CLL: State of the Art 2018

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Speaker Disclosures

Sponsor/Company	Affiliation(s)
Amgen	Consultant
Astellas	Consultant
Celgene	Consultant
GlaxoSmithKline	Consultant
Janssen Oncology	Consultant
Aptose Biosciences Inc.	Consultant
Vaniam Group LLC	Consultant
AbbVie	Consultant
Alexion	Consultant
Kite	Research Support
Regeneron	Research Support
Acerta	Research Support
Gilead	Consultant/Research Support
Pharmacyclics	Consultant/Research Support
TG Therapeutics	Consultant/Research Support
Pfizer	Consultant/Research Support
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**This program may contain discussion of off-label content*

Treatment Strategies for CLL Patients

Group 1	Group 2	Group 3
• Fit • No comorbidity • Normal life expectancy	• Less fit • Comorbidity present	• Not fit • High comorbidity
'Go go'	**'Slow go'**	**'No go'**
Intensive therapy	Mild therapy/new oral agents	Palliative care
→ Long-lasting remissions and treatment -free	→ Control of disease	

Balducci L & Extermann M, *Oncologist* 2000; 5:224–237.

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ORIGINAL REPORT

Early Results of a Chemoimmunotherapy Regimen of Fludarabine, Cyclophosphamide, and Rituximab As Initial Therapy for Chronic Lymphocytic Leukemia

Michael J. Keating, Susan O'Brien, Maher Albitar, Susan Lerner, William Plunkett, Francis Giles, Michael Andreeff, Jorge Cortes, Stefan Faderl, Deborah Thomas, Charles Koller, William Wierda, Michelle A. Detry, Alice Lynn, and Hagop Kantarjian

From the Departments of Leukemia, Hematopathology, Experimental Therapeutics, Blood and Marrow Transplantation, and the Biostatistics and Applied Mathematics, The University of Texas M.D. Anderson Cancer Center, Houston, TX.

Submitted December 9, 2003; accepted November 11, 2004.

ABSTRACT

Purpose

Fludarabine and cyclophosphamide (FC), which are active in treatment of chronic lymphocytic leukemia (CLL), are synergistic with the monoclonal antibody rituximab in vitro in lymphoma cell lines. A chemoimmunotherapy program consisting of fludarabine, cyclophosphamide, and rituximab (FCR) was developed with the goal of increasing the complete remission (CR) rate in previously untreated CLL patients to ≥ 50%.

CLL10 Study: FCR VS BR in Front-Line

Design

Patients with untreated, active CLL without del(17p) and good physical fitness (CIRS ≤ 6, creatinine clearance ≥ 70 ml/min)

Randomization

FCR

Fludarabine 25 mg/m² i.v., days 1-3

Cyclophosphamide 250 mg/m², days 1-3,

Rituximab 375 mg/ m² i.v. day 0, cycle 1

Rituximab 500 mg/m² i.v. day 1, cycle 2-6

BR

Bendamustine 90mg/m² day 1-2

Rituximab 375 mg/m² day 0, cycle 1

Rituximab 500 mg/m² day 1, cycle 2-6

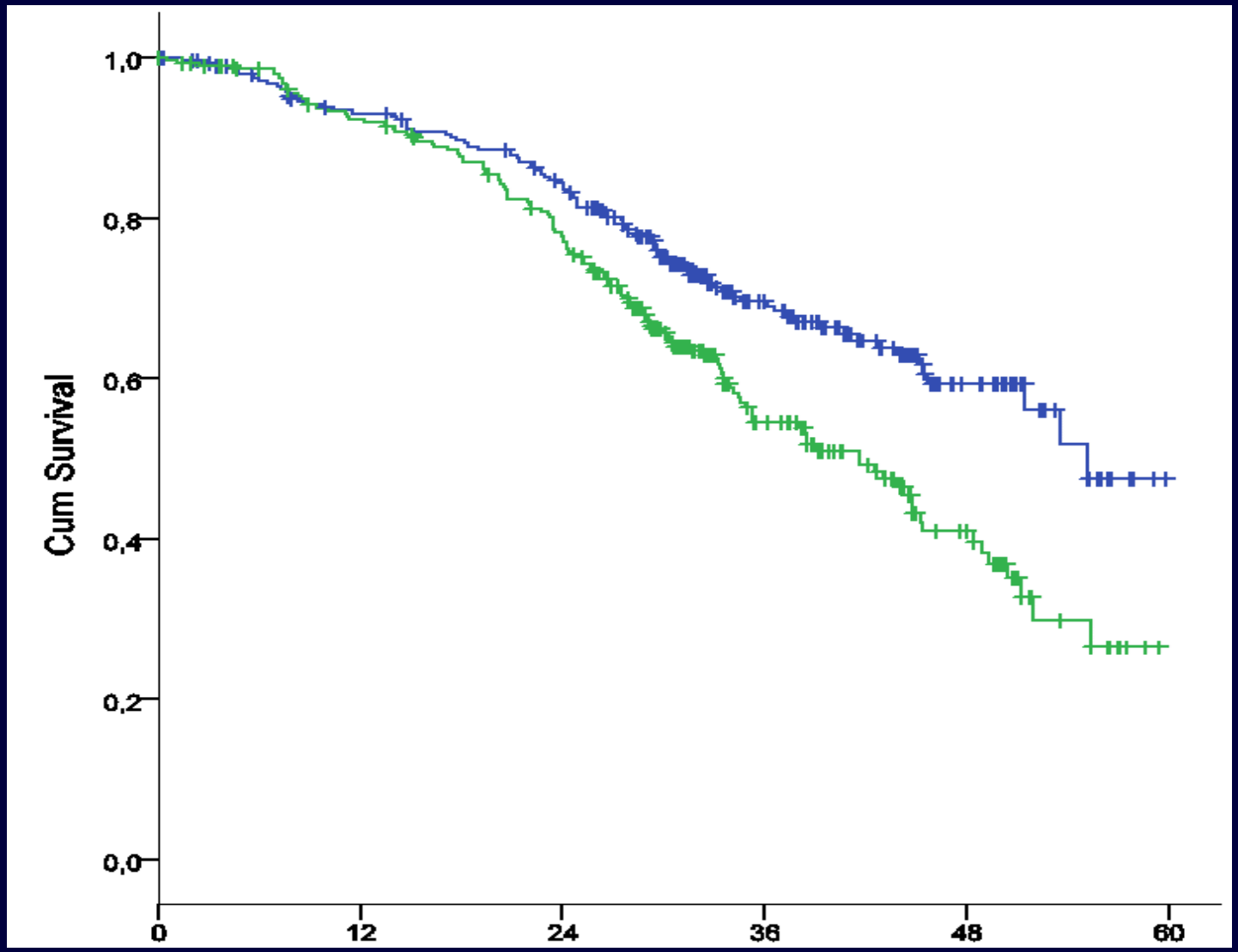
Non-Inferiority of BR in comparison to FCR for PFS:

HR (λ BR/FCR) less than 1.388

Eichhorst et al Lancet Oncol 2016 Jul; 17(7):925-42

CLL10 Study: FCR VS BR in Front-Line

ITT Progression-free Survival = Primary Endpoint



Median PFS

FCR 55.2 months

BR 41.7 months

***P* < 0.001**

HR = 1.626 = > 1.388

CLL10 Study: FCR VS BR in Front-Line

Adverse Events CTC °3-4 (1st cycle until end of study)

Adverse event	FCR (%) N= 279	BR (%) N=278	p value
Neutropenia	84.2	59.0	<0.001
Anemia	13.6	10.4	0.20
Thrombocytopenia	21.5	14.4	0.03
Infection	39.1	26.8	<0.001
Sec Neoplasm*	6.1	3.6	0.244

***sAML/MDS: FCR=6, BR = 1**

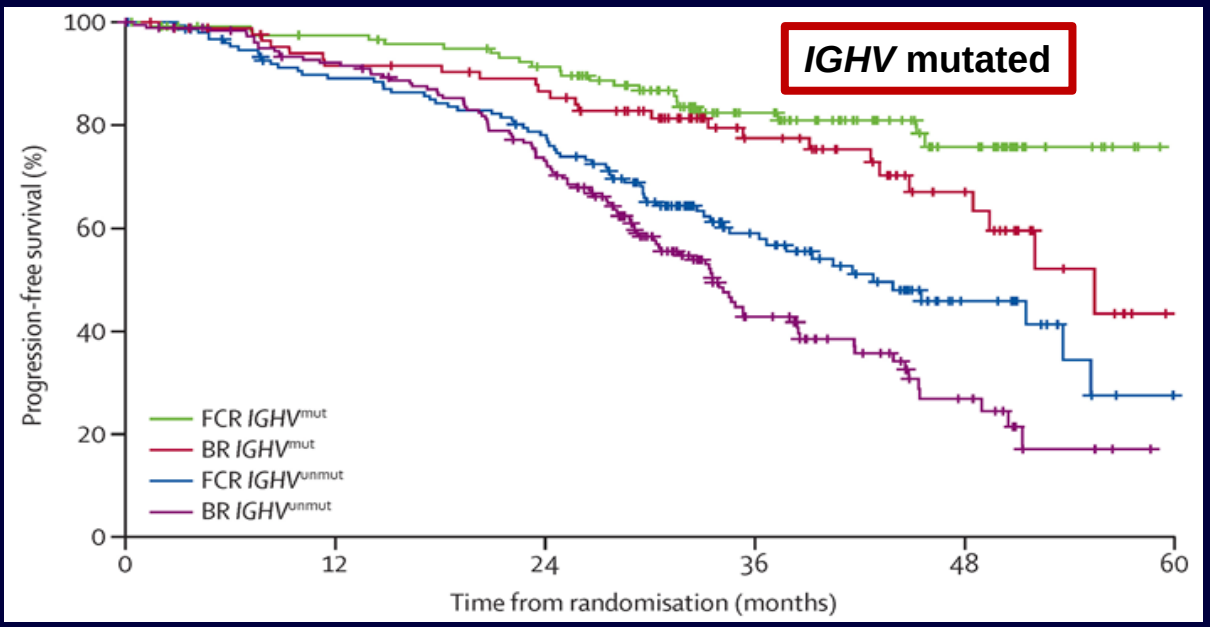
TRM	**4.6**	**2.1**	**0.107**
Infections	2.5	2.1	-
Sec Neoplasm	1.1	0	-
Other	1.0		

OK, FCR produces a year longer PFS then BR but at the expense of more myelosuppression and serious infections.

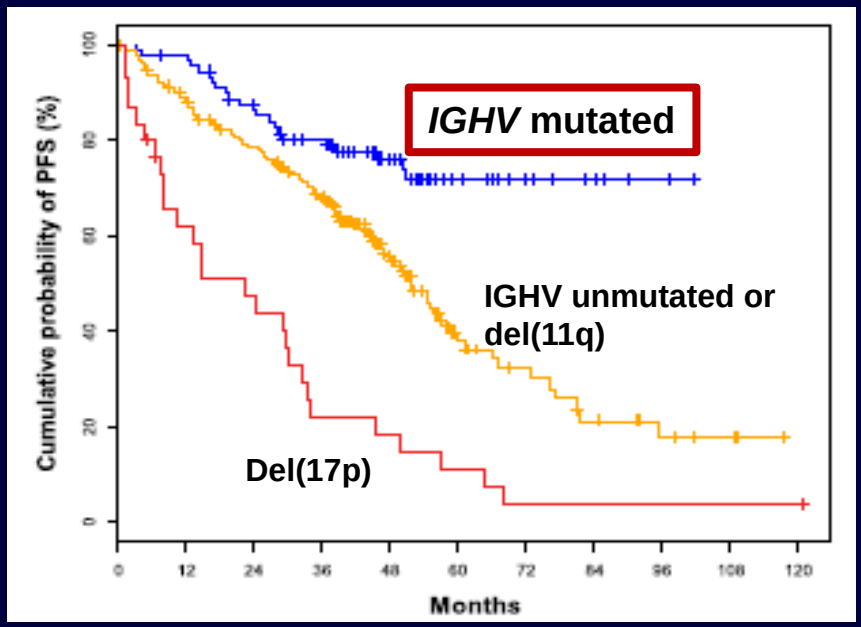
Also, I have a great salvage treatment in ibrutinib.

