Il ruolo terapeutico dei nuovi farmaci

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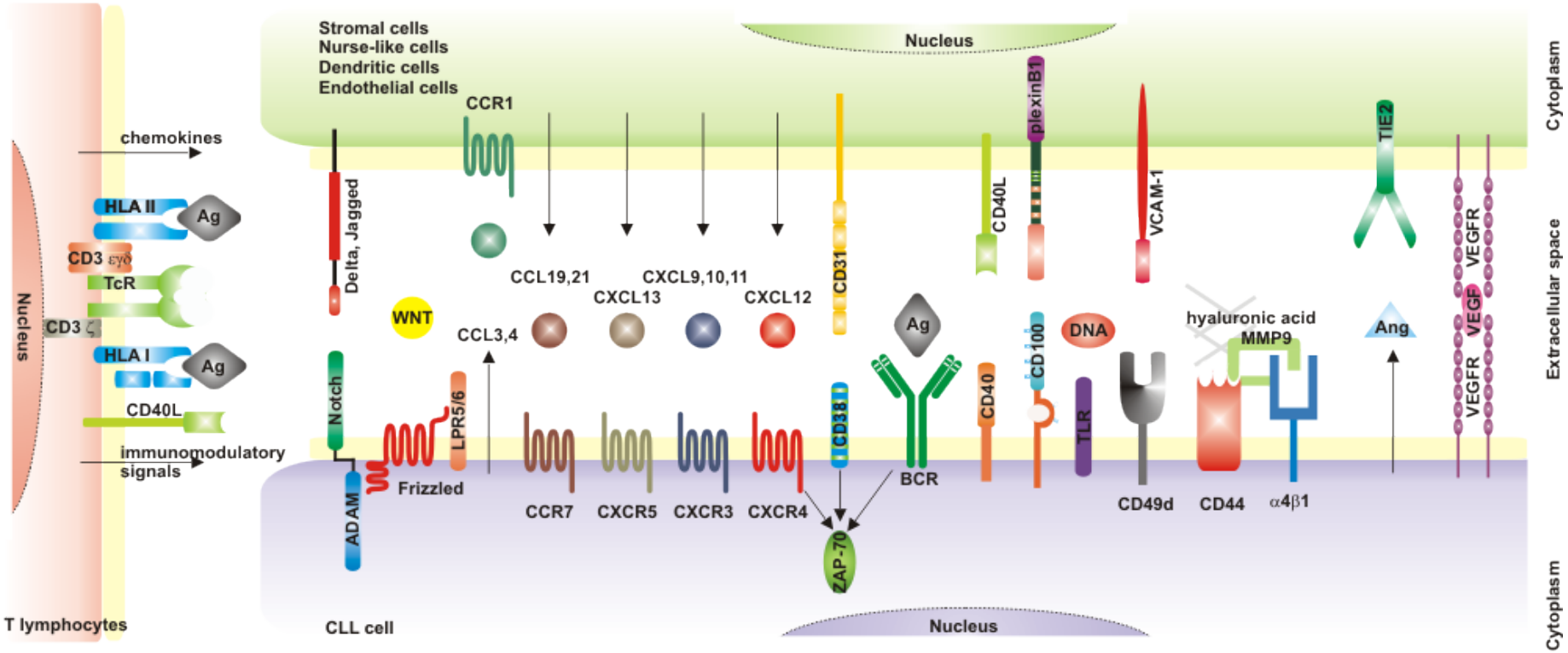
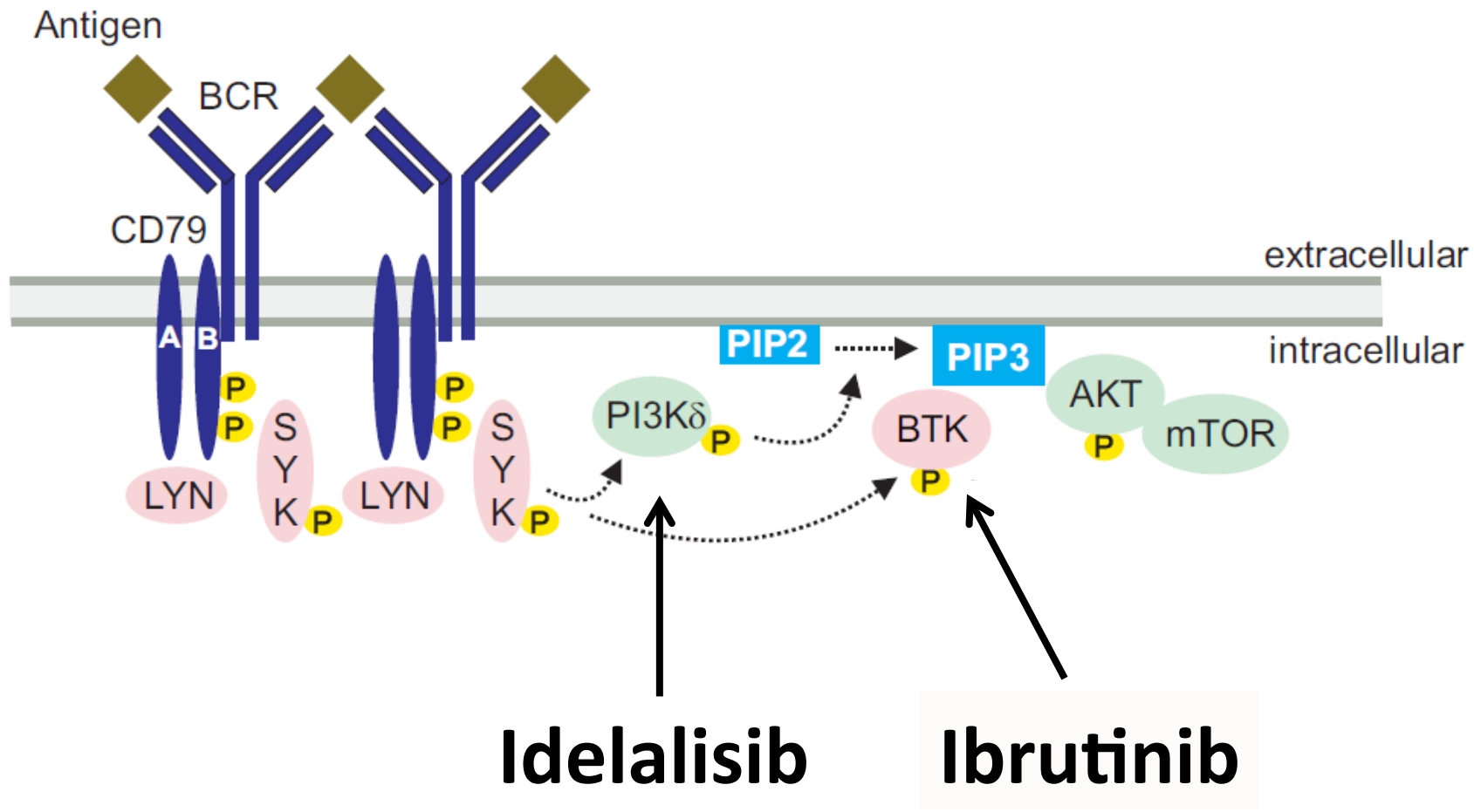
CLL is a tumor that is “addicted to the host”

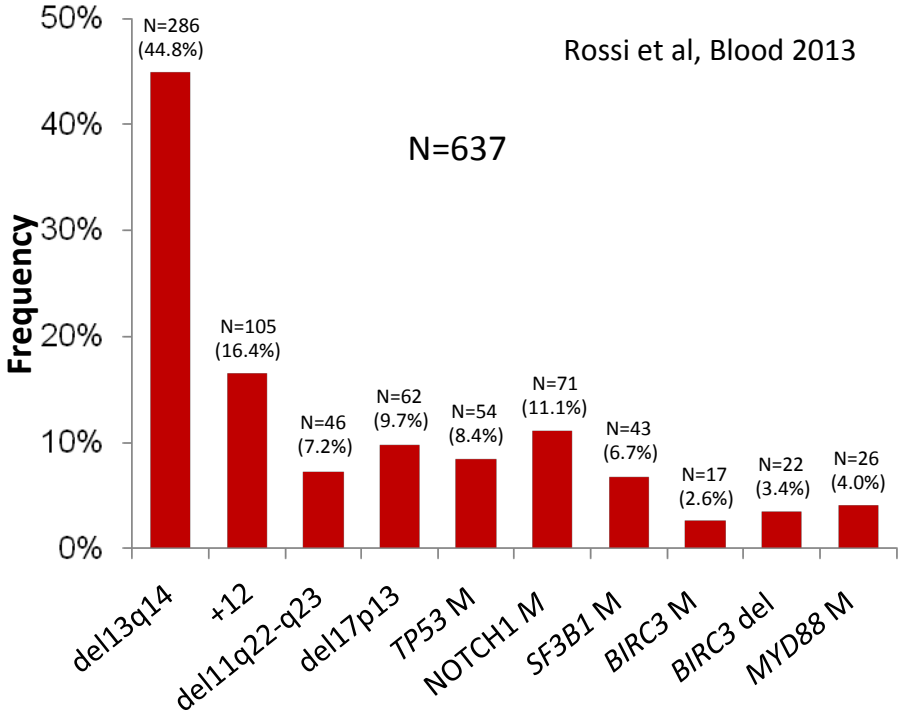
“an opportunistic tumor”

