DEUTSCHE STUDIENGRUPPE

THERAPIE DER CHRONISCHEN LYMPHATISCHEN LEUKÄMIE (CLL)

Häamtologie/Onkologie im Dialog

10. Mai 2023

Barbara Eichhorst

DISCLOSURES

Barbara Eichhorst

Consulting or Advisory Boards:

AbbVie, AstraZeneca, BeiGene, Gilead, Lilly, Janssen, MSD, Miltenyi

Speaker / Speaker's Bureau

AbbVie, AstraZeneca, BeiGene, Janssen, MSD, Roche

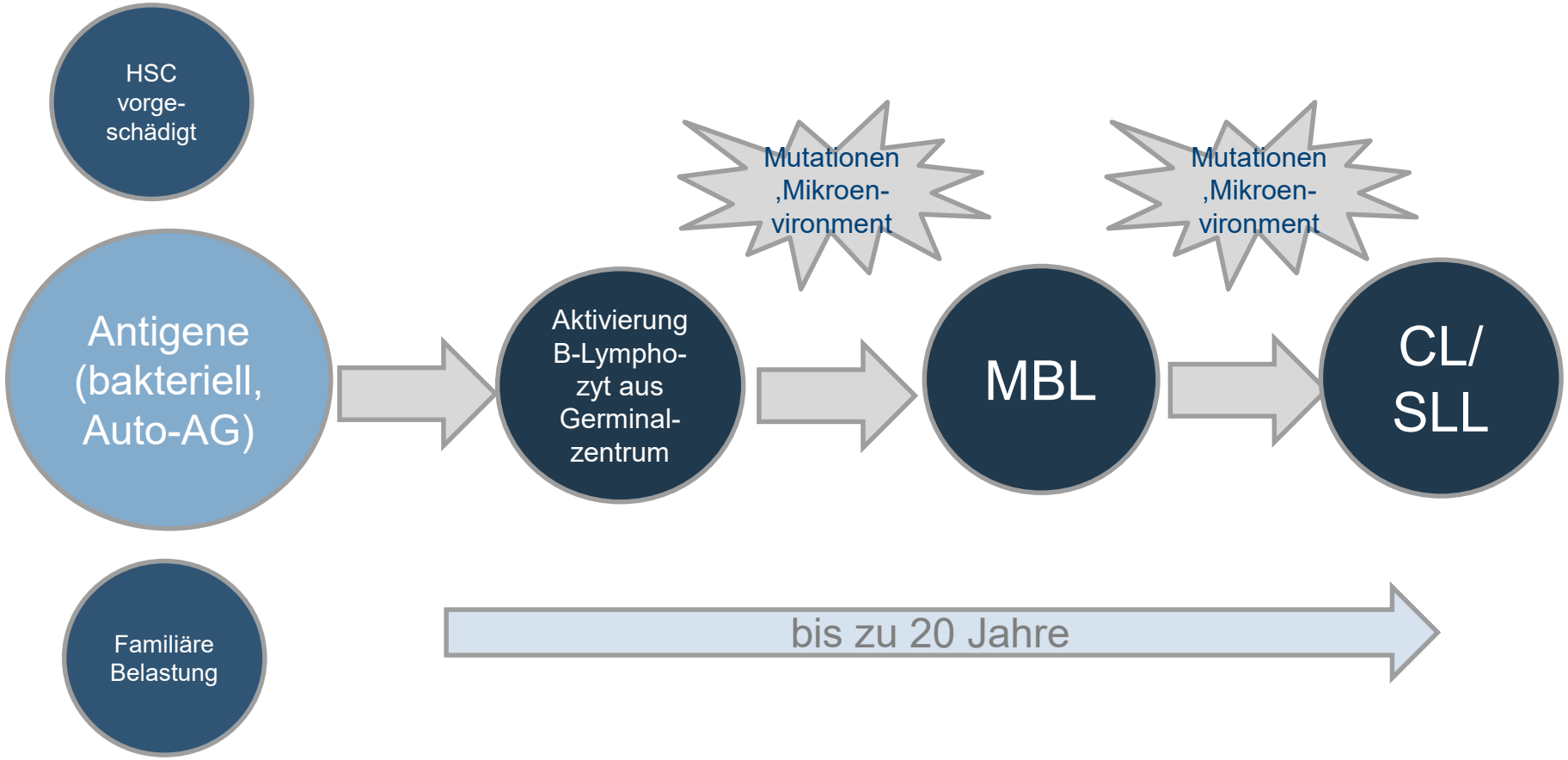
Research funding:

AbbVie, Astra Zeneca, BeiGene, Janssen, Roche

Pathogenese und Prognosefaktoren

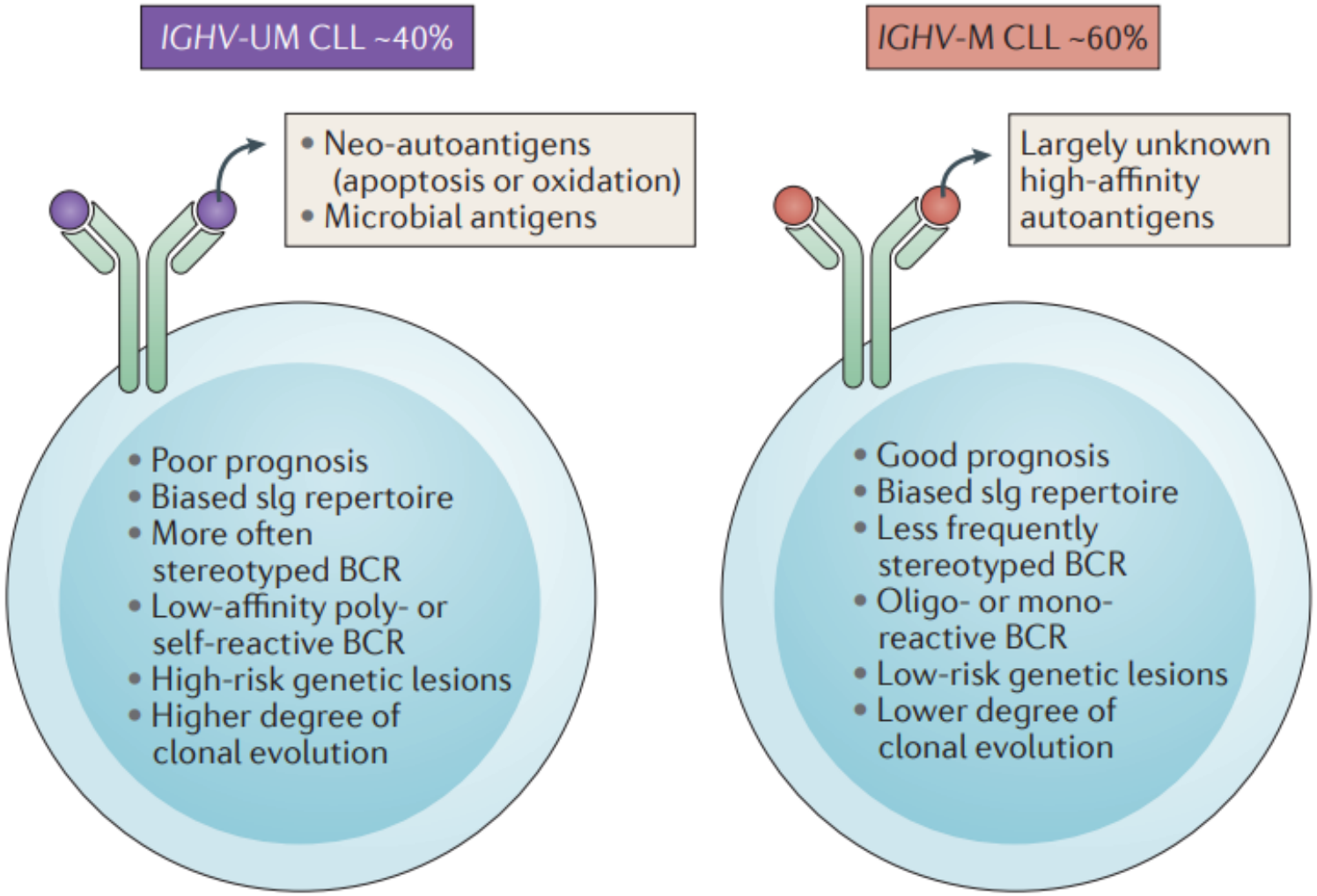
Pathogenese

Sehr vereinfacht !



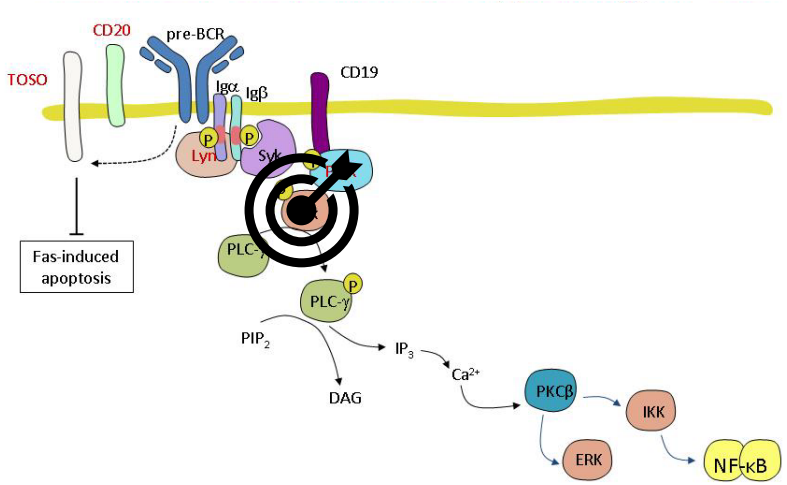
Biologische Charakterisierung der 2 Subtypen der CLL

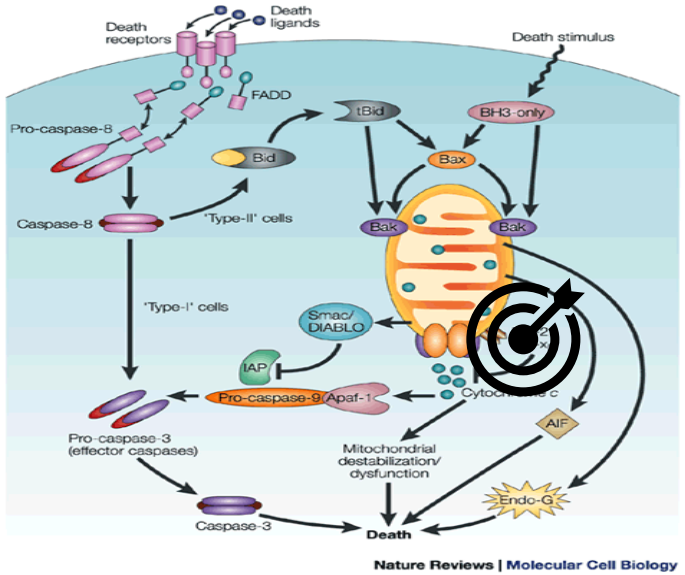
Unmutierter und mutierter IGHV



Fabbri & Della-Favera, Nature Reviews 2016: Vol16:143

Targeted therapies in CLL: Restoration of balance of survival and cell death





Cell Survival

Programmed Cell Death

Therapieindikation

Keine Indikation im frühen, asymptomatischen

Binetstadium A oder B !

Wann, welche Prognosefaktoren ?

ESMO guidelines CLL 2020

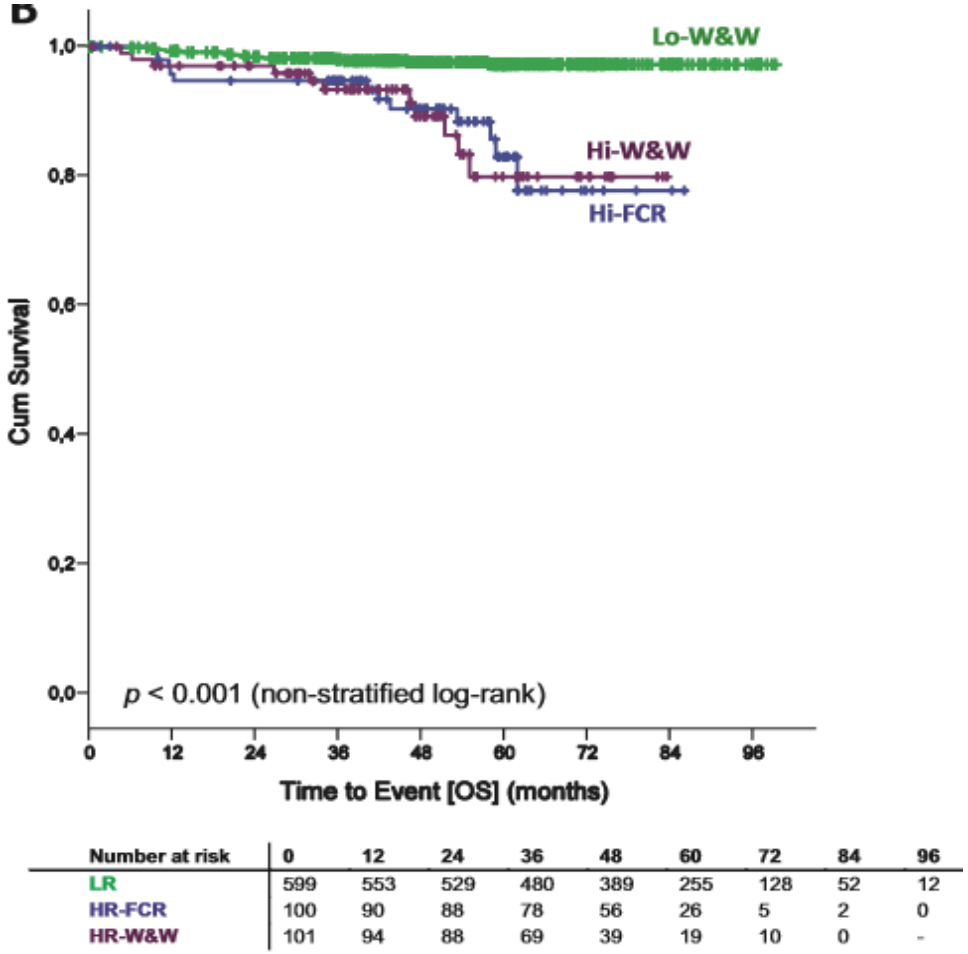
	Pre-treatment evaluation	Staging	FU before treatment/treatment-free interval
History, physical examination and performance status	+	+	+
Complete blood count and differential	+	+	+
Serum chemistry including serum immunoglobulin and direct antiglobulin test	+	+	-
Cytogenetics (FISH) and molecular genetics for TP53 mutation or del(17p)	+	-	(+)[a]
IGHV mutational status	+	-	(+)[a]
Marrow aspirate and biopsy	+[b]	+[c]	-
HBV, HCV, CMV and HIV serology	+	-	-
Radiologic imaging (CT scan)	+[d]	+[d]	-

[a]Only if patient requests the evaluation of his prognostic score.
[b]Only if clinically indicated.
[c]Only for confirmation of CR within clinical studies.
[d]Only within clinical studies, in patients with clinical symptoms and before any venetoclax treatment.

Frühes asymptomatisches Stadium:

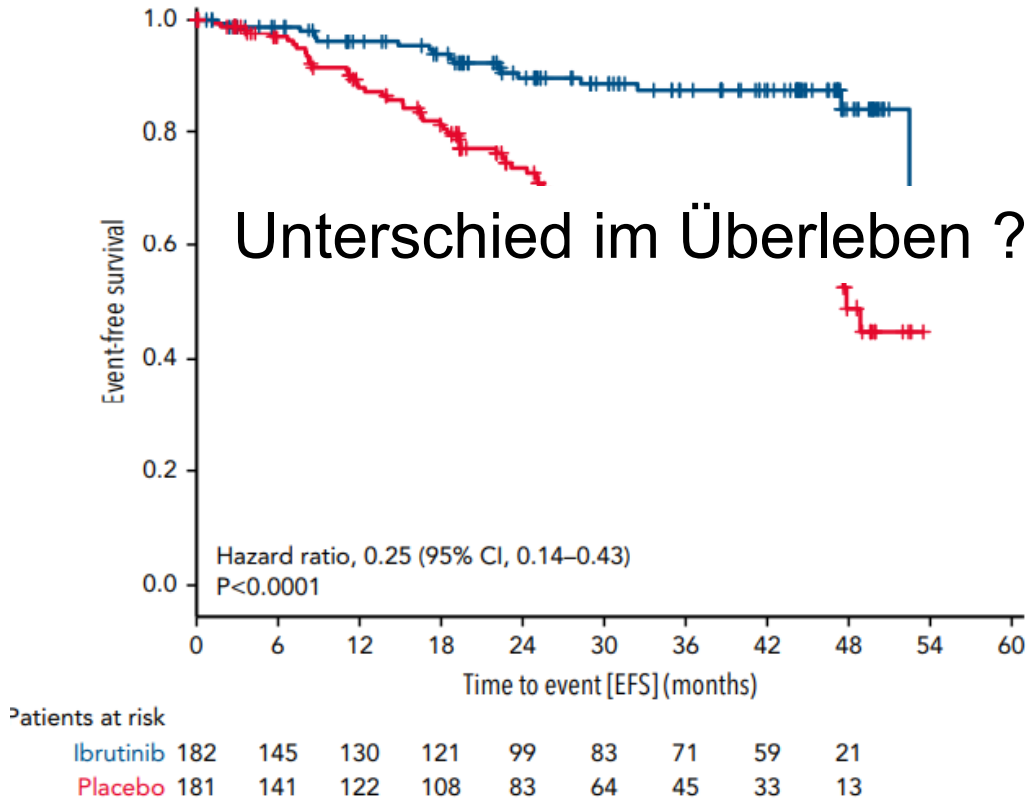
Kein Benefit durch frühzeitigen Start einer CIT bei HR. Aber evtl. mit Ibrutinib?

Herling CD et al., Leukemia. 2020; 34:2038-2050: FCR im frühen Stadium



Number at risk	0	12	24	36	48	60	72	84	96
LR	599	553	529	480	389	255	128	52	12
HR-FCR	100	90	88	78	56	26	5	2	0
HR-W&W	101	94	88	69	39	19	10	0	-

Langerbeins P et al., Blood. 2022; 139: 177: Ibrutinib im frühen Stadium



Patients at risk

Ibrutinib	182	145	130	121	99	83	71	59	21
Placebo	181	141	122	108	83	64	45	33	13

Erstlinientherapie fortgeschrittenes Stadium

Symptomatisches

Binetstadium A oder B und Binet C

Erstlinientherapie-Optionen bei der CLL

Dauertherapie ∞

BTKi +/- Anti-CD20

- Ibrutinib +/- R or O
- Acalabrutinib +/- O
- Zanubrutinib

BCL2i

- Venetoclax
  only in pts with *TP53* aberration*

Zeitlich limitierte Therapie ⛔

BCL2i + Anti-CD20

- Venetoclax + O
  12 cycles

BTKi + BCL2i

- Ibrutinib + Venetoclax
  15 cycles

CIT nur bei mut.IGHV / keine TP53 Aberration

- FCR/BR/Clb+O

R = Rituximab; O = Obinutuzumab; *and not eligible/failed BTKi or in pts w/o TP53 aberration who failed CIT and BCRi

Erstlinientherapie-Optionen bei der CLL

Dauertherapie ∞

BTKi +/- Anti-CD20
- Ibrutinib +/- R or O
- Acalabrutinib +/- O
- Zanubrutinib (neu)

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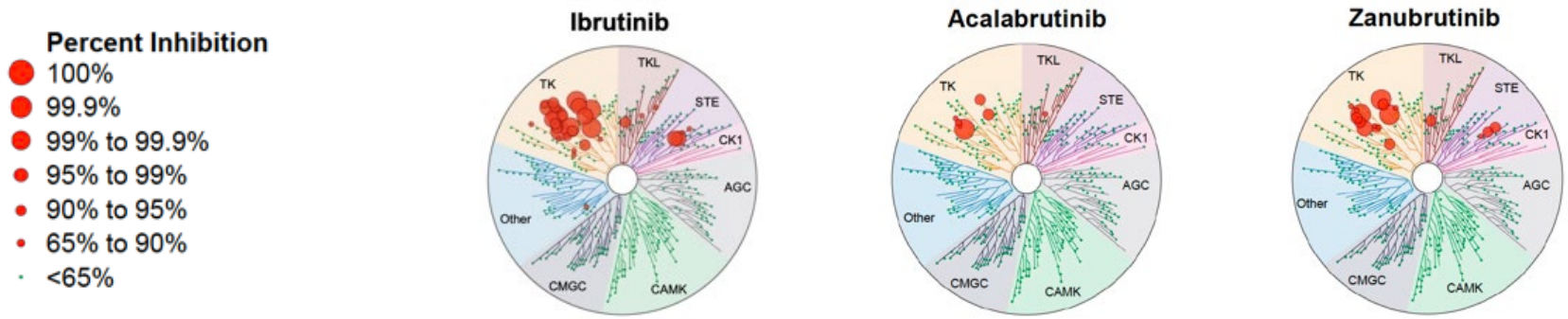
Wahl des BTK-Inhibitors: Selektivität des Inhibitors (Average IC50 nmol/L)

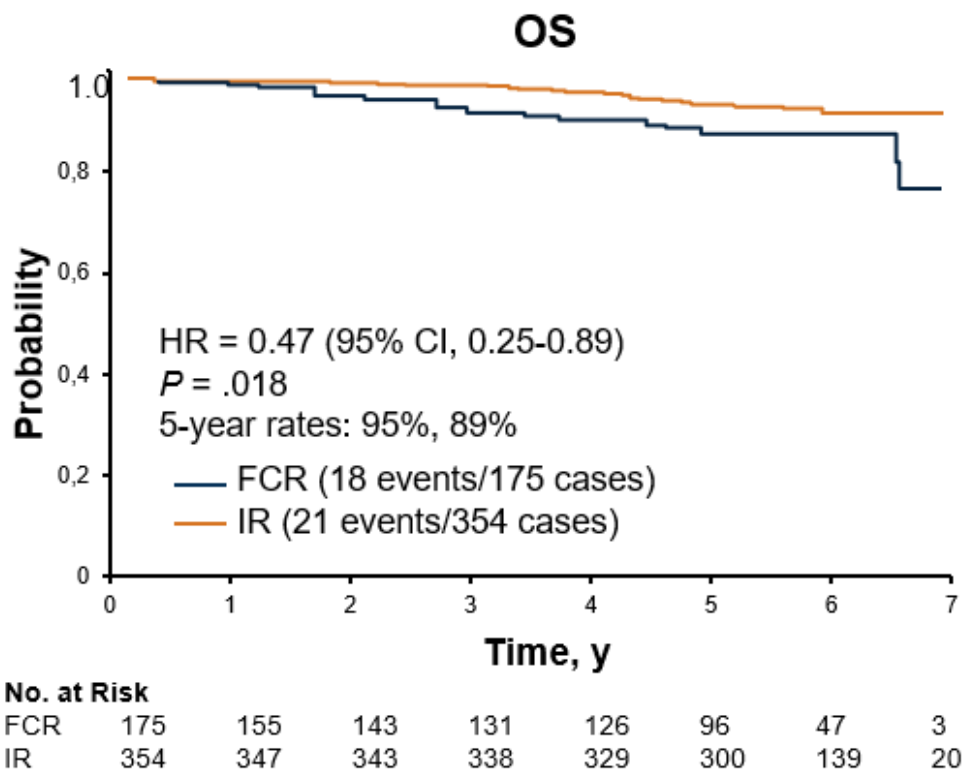


TEC Kinases	Ibrutinib	Acalabrutinib	Zanubrutinib
BTK	1.5	5.1	0.5
TEC	10	126	44
BMX	0.8	46	1.4
TXK	2.0	368	2.2
ERBB2/HER2	6.4	~1,000	88
EGFR	5.3	>1,000	21
ITK	4.9	>1,000	50
JAK3	32	>1,000	1,377
BLK	0.1	>1,000	2.5

Kaptein A et al. *Blood.* 2018;132(suppl 1):1871.

