Therapiealgorithmen für die CLL

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Akademisches Lehrkrankenhaus der

Ludwig-Maximilians-Universität (LMU)

München

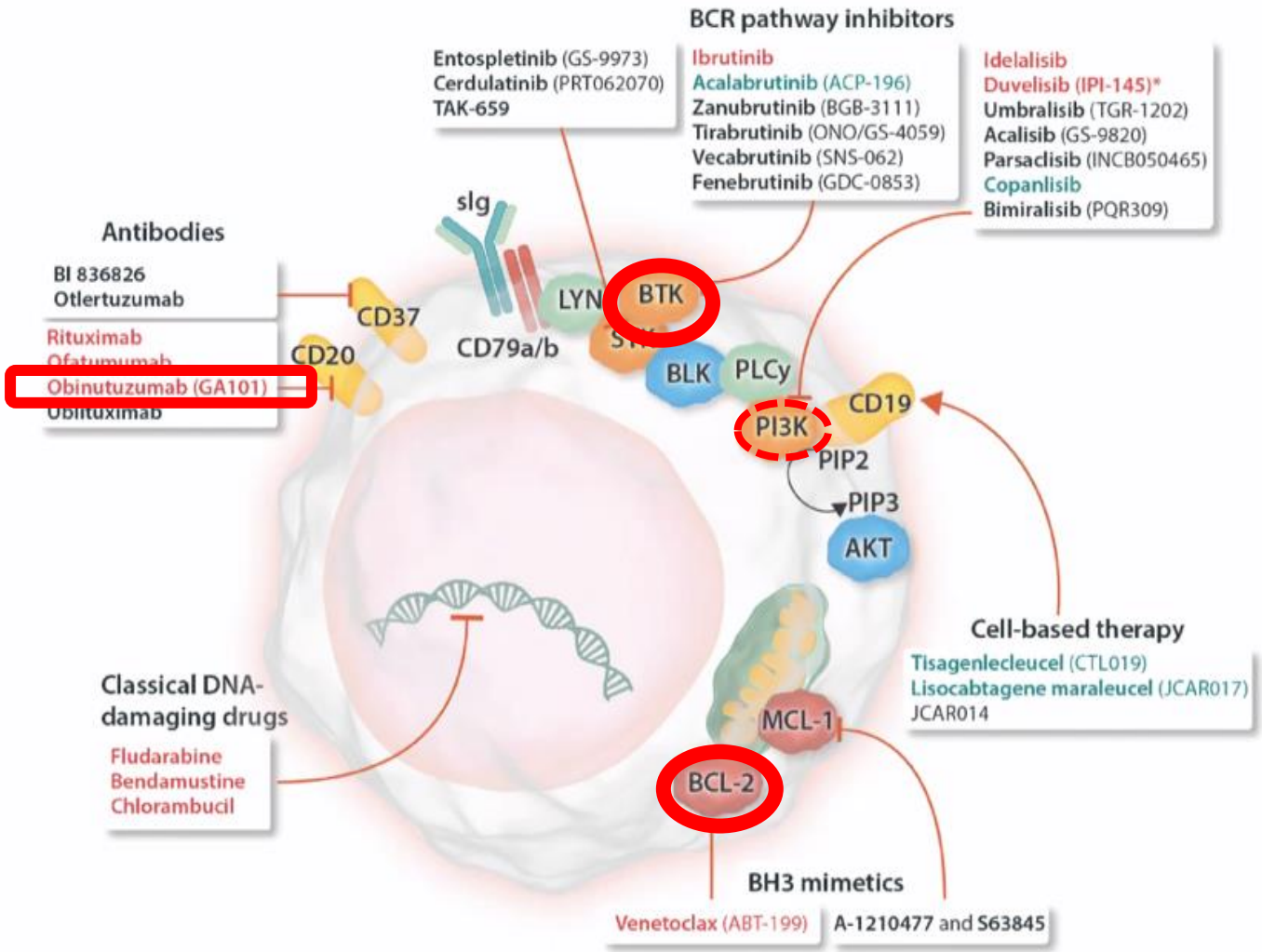
DGHO Jahrestagung, Hamburg, 13.10.2023

Potentielle Interessenkonflikte

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, Moderna, BeiGene**
Major Stockholder	**NA**
Speakers Bureau	**NA**
Honoraria	**Hoffmann-La Roche, GSK, Cilag-Janssen, Gilead, Genentech, Morphosys, AbbVie, Amgen, AstraZeneca, BioNTech, Moderna, BeiGene**
Scientific Advisory Board	**Hoffmann-La Roche, GSK, Cilag-Janssen, Gilead, Genentech, Morphosys, AbbVie, AstraZeneca, BioNTech, Moderna, BeiGene**

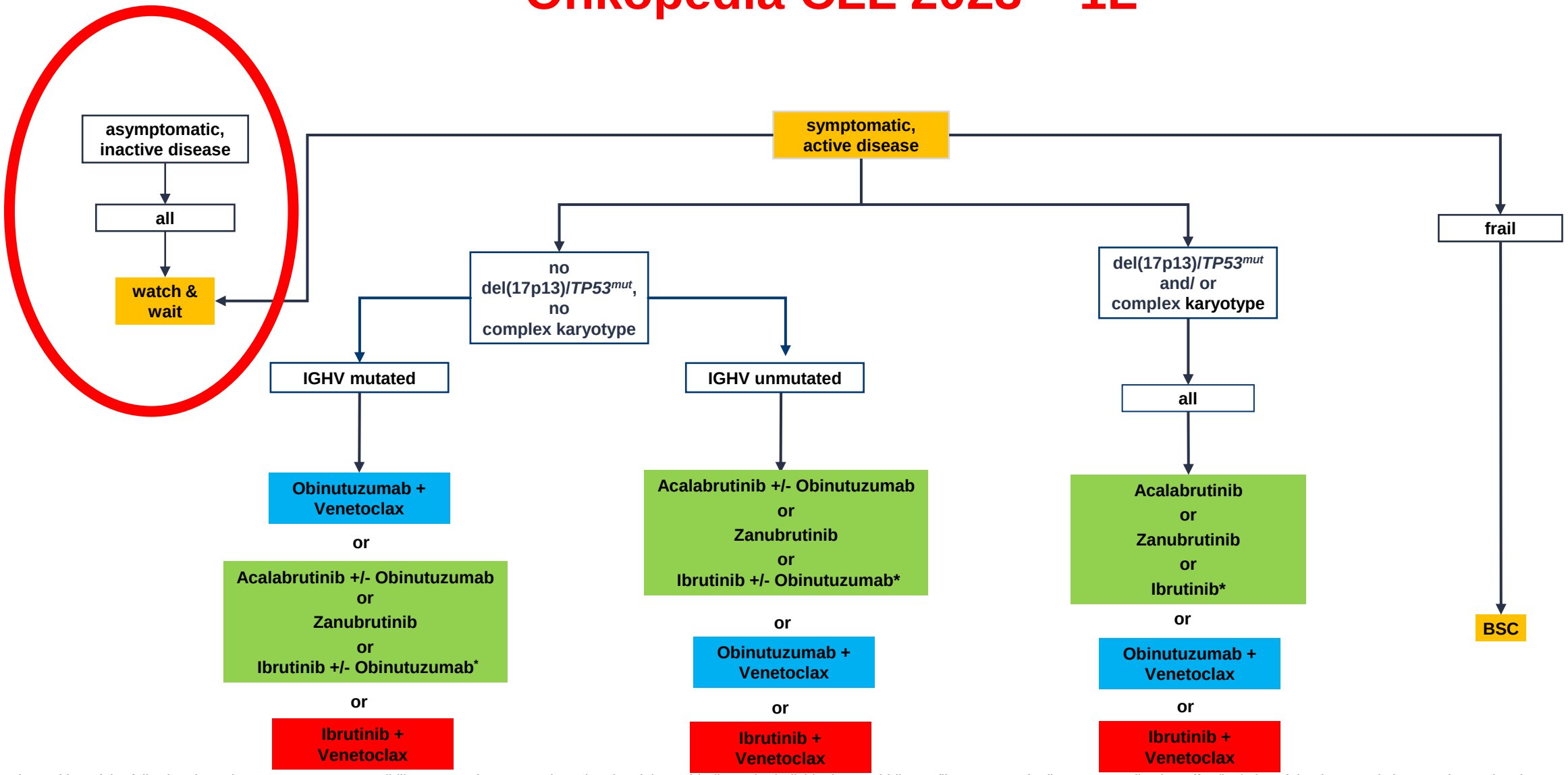
From Biology to Therapy: Model System CLL

Yosifov, et al. Hemashere 2019



Der griechische Gott Kairós, auf einem Gemälde von Francesco de' Rossi, schätzungsweise aus dem Jahr 1544 © Fine Art Images/Heritage Images/Getty Images

Onkopedia CLL 2023 – 1L



The ranking of the following therapies represents one possibility. Due to the current data situation, it is not binding. The individual comorbidity profile, aspects of adherence, application effort/logistics of the therapeutic intervention and patient preference for the final therapy determination should be taken into account. **[+]If acalabrutinib or zanubrutinib is contraindicated or not available, ibrutinib (+/- obinutuzumab) remains a therapy option, taking into account increased cardiac side effects. Acalabrutinib and zanubrutinib were not systematically evaluated in younger/fit patients in first-line therapy.**

Wendtner CM et al., https://www.onkopedia.com/de/onkopedia/guidelines/chronische-lymphatische-leukaemie-cll/@@guideline/html/index.html (Stand 01/2023)

UNIKLINIK KÖLN

DEUTSCHE STUDIENGRUPPE

IBRUTINIB VERSUS PLACEBO IN PATIENTS WITH ASYMPTOMATIC, TREATMENT-NAÏVE EALRY STAGE CLL

FINAL RESULTS OF THE PHASE 3, DOUBLE-BLIND, PLACEBO-CONTROLLED CLL12 TRIAL

Petra Langerbeins, Sandra Robrecht, Pascal Nieper, Paula Cramer, Moritz Fürstenau, Othman Al-Sawaf, Anna-Maria Fink, Karl-Anton Kreuzer, Ursula Vehling-Kaiser, Eugen Tausch, Christof Schneider, Lothar Müller, Michael Josef Eckart, Rudolf Schlag, Werner Freier, Tobias Gaska, Christina Balser, Marcel Reiser, Martina Stauch, Clemens-Martin Wendtner, Kirsten Fischer, Stephan Stilgenbauer, Barbara Eichhorst, and Michael Hallek

28th Annual Meeting European Hematology Association (EHA), Frankfurt, June 8 – 11, 2023

CLL12 STUDY DESIGN

DEUTSCHE STUDIENGRUPPE

RISK ASSESSMENT

del(17p)	IGHV
del(11q)	ECOG PS
thymidine kinase	sex
β2 microglobulin	age

648 PATIENTS WITH CLL
BINET STAGE A
ASYMPTOMATIC
TREATMENT-NAIVE

152 PATIENTS
NO RISK

152 PATIENTS
WATCH & WAIT

363 PATIENTS
INCREASED RISK

182 PATIENTS
IBRUTINIB

versus

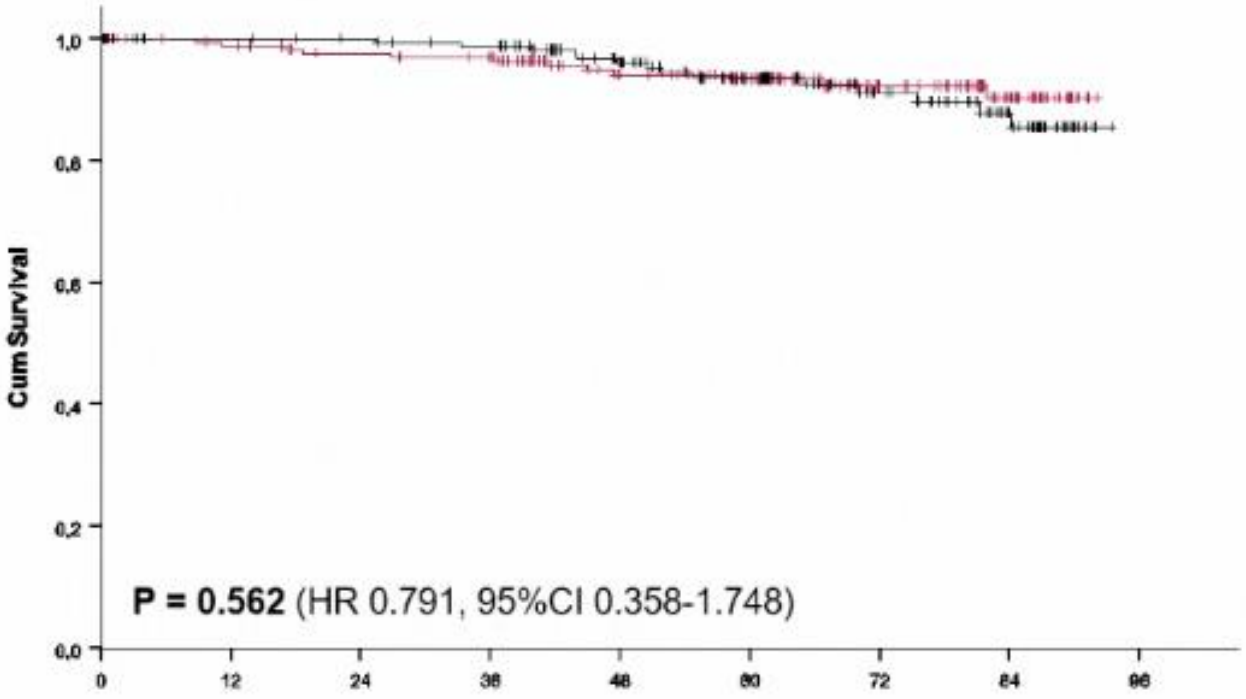
181 PATIENTS
PLACEBO

420 [mg/d] UNTIL SYMPTOMATIC DISEASE PROGRESSION

FPI
APR-2014

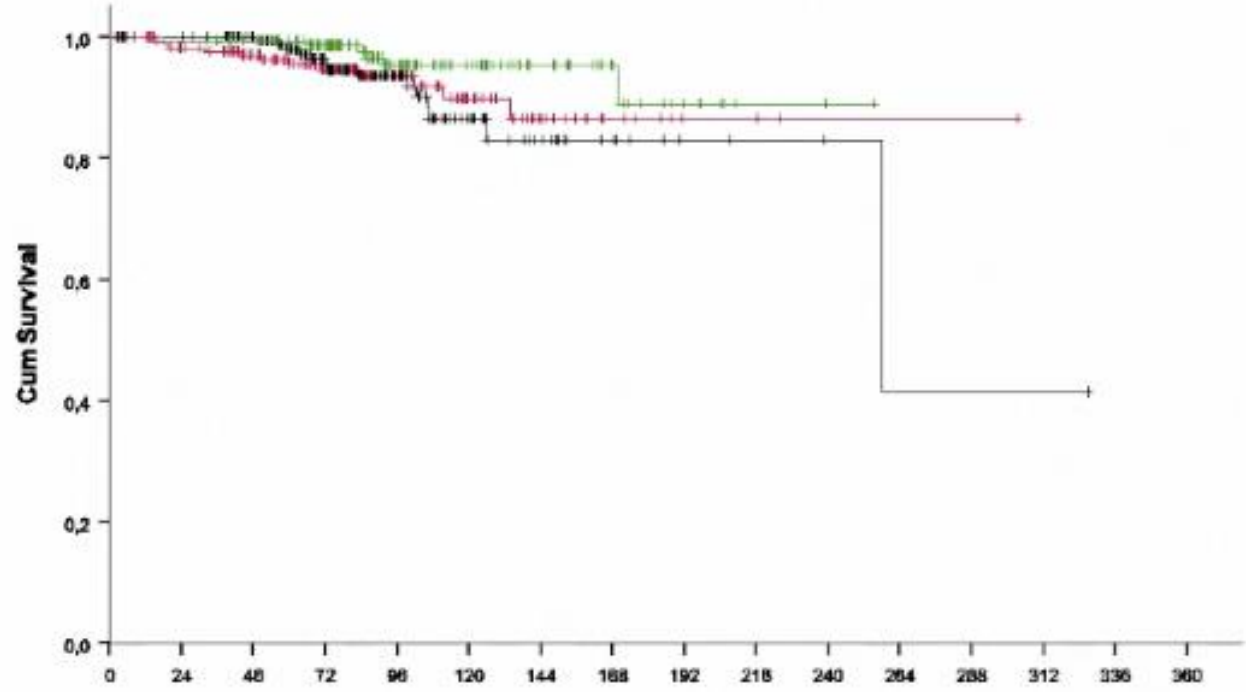
EOS
JUL-2022

OVERALL SURVIVAL (OS)



