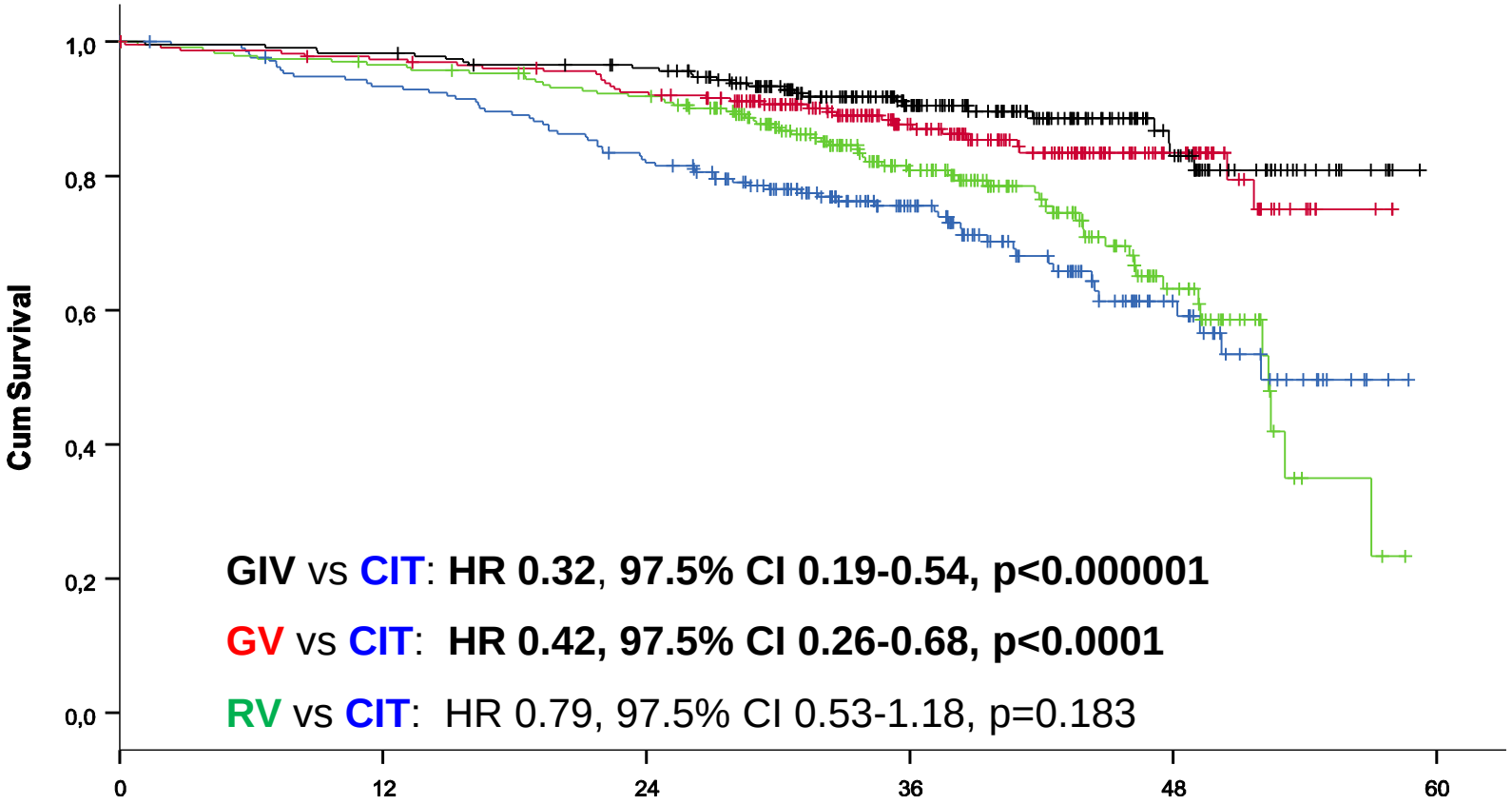


	uMRD%	97.5% CI
GIV	92.2	87.3 – 95.7
GV	86.5	80.6 – 91.1
RV	57.0	49.5 – 64.2
CIT	52.0	44.4 – 59.5

Eichhorst B. et al., ASH 2021: abstract 72

Results of the coprimary endpoint progression-free survival (PFS)

Median FU 38.8 months (range: 0.0 – 59.2)

