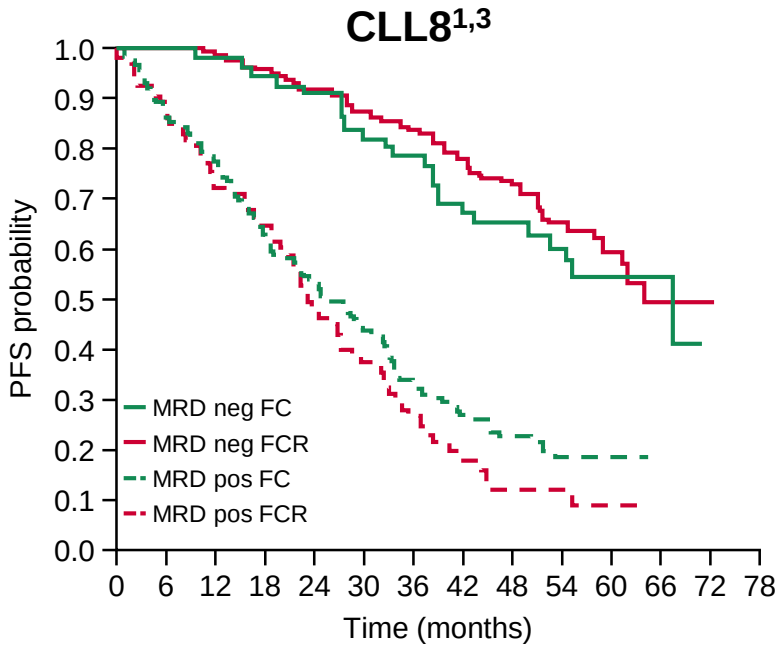
First prospective data on impact of minimal residual disease on long-term clinical outcomes after venetoclax plus rituximab versus bendamustine plus rituximab: Phase III MURANO study

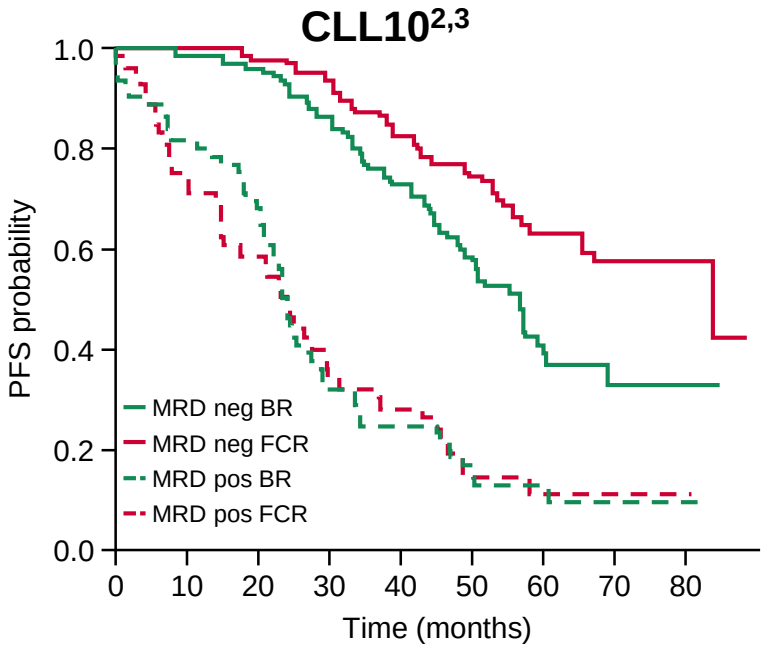
Arnon P Kater,[1] Peter Hillmen,[2] Anton W Langerak,[3] Barbara Eichhorst,[4] Thomas J Kipps,[5] Carolyn Owen,[6] Michelle Boyer,[7] Kathryn Humphrey,[7] Elizabeth A Punnoose,[8] Jue Wang,[8] Brenda J Chyla,[9] Maria Verdugo,[9] Jenny Wu,[8] Yanwen Jiang,[8] Mehrdad Mobasher,[8] John F Seymour[10]

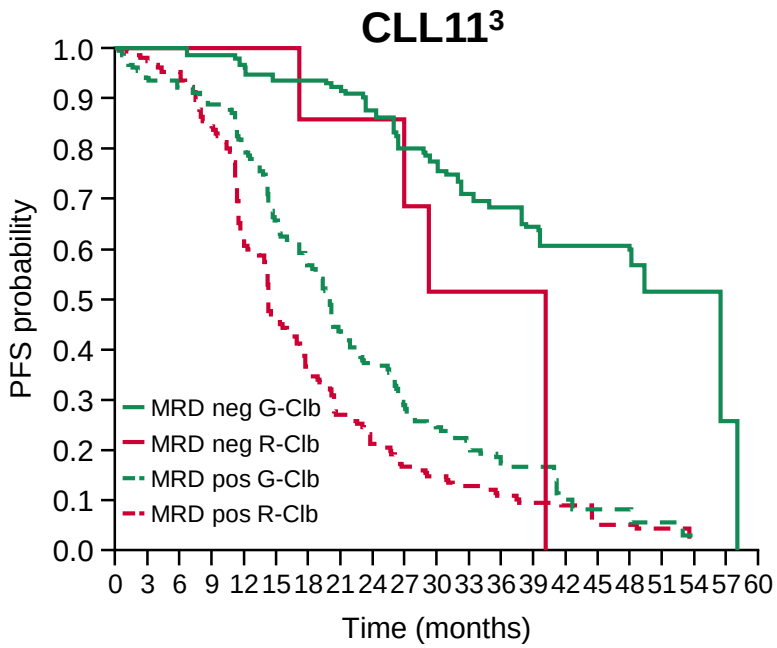
[1]Amsterdam UMC, University of Amsterdam, Hovon CLL working group, Amsterdam, The Netherlands; [2]St. James's University Hospital, Leeds, UK; [3]Erasmus MC, University Medical Center, Rotterdam, Netherlands; [4]University of Cologne, Cologne, Germany; [5]University of California School of Medicine, San Diego, CA; [6]University of Calgary, Calgary, AB; [7]Roche Products Limited, Welwyn Garden City, UK; [8]Genentech Inc, South San Francisco, CA; [9]AbbVie, North Chicago, IL; [10]Peter MacCallum Cancer Centre, Royal Melbourne Hospital, and University of Melbourne, Melbourne, Australia

Background

- MRD is predictive of PFS with chemoimmunotherapy in CLL[1–4]







MRD, minimal residual disease

1. Böttcher S, et al. J Clin Oncol 2012;30:980–8; 2. Kovacs G, et al. J Clin Oncol 2016;34:3758–65;
3. Dimier N, et al. Blood 2018;131:955–62; 4. Langerak AW, et al. Blood 2018:blood-2018-03-839688