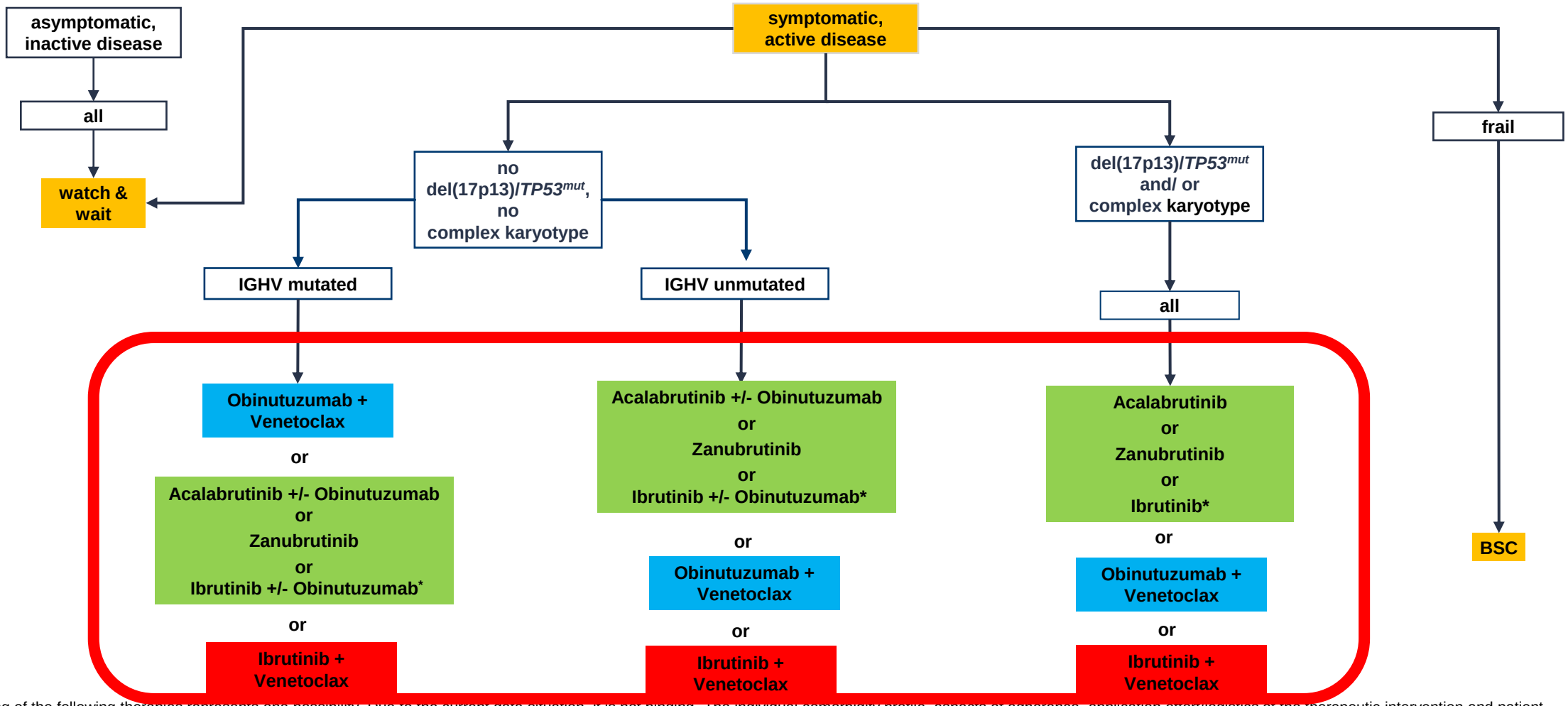
OS	Pts, N	Events, N (%)	Median months	1-year Survival, %	2-year Survival, %	3-year Survival, %	4-year Survival, %	5-year Survival, %
All patients [ITT]	**363**	**26 (7.2)**						
Ibrutinib	182	12 (6.6)	NR	98.8	97.6	97.0	94.1	93.3
Placebo	181	14 (7.7)	NR	100.0	100.0	98.8	96.0	93.6

OS FROM DIAGNOSIS



OS from diagnosis	Pts, N	Events, N (%)	Median months	2-year Survival, %	4-year Survival, %	6-year Survival, %	8-year Survival, %	10-year Survival, %
All patients [ITT]	**515**	**32 (6.2)**						
Ibrutinib	182	12 (6.6)	NR	98.2	97.0	94.7	93.6	89.8
Placebo	181	14 (7.7)	258.0	100.0	100.0	96.4	93.5	86.5
Watch & Wait	152	6 (3.9)	NR	99.3	99.3	98.6	95.3	95.3

Onkopedia CLL 2023 – 1L



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UNIKLINIK KÖLN
Department I of Internal Medicine
University Hospital of Cologne

DEUTSCHE STUDIENGRUPPE

Abstract N.025

Venetoclax-Obinutuzumab for previously untreated chronic lymphocytic leukemia: 6-year results of the randomized CLL14 study

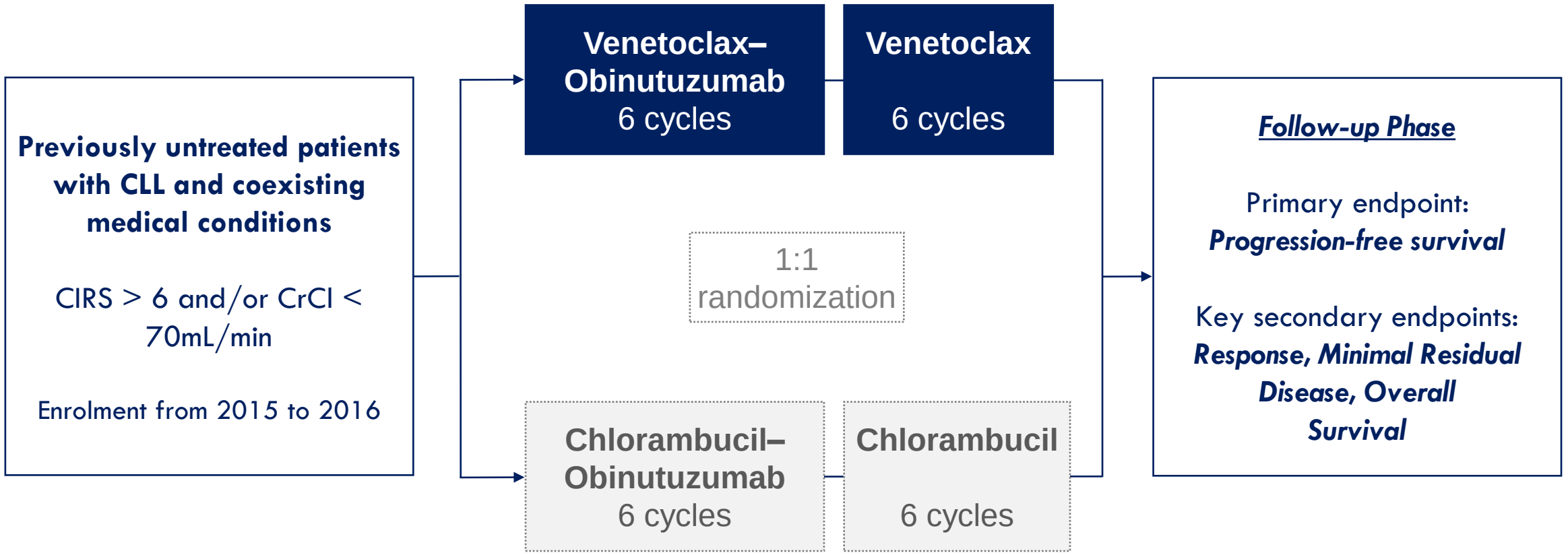
Othman Al-Sawaf, Sandra Robrecht, Can Zhang, Stefano Olivieri, Naomi Chang, Anna Maria Fink, Eugen Tausch, Christof Schneider, Matthias Ritgen, Karl-Anton Kreuzer, Liliya Sivcheva, Carsten Niemann, Anthony Schwarer, Javier Loscertales, Robert Weinkove, Dirk Strumberg, Allanah Kilfoyle, Eva D Runkel, Barbara Eichhorst, Stephan Stilgenbauer, Yanwen Jiang, Michael Hallek, Kirsten Fischer

