Bridging Gaps in Oncology 2018

In collaboration with

Mediterranean multidisciplinary Oncology forum (MMOF) | Hiroshima University

Karmanos Cancer Institute (Wayne State University)

"The treatment of CLL in real life depending on the availability of drugs"

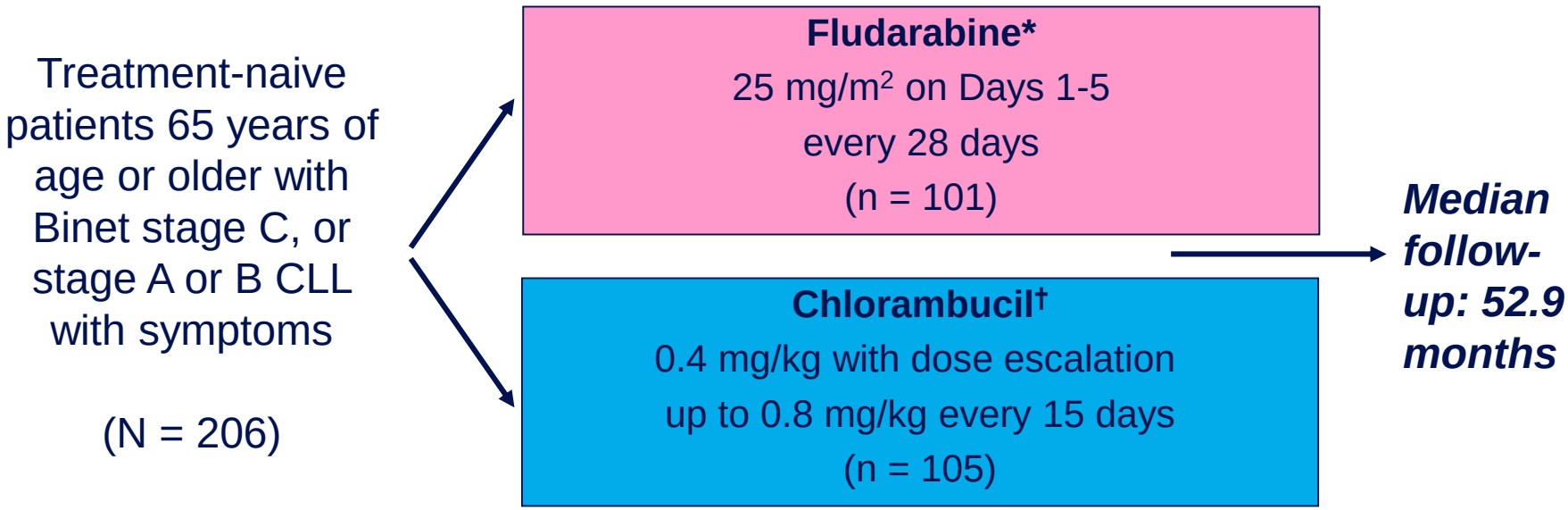
Prof. Antonio Cuneo, MD, PhD

università di ferrara
DA SEICENTO ANNI GUARDIAMO AVANTI.

- Chemotherapy
  - Chlor
  - Bendamustine
  - Fluda
  - Fluda + Cyclo
- Chemoimmunotherapy
- Allo BMT
- Mechanism-based treatment

First-Line Fludarabine vs Chlorambucil in Elderly Patients With CLL

- **Randomized, phase III trial (German CLL Study Group)**
- **Patients enrolled between 1999 and 2004**



*6 courses planned.
†Administered for maximum of 12 months or until maximum response achieved.

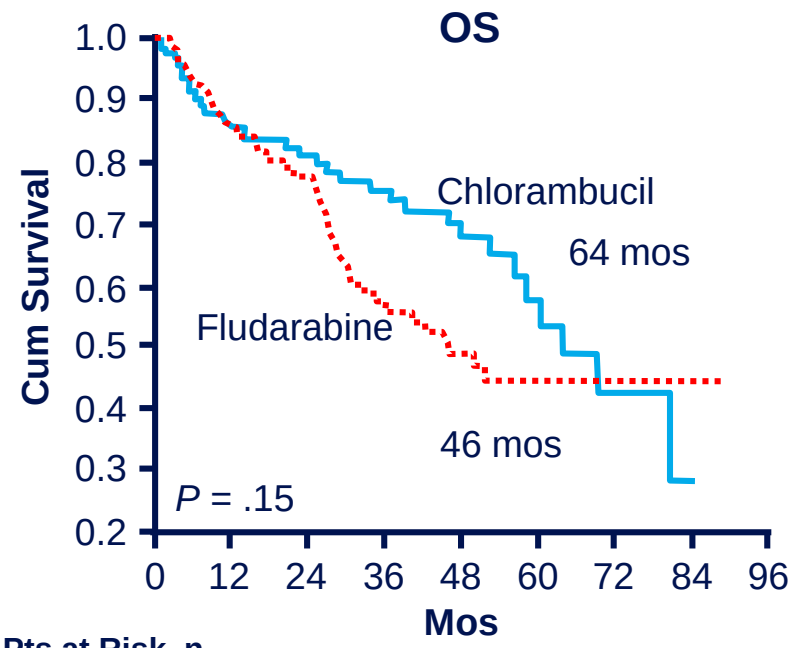
Eichhorst BF, et al. *Blood.* 2009;114:3382-3391.

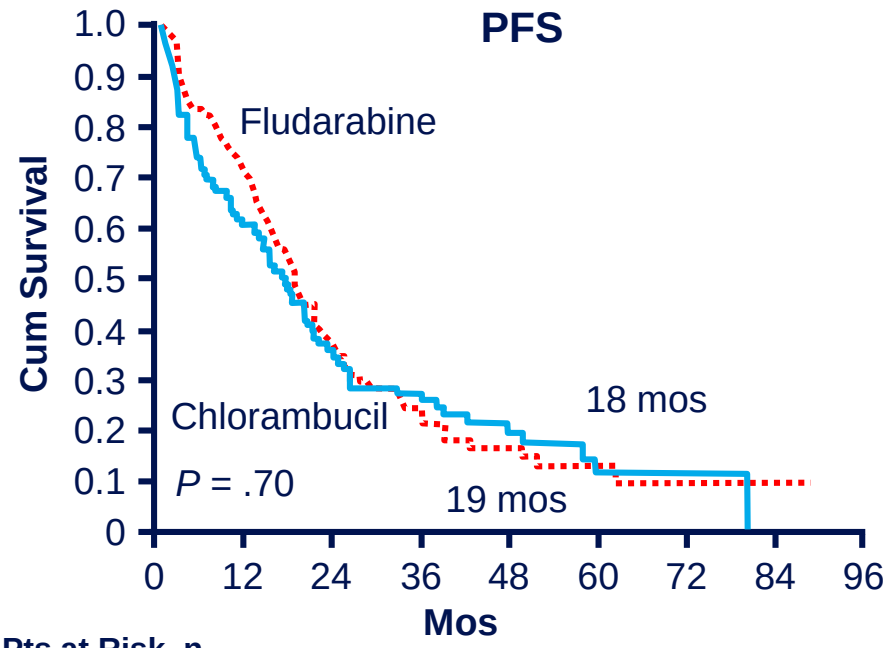
Phase III Trial of Fludarabine vs Chlorambucil in Elderly CLL: Responses

Patients, %	Chlorambucil (n = 100)	Fludarabine (n = 93)	*P* Value
All patients			
OR	51	72	.003
CR	0	7	.011

CTC Grade 3/4 Adverse Event, %	Chlorambucil (n = 96)	Fludarabine (n = 87)	*P* Value
Any myelotoxicity	23	42	.005
Leukocytopenia	3	28	<.001
Neutropenia	12	12	1.0
Anemia	27	15	.05
AIHA	2	8	.08
Thrombocytopenia	20	15	.40
Infection	4	8	.30

Phase III Trial of Fludarabine vs Chlorambucil in Elderly CLL: OS and PFS





Pts at Risk, n

Chlorambucil	98	75	63	47	33	14	7	1	0
Fludarabine	87	71	59	39	26	16	6	1	0

Pts at Risk, n

Chlorambucil	96	54	30	20	11	4	1	0
Fludarabine	87	61	29	18	10	6	2	0

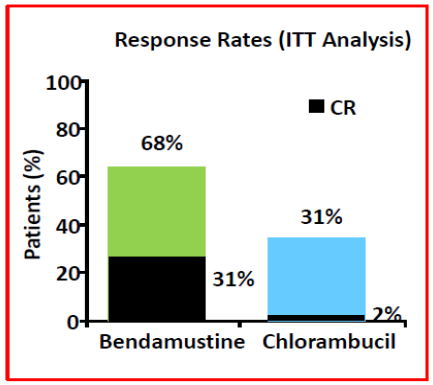
No significant difference seen in either OS or PFS between arms

Eichhorst BF, et al. *Blood.* 2009;114:3382-3391.

Randomized study Benda vs CLB

bendamustine (100 mg/mq days 1 and 2 every 4 weeks)
chlorambucil (0.8 mg/Kg days 1 and 15 every 4 weeks)

Bendamustine vs Chlorambucil: response rates

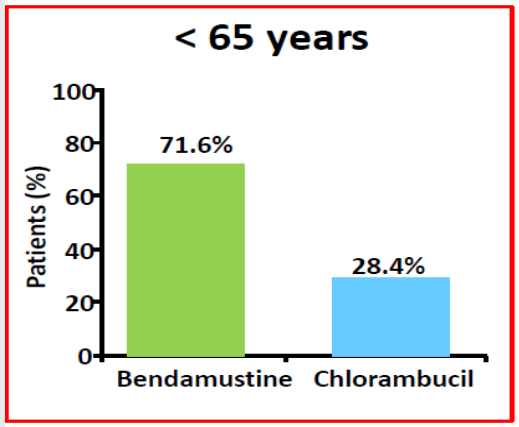


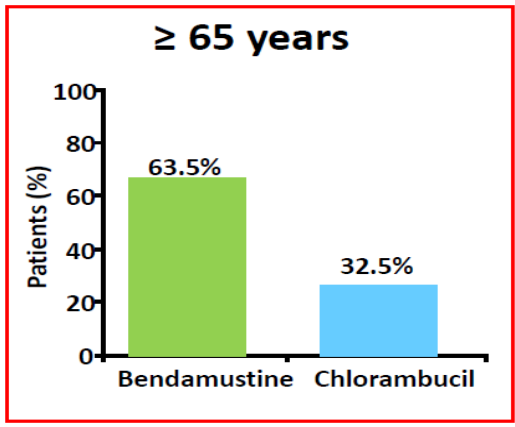
	Benda (n=162)	Chlor (n=157)	p [1,2]
OR, n (%)	110 (68)	48 (31)	<.0001
CR, n (%)	50 (31)	3 (2)	<.0001

1. Knauf W et al. J Clin Oncol 2009;27:4378–
2. Knauf W et al. Blood (ASH Annual Meeting Abstracts) 2010; 116: abstract 24

FRM 1

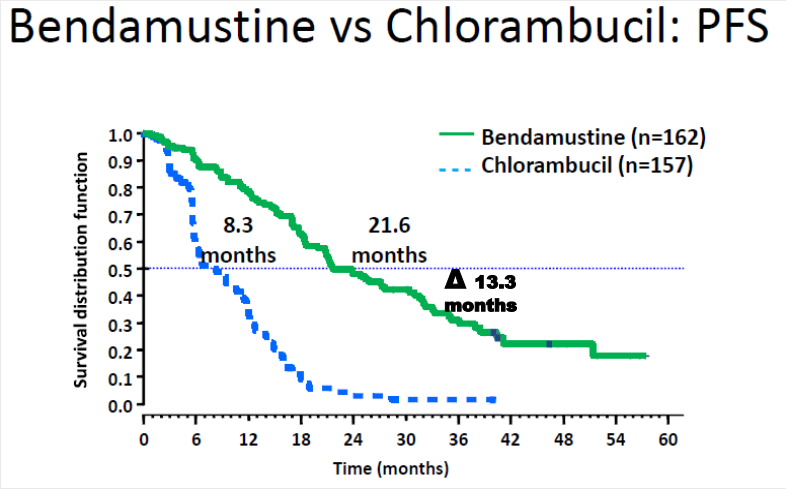
Bendamustine vs Chlorambucil: response by age





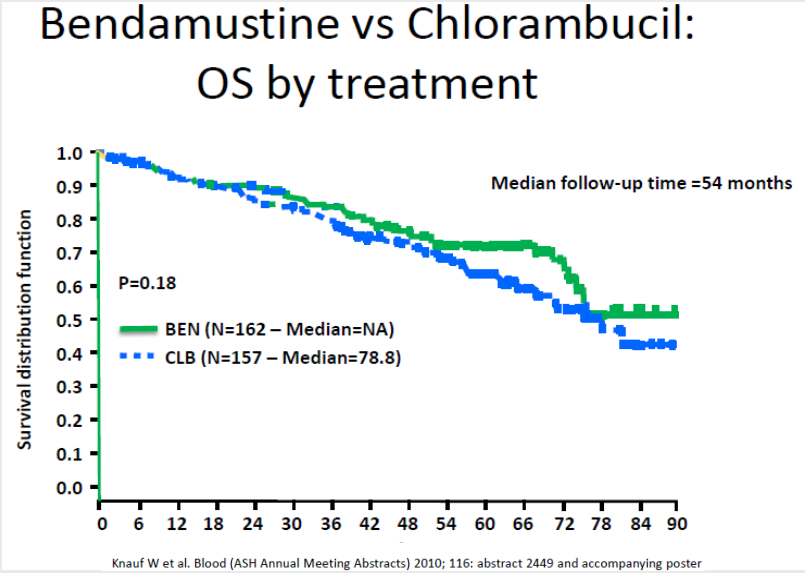
FRM 12

Studio randomizzato B vs CLB



Knauf W et al. J Clin Oncol 2009;27:4378–84

FRM 12



Knauf W et al. Blood (ASH Annual Meeting Abstracts) 2010; 116: abstract 2449 and accompanying poster

