Unmet challenges in high risk hematological malignancies: from benchside to clinical practice

Scientific Board:
Marco Ladetto (Alessandria)
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How I Treat High Risk CLL

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Disclosures

- Roche: Honoraria, research grants
- Celgene: Honoraria, research grants
- Takeda: Honoraria, research grants
- Astra-Zeneca: Honoraria, research grants
- Novartis: Honoraria, research grants
- AbbVie: Honoraria, research grants
- Janssen: Honoraria, research grants

Outline

1. High-risk CLLs respond poorly to CIT
2. New targeted therapies are active in (almost) all high-risk CLL
3. Need for predictive biomarkers for the newer therapies

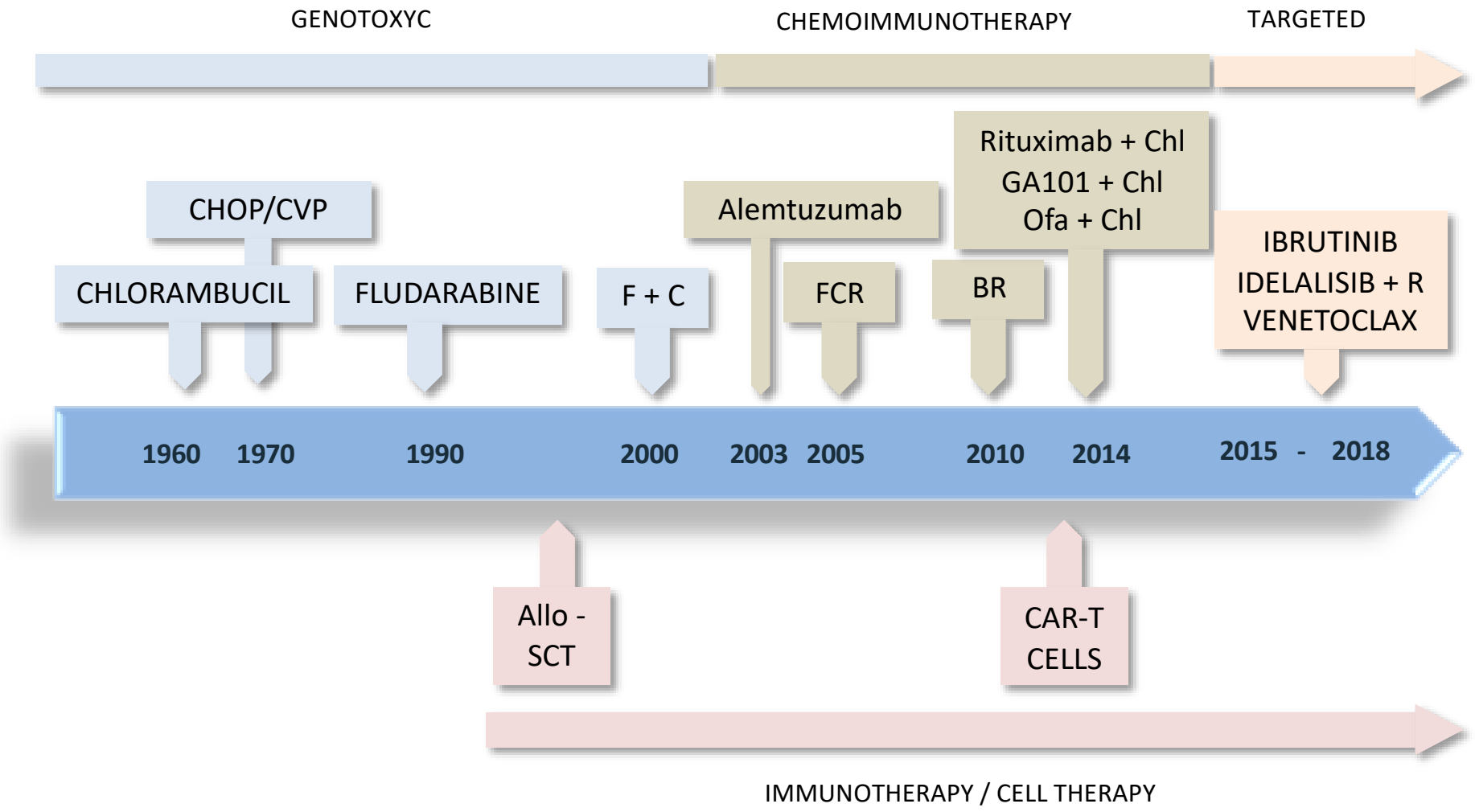
Vall d'Hebron
Barcelona Campus Hospitalari

How I treat refractory CLL

Emili Montserrat, Carol Moreno, Jordi Esteve, Alvaro Urbano-Ispizua, Eva Giné, and Francesc Bosch

Therapy for patients with chronic lymphocytic leukemia (CLL) has greatly changed over the past few years. After years of stagnation, with treatment revolving around the use of rather ineffective drugs such as alkylators, many patients are now being treated with more effective agents such as purine analogs either alone or combined with other drugs and/or monoclonal antibodies. Treatment of patients refractory to these treatments is particularly challenging and should be decided only upon a careful evaluation of the disease, patient characteristics, and prognostic factors. Refractory disease should be clearly separated from relapsing disease. The only curative therapy for patients with CLL, including those with refractory disease, is allogeneic stem cell transplantation. However, the use of allogeneic transplantation is limited because of the advanced age of most patients and the high transplant-related mortality (TRM). Transplants with nonmyeloablative regimens may reduce TRM and allow more patients to receive transplants more safely. For patients in whom an allogeneic transplantation is not feasible or in whom it is deemed inappropriate, participation in phase 2 trials should be encouraged. Finally, to investigate mechanisms to overcome resistance to therapy in CLL and to identify patients that might gain benefit from early, intensive therapies (eg, based on biologic markers) constitute a challenge that needs active investigation. (Blood. 2006;107:1276-1283)

ENORMOUS PROGRESS IN THE TREATMENT OF CLL



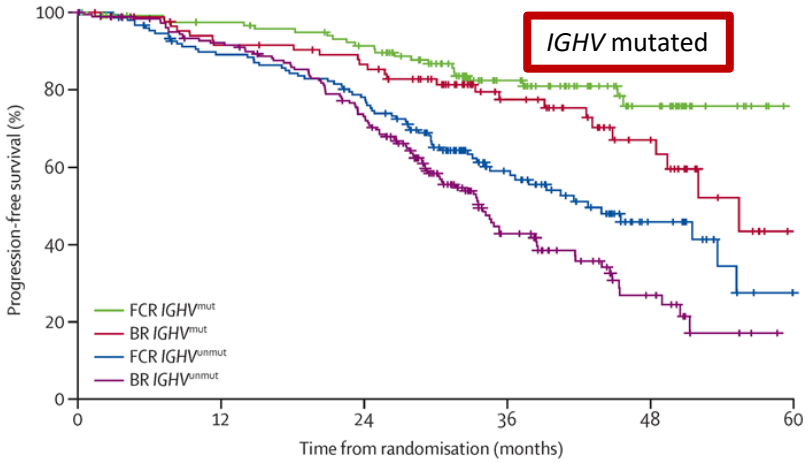
Frontline Therapy of CLL

- Current standard of care:
  - FCR / BR
  - Chlorambucil with obinutuzumab

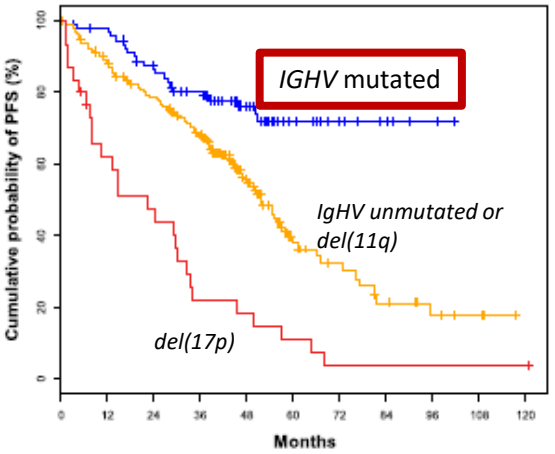
- FCR produces 1 yr longer PFS than BR (at the expense of more toxicity)

- So why use FCR?

Favorable long-term PFS with Firstline FCR in *IGHV*-M Subgroup

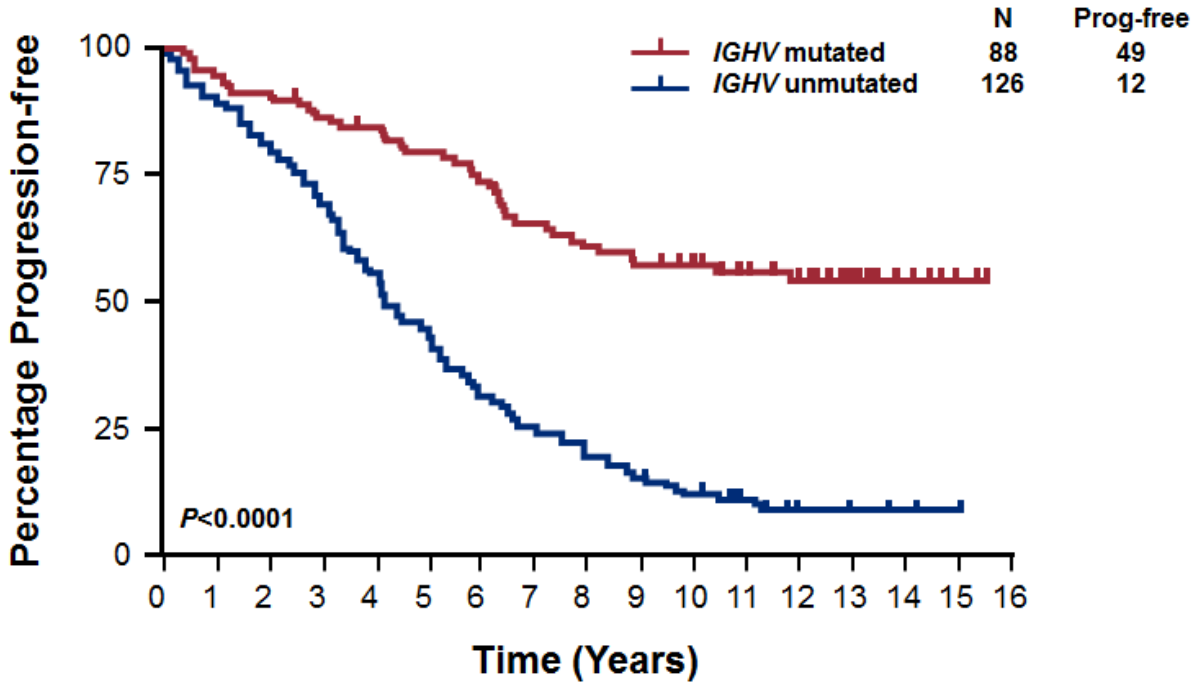


Eichhorst et al Lancet Oncol 2016



Rossi et al, Blood 2015

Favorable long-term PFS with Firstline FCR in *IGHV*-M Subgroup



Thompson et al, Blood 2015

Who can benefit from FCR?

