Therapiekonzepte bei der Hochrisiko CLL

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High-risk CLL: Definition

Deletion of chromosome 17p (del(17p)):
- Incidence in 5%–8% of chemotherapy-naïve patients.[1]
- Method: Fluorescence in situ hybridization (FISH)

***TP53* mutation**:
- Incidence in 5-7% at initial diagnosis[2,3];
- Incidence up to 40% in relapsed/refractory CLL[2,3]
- Method: Sanger Sequencing (cutoff ≥ 10%)[4]
- Method: Next generation sequencing (cutoff ≥ 0.1%)[7]

- CLL with del(17p): 50-80% of the patients have additional mutations in the remaining *TP53* allele.[2,5]
- CLL with sole *TP53* mutation(s): rarer, but similarly detrimental effect on chemotherapy response and overall survival.[6,7]

Further risk marker in CLL?

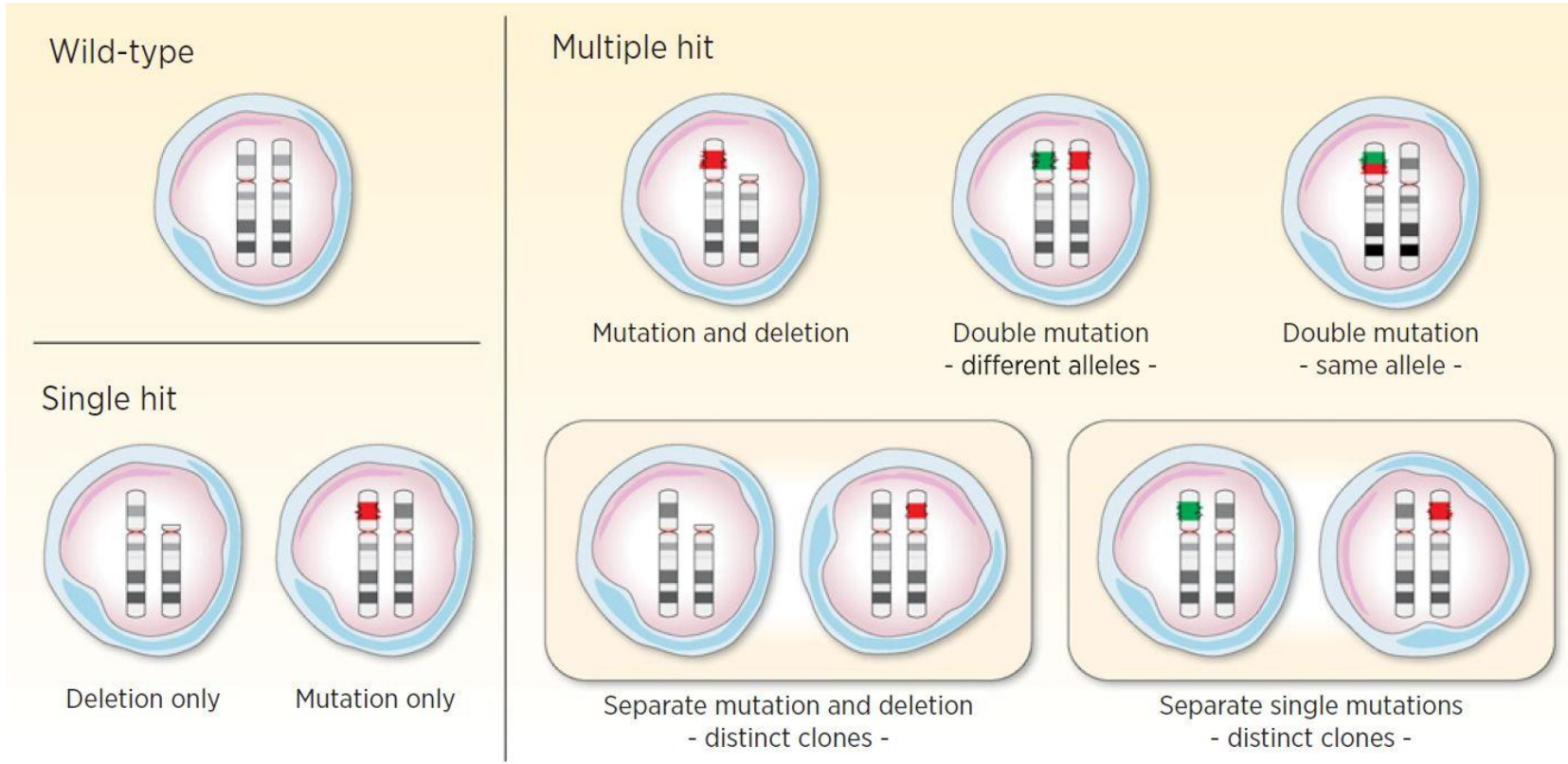
Complex karyotype (CKT):
[≥3 chromosomal abnormalities (CKT) [8]]
≥5 chromosomal abnormalities (highly CKT) [9]
- Incidence in 14-34% of patients[10]

Unmutated IGHV status
Incidence of 33% in Binet A CLL[11]
Incidence of 60% in CLL requiring treatment[12]

1. Hallek M, et al., *Lancet.*2010;376:1164-1174.
2. Zenz T, et al. *Leukemia.* 2010;24:2072-2079.
3. Stilgenbauer S, et al. *Blood.* 2014; 123:3247-3254.
4. Malcikova J, et al. *Leukemia.* 2018;32(5):1070-1080.
5. Bertossi C, et al. DGHO 2023
6. Seiffert M, et al. *Leuk Lymphoma*. 2012;53:1023-1031.
7. Malcikova J, et al. *Blood* 2021; 128: 2670-2685.
8. Baliakas P, et al. *Blood.* 2019 Mar 14;133(11):1205-1216.
9. Fürstenau M, et al. *Blood*. 2023 Aug 3;142(5):446-459.
10. Baliakas P, et al. *Am J Hematol*. 2014; 89(3):249-255.
11. Bergmann MA et al., *Leukemia.* 2017 Dec;31(12):2833-2837.
12. Fischer K et al. *N Engl J Med*. 2019 Jun 6;380(23):2225-2236.

High-risk CLL: Mutation in chromosome 17p: Variant outcomes and approach of an explanation

„Single hit“ CLL[1]:
- Presence of a sole del(17p)
- Presence of one *TP53*^{mut}



„Multiple hit“ CLL[1]:
- Presence of both del(17p) and *TP53*^{mut}
- More than one *TP53* mutations

Clinical impact:
- *TP53* aberrations: important biomarker with resistance to chemoimmunotherapy
- „Single hit“ CLL versus „multiple hit“ CLL: Do novel agents have an impact on outcome?[2-4]

1. Bomben R et al., *Clin Cancer Res*. 2021 Aug 15;27(16):4462-4464.
2. Bomben R et al. *Leukemia*. 2023 Apr;37(4):914-918.
3. Brieghel C et al *Clin Cancer Res*. 2021 Aug 15; Aug 15;27(16):4531-4538.
4. Huber H, *et al. Blood.* 2023 Sept 14; *142* (11): 961–972.

CLL del(17p)/*TP53*^{mut}: Landscape of phase 3 clinical trials for high-risk CLL

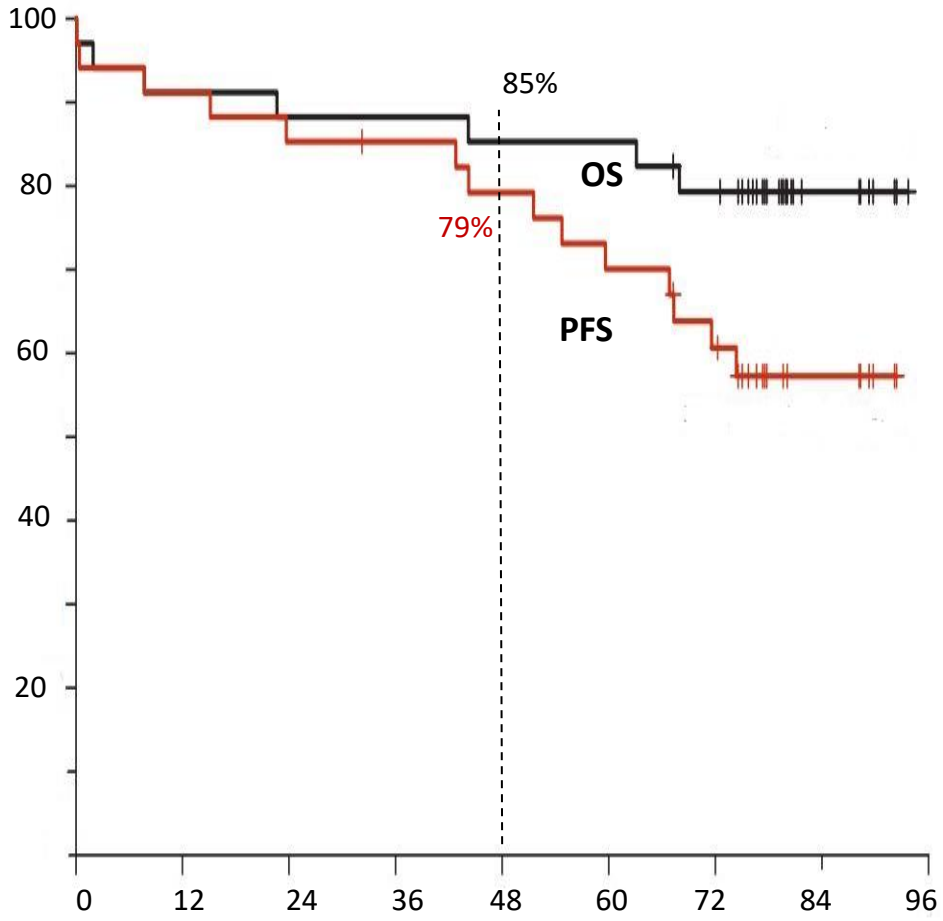
Trial	Patients with challenging molecular subtypes, n (%)		
	del(17p)	Mutated *TP53*	Unmutated IGHV
CLL13[1] **IVO/VenO/VenR vs CIT**	**del(17p) ineligible**	–	**518 (56%)**
RESONATE-2[2] **Ibr vs Clb**	**del(17p) ineligible**	**15 (7%)**	**118 (58%)**
Alliance A041202[3] **Ibr vs IR vs BR**	**34 (6%)**	**51 (10%)**	**218 (61%)**
iLLUMINATE[4] **IO vs Oclb**	**32 (14%)**	**29 (13%)**	**123 (57%)**
SEQUOIA[5](Cohorts A & B) **Zanu vs BR**	**del(17p) ineligible**	**28 (6%)**	**246 (53%)**
GLOW[6] **IVen vs Oclb**	**del(17p) ineligible**	**IVen: 6.6% OClb: 1.9%**	**IVen: 51.9% OClb: 51.4%**
CLL14[7] **VenO vs Oclb**	**31 (8%)**	**32 (10%)**	**244 (60%)**
CLL16 **VenOAlaca vs VenO**	**recruiting**	**recruiting**	**recruiting**

1. 3. Eichhorst B, *et al. N Engl J Med.* 2023 May 11;388(19):1739-1754. ;
2. Burger JA, *et al. Leukemia* 2020; **34:**787–798; 3. Woyach JA, *et al. N Engl J Med* 2018; **379:**2517–2528; 4. Moreno C, *et al. Lancet Oncol* 2019; **20:**43–56;
5. Tam CS, *et al. Lancet Oncol* 2022; **23**:1031–1043; 6. Kater AP, *et al.* EHA 2021. Abstract LB1902 (Oral); 7. Fischer K, *et al. N Engl J Med* 2019; **380:**2225–2236 (incl. suppl.).