FRM 12

Randomized study B vs CLB

Bendamustine vs Chlorambucil: grade 3-4 toxicities

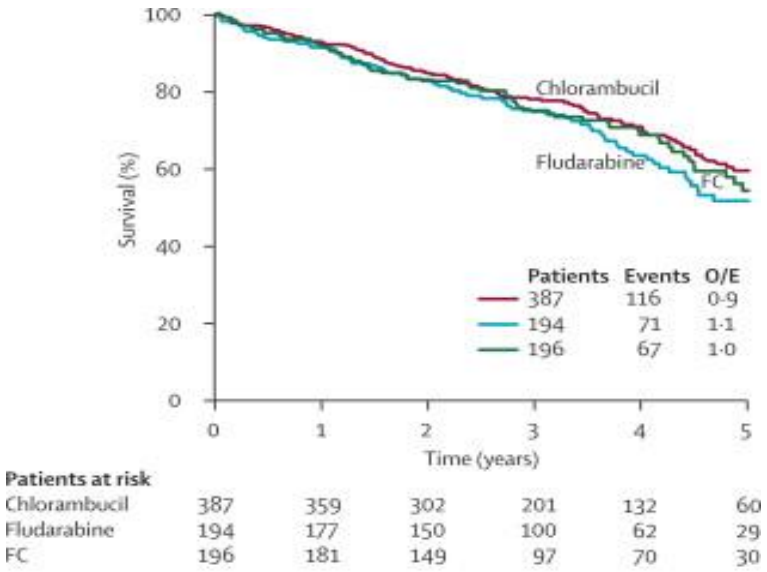
	Bendamustine	Chlorambucil
Granulocytopenia, %	23	11
Thrombocytopenia, %	12	8
Anemia, %	3	0
Infections, %	8	3
Skin, %	2.5	2
Gastrointestinal disorders, %	3	1
Tumour lysis syndrome, %	1	0

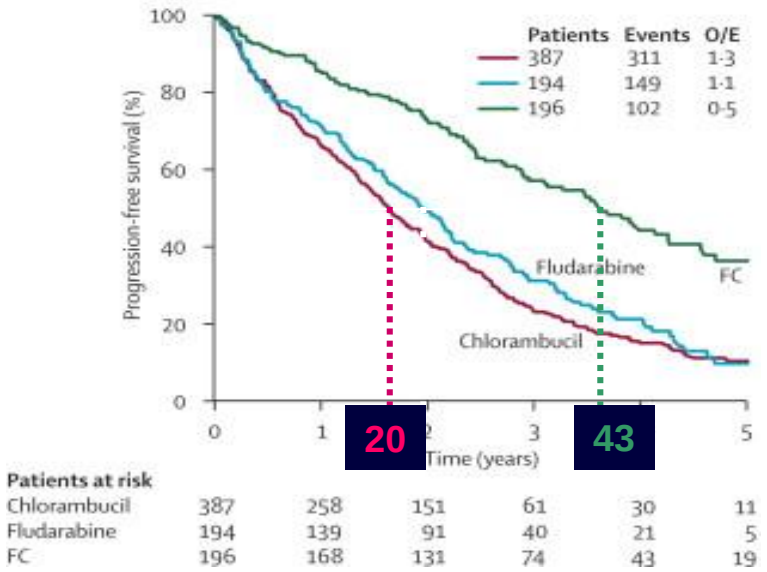
Fludarabine + Cyclophosphamide (FC) superior to Fludarabine in previously untreated CLL patients - *Results of 3 randomized studies*

	Catovsky *Lancet*, 2007			Flinn *J Clin Oncol*, 2007		Eichhorst *Blood*, 2006	
Regimen	Chl	F	FC	F	FC	F	FC
N	387	194	196	137	141	182	180
% CR	7	15	**38**	5	**23**	7	**24**
% OR	72	80	**94**	59	**74**	83	**94**
Med PFS (mo)	20	23	**43**	19.2	**31.6**	20	**48**

Chlor vs F vs FC in CLL LRF CLL4 trial

Chlorambucil was given orally at 10 mg/m² per day for 7 days, up to 12 courses





Severe adverse events (% of the cases)

Chlor	Fluda	FC
4%	7%	11%

Neutropenia < 1X10^9/L (% of the cases)

Chlor	Fluda	FC
28%	41%	56%

Febrile episodes (% of the cases)

Chlor	Fluda	FC
25%	27%	35%

Catovsky et al, Lancet 2007

- Chemotherapy
- Chemoimmunotherapy
  - Chlor + anti CD20
  - FCR
  - BR
  - Allo BMT
- Mechanism-based treatment

Elderly CLL

Efficacy of chlorambucil + Rituximab as first line treatment

	No. of patients	Median age	Total dose of Chlor	%CR/CRi	Median PFS (months)
	100	70	420 mg/sqm	10	23,5
	85	70	448 mg/sqm	19	34,7
	233	73	6 mg / Kg	8,3	15,7

UK: Hillmen P, JCO, Mar 17. [Epub ahead of print] 2014

Italy: Foà R on behalf of the GIMEMA group: Am J Hematol. 2014;89: 480-6

CLL11: Goede V, on behalf of CCLLSG: N Engl J Med. 2014;370:1101-10

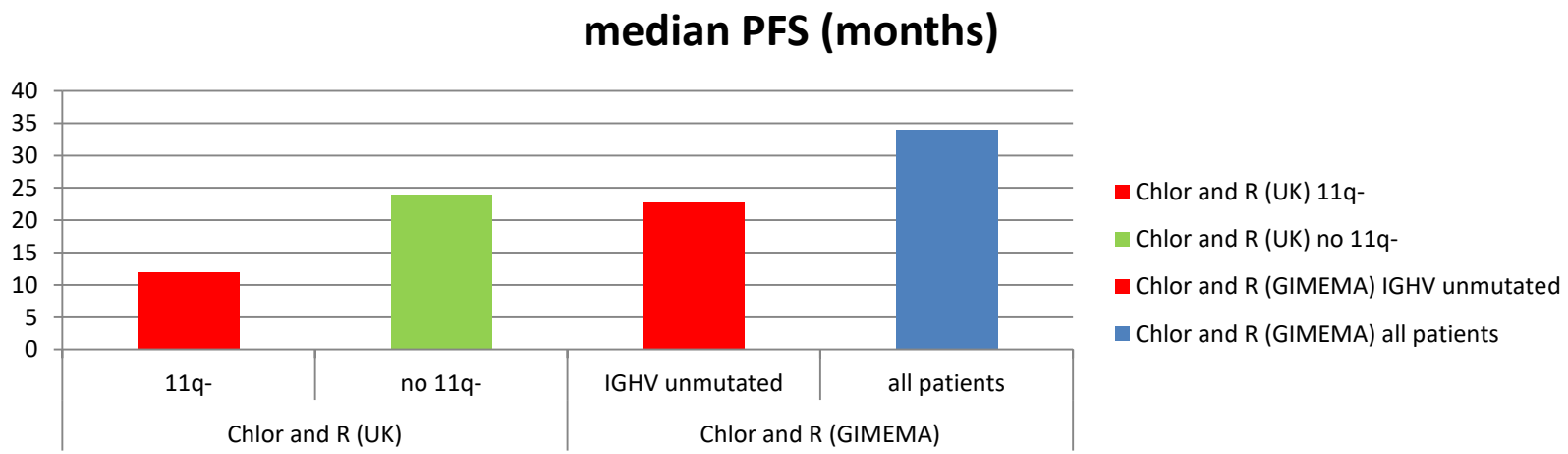
Elderly CLL

Safety of chlorambucil + Rituximab as first line treatment

	% of pts with grade 3/4 AE	
	neutropenia	Infections
UK	41	4
Italy	19,6	1
CLL11	25	8

Adverse prognostic factors with chlorambucil and rituximab (phase II studies)

Median PFS (elderly/unfit)



1. Hillmen P et al, J Clin Oncol. 2014 Apr 20;32(12):1236-41
2. Foà R et al. Am J Hematol. 2014 May;89(5):480-6

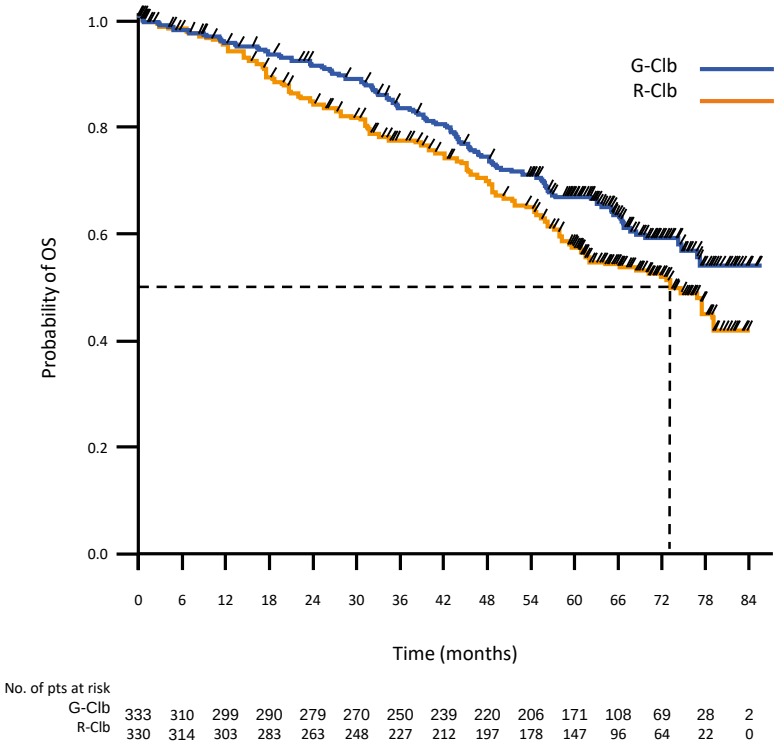
Overall survival benefit of obinutuzumab over rituximab when combined with chlorambucil in patients with chronic lymphocytic leukemia and comorbidities: final survival analysis of the CLL11 study

Valentin Goede,[1,2] Kirsten Fischer,[1] Martin JS Dyer,[3] Michael J Eckart,[4]
Lothar Müller,[5] Lukas Smolej,[6] Maria Chiara Di Bernardo,[7] Andrea Knapp,[8]
Tina Nielsen,[8] Michael Hallek[1,9]

[1]German CLL Study Group, Department I of Internal Medicine, Center of Integrated Oncology, University Hospital, Cologne, Germany; [2]Oncogeriatric Unit, Department of Geriatric Medicine, St Marien Hospital, Cologne, Germany; [3]The Ernest and Helen Scott Haematological Research Institute, University of Leicester, Leicester, UK; [4]Oncology Practice, Erlangen, Germany; [5]Oncology Practice, Leer, Germany; [6]Charles University Faculty of Medicine, University Hospital, Hradec Králové, Czech Republic; [7]On assignment to F. Hoffmann-La Roche Ltd, Basel, Switzerland; [8]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [9]Cologne Cluster of Excellence in Cellular Stress Responses in Aging-Associated Diseases, University of Cologne, Cologne, Germany

Goede et al; EHA 2018 abs S151 https://learningcenter.ehaweb.org/eha/2018/stockholm/215923/

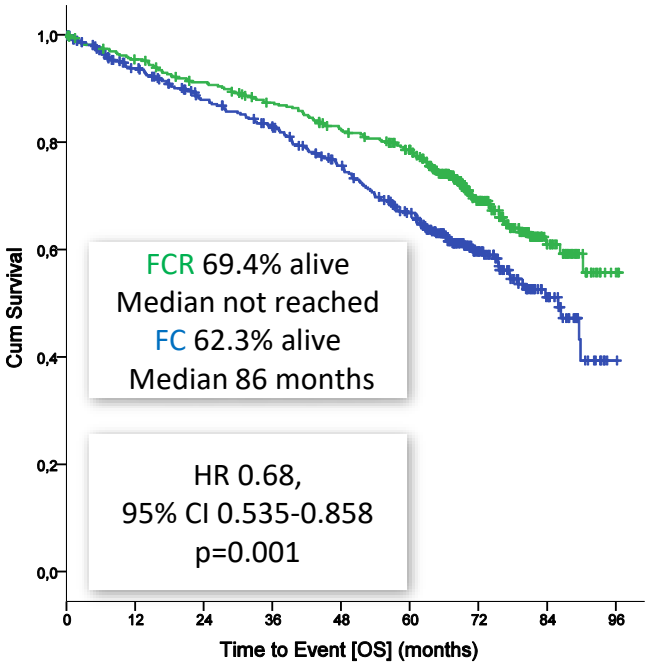
OS: G-Clb vs R-Clb

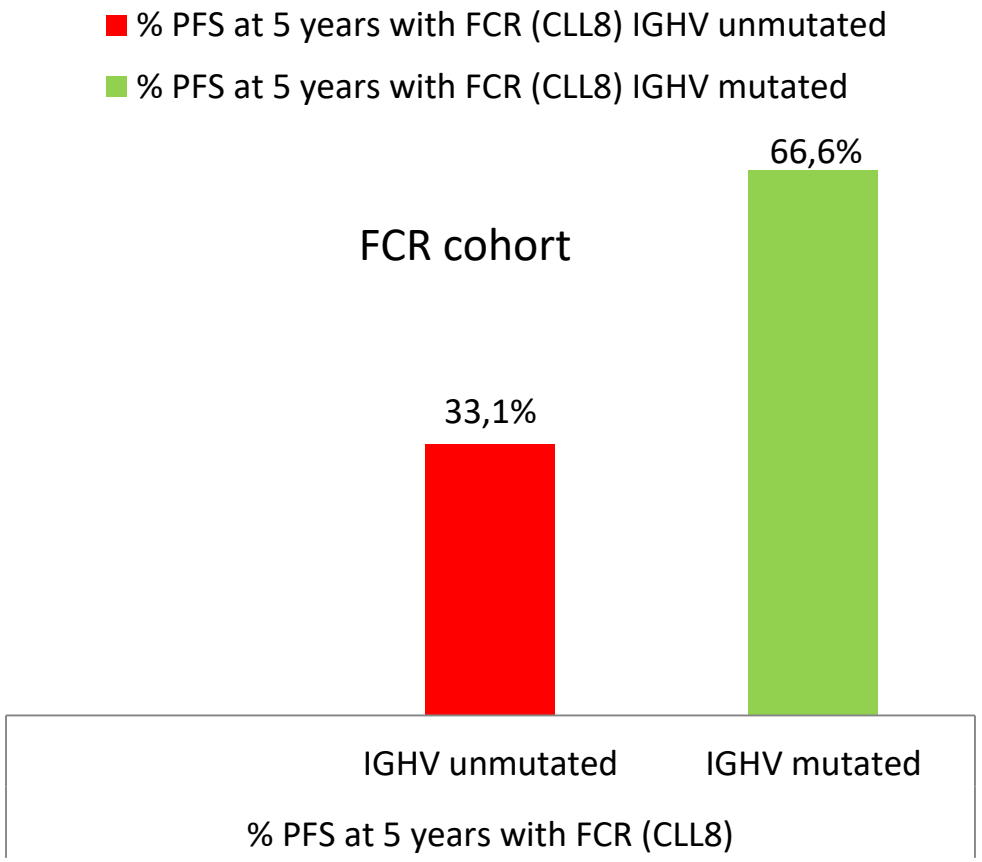


	G-Clb n=333	R-Clb n=330
Patients with events, n (%)	121 (36.3)	147 (44.5)
5-year OS, % (95% CI)	66 (61–72)	57 (51–62)
Median OS, months	NR	73.1
HR (95% CI), p-value	0.76 (0.60–0.97), p=0.0245	