June 15th, 2023
SESSION 4 - CLL AND RICHTER SYNDROME

ICML 2023

TRIAL DESIGN

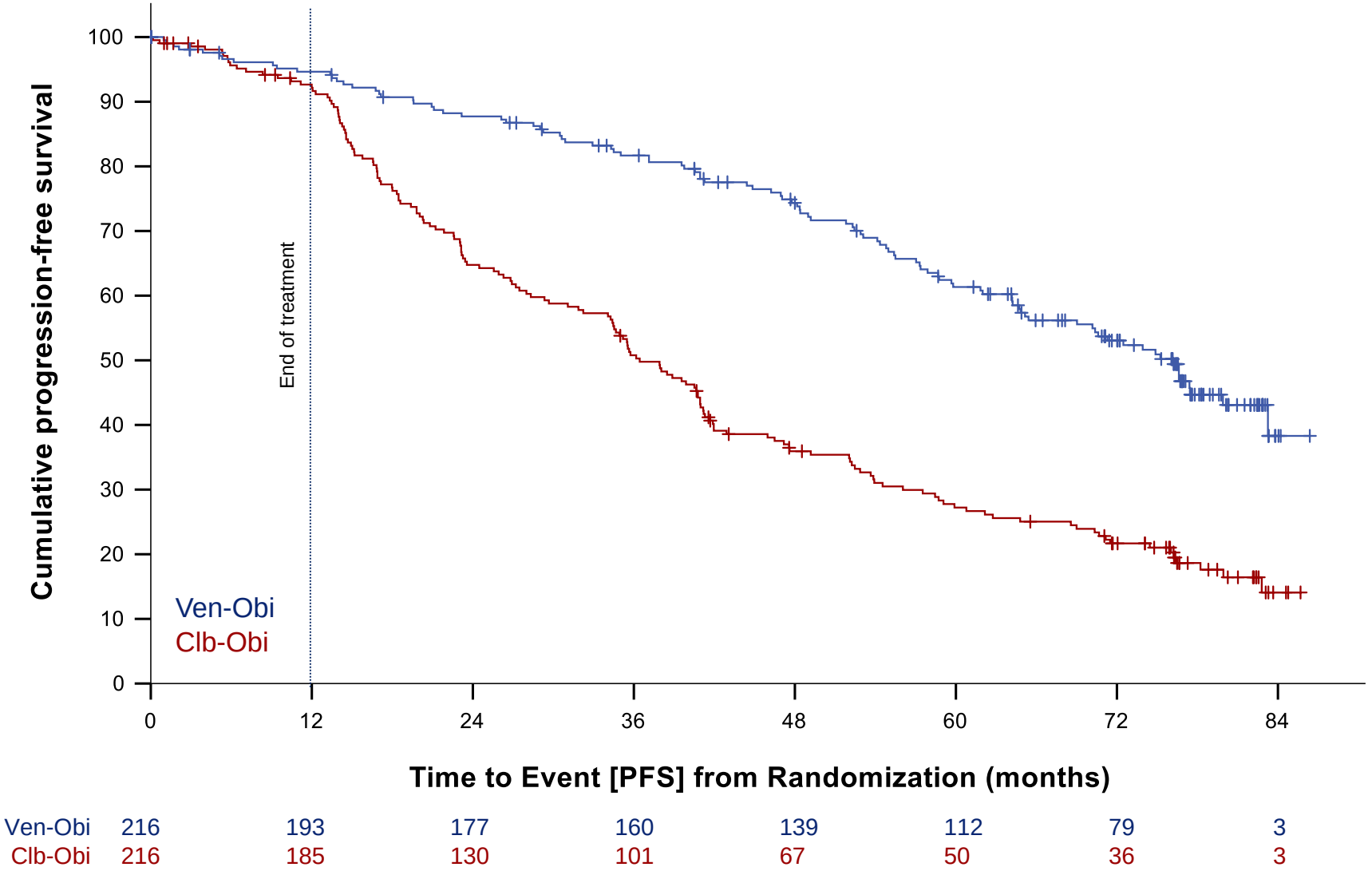
CLL-14



Current median observation time: 76.4 months

PROGRESSION-FREE SURVIVAL

Investigator-assessed PFS



Median PFS

Ven-Obi: 76.2 months

Clb-Obi: 36.4 months

6-year PFS rate

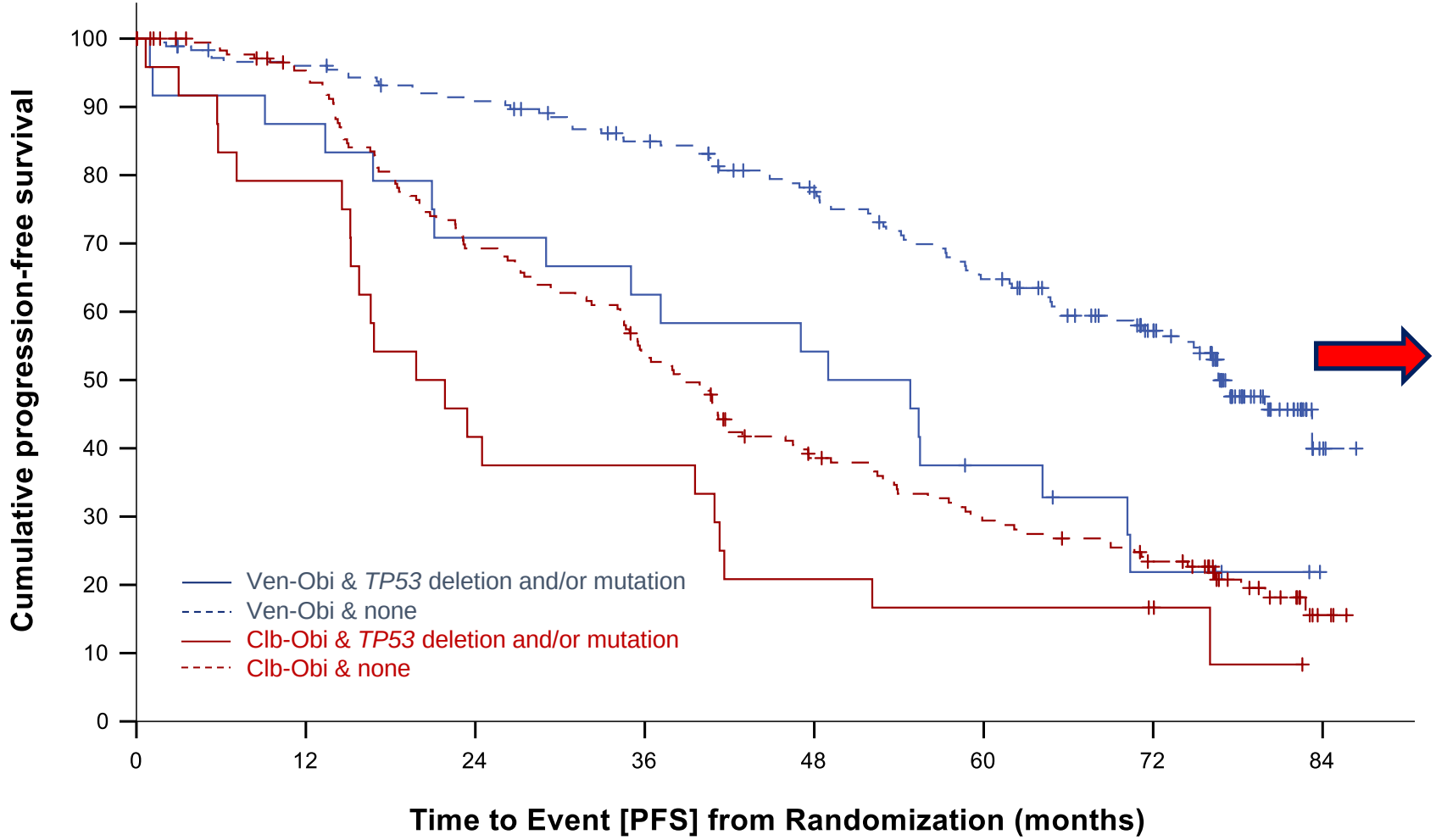
Ven-Obi: 53.1%

Clb-Obi: 21.7%

HR 0.40, 95% CI [0.31-0.52]
P<0.0001

PROGRESSION-FREE SURVIVAL – *TP53* status

Median observation time 76.4 months



Ven-Obi & *TP53* del/mut	25	21	17	15	13	8	4	0
Ven-Obi & none	184	168	157	142	123	101	73	3
Clb-Obi & *TP53* del/mut	24	19	10	9	5	4	3	0
Clb-Obi & none	184	160	117	90	60	45	33	3

Median PFS

Ven-Obi & no *TP53*del/mut: 76.6 m

Ven-Obi & *TP53*del/mut: 51.9 m

HR 2.29, 95% CI [1.37-3.83], p=0.001

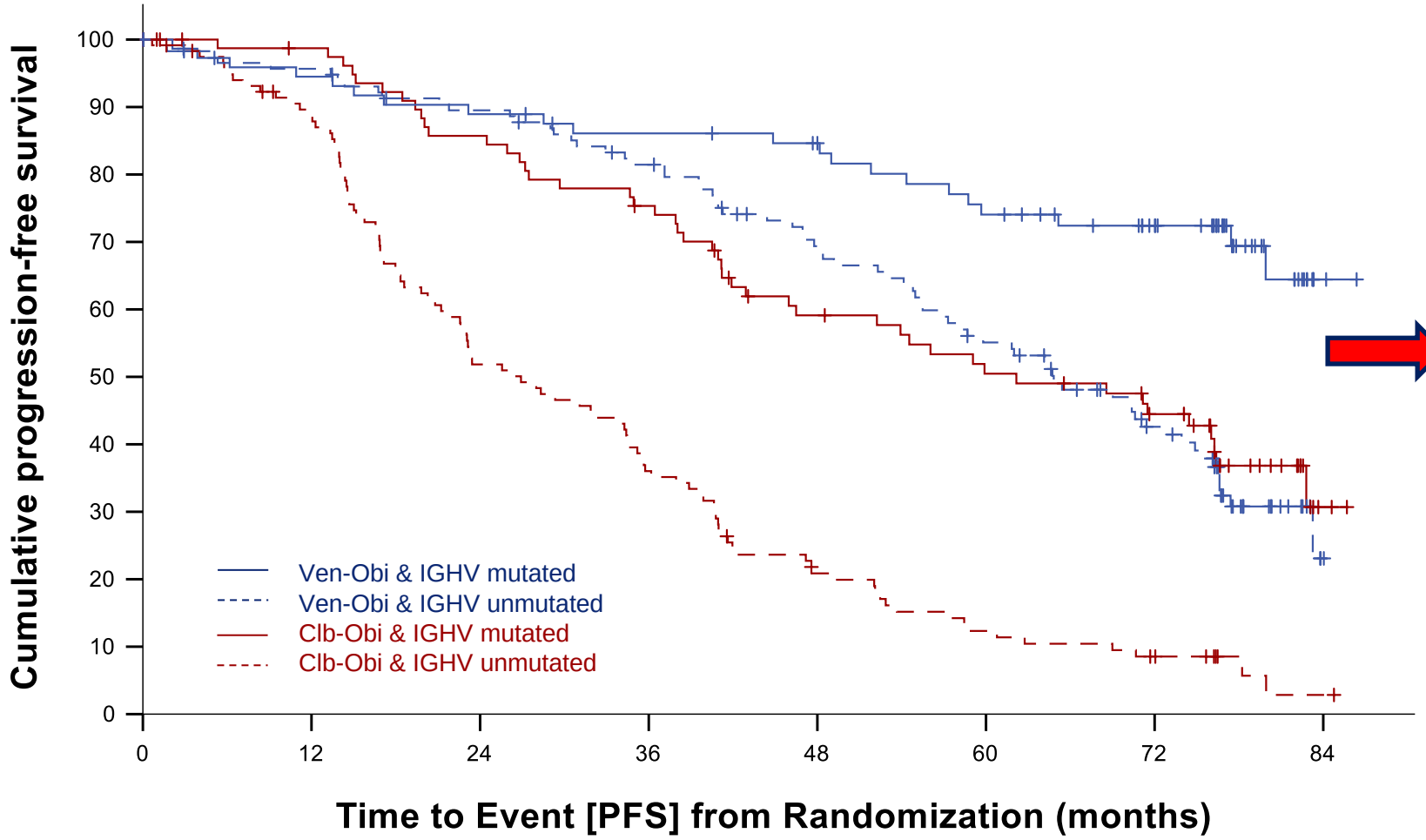
Clb-Obi & no *TP53*del/mut: 38.9 m

Clb-Obi & *TP53*del/mut: 20.8 m

HR 1.66, 95% CI [1.05-2.63], p=0.03

PROGRESSION-FREE SURVIVAL – IGHV status

Median observation time 76.4 months



Ven-Obi & IGHV mutated	76	68	64	60	57	49	39	2
Ven-Obi & IGHV unmutated	121	110	101	90	73	57	37	1
Clb-Obi & IGHV mutated	83	76	66	57	42	35	28	2
Clb-Obi & IGHV unmutated	123	101	59	41	22	13	8	1

Median PFS

Ven-Obi & IGHVmut: NR

Ven-Obi & IGHVunmut: 64.8 m

HR 0.38, 95%CI [0.23-0.61], p<0.001

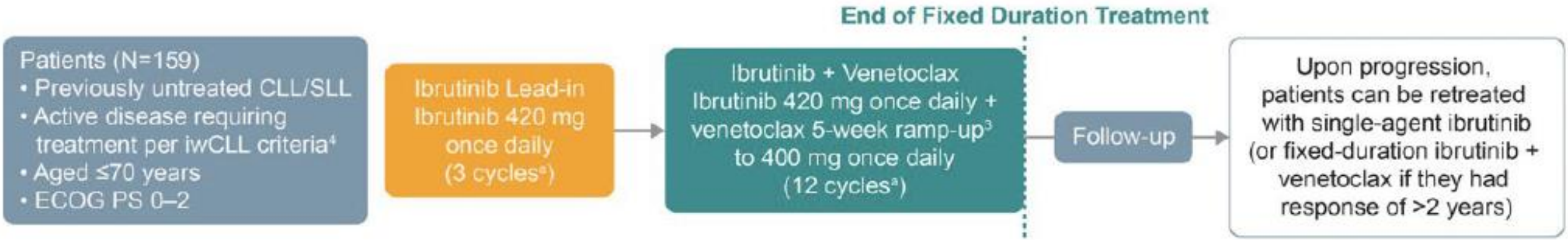
Clb-Obi & IGHVmut: 62.2 m

Clb-Obi & IGHVunmut: 26.9 m

HR 0.33, 95% CI [0.23-0.47], p<0.001

CAPTIVATE: Ibrutinib + Venetoclax Therapie mit fester zeitlicher Begrenzung

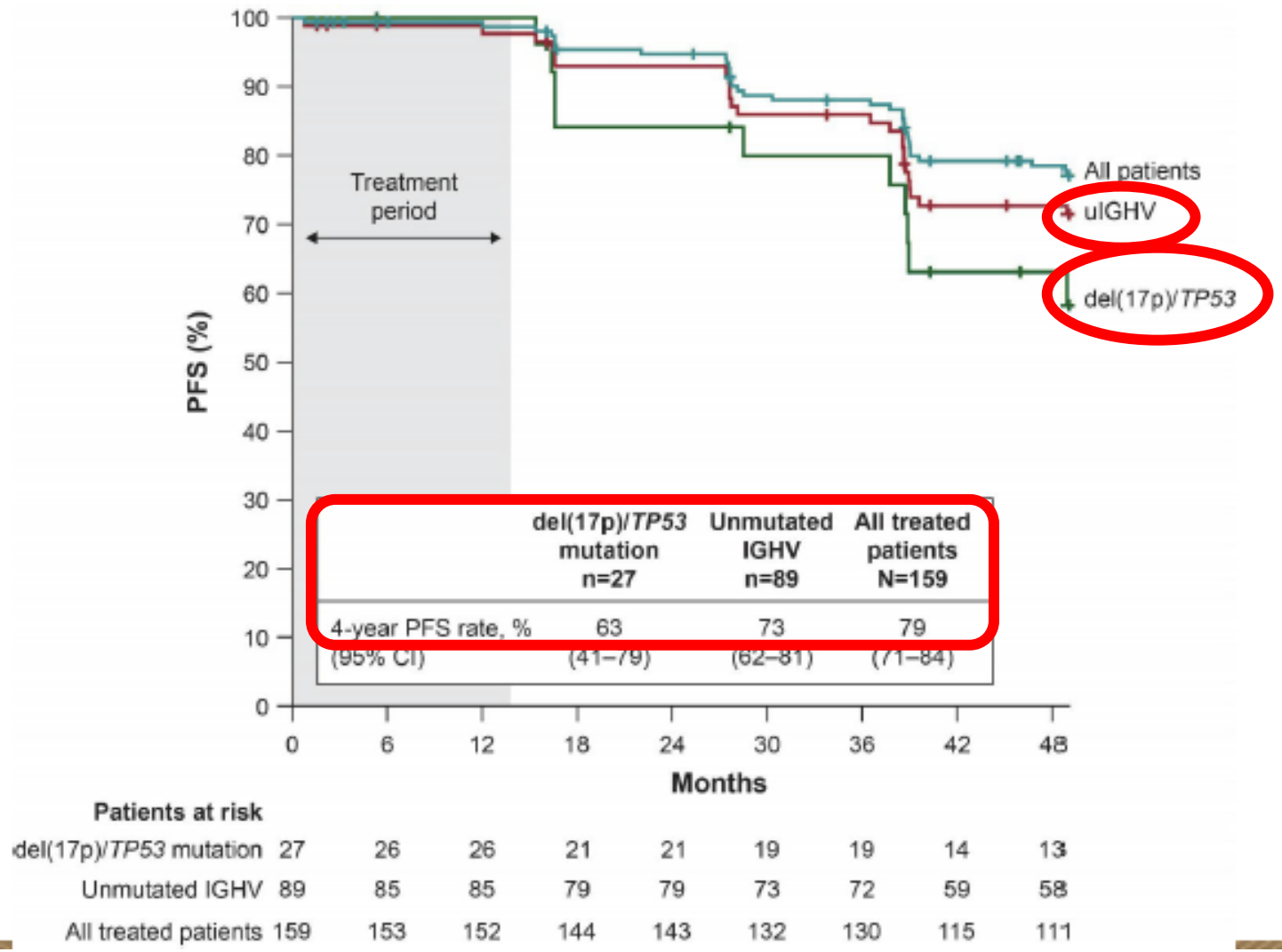
Studiendesign: 2 Kohorten (MRD-gesteuert und zeitlich feste Begrenzung)



