Sabati Ematologici della Romagna

Quando e se è possibile e utile ottenere una remissione completa

1) Clinical heterogeneity

- Disease characteristics
- Patient characteristics

2) Modern chemoimmunotherpy approaches

3) New mechanism-based treatment

Prof. Antonio Cuneo, MD, PhD

università di ferrara
DA SEICENTO ANNI GUARDIAMO AVANTI.

Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute–Working Group 1996 guidelines

Table 4. Response definition after treatment for patients with CLL, using the parameters of Tables 1 and 3

Parameter	CR*	PR*	PD*
Group A			
Lymphadenopathy†	None > 1.5 cm	Decrease ≥ 50%	Increase ≥ 50%
Hepatomegaly	None	Decrease ≥ 50%	Increase ≥ 50%
Splenomegaly	None	Decrease ≥ 50%	Increase ≥ 50%
Blood lymphocytes	< 4000/μL	Decrease ≥ 50% from baseline	Increase ≥ 50% over baseline
Marrow‡	Normocellular, < 30% lymphocytes, no B-lymphoid nodules. Hypocellular marrow defines CRi (5.1.6).	50% reduction in marrow infiltrate, or B-lymphoid nodules	
Group B			
Platelet count	> 100 000/μL	> 100 000/μL or increase ≥ 50% over baseline	Decrease of ≥ 50% from baseline secondary to CLL
Hemoglobin	> 11.0 g/dL	> 11 g/dL or increase ≥ 50% over baseline	Decrease of > 2 g/dL from baseline secondary to CLL
Neutrophils‡	> 1500/μL	> 1500/μL or > 50% improvement over baseline	

Group A criteria define the tumor load, group B criteria define the function of the hematopoietic system (or marrow).

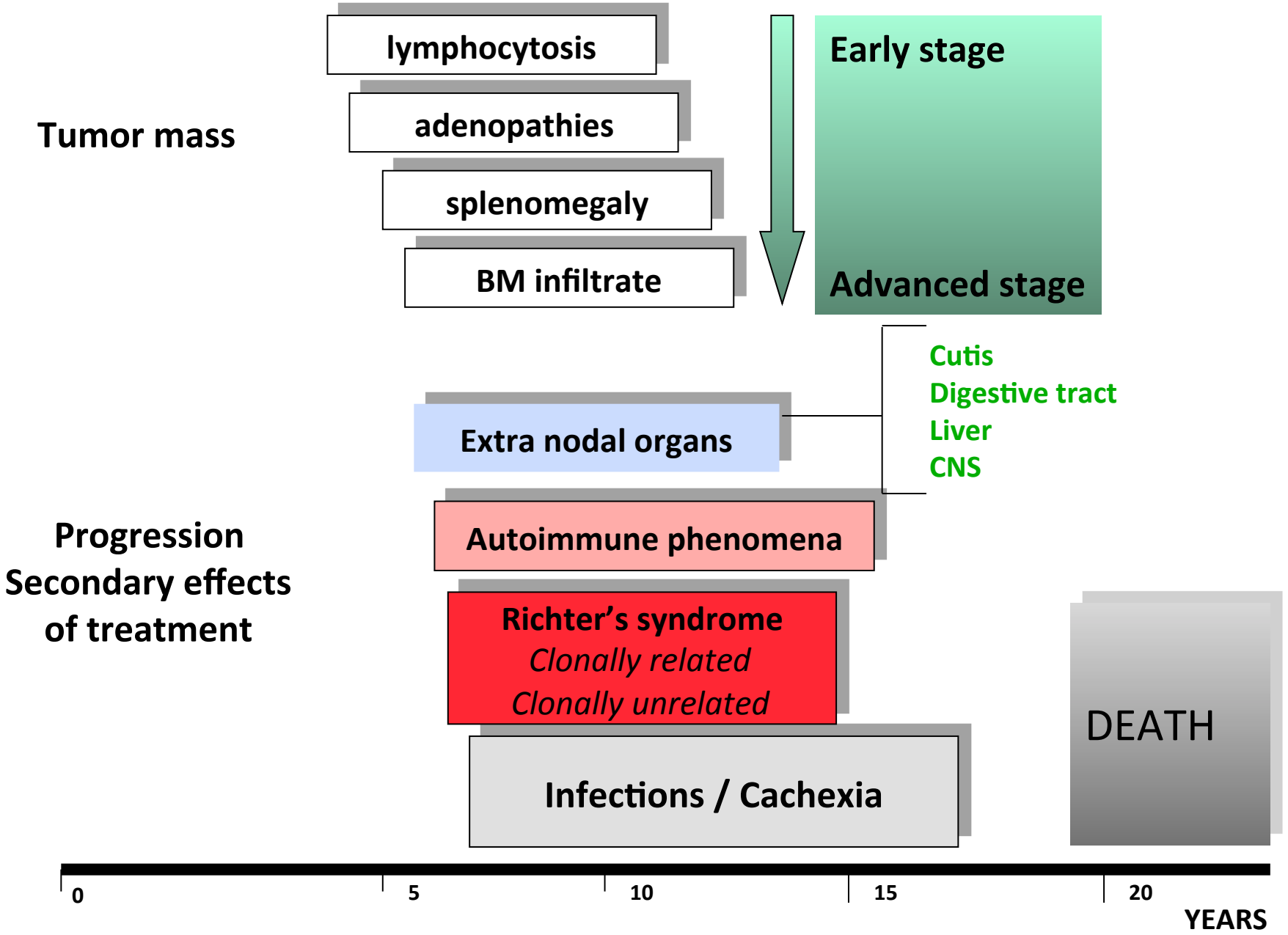
*CR (complete remission): all of the criteria have to be met, and patients have to lack disease-related constitutional symptoms; PR (partial remission): at least two of the criteria of group A plus one of the criteria of group B have to be met; SD is absence of progressive disease (PD) and failure to achieve at least a PR; PD: at least one of the above criteria of group A or group B has to be met.

†Sum of the products of multiple lymph nodes (as evaluated by CT scans in clinical trials, or by physical examination in general practice).

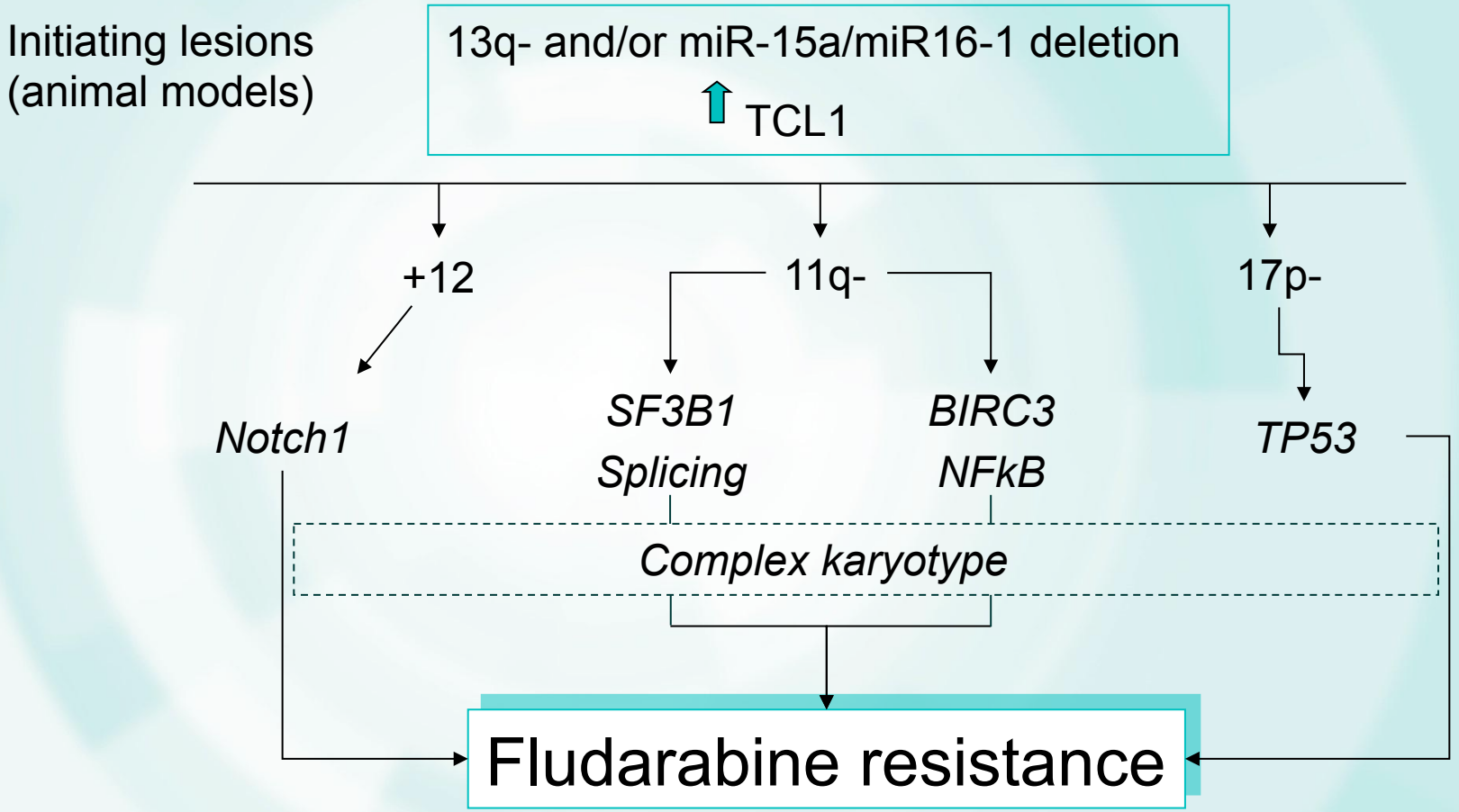
‡These parameters are irrelevant for some response categories.