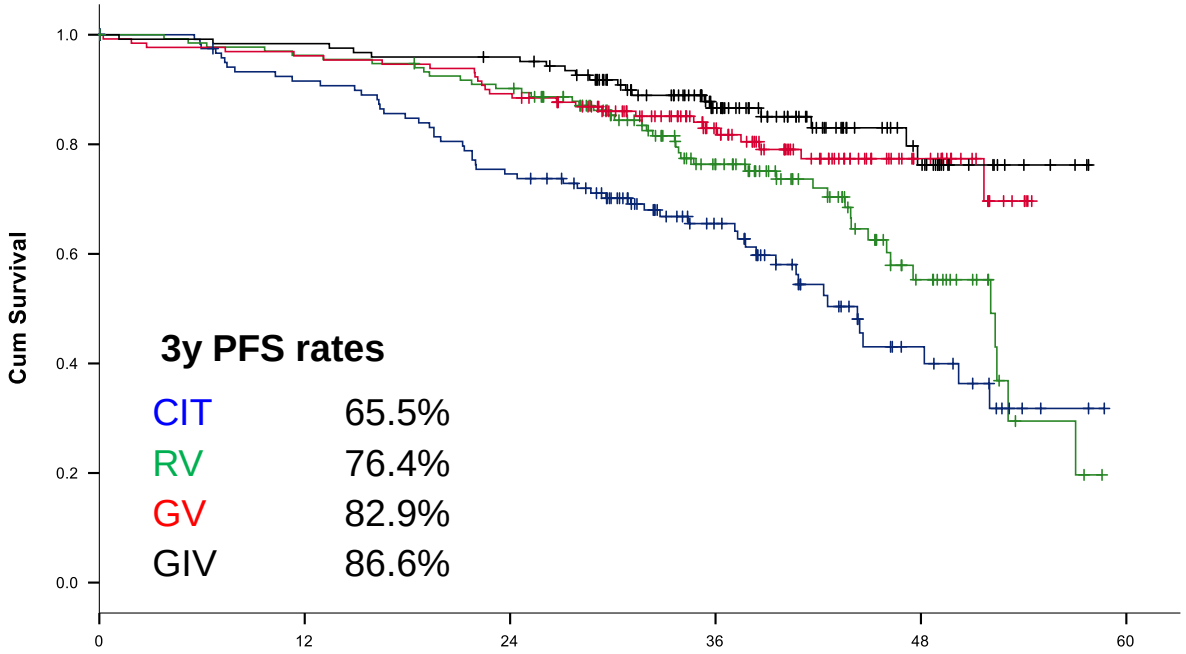


CIT	229	197	172	98	28
RV	237	226	212	119	32
GV	229	221	208	125	42
GIV	231	227	217	132	44

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

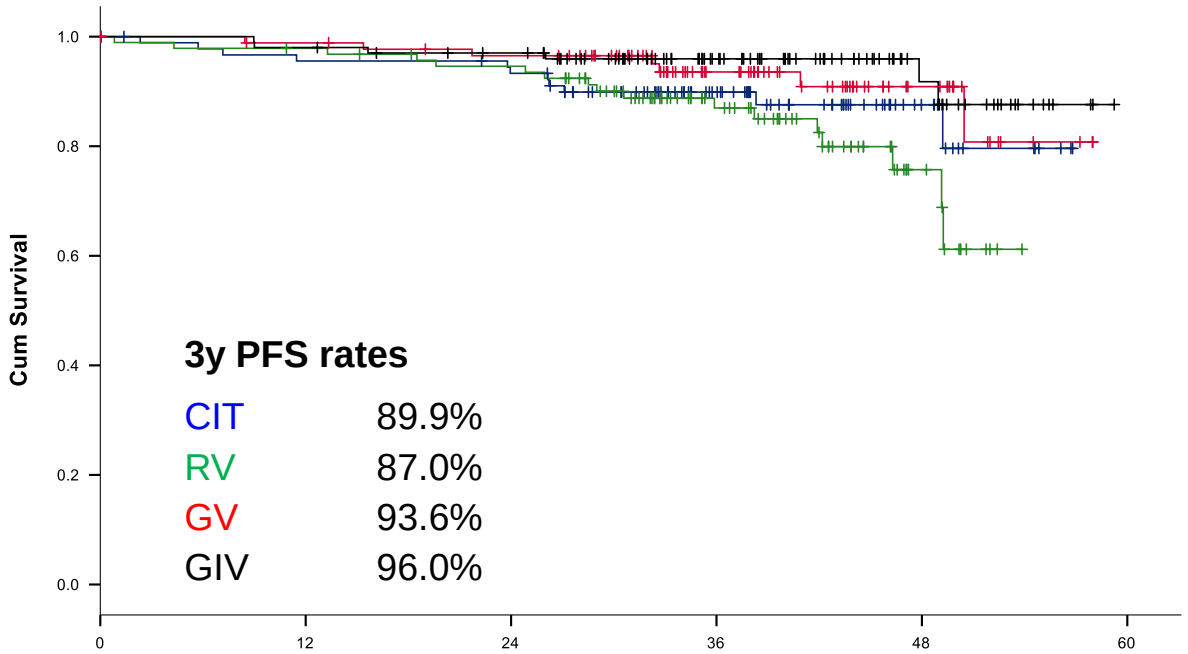
PFS according to IGHV status

Unmutated IGHV



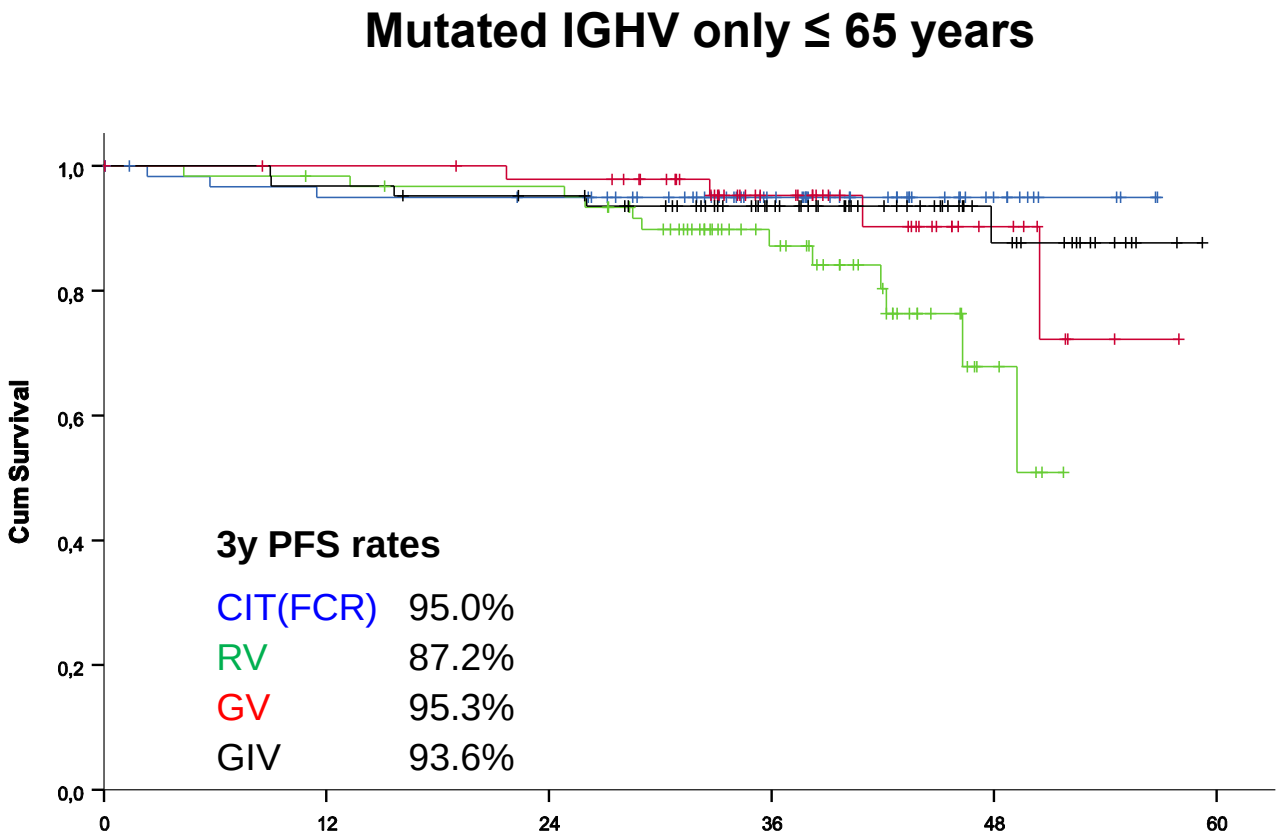
CIT	131	108	88	48	14
RV	134	128	119	67	20
GV	130	125	116	71	21
GIV	123	121	117	70	22

Mutated IGHV



CIT	95	86	83	50	14
RV	95	91	86	49	12
GV	89	86	82	48	17
GIV	101	99	94	59	22

PFS according to IGHV status: Subgroup mutated IGHV AND ≤ 65 years



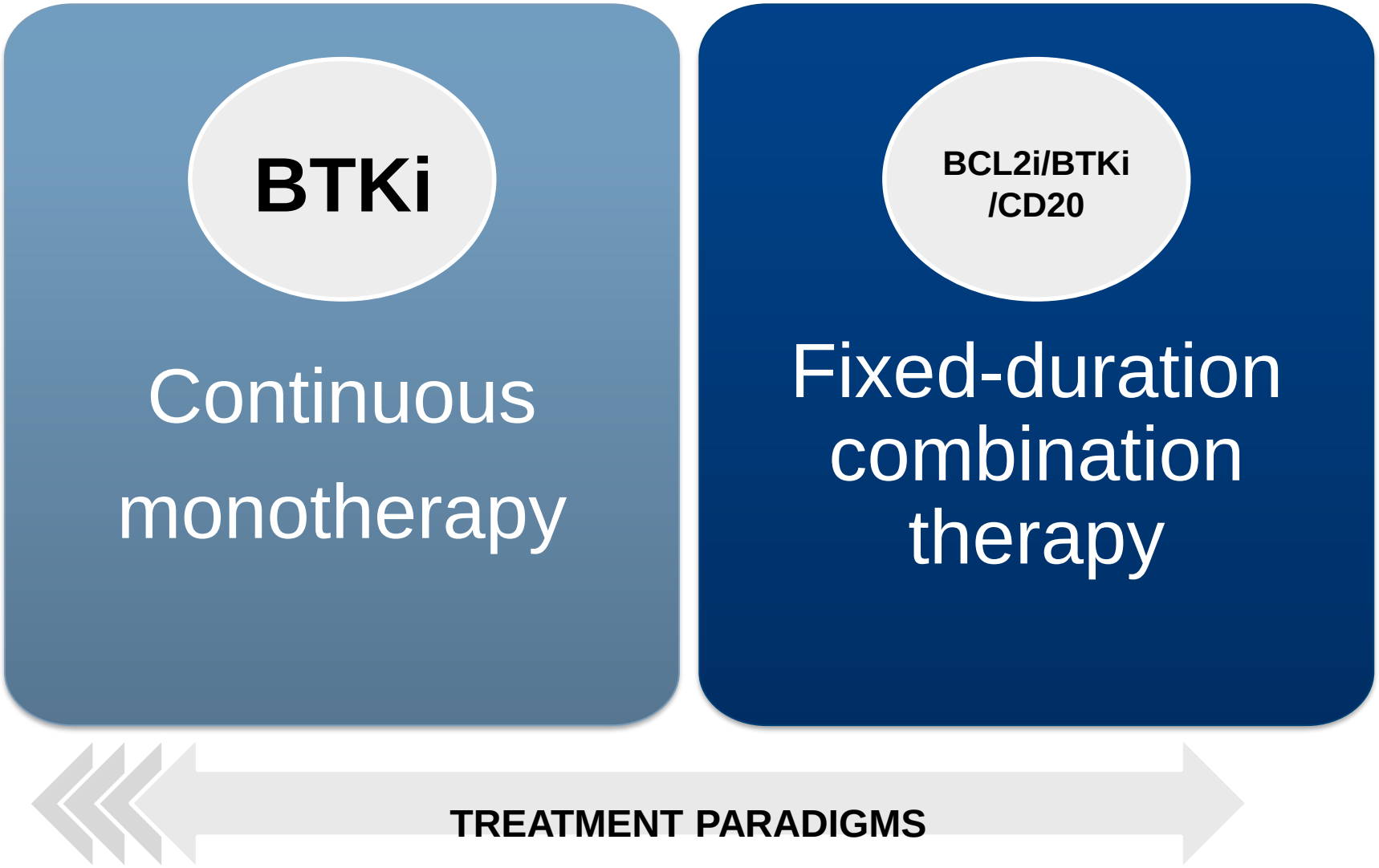
FCR	65	57	56	34	10
RV	62	60	58	33	5
GV	50	48	46	27	8
GIV	63	61	58	40	15

Adverse Events ≥ CTC Grade 3 Overview

Severe AEs occurring in ≥5% of pts in at least one arm and of interest

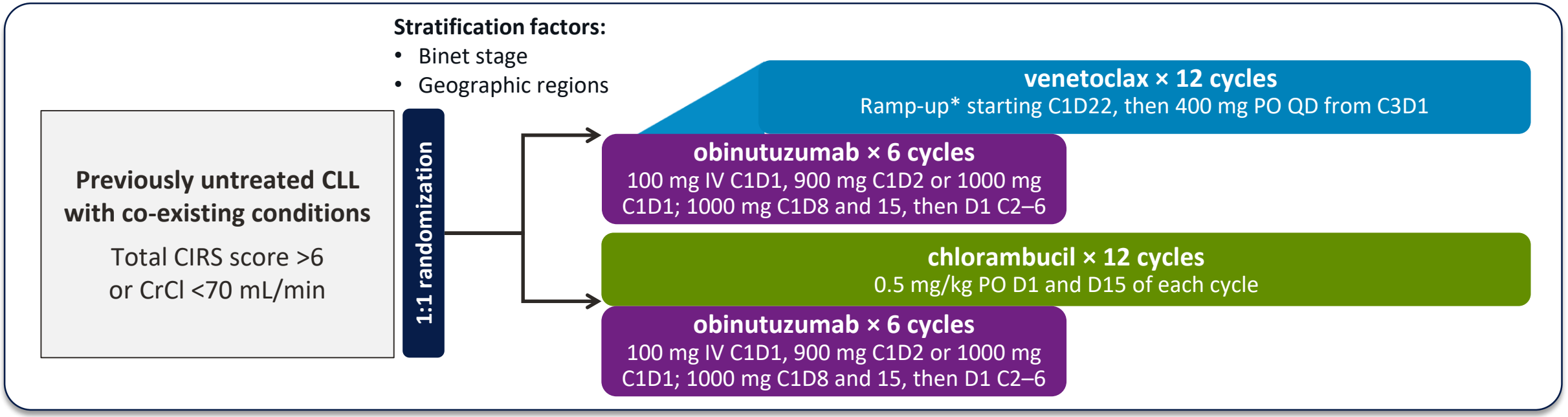
	CIT	RV	GV	GIV
All patients of safety population	**216**	**237**	**228**	**231**
All ≥ CTC grade 3 events (%)	**176 (81.5)**	**173 (73.0)**	**192 (84.2)**	**193 (83.5)**
Blood and lymphatic system (%)	122 (56.5)	103 (43.5)	128 (56.1)	117 (50.6)
Infections and infestations (%)	44 (20.4)	27 (11.4)	34 (14.9)	**51 (22.1)**
Febrile neutropenia (%)	24 (11.1)	10 (4.2)	7 (3.1)	18 (7.8)
Infusion related reaction (%)	12 (5.6)	19 (8)	26 (11.4)	10 (4.3)
Tumor lysis syndrome (%) *	9 (4.2)	24 (10.1)	19 (8.3)	15 (6.5)
Hypertension (%)	3 (1.4)	5 (2.1)	4 (1.8)	13 (5.6)

