Leucemia Linfatica Cronica
Terapia di I linea

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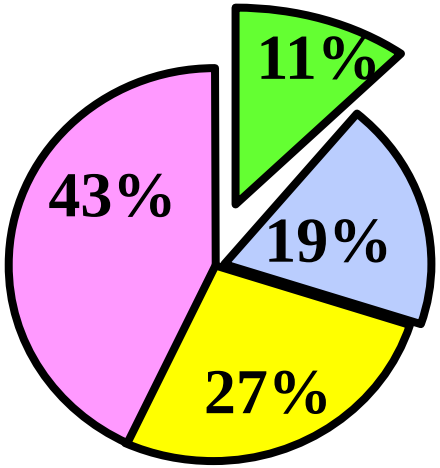
EPIDEMIOLOGIA

Leucemia cronica più frequente nel mondo occidentale

- **incidenza 4/100.000 anno**
- **età > di 80 anni 30/100.000 anno**
- **età mediana alla diagnosi 72 anni**

INCIDENZA DI LLC PER FASCIA D'ETA'

< 54	aa	11%
55-64	aa	19% dei casi
65-74	aa	27% dei casi
> 75	aa	43% dei casi

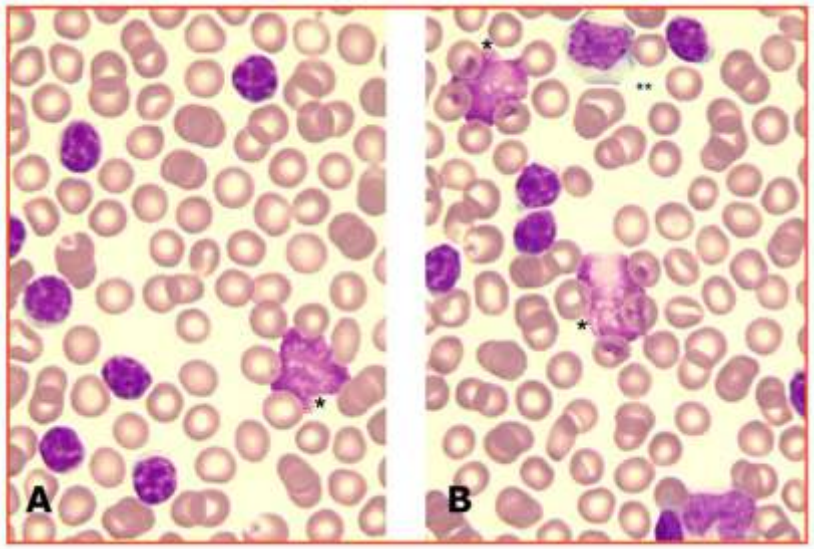


DIAGNOSI

- linfociti B > 5000/mmc sangue periferico per almeno tre mesi e dimostrazione di clonalità in citoflussimetria

morfologia tipica:

- piccoli linfociti maturi con scarso citoplasma, nucleo denso senza nucleoli evidenti e qualche aggregato cromatinico
- linfociti grandi e prolinfociti < 55%, una presenza di prolinfociti > 10% sembra indicare un una forma più aggressiva (con NOTCH1 o alterazioni di TP53)
- ombre di Gumprecht



Immunofenotipo

CD5+, CD19+, CD23+, ridotta espressione delle catene leggere K o lambda CD 200 positive, CD20 e CD79b poco espressi

Hallek Blood 2017

blood®
Prepublished online March 14, 2018;
doi:10.1182/blood-2017-09-806398

Guidelines for diagnosis, indications for treatment, response assessment and supportive management of chronic lymphocytic leukemia

Michael Hallek, Bruce D. Cheson, Daniel Catovsky, Federico Caligaris-Cappio, Guillermo Dighiero, Hartmut Döhner, Peter Hillmen, Michael Keating, Emili Montserrat, Nicholas Chiorazzi, Stephan Stilgenbauer, Kanti R. Rai, John C. Byrd, Barbara Eichhorst, Susan O'Brien, Tadeusz Robak, John F. Seymour and Thomas J. Kipps

Obligatori **prima di decidere di iniziare un trattamento**

- **Anamnesi e visita clinica con valutazione delle adenopatie superficiali**
- **Emocromo con formula leucocitaria**
- **ematochimici con creatinina, LDH, bilirubina, dosaggio Ig**
- **Test di Coombs**
- **Markers epatite HBV, HCV, CMV e HIV.**
- **Rx torace 2P ed ecografia addome completo**
- **TAC collo, torace ed addome se clinicamente indicata**

RAI STAGING SYSTEM

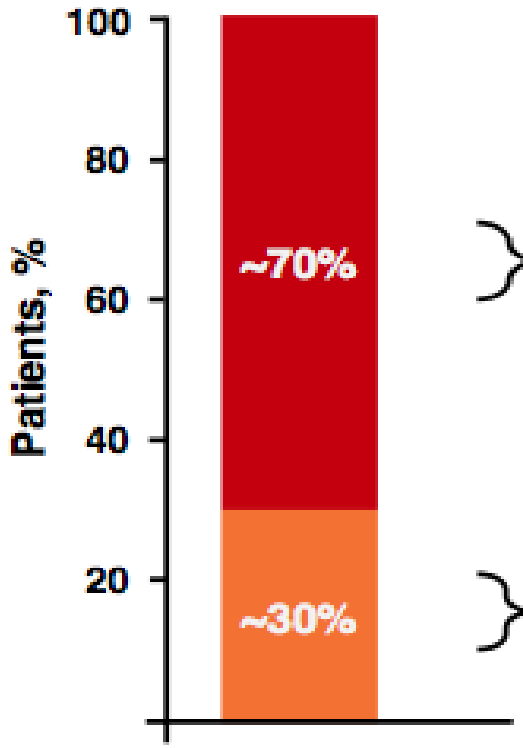
stage	Rai mod. stage (risk)	Clinical characteristics	median survival (years)
0	Low	only lymphocytosis in the peripheral blood and bone marrow infiltration (>30%)	> 10
I II	Intermediate	presence of lymphadenopathies presence of hepatosplenomegaly	6
III IV	High	presence of anemia (Hb <11 g/dl) presence of thrombocytopenia (PLTs <100 x 10^9/L)	2

BINET STAGING SYSTEM

stage	Clinical characteristics	median survival (years)
A	Hb ≥10 g/dL, platelets ≥100 x 10^9/L, and up to 2 lymphoid sites involved	> 7
B	Hb ≥10 g/dL, platelets ≥100 x 10^9/L, and >2 lymphoid sites involved	< 5
C	Hb ≤ 10 g/dL, platelets ≤100 x 10^9/L or both irrespective of lymphoid sites involved	< 2

involved sites: head and neck, including the Waldeyer ring, axillae, groins, palpable spleen, palpable liver

La maggior parte dei pazienti non necessita di terapia



Asymptomatic at diagnosis
- ~70% of patients
- Many will never progress
- Treatment is usually not required

Symptomatic at diagnosis
- ~30% of patients
- Shortened life expectancy
- Effective treatment becomes essential

Hamblin TJ, *et al. Br J Haematol* 1987; 66:21–26.

IWCLL 2017 revised guidelines indications for treatment

At least one of the following criteria should be met:

1) **progressive marrow failure** (development or worsening of anemia & / or thrombocytopenia)

2) **massive splenomegaly** (at least 6 cm below the left costal margin) or **progressive or symptomatic splenomegaly**

3) **massive nodes** (at least 10 cm in longest Φ) or **progressive or symptomatic lymphadenopathy** (development of enlarged nodes or >50% increase in longest diameter)

1. Hallek M, et al. *Blood*. 2008;111:5446-5456,
2. Hallek M. Am J Hematol. 2017;92:946-965.

IWCLL 2017 revised guidelines indications for treatment

4) **Progressive lymphocytosis** i.e. an increase of >50% over a 2-months period or lymphocyte doubling time (LDT) of <6 months.
- Patients with initial blood lymphocyte counts of <30.000/μL LDT may require a longer oservation period to determine LDT
- LDT should not be used as a single parameter to define a treatment indication.

Factors contributing to lymphocytosis or lymphadenopathy other than CLL (eg, infections) should be excluded

5) **Autoimmune anemia and/or thrombocytopenia** poorly responsive to corticosteroids or other standard therapy

6) **Constitutional symptoms,** (any one or more) of:
a. unintentional weight loss of ≥10% within the previous 6 months;
b. significant fatigue (ECOG PS ≥ 2; inability to work or perform usual activities);
c. fevers > 38.0° C for ≥ 2 weeks without other evidence of infection;
d. night sweats for > 1 month without evidence of infection

Biomarker: variable that associates with disease outcome

Host Factors: **Age, fitness**, sex, etc

Disease Markers: **Stage**, lymphocyte count, **LDT**, etc

Ag expression: CD38, Zap70, **CD49d**, etc

Serology: **Beta2M**, TK, LDH, sCD23, etc

Genetics: **del17p, TP53 mutation**, del11q22, del13q14, trisomy 12, NOTCH1 mutation, SFRB1 mutation, etc

Biology Markers: **IGVH-sequence**, BCR-structure

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Prognostic factors in daily practice:

- RAI e BINET stages help stratify patients according to the disease risk.

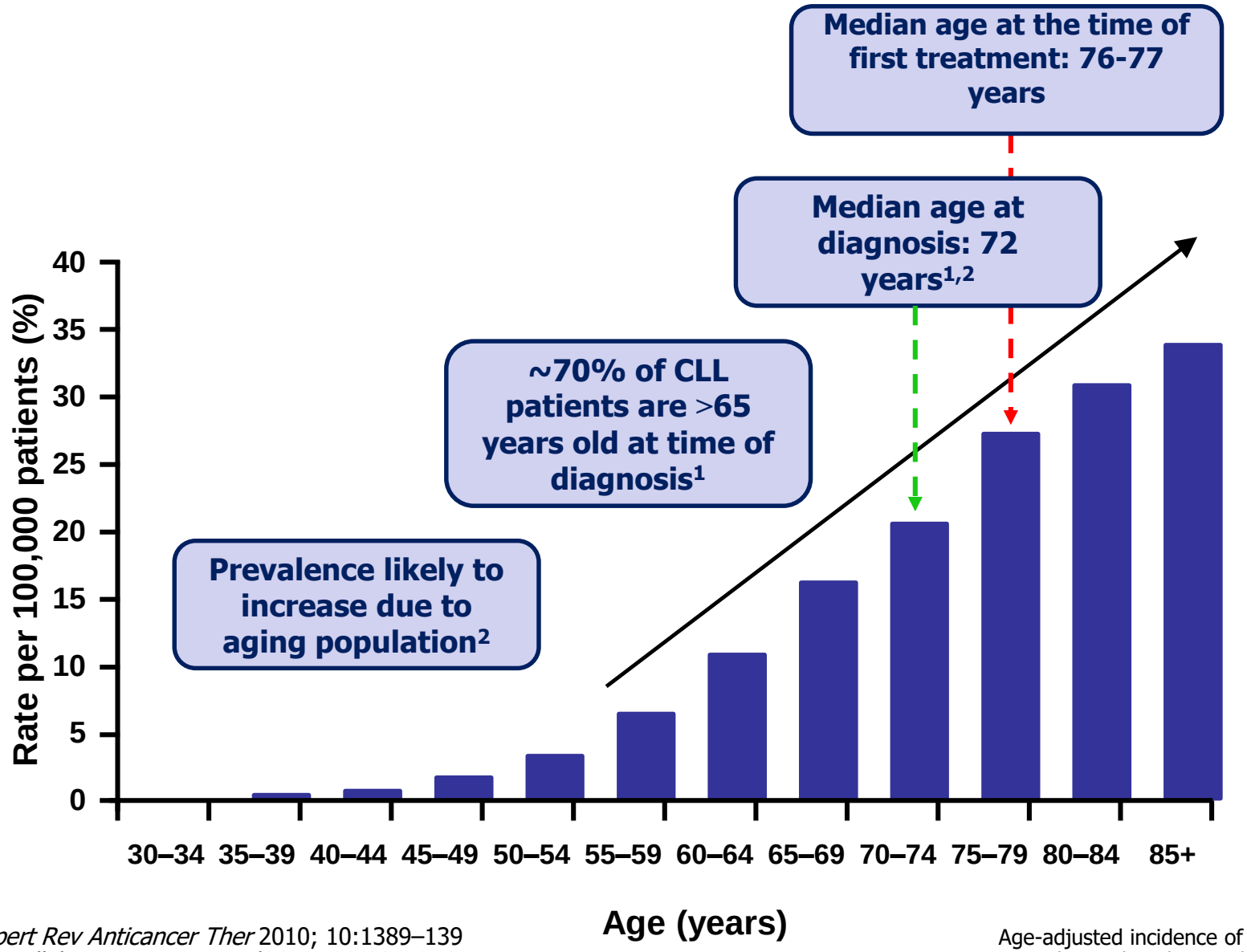
The most relevant prognostic parameters are **IGHV** mutational status, serum **ß2-microglobulin**, and the presence of **del(17p) and/or *TP53* mutations**. Usually, high-risk CLL is defined, at least in part, by a genetic aberration of the *TP53* gene (i.e. del(17p) or *TP53* mutation).

- The **assessment of both del(17p) and TP53 mutation** has prognostic and predictive value and should guide therapeutic decisions in routine practice.
- As additional genetic abnormalities may be acquired during the course of the disease, **genetic analyses (in particular for del(17p)/TP53 mutations) should be repeated prior to any subsequent, second- or third-line of treatment.**

Hallek M et al. *Blood* 2018; *doi: https://doi.org/10.1182/blood-2017-09-806398*

Età e fitness

CLL is a disease of the elderly



1. Gribben J. *Expert Rev Anticancer Ther* 2010; 10:1389–139
2. Hallek M. *Am J Hematol* 2013; 88:804–816.

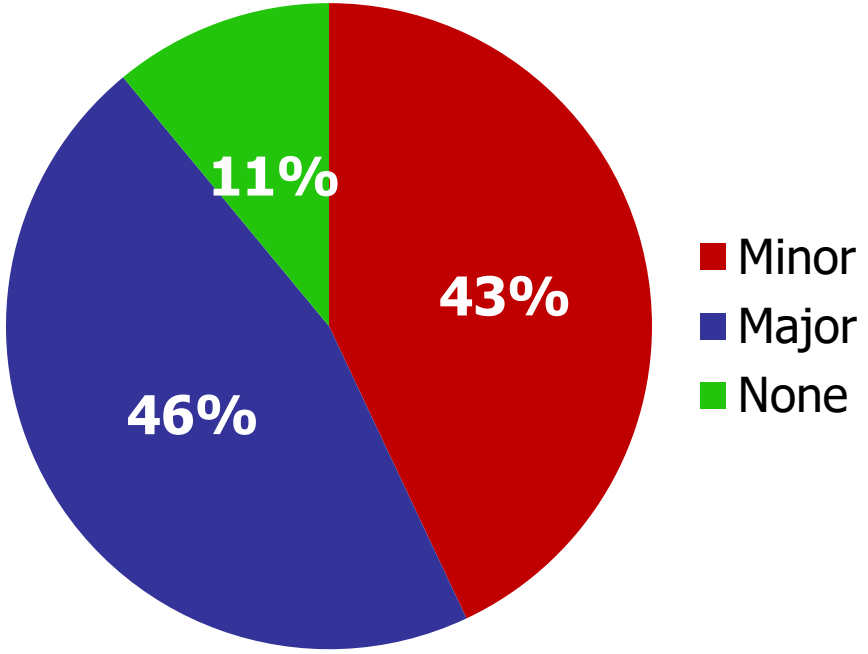
Age-adjusted incidence of CLL
CLL: chronic lymphocytic leukaemia

Most CLL patients have comorbidities at time of diagnosis

Retrospective Review of Unselected, Newly Diagnosed Patients with CLL (n=373, between january 1995-December 2006) at Mayo Clinic

- **Major comorbid conditions**
  - CAD/Perpheral vascular disease 16,1%
  - Cerebrovascular disease (stroke, TIA) 5,6%
  - Heart (cardiomyopathy, valvular disease, atrial fibrillation) 13,1%
  - Diabetes Mellitus (DM) 11%
  - Respiratory 7%
- **Malignancy prior to CLL (any)** 13,9%
- **At least one major comorbidity** 46,1%

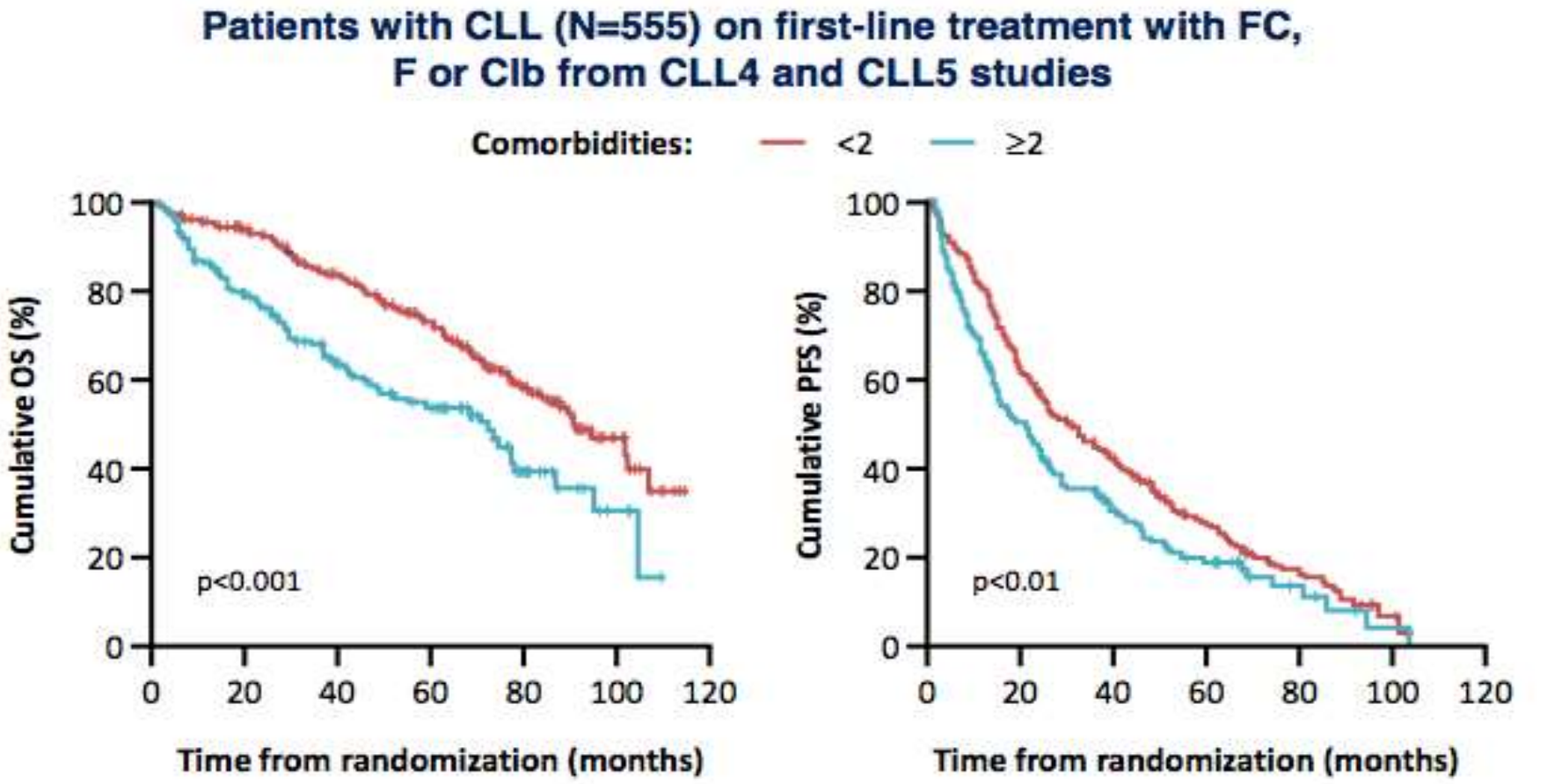
- **Other**
  - **Hypertension 46,1%**
  - **Rheum/joint 44,5%**
  - **Hyperlipidemia 33,5%**
  - **.....**



Nearly 90% of CLL patients had ≥1 comorbid condition

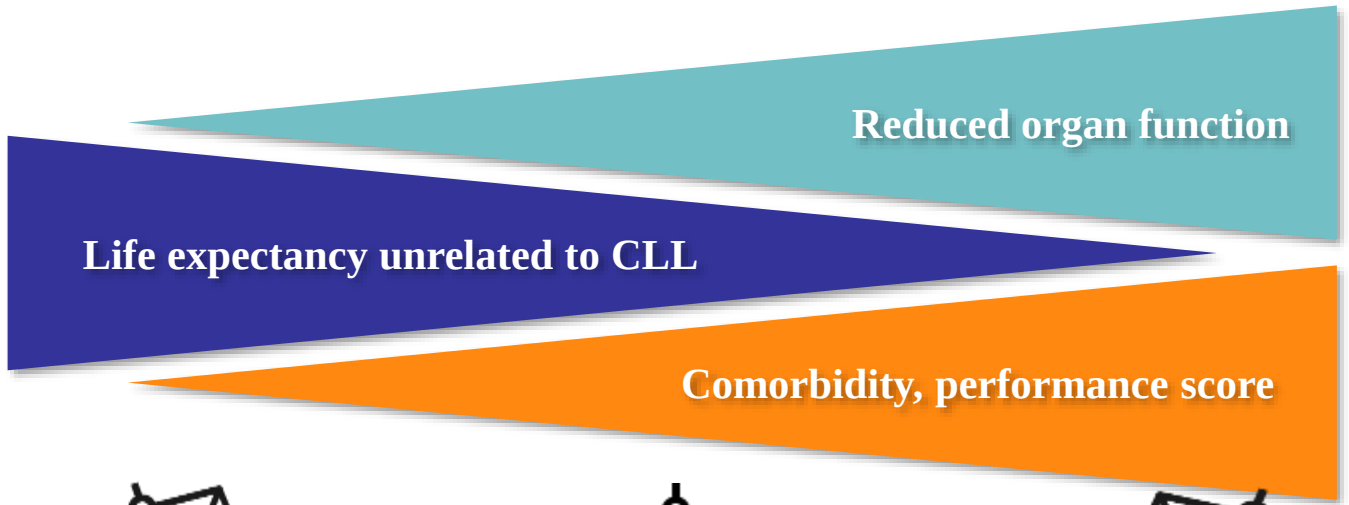
Thurmes P, et al. *Leuk. Lymphoma*. 2008;49:49–56

Le comorbidità si associano ad una prognosi peggiore



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

Determining the goals of treatment for older patients with CLL



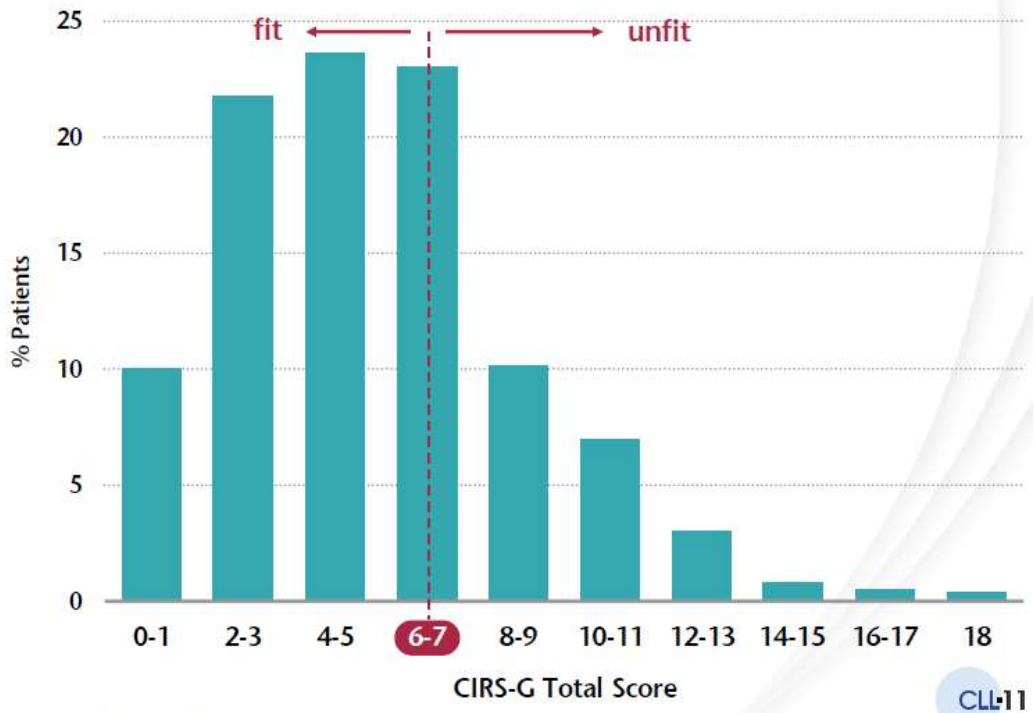
	Deep remission	Balance of efficacy/toxicity	Do no harm
Goal:	MRD negative remission	Good response	Palliation
Priority:	Efficacy	Combination efficacy and tolerability	Low toxicity