Paolo Ghia et al., ICML 2023

CAPTIVATE: Ibrutinib + Venetoclax Therapie mit fester zeitlicher Begrenzung

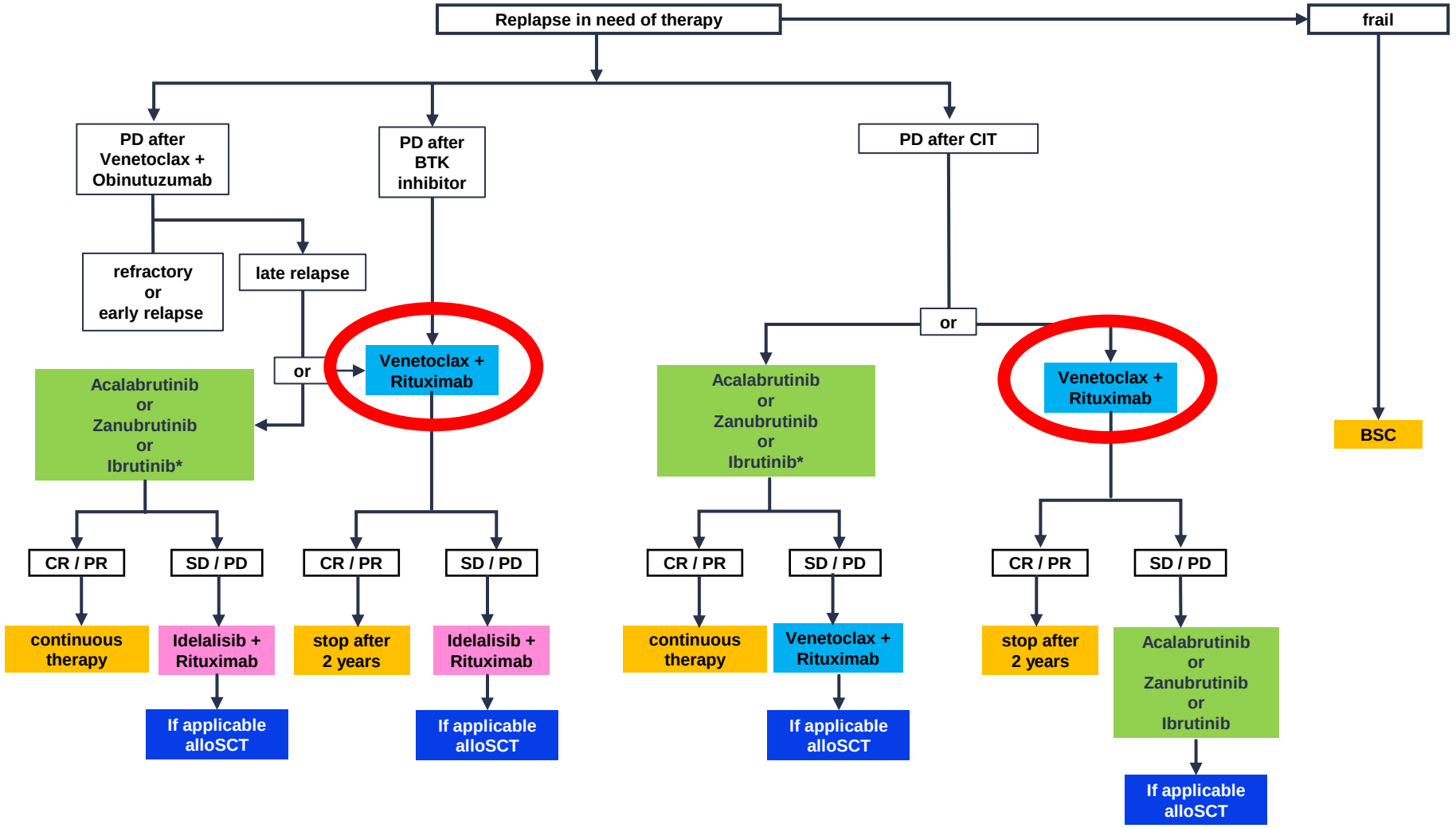
Progressions-freies Überleben von 159 Patienten nach median 49.8 Monaten Beobachtung



	del(17p)/*TP53* mutation n=27	Unmutated IGHV n=89	All treated patients N=159
4-year PFS rate, % (95% CI)	63 (41–79)	73 (62–81)	79 (71–84)

Patients at risk									
del(17p)/*TP53* mutation	27	26	26	21	21	19	19	14	13
Unmutated IGHV	89	85	85	79	79	73	72	59	58
All treated patients	159	153	152	144	143	132	130	115	111

Onkopedia CLL 2023 – R/R CLL



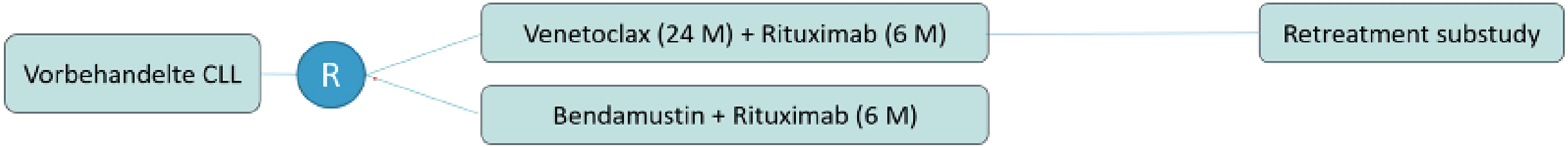
AlloSCT, allogeneic stem cell transplant; BSC, best supportive care; BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

***In case of contraindications or non-availability of acalabrutinib or zanubrutinib, ibrutinib can be offered while cardiac side effects have been shown to be significantly increased.**

Wendtner CM et al., https://www.onkopedia.com/de/onkopedia/guidelines/chronische-lymphatische-leukaemie-cll/@@guideline/html/index.html (Stand 01/2023)

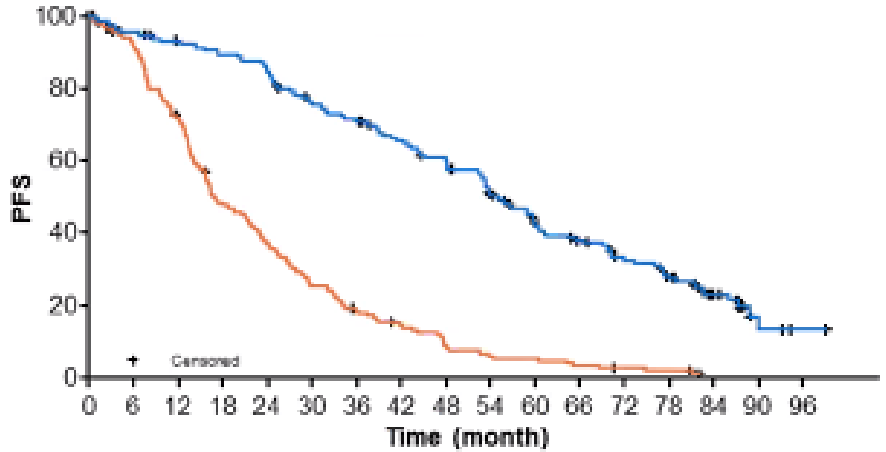
MURANO: VenR im Rezidiv der CLL – 7-Jahres-Follow-up

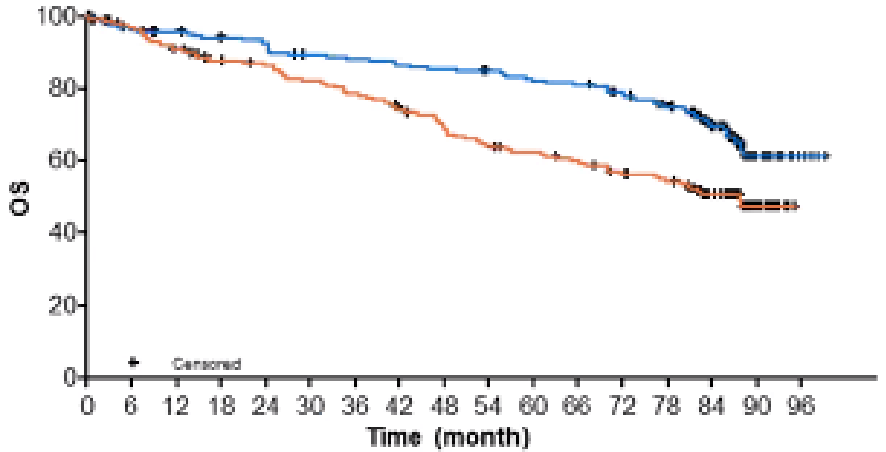
FINAL 7-YEAR FOLLOW UP AND RETREATMENT SUBSTUDY ANALYSIS OF MURANO: VENETOCLAX-RITUXIMAB (VENR)-TREATED PATIENTS WITH RELAPSED/REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA (R/R CLL), Kater et al.



	Median PFS (95% CI), months	HR* (95% CI)	7-year PFS (%)
VenR (n=194)	54.7 (52.3-59.9)	0.23 (0.18-0.29) Stratified P-value <0.0001†	23.0
BR (n=195)	17.0 (15.5-21.7)		NE

	Median OS (95% CI), months	HR‡ (95% CI)	7-year OS (%)
VenR (n=194)	NE	0.53 (0.37-0.74) Stratified P-value <0.0002†	69.6
BR (n=195)	87.8 (70.1-NE)		51.0

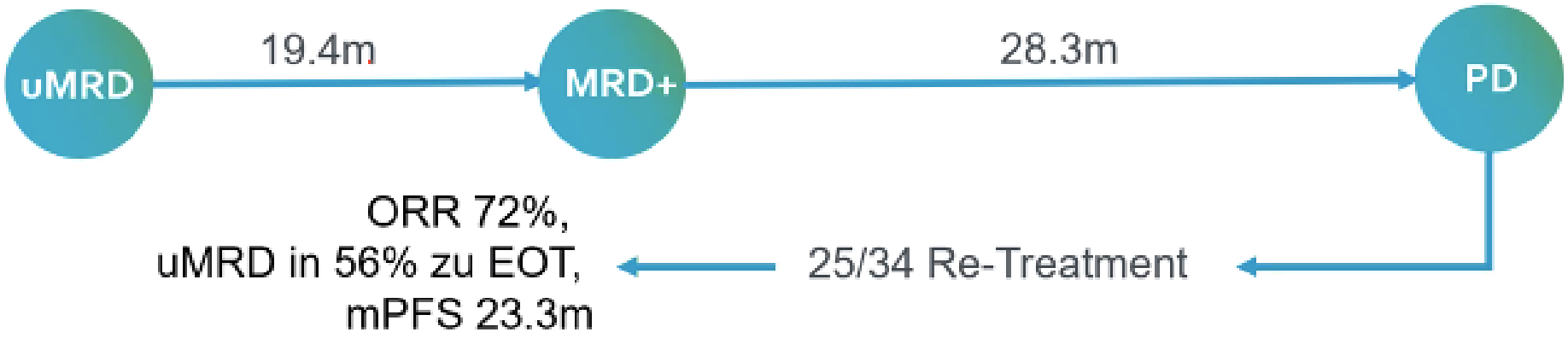




- Median follow up for efficacy (range) was 86.8 months (0.3-99.2) for VenR and 84.4 months (0.0–95.0) for BR
- No new safety signals were identified since the 5-year data cut,[1] with all patients outside of the AE reporting window[§]

Adapted from Kater et al., EHA 2023 #S201

MURANO: VenR nach VenR sinnvoll?

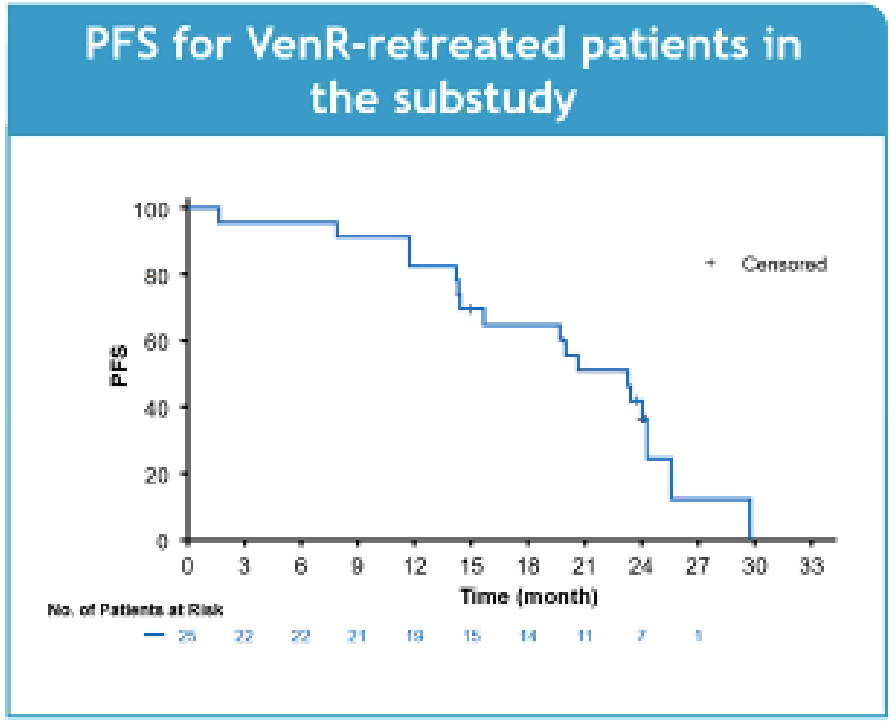


Amongst VenR-retreated patients, median follow up (range) was 33.4 months (2.7–44.0)

Median PFS (95% CI) was 23.3 months (15.6–24.3)

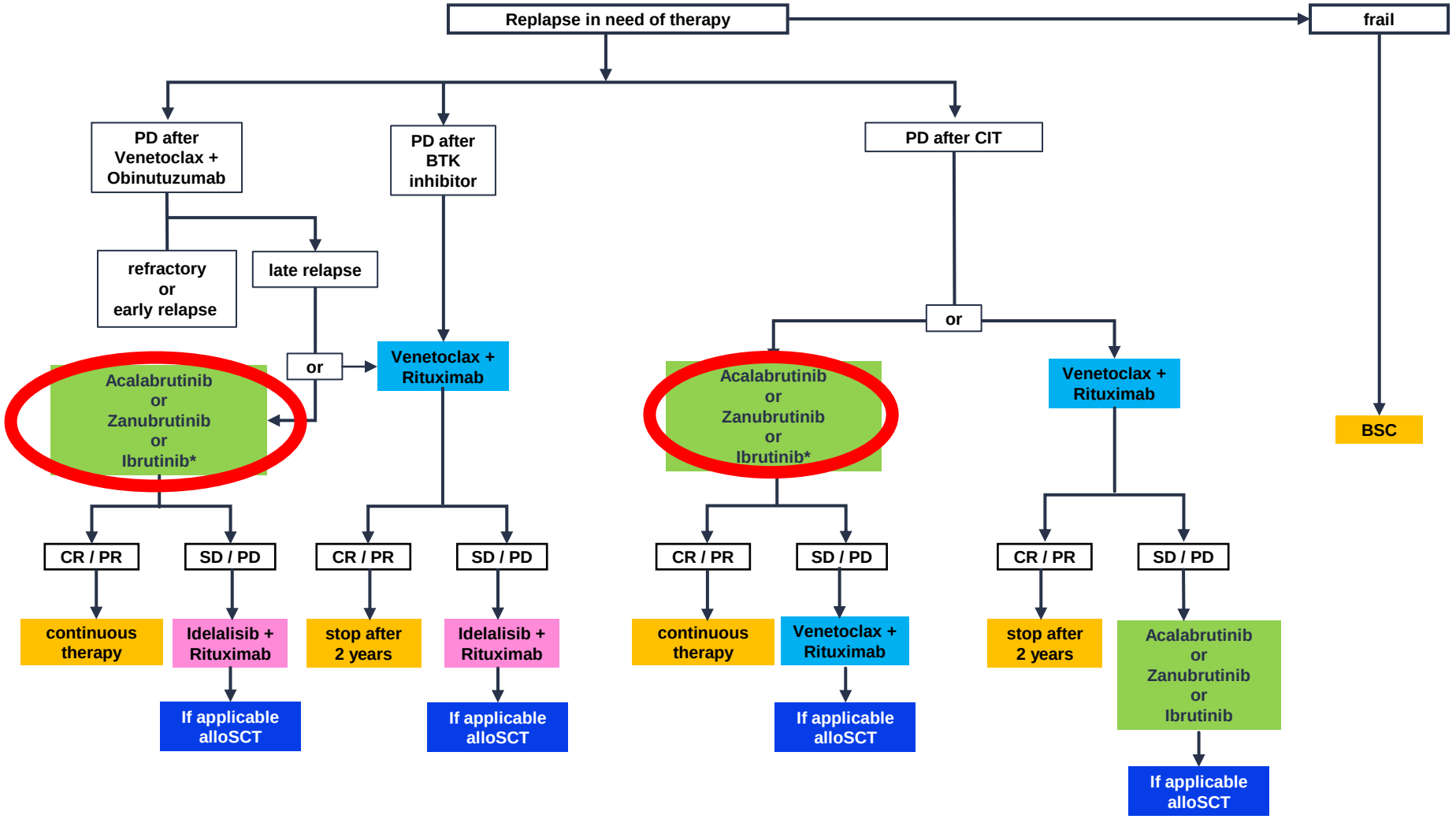
Best ORR: 72.0%; CR rate: 24%

Median OS was not reached



Adapted from Kater et al., EHA 2023 #S201

Onkopedia CLL 2023 – R/R CLL



AlloSCT, allogeneic stem cell transplant; BSC, best supportive care; BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