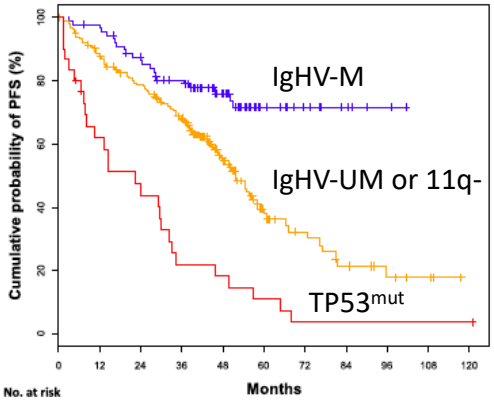
MRD + (40%)

7%

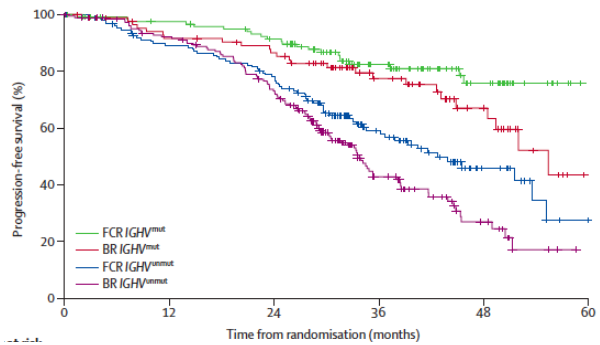
NO NEEED FOR TREATMENT (30%)

IgHV-UM & 11q- have a poor response to CIT but not to BCRi

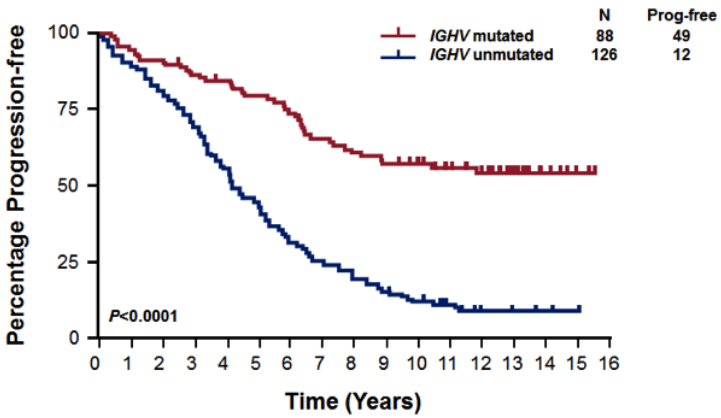
Del11q or unmutated IgHV have por PFS after chemoimmunotherapy



Rossi et al, Blood 2015



Eichhorst et al., Lancet Oncol 2015

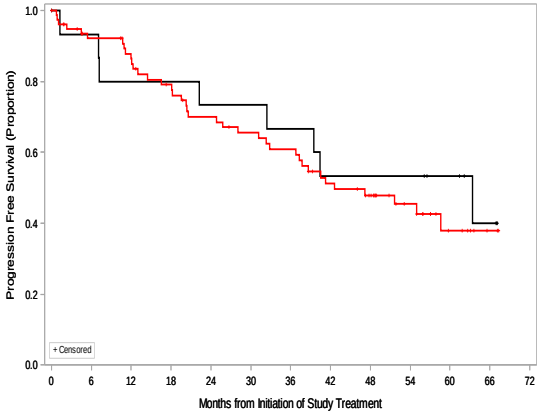


Thompson et al., Blood 2016

		Median PFS IgHV-UM
Thompson et al, Blood 2016	FCR300	48 m
Eichhorst et al, Lancet Oncol, 2016	CLL10	FCR: 38 m BR: 25 m
Rossi et al, Blood 2015	Italian study	50 m

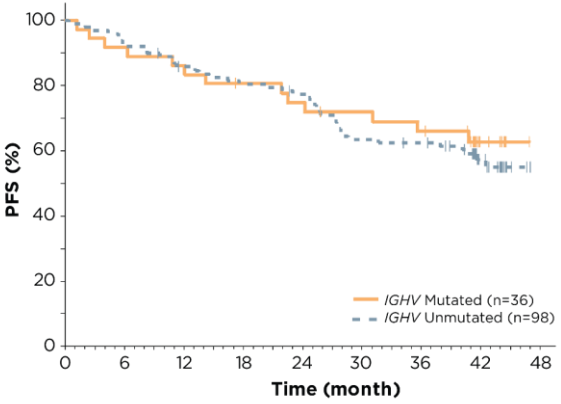
Ibrutinib is equally active in IgHV-UM

PCY 1102/1103 trials



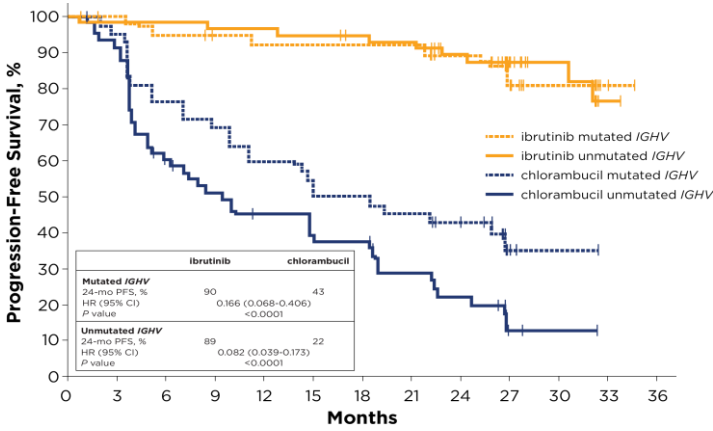
O'Brien SM, et al; ASH 2016

RESONATE trial



Byrd et al, ASCO 2017

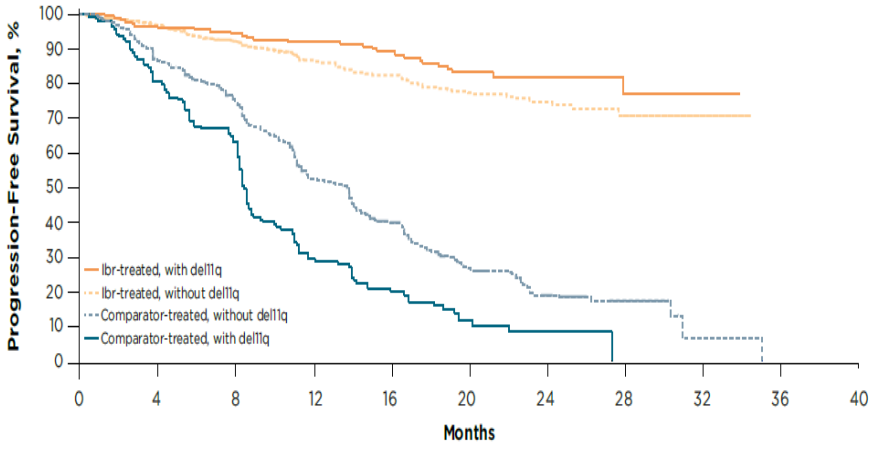
RESONATE-2 trial



Barr et al., ASH 2016 (abstract 234)

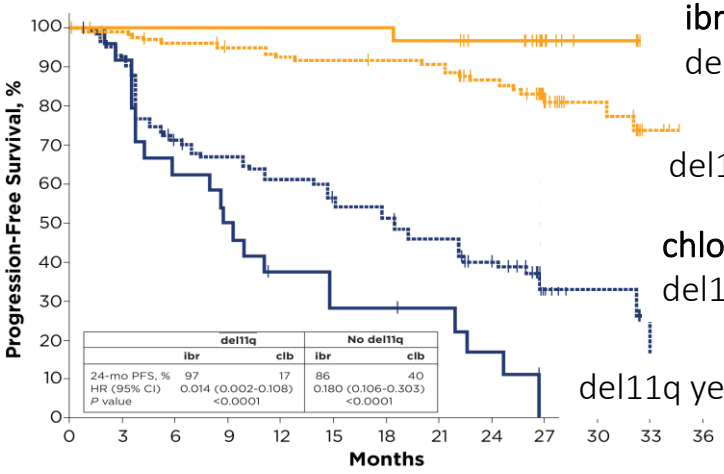
Del11q is not a prognostic factor for adverse outcomes in CLL/SLL patients treated with ibrutinib

Progression-free survival



Kipps et al., ASH 2016 (abstract 2042)

RESONATE-2 trial



ibrutinib
del11q yes (n=29)

del11q no (n=101)

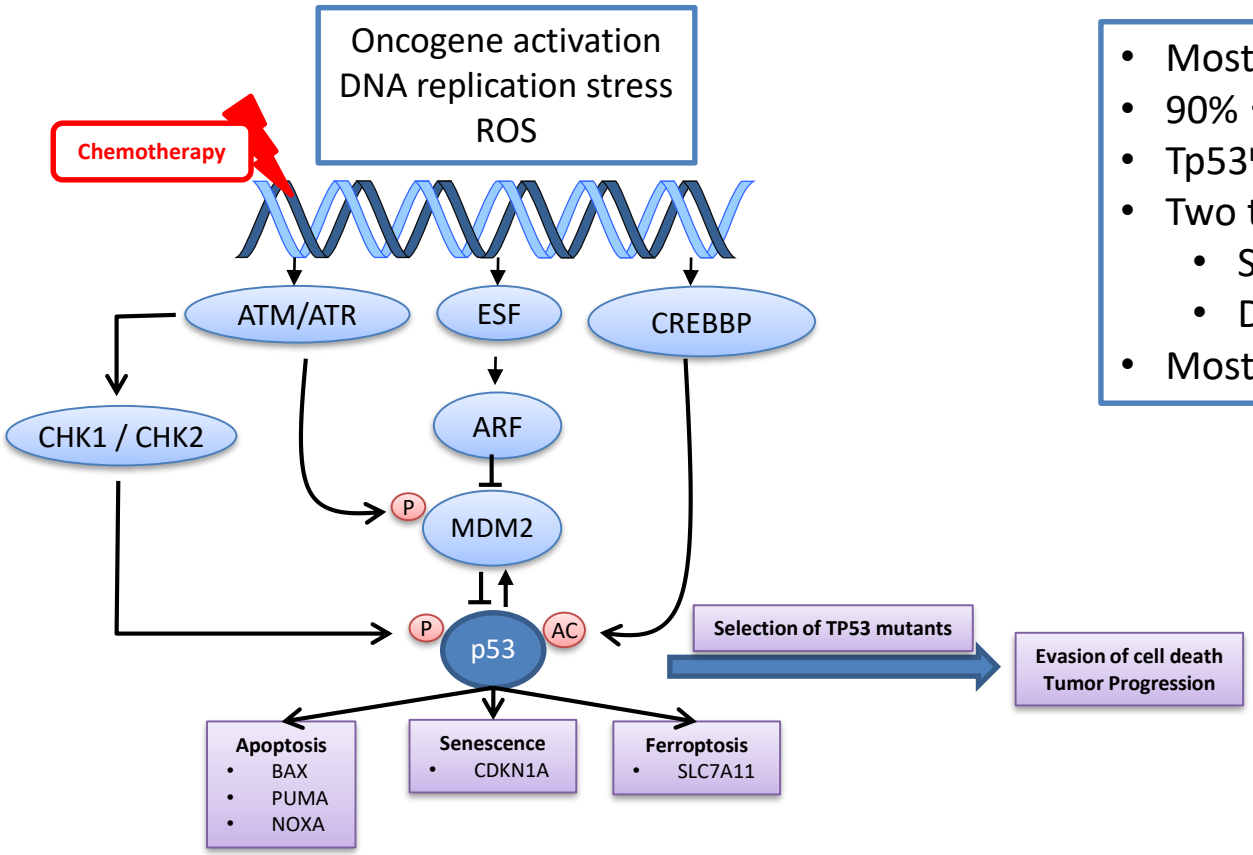
chlorambucil
del11q no (n=96)

del11q yes (n=25)

