DEUTSCHE STUDIENGRUPPE

Chronische lymphatische Leukämie (CLL)

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Sommersymposium 2022

21. Mai 2022

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

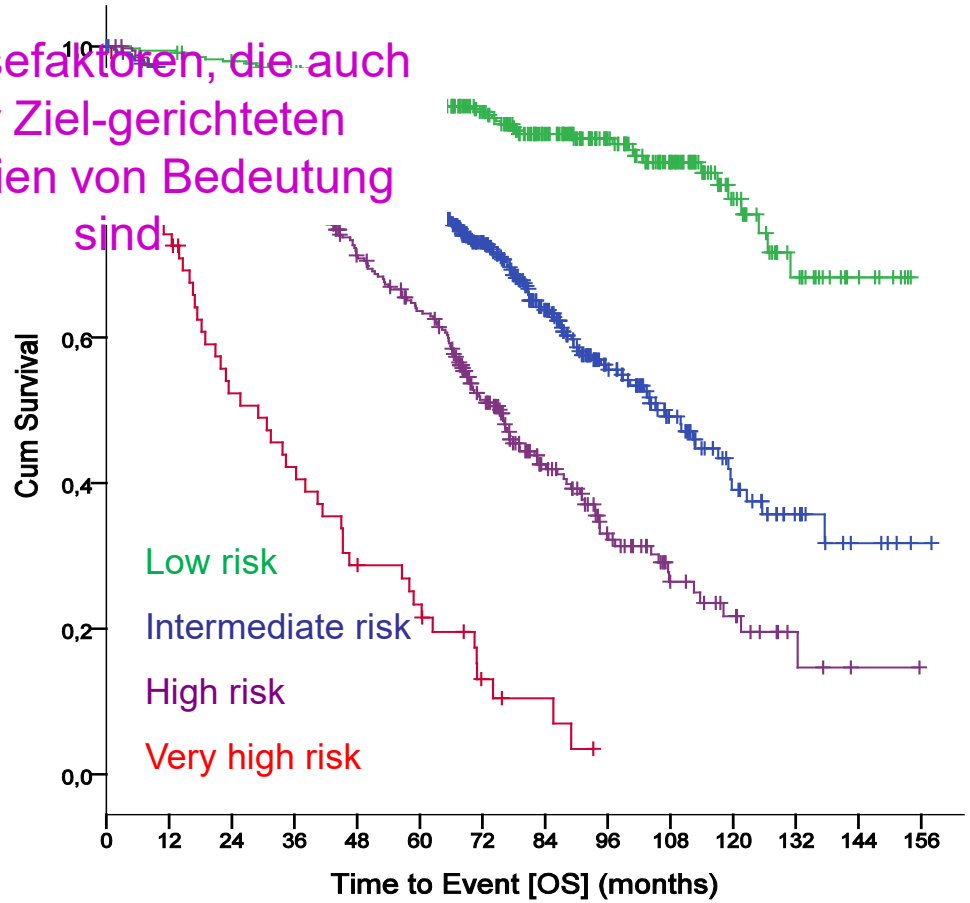
Prognosescore: CLLIPI

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

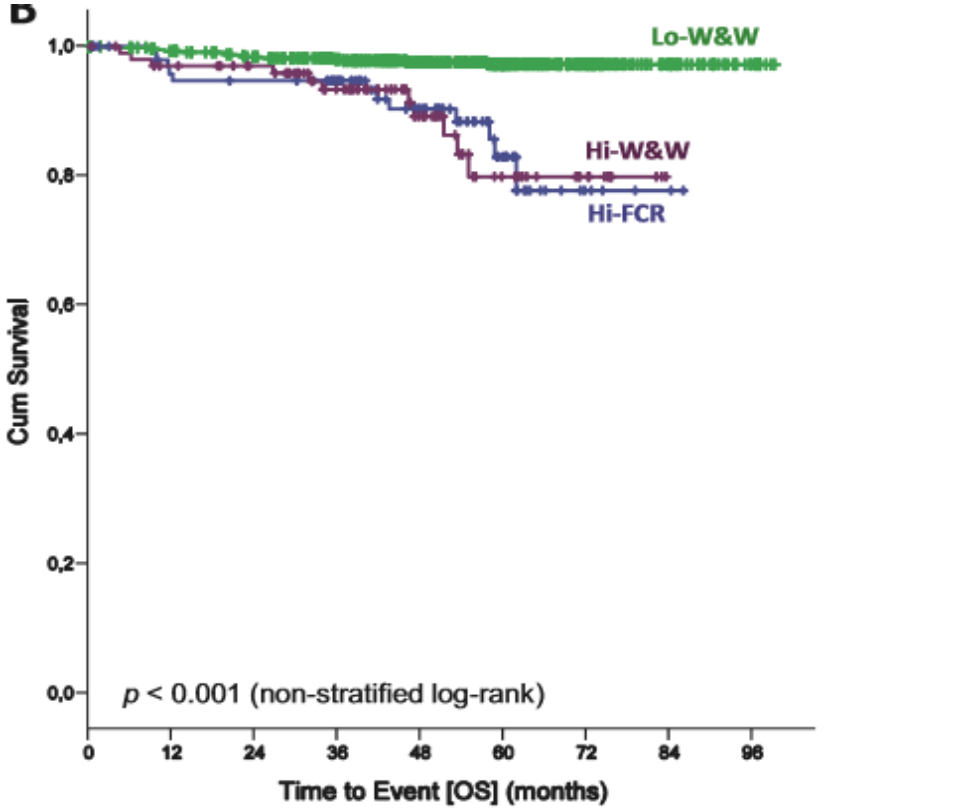
Keine Indikation im frühen, asymptomatischen

Binetstadium A oder B !

Frühes asymptomatisches Stadium:

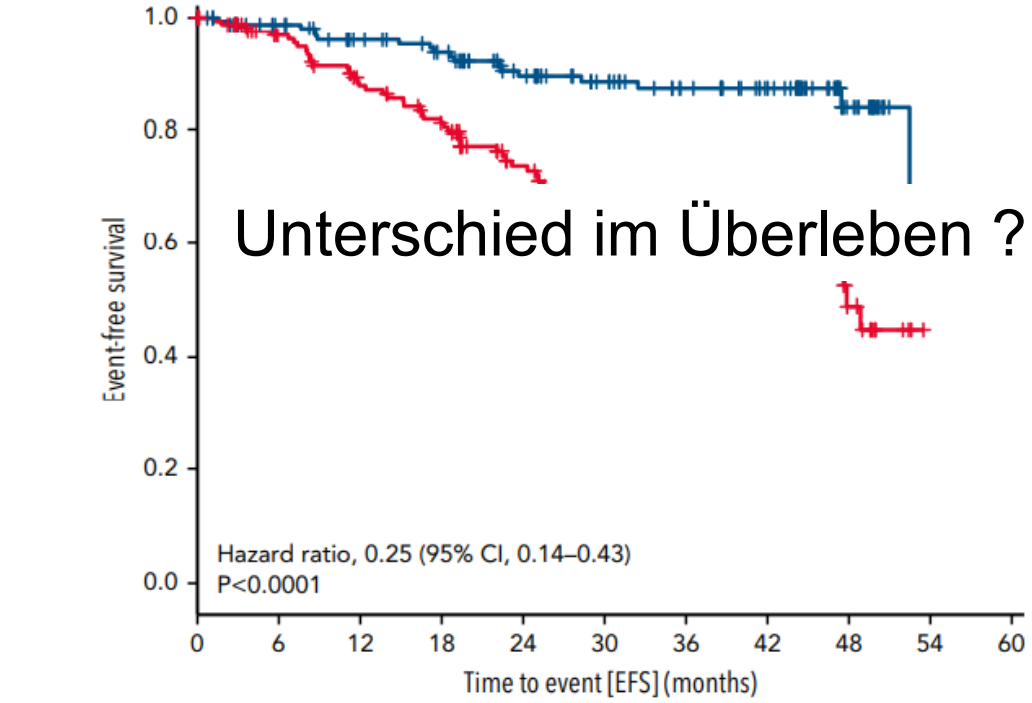
Kein Benefit durch frühzeitigen Start einer CIT bei HR. Aber evtl. mit Ibrutinib?