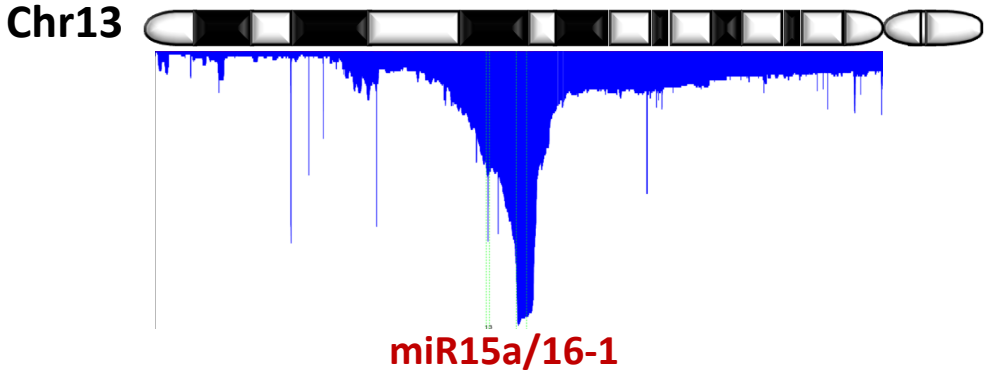


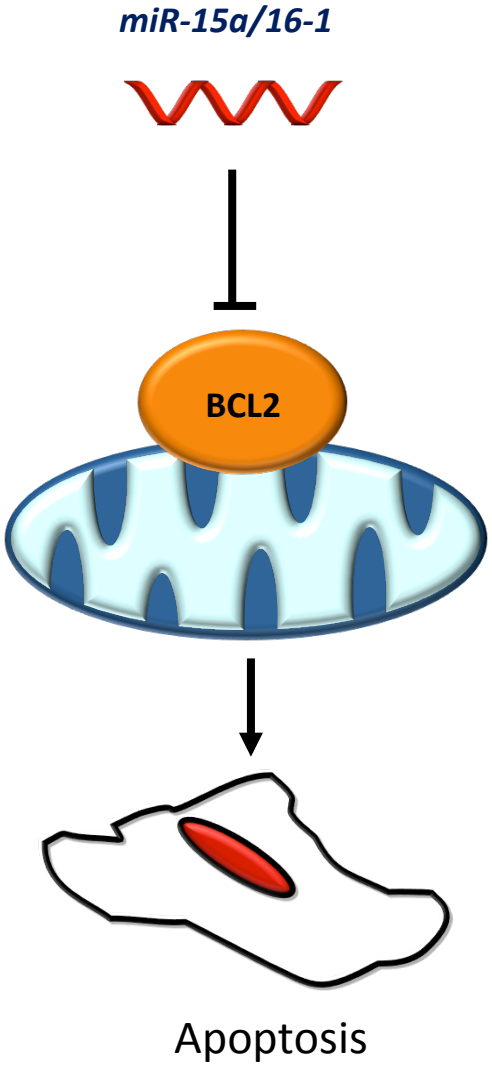
Targeting kinases in the BCR pathway



13q14 deletion is the most frequent genetic lesion of CLL

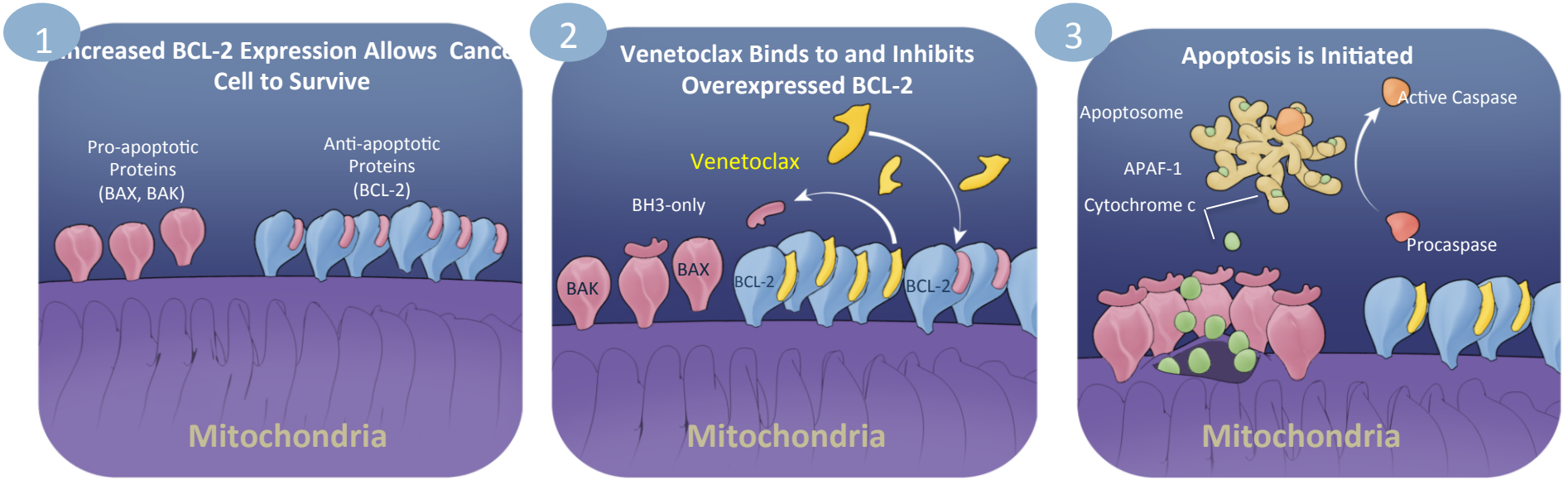




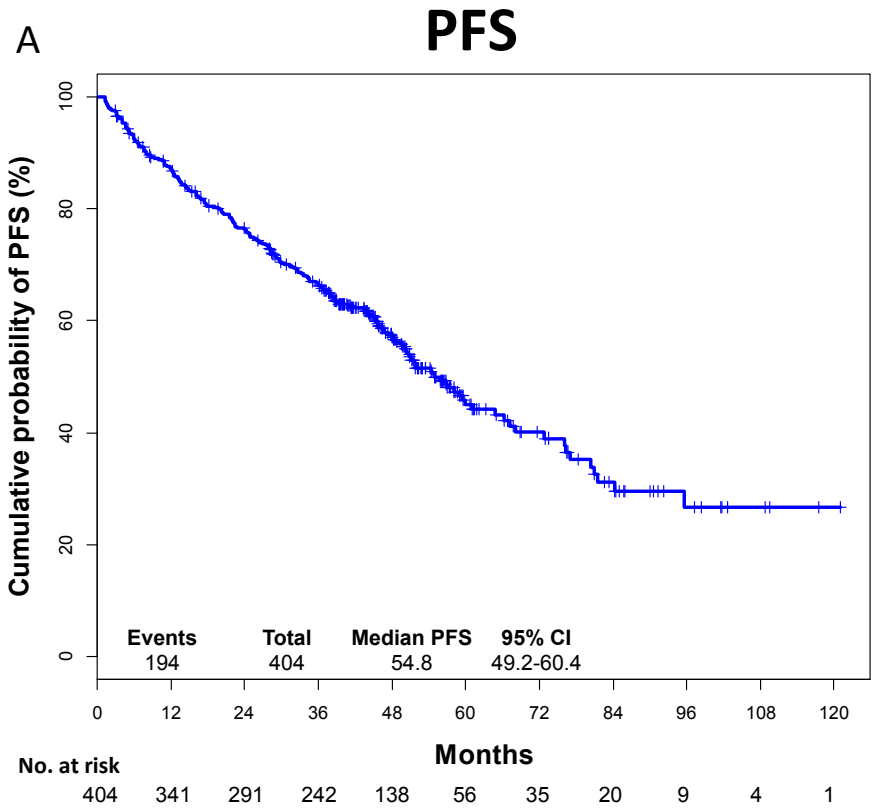


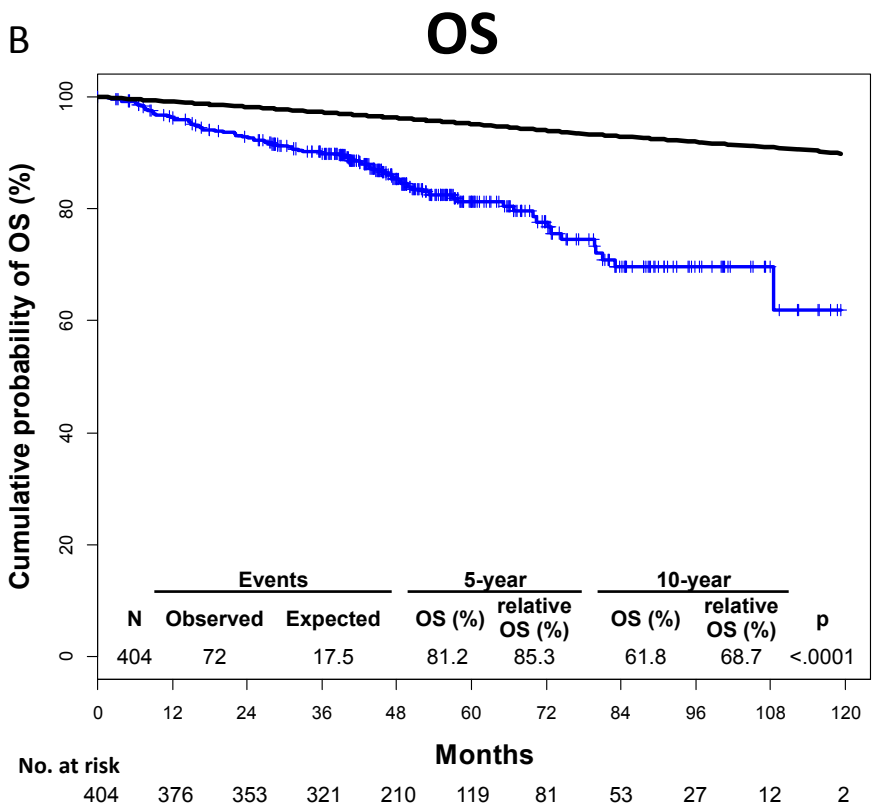
Cimmino et al, PNAS 2005

Targeting BCL2 in the apoptotic pathway



General outcome after upfront FCR in CLL (n=404 from the real world practice)

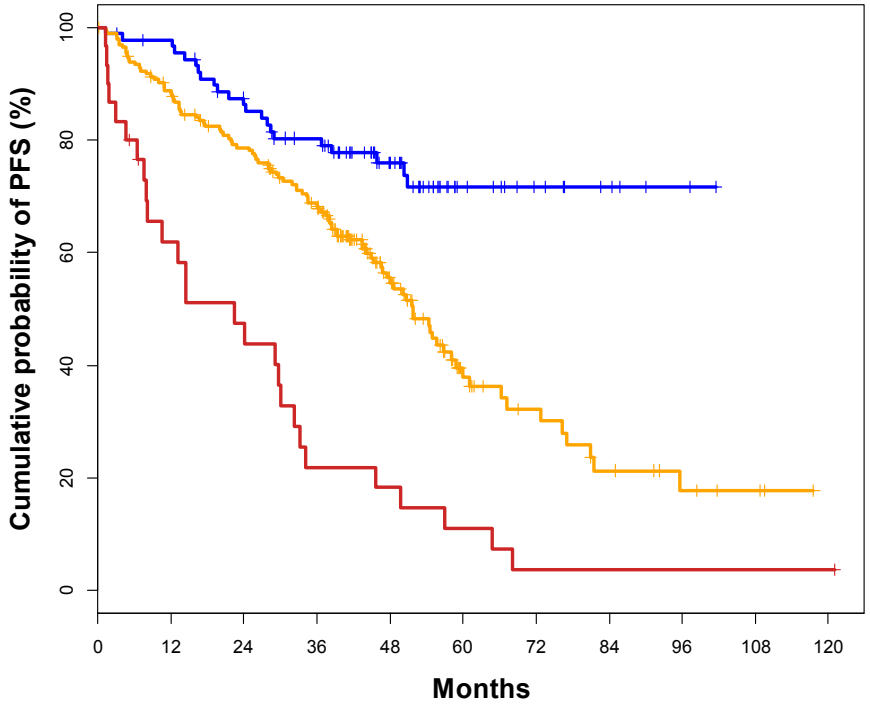




Rossi D, Blood 2015

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

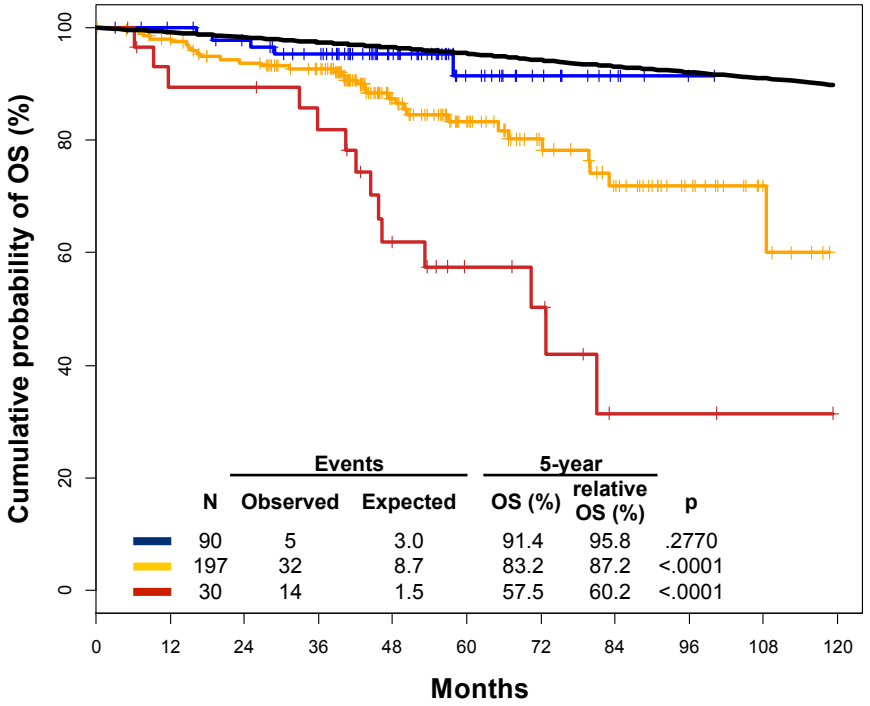
Low-risk group (*IGHV* mutated) Intermediate-risk group (*IGHV* unmutated and/or 11q deletion) High-risk group (17p deletion)



Events	Total	Median PFS	95% CI
22	90	nr	na
102	197	51.7	46.1-57.2
27	30	22.5	8.5-36.4

Pairwise comparisons

p			
	-	0.0001	<0.0001
	0.0001	-	<0.0001
	<0.0001	<0.0001	-



Events	Total	5-years OS	95% CI
5	90	91.4	87.1-95.7
32	197	83.2	80,0-86.4
14	30	57.5	47.6-67.4

Pairwise comparisons

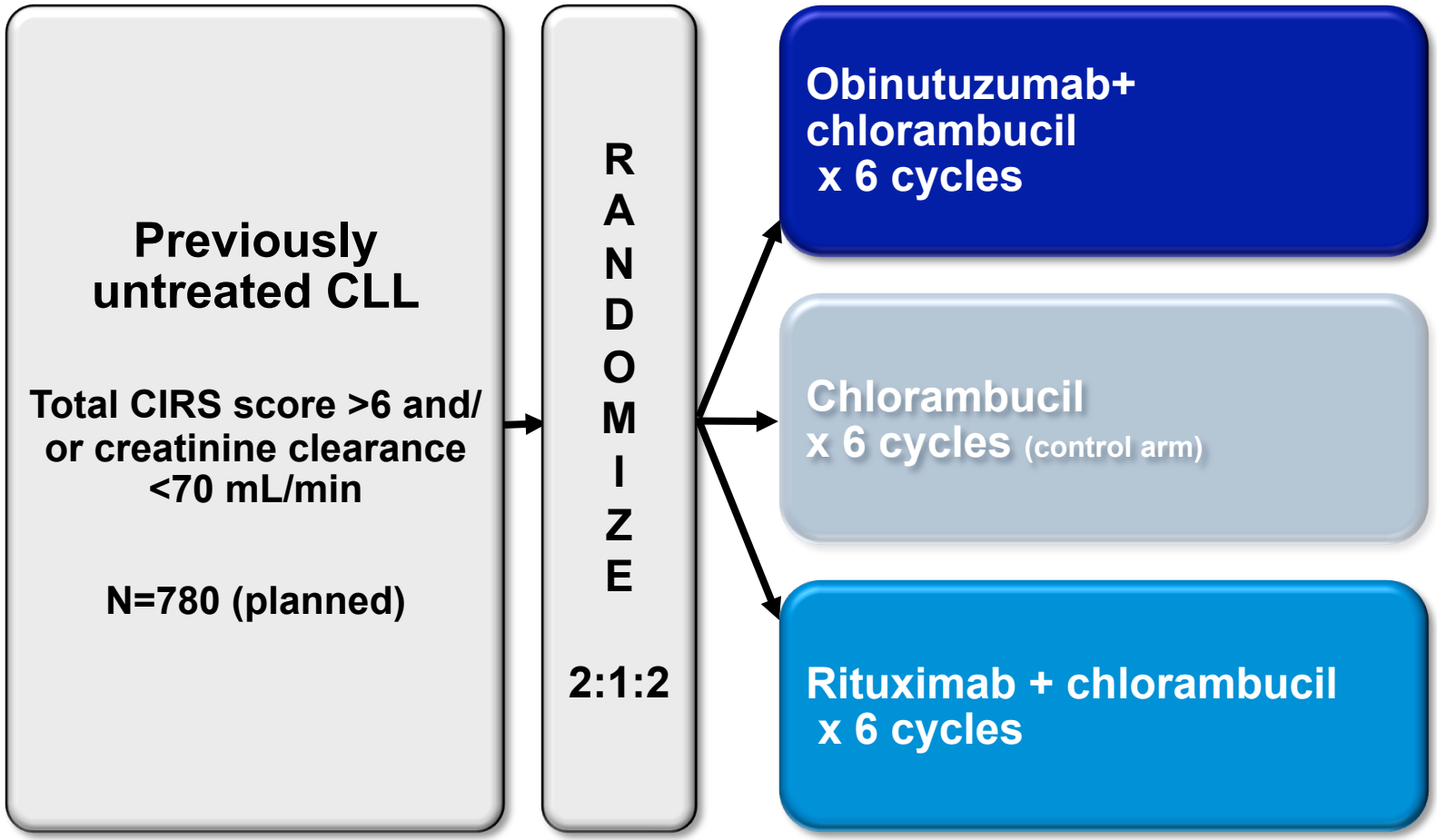
p			
	-	0.0341	<0.0001
	0.0341	-	0.0004
	<0.0001	0.0004	-

Rossi et al, Blood 2015

CLL treatment subgroups

- **Treatment naïve**
- **Relapsed/refractory CLL**
- **High risk *TP53* disrupted CLL**
- **BCRi resistant/intolerant CLL**

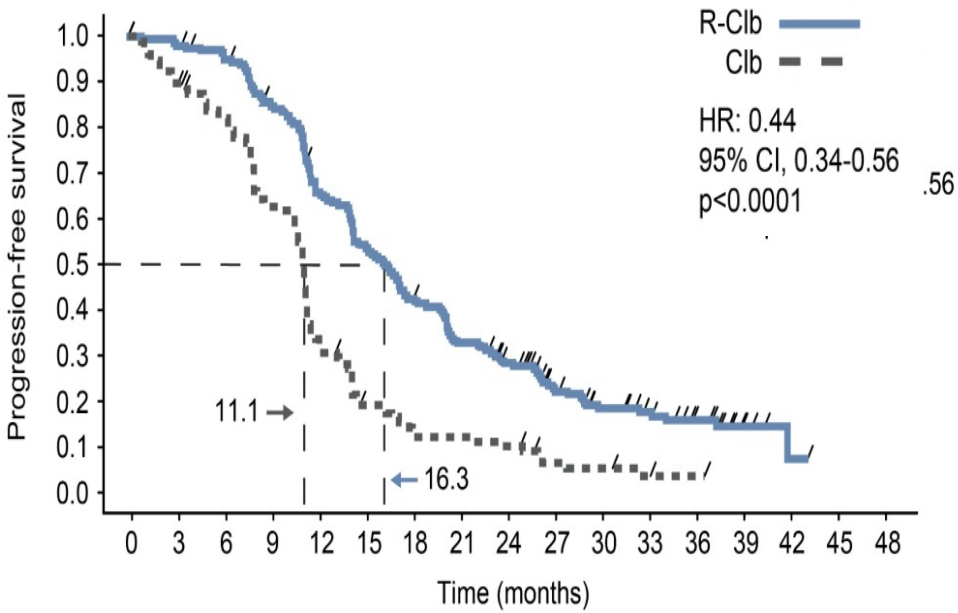
First line treatment of unfit CLL patients

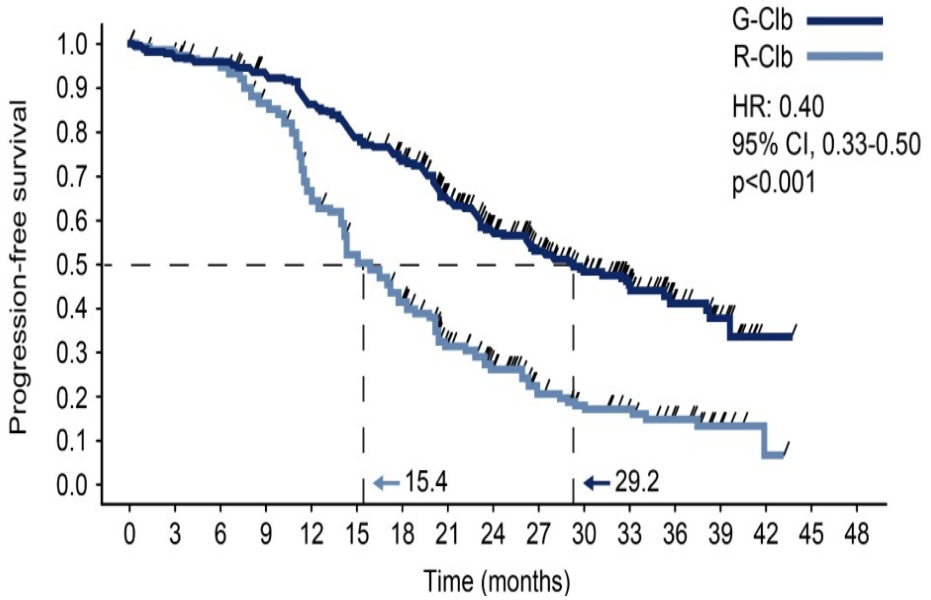


Obinutuzumab1,000mg days 1, 8, and 15 cycle 1; day 1 cycles 2–6, every 28 days
Chlorambucil: 0.5mg/kg day 1 and day 15 cycle 1–6, every 28 days
Rituximab: 375mg/m^2 day 1 cycle 1, 500 mg/m^2 day 1 cycles 2–6, every 28 days

Goede *et al. N Engl J Med.* 2014 Mar 20;370(12):1101-10.

