INSTITUTE OF APPLIED BIOSCIENCES
ΙΝΣΤΙΤΟΥΤΟ ΕΦΑΡΜΟΣΜΕΝΩΝ ΒΙΟΕΠΙΣΤΗΜΩΝ
CERTH

Realizing Precision Medicine in CLL

facts, challenges and considerations

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Disclosures

Honoraria	Janssen, Gilead, Novartis, Abbvie
Scientific Advisory Board	Janssen, Gilead
Research funding	Janssen, Gilead, Abbvie

CLL treatment evolution

1960 – 2013
only 5 drugs

CLL treatment evolution

1960 – 2013
only 5 drugs

2014 – 2019
many new options

drastic changes in the overall treatment strategy

CLL treatment in 2019 – considerations

age and physical status

patient preferences

biological background

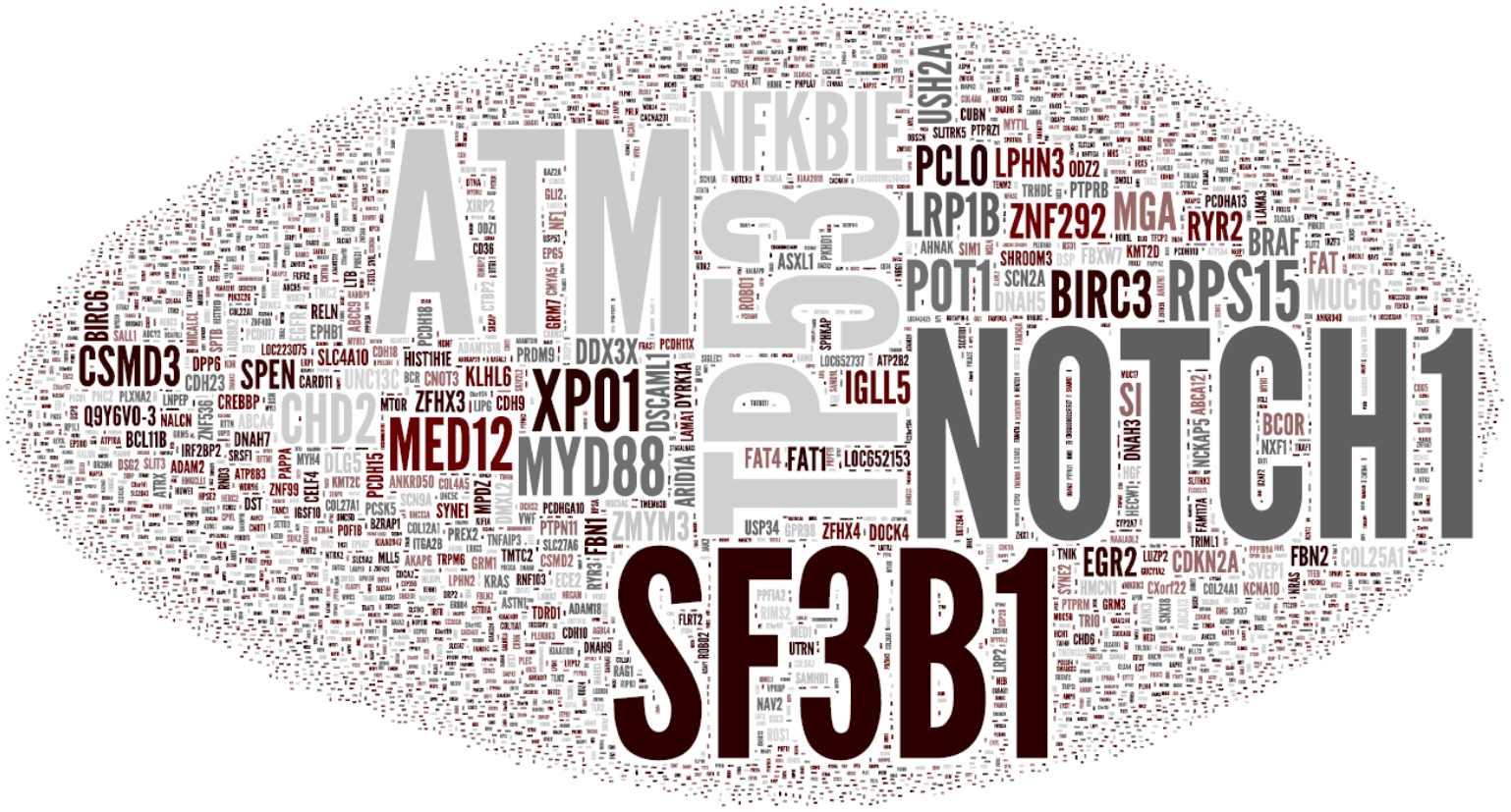
blood®
Prepublished online March 14, 2018;
doi:10.1182/blood-2017-09-806398

Guidelines for diagnosis, indications for treatment, response assessment and supportive management of chronic lymphocytic leukemia

Michael Hallek, Bruce D. Cheson, Daniel Catovsky, Federico Caligaris-Cappio, Guillermo Dighiero, Hartmut Döhner, Peter Hillmen, Michael Keating, Emili Montserrat, Nicholas Chiorazzi, Stephan Stilgenbauer, Kanti R. Rai, John C. Byrd, Barbara Eichhorst, Susan O'Brien, Tadeusz Robak, John F. Seymour and Thomas J. Kipps

	General practice	Clinical trial
FISH for del(13q), del(11q), del(17p), add(12)	Always	Always
TP53 mutations	Always	Always
IG genes	Always	Always