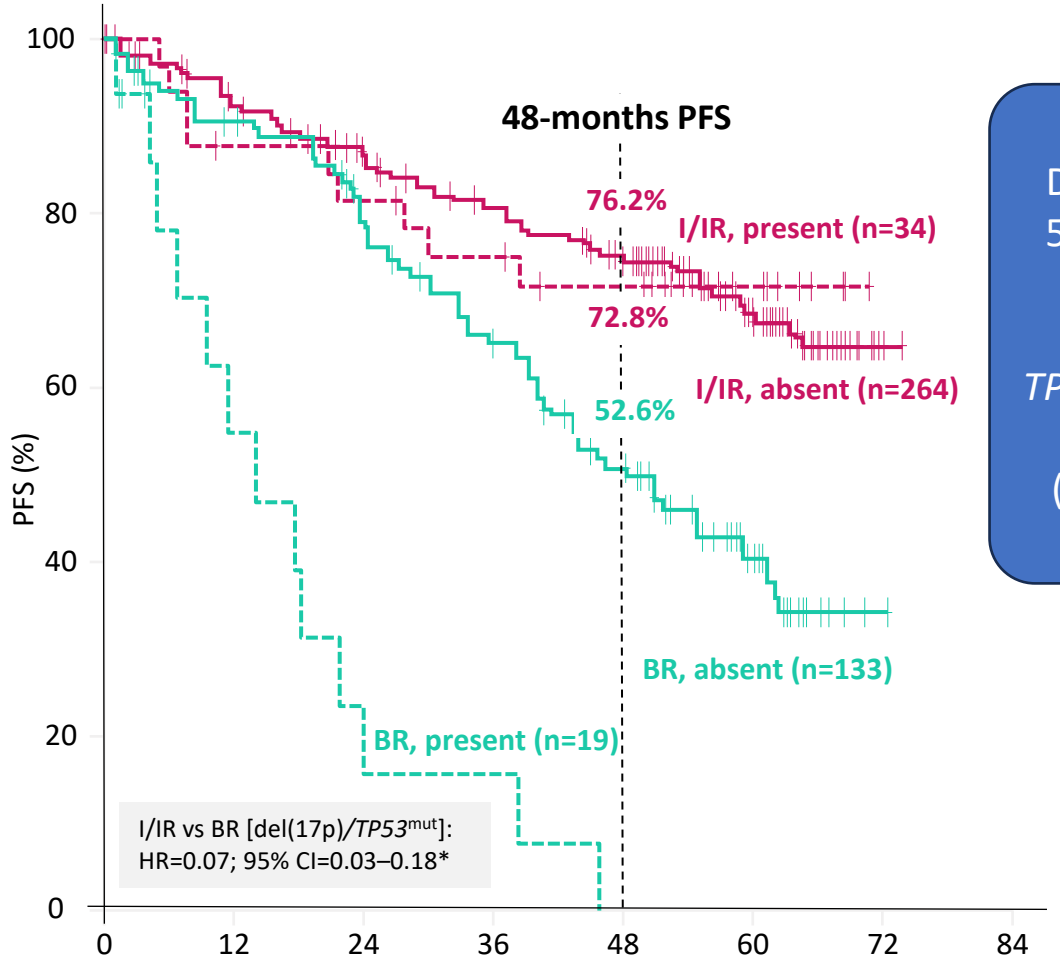
Continuous BTKi Monotherapy (+/- CD20 antibody)

CLL del(17p)/*TP53*^{mut} under continuous BTKi first-line treatment

Phase 2 IIT (NCT01500733): PFS Ibrutinib monotherapy in patients with del(17p)/*TP53*^{mut}
(median follow-up: 6.5 years)[1]



Alliance A041202 : PFS I/IR vs BR by del(17p)/*TP53*^{mut} status (absent/present)
(median follow-up: 55 months)[2,3]



Del(17p): 5% of pts (9/181)

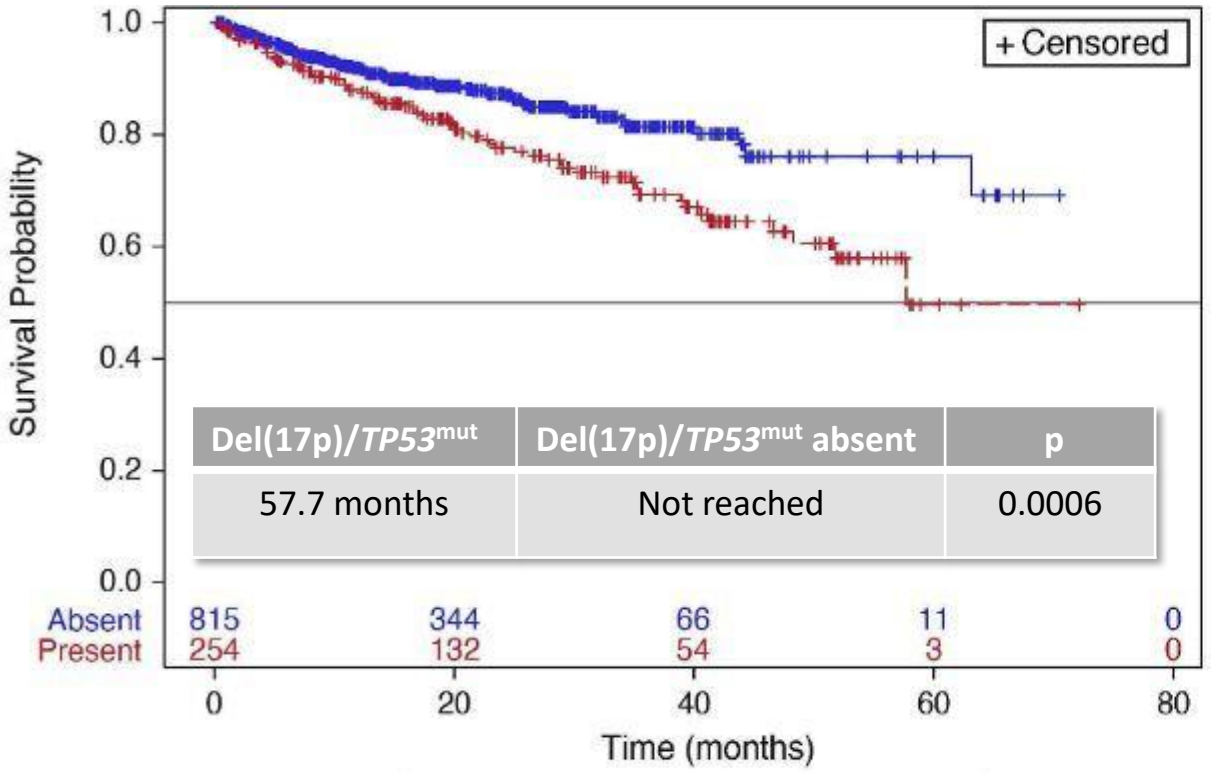
TP53^{mut}: 9% of pts (15/168)

1. Ahn IE, *et al. NEJM* 2020; 2. Woyach J, *et al.* ASH 2021. Abstract 639 (Oral).
3. Woyach J *et al. N Engl J Med* 2018 Dec 27;379(26):2517-2528.

Real world data suggest inferior survival in high-risk CLL with BTKi therapy

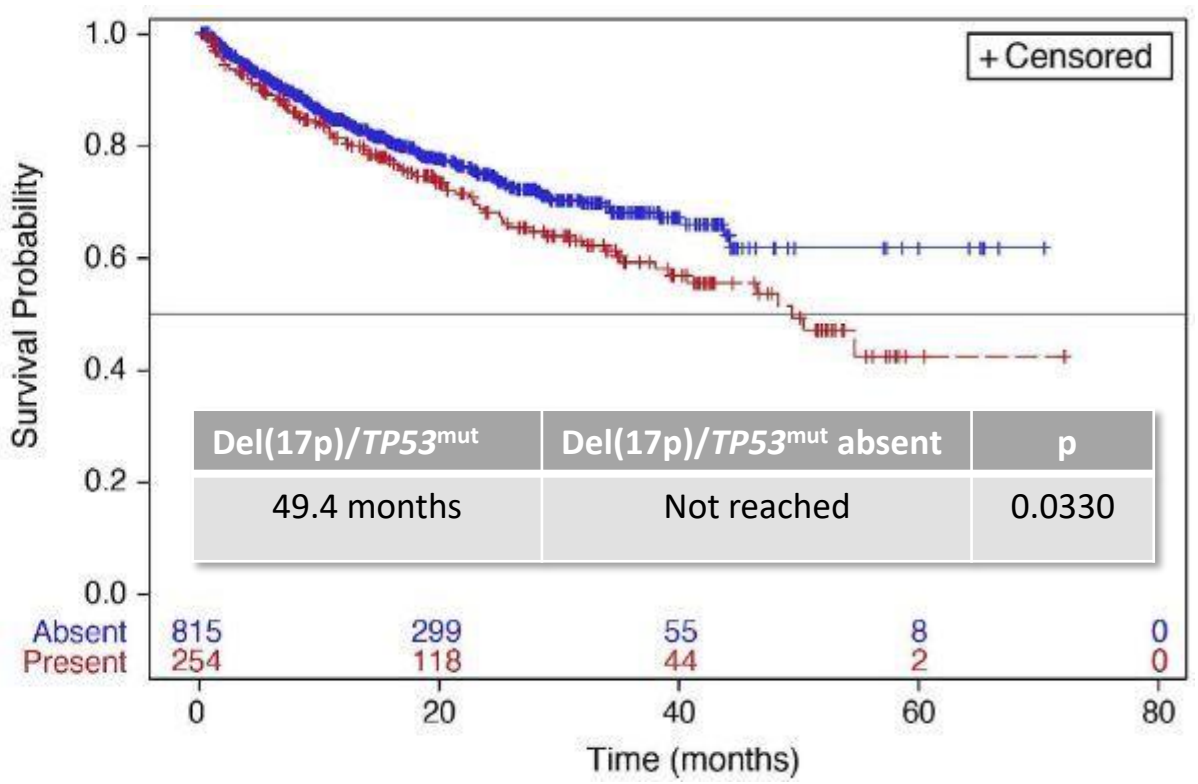
- n = 1069 patients; 254/1069 had del(17p), 1L ibrutinib monotherapy between 01/2011 – 12/2019
- Reason for treatment discontinuation: toxicity in both arms, due to PD: significantly more frequent in del(17p) CLL (20% vs. 6%; P<0.0001).

