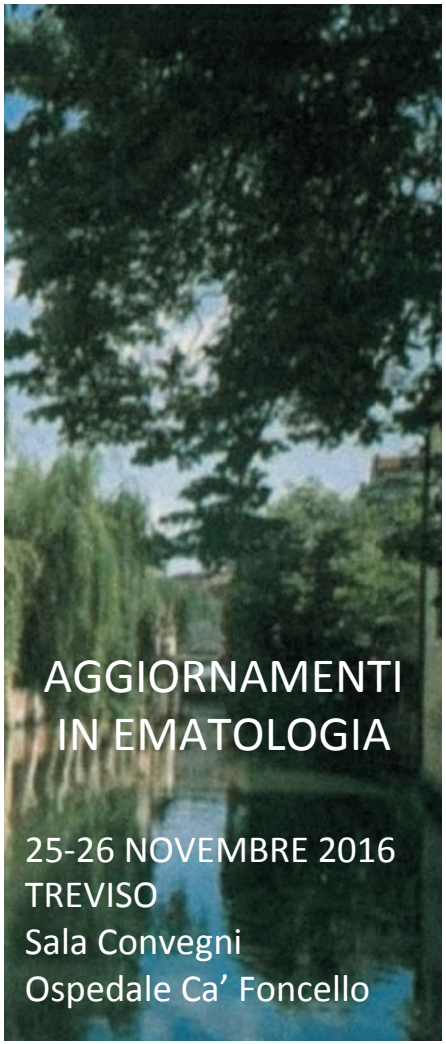


Regimi di trattamento chemotherapy-free

Nella Leucemia linfatica cronica

università di ferrara
DA SEICENTO ANNI GUARDIAMO AVANTI.

Prof. Antonio Cuneo, MD, PhD

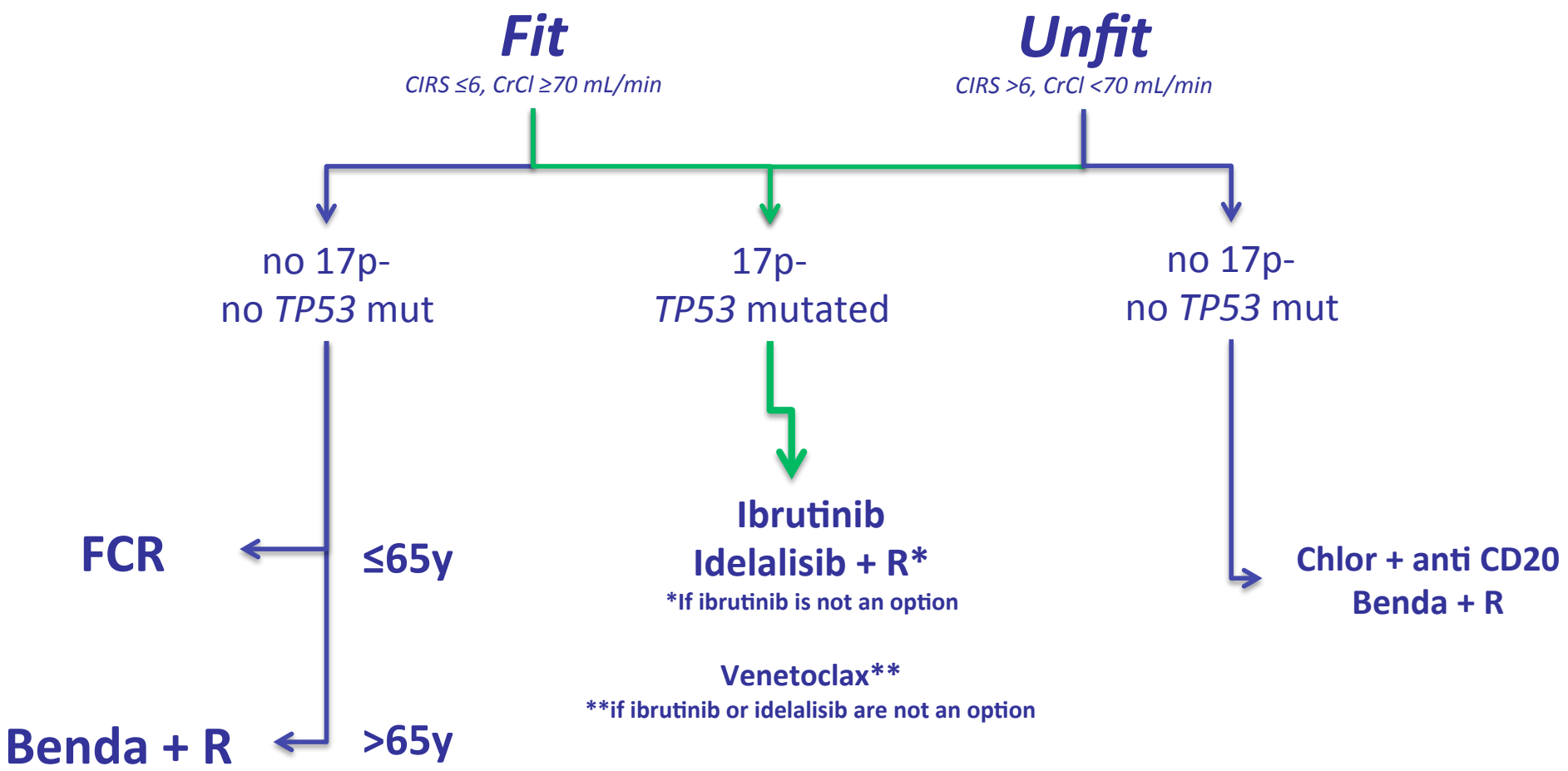
Chemo-free regimens

First line

Relapsed/refractory CLL

Failure of a kinase targeted agent

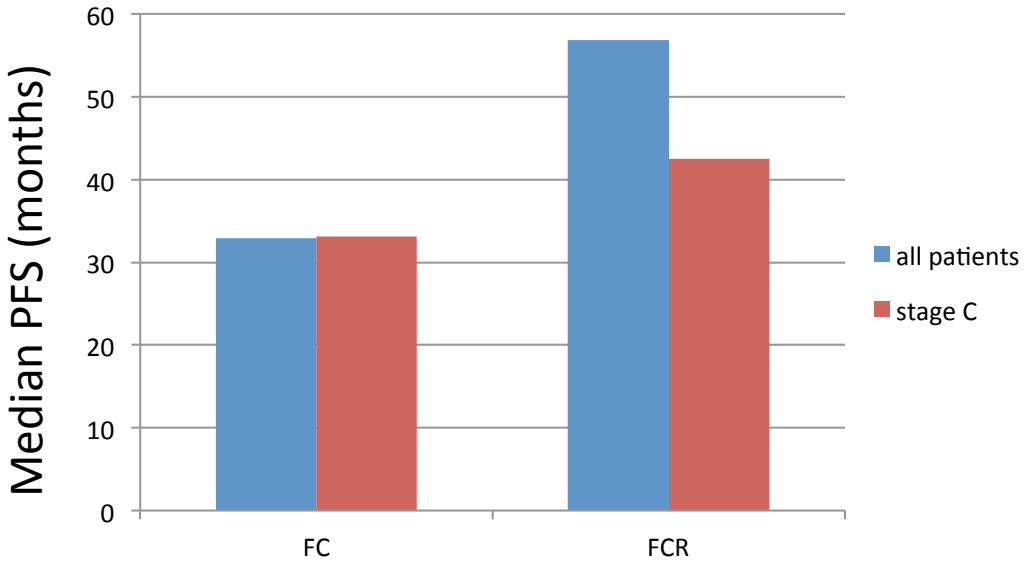
Options for first line treatment in CLL



Cuneo A, personal view,
adapted from NCCN 2015; Hallek M. Am J Hematolol 2015; Stilgenbauer S Education book ASCO 2015

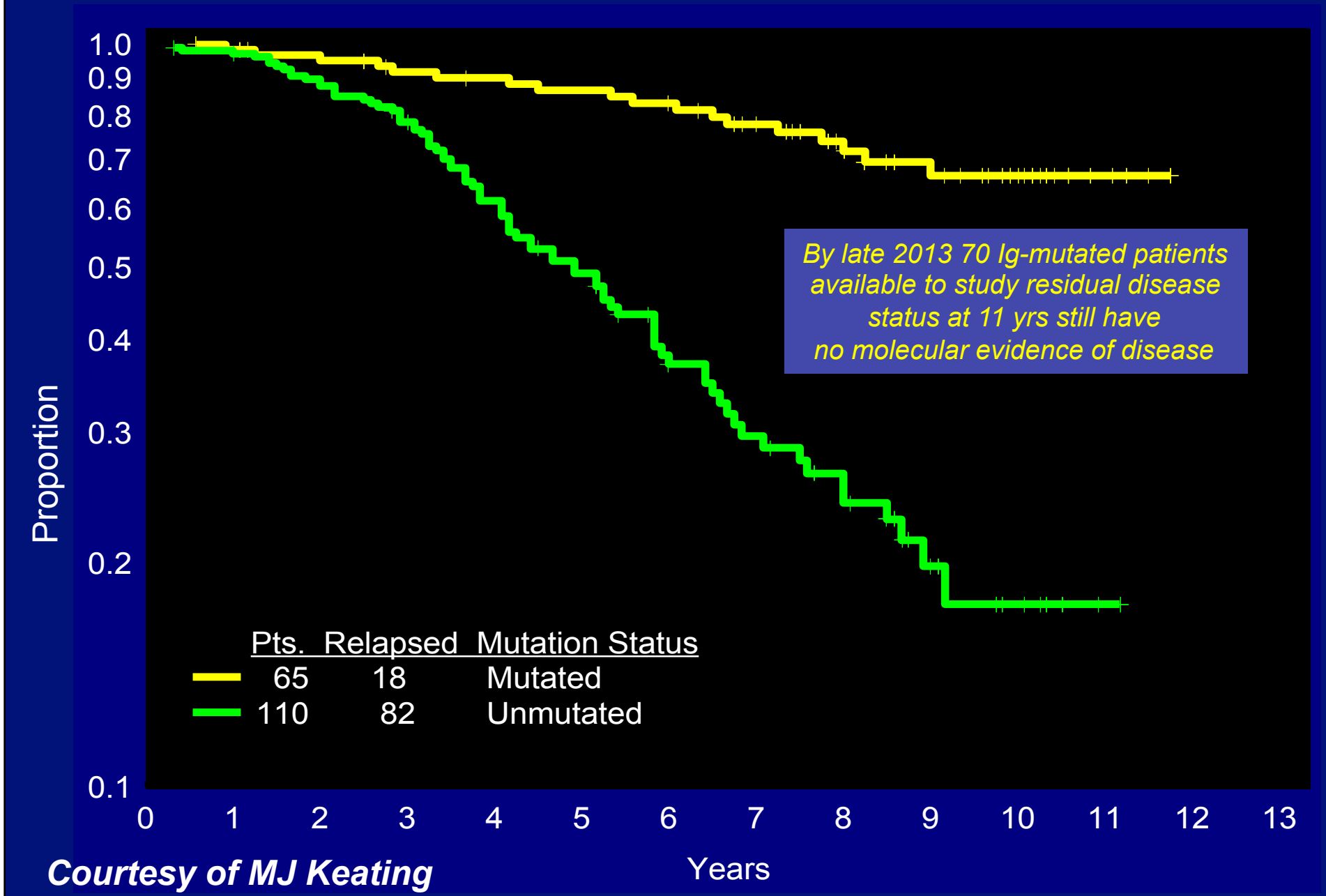
FCR is the standard treatment in young and fit CLL

Median PFS with FCR 56.8 months vs 32.9 months with FC
HR, 0.59; 95% CI, 0.50-0.69;(p<0.001)



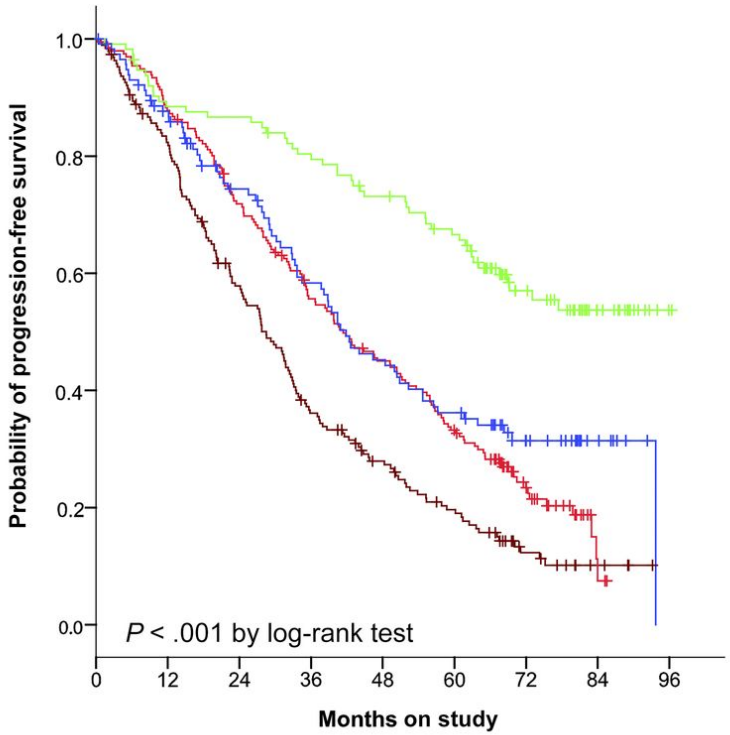
median observation of 5.9 years

Importance of prognostic factors on the durability of response
FCR Time to Progression by Mutation Status FCR300 (logarithmic scale)



Courtesy of MJ Keating

Long term PFS with FCR (GCLLSG – CLL8)



66% progression free
at 5r yrs with plateau?

