UNIKLINIK KÖLN

DEUTSCHE STUDIENGRUPPE

CLL: CHRONISCHE LYMPHATISCHE LEUKÄMIE

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26. Juni 2021

Sommersymposium Lymphome Köln

Potentielle Interessenskonflikte

Forschungsunterstützung:

Roche, Janssen, AbbVie, Gilead, BeiGene, AstraZeneca

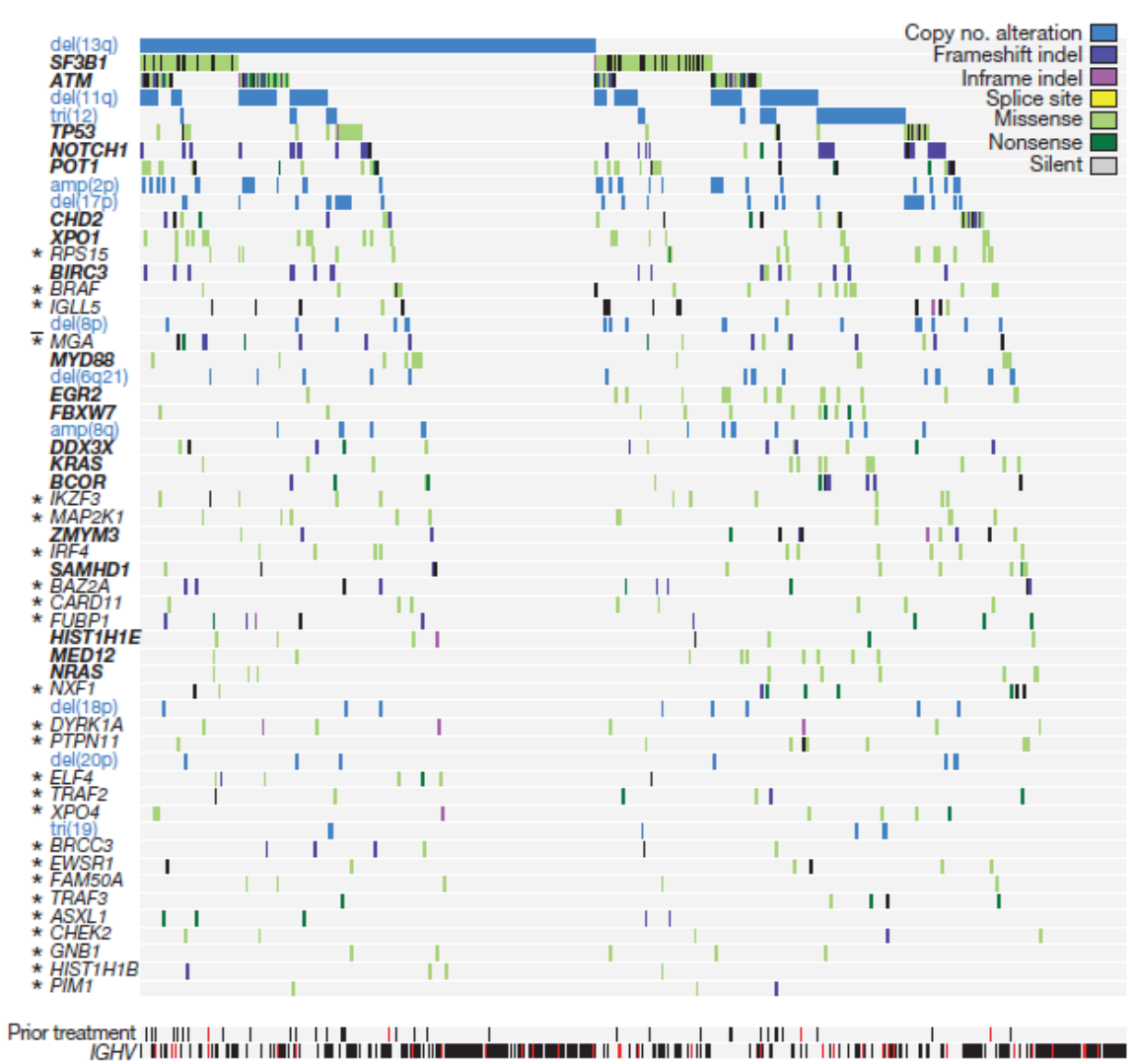
Vortragstätigkeit:

Roche, Novartis, Gilead, Janssen, AbbVie, Celgene, Hexal, Adaptive Biotechnologies

Beratertätigkeit:

Janssen, Roche, Novartis, AbbVie, Gilead, Celgene, ArQule, AstraZeneca, Oxford Biomedica, MSD

Die CLL ist eine sehr heterogene Erkrankung



Landau, Tausch et al., Nature 2015

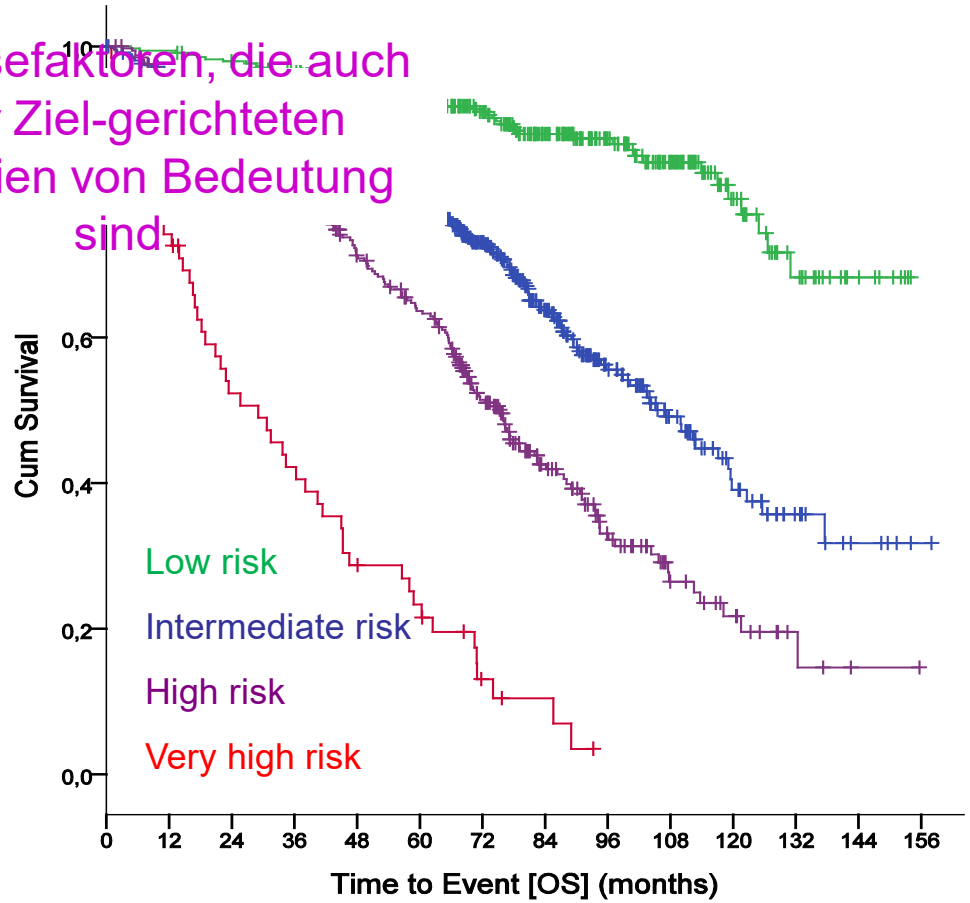
Prognosescore: CLLIPI

3472 patients from 5 study groups in US and Europe
1254 patients from an US and Scandinavian cohort for validation

Variable	Adverse factor	Coeff.	HR	Grading
TP53 (17p)	deleted and/or mutated	1.442	4.2	4
IGHV status	Unmutated	0.941	2.6	2
B2M, mg/L	> 3.5	0.665	2.0	2
Clinical stage	Binet B/C **or** Rai I-IV	0.499	1.6	1
Age	> 65 years	0.555	1.7	1
Prognostic Score				0 – 10

Risk group	Score	Patients N (%)	5-year OS, %	HR (95% CI)	*p* value
Low	0 – 1	340 (29)	93.2		
Intermediate	2 – 3	464 (39)	79.4	3.5 (2.5 - 4.8)	< 0.001
High	4 – 6	326 (27)	63.6	1.9 (1.5 - 2.3)	< 0.001
Very High	7 – 10	62 (5)	23.3	3.6 (2.6 - 4.8)	< 0.001

Prognosefaktoren, die auch unter Ziel-gerichteten Therapien von Bedeutung sind



CLL-IPI Working Group , Lancet Oncol 2016

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]	-

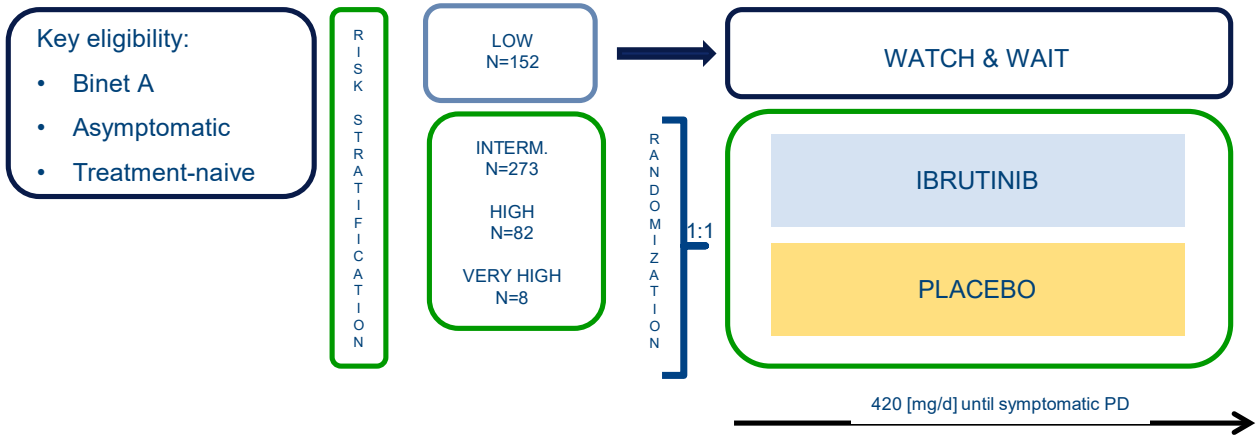
[a]Only if patient requests the evaluation of his prognostic score.
[b]Only if clinically indicated.
[c]Only for confirmation of CR within clinical studies.
[d]Only within clinical studies, in patients with clinical symptoms and before any venetoclax treatment.