OS ibrutinib monotherapy by del(17p)/*TP53*^{mut} status (absent/present)
(median follow-up: 17.5 months)



Del(17p)/*TP53*^{mut}	Del(17p)/*TP53*^{mut} absent	p
57.7 months	Not reached	0.0006

Time to next treatment - ibrutinib monotherapy by del(17p)/*TP53*^{mut} status (absent/present)
(median follow-up: 17.5 months)



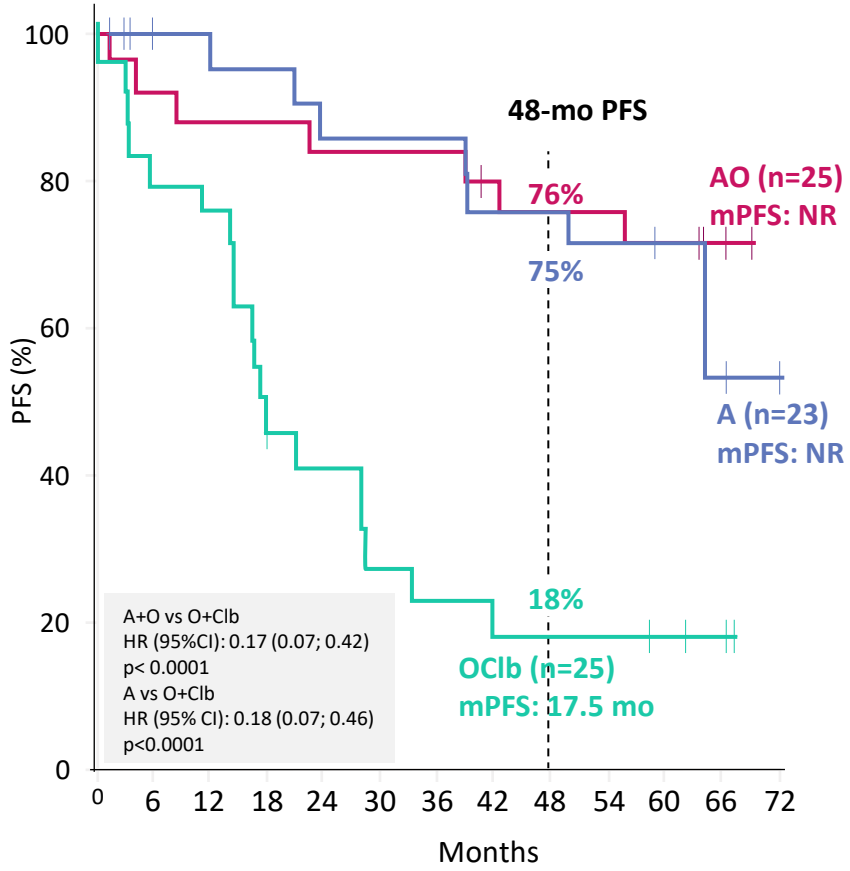
Del(17p)/*TP53*^{mut}	Del(17p)/*TP53*^{mut} absent	p
49.4 months	Not reached	0.0330

BTKi, Bruton's tyrosine kinase inhibitor; I, ibrutinib; R, rituximab.

Mato AR, *et al. Haematologica* 2022; doi: 10.3324/haematol.2021.280376.

CLL del(17p)/*TP53*^{mut} under continuous BTKi first-line treatment

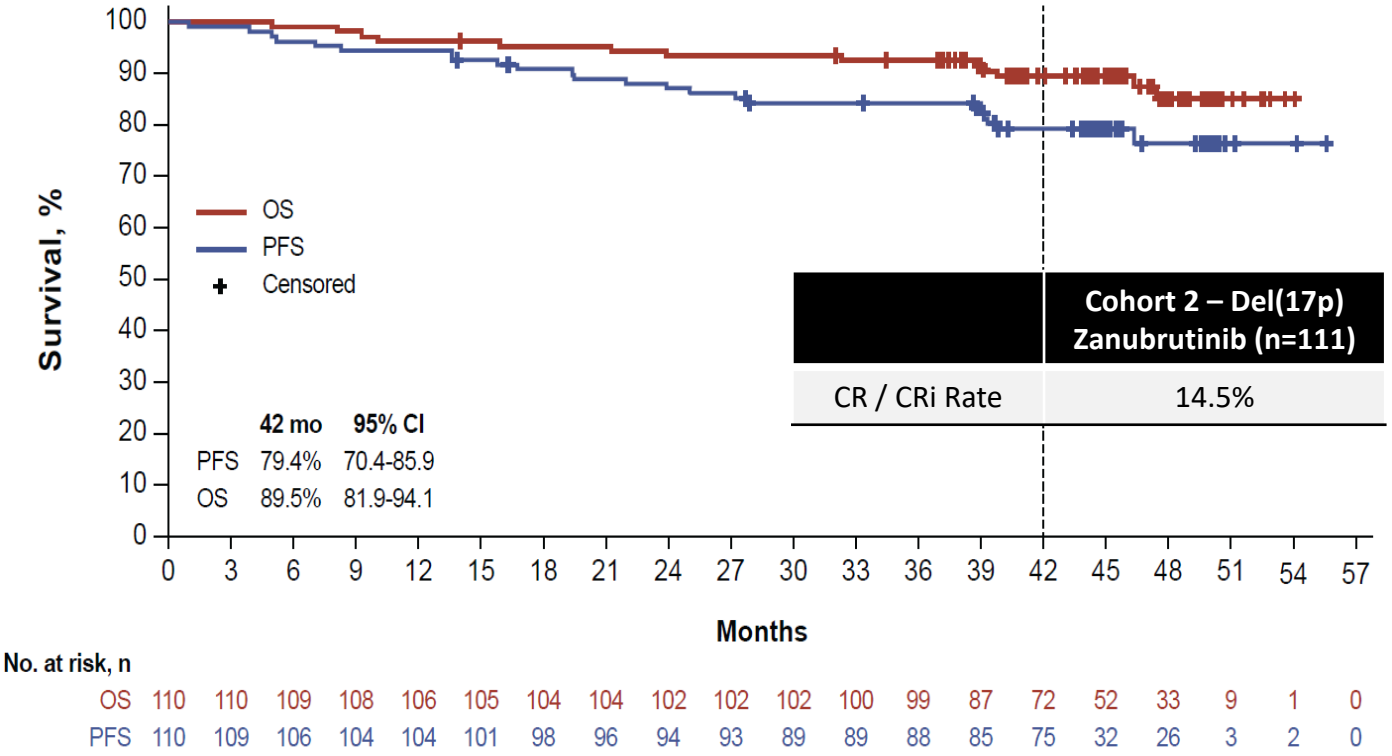
ELEVATE TN: PFS A/AO vs OClb by del(17p)/*TP53*^{mut} status (present)
(median follow-up: 46.9 months)[1,2]



del(17p) and/or T*P53*^{mut}:
14% (25/179 pts)

SEQUOIA Cohort 2 – Extended Follow-Up:
CR rate, PFS and OS (median follow-up: 47.9 months)[3]

Del(17p)/*TP53*^{mut}
n=111



- Median PFS and OS: not reached
- 42-month PFS: 79.4% 42-month OS rate: 89.5%

1. Sharman JP, *et al. Leukemia* 2022; 36:1171–1175; 2. Sharman JP, *et al.* EHA 2022. Abstract 666 (Poster)
3. Munir T *et al.* EHA 2023, Abstr #P639

Doublets

Time-limited treatment with Venetoclax/Obinutuzumab (VenO) (CLL14): CLL with del(17p)/*TP53*^{mut} – 5-and 6-year follow-up

del(17p) and/or *TP53*^{mut}: 12% (25/209 pts)

Main inclusion criteria[a]
- Previously untreated CLL with comorbidities
- CIRS >6 and/or CrCl <70ml/min

R 1:1

VenO 6 Cycles → Median Age: 72 years | Median CIRS: 9 (0-23)

Venetoclax 6 Cycles

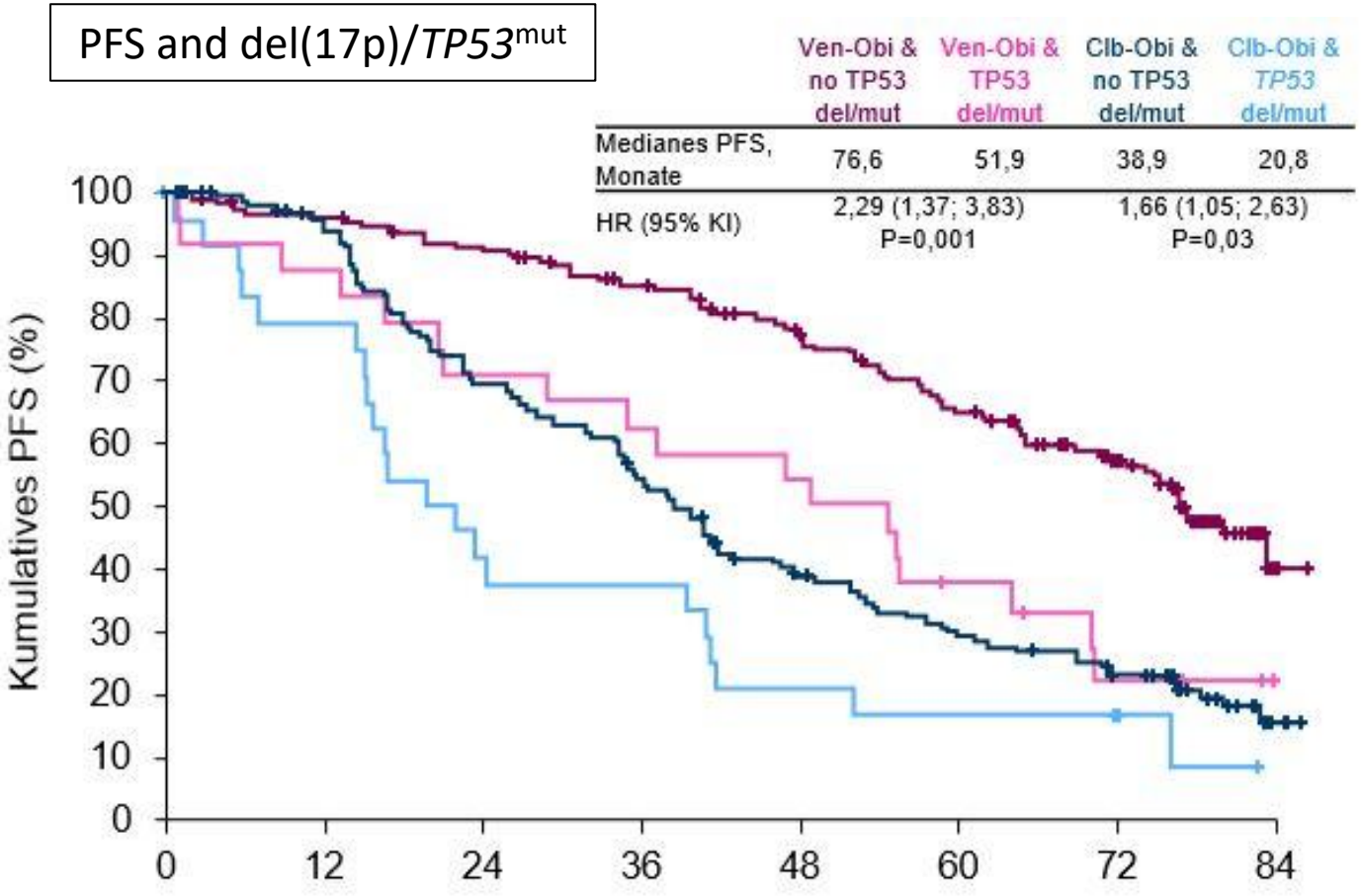
ChlorambucilO 6 Zyklen → Median age: 71 years | Median CIRS: 8 (1-28)

