Guarire di LLC senza trapianto è oggi possibile?

Moderatori: L. Guardigni, P.L. Zinzani

- **Impiegando la chemioterapia convenzionale?**

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Guarire di LLC senza trapianto, Impiegando la chemioterapia convenzionale è oggi possibile?

Outline

- Cure of CLL: criteria
- Cure with HSCT: how many patients?
- Cure with CIT: how mant patients?
- Cure or mantain a disease control?

It is possible to eradicate CLL cells?

Cure of CLL

- No clinical signs of CLL➔CR
- No residual disease at flow-cytometry/PCR ➔MRD negative
- Persiting MRDneg-CR➔ relapse-freesurvival (PFS >5 years?)

MRD negativity

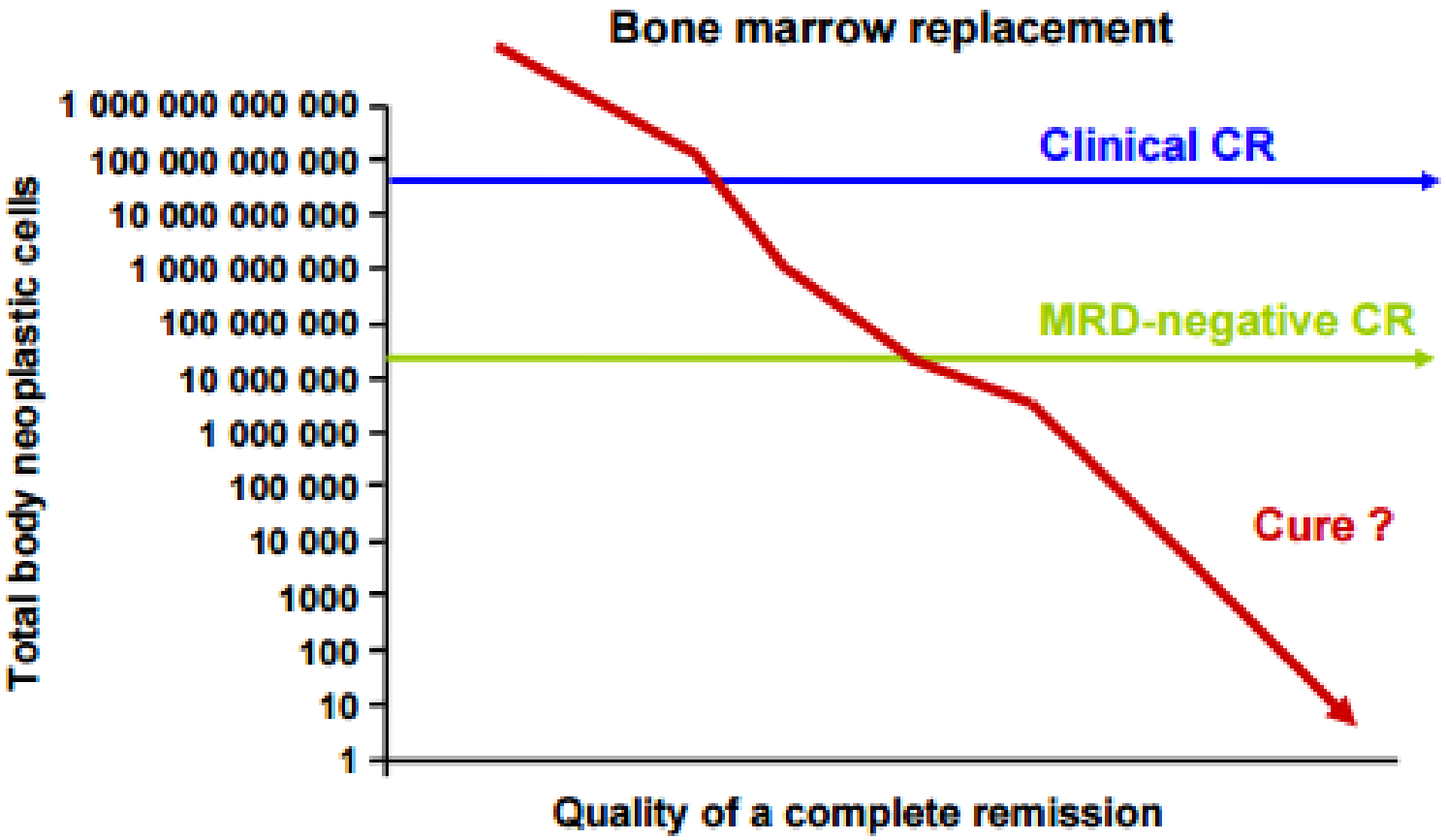
Sensitivity of approximately one CLL cell in ≥10.000 leucocytes detected by:

- Immunophenotype (flow-MRD)
  >4 color flow-cytometry

- IGH rearrangement (ASO-PCR MRD)
  Allele-Specific Oligonucleotide PCR (ASO-PCR)

MRD negativity= less than one CLL cell per 10^{-4} leucocytes

Is it meaningful to reach MRD negativity?



Modified from Moreno et al, Best Pract 2010

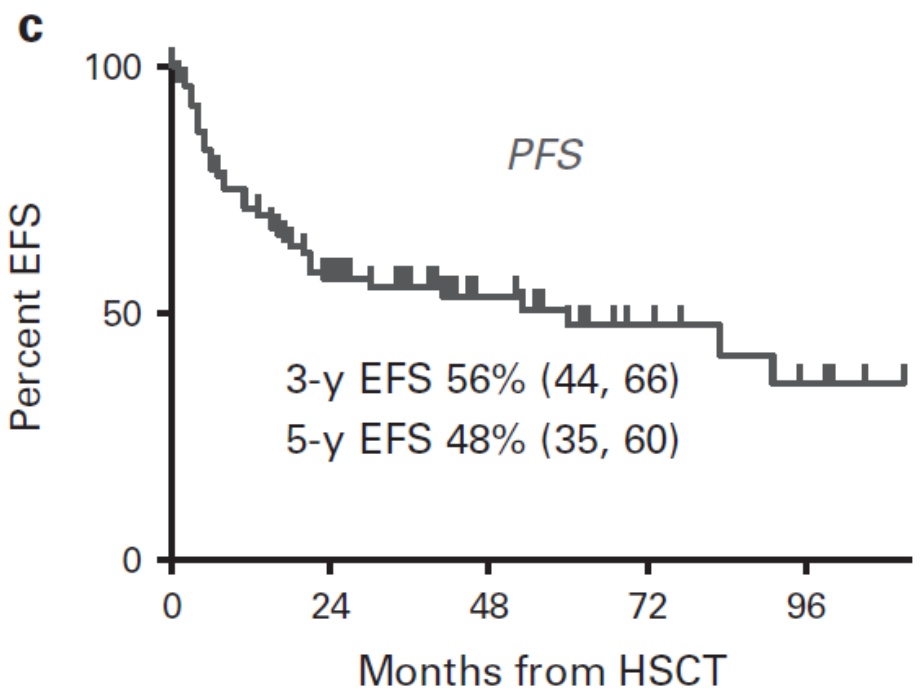
How many patients are cured after allogeneic after HSCT?

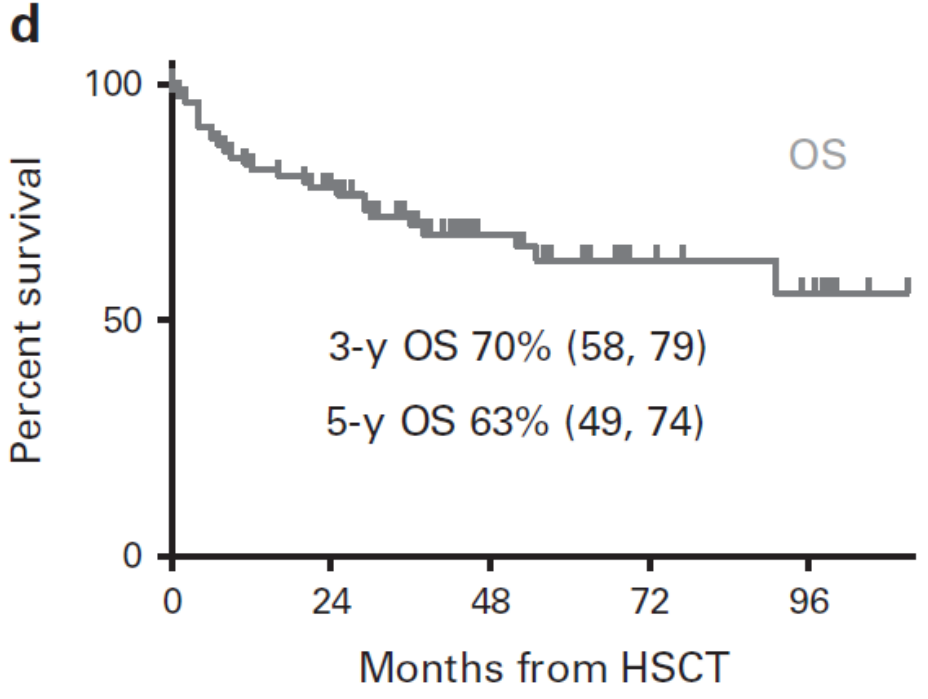
Long-term follow-up for RIC allogeneic SCT in CLL