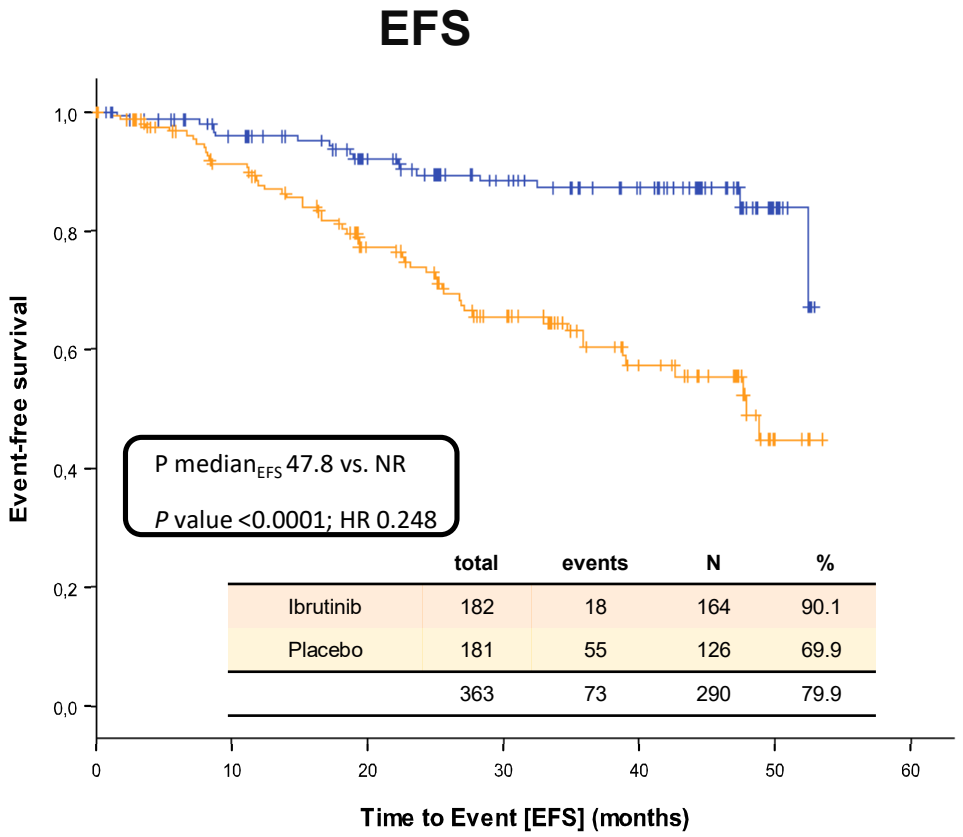
Therapieindikation

Keine Indikation im frühen, asymptomatischen

Binetstadium A oder B !

CLL12 trial: Early treatment (Binet A) with ibrutinib delays PD requiring treatment, but data on OS are pending





Langerbeins, EHA 2019 Abstract LB2602 (presidential)

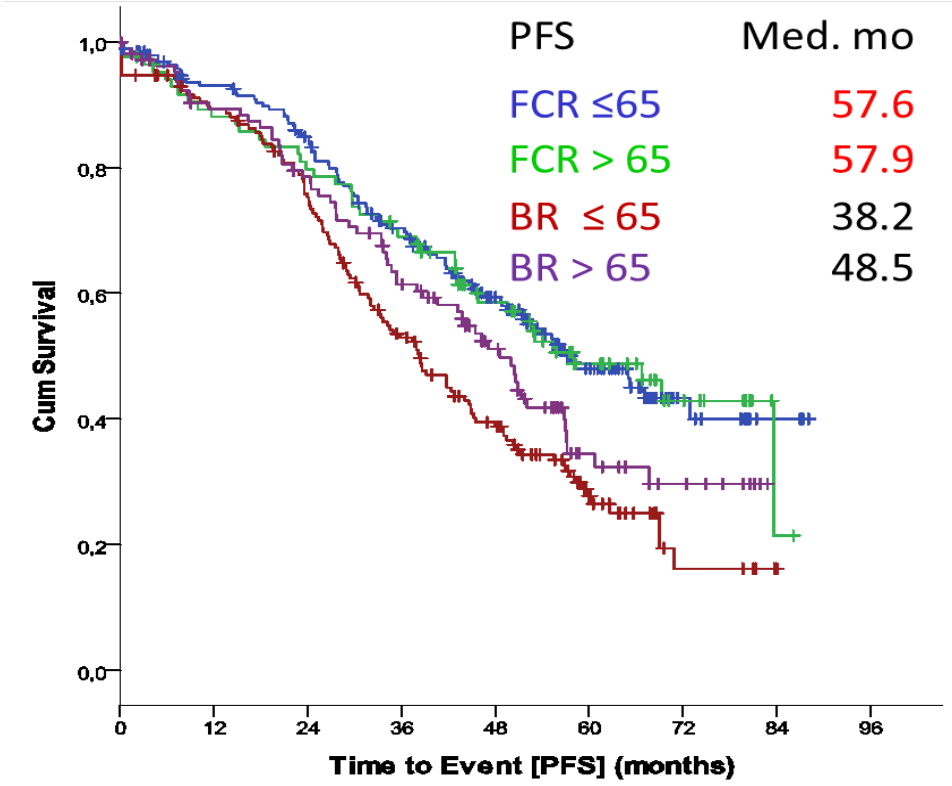
Therapieindikation

Symptomatisches

Binetstadium A oder B und Binet C

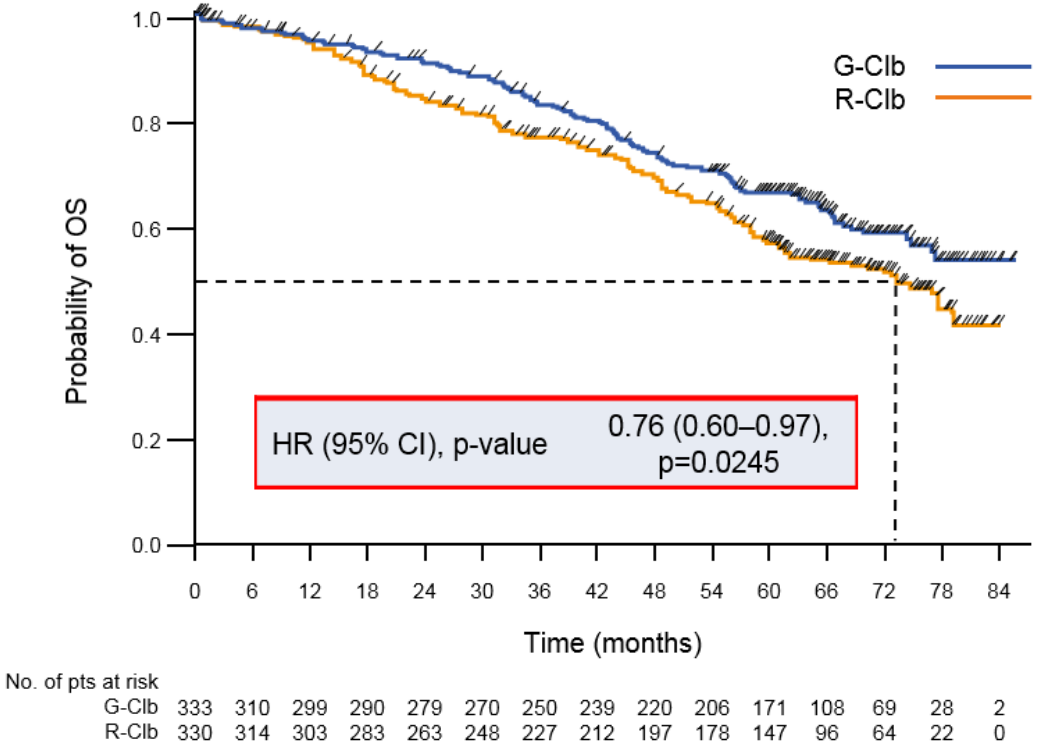
Lange Jahre Standard: Chemoimmuntherapie

CLL10: BR ist der Therapie von FCR bei fitten Patienten bzgl **PFS** unterlegen

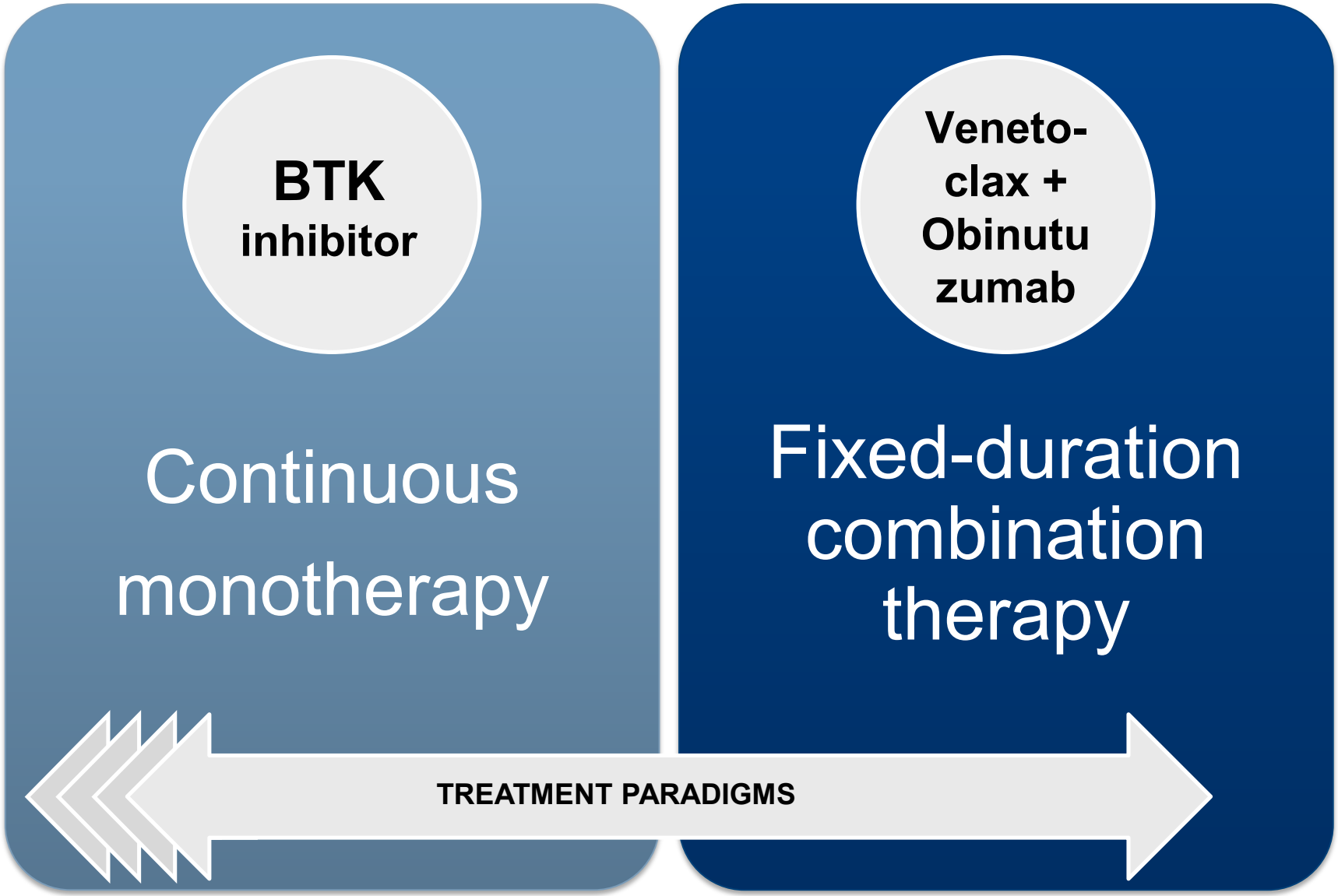


Eichhorst B et al., Lancet Oncology 2016
& Updated unpublished data

CLL11:CLB+Obinutuzumab ist CLB+R und CLB mono überlegen bzgl **OS**



Goede et al., EHA 2018


BTK inhibitor
Continuous monotherapy
Veneto-clax + Obinutu zumab
Fixed-duration combination therapy
TREATMENT PARADIGMS