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Wendtner CM et al., https://www.onkopedia.com/de/onkopedia/guidelines/chronische-lymphatische-leukaemie-cll/@@guideline/html/index.html (Stand 01/2023)

ELEVATE-RR: Study Design

Previously treated CLL patients (N=533)

Must have ≥1 of the following:
- del(17)(p13.1)
- **or** del(11)(q22.3) by central laboratory testing

R (1:1)

- **Acalabrutinib (100 mg PO BID)[a]**
- **Ibrutinib (420 mg PO QD)[a]**

Stratification:
- del (17p) status (yes or no)
- ECOG PS (2 vs ≤1)
- Number of prior therapies (1-3 vs ≥4)

Primary endpoint

Non-inferiority on IRC assessed PFS[b]

Secondary endpoints (hierarchical order)

- **Incidence of any grade atrial fibrillation/flutter**
- **Incidence of grade ≥3 infections**
- **Incidence of Richter's transformation**
- **OS**

Exploratory endpoints

Investigator assessed PFS
Investigator & IRC assessed EFS[c]
Investigator & IRC assessed ORR

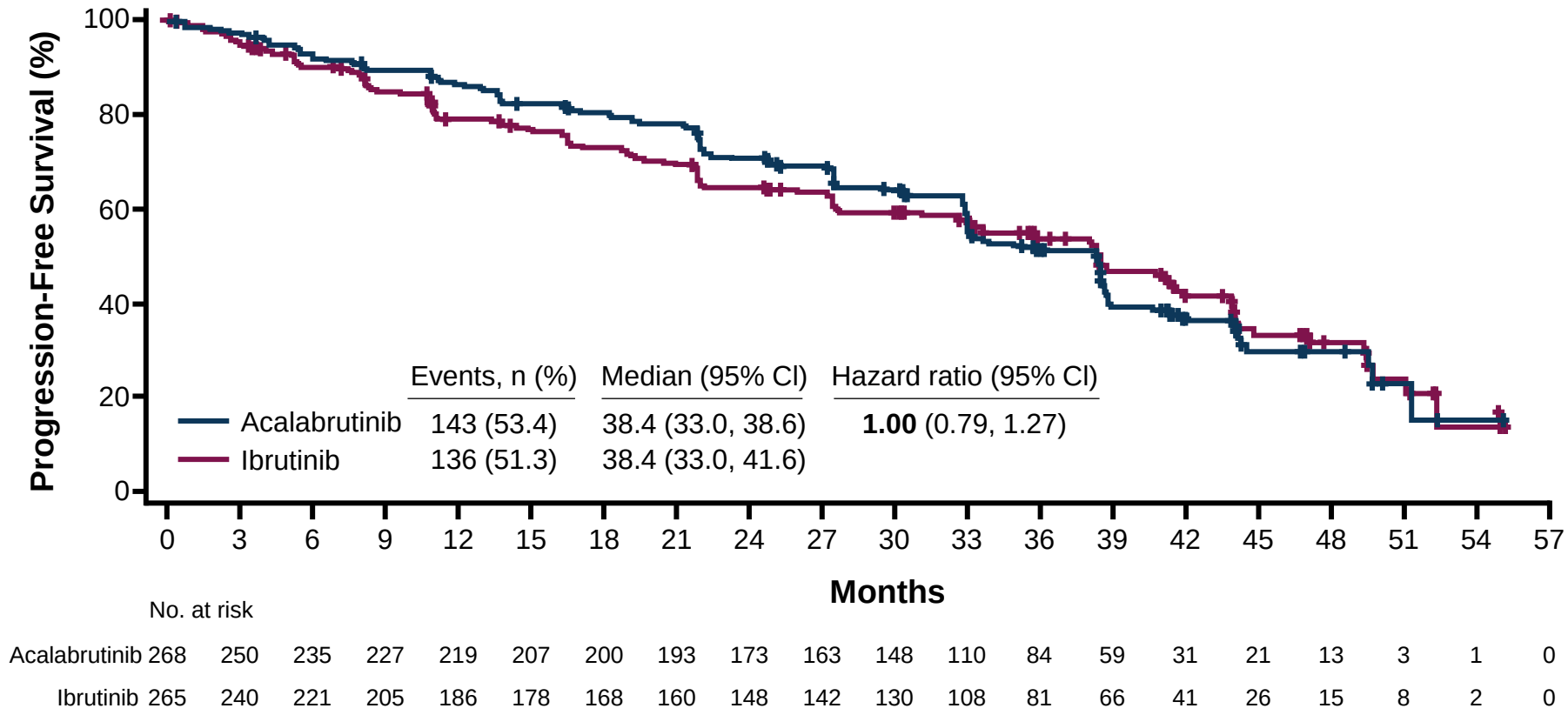
[a]Continued until disease progression or unacceptable toxicity. [b]Conducted after enrollment and accrual of ~250 IRC-assessed PFS events. [c]defined as the time from date of randomization to the date of first disease progression, any-cause death, start of subsequent anticancer therapy, or discontinuation of treatment due to adverse events

BID = twice daily; CLL = chronic lymphocytic leukemia; ECOG PS = eastern cooperative oncology group performance status; EFS = event free survival; IRC = independent review committee; OS = overall survival; PFS = progression-free survival; PO = orally; R = randomization; QD = once daily.

Byrd JC et al. *J. Clin. Oncol.* 2021. https://doi.org/10.1200/JCO.21.01210.

Primary Endpoint: Non-inferiority Met on IRC-Assessed PFS

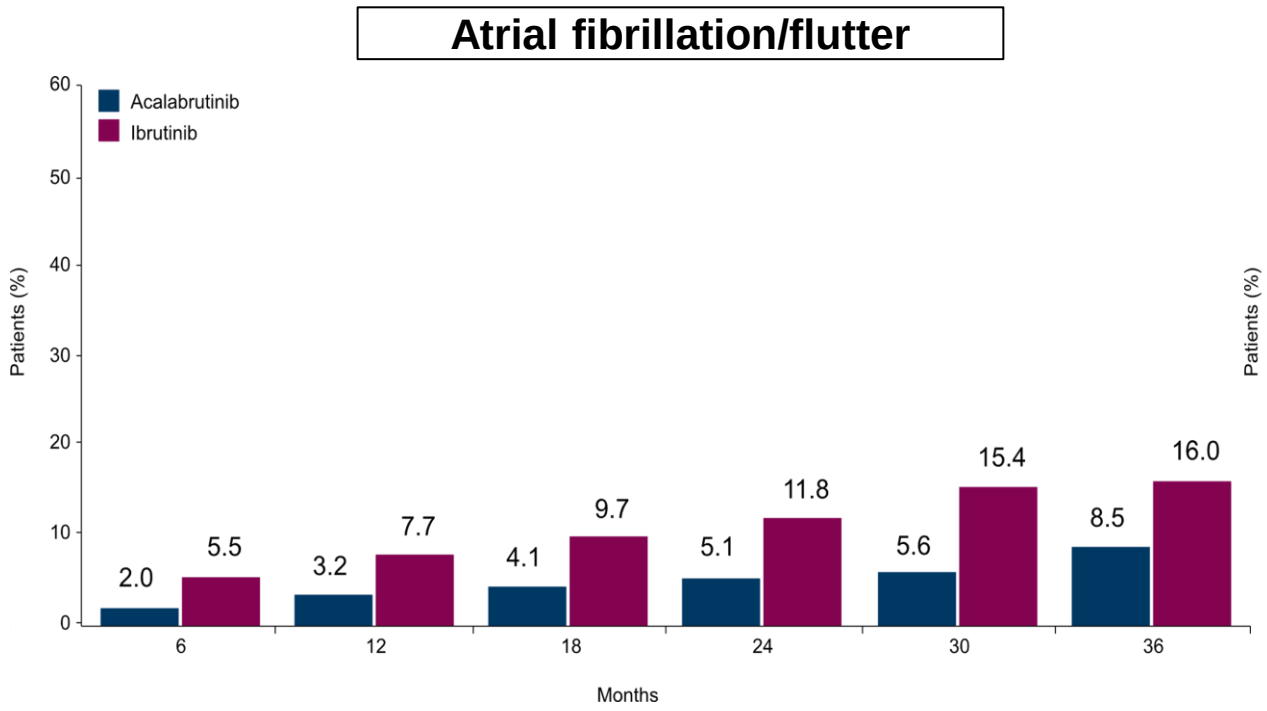
- At a median follow-up of 40.9 months (range 0.0–59.1), acalabrutinib was non-inferior to ibrutinib with a median PFS of 38.4 months in both arms (HR: 1.00; 95% CI 0.79–1.27)

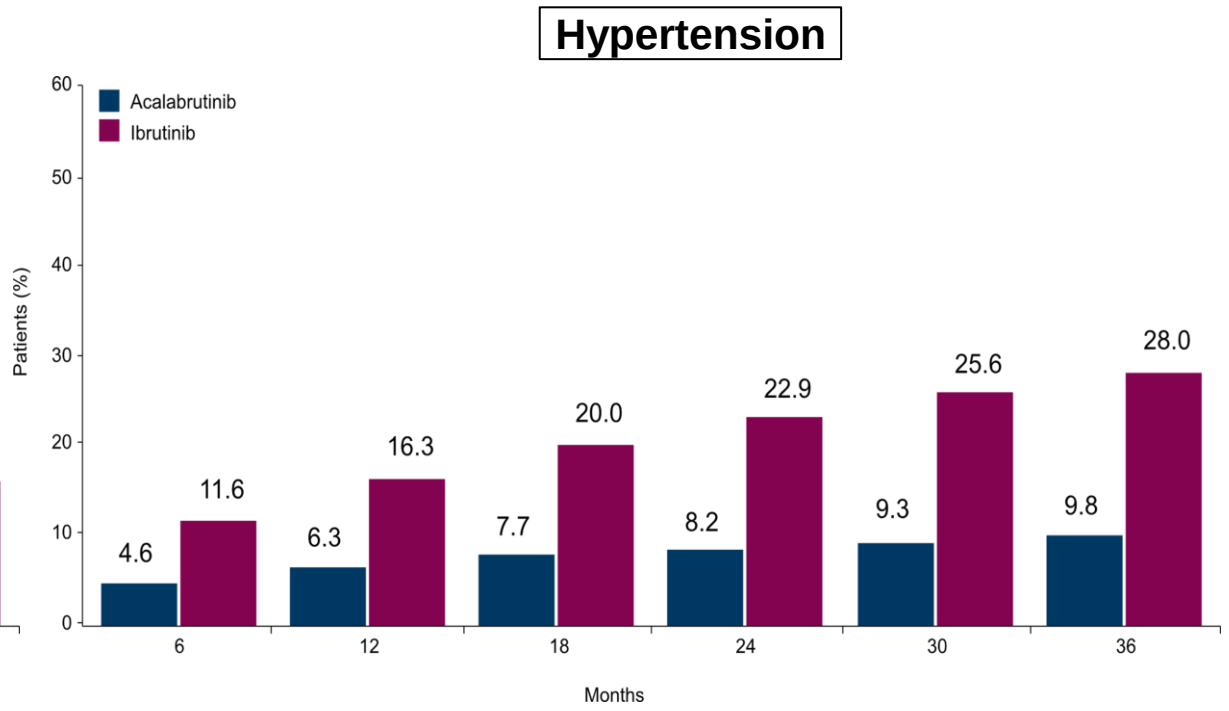


CI = confidence interval; IRC = independent review committee; HR = hazard ratio; PFS = progression-free survival.

Byrd JC et al. *J. Clin. Oncol.* 2021. https://doi.org/10.1200/JCO.21.01210.

Cumulative Incidences of Afib/flutter and HTN were Lower for Acalabrutinib at Each Time Point





Afib = atrial fibrillation; HTN = hypertension.

Seymour JF et al. Poster Presented at: ASH; December 11-14, 2021; Atlanta, GA. Abs 3721.

ALPINE Study Design

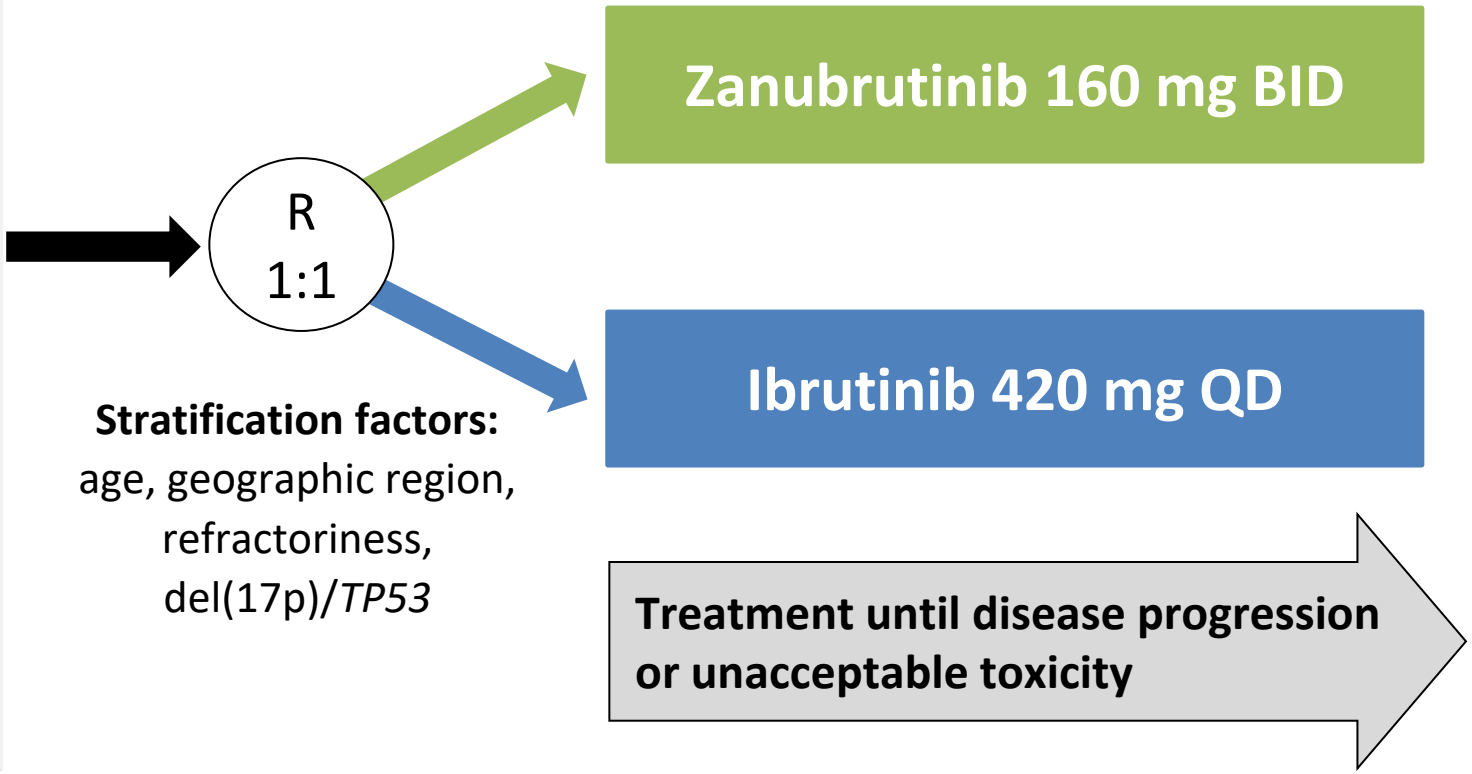
R/R CLL/SLL with ≥ 1 prior treatment
(Planned N=600, Actual N=652)

