NIGUARDA 80
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Sistema Socio Sanitario
Ospedale Niguarda Cancer Center
Regione Lombardia

Progetto Ematologia-Romagna
Faenza – 19 Ottobre 2019

Una chemioterapia «mirata»

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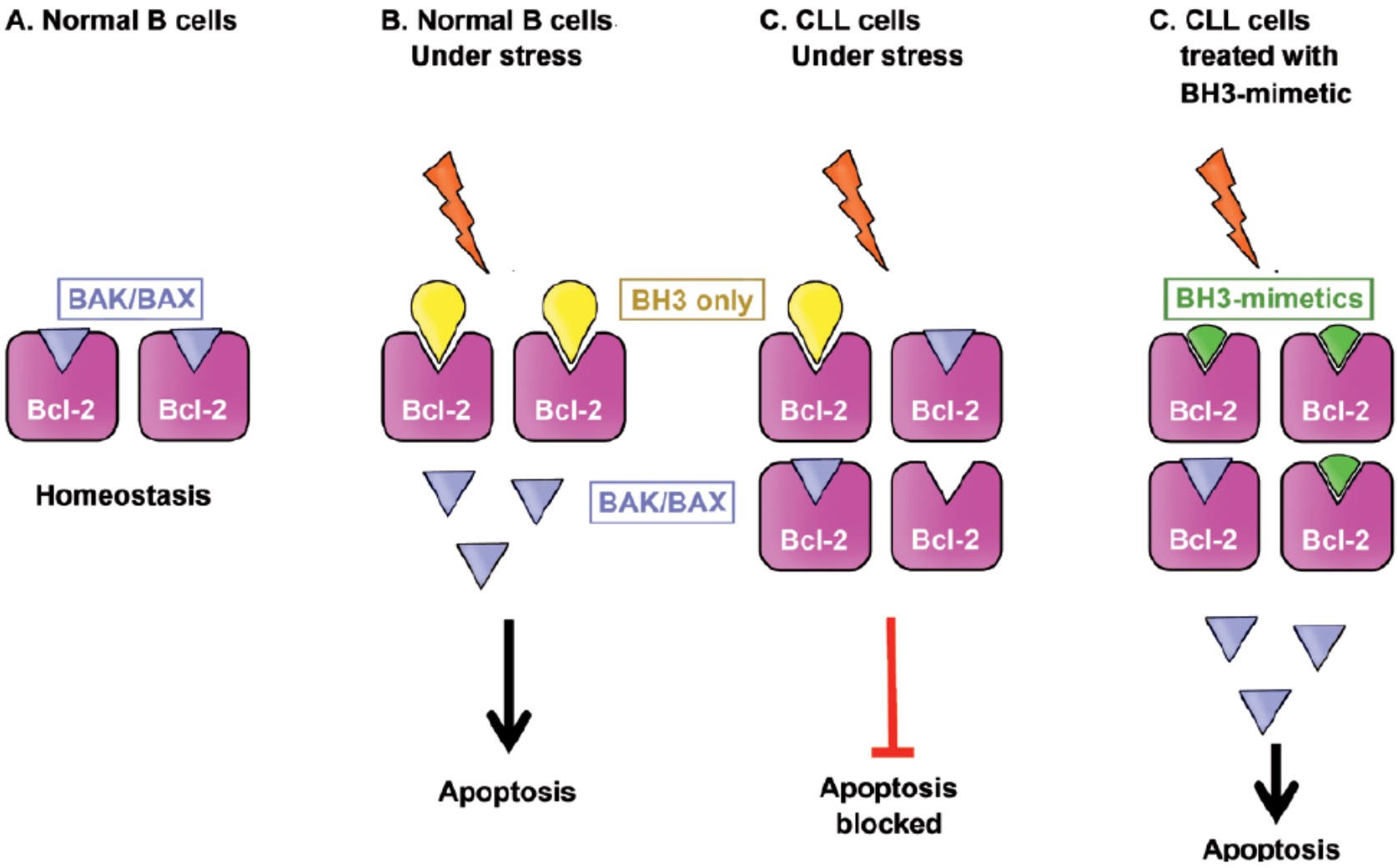
Conflict of Interest

- Janssen
- Gilead
- Abbvie
- Roche
- Astra Zeneca
- Mundipharma

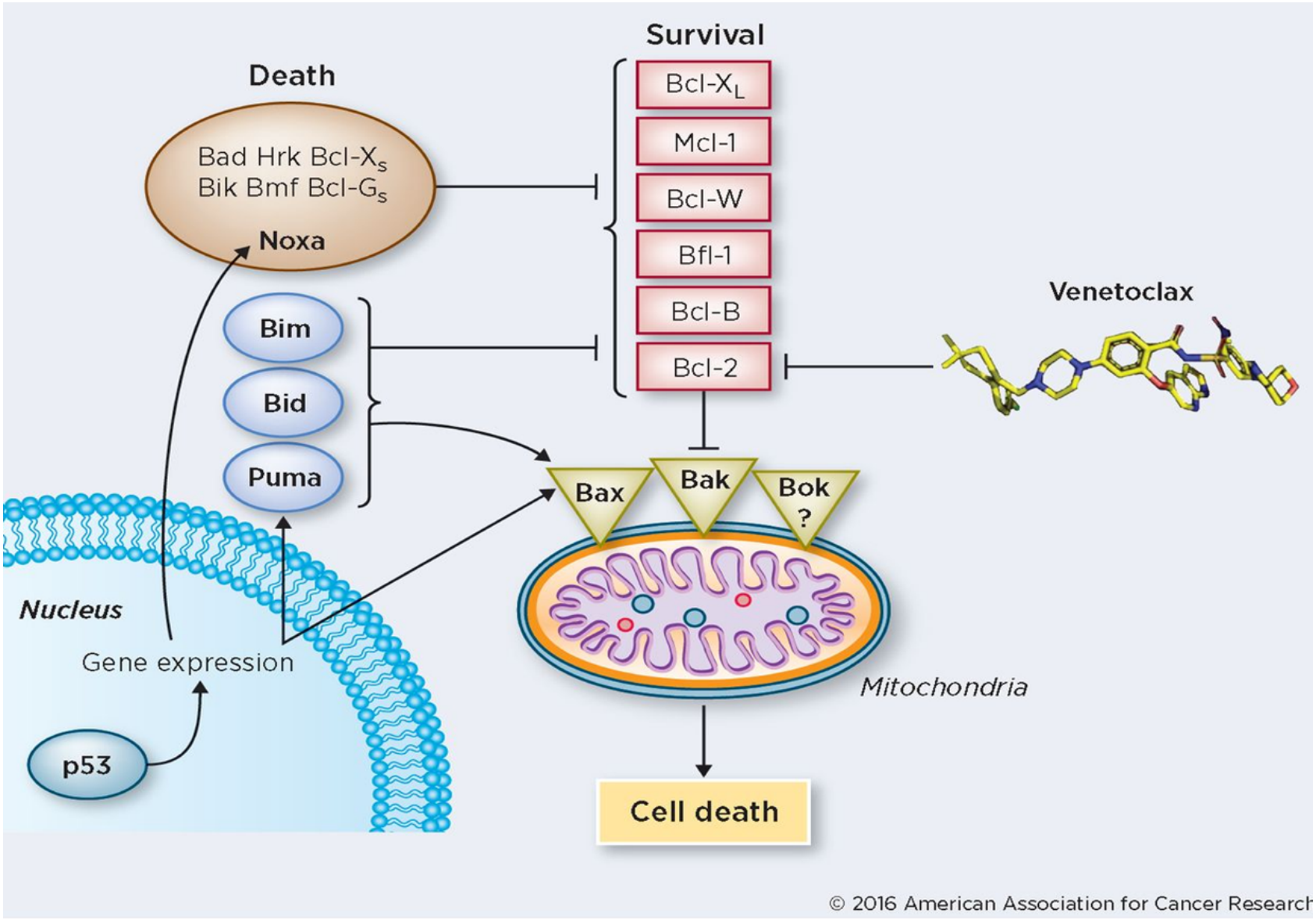
BH3 mimetics

Mimics the action of the BH3-only proteins



Itchaki G & Brown J, Ther Adv Hematol 2016

Venetoclax Induces Apoptosis by Acting as a BH3 Mimetic to Inhibit BCL2



Venetoclax in patients progressing after ibrutinib or idelalisib

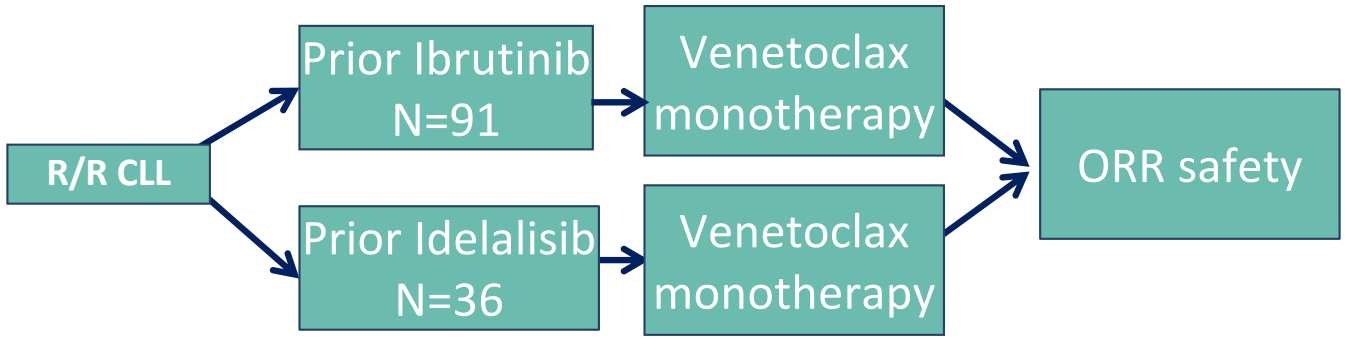
Venetoclax for chronic lymphocytic leukaemia progressing after ibrutinib: an interim analysis of a multicentre, open-label, phase 2 trial

Jeffrey A Jones, Anthony R Mato, William G Wierda, Matthew S Davids, Michael Choi, Bruce D Cheson, Richard R Furman, Nicole Lamanna, Paul M Barr, Lang Zhou, Brenda Chyla, Ahmed Hamed Salem, Maria Verdugo, Rod A Humerickhouse, Jalaja Potluri, Steven Coutre, Jennifer Woyach, * John C Byrd*

blood®
Prepublished online January 5, 2018;
doi:10.1182/blood-2017-06-788133

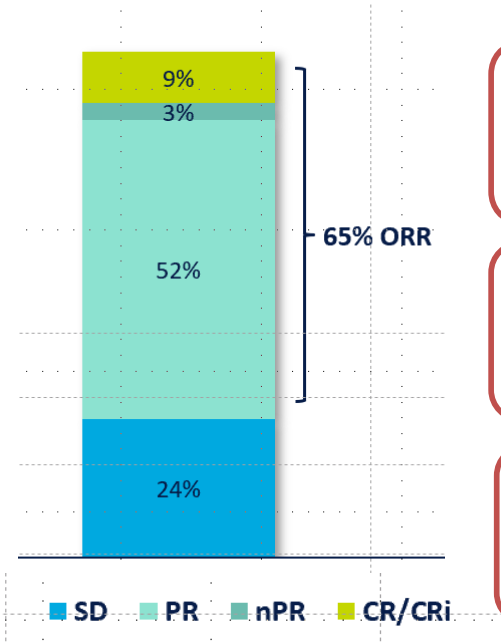
Venetoclax for patients with chronic lymphocytic leukemia who progressed during or after idelalisib therapy

Steven Coutre, Michael Choi, Richard R. Furman, Herbert Eradat, Leonard Heffner, Jeffrey A. Jones, Brenda Chyla, Lang Zhou, Suresh Agarwal, Tina Waskiewicz, Maria Verdugo, Rod A. Humerickhouse, Jalaja Potluri, William G. Wierda and Matthew S. Davids



Venetoclax for CLL progressing after ibrutinib: an interim analysis of a multicenter phase 2 trial

Characteristics	n=91
Unmutated IGVH, n/N (%)	50/67 (75%)
Del(17p), n/N (%)	42/90 (47%)
TP53 mutations, n/N (%)	29/87 (33%)
Del(11q) n/N (%)	30/91 (33%)
Prior therapies, median (range)	4 (1-15)



Median Follow-up to first response
2,5 m (IQR 1,6-2,6)

Median Follow-up to best response
7,9 m (IQR 5,3-8,1)

Median time to CR/CRi
8,2 m (IQR 4,9-9,0)

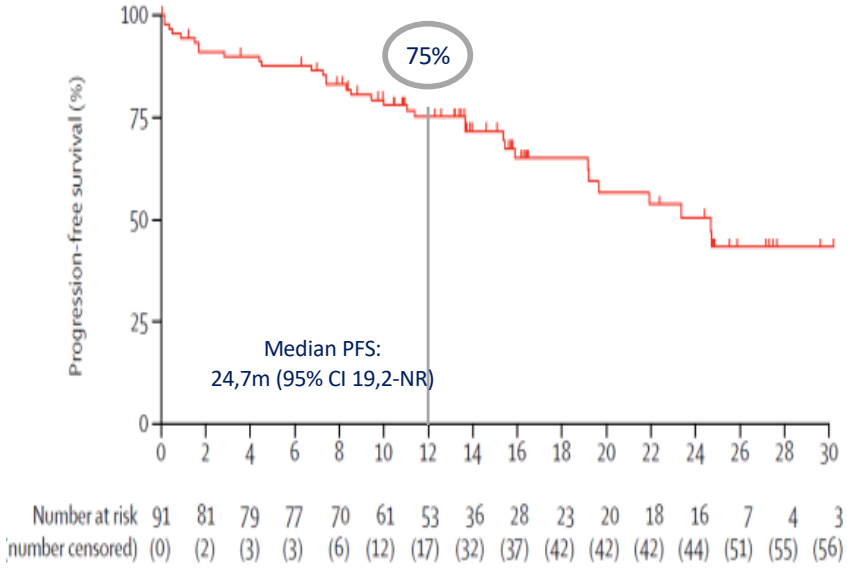
No difference in terms of response:

- *ibrutinib discontinued due to AE or disease progression: 63% versus 54%*
- *del (17p) or TP53 mutated versus NO del (17p) or TP53: 61% versus 67%*

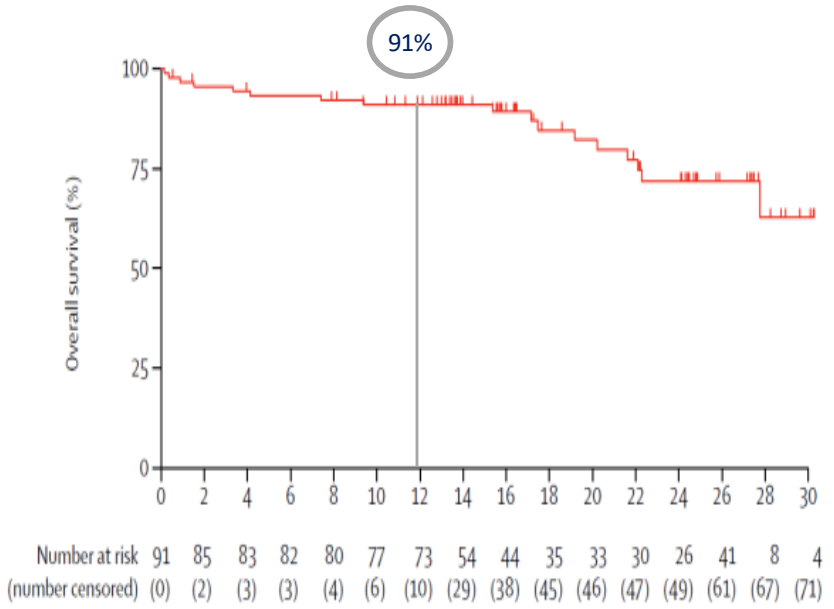
Jones et al 2017

Venetoclax for CLL progressing after ibrutinib: an interim analysis of a multicentre, phase 2 trial

Progression Free Survival



Overall Survival

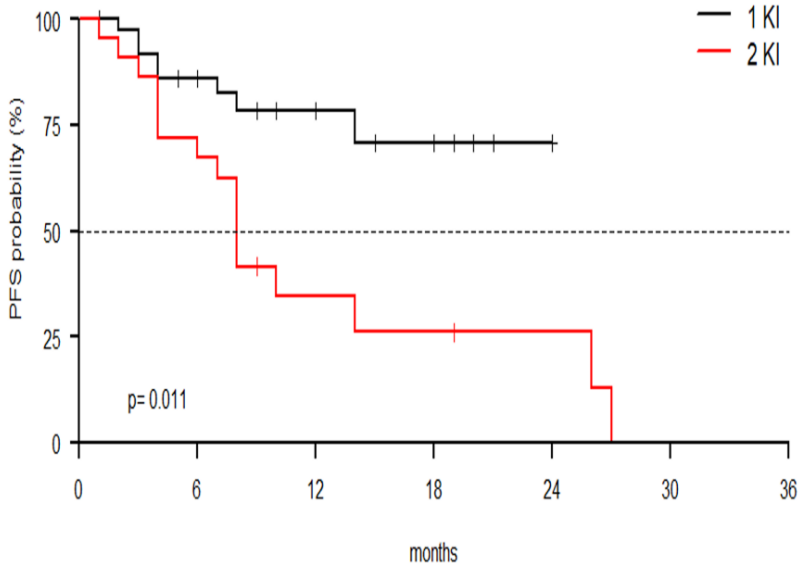


No difference in PFS between patients with *BTK* or *PLCG2* mutations vs those without (HR=1.04, 95% CI 0.22–4.80; p=0.96)

