Manejo del paciente en recaída

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Workshop Leucemia Linfática Crónica
Sociedad Chilena de Hematología
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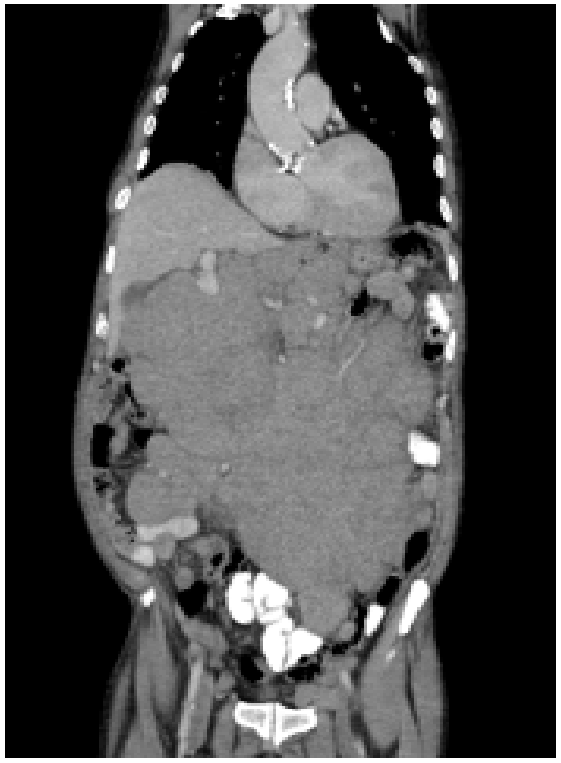
Outline

- Relapsed CLL
  - after chemoimmunotherapy
  - With TP53 abnormalities

RELAPSED AFTER FCR/BR

Case 1: Young, fit

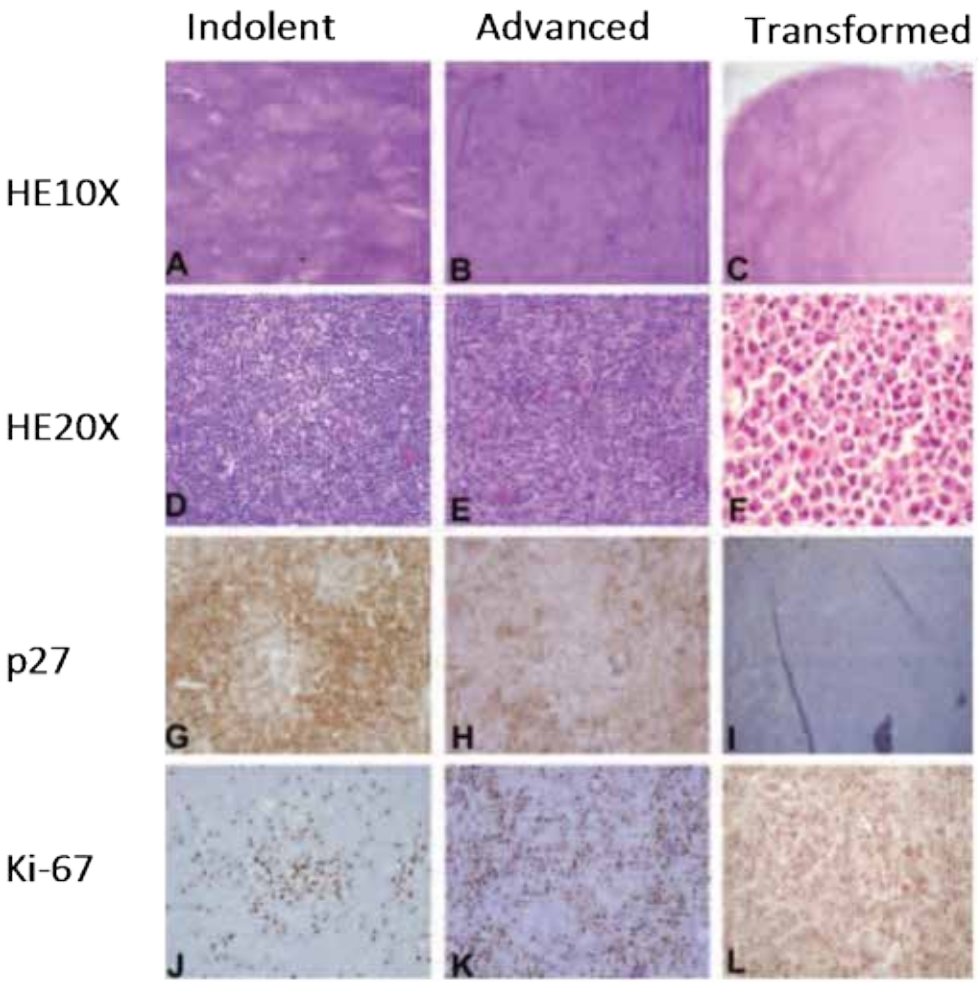
- 56 y.o. male, no comorbidities
- 2011 à Diagnosis of CLL, stage A(I), ZAP-70+. UM IgHV
- 2013 à Stage B(II); FISH: del11q à FCR x 6 cycles à CR, MRD+
- 2016 à Relapse: Abdominal mass, LDH: 570 IU/L (NV < 450), FISH: del11q23 (TP53 wt)



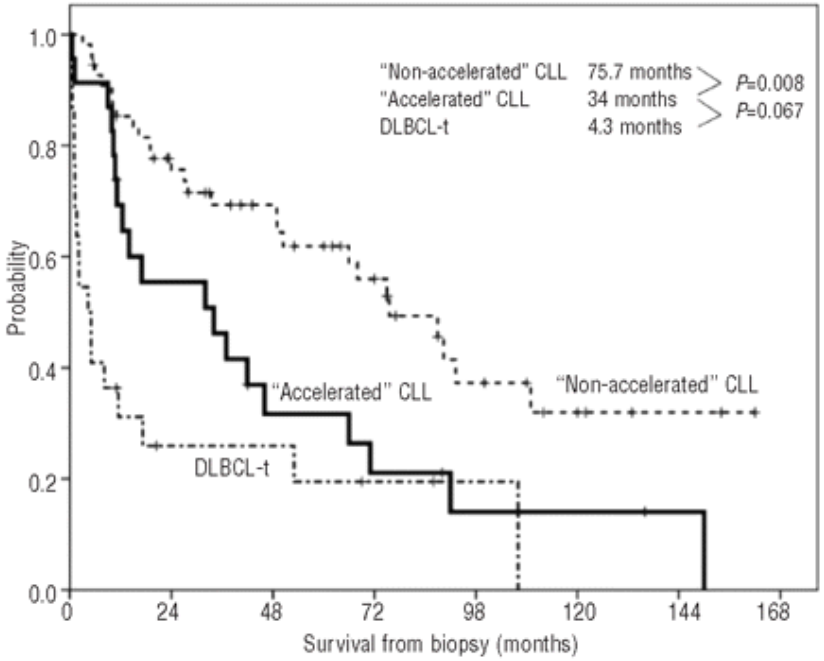
What is your recommendation?

1. Watch & Wait
2. Repeat FCR
3. Bendamustine + rituximab
4. Ibrutinib
5. Idelalisib + rituximab
6. Lymph-node biopsy

“Accelerated CLL”: cell proliferation as prognostic marker



Giné et al, Haematologica, 2010

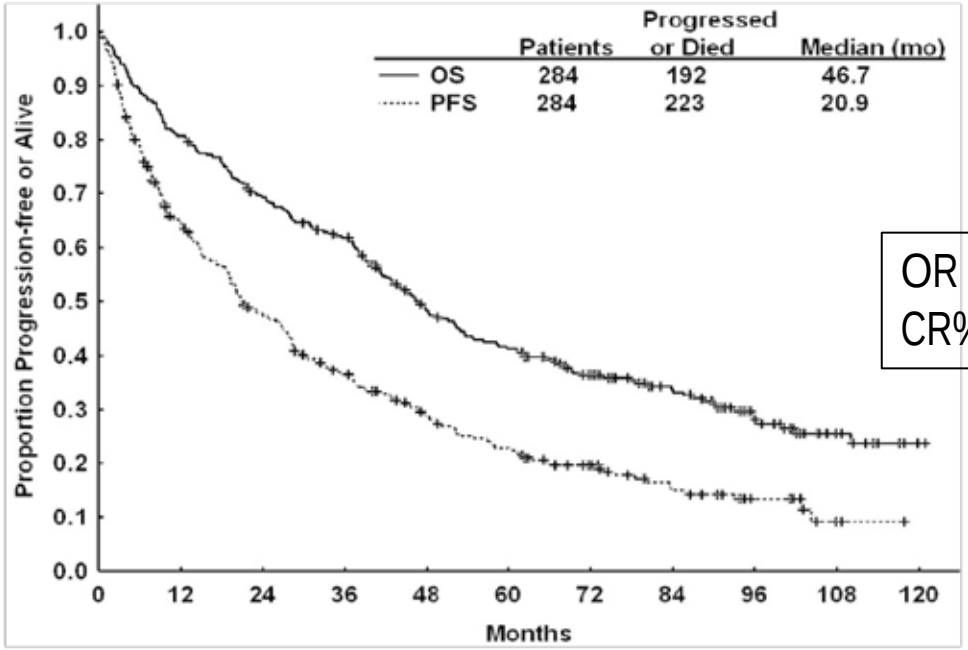


Giné et al, Haematologica, 2010

How would you treat this patient?