Goede et al; EHA 2018 abs S151 https://learningcenter.ehaweb.org/eha/2018/stockholm/215923/

Long term follow-up (median 5,9 y) of the GCLLSG – CLL8 study: *PFS and unmutated IGHV*

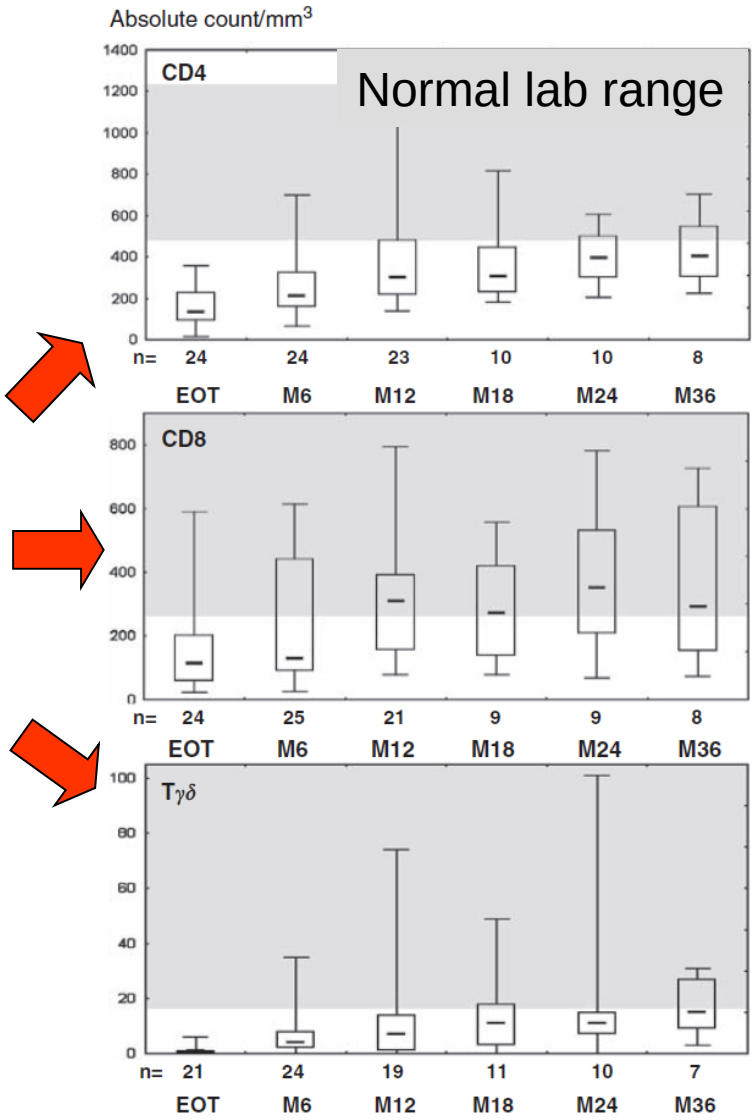




Fischer K et al. Blood. 2016;127:208-215

Immune recovery after fludarabine–cyclophosphamide–rituximab treatment in CLL

sustained depletion of all T-cells



Ysebaert L et al, Leukemia 2010 24: 1310–1316

Late cytopenia and infections after FCR

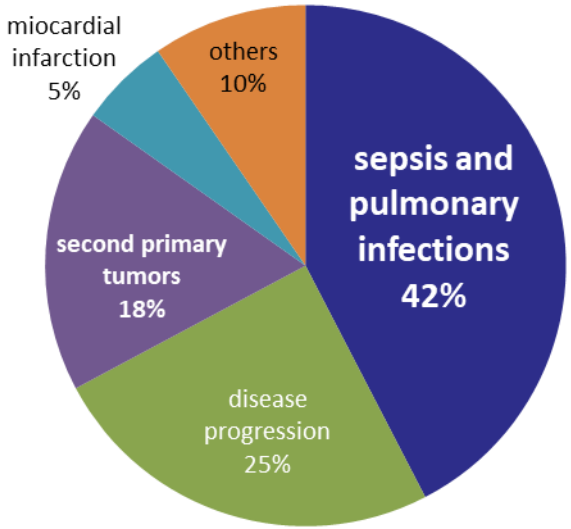
months after the completion of therapy	Grade 2-4 cytopenia MDACC* (% pts)	Grade 3-4 neutropenia CLL8 (%pts)	Grade 3-4 neutropenia CLL8 (%pts)	Late infection MDACC (%pts)
	FCR	FCR	FC	
3	35			
6	24			
9-12	12	16,6	8,8	
12 24				10% 4%

** Associated with age*

Strati et al, Cancer, 2013; Tam et al, Blood 2009; Fischer, ASH 2012

Causes of death after FCR in the CLL8 trial

FCR arm (n.125 events / 408 patients; 5,9 yrs median f.u.)



Median time to onset (months) after last dose of study treatment	
sepsis and pulmonary infections	46
second primary tumors	27

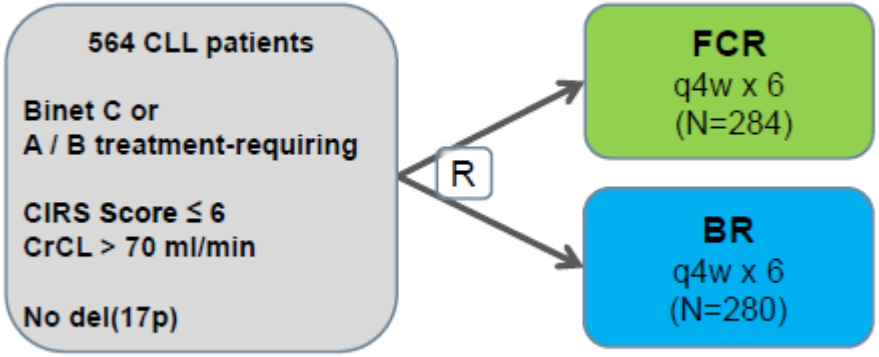
Fischer K et al. Blood. 2016;127(2):208-215

FCR vs BR in Previously Untreated and Physically Fit Patients with CLL: Final Analysis of the GCLLSG- CLL10 Study (17p- excluded per protocol)

- Study hypotheses
- 1. BR non-inferior to FCR in terms of PFS
- 2. BR potentially better tolerability compared to FCR

- Assumptions*:
- PFS @ 2 yearss
  - under FCR: 75%
  - under BR: > 67,5% for non-inferiority (7.5% difference or less)
  - → Complete 95% CI of the HR [λ BR/FCR] has to be < 1.388

Study Design



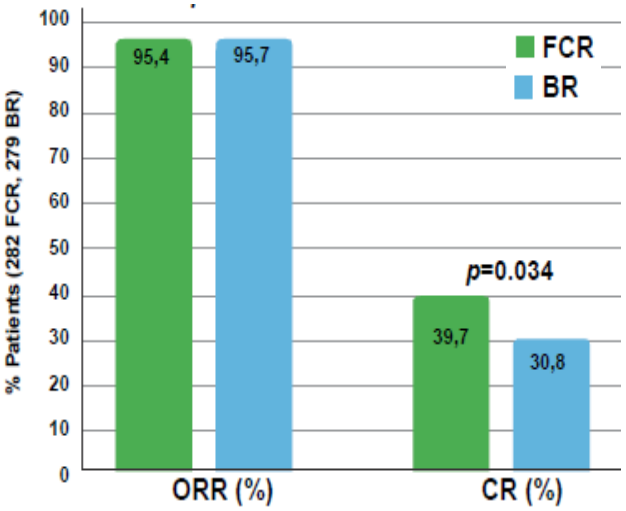
Median observation time for all patients: 37,1 (0-59,9) m

Baseline patient characteristics	FCR n=284	BR n=280	p value
Med. age	61	62,1	0,131
Age > 65	30,5%	38,7%	0,042
Age ≥ 70	14%	22%	0.020
Male	71,3%	74,2%	0,45
Median time since diagnosis (m)	21,6	24,6	0,846
ECOG PS 0	64,1%	64,1%	0,194
Med. CIRS	2	2	0,489
Binet A	22,3%	22,2%	0,846
Binet B	37,3%	38,4%	
Binet C	40,4%	39,4%	
IGHV unmutated	55,3%	67,8%	0,003
11q deletion	24,1%	22,6%	0,691
Trisomy 12	12,4%	12,2%	1
13q deletion	55%	52,7%	0,612
s-TK (U/l) > 10.0	72,8%	72,6%	1
s-β2m (mg/l) > 3.5	30,9%	38,1%	0,086

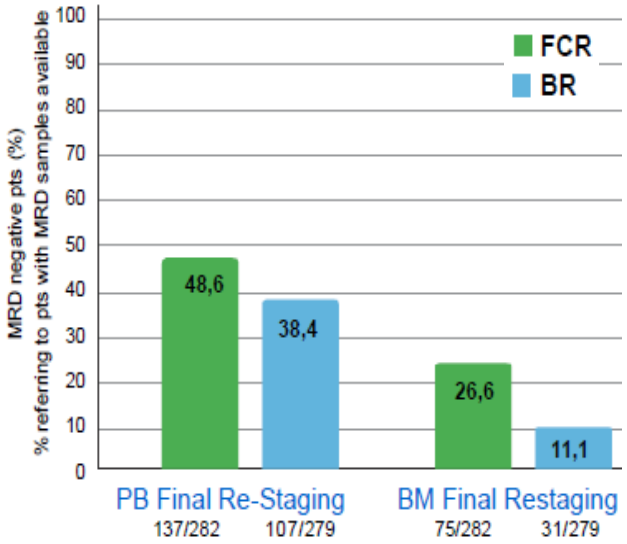
Eichhorst et al., ASH 2014, Abstract # 19

FCR vs BR in Previously Untreated and Physically Fit Patients with CLL: Final Analysis of the GCLLSG- CLL10 Study

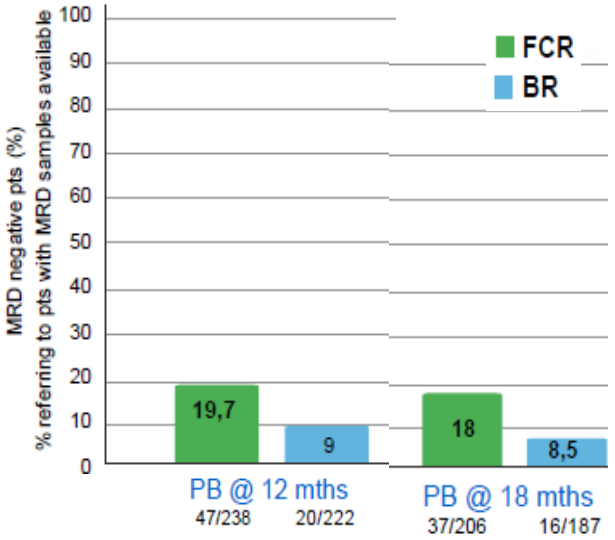
Best Response



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

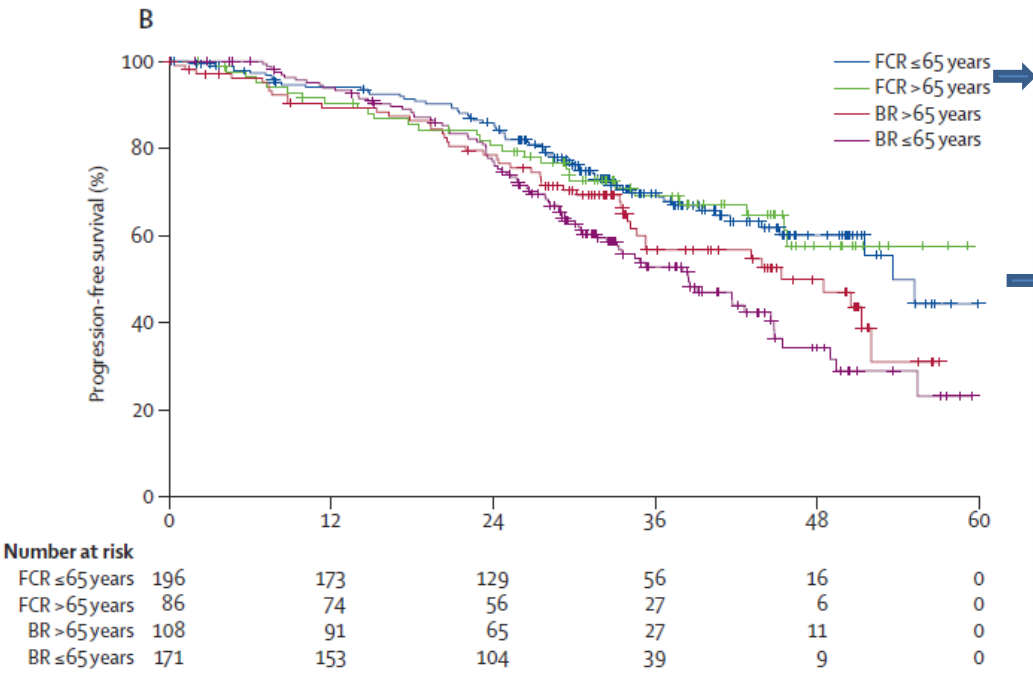


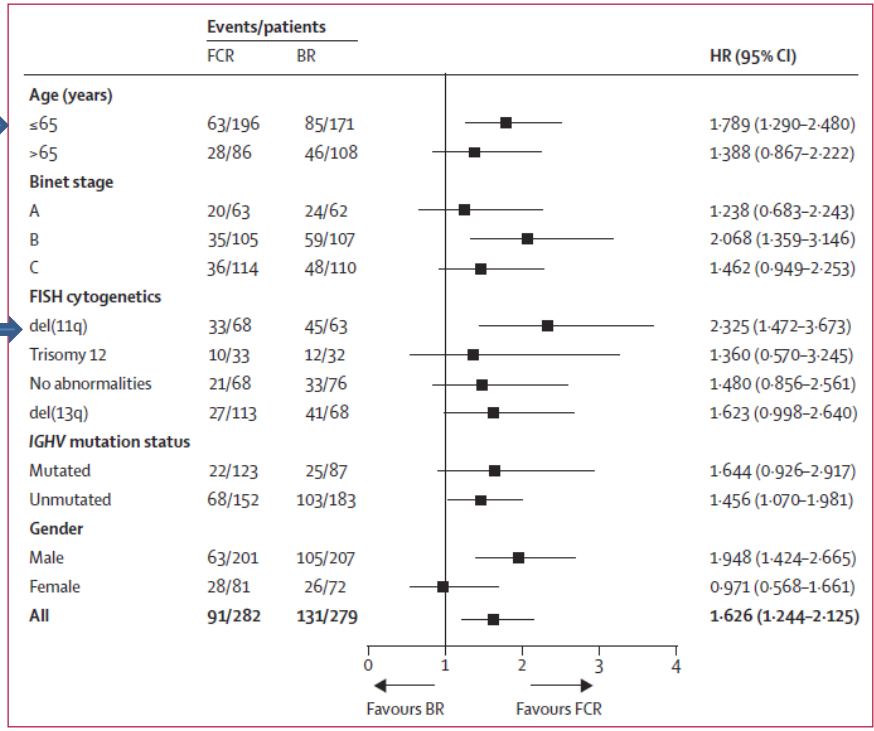
MRD-negativity ($<10^{-4}$) in PB at 12 and 18 months



