Quesiti aperti nella LLC: la prognosi è cambiata anche per il paziente anziano ?

F. Zaja - Trieste

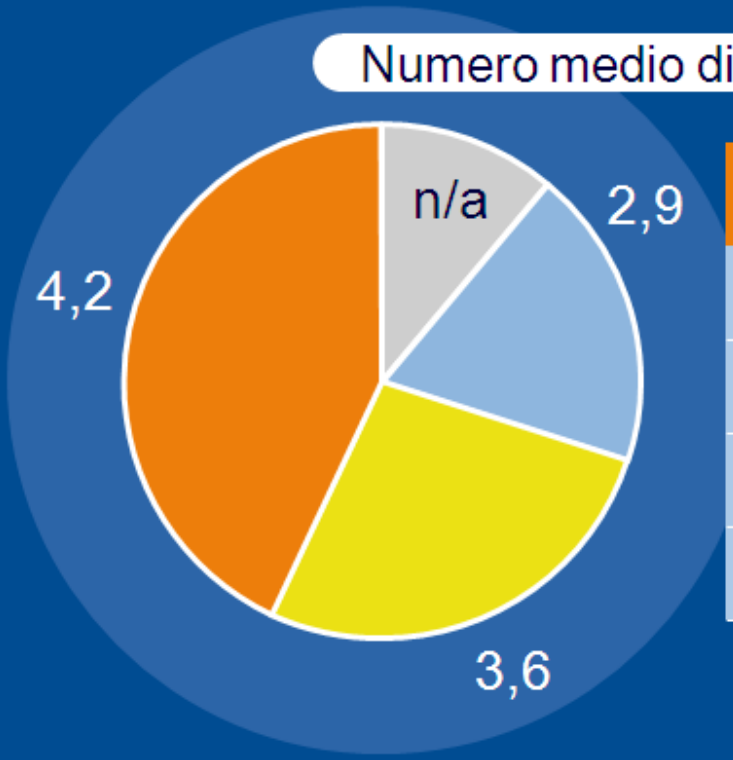
Epidemiology of CLL

- Diagnosis is around 72 years of age
- The incidence of CLL increases with age
- Almost 70% of CLL patients are older than 65 years at the time of diagnosis
  - → 29% diagnosed between 45-64 years of age;
  - → 56% diagnosed between 65-84 years of age;
  - → 13% diagnosed above 85 years of age.
- More than 50% of patients who require therapy are > 70 years of age
- Median age at death from CLL is 79 years

Zent CS, *et al*. *Cancer* 2001; 92:1325–1330. 2Ries LAG, *et al*. SEER data 2008. Available at: http://seer.cancer.gov/csr/1975_2008/ (accessed Nov 2011). Jemal A, *et al*. *CA Cancer J Clin* 2008; 58:71–96. 4Montillo M, *et al*. *Haematologica* 2005; 90:391–399.

Caratteristiche dei pazienti affetti da LLC

- Età media alla diagnosi: 72 anni[1]
- Molti pazienti anziani sono in buona salute, ma alcuni presentano comorbilità



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 Cancer Statistics Review 1975–2005. Available at: http://seer.cancer.gov/csr/1975_2005/ accessed February 2009.
2. Yancik R, Cancer 1997; 80: 1273–83.

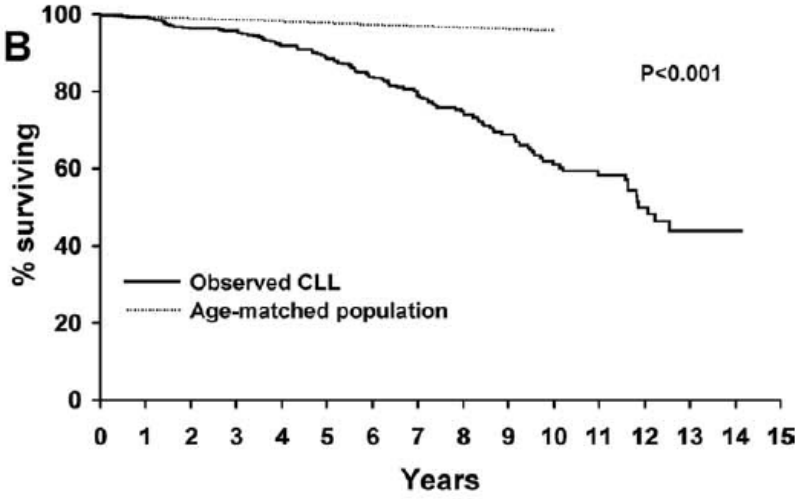
Stratificazione dei pazienti in diversi gruppi clinici a seconda della presenza o meno di comorbidità loro stato di “fitness”

‘Go-go’	‘Slow-go’	‘No-go’
• Completamente indipendenti • No comorbidità • Normale aspettativa di vita → Approccio terapeutico intensivo	• Alcune comorbidità • Alcune funzioni d’organo compromesse • Performance status alterato → Approccio terapeutico meno intensivo	• Condizioni generali compromesse • Alcune importanti comorbidità • Aspettativa di vita ridotta → Approccio terapeutico palliativo

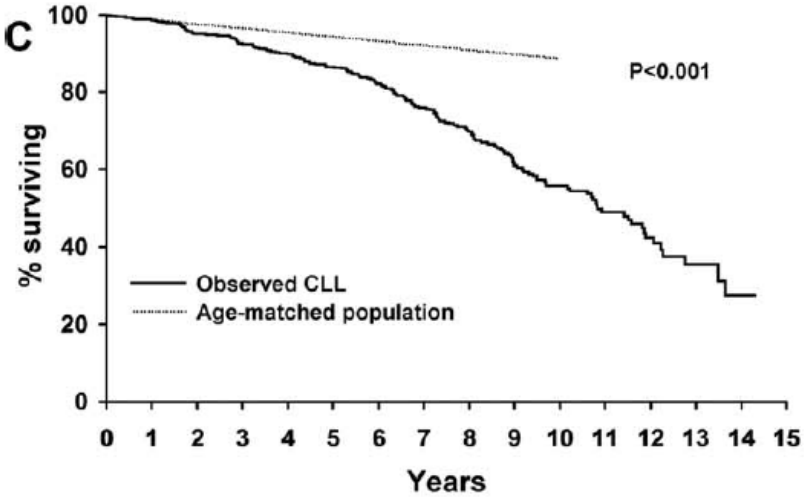
Eichhorst B, et al. Leuk Lymphoma 2009; 50:171–178; Leblond V. Eur Oncol Haematol 2012; 8:52–57.

Survival of CLL pts compared with age-matched individuals

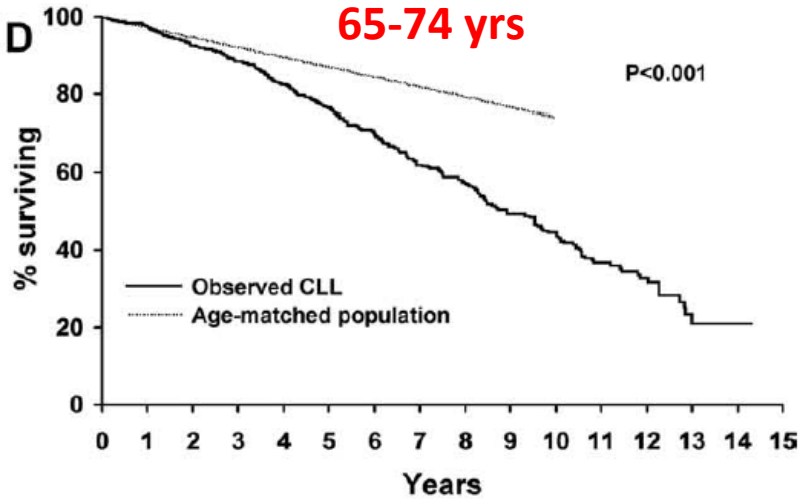
< 55 yrs



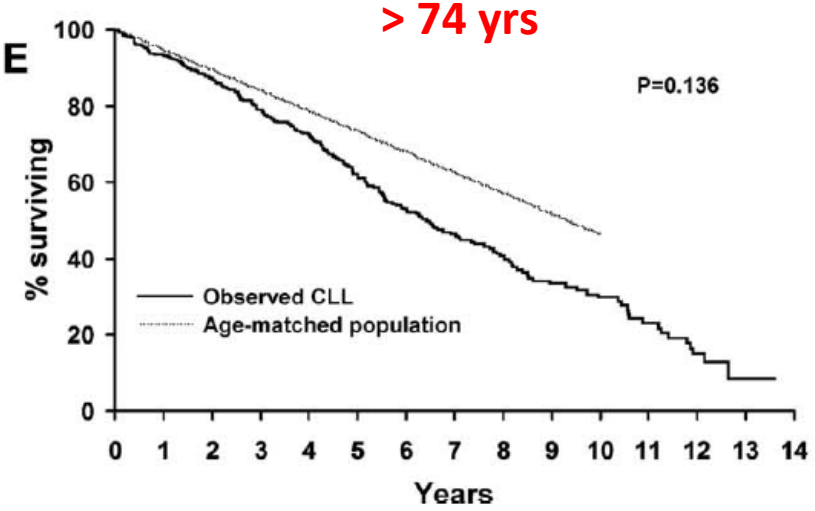
55-64 yrs



65-74 yrs



> 74 yrs



Shanafelt TD et al., Cancer 2010;116:4777–87.