* Defined by Cairo-Bishop criteria


BTKi
Continuous monotherapy
BCL2i/BTKi /CD20
Fixed-duration combination therapy
TREATMENT PARADIGMS
ECOG1912: I/R
RESONATE: I
iLLUMINATE: I+Obi
ELEVATE-TN: Acala+/- Obi
SEQUOIA: Zanubrutinib
CLL13/CLL14: VenObi
GLOW: I+V

CLL14 Study Design

DEUTSCHE STUDIENGRUPPE



Primary Endpoint (ITT population):
- PFS – investigator-assessed

Key Secondary Endpoints (ITT population):
- PFS – IRC-assessed
- ORR and CR 3 months after EoT
- MRD response rate (PB and BM) 3 months after EoT:
  - All patients
  - Patients with CR
- Overall survival

Analyses:
- Interim analysis: 110 PFS events
- Final PFS analysis: 170 PFS events
- Final OS analysis: End of study, 5 years after last patient enrolled

28-day cycles.
* Venetoclax 5-week dose ramp-up starting C1D22: 1 week each of 20, 50, 100, and 200 mg, then 400 mg for 1 week, thereafter continuing at 400 mg until completion of cycle 12. BM, bone marrow; CIRS, cumulative illness rating scale; CR, complete remission; CrCl, creatinine clearance; EoT, end of treatment; IRC, Independent Review Committee; ITT, intention-to-treat; IV, intravenous; ORR, overall response rate; PB, peripheral blood; PO, orally; QD, daily.

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

Based on CLL14 (VenObi vs ClbObi), which statement is wrong?

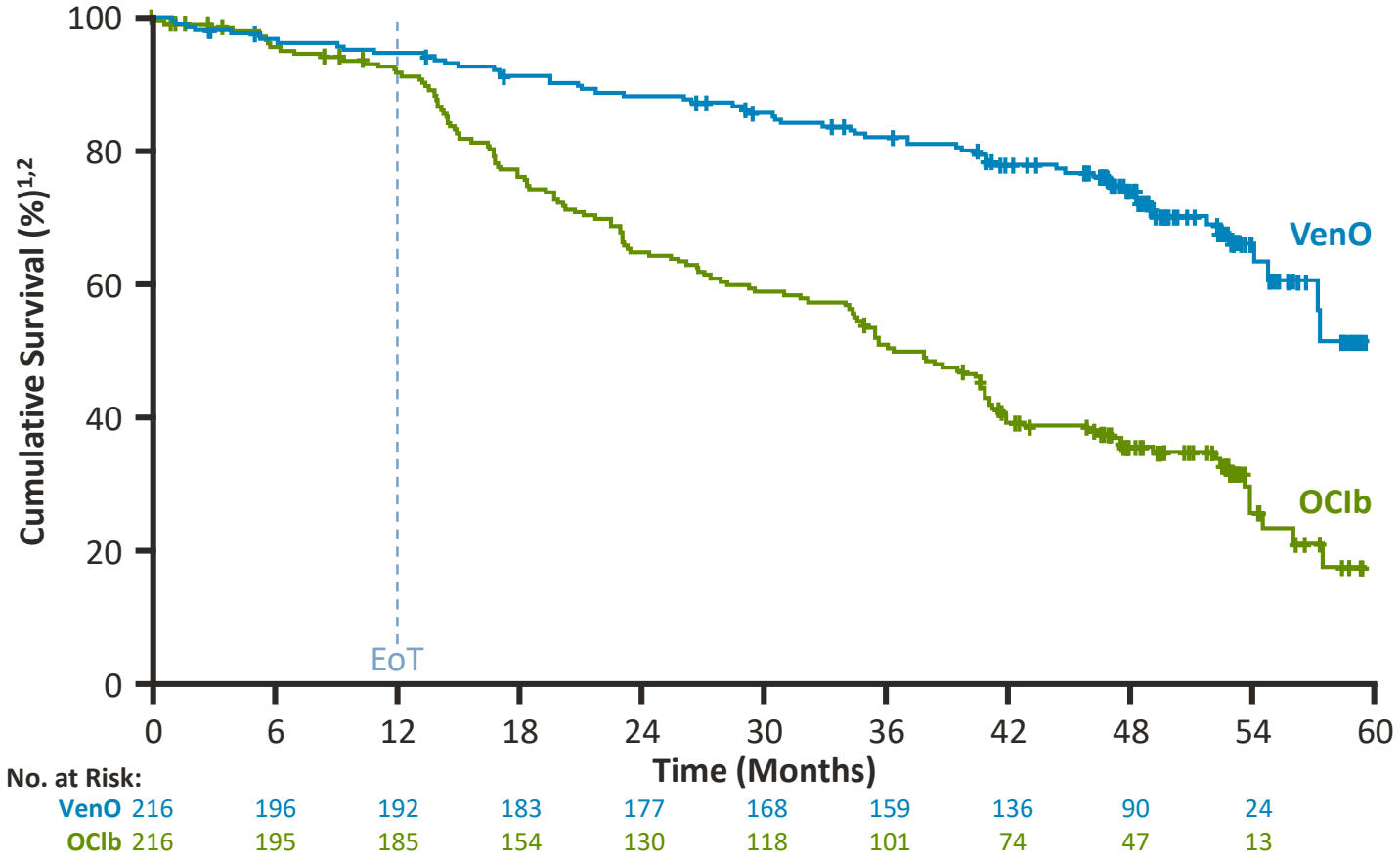
1) **4 yrs after treatment start, 3 out of 4 pts showed no progression on VenObi.**

2) **4 yrs after treatment start, 1 out of 3 pts showed no progression on ClbObi.**

3) **In pts with an aberrant TP53 status, 2 out of 3 were without progression with VenObi after 4 yrs.**

4) **Pts with $IGHV_{unmut}$ (vs. $IGHV_{mut}$) showed an inferior PFS on VenObi.**

Investigator-Assessed PFS (ITT Population): 4 Years Post-Randomization



- **Median follow-up: 52.4 months (range, 0–61.1 months)[2]**
- **All patients off treatment for ≥3 years**

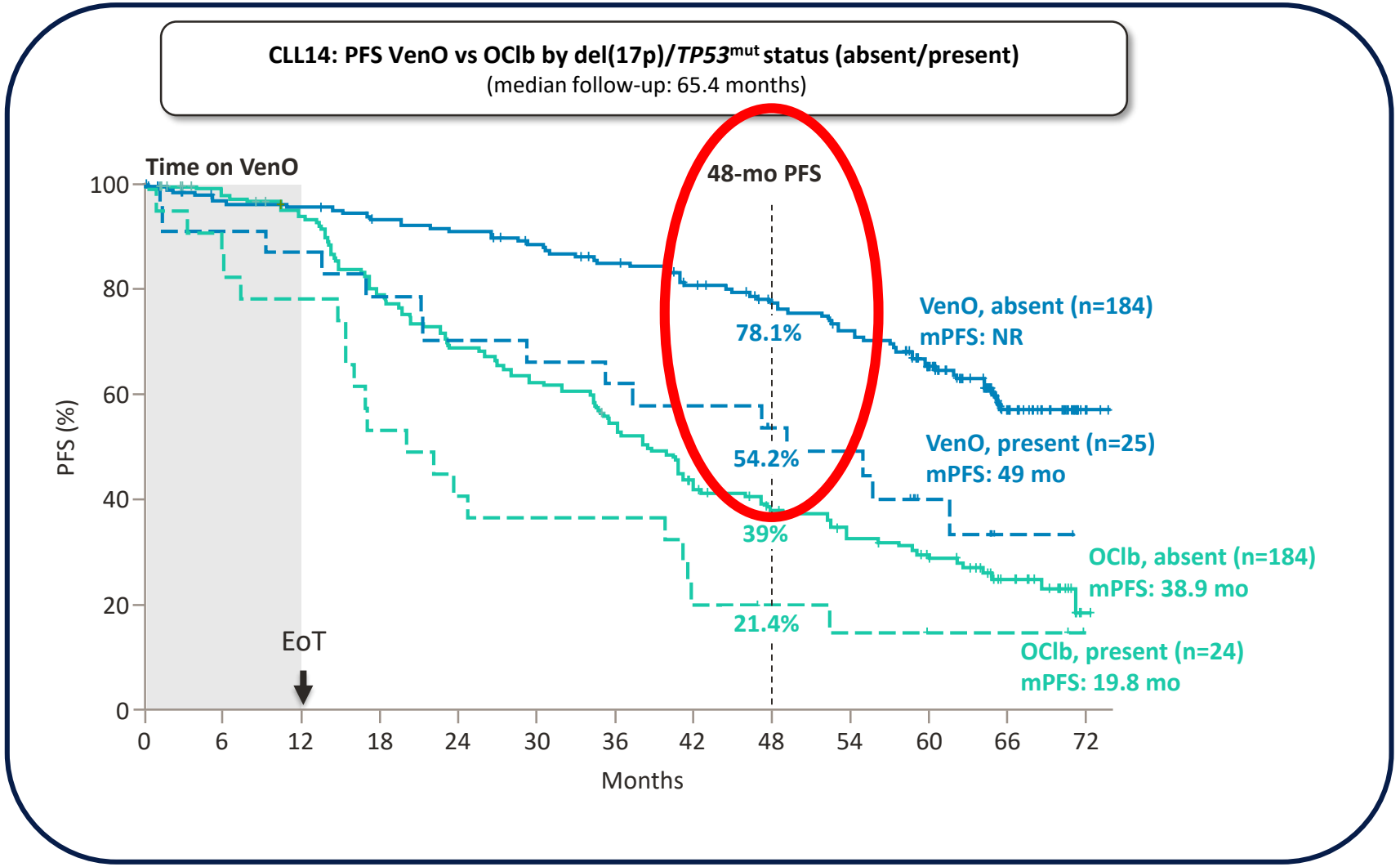
	VenO (n=216)	OClb (n=216)
Median PFS, months (95% CI)[1]	NR	36.4
HR (95% CI)*, descriptive p-value[1]	0.33 (0.25–0.45); **<0.0001**	
48-month PFS estimate, %[1]	**74.0**	**35.4**