So why use FCR?

Favorable long-term PFS with Firstline FCR in *IGHV*-M Subgroup



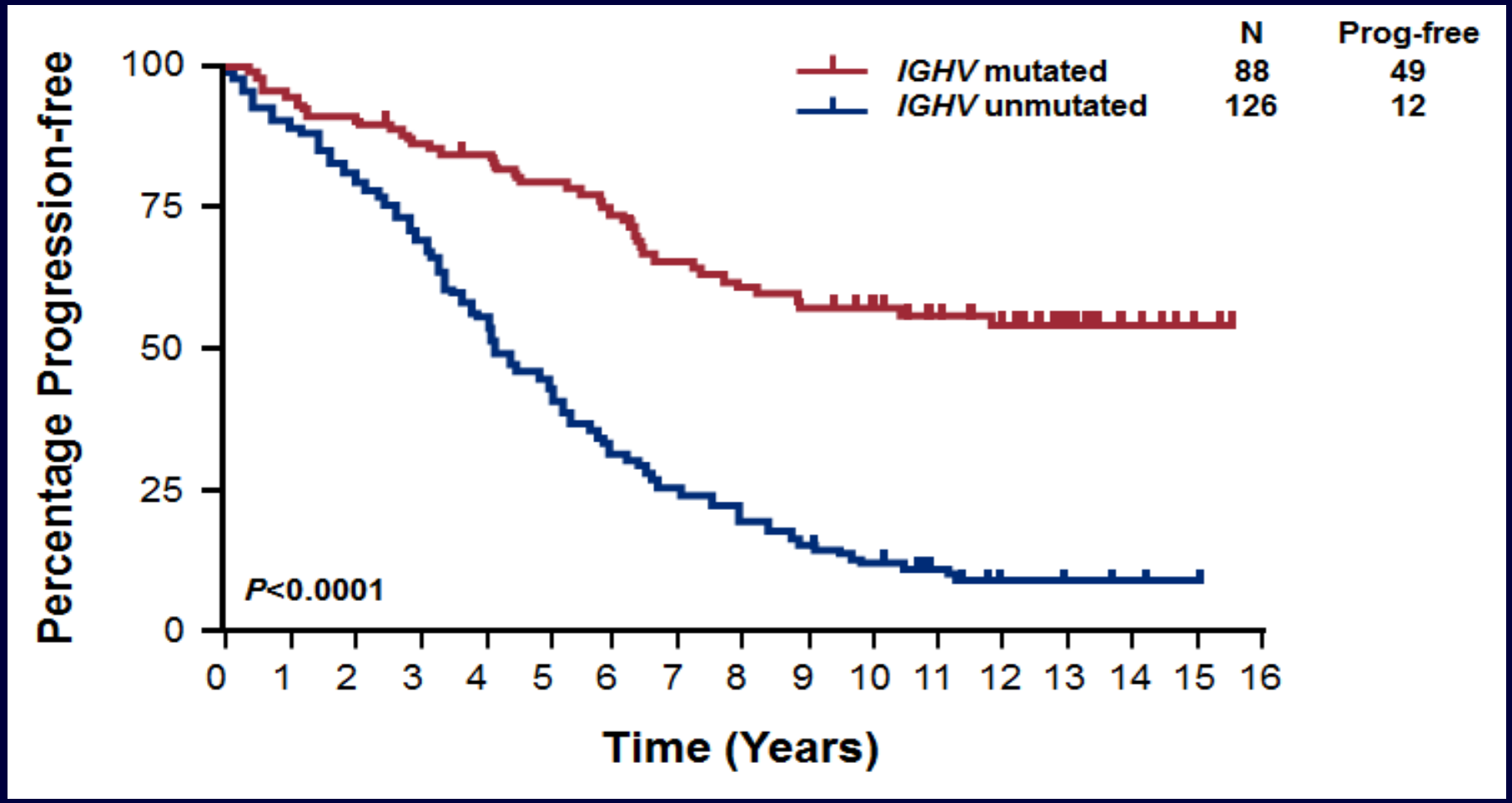
Eichhorst, Lancet Oncology 2016.



Rossi, Blood 2015.

PFS = Progression Free Survival
So living without evidence of CLL

Favorable long-term PFS with Firstline FCR in *IGHV*-M Subgroup



Thompson, Blood 2016.

- **OK, so maybe the fit mutated patients should still be offered FCR.**
- **What about the fit unmutated?**

RESONATE™-2 (PCYC-1115) Study Design

Patients (N=269)
- Treatment-naïve CLL/SLL with active disease
- Age ≥65 years
- For patients 65-69 years, comorbidity that may preclude FCR
- del17p excluded
- Warfarin use excluded

Stratification factors
- ECOG status (0-1 vs. 2)
- Rai stage (III-IV vs. ≤II)

RANDOMIZE 1:1

ibrutinib 420 mg once daily until PD or unacceptable toxicity

chlorambucil 0.5 mg/kg (to maximum 0.8 mg/kg) days 1 and 15 of 28-day cycle up to 12 cycles

IRC-confirmed progression

PCYC-1116 Extension Study*

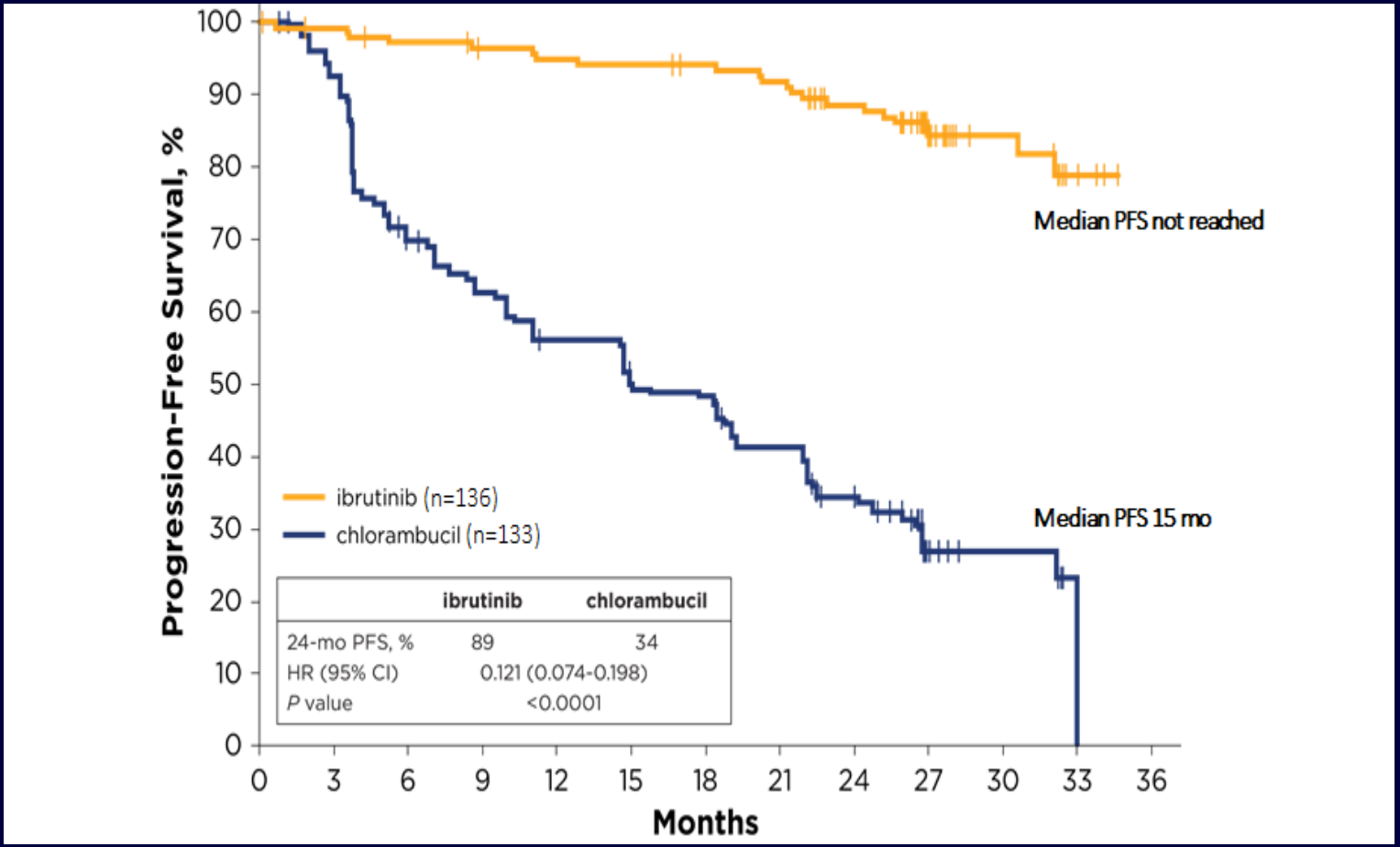
In clb arm, n=43 crossed over to ibrutinib

*Patients with IRC-confirmed PD enrolled into extension Study 1116 for follow-up and second-line treatment per investigator's choice (including ibrutinib for patients progressing on chlorambucil with iwCLL indication for treatment).

- Phase 3, open-label, multicenter, international study
- Primary endpoint: PFS as evaluated by IRC (2008 iwCLL criteria)[1,2]
- Secondary endpoints: OS, ORR, hematologic improvement, safety

1. Hallek et al. *Blood*. 2008;111:5446-5456; 2. Hallek et al, *Blood.* 2012; e-letter, June 04, 2012.

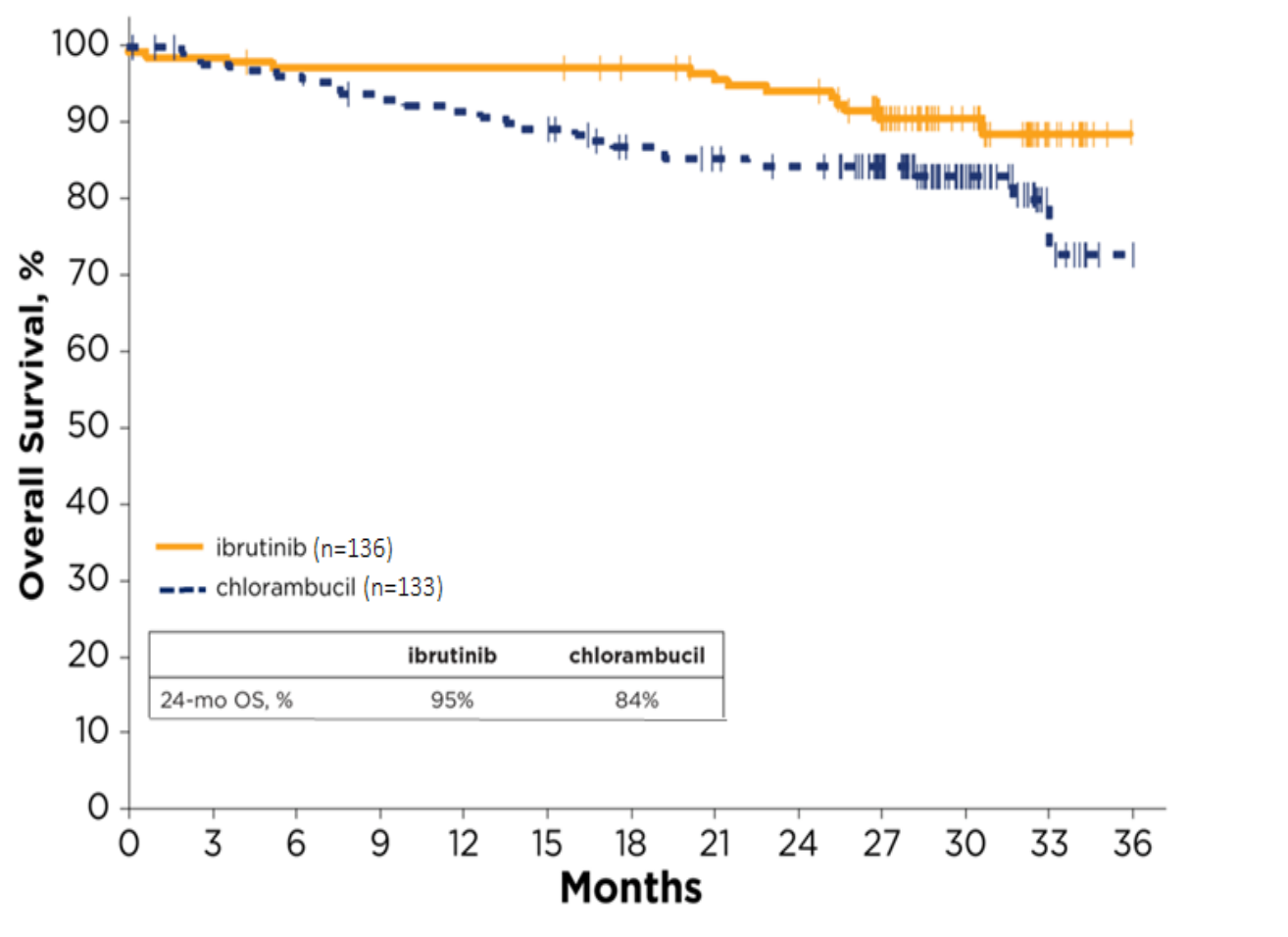
Ibrutinib Prolonged PFS Over Chlorambucil



- **88% reduction in the risk of progression or death for patients randomized to ibrutinib**
- **Subgroup analysis of PFS revealed benefit was observed across all subgroups**

Barr P, et al. *Blood.* 2016;128: Abstract 234.