Eichhorst et al., ASH 2014, Abstarct # 19

PFS according to risk groups in the CLL10 study:



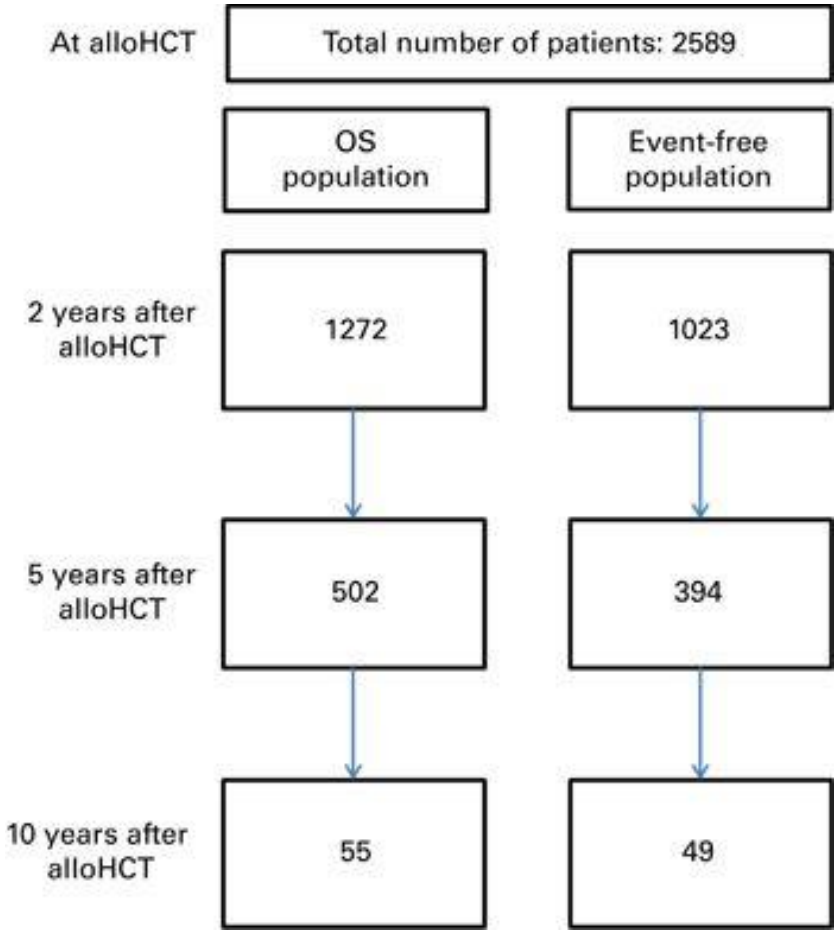


- FCR better than BR in the total population
- FCR better than BR in patients with IGHV unmutated and in patients with 11q-
- NO difference in the patients >65 years (post-hoc analysis)

Eichhorst et al Lancet Oncol 2016;17:928-42

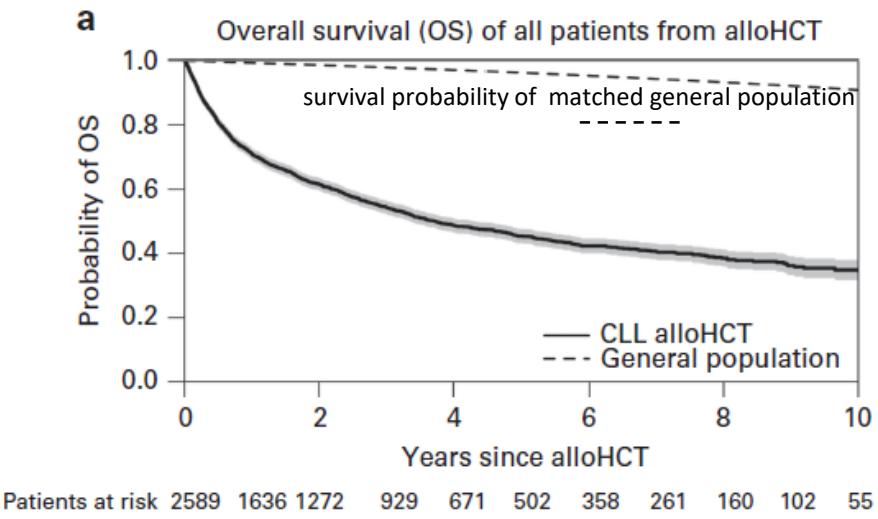
- Chemotherapy
- Chemoimmunotherapy
  - Chlor + anti CD20
  - FCR
  - BR
- Allo BMT
- Mechanism-based treatment

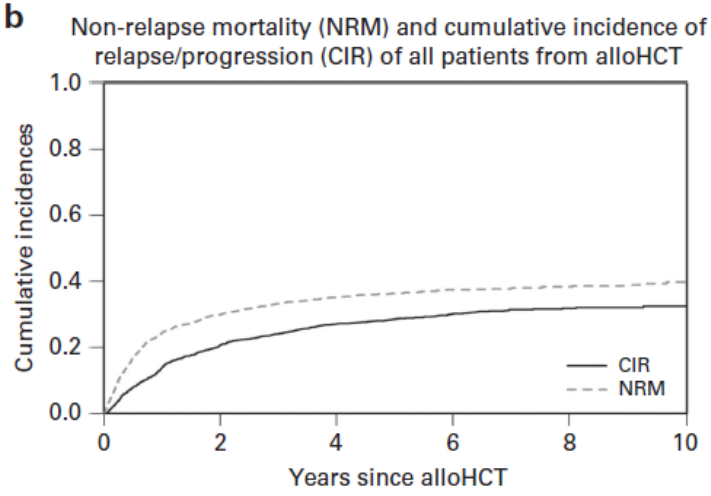
Long-term survival of patients with CLL after allogeneic transplantation: a report from the European Society for Blood and Marrow Transplantation

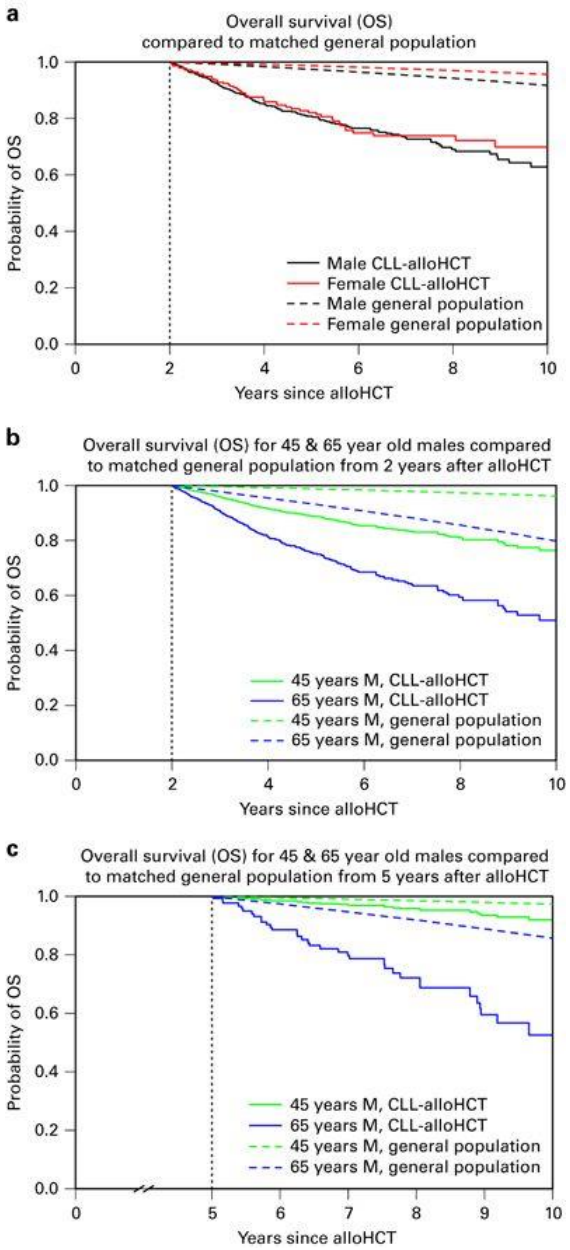


van Gelder M et al.
Bone Marrow Transplantation (2017) 52, 372–380

Long-term survival after allo-HCT in CLL: The prospect of long-term disease-free survival remains an argument to consider allo-HCT for young patients with high-risk CLL



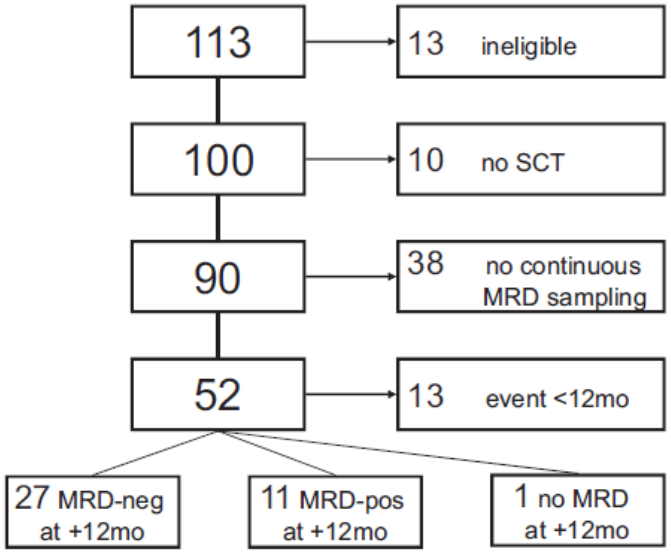


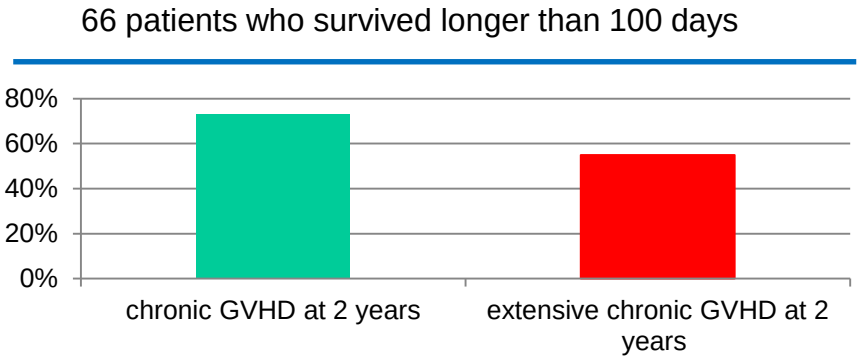


van Gelder M et al. Bone Marrow Transplantation (2017) 52, 372–380

Allogeneic stem cell transplantation provides durable disease control in poor-risk chronic lymphocytic leukemia: long-term clinical and MRD results of the German CLL Study Group CLL3X trial

Chronic and extensive GVDH





Dreger P et al,
Blood. 2010;116:2438-2447

Bridging Gaps in Oncology 2018

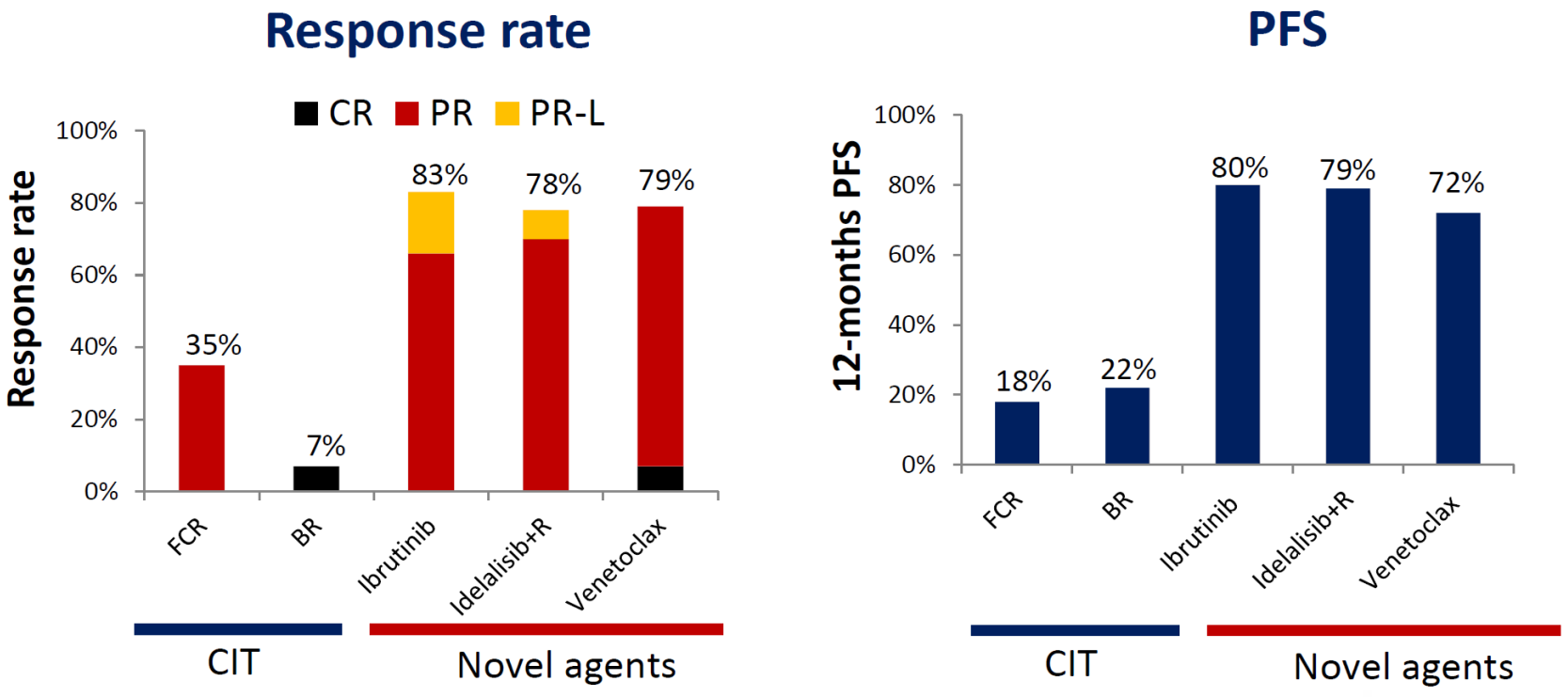
In collaboration with

Mediterranean multidisciplinary Oncology forum (MMOF) | Hiroshima University

Karmanos Cancer Institute (Wayne State University)