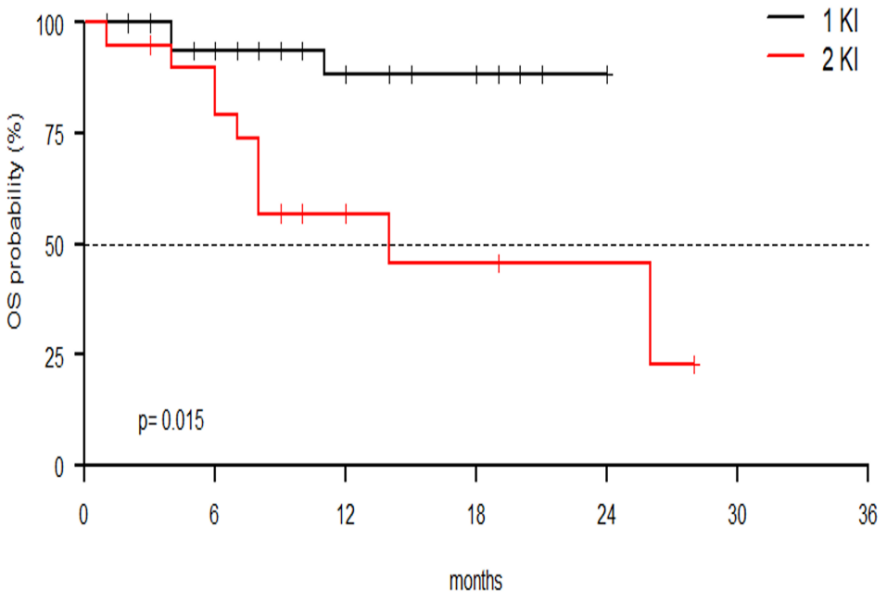
Jones et al 2017

Venetoclax in CLL patients who progress after BCR inhibitor treatment: a retrospective multi-centre Italian experience

PFS



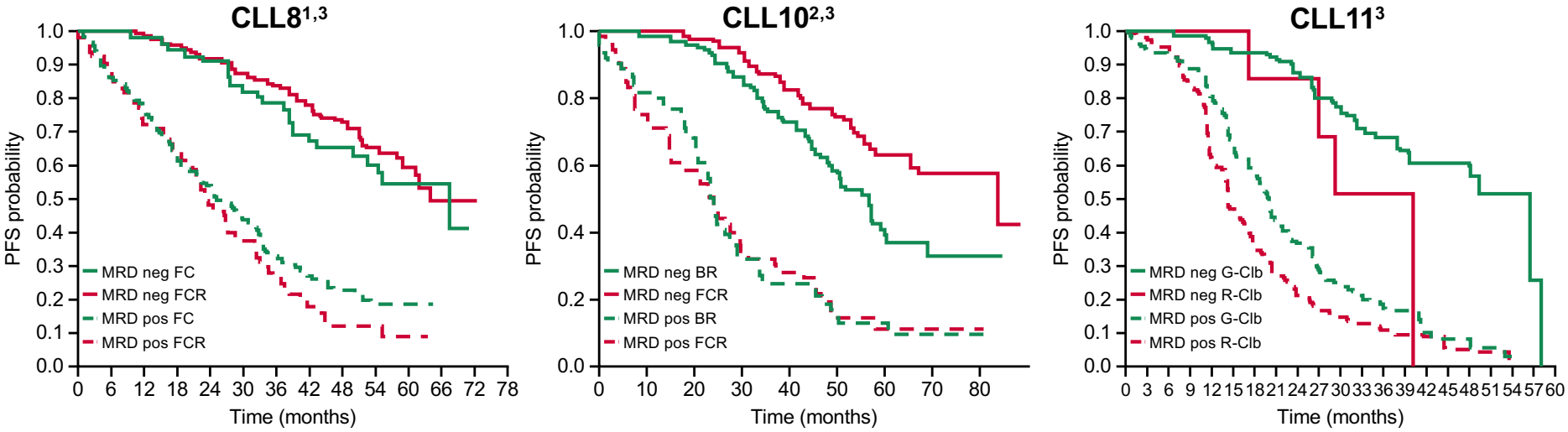
OS



Innocenti I et al., Br J Haematol 2019

MRD Background

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

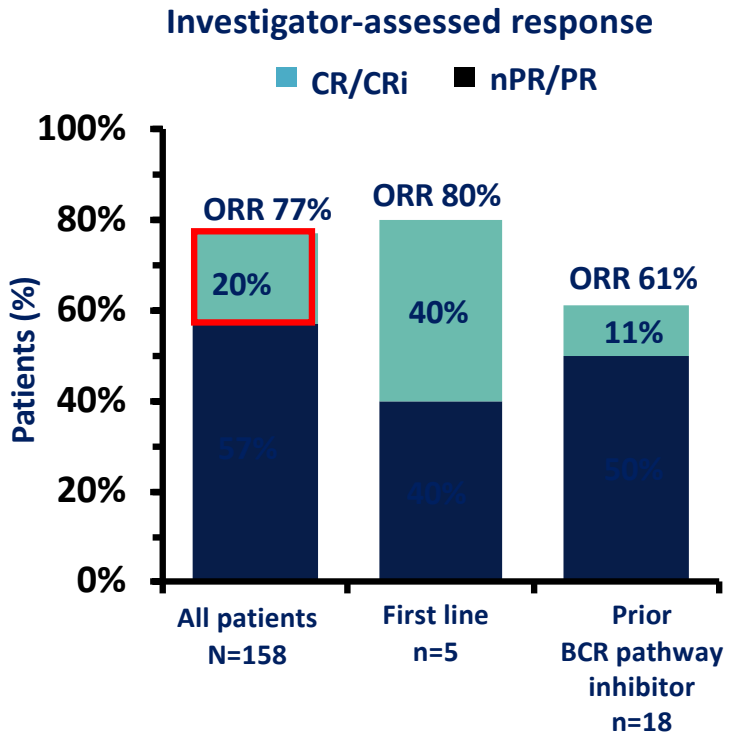


MRD, minimal residual disease

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: 03-839688

Phase 2 venetoclax monotherapy in R/R CLL with del(17p) (M13-982)

158 del(17p) pts
Median Prior Treatments 2 (0-10)



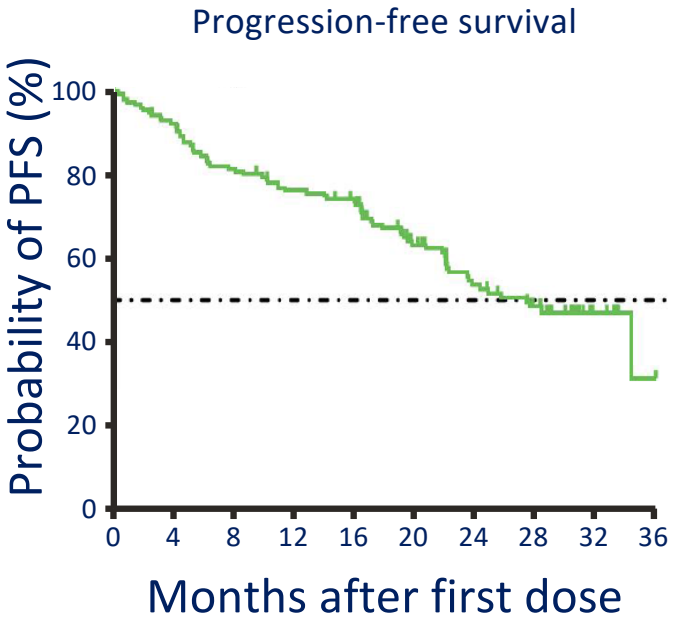
Best MRD status by flow cytometry and/or NGS*	
PB, n=101	
MRD negative, n	48 (30%)
MRD positive, n	61
BM, n=74	
MRD negative, n	18
MRD positive, n	56

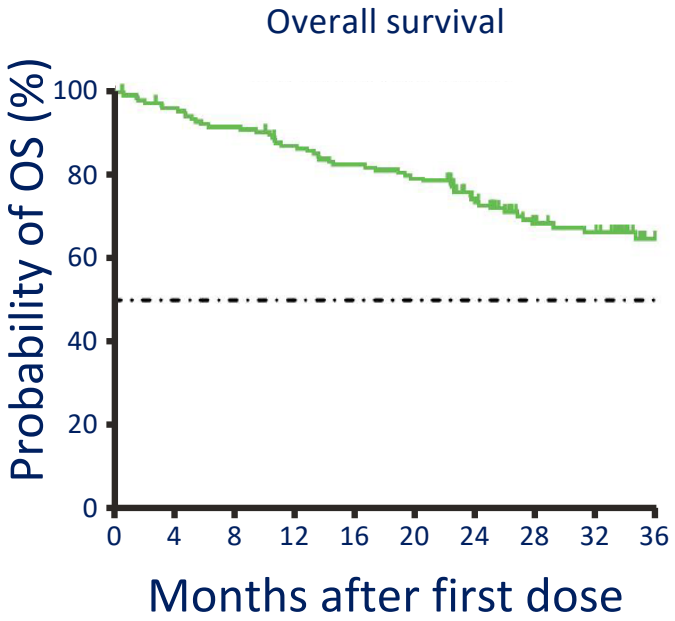
- Median time to first response: 1 month (range 0.5–4.4)
- Median time to CR/CRi: 9.8 months (range 2.7–31.1)

- Out of the patients with MRD negativity confirmed in both PB and BM:
  - 14 achieved CR/CRi
  - 4 achieved PR

Stilgenbauer S et al., 2016-2018

Phase 2 venetoclax monotherapy in R/R CLL with del(17p) (M13-982)



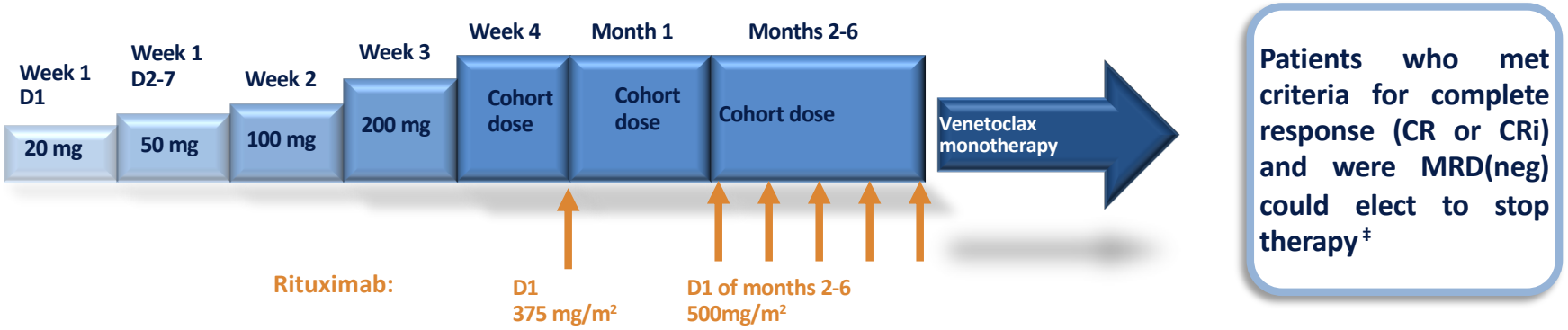


- Median PFS = 27.2 months (95% CI = 21 – NR)
- 24-month estimate: 54% (95% CI = 45–62)

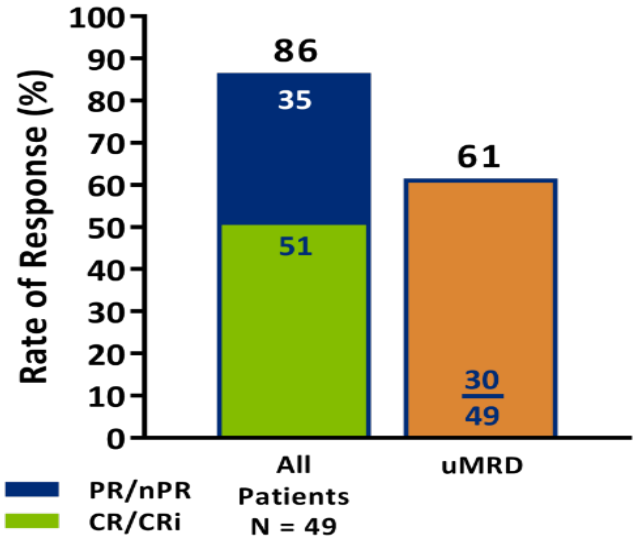
- 24-month estimate: 73% (95% CI = 65–79)

Stilgenbauer S, *et al. 2016-2017*

Venetoclax plus rituximab in relapsed or refractory chronic lymphocytic leukaemia: a phase 1b/2 study

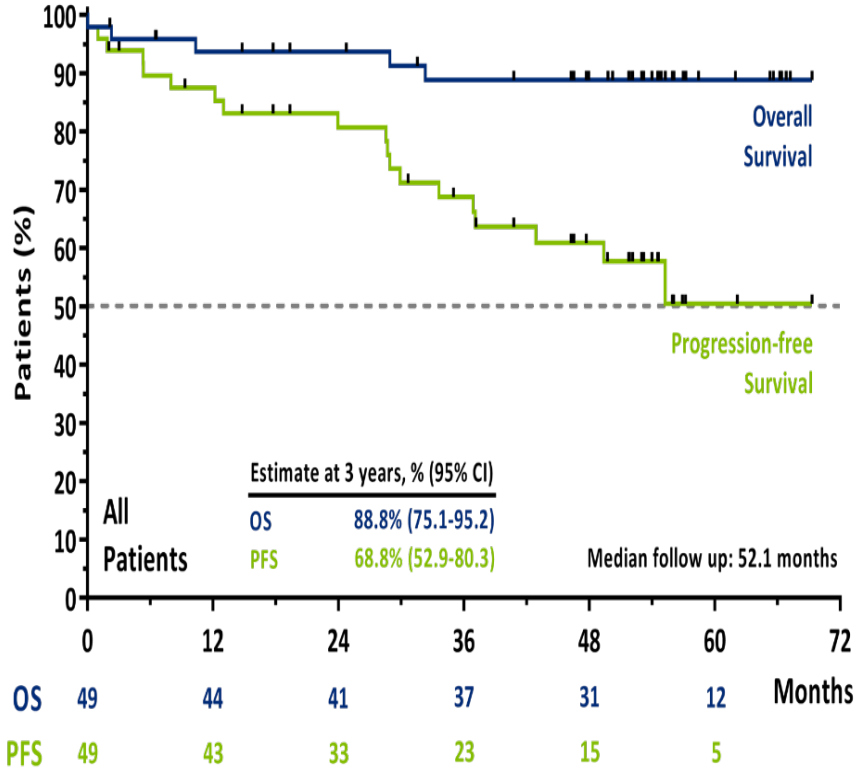


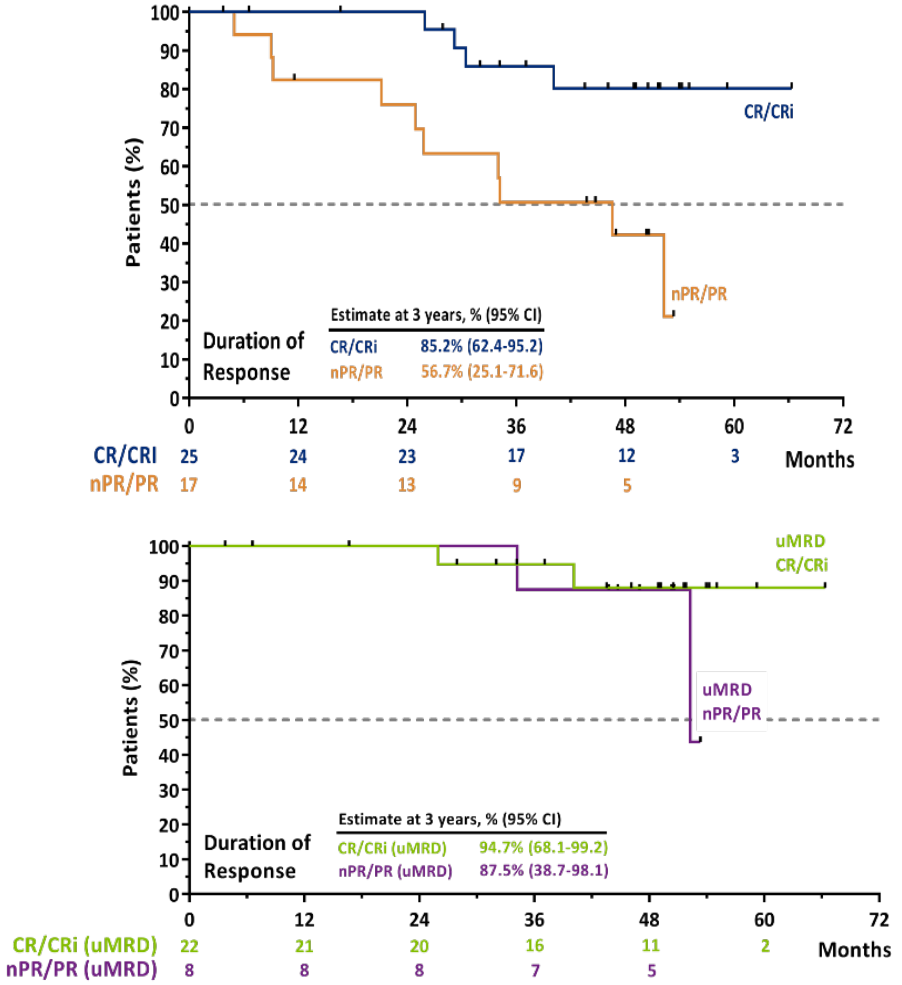
Patients	N 49
• Median prior therapies	2
• *IGHV* unmutated	68%
• *TP53* mutation and/or del(17p)	27%
• 11q deletion	44%



Seymour et al., 2017; Brander et al., 2018

Venetoclax plus rituximab in relapsed or refractory chronic lymphocytic leukaemia: a phase 1b/2 study