FCR in Elderly

FCR not well tolerated by patients > 70 years[a,b,c]

- Age > 65 years predict premature discontinuation FCR[a]
- 75% patients ≥ 70 years have grade 3/4 myelosuppression[b]
- 46% patients ≥ 70 years completed 6 cycles[b,c]
  - 50% due to prolonged cytopenia

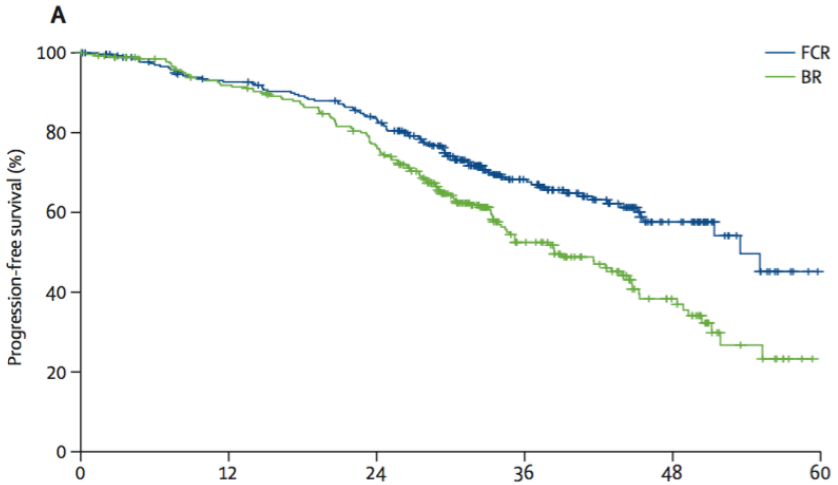
FCR less effective patients > age 70 years[c]

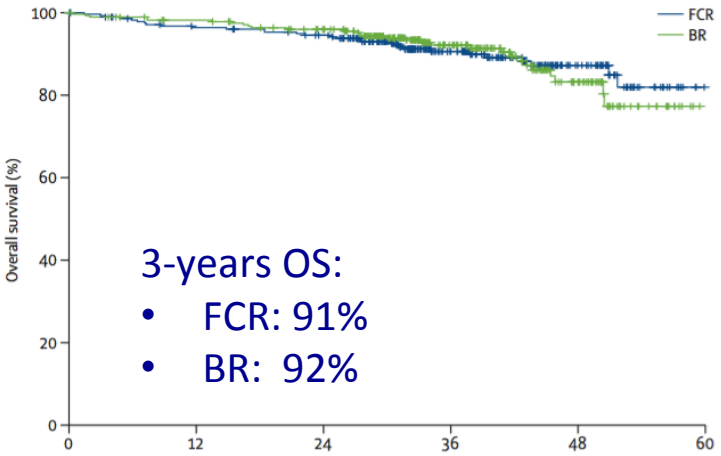
Age	CR Rate	*P* Value
< 60	75%	
60-69	77%	.02
≥ 70	51%	

a. Keating MJ, et al. *J Clin Oncol*. 2005;23:4079-4088[52]; b. Ferrajoli A, et al. *Leuk Lymph*. 2005;46:S86[53]; c. Tam CS, et al. *Blood*. 2008;112:975-980.[50]

1L chemoimmunotherapy: FCR vs BR (CLL-10)

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**

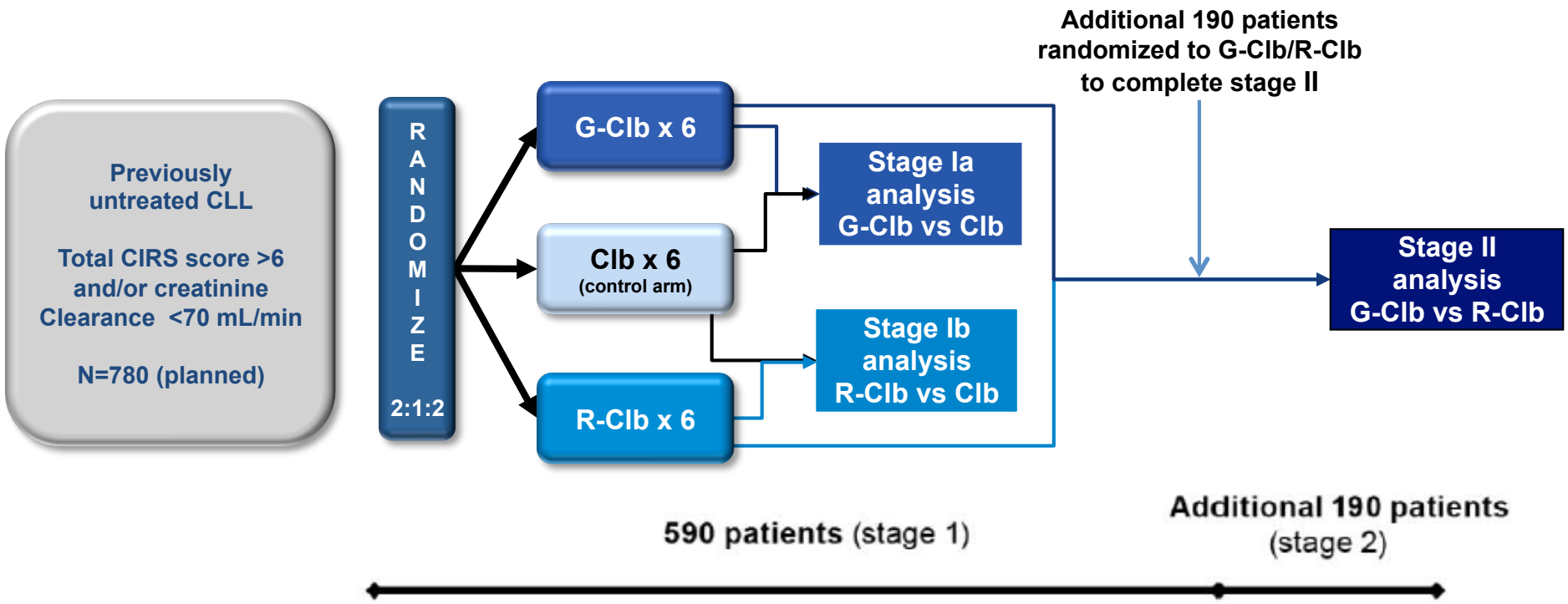




3-years OS:
- FCR: 91%
- BR: 92%

Eichhorst et al. Lancet Oncol 2016

CLL11: Obinutuzomab plus Chlorambucil in patients with CLL and coexisting conditions



- GA101: 1000 mg days 1, 8, and 15 cycle 1; day 1 cycles 2–6, every 28 days
- Rituximab: 375 mg/m2 day 1 cycle 1, 500 mg/m2 day 1 cycles 2–6, every 28 days
- Chlorambucil: 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