1. Watch & Wait
2. Repeat FCR
3. Bendamustine + rituximab
4. Ibrutinib
5. Idelalisib + rituximab
6. Venetoclax

Survival in previously treated CLL from salvage treatment



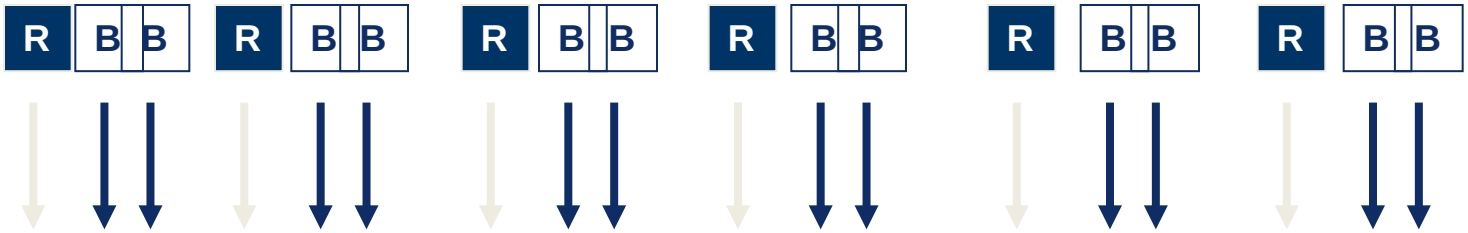
OR %	74
CR%	30

	OR %	CR %	Median PFS months	Median OS months
All	74	30	21	46.5
Abnormal 17p	35	0	5	10.5
Fludarabine refractory	56	7	8	38
>70 years	68	13	13	22

Badoux et al. Blood. 2011;117(11):3016-3024

Bendamustine + Rituximab

Treatment schedule



Day 0 1+2 28, 28+29 57; 57+58 85; 85+86 113; 113+114 141; 141+142

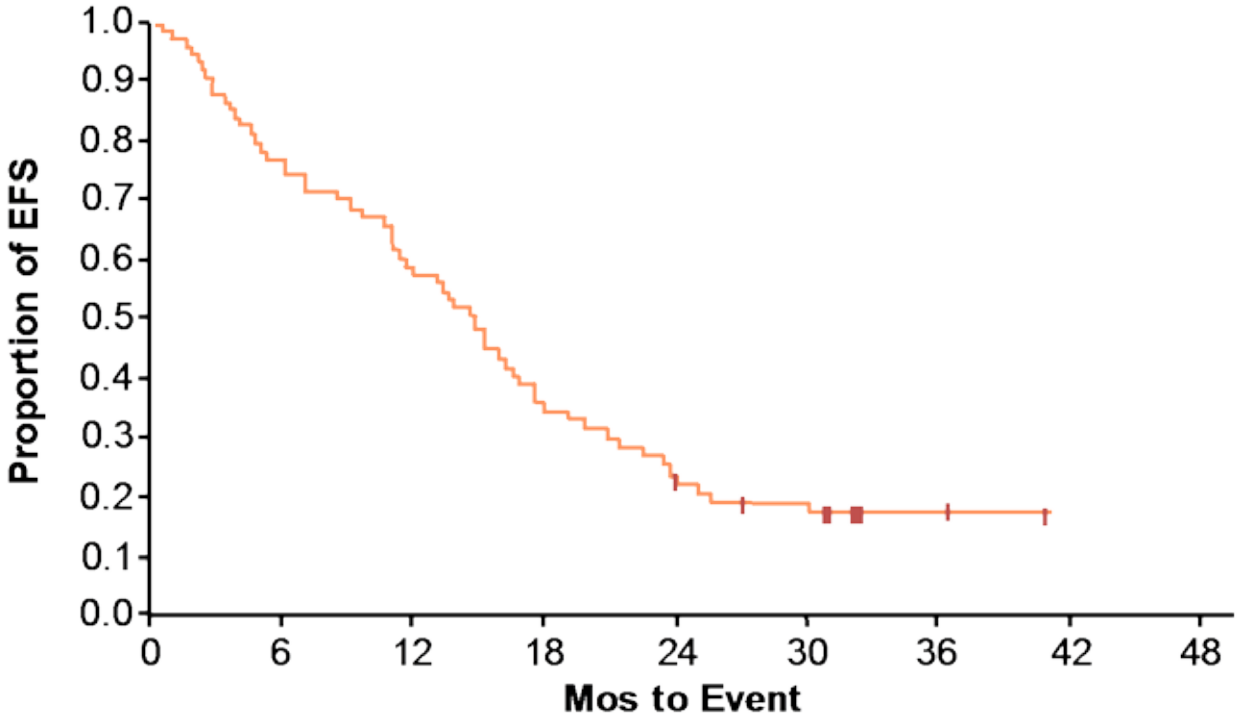
R = Rituximab	375 mg/m^2 day 0, cycle 1, 500 mg/m^2 cycle 2-6
B = Bendamustine	70mg/m^2 day 1-2 q4wks, cycle 1-6

Fischer et al. JCO Sep. 10, 2011:3559-3566

Bendamustine + Rituximab in relapsed CLL

Best Response (N = 78*)

Response	N	(%)
ORR	46	59
CR (CRu)	7	9
nPR	2	-
PR	37	47
SD	20	26
PD	5	6



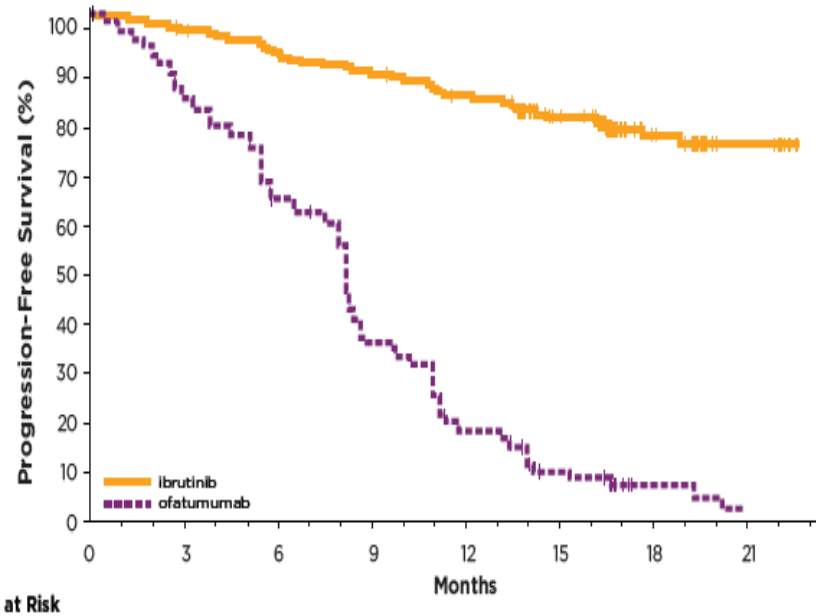
Fischer et al. JCO Sep. 10, 2011:3559-3566

Response to FCR or BR in Relapsed CLL

	FCR	BR
CR%	30	9
OR%	74	59
Median		
PFS	21 Months	15 Months
OS	47 Months	36 Months
PFS	30 Months *	15 Months **
OS	50 Months	36 Months

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

PFS

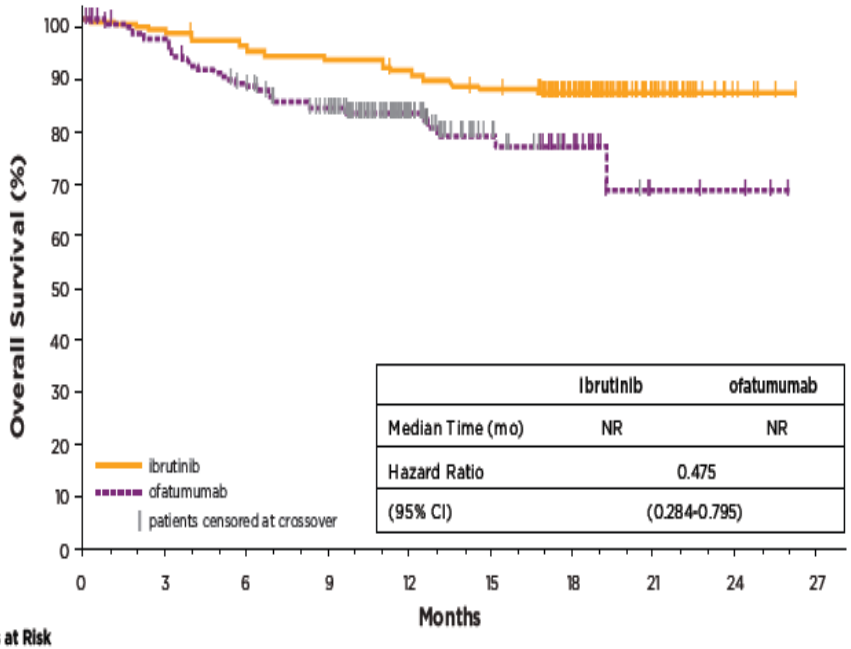


Patients at Risk

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

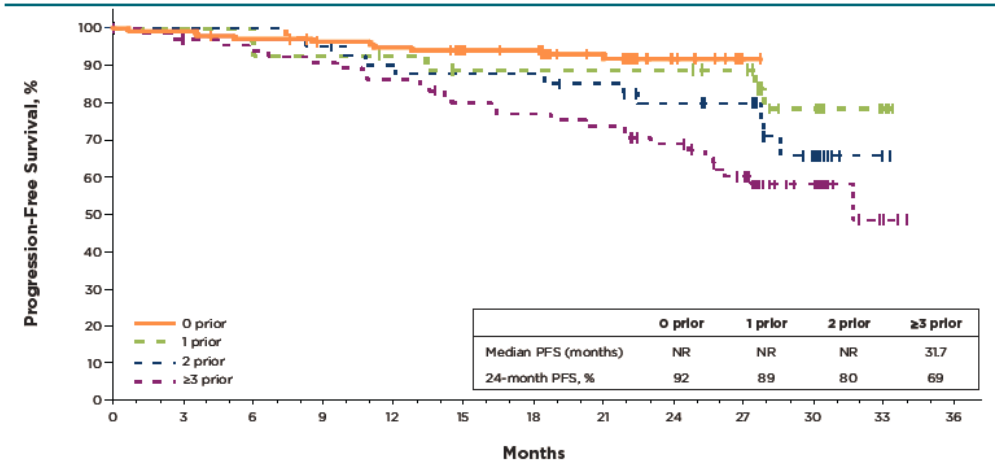
ibrutinib	195	191	183	179	174	166	116	40	6
ofatumumab	196	183	163	137	75	37	19	4	3

