CITTA' DI SAN GIOVANNI ROTONDO
RETE CIVICA 2.0

GITMO

Rete Ematologica Pugliese

SIE
"Società Italiana di Ematologia"

fondazione GIMEMA onlus

LLC e LNH: Confronto real world e studi registrativi

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"Istituto Tumori Giovanni Paolo II"
Bari

disclosure

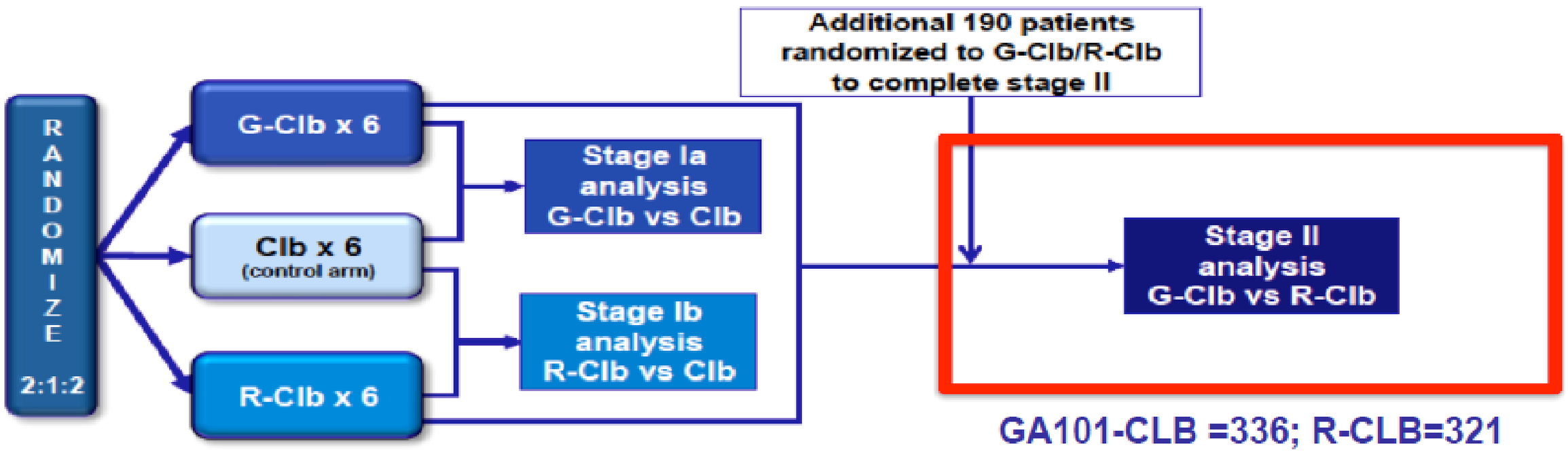
- Posizione di dipendente in aziende con interessi commerciali in campo sanitario: NIENTE DA DICHIARARE
    - Consulenza ad aziende con interessi commerciali in campo sanitario: NIENTE DA DICHIARARE
  - Fondi per la ricerca da aziende con interessi commerciali in campo sanitario: NIENTE DA DICHIARARE
    - Partecipazione ad Advisory Board: **ROCHE, AMGEN**, **GILEAD, JANSSEN CILAG,CELGENE**
- Titolarietà di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario: NIENTE DA DICHIARARE
  - Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario: NIENTE DA DICHIARARE
  -

CLL 11

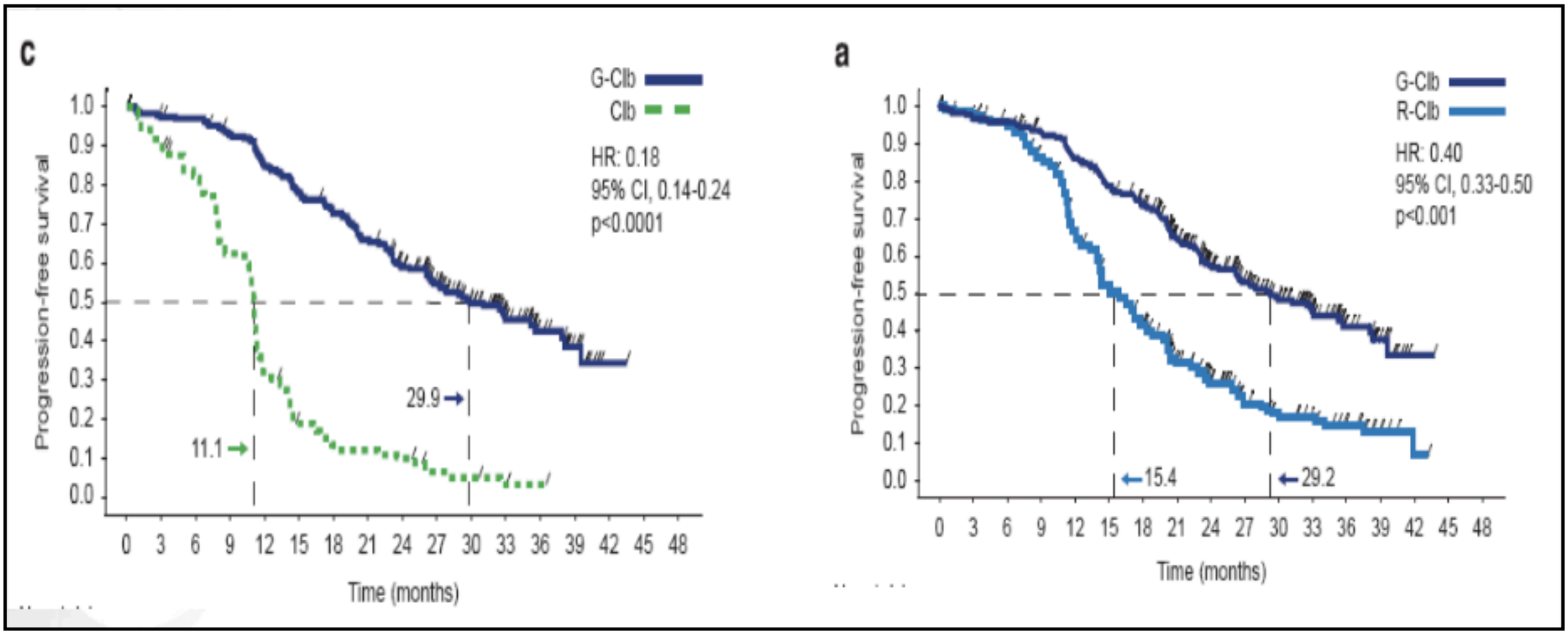
Obinutuzumab plus Chlorambucil in Patients with CLL and Coexisting Conditions

Valentin Goede, M.D., Kirsten Fischer, M.D., Raymonde Busch, M.S., Anja Engelke, M.D., Barbara Eichhorst, M.D., Clemens M. Wendtner, M.D., Tatiana Chagorova, M.D., Javier de la Serna, M.D., Marie-Sarah Dilhuydy, M.D., Thomas Illmer, M.D., Stephen Opat, M.D., Carolyn J. Owen, M.D., Olga Samoylova, M.D., Karl-Anton Kreuzer, M.D., Stephan Stilgenbauer, M.D., Hartmut Döhner, M.D., Anton W. Langerak, Ph.D., Matthias Ritgen, M.D., Michael Kneba, M.D., Elina Asikanius, M.Sc., Kathryn Humphrey, B.Sc., Michael Wenger, M.D., and Michael Hallek, M.D.

N ENGL J MED 370;12 NEJM.ORG MARCH 20, 2014

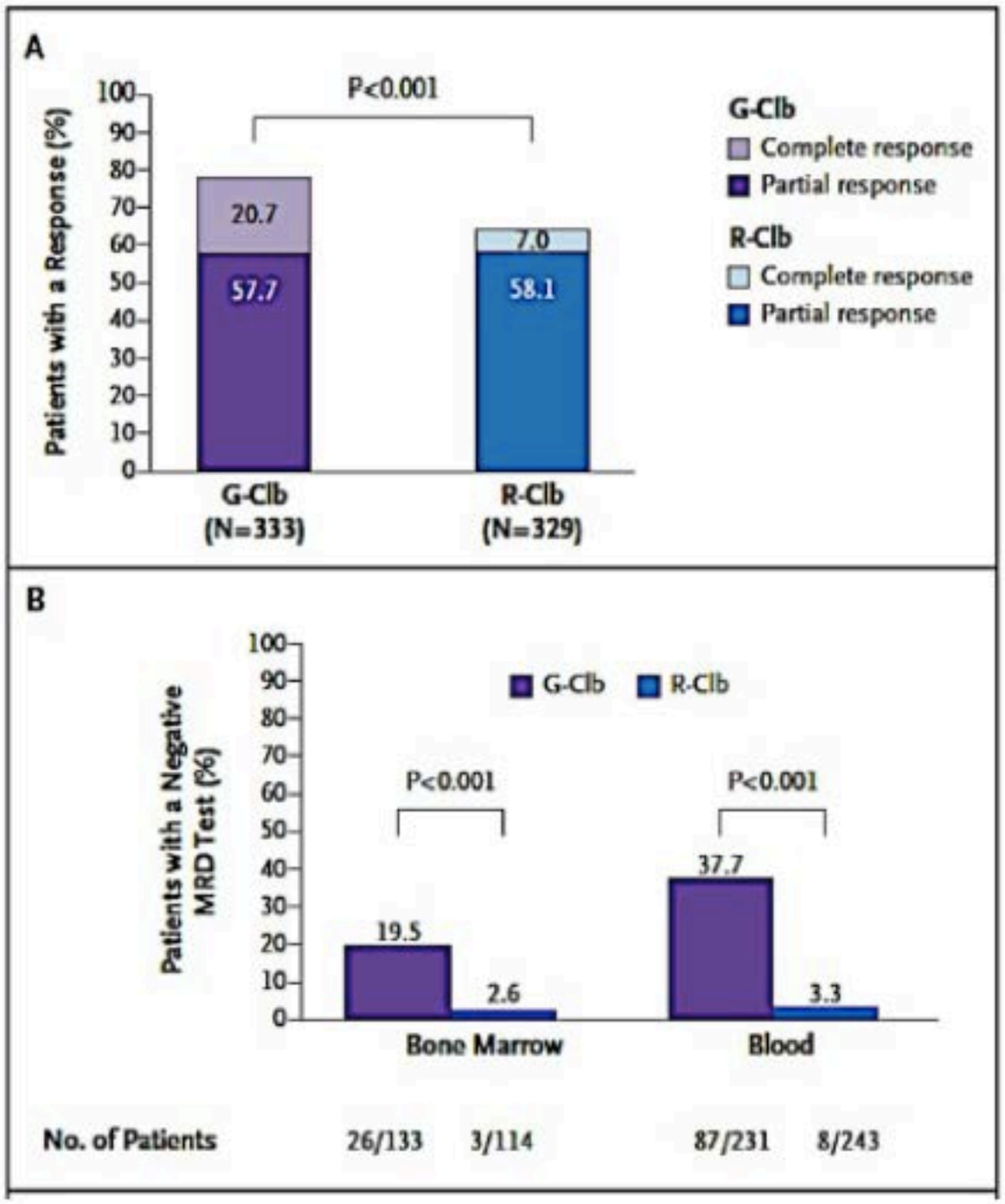


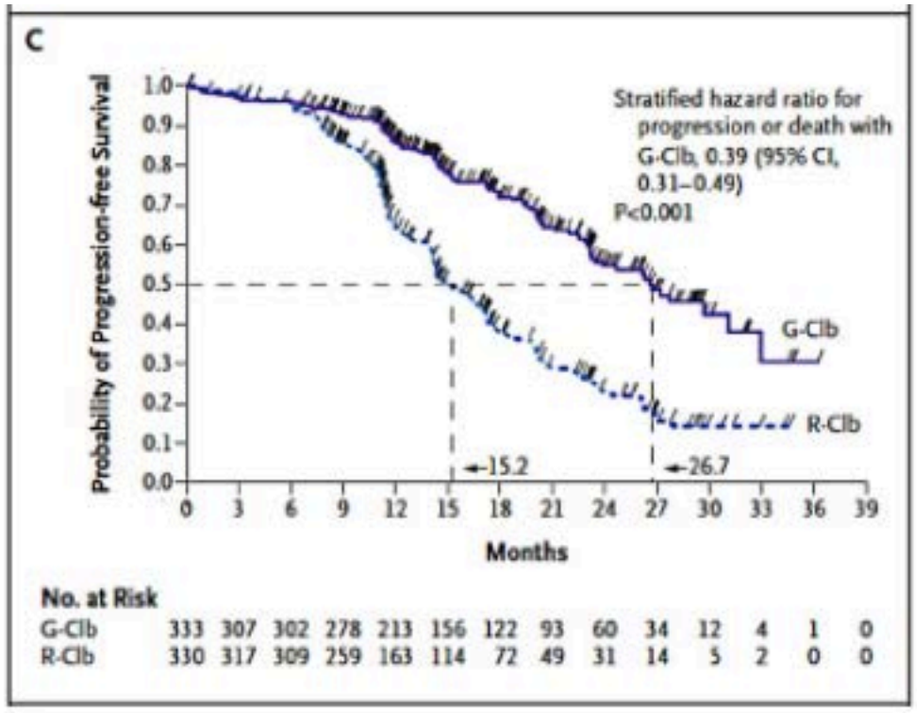
Obinotuzumab as frontline treatment of CLL11 study
Progression Free Survival