Key Inclusion Criteria

- R/R to ≥1 prior systemic therapy for CLL/SLL
- Measurable lymphadenopathy by CT or MRI

Key Exclusion Criteria

- Prior BTK inhibitor therapy
- Treatment with warfarin or other vitamin K antagonists



Jennifer R. Brown et al., NEJM 2023;388:319-332

Endpoints and Statistical Design

Primary Endpoint

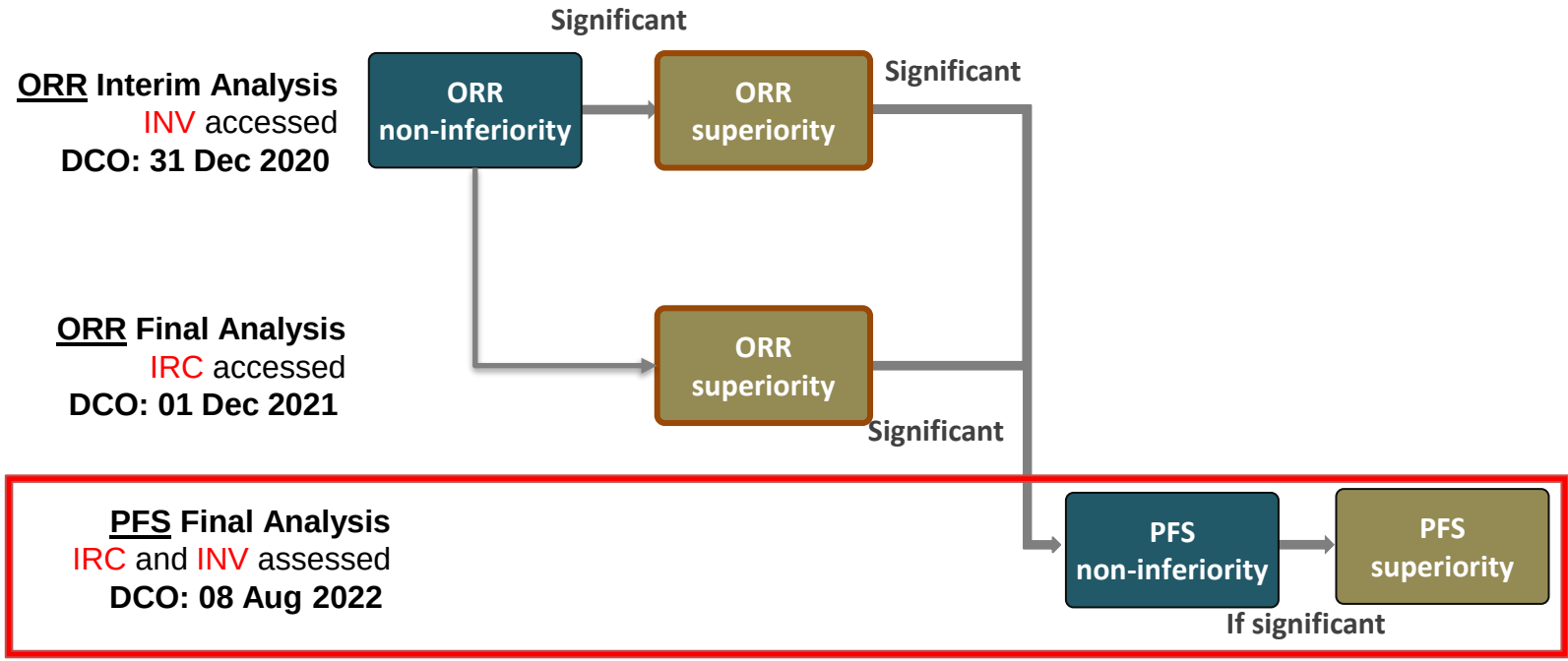
- ORR (PR+CR) noninferiority and superiority (by investigator)

Key Secondary Endpoints

- PFS
- Incidence of atrial fibrillation

Other Secondary Endpoints

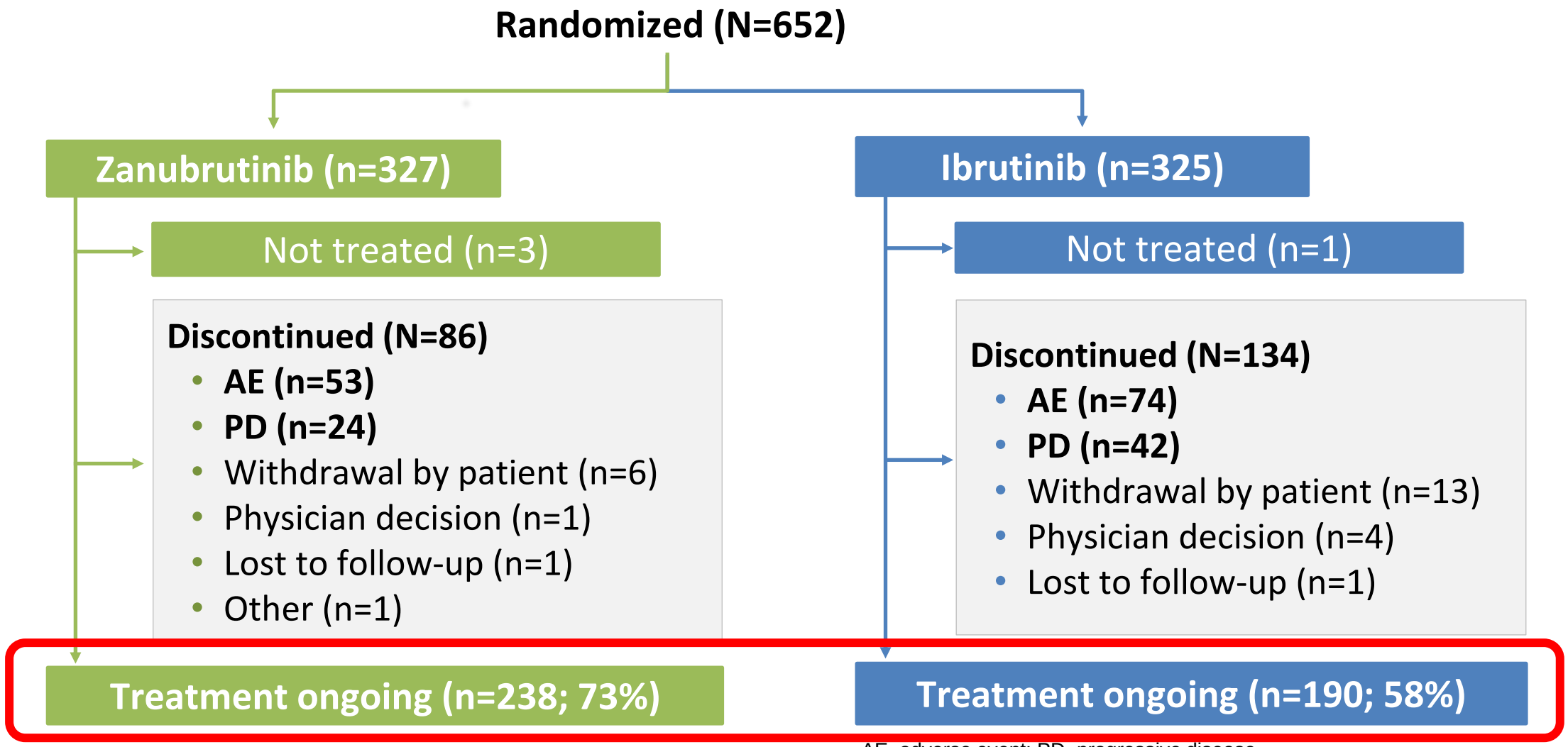
- DoR, OS
- Time to treatment failure
- PR-L or higher
- Patient-reported outcomes
- Safety



Overall response rate noninferiority and superiority were demonstrated in the ORR interim and final analyses; PFS was tested for noninferiority under hierarchical testing when 205 events had occurred

Jennifer R. Brown et al., NEJM 2023;388:319-332

Patient Disposition



AE, adverse event; PD, progressive disease.

Jennifer R. Brown et al., NEJM 2023;388:319-332

Zanubrutinib Had A Favorable Cardiac Profile

Lower rate of cardiac events, serious cardiac events, treatment discontinuation, and deaths

- Lower rate of serious cardiac adverse events reported with zanubrutinib
  - A fib/flutter (n=2)
  - MI/ACS (n=2)
  - CHF (n=2)
- **Fatal cardiac events:**
  - **Zanubrutinib, n=0 (0%)**
  - **Ibrutinib, n=6 (1.9%)**

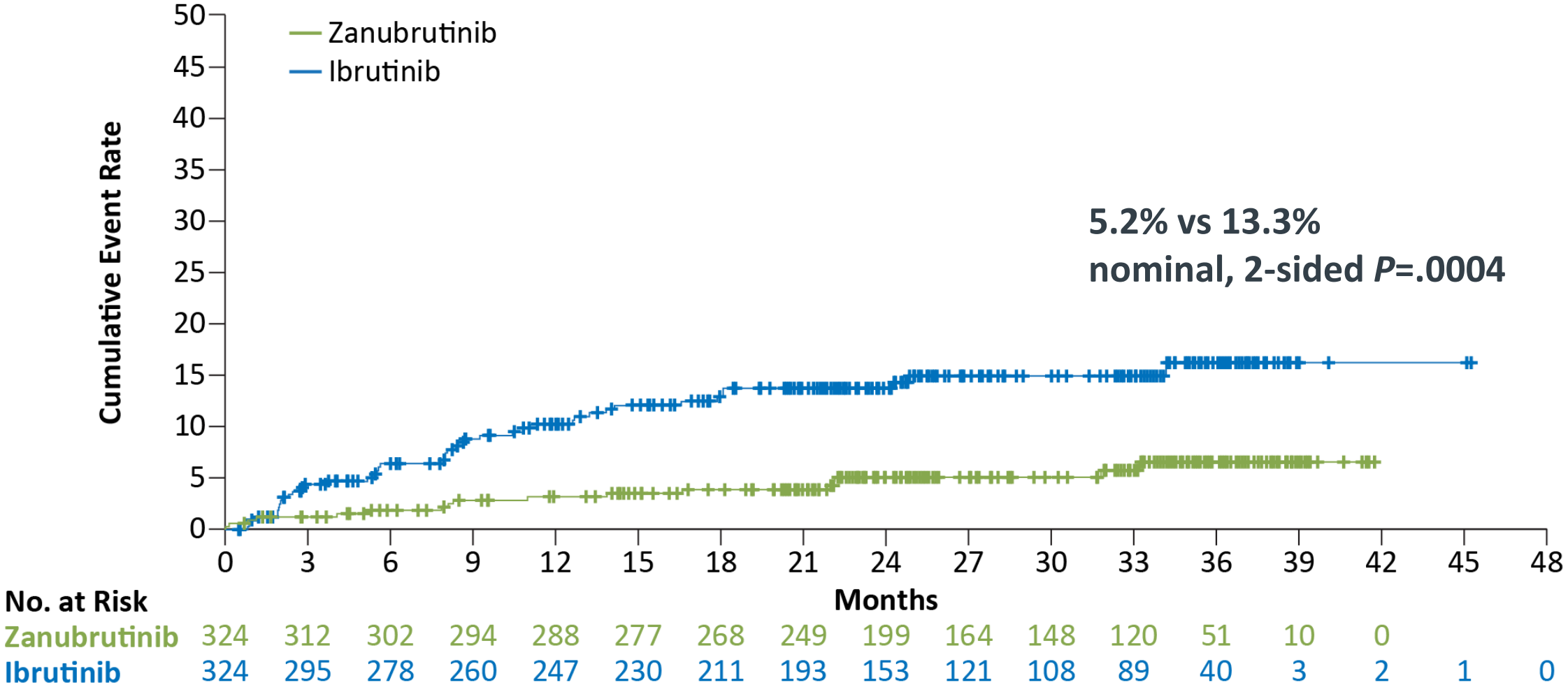
	Zanubrutinib (n=324)	Ibrutinib (n=324)
Cardiac adverse events	**69 (21.3%)**	**96 (29.6%)**
Serious cardiac adverse events	**6 (1.9%)**	**25 (7.7%)**
Cardiac adverse events leading to treatment discontinuation	**1 (0.3)**	**14 (4.3)**
Ventricular extrasystoles	1 (0.3)	0
Atrial fibrillation	0	5 (1.5)
Cardiac arrest	0	2 (0.6)*
Cardiac failure	0	2 (0.6)
Cardiac failure acute	0	1 (0.3)*
Congestive cardiomyopathy	0	1 (0.3)*
Myocardial infarction	0	1 (0.3)*
Palpitations	0	1 (0.3)
Ventricular fibrillation	0	1 (0.3)

Data cutoff: 8 Aug 2022

*Cardiac deaths. One death not listed due to myocardial infarction with ibrutinib discontinuation due to diarrhea 14 days prior to the fatal event.