Herling CD et al., Leukemia. 2020; 34:2038-2050



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

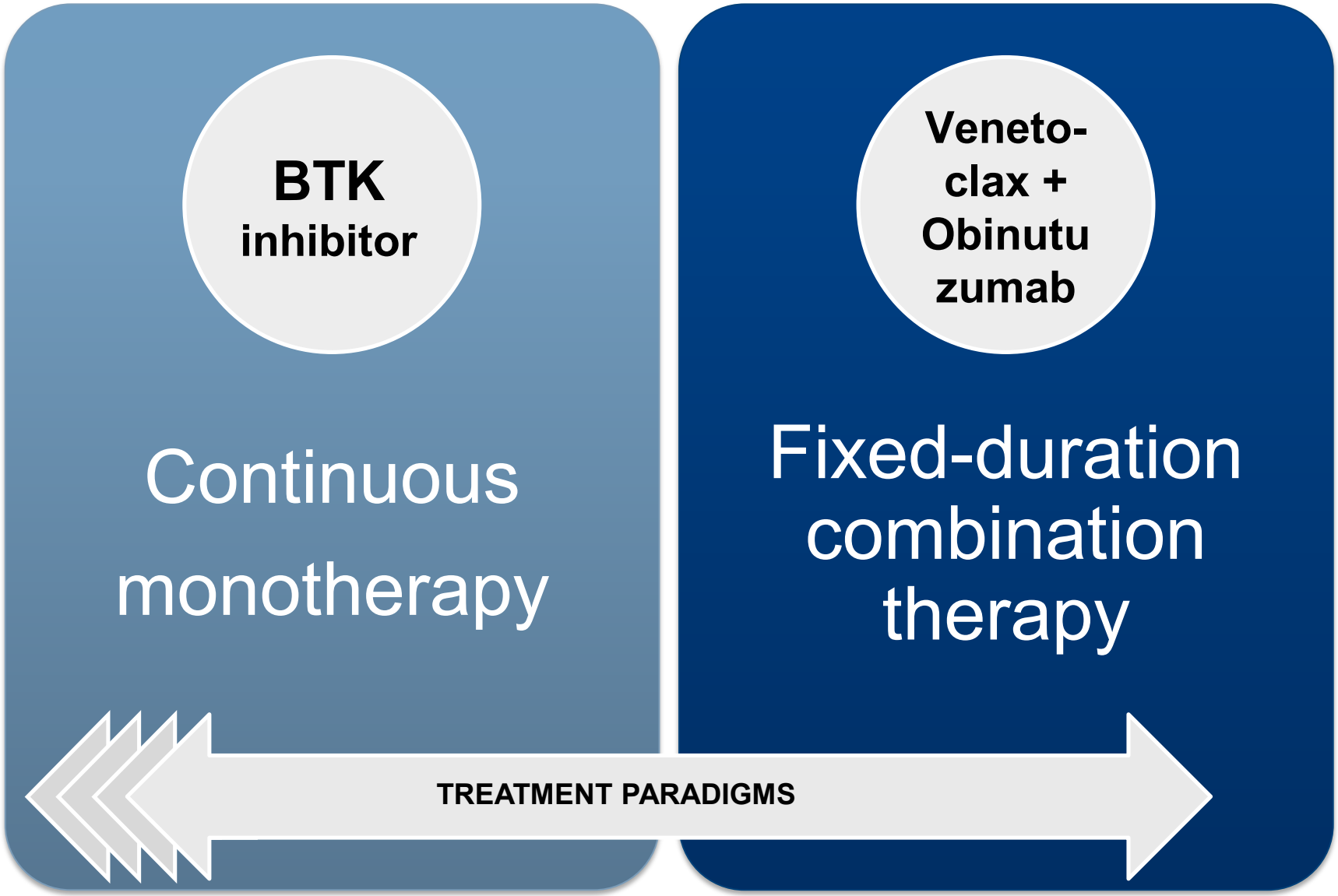


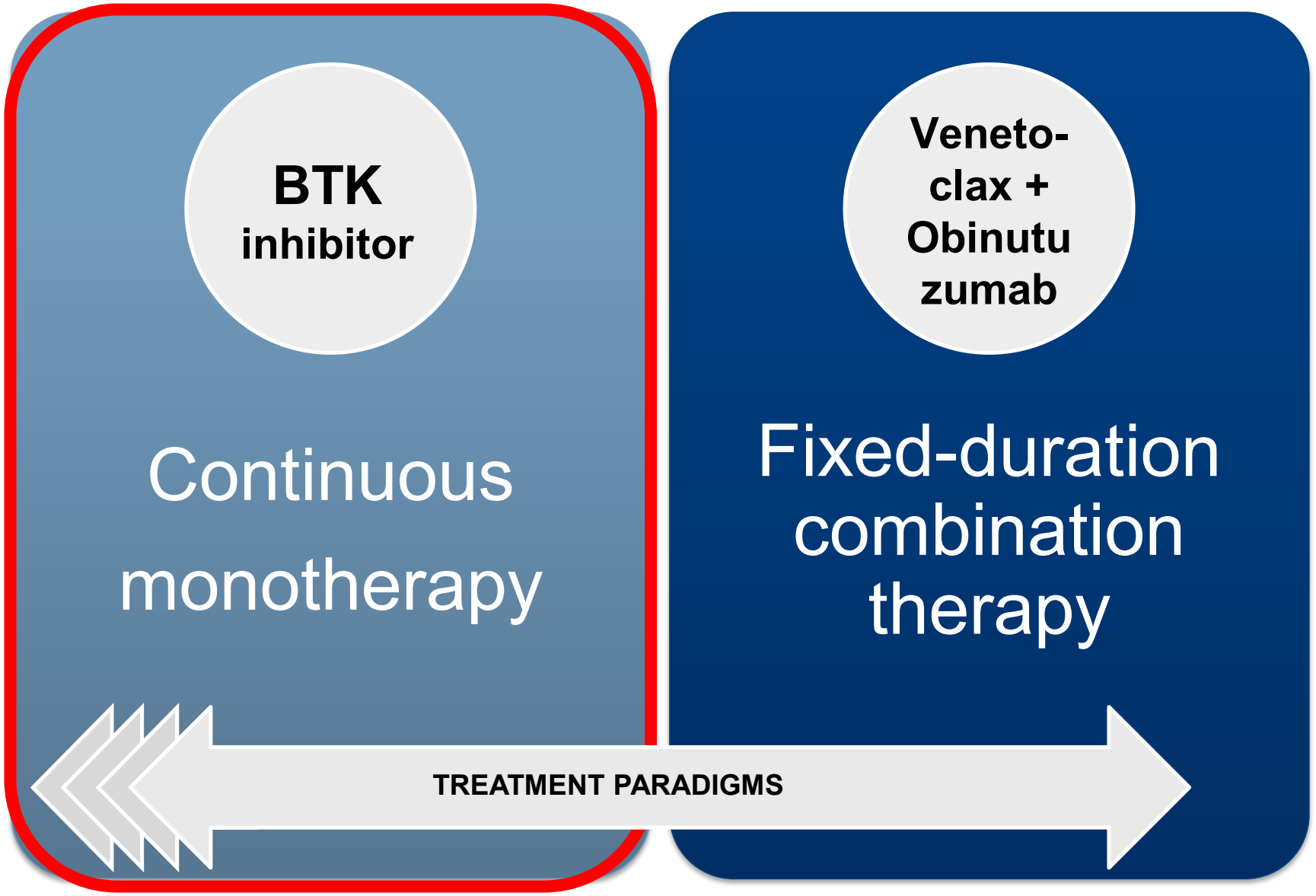
Patients at risk									
Ibrutinib	182	145	130	121	99	83	71	59	21
Placebo	181	141	122	108	83	64	45	33	13

Erstlinientherapie fortgeschrittenes Stadium

Symptomatisches

Binetstadium A oder B und Binet C


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


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

BTK Inhibitoren

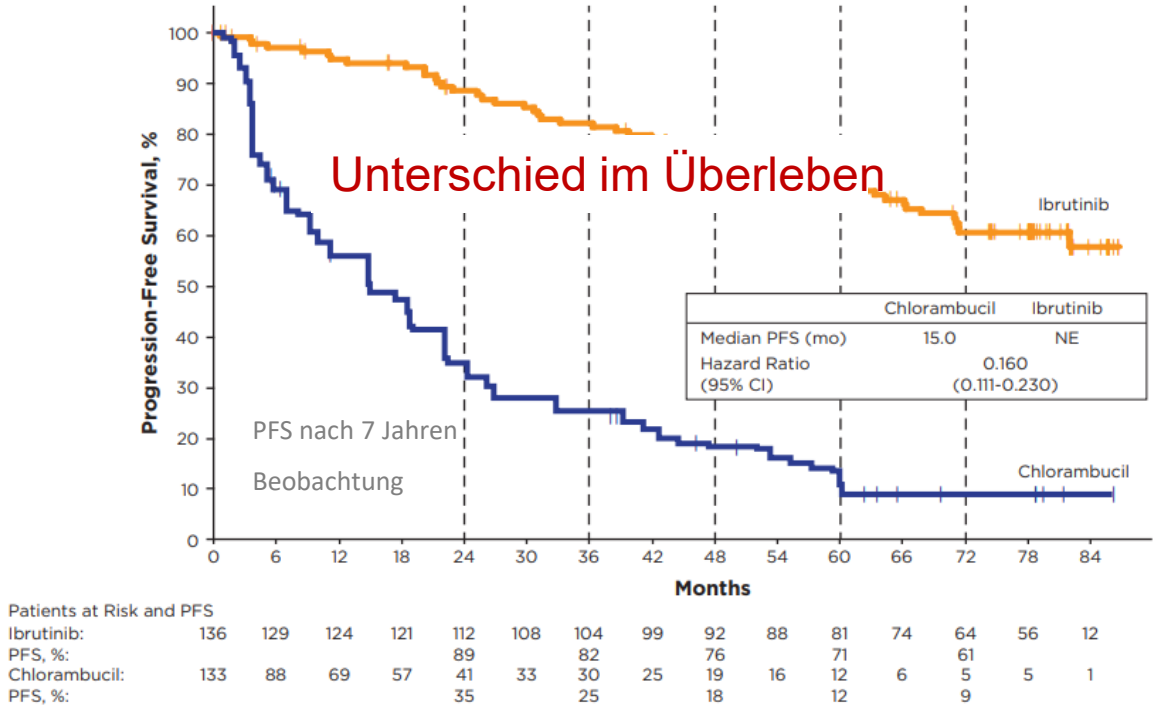
Ibrutinib

Acalabrutinib

(Zanubrutinib)

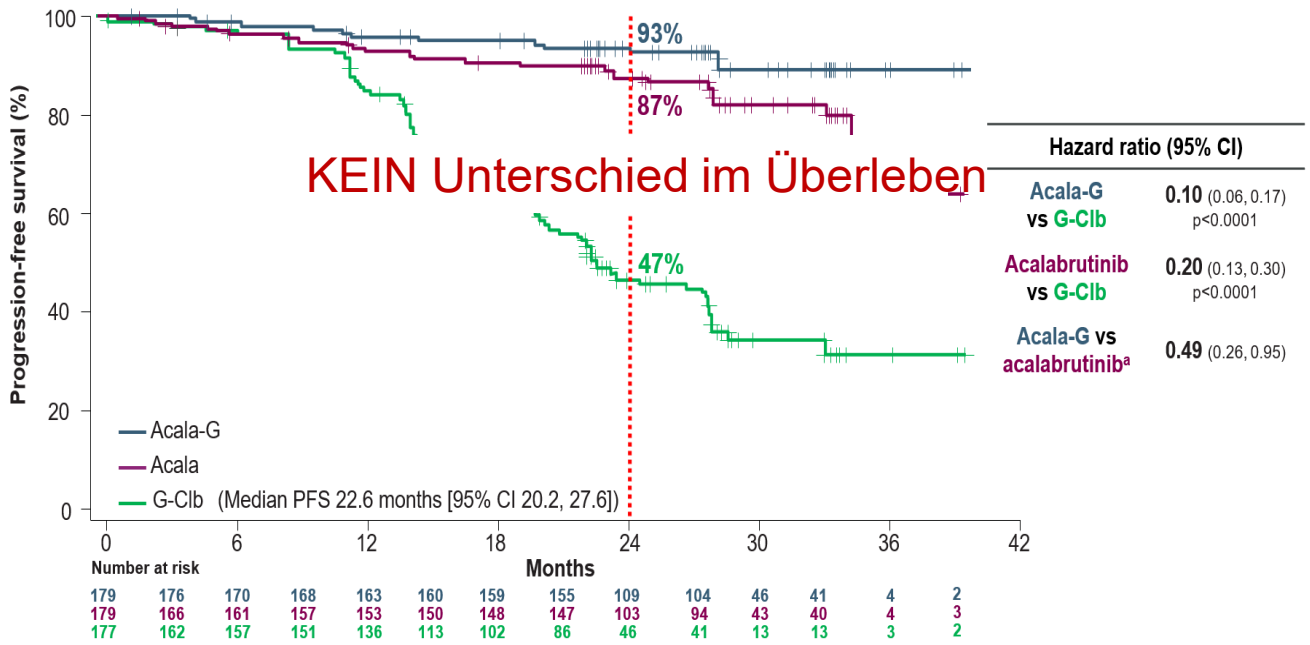
BTK Inhibitoren in der Erstlinientherapie **älterer** Patienten

RESONATE 2-Studie: Erstlinie Ibrutinib vs Chlorambucil bei älteren Patienten



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

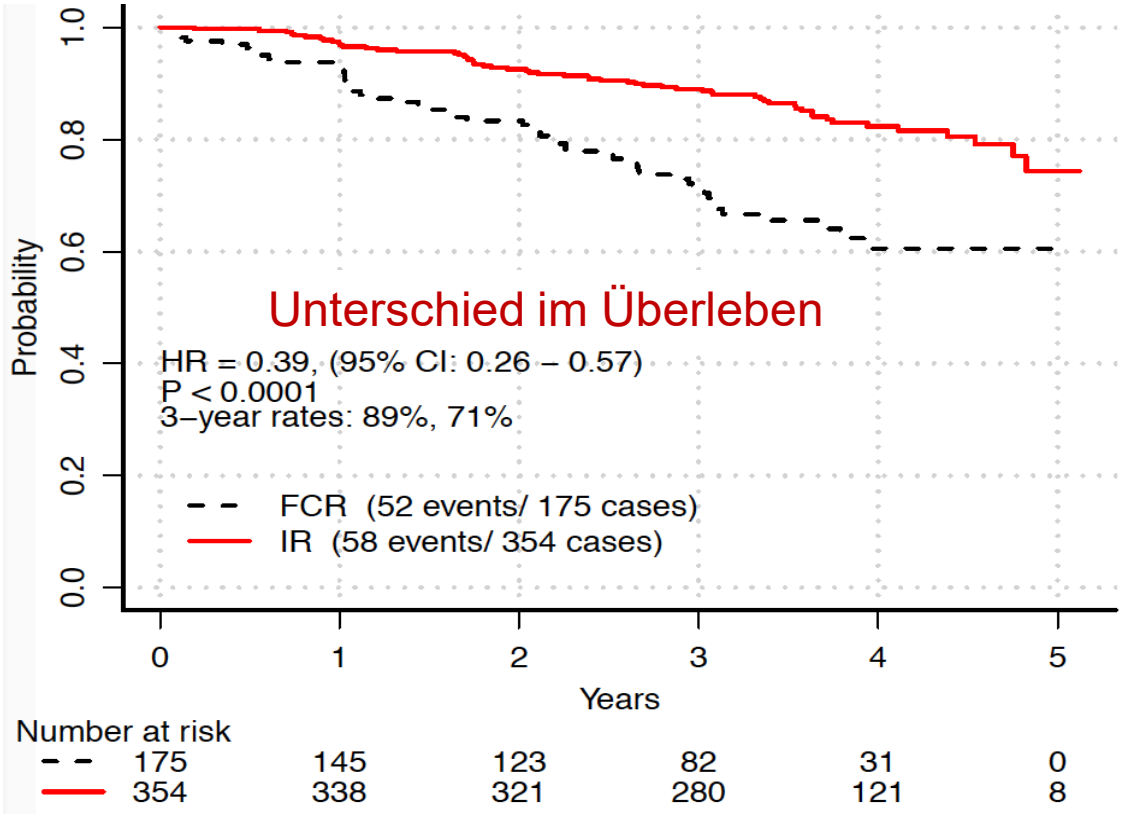
ELAVATE TN Studie: Acalabrutinib vs Acalabrutinib + Obinutuzumab vs. CLB + Obinutuzumab bei älteren Pat