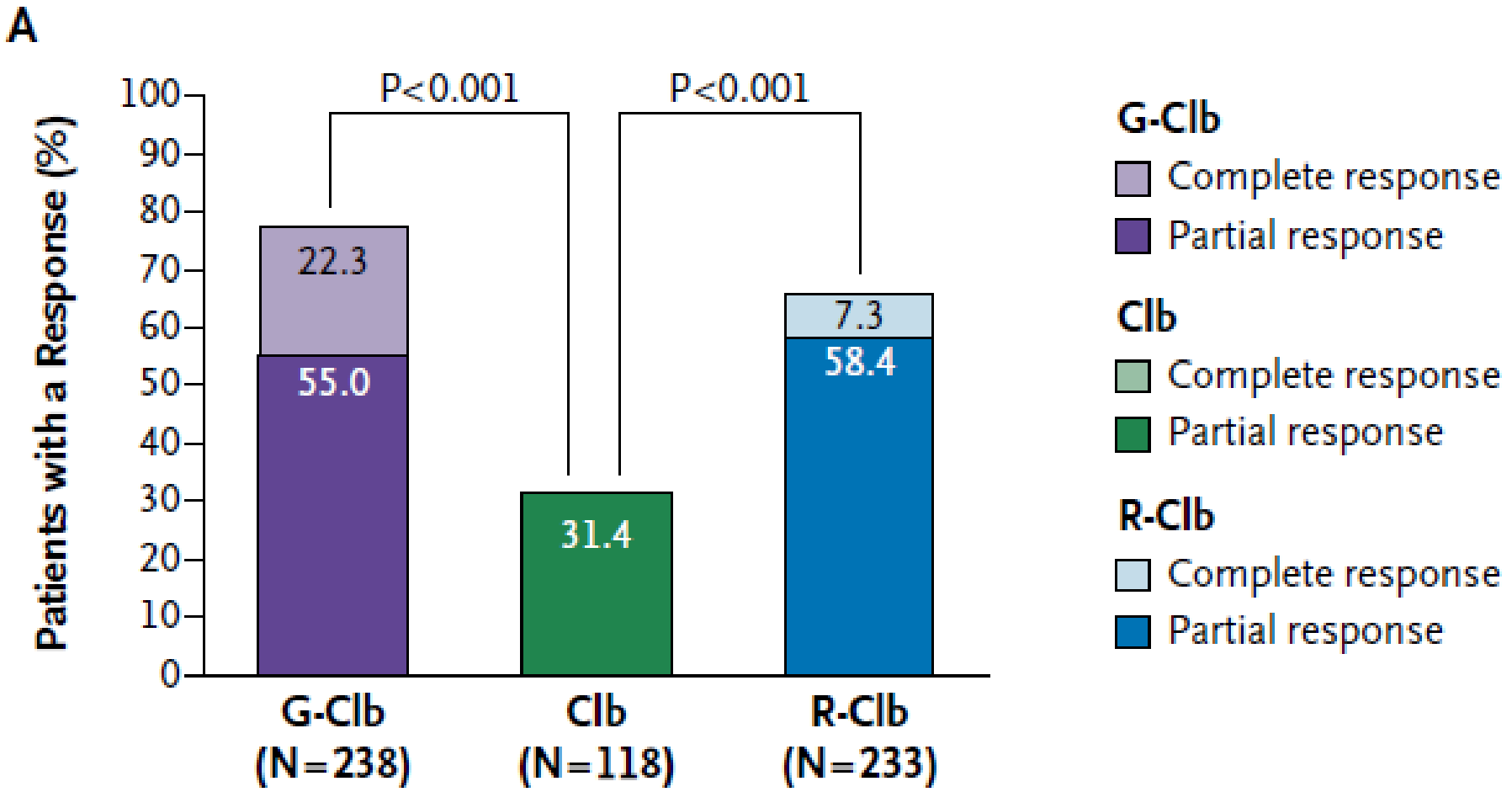
Goede V et al., N Engl J Med 2014.

Obinutuzumab plus Chlorambucil in Patients with CLL and Coexisting Conditions

Characteristic	Obinutuzumab–Chlorambucil vs. Chlorambucil Alone		Rituximab–Chlorambucil vs. Chlorambucil Alone		Obinutuzumab–Chlorambucil vs. Rituximab–Chlorambucil	
	Obinutuzumab–Chlorambucil (N=238)	Chlorambucil Alone (N=118)	Rituximab–Chlorambucil (N=233)	Chlorambucil Alone (N=118)	Obinutuzumab–Chlorambucil (N=333)	Rituximab–Chlorambucil (N=330)
Age — yr						
Median	74	72	73	72	74	73
Range	39–88	43–87	40–90	43–87	39–89	40–90
Cumulative Illness Rating Scale†						
Score — median (range)	8 (1–20)	8 (0–18)	8 (0–18)	8 (0–18)	8 (0–22)	8 (0–18)
Unmutated *IGHV* — no./total no. (%)	129/210 (61)	58/99 (59)	126/204 (62)	58/100 (58)	188/305 (62)	182/298 (61)
del(17p) on FISH — no./total no. (%)	16/203 (8)	10/96 (10)	9/196 (5)	10/97 (10)	22/295 (7)	20/287 (7)

Goede V et al., N Engl J Med 2014.

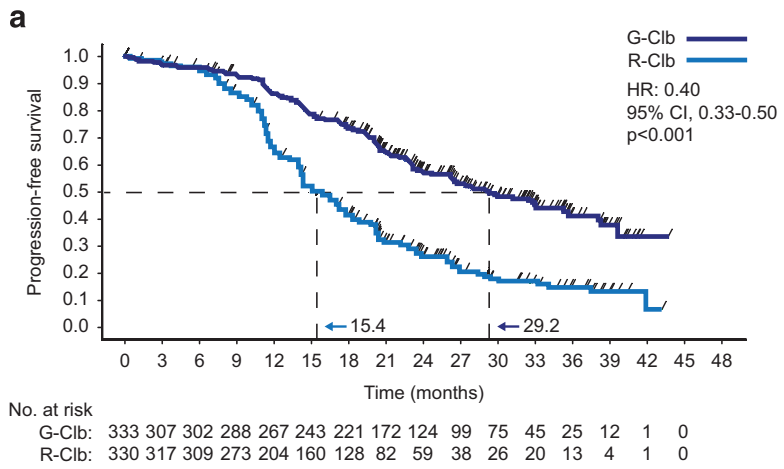
Response rates



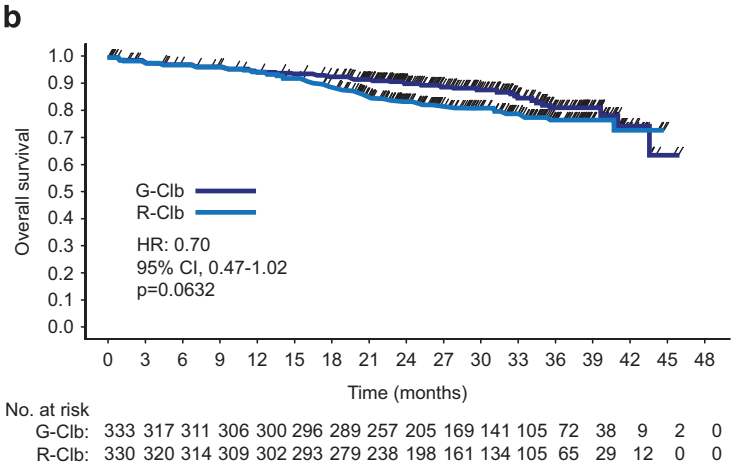
Goede V et al., N Engl J Med 2014.

Obinutuzomab as front line treatment of Chronic Lymphocytic leukemia: updated results of CLL11 study with 12 months more of follow-up

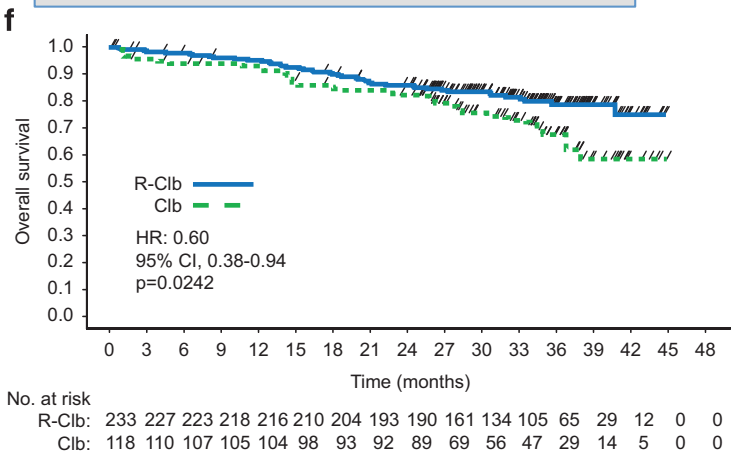
Progression Free survival of G-Clb vs R-Clb



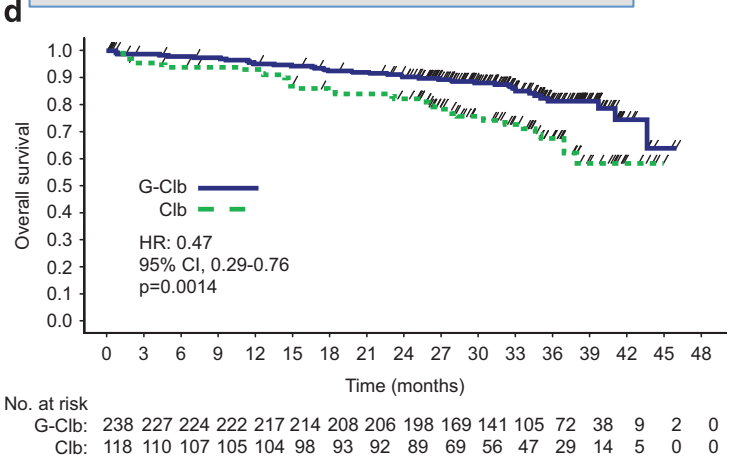
Overall survival of G-Clb vs R-Clb



Overall survival of R-Clb vs Clb



Overall survival of G-Clb vs Clb



Goede V et al., N Engl J Med 2014.