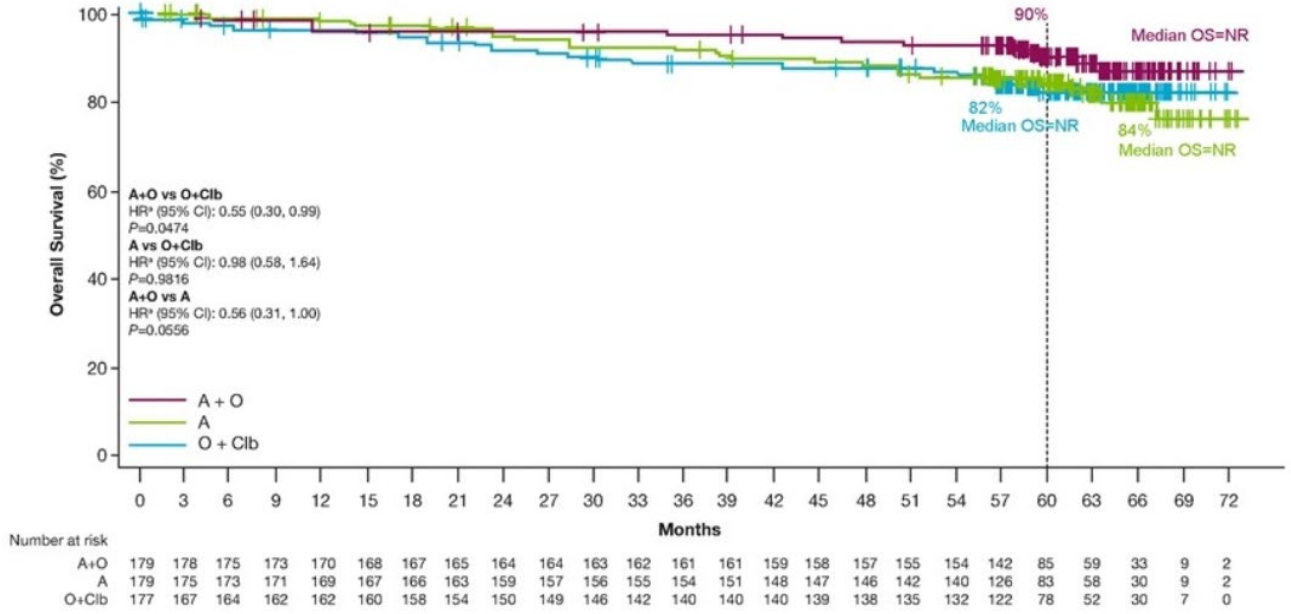
Ibrutinib + Rituximab and **Acalabrutinib** + Obinutuzumab improve OS in comparison to CIT

ECOG1912: Ibrutinib + R vs FCR



Shanafelt T et al. *Blood.* 2022;140:112-120.

ELEVATE TN:
Acalabrutinib + O vs Acalabrutinib vs Clb +O



Sharman JP, et al. EHA 2022. Abstract P666.

Nebenwirkungsprofile der verschiedenen BTK Inhibitoren

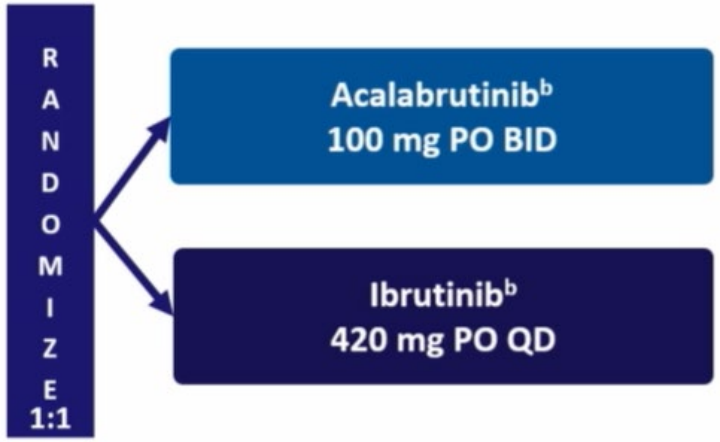
AE ≥ CTC Grade 3	Ibrutinib			Acalabrutinib	Zanubrutinib
	E1912 (I + Rituximab)[1]	RESONATE-2[2]	ALLIANCE[3]	ELEVATE-TN[4]	SEQUOIA[5]
Median observation time, mo	**70**	**60**	**38**	**47**	**24**
Hypertension, %	11.4	8	29	2.8	6.3
Cardiac, %	7.7	N/A	N/A	8.4	N/A
AF, %	4.5	5	9	1.1	0.4
Neutropenia, %	28.4	13	15	11.2	11.3
Infection, %	11.4	12[a]	19	16.2	16.3

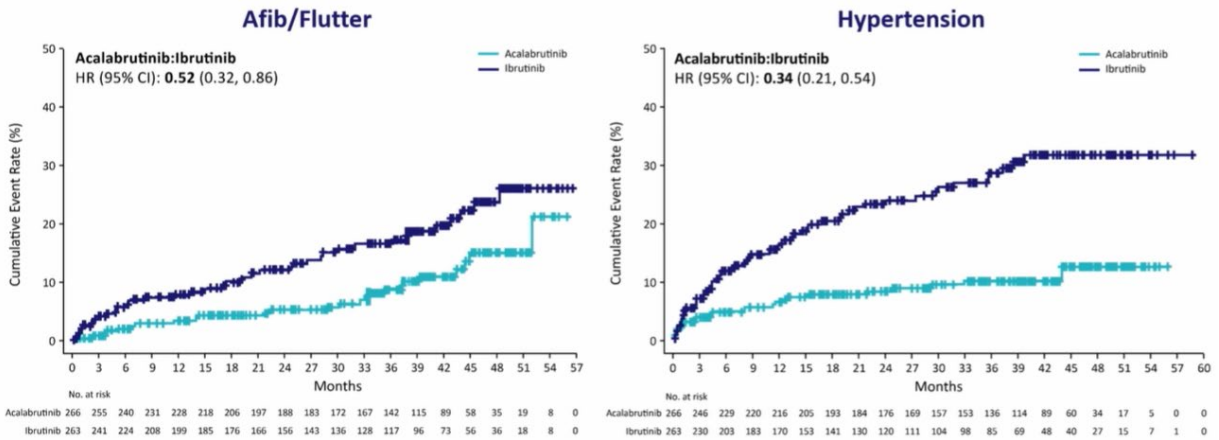
[a] Pneumonia only.

1. Shanafelt TD et al. *Blood.* 2022;140:112-120. 2. Barr PM et al. *Blood Adv*. 2022;6:3440-3450. 3. Woyach JA et al. *N Engl J Med*. 2018;379:2517-2528. 4. Sharman JP et al. *Lancet*. 2020;395:1278-1291. 5. Tam C et al. ASH 2021. Abstract 396.

Direkter Vergleich verschiedener BTK Inhibitoren (Rezidivstudien!)

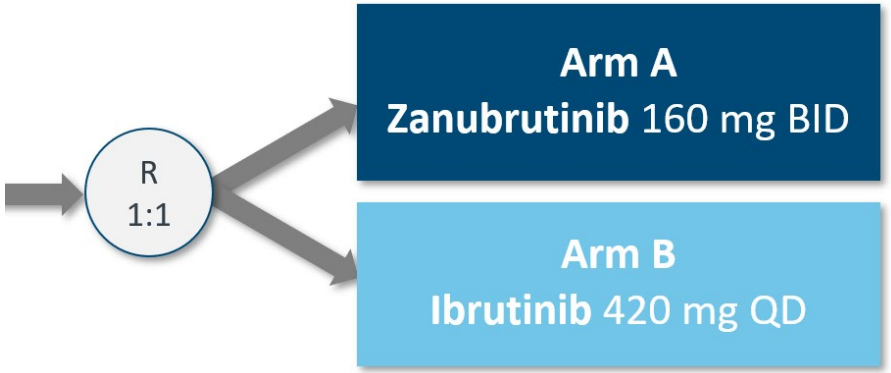
Acalabrutinib

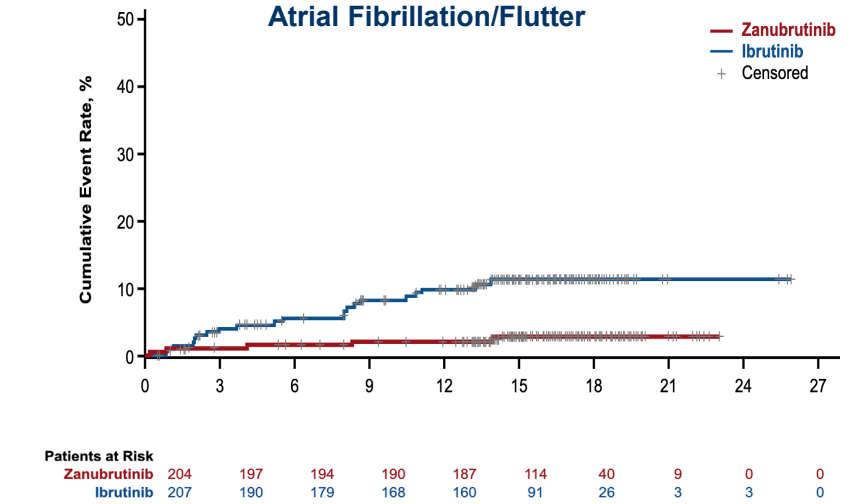




Hillmen P et al. Oral presentation. EHA 2021. Abstract S145

Zanubrutinib

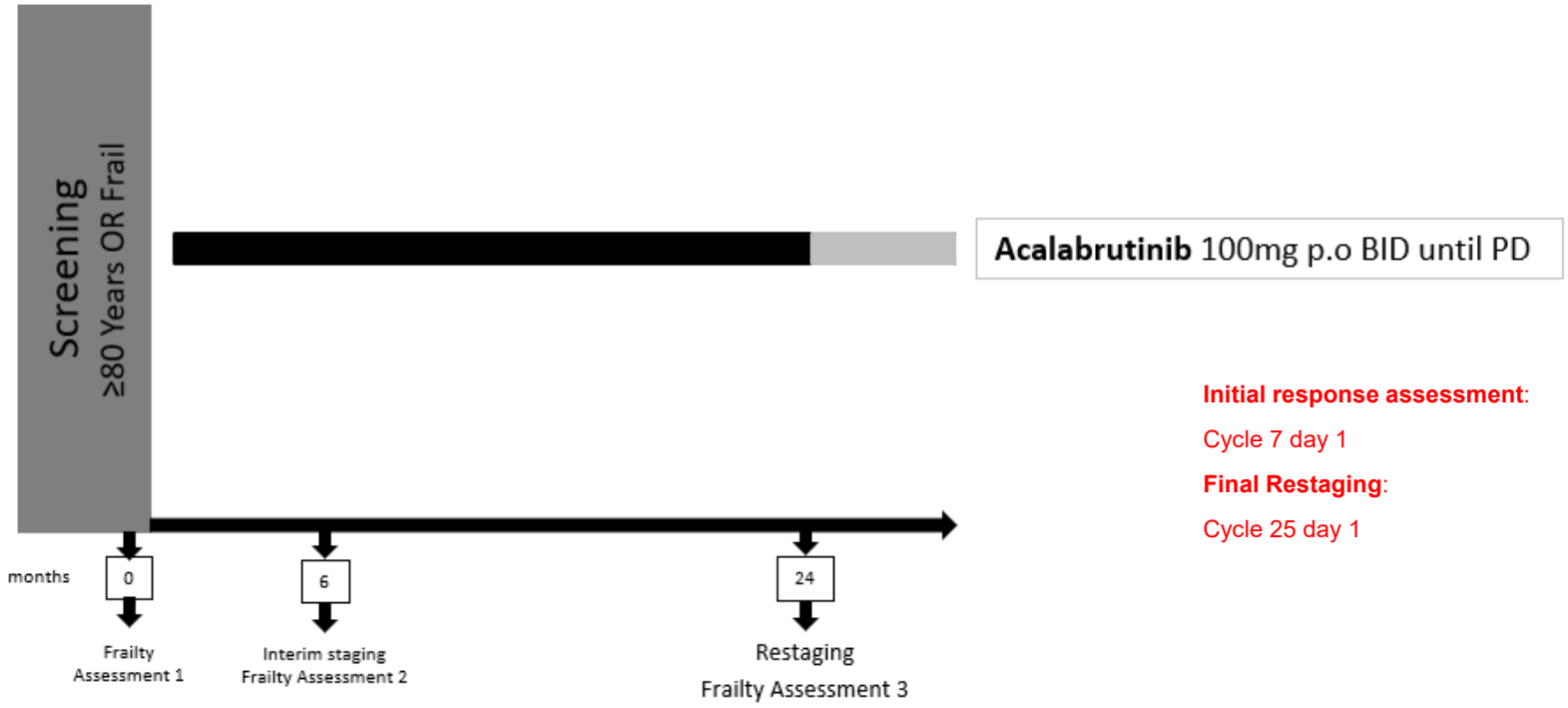




Hillmen P et al. Oral presentation. EHA 2021. LB Abstract 1900

CLL-FRAIL STUDY

- Prospective, multicenter, single-arm phase-II study
- Approximately 50 eligible patients to be included in 20 sites in Germany and Austria
- Target population: Pts very old (≥80y) AND/OR frail patients with treatment-naive or relapsed/ refractory CLL



Initial response assessment:

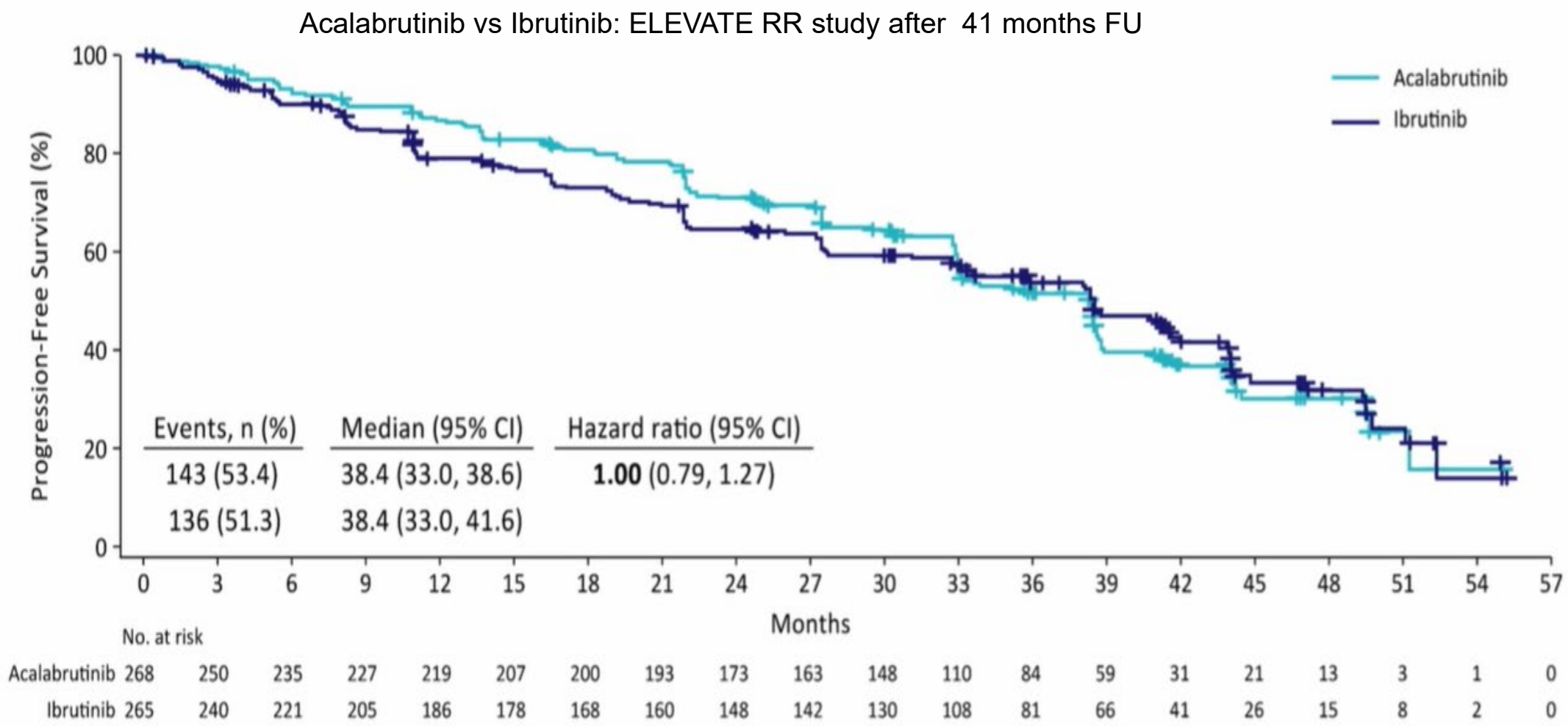
Cycle 7 day 1

Final Restaging:

Cycle 25 day 1

ELEVATE RR phase 3 trial in **relapsed** CLL: acalabrutinib vs ibrutinib

PFS

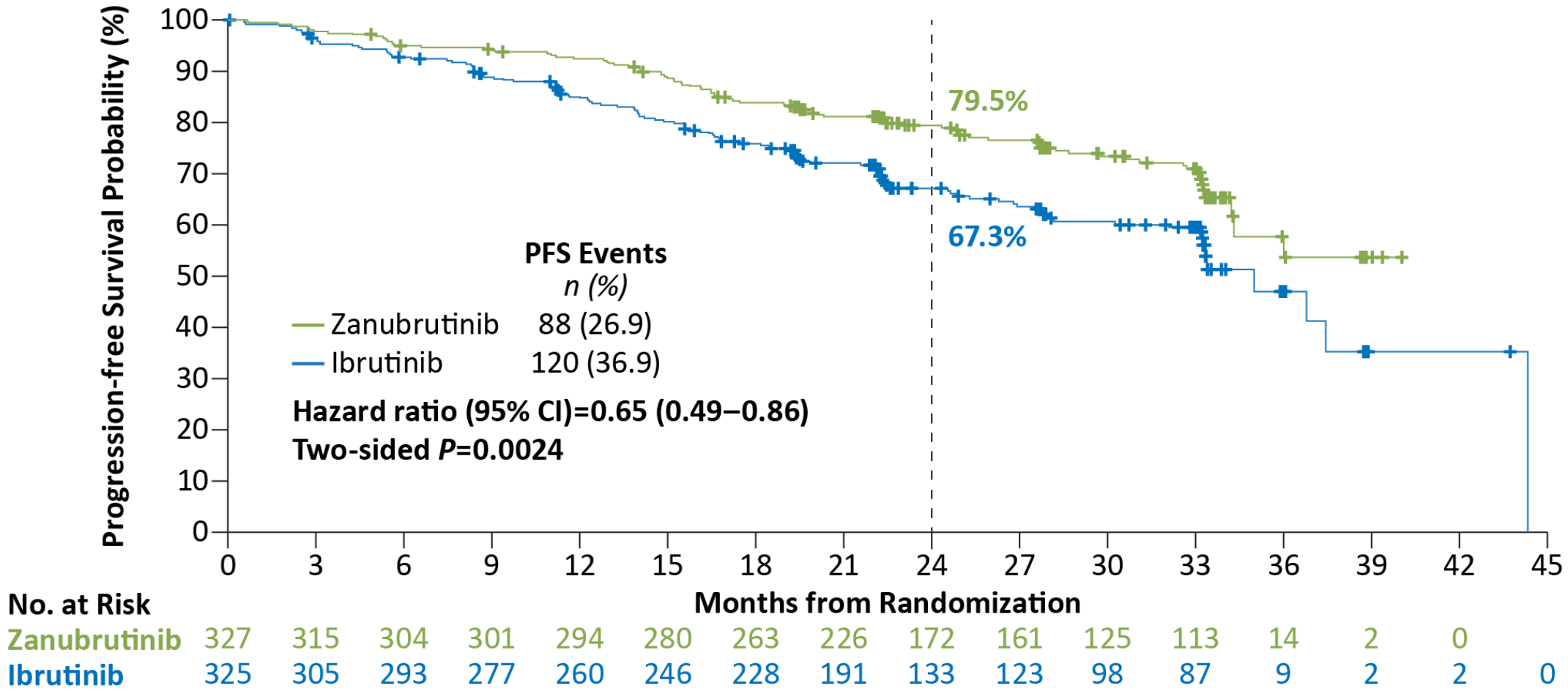


Byrd J. et al. JCO 2021; 39: 31: 3441

Alpine phase 3 trial in **relapsed** CLL: Zanubrutinib vs. ibrutinib

PFS

Median study follow-up of 29.6 months



Brown et al., NEJM 2023; 388, 4: 319 - 332

Erstlinientherapie-Optionen bei der CLL

Dauertherapie ∞

BTKi +/- Anti-CD20
- Ibrutinib +/- R or O
- Acalabrutinib +/- O
- Zanubrutinib (neu)

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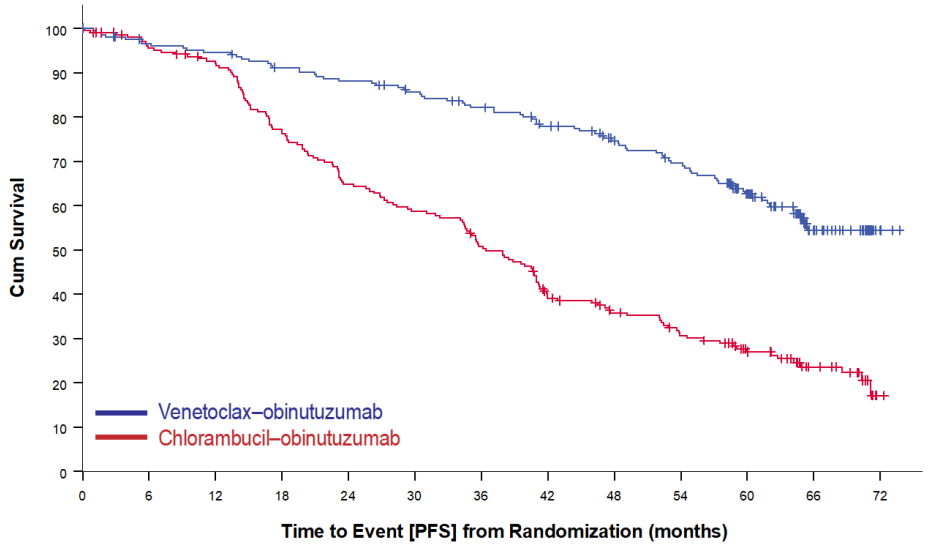
R = Rituximab; O = Obinutuzumab; *and not eligible/failed BTKi or in pts w/o TP53 aberration who failed CIT and BCRi

