UNIKLINIK KÖLN

DEUTSCHE STUDIENGRUPPE

Firstline CLL studies: the vision of the German CLL study group

24. November 2022

8es Journées du FILO

Dijon

DISCLOSURES

Consulting or Advisory Boards:

Janssen, Roche, Novartis, AbbVie, Gilead, Celgene, AstraZeneca, MSD, Miltenyi

Speaker / Speaker's Bureau

Janssen, Gilead, Roche, AbbVie, Novartis, Celgene, AstraZeneca, BeiGene, MSD

Research funding:

Janssen, Gilead, Roche, AbbVie, BeiGene, Astra Zeneca

GCLLSG was founded in 1996

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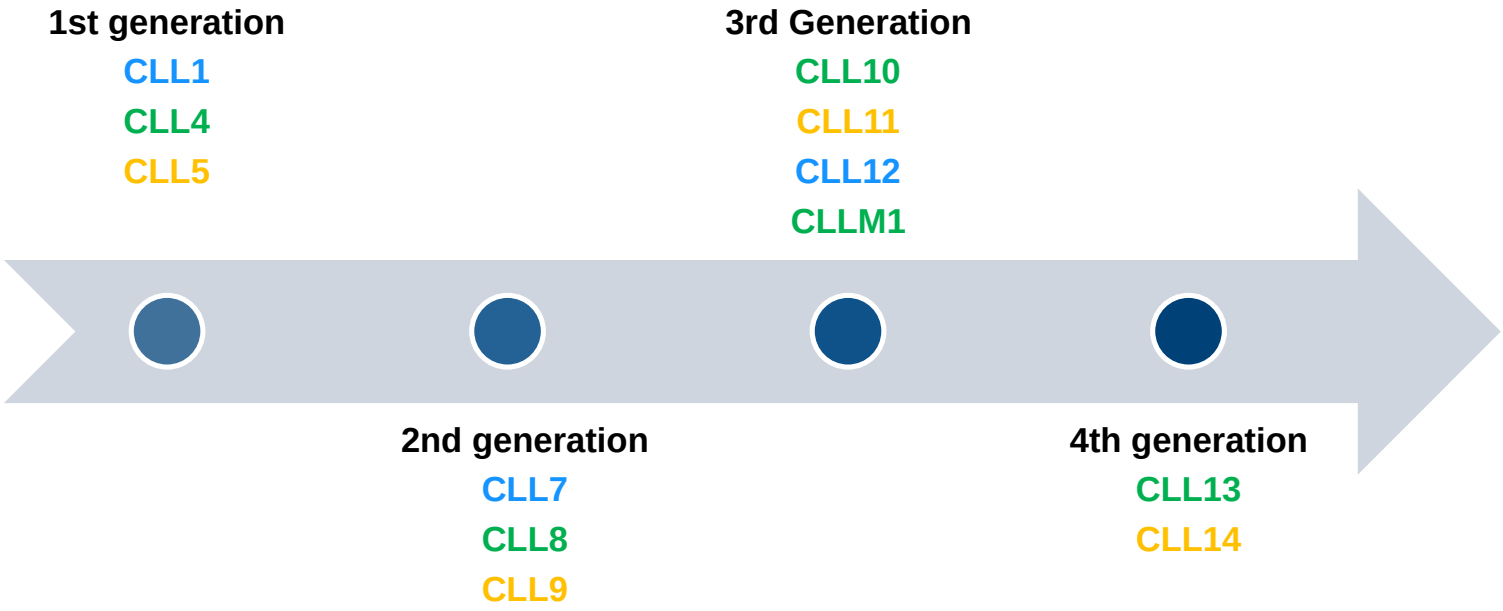
2003: 1st digital Photo of the GCLLSG core team in Munich

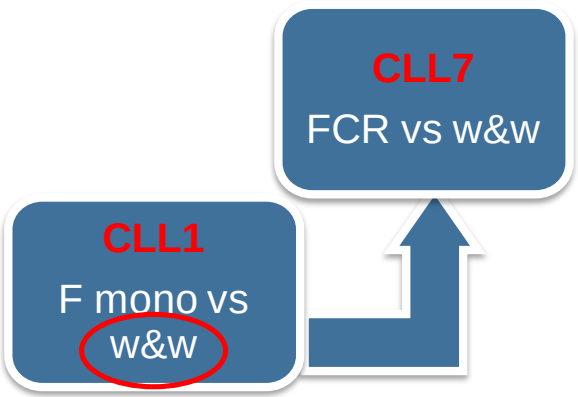
Concept of GCLLSG trials



Early stage disease Advanced stge + fit Advanced stage + less fit

Early stage

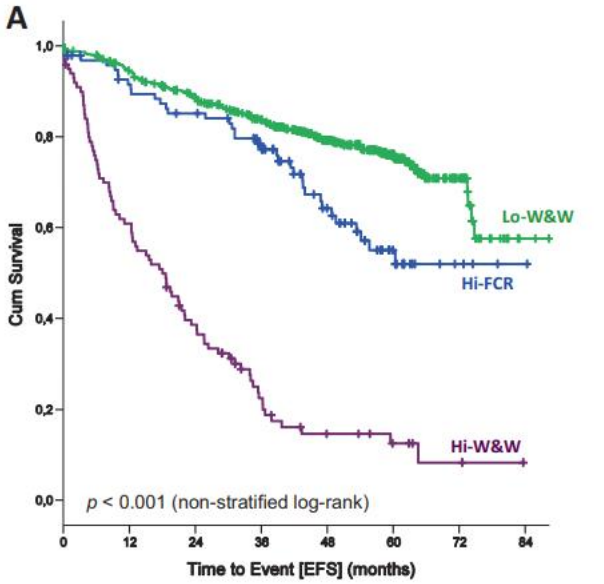
Trials Early stage CLL



Chemoimmunotherapy in early stage CLL without impact on OS

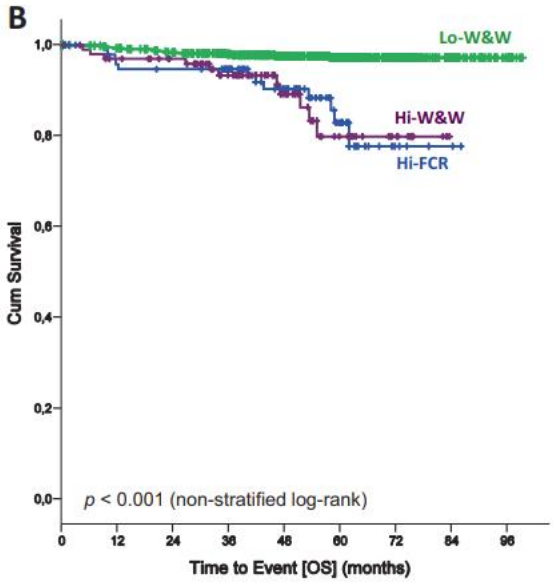
CLL7-Study

EFS



Number at risk	0	12	24	36	48	60	72	84
LR	599	525	474	418	323	180	35	4
HR-FCR	100	86	79	63	40	18	4	1
HR-W&W	101	61	37	18	9	5	2	0

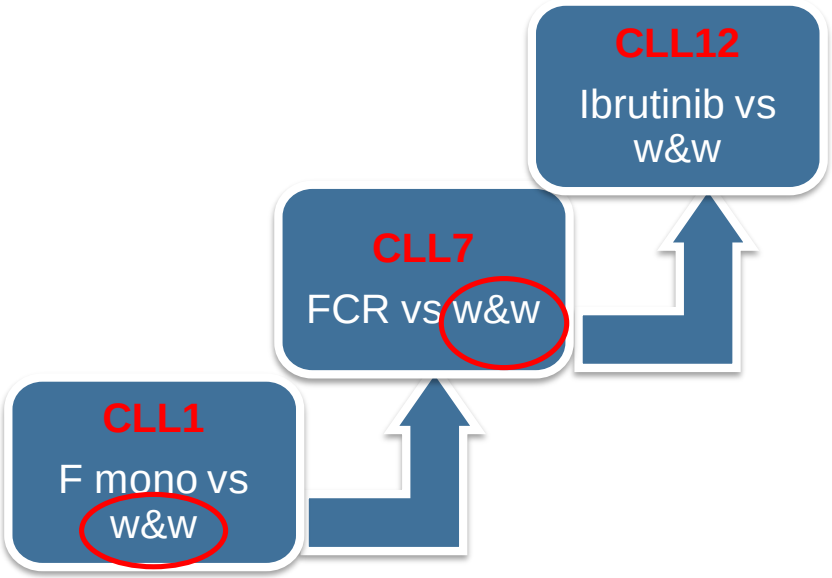
OS



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	-

Herling C., Cymbalista F.,…..Levy V. Leukemia 2020; 34:2038–2050

Trials early stage CLL



CLL12: STUDY DESIGN

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Key eligibility:

- Binet A
- Asymptomatic
- Treatment-naive

RISK STRATIFICATION

LOW
N=152

INTERM.
N=273

HIGH
N=82

VERY HIGH
N=8

RANDOMIZATION **1:1**

WATCH & WAIT N=152

IBRUTINIB N=182

PLACEBO N=181

420 [mg/d] until **symptomatic** PD

Median observation time is 31.0 months

FPI
APR-2014

LPI
FEB-2019

Langerbeins P et al., Blood. 2022; 139: 177

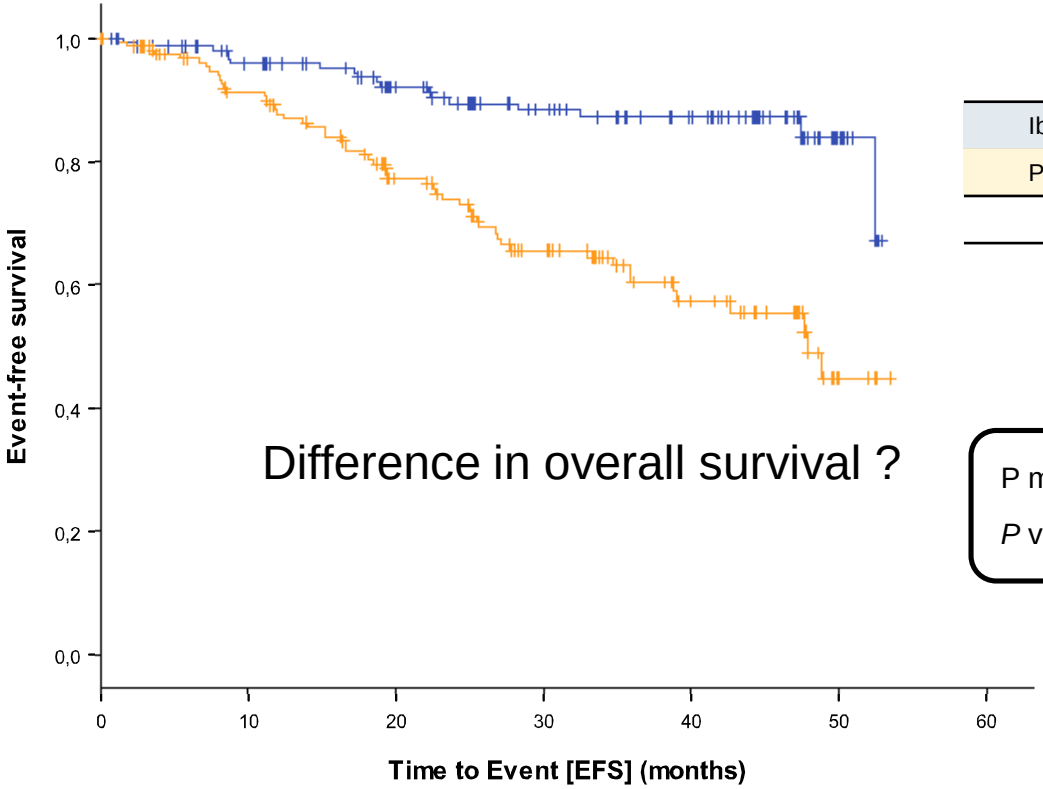
CLL12: ADVERSE EVENTS OF SPECIAL INTEREST

	Ibrutinib n=185	Placebo n=178	*P*-value
AE of clinical interest (%)	106 (57.3)	71 (39.9)	0.001
Bleeding - CTC ≥ 3	**51 (27.6)** 6 (3.2)	**17 (9.6)** 2 (1.2)	0.000
Atrial fibrillation - CTC ≥ 3	**33 (17.8)** 11 (6.5)	**13 (7.3)** 3 (1.7)	0.003
Hypertensive disorders - CTC ≥ 3	**18 (9.7)** 3 (1.6)	**7 (3.9)** 3 (1.7)	0.04
Diarrhea - CTC ≥ 3	**58 (31.4)** 2 (1.1)	**44 (24.7)** 5 (2.8)	n.s.
Other cardiac event - CTC ≥ 3	**10 (5.4)** 4 (2.1)	**14 (7.9)** 7 (3.9)	n.s.