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

Systems Assessed
Cardiac
Vascular
Hematological
Respiratory
Ophthalmological and ORL
Upper gastrointestinal
Lower gastrointestinal
Hepatic and pancreatic
Renal
Genitourinary
Musculoskeletal and tegumental
Neurological
Endocrine, metabolic, breast
Psychiatric

Total score:

Severity rating in the CIRS scoring system	
0	No problem affecting that system
1	Current mild problem, does not interfere with normal activity or past significant problem
2	Interferes with normal activity and/or requires therapy
3	Severe problem and/or constant and significant disability and/or hard to control chronic problem
4	Extremely severe problem and/or treatment is urgent and/or severe functional impairment or organ failure



Extermann et al., JCO 1998

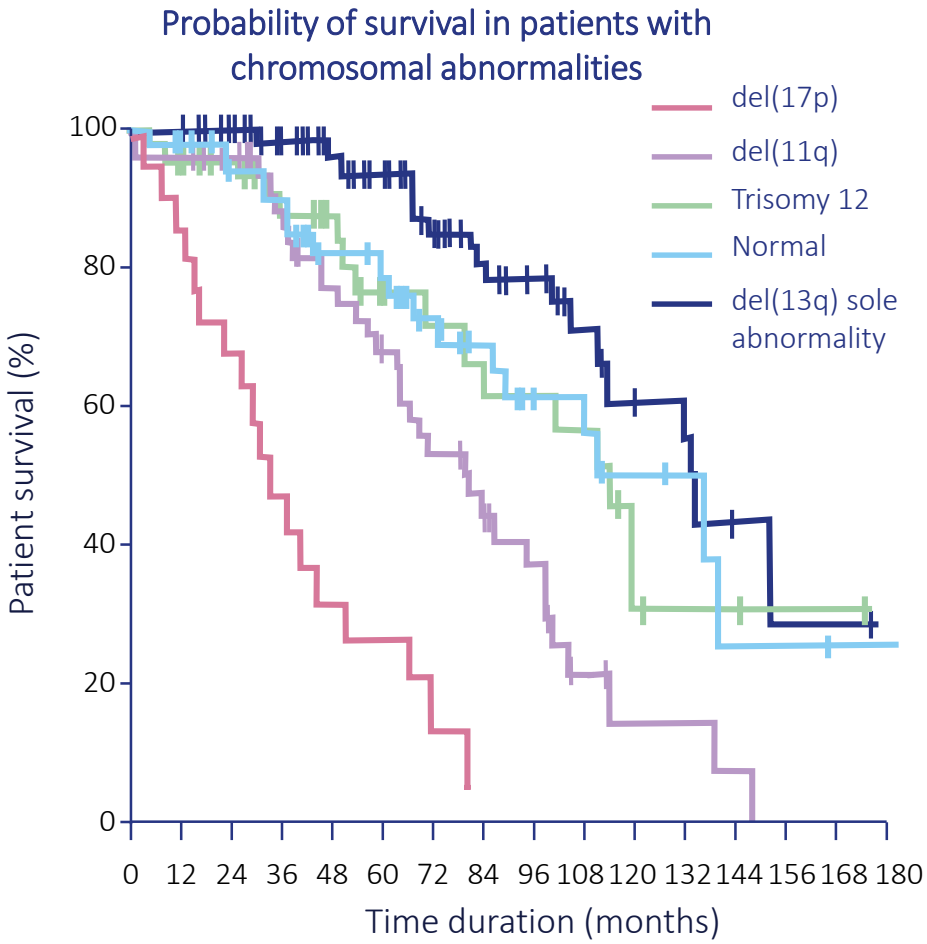
SIOG recommendation for categorization of elderly patients with CLL according

Robust/Fit	Vulnerable/Unfit	Terminally ill
Normal renal function **AND** No/minor comorbidity **AND** Lack of geriatric impairments	Abnormal renal function **OR** Moderate/severe comorbidity or multimorbidity **OR** Geriatric impairments	Age adjusted life expectancy unrelated to CLL <3 months
Suitable for intensive therapy **INTENSIVE THERAPY** **(GO)**	Unsuitable for intensive therapy **ADAPTED THERAPY** **(SLOW)**	Unsuitable for antileukemic therapy **BEST SUPPORTIVE CARE** **(NO)**

Adapted from Stauder R et al Annals of Oncol 2016

Rischio genetico

TP53 aberrations are associated with a poorer outcome than many other genetic mutations in CLL



- *TP53* aberrations are associated with one of the **poorest OS rates** and the **shortest times to treatment** compared with other genetic/chromosomal abnormalities or clinicobiological features

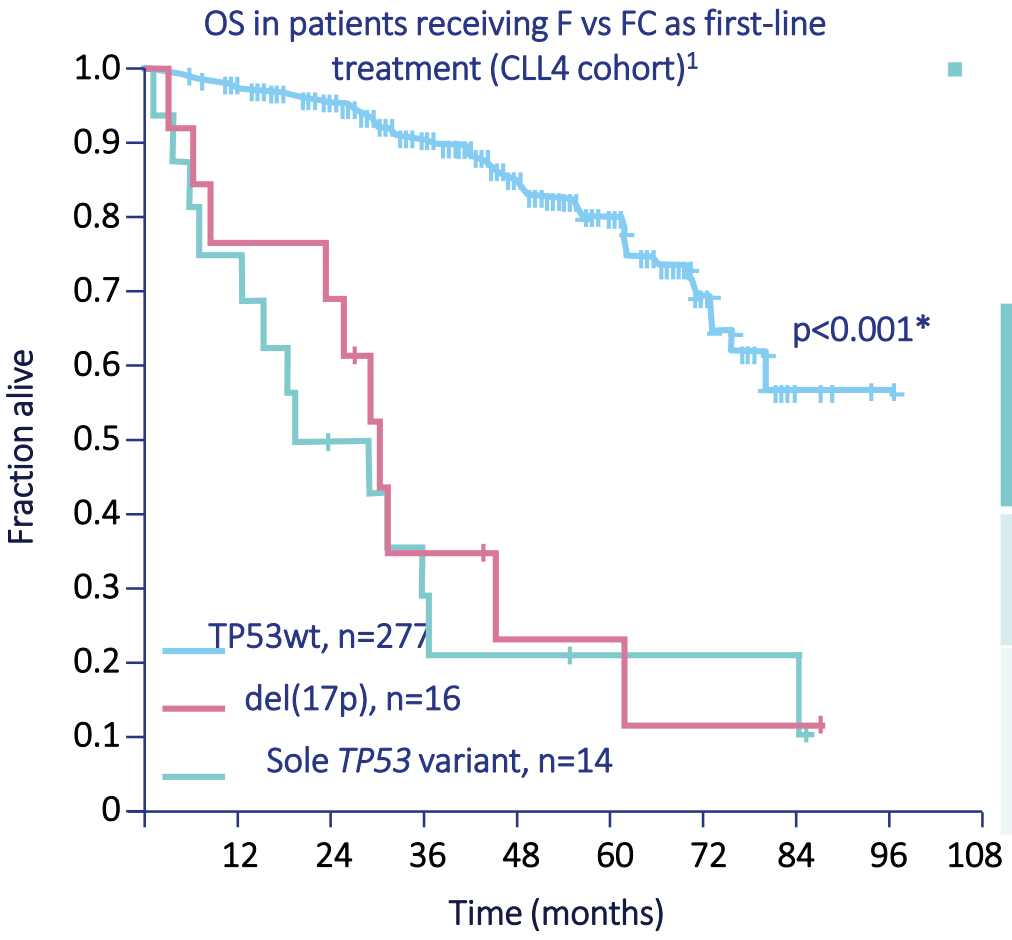
Variable	HR for death (CI)
del(17p)	8.08 (4.24–15.40)
No del(11q) del(11q)	2.04 (1.56–2.67) 1.12 (0.74–1.69)
Binet stage: B vs A C vs A	 1.27 (0.76–2.13) 3.77 (1.64–8.66)

Cox regression analysis of survival time from diagnosis

CI, confidence interval; HR, hazard ratio; OS, overall survival.

Döhner, H *et al. N Engl J Med* 2000;**343**:1910–6.

TP53 variants and del(17p) are independent prognostic markers of poor survival in CLL



- Patients with sole *TP53* variants have a similar adverse prognosis as those with del(17p)[1]

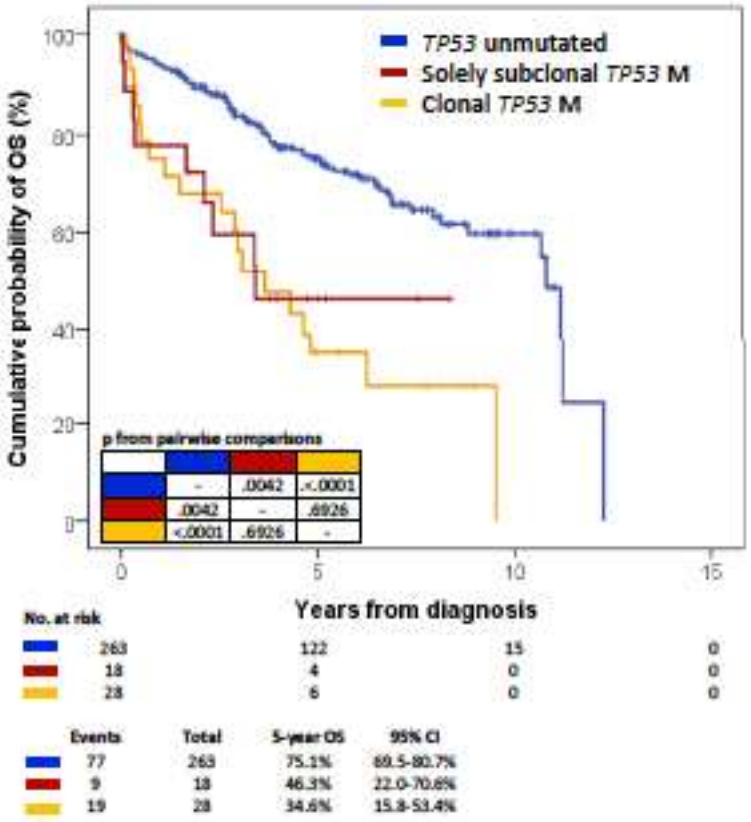
	del(17p)	Sole *TP53* variant	wt
Median OS (months)	19.2	30.2	NR
HR†	2.31 (p=0.029) *	7.24 (p<0.001) *	–

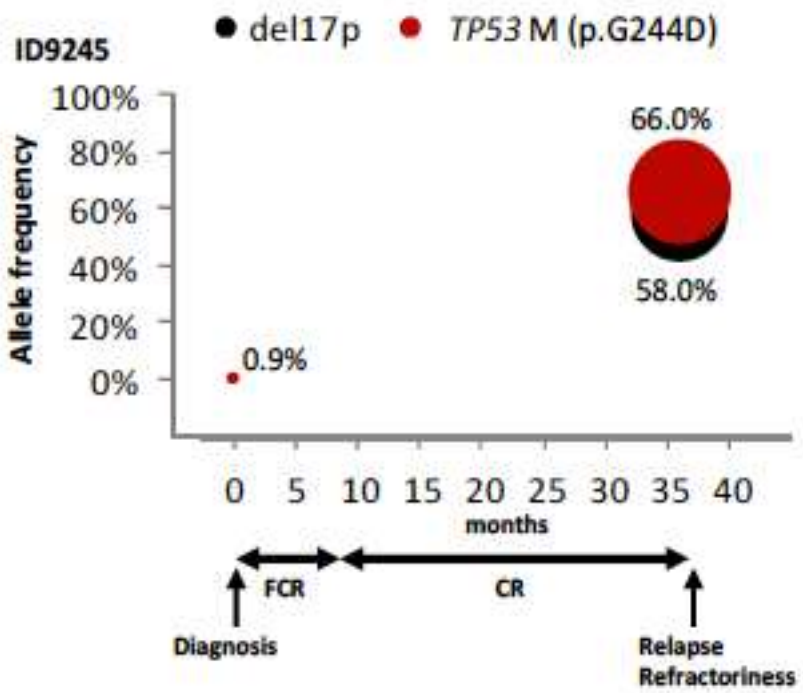
*del(17p) and sole *TP53* variant versus wt; †Multivariate Cox regression analysis of OS.

F, fludarabine; FC, fludarabine, cyclophosphamide; NR, not reached.

1. Zenz T, *et al. J Clin Oncol* 2010;**28**:4473–9.

Small *TP53* mutated subclones have the same unfavorable prognostic impact as clonal *TP53* defects

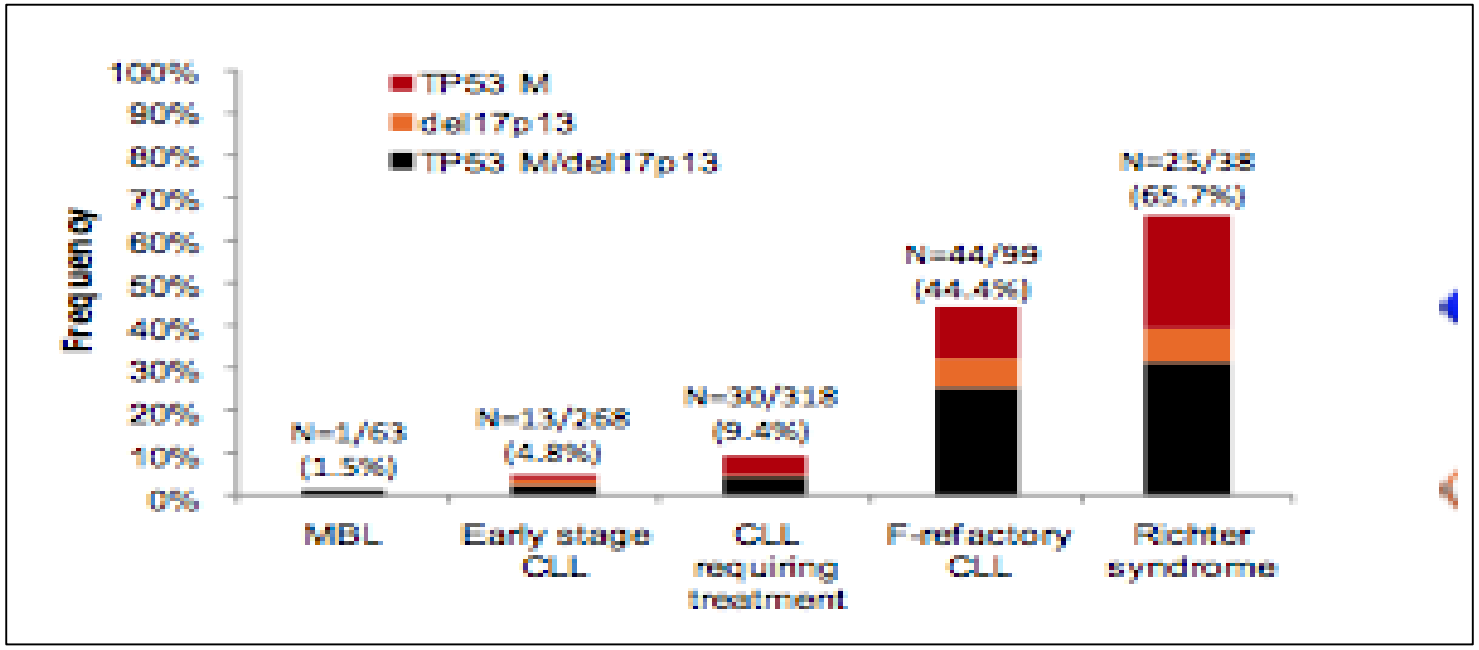




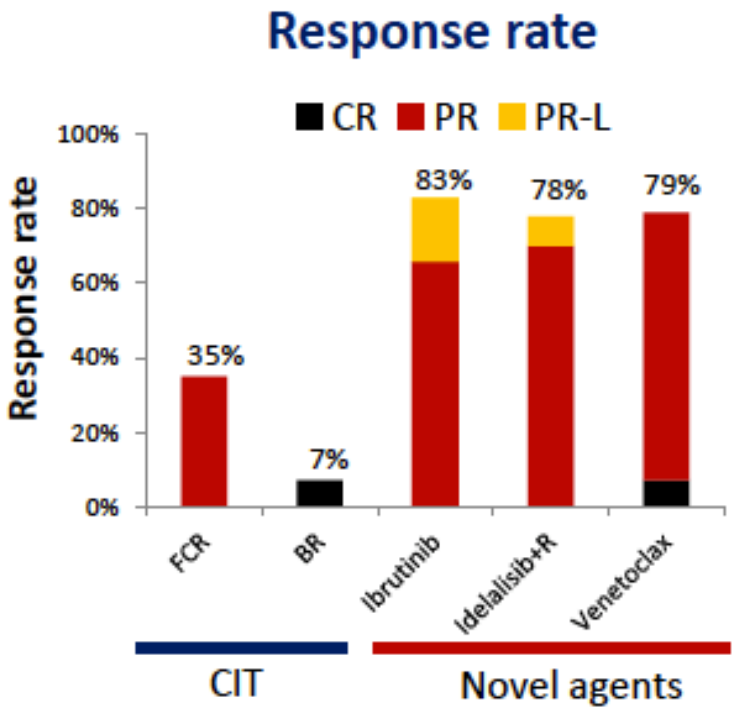
Rossi, Blood 2014

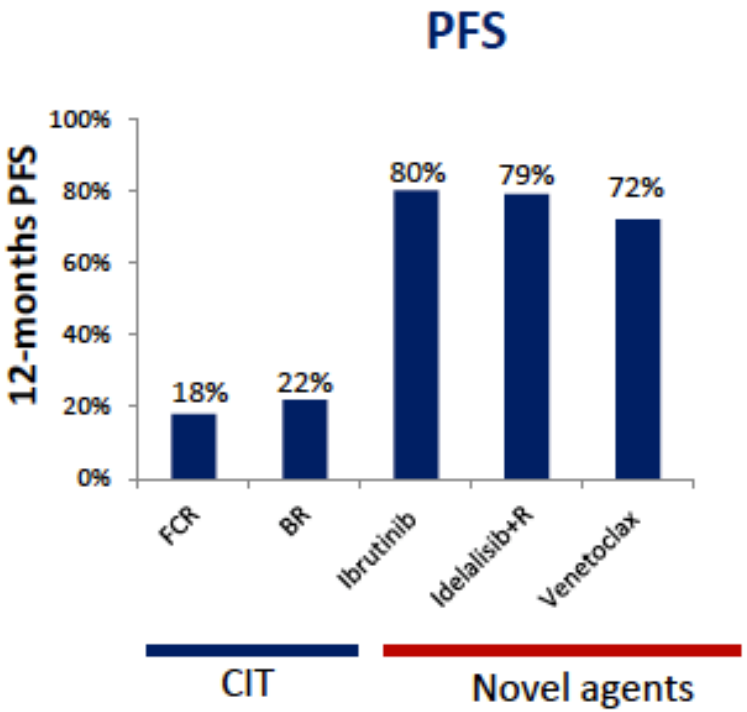
Delezione 17p e TP53

Più frequenti con la progressione della malattia



Chemoimmunotherapy (CIT) vs novel agents in *TP53* disrupted CLL



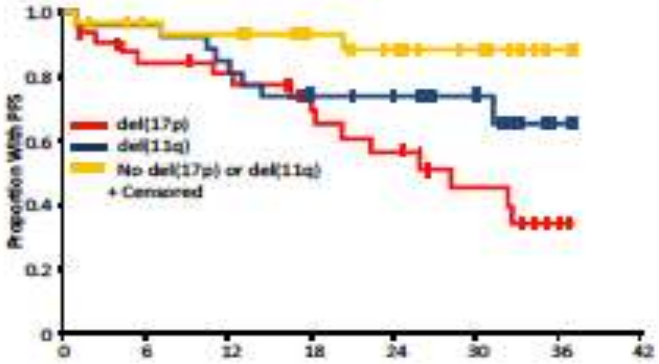


Badoux Blood 2011; Fisher J Clin Oncol 2011; O'Brien, Lancet Oncol 2016; Sharman ASH 2014; Byrd ASH 2015; Stilgenbauer, Lancet Oncol 2016; Jones, EHA 2016

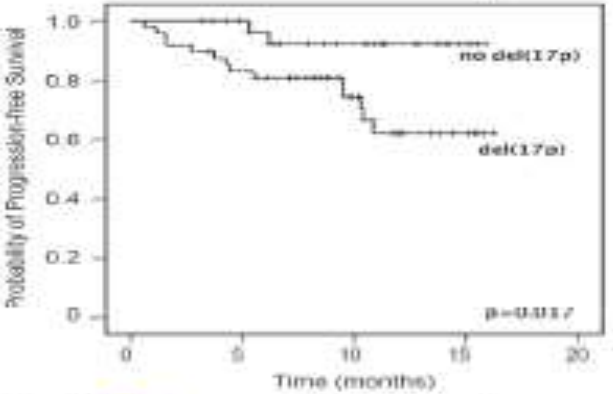
TP 53 e nuovi farmaci

TP53 disruption is a prognostic biomarker in CLL treated with novel agents

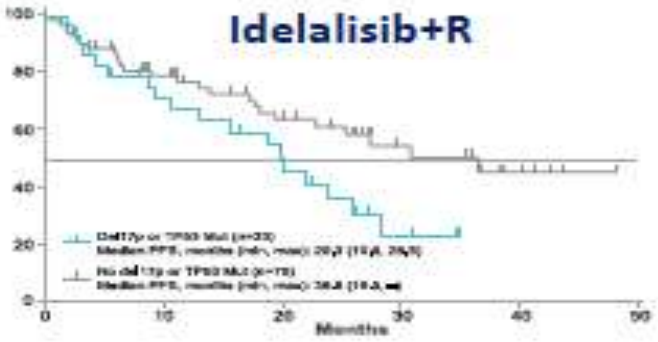
Ibrutnib in trials



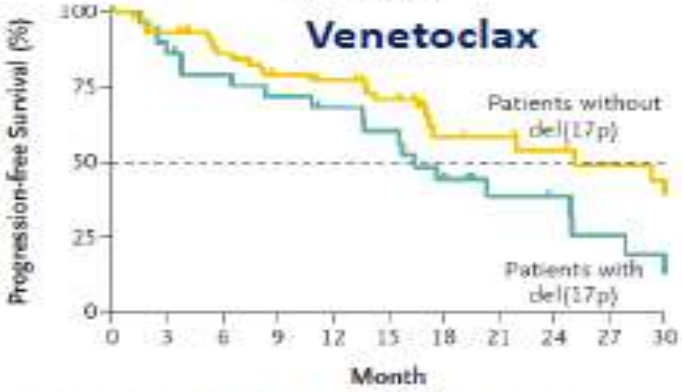
Ibrutinib in real-world practice



Idelalisib+R

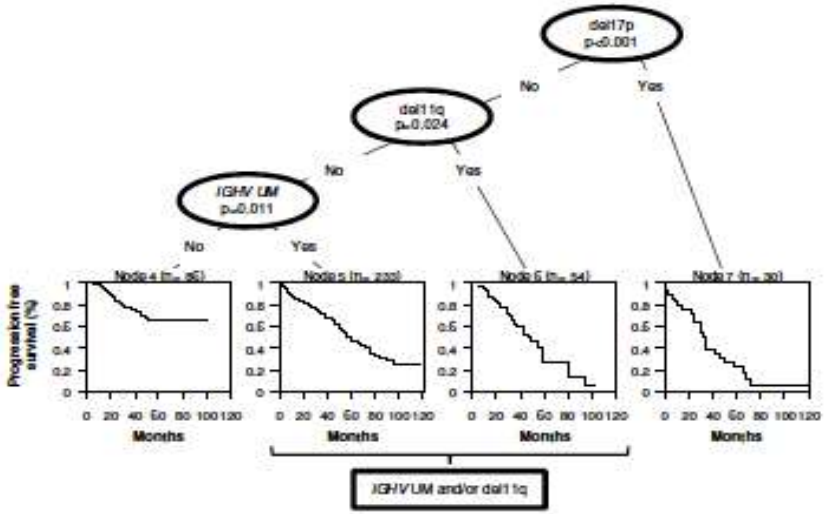


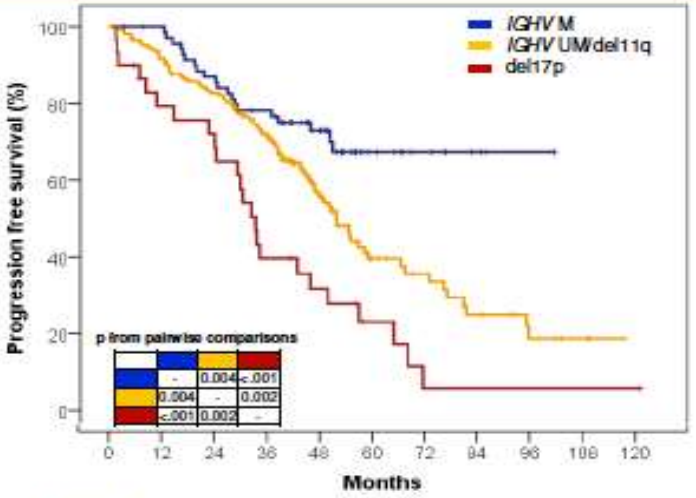
Venetoclax

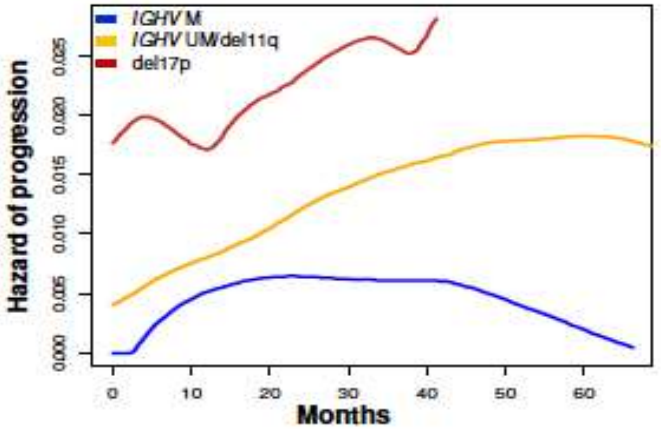


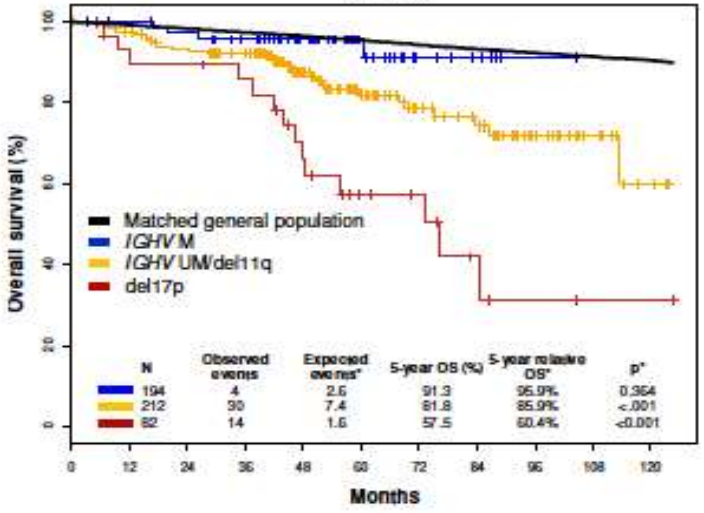
Byrd JC, Blood 2015; Thompson PA, Cancer 2015; Winqvist M, Haematologica 2016; Barrientos, ASCO,2015, 7011; Roberts, et al New Engl J Med 2016