BTKI Inhibitoren

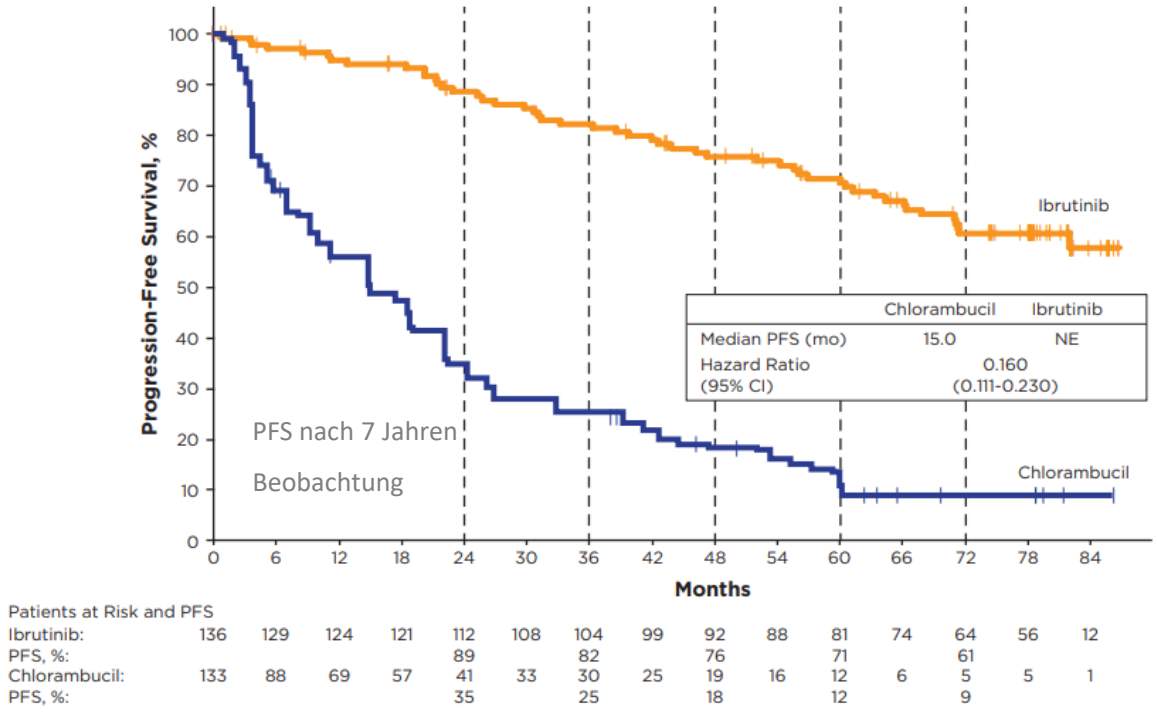
Ibrutinib

Acalabrutinib

(Zanubrutinib)

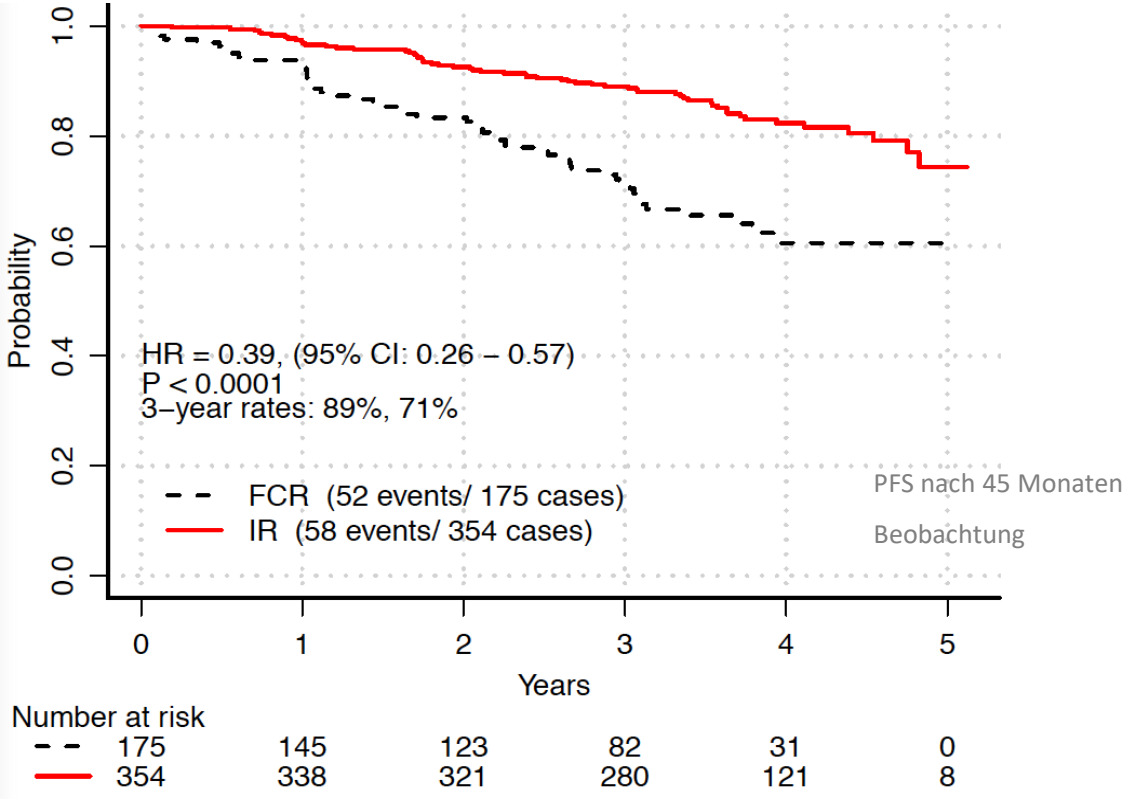
BTK INHIBITOR IBRUTINIB VS CHEMO/-IMMUNTHERAPIE: PFS

RESONATE 2-STUDIE: ERSTLINIE IBRUTINIB VS CHLORAMBUCIL BEI ÄLTEREN PATIENTEN



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

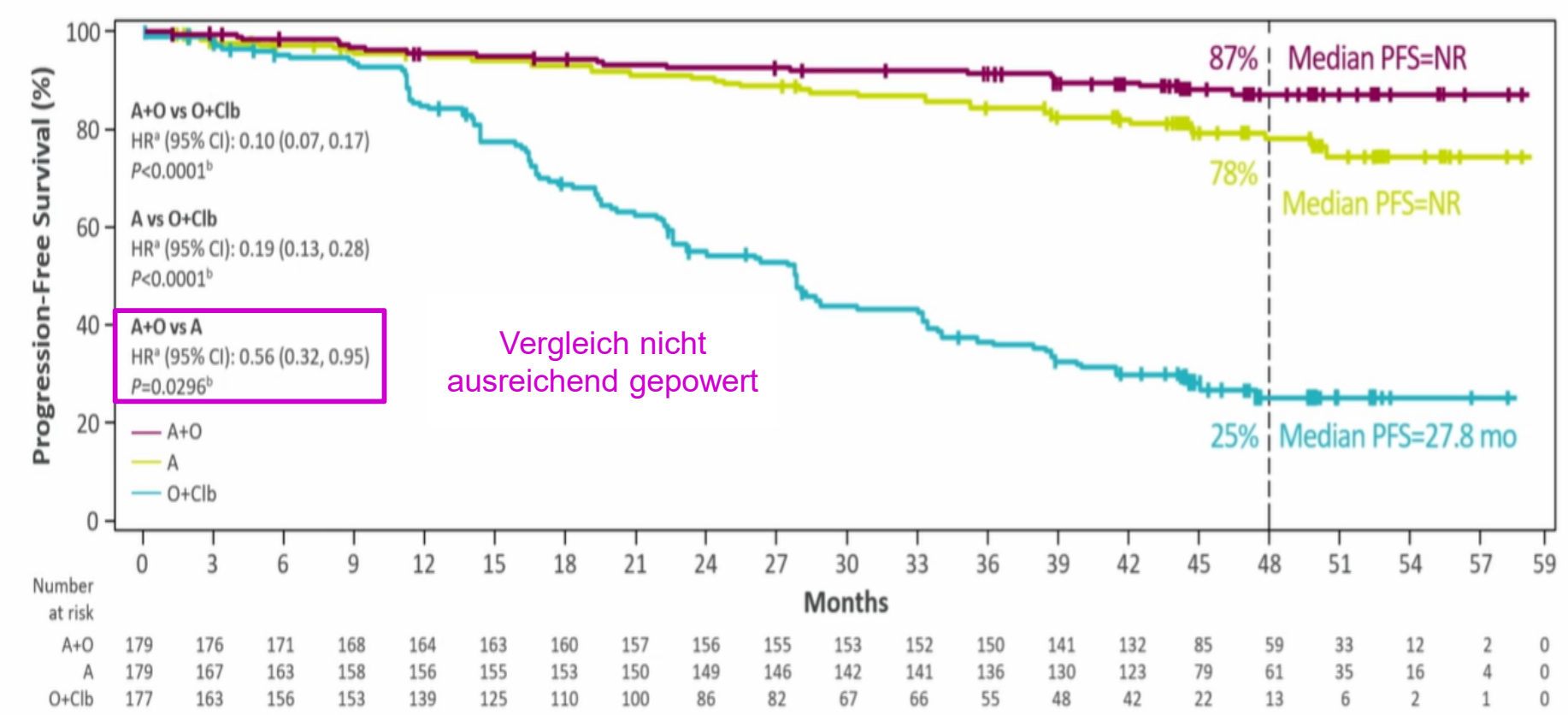
E1912-STUDIE: ERSTLINIE IBRUTINIB VS FCR BEI FITTEN PATIENTEN



Shanafelt T. et al., ASH 2019, Abstract 33

BTK INHIBITOR ACALABRUTINIB VS CHEMO/-IMMUNTHERAPIE: PFS

ELEVATE-TN STUDIE:
ERSTLINIE ACALABRUTINIB VS ACALABRUTINIB+ OBINUTUZUMAB VS CHLORAMBUCIL+ OBINUTUZUMAB BEI ÄLTEREN PATIENTEN



Sharman J. et al., EHA 2021, Abstract 148

Übersicht Phase III Studien zu zugelassenen BTK Inhibitoren mit und ohne CD20-Antikörper