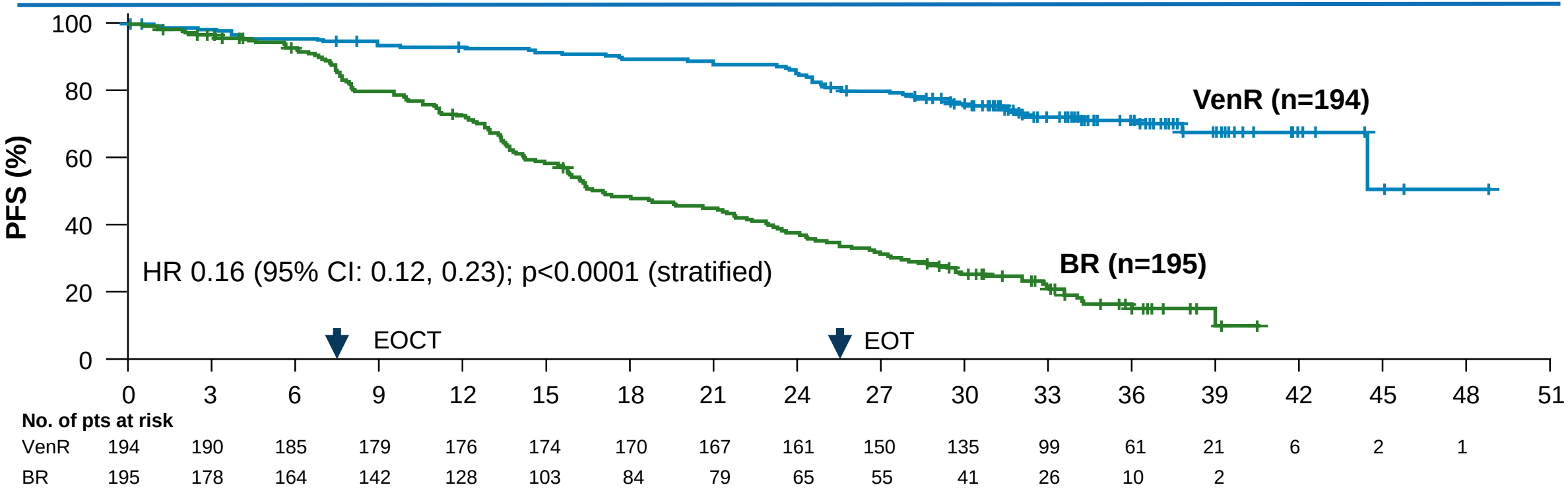
Background

- MRD is predictive of PFS with chemoimmunotherapy in CLL[1–4]
- In contrast, predictive value of MRD with novel agents is less certain
- Treatment with novel agents in general requires continuous therapy
- Venetoclax (Ven) is a novel oral, highly selective, potent BCL-2 inhibitor, with substantial activity, inducing deep response and high rates of undetectable MRD (uMRD), in CLL[5–7]
- MURANO is the first Phase III study of **fixed-duration** treatment with targeted therapy in R/R CLL
- In MURANO, fixed-duration VenR demonstrated significantly prolonged PFS (HR 0.17; p<0.001) and higher rates of uMRD (64.2 vs 13.3%) vs BR at the end of combination therapy (EOCT)[8]
- We present MRD kinetics and relation to PFS from the MURANO study, with long follow-up, when all patients have completed therapy

1. Böttcher S, et al. J Clin Oncol 2012;30:980–8; 2. Kovacs G, et al. J Clin Oncol 2016;34:3758–65;
3. Dimier N, et al. Blood 2018;131:955–62; 4. Langerak AW, et al. Blood 2018:blood-2018-03-839688;
5. Souers AJ, et al. Nat Med 2013;19:202–8; 6. Roberts AW, et al. N Engl J Med 2016;374:311–22;
7. Stilgenbauer S, et al. Lancet Oncol 2016;17:768–78; 8. Seymour JF, et al. N Engl J Med 2018;378:1107–20

BR, bendamustine + rituximab; R/R, relapsed/refractory; VenR, venetoclax + rituximab

MURANO: Superior PFS benefit with fixed-duration VenR at 3 yrs



- **389 R/R CLL** pts randomized to **VenR** (5-wk schedule of gradual dose increase [ramp-up] from 20 mg daily to 400 mg daily; Ven 400 mg daily for up to 2 yrs or unacceptable toxicity from C1D1 + R 375 mg/m^2 C1D1, 500 mg/m^2 C2–6D1) or **BR** (B 70 mg/m^2 C1–6D1,2 + R)

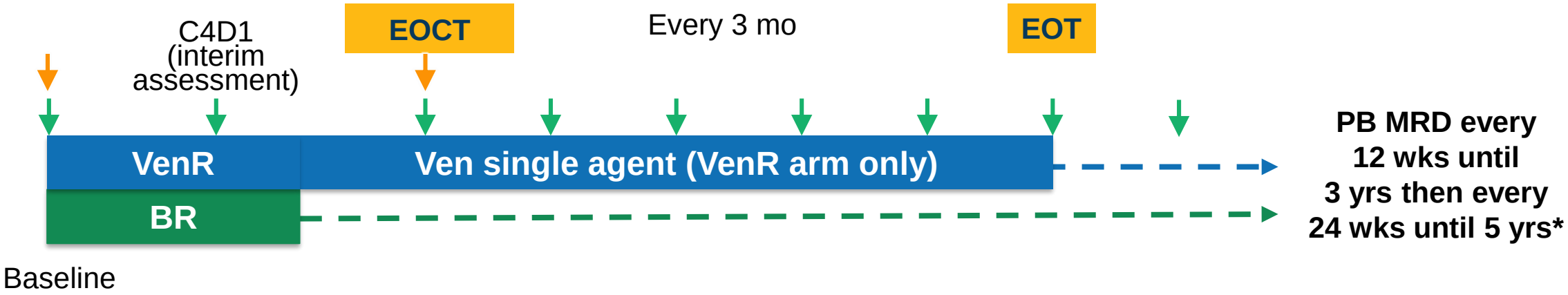
Data cut-off May 8, 2018; median follow-up: 36.0 months

C, cycle; D, day; EOT, end of therapy

Seymour JF, et al. ASH 2018 (abstract 184)

Assessment of MRD in MURANO

- Sample collection times for PB (↓) and BM (↓) identical in both arms



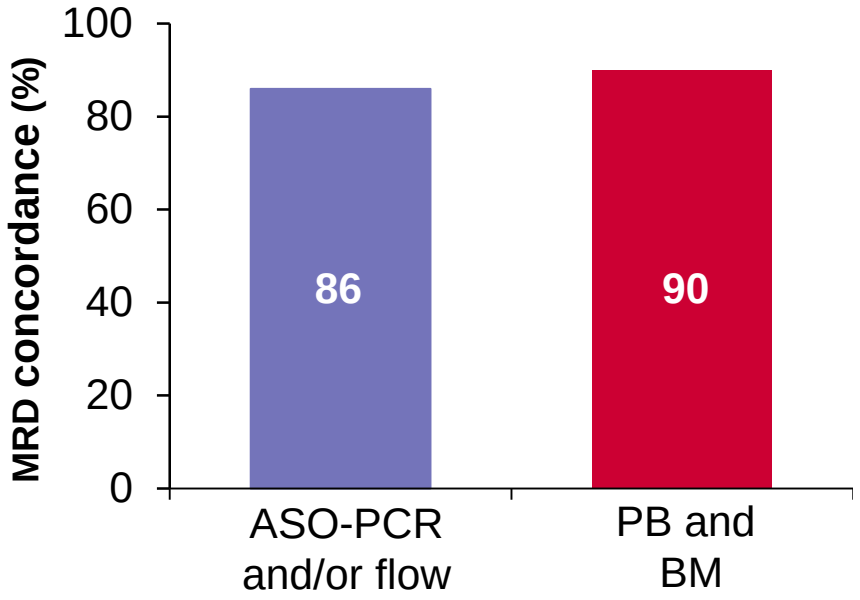
- MRD centrally assessed by ASO-PCR[1] and/or multicolour flow cytometry[2] at sequential time points
- MRD+ outcome was determined if either assessment reported MRD
- We present MRD to PFS correlations at two key time points: EOCT and EOT

*BM MRD assessment performed in all responding pts (CR + PR at the EOCT response visit)
ASO-PCR, allele-specific-oligonucleotide polymerase chain reaction; BM, bone marrow; PB, peripheral blood

1. Van der Velden VH, et al. Leukemia 2007;21:604–11
2. Rawstron AC, et al. Leukemia 2013;27:142–9

High concordance between MRD methodologies and between BM and PB analysis

- MRD was highly concordant (**86%**) between ASO-PCR and/or multicolour flow cytometry
  - Compared in 1859 pairs (from 316 pts) of post-baseline PB samples
- **90%** concordance between PB and BM uMRD with VenR (50 paired samples),[1] so we focus here on PB MRD