	Sorror et al*	Dreger et al†	Brown et al‡	Khouri et al§
No. of patients	82 (n = 64 with 5-y follow-up)	90	76	86
Median follow-up	5 y	72 mo	5.1 y	37.2 mo
Time period	1997-2006	2001-2007	1998-2009	1996-2007
Purine analog refractory disease, %	87	47	55	83
Cytogenetics	n = 7 (del17p), n = 7 (del11q), n = 9 (complex karyotype)	18% del17p, 36% del11q	17% del17p, 8% del11q	Not reported
Disease status SCT	55% refractory disease	21% refractory disease	43% SD/PD	17% refractory disease
Bulky disease SCT	24%	Not reported	21%	Not reported
Conditioning regimen	2-Gy TBI ± fludarabine (URD)	Fludarabine + cyclophosphamide ± ATG (URD)	Fludarabine + busulphan	Fludarabine + cyclophosphamide + rituximab
Donor status	37% URD	45% URD	63% URD	Not reported
Relapse rate	38% (5 y)	46% (6 y)	40% (5 y)	39% (3 y)
PFS	39% (5 y)	38% (6-y EFS)	43% (5 y)	36% (5 y)
OS	50% (5 y)	58% (6 y)	63% (5 y)	51% (5 y)
Chronic extensive GVHD	49% sib donor, 53% URD	53% (35/66)	65% (limited + extensive) at 2 y	56% (5 y)
NRM	23% (5 y)	23% (6 y)	16% (5 y)	17.4% (1 y)
Reported use of MRD monitoring/DLI	No	Yes	No	Yes
Impact of pre-SCT cytogenetics on SCT outcomes	No impact	No impact	No impact	Not assessed
Prognostic factors that influenced outcome	Model to predict 3-y inferior OS: LN size ≥5 cm, HCT CI score ≥1	Model to predict inferior EFS, OS, NRM: refractory disease at SCT, use of alemtuzumab prior to SCT	Model to predict inferior PFS: disease status at SCT, LDH, comorbidity, ALC	Model to predict inferior OS: hypogammaglobulinemia, CD4 <100/mm^3

Mato and Porter, Blood 2016

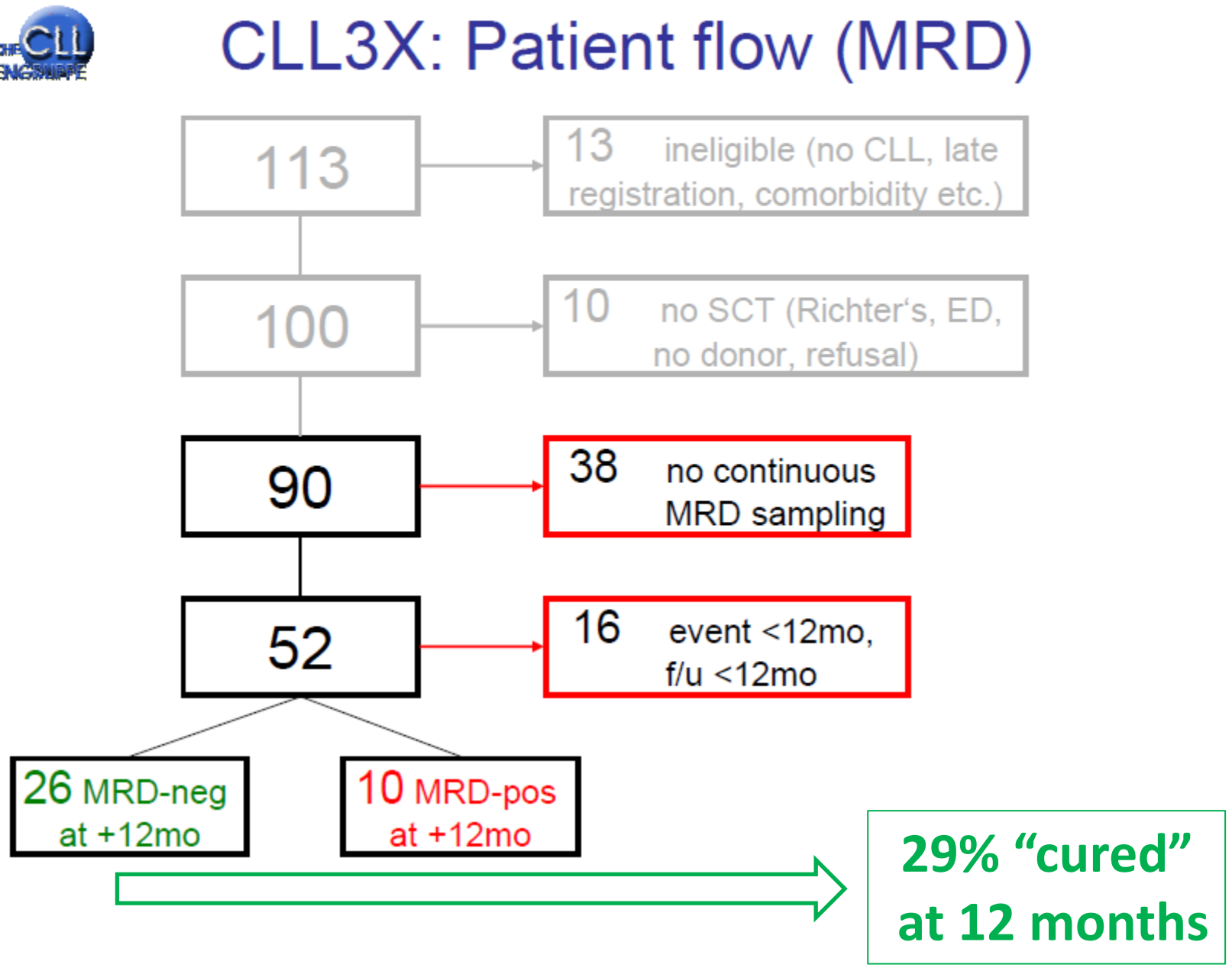
Allogeneic HSCT for poor-risk CLL: dissecting immune-modulating strategies for disease eradication and treatment of relapse