IGHV mutated patients devoid of del17p and del11q gain the greatest benefit from FCR

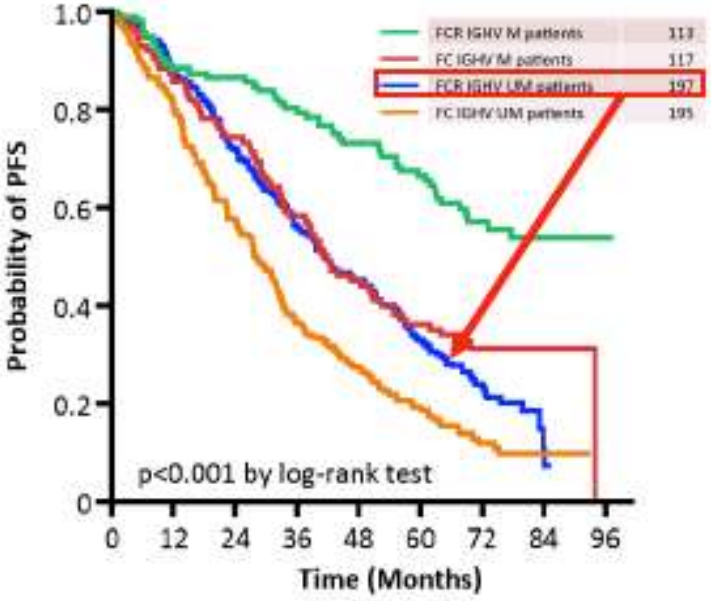






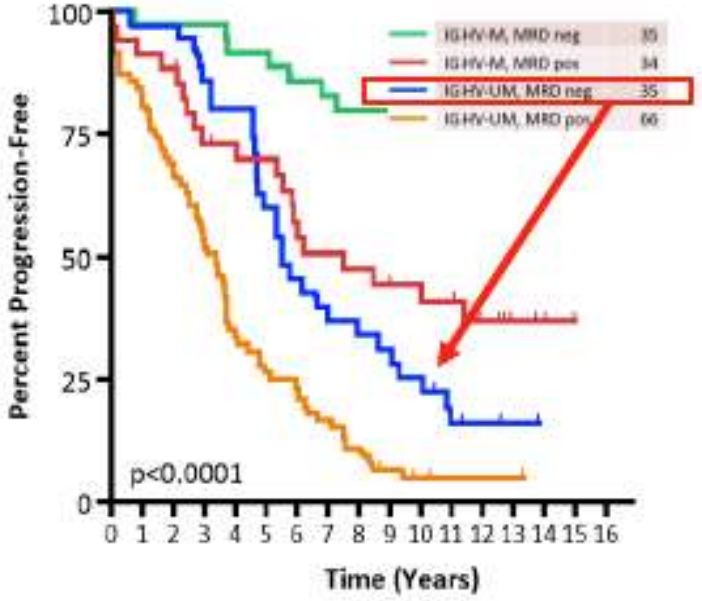


PFS by IGHV after front-line FCR: FCR300 and CLL8 trials



IGVH mutated
54% Prog-free @ 13 yrs
curve plateaued beyond 10.4 yrs

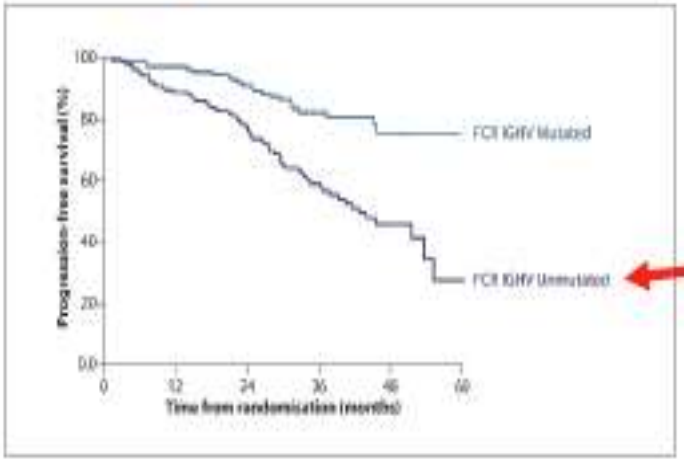
Thomson et al., Blood 2015



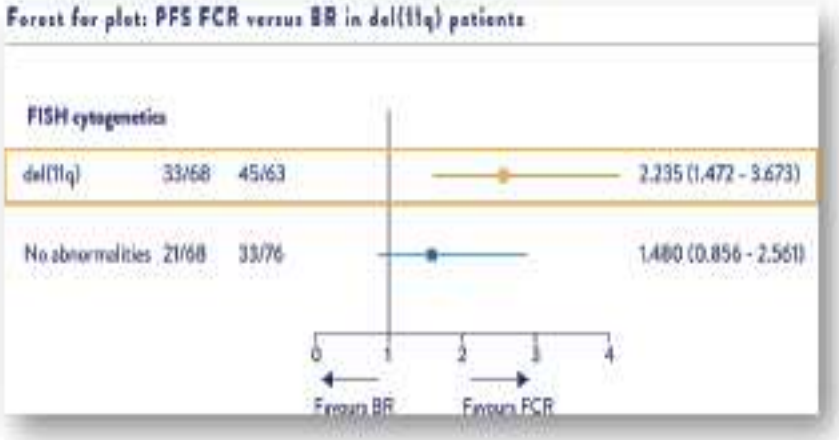
IGVH mutated
>50% Prog-free @ 6yrs

Fisher et al., Blood 2015

FCR PFS by unmutated IGHV or del(11q) : CLL 10



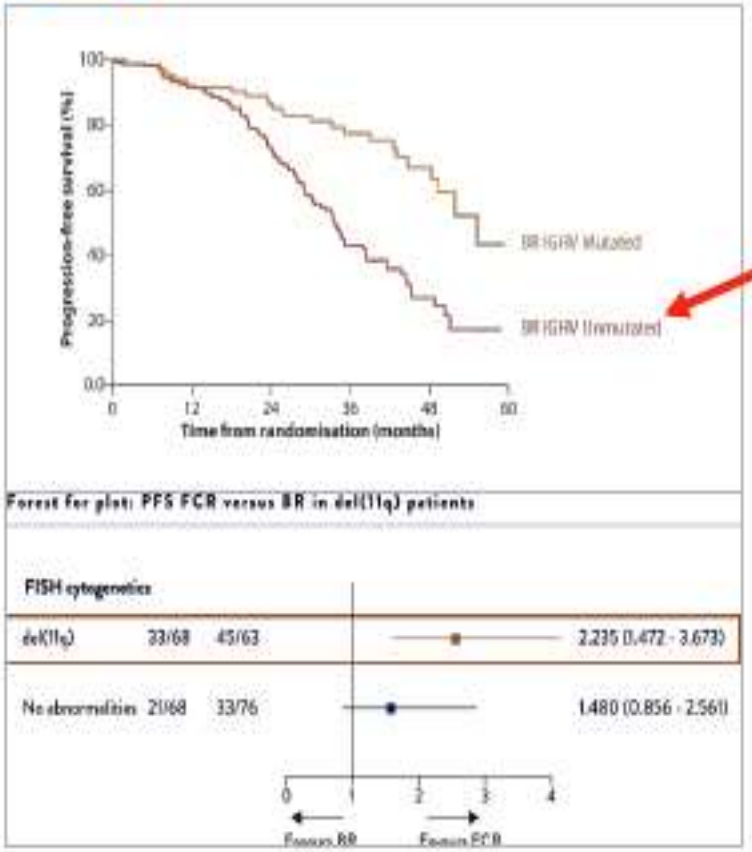
FCR CLL10	IGHV-unmutated N=152	IGHV-mutated N=123
Median PFS	**42.7 months**	**Not reached**
Median OS	Not reported	Not reported



FCR CLL10	Del(11q) present N=68	All patients N=282
Median PFS	37.8 months	55.2 months
Median OS	Not reported	Not reported

Eichhorst B, et al. Lancet Oncol 2016; 17(7): 928-42.

CLL 10: BR PFS by unmutated IGHV or del(11q)

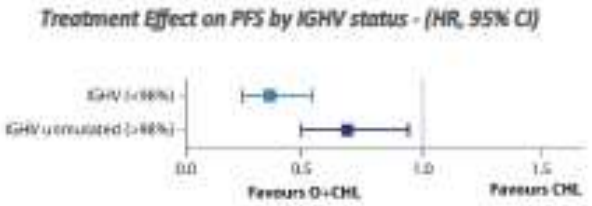


BR CLL10	IGHV-unmutated N=183	IGHV-mutated N=87
Median PFS	33.6 months	55.4 months
Median OS	Not reported	Not reported

BR CLL10	Del(11q) present N=63	All patients N=279
Median PFS	25.3 months	41.7 months
Median OS	Not reported	Not reported

Eichhorst B, et al. Lancet Oncol 2016; 17(7): 928-42.

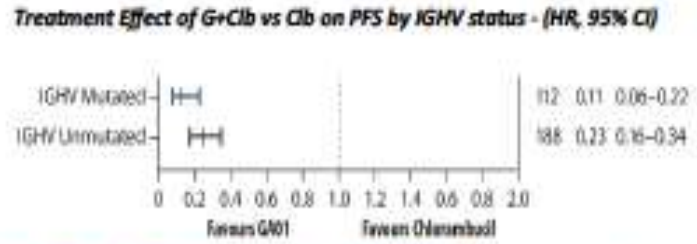
CLL 11: Chl + Ofatumumab efficacy by IGHV mutational status



O+Clb vs Clb Complement-1	IGHV-unmutated N= 114 vs 113	IGHV-mutated N= 87 vs 90
Reduction in risk of PD or death with O+Clb vs Clb	HR for PFS is improved with O+Clb vs Clb regardless of IGHV status But there is a trend suggesting outcomes are reduced in patients with unmutated IGHV vs mutated IGHV *(Forrest Plot on right)*	

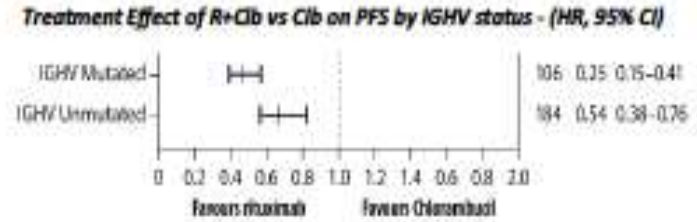
Hillmen P, et al. Lancet 2015; 385: 1873-83.

CLL 11: Chl + Obinutuzumab PFS is decreased by unmutated IGHV



G+Clb vs Clb CLL11	IGHV-unmutated N= 129 vs 58	IGHV-mutated N= 76 vs 36
PFS, HR (95% CI)	**0.23** (0.16-0.34)	0.11 (0.06-0.22)
Reduction in risk of PD or death with G+Clb vs Clb	77%	89%

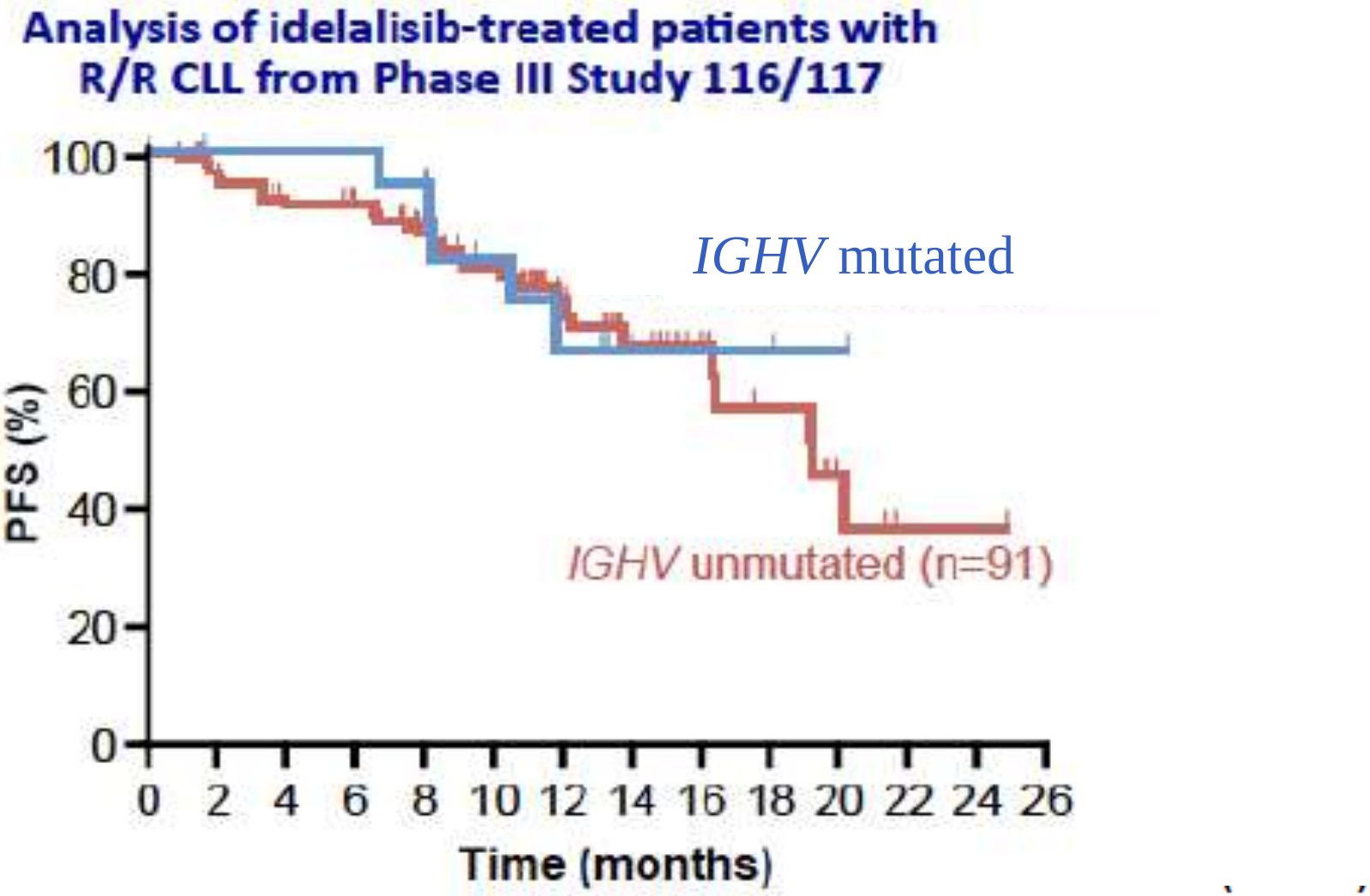
CLL: Chl + Rituximab PFS is decreased by unmutated IGHV



Goede V, et al. N Engl J Med 2014; 370(12): 1101-10.

R+Clb vs Clb CLL11	IGHV-unmutated N= 126 vs 58	IGHV-mutated N= 70 vs 37
PFS, HR (95% CI)	0.54 (0.38-0.76)	0.25 (0.15-0.41)
Reduction in risk of PD or death with R+Clb vs Clb	46%	75%

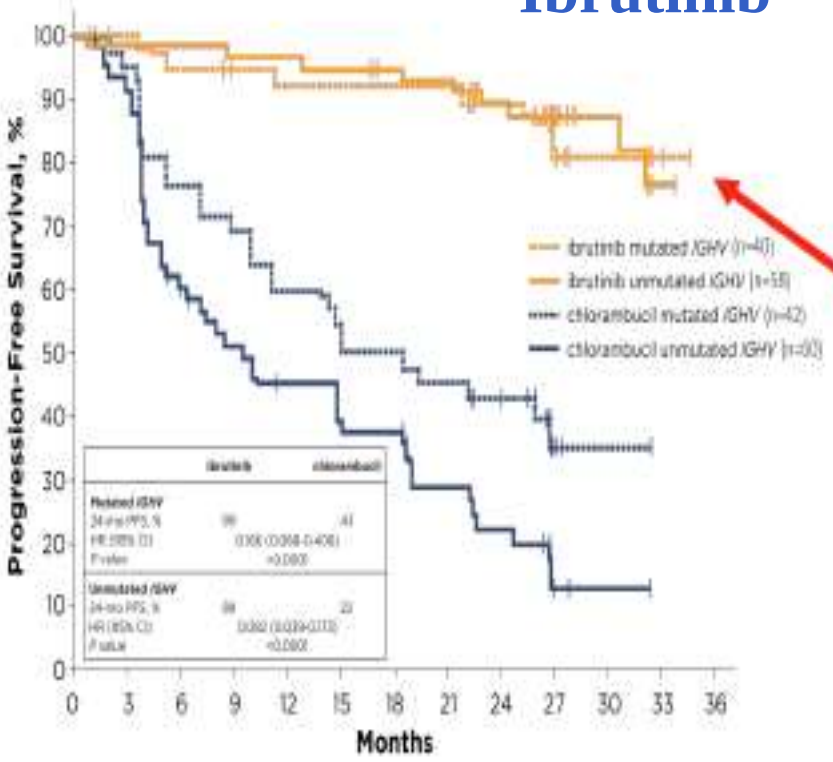
BCRi are efficacious regardless of *IGHV* status



Sharman JP, *et al.* ASH 2014, #330;

BCRi are efficacious regardless of *IGHV* status

Ibrutinib

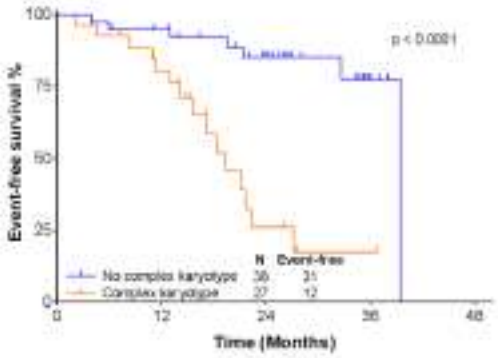


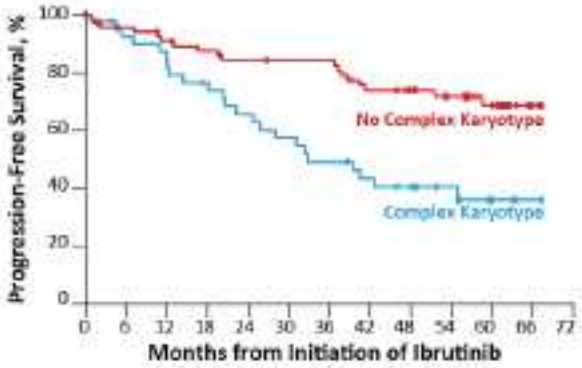
Ibrutinib vs Clb RESONATE-2	IGHV-unmutated N=58 vs 60	IGHV-mutated N=40 vs 42
PFS, HR (95% CI)	**0.082** (0.039-0.173) P<0.0001	**0.166** (0.068-0.406) P<0.0001
Reduction in risk of PD or death with Ibrutinib vs Clb	**92%**	**83%**

Barr P et al. Oral presentation at ASH 2016

Complex karyotype in the era of novel agents

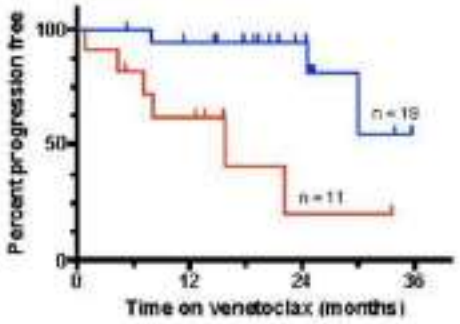
Ibrutinib
MDACC
Thompson et al, Cancer 2015

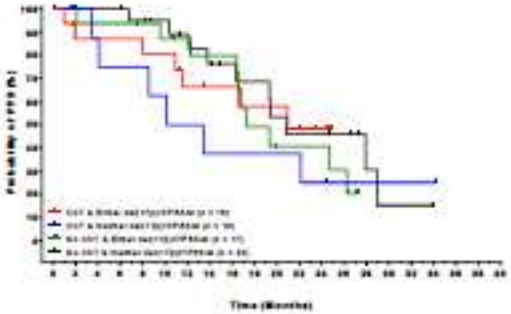




Ibrutinib
PCYC-1102/1103
O'Brien S, et al. ASH 2016

Venetoclax
Anderson et al, Blood 2017





Idelalisib-R
GS 0116/0117
Kreuzer, et al, ASH 2016

An international prognostic index for patients with chronic lymphocytic leukaemia (CLL-IPI): a meta-analysis of individual patient data

*The International CLL-IPI working group**

Variable	Adverse factor	Coeff.	HR	Grading
TP53 (17p)	deleted and/or mutated	1.442	4.2	4
IGHV status	Unmutated	0.941	2.6	2
B2M, mg/L	> 3.5	0.665	2.0	2
Clinical stage	Binet B/C or Rai I-IV	0.499	1.6	1
Age	> 65 years	0.555	1.7	1
Prognostic Score				0 – 10