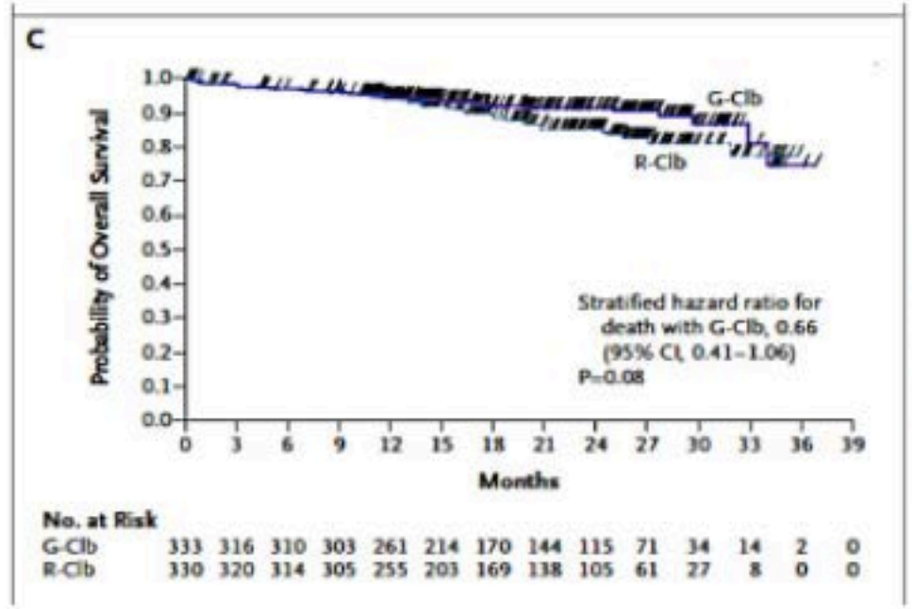


PFS favourable in all age groups: (< 65,≥ 65,< 75, ≥ 75)

CLL11 trial: main results







NEJM 2014

RESONATE-2 trial: Ibrutinib versus Chlorambucil

Table 1. RESONATE-2 reasons for initiation of treatment and baseline patient characteristics.[1]

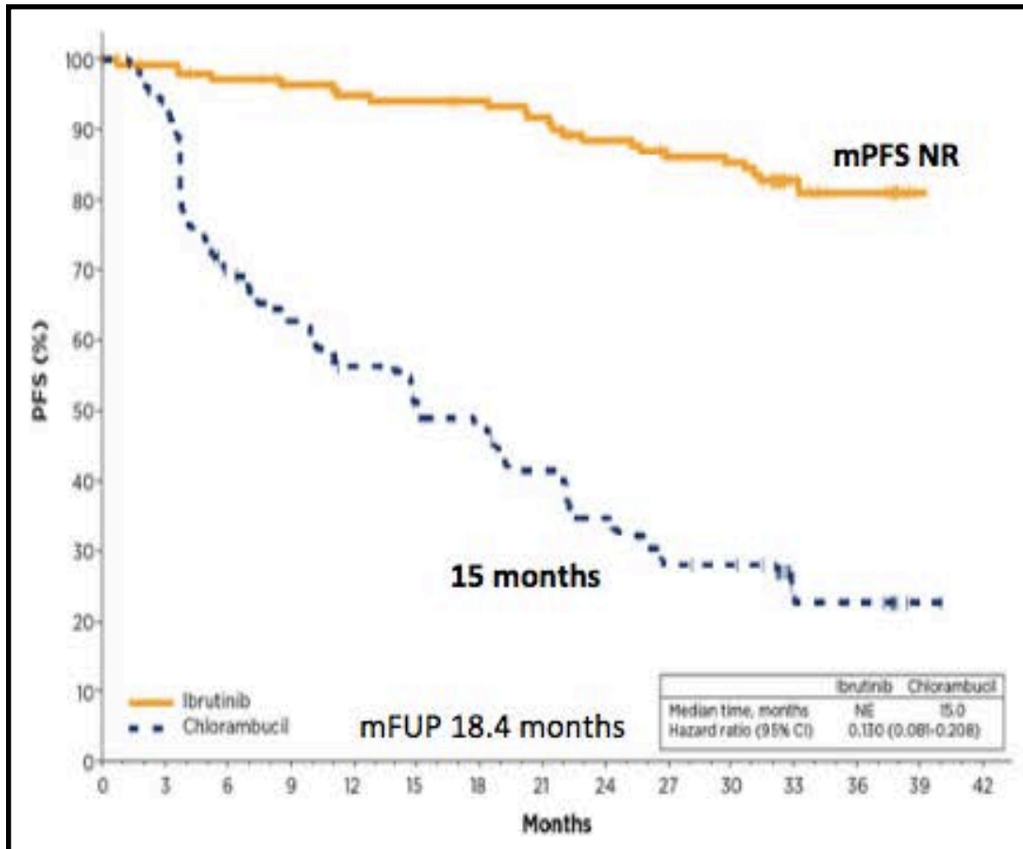
	Ibrutinib (n=136)	Chlorambucil (n=133)
Baseline Characteristic		
Median age (range), y	73 (65-89)	72 (65-90)
≥ 75 y, (%)	46 (34)	47 (35)
Male, n (%)	88 (65)	81 (61)
ECOG performance status, n (%)		
0	60 (44)	54 (41)
1	65 (48)	67 (50)
2	11 (8)	12 (9)
Rai stage III or IV, n (%)	60 (44)	62 (47)
Bulky disease ≥ 5 cm, n (%)	54 (40)	40 (30)
Hierarchical Classification, n (%)		
Del(11q)	29/130 (22)	25/121 (21)
Trisomy 12	20/117 (17)	23/108 (21)
Del(13q)	25/112 (22)	32/108 (30)
None of above	38/112 (34)	28/108 (26)
IGHV status*, n/N (%)		
Mutated	40/121 (33)	42/127 (33)
Unmutated	58/121 (48)	60/127 (47)
Unclassifiable†	23/121 (19)	25/127 (20)
Patients meeting criteria for active disease, n (%)		
Progressive marrow failure	54 (40)	49 (37)
Lymphadenopathy	55 (40)	44 (33)
Splenomegaly	36 (26)	44 (33)
Progressive lymphocytosis	23 (17)	28 (21)
Autoimmune anemia and/or thrombocytopenia	3 (2)	5 (4)
Any documented constitutional symptoms	64 (47)	56 (42)
Unintentional weight loss (>10% within 6 months)	14 (10)	16 (12)
Significant fatigue	44 (32)	29 (22)
Fever	4 (3)	3 (2)
Night sweats	32 (24)	35 (26)

- **269 previously untreated patients ≥ 65 years of age** (median 73 yrs)
  - Active disease
  - Patients ≤70 yrs had comorbidity that precluded treatment with FCR
  - del(17p) CLL were excluded
- **Patients were randomly assigned in a 1:1 ratio to treatment**
  - Oral ibrutinib, 420 mg once daily until disease progression
  - Chlorambucil, 0.5 mg/kg (up to 0.8 mg/kg based on tolerability) on days 1 and 15 of a 28-day cycle for 12 cycles.
- **End Point**
  - PFS, OS
  - ORR, improvement in hematologic variables
  - Safety and QOL

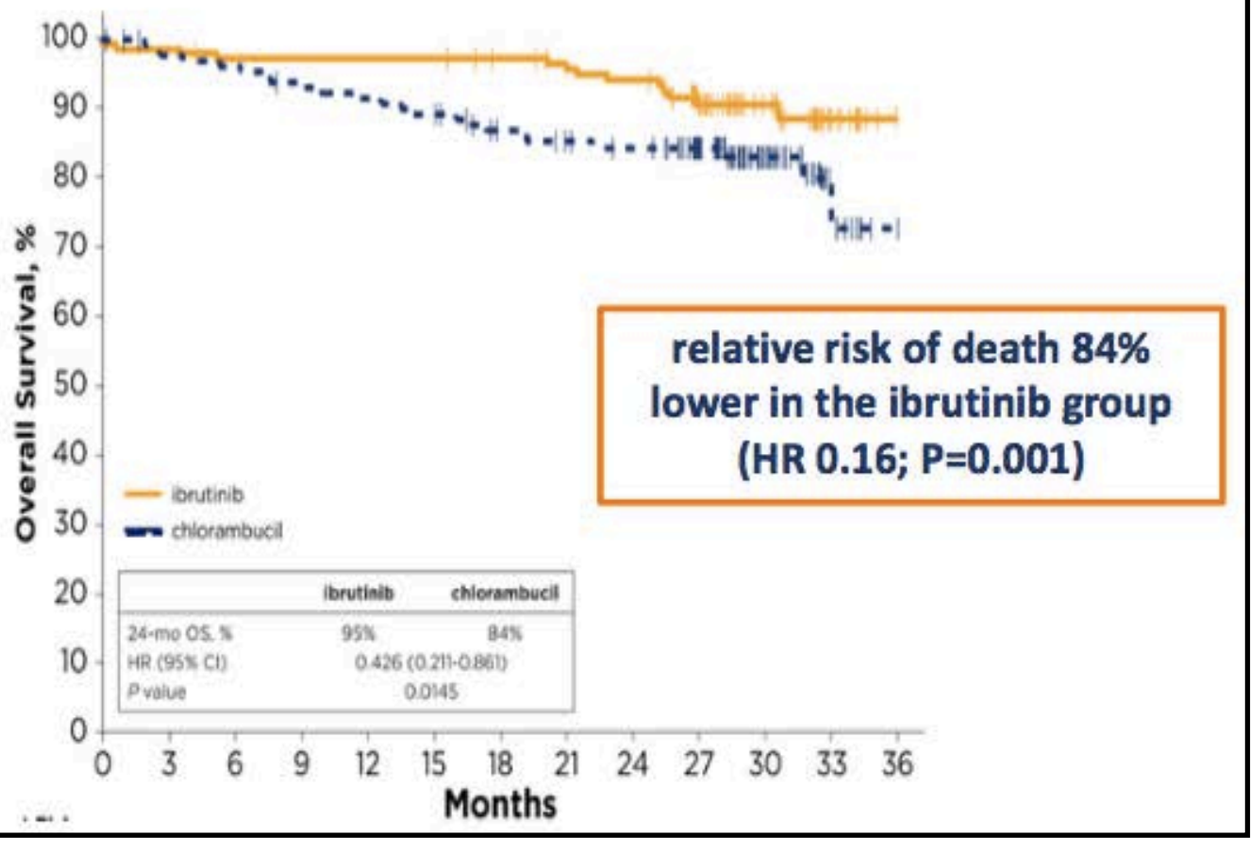
Burger et al 2015, Barr et al 2017, Tedeschi et al 2017