Ibrutinib Continues to Demonstrate OS Benefit Over Chlorambucil With Longer Follow-Up and Cross-Over



Barr P, et al. *Blood.* 2016;128: Abstract 234.

- **Well yes ibrutinib is significantly better then chlorambucil but I wouldn’t use chlorambucil in my fit patient.**

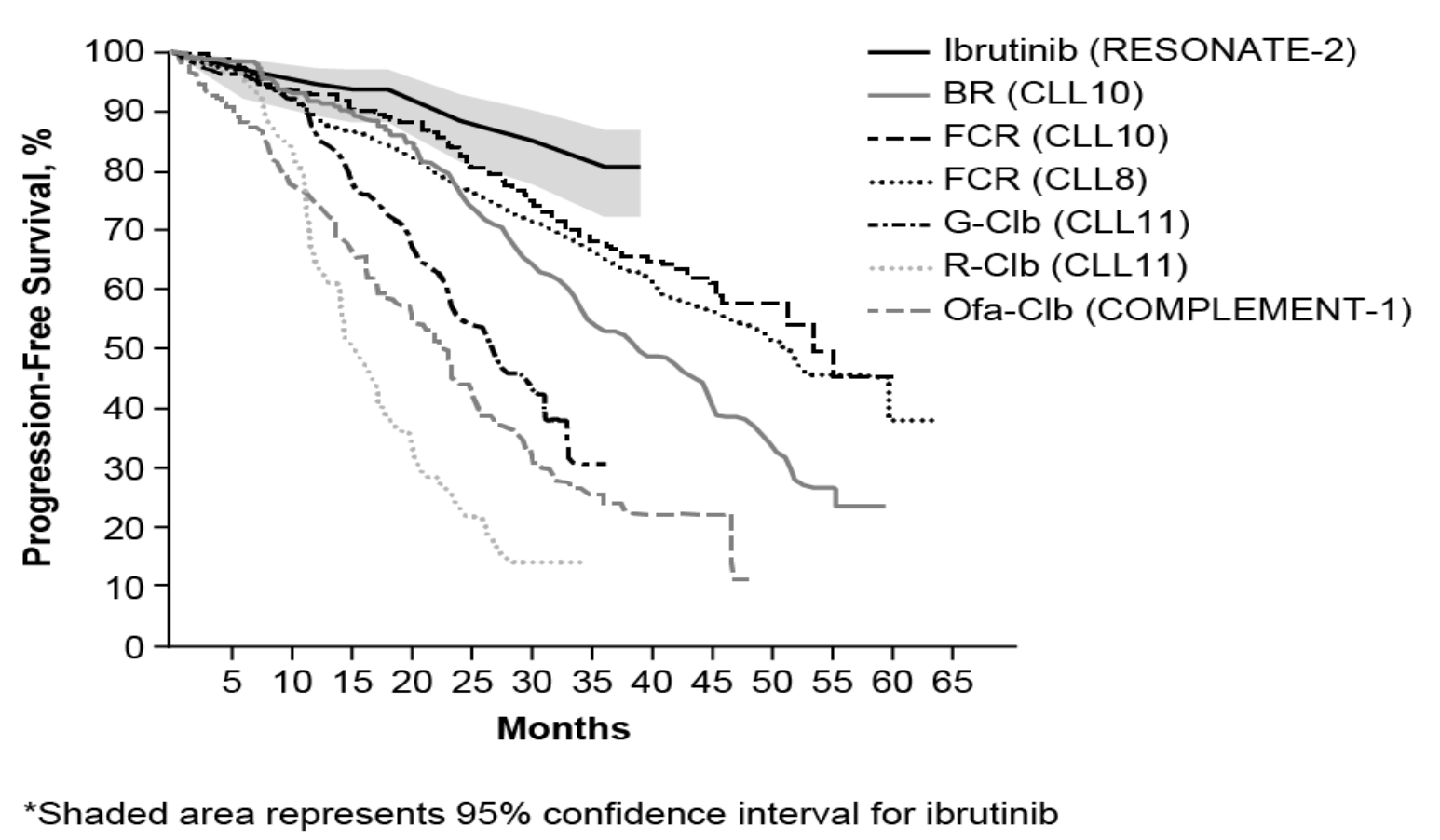
Indirect Comparison of Single-Agent Ibrutinib With Chemoimmunotherapy Regimens for First-Line Treatment of Chronic Lymphocytic Leukemia (CLL)

Tadeusz Robak

Atlanta, 59th ASH Meeting, December 9, 2017

Single-Agent Ibrutinib vs Chemoimmunotherapy Regimens for Treatment-Naïve Patients With CLL: a Cross-Trial Comparison – PFS

- All Comparator Studies



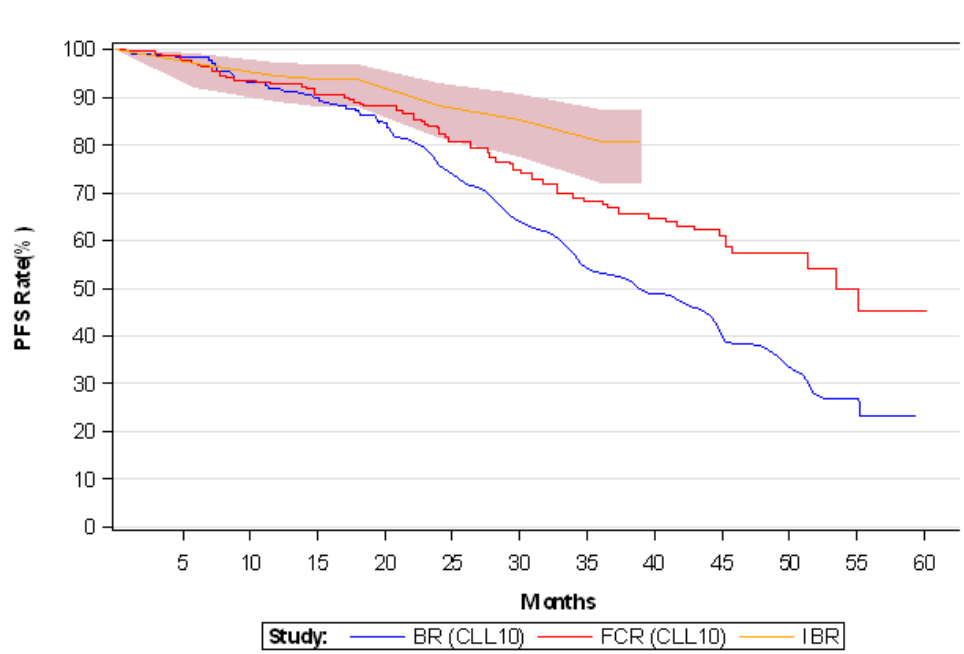
Progression-Free Survival (PFS) in RESONATE-2 and Comparator Studies

Robak et al. ASH. 2017 Abstract 1750

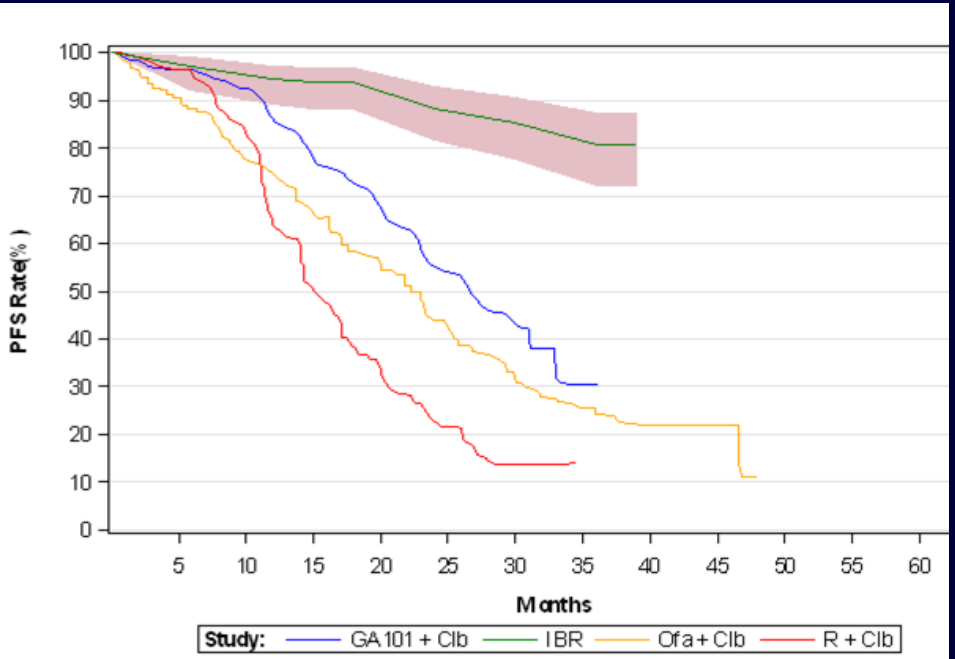
Robak et al. Am J Hematol. 2018 Aug 20. doi: 10.1002/ajh.25259

Single-Agent Ibrutinib vs Chemoimmunotherapy Regimens for Treatment-Naïve Patients With CLL: a Cross-Trial Comparison - PFS