FCR *IGHV* MUT patients (N=113)

FC *IGHV* MUT patients (N=117)

FCR *IGHV* UNM patients (N=197)

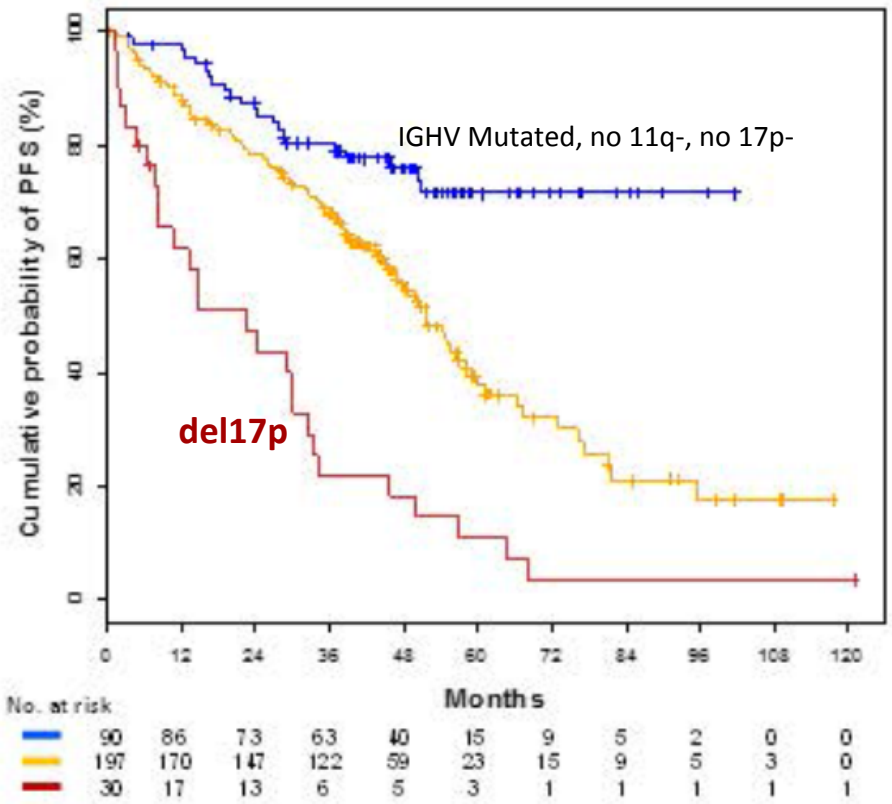
FC *IGHV* UNM patients (N=195)

Number at risk	0	12	24	36	48	60	72	84	96
FCR *IGHV* MUT	113	99	97	89	80	71	37	15	1
FC *IGHV* MUT	117	96	75	58	45	36	21	7	0
FCR *IGHV* UNM	197	173	140	106	85	61	25	2	0
FC *IGHV* UNM	195	153	105	65	45	30	12	4	0

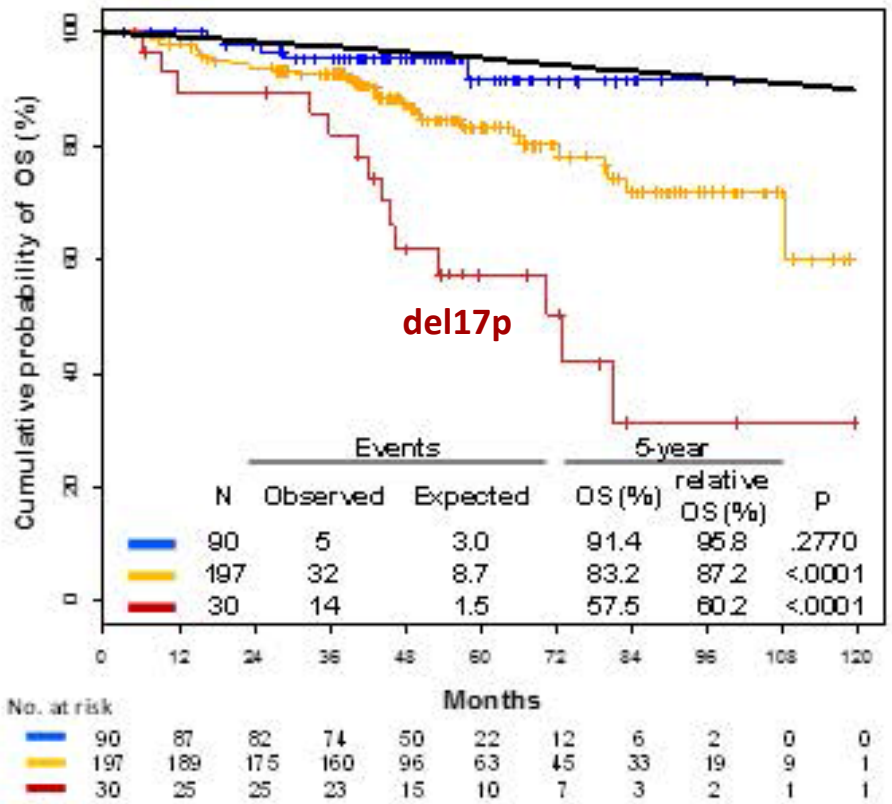
Fischer K et al. Blood. 2016; 127:208-215

MOLECULAR PREDICTION OF DURABLE REMISSION AFTER FIRST LINE FCR IN CLL TREATED IN THE EVERYDAY PARACTICE

PFS



OS



Low-risk group (IGHV Mutated)

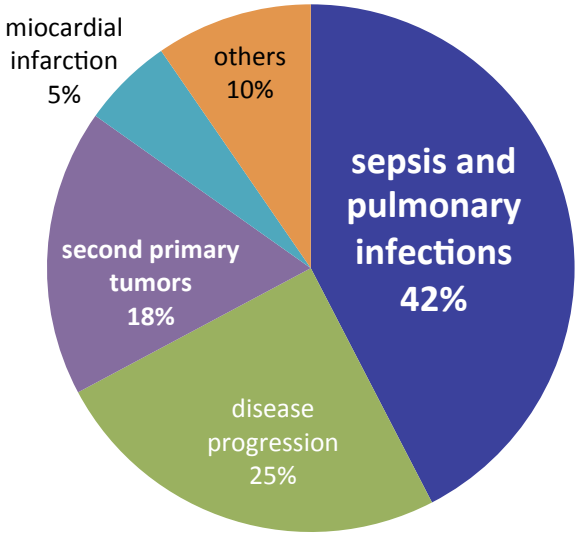
Intermediate-risk group (IGHV un-mutated and/or 11q del)

High-risk group (I17p deletion)

Rossi D, Blood 2015

Causes of death after FCR in the CLL8 trial

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

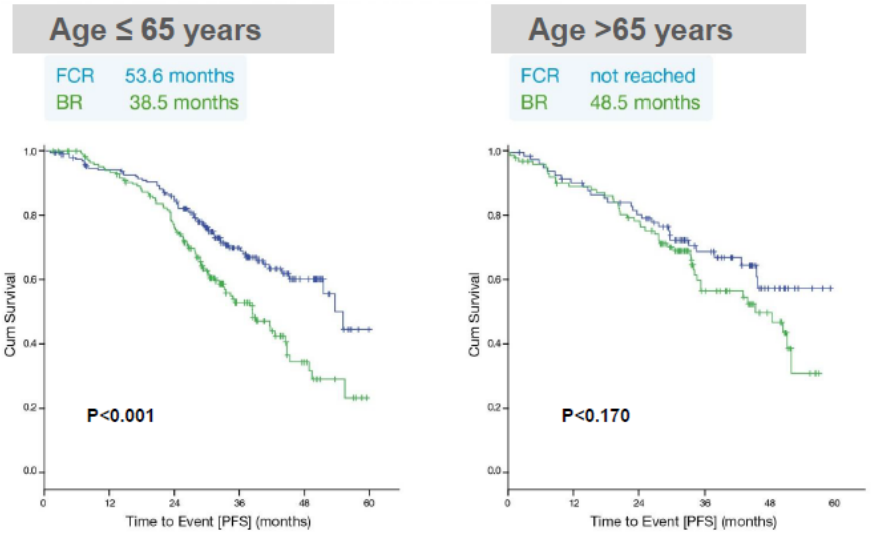


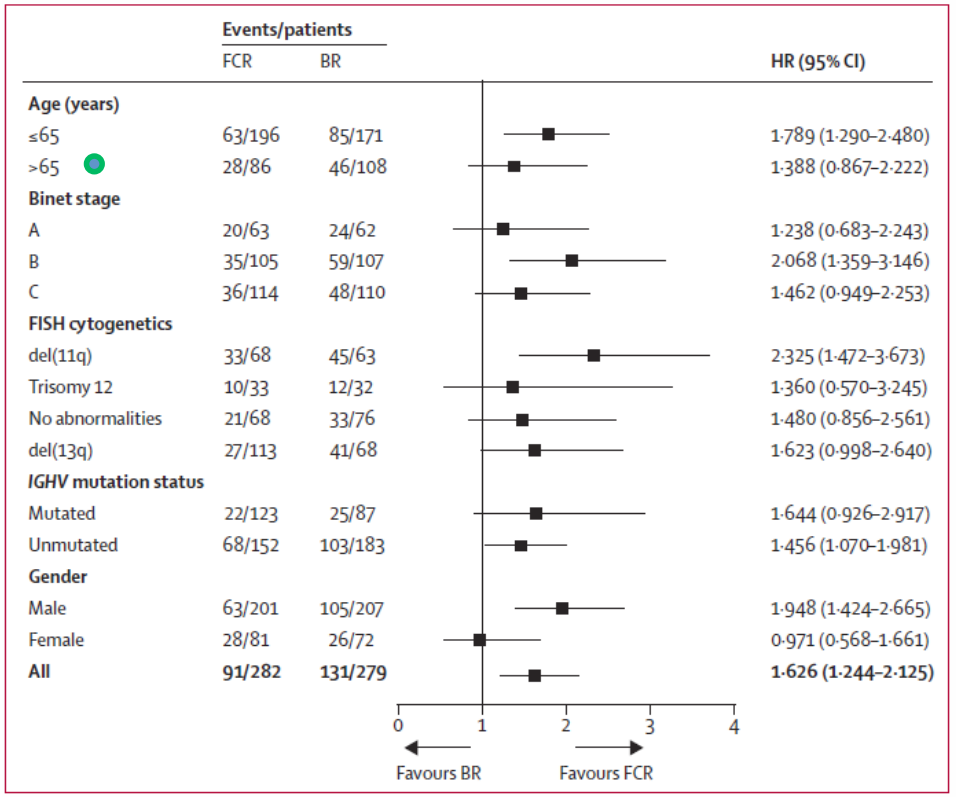
Median time to onset (months) after last dose of study treatment	
sepsis and pulmonary infections	46
second primary tumors	27

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

FCR is more effective than Bendamustine and rituximab (CLL10)

- No PFS advantage in pts >65 y



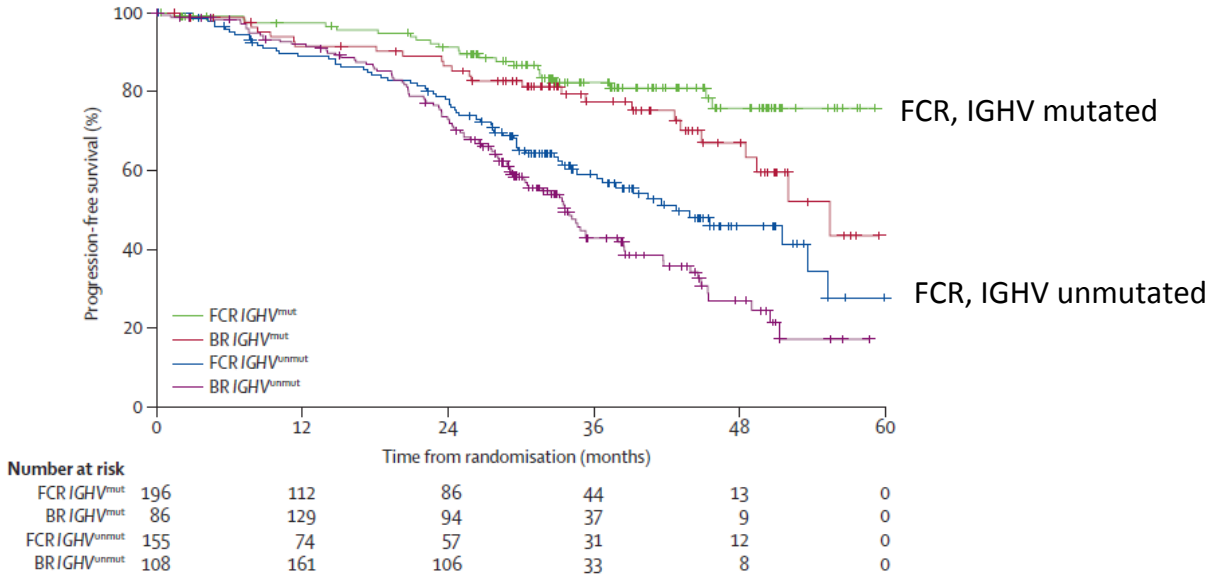


Eichhorst et al., ASH 2014, Abstract # 19

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

FCR is more effective than Bendamustine and rituximab (CLL10): PFS according to risk groups

