MODENA
18-19 maggio 2017

Aula Magna Centro Servizi
Università degli Studi di Modena e Reggio Emilia

NOVITÀ IN EMATOLOGIA:
la comunicazione,
le terapie innovative e di supporto,
la sostenibilità

Nuove terapie ed indicazioni nella leucemia linfatica cronica

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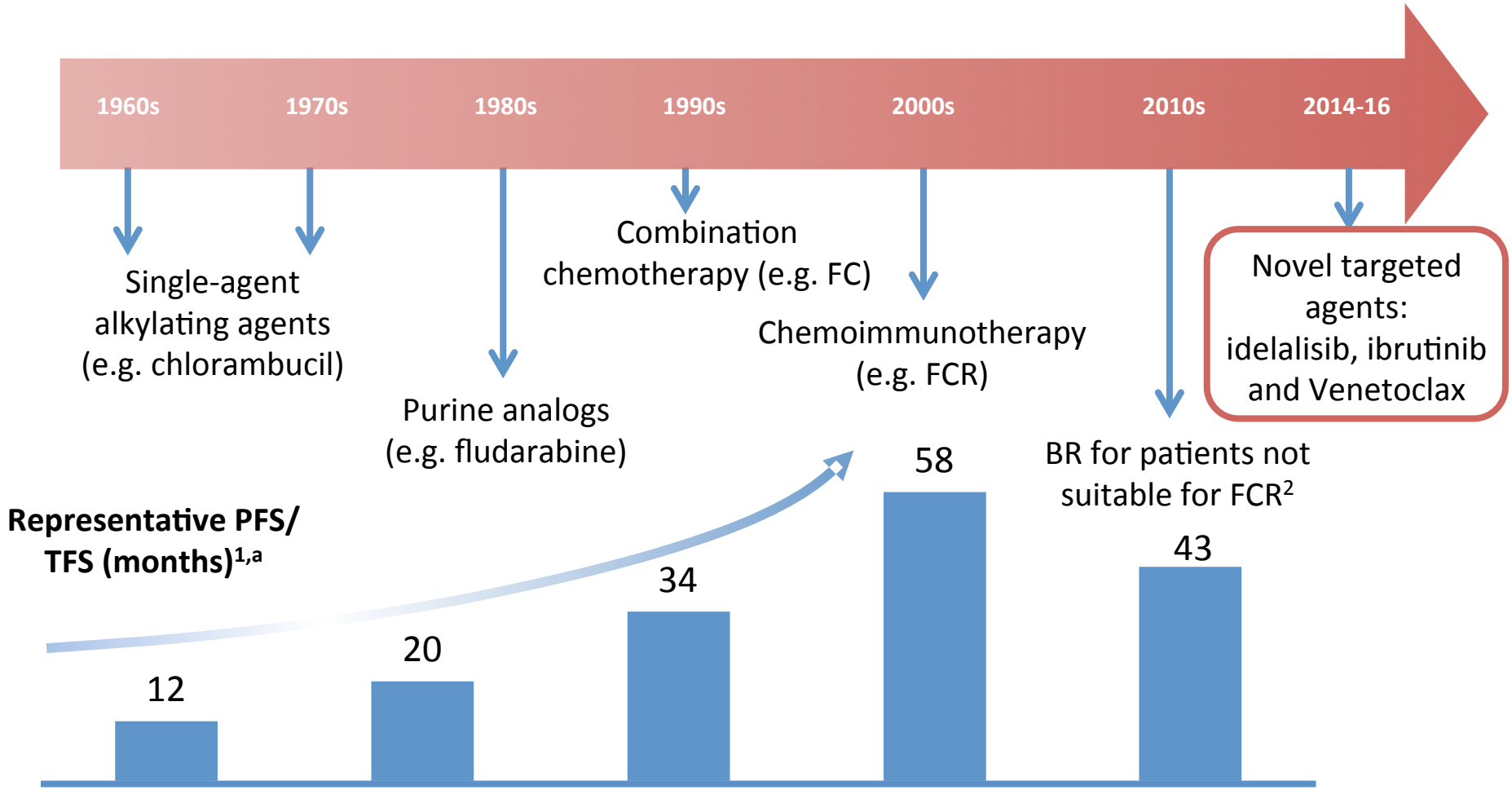
Istituto Scientifico San Raffaele – Milano

OSPEDALE SAN RAFFAELE

UNIVERSITÀ VITA-SALUTE SAN RAFFAELE
UniSR
QUID EST HOMO?

PHBE/IBR/0217/0003

CLL treatment has evolved over multiple decades

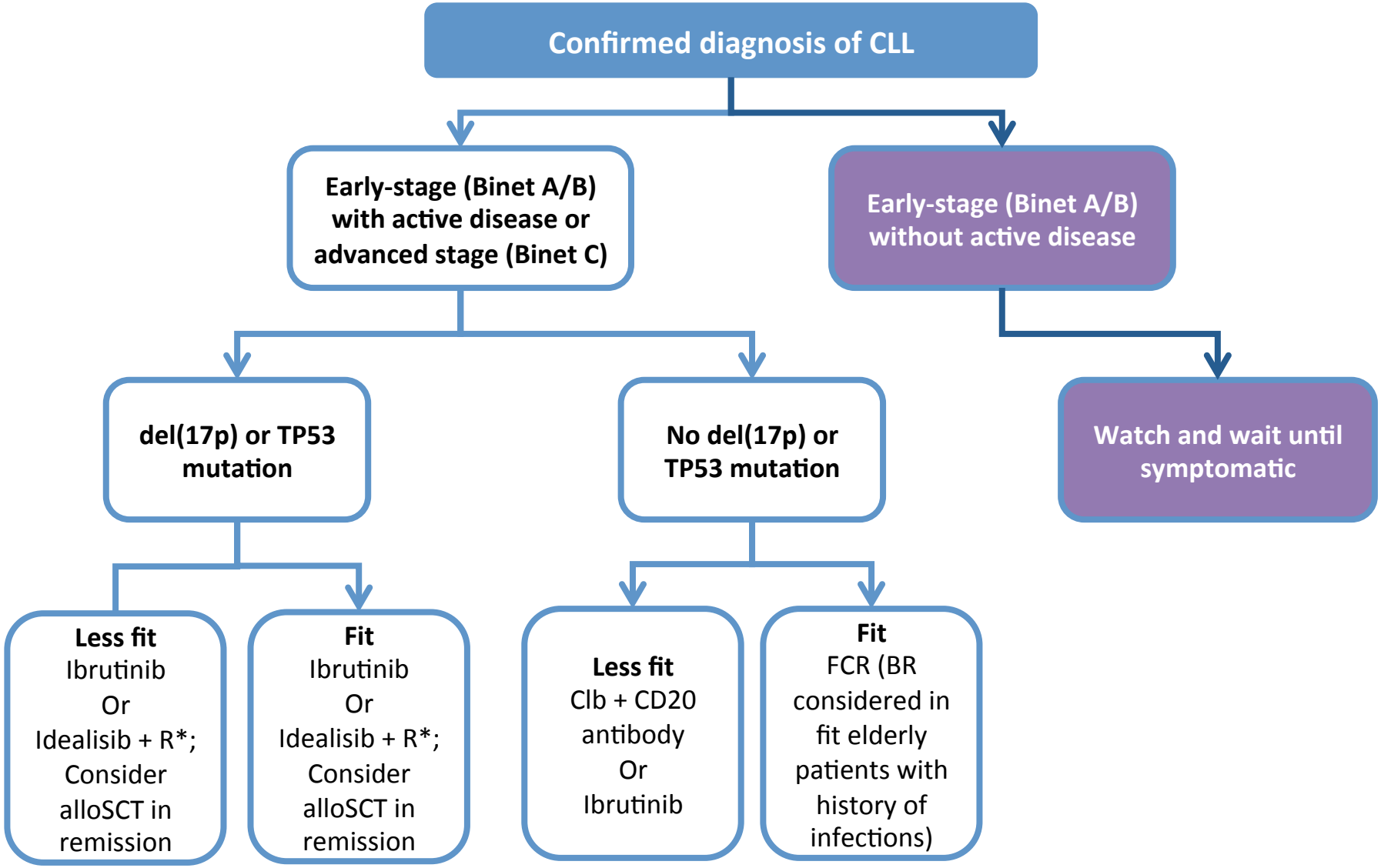


[a] PFS representative only; cannot be used to compare regimens directly because results are drawn from across trials with different patient characteristics

B: bendamustine; C: cyclophosphamide; CIT: chemoimmunotherapy; CLL: chronic lymphocytic leukemia; F: fludarabine; PFS: progression-free survival; R: rituximab

1. Shanafelt T. *Hematology Am Soc Hematol Educ Program* 2013; 2013:158–167.
2. Eichhorst B, *et al.* ASH 2014 (Abstract 19; oral presentation).

ESMO 2016 guidelines update for first line CLL



** only if not suitable for alternative treatment*

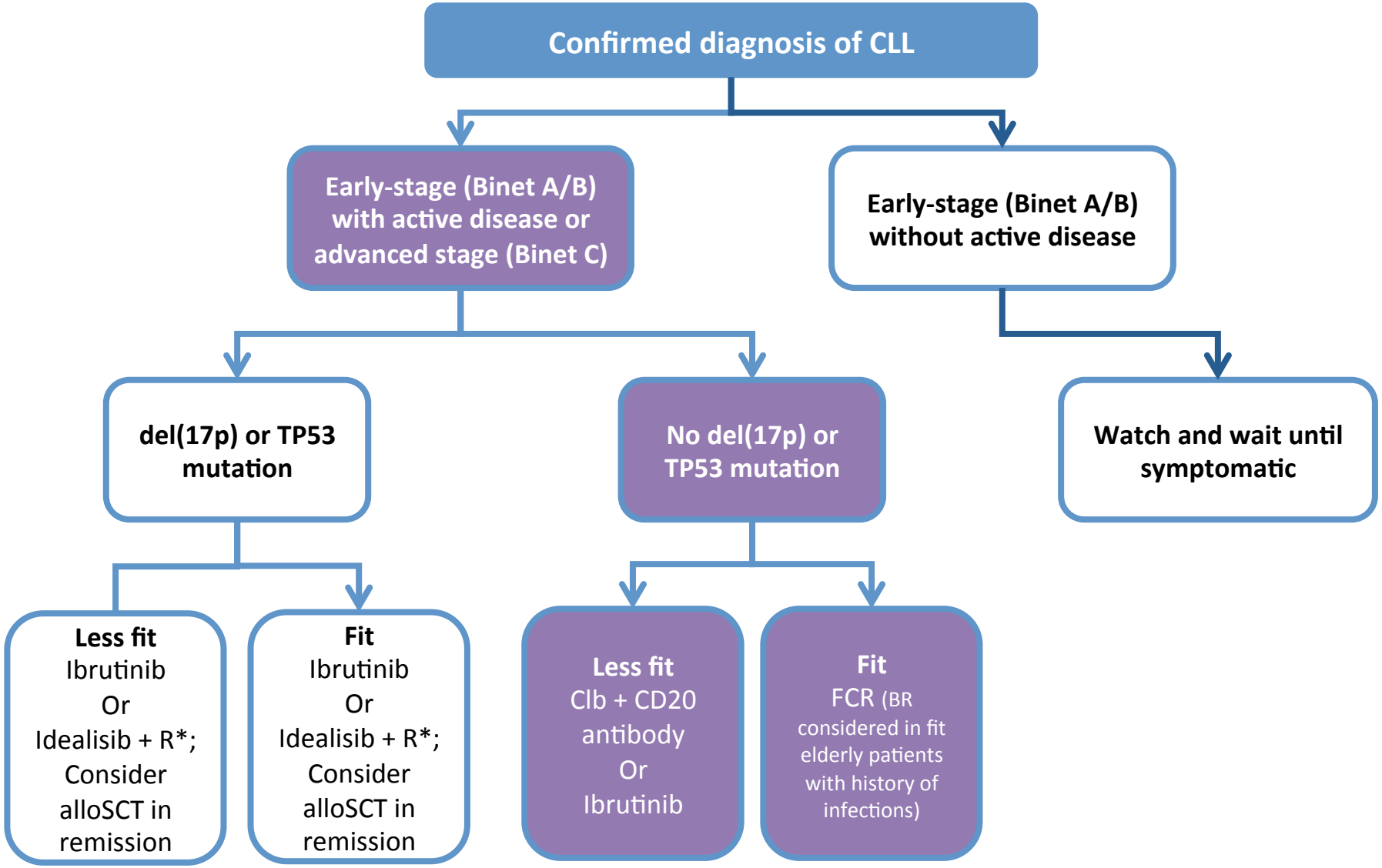
Eichhorst B, et al. Appendix 6: CLL: eUpdate. Ann Oncol 2016

Second line treatment decisions

- **Disease relapse** is **not a criterion** to re-start therapy unless the disease is progressive and symptomatic
- **Second-line** treatment decisions should follow the **same indications** as those used for **first-line** treatment

Hallek, M. iwCLL 2017 (invited oral presentation)

ESMO 2016 guidelines update for first line CLL



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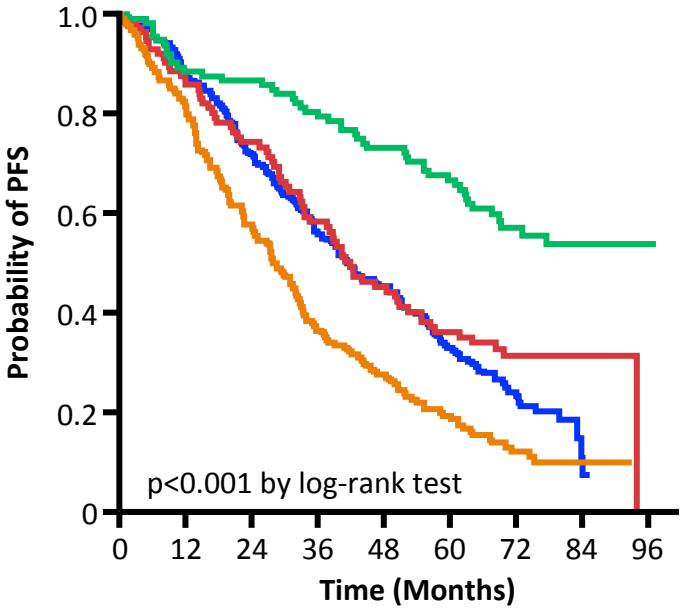
Eichhorst B, et al. Appendix 6: CLL: eUpdate. Ann Oncol 2016

Long term remissions with FCR

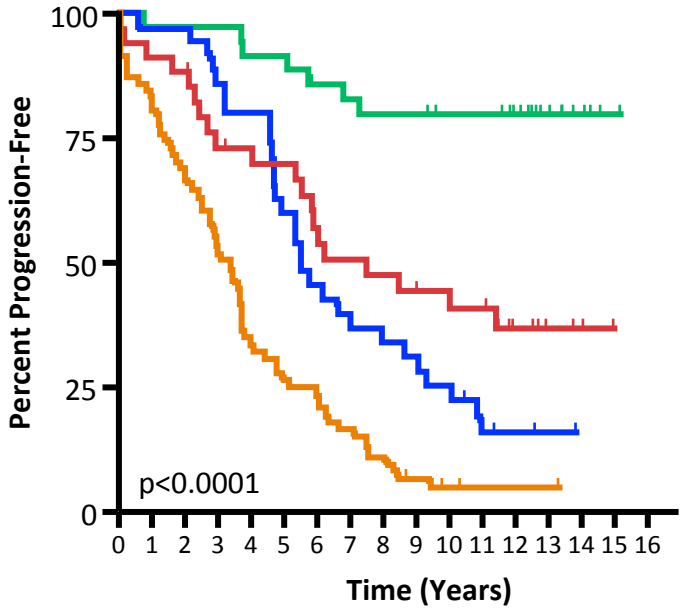
CLL8[1]

	N
FCR IGHV M patients	113
FC IGHV M patients	117
FCR IGHV UM patients	197
FC IGHV UM patients	195



MDACC[2]

	N
IGHV-M, MRD neg	35
IGHV-M, MRD pos	34
IGHV-UM, MRD neg	35
IGHV-UM, MRD pos	66

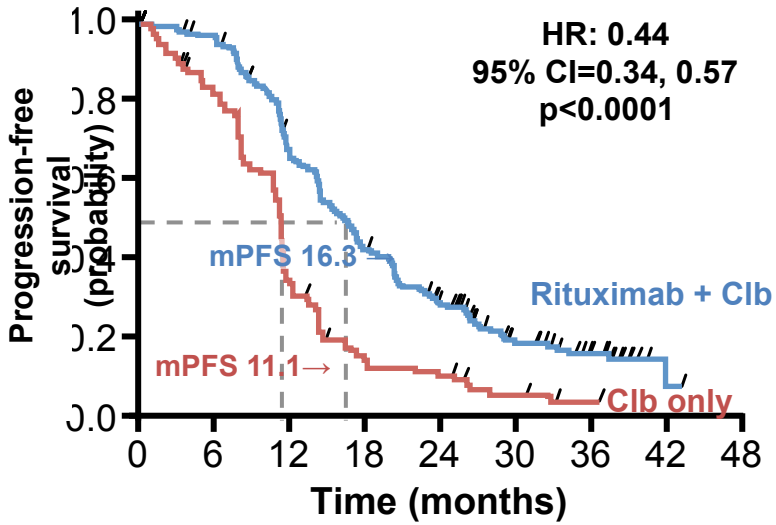


IGHV, immunoglobulin heavy chain; M, mutated;
MDACC, MD Anderson Cancer; UM, unmutated.