Barr et al., ASH 2016 (abstract 234)

CLL patients with TP53 dysruptions should not be treated with CIT

Pressure on TP53 pathway in Cancer



- Most mutated gene in cancer
- 90% → Missense mutants
- $Tp53^{mut}$ → gain of function
- Two types of mutants
  - Structural
  - DNA contact
- Most mutants are overexpressed!

Adapted from Bykov V. et al, Nature Review Cancer, 2018

TP53 gene and elephants

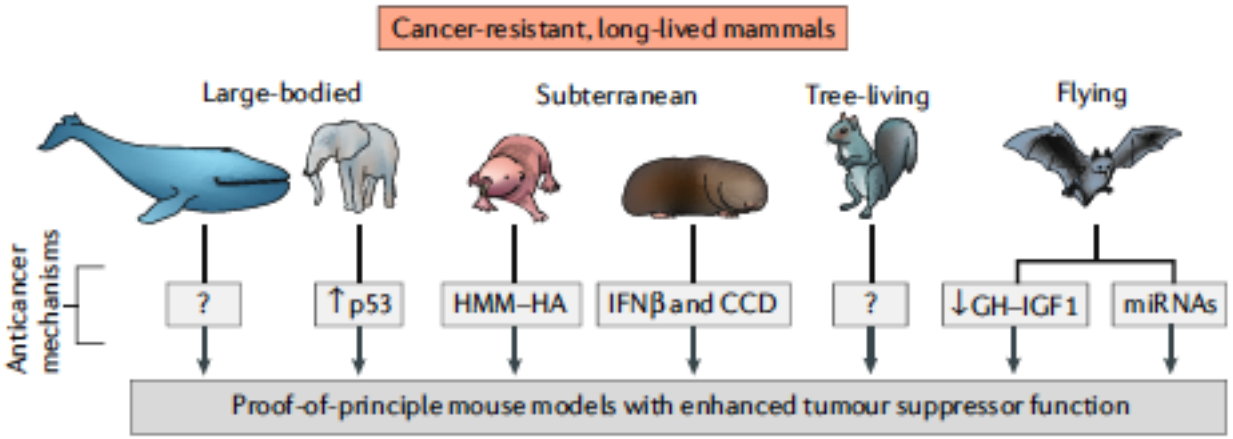
Preliminary Communication

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

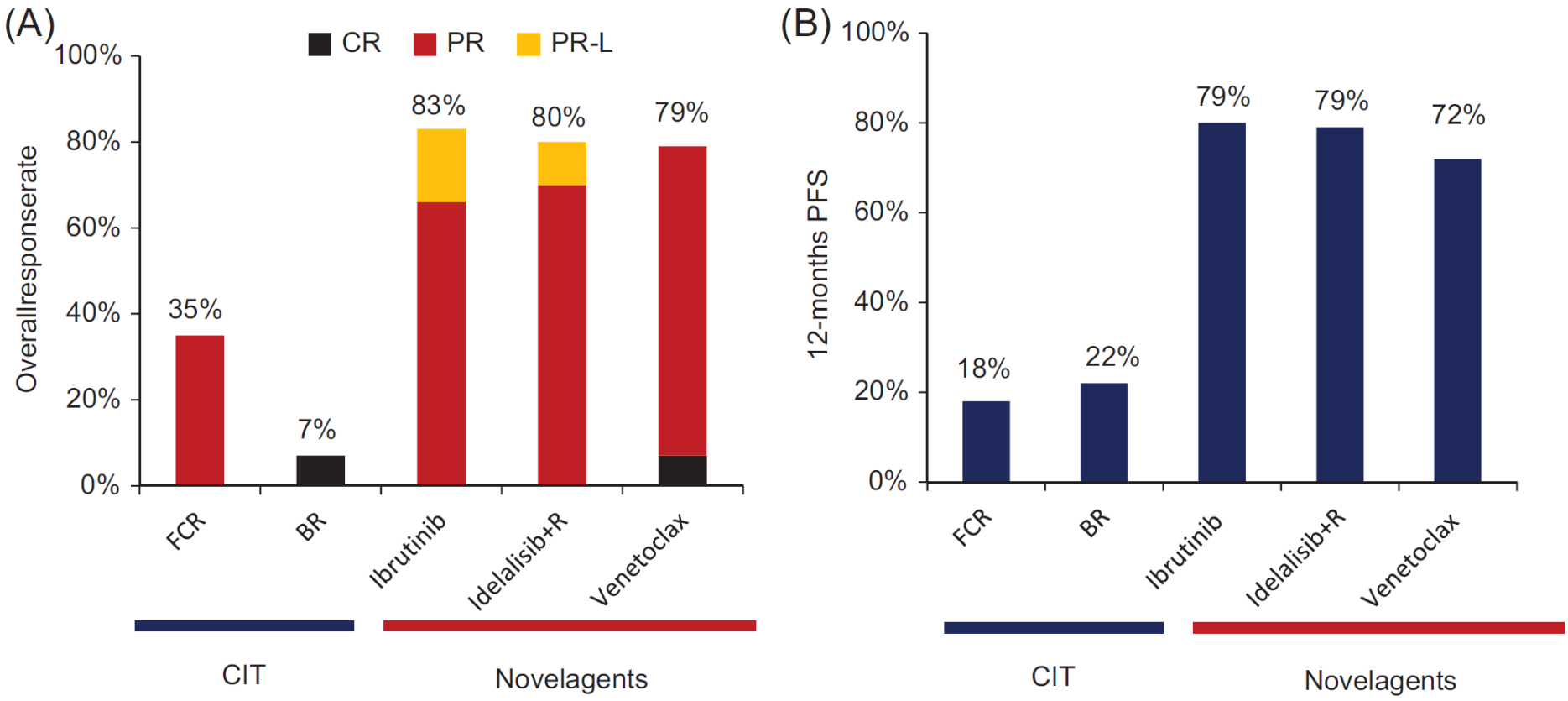
lion, 2% [95% CI, 0%-7%]). Despite their large body size and long life span, elephants remain cancer resistant, with an estimated cancer mortality of 4.81% (95% CI, 3.14%-6.49%), compared with humans, who have 11% to 25% cancer mortality. While humans have 1 copy (2 alleles) of *TP53*, African elephants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

Abegglen et al, JAMA 2015



Seluanov et al, Nat Rev Cancer 2018

TP53 mutations and treatment in CLL



Rossi D, Gerber B, Stüssi G. Predictive and prognostic biomarkers in the era of new targeted therapies for chronic lymphocytic leukemia. Leuk Lymphoma. 2017 Jul;58(7):1548-1560

Hospitales de referencia

- **Hospital Clínico de Valencia**
  - María José Terol
  - Blanca Navarro
  - Javier Chaves
- **Hospital Vall d´Hebron, Barcelona**
  - Francesc Bosch
  - Marta Crespo
- **Hospital Clínico de Salamanca**
  - Marcos González
  - Miguel Alcoceba
- **Hospital Puerta de Hierro, Madrid**
  - José Antonio García-Marco
  - Sandra Nova


GOOD LABORATORY PRACTICE

ERIC european research initiative on CLL TP53 Certified Center

Diploma

Internal ERIC certification on the assessment of *TP53* mutations

Valencia, Clinic University Hospital-INCLIVA. Hematology Lab-GGDU (Genomic and genetics diagnosis unit of INCLIVA)

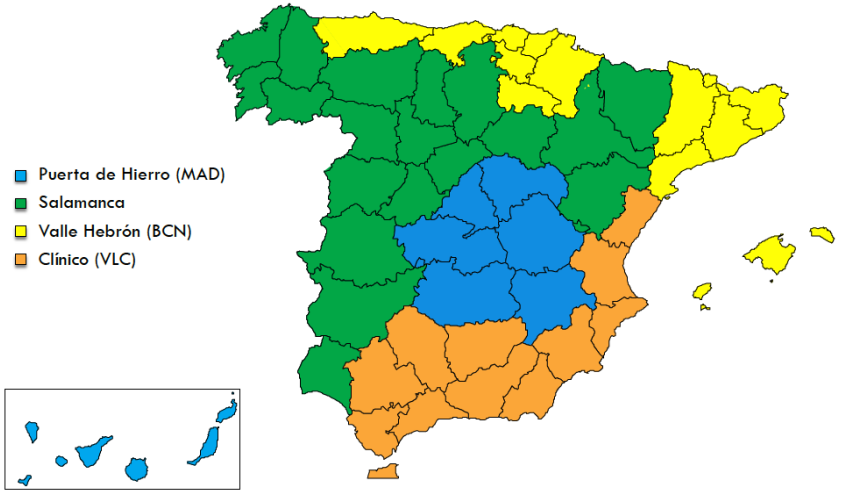
Technique: Next Generation Sequencing and Sanger Sequencing

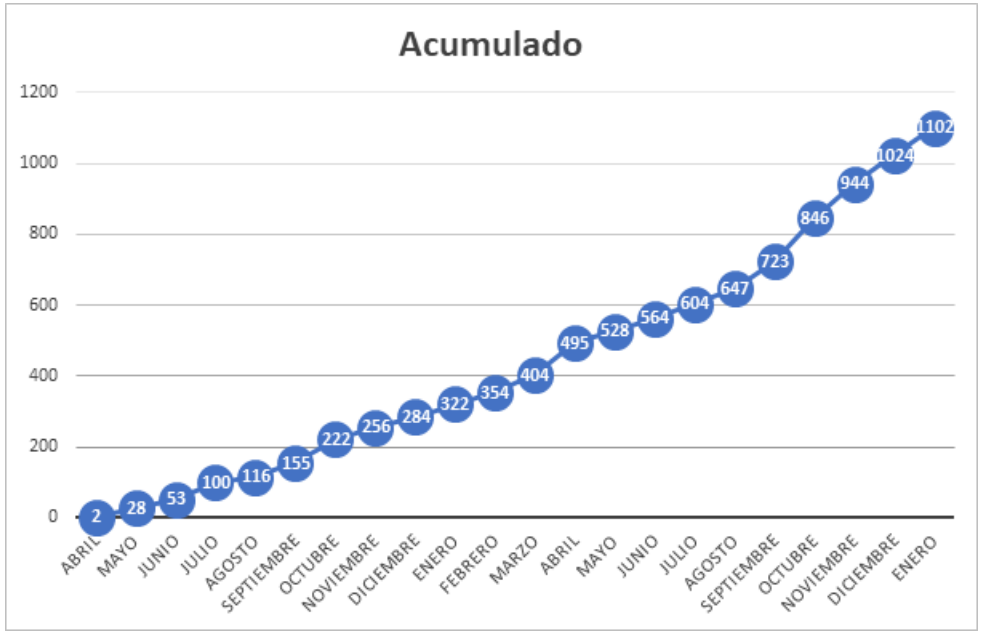
PASS: The laboratory meets highest ERIC standards for TP53 mutation detection. In 5 CLL samples TP53 mutation status was assessed correctly.