- Shorter PFS in pts with IGHV unmutated or with 11q-



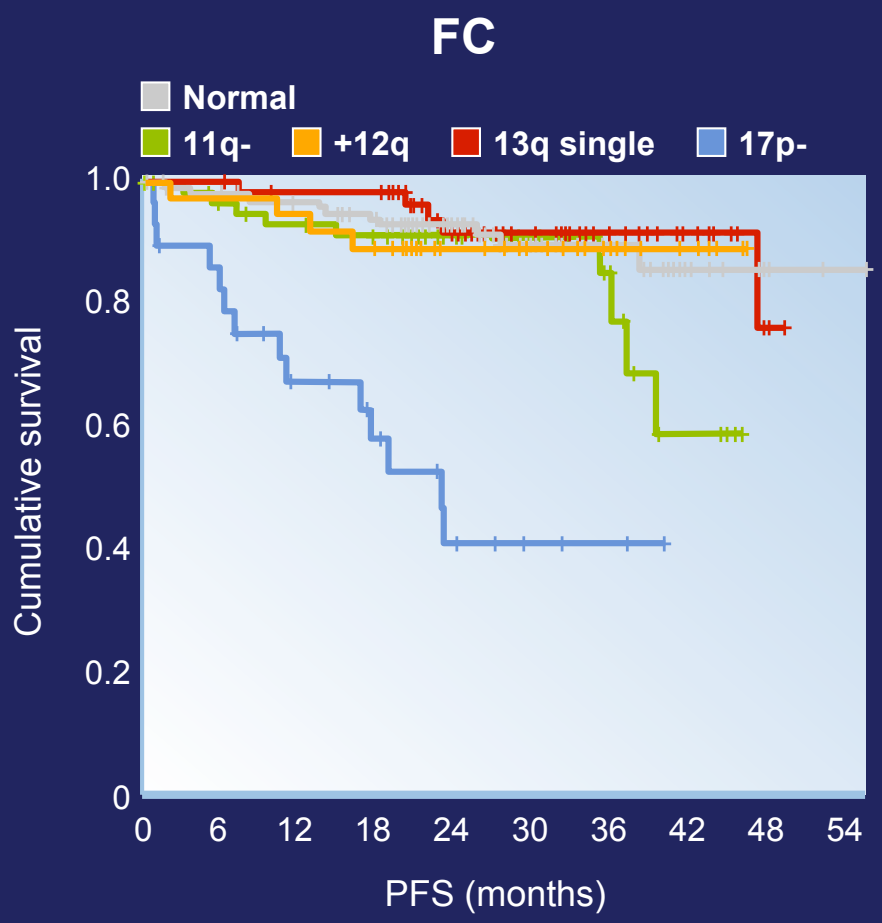
Estimated Progression-free survival at three years: BR vs FCR and impact of genetics

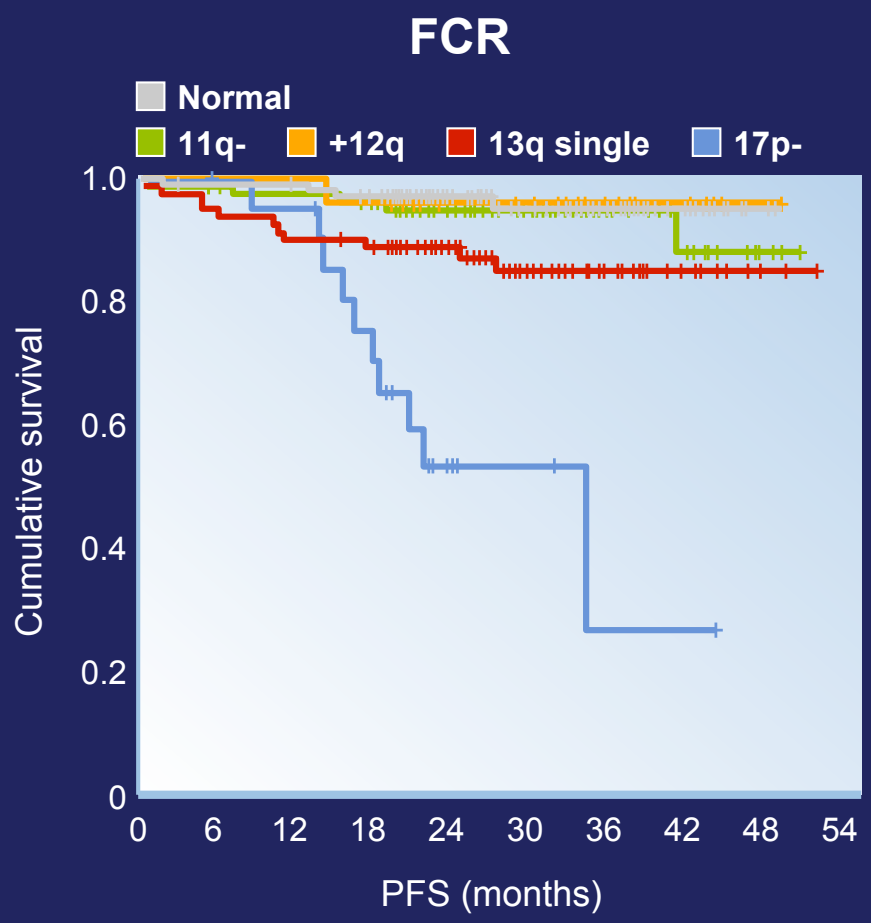
	FCR n = 282	BR n = 279	Hazard ratio (95% CI)	p value
IGVH mutated (n=210)	82·4% (75·1-89·6)	77·5% (67·8-87·1)	1·644 (0·926 - 2·917)	0·089
IGHV unmutated (n=335)	59·1% (50·6-67·6)	42·8% (34·5-51·1)	1·456 (1·070 - 1·981)	0·017
Del (11q) (n=131)	56·8% (43·7-70·0)	14·2% (3·4-25·0)	2·325 (1·472 - 3·673)	0·000297

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

Addition of rituximab to fluda and CTX in CLL: a randomised, open-label, phase 3 trial
M Hallek et al Lancet 2010; 376: 1164–74

Poor outcome for 17p- patients





Elderly CLL

Efficacy of chlorambucil + Rituximab as first line treatment

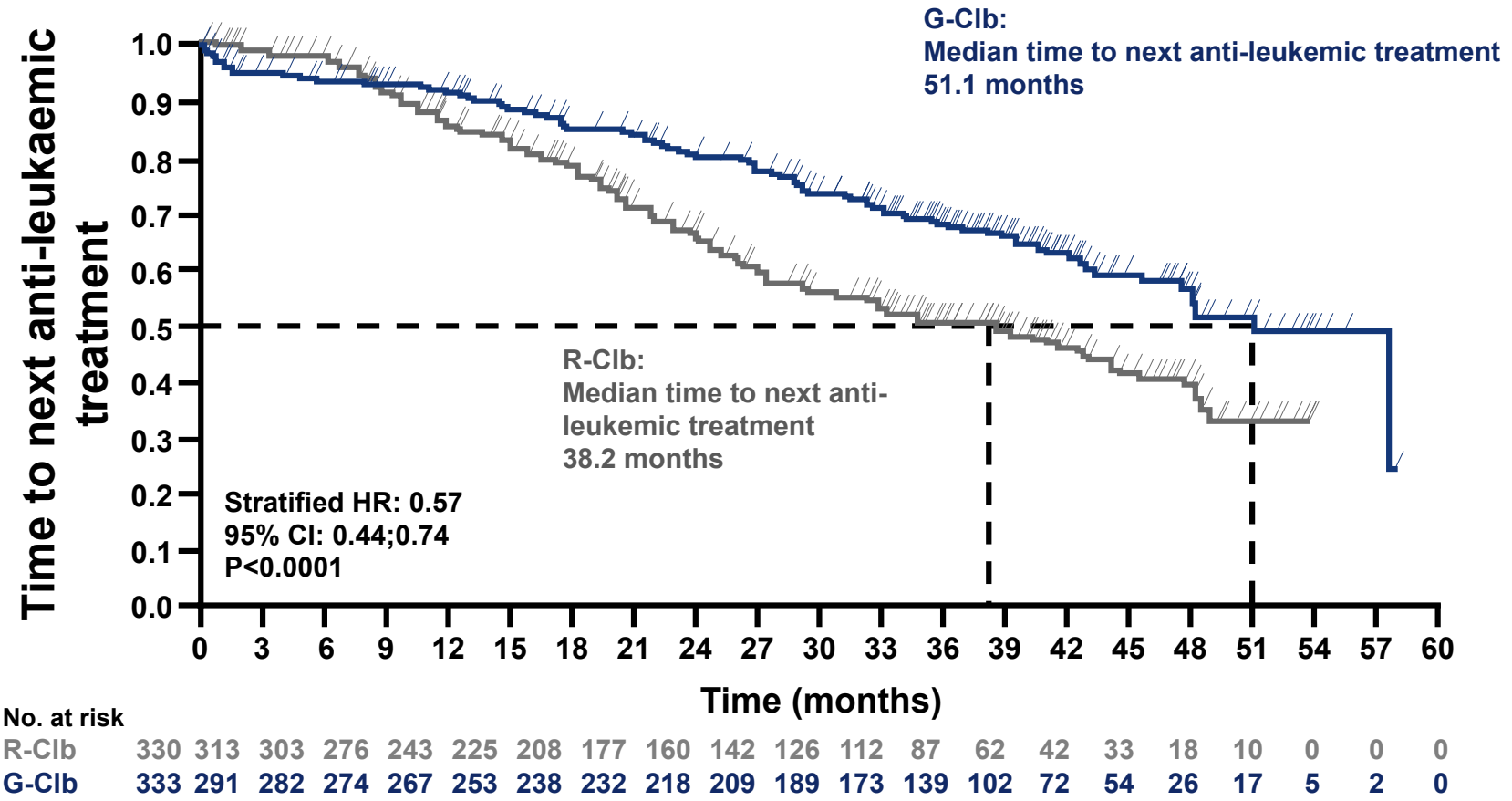
	No. of patients	Inclusion criteria	Median age	Total dose of Chlor	%CR/CRi	Median PFS (months)
	100	age18 years deemed non eligible to fluda	70	420 mg/sqm	10	23,5
	85	>65 or 60-65 non eligible to fluda	70	448 mg/sqm	19	34,7
	233	CIRS >6 Cr Clear<70	73	6 mg / Kg	8,3	15,7

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

CLL11 stage II: Time to next anti-leukaemic treatment



CI, confidence interval; Clb, chlorambucil; CLL, chronic lymphocytic leukaemia;
G-Clb, Obinutuzumab + Clb; HR, hazard ratio; OS, overall survival; R-Clb, MabThera + Clb

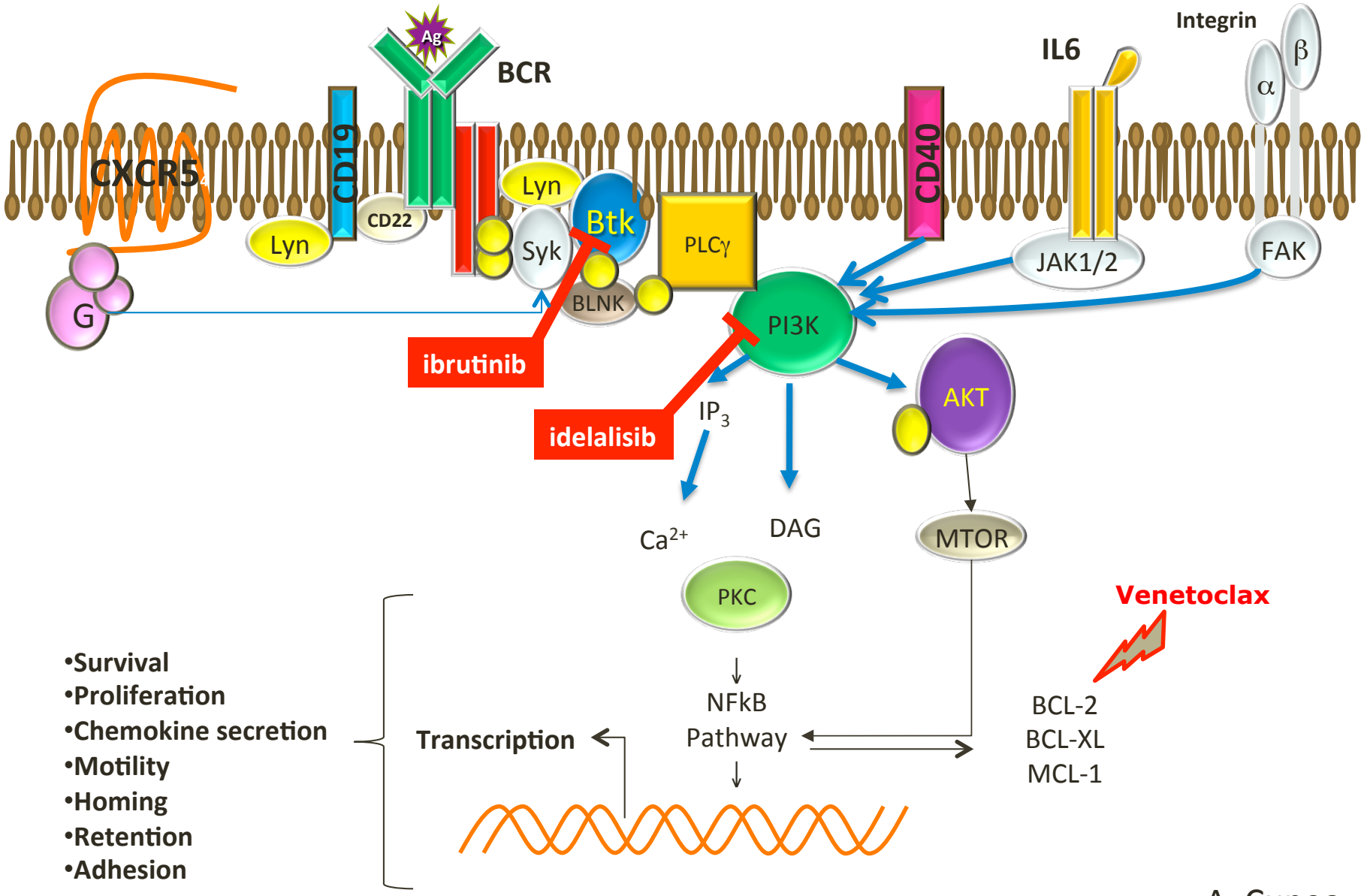
Goede V, et al. Blood 2015;126:abstract 1733

Median PFS in high risk CLL treated by Chlor + anti CD20 (elderly/unfit)

	11q-	No 11q-	Unmutated IGHV
Treatment	**Chlor + R (UK trial)[1]**		**Chlor + R (GIMEMA trial)[2]**
Median TTP or PFS (months)	**12**	**24**	**22,8**

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

IBRUTINIB and IDELALISIB + R are approved in Europe for first line treatment of CLL with 17p-/TP53 mutations



A. Cuneo

Ibrutinib for previously untreated and relapsed or refractory CLL with TP53 aberrations: a phase 2, single-arm trial.