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

Ibrutinib: Better activity in early phases
O'Brien et al. ASCO 2016 # 7520

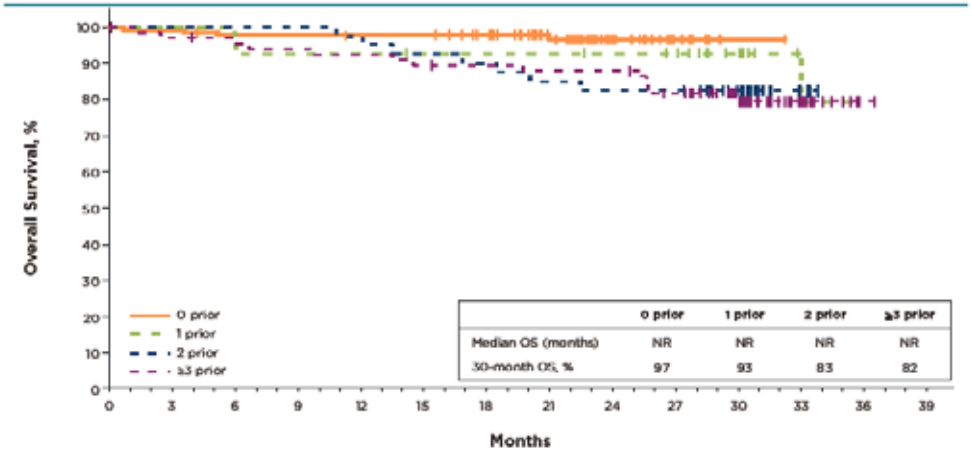
- RESONATE + RESONATE-2 (EXCLUDING DEL17p)
- Median FU: 22 m front-line, 30 months for R/R

Figure 2. PFS by Prior Lines of Therapy



	0 prior	1 prior	2 prior	≥3 prior
Median PFS (months)	NR	NR	NR	31.7
24-month PFS, %	92	89	80	69

Figure 3. OS by Prior Lines of Therapy



	0 prior	1 prior	2 prior	≥3 prior
Median OS (months)	NR	NR	NR	NR
30-month OS, %	97	93	83	82

Ibrutinib: Toxicity by line of treatment

O'Brien et al. ASCO 2016 # 7520

Table 5. Summary of Ibrutinib Exposure and Discontinuation

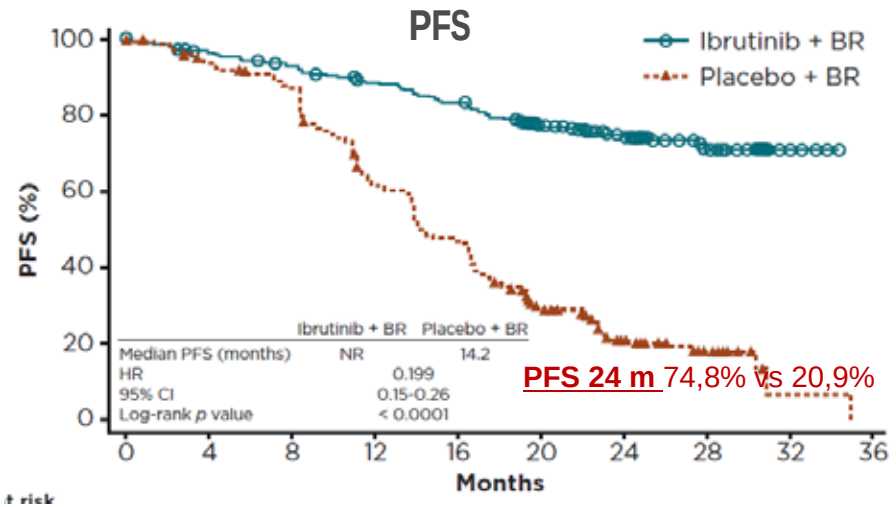
	Subgroups by Prior Lines of Therapy (N=271)			
	0 (n=136)	1 (n=27)	2 (n=41)	≥3 (n=67)
Median duration of ibrutinib treatment, months (range)	23 (1-30)	31 (6-37)	31 (1-35)	30 (1-36)
Treatment duration >1 year, n (%)	121 (89%)	24 (89%)	35 (85%)	54 (81%)
Continuing ibrutinib on study, n (%)*	115 (85%)	20 (74%)	28 (68%)	40 (60%)
Discontinuation due to, n (%)*				
PD	4 (3%)	2 (7%)	5 (12%)	11 (16%)
AEs	13 (10%)	1 (4%)	6 (15%)	7 (10%)
Deaths	2 (2%)	2 (7%)	1 (2%)	5 (7%)
Other	1 (1%)	2 (7%)	1 (2%)	4 (6%)
AEs leading to discontinuation†, n				
Pneumonia‡	2	1	0	4
Atrial fibrillation	2	0	1	0
Subdural hematoma	1	0	0	2
Other neoplasms	1	1	2	2

**5 patients who discontinued study ibrutinib to receive commercial ibrutinib are not included. †Occurring in more than 2 patients. ‡ Includes multiple terms.*

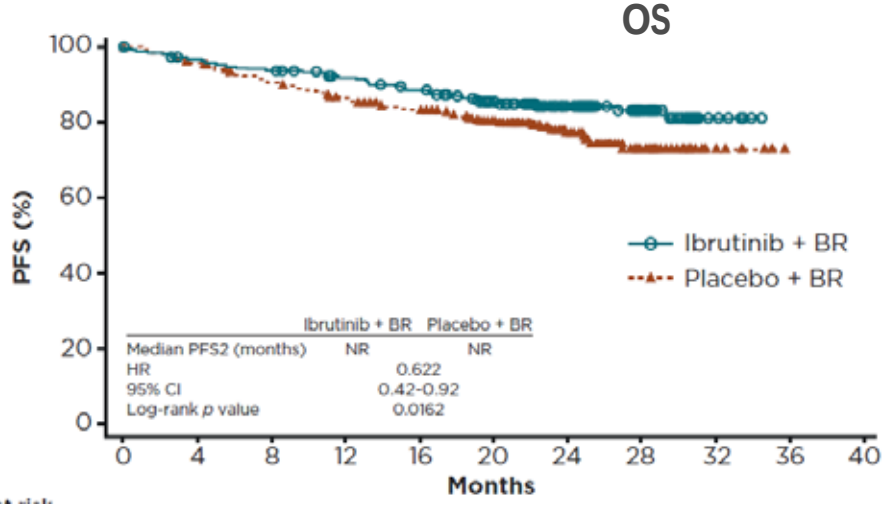
HELIOS: Phase 3 Study Design

Chanan-Khan et al, ASCO, 2015

HELIOS trial
Update at 2 years. *Fraser et al. EHA #S430*

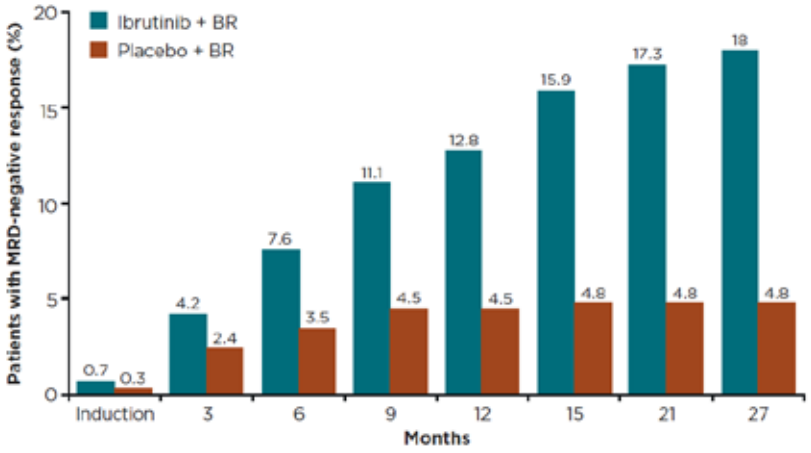


PFS 24 m 74,8% vs 20,9%

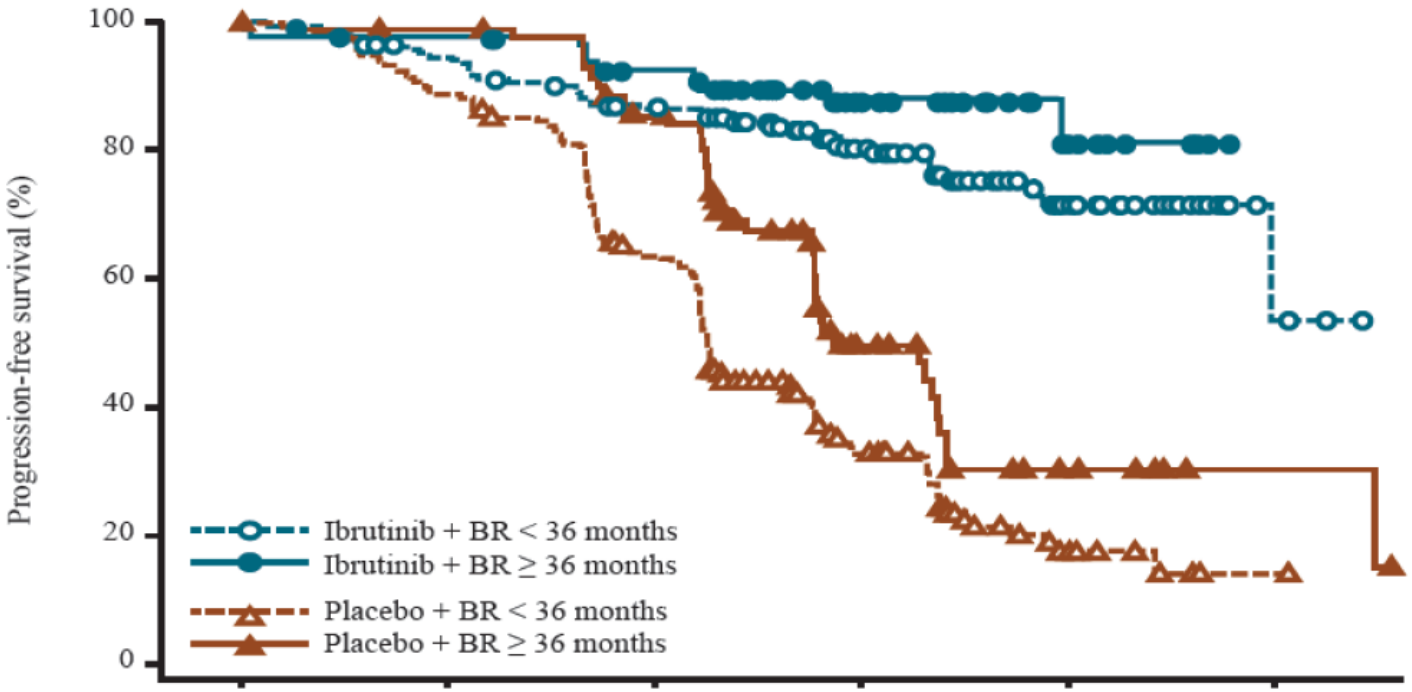


Results: Increased Depth of Response

	CR/CRi (Investigator-Assessed)		MRD-Negative (Central Laboratory)	
	Ibrutinib + BR	Placebo + BR	Ibrutinib + BR	Placebo + BR
Median follow-up, 17 months[1]	21.4%	5.9%	12.8% (n = 37)	4.8% (n = 14)
Median follow-up, 25.4 months	33.9%	7.3%	18.0% (n = 52)	4.8% (n = 14)