RESONATE-2 trial: Ibrutinib versus Chlorambucil PSF and OS

Progression Free Survival



Overall Survival

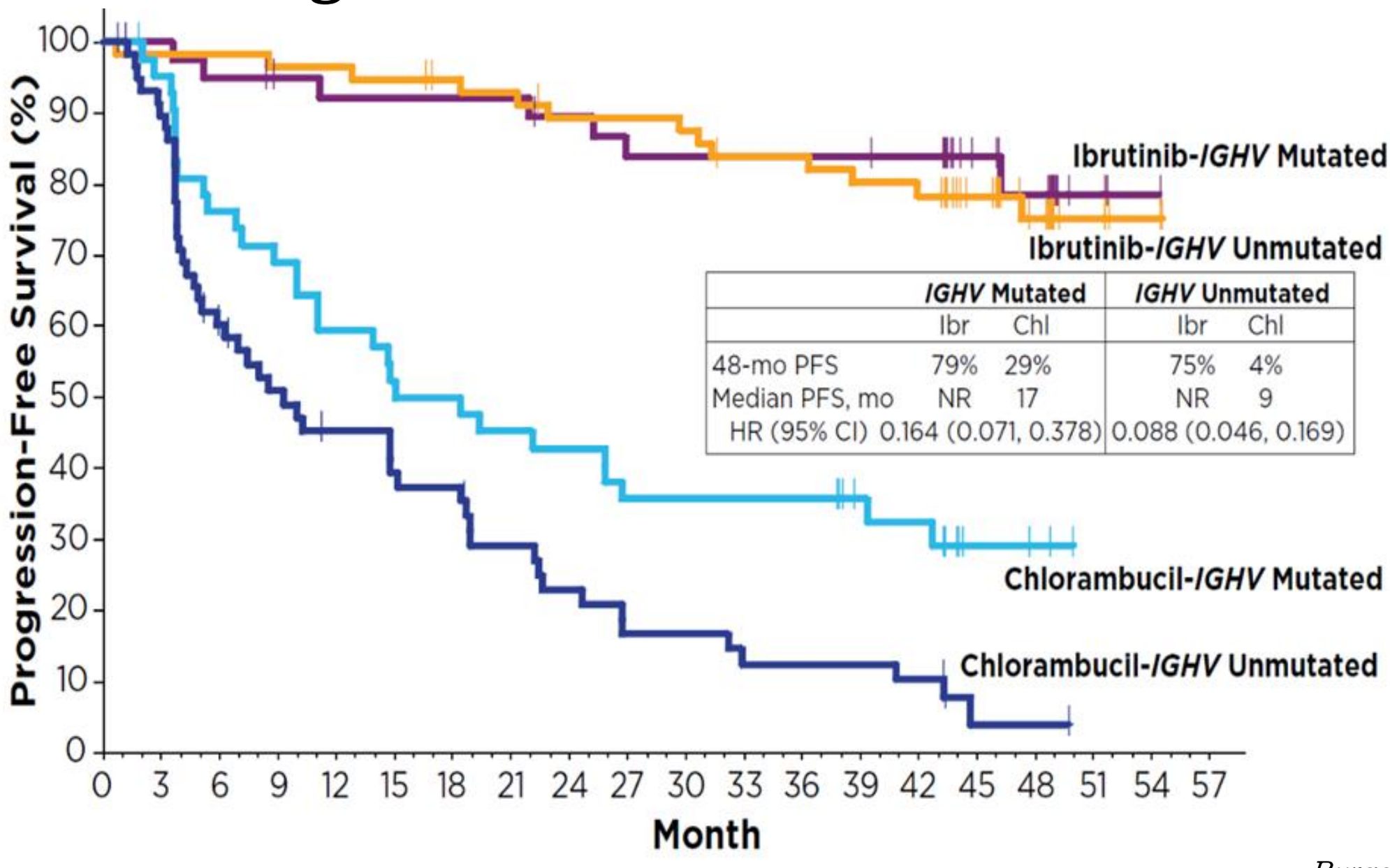


2 yrs-PFS with ibrutinib 89%:

- Del11q 97%; UM 89%
- <75 yrs 88%; ≥75 yrs 89%

Burger et al 2015, Barr et al 2017, Tedeschi et

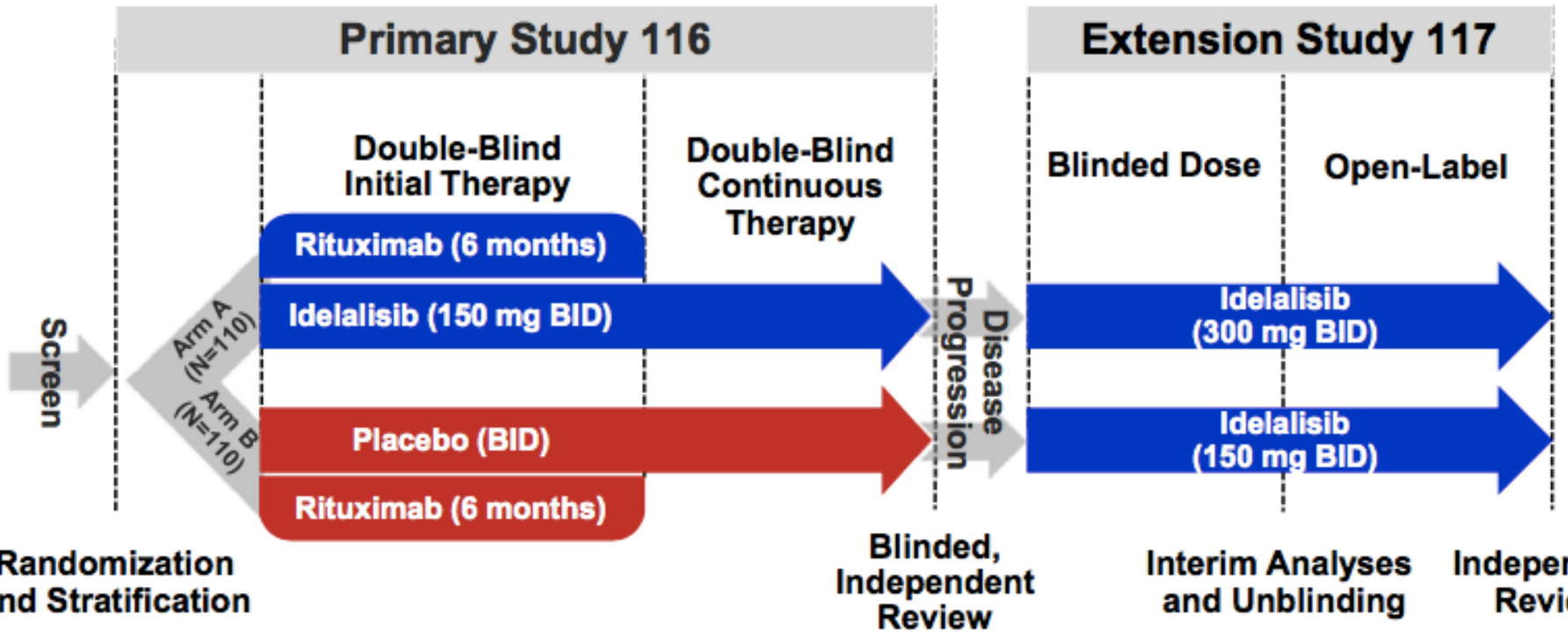
Resonate-2 trial: 4 years follow-up, front-line ibrutinib vs chlorambucil in ≥65 yrs patients with CLL, PFS according to IGHV status



	IGHV Mutated		IGHV Unmutated	
	Ibr	Chl	Ibr	Chl
48-mo PFS	79%	29%	75%	4%
Median PFS, mo	NR	17	NR	9
HR (95% CI)	0.164 (0.071, 0.378)		0.088 (0.046, 0.169)	

Burger, EHA 2018

Idelalisib: CLL registration study

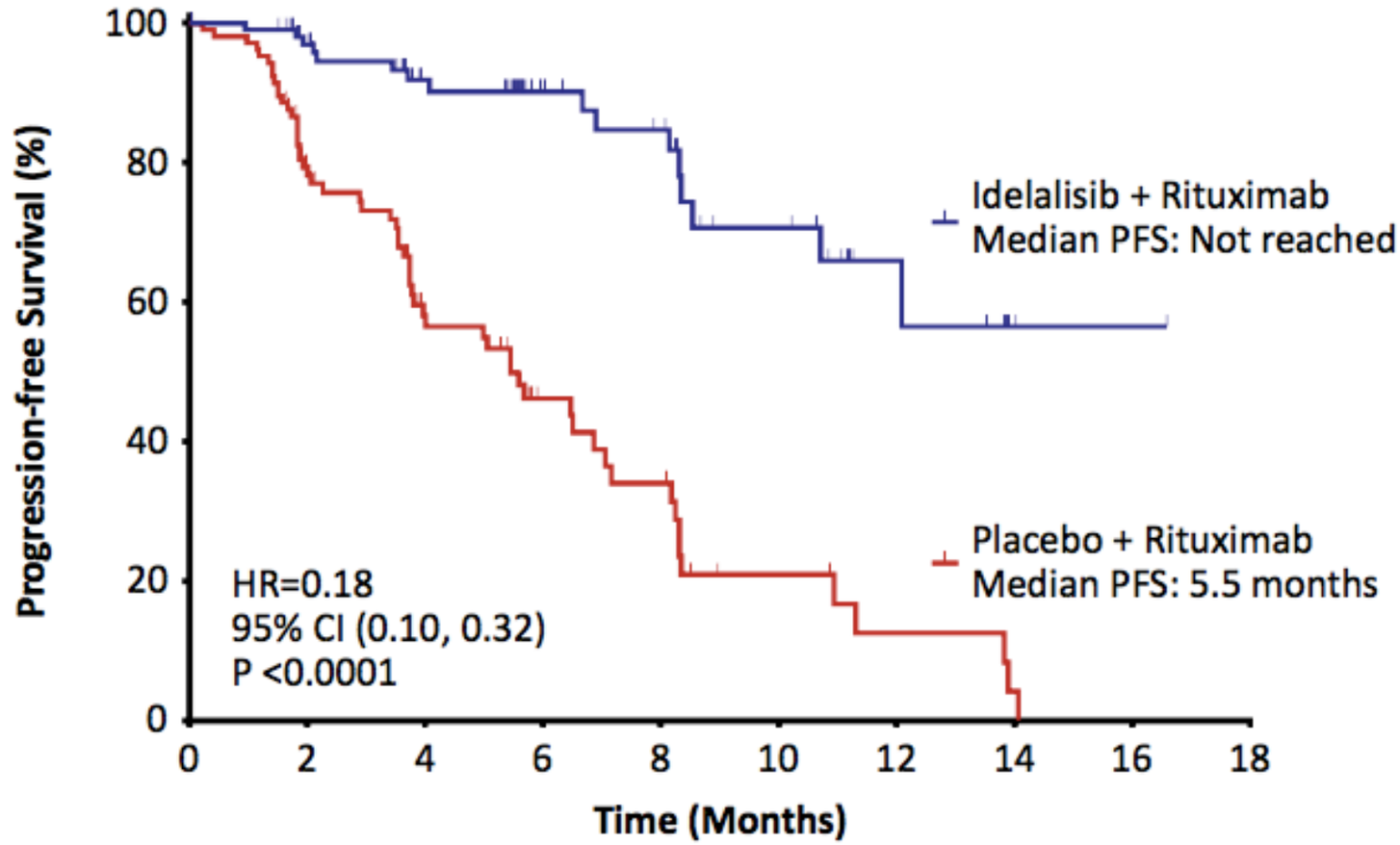


- Primary Endpoint: PFS; Secondary: ORR, LNR, OS
- IAs planned at 50% and 75% of total events, DMC recommended early study stop after 1st IA (Furman et al., NEJM 2014)
- 2nd IA conducted at end of the blinded-phase according to amendment (data cut-off 09 October 2013 with 63% of total PFS events)

BID, twice daily; DMC, data monitoring committee; IA, interim analysis; LNR, lymph node response; N, number of patients; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Coutre et al., J Clin Oncol 32:5s, 2014 (suppl; abstr 7012)

Progression Free Survival: All Patients

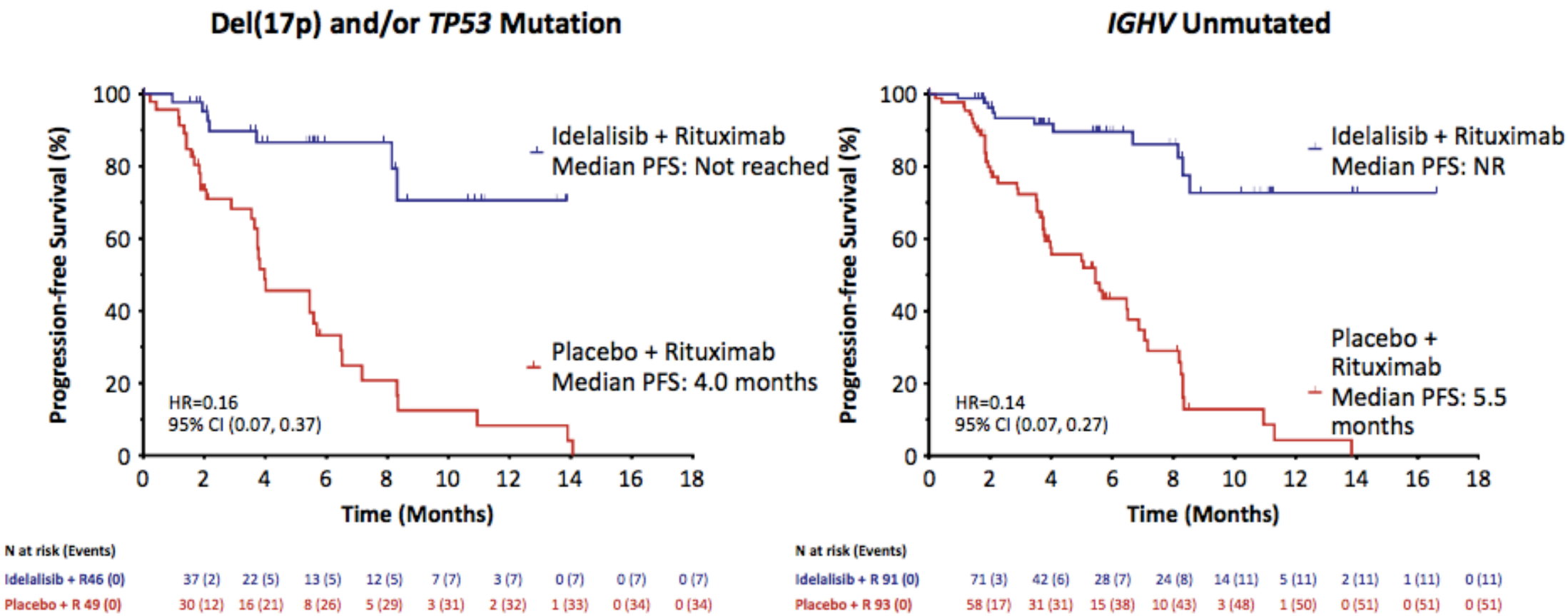


N at risk (Events)										
Idelalisib + R	110 (0)	87 (3)	54 (7)	35 (8)	30 (10)	17 (14)	7 (15)	2 (16)	1 (16)	0 (16)
Placebo + R	110 (0)	69 (21)	37 (37)	19 (44)	14 (49)	6 (54)	3 (56)	1 (58)	0 (59)	0 (59)

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; R, rituximab.