Low risk	0-1
Intermediate risk	2-3
High risk	4-6
Very high risk	7-10

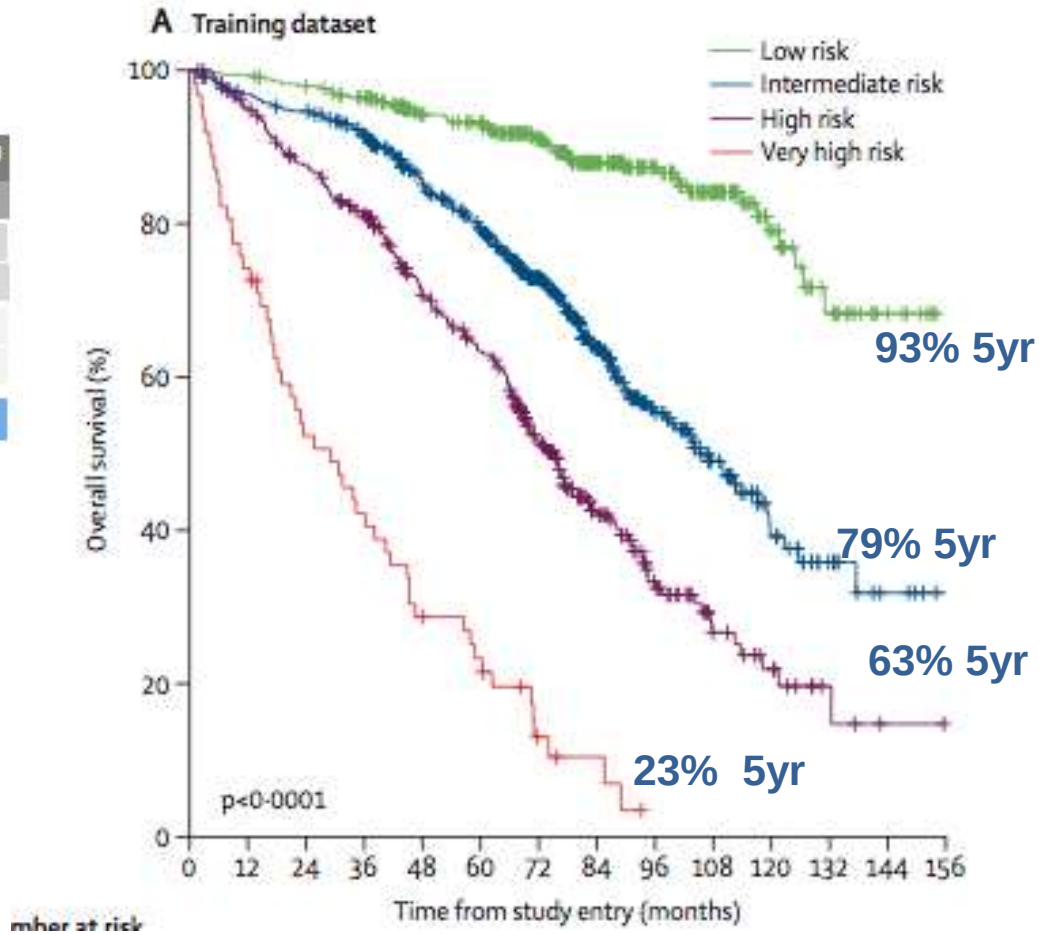
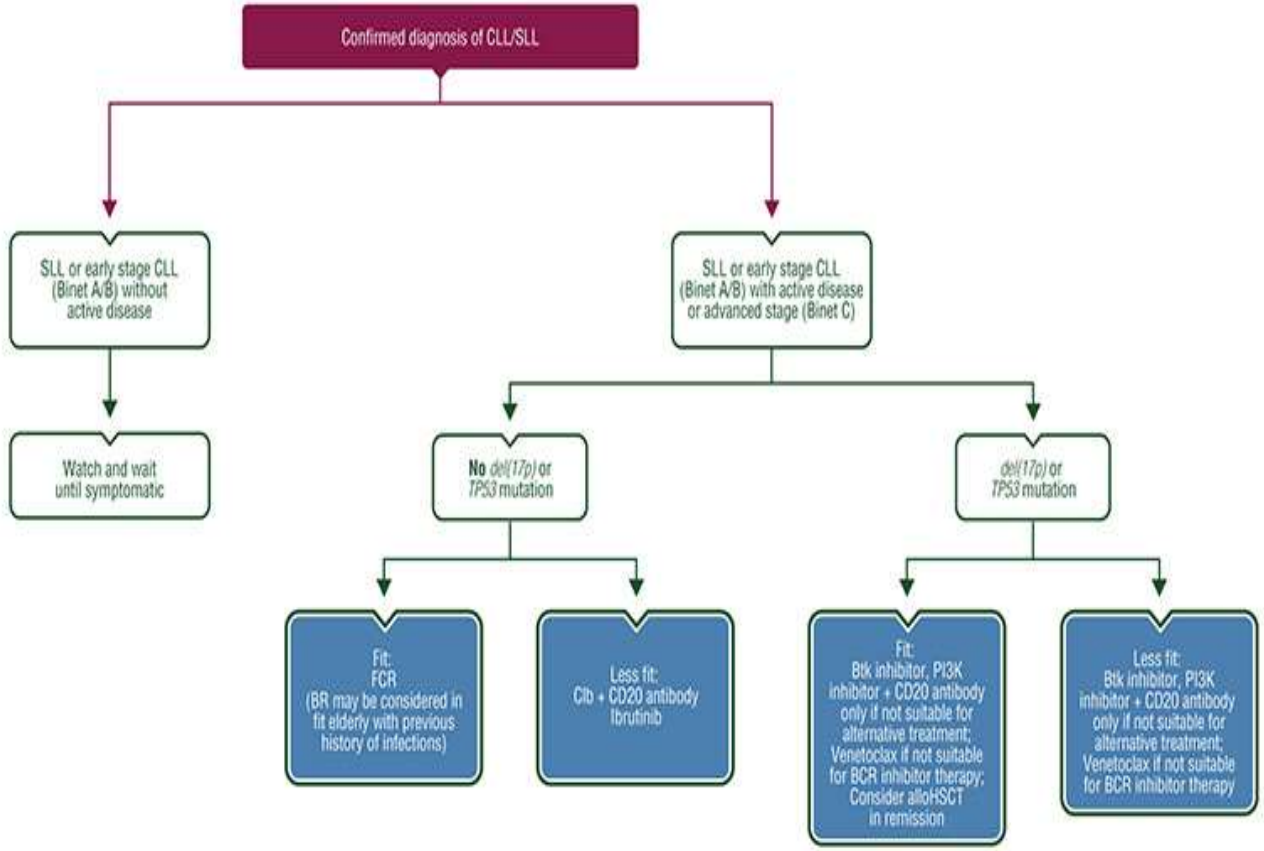


Figure 1: Overall survival according to the CLL-IPI risk groups

ESMO CLL Guidelines in frontline setting – Update June 2017



alloHSCT, allogeneic haematopoietic stem cell transplantation; BCR, B-cell receptor; Btk, Bruton's tyrosine kinase; BR, bendamustine plus rituximab; Clb, chlorambucil; CLL, chronic lymphocytic leukaemia; FCR, fludarabine, cyclophosphamide and rituximab; PI3K, phosphatidylinositide 3-kinase; SLL, small lymphocytic leukaemia; TP53, tumour protein p53

Eichhorst B, Robak T, Montserrat P et al. Ann Oncol 2015; 26 (Suppl 5): v78-v84 ePub June 2017

SUGGESTED TREATMENT REGIMENS[a,b]
CLL/SLL without del(17p)/*TP53* mutation
(alphabetical by preference and category)

First-line therapy

- Frail patient with significant comorbidity (not able to tolerate purine analogs)
  - Preferred regimens
    - Chlorambucil + obinutuzumab (category 1)
    - Ibrutinib[c] (category 1)
    - Chlorambucil + ofatumumab
    - Chlorambucil + rituximab
  - Other recommended regimens
    - High-dose methylprednisolone (HDMP) + rituximab (category 2B)
    - Obinutuzumab (category 2B)
    - Chlorambucil (category 3)
    - Rituximab (category 3)

First-line therapy

- Age ≥65 y and younger patients with significant comorbidities
  - Preferred regimens
    - Chlorambucil + obinutuzumab (category 1)
    - Ibrutinib[c] (category 1)
    - Bendamustine (70 mg/m^2 in cycle 1 with escalation to 90 mg/m^2 if tolerated) ± CD20 monoclonal antibody[d]
    - Chlorambucil + ofatumumab
    - Chlorambucil + rituximab
  - Other recommended regimens
    - HDMP + rituximab (category 2B)
    - Obinutuzumab (category 2B)
    - Chlorambucil (category 3)
    - Rituximab (category 3)

First-line therapy

- Age <65 y without significant comorbidities
  - Preferred regimens
    - FCR[f] (fludarabine,[g] cyclophosphamide, rituximab[h]) (category 1)[d]
    - Bendamustine ± CD20 monoclonal antibody[d]
    - Ibrutinib[c]
  - Other recommended regimens
    - FR[f] (fludarabine,[g] rituximab)[i]
    - HDMP + rituximab (category 2B)
    - PCR (pentostatin, cyclophosphamide, rituximab) (category 3)

Chronic lymphocytic leukaemia

Michael Hallek, Tait D Shanafelt, Barbara Eichhorst

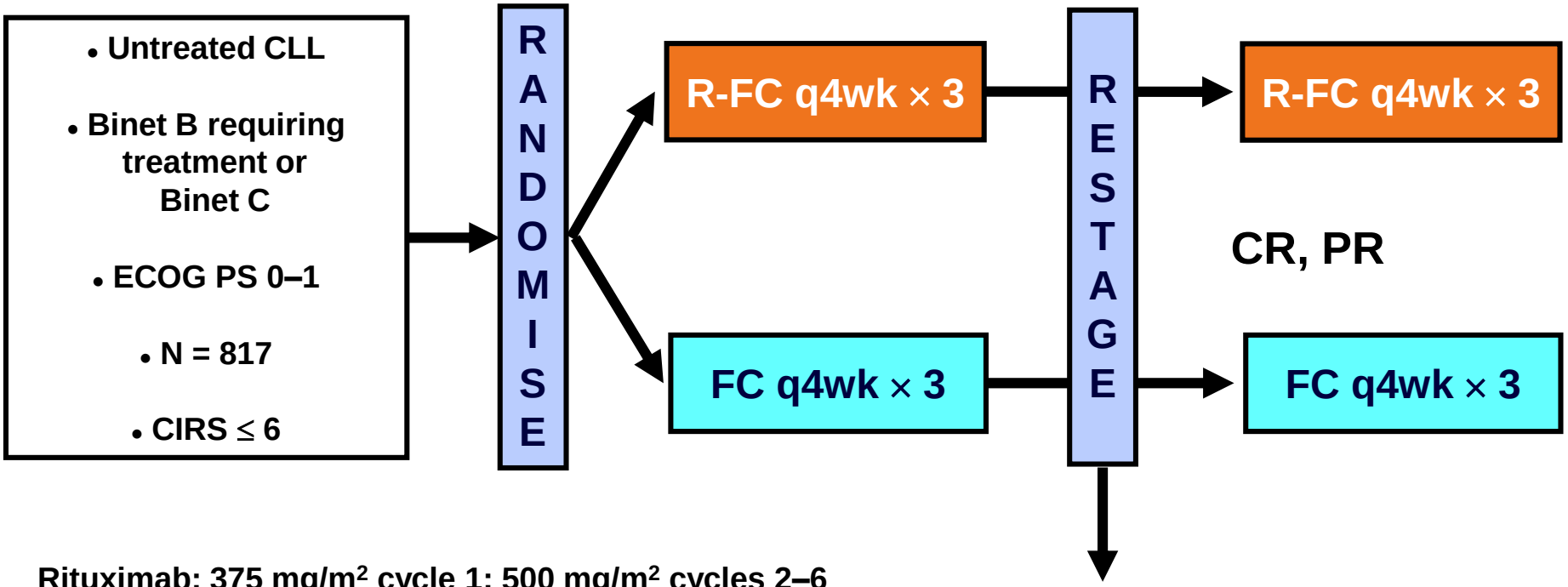
	No *TP53* aberration	*TP53* aberration
Physically fit	Fludarabine plus cyclophosphamide plus rituximab (age ≤ 65 years); or bendamustine plus rituximab (age > 65 years)	Ibrutinib or idelalisib plus rituximab or venetoclax (if ibrutinib therapy is not suitable because of comorbidities or comedication)
Physically unfit	Chlorambucil plus obinutuzumab; or chlorambucil plus ofatumumab; or chlorambucil plus rituximab; or ibrutinib monotherapy	Ibrutinib or idelalisib plus rituximab or venetoclax (if ibrutinib is not suitable because of comorbidities or comedication)

Table 2: First-line treatment of chronic lymphocytic leukaemia in physically fit and physically unfit patients

www.thelancet.com Published online February 21, 2018 http://dx.doi.org/10.1016/S0140-6736(18)30422-7

Terapia del paziente FIT

GCLLSG CLL8 TRIAL : FC vs R-FC



Rituximab: 375 mg/m^2 cycle 1; 500 mg/m^2 cycles 2–6
Fludarabine: 25 mg/m^2
Cyclophosphamide: 250 mg/m^2

Hallek M *et al*. *Lancet* 2010; 376;1164–1174.

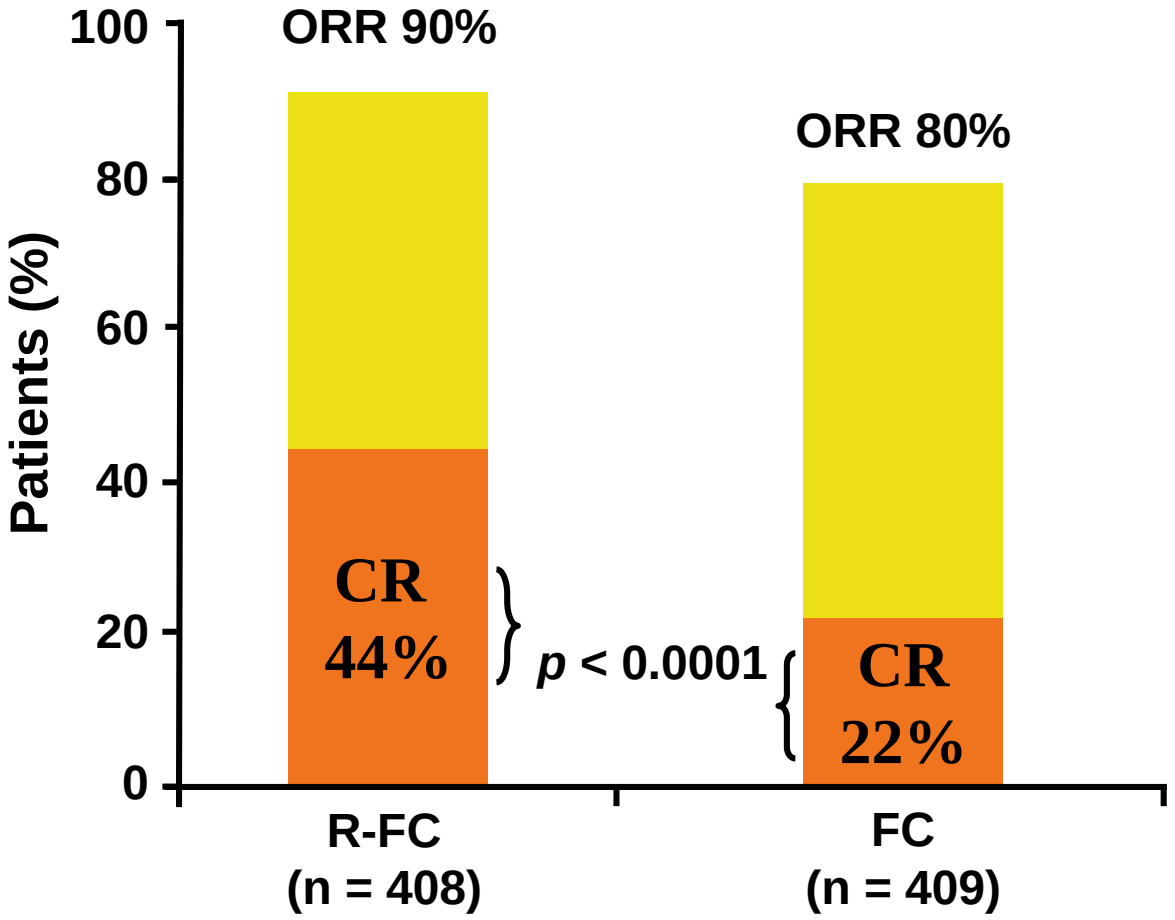
Criteri di inclusione
CLL8

Età > 18 anni
ECOG 0/1
GFR > 70 ml/min
CIRS < 6

Median age, years (range)	61
Aged ≥ 65 years, %	28
Aged ≥ 75 years, %	2
Median ECOG PS	0

Hallek M et al., *Lancet* 2010, 376:1164-74

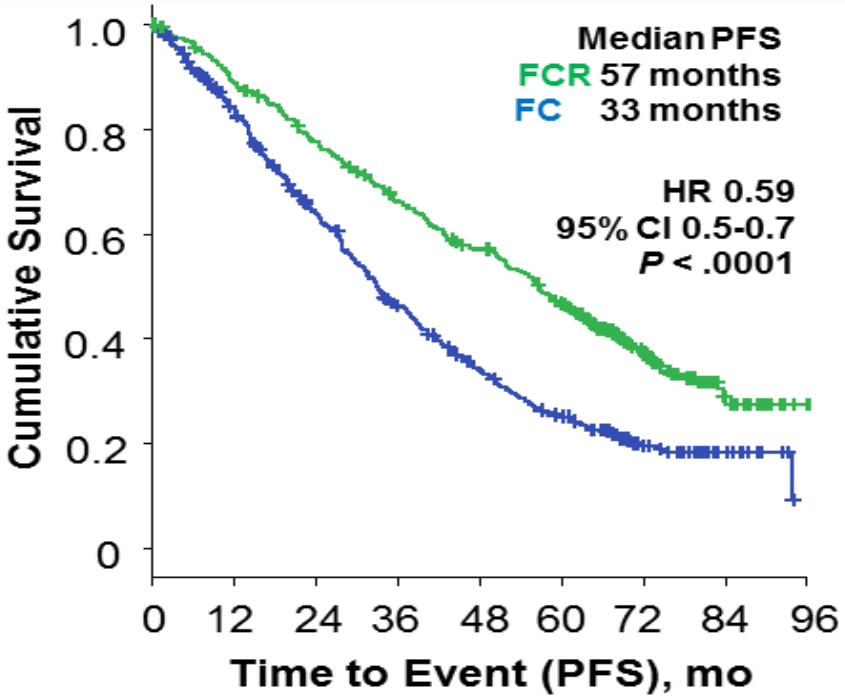
Response: FCR better than FC

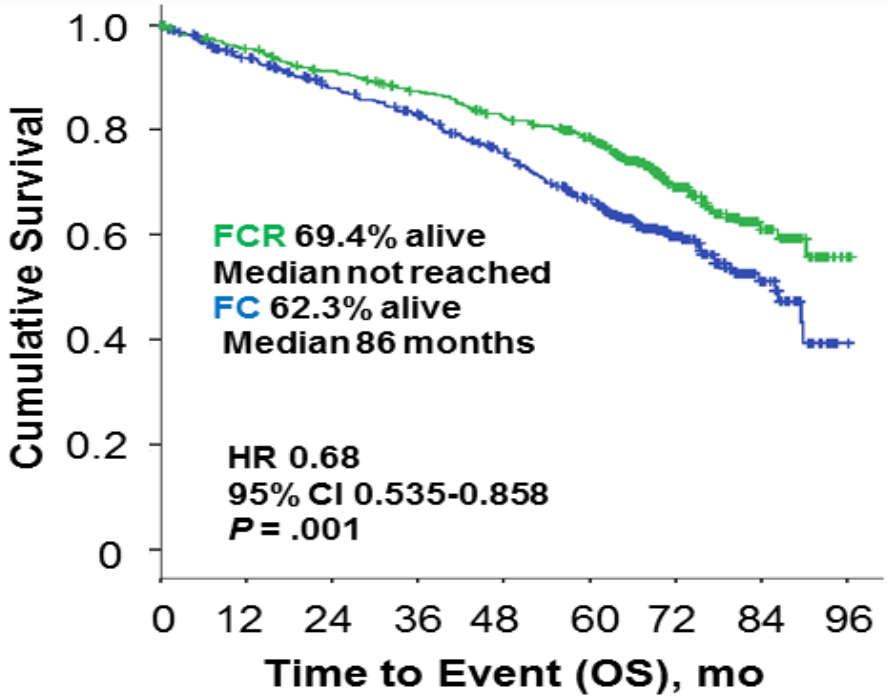


blood

Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: updated results of the CLL8 trial

Update PFS CLL8 Trial: F/U 5.9 years

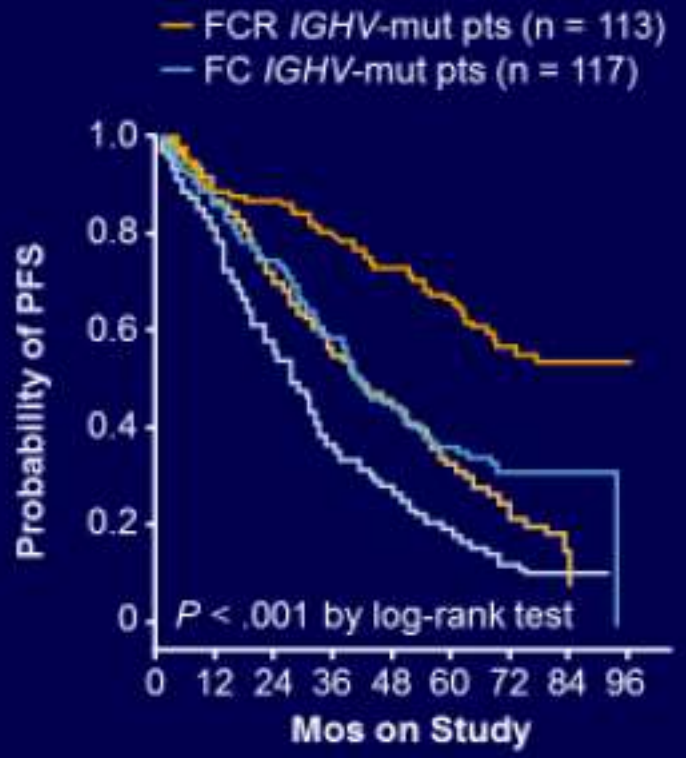


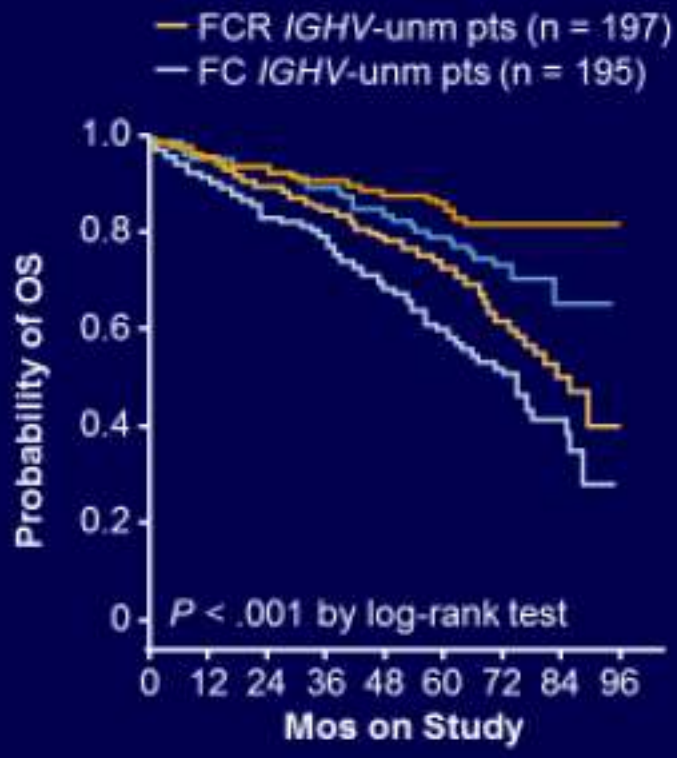


Despite indolent and recurrent nature of CLL, efficient first-line treatment is important

Fisher K, et al. *Blood*. 2012;120: Abstract 435.[49]

CLL8: Plateau in PFS and OS With FCR as Initial Therapy for CLL



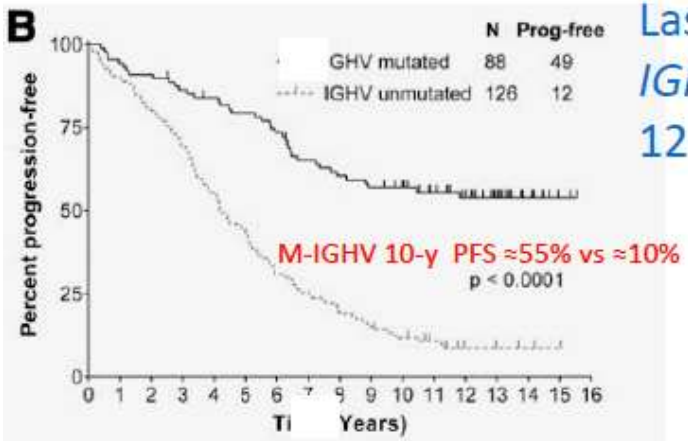


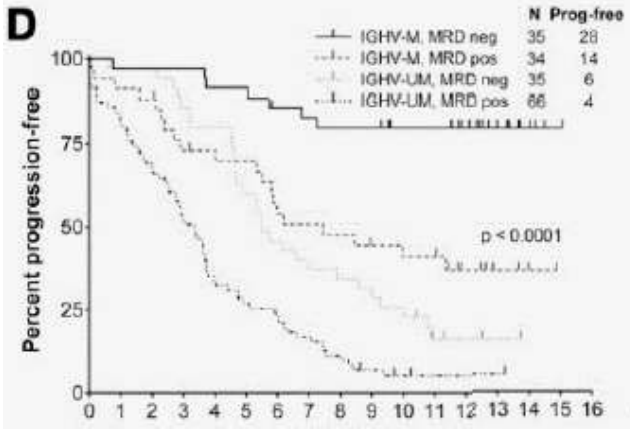
Fischer K, et al. Blood. 2016;127:208-215.