Hallek M et al. Blood. 2008;111:5446-5456

CLL: single disease with variable clinicobiologic features



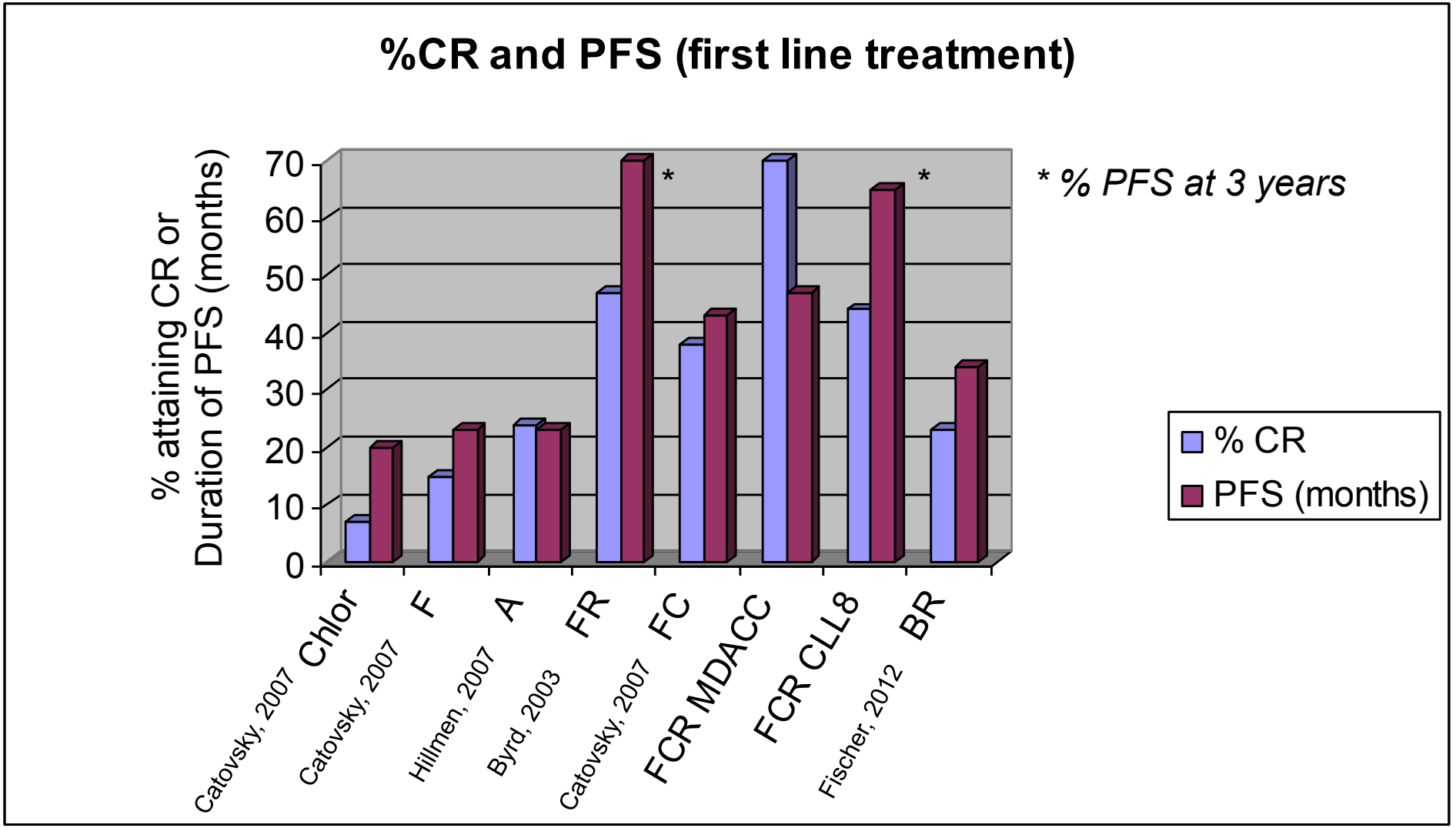
Sequential development of molecular cytogenetic lesions in CLL



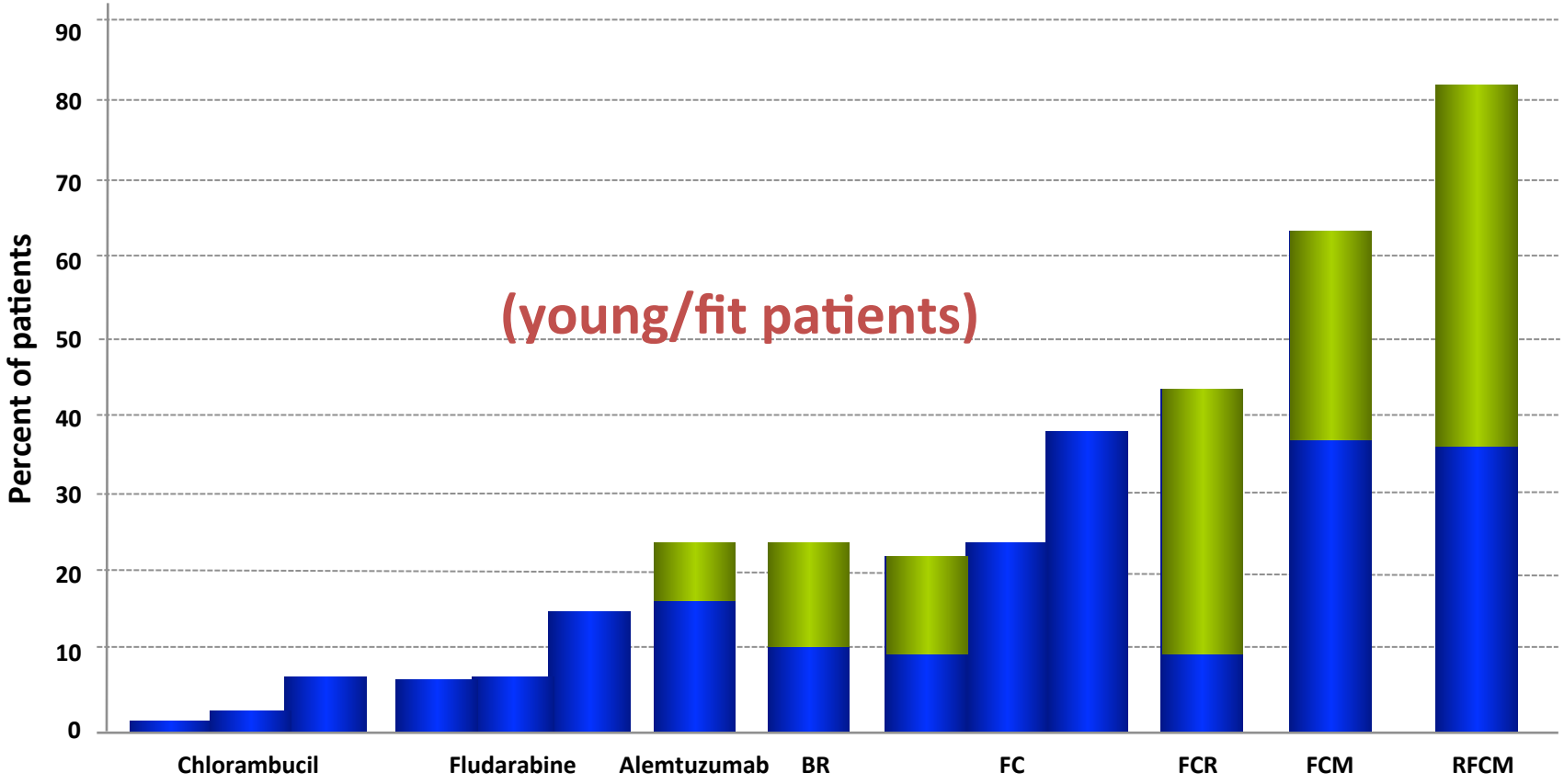
BIRC3, baculoviral IAP repeat containing 3;
SF3B1, splicing factor 3B subunit 1;
TCL1, T cell leukaemia/lymphoma 1; TP53, tumour protein 53.

Cuneo A, personal communication.

Increasing efficacy of chemo/immunotherapy in first line (fit patients)



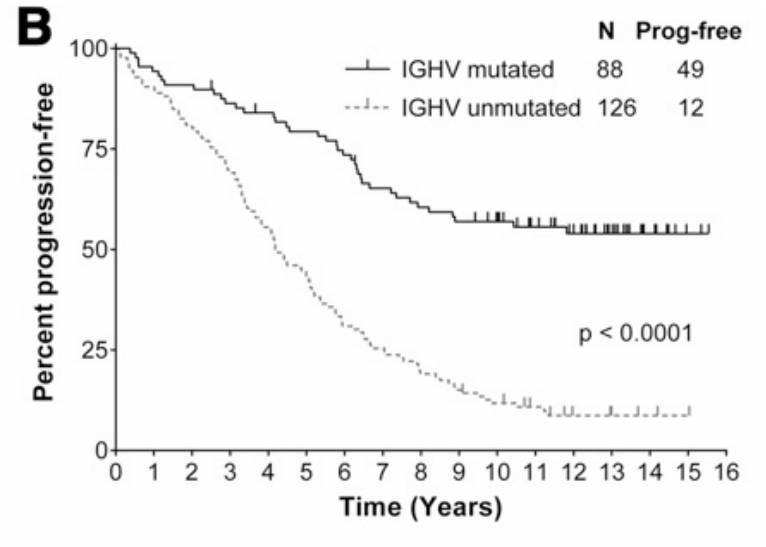
Increasing MRD negativity in CLL is a strong dynamic prognostic factor

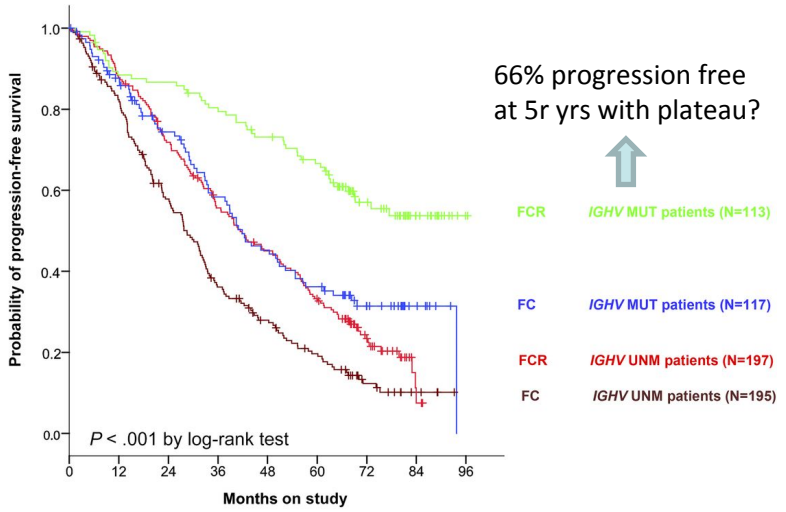


Rai et al. 2000
Leporrier et al. 2001
Lundin et al. 2002
O'Brien et al. 2001
Bosch et al. 2008
Tam et al. 2008
Fischer et al, 2012

Ghia P, ASH 2012; educational book

Long term PFS with FCR in low-risk CLL (IGHV «mutated) (MDACC and GCLLSG – CLL8)



