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GELLC Grupo Español de Leucemia Linfocítica Crónica

SOCIEDAD ESPAÑOLA DE HEMATOLOGÍA Y HEMOTERAPIA

PROGRAMA DE FORMACIÓN

FEHH FUNDACIÓN ESPAÑOLA DE HEMATOLOGÍA Y HEMOTERAPIA

Inhibidores de la vía del BCR

Tratamiento antineoplásico en Hematologia
Madrid, 23 y 24 de octubre de 2014

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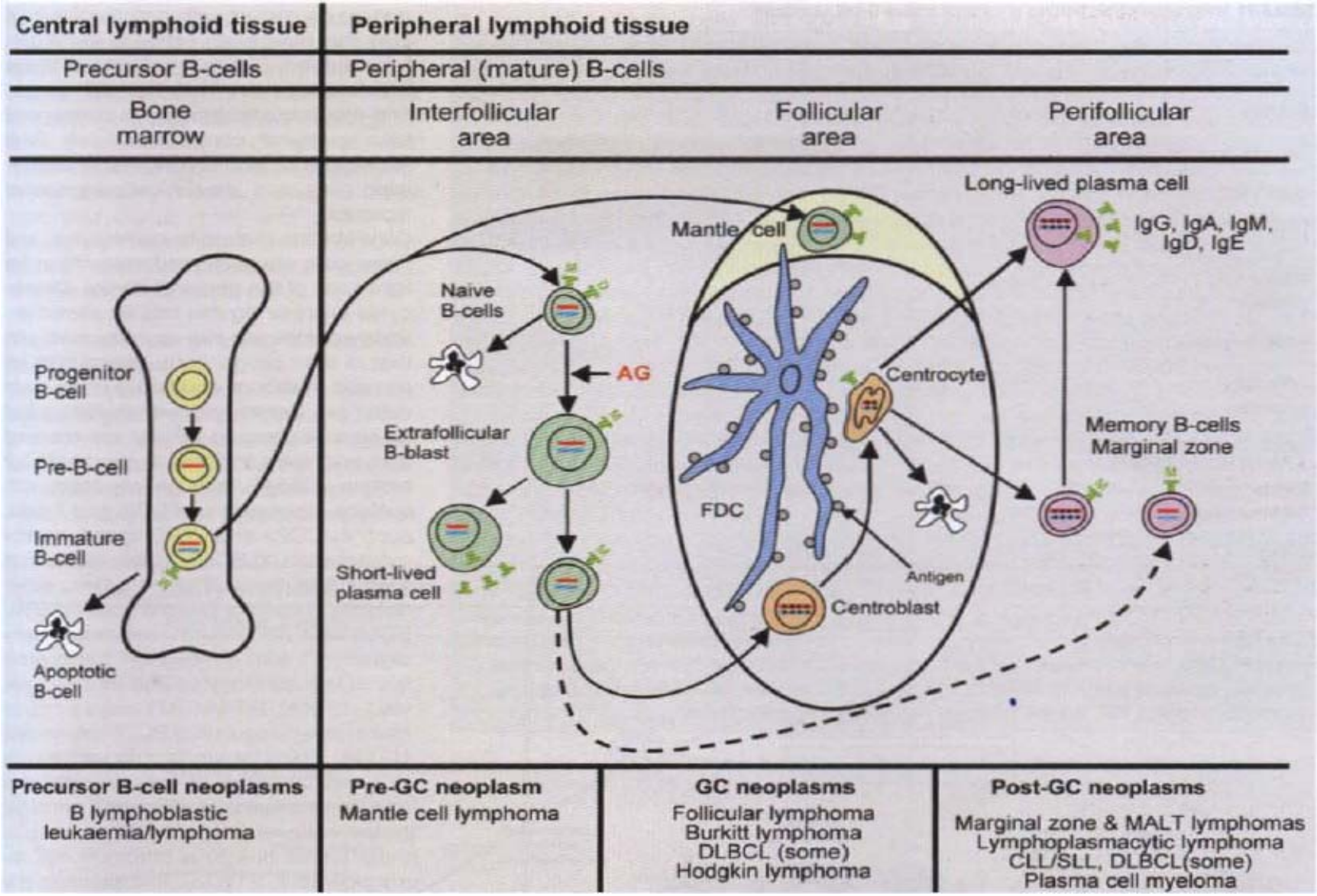
GOALS

1. Normal B-cell development and lymphomagenesis

1. Importance of the BCR in normal B-cells and lymphoid neoplasms

2. Mechanisms of action of the BCR pathway inhibitors

Origin & classification of B-cell neoplasms



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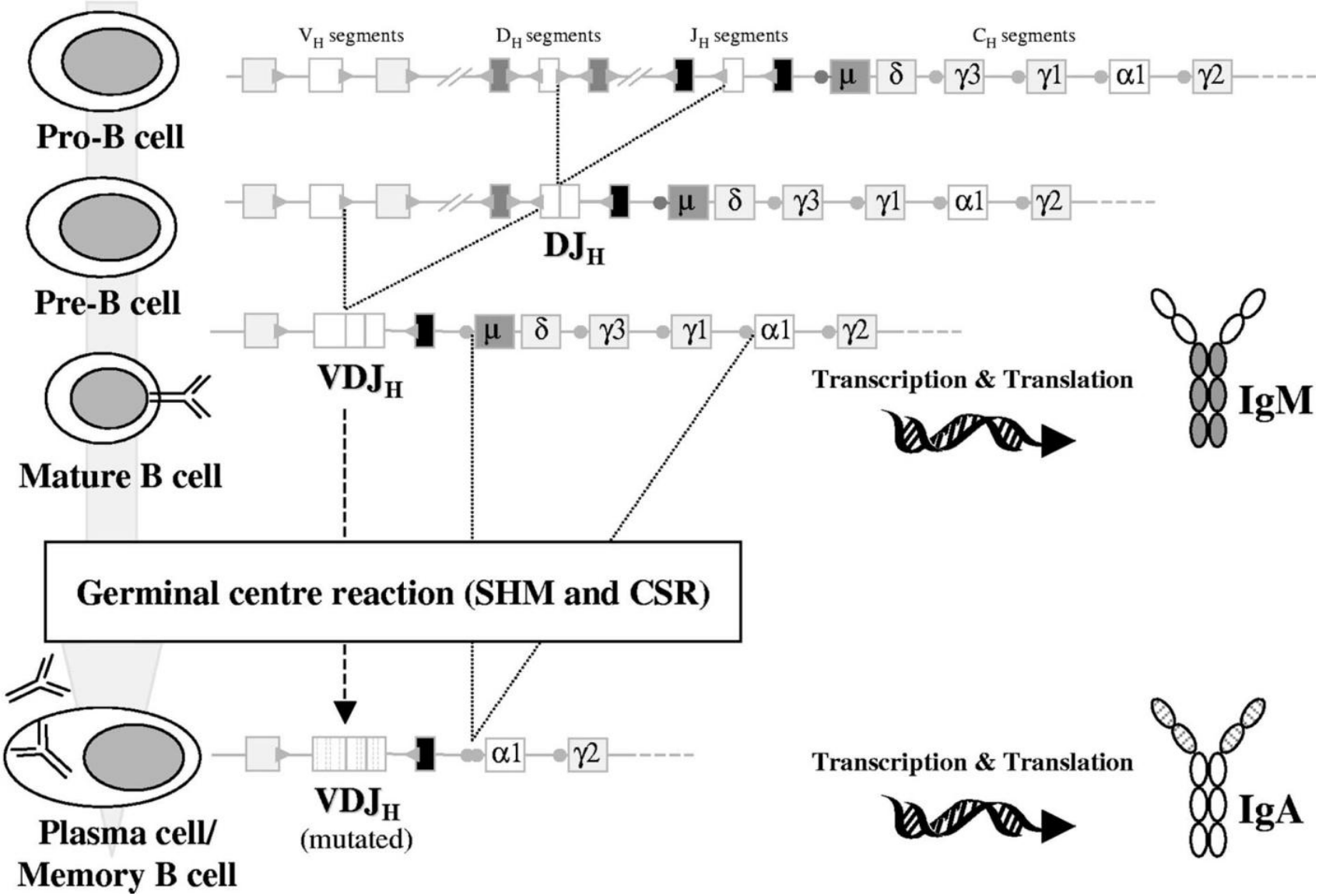
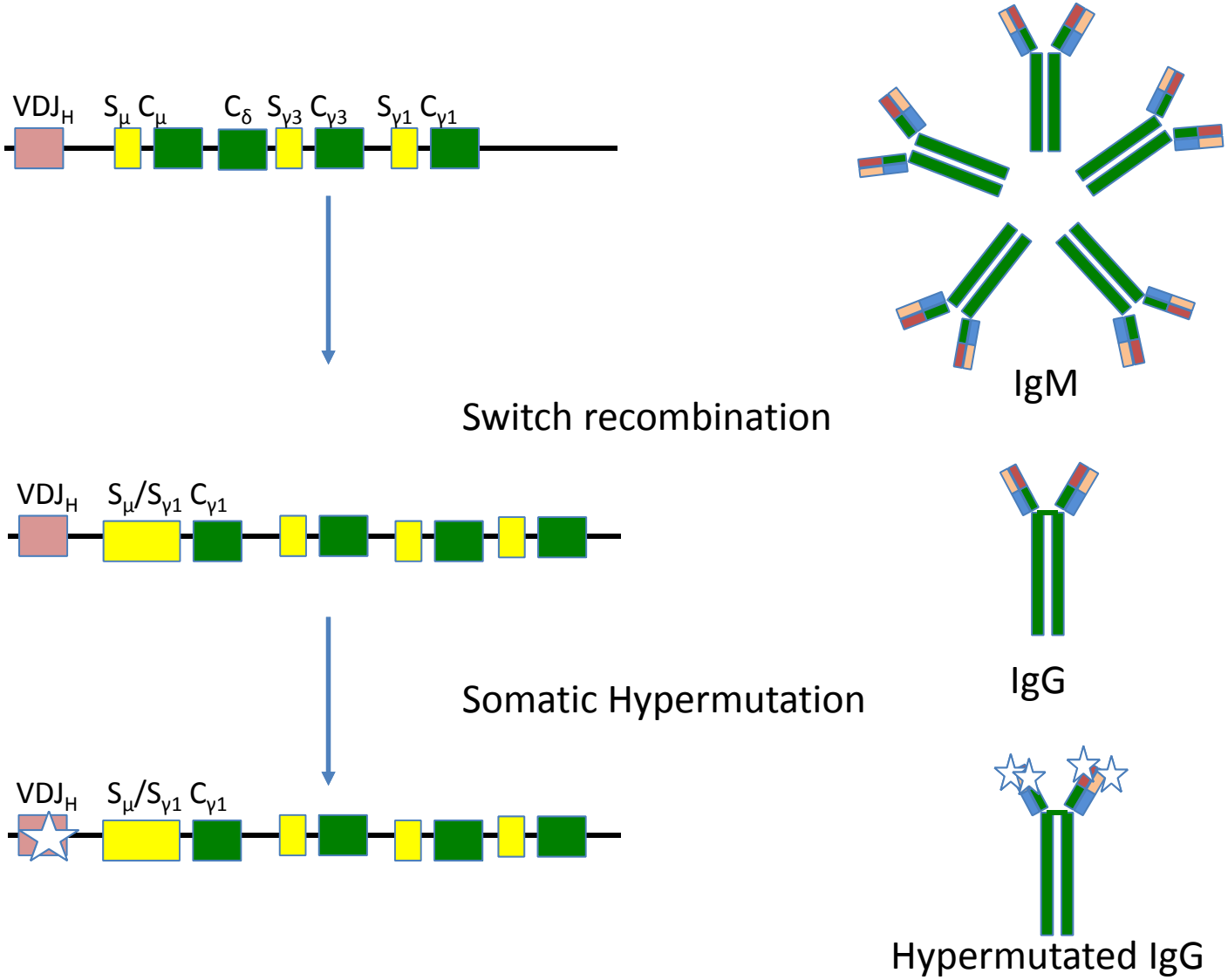
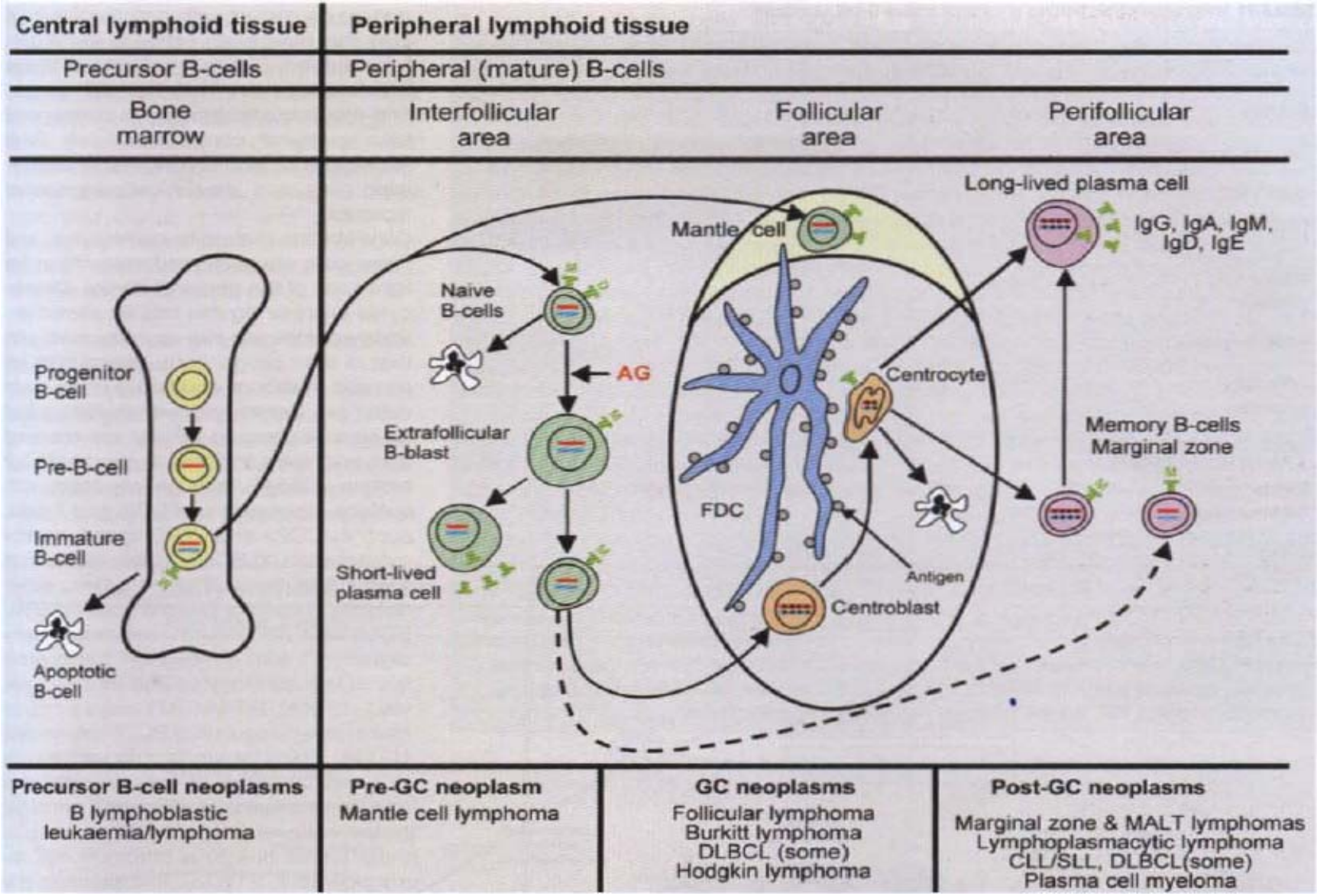