Chlorambucil 6 Zyklen

Primary endpoint
- PFS

Secondary endpoints
- Overall response rate
- MRD
- OS

PFS and del(17p)/*TP53*^{mut}



Median Follow-up 65.4 months[2]

Del(17p)/*TP53*^{mut}	VenO	ClbO
5-year PFS[2]	40.6%	15.6%

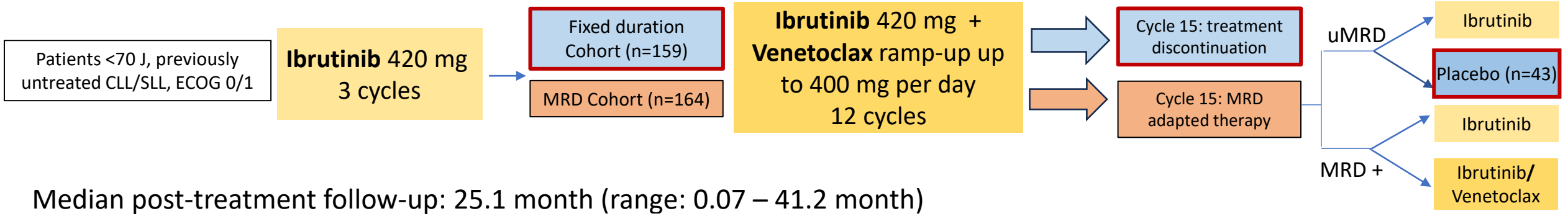
HR 0.48, 95% CI 0.24–0.94

Patients without del(17p)/*TP53*^{mut}	VenO	ClbO
5-year PFS[2]	65.8%	29.3%

HR 2.37, 95% CI 1.34–4.17

1. Al-Sawaf.O et al. EHA 2023 Abstract S145
2. Al-Sawaf O et al. *Nat Commun.* 2023 Apr 18;14(1):2147.

Time-limited treatment with Ibrutinib/Venetoclax (CAPTIVATE): Fixed duration Cohort (pooled analysis)



Median post-treatment follow-up: 25.1 month (range: 0.07 – 41.2 month)

Time-limited treated patients: n=202

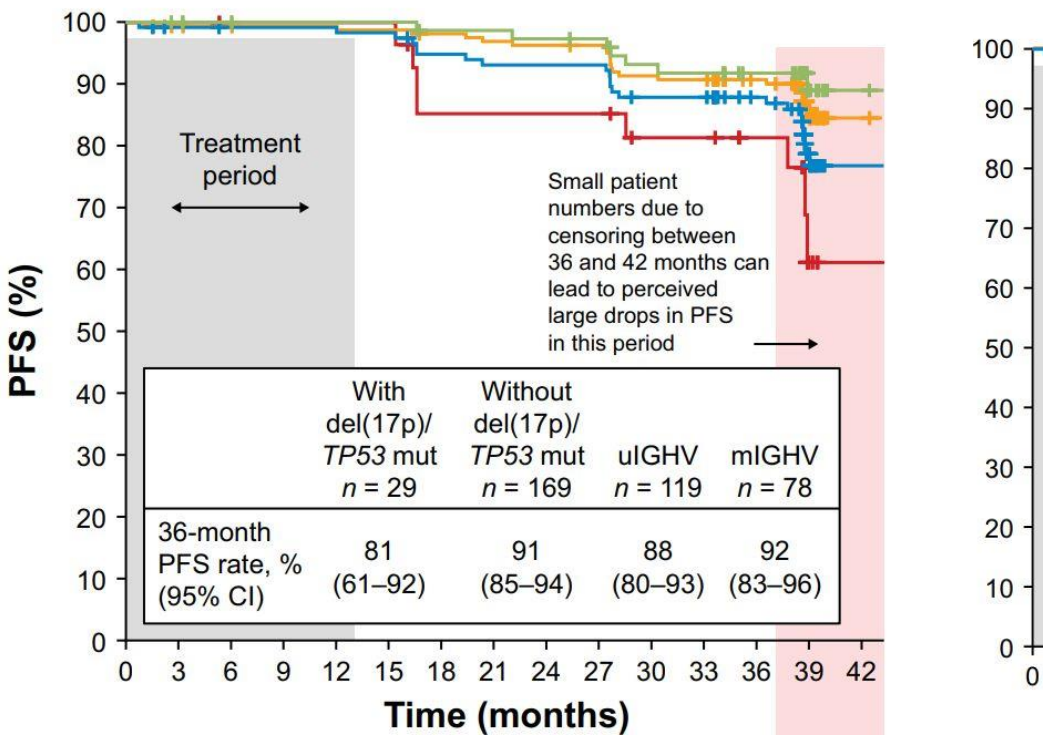
→ high-risk features: n=129

High-risk features	patients - n (%)
TP53^{mut}	17 (13)
Del(17p) or *TP53*^{mut}	29 (22)
IGHV unmut ⇔ mut	119 (92) ⇔ 10 (8)
CKT (≥ 3 abnormalities)	27 (21)

Results del(17p)/*TP53*^{mut}(n=29)

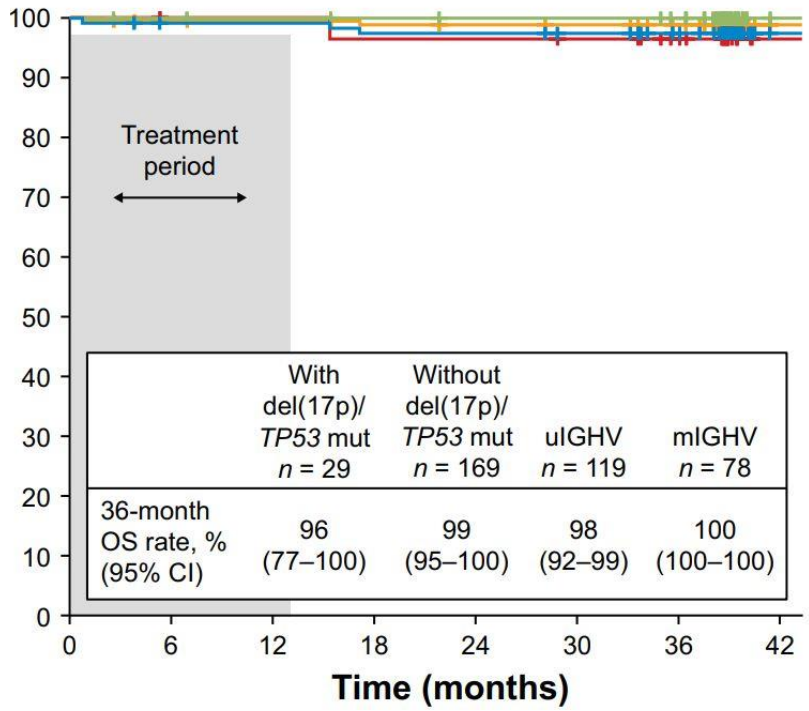
- CR/CRi rate: 52%
- uMRD rate peripheral blood: 83%
- uMRD rate bone marrow: 45%

PFS by del(17p)/*TP53* and IGHV status[a]



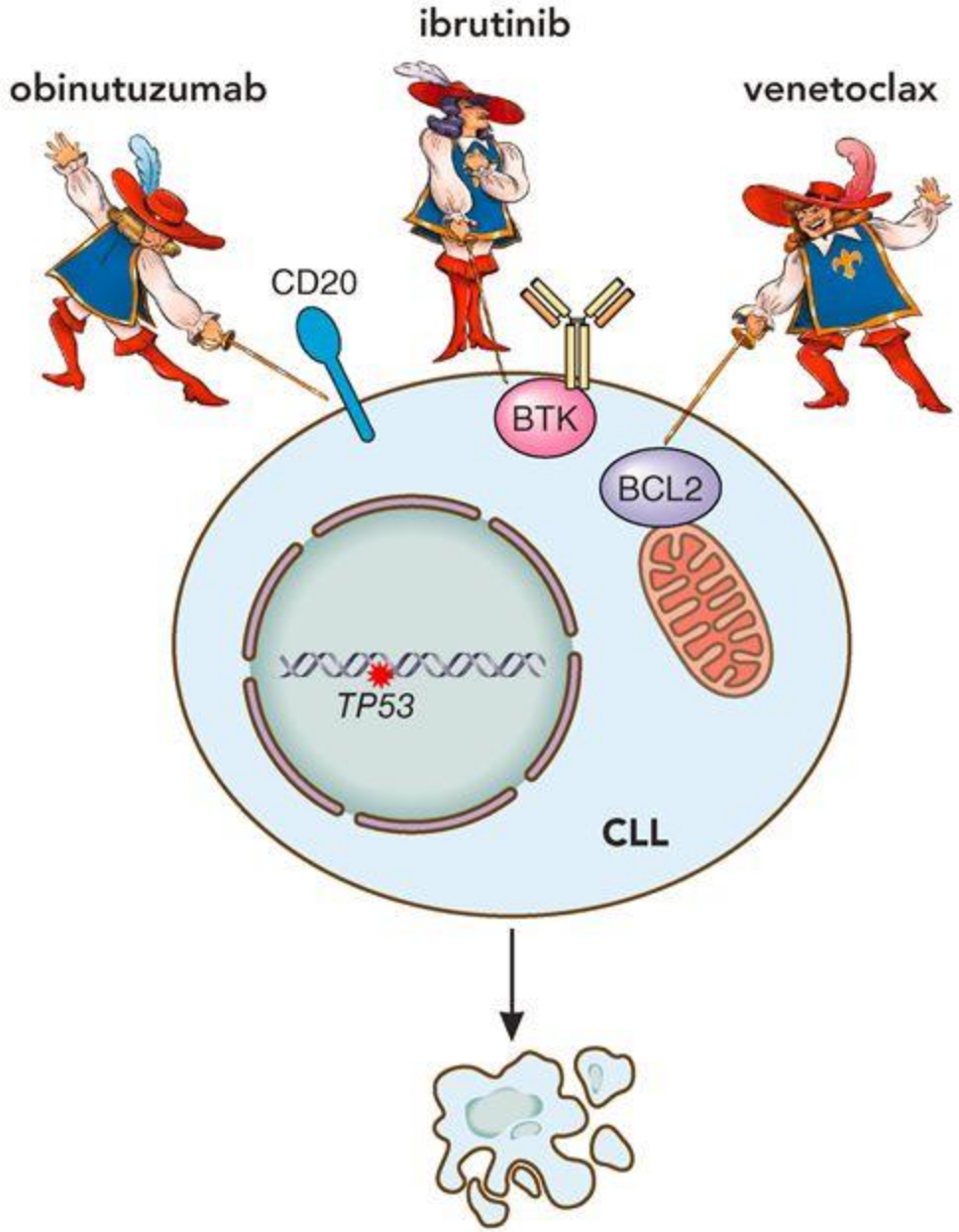
	With del(17p)/*TP53* mut *n* = 29	Without del(17p)/*TP53* mut *n* = 169	uIGHV *n* = 119	mIGHV *n* = 78
36-month PFS rate, % (95% CI)	81 (61–92)	91 (85–94)	88 (80–93)	92 (83–96)