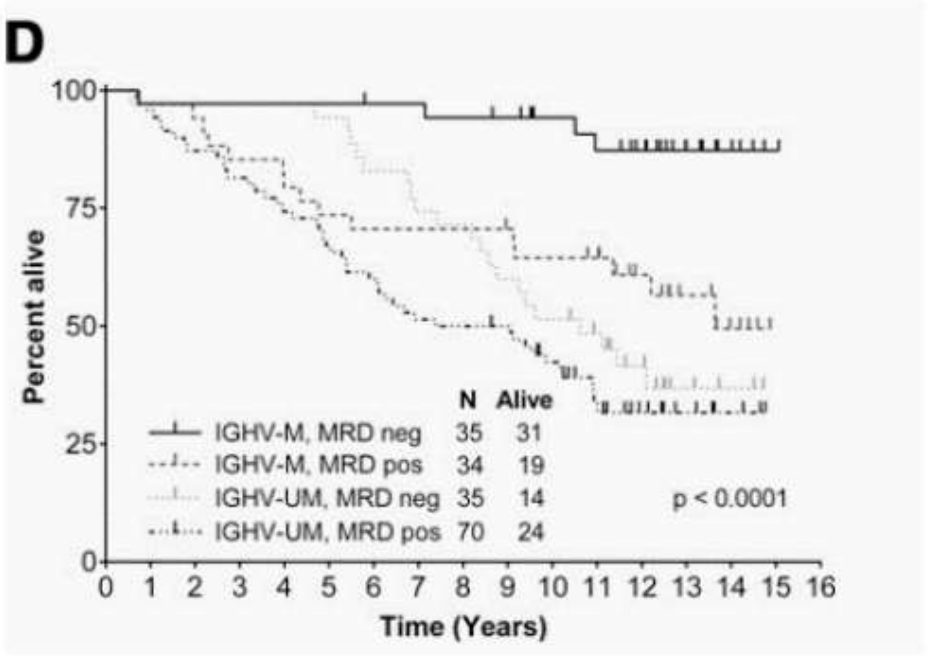
FCR300 Phase II Trial: Plateau in PFS With FCR as 1st line therapy

Last relapses occurred at Yr 10, with a plateau in PFS for *IGHV*-mutated pts.

12·8-year PFS was 80% for M-IGHV pts who were MRD-neg







43% of all patients treated with FCR were MRD neg

Thompson et al., Blood 2016

CLL8
Efficacy in older *vs* younger patients

	R-FC	
	< 65 years (n = 282)	≥ 65 years (n = 126)
CR (%)	45	43
ORR (%)	89	93
PFS at 3 yrs (%)	64	68
OS at 3 yrs (%)	87	88

Hallek M *et al*. *Lancet* 2010; 376;1164–1174.

Incidence Of Grade 3 And 4 Adverse Events

	Chemotherapy (n=396)	Chemoimmunotherapy (n=404)	p value	<65 years (n=560)	≥65 years (n=240)	p value
Total number of patients with at least one grade 3 or 4 event	249 (63%)	309 (76%)	<0·0001	375 (67%)	183 (76%)	0·009
Haematological toxicity	157 (40%)	225 (56%)	<0·0001	254 (45%)	128 (53%)	0·04
Neutropenia	83 (21%)	136 (34%)	<0·0001	146 (26%)	73 (30%)	0·21
Leucocytopenia	48 (12%)	97 (24%)	<0·0001	106 (19%)	39 (16%)	0·37
Thrombocytopenia	44 (11%)	30 (7%)	0·07	50 (9%)	24 (10%)	0·63
Anaemia	27 (7%)	22 (5%)	0·42	35 (6%)	14 (6%)	0·82
Autoimmune haemolytic anaemia	4 (1%)	3 (<1%)	0·69	4 (<1%)	3 (1%)	0·46
Tumour lysis syndrome	2 (<1%)	1 (<1%)	0·55	3 (<1%)	0	0·26
Cytokine release syndrome	0	1 (<1%)	0·32	1 (<1%)	0	0·51
Infections, total	85 (21%)	103 (25%)	0·18	127 (23%)	61 (25%)	0·4
Infections, not specified	68 (17%)	83 (21%)	0·19	104 (19%)	46 (19%)	0·84
Bacterial infection	5 (1%)	11 (3%)	0·14	6 (1%)	10 (4%)	0·004
Viral infection	17 (4%)	17 (4%)	0·95	26 (5%)	8 (3%)	0·4
Fungal infection	1 (<1%)	3 (<1%)	0·33	3 (<1%)	1 (<1%)	0·83
Parasitic infection	0	1 (<1%)	0·32	0	1 (<1%)	0·13

Data are number (%), unless otherwise indicated. Chemotherapy=fludarabine and cyclophosphamide. Chemoimmunotherapy=fludarabine, cyclophosphamide, and rituximab.

Table 6: Incidence of grade 3 and 4 adverse events

Hallek M *et al*. *Lancet* 2010; 376;1164–1174.

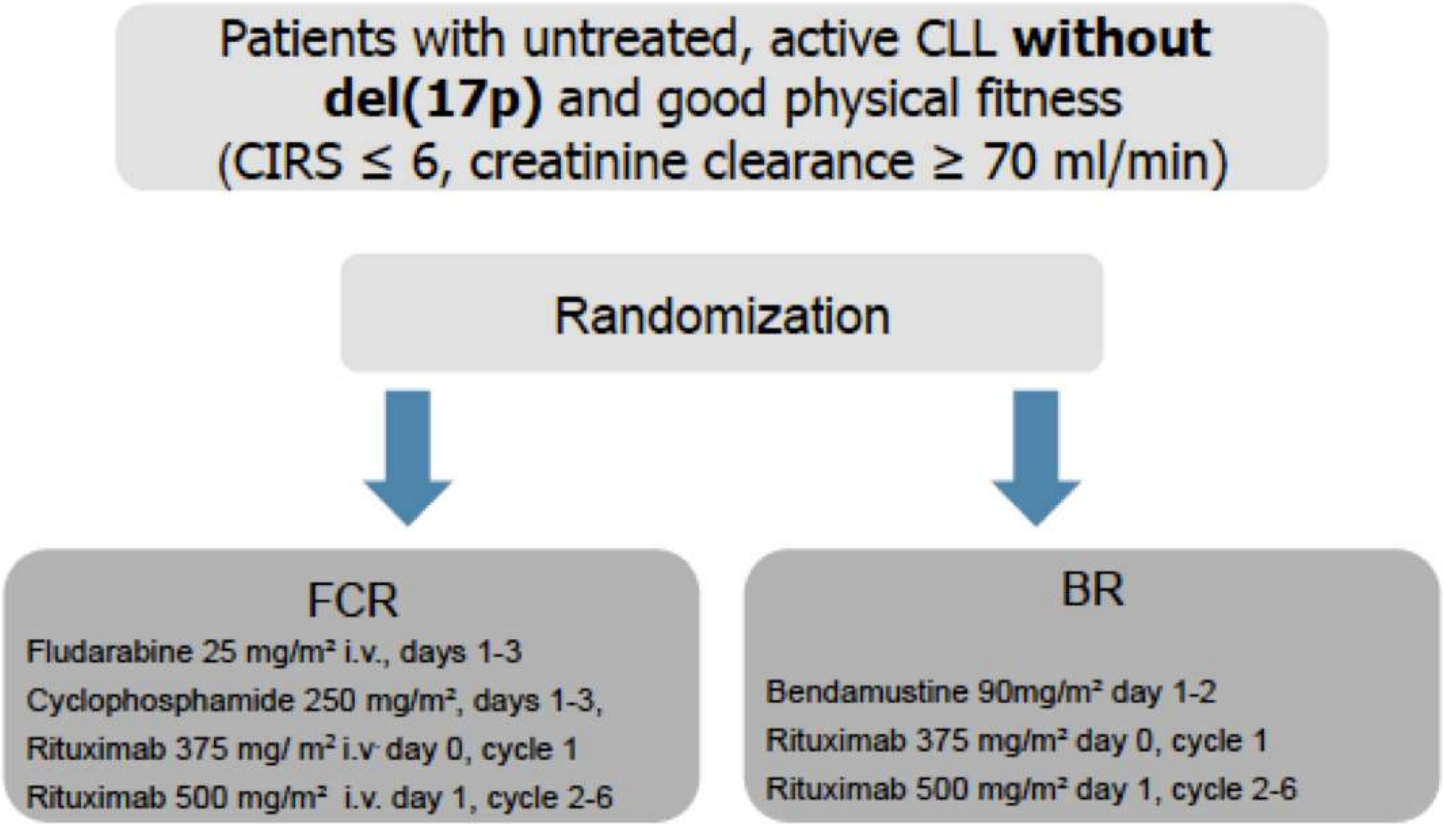
Incidence Of Grade 3 And 4 Adverse Events

Per i pazienti FIT ma con età > 65 anni o con comorbità ci vuole una terapia efficace ma con meno rischi di tossicità

Goede et al., *oral presentation*, EHA Annual Meeting 2012

CLL10 STUDY: FCR VS BR IN FRONT-LINE

Design: Phase III non-inferiority trial



Eichhorst B et al. Lancet Oncology 2016

CLL10 STUDY: FCR VS BR IN FRONTLINE

ITT Best Response according to IWCLL & MRD

Response	FCR (%) n=282	BR (%) n=279	p value
CR (CR + CRi)	39.7	30.8	0.034
ORR	95.4	95.7	1.0
MRD negativity	**FCR %(N) n=282**	**BR %(N) n=279**	
BM at FR	26.6% (75/282)	11.1% (31/279)	
PB at FR	48.6% (137/282)	38.4% (107/279)	

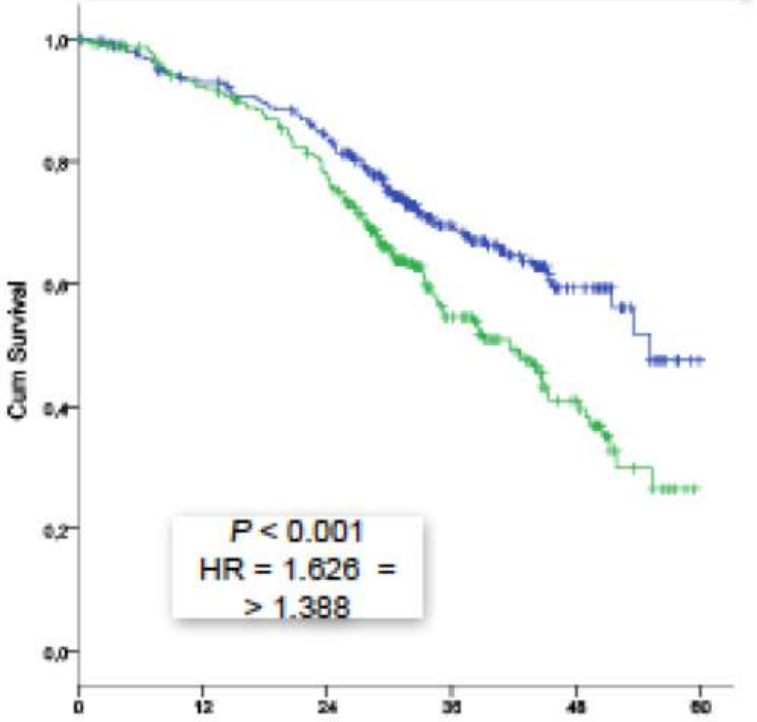
Eichhorst B et al. Lancet Oncology 2016

CLL10 STUDY: FCR VS BR IN FRONT-LINE

ITT Progression-free survival = Primary endpoint

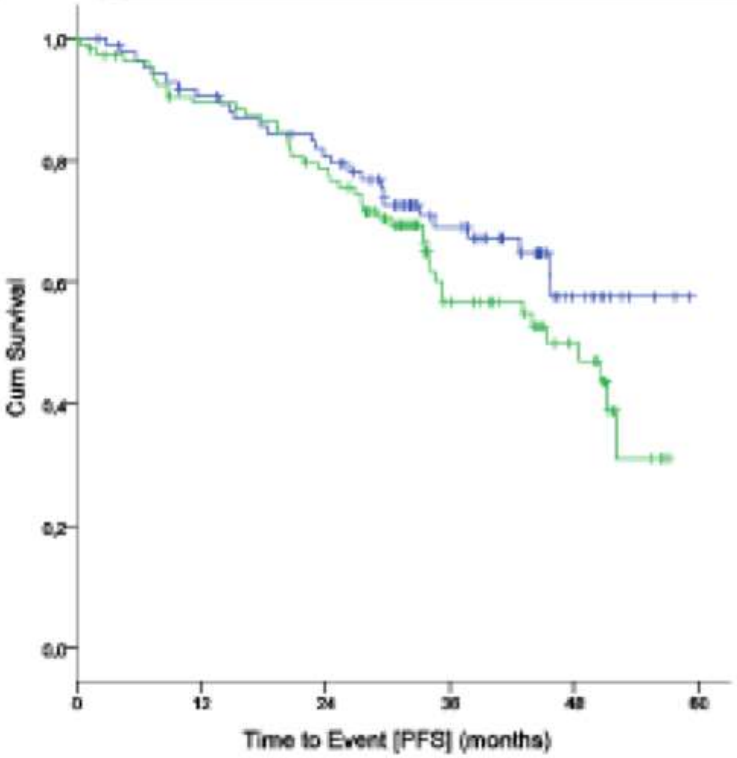
Median PFS all patients

FCR 55.2 months BR 41.7 months



Patients > 65 years: *P = 0.170*

FCR not reached BR 48.5 months



Eichhorst B et al. Lancet Oncology 2016

CLL10 TRIAL: TOXICITY

		FCR (n=279)	BR (n=278)
Severe infections	all	35.2	27.5
	> 65 only	47.7	20.6
SPM		49 (18%)	35 (12%)
Solid tumor		28 (10%)	25 (9%)
Skin tumor		9 (3%)	8 (3%)
AML/MDS	all	12 (4%)	2 (1%)
	> 65 only	6 (7%)	1 (1%)
RT		5 (2%)	8 (3%)

GCLLSG CLL10 updated analysis 2016 unpublished

CLL 10 Conclusioni

FCR è la terapia standard per il paziente FIT giovane: maggiori CR, MRD negatività e più lungo PFS

Pazienti FIT anziani (> 65 anni) hanno maggiori tossicità e maggiori rischi infettivi

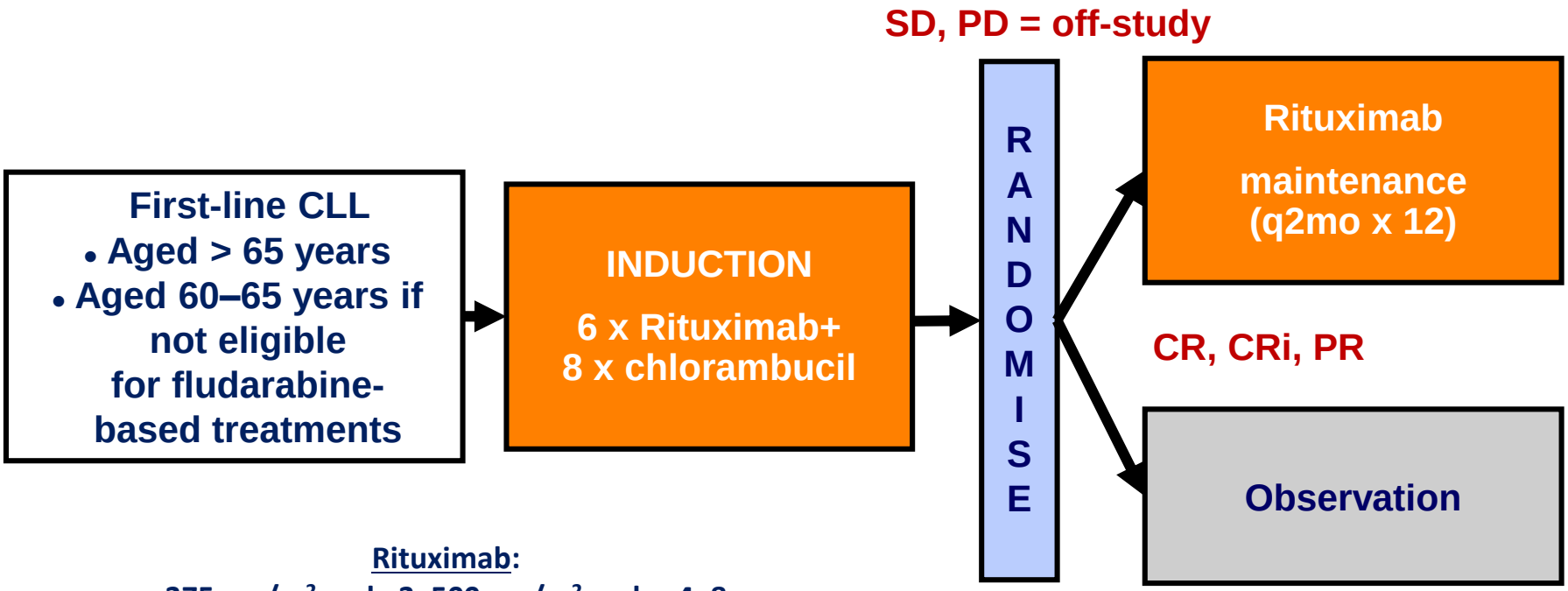
Il trattamento BR è da preferire nei pazienti anziani FIT o giovani con precedenti infezioni

Terapia dei pazienti UNFIT

Chlorambucil ± anti-CD20 MoAb (1997-2017)

Study	Treatment	Patients		Dose (m^2) /per 4 week cycle	7/28 days or 1/14 days	Number of cycles delivered	Total dose of clb	Anti-CD20 antibody	Response rate		
		No	Med age						CR/CRI	ORR	PFS
Jaksic et al 1997	Clb mono	228	??	150–180/m2	Continuous	??	??	None	??	89.5%	68 (OS)
Ral et al 2000	Clb mono	193	62	40mg/m^2	1/28	Up to 12	??	None	4%	37%	14
Eichhorst et al 2009	Clb mono	100	70	38mg/m^2	1/14	6.5	0.5mg/kg	None	0%	51%	18
Hillmen et al 2007	Clb mono	148	60	40mg/m^2	1/28	7	515mg	None	2%	55%	11.7
Knauf et al 2009	Clb mono	156	66	60mg/m^2	1/14	6	522mg	None	2%	31%	8.3
Catovsky et al 2007	Clb mono	387	65	70mg/m^2	7/28	??	??	None	7%	72%	20
Hillmen et al CLL208	Clb + ritux	100	70	70mg/m^2	7/28	6	??	Ritux	10%	84%	23.5
Foa et al (Clb+rit)	Clb + ritux	85	70	56mg/m^2	7/28	8	~700mg	Ritux	18.9%	82.4%	34.7**
Hillmen et al (Compl	Clb	226	70	70mg/m^2	7/28	6 (12)	728mg	None	1%*	69%*	13.1
	Clb + Ofa	221	69	70mg/m^2	7/28	6 (12)	763mg	Ofatum	14%*	82%*	22.4
Goede et al (CLL11	Clb	118	72	38mg/m^2	1/14	6 (6)	384mg	None	0	31.4%	11.1
	Clb + ritux	330	73	38mg/m^2	1/14	6 (6)	396mg	Rituxmab	7%	65.1%	15.2
	Clb + Obin	333	74	38mg/m^2	1/14	6 (6)	366mg	Obinutuz	20.7%	78.4%	26.7

ML21445: Rituximab plus chlorambucil followed by maintenance for elderly patients with first-line CLL

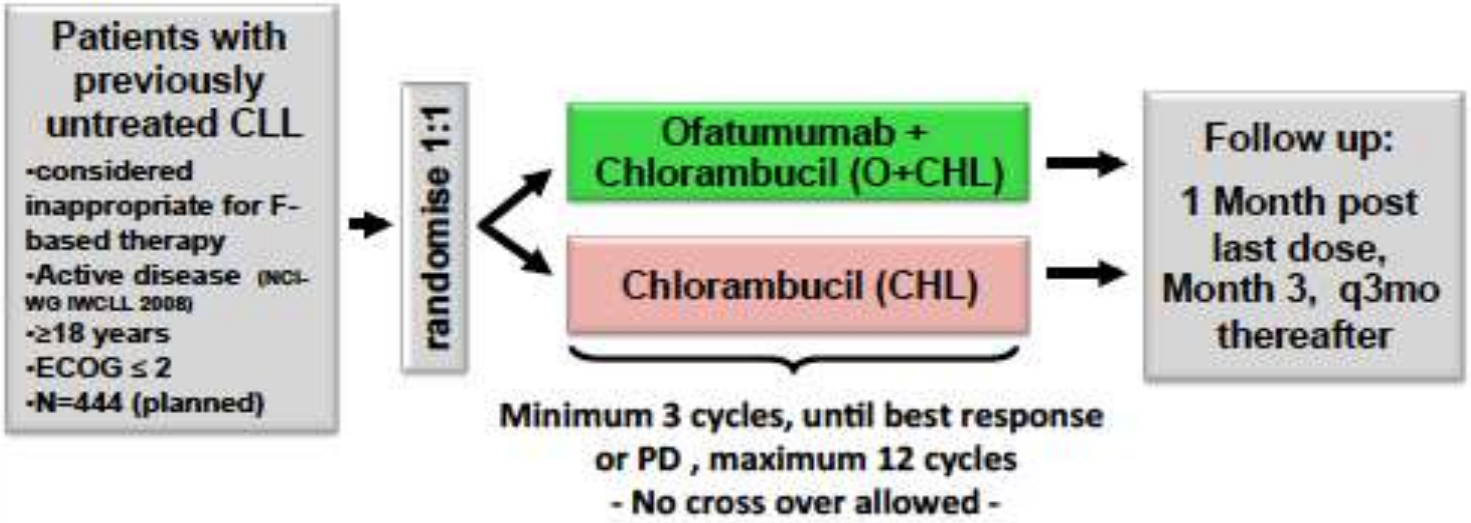


Rituximab:
375 mg/m^2 cycle 3, 500 mg/m^2 cycles 4–8
Chlorambucil:
8 mg/m^2/day for 7 days cycles

Complete Remission	Overall Response Rate	Median Age	Evaluable patients	Grade III-IV Neutropenia % patients
16.5%	82.4 %	70 (R: 61-84)	85	19.6

Foà R Am J Hematol. 2014

COMPLEMENT 1: Ofatumumab in CLL



O: cycle 1 d1 300 mg, d8 1000 mg, Cycle 2-12 d1 1000 mg every 28 days

CHL: 10 mg/m² d1-7 every 28 days

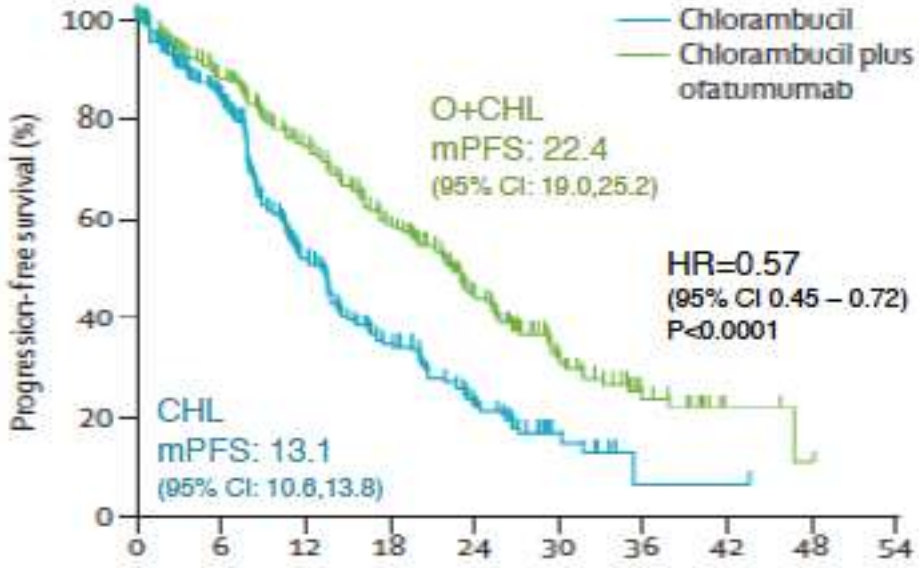
Dose rationale: evidence of highest ORR and longest PFS with low toxicity compared to any other CHL monotherapy regimen

Hillmen *et al.*, Lancet. 2015;385:1873-83.

COMPLEMENT 1

Complement-1: Median PFS (months)

as assessed by an Independent Review Committee

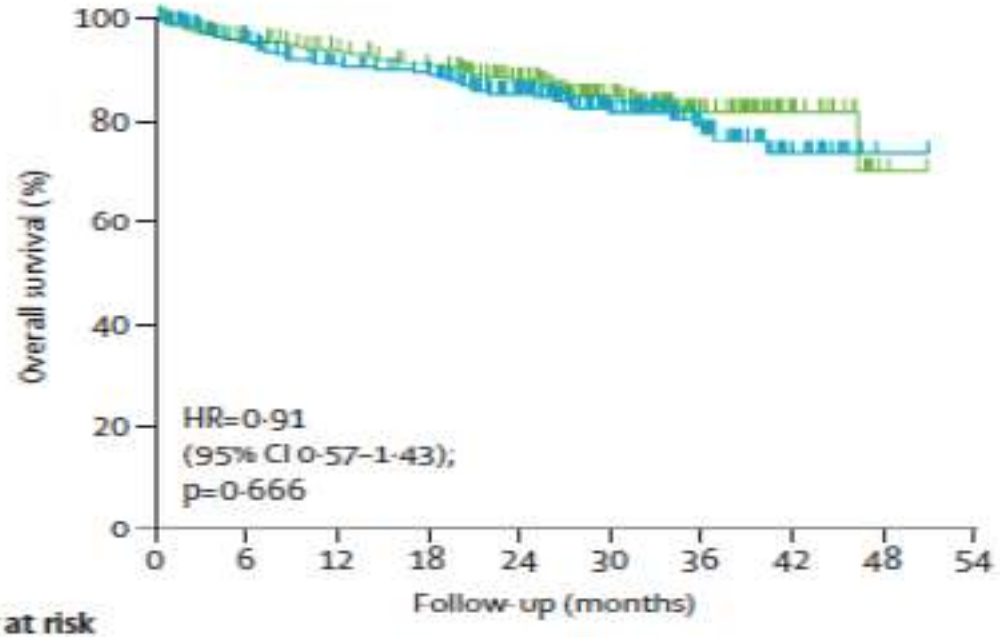


Number at risk					
Chlorambucil	226	92	33	1	0
Chlorambucil plus ofatumumab	221	149	70	15	1

Hillmen *et al.*, Lancet. 2015;385:1873-83.