it’s not only about *TP53*

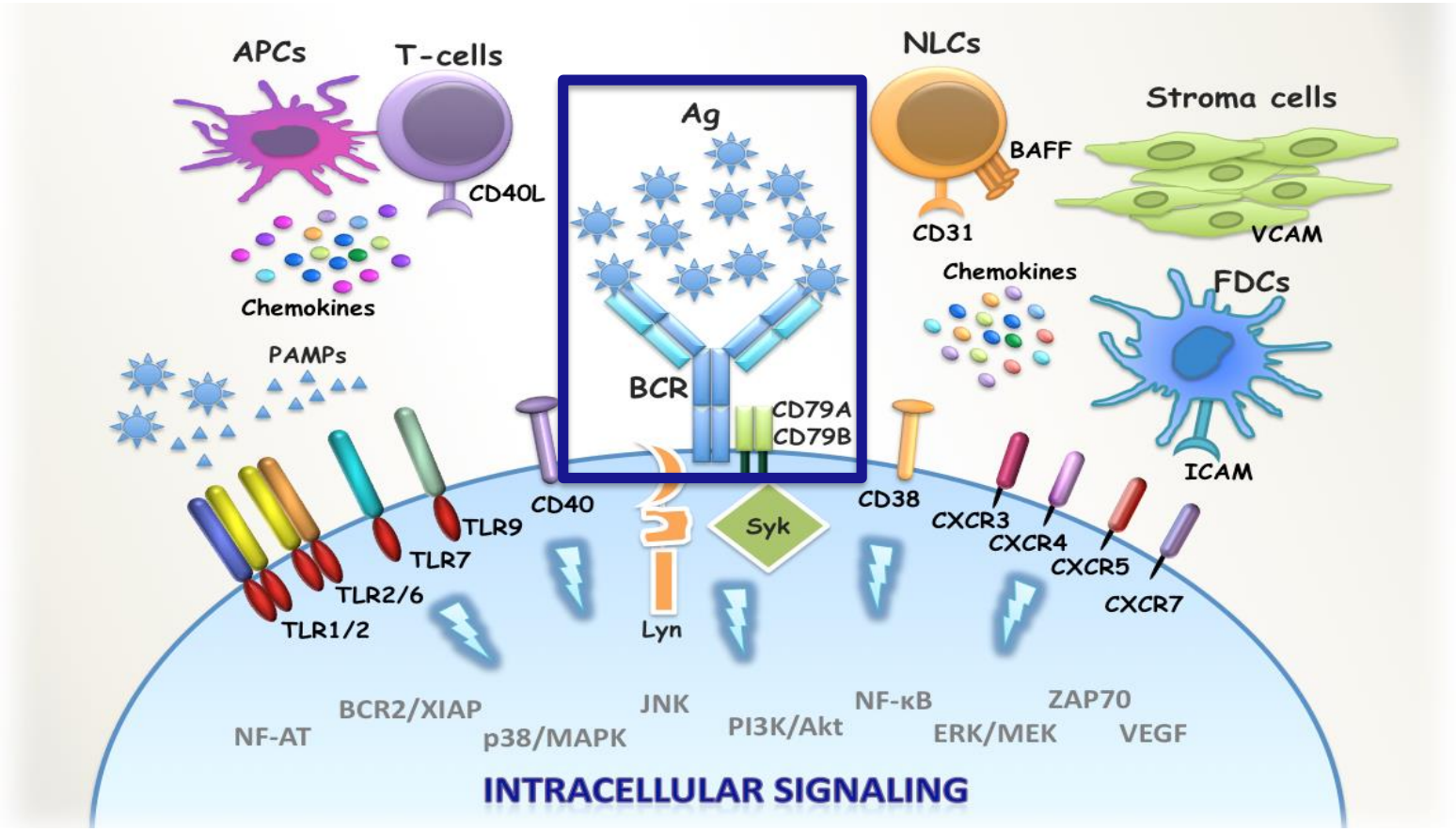


the genomic background of CLL is heterogeneous

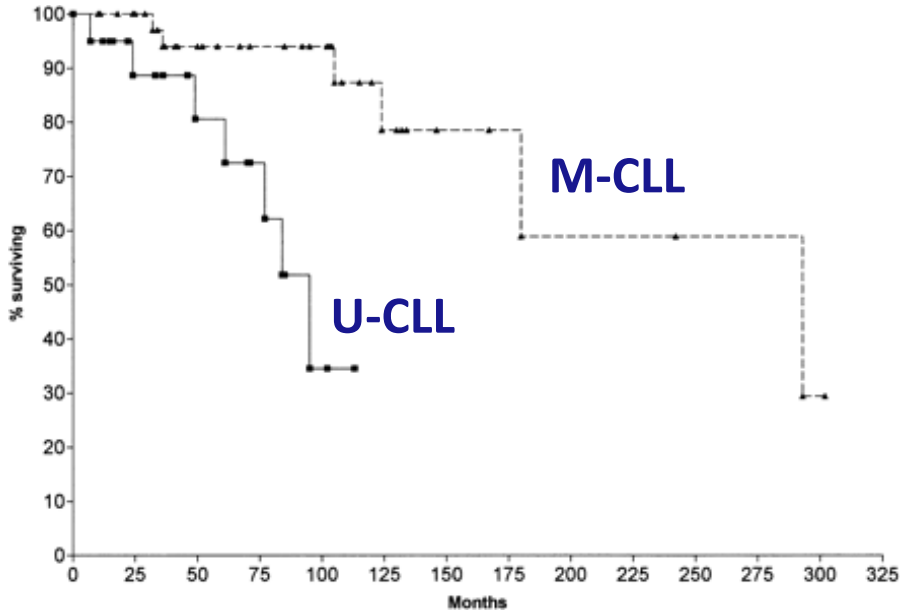
no single lesion accounts for more than 10-15% of cases