At the 4-year analysis (median follow-up 52.4 months), the risk of progression or death was decreased by 67% with VenO vs OClb

Data cutoff: September 11, 2020.
* Stratified by Binet and geographic region; hazard ratio estimated by Cox regression model.
CI, confidence interval; HR, hazard ratio; NR, not reached; PFS, progression-free survival.

Al-Sawaf et al, JCO, 2021

In patients with **del(17p)/*TP53*^{mut}** CLL, fixed-duration **BCL-2i-**based therapy improves PFS vs CIT

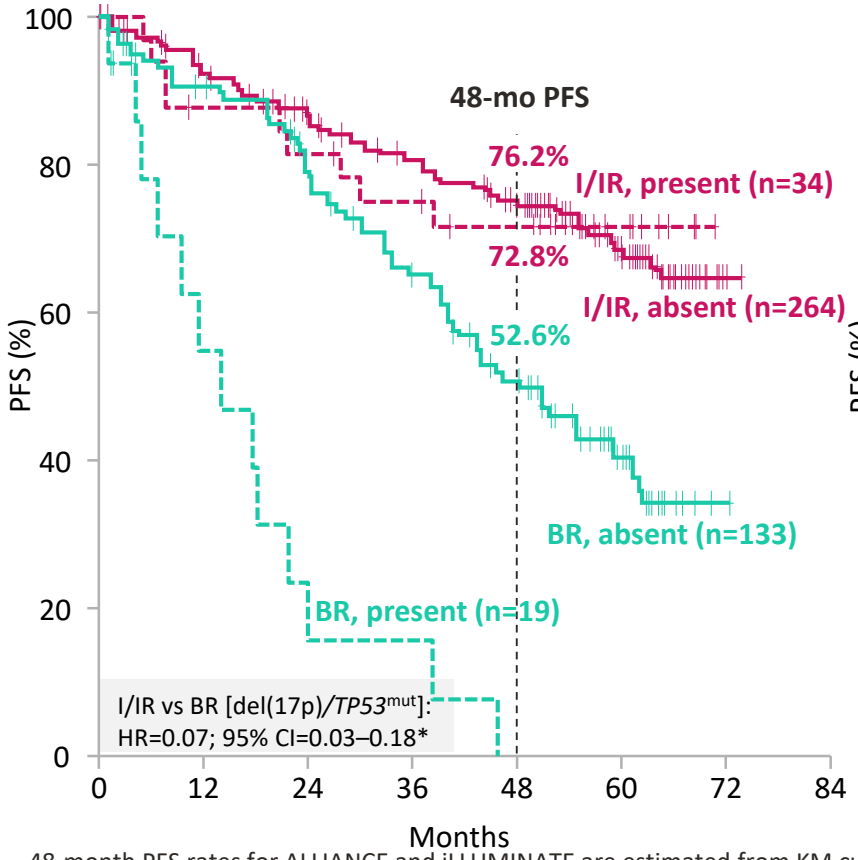


48-month PFS rates are estimated from KM curve using Graphreader (http://www.graphreader.com/).
BCL-2i, B-cell lymphoma 2 inhibitor; CIT, chemoimmunotherapy; Clb, chlorambucil; EoT, end of treatment; NR, not reached; O, obinutuzumab; Ven, venetoclax.

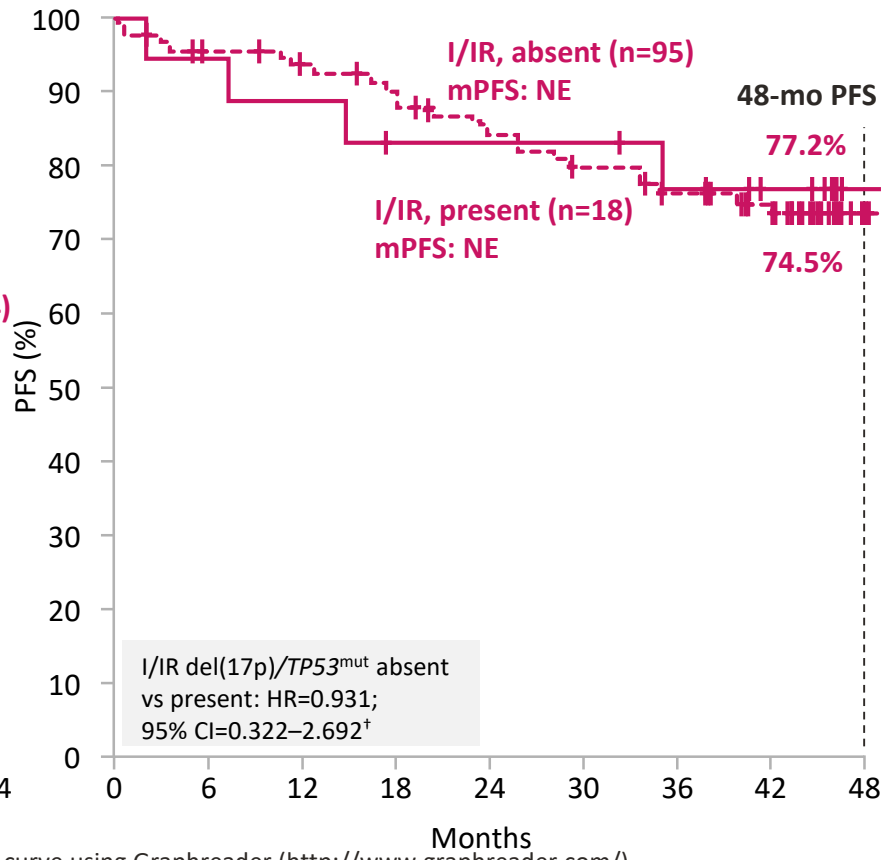
Al-Sawaf O, *et al.* EHA 2022. Abstract S148 (Oral).

In 1L **del(17p)/*TP53*^{mut}** CLL, continuous **BTKi** therapies improve PFS vs CIT

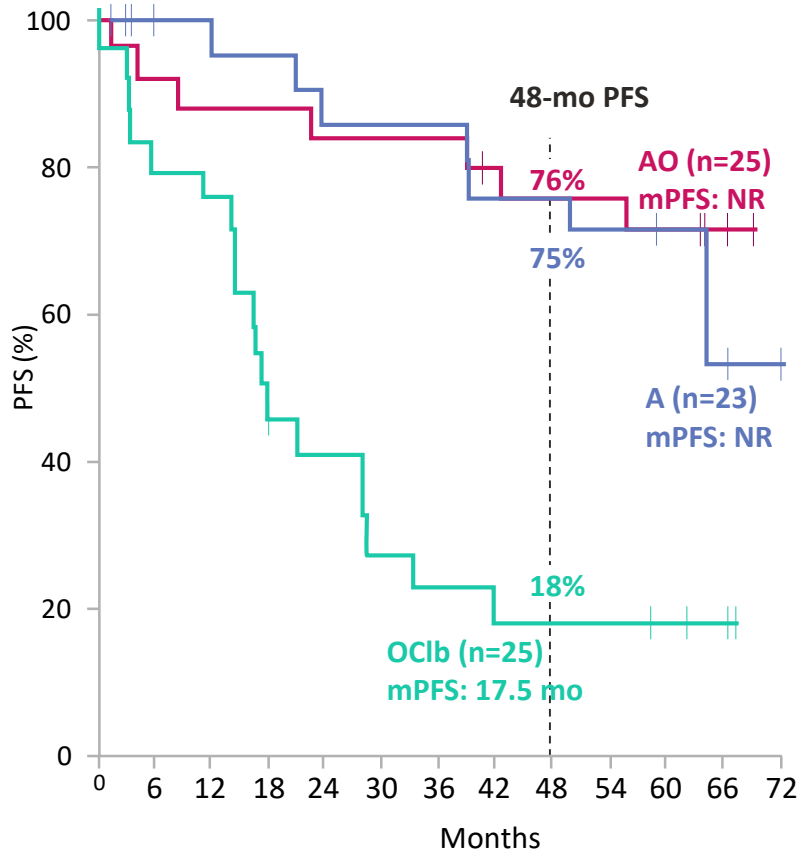
Alliance A041202: PFS I/IR vs BR by del(17p)/*TP53*^{mut} status (absent/present)
(median follow-up: 55 months)[1]



iLLUMINATE: PFS with IO by del(17p)/*TP53*^{mut} status (absent/present)
(median follow-up: 45 months)[2]



ELEVATE TN: PFS A/AO vs OClb by del(17p)/*TP53*^{mut} status (present)
(median follow-up: 46.9 months)[3,4]