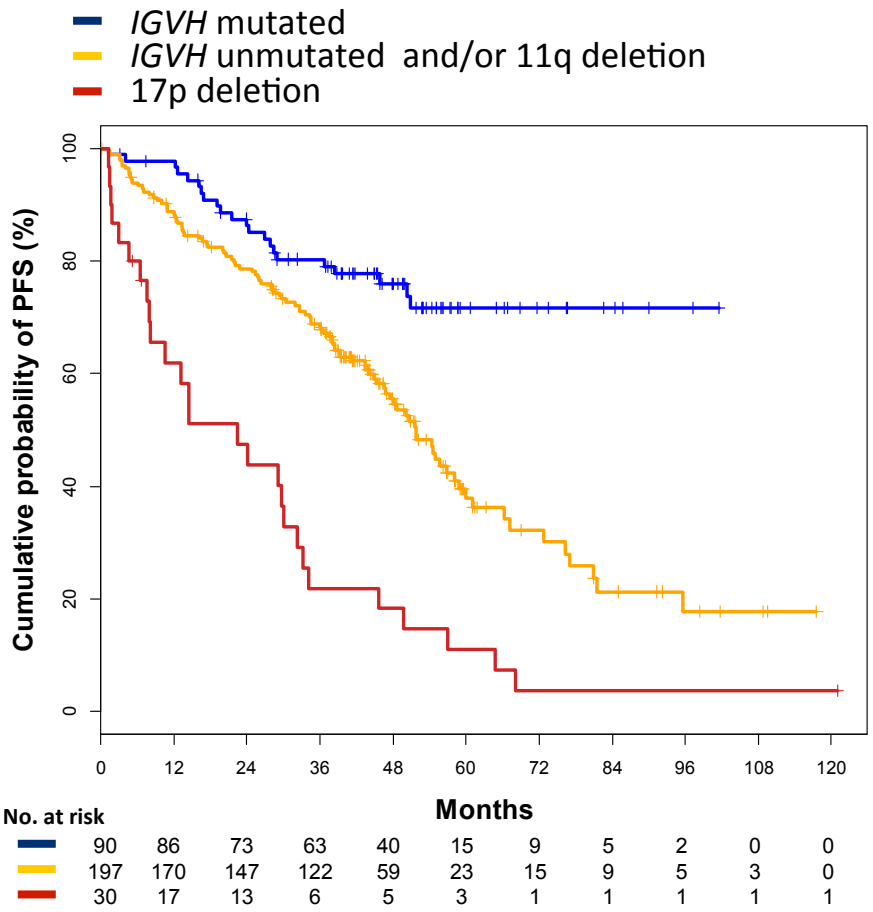


Number at risk	0	12	24	36	48	60	72	84	96
FCR *IGHV* MUT	113	99	97	89	80	71	37	15	1
FC *IGHV* MUT	117	96	75	58	45	36	21	7	0
FCR *IGHV* UNM	197	173	140	106	85	61	25	2	0
FC *IGHV* UNM	195	153	105	65	45	30	12	4	0

Thompson PA et al, Blood 2016; 127:303-9

Fischer K et al. Blood. 2016;127(2):208-215

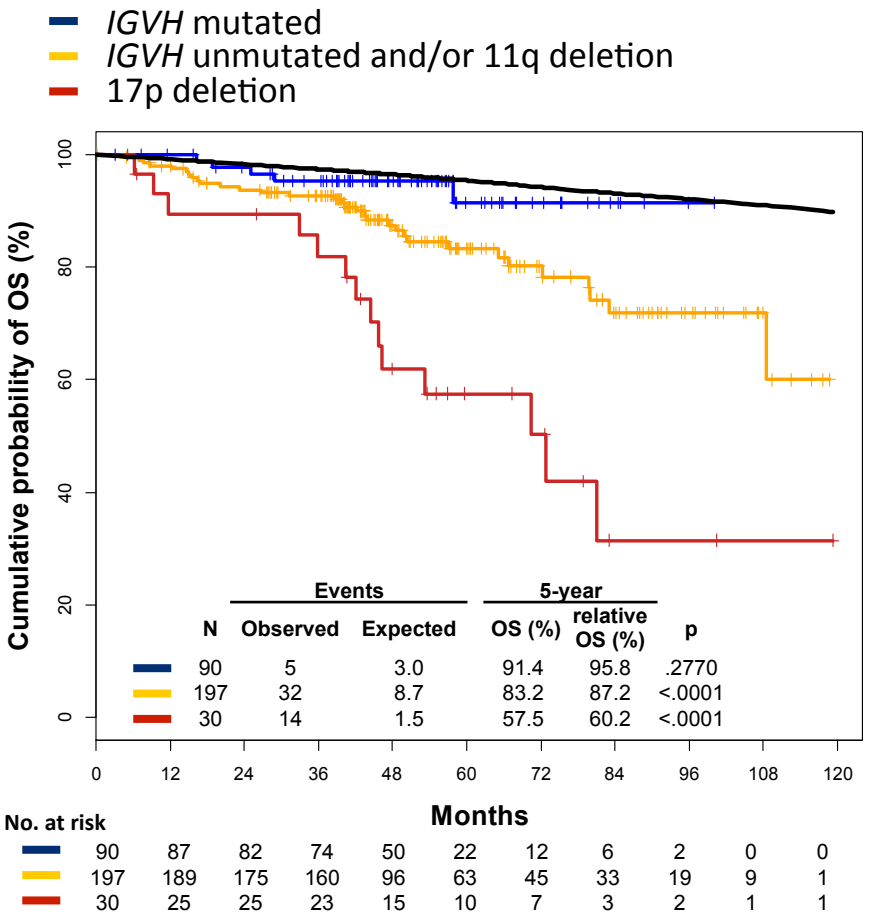
Long term PFS with FCR in low-risk CLL (IGHV «mutated, no 11q-, no 17p-): the italian experience



	Events	Total	Median PFS	95% CI
	22	90	nr	na
	102	197	51.7	46.1-57.2
	27	30	22.5	8.5-36.4

Pairwise comparisons

p			
	-	0.0001	<0.0001
	0.0001	-	<0.0001
	<0.0001	<0.0001	-



	Events	Total	5-years OS	95% CI
	5	90	91.4	87.1-95.7
	32	197	83.2	80,0-86.4
	14	30	57.5	47.6-67.4

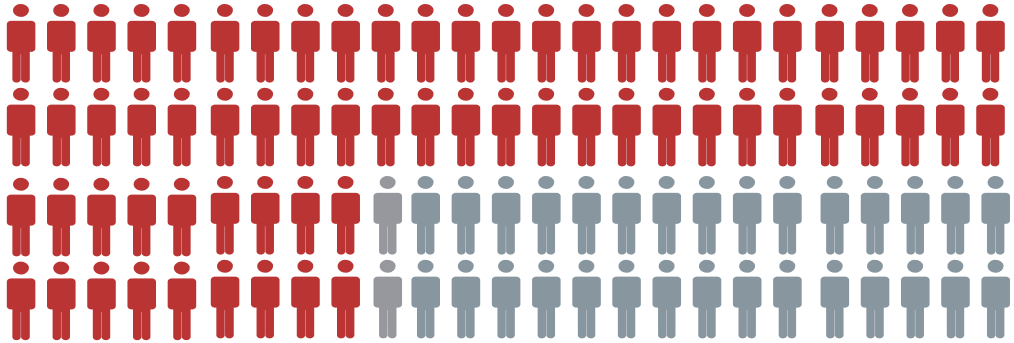
Pairwise comparisons

p			
	-	0.0341	<0.0001
	0.0341	-	0.0004
	<0.0001	0.0004	-

Rossi et al, Blood 2015

Patients with CLL have a median age at diagnosis of 72 years and most have comorbidities

68% of CLL patients are aged ≥65 years:[1]



- Median age at diagnosis is 72 years[3]
- 40% of patients are aged >75 years[1]

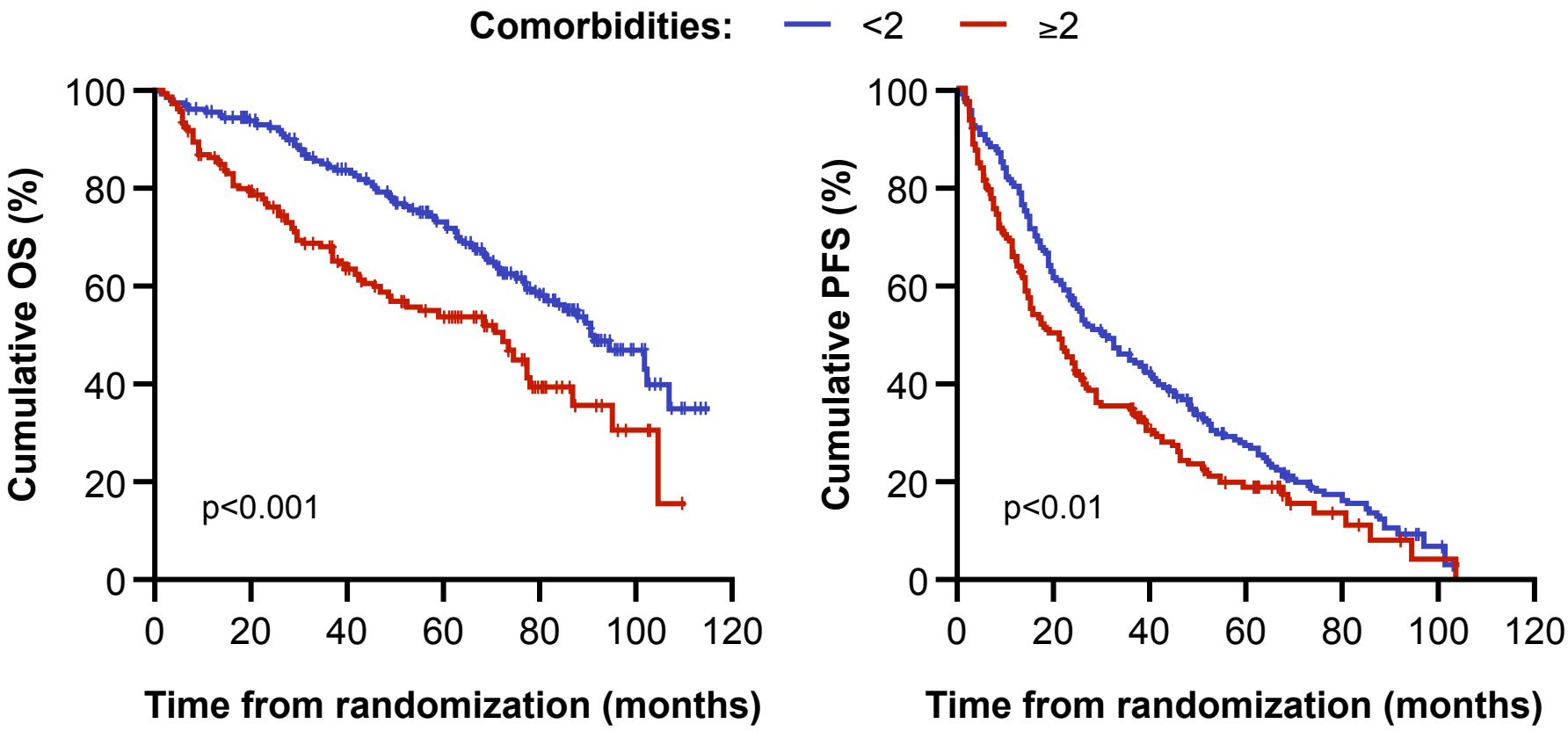
89% of CLL patients have one or more comorbidity:[2]

- 46% of patients have at least one MAJOR comorbidity[2]

1. Howlader N, *et al.* SEER Cancer Statistics Review, 1975-2011. Available at: http://seer.cancer.gov/csr/1975_2011/. Accessed February 2015; 2. Thurmes P, *et al. Leuk Lymphoma* 2008; 49:49–56.
3. Eichhorst B, *et al. Ann Oncol* 2011;22 (Suppl 6):vi50–vi54.

