CLL:

quale ruolo per la chemioterapia oggi?

Giovanni Pizzolo


Forum
in Ematologia:
open questions
TRANI
13-14 marzo 2014
Palazzo San Giorgio

2014

SINDROMI LINFOPROLIFERATIVE CRONICHE

PERCORSI DIAGNOSTICI E TERAPEUTICI

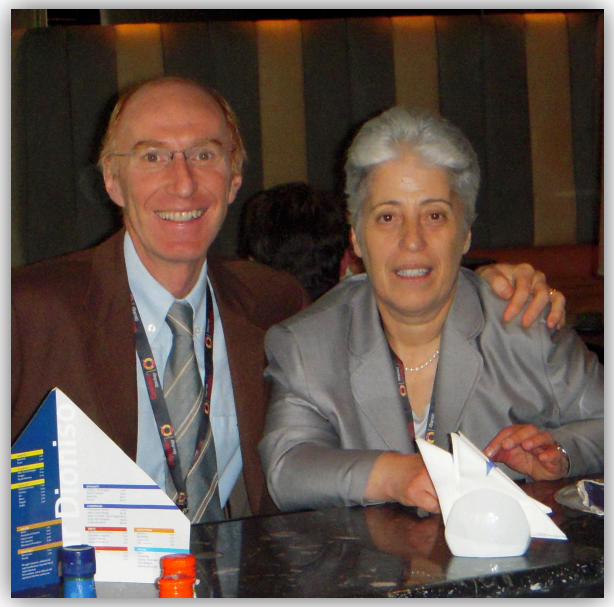
Direttore del Corso:
Prof. Vincenzo Liso

30/31 OTTOBRE 2008

BARI
VILLA ROMANAZZI CARDUCCI

2008


2008
X CONGRESSO NAZIONALE SIES
SOCIETÀ ITALIANA DI EMATOLOGIA SPERIMENTALE
SIES 2008
PROGRAMMA PRELIMINARE
24-26 settembre 2008
Bari
HOTEL SHERATON NICOLAUS
Presidenti
Antonio Cuneo
Vincenzo Liso




E.C.M.
L'evento (295182) è stato accreditato secondo il Programma di Educazione Continua in Medicina per 30 Medici Specialisti in Ematologia, Medicina Interna ed Oncologia e ha ottenuto n. 16 crediti formativi
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Con il contributo educazionale di
Roche
Cattedra di Ematologia
Università degli Studi di Bari
NOVITÀ NELLA DIAGNOSI E NELLA TERAPIA DELLE MALATTIE LINFOPROLIFERATIVE
Bari, 21-22 Novembre 2007
Aula Ematologia
Padiglione Morgagni
Azienda Ospedaliera Policlinico
8
2007
1


Giovanni Pizzolo
Diagnostica differenziale dei disordini linfoproliferativi cronici leucemici


2006
Cattedra di Ematologia
Università degli Studi di Bari
Attualità in Ematologia
Linfomi non Hodgkin:
dalla Biologia alla Terapia
Programma
BARI, 9-11 Marzo 2006
Aula Ematologia, Padiglione Morgagni
Azienda Ospedaliera Policlinico


B. ROTOLI
V. LISO
R. FOA'

CLL

armamentario terapeutico disponibile (±)

Established Drugs
- Chlorambucil
- Cyclophosphamide
- Fludarabine
- Glucocorticoids
- Bendamustine
- Others (Cladribine, Pentostatin)

"Intelligent" new drugs
- Lenalidomide
- BH3-Agonists (e.g. ABT-263)
- BCL2-Inh (e.g. ABT-199)
- Signaling Inh (e.g. PI3K, Syk, Btk)
- CXCR4 Inhibitors
- Hsp90 Antagonists

Antibodies
- (Alemtuzumab)
- Obinutuzumab (GA101)
- Ofatumumab
- Rituximab
- BITE Abs
- others

Immune Therapies
- Immunomodulatory agents
- Allo HSC transplantation
- Leukemia Ag Vaccines
- Gene Therapy
- CAR T cell therapy

CLL

evoluzione dei trattamenti

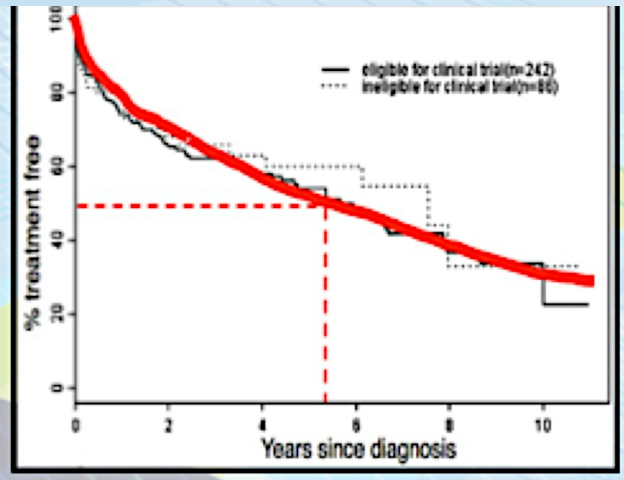
olution of treatment options in CLL

70s | 1980s | 1990s | 2000s | 2012-13

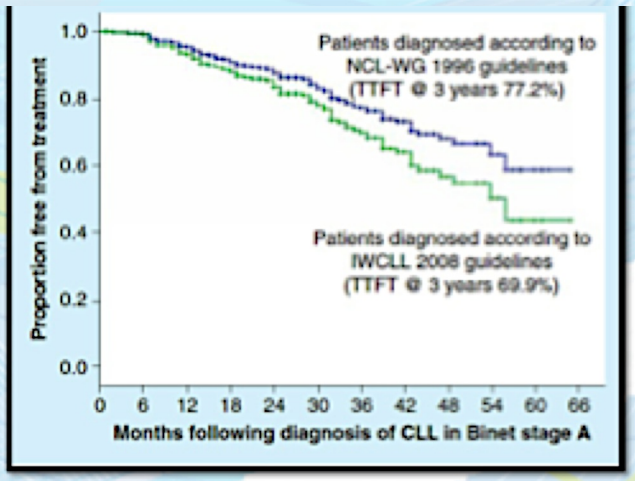
Wait and watch or:

CLL

la maggior parte dei paz. prima o poi necessita di terapia



Thurmes et al, 2008



Molica et al, Expert Rev Hematol, 2014

CLL
la chemioterapia

Established Drugs
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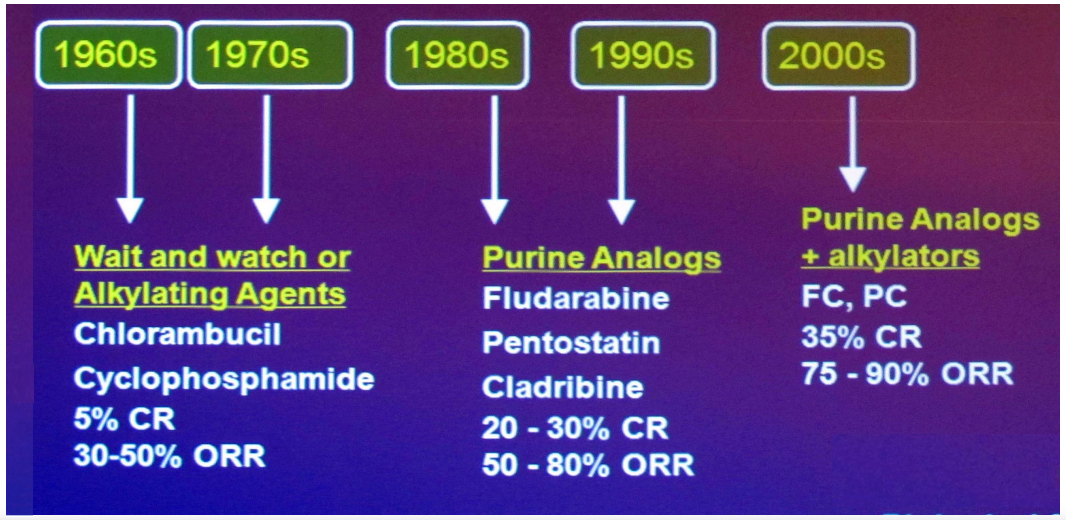
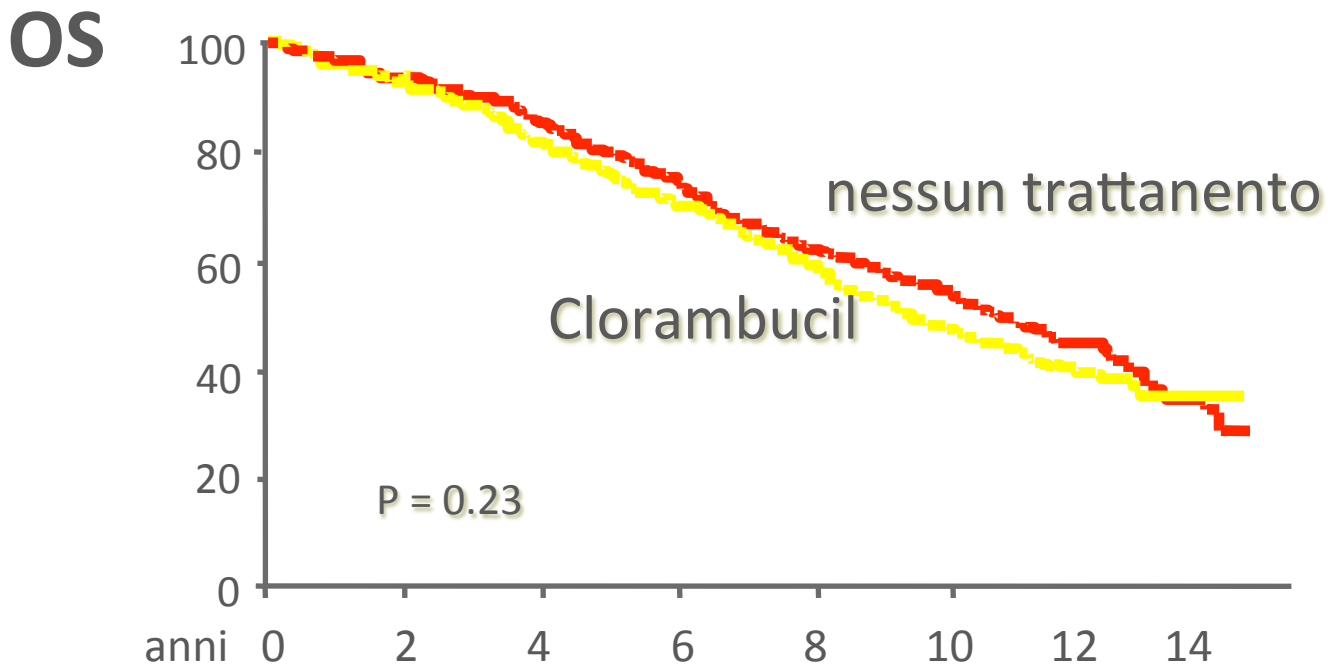