Studies Excluding Patients



Studies in Older Patients or Patients with Comorbidities



Robak et al. ASH. 2017 Abstract 1750

Robak et al. Am J Hematol. 2018 Aug 20. doi: 10.1002/ajh.25259

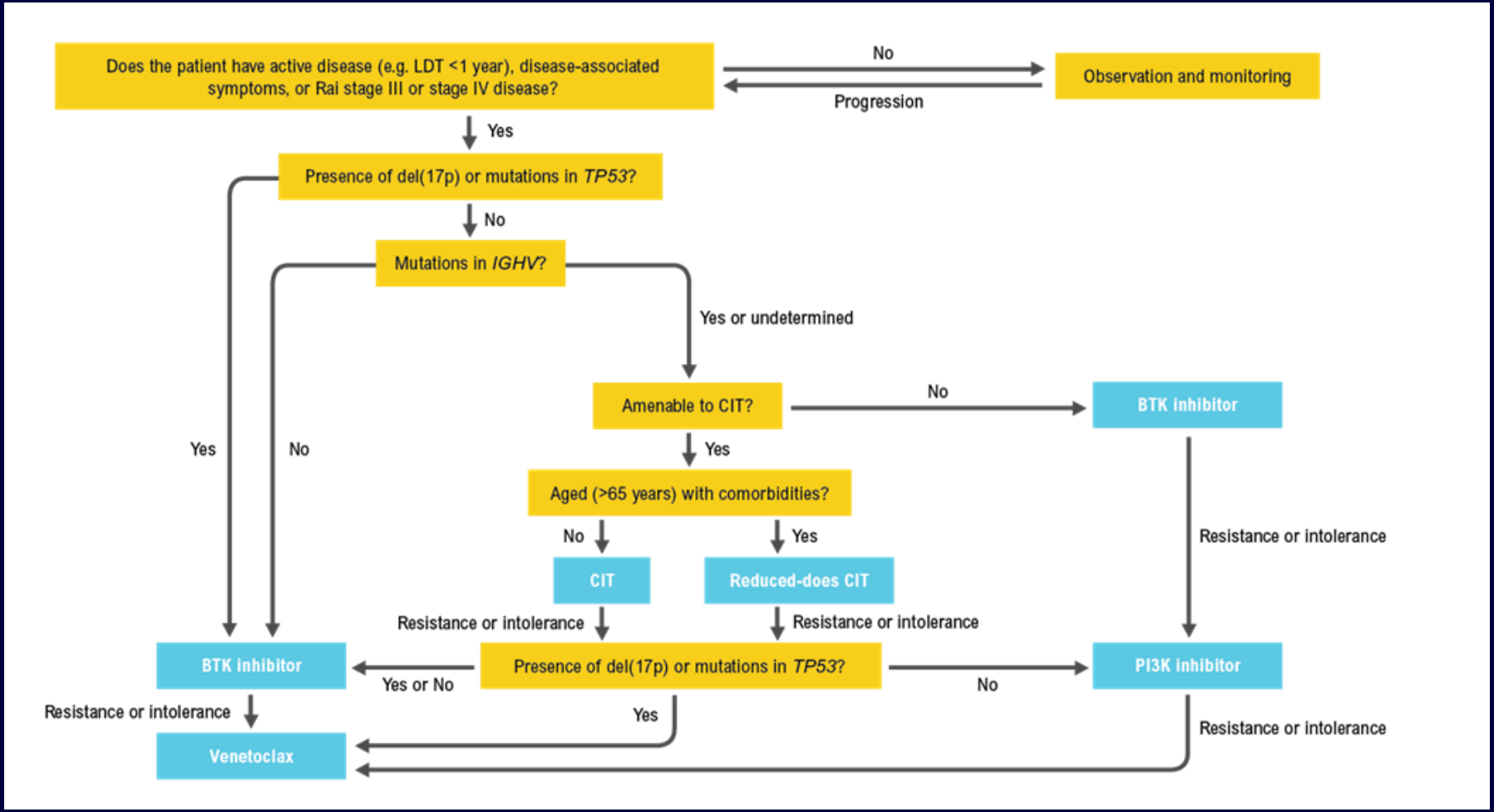
Frontline Treatment Strategies for CLL Patients

Group 1	Group 2	Group 3
• Older • Comorbidities • Not fit	• Fit • Unmutated	• Fit • Mutated
Clinical Trial **Ibrutinib**	**Clinical Trial** **Ibrutinib**	**Clinical Trial** **FCR or Ibrutinib?**

Relapse post ibrutinib: Venetoclax and rituximab

Balducci L & Extermann M, *Oncologist* 2000; 5:224–237.

A CLL treatment algorithm that includes *IGHV* testing

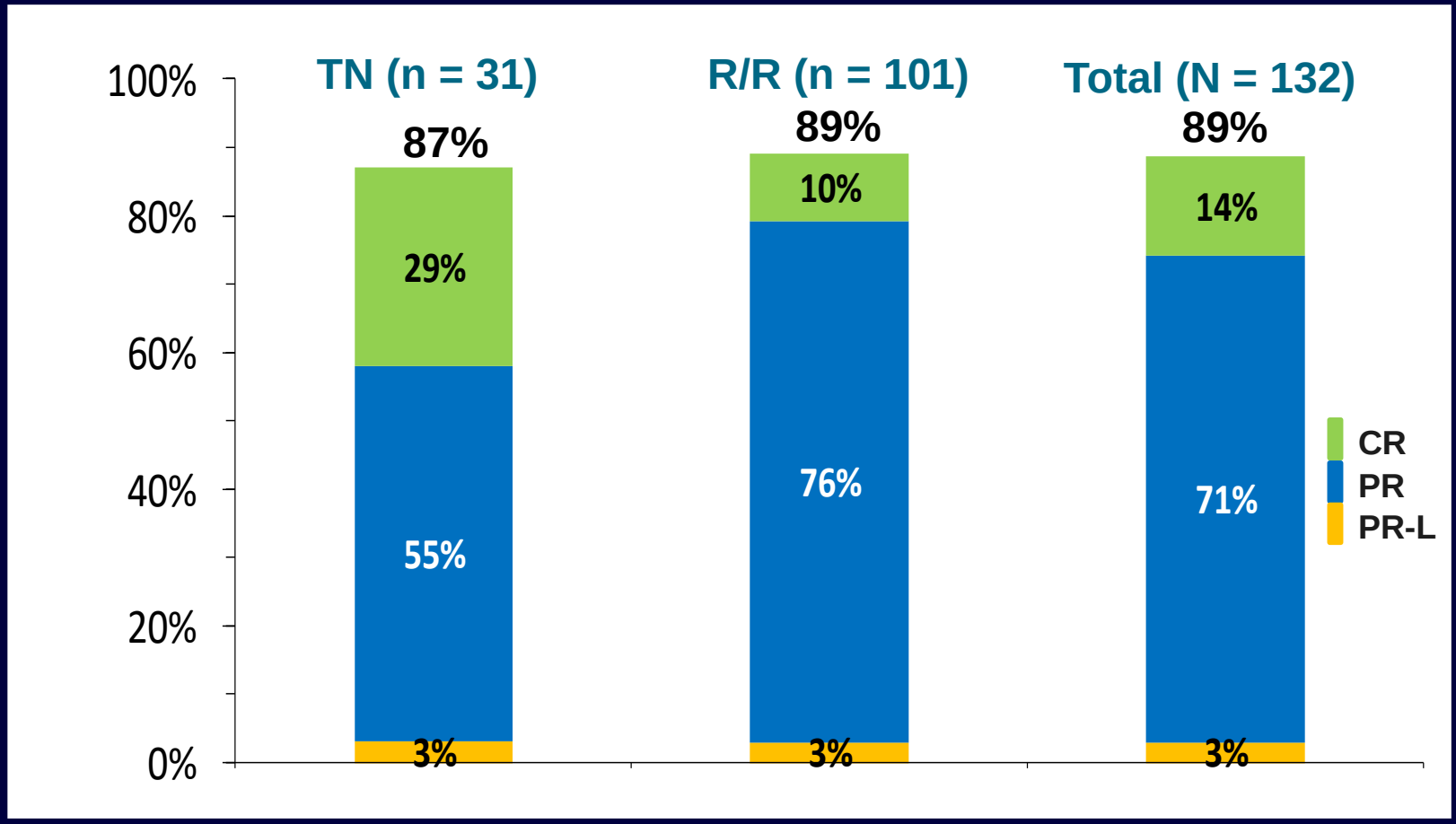


LDT=lymphocyte doubling time; CIT=chemoimmunotherapy; BTK=Bruton's tyrosine kinase.

References: 1. Kipps TJ et al. *Nat Rev Dis Primers* 2017;(3):17008.

What about therapy for relapse?

Ibrutinib 5-Year Update Best Response



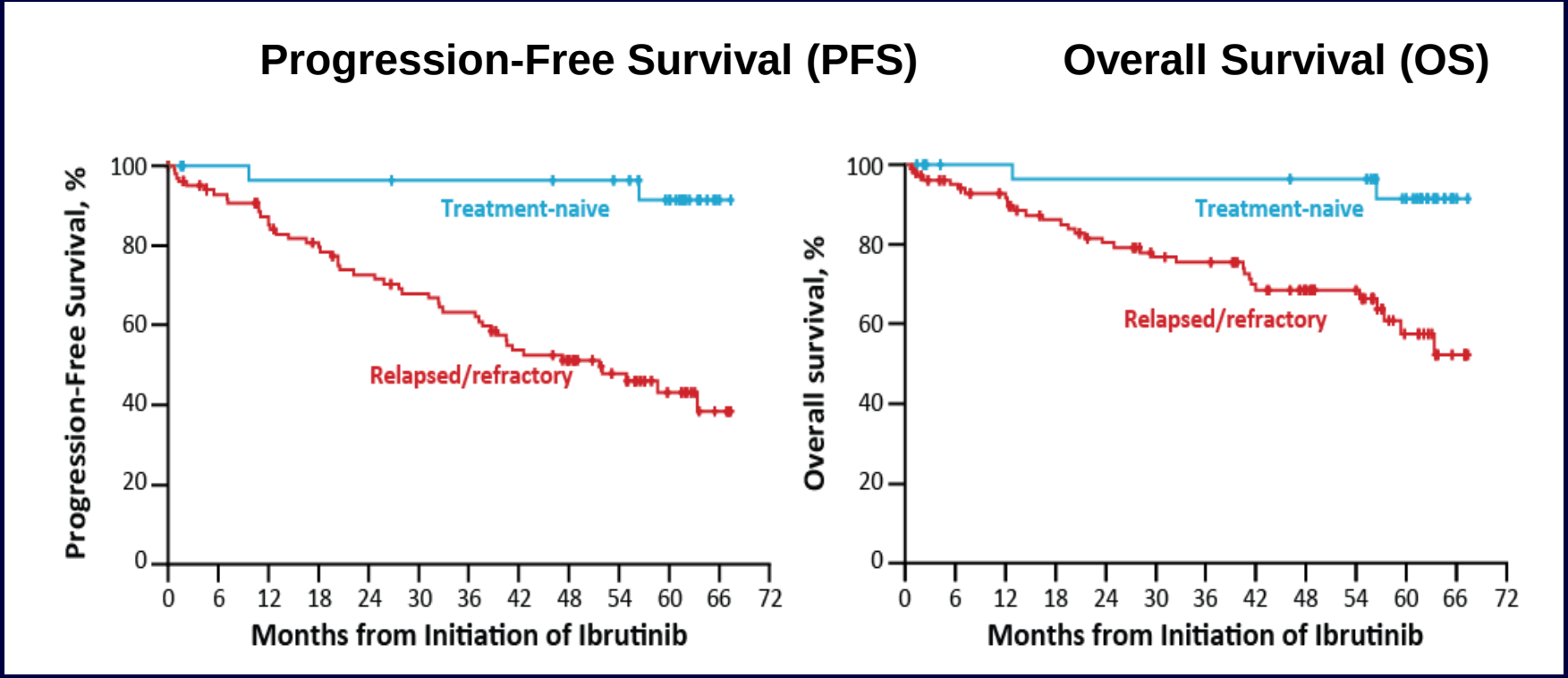
Median DOR, months (range)	NR (0.0+ to 65.5+)	56.8 (0.0+ to 65.5+)	NR (0.0+ to 65.5+)
Median follow-up, months (range)	62 (1–67)	49 (1+–67)	56 (1+–67)

CR, complete response; DOR, duration of response; NR, not reached; PR, partial response; PR-L, partial response with lymphocytosis; R/R, relapsed/refractory; TN, treatment-naïve

O'Brien S, et al. *Blood.* 2016;128: Abstract 233.