G-CLB > R-CLB > CLB

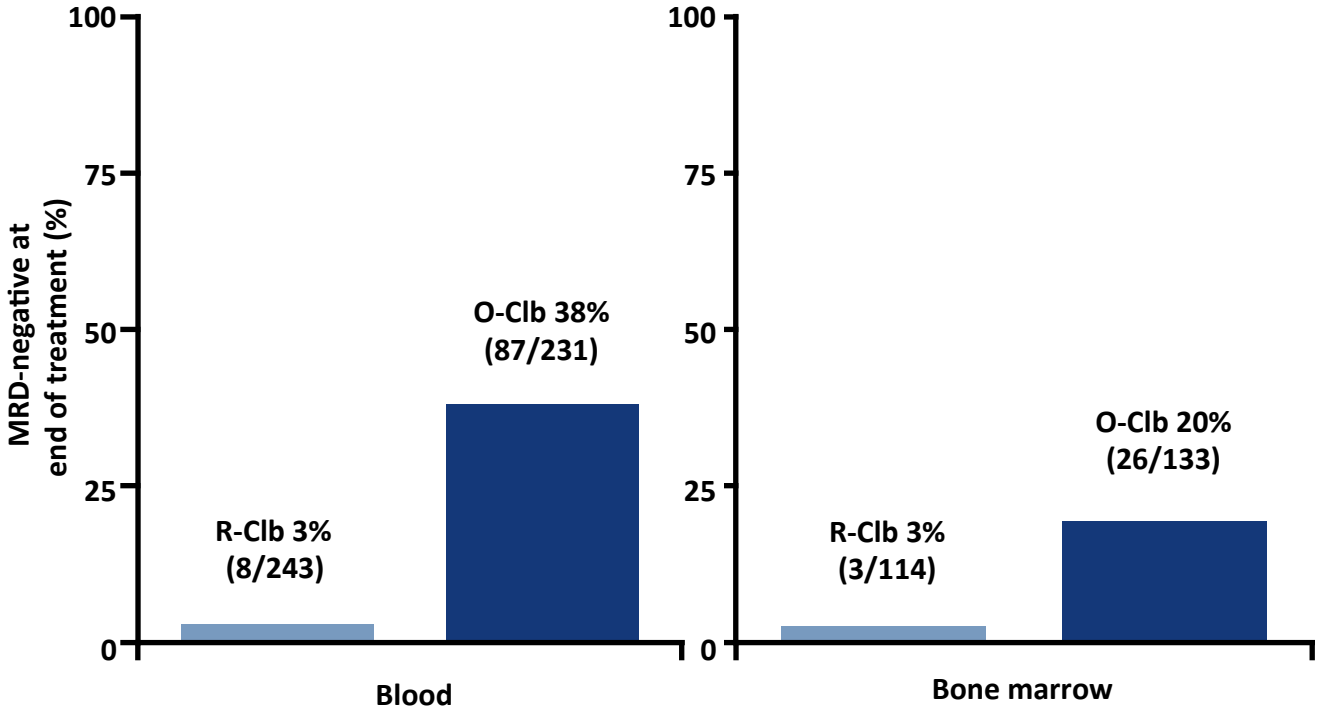




Goede *et al. Leukemia.* 2015 Jun;56(6):1585-92.

Depth of response is higher with obinutuzumab-chlorambucil than rituximab-chlorambucil

MRD clearance was higher in the O-Clb arm (May 2013 data cut-off)[1]



- MRD measured by central laboratory assessment (ASO-RQ-PCR) of blood and/or bone marrow samples taken at baseline and 3 months after last dose of study medication
- Patients are considered MRD-negative if they have fewer than one CLL cell in 10,000 cells (iwCLL guidelines[2])
- Bone marrow samples were usually only taken from patients thought to be in CR
- Patients who progressed or died prior to MRD measurement were counted as MRD-positive; patients without MRD results, and one in the R-Clb arm who had not reached their end-of-treatment analysis by the time of the data cut-off, were excluded

ASO-RQ-PCR = allele-specific oligonucleotide real-time quantitative polymerase chain reaction.

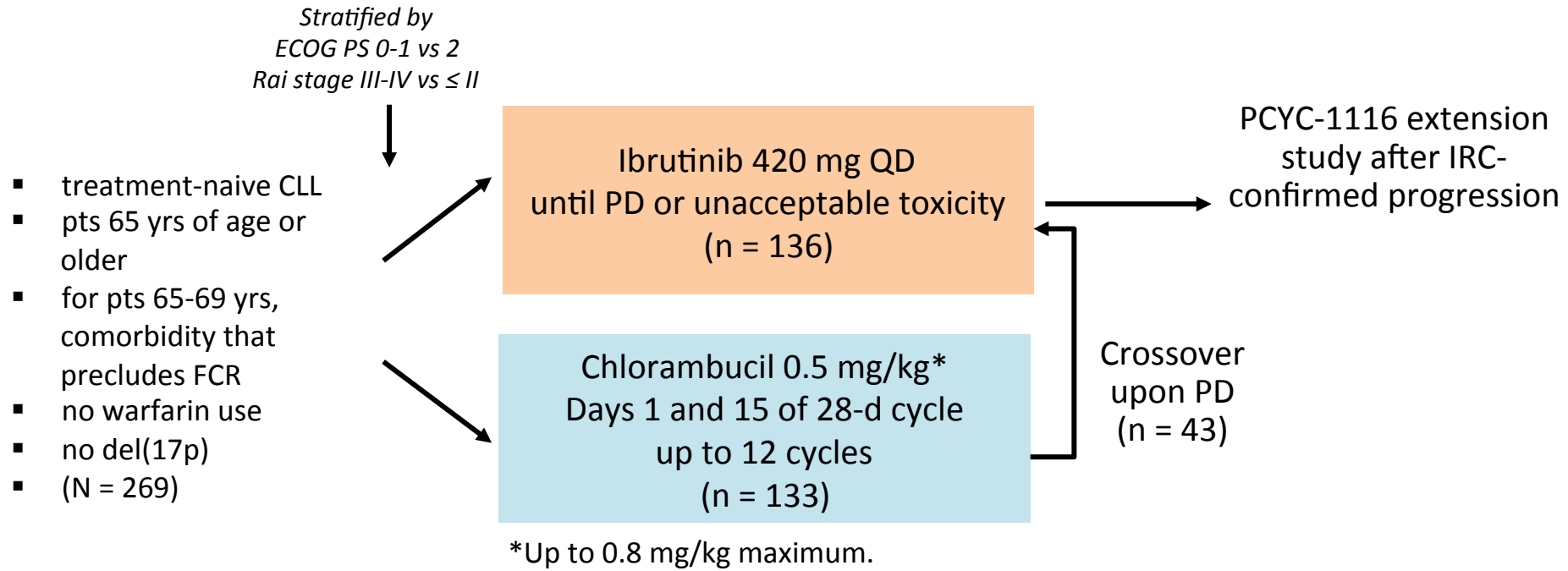
1. Goede V, *et al*. N Engl J Med 2014; 370:1101–1110;
2. Hallek M, *et al*. Blood 2008; 111:5446–5456.

Toxicity is higher with obinutuzumab-chlorambucil than rituximab-chlorambucil

AE	GAZYVA® + Chlorambucil	Rituximab + Chlorambucil	Chlorambucil
Hematological G3-5			
Neutrophils	33%	28%	16%
Hemoglobin	4%	4%	4%
Platelets	12%	3%	4%
Infection G3-5	12%	14%	14%
Infusion-related reaction G3-5	20%	4%	0%

Adapted from Goede *et al. N Engl J Med.* 2014 Mar 20;370(12):1101-10.

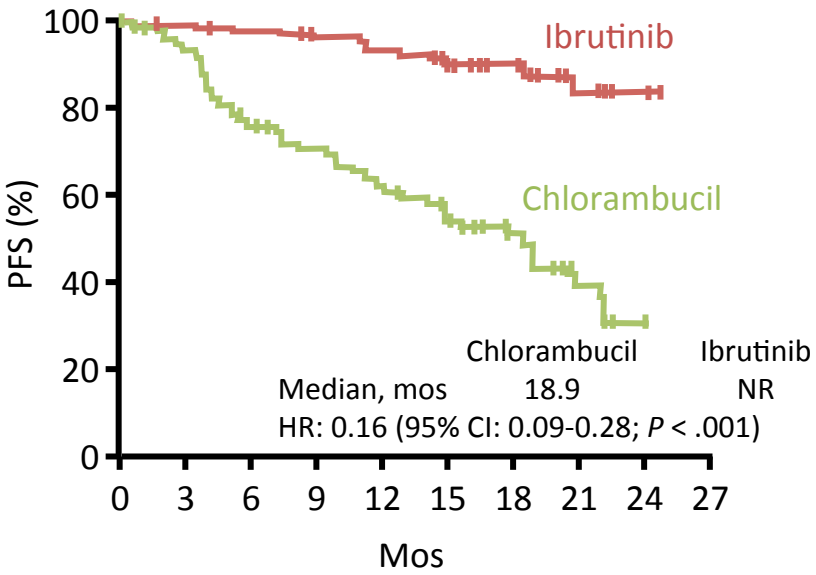
Ibrutinib as first line treatment in unfit CLL

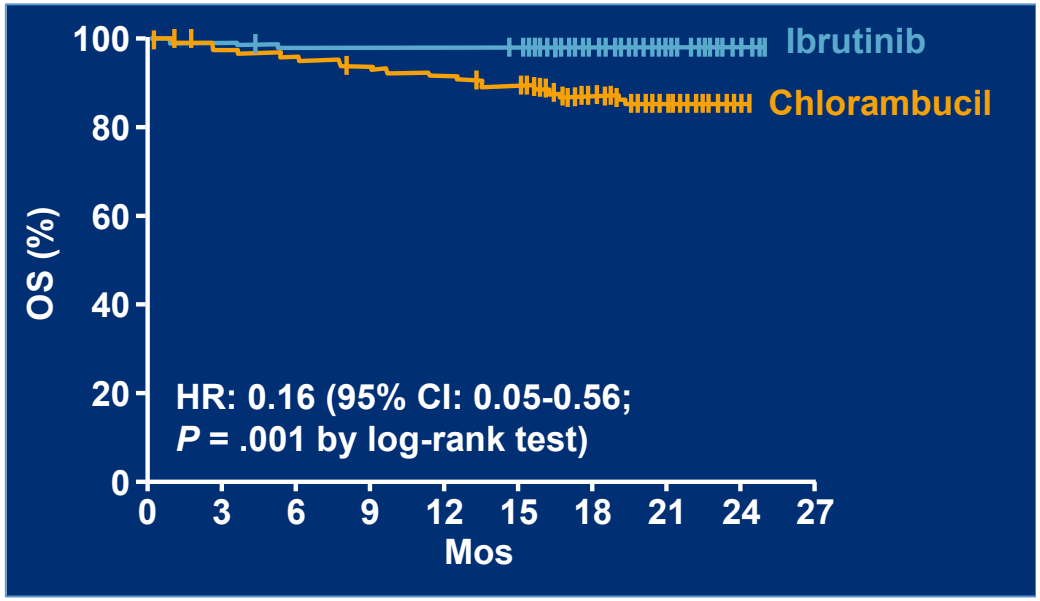


Courtesy of A. Tedeschi

Tedeschi A, et al. ASH 2015. Abstract 495.

Ibrutinib is superior to chlorambucil as first line treatment in unfit CLL





Outcome	Ibrutinib (n = 136)	Chlorambucil (n = 133)	P Value
Median PFS, mos	NE	18.9	< .0001
18-mo PFS rate, %	90	52	

Courtesy of A. Tedeschi

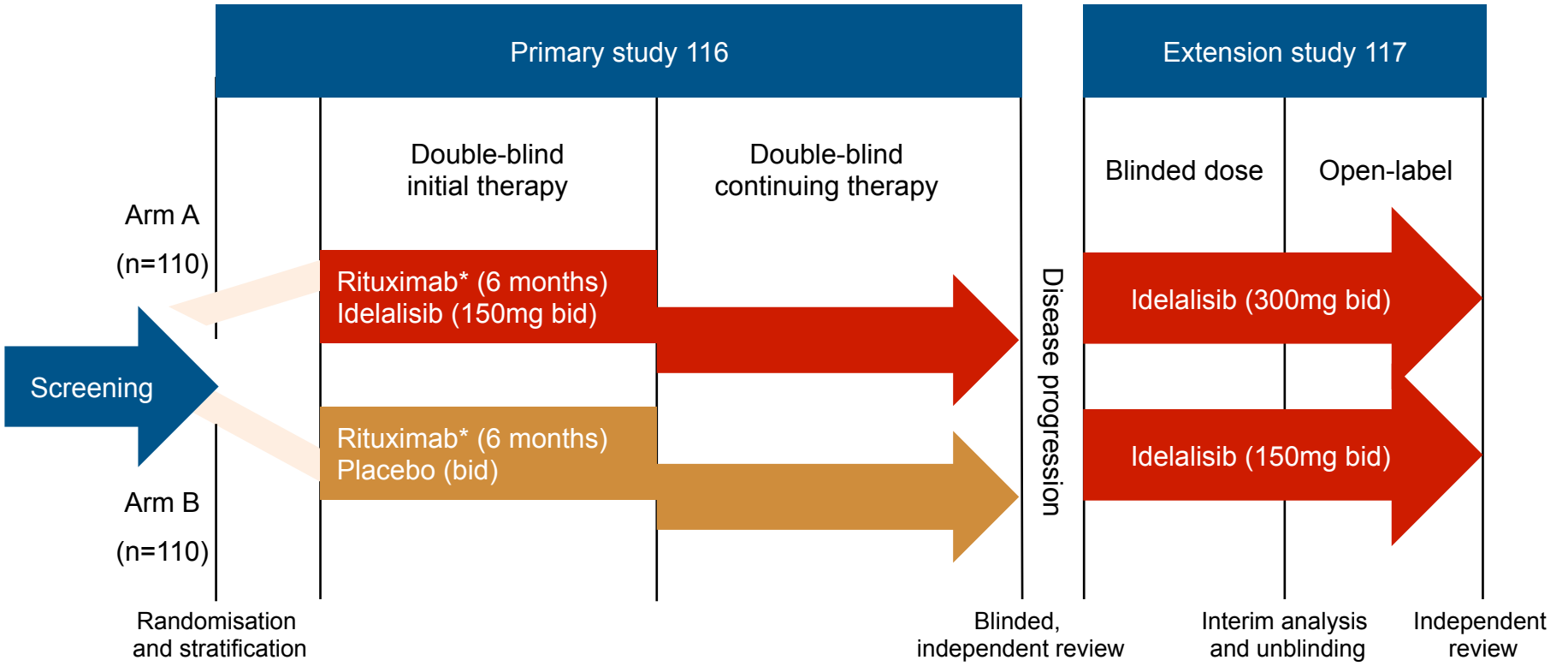
Tedeschi A, et al. ASH 2015. Abstract 495.