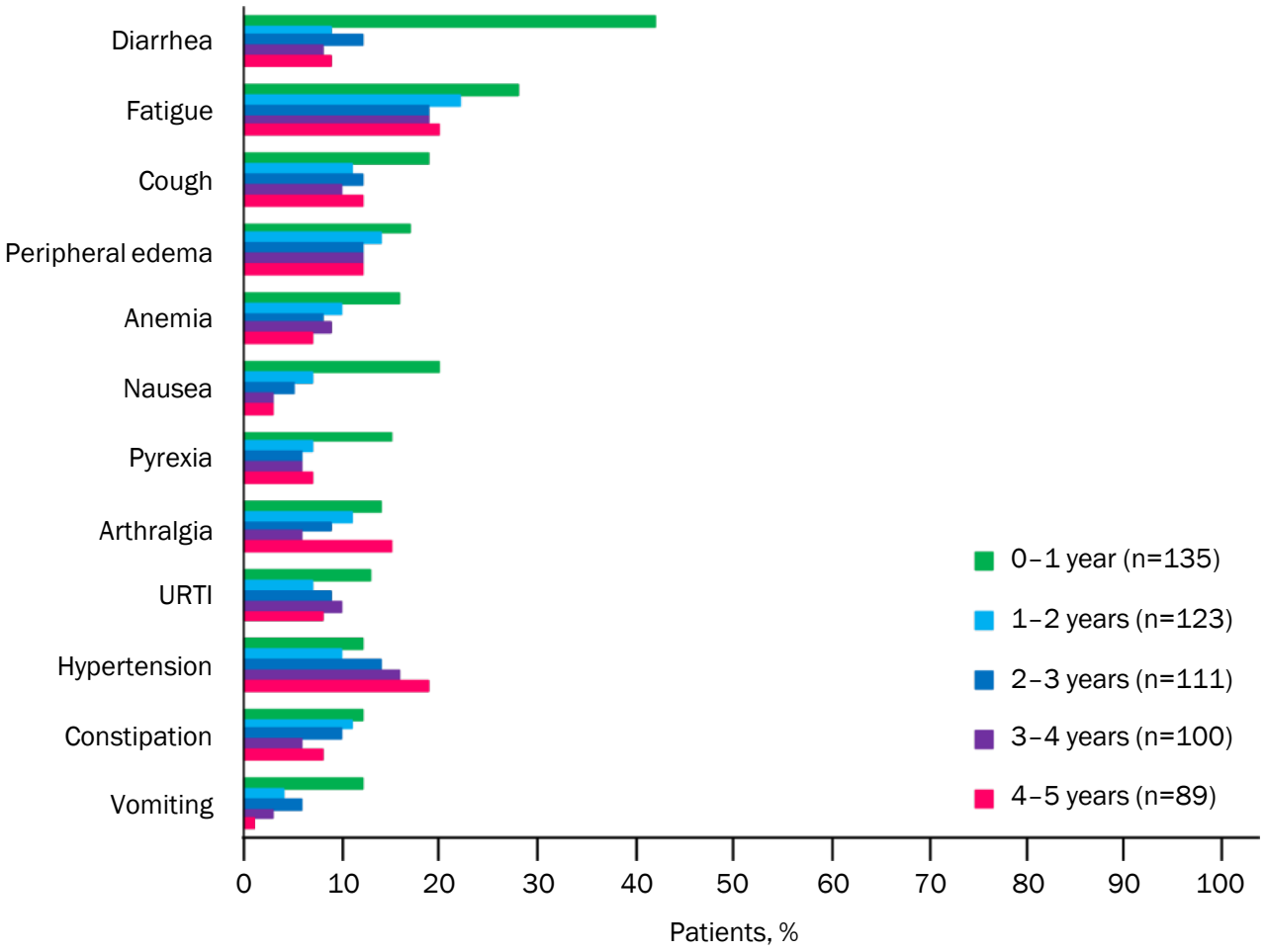
Treatment	Trial	Treatment duration	PFS rate	Reference
Ibrutinib	RESONATE II	continuous	at 60 months: 70%	Burger et al, Leukemia. 2020 34(3):787-798
Ibrutinib **Ibrutinib + Rituximab**	Alliance	continuous	at 24 months: 87% and 88%	Woyach et al., NEJM 2018;379:2517-28.
Ibrutinib + Rituximab	ECOG E1912	continuous	at 48 months: 82%	Shanafelt et al., NEJM 201) 2019;381:432-43; Shanafelt T. et al., ASH 2019, Abstract 33
Ibrutinib + Obinutuzumab	Illuminate	continuous	at 30 months: 79%	Moreno et al., Lancet Oncol 2019, 20(1):43-56
Acalabruinib **Acalabrutinib+Obinutuzumab**	ASCEND	continuous	at 24 months: 87% and 93%	Sharman et al., Lancet. 2020 Apr 18;395(10232):1278-1291

BTK Inhibitoren

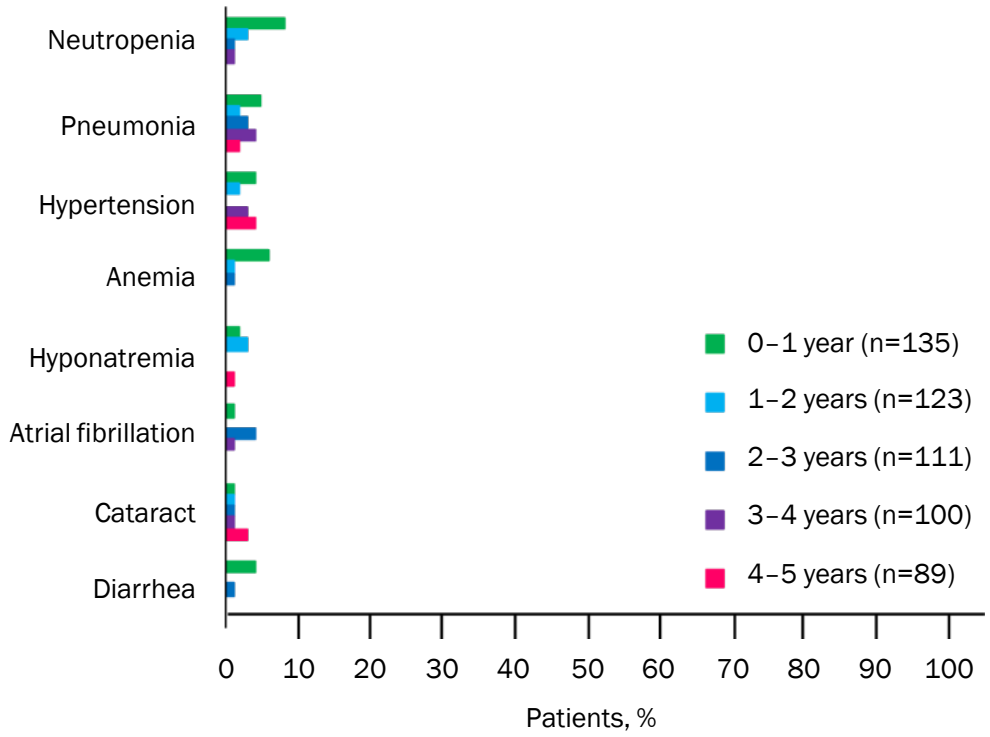
Unterschiedliches Nebenwirkungsspektrum?

AEs Over Time in Patients Treated With Ibrutinib

All AEs



Severe AEs

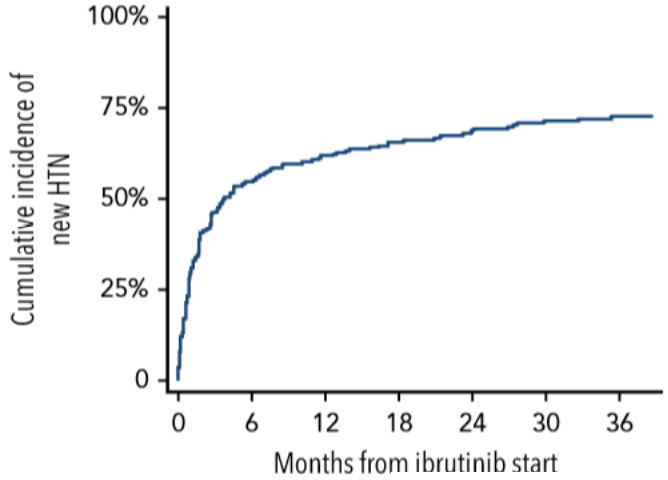


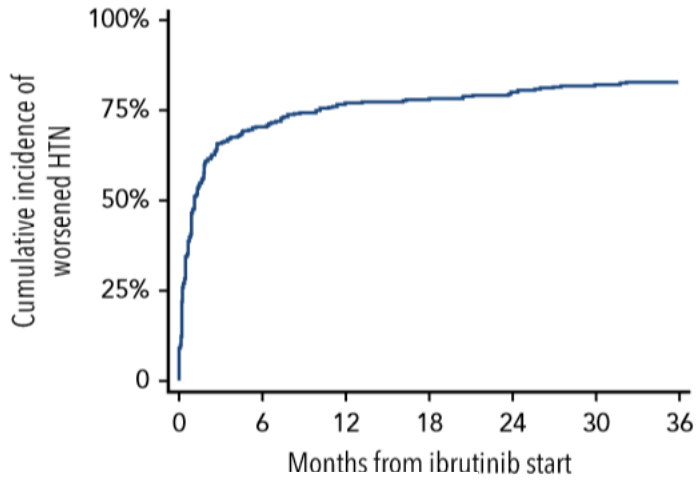
Tedeschi A, et al. *HemaSphere.* 2018;3: Abstract S107.

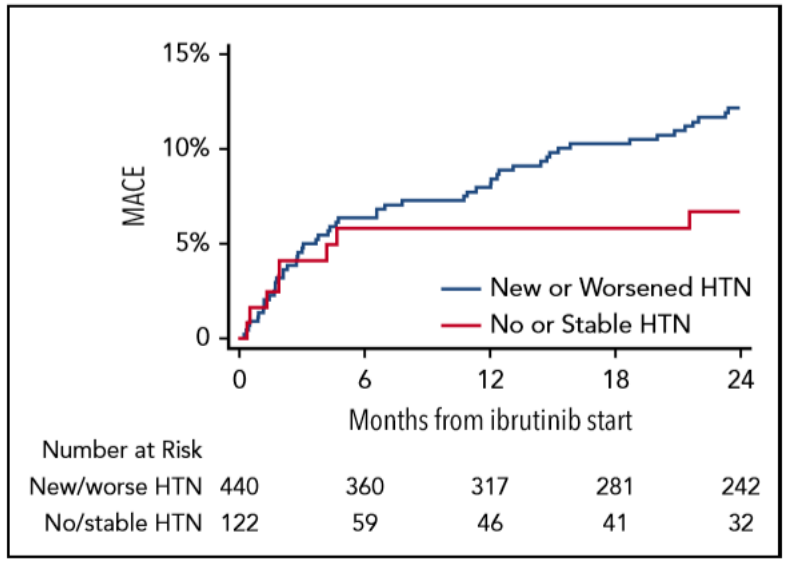
Toxicity Ibrutinib: Hypertension And Cardiovascular Events

562 patients from single center on ibrutinib therapy due to lymphoid malignancies

93 (16.5%) major cardiovascular events



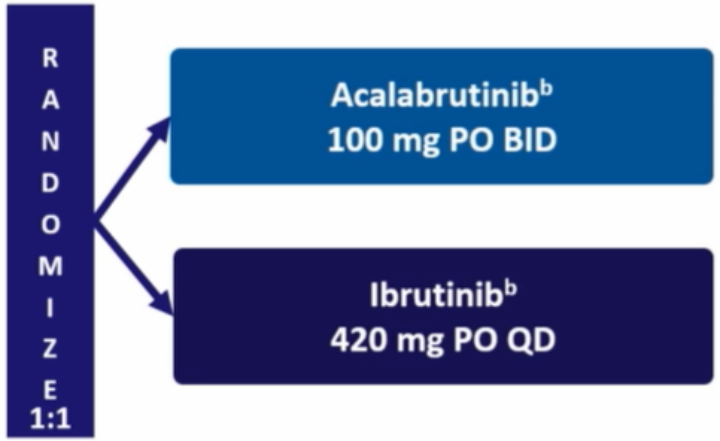


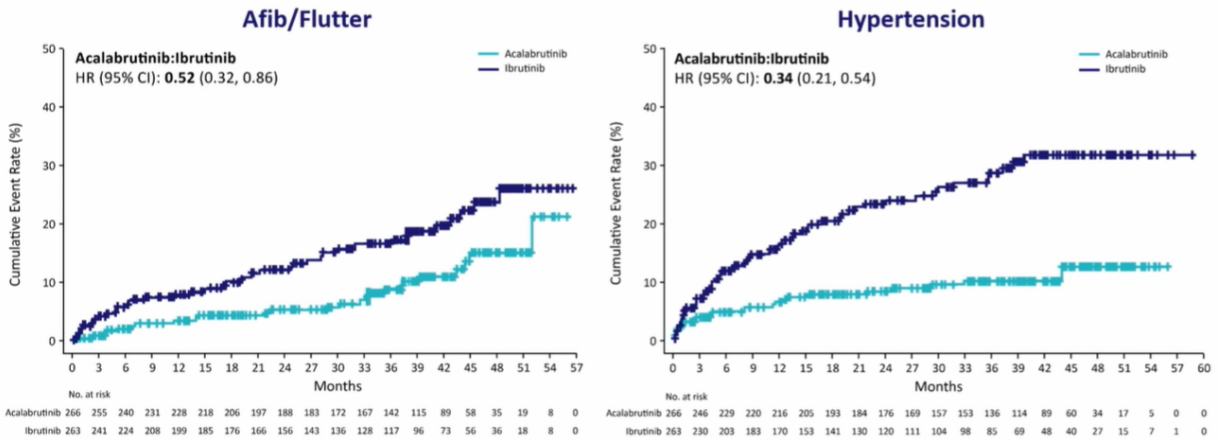


Dickerson J. et al., Blood 2019:134

Direkter Vergleich verschiedener BTK Inhibitoren (Rezidivstudien!)