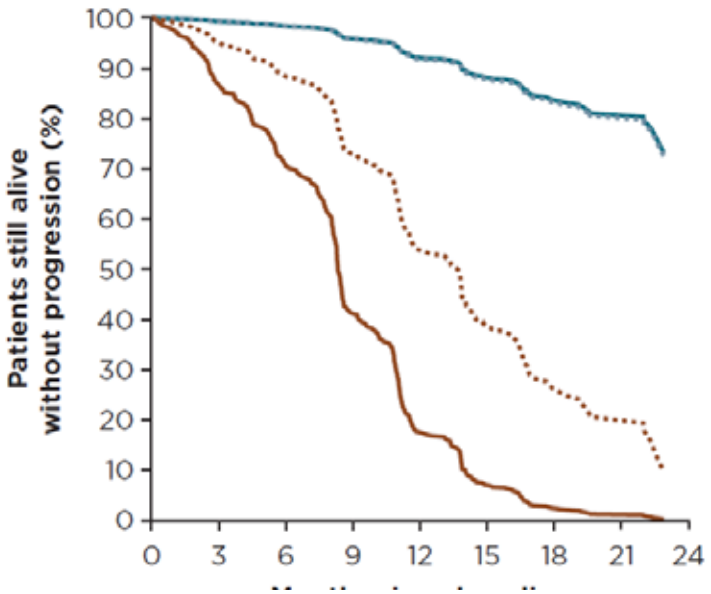
HELIOS: PFS by Treatment-Free Interval From Last Therapy (≥ 36 Months Vs < 36 Months)



Patients at risk:						
Ibrutinib + BR ≥ 36 mo	85	77	68	36	11	0
Placebo + BR ≥ 36 mo	82	77	64	21	7	2
Ibrutinib + BR < 36 mo	204	184	165	104	41	3
Placebo + BR < 36 mo	207	176	122	45	10	1

Chanan-Khan et al. Lancet Oncol 2015; [epub] (Suppl Info)

Comparación HELIOS vs RESONATE (Ibr vs BR)



Ibr (RESONATE™; n = 127)
Ofa (RESONATE™; n = 129)
Ibr + BR (HELIOS; n = 255)
BR (HELIOS; n = 257)

	HR (95% CI)	*p* Value
Ibr	0.13 (0.08-0.21)	< 0.0001
Ofa	2.81 (2.08-3.8)	< 0.0001
Ibr + BR	0.14 (0.1-0.2)	< 0.0001
BR[b]	1.00	-

Table 1. AEs In > 20% of Patients

Safety Population	Ibrutinib + BR (N = 287)		Placebo + BR (N = 287)	
AE, %	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Neutropenia	58.2	53.7	54.7	50.5
Nausea	36.9	0.7	35.2	0.3
Diarrhea	35.5	2.1	23.3	1.4
Thrombocytopenia	30.7	15.0	24.0	15.0
Pyrexia	24.7	3.5	21.6	1.7
Anemia	22.6	3.5	28.9	8.0
Fatigue	21.6	3.1	22.6	3.5
Cough	19.2	0	24.4	0.7
Infusion-related reaction	16.7	1.4	22.0	1.7

American Society of Hematology
Helping hematologists conquer blood diseases worldwide

Hillmen P et al., ASH 2015 (abstract 2944, poster presentation)
Chanan-Khan A, et al. Lancet Oncol. 2015. [Epub ahead of print]

TP53 / DEL17P ABNORMALITIES (& REFRACTORY CLL)

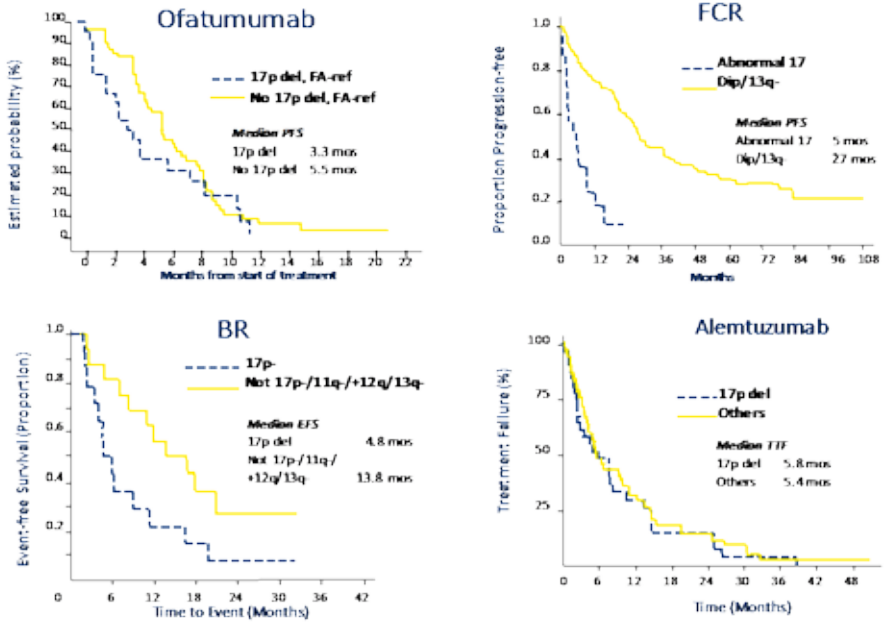
Case 2: del17p

- 72 yo male
- Hypertension à enalapril
- 2014 à Bendamustine + Rituximab
- 2015 à Rapid relapse
  - Palpable lymph-nodes, rapid enlargment
  - ”B-symtomps” (weight loss)
  - lymphocytes 78,000/mm3
  - Hb 112 g/L
  - Platelets 120,000/mm3
  - **FISH: del17p 80% of nuclei**
- What are your therapeutic options?

1. W & W
2. Obinutuzumab + chlorambucil
3. BR
4. Alemtuzumab + transplant
5. Ibrutinib
6. Idelalisib + rituximab
7. Venetoclax

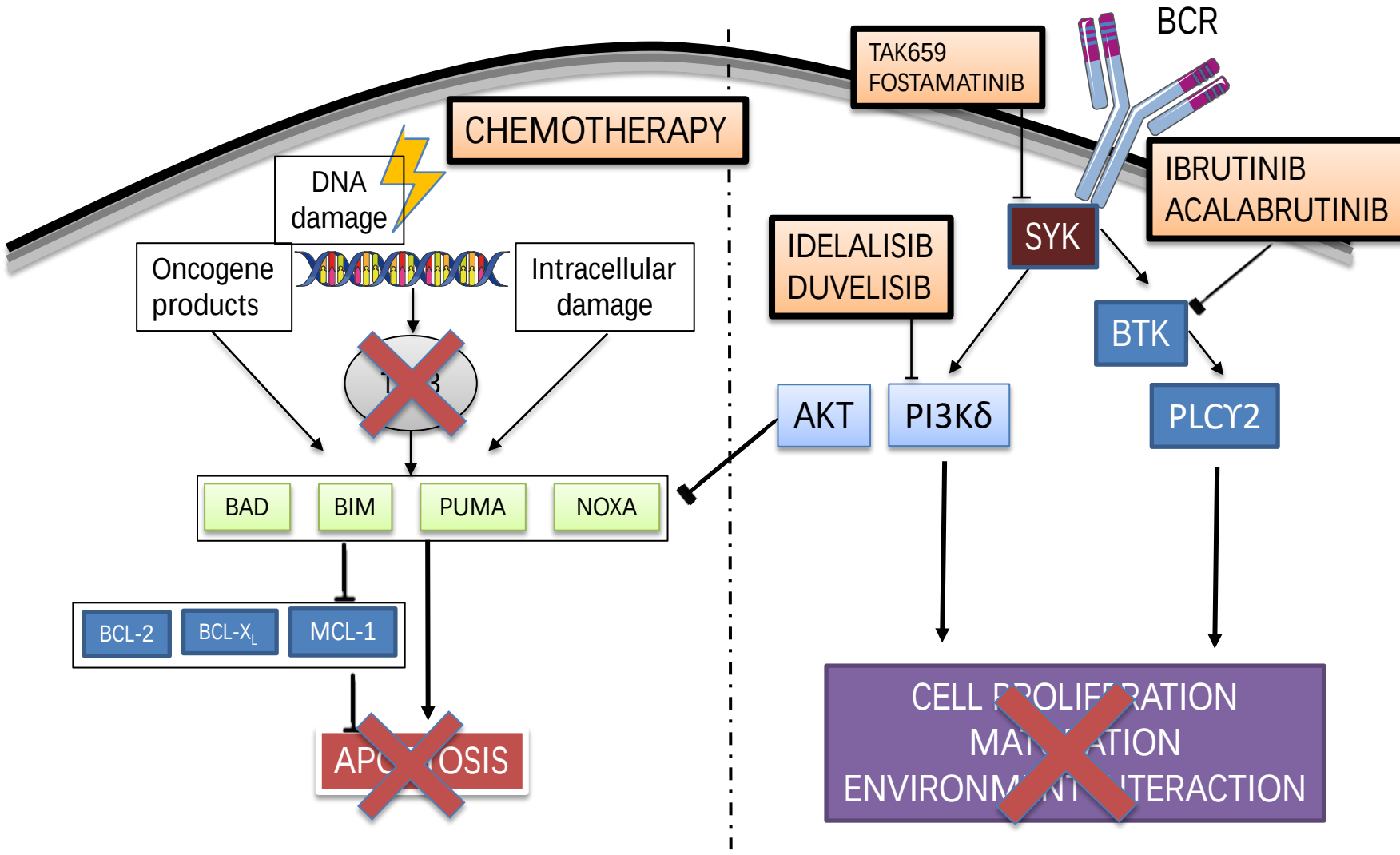
TP53 Deletions and Mutations in CLL

	MBL	Early stage	Treatment requirement	CLL Refractory	Richter
Abnormal 17p/TP53	1.5%	4.8%	10%	44%	66%
TP53 mut			3%	12%	25%
Del17p / TP53			7%	25%	30%
Del17p (only)			1%	7%	10%



Zenz et al, Blood 2008
Rossi et al, Clin Cancer Res 2009
Dicker et al, Leukemia 2009
Malcokiva et al, Blood 2009
Rossi et al, Blood 2014

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.