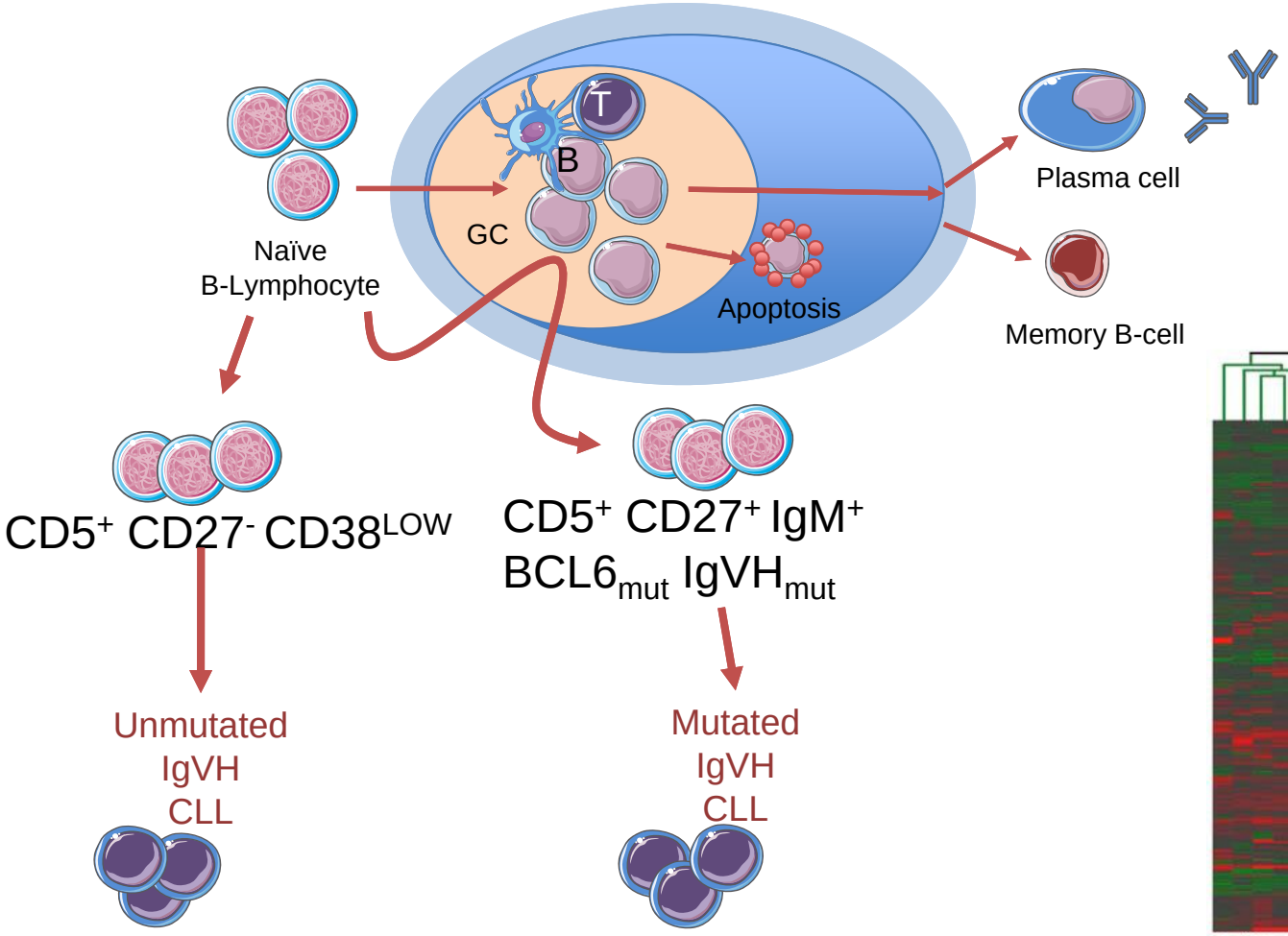
Somatic Hypermutation in CLL

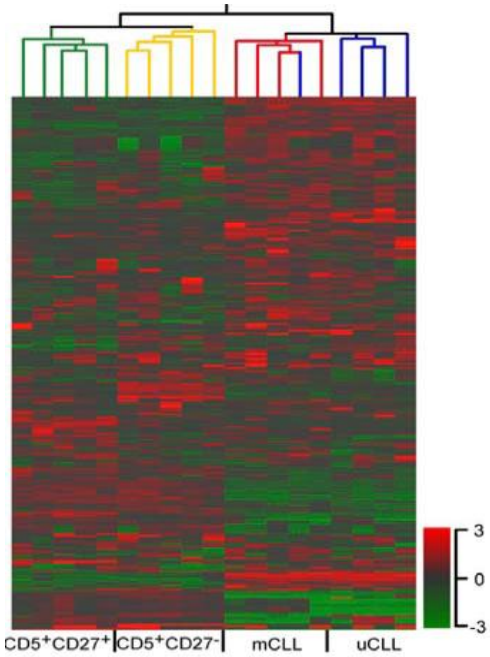


Origin & classification of B-cell neoplasms



CLL: Normal cell counterpart

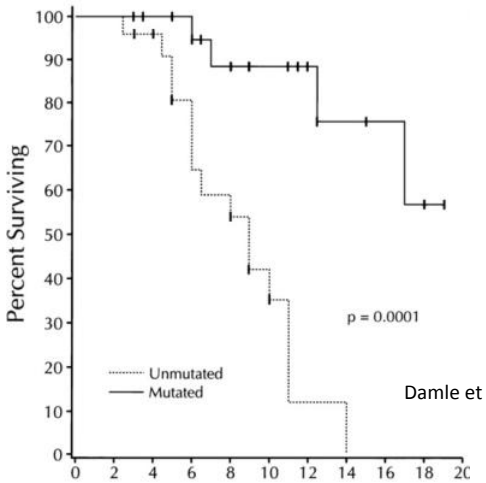




Seifert et al, JEM 2012; 209:2183-2198

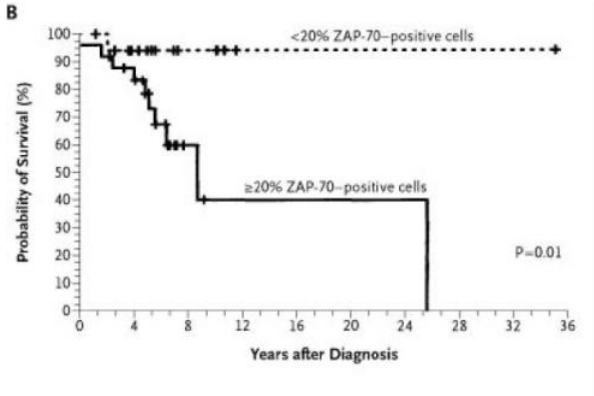
Clinical relevance of factors related to BCR