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

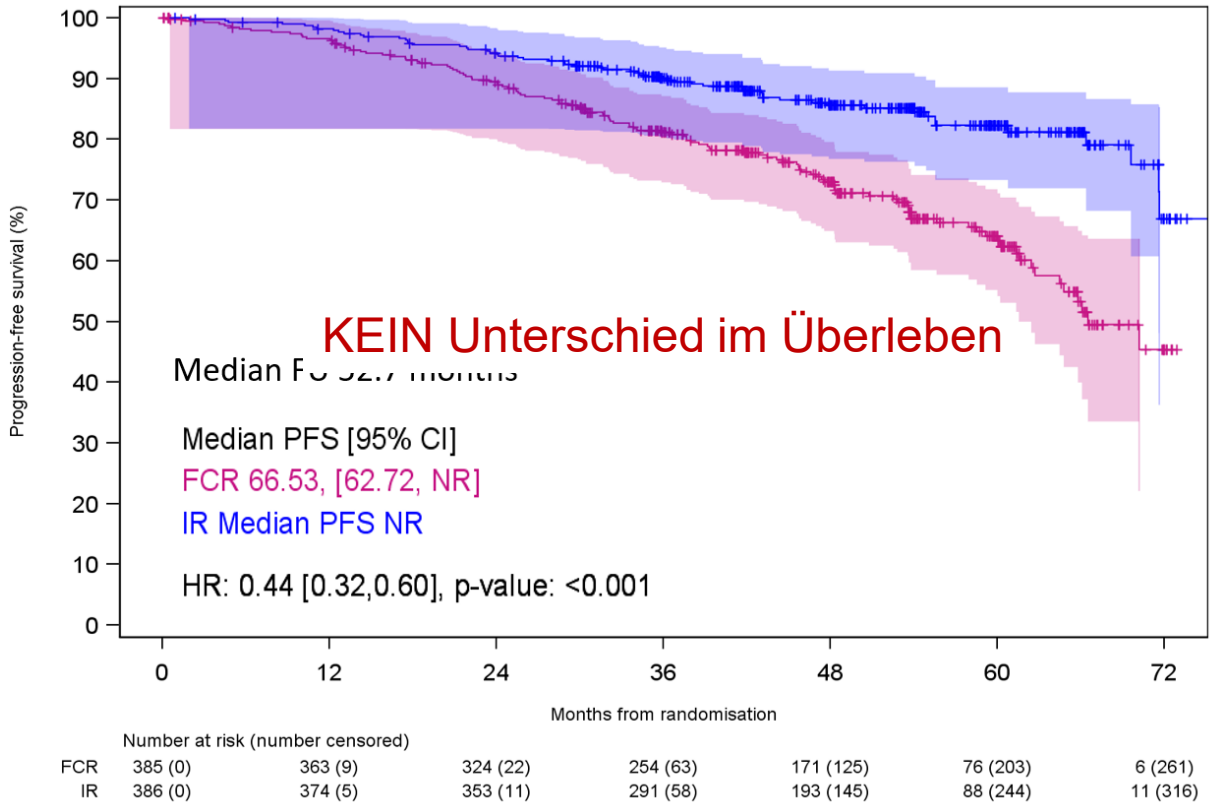
BTK Inhibitoren in der Erstlinientherapie **jüngerer** Patienten

ECOG1912-Studie: Ibrutinib+R vs. FCR bei jüngeren Pat



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

FLAIR-Studie: Ibrutinib+R vs. FCR bei jüngeren Pat



Hillmen P et al., ASH. 2021; abstract 642

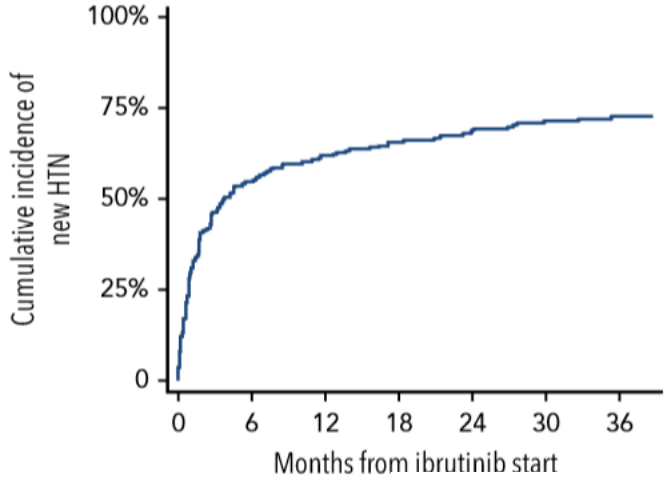
BTK Inhibitoren

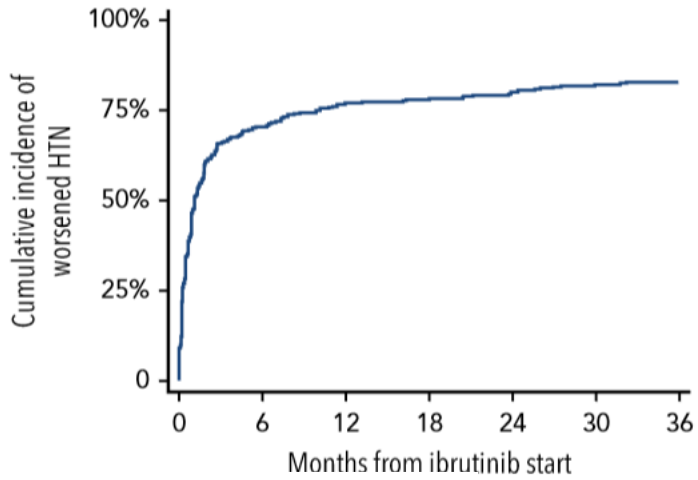
Unterschiedliches Nebenwirkungsspektrum?

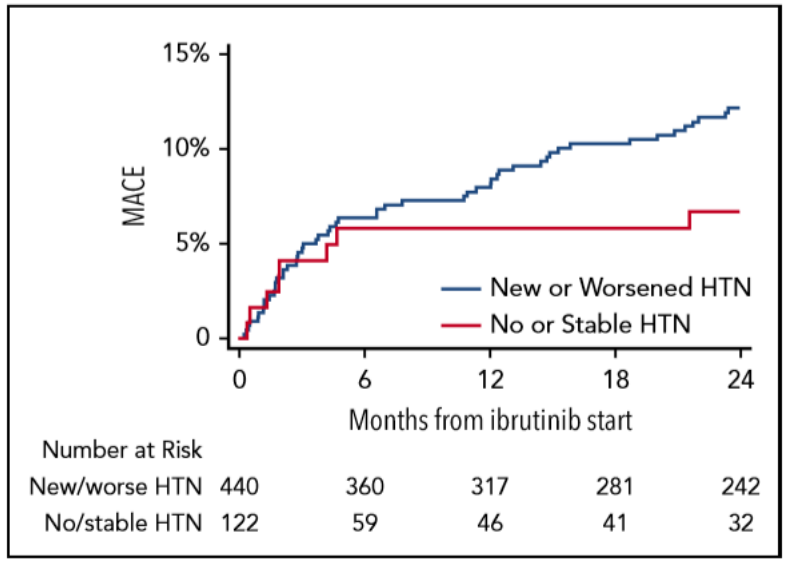
Toxicity Ibrutinib: Hypertension And Cardiovascular Events

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

93 (16.5%) major cardiovascular events



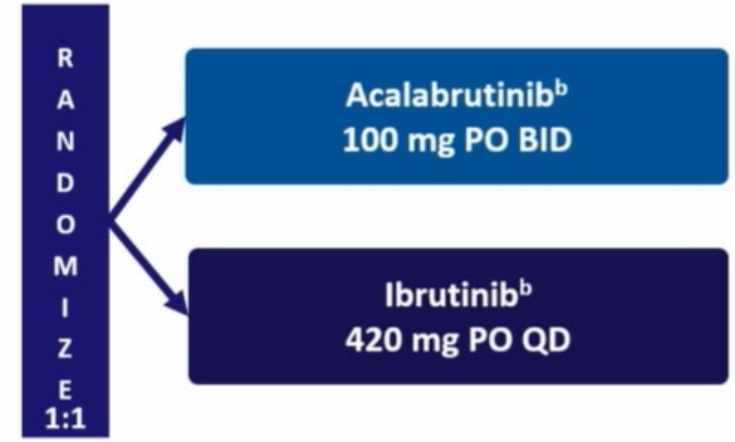


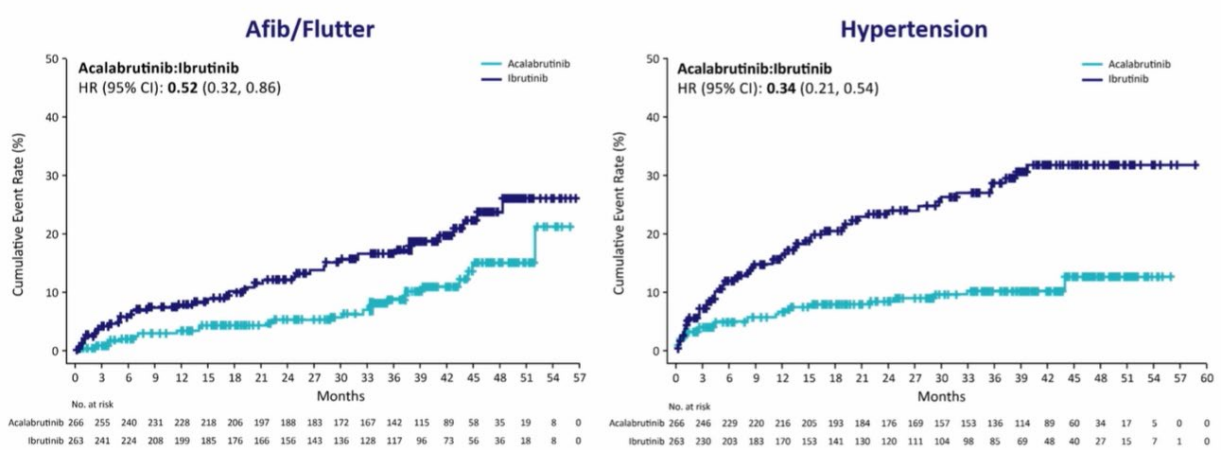


Dickerson J. et al., Blood 2019:134

Direkter Vergleich verschiedener BTK Inhibitoren (Rezidivstudien!)