Coutre et al., J Clin Oncol 32:5s, 2014 (suppl; abstr 7012)

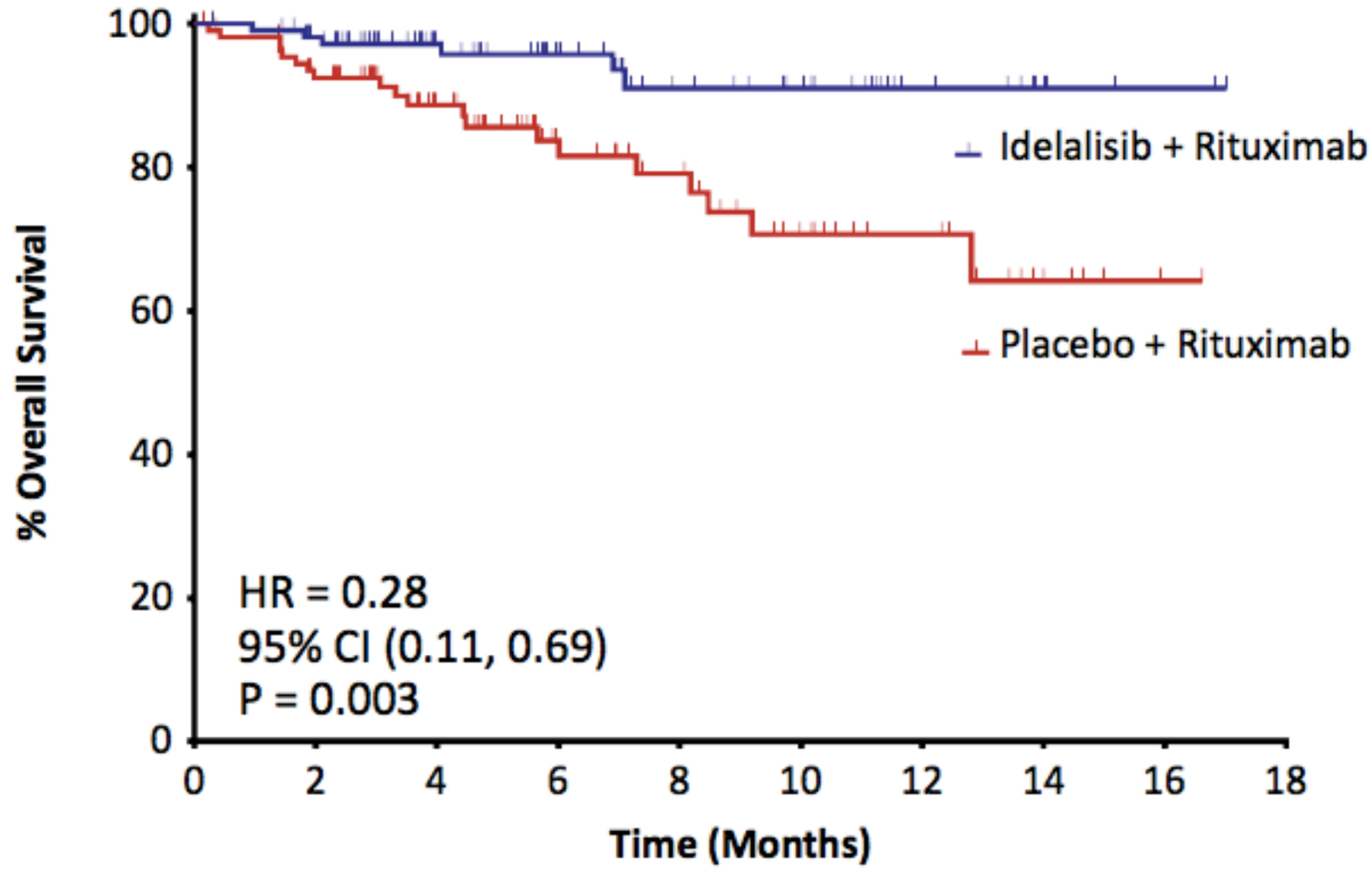
Progression Free Survival: Patients subgroups



CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; R, rituximab.

Coutre et al., J Clin Oncol 32:5s, 2014 (suppl; abstr 7012)

Overall Survival



N at risk (Events)									
Idelalisib + R 110 (0)	102 (2)	68 (3)	47 (4)	33 (6)	25 (6)	11 (6)	6 (6)	2 (6)	0 (6)
Placebo + R 110 (0)	93 (8)	61 (11)	39 (14)	31 (16)	20 (19)	13 (19)	5 (20)	1 (20)	0 (20)

[a]Evaluable patients.

mut, mutation; SPD, sum of products of lymph node dimension; R, rituximab.

Coutre et al., J Clin Oncol 32:5s, 2014 (suppl; abstr 7012)

Response Rates

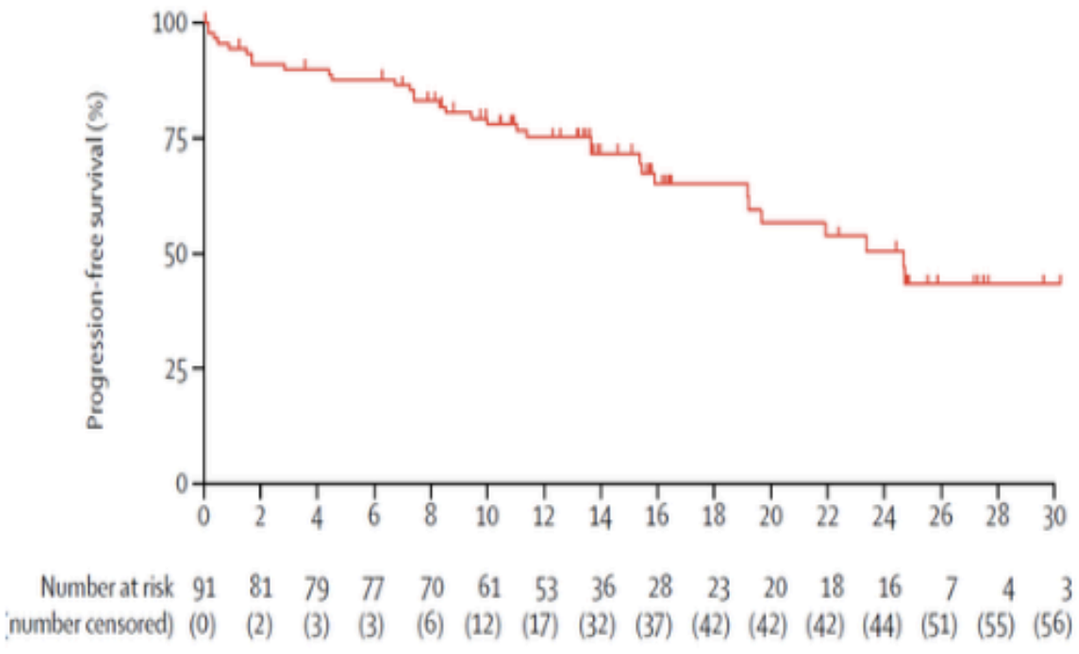
		Idelalisib + R	Placebo + R
Overall response rate[a], %, (95% CI) (n=102; 101)[b]		77 (68–85)	15 (9–23)
≥50% reduction in lymph nodes[c], %, (95% CI) (n=102; 101)[b]		92 (85–97)	6 (2–13)
Organomegaly response, %			
Spleen	(n=76; 64)[b]	72	22
Liver	(n=52; 59)[b]	46	19
Hematologic response, %			
Hemoglobin	(n=59; 57)[b]	73	40
Neutrophils	(n=27; 25)[b]	74	68
Platelets	(n=48; 49)[b]	88	55

[a]p<0.0001; [b]number of evaluable patients (idelalisib; placebo); [c]≥50% reduction in sum of products of lymph node dimension.
CI, confidence interval; ORR, overall response rate; R, rituximab.

Venetoclax effective after BCRi

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

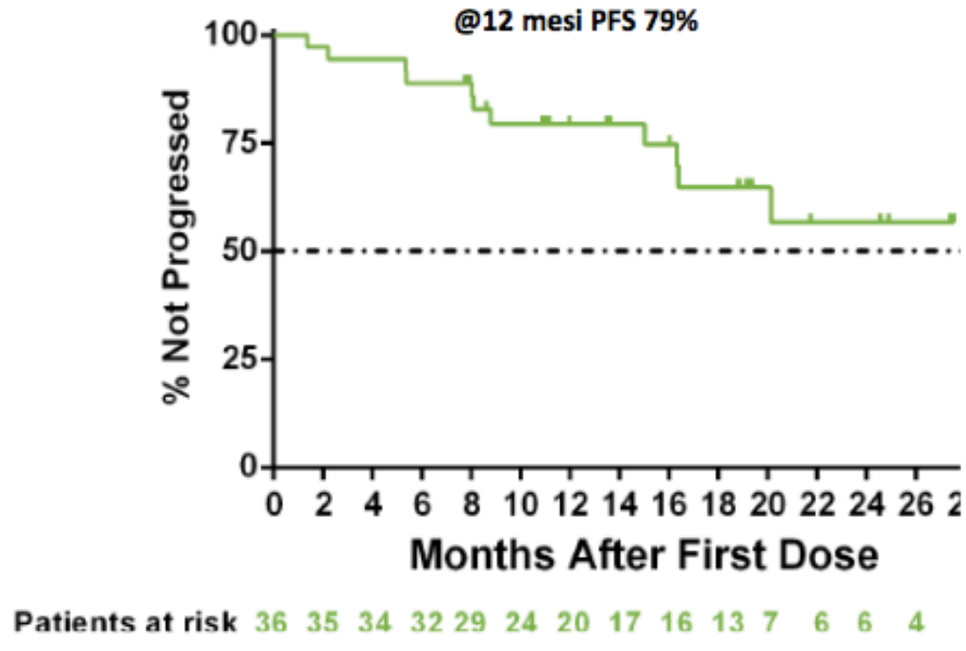
Jeffrey A Jones, Anthony R Mato, William G Wierda, Matthew S Davids, Michael Choi, Bruce D Cheson, Richard R Furman, Nicole Lamanna, Paul M Barr,



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

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

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



M14-032
Phase 2 Study of Venetoclax Monotherapy CLL Relapsed After or Refractory to Ibrutinib or Idelalisib Therapy

Jones JA, et al. Venetoclax for chronic lymphocytic leukaemia progressing after ibrutinib: an interim analysis of a multicentre, open-label, phase 2 trial.
Lancet Oncol. 2018 Jan;19(1):65-75.

Coutre S, et al. Venetoclax for patients with chronic lymphocytic leukemia who progressed during or after idelalisib therapy.
Blood. 2018 Jan 5.