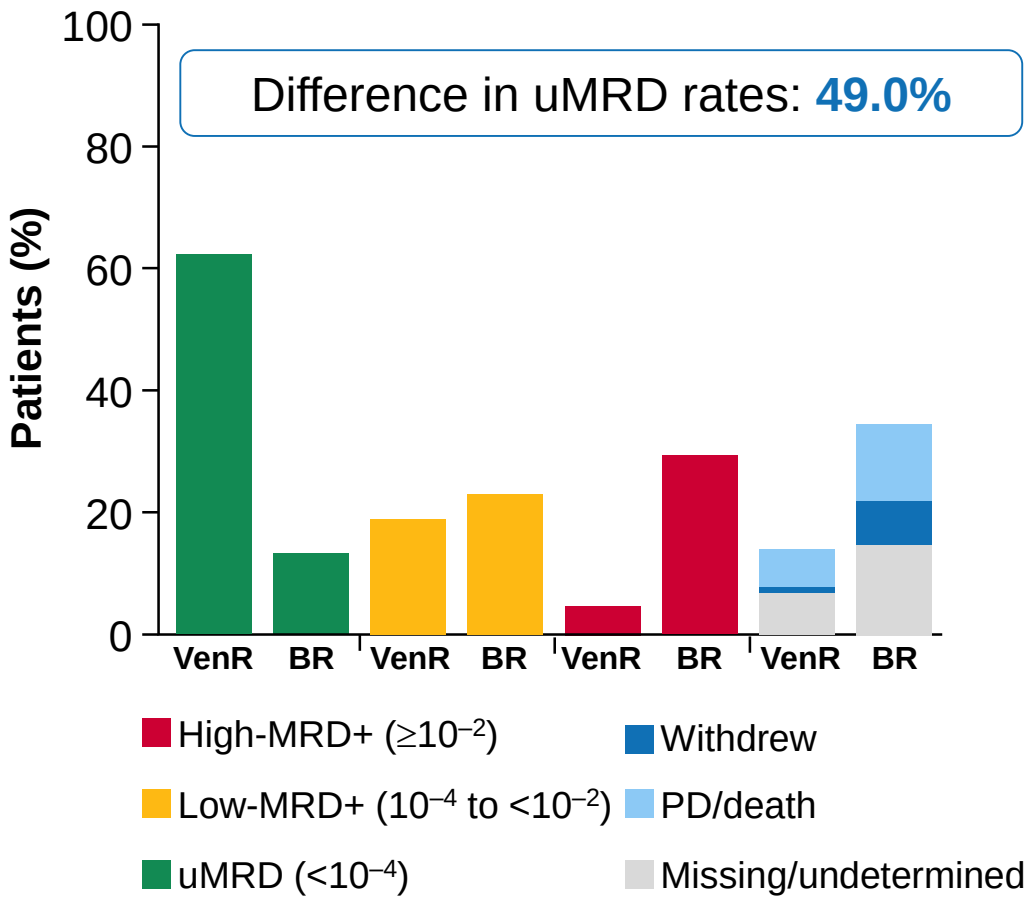


MRD status according to		ASO-PCR	
		uMRD	MRD+
Flow cytometry	uMRD	755	202
	MRD+	49	853

MRD concordance of ASO-PCR and/or flow cytometry based on all samples;
MRD concordance of PB and BM based on paired samples only

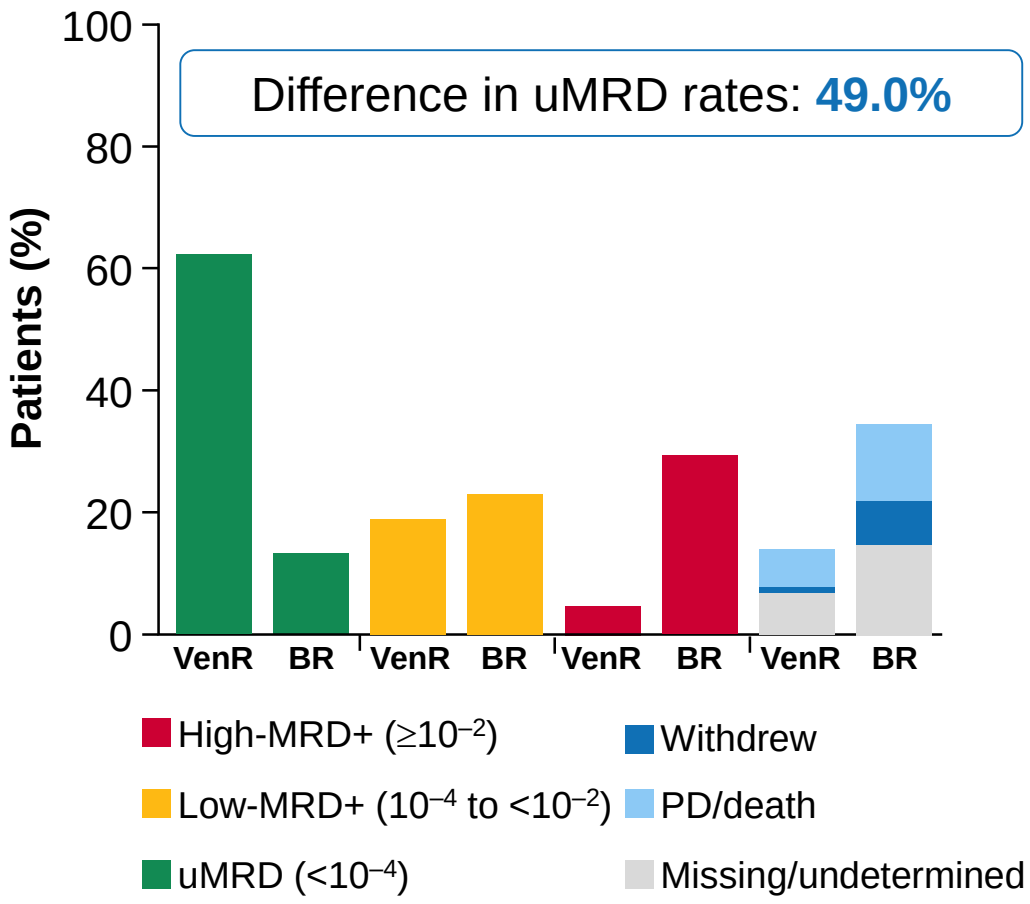
1. Hillmen P, et al. ASCO 2018 (abstract 7508)

PB uMRD rates higher with VenR than BR at EOCT



VenR (n=194); BR (n=195)

PB uMRD rates higher with VenR than BR at EOCT

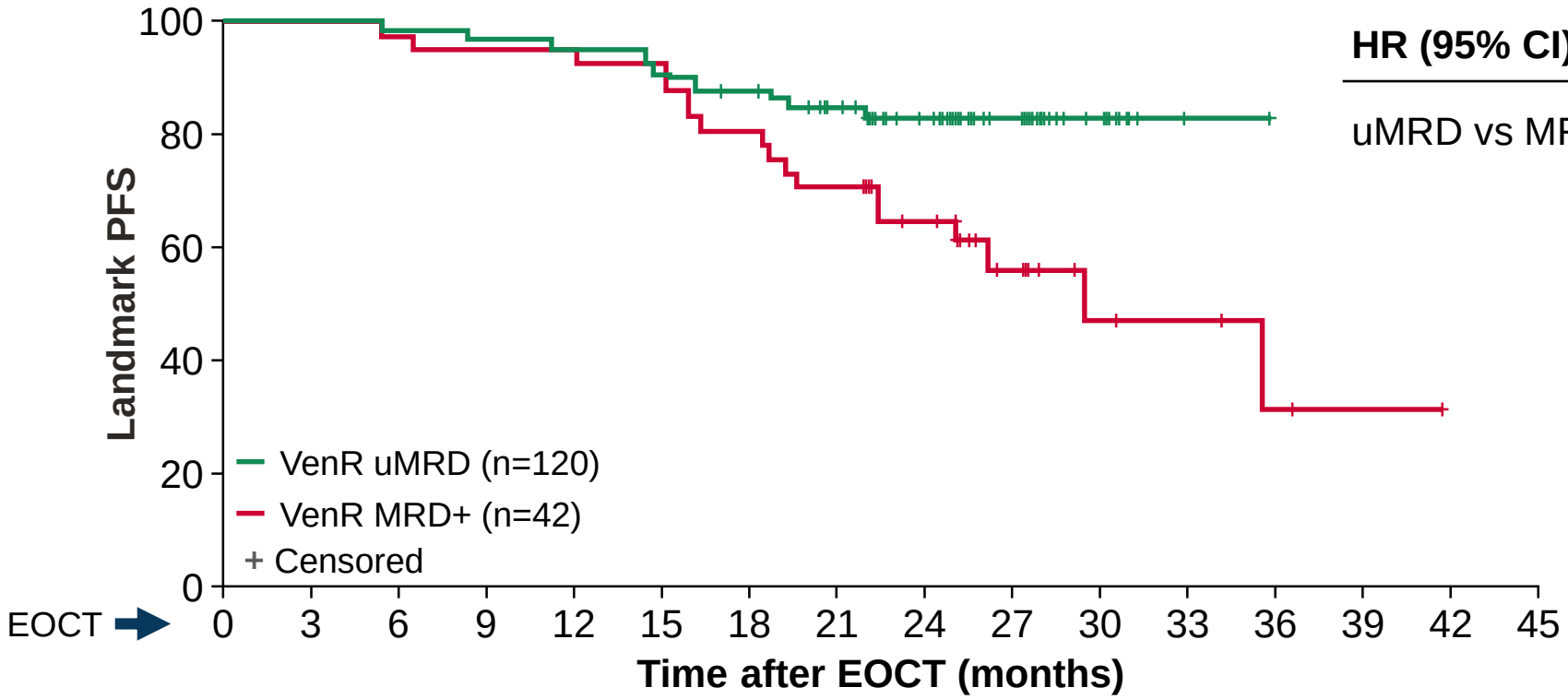


VenR (n=194); BR (n=195)

