LEUCEMIA LINFATICA CRONICA

Fisiopatologia

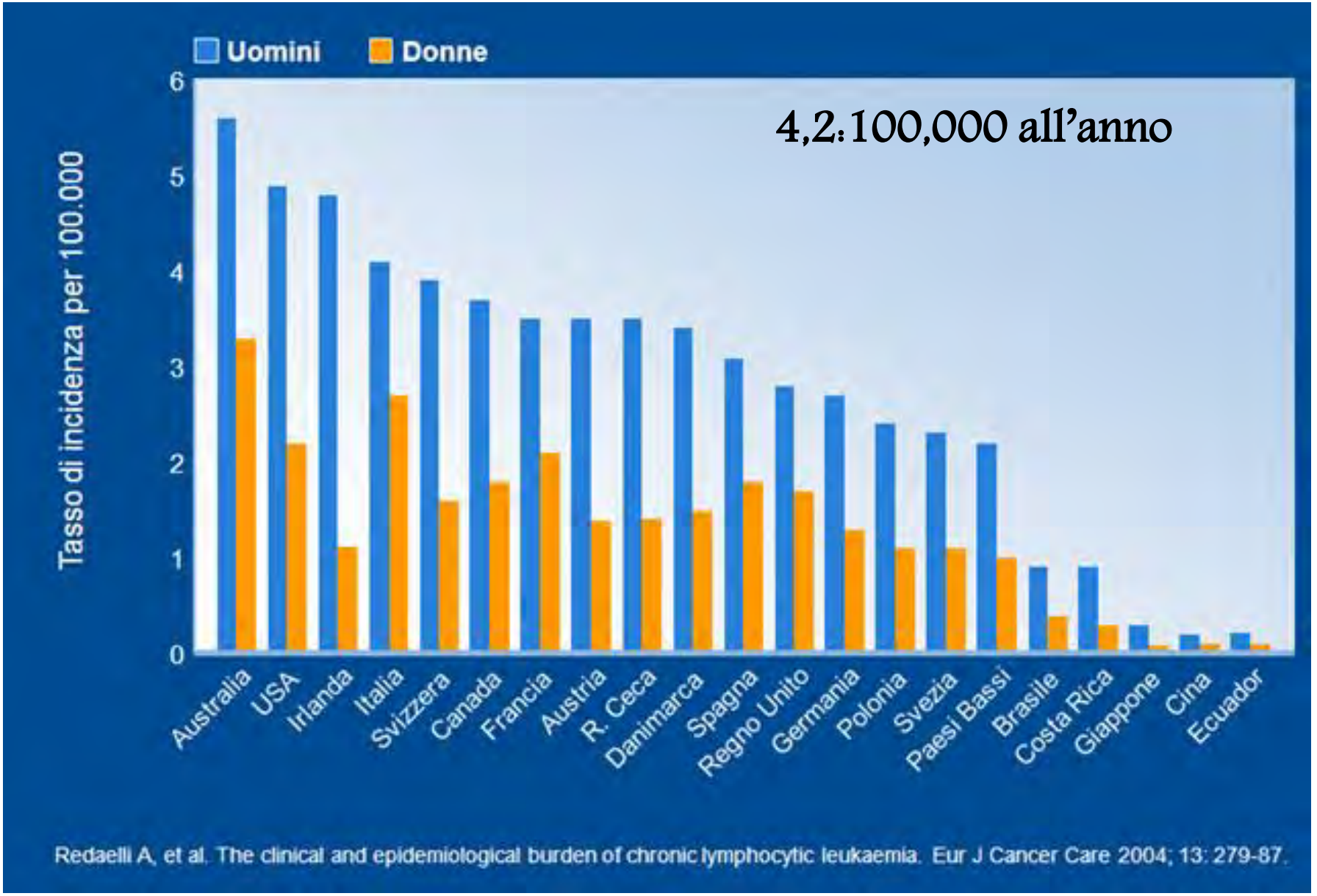
- La LLC è caratterizzata dall'accumulo di linfociti B maturi ma immunologicamente incompetenti

- La LLC è spesso diagnosticata in seguito ad analisi ematochimiche di routine quando è ancora asintomatica e spesso ha un decorso indolente

- I principali sintomi sono:
  - Infezioni ricorrenti
  - Anemia
  - Ecchimosi o sanguinamenti
  - Reazioni autoimmuni
  - Linfoadenomegalie
  - Splenomegalia
  - Epatomegalia

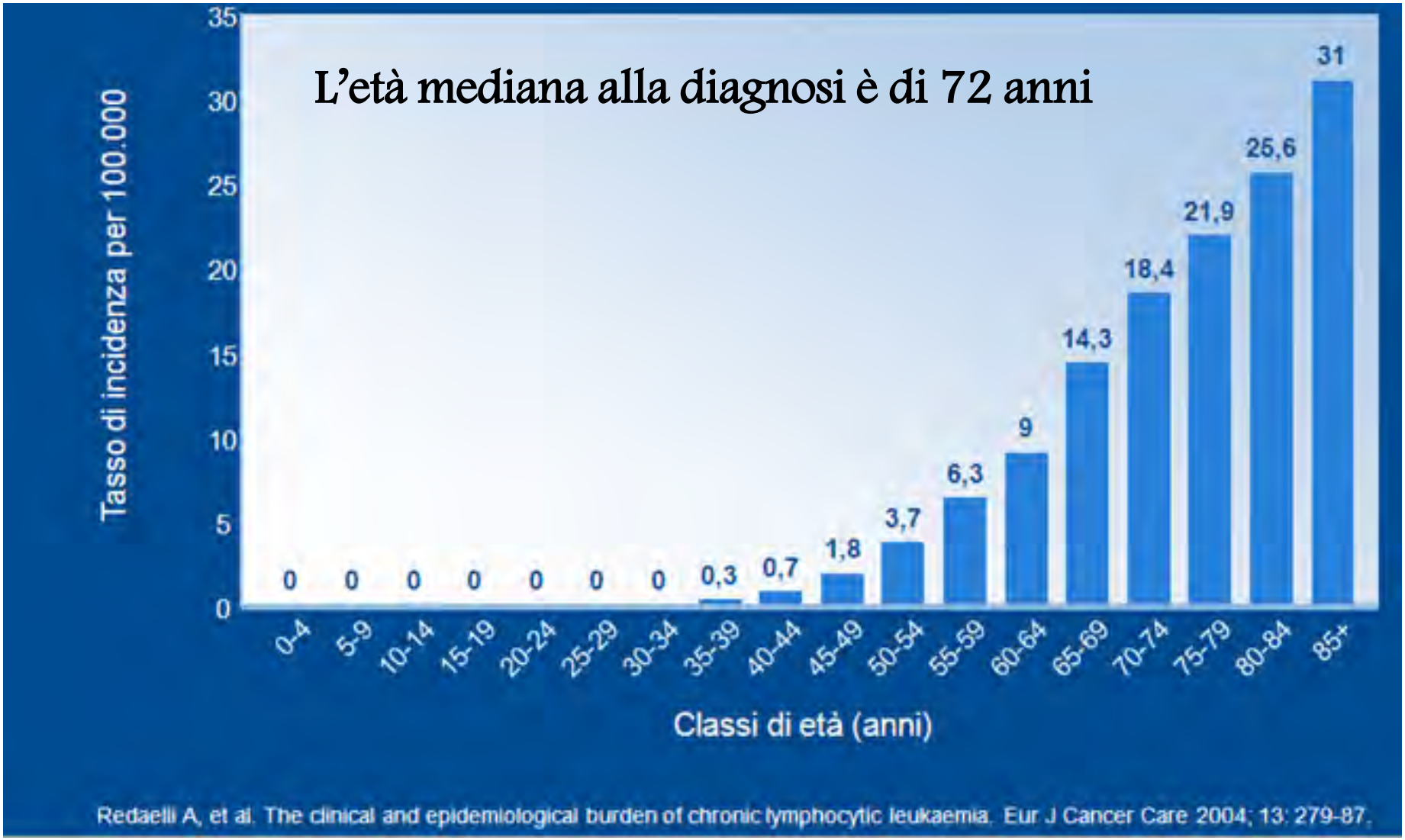
Muller – Hermelink HK et al. WHO Classification Of Tumors 2001; 127-30

Incidenza della Leucemia Linfatica Cronica



Redaelli A, et al. The clinical and epidemiological burden of chronic lymphocytic leukaemia. Eur J Cancer Care 2004; 13: 279-87.

Incidenza secondo l'età

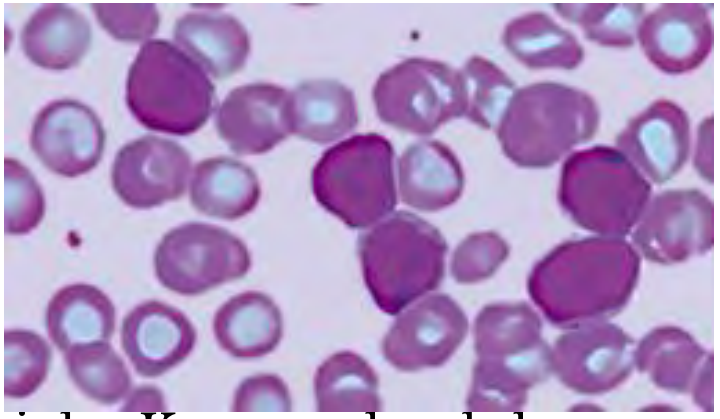


Redaelli A, et al. The clinical and epidemiological burden of chronic lymphocytic leukaemia. Eur J Cancer Care 2004; 13: 279-87.

Diagnosi

- Confermata dai seguenti criteri:
  - Presenza nel sangue periferico di linfociti monoclonali B ≥5000. La clonalità è confermata dalla citofluorimetria.

  - Lo striscio di sangue periferico mostra cellule leucemiche piccole, di aspetto maturo con citoplasma sottile e un nucleo senza evidenti nucleoli con cromatina parzialmente addensata. Più grandi e atipici linfociti (prolinfociti) possono essere presenti ma non devono essere maggiori del 55%.



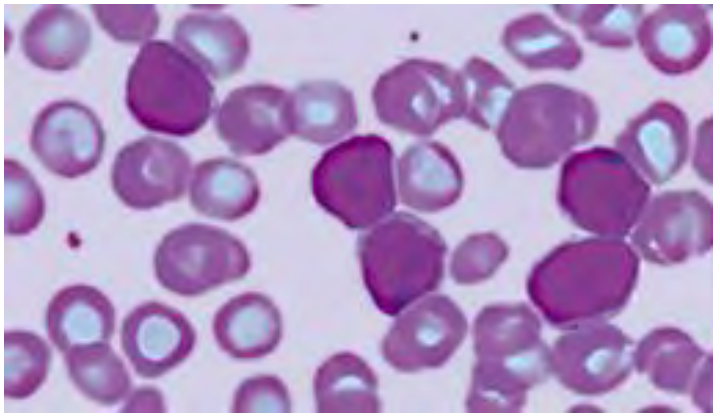
- Fenotipo più frequente:
  - CD5+
  - CD19+
  - CD23+
  - Restrizione catene immunoglobuliniche Kappa e lambda

Eichhorst B. Et al.
Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up
Annals of Oncology 26 (Supplement 5): v78–v84, 2015

Diagnosi

- Diagnosi differenziale
  - linfoma marginale
  - linfoma linfoplasmocitico
  - linfoma mantellare

- Linfoma a piccoli linfociti = Leucemia Linfatica Cronica
  - presenza di linfoadenomegalie e/o splenomegalia con un numero di linfociti B clonali < 5 × 10e9/l.
  - stesso immunofenotipo



Eichhorst B. Et al.
Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up
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IMMUNOFENOTIPIZZAZIONE

Marcatore	CLL	HCL	WM	BPLL	MM	MCL	FL
Ig di superficie	Incerto +	Forte +	Forte +	Forte +	–	Intenso +	+
CD5	+	–	–	20-30%+		+	–
CD10	–	-/+	–		+/–	–/+	+
CD11c	Debole +	Forte +	–				
CD19	+		+	+	–		+
CD20	+	Forte +	+	+	+/-		+
CD22	+	Forte +	+	+			+
CD23	+	–	–	10-20% +		–	
CD25	–	+	–			–	–
CD38			Spesso +	46% +	Forte +		
CD79a	+		+	+	+		+
CD79b	Solita-mente -			+			
CD138			+		+		
FMC7	Solita-mente -	+		+		+	
Ciclina D1	–	Debole +			Alcuni +	+	
Annessina A1	–	+	–	–	–	–	–

CLL B cells express CD5, CD19, CD23, and low levels of surface Ig.