O'Brien et al Blood Epub 2/2/18

Survival Outcomes: Overall Population



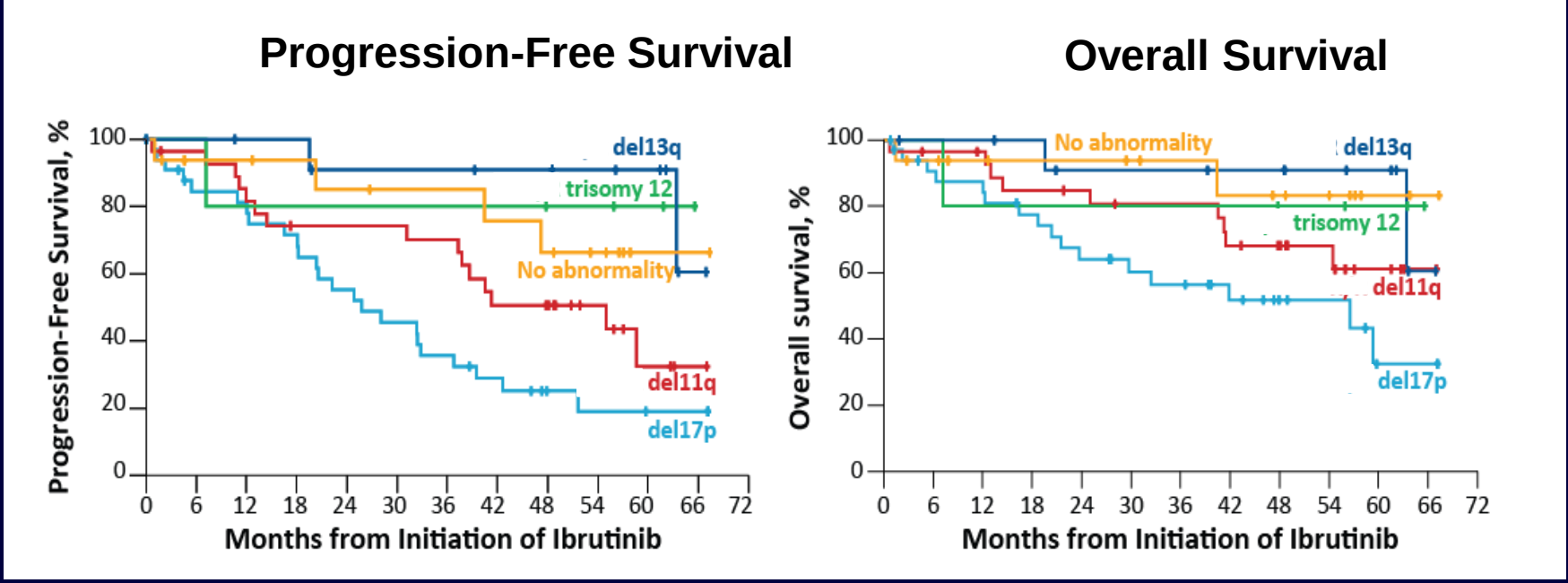
	Median PFS	5-year PFS
TN (n = 31)	NR	92%
R/R (n = 101)	52 months	43%

	Median OS	5-year OS
TN (n = 31)	NR	92%
R/R (n = 101)	NR	57%

O'Brien S, et al. *Blood.* 2016;128: Abstract 233.

O'Brien et al Blood Epub 2/2/18

Survival Outcomes by Chromosomal Abnormalities Detected by FISH in R/R Patients*



	Median PFS	5-year PFS
Del17p (n = 34)	26 months	19%
Del11q (n = 28)	55 months	33%
Trisomy 12 (n = 5)	NR	80%
Del13q (n = 13)	NR	91%
No abnormality** (n = 16)	NR	66%

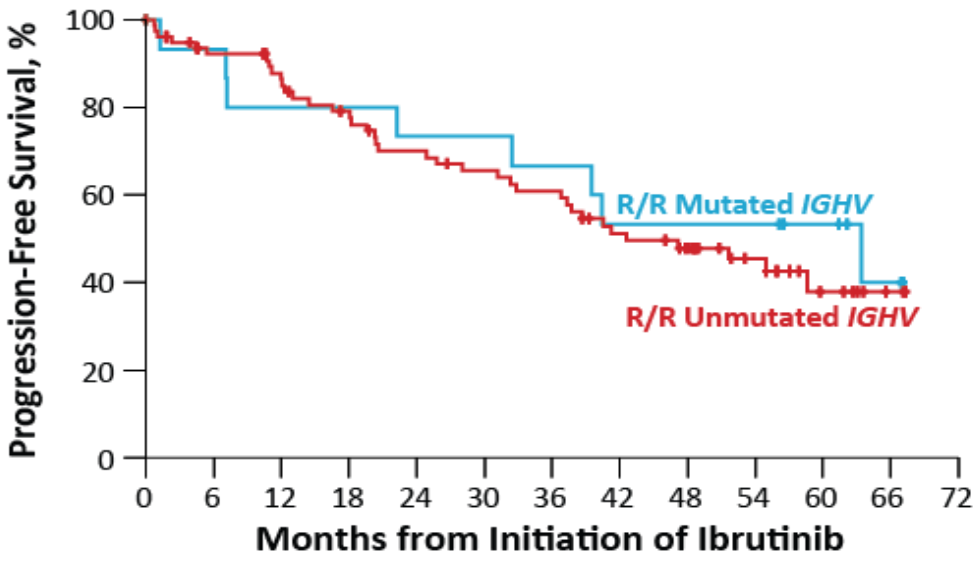
	Median OS	5-year OS
Del17p (n = 34)	57 months	32%
Del11q (n = 28)	NR	61%
Trisomy 12 (n = 5)	NR	80%
Del13q (n = 13)	NR	91%
No abnormality** (n = 16)	NR	83%

O'Brien S, et al. *Blood.* 2016;128: Abstract 233.

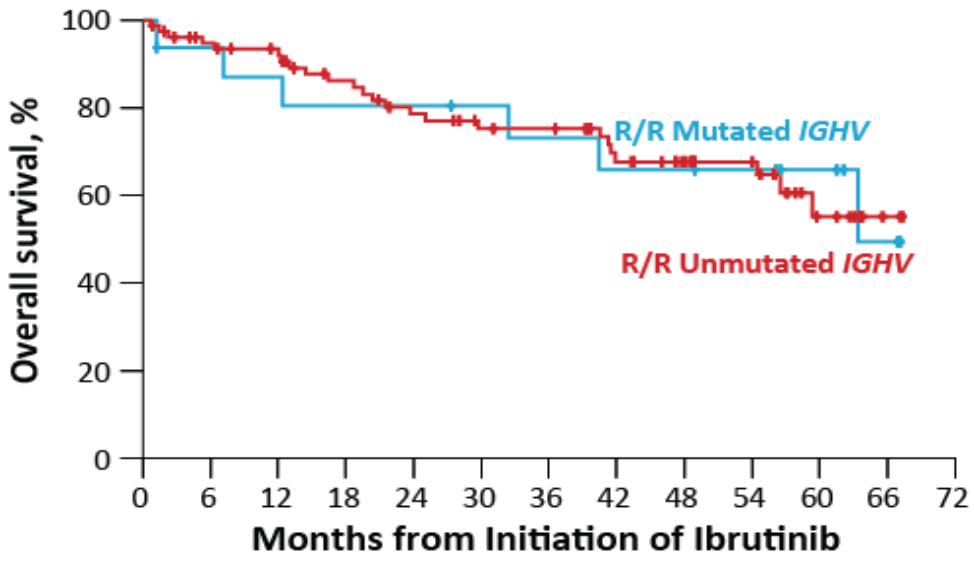
**O'Brien S. et al. Blood. Epub 2/2/18

Survival by *IGHV* Mutational Status in R/R Patients*

Progression-Free Survival



Overall Survival



	Median PFS	5-year PFS
Mutated *IGHV* (n=16)	63 mo	53%
Unmutated *IGHV* (n=79)	43 mo	38%

	Median OS	5-year OS
Mutated *IGHV* (n=16)	63 mo	66%
Unmutated *IGHV* (n=79)	NR	55%

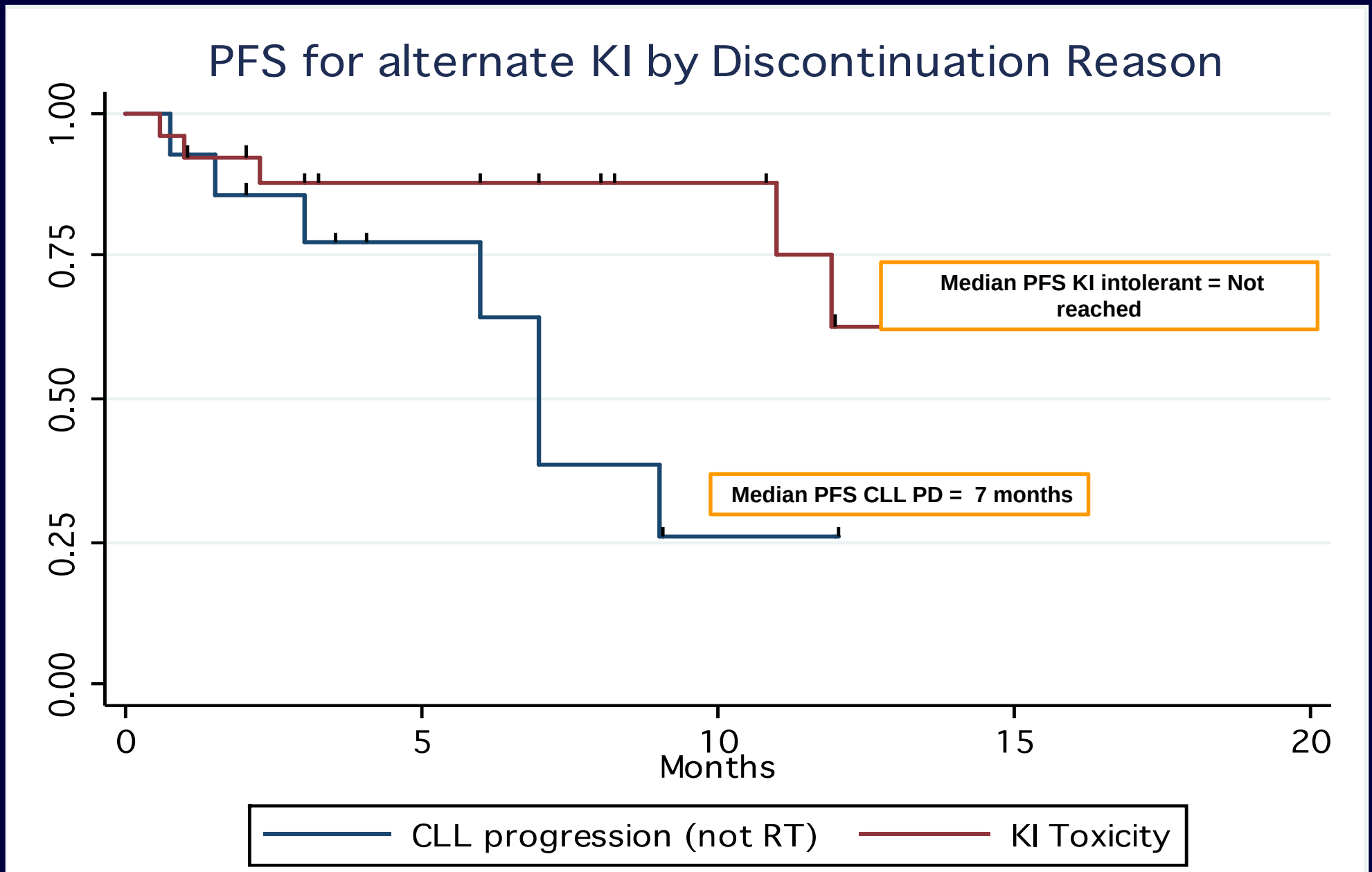
*Only 2 patients in the TN group showed disease progression or death. Subgroup analyses, therefore, focused on the R/R population.

NR, not reached.