Consistently high uMRD rates observed in all VenR subgroups, including pts with high-risk cytogenetics and molecular factors

n (%)	n	uMRD	p-value
Del(11q)			
Yes	61	40 (65.6)	0.813
No	112	70 (62.5)	
Del(17p) and/or *TP53* mut			
Yes	72	41 (56.9)	0.284
No	106	70 (66.0)	
IGHV mutation			
Absent	123	75 (61.0)	0.819
Present	53	34 (64.2)	
Bulky disease			
<10 cm	161	99 (61.5)	0.909
≥10 cm	23	15 (65.2)	
Lines of prior therapy			
1	111	71 (64.0)	0.704
>1	83	50 (60.2)	

uMRD status at EOCT highly predictive of prolonged PFS



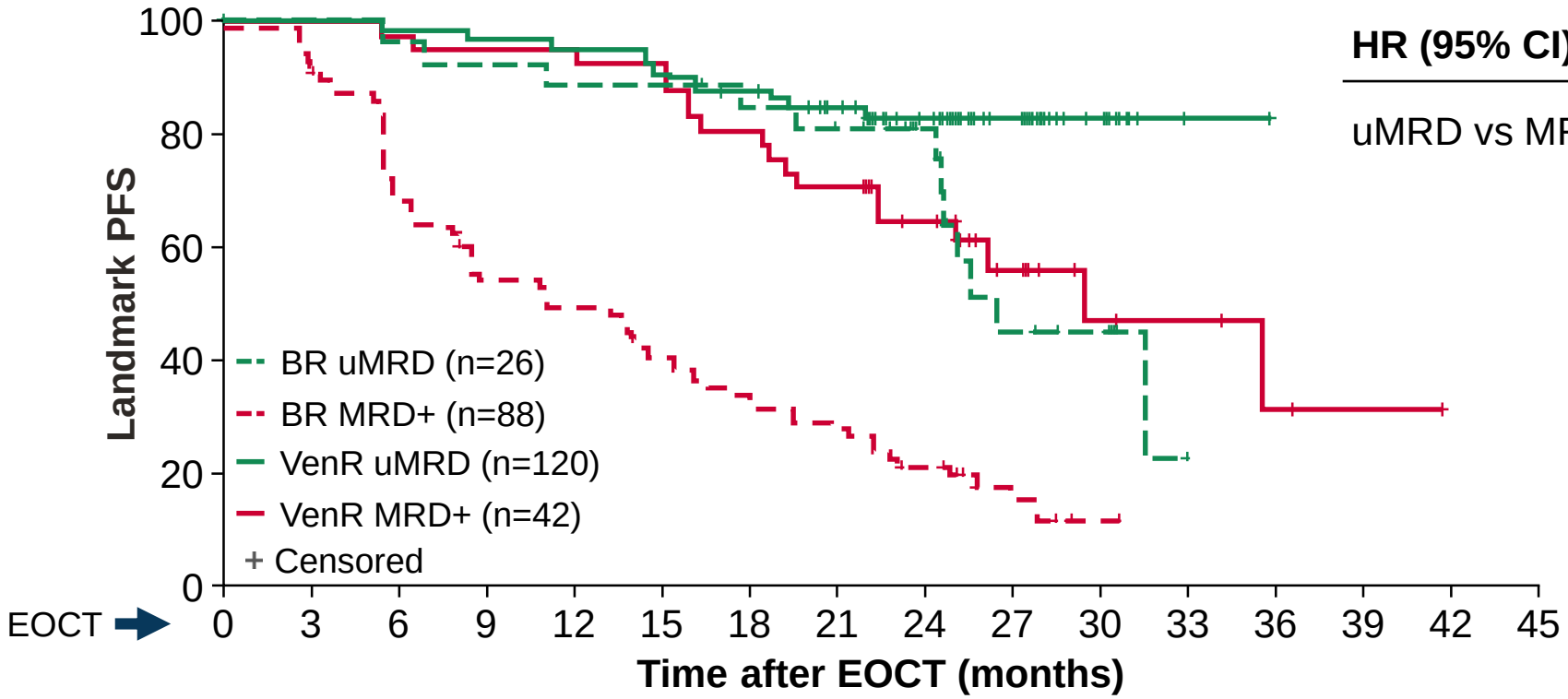
HR (95% CI)	VenR
uMRD vs MRD+	0.38 (0.20, 0.72)

No. of pts at risk

VenR uMRD	120	120	119	116	114	109	102	93	66	41	15	1		
VenR MRD+	42	41	40	39	39	38	33	29	21	10	5	4	2	1

Data cut-off May 8, 2018; median follow-up: 36.0 months
Including pts who have not progressed, died, or withdrawn from study before EOCT who are all censored
Response visit MRD PB status derived from combining ASO-PCR and flow cytometry results

uMRD status at EOCT highly predictive of prolonged PFS in both treatment arms



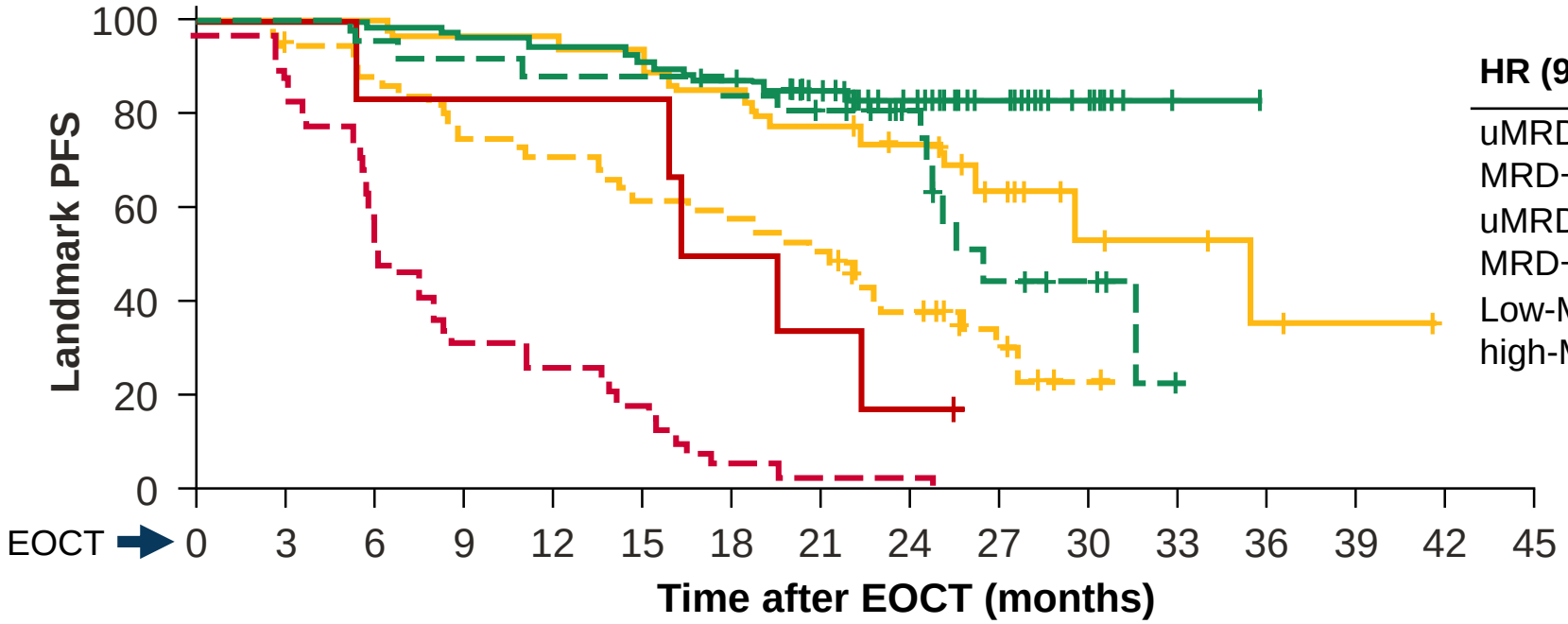
HR (95% CI)	VenR	BR
uMRD vs MRD+	0.38 (0.20, 0.72)	0.27 (0.14, 0.52)