B cell receptor immunoglobulin

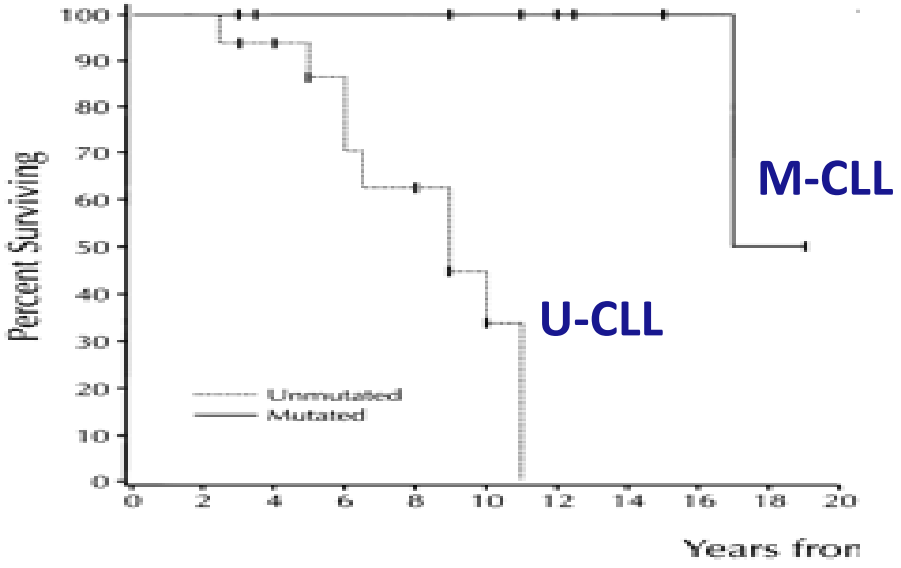
a unique biomarker for ***all CLL***



CLL - better with mutated IG receptors



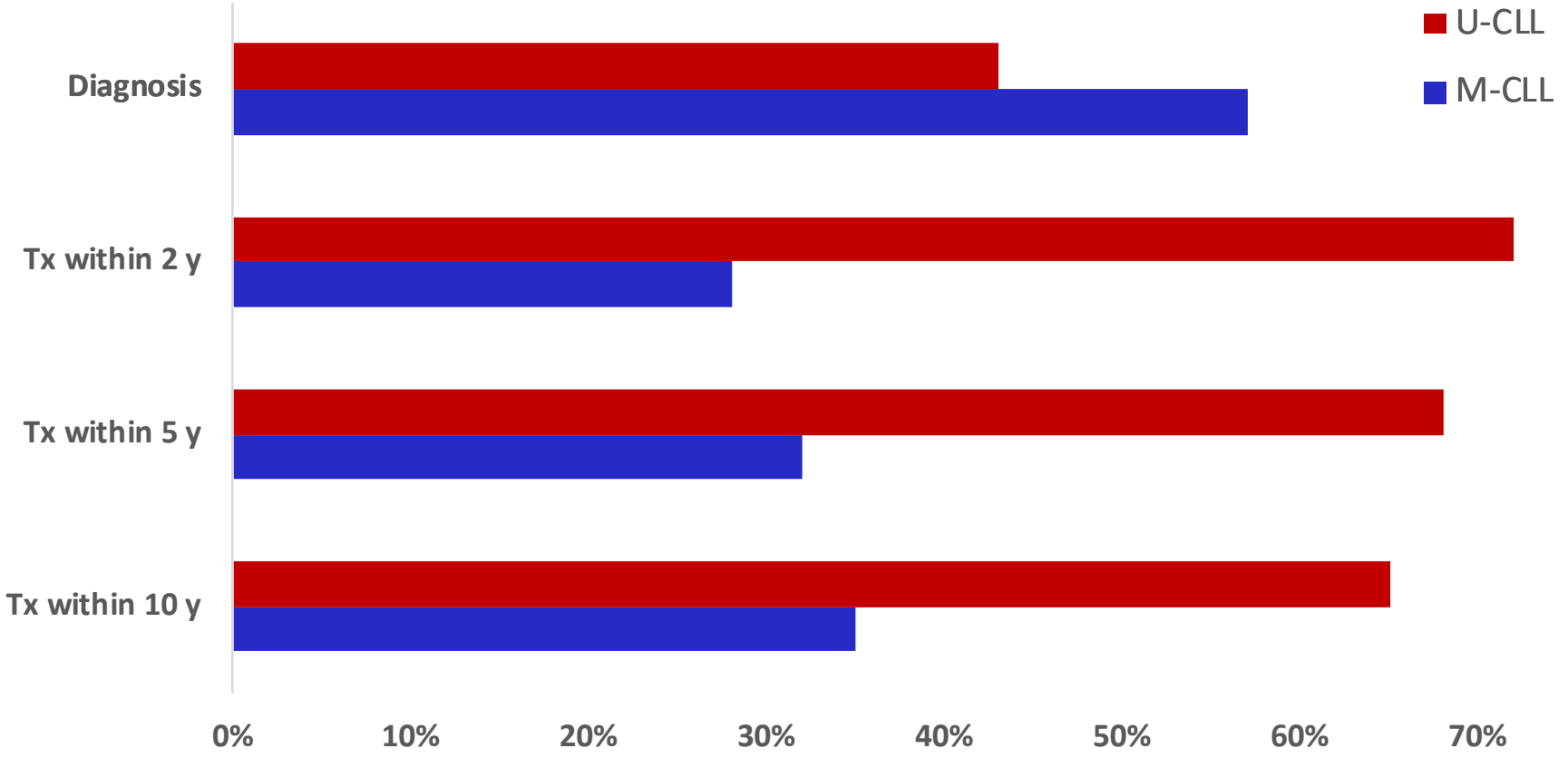
Hamblin et al. Blood 1999;94:1848-54



Damle et al. Blood 1999; 94:1840-7

U-CLL: unmutated IG; M-CLL: mutated IG

U-CLL vs M-CLL
let's see what happens



U-CLL: unmutated IG; M-CLL: mutated IG

Agathangelidis et al. Blood 2012; 119(19):4467-75
Baliakas et al. Lancet Haematol 2014 ;1(2):e74-84

BcR IG
the ultimate driver in CLL

CLL treatment in 2019

facts and considerations

frontline paradigms

chemoimmunotherapy

biological agents

only a **minority** of CLL patients are eligible for intensive chemoimmunotherapy

10-12% of the annual symptomatic population of CLL patients are del17p/*TP53* mutated

no place for chemoimmunotherapy

Jeyakumaran D, et al. Value Health 19:A574-A5

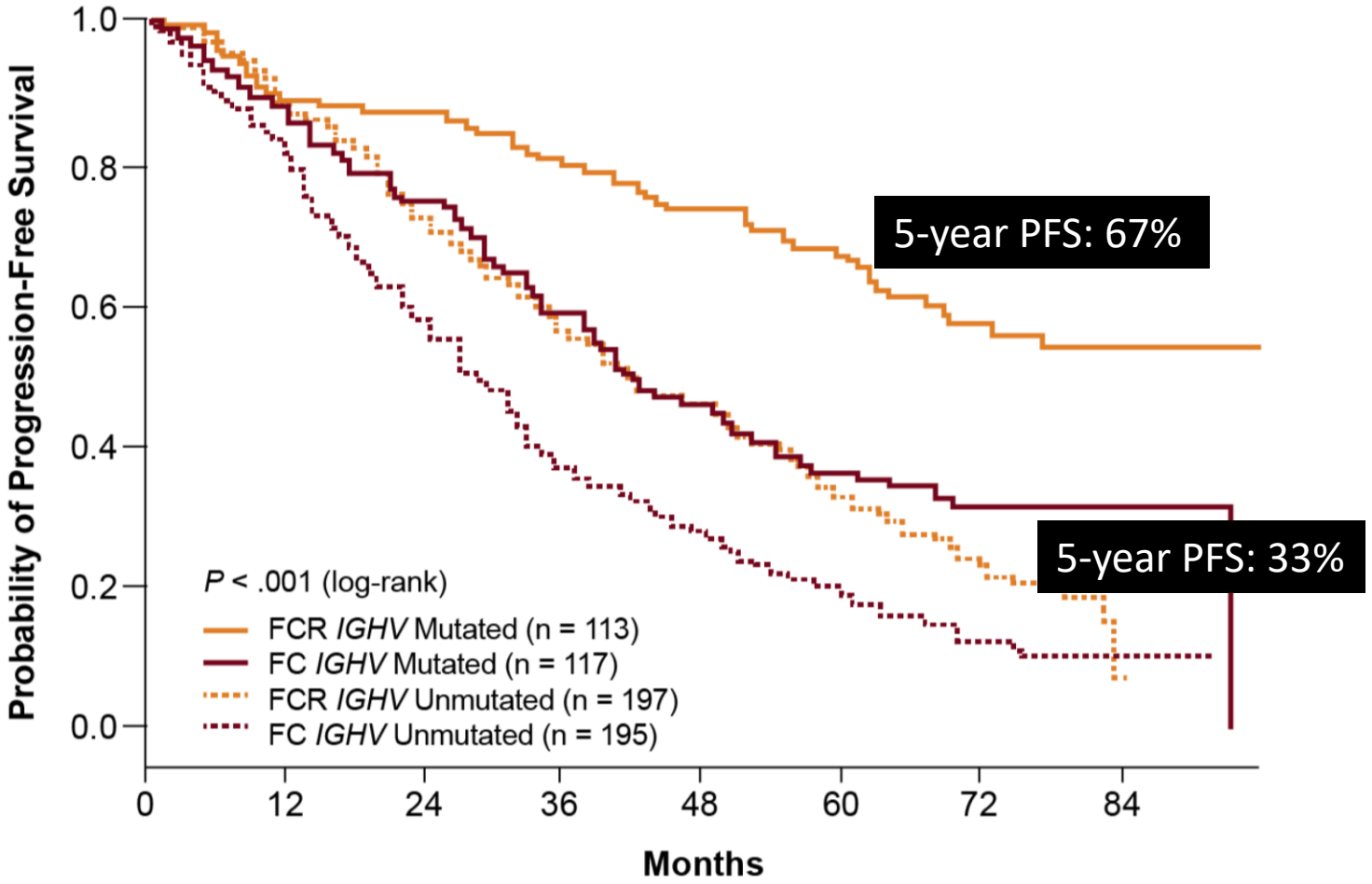
60% of the annual symptomatic population of CLL patients in the EU are considered elderly or younger with a major comorbidity

no place for chemoimmunotherapy

Jeyakumaran D, et al. Value Health 19:A574-A5

TP53 wildtype CLL fit patients

FCR: maximum benefit for IG-mutated
FCR: limited benefit for IG-unmutated



Fischer et al. Blood 2016;127:208-15.