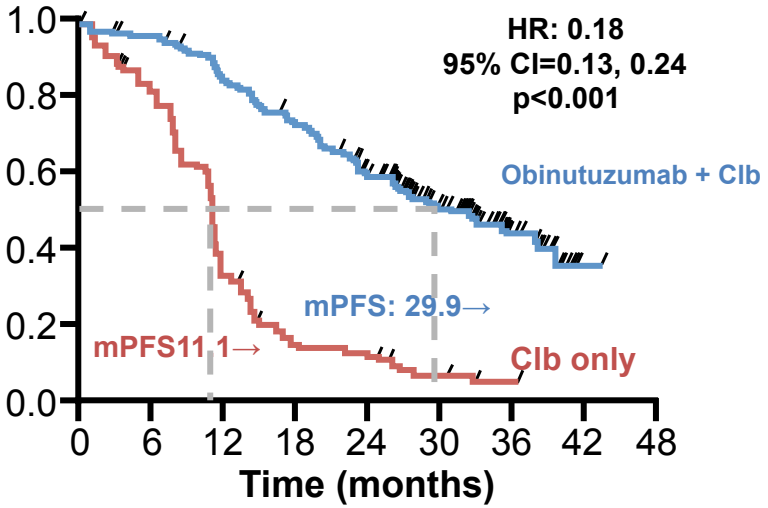
1. Fischer K, et al. Blood 2016; 127:208–215;
2. Thompson PA, et al. Blood 2016; 127:303–309.

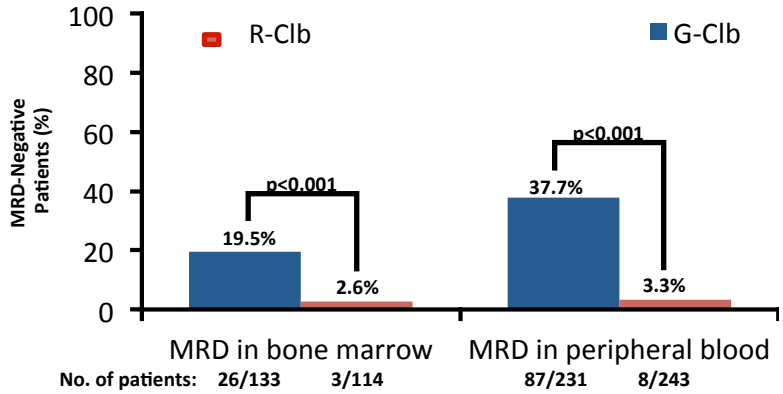
CLL11: Phase III, randomized, open-label, multicenter trial in elderly patients with comorbidities (N=781)

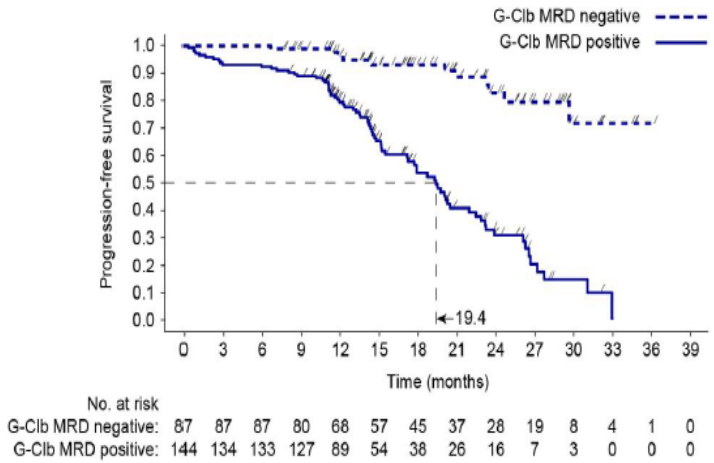
PFS: rituximab + Clb vs. Clb only2



PFS: obintuzumab + Clb vs. Clb only2



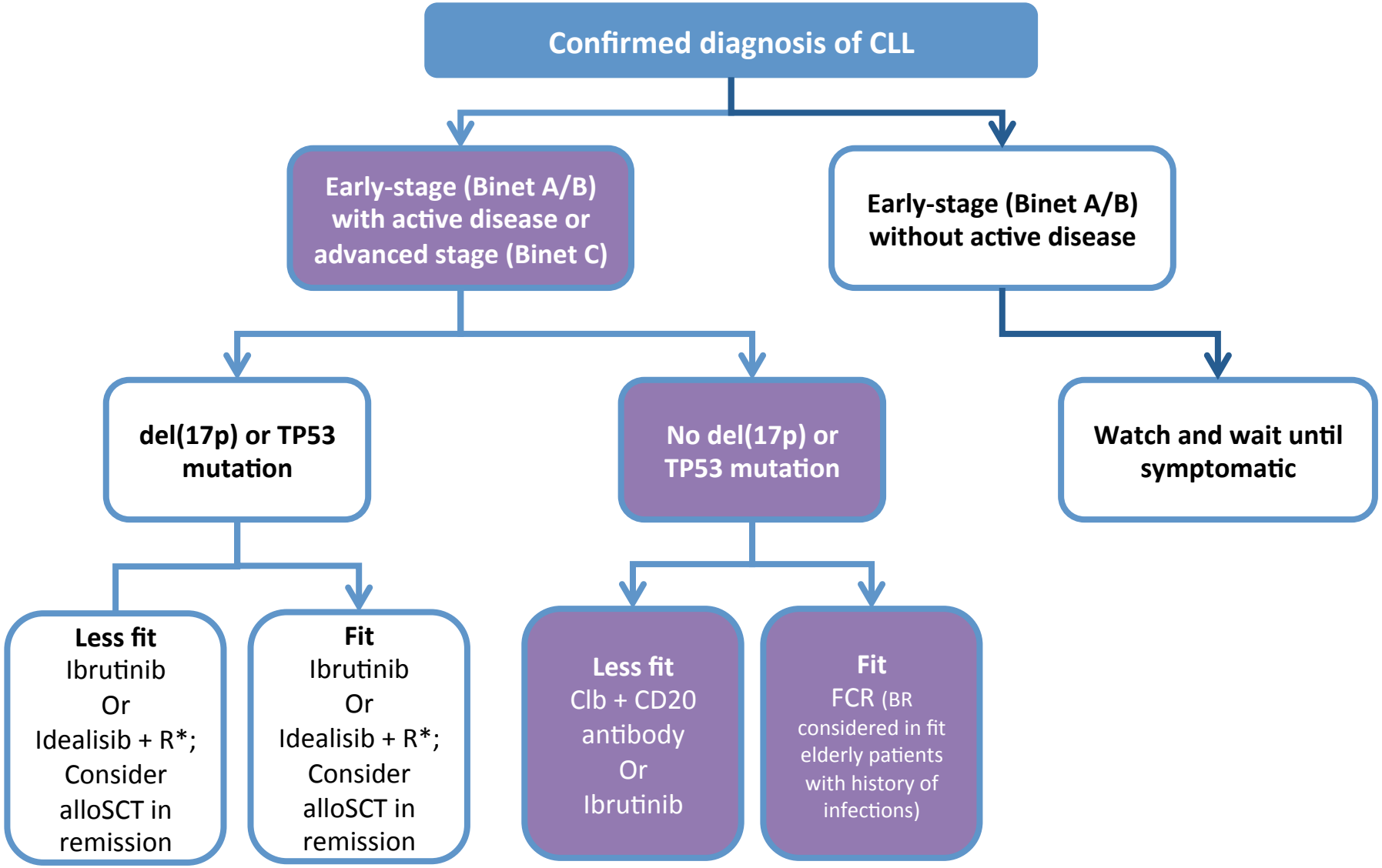




NR, No response;TFS, treatment-free survival.
*Peripheral blood at first restaging.

Goede V, et al. N Engl J Med 2014.

ESMO 2016 guidelines update for first line CLL



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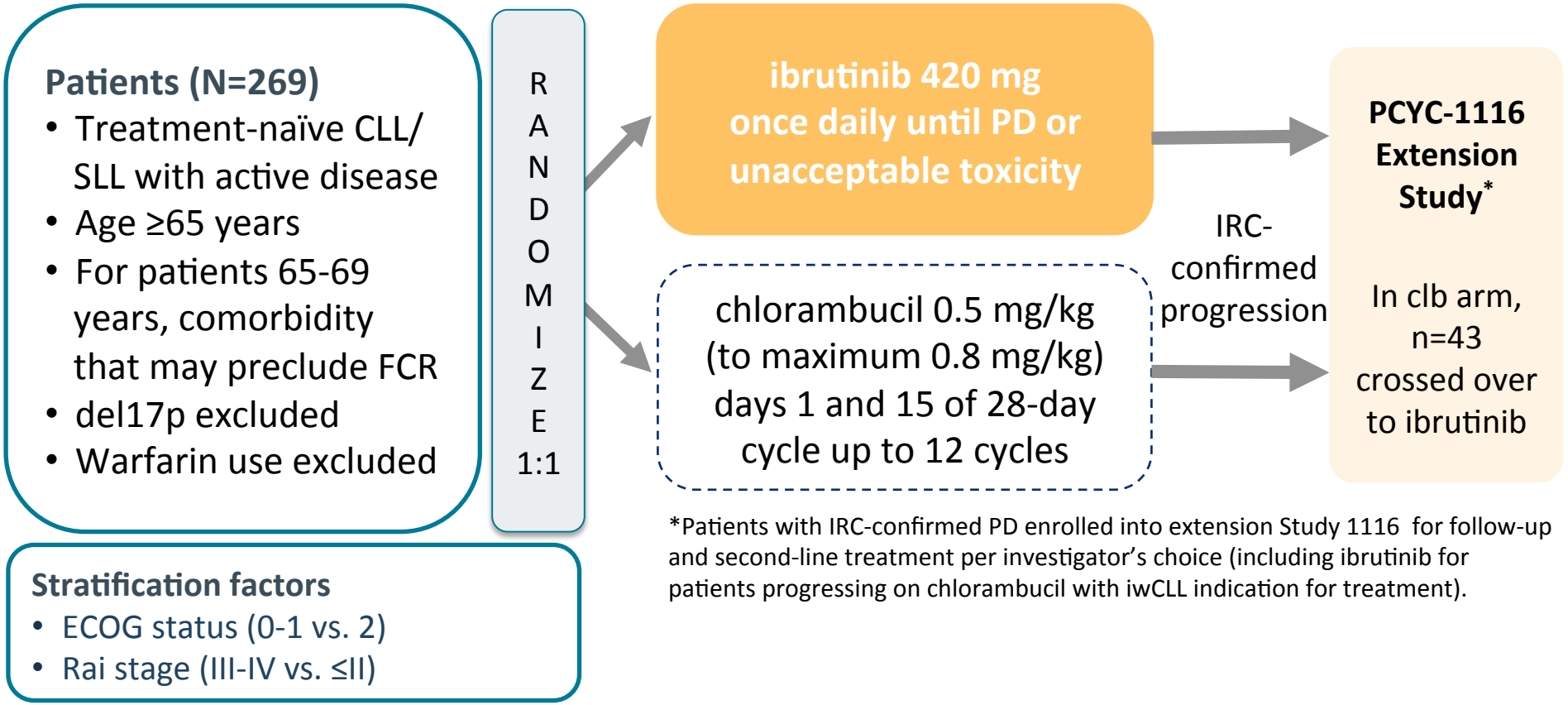
Eichhorst B, et al. Appendix 6: CLL: eUpdate. Ann Oncol 2016

RESONATE-2 (PCYC-1115) Study Design



*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

PHBE/IBR/0217/0003

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

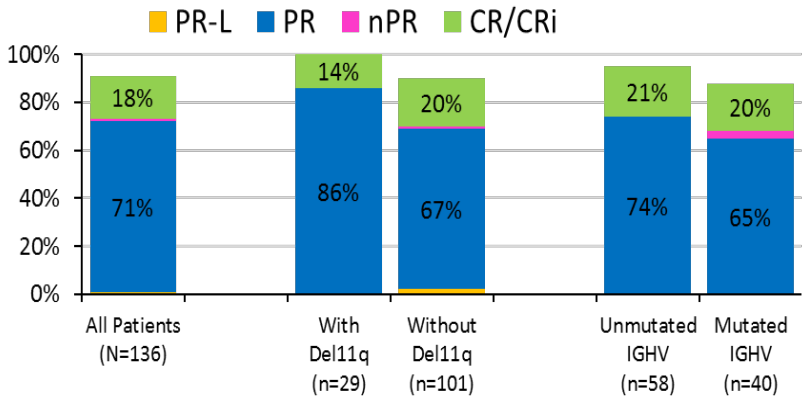
Burger J et al, NEJM 2015

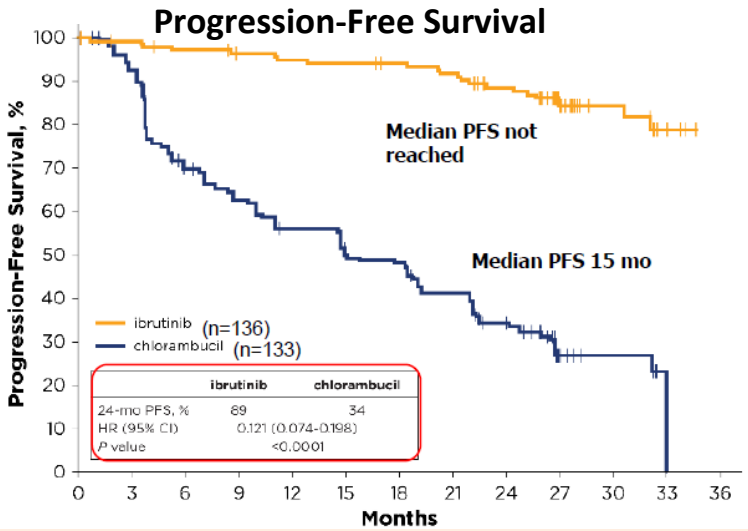
Updated Efficacy and Safety from the Phase 3 Resonate-2 Study: Ibrutinib As First-Line Treatment in Patients ≥65 Years with CLL/SLL