CLL: terapia di prima linea

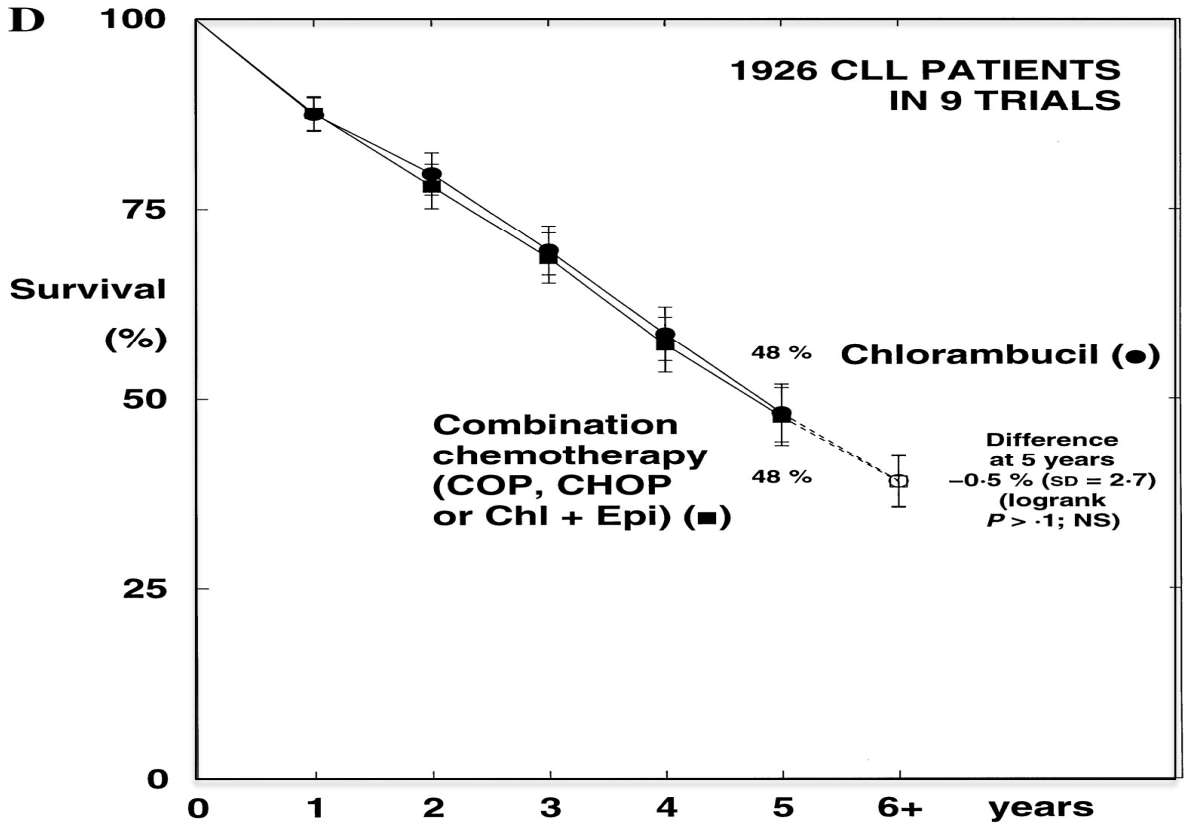
Clorambucil vs nessun trattamento



ICSG on CLL; Blood 1998

CLL: terapia di prima linea

Clorambucil vs poli-CHT

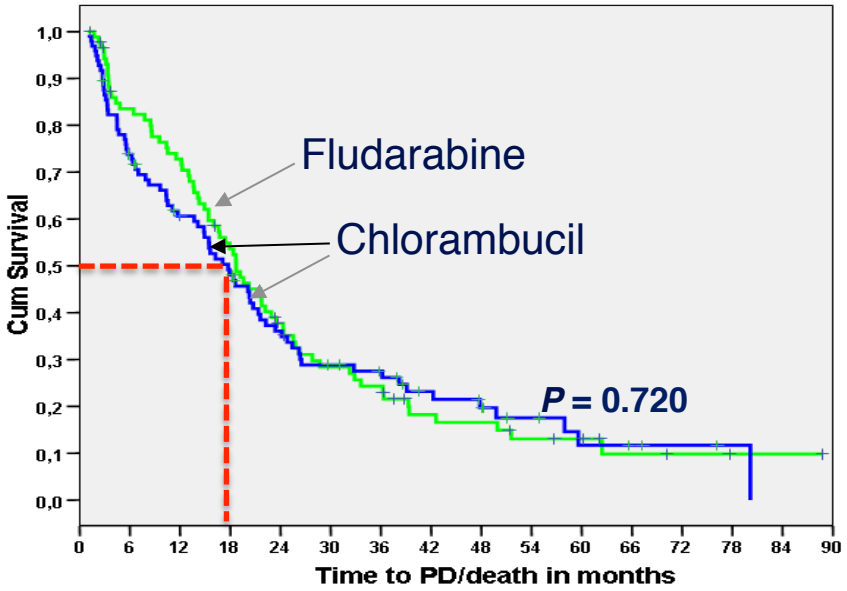


CLL Trialists' Collaborative Group, JNCI 1999

CLL: terapia di prima linea

Clorambucil vs Fludarabina

PFS

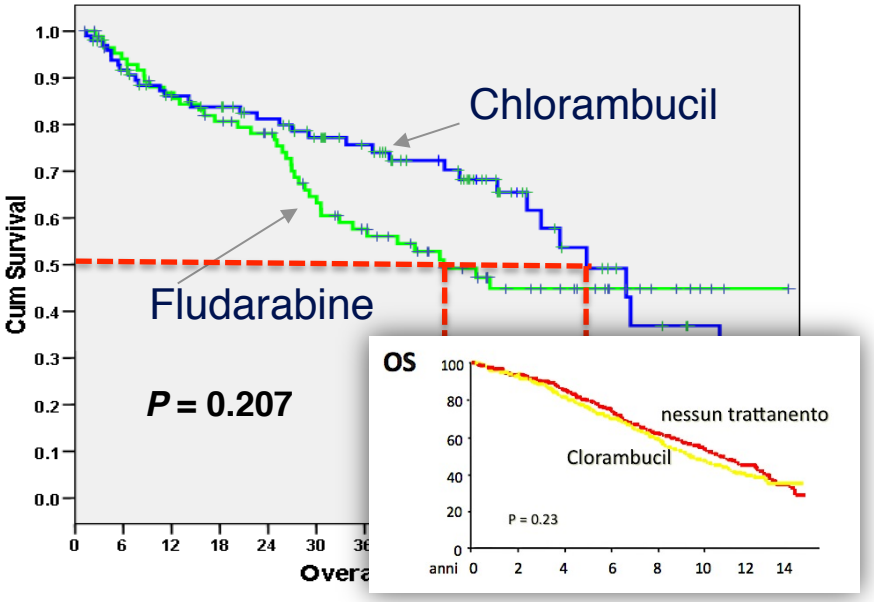


Fludarabine 18.7 months

vs.

Chlorambucil 17.8 Months

OS



Fludarabine 45.8 Months

vs.

Chlorambucil 63.6 Months

Eichhorst BF, et al. Blood 2009

CLL

ruolo dei "vecchi" farmaci

Impatto complessivo modesto

- **risposte ematologiche:** *variabili*
- **risposte complete:** *tra 5 e < 35%*
- **PFS:** *tra 5 e < 36 mesi*
- **OS:** *nessun reale vantaggio*

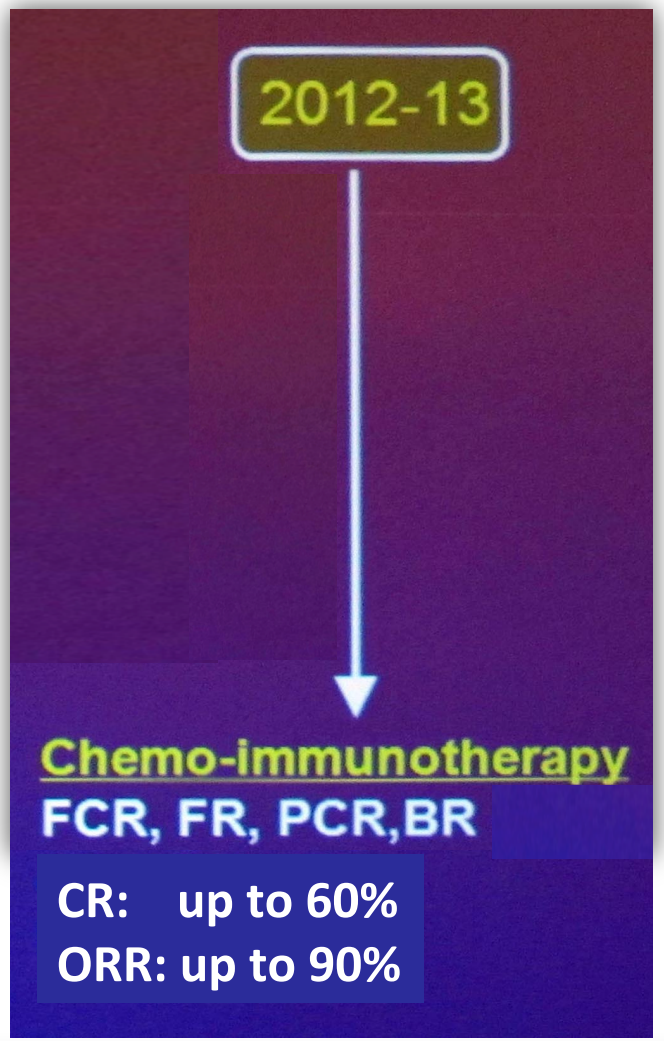
CLL

ChT + mAb

Established Drugs
- Chlorambucil
- Cyclophosphamide
- Fludarabine
- Glucocorticoids
- Bendamustine
- Others (Cladribine, Pentostatin)

+

Antibodies
- (Alemtuzumab)
- **Rituximab**
- **Ofatumumab**
- **Obinutuzumab** (GA101)
- BITE Abs
- others

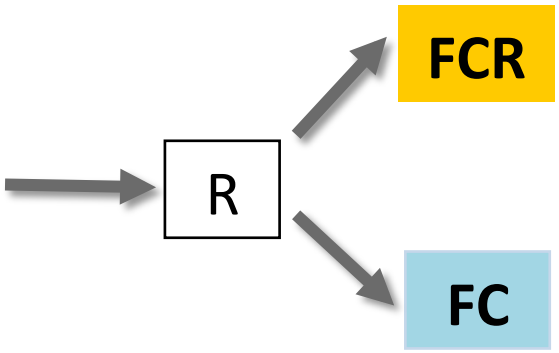


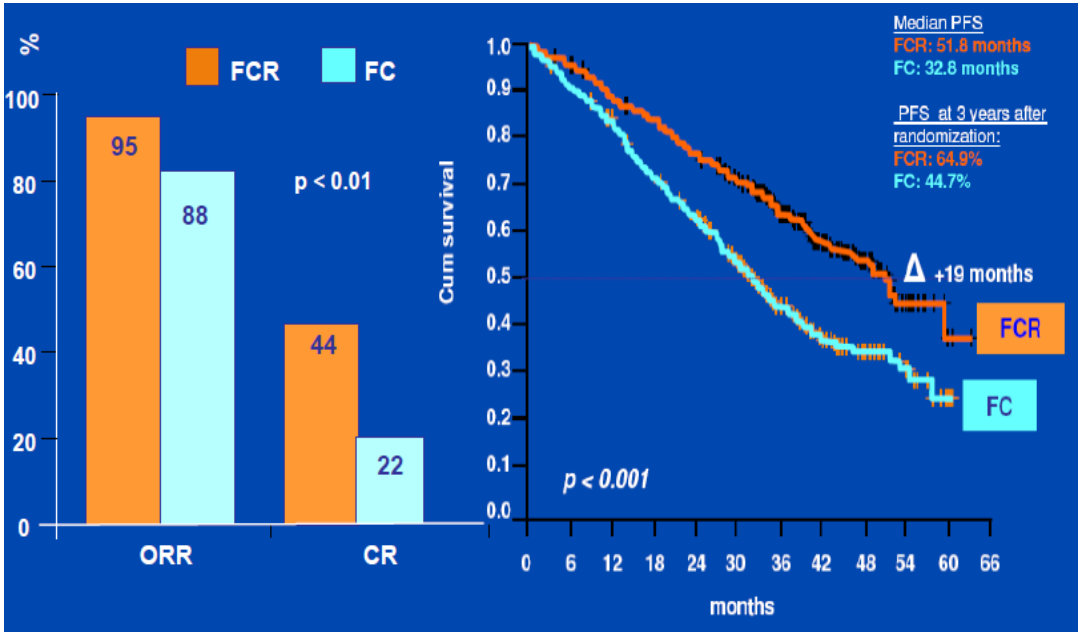
...e arrivò FCR

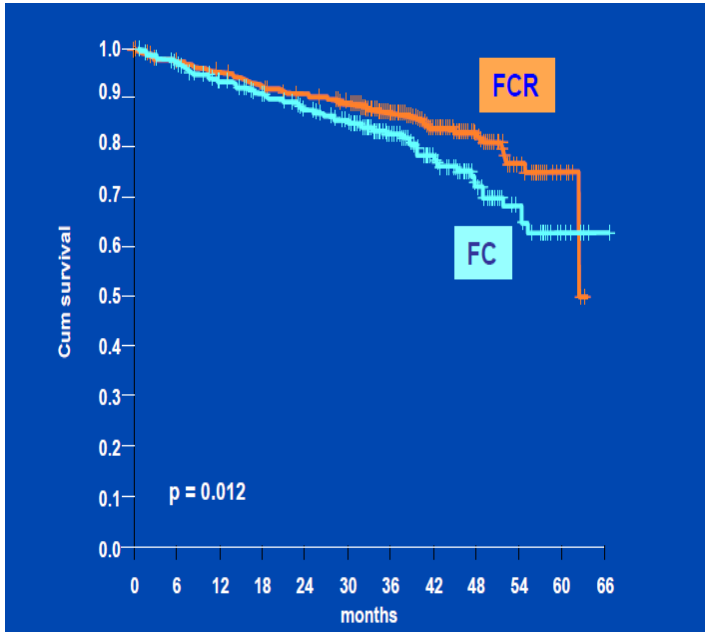
FCR vs FC (studio CLL8)

817 pts

- untreated, active CLL
- good physical fitness
- CIRS ≤ 6
- CrCL ≥ 70 mL/min)





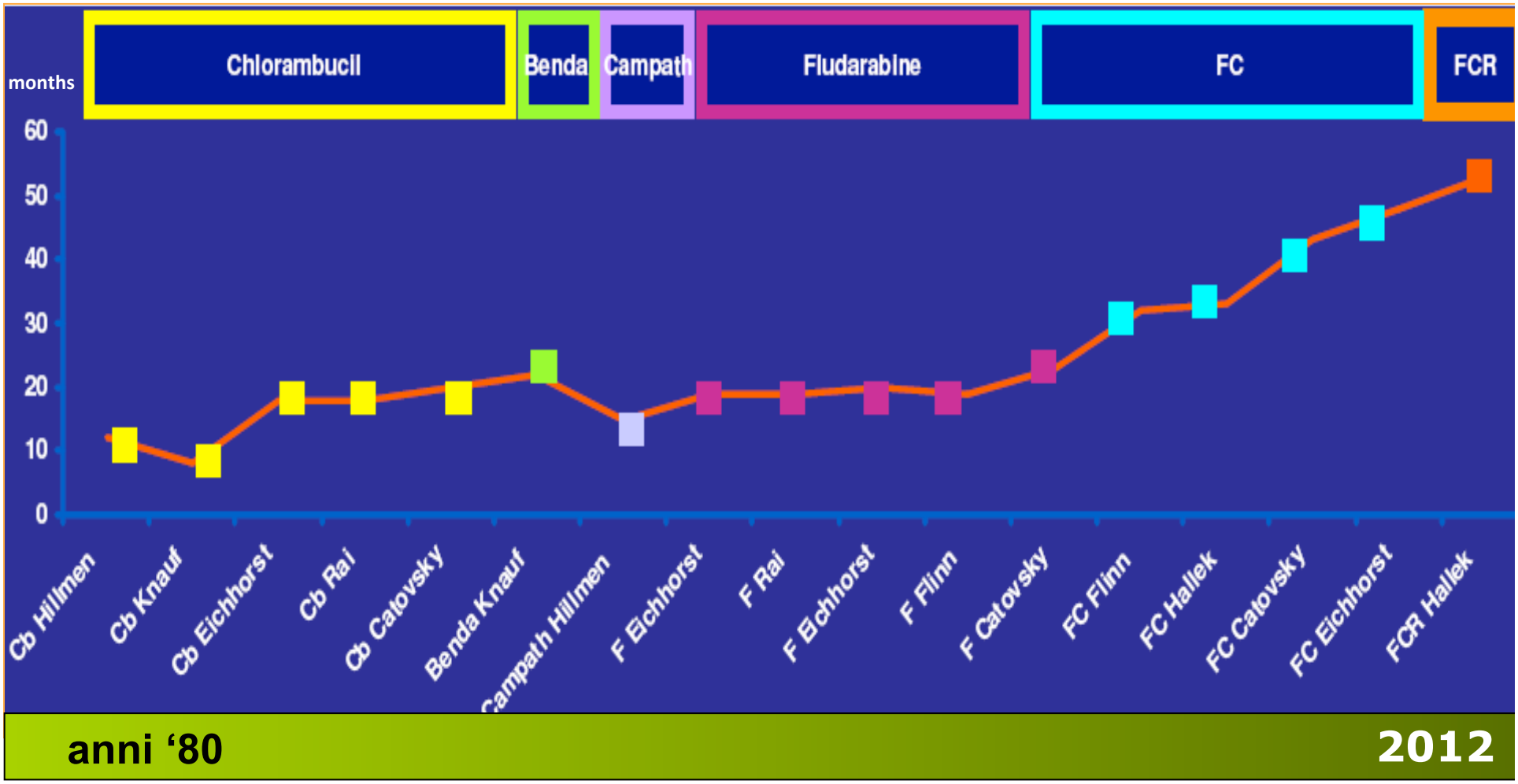


Hallek M, et al. Lancet. 2010

OR PFS OS

CLL

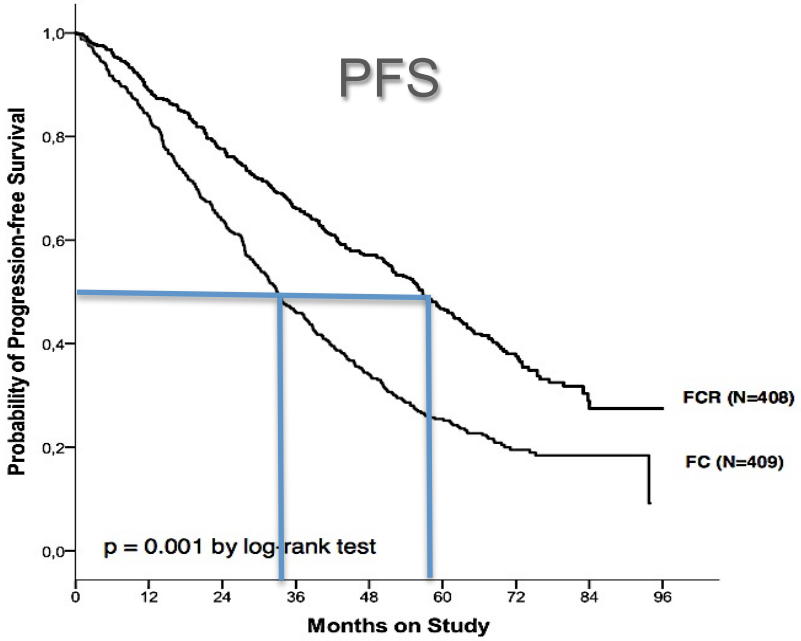
miglioramento dei risultati (PFS) negli anni