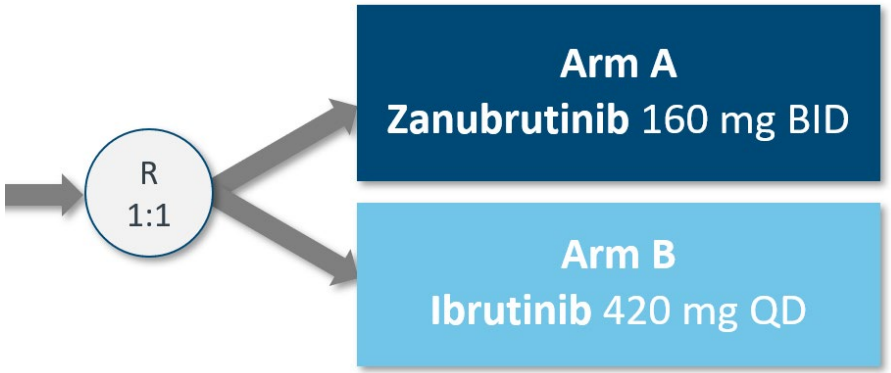
Acalabrutinib

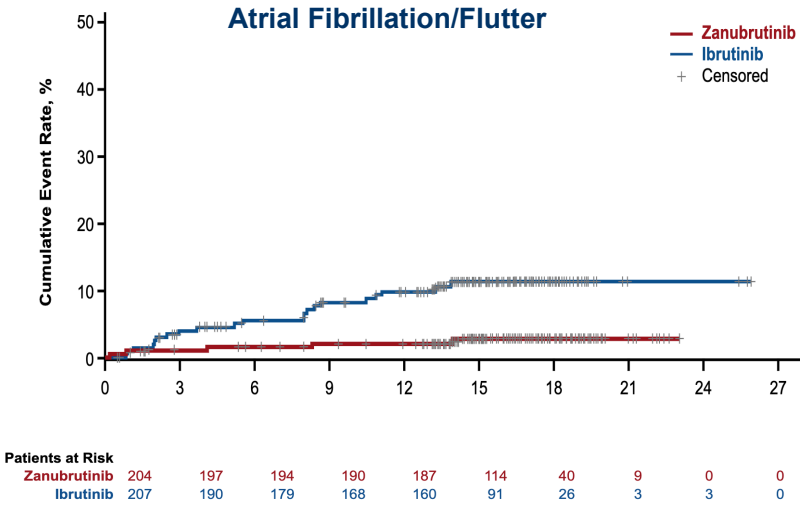




Hillmen P et al. Oral presentation. EHA 2021. Abstract S145

Zanubrutinib

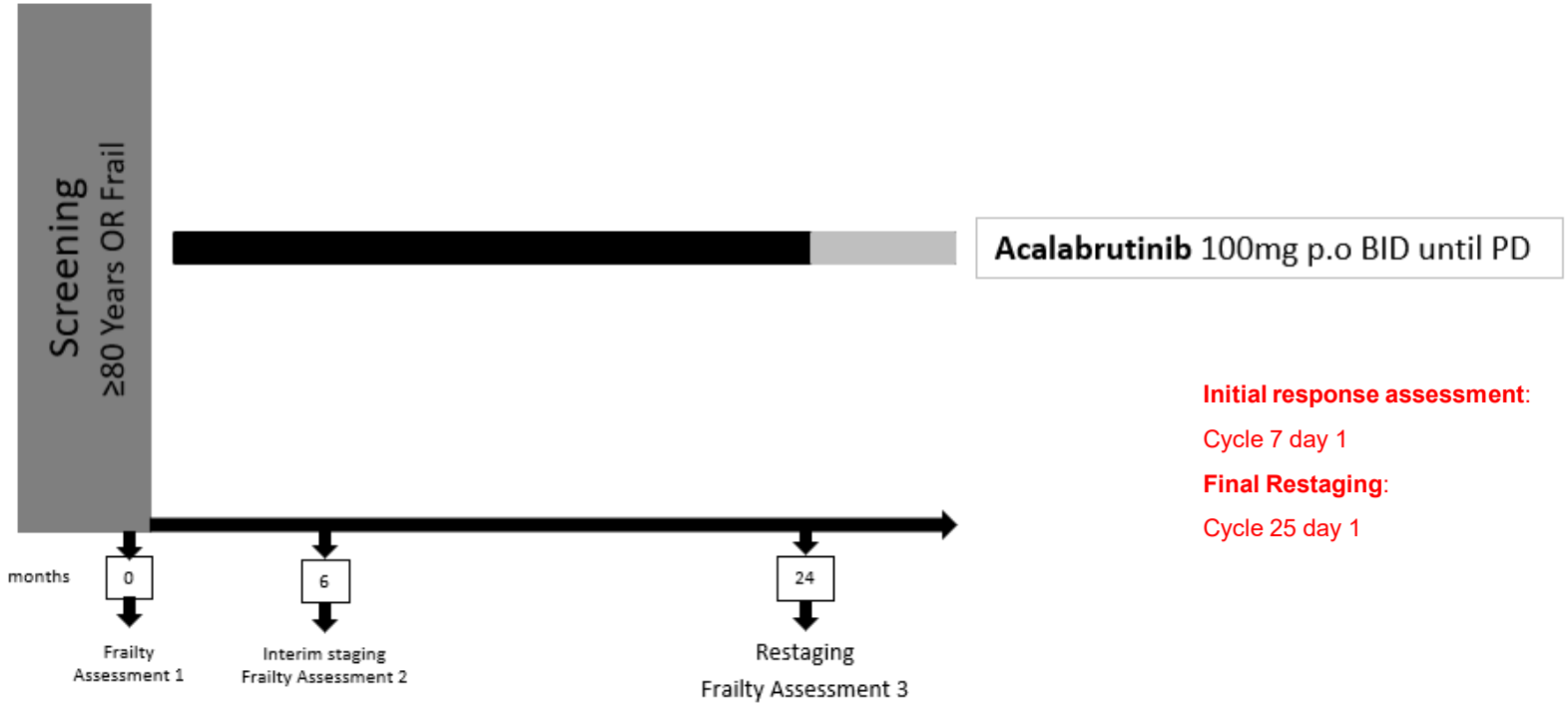




Hillmen P et al. Oral presentation. EHA 2021. LB Abstract 1900

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

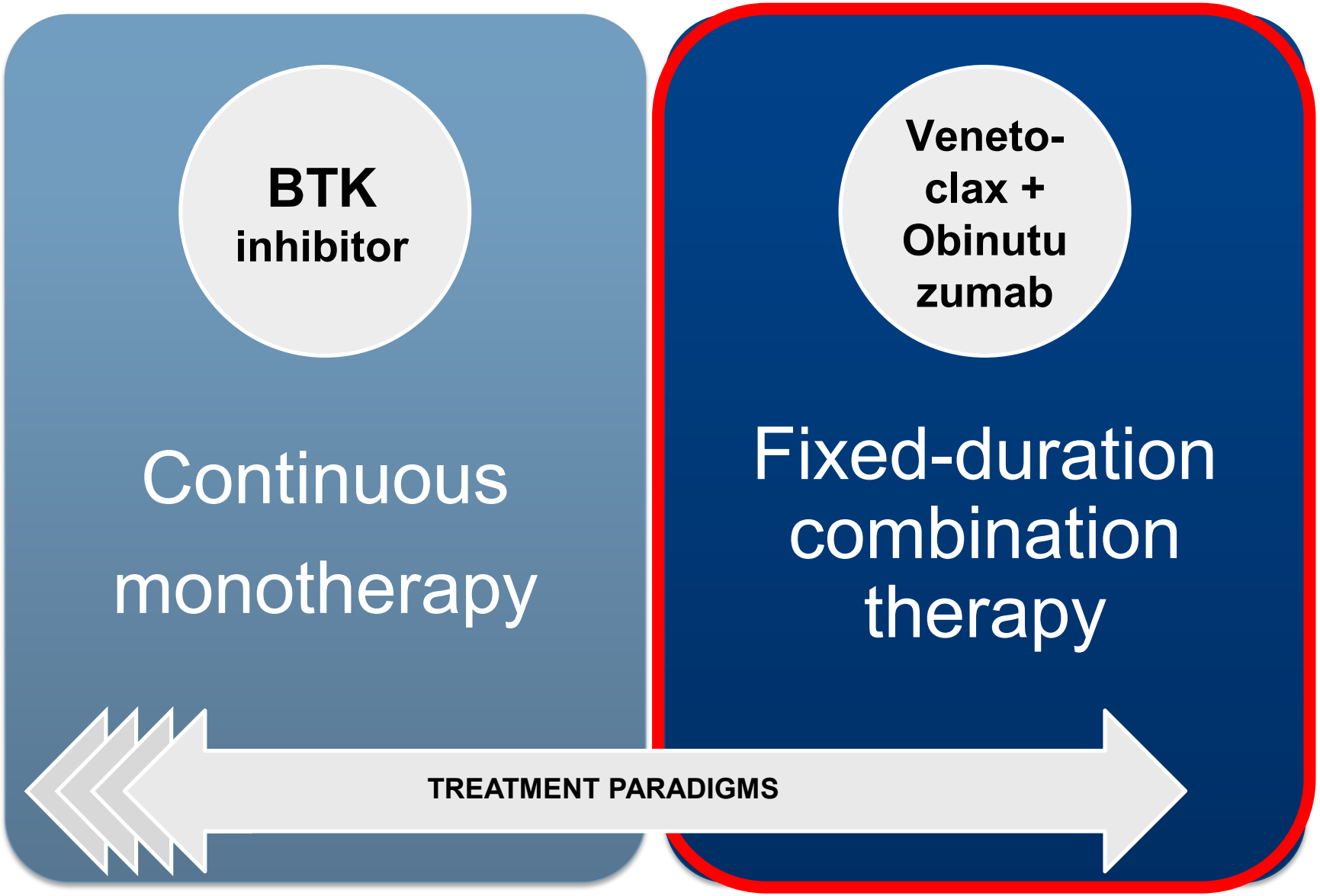


Initial response assessment:

Cycle 7 day 1

Final Restaging:

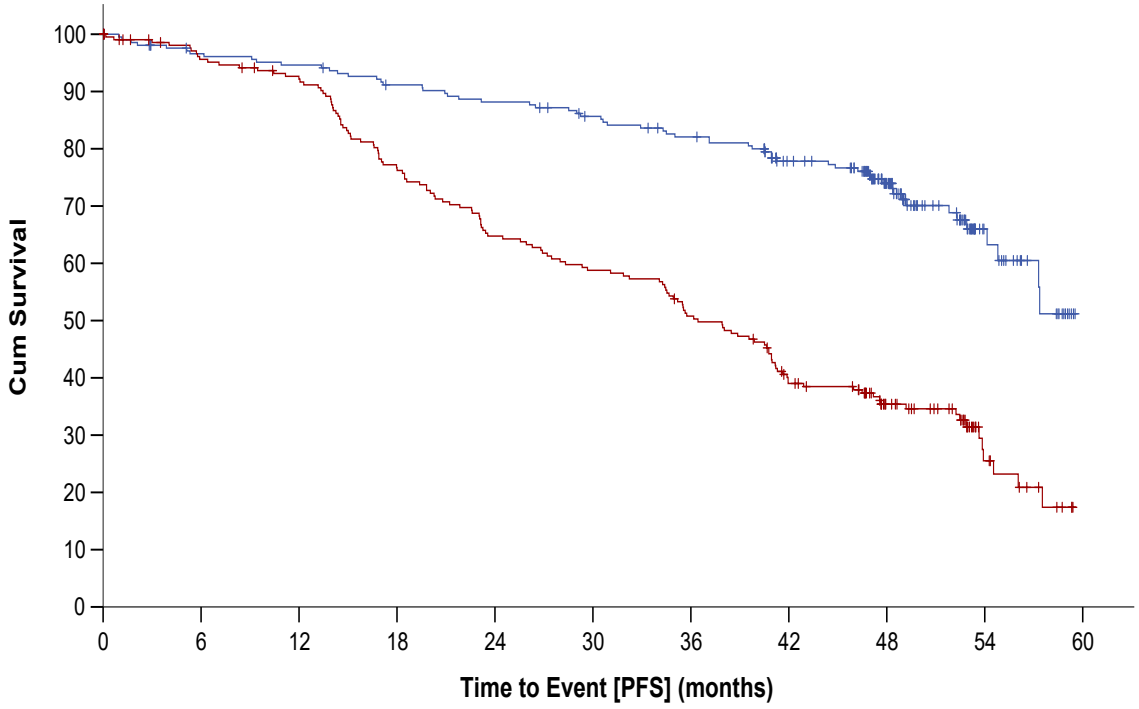
Cycle 25 day 1


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

Venetoclax Erstlinientherapie bei weniger fitten und fitten Patienten

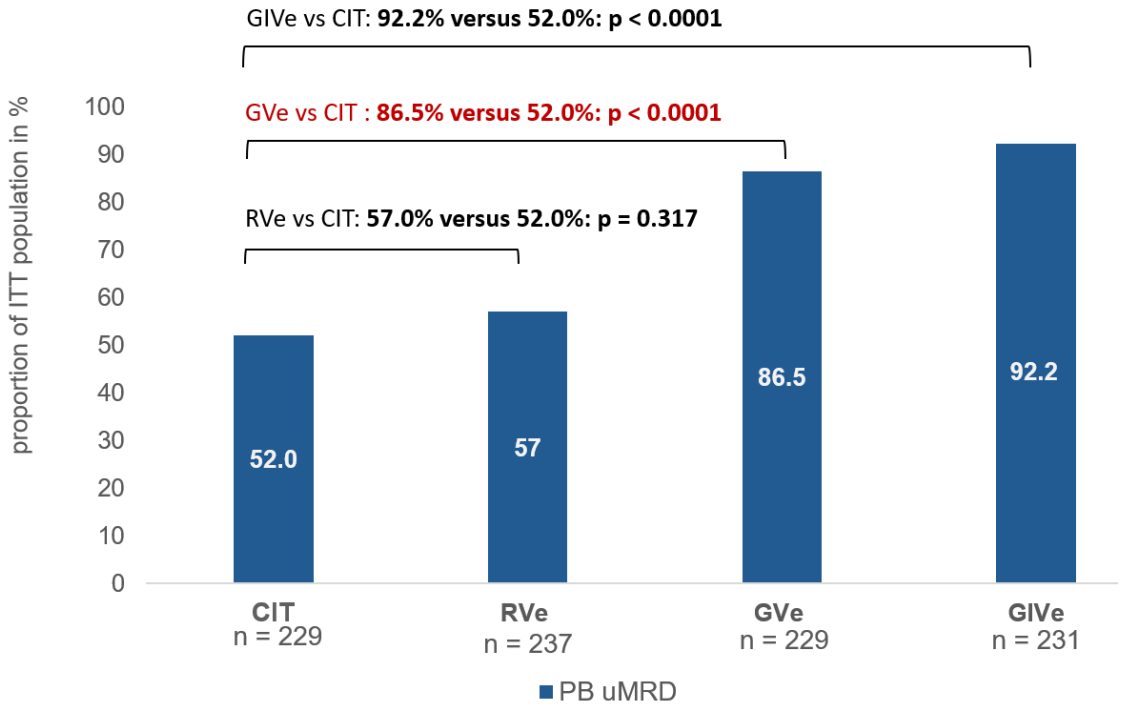
DEUTSCHE STUDIENGRUPPE

CLL14-Studie: Venetoclax+ Obinutuzumab vs. CLB + Obinutuzmab bei weniger fitten Patienten