Ibrutinib: indicazioni AIFA per CLL

Prima linea:

- Pazienti con 17p-/mutazione p53
- Pazienti età > 70 anni
- Pazienti 65 – 69 anni:
  - con clearance creatinina < 70 ml/min
  - PLT < 100 x 10^9/L o Hb < 100 g/L
  - AHA o ITP
  - ECOG 1 o 2

Seconda linea:

- Tutti

Ibrutinib as initial therapy for patients with CLL

An international open-label, randomized phase 3 trial to compare Ibrutinib vs Chlorambucil in previously untreated **older patients > 65 years** with CLL or SLL. (**RESONATE-2**)
Primary end-point: progression free survival

269 patients randomized 1:1 to receive either oral Ibrutinib (420 mg/day) until disease progression or unacceptable toxicities, or up to 12 cycles of Chlorambucil

136 patients received Ibrutinib:

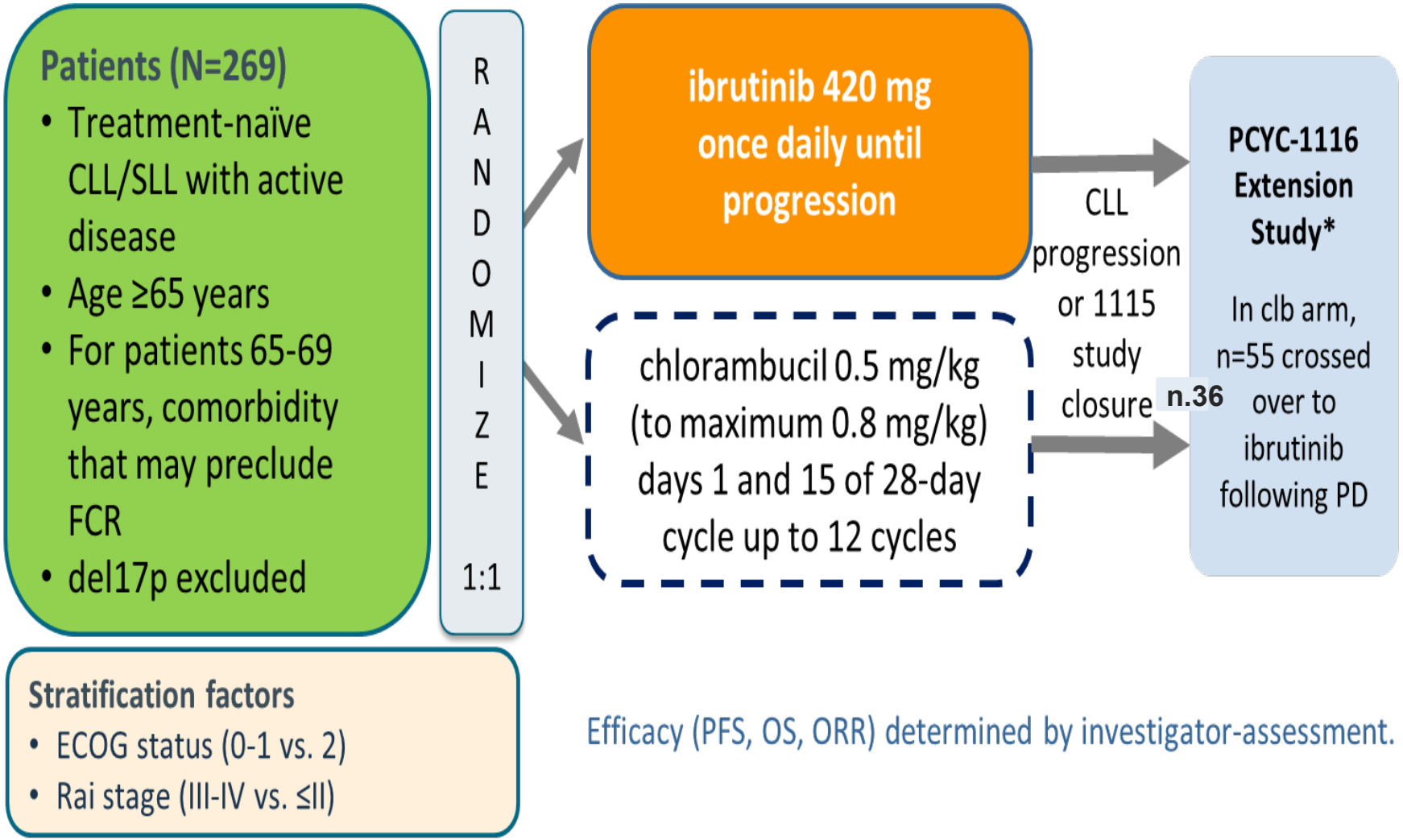
- **Median Age:** **73 (65-89)**
- ECOG PS 0-1 92%
- CLL patients 90%
- RAI stage III-IV 44%
- Del(11q) 21%
- Unmutated IgHV 43%

Key inclusion criteria:

- Age ≥ 65 years
- Previously untreated CLL or SLL
- ECOG PS ≤ 2
- Absence of del(17p)
- Creatinine clearance <70 mL/min
- PLT count <100,000/µL or Hb <10 g/dL
- Autoimmune cytopenia (AIHA, AIT)
- ECOG performance score = 1 or 2

Burger et al NEJM 2015

RESONATE-2 (PCYC-1115/1116)



*Patients could enroll in separate extension study PCYC-1116 after independent review committee-confirmed PD or at study PCYC-1115 closure for continuing treatment and follow-up.