- Chemotherapy
- Chemoimmunotherapy
- Allo BMT
- Mechanism-based treatment
- - ibrutinib
  - Idelalisib and rituxumab
  - venetoclax+/-Rituximab

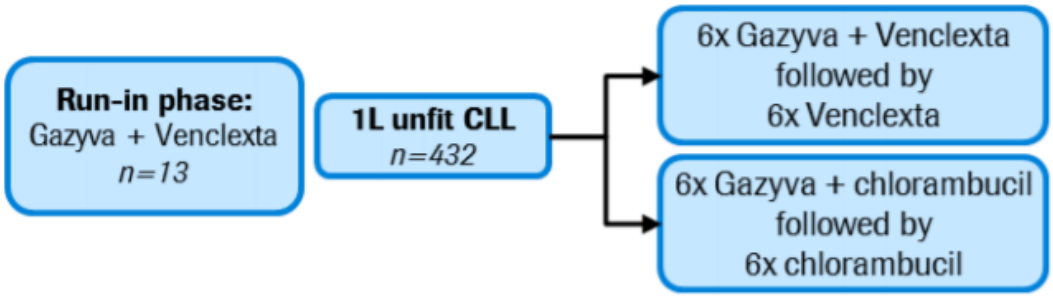
CIT versus Novel Agents in TP53 disrupted CLL



Badoux 2011, Fisher 2011, O'Brien 2016, Sharman 2014, Byrd 2015, Stilgenbauer 2016

Final Results of the Run-in Phase from the CLL14 Study of Venetoclax and Obinutuzumab in Patients With TN CLL With Coexisting Medical Conditions: Study Design and Patients

CLL14 study design



Key eligibility criteria

- **TN CLL**
- **CIRS >6 and/or CrCl <70 mL/min**

Obinutuzumab

- cycle 1: 100 mg day 1, 900 mg day 2, 1000 mg days 8 and 15
- cycles 2-6: 1000 mg day 1

Venetoclax

- From day 22 of cycle 1- ramp-up 20 mg to 400 mg
- followed by 6 cycles single-agent venetoclax

Baseline Characteristics		(N=13)
Median age, years (range)		**75 (59-88)**
≥70 years, n (%)		**11 (85)**
CIRS score	>6, n (%)	**10 (77)**
CrCl ml/min <70, n (%)		10 (77)
Cytogenetic subgroups	Del(17p)	2 (25)
	Del(11q)	2 (25)
TP53 deleted and/or mutated (n=8)		2 (25)
Unmutated IGHV (n=7)		6 (86)
% TLS risk intermediate/ high		**62/38**

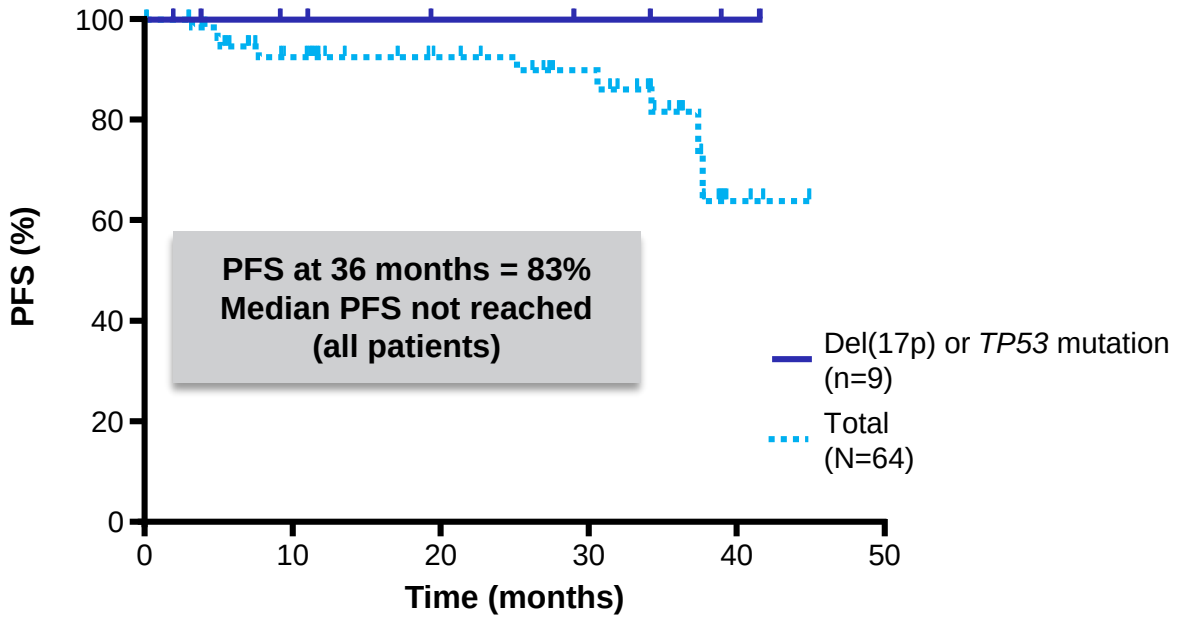
Response rates	N (100)
ORR	**12 (100)**
CR	**7 (58)**
PR	5 (42)
MRD neg	**10 (91)**

AEs in > 15% of patients	Any Grade	Grade 3/4
Any AE	12 (100)	10 (83)
Neutropenia	**8 (67)**	**7 (58)**
Febrile neutropenia	**3 (25)**	**3 (25)**
Infections (pooled)	**8 (67)**	**2 (17)**
Syncope	2 (17)	2 (17)
Thrombocytopenia	2 (17)	2 (17)
Laboratory TLS (No clinical TLS)	**2 (17)**	**2 (17)**

Fischer et al. ASH 2016. abstr. #2054.

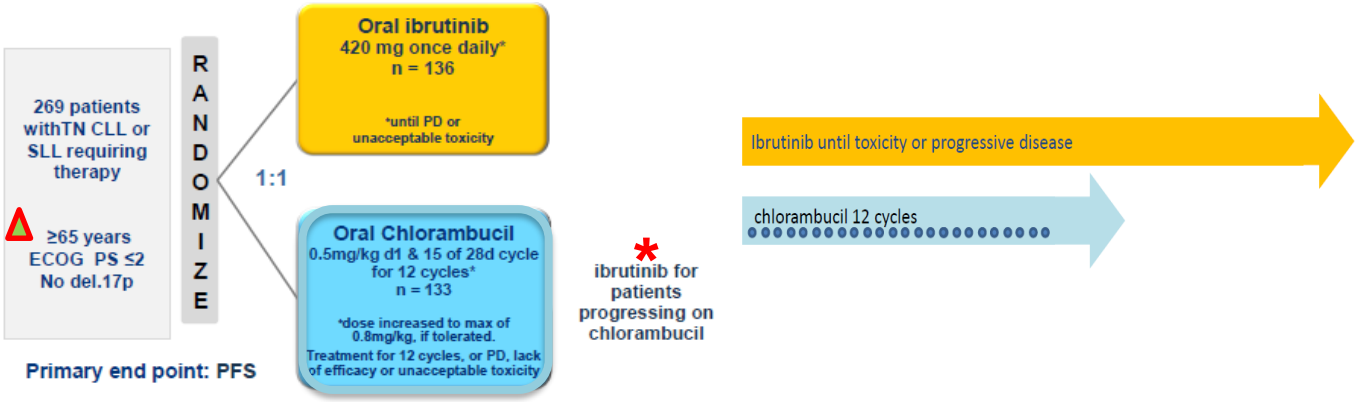
Thanks to dr. Francesca Mauro; University “La Sapienza” Rome

Idelalisib + R provided a long PFS in front-line CLL patients with del(17p)/*TP53* mutation



O'Brien SM, *et al*. ASH 2014 (Abstract 1994; poster presentation).

Phase III RESONATE-2: Frontline Ibrutinib vs Chlorambucil in Elderly Patients With CLL



Baseline Characteristics

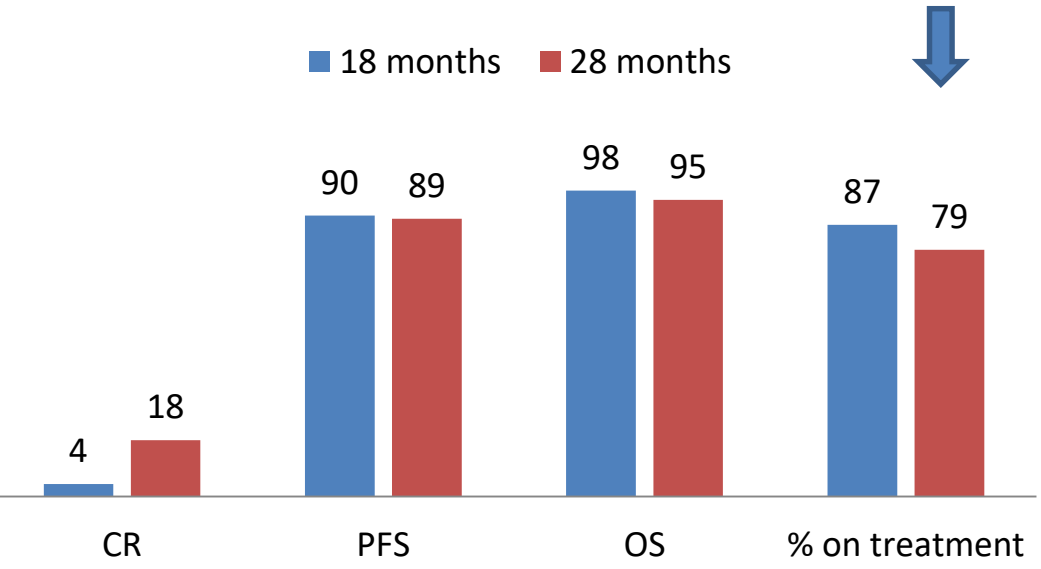
	Ibrutinib (N=136)	Chl (N=133)
Median age, years (range)	73 (65-89)	72 (65-90)
≥70 years	96 (71%)	93 (70%)
ECOG PS 2	60 (44%)	54 (41%)
CIRS >6	42 (31%)	44 (33%)
CrCL <60ml/min	60 (44%)	67 (50%)
CLL	123 (90%)	126 (95%)
SLL	13 (10%)	7 (5%)
Rai stage III or IV	60 (44%)	62 (47%)
Bulky disease ≥5cm,	54 (40%)	40 (30%)
Del 11q22.3	29 (21%)	25 (19%)
Unmutated IGHV	58 (43%)	60 (45%)
Baseline cytopenias,	72 (53%)	73 (55%)

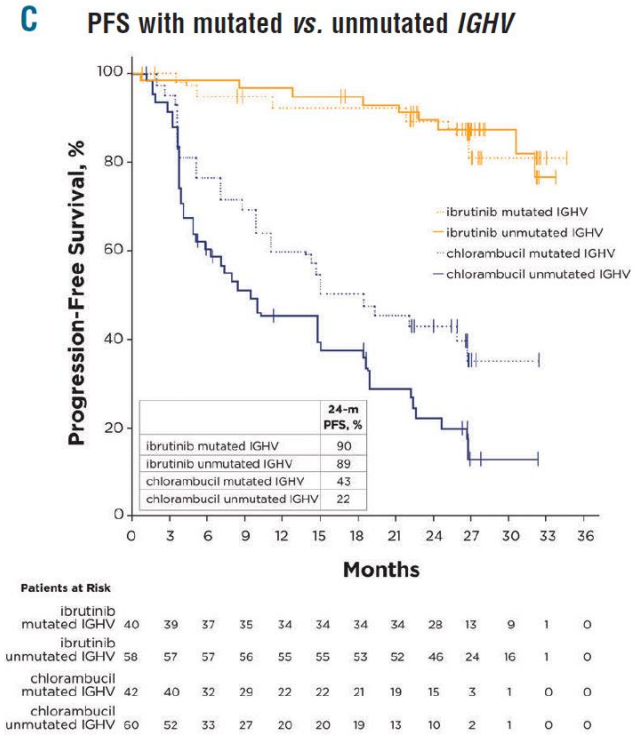
Patient Disposition

	Ibrutinib (N=136)*	Chl (N=133)*
Medi.duration of follow-up, months	18.4	
Med.duration of treatment (range), months	17.4 (0.7-24.7)	7.1 (0.5-11.7)
Patients completing max.12 CHL cycles	-	53 (40%)
Patients still on treatment at study closure	118	-
Patients on study follow up at study closure	131	114
Patients discontinued treatment	17	79
IRC confirmed disease progression	2	6
New anticancer therapy	0	4
Progressive disease	0	11
Lack of efficacy	0	21
Unacceptable toxicity/AE/death	14	30
Patient decision	1	6
Investigator decision	0	37
Other	0	1

Burger et al. , NEJM 2015; Tedeschi et al., ASH 2015

Resonate-2: Efficacy and tolerability of ibrutinib is maintanied at 28 months in treatment naive CLL, irrespective of IGHV mutational status





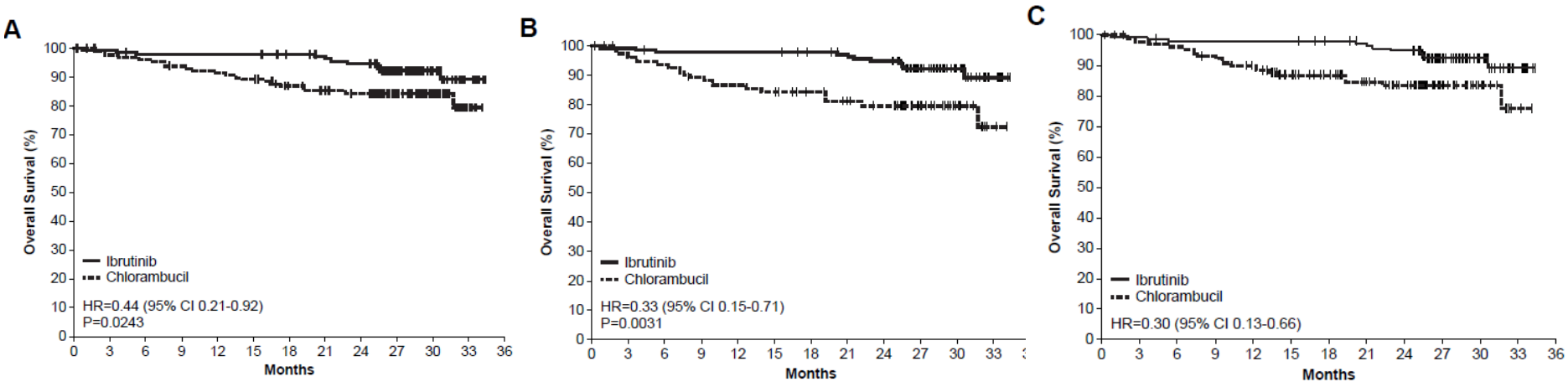
Barr P, ASH 2016 abs# 234
Burger NEJM, 2015
Barr et al. Haematologica 2018;103:1502-1510