This phenotypic profile differs from that of most normal B cell subsets.

Recent gene-expression profiling studies have confirmed that CLL is probably derived from CD5 B cells similar to those found in the blood of healthy adults.

Lobetti-Bodoni C, Bertoni, F., et al. 2013. Eur J Internal Med, 24(5); 401–410
Kipps et al, Annu Rev Pathol. 2014 ; 9: 103–118. doi:10.1146/annurev-pathol-020712-163955

Stadiazione

	Valutazione prima del trattamento	Valutazione della risposta
Anamnesi, esame obiettivo e performance status	+	+
Esami ematochimici completi	+	+
Aspirato midollare e biopsia	+	+
Citogenetica (FISH) per la del(17p)/ mutazione TP53	+	–
Valutazione stato mutazionale IgVH	+	–
Indagini strumentali	+	+

Table 2. Staging systems for chronic lymphocytic leukaemia (CLL)

Stage	Definition	Median survival
Binet system		
Binet A	Hb ≥ 10.0 g/dl, thrombocytes ≥100 × 10^9/l, <3 lymph node regions	>10 years
Binet B	Hb ≥ 10.0 g/dl, thrombocytes ≥100 × 10^9/l, ≥3 lymph node regions	>8 years
Binet C	Hb < 10.0 g/dl, thrombocytes <100 × 10^9/l	6.5 years
Rai system		
Low risk		
Rai 0	Lymphocytosis >15 × 10^9/l	>10 years
Intermediate risk		
Rai I	Lymphocytosis and lymphadenopathy	>8 years
Rai II	Lymphocytosis and hepatomegaly and/or splenomegaly with/without lymphadenopathy	
High risk		
Rai III	Lymphocytosis and Hb < 11.0 g/dl with/without lymphadenopathy/ organomegaly	6.5 years
Rai IV	Lymphocytosis and thrombocytes <100 × 10^9/l with/without lymphadenopathy/ organomegaly	

The overall survival times included in this table were adapted and have changed during the past 30 years [7].
Binet's lymphoid areas consist in: lymphadenopathy either uni- or bilateral in (1) cervical, (2) axillary, (3) inguinal areas, (4) spleen, (5) liver.
Hb, haemoglobin.

Eichhorst B. Et al.
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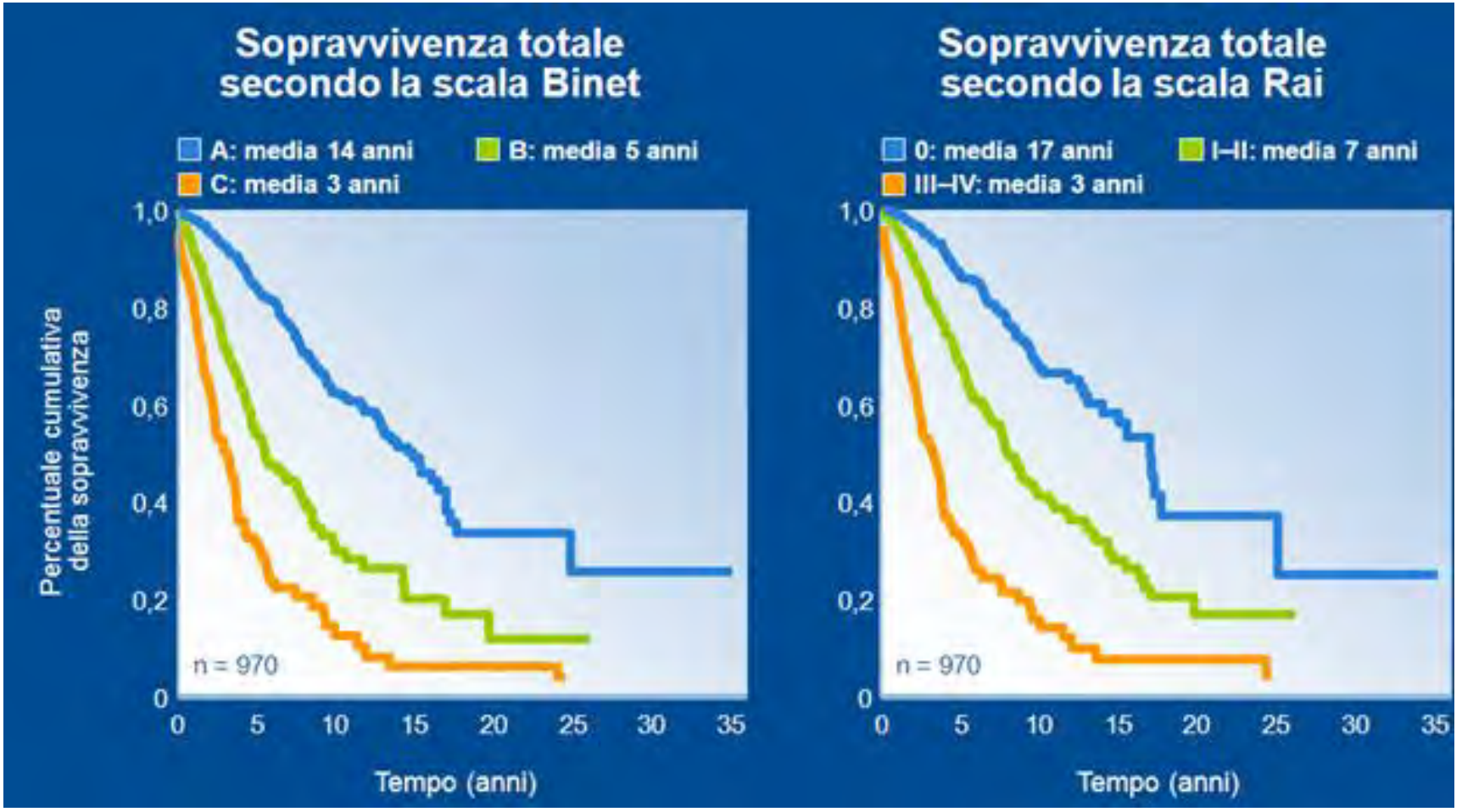
Stadiazione



Montserrat E, et al. New progostic markers in CLL [Am Soc Hematol Educ Program]. Hematology 2006; 279-84

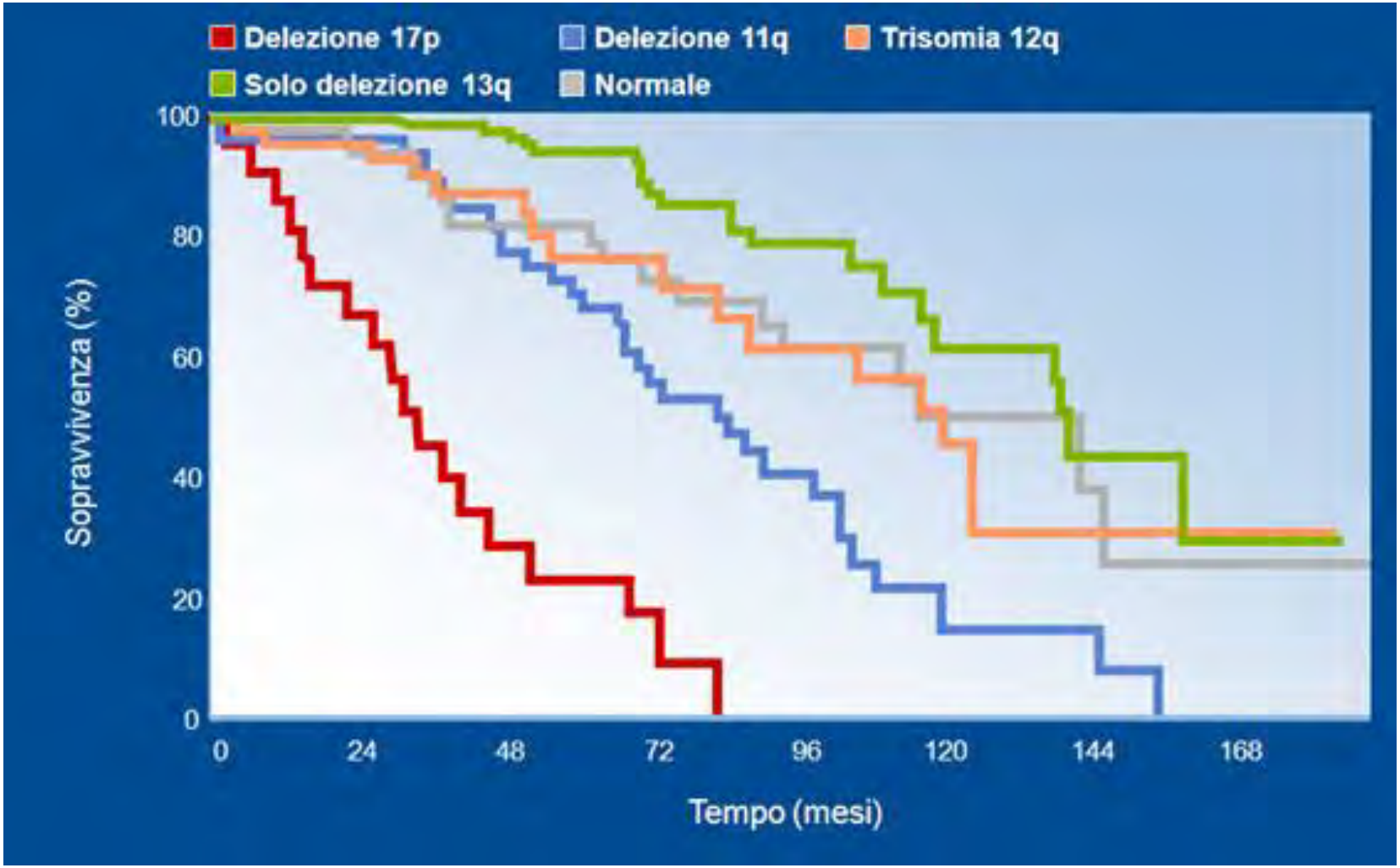
Fattori prognostici chiave CLL

Alterazioni genetiche

	Tipo di alterazione	Frequenza (%)	Correlati Clinici
Cromosoma 13	delezione	50-70	Prognosi favorevole
Cromosoma 12	Trisomia	10-30	Possibile LLC ad alto rischio
Cromosoma 11	Delezione	10-20	LLC più aggressiva per i più giovani
Cromosoma 6	Delezione	3-6	LLC più aggressiva
Cromosoma 14	Translocazione	9	LLC più aggressiva
Cromosoma 17	Mutazione	1,5-7	Malattia avanzata, resistenza farmacologica, sopravvivenza ridotta
BCL-2	Riarrangiamento	5	Gene antiapoptotico

Redaelli A, et al. The clinical and epidemiological burden of chronic lymphocytic leukemia. Eur J Cancer Care 2004; 13: 279–87