Seymour et al., 2017; Brander et al., 2018

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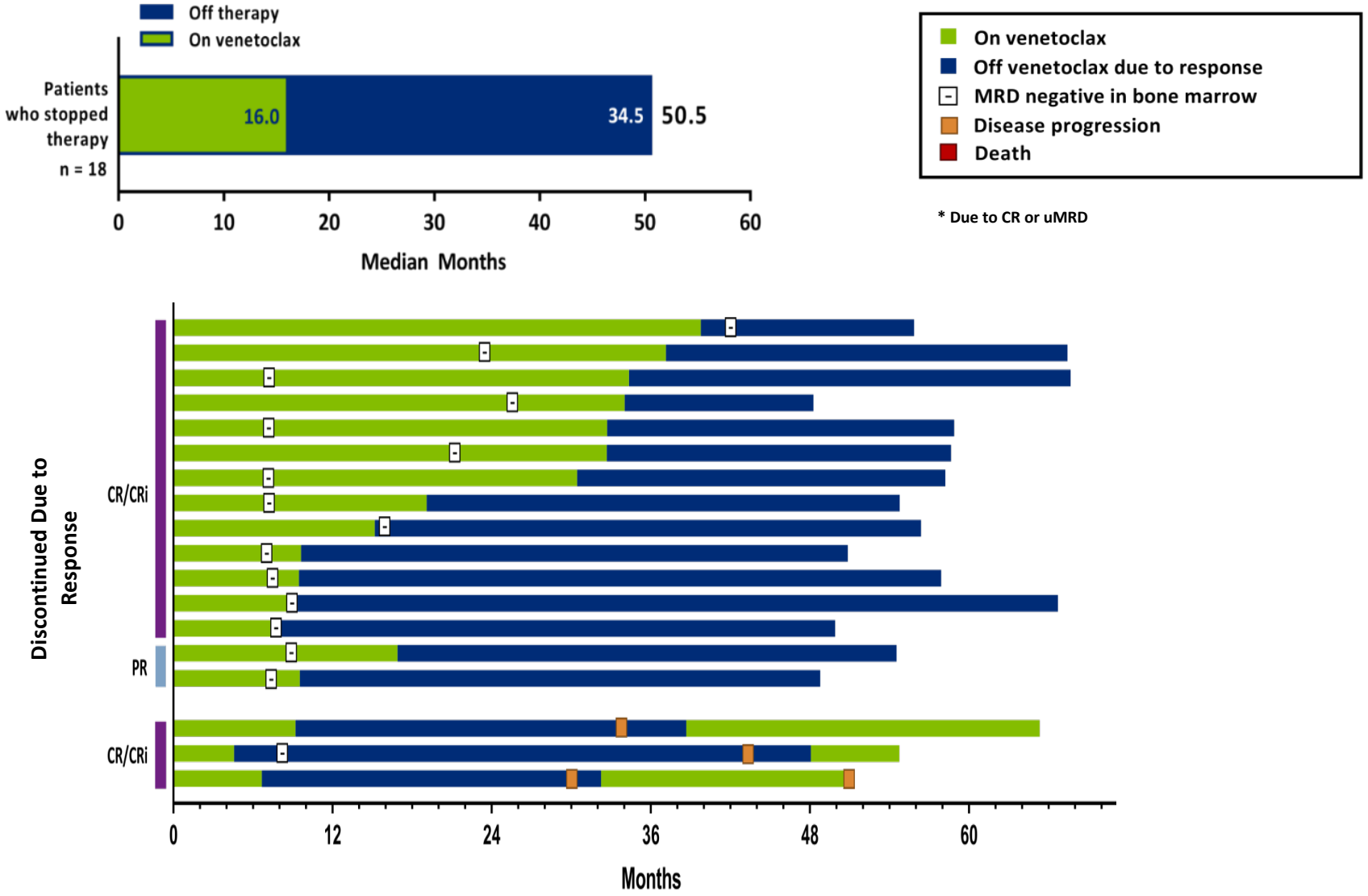


Seymour et al., 2017; Brander et al., 2018

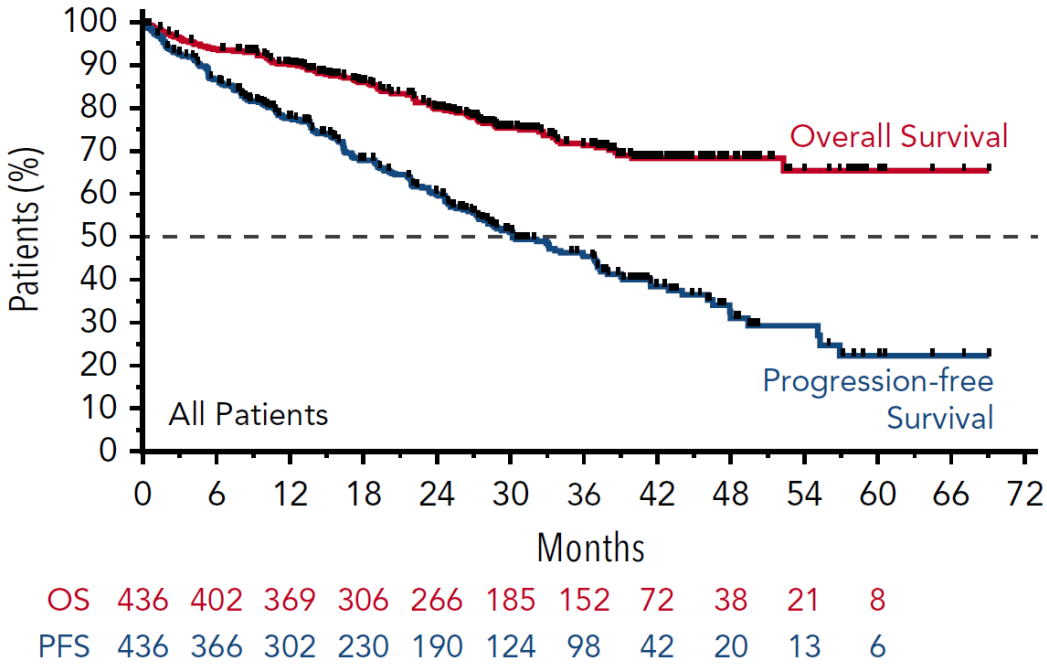
Efficacy of venetoclax in relapsed CLL is influenced by disease and response variables

436 R/R pts

- M12-175, first-in-human dose escalation study
- M13-365, phase 1b combination with rituximab study
- M13-982, phase 2 del(17p) study
- M14-032, phase 2 prior BCRi study

Median prior therapies 3 (1-15)

Prior BCRi:	***34%***
IgHV unmutated:	***76%***
del (17p) &/or TP53m:	***71%***



Roberts S et al., Blood 2019

Efficacy of venetoclax in relapsed CLL is influenced by disease and response variables

Multivariate Predictors of Response and DoR

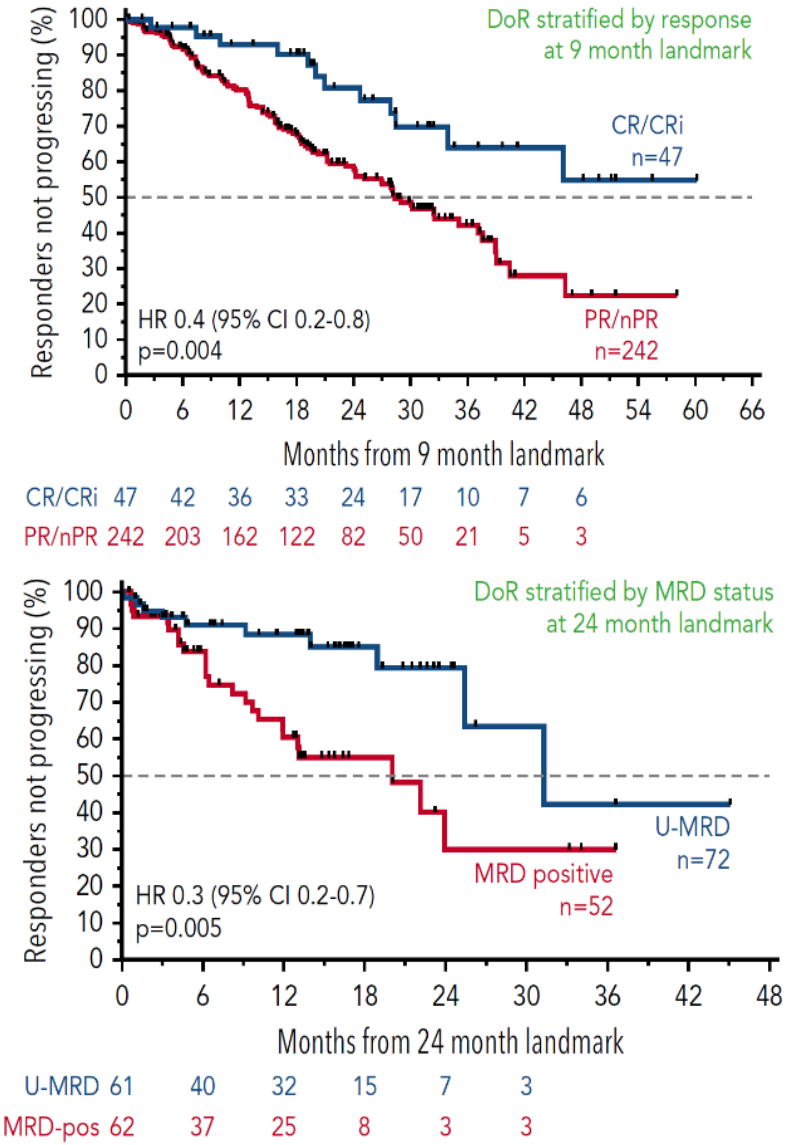
436 R/R pts

Median prior therapies 3 (1-15)

Prior BCRi:	***34%***
IgHv unmutated:	***76%***
del17p &/or TP53m:	***71%***

- **Node size (5/10 cm)**
- **F refractory**
- **BCR refractory**
- **TP53 m/del17p**
- **NOTCH-1 mut**

✓Quality of response
✓MRD



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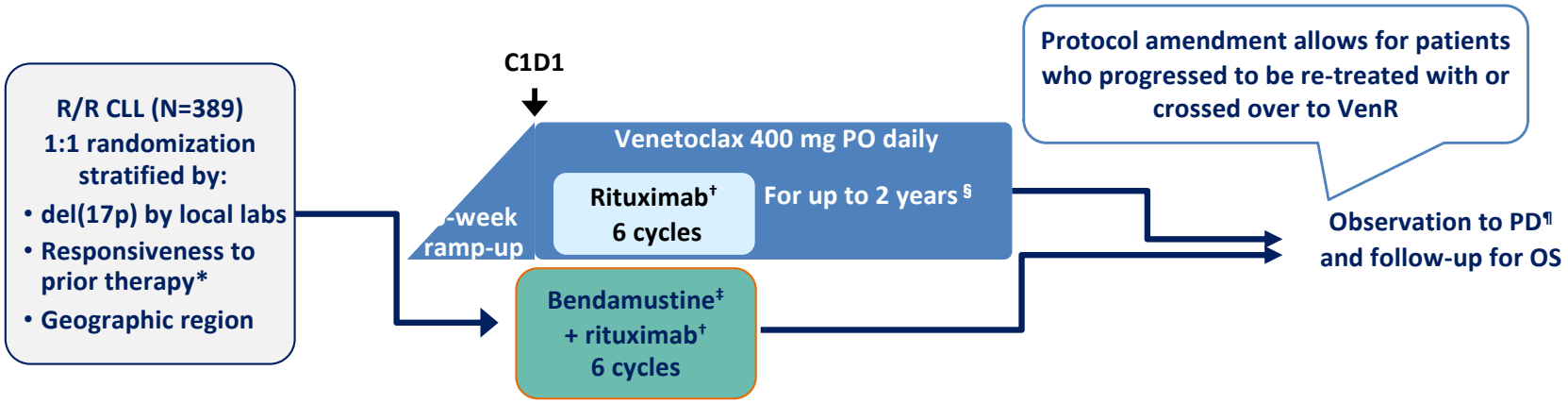
- **F refractory**
- **BCR refractory**
- **TP53 m/del17p**
- **NOTCH-1 mut**
- **Quality of response**
- **MRD**

Multiple regression analyses

- **addition of rituximab: higher CR rate more than 2-fold compared with venetoclax monotherapy**
- **no statistically significant correlation with duration of response was observed with current follow-up**

Roberts S et al., Blood 2019

MURANO:
Venetoclax-Rituximab vs Bendamustine-Rituximab



Primary Analysis[1]
Cut-off: May 8, 2017

23.8-month median follow-up, with all BR patients and 146/194 VenR patients off treatment

68/194 patients completed 2-year VenR regimen without PD (n=12 had ≥3 months' follow-up)

36-Month Analysis[2]
Cut-off: May 8, 2018

36-month median follow-up, with all patients off treatment

130/194 patients completed 2-year VenR regimen without PD (9.9 months' median follow-up)

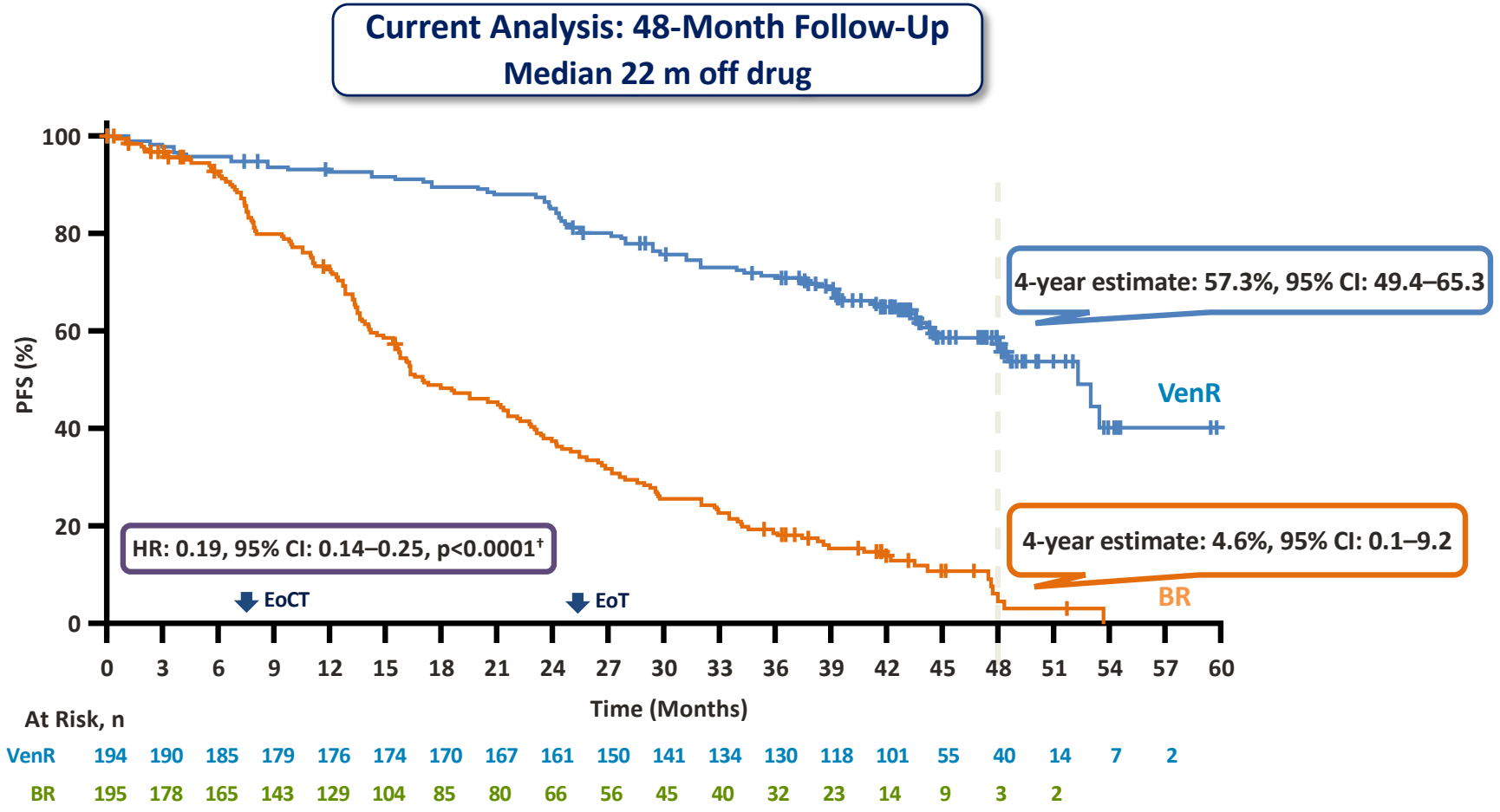
48-Month Analysis[3]
Cut-off: May 8, 2019

48-month median follow-up, with all patients off treatment

130/194 patients completed 2-year VenR regimen without PD (22 months' median follow-up)

Seymour et al., 2017-2019

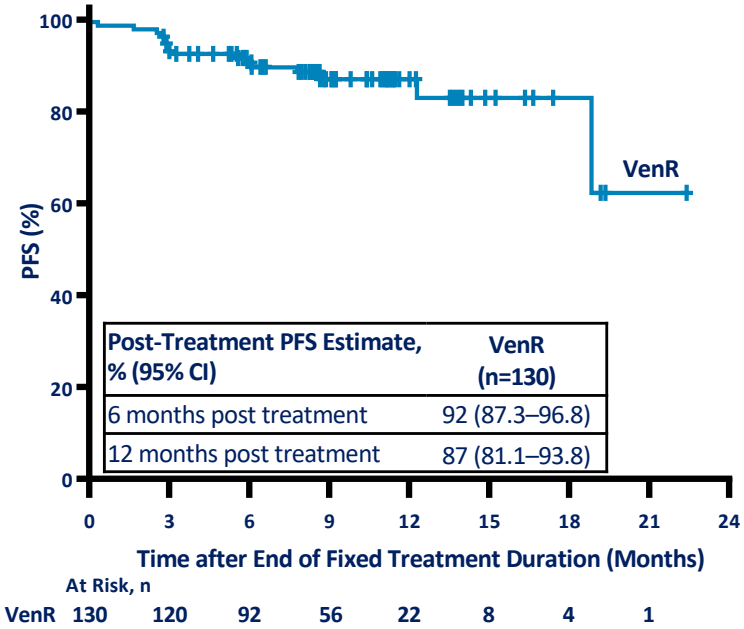
MURANO:Venetoclax Rituximab vs Bendamustine Rituximab PFS benefit maintained at 48 m



Seymour et al., 2017-2019

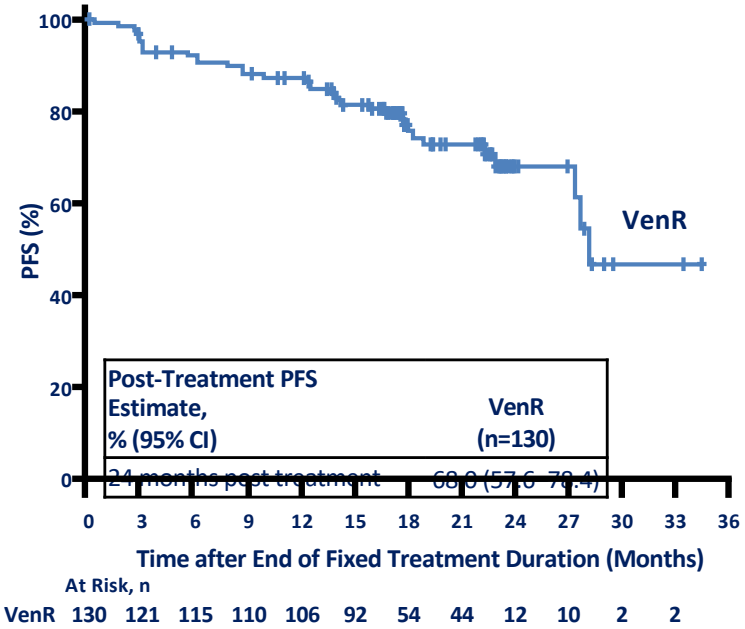
MURANO: PFS Sustained in Most Patients 22 Months after Completion of the 2-Year Fixed-Treatment-Duration Regimen