No. of pts at risk

BR uMRD	26	26	25	24	23	23	22	20	15	7	5		
BR MRD+	88	79	61	45	41	34	27	23	15	7	1		
VenR uMRD	120	120	119	116	114	109	102	93	66	41	15	1	
VenR MRD+	42	41	40	39	39	38	33	29	21	10	5	4	2	1

Data cut-off May 8, 2018; median follow-up: 36.0 months
Including pts who have not progressed, died, or withdrawn from study before EOCT who are all censored
Response visit MRD PB status derived from combining ASO-PCR and flow cytometry results

Low-MRD+ at EOCT associated with better outcomes than high-MRD+



HR (95% CI)	VenR	BR
uMRD vs low-MRD+	0.48 (0.24, 0.98)	0.44 (0.22, 0.89)
uMRD vs high-MRD+	0.15 (0.06, 0.40)	0.08 (0.03, 0.18)
Low-MRD+ vs high-MRD+	0.24 (0.08, 0.72)	0.22 (0.13, 0.38)

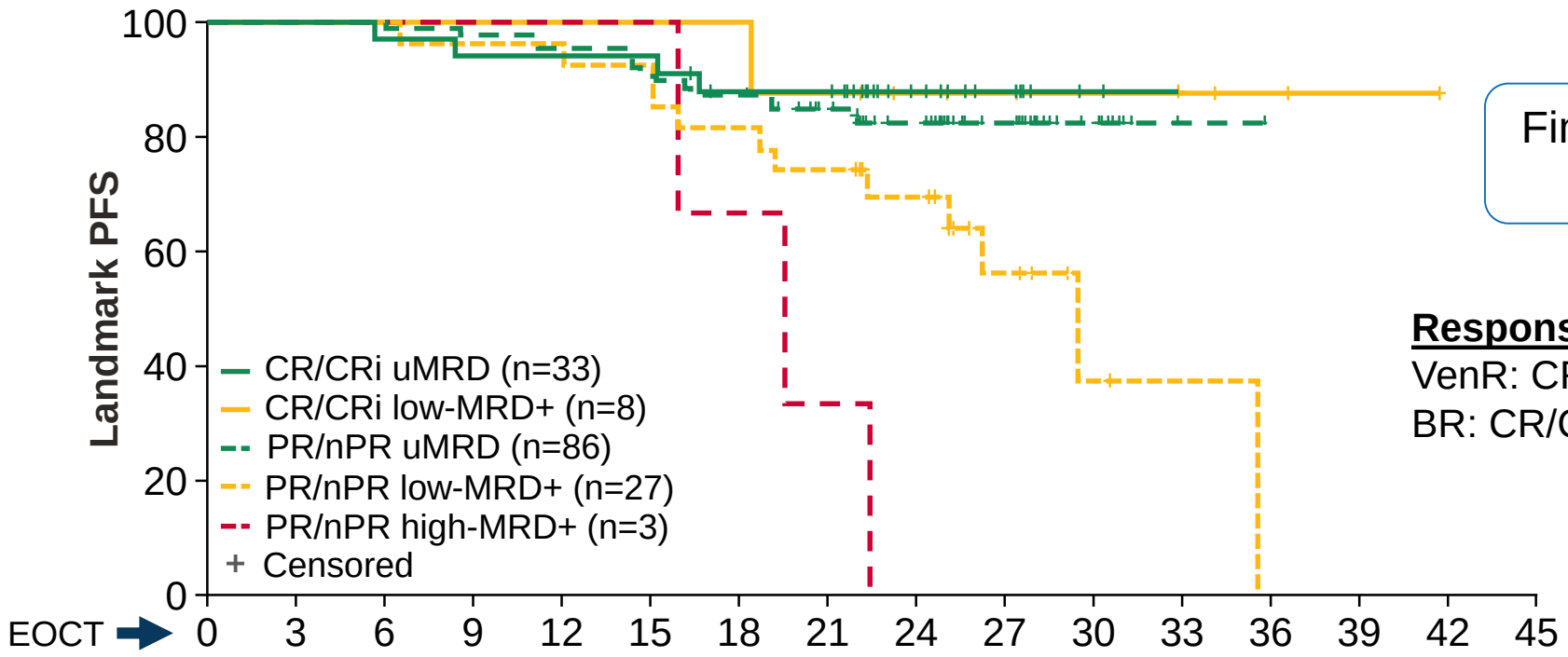
No. of pts at risk

VenR uMRD	120	120	119	116	114	109	102	93	66	41	15	1		
VenR low-MRD+	36	35	35	34	34	33	30	27	20	10	5	4	2	1
VenR high-MRD+	6	6	5	5	5	5	3	2	1					
BR uMRD	26	26	25	24	23	23	22	20	15	7	5			
BR low-MRD+	45	43	39	33	31	27	25	22	14	7	1			
BR high-MRD+	43	36	22	12	10	7	2	1	1					

- VenR uMRD (n=120; 62%)
- VenR low-MRD+ (n=36; 19%)
- VenR high-MRD+ (n=6; 3%)
- BR uMRD (n=26; 13%)
- BR low-MRD+ (n=45; 23%)
- BR high-MRD+ (n=43; 22%)

Data cut-off May 8, 2018; median follow-up: 36.0 months
Including pts who have not progressed, died, or withdrawn from study before EOCT who are all censored
Response visit MRD PB status derived from combining ASO-PCR and flow cytometry results

PFS similar for VenR pts with CR or PR and uMRD



No. of pts at risk

CR/CRi uMRD	33	33	32	31	31	31	26	26	15	8	2			
CR/CRi low-MRD+	8	8	8	8	8	8	8	7	5	4	3	3	2	1
PR/nPR uMRD	86	86	86	84	82	77	75	67	51	33	13	1		
PR/nPR low-MRD+	27	27	27	26	26	25	22	20	15	6	2	1		
PR/nPR high-MRD+	3	3	3	3	3	3	2	1						

