LLC: Tratamiento de primera línea

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Sociedad Chilena de Hematología
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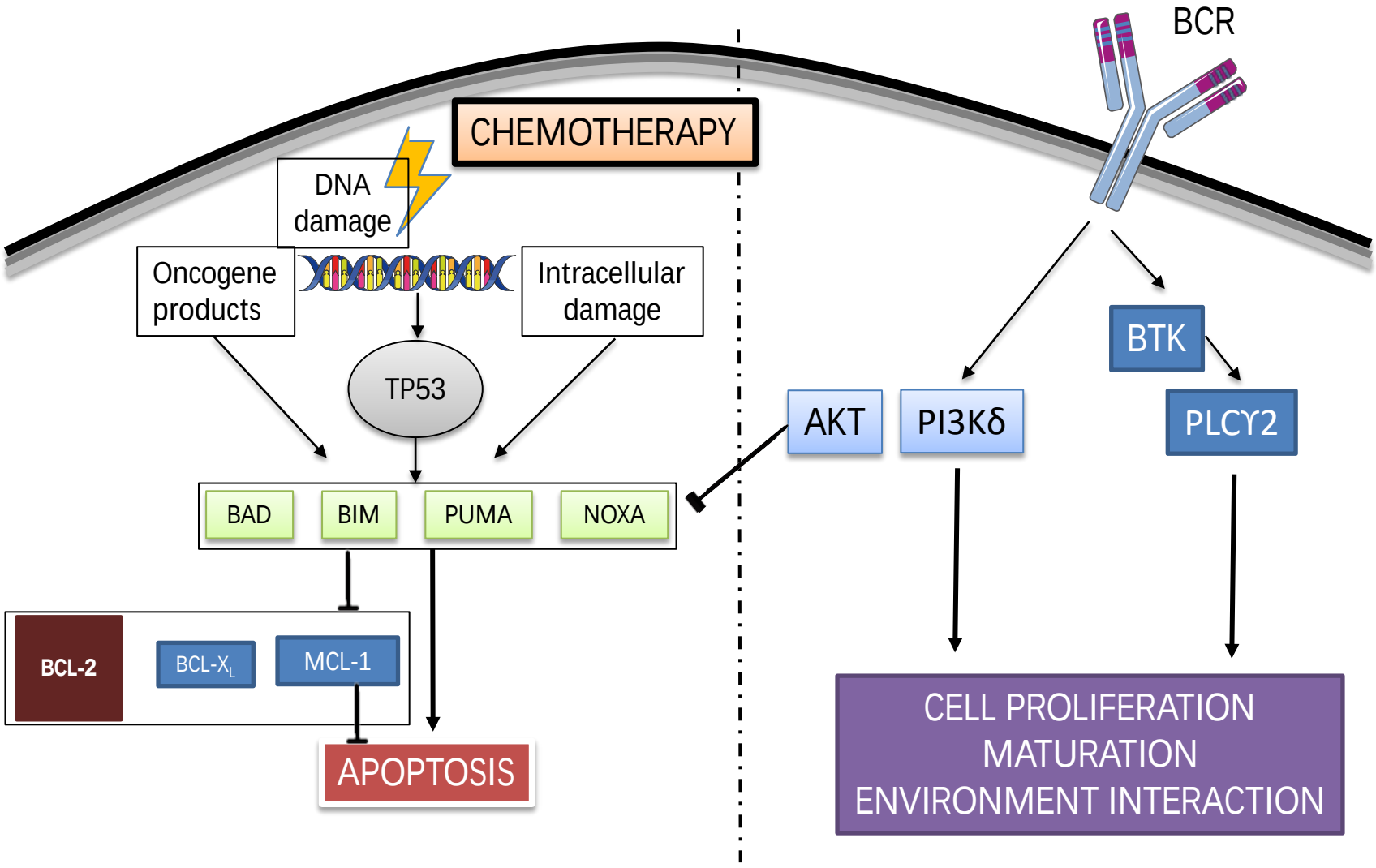
OUTLINE

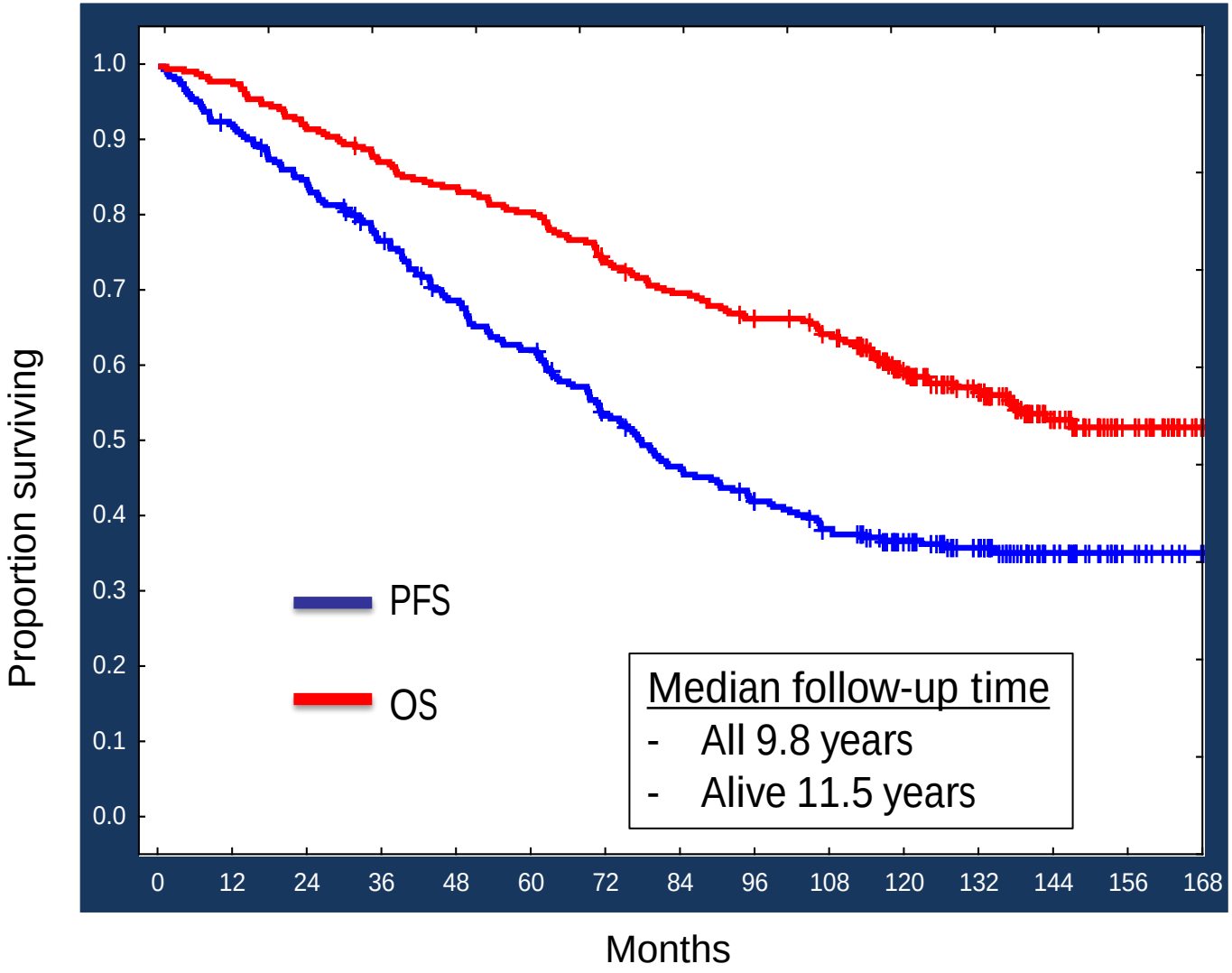
- Front-line therapy
  - Chemoimmunotherapy
  - Targeted therapies
  - (Del17p / TP53 à R/R CLL)

Important signaling pathways in CLL



Adapted from Czabotar PE et al. *Nat Rev Mol Cell Biol*. 2014;15(1):49-63, Ashkenazi A. *Nat Rev Drug Discov*. 2008;7(12):1001-12, and Elmore S. *Toxicol Pathol*. 2007;35(4):495-516.

FCR is the "gold standard"



Wierda WG et al, IWCLL 2013. Abstract 5.21

Chemoimmunotherapy combinations based on fludarabine

	n=	ORR	CR rate	MRD(-)	PFS (median)
FCR (MDACC)[1]	300	95%	72%	-	80 months
FCR (CLL8)[2]	408	90%	44%	35%	52 months
R-FCM[3]	89	90%	77%	47%	60 months
FCR (CLL10 trial)[4]	282	98%	41%	58%	54 months
FCR "Lite"[5]	48	100%	77%	-	70 months

ORR
> 90%

CR
40% - 77%

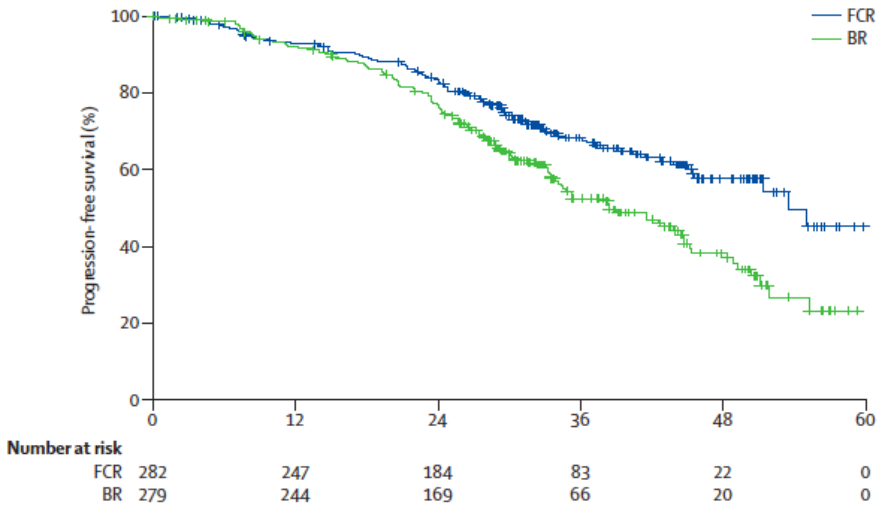
PFS
52 – 80 months

[1]Tam et al, J Clin Oncol 2008; [2]Hallek et al, Lancet 2010; [3]Bosch et al, J Clin Oncol 2009
[4]Eichhorst et al, ASH 2014; [5]Foon et al, J Clin Oncol 2009

CLL10 Study: FCR vs BR in FrontLine

	FCR (%) N=282	BR (%) N=279	P value
ORR	97.8	97.8	1.0
CR (CR+CRi)	40.7	31.5	.034
MRD PB BM	 48.6 26.6	 38.4 11.1	 .024 .001