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

CLL13-Studie, Coprimärer Endpunkt MRD: FCR/BR vs Venetoclax + Rituximab (Rve) vs Venetoclax + Obinutuzumab (Gve) vs. Venetoclax + Ibrutinib + Obinutuzmab bei fitten Patienten

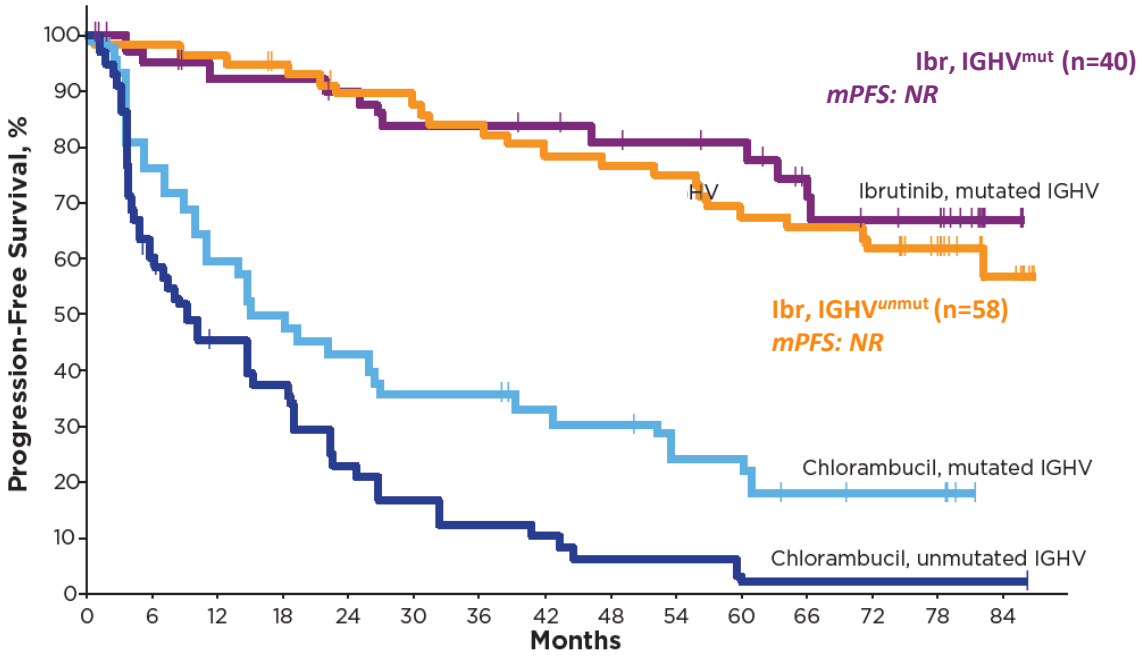


Eichhorst B et al., ASH. 2021; abstract 71

Erstlinientherapie fortgeschrittenes Stadium bei CLL mit hohem Risiko: IGHV unmutiert, TP53 Mutation oder Deletion

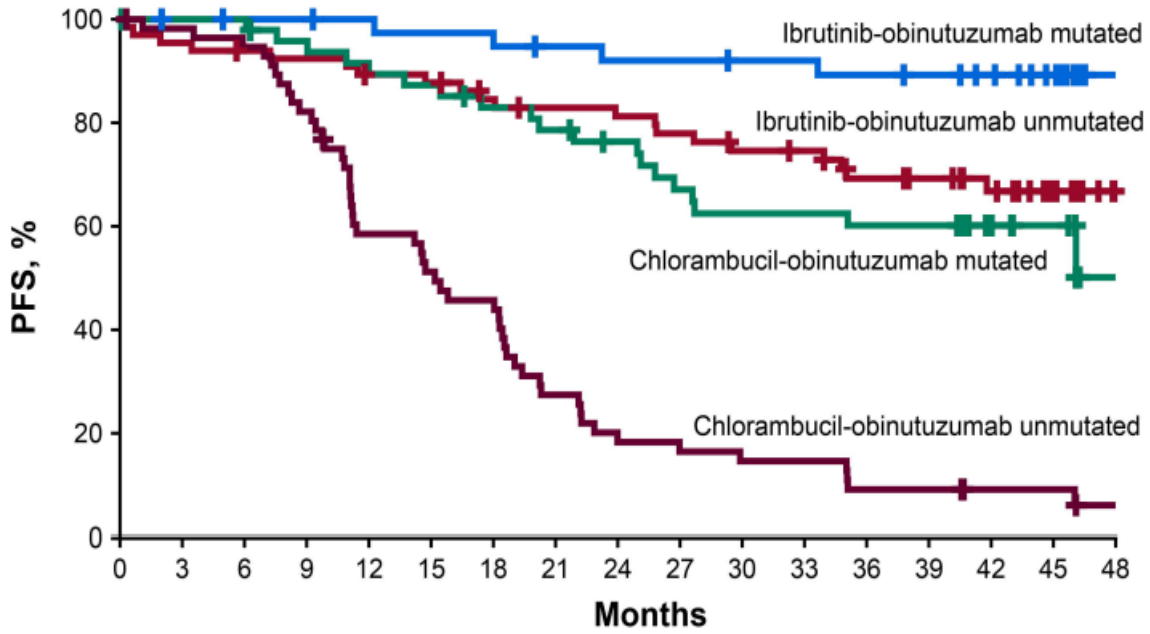
BTK-Inhibitoren in der Erstlinientherapie der CLL nach IGHV Status

RESONATE2-Studie:
Ibrutnib vs. CLB bei älteren Pat



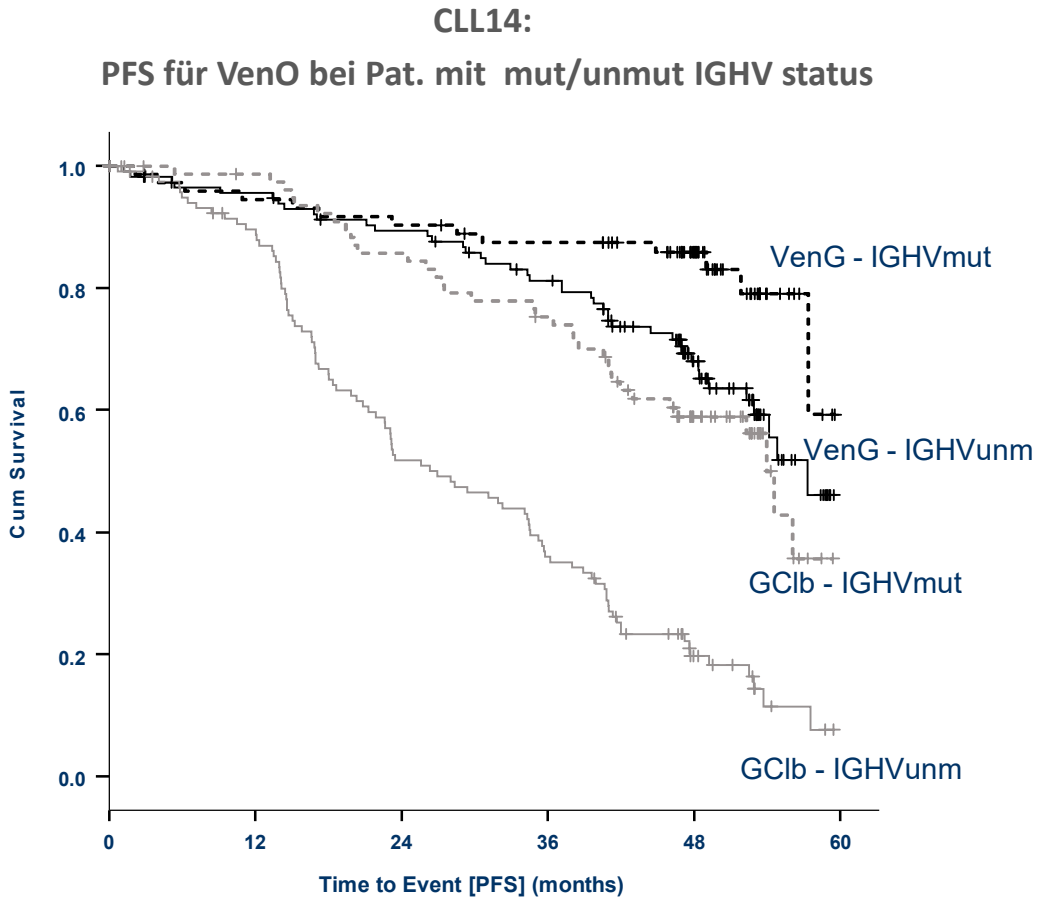
Ghia P et al., EHA. 2021; Abstract EP 636