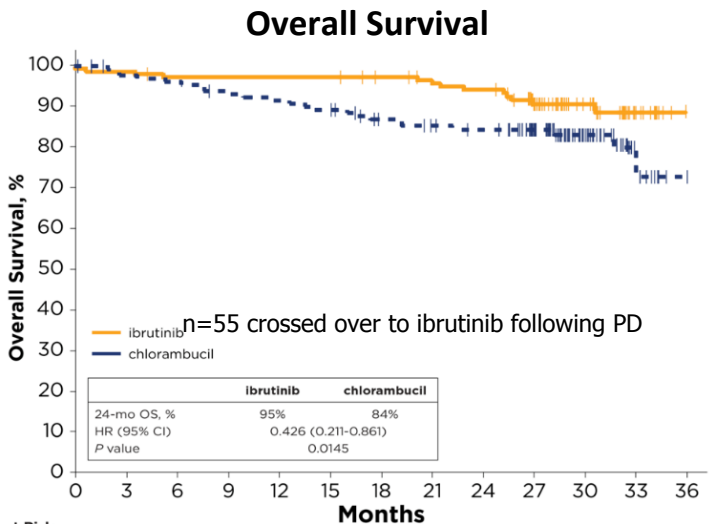
ibrutinib (n=136) **vs** **chlorambucil (n=133)**

follow-up 18,4 months ➔ 29 months

CR rates continue to improve:
7% @12 mo ➔ 15% @24 mo➔18%@ 29 mo







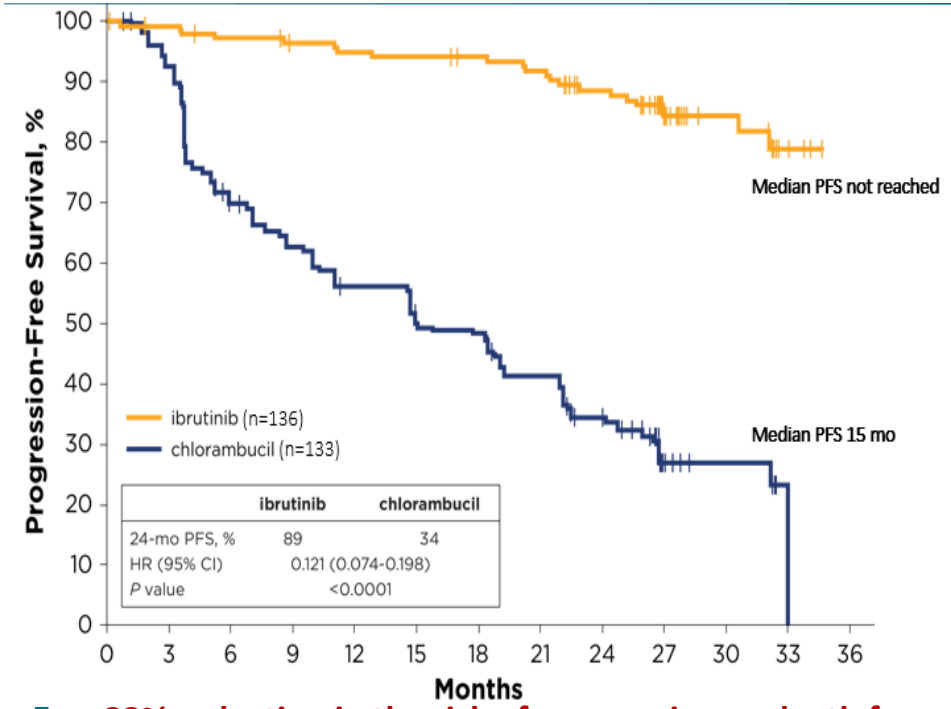
- **PFS @ 18 mo: 90% ➔PFS @ 24 mo: 89%**
- **PFS benefit across all sub-groups**
- **(Fit patients: median PFS FCR➔ 55 mo; BR➔ 42 mo)**

Barr et al., ASH 2016; abstr.# 234

Are We Harming Our Patients without MRD?

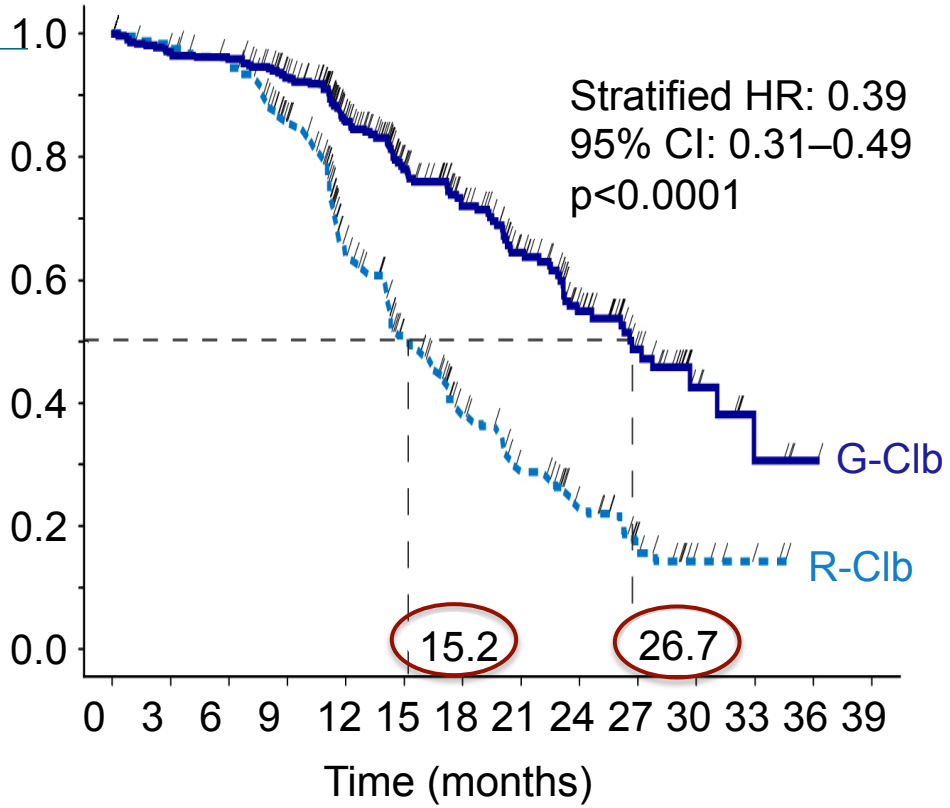
RESONATE-2:
Ibrutinib vs chlorambucil[1]

No MRD-negative cases were reported



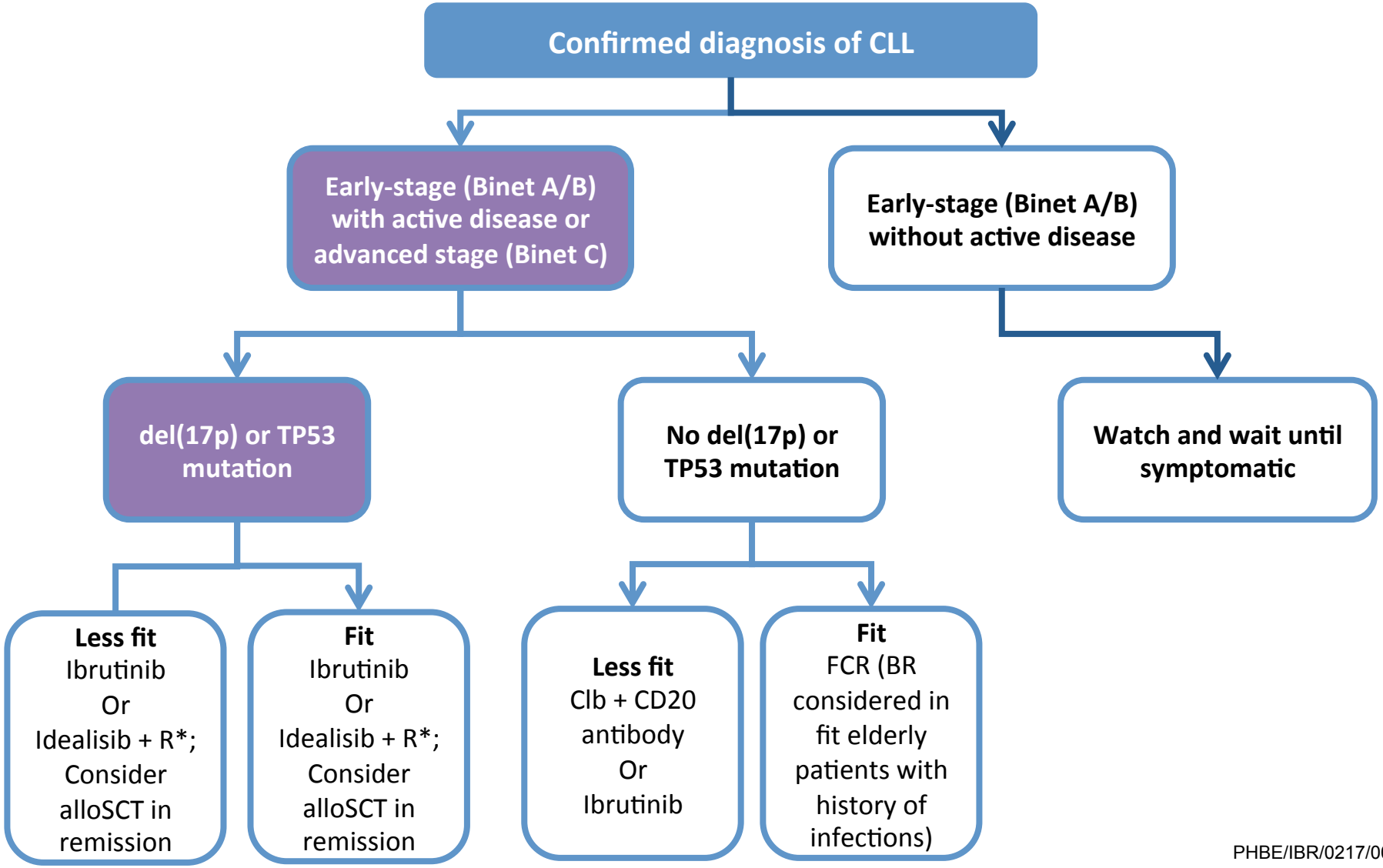
- **88% reduction in the risk of progression or death for patients randomized to ibrutinib**
- **41% of patients receiving chlorambucil have crossed over to receive ibrutinib**

GCLLSG CLL11:
Obinutuzumab + chlorambucil[2]



1. Barr et al., ASH 2016; 2. Goede V, et al. N Engl J Med 2014

ESMO 2016 guidelines update for first line CLL

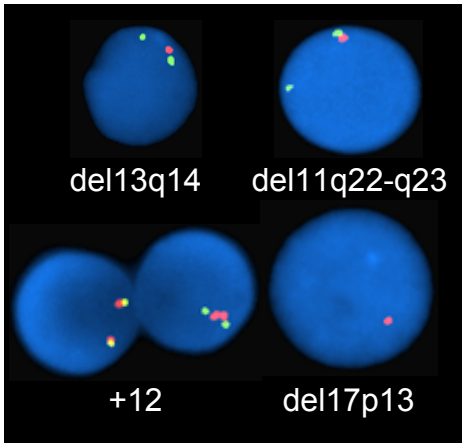


PHBE/IBR/0217/0003

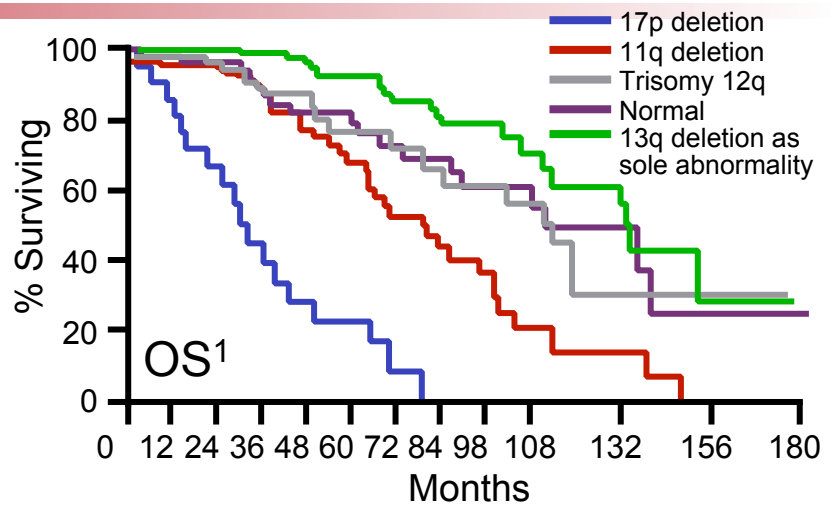
** only if not suitable for alternative treatment*

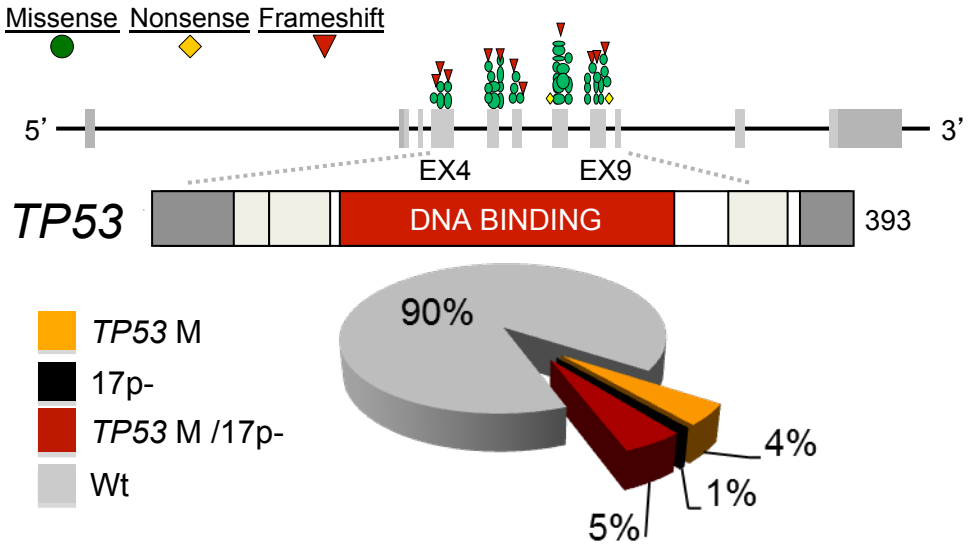
Eichhorst B, et al. Appendix 6: CLL: eUpdate. Ann Oncol 2016

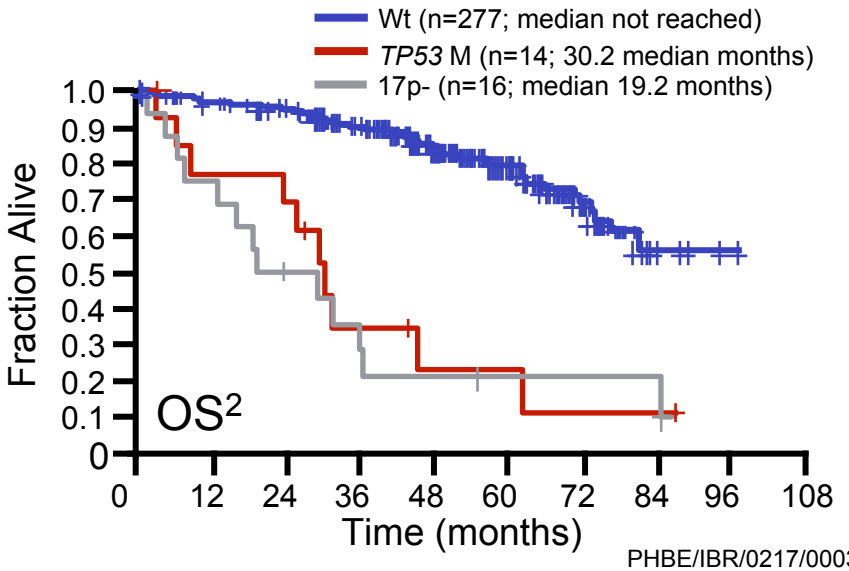
TP53 disruption is associated with poor prognosis



Aberration	Incidence (%)[1]	Median OS (months)[1]
17p del	7	32
11q del	18	79
+12	16	114
Normal	18	111
13q del	55	133