CLL14-Studie: Venetoclax + Obinutuzumab vs Chlorambucil + Obinutuzumab

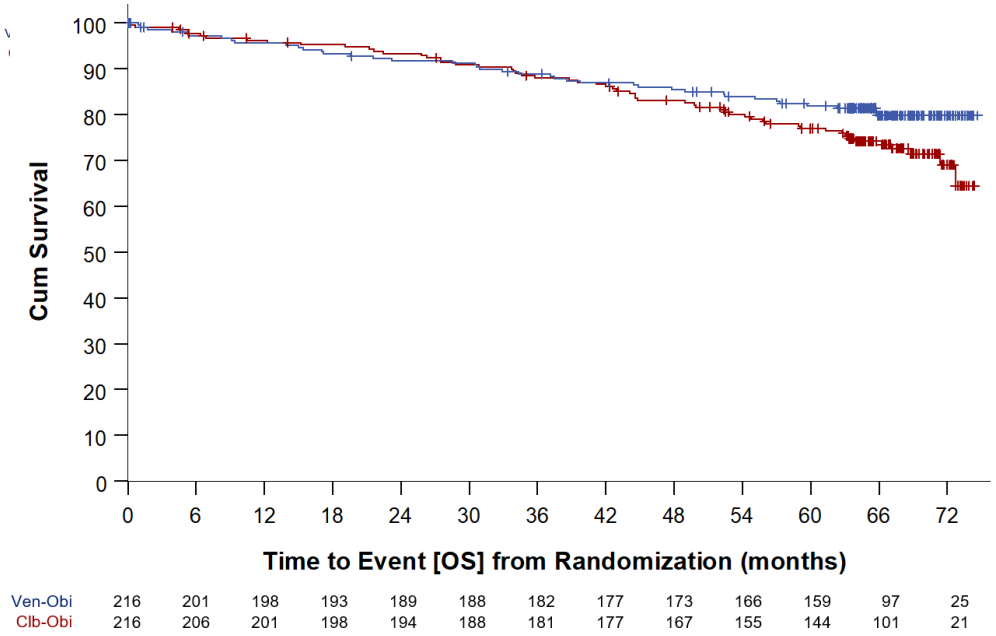
5 Jahre Follow-up



Median PFS
Ven-Obi: not reached
Clb-Obi: 36.4 months

5-year PFS rate
Ven-Obi: 62.6%
Clb-Obi: 27.0%

HR 0.35, 95% CI [0.26-0.46]
P<0.0001



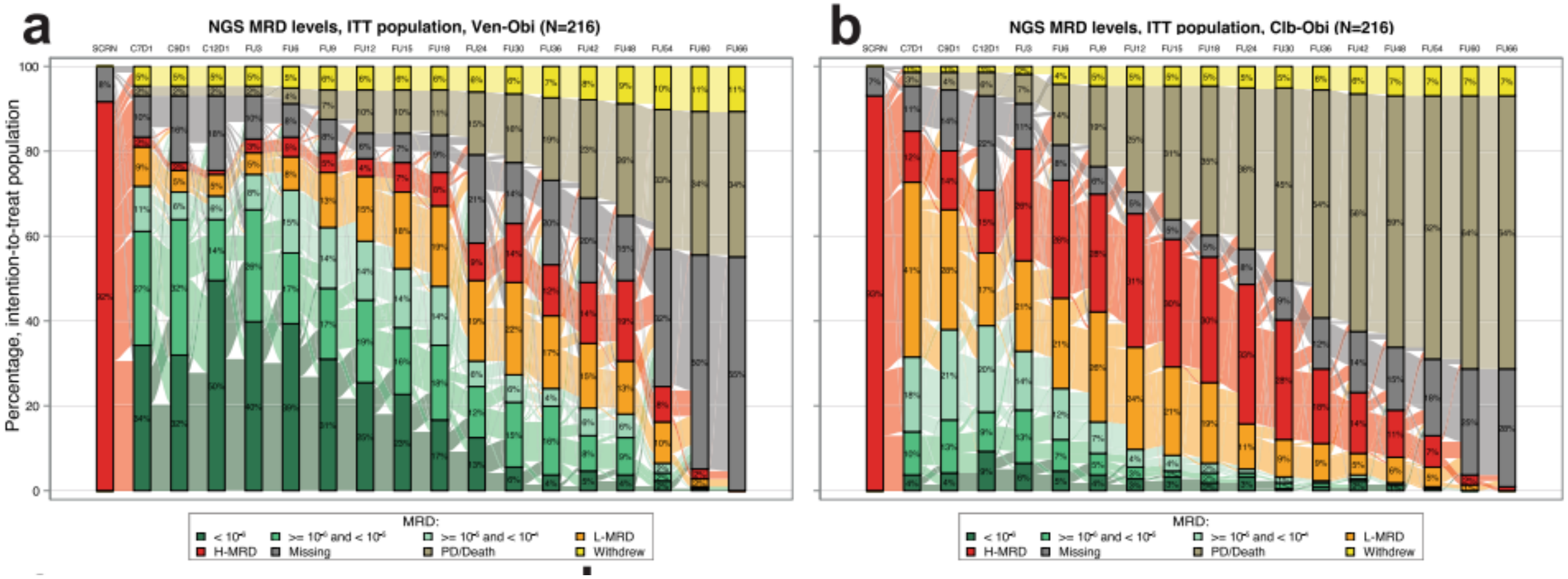
Median OS
Ven-Obi: not reached
Clb-Obi: not reached

5-year OS rate
Ven-Obi: 81.9%
Clb-Obi: 77.0%

HR 0.72, 95% CI [0.48-1.09]
P=0.12

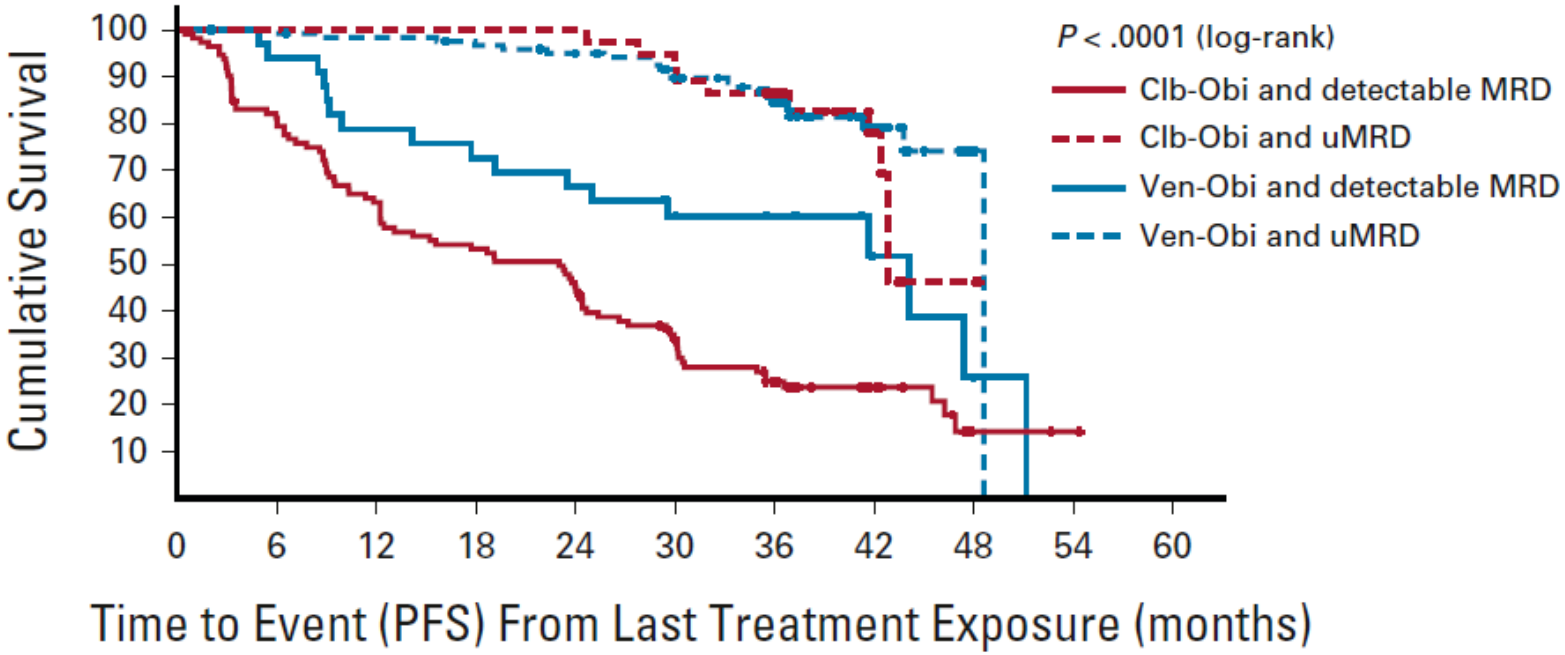
Al Sawaf et al., Nature Communications| (2023) 14:2147

CLL14-Studie: nicht nachweisbarer MRD nach Therapie und im FU



Al Sawaf et al., Nature Communications| (2023) 14:2147

CLL14-Studie: PFS nach MRD zum Therapieende

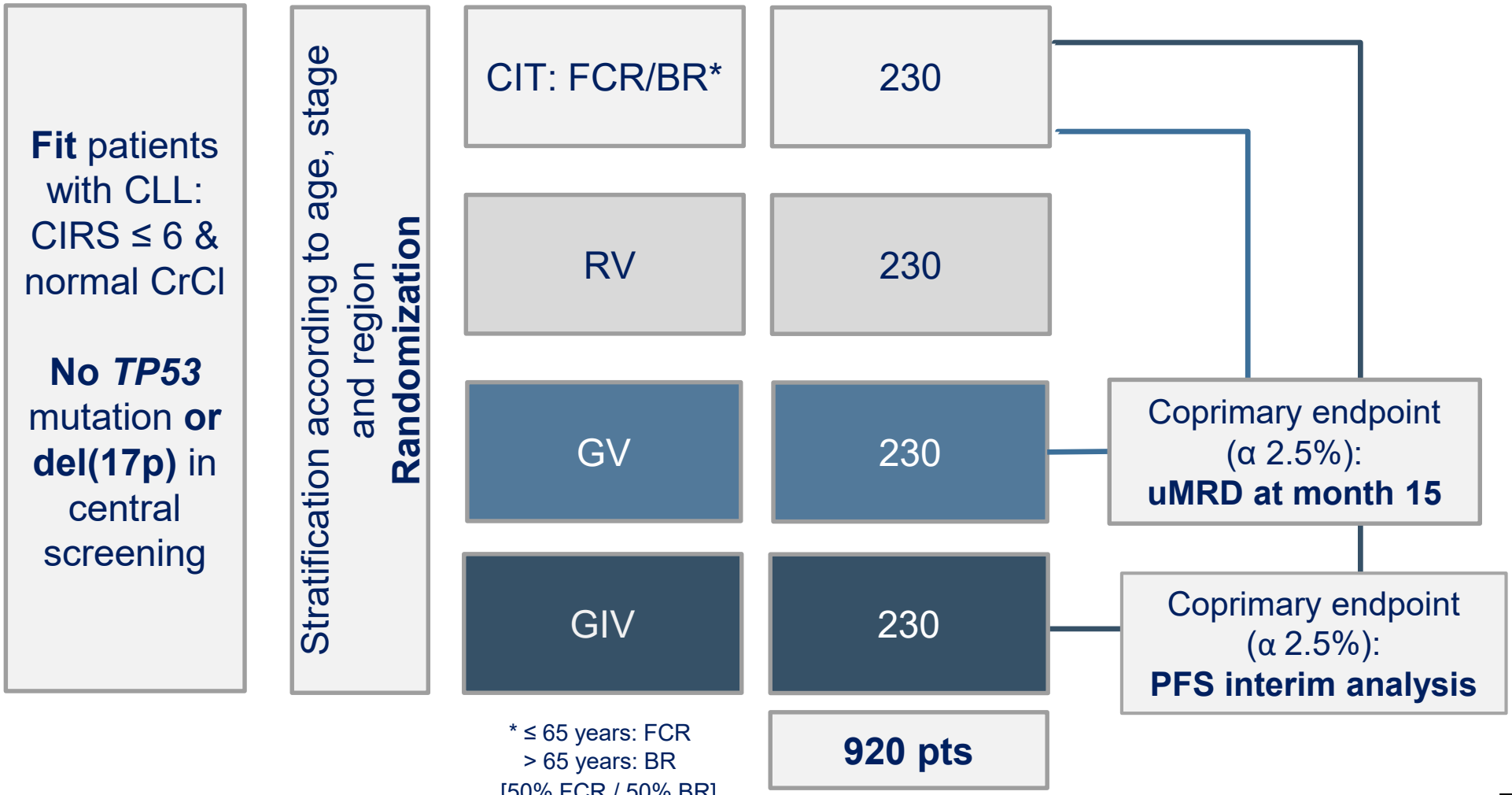


No. at risk:											
Ven-Obi & uMRD	123	121	119	115	111	96	66	25	3	0	0
Ven-Obi & detectable MRD	33	31	26	24	22	18	12	4	2	0	0
Clb-Obi & uMRD	37	37	37	37	37	34	27	12	2	0	0
Clb-Obi & detectable MRD	112	90	70	59	50	34	22	12	2	1	0

Al Sawaf et al., Nature Communications| (2023) 14:2147

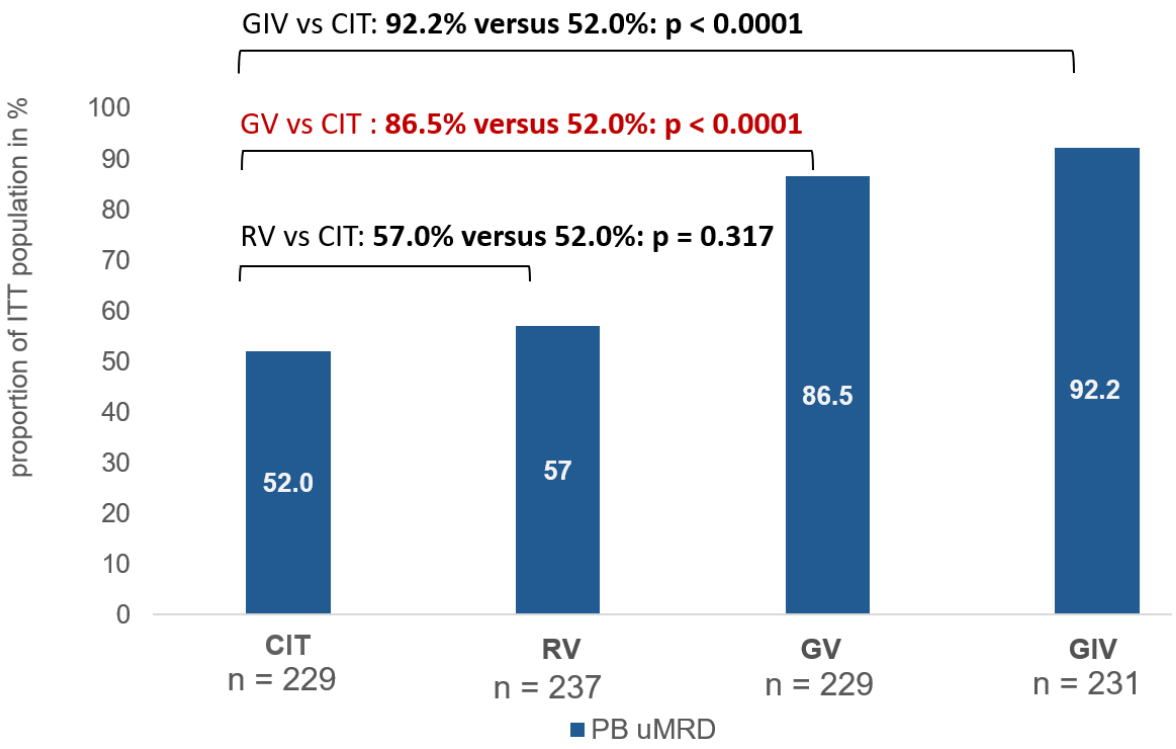
GAIA/CLL13 study design for fit patients with CLL

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)

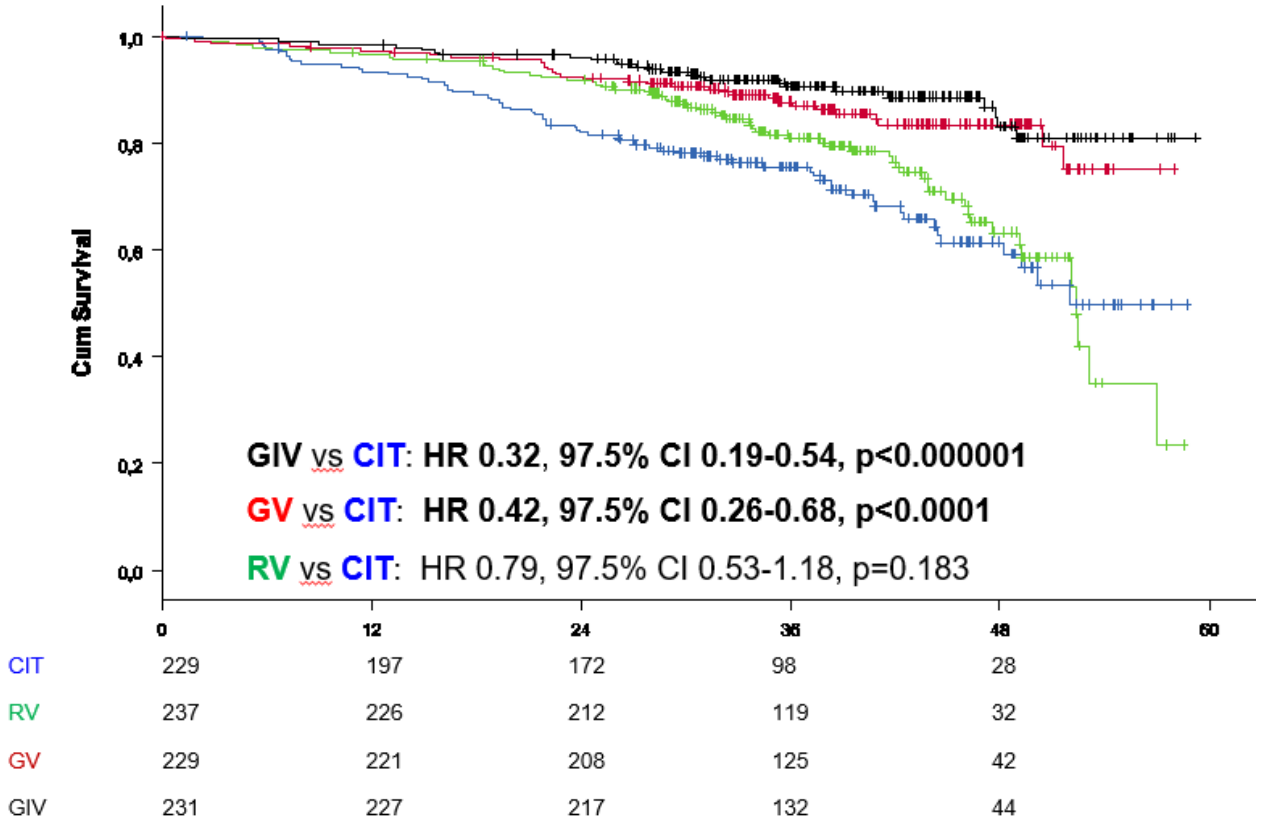


Eichhorst et al., EHA 2022 LBA-2365

Higher efficacy of targeted agents over FCR/BR: Venetoclax+Obinutuzumab and Venetoclax+Obinutuzumab+Ibrutinib



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



Median observation time: 38.8 months

Eichhorst et al., NEJM in press

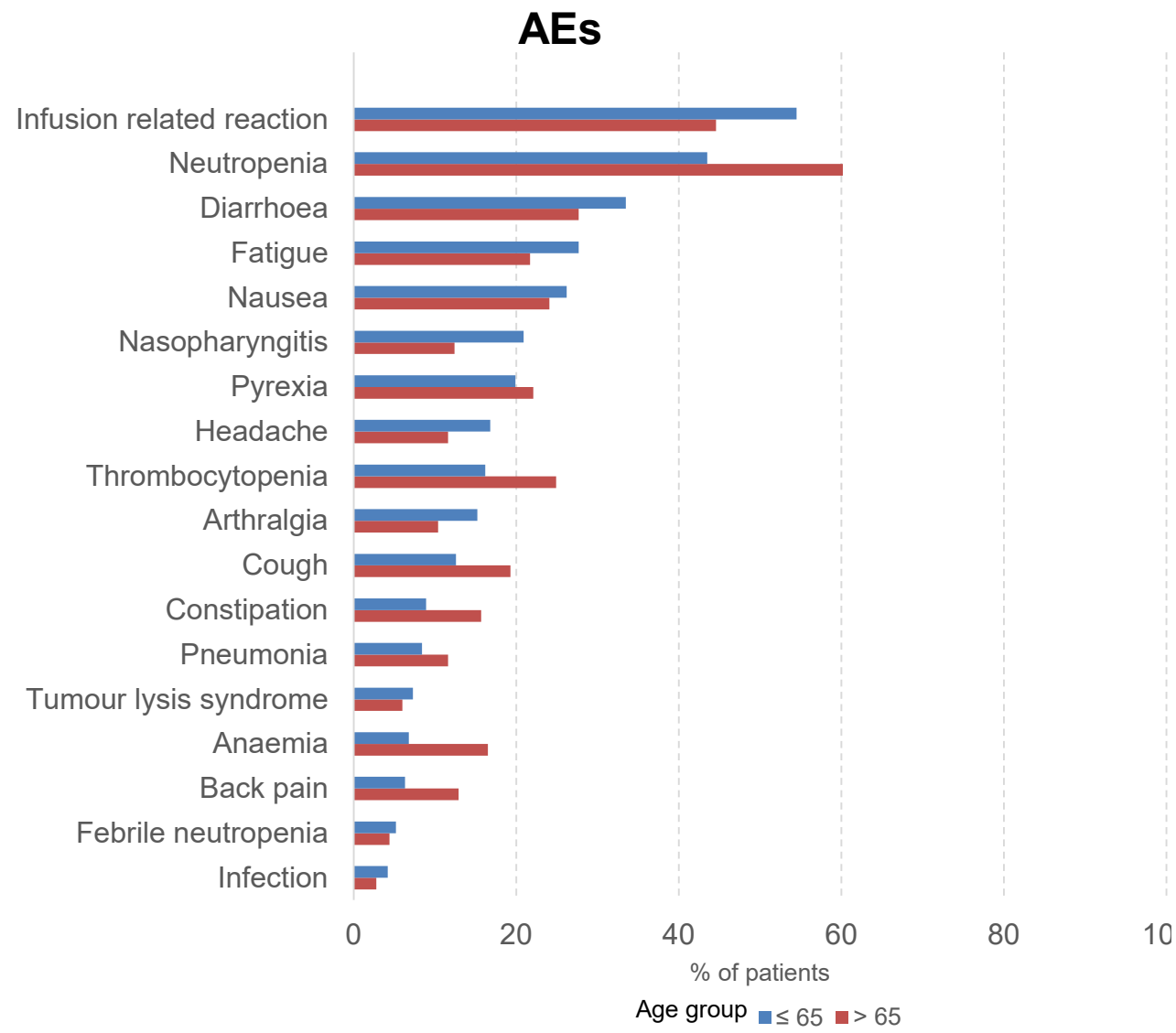
DEUTSCHE STUDIENGRUPPE

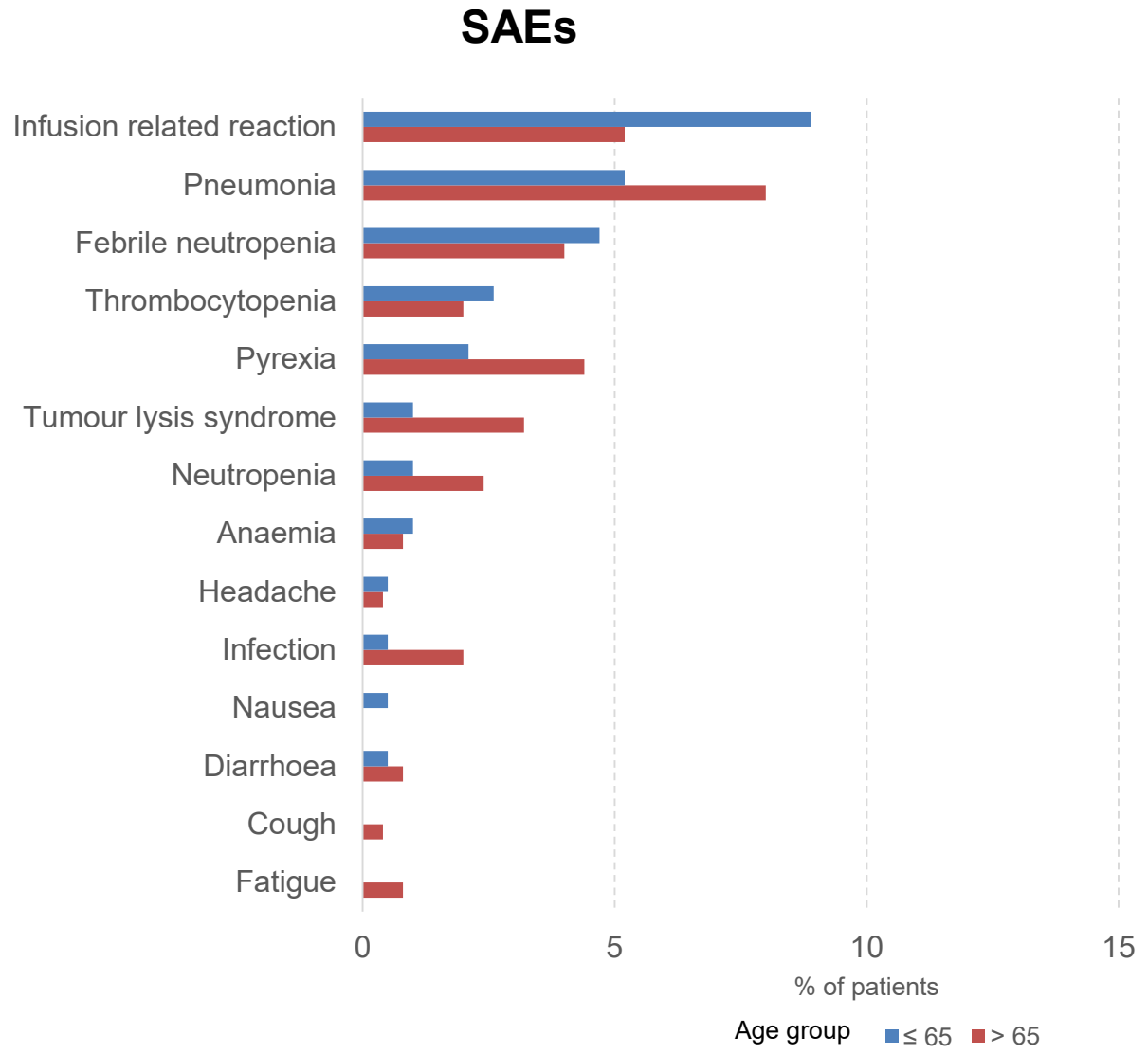
Rolle von Alter und Begleiterkrankungen:

Meta-Analyse zu Ven+Obin aus CLL13 (fit = 229) und CLL14 (unfit = 214)

Pooled safety analysis of Ven+Obin from CLL13 (fit = 229) and CLL14 (unfit = 214)

Adverse events/Severe adverse events according to age

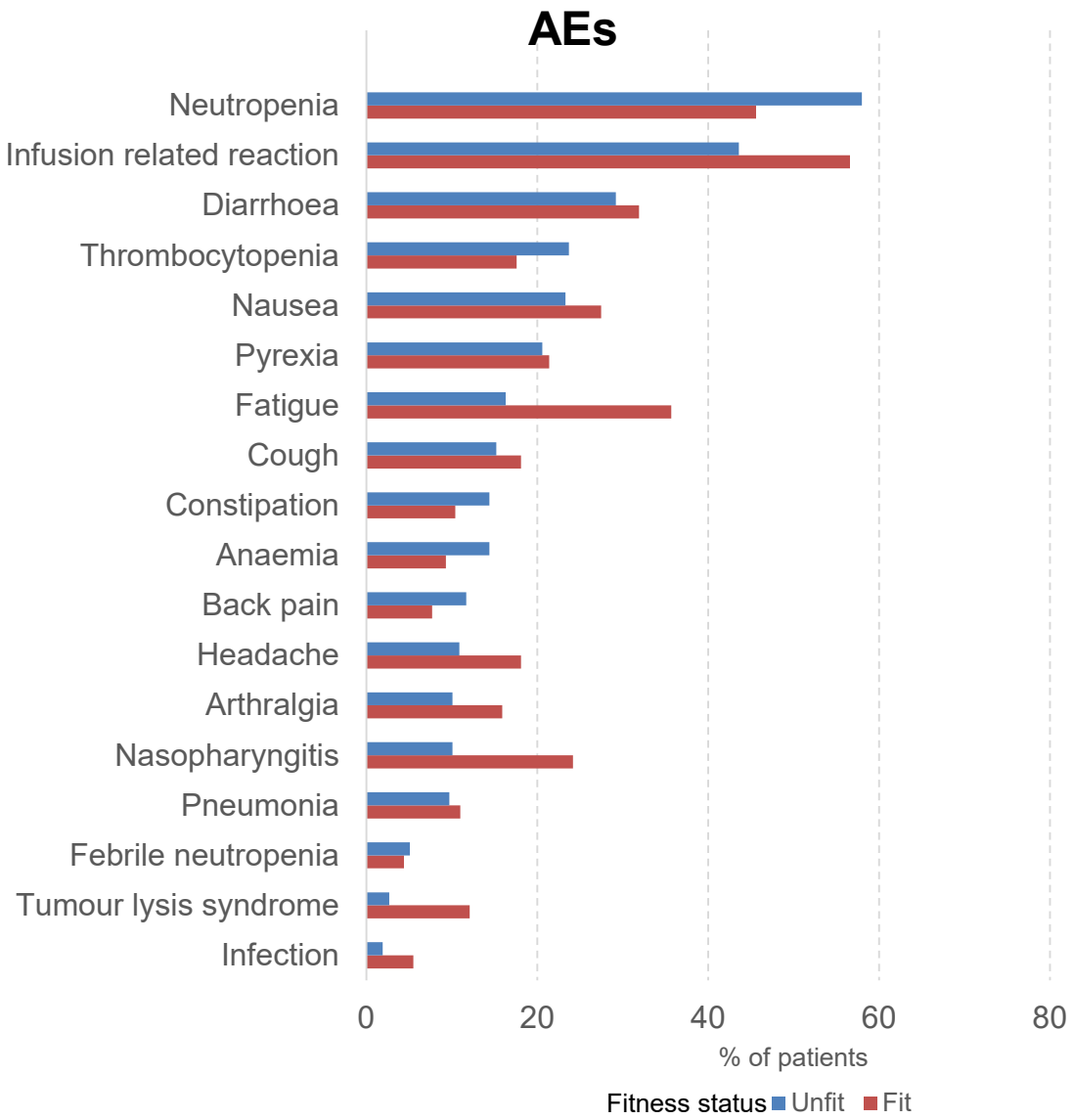


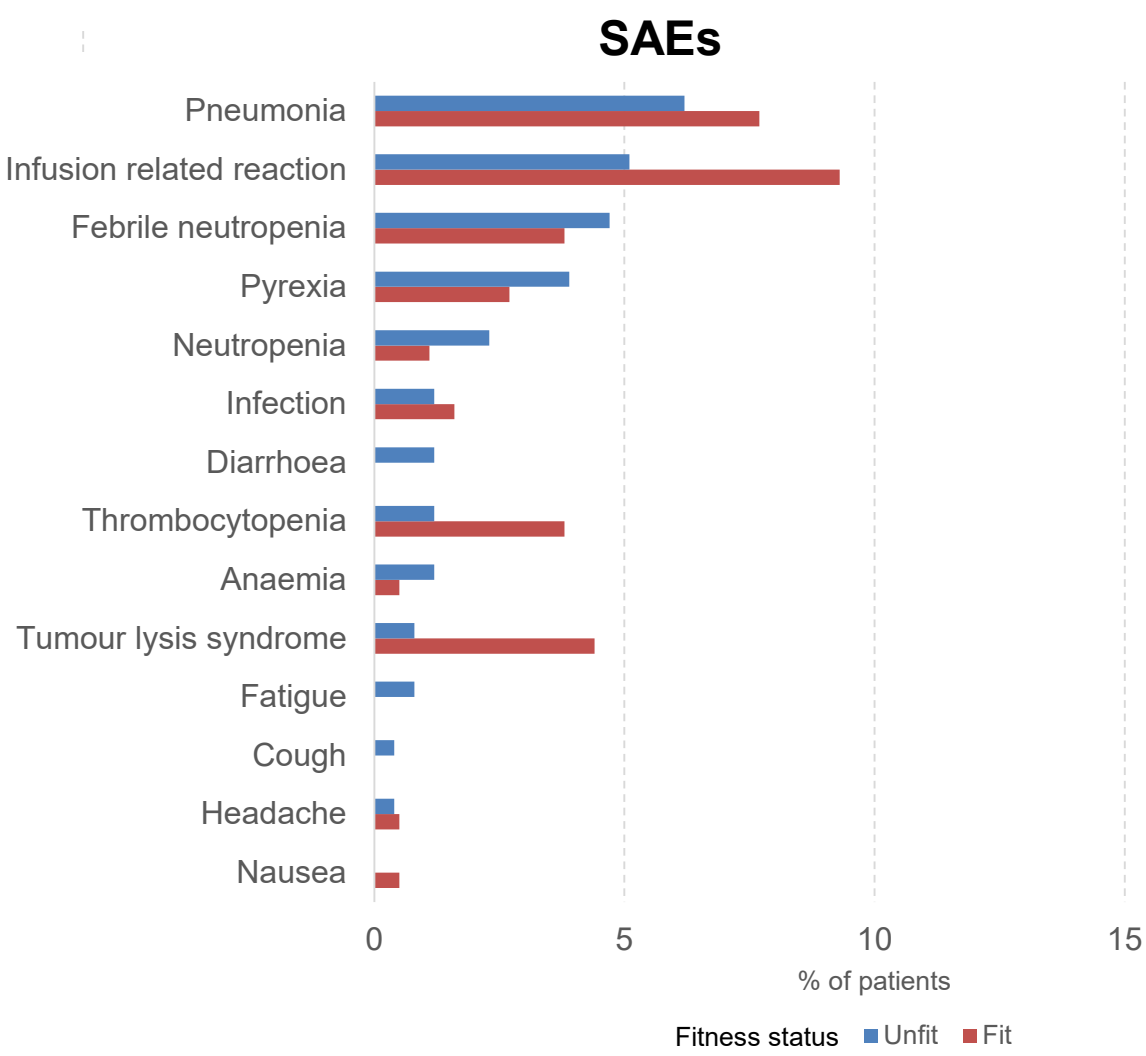


GCLLSG 2023, unpublished data

Pooled safety analysis of Ven+Obin from CLL13 (fit = 229) and CLL14 (unfit = 214)

Adverse events/Severe adverse events according to fitnes

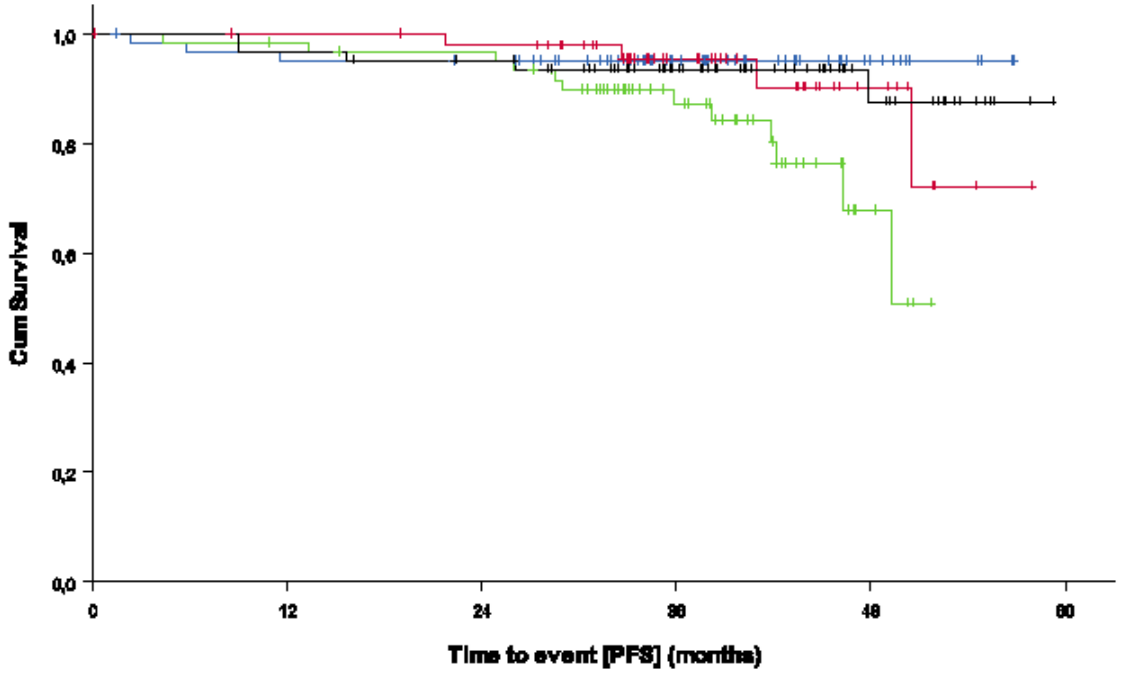




GCLLSG 2023, unpublished data

CLL13: PFS according to IGHV status and age

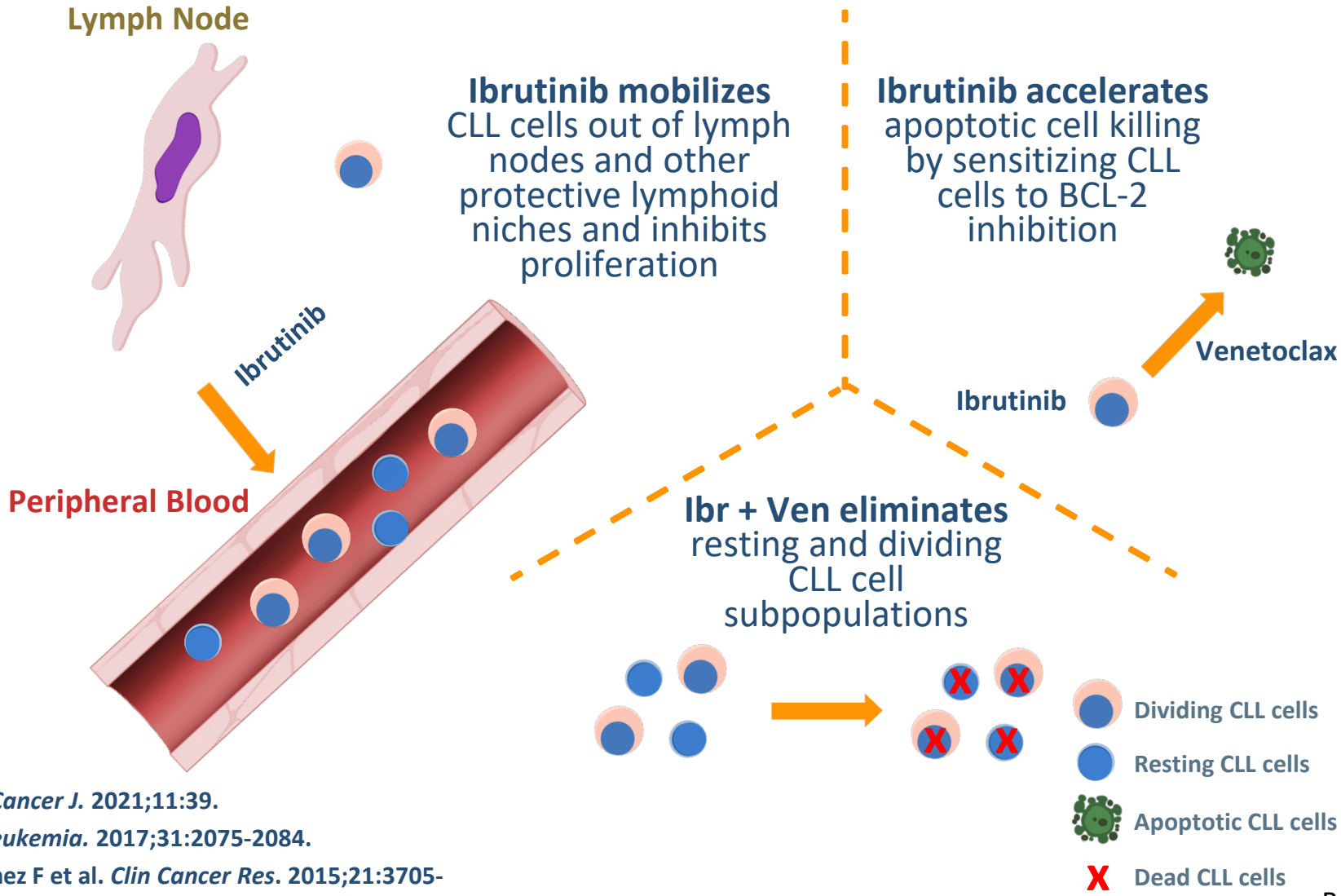
PFS for patients with mutated IGHV status and up to 65 years only, receiving FCR treatment in the control arm



Patients at risk	0	12	24	36	48
SCIT (FCR)	65	57	56	34	10
RVe	62	60	58	33	5
GVe	50	48	46	27	8
GIVe	63	61	58	40	15

GCLLSG 2022, unpublished data

Rational for combining Ibrutinib + Venetoclax

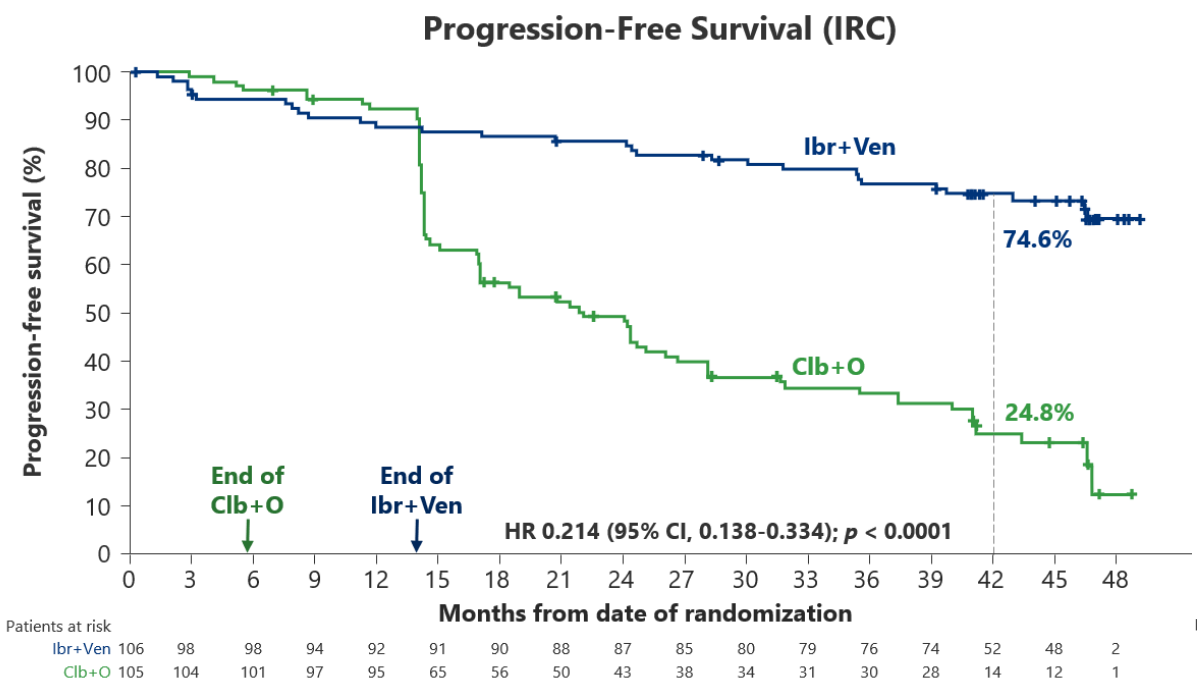


1. Lu P et al. *Blood Cancer J.* 2021;11:39.
2. 2. Deng J et al. *Leukemia.* 2017;31:2075-2084.
3. 3. Cervantes-Gomez F et al. *Clin Cancer Res*. 2015;21:3705-3715.