CLL treatment subgroups

- **Treatment naïve**
- **Relapsed/refractory CLL**
- **High risk *TP53* disrupted CLL**
- **BCRi resistant/intolerant CLL**

Salvage treatment: idelalisib

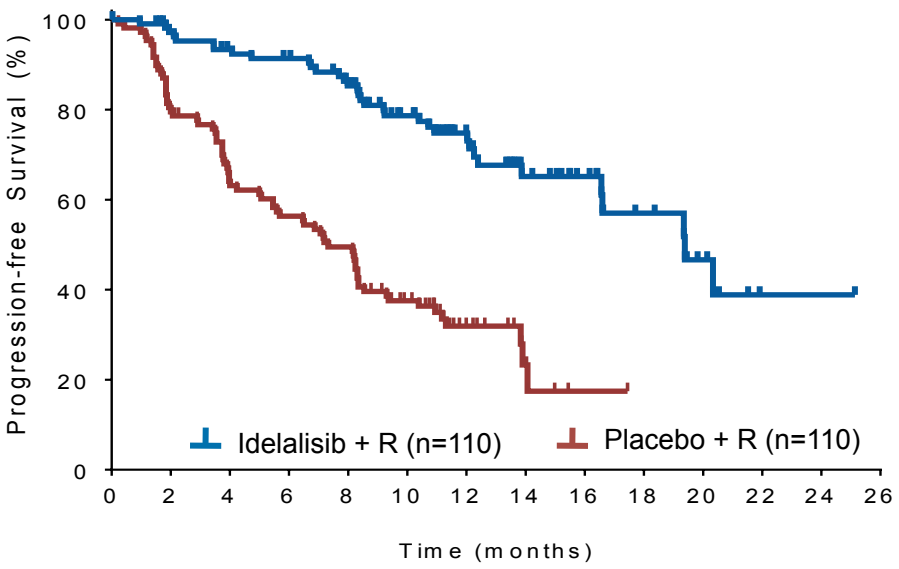
Comparative trials with kinase inhibitor: Study 116/117



Furman *et al. New Engl J Med.* 2014 Mar 13;370(11);997-1007.

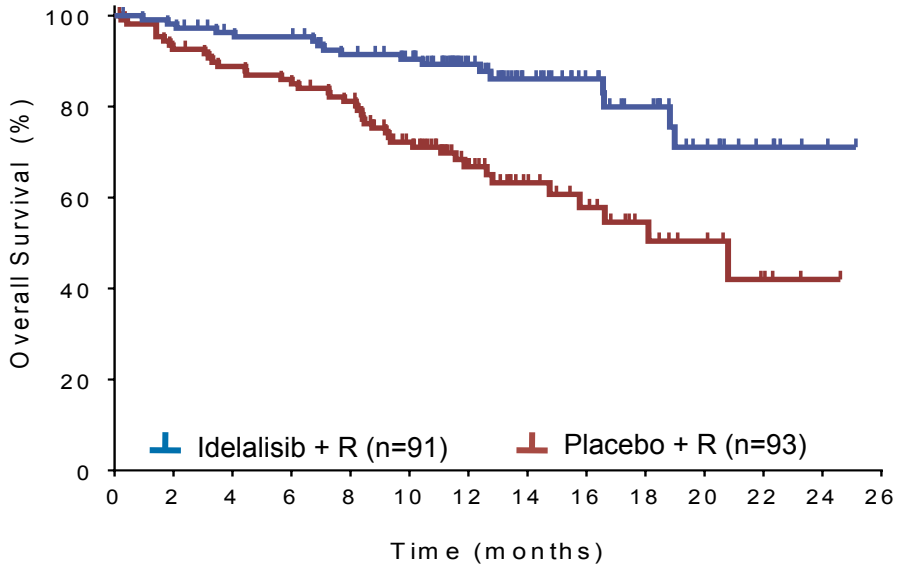
Salvage treatment: idelalisib

Progression-free and overall survival



Progression-free survival

n at risk														
IDELA+R	110	102	95	92	83	64	43	26	19	12	7	1	1	0
PBO+R	110	86	66	58	51	33	15	5	1	0	-	-	-	-



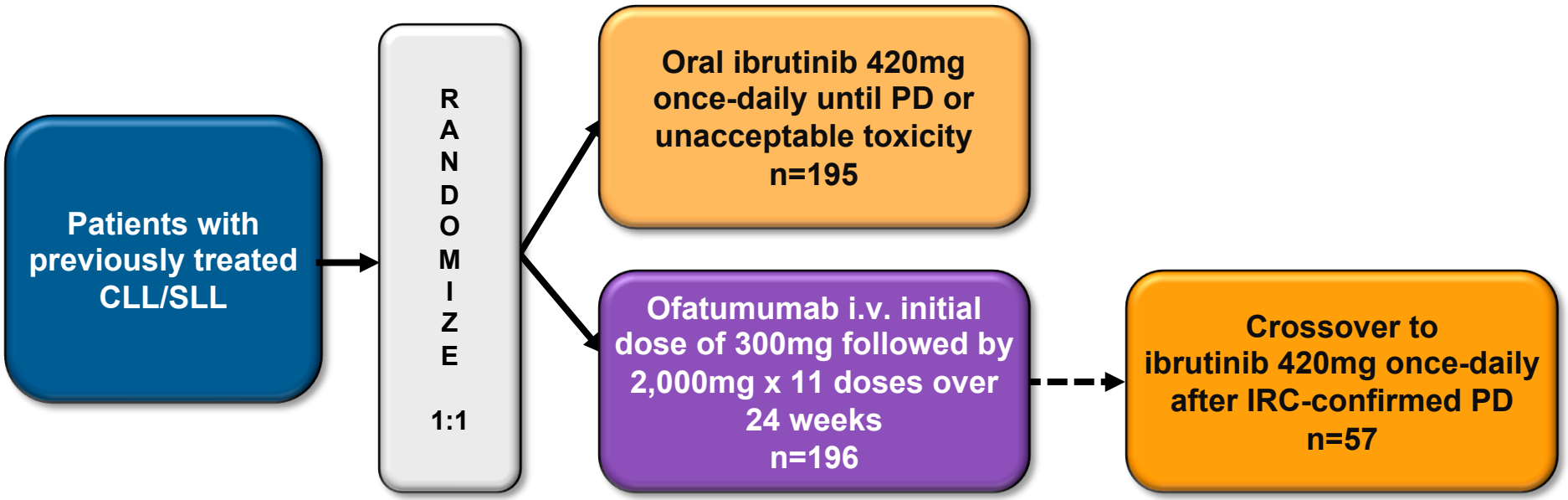
Overall survival

n at risk														
IDELA+R	110	107	101	100	93	85	60	41	30	23	13	7	3	0
PBO+R	110	99	93	90	84	66	42	27	20	13	8	4	1	0

Sharman *et al. Blood* 2014 124:330 (ASH meeting abstracts).

Salvage treatment: ibrutinib

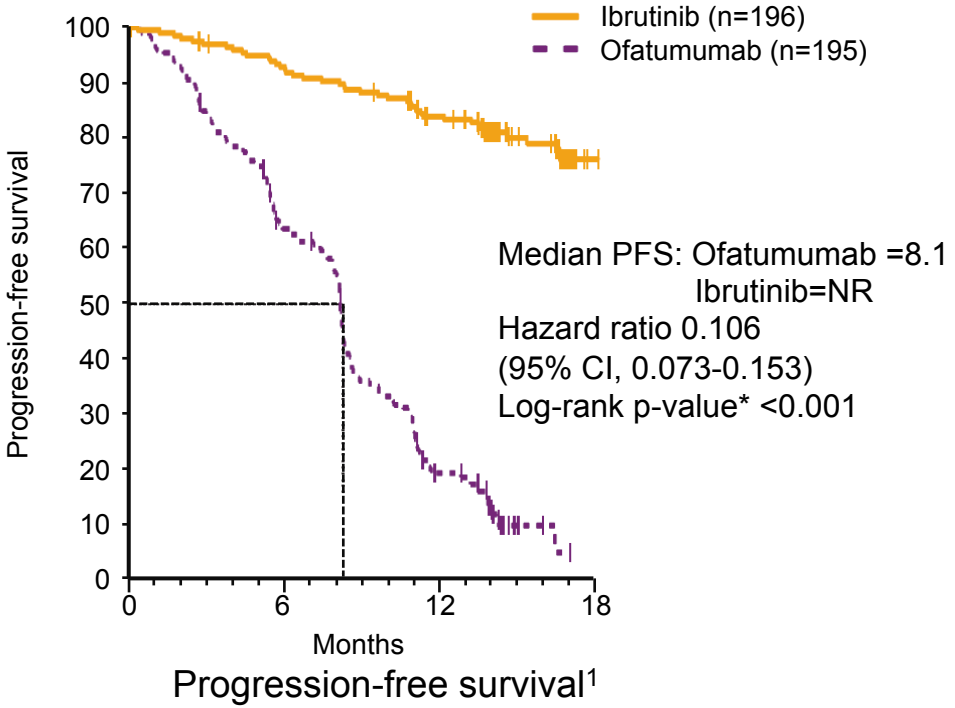
Comparative trials with kinase inhibitor: RESONATE



Byrd *et al. New Engl J Med.* 2014 Jul 17;371(3):213-2.

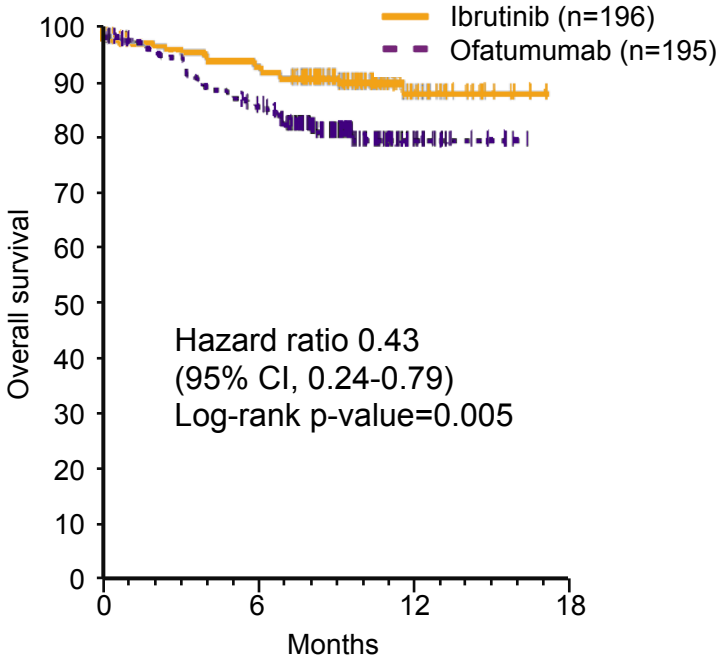
Salvage treatment: ibrutinib

Progression-free and overall survival



Progression-free survival[1]

*p<0.0001 for ibrutinib vs. ofatumumab. †5 patients for ibrutinib and 17 for ofatumumab were nonevaluable for response but included in denominator (ITT population).



Overall survival[2]

[1]Brown *et al*, *Blood* 2014 124:3331 (Poster presented at ASH meeting 2014);
[2]Byrd *et al. New Engl J Med.* 2014 Jul 17;371(3):213-2.

Toxicities of BCR inhibitors

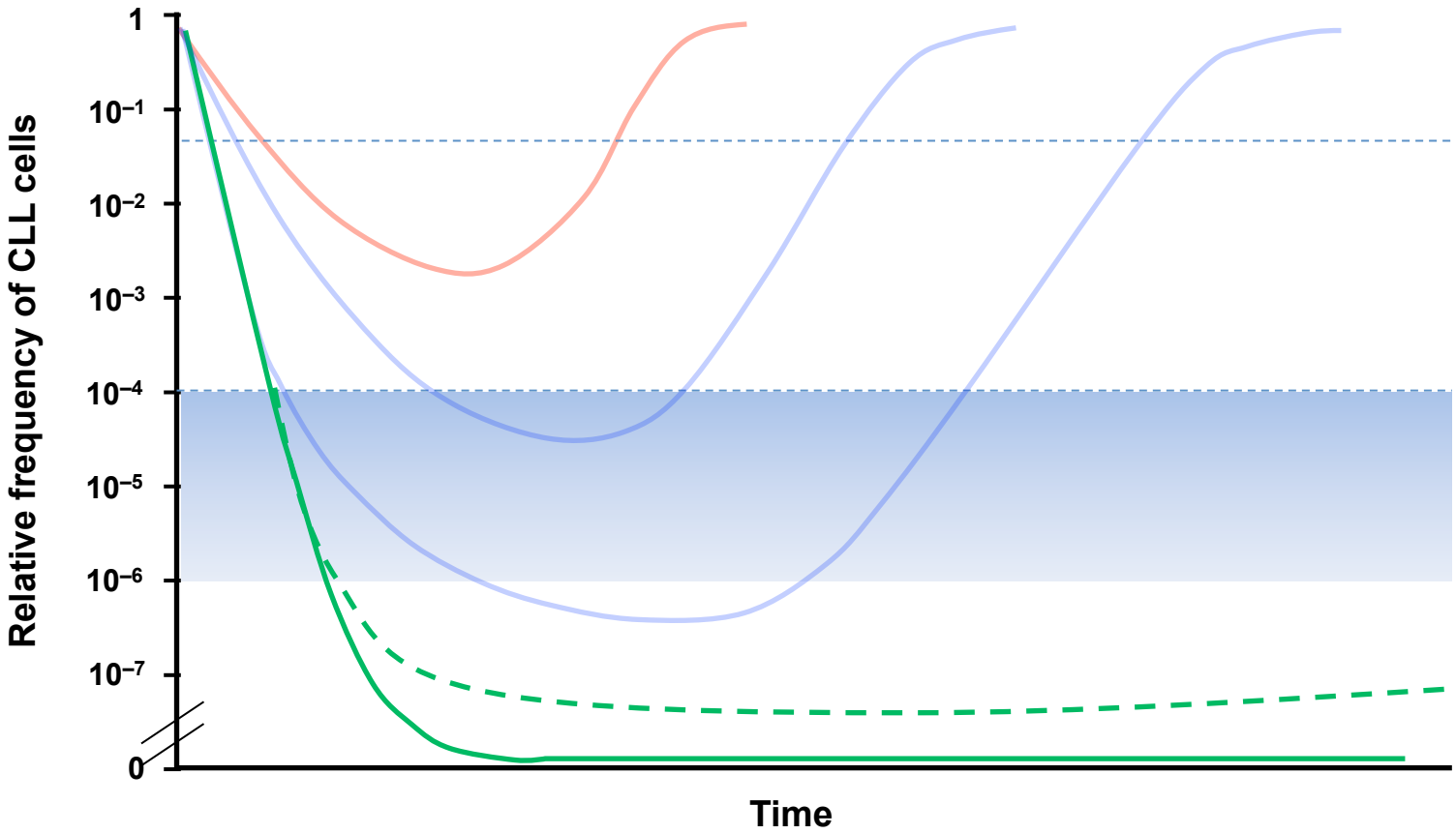
Ibrutinib:

- Bleeding
- Atrial fibrillation
- Hypertension
- Arthralgia
- Drug interactions
- Costs
- Compliance?
- Long term safety?

Idelalisib:

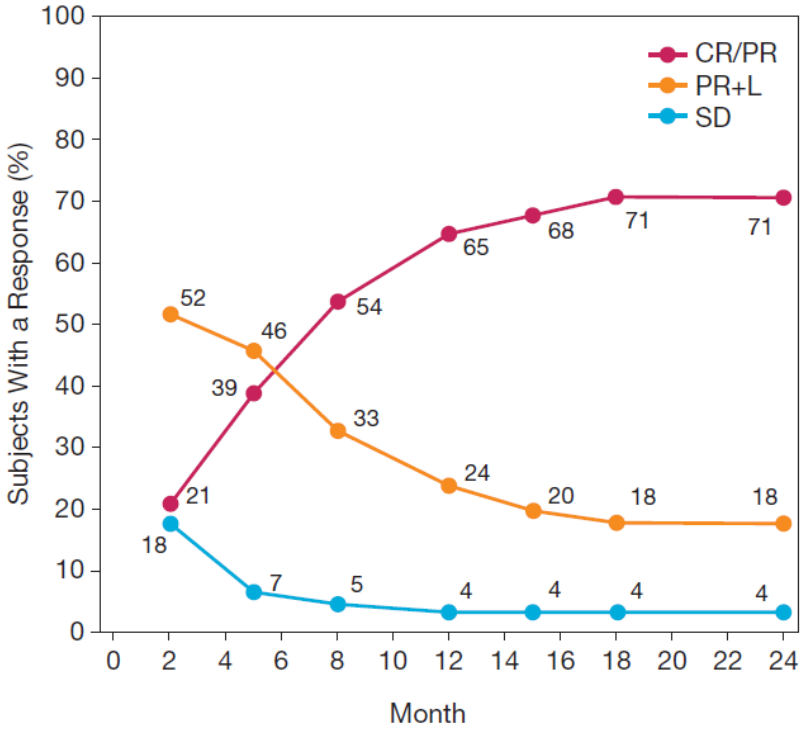
- Transaminitis
- Diarrhea/colitis
- Pneumonitis
- Infections
- Drug interactions
- Costs
- Compliance
- Long term safety?