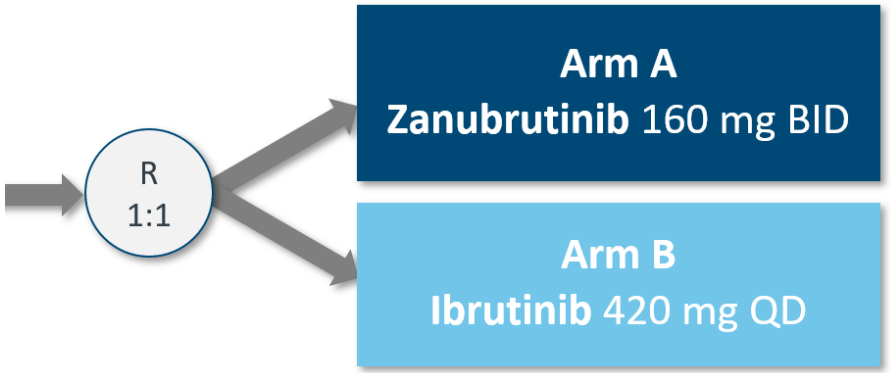
Acalabrutinib

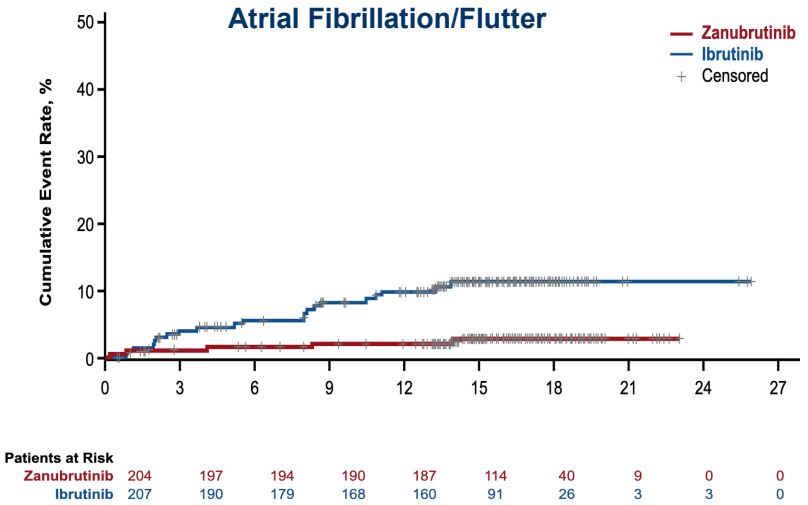




Hillmen P et al. Oral presentation. EHA 2021. Abstract S145

Zanubrutinib

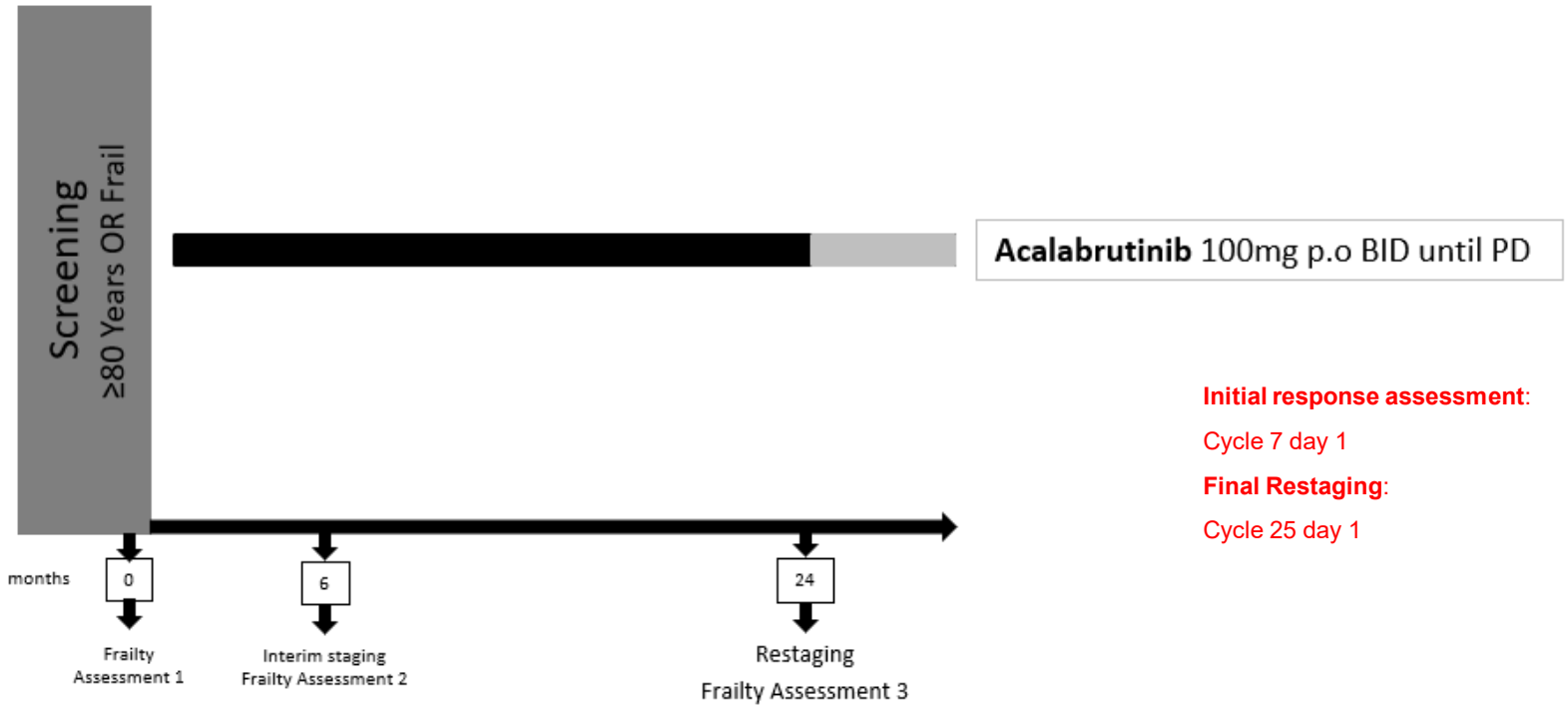




Hillmen P et al. Oral presentation. EHA 2021. LB Abstract 1900

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:

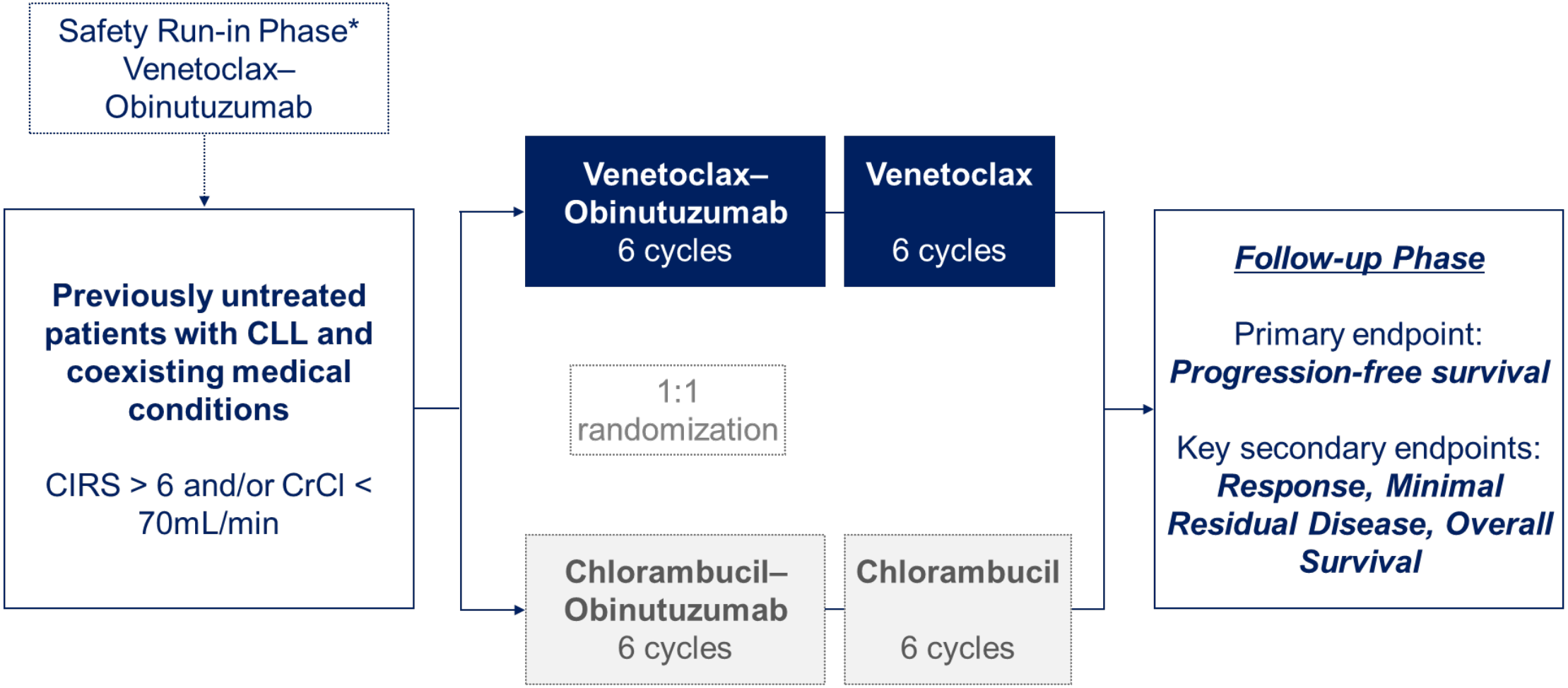
Cycle 7 day 1

Final Restaging:

Cycle 25 day 1

CLL14 Study: First line CLL, unfit pateints

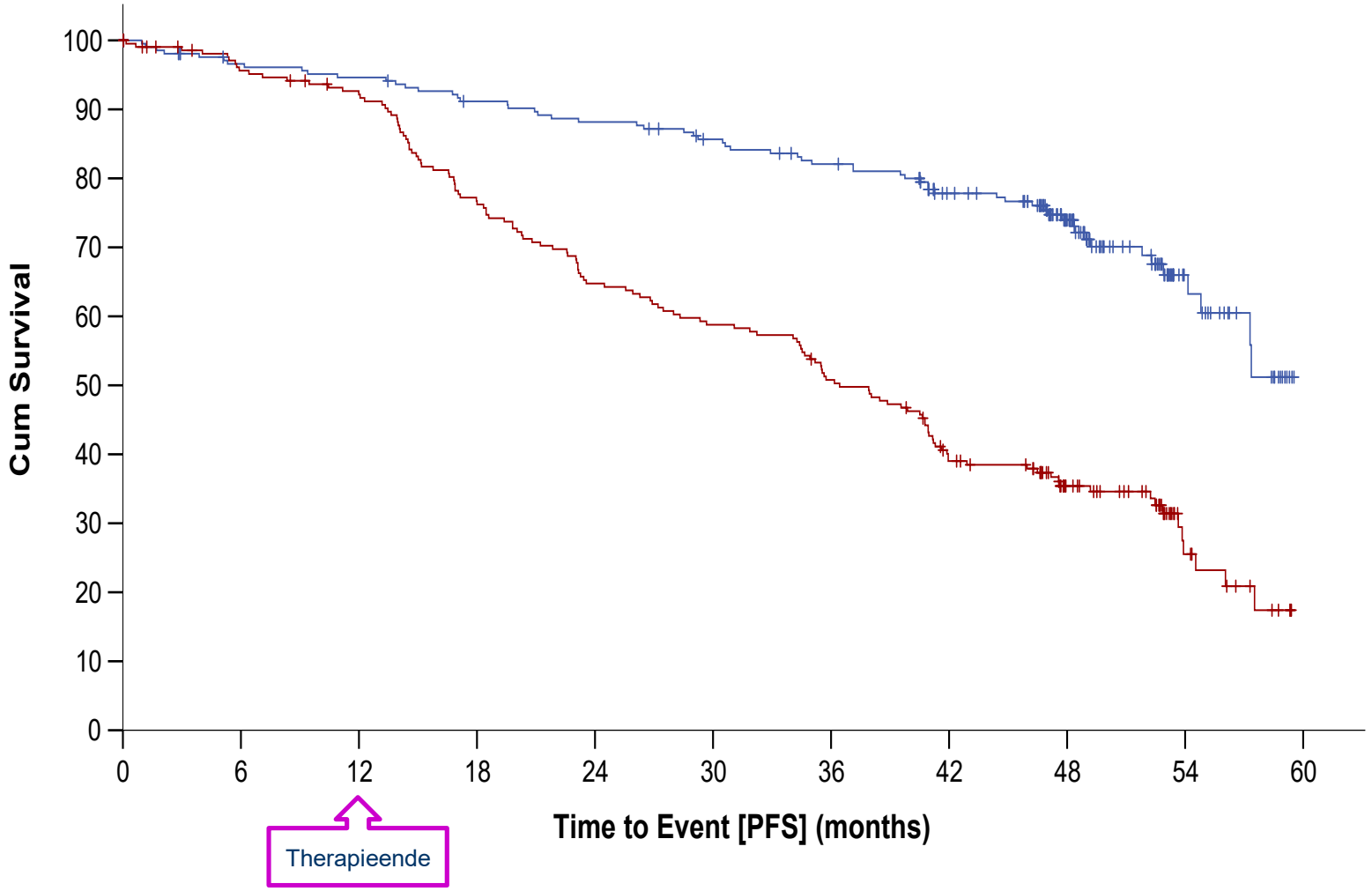
Design



Fischer K. et al. NEJM 2019; 380:225

4-YEAR FOLLOW-UP: PFS & OS

Median observation time 52.4 months



Median PFS

Ven-Obi: not reached

Clb-Obi: 36.4 months

4-year PFS rate

Ven-Obi: 74.0%

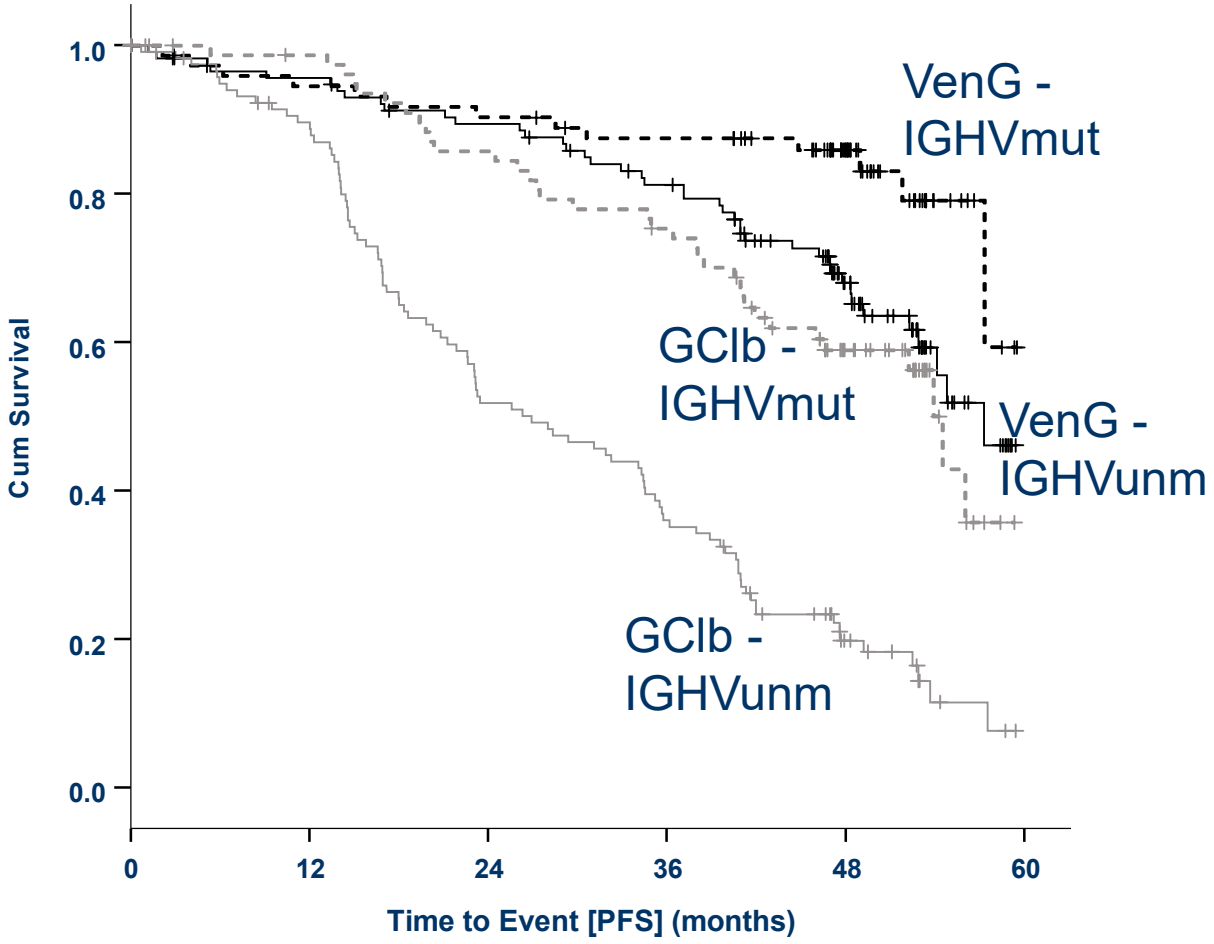
Clb-Obi: 35.4%

HR 0.33, 95% CI [0.25-0.45] **P<0.0001**

Al Sawaf O et al. Oral presentation. EHA 2021. Abstract 146

4-YEAR FOLLOW-UP: PFS & OS

Median observation time 52.4 months



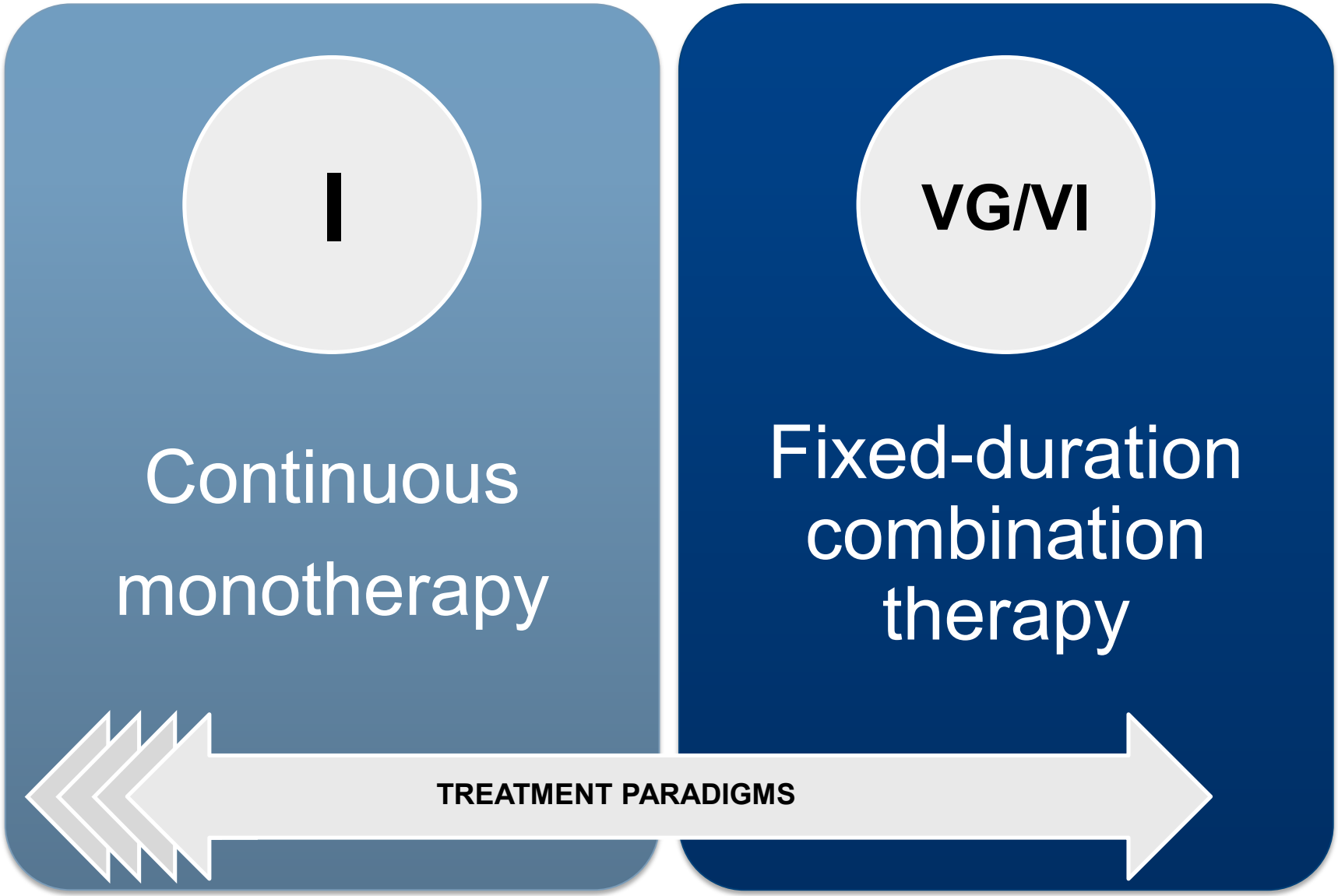
VenG vs. GClb in dependence of IGHV status

IGHVunm - VenG
IGHVunm - GClb
HR 0.25 (95%CI 0.17-0.37)