Jennifer R. Brown et al., NEJM 2023;388:319-332

Fewer Atrial Fibrillation/Flutter Events With Zanubrutinib

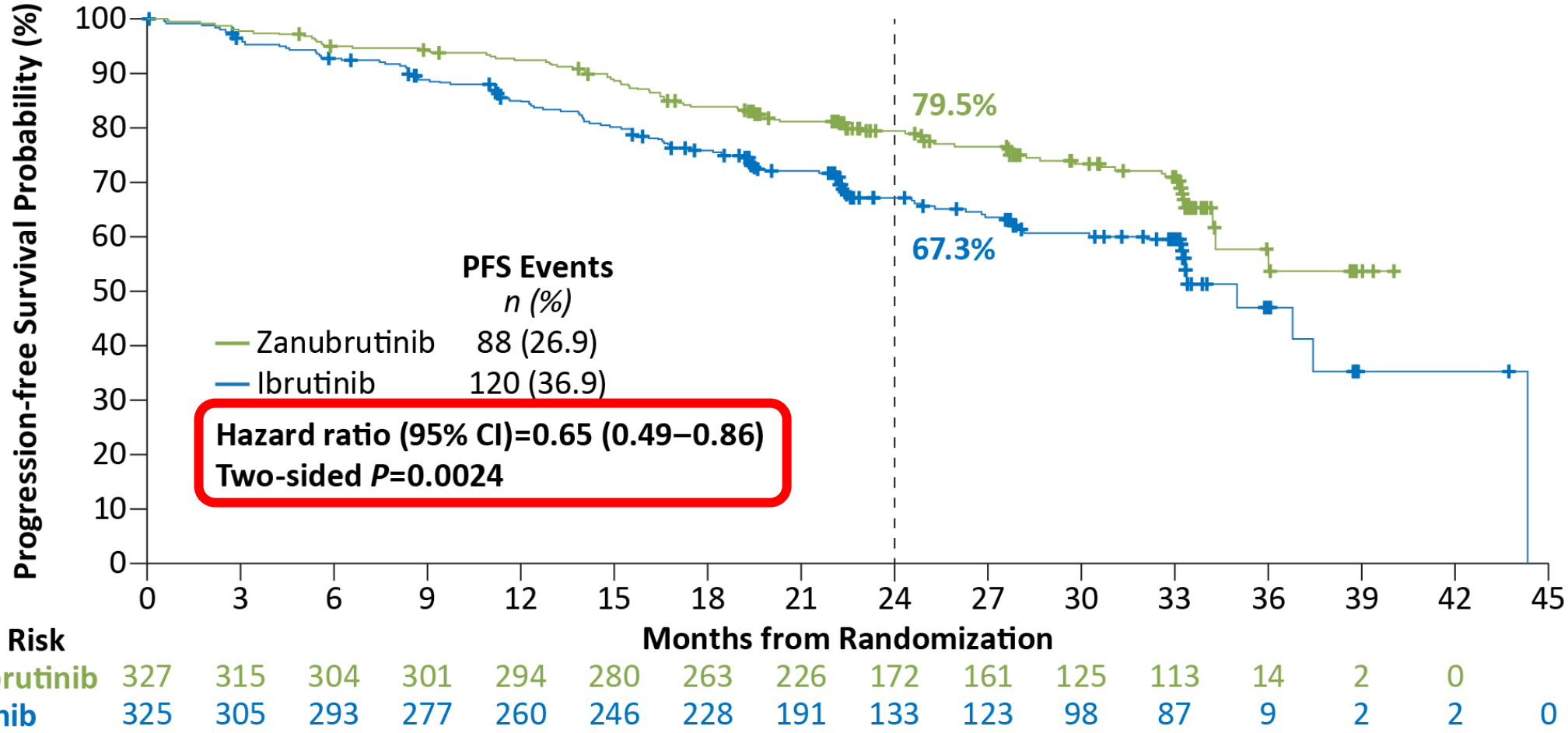


Data cutoff: 8 Aug 2022

Jennifer R. Brown et al., NEJM 2023;388:319-332

Zanubrutinib PFS by IRC Significantly Superior to Ibrutinib

Median study follow-up of 29.6 months

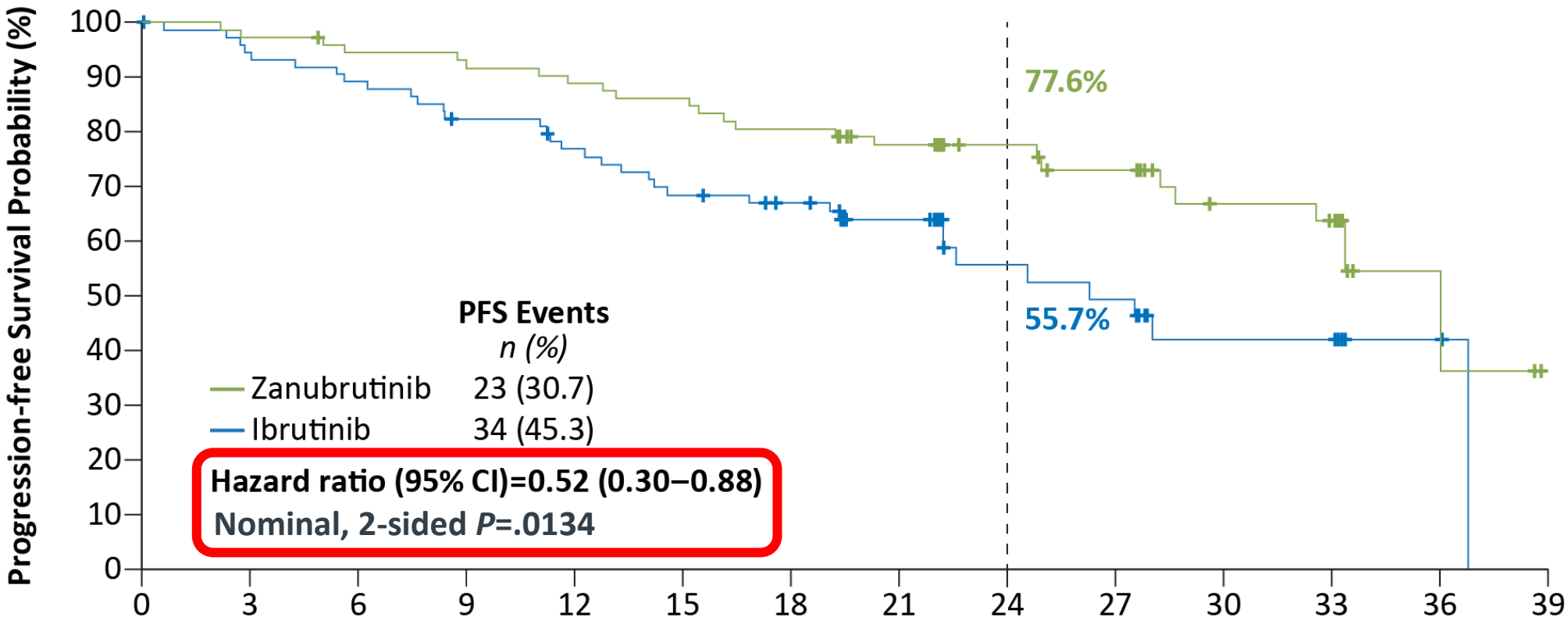


No. at Risk															
Zanubrutinib	327	315	304	301	294	280	263	226	172	161	125	113	14	2	0
Ibrutinib	325	305	293	277	260	246	228	191	133	123	98	87	9	2	2	0

Data cutoff: 8 Aug 2022

Jennifer R. Brown et al., NEJM 2023;388:319-332

Zanubrutinib Improved PFS in Patients with del(17p)/*TP53*^{mut}



No. at Risk														
Zanubrutinib	75	71	68	67	64	62	58	49	35	30	21	19	3	0
Ibrutinib	75	70	66	60	55	49	45	34	18	16	10	10	2	0

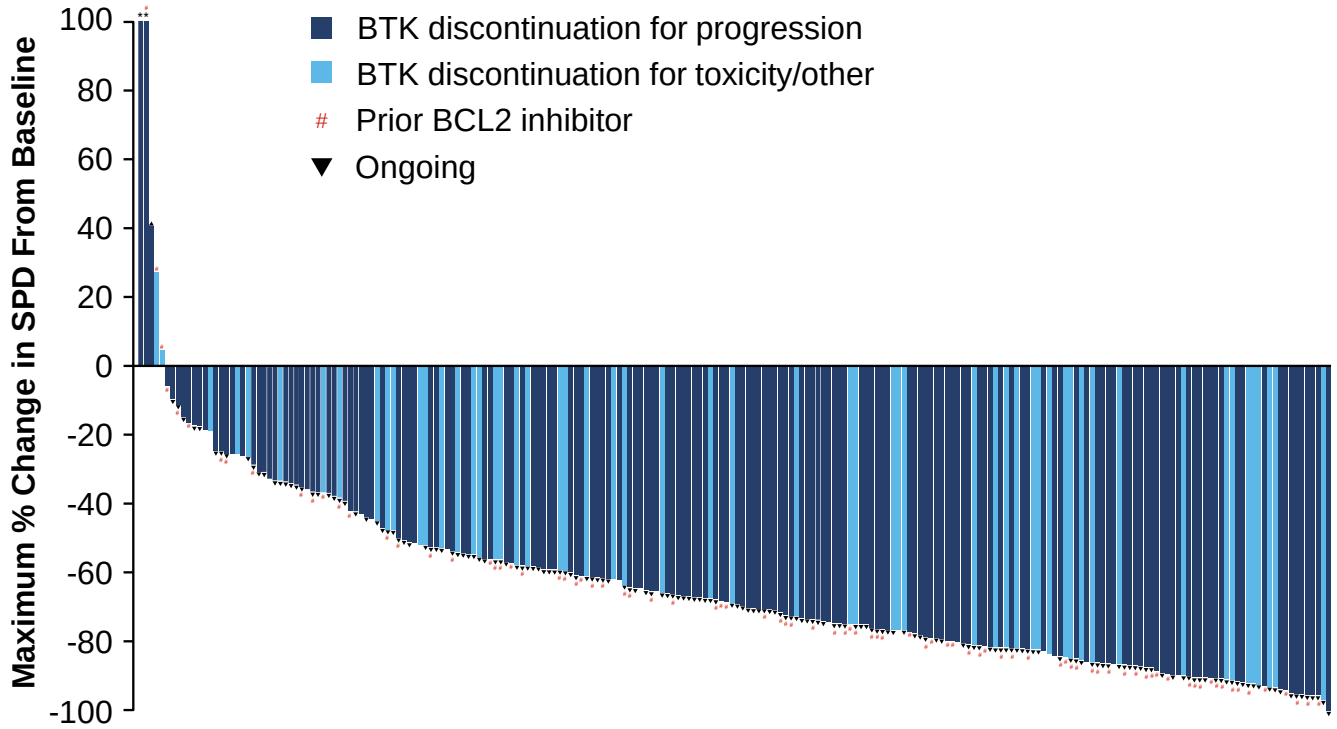
PFS data assessed by IRC

Data cutoff: 8 Aug 2022

Jennifer R. Brown et al., NEJM 2023;388:319-332


CLL:
Künftige
Therapie-
optionen?

Pirtobrutinib Efficacy in BTK-pretreated CLL/SLL Patients

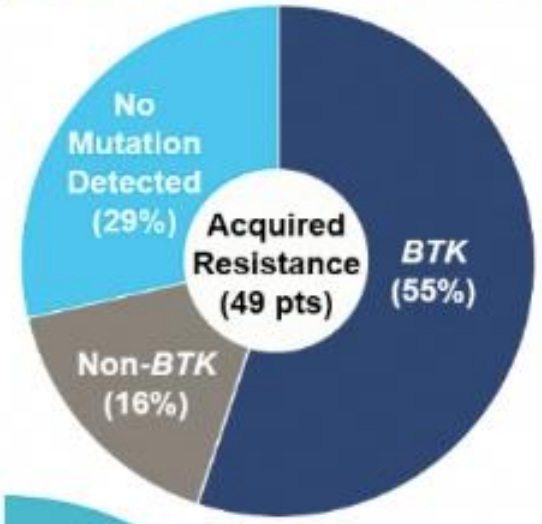


Efficacy-evaluable BTK-pretreated CLL/SLL patients[a]	n=252
ORR, % (95% CI)[b]	**68 (62-74)**
Best response	
CR, n (%)	2 (1)
PR, n (%)	137 (54)
PR-L, n (%)	32 (13)
SD, n (%)	62 (25)

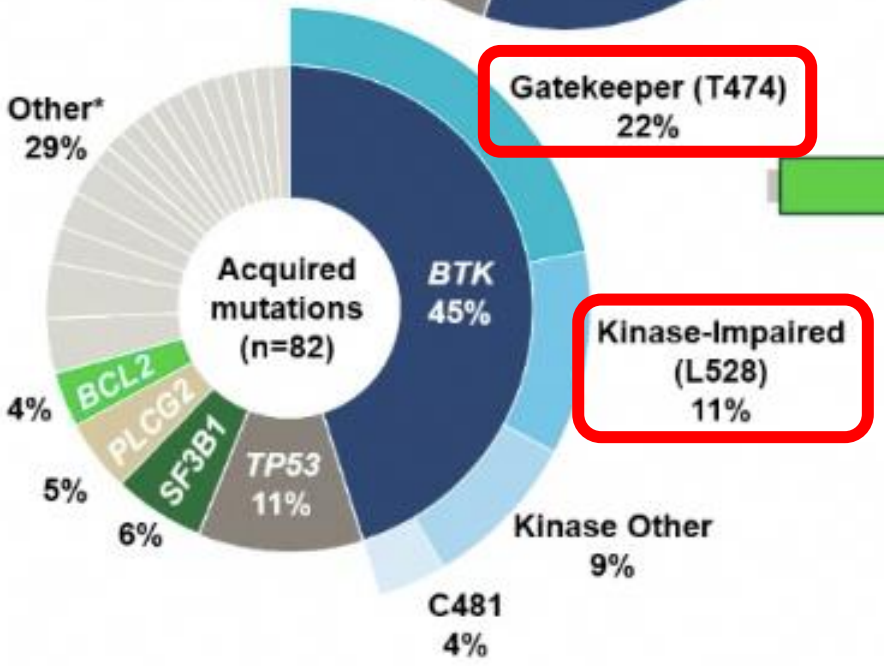
Data cutoff date: July 16, 2021.
*Patients with >100% increase in SPD. Data for 30 patients are not shown in the waterfall plot due to no measurable target lesions identified by CT at baseline, discontinuation prior to first response assessment, or lack of adequate imaging in follow-up. [a]Efficacy-evaluable patients are those who had at least 1 post-baseline response assessment or had discontinued treatment prior to first post-baseline response assessment. [b]ORR includes patients with a best response of CR, PR, and PR-L. Response status per iwCLL 2018 according to investigator assessment. Total percentage may be different from the sum of the individual components because of rounding.
Abbreviations are defined in the speaker notes.