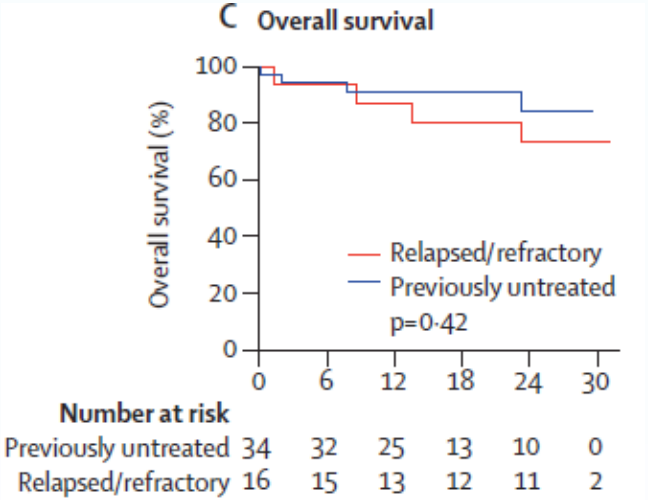
Response to treatment

	All evaluable patients (n=48)	Previously untreated patients (n=33)	Relapsed or refractory patients (n=15)
Response at 24 weeks			
Complete response	..	..	..
Partial response	24 (50%)	18 (55%)	6 (40%)
Partial response with lymphocytosis	20 (42%)	14 (42%)	6 (40%)
Stable disease	3 (6%)	..	3 (20%)
Progressive disease	1 (2%)	1 (3%)	..
Best response			
Complete response	5 (10%)	4 (12%)	1 (7%)
Partial response	32 (67%)	23 (70%)	9 (60%)
Partial response with lymphocytosis	8 (17%)	5 (15%)	3 (20%)
Stable disease	2 (4%)	..	2 (13%)
Progressive disease	1 (2%)	1 (3%)	

Farooqui MZ et al, Lancet Oncol. 2015 Feb;16(2):169-76

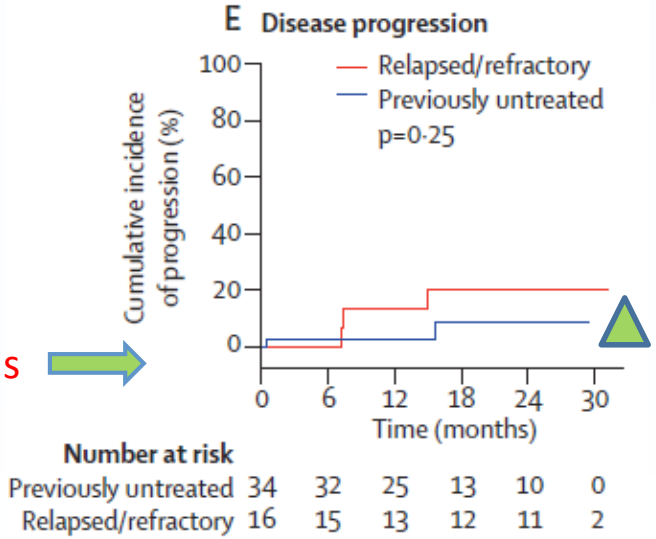
Ibrutinib monotherapy in First-Line CLL: Impact of del(17p) on treatment response (Phase II)

Overall survival in subgroups by treatment history



Cumulative incidence of disease progression by treatment history

Median follow-up for the previously untreated cohort was 15 months

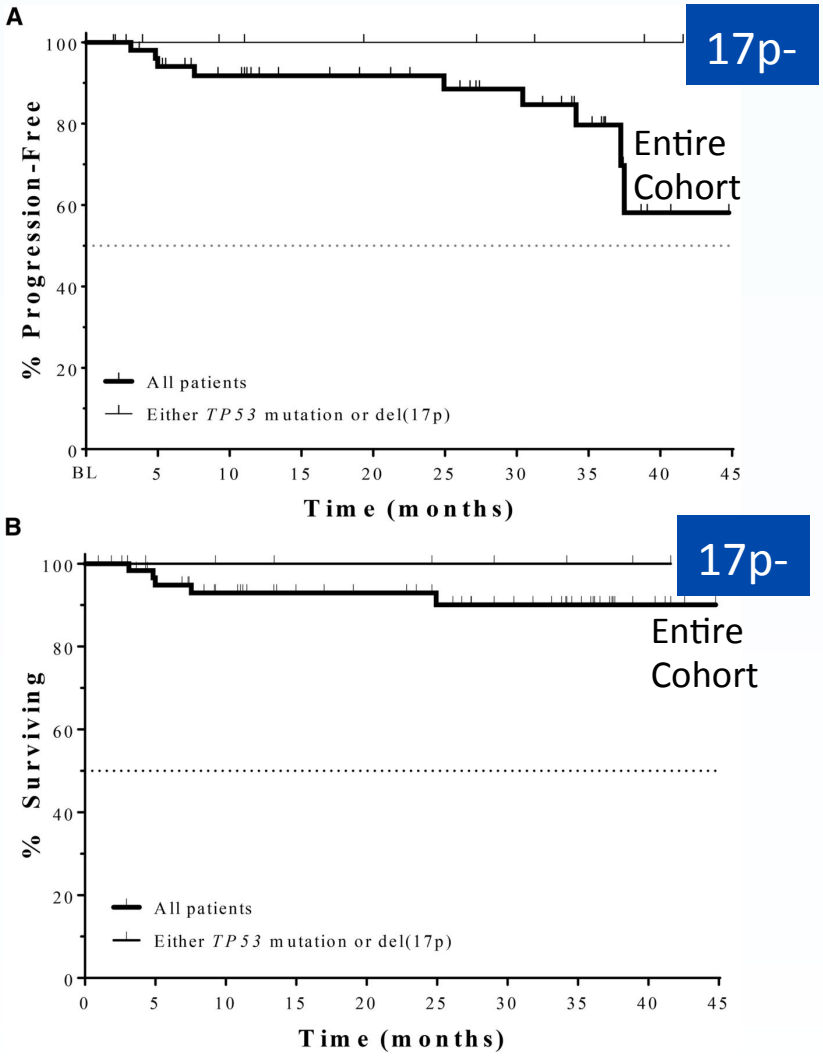


Farooqui M, *et al. Lancet Oncol* 2015;16:169–176.

Idelalisib + Rituximab first-line therapy in the elderly

Patients (%)	Idelalisib (n = 64) with 17p-: 9 patients
Treatment response[1]	
ORR	97*
CR	19
PR	78
Safety[1]	
Diarrhea/colitis (Grade 3)	42
Pneumonia (Grade 3)	19
AST/ALT (Grade 3)	23

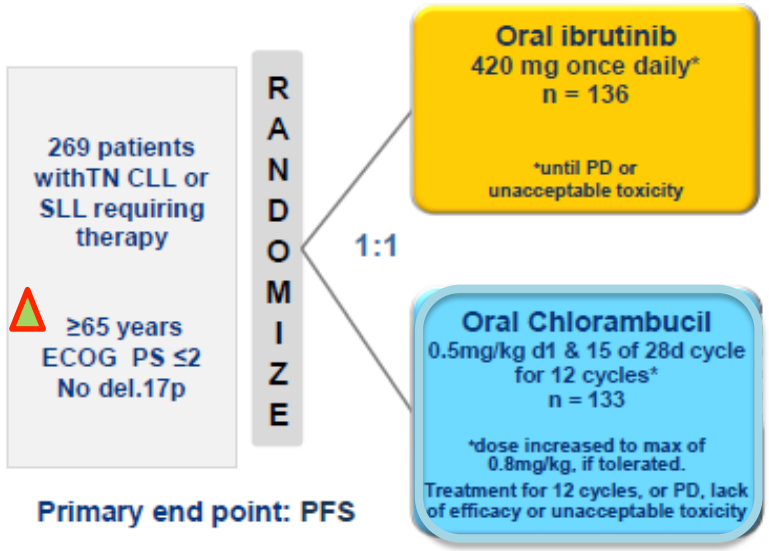
- Median age: **71 years** (65–90 years)[1]
- Median time to response: 1.9 months[1]
- Median time on idelalisib: **22.9 months**[1]
- Completed 48 weeks of therapy: 67%, most discontinuations due to AEs[1]



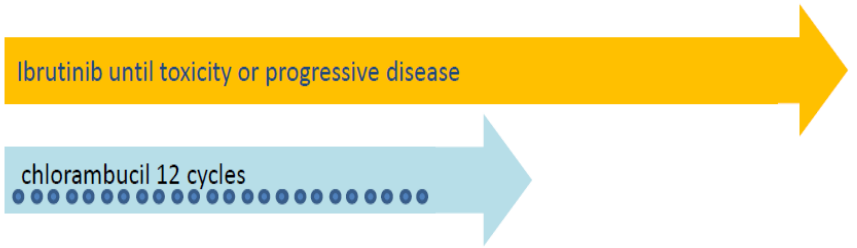
AE = adverse event; ALT = alanine transaminase; AST = aspartate transaminase.
* 3% of patients unevaluable.[1]

1. O'Brien S, *et al.* ASH 2014. Abstract 1994; 2. Lamanna N, *et al.* iwCLL 2013; 3. Zydelig SmPC, October 2014.

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



* ibrutinib for patients progressing on chlorambucil



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

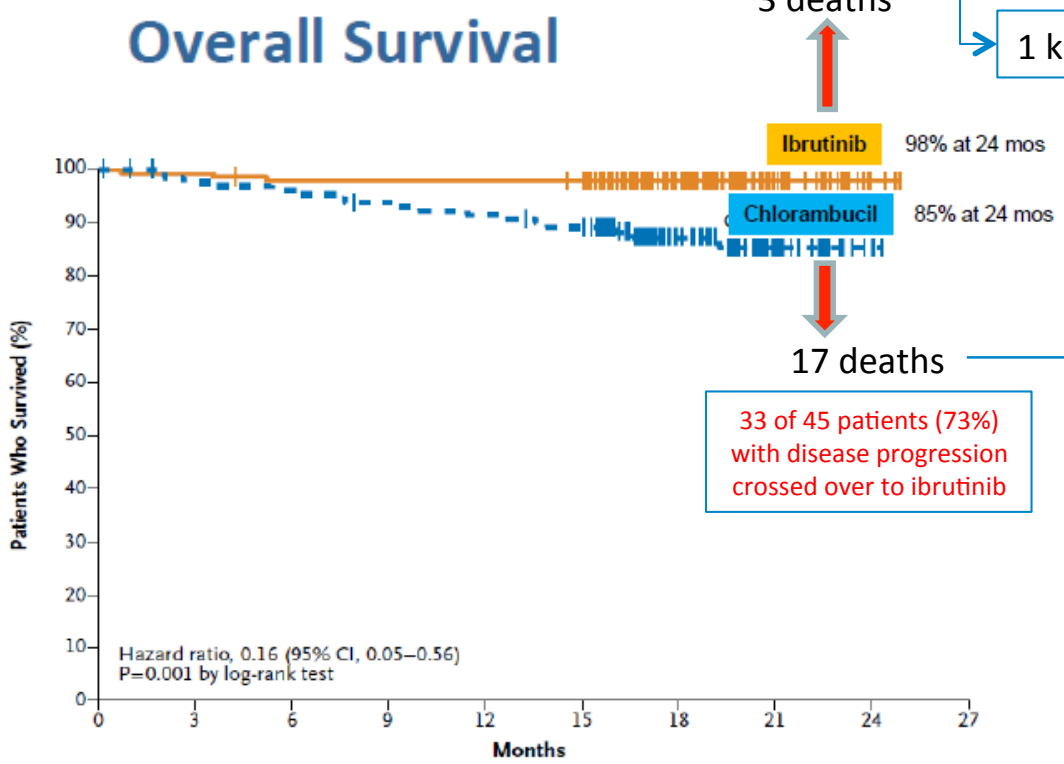
1.5% vs 32%

10% vs 22,5%

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

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

Approved by FDA and EMA for first line treatment of CLL (independent of 17p/TP53 status)



3 deaths

- 2 unknown causes
  - 73 y.o. at home
  - 87 y.o. during sleep
- 1 klebsiella sepsis