Langerbeins P et al., Blood. 2022; 139: 177

CLL12: PRIMARY EFS ENDPOINT ANALYSIS

Time to symptomatic progression, CLL treatment and/or death



	total	events	N	%
Ibrutinib	182	18	164	90.1
Placebo	181	55	126	69.9
	363	73	290	79.9

P median$_{EFS}$ 47.8 vs. NR

P value <0.0001; HR 0.248

Langerbeins P et al., Blood. 2022; 139: 177

Trials Early stage CLL

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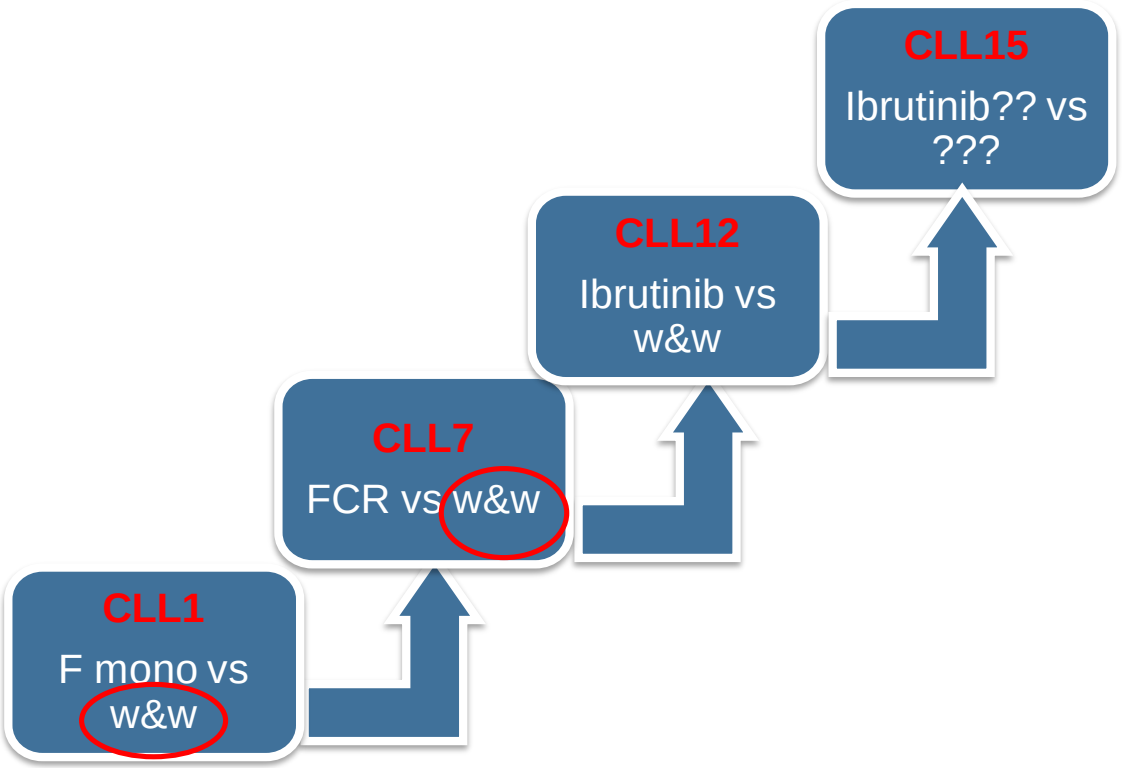


Advanced stage

Frontline options

Continuous ∞

BTKi
- Ibrutinib +/- R or O
- Acalabrutinib +/- O
- Zanubrutinib
  in regulatory review

BCL2i
- Venetoclax
  only in pts with *TP53* aberration*

Time limited therapy ⛔

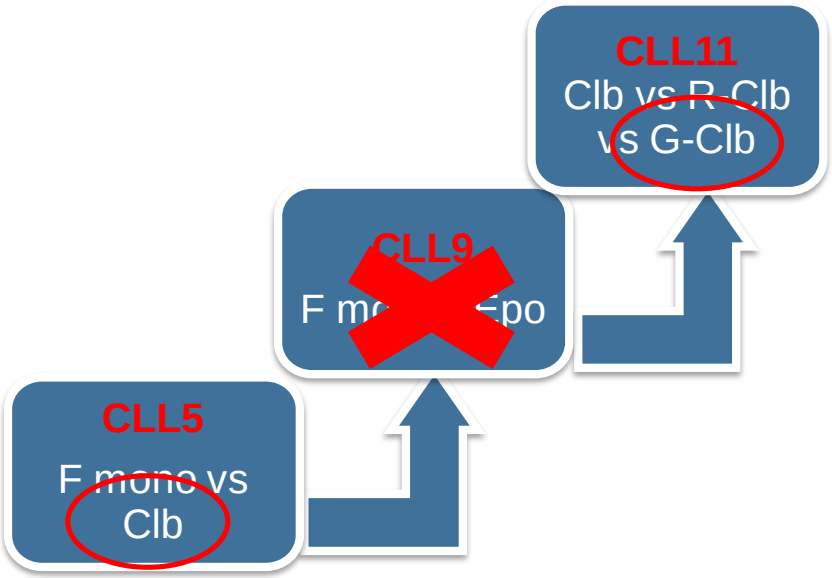
BCL2i + Anti-CD20
- Venetoclax + O
  12 cycles

BTKi + BCL2i
- Ibrutinib + Venetoclax
  15 cycles

CIT+BTKi
- FCR+Ibrutinib in mutated IGHV

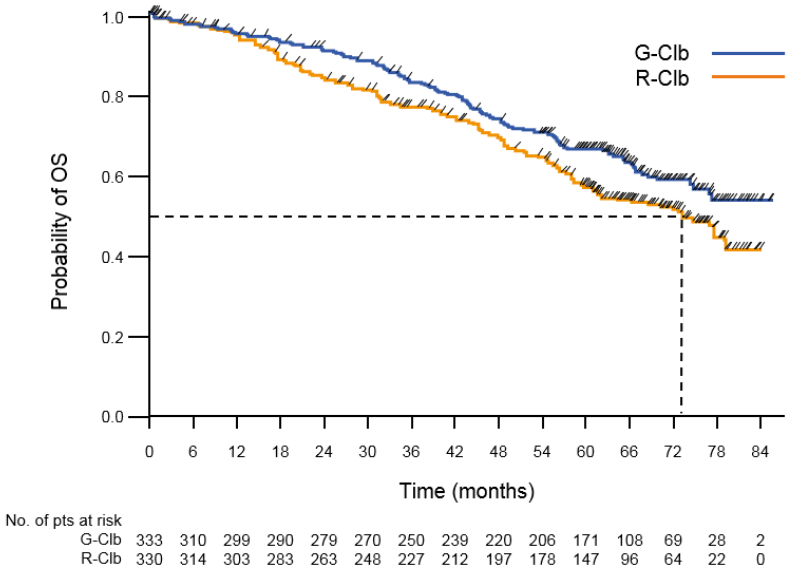
R = Rituximab; O = Obinutuzumab; *and not eligible/failed BTKi or in pts w/o TP53 aberration who failed CIT and BCRi

Trials firstline of unfit patients



Overall Survival: Obinutuzumab-CLB versus Rituximab-CLB

Median observation: 59 months



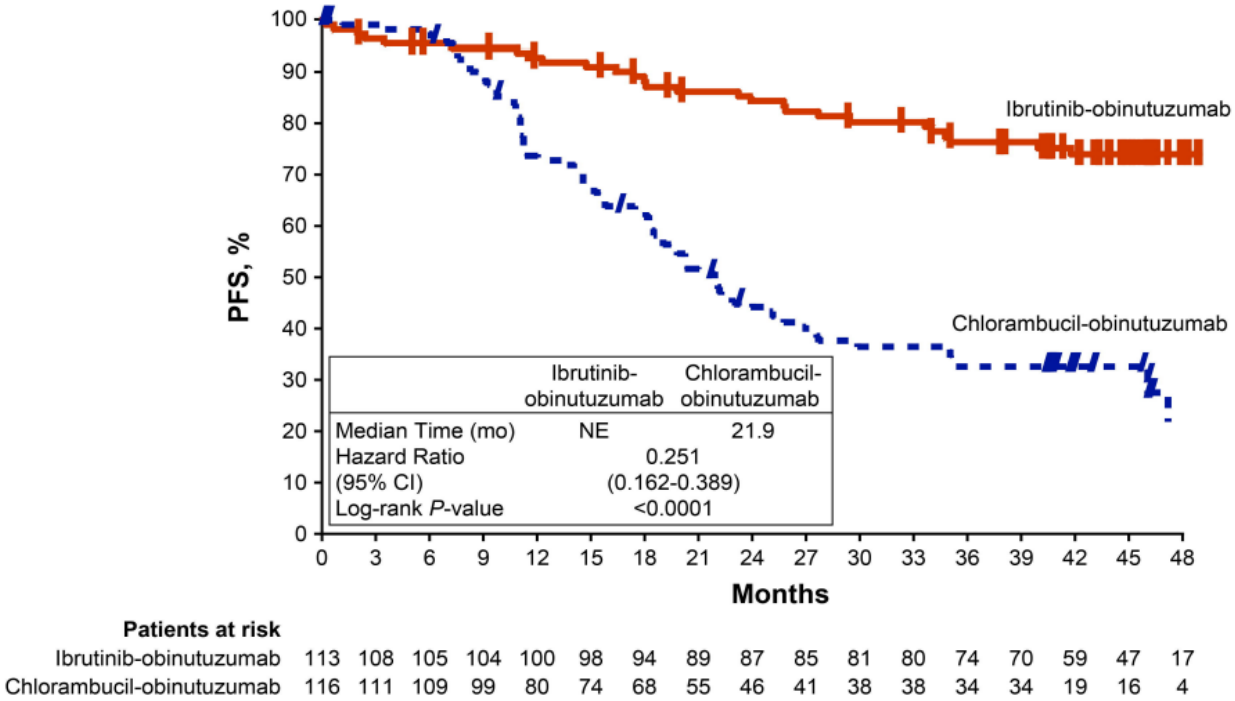
	G-Clb n=333	R-Clb n=330
Patients with events, n (%)	121 (36.3)	147 (44.5)
5-year OS, % (95% CI)	66 (61–72)	57 (51–62)
Median OS, months	NR	73.1
HR (95% CI), p-value	0.76 (0.60–0.97), p=0.0245	

Median observation time: 59.4 months

G-Clb indicates obinutuzumab and chlorambucil; R-Clb, rituximab and chlorambucil.

Goede V, et al. Presented at: EHA 2018. Abstract S151.