OS by del(17p)/*TP53* and IGHV status[a]



	With del(17p)/*TP53* mut *n* = 29	Without del(17p)/*TP53* mut *n* = 169	uIGHV *n* = 119	mIGHV *n* = 78
36-month OS rate, % (95% CI)	96 (77–100)	99 (95–100)	98 (92–99)	100 (100–100)

Allan JN *et al. Clin Cancer Res*. 2023 Jul 14;29(14):2593-2601.

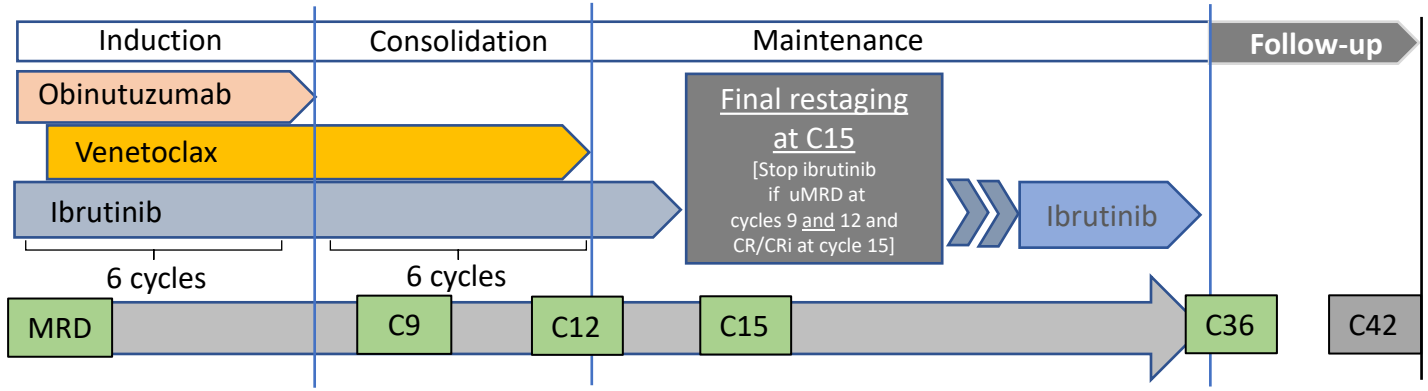


Triplet

Kwok M, Stankovic T. *Blood* 2022 Mar 3;139(9):1264-1265.

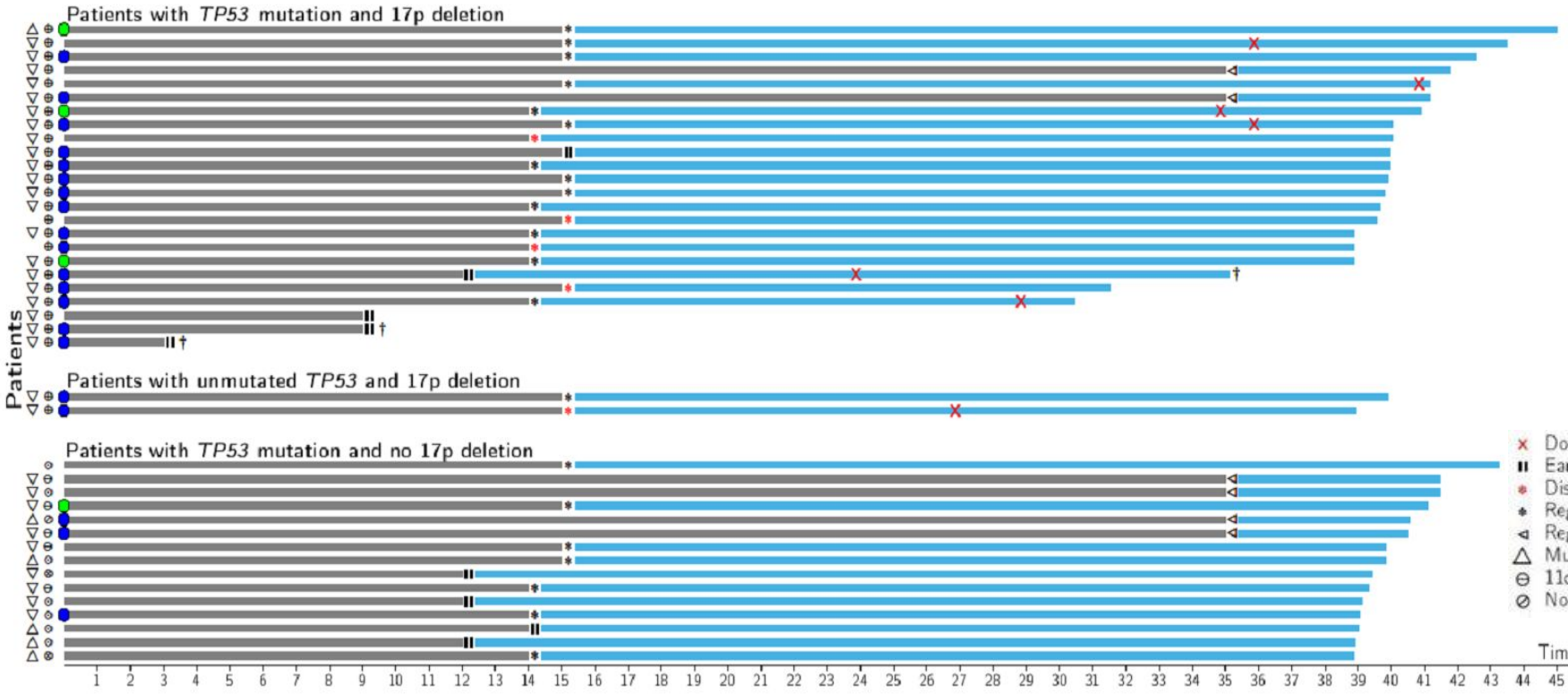
Obinutuzumab, ibrutinib and venetoclax in CLL with del(17p)/*TP53*^{mut} – CLL2-GIVe

- Phase 2 trial
- 41 patients
- Previously untreated CLL
- Adequate renal function (CrCl > 50mL/min)
- Del(17p)/*TP53* mut



Primary endpoint
- CR rate at C15

Secondary endpoints
- PFS, OS, EFS
- Safety
- MRD levels

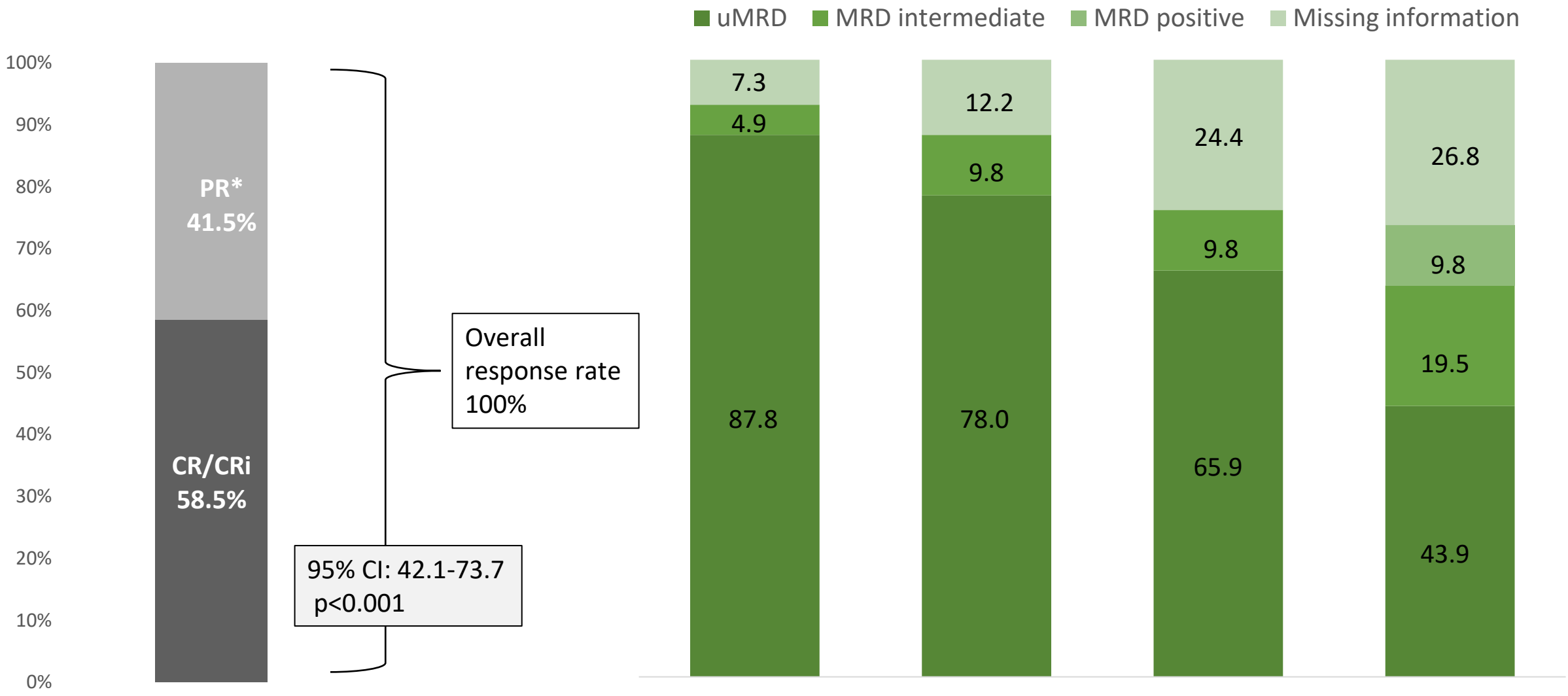


Genetic parameters	n (%)
IGHV unmutated	32 (78.0)*
Complex karyotype	24 (61.6)**
Del(17p) and *TP53*^{mut}	24 (58.5)
Del(17p), no *TP53*^{mut}	2 (4.9)
TP53^{mut}, no del(17p)	15 (36.6)
SF3B1^{mut}	7 (17.1)
NOTCH1^{mut}	3 (7.3)

*IGHV: 3 patients were not evaluable;
**Karyotype: 2 patients were not evaluable

Huber H, *et al. Blood.* 2023 Sept 14; *142* (11): 961–972.