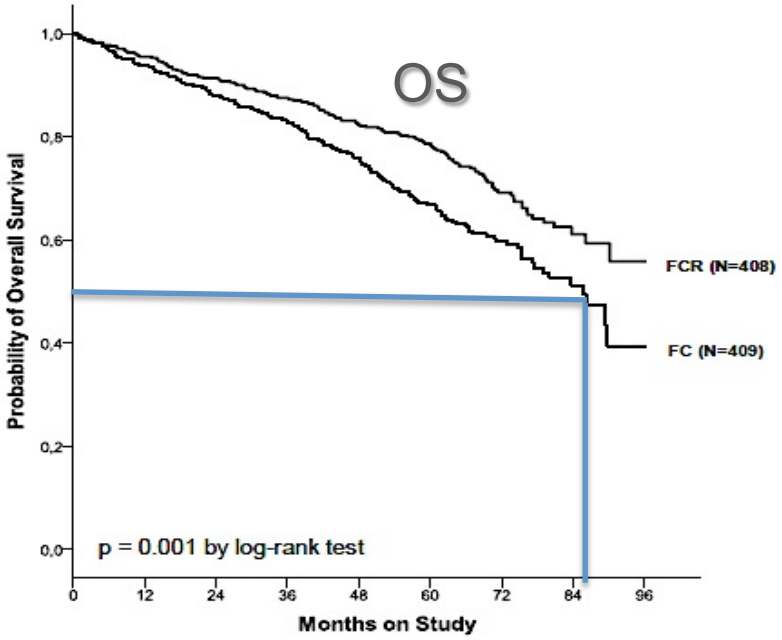
da Francesca Mauro

CLL8 study

FCR vs FC: 2015 update



Number at risk	0	12	24	36	48	60	72	84	96
FCR	408	358	310	261	222	178	76	18	1
FC	409	232	236	167	119	86	39	13	0



Number at risk	0	12	24	36	48	60	72	84	96
FCR	408	384	363	342	318	290	134	41	2
FC	409	360	232	297	262	220	100	33	1

Fischer et al., Blood, October 2015

CLL

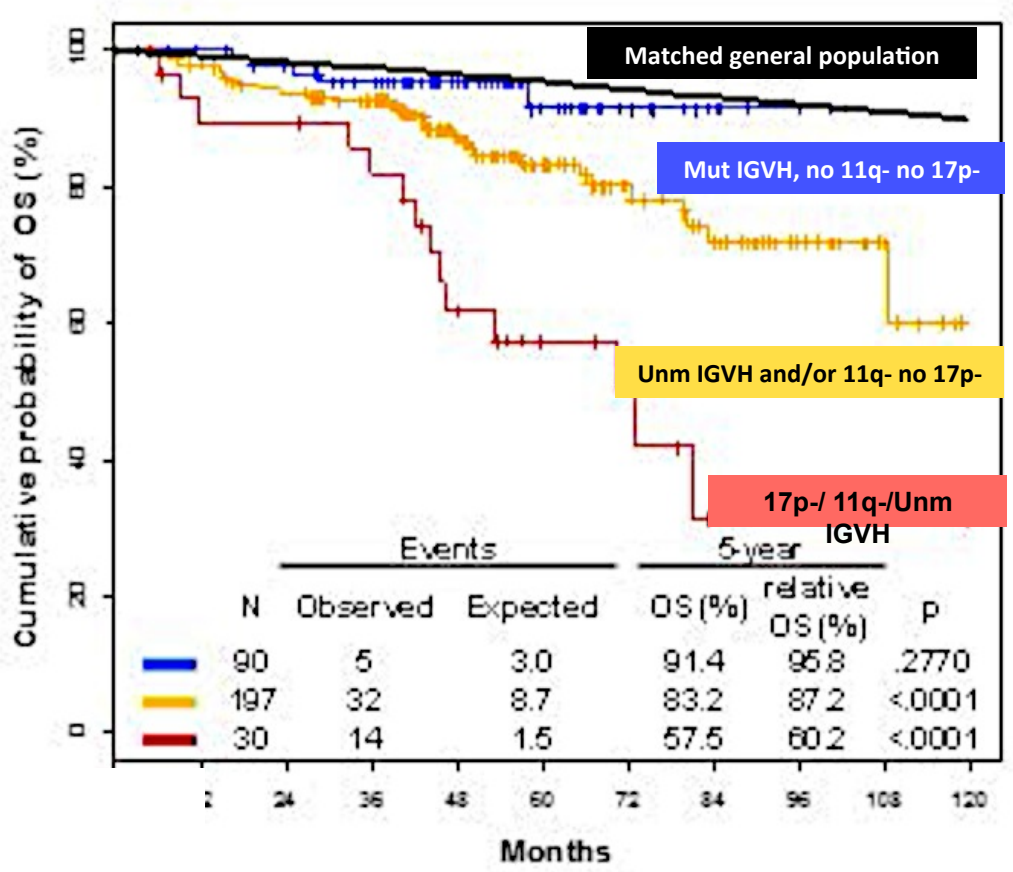
FCR il gold standard

FCR per tutti?

CLL

FCR is NOT the "right" treatment for the majority of pts.

multicenter retrospective analysis of 404 pts. receiving frontline FCR

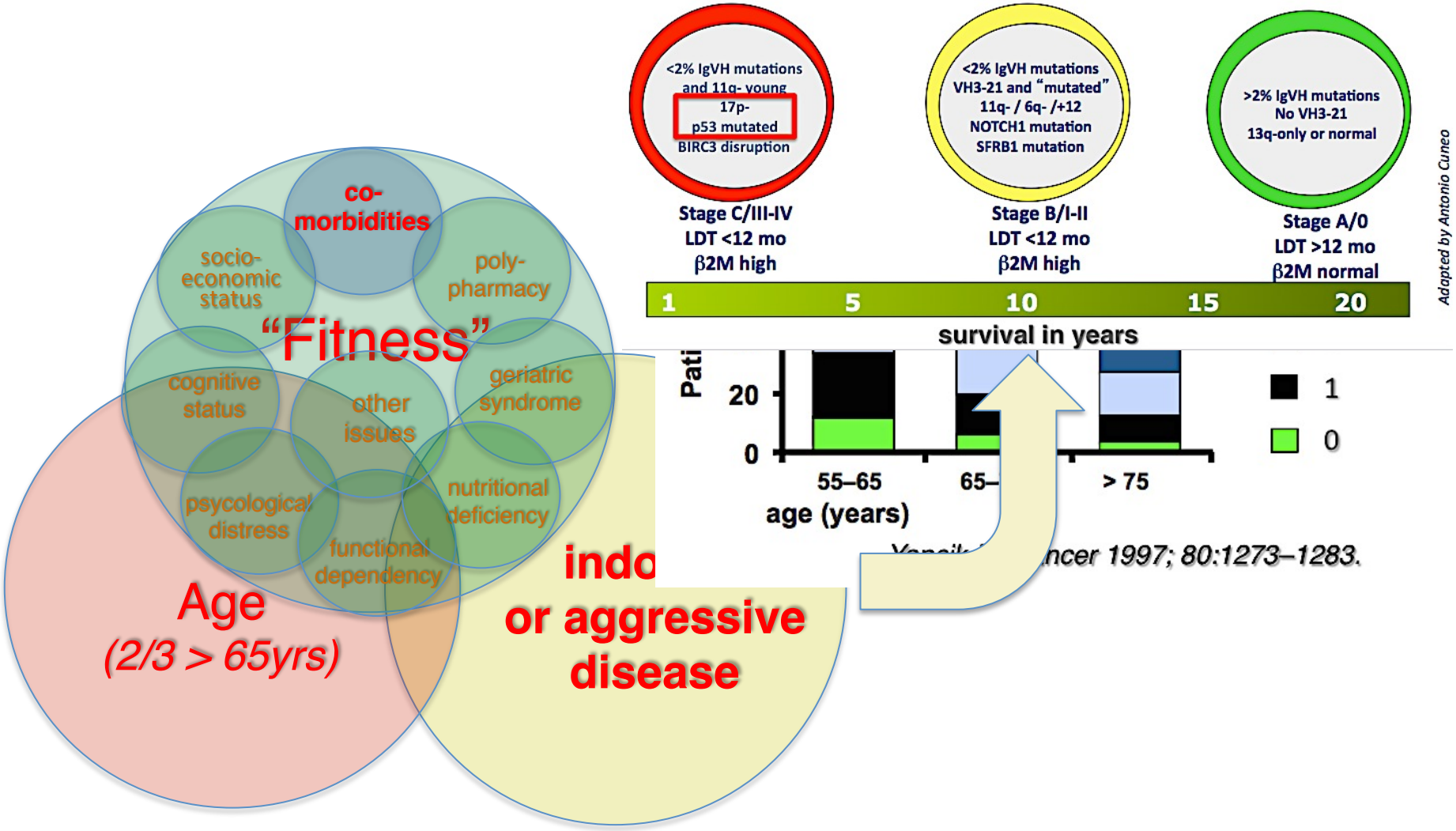


- unfavourable efficacy/toxicity ratio ***(NO for UNFIT & FRAIL pts.)***
- best results if mut IGHV, no 11q- no 17p-/p53mut ***(GOLD STANDARD)***
- no efficacy in 17p-/p53mut pts.
- in daily practice applied in **<30** of pts.

Rossi et al., Blood 2015

CLL

Treatment: patient vs disease



CLL

FCR nei pazienti anziani (>60? >65? > 70 anni?)

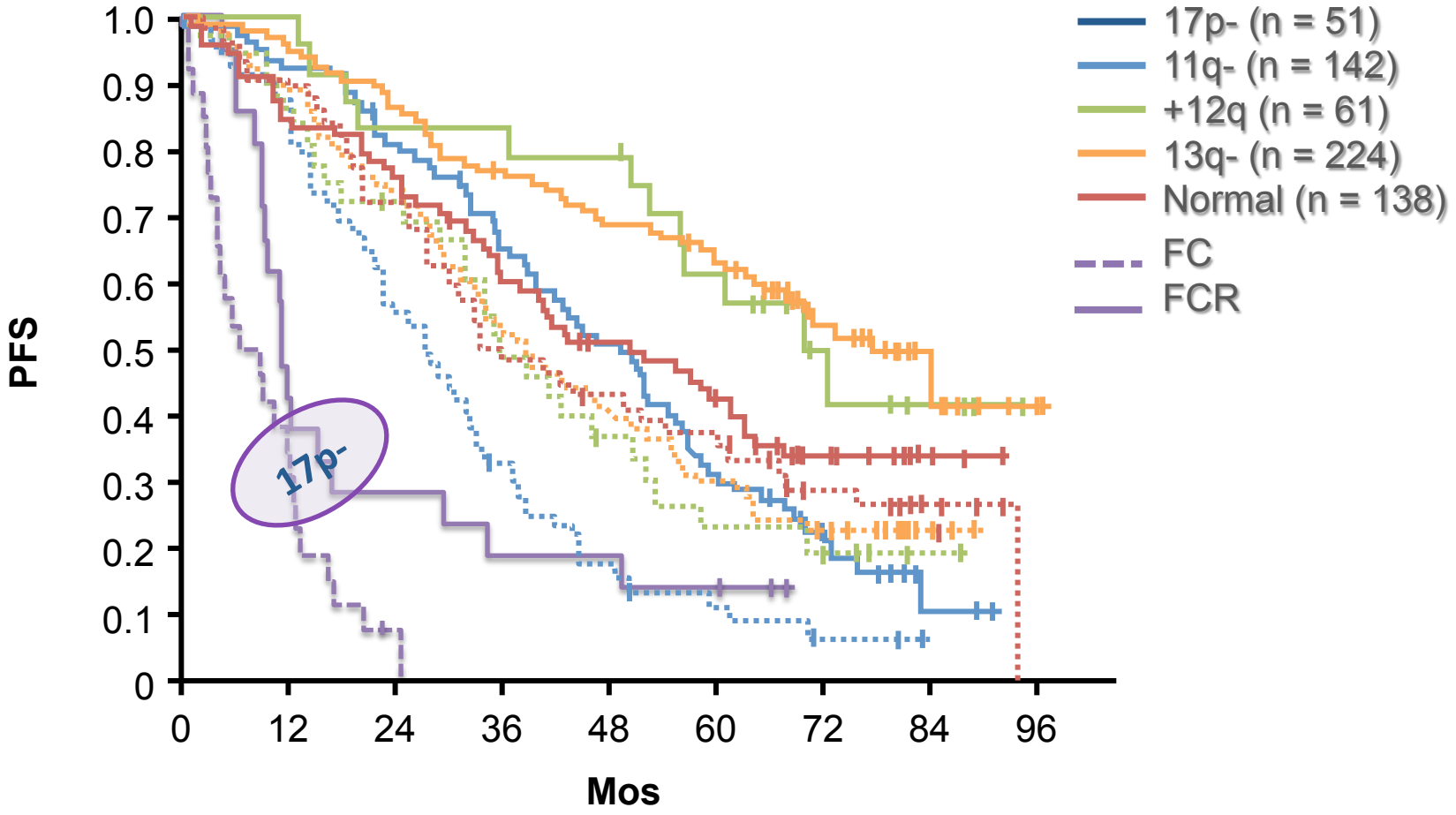
NON ben tollerato e meno efficace rispetto ai pazienti più giovani:

- *75% dei pazienti hanno tossicità ematologica di grado 3-4*
- *meno del 50% dei pazienti sono in grado di completare 6 cicli a casua della citopenia*
- *più bassa percentuale di risposte complete*

Keating et al, JCO 2005; Ferrajoli et al., Leuk & Lymph.2005; Tam et al., Blood 2008