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

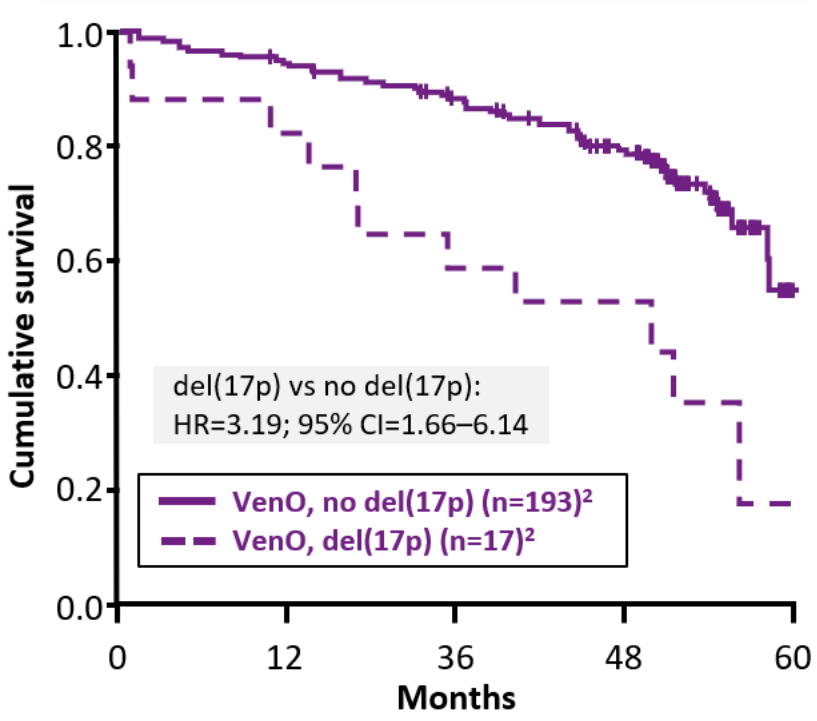


Al Sawaf O et al., JCO. 2021; 39(36):4049-4060

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

Venetoclax + Obinutuzumab

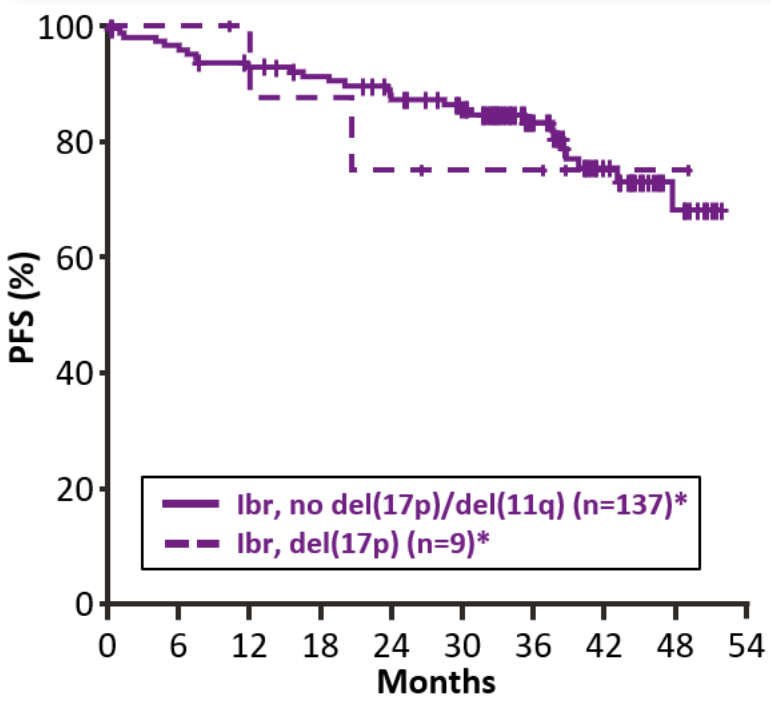
CLL14: PFS für VenO bei Pat. mit T*P53*



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

Ibrutinib Dauertherapie

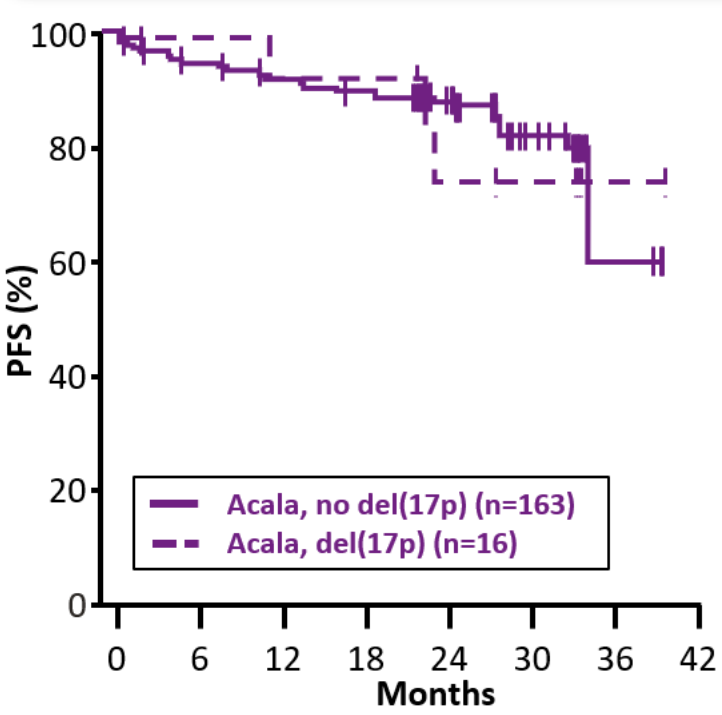
Alliance: PFS für Ibr bei Pat mit *TP53*



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

Acalabrutinib Dauertherapie

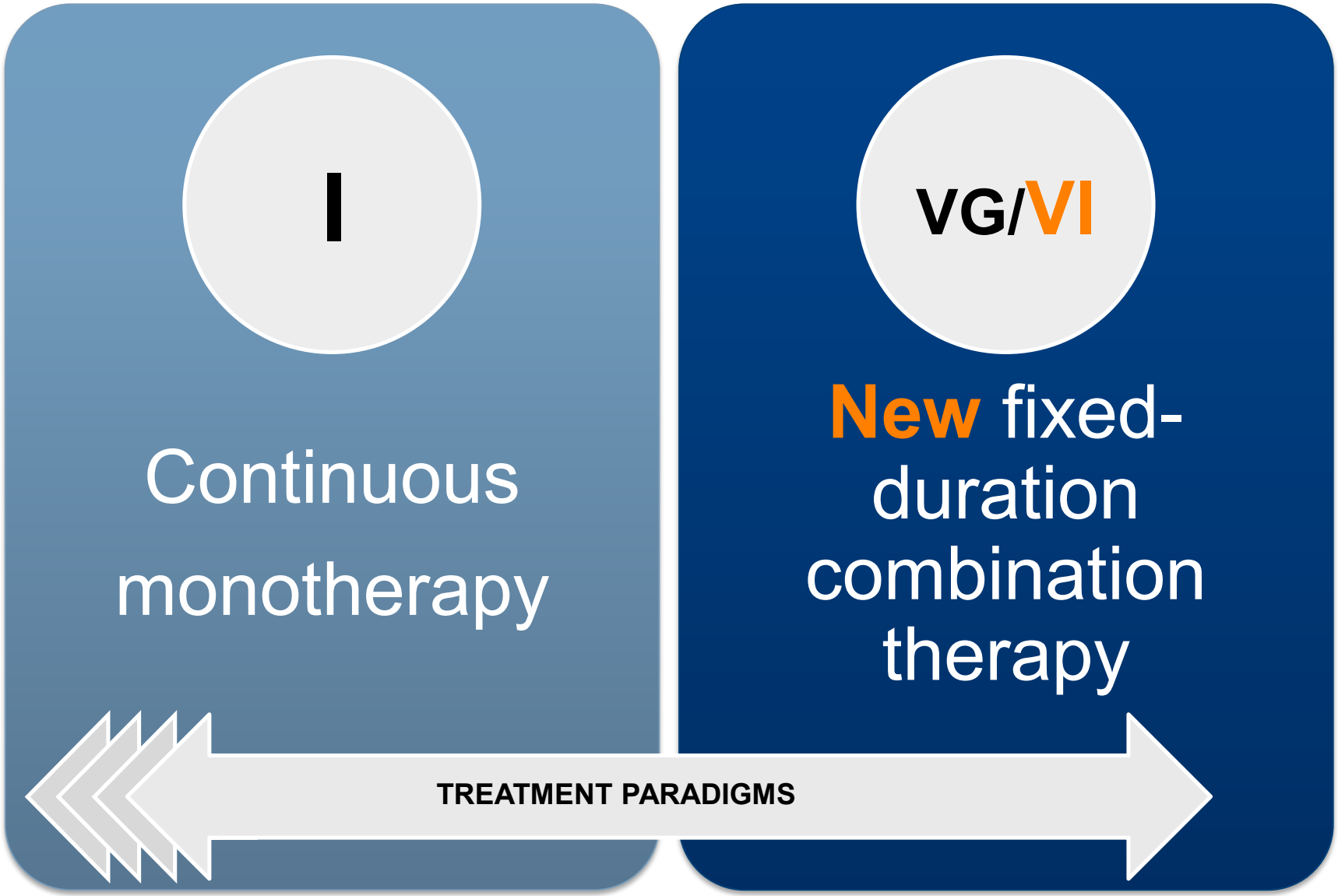
ELEVATE: PFS für Ibr bei Pat mit *TP53*



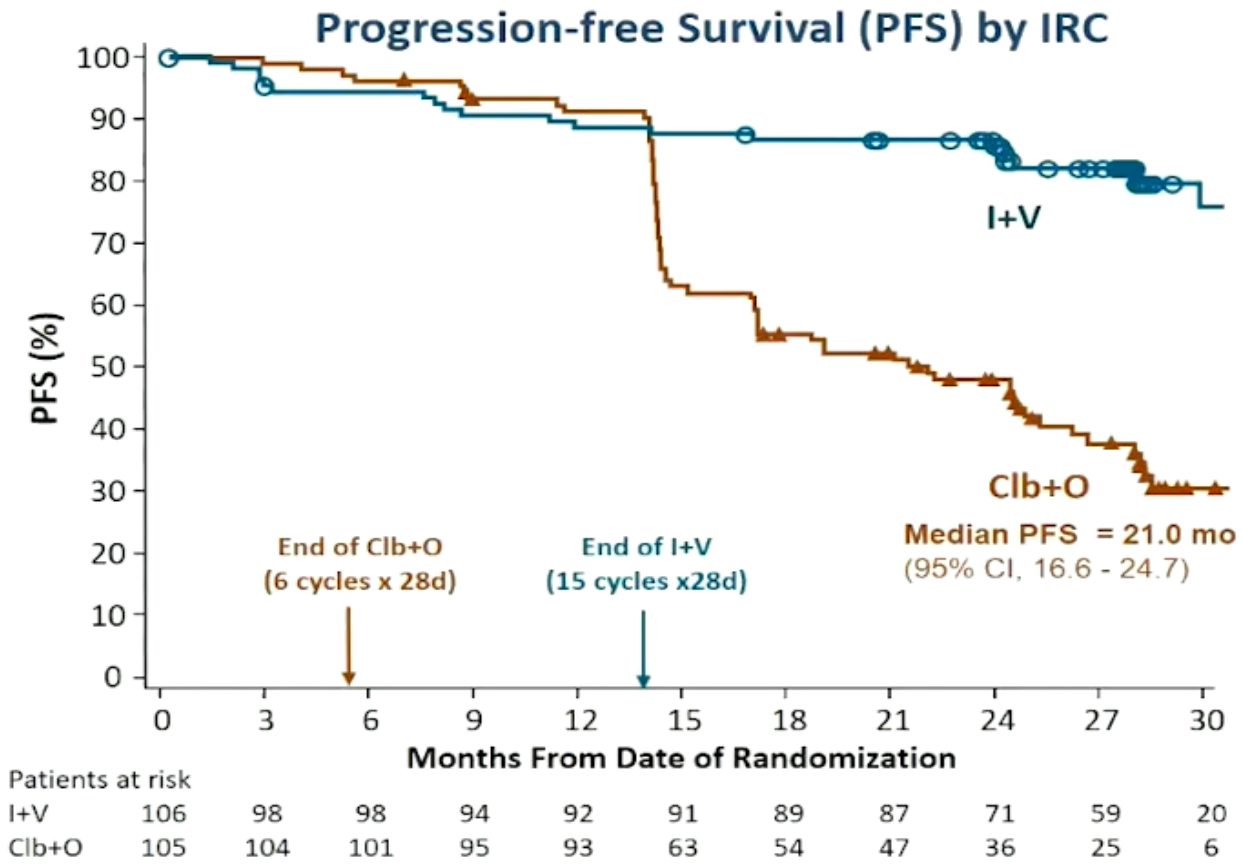
Sharman J et al., Lancet. 2020; 395:1278

Erstlinientherapie CLL

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
New fixed-duration combination therapy
TREATMENT PARADIGMS

Glow-Studie (IV 15 Monate vs. ClbObin 6 Monate): PFS nach 27.7 Monaten



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

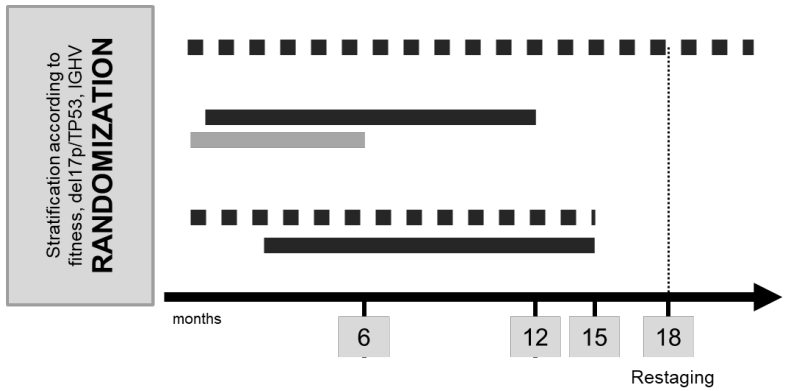
Stratification according to fitness, del17p/TP53, IGHV

Ibrutinib	Venetoclax Obinutuzumab	Venetoclax Ibrutinib

897 patients

Primary endpoint:
Progression-free survival

TREATMENT SCHEDULE



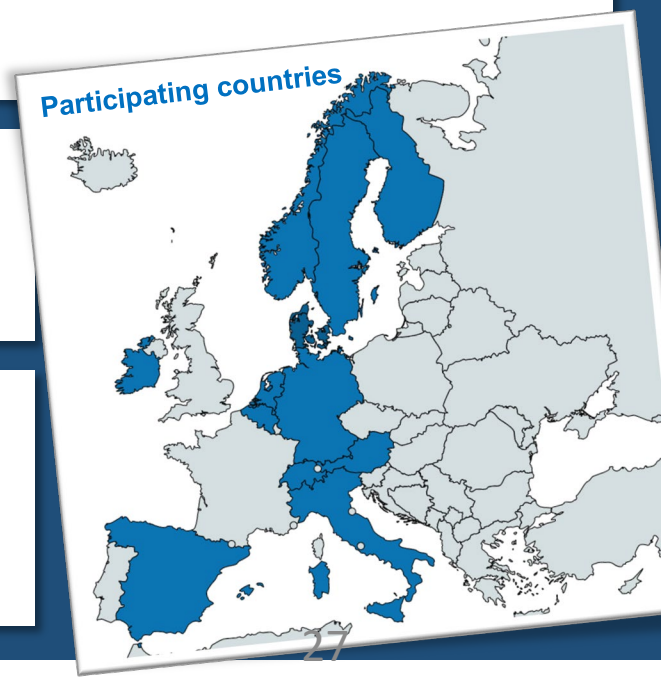
Ibrutinib d1 420 mg po daily until PD or intolerance

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



Rezidivtherapie

Therapieindikation Rezidiv

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

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.