14 June 2016

Date of Validation - Valid for 3 years

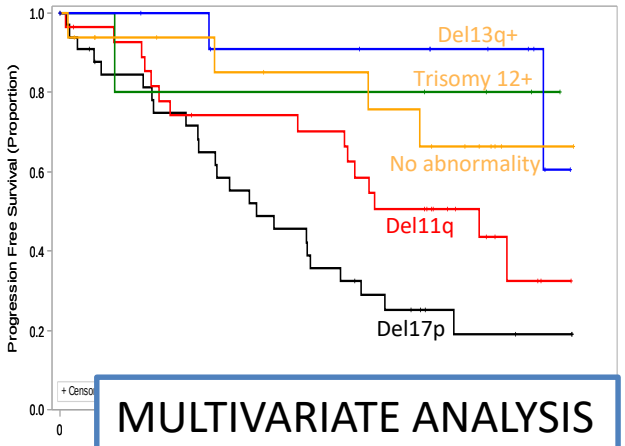
Distribución geográfica





Suboptimal activity of target therapies in del17p

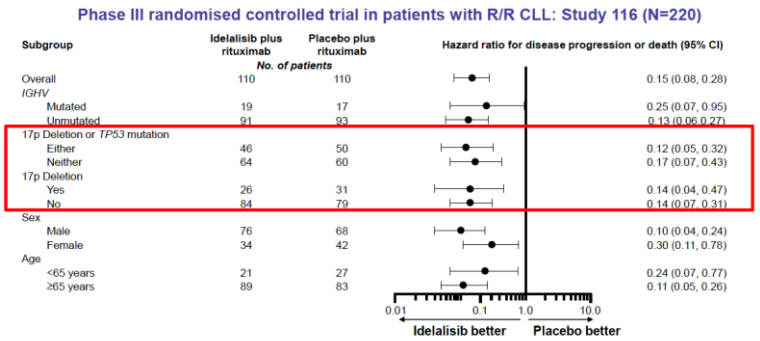
PYC 1102/1103



O'Bri

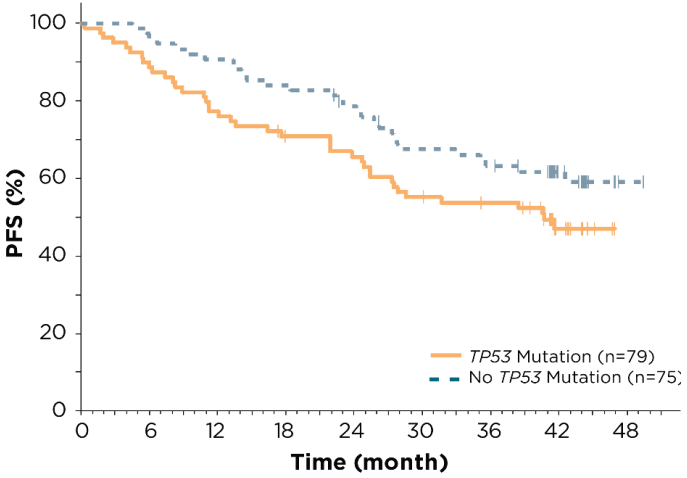
MULTIVARIATE ANALYSIS
- *TP53* abnormalities
- Nr of prior lines

IDELALISIB + RITUXIMAB



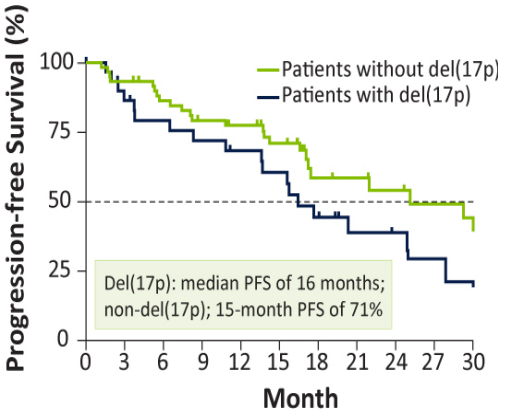
Furman et al, NEJM 2014

RESONATE trial



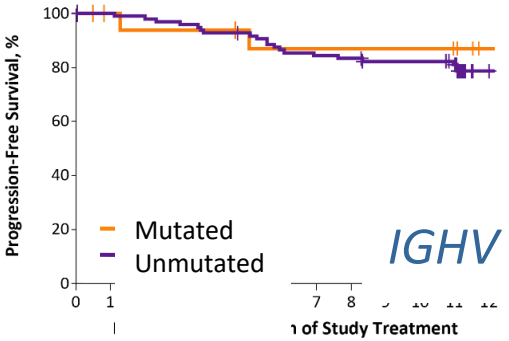
Byrd et al, ASCO 2017

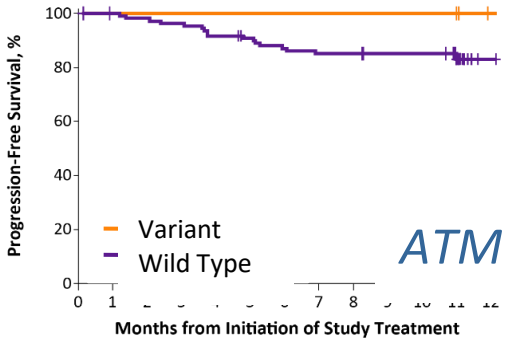
VENETOCLAX

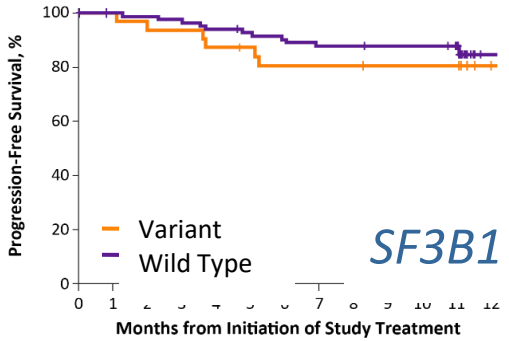


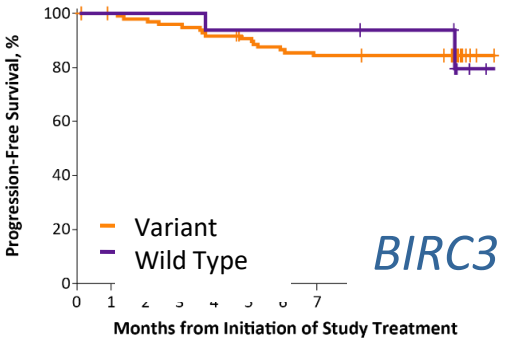
Roberts et al, NEJM 2016

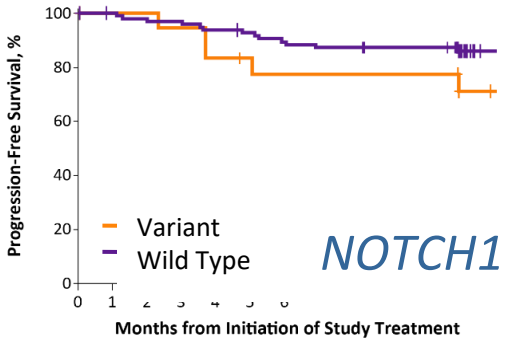
Ibrutinib is active in CLL with additional genomic abnormalities