Higher efficacy of targeted agents over Chlorambucil + Obinutuzmab: Ibrutinib + Obinutuzumab



Median observation time: 45 months

C. Moreno et al., Haematologica 2022

Trials firstline of unfit patients

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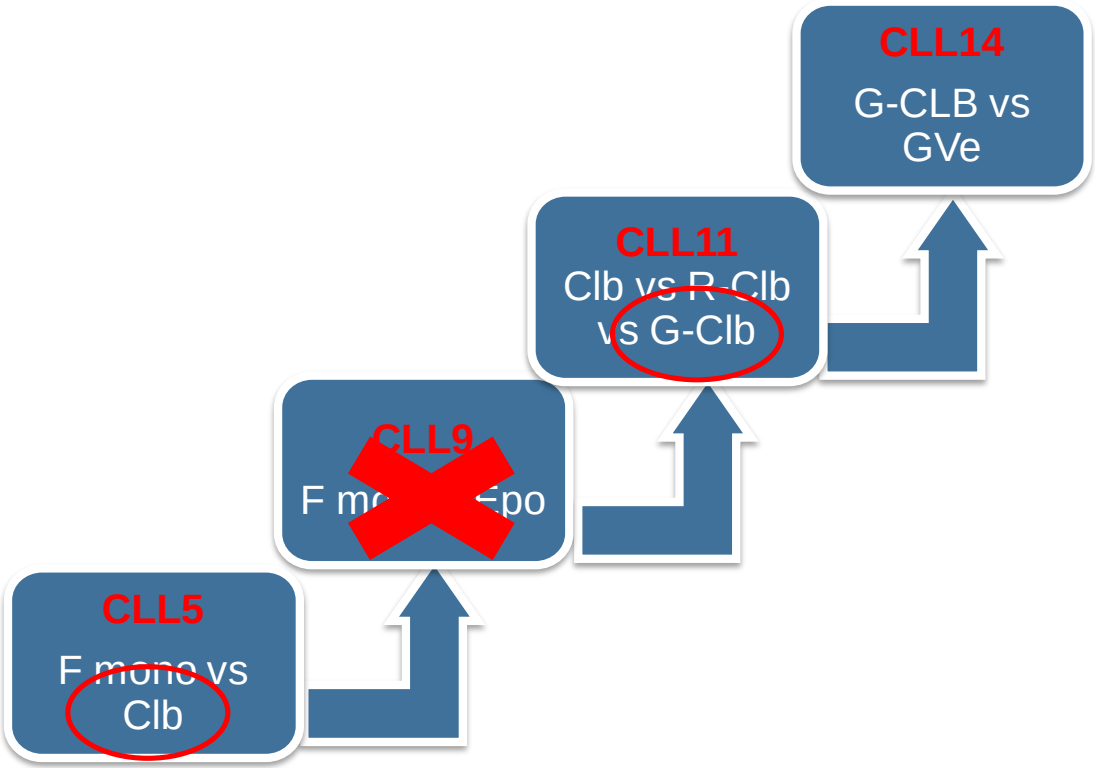
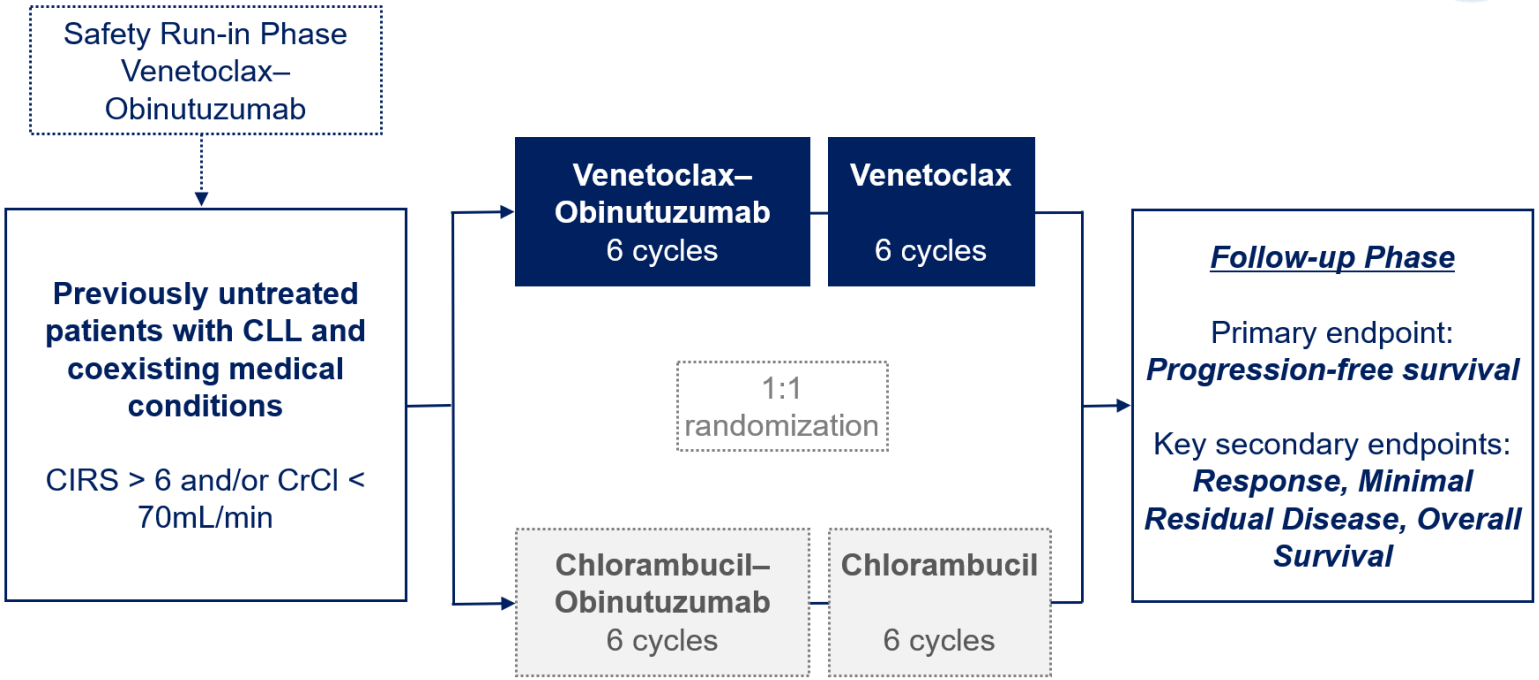


CLL14 study: firstline Venetoclax + Obinutuzumab in unfit patients



Al Sawaf et al., EHA 2022 S 148

Most frequent ≥ grade 3 adverse events

	Venetoclax-obinutuzumab (N=212)		Chlorambucil-obinutuzumab (N=214)	
	During Treatment	**After Treatment**	**During Treatment**	**After Treatment**
Neutropenia	51.9%	4.0%	47.2%	1.9%
Thrombocytopenia	14.2%	0.5%	15.0%	0.0%
Anemia	7.5%	2.0%	6.1%	0.5%
Febrile neutropenia	4.2%	1.0%	3.3%	0.5%
Leukopenia	2.4%	0.0%	4.7%	0.0%
Pneunomia	3.8%	3.0%	3.3%	1.4%
Infusion-related reaction	9.0%	0.0%	9.8%	0.5%
Tumour lysis syndrome	1.4%	0.0%	3.3%	0.0%

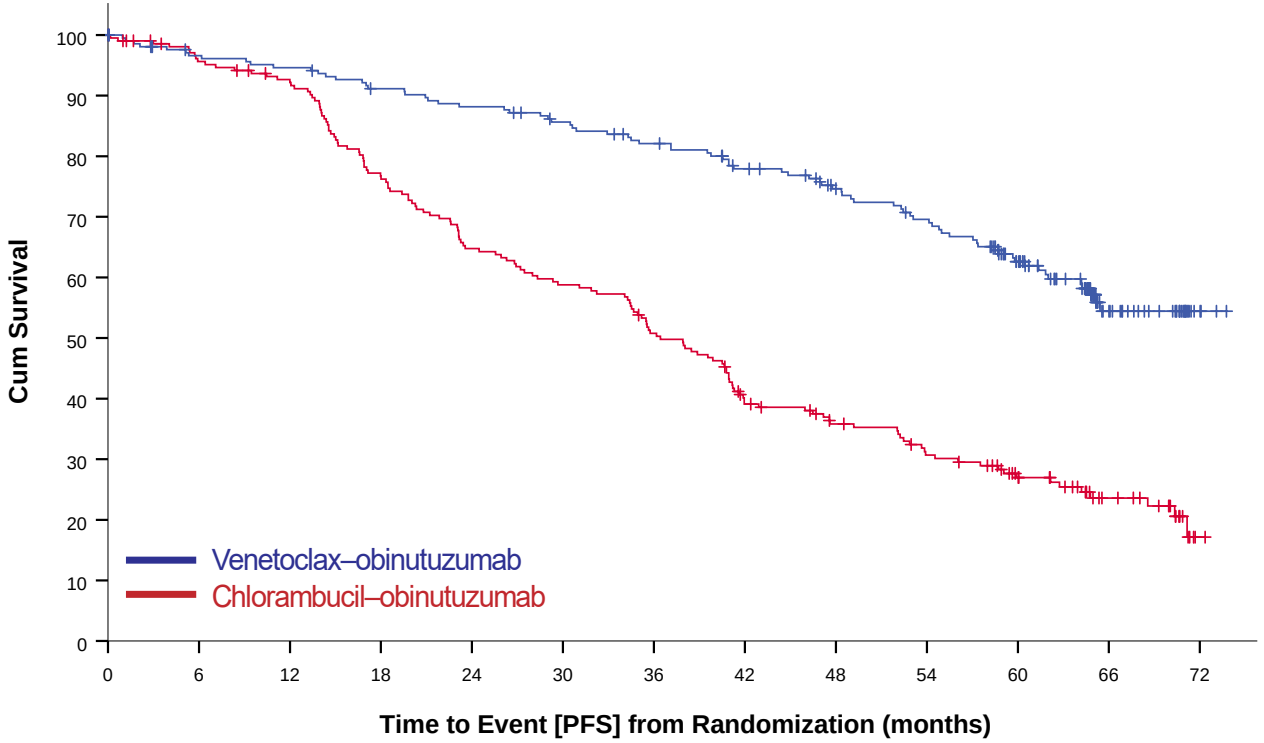
Al Sawaf et al., EHA 2022 S 148

Second primary malignancies

	Venetoclax-Obinutuzumab (N=212)	Chlorambucil-Obinutuzumab (N=214)
Overall total number of events	**55**	**44**
Number of patients with at least one SPM	44 (20.8%)	32 (15.0%)
Non-melanoma skin cancer	19 (9.0%)	18 (8.4%)
Melanoma	8 (3.8%)	3 (1.4%)
Solid organ tumours	15 (7.1%)	10 (4.7%)
Haematological malignancies	3 (1.4%)	2 (0.9%)
Other	1 (0.5%)	1 (0.5%)

Progression-free survival

Median observation time 65.4 months



Ven-Obi	216	196	192	183	177	169	160	147	134	123	97	35	4
Clb-Obi	216	195	185	154	130	118	101	75	64	53	39	21	1

Median PFS

Ven-Obi: not reached

Clb-Obi: 36.4 months

5-year PFS rate

Ven-Obi: 62.6%

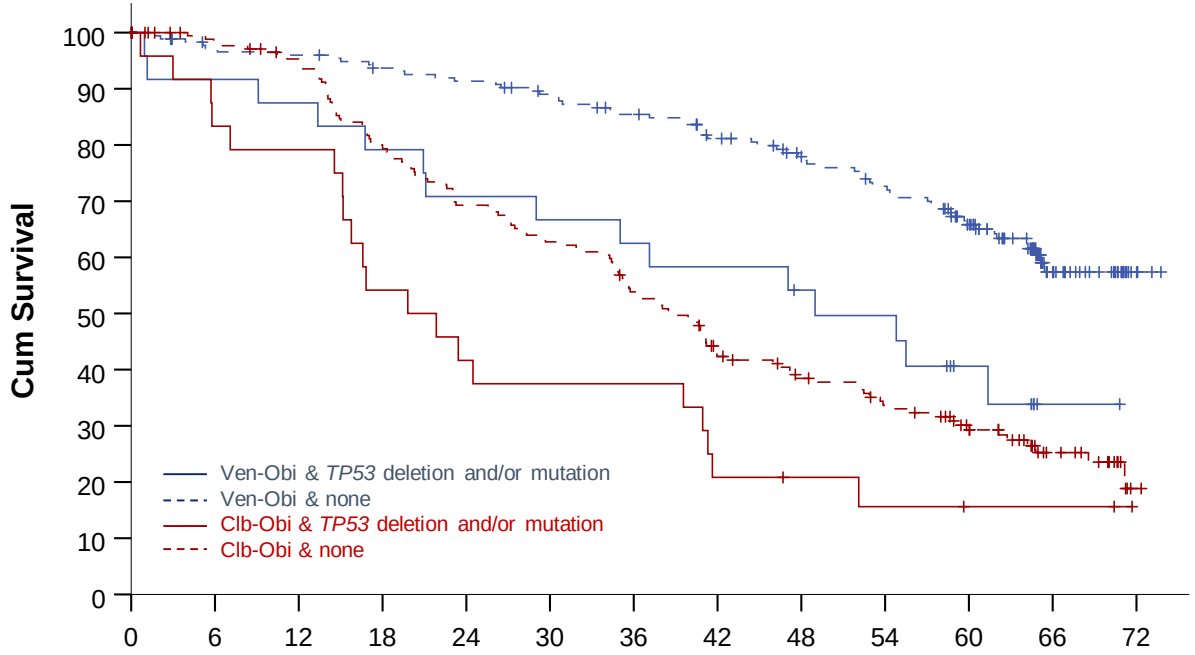
Clb-Obi: 27.0%

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

Al Sawaf et al., EHA 2022 S 148

Progression-free survival – *TP53* status

Median observation time 65.4 months



Ven-Obi & *TP53* del/mut	25	22	21	19	17	16	15	14	12	11	6	1	0
Ven-Obi & none	184	169	167	161	157	150	142	130	119	109	89	33	4
Clb-Obi & *TP53* del/mut	24	20	19	13	10	9	9	5	4	3	2	2	0
Clb-Obi & none	184	169	160	135	117	106	90	68	58	48	36	18	1