- IgVH Mutational status



Damle et al, Blood 1999

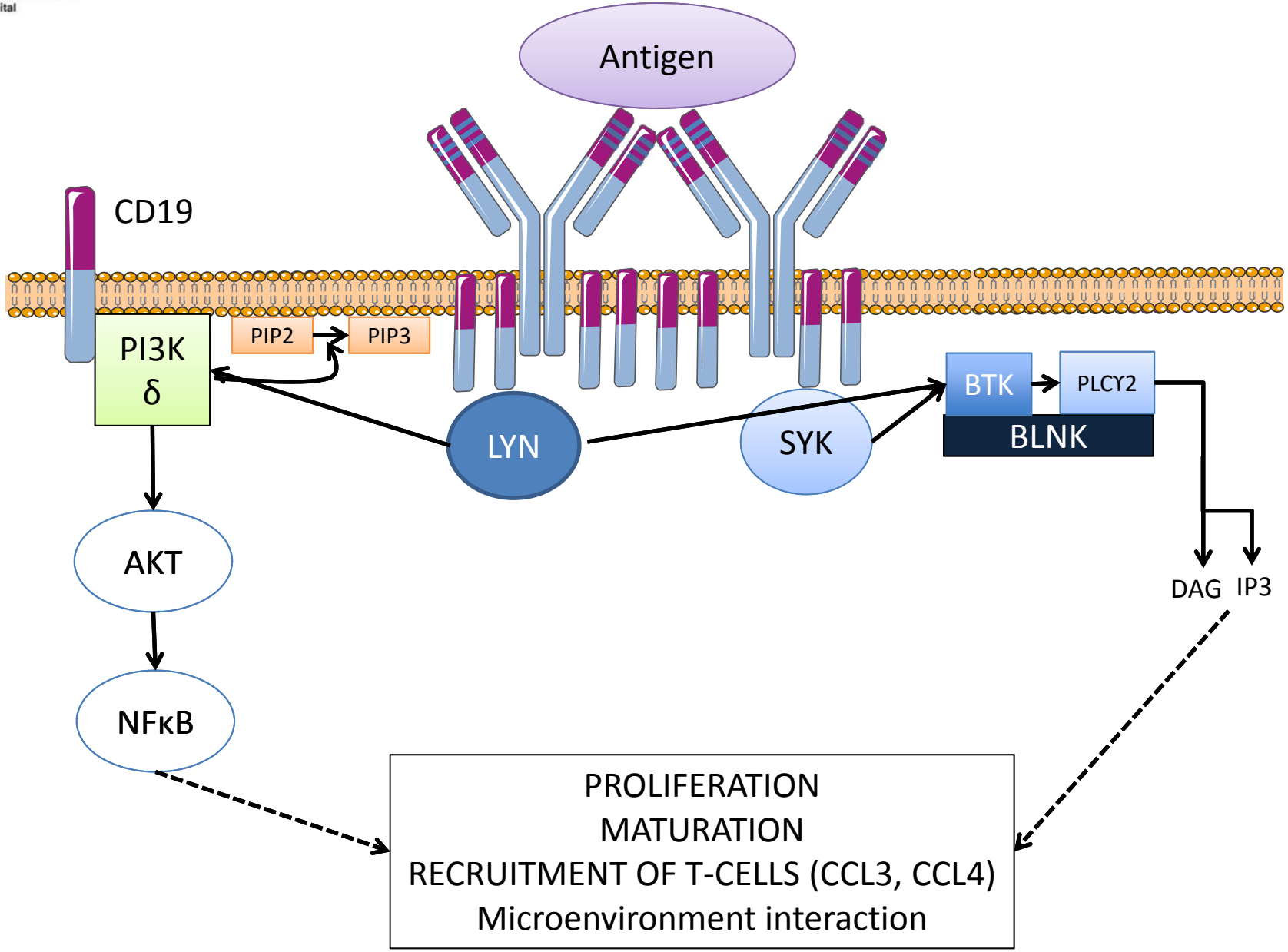
-ZAP-70 expression



Crespo et al, NEJM 2003

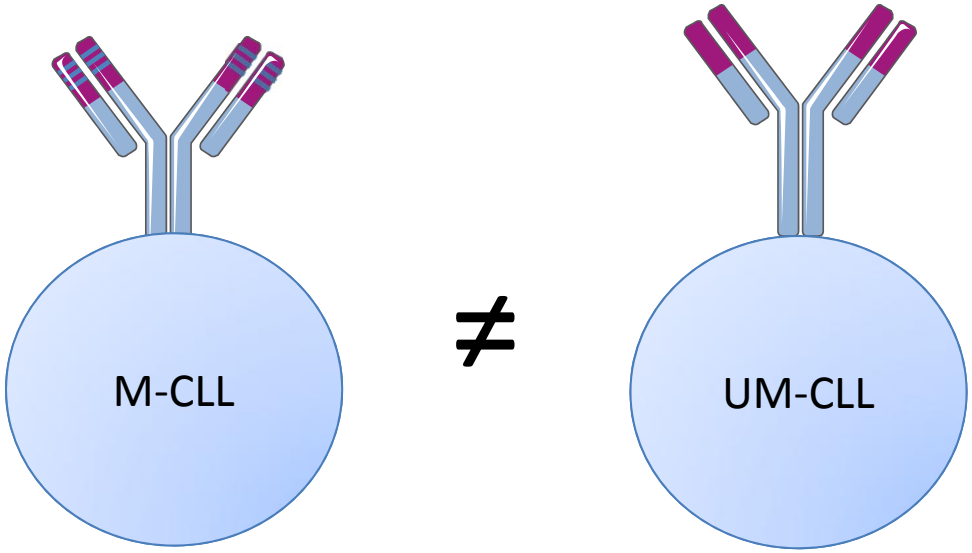
BCR and surrogates (ZAP-70, CD38, CD49d)

- Most important prognostic variable → reflect CLL biology
- Predict for TTFT, PFS, OS
- Best predictor for MRD status duration
- Do not predict response


Antigen
CD19
PI3K
δ
PIP2
PIP3
LYN
SYK
BTK
PLCY2
BLNK
AKT
NFκB
DAG
IP3
PROLIFERATION
MATURATION
RECRUITMENT OF T-CELLS (CCL3, CCL4)
Microenvironment interaction

BCR pathway in CLL cells

Unique activation of BCR in vivo



⇧ Expression of sIgM
⇧ Response to IgM engagement
⇧ Proliferation
⇧ Survival
Different interaction with the microenvironment

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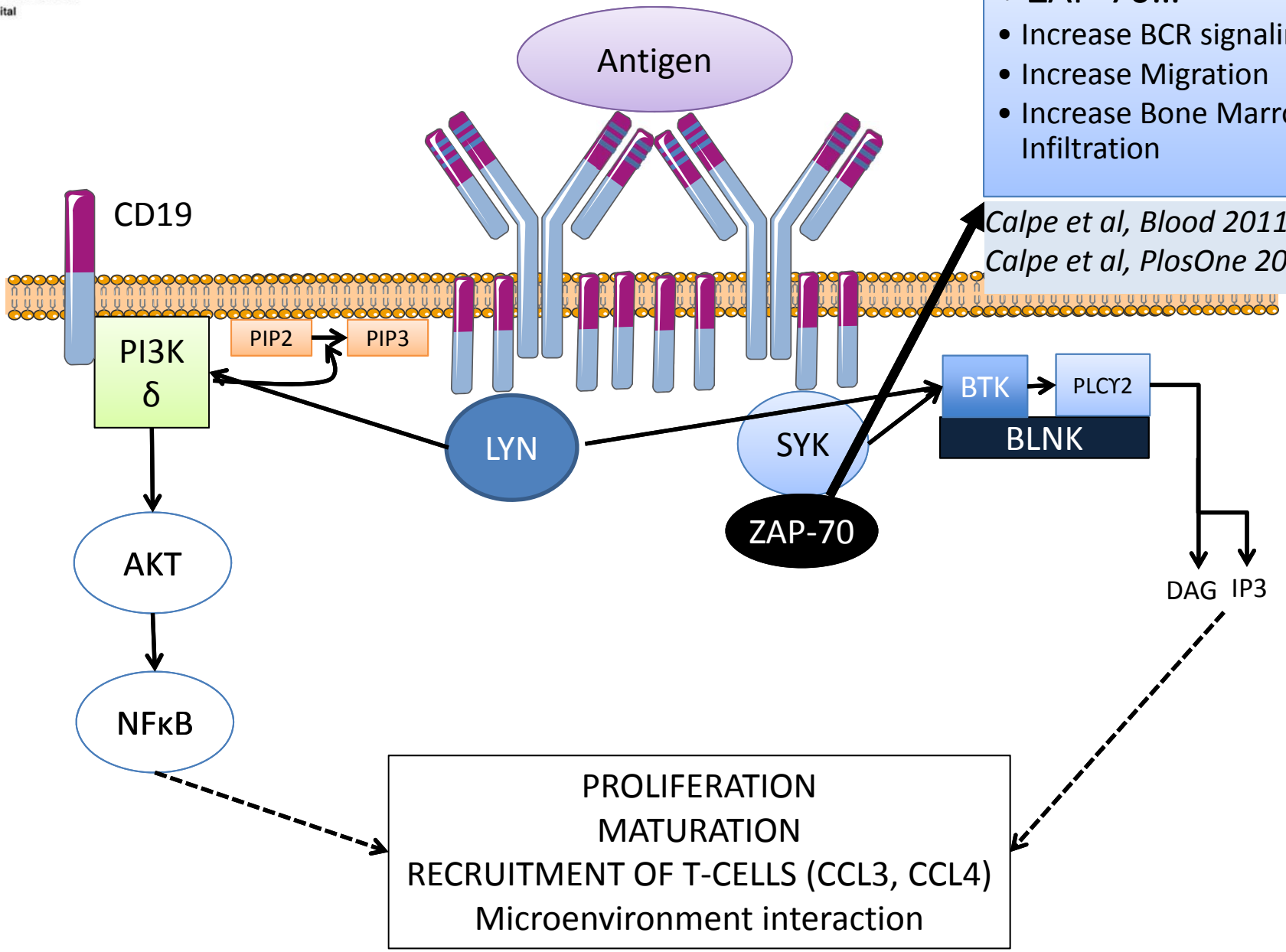

+ ZAP-70…

- Increase BCR signaling
- Increase Migration
- Increase Bone Marrow Infiltration

Calpe et al, Blood 2011
Calpe et al, PlosOne 2013

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BCR-activation in MCL

- **BCR** pathway activation
  - Mutation in the Coiled-Coil **(CC)** domain of caspase recruitment domain 11 **(CARD11)**
  - Mutations of the Immunoreceptor Tyrosine-based Activation Motifs **(ITAMs)** within the **CD79B** and **CD79A.**

- **PI3KCA** gene amplification and mRNA expression in **MCL** cells, → overactivity of the **BCR** signaling *pathway*

- The **SDF-1(CXCL12)/CXCR4** interaction was also shown to be essential in the recruitment and retention of **MCL** in the bone marrow

Burguer J. et al. Trends in Immunology 2013.
Stevenson F. et al, 2011 Volume 118, Number 16