Outcomes of CLL Patients Treated With Sequential Kinase Inhibitor Therapy: A Real World Experience

Mato AR, Nabhan C, Barr PM, Ujjani CS, Hill BT, Lamanna N, Skarbnik AP, Howlett C, Pu JJ, Sehgal AR, Strelec LE, Vandegrift A, Fitzpatrick DM, Zent CS, Feldman T, Goy A, Claxton DF, Bachow SH, Kaur G, Svoboda J, Nasta SD, Porter D, Landsburg DJ, Schuster SJ1, Cheson BD, Kiselev P, Evens AM

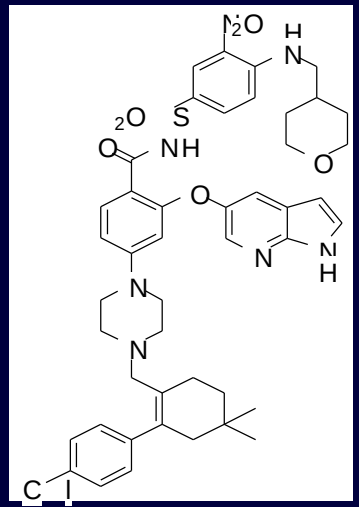
Mato et al. Blood. 2016 Nov 3;128(18):2199-2205. Epub 2016 Sep 6;



RT excluded from analysis

Venetoclax: Potent and Selective Bcl-2 Inhibition

- Small molecule, orally bioavailable
- High affinity for Bcl-2, lower affinity for BCL-xL, Mcl-1
- >100-fold improved functional selectivity for Bcl-2 over Bcl-x_L in assays with tumor cell lines



ABT-199

	Affinity				Cellular Efficacy, EC_{50}, nM				
	TR FRET K_i, nM				FL5.12, 3% FBS			Human tumor cell lines, 10% HS	
Agents	Bcl-2	Bcl-x_L	Bcl-w	Mcl-1	Bcl-2	Bcl-x_L	Functional Selectivity	RS4;11 (Bcl-2)	H146 (Bcl-x_L)
Navitoclax	0.04	0.05	7	>224	20	13	0.6	110	75
ABT-199	< 0.01	48	21	>440	4	261	65	12	3600

S. Jin, P. Kovar, P. Nimmer, M. Smith, Y. Xiao

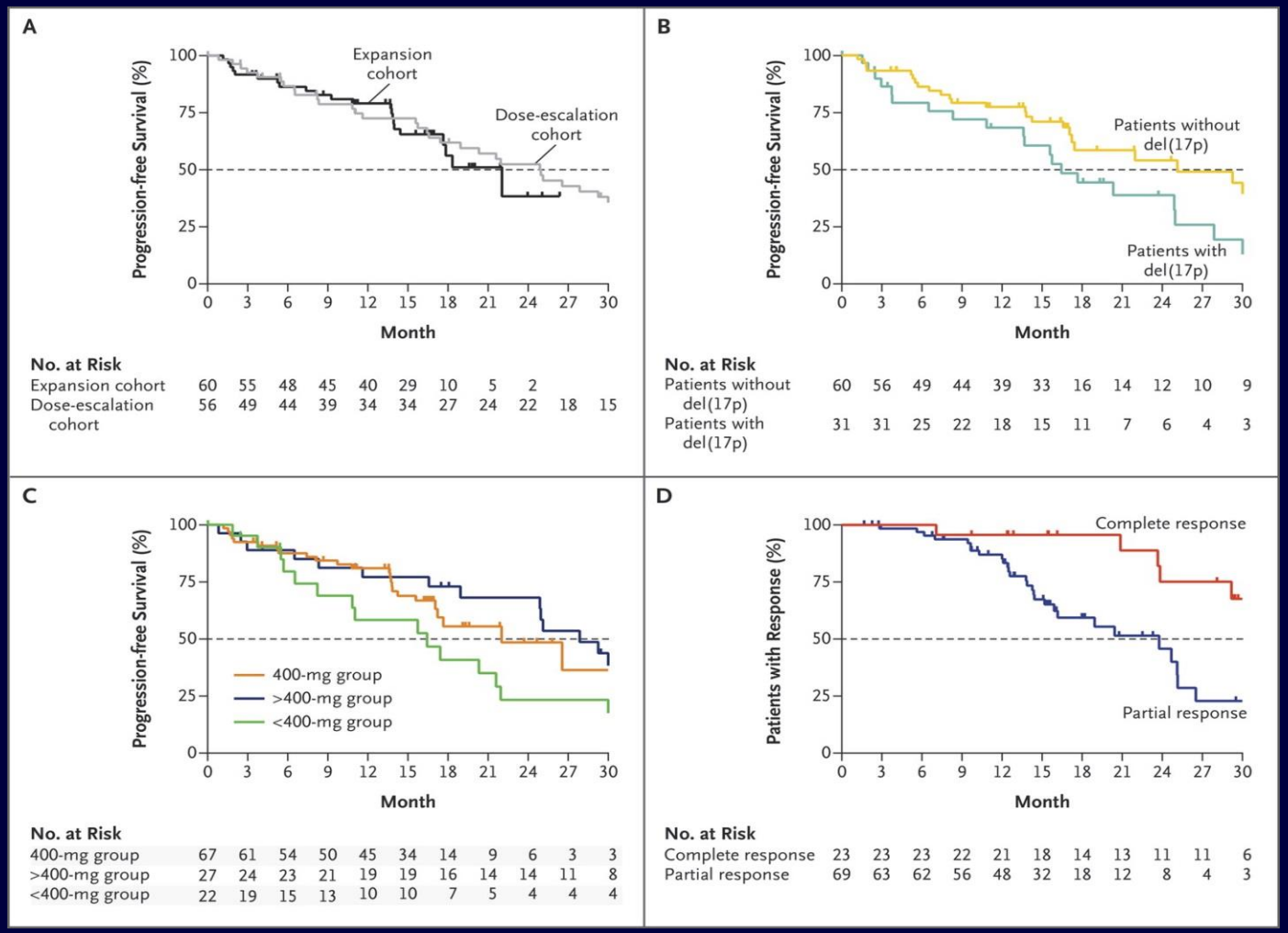
Venetoclax
CRR and ORR Rates by Subgroups

Variable	No.	ORR %	CR %
All patients	116	79	20
17p deletion	31	71	16
Unmutated	46	76	17
Flu - refractory	70	79	16
Prior Rx ≥ 4	56	73	16
Age ≥ 70	34	71	21
Nodes > 5cm	67	78	8

Of 23 CR patients, 17 tested for MRD in BM, 6 (35%) negative

Roberts et al N. Engl J Med 2016; 374; 311-22

PFS by Subgroups; DOR by PR vs CR



Roberts AW et al. N Engl J Med 2016;374:311-322.

Venetoclax Monotherapy for Patients with Chronic Lymphocytic Leukemia (CLL) Who Relapsed After or Were Refractory to Ibrutinib or Idelalisib

Abstract 637

ASH 2016

Jones J, Choi MY, Mato AR, Furman RR, Davids MS, Heffner L, Cheson BD, Lamanna N, Barr PM, Eradat H, Halwani A, Chyla B, Zhu M, Verdugo M, Humerickhouse RA, Potluri J, Wierda WG, Coutre S

Patient Characteristics N=91 (Prior Ibrutinib)

Age (years)	66 (28-81)
No. of prior Rx	4 (1-15)
Time on ibrutinib (mos)	20 (1-61)
Refractory	68%
Prior idelalisib	12%
Unmutated	75%
Del17p	45%
TP53 mutation	33%

Jones J, et al. Lancet Oncol 2018; 19:65-75 .

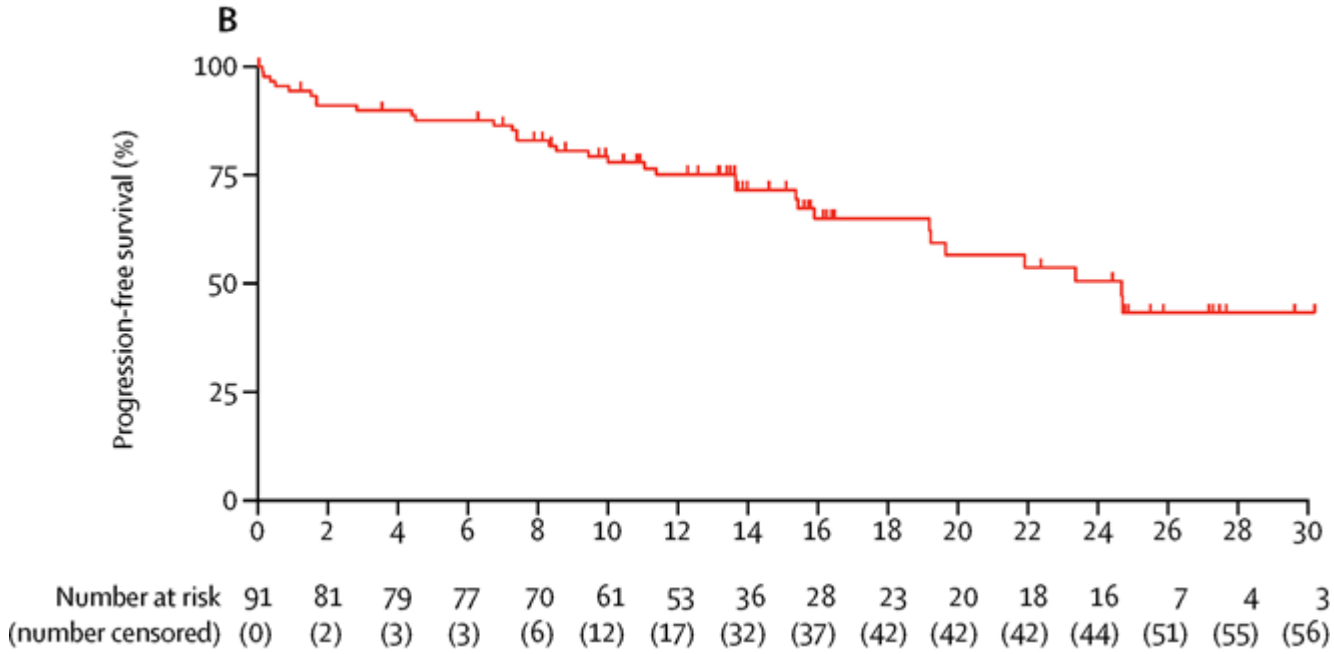
Venetoclax Efficacy (Prior Ibrutinib)

Response	Percent
OR	65
CR/Cri	9
nPR	3
PR	48

Median follow-up: 14 months
Still on venetoclax: 51%

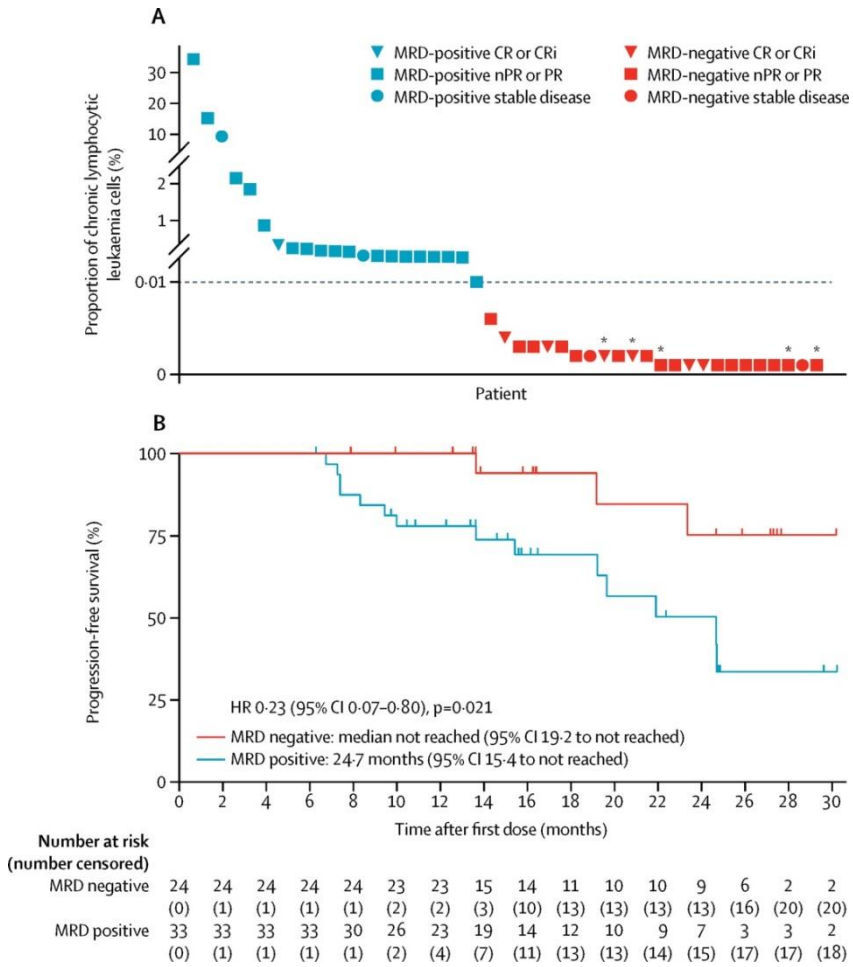
Jones J, et al. Lancet Oncol 2018; 19:65-75 .