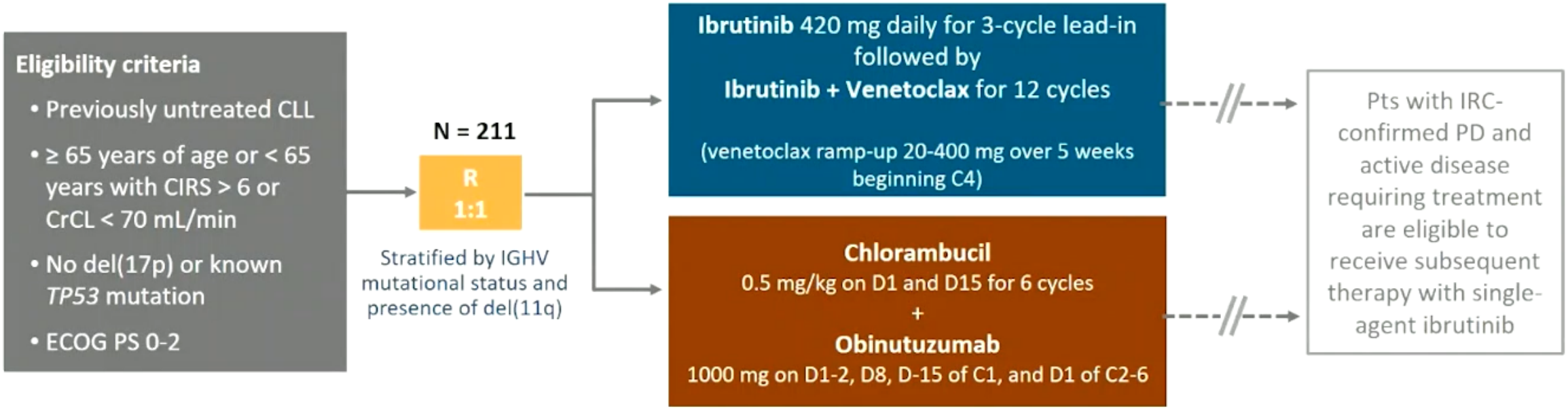
IGHVmut - VenG
IGHVmut - GClb
HR 0.36 (95%CI 0.19-0.68)

Al Sawaf O et al. Oral presentation. EHA 2021. Abstract 146

Stage	del(17p) or p53mut	Fitness	IGVH	Therapy
Binet A-B, Rai 0-II, inactive disease	Irrelevant	Irrelevant	Irrelevant	None
Active disease or Binet C or Rai III-IV	Yes	Irrelevant	Irrelevant	Ibrutinib/Acalabrutinib or Venetoclax + Obinutuzumab or Idelalisib + Rituximab (if contraindications for ibrutinib)*
	No	Go go	M	FCR (BR above 65 years) or Ibrutinib or Venetoclax + Obinutuzumab*
			U	Ibrutinib or FCR (BR above 65 years) or Venetoclax + Obinutuzumab*
		Slow go	M	Venetoclax + Obinutuzumab or Chlorambucil + Obinutuzumab or Ibrutinib/Acalabrutinib*
			U	Venetoclax + Obinutuzumab or Ibrutinib/Acalabrutinib or Chlorambucil + Obinutuzumab*


I
Continuous monotherapy
VG/VI
Fixed-duration combination therapy
TREATMENT PARADIGMS

Kombination BTK Inhibitor Ibrutinib + Bcl2 Inhibitor Venetoclax

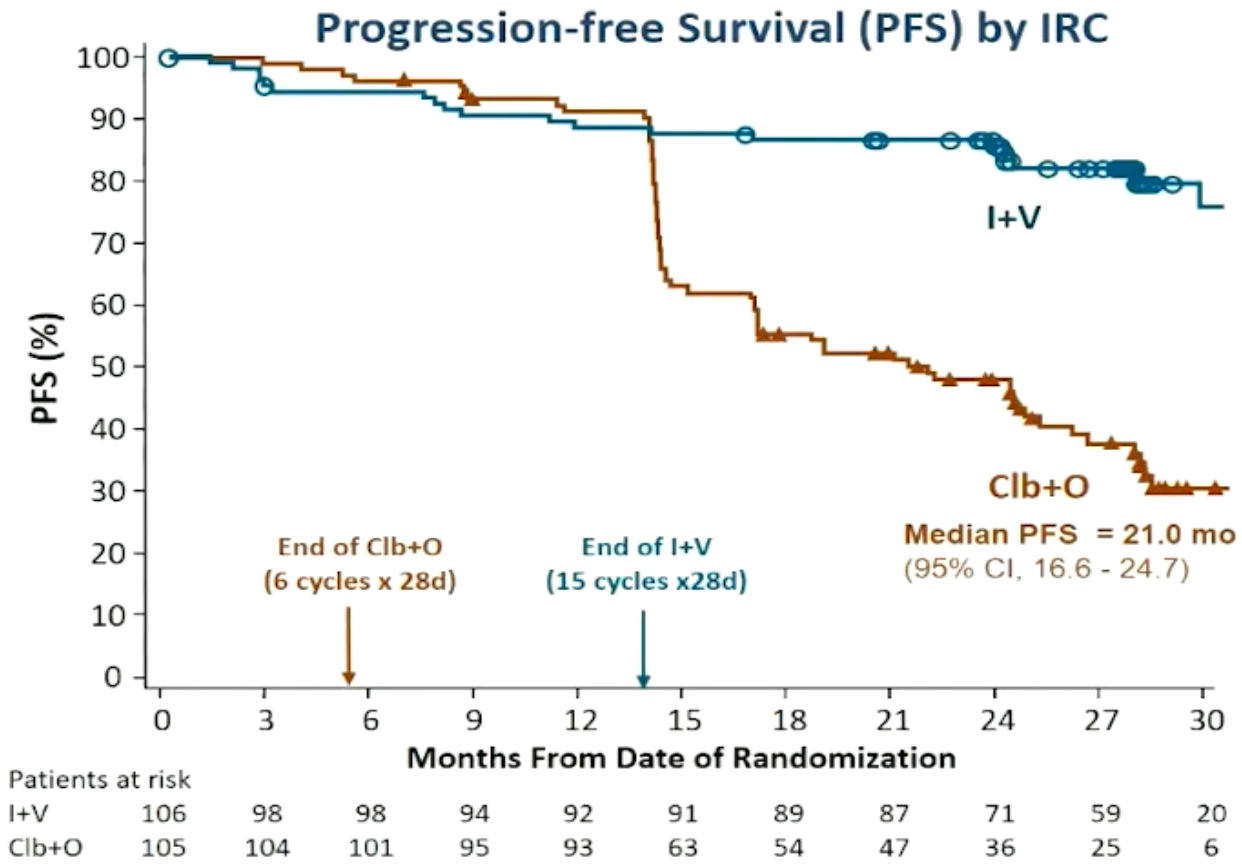


Primary end point: Progression-free survival by independent review committee (IRC)

- 71 PFS events to detect an effect size with an HR = 0.5 (80% power at a 2-sided significance level of 0.05)

Kater et al. , EHA 2021. Abstract LBA 1902

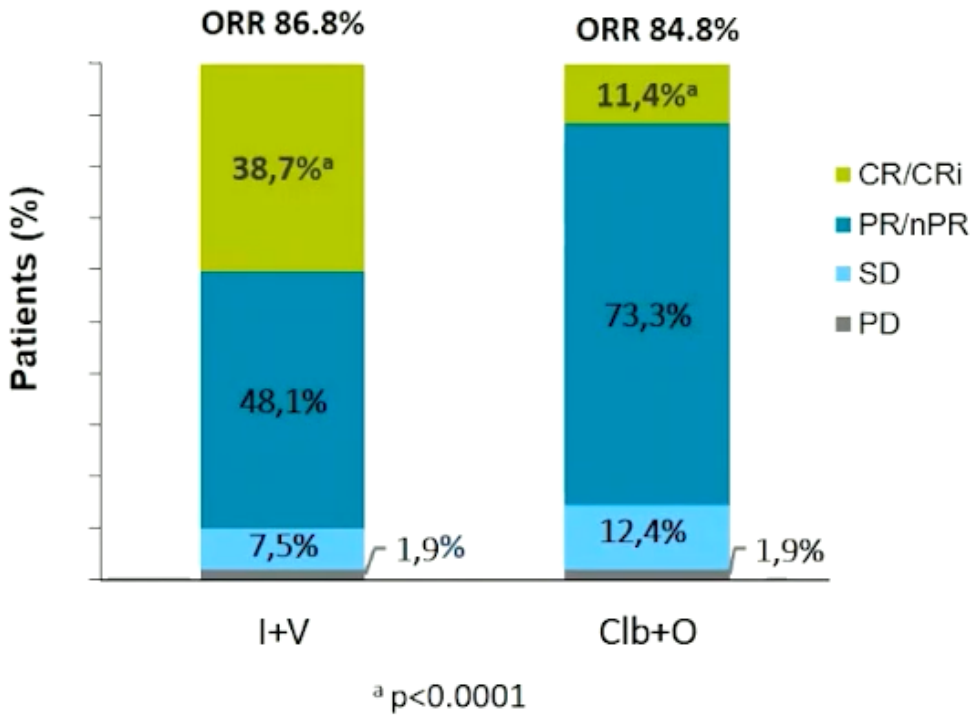
Glow-Studie (IV vs. ClbObin): PFS nach 27.7 Monaten



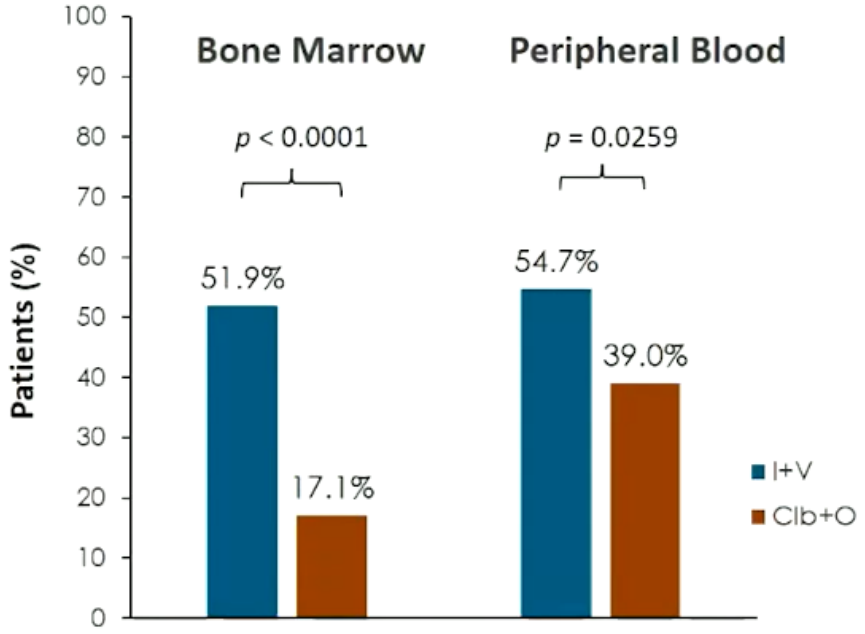
Kater et al. , EHA 2021. Abstract LBA 1902

Glow-Studie (IV vs. ClbObin): Ansprechen nach IWCLL und MRD

Ansprechen nach IWCLL



Ansprechen nach MRD (Flow und NGS, Cutoff 10 -4)