17 deaths

33 of 45 patients (73%) with disease progression crossed over to ibrutinib

5 disease progressions, including 2 switched to ibrutinib

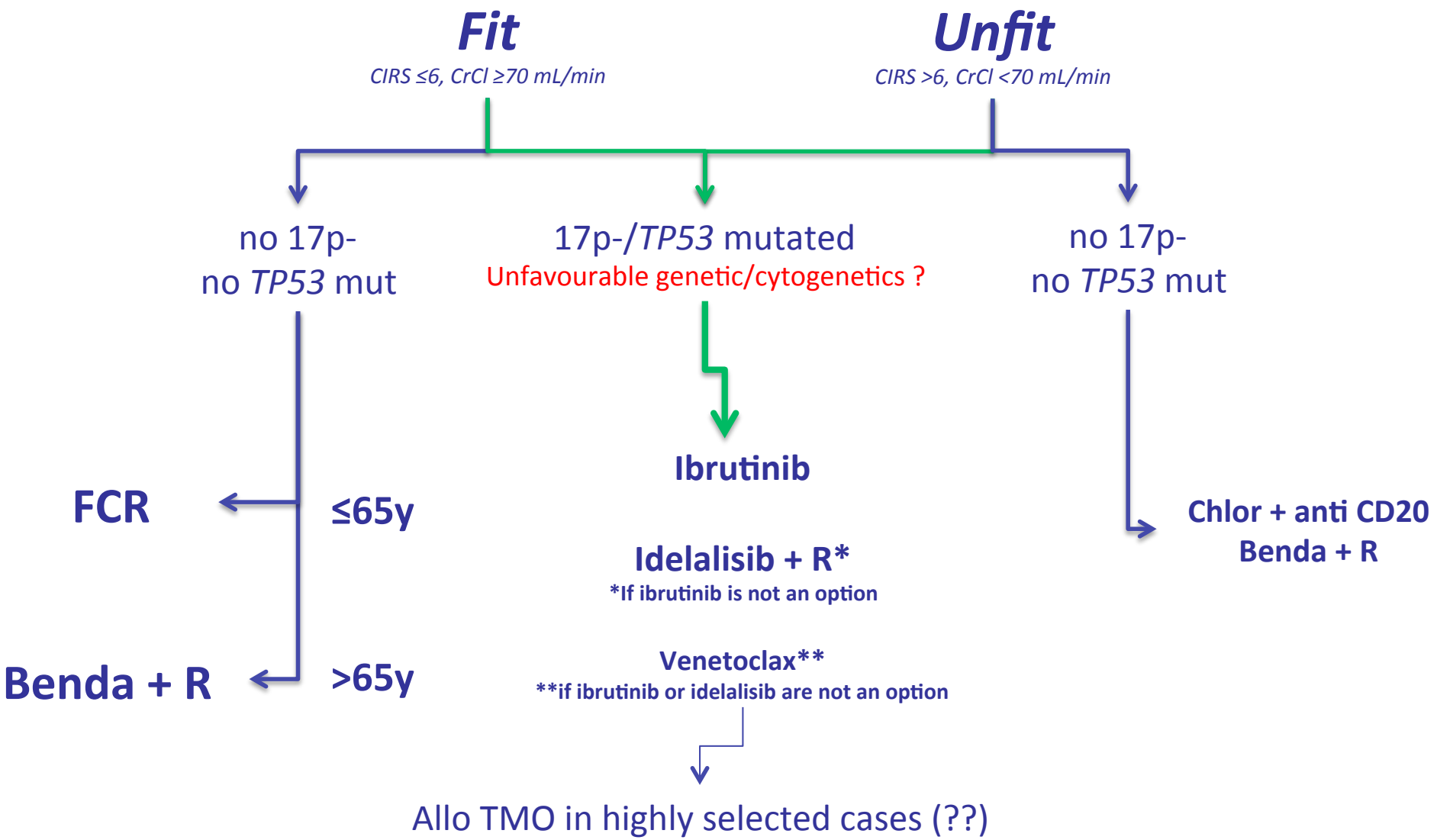
12 other causes, including 2 switched to ibrutinib

- 3 infections
- 2 strokes
- 2 secondary cancers
- 1 toxic hepatitis
- 1 PTE pulmonary
- 1 worsening of the general condition
- 2 unknown causes

- 84% reduction in the risk of death (HR 0.16; 95%CI, 0.05-0.56; P = 0.001)

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

Possible impact of genetic markers on treatment algorithm



Cuneo A, personal view,
adapted from NCCN 2015; Hallek M. Am J Hematolol 2015; Stilgenbauer S Education book ASCO 2015

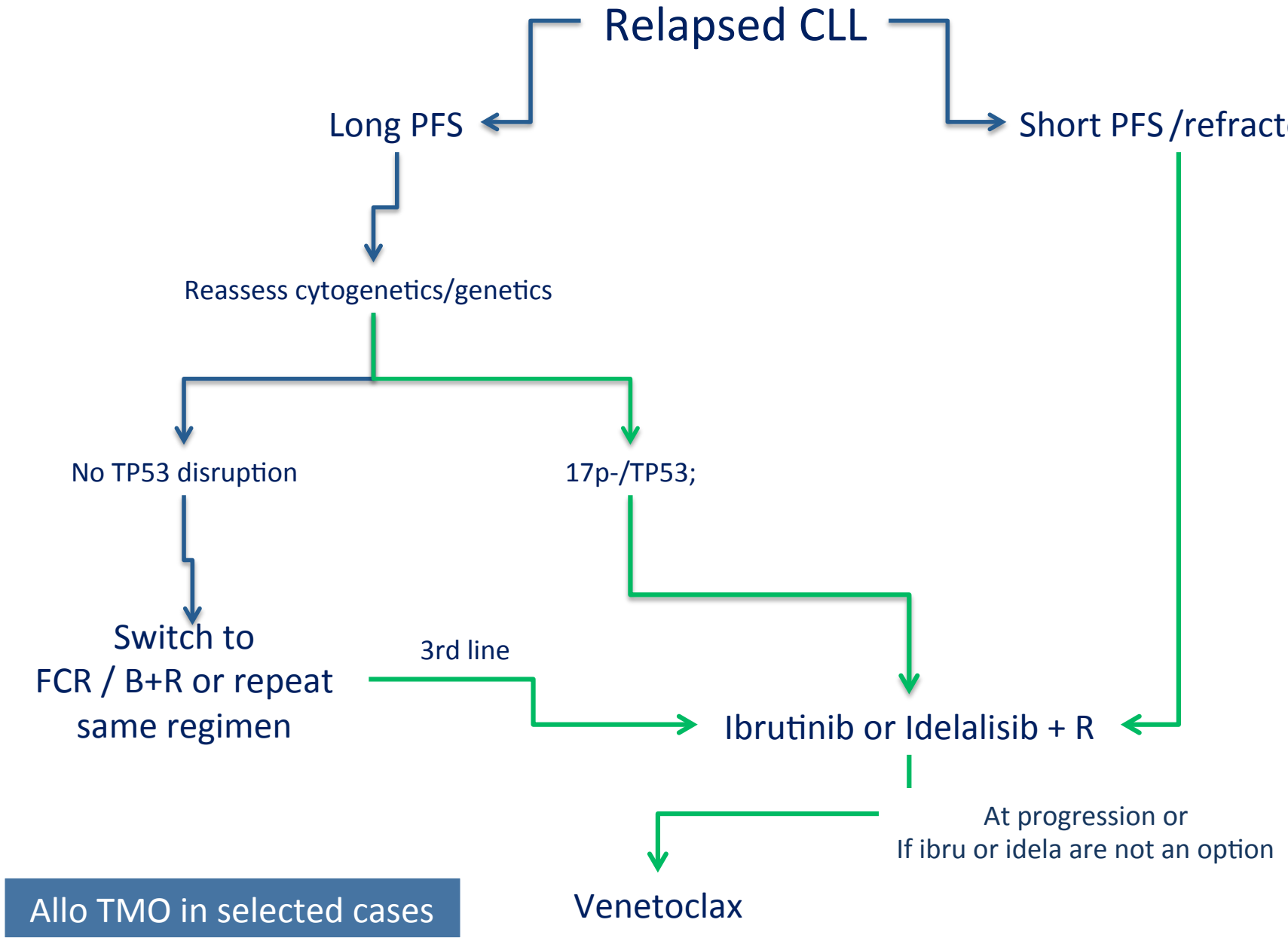
Chemo-free regimens

First line

Relapsed/refractory CLL

Failure of a kinase targeted agent

Proposed treatment algorithm for relapsed/refractory CLL toady



Poor outcome with conventional chemo/immunotherapy in fludarabine-refractory CLL and in patients with early relapse

	Various regimens at MDACC in FA refractory and F refractory with bulky adenopathy	Ofatumumab in FA refractory and F refractory with bulky adenopathy	Various regimen in patients treated in GCLLSG protocols (***)
No. of patients	99	138	305
No. previous regimens (median)	NA	4-5	1-2 (early relapse)
Percentage			
CR	0	0-1	NA
PR	23	47-58	NA
Months			
PFS	2-3	5,7-5,9	11-18
Survival	9	13,7-15,4	30-61

Modified from: Cuneo A et al, Cancer Med, 2014

***Cramer P et al. Haematologica 2015 [Epub ahead of print]

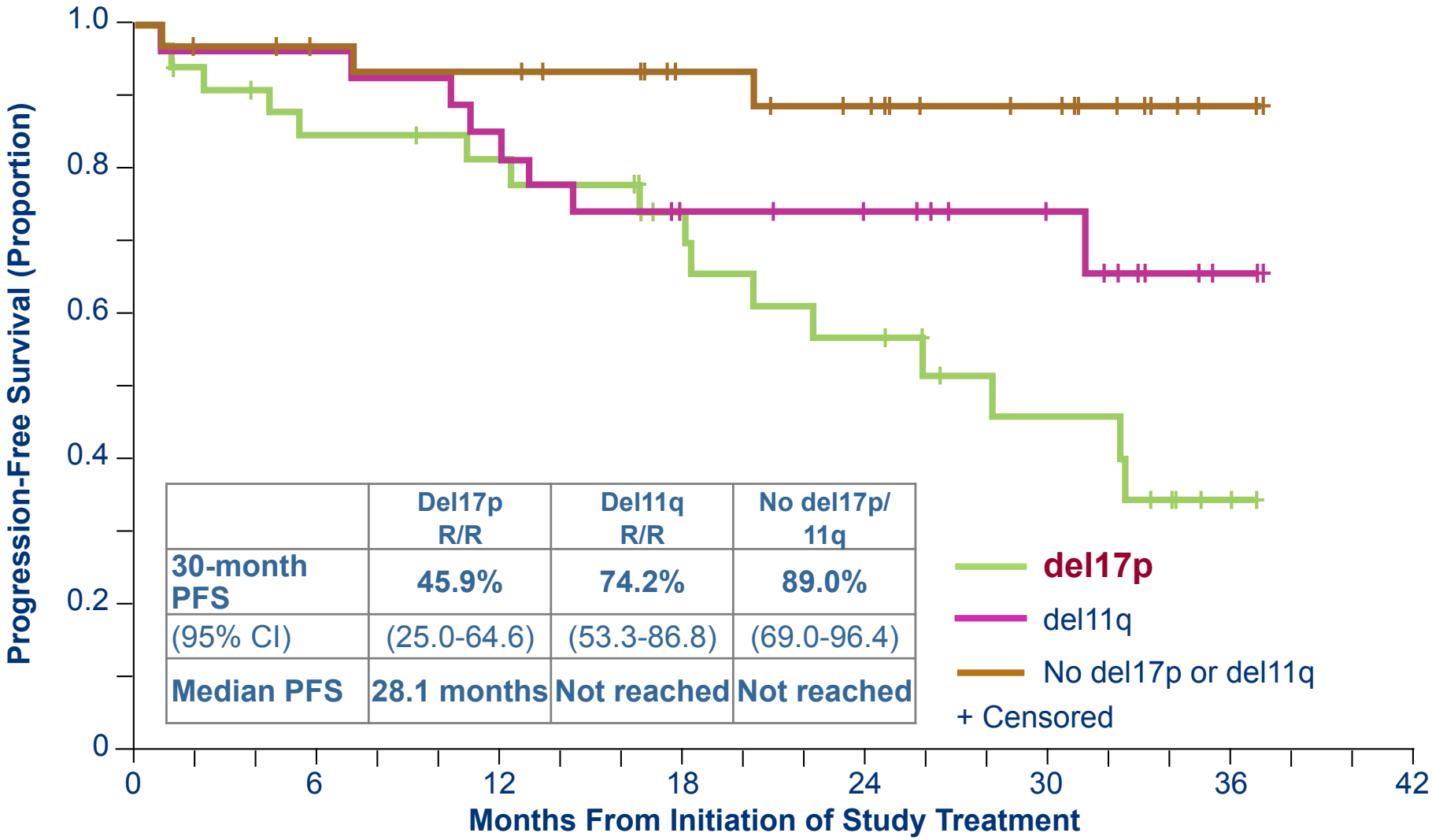
ORR and PFS

Ibrutinib (+/- R) in relapsed / refractory CLL

Study	No. pts / median follow-up	% responding	PFS	% on treatment	% discontinued		
					Disease Progression	Adverse Event	Other*
Byrd, NEJM 2013	85 21 months	89% 71% NCI	75% at 26 months	64%	13%	8%	16%
Byrd, NEJM 2014	195 9 months	63% 43% NCI	88% at 6 months	86%	5%	4%	5%
Burger, Lancet Oncol 2014	40 17 months	95% 87% NCI	78% at 18 months	77%	8%	5%	10%
Byrd JC Blood 2015	101 36 months	90%	69% at 30 months	53%	21%	12%	27%

Byrd 2013: ibrutinib in rel/ref CLL
Byrd 2014: random ibrutinib vs ofatumumab in rel/ref CLL
Burger 2014: ibrutinib and rituximab in high risk CLL (4/40 pts were untreated and had 17p-rel)
O'Brien 2014: ASCO meeting 3 year post initiation of ibrutinib
* Stem cell transplant, Subject decision, investigator decision, 13% death

PFS by Cytogenetics (FISH) in R/R Population



	Del17p R/R	Del11q R/R	No del17p/ 11q
30-month PFS	45.9%	74.2%	89.0%
(95% CI)	(25.0-64.6)	(53.3-86.8)	(69.0-96.4)
Median PFS	28.1 months	Not reached	Not reached