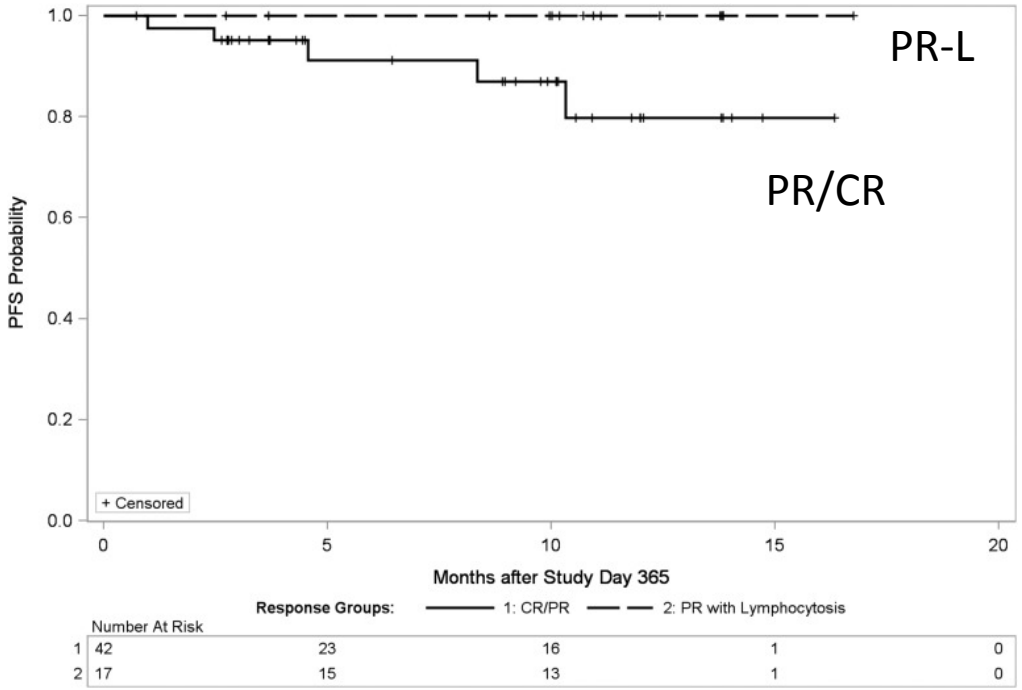
CLL enspoints:
Depth of response and progression free survival



1 Böttcher S, *et al*. *Hematol Clin N Am* 2013; 27:267–288;
2. Hallek M, *et al. Blood* 2008; 111:5446–5456;
3. Moreno C, *et al. Best Pract Res Clin Haematol* 2010; 23:97–107.

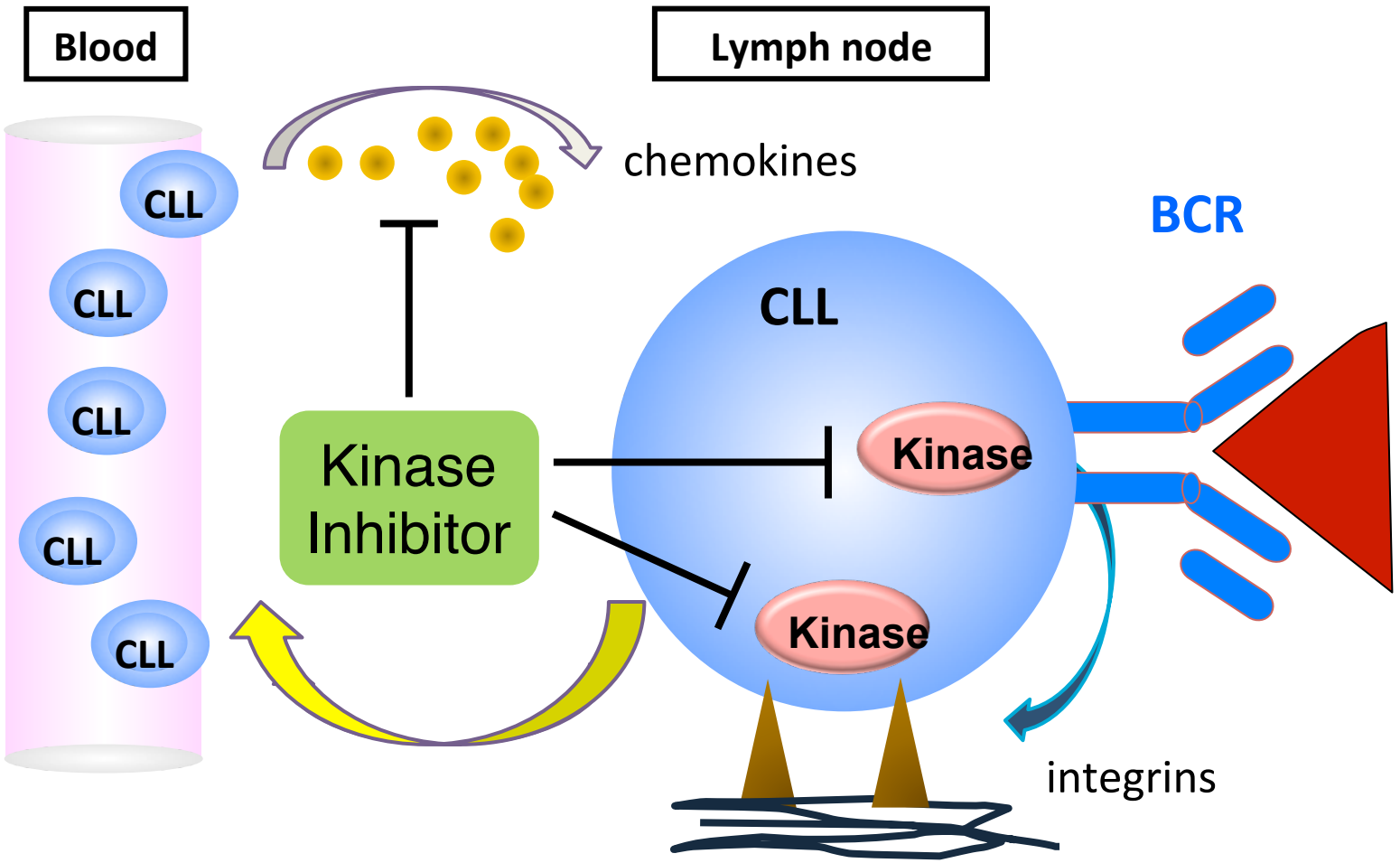
Evolution of response over time





Byrd JC, et al. N Engl J Med. 2013;369:32-42
Byrd JC, et al. Blood. 2015;125:2497-506

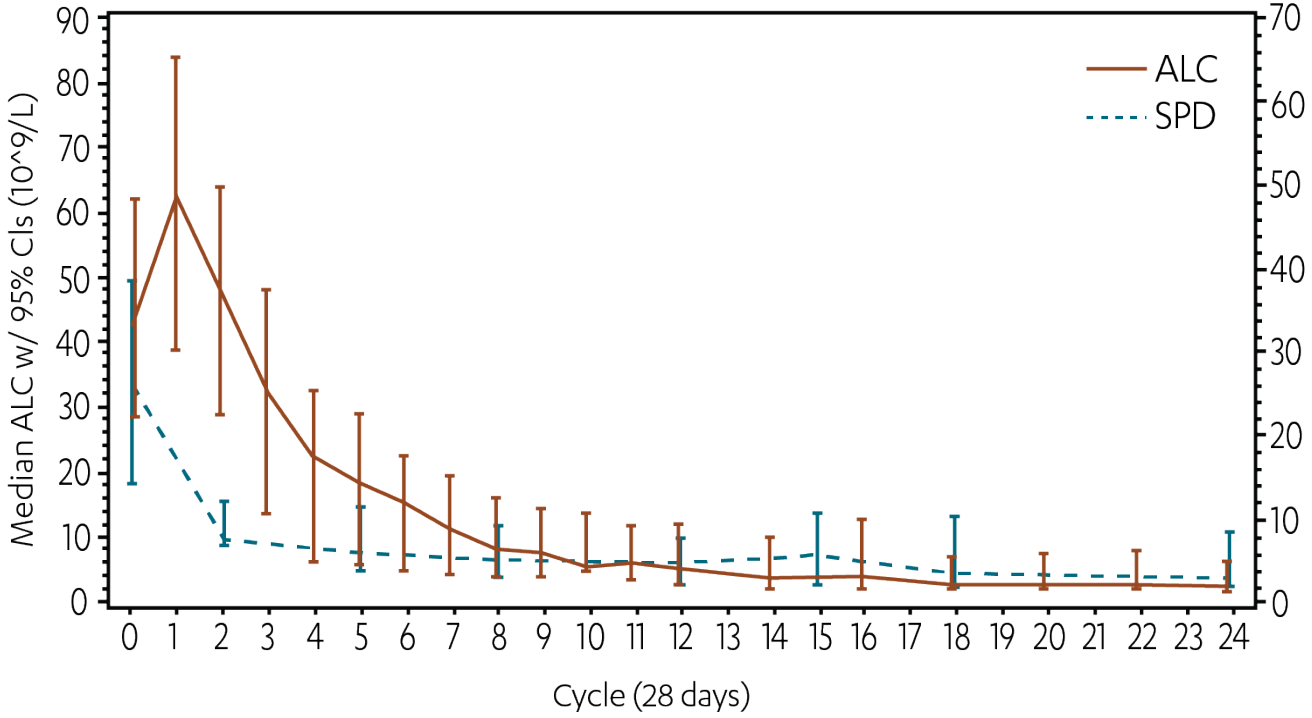
"Redistribution Lymphocytosis": possible mechanisms



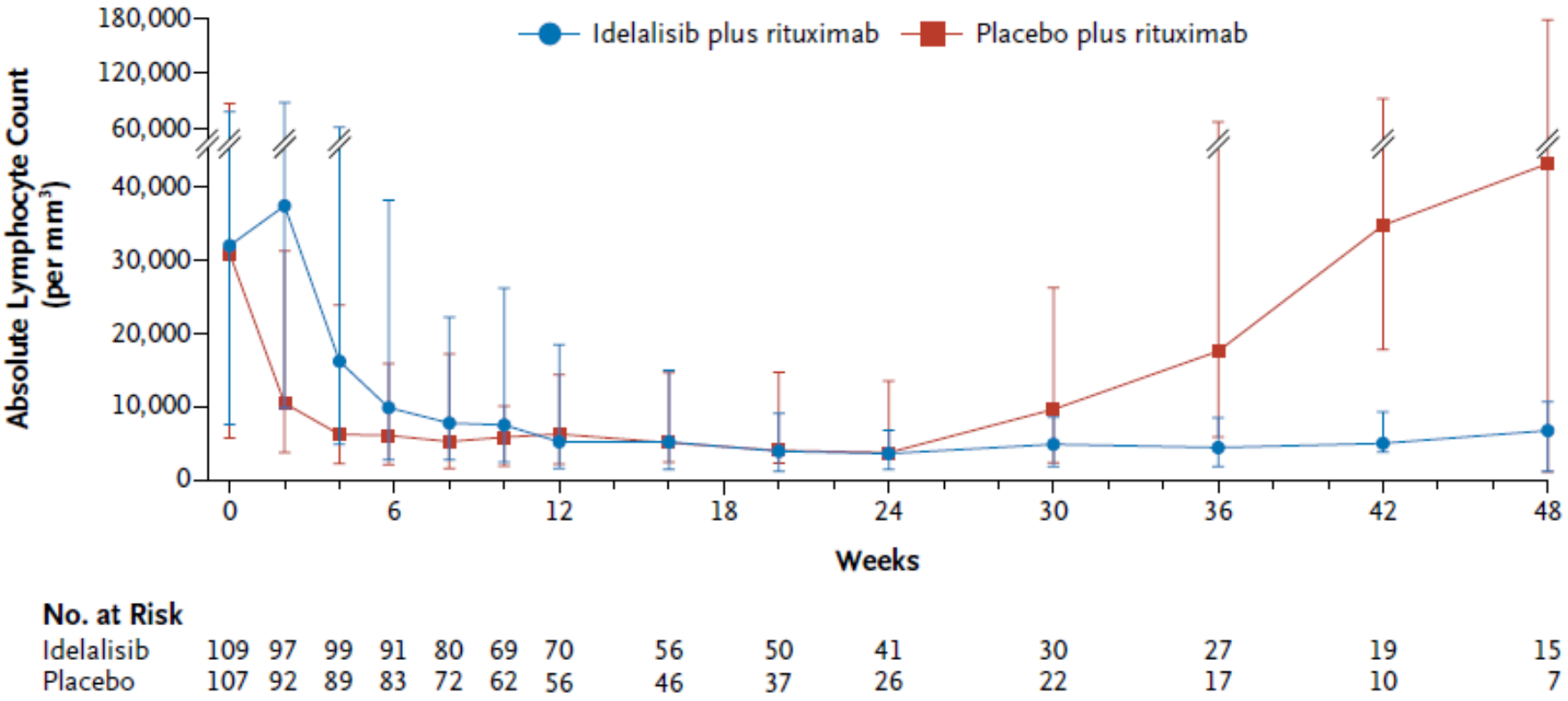
De Rooij, Blood 2012; Ponader, Blood 2012; Herman, abstract #185

New response criteria are required

Lymphocytosis + Nodal Reduction with BCR Antagonists



Lymphocytosis is less pronounced if BCRi are combined with rituximab



Furman R, NEJM 2014

CLL treatment subgroups

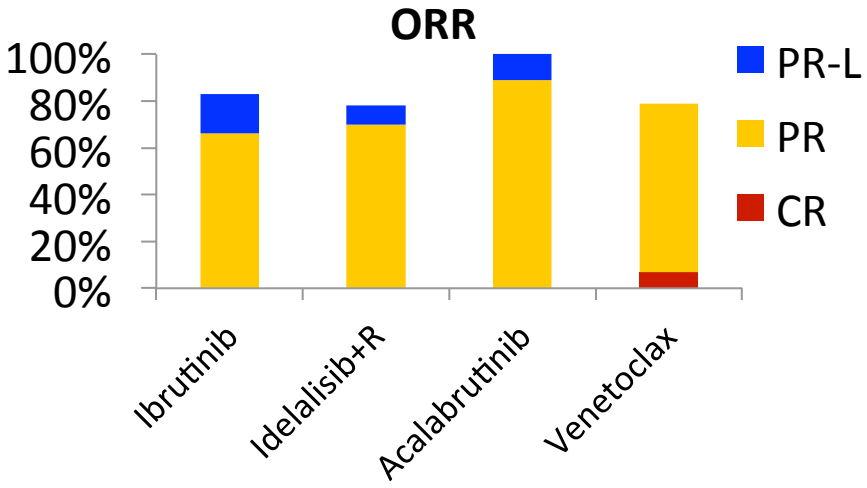
- **Treatment naïve**
- **Relapsed/refractory CLL**
- **High risk *TP53* disrupted CLL**
- **BCRi resistant/intolerant CLL**