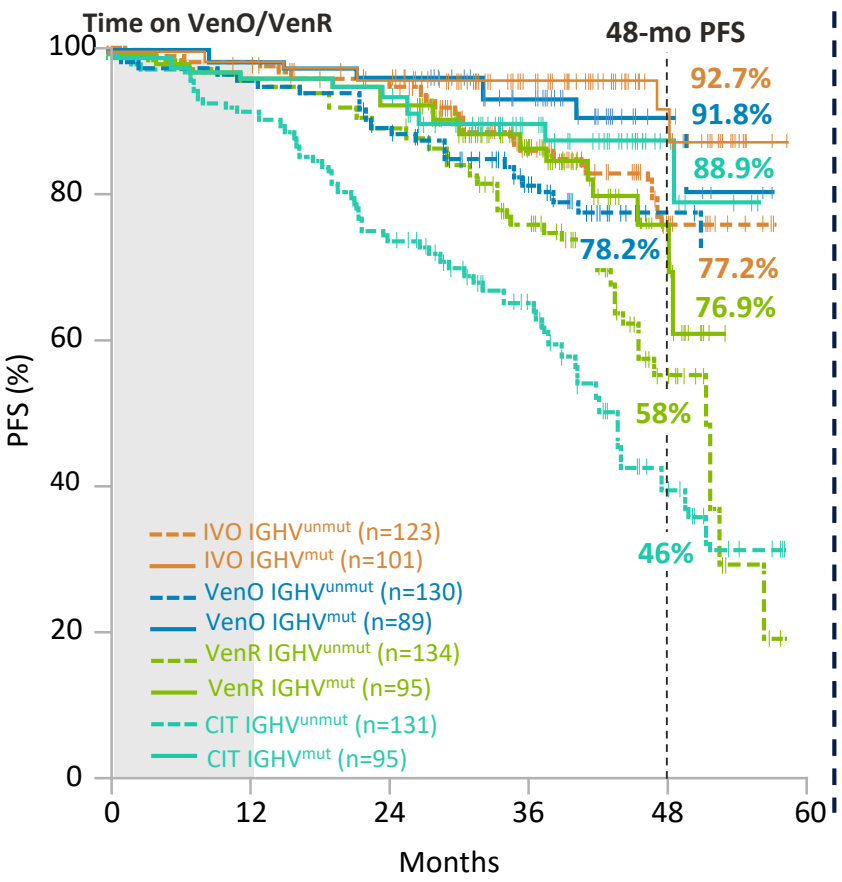


48-month PFS rates for ALLIANCE and iLLUMINATE are estimated from KM curve using Graphreader (http://www.graphreader.com/).
* p=0.0006; † p=0.8945.
A, acalabrutinib; B, bendamustine; CIT, chemoimmunotherapy; Clb, chlorambucil; I, ibrutinib; NE, not estimable; NR, not reached; O, obinutuzumab; R, rituximab.

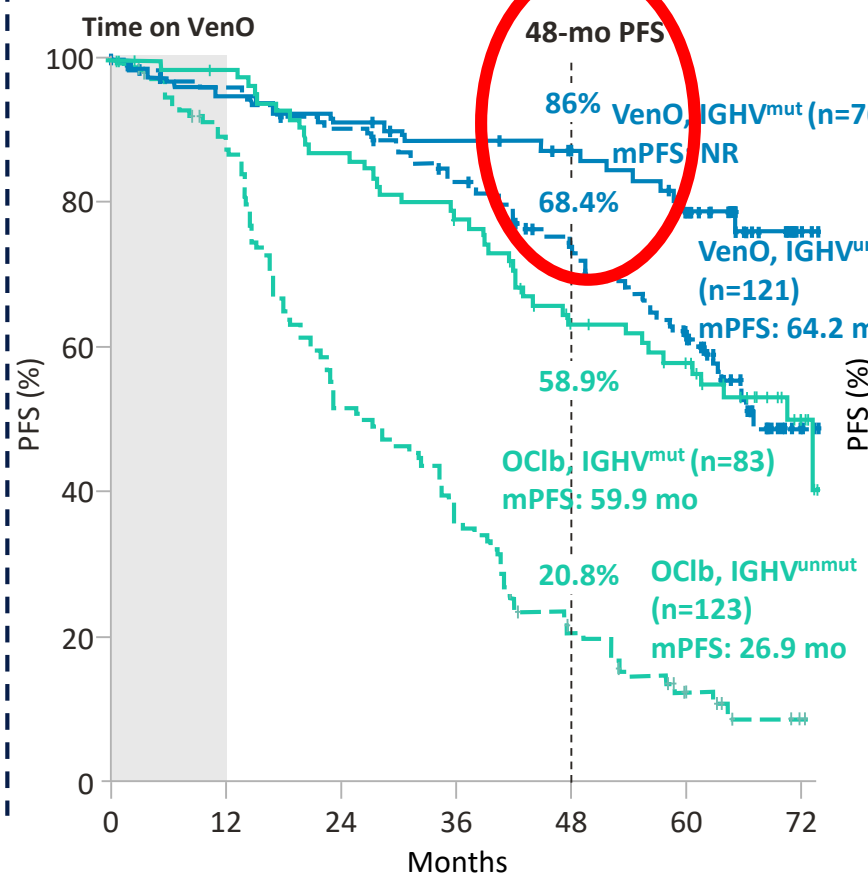
1. Woyach J, *et al.* ASH 2021. Abstract 639 (Oral); 2. Moreno C, *et al. Haematologica* 2022; doi: 10.3324/haematol.2021.279012; 3. Sharman JP, *et al. Leukemia* 2022; **36**:1171–1175; 4. Sharman JP, *et al.* EHA 2022. Abstract P666 (Poster).

In patients with IGHV^{unmut} CLL, fixed-duration BCL-2i-based therapies improve PFS vs CIT

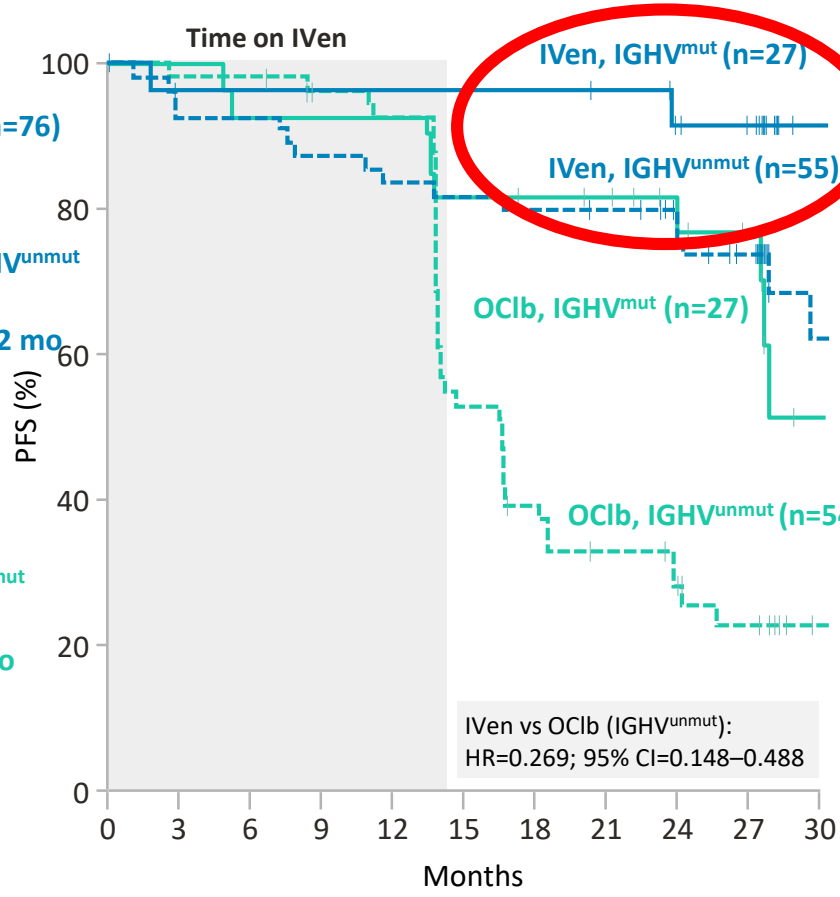
GAIA/CLL13: PFS VenO/IVO/VenR vs CIT by IGHV status
(median follow-up: 38.8 months)[1]



CLL14: PFS VenO vs OClb by IGHV status
(median follow-up: 65.4 months)[2]



GLOW: PFS IVen vs OClb by IGHV status
(median follow-up: 27.7 months)[3]