Median PFS

Ven-Obi & no *TP53*del/mut: NR

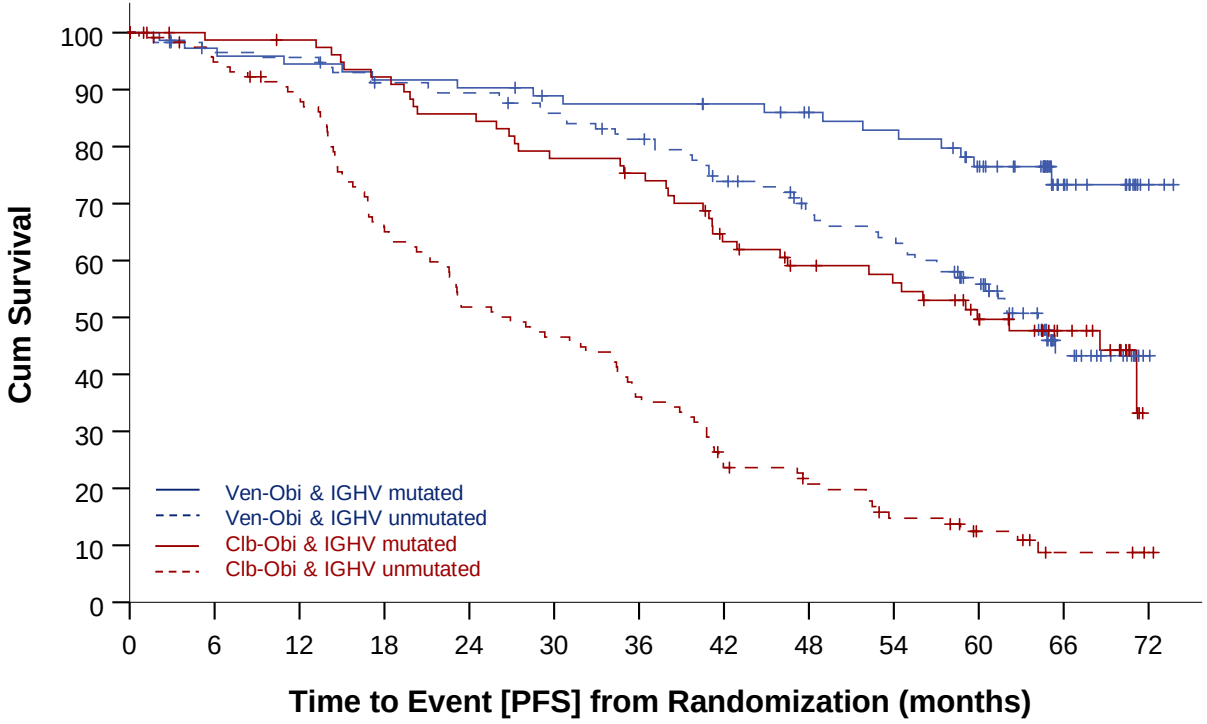
Ven-Obi & *TP53*del/mut: 49.0 m

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

Clb-Obi & *TP53*del/mut: 19.8 m

Progression-free survival – IGHV status

Median observation time 65.4 months



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

Median PFS

Ven-Obi & IGHVmut: NR

Ven-Obi & IGHVunmut: 64.2m

Clb-Obi & IGHVmut: 59.9m

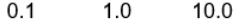
Clb-Obi & IGHVunmut: 26.9m

Progression-free survival

Multivariable models

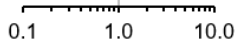
Ven-Obi

COX regression PFS	Univariate comparison	Hazard ratio	95% Wald CI
Disease burden category (TLS risk category)			
High	Vs. intermediate/low	2.815	1.773-4.469
Deletion 17p			
del(17p)	vs. no del(17p)	3.150	1.727-5.745



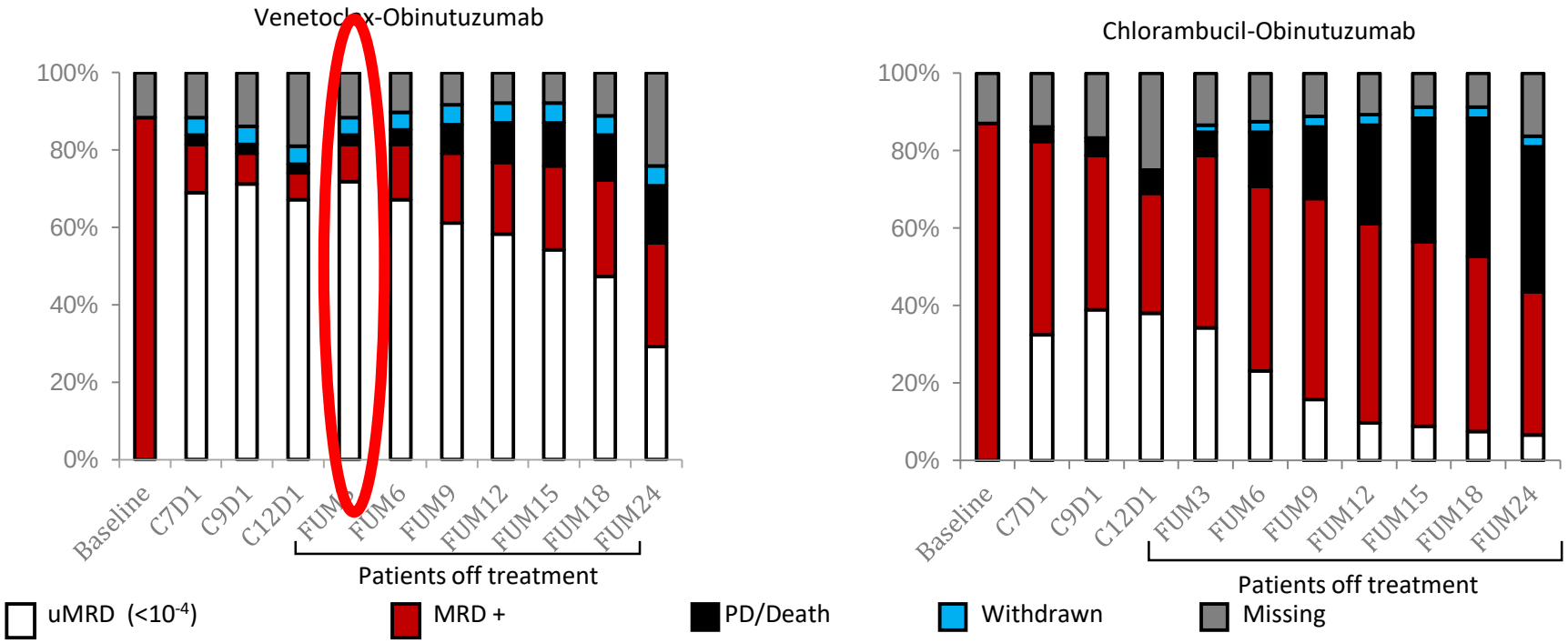
Clb-Obi

COX regression PFS	Univariate comparison	Hazard ratio	95% Wald CI
Serum β2 microglobulin			
> 3.5	vs. <= 3.5	1.534	1.037-2.269
IGHV mutational status			
unmutated	Vs. mutated	2.765	1.847-4.141
Deletion 17p			
del(17p)	vs. no del(17p)	2.667	1.413-5.036
Deletion 11q			
del(11q)	vs. no del(11q)	2.056	1.331-3.177
Complex Karyotype			
CKT/HCKT	vs. NCKT	2.761	1.720-4.433



In the context of Ven-Obi, **pre-treatment disease burden** (max. lymph node size >5 cm and absolute lymphocyte count > 25 G/l) and **deletion 17p** are independent prognostic factors for PFS.

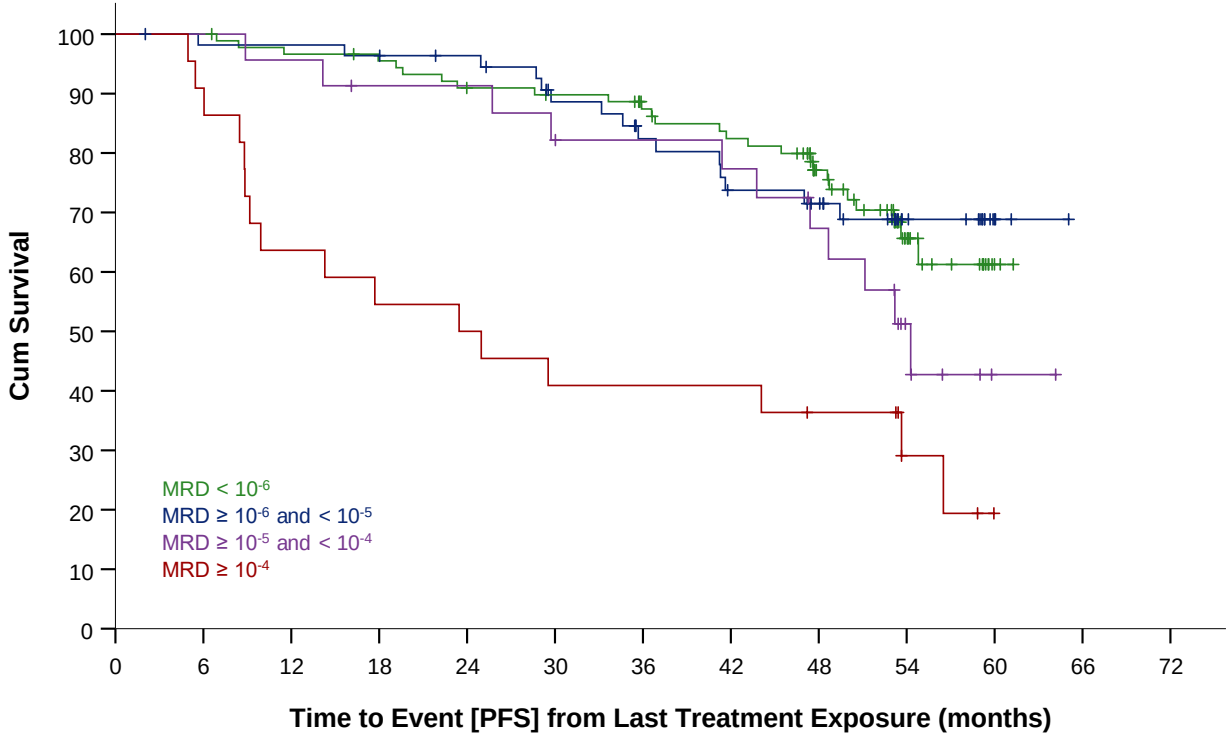
MRD kinetics by ASO-PCR in pB



Fischer K. et al., ASH 2019, Abstract #36

PFS after ven-obi according to MRD status

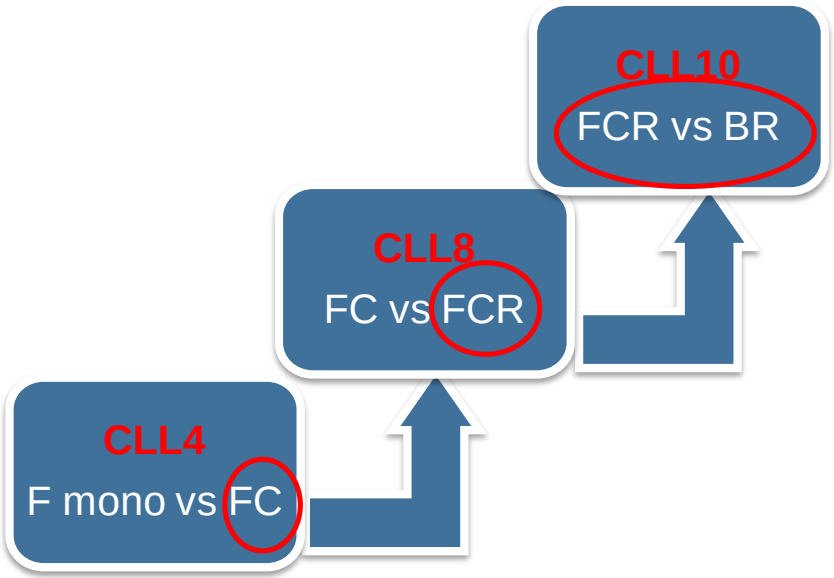
End of treatment MRD status in peripheral blood, by NGS