Comorbidities are associated with poor prognosis

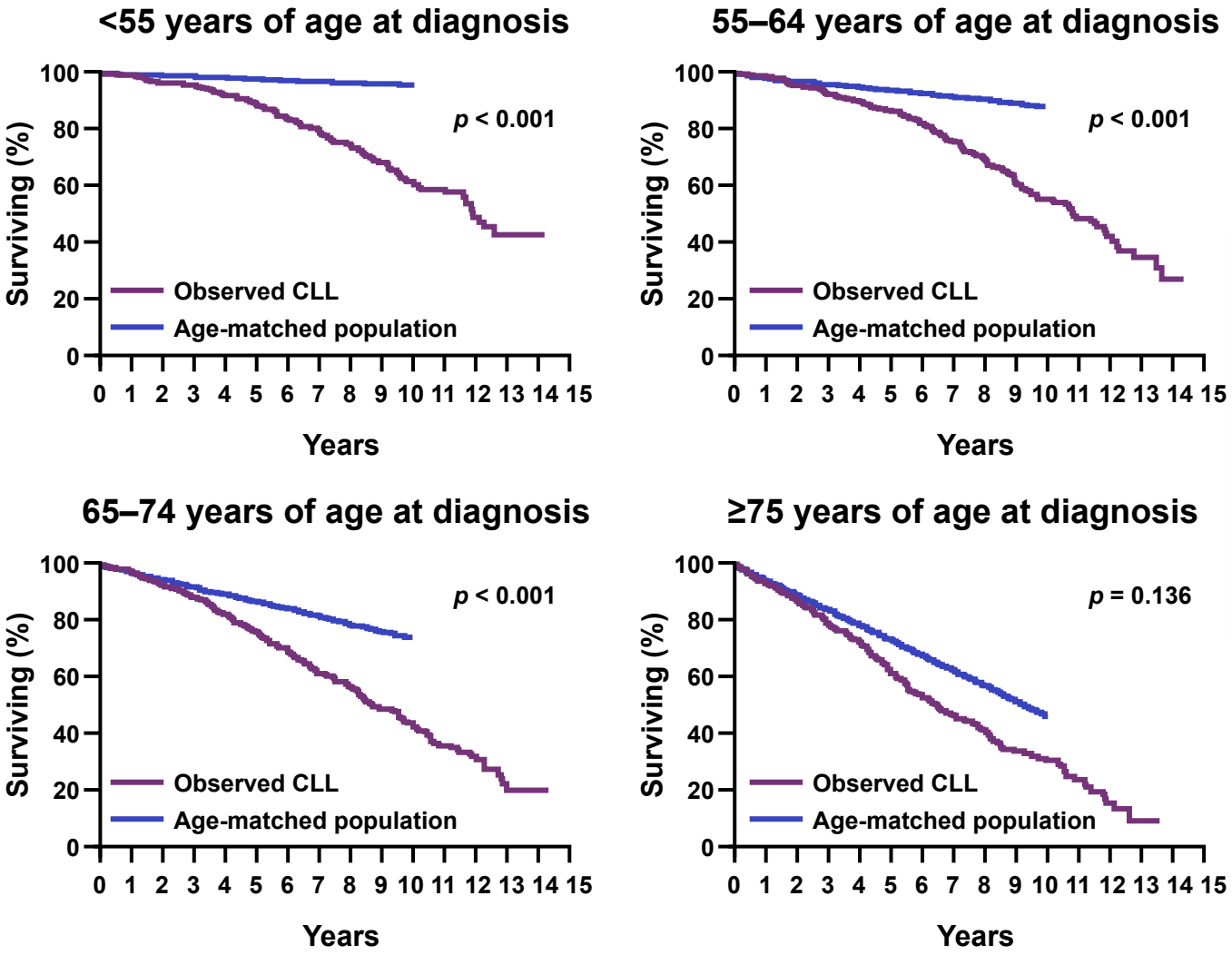
Patients with CLL (N=555) on first-line treatment with FC, F or Clb from CLL4 and CLL5 studies



Clb: chlorambucil; F: fludarabine; OS: overall survival; PFS: progression-free survival

Goede V, *et al*. *Haematologica* 2014; 99:1095–1100.

Patients of all ages and fitness require effective treatments that are well tolerated

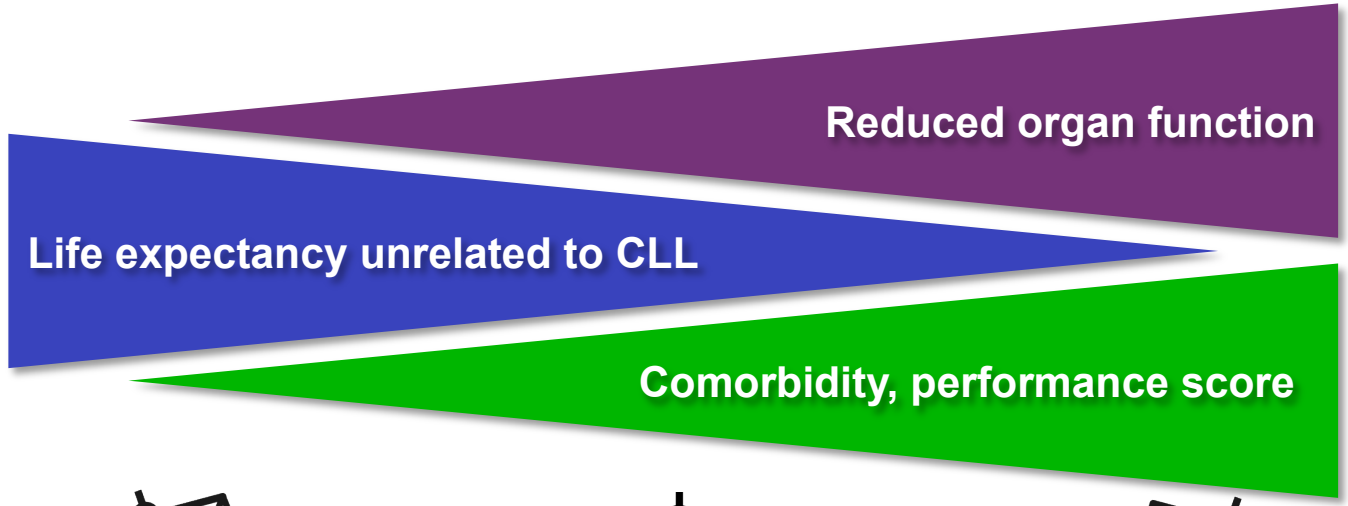


CLL shortens lifespan even in elderly patients

Shanafelt TD, *et al. Cancer* 2010; 116:4777–4787.

Comorbidity, and not age, is the limiting factor in the use of chemoimmunotherapy in CLL[1]

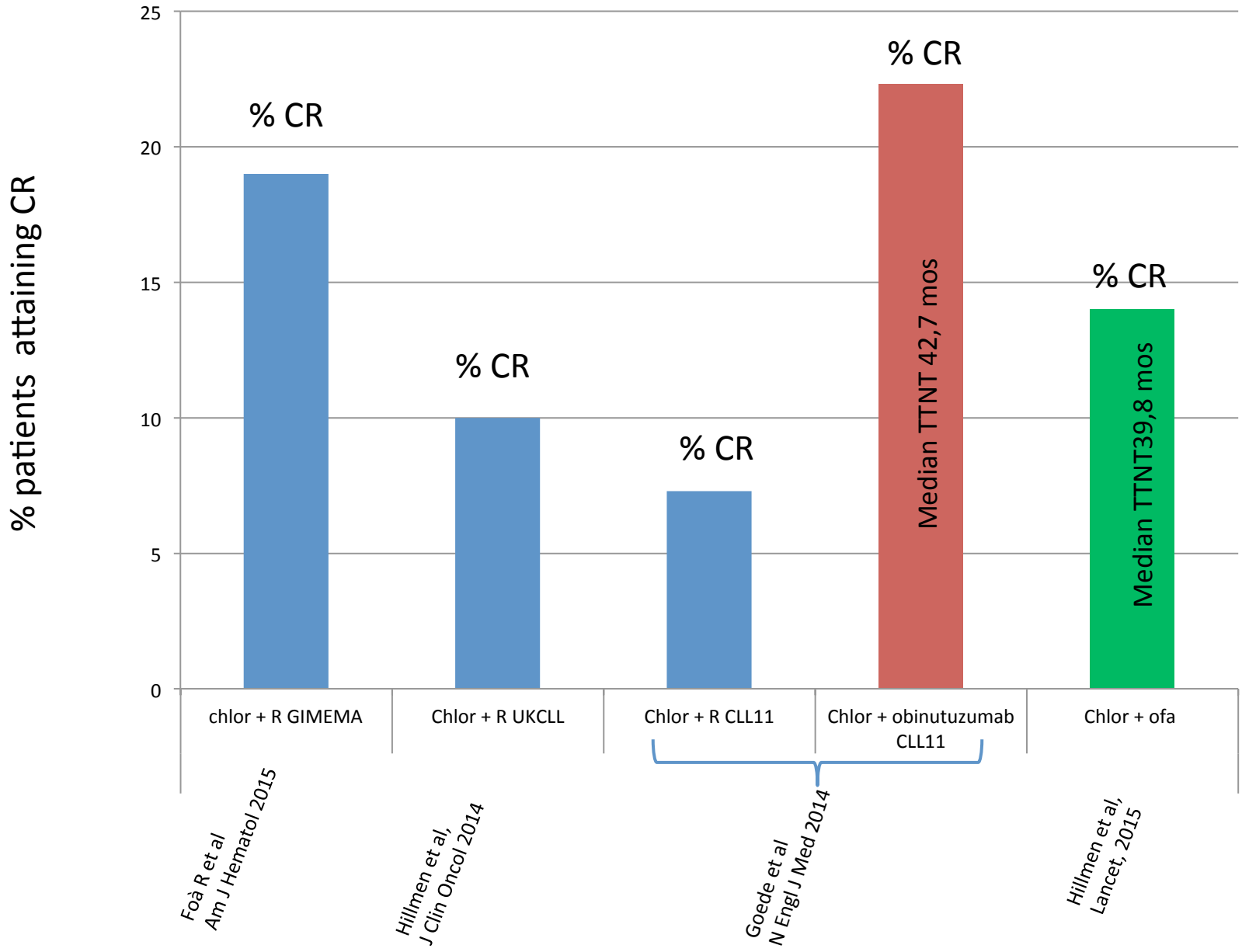
Determining the goals of treatment for older patients with CLL:[2]



	Deep remission	Balance of efficacy/toxicity	Do no harm
Goal:	CR (MRD- remission)	Good response	Palliation
Priority:	Efficacy	Combination efficacy and tolerability	Low toxicity

1. Gribben JG. *Expert Rev Anticancer Ther* 2010; 10:1389–94.
2. Shanafelt T. *Hematology Am Soc Hematol Educ Program* 2013:158–167.