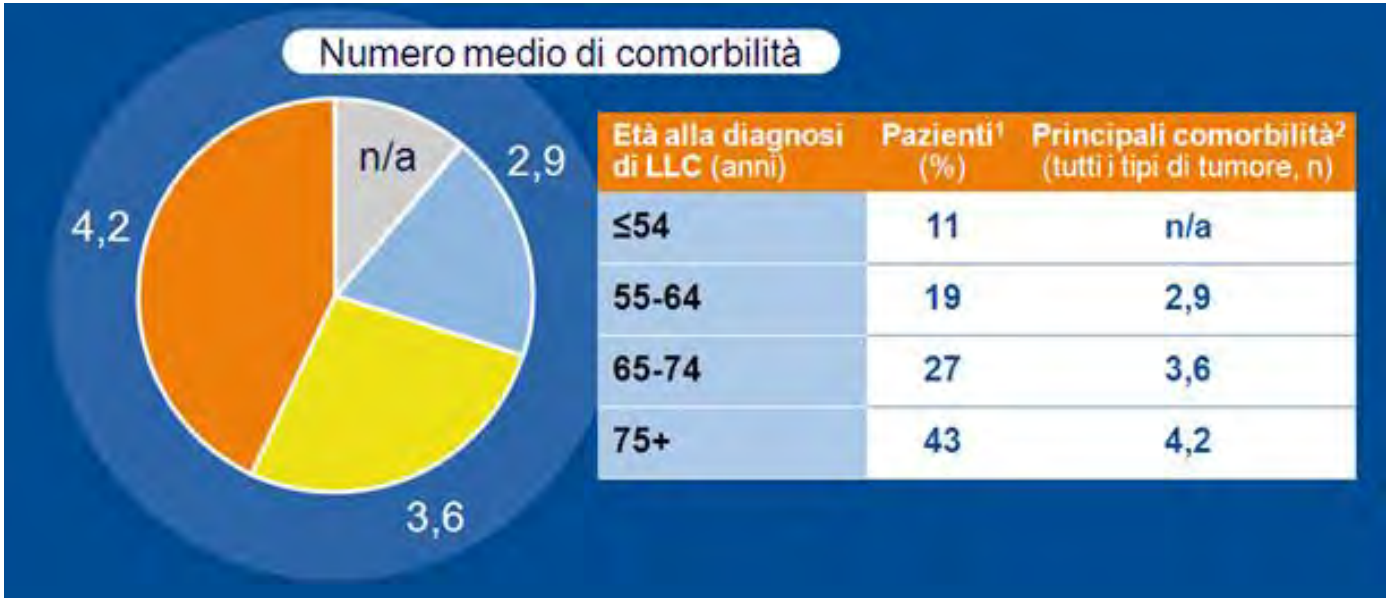
Fattori prognostici: anomalie citogenetiche e sopravvivenza



Dohner H, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. N Engl J Med 2000; 343: 1910-16

Caratteristiche dei pazienti affetti da LLC

- Età media alla diagnosi: 72 anni
- Molti pazienti anziani sono in buona salute, ma alcuni presentano comorbidità



Età alla diagnosi di LLC (anni)	Pazienti[1] (%)	Principali comorbilità[2] (tutti i tipi di tumore, 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 Camcer Statistics review 1975-2005.
2, Yancik R, Cancer 1997; 80; 1273-83

Definizione di malattia attiva
(almeno un criterio)

blood 2008 111: 5446-5456
doi:10.1182/blood-2007-06-093906 originally published online January 23, 2008

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

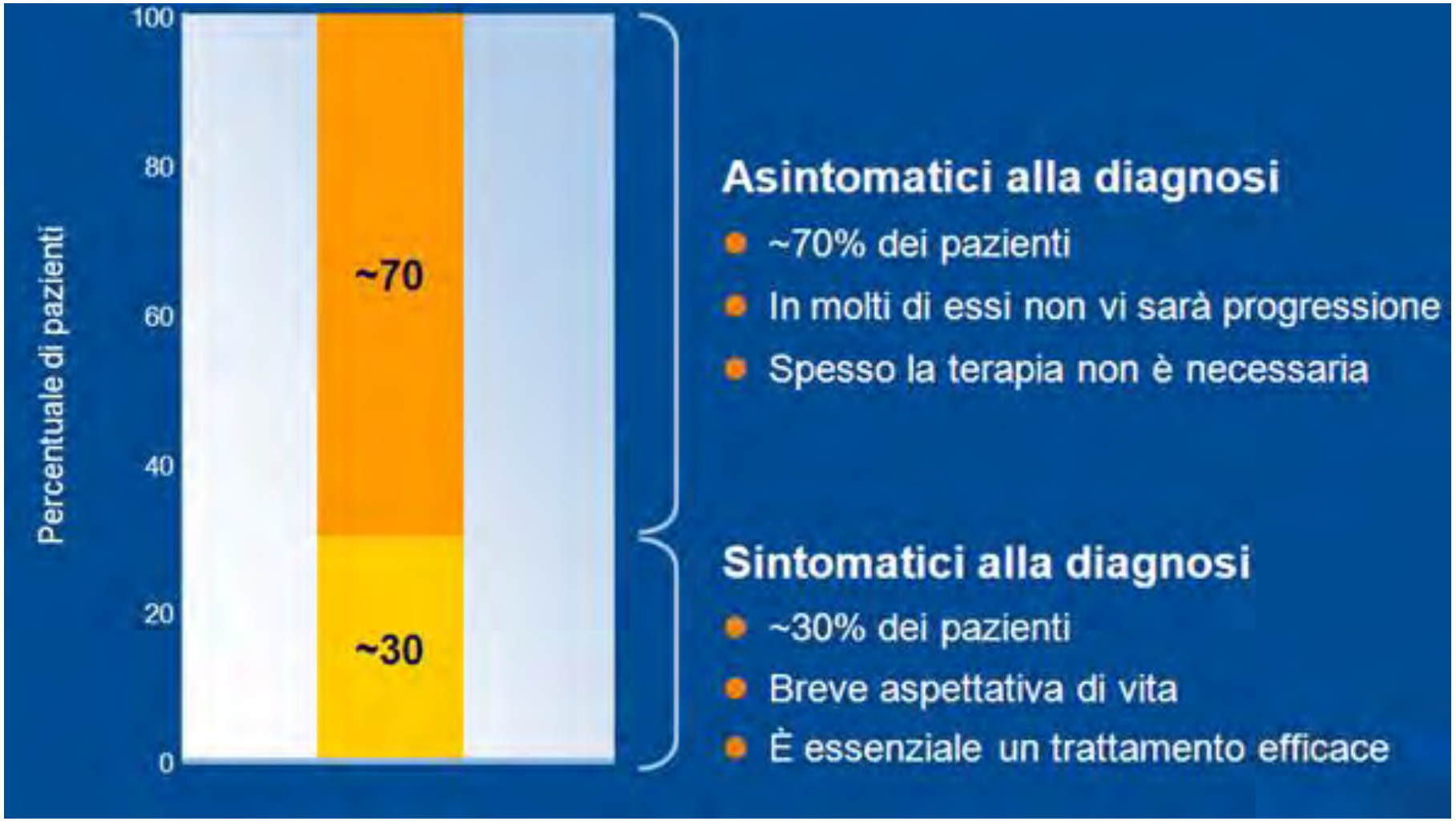
Michael Hallek, Bruce D. Cheson, Daniel Catovsky, Federico Caligaris-Cappio, Guillaume Dighiero, Hartmut Döhner, Peter Hillmen, Michael J. Keating, Emili Montserrat, Kanti R. Rai and Thomas J. Kipps

- ✓ Insufficienza midollare (anemia e/o piastrinopenia)
- ✓ Importante (per esempio 6 cm sotto l'arcata costale) o progressiva o sintomatica splenomegalia
- ✓ Importanti (per esempio 10 cm nel diametro maggiore) o progressive o sintomatiche linfoadenomegalie
- ✓ Progressiva linfocitosi con aumento di più del 50% in un periodo di 2 mesi o un tempo di duplicazione linfociti (LDT: Lymphocyte doubling time) inferiore a 6 mesi
- ✓ Anemia o piastrinopenia autoimmune che non risponde a corticosteroidi o altre terapie standard
- ✓ Sintomi costituzionali:
  - Calo ponderale ≥10% entro 6 mesi
  - Fatigue (ECOG≥2)
  - Febbre>38°C per due o più settimane
  - Sudorazioni notturne >1 mese

Ipogammaglobulinemia o paraproteinemia o monoclonale o policlonale da sole non costituiscono una base per l'inizio della terapia; tuttavia si raccomanda la documentazioni di un loro cambiamento nei pazienti in terapia.

Pazienti con LLC possono presentarsi con marcata leucocitosi; tuttavia, i sintomi associati con sviluppo di aggregati leucocitari (come si osserva nelle leucosi acute) si verificano raramente in pazienti con CLL. Pertanto, la linfocitosi assoluta non dovrebbe essere utilizzata come solo indicatore per il trattamento.

Indicazioni al trattamento



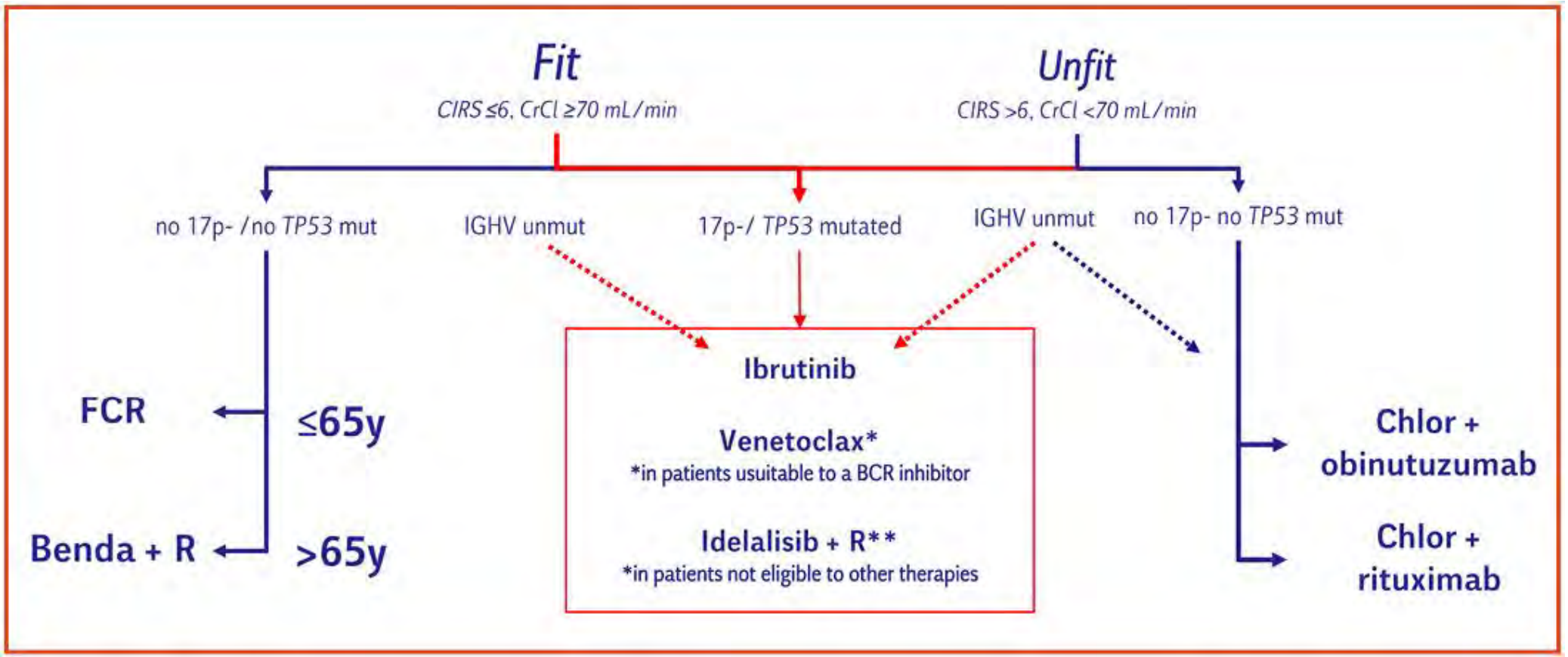
Hamblin Tj, et al. Long survival in B-CLL correlates with surface IgM kappa phenotype. Br J Haematol 1987; 66; 21-6

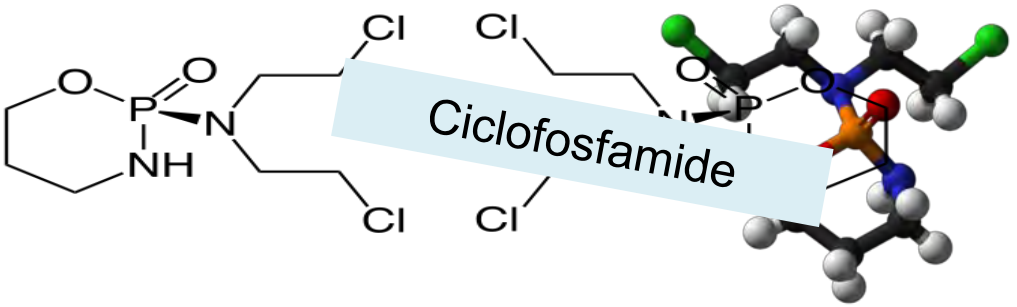
Classificazione del paziente secondo il fitness status

'Go-go' o fit	'Slow-go' o unfit	'No-go' o frail
• Completamente indipendente • Nessuna comorbidità • Normale aspettativa di vita • Habitus psicologico ottimale	• Qualche comorbidità • Ridotte funzionalità d'organo • Ridotto performance status • Habitus psicologico buono	• Gravi handicap • Gravi comorbidità • Ridotta aspettativa di vita • Habitus psicologico compromesso

Quale è l'obiettivo terapeutico?