MRD < 10^{-6}	90	90	86	84	79	77	71	66	48	21	2	0	0
MRD ≥ 10^{-6} and < 10^{-5}	56	54	54	53	51	44	38	33	30	14	3	0	0
MRD ≥ 10^{-5} and < 10^{-4}	23	23	22	20	20	18	17	16	13	6	1	0	0
MRD ≥ 10^{-4}	22	20	14	12	11	9	9	9	7	3	0	0	0

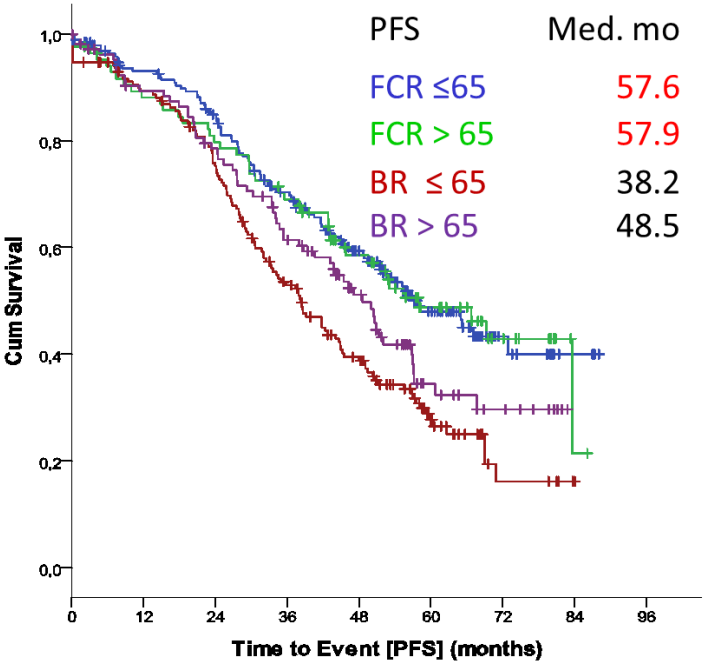
Depth of remission **beyond 10^{-4}** correlates with **long-term PFS**, indicating the value of ultra-sensitive MRD assessments.

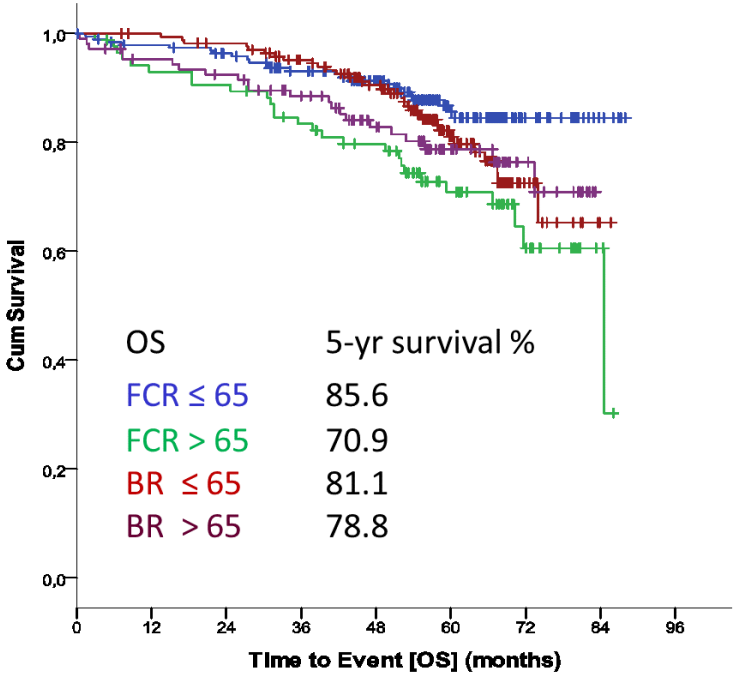
Trials firstline fit patients



CLL10 non-inferiority study: FCR VS BR in frontline of fit patients

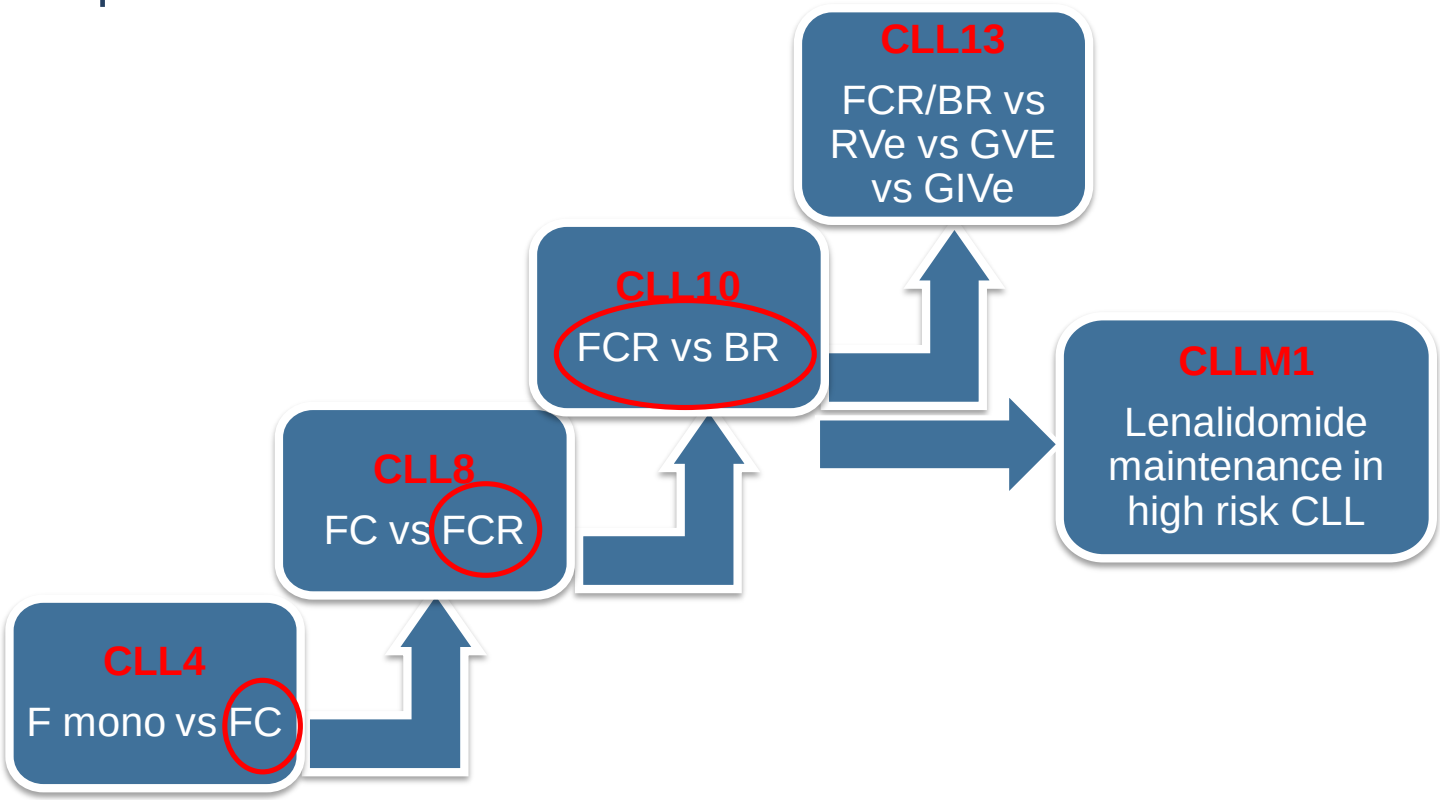
Median observation time of 57 months





Kutsch N et al., 2020 Hemasphere

Trials firstline fit patients

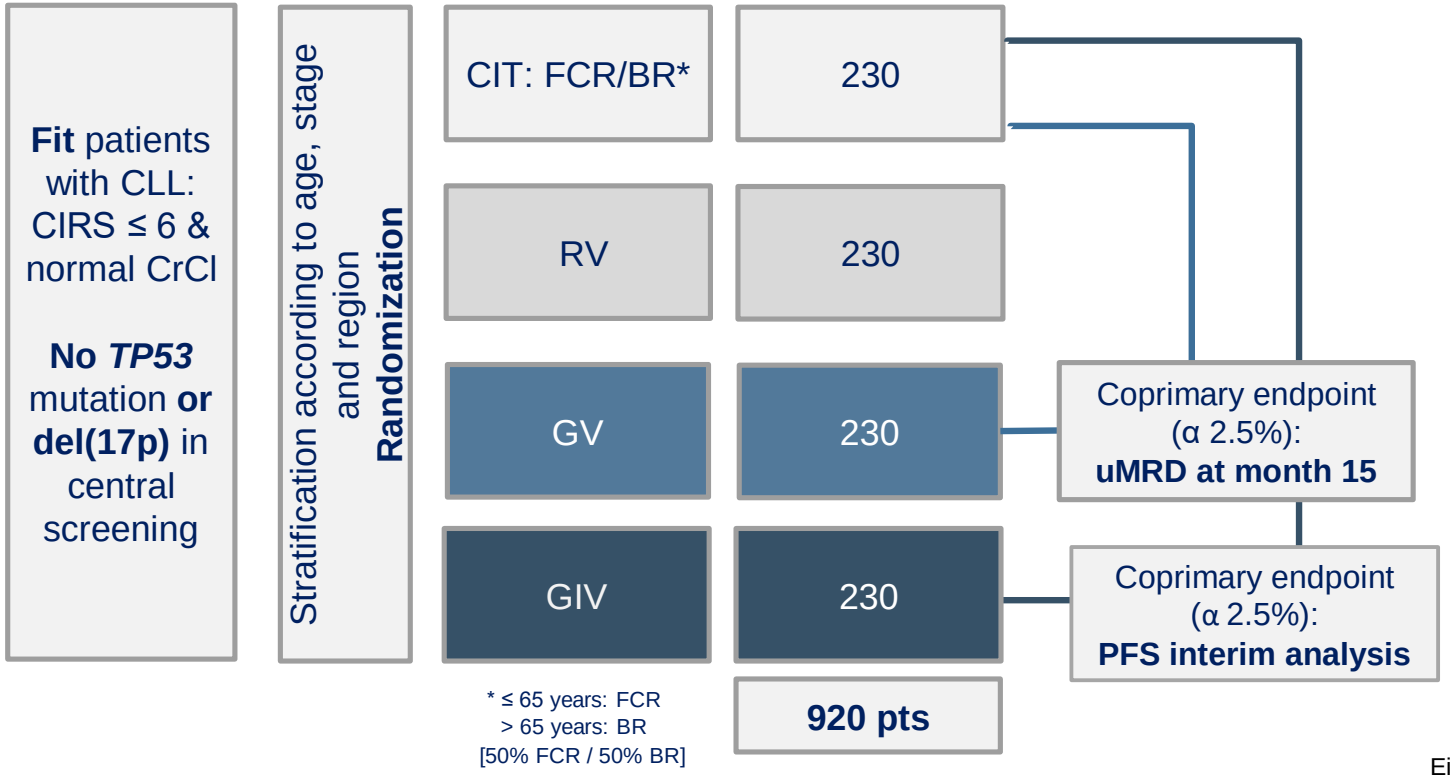


TIME-LIMITED VENETOCLAX-OBINUTUZUMAB +/- IBRUTINIB IS SUPERIOR TO CHEMOIMMUNOTHERAPY IN FRONTLINE CHRONIC LYMPHOCYTIC LEUKEMIA (CLL): PFS CO-PRIMARY ENDPOINT OF THE RANDOMIZED PHASE 3 GAIA/CLL13 TRIAL