Findings were similar in the BR arm

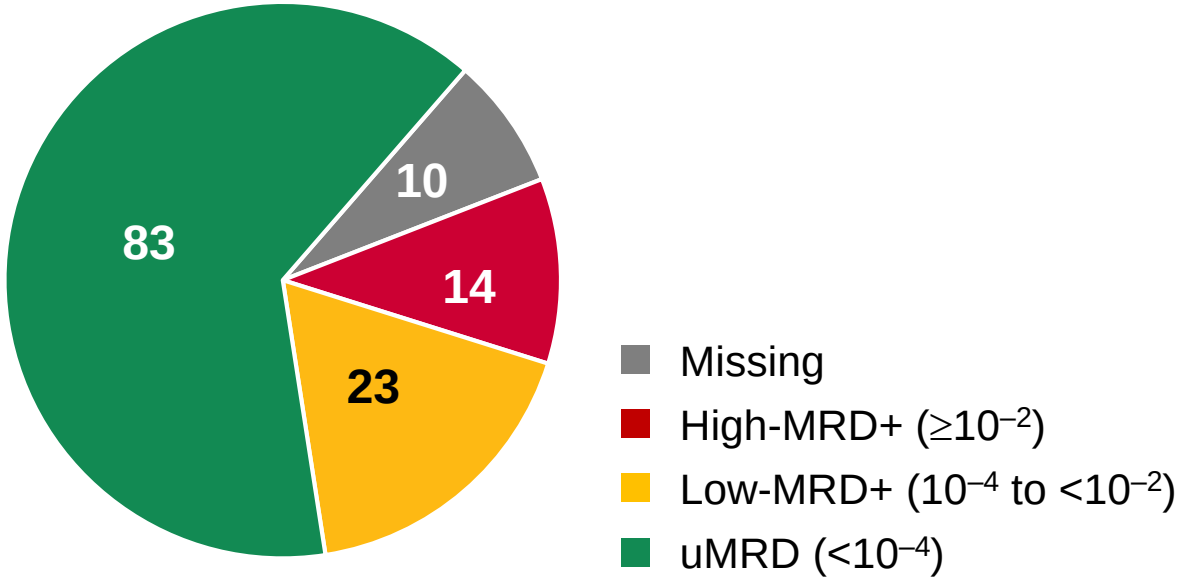
Response rates

VenR: CR/CRi 27.8%, PR/nPR 65.5%

BR: CR/CRi 8.7%, PR/nPR 59.0%

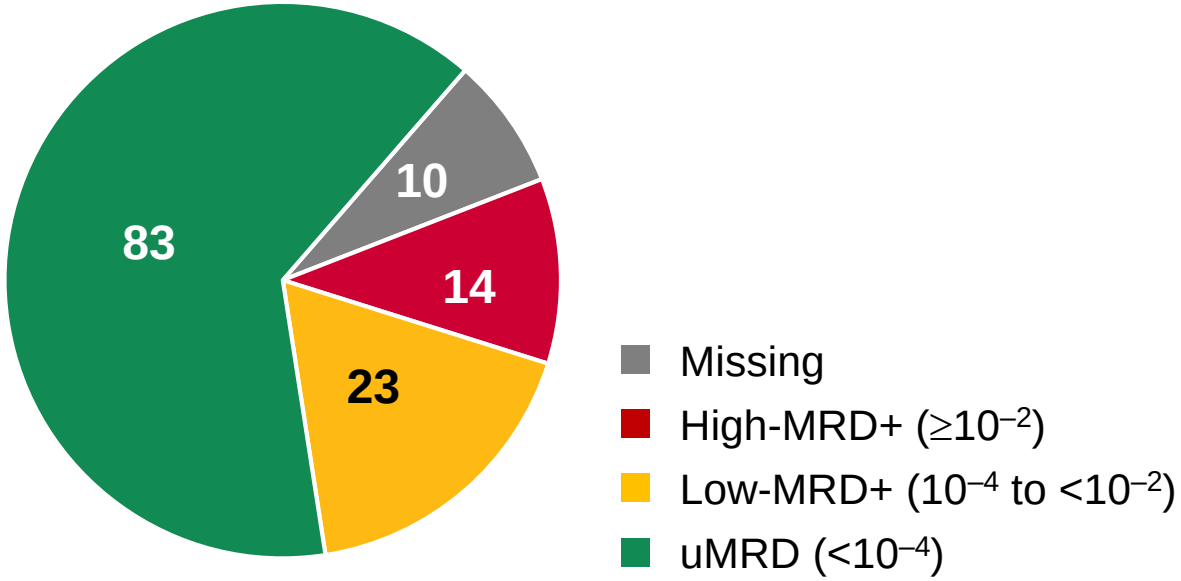
Data cut-off May 8, 2018; median follow-up: 36.0 months. MRD+ does not include “missing” samples. The analysis subset includes pts who have not progressed, died or withdrawn from study before EOCT response visit. MRD PB status derived from combining ASO-PCR and flow cytometry results

Higher PB uMRD with VenR sustained at EOT



- Pts who completed 2 yrs of VenR combination treatment

Higher PB uMRD with VenR sustained at EOT

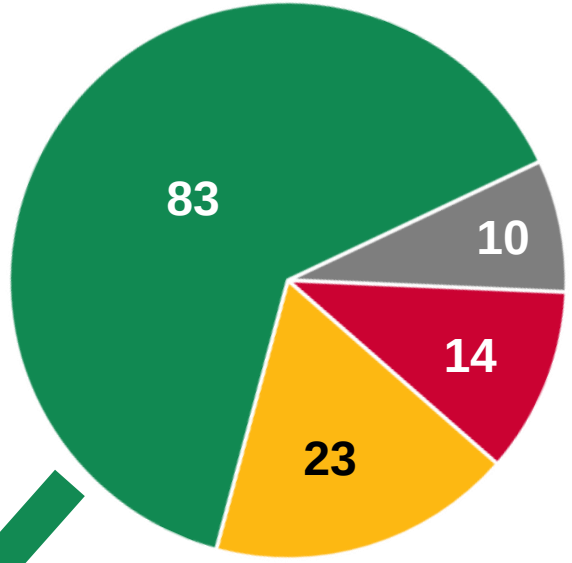


n (%)	n	uMRD	p-value
Del(11q)			
Yes	38	27 (71.1)	0.481
No	80	50 (62.5)	
Del(17p) and/or *TP53* mut			
Yes	43	22 (51.2)	0.038
No	78	56 (71.8)	
IGHV mutation			
Absent	84	56 (66.7)	0.651
Present	38	23 (60.5)	
Bulky disease			
<10 cm	104	64 (61.5)	0.446
≥10 cm	16	12 (75.0)	
Lines of prior therapy			
1	78	51 (65.4)	0.794
>1	52	32 (61.5)	

- Pts who completed 2 yrs of VenR combination treatment

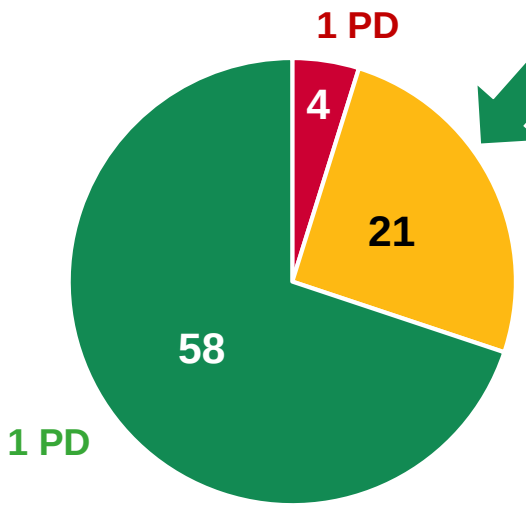
MRD conversion after stopping Ven monotherapy for pts who were progression-free at EOT

At EOT (Month 24; n=130):



- Missing
- High-MRD+ ($\geq 10^{-2}$)
- Low-MRD+ (10^{-4} to $<10^{-2}$)
- uMRD ($<10^{-4}$)

At 9.9 months median follow-up since EOT:



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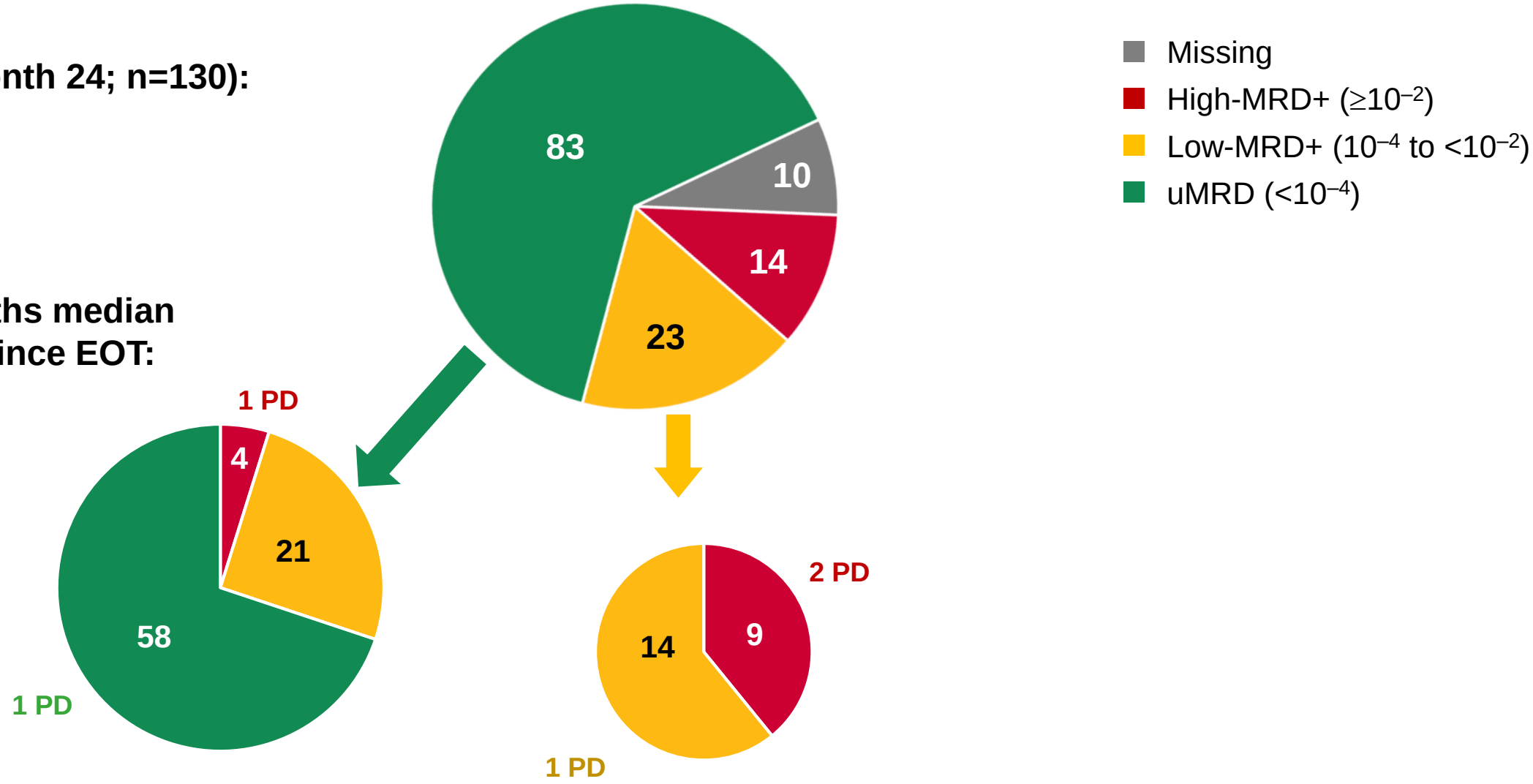