CLL8

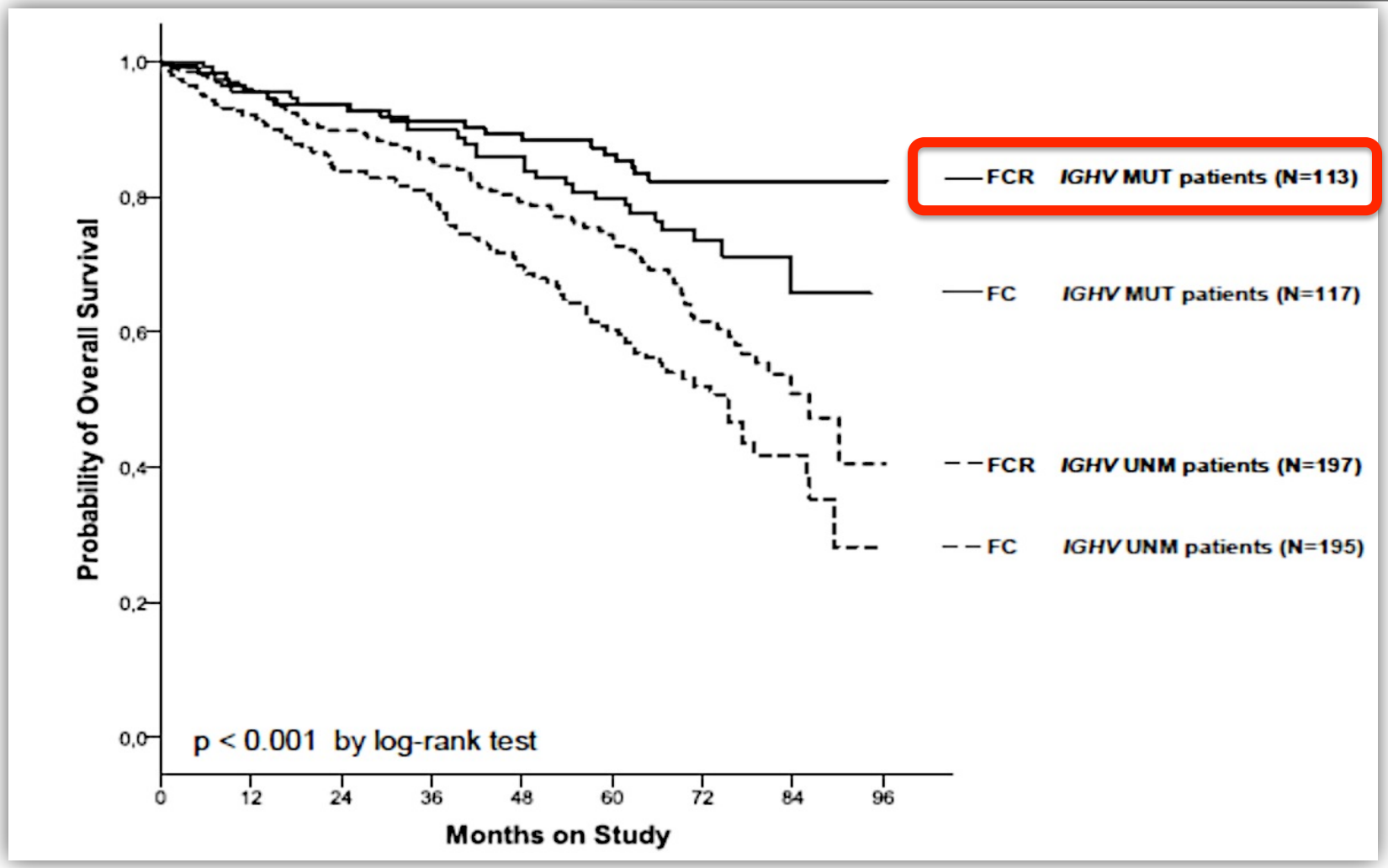
PFS in genomic subroups



Stilgenbauer S, et al. Blood. 2014

CLL8

OS by treatment arms and IGHV



Fischer et al., Blood 2015

CLL

MDACC: 300 pazienti trattati con FCR

(1999-2003, mediana post trattamento 12.8 anni)

FCR ottiene maggiori % di CR e MRD-neg. nei pazienti IGHV-mutati

• Median age	57 (17-86)
• ≥ 65	24 %
• ECOG PS < 2	97 %
• RAI stage III-IV	36 %
• Unmutated IgHV	59 %
• del(17p)	2%

All patients	**CR: 72%**	**MRD-neg: 43%**
• Mutated IgHV	83 %	51 %
• Unmutated IgHV	72 %	33 %
• del(17p)	20%	0%
• no del(17p)	75%	43%
• 1-3 cycles	30%	10%
• 4-5 cycles	64%	39%
• 6 cycles	81%	47%

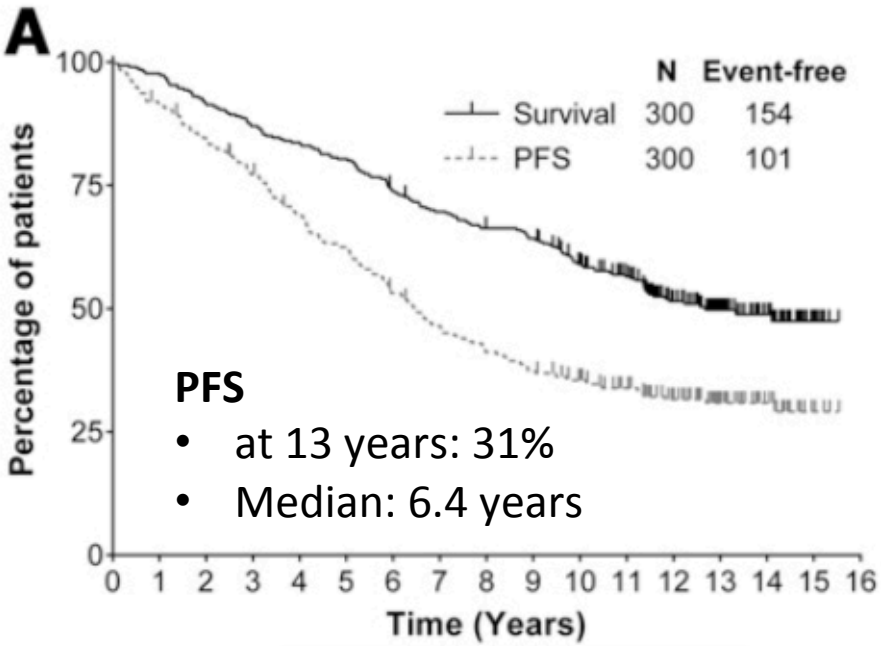
Thompson et al Blood 2016

CLL

MDACC: 300 pazienti trattati con FCR

(1999-2003, mediana post trattamento 12.8 anni)

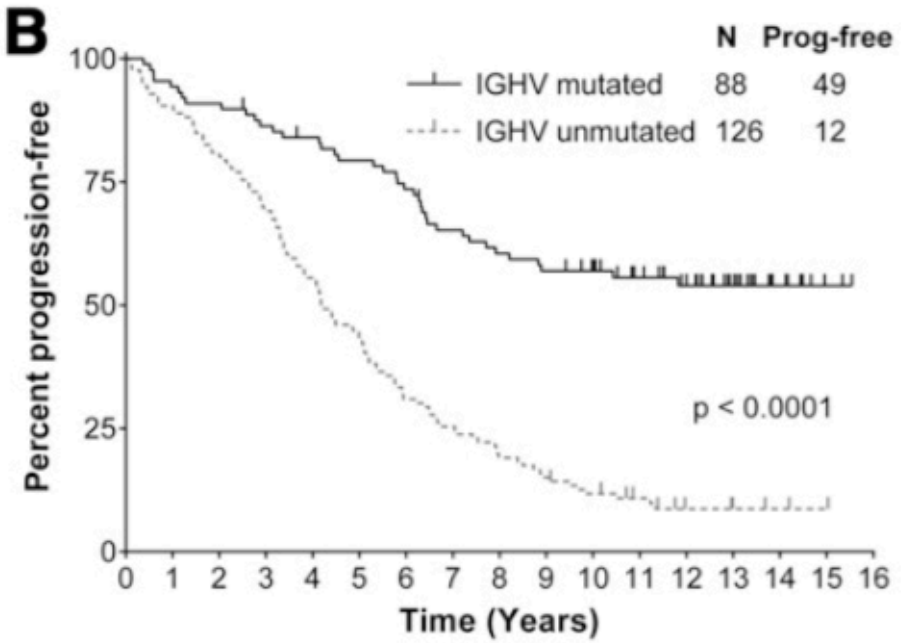
FCR ottiene lunghe OS e PFS nei pazienti IGHV-mutati



PFS

- at 13 years: 31%
- Median: 6.4 years

Median OS: 12.7 years



Median PFS (years):

- Unmutated IgHV: 4.2
- Mutated IgHV: NR (plateau)

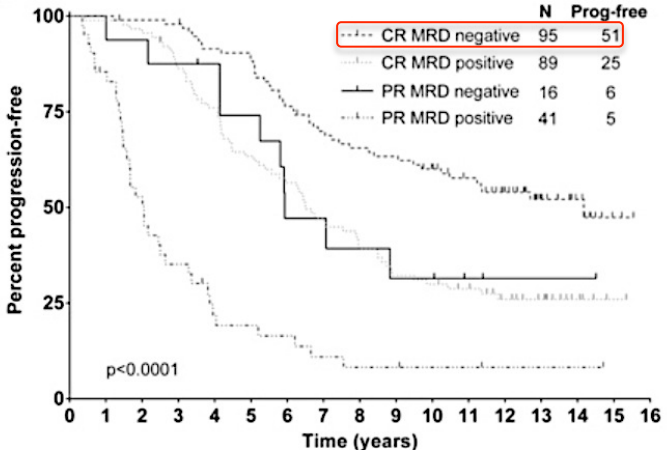
Thompson et al Blood 2016

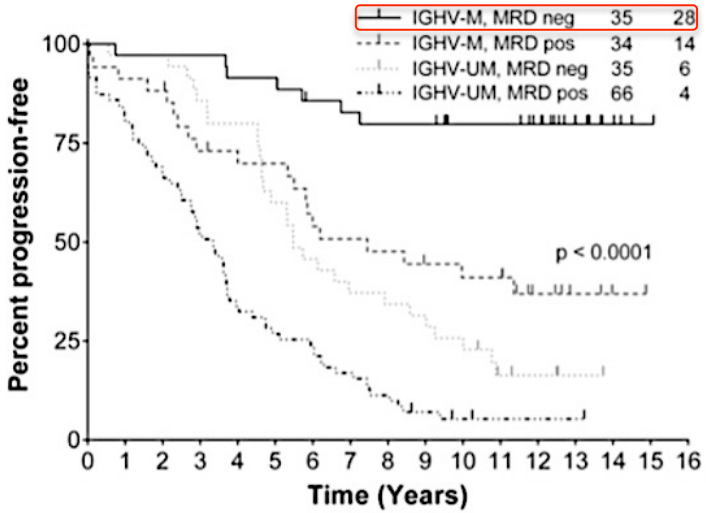
CLL

MDACC: 300 pazienti trattati con FCR

(1999-2003, mediana post trattamento 12.8 anni)

MRD-neg. si associa a PF prolungata nei pazienti IGHV-mutati



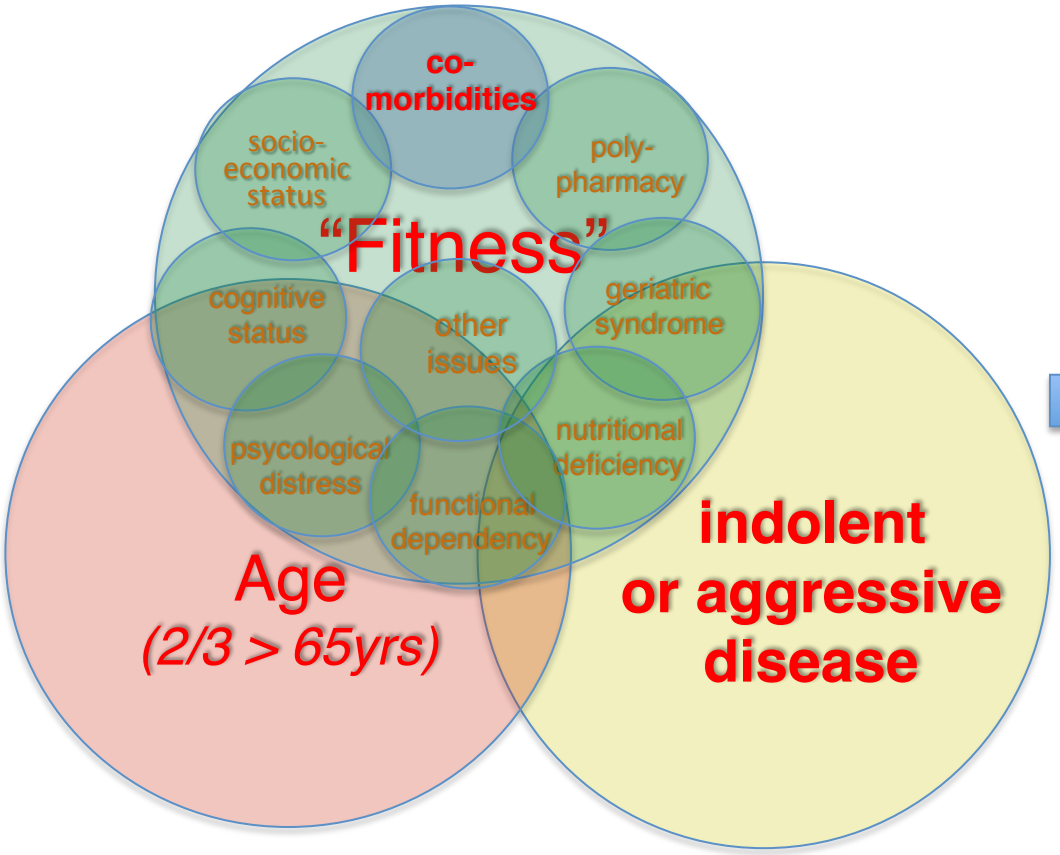


"The high rate of very long-term PFS in patients with IGHV-M after FCR argues for the continued use of chemoimmunotherapy in this patient subgroup outside clinical trials; alternative strategies may be preferred in patients with IGHV-UM, to limit long-term toxicity".