O'Brien S, et al. ASCO 2014; Oral/Abstract #7014.
Published by Byrd J et al. Blood 2015;125:2497-2506

Routine Clinical Practice in rel/ref CLL
Rate of discontinuation, post Ibrutinib Outcome and Ibrutinib Safety Data

	Parikh *et al*[1]	Sandoval-Sus *et al*[2]	Finnes *et al*[3]
	R/R CLL	R/R CLL	TN & R/R CLL
Patients, n	***124***	***54***	***96***
Median Follow up, months	***6.4***	***9.1 (0.5 – 23.3)***	***7.6***
Total Discontinued , n (%)	***23 (18%)***	***15 (28%) excluding BMT***	***23 (24%)***
Discontinuation due to toxicity , n (%)	***13 (10,5%)***	***8 (15%)***	***-***
Median Age	65 (46-93)	60 (35-89)*	66 (46 – 89)
Median prior therapies (range)	3 (1 – 15)	2 (1-5)*	-
Biological Characteristics			
Unmutated IGHV, n (%)	79 (81%)	12 (60%)*	67 (80%)
Del17p, n (%)	15 (15%)	9 (45%)*, #	20 (23%)
Authors comments	**% discontinuation higher than in trials**	**Poor oucome after discontinuation**	**2/3 pts take potentially interfering drugs in the routine practice**

*Data reported within the group of 20 patients who discontinued treatment
Del17p/TP53; TN, Treatment Naïve; R/R, Relapsed/Refractoy, f/u, follow up

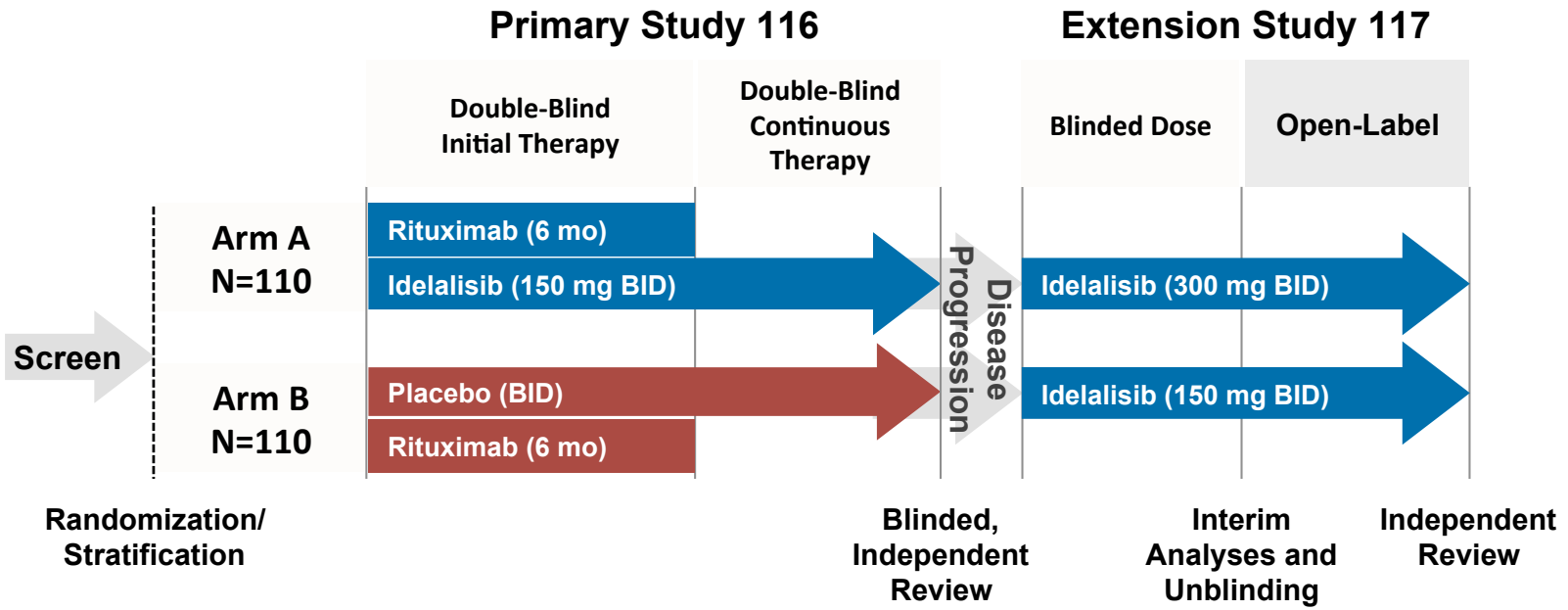
[1]Parikh ASH 2015 #2935, [2]Sandoval-Sus ASH 2015 #2945[3]Finnes ASH 2015 #717

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

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

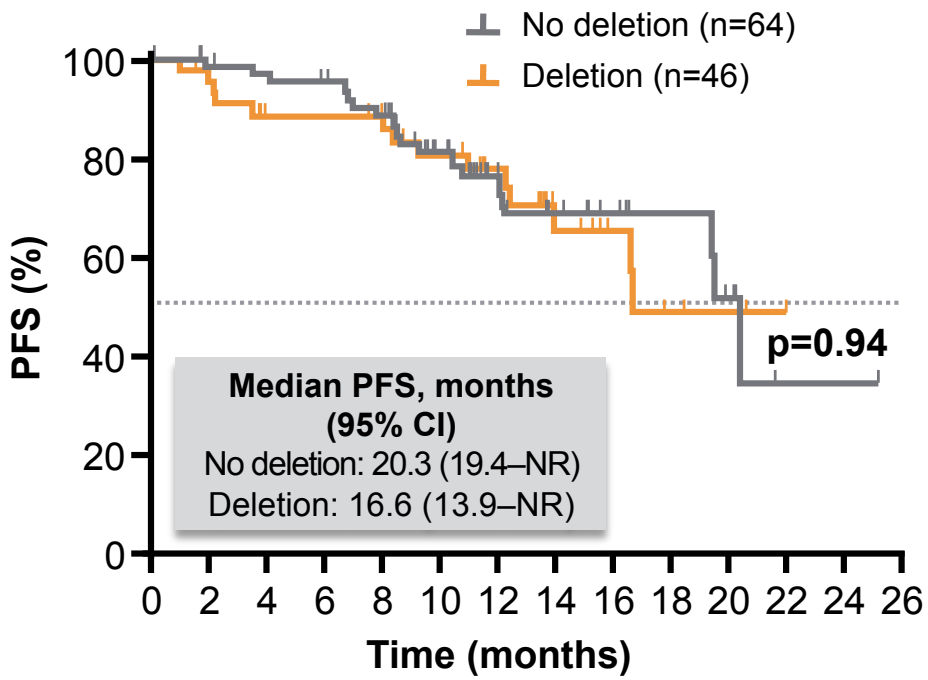
[a] German Tumour Registry Lymphatic Neoplasms (patients recruited between 2009 and 2013) at start of second-line therapy (n=186)
[b] Ipsos Healthcare Global Oncology Monitor real world evaluation of CLL patient from Germany, France, UK, Spain and Italy (n=5163)
[c] Equivalent to Karnofsky score 0–70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

1. Knauf W, *et al. Hematol Oncol* 2014 [published online ahead of print].
2. Ysebaert L, *et al.* EHA 2014 abstract P1275).
3. Byrd JC, *et al. N Engl J Med* 2014; 371–323 (incl online suppl).
4. Hx-CD20-406 Wierda WG, *et al. J Clin Oncol* 2010; 28:1749–1755.
5. Lozanski G, *et al. Blood* 2004; 103:3278–3281.
6. Furman RR, *et al. N Engl J Med* 2014; 370:997–1007.

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

Second interim analysis: PFS

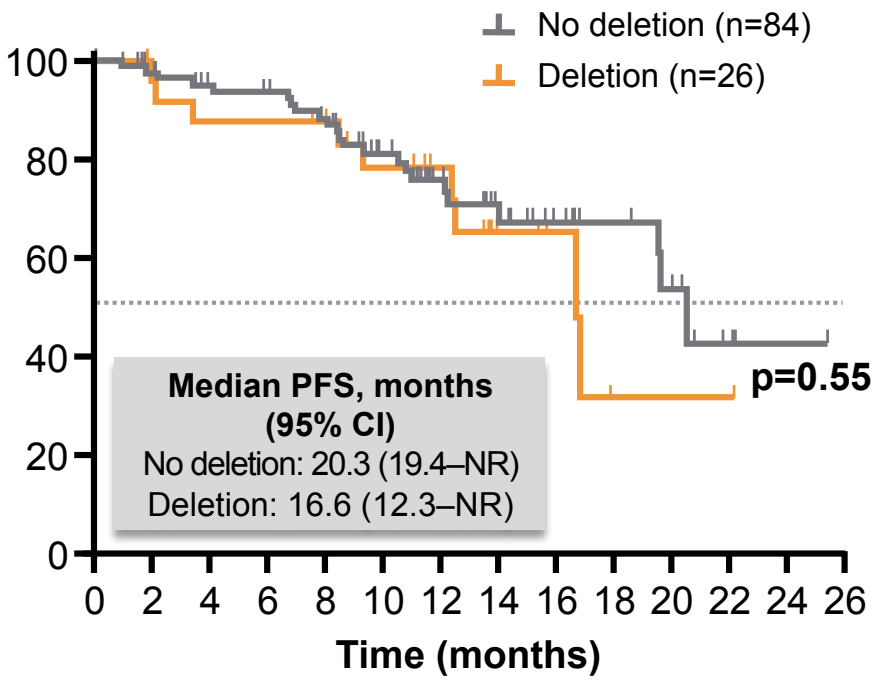
Del(17p)/*TP53* mutation



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)



No del	84	78	73	71	65	49	31	20	15	11	6	1	1	1
Del	26	23	22	22	20	17	12	6	4	1	1	0	0	–

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

Pooled Analysis: GS-US-312-0116 and GS-US-312-0119

Results: Summary of Study Discontinuations

n (%)	Study 116/117 IDL+R/IDL (n=110)	Study 116/117 PBO+R(PD) / IDL[a] (n=42)	Study 116/117 PBO+R/IDL[a] (n=44)	Study 119 IDL +OFA (n=173)	Total (N=369)
Median duration of IDL exposure (range), months	16.2 (0.3-39.9)	5.7 (0.4-26.2)	9.2 (0.2, 22.1)	13.9 (0.2-28.5)	–
IDL treatment ongoing	20 (18.2%)	5 (11.9)	12 (27.3)	46 (26.6)	83 (22.5)
IDL treatment discontinued	90 (81.8)	37 (88.1)	32 (72.7)	127 (73.4)	286 (77.5)
Due to PD	18 (16.4)	5 (11.9)	3 (6.8)	31 (17.9)	57 (15.4)
CLL progression	16 (14.5)	4 (9.5)	2 (4.5)	27 (15.6)	49 (13.3)
Richter's transformation	2 (1.8)	1 (2.4)	1 (2.3)	4 (2.3)	8 (2.2)[b]
Due to adverse events	47 (42.7)	20 (47.6)	21 (47.7)	62 (35.8)	150 (40.7)
Due to other reasons	25 (22.7)	12 (28.6)	8 (18.2)	34 (19.7)	79 (21.4)
Withdrawal by patient	12 (10.9)	6 (14.3)	3 (6.9)	12 (6.9)	33 (8.9)
Physician's decision	7 (6.4)	4 (9.5)	2 (4.5)	14 (8.1)	27 (7.3)
Death	2 (1.8)	2 (4.8)	2 (4.5)	8 (4.6)	14 (3.8)
Other	4 (3.6)	0	1 (2.3)	0	5 (1.4)

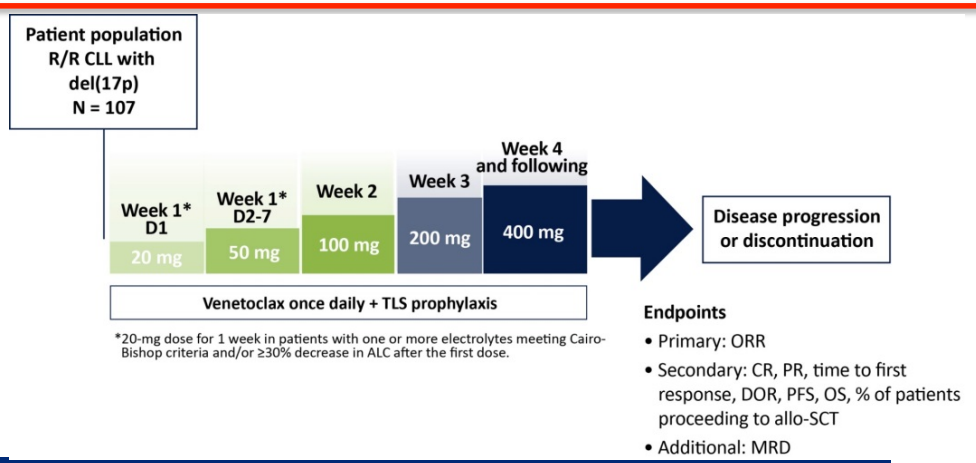
IDL: idelalisib; OFA: ofatumumab; PBO: placebo; PD: progressive disease; R: rituximab; RT: Richter's transformation
[a]Study 117 included patients from Study 116 who 1) had PD while receiving placebo (PBO+R [PD]/IDL) or 2) were actively participating in Study 116 as a placebo-treated patient at the time the study was stopped (November 8, 2013) (PBO+R/IDL)
[b]4 additional patients were subsequently diagnosed with RT after discontinuing treatment for reasons other than RT: investigator-reported reasons for discontinuation of these patients included "Other" (n=1) and "Physician Decision" (n=3). These patients were not included in the analyses