CLL2-GIVe: Results: Efficacy: CR rate at final restaging and MRD results



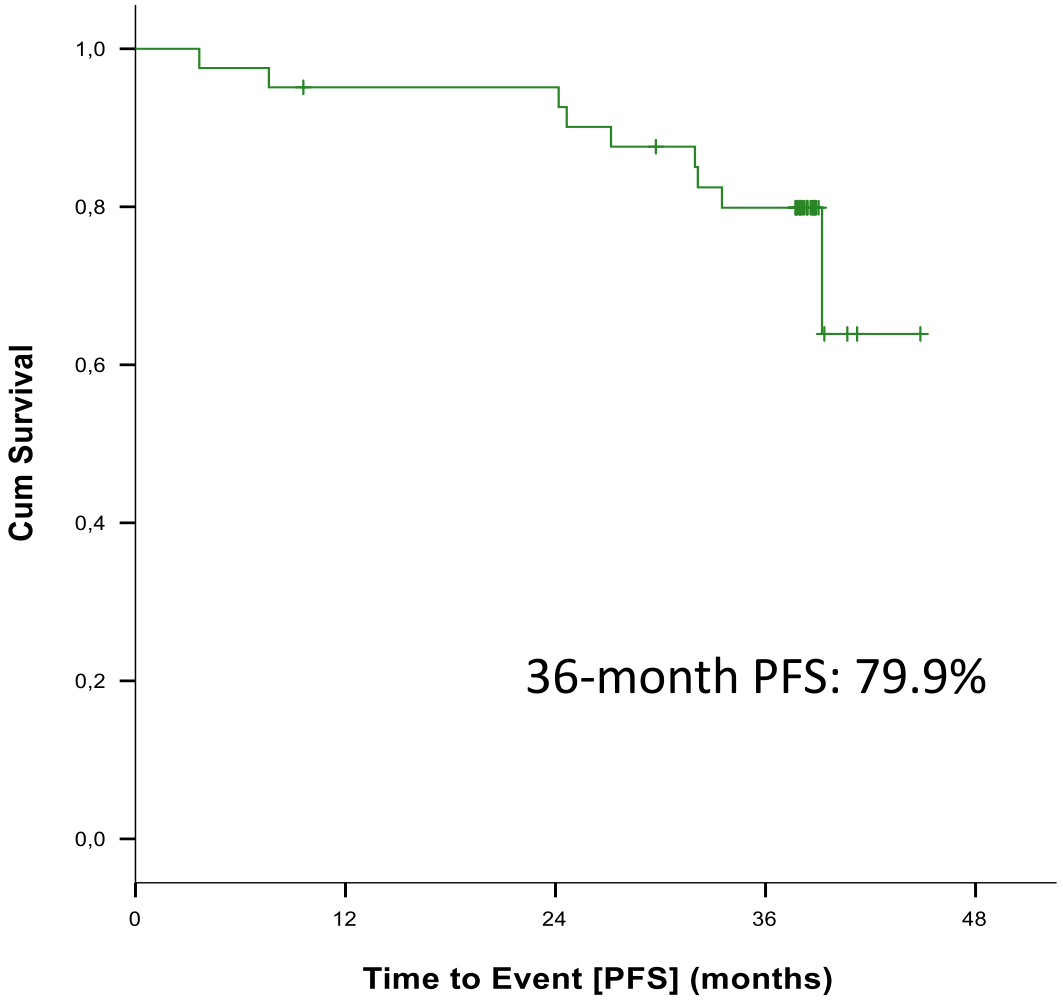
*7,3% not assessable due to 2 deaths at C3 and C9 and 1 withdrawal of informed consent at C9

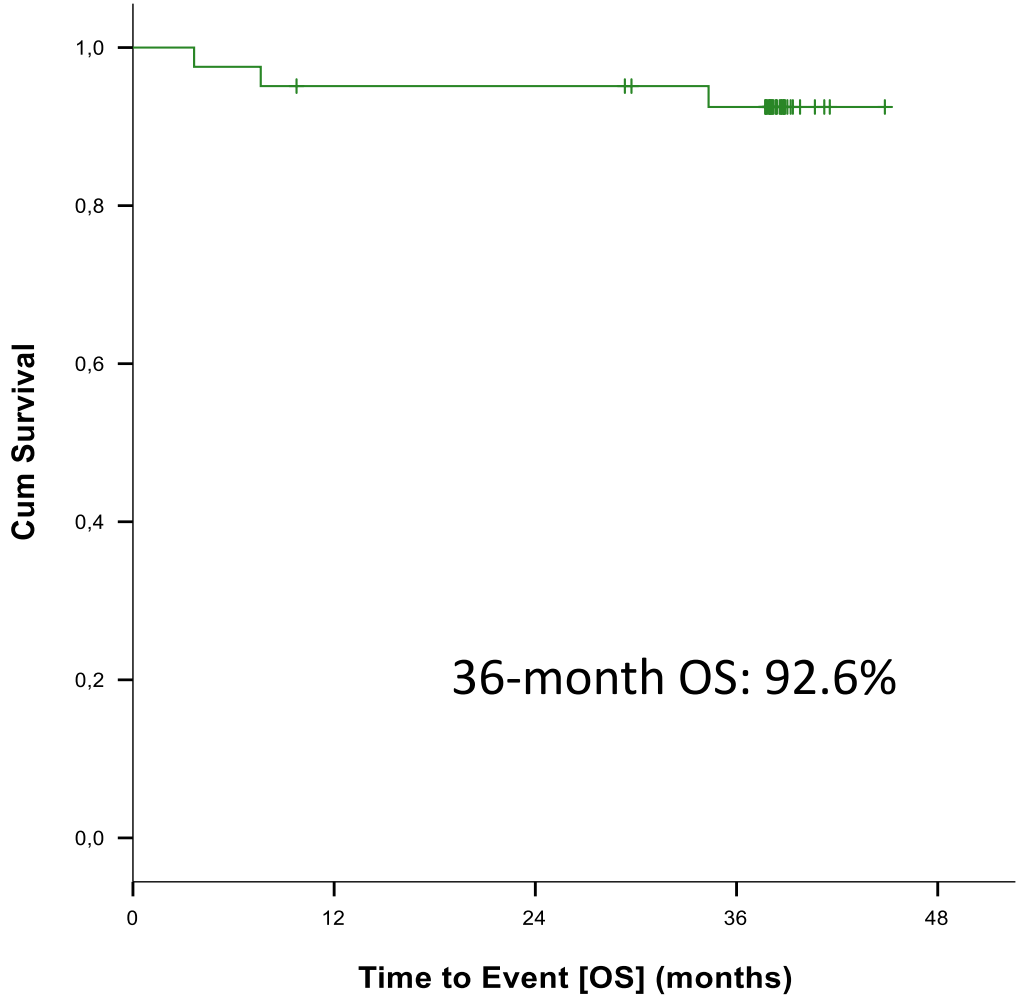
uMRD: $<10^{-4}$
MRD intermediate: $\geq 10^{-4}$, $<10^{-2}$
MRD positive $\geq 10^{-2}$

Huber H, *et al. Blood.* 2023 Sept 14; *142* (11): 961–972.

CLL2-GIVe: Results: Progression-free survival and overall survival

Median observation time: 38.4 months (range 3.7-44.9)