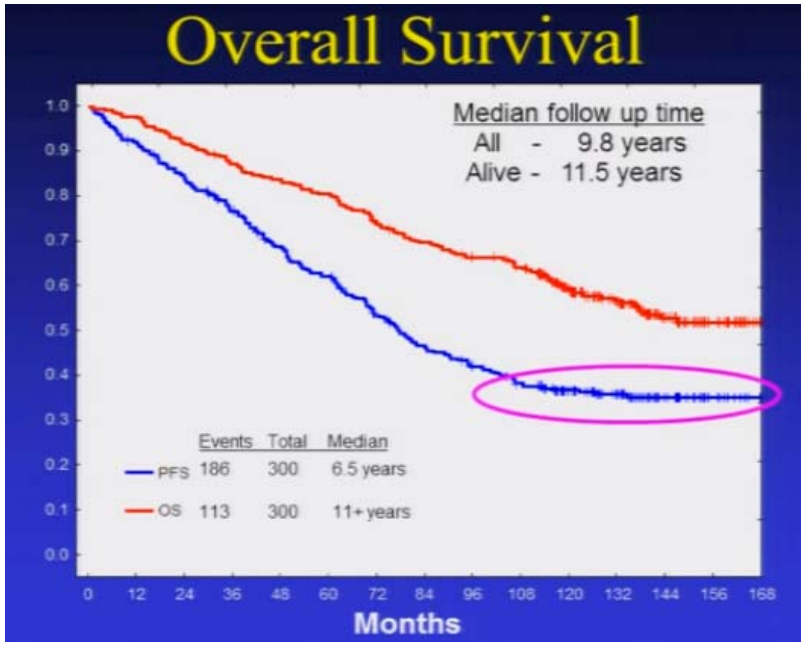
Chemoimmunotherapy in CLL

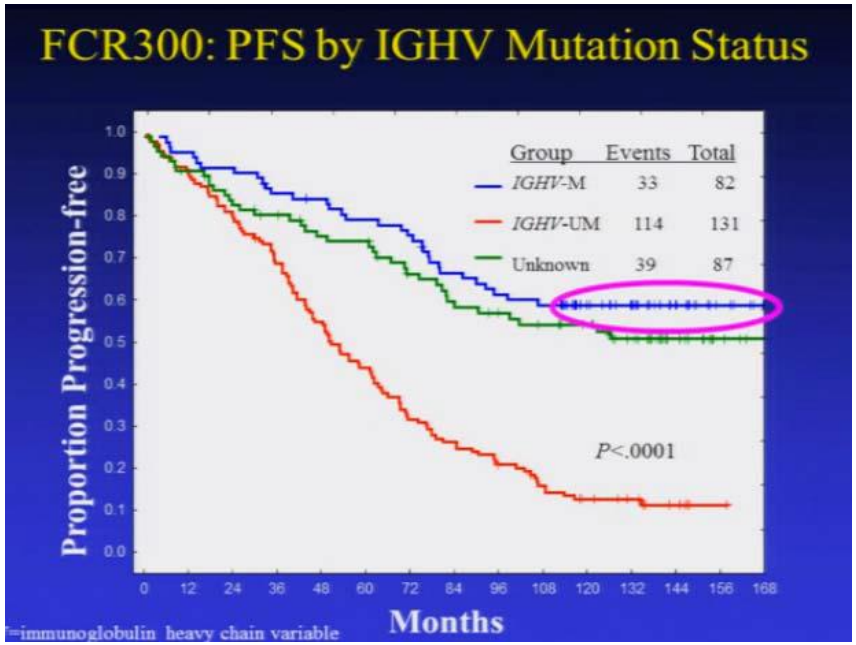
FCR: ORR 95%, CR 45%

R-FCM: ORR 93%, CR 80%, CRMRD- 45%

Bosch et al, JCO 2010

Hallek Lancet 2011

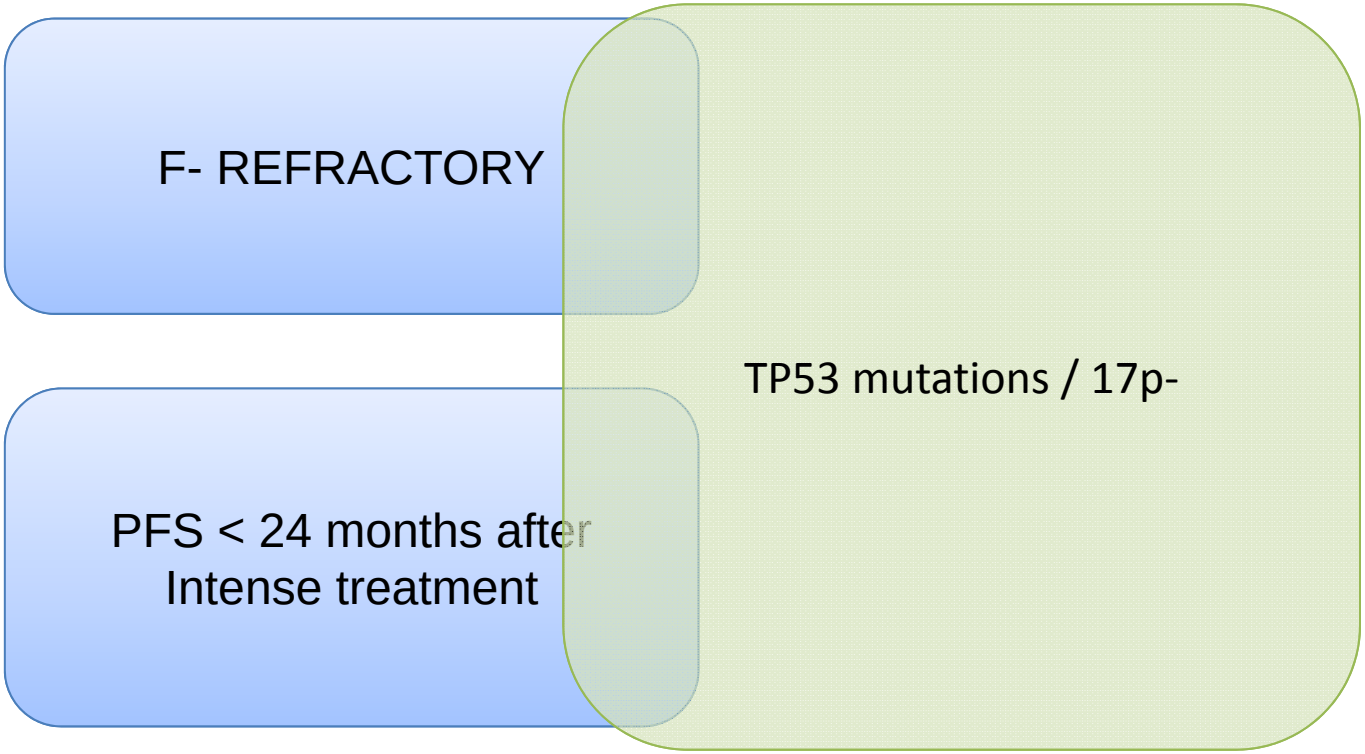




W. Wierda et al. IWCLL 2013

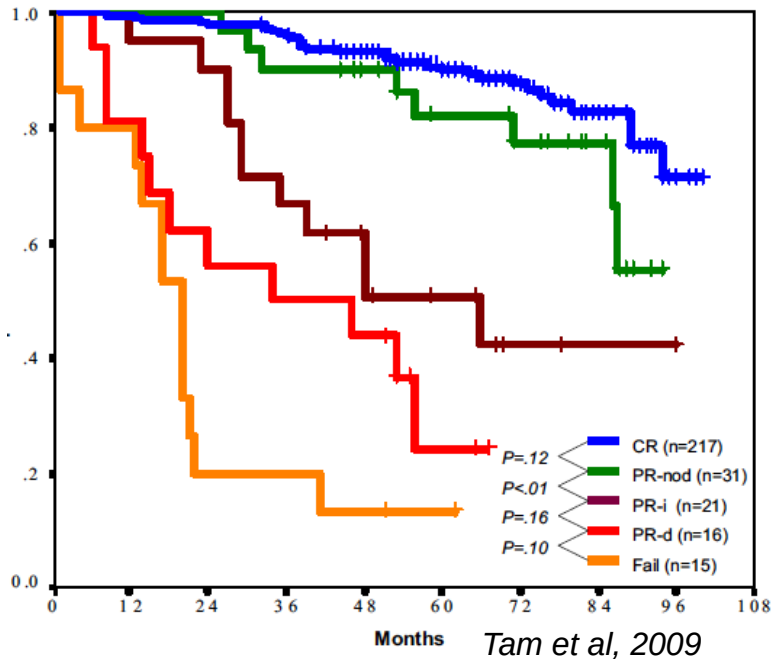
High-risk CLL

- High-risk CLL: survival < 36 months at the treatment time point



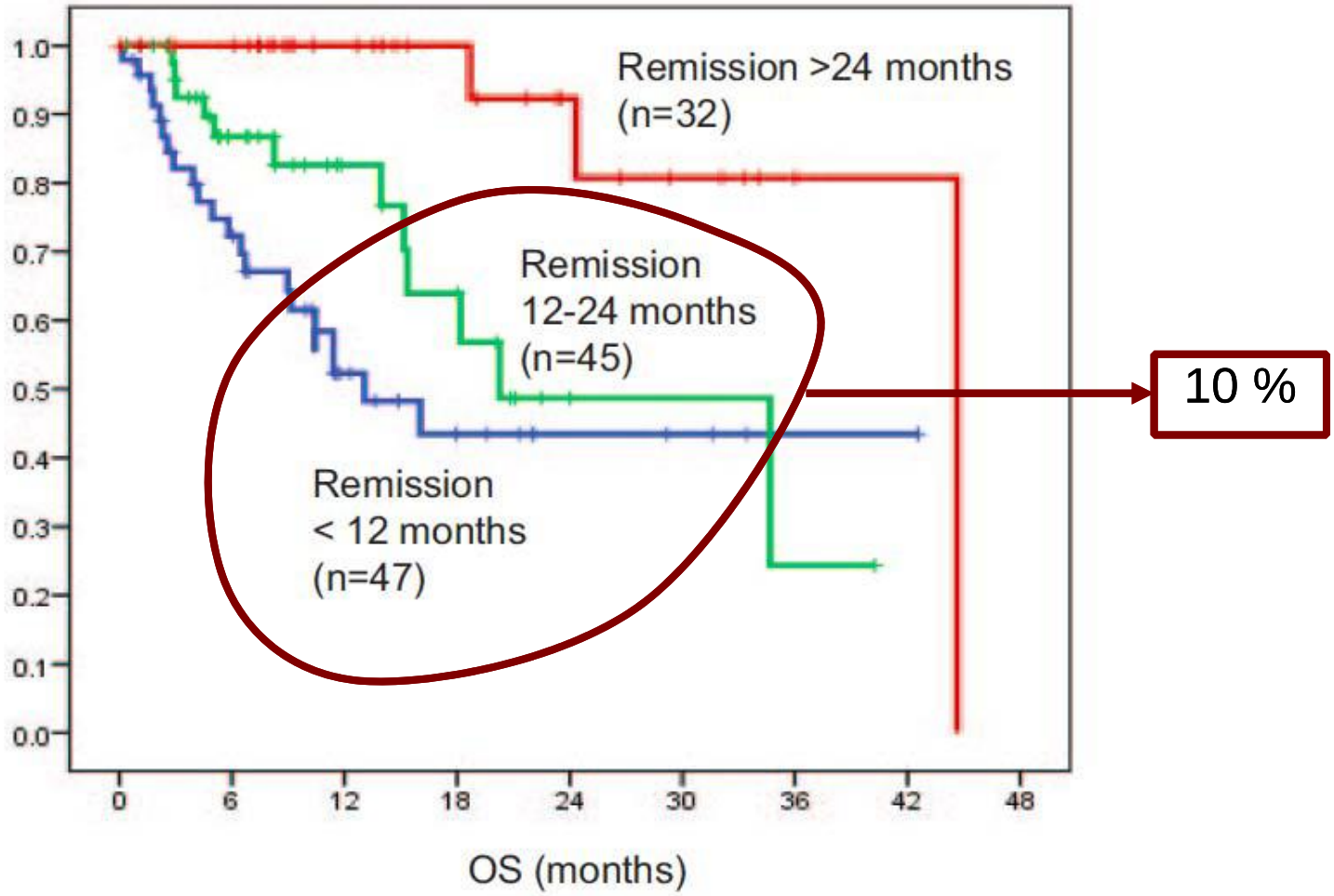
CLL: OS in F-Refractory cases

	Regimen	Refractory cases	Median OS
Eichhorst et al, Blood 2006	FC (vs. F)	5%	30 months
Tam et al, Blood 2009	FCR	5%	20 months
Hallek et al, Lancet 2009	FCR (vs. FC)	15%	22 months
Bosch et al, JCO 2010	R-FCM	7%	22 months



Tam et al, 2009

CLL: OS according to PFS < 24 mos

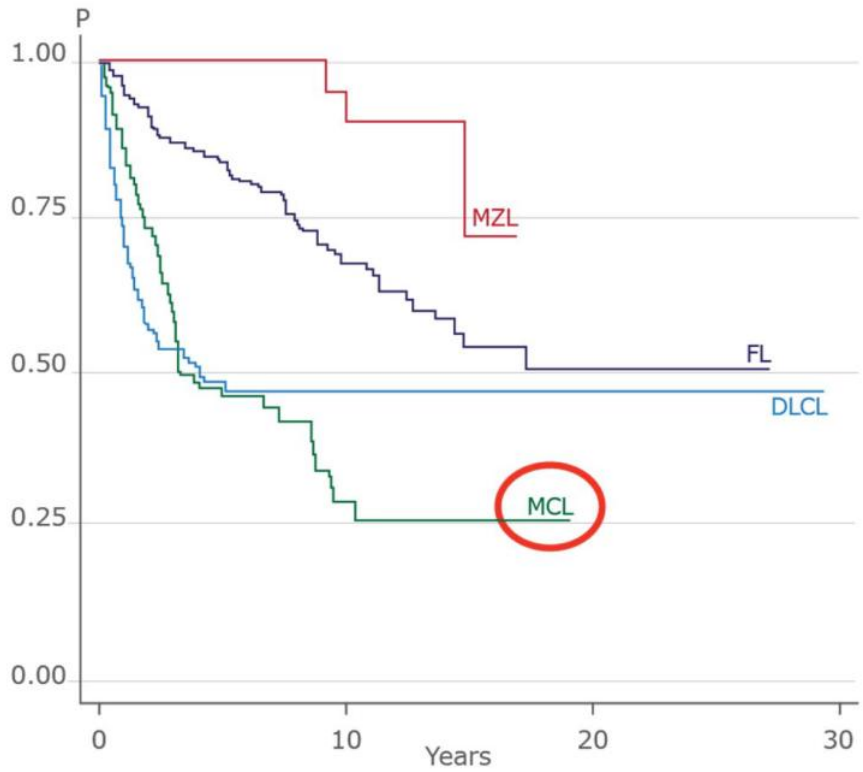


GCLLSG CLL8 trial (FCR and FC patients)

Stilgenbauer et al,Hematology ASH 2010

Mantle cell lymphoma: survival

- The disease, with time, shows the worst long term survival among all **B-cell** lymphoma subtypes.
- Median survival 5-7 years



MZL: Marginal Zone Lymphoma; **DLCL:** Diffuse Large Cell Lymphoma; **FL:** Follicular Lymphoma; **MCL:** Mantle Cell Lymphoma.