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

GAIA/CLL13 study design for fit patients with CLL

Chemoimmunotherapy (**FCR/BR**) versus **R**ituximab + **V**enetoclax versus Obinutuzumab (**G**) + **V** versus **G** + **I**brutinib + **V**
Recruitment in 10 countries (DE, AT, CH, NL, BE, DK, SE, FI, IE, IL)



Eichhorst et al., EHA 2022 LBA-2365

Adverse Events ≥ CTC Grade 3 Overview of GAIA/CLL13 trial

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

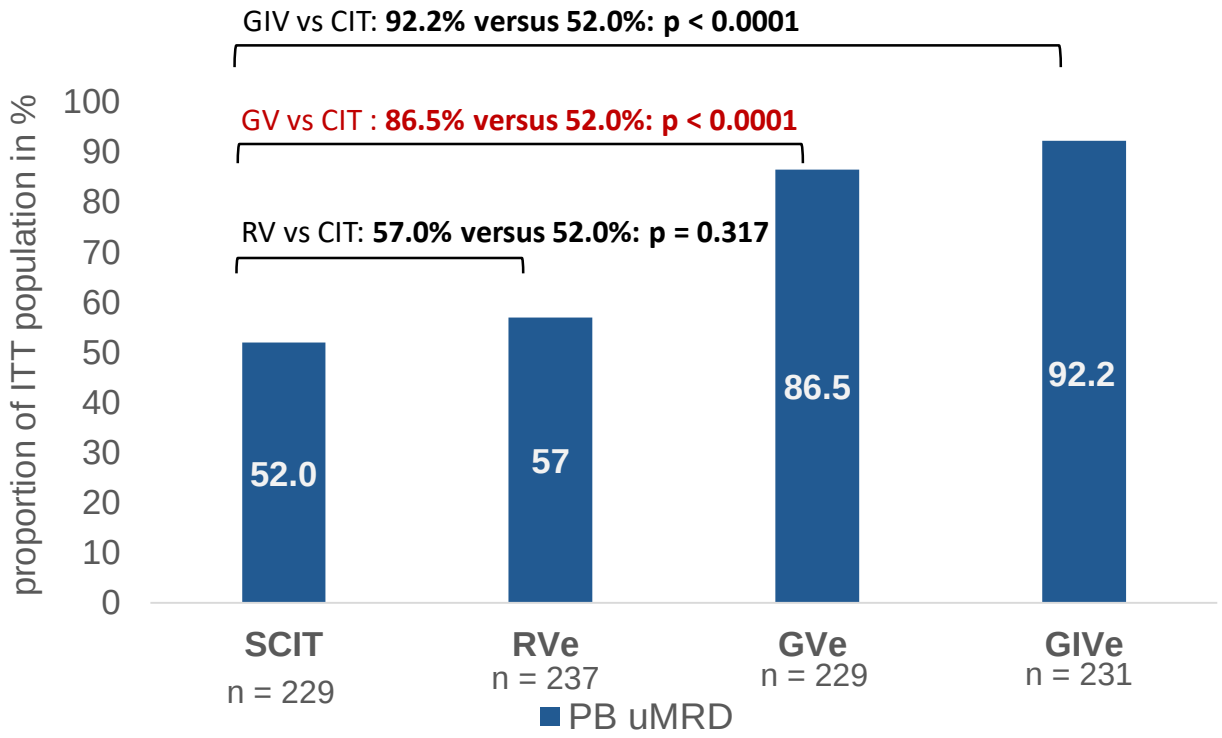
	CIT	RV	GV	GIV
All patients of safety population	**216**	**237**	**228**	**231**
All ≥ CTC grade 3 events (%)	**176 (81.5)**	**173 (73.0)**	**192 (84.2)**	**193 (83.5)**
Blood and lymphatic system (%)	122 (56.5)	103 (43.5)	128 (56.1)	117 (50.6)
Infections and infestations (%)	44 (20.4)	27 (11.4)	34 (14.9)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

* Defined by Cairo-Bishop criteria

Eichhorst et al., EHA 2022 LBA-2365

CLL13: Results of coprimary endpoint rate of undetectable minimal residual disease (uMRD)

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

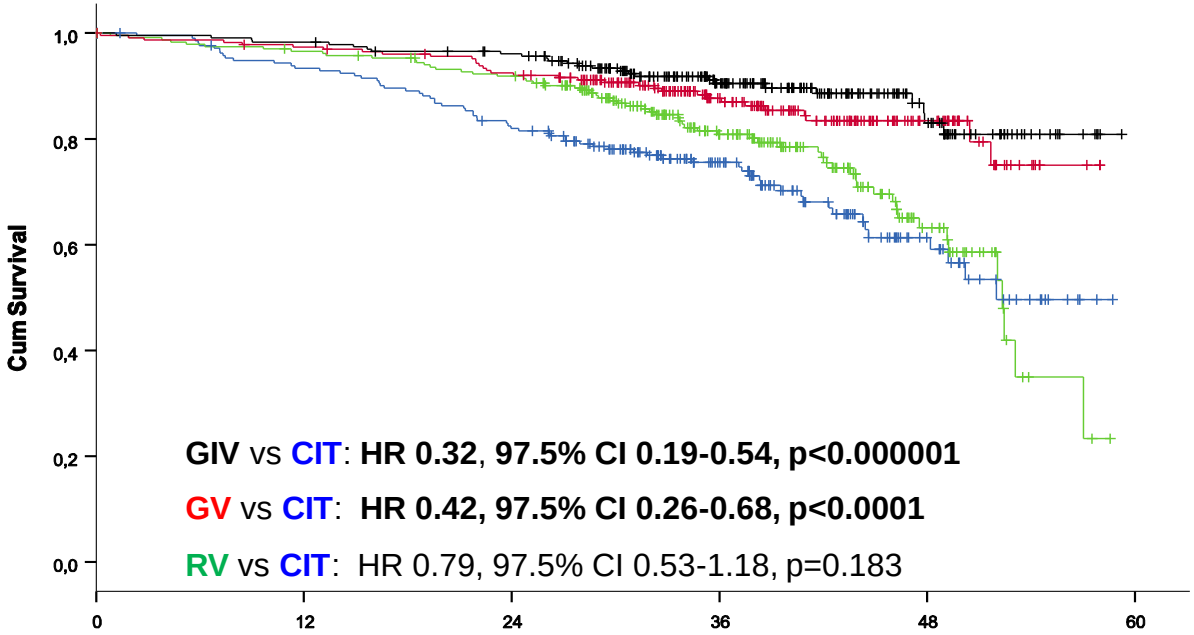


	uMRD%	97.5% CI
GIV	92.2	87.3 – 95.7
GV	86.5	80.6 – 91.1
RV	57.0	49.5 – 64.2
CIT	52.0	44.4 – 59.5

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

CLL13: Results of the coprimary endpoint progression-free survival (PFS)

Median FU 38.8 months (range: 0.0 – 59.2)



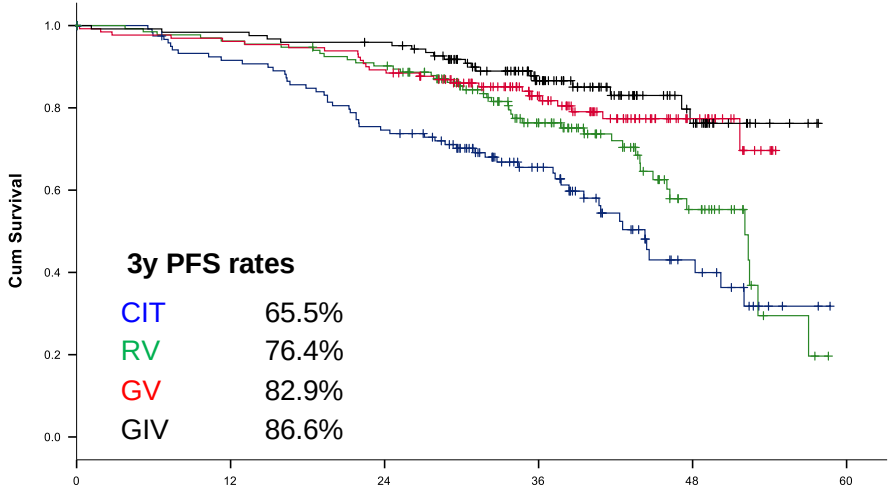
	0	12	24	36	48	60
CIT	229	197	172	98	28	
RV	237	226	212	119	32	
GV	229	221	208	125	42	
GIV	231	227	217	132	44	

PFS	Median months	3y PFS (%)
CIT	52.0	75.5
RV	52.3	80.8
GV	Not reached	87.7
GIV	Not reached	90.5

Eichhorst et al., EHA 2022 LBA-2365

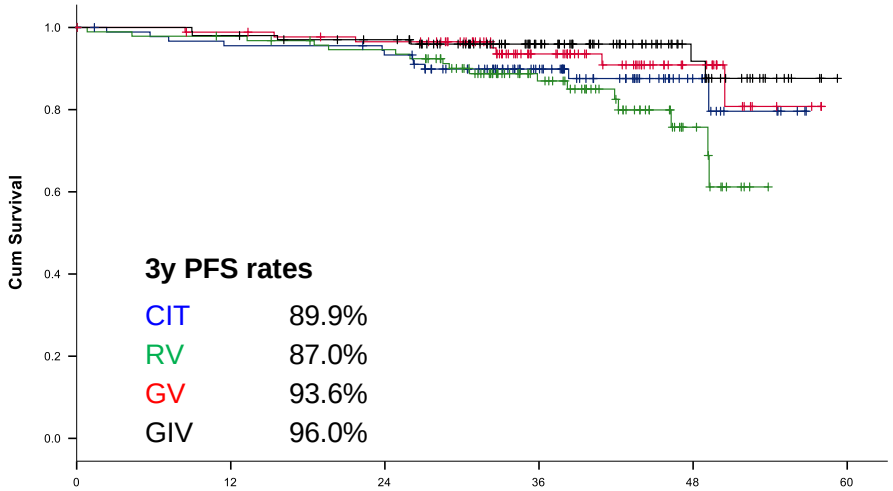
PFS according to IGHV status

Unmutated IGHV



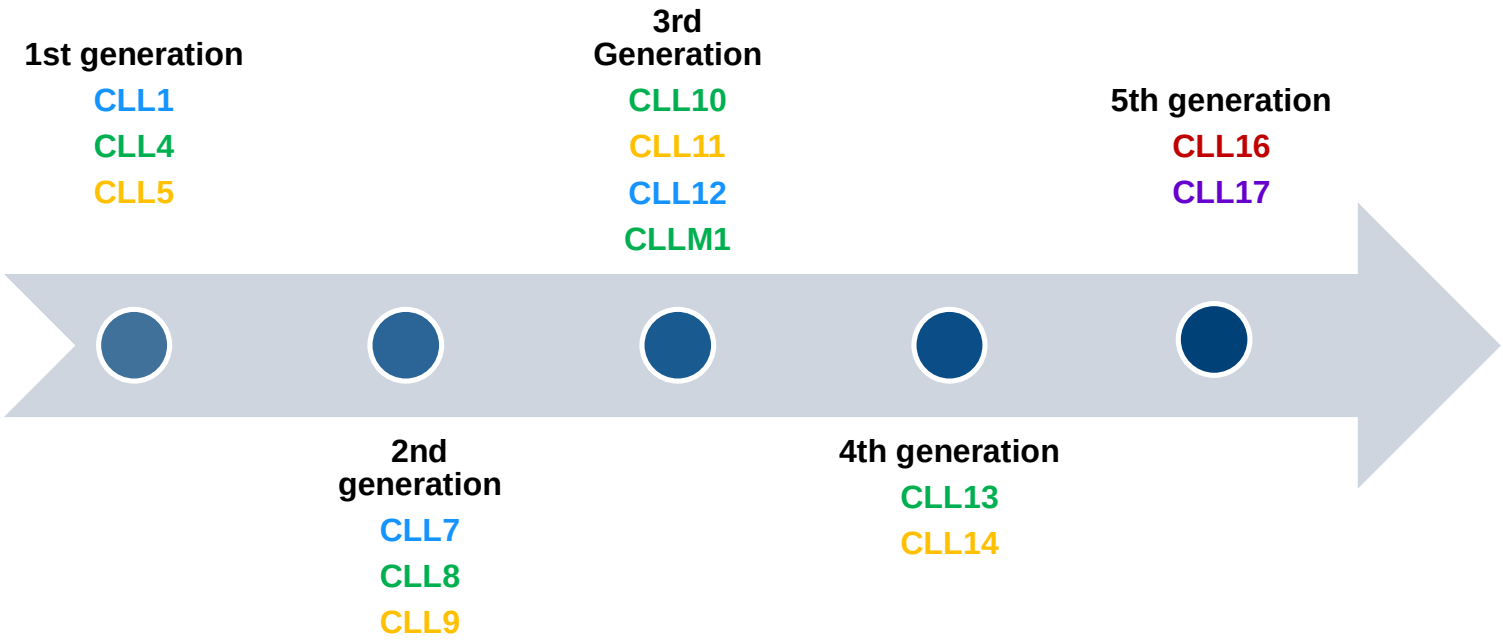
CIT	131	108	88	48	14
RV	134	128	119	67	20
GV	130	125	116	71	21
GIV	123	121	117	70	22