COMPLEMENT 1

Complement-1: Overall Survival

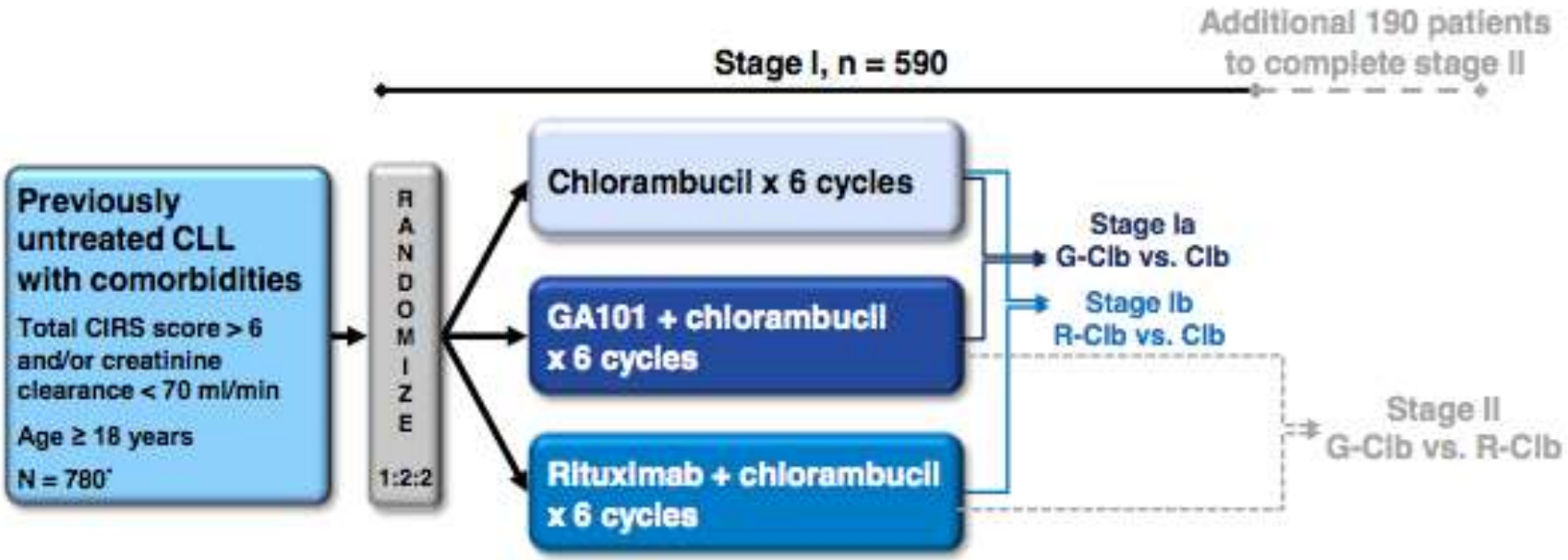


Number at risk					
Chlorambucil	226	191	148	53	1
Chlorambucil plus ofatumumab	221	193	153	57	2

Hillmen *et al.*, Lancet. 2015;385:1873-83.

COMPLEMENT 1

CLL 11 study design



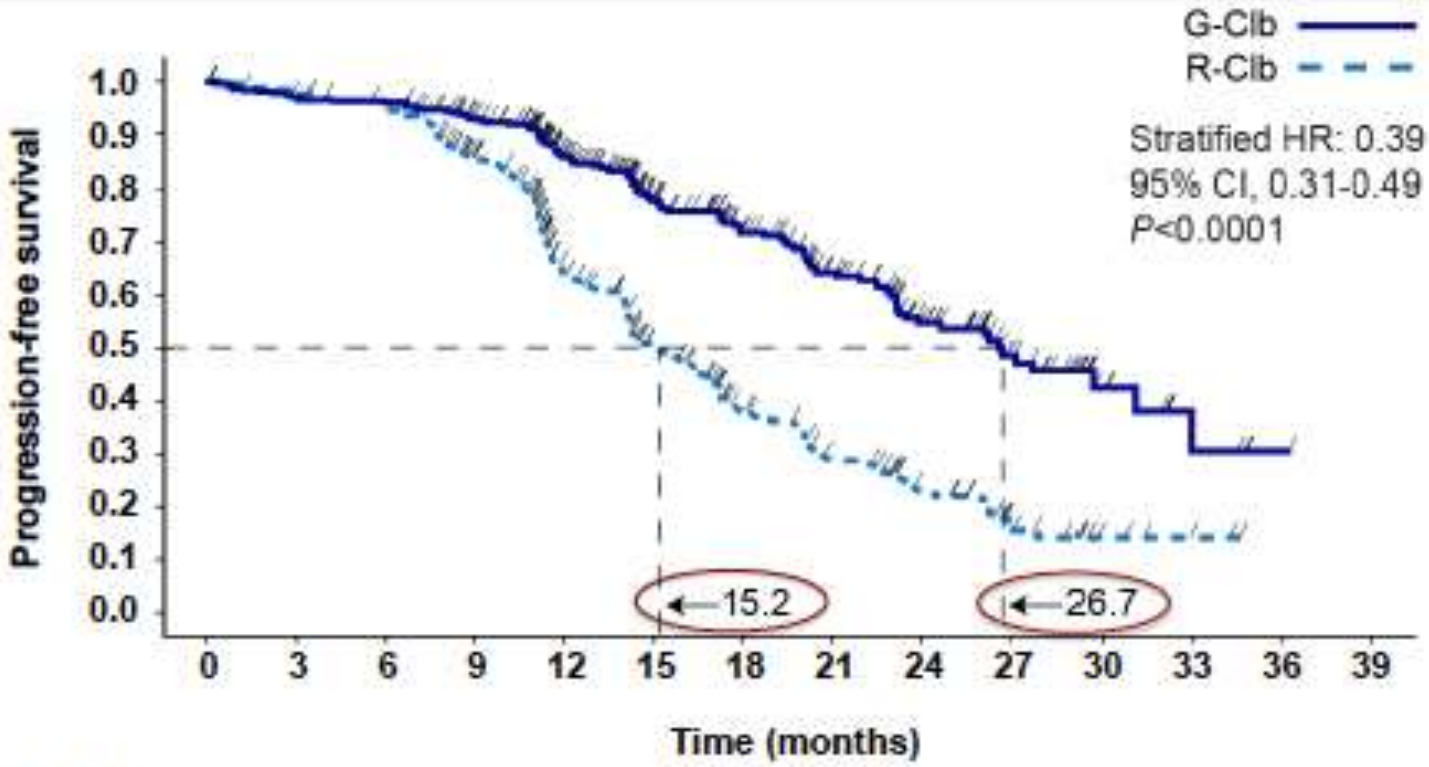
Primary endpoint	Investigator-assessed PFS
Secondary endpoints	ORR, CR rate, PR rate, IRC-assessed PFS, response duration, DFS, overall survival, MRD, safety, PK of G-Clb, patient-reported outcomes and symptom burden by EORTC questionnaire

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
Patients with progressive disease in the Clb arm were allowed to cross over to G-Clb arm.

* Plus six additional G-Clb patients in safety run-in[1]

Goede et al., N Engl J Med. 2014 Jan 8

GCLLSG CLL11 Trial: PFS for G-Clb vs R-Clb



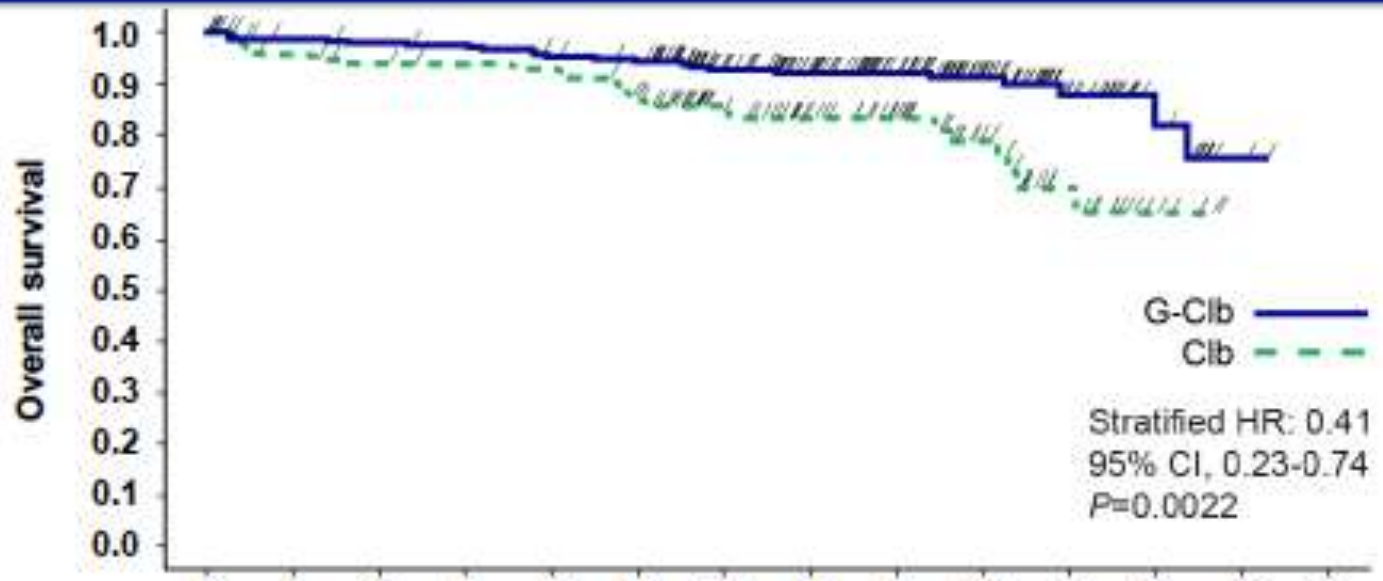
No. at risk

G-Clb:	330	307	302	278	213	156	122	93	60	34	12	4	1	0
R-Clb:	330	317	309	259	163	114	72	49	31	14	5	2	0	0

Median observation time: G-Clb, 18.8 months; R-Clb, 18.6 months
Type 1 error controlled through closed test procedure; *P* value of the global test was <0.0001
Independent Review Committee-assessed progression-free survival (PFS) was consistent with investigator-assessed PFS

Goede *et al.*, N Engl J Med, 2014; 370: 1101-10.

GCLLSG CLL11 Trial: Overall survival G-Clb vs Clb



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

Total number of deaths: G-Clb, 22 (9%); Clb, 24 (20%)

Median observation time: G-Clb, 23.2 months; Clb, 20.4 months
No multiplicity adjustment was done for secondary endpoints

Goede *et al.*, N Engl J Med, 2014; 370: 1101-10.

CLL11 - Most frequent AEs (any grade)

	Patients, n (%)			Patients, n (%)	
	R-Clb (n = 321)	G-Clb (n = 336)		G-Clb (n = 321)	R-Clb (n = 336)
Any AE	286 (89)	315 (94)	Abdominal pain	10 (3)	14 (4)
IRRs	121 (38)	221 (66)	Fatigue	30 (9)	27 (8)
Neutropenia	103 (32)	128 (38)	Asthenia	25 (8)	23 (7)
Thrombocytopenia	21 (7)	48 (14)	Pyrexia	24 (7)	29 (9)
Anemia	35 (11)	37 (11)	Cough	19 (6)	25 (7)
Nausea	42 (13)	40 (12)	Rash	19 (6)	8 (2)
Diarrhea	24 (7)	34 (10)	Back Pain	9 (3)	16 (5)
Vomiting	22 (7)	19 (6)	Peripheral Edema	17 (5)	11 (3)
Constipation	16 (5)	28 (8)			

AEs occurring at any time up to clinical cut-off in ≥ 5% of patients are shown

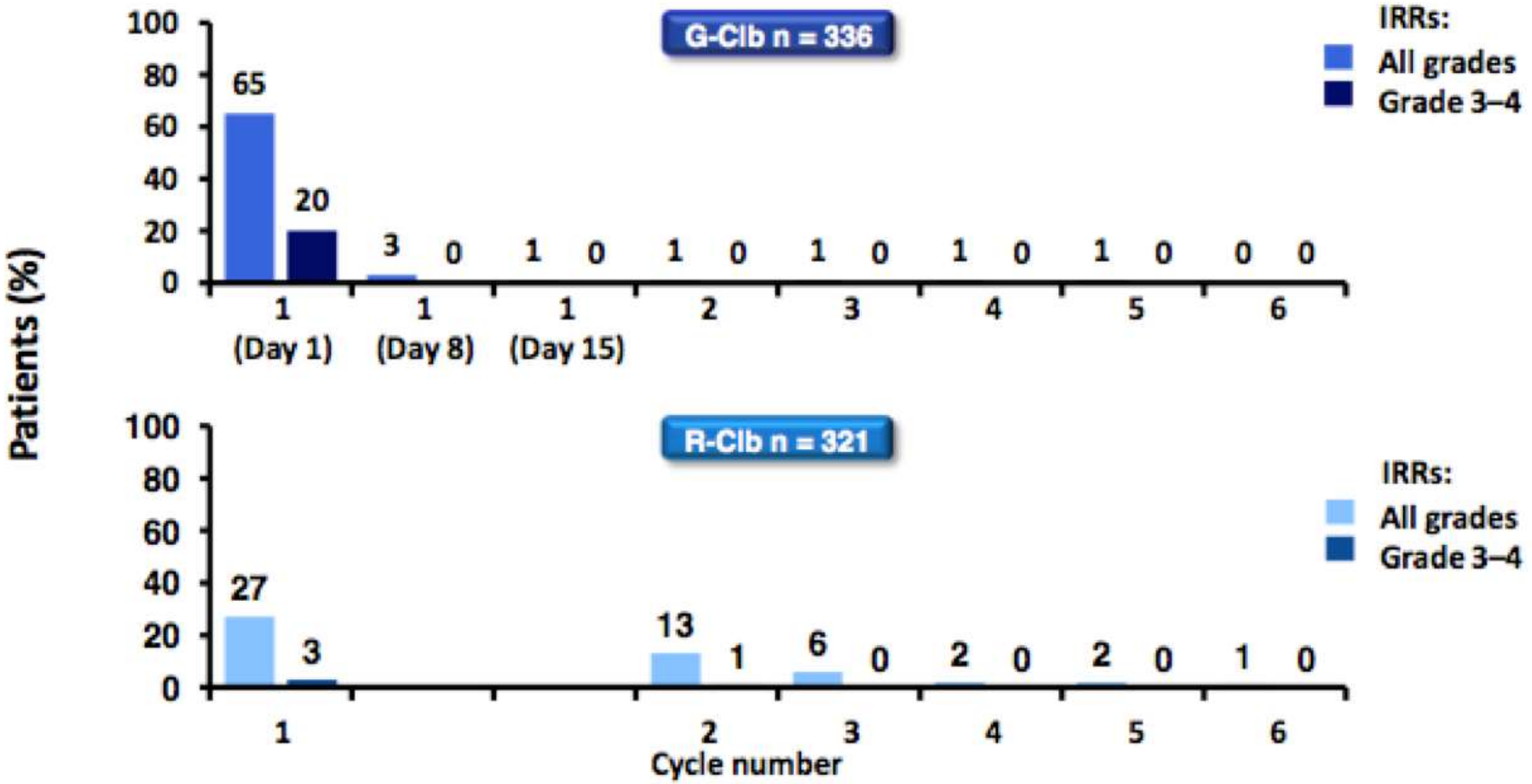
Five patients who were randomized to R-Clb received one infusion of GA101 in error and are included in the safety population for G-Clb and not R-Clb.

Graphical Elaboration from text data

Goede et al., N Engl J Med.* 2014 Jan 8, Suppl Materials

IRRs by cycle

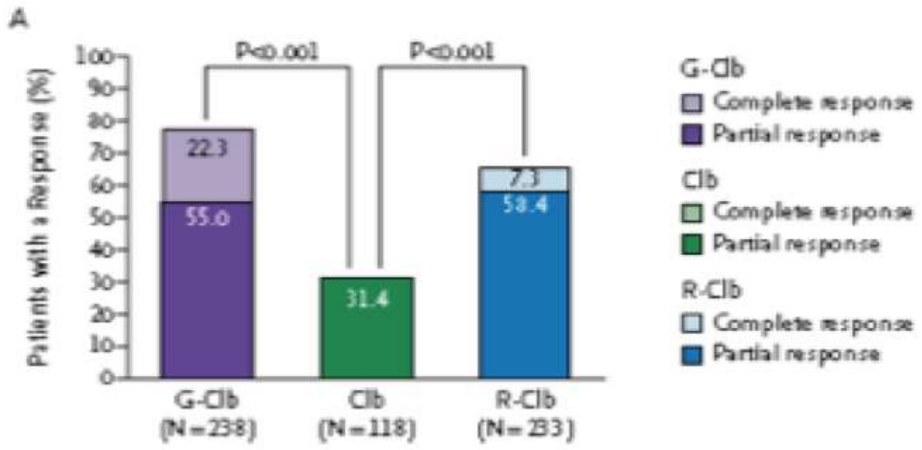
IRRs were rare after the first dose of GA101

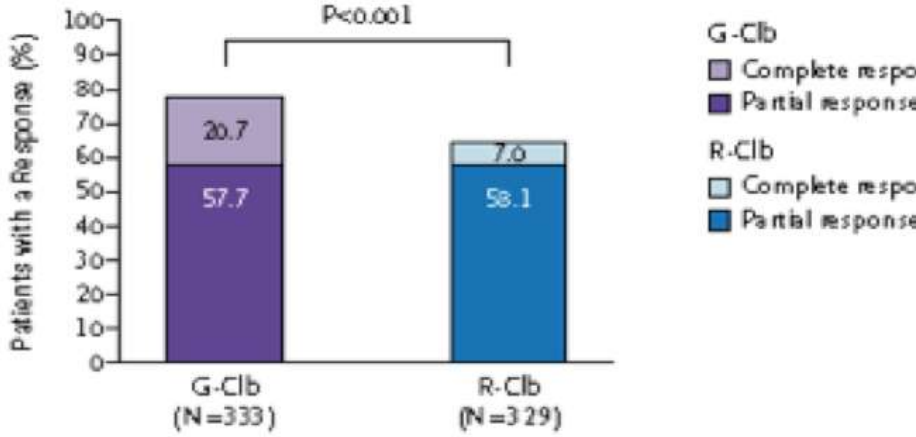


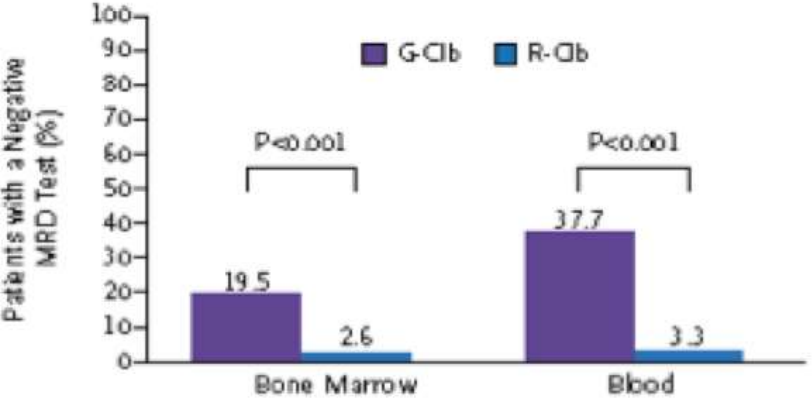
Patients with grade 4 or recurring grade 3 IRRs were discontinued; 7% of patients in the G-Clb arm discontinued due to IRRs
IRRs occurring on day 2 (after the amendment to split the first dose for GA101) are included in the figures for day 1.

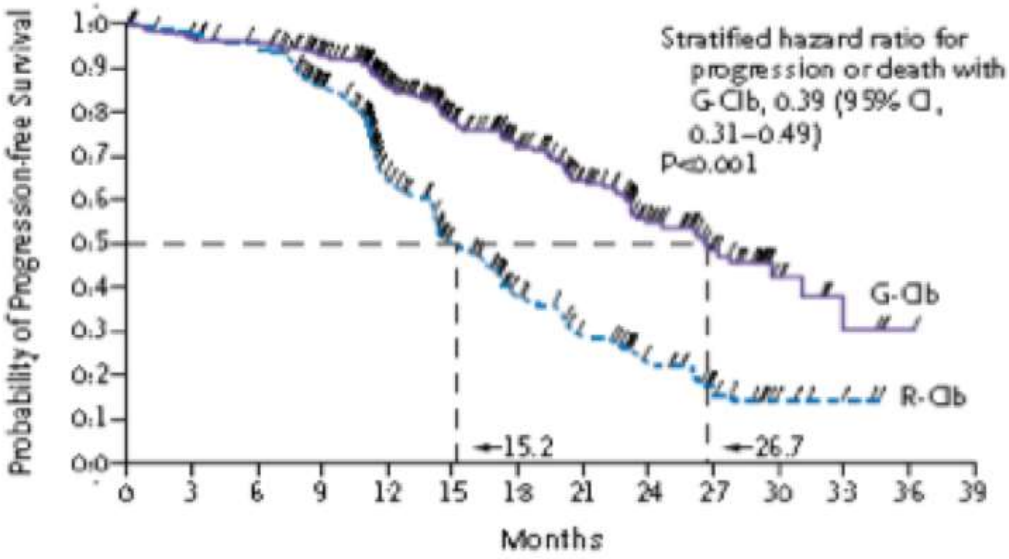
Adapted from
Goede et al., N Engl J Med.* 2014 Jan 8, Supp Materials

CLL 11 result







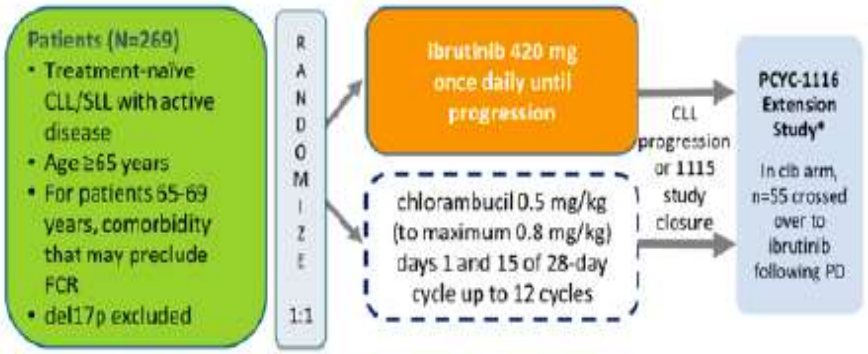


Goede et al., N Engl J Med. 2014 Jan 8

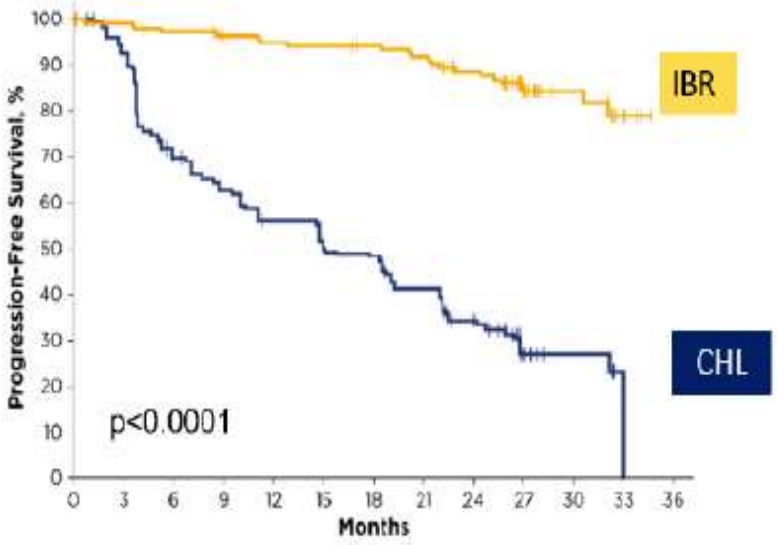
AUTORIZZAZIONE (2017)

Gazyvaro in associazione a clorambucile è indicato nel trattamento di pazienti adulti affetti da Leucemia linfatica cronica (LLC) non pretrattata e con comorbilità che li rendono non idonei a una terapia a base di fludarabina a dose piena.

Resonate-2 trial: front-line ibrutinib vs chlorambucil in ≥65 yrs patients with CLL



CR increasing on ibrutinib from 7% at 12 months to 18% with median follow-up of 29 months.