FCR is a valid option for a **small minority** of fit CLL patients with low risk disease

First-line CIT options for unfit patients

Study	Regimen	Median PFS (months)
Hillmen P et al, Lancet, 2015 Phase III	Ofatumumab- Chlorambucil	22.4
Goede V et al, NEJM, 2014 Phase III	Rituximab-Chlorambucil	16.3
	Obinutuzumab-Chlorambucil	26.7

not optimal

frontline paradigms in 2019

biological agents

ibrutinib

venetoclax

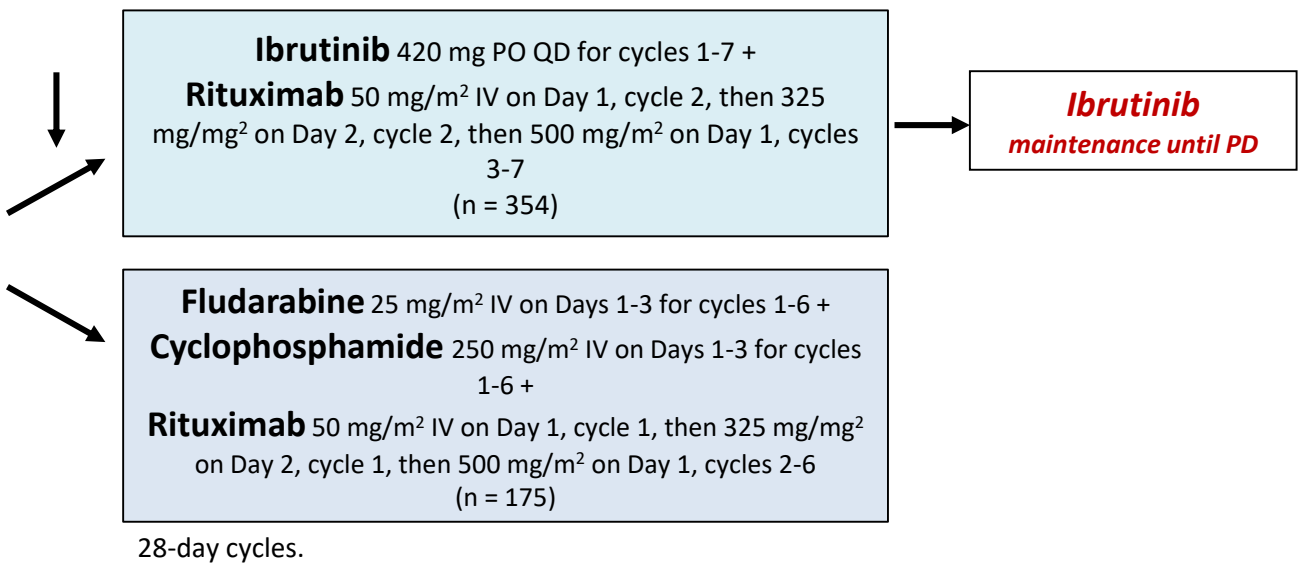
E1912: ECOG-E1912

ibrutinib plus rituximab versus FCR in patients with untreated CLL aged 70 years or younger

E1912: ECOG-E1912 | study design

Stratified by age (< vs ≥ 60 yrs), ECOG PS (0/1 vs 2), stage (III-IV vs I-II), del(11q22.3) vs other

Patients with **previously untreated CLL** requiring treatment per IWCLL 2008, aged ≤ 70 yrs, ECOG PS 0-2, CrCl > 40 mL/min, ability to tolerate FCR, **no del(17p) by FISH** (N = 529)



28-day cycles.

Primary endpoint: PFS

Secondary endpoints: OS, safety

Shanafelt. ASH 2018. Abstr LBA-4.

PFS significantly prolonged with ibrutinib + R vs FCR

PFS Outcome	ITT Population		Eligible Population	
	Ibrutinib + R	FCR	Ibrutinib + R	FCR
No. events/cases	37/354	40/175	33/332	39/166
HR (95% CI)	0.35 (0.22-0.50)		0.32 (0.20-0.51)	
1-sided P value	**< .00001**		**< .00001**	

Shanafelt. ASH 2018. Abstr LBA-4.

Significant PFS benefit with ibrutinib + R vs FCR in U-CLL, trend toward PFS improvement in M-CLL

PFS Outcome by IGHV Status	U-CLL		M-CLL	
	Ibrutinib + R	FCR	Ibrutinib + R	FCR
No. events/cases	20/210	21/71	8/70	6/44
HR (95% CI)	0.26 (0.14-0.50)		0.44 (0.14-1.36)	
1-sided P value	**< .00001**		.07	

U-CLL: unmutated IGHV genes | M-CLL: mutated IGHV genes

Shanafelt. ASH 2018. Abstr LBA-4.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL

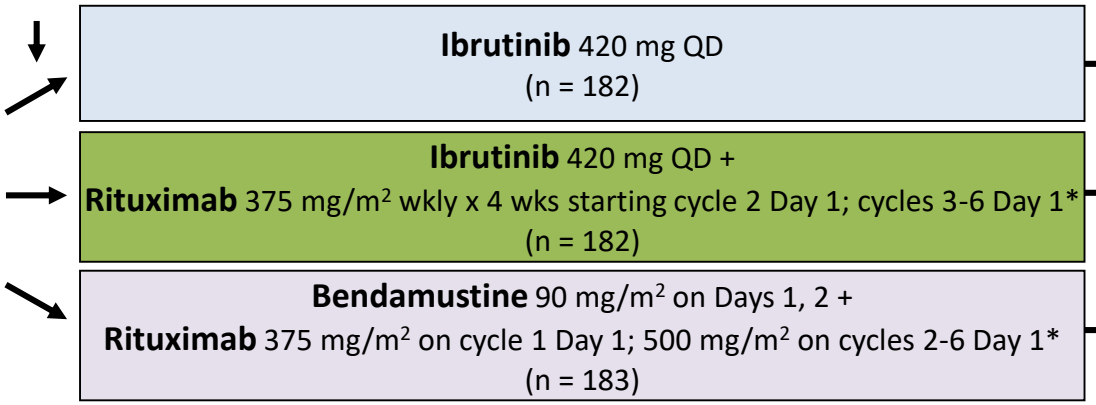
J.A. Woyach, A.S. Ruppert, N.A. Heerema, W. Zhao, A.M. Booth, W. Ding, N.L. Bartlett, D.M. Brander, P.M. Barr, K.A. Rogers, S.A. Parikh, S. Coutre, A. Hurria,* J.R. Brown, G. Lozanski, J.S. Blachly, H.G. Ozer, B. Major-Elechi, B. Fruth, S. Nattam, R.A. Larson, H. Erba, M. Litzow, C. Owen, C. Kuzma, J.S. Abramson, R.F. Little, S.E. Smith, R.M. Stone, S.J. Mandrekar, and J.C. Byrd