% CR in trials designed for elderly/unfit CLL patients



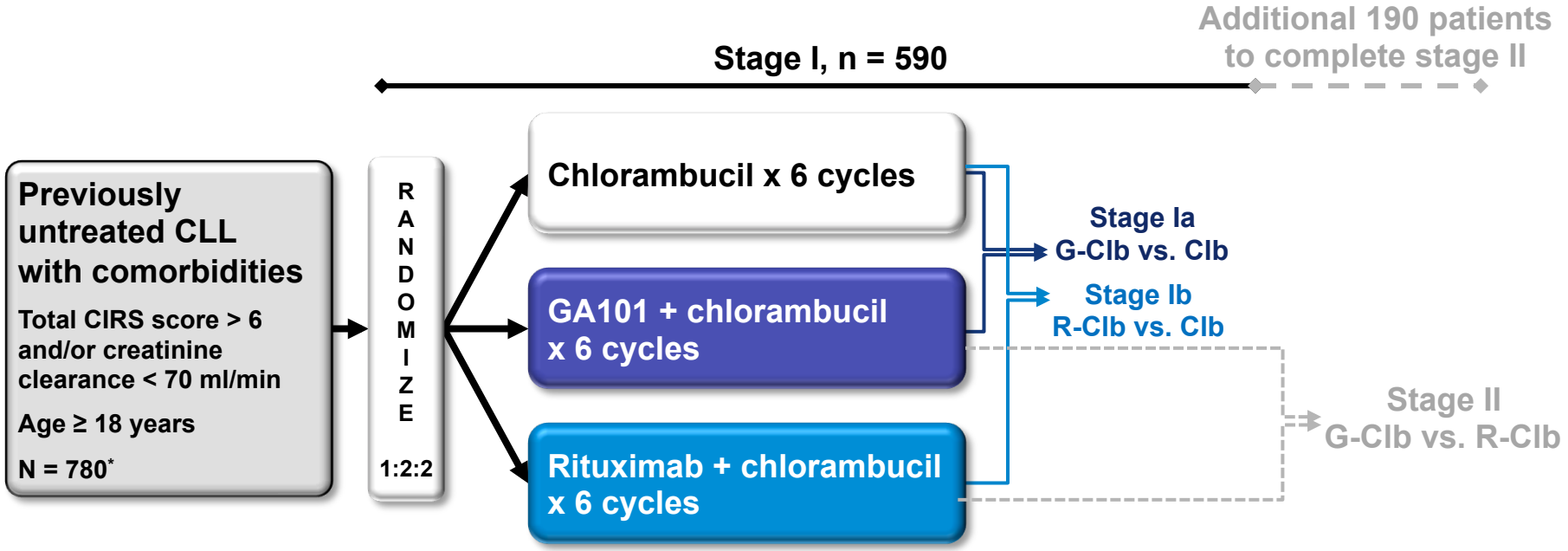
TTNT: time to next treatment

CR may be a goal of therapy in the elderly/unfit CLL requiring treatment (NCI criteria)
Which patient among the elderly/unfit?

Take a look at inclusion/exclusion criteria in clinical trials!

Study	treatment	Inclusion criteria
Foà et al Am J Hematol 2014	Chlor + R	• >65 years • 60–65 years not eligible for fludarabine-based regimens • No severe cardiac disease
Goede et al N Engl J Med 2014	Chlor + R Chlor + obinutuzumab	• Total Cumulative Illness Rating Scale (CIRS) > 6 and/or creatinine clearance < 70 ml/min • No active infection requiring systemic treatment • No positive hepatitis serology (HBV, HCV) • No history of other malignancy unless at least 2 yrs in remission without treatment
Hillment et al Lancet 2015	Chlor + oafatumumab	• Pts considered inappropriate for fluda-based therapy • fully capable of selfcare and up and about more than 50% of waking hours • certain heart problems, serious significant diseases • inability to comply with the protocol activities

CLL11 Phase III: Study design



GA101: 1,000 mg Days 1, 8, and 15 Cycle 1; Day 1 Cycles 2–6, every 28 days

Rituximab: 375 mg/m^2 Day 1 Cycle 1, 500 mg/m^2 Day 1 Cycles 2–6, every 28 days

Clb: 0.5 mg/kg Day 1 and Day 15 Cycle 1–6, every 28 days

Goede V, *et al*. *J Clin Oncol* 2013: 31 suppl: Abstract 7004 (presentation update).
www.clinicaltrials.gov NCT01010061.

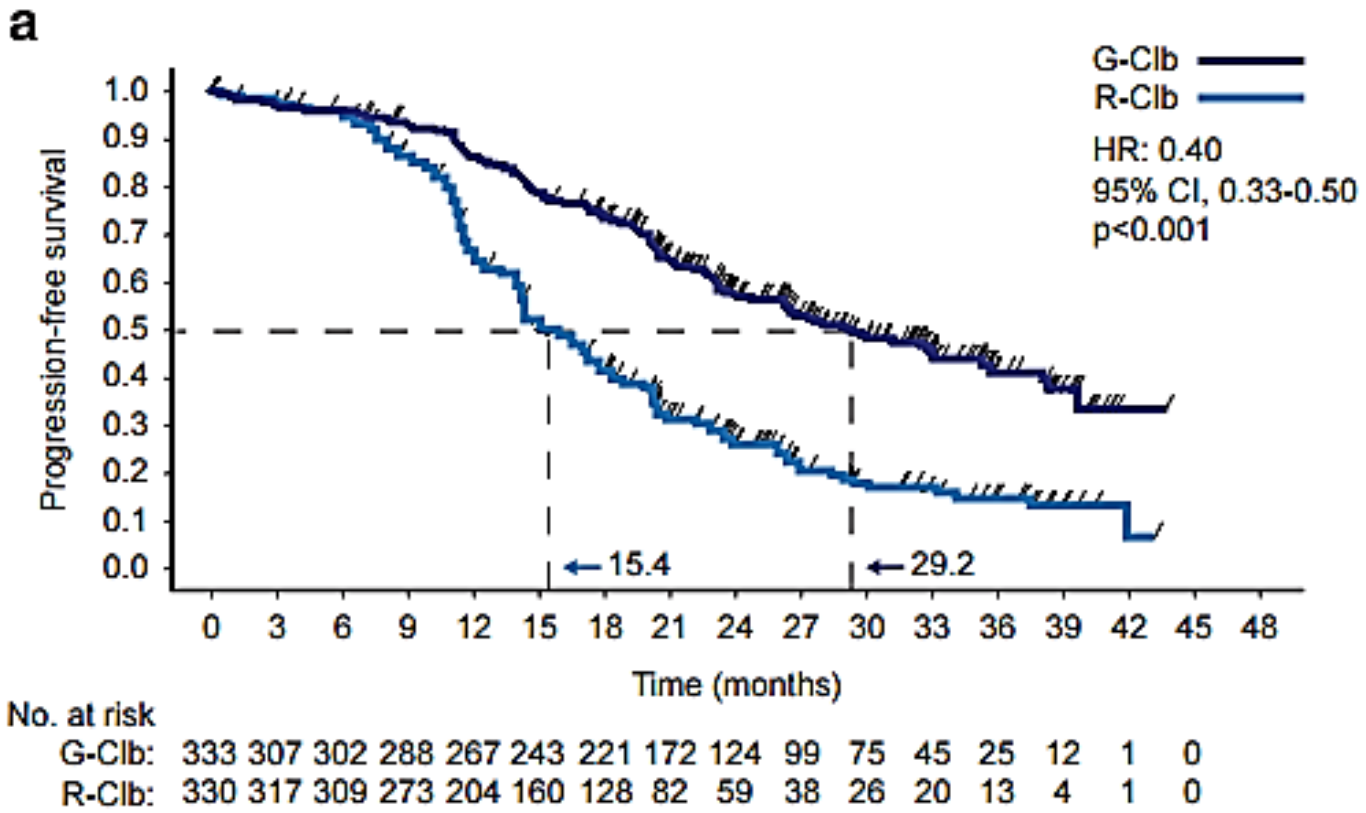
CLL11 stages Ia and Ib: Baseline disease characteristics

Characteristic	Patients, n (%)			
	Stage Ia		Stage Ib	
	Clb (n = 118)	G-Clb (n = 238)	Clb (n = 118)	R-Clb (n = 233)
Median age, years (range)	72 (43–87)	74 (39–88)	72 (43–87)	73 (40–90)
Male	64	59	64	64
Aged ≥ 75 years	37	45	37	45
CIRS score > 6	78	75	78	72
CrCl < 50 ml/min	21	29	21	24
Binet stage				
A	20	23	20	21
B	42	41	42	43
C	37	36	37	36
Circulating lymphocyte count ≥100 x10^9/l	37*	24*	37*	26*

* Circulating lymphocyte counts available for 116 patients in the Clb arm, 237 in the G-Clb arm, and 231 in the R-Clb arm. CrCl data available for 117/118 patients in the Clb arm. CrCl = creatinine clearance rate.

Adapted from Goede V, *et al*. *J Clin Oncol* 2013: 31 suppl: Abstract 7004 (presentation update).