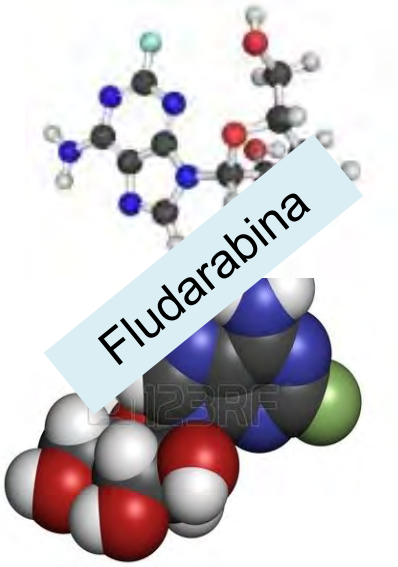
1) Prolungamento della OS
2) MRD –
3) Palliazione dei sintomi
4) Prolungamento della PFS

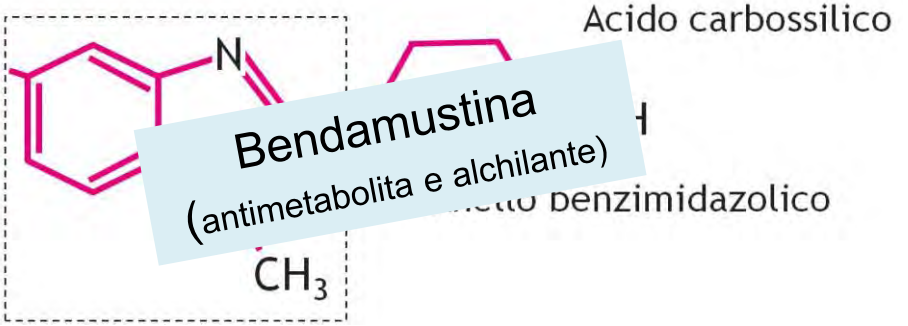

Fit
CIRS ≤6, CrCl ≥70 mL/min
Unfit
CIRS >6, CrCl <70 mL/min
no 17p- /no TP53 mut
IGHV unmut
17p-/ TP53 mutated
IGHV unmut
no 17p- no TP53 mut
FCR
≤65y
Benda + R
>65y
Ibrutinib
Venetoclax*
*in patients usuitable to a BCR inhibitor
Idelalisib + R**
*in patients not eligible to other therapies
Chlor + obinutuzumab
Chlor + rituximab

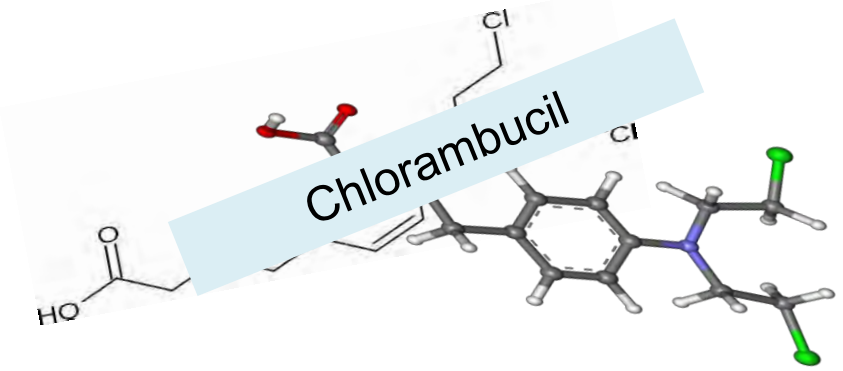


Current treatment options for first-line patients with CLL –

Including patients with coexisting medical conditions

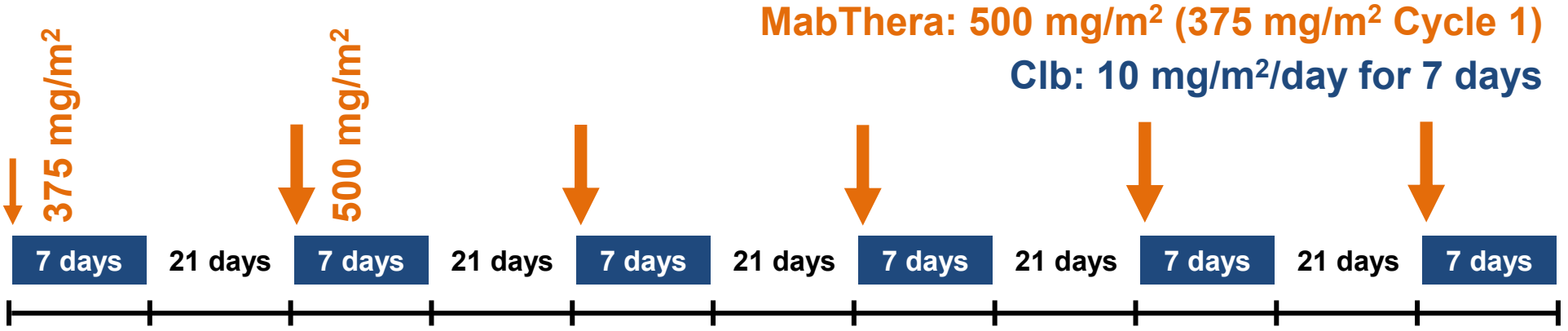






CLL208: R-Clb in first-line CLL
Study design

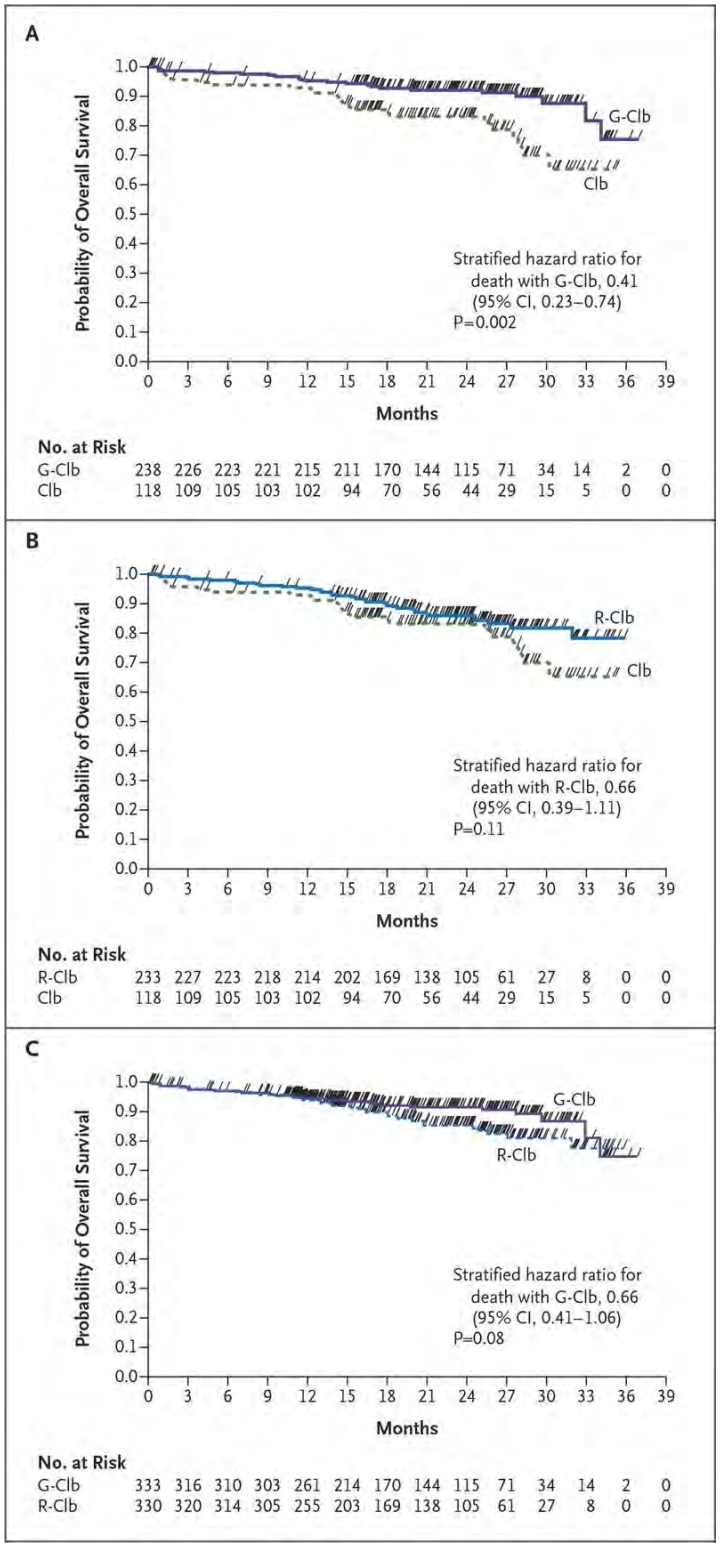
- Single-arm, Phase II study to assess the safety of treating first-line patients with CLL with R-Clb



28-day cycles
Further 6 cycles of Clb alone if patient not in CR and continuing to respond

- Patients (N = 100) were in Binet stage B or C, with a median age of 70 years

Hillmen P, *et al*. ICML 2011; Abstract 120. Presentation update.


A
Probability of Overall Survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
G-Clb
Clb
Stratified hazard ratio for death with G-Clb, 0.41 (95% CI, 0.23–0.74)
P=0.002
0 3 6 9 12 15 18 21 24 27 30 33 36 39
Months
No. at Risk
G-Clb 238 226 223 221 215 211 170 144 115 71 34 14 2 0
Clb 118 109 105 103 102 94 70 56 44 29 15 5 0 0
B
Probability of Overall Survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
R-Clb
Clb
Stratified hazard ratio for death with R-Clb, 0.66 (95% CI, 0.39–1.11)
P=0.11
0 3 6 9 12 15 18 21 24 27 30 33 36 39
Months
No. at Risk
R-Clb 233 227 223 218 214 202 169 138 105 61 27 8 0 0
Clb 118 109 105 103 102 94 70 56 44 29 15 5 0 0
C
Probability of Overall Survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
G-Clb
R-Clb
Stratified hazard ratio for death with G-Clb, 0.66 (95% CI, 0.41–1.06)
P=0.08
0 3 6 9 12 15 18 21 24 27 30 33 36 39
Months
No. at Risk
G-Clb 333 316 310 303 261 214 170 144 115 71 34 14 2 0
R-Clb 330 320 314 305 255 203 169 138 105 61 27 8 0 0

CLL8: R-FC in first-line CLL
Key efficacy results

Patients (%)	R-FC (n = 408)	FC (n = 409)
ORR[1]	90*	80
CR	44*	22
OS (median follow-up 5.9 y)[2]	69	62

Younger vs older patients (%)[1]	R-FC	
	< 65 years (n = 282)	≥ 65 years (n = 126)
CR	45	43
ORR	89	93
PFS at 3 years	64	68
OS at 3 years	87	88

- R-FC significantly improves overall survival in first-line treatment of CLL

Patients (%)†	R-FC	FC
MRD-negativity in peripheral blood at final staging[3]	63	35

- MRD-negativity defined as < 10^{-4} CLL cells according to the iwCLL definition[4]
- Low MRD levels during and after therapy were associated with longer PFS and OS (OS: $p < 0.0001$)[3]

MRD = minimal residual disease.
*** $p < 0.0001$; † Blood samples were taken from 493 patients.**

1. Hallek M, *et al*. *Lancet* 2010; 376:1164–1174;
2. Fischer K, *et al.* ASH 2012; Abstract 435;
3. Böttcher S, *et al*. *J Clin Oncol* 30: 980–989;
4. Hallek M, *et al. Blood* 2008; 111:5446–5456.