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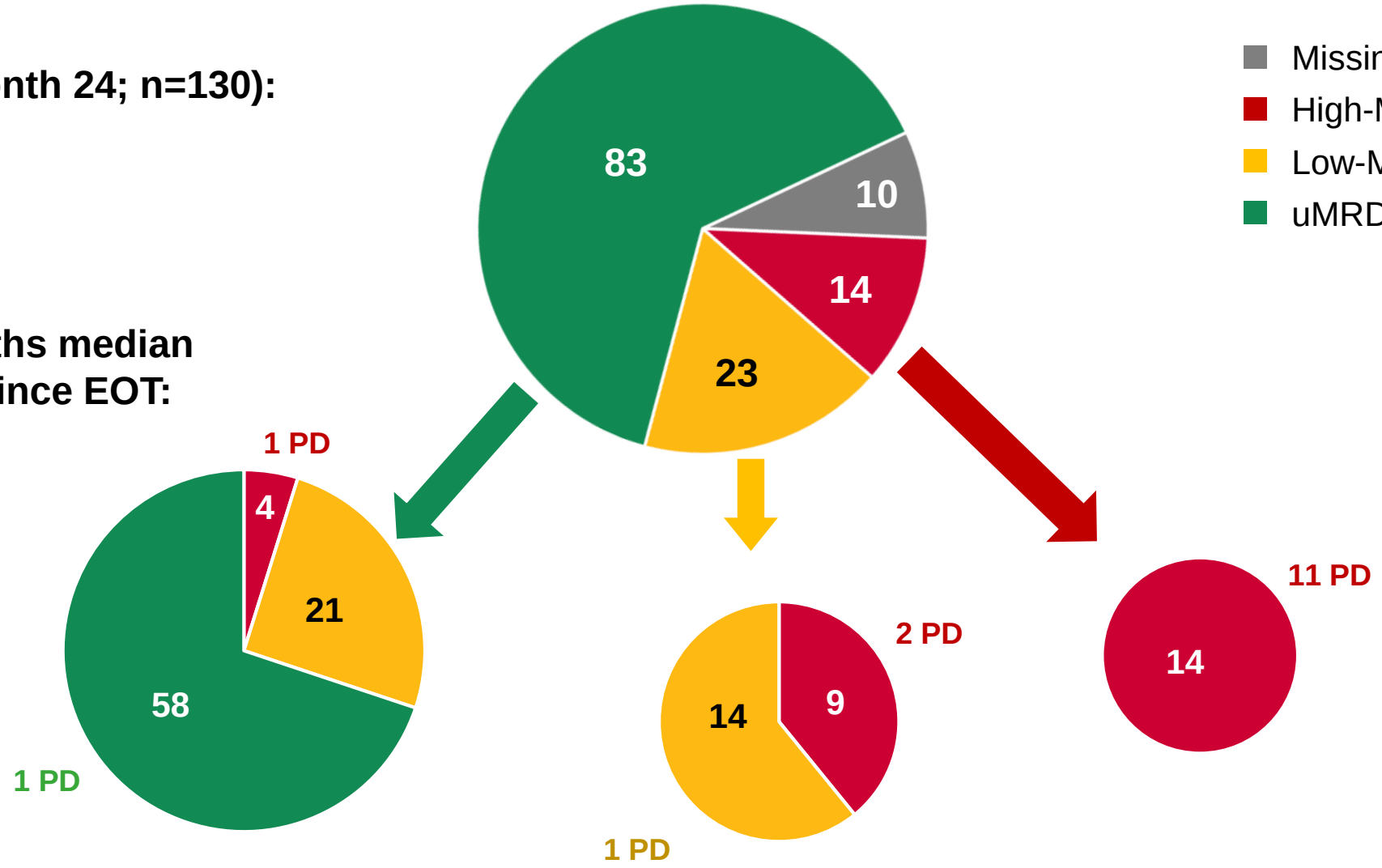
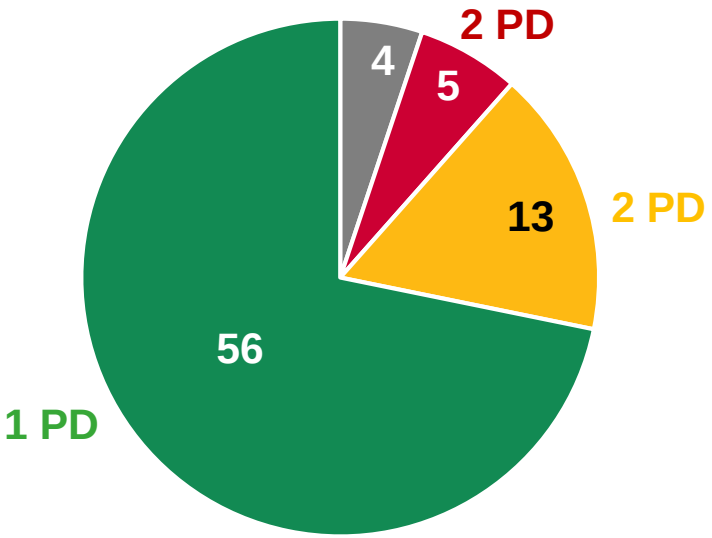


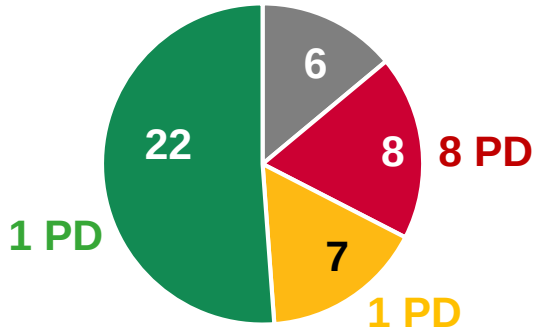
At 9.9 months median follow-up since EOT:

Association of del(17p)/*TP53* mut with increased risk of PD post-treatment

Non-del(17p) and/or *TP53* unmutated



del(17p) and/or *TP53* mutation

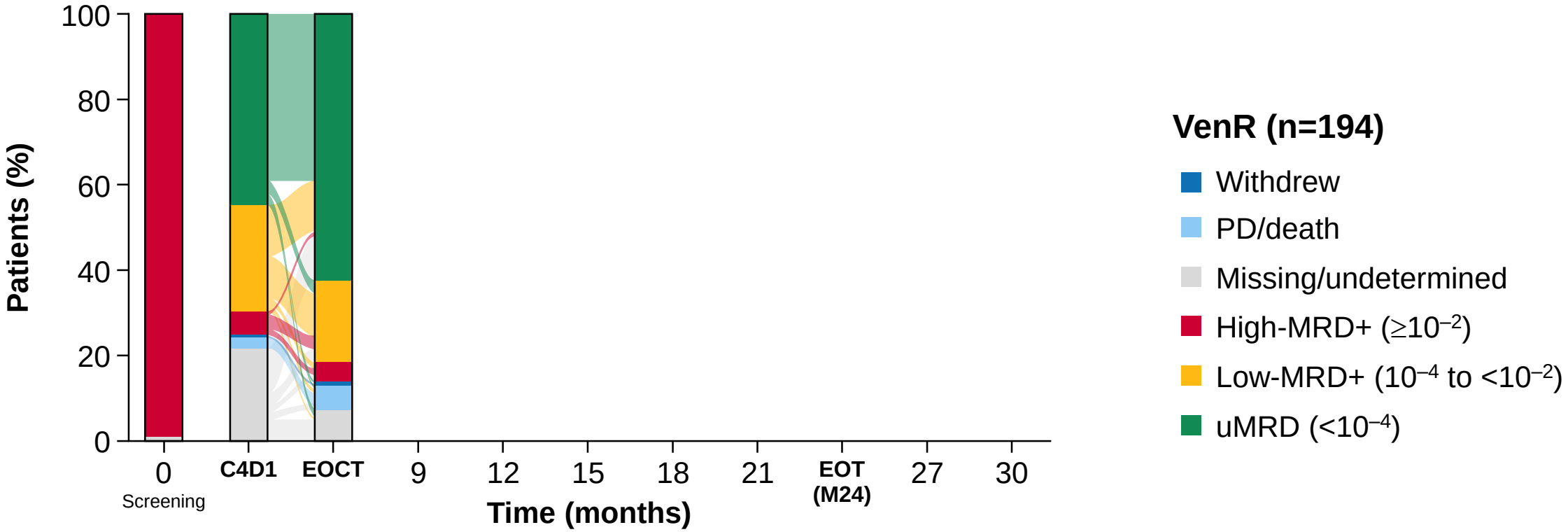


uMRD (<10^{-4}) Low-MRD+ (10^{-4} to <10^{-2}) High-MRD+ (≥10^{-2}) Missing

PD was reported after EOT (Month 24)