Mutated IGHV



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

Concept of GCLLSG trials

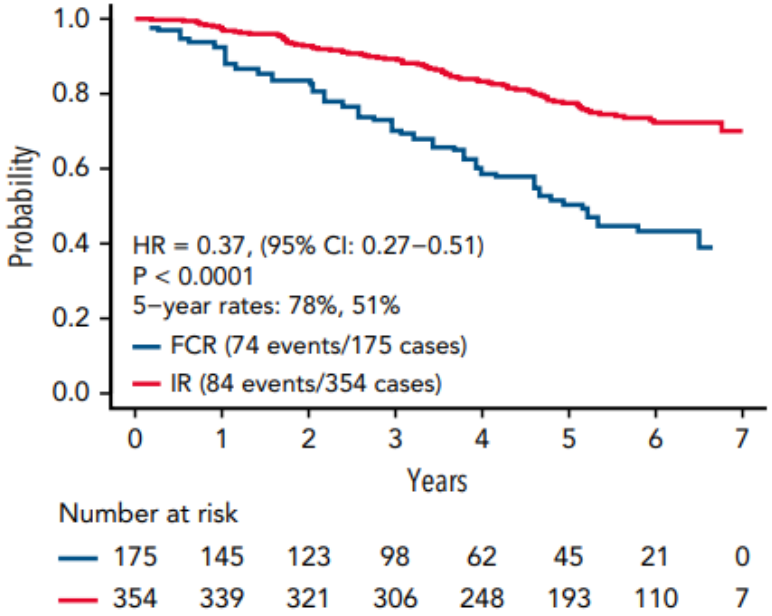


Early stage disease Advanced stge + fit Advanced stage + less fit

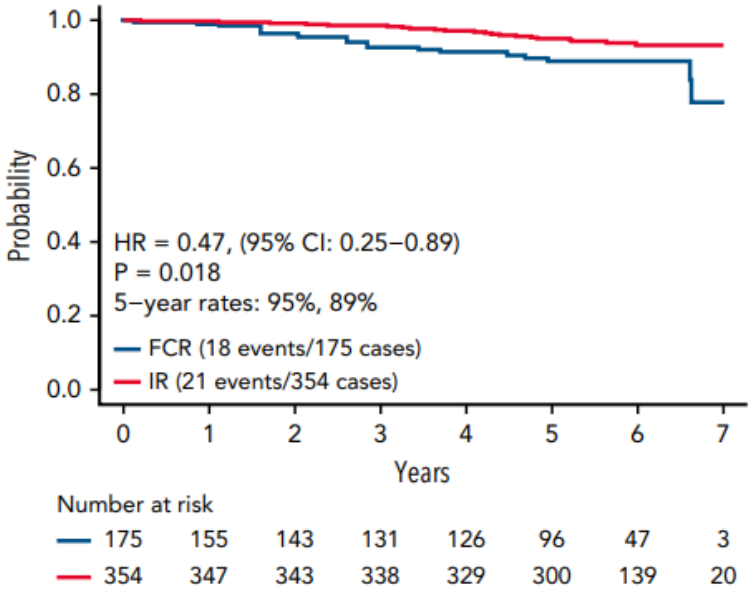
High risk All comer

Higher efficacy of targeted agents over FCR: E1912 Ibrutinib+Rituximab

PFS



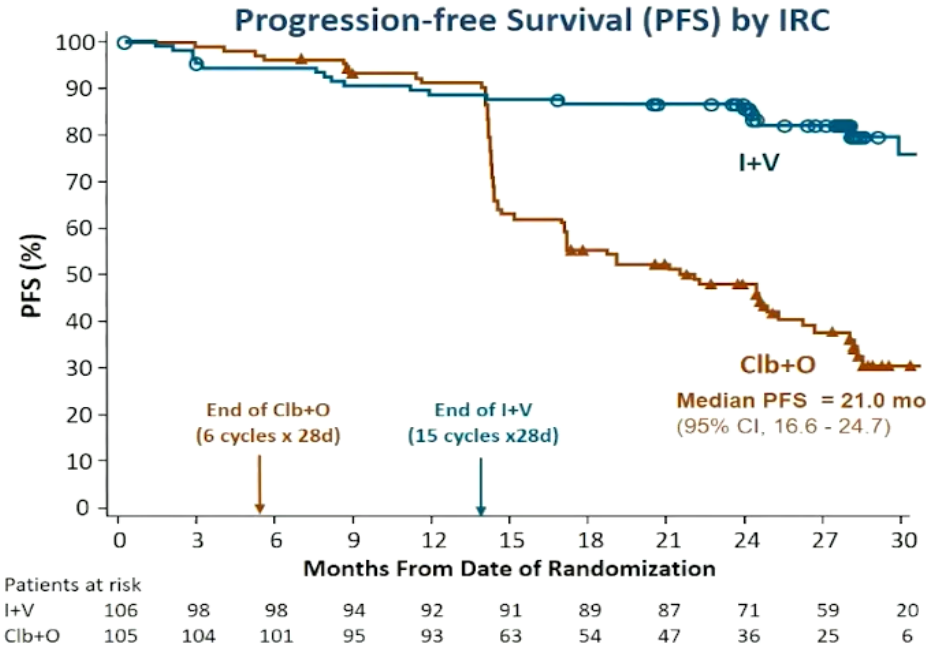
OS



Median observation time: 70 months

Shanafelt T. et al., Blood 2022; 140:2

Glow study (IV vs. ClbObin): PFS after 27.7 months



HR 0.216 (95% CI, 0.131-0.357; p < 0.0001)

Kater A.P. et al. NEJM evidence 2022; Vol1 No. 7

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

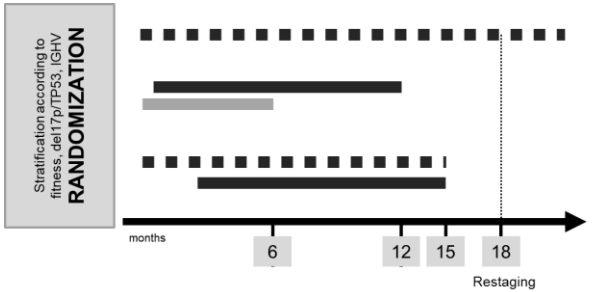
Stratification according to fitness, del17p/TP53, IGHV

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

DEUTSCHE STUDIENGRUPPE CLL

Swiss CLL Study Group

cancer trials ireland

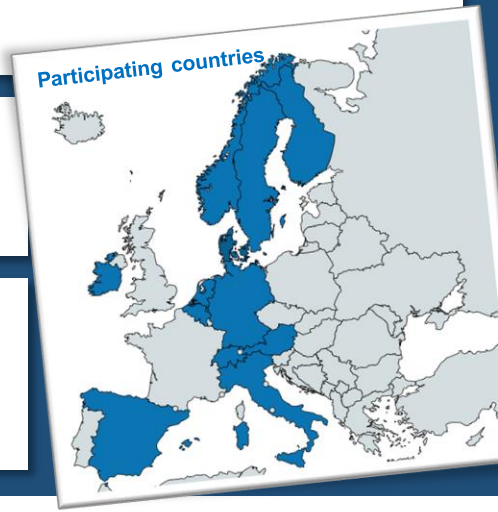
The Israeli CLL Association (ICLLA)
CLL
The Israeli CLL Study Group (ICLLSG)

HOVON

GELLC Grupo Español de Leucemia Linfocítica Crónica

fondazione GIMEMA FRANCO MANDELLI

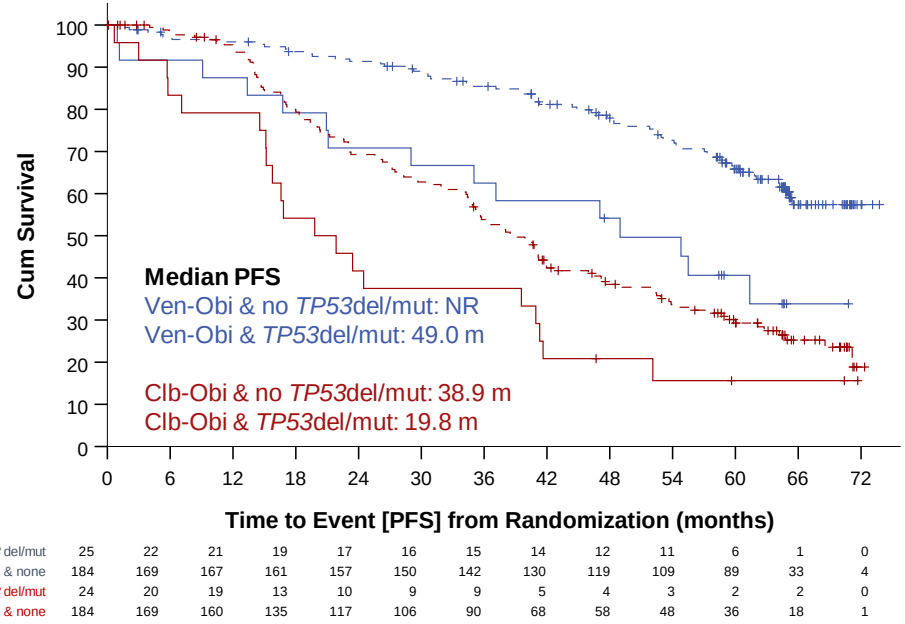
SAKK



Treatment of very high risk CLL with *TP53* aberration

Higher efficacy of targeted agents over CIT in pts with del(17p)/TP53 mutation

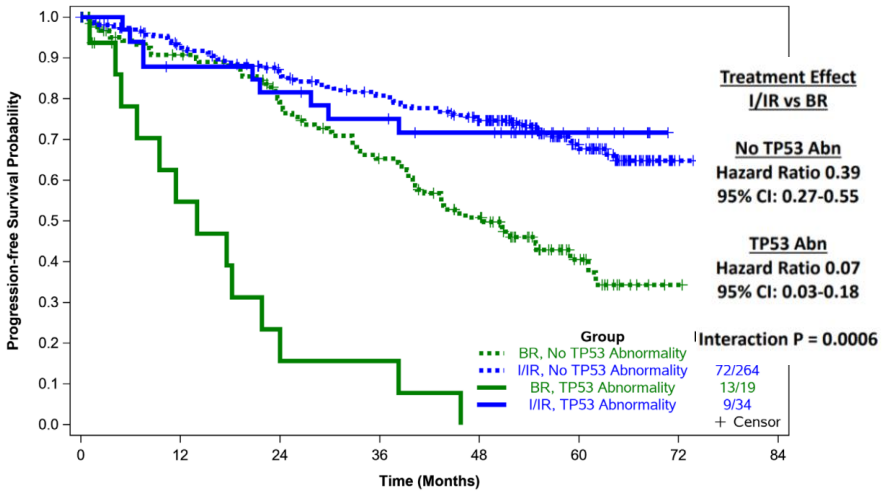
Ven + Obin vs



Ven-Obi & *TP53* del/mut	25	22	21	19	17	16	15	14	12	11	6	1	0
Ven-Obi & none	184	169	167	161	157	150	142	130	119	109	89	33	4
Clb-Obi & *TP53* del/mut	24	20	19	13	10	9	9	5	4	3	2	2	0
Clb-Obi & none	184	169	160	135	117	106	90	68	58	48	36	18	1