TP53 and elephants

Preliminary Communication

Potential Mechanisms for Cancer Resistance in Elephants and Comparative Cellular Response to DNA Damage in Humans

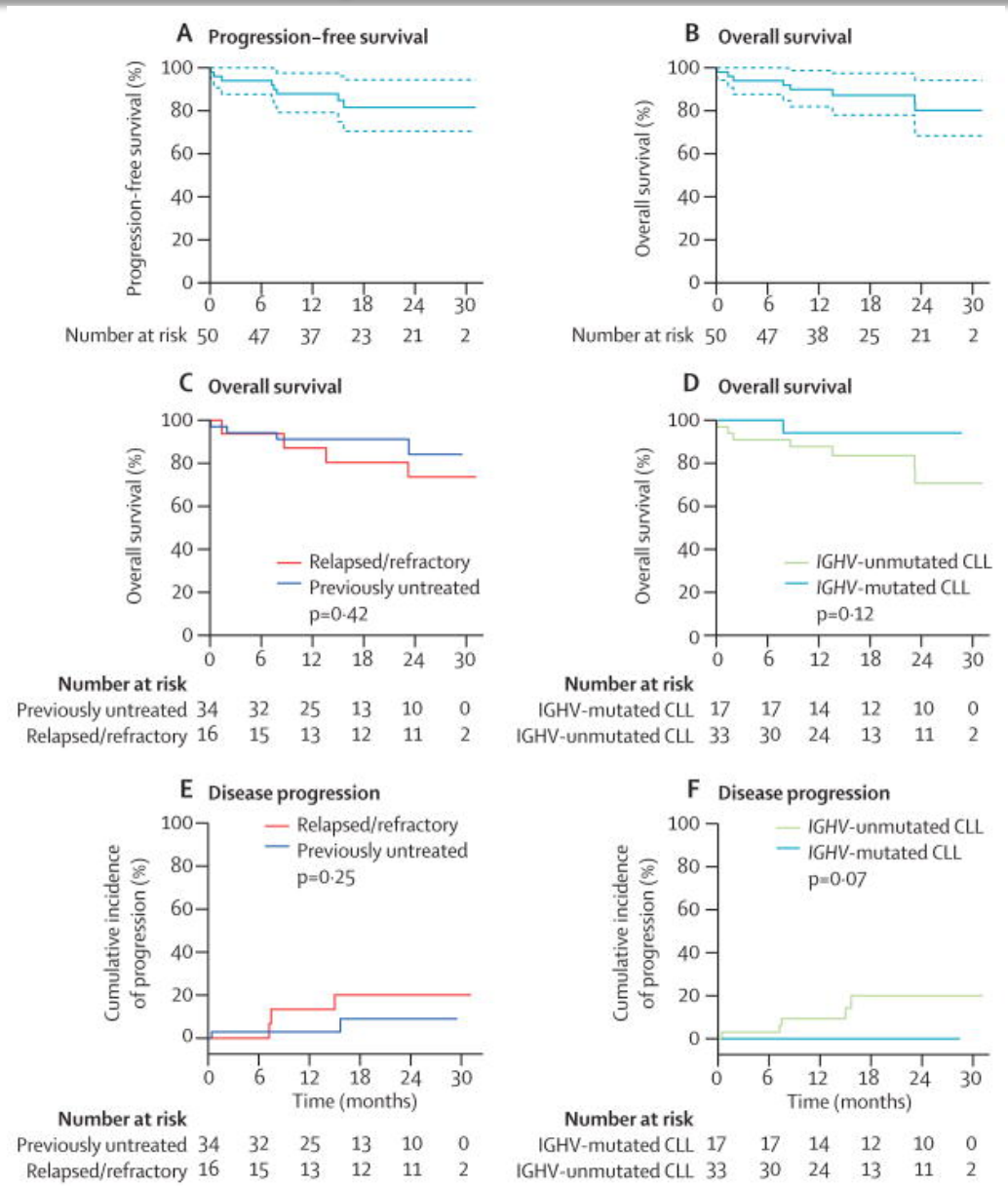
Lisa M. Abegglen, PhD; Aleah F. Caulin, PhD; Ashley Chan, BS; Kristy Lee, PhD; Rosann Robinson, BS; Michael S. Campbell, PhD; Wendy K. Kiso, PhD; Dennis L. Schmitt, DVM, PhD; Peter J. Waddell, PhD; Srividya Bhaskara, PhD; Shane T. Jensen, PhD; Carlo C. Maley, PhD; Joshua D. Schiffman, MD

lion, 2% [95% CI, 0%-7%]). Despite their large body size and long life span, elephants remain cancer resistant, with an estimated cancer mortality of 4.81% (95% CI, 3.14%-6.49%), compared with humans, who have 11% to 25% cancer mortality. While humans have 1 copy (2 alleles) of *TP53*, African elephants have at least 20 copies (40 alleles), including 19