Survival adjusting for crossover: phase 3 study of ibrutinib vs chlorambucil in older patients with untreated CLL: median f.u. 28 months

intent-to-treat population

excluding patients who crossed over to ibrutinib

rank-preserving structural failure time method



Kaplan-Meier curves of overall survival

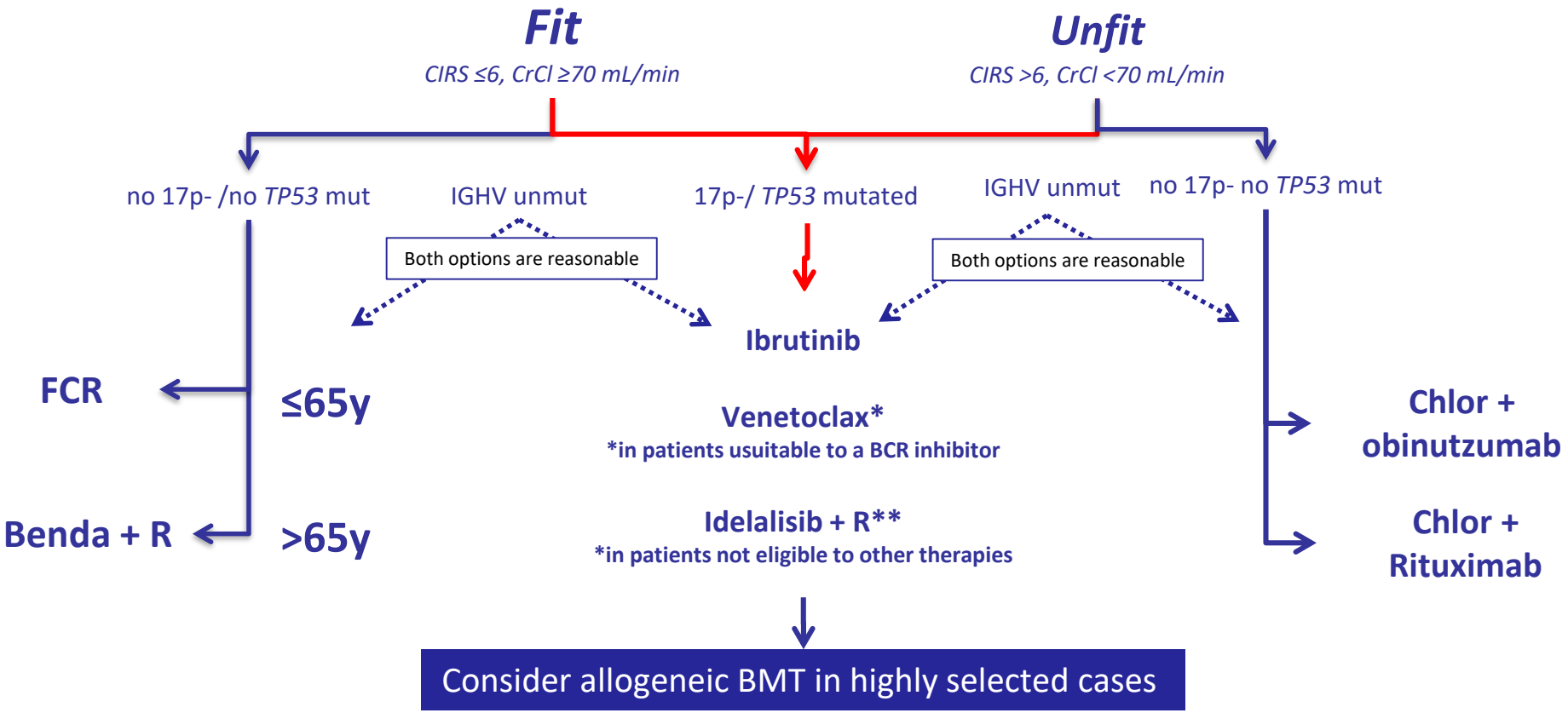
Coutre SE et al. Haematologica. 2017 Nov 23

Characterization of select AEs of clinical interest in ibrutinib-treated patients observed at any time during follow up

AE Grade	Ibrutinib-treated patients n=135 n (%) Any	2	3	4	5	Resolution, n (%) Complete	Partial	Median time to first event, days Any	2	3	4	5	Median time from onset to resolution/improvement, days Any	2	3	4
Diarrhea	61 (45)	16 (12)	5 (4)	0	0	58 (95)	0	26	131	219	NA	NA	6	3	6.5	NA
Visual disturbances[b]	30 (22)	6 (4)	0	0	0	17 (57)	0	100	201	NA	NA	NA	37.5	74.5	NA	NA
Hypertension[c]	27 (20)	13 (10)	7 (5)	0	0	12 (44)	1 (4)	187	187	109.5	NA	NA	14	36	9	NA
Arthralgia	27 (20)	9 (7)	3 (2)	0	0	21 (78)	1 (4)	135	55	135	NA	NA	22	22	15	NA
Atrial fibrillation	14 (10)	7 (5)	6 (4)	0	0	8 (57)	1 (7)	249.5	85	773.5	NA	NA	3	2	7	NA
Major hemorrhage	9 (7)	1 (<1)	7 (5)	1 (1)	0	9 (100)	0	310	155	446	254	NA	13.5	14.0	11.0	45.0
Infections (grade ≥3)	31 (23)	NA	28 (21)	4 (3)	2 (1)	28 (90)	0	138	NA	119	367.5	422	9	NA	9	16

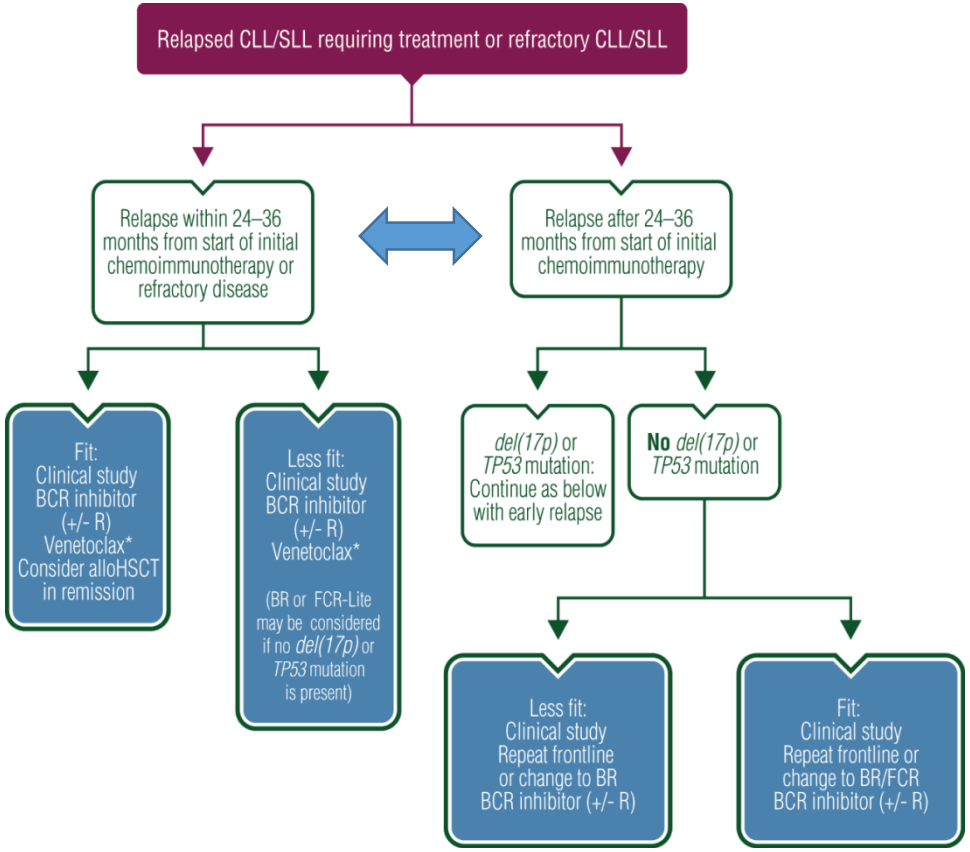
Barr PM et al. Haematologica. 2018;103(9):1502-1510

Principal options for first line treatment of CLL



Cuneo A. personal view, Nov 2018

esmo.org/Guidelines/Haematological-Malignancies

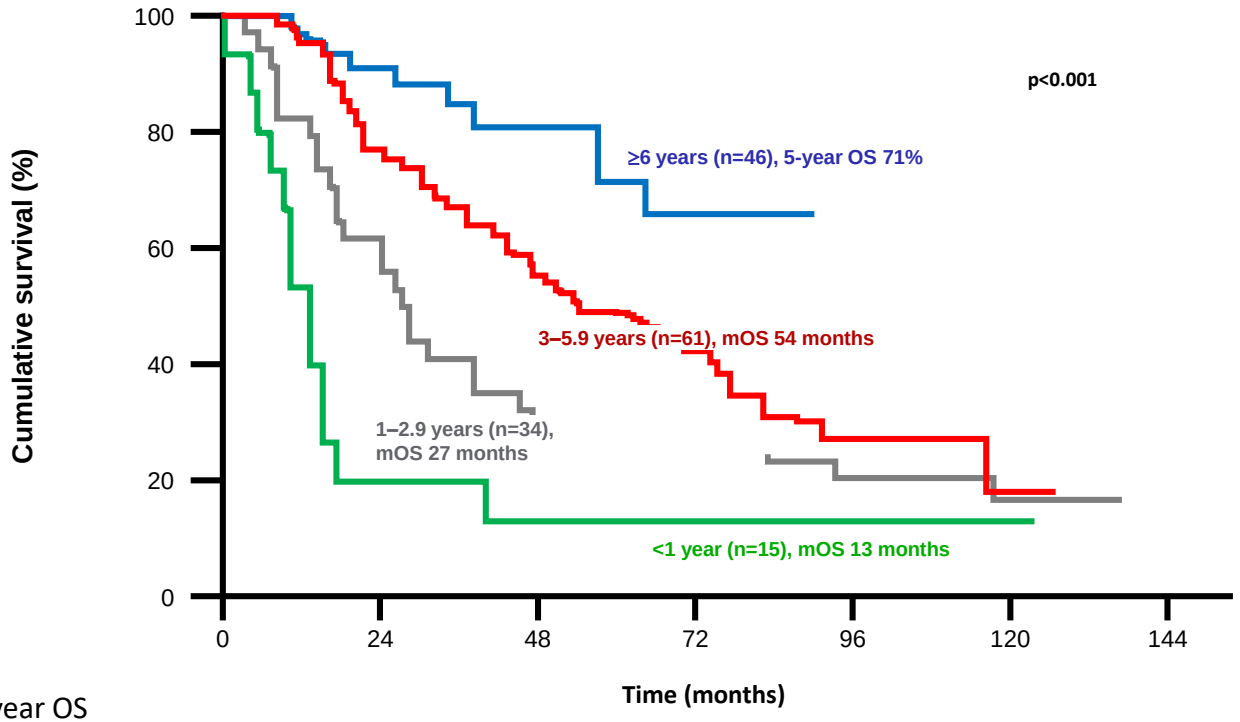


From: Appendix 4: Chronic lymphocytic leukaemia: eUpdate published online 27 June 2017 (www.esmo.org/Guidelines/Haematological-Malignancies)
Ann Oncol. 2017;28(suppl_4):iv149-iv152. doi:10.1093/annonc/mdx242

Survival is short in patients who relapse early

32% of patients relapse ≤ 3 years after FCR, median OS 2.5 years

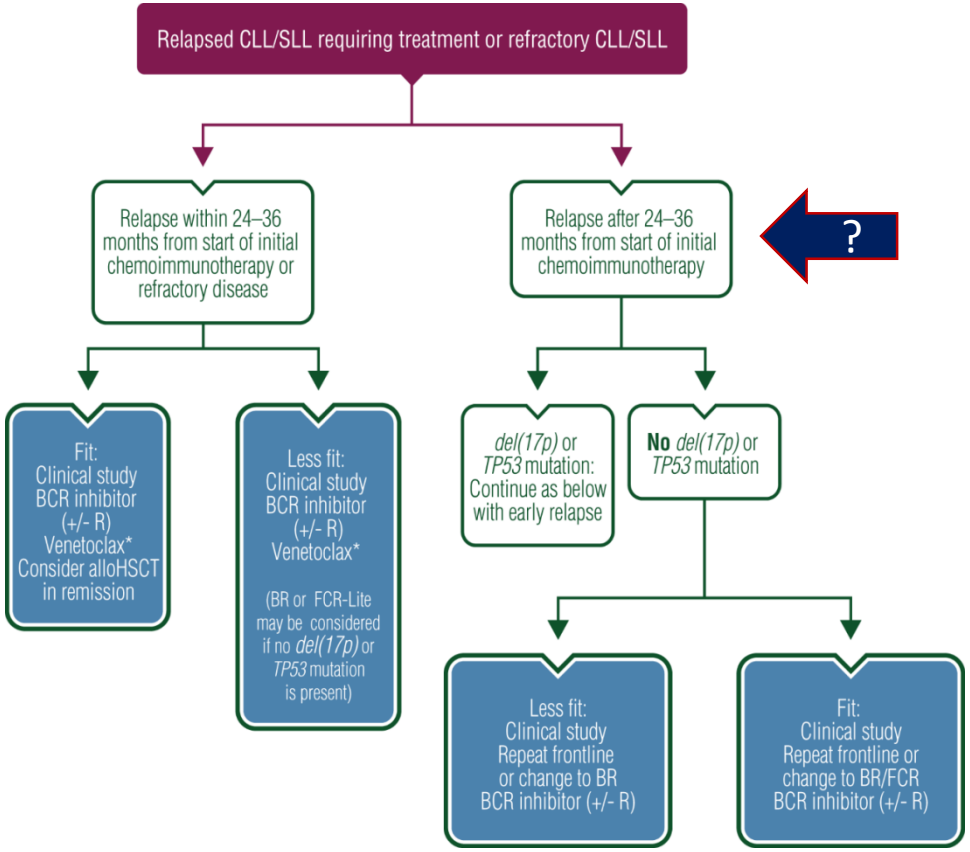
Phase II study of 156 patients who progressed after first-line FCR



[a] 5-year OS
mOS: median OS; OS: overall survival

Tam CS, *et al. Blood* 2014 124:3059–3064.