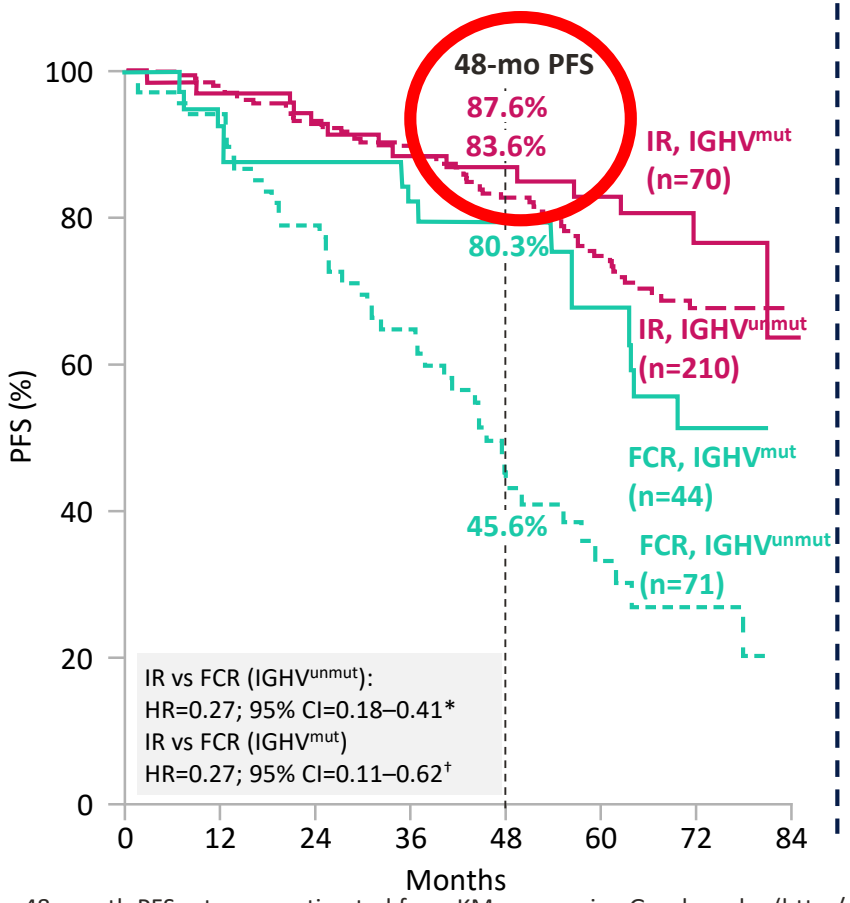


48-month PFS rates are estimated from KM curve using Graphreader (http://www.graphreader.com/).
BCL-2i, B-cell lymphoma 2 inhibitor; CIT, chemoimmunotherapy; Clb, chlorambucil;
I, ibrutinib; NR, not reached; O, obinutuzumab; R, rituximab; V / Ven, venetoclax.

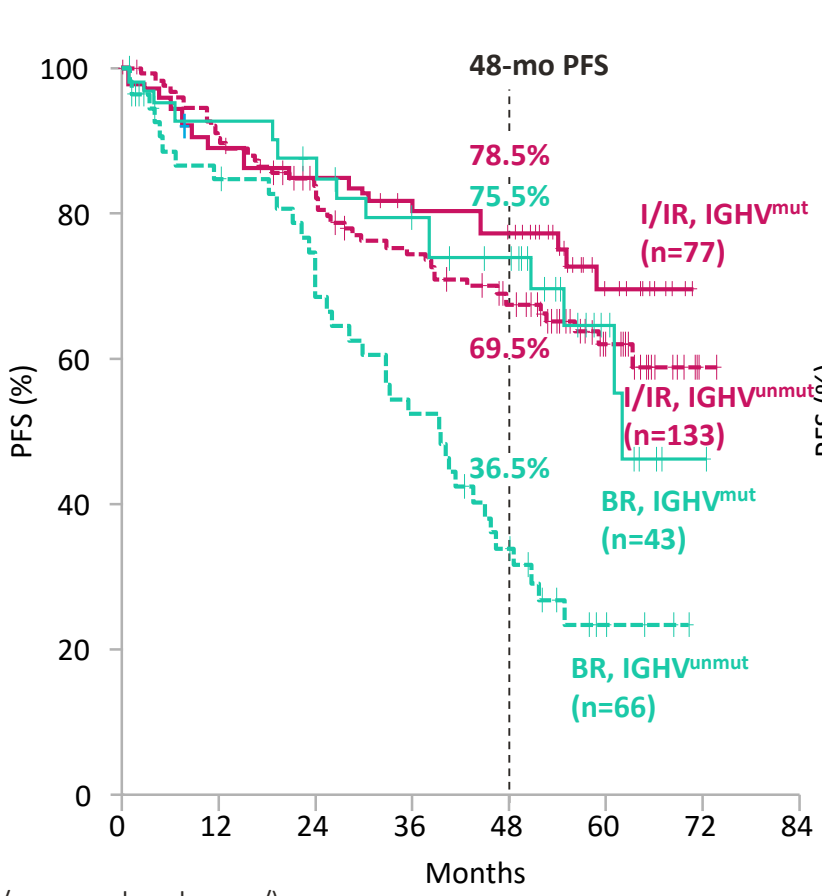
1. Eichhorst B, *et al.* EHA 2022. Abstract LB2365 (Oral); 2. Al-Sawaf O, *et al.* EHA 2022. Abstract S148 (Oral);
3. Kater AP, *et al. NEJM Evid* 2022; **1** (incl. suppl.).

In patients with **IGHV^{unmut}** CLL, continuous **1L BTKi** therapies improve PFS vs CIT

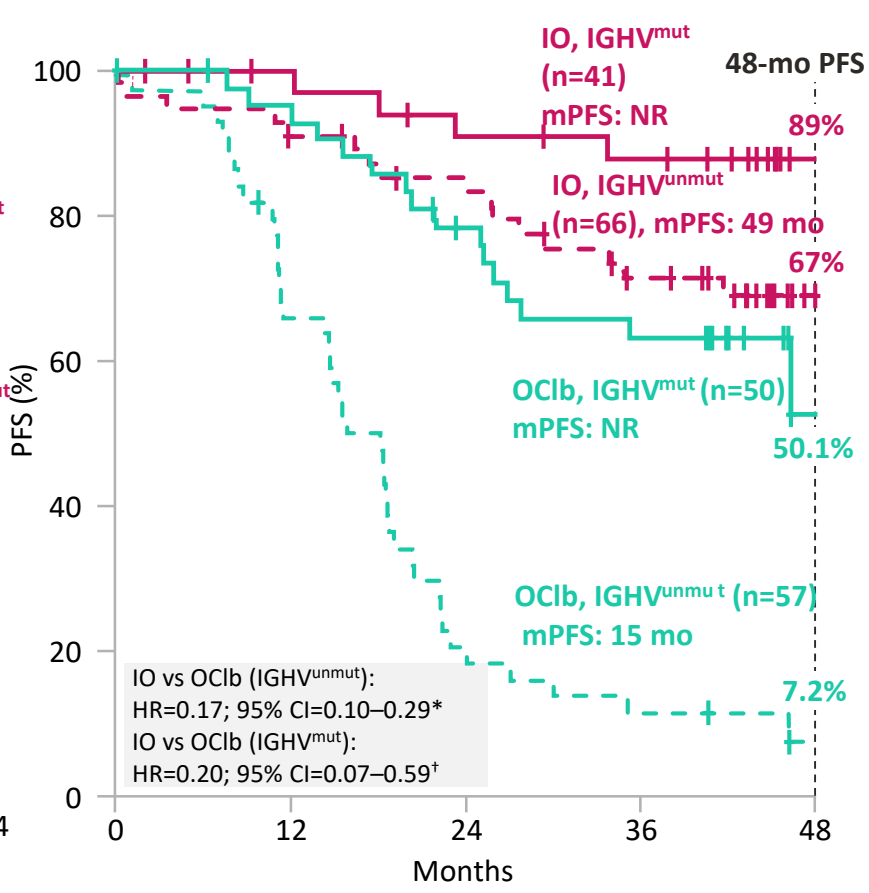
ECOG 1912: PFS IR vs FCR by IGHV status
(median follow-up: 70 months)[1]



Alliance A041202: PFS I/IR vs BR by IGHV status
(median follow-up: 55 months)[2]



iLLUMINATE: PFS IO vs OClb by IGHV status
(median follow-up: 45 months)[3]



48-month PFS rates are estimated from KM curve using Graphreader (http://www.graphreader.com/).
* p<0.0001; † p<0.001.
B, bendamustine; BTKi, Bruton's tyrosine kinase inhibitor; C, cyclophosphamide; CIT, chemoimmunotherapy; Clb, chlorambucil; F, fludarabine; I, ibrutinib; NR, not reached; O, obinutuzumab; R, rituximab.

1. Shanafelt TD, *et al. Blood* 2022; **140:**112–120; 2. Woyach J, *et al.* ASH 2021. Abstract 639 (Oral); 3. Moreno C, *et al. Haematologica* 2022; doi: 10.3324/haematol.2021.279012.

CLL17

A PROSPECTIVE, RANDOMIZED, OPEN-LABEL, MULTICENTRE PHASE-III TRIAL OF **IBRUTINIB** VERSUS **VENETOCLAX PLUS OBINUTUZUMAB** VERSUS **IBRUTINIB PLUS VENETOCLAX** FOR PATIENTS WITH PREVIOUSLY UNTREATED CHRONIC LYMPHOCYTIC LEUKAEMIA

Patients with previously untreated CLL

Incl. fit and unfit patients
Incl. patients with del17p/TP53 mut

1:1:1 Randomization

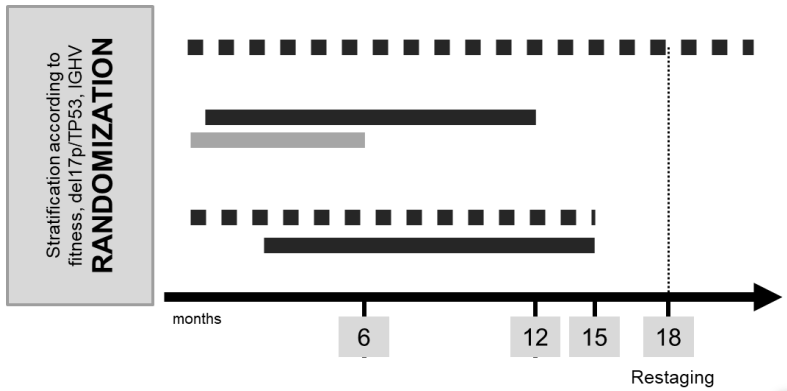
Stratification according to fitness, del17p/TP53, IGHV

Ibrutinib	Venetoclax Obinutuzumab	Venetoclax Ibrutinib

897 patients

Primary endpoint:
Progression-free survival

TREATMENT SCHEDULE



Ibrutinib d1 420 mg po daily until PD or intolerance

Venetoclax 400 mg po daily (c1 d22 – c12 d28)
Obinutuzumab 1000 mg iv (c1 d1(2)/8/15, c 2-6 d1)