R-bendamustine in first-line CLL
Key results

Response, patients (%)	All patients (N = 117)	Patients > 70 years (n = 26)
ORR	103 (88)	22 (85)
CR	27 (23)	3 (12)
nPR/PR	76 (65)	19 (73)
SD	11 (9)	4 (16)
PD	–	–
Missing	3 (3)	–

- At final staging, 26 of 45 patients (57.8%) had peripheral blood MRD-negativity. Seven of 24 patients (29.2%) achieved MRD-negativity in bone marrow. Patients stratified in the high MRD ($> 10^{-2}$) group had a median OS of 23.2 months and the median OS was not reached for those patients in the low- ($< 10^{-4}$) and intermediate-MRD ($\geq 10^{-4}$ to $<10^{-2}$) groups
- The most common grade 3/4 AEs were hematologic (52% patients), including leukopenia (30%), neutropenia (20%), thrombocytopenia (22%), and anemia (20%)
- Fischer *et al.* concluded that R-bendamustine was effective and safe in these patients with previously untreated CLL, many of whom were in an advanced stage of disease and/or were ineligible for fludarabine treatment

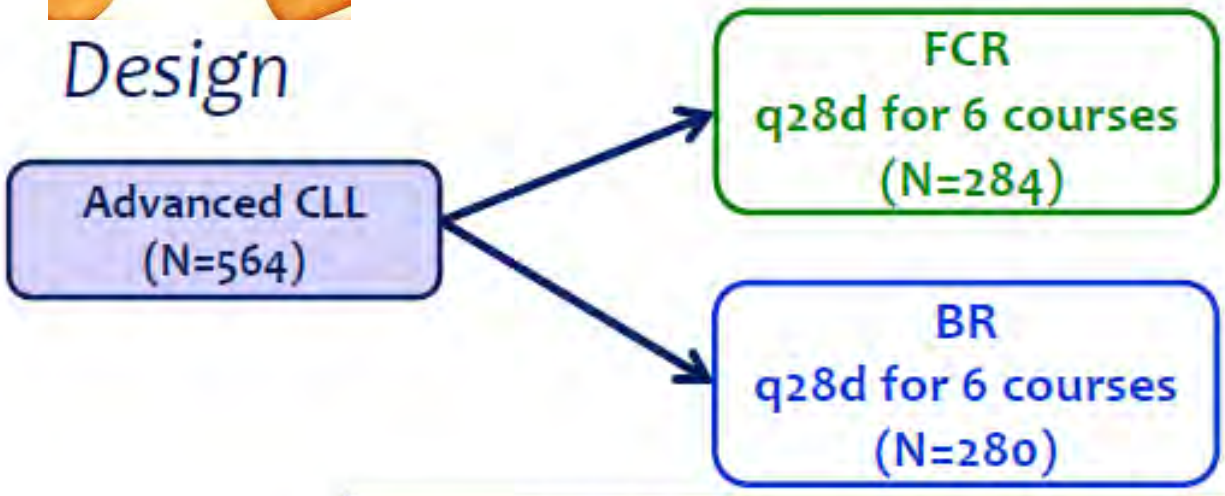
nPR = nodular partial response.

Fischer K, *et al. J Clin Oncol* 2012; 30:3209–3216.

CLL10: FCR vs RB

Studio randomizzato di fase III

Design



Inclusion criteria:

- CIRS score ≤6
- CrCL ≥70 mL/min
- No del(17p)

Median observation time: 28 months

Regimens:

FCR:	Fludarabine 25 mg/m² i.v. d1–3
	Cyclophosphamide 250 mg/m² i.v. d1–3
	Rituximab 375 mg/m² i.v. do (C1) then 500 mg/m² d1 (C2-6)
BR:	Bendamustine 90 mg/m² i.v. d1-2
	Rituximab 375 mg/m² i.v. do (C1) then 500 mg/m² d1 (C2-6)

CIRS, Cumulative Illness Rating Scale; CrCL, creatinine clearance; i.v., intravenous; q28d, every 28 days

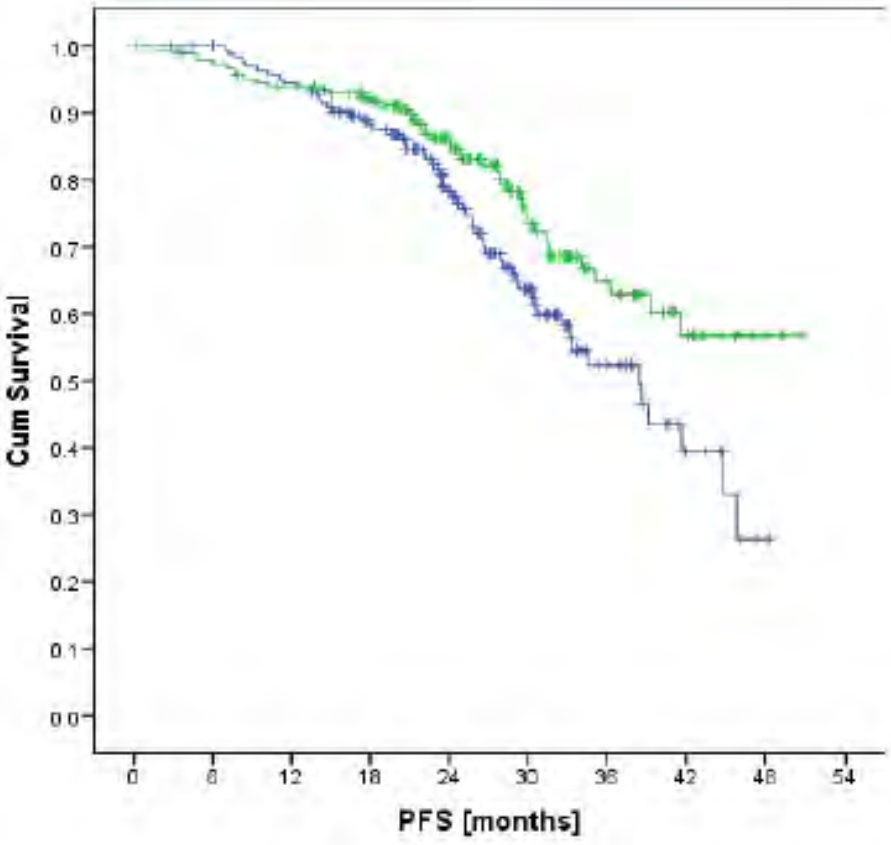
Eichhorst et al., ASH 2013; abstract 526 (oral presentation)