ITT Progression-free survival = Primary endpoint



Median PFS

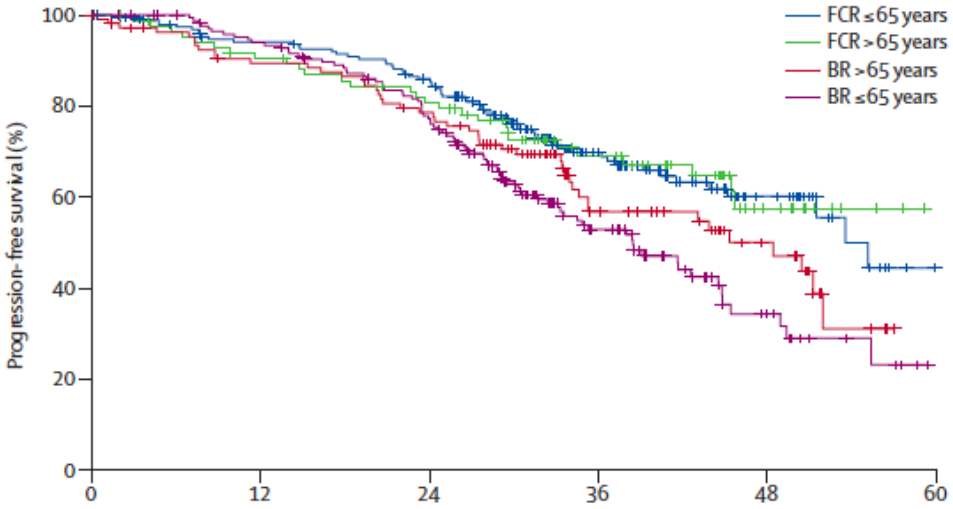
FCR 55.2 months

BR 41.7 months

***P* = 0.0003**
HR = 1.626 =
> 1.388

Eichhorst B. et al, Lancet Oncol 2016

CLL10: PFS by Age group



Adverse event	FCR (% of pt)	BR (% of pt)	p value
All	90.8	78.5	<0.001
Haematological 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

Eichhorst B. et al, Lancet Oncol 2016

Caveats on the treatment with FCR

- Not all the patients respond equaly to FCR

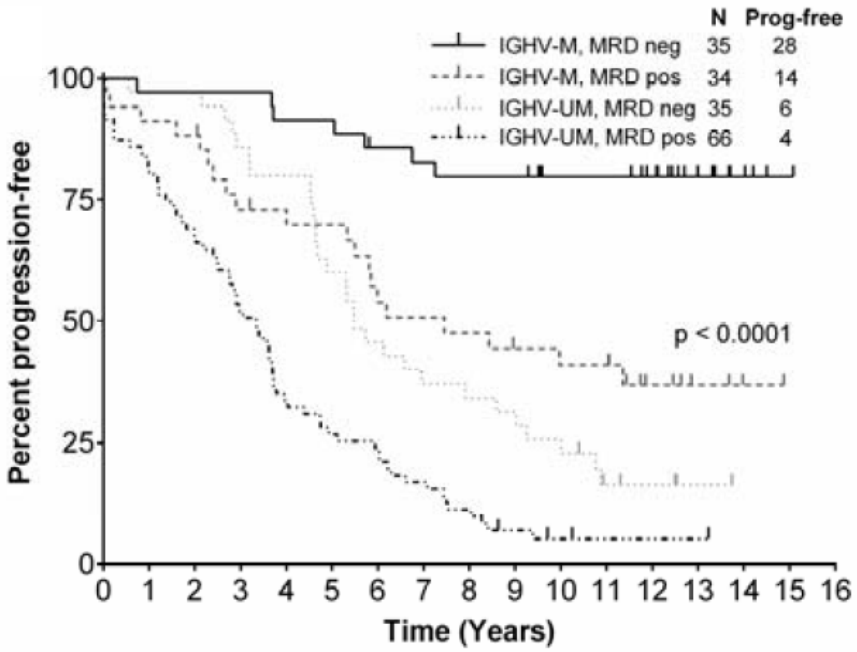
	UM *IgVH*	Del 17p / *TP53* mut	MRD	Del 11q	*SF3B1* mut	*NOTCH1* mut	β2m
ORR		●					●
PFS	●	●	●	●	●	●	●
OS	●	●	●				●

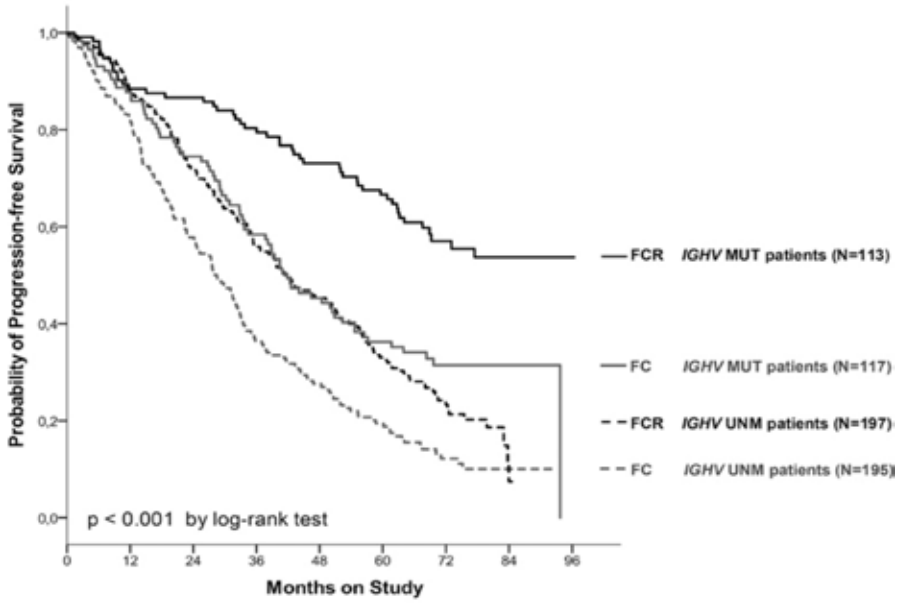
- Not all patients tolerate FCR
  - Hematological toxicity increases with age (and median age is 73 y)

- Clonal selection!

Hallek M et al, Lancet 2010
Stilgenbauer et al, Blood 2014
Bottcher et al, J Clin Oncol 2012
Bosch F et al, JCO 2009
Eichhorst et al, Blood 2009
Tam et al, Blood 2014
Strati P et al, Cancer 2013
Haeusler GM, Eur J Haematol 2013

FCR: long-term follow-up

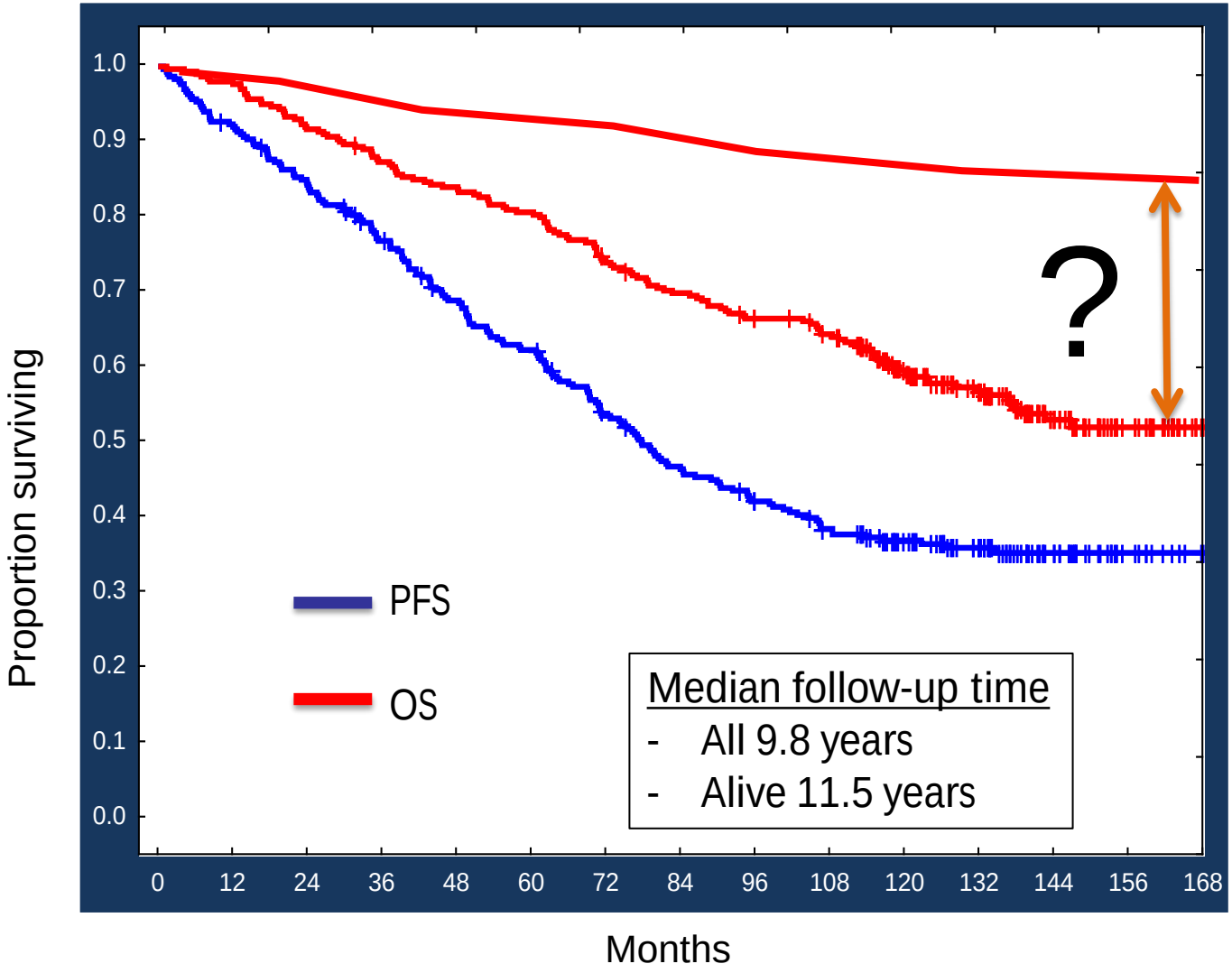




Thompson PA et al, Blood 2015

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

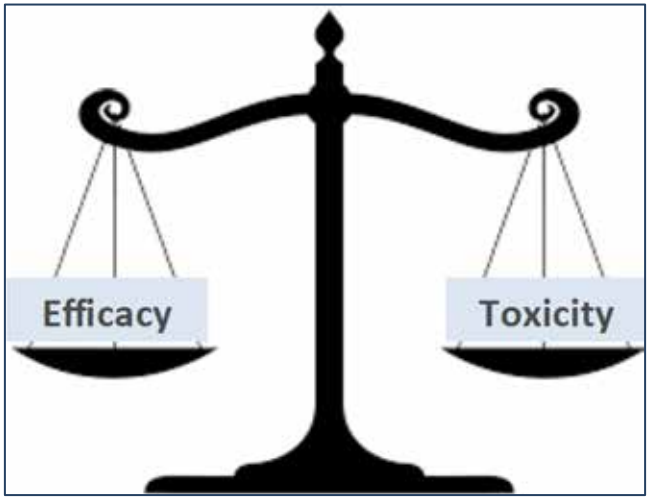
FCR300: long-term follow-up



Wierda WG et al, IWCLL 2013. Abstract 5.21

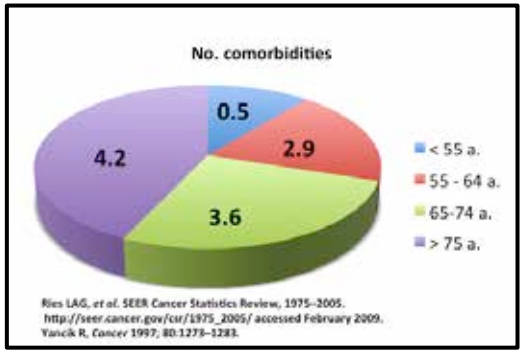
How to improve upon FCR?