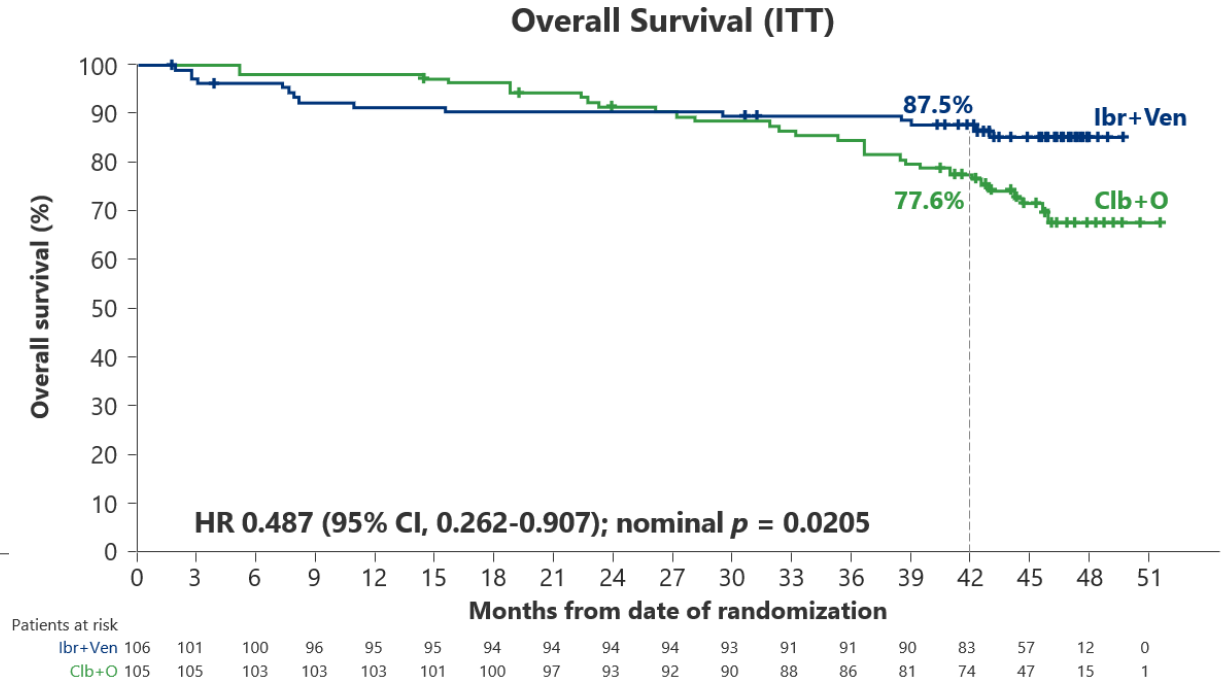
By Ghia P., ASH 2021, Abstract 68

Frontline therapy ibrutinib + venetoclax (IV): GLOW-study in elderly patients

PFS and OS



Median study follow-up: 46 months



Median study follow-up: 46 months

C. Niemann et al., ASH 2022 abstract 93

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

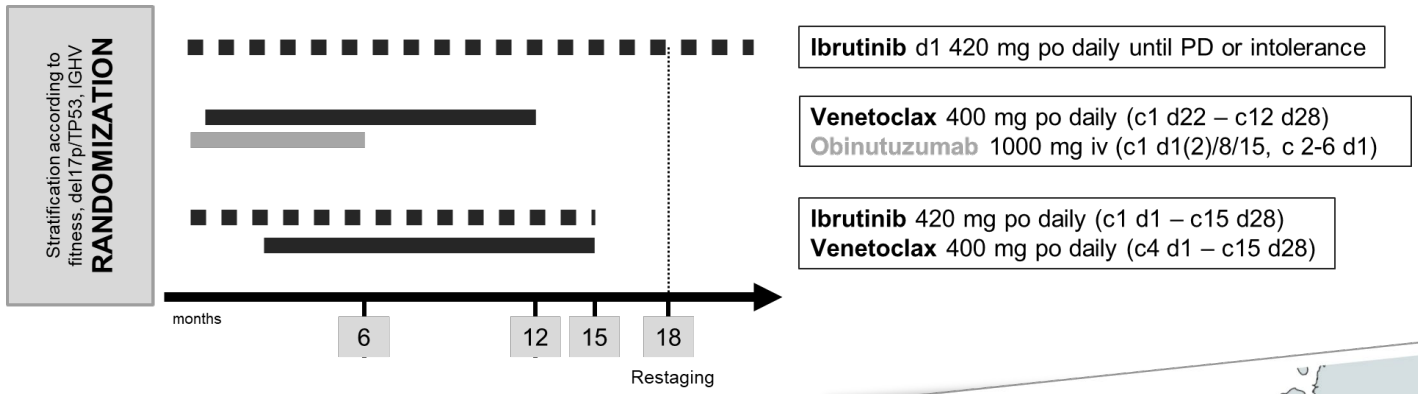
Venetoclax Obinutuzumab

Venetoclax Ibrutinib

897 patients

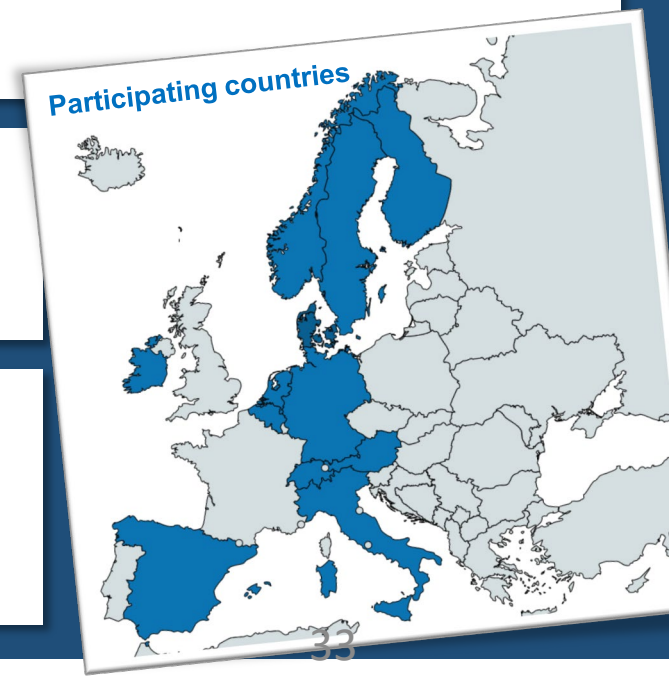
Primary endpoint:
Progression-free survival

TREATMENT SCHEDULE

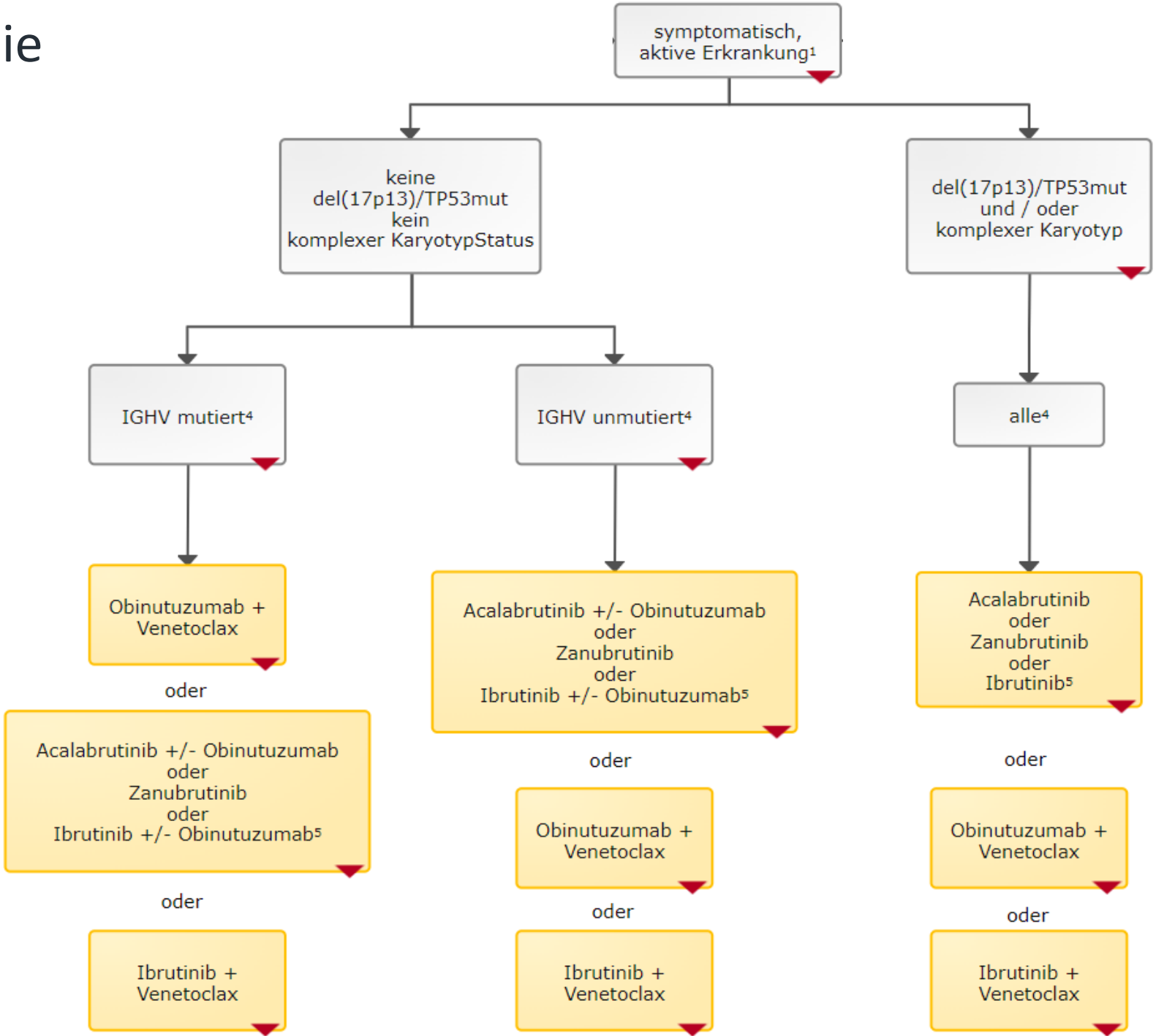


TIMELINES

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



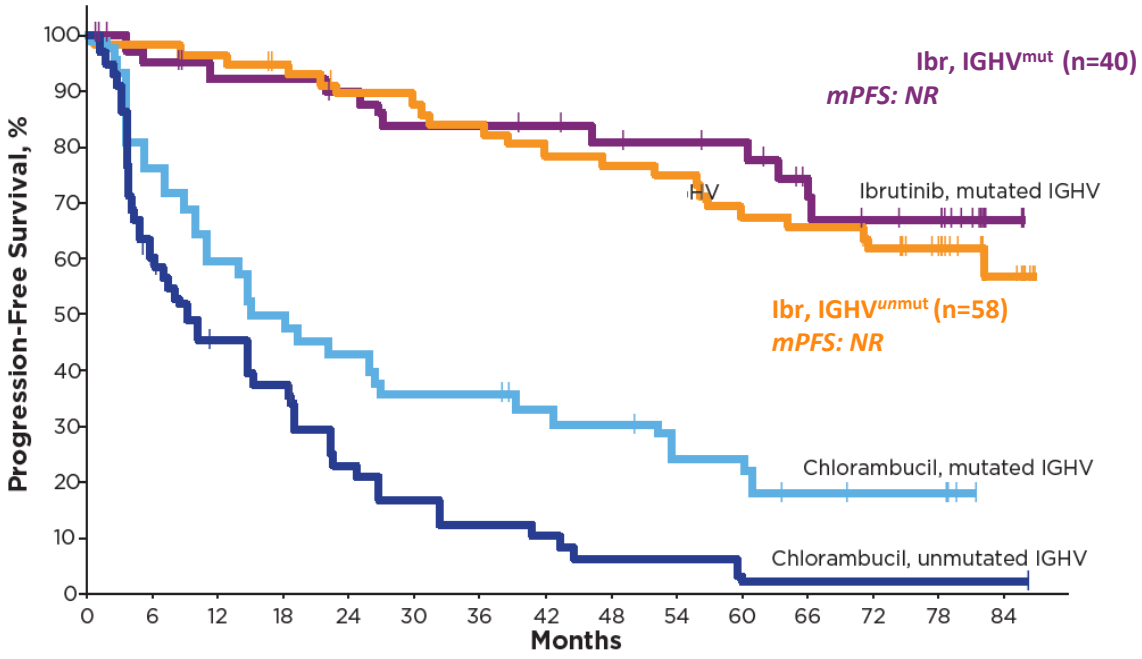
Erstlinie



Onkopedia, Stand Januar 2023
Wendter, …….Stilgenbauer

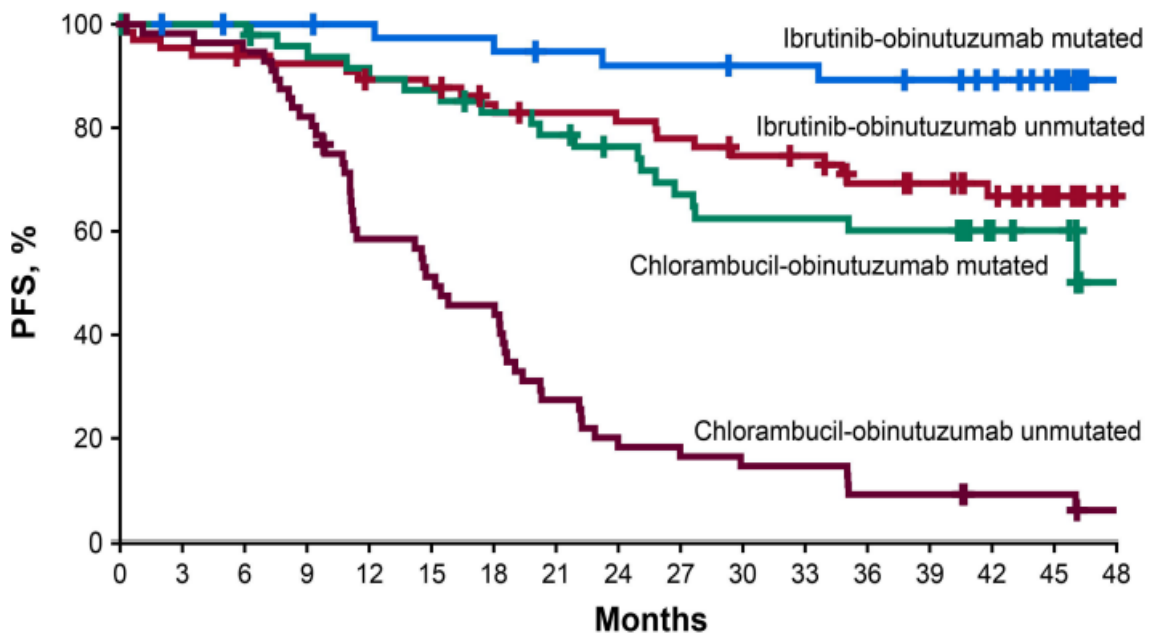
BTK-Inhibitoren in der Erstlinientherapie der CLL nach IGHV Status

RESONATE2-Studie:
Ibrutnib vs. CLB bei älteren Pat



Ghia P et al., EHA. 2021; Abstract EP 636

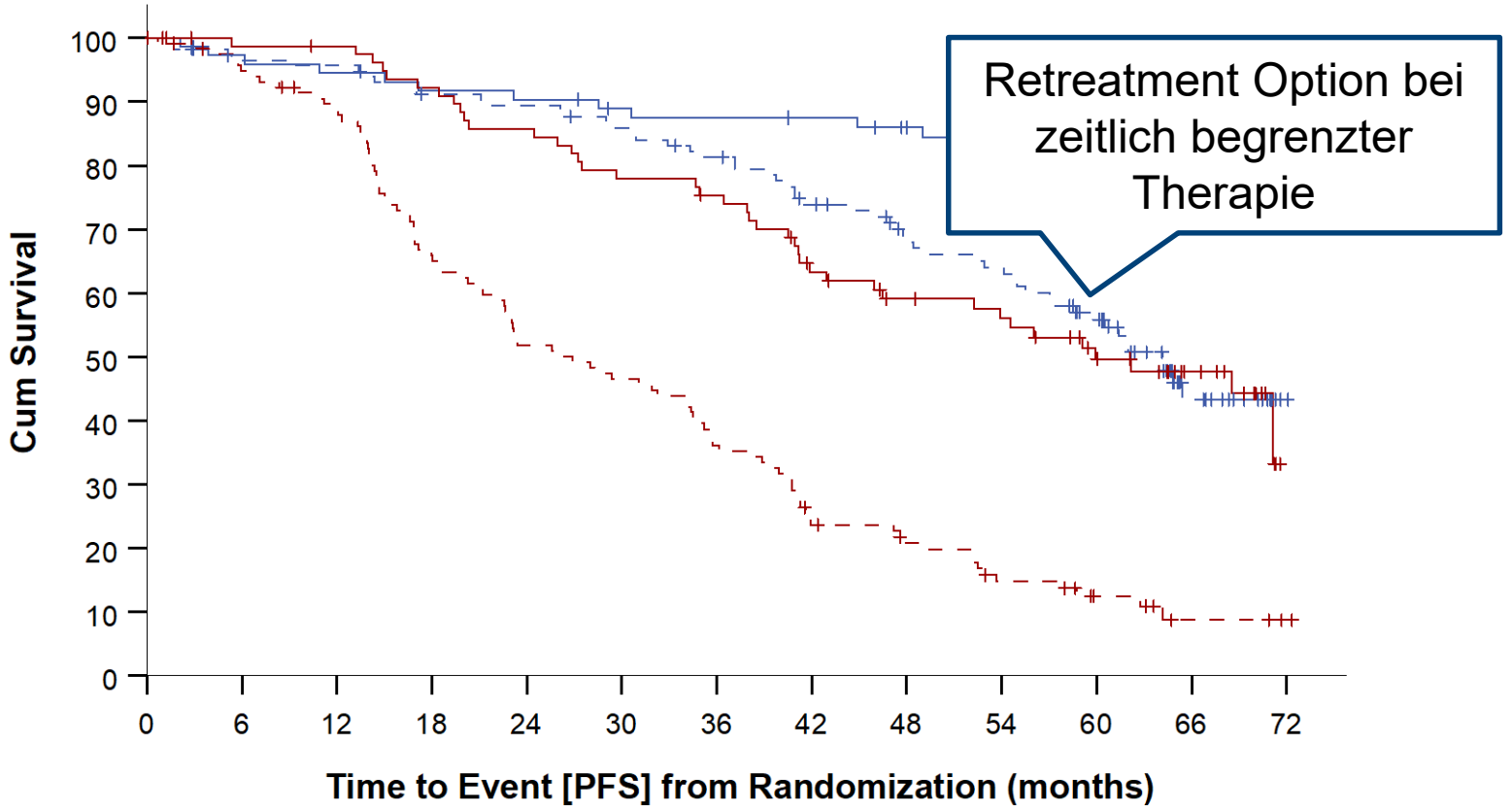
ILLUMINATE:
PFS für IbrutO bei Pat. mit mut/unmut IGHV status



Moreno C et al., Haematologica. 2022; online

Venetoclax + CD20-Antikörper in der Erstlinientherapie der CLL nach IGHV Status

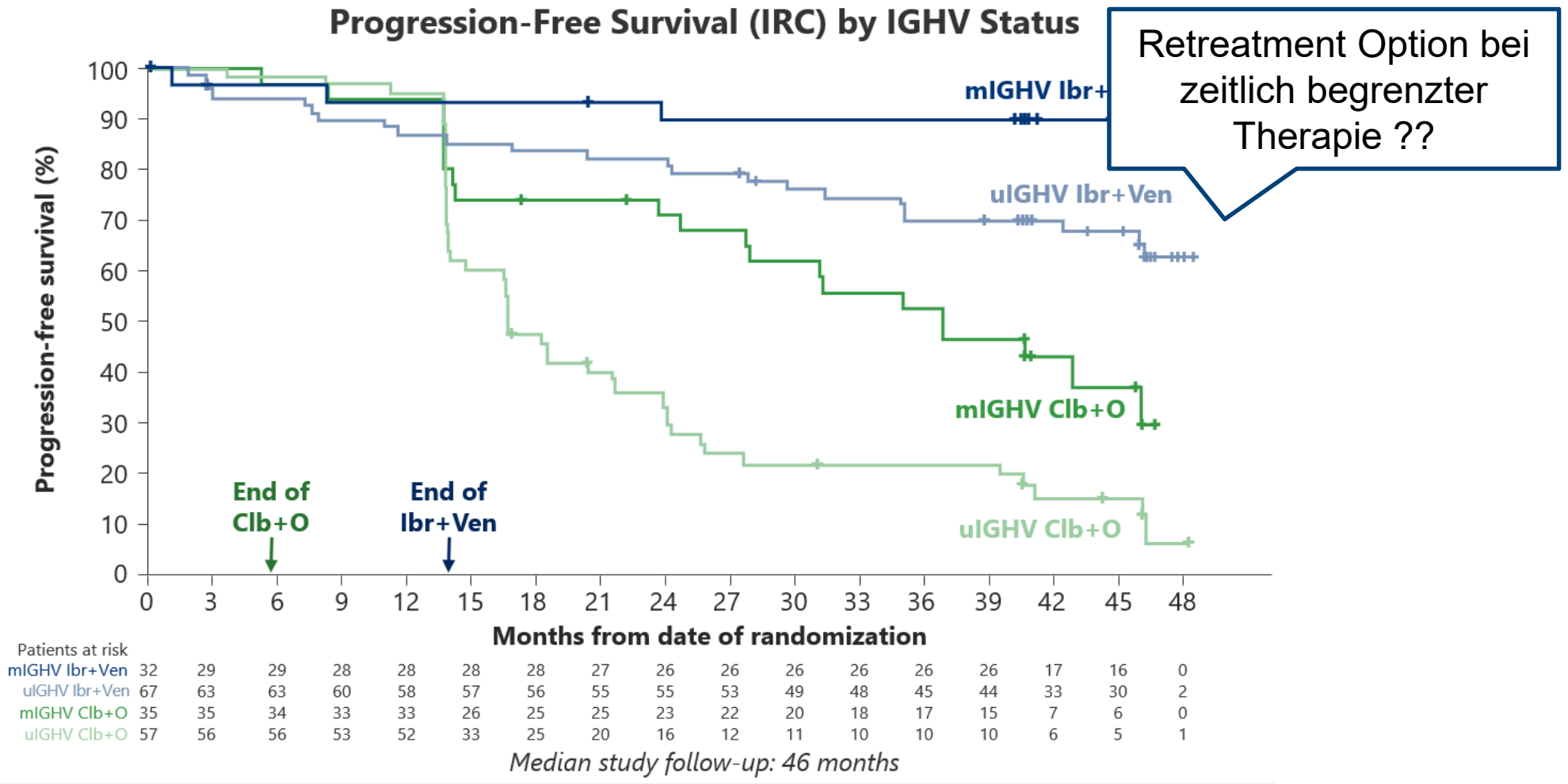
CLL14: PFS für VenO bei Pat. mit mut/unmut IGHV status



Ven-Obi & IGHV mutated	76	70	68	66	65	62	61	59	56	53	45	18	3
Ven-Obi & IGHV unmutated	121	110	109	102	100	95	89	79	69	64	49	16	1
Clb-Obi & IGHV mutated	83	77	76	71	66	60	57	46	40	37	29	17	0
Clb-Obi & IGHV unmutated	123	110	101	75	59	53	41	26	21	14	8	3	1

Al Sawaf et al., Nature Communications| (2023) 14:2147

Ibrutinib + venetoclax (IV): PFS nach Therapie und IGHV Status



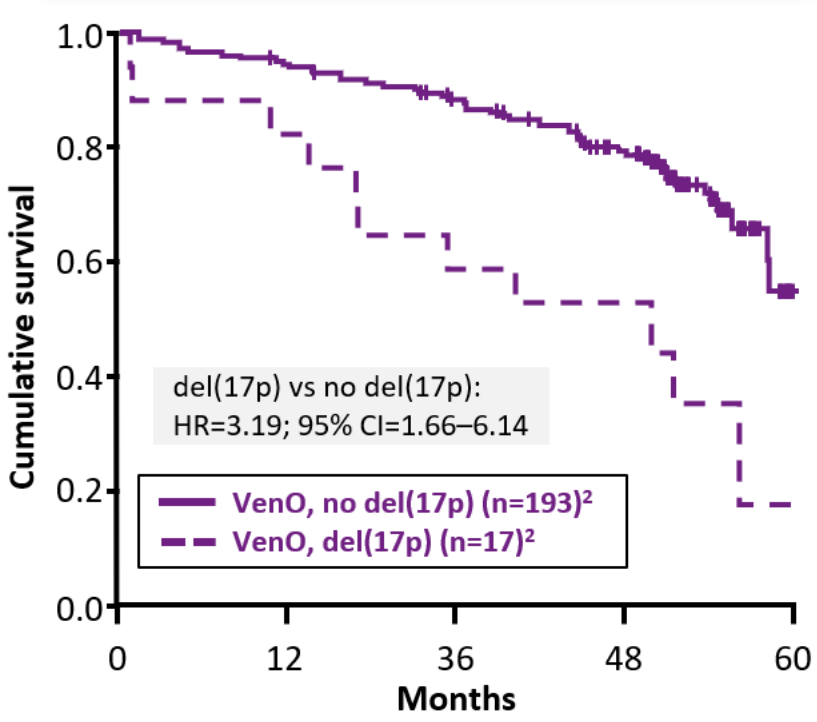
Retreatment Option bei zeitlich begrenzter Therapie ??