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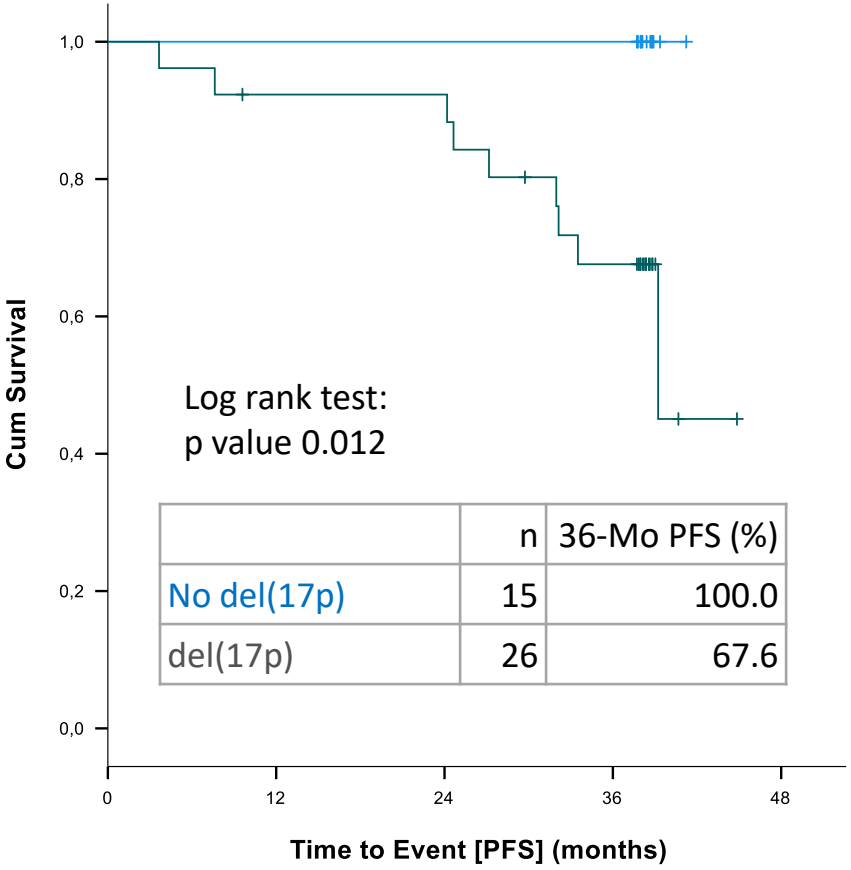
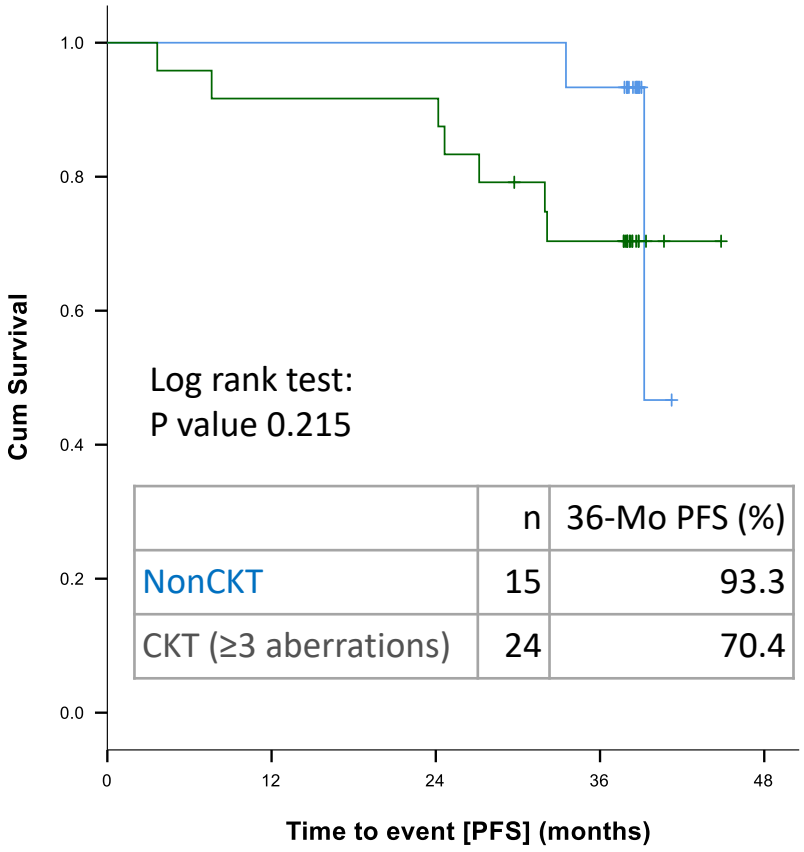
CLL2-GIVe: Results: Correlation between PFS and genetics

PFS and del(17p)