PATIENTS' AND DISEASE FEATURES	
FITNESS	**BIOLOGY**
Age Comorbidity Burden / PS Renal function	Del17p / TP53^{mut} Favourable markers (IgHV^{mut}; del13q14)



Comorbidities in front-line trials

Study	MDACC[1,2]	CLL8[3]	CLL10[4]	REACH[5]
Age (median)	57 yrs	61 yrs	61 yrs	62 yrs
CrCl (median)	NR	>70 mL/min	> 70 mL/min	> 70 mL/min
CIRS (median)	NR	1	2	NR
ECOG (median)	1	0	0	0



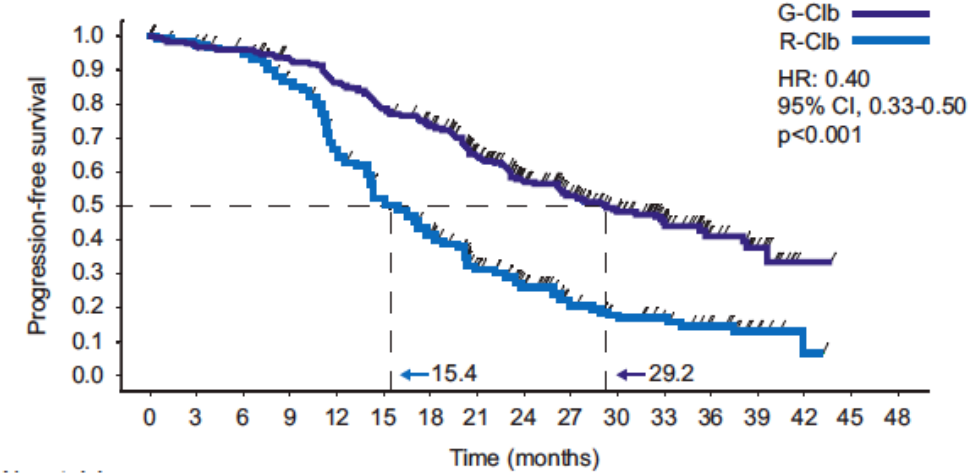
[1]Keating et al., J Clin Oncol 2005
[2]Tam et al., Blood 2008
[3]Hallek et al., Lancet 2010
[4]Eichhorst et al., ASH Annual Meeting 2014
[5]Robak et al., J Clin Oncol 2010

CrCl, creatinine clearance; CIRS, cumulative illness rating scale; ECOG, eastern cooperative oncology group

CLL: Treatment of "unfit" patients

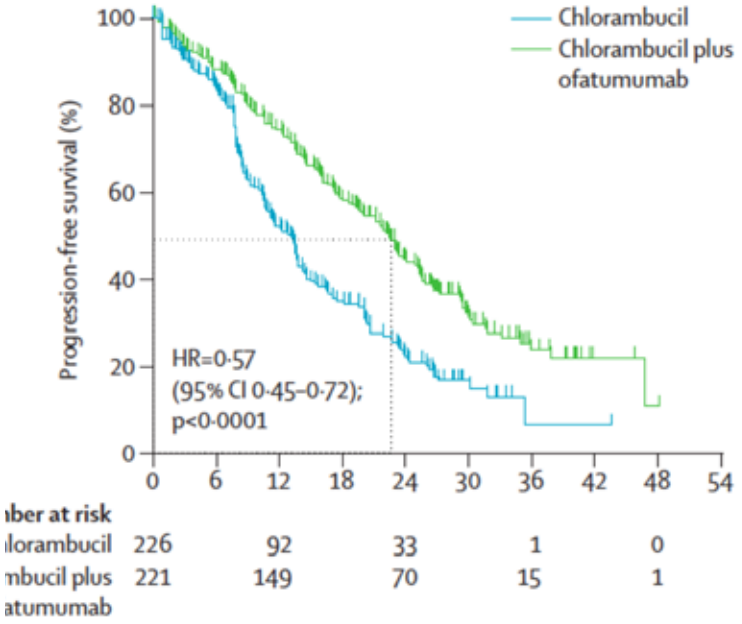
	n=	ORR	CR rate	PFS
[1]GCLL5 (> 65 yrs); *Eichhorst et al, Blood 2009*				
Chlorambucil	193	51%	2%	11 m
Fludarabine	193	72%	20%	18 m*
[3]CLL11* (CIRS > 6, CrCl < 70 mL/min); *Goede et al, NEJM 2014*				
Chlorambucil	118	31%	0%	11 m
Rituximab + Chl	330	66%	5%	17 m*
GA101 + Chl	333	78%	20%	30 m*
[4]COMPLEMENT-1 (not candidates for fludarabine); *Hillmen et al, Lancet 2015*				
Chlorambucil	221	69%	1%	13 m
Ofatumumab + Chl	226	82%	14%*	23 m*
[5]RESONATE 2 (> 65, not candidates for fludarabine); *Burger et al, NEJM 2015*				
Chlorambucil	136	35%	1%	NR
Ibrutinib	133	86%	2%	13 m

CLL: Treatment of "unfit" patients



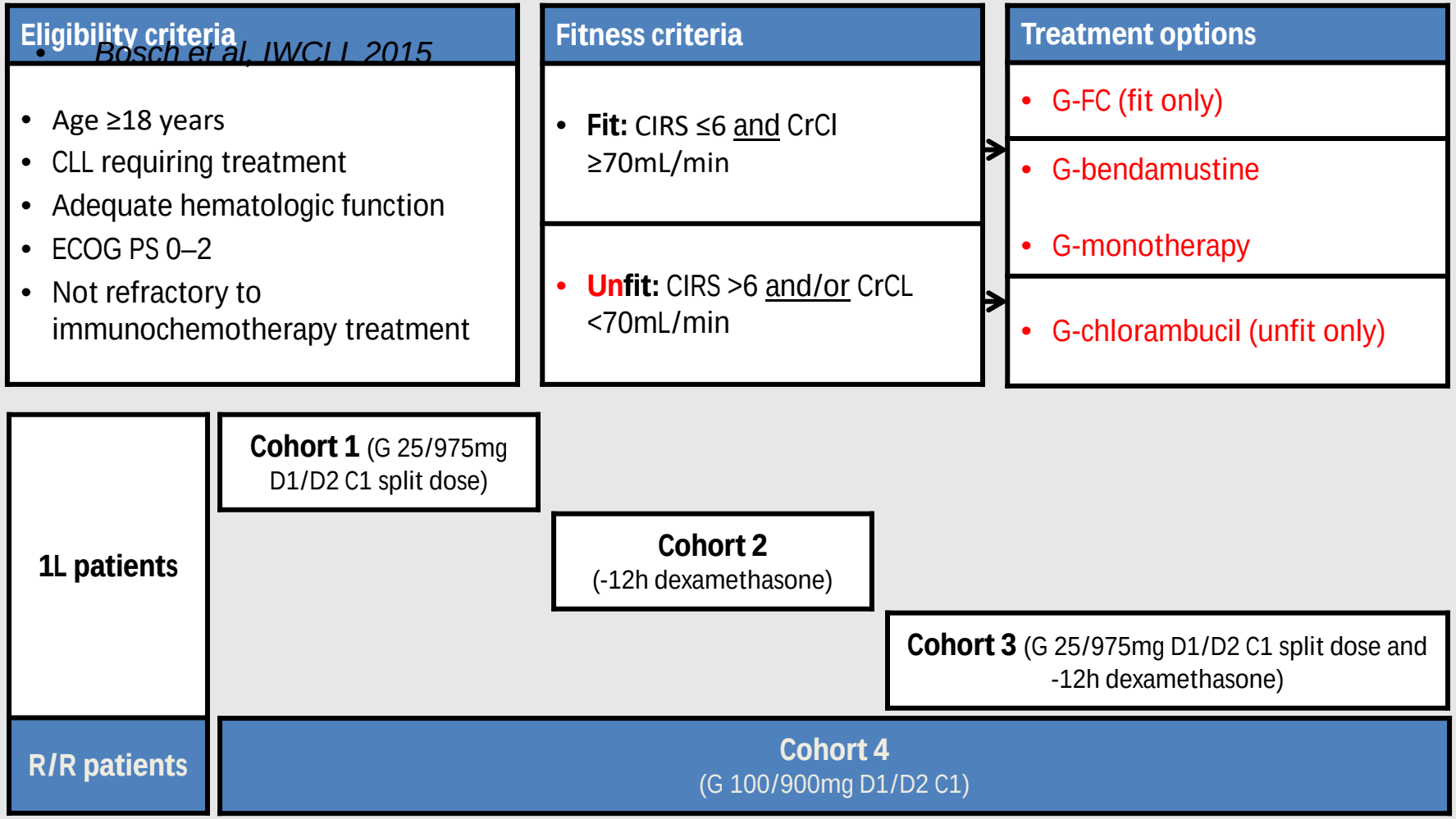
Goede V, et al. N Engl J Med 2014; 370:1101–1110

Goede V et al, Leukemia 2015



Hillmen et al. Lancet 2015; 385: 1873–83

GREEN: ongoing, non-randomized, open-label, single-arm Phase IIIb study



Bosch et al, IWCLL 2015

GREEN: response assessment in fit / non-fit patients

Response, n (%)	*Fit patients*, n=74*	*Non-fit patients†, n=84*
Overall response	60 (**81.1**)	64 (**76.2**)
Complete response‡	22 (**29.7**)	29 (**34.5**)
Partial response	38 (**51.4**)	35 (**41.7**)
Stable disease	8 (**10.8**)	9 (**10.7**)
Progressive disease	0	1 (**1.2**)
Missing	6 (**8.1**)	1 (**11.9**)

*CIRS ≤6 and CrCl ≥70 mL/min; †CIRS >6 and/or CrCL <70mL/min; ‡including CRi (CR with incomplete marrow recovery)

GREEN: MRD-negativity rates

MRD-negativity rate, %

Blood	**ITT analysis***	**58.9%** (93/158)
	Intent-to-ship analysis†	**66.4%** (93/140)
	MRD-evaluable analysis‡	**90.3%** (93/103)
Bone marrow	**ITT analysis***	**28.5%** (45/158)
	MRD-evaluable analysis‡	**70.3%** (45/64)

*all patients at all sites

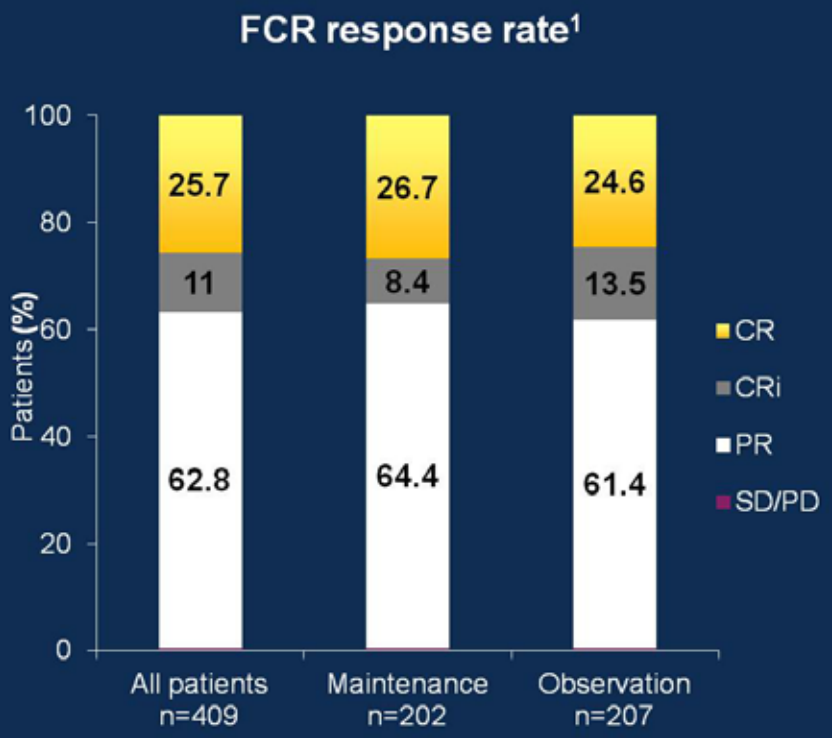
†all patients at sites that could perform timely shipment of samples to allow delivery to the central laboratory in Kiel, Germany within 48 hours of being taken (sites unable to ship with 48 hours included those in Brazil, Canada, Korea, Mexico and Thailand)