C. Niemann et al., ASH 2022 abstract 93

Behandlung der Hochrisiko - CLL: zeitlich unbegrenzt versus begrenzt: Phase III Studien im Vgl

Venetoclax + Obinutuzumab

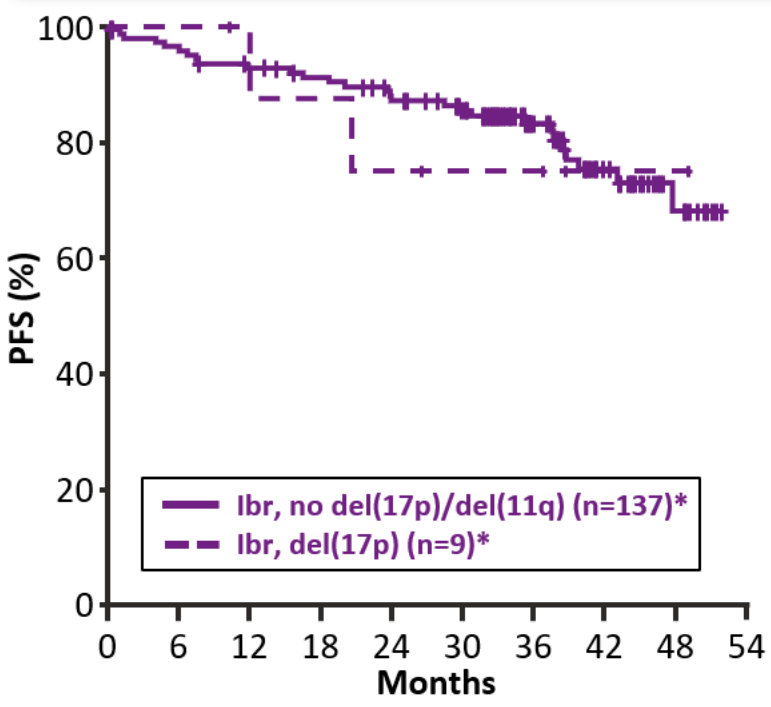
CLL14: PFS für VenO bei Pat. mit T*P53*



Al Sawaf O et al., JCO. 2021; 39(36):4049-4060

Ibrutinib Dauertherapie

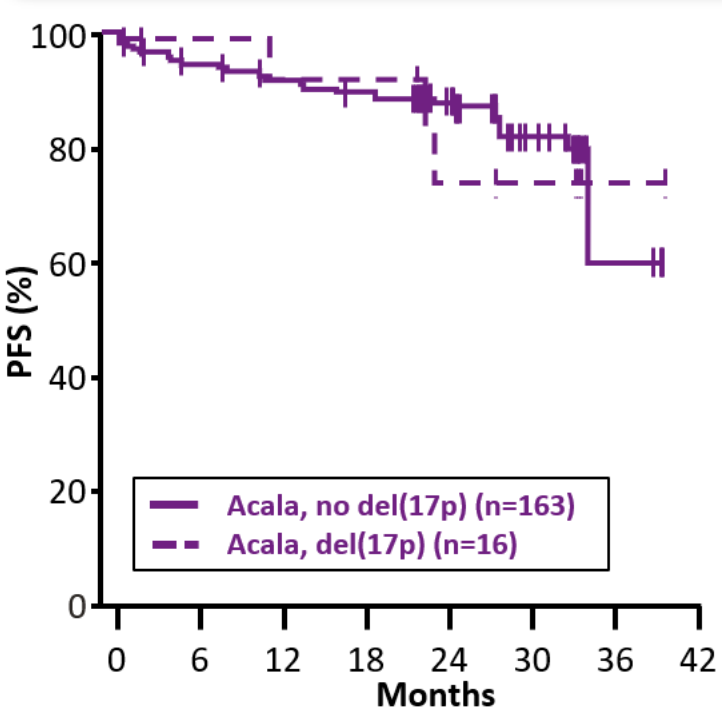
Alliance: PFS für Ibr bei Pat mit *TP53*



Woyach JA et al., NEJM. 2018; 379(26):2517-28; Suppl.

Acalabrutinib Dauertherapie

ELEVATE: PFS für Ibr bei Pat mit *TP53*

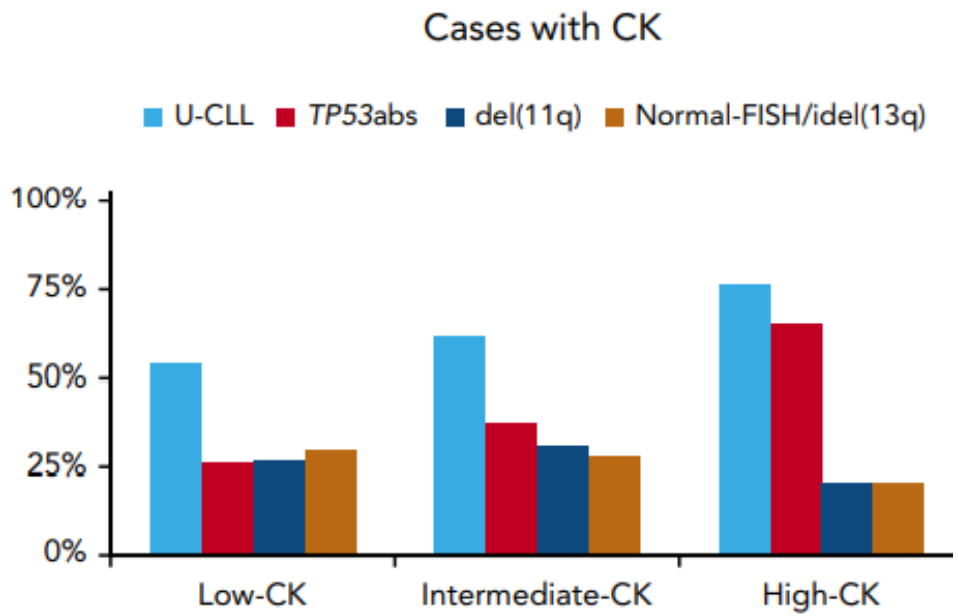


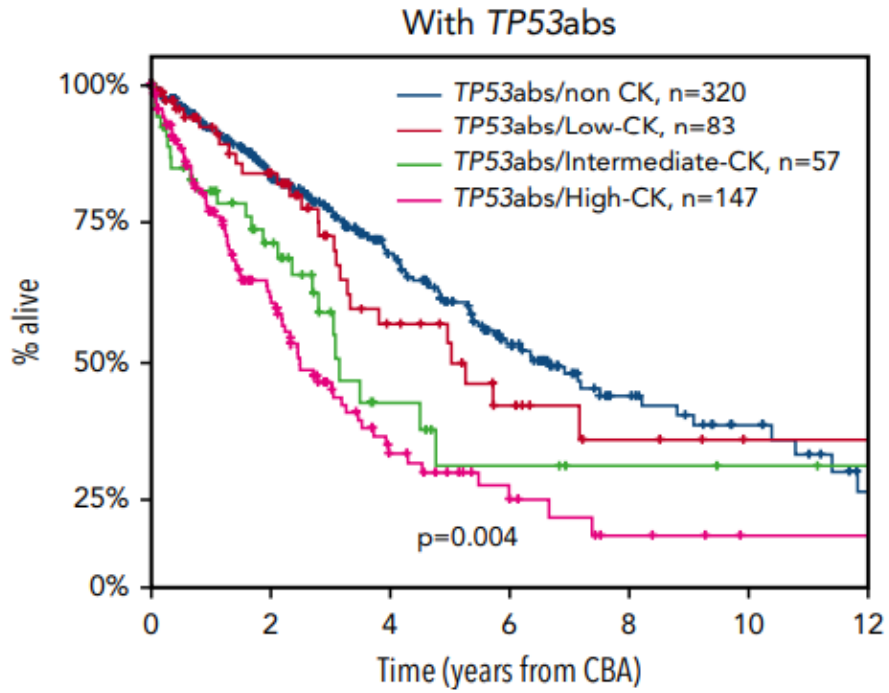
Sharman J et al., Lancet. 2020; 395:1278

Definition of Complex Karyotype (CKT): an ERIC (european research initiative on CLL) approach

Evaluation on 5290 CLL patients

Definition of low CKT: 3 chromosomal aberrations
Definition of intermediate CKT: 4 chromosomal aberrations
Definition of high CKT: ≥ 5 chromosomal aberrations

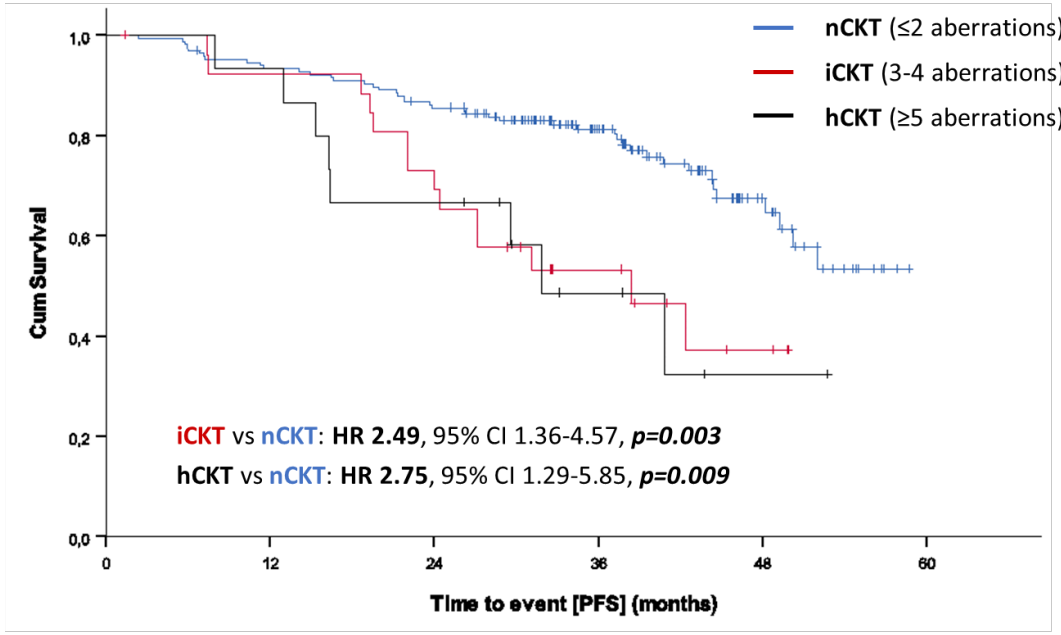




Baliakas et al., Blood 2019; Vol133, Nr 11

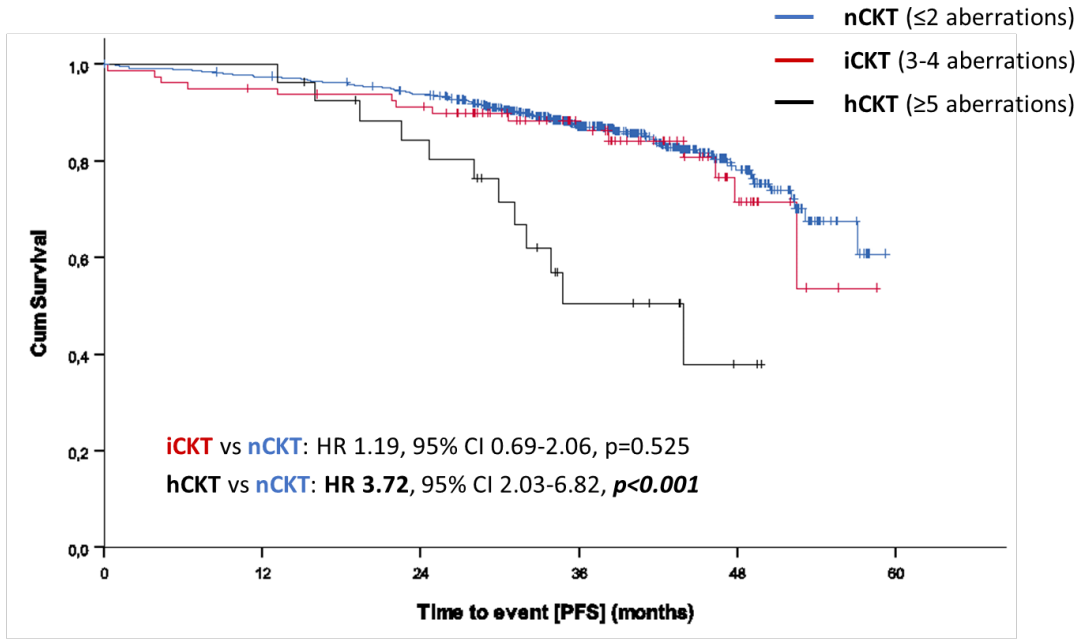
High and intermediate complex karyotype in CLL13 and association with PFS

PFS, chemoimmunotherapy arm



Patients at risk					
nCKT	177	155	141	84	24
iCKT	30	24	18	9	3
hCKT	16	14	10	4	1

PFS, pooled venetoclax arms



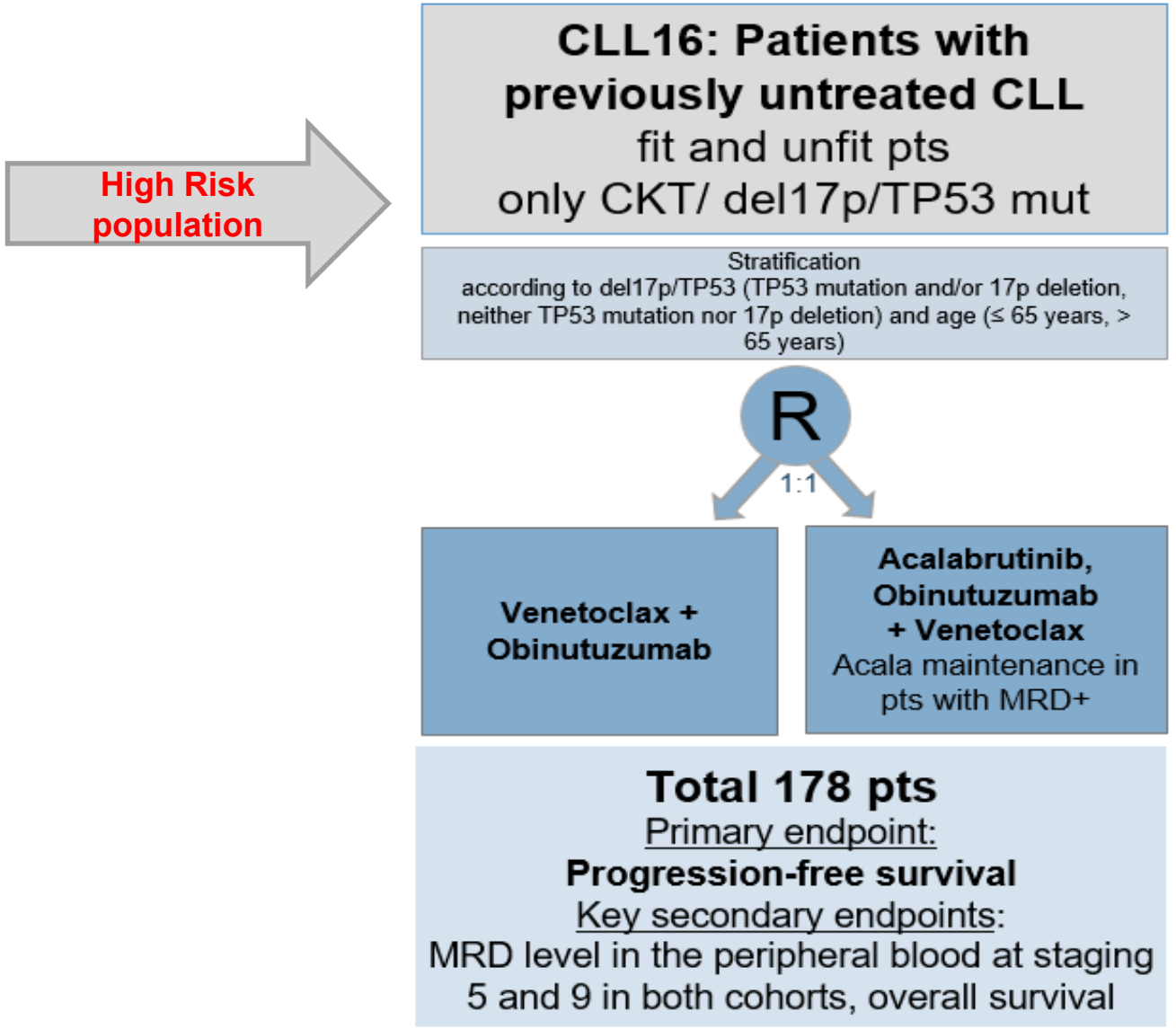
Patients at risk					
nCKT	565	547	522	308	99
iCKT	80	75	71	44	14
hCKT	27	27	21	8	2

→ Presence of **hCKT but not iCKT is associated with shorter PFS in** in pooled venetoclax arms

Fürstenau M. et al., Blood in press

CLL16 phase 3 trial: Ven+O vs Ven+O+Acalabrutinib in HR-CLL

DEUTSCHE STUDIENGRUPPE



Rezidivtherapie

Therapieindikation Rezidiv

Erst bei **symptomatischen** Progreß –
außer bei PD unter laufender Therapie

Rezidivtherapie-Optionen bei der CLL

Dauertherapie ∞

BTKi
- Ibrutinib
- Acalabrutinib
- Zanubrutinib in regulatory review

BCL2i
Venetoclax in *TP53* & after BTKi

PI3K inhibitors
- Idelalisib + R
- Duvelisib

Zeitlich limitierte Therapie ⛔

BCL2i + Anti-CD20
- Venetoclax + R
  24 cycles

Zelluläre Therapien 🧬

Cellular therapies
- Allo SCTx
- CART only within clinical trials

Rezidivtherapie:
Faktoren zur Überlegung zur Wahl der Therapie

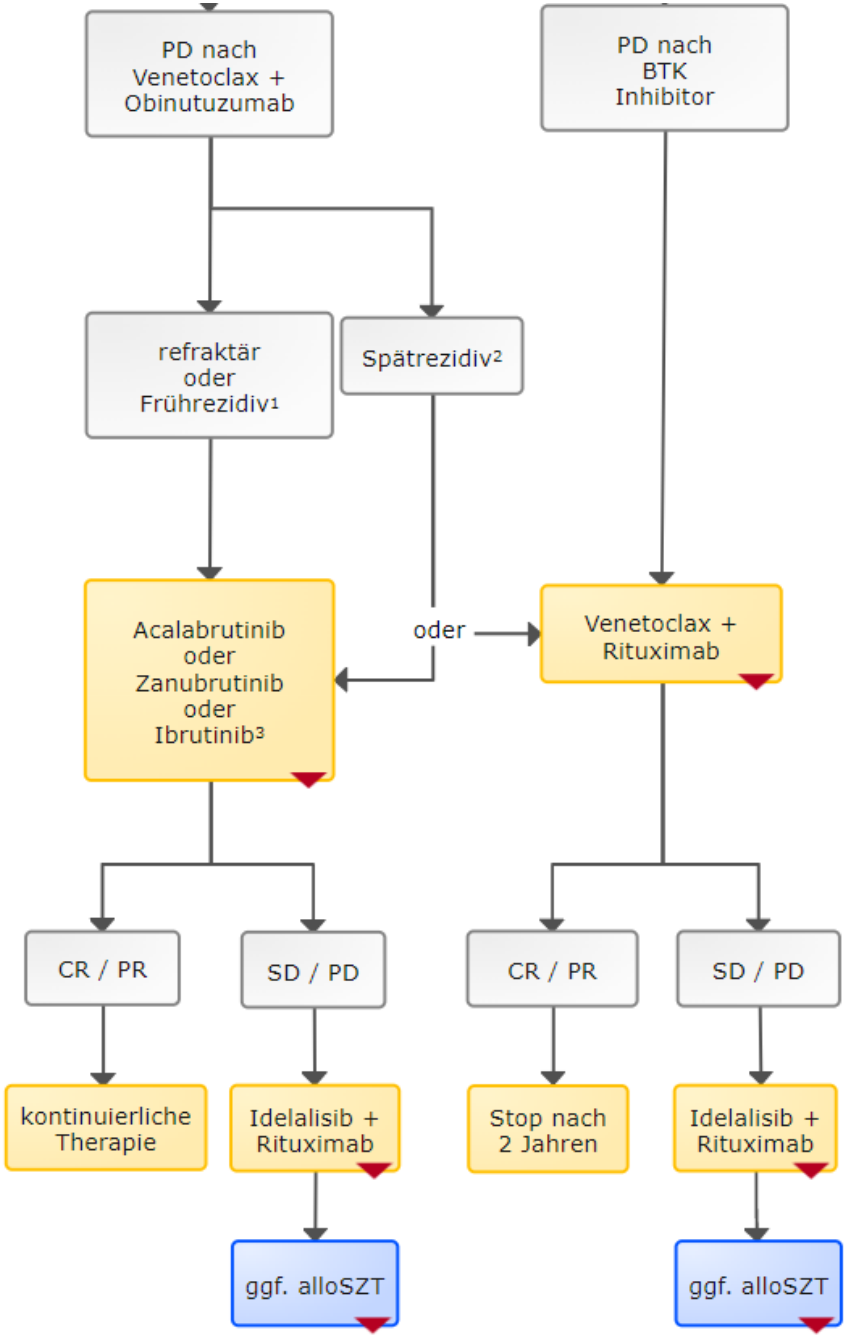
Vorherige Therapie:
Ansprechen
Verträglichkeit

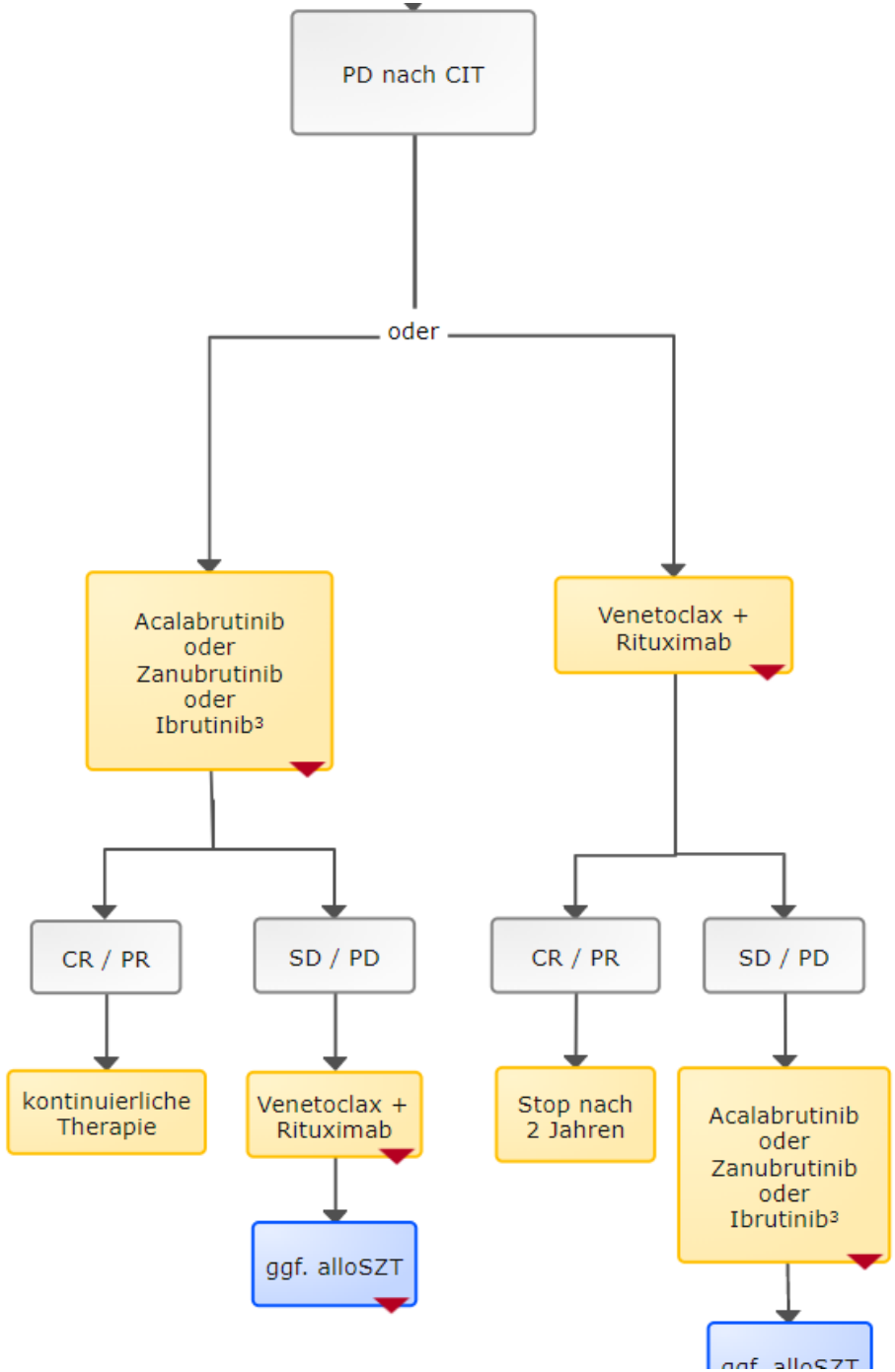
Genetische Evolution:
Neue TP53 Veränderung
Resistenzmutation