ALLIANCE A041202: Study Design

Multicenter, randomized, double-blind phase III study (data cutoff: October 4, 2018)

Stratified by Rai stage (high vs intermediate risk), del(11q22.3) or del(17p13.1) (presence vs absence), ZAP-70 methylation (< vs ≥ 20%)

Untreated patients with CLL meeting IWCLL 2008 criteria for tx initiation; **aged ≥ 65 yrs**; EGOG PS 0-2; ANC ≥ 1000 unless due to BM involvement; PLT ≥ 30; $CrCl_{CG}$ ≥ 40; AST/ALT ≤ 2.5 x ULN; no heparin or warfarin
(N = 547)

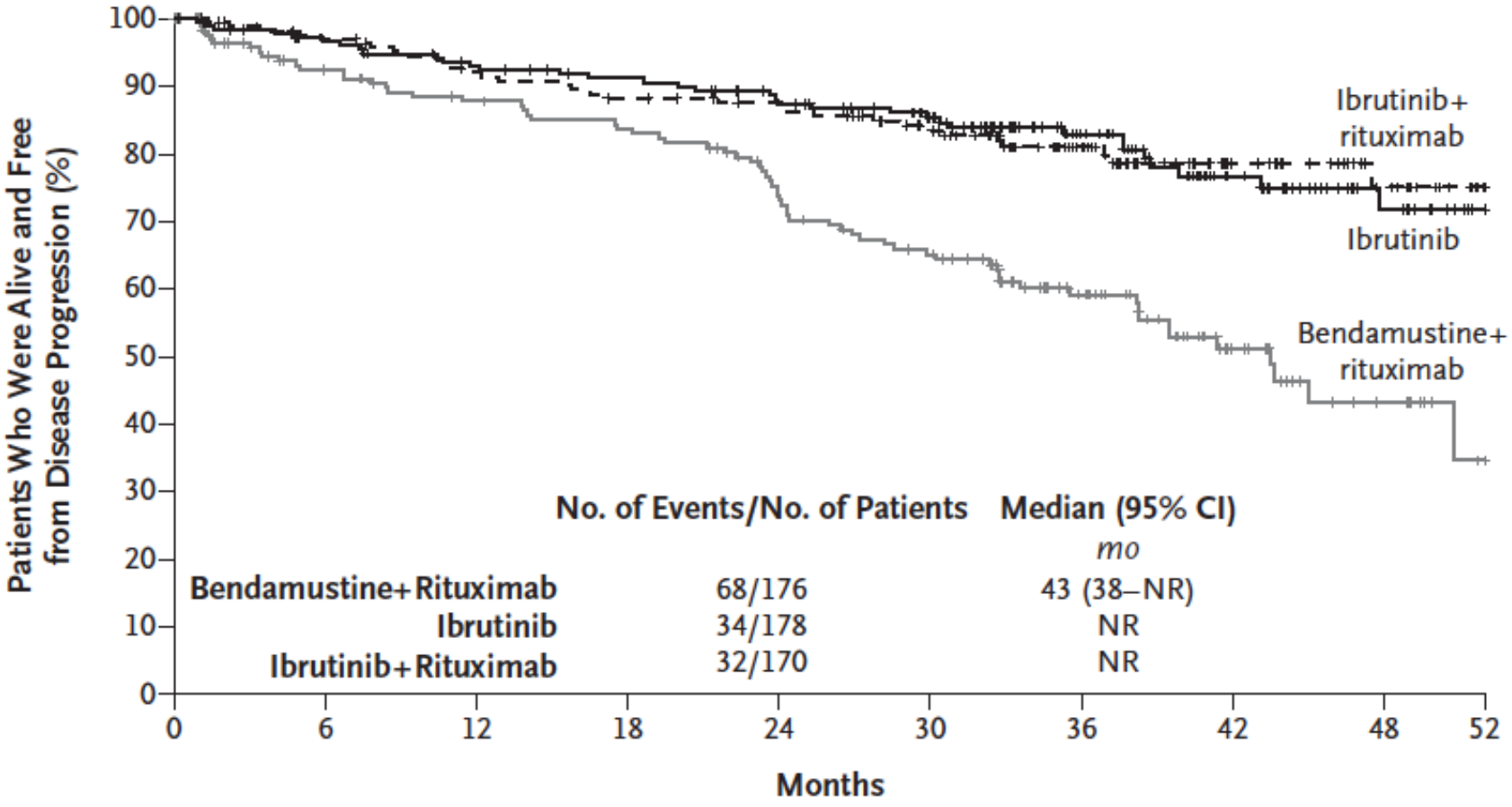


*28-day cycles.