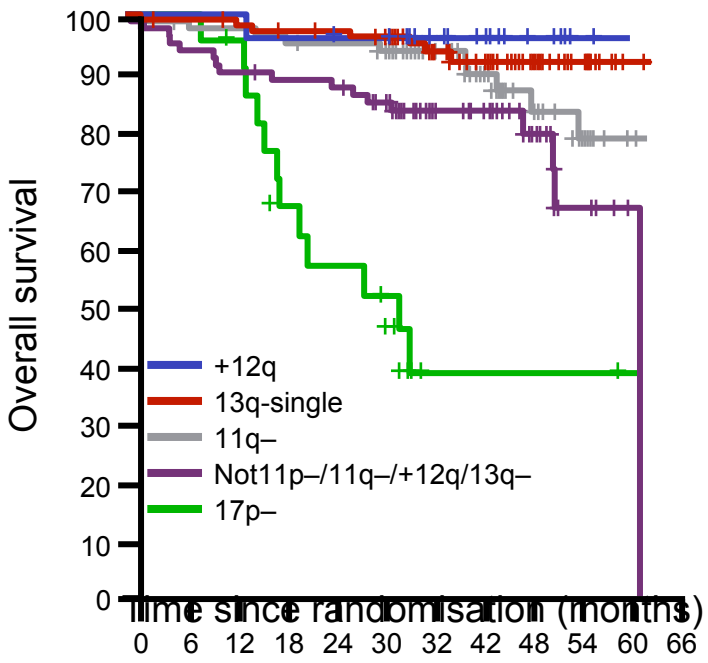
PHBE/IBR/0217/0003

*N*t: wildtype; OS: overall survival

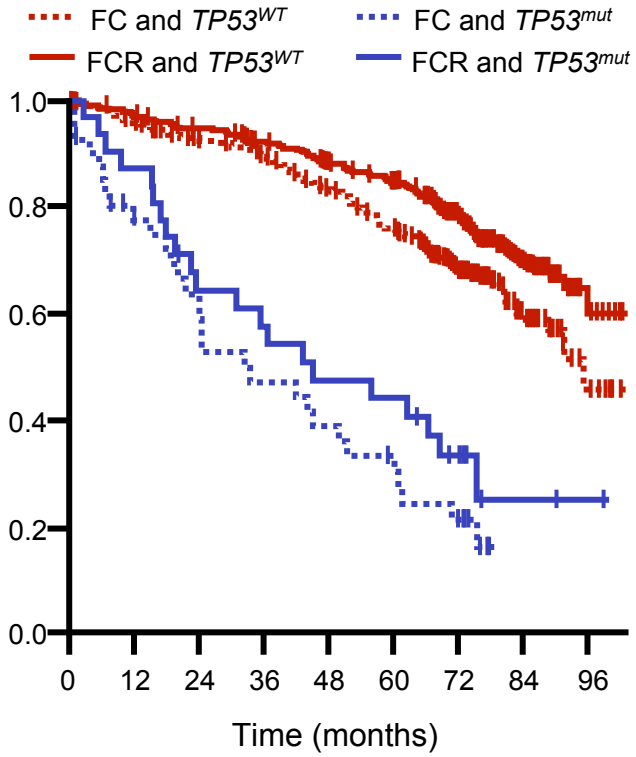
1. Döhner H, et al. N Engl J Med 2000;343:1910–6; 2. Zenz T, et al. J Clin Oncol 2010;28:4473–9.

FCR not effective in del17p/TP53 disrupted patients

CLL8: FCR



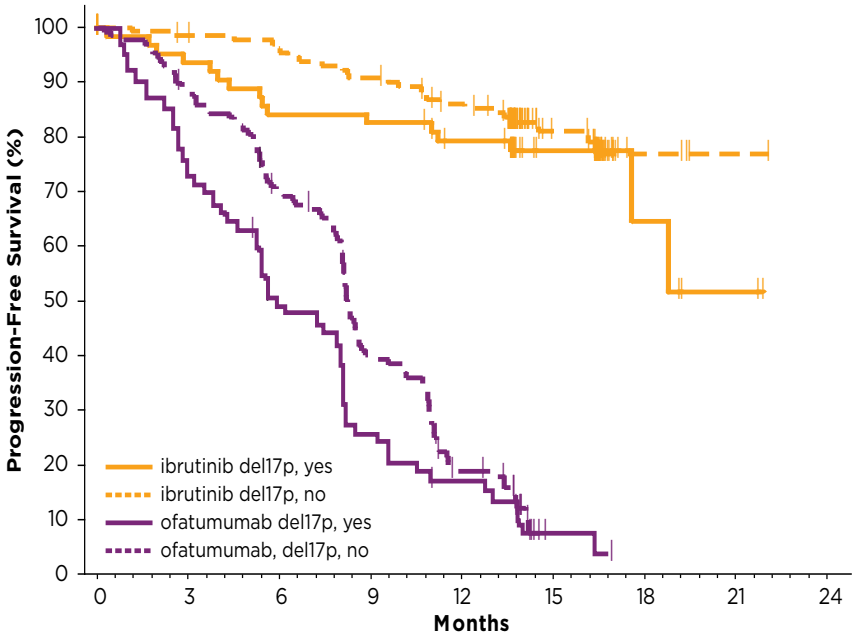
CLL8: FCR and FC in patients with TP53 mut



PHBE/IBR/0217/0003

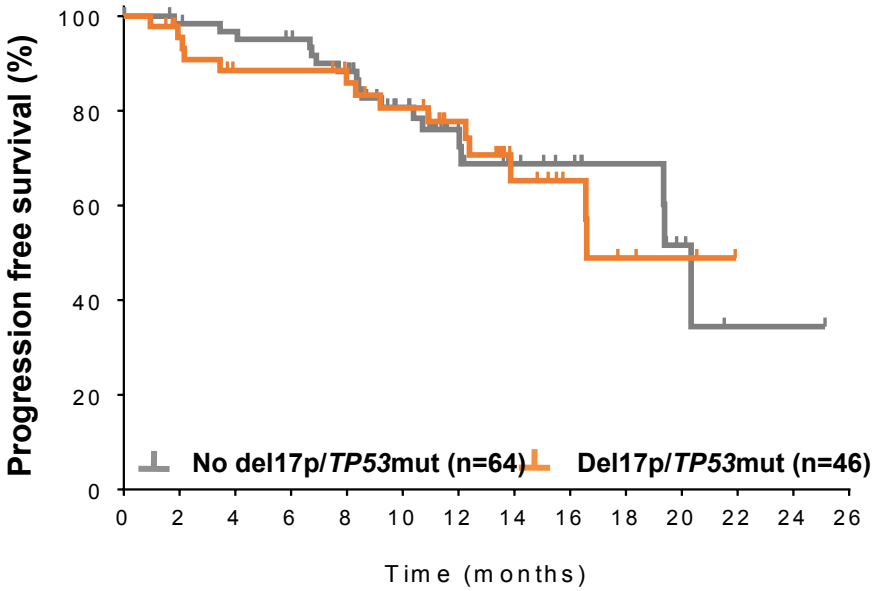
Hallek M, et al. Lancet 2010; Stilgenbauer S, et al. Blood 2014; Pettitt A, et al. J Clin Oncol 2012

No Difference in PFS With or Without Del17p



	ibrutinib del17p, no	ibrutinib del17p, yes	ofatumumab del17p, no	ofatumumab del17p, yes
Median PFS (mo)	NR	NR	8.2	5.9
Hazard ratio	1.314		1.413	
(95% CI)	(0.698-2.473)		(1.017-1.963)	
P value	0.396		0.039	

Del17p/TP53mut: Present vs Not Present



No del	64	61	59	59	52	37	21	14	11	8	4	1	1	1
Del	46	41	36	36	33	30	22	12	8	4	3	0		

	Median PFS (95% CI)	p-value
No del	20.3 mo (19.4, –)	0.94
Del	16.6 mo (13.9, –)	

PHBE/IBR/0217/0003

Thornton et al, EHA 2015 Vienna

Sharman, ASH, 2014, Abstract 330

TP53 Network

- **ERIC aims to advance assessment of *TP53* aberrations through education about:**
  - **Importance of testing all cases needing therapy, before first and later lines of treatment**
  - **Quality of appropriate techniques in diagnostic laboratories to ensure reliabl and comparable results between institutions**
    → Certification of laboratories

ERIC
european research initiative on CLL

ITALY - Reference Centre Contact Information

Name of Reference Centre: Division of Hematology, University of Eastern Piedmont

Address: Division of Hematology, Department of Translational Medicine, University of Eastern Piedmont, Via Solaroli 17, 28100 Novara, Italy

Webpage: https://www.uniupo.it/it

Full name of Reference Centre Contact (1): Gianluca Gaidano

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Certified Centres in Italy

Aviano, IRCCS CRO

Bologna, University of Bologna

Brescia, Spedali Civili Di Brescia

Ferrara, University of Ferrara

Milano, AO Ospedale Niguarda Ca' Granda

Milano, Ospedale San Raffaele

Modena, Azienda Ospedaliero - Universitaria Policlinico de Modena

Novara, Amedeo Avogadro University of Eastern Piedmont

Nuoro, San Francisco Hospital (2 methods)

Pavia, Fondazione IRCCS Policlinico San Matteo

Perugia, University of Perugia

Rome, Sapienza University of Rome

Torino, SC Anatomia e Istologia Patologica 1U

Vicenza, San Bortolo Hospital

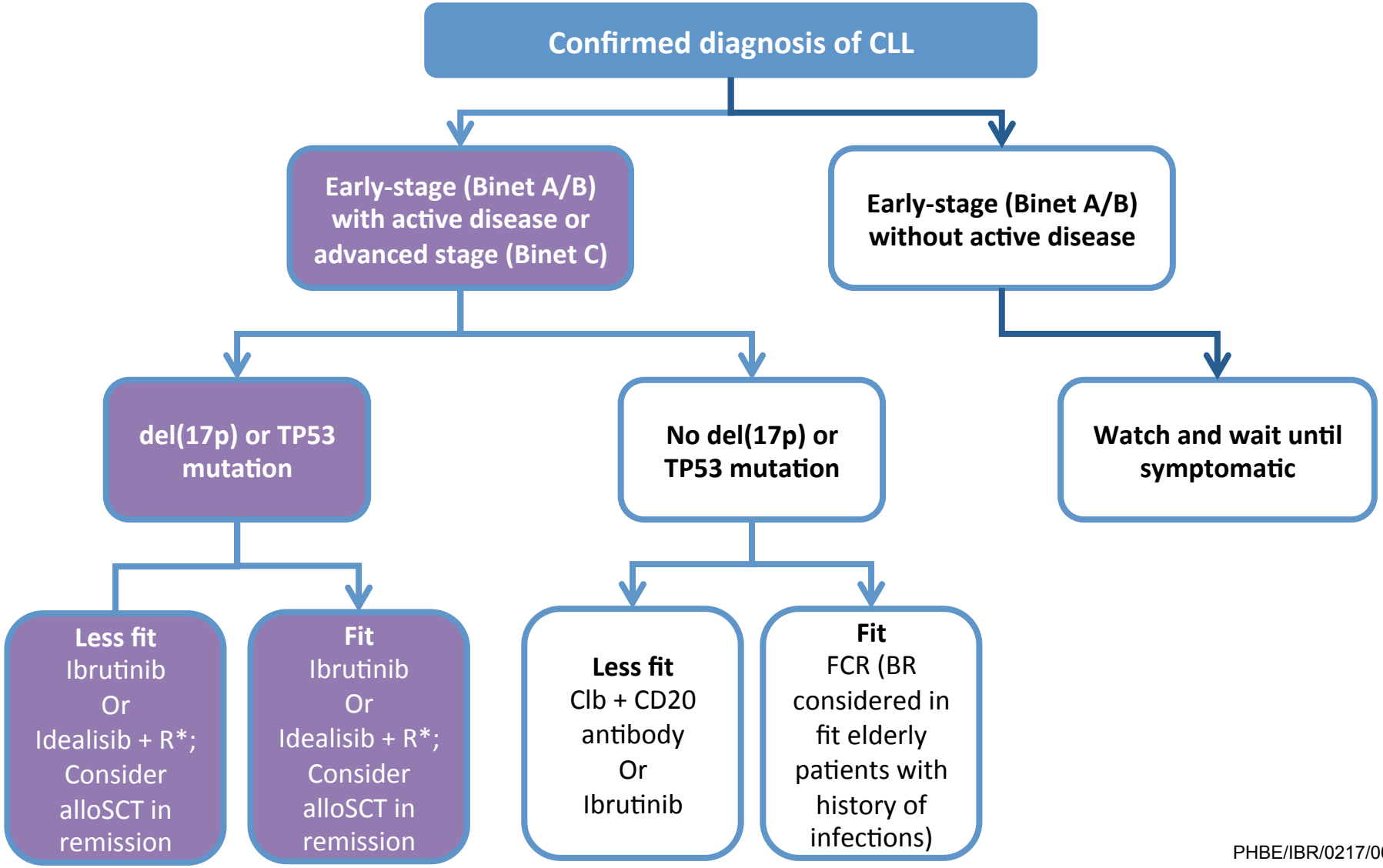
Disease stage	Clinical trial	General practice	Comment
Diagnosis	Recommended	Not indicated	testing will not influence nd wait strategy
1L treatment	**Recommended**		**Patients should be treated with BCR pathway inhibitor**
>2L treatment			

Update coming soon

1L: first-line; 2L: second-line

www.ericll.org. *Pospisilova S, et al. Leukemia 2012; 26:1458–1461.*

ESMO 2016 guidelines update for first line CLL



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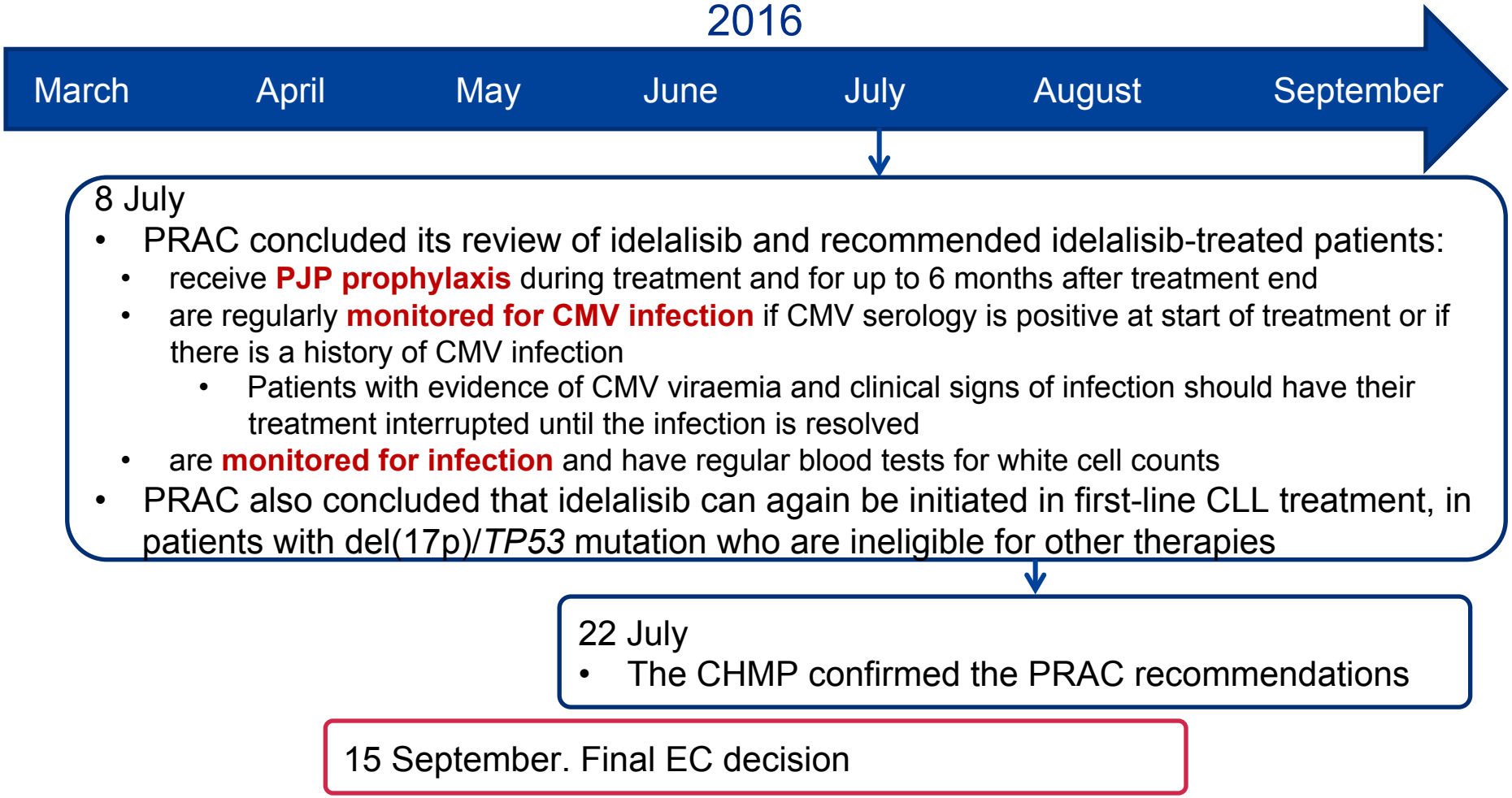
** only if not suitable for alternative treatment*