Ghielmini et al., Blood 2009 114: 1469-1476

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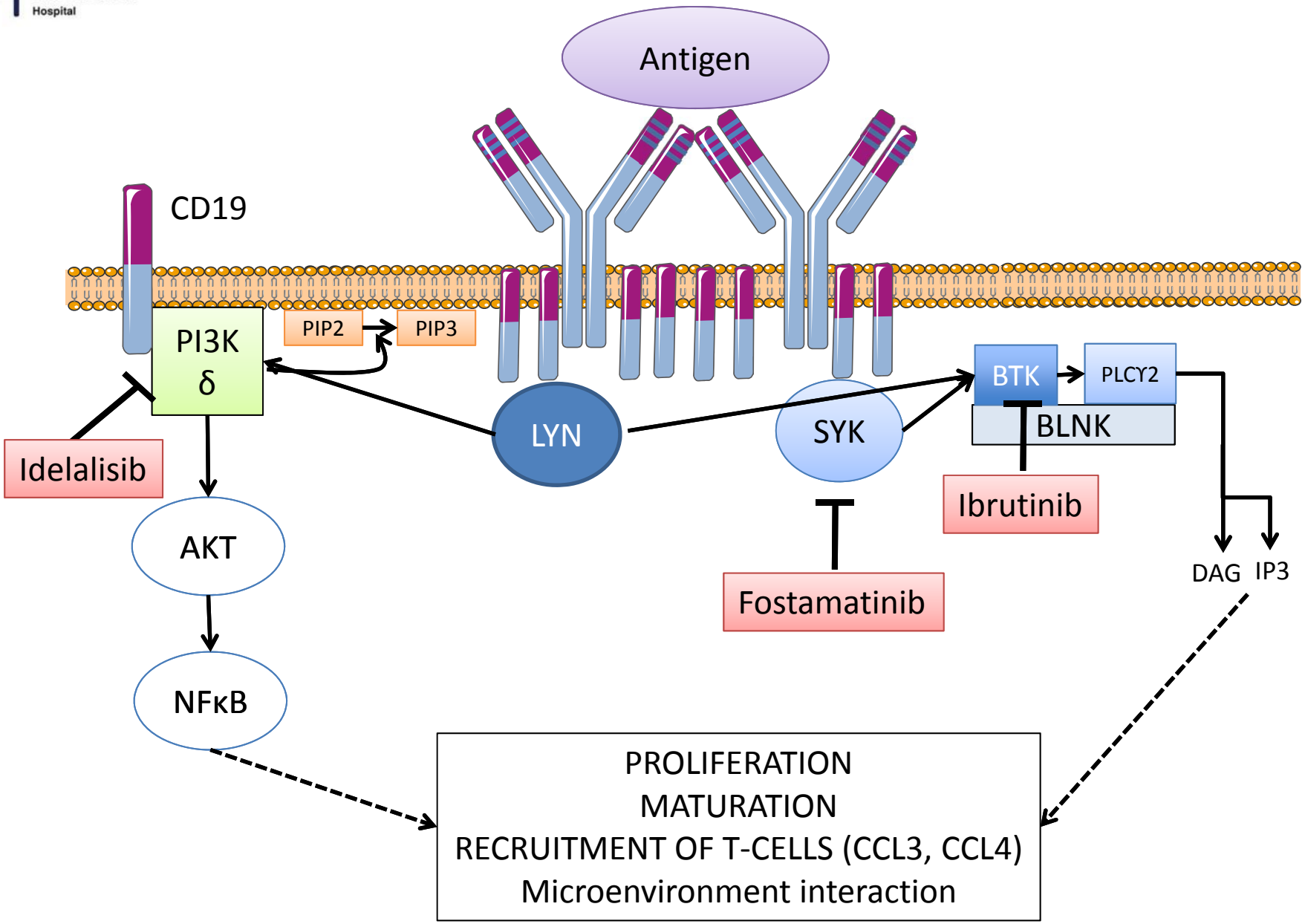
CLL: Targeted therapies


Antigen
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Ibrutinib
Fostamatinib
AKT
NFκB
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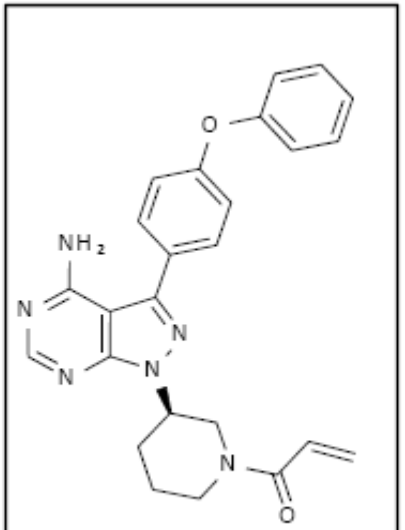
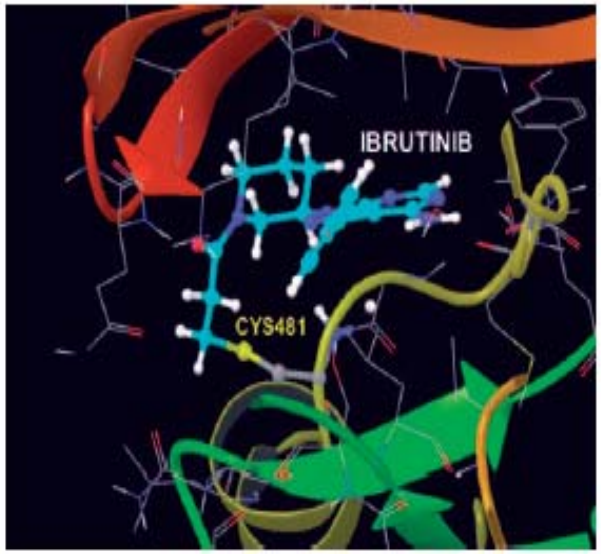
IP3
PROLIFERATION
MATURATION
RECRUITMENT OF T-CELLS (CCL3, CCL4)
Microenvironment interaction

Ibrutinib: First-in-Class Inhibitor of Bruton's Tyrosine Kinase (BTK)



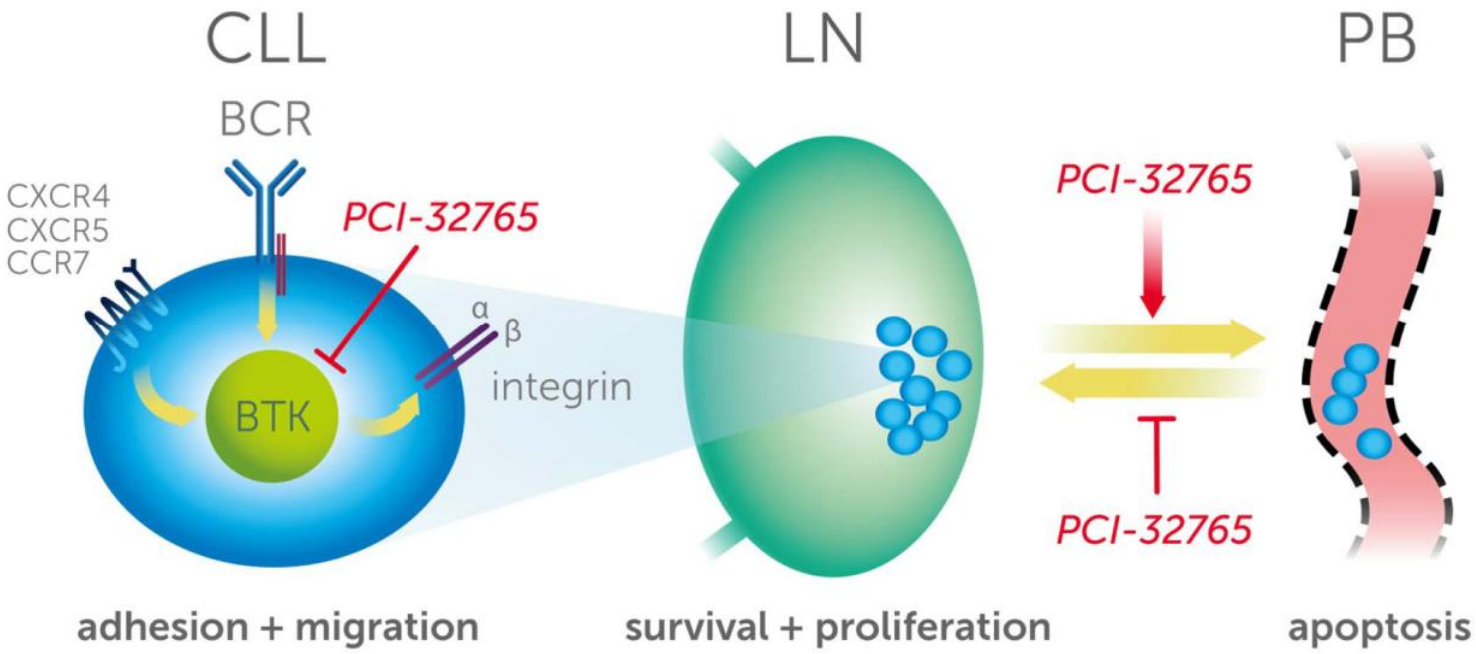
PCI-32765



- Co-development by Janssen and Pharmacyclics
- Oral, small-molecule inhibitor of BTK, previously PCYC 32765
- Forms a specific and covalent bond that causes highly potent BTK inhibition (IC_{50}=0.5nM)
- Orally administered with once daily dosing resulting in 24-hr target inhibition
- No cytotoxic effect on T-cells or NK-cells

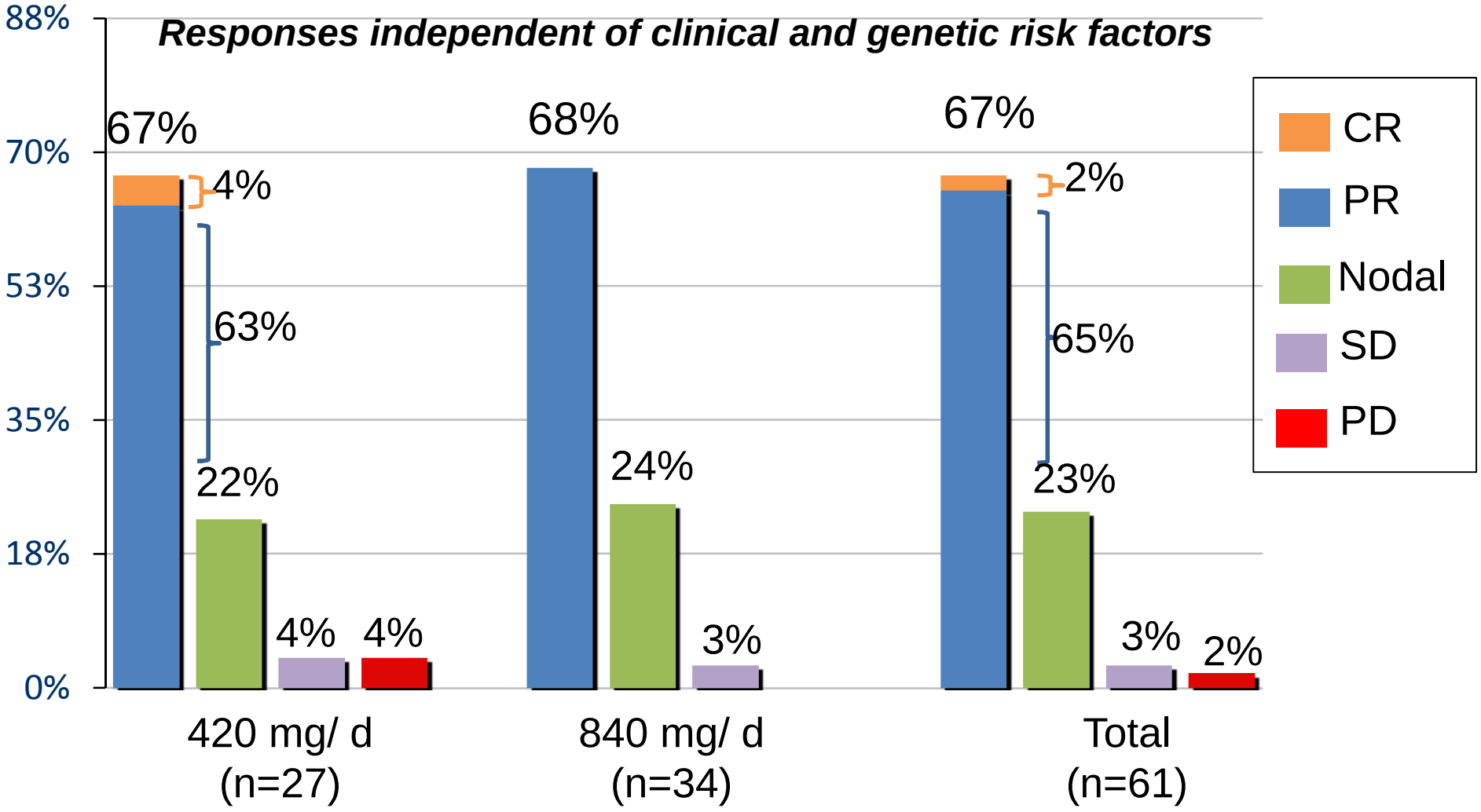
Honigberg LA et al, *Proc Natl Acad Sci USA.107:*13075, 2010
Herman SEM et al: *Blood 117:*6287-6296, 2011
Ponader, et al., *ASH Meeting Abstracts 116:*45, 2010