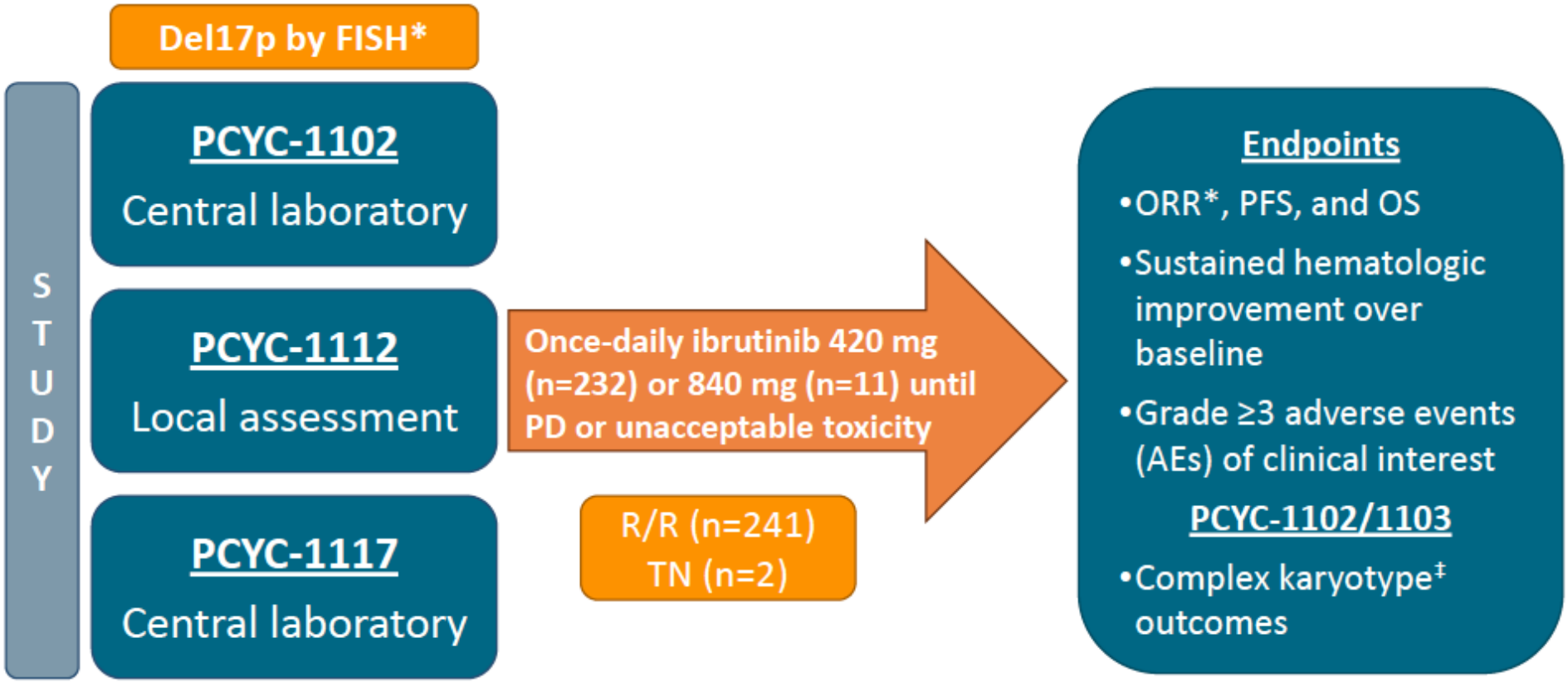
Abegglen et al, JAMA 2015

Ibrutinib in untreated and R/R CLL

Farooqui et al, Lancet Oncol 2015



Del17p and Ibrutinib

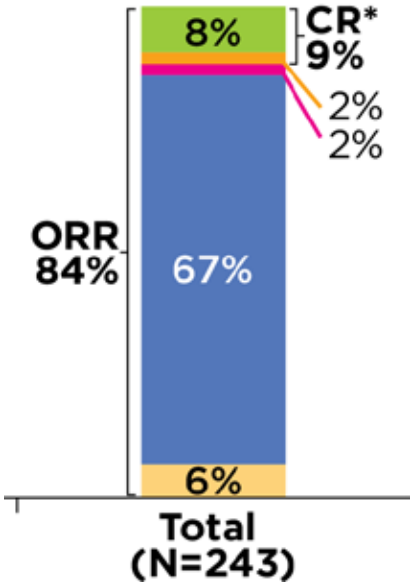


Jones J et al., EHA 2016

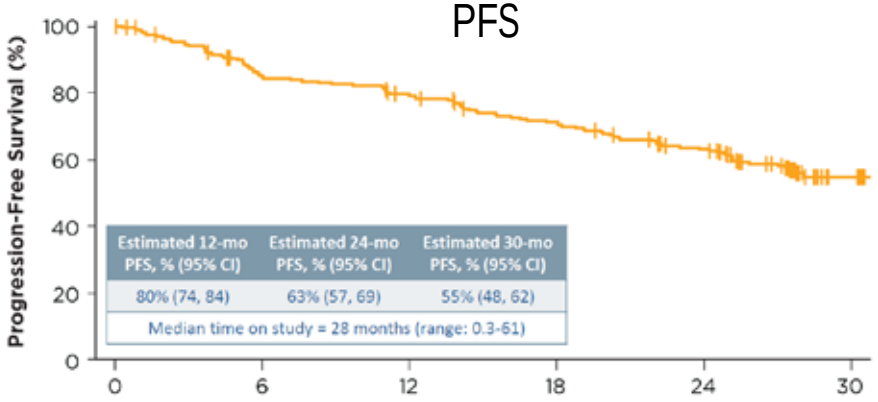
Ibrutinib in del17p

Jones et al. EHA Oral presentation #S429

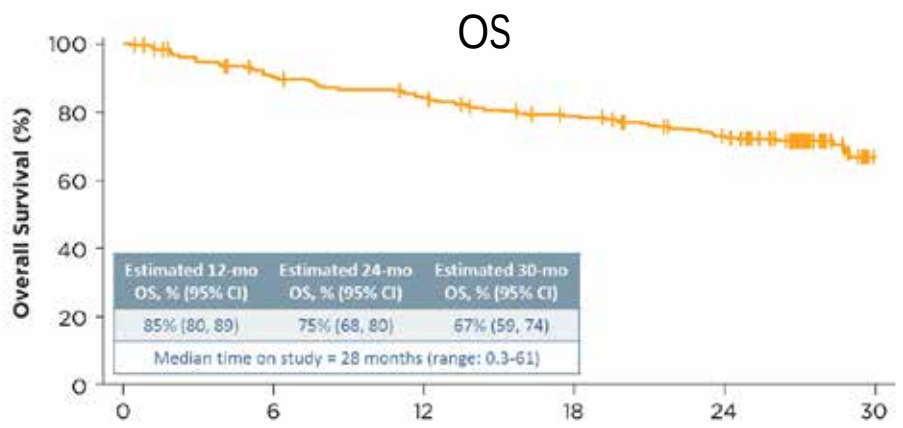
- N=243 pts with del17p (**PCYC-1102, RESONATE and RESONATE-17)**
- 50% with ≥ 3 prior lines of therapy
- Median FU 28 months



PFS



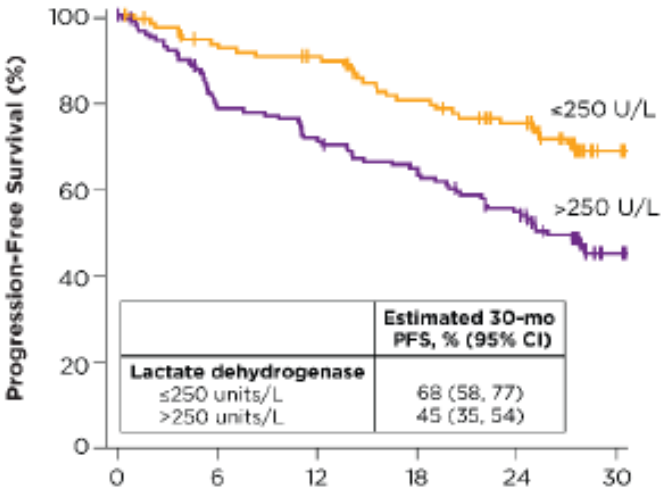
OS



Ibrutinib in del17p: Prognostic factors

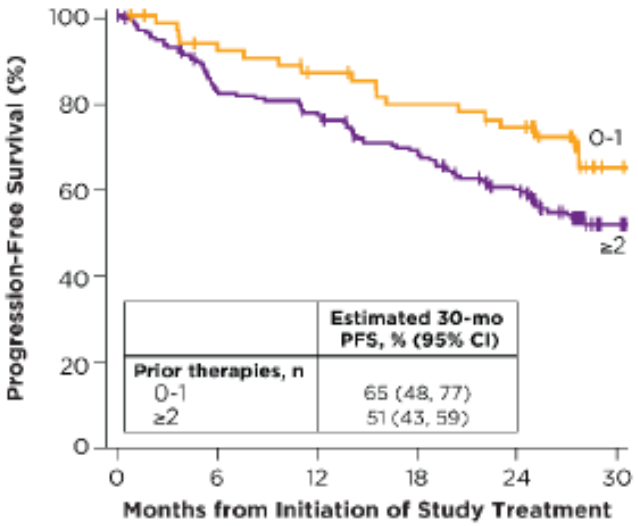
Jones et al. EHA Oral presentation #S429

Lactate Dehydrogenase



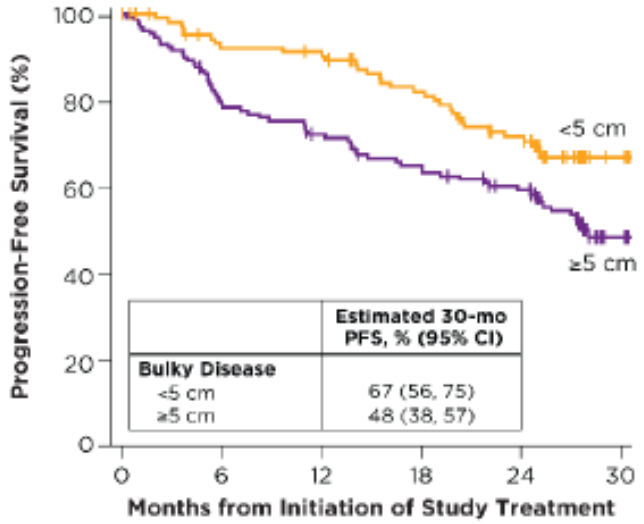
	Estimated 30-mo PFS, % (95% CI)
Lactate dehydrogenase	
≤250 units/L	68 (58, 77)
>250 units/L	45 (35, 54)

Prior Therapies

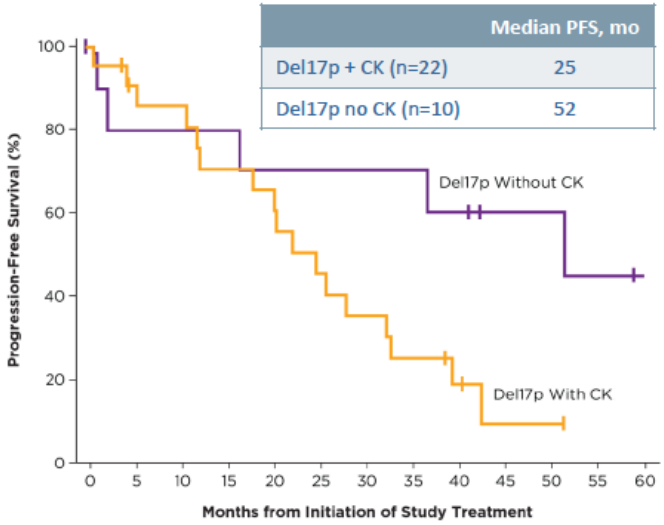


	Estimated 30-mo PFS, % (95% CI)
Prior therapies, n	
0-1	65 (48, 77)
≥2	51 (43, 59)

Bulky Disease

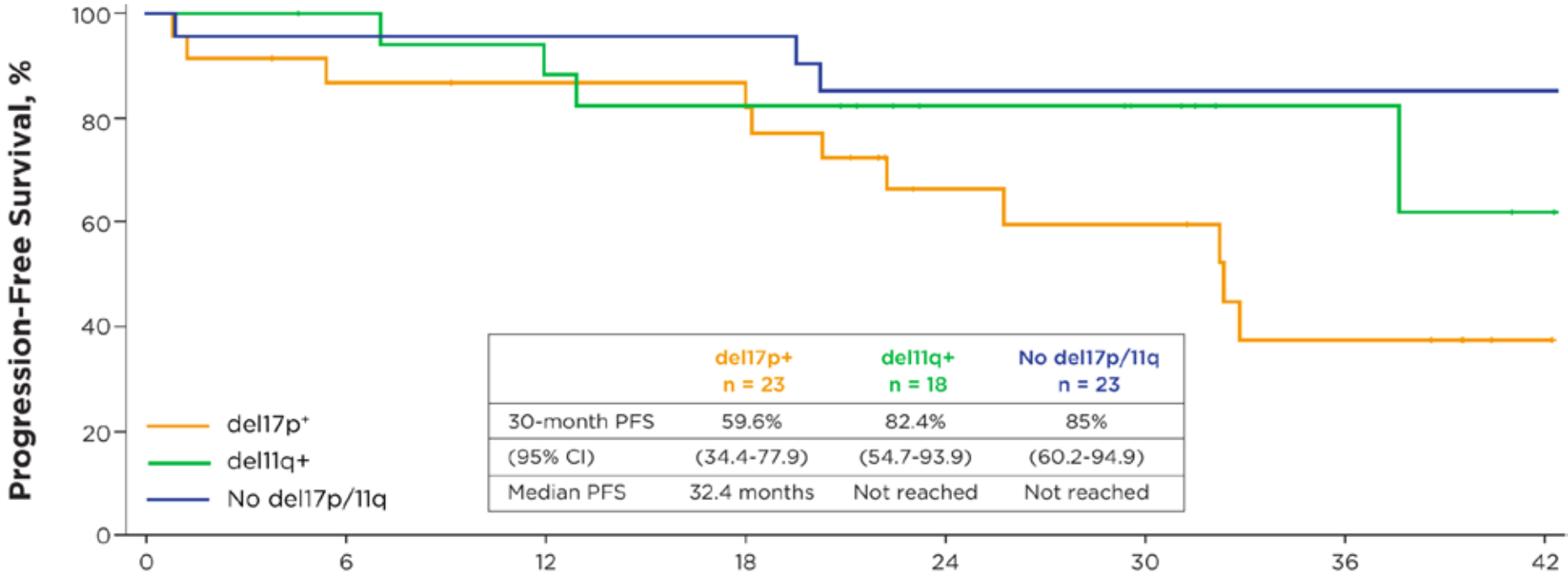


	Estimated 30-mo PFS, % (95% CI)
Bulky Disease	
<5 cm	67 (56, 75)
≥5 cm	48 (38, 57)