Venetoclax Progression Free Survival (Prior Ibrutinib)



Jones et al. Lancet Oncology 2018; 19:65-75.

Venetoclax Minimal Residual Disease Status (Prior Ibrutinib)



Jones et al. Lancet Oncology 2018; 19:65-75.

Venetoclax followed by Ibrutinib

- Six of 8 patients with progressive CLL/SLL on venetoclax were treated with ibrutinib as their first postprogression therapy
- Five achieved a PR
- 3 remain alive on therapy at last follow-up (6, 13, and 16 months)
- 3 died, 2 of toxicity and 1 of PD

Anderson et al. Blood. 2017 June 22;129(25):3362-3370

Venetoclax Plus Rituximab is Superior to Bendamustine Plus Rituximab in Patients with Relapsed / Refractory Chronic Lymphocytic Leukemia – Results from Pre-Planned Interim Analysis of the Randomized Phase 3 MURANO Study

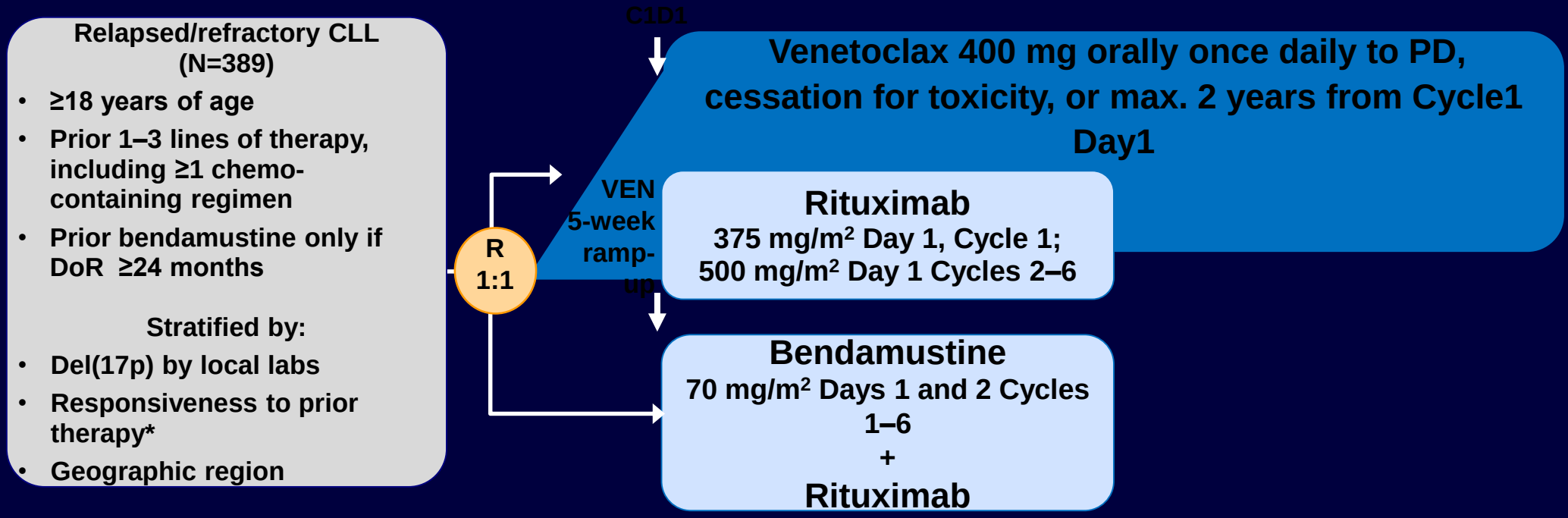
John F. Seymour[1], Thomas Kipps[2], Barbara Eichhorst[3], Peter Hillmen[4], James D'Rozario[5], Sarit Assouline[6], Carolyn Owen[7], John Gerecitano[8], Tadeusz Robak[9], Javier De la Serna[10], Ulrich Jaeger[11], Guillaume Cartron[12], Marco Montillo[13], Rod Humerickhouse[14], Elizabeth A. Punnoose[15], Yan Li[15], Michelle Boyer[16], Kathryn Humphrey[16], Mehrdad Mobasher[15], Arnon P. Kater[17]

[1]Peter MaCallum Cancer Centre, Royal Melbourne Hospital, and University of Melbourne, Australia; [2]University of California School of Medicine, San Diego, CA, USA; [3]Bonn University Hospital Cologne, Germany; [4]St. James University Hospital, Leeds, UK; [5]The John Curtin School of Medical Research, Australian National University, Canberra, Australia; [6]Segal Cancer Center, Lady Davis Institute, Jewish General Hospital, Montreal, QC, Canada; [7]Departments of Medicine and Oncology, University of Calgary, Alberta, Canada; [8]Memorial Sloan Kettering Cancer Center, New York City, NY; [9]Department of Hematology, Medical University of Lodz and Copernicus Memorial Hospital, Lodz, Poland; [10]Hospital Universitario 12 de Octubre, Madrid Spain; [11]Medical University of Vienna, Dept. of Medicine I, Division of Hematology and Hemostaseology, Vienna, Austria; [12]Department of Hematology CHU Montpellier, France; [13]Department of Onco-Hematology, Division of Hematology, Niguarda Ca' Granda Hospital, Milan, Italy; [14]AbbVie, Inc., Chicago, IL; [15]Genentech, Inc, South San Francisco, CA; [16]F. Hoffmann-La Roche, Ltd. Welwyn Garden City, United Kingdom; [17]Academic Medical Center, HOVON CLL working group, Amsterdam, The Netherlands.

The American Society of Hematology – 59th Annual Meeting and Exposition
Atlanta, Georgia ● December 9–12, 2017

Seymour et al. N Engl J Med 2018 Mar 22; 378(12):1107-1120

MURANO Study Design

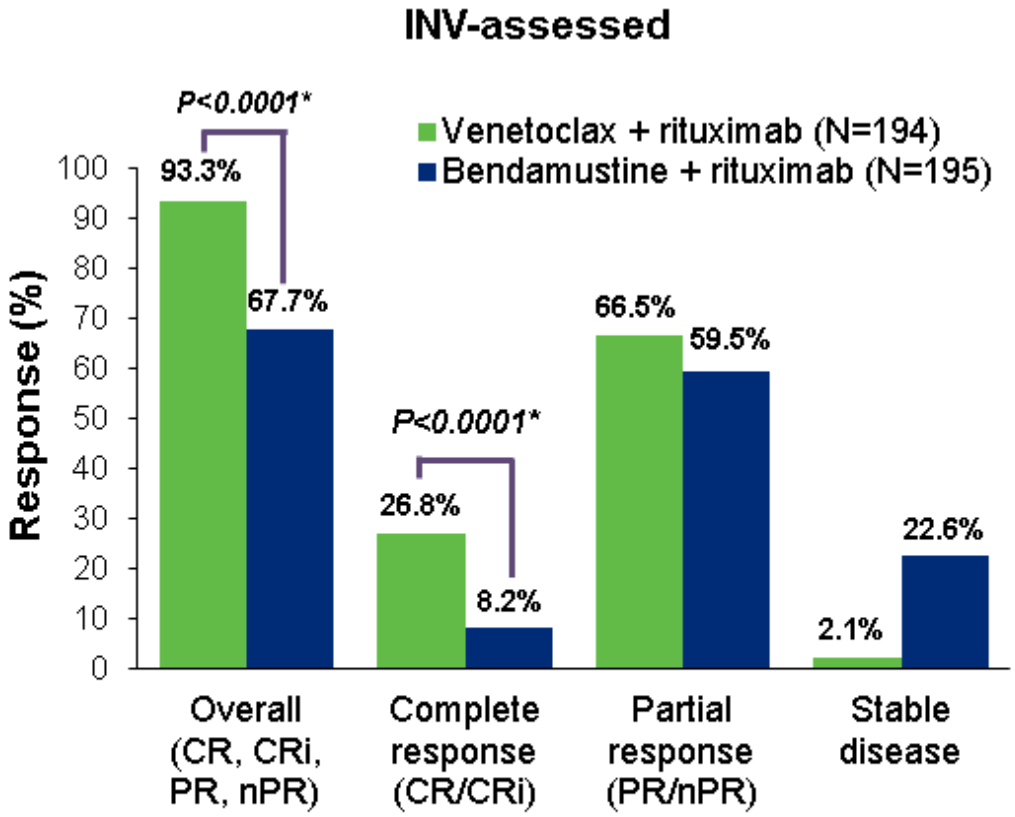


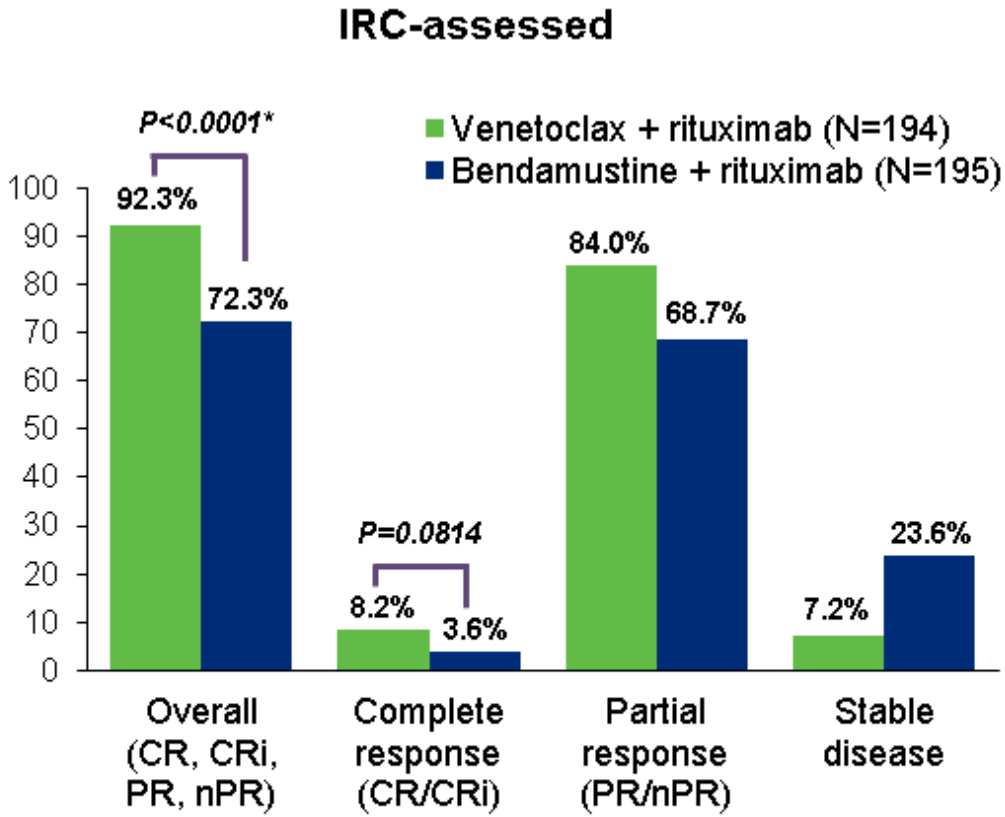
Primary Endpoint	INV-assessed PFS
Major Secondary Endpoints	• IRC-CR ⇒ IRC-ORR ⇒ OS (hierarchical testing) • IRC-assessed PFS and MRD-negativity
Key Safety Endpoints	Overall safety profile, focusing on serious adverse events and Grade ≥3 adverse events
Interim Analysis	Approximately 140 INV-assessed PFS events (75% of total information)

NCT02005471

*High-risk CLL – any of following features: del(17p) or no response to front-line chemotherapy-containing regimen or relapsed ≤12 months after chemotherapy or within ≤24 months after chemoimmunotherapy.