Eichhorst B, et al. Appendix 6: CLL: eUpdate. Ann Oncol 2016

Idelalisib in first line: changes in 2016



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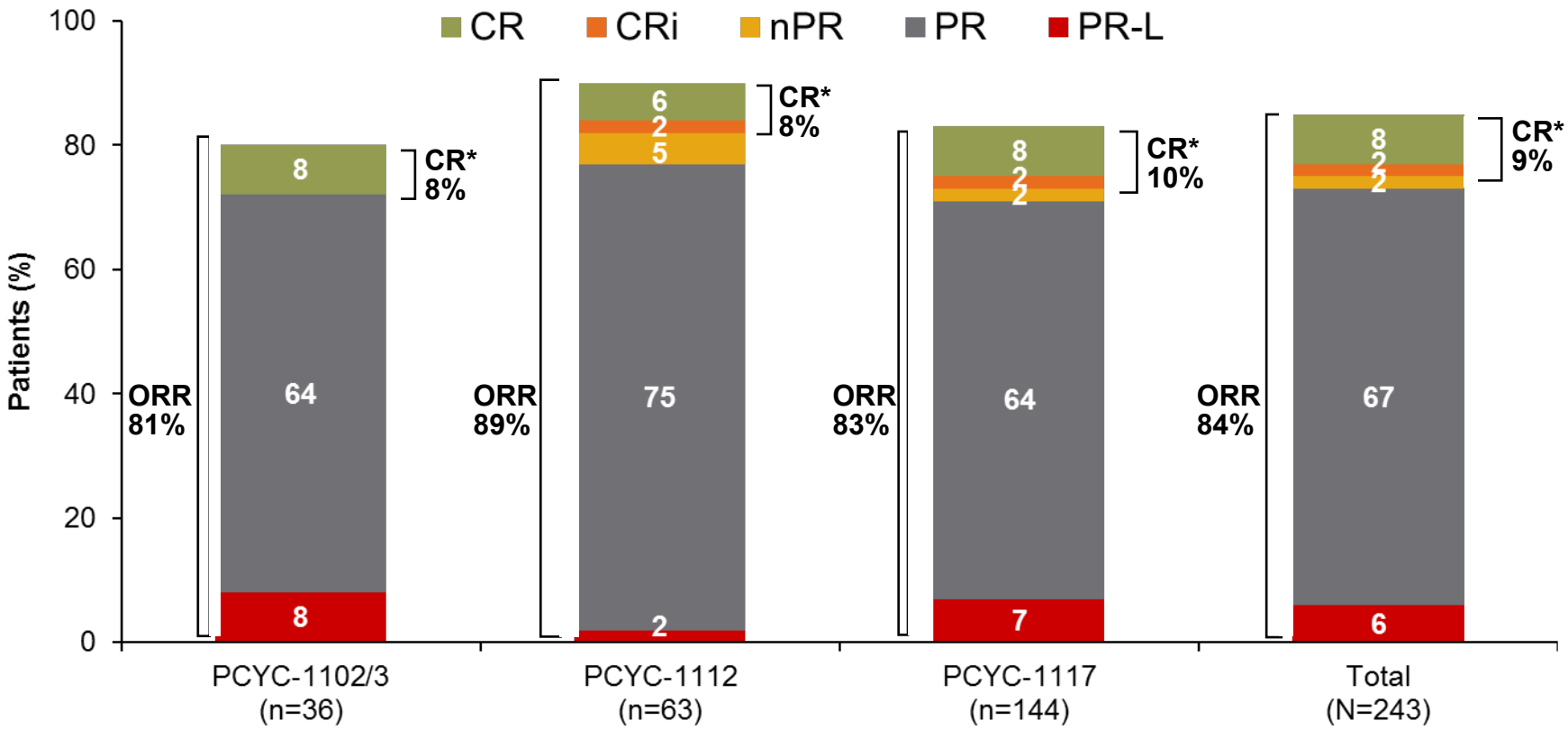
EC: European Commission; EMA: European Medicines Agency; CHMP: Committee for Medicinal Products for Human Use; PJP: *Pneumocystis jirovecii* pneumonia; PRAC: Pharmacovigilance Risk Assessment Committee

EMA press release (8 July 2016; available at www.ema.europa.eu).
EMA press release (22 July 2016; available at www.ema.europa.eu).
Zydelig SmPC (Date TBC 2016; available at www.ema.europa.eu).

A cross-study analysis: ORR, del(17p)



Median time on study, mo (range)	42 (0.9-61)	31 (0.3-37)	28 (0.5-31)	28 (0.3-61)

*CR = CR + CRi

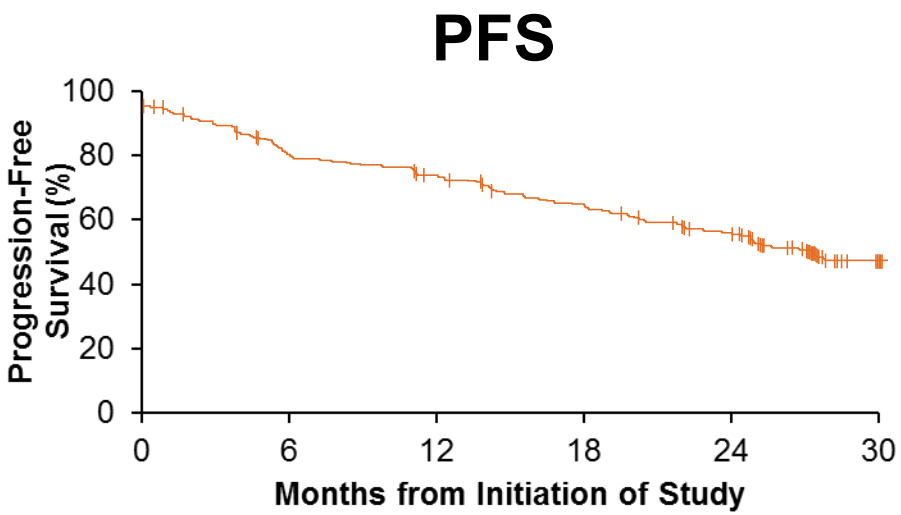
- Median duration of response not reached at 30 months
  - Of patients with CR/CRi (n=23), 81% maintained response at 30 months

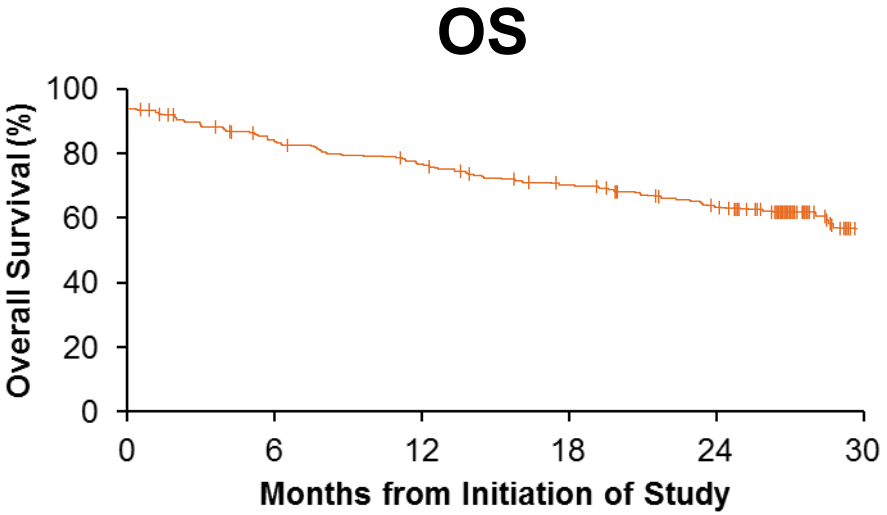
CLL, chronic lymphocytic leukemia; CR, complete response; CRi, CR with incomplete marrow recovery; IBR, ibrutinib; ORR, overall response rate; PR, partial response; PR-L, partial response with lymphocytosis; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; TN, treatment-naïve

PHBE/IBR/0217/0003

Jones, EHA 2016, S429

Results: PFS and OS, del(17p)





12-mo PFS, % (95% CI)	24-mo PFS, % (95% CI)	30-mo PFS, % (95% CI)
80% (74, 84)	63% (57, 69)	55% (48, 62)
Median PFS not reached		

12-mo OS, % (95% CI)	24-mo OS, % (95% CI)	30-mo OS, % (95% CI)
85% (80, 89)	75% (68, 80)	67% (59, 74)
Median OS not reached		

- With a median (range) study duration of 28 (0.3-61+) months, median PFS and OS were not reached

CLL, chronic lymphocytic leukemia; IBR, ibrutinib; OS, overall survival; PFS, progression-free survival; R/R, relapsed/ refractory; SLL, small lymphocytic lymphoma

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Jones, EHA 2016, S429

EMA approval for Venclyxto on 08DEC16

- **Venclyxto monotherapy is conditionally approved for the treatment of chronic lymphocytic leukaemia (CLL) in the presence of *17p deletion or TP53 mutation* in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor**

- **Venclyxto monotherapy is conditionally approved for the treatment of CLL in without 17p deletion or TP53 mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor**

Ultra-high Risk R/R CLL patients with del17p

Best Response with Venetoclax

	IRC, n (%)	Investigator, n (%)
Overall Response	85 (79.4)	79 (73.8)
CR or CRi	8 (7.5)	17 (15.9)
nPR	3 (2.8)	4 (3.7)
PR	74 (69.2)	58 (54.2)
No response	22 (20.6)	28 (26.2)
Stable disease	NA	24 (22.4)
Disease progression	NA	2 (1.9)
Incomplete data	NA	2 (1.9)

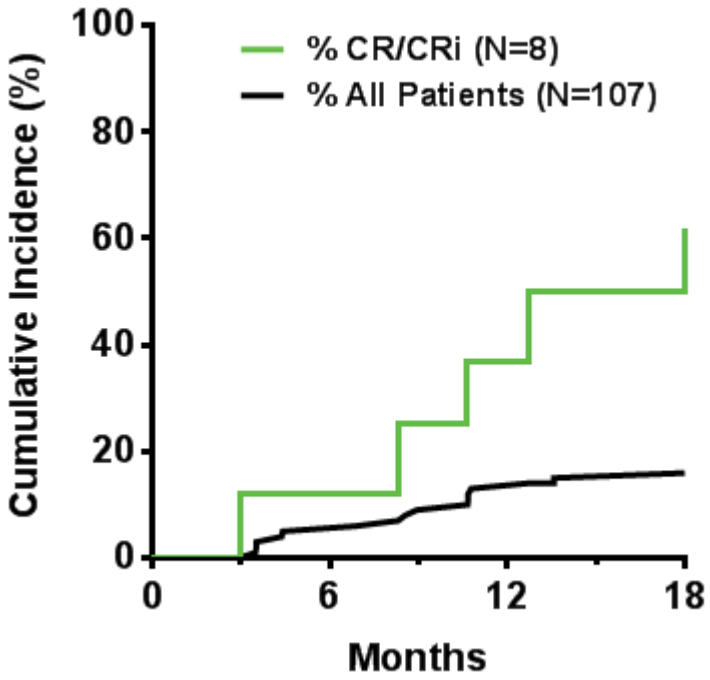
- 25 of 48 patients with no CLL in the bone marrow
- 18 of 45 patients assessed were MRD-negative in PB

PHBE/IBR/0217/0003

Stilgenbauer et al, Lancet Oncology 2016

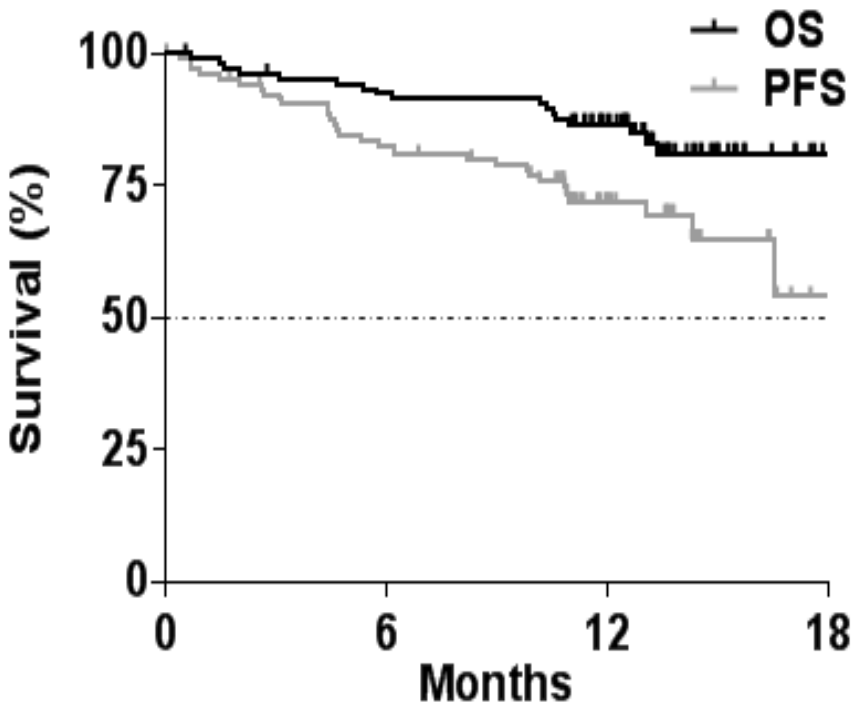
Cumulative Incidence of Response

MRD-Negativity



- **Of 45 patients tested, 18 achieved MRD-negativity in peripheral blood**

PFS and OS (N=107)