Approval study

M14-032: Ibrutinib arm_Study design

Fase 2
CLL R/R
dopo BCRi

→ **Venetoclax 400 mg**

Endpoint Primario:
ORR
Endpoints Secondari:
DOR, PFS, TTP, OS
Endpoints Esplorativi:
MRD, BTK/PLC2 mut

Sep 2014 – Nov

Criteri di Inclusione

- R/R CLL
- **Progressione durante o dopo terapia con BCRi (ibrutinib** o idelalisib)
- ECOG ≤2
- Adeguata funzionalità midollare
- Creat/Clear ≥50ml/min

Criteri di Esclusione

- Trasformazione di Richter
- Precedente AlloTMO
- Citopenia autoimmune non controllata e attiva
- Tossicità non risolta di precedenti terapie

Washout 7 giorni →

Coorte Principale:
Venetoclax fino a PD o tossicità inaccettabile (o fino a 2 anni) **(N=43)**

Emendamento al Protocollo Sett 2016

Washout 3 giorni →

Coorte di espansione:
Venetoclax fino a PD o tossicità inaccettabile (o fino a 2 anni) **(N=48)**

Jones JA, et al. Lancet Oncol. 2017 Dec 12.

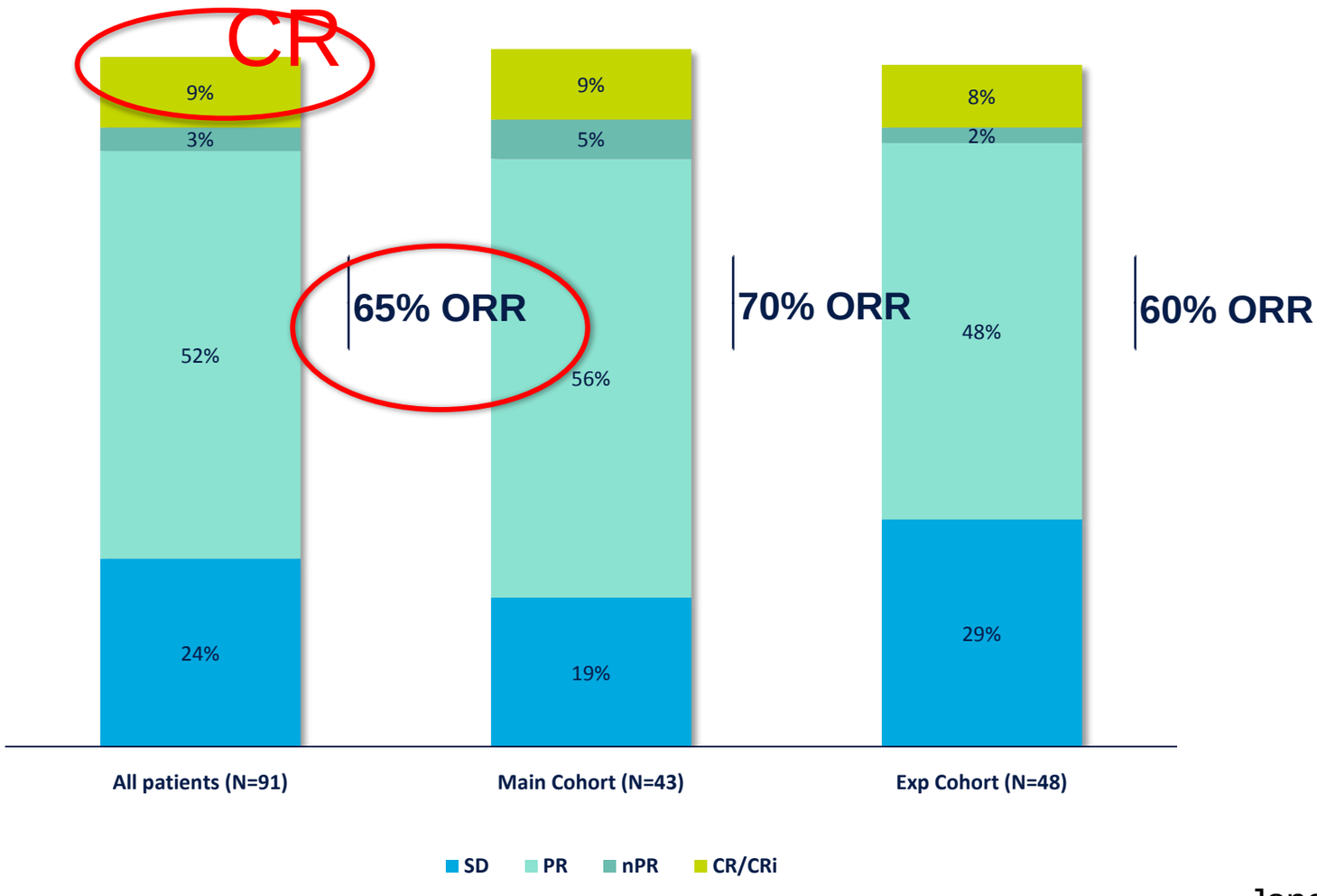
M14-032 Ibrutinib arm – pts characteristics :
heavly pretreated / unfavorevorable

Characteristics	Main Cohort (n= 43)	Expansion Cohort (n=48)	All (n=91)
Age, median (range), years	66 (48-80)	65(28-81)	66 (28-81)
Unmutated IGHV, n/N (%)	25/29 (86%)	25/38(66%)	**50/67(75%)**
del(17), n/N (%)	21/43 (49%)	21/47(40%)	**42/90(47%)**
Baseline laboratory values, median (range) CrCl, mL/min Neutrophil count, × 10^9/L Lymphocyte count, × 10^9/L	 78.2 (65.4–94.1) 3.7 (2.–11) 19 (2.5–43.2)	 75.7 (63.8-100.4) 3.4 (2.3-10.4) 6.6(1-32.8)	 76.0 (64.5-96.7) 4.2 (2-11) 10.1 (2.5-43.6)
Bulky nodal disease, n (%) ≥5 cm ≥10 cm	 15 (35%) 7 (16%)	 21(44%) 2(4%)	 36(40%) 9(10%)
Prior therapies, median (range)	5 (1–12)	4 (1-15)	**4(1-15)**
Prior ibrutinib, n (%) Months on ibrutinib, median (range) Refractory, n (%)	43 (100%) 18 (1–56) 32 (74%)	48(100%) 21(1-61) 30(63%)	91(100%) 20(1-61) 62(68%)
Prior idelalisib, n (%) Months on idelalisib, median (range)	4 (9%) 10 (2–31)	7(15%) 9(2-33)	11(12%) 9(2-33)

Jones JA, et al. Lancet Oncol. 2017 Dec 12.

M14-032: Ibrutinib arm _ Efficacia

- **Interim analysis. Data cut-off 30 Giugno 2017**
- **Follow up mediano: 14 mesi (19 mesi per la *coorte principale* e 12 mesi per la coorte di espansione*)***
- **Il 51% dei pazienti ancora in trattamento con venetoclax**



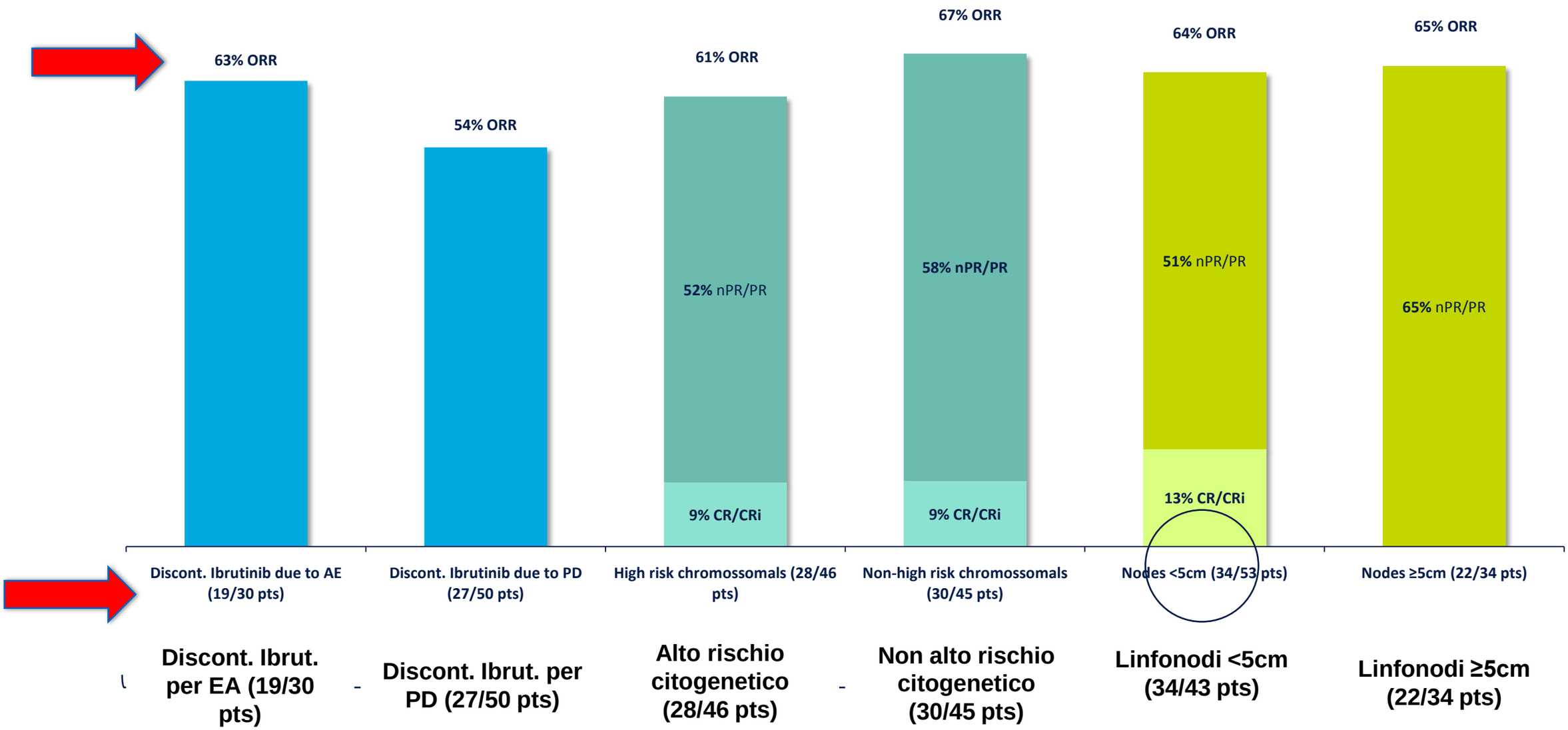
FUP mediano alla ***1°*** ***Risposta***
2,5 mesi (IQR 1,6-2,6)

FUP mediano alla ***Miglior Risposta***
7,9 mesi (IQR 5,3-8,1)

FUP mediano alla **CR/CRi**
8,2 mesi (IQR 4,9-9,0)

Jones JA, et al. Lancet Oncol. 2017 Dec 12.