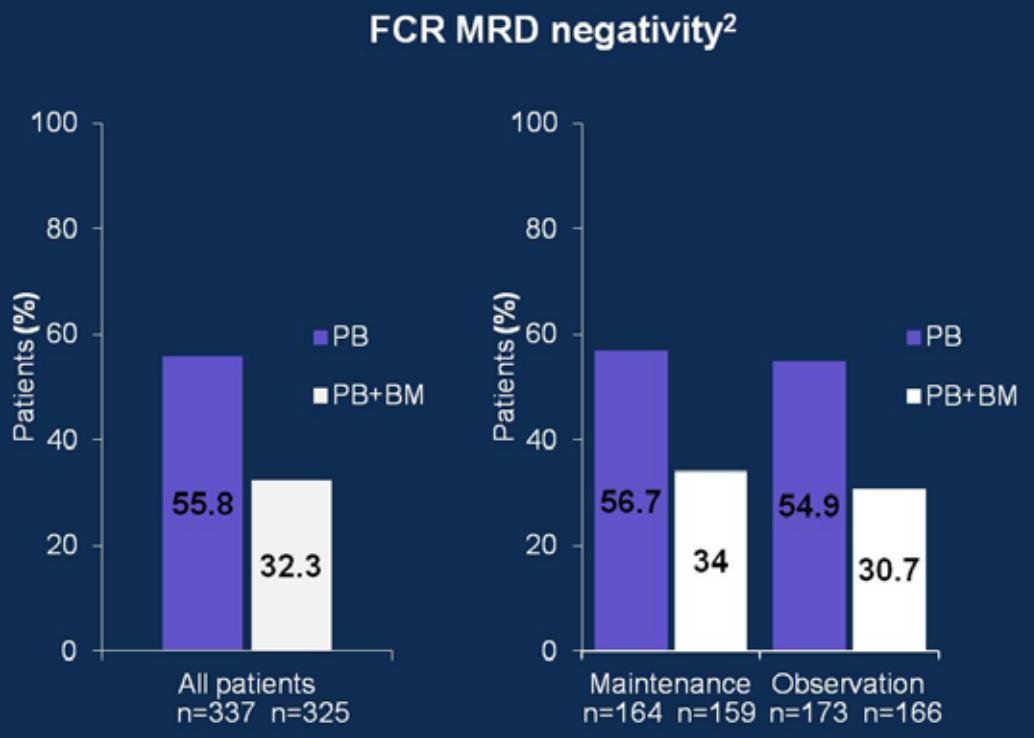
‡as above, but including only those patients with evaluable blood or bone marrow samples at the end-of-treatment assessment

Study design - CLL 2007 SA

[1] Recovery from FCR toxicities

Patient characteristics - CLL 2007 SA

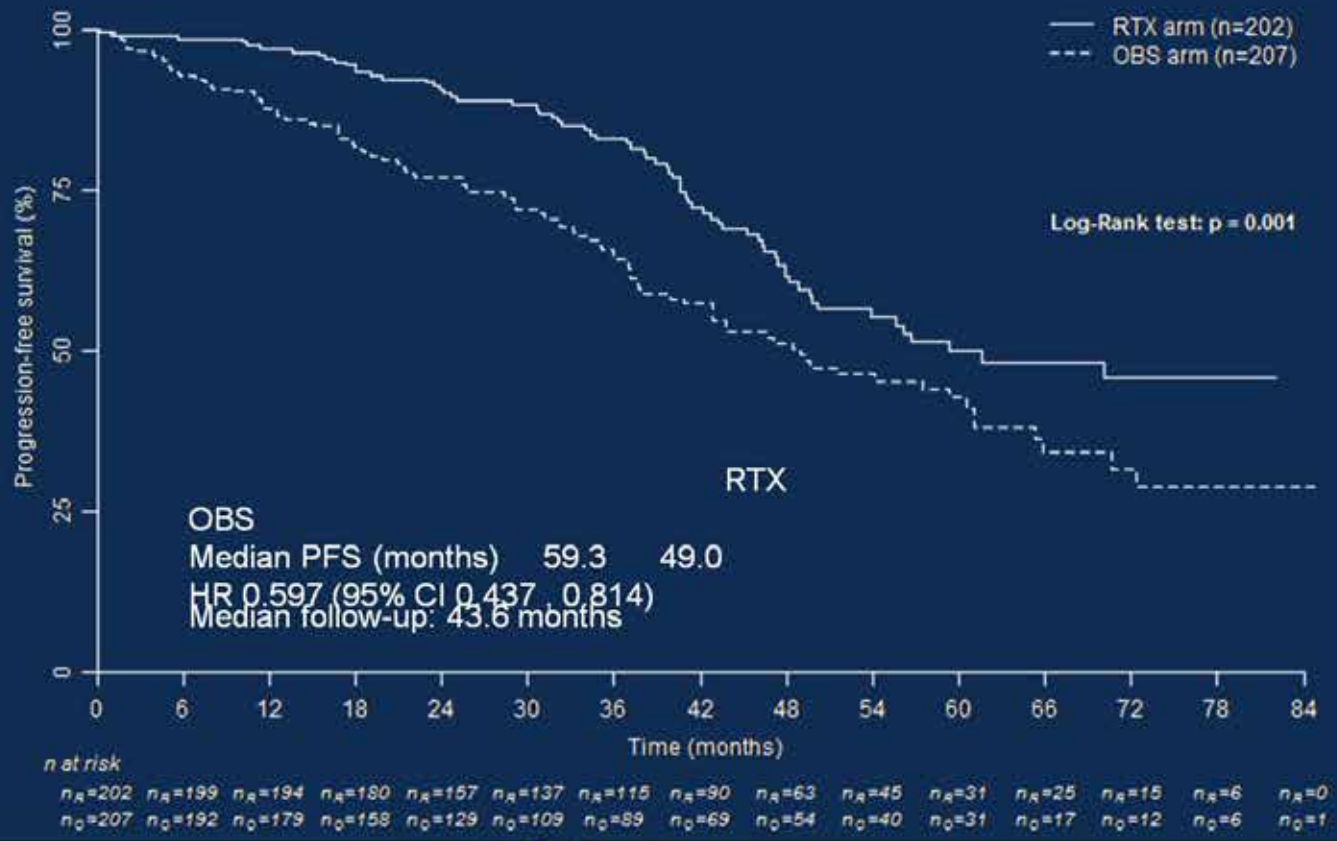




[1]Centralized review according to iwCLL 08
[2]6-color FC assay, limit of detection 0.7×10^{-5}

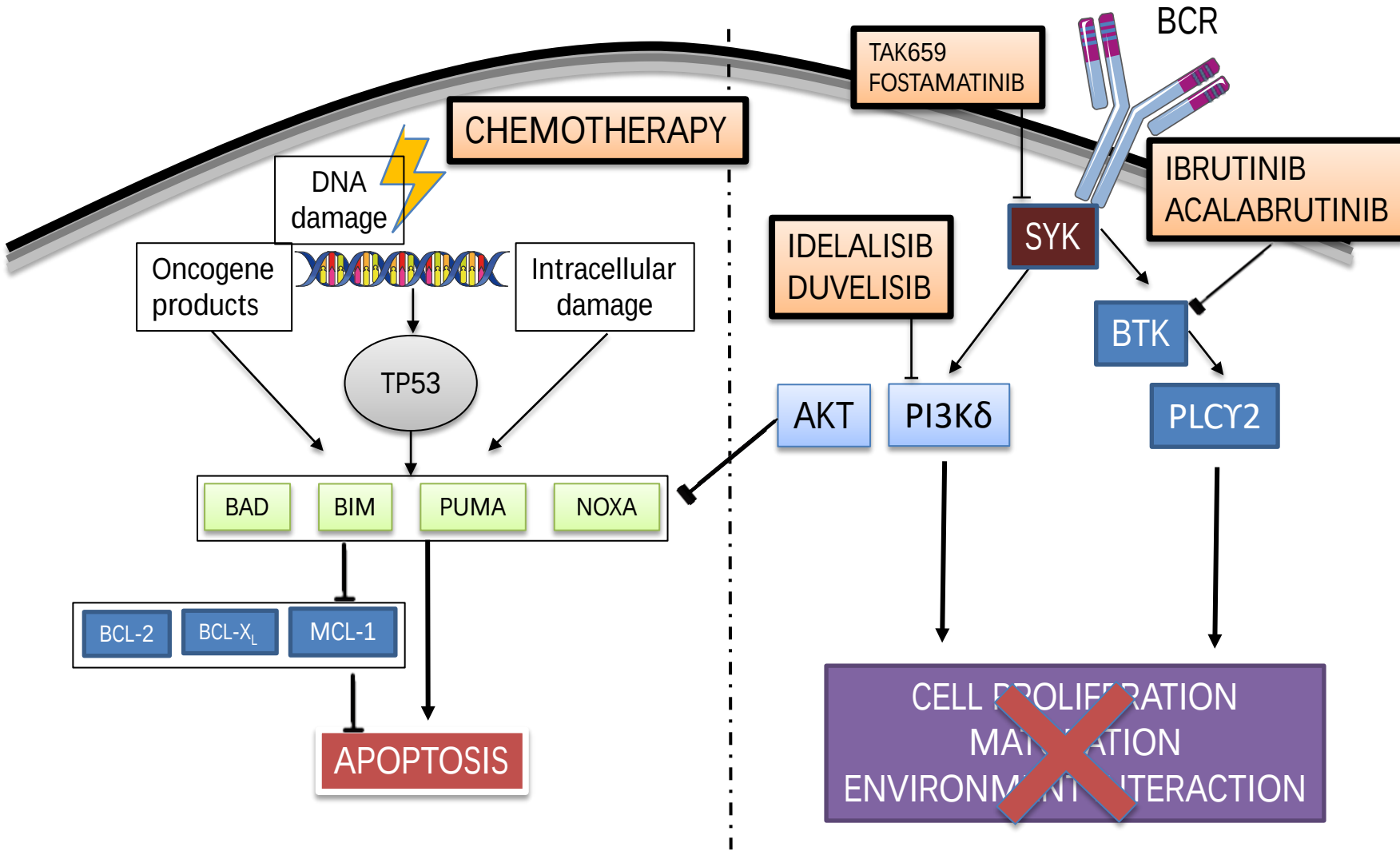
Presented By Caroline Dartigeas at 2016 ASCO Annual Meeting

Progression-free survival - CLL 2007 SA



Presented By Caroline Dartigeas at 2016 ASCO Annual Meeting

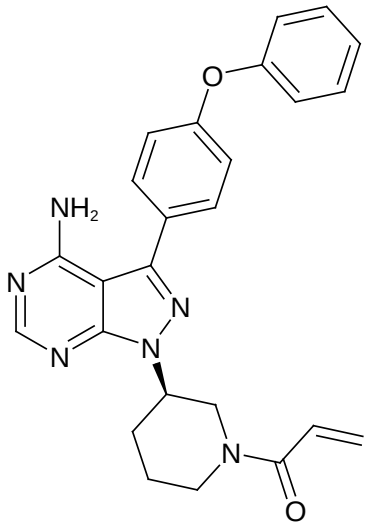
Important signaling pathways in CLL



Adapted from Czabotar PE et al. *Nat Rev Mol Cell Biol*. 2014;15(1):49-63, Ashkenazi A. *Nat Rev Drug Discov*. 2008;7(12):1001-12, and Elmore S. *Toxicol Pathol*. 2007;35(4):495-516.