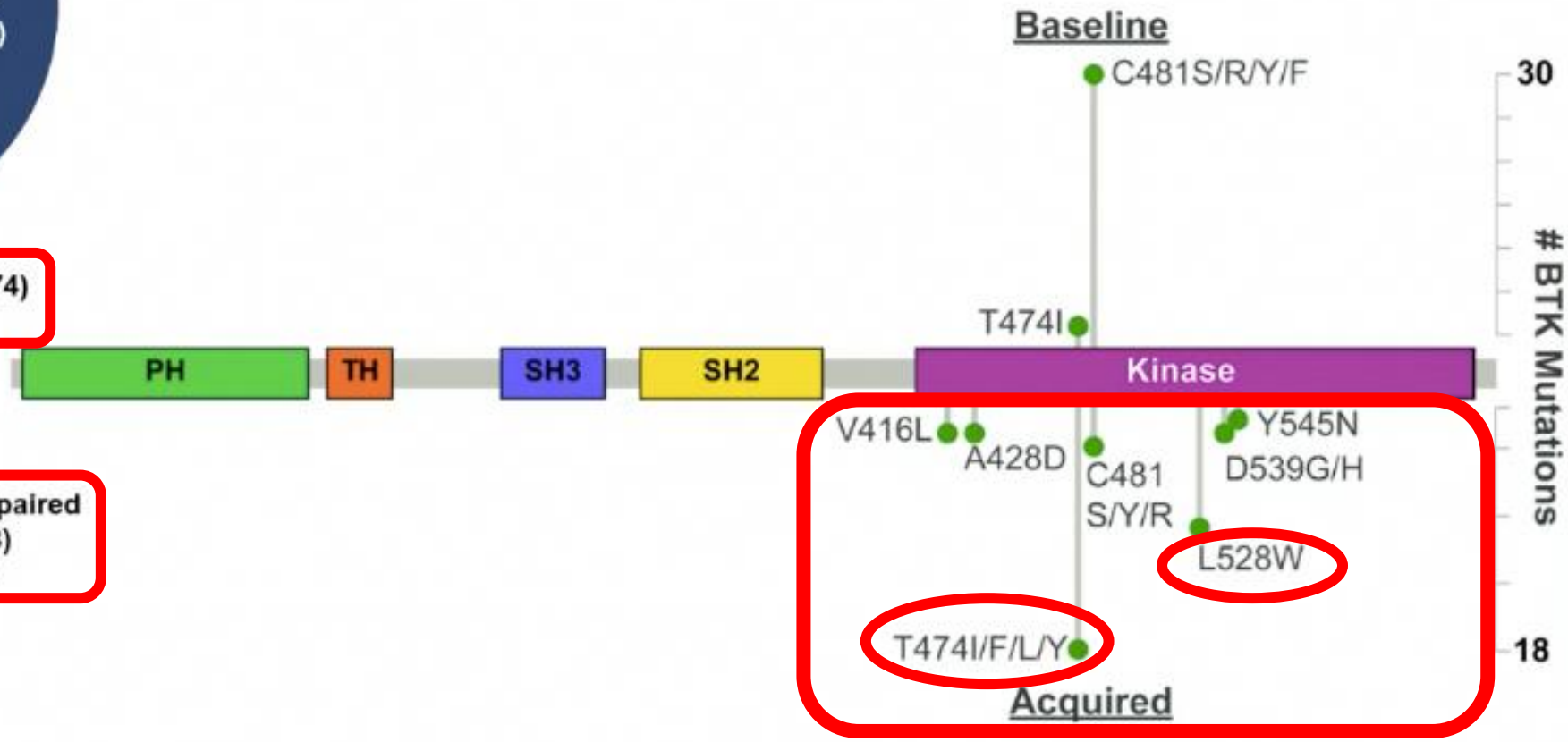
Mato AR, et al. *Lancet.* 2021;397(10277):892-901.

Acquired Resistance to Pirtobrutinib Mostly Converged Around On-target *BTK* Mutations (Non-C481)



- 71% (35/49) of patients had at least one acquired mutation at progression
- Total of 82 acquired mutations in 35 patients





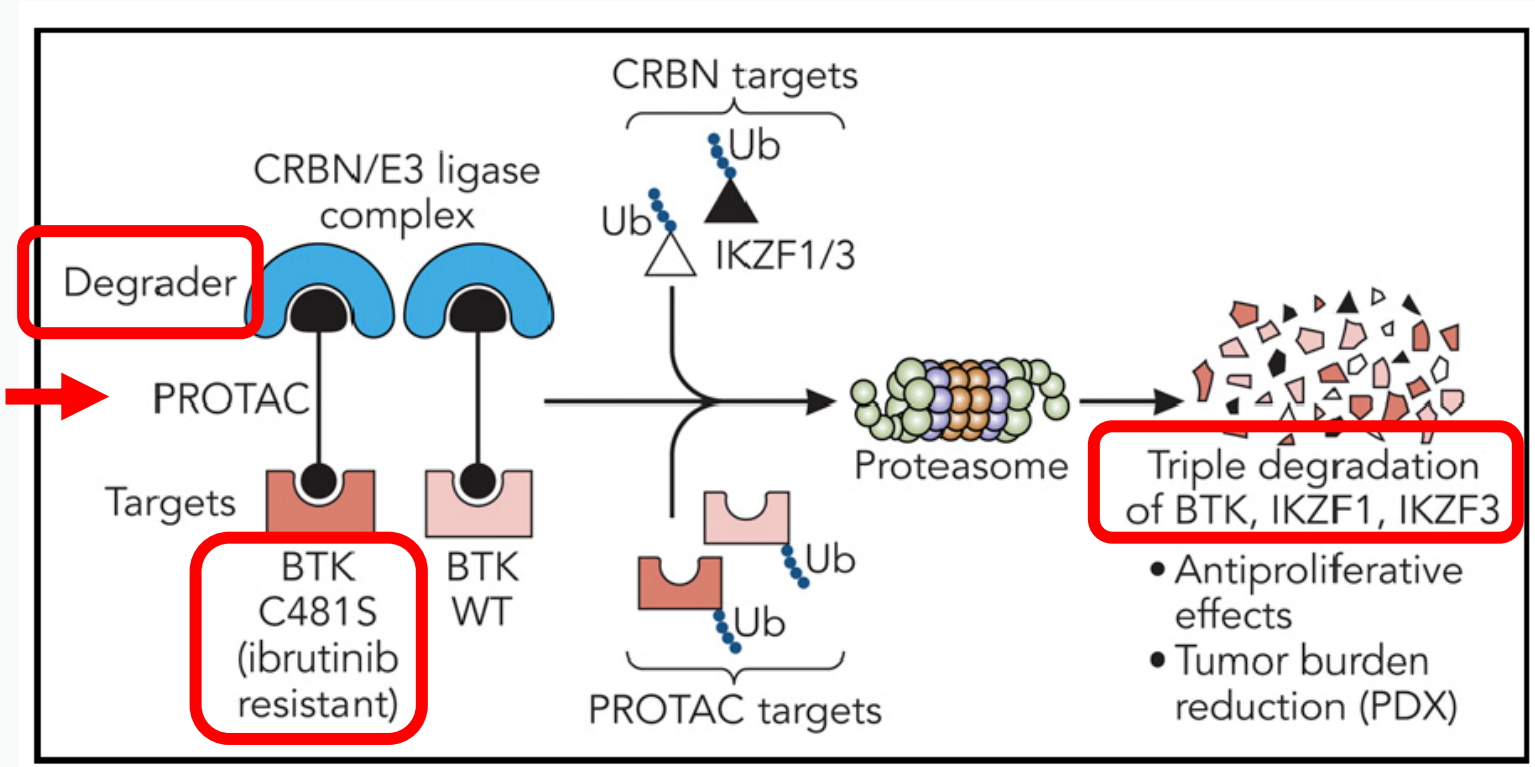
*Others: APC, ATM, CDKN2A, CDKN2B, EP300, ERBB3, IRF4, KIT, KMT2C, NOTCH1, NRAS, NTRK1, PIK3CG, RB1, SMARCA4, TNFAIP3, XPO1.

Brown JR et al., EHA 2023

Concept of BTK Degrader:

Three targets in 1 shot against ibrutinib resistance
David Chiron

proteolysis **ta**rgeting **c**himeras



The PROTAC designed by Dobrovolsky et al leads to the triple degradation of BTK, IKZF1, and IKZF3 through their Ub and consequent degradation by the proteasome. This small molecule degrades both WT and C481S-mutated BTK proteins and overcomes ibrutinib resistance in B-cell malignancies in vivo. CRBN, cereblon; PDX, patient-derived xenograft; Ub, ubiquitination; WT, wild-type. Professional illustration by Somersault18:24.

Chiron, D. Blood. 2019 Feb 28;133(9):888-889

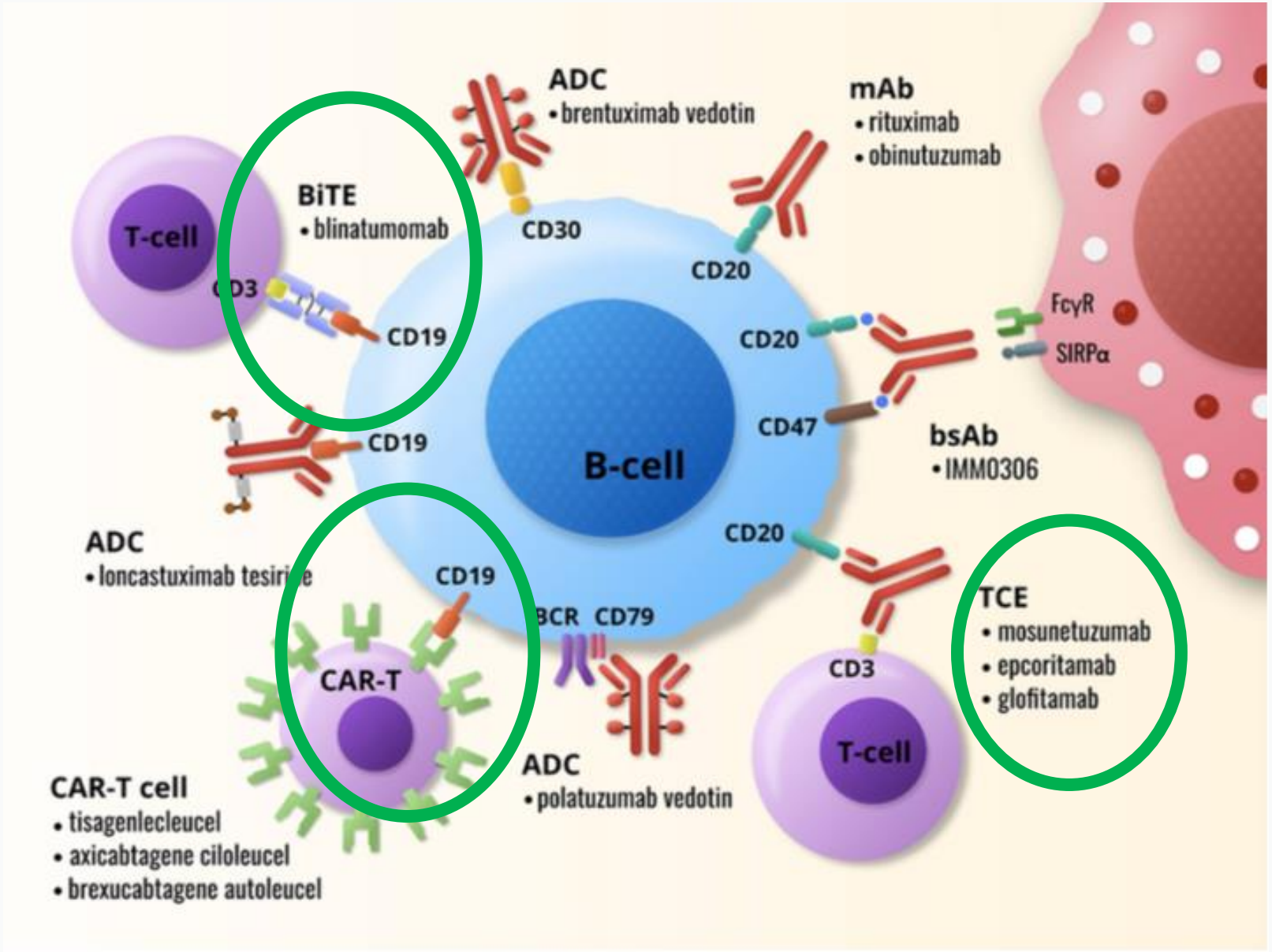
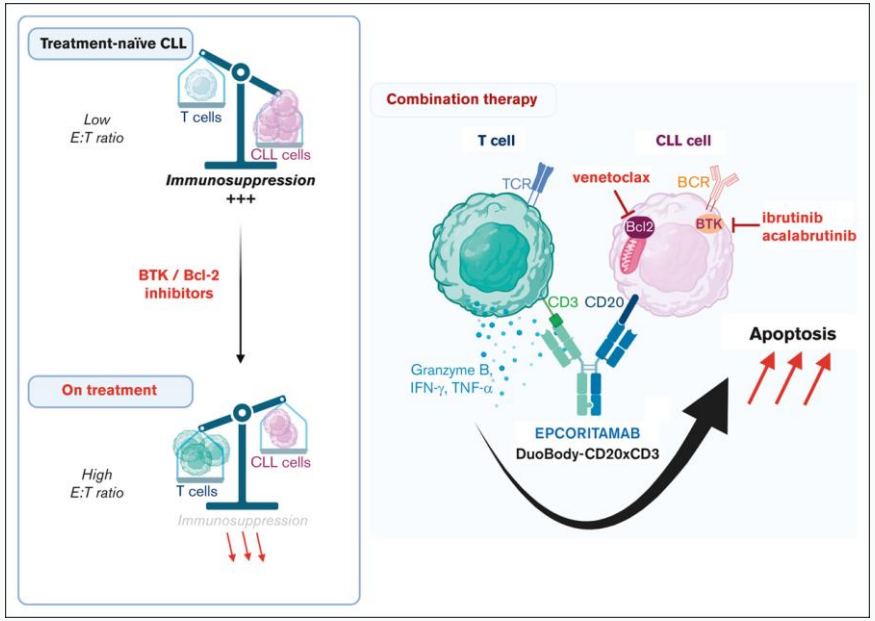


Figure 1. Examples of currently used and tested immunotherapeutic modalities in the treatment of B-cell non-Hodgkin lymphomas. mAb, monoclonal antibody; bsAb, bispecific antibody; TCE, T-cell engager; BiTE, bispecific T-cell engager; CAR-T cell, chimeric antigen receptor T cell; ADC, antibody-drug conjugate; BCR, B-cell receptor.

Mihályová, J. et al. Int J Mol Sci. 2021 Oct 25;22(21):11470

Cytotoxicity of the CD3×CD20 bispecific antibody epcoritamab in CLL is increased by concurrent BTK or BCL-2 targeting



Maissa Mhibik,Erika M. Gaglione,David Eik,John Herrick,Janet Le,Inhye E. Ahn,Christopher Chiu,Monica Wielgos-Bonvallet,Ida H. Hiemstra,Esther C. W. Breij,Jenny Chen,Edward B. Reilly,Pearlie K. Epling-Burnette,Edith Szafer-Glusman,Clare Sun,Adrian Wiestner, **Cytotoxicity of the CD3×CD20 bispecific antibody epcoritamab in CLL is increased by concurrent BTK or BCL-2 targeting, Blood Adv, 2023,**

Take home message:

- ✓ **Watch & wait bleibt Standard für Frühstadien der CLL (CLL12)**
- ✓ **VenObi mit eingeschränkter Effektivität (PFS) bei Hochrisiko-CLL (TP53, $IGHV^{unmut}$)**
- ✓ **Zanubrutinib besonders effektiv bei TP53-aberranten CLL Patienten**
- ✓ **Resistenzmutationen (u.a. T474, L528W) auch nach Pirtobrutinib-Therapie beschrieben**
- ✓ **BTK Degrader, CAR T-Zellen und bispezifische Antikörper als potentielle künftige Therapieoptionen bei R/R Patienten**