Hahn et al. BMT 2015

How many cured of CLL with allogeneic SCT

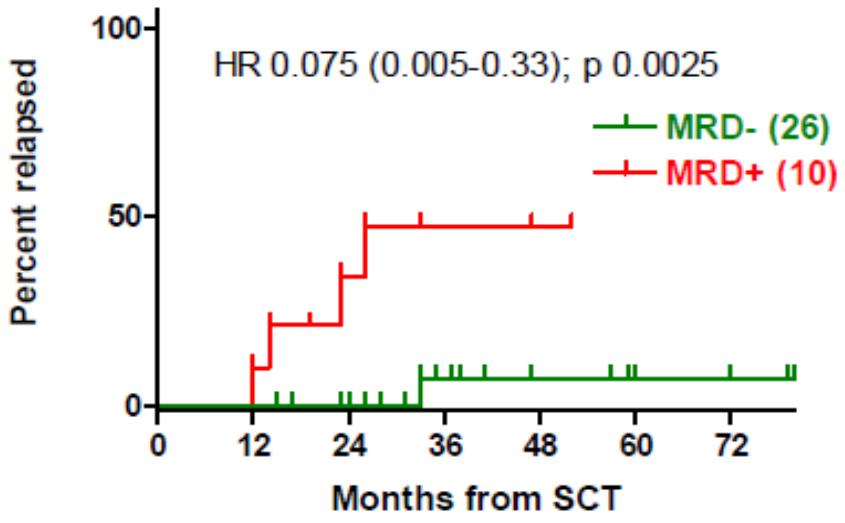


How many cured of CLL with SCT

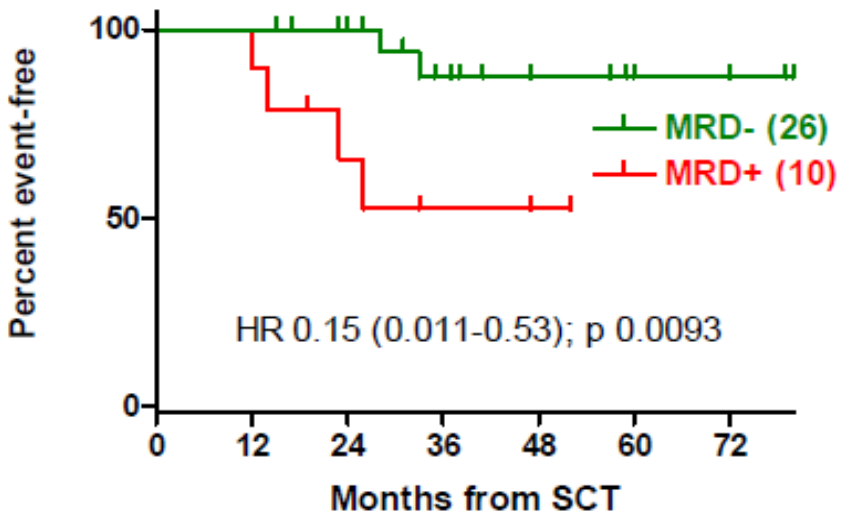
CLL3X: Clinical impact of MRD negativity at +12mo

(of 36 patients with MRD marker and event-free at mo +12)

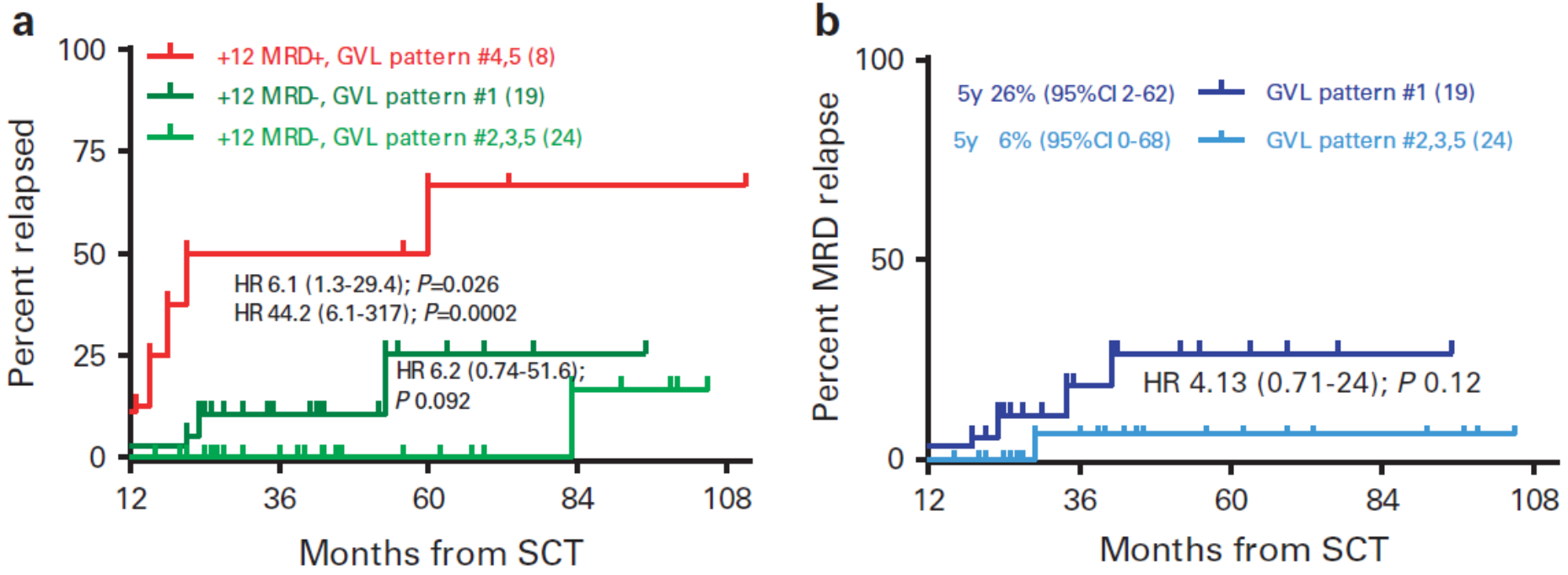
Relapse



EFS



Allogeneic HSCT for poor-risk CLL: dissecting immune-modulating strategies for disease eradication and treatment of relapse



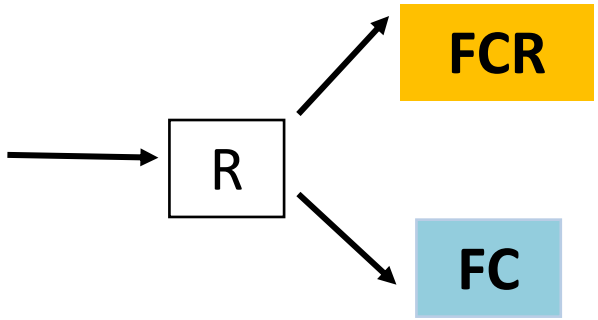
Relapse incidence by MRD status (a) and MRD recurrence (b) in patients who were event free at the 12-month landmark. (a) MRD-negative at the 12-month landmark immediately after HCT; light-green curve, MRD-negative at the 12-month landmark after immunomodulation; and red curve, MRD-positive at the 12-month landmark. (b) Dark-blue curve, MRD-negative at the 12-monthlandmark immediately after HSCT; and light-blue curve, MRD-negative at the 12-month landmark after immunomodulation.

Hahn et al. BMT 2015

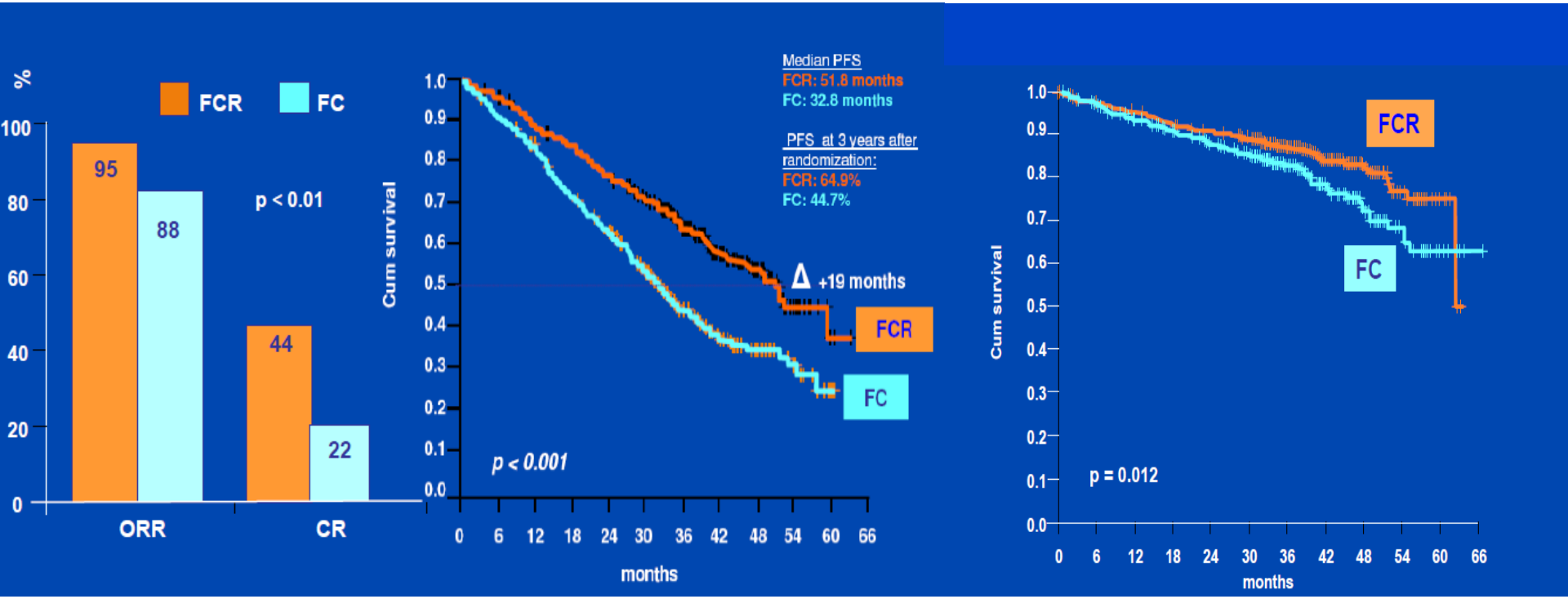
How many patients are cured after chemoimmunotherapy?