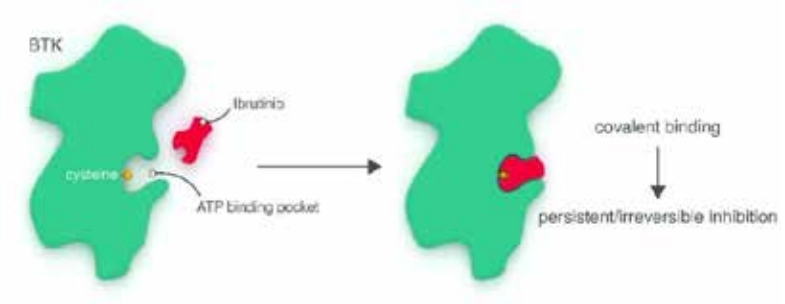
Ibrutinib (PCI-32765)
A Selective Inhibitor of BTK

Colonel Ogden Bruton (*1908, †2003)
Chief of Pediatrics at the
Walter Reed Army Hospital



- Forms a specific bond with cysteine-481 in BTK
- Highly potent BTK inhibition at IC_{50} = 0.5 nM
- Orally administered with once daily dosing resulting in 24-hr target inhibition
- No cytotoxic effect on T-cells or natural killer (NK)-cells
- In chronic lymphocytic leukemia (CLL) cells promotes apoptosis and inhibits CLL cell migration and adhesion

Summary of biological and clinical effects of Ibrutinib



BCR ACTIVATION

Increases proliferation
↑ Survival Signals

Microenvironment interaction
↑ Union CXCL12-CXCR4
T-cell interaction

BTK INHIBITION

Acute Cell Death

Exit from Proliferation Centers

CLINICAL EFFECTS

↓ TUMOR BURDEN

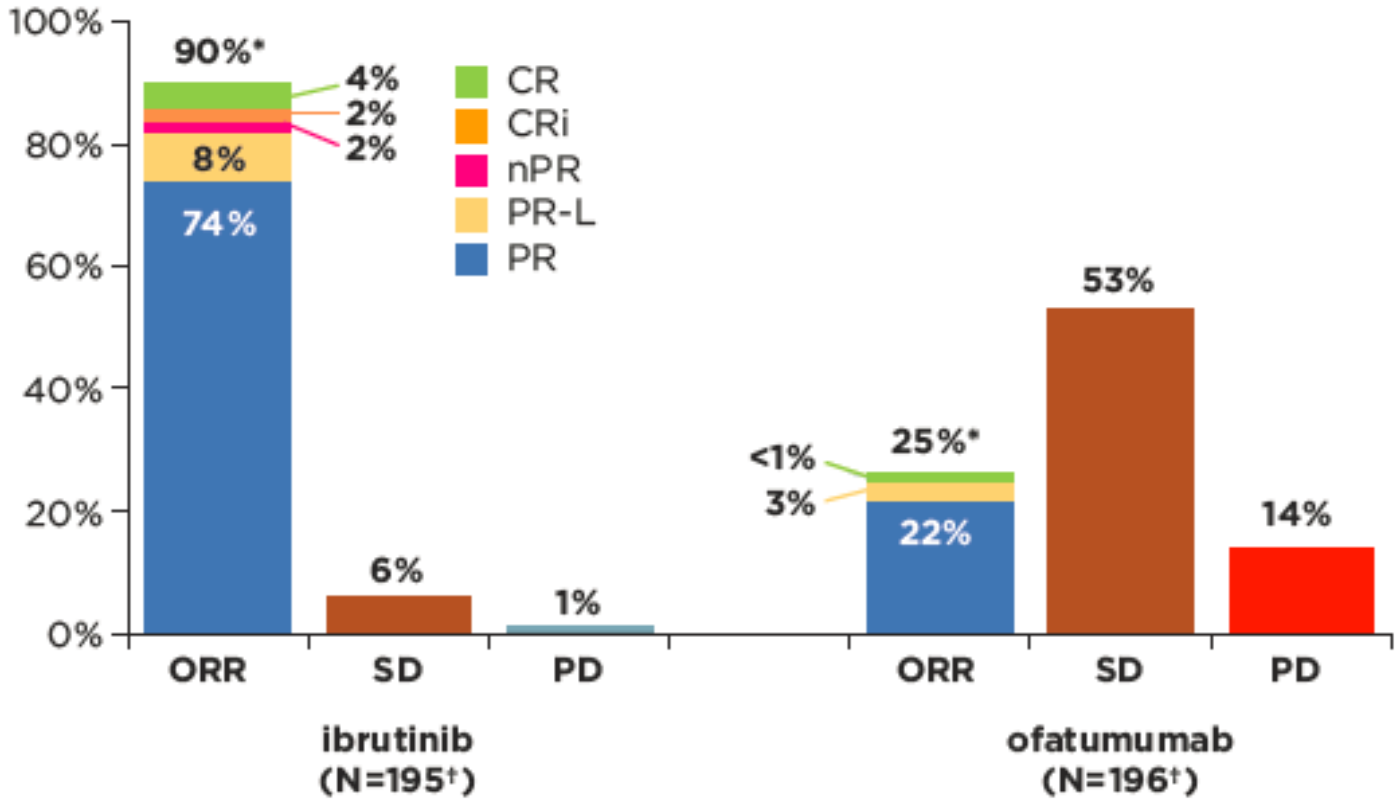
Lymphocytosis

↓ Lymph nodes

Long-term apoptossis

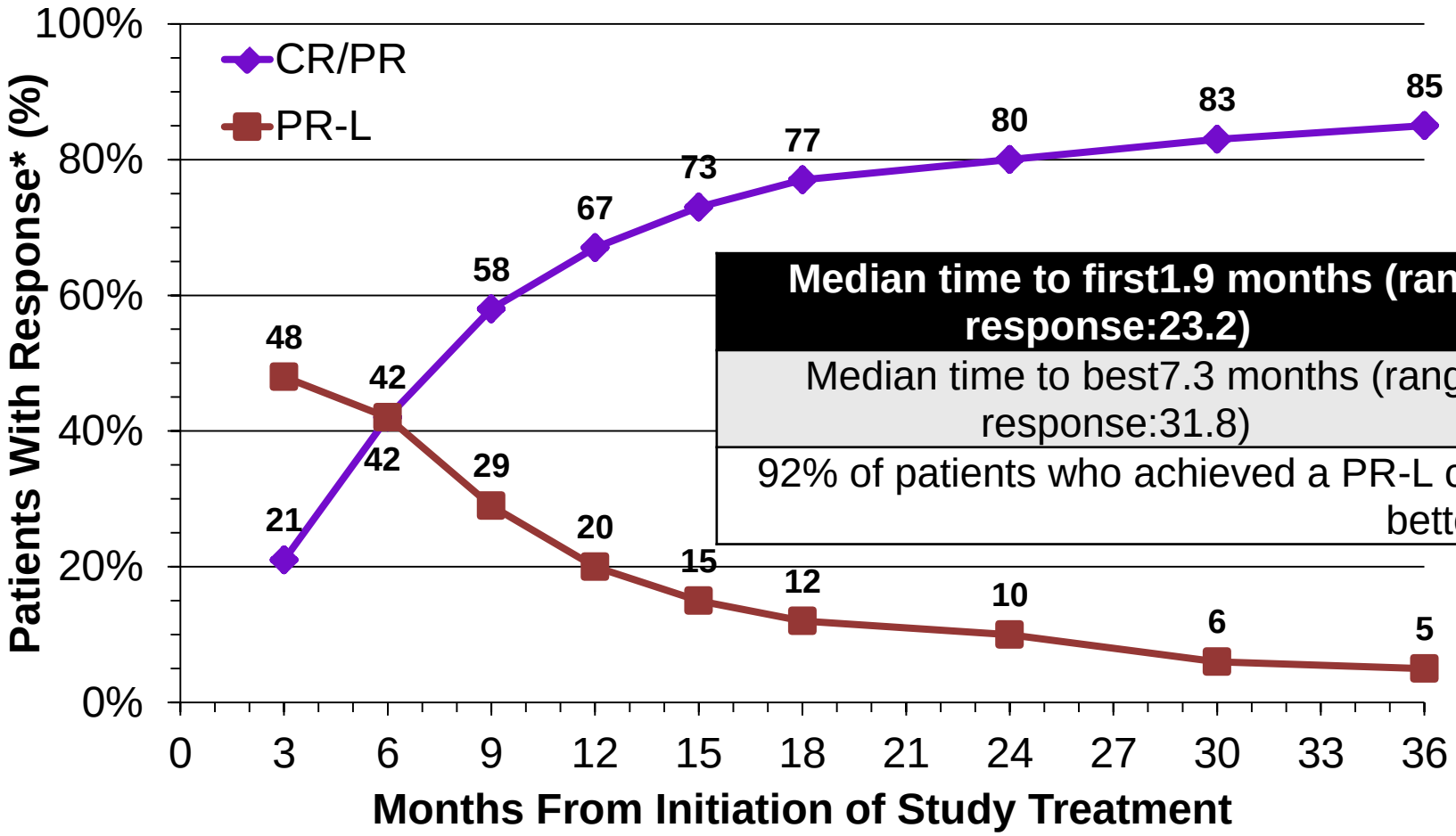
Brown et al. RESONATE (PCYC-1112) UPDATE IWCLL 2015

BEST RESPONSE



ORR = CR + CRi + nPR + PR-L + PR.
**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).*

Response Over Time



Median time to first1.9 months (range, 1.4–response:23.2)

Median time to best7.3 months (range, 1.7–response:31.8)

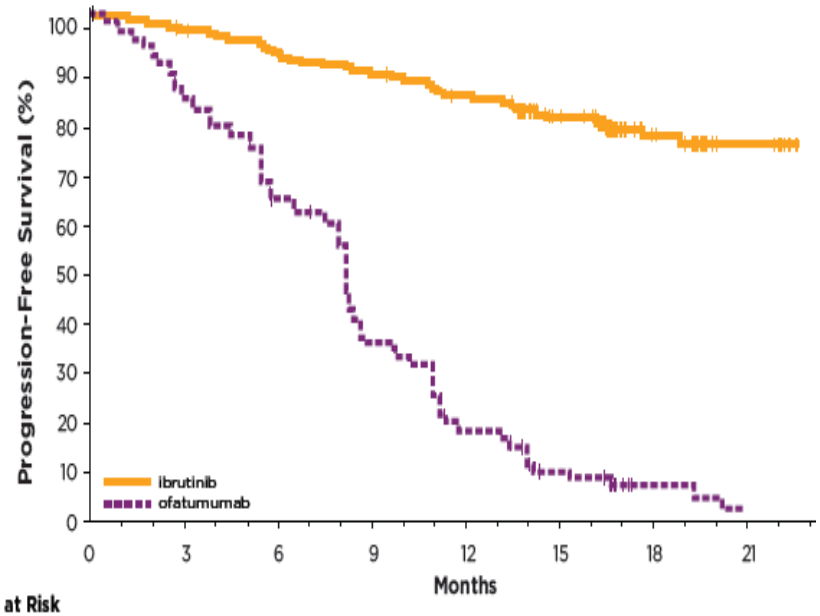
92% of patients who achieved a PR-L converted to better response