M14-032 Ibrutinib arm – Analisi esplorativa post-hoc

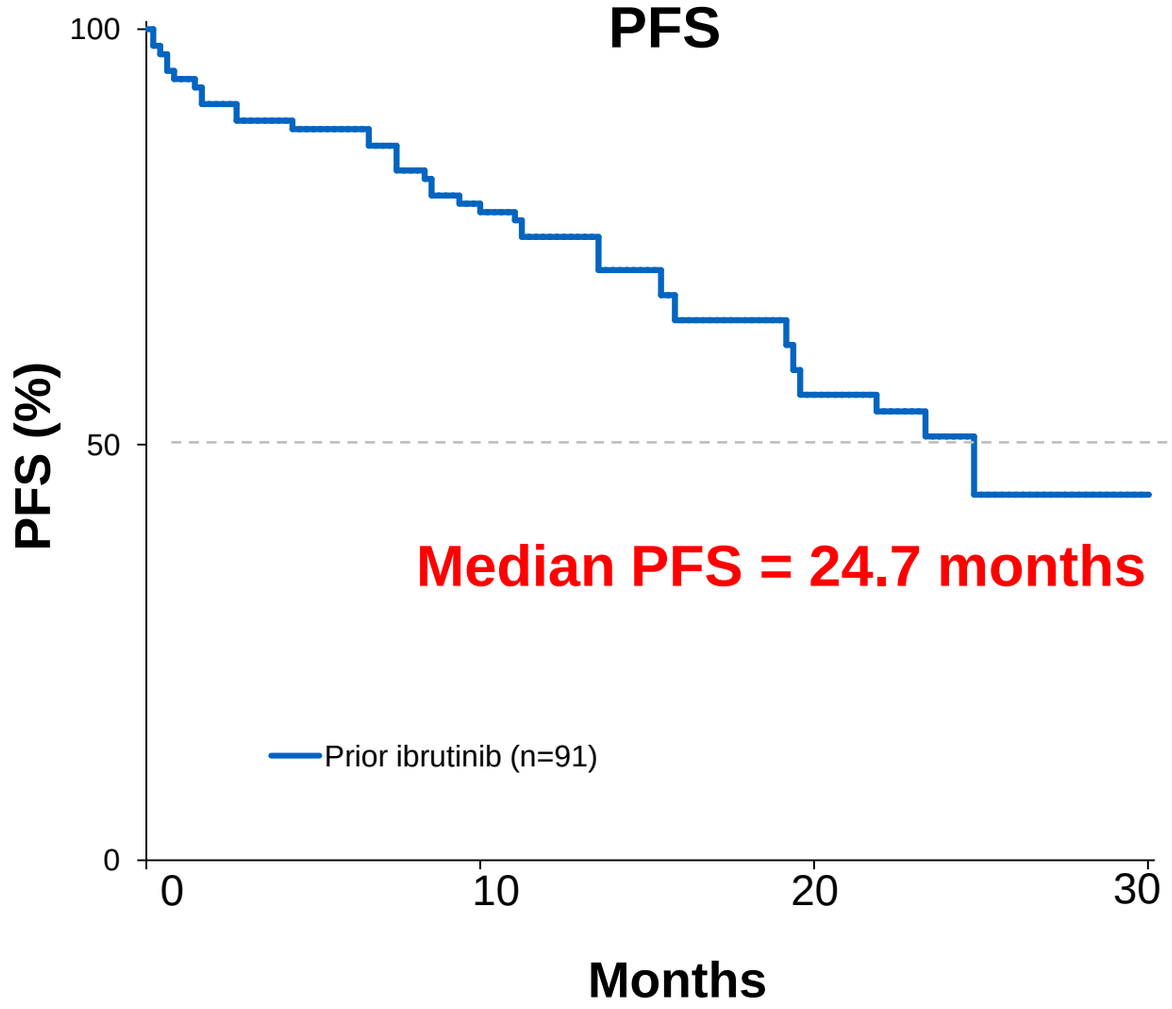


***Risposte sovrapponibili in TUTTI I GRUPPI*!**
si sono osservate anche in pazienti con autcome sfavorevole, inclusi i pz che avevano discontinuato Ibrutinib per progressione, e i pz con anomalie citogenetiche ad alto rischio

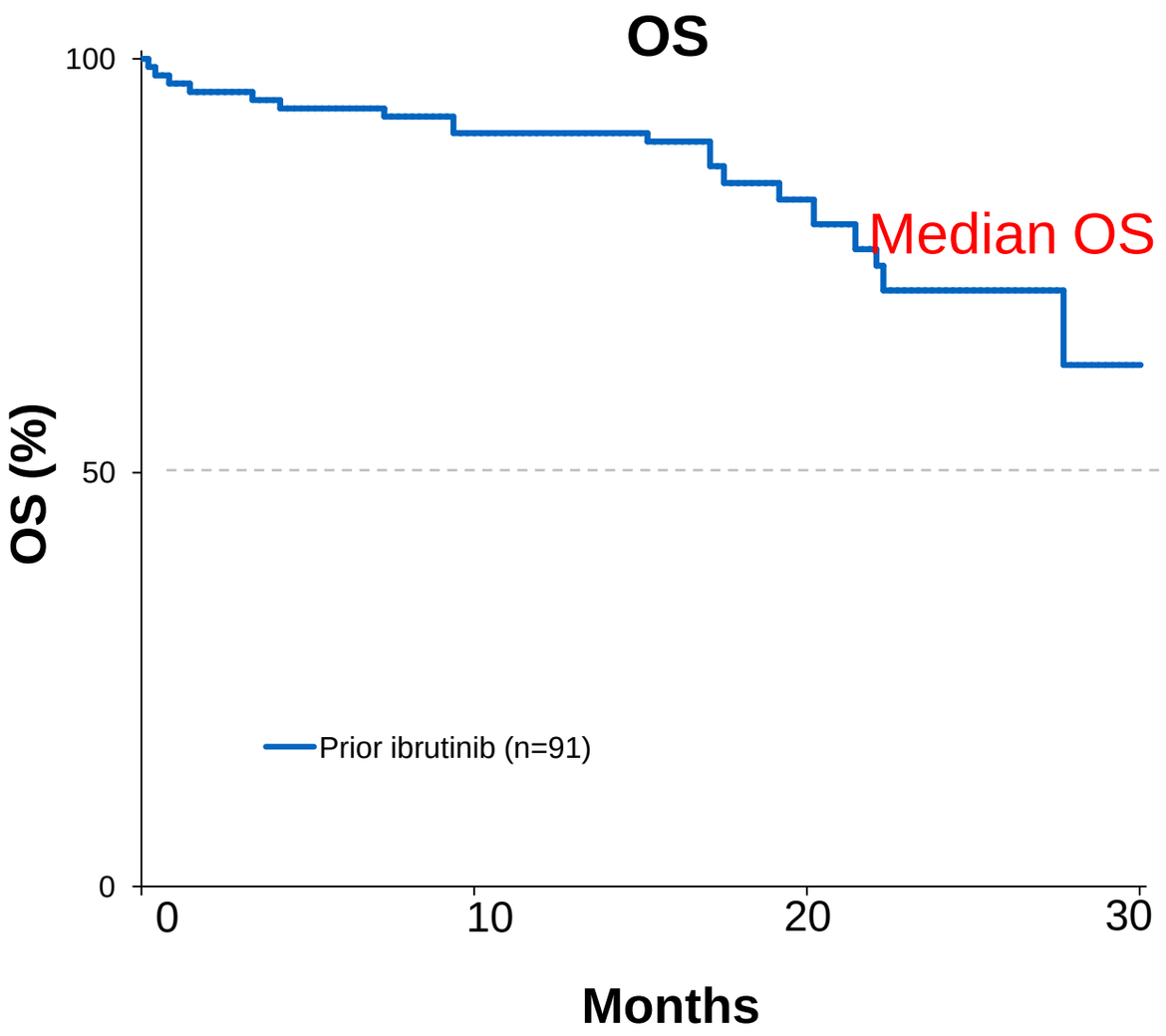
I pz con ***linfonodi <5*** cm hanno ottenuto risposte più profonde, una più lunga DOR, con una PFS più duratura (mPFS 24.7 mesi *versus* 15.9 mesi)

Jones JA, et al. Lancet Oncol. 2017 Dec 12.

M14-032 Ibrutinib arm – PFS and OS



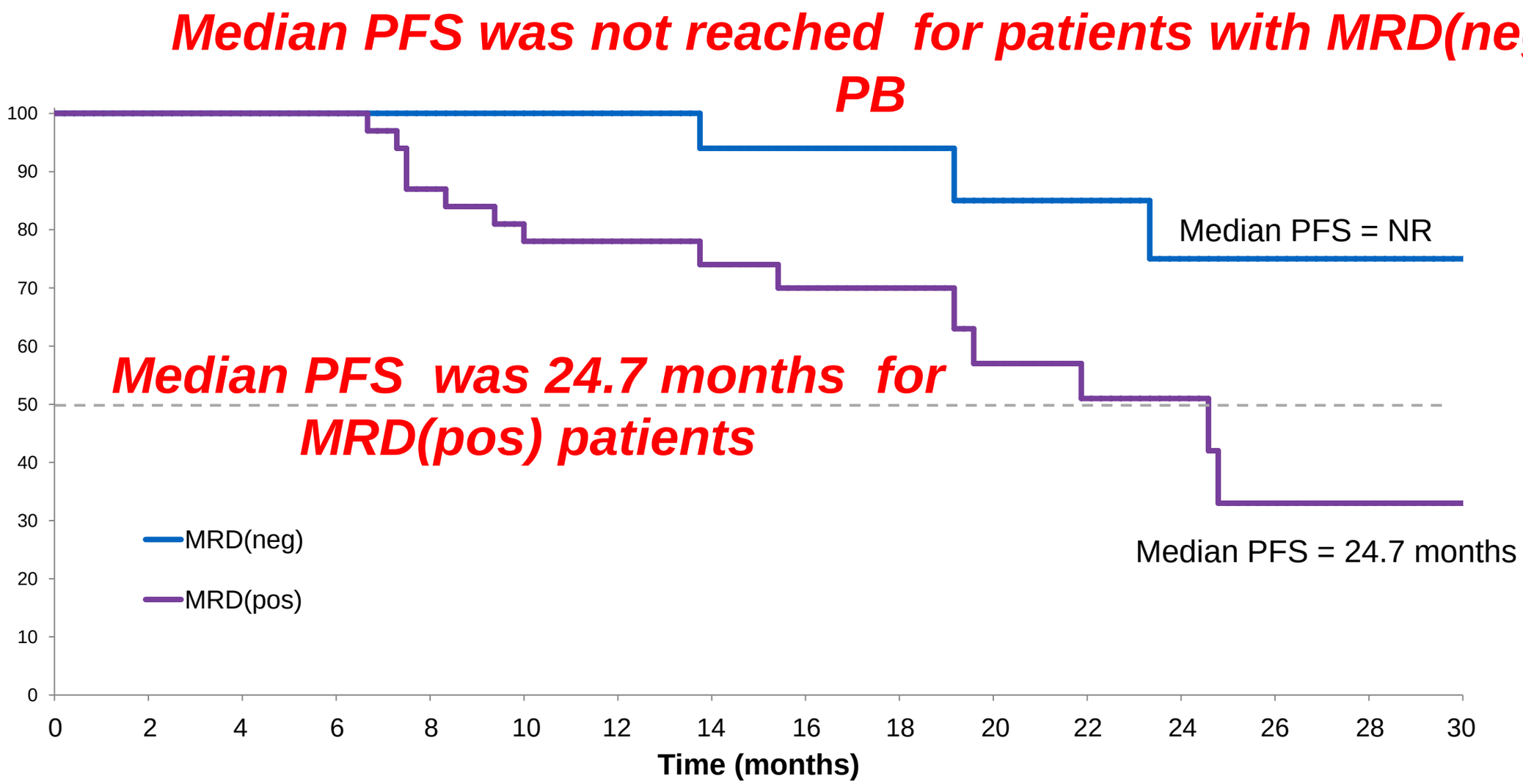
The estimated 12-month PFS for the prior ibrutinib was 75%



Median OS was not reached
estimated 12-mth OS 91%

Jones JA, et al. Lancet Oncol. 2017 Dec 12.

M14-032 **Ibrutinib arm** – PFS by MRD



Jones JA, et al. Lancet Oncol. 2017 Dec 12.

M14-032 Ibrutinib arm_mutazioni BTK o PLCG2

Table S10. *BTK* and *PLCG2* Mutations Identified at Baseline

Patient ID	*BTK* Mutation (allelic frequency)	*PLCG2* Mutation (allelic frequency)	Best Response	PFS (months)	Censored?
1	-	D993G (33·7%)	Patient discontinued prior to first response assessment	0·16	No
2	-	-	PR	24·6711	Yes
3	C481S (6·4%)	-	Patient discontinued prior to first response assessment	0·3618	No
4	C481Y (1·2%)	-	Patient discontinued due to CLL progression prior to first response assessment	1·5132	No
5	C481S (7·5%)	L845F (2%)	PR	8·7829	Yes
6	C481A (85·9%)	-	PR	6·7434	No
7	C481S (98·8%)	-	PR	13·6513	No
8	C481S (26·5%)	-	PR	22·3684	Yes
9	C481S (95%)	-	PR	21·9079	No
10	C481S (91·1%)	-	PR	21·9079	Yes
11	C481S (96·2%)	-	CRi	21·9079	Yes
12	C481S (22·5%)	-	SD	4·4079	No
13	C481A (44·3%); C481S (25·2%)	-	PR	21·9079	Yes
14	C481S (39·8%)	-	PR	19·2105	Yes
15	-	S707F (35·9%)	PR	19·2105	No
16	-	D993G (12·1%)	Patient discontinued prior to first response assessment	0·0329	Yes
17	-	-	PR	15·3618	No
18	C481S (22·8%)	-	PR	22·1382	Yes
19	-	-	SD	11·0526	No
20	-	-	PR	15·0987	Yes
21	C481S (5·30%)	-	PR	19·375	Yes