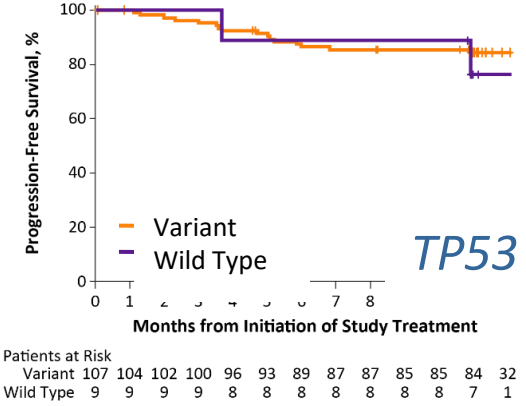












Stilgenbauer et al, ASH 2016 – Resonate 17p

Prognostic & Predictive value of genetic lesions in CLL

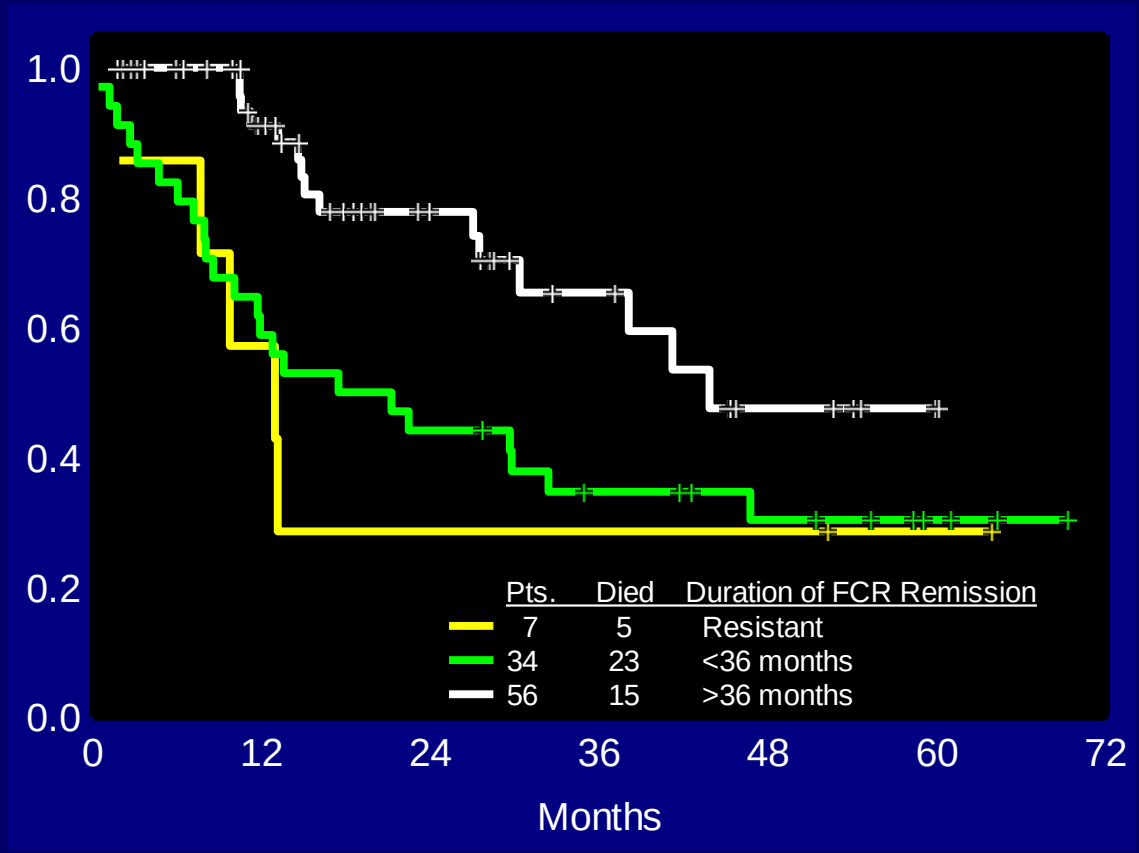
		PROGNOSTIC		PREDICTIVE VALUE	
	FREQ	TTFT	OS 5 yrs	Response to CIT	Response to Target treatment
del13q14	55%	+	90%	=	=
NOTCH-1	15%	+	~55%	*	=
17p / TP53	8%	+	~40%	PFS / OS	PFS
ATM / 11q-	9%	+	60%	PFS / OS	=
SF3B1	8%	+	~55%	PFS	=
BIRC-3	4%	+	~60%	=	=
MYD88	4%	+	100%	=	=

** No differences with or without rituximab*

Bosch & Dalla-Favera, (in press)

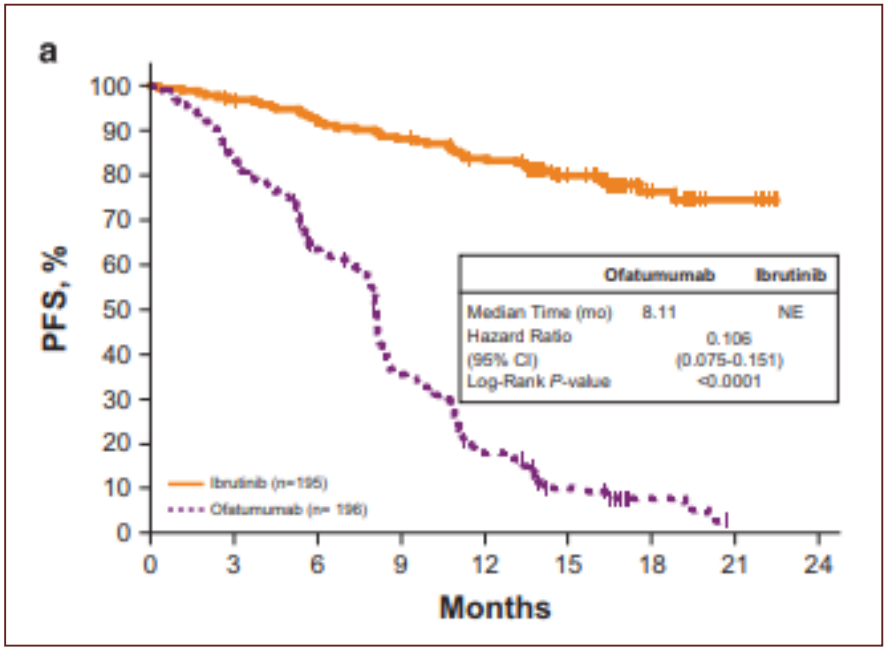
Treatment of early relapse (<36 m) or refractoriness to CIT

Survival from First Salvage by Duration of Initial FCR Response

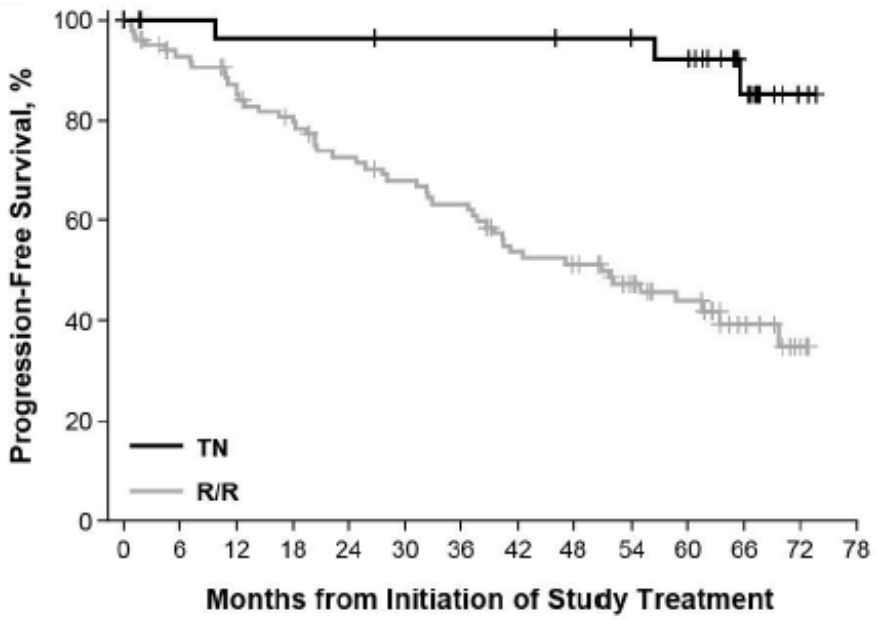


Courtesy Susan O'Brien

High activity of ibrutinib in R/R CLL



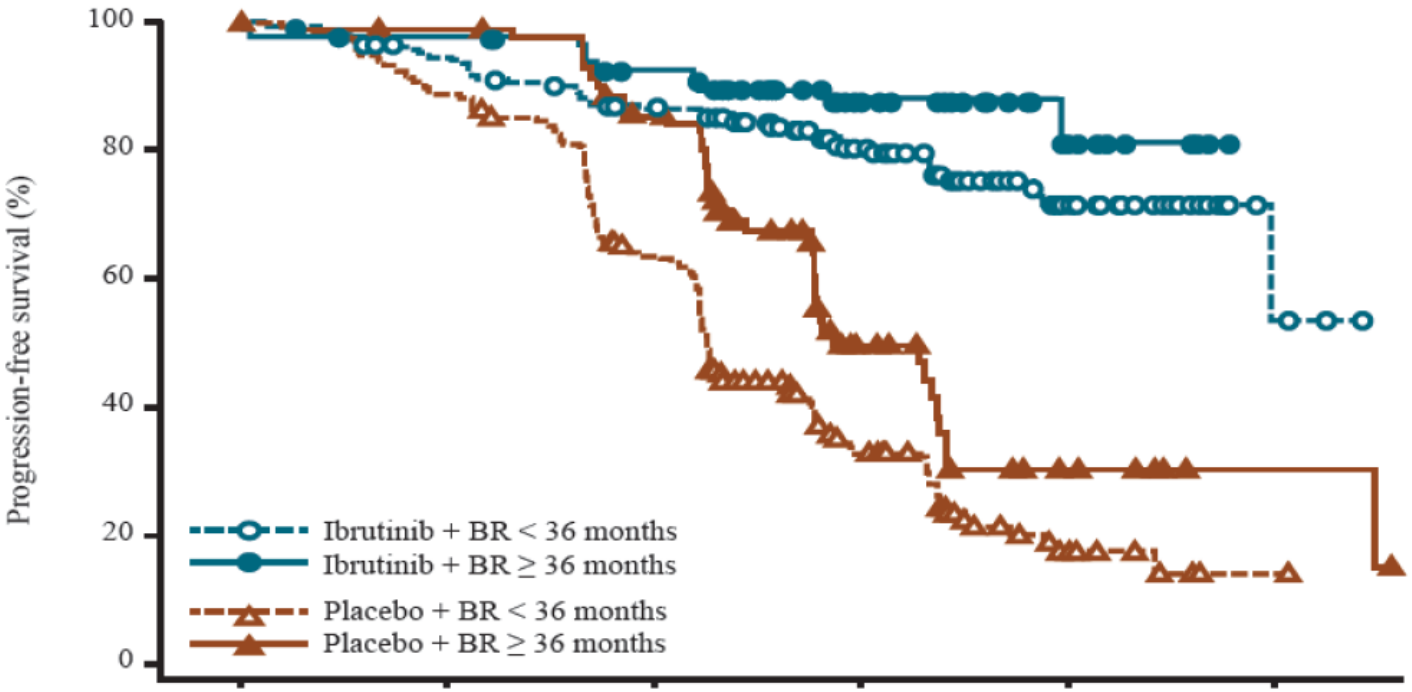
Brown J et al. Leukemia 2018



	Median PFS	5-year PFS
TN (n=31)	NR	92%
R/R (n=101)	51 mo	43%

S. O'Brien et al., Blood 2018

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



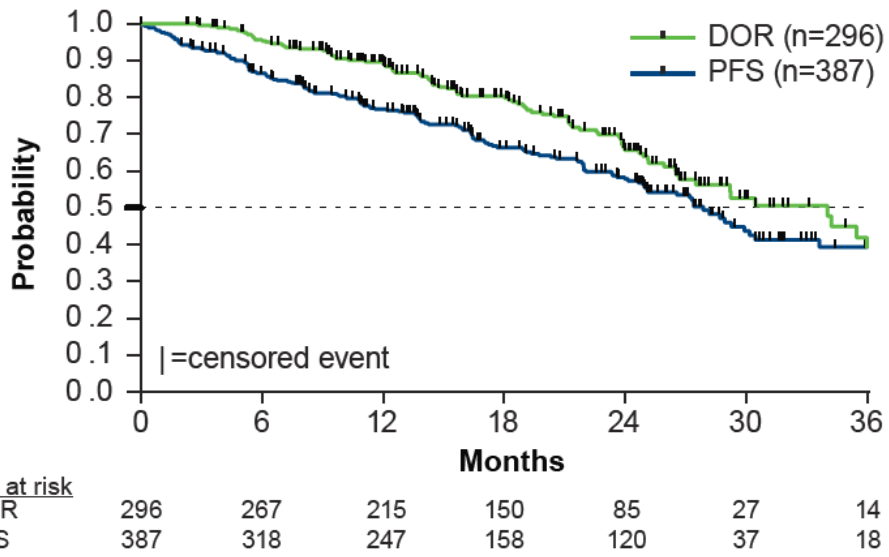
Patients at risk:						
Ibrutinib + BR ≥ 36 mo	85	77	68	36	11	0
Placebo + BR ≥ 36 mo	82	77	64	21	7	2
Ibrutinib + BR < 36 mo	204	184	165	104	41	3
Placebo + BR < 36 mo	207	176	122	45	10	1