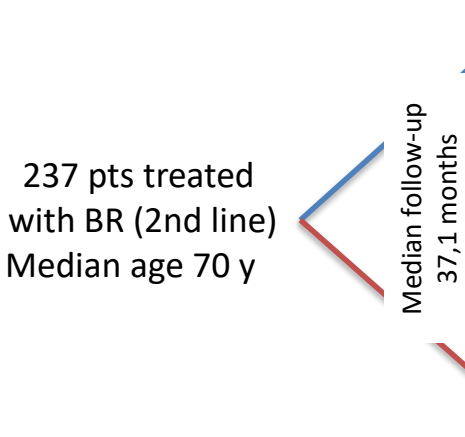
esmo.org/Guidelines/Haematological-Malignancies



From: Appendix 4: Chronic lymphocytic leukaemia: eUpdate published online 27 June 2017 (www.esmo.org/Guidelines/Haematological-Malignancies)
Ann Oncol. 2017;28(suppl_4):iv149-iv152. doi:10.1093/annonc/mdx242

Is there a role for chemoimmunotherapy as first salvage treatment in CLL? Efficacy of Bendamustine and rituximab in a real-world patient population

Efficacy of bendamustine and rituximab as first salvage treatment in CLL and indirect comparison with ibrutinib: a GIMEMA, ERIC and UK CLL FORUM study



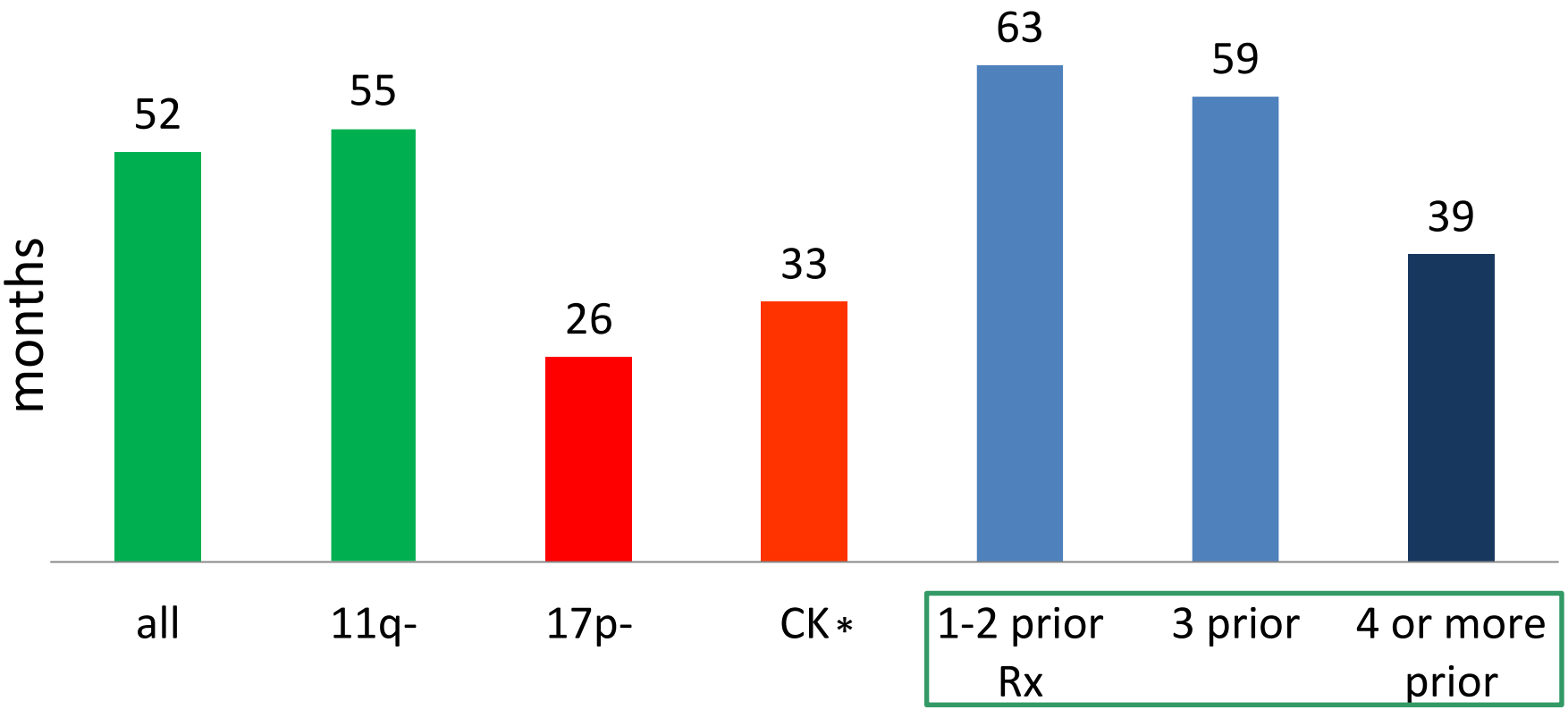
Multivariable analysis

Parameters	P	Hazard Ratio	95% C.I.	
17p- vs others	0.0004	2.92	1.631	5.296
IGVH mut/unmut	0.0299	0.53	0.299	0.94
Others vs Binet C	0.0192	0.536	0.319	0.903

Parameters	P	Hazard Ratio	95% C.I.	
Stage A-B vs C	0,0276	0,547	0,320	0,935
CR+PR vs NR	0.0001	0.344	0.198	0.595

Cuneo A et a. Haematologica. 2018 Jul;103(7):1209-1217

Median PFS in 101 rel/ref CLL under ibrutinib (5 yr follow-up) genetics and previous treatment



*Not reached for non complex karyotype

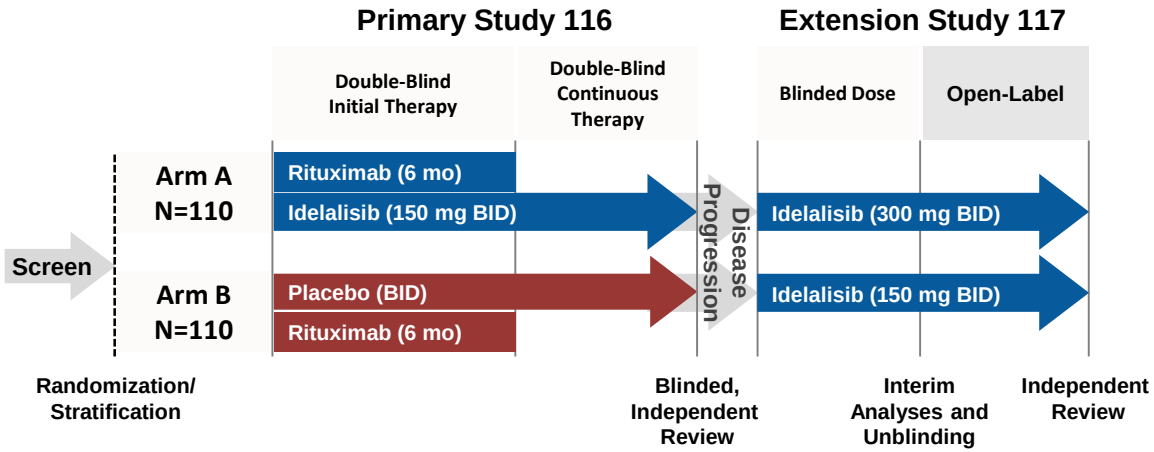
O'Brien ASH 2016 abs#233

Study GS-US-312-0116 (Phase 3)

Idelalisib and Rituximab in rel/ref

Population:

Relapsed CLL warranting treatment (iwCLL); progression < 24 mo since last treatment



	Median Follow-up, months		
	IDELA + R	PBO + R	
1st Interim Analysis	4	4	DMC halted trial (Furman NEJM 2014) 50% events
2nd Interim Analysis	6	5	Blind ended (Coutre ASCO 2014) 63% events • Arm A continues (amendment to be all 150mg) • Arm B crosses over
Update	13	11	PFS, OS by subgroup analysis

Furman R et al *NEJM* 2014;370:997-1007

Patients included in Study 116 were elderly, had a poor performance status and cytopenias

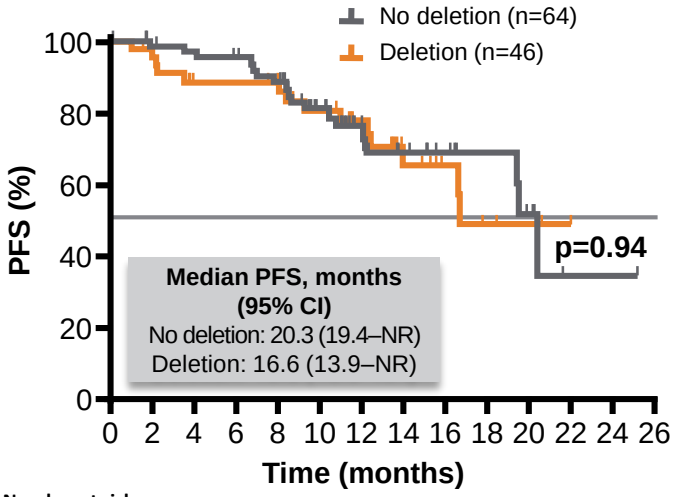
	Typical relapsed CLL patient	Ibrutinib RESONATE population[3]	Zydelig + R Study 116 population[6]	Ofatumumab licensing study[4] (FA-ref/BF-ref)
Trial design	Registry	Open-label randomised	Double-blind placebo controlled	Non-randomised Phase II
Median age (years)	72.5[1a]	67	71	64/62
ECOG PS, 1–3 (%)	N/A	59	87	65
ECOG PS, 2–3 (%)	23.2[2b]	0	28	N/A
del(17p) and/or *TP53* mutation (%)	42[5]	33	43	29/18
Blood count criteria	N/A	Platelets ≥30 x 10^9/L Neutrophils ≥0.75 x 10^9/L	No restrictions 35% Grade 3 or 4 cytopenias	No blood counts or transfusion restrictions

- [a] German Tumour Registry Lymphatic Neoplasms (patients recruited between 2009 and 2013) at start of second-line therapy (n=186)
- [b] Ipsos Healthcare Global Oncology Monitor real world evaluation of CLL patient from Germany, France, UK, Spain and Italy (n=5163)
- [c] Equivalent to Karnofsky score 0–70
- ECOG: Eastern Cooperative Oncology Group

Del(17p) or *TP53* prognostic factors do not impact on the efficacy of Zydelig + R

Second interim analysis: median PFS 19,4 months in the idela + R arm

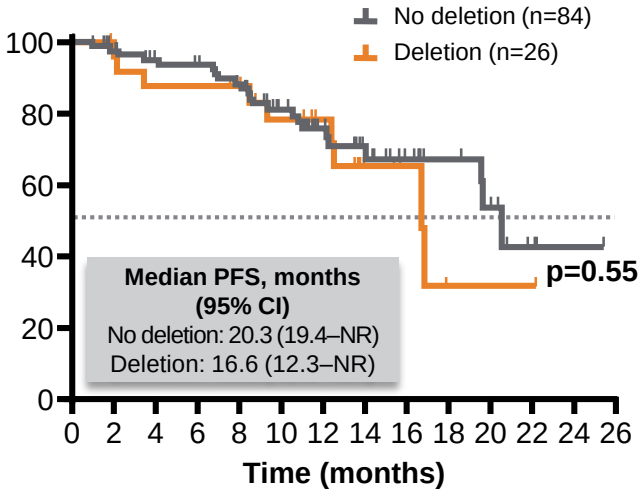
Del(17p)/*TP53* mutation



Number at risk

No del	64	61	59	59	52	37	21	14	11	8	4	1	1	1
Del	46	41	36	36	33	30	22	12	8	4	3	0	0	0

Del(17p)



	84	78	73	71	65	49	31	20	15	11	6	1	1	1
	26	23	22	22	20	17	12	6	4	1	1	0	0	–

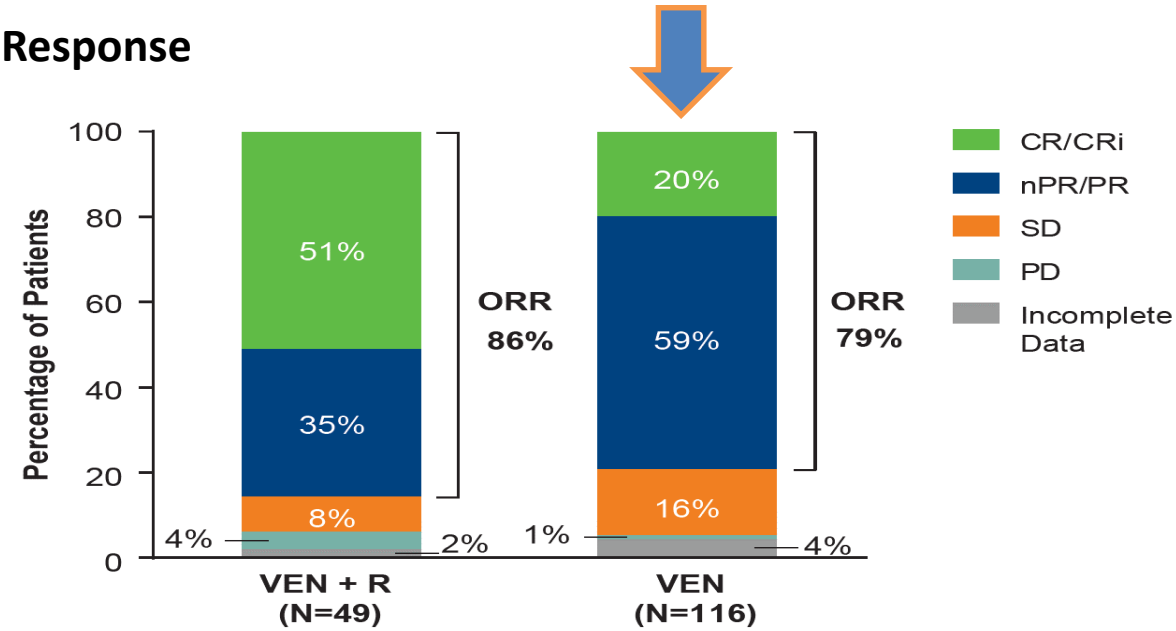
Sharman JP, *et al.* ASH 2014 (Abstract 330; oral presentation).