CLL10: FCR vs RB

PFS per età

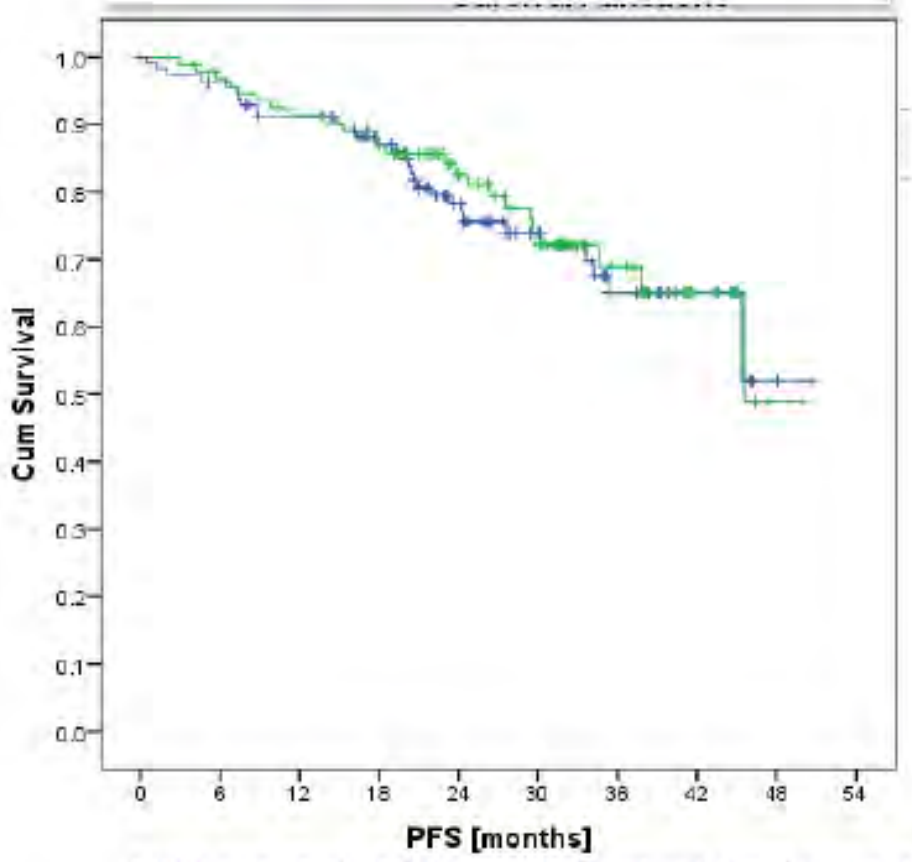
Patients < 65 years $p = 0.016$

FCR not reached
BR 38.5 months

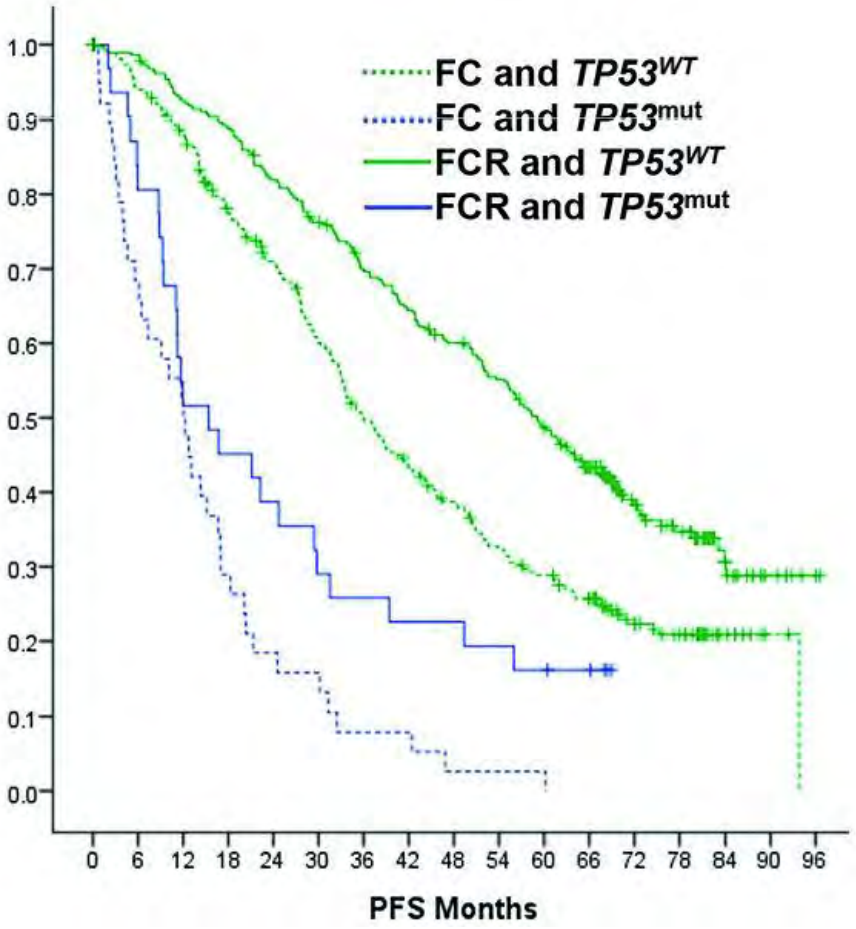


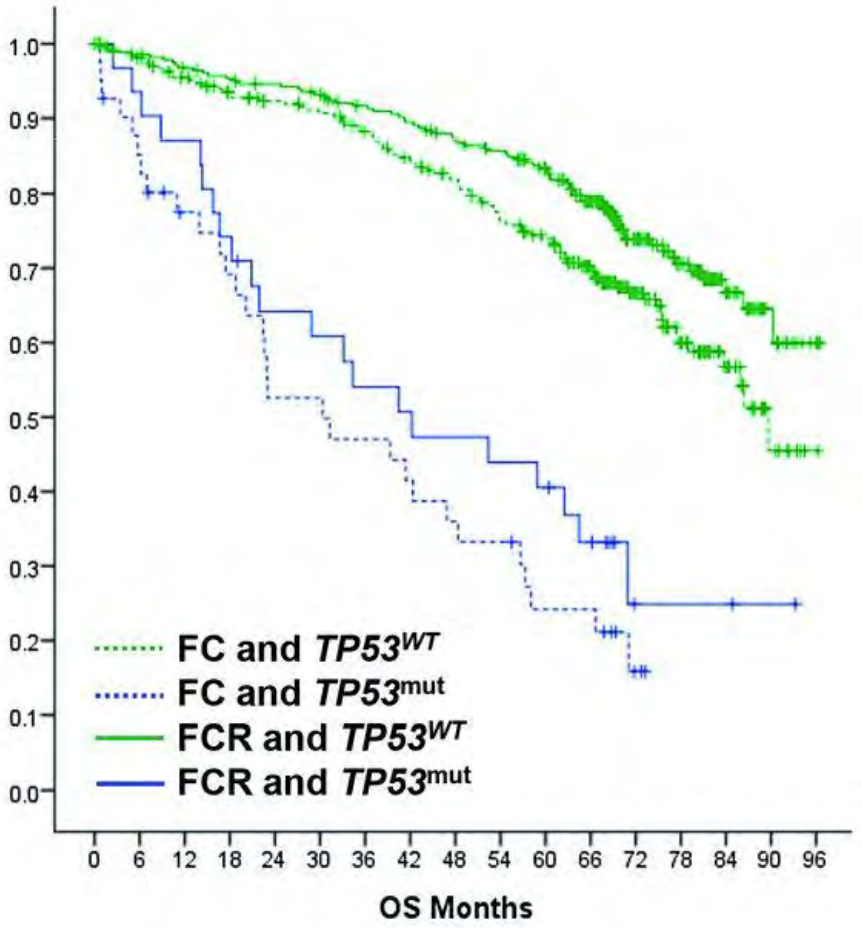
Patients ≥ 65 years: $p = 0.757$

FCR 45.6 months
BR not reached



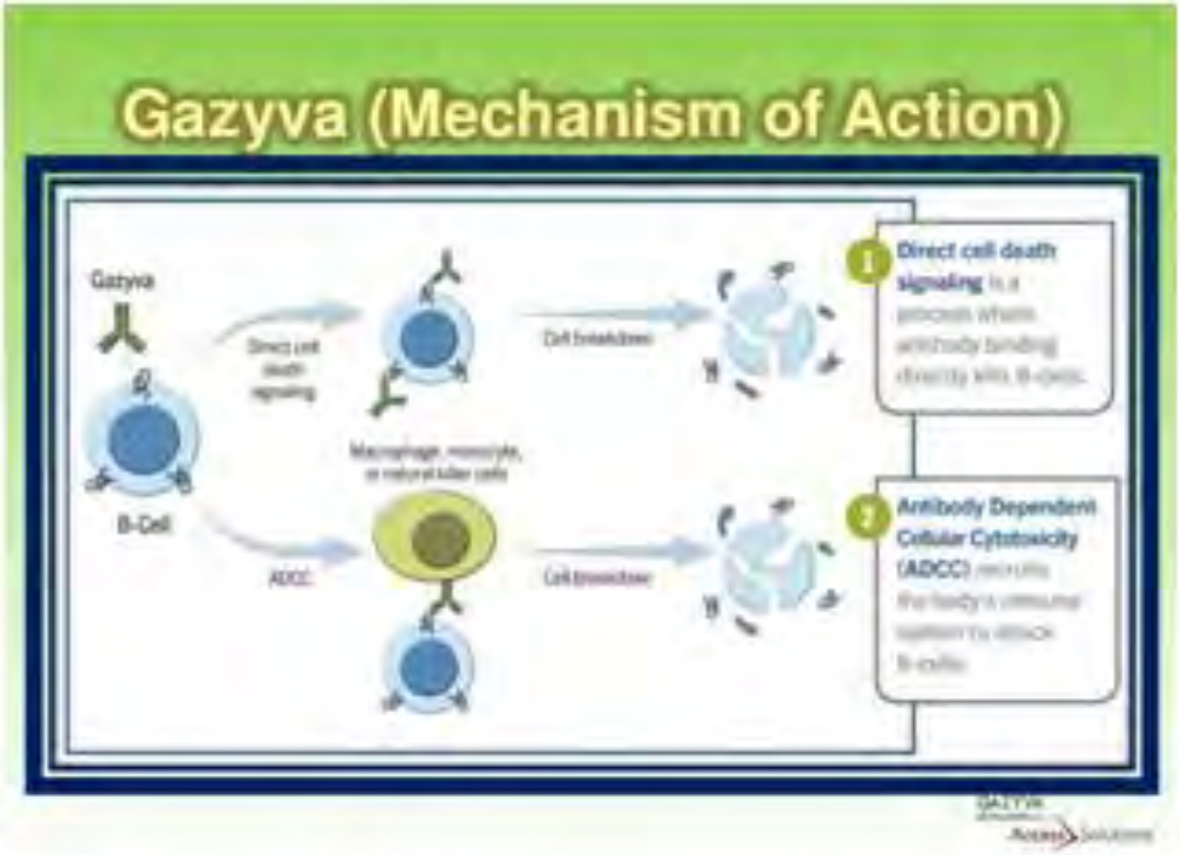
Eichhorst et al., ASH 2013; abstract 526 (oral presentation)



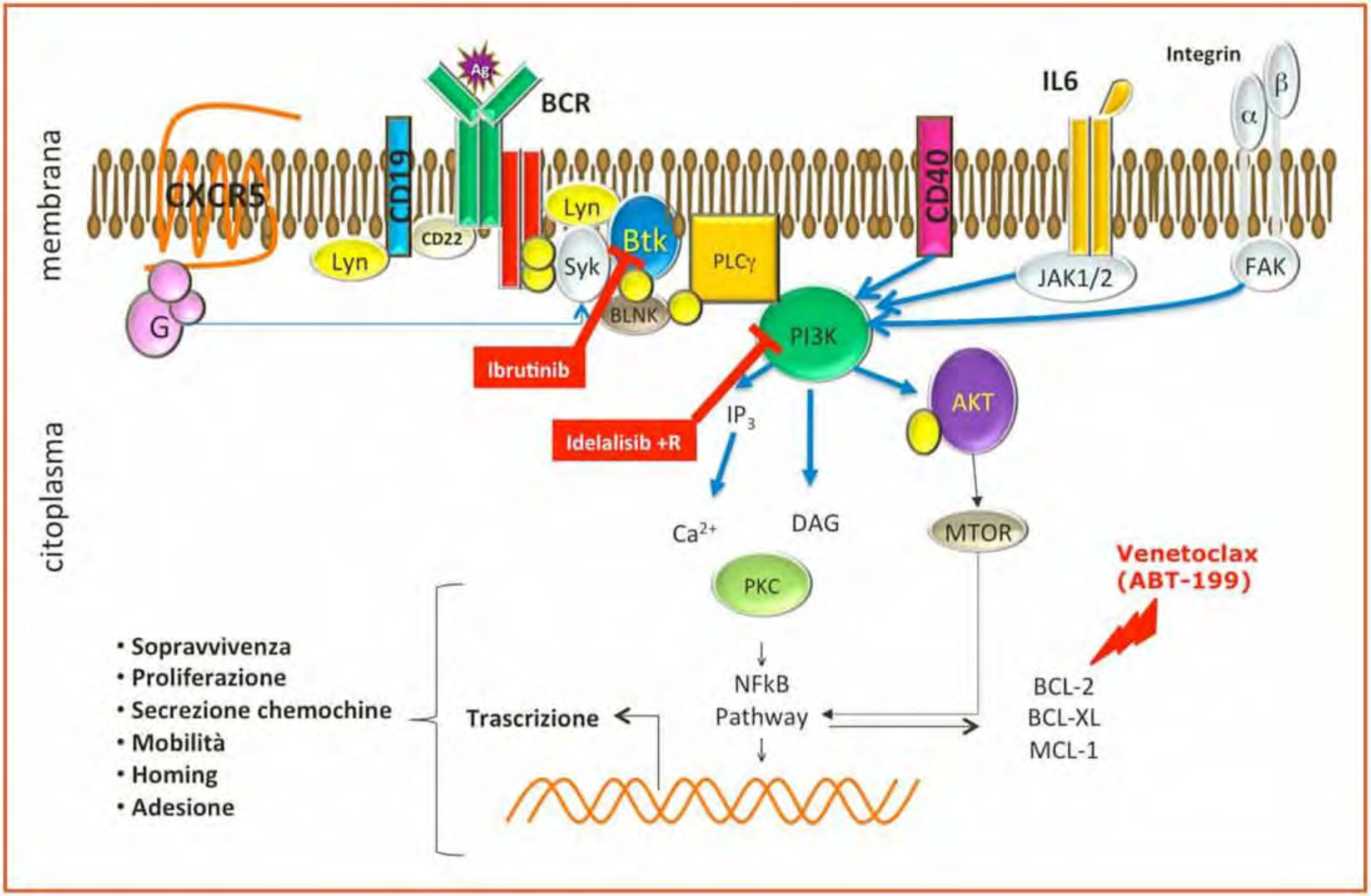


FCR e mutazione TP53

OBINUTUZUMAB



NUOVI FARMACI



Farmaci che interferiscono con il signaling intracellulare o con il BCL.2

B-cell receptor signaling

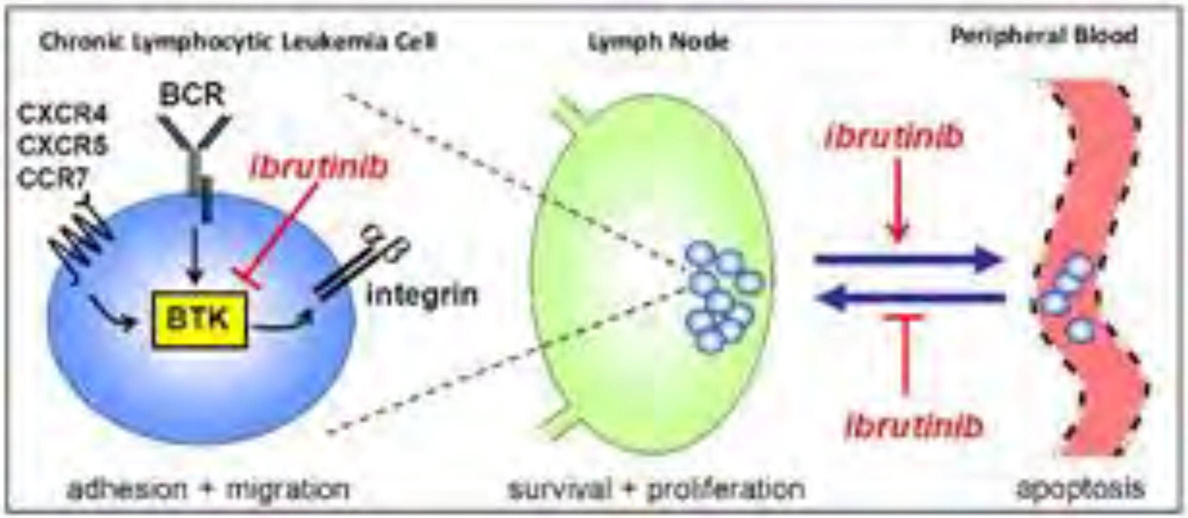
Bruton's tyrosine kinase (BTK)

- is a non-receptor kinase
- its function is essential to normal B cells
- is phosphorylated by SYK and then phosphorylates phospholipase Cγ2, leading to activation of protein kinase C beta and, in turn, CARD11