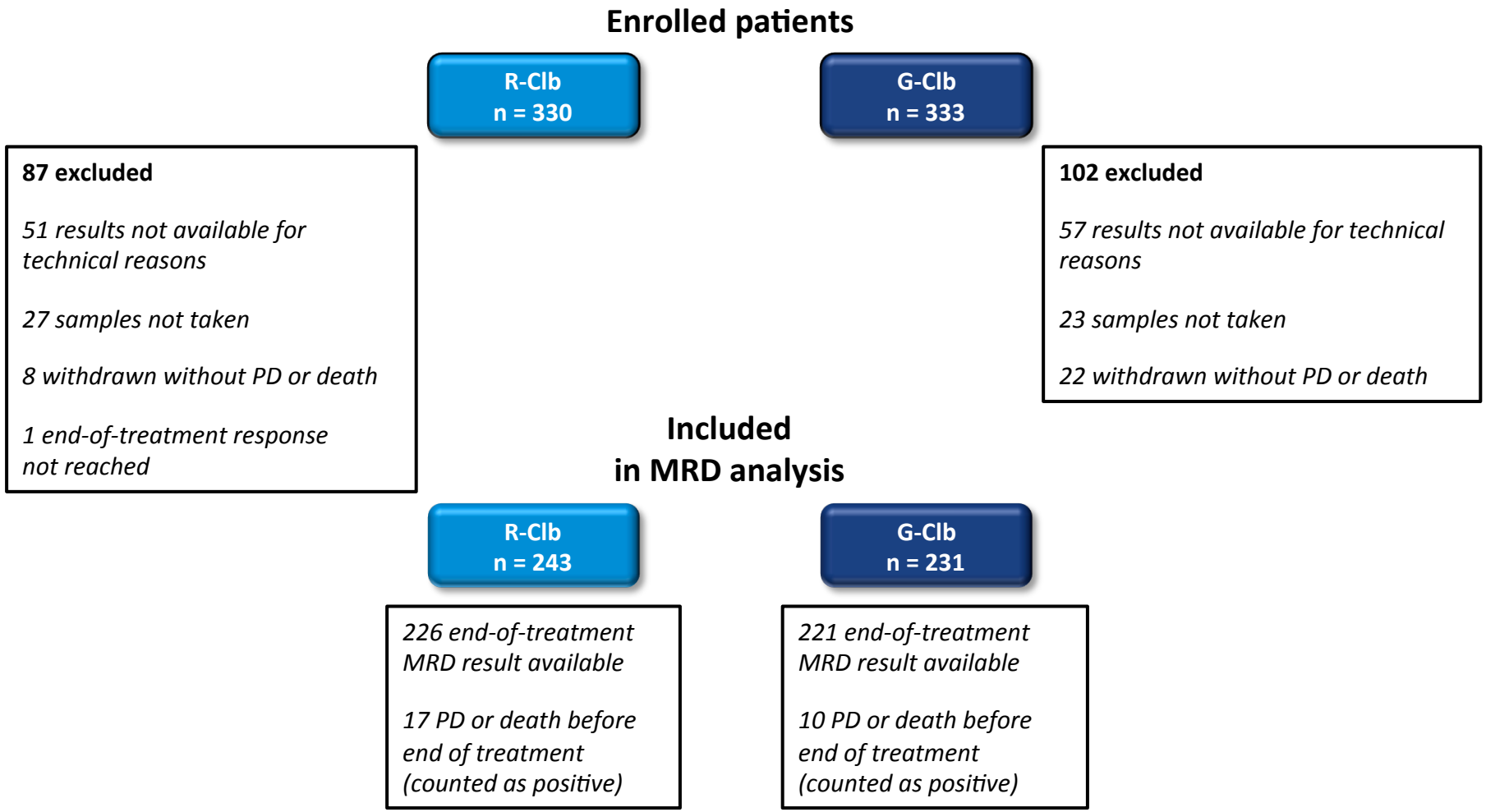
Update results of CLL11



Time to next antileukemic treatment was also longer with G-Clb than with R-Clb (42.7 versus 32.7 months, HR 0.54, 95% CI 0.40–0.72, Po0.001)

Goede et al. Leukemia (2015) 29, 1602–1604; doi:10.1038/leu.2015.14; published online 17 February 2015

CLL11 stage II: Blood MRD sampling

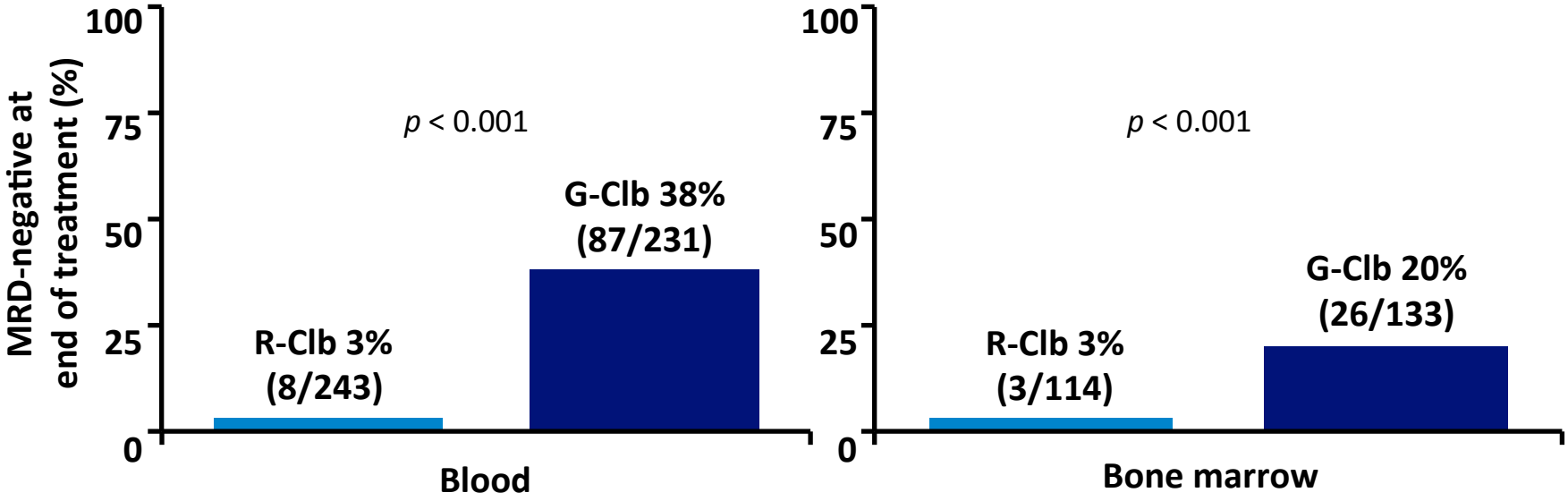


BM for MRD analysis was usually only taken from patients thought to be in CR

Goede V, *et al. N Engl J Med* 2014; 370:1101–1110.

CLL11 stage II:
MRD at the end of treatment

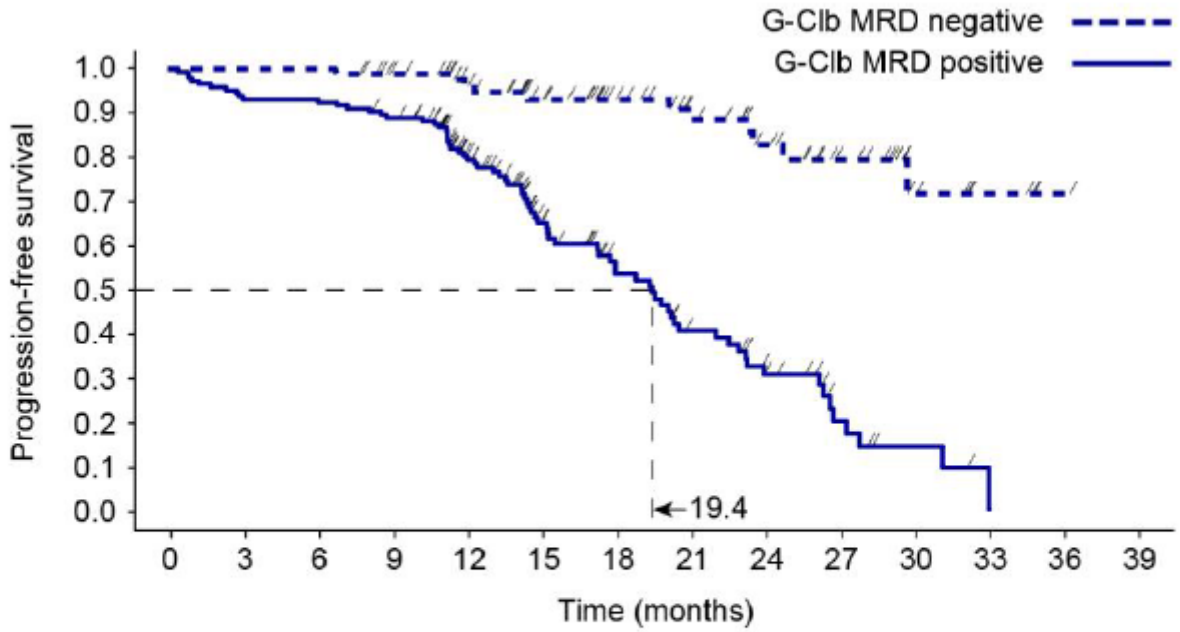
- 38% of patients in the G-Clb arm were MRD-negative in peripheral blood and 20% in the BM at final response assessment, compared with 3% in the R-Clb arm



- MRD by ASO-RQ-PCR at final response assessment
- BM samples were usually only taken from patients thought to be in CR
- Patients who progressed or died prior to MRD measurement were counted as MRD-positive

Goede V, *et al. N Engl J Med* 2014; 370:1101–1110.

PFS by MRD status in patients treated with G-Clb



No. at risk														
G-Clb MRD negative:	87	87	87	80	68	57	45	37	28	19	8	4	1	0
G-Clb MRD positive:	144	134	133	127	89	54	38	26	16	7	3	0	0	0

G-Clb, GA101 plus chlorambucil; MRD, minimal residual disease; PFS, progression-free survival.

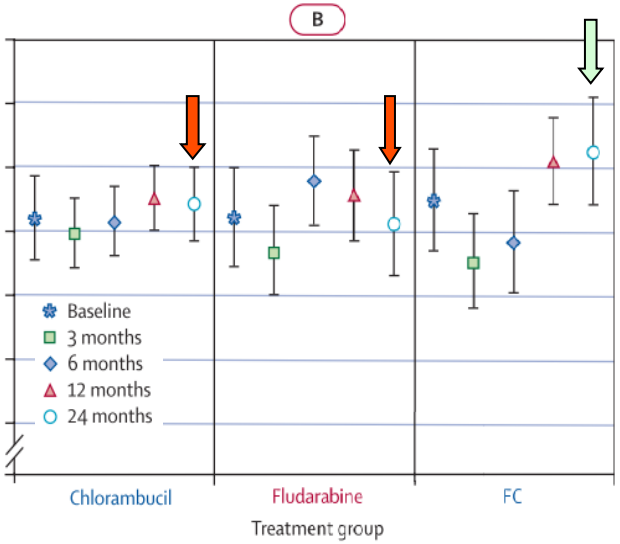
Goede V, *et al. N Engl J Med* 2014; 370:1101–1110. supl material

Better response translates into improved QOL: 5-year results from theUKCLL4 trial

EORTC-QLQ-C30 at baseline, months 3, 6 and 12, then annually until 5 years

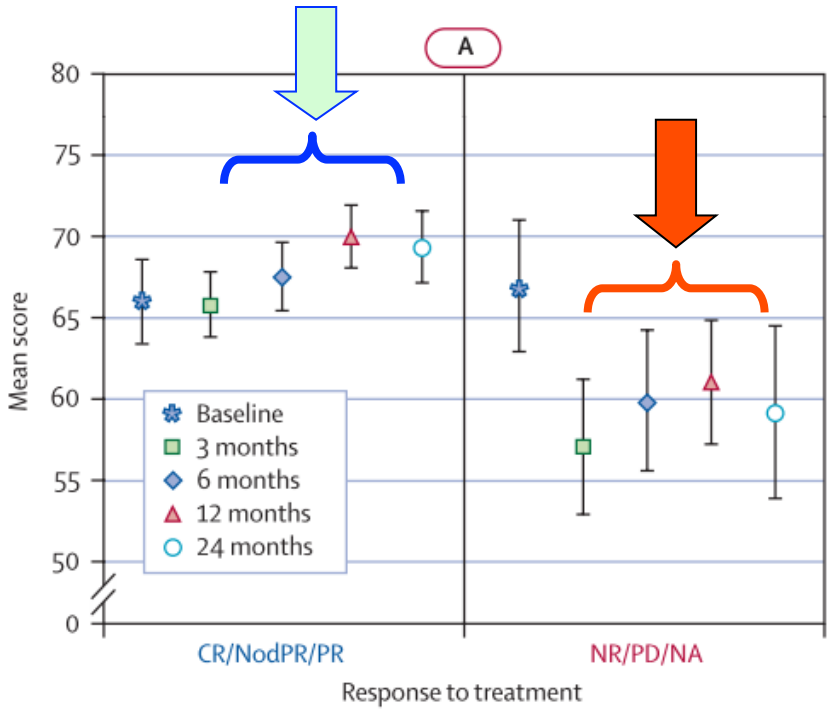
Compliance 76% in 777 patients

	% of patients with ≥ 10 points QOL worse than baseline at 3 months		
	Chlor	Fluda	FC
Role	29%	41%	48%
Social functioning	31%	46%	54%
Fatigue	40%	56%	60%



Else M, et al Leuk Lymphoma. 2012;53:1289-98.