36-Month Analysis (May 8, 2018):[1]
PFS after Median Follow-Up of 9.9 Months off Venetoclax (Range 1.4–22.5)



Post-Treatment PFS Estimate, % (95% CI)	VenR (n=130)
6 months post treatment	92 (87.3–96.8)
12 months post treatment	87 (81.1–93.8)

48-Month Analysis (May 8, 2019):[2]
PFS after Median Follow-Up of 22 Months off Venetoclax (Range 1–35)



Post-Treatment PFS Estimate, % (95% CI)	VenR (n=130)
24 months post treatment	68.0 (57.6–78.4)

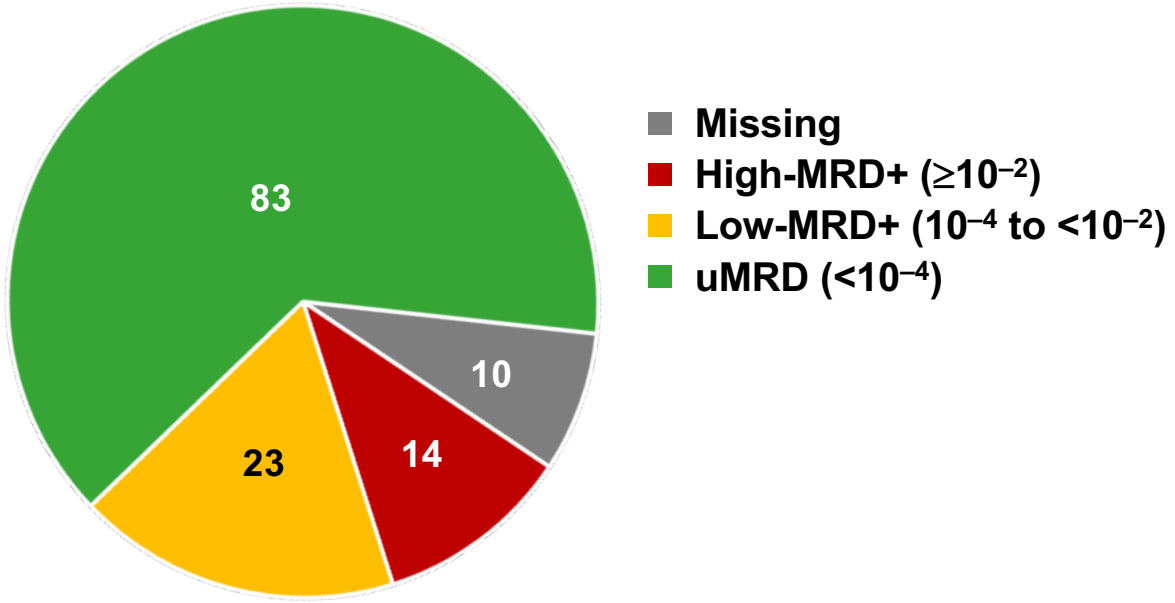
After a median follow-up of 22 months, only 27% (35/130) of patients progressed after completing the 2-year fixed-treatment-duration venetoclax regimen

Seymour et al., 2019

MURANO

Most patients did not progress after cessation of Ven monotherapy at EOT

MRD status at EOT (Month 24; n=130):



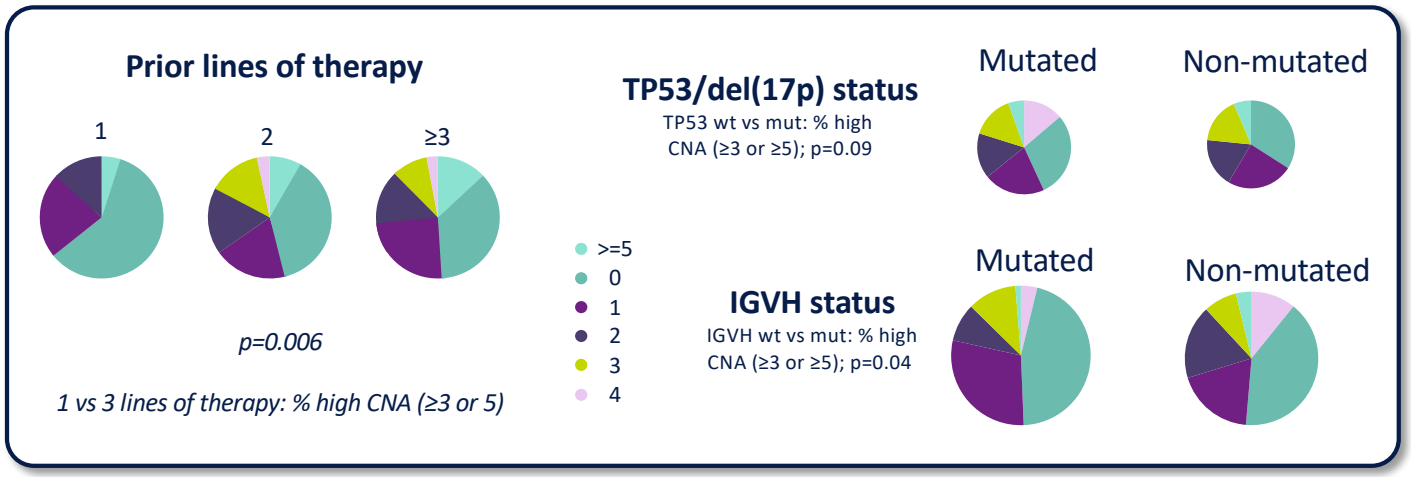
Status off-therapy (median follow up: 9.9 mo)	uMRD (n=83)	Low-MRD+ (n=23)	High-MRD+ (n=14)	Missing (n=10)
Progression-free, n (%)	81 (97.6%)	20 (87.0%)	3 (21.4%)	10 (100%)
PD, n (%)	2 (2.4%)	3 (13.0%)	11 (78.6%)	0 (0%)

Data cut-off date: May 8, 2018

Seymour J et. Al Blood 2018:132: abstract 164

MURANO Genomic Analysis
CK

Association of CK with patient characteristics



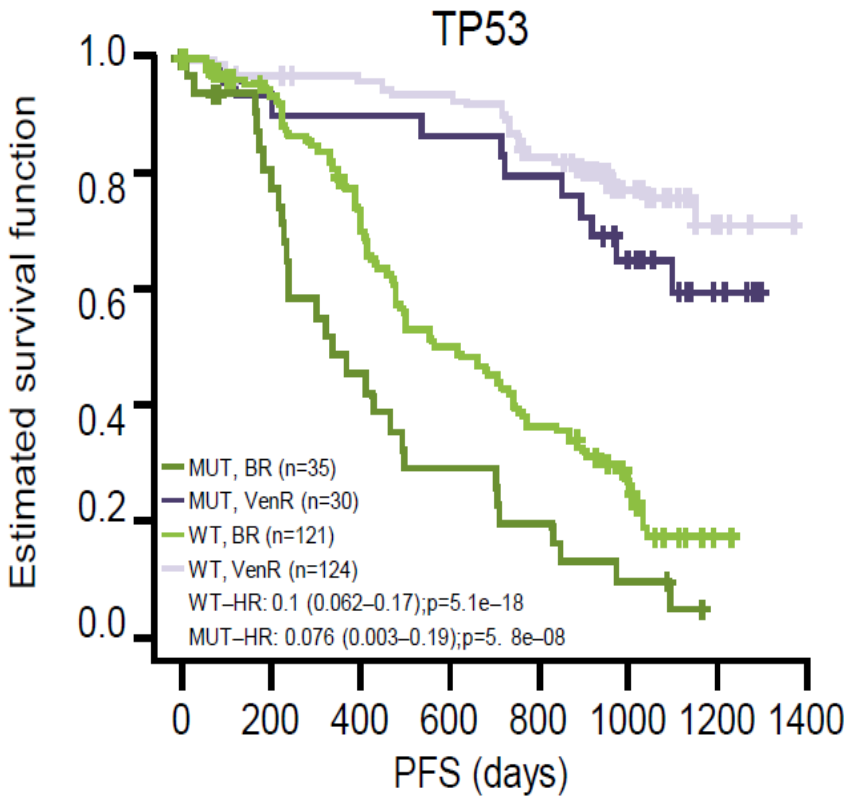
- CK and non-CK were identified in 48/142 (33.8%) and 94/142 (66.2%) of VEN+R patients and 46/147 (31.3%) and 101/147 (68.7%) of B+R patients, respectively.
- TP53mut/del(17p) was detected in 19/45 (42.2%) and 23/41 (56.0%) CK patients in the VEN+R and B+R arms, respectively. Most CK patients were high or very high CLL-IPI risk (63.8% and 78.3%, respectively).

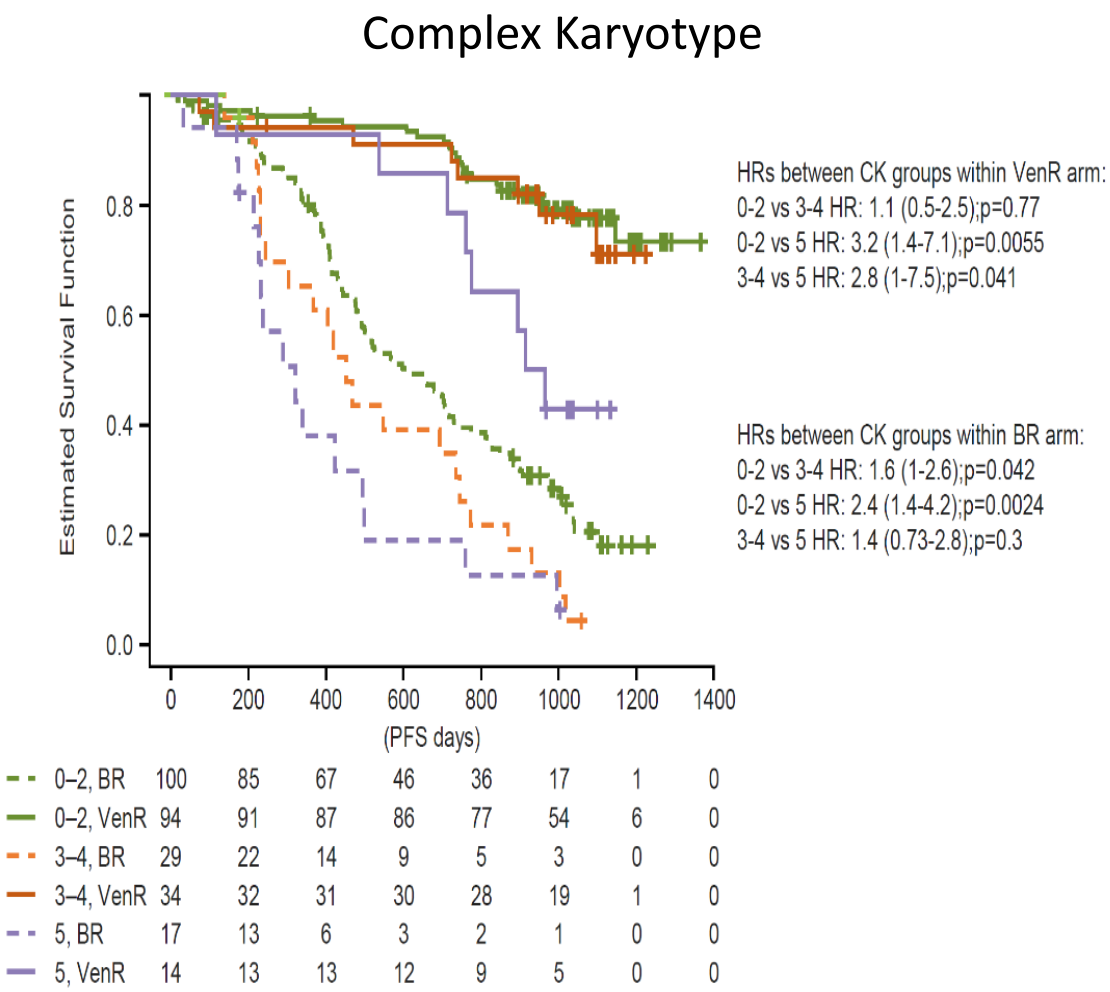
Increased numbers of CNAs were observed in patients with higher prior lines of treatment and with more aggressive CLL (TP53/del(17p) or U-IGVH).

B=Bendamustine. CK=Complex Karyotype. CLL=Chronic Lymphocytic Leukemia. CNA=Copy Number Alterations. mut=Mutant. R=Rituximab. U=Unmutated. VEN=Venetoclax. wt=Wildtype.

Wu J, et al. Poster #1123. EHA 2019

MURANO: Venetoclax Rituximab vs Bendamustine Rituximab PFS benefit maintained at 48 m





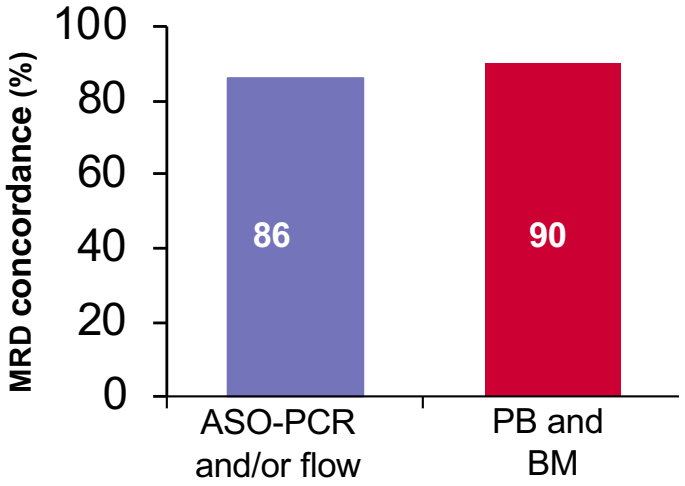
Seymour et al., 2019

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



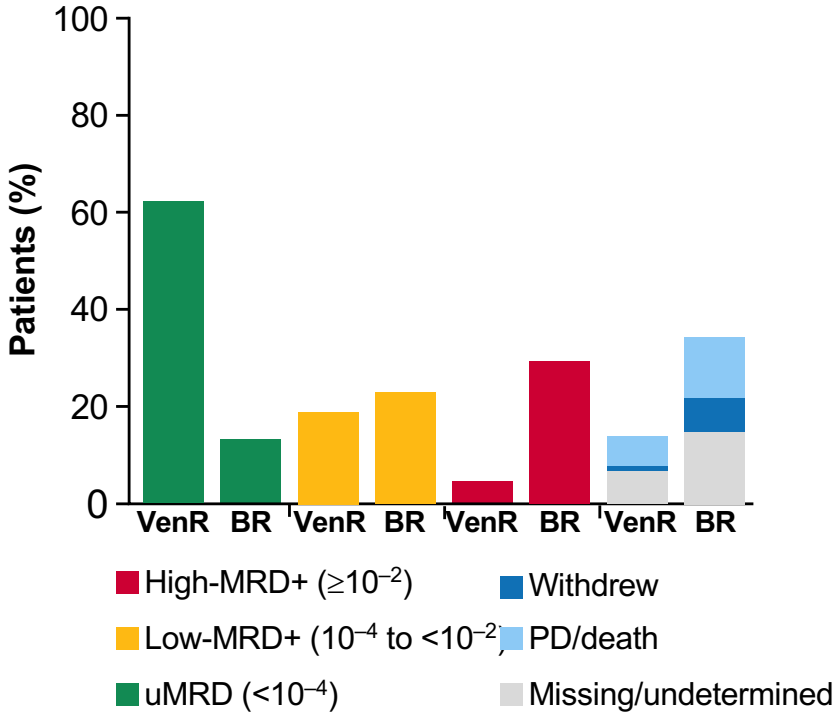
MRD status according to		ASO-PCR	
		uMRD	MRD+
Flow cytometry	uMRD	755	202
	MRD+	49	853

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

Difference in uMRD rates: 49.0%



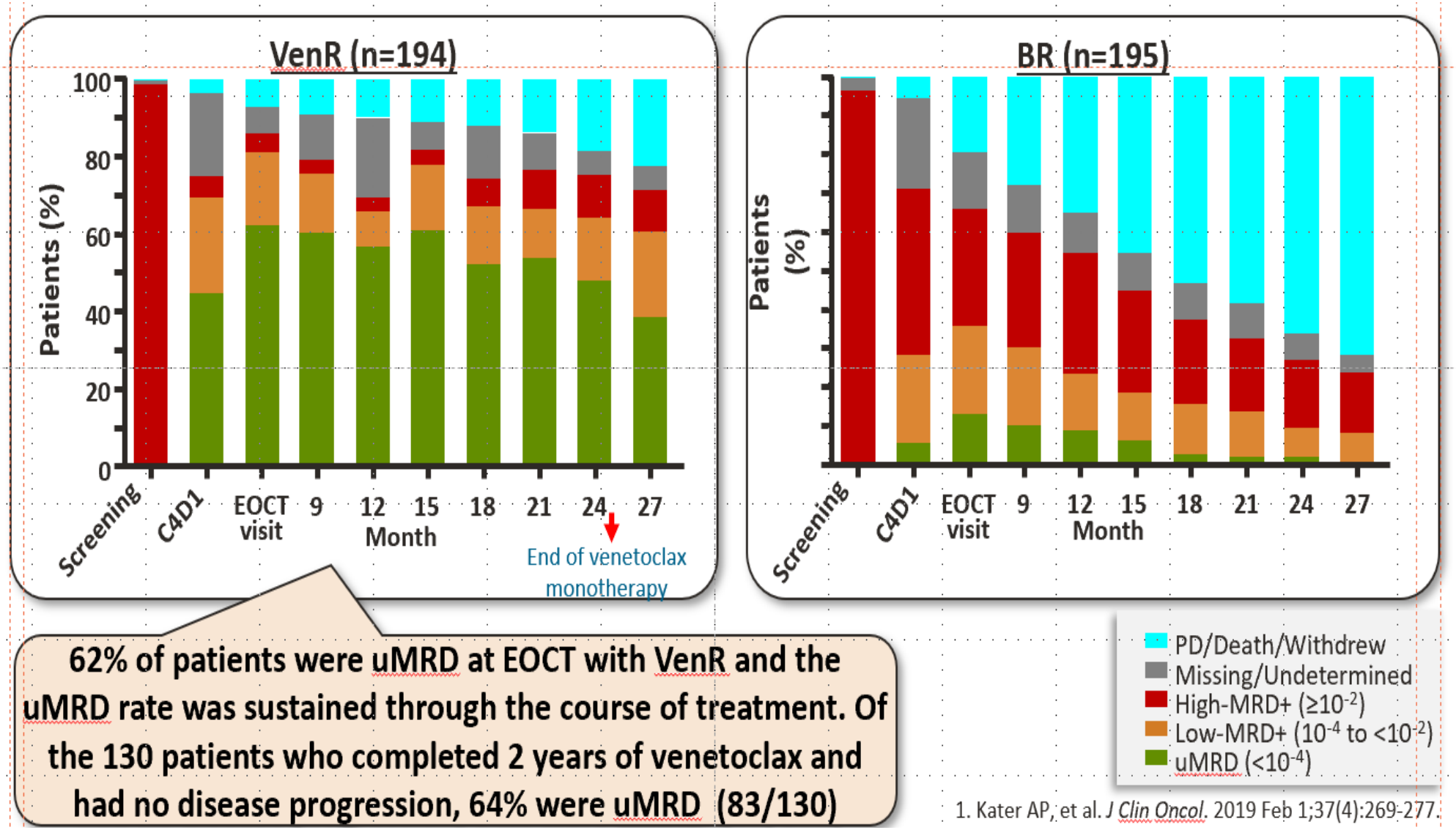
Consistently high uMRD rates observed in all VenR subgroups, including pts with high-risk cytogenetics and molecular factors