	n	36-Mo PFS (%)
No del(17p)	15	100.0
del(17p)	26	67.6

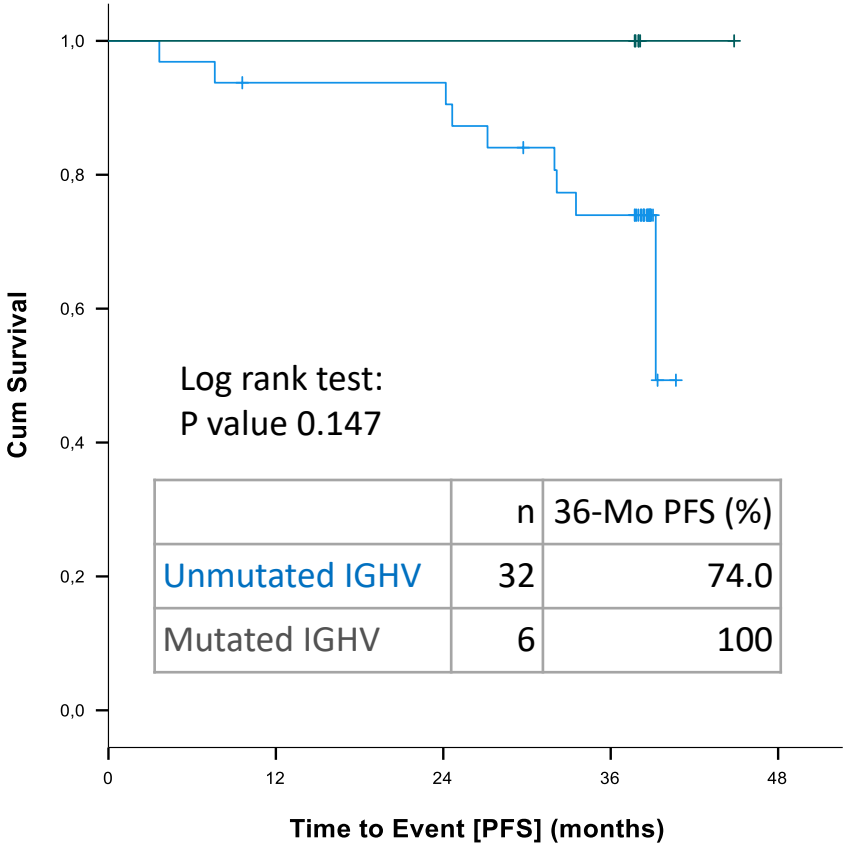
PFS and complex karyotype*



	n	36-Mo PFS (%)
NonCKT	15	93.3
CKT (≥3 aberrations)	24	70.4

*Karyotype: 2 patients were not evaluable

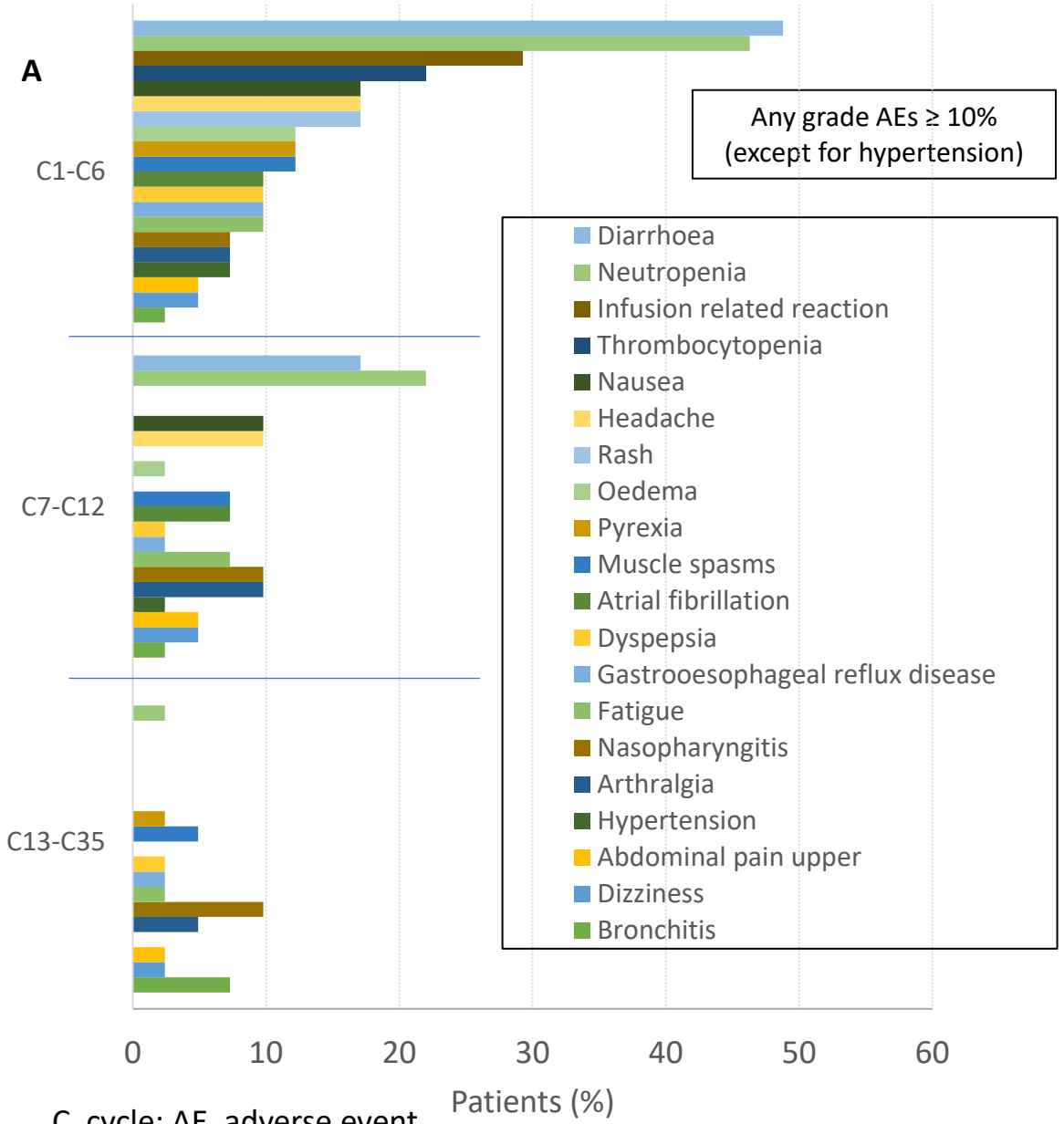
PFS and IGHV mutational status

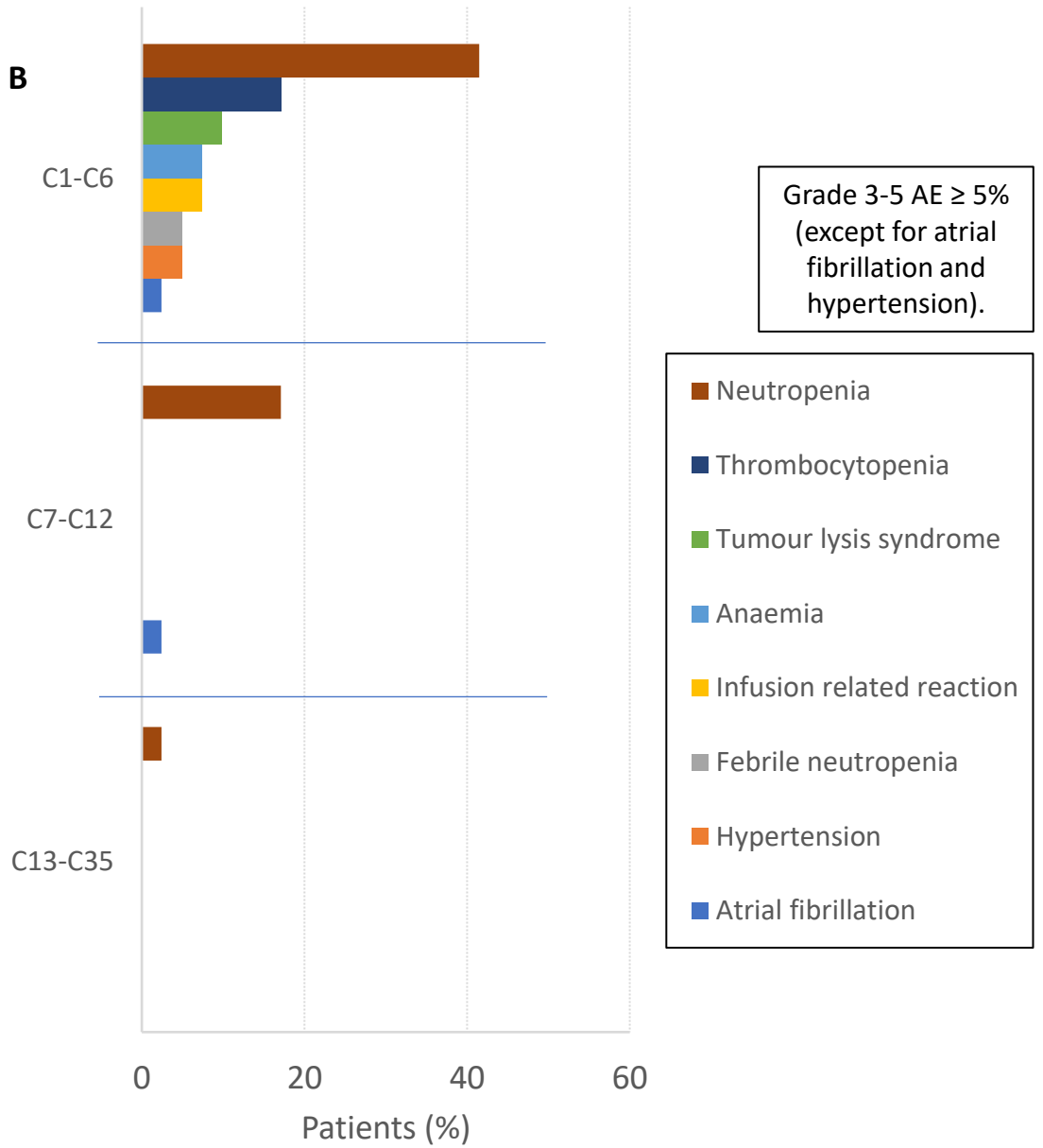


	n	36-Mo PFS (%)
Unmutated IGHV	32	74.0
Mutated IGHV	6	100

Huber H, *et al. Blood.* 2023 Sept 14; *142* (11): 961–972.

CLL2-GIVe: Adverse events of any grade (A) and ≥ grade 3 (B) over the course of treatment





C, cycle; AE, adverse event.

Huber H, *et al. Blood.* 2023 Sept 14; *142* (11): 961–972.

Adverse events ≥ grade 3 in continuous and time-limited treatment

Study		Treatment Duration (6m to PD)	Neutropenia	Febrile Neutropenia	Infections	TLS	Atrial Fibrillation	Bleeding	Hypertension
Alliance A041202 [1,2] *	IR	→	22%	1%	19%	–[x]	6%	3%	34%
	I	→	15%	2%	19%		9%	2%	29%
	BR	→	40%	7%	13%		3%¶	0%	14%
ELEVATE TN[3,4] *	AO	→	31%	–[x]	24%	–[x]	1%	3%	3%
	A	→	11%		16%		1%	3%	3%
	Oclb	→	41%		8%		0%	0%	4%
SEQUOIA[5] * (Cohort 2)	Zanu	→	16.2%	–[x]	27%	–[x]	2%	5.4%	6.3

Study		Treatment Duration (12-15 Cycles)	Neutropenia	Febrile Neutropenia	Infections	TLS	Atrial Fibrillation	Bleeding	Hypertension
CLL14[6] **	VenO	→	53%	5%	18%	1%	2%	–[x]	3%
	OClb	→	48%	4%	15%	3%	1%		1%
CAPTIVATE[7] * (FD Cohort)	IVen	→	33%	1%	8%	0%	1%	1%	6%
CLL2-GIVe[8] ***	IVenO	→	48.8%	2.4%	19.5%	9.8%	2.4%	–[x]	2.4%

[x] Not specified

* AE reporting period: 30 days after the last study treatment

** AE reporting period: 28 days after last venetoclax and 90 days after the last obinutuzumab treatment

*** AE reporting period: 28 days after the end of study treatment

1. Woyach J, *et al.* ASH 2021. Abstract 639 (Oral) | 2. Woyach J, *et al. N Engl J Med.* 2018 Dec 27;379(26):2517-2528
3. Sharman JP, *et al. Leukemia* 2022; 36:1171–1175 | 4.Sharman JP, *et al.* EHA 2022. Abstract 666 (Poster)
5. Munir T et al. EHA 2023, Abstr #P639| 6. Fischer K, *et al. N Engl J Med.* 2019 Jun 6;380(23):2225-2236
7. Tam CS, *et al. Blood.* 2022 Jun 2;139(22):3278-3289 | 8. Huber H, *et al. Blood.* 2022 Mar 3;139(9):1318-1329

Conclusion: Continuous versus time-limited treatment in high-risk CLL?

Efficacy:

- Continuous BTKi monotherapy is a first-line standard regimen in high-risk CLL
- Time-limited doublet regimens are further options according to patient‘s risk profile and preference
- Triplets are part of clinical trials

Adverse events:

- In time-limited treatment: adverse events occur primarily during the first six cycles, especially hematotoxicity
- Continuous risk of adverse events, especially cardiotoxicity in BTKi (ibrutinib > acala-/zanubrutinib), infections (e.g. ITK inhibition, T-cell dysfunction)

Risk profile:

- CLL del(17p) and/or *TP53*^{mut}: hetergeneous group of patients with distinct treatment options in future?

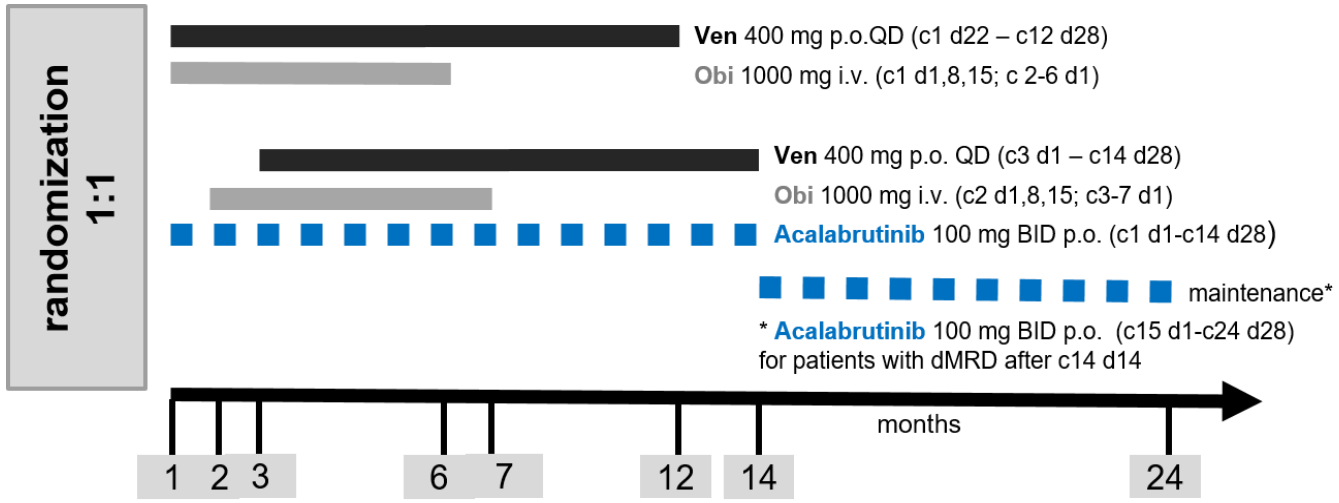
Clinical trials:

- Testing time-limited versus continuous therapy in CLL, including high-risk CLL.

Ongoing clinical trial of the GCLLSG in high-risk CLL

Phase 3 CLL16 Trial[1] (NCT05197192)

Treatment schedule



n=178 patients

Main inclusion criteria

- CLL with del17p/*TP53*mut or complex karyotype (≥3 chromosomal abnormalities)
- > 18 years
- Creatinine clearance ≥ 30ml/min
- Adequate liver function

Endpoints

- Primary endpoint: Progression-free survival
- Main secondary endpoints:
  - Minimal residual disease (MRD) levels in the peripheral blood and in bone marrow at final restaging
  - Survival: Overall survival, event-free survival, time to next treatment
  - CR rate, overall response rate

Recruiting!
Estimated Study Completion Date 02/2027

[1]https://www.dcllsg.de/studie/cll16/index.php

Vielen Dank für Ihre Aufmerksamkeit!

Back-up

CLL2GIVe: Disease Progression and subsequent therapy

Pat	Genetics baseline	C15 remission	MRD at C15	EOT date	PFS date	Time point of PD in mo, from registration date	Period of subsequent therapy	Name of the first subsequent therapy
1	Del(17p) 88% *TP53*mut Exon 8 60%	CR	uMRD	February 2018	September 2019	32.0		
2	Del(17p) 21.5% *TP53*mut Exon 8 20%	CR	uMRD	November 2017	February 2019	27.2		
3†	Del(17p) 85% *TP53*mut Exon 5 60%	CR	uMRD	December 2017	September 2019	33.5	From November 2018 to February 2019	Obinutuzumab
4	Del(17p) 93.5% *TP53*mut Exon 8 70%	CR	uMRD	May 2018	December 2019	32.1	February 2020	Acalabrutinib/obinutuzumab/ venetoclax
5	Del(17p) 93% *TP53* umut	PR	uMRD PB; no BM	November 2018	September 2019	24.6	February 2020	Acalabrutinib/obinutuzumab/ venetoclax
6*	Del(17p) 93.5% *TP53*mut Exon 7 95%	PR	uMRD	December 2018	January 2020	24.2	from April 2020 to July 2020	Venetoclax
7	Del(17p) 16.5% *TP53*mut Exon 6 70%	CR	uMRD PB; iMRD BM	April 2019	June 2021	38.6		

*TP53*mut, *TP53* mutation; umut, unmutated. Pat, patient; del, deletion; mut, mutated; umut, unmutated; C, cycle; CR, complete remission; PR, partial remission; uMRD, undectable minimal residual disease; iMRD, intermediate minimal residual disease; PB, peripheral blood; EOT, end of treatment; PFS, progression-free survival.

*A Richter transformation (other: diffuse large B-cell lymphoma clonal relationship not analyzed) has been documented 12 months after EOT in May 2020, after treatment with venetoclax, rituximab/idelalisib, and ibrutinib monotherapy was administered.

†Due to detectable MRD in November 2018, the patient receieved obinutuzmab. The patient had a disease progression in September 2019.

Huber H, *et al. Blood.* 2023 Sept 14; *142* (11): 961–972.