Ibrutinib



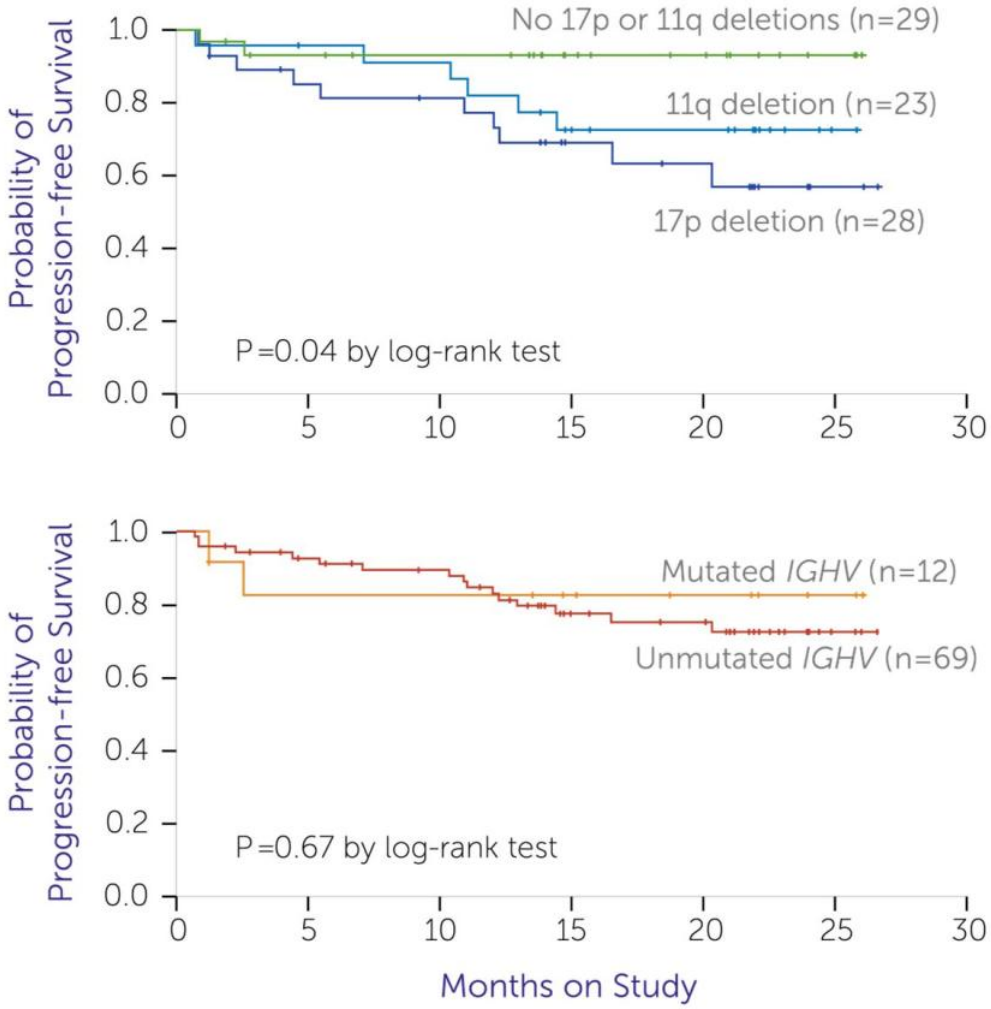
Rooij M., et al., The clinically active BTK inhibitor PCI-32765 targets B-cell receptor– and chemokine-controlled adhesion and migration in chronic lymphocytic leukemia. ***Blood***. 2012;119(11):2590-2594)

Targeting BTK with Ibrutinib in Relapsed Chronic Lymphocytic Leukemia Phase 1b/2



Byrd et al, NEJM 2013

Ibrutinib in R/R CLL: PFS independent of mutational status



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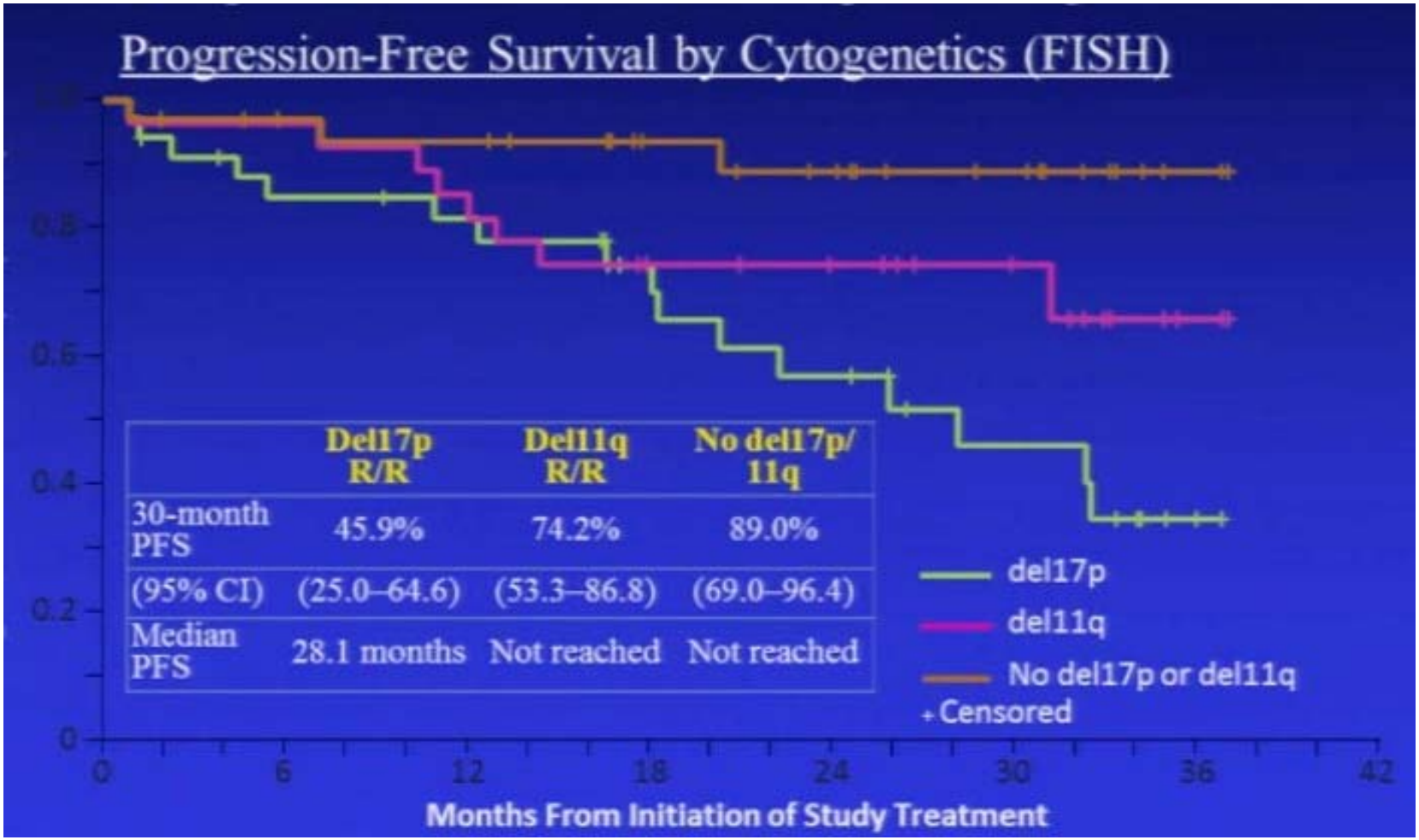
Ibrutinib in high-risk CLL: ASCO 2014



	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

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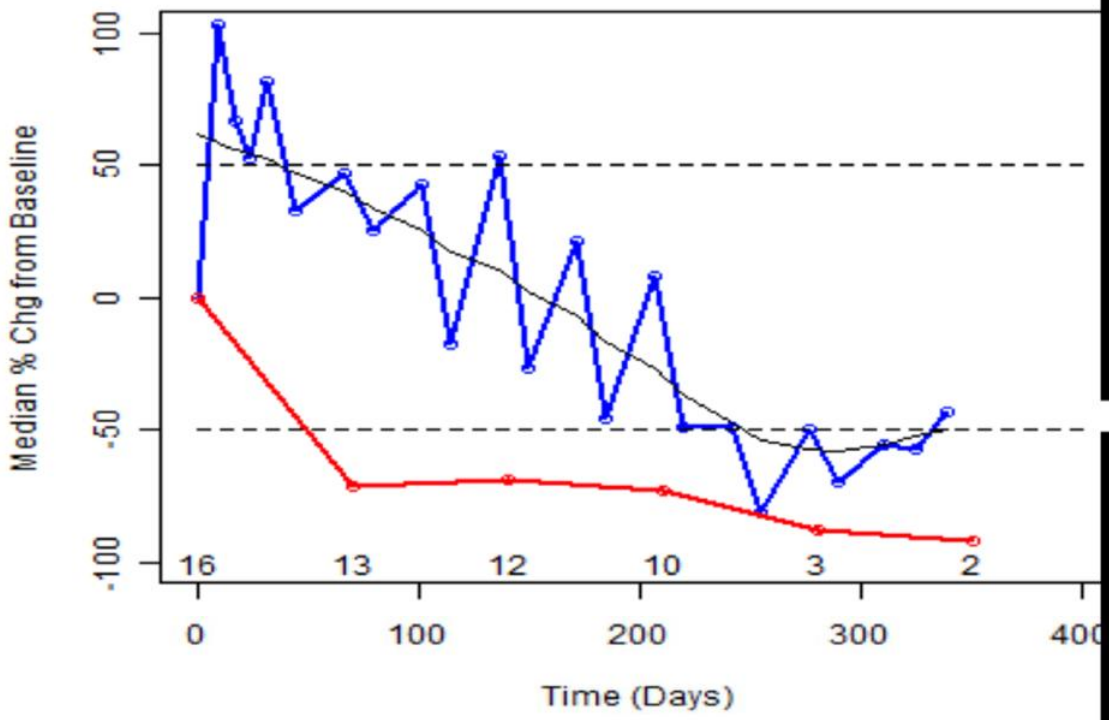
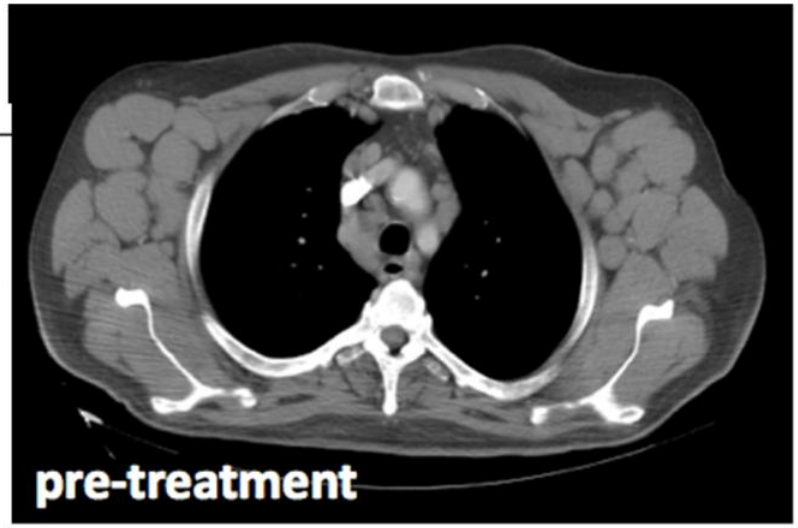
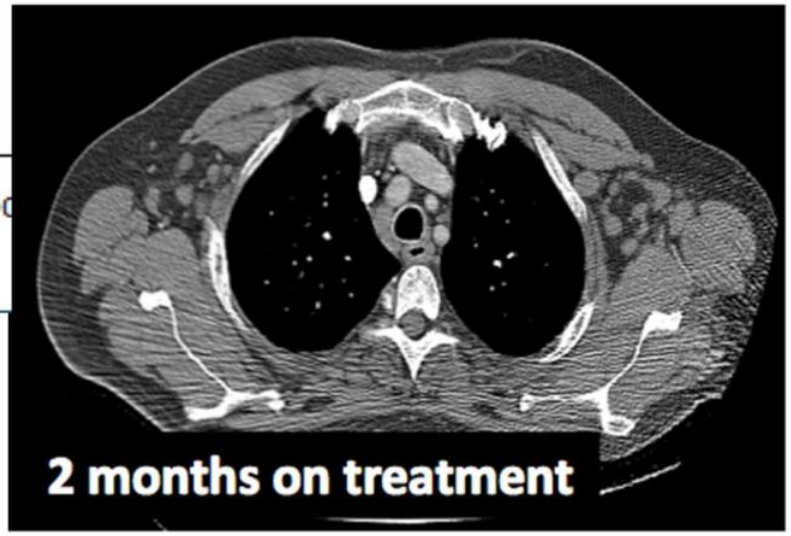
Differential response by tissue compartments