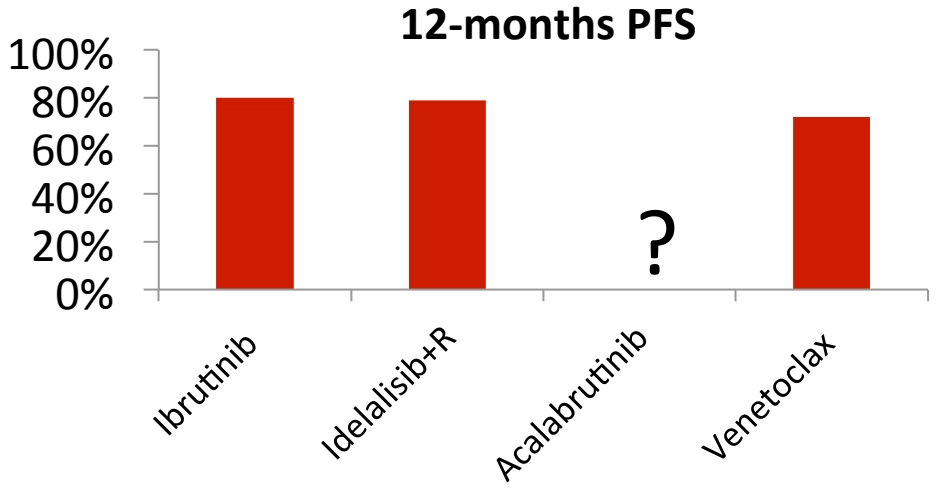
Novel agents in R/R 17p deleted CLL

(from chemo+/- immunotherapy)

RESONATE -17 n=144
M13-982 n=107
Study 116 (post-hoc) n= 71
ACE-CL-001 (post-hoc) n=18

O'Brien, ASH 2014
Sharman ASH 2014
Byrd ASH 2015
Stilgenbauer, ASH 2015

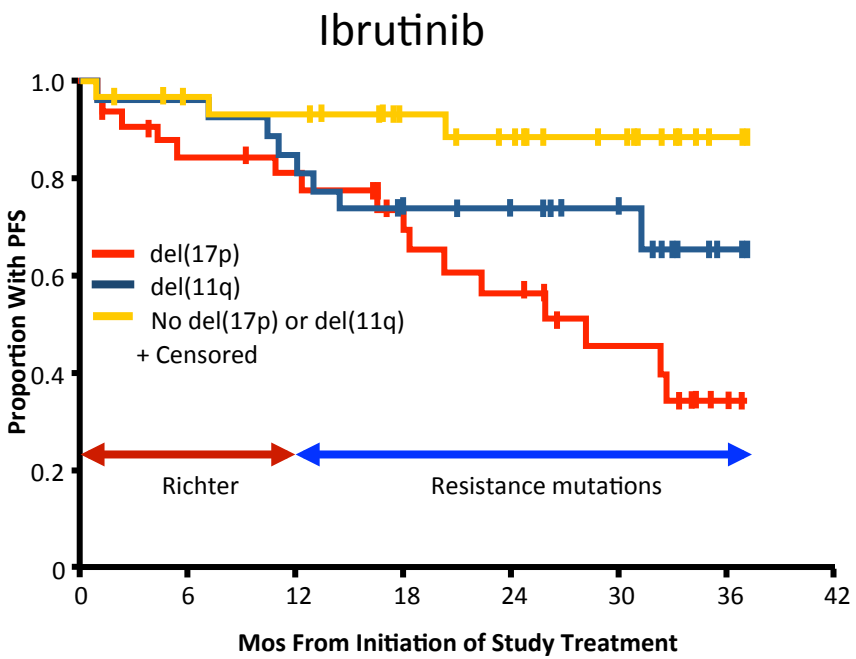


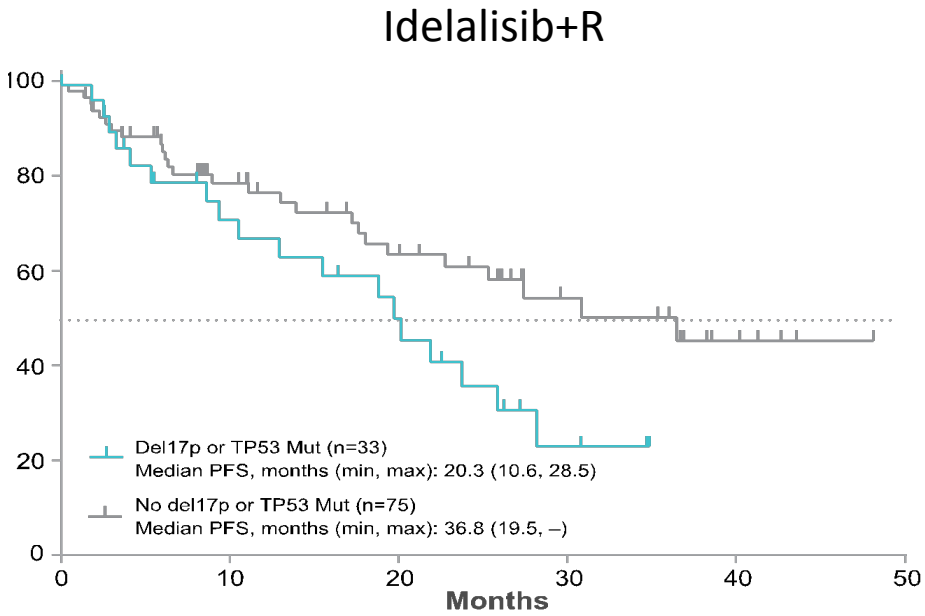


	Ibrutinib	Idelalisib+R	Acalabrutinib	Venetoclax
MRD negative	No	No	No	Yes
Stop treatment	No	No	No	?
Sites of residual disease	PB	PB	PB	LN
Activity in compartments	LN > PB/BM	LN > PB/BM	LN > PB/BM	PB/BM > LN

Other differences: safety profile; logistics (outpatient vs hospitalization)

PFS by Cytogenetics (FISH) in R/R CLL

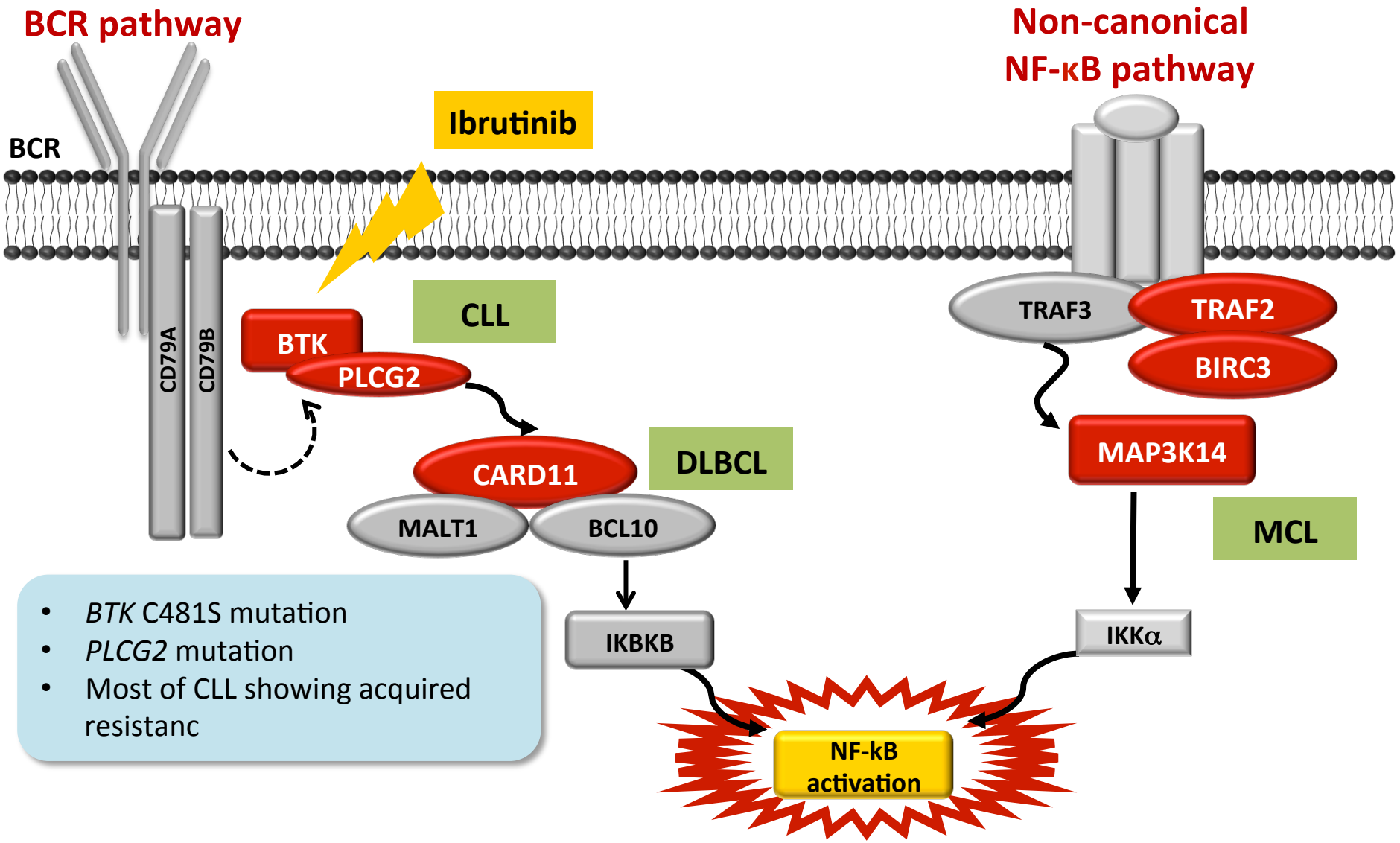




O'Brien S, et al. ASCO 2014. Abstract 7014.

Barrientos, ASCO, 2015, 7011

Molecular mechanisms of resistance to ibrutinib



1. Davis RE et al. Nature 2010;463:88–92; 2. Woyach JA et al. NEJM 2014;370:2286–94; 3. Furman RR et al. NEJM 2014;370:2352–4; 4. Famà R et al. Blood 2014;124:3831–3; 5. Rahal R et al. Nat Med 2014;20:87–92.

CLL treatment subgroups

- **Treatment naïve**
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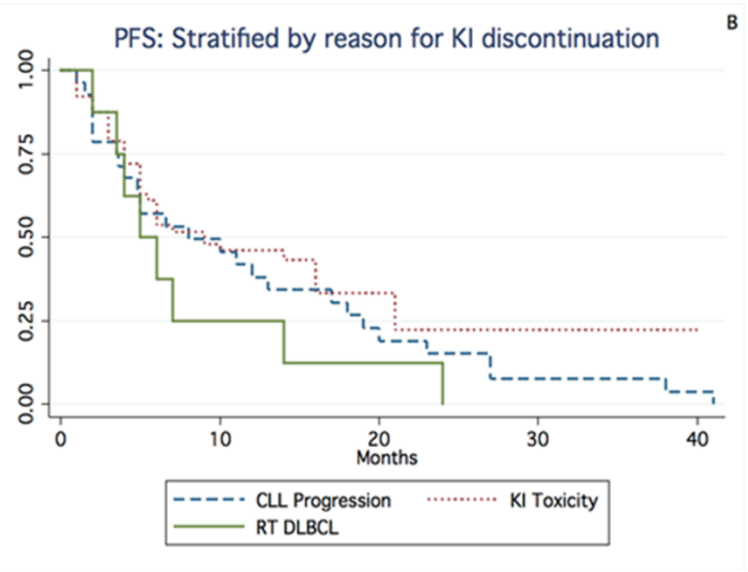
Switch to another novel agent