CLL8 study - FCR vs FC

817 patients with untreated, active CLL and good physical fitness
CIRS ≤ 6
CrCL ≥ 70 mL/min)



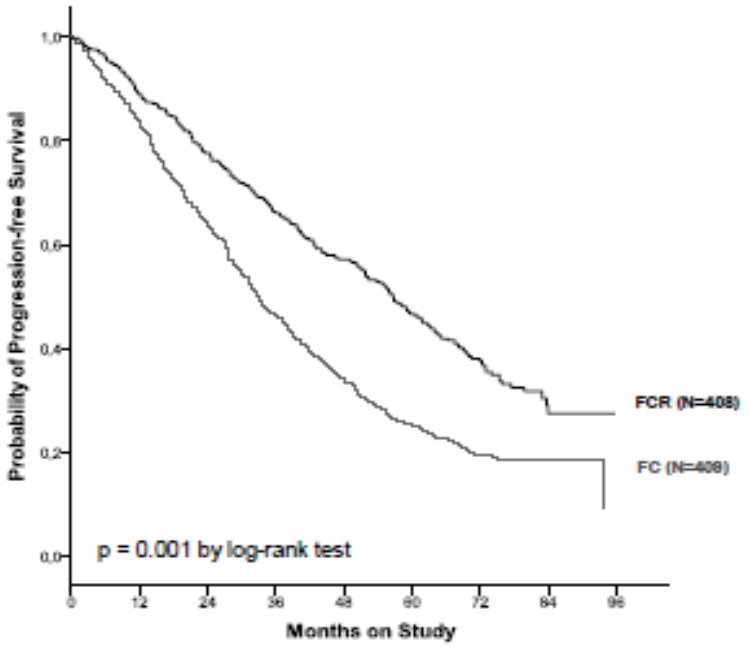
Response | Progression-Free Survival | Overall Survival