Impact of adding Rituximab to Venetoclax in RR CLL: a Cross-Study Multivariable Analysis

- High ORR were achieved with Venetoclax combined with rituximab (86%), or Venetoclax monotherapy (79%)
  CR was higher with Venetoclax combined with rituximab (51%) than Venetoclax monotherapy (20%)

Best Objective Response

BM MRD- (flow)
59% (29/49)



"Incomplete data for M13-365 (VEN + R) was due to one death due to TLS. 5 patients had incomplete data for M12-175 (VEN), which were due to TLS (n=2, 1 fatal), thrombocytopenia (1), viral pneumonia (1), and management of diabetes mellitus (1).

Roberts EHA 2016 P209

MURANO Study Design

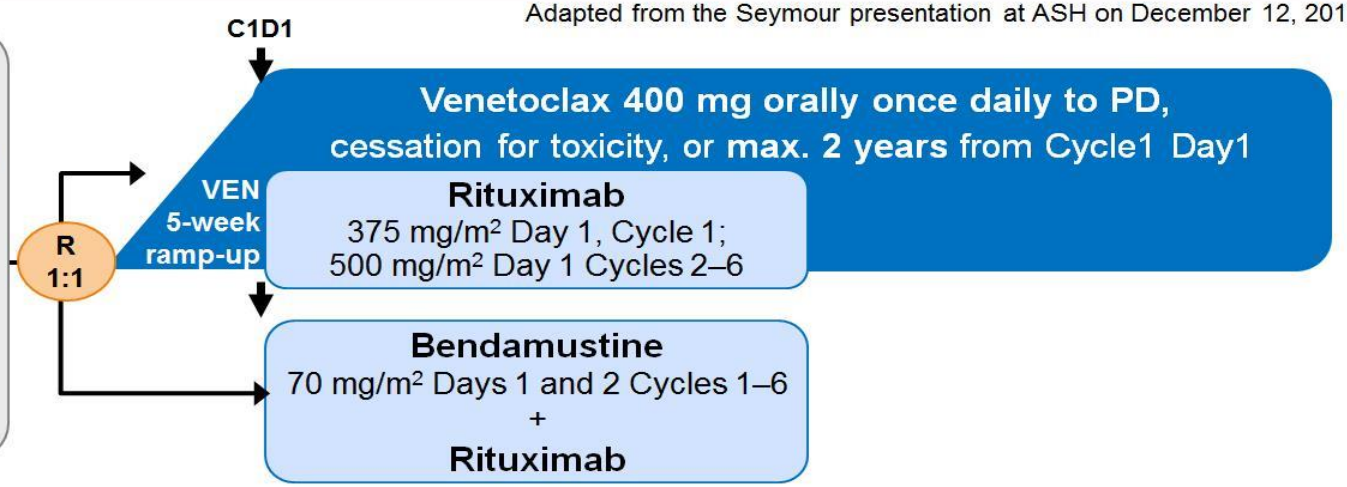
Adapted from the Seymour presentation at ASH on December 12, 2017

Relapsed/refractory CLL (N=389)

- ≥18 years of age
- Prior 1–3 lines of therapy, including ≥1 chemo-containing regimen
- Prior bendamustine only if DoR ≥24 months

Stratified by:

- Del(17p) by local labs
- Responsiveness to prior therapy*
- Geographic region

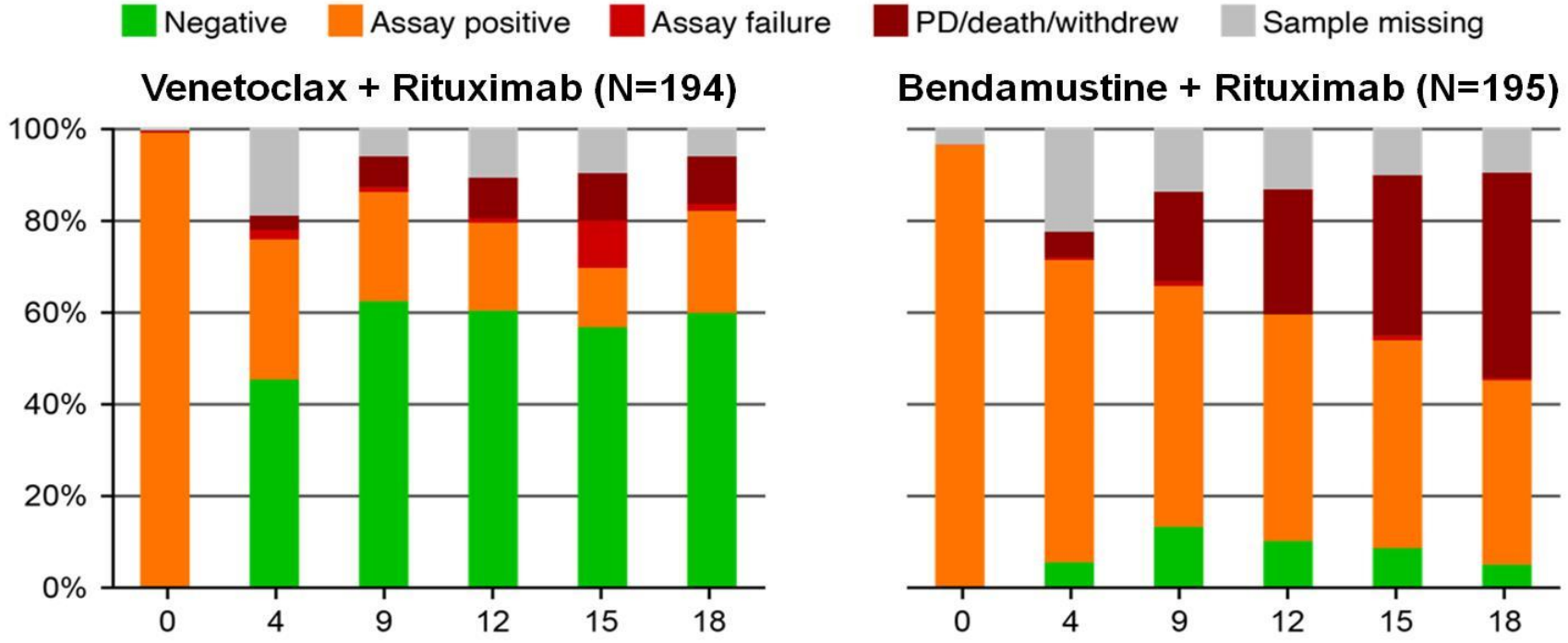


Primary Endpoint	INV-assessed PFS
Major Secondary Endpoints	• IRC-CR ⇒ IRC-ORR ⇒ OS (hierarchical testing) • IRC-assessed PFS and MRD-negativity
Key Safety Endpoints	Overall safety profile, focusing on serious adverse events and Grade ≥3 adverse events
Interim Analysis	Approximately 140 INV-assessed PFS events (75% of total information)

NCT02005471

*High-risk CLL – any of following features: del(17p) or no response to front-line chemotherapy-containing regimen or relapsed ≤12 months after chemotherapy or within ≤24 months after chemoimmunotherapy.

High Peripheral Blood MRD Negativity Rate Maintained Over Time for VenR vs. BR

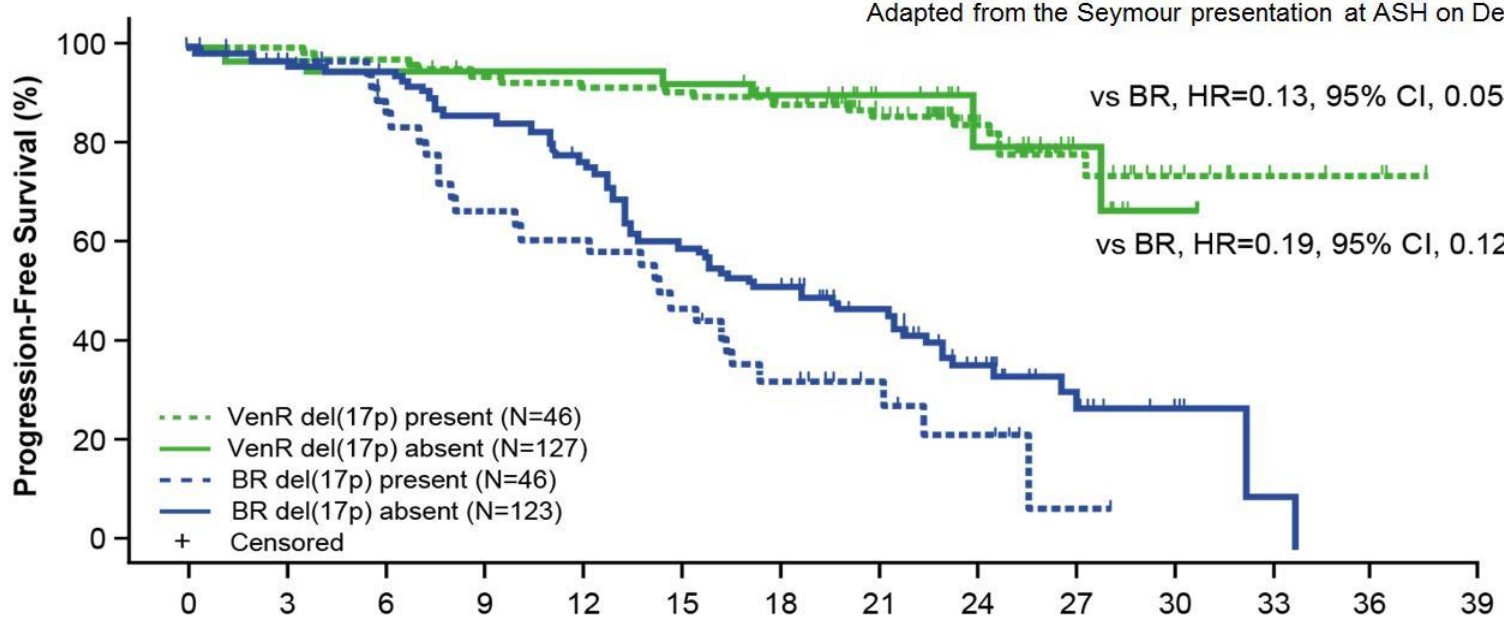


Adapted from the Seymour presentation at ASH on December 12, 2017

As of 8 May 2017

Investigator-assessed PFS Superior for VenR vs. BR Among Patients With and Without del(17p)

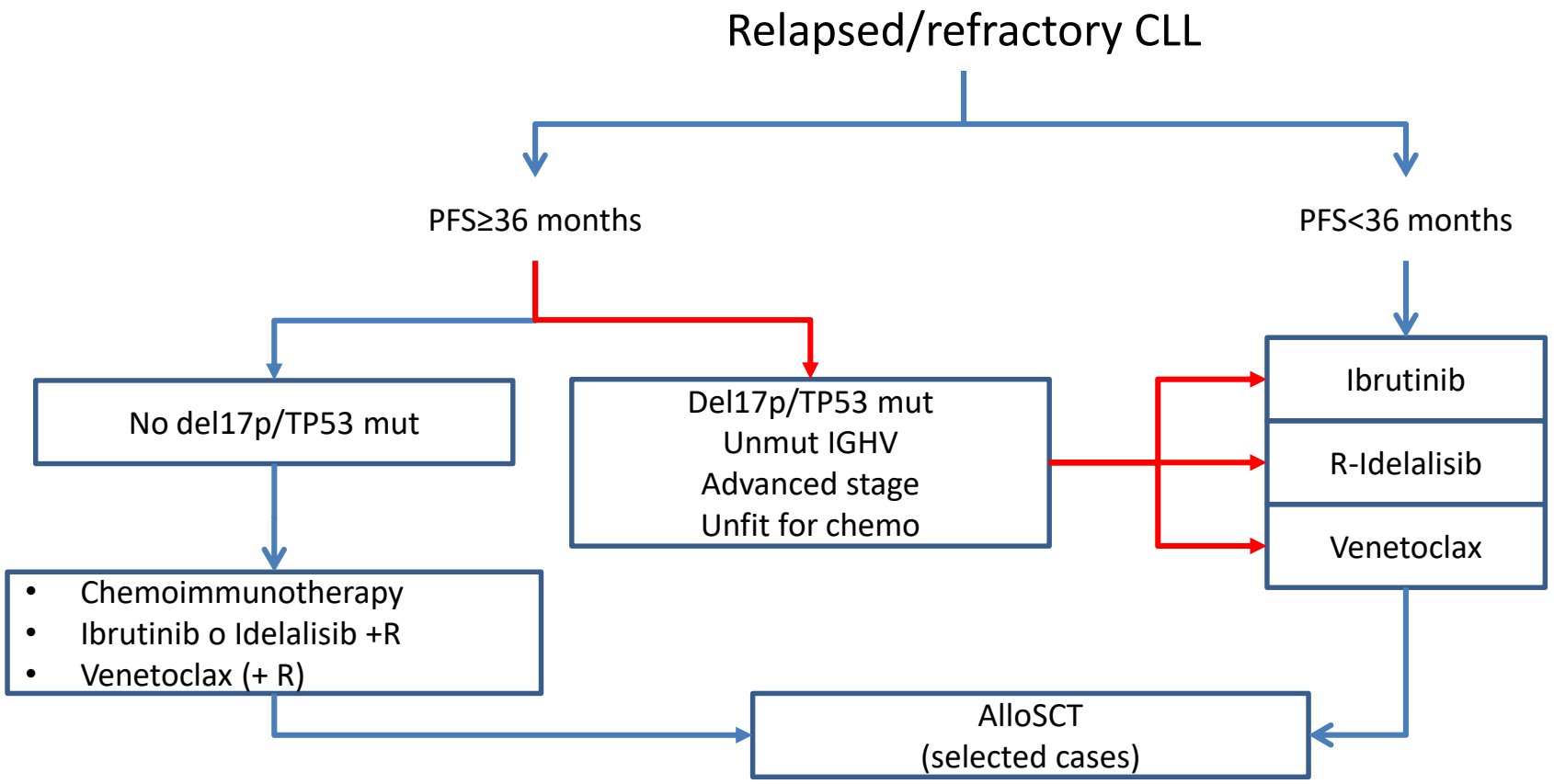
Adapted from the Seymour presentation at ASH on December 12, 2017



No. of patients at risk:													
VenR del(17p) present	46	44	43	43	43	42	36	25	17	7	2		
VenR del(17p) absent	127	127	124	118	116	114	105	76	48	20	10	4	3
BR del(17p) present	46	40	34	27	25	20	14	8	5	1			
BR del(17p) absent	123	114	108	99	88	70	60	44	26	10	3	1	

As of 8 May 2017

Principal options for relapsed/refractory CLL



Cuneo A. personal view, Nov 2018