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)	

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

Seymour J et. Al Blood 2018:132: abstract 164

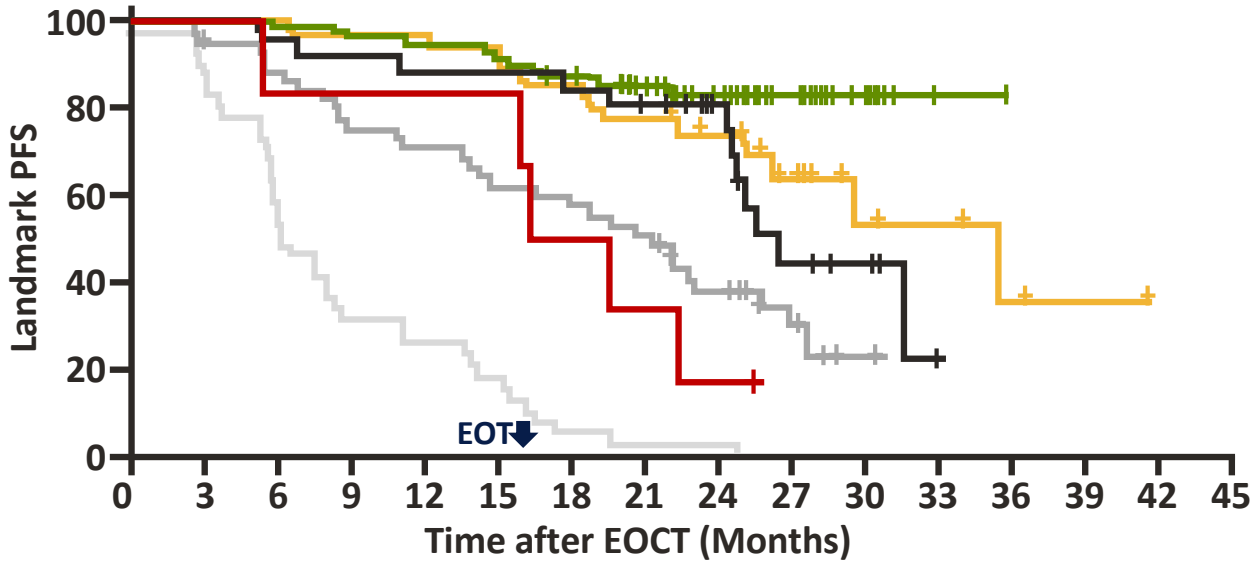
PB uMRD Rates Were Maintained during the Venetoclax Monotherapy Phase

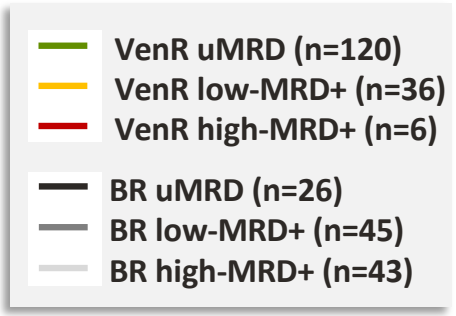


62% of patients were uMRD at EOCT with VenR and the uMRD rate was sustained through the course of treatment. Of the 130 patients who completed 2 years of venetoclax and had no disease progression, 64% were uMRD (83/130)

1. Kater AP, et al. *J Clin Oncol*. 2019 Feb 1;37(4):269-277.

Landmark PFS Analysis According to PB MRD Status at EOCT Response Visit (ITT Population)





No. 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				

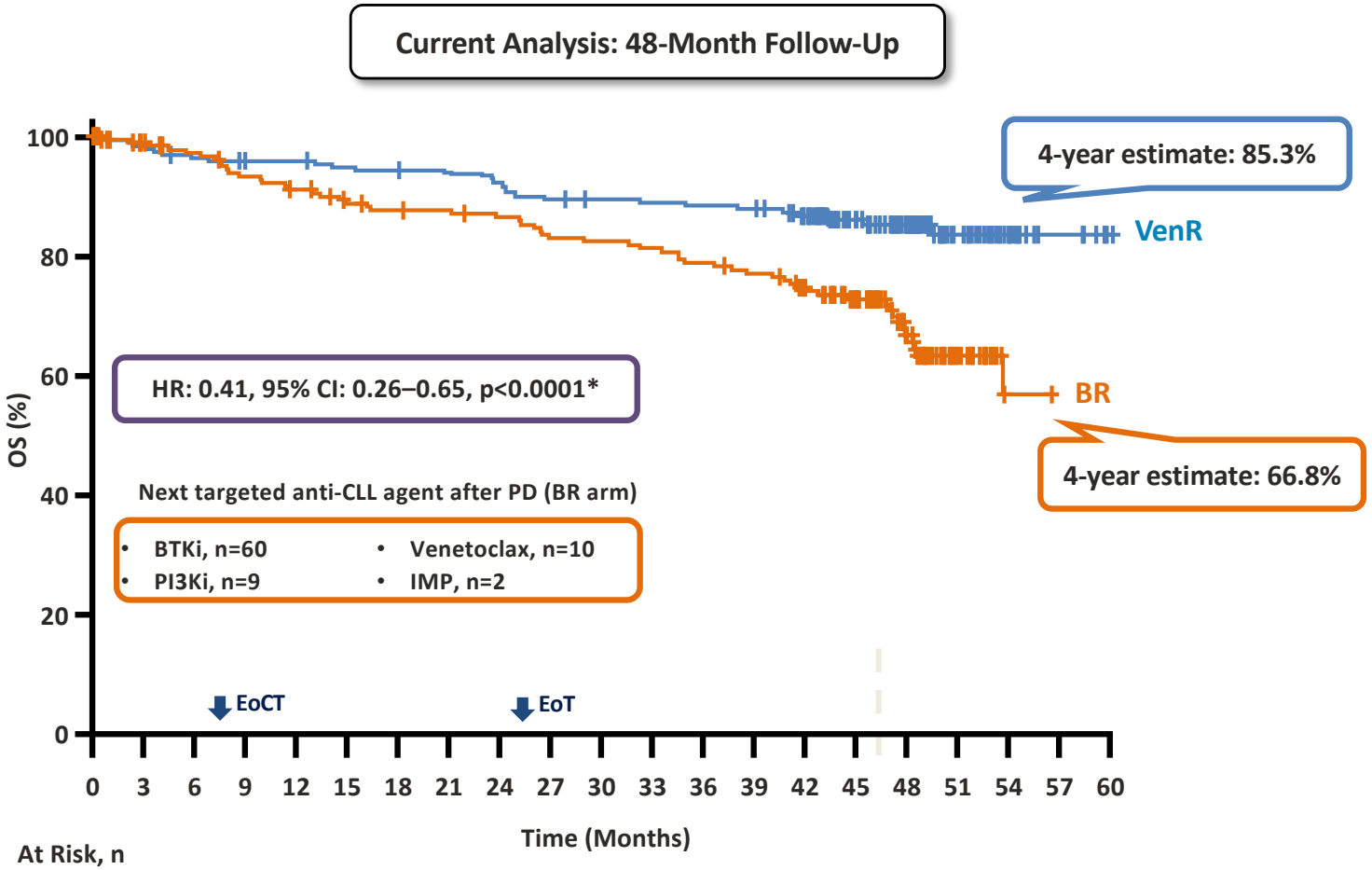
HR (95% CI)	VenR	BR
uMRD vs low-MRD+	0.48 (0.24–0.98)	0.44 (0.22–0.89)
uMRD vs high-MRD+	0.15 (0.06–0.40)	0.08 (0.03–0.18)

In both treatment arms, patients with uMRD had longer PFS than those with detectable MRD

The analysis subset includes patients that have not progressed, died, or withdrawn from study before EOCT response visit.
MRD PB status derived from combining ASO-PCR and flow cytometry results.

Kater AP, et al. *J Clin Oncol*. 2019 Feb 1;37(4):269-277.

MURANO: Improved OS with VenR vs BR Continues to Be Maintained at 48 Months



The risk of death was decreased by 59% with VenR vs BR, despite 81 (79%) patients in the BR arm going on to receive a novel targeted CLL treatment

Seymour et al., 2019

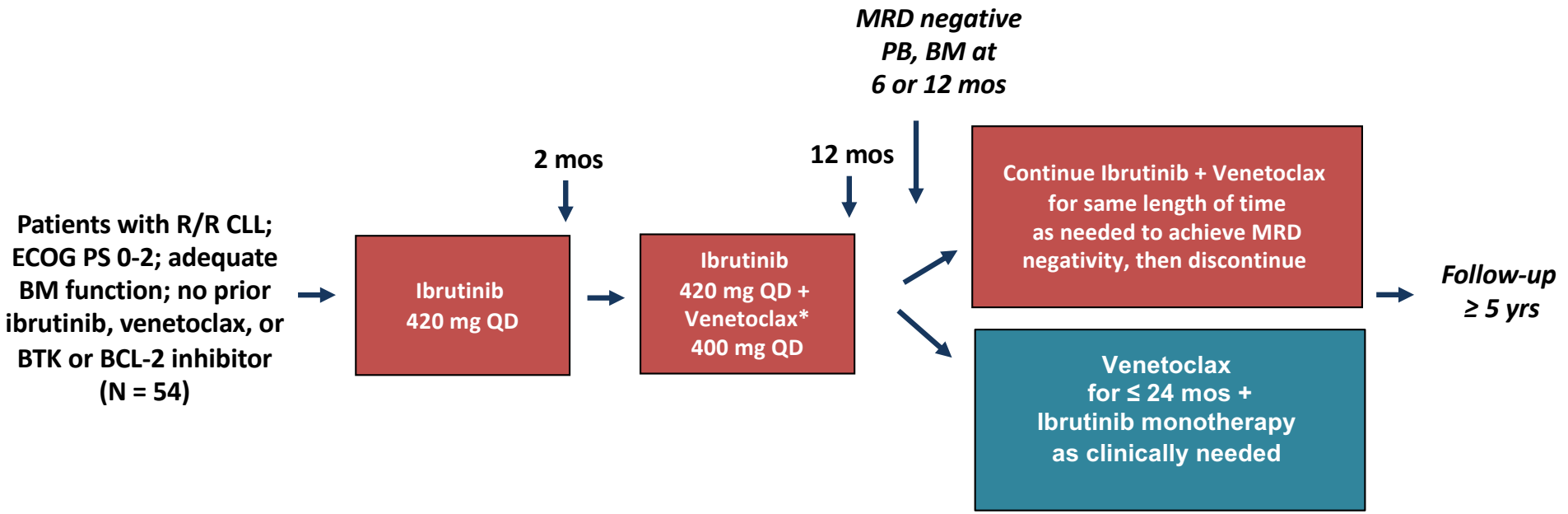
MURANO: Safety
Grade ≥3 AEs by Treatment Period

Patients, n (%)	B + R (N=188)	V + R (N=194)		
Protocol planned treatment duration	6 months	24 months	6 months	18 months
		Overall	Combination period (n=194)	Monotherapy period (n=171)
Total number of patients with ≥1 AE	135 (71.8)	161 (83.0)	146 (75.3)	53 (31.0)
Neutropenia	73 (38.8)	112 (57.7)	105 (54.1)	19 (11.1)
Anemia	26 (13.8)	21 (10.8)	16 (8.2)	5 (2.9)
Thrombocytopenia	19 (10.1)	12 (6.2)	9 (4.6)	4 (2.3)
Febrile neutropenia	18 (9.6)	7 (3.6)	7 (3.6)	0
Pneumonia	15 (8.0)	12 (6.2)	9 (4.6)	3 (1.8)
Infusion related reaction	10 (5.3)	3 (1.5)	3 (1.5)	0
Tumor lysis syndrome	2 (1.1)	6 (3.1)	6 (3.1)	0
Hyperglycemia	0	4 (2.1)	4 (2.1)	0
Hypogammaglobulinemia	0	4 (2.1)	3 (1.5)	1 (0.6)
Neoplasm (benign/malignant)	10 (5.3)	12 (6.2)	6 (3.1)	6 (3.5)

- Overall, fewer grade ≥3 events, including grade 3–5 neutropenia and grade 3–5 pneumonia, were observed in the monotherapy period
- Infection rate (all grades): 61.7% with BR, 74.7% with VR

Seymour et al., 2018, 2019

CLARITY: Study Design



Primary endpoint: MRD eradication in BM after 12 mos of IBR + VEN

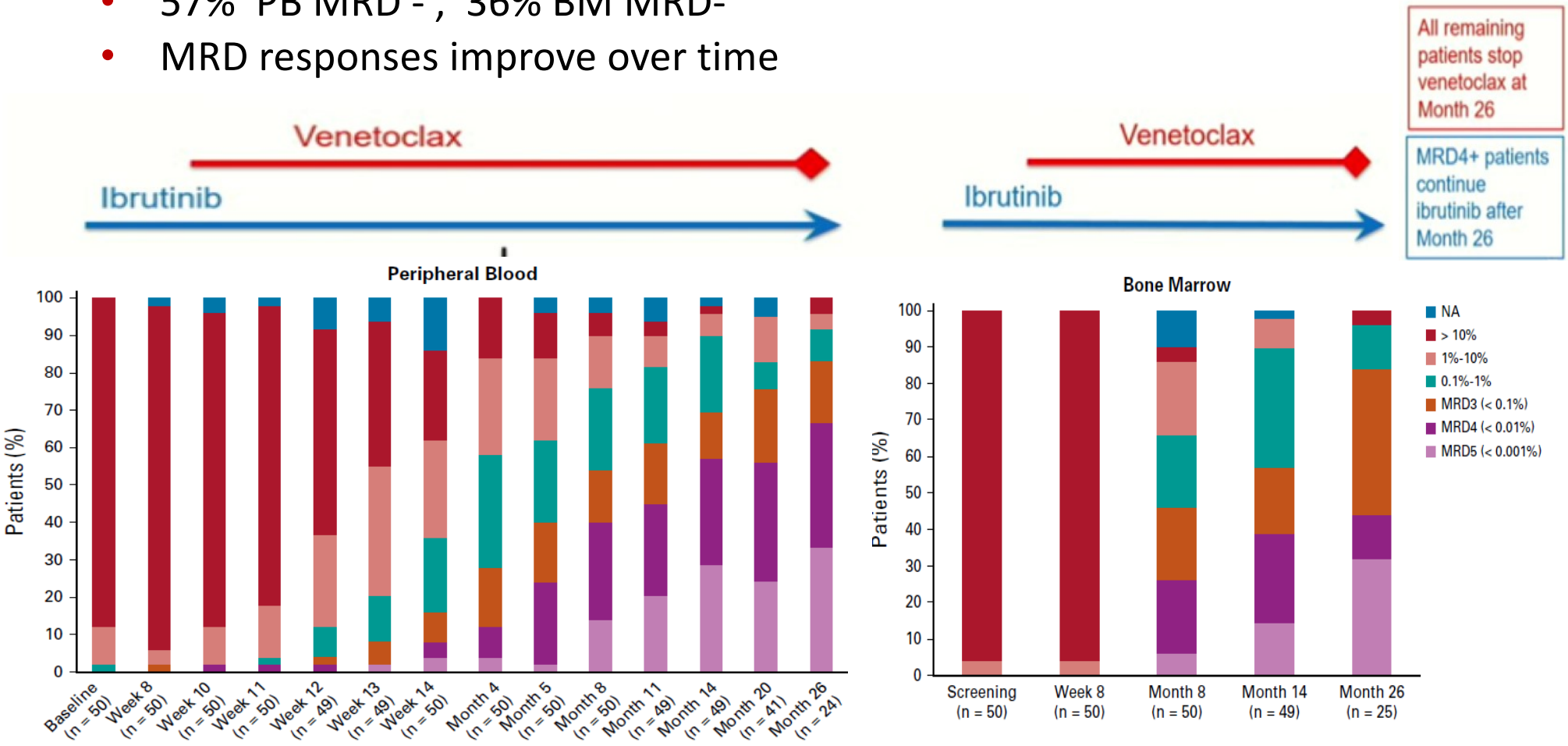
Key secondary endpoints: MRD eradication in BM after 6, 24 mos of IBR + VEN, response, PFS, OS, safety

***VEN escalated weekly up to final dose of 400 mg/day: 10 mg (first 3 patients only) → 20 mg → 50 mg → 100 mg → 200 mg→ 400 mg. Patients evaluated for MRD in PB every 3 mos, in BM (along with CT) at BL and at 6, 12, 24 mos of IBR + VEN. MRD negativity = < 0.01% CLL cells. IBR + VEN stopped at 14 mos if 8-mo BM MRD negative; at 26 mos if 14-mo BM MRD negative. VEN stopped, IBR continued at 26 mos if BM MRD positive. Datalock: 12/1/17.**

Hillmen P, et al. ASH 2017. Abstract 428.