Improved Response Rates for VenR vs. BR





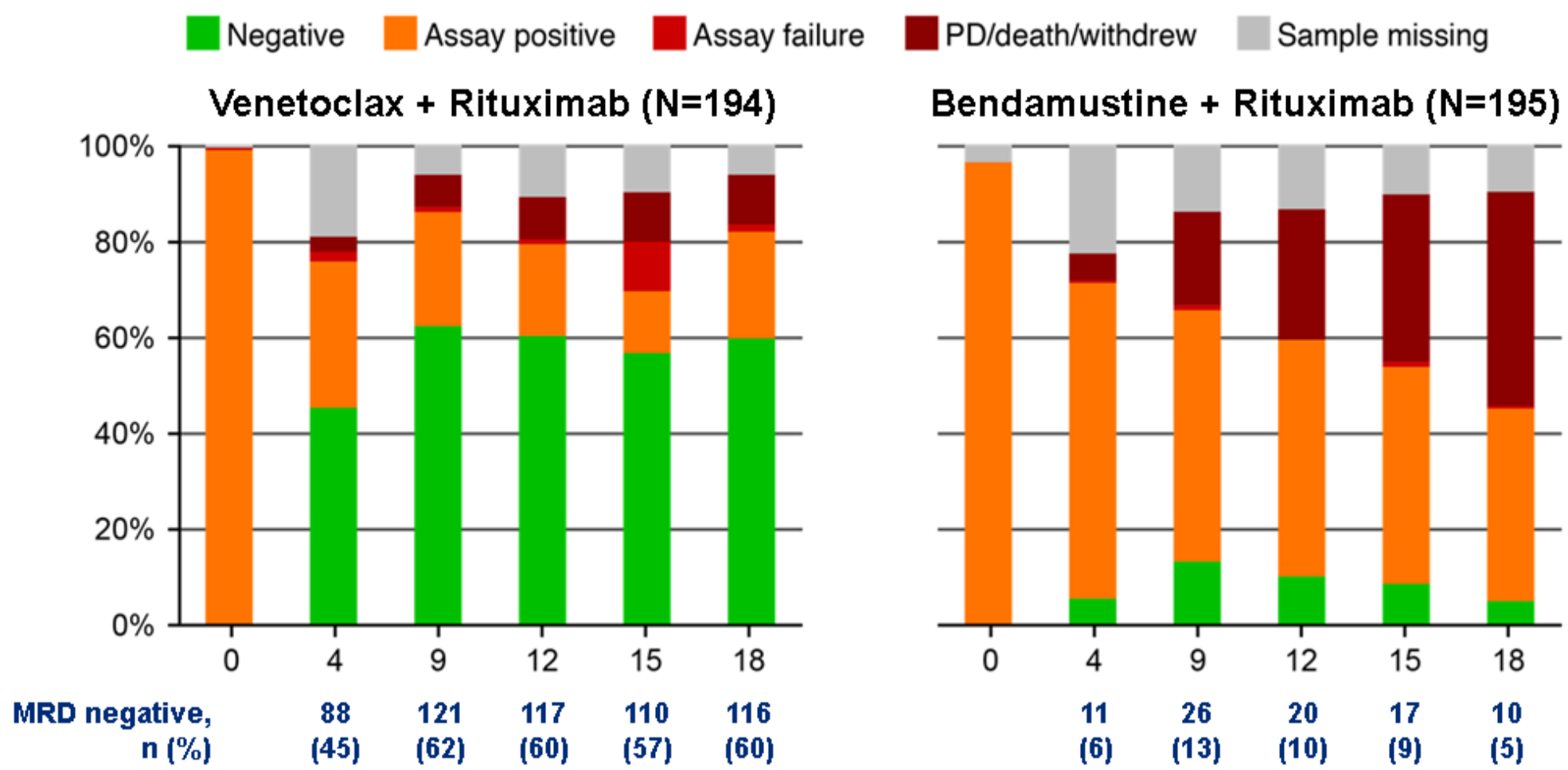
Of 42 INV-assessed CRs discrepant in VenR arm, 28 due to residual CT scan nodes 16–30 mm diameter; 88% of these were PB MRD negative

* Descriptive P-values.

As of 8 May 2017

Seymour et al. N Engl J Med 2018 Mar 22; 378(12):1107-1120

High Peripheral Blood MRD Negativity Rate Maintained Over Time for VenR vs. BR



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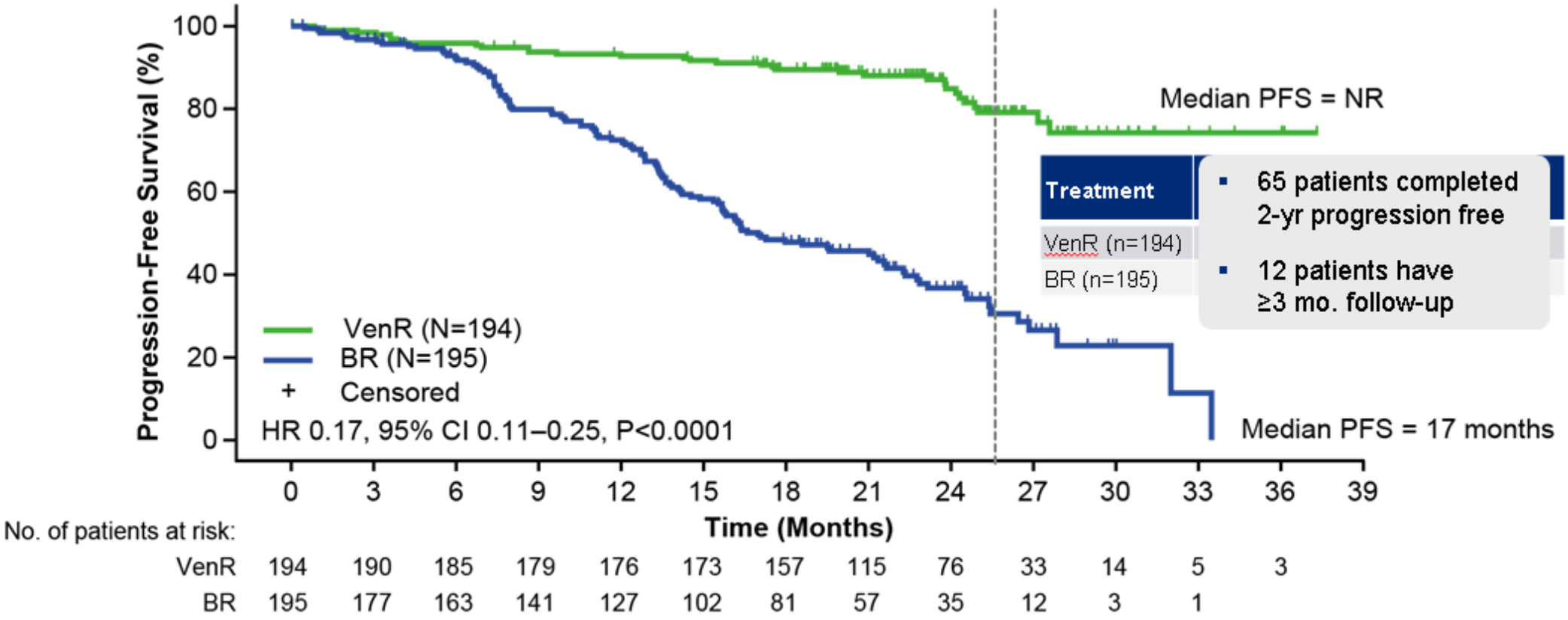
Investigator-Assessed PFS Superior for VenR vs. BR



- Median (range) duration of follow-up, 23.8 (0.0–37.4) months:
- Venetoclax + rituximab, 24.8 months; bendamustine + rituximab, 22.1 months

As of 8 May 2017

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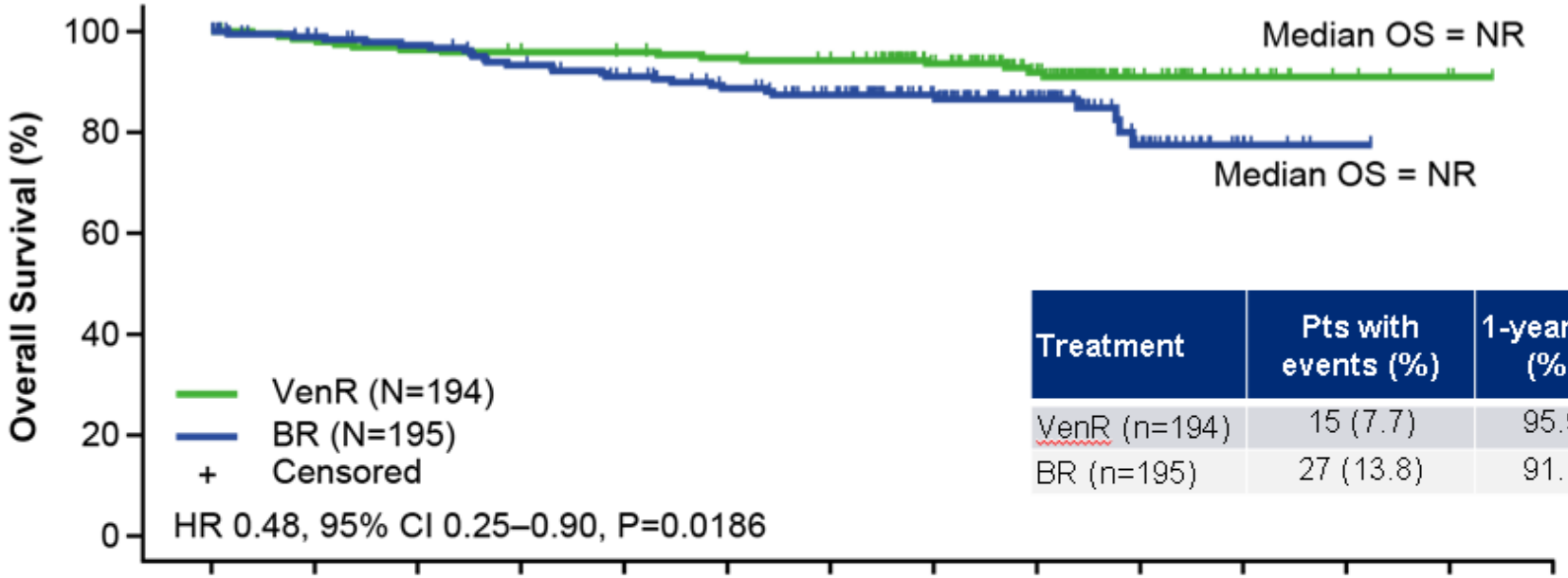
Clinically Meaningful Improvement in Overall Survival for VenR vs. BR



Treatment	Pts with events (%)	1-year OS (%)	2-year OS (%)
VenR (n=194)	15 (7.7)	95.9	91.9
BR (n=195)	27 (13.8)	91.1	86.6

No. of patients at risk:

VenR	194	190	185	183	181	178	175	142	102	36	15	5	3
BR	195	181	175	166	158	146	134	102	66	29	8	2	

Descriptive p-values
Pre-specified boundary, P=0.0001.

As of 8 May 2017

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Conclusions

- IGHV mutation status important for deciding treatment
- Ibrutinib appears more effective than CIT as initial therapy in patients with CLL
- Patients with mutated IGHV gene have very long term remissions with FCR – cure?
- Venetoclax is excellent salvage treatment for patients relapsing on ibrutinib
- Venetoclax and rituximab produces high rates of MRD negativity and prolonged PFS
- VenR or ibrutinib first?