QOL in UK LRF CLL4 trial Responders vs non responders



Valid replies (to date)	317	414	416	440	386	114	122	110	114	81
Patients alive	580	580	576	564	528	197	175	165	152	123

QOL of responders vs non-responders

at 3 months: 9·1 points higher, p=0·0001

at 2 years: 10·5 points higher, p=0·0004

Modified from Catovsky et al, Lancet 2007; 370: 230–39

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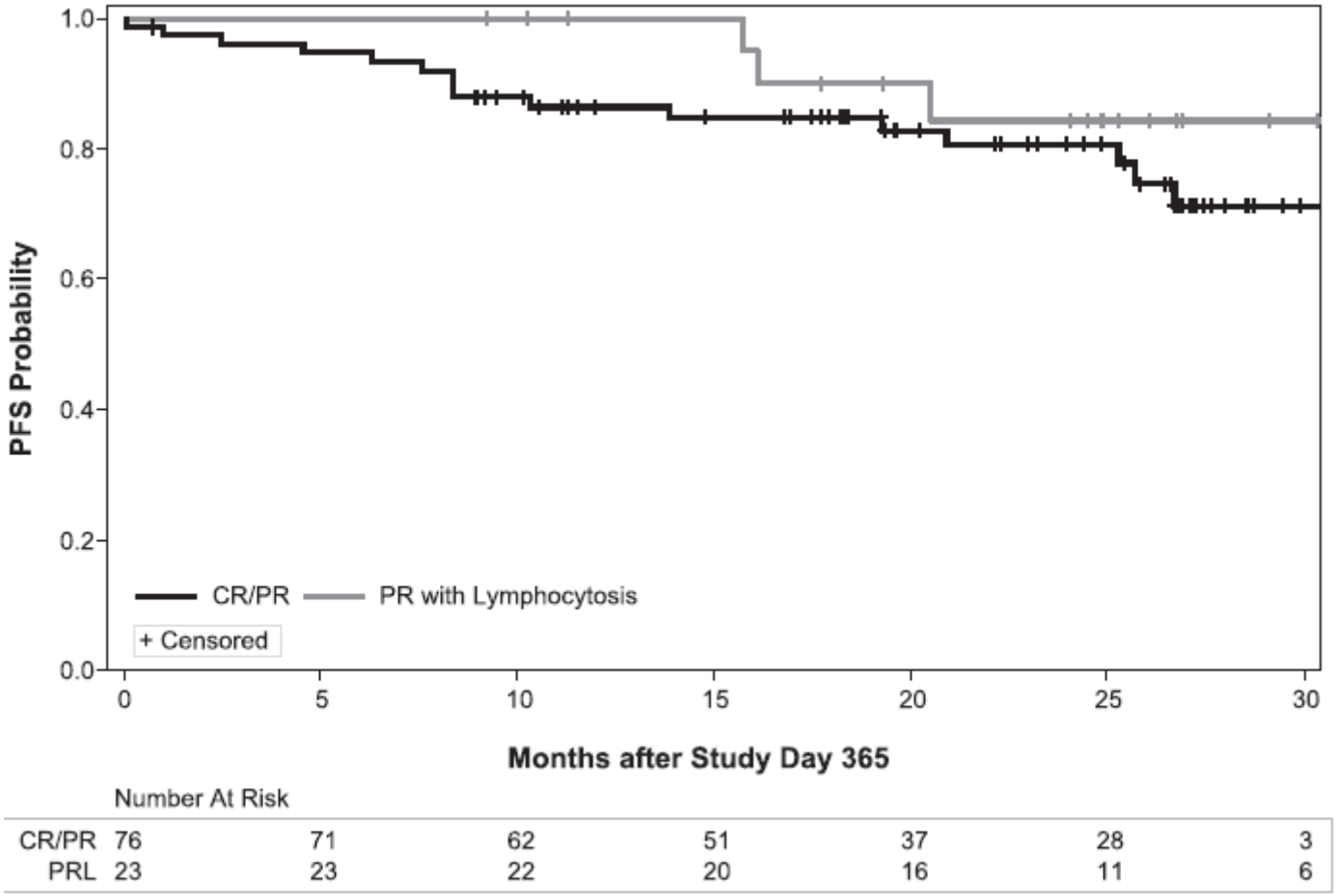
Overall response and CR rate at a 3 year follow-up of previously treated patients with CLL and SLL receiving single-agent ibrutinib.

Best response	R/R (n = 101)	R/R del(17p) (n = 34)
ORR (CR+PR+PR-L)	91 (90)	27 (79)
CR	7 (7)	2 (6)
PR	81 (80)	22 (65)
PR-L	3 (3)	3 (9)
SD	4 (4)	4 (12)
PD	2 (2)	1 (3)
Missing	4 (4)	2 (6)

Byrd JC Blood. 2015 Apr 16;125(16):2497-506.

Kaplan-Meier curves of PFS from day 365 in patients who achieved CR and PR or PR-L within the first 364 days on study with ibrutinib



Number At Risk							
CR/PR	76	71	62	51	37	28	3
PRL	23	23	22	20	16	11	6

Three-year follow-up of treatment-naive and previously treated patients with CLL and SLL receiving single-agent ibrutinib

Byrd J et al. Blood 2015;125:2497-2506

Overall response and CR rate in 3 studies of idelalisib in combination with R, Ofa or BR in previously treated patients with CLL

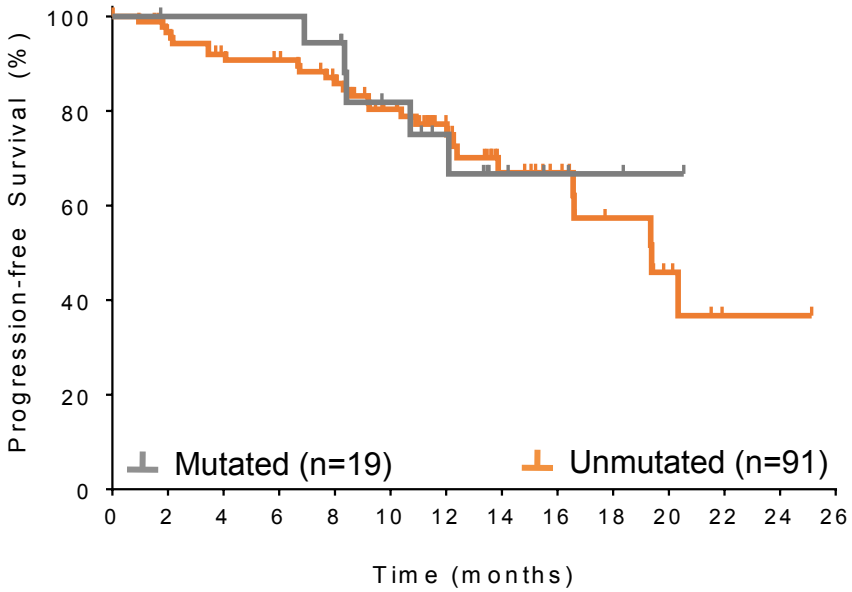
Study	Phase	n	Regimen (idelalisib +)	ORR (CR)	Median PFS	Median OS
Furman et al. [2014]	III	n = 217	+ rituximab	81% (0%)	19.3 months	92% at 12 mos.
Jones et al. [2015]	III	n = 173	+ ofatumumab	75% (0%)	16.3 months	20.9 months
Zelenetz et al [2015]	III	207	+ BR	68% (2%)	23,1	NR

Furman : N Engl J Med 2014
Jones. ASCO 2015, abstract
Zelenetz: ASH 2015, late breaking abstract

NR: not reached

PFS Subgroup Analysis in patients treated by idelalisib and rituximab

IGHV: Unmutated vs Mutated



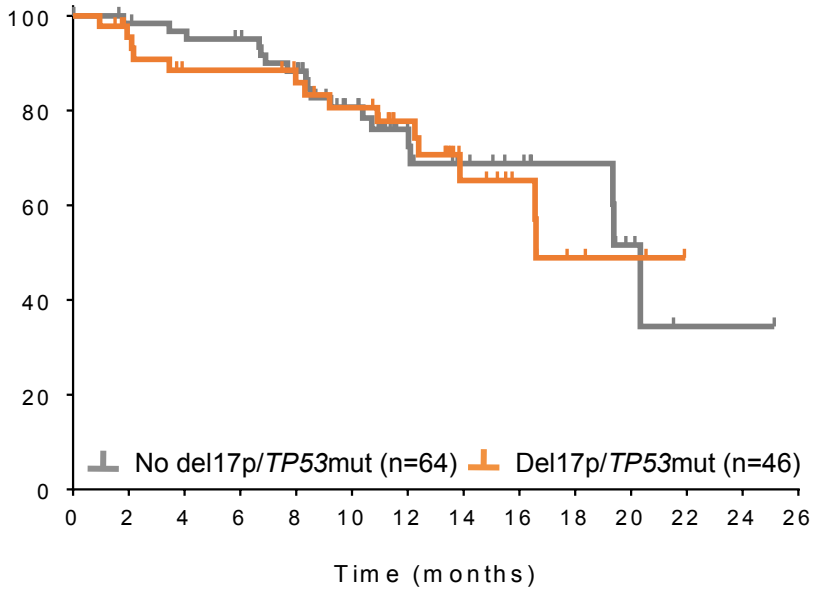
N at risk

Mutated	19	18	18	18	17	12	9	5	3	2	1	0	
Unmut	91	84	77	75	68	54	34	21	16	10	6	1	1	0

	Median PFS (95% CI)	p-value
Mut	NR (10.7, –)	0.75
Unmut	19.4 mo (16.6, –)	

*Including extension study

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, –)	

Sharman, ASH, 2014, Abstract 330

April 11, 2016

FDA approves Venetoclax for patients with CLL and 17p- who have been treated with at least one prior therapy

Venetoclax (ABT-199/GDC-0199) Monotherapy Induces Deep Remissions, Including Complete Remission and Undetectable MRD, in Ultra-High Risk Relapsed/Refractory Chronic Lymphocytic Leukemia with 17p Deletion: Results of the Pivotal International Phase 2 Study

Stephan Stilgenbauer[1], Barbara Eichhorst[2], Johannes Schetelig[3], Steven Coutre[4], John F Seymour[5], Talha Munir[6], Soham D Puvvada[7], Clemens-Martin Wendtner[8], Andrew W Roberts[9], Wojciech Jurczak[10], Stephen P Mulligan[11], Sebastian Böttcher[12], Mehrdad Mobasher[13], Ming Zhu[14], Brenda Chyla[14], Maria Verdugo[14], Sari Heitner Enschede[14], Elisa Cerri[14], Rod Humerickhouse[14], Gary Gordon[14], Michael Hallek[2], William G Wierda[15]

[1]University of Ulm, Germany; [2]Universitätsklinikum Köln, Germany; [3] University Hospital, Technische Universität Dresden, Germany; [4]Stanford University Medical Center, USA; [5]Peter MacCallum Cancer Centre, Australia; [6]St James's University Hospital, UK; [7] University of Arizona, USA; [8] Klinikum Schwabing, Munich, Germany; [9]Royal Melbourne Hospital, Australia; [10]Jagiellonian University, Poland; [11]Royal North Shore Hospital, Sydney, Australia; [12]University Hospital of Schleswig-Holstein, Campus Kiel, Germany [13]Genentech Inc, USA; [14]AbbVie Inc, USA; [15] UT MD Anderson Cancer Center, USA

Adapted from Stilgenbauer et al. Oral Presentation at ASH 2015, Orlando, Florida.