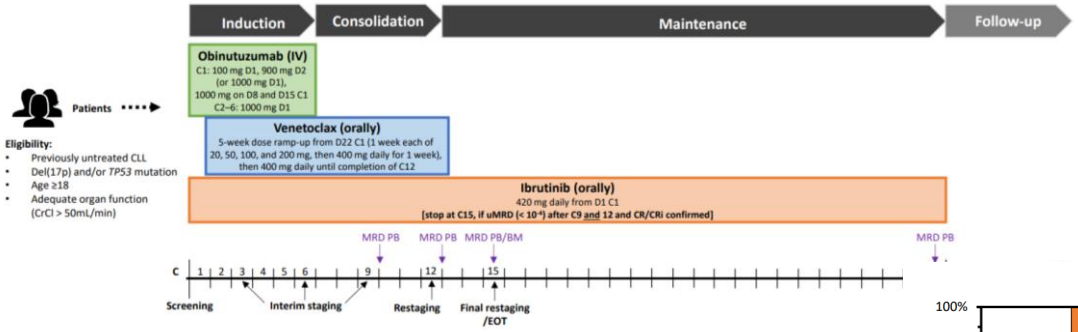
Al Sawaf et al., EHA 2022 S 148

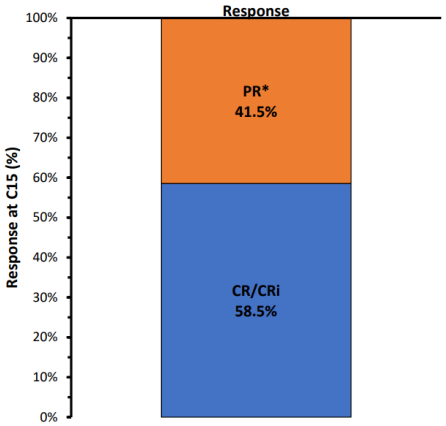
Ibrutinib +/- R vs BR

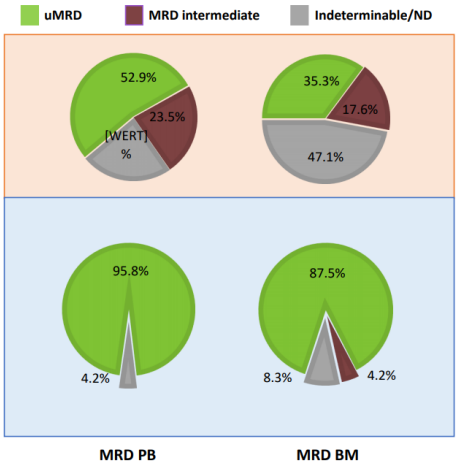


Woyach J et al., ASH 2021 abstract 639

Evaluating triple combination (ibrutinib + venetoclax + obinutuzumab) in high risk CLL: CLL2 GIVE study of the GCLLSG



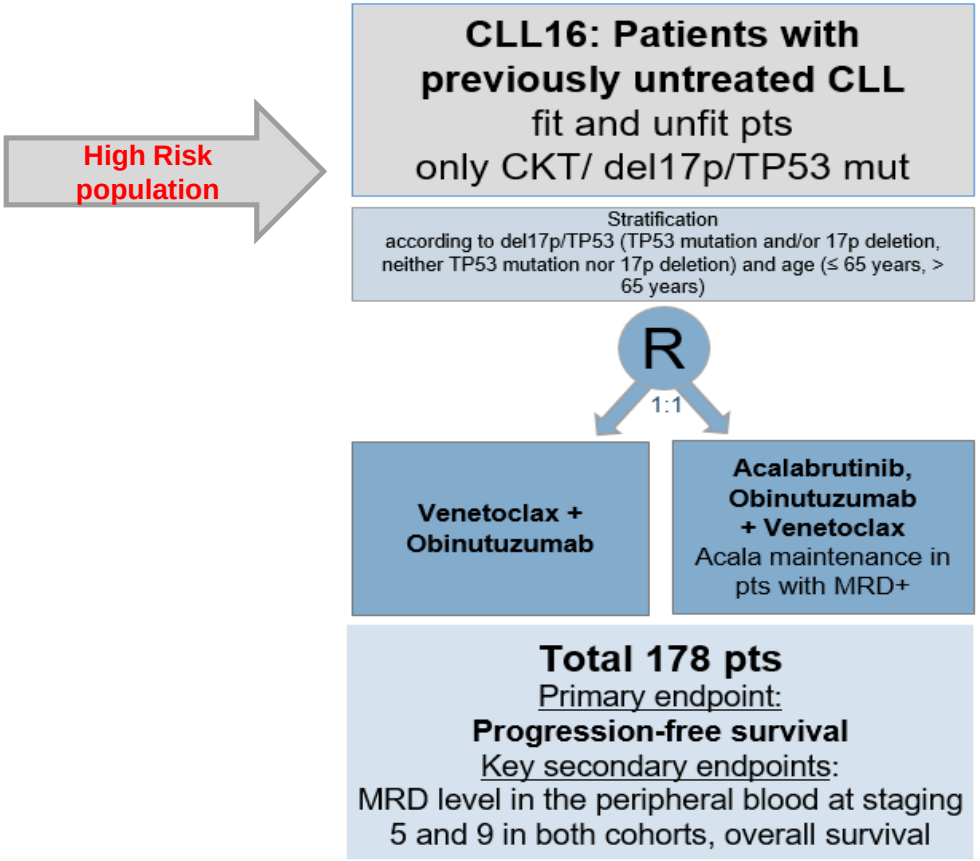




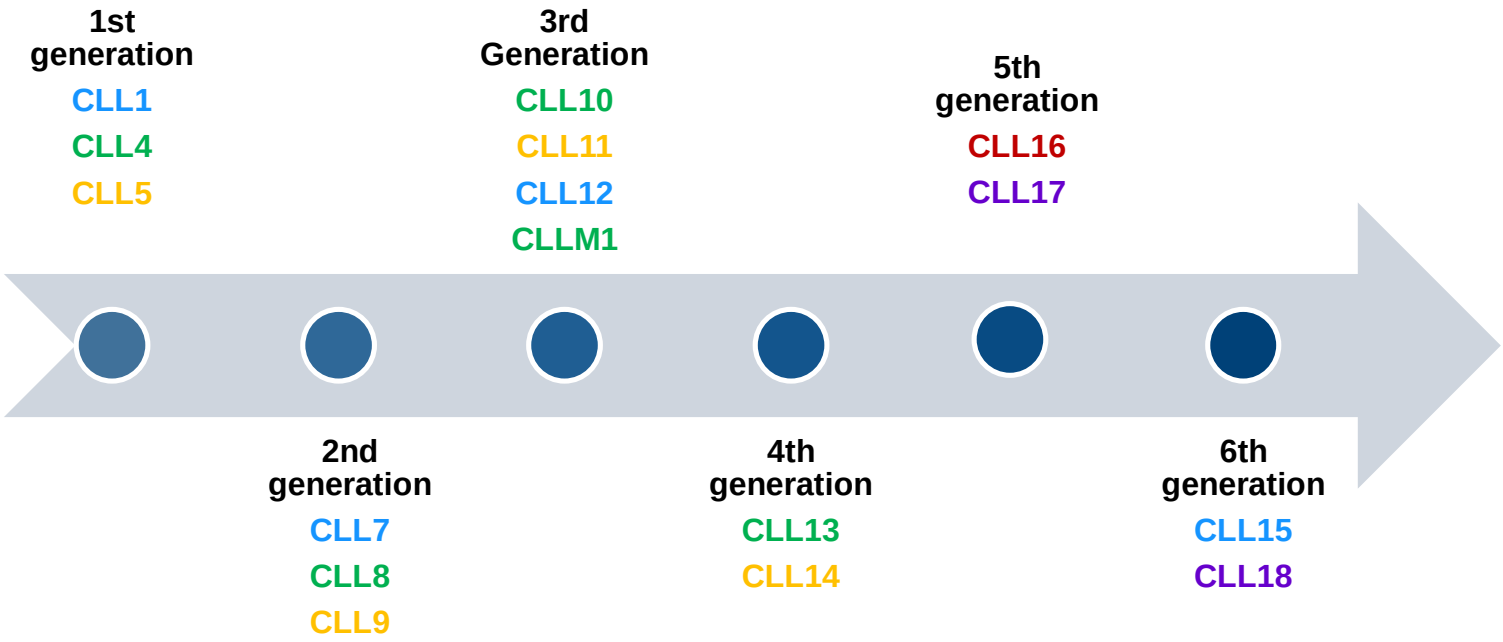
H Huber et al.,Blood 2022; Vol 139; 9

CLL16 study for HR-CLL

DEUTSCHE STUDIENGRUPPE

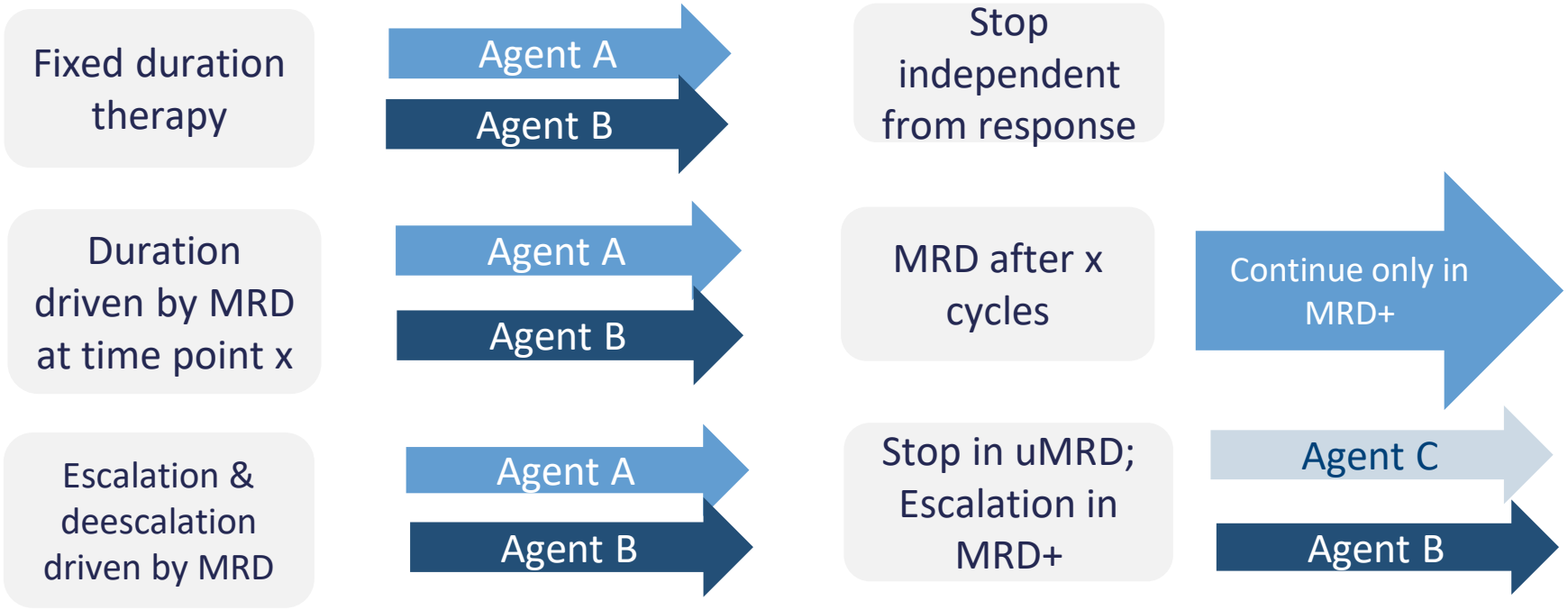


Concept of GCLLSG trials



Even more challenges in CLL

Optimizing treatment outcome in CLL



In addition to that:

- Measuring MRD to 10^{-6} (+ X)
- Select agent according to genetic/genomic risk profile

…and many other questions

- ✓ Concepts for early stage CLL?

- ✓ Reexposure to BTKi/BCL2i after prior therapy ?
- ✓ Routine testing for BTK resistance mutation ?
  - → Quinquenel et al., Blood 2019
- ✓ Role of non-covalent BTKi ?

- ✓ Treatment of double refarctory patients


Moritz Fürstenau
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Janina Stumpf
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