Hallek M, et al. Lancet. 2010

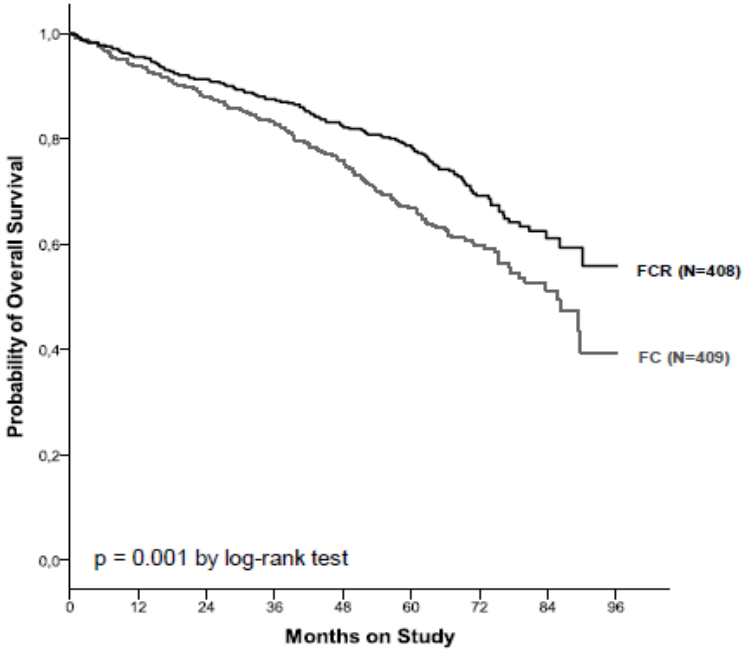
CLL 8: OS and PFS: FCR vs FC

PFS



Median PFS:
FC➔ 32.9 months
FCR➔ 56.9 months

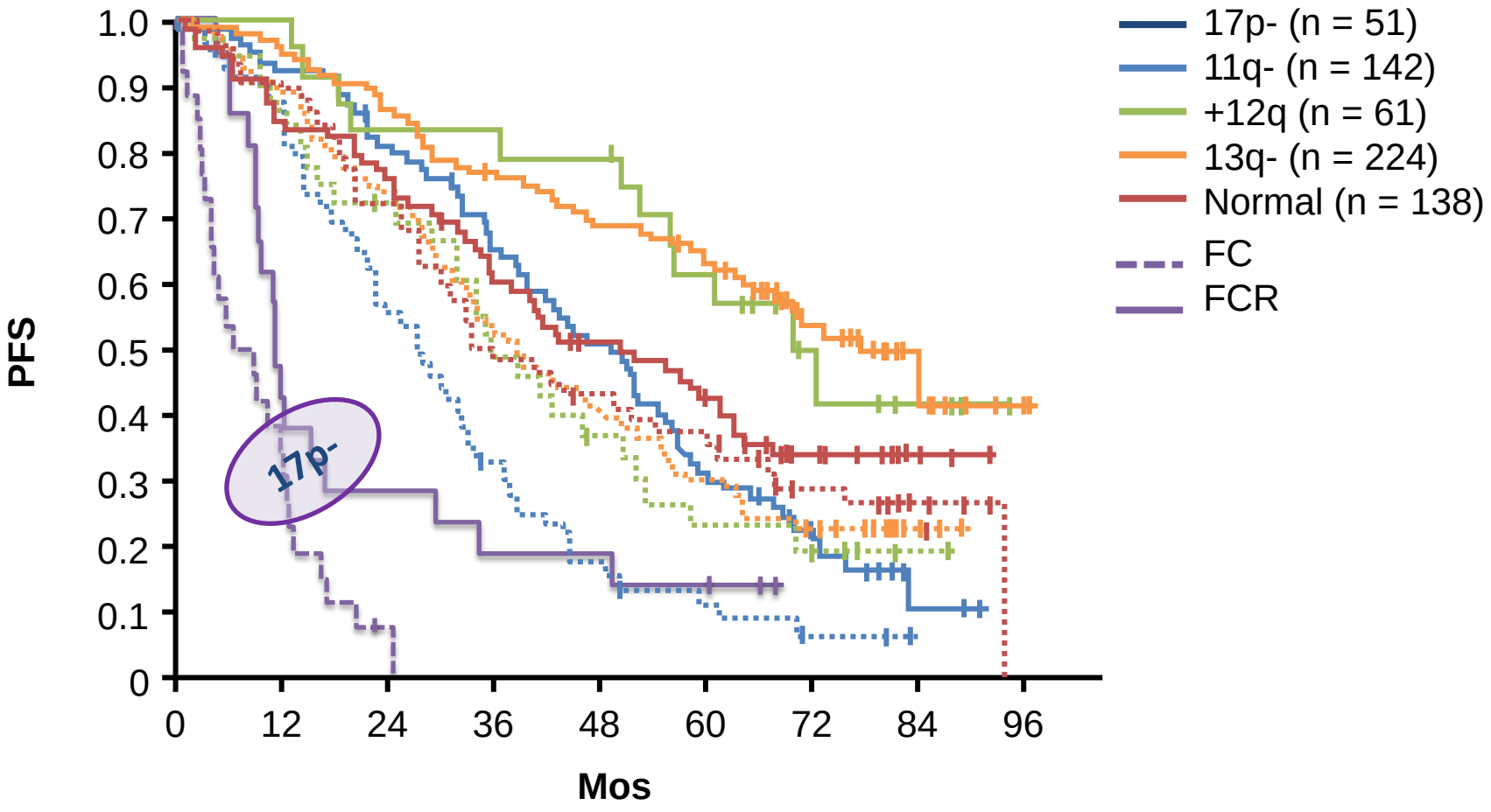
OS



Median OS:
FC➔ 86.0 months
FCR➔not reached

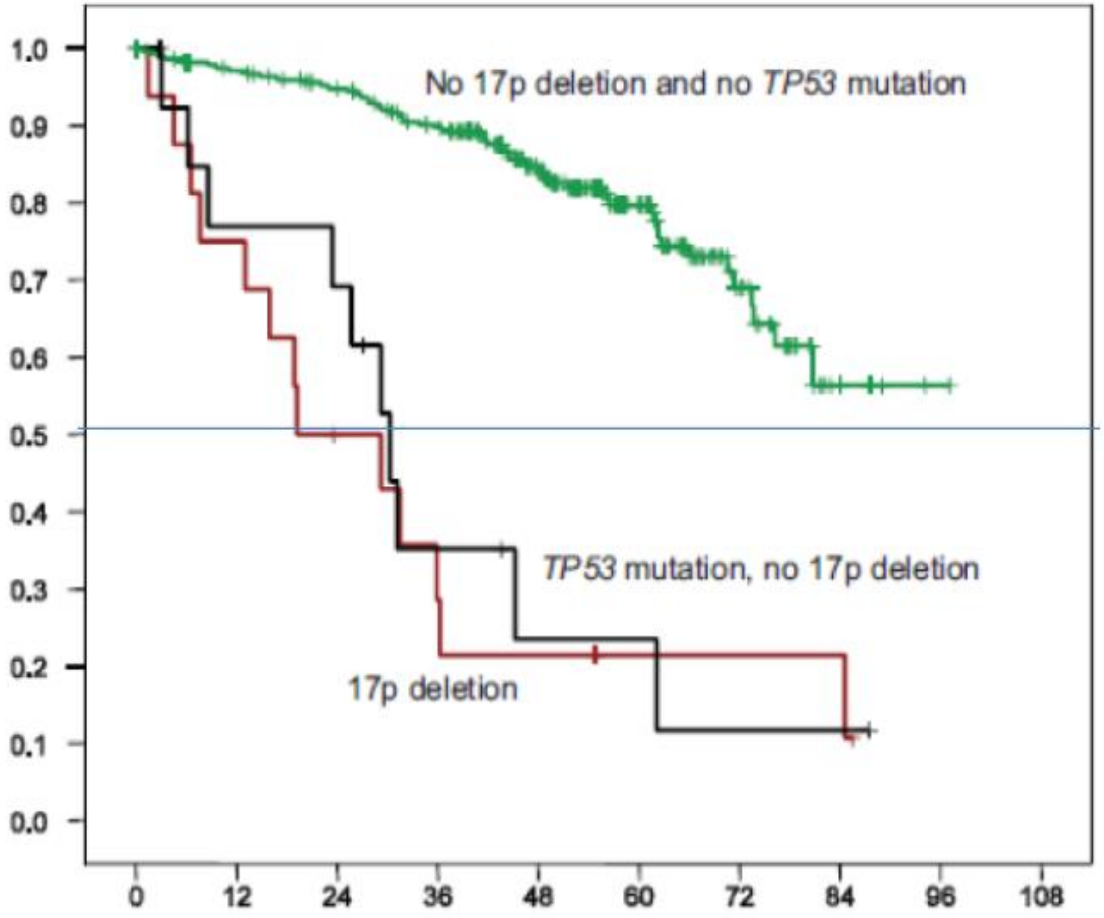
Fisher et al., Blood 2015

CLL8 Trial: PFS in Genomic Subgroups



Stilgenbauer S, et al. Blood. 2014

Del 17p and *TP53* mutations: effect on survival

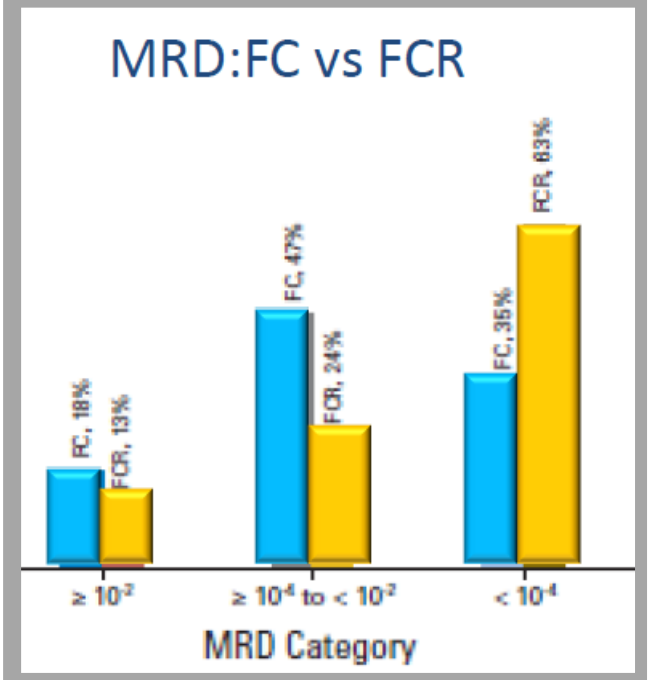


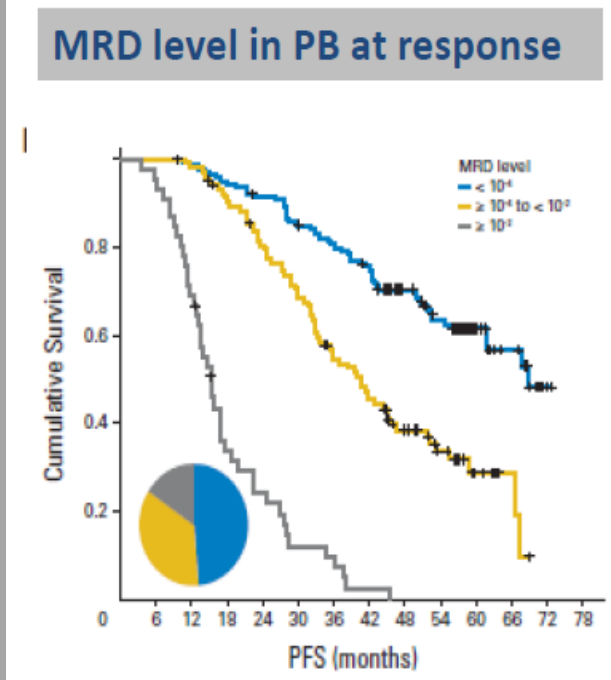
OS after first line FC/FCR

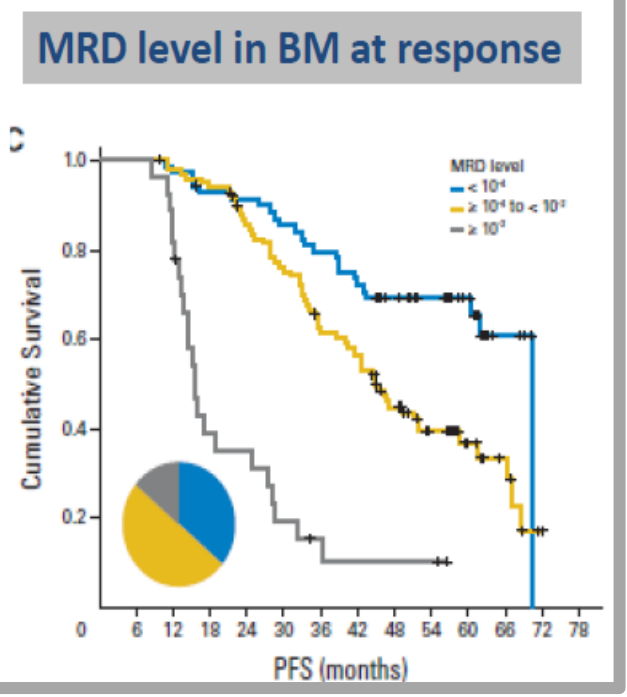
NCI-IWCLL 2008 guidelines
ESMO guidelines
ERIC recommendations
SIE, SIES, GITMO recommendations

Deletion 17p *and TP53* mutations should be investigated immediately before treatment decision