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

Pooled Multi-Trial Analysis of Venetoclax Efficacy in R/R CLL

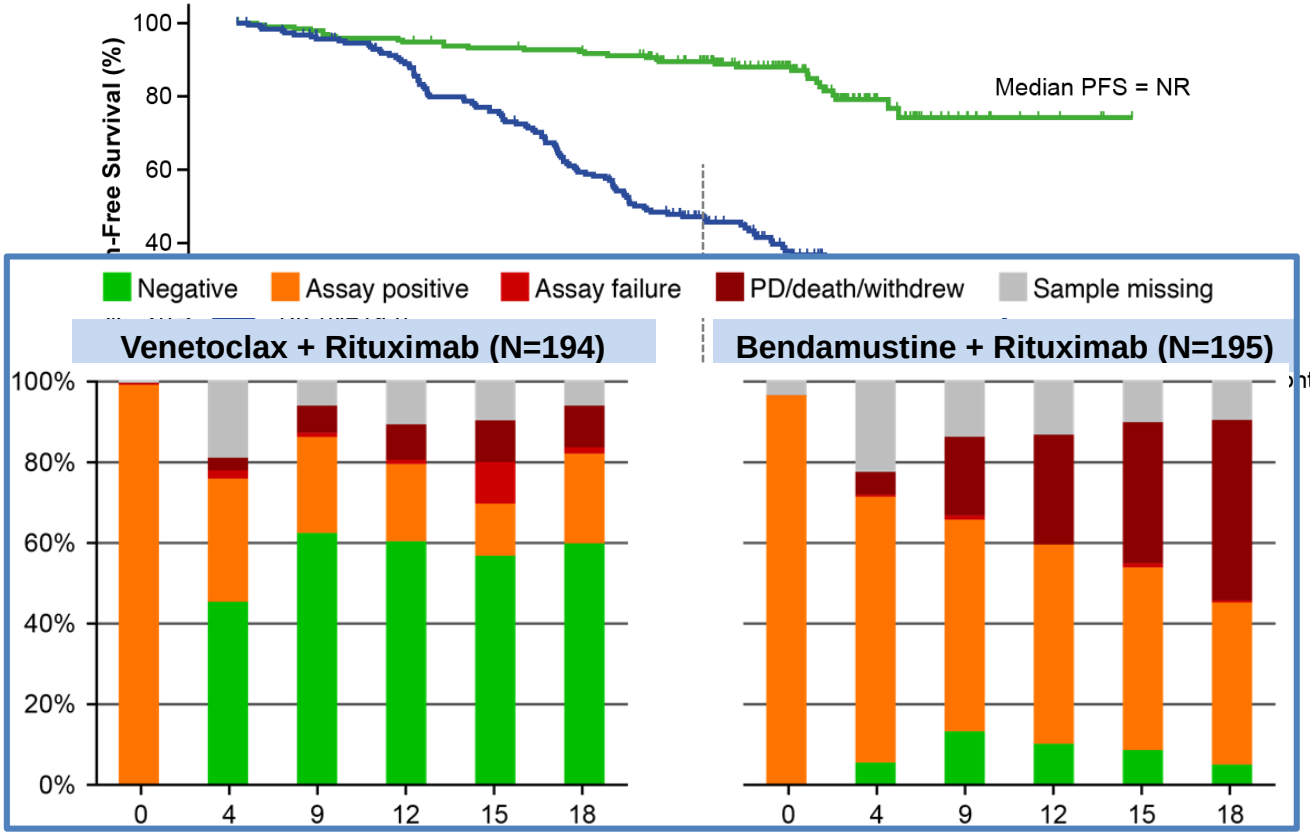
- **ORR 76%**
- **CR/CRi → 22%; median time to CR/CRi was 8.3 months**
- **MRD-negativity (BM) in 15%**

Patient Disposition	N=387
Venetoclax 400 mg/day	305
Median duration of venetoclax, months	16.3 (0.03-54)
Discontinuation, % Due to PD Due to AEs Due to SCT Withdrew consent	50 34 10 3 3



Courtesy J. Brown, Boston

Investigator-Assessed PFS Superior for VenR vs. BR (Murano Trial)



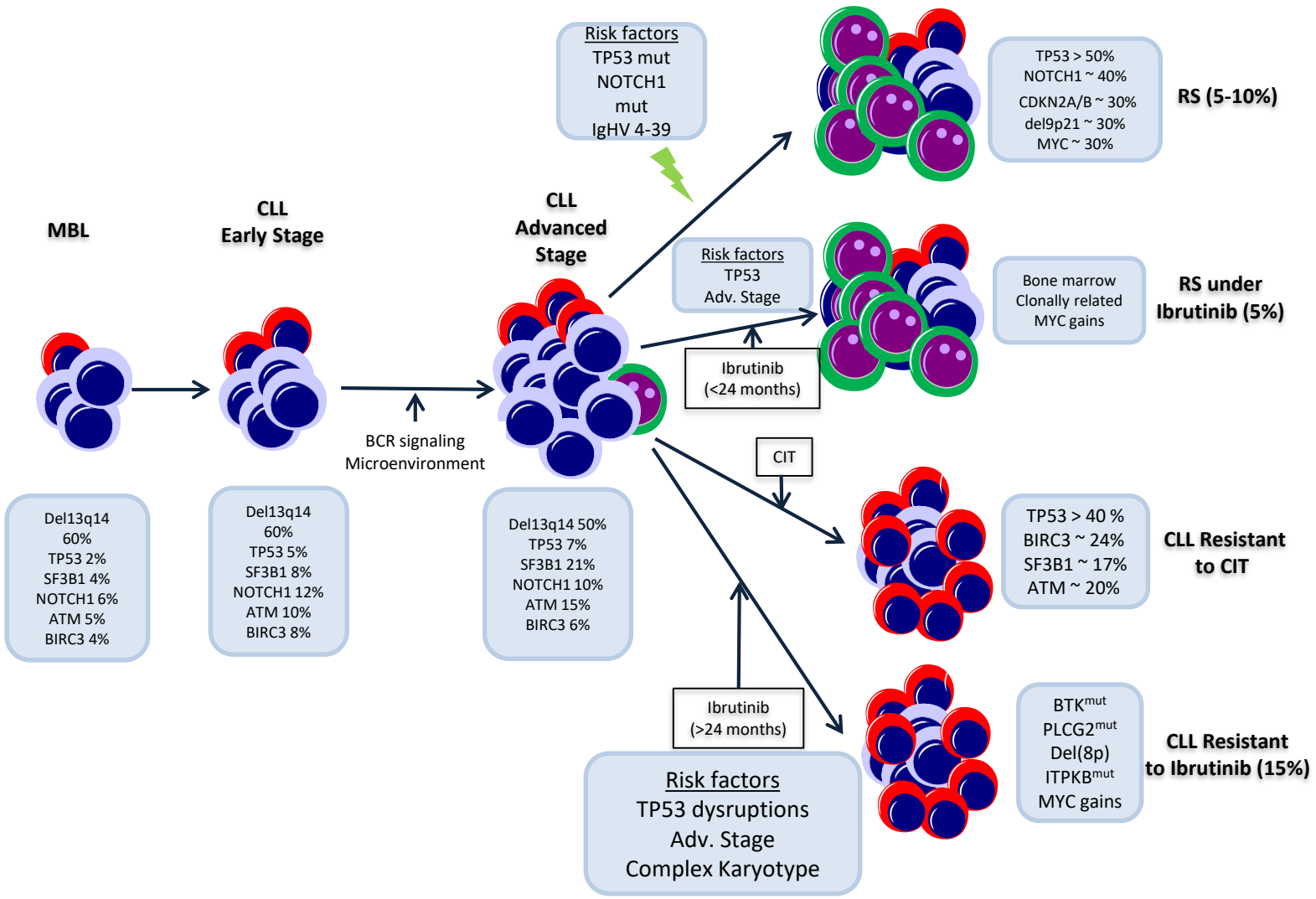
J Seymour et al, NEJM 2018

Contending with Progression to Ibrutinib

Ibrutinib in CLL: Real-World experience

	Mayo[1]	Poland[2]	UK[3]	France[4]	USA[5]
N	124	224	315	428	621
Median age	65	63	69	70	62
Previous Tx	NR	3 (1-10)	2(1-14)	3 (0-10)	NR
Median FU (months)	6	10	16	3	17
PFS	NR	79% at 12 m	NR	NR	35 m (median)
OS	NR	82% at 12 m	77% at 16m	NR	75% at 30 m
Discontinuation	22%	19% AEs→ 50% PD→ 38%	26% AE→52% PD→37%	13% AE→37% PD→28%	37% AEs→ 50% PD→ 21%
Dose reduction	NR	15%	26%	NR	20%
Predictive variables			Age, ECOG,		CK

[1]*Parikh SA et al, Blood 2015*
[2]*Iskierka-Jażdżewska et al, L&L 2017*
[3]*UK CLL Forum. Haematologica, 2016*
[4]*Ysebaert et al, Am J Hematol 2017*
[5]*Mato et al, Haematologica 2018*

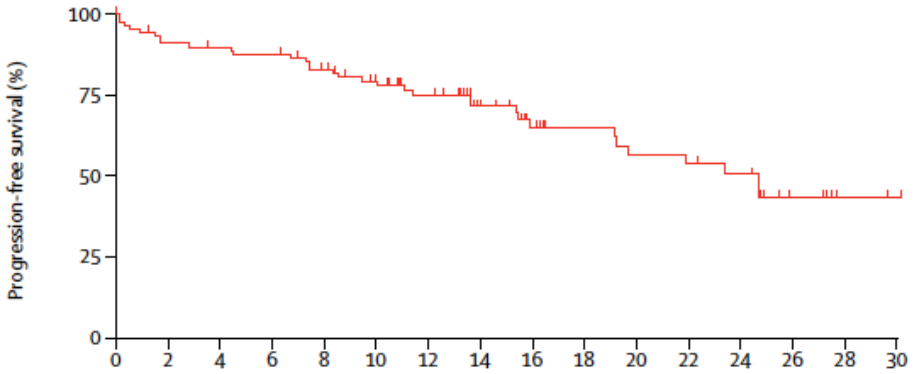


Bosch & Dalla-Favera, NRCO 2018 (in press)