Thompson et al Blood 2016

CLL

patient & disease ⟹ possible options

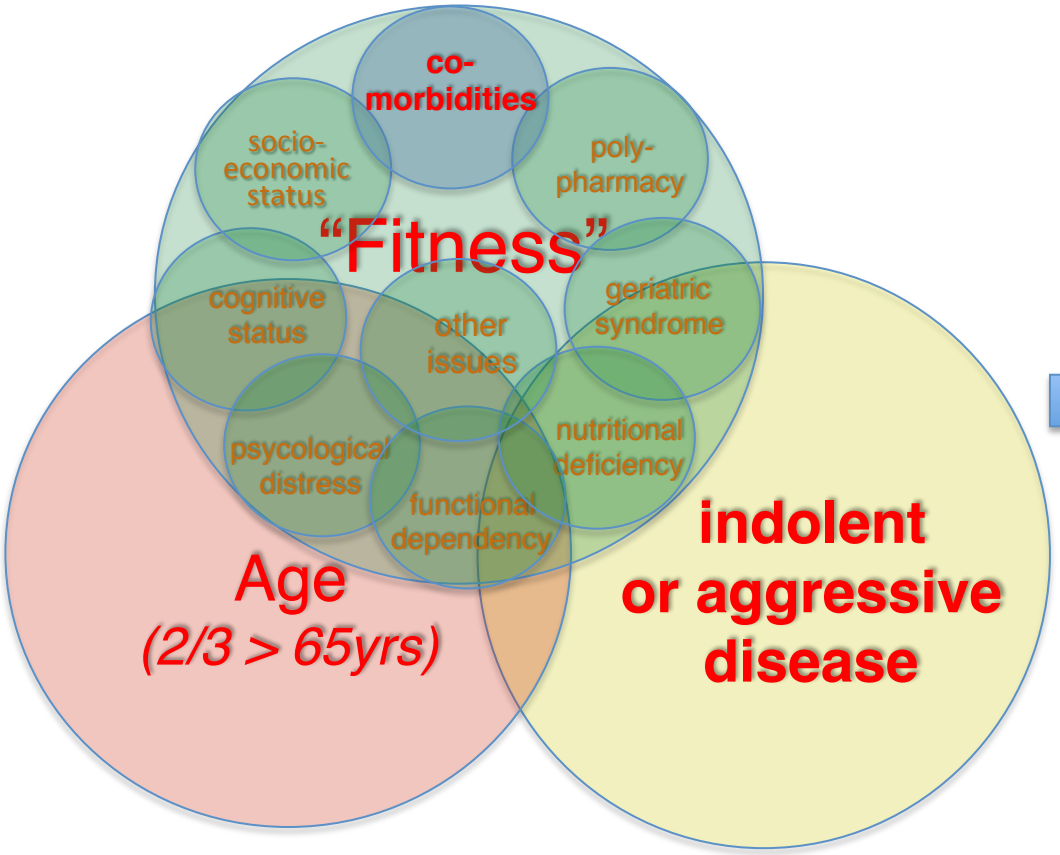


- "soft" treatment
- "aggressive" treatment

- ChT only
  - Chlorambucil
  - Benda
  - Steroids
  - Purine analogs
  - others
- FCR
- "soft" ChT + R
- "soft" ChT + new α-CD20
- New biologicals & strategies
  (Ibrutinib, Idelalisib, Venetoclax, others)

CLL

patient & disease ⟹ possible options



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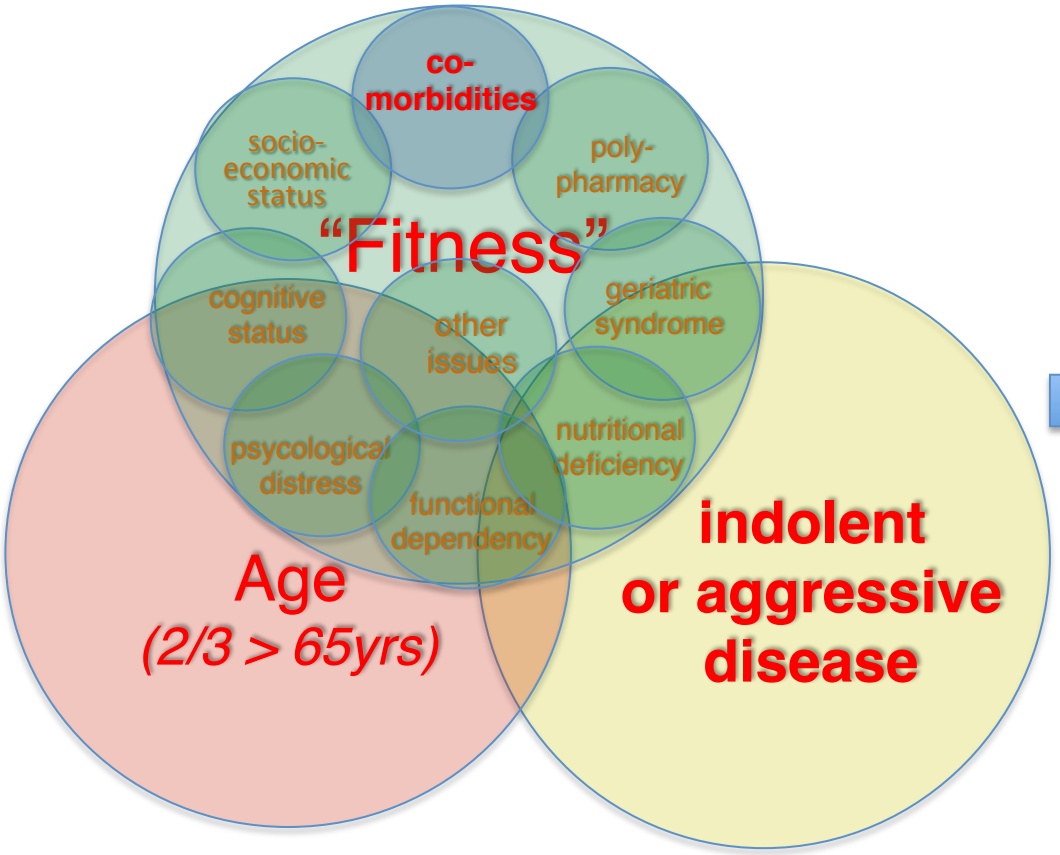

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CLL

principali dati da studi con R-Clorambucil

Study	Phase	N	Patient population	Treatment	Key results
CLL208[1]	II	100	1L, unable to tolerate fludarabine	R-Clb	ORR: 84%, CR: 10%, G3/4 neutropenia: 41%
ML21445[2]	II	ITT: 85	1L, ≥ 65 years or ≥ 60 years and ineligible for fludarabine	R-Clb	ORR: 82,4%, CR: 18,9%, G3/4 neutropenia: 19,6%

1. Hillmen P, et al J Clin Oncol. 2014; 2. Foà R, et al. Am J Hematol. 2014

CLL

principali dati da studi con R-Bendamustina

Study or author	Phase	N	Patient population	Treatment	Key results
Fischer *et al.* 2011[1]	II	78	R/R	R-Benda	ORR: 59%, CR: 9%, G3/4 neutropenia: 23% MRD in PB: 7.4%* MRD-neg. in BM 7.7%
Fischer *et al.* 2012[2]	II	117	1L	R-Benda	ORR: 88%, CR: 23%, G3/4 neutropenia: 20% MRD-neg in PB: 57.8%‡ MRD-neg. in BM 29.2%§
MaBLe[3]	IIIb	358	1L or 2L and relapsed after ≥ 12 mo, ineligible for fludarabine	R-Benda Vs R-Clb	Interim results for 1L patients R-Clb ORR: 81%, CR: 10%, G3/4 neutropenia: 34% **R**-Benda ORR: 88%, CR: 34%, G3/4 neutropenia: 32%

2L = second-line. 2 of 27 evaluable patients;† 1 of 13 Evaluable patients; ‡ 26 of 45 patients; § 7 of 24 patients.

1.Fischer K, *et al. J Clin Oncol* 2011;
2. Fischer K, *et al. J Clin Oncol* 2012;
3. Leblond V, *et al*. ASH 2012; Abstract 2744.

CLL10

FCR vs BR (treatment naive pts.)

International, open-label, randomised, phase 3: primary endpoint: PFS

	FCR	B-R	P
Patients	282	279	
Age (years) > 70 years	62 (55-67) 10%	61 (54-69) 18%	NS
RAI stage: 0-2 3-4	 55% 45%	 56% 44%	NS
ECOG PS: 0-1 2	 98% 2%	 >99% <1%	NS
del(11q) 12q+ del(13q)	24% 12% 55%	23% 11% 53%	NS
Unmutated IgHv	55%	68%	0.003

Eichhorst et al. Lancet Oncol 2016

CLL10

FCR vs BR (treatment naive pts.)

	FCR (%)	BR (%)	P
ORR	95	96	NS
CR	40	31	**0.034**
age ≤ 65 years	41	30	**0.022**
age > 65 years	36	32	NS
del(11q)	38	19	**0.016**
del(13q)	35	34	NS
IgHV mutated	39	28	NS
IgHV unmutated	39	33	NS

Eichhorst et al. Lancet Oncol 2016

CLL10

FCR vs BR (treatment naive pts.)

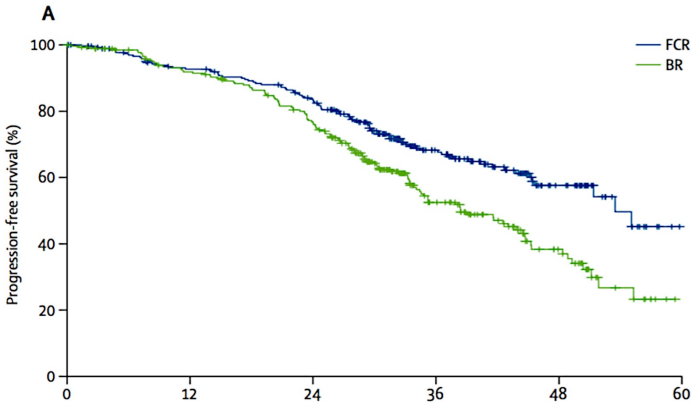
	FCR	BR	p
Evaluable patients	274	273	
ORR	95%	96%	NS
CR	40%	31%	**0.034**
MRD PB (355 patients)	74%	63%	**0.024**
MRD M (227)	58%	32%	**< 0.001**
MRD PB at 12 months	58%	26%	**< 0.001**
MRD PB at 18 months	54%	25%	**0.006**

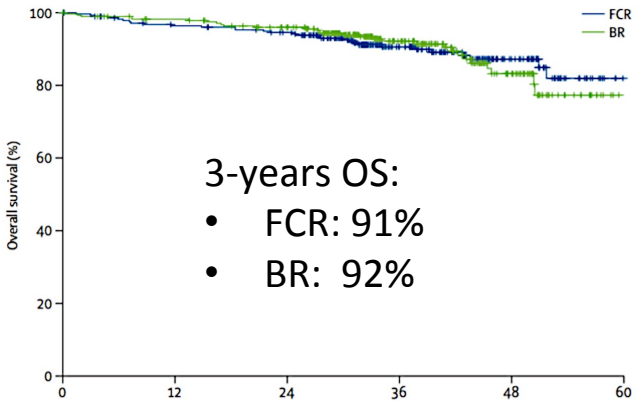
Eichhorst et al. Lancet Oncol 2016

CLL10

FCR vs BR (treatment naive pts.)

Median follow up: 37.1 months	Median PFS (months)		
	FCR	**BR**	**P**
All patients	55	42	
≤ 65 years	54	38.5	**0.0004**
> 65 years	NR	48.5	NS
unmutated IgHV	42.7	34	**0.017**
mutated IgHV	NR	55	NS
del (11q)	38	25	**0.0002**





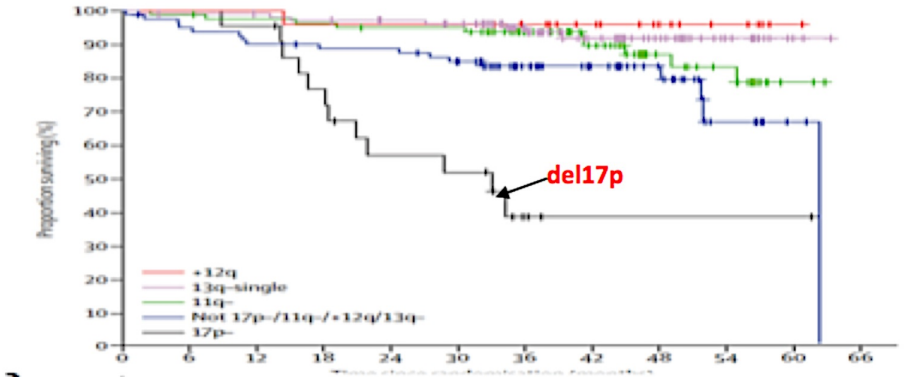
3-years OS:

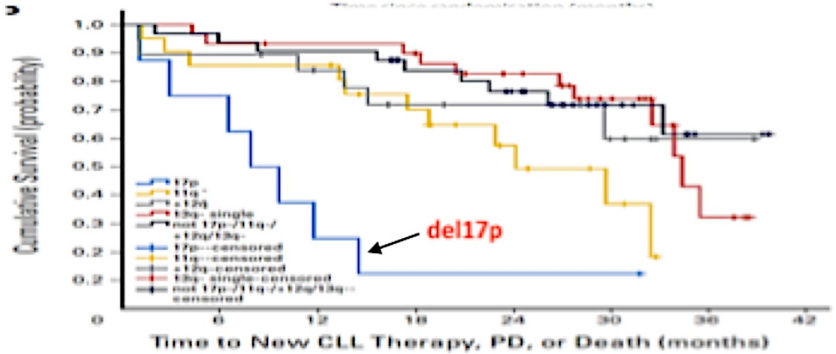
- FCR: 91%
- BR: 92%

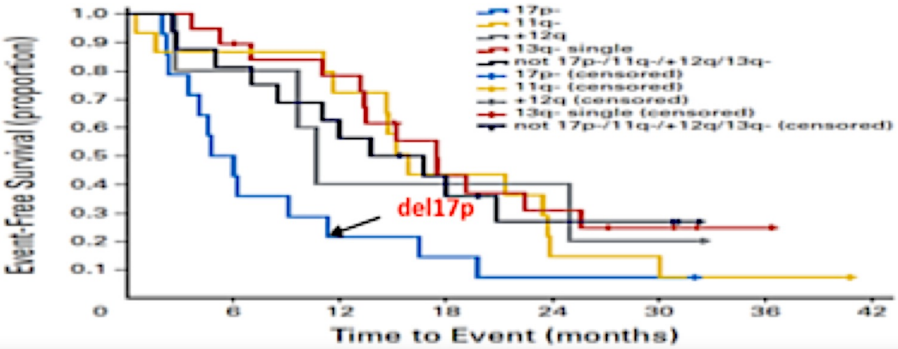
Eichhorst et al. Lancet Oncol 2016

CLL

FCR & BR: outcome for del17p/p53m







FCR TN

OS at 3 years

Del17p	= 38%
Not abnormal	= 83%

BR TN

Median Cumulative Survival

Del17p:	**= 7.8 mo.**
Not abnormal:	**= not reached**

BR RR

Median EFS

Del17p:	= 4.8 mo.
Not abnormal:	= 13.8 mo.