	Ibrutinib (N=136)	Chlorambucil (N=133)
Median PFS (months)	NR	15
PFS at 24 months	89%	34%

RESONATE-2: Patient Characteristics

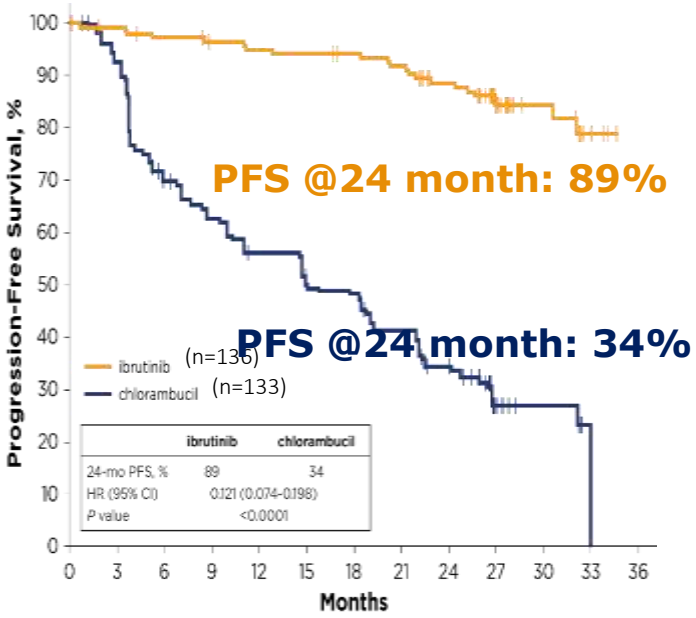
Characteristic	Ibrutinib (n=136)	Chlorambucil (n=133)
Median age, years (range) ≥70 years, %	73 (65–89) 71	72 (65–90) 70
ECOG performance status, % 0 1 2	 44 48 8	 41 50 9
Rai stage III or IV, %	44	47
CIRS score >6, %	31	33
Creatinine clearance <60 mL/min, %	44	50
Bulky disease ≥5 cm, %	40	30
β2-microglobulin >3.5 mg/L, %	63	67
Hemoglobin ≤11 g/dL, %	38	41
Platelet count ≤100 x 10^9/L, %	26	21
Del11q, %	21	19
Unmutated IGHV, %	43	45

janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Burger J et al. N Engl J Med 2015; 373(25): 2425-37

RESONATE-2: PFS over time

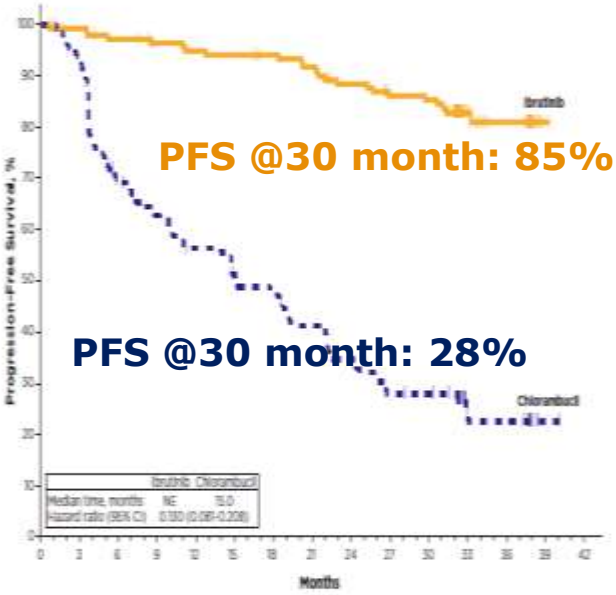
Median F-UP 29 months



PFS @24 month: 89%

PFS @24 month: 34%

Median F-UP 35.7 months



PFS @30 month: 85%

PFS @30 month: 28%

- At 3 years of follow-up significantly longer PFS for ibrutinib (median, not reached vs 15.0 months with chlorambucil), with an **87% reduction in risk of progression or death vs chlorambucil** (HR 0.13; 95% CI: 0.081, 0.208)
- Subgroup analysis of PFS revealed benefit was observed across all sub-groups

Barr et al. ASH 2016 Oral Presentation

Tedeschi et al. ASH 2017;Abstract 1746 (Poster Presentation)

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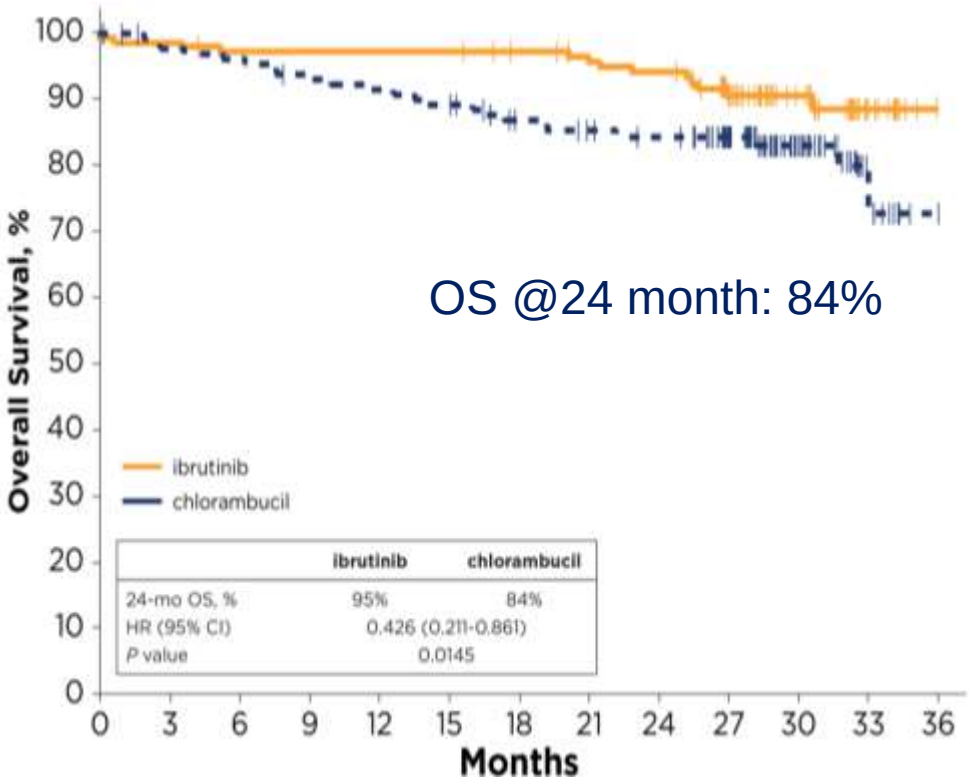
Ibrutinib Continues to Demonstrate OS Benefit Over Chlorambucil With Longer Follow-Up and Cross-Over

Median F-UP: 29 months

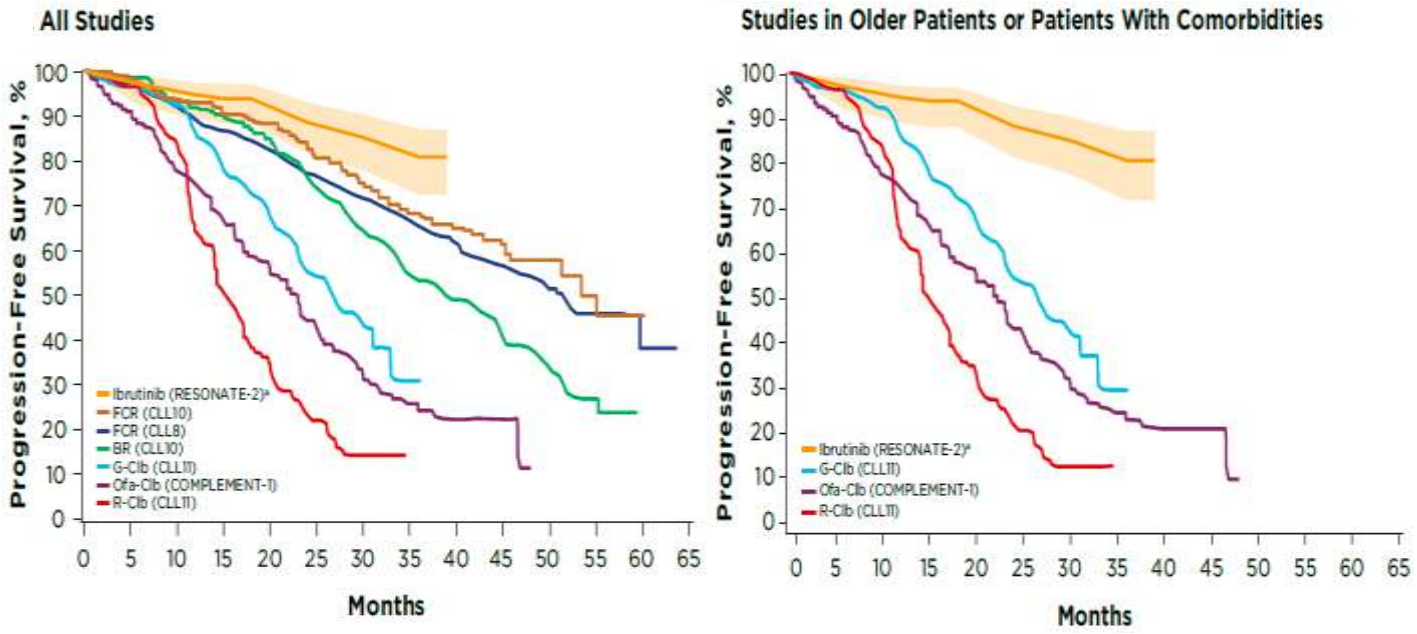


OS @24 month: 95%

- **At median follow-up of 29 months, 55 pts crossed over to ibrutinib from chlorambucil**
- **Significant OS benefit, even with a high number of patients crossing over to ibrutinib**

Barr et al. ASH 2016 Oral Presentation

Single-agent ibrutinib associated with longer PFS as compared with all CIT regimens



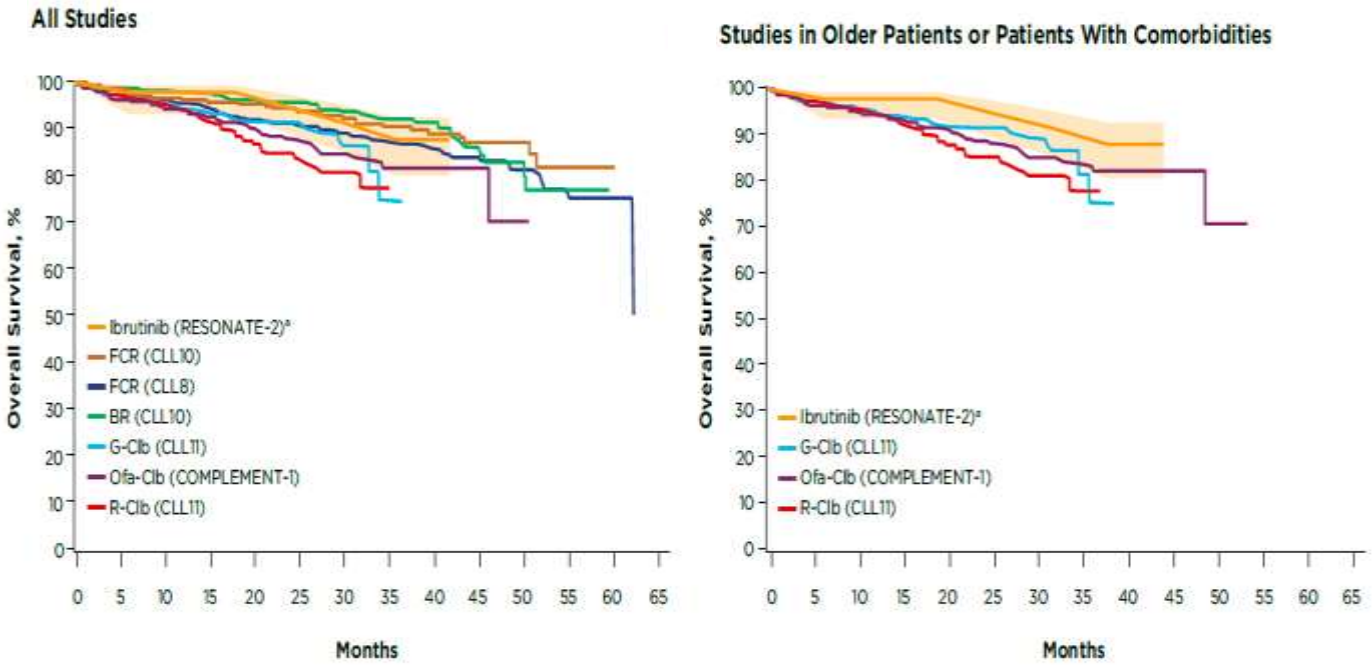
[a]Shaded area represents 95% confidence band with ibrutinib

- Older, less-fit pts treated with ibrutinib experienced a longer PFS than younger, fit pts treated with FCR from CLL8.
- When comparing RESONATE-2 and CLL10 studies (excluding pts with del17p), ibrutinib was associated with improved PFS compared with that for FCR or BR treatment.

- In older pts or those with comorbidities, ibrutinib was associated with improved PFS outcomes relative to those for R-Clb or G-Clb.

Robak et al. ASH 2017; Abstract 1750 (Poster Presentation)

OS outcomes with single-agent ibrutinib compared with all CIT regimens



[a]Shaded area represents 95% confidence band with ibrutinib

- **OS outcomes with single-agent ibrutinib appeared comparable or favorable to CIT regimens**
- **In studies with an older or less fit population, ibrutinib appeared to show more favorable OS relative to Ofa-Clb, R-Clb, and G-Clb.**

Robak et al. ASH 2017; Abstract 1750 (Poster Presentation)

Studio multicentrico di fase 2 per valutare attività e sicurezza di Ibrutinib associato a Rituximab in prima linea nei pazienti unfit affetti da Leucemia Linfocitica Cronica (LLC)

Studio GIMEMA LLC1114

Ibrutinib (PCI-32765) 420 mg (3 capsule da140 mg) sarà somministrato per via orale una volta al giorno. La prima dose sarà somministrata in ospedale al giorno 1, dopo di che le successive sono normalmente assunte dal paziente a casa. La durata del trattamento con Ibrutinib si baserà su quale dei tre eventi si verificherà prima:

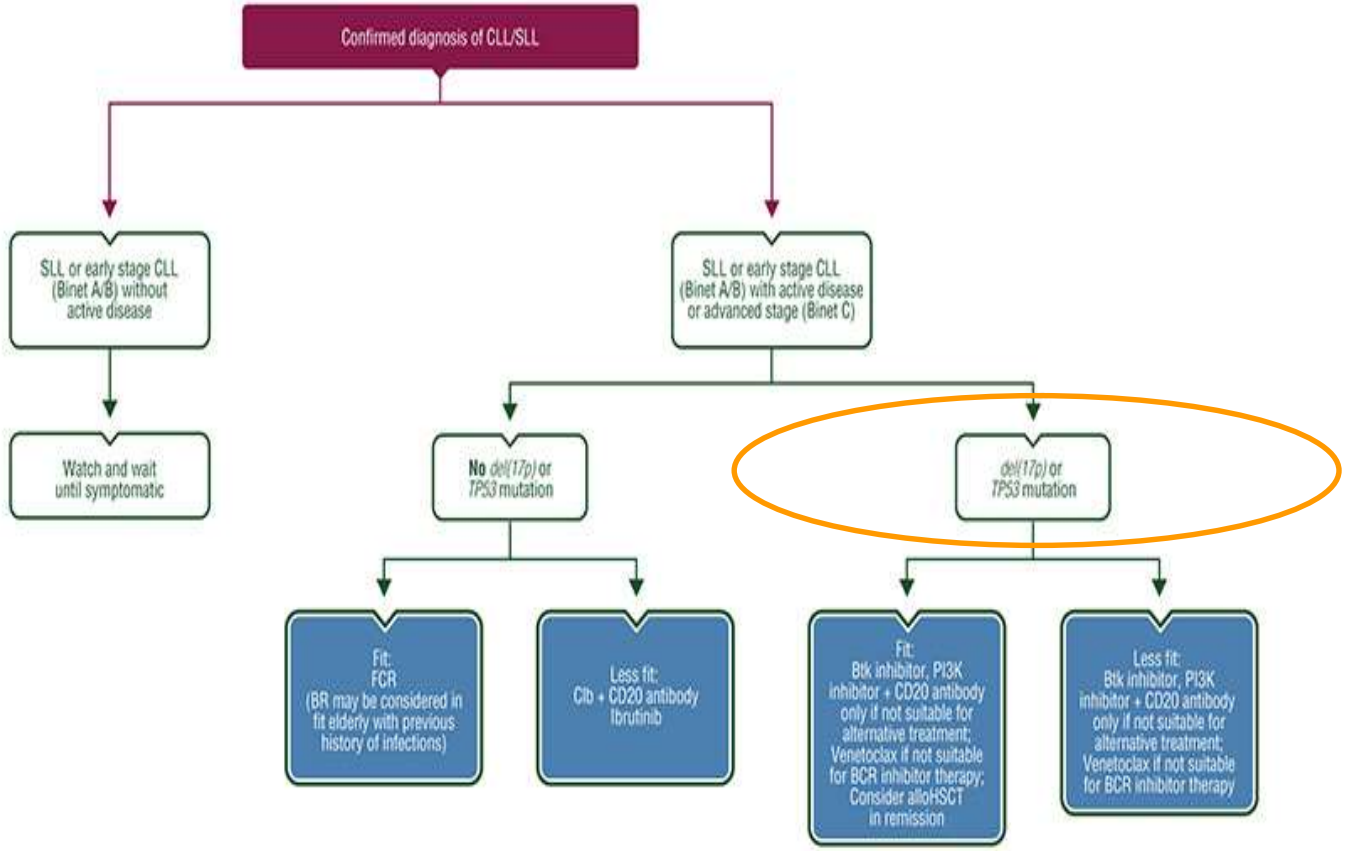
- Trattamento fino a progressione o tossicità;
- Trattamento fino a negatività MRD per sei mesi;
- Trattamento per 6 anni.

Rituximab 375 mg/m^2 endovena: mese 1: giorno 1 delle settimane 1, 2, 3, 4; mesi 2-6: giorno 1 della settimana 1.

Criteri di inclusione:

1. 18 o più anni di età;
2. CIRS totale > 6 e/o *clearance* della creatinina < 70 ml/min |

ESMO CLL Guidelines in frontline setting – Update June 2017

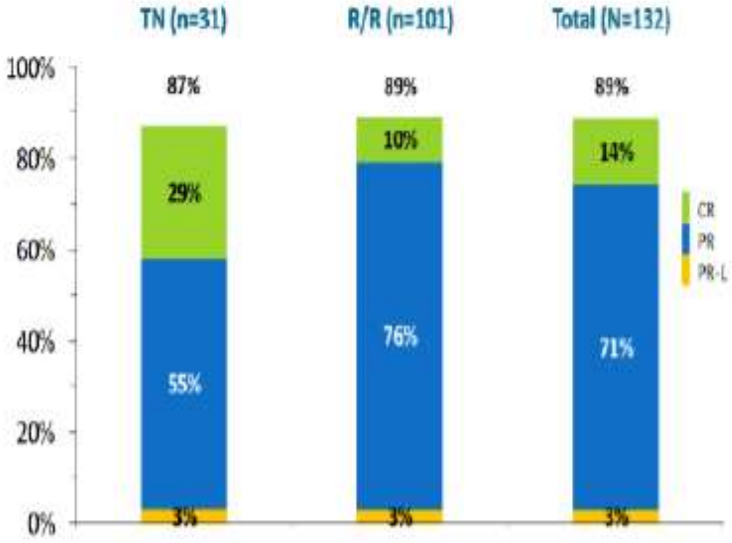


alloHSCT, allogeneic haematopoietic stem cell transplantation; BCR, B-cell receptor; Btk, Bruton's tyrosine kinase; BR, bendamustine plus rituximab; Clb, chlorambucil; CLL, chronic lymphocytic leukaemia; FCR, fludarabine, cyclophosphamide and rituximab; PI3K, phosphatidylinositide 3-kinase; SLL, small lymphocytic leukaemia; TP53, tumour protein p53

Eichhorst B, Robak T, Montserrat P et al. Ann Oncol 2015; 26 (Suppl 5): v78-v84 ePub June 2017

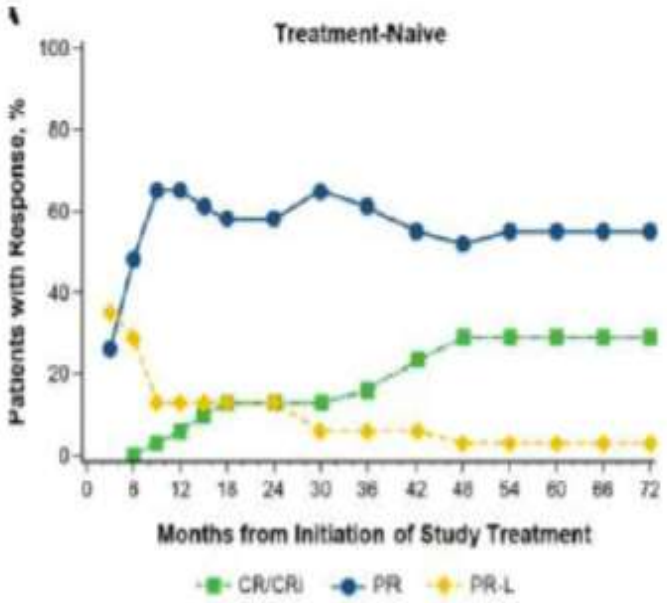
Single-Agent Ibrutinib in TN and R/R CLL. A 5-Year Experience of PCYC 1102/1103 trials

Characteristic	TN (n=31)	R/R (n=101)
Median age, years (range)	71 (65–84)	64 (37–82)
Rai stage III–IV	55%	57%
Bulky disease ≥5 cm	19%	54%
Med.prior therapies, n (range)	-	4 (1–12)
Unmutated IGHV	48%	78%
Del17p Del11q	6% 3%	34% 35%



%CR increases over time:

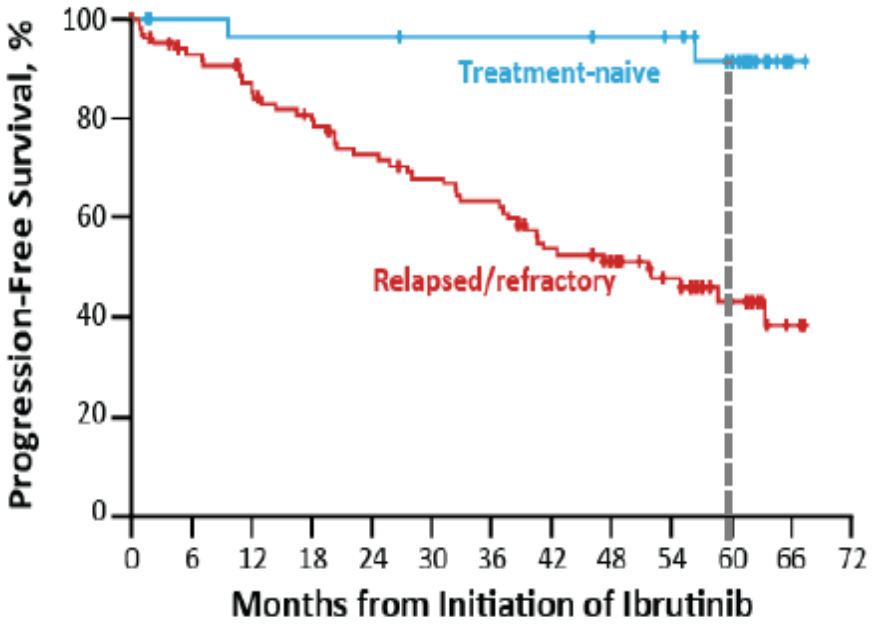
- TN 29%
- R/R 10%



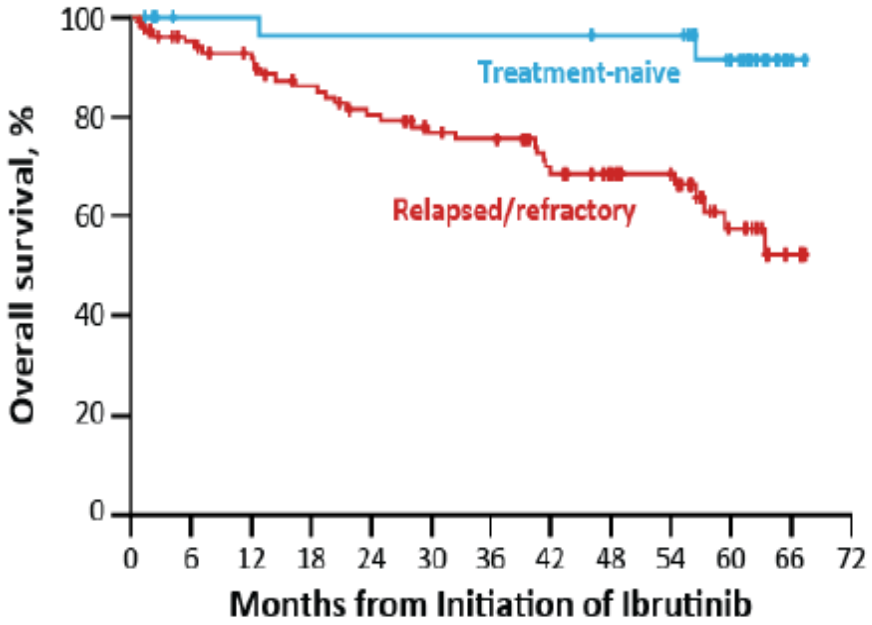
O'Brien et al., Blood 2018

Single-Agent Ibrutinib in TN and R/R CLL. A 5-Year Experience of PCYC 1102/1103 trials