PFS and MRD level at response



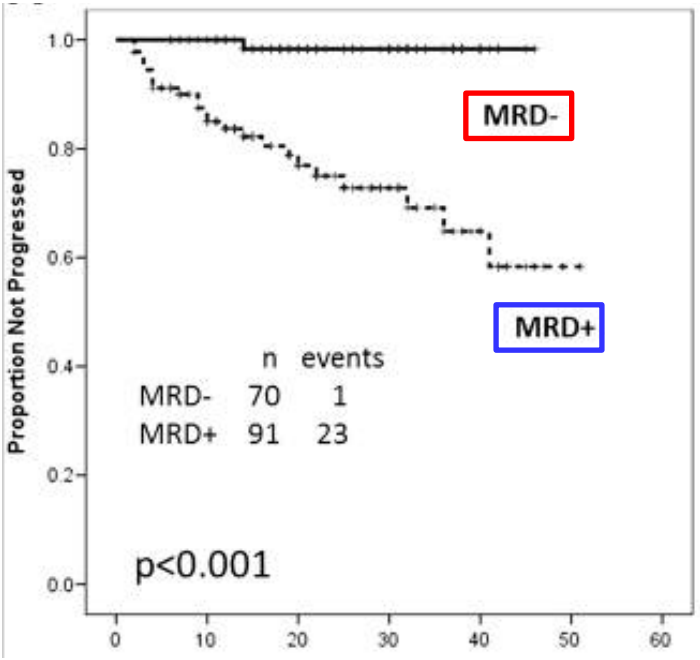


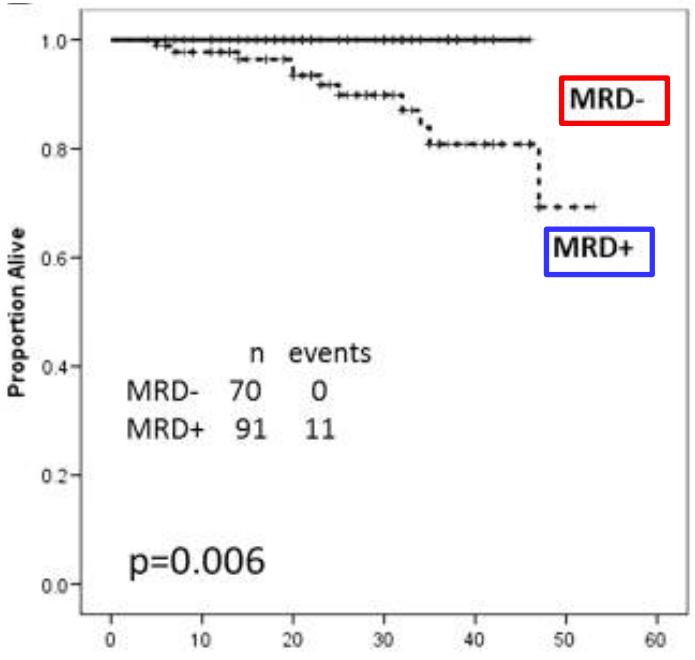


Bottcher et al., JCO 2012

Eradication of BM MRD may prompt early treatment discontinuation in CLL

- 237 patients with CLL treated with front-line FCR at MDACC
- MRD assessed by 4-color flow cytometry in BM after course 3 and at final response





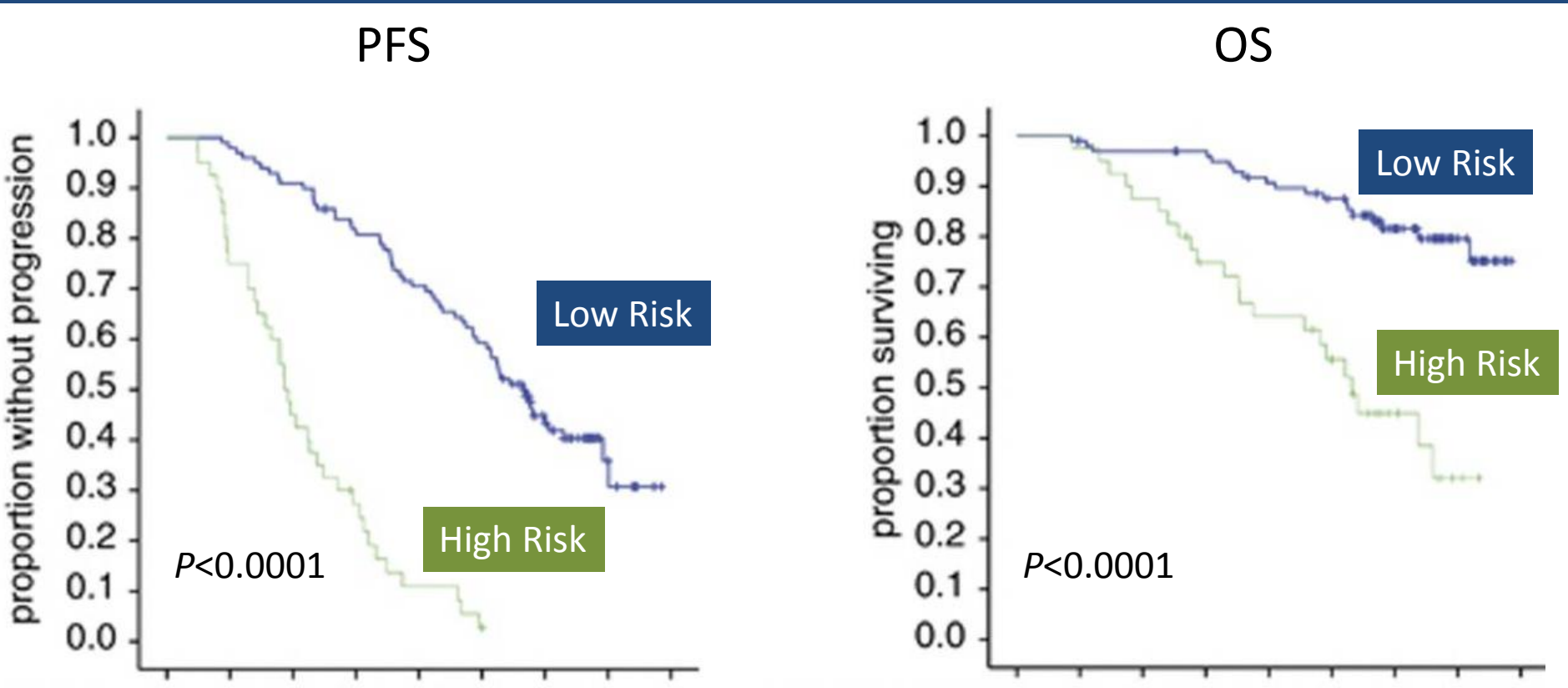
- MRD negative cases: 17% after course 3; 43% at final response assessment
- Mutated IGVH and trisomy 12 independently associated with MRD-negative status

Patients with a MRD-negative status showed a significantly longer PFS and OS independently of the number of courses received, 3 or 6

Early MRD eradication may propt consideration of early discontinuation of treatment.
Such a strategy could reduce secondary complications (infection, myelosuppression, MDS/AMLother malignancies

Strati et al., Blood 2014

Outcome of CLL patients treated with FCR by Risk and MRD



Patients with low or intermediate MRD levels and no adverse biologic factors show a significantly better PFS and OS

High risk (29% of patients)- Median PFS 22 months; median OS: 64 months
high MRD levels
intermediate MRD levels plus *TP53* aberrations and/or unmutated *IGHV* status

Low Risk (71% of patients)- Median PFS 68 months; median OS not reached
low MRD levels ($<10^{-4}$) irrespective of any additional feature
intermediate MRD levels with no unmutated *IGHV* genes nor a *TP53* aberration

Fink et al., Leukemia 2013

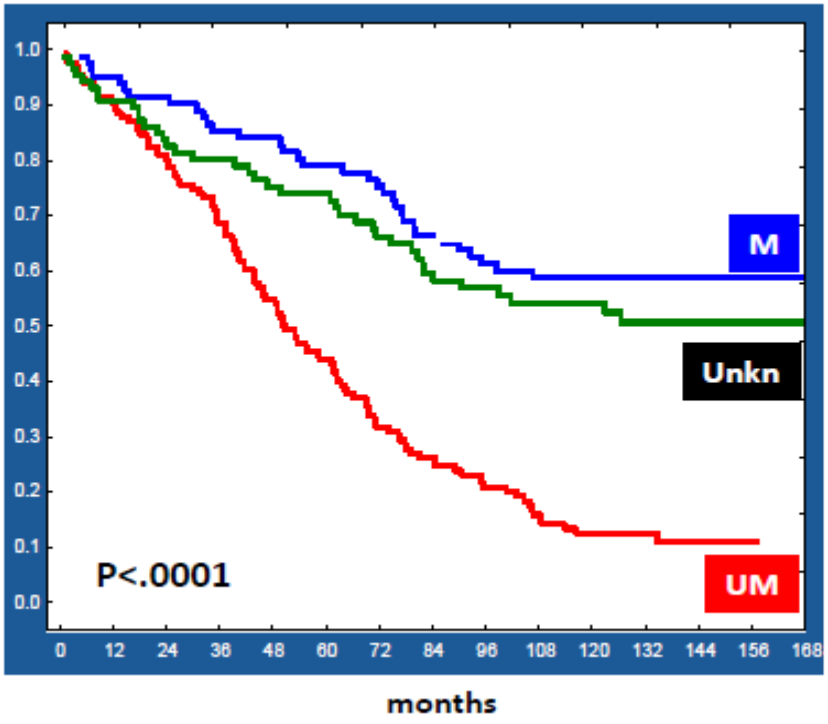
The lessons from patients treated with FCR