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

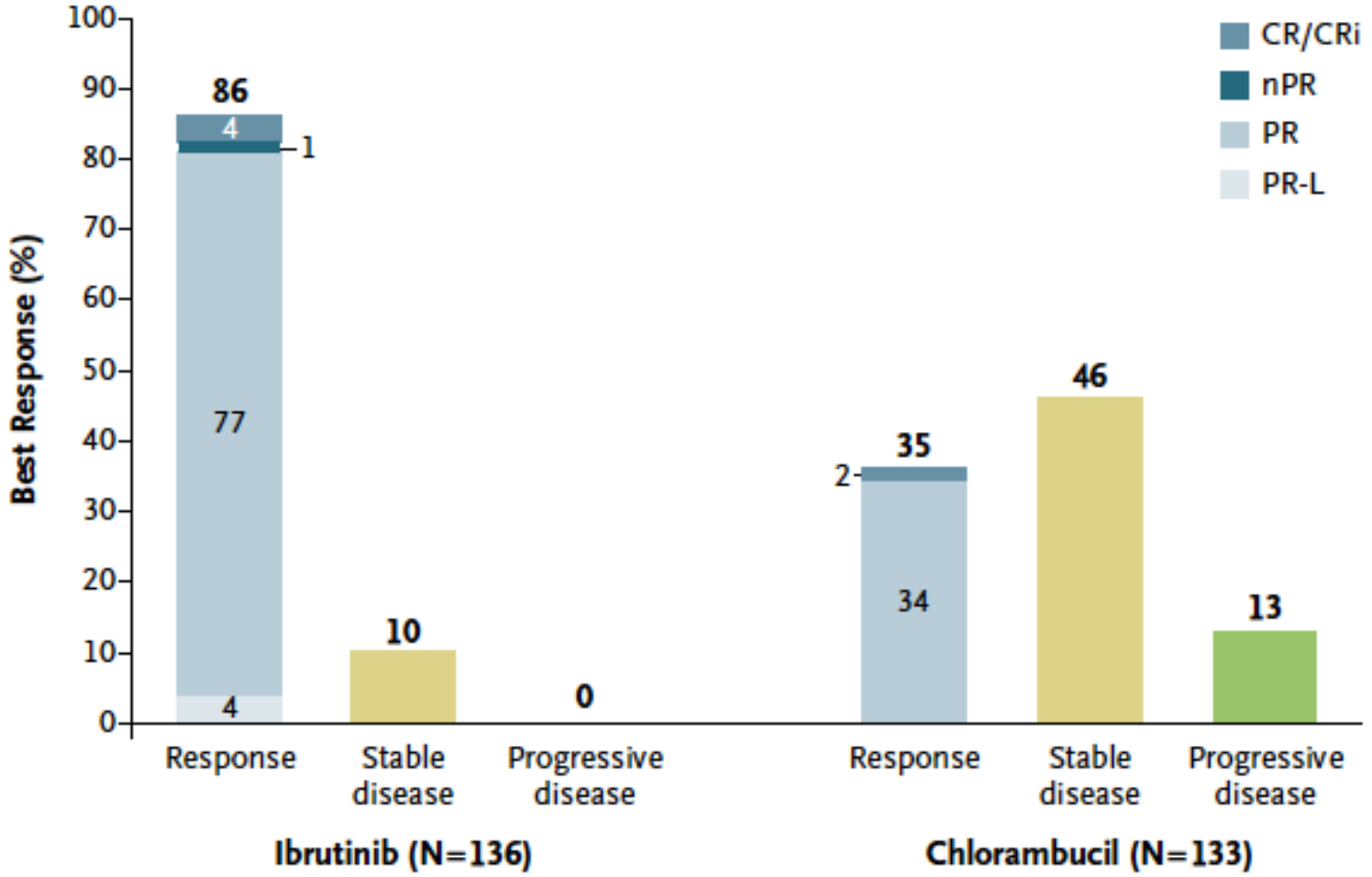
RESONATE2: Patient Characteristics

Characteristic	ibrutinib (n=136)	chlorambucil (n=133)
Median age, years (range)	73 (65–89)	72 (65–90)
≥70 years, %	71	70
ECOG performance status, %		
0	44	41
1	48	50
2	8	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

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

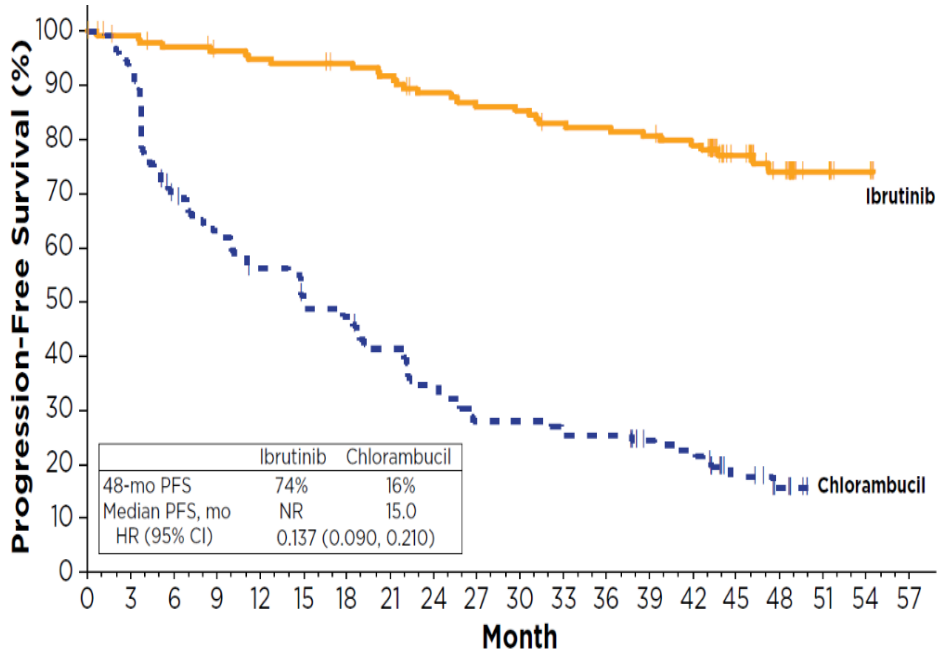
Ibrutinib as initial therapy for patients with CLL

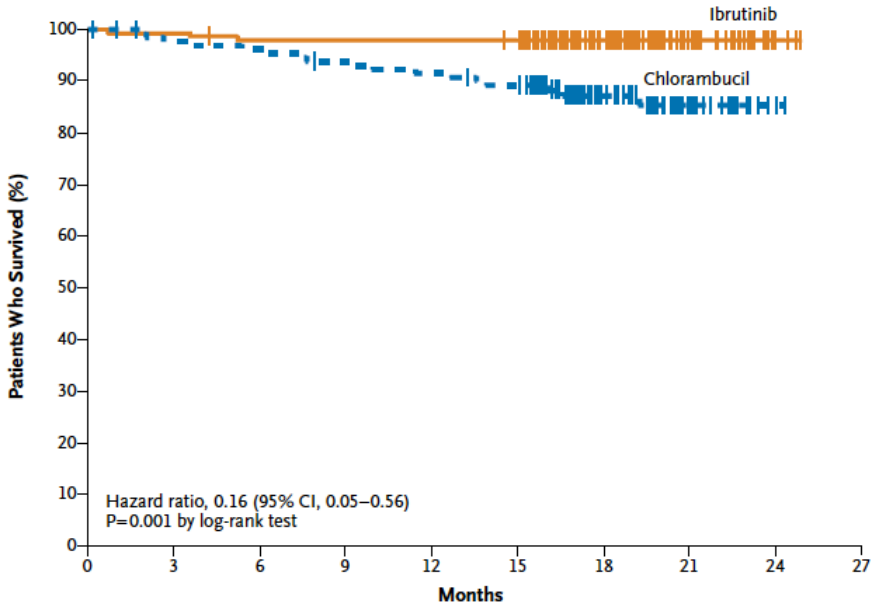
Overall Response Rate	Ibrutinib	Chlorambucil	Rate Ratio (95% CI)	P Value
	% of patients			
With PR-L	86	35	2.42 (1.91–3.07)	<0.001
Without PR-L	82	35	2.32 (1.82–2.95)	<0.001

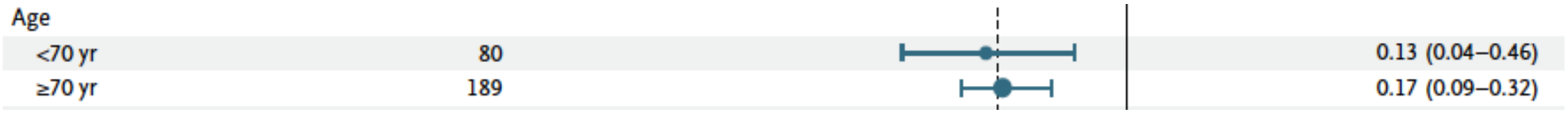


Burger et al NEJM 2015

Ibrutinib as initial therapy for patients with CLL

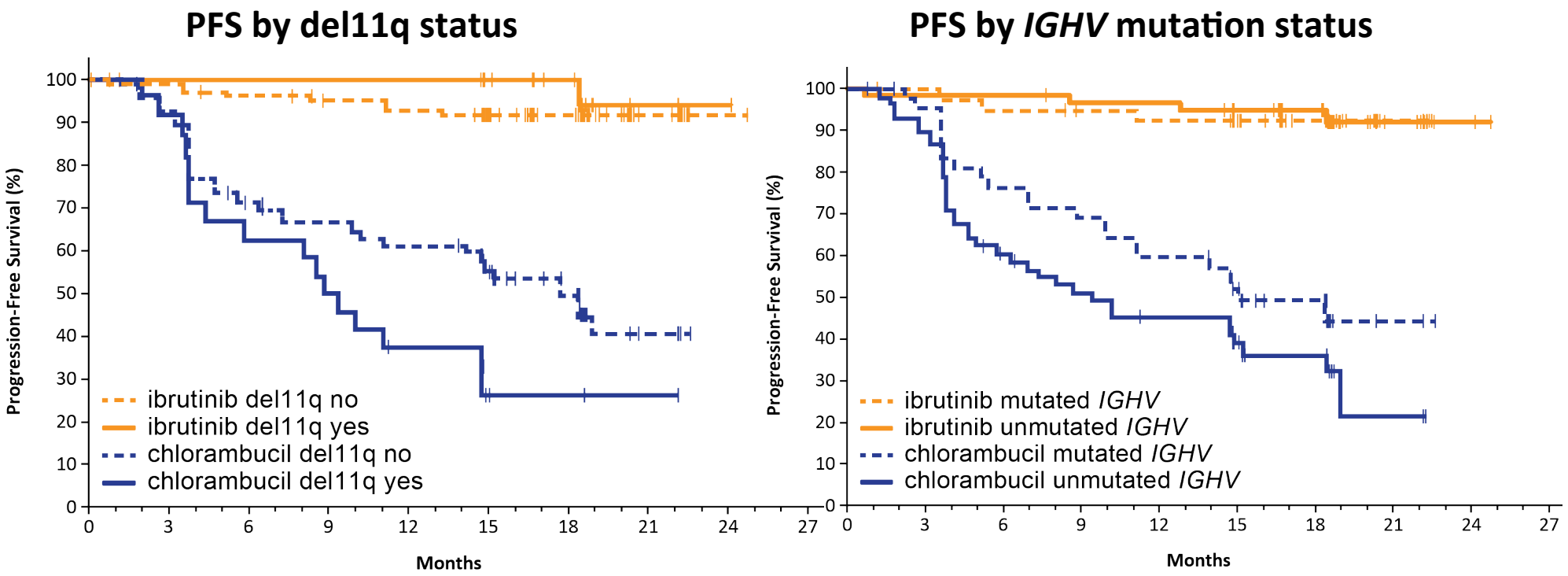






Burger et al NEJM 2015; Burger et al. - PCYC1115/1116 RESONATE 2 Poster PF343 – EHA 2018