Ibrutinib 420 mg po daily (c1 d1 – c15 d28)
Venetoclax 400 mg po daily (c4 d1 – c15 d28)

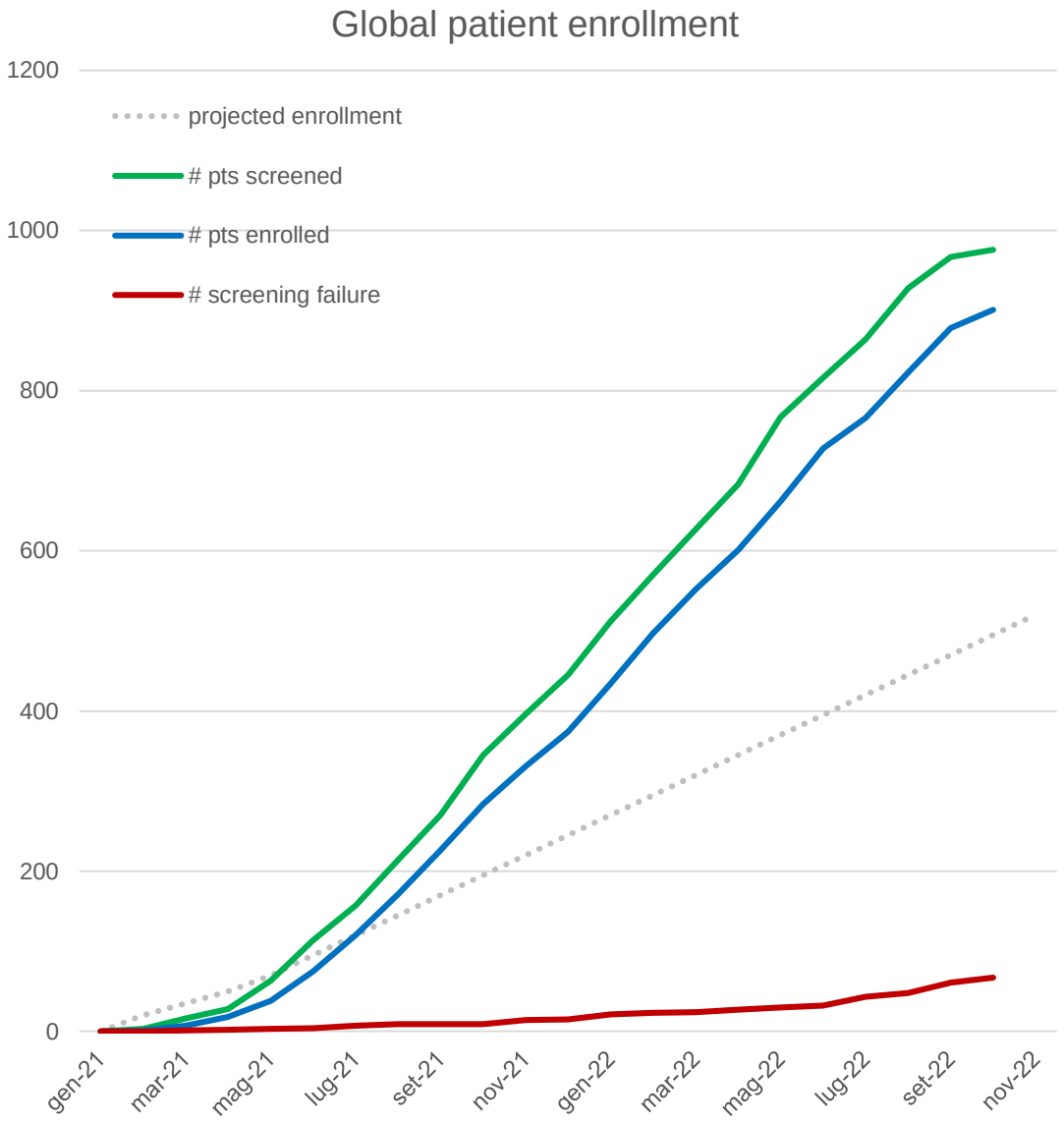
TIMELINES

Start of recruitment	Q4/2020
Expected end of recruitment	Q4/2023
End of study	Q1/2027

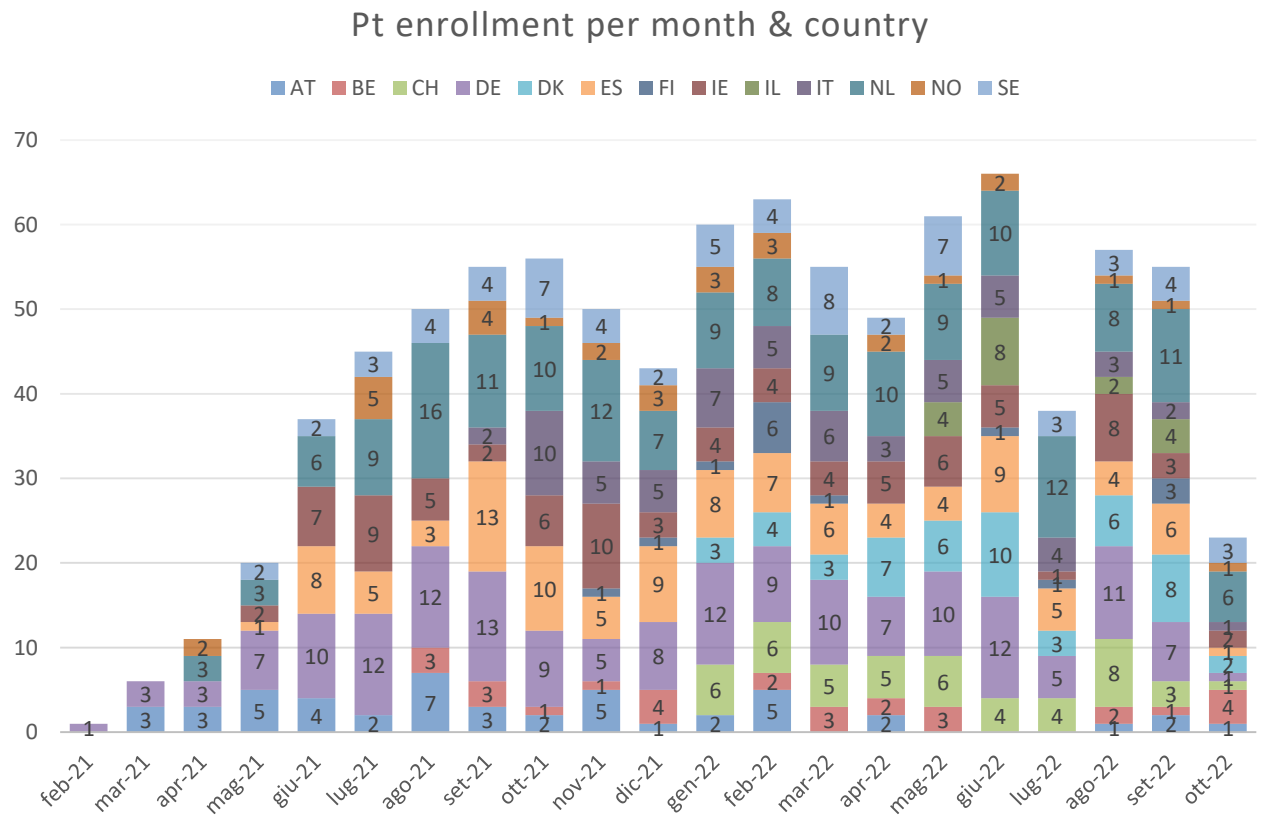
Modifiziert nach https://www.dcllsg.de/studie/cll17/index.php, letzter Zugriff 25.10.2021