The outcome of patients strongly related to:

- **IGVH mutational status**

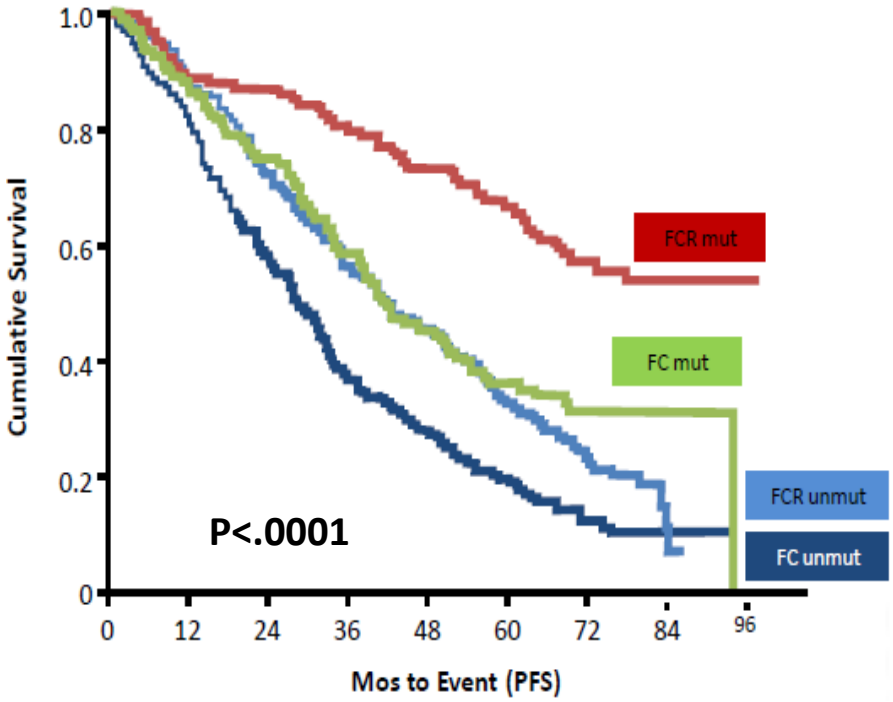
FCR300 and CLL8 PFS by IGVH mutation status

300 CLL patients treated with frontline FCR at the MDACC



60% IGVH mutated
Prog-free @ 9yr

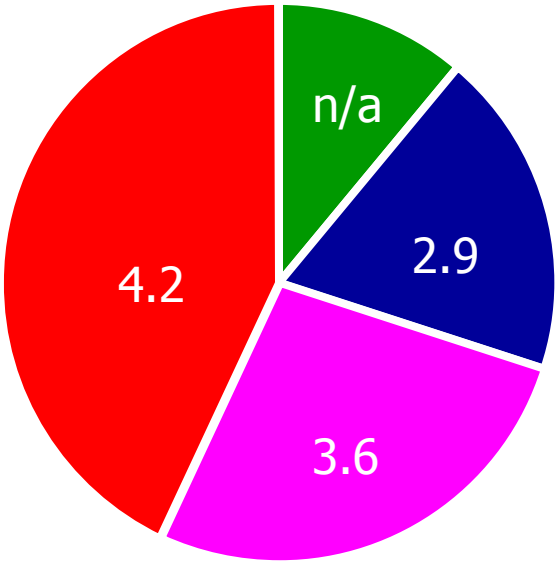
817 CLL patients treated with frontline FCR or FC in the CLL8 trial



>50% IGVH mutated
Prog-free @ 6yr

Elderly patients with CLL frequently have comorbidities

- Median age of CLL patients at diagnosis: 72 years1
- Median age at first treatment 75 years
- The number of comorbidities increases with age



Age at CLL diagnosis (years)	Patients[1] (%)	Mean comorbidities[2] (all cancer types, n)
≤54	11	n/a
55–64	19	2.9
65–74	27	3.6
75+	43	4.2

[1] Ries LAG et al. SEER Cancer Statistics Review 1975–2005.
[2] Yancik R. *Cancer* 1997; 80:1273–83.

The German CLL10 Trial: FCR vs BR

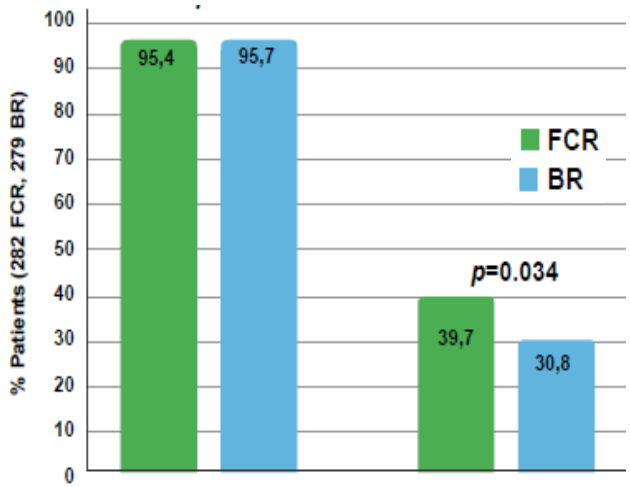
Can BR regimen improve the results of FCR in fit patients ?

Untreated B-cell CLL
Binet Stage C or
A/ B with B symptoms
No deletion 17p
Good fitness status (CrCl ≥ 70ml/min; CIRS ≤6)

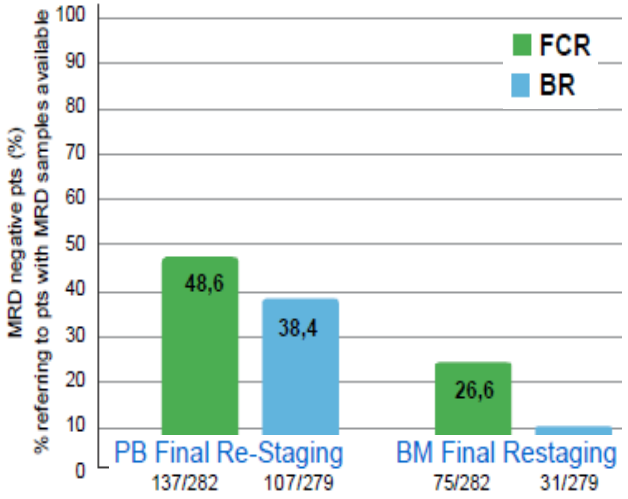
R → FCR (282)
R → BR (279)

Primary Endpoint: PFS after 24 months➔
non inferiority of BR vs FCR [HR (γ BR/FCR)] <1.388

Best Response



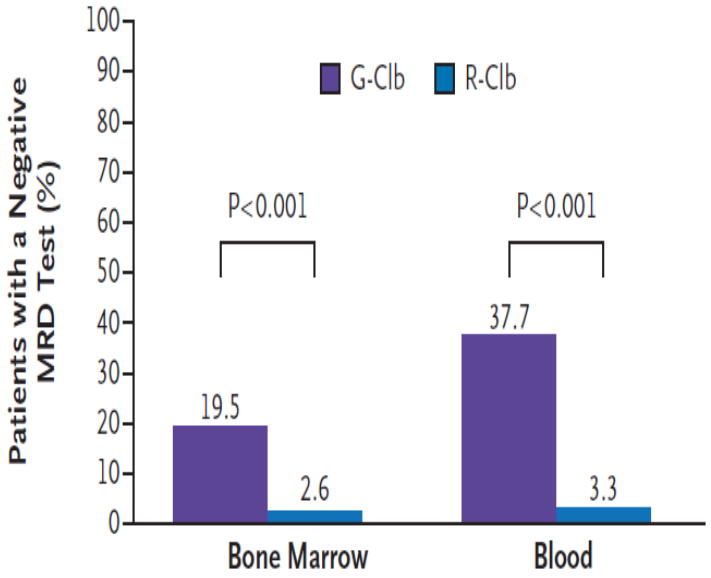
MRD-negativity ($<10^{-4}$) in PB and BM at response