PFS by Investigator for High-Risk Subgroups



- Median PFS in **del11q** subgroup: NR with ibrutinib vs. 9 months with chlorambucil (HR=0.02, *P*<0.0001)
- Median PFS in **unmutated *IGHV*** subgroup: NR with ibrutinib vs. 9 months with chlorambucil (HR=0.06, *P*<0.0001)
- Ibrutinib: 18-month PFS 92% in *IGHV* mutated, 95% in unmutated subgroup

Tedeschi A. et al, ASH 2015 Abst 495

CLL 1L therapy in elderly: G-Clb vs BR vs Ibrutinib

	G-Clb Hallek NEJM 2014	BR Eichhorst Lancet Onc 2016	Ibrutinib Resonate 2
Patients	333	273	136
Median age	74 > 65 years= 81% > 75 years= 46%	61 > 65 years= 81% > 70 years= 22%	73
ORR	77%	98%	86%
CR	22%	31.5%	4%
MRD PB	38%	63%	
Median PFS	29 months	43 months	Not reached
2-years PFS	60%	75%	85%
OS	3 years: 75%	3 years: 92%	2 years OS: 98%

RESONATE study: duration of Ibrutinib Treatment

	First-line Ibrutinib (n=136)
Median (range) duration of ibrutinib treatment, mo[a]	47 (1-55)
Treatment duration, n (%)	
≥3 years	99 (73)
≥4 years	56 (41)
Continuing ibrutinib on study, n (%)	89 (65)
Discontinued ibrutinib, n (%)	
PD	7 (5)
AEs	26 (19)
Death	7 (5)
Withdrawal of consent	4 (3)
Investigator decision	2 (1)

[a]n=135; one patient did not receive any doses of ibrutinib.

- 65% of patients continued first-line ibrutinib treatment on study
- 12% rate of discontinuation for Aes (Barr et al Haematologica 2018)
- 55% of patients crossed over from chlorambucil to ibrutinib following PD

Burger et al., EHA 2018; PF343 (poster presentation)

Update of RESONATE study

AE Grade	Ibrutinib-treated patients n=135 n (%) Any	2	3	4	5
Diarrhea	61 (45)	16 (12)	5 (4)	0	0
Visual disturbances[b]	30 (22)	6 (4)	0	0	0
Hypertension[c]	27 (20)	13 (10)	7 (5)	0	0
Arthralgia	27 (20)	9 (7)	3 (2)	0	0
Atrial fibrillation	14 (10)	7 (5)	6 (4)	0	0
Major hemorrhage	9 (7)	1 (<1)	7 (5)	1 (1)	0
Infections (grade ≥3)	31 (23)	NA	28 (21)	4 (3)	2 (1)

Barr et al. Haematologica 2018

Ibrutinib discontinuation in CLL: reasons

Discontinuation Reason,%	Ibrutinib in Frontline Setting		Ibrutinib in Relapse Setting	
	Real World (n = 10)	Clinical Trial (n = 9)	Real World (n = 200)	Clinical Trial (n = 31)
AE	50.0	77.7	52.5	38.7
CLL progression	10.0	22.2	19.0	35.5
Other/unrelated death	10.0	0	12.0	12.9
Physician or pt preference	20.0	0	6.0	9.7
RT into DLBCL	0	0	4.5	0
SC transplantation/CAR-T	0	0	3.5	3.2
Financial concerns	0	0	1.0	0
Secondary malignancy	10.0	0	1.0	0
RT into HL	0	0	0.5	0

- 40% of pts discontinued ibrutinib during study period
- Ibrutinib starting dose did not affect d/c rate

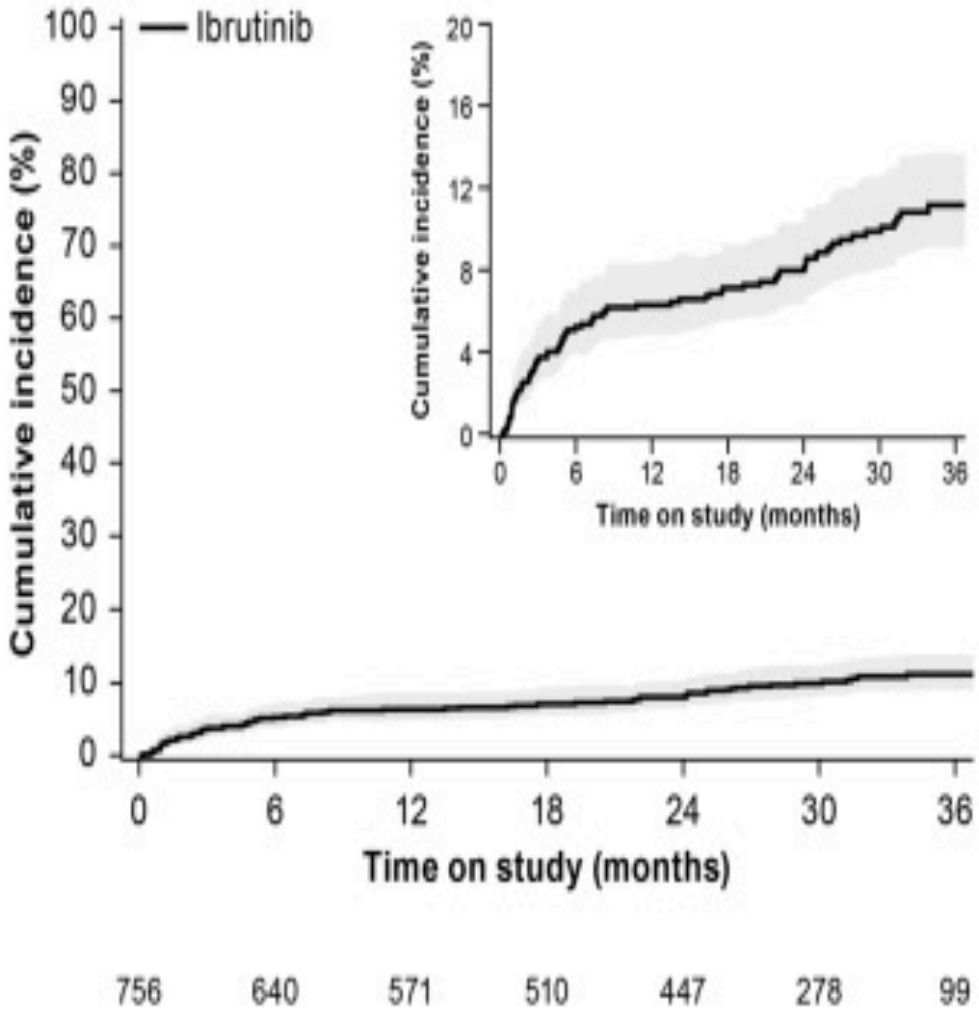
Mato AR, et al. ASH 2016. Abstract 3222.