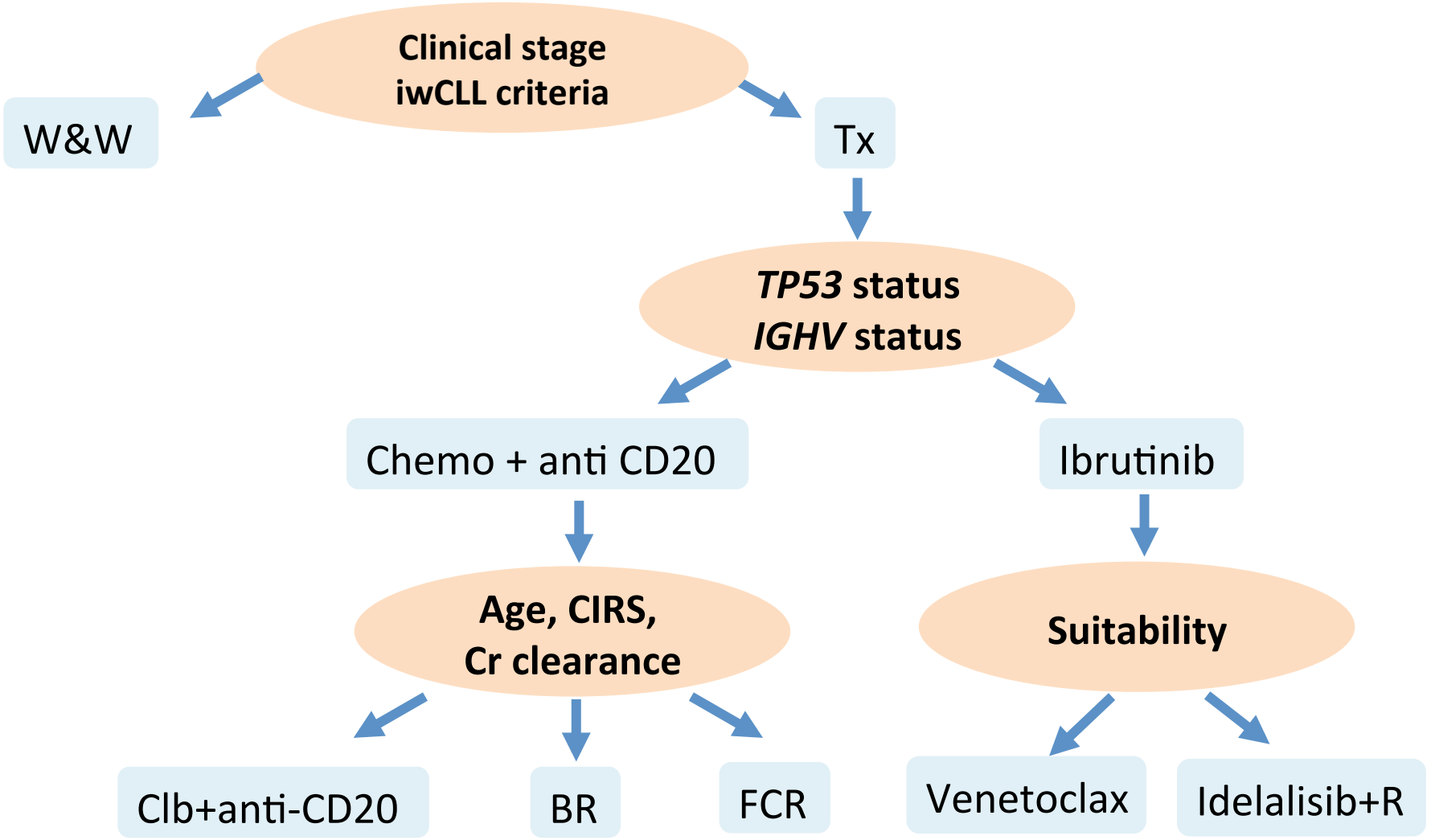


- **12-month estimates (95% CI):**
  - **PFS: 72.0% (61.8, 79.8)**
  - **OS: 86.7% (78.6, 91.9)**

PHBE/IBR/0217/0003

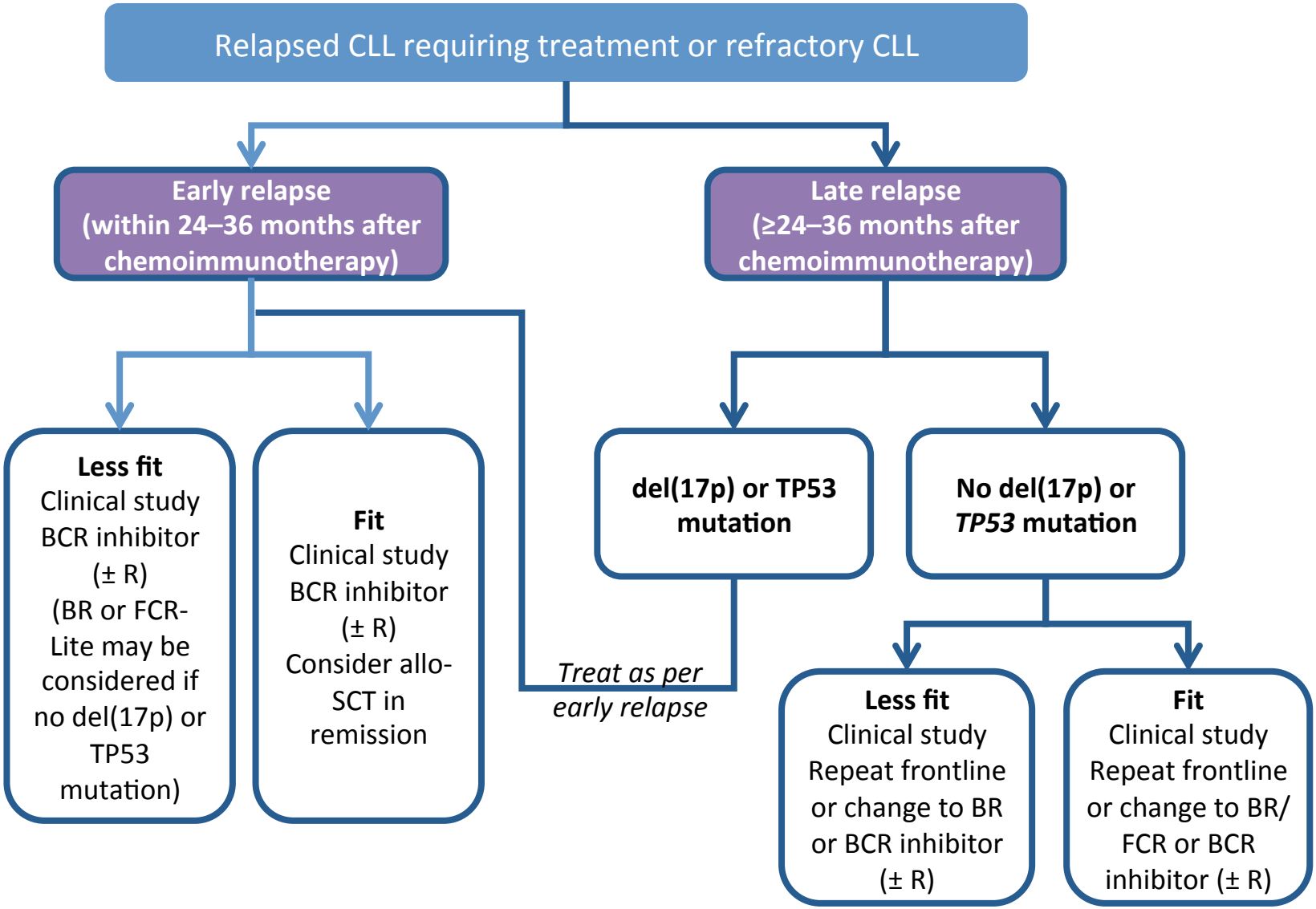
Stilgenbauer et al, Lancet Oncology 2016

CAN TREATMENT DECISION BE INFORMED BY BIOMARKERS?



Modified from Rossi D., iwCLL 2017 (invited oral presentation)

ESMO 2015 clinical practice guidelines for R/R CLL

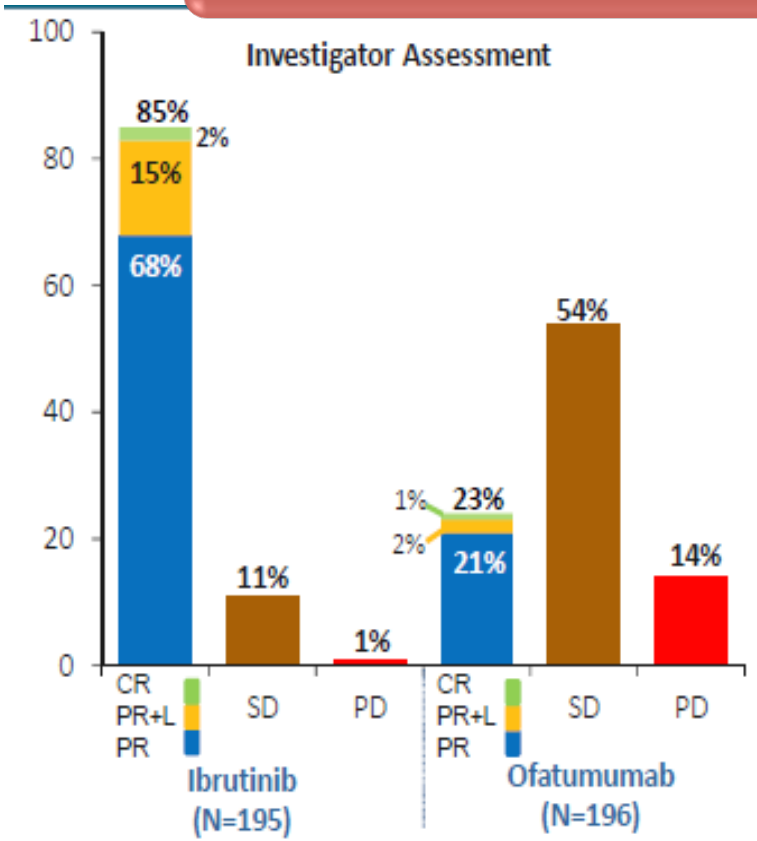


Eichhorst B, et al. Ann Oncol 2015; 26(Suppl 5):v78–v84

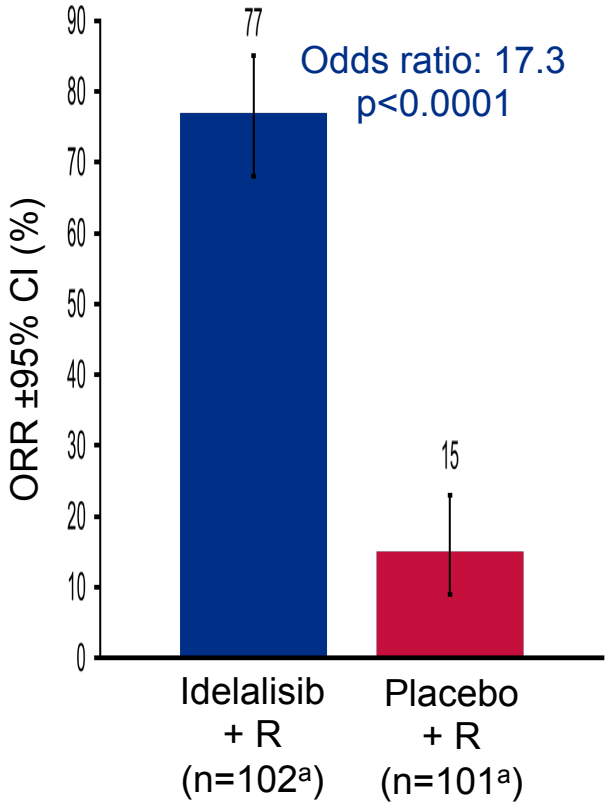
Impressive Overall response rate (ORR)

Previously-treated CLL

RESONATE: Ibrutinib versus ofatumumab[1]



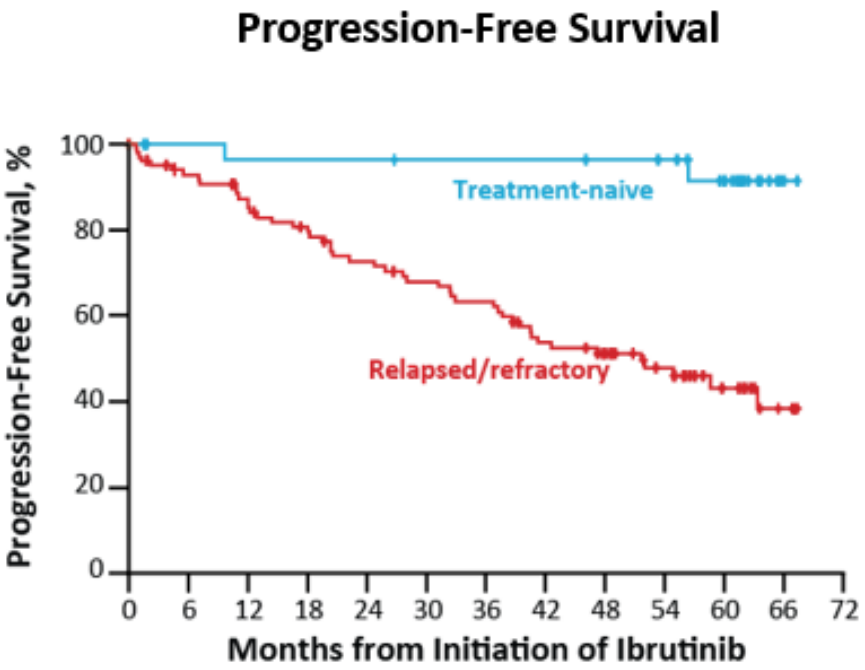
Study 116 (second interim analysis): Idelalisib + R versus placebo + R[2,3]

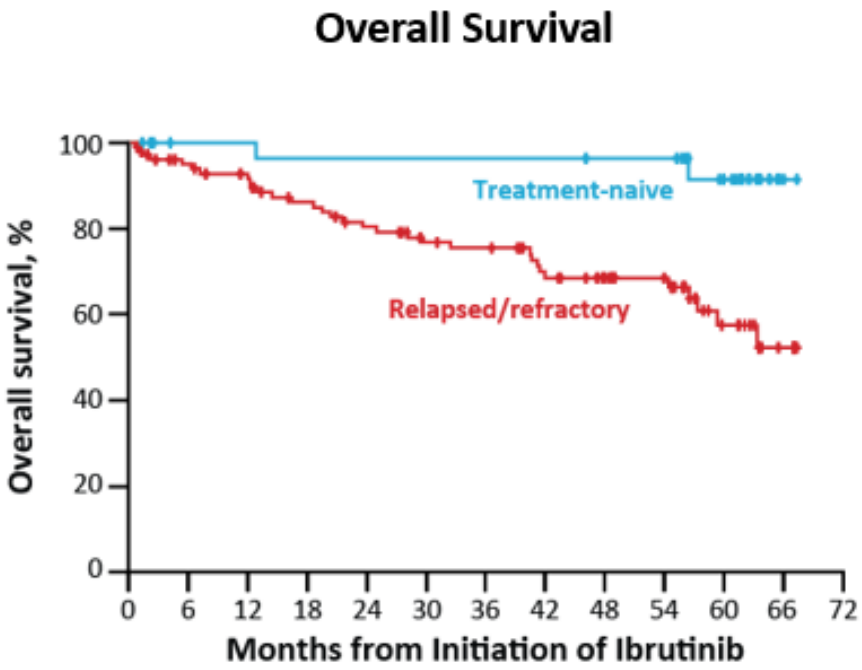


[a] Number of evaluable patients
R: rituximab

Furman et al, NEJM 2014; Coutre SE, et al. EHA 2014; Byrd et al, NEJM 2014.