Baseline Characteristics

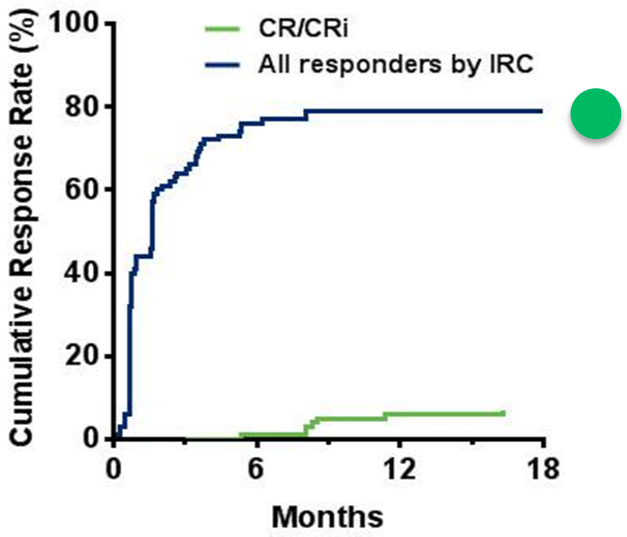
N=107[a]	n (%)
Median age (years), range	67, 37–85
Male	70 (65)
Prior therapies: median, range	2, 1–10
Prior bendamustine / refractory	54 (50) / 38 (70)
Prior fludarabine / refractory	78 (73) / 34 (44)
Prior CD20 mAb	90 (84)
ECOG grade 1/2	56 (52) / 9 (8)
One or more nodes ≥ 5 cm	57 (53)
ALC ≥25 x 10^9/L	54 (51)
TLS risk category	
Low	19 (18)
Medium	43 (40)
High	45 (42)
Rai stage III or IV	51(48)
IGHV unmutated	30 (81)

[a]Includes 1 patient without 17p–; [b]Low defined as ALC<25 and nodes <5cm, medium defined as ALC>20 OR nodes ≥5 and < 10cm), high defined as (ALC>25 nodes ≥5 and < 10cm OR nodes > 10cm

Adapted from Stilgenbauer et al. Oral Presentation at ASH 2015, Orlando, Florida.

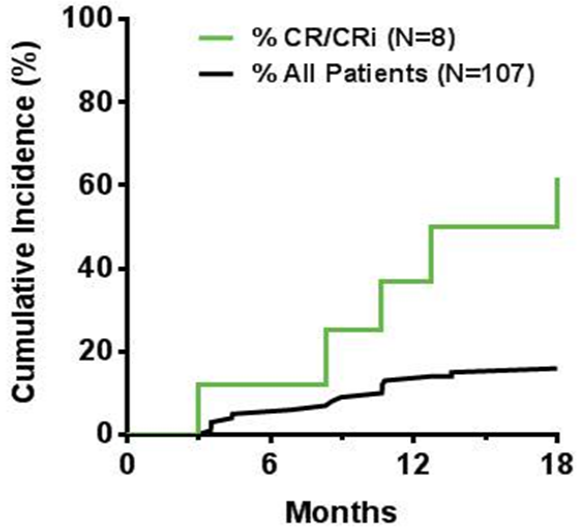
Cumulative Incidence of Response

iwCLL Response



- Median time-to-first response: 0.8 months (0.1–8.1)
- Median time to CR/CRi: 8.2 months (3.0–16.3)

MRD-Negativity

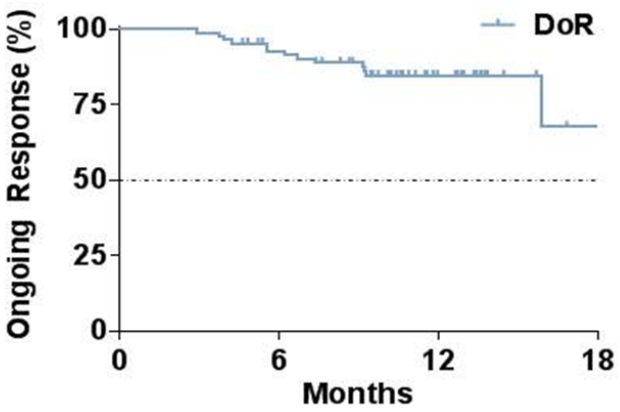


- Of 45 patients tested, 18 achieved MRD-negativity in peripheral blood

Adapted from Stilgenbauer et al. Oral Presentation at ASH 2015, Orlando, Florida. [11]

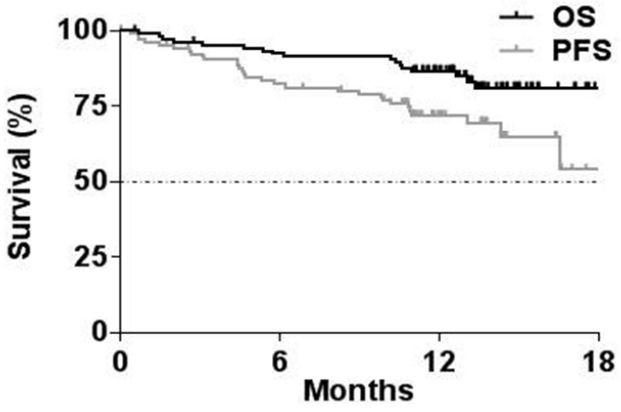
Durability of Venetoclax Activity

Duration of Response (N=85)



- 12-month estimates:
  - All responders: 84.7%
  - CR/CRi/nPR: 100%
  - MRD-negative: 94.4%

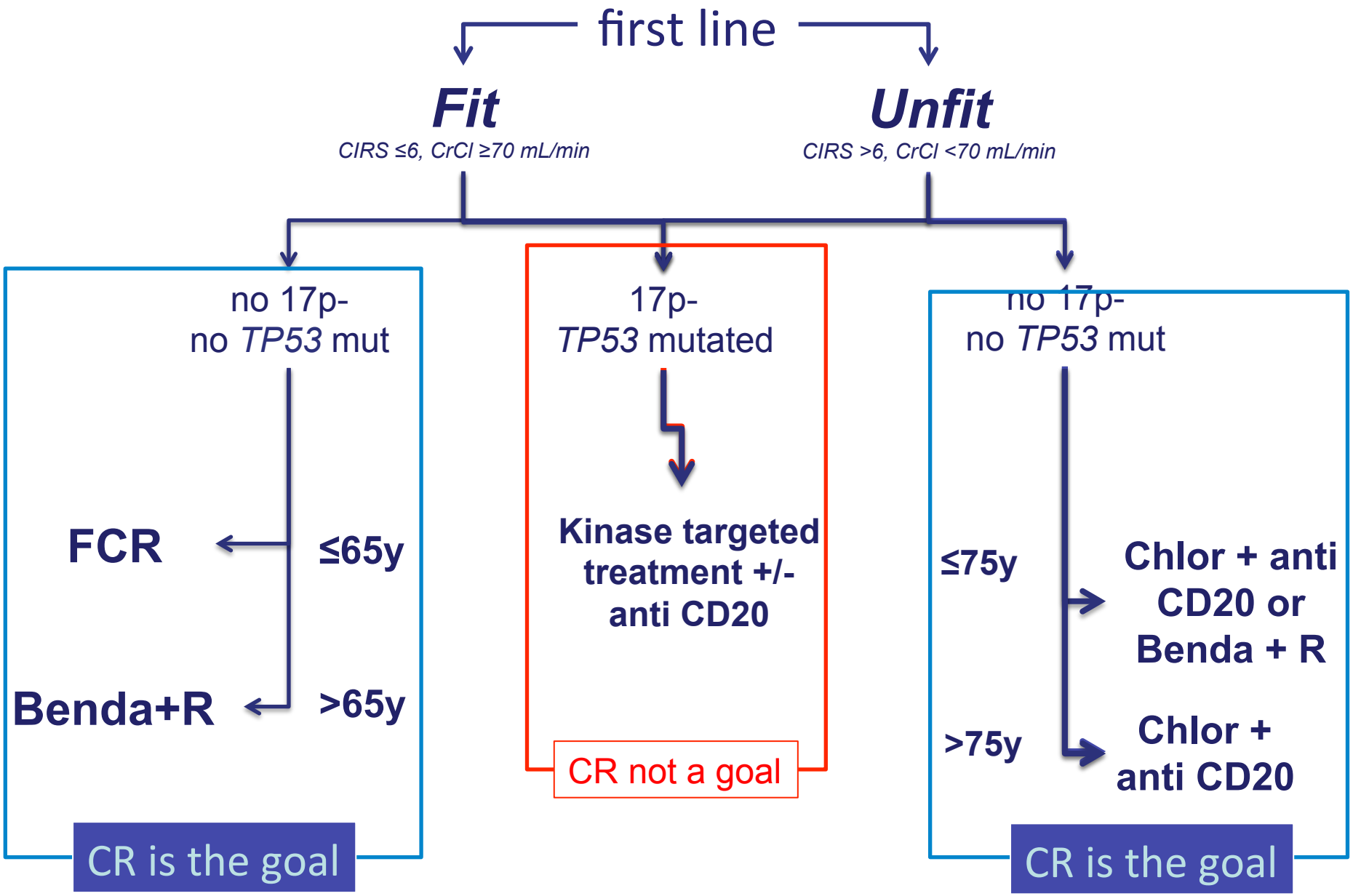
PFS and OS (N=107)



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

Adapted from Stilgenbauer et al. Oral Presentation at ASH 2015, Orlando, Florida.

When is CR a reasonable goal in the treatment algorithm of CLL?



When is CR a reasonable goal in the treatment algorithm of CLL?