Primary endpoint: PFS

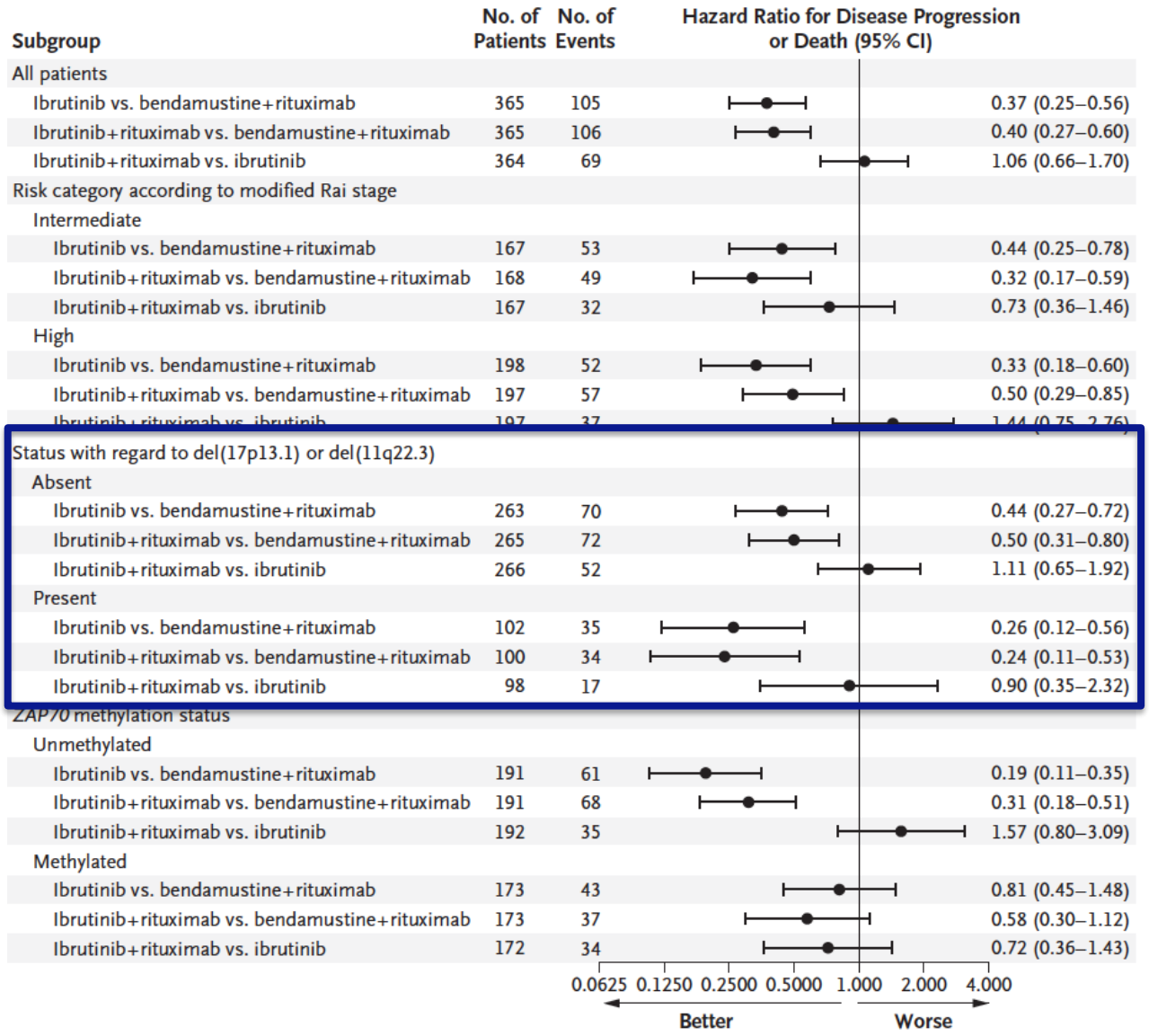
Woyach. NEJM. 2018

PFS significantly better for ibrutinib vs BR and ibrutinib + R vs BR
no difference for ibrutinib + R vs ibrutinib



Woyach. NEJM. 2018

PFS significantly better for ibrutinib vs BR and ibrutinib + R vs BR no difference for ibrutinib + R vs ibrutinib



Woyach. NEJM. 2018

ibrutinib

venetoclax

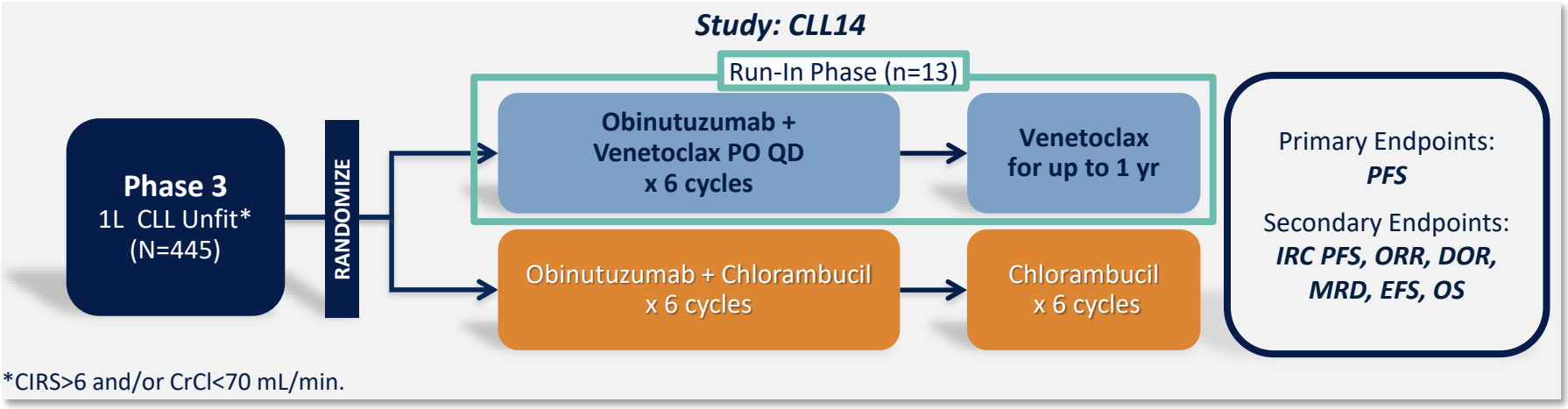
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Venetoclax and Obinutuzumab in Patients with CLL and Coexisting Conditions

K. Fischer, O. Al-Sawaf, J. Bahlo, A.-M. Fink, M. Tandon, M. Dixon, S. Robrecht, S. Warburton, K. Humphrey, O. Samoylova, A.M. Liberati, J. Pinilla-Ibarz, S. Opat, L. Sivcheva, K. Le Dû, L.M. Fogliatto, C.U. Niemann, R. Weinkove, S. Robinson, T.J. Kipps, S. Boettcher, E. Tausch, R. Humerickhouse, B. Eichhorst, C.-M. Wendtner, A.W. Langerak, K.-A. Kreuzer, M. Ritgen, V. Goede, S. Stilgenbauer, M. Mobasher, and M. Hallek

CLL14 – study design



Treatment Schedule	
Obinutuzumab (IV)	
Cycle 1:	100 mg D1; 900 mg D2; 1000 mg D8/D15
Cycles 2-6:	1000 mg D1
Venetoclax‡ (PO)	
Cycle 1:	20 mg QD D22-28
Cycle 2:	50 mg QD D1-7; 100 mg QD D8-14; 200 mg QD D15-21; 400 mg QD D22-28
Cycles 3-12:	400 mg QD D1-28

‡Venetoclax ramp-up during course 1 and 2.

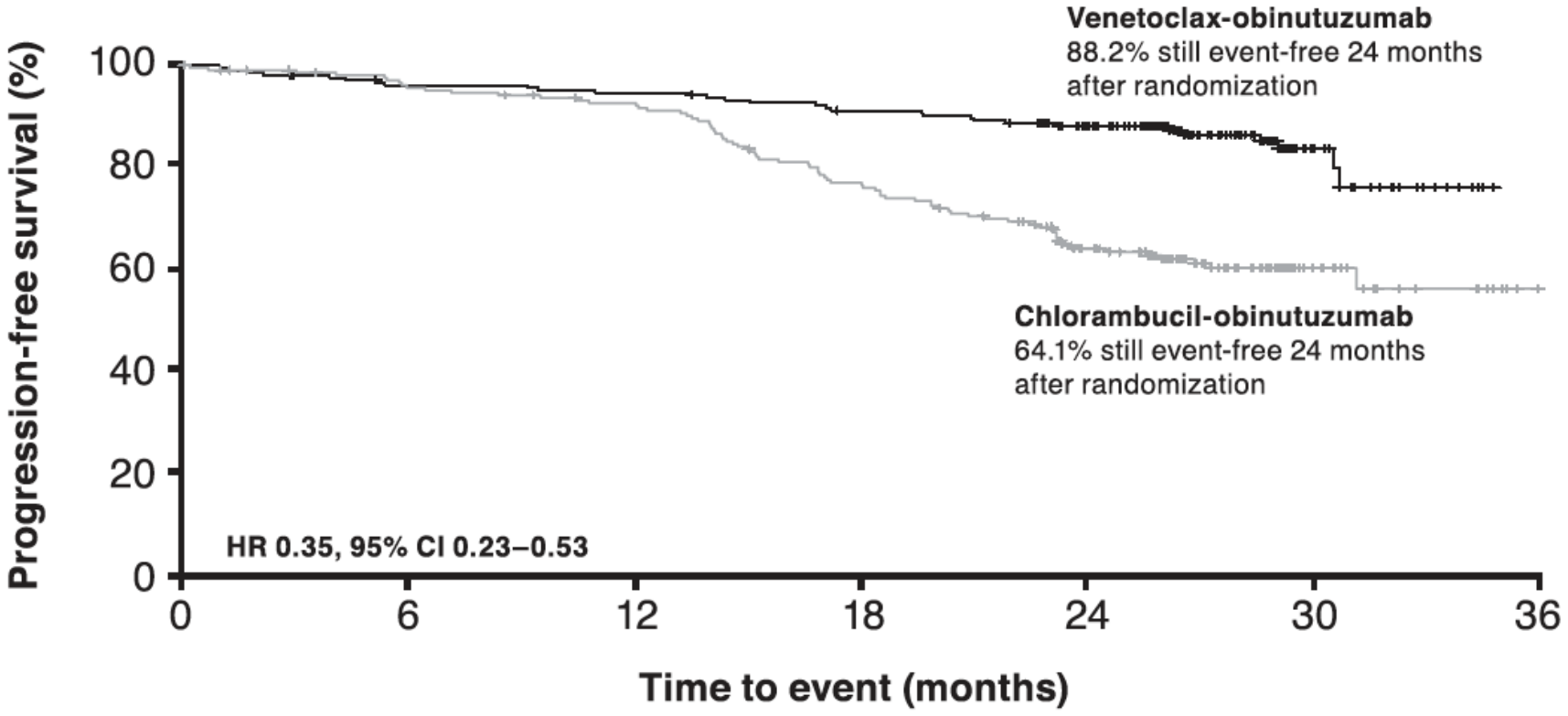
Fixed-duration **Ven+G** induced **deep** **MRD-negativity** **rates** in previously untreated pts with CLL and comorbidities