5-year experience with ibrutinib in TN and R/R CLL





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

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

PHBE/IBR/0217/0003

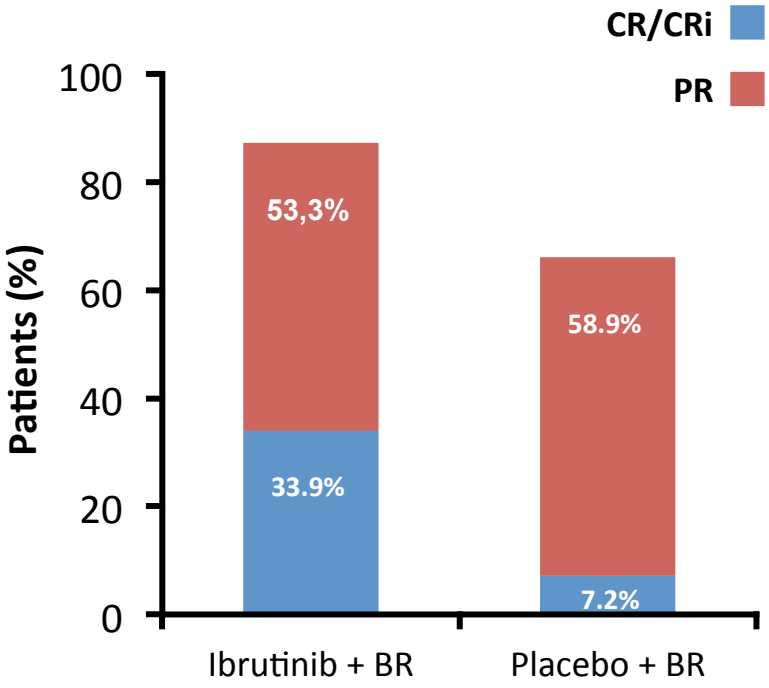
O'Brien et al., ASH 2016 (abstract 233, oral presentation)

Searching for MRD

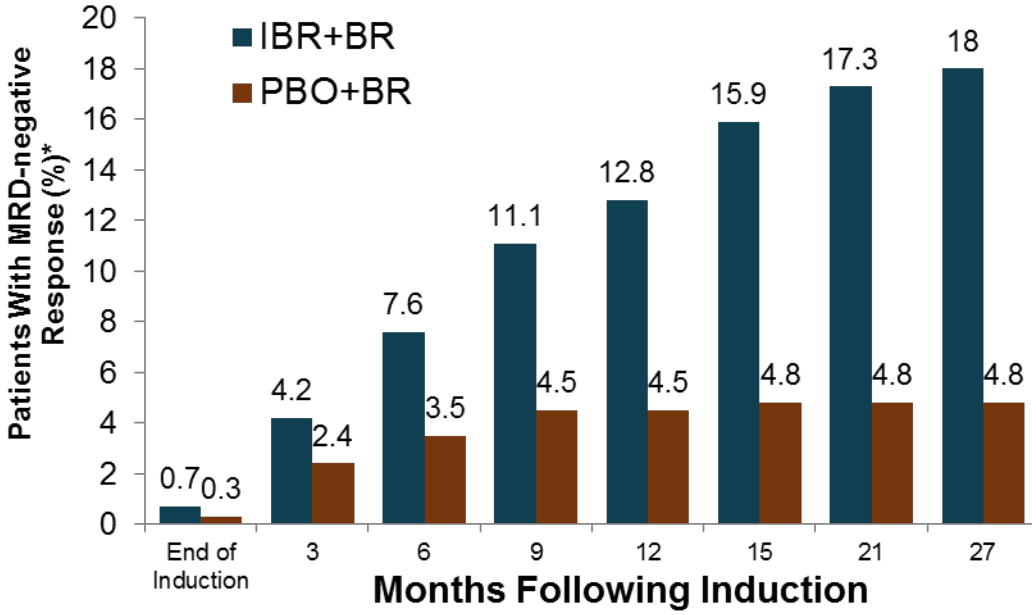
HELIOS (BRI versus BR)

ORR (investigator assessment)

OR = 87.2% versus 66.1% (p<0.0001)



2-yr update (October 2015)



- **As of March 2016, 60/289 (20.7%) on IBR+BR demonstrated MRD-negativity**

PHBE/IBR/0217/0003

Fraser G, et al. EHA 2016

Fraser G, et al. J Clin Oncol 2016; 34(suppl):Abstract 7525.

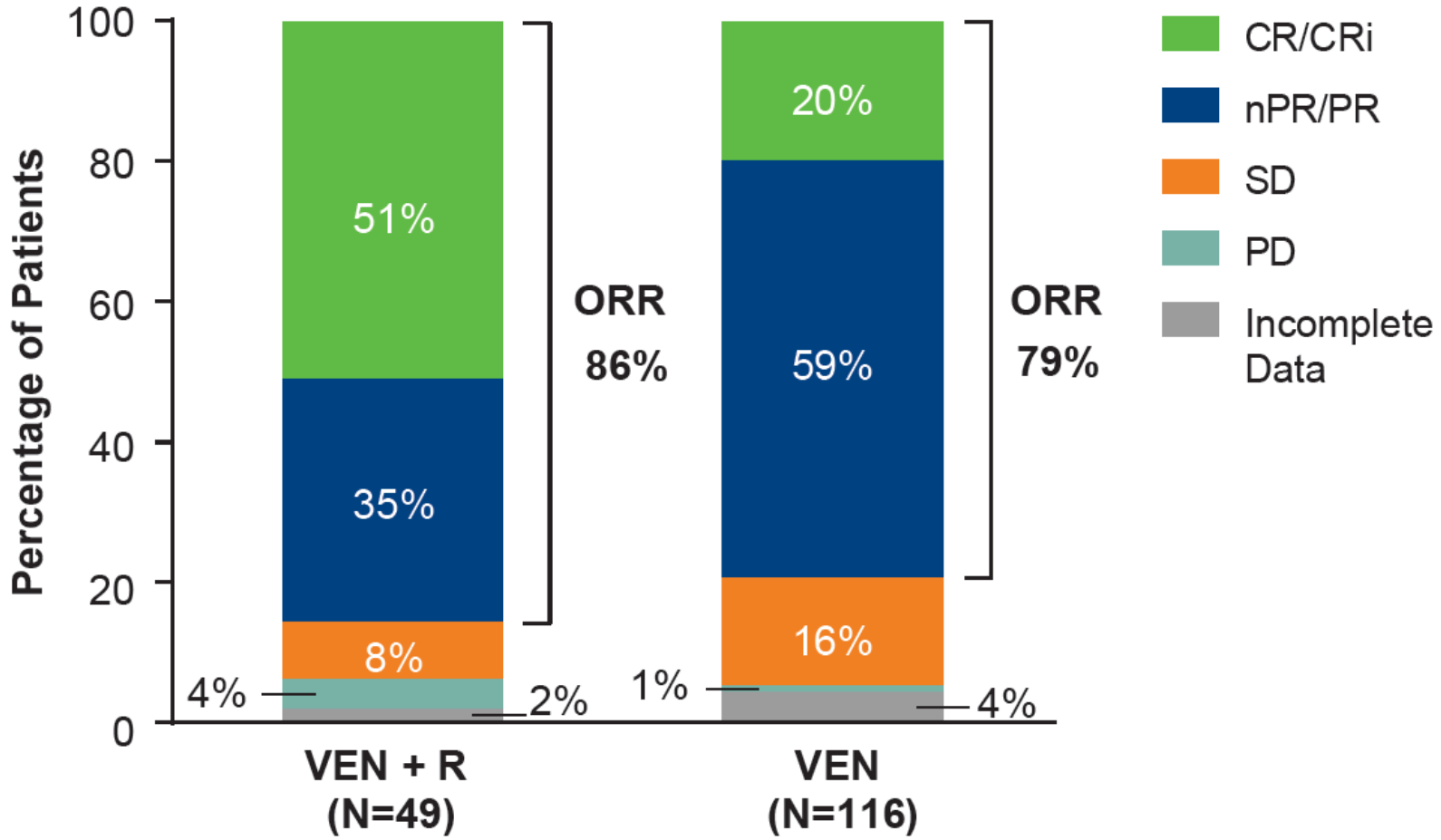
BR, bendamustine + rituximab;
CRi, CR with incomplete marrow recovery; OR, overall response.

EMA approval for Venclyxto on 08DEC16

- **Venclyxto monotherapy is conditionally approved for the treatment of chronic lymphocytic leukaemia (CLL) in the presence of *17p deletion or TP53 mutation* in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor**

- **Venclyxto monotherapy is conditionally approved for the treatment of CLL in without 17p deletion or TP53 mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor**

Complete responses with BCL2 inhibitors: ABT-199



MRD-neg (% of CR)	**80%**	**35%**

PHBE/IBR/0217/0003

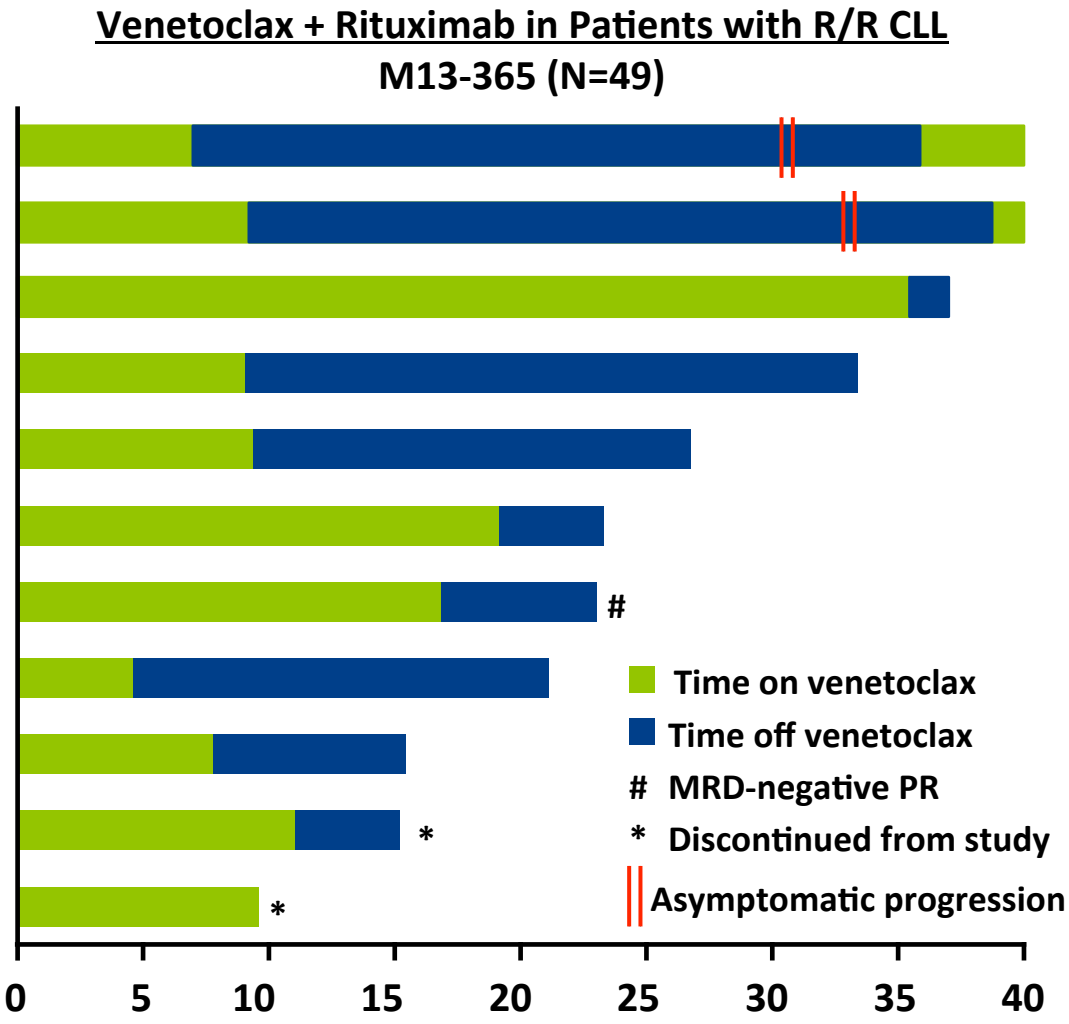
Roberts AW, et al. N Engl J Med 2016; 374(4): 311-22; EHA 2016 P209

M13-365: Venetoclax Combined with Rituximab in Patients with R/R CLL/SLL

55% of patients MRD-negative (27/49)

11 patients stopped venetoclax after achieving an objective response (9 MRD-negative); 9 remain in follow-up*

None of the MRD-negative patients have progressed; 2 patients with MRD-positive CR/CRi had asymptomatic progression

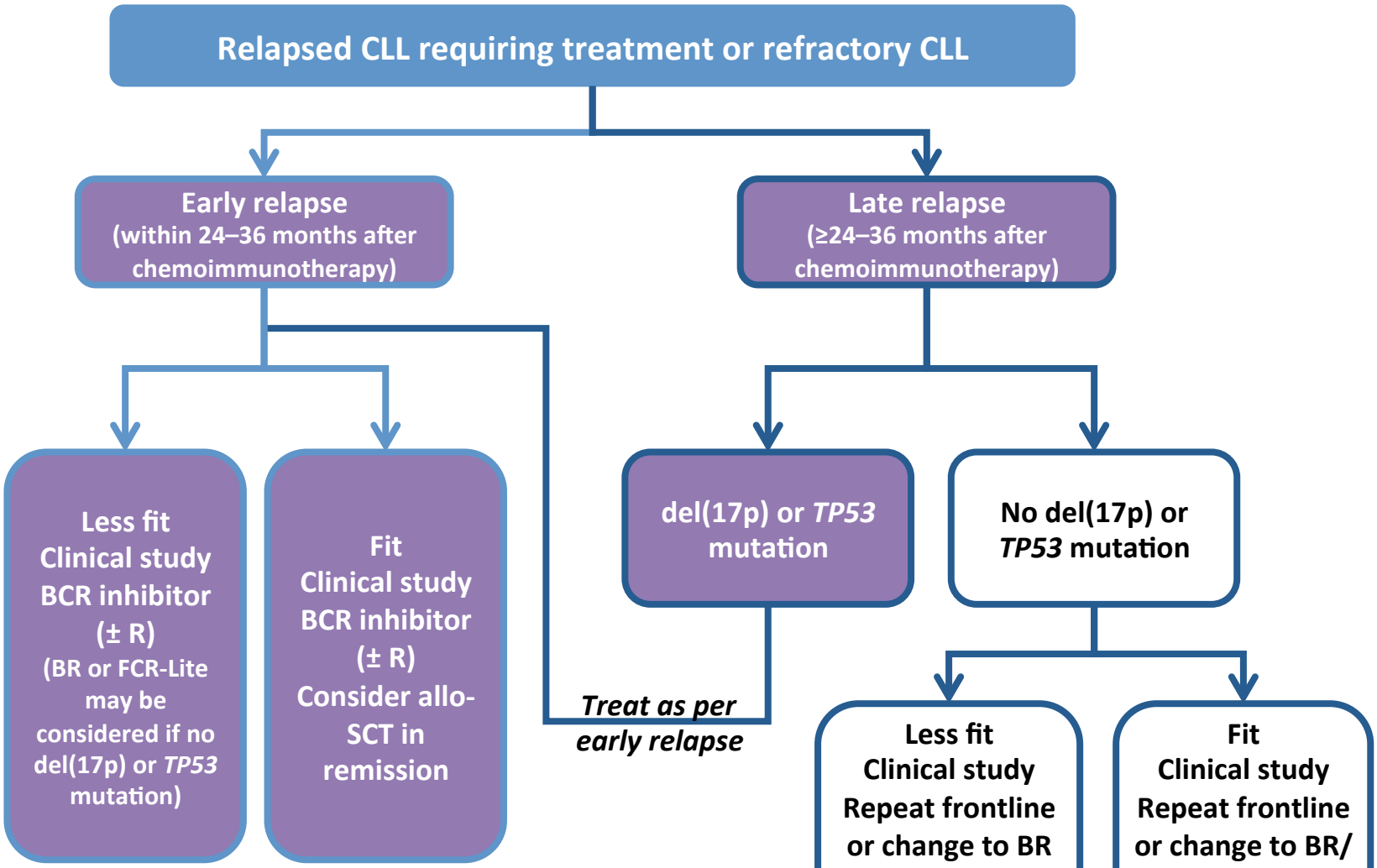


* Two discontinued with no evidence of progression.