Clarity Study of Ibrutinib + Venetoclax
PB and BM MRD

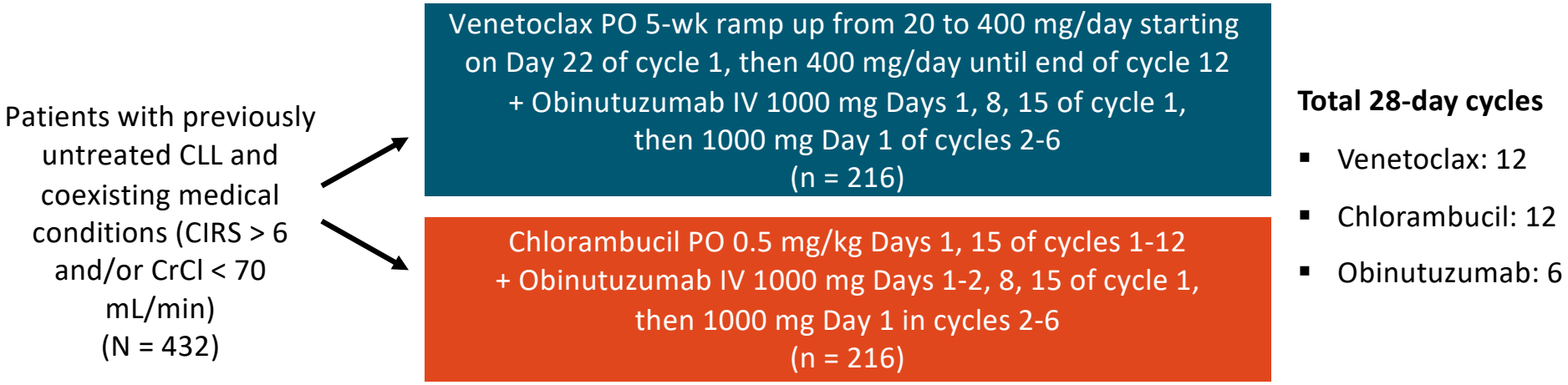
- N= 53; CR+Cri 51%;
- Analysis of MRD after 12 months of combinationn therapy :
- 57% PB MRD - , 36% BM MRD-
- MRD responses improve over time



Hillmen P, et al. JCO 2019

CLL14: Study Design

- Open-label, multicenter, randomized phase III trial



- Primary endpoint: investigator-assessed PFS
- Secondary endpoints: IRC-assessed PFS, ORR, MRD negativity, OS, safety

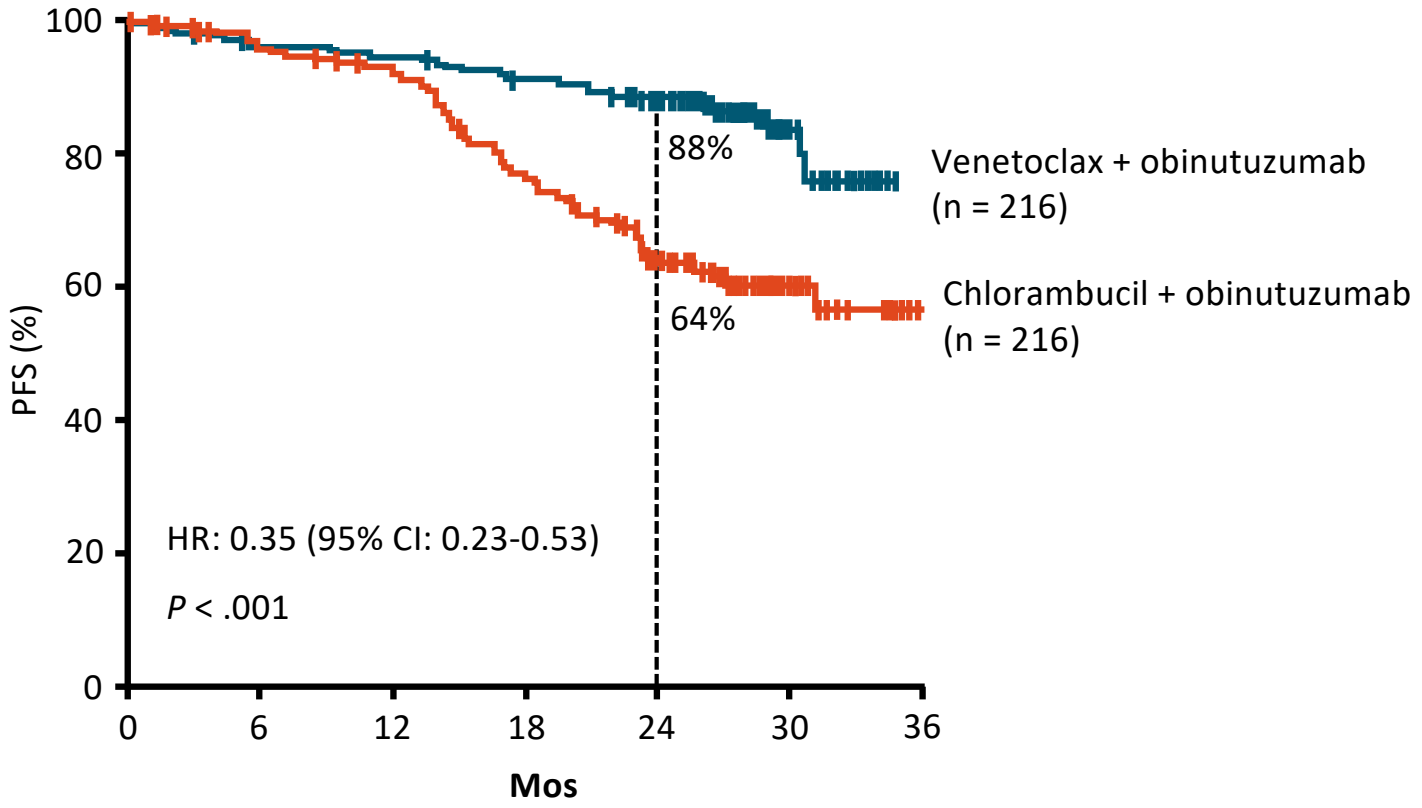
Fischer. ASCO 2019. Abstract 7502. Fischer. NEJM. 2019;380:2225.

CLL14: Baseline Characteristics

Characteristic	Venetoclax + Obinutuzumab (n = 216)	Chlorambucil +Obinutuzumab (n = 216)
Median age, yrs	72	72
Binet stage A/B/C, %	21/36/43	20/37/43
Median total CIRS score	9	8
Median CrCl, mL/min	65.2	67.5
TLS risk category low/int/high, %	13/64/22	12/68/20
IGVH unmutated, %	61	59
TP53 deleted and/or mutated, %	12	12
Cytogenetics, %		
▪ del(17p)	9	7
▪ del(11q)	18	20
▪ Trisomy 12	18	21
▪ No abnormalities	25	22
▪ del(13q) alone	31	31

Fischer. ASCO 2019. Abstr 7502. Fischer. NEJM. 2019;380:2225.

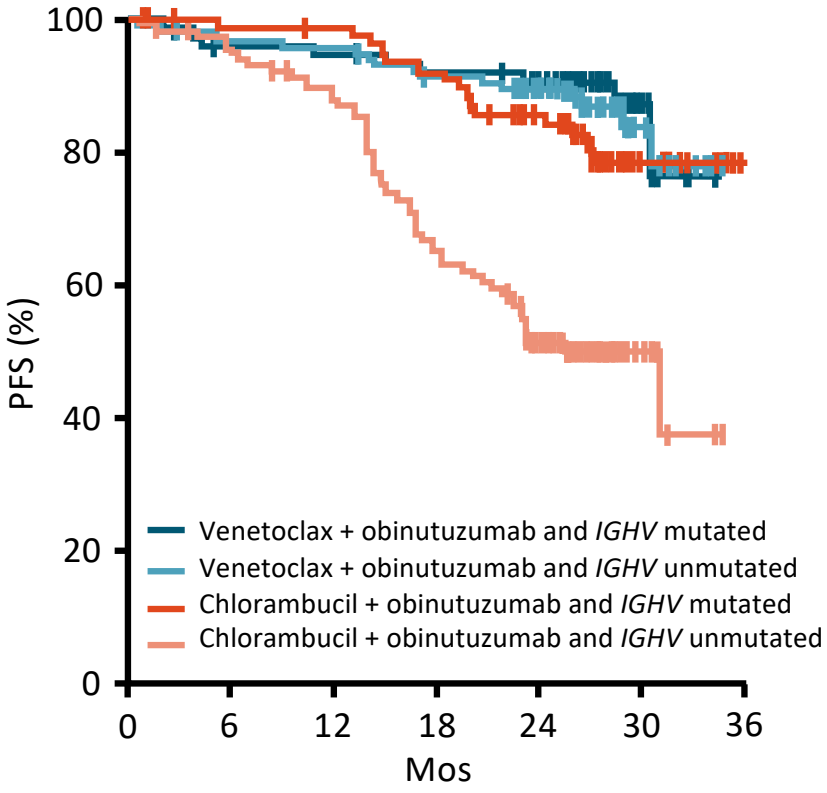
CLL14: Investigator-Assessed PFS (Primary Endpoint)



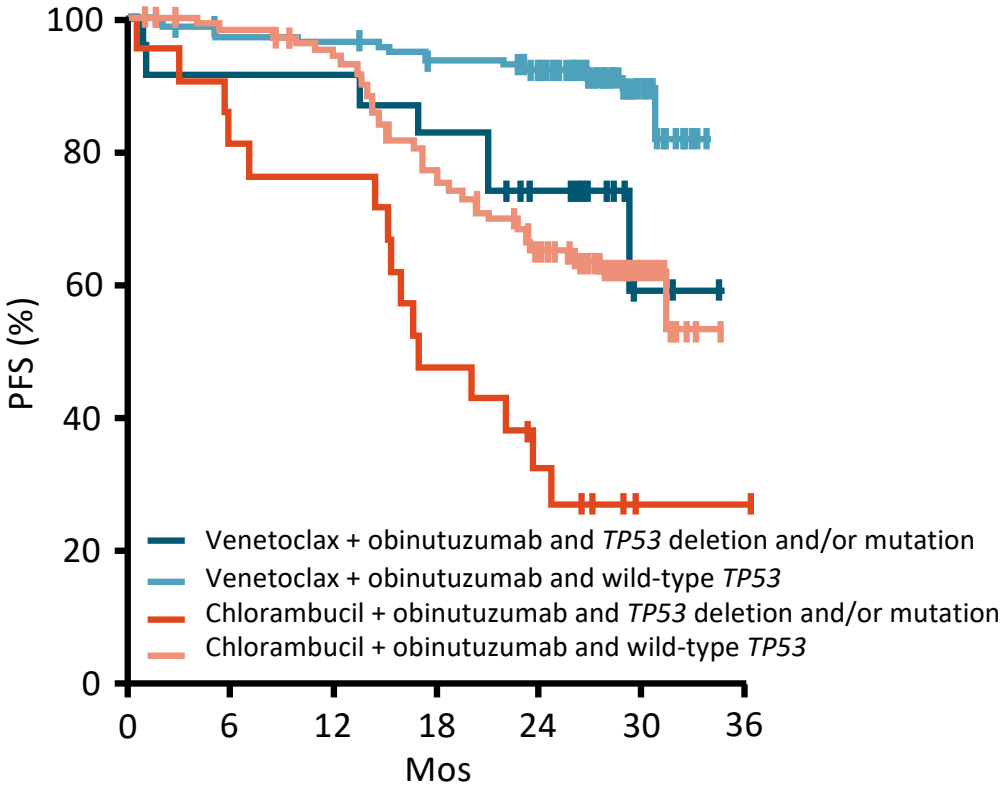
Fischer. ASCO 2019. Abstr 7502. Fischer. NEJM. 2019;380:2225.

CLL14: PFS by *IGVH* Mutation and *TP53* Status

PFS by *IGHV* Mutation

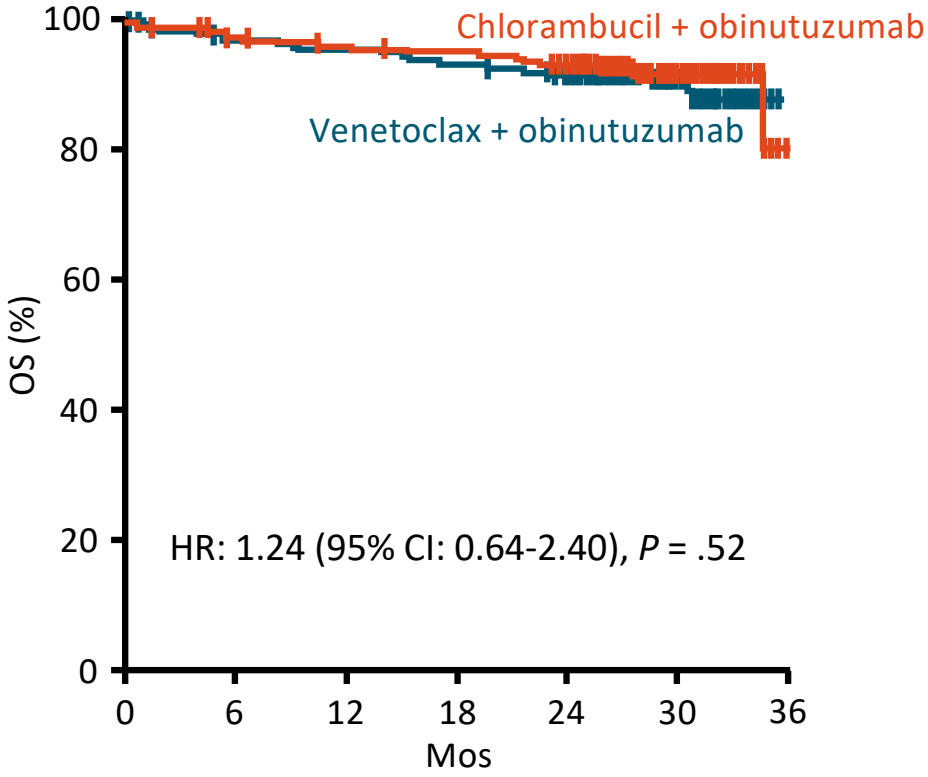


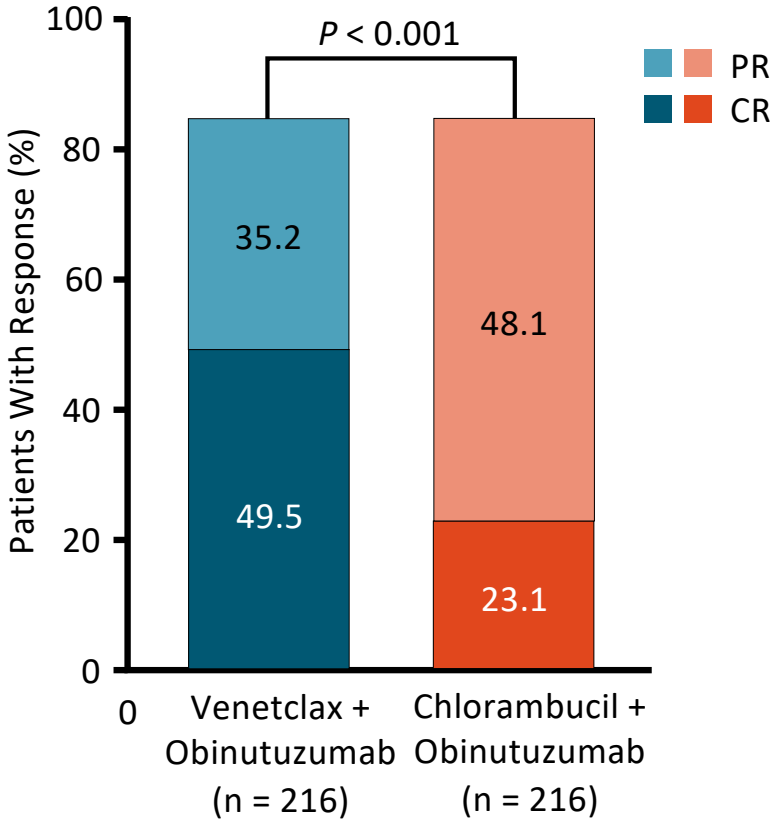
PFS by *TP53* Status



Fischer. ASCO 2019. Abstract 7502. Fischer. NEJM. 2019;380:2225.

CLL14: OS and Response

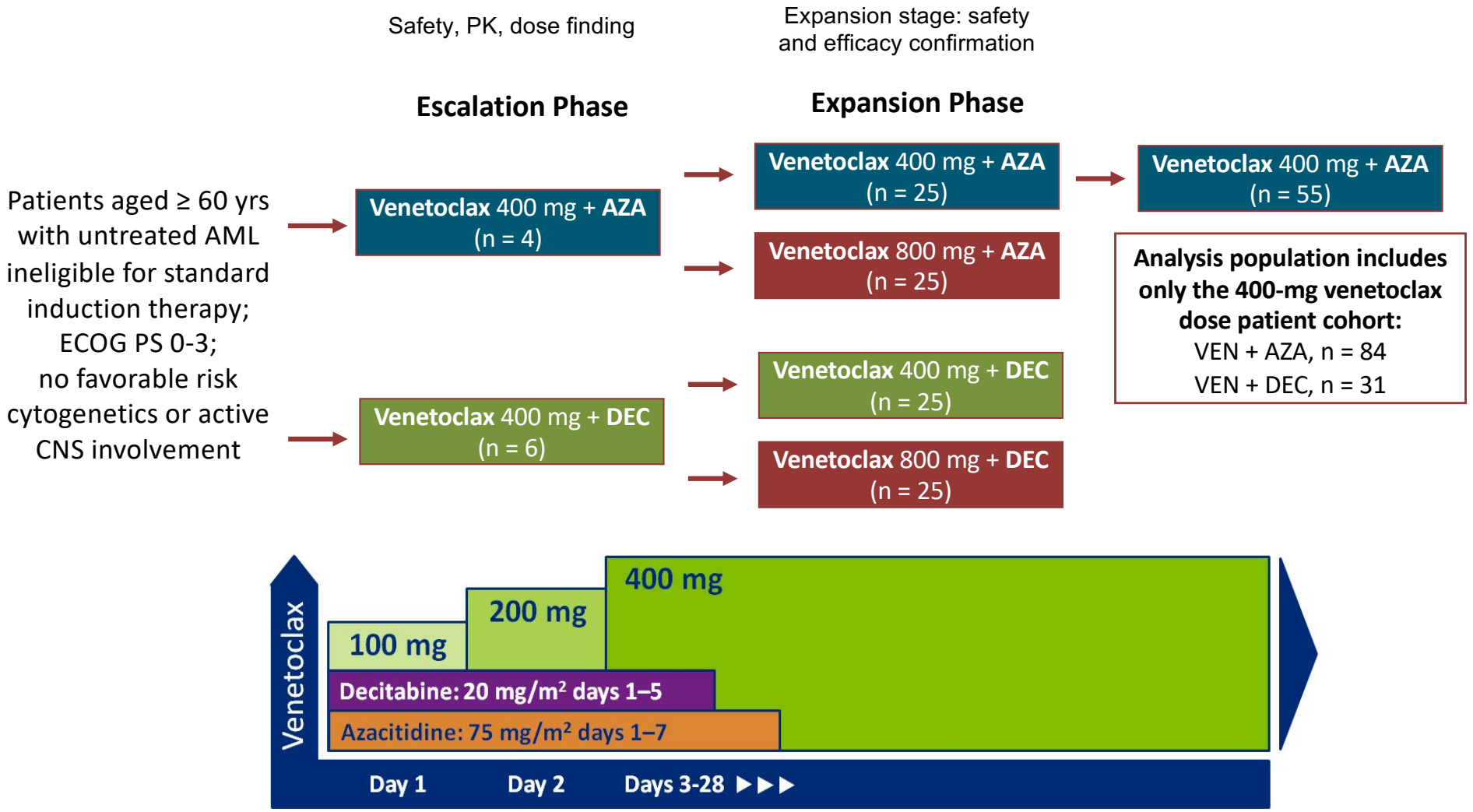




Fischer. ASCO 2019. Abstr 7502. Fischer. NEJM. 2019;380:2225.