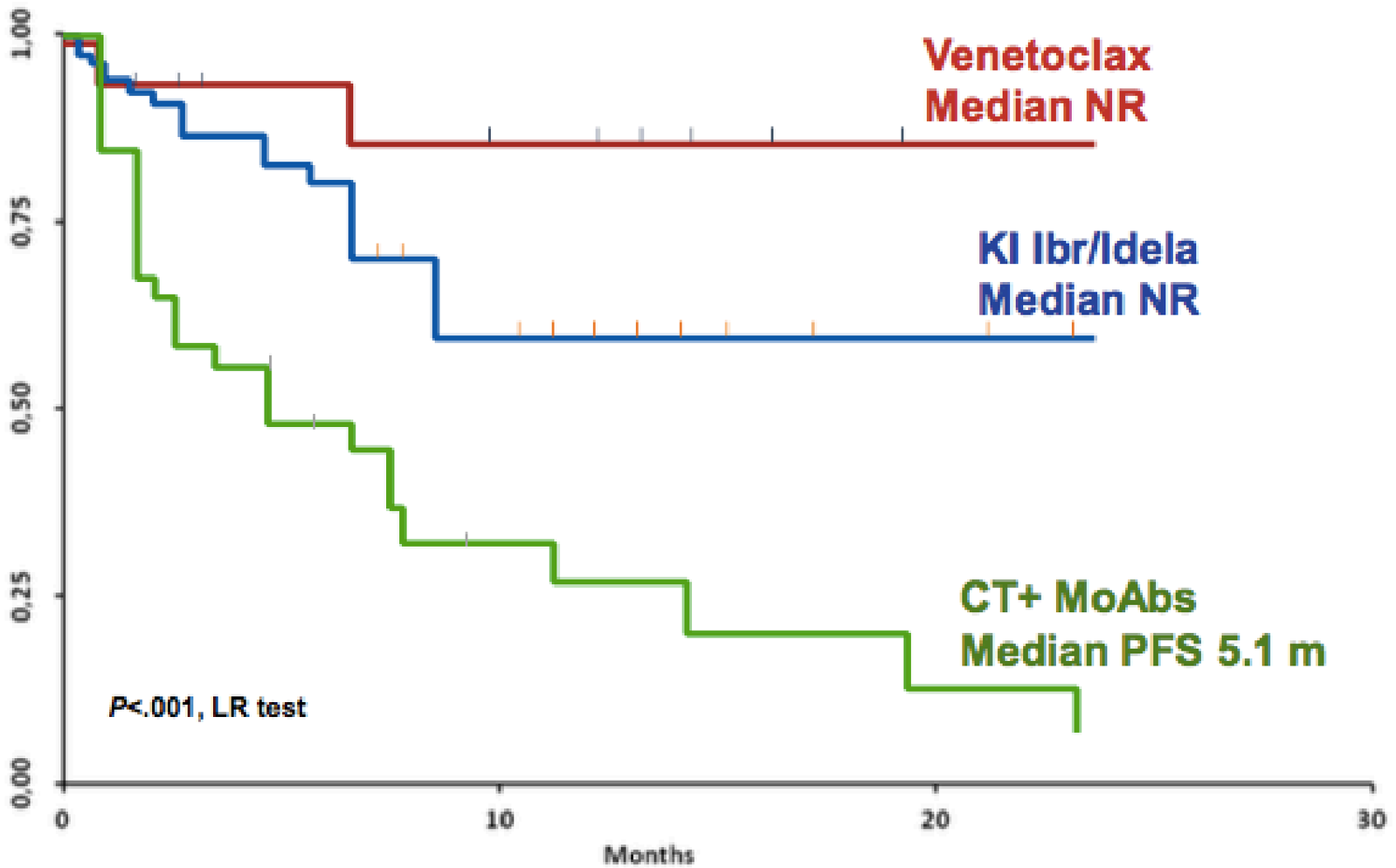
Venetoclax sembra in grado di eradicare i cloni di CLL resistenti ad Ibrutinib

ORR 71% pazienti con mutazioni *BTK* o *PLCG2*

Nessuna differenza in PFS tra i pazienti ***con e senza mutazioni***

Optimal Sequencing of Ibrutinib, Idelalisib, and Venetoclax in CLL Results from a Multi-Center Study of 683 Patients

PFS following TKI discontinuation

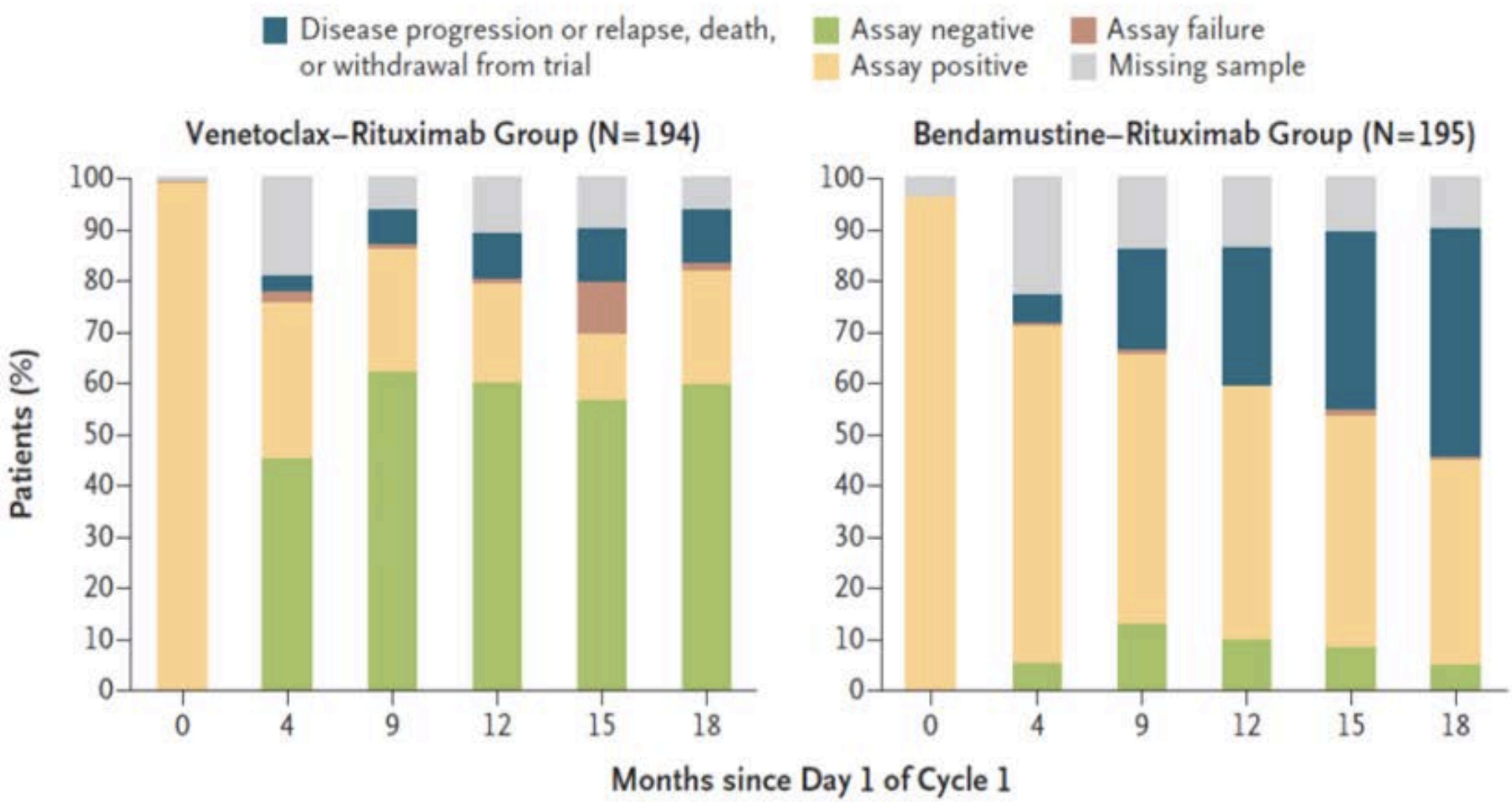


Mato et al. 2017

PHASE III MURANO STUDY

VENETOCLAX RITUXIMAB versus

BENDAMUSTINE RITUXIMAB

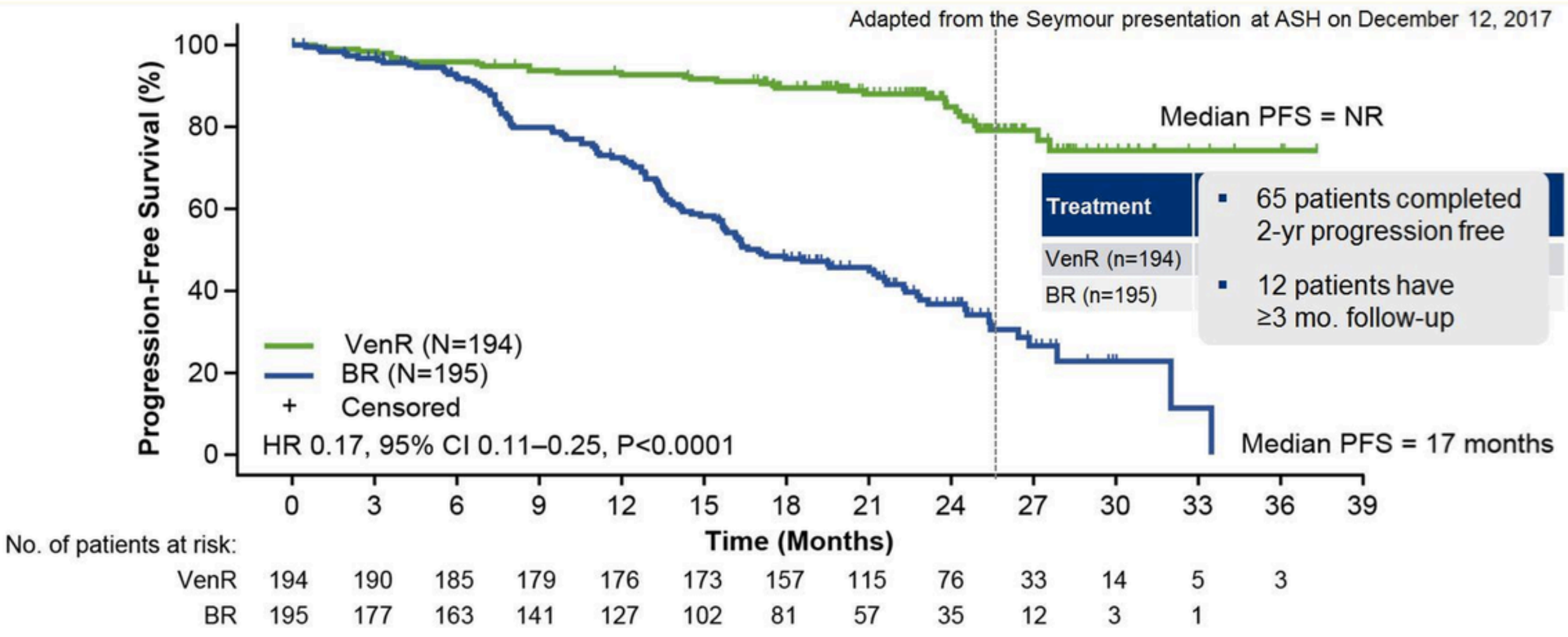


Seymour et al 2018

PHASE III MURANO STUDY

VENETOCLAX RITUXIMAB versus

BENDAMUSTINE RITUXIMAB



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

Seymour et al 2018

FDA APPROVAL (JUNE 2018)

FDA has granted a standard approval to venetoclax (Venclexta) for the treatment of patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), with or without 17p deletion, following at least 1 prior therapy.

The BCL-2 inhibitor is now also approved for use in combination with retuximab (Rituxan) in the same patient population (based on Murano study).

COMBINATIONS TREATMENT

MRD negativity

The only biologic
Parameters that TODAY
can guide BCLL-treatment are:

17p DELETION and/or

TP53 MUTATION

(tested at 1° treatment and in rel/ref patients)

11q deletion
IGVH status

Do molecular biomarkers inform first line CLL treatment in 2018?