Phosphoinositide 3-kinase (PI3K)

- PI3K/AKT pathway is critical for essential cellular processes such as metabolism, growth, and proliferation
- The p110 delta and p110 gamma isoforms are expressed primarily in cells of hematopoietic origin

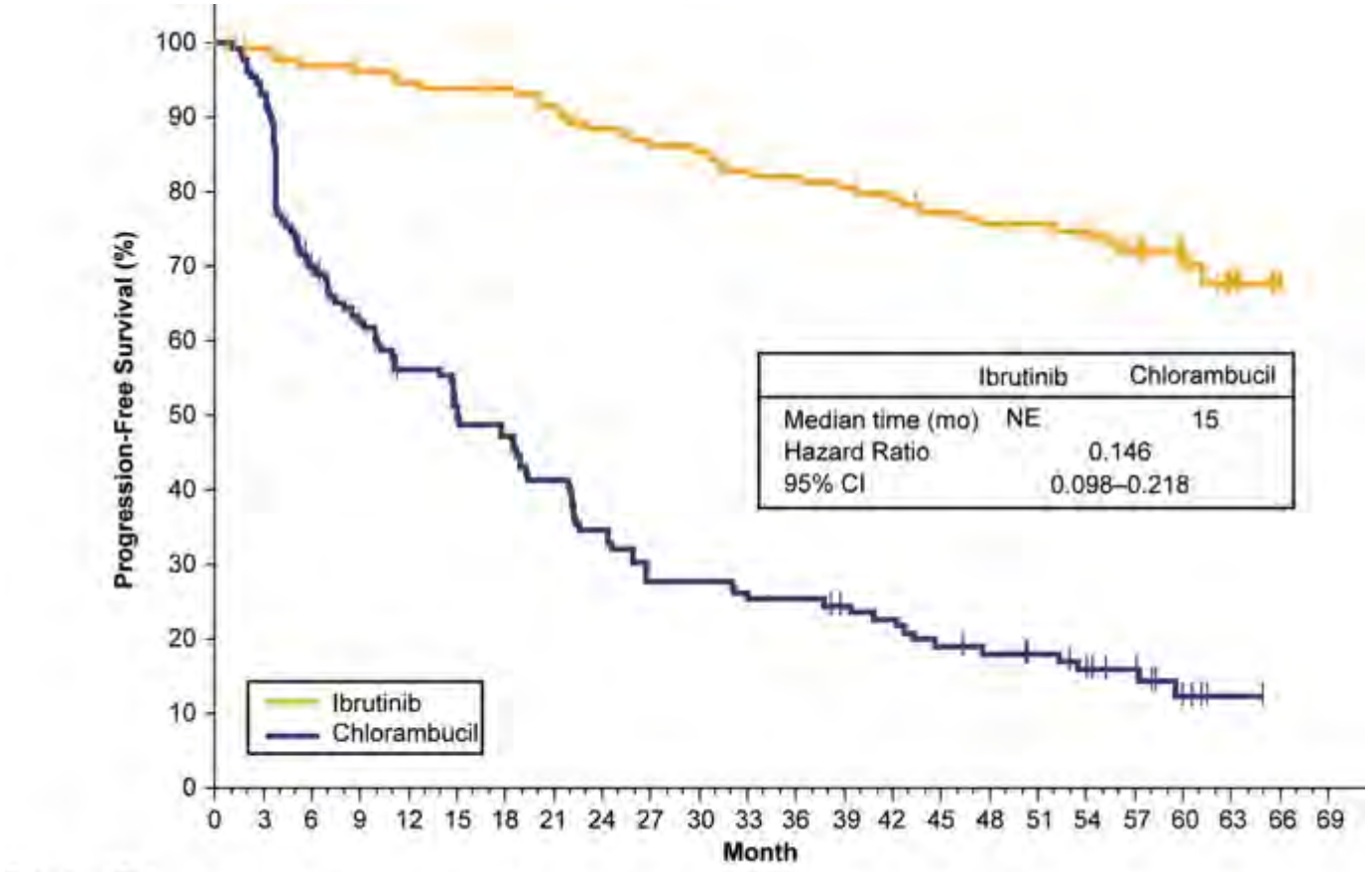
Mechanism of BTK: IMBRUVICA (ibrutinib – PCI-32765) Blocks Malignant B-cell Growth and Proliferation



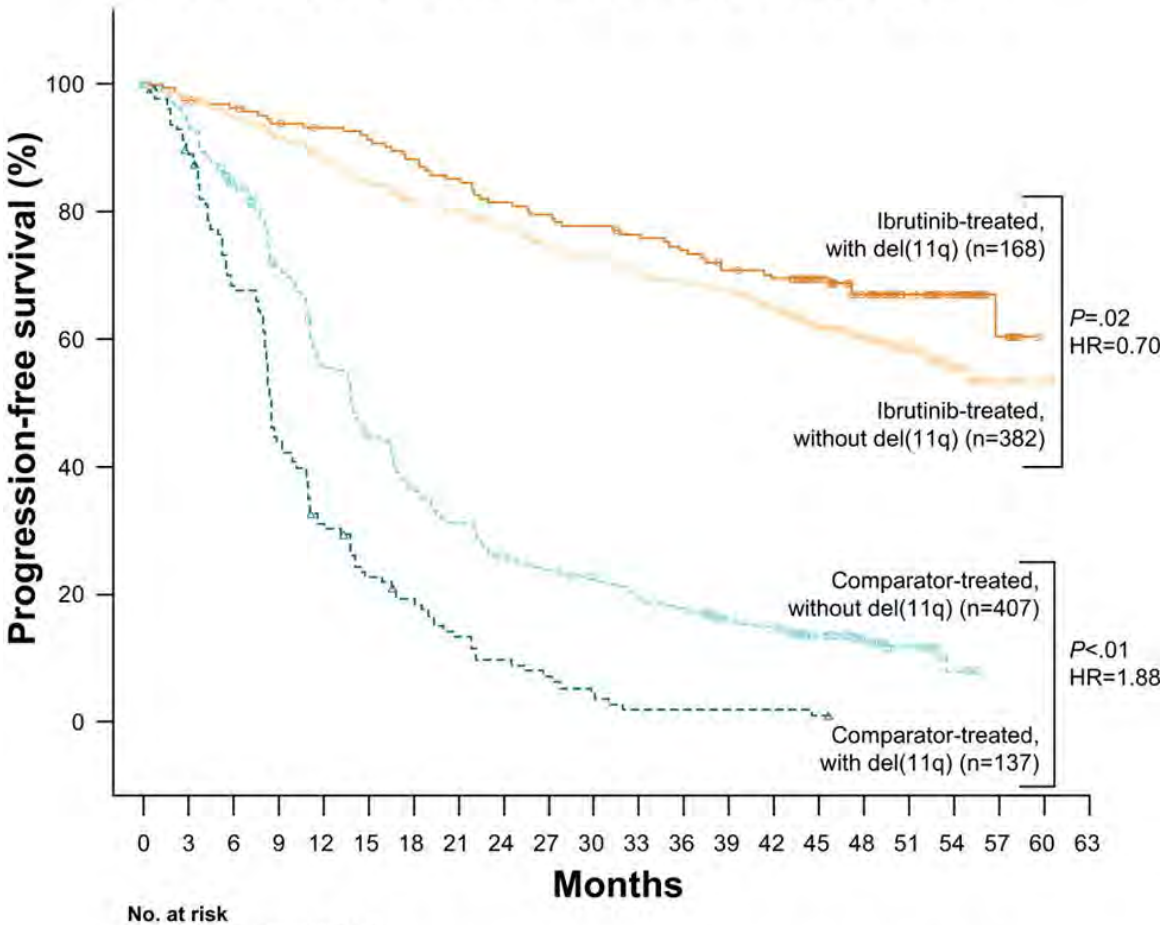
From de Rooij et al. Blood 119: 2590-2594

Ibrutinib

Oral drug
Favorable side effect profile
Extremely active in both CLL and mantle cell lymphoma
FDA will meet in early 2014 to consider approval in both


Progression-Free Survival (%)
100
90
80
70
60
50
40
30
20
10
0
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48 51 54 57 60 63 66 69
Month
Ibrutinib
Chlorambucil
Ibrutinib Chlorambucil
Median time (mo) NE 15
Hazard Ratio 0.146
95% CI 0.098–0.218
Patients at Risk
Ibrutinib: 136 133 129 126 124 123 121 118 112 109 108 104 103 101 98 93 91 90 87 79 34 17 1
Chlorambucil: 133 121 88 78 69 61 57 49 41 33 33 31 30 27 25 21 19 17 14 11 4 1

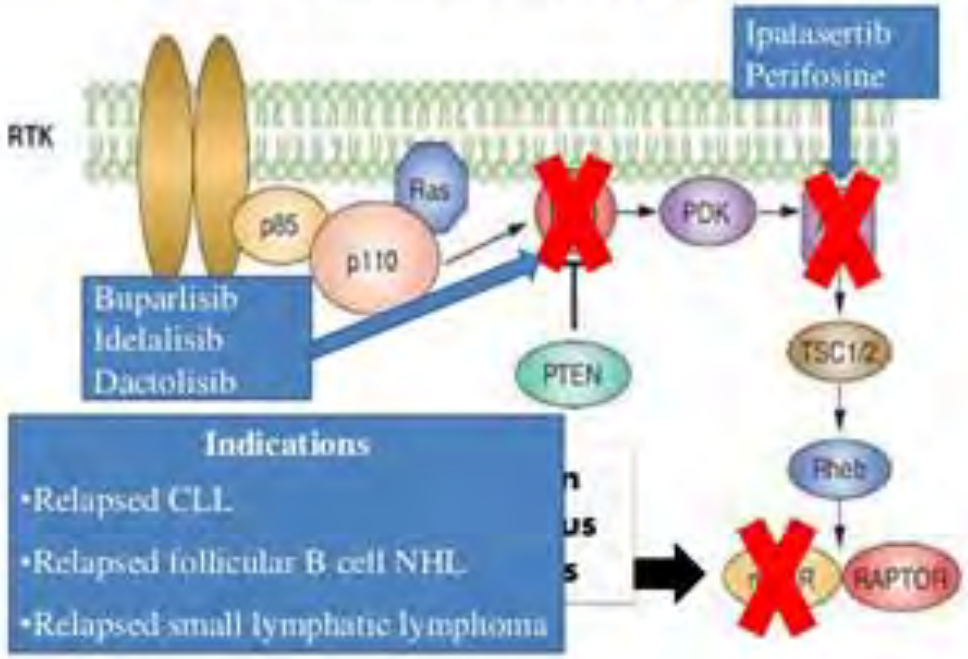
Progression-free survival in ibrutinib-treated and comparator-treated patients by del(11q) status



No. at risk

Ibrutinib, without del(11q)	382	367	353	339	325	310	297	291	280	266	259	252	244	240	226	172	128	79	40	7	2	0
Comparator, without del(11q)	407	377	330	276	216	172	138	119	98	89	83	71	65	53	49	32	22	12	4	0	0	0
Ibrutinib, with del(11q)	168	161	158	153	150	147	142	137	131	128	125	122	118	112	109	92	74	52	37	9	0	0
Comparator, with del(11q)	137	113	86	55	38	27	22	15	11	8	6	2	2	2	2	1	0	0	0	0	0	0