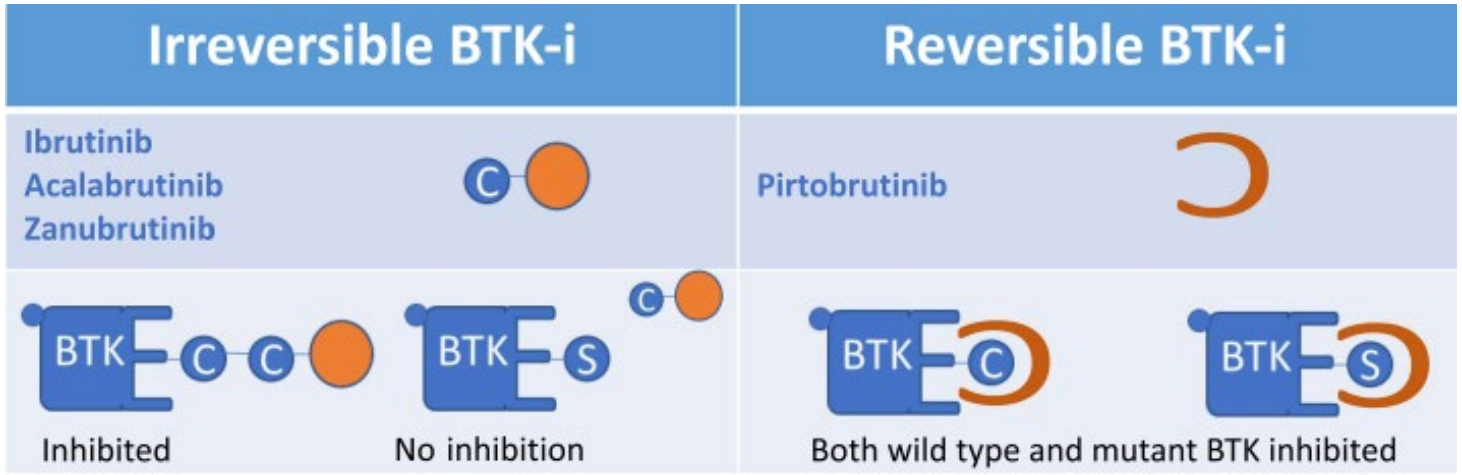
Rezidivtherapie: Therapiesequenz

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: 65
BCR inhibitor	Ventoclax	26	74 %	n.r. after 17 mo.	Mato et al., Ann Oncol 2017; 28(5):1050
Ven	**BCRi**				
VenetoclaxR	Ibrutinib	10	100 %	n.r.	Kater A, et al. JCO 2020; 38:4042
Venetoclax	Ibrutinib/Acalabrutinib	44	84 %	32 mo.	Mato et al., ASH 2019; Abstract 502
VenR	**Ven**				
VenentoclaxR	Venetoclax	8	62 %	-	Kater A, et al. JCO 2020; 38:4042

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

Non-covalent BTK inhibitors

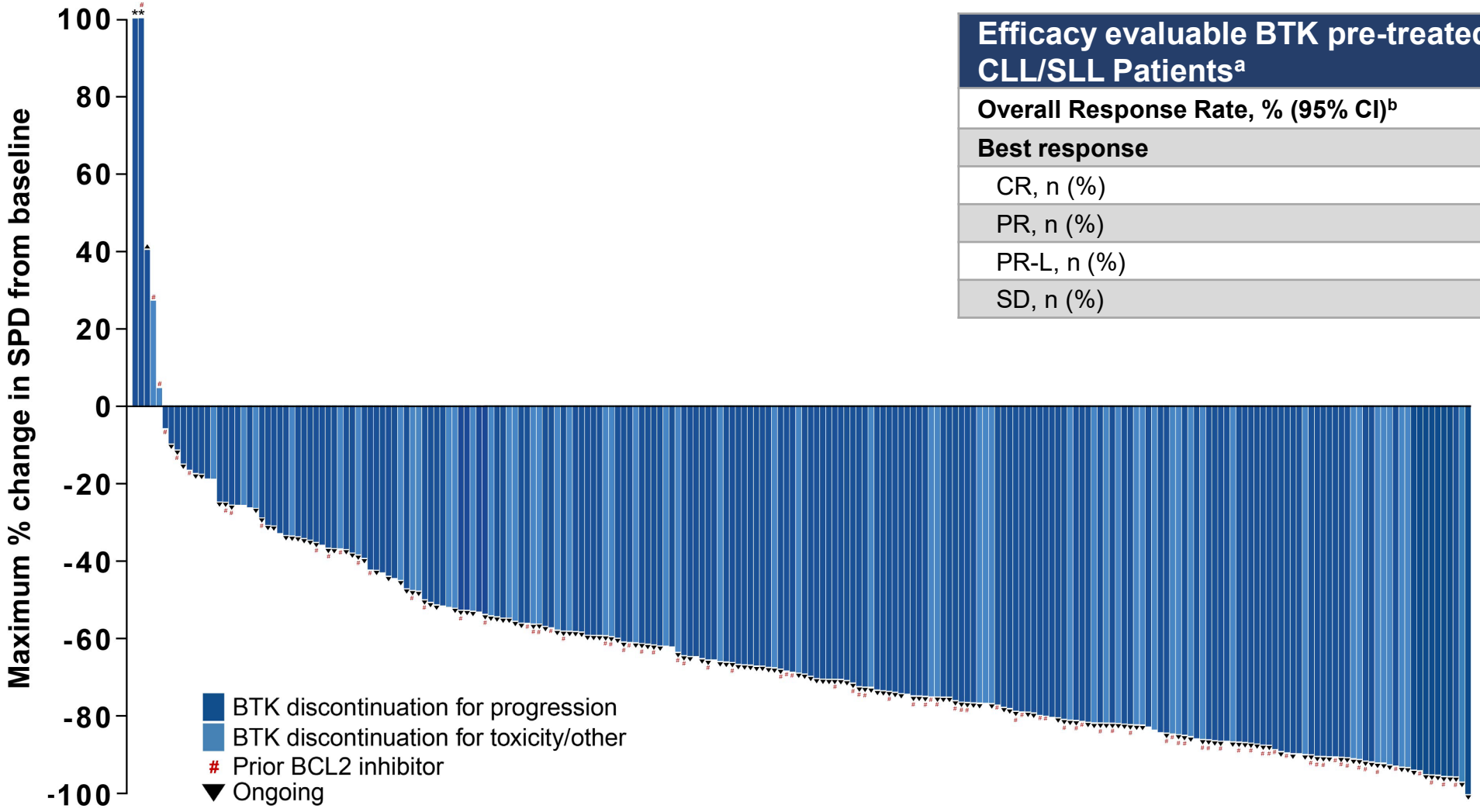
- Pirtobrutinib (LOXO 305)
- Nemtabrutinib (ARQ 531)
- Vecabrutinib (SNS-062)
- Fenebrutinib (GDC-0853)



Tambaro, Novellis, Wierda, J Exp Pharm, 2021:13 923–935

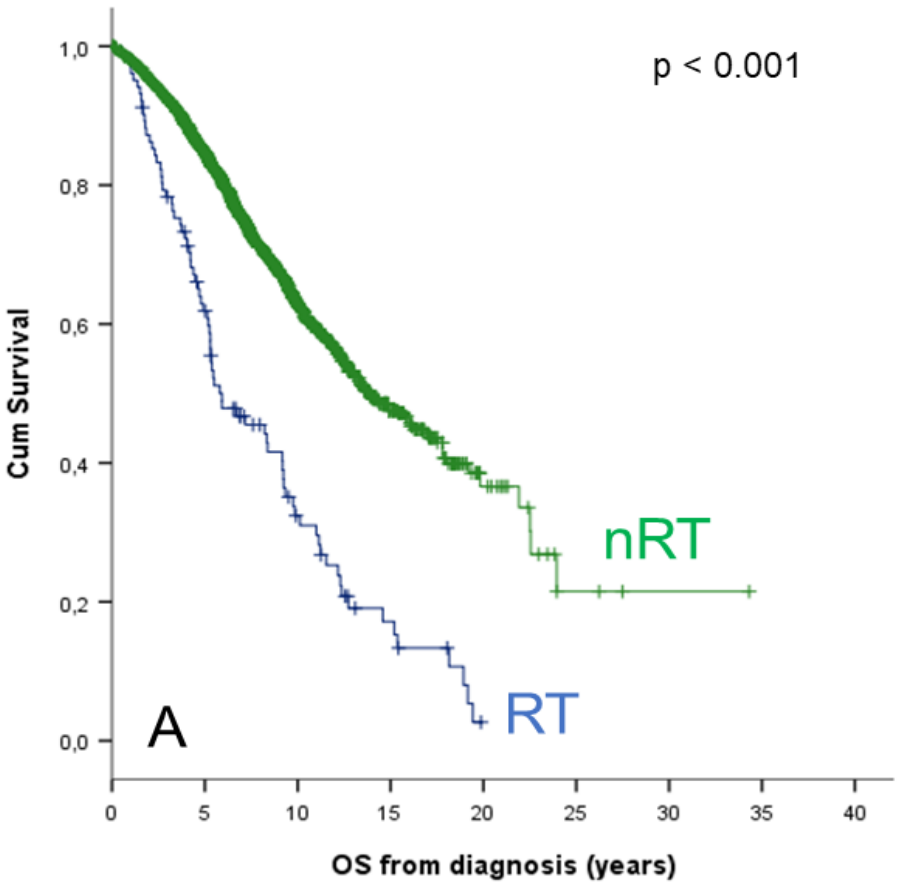
Pirtobrutinib efficacy in BTK pre-treated CLL/SLL patients