Hallek M et al. Lancet 2010; Fischer K et al. J Clin Oncol. 2012;
Fischer K et al. J Clin Oncol. 2011;2

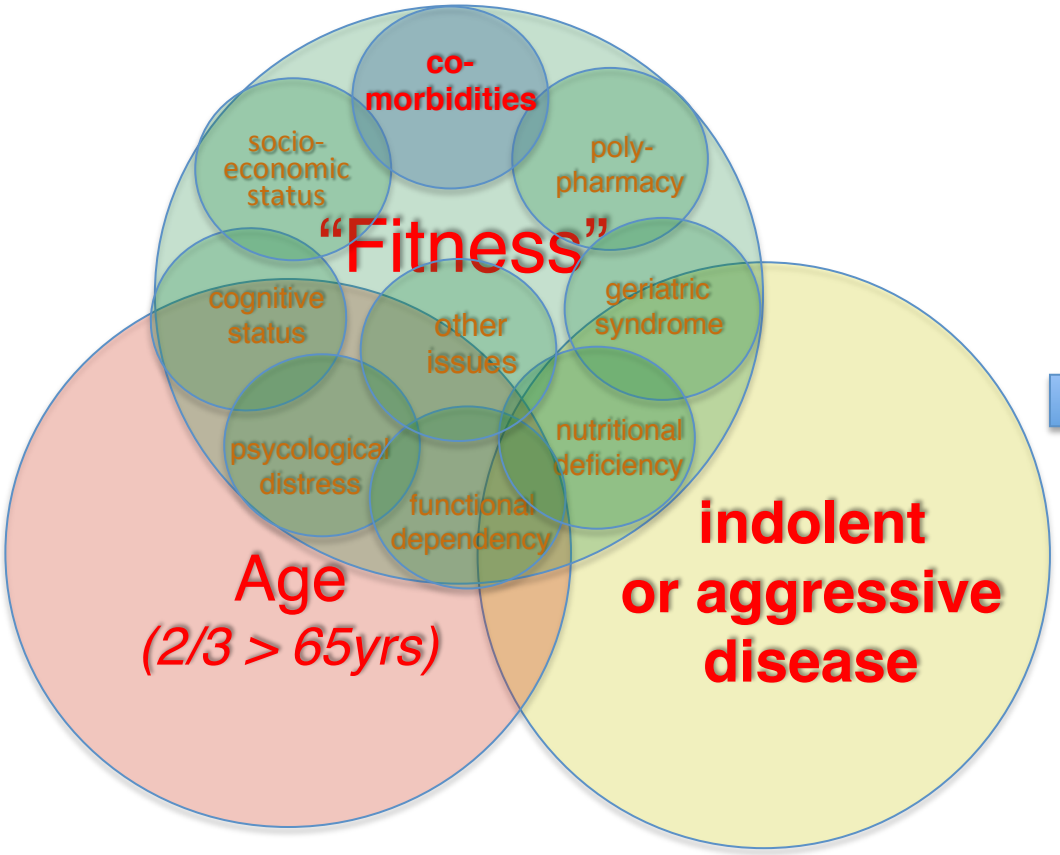
CLL: *FCR vs BR*

confronto (metodologicamente SCORRETTO) tra vari studi

	FCR (CLL-10)	FCR MDACC	BR (CLL-10)	BR (Fischer)
Median age	62.1 (55-67)	57 (17-86)	61 (55-69)	64 (34-78)
Median FU (mths)	37.1	152	37.1	27
ORR **CR**	95% 40%	95% 72%	96% 31%	88% 23%
Median PFS (mths) • **<70/65 years** • **Del (11q)** • Mutated IGHV	55 54 38 Not reached	76 ND Not reached	42 38.5 25 55	34 34 30
MRD negativity	PB 49% BM 27%	BM 43%	PB 38% BM 11%	PB 58% BM 29%

CLL

patient & disease ⟹ possible options



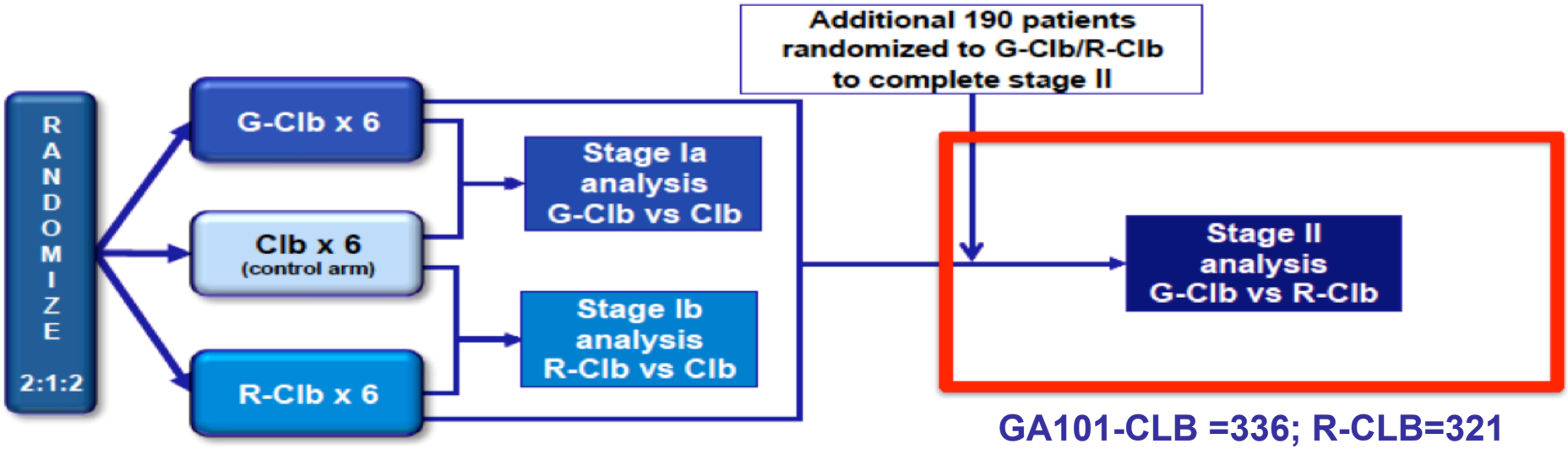
- "soft" treatment
- "aggressive" treatment

- ChT only
  - Chlorambucil
  - Benda
  - Steroids
  - Purine analogs
  - others
- FCR
- "soft" ChT + R
- "soft" ChT + new α-CD20
- New biologicals & strategies
  (Ibrutinib, Idelalisib, Venetoclax, others)

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.

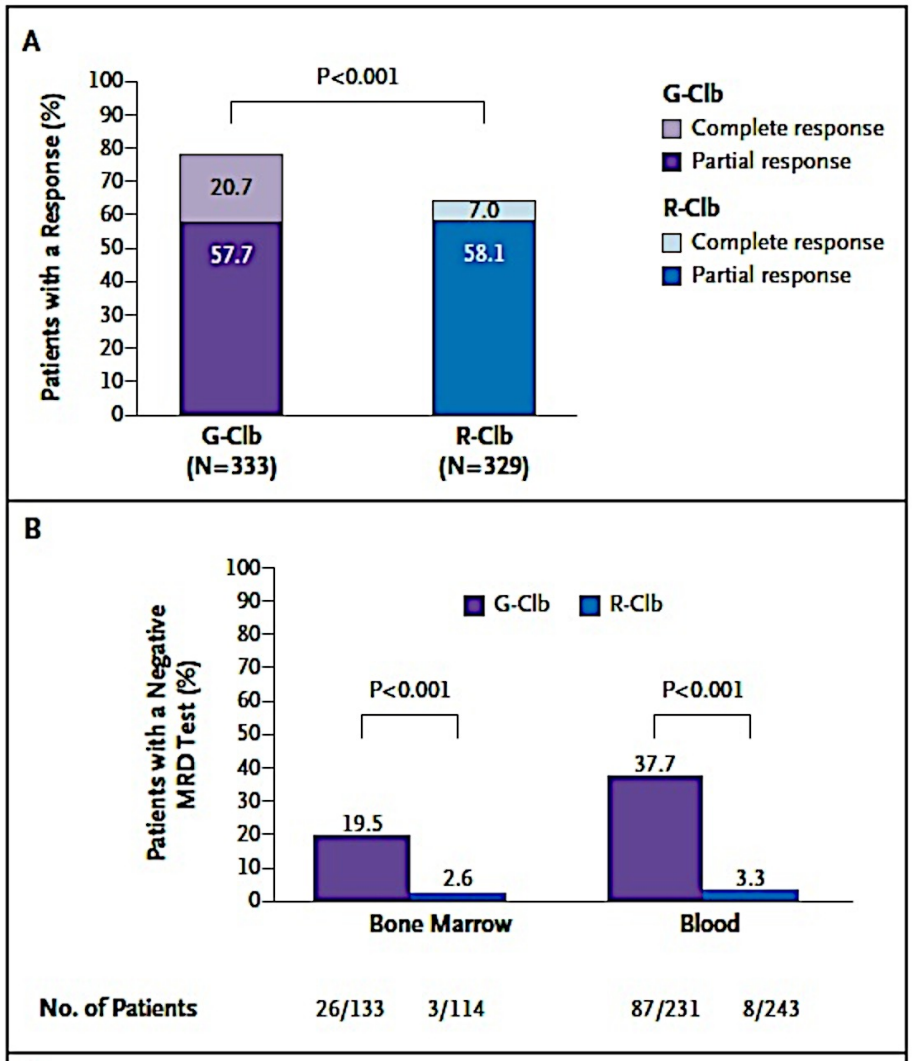
N ENGL J MED 370;12 NEJM.ORG MARCH 20, 2014