Begleiterkrankung und Begleitmedikation

Optimale Therapiesequenz

Rezidiv



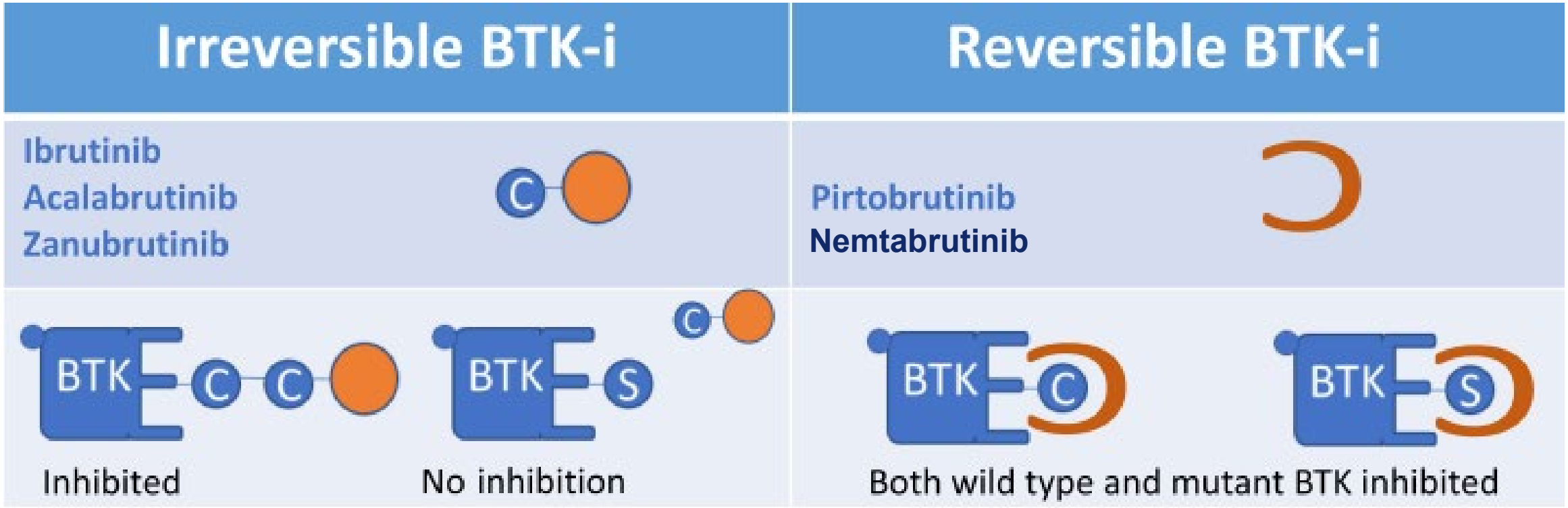


Onkopedia, Stand Januar 2023
Wendter, …….Stilgenbauer

Relapse treatment after prior therapy with targeted agents

Last prior Treatment	Relapse Treatment	N pts	ORR	PFS	Reference
BCRi → Ven					
Ibrutinib	Venetoclax	92	65%	med 25 mo.	Jones et al., Lancet Oncol 2018; 19: 65
Idelalisib	Venetoclax	36	67%	79% at 12 mo.	Coutre et al., Blood 2018;131(15):1704
BCR inhibitor	Ventoclax	26	74%	n.r. after 17 mo.	Mato et al., Ann Oncol 2017; 28(5):1050
Ven → BCRi					
VenetoclaxR	Ibrutinib	18	100%	-	Seymour J. et al., Blood 2022; Vol 140, Nr 8
Venetoclax	Ibrutinib/Acalabrutinib	44	84%	32 mo.	Mato et al., ASH 2019; Abstract 502
VenR → Ven					
VenentoclaxR	Venetoclax	32	72%	-	Seymour J. et al., Blood 2022; Vol 140, Nr 8
Covalent BTKi → Non-covalent BTKi					
Ibr/Acala/Zanu	Pirtobrutinib	121	62%	-	Mato A. et al., Lancet 2021; 397: 892–9012021; 397: 892–901

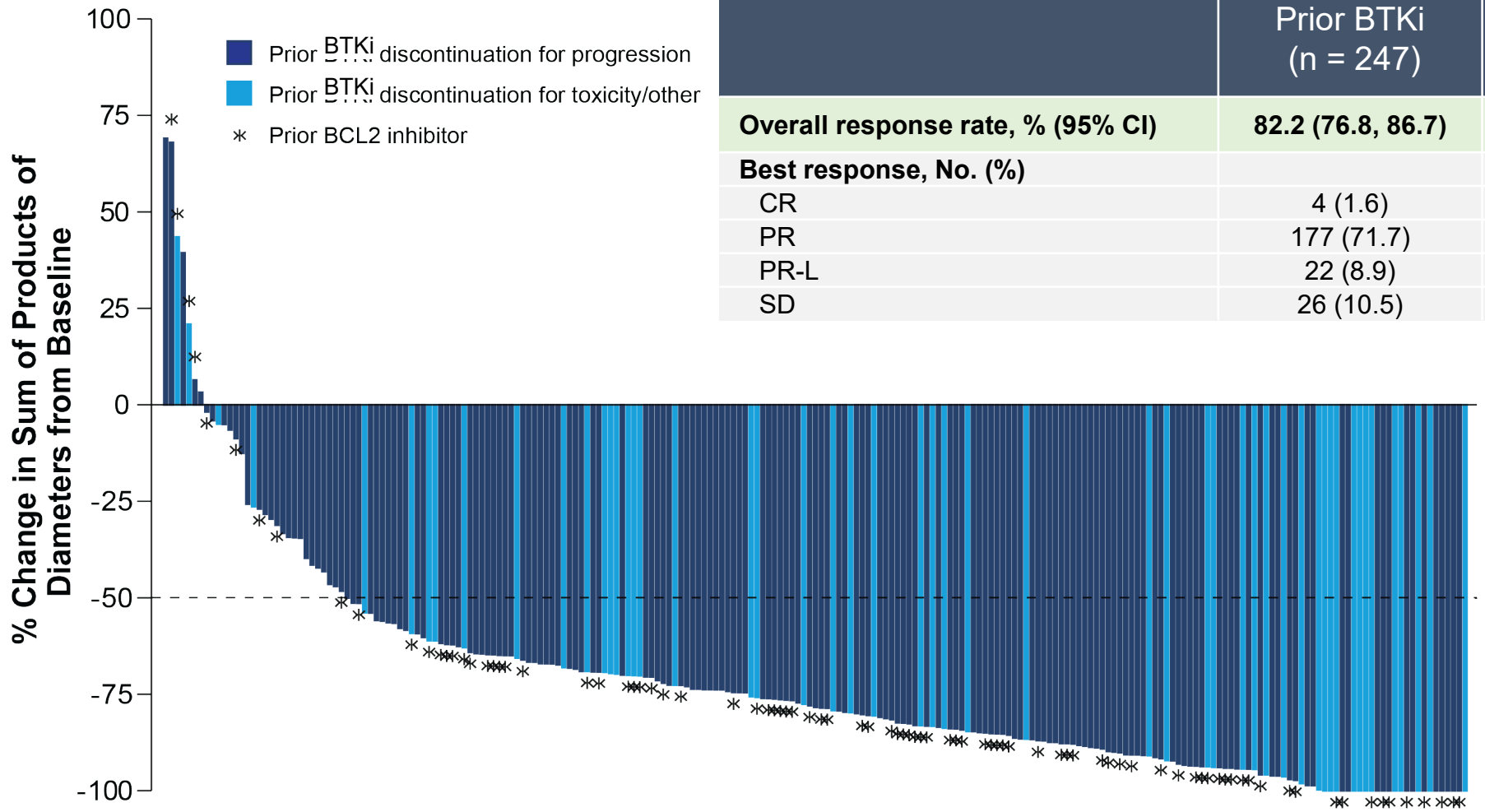
Noncovalent BTK Inhibitors



BTK = Bruton tyrosine kinase; BTK-i = Bruton tyrosine kinase inhibitor.

Tambaro FP et al. *J Exp Pharmacol.* 2021;13 923–935.

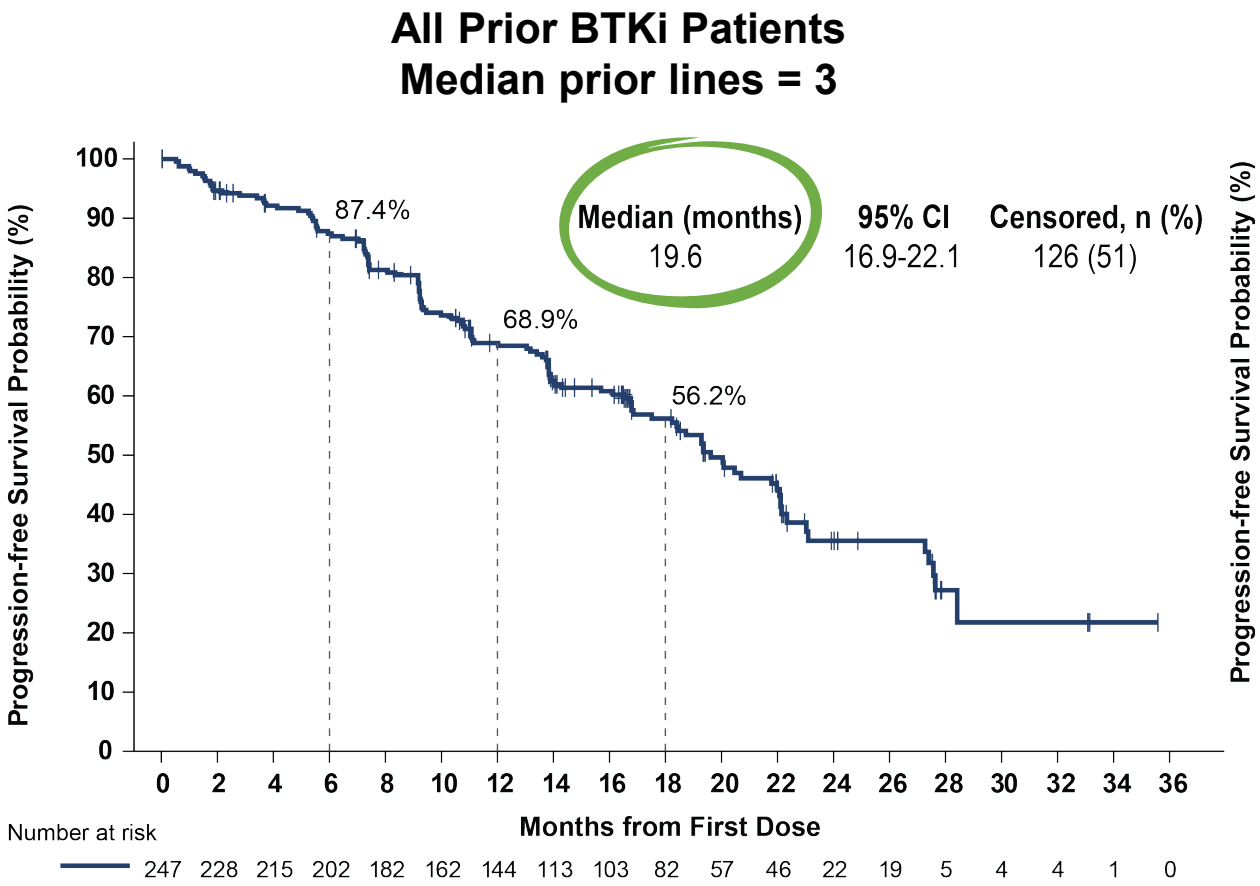
Pirtobrutinib in Covalent BTKi-Pretreated R/R CLL/SLL
BRUIN: Efficacy

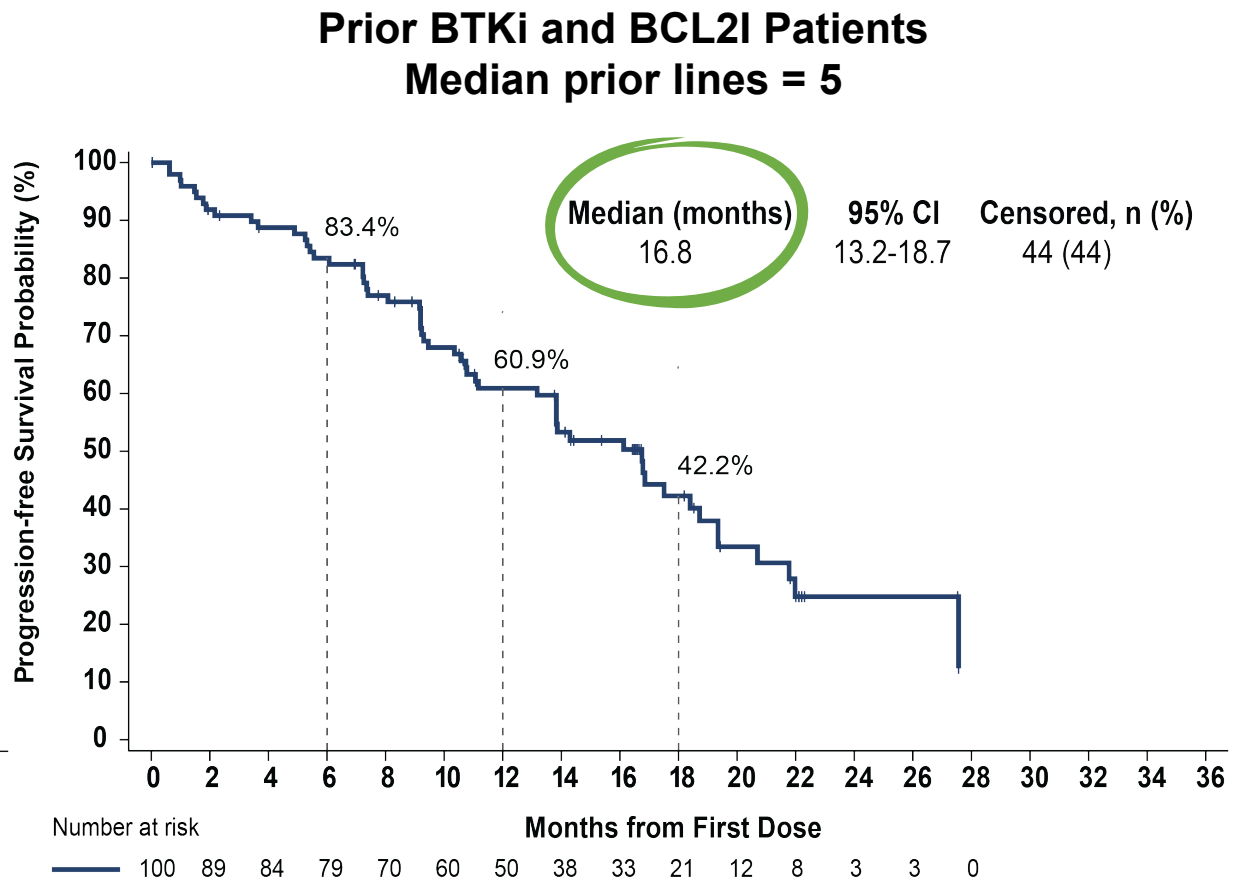


	Prior BTKi (n = 247)	Prior BTKi + BCL2I (n = 100)
Overall response rate, % (95% CI)	**82.2 (76.8, 86.7)**	**79.0 (69.7, 86.5)**
Best response, No. (%)		
CR	4 (1.6)	0 (0.0)
PR	177 (71.7)	70 (70.0)
PR-L	22 (8.9)	9 (9.0)
SD	26 (10.5)	11 (11.0)

Mato AR, et al. Blood. 2022;140(suppl 1): Abstract 961.

Pirtobrutinib in Covalent BTKi-Pretreated R/R CLL/SLL
BRUIN: PFS





- Median follow-up of 19.4 mo for patients who received prior BTKi

- Median follow-up of 18.2 mo for patients who received prior BTKi and BCL2I

Mato AR, et al. Blood. 2022;140(suppl 1): Abstract 961.

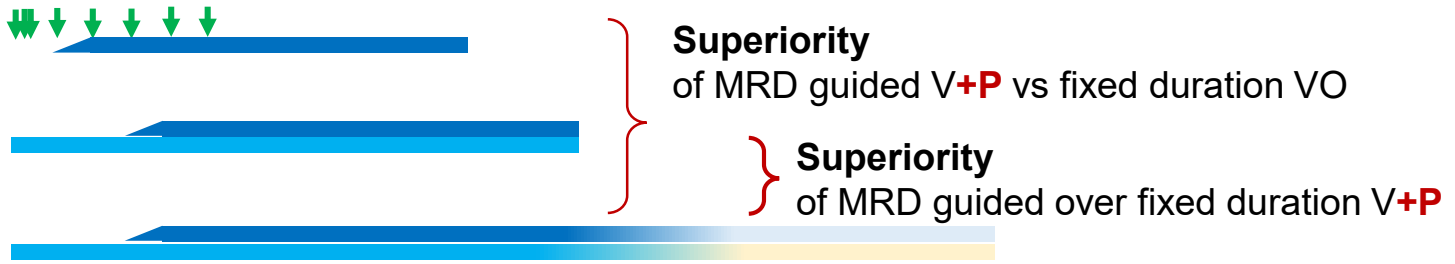
CLL18: Next phase 3 trial for frontline of CLL
Venetoclax + Pirtobrutinib (VP) MRD guided vs VP fixed vs. VO

DEUTSCHE STUDIENGRUPPE

Arm A: V+O fixed-duration (12 mo)

Arm B: V**+P** fixed-duration (15 mo)

Arm C: V**+P** MRD guided



Primary endpoint: PFS

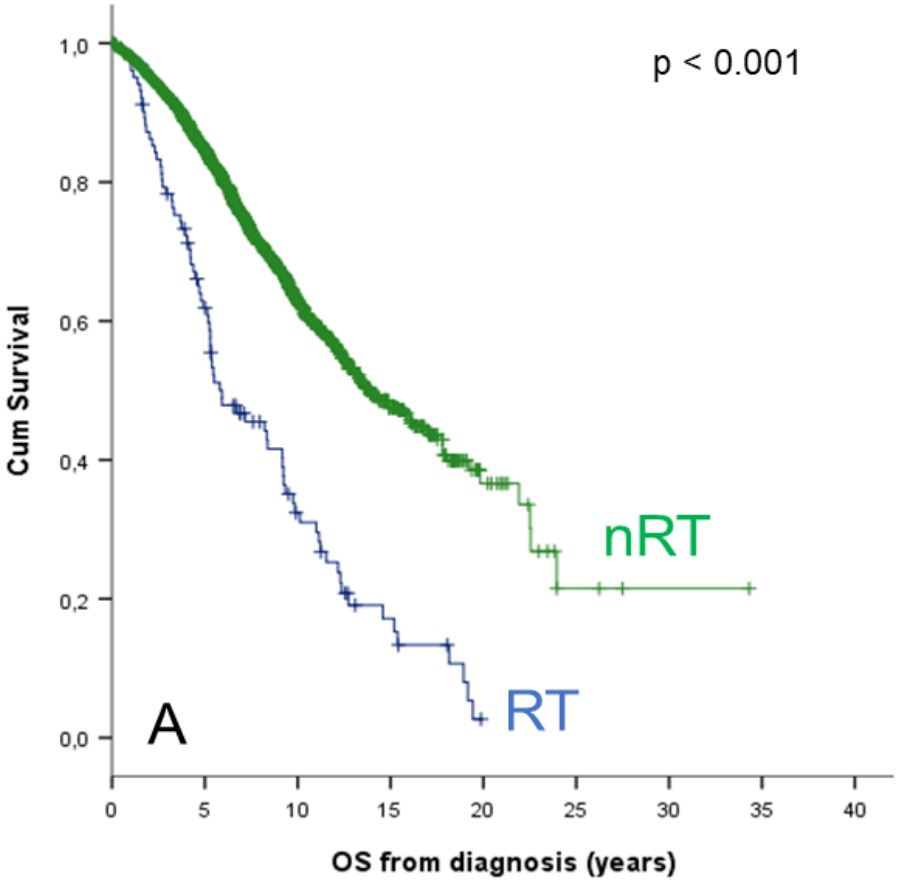
Assumptions: PFS @36 months: 80% for arms A & B, 90% for arm C.