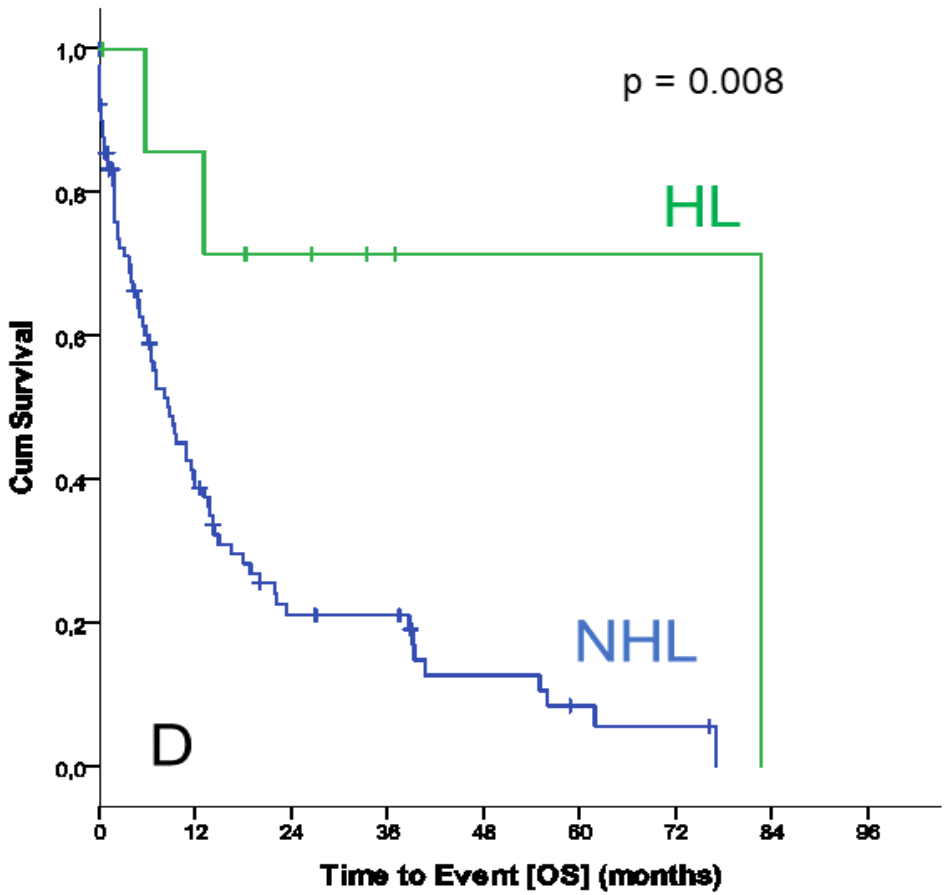
Efficacy evaluable BTK pre-treated CLL/SLL Patients[a]	n = 252
Overall Response Rate, % (95% CI)[b]	**68 (62 – 74)**
Best response	
CR, n (%)	2 (1)
PR, n (%)	137 (54)
PR-L, n (%)	32 (13)
SD, n (%)	62 (25)



Mato, et al., ASH abstract 2021

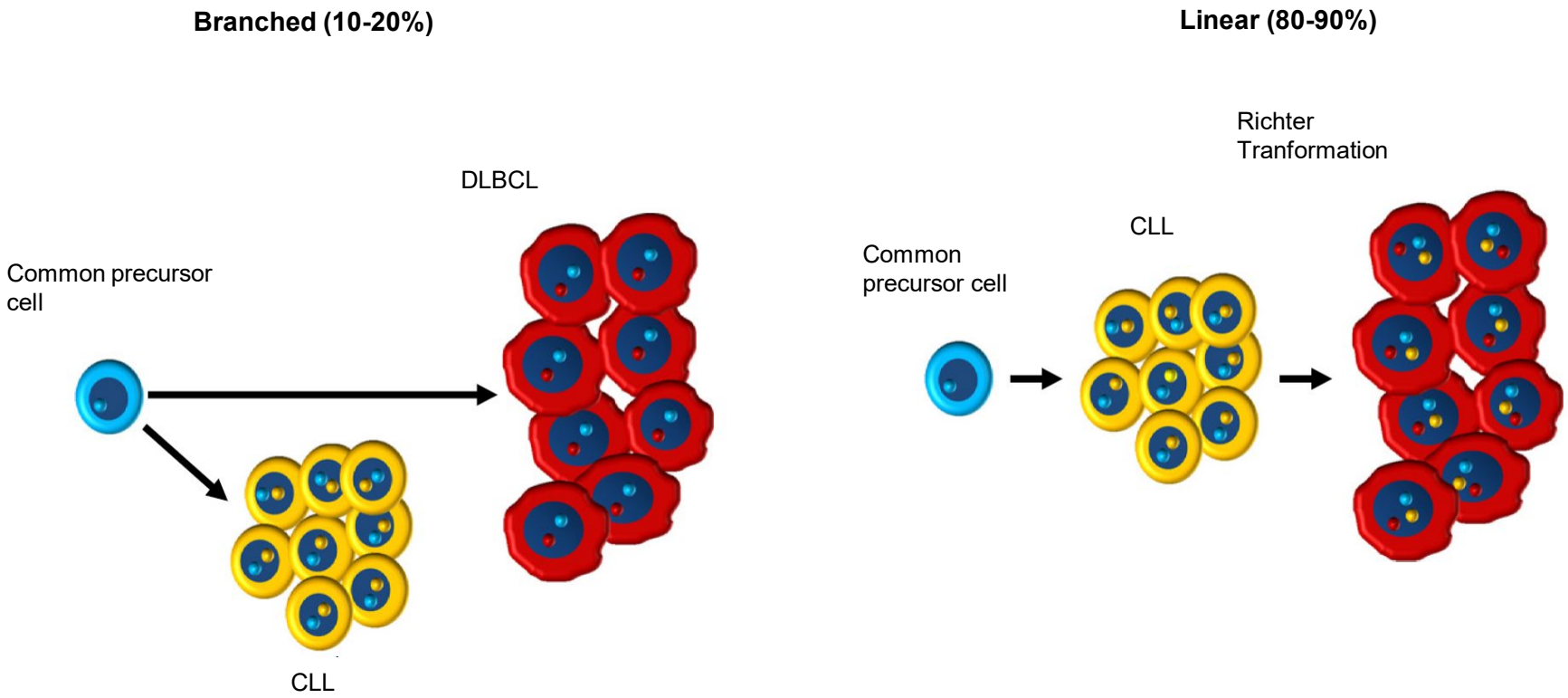
Worst case scenario RT: Pooled analysis of the GCLLSG





Al Sawaf et al. , Leukemia 2020

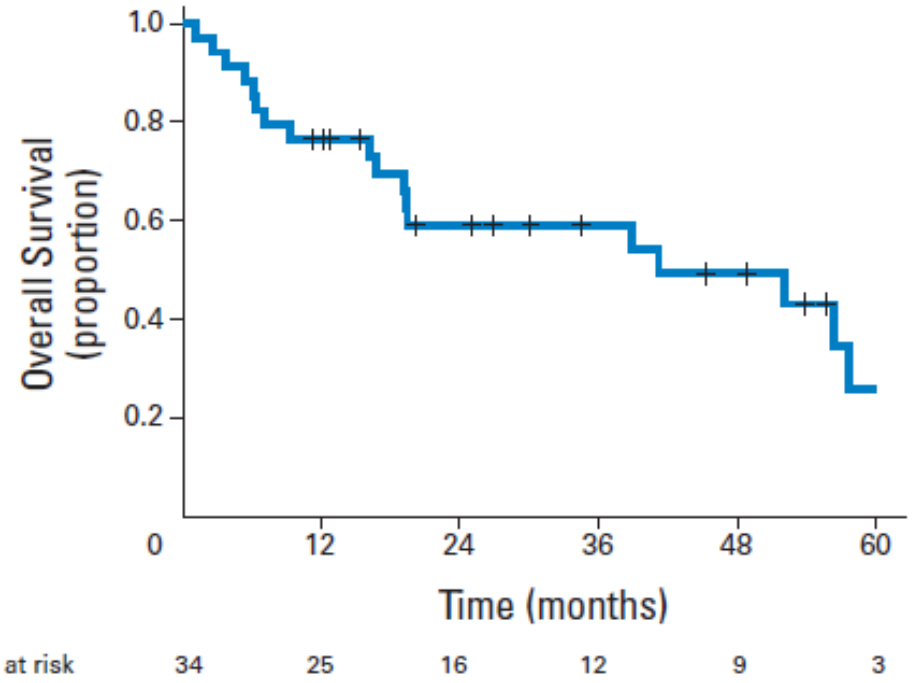
Differenzierung de novo vs klonal verwandtes DLBCL



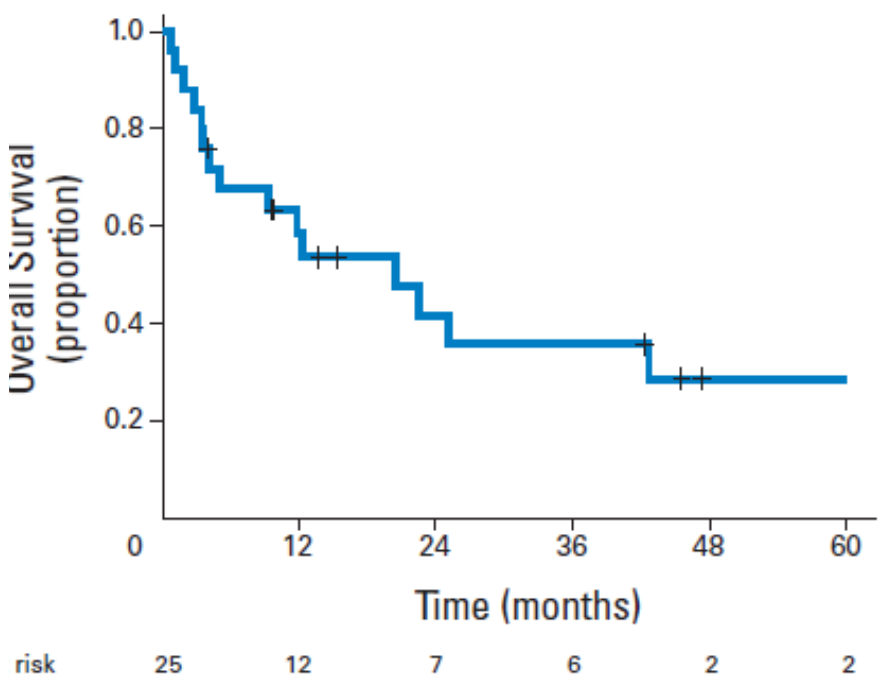
Adapted from Rossi & Gaidano , Sem. Oncol. 2016

Autologe/allogene Transplantation bei RT

Autologe TX

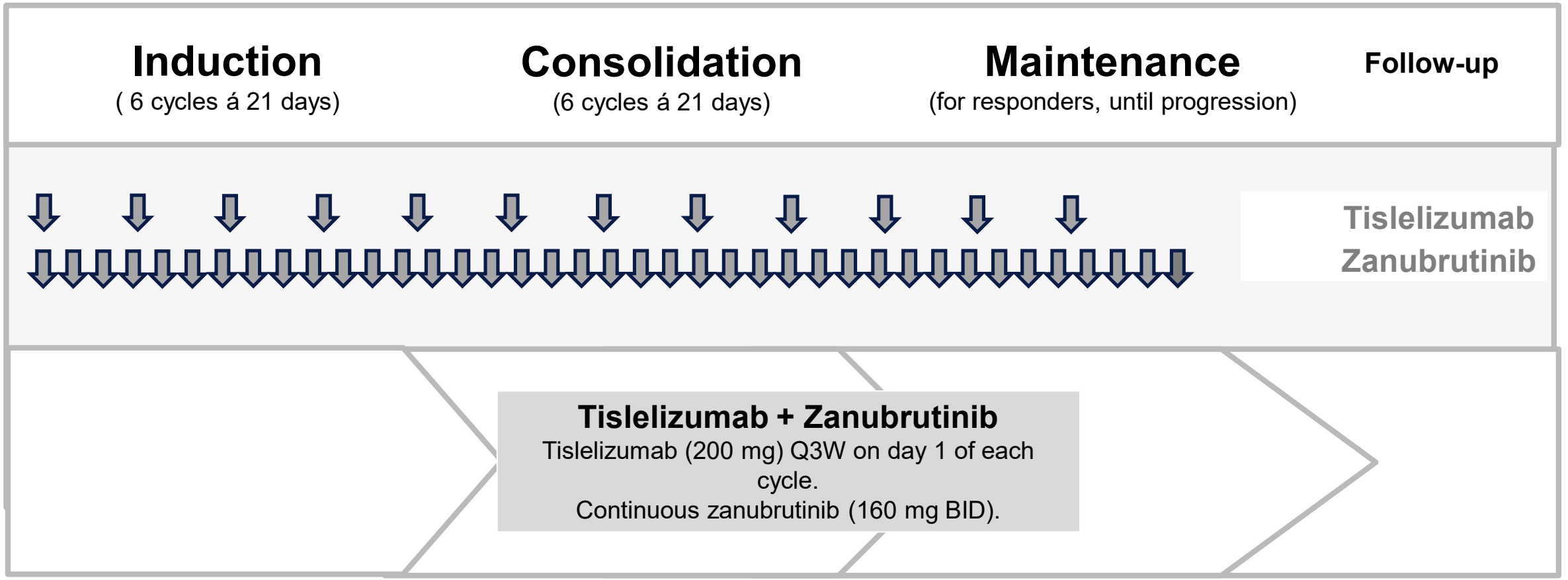


Allogene TX



Cwynarski et al, *JCO*, 2012

RT-Studie der DCLLSG

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