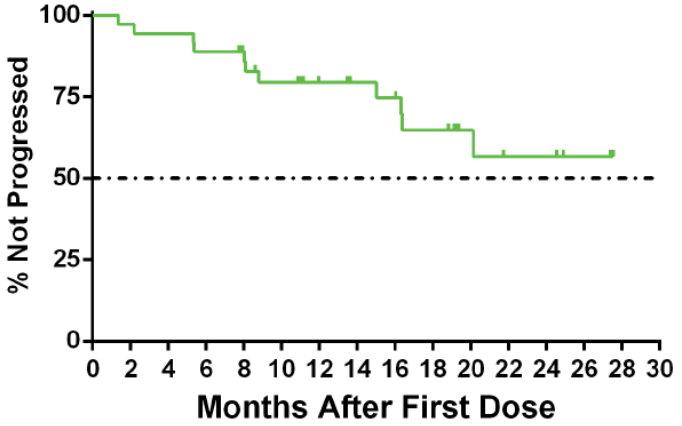
Venetoclax after Ibrutinib or idelalisib

	After Ibrutinib[1]	After Idelalisib[2]
N=	91	31
ORR	65%	67%
CR	9%	6%
Neutropenia G3-4	52%	50%
TTP (median)	24 months	NR

Venetoclax after ibrutinib

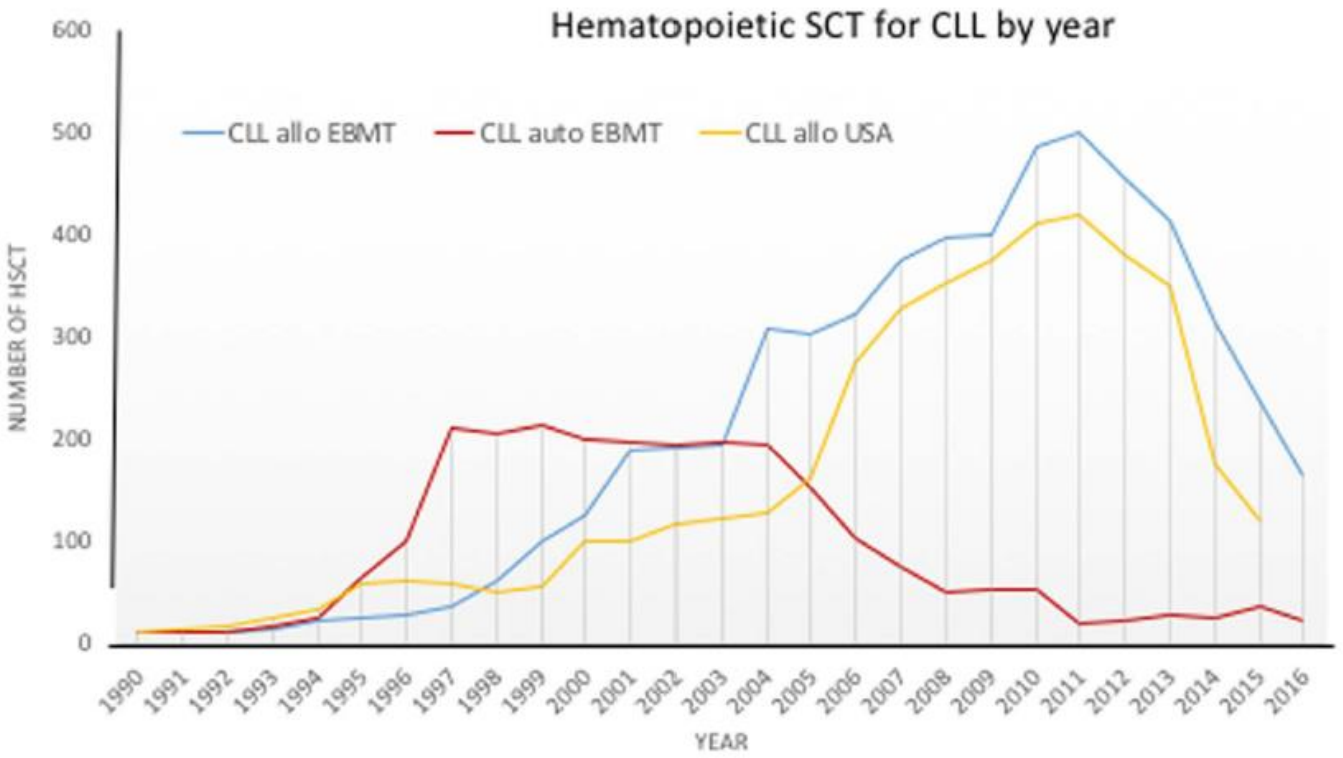


Venetoclax after idelalisib



1. Jones et al, Lancet Oncology, 2018; *2. Coutré et al, Blood 2018*

What happened to allogeneic HCT?



Gribben et al, Blood 2018

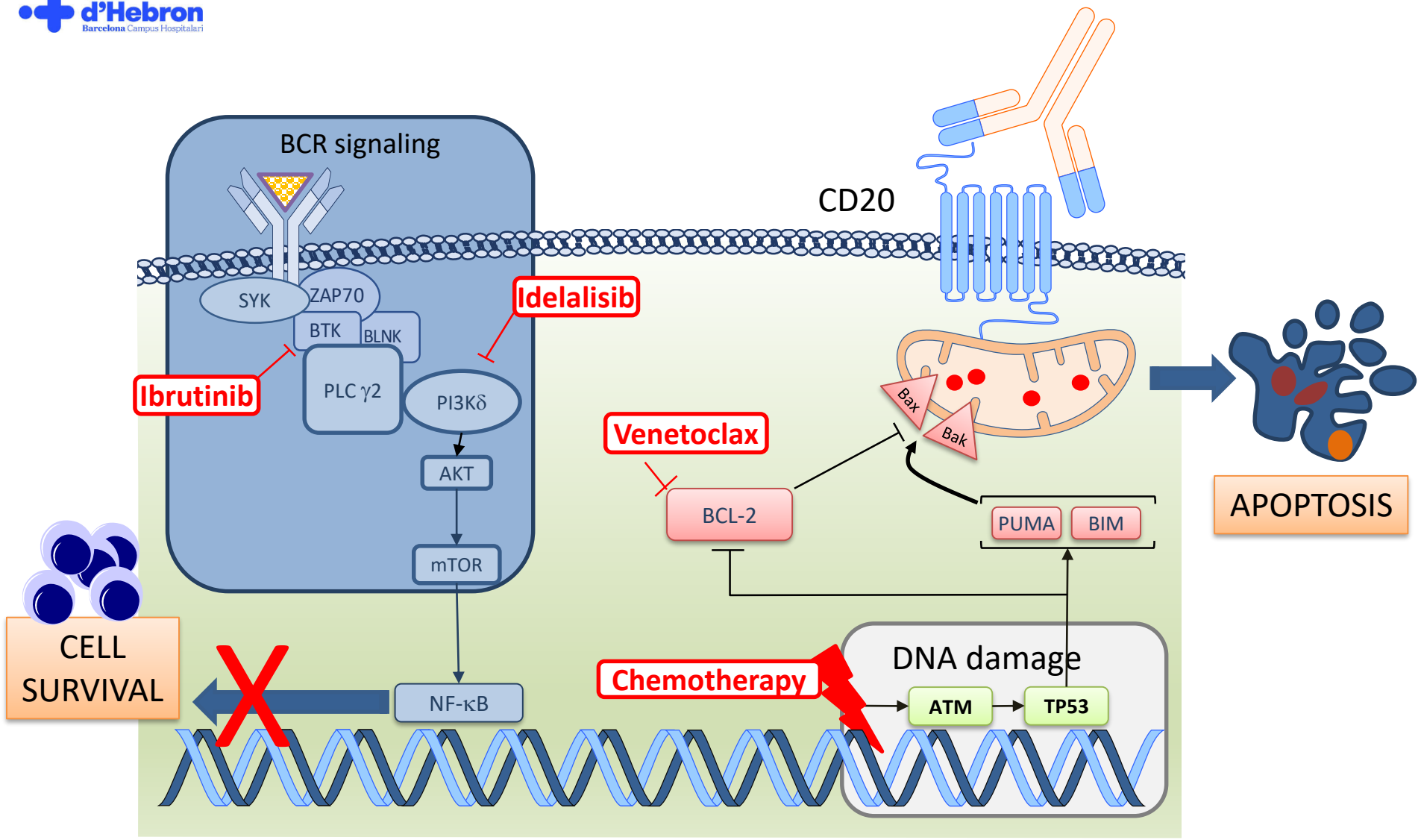
Summary of clinical outcome with 2nd generation (CD28, 41BBz) CAR T cells for CLL

Site	Ref	N	Gene Transfer	Costim Domain	Conditioning	CAR T cell Dose	ORR	CR
MSKCC	Brentjens, Blood, 2011	8	Gamma-retrovirus	CD28	None or Cy 1.5-3 g/m^2	Cohort receiving no CCT: 1.2-3.0x10^7 CAR$^+$ T cells/kg Cy cohort: 0.4-1.0x10^7 CAR$^+$ T cells/kg	0/8 (↓LN short of PR, 1/8; SD x ≥2 months, 2/8)	0%
MSKCC	Geyer, ASCO, 2016	8	Gamma-retrovirus	CD28	Cy 600 mg/m^2	3x10^6, 1x10^7, or 3x10^7 CAR$^+$ T cells/kg	4/8 (clinical CR, n=2; PR, n=2; SD, n=1)	25%
NCI	Kochenderfer, Blood, 2012	4	Gamma-retrovirus	CD28	Cy 60 mg/kg x 2d + Flu 25 mg/m^2 x 5d	0.3-2.8x10^7 CAR$^+$ T cells/kg	3/4 (CR, n=1; PR, n=2; SD, n=1)	25%
NCI	Kochenderfer, J Clin Oncol, 2014	4	Gamma-retrovirus	CD28	Cy 60 mg/kg x 1-2d + Flu 25 mg/m^2 x 5d	1–4x10^6 CAR$^+$ T cells/kg	4/4 (CR, n=3; PR, n=1)	75%
NCI	Brudno, J Clin Oncol, 2016	5	Gamma-retrovirus	CD28	None (post-AlloHSCT)	0.4-8.2x10^6 CAR$^+$ T cells/kg	2/5 (CR, n=1; PR, n=1; SD, n=1)	20%
FHCRC	Turtle, ASH, 2016	18	Lentivirus	4-1BB	Cy 30-60 mg/kg x1 + Flu 25 mg/m^2 x 3d (n=15)	2x10^5, 2x10^6, and 2x10^7 CAR$^+$ T cells/kg;1:1 CD4$^+$:CD8$^+$	13/17 (CR, n=5; PR, n=8)	29%
UPenn	Porter, Sci Trans Med, 2015	14	Lentivirus	4-1BB	Investigator's choice	0.14–11x10^8 CAR$^+$ T cells	8/14 (MRD negative CR, n=4; PR, n=4)	29%
UPenn	Porter, ASCO, 2016	35	Lentivirus	4-1BB	Investigator's choice	Stage 1: 5x10^7 vs. 5x10^8 CAR$^+$ T cells Stage 2: 5x10^8 CAR$^+$ T cells	9/17 (CR, n=6; PR, n=3) among pts treated w/stage 2 CAR T cell dose:	35%