Eichhorst et al., ASH 2014, Abstarct # 19

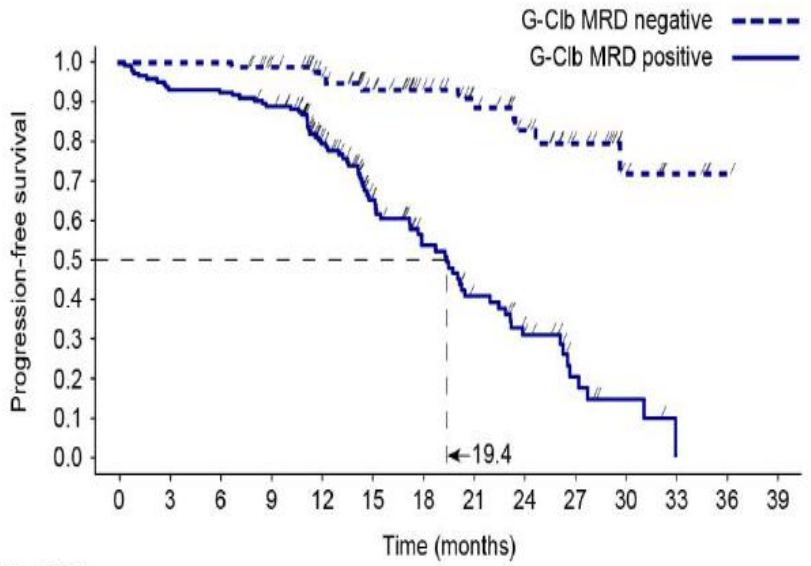
CLL11 - MRD at the end of treatment

CHL+GA101 vs **CHL+R**



No. of Patients	26/133	3/114	87/231	8/243

CHL+GA-101: MRD+ vs MRD-



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 et al NEJM 2014

Chlorambucil plus ofatumumab versus chlorambucil alone in previously untreated patients with CLL (COMPLEMENT 1)

447 patients, median age 69 years

Patients with previously untreated CLL

considered inappropriate for F- based therapy

- Active disease
- ≥ 18 years
- ECOG ≤ 2
- N = 447

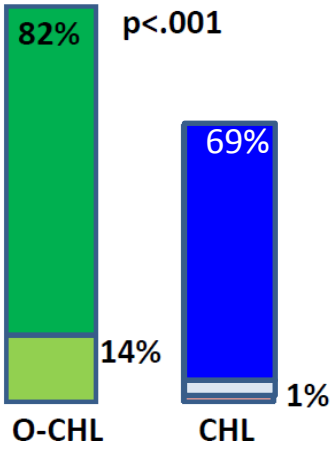
Ofatumumab
Cycle 1, Day 1 300 mg Day 8 1000 mg, cycle 2-12 Day 1 1000 mg q28d
+
Chlorambucil 10 mg/m²
Days 1-7 q28d

Chlorambucil
10 mg/m² Days 1-7 q28d

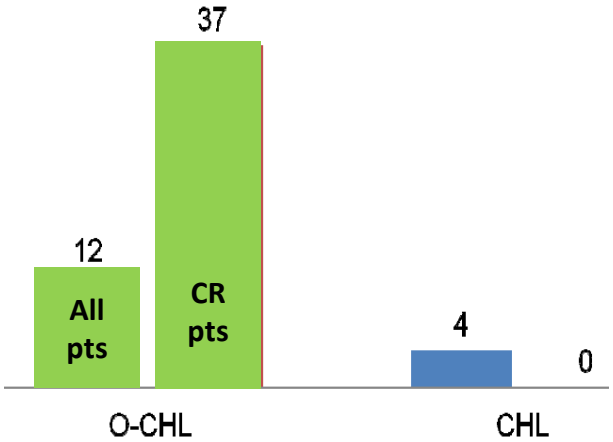
Characteristics of patients

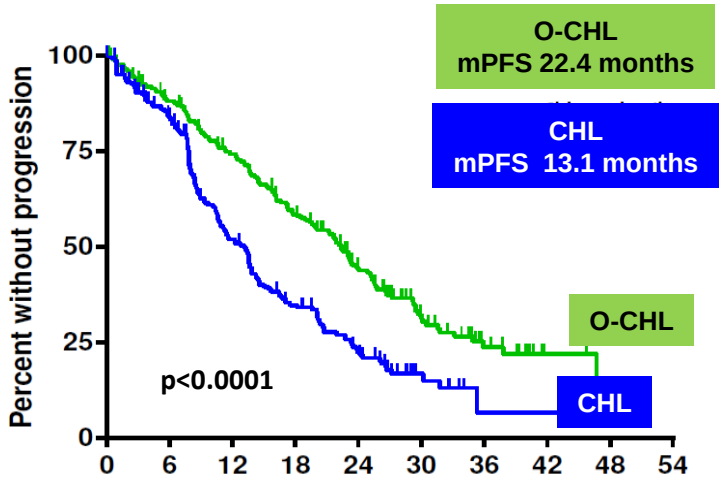
	O-CHL 226	O-CHL 221
Age, Years, median (range)	70 (36-91)	69 (35-92)
≥ 65, %	69	69
≥ 75, %	28	25
Male, %	62	64
ECOG - 0,1, %	91	91
Comorbidities, median (range)	3 (0-10)	3 (0-10)
≥2, %	70	73
CrCl mL/min, median (min-max)	69 (21-209)	72 (26-172)
<70 mL/min, %	51	45
≥65 yrs or ≥2 comorbidities or CrCl <70 ml/min, %	87	87
CIRS, median (range)	8 (4-19)	9 (4-21)

Response



MRD at the end of treatment





Hillmen et al., Lancet 2015

Clinical significance of posttreatment MRD analysis as determined by a method with sensitivity of at least 10^{-4}, after first-linecombination chemotherapy or chemoimmunotherapy

Study	Treatment	No. of patients with MRD testing, (% MRD negative)	MRD threshold, sample source, method	PFS	*P* value	Overall survival	*P* value
Bosch et al 2008[3]	FCM	18 (41%)	10^{-4}, FLC BM	MRD-positive CR < MRD-negative CR	.2	Not reported	NA
Lamanna et al 2009[43]	F→C→R	23 (52%)	Nested ASO *IGHV* PCR 10^{-5}	35 months vs NR	.007	Not reported	NA
Maloum et al 2009[44]	FC	21 (64%)	10^{-4}, FLC PB	DFS, median/HR not reported	<.001	No difference	NS
Bottcher et al 2012[10]	FC or FCR	290*†	10^{-2} and 10^{-4}, FLC PB	15, 41, and 69 months for $\geq 10^{-2}$, $\geq 10^{-4}$ to $<10^{-2}$, and $<10^{-4}$, respectively‡	<.001	Significantly inferior for $\geq 10^{-2}$ vs $<10^{-2}$	<.001
Fischer et al 2012[46]	BR	45 (58%)	10^{-2} and 10^{-4}, FLC PB	12 months, 32 months, and NR for $\geq 10^{-2}$, $\geq 10^{-4}$ to $<10^{-2}$, and $<10^{-4}$, respectively	<.001	23.2 months for $\geq 10^{-2}$ vs NR for $<10^{-2}$	Not reported
Abrisqueta et al 2013[47]	R+FCM	63 (56%)	10^{-4}, FLC BM	4 years; 86% vs 60%‡	.03	Not reported	Not reported
Strati et al 2014[48]	FCR	161 (43%)	10^{-4}, FLC BM	HR 0.1 (median NR)‡	.03	HR 0.6 (median NR)‡	.02
Goede et al 2014[15]	Obinutuzumab + Clb	133 (20%) in BM, 231 (38%) in PB	10^{-4}, FLC PB/BM	19.4 months vs NR†‡	<.001	Not reported	NA
Kwok et al 2014[45]	Predominantly F-based combinations	57 first-line (42%)	10^{-4}, FLC BM	5 years; 81% vs 16%‡	<.001	10 years; 53% vs 24%‡	<.001

Thompson and Wierda, Blood 2016

Cure of CLL

Some evidence that a little proportion of patients (20-28%) with a very favorable clinical and genetic profile is probably cured with FCR:

- **≤65 years, fit**
- **IGVH mutated**
- **favorable FISH profile**

In this era the treatment paradigm is shifting from one of potential cure at high risk to one of long-term disease control with new chemo-free regimens.

Is the “cure” of CLL a still a target of treatment?