	Median PFS, mo
Del17p + CK (n=22)	25
Del17p no CK (n=10)	52

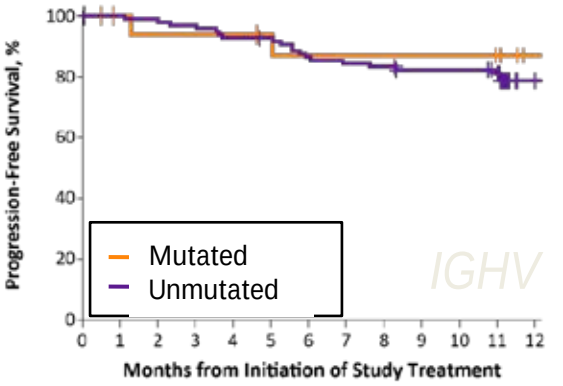
PFS Outcomes by Cytogenetics (FISH) in Relapsed/Refractory Population



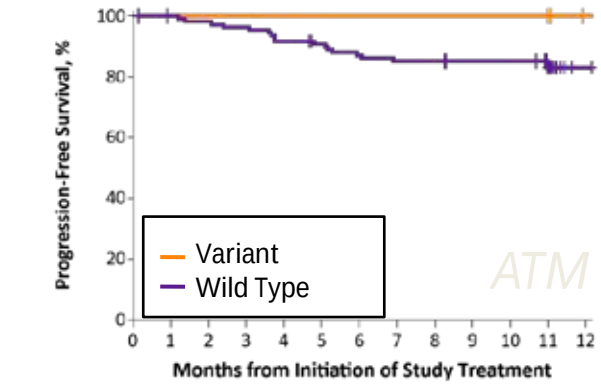
	del17p+ n = 23	del11q+ n = 18	No del17p/11q n = 23
30-month PFS	59.6%	82.4%	85%
(95% CI)	(34.4-77.9)	(54.7-93.9)	(60.2-94.9)
Median PFS	32.4 months	Not reached	Not reached

Patients at Risk								
del17p+	23	19	18	18	10	9	5	1
del11q+	18	17	15	14	9	7	4	2
No del17p/del11q	23	19	19	18	11	8	5	4

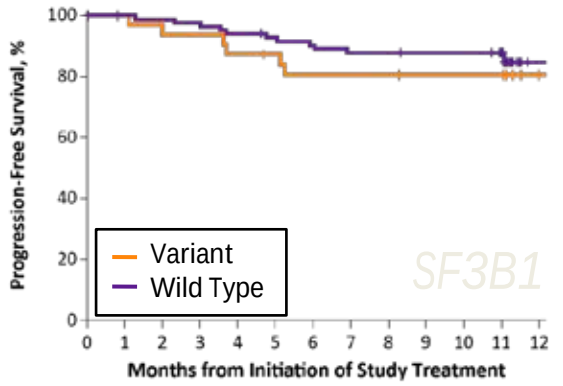
Resonate 17
PFS by Baseline Genomic Variants



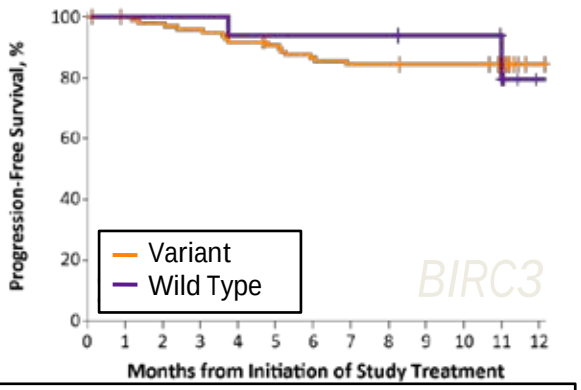
Patients at Risk													
Variant	19	16	15	15	15	14	13	13	13	13	13	12	5
Wild Type	97	96	95	93	89	88	82	80	79	76	76	73	28



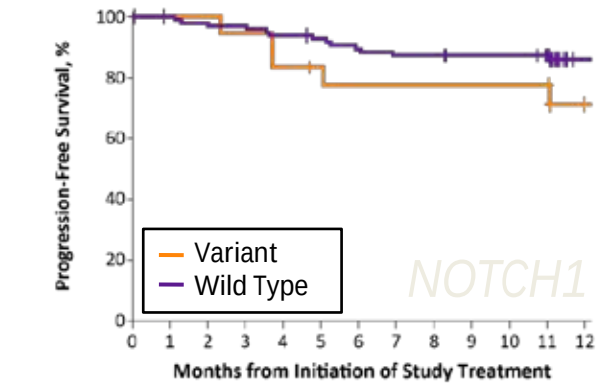
Patients at Risk													
Variant	4	4	4	4	4	4	4	4	4	4	4	4	1
Wild Type	112	109	107	105	100	97	93	91	91	89	89	87	32



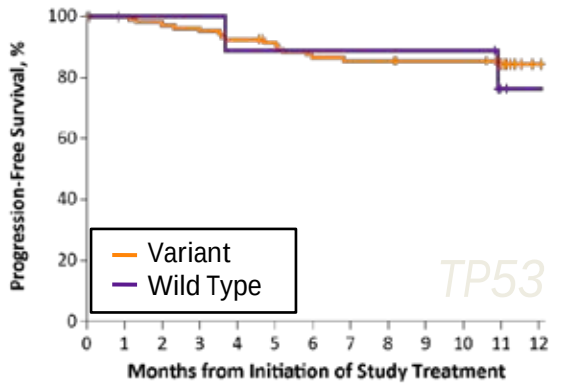
Patients at Risk													
Variant	31	31	30	29	27	26	24	24	24	23	23	23	14
Wild Type	85	82	81	80	77	75	73	71	71	70	70	68	19



Patients at Risk													
Variant	16	16	16	16	15	15	15	15	15	14	14	14	5
Wild Type	100	97	95	93	89	86	82	80	80	79	79	77	28



Patients at Risk													
Variant	19	18	18	17	15	14	13	13	13	13	13	13	5
Wild Type	97	95	93	92	89	87	84	82	82	80	80	78	28



Patients at Risk													
Variant	107	104	102	100	96	93	89	87	87	85	85	84	32
Wild Type	9	9	9	9	8	8	8	8	8	8	8	7	1

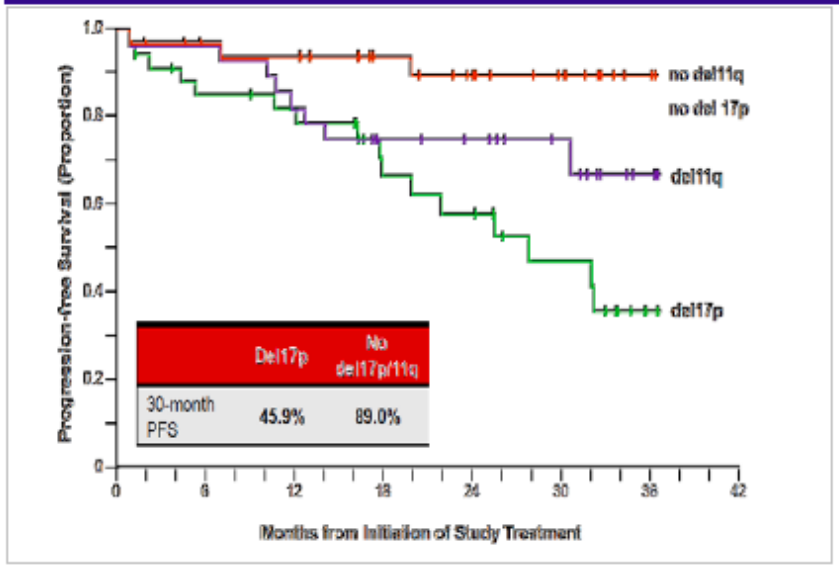
Stilgenbauer et al, Lancet Oncol 2016

BCR inhibitors in CLL with TP53 lesions

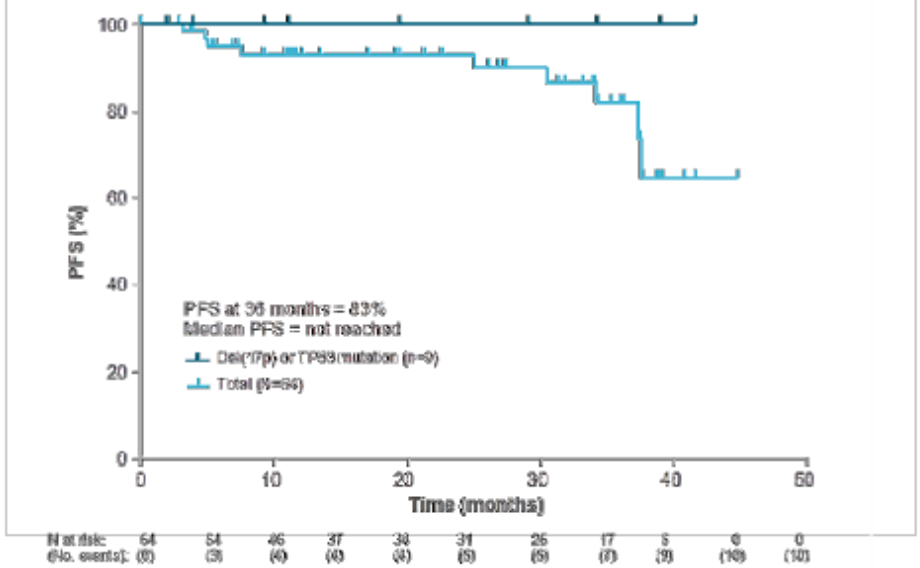
Response rate in CLL harboring *TP53* abnormalities

	N	Treatment	ORR	PR/PRL	CR
Farooqui et al. 2015[1]	51	Ibrutinib	94%	84%	10%
O'Brien et al. 2014[2]	137	Ibrutinib	82%	80%	2%
Burger et al. 2014[3]	20	Ibrutinib + R	90%	80%	10%
Byrd et al. 2013[4]	82	Ibrutinib	68%	65%	3%
Sharman et al. 2014[5]	34	Idelalisib + R	79%	NA	NA
O'Brien et al. 2014[6]	9	Idelalisib + R	100%	67%	33%

Ibrutinib[7]