Switch to another kinase inhibitor

ORR = 67%



Mato et al, ASH 2015

Switch to venetoclax

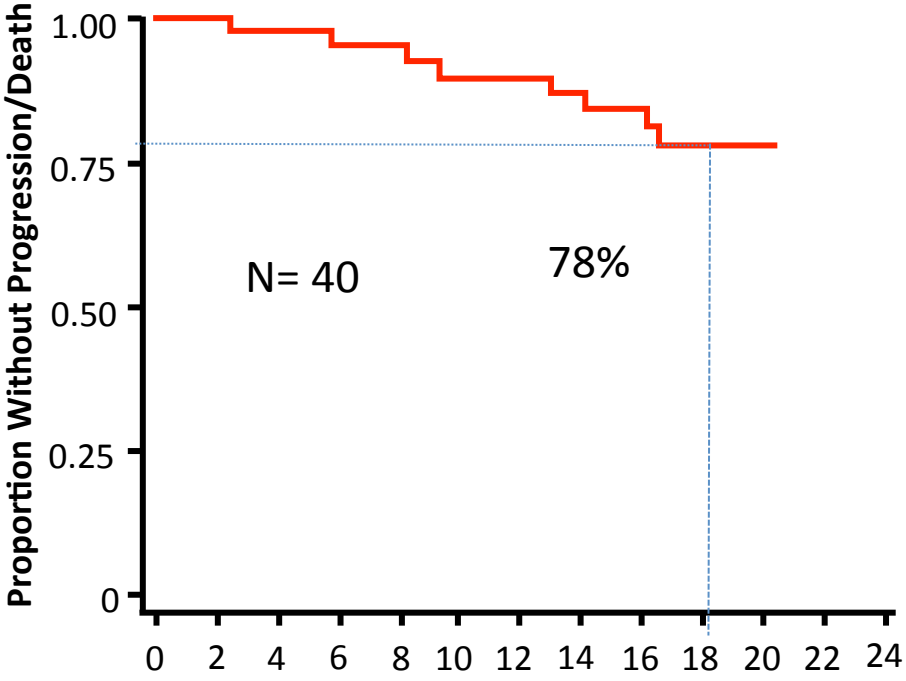
Ibrutinib→venetoclax: **53% PR**

Ibrutinib→venetoclax: **50% PR**

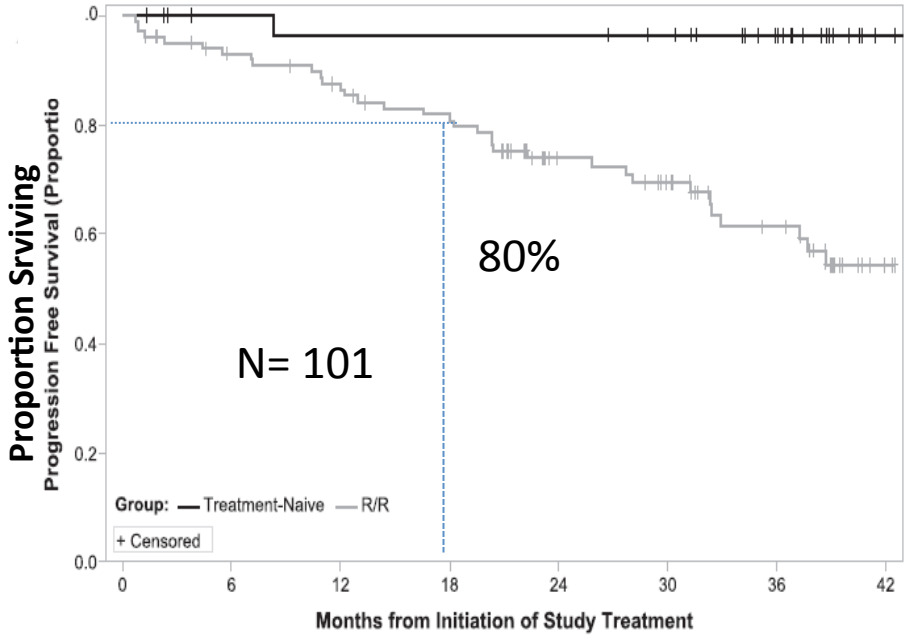
Jones et al, ASH 2015

Combining Ibrutinib with rituximab

Ibrutinib +Rituximab



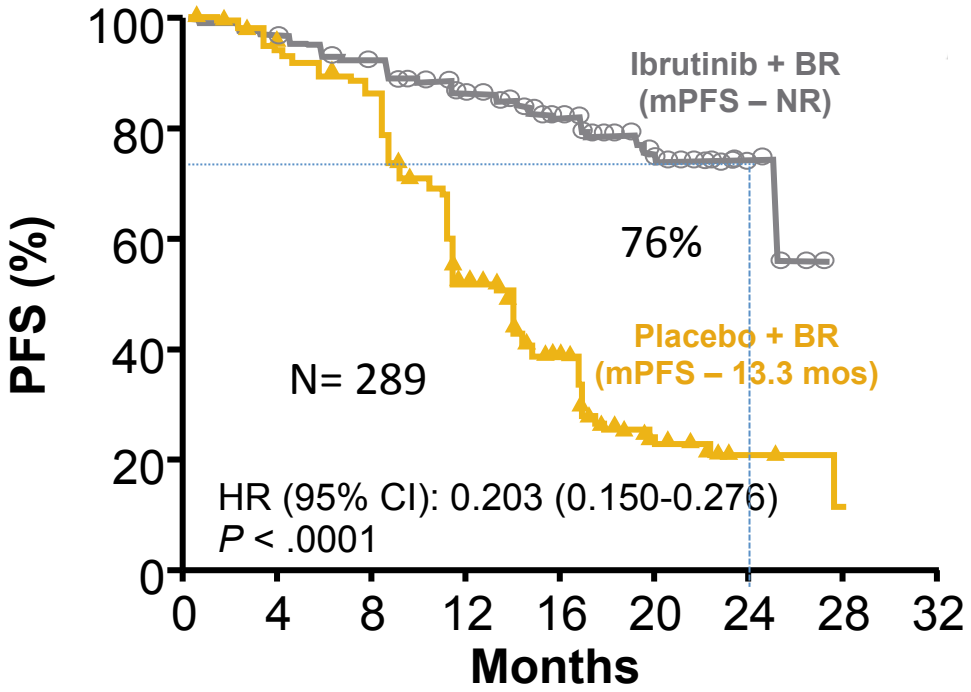
Ibrutinib



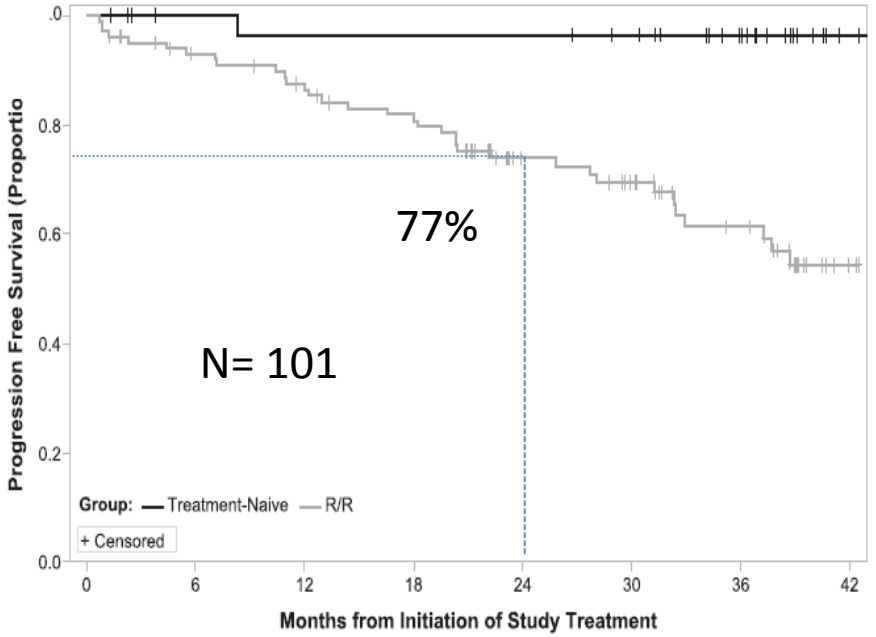
Burger Lancet Oncol 2014)- Byrd Blood 125;2497, 2015

Combining ibrutinib with Chemotherapy

BR+Ibrutinib



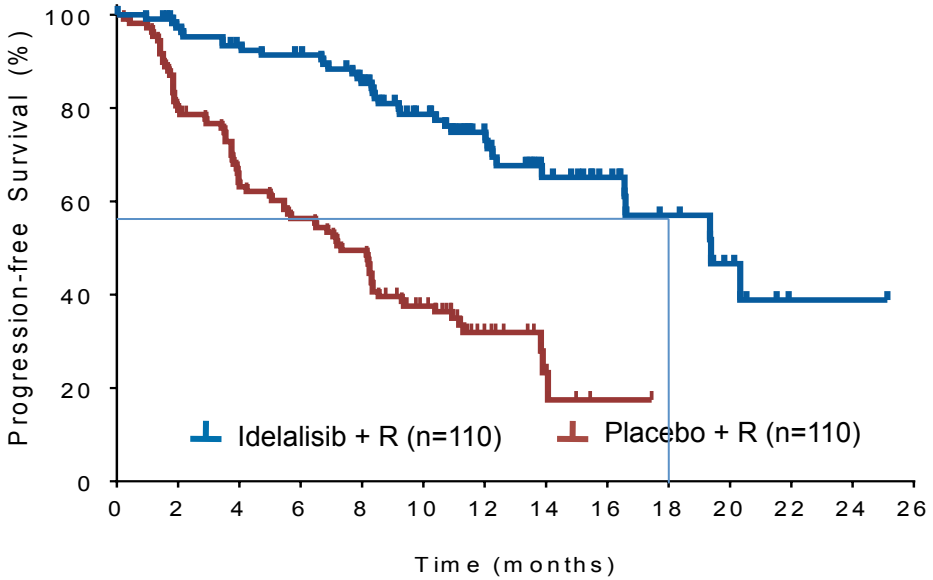
Ibrutinib



Chanan-Khan JCO (ASCO 2015) - Byrd Blood 125;2497, 2015

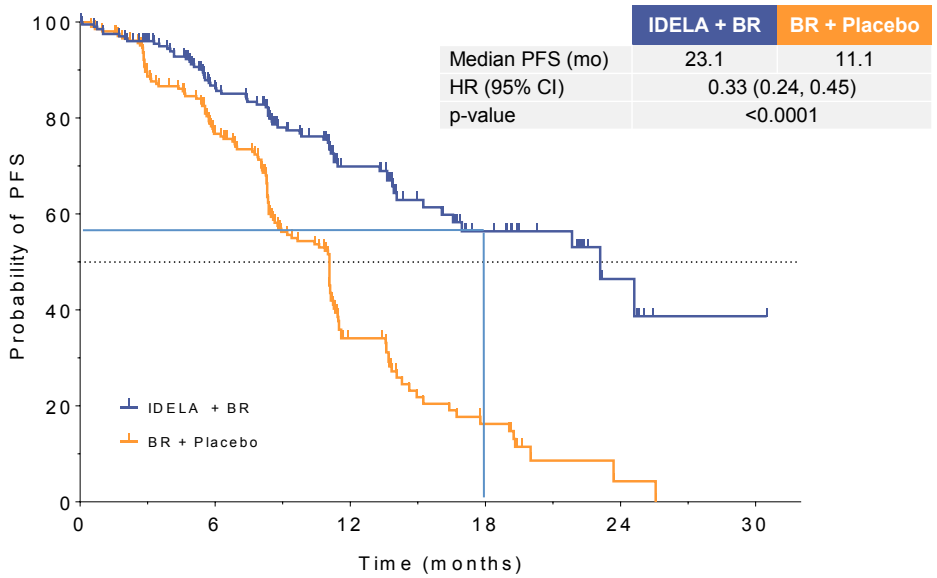
Combining idelalisib with Chemotherapy

Study 116



Furman *et al. New Engl J Med.* 2014 Mar 13;370(11);997-1007.

Study 115



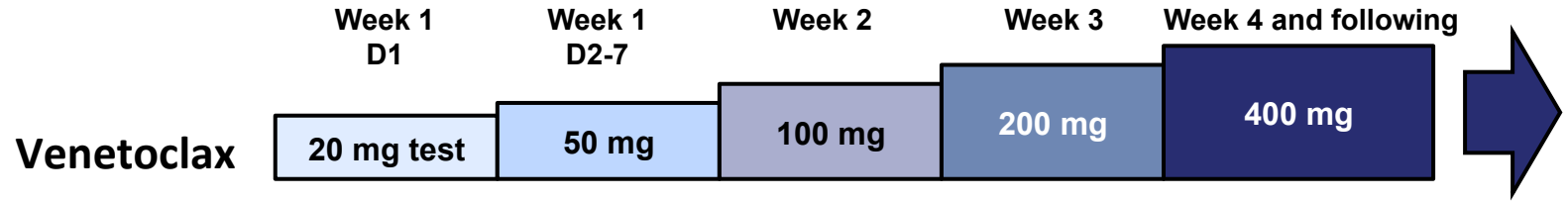
Zelenetz et al., ASH 2015 Abstract LBA-5

Baseline Characteristics

Main inclusion criteria:

- Rel/ref CLL, 17p– confirmed by central laboratory
- ECOG score ≤ 2
- ANC ≥1000/μL; Plt ≥40,000/mm^3; Hb ≥8 g/dL
- Creatinine clearance ≥50 mL/min

N=107	n (%)
Median age (years), range	67, 37–85
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)
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)



*20mg dose for 1 week in patients with electrolyte abnormalities after first dose

TLS risk category:

- Low: ALC<25 and nodes <5 cm
- Mmedium: ALC>25 OR nodes ≥5 and < 10cm
- High: ALC>25 nodes ≥5 but < 10cm OR nodes > 10cm

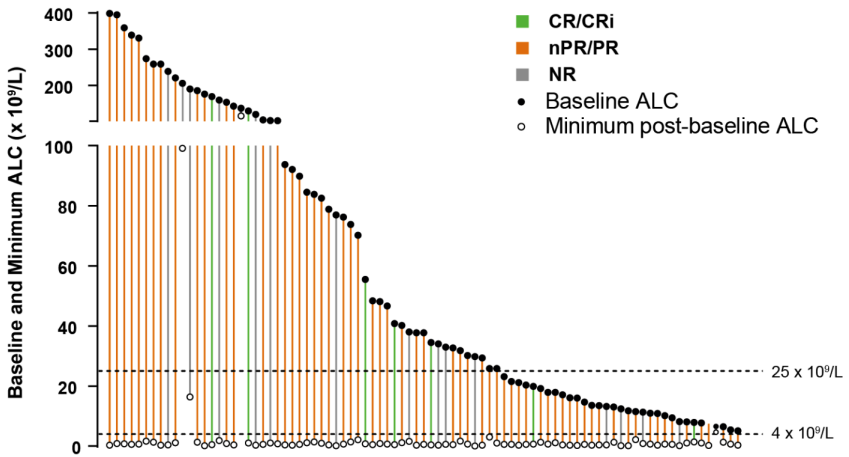
Courtesy of S. Stilgenbauer

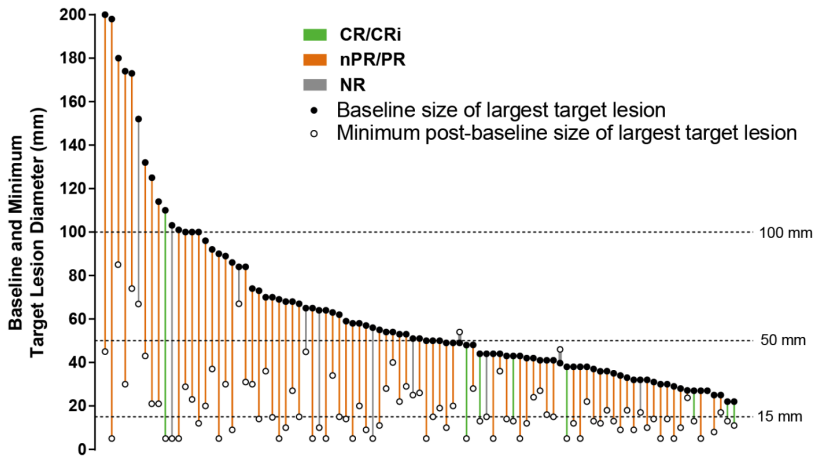
Best Response

	IRC, n (%)	Investigator, n (%)
Overall Response	85 (79.4)	79 (73.8)
CR or CRi	8 (7.5)	17 (15.9)
nPR	3 (2.8)	4 (3.7)
PR[a]	74 (69.2)	58 (54.2)

[a]47 of 74 patients assessed as PR met all criteria for CR or CRi, except for residual lymphadenopathies (median 2.1 cm)

18 of 45 patients assessed were MRD-negative in PB

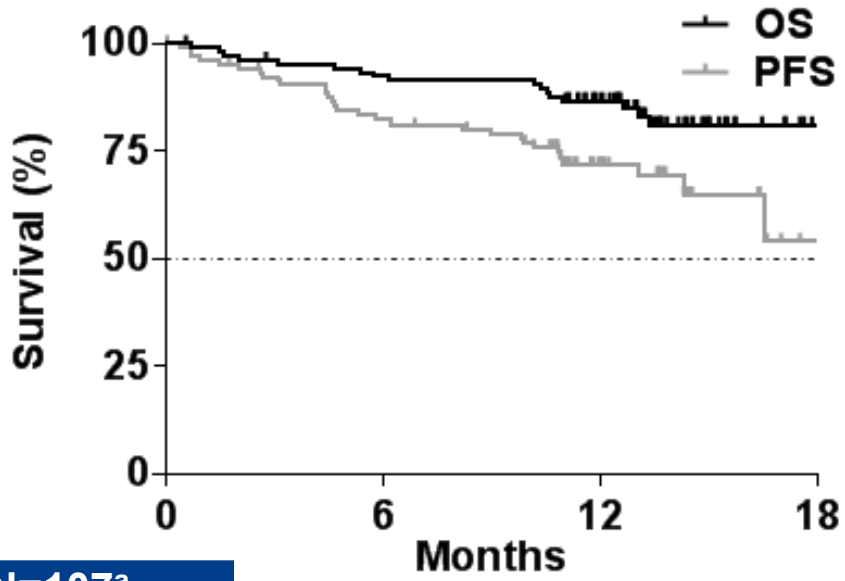




Durability of Venetoclax Activity

12-month estimates (95% CI):

- PFS: 72.0% (61.8, 79.8)
- OS: 86.7% (78.6, 91.9)



	N=107[a]
Median (range) time on study, months	12.1 (0.03–21.5)
Active on venetoclax, n (%)	70 (65)
Discontinued venetoclax, n	37
Disease progression	22
Richter's transformation	11
CLL progression	11
Adverse events	9
Proceed to stem cell transplant	3
Withdrew consent	2
Non-compliance	1