CR ~20-35%

Courtesy of J Park

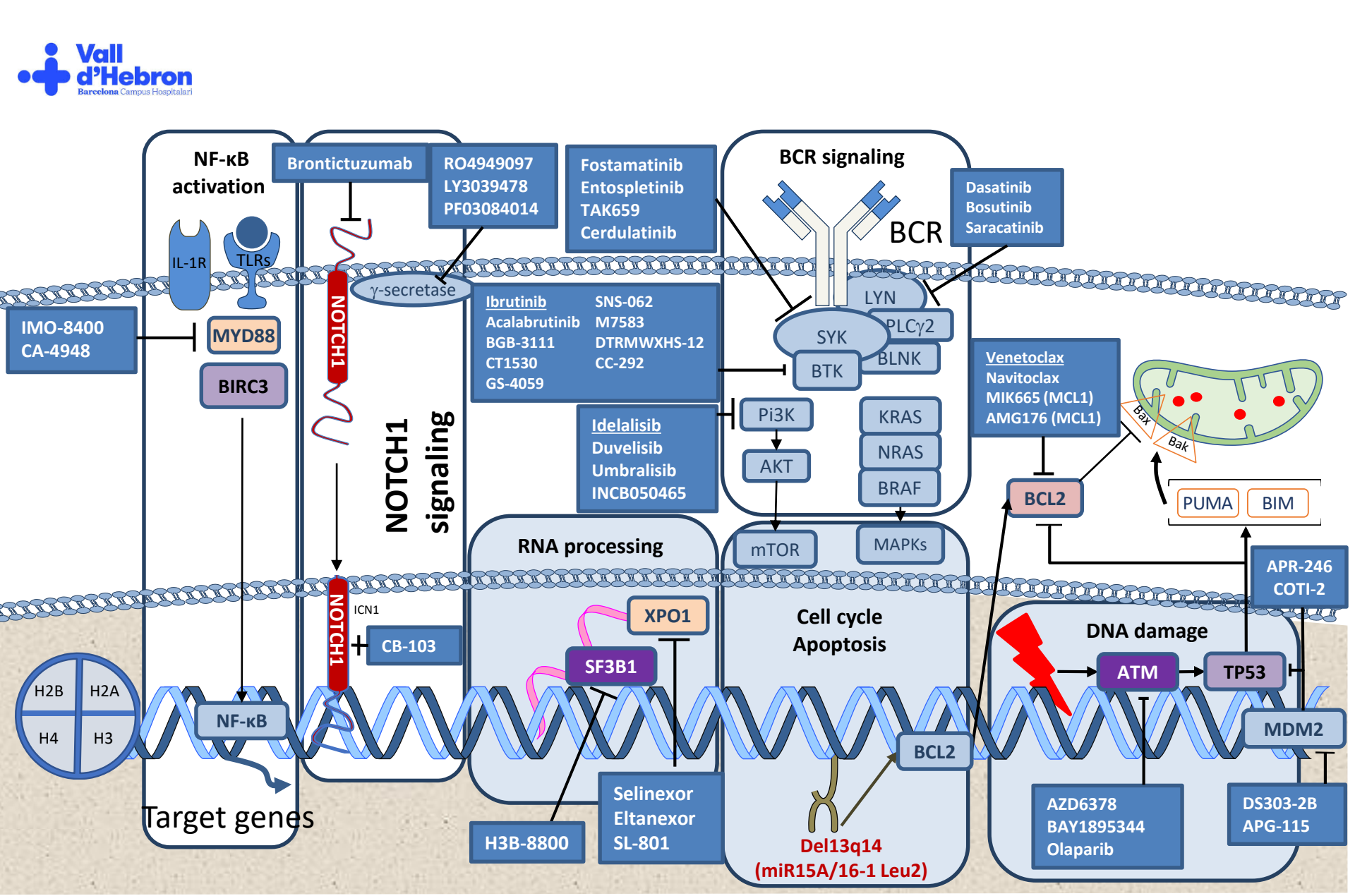
Park J et al. *Blood* 2016;127(26):3312-20



Bosch & Hallek, Blood, Apr 2018

CT		mAB		Targeted			Study	Line	n	CR(%)	MRD(%)
FC	B	R	Ob	Ibru	Idela	V					
*		*		*			Davids et al.	TN	35	21	20
	*	*		*			Helios	R/R	289	40	25
*			*	*				TN	32		87*
	*	*			*		Barrientos	R/R	207	*PFS 23 months*	
		*				*	Murano	R/R	194	60	60
		*		*			ILLUMINATE	TN	212		
		*		*			Burger et al.	TN	104	28	5 pts
		*		*			Bosch et al.	TN	83		
			*			*	G-CLL14	TN	13	58%	100%
			*			*	Flinn et al	TN	32	72	78
		*	*	*		*	G-CLL13	TN			
				*		*	Jain et al	TN R/R	40 37	100 80	100 40
				*		*	Hillmen et al	R/R	38	49	30
				*		*	Rogers et al	TN	24	20	46
				*		*	CAPTIVATE	TN	164	36	100

30 pts reported

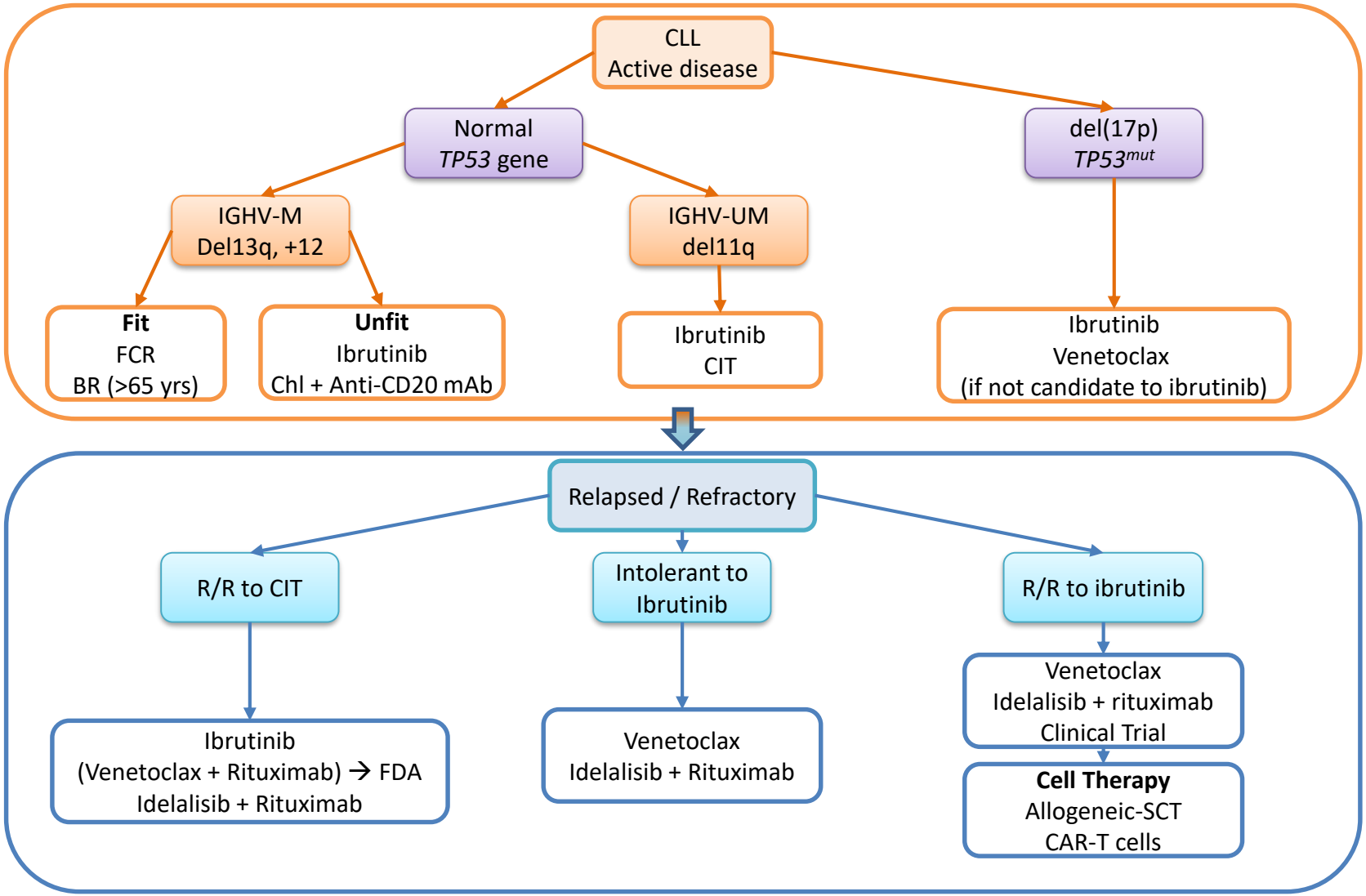


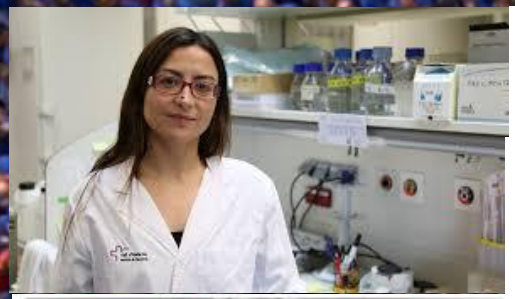
Bosch & Dalla-Favera, NRCO 2018 (in press)

How do I treat High-Risk CLL?

- CLL patients should be tested for biomarkers predicting response
- High-risk CLL usually do not respond to CIT → Use Novel agents
- Three classes of highly effective oral targeted inhibitors, mostly approved as single agents given continuously *about to change*
- Combine best agents
  - To maximize number of MRD-negative remissions
  - To limit treatment duration → less toxicity and cost
- Test *Immunotherapies (checkpoint inhibitors, Allo-SCT, CAR-T cells)* in high-risk / Richter syndrome

How do I treat (high-risk) CLL





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