Best response to ibrutinib improves over time

*Cumulative response as assessed by investigator

RESONATE (PCYC-1112)
Update at 19 months- IwCLL

PFS

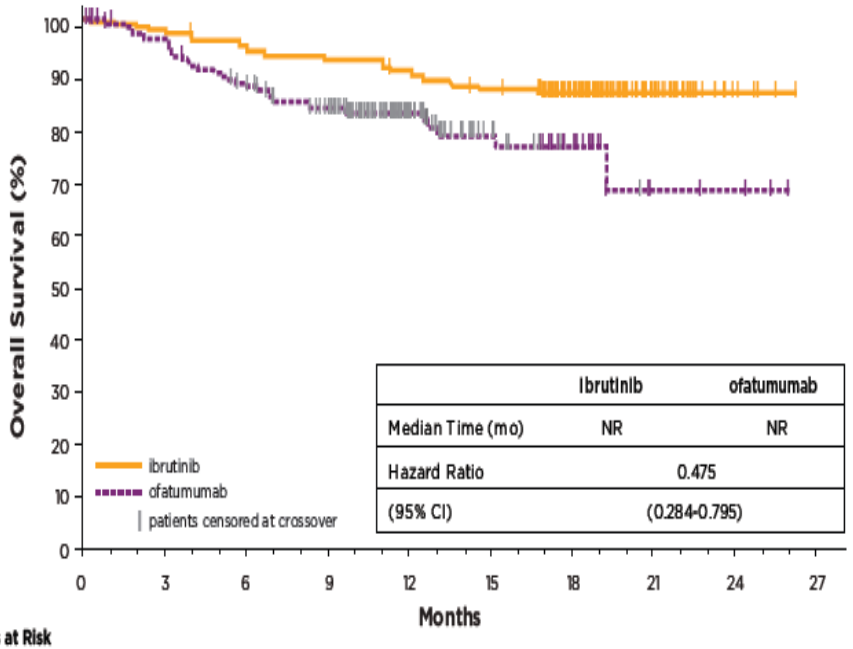


Patients at Risk

ibrutinib:	195	187	177	169	158	126	44	14
ofatumumab:	196	158	115	63	31	14	3	

	ibrutinib	ofatumumab
Median Time (mo)	NR	8.1
Hazard Ratio	0.106	
(95% CI)	(0.075-0.151)	
P-value	<0.0001	

OS



	Ibrutinib	ofatumumab
Median Time (mo)	NR	NR
Hazard Ratio	0.475	
(95% CI)	(0.284-0.795)	

Patients at Risk

ibrutinib	195	191	183	179	174	166	116	40	6
ofatumumab	196	183	163	137	75	37	19	4	3

	R/R	R/R del.(17p)
PFS 30 mos, % (IC 95%)	69 (58-78)	48 (29-65)
Median PFS, months (IC 95%)	NA (32,9-NA)	28,1 (18,2-NA)

Pagel et al. iwCLL 2015; 146 (Poster Presentation)

RESONATE™-2 (PCYC-1115) Study Design

Patients (N=269)

- Treatment-naïve CLL/SLL with active disease
- Age ≥65 years
- For patients 65-69 years, comorbidity that may preclude FCR
- del17p excluded
- Warfarin use excluded

RANDOMIZE 1:1

ibrutinib 420 mg once daily until PD or unacceptable toxicity

chlorambucil 0.5 mg/kg (to maximum 0.8 mg/kg) days 1 and 15 of 28-day cycle up to 12 cycles

IRC-confirmed progression

PCYC-1116 Extension Study*

In clb arm, n=43 crossed over to ibrutinib

*Patients with IRC-confirmed PD enrolled into extension Study 1116 for follow-up and second-line treatment per investigator's choice (including ibrutinib for patients progressing on chlorambucil with iwCLL indication for treatment).

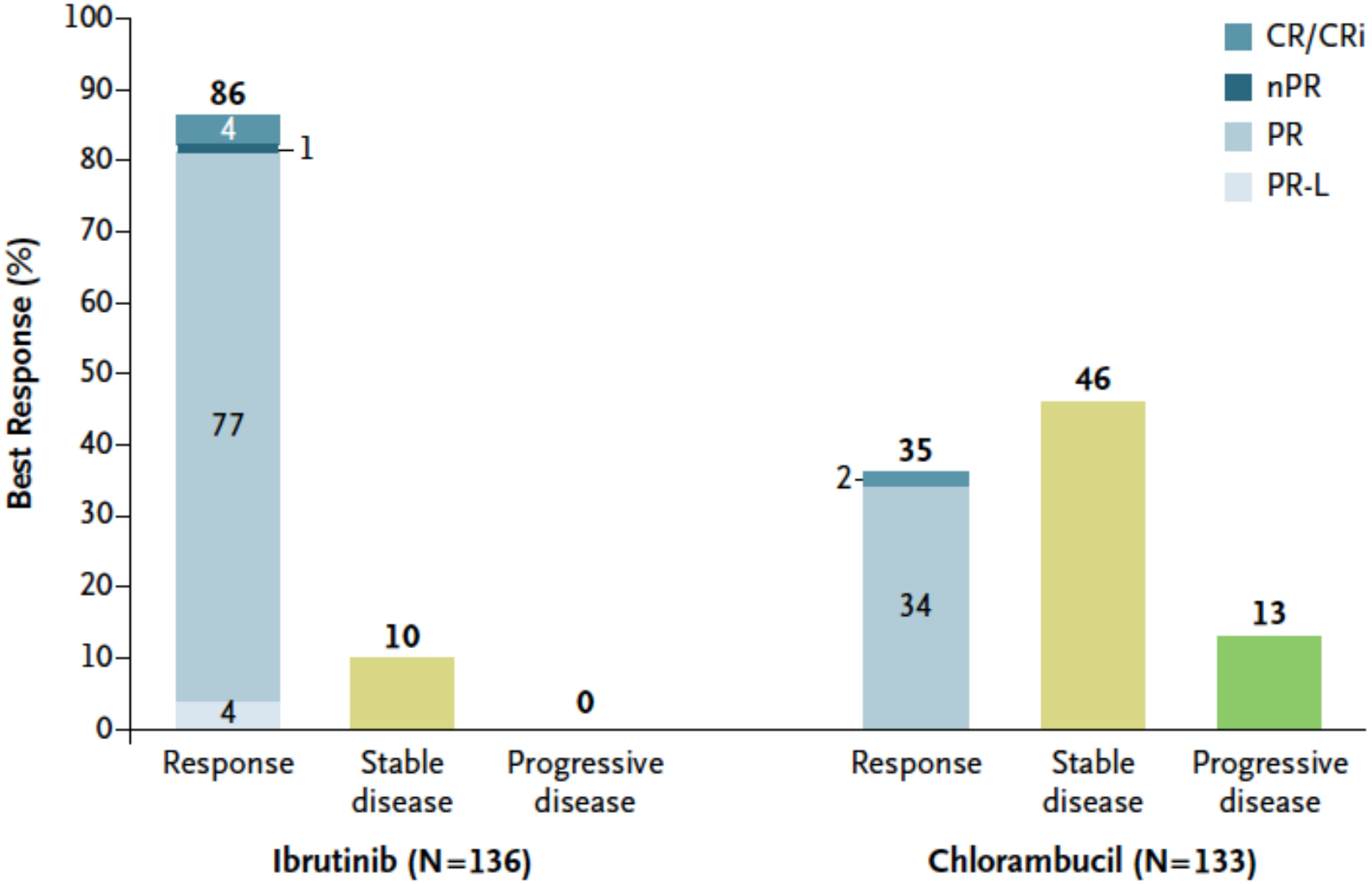
Stratification factors

- ECOG status (0-1 vs. 2)
- Rai stage (III-IV vs. ≤II)

- Phase 3, open-label, multicenter, international study
- **Primary endpoint**: PFS as evaluated by IRC (2008 iwCLL criteria)[1,2]
- **Secondary endpoints**: OS, ORR, hematologic improvement, safety

1. Hallek et al. *Blood*. 2008;111:5446-5456; 2. Hallek et al, *Blood.* 2012; e-letter, June 04, 2012.

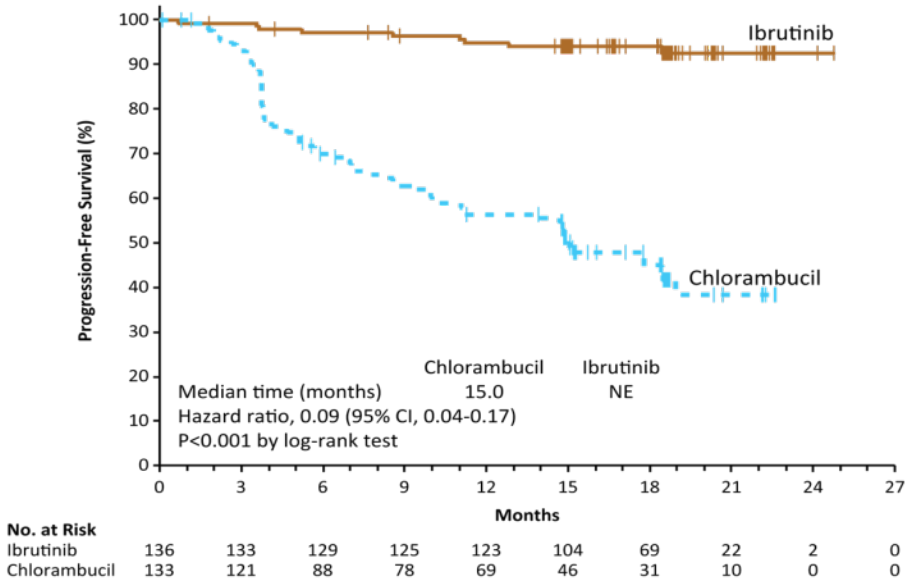
Resonate2: responses by Arm



Tedeschi et al., ASH 2015 (abstract 495, oral presentation)
Burger J. et al NEJM 2015