All pts (ITT) N	ClbG 216	VenG 216
MRD level, n (%)		
$<10^{-6}$	9 (4.2)	67 (31.0)
$\geq 10^{-6}$ and $<10^{-5}$	33 (15.3)	75 (34.7)
$\geq 10^{-5}$ and $<10^{-4}$	32 (14.8)	26 (12.0)
$\geq 10^{-4}$ and $<10^{-2}$	50 (23.1)	13 (6.0)
$\geq 10^{-2}$	62 (28.7)	10 (4.6)
No sample/not evaluable	30 (13.9)	25 (11.6)

MRD assessment: ASO-PCR, NGS

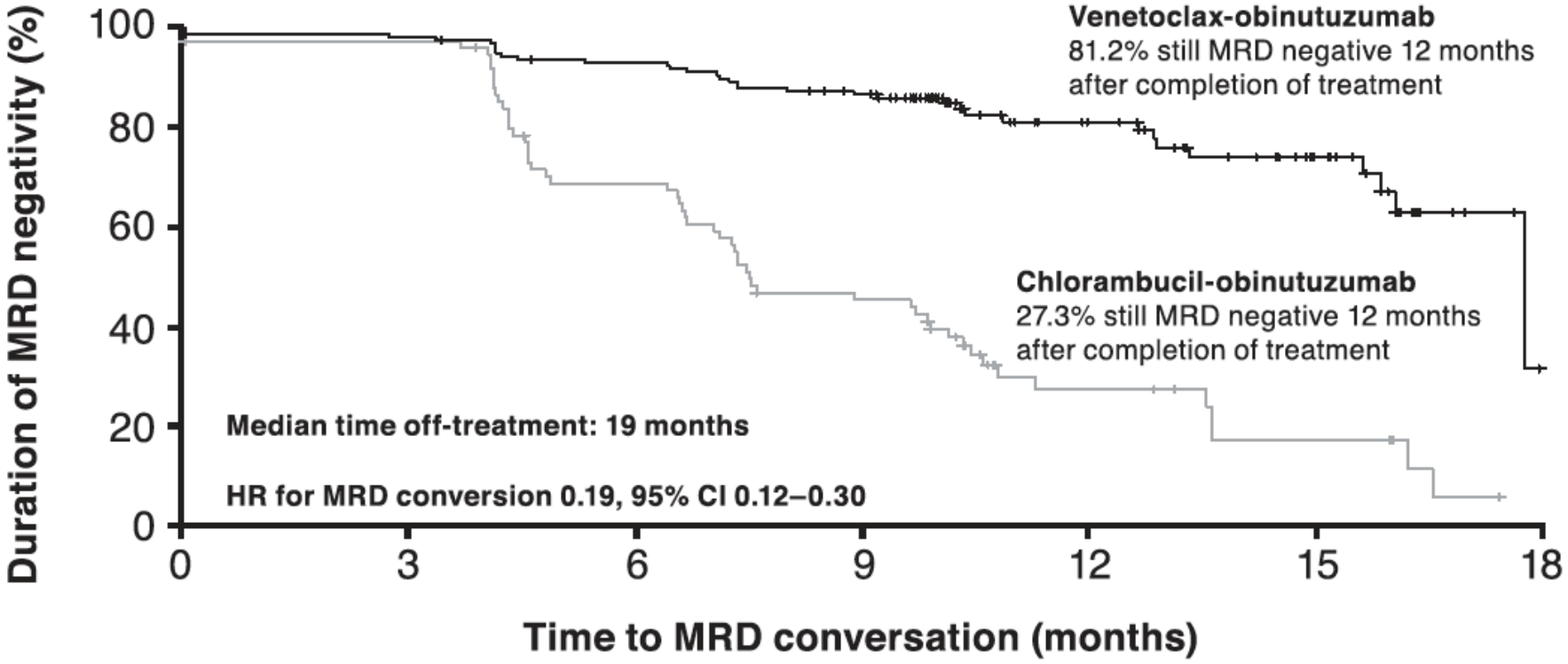
Fischer K, et al. ICML 2019

Fixed-duration **Ven+G** induced **high** **MRD-negativity** **rates** in previously untreated pts with CLL and comorbidities



Fischer K, et al. ICML 2019

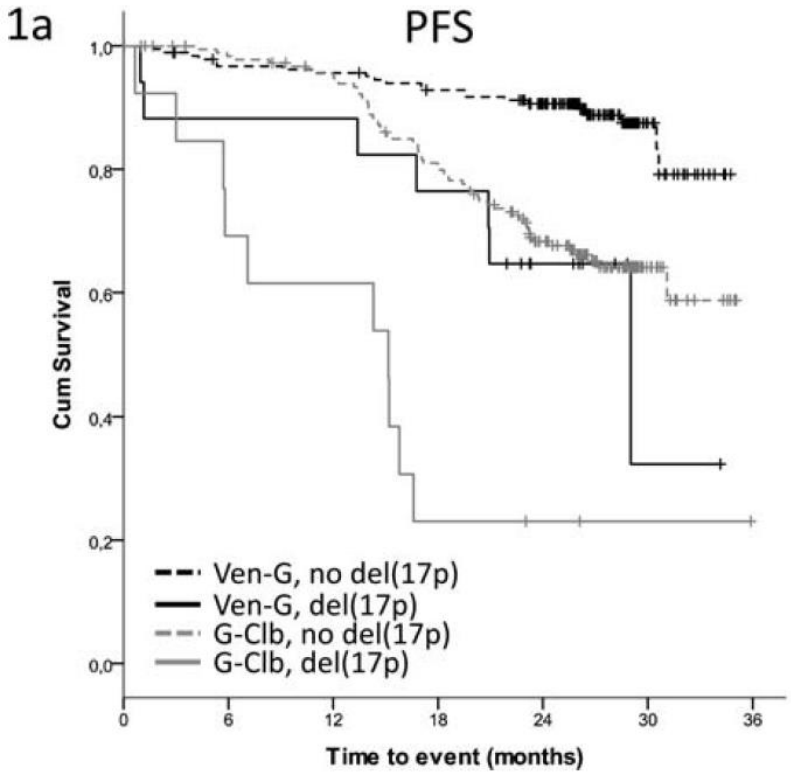
Fixed-duration **Ven+G** induced **long-lasting** **MRD-negativity** **rates** in previously untreated pts with CLL and comorbidities