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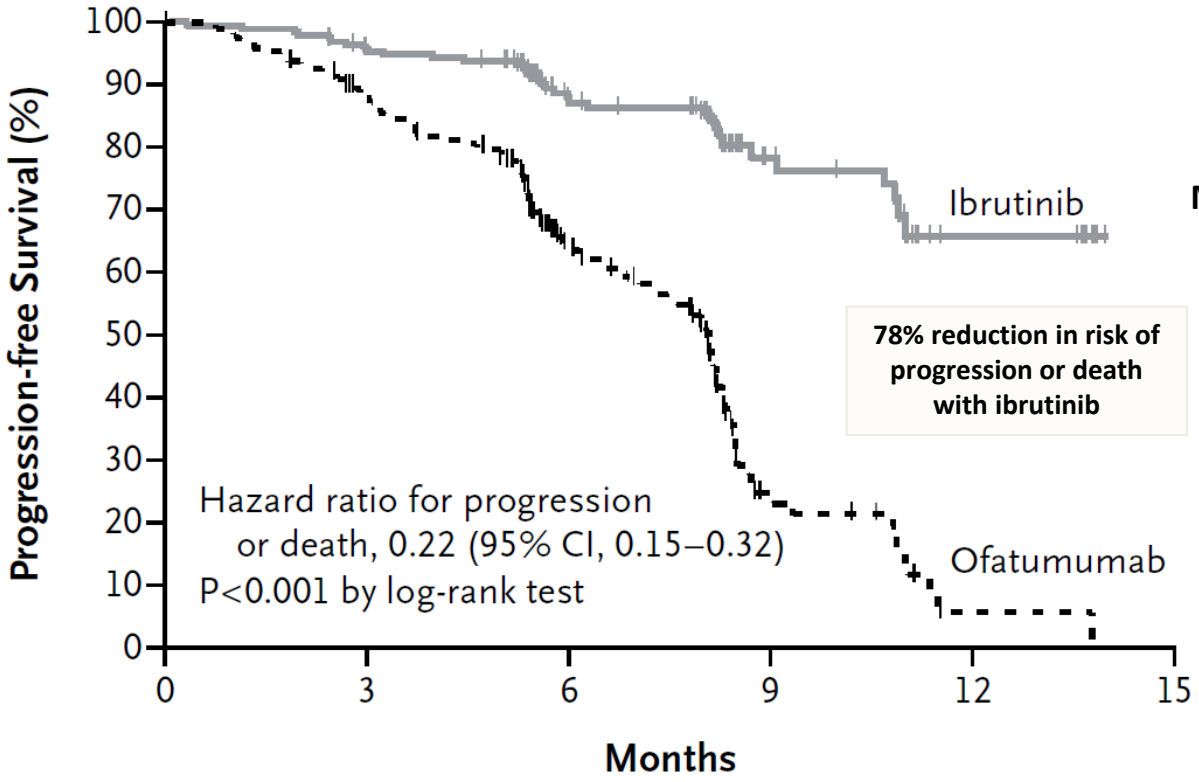
RESONATE (PCYC-1112) Study
Primary End Point: IRC-Evaluated PFS



Median PFS not reached (PFS rate: 88% at 6 mo)

78% reduction in risk of progression or death with ibrutinib

Median PFS of 8.1 mo (PFS rate: 65% at 6 mo)

No. at Risk						
Ibrutinib	195	183	116	38	7	
Ofatumumab	196	161	83	15	1	0

Byrd JC, et al. *N Engl J Med*. 2014; ePub 31May2014.

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RESONATE (PCYC-1112) Study

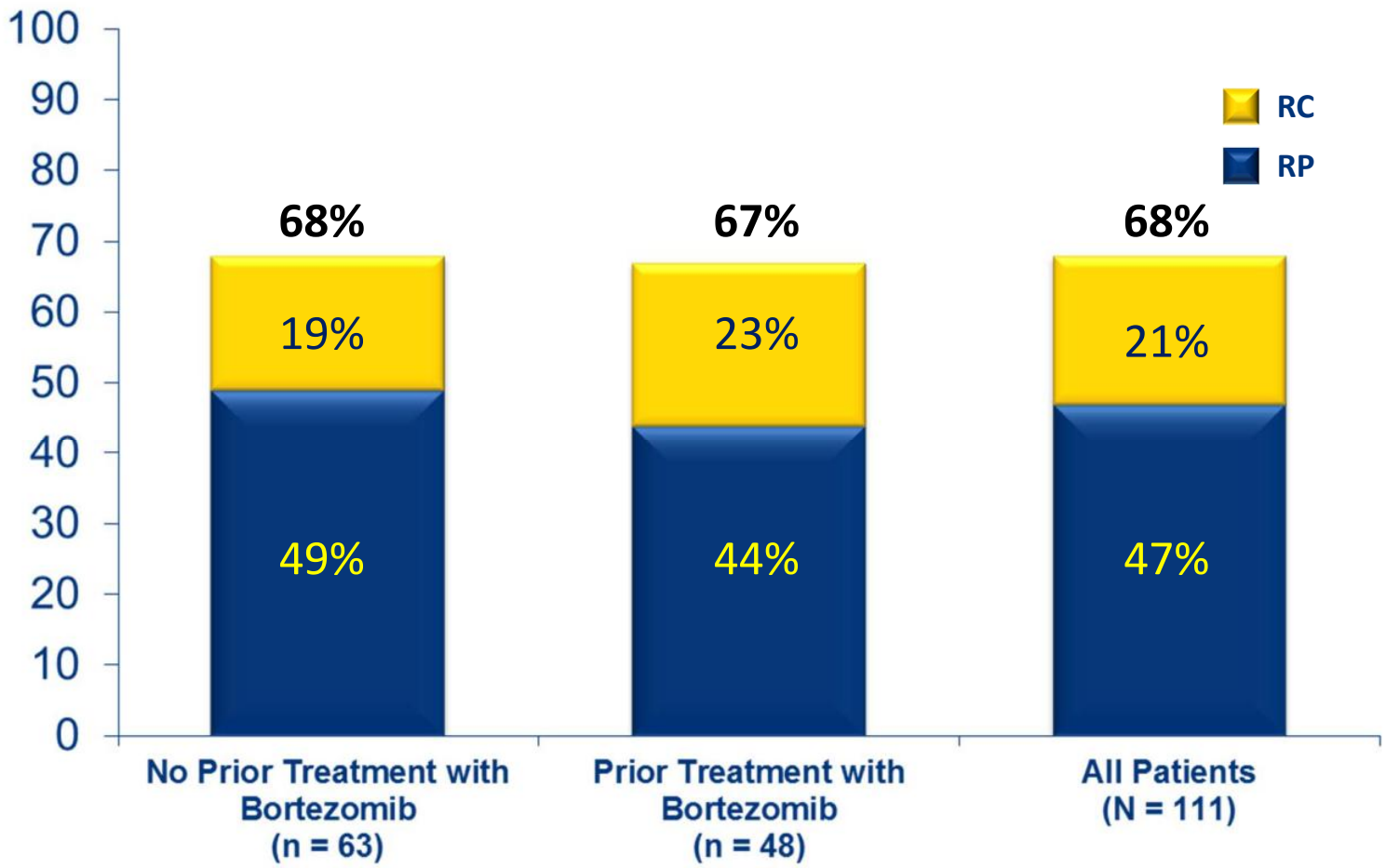
AEs (occurring in ≥15% of patients in either group)

	Ibrutinib (N = 195)		Ofatumumab (N = 196)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Any AE during treatment	194 (99)	99 (51)	187 (98)	74 (39)
Diarrhea	93 (48)	8 (4)	34 (18)	3 (2)
Fatigue	54 (28)	4 (2)	57 (30)	3 (2)
Nausea	51 (26)	3 (2)	35 (18)	0 (0)
Pyrexia	46 (24)	3 (2)	28 (15)	2 (1)
Anemia	44 (23)	9 (5)	33 (17)	15 (8)
Neutropenia	42 (22)	32 (16)	28 (15)	26 (14)
Cough	38 (19)	0 (0)	44 (23)	2 (1)
Thrombocytopenia	33 (17)	11 (6)	22 (12)	8 (4)
Arthralgia	34 (17)	2 (1)	13 (7)	0 (0)
URTI	31 (16)	1 (1)	20 (10)	3 (2)
Constipation	30 (15)	0 (0)	18 (9)	0 (0)

AE, adverse event; URTI, upper respiratory tract infection.

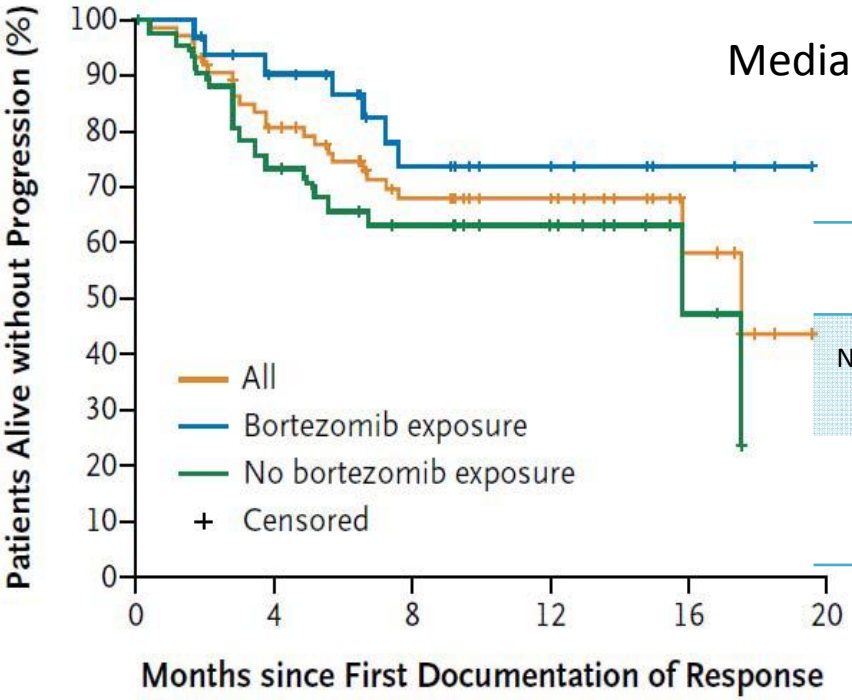
Byrd JC, et al. *N Engl J Med*. 2014; ePub 31May2014.

Ibrutinib en LCM R/R Respuesta



Wang ML et al. 2013; 369: 507-16

Inhibidores de BTK: Ibrutinib
Duración de la Respuesta



Median follow-up: 15,3 m.

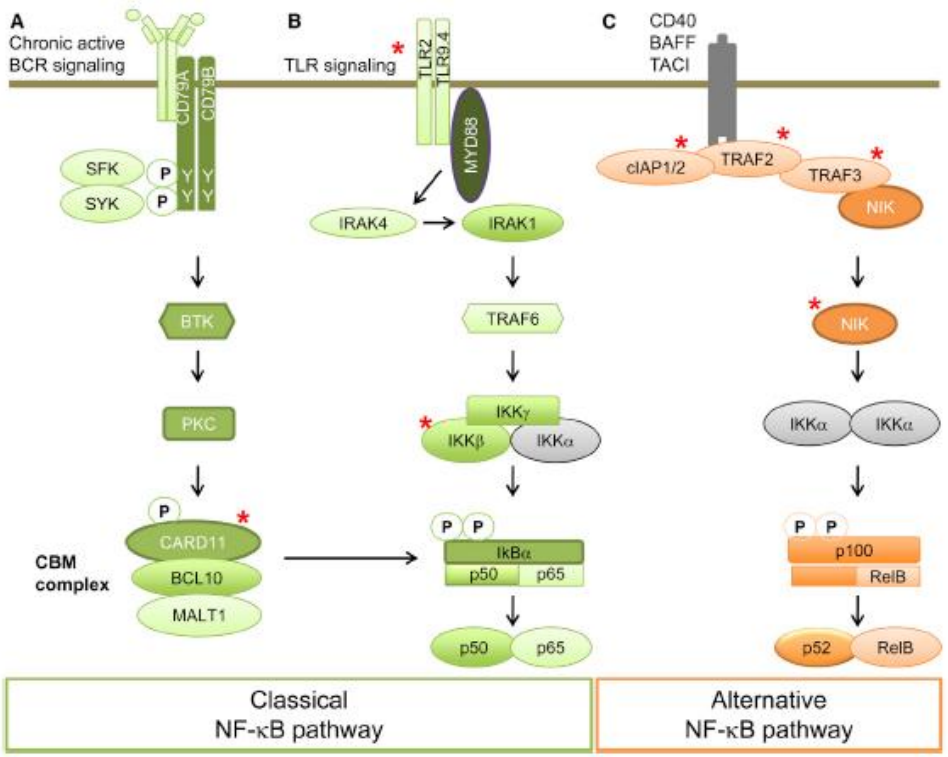
Median Response Duration in Months (95% CI)		
No Bortezomib Exposure	Bortezomib Exposure	All Patients
15.8 (5.6-NR)	NR (NR-NR)	17.5 (15.8-NR)

No. at Risk

No bortezomib exposure	43	30	23	15	3	0
Bortezomib exposure	32	26	17	9	3	0
All	75	56	40	24	6	0