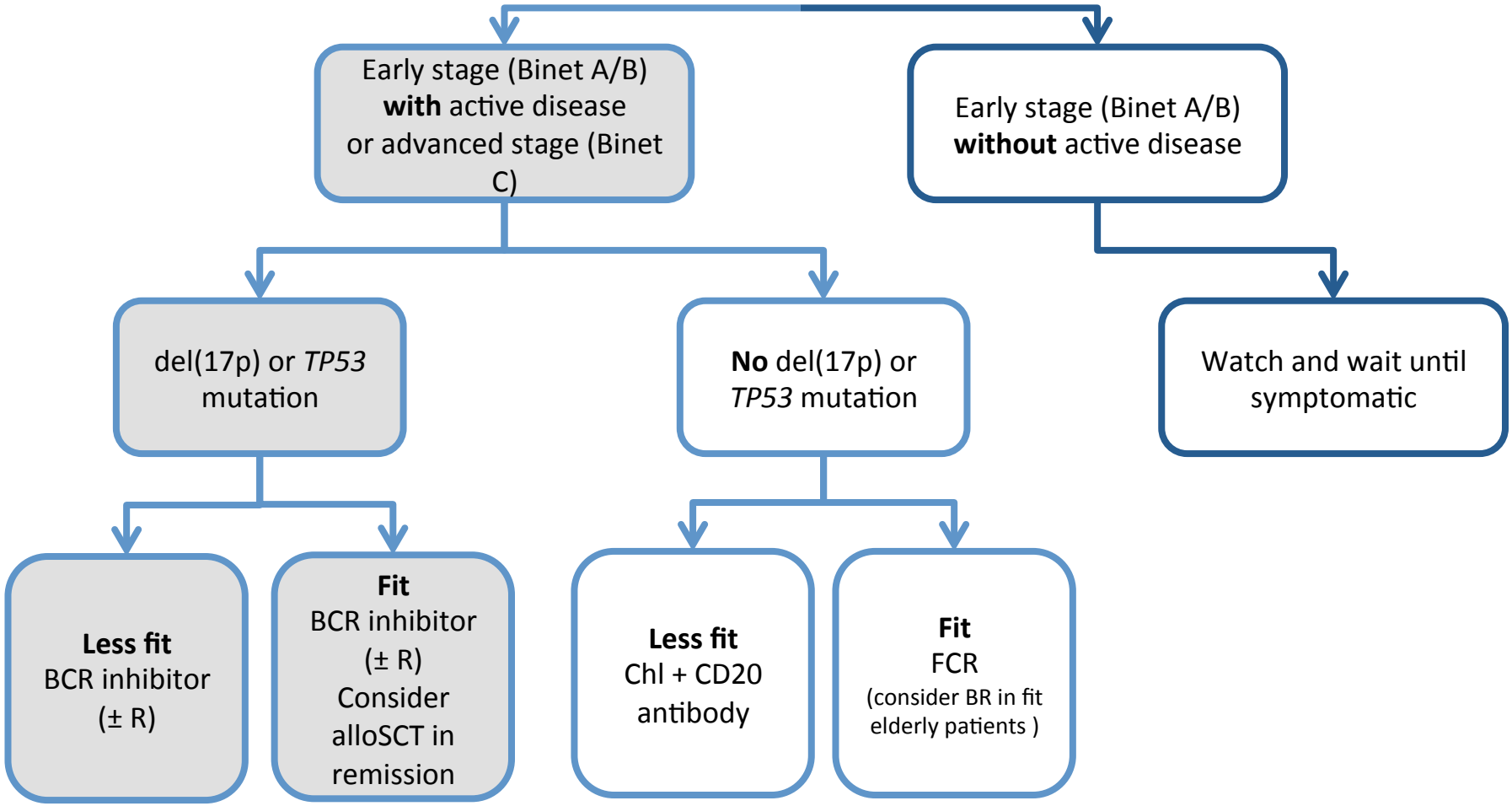
Courtesy of S. Stilgenbauer

Adverse Events of Special Interest

- Grade 3/4 neutropenia in 40% of patients
  - 22.4% had baseline neutropenia (any-grade)
  - Manageable: dose interruption/reduction, G-CSF and/or antibiotics
- Infections in 72% of patients (20% grade ≥3)
  - Most common (all-grade): upper respiratory tract infection (15%), nasopharyngitis (14%), and urinary tract infection (9%)
- Laboratory TLS in 5 patients during the ramp-up period
  - 2 with dose interruption (1 day each)
  - No clinical TLS events
- Serious adverse events in 55% of patients
  - Most common: pyrexia (7%), AIHA (7%), pneumonia (6%), and febrile neutropenia (5%)

Courtesy of S. Stilgenbauer

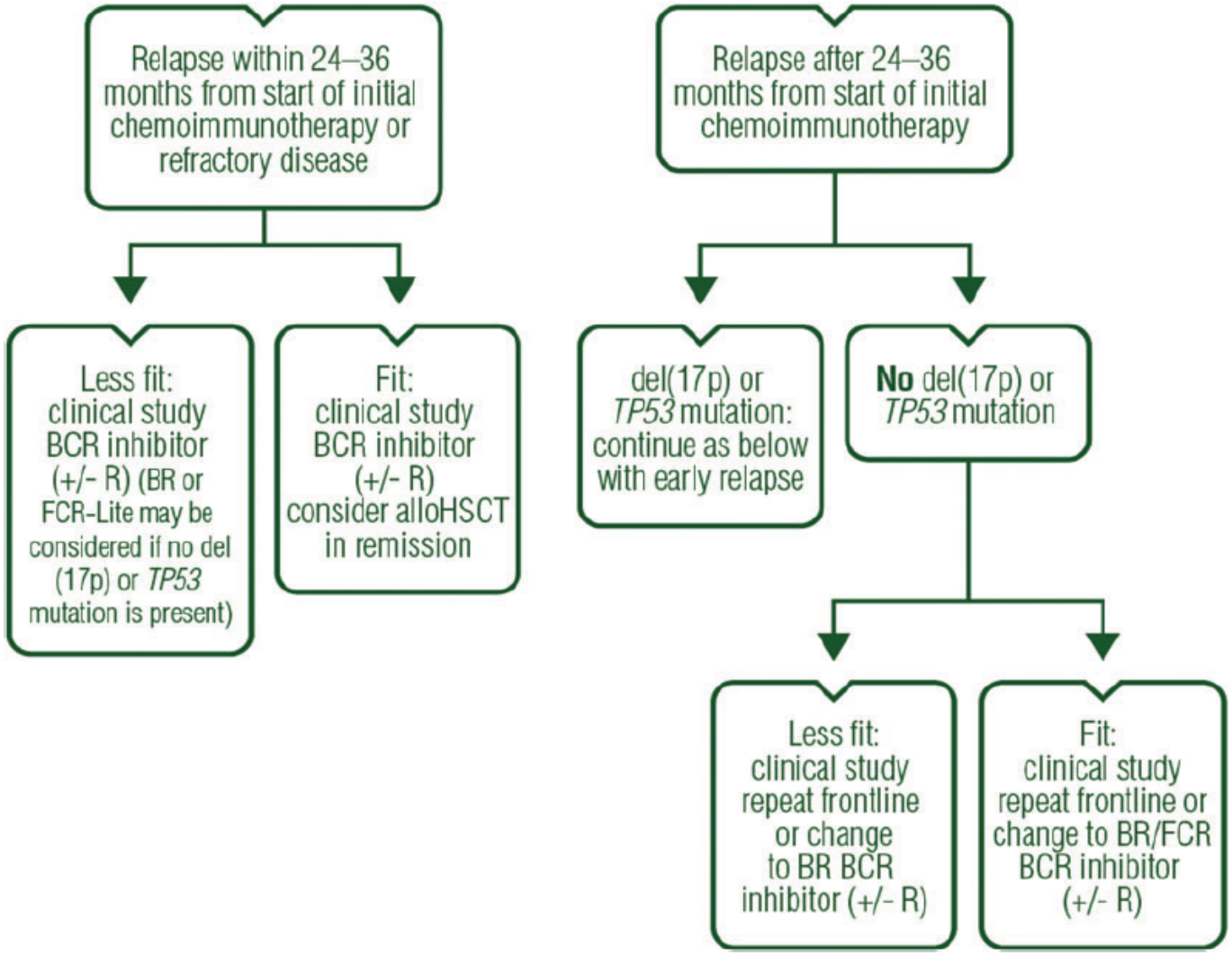
ESMO 2015 clinical practice guidelines for first-line treatment of CLL



'Fit': defined as physically active, with no major health problems and normal renal function; BCR inhibitor = ibrutinib or idelalisib
AlloSCT: allogeneic stem cell transplantation; B: bendamustine; C: cyclophosphamide; Chl: chlorambucil; CLL: chronic lymphocytic leukaemia; F: fludarabine; R: rituximab

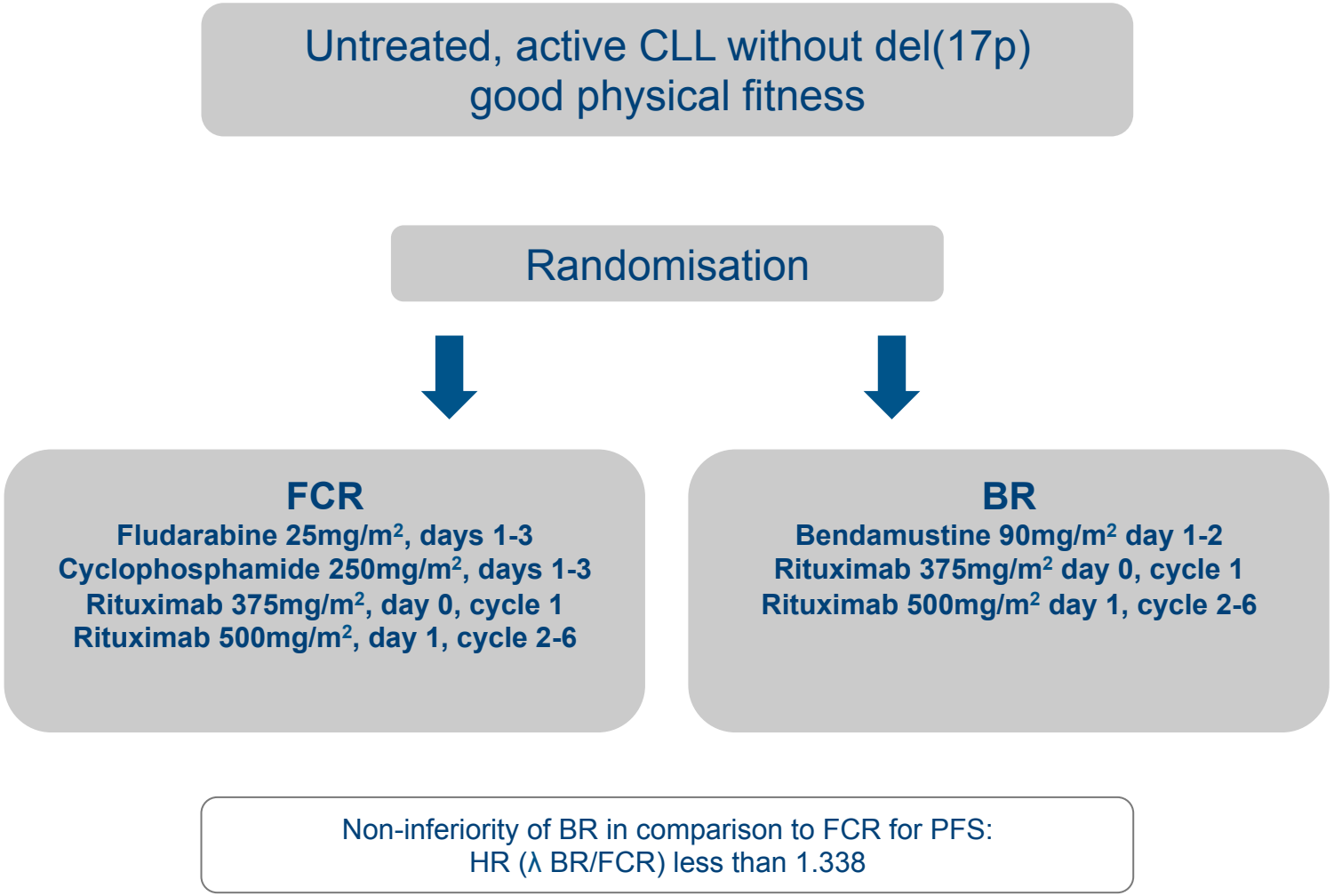
Eichhorst B, *et al. Ann Oncol* 2015; 26(Suppl 5):v78–v84.

ESMO 2015 clinical practice guidelines for treatment of relapsed –refractory CLL



ESMO Clinical Practice Guidelines: Annals of Oncology 26 (Supplement 5): v78–v84, 2015

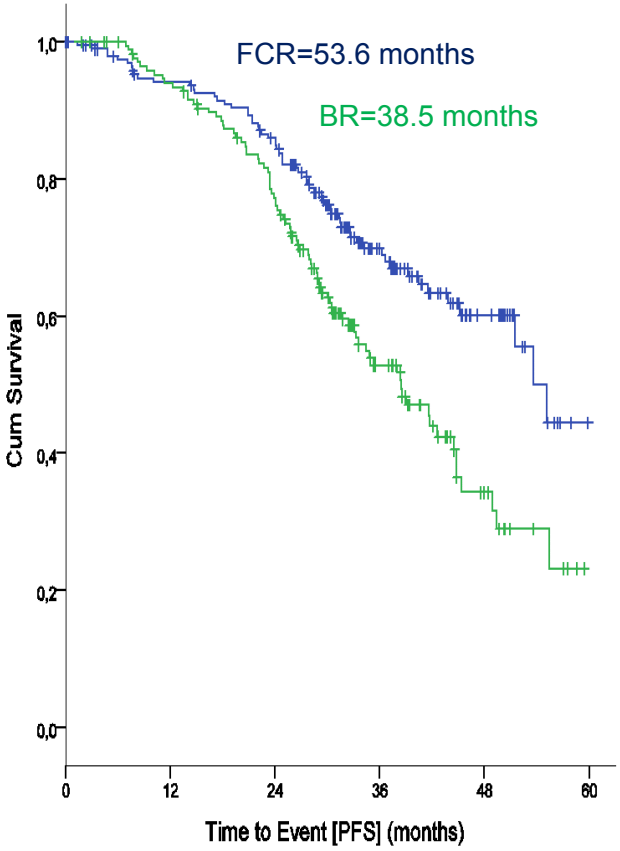
FCR vs BR as first line treatment in fit CLL patients



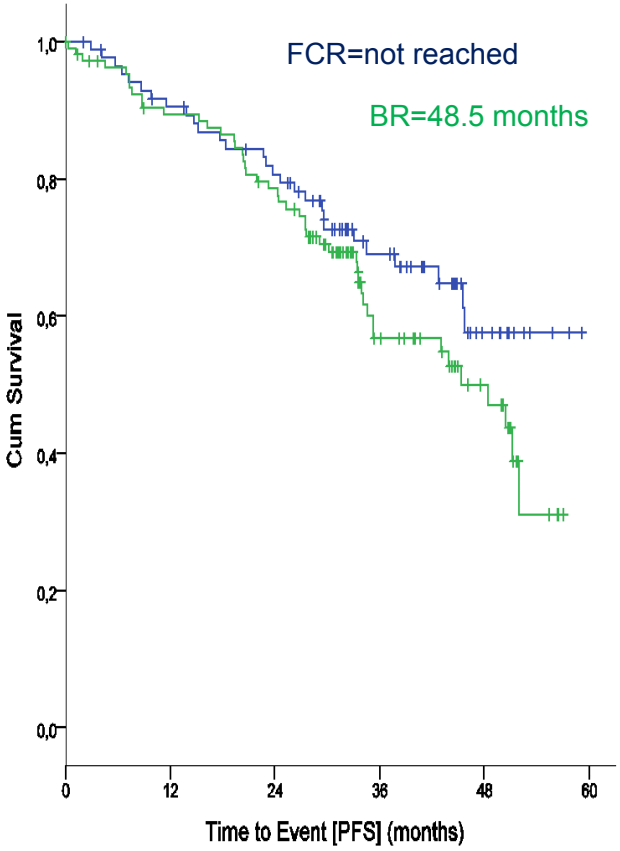
Eichhorst *et al. Blood.* 2014; 124 (ASH Meeting Abstracts):19

FCR is superior to BR as first line treatment in fit CLL patients younger than 65y

Patients ≤65 years: p<0.001



Patients >65 years: p<0.170



Eichhorst *et al. Blood.* 2014; 124 (ASH Meeting Abstracts):19

FCR is more toxic than BR

Adverse Events CTC °3-5 (Interval 1st cycle until 3 months after Final staging)

Adverse event	FCR (% of pt)	BR (% of pt)	p value
All	90.8	78.5	<0.001
Hematological AEs	90.0	66.9	<0.001
Neutropenia	81.7	56.8	<0.001
Anemia	12.9	9.7	0.28
Thrombocytopenia	21.5	14.4	0.036
Infection	39.0	25.4	0.001
TRM	3.9	2.1	0.23

Courtesy of S. Stilgenbauer