Progression-Freel Survival

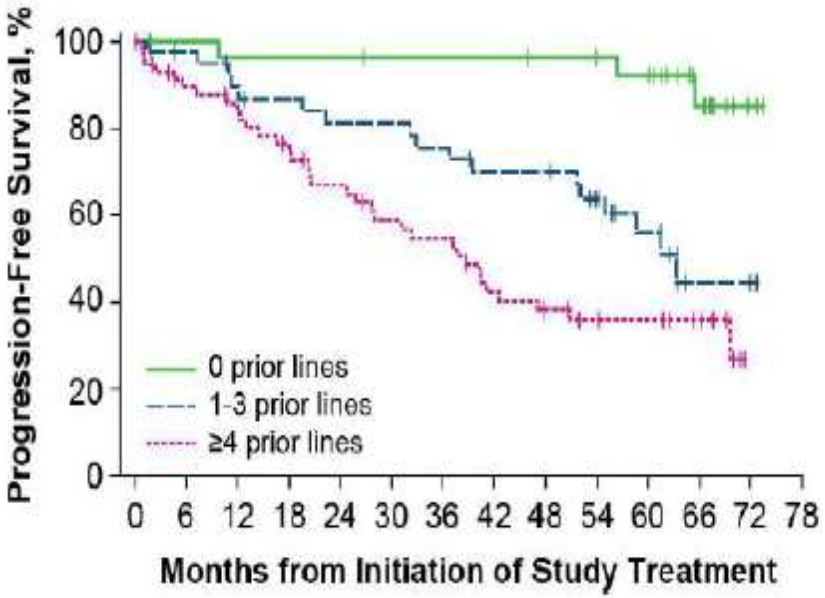


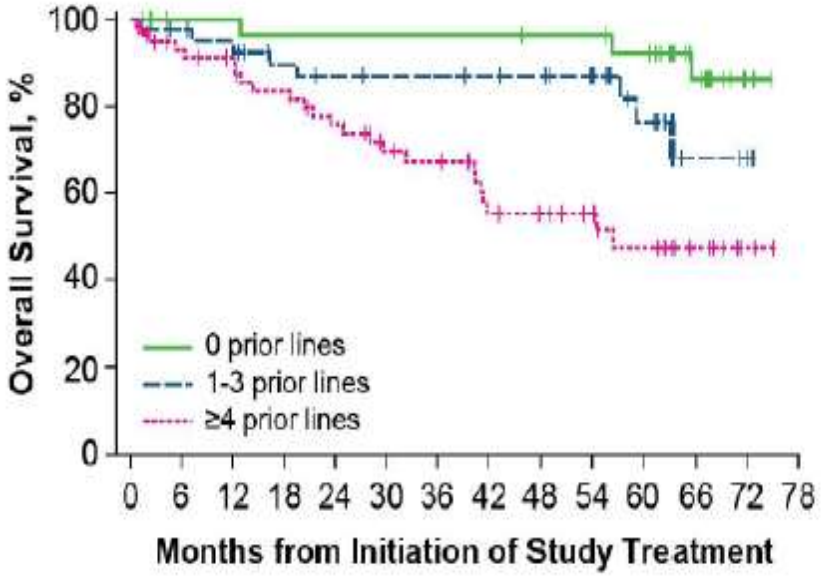
Overall Survival



O'Brien et al., Blood 2018

Single-Agent Ibrutinib in TN and R/R CLL. A 5-Year Experience: impact of prior treatments





O'Brien et al., Blood 2018

A phase 2 study of idelalisib plus rituximab in treatment-naive older patients with chronic lymphocytic leukemia

Table 4. Overall response rate, combined primary and extension studies (N = 64)

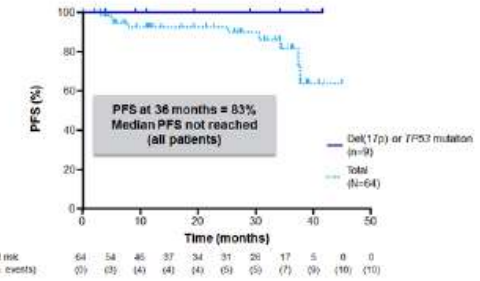
		Del(17p)/*TP53* mutation*		*IGHV* mutation*	
Response, n (%)	Total (N = 64)	Either (N = 9)	Neither (N = 52)	Mutated (N = 23)	Unmutated (N = 37)
CR	12 (18.8)	3 (33.3)	7 (13.5)	7 (30.4)	3 (8.1)
PR	50 (78.1)	6 (66.7)	43 (82.7)	15 (65.2)	33 (89.2)
PR-L	0	0	0	0	0
SD	0	0	0	0	0
PD	0	0	0	0	0
NE	2 (3.1)	0	2 (3.8)	1 (4.3)	1 (2.7)
ORR†	62 (96.9)	9 (100.0)	50 (96.2)	22 (95.7)	36 (97.3)
95% CI‡	89.2-99.6	66.4-100	86.8-99.5	78.1-99.9	85.8-99.9

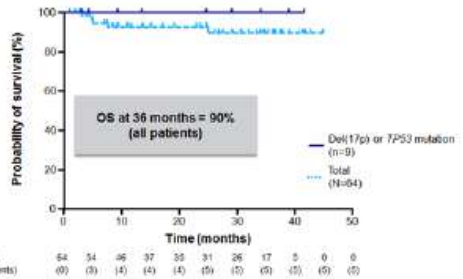
CI, confidence interval; CR, complete response; *IGHV*, immunoglobulin heavy-chain variable region; NE, not evaluable; PD, progressive disease; PR, partial response; PR-L, PR with lymphocytosis; SD, stable disease.

*Patients with missing mutation data were not included.

†ORR = CR + PR.

‡95% exact binomial CI of ORR.





- In 64 older patients with untreated CLL or small lymphocytic leukemia, treatment with idelalisib plus rituximab produced a very high response rate (97%), including 19% CR
- SAEs occurred in 66% of patients; Most common Grade ≥3 AEs were diarrhea/colitis, transaminase elevations, neutropenia, and pneumonia

AEs in ≥20% of patients (All patients, N=64)

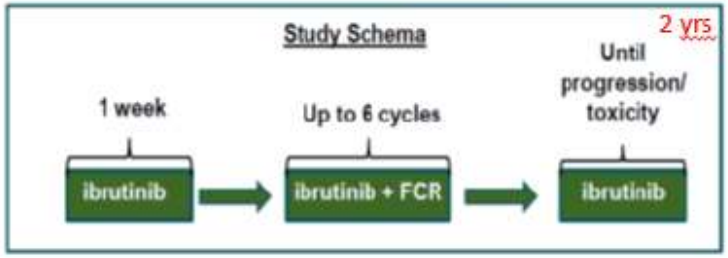
Patients, n (%)	Any grade	Grade ≥3
Any AE	64 (100)	57 (89)
Diarrhoea/colitis	49 (77)	27 (42)
Rash	37 (58)	8 (13)
Pyrexia	27 (42)	2 (3)
Nausea	24 (38)	1 (2)
Chills	23 (36)	0
Cough	21 (33)	1 (2)
Fatigue	20 (31)	0
Pneumonia	18 (28)	12 (19)
Dyspnoea	16 (25)	4 (6)
Headache	15 (23)	0
Vomiting	14 (22)	2 (3)
Insomnia	13 (20)	0

Laboratory abnorma (Grade ≥3)

Patients, n (%)
Transaminase elevation
Neutropenia
Anaemia
Thrombocytopenia


Futuro…..

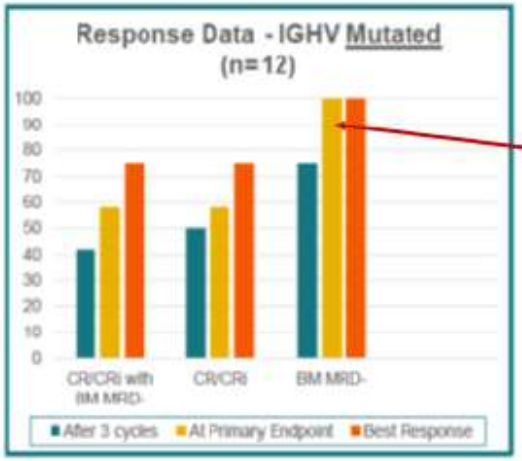
A phase II study of ibrutinib + FCR for younger, TN CLL

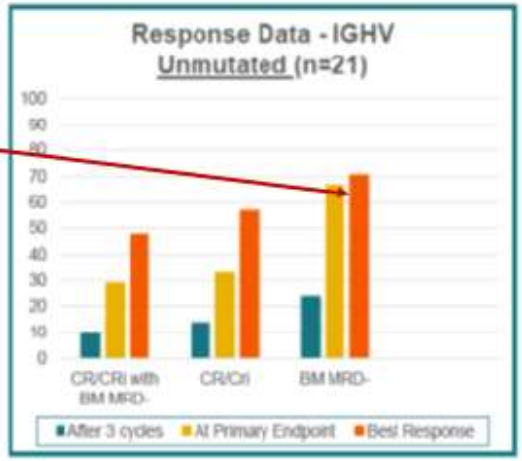


Baseline	n=35
Age, median (range)	55 (38-65)
Del17p, %	4
Unmutated *IGHV* (n=33), %	64
TP53 mutation, %	6

	Best response
ORR	100% (35/35)
PR	37% (13/35)
CR/CRi	63% (22/35)
CR with BM MRD neg. (FCR=20%)	57% (20/35)
BM MRD negative (37% after iFCR)	83% (29/35)

MRD: assessed by 4-color FC (sensitivity 10^{-4}) in BM and PB

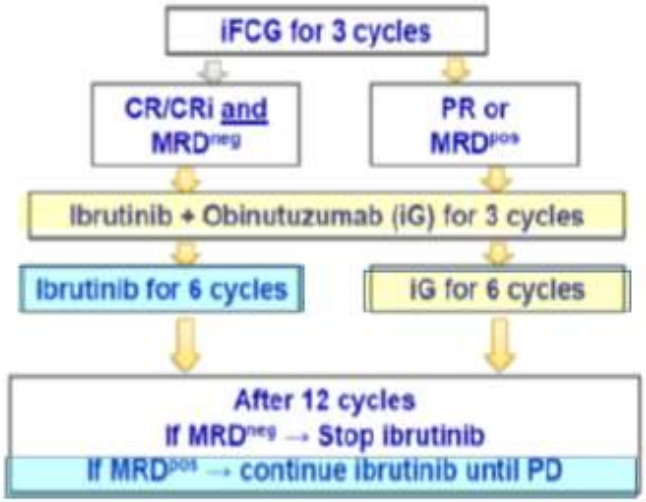




- **Grade 3/4 hematologic AEs**
  - 29% (23% grade 3, 6% grade 4) neutropenia
  - 26% (all grade 3) thrombocytopenia
  - 17% infections (all pooled)

Davids et al., ASH 2017, abstr.# 496

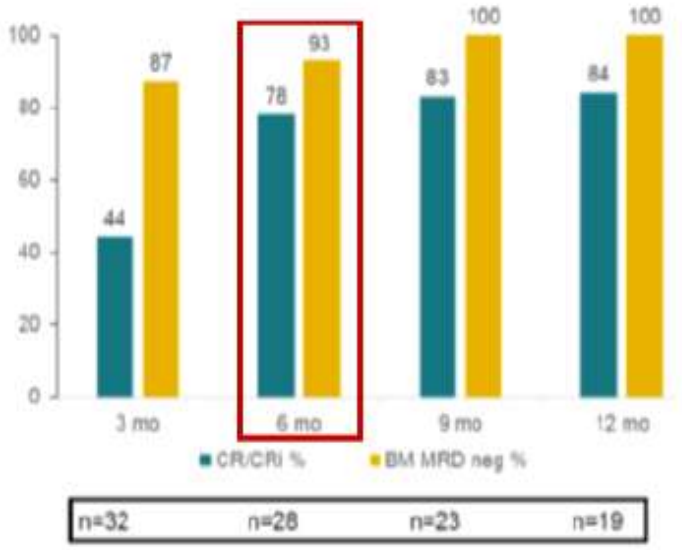
Ibrutinib, fludarabine, cyclophosphamide, obinutuzumab (iFC-G) for TN-CLL with mutated IGHV and without TP53 aberrations



Median follow-up 13.6 mo (range, 0.5-19.9)

Baseline, n (%) or median (range)	(N=36)
Age, yrs (range)	60 (25-71)
Del(13q)	26 (72)

Trial	Regimen	N	CT scan	CR / CRi %	BM MRDneg %
MDACC	FCR x6	88	No	83	51
MDACC	FCR x6	82	No	66	56
CLL8	FCR x6	113	No	50	50
CLL10	FCR x6	123	Yes	39	62
MDACC	iFCG x3 → iG x3	28	Yes	78	93



All 19 pts MRD-negative at 1 year discontinued ibrutinib

Jain et al. ASH 2017. abstr. #495

Venetoclax + Ibrutinib TN High-Risk and R/R CLL (FLAIR TRIAL)

Cohort 1 R/R CLL

Cohort 2 HR-TN CLL
(at least one HR feature: del(17p), mutated TP53, del(11q), unmutated IGHV, ≥65 yrs)

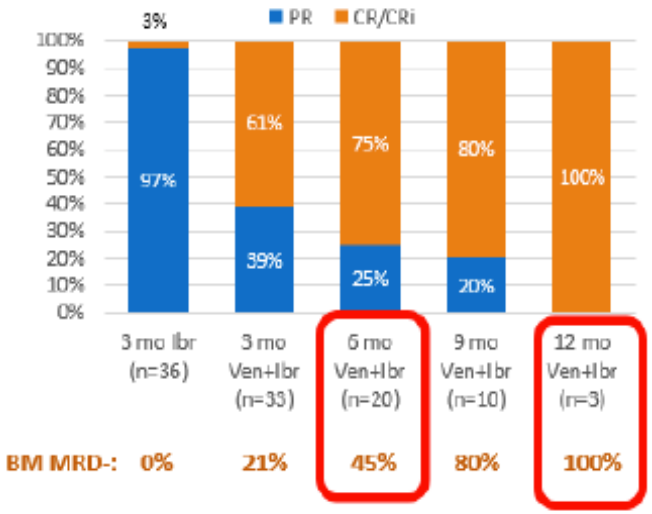
IBRUTINIB

VENETOCLAX

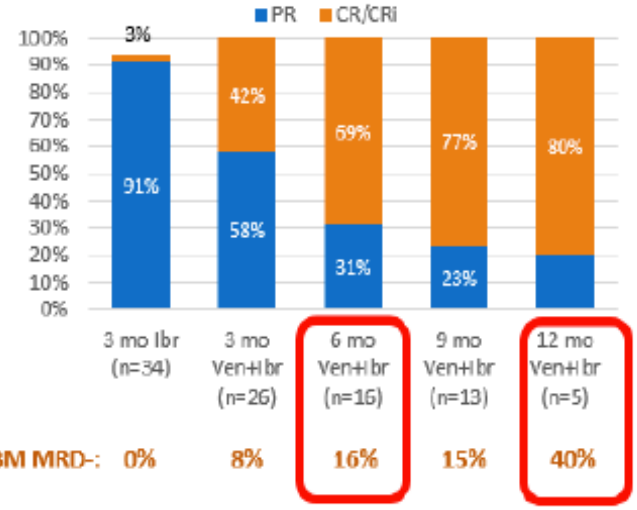
IBR, 420mg daily for the first 3 months, followed by addition of VEN (weekly dose escalation to 400mg daily).
IBR continued indefinitely;
VEN for a total of 2 yrs

- Median follow-up is 7.5 months (range, 0.6-12.1)

First line: 36 patients



R/R Cohort: 34 patients

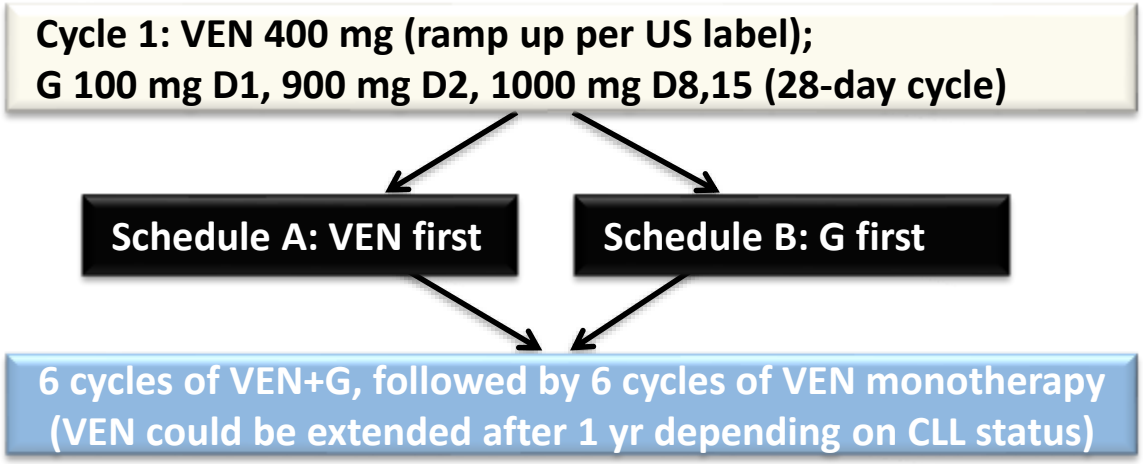


Jain et al. ASH 2017. Abstract #429

Phase 1b Venetoclax + Obinutuzumab in TN-CLL: Study Design

Key eligibility criteria
- Treatment-naïve CLL
- ECOG PS 0-1
- Adequate organ function

Primary objective: MTD, Safety, and tolerability **Secondary objective**: Efficacy **Exploratory**: MRD



Baseline Characteristics	1L CLL (N=32)
Median age; years (range)	63 (47-73)
Male; n (%)	20 (63)
TLS risk; n (%)	
Medium	23 (72)
High	7 (22)
Schedule A (VEN first); n	6
Schedule B (G first); n	26
β2M ≥3.5 mg/mL, n/N (%)	19/32 (59)

Baseline Characteristics	1L CLL (N=32)
Cytogenetic assessment available, n/N (%)	
Del(17p)	5/29 (17)
Del(11q)	6/29 (21)
Trisomy 12	6/29 (21)
Del (13q)	11/29 (38)
TP53 mutation, n/N (%)	5/26 (19)
IGHV unmutated, n/N (%)	16/27 (57)
CD38+, n/N (%)	12/25 (48)

Flinn et al. ASH 2017. Abstract #430.

Phase 1b/2: Obinutuzumab, Ibrutinib, and Venetoclax in CLL - Treatment Naive Cohort: Study Design and Baseline

Inclusion criteria
- TN, symptomatic CLL
- ECOG PS ≤1
- Preserved end-organ and BM function

Exclusion criteria
- Uncontrolled autoimmune thrombocytopenia or anemia
- Clinically apparent Richter's Transformation
- CNS involvement by leukemia
- Use of Warfarin or potent CYP3A4 inhibitors or inducers ≤ 7 days prior to study treatment

Fourteen 28-day cycles OBI+IBR+VEN started sequentially over the first 3 cycles
- C1: OBI (D1: 100mg, D2: 900mg, D8,D15: 1,000mg, C2-8 D1: 1,000mg)
- C2: add IBR in C2 (C2-14 D1-28: 420mg)
- C3: add VEN in C3 with dose escalation according to its US label

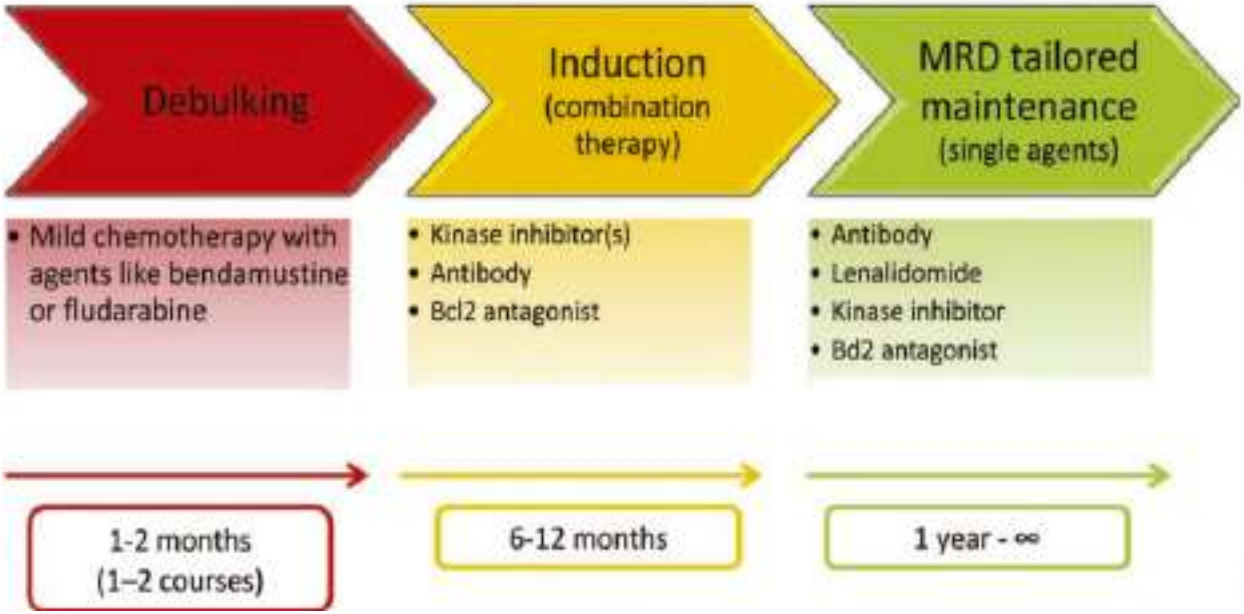
Primary objective: MRD (-) CR after C14 are expected in May 2018

Baseline Characteristics, %	N=25	Baseline Characteristics, %	N=25
Median age, yrs (range)	59 (24-77)	**Unmutated IGHV**	71
Male	60	**Complex karyotype**	24
Del(11)q	20	**Trisomy 12**	12
Del(17)p	12	**TLS Risk high**	28
Del(13)q	20	**TLS Risk medium**	72
		TLS Risk low	0

Rogers et al. ASH 2017. Abstract #431

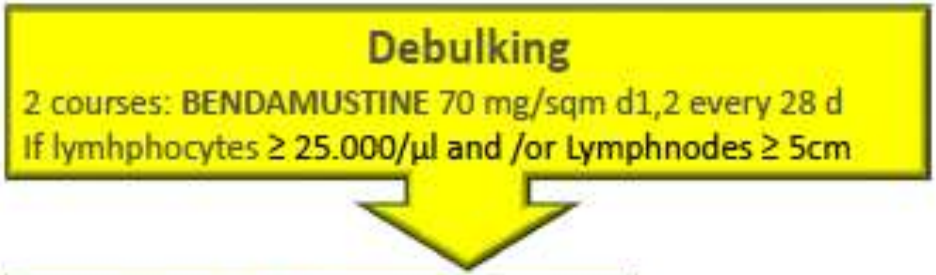
- Many of the previous observations have raised the question of whether combinations of novel drugs w/o CIT might achieve longer remissions or even cure.
- The GCLLSG aiming for a total MRD eradication tested the so-called *sequential triple-T*: an optional debulking with up to 2 cy of a single drug (eg bendamustine) followed by 6 mo of induction therapy using combinations of MoAbs and KIs or Venetoclax, or both, followed by MRD-tailored maintenance.

von Tresckow, ASH 2016

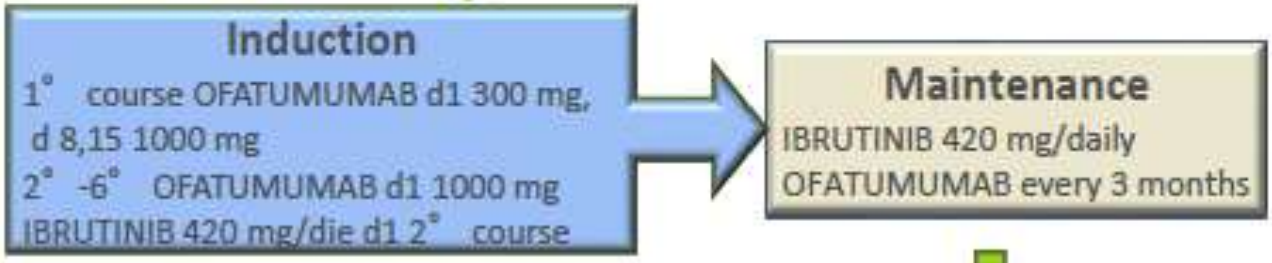


Hallek , Blood. 2013

Bendamustine Followed By Ofatumumab and Ibrutinib in CLL: CLL2-BIO Trial of the German CLL Study Group (GCLLSG)



fit and unfit CLL patients treatment-naïve (TN) and relapsed/refractory (R/R) irrespective of high-risk genetic markers.



Therapy until

MRD-

or 24 m

Primary Objective

- ORR at the end of Induction Treatment

Secondary Objective

- MRD assessment
- Survival
- Tolerability

Cramer P et al Abstract 494 ASH 2017

Grazie per l’attenzione