PATIENT STATUS – CLL17 – OCT 28TH, 2022

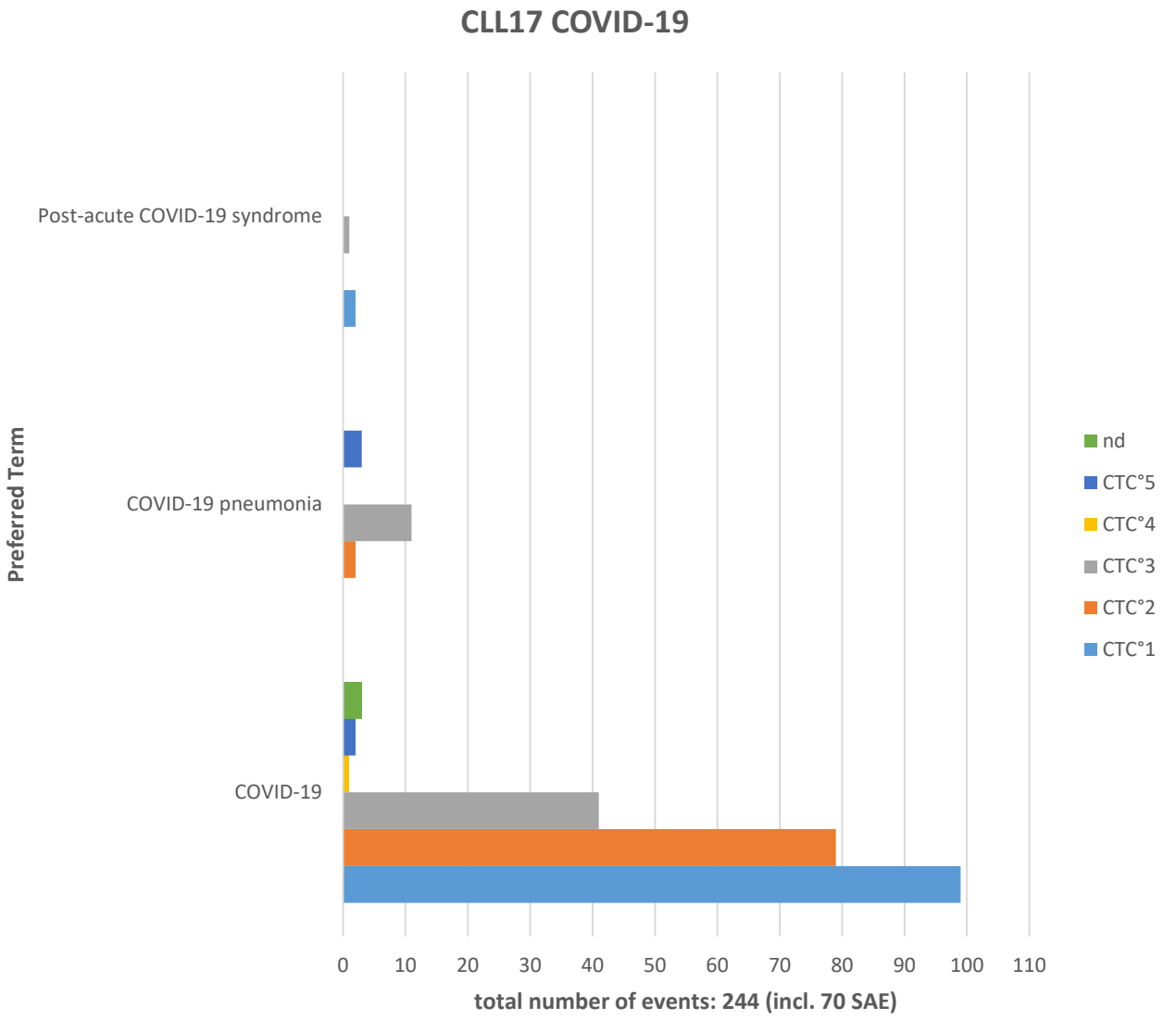
DEUTSCHE STUDIENGRUPPE

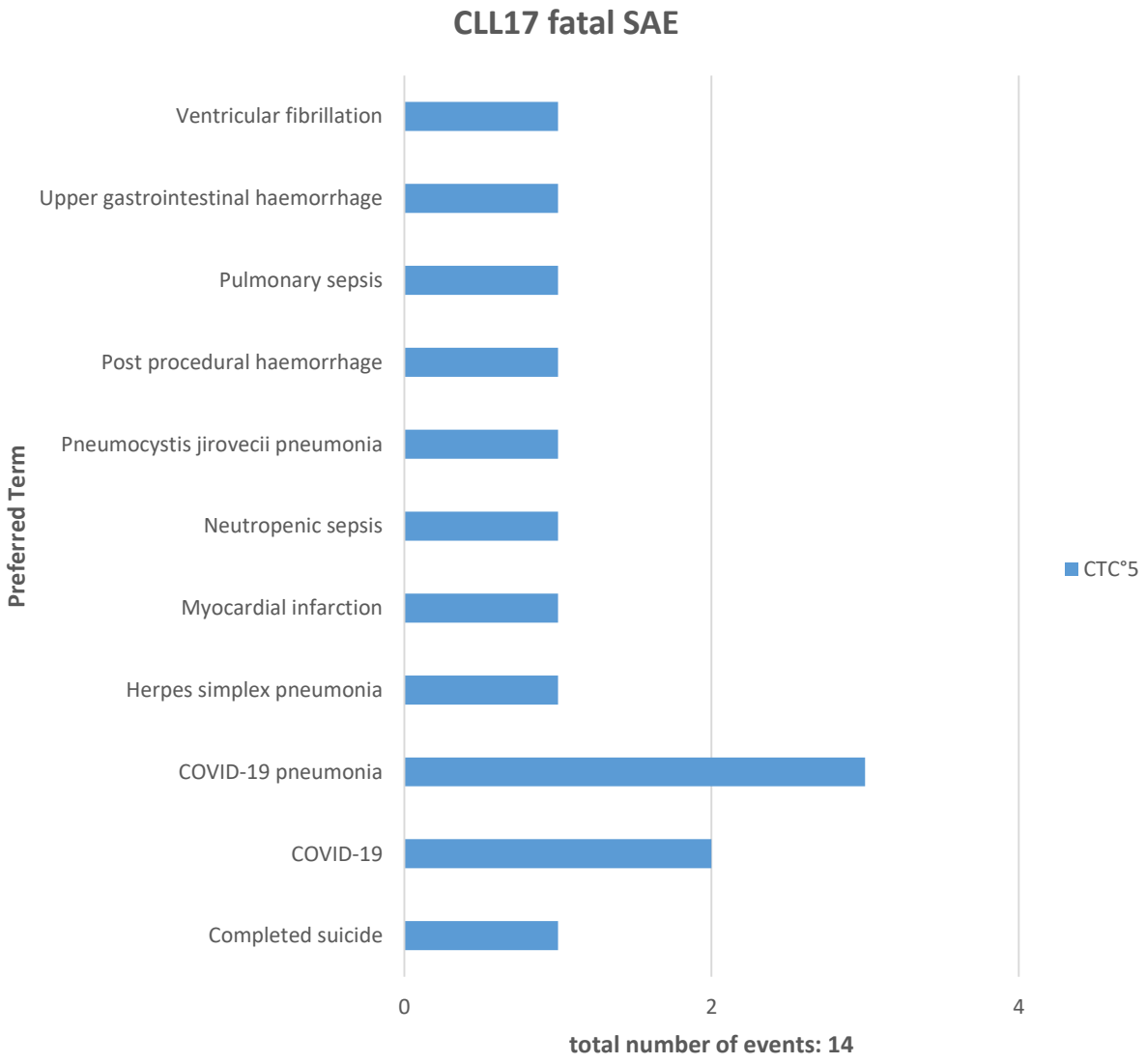


pts screened: 976
pts enrolled: 901 (99,3%) of 907
screening failure: 67
pts screening ongoing: 8



SAFETY STATUS





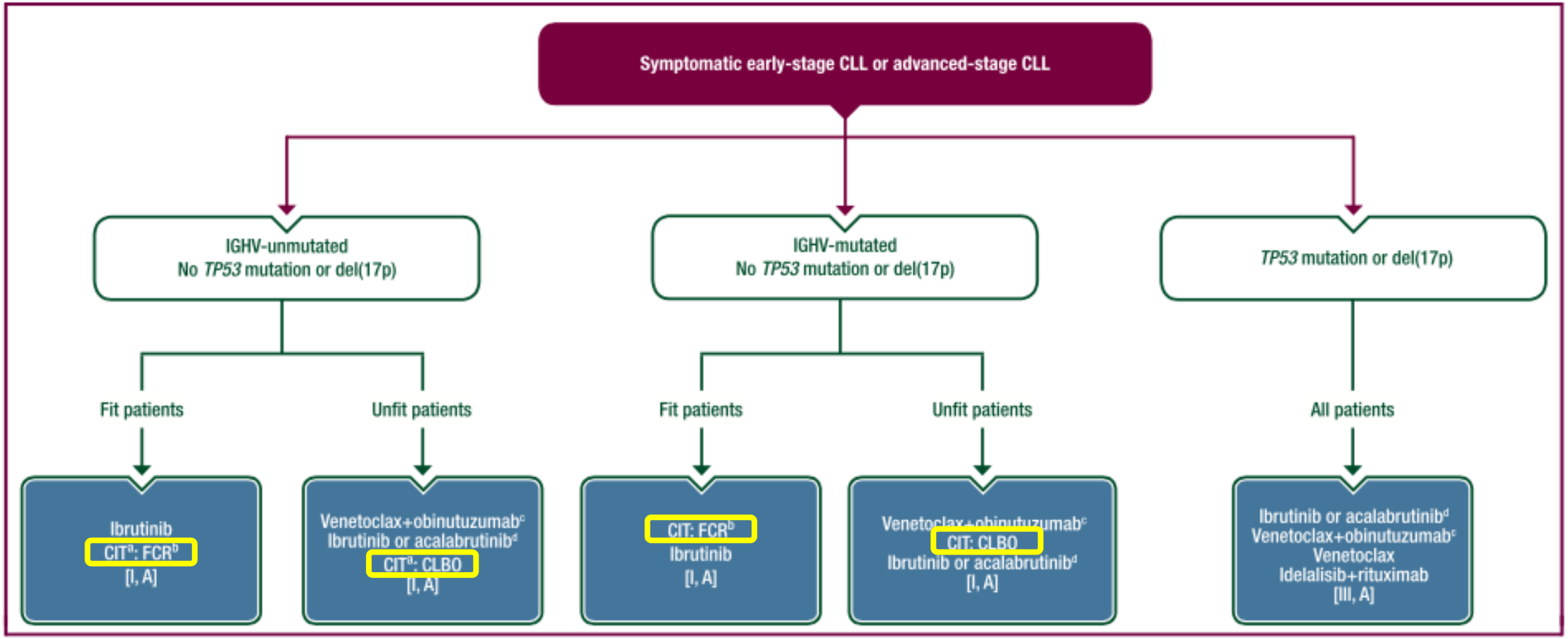


Figure 1. Front-line therapy.

The order of the recommended treatments for each subgroup is based on expert opinion considering time-limited as more valuable therapy, if there is equal evidence for two different treatment options.

BR, bendamustine plus rituximab; CIT, chemoimmunotherapy; CLBO, chlorambucil plus obinutuzumab; CLL, chronic lymphocytic leukaemia; FCR, fludarabine, cyclophosphamide and rituximab; IGHV, immunoglobulin heavy chain variable.

[a] CIT as alternative treatment, only if reasons against treatment with targeted therapies or non-availability.

[b] BR might be considered alternatively in patients above the age of 65 years.

[c] If available.

[d] If approved and available.

https://doi.org/10.1016/j.annonc.2020.09.019

Chemo-free 1st line algorithm in CLL ?