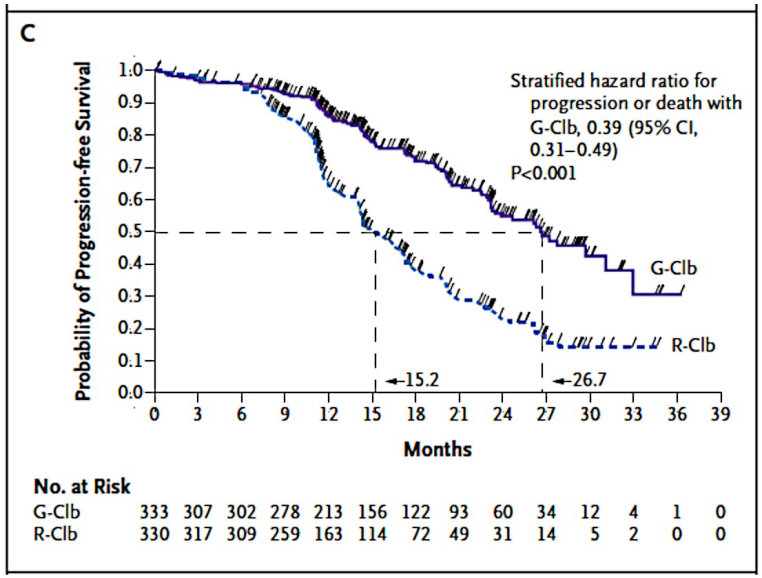


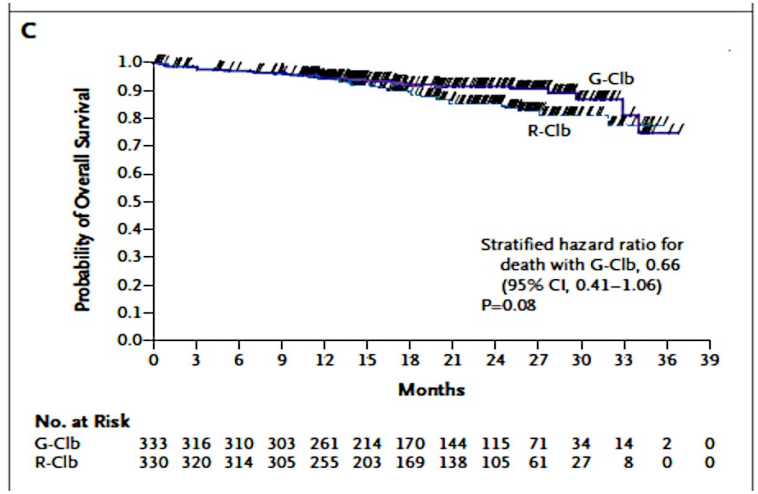
GA101-CLB =336; R-CLB=321

CLL11

main results





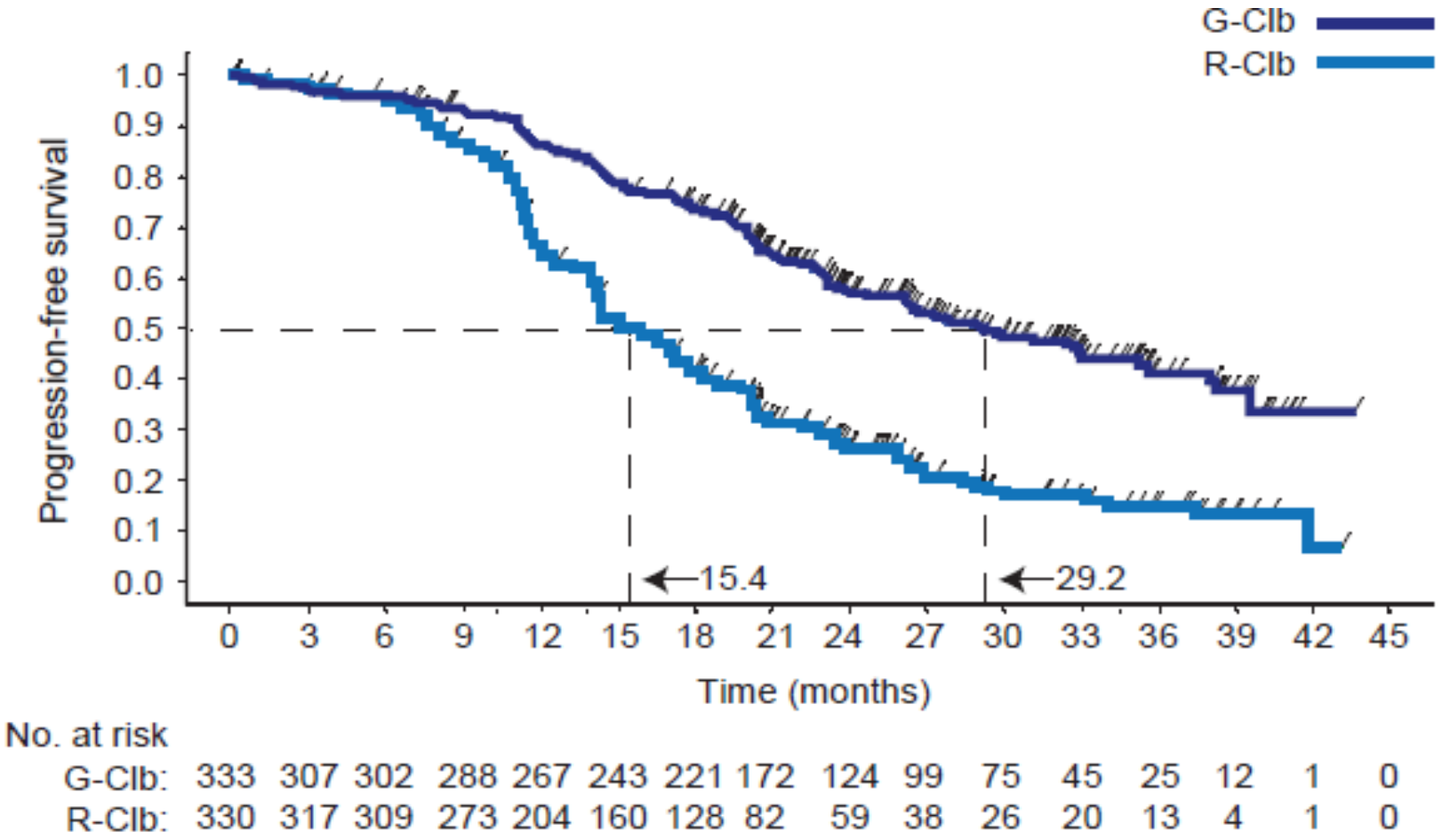


NEJM 2014

CLL11 stage II

investigator-assessed PFS

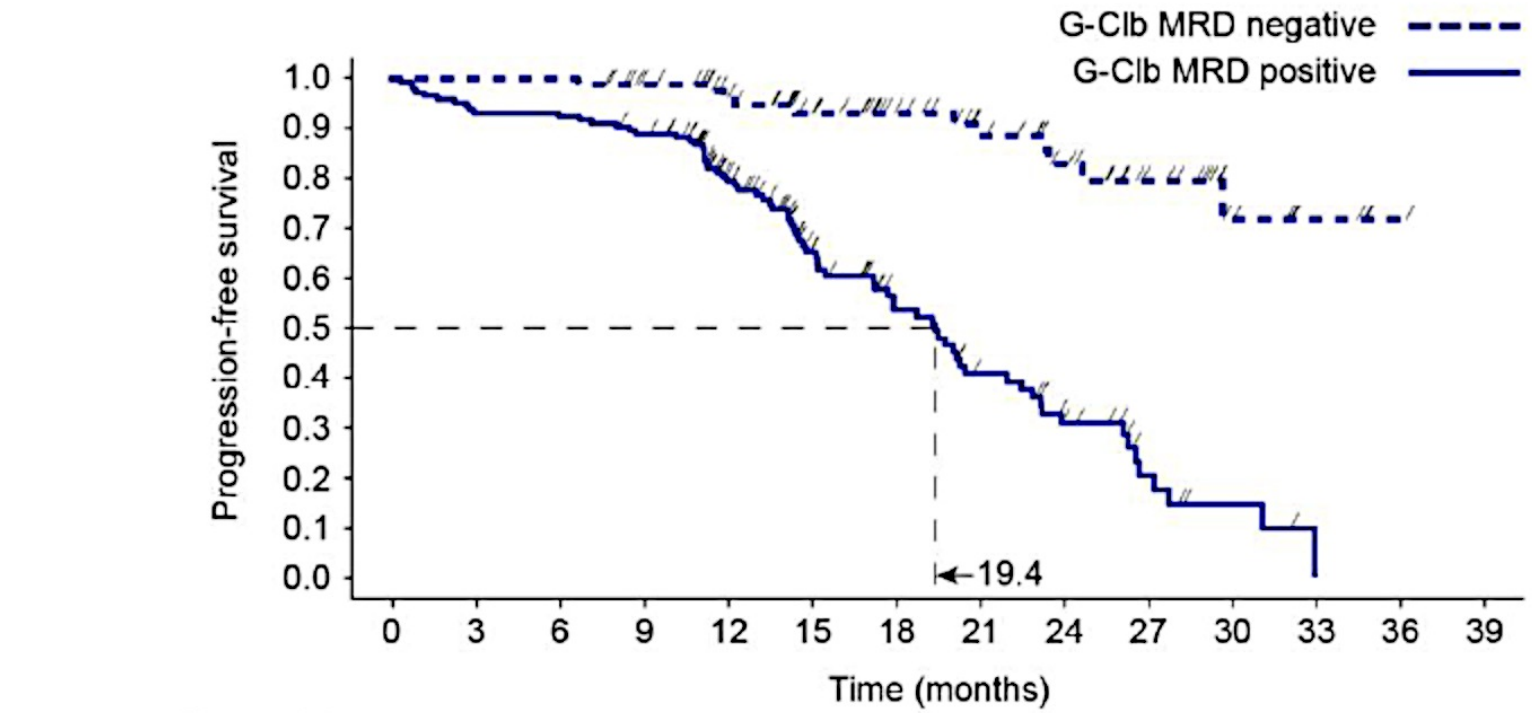
median patient observation time 27 months



Goede et al, Leukemia 2015

CLL11 stage II

PFS by MRD status in pts treated with G-Chl



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, Leukemia 2015

CLL

better results in MRD negative patients

Reference	Therapy	N	Technique	MRD threshold	Parameter*	Value MRD– vs MRD+	*P*-value
Moreno 2006	Stem cell transplant	17	ASO RQ-PCR	10^{-5}	TTP	NR vs 19 mo	0.02
		22	Flow	10^{-4}	TTP	75 vs 16 mo	< 0.001
Bosch 2008	FCM	44	Flow	10^{-4}	2-year PFS	91% vs 80%	NS
Kwok 2009	Various	58	Flow	10^{-4}	5-year PFS	89% vs 0%	< 0.001
Böttcher 2012	FC/R-FC	290	Flow	10^{-4}, 10^{-2}	PFS	69 vs 41 vs 15 mo	< 0.001
Fischer 2012	R-bendamustine	45	Flow	10^{-4},10^{-2}	PFS	NR vs 32 vs 12 mo	< 0.001
Pettitt 2012	Alemtuzumab + HDMP	25	Flow	10^{-4}	PFS	24 vs 10 mo	0.009
Santacruz 2014	Various	255	Flow	10^{-4}	TFS OS	76 vs 16 mo 108 vs 78 mo	< 0.001 0.014

All MRD measurements were in peripheral blood
* Survival values are median unless stated

CLL: *BR vs G-Clb*

confronto (metodologicamente SCORRETTO) tra 2 studi

	G-Clb **Goede NEJM 2014**	**BR** **Eichhorst Lancet Oncol 2016**
Patients	333	273
Median age	74 > 65 years= 81% > 75 years= 46%	61 > 65 years= 39% > 70 years= 18%
ORR	77%	96%
CR	22%	32%
MRD PB	38%	63%
Median PFS (months)	29	42
OS at 36 months	75%	92%

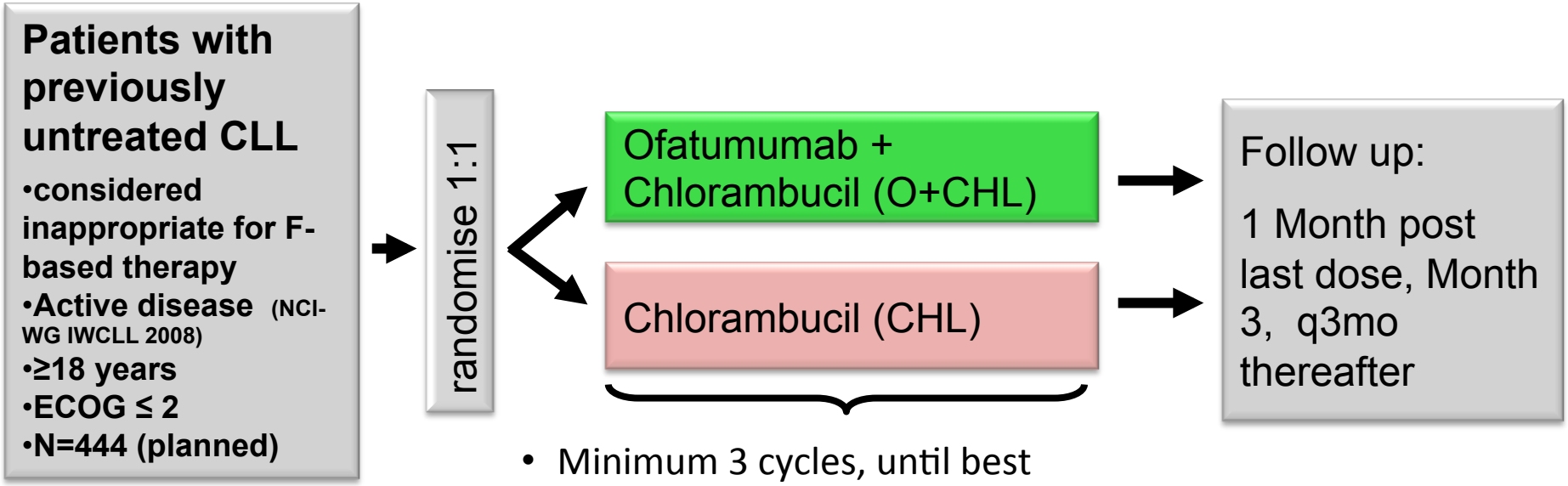
CLL: *BR vs G-Clb*

confronto (metodologicamente SCORRETTO) tra 2 studi

	G-Clb **Goede NEJM 2014**	**BR** **Eichhorst Lancet Oncol 2016**
Severe neutropenia	33%	59%
Anemia	4%	12%
Thrombocytopenia	10%	14%
Severe infections	12%	26%

CLL

COMPLEMENT 1: study design



- Minimum 3 cycles, until best response or PD maximum 12 cycles
- No cross over allowed

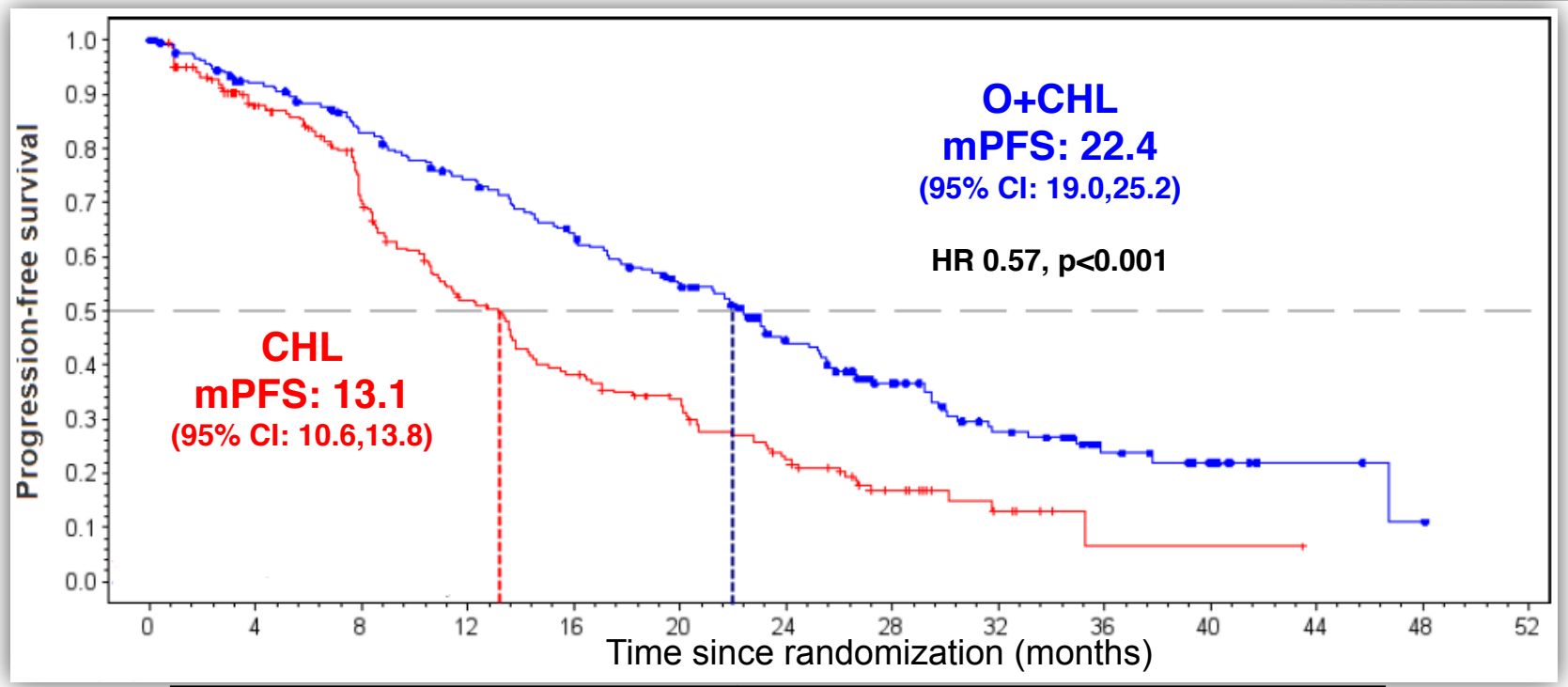
O: cycle 1 d1 300 mg, d8 1000 mg, Cycle 2-12 d1 1000 mg every 28 days
CHL: 10 mg/m^2 d1-7 every 28 days

Dose rationale: evidence of highest ORR and longest PFS with low toxicity compared to any other CHL monotherapy regimen

Hillmen et al, ASH 2013

CLL

COMPLEMENT 1: PFS probability



	CHL (n=226)	O+CHL (n=221)
Overall Response Rate*, %	**69**	**82**
p-value	<0.001	
CR, %	**1**	**14**
PR, %	**67**	**68**

Hillmen et al, ASH 2013

CLL

Quale ruolo per la ChT oggi?

ChT da sola?

molto marginale, quasi inesistente: ***Clorambucile*** *nei vecchi "FRAIL"?*

ChT + anti-CD20

FCR: **< 60 anni, FIT, IGHV-mutati**

60-65 anni, FIT, IGHV-mutati: *valutare caso per caso*

BR: < 60 anni, UNFIT

60-65 anni, FIT: *valutare caso per caso*

> 65 anni (ma <75?), FIT

Chl: > 65 anni, UNFIT

(***R/OFA/OBINO***)

del (17p) e/o mut p53 negativi

RIEPILOGANDO

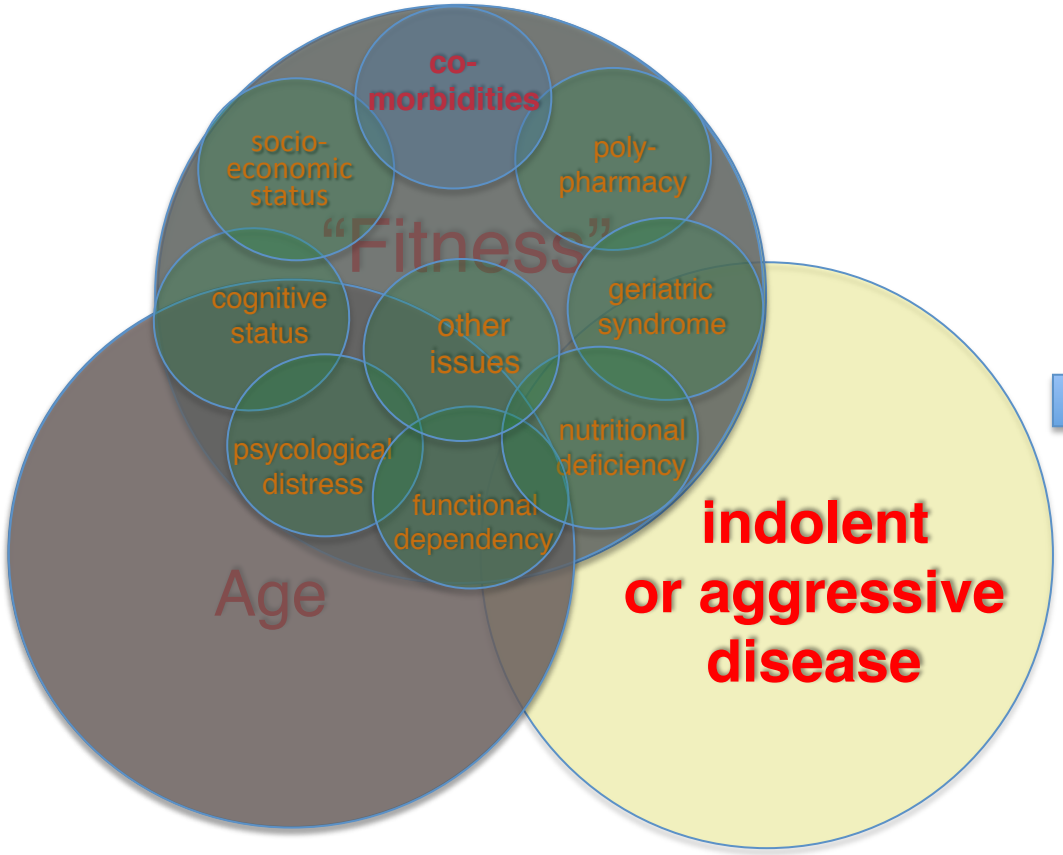
quale ruolo per la ChT oggi nella CLL?