Ibrutinib discontinuation in CLL: most common AEs causing discontinuation

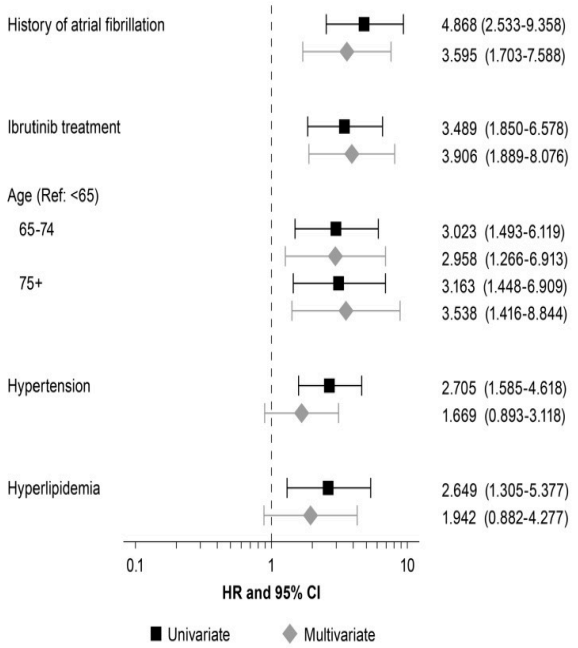
Ibrutinib-Associated Toxicity Causing D/c	Ibrutinib in Relapsed Setting, %	Ibrutinib in Frontline Setting, %	Median Time to D/c, Mos
Atrial fibrillation	12.3	25.0	7.0
Infection	10.7	--	6.0
Pneumonitis	9.9	--	4.5
Bleeding	9.0	--	8.0
Diarrhea	6.6	--	7.5
Arthralgia	--	41.6	5.0
Rash	--	16.7	3.5

Mato AR, et al. ASH 2016. Abstract 3222.

ATRIAL FIBRILLATION



- Pooled analysis of 4 phase 3 trials
- 10% after a follow-up of 36 months
- **RISK FACTORS**: age (in particular >75yy), history of AF and ibrutinib treatment



Brown J, Haematologica 2017

Targeting BCL2 with Venetoclax in Relapsed Chronic Lymphocytic Leukemia

Roberts et al. N Engl J Med. 2015

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Dose-Escalation Cohort (N=56)	Expansion Cohort (N=60)	All Patients (N=116)
Age			
Median (range) — yr	67 (36–86)	66 (42–84)	66 (36–86)
≥70 yr — no. (%)	20 (36)	14 (23)	34 (29)
Sex — no. (%)			
Male	41 (73)	48 (80)	89 (77)
Female	15 (27)	12 (20)	27 (23)
Diagnosis — no. (%)			
Chronic lymphocytic leukemia	49 (88)	53 (88)	102 (88)
Small lymphocytic lymphoma	7 (12)	7 (12)	14 (12)
Rai stage III or IV — no. (%)	28 (50)	39 (65)	67 (58)
Median no. of previous therapies (range)†	4 (1–10)	3 (1–11)	3 (1–11)
Resistance to most recent therapy — no. (%)‡	23 (41)	22 (37)	45 (39)
Previous fludarabine-based therapy — no. (%)			
Any previous fludarabine	51 (91)	49 (82)	100 (86)
Resistance to fludarabine	28 (50)	42 (70)	70 (60)
ECOG performance status — no. (%)			
Grade 0	29 (52)	27 (45)	56 (48)
Grade 1	27 (48)	31 (52)	58 (50)
Missing data	0	2 (3)	2 (2)
Peripheral-blood lymphocytosis			
Absolute lymphocyte count >5000 per mm^3 — no. (%)	31 (55)	35 (58)	66 (57)
Median count per mm^3 (range)	27,600 (5400–204,500)	25,100 (5200–259,900)	27,500 (5200–259,900)
Bulky nodes — no. (%)			
>5 cm	29 (52)	38 (63)	67 (58)
>10 cm	10 (18)	12 (20)	22 (19)
Interphase cytogenetic abnormality — no./total no. with CLL (%)§			
Chromosome 17p deletion	19/49 (39)	12/53 (23)	31/102 (30)
Chromosome 11q deletion	13/49 (27)	15/53 (28)	28/102 (27)
No chromosome 17p or 11q deletion	16/49 (33)	27/53 (51)	43/102 (42)
Data missing or indeterminate	7/49 (14)	3/53 (6)	10/102 (10)
IGHV mutation status — no./total no. with CLL (%)			
Unmutated	26/49 (53)	20/53 (38)	46/102 (45)
Mutated	6/49 (12)	11/53 (21)	17/102 (17)
Data missing	17/49 (35)	22/53 (42)	39/102 (38)

Table 3. Complete and Overall Response Rates, According to Cohort and Subgroup.

Variable	No. of Patients	Complete Response Rate*	Overall Response Rate
		percent of patients (95% CI)	
All patients	116	20 (13–28)	79 (71–86)
Dose-escalation cohort	56	30 (19–44)	77 (64–87)
Expansion cohort	60	10 (4–21)	82 (70–91)
Age			
≥70 yr	34	21 (9–38)	71 (53–85)
<70 yr	82	20 (12–30)	83 (73–90)
No. of previous therapies			
≥4	56	16 (8–28)	73 (60–84)
<4	60	23 (13–36)	85 (73–93)
Fludarabine resistance			
Yes	70	16 (8–26)	79 (67–88)
No	44	27 (15–43)	82 (67–92)
Bulky nodes of>5 cm			
Yes	67	8 (3–17)	78 (66–87)
No	48	38 (24–53)	83 (70–93)
Chromosome 17p deletion			
Yes	31	16 (6–34)	71 (52–86)
No	60	18 (10–30)	80 (68–89)
Chromosome 11q deletion			
Yes	28	11 (2–28)	82 (63–94)
No	62	21 (12–33)	76 (63–86)
IGHV status			
Unmutated	46	17 (8–31)	76 (61–87)
Mutated	17	29 (10–56)	94 (71–100)

Roberts et al. N Engl J Med. 2016

MURANO: Patient characteristics

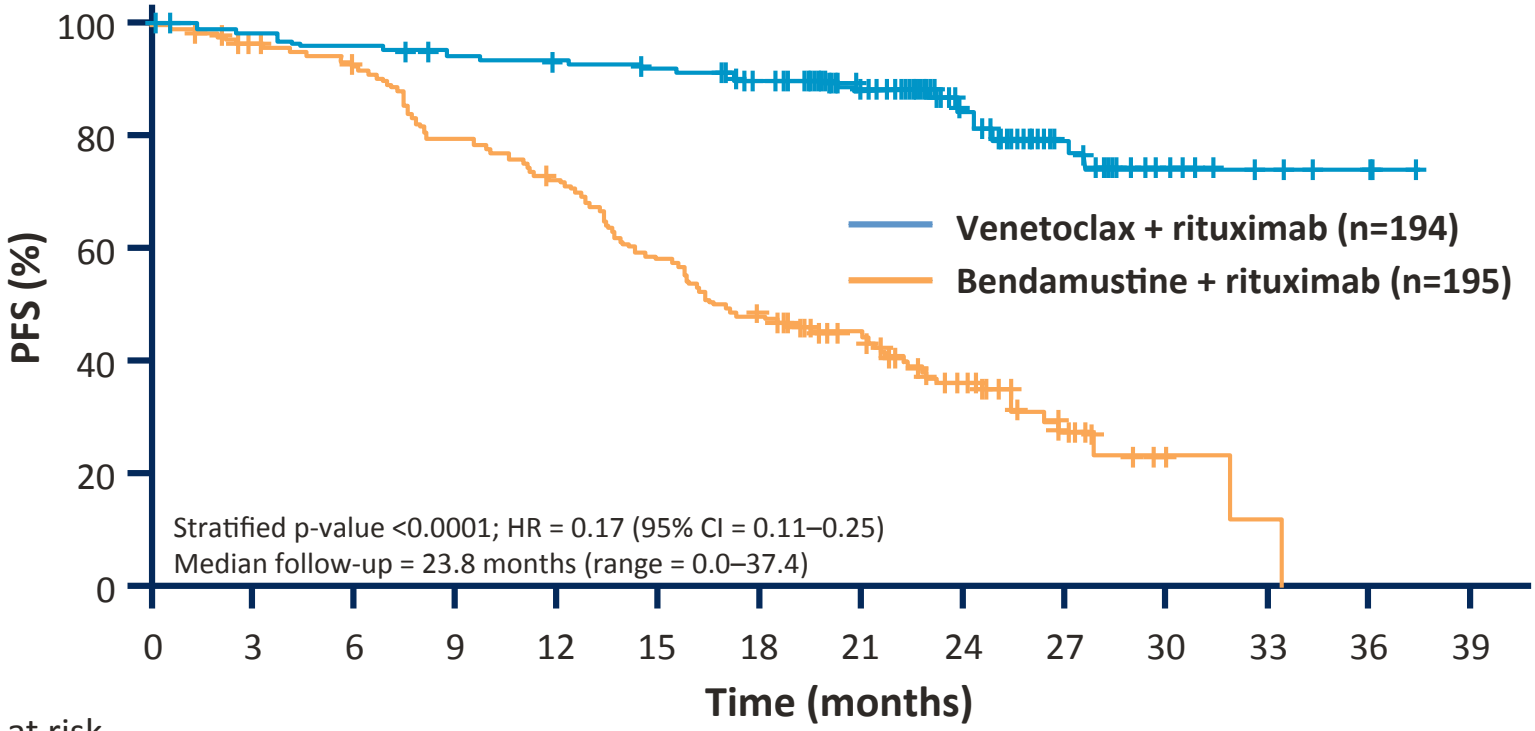
Characteristics	BR (n=195)	VR (n=194)
Age, median, years (range)	66 (22–85)	64.5 (28–83)
Male, n (%)	151 (77.4)	136 (70.1)
ECOG PS, n/N (%)		
0	108/194 (55.7)	111/194 (57.2)
1	84/194 (43.3)	82/194 (42.3)
2	2/194 (1.0)	1/194 (0.5)
Prior cancer therapies, n (%)		
1	117 (60)	111 (57.2)
2	43 (22.1)	57 (29.4)
3	34 (17.4)	22 (11.3)
>3	1 (0.5)	4 (2.1)
Fludarabine refractory, n/N (%)	30/194 (15.5)	27/191 (14.1)