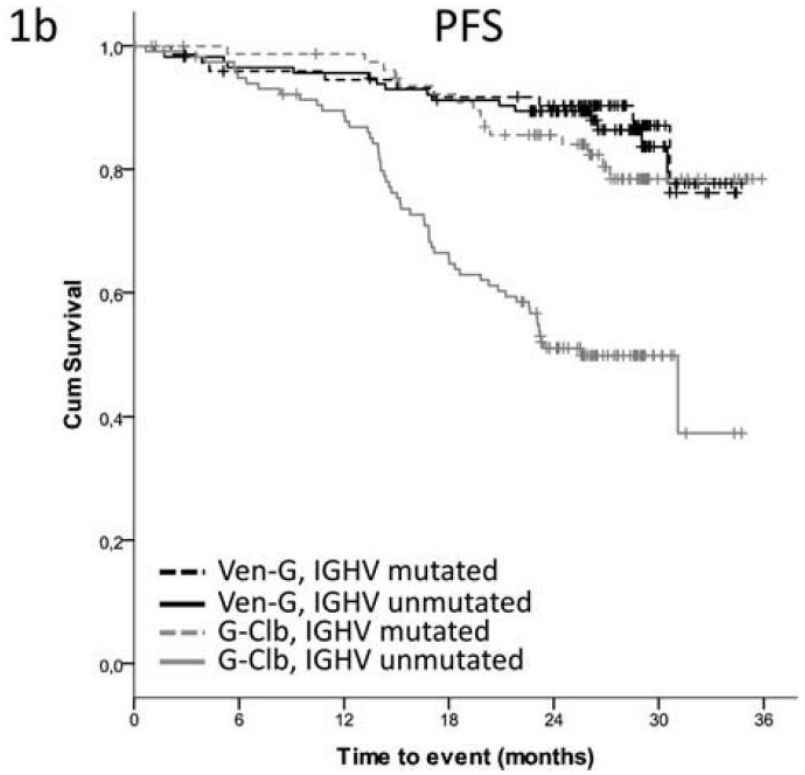


Fischer K, et al. ICML 2019

Ven+G

only TP53 aberrations are adverse
IGHV-unmutated experience particular benefit





Tausch E et al. ICML 2019

a bright future for CLL

CLL treatment in 2019 – facts and goals

targeted agents, particularly ibrutinib and venetoclax, have improved our therapeutic armamentarium in a very impressive way

complete eradication of CLL is an obvious and desired endpoint

therapies leading to MRD negative remissions consistently result in a significant improvement in clinical outcome, including longer OS

precision medicine is becoming a **reality** in the clinical management of **CLL**

things in perspective

Case 1

2015/08

Female age 63 yrs

Lymphocytosis, anemia, bulky lymph nodes

Flow-cytometry: typical CLL (score 5)

Clinical Stage: Binet C

FISH	Monoallelic interstitial deletion of 13q14.3 (75%)
IGHV genes	IGHV3-23 | 100% germline identity | U-CLL

TP53 gene analysis by Sanger Sequencing (2015-08-23)
no pathogenic *TP53* variant was detected

Case 1

ultra-high risk CLL

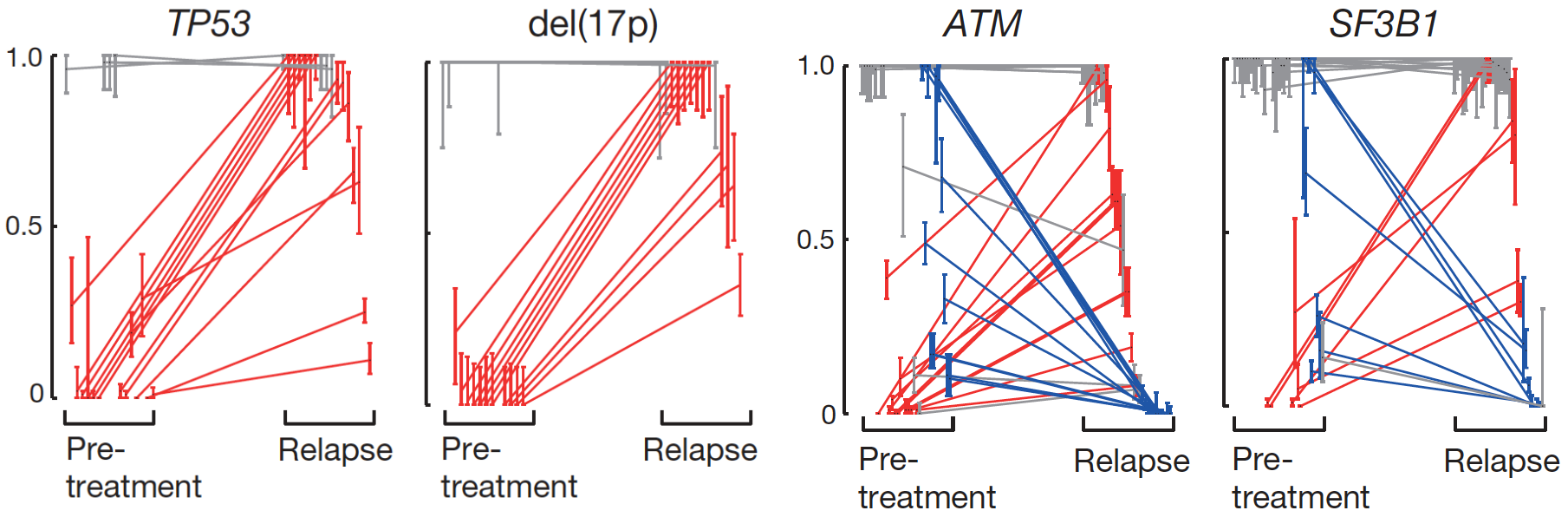
Case 1

FISH	Monoallelic interstitial deletion of 13q14.3 (67%)

***TP53* gene analysis by NGS (2017-01-26)**			
Variant (Protein)	**VAF**	**Depth**	**Interpretation**
p.S215G	33%	3363	Pathogenic

***TP53* gene analysis by NGS (2015-08-23)**			
Variant (Protein)	**VAF**	**Depth**	**Interpretation**
p.S215G	6%	4352	Pathogenic

Chemo(immuno)therapy selects *TP53* mutant subclones



Landau D et al. Nature 2015

Case 1

had you known in 2015, would you have treated with FCR?

we must and
will change this!

join forces!


ERIC
european research initiative on CLL

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