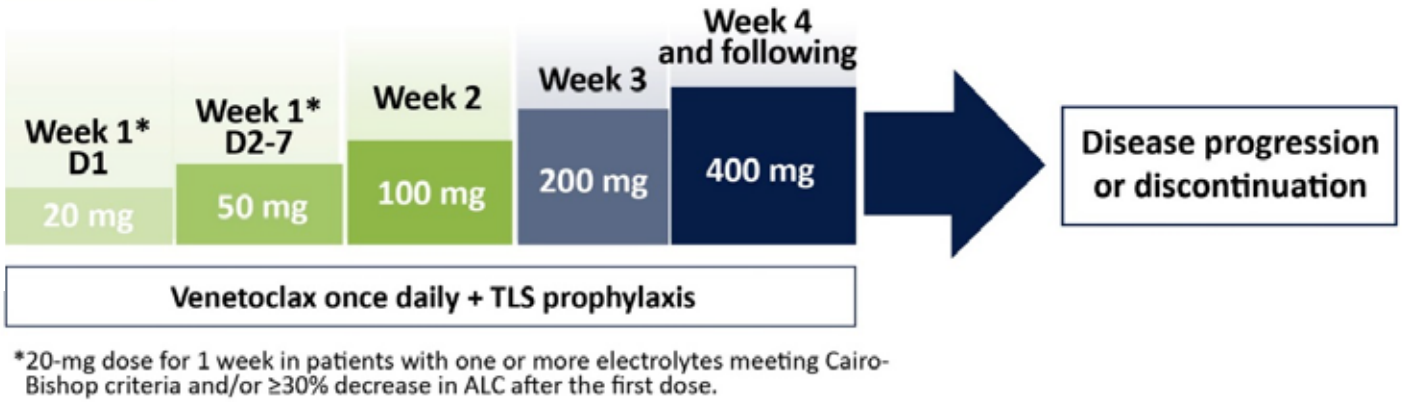
Idelalisib + R[5]



1. Farooqui MZ et al 2015;16:169–76; 2. O'Brien, ASH 2014. Abstract 327; 3. Burger JA et al 2014; Lancet Oncol 2014;15:1090–9; 4. Byrd JC et al. N Engl J Med 2013;369:32–42; 5. Sharman JP et al. J Clin Oncol 2014;32:5s(suppl; abstr 7011); 6. O'Brien et al., ASH, 2014, Abstract #1994; 7. O'Brien, ASCO 2014 abstract #7014.

VENETOCLAX studies in CLL

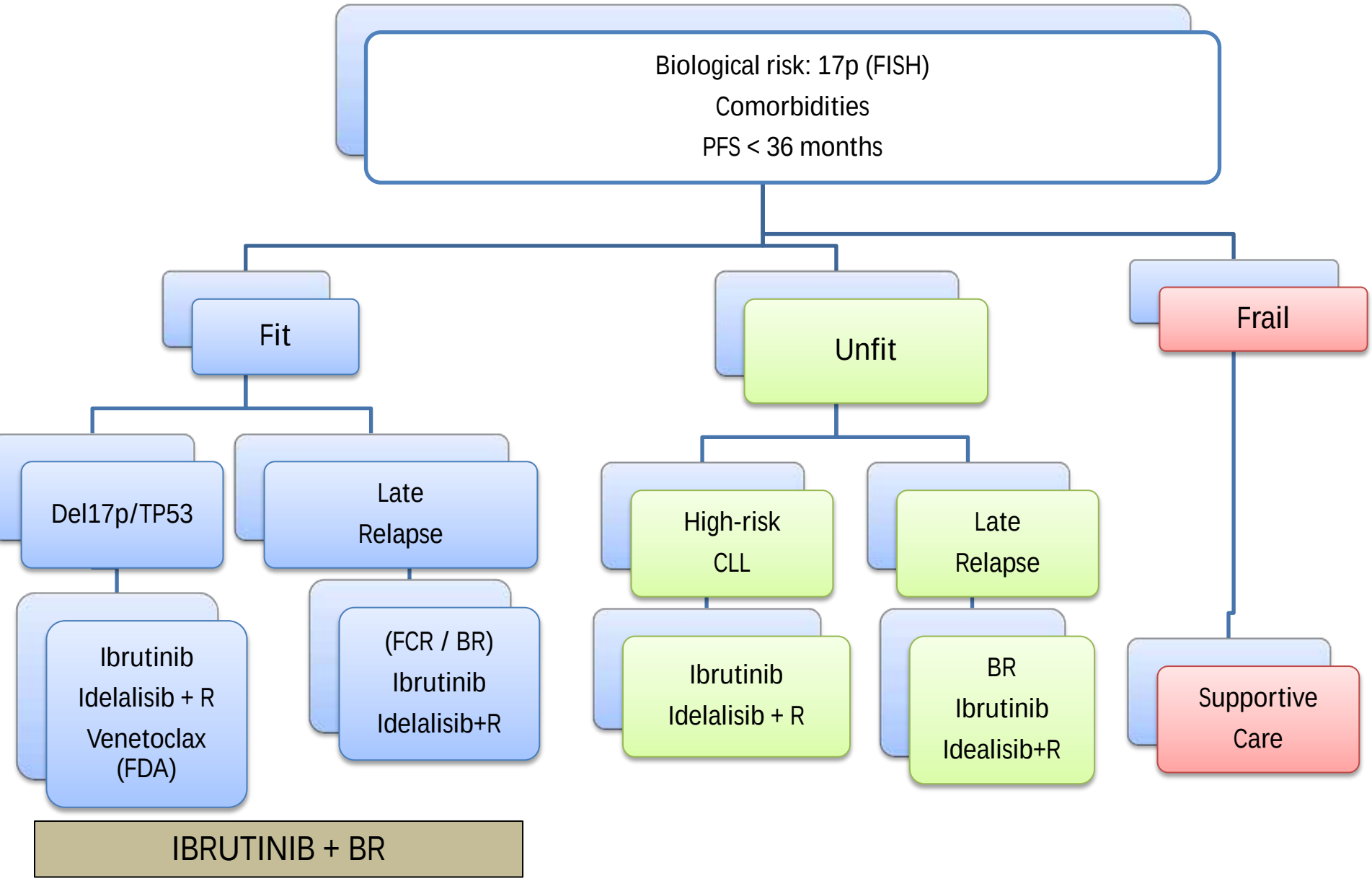
	N=	Phase	Population	ORR	ORR Flud Ref	CRR	MRD neg
M12-175[1]	99	Phase 1	R/R CLL	80%	79%	20%	6/17 tested
M13-982[2]	107	Phase 2	del17p	79%		10%	18/45 tested

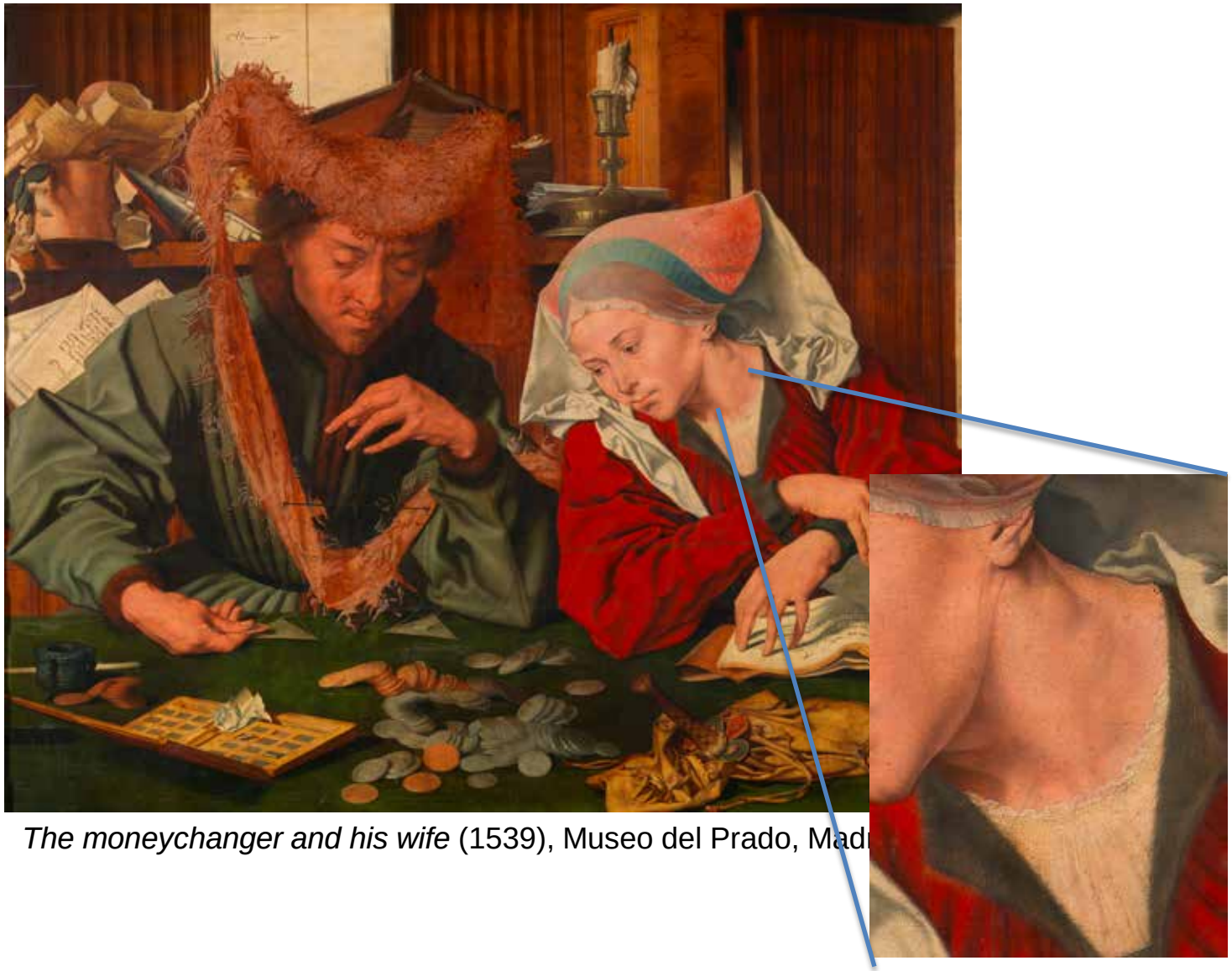


*20-mg dose for 1 week in patients with one or more electrolytes meeting Cairo-Bishop criteria and/or ≥30% decrease in ALC after the first dose.

1. *Roberts AW. NEJM 2016;374:311–322*
2. *Stilgenbauer S, et al. Lancet Oncology, 2016*

Salvage therapy for CLL: 2016 algorithm





The moneychanger and his wife (1539), Museo del Prado, Mad