1 PD in the n=9 pts with missing del(17p) and/or *TP53* status

MRD status over time in VenR arm: high uMRD rate is sustained



- At EOCT, the majority of pts had uMRD status
- Most MRD+ pts at EOCT had low-MRD+ status

Data cut-off May 8, 2018; median follow-up: 36.0 months. Missing values also include pts who have not yet reached the time point

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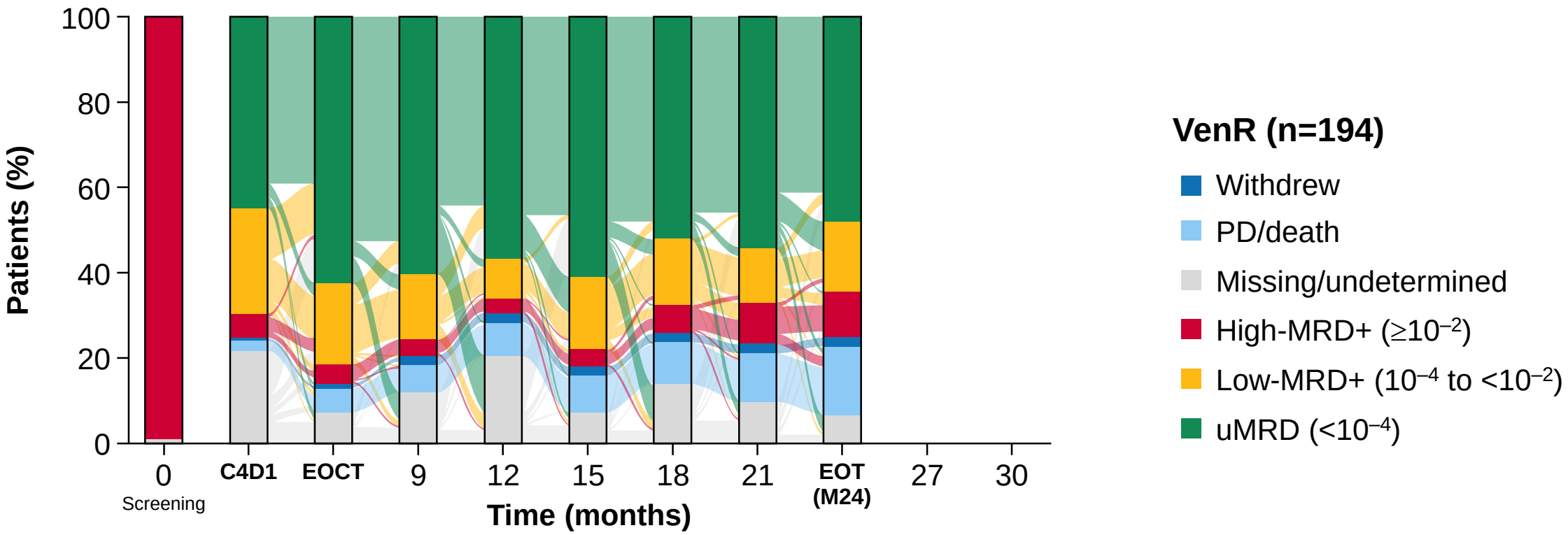

- High uMRD rates sustained
- Among pts converting from uMRD to MRD+, most change to low-MRD+ and many remain low-MRD+ over time

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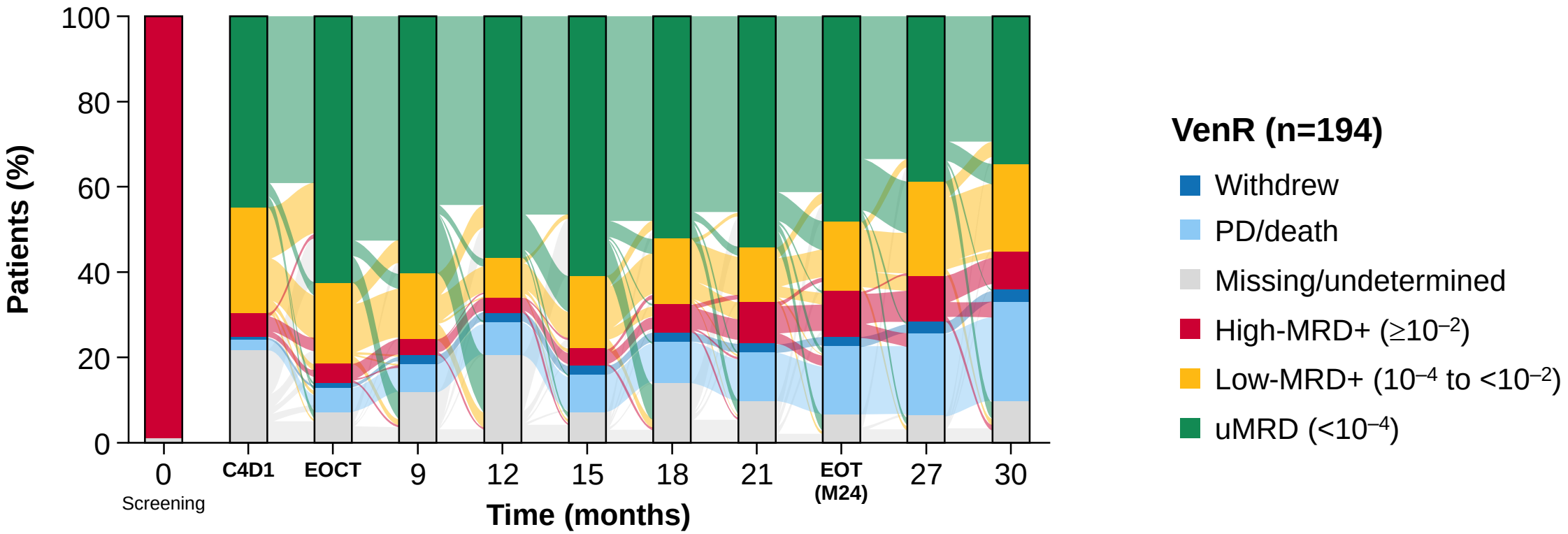
MRD status over time in VenR arm: high uMRD rate is sustained



- Few low-MRD+ pts progressed
- Pts who did progress had mainly converted to high-MRD+ first

Data cut-off May 8, 2018; median follow-up: 36.0 months. Missing values also include pts who have not yet reached the time point

Conclusions

- PB MRD status is a good surrogate for BM MRD status with VenR

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- After completion of fixed-duration VenR (median follow-up 9.9 months), rates of PD and re-emergence of MRD positivity were low
- First data to demonstrate value of uMRD as a predictive marker of improved clinical outcome for a fixed-duration chemotherapy-free regimen

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Fixed Duration of Venetoclax-Rituximab in Relapsed/Refractory Chronic Lymphocytic Leukemia Eradicates Minimal Residual Disease and Prolongs Survival: Post-Treatment Follow-Up of the MURANO Phase III Study

Arnon P Kater, MD[1]; John F. Seymour, MD[2]; Peter Hillmen, MD[3]; Barbara Eichhorst, MD[4]; Anton W Langerak, PhD[5]; Carolyn Owen MD[6]; Maria Verdugo MD[7]; Jenny Wu, MS[8]; Elizabeth A. Punnoose, PhD[8]; Yanwen Jiang, PhD[8]; Jue Wang, PhD[8]; Michelle Boyer, PhD[9]; Kathryn Humphrey, BSc[9]; Mehrdad Mobasher, MD[8]; and Thomas J. Kipps, MD[10]

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