Brown, ASCO, 2016, 7531
Brown, EHA, 2016, P215

Venetoclax for patients with CLL and 17p- who have been treated with at least one prior therapy

Inclusion criteria

- ECOG PS 0-2
- Neutrophils ≥1000
- Plts ≥40.000
- Hb ≥8
- CrCl ≥50 ml/min



Baseline Characteristics

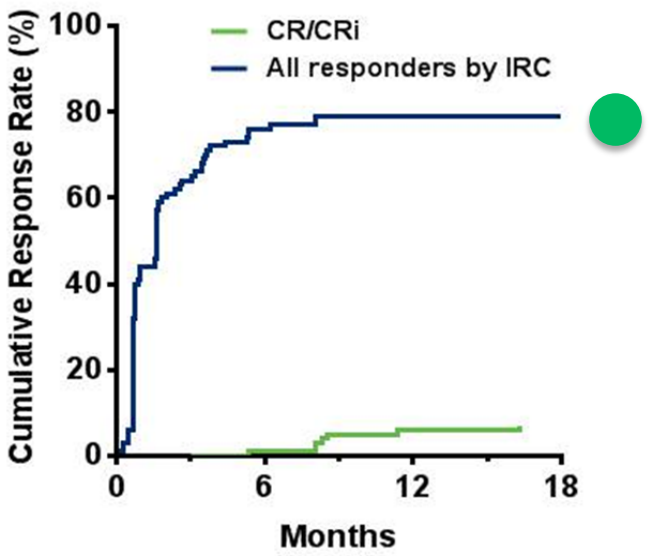
N=107[a]	n (%)
Median age (years), range	67, 37–85
Male	70 (65)
Prior therapies: median, range	2, 1–10
Prior bendamustine / refractory	54 (50) / 38 (70)
Prior fludarabine / refractory	78 (73) / 34 (44)
Prior CD20 mAb	90 (84)
ECOG grade 1/2	56 (52) / 9 (8)
One or more nodes ≥ 5 cm	57 (53)
ALC ≥25 x 10^9/L	54 (51)
TLS risk category	
Low	19 (18)
Medium	43 (40)
High	45 (42)
Rai stage III or IV	51(48)
IGHV unmutated	30 (81)

[a]Includes 1 patient without 17p–; [b]Low defined as ALC<25 and nodes <5cm, medium defined as ALC>20 OR nodes ≥5 and < 10cm), high defined as (ALC>25 nodes ≥5 and < 10cm OR nodes > 10cm

Adapted from Stilgenbauer et al. Oral Presentation at ASH 2015, Orlando, Florida.

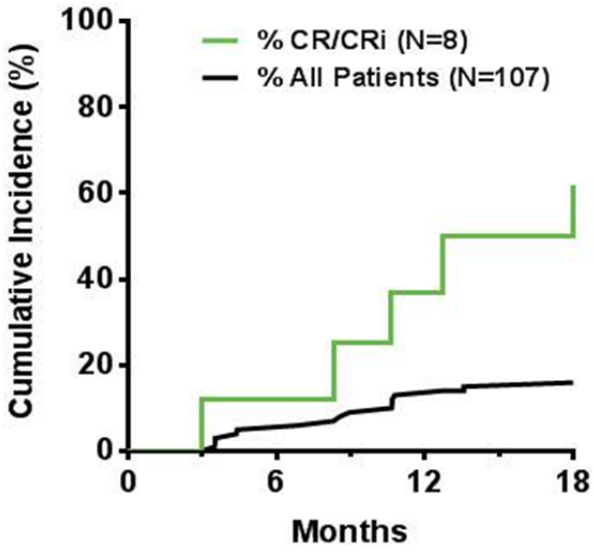
Cumulative Incidence of Response

iwCLL Response



- Median time-to-first response: 0.8 months (0.1–8.1)
- Median time to CR/CRi: 8.2 months (3.0–16.3)

MRD-Negativity

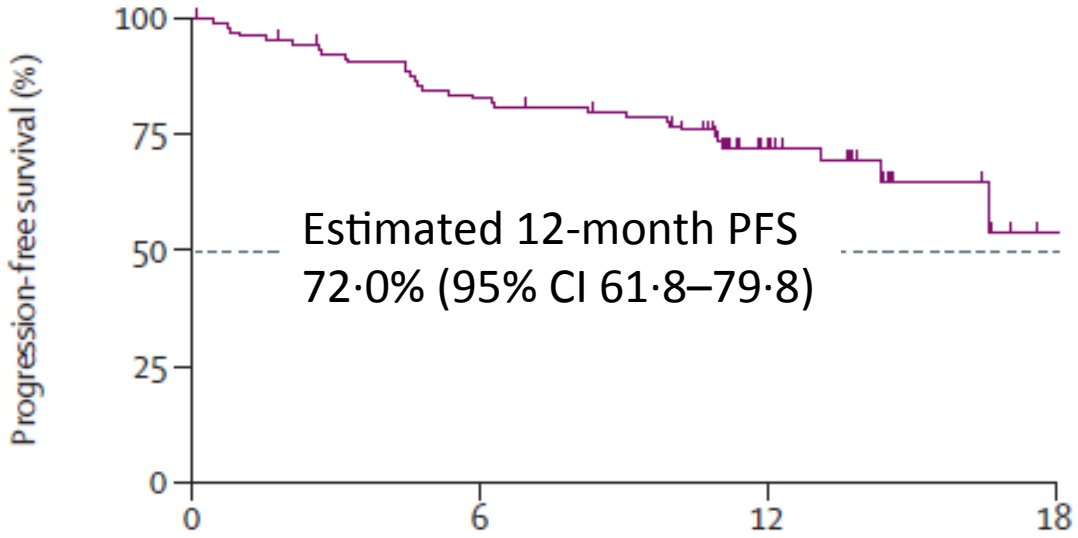


- Of 45 patients tested, 18 achieved MRD-negativity in peripheral blood

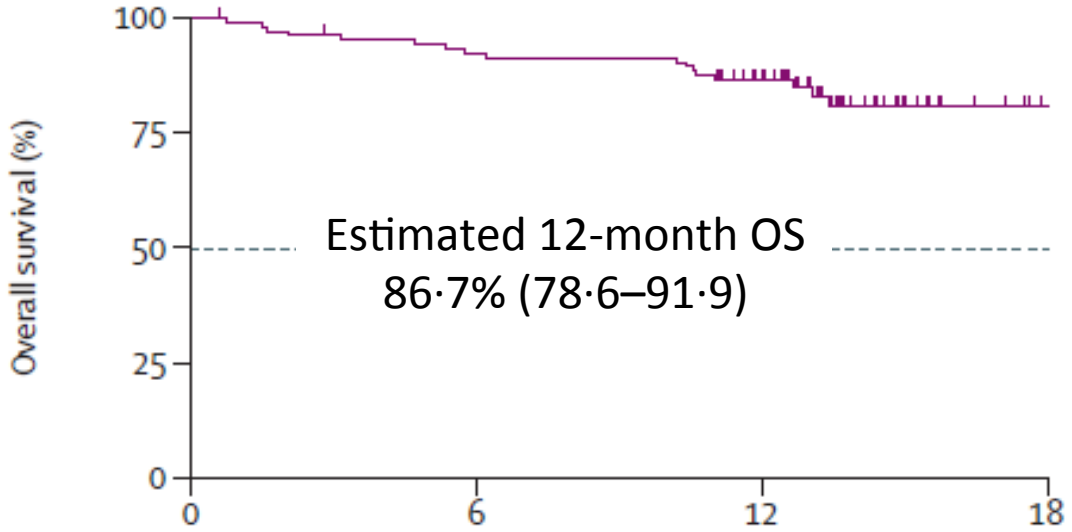
Adapted from Stilgenbauer et al. Oral Presentation at ASH 2015, Orlando, Florida. [11]

PFS and OS in 107 pts with rel/ref CLL and 17p-
Median duration of follow-up 12·1 months

PFS



OS



Stilgenbauer S et al, Lancet Oncology 2016

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

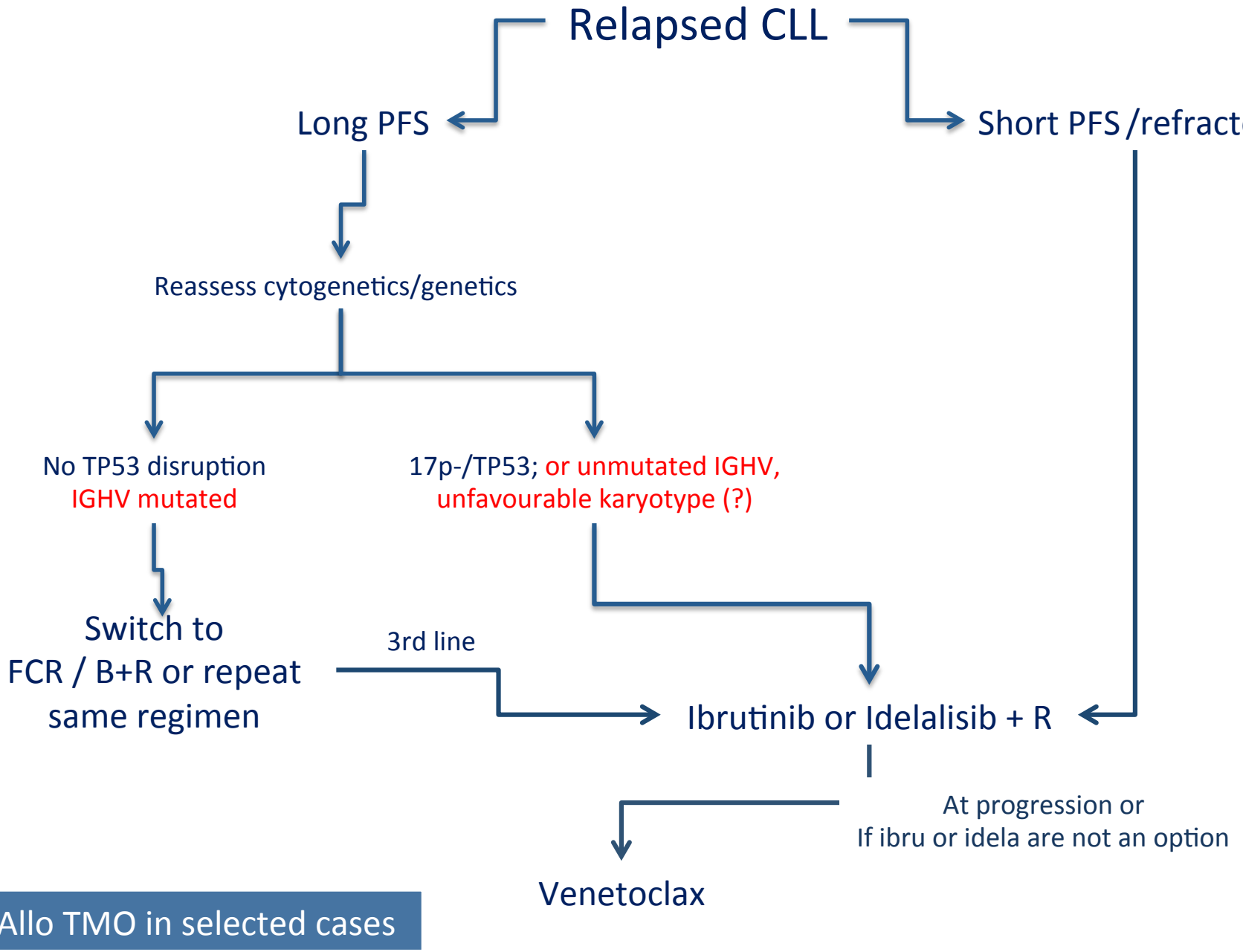
Patient Disposition

	VEN + R	VEN
Enrolled, n	49	116
Time on Venetoclax, median (range), months	22 (<1 – 42)	17 (<1 – 44)
Discontinued, n	15 (31%)	65 (56%)
Disease progression[a]	9	41
AE/Toxicity	3	13
Withdrew consent	3[b]	2
Management of co-morbidities	0	2[c]
Allogeneic transplantation	0	7[d]
Active patients, n	34[e] (69%)	51 (44%)
Time on venetoclax, median (range), months	28 (5 – 42)	22 (15 – 44)[f]

[a]Including Richter's transformation for 5 patients in M13-365 and 18 in M12-175. [b]One after achieving MRD-negative CR. [c]One for management of diabetes mellitus and one required long-term coumadin. [d]Six achieved best response of PR and one had SD. [e]25 patients are active on venetoclax treatment. 9 patients are not on active therapy and remain on study. [f]Time on venetoclax for M12-175 (VEN) is from 25Aug2015 and does not represent current time on study.