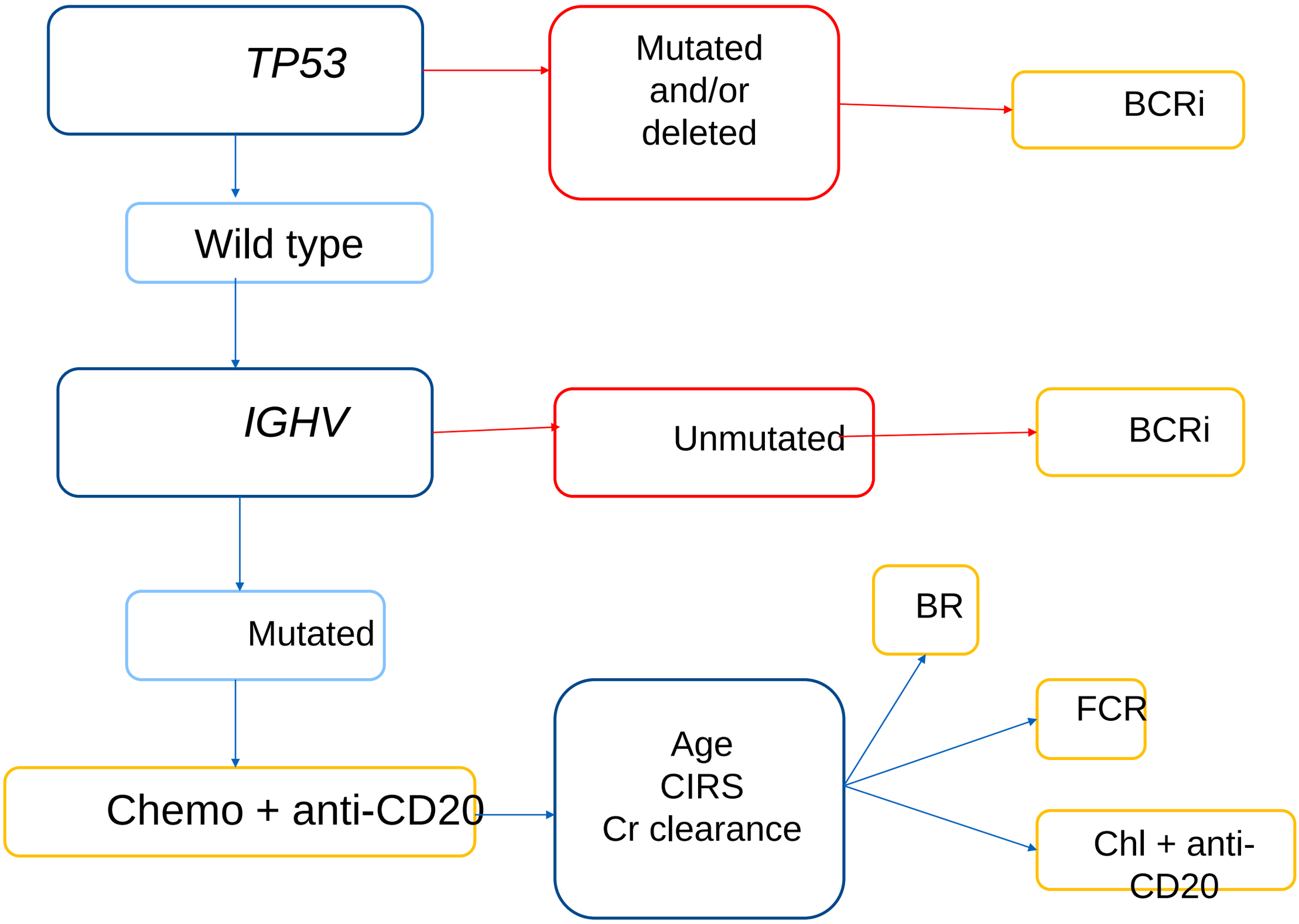
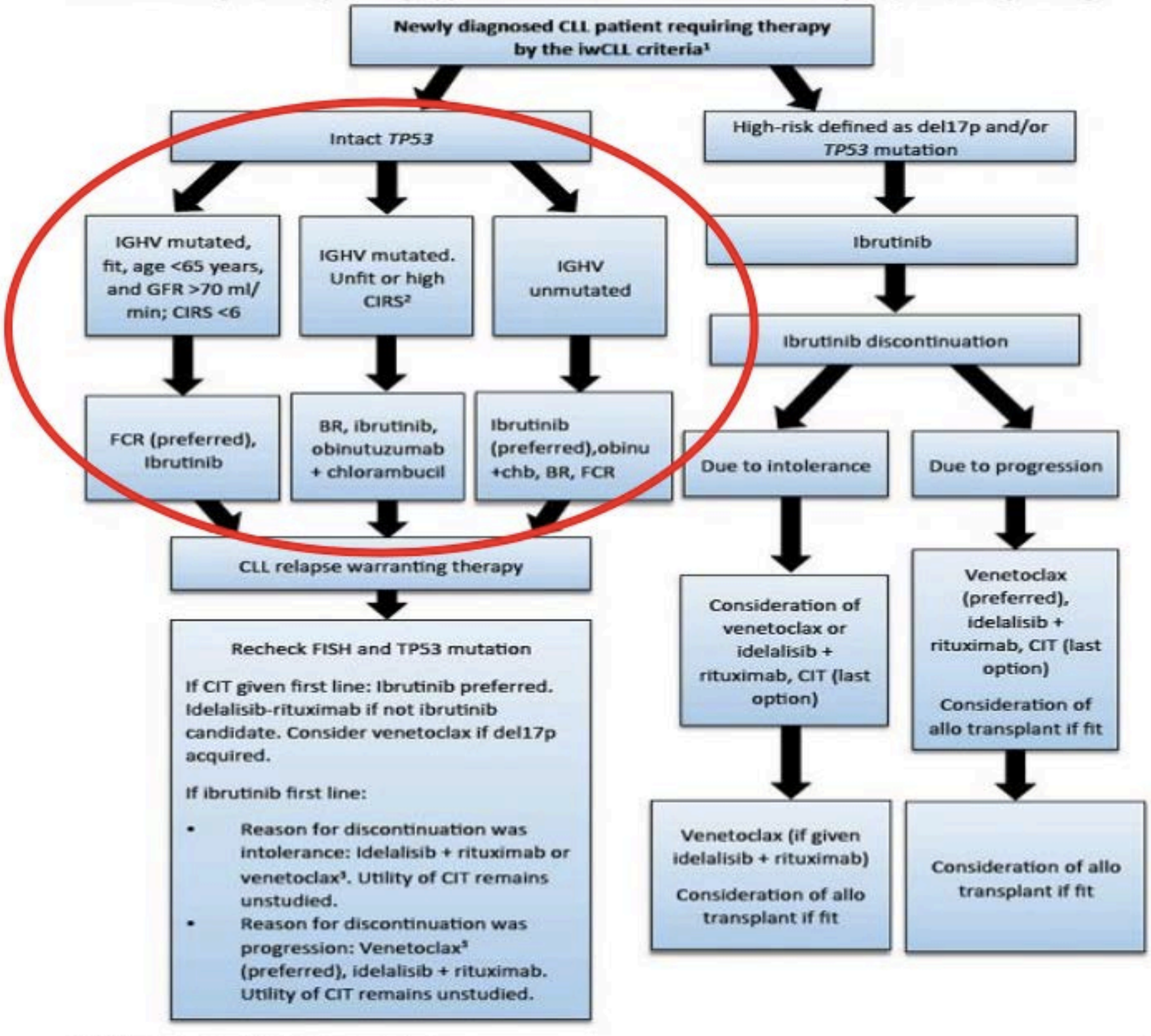


FIGURE 2. Proposed Sequencing Approach: Combined Frontline and Relapsed/Refractory Settings



[1]Evaluate for clinical trial at each sequencing step
[2]Cumulative Illness Rating Scale
[3]Use is off label in US if patient does not have 17p deletion and prior therapy. Please see EMA SMPC for additional indications in the EU.
[4]Allogenic stem cell transplant

MARCH 4, 2016

FDA approves ibrutinib for first line treatment of CLL

JULY 11, 2016

EMA approves ibrutinib as a single agent for first line treatment of CLL

SEPT 2018

AIFA approved ibrutinib for first line treatment of CLL

MAJOR CHALLENGE

WILL **ALL CLL PATIENTS** –
IRRESPECTIVE OF AGE AND BIOLOGY

UNDERGO IBRUTINIB AS
FRONT LINE TREATMENT?

IS IT FEASIBLE?

Safety and Efficacy of Obinotuzumab plus Bendamustine in Previous untreated patients with CLL: Subgroup analysis of the GREEN Study (Stilgenbauer S, R.Foa', et al Leukemia 2018))

58,9% and 28,5% MRD negativity in blood and bone marrow

Mainly IGVH mutated
TP53 negative

PRACTICAL APPLICATIONS

- **Novel agents are currently indicated in both the frontline (ibrutinib) and relapsed/refractory settings (ibrutinib, idelalisib/rituximab, venetoclax).**
- **Although ibrutinib is indicated for all patients in the frontline setting, comparative data on ibrutinib versus chemoimmunotherapy and sequencing after ibrutinib discontinuation are limited; In addition, a subset of fit patients with mutated *IGHV* experience prolonged remissions and may be cured with FCR.**
- **In older patients (not candidates for FCR or BR), ibrutinib produces significantly higher ORR and longer PFS and OS than those seen with chlorambucil; nevertheless, financial exigencies may prohibit initial therapy with ibrutinib in some patients.**
- **In the relapsed setting, ibrutinib, idelalisib/rituximab, and venetoclax all can be used; however, current data about sequencing these agents are limited to one prospective study and retrospective real-world evidence studies.**
- **Continued enrollment of patients with CLL into clinical trials with relevant controls and observational studies is important to resolve ongoing sequencing questions.**

CHEMOIMMUNOTHERAPY
SOME CONSIDERATIONS

- **These observations indicate that a proportion of patients witness a profound response following a short course of chemoimmunotherapy.**

- These patients may have a specific biologic profile and could be identified at the time of treatment.

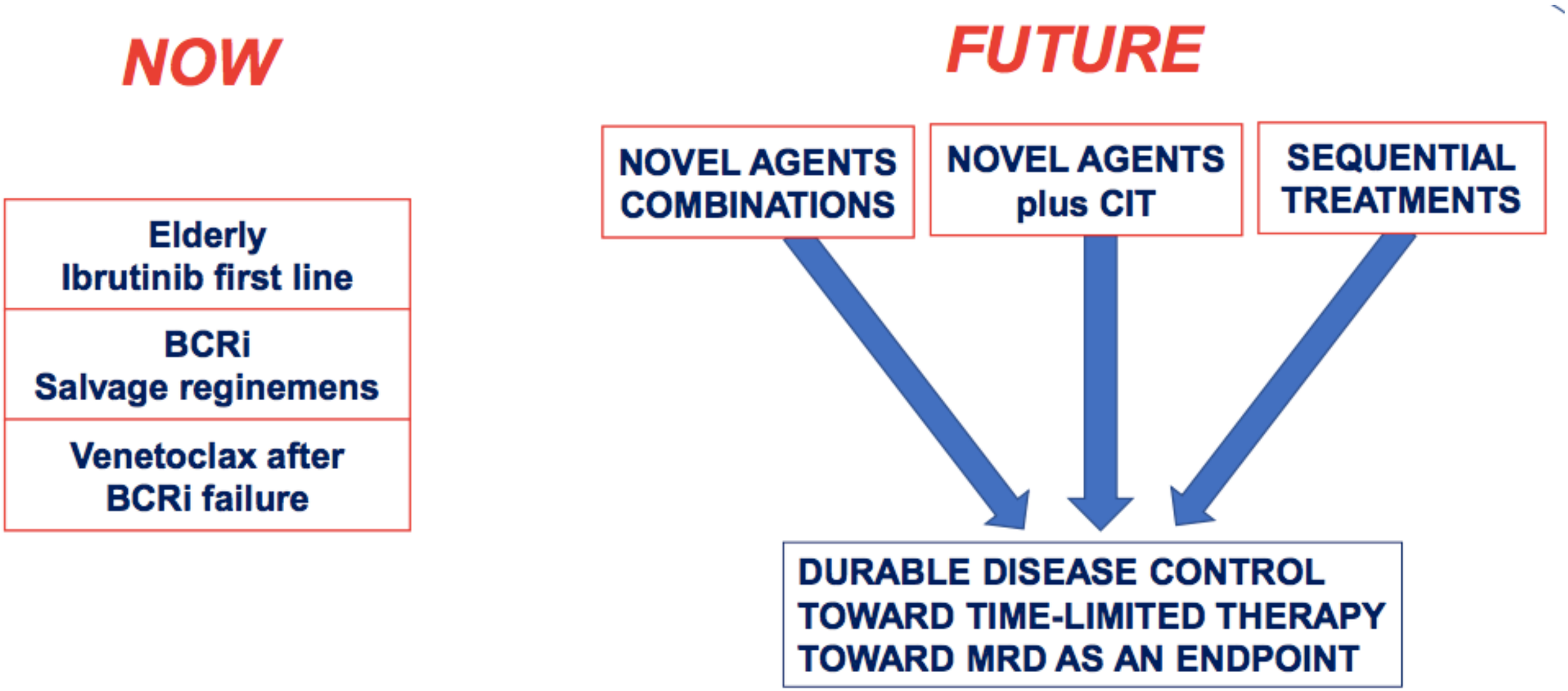
- Some of these patients achieve a status of MRD negativity.

- Some appear to have a life expectancy – despite disease progression and treatment requirement – similar to that of the normal age-matched population.

- Could maintenance increase the percent of CR/MRD-??

- Encouraging data with retuximab, ofatumumab, lenalidomide.

CONCLUSIONS



Grazie per l'attenzione