PI3K/PKB(Akt) /MTOR inhibitors

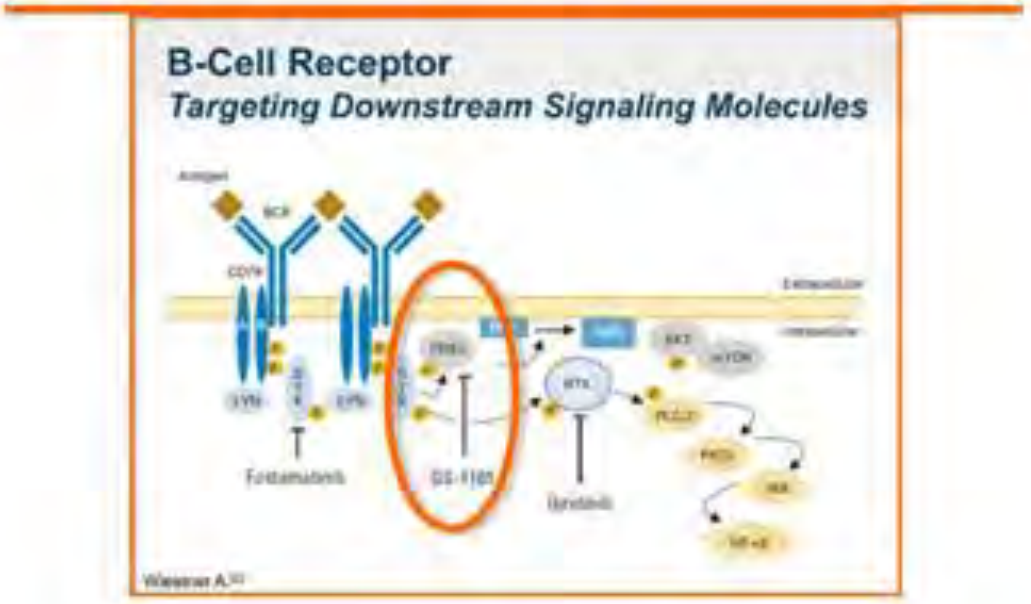


Indications

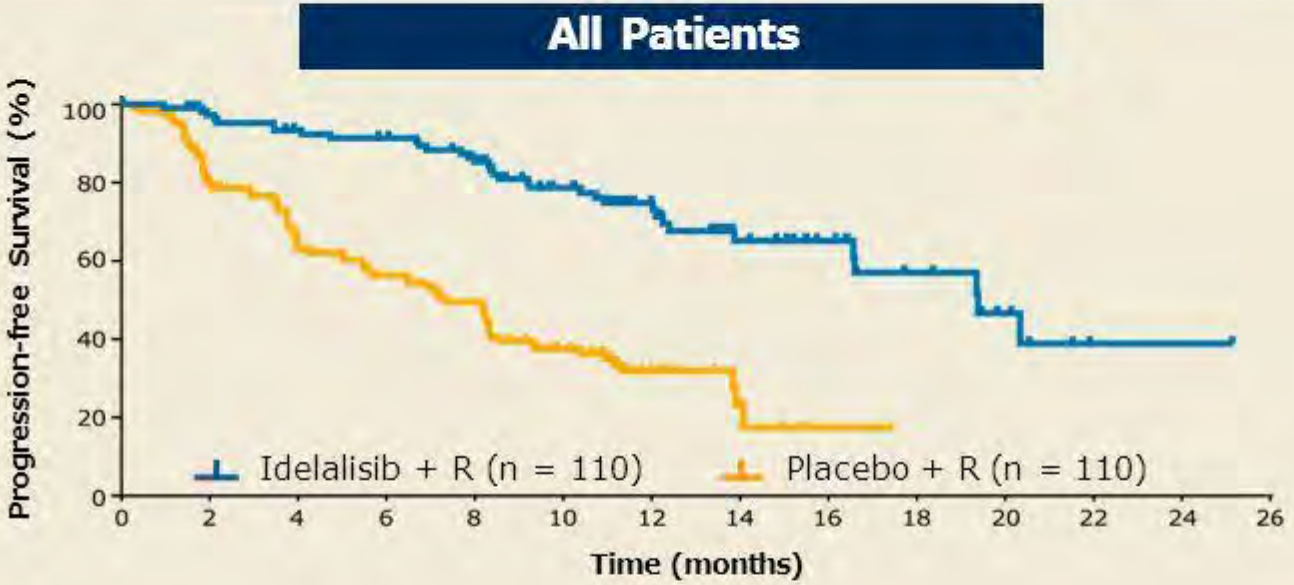
- Relapsed CLL
- Relapsed follicular B cell NHL
- Relapsed small lymphatic lymphoma

inibisce la fosfatidilinositolo 3-chinasi p110δ (PI3Kδ), che è iperattiva nelle neoplasie delle cellule B ed è fondamentale per molte vie di segnalazione che guidano la proliferazione, la sopravvivenza, la migrazione e la ritenzione delle cellule neoplastiche nei tessuti linfatici

Idelalisib



PFS (Including Extension Study*)



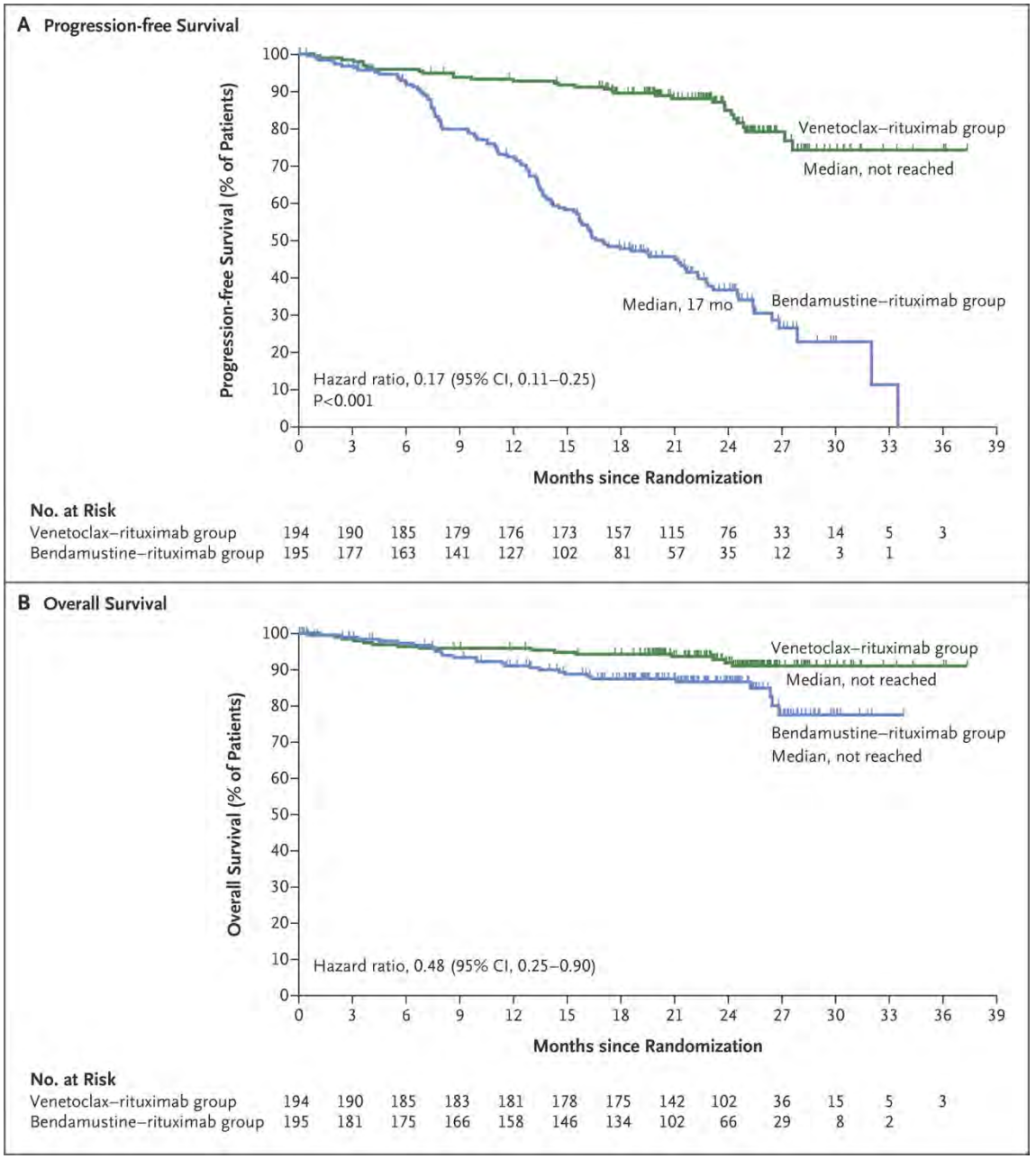
	Median PFS	HR	*p*-value
IDELA + R	19.4 mo	0.25	<0.0001
PBO + R	7.3 mo		

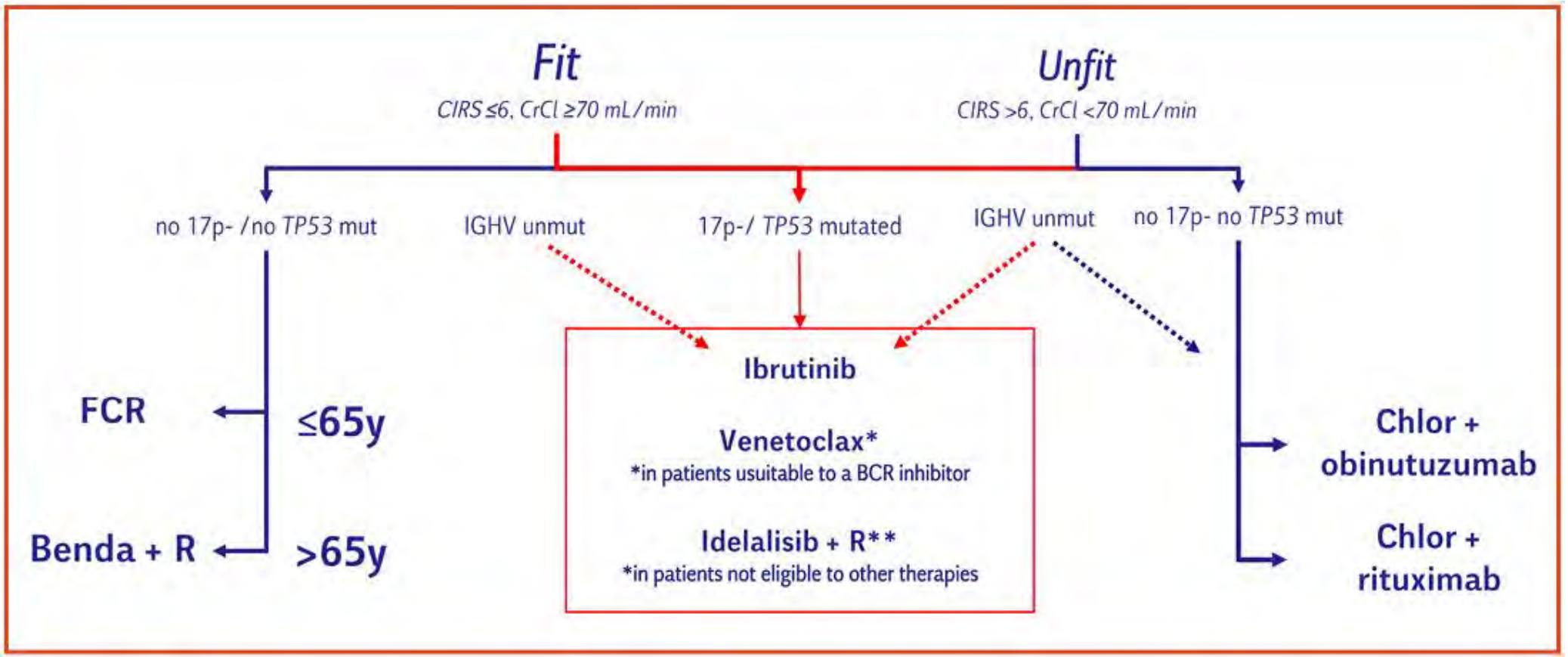
* Placebo + R includes those patients who received open-label idelalisib after unblinding without prior disease progression (n = 42).

With permission from Sharman JP et al. *Proc ASH* 2014;Abstract 330.

VENETOCLAX

Inibitore del BCL-2 (C-cell lymphoma 2)proteina che regola l'apoptosi di alcune cellule tra cui linfociti.




Fit
CIRS ≤6, CrCl ≥70 mL/min
Unfit
CIRS >6, CrCl <70 mL/min
no 17p- /no TP53 mut
IGHV unmut
17p-/ TP53 mutated
IGHV unmut
no 17p- no TP53 mut
FCR
≤65y
Benda + R
>65y
Ibrutinib
Venetoclax*
*in patients usuitable to a BCR inhibitor
Idelalisib + R**
*in patients not eligible to other therapies
Chlor + obinutuzumab
Chlor + rituximab