Characteristics	BR (n=195)	VR (n=194)
Baseline TLS risk, n (%)		
High	55 (28.2)	54 (27.8)
Medium	104 (53.3)	106 (54.6)
Low	36 (18.5)	34 (17.5)
High risk status,* n (%)	107 (54.9)	104 (53.6)
del(17p) – central lab, n/N (%)	46/169 (27.2)	46/173 (26.6)
***TP53* mutated**, n/N (%)	51/184 (27.7)	48/192 (25.0)
IGHV n/N (%)		
Unmutated	123/180 (68.3)	123/180 (68.3)
Mutated	51/180 (28.3)	53/180 (29.4)
Unknown	6/180 (3.3)	4/180 (2.2)

* High risk defined as: harbouring del(17p), or no response to first-line chemotherapy-containing regimen, or relapsed within 12 months after chemotherapy or 24 months after chemoimmunotherapy.
ECOG PS, Eastern Cooperative Oncology Group performance status.

Seymour JF, et al. New Engl J Med. 2018.

MURANO: PFS



No. of patients at risk

Venetoclax + rituximab	194	190	185	179	176	173	157	115	76	33	14	5	3	0
Bendamustine + rituximab	195	177	163	141	127	102	81	57	35	12	3	1	0	0

Treatment	Patients with events (%)	Median PFS, months	HR (95% CI)	Stratified p-value	1-year PFS (%)	2-year PFS (%)
VR (n=194)	32 (16.5)	NE	0.17 (0.11–0.25)	<0.0001	92.7	84.9
BR (n=195)	114 (58.5)	17.0			72.5	36.3

Seymour JF, et al. New Engl J Med. 2018.

Unstratified p-value <0.0001; HR = 0.17.

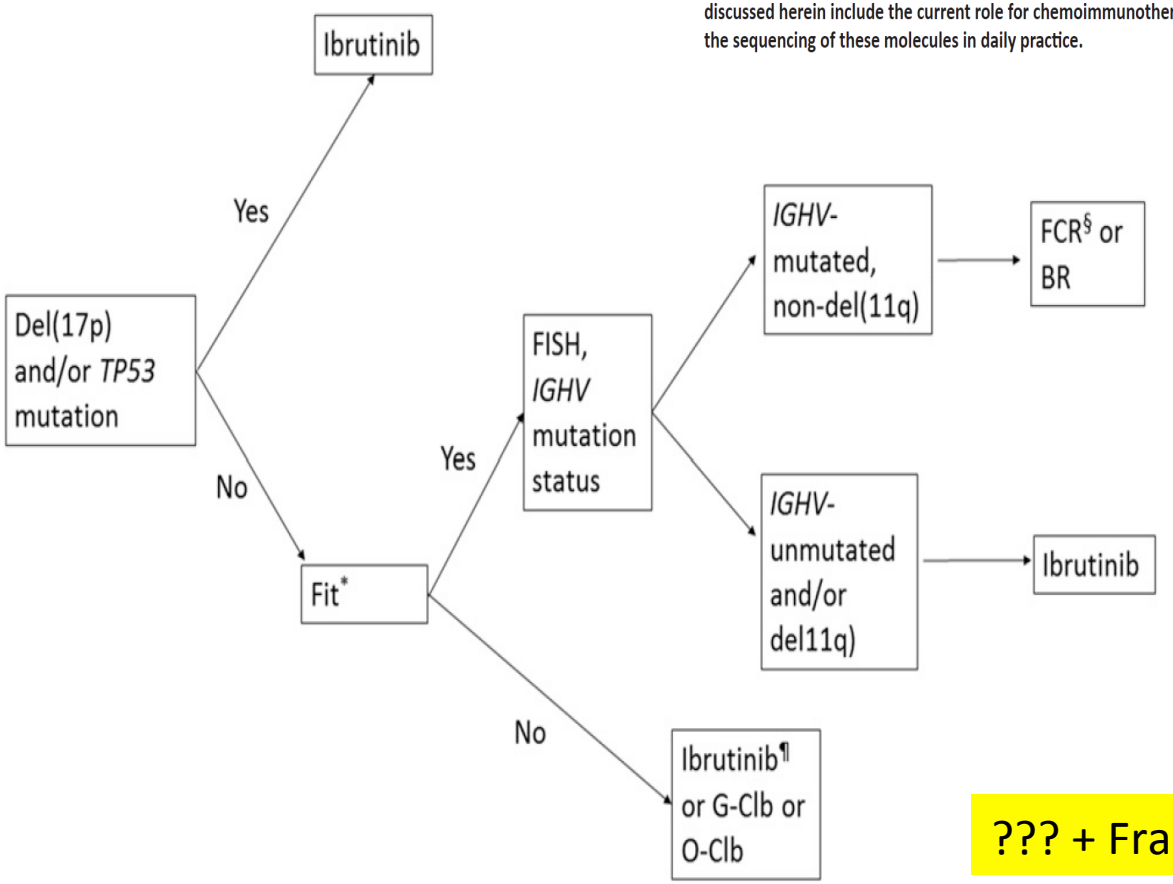
ASCO Guidelines 2018: Treatment of Patients With CLL According to Currently Available Therapies

Approaches to Chronic Lymphocytic Leukemia Therapy in the Era of New Agents: The Conundrum of Many Options

Nitin Jain, MD, Philip Thompson, MD, Alessandra Ferrajoli, MD, Chadi Nabhan, MD, MB, Anthony R. Mato, MD, MSCE, and Susan O'Brien, MD

OVERVIEW

Three small molecule inhibitors have been approved for the treatment of chronic lymphocytic leukemia (CLL) in the last 4 years. Ibrutinib, idelalisib, and venetoclax are oral agents with excellent efficacy and different toxicity profiles. Issues discussed herein include the current role for chemoimmunotherapy in CLL, the use of oral inhibitors in older patients, and the sequencing of these molecules in daily practice.



??? + Frail/no go: Clb

*Fit is defined as CIRS score of 6 or less and an eGFR of 70mL/min/1.73m^2 or greater.

§FCR is preferred instead of BR in patients with favorable genomic risk who are predicted to tolerate FCR, given the proven potential to achieve very-long-term remissions in this patient population.

¶Ibrutinib is preferred instead of G-Clb or O-Clb for this population on the basis of cross-study comparative data, unless comorbidities or financial considerations preclude its use.

Abbreviations: BR, bendamustine and rituximab; G-Cl, obinutuzumab + chlorambucil; FCR, floudarabine, cyclophosphamide, rituximab; FISH, fluorescence in situ hybridization; O-Clb, ofatumumab + chlorambucil.

Nitin Jain, Philip Thompson, Alessandra Ferrajoli, Chadi Nabhan, Anthony R. Mato and Susan O'Brien – ASCO Educational Book 2018

Quesiti aperti nella LLC: la prognosi è cambiata anche per il paziente anziano ?

SI, in particolare per gli anziani FIT/UNFIT

Quesiti aperti nella LLC: la prognosi è cambiata anche per il paziente anziano ?

- Rispetto a pochi anni fa, disponiamo diverse opzioni terapeutiche per il paziente anziano
- Queste nuove opportunità terapeutiche si caratterizzano per:
  - alto tasso di risposta
  - significativo prolungamento della PFS
  - prolungamento dell'OS (in alcuni gruppi di pazienti)
  - possibili tossicità
  - costi molto elevati
- Difficile poter oggi trattare tutti i pazienti anziani in 1L con i nuovi farmaci
- Probabile che spesso essi possano essere riservati nei casi R/R
- Importanza della selezione del paziente anziano sulla base di caratteristiche:
  - cliniche (fit, unfit, frail)
  - biologiche (FISH, IGHV, mutazioni geniche)