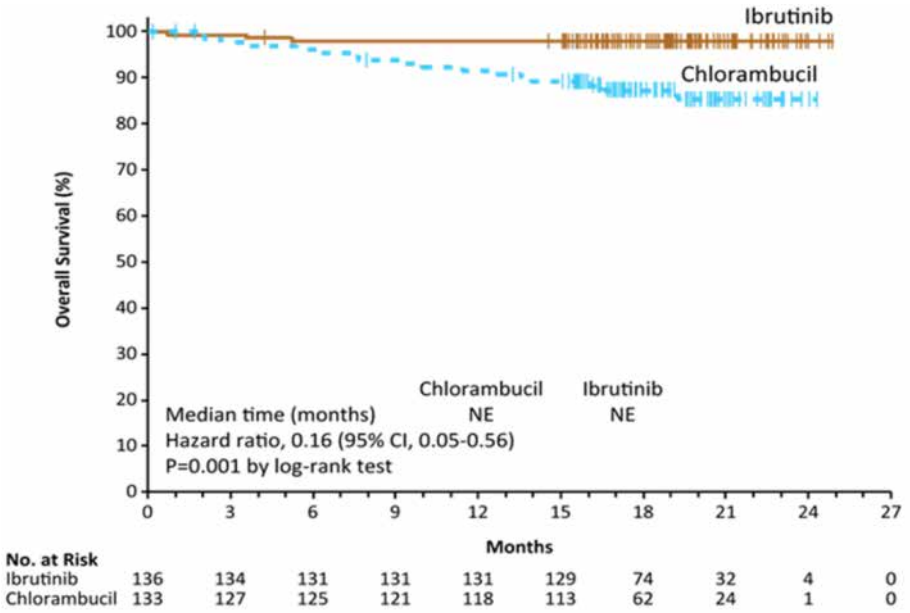
Resonate-2: PFS & OS

Progression Free Survival



SLP 18 m: 90% vs. 52%

Overall Survival

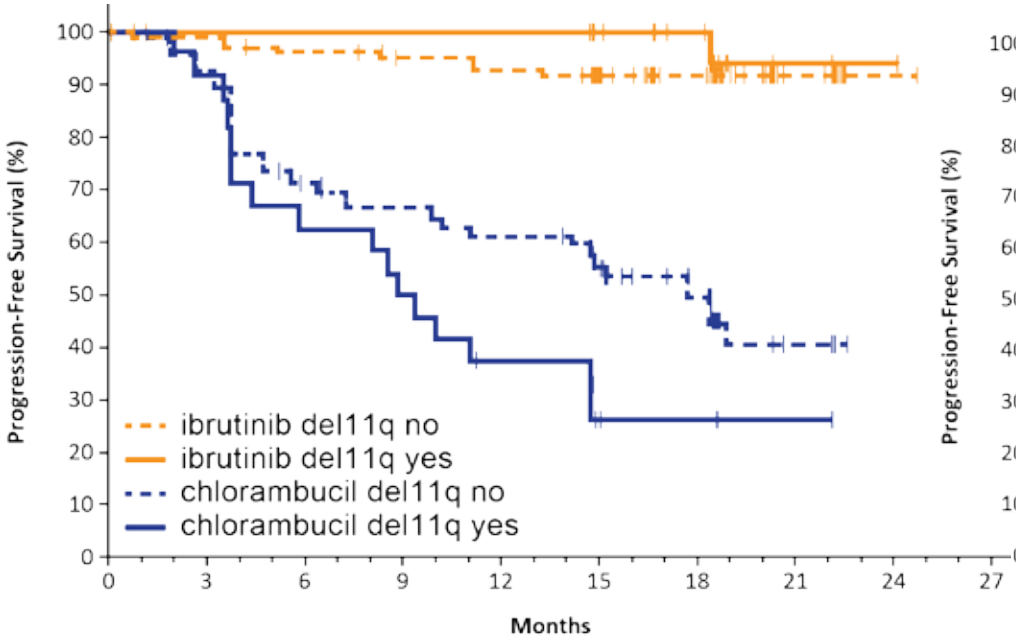


SG 24 m: 98% vs. 85% *

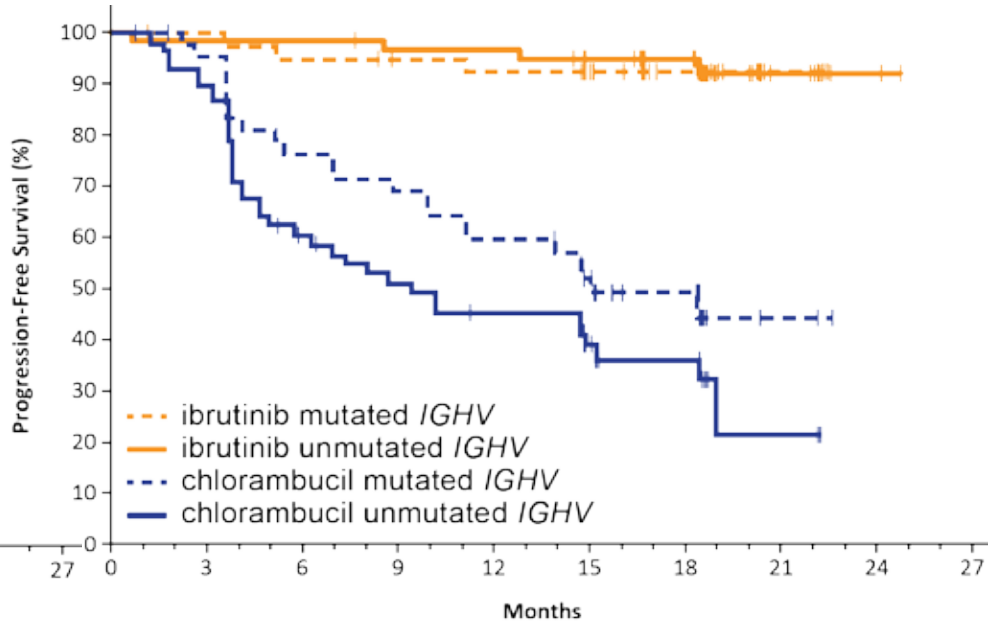
Tedeschi et al., ASH 2015 (abstract 495, oral presentation)
Burger J. et al NEJM 2015

PFS by Investigator for High-Risk Subgroups

PFS by del11q status



PFS by *IGHV* mutation status

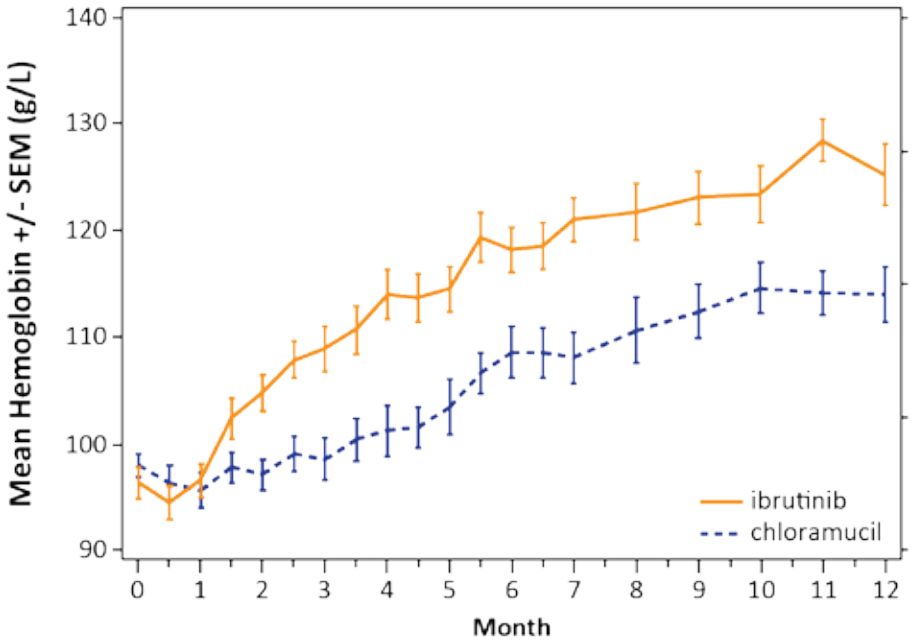


- Median PFS in del11q subgroup: NR with ibrutinib vs. 9 months with chlorambucil (HR=0.02, *P*<0.0001)
- Median PFS in unmutated *IGHV* subgroup: NR with ibrutinib vs. 9 months with chlorambucil (HR=0.06, *P*<0.0001)
- Ibrutinib: 18-month PFS 92% in *IGHV* mutated, 95% in unmutated subgroup

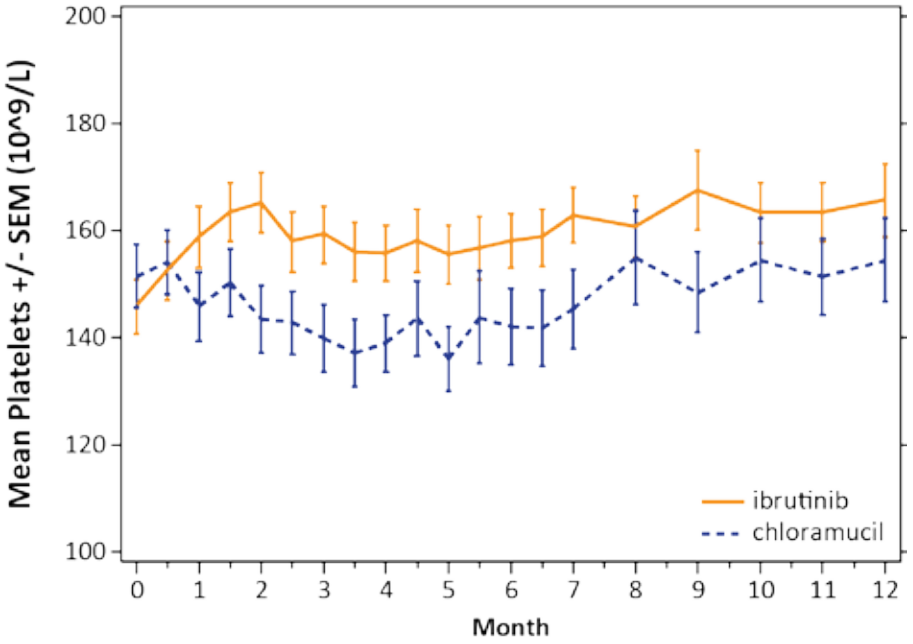
Burger JA et al., NEJM 373(25):2425-37, 2015