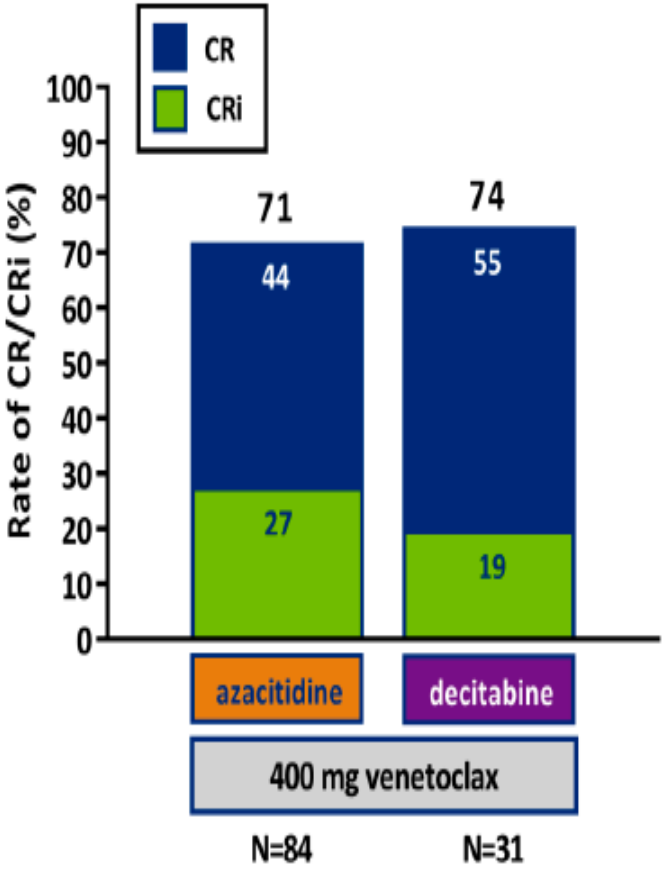
Venetoclax + HMA in Elderly Patients With Untreated AML: Phase Ib Study Design

Multicenter, open-label phase Ib dose-escalation and dose-expansion study



Pollyea. ASH 2018. Abstr 285.

Response Rates of CR/Cri by combination



	Ven + Aza	Ven + Dec
Time to CR		
median (range)	1.2 (0.7–5.5)	1.9 (0.9–4.6)
No. of treatment cycles for these patients		
median (range)	6.0 (1–32)	6.0 (1–29)

Pollyea DA, et al. *Blood*. 2018;132: Abstract 285.

Venetoclax + HMA in Older AML Patients: Response

Outcome	Venetoclax 400 mg + AZA (n = 84)	Venetoclax 400 mg + DEC (n = 31)
CR	44	55
CRi	27	19
Median time to CR, mos (range)	1.2 (0.7-5.5)	1.9 (0.9-4.6)
Median no. treatment cycles in patients with CR, n (range)	6 (1-32)	6 (1-29)
Median DoR after CR/CRi, mos (95% CI) ▪ 12-mo EFS in patients with CR/CRi, % (95% CI)	21.2 (14.4-30.2) 69 (52-80)	15.0 (5.0-22.5) 57 (32-76)
12-mo overall EFS, % (95% CI) ▪ 12-mo EFS in patients **with CR/CRi,** % (95% CI) ▪ 12-mo EFS in patients **with no CR/CRi**, % (95% CI)	57 (46-67) 72 (58-81) 19 (6-37)	61 (42-76) 74 (51-87) 25 (4-56)
Median overall OS, mos (95% CI) ▪ Median OS in patients **with CR/CRi**, mos (95% CI) ▪ Median OS in patients **with no CR/CRi**, mos (95% CI)	16.9 (11.3-NR) 40.3 (16.9-NR) 4.5 (2.4-8.9)	16.2 (9.1-27.8) 18.2 (12.3-42.7) 4.8 (0.7-17.0)
MRD negativity, n/n (%)	29/60 (48)	9/23 (39)

Pollyea. ASH 2018. Abstr 285.

Venetoclax + HMA in Older Patients With de Novo AML: CR/CRi by Subgroup

Patient Group, CR/CRi n/n (%) of Each Subgroup	Venetoclax 400 mg + AZA	Venetoclax 400 mg + DEC
Cytogenetic risk		
▪ Intermediate	38/50 (76)	11/16 (69)
▪ Poor	22/33 (67)	12/15 (80)
AML type		
▪ de novo	48/63 (76)	16/22 (73)
▪ Secondary	12/21 (57)	7/9 (78)
Mutations		
▪ *TP53*	13/20 (65)	6/7 (86)
▪ *IDH1/2*	18/20 (90)	5/5 (100)
▪ *FLT3*	8/11 (73)	1/3 (33)
▪ *NPM1*	11/14 (79)	3/3 (100)

Pollyea. ASH 2018. Abstr 285.

Venetoclax and LD Ara-C in AML

Study Design and Objectives

- **Design:** Phase I/II, open-label, multicenter dose escalation and expansion
- **Endpoints:** CR, CRi, Overall Survival (OS), Duration of Response (DOR), and Safety

PRIMARY OBJECTIVE

To assess the efficacy and safety of venetoclax 600 mg with LDAC in patients ≥60 years of age with untreated AML who are ineligible for standard induction chemotherapy

SECONDARY OBJECTIVE

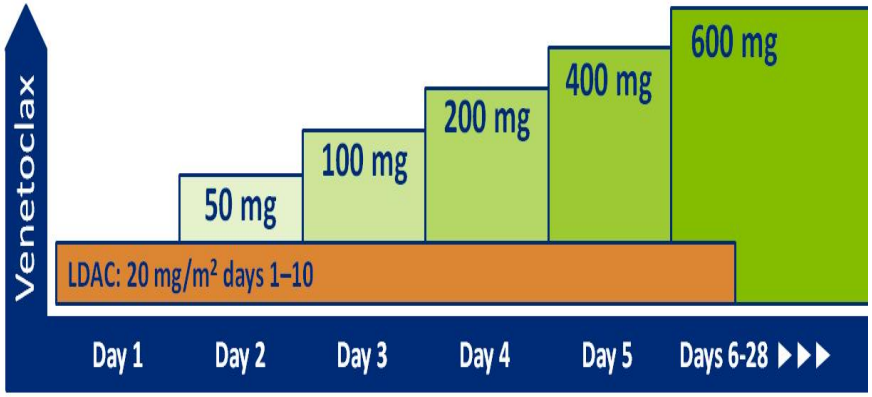
To assess CR, CRi, DOR, and OS

Data cutoffs Efficacy Nov 8, 2017 | Safety Jan 30, 2018

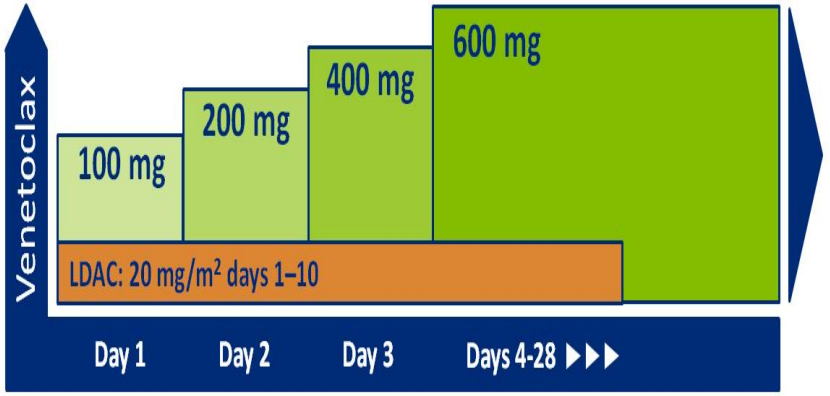
Wei AH et al ASH oral presentation 2018

Venetoclax and LD Ara-C in AML

Initial 5 days and Subsequent 4 days Rumping up



- 1 patient with laboratory TLS
- No patients with clinical TLS



- 1 patient with laboratory TLS
- No patients with clinical TLS

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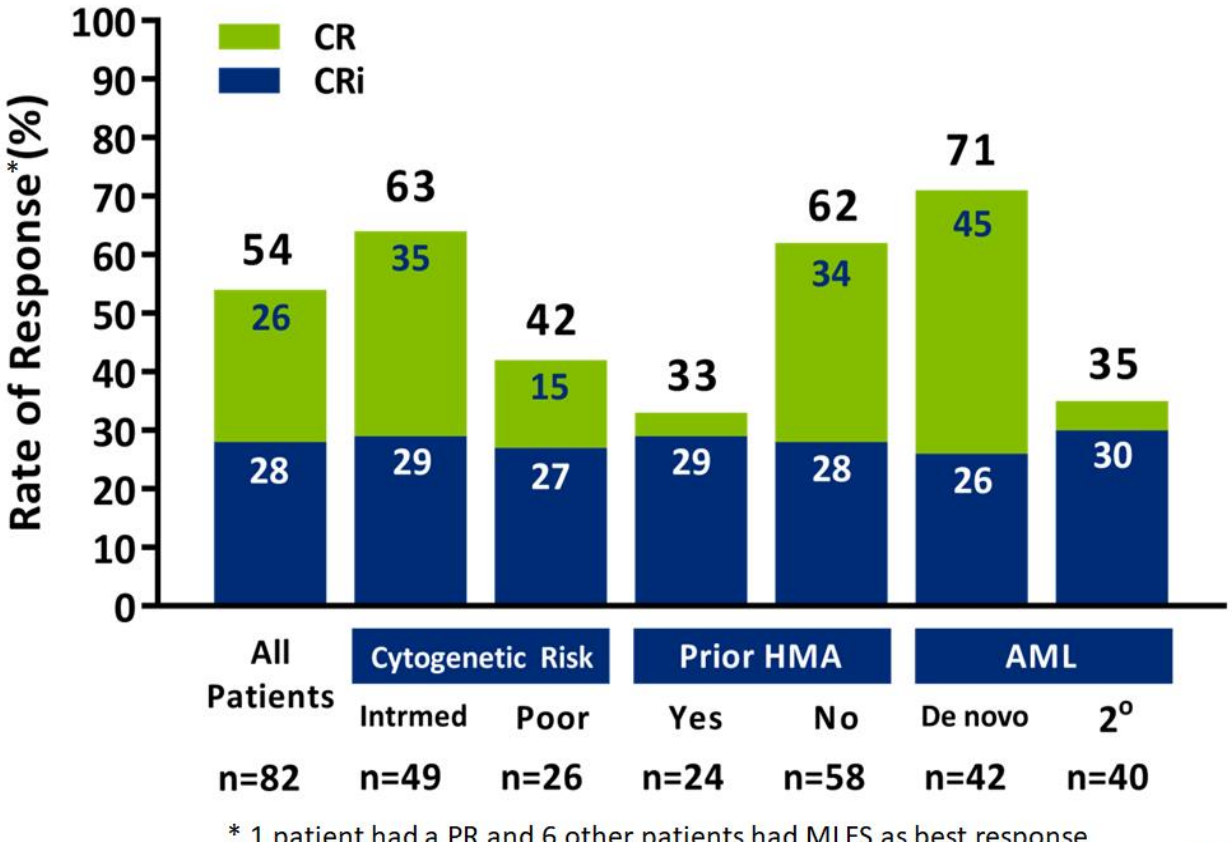
Venetoclax and LD Ara-C in AML

Response Rates by Key Patient Subgroups



Percentage of patients with CR/CI
shown at the top of each ba

For patients with CR/CRi

Median time to first response

1.4 months (range 0.8–14.9)

Median time to best response

2.8 months (range 0.8–22.4)

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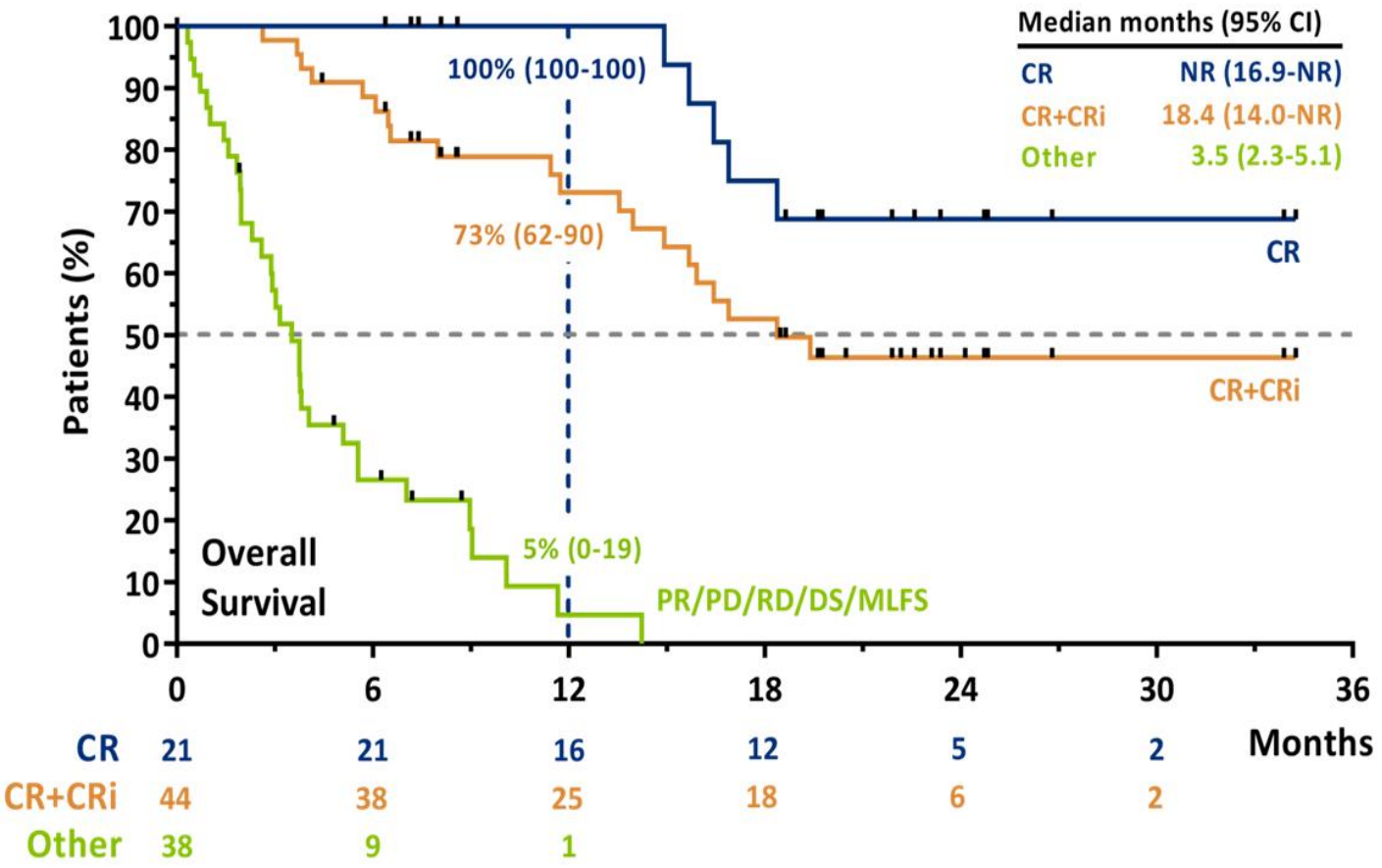
Venetoclax and LD Ara-C in AML

Overall Survival by Response



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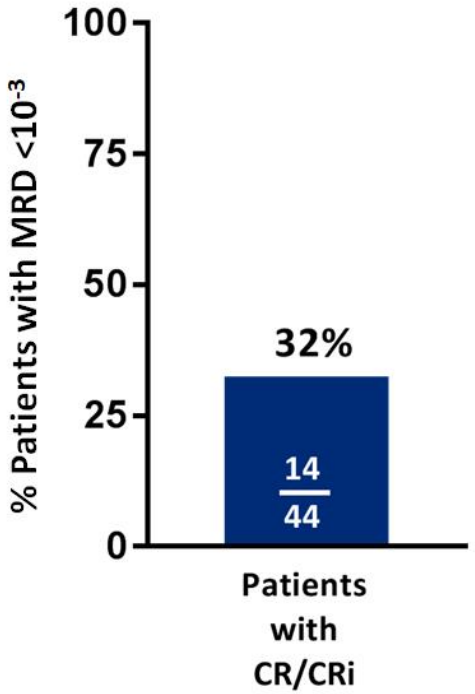
Venetoclax and LD Ara-C in AML

Minimal Residual Disease



MRD Assessment

Minimal residual disease (MRD) was centrally assessed by multicolor flow cytometry

MRD response was determined at a threshold of 10^{-3} cutoff (1 leukemic cell per 1,000)

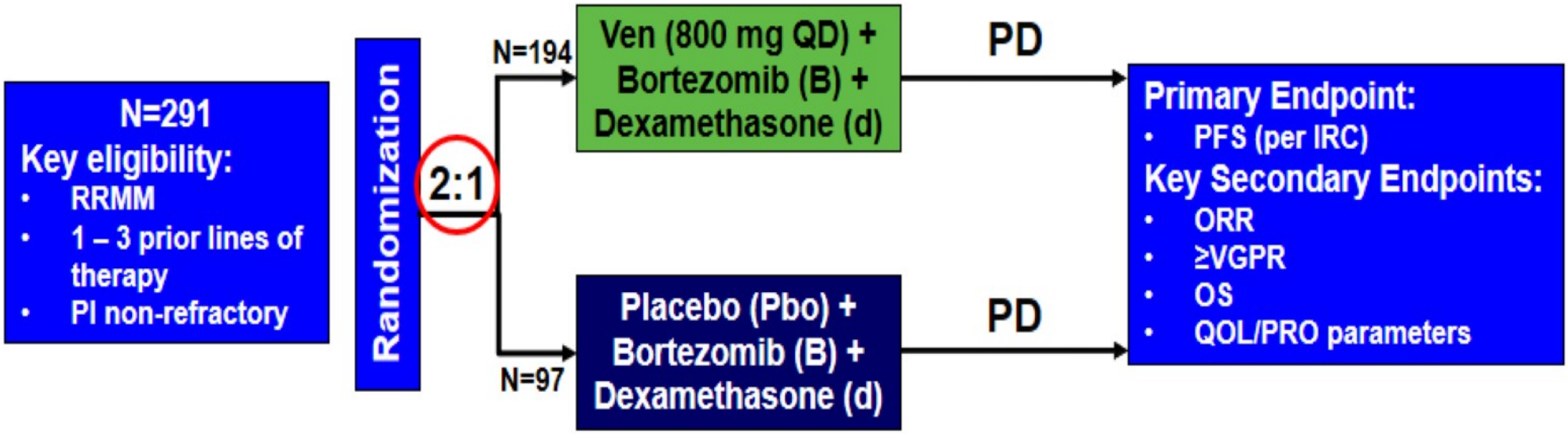
- Overall: 17/82 patients achieved MRD $<10^{-3}$
  - 3 such patients had best response of MLFS

Wei AH et al ASH oral presentation 2018

FDA Approval: Nov 21, 2018

The U.S. FDA has granted accelerated approval to venetoclax in combination with azacitidine, or decitabine, or low-dose cytarabine (LDAC) for the treatment of newly-diagnosed acute myeloid leukemia (AML) in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.