FCR, BR, R-Clb, G-Clb, O-Clb, altre combinazioni:

1. **NELLA PRATICA CLINICA:** è obbligatorio verificare la eventuale presenza della del17p e/o della mutazione di p53 prima di iniziare il trattamento
2. ruolo consolidato in varie tipologie di pazienti *(giovani piuttosto che anziani o vecchi, FIT piuttosto che UNFIT piuttosto che FRAIL*) **PURCHE' SENZA del(17p) e/o mutazione di p53**
3. il ruolo attuale come ***dal punto 2*** potrebbe essere modificato dall'avvento dei nuovi "farmaci"

CLL

patient & disease ⟹ possible options



- "soft" treatment
- "aggressive" treatment

- ChT only
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  - Purine analogs
  - others
- FCR
- "soft" ChT + R
- "soft" ChT + new α-CD20
- New biologicals & strategies
  (Ibrutinib, Idelalisib, Venetoclax, others)

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2014
CLL/SLL

SUGGESTED TREATMENT REGIMENS[a]
(in order of preference)

CLL without del (11q) or del (17p)

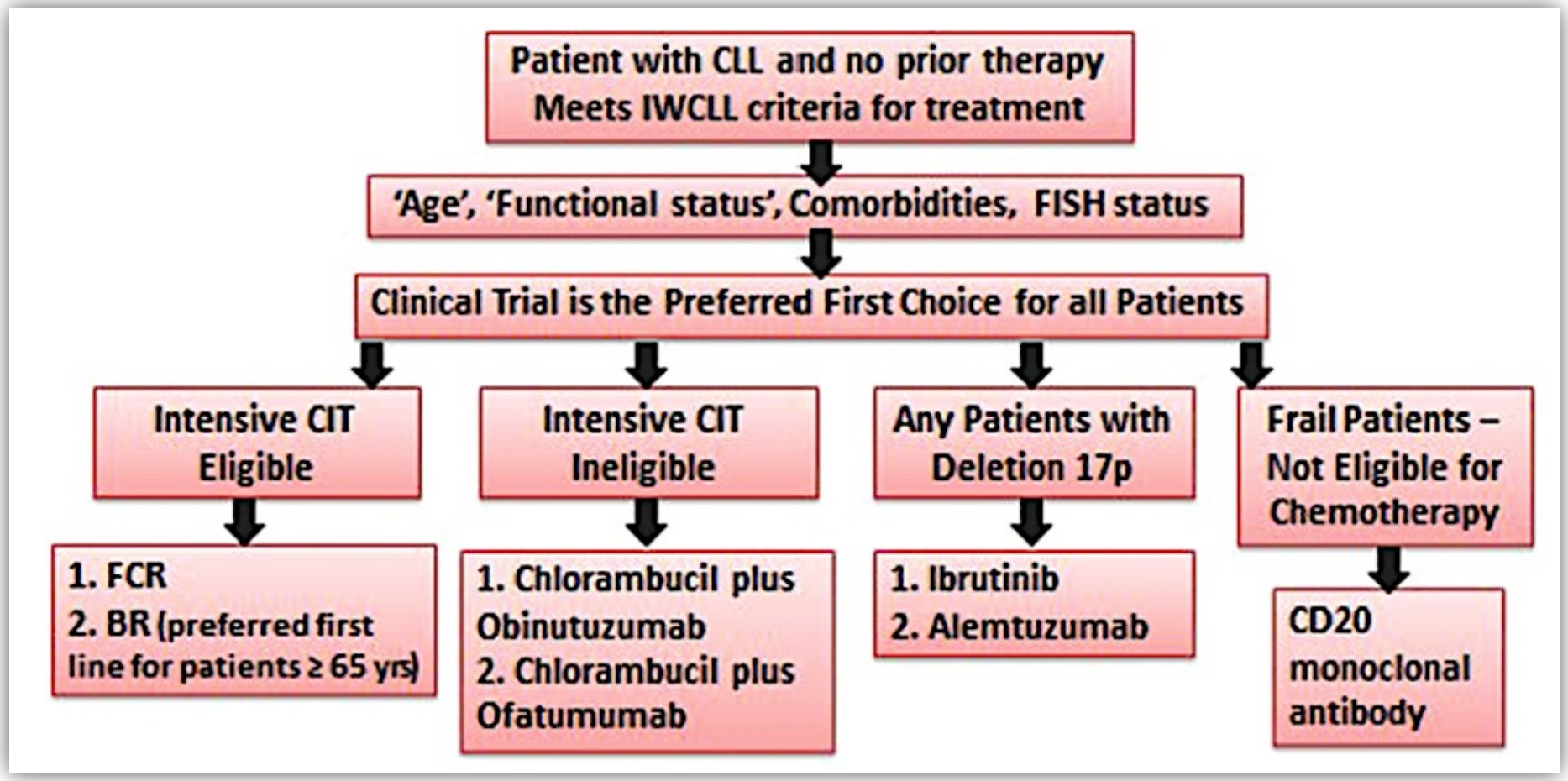
First-line therapy[b]

- Age ≥70 y or younger patients with comorbidities
  - Obinutuzumab + chlorambucil
  - Rituximab + chlorambucil
  - Bendamustine (70 mg/m^2 in cycle 1 with escalation to 90 mg/m^2 if tolerated) ± rituximab
  - Cyclophosphamide, prednisone ± rituximab
  - Rituximab
  - Fludarabine[c,d,e] ± rituximab
  - Cladribine
  - Chlorambucil
- Age <70 y or older patients without significant comorbidities
  - Chemoimmunotherapy
    - FCR[c] (fludarabine,[e] cyclophosphamide, rituximab)
    - FR[c] (fludarabine,[e] rituximab)
    - PCR (pentostatin, cyclophosphamide, rituximab)
    - Bendamustine ± rituximab
    - Obinutuzumab + chlorambucil

CLL

algoritmo terapeutico

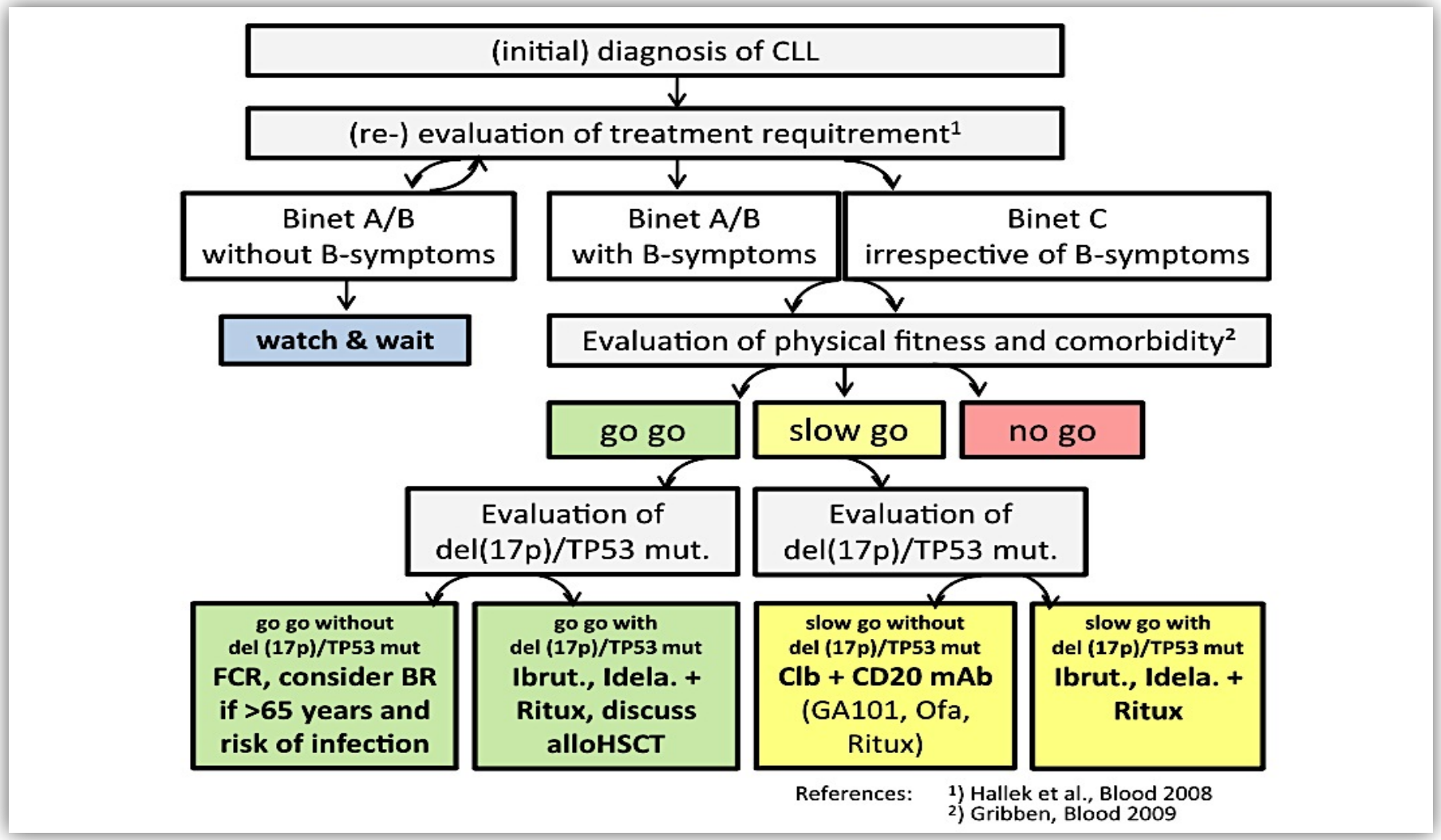
Treatment algorithm for first-line therapy



Nitin & O'Brien, Blood 2015

CLL
algoritmo terapeutico

DEUTSCHE STUDIENGRUPPE CLL



Cramer et al, Eur J Haematol, 2015

CLL: terapia prima linea età >65 anni

raccomandazioni SIE 10/2016

a) Il *backbone* chemioterapico raccomandato per i pazienti >65 anni *unfit* (CIRS >6 e/o clearance della creatinina <70 ml/min) senza delezione 17p o mutazioni di TP53 è il clorambucile che in questi pazienti è da preferirsi a bendamustina e fludarabina

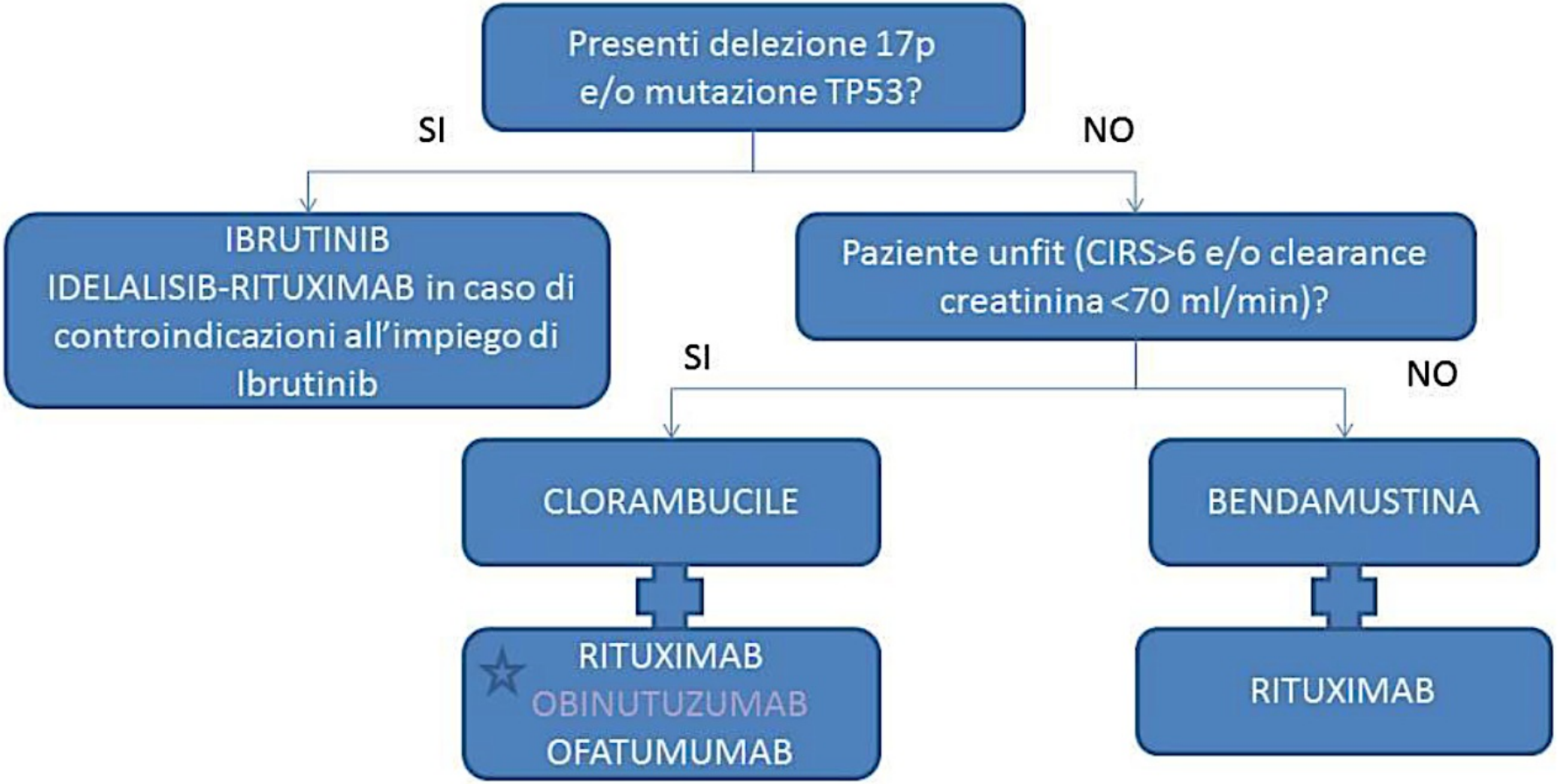
b) E' fortemente raccomandata l'aggiunta al clorambucile di un anticorpo monoclonale anti-CD20 rituximab (disponibile in Italia al 1.9.2016), ofatumumab (disponibile in Italia al 1.9.2016) o obinutuzumab (non disponibile in Italia al 1.9.2016). Non vi sono sufficienti dati che dimostrino in maniera inequivoca la superiorità di un anticorpo rispetto ad un altro.

c) Bendamustina-rituximab è il trattamento raccomandato nei pazienti >65 anni "fit" (CIRS <=6 e clearance della creatinina >=70 ml/min) senza delezione 17p o mutazioni TP53. In questi pazienti questo trattamento è da preferirsi a FCR.

d) Il trattamento raccomandato per i pazienti >65 anni (*fit* e *unfit*) con delezione 17p e/o mutazioni TP53 è ibrutinib o, in caso di controindicazioni all'impiego di questo medicinale, idelalisib in associazione a rituximab.

CLL: terapia prima linea età >65 anni

raccomandazioni SIE 10/2016



★ elenco farmaci in base all'ordine di autorizzazione EMA

in LILLA i farmaci non disponibili in Italia al 1.9.2016

CLL:

quale ruolo per la chemioterapia oggi?

Giovanni Pizzolo