Kater et al. , EHA 2021. Abstract LBA 1902

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

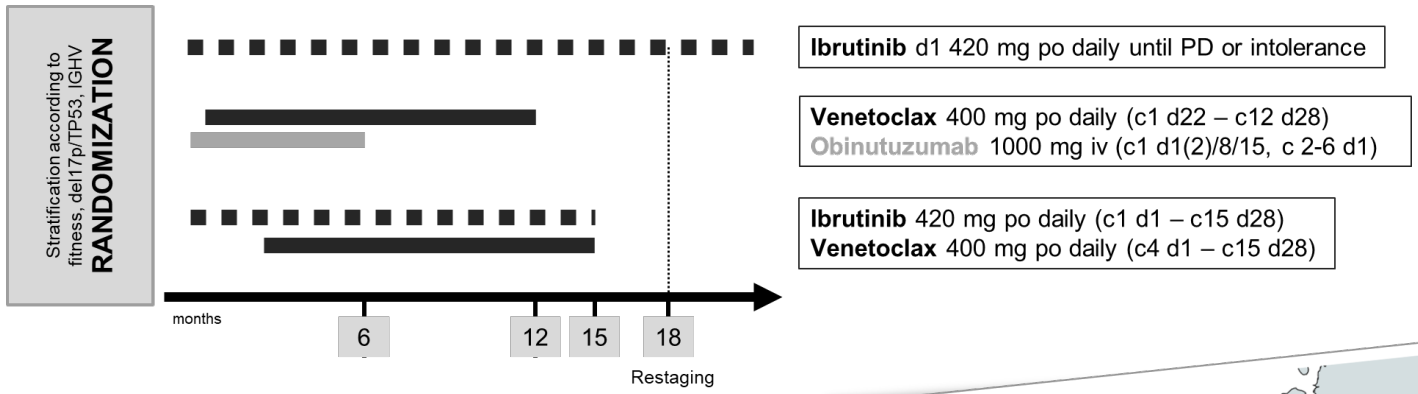
Stratification according to fitness, del17p/TP53, IGHV

Ibrutinib	**Venetoclax Obinutuzumab**	**Venetoclax Ibrutinib**

897 patients

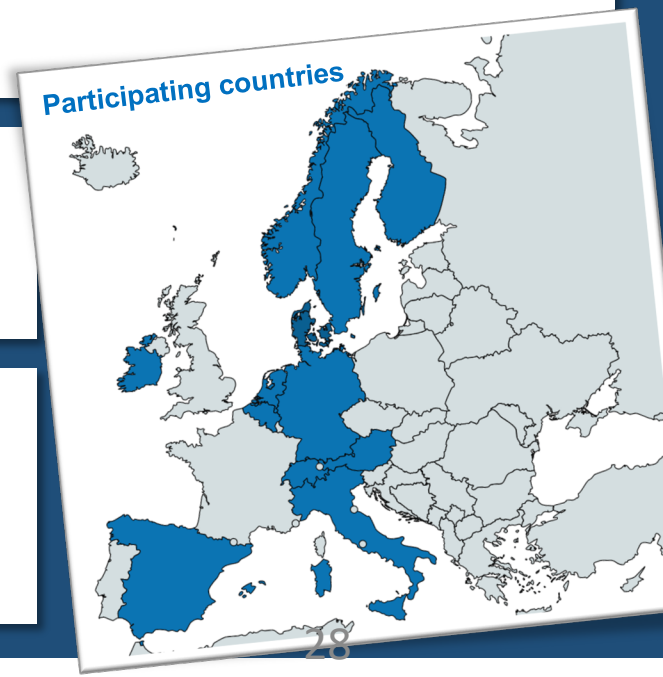
Primary endpoint:
Progression-free survival

TREATMENT SCHEDULE



TIMELINES

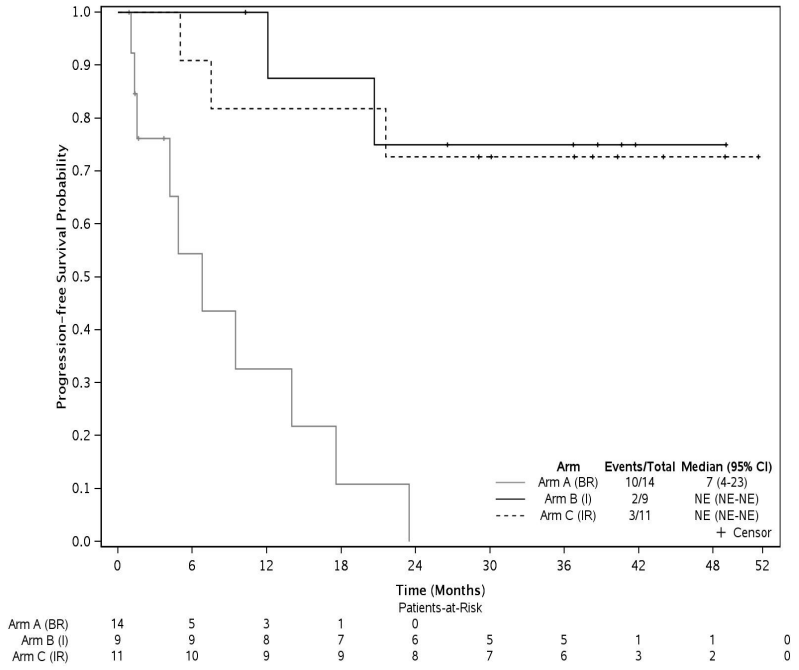
Start of recruitment	Q4/2020
Expected end of recruitment	Q4/2023
End of study	Q1/2027



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

Ibrutinib Dauertherapie

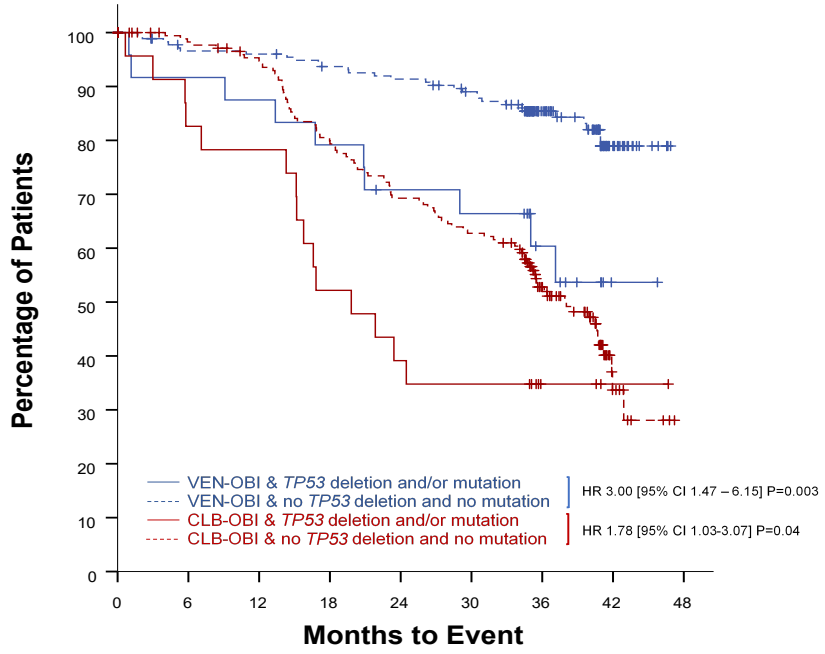
Alliance: PFS BR vs I vs I+R bin patients with *TP53*



Woyach et al., NEJM. 2018; 379: 2517–2528.
DOI: 10.1056/NEJMoa1812836

Venetoclax + Obinutuzumab

CLL14: PFS according to *TP53* Status



Al-Sawaf et al., EHA. 2020; Abstract #S155.

Therapieindikation Rezidiv

Erst bei **symptomatischen** Progreß

Rezidivtherapie:
Faktoren zur Überlegung zur Wahl der Therapie

Vorherige Therapie:
Ansprechen
Verträglichkeit

Genetische Evolution:
Neue TP53 Veränderung
Resistenzmutation

Begleiterkrankung und Begleitmedikation

Optimale Therapiesequenz

Übersicht Rezidivtherapie mit Ziel-gerichteten Substanzen

Treatment	Trial name	PFS HR (CI)	OS HR (CI)	Reference
Ibrutinib Ofatumumab	RESONATE 1	0.133 (0.099-0.178)	0.591 (0.378-0.926)	Byrd et al., Blood 2019; 133(19):2031–2042.
Acalabrutinib BR/Idelalisib + rituximab	ASCEND	0.31 (0.20-0.49)	0.84 (0.42-1.66)	Ghia et al., JCO. 2020; 38:(25): 2849–2861.
Idelalisib + rituximab Placebo + rituximab	116	0.15 (0.08–0.28)	0.8 (0.5 - 1.1)	Sharman et al., JCO. 2019; 37(16): 1391–1402.
Venetoclax + rituximab BR	MURANO	0.13 (0.05-0.29)	0.48 (0.25-0.90)	Seymour et al., NEJ. 2018; 378(12): 1107–1120.

Rezidivtherapie: Therapiesequenz

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(1): 65–75.
BCR inhibitor	Ventoclax	26	74%	n.r. after 17 mo.	Mato et al., Ann Onco.l 2017; 28(5): 1050 - 1056.
Ven → BCRi					
VenetoclaxR	Ibrutinib	18	100%	-	Harrop, et al. ASH 2020; Abstract 3139
Venetoclax	Ibrutinib/Acalabrutinib	44	84%	32 mo.	Mato et al., ASH 2019; Abstract 502
VenR → Ven					
VenentoclaxR	Venetoclax	32	72%	-	Harrop, et al. ASH 2020; Abstract 3139

BCRi = B-cell receptor inhibitor, here ibrutinib or idelalisib; n.r. not reched.

DCLLSG Clinical Trials Juni 2021

DEUTSCHE STUDIENGRUPPE

Planned

CLL16
Treatment naive High Risk
Venetoclax-Obinutuzumab vs
Acalabrutinib-Venetoclax-
Obinutuzumab
Q4/2021

CLL LOXO
Pirtobrutinib vs
Pirtobrutinib+Venetoclax for
relapsed CLL

CLL ReVenG
Venetoclax-Obinutuzumab
retreatment for relapsed CLL
Q4/2021

CLL Y1-TOSO
Anti-FCμR CAR-T cells in CLL
Q2/2022

Recruiting

CLL17
Treatment Naive
Ibrutinib vs Venetoclax-
Obinutuzumab vs Ibrutinib-
Venetoclax

CLL-Frail
Very old or frail
Acalabrutinib

CLL2-BZAG
Relapse
Benda Debulking, Obi-Ven-
anubrutinib Induction, Obi-Ven-Z
Maintenance

CLL2-BAG
Relapse
Benda Debulking,Obi-Ven-
ZAnunrutinib Induction, Obi-Ven-Z
Maintenance

CLL-RT1
Richter's Transformation
Zanubutinib plus Tislelizumab

Follow-up

CLL12
Risk of Early Progression
Ibru vs. Placebo
Low Risk Watch&Wait

CLL13
Go Go
FCR/BR vs Ven-R vs Ven-Obi vs Ven-
Obi-Ibru

CLL14
Slow Go
Ven-Obi vs CLB-Obi

CLL2-BAAG
Relapse
Benda Debulking, Obi-Ven-
calabrutinib Induction, Obi-Ven-A
Maintenance

CLL2-GIVe
High Risk
17p(del)+ TP53 mut:
Ven-Obi-Ibru

CLL2-BCG
Relapse 17pdel, TP53mut
Benda Debulking,Idela+Obi
Induction, Idela+Obi Maintenance

CLLR 3
Relapse
Max. 3 Pretreatments
Induction: Benda-Obinutuzumab
Obi- Maintenance

International trials in cooperation with collaborative/academic partners in other countries

GCLLSG Registry
All patients with CLL, SLL, B-PLL, T-PLL, LGL, Richter's Syndrome, HCL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Thank you!