Improvement in Hematologic Function

Hemoglobin Over Time

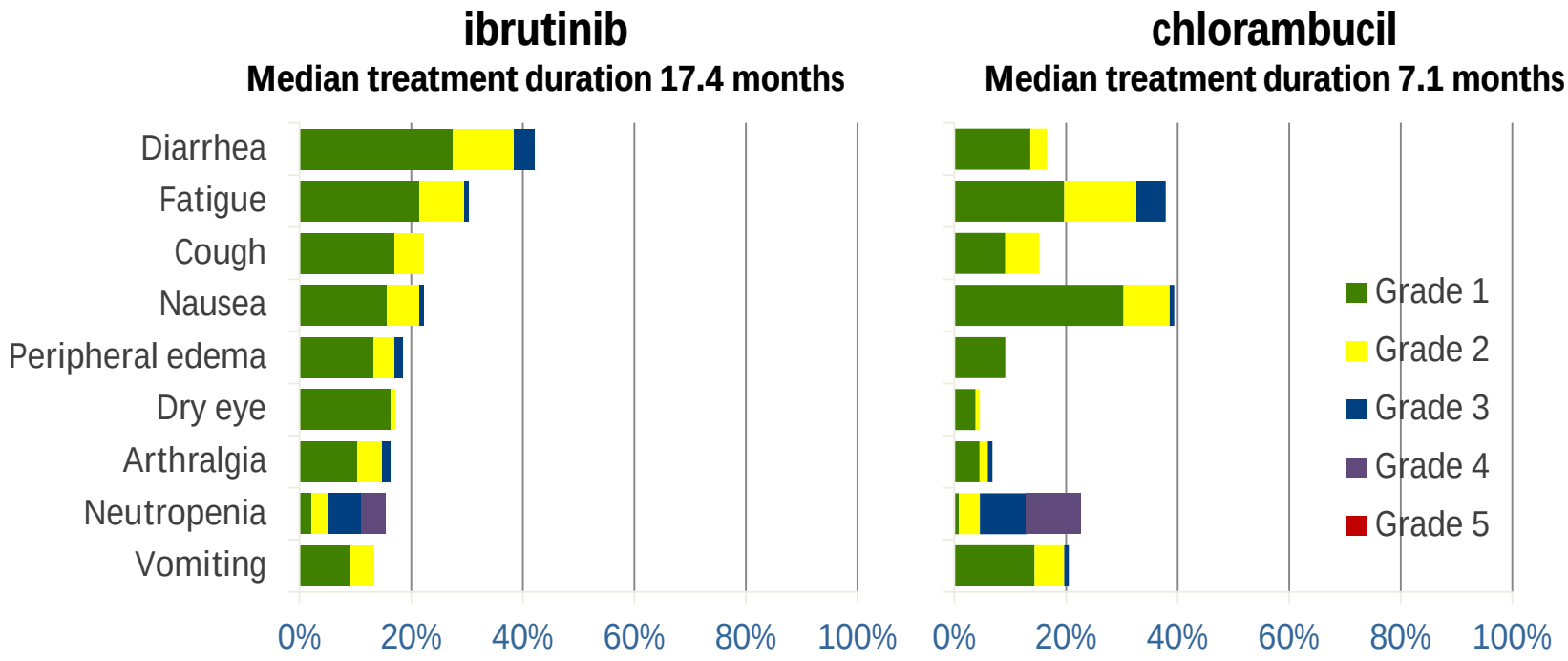


Platelet Count Over Time



- Sustained improvement in hemoglobin in patients with anemia:
  84% with ibrutinib vs. 45% with chlorambucil (*P*<0.0001)
- Sustained improvement in platelet count in patients with thrombocytopenia:
  77% with ibrutinib vs. 43% with chlorambucil (*P*=0.0054)

Most Common Adverse Events*



*Adverse event that occurred in ≥15% of patients in either treatment arm, and that were imbalanced between treatment arms by a difference in frequency of ≥5%.

- Majority of the common AEs on ibrutinib arm were grade 1 and did not result in treatment discontinuation
- On the chlorambucil arm, fatigue, nausea, vomiting, and cytopenias occurred more frequently vs. ibrutinib
- Grade 3 maculopapular rash (no grade 4) in 3% for ibrutinib vs. 2% for chlorambucil

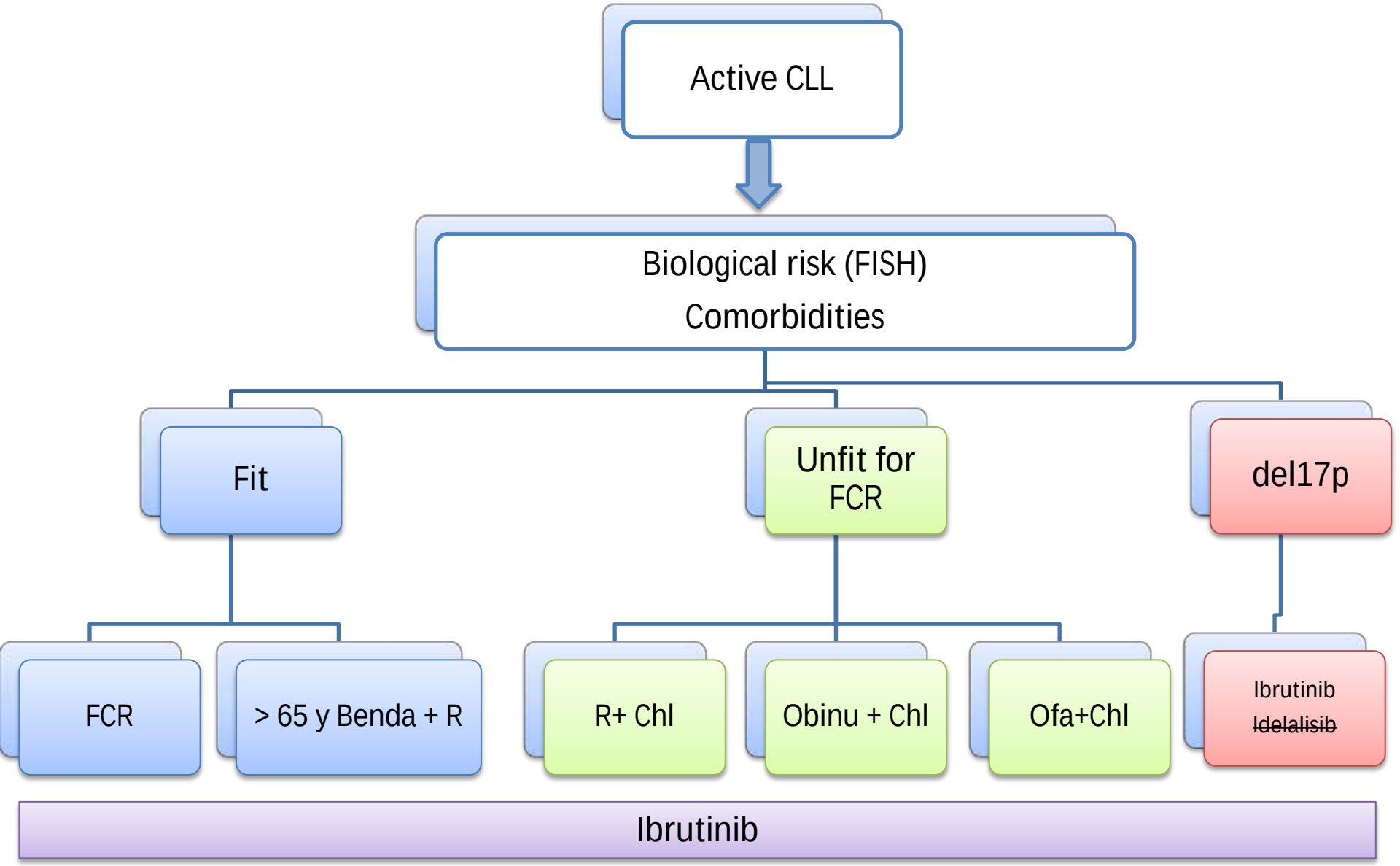
Additional Safety Results

	ibrutinib (n = 135)			chlorambucil (n = 132)		
Median exposure, months (range)	17.4 (0.7-24.7)			7.1 (0.5-11.7)		
Adverse event	**Any**	**G3**	**G4**	**Any**	**G3**	**G4**
Hypertension	14%	4%	0	0	0	0
Atrial fibrillation	6%	1%	0	1%	0	0
Major hemorrhage	4%	3%	1%	2%	2%	0

- On ibrutinib arm
  - The 6 patients (4%) with grade 3 hypertension were managed with anti-hypertensive medication and did not require dose modification of ibrutinib
    - 4 of 6 patients: history of hypertension
  - Among 8 patients (6%) with atrial fibrillation, 2 discontinued ibrutinib
    - 7 of 8 patients: history of hypertension, CAD, and/or myocardial ischemia
  - Among 6 patients (4%) with major bleeding, 3 discontinued ibrutinib
    - 3 of 6 patients: concomitant LMWH, aspirin, or vitamin E at time of event

Overall, 19% of patients on the ibrutinib arm received anticoagulants and 47% received antiplatelet agents

Front-line therapy for CLL: 2016 algorithm



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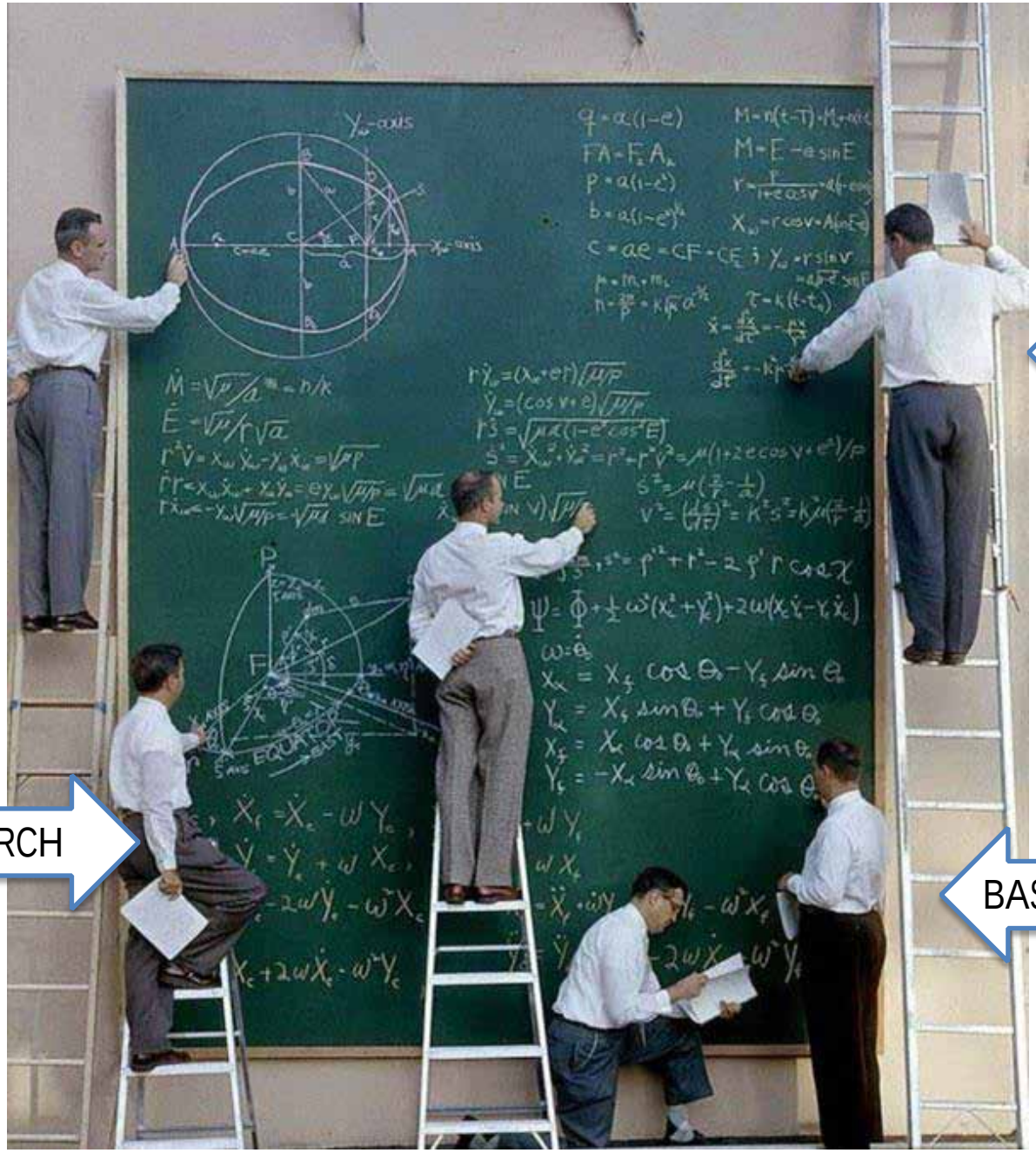

CLINICIANS

INDUSTRY

CLINICAL RESEARCH

BASIC SCIENTISTS

It's fine to discover cures, but remember, chronic conditions are our bread and butter