Roberts EHA 2016 P209

Proposed treatment algorithm for relapsed/refractory CLL toady



Practical implications

1) 17p-/TP53 mutation must be assessed before treatment in all patients

2) Assessment of other genetic predictors of response duration appears useful
- *IGHV* mutational status

3) Standardization of methods (*;**)

4) Certified laboratories (ERIC)

5) Novel markers
- karyotype using novel mitogens
- gene mutations
- validation within prospective trials

*Ghia P et al, Leukemia 2007; 21:1-3
**Pospisilova S et al, Leukemia 2012; 26:1458-61

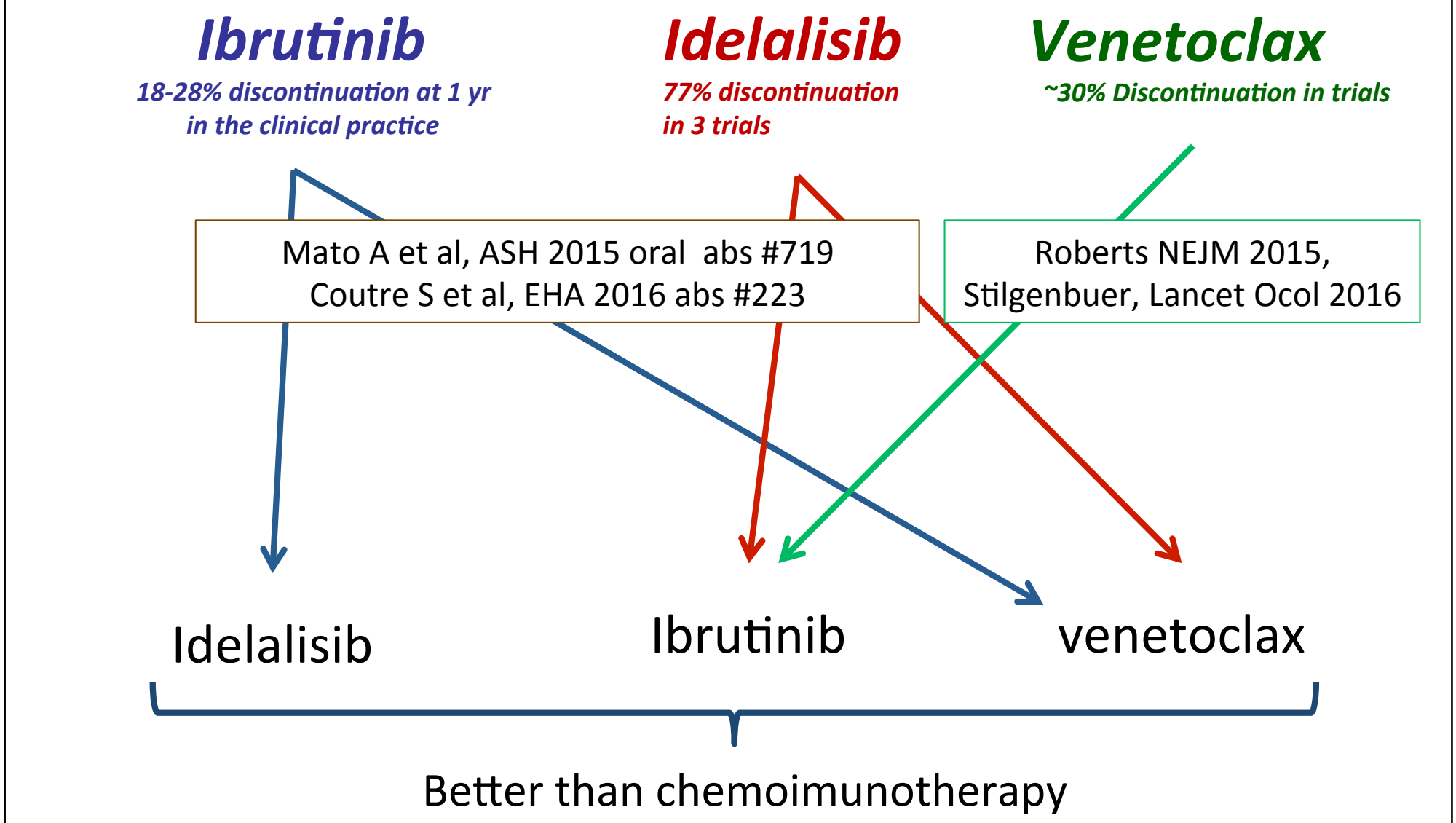
La target therapy

First line

Relapsed/refractory CLL

Failure of a kinase targeted agent

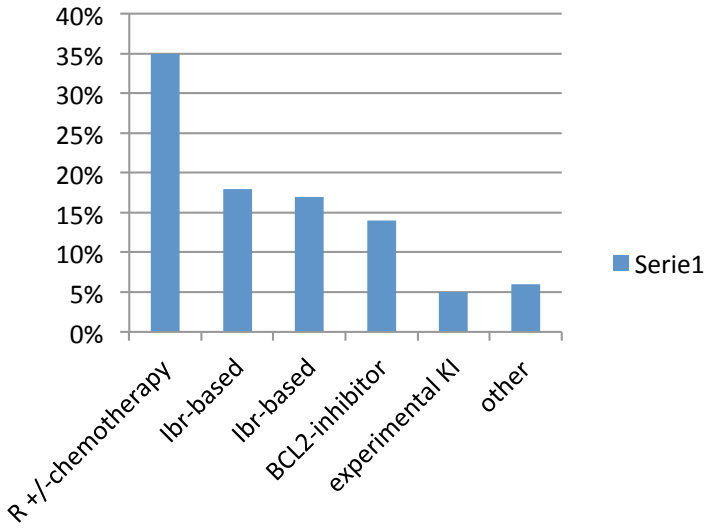
Possibility to cross in case of discontinuation in rel/ref CLL (toxicity or progression)

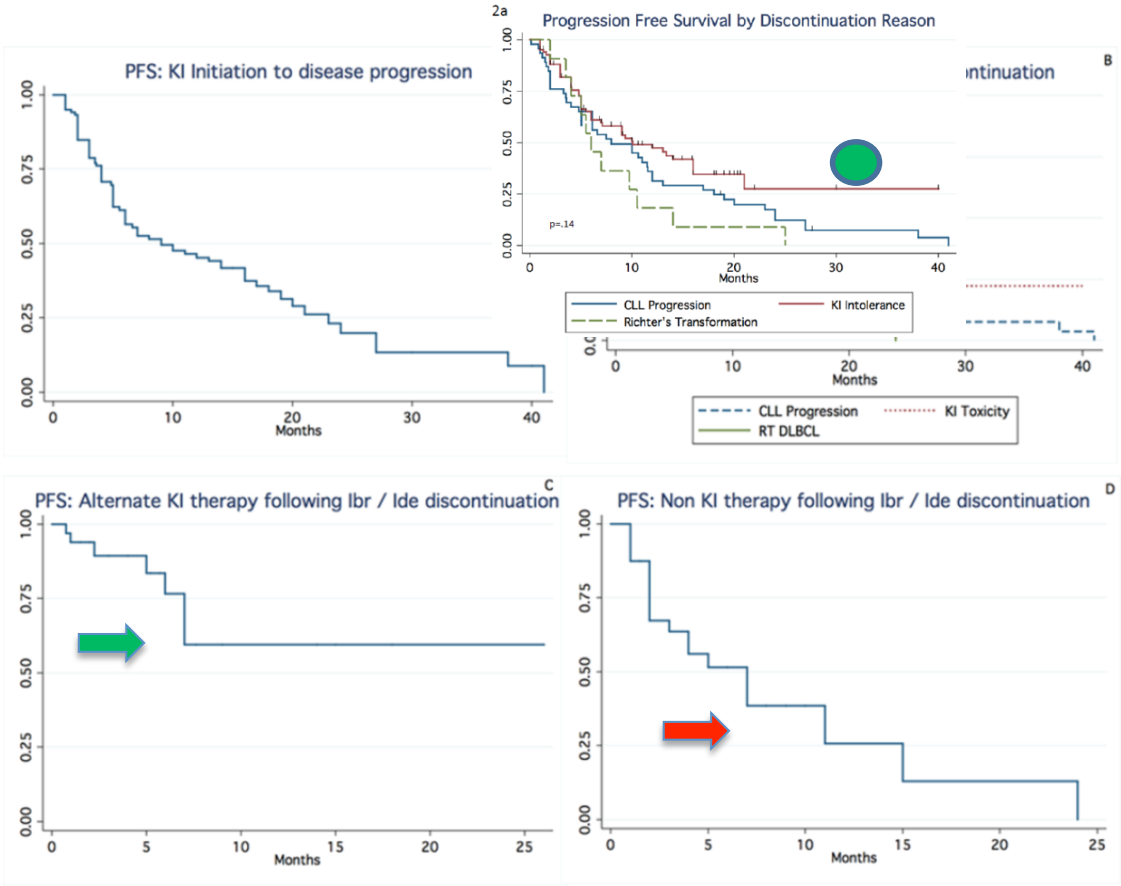


Type of treatment and outcome after KI discontinuation

123 patients

Mato A et al, ASH abs #719; Blood 2016

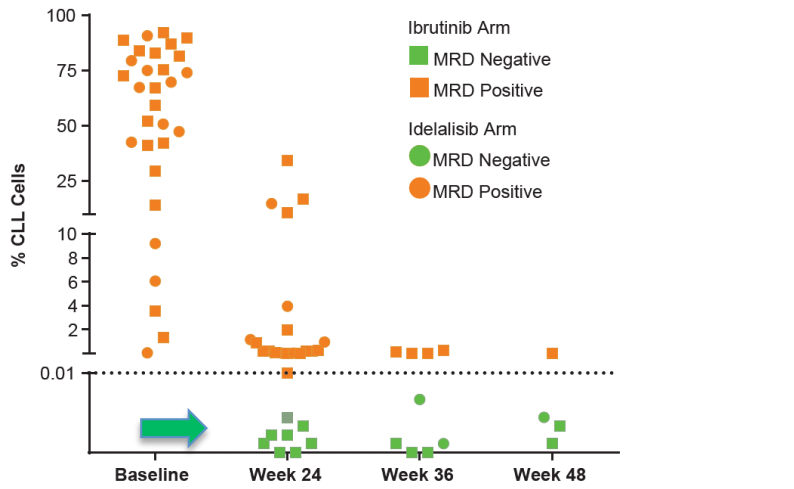




Venetoclax after KI discontinuation

64 patients treated by venetoclax
Coutre et al., EHA 2016, #P559

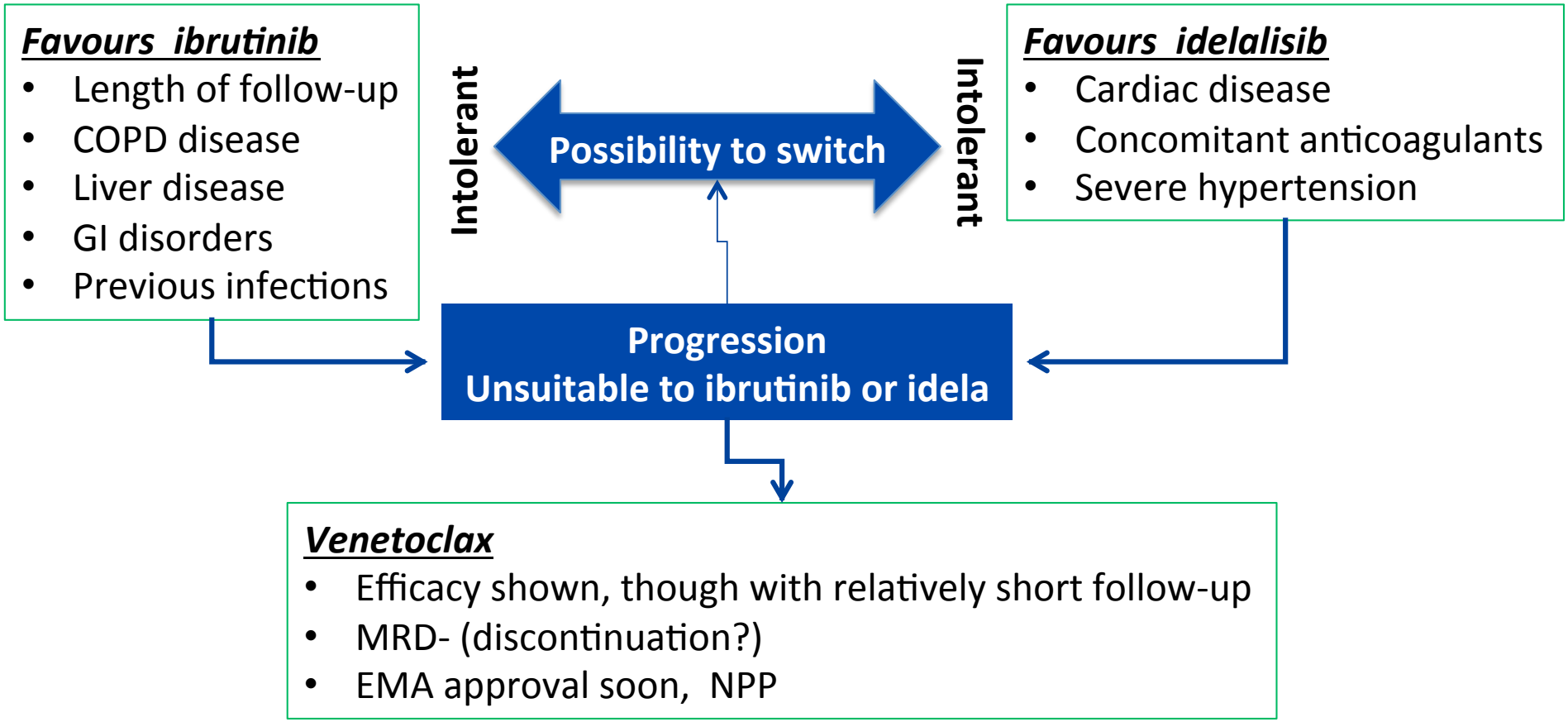
	Ibrutinib Arm n=43		Idelalisib Arm n=21	
	Assessed by		Assessed by	
Best response, n (%)	Investigator	IRC	Investigator	IRC
ORR	26 (61)	30 (70)	7 (33)	10 (48)
CR / CRi	2 (5) / 0	0 / 1 (2)	1 (5) / 1 (5)	0 / 0
nPR	2 (5)	0	0	0
PR	22 (51)	29 (67)	5 (24)	10 (47)
Stable disease	12 (28)	-	12 (57)	-
Disease progression	1 (2)	-	1 (5)	-
Non-responder	-	13 (30)	-	11 (52)



Which kinase targeted treatment in clinical practice in Italy today?

There are no solid scientific data allowing for a comparison to be made between drugs

Yet a choice has to be made….



GI: gastrointestinal; NPP: named patient program