PHBE/IBR/0217/0003

Seymour JF et al, Lancet Oncol 2017

ESMO 2015 clinical practice guidelines for R/R CLL

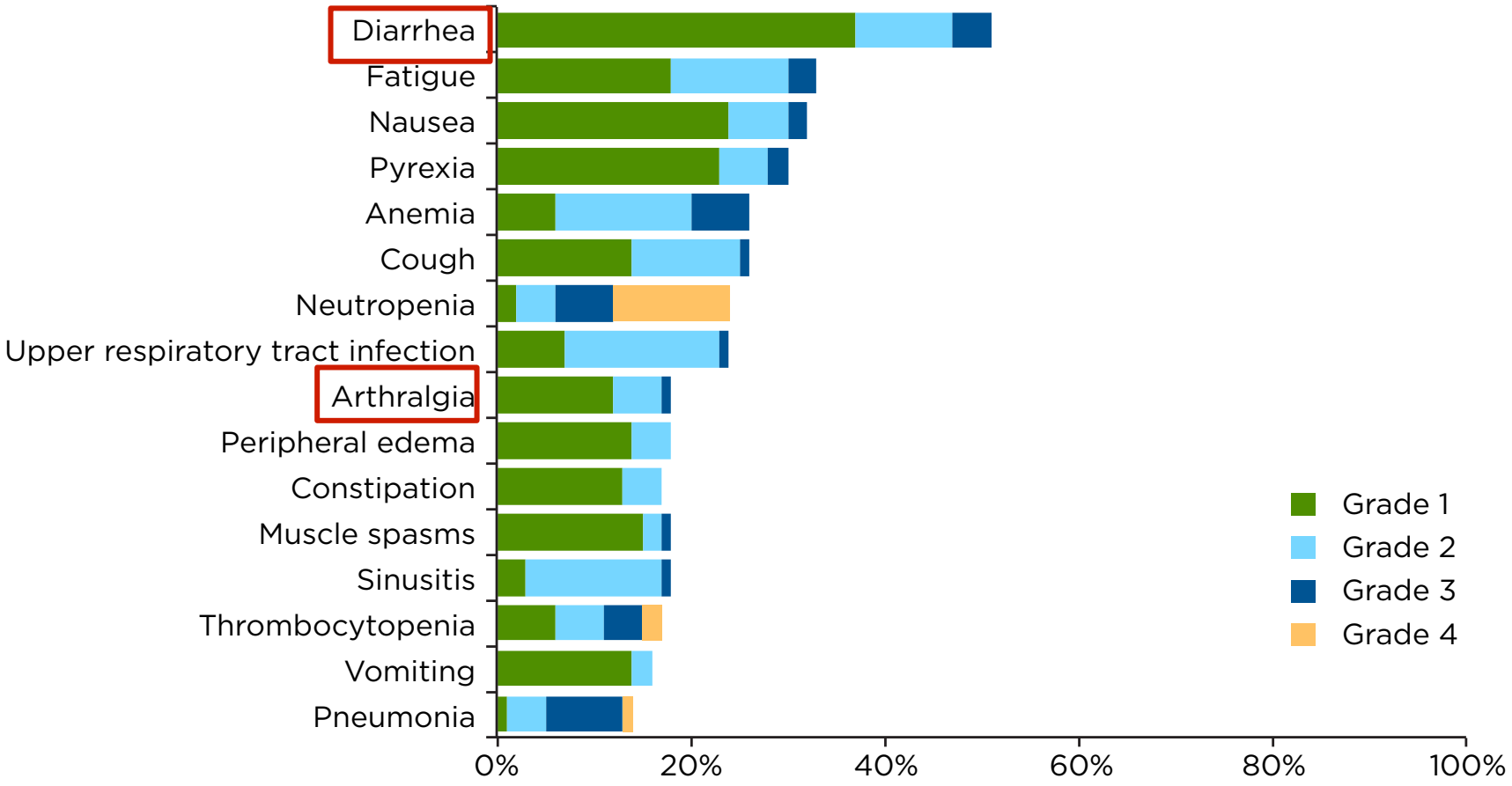


PHBE/IBR/0217/0003

Patients not responding nor progressing upon therapy with kinase inhibitors might be switched to a different kinase inhibitor or to BCL2 antagonists when available (according to clinical trials)

Eichhorst B, et al. Appendix 6: CLL: eUpdate. Ann Oncol 2016
Eichhorst B, et al. Ann Oncol 2015; 26(Suppl 5):v78–v84

RESONATE: Serious Adverse Events (SAEs)



- **13 (7%) of ibrutinib-treated patients discontinued due to AE/ unacceptable toxicity**

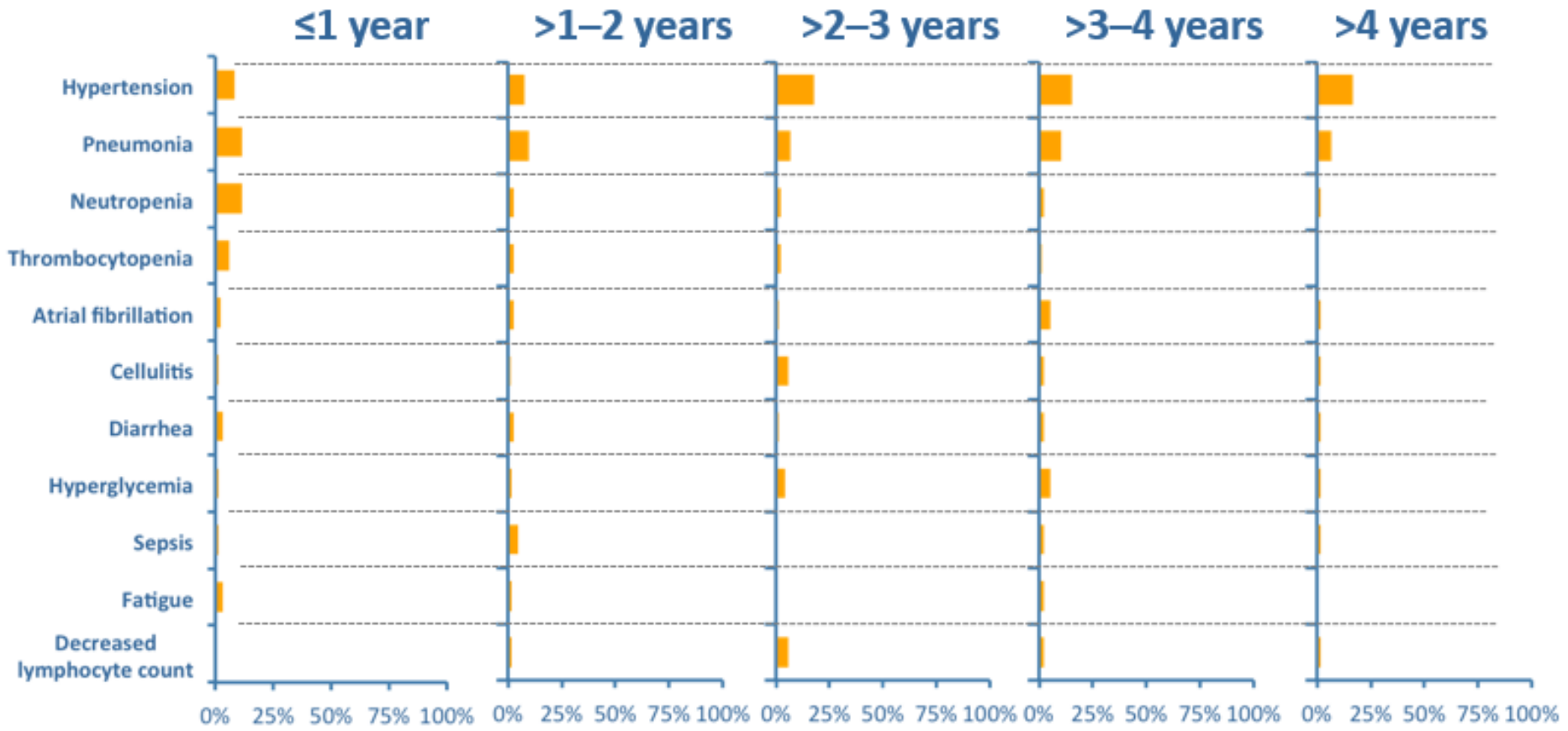
Thornton et al, ICML 2015

RESONATE: Serious Adverse Events (SAEs)

Adverse event, %	Ibrutinib (n=195)	Ofatumumab (n=191)
Median treatment duration	8.6 months	5.3 months
Subjects reporting ≥1 SAE	42%	30%
Reporting ≥1 AE grade ≥3	57%	47%
Any infection grade ≥3	24%	22%
Atrial fibrillation	5%	1%
Grade ≥3 AE atrial fibrillation	3%	0%
Any hemorrhage	44%	12%
Major hemorrhage	1%	2%

Byrd et al. NEJM 2014

5-year experience with ibrutinib in TN and R/R



- **Dose reductions and dose discontinuations due to AEs occurred more frequently in R/R patients than in TN patients, and during the first year after treatment compared with subsequent time periods.**

O'Brien et al., ASH 2016 (abstract 233, oral presentation)

Pooled analysis: Treatment-emergent AEs and laboratory abnormalities

AE, n (%)	Idelalisib monotherapy (n=354)		Idelalisib combination therapy (n=406)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Pyrexia	96 (27)	7 (2)	169 (42)	47 (12)
Diarrhea/colitis	131 (37)	38 (11)	161 (40)	68 (17)
Fatigue	112 (32)	6 (2)	130 (32)	13 (3)
Nausea	91 (26)	5 (1)	125 (31)	30 (7)
Cough	80 (22)	3 (1)	118 (29)	21 (5)
Rash	60 (17)	7 (2)	99 (24)	30 (7)
Chills	49 (14)	0	86 (21)	23 (6)
Pneumonia	47 (13)	40 (11)	74 (18)	56 (14)
Constipation	39 (11)	0	68 (17)	1 (<1)
Dyspnea	43 (12)	7 (2)	68 (17)	10 (3)
Abdominal pain	40 (11)	4 (1)	67 (17)	5 (1)
Vomiting	53 (15)	5 (1)	60 (15)	18 (4)
Decreased appetite	46 (13)	8 (2)	62 (15)	2 (<1)

Laboratory abnormality, n (%)	Idelalisib monotherapy (n=354)		Idelalisib combination therapy (n=406)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Hematologic				
Neutropenia	162 (46)	83 (23)	234 (58)	151 (37)
Anemia	102 (29)	18 (5)	145 (36)	34 (8)
Thrombocytopenia	94 (27)	37 (11)	143 (35)	50 (12)
Transaminases				
ALT/AST elevation	176 (50)	56 (16)	190 (47)	53 (13)

Includes patients receiving idelalisib in Studies 101-02, 101-07, 101-08, 101-09, 101-10, 101-11, 101-99 and 312-0116

Ghia et al, EHA 2016, poster #226; Li et al, poster #594; Robak et al, poster #1063; Vinson et al, poster #1078

Coutré S, et al. EHA 2015, oral presentation #433;).

ABT-199 monotherapy phase 1 in CLL

Adverse Events

Number of Patients (%)[a]	Any Grade	Grade 3/4
Any Adverse Event (AE)	**115 (99)**	**96 (83)**
Diarrhea	60 (52)	2(2)
Upper respiratory tract infection	56 (48)	1 (1)
Nausea	55 (47)	2 (2)
Neutropenia	52 (45)	48 (41)
Fatigue	46 (40)	4 (3)
Cough	35 (30)	0
Pyrexia	30 (26)	1 (1)
Anemia	29 (25)	14 (12)
Headache	28 (24)	1 (1)
Constipation	24 (21)	1 (1)
Thrombocytopenia	24 (21)	14 (12)
Arthralgia	21 (18)	1 (1)
Vomiting	21 (18)	2 (2)
Peripheral edema	18 (16)	0
Hyperglycemia	17 (15)	10 (9)

Number of Patients (%)[b]	Total
Any serious adverse event (SAE)	**52 (45)**
Febrile neutropenia	7 (6)
Pneumonia	5 (4)
Upper respiratory tract infection	4 (3)
Immune thrombocytopenia	3 (3)
Tumor lysis syndrome	3 (3)
Diarrhea	2 (2)
Fluid overload	2 (2)
Hyperglycemia	2 (2)
Prostate cancer	2 (2)
Pyrexia	2 (2)

[a] Listed are adverse events that were reported in ≥15% irrespective of cause. Pre-existing grade 1 or 2 laboratory abnormalities are not reported, unless the grade increased.
[b] Serious adverse events (SAEs) occurring in at least 2 patients; excludes SAEs related to disease progression in 2 patients.
AE, adverse event; SAE, serious adverse event; TLS, tumor lysis syndrome

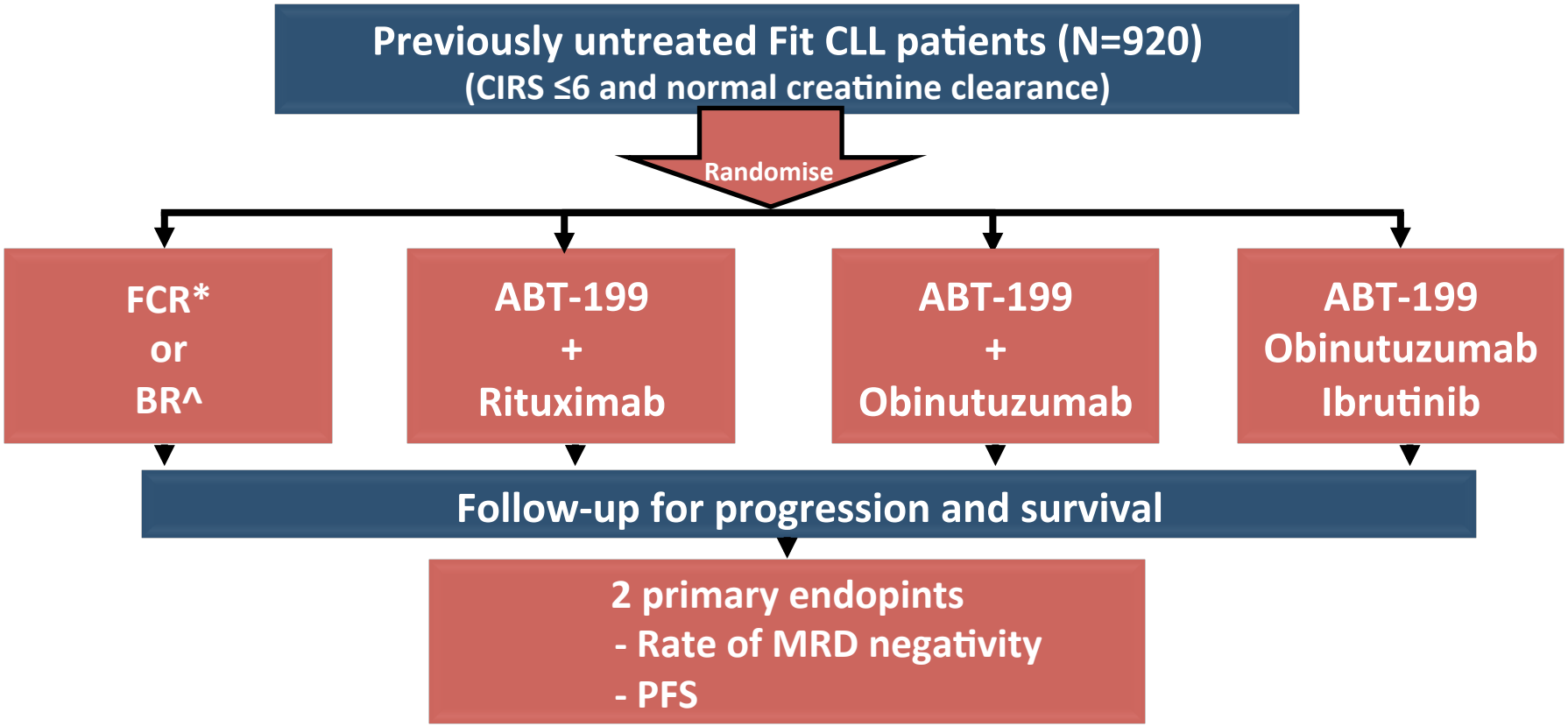
- Clinical TLS was observed in 3 patients with high tumor burden who were treated with doses of ≥ 50 mg/day; 2 of these patients had severe sequelae
- Following data review, the expansion cohort was enrolled under a protocol that incorporated amended dosing, prophylaxis and monitoring for TLS
- **No clinical events of TLS were seen after a change in the dosing and administration protocol**

Davids et al, EHA 2016, poster #225

Roberts AW, NEJM 2016

IS THIS THE END OF CHEMOTHERAPY?

CLL13-TRIAL OF THE GCLLSG in cooperation with HOVON, Nordic CLL Study Group and SAKK (GAIA)



Obinutuzumab: 6 cycles
Venetoclax: 12 cycles
Ibrutinib: 36 cycles or MRD^{neg}

**<65 years of age*
^>65 years of age

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