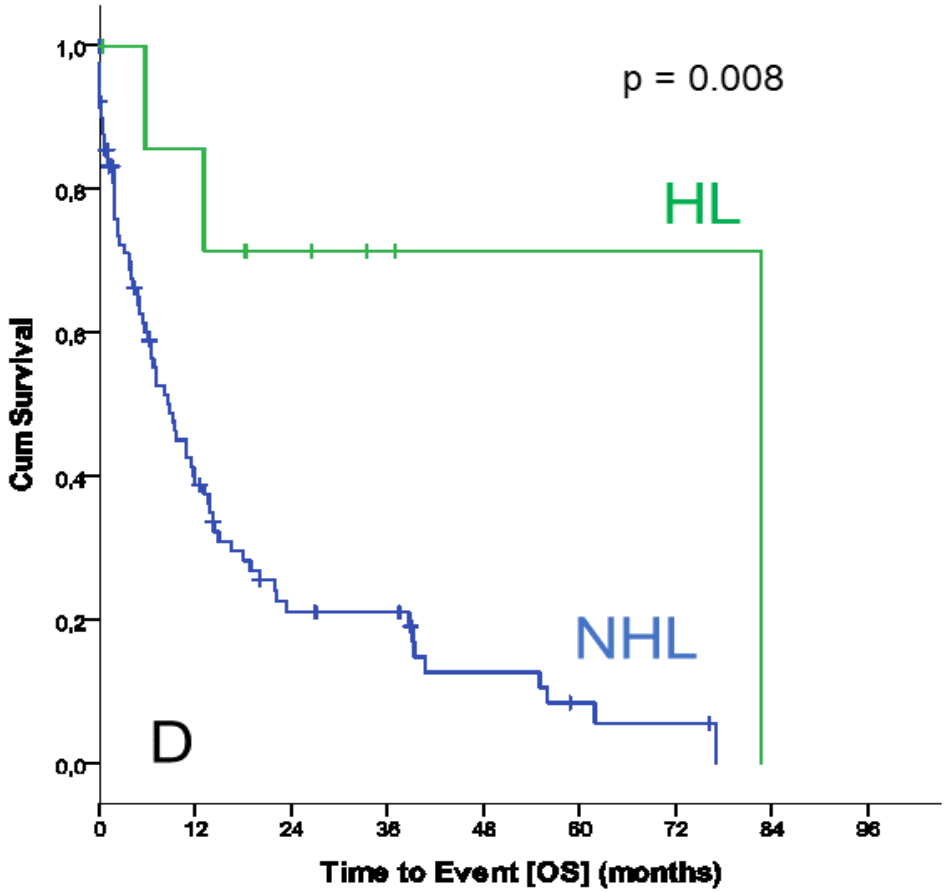
Test design: Two-sided 2.5% significance level per each superiority testing with targeted hazard ratio = 0.472

Total required sample size: 813 pts (271 per arm, 1:1:1 randomization)

Worst case scenario RT: Pooled analysis of the GCLLSG of 2975 patients

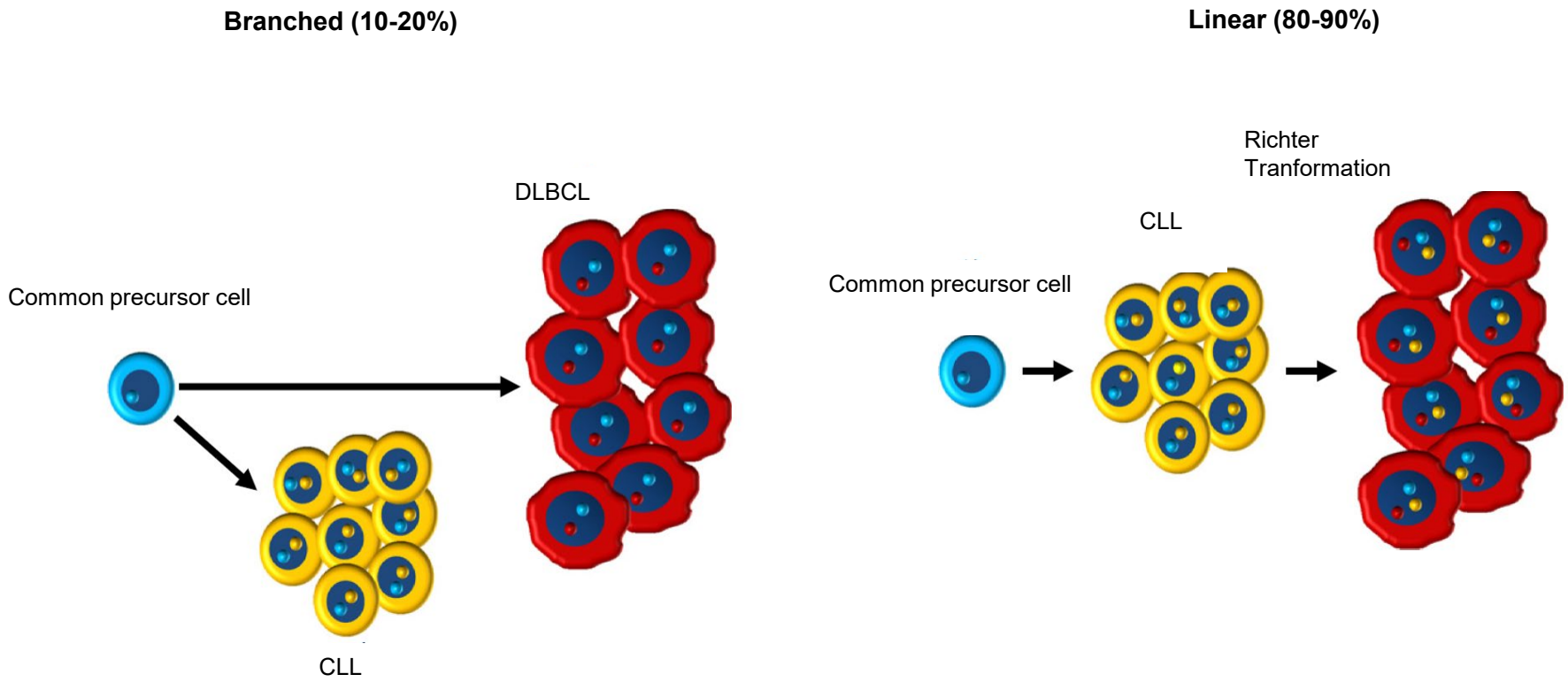
103 patients (3%) developed RT (95 NHL and 8 HL) after 53 months median observation time





Al Sawaf et al. , Leukemia 2020

Differenzierung de novo vs klonal verwandtes DLBCL



Adapted from Rossi & Gaidano , Sem. Oncol. 2016

Definition Richter-Transformation

- DLBCL (>90%):
    - 80% genetisch verwandt zur CLL (Leichtkettenrestriktion, IGHV)
    - 20% de novo DLBCL
    - ABC-type 90%

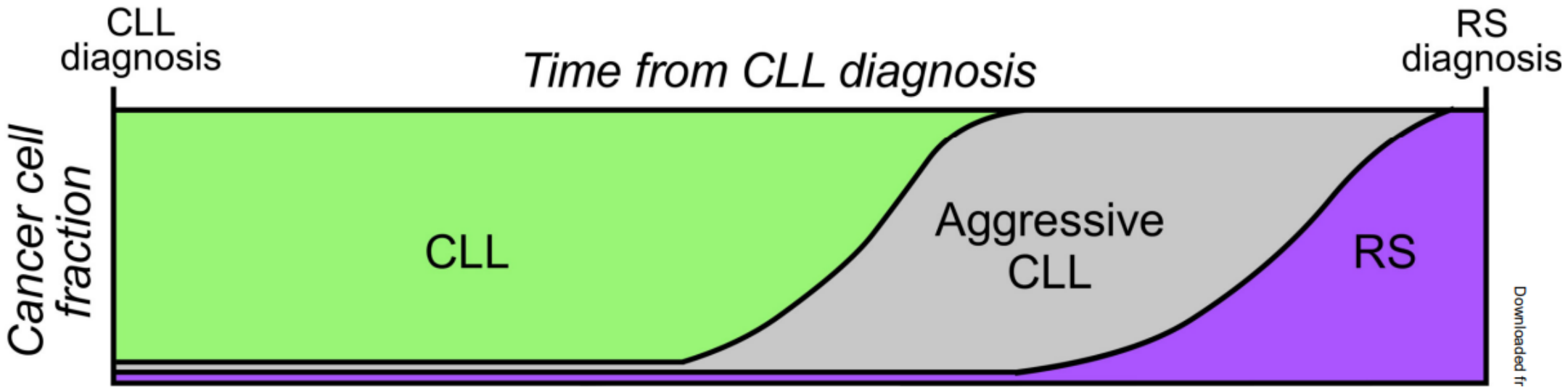
- Hodgkin Lymphom (<10%)
    - Nur 30% genetisch verwandt zur CLL
    - 70% de novo HL !

NICHT:
Prolymphozyten Leukämie, bzw. nach neuer WHO CLL mit erhöhtem Anteil an Prolymphozyten

Epidemiologie

Trial	Treatment	Nr of RT/nr of CLL	% RT
CLL4 LRF	F vs FC vs Clb	13/777	1.7
CLL8 GCLLSG	FC vs FCR	38/800	4.8
CLL10 GCLLSG	FCR vs BR	13/561	2.3
Alliance	I vs IR vs BR	3/547	0.5
ECOG 1912	IR vs FCR	3/529	0.6
CLL14 GCLLSG	VG vs ClbR	5/432	1.2
CLL13 GCLLSG	FCR/BR vs VR vs VG vs IVG	18/926	1.9

Entwicklung der CLL über die Zeit



Nadeu F. et al., Nature Medicine 2022; Volume 28, Issue 8
Parry E. et al, Blood 2022; Volume 41, Issue 2 395

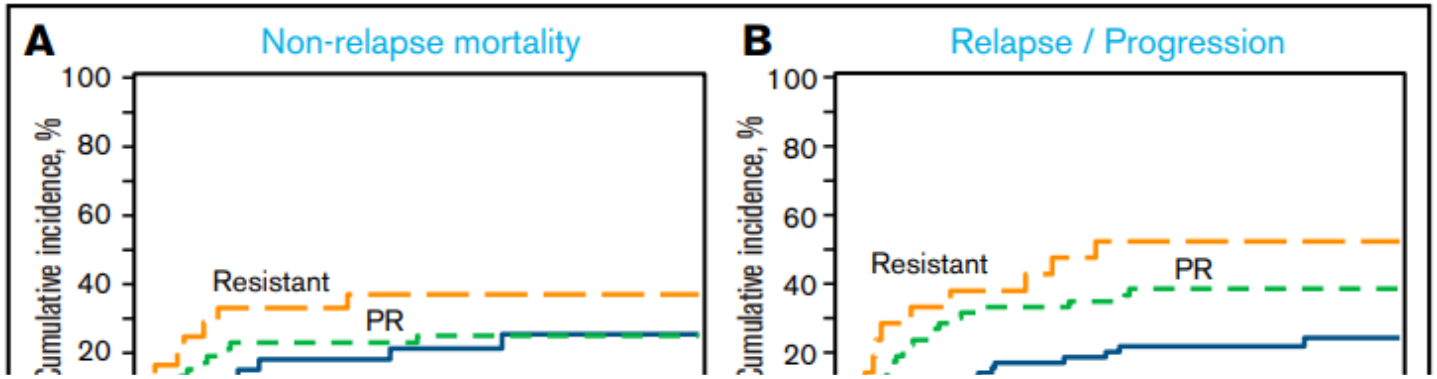
Chemoimmuntherapien bei RT vom DLBCL Typ

Regimen	Author	Trial Design	No. of Patients	Treatment-Related Mortality, %	ORR, %	CR, %	PFS Median, months	OS Median, months
R-CHOP	Langerbeins et al[54]	Prospective phase II	15	0	67	7	10	21
O-CHOP + O maintenance	Eyre et al[43]	Prospective phase II	37	0	46	27	6	11
Platinum and high-dose AraC regimens[a]	Durot et al[55]	Retrospective	28	15[b]	43	25	7	8
R Hyper-CVAD + GMCSF/R HDM + AraC	Tsimberidou et al[56]	Prospective phase II	30[c]	Early mortality rate: 18%[b]	43	27	NR separately for RT cohort	12 month survival rate: 28%
R-EPOCH	Rogers et al[57]	Retrospective	44	30	39	NR	3.5	6
Hyper CVAD	Dabaja et al[58]	Prospective phase II	29[d]	14	41	38	NR	10
OFAR2	Tsimberidou et al[59]	Prospective phase I/II	31	8	38	6	3	6
OFAR1	Tsimberidou et al[60]	Prospective phase I/II	20	5	50	20	3	8

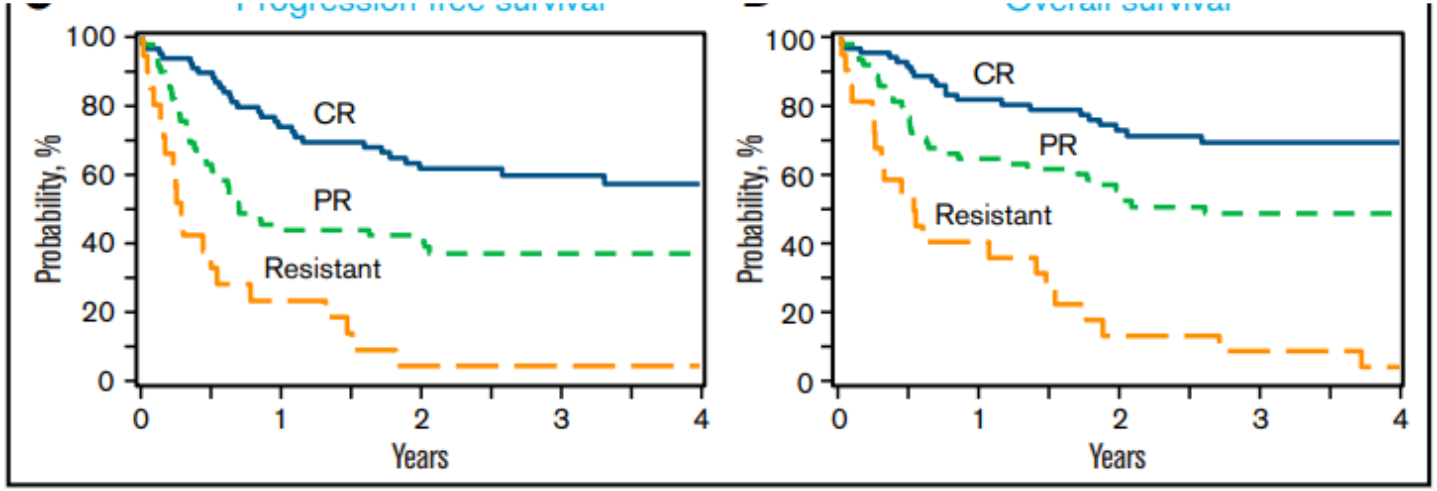
Smyth E., Eyer T., Chea C.: JCO 2022; Volume 41, Issue 2

Allogene SCTx bei RT

Retrospective Registeranalyse in 118 Patienten

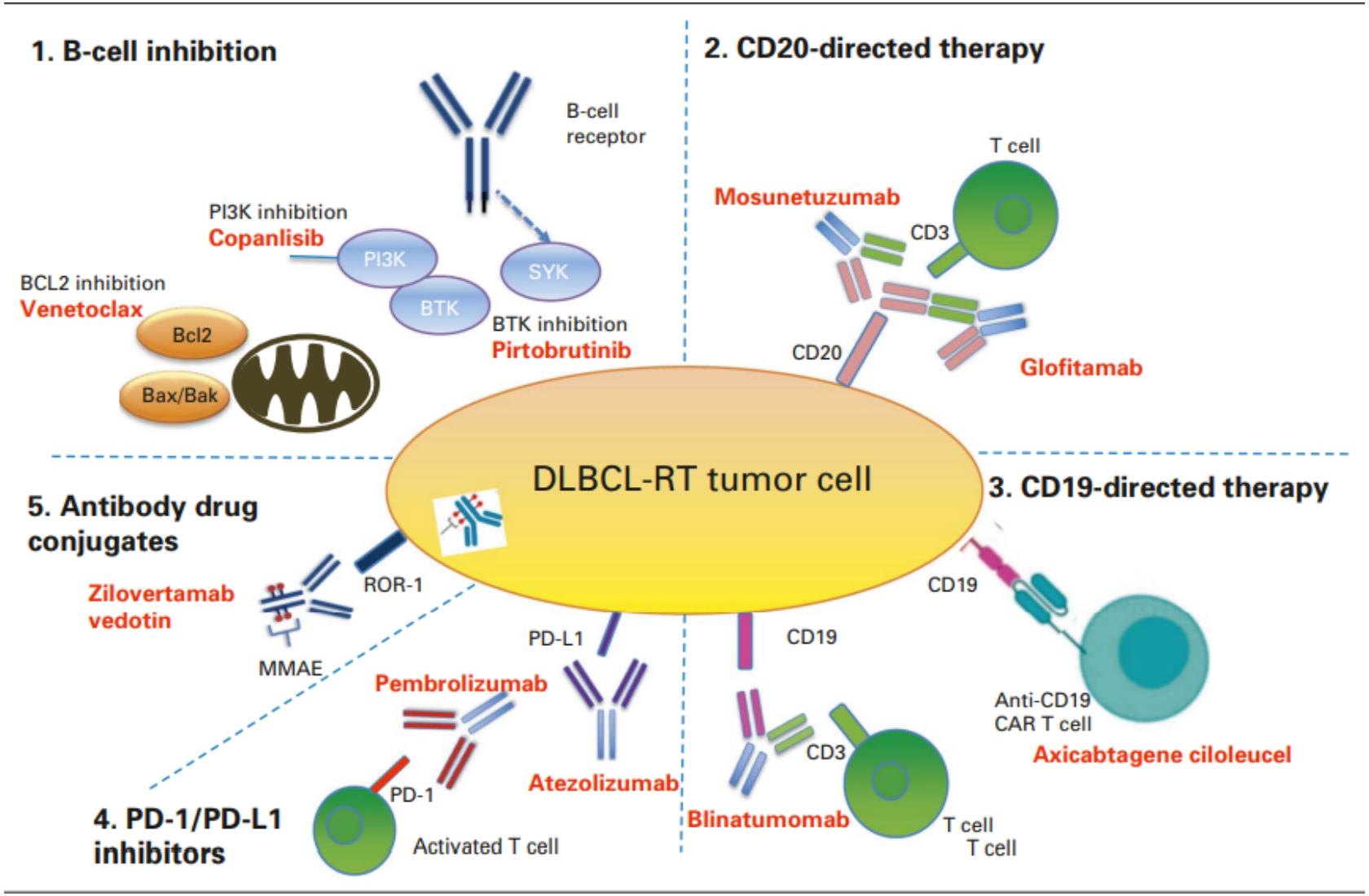


Nur 40% hatten eine del(17p)/*TP53* Mutation



Herrera et al, Blood advances 2021; Volume 5, Issue 18

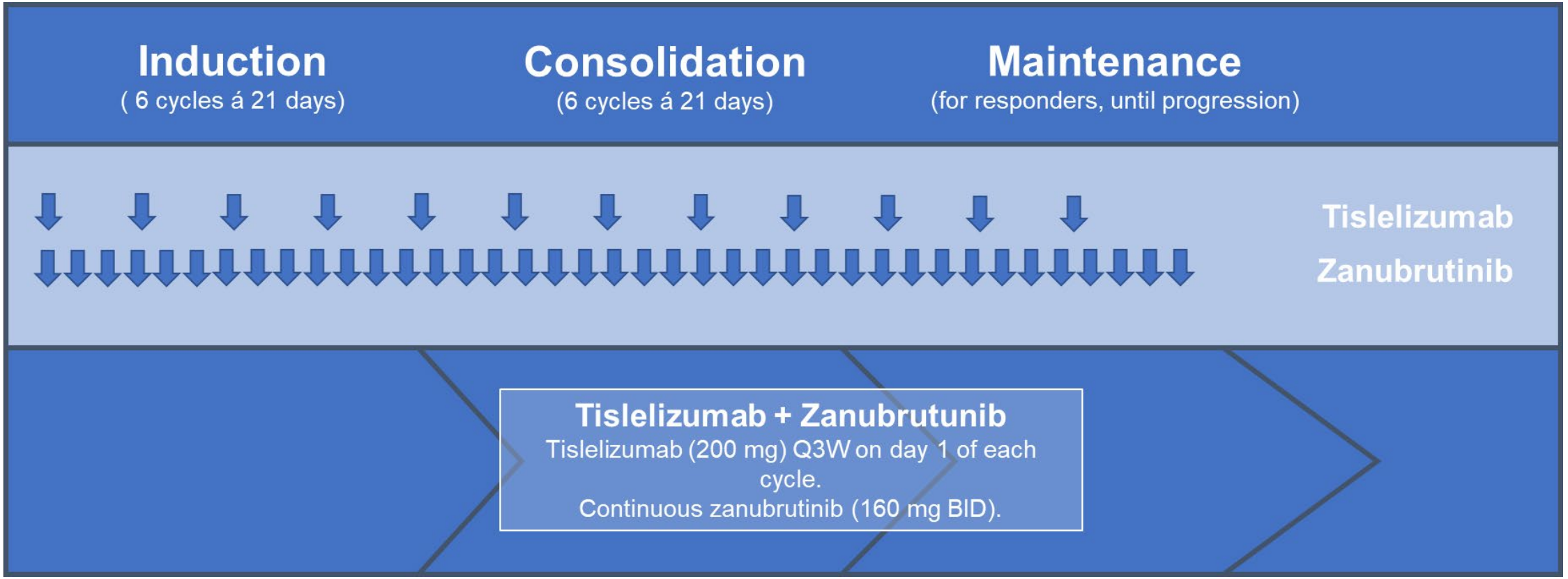
Neue Kombinationstherapien ?



Smyth E., Eyer T., Chea C.: JCO 2022; Volume 41, Issue 2

RT1-trial: Checkpointinhibitor + BTK inhibitor

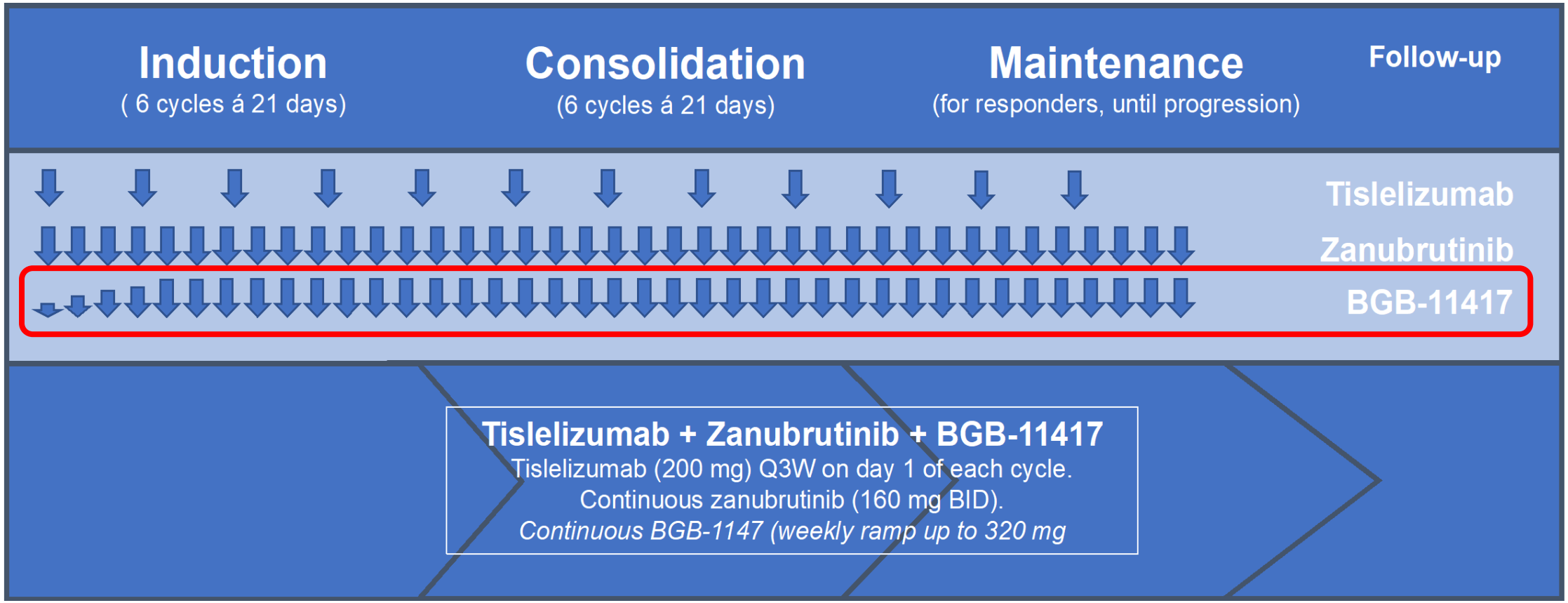
Treatment regimen



Primary endpoint:

- Overall response rate (ORR) after induction therapy and according to the refined Lugano Classification
- > 60% ORR
- N=48

RT 1-Studie der DCLLSG: Studienextensions-Kohorte (n=26)



Zusammenfassung CLL

- Behandlung immer noch erst bei Symptomen.
- Erstlinientherapie mit:
  - BTKi: Acalabrutinib, Zanubrutinib, Ibrutinib
  - Venetoclax + Obinutuzumab
  - Venetoclax + Ibrutinib
- Bei Unverträglichkeit von BTKi:
  - Dosisreduktion
  - Wechsel BTKi
- Rezidiv:
  - Wechsel der Substanzklasse
  - Nach zeitlich begrenzter Therapie: erneute Therapie (Ausnahme: CIT)
  - RT ausschließen bei raschem PD

DEUTSCHE STUDIENGRUPPE