BELLINI Study Design



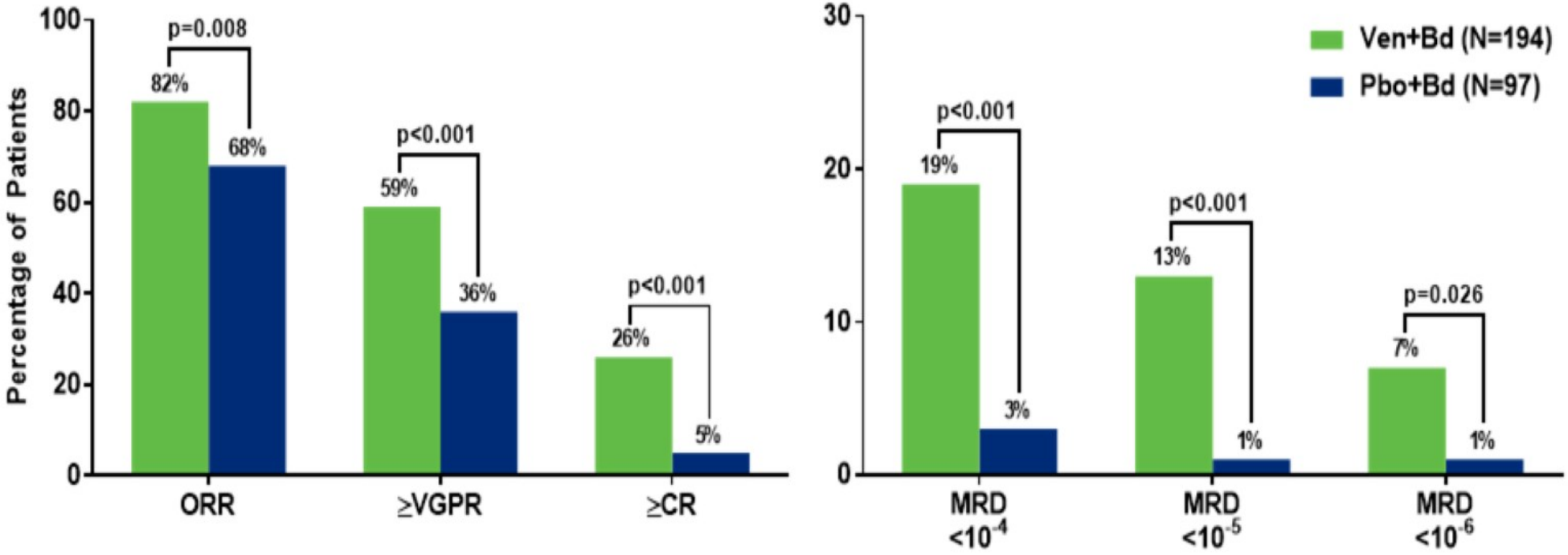
Cycles 1 – 8: 21-day, Bortezomib 1.3 mg/m^2 Days 1, 4, 8, 11 and dexamethasone 20 mg Days 1, 2, 4, 5, 8, 9, 11, 12

Cycles 9+: 35-day, Bortezomib 1.3 mg/m^2 Days 1, 8, 15, 22 and dexamethasone 20 mg Days 1, 2, 8, 9, 15, 16, 22, 23

Stratification factors	• Bortezomib sensitive vs naïve • Prior lines of therapy: 1 vs 2–3
Non-ranked secondary endpoints	PFS in BCL-2^{high} (IHC), DOR, TTP, MRD negativity rate, other PROs (GHS, fatigue)
Key subgroup analyses	t(11;14), high/standard-risk cytogenetics, and *BCL2* expression (gene expression)

DOR, duration of response; GHS, global health status; IHC, immunohistochemistry; MRD, minimal residual disease; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; PRO, patient reported outcome; QD, daily; QOL, quality of life; RRMM, relapsed/refractory multiple myeloma; TTP, time to progression; VGPR, very good partial response.

Clinical Response Rates in All Patients
26 Nov 2018

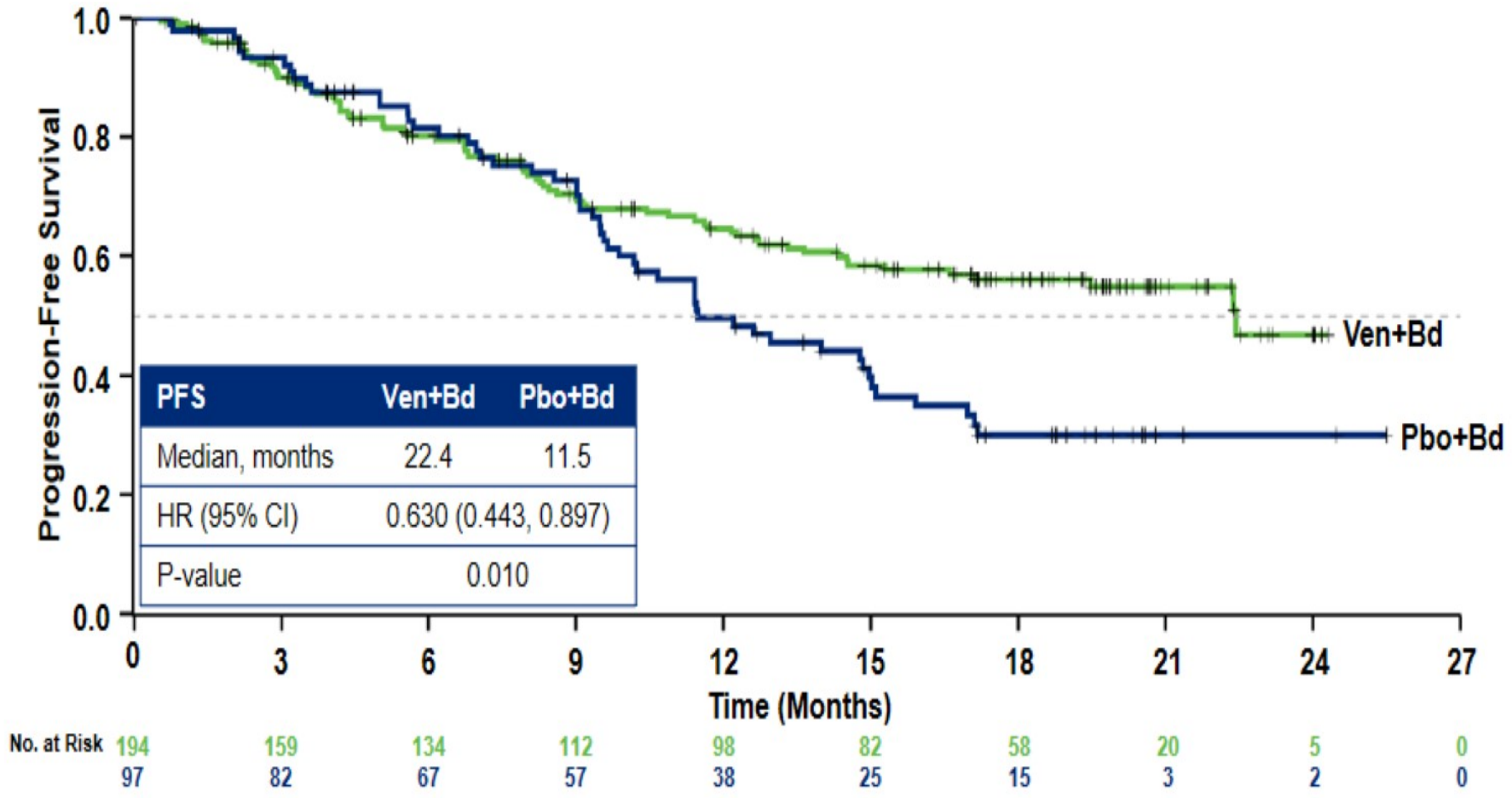


Overall response, ≥VGPR, ≥CR and MRD negativity rates were significantly higher with Ven+Bd

MRD assessment was performed by next-generation sequencing on bone marrow aspirate at time of CR/sCR

Primary Endpoint Analysis: Progression-Free Survival

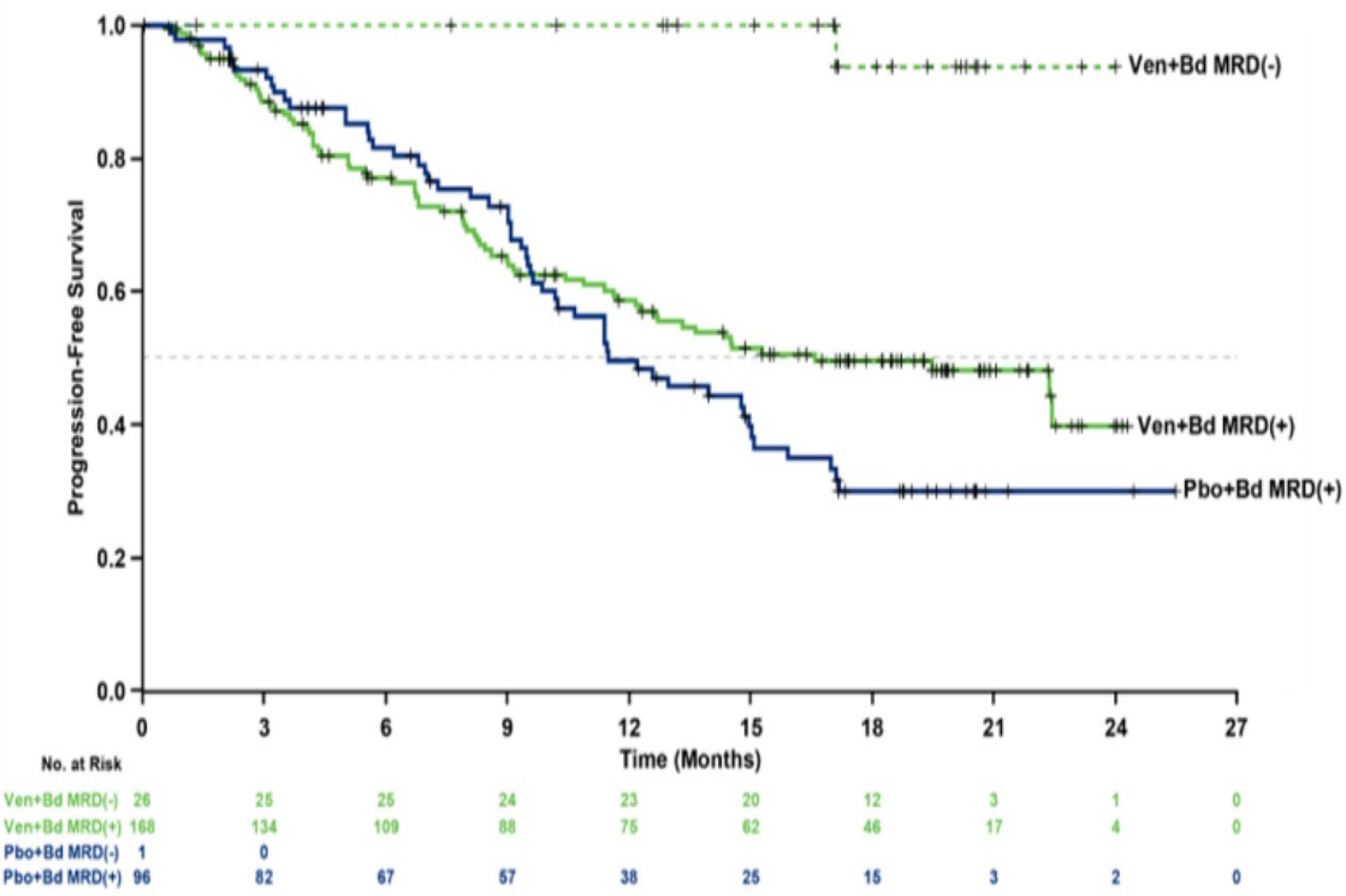
All Patients (ITT), 26 Nov 2018



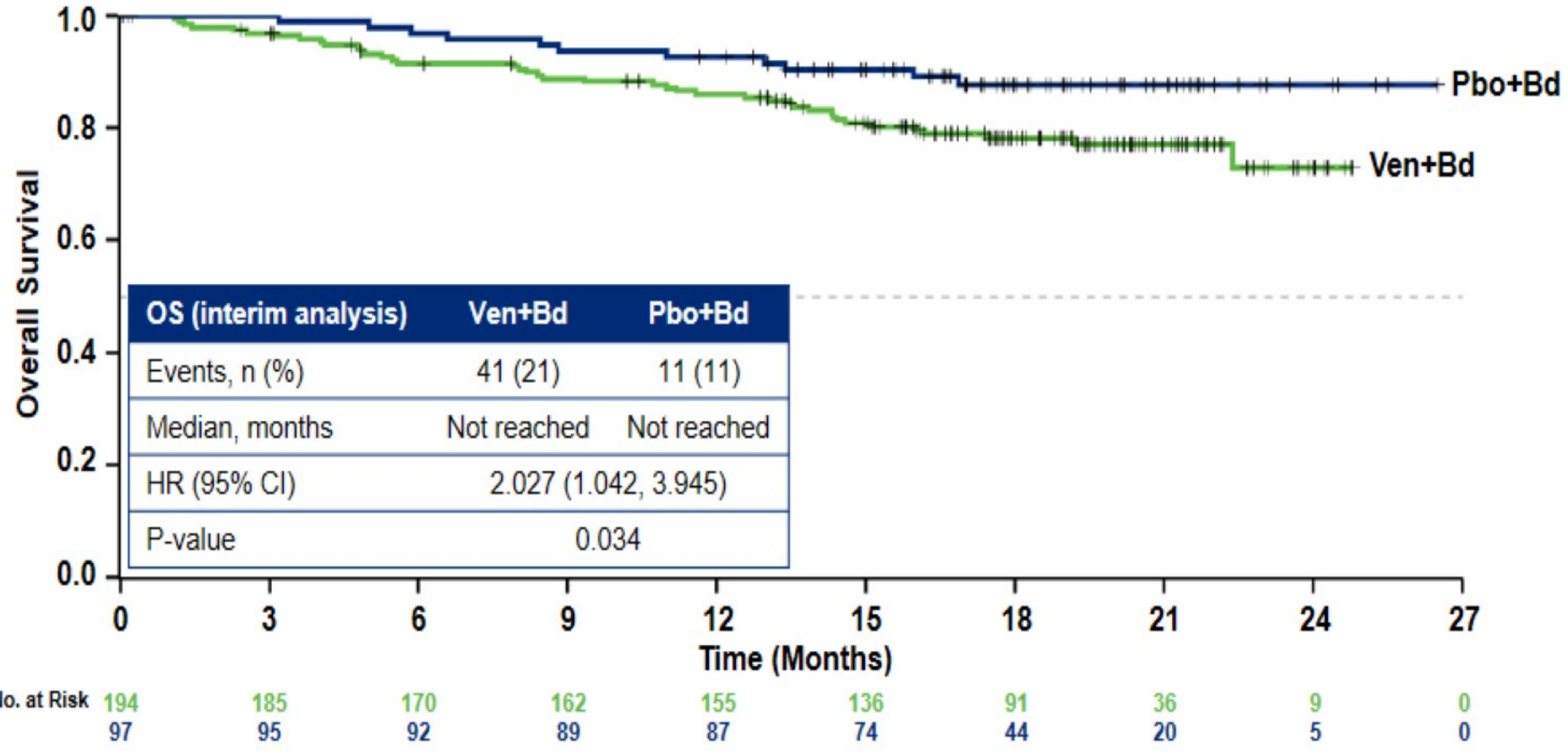
PFS	Ven+Bd	Pbo+Bd
Median, months	22.4	11.5
HR (95% CI)	0.630 (0.443, 0.897)	
P-value	0.010	

The BELLINI study met its primary endpoint with superior median PFS in the Ven+Bd arm versus Pbo+Bd

Progression Free Survival by MRD (10^{-5}) Status
26 Nov 2018



Overall Survival
All Patients (ITT), 26 Nov 2018



OS (interim analysis)	Ven+Bd	Pbo+Bd
Events, n (%)	41 (21)	11 (11)
Median, months	Not reached	Not reached
HR (95% CI)	2.027 (1.042, 3.945)	
P-value	0.034	

A higher risk of death was observed in the Ven+Bd arm compared to Pbo+Bd at interim OS analysis

Conclusions

- BCL2 mimetics represent a new class of targeted agents active in many hematologic malignancies.
- The larger experience with Venetoclax is in CLL and now is moving towards the use in earlier lines of therapy and fixed duration treatment.
- Venetoclax plus HMAs was well tolerated and effective in previously untreated, older patients , with AML who were ineligible for intensive chemotherapy.
- MM patients with t(11;14) or $BCL2^{high}$ had consistent clinical benefit when treated with Ven+Bd, and the benefit-risk profile appears to be favorable in these subsets
- Patients who achieved MRD negativity status have better outcome in CLL (PFS) and MM (PFS and OS).

Grande Ospedale Metropolitano Niguarda