Wang ML et al. 2013; 369: 507-16

Inhibidores de BTK: Ibrutinib



Somatic Mutation and Activation of the NF-κB Pathway in MCL

-1/3 de los pacientes presenta resistencia inicial
- Aparecen resistencias durante el tratamiento
-Vías alternativas , al BCR y TLR, de activación del NFkB

Colomer D & Campo E. Cancer Cells, 2014; 25: 8-9

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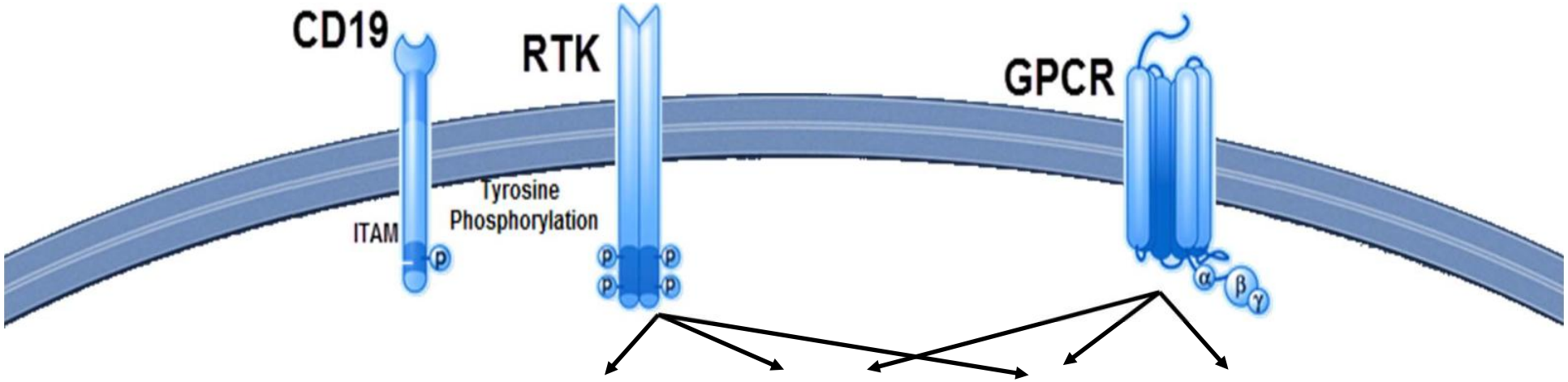
PI3Kδ inhibitors selectively target hematological malignancies



Class I PI3K Isoforms	p85 p110α	p85 p110β	p85 p110δ	p101 p110γ
Isoform	Alpha	Beta	**Delta**	Gamma
Expression	Broad	Broad	**Leukocytes**	Leukocytes
Gene KO effect on development	Lethal	Lethal	**Benign**	Benign
Primary physiological role	Insulin signaling Angiogenesis	Insulin Signaling Male fertility	**B-cell signaling, development & survival**	Neutrophil & T-cell function

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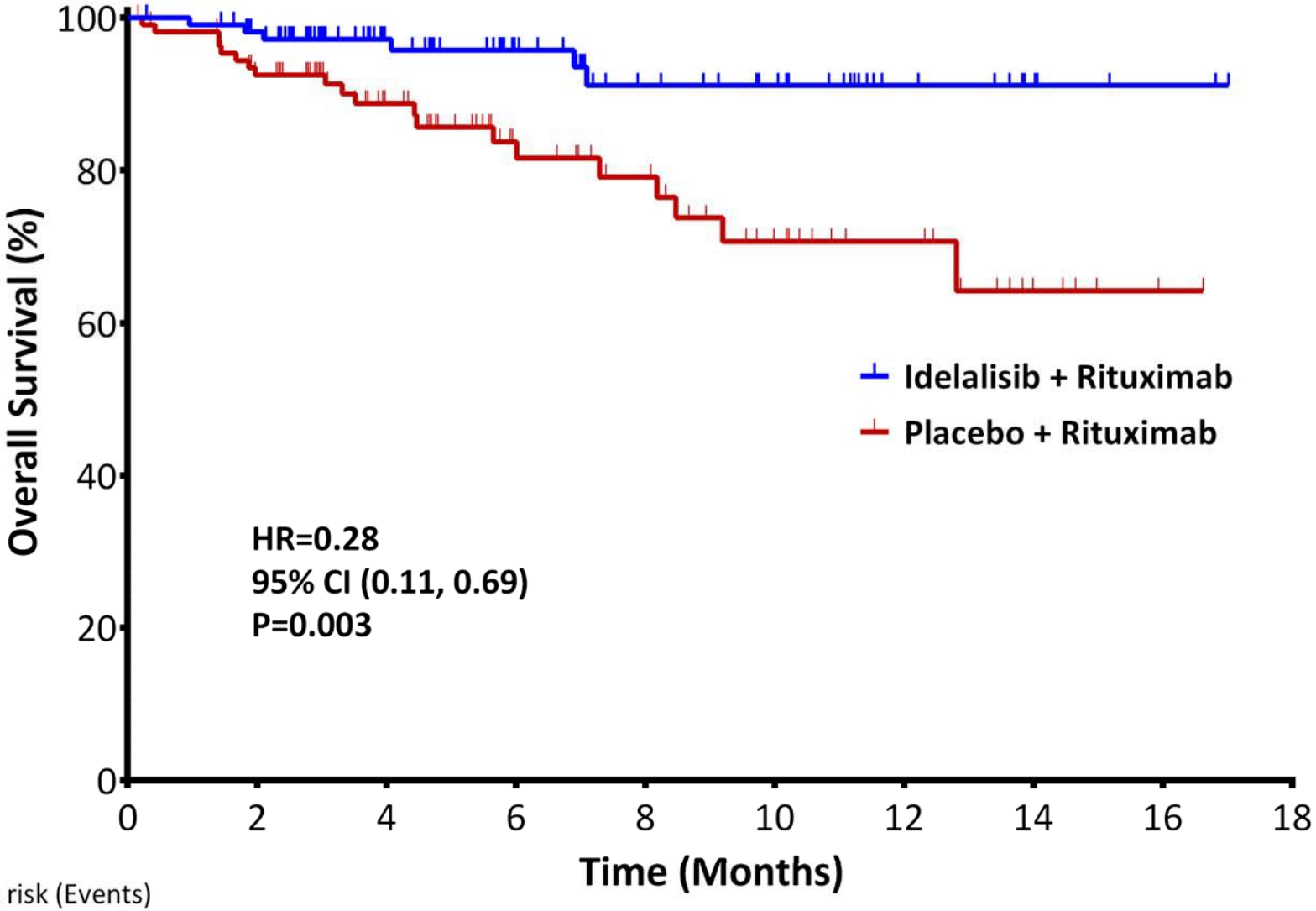
Overall Survival



N at risk (Events)

Idelalisib + R	110 (0)	102 (2)	68 (3)	47 (4)	33 (6)	25 (6)	11 (6)	6 (6)	2 (6)	0 (6)
Placebo + R	110 (0)	93 (8)	61 (11)	39 (14)	31 (16)	20 (19)	13 (19)	5 (20)	1 (20)	0 (20)

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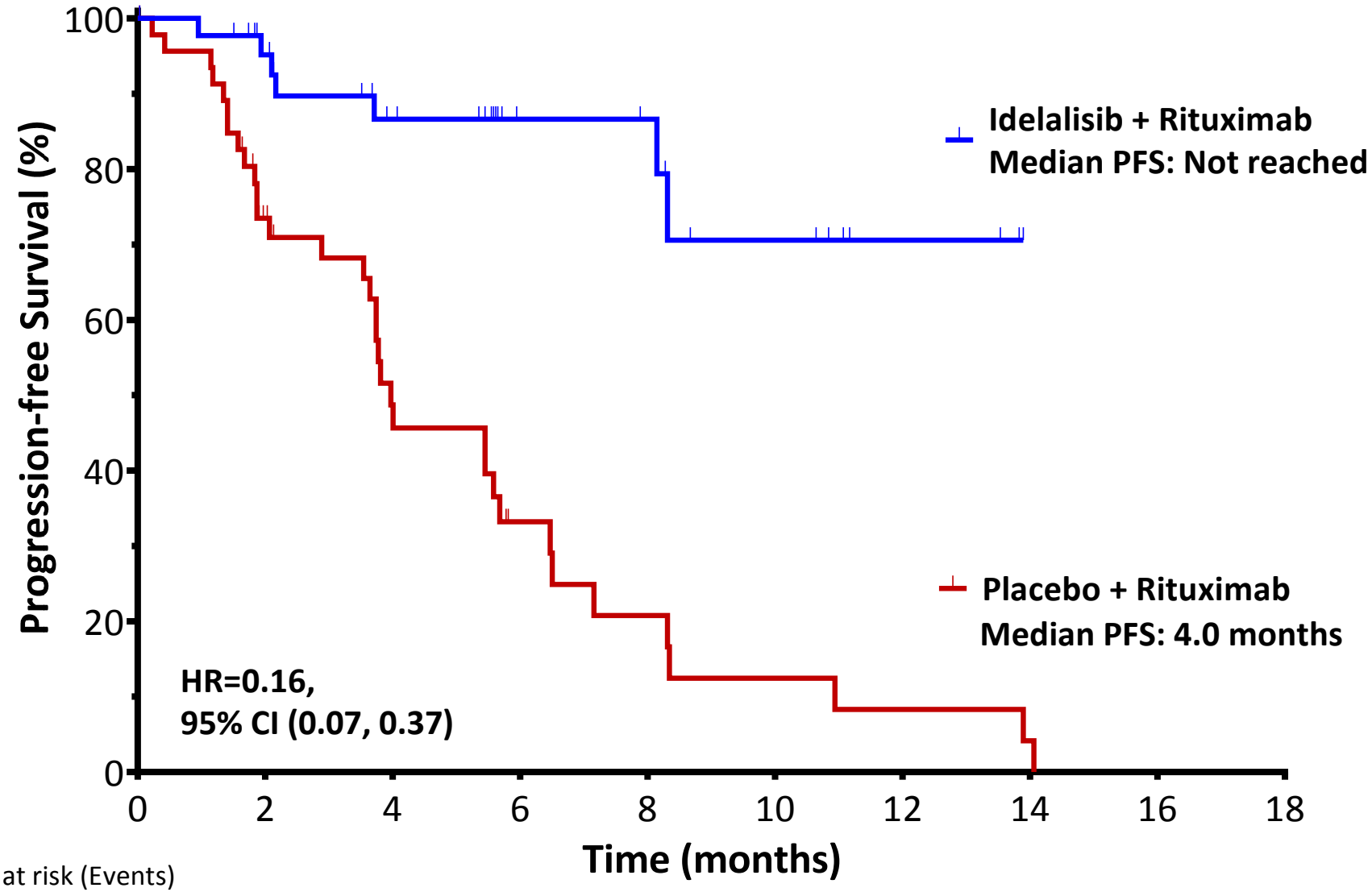
PFS: Subgroup del(17p) and/or *TP53* mutation



N at risk (Events)										
Idelalisib + R	46 (0)	37 (2)	22 (5)	13 (5)	12 (5)	7 (7)	3 (7)	0 (7)	0 (7)	0 (7)
Placebo + R	49 (0)	30 (12)	16 (21)	8 (26)	5 (29)	3 (31)	2 (32)	1 (33)	0 (34)	0 (34)

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Adverse Events ≥10% In Either Study Arm

AE, n (%)	IDELA + R (N=110)		Placebo + R (N=108)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Patients with any AE	106 (96)	70 (64)	106 (98)	56 (52)
Pyrexia	38 (35)	3 (3)	18 (17)	1 (1)
Fatigue	28 (26)	5(5)	30 (28)	3 (3)
Nausea	28 (26)	0	23 (21)	0
Chills	23 (21)	2 (2)	17 (16)	0
Diarrhea*	21 (19)	4 (4)	16 (15)	0
Infusion-related reaction	21 (19)	0	32 (30)	4 (4)
Cough	19 (17)	1 (1)	30 (28)	2 (2)
Bleeding **	15 (14)	1 (1)	20 (19)	1 (1)
Dyspnea	14 (13)	3 (3)	21 (19)	3 (3)
Constipation	14 (13)	0	12 (11)	0
Vomiting	14 (13)	0	9 (8)	0
Decreased appetite	13 (12)	0	11 (10)	2 (2)
Night sweats	12 (11)	0	11 (10)	0
Pneumonia	11 (10)	9 (8)	14 (13)	10 (9)
Rash	11 (10)	1 (1)	5 (5)	0
Headache	11 (10)	1 (1)	5 (5)	0
Edema peripheral	11 (10)	0	10 (9)	2 (2)
Up. Resp. Tract Infection	8 (7)	2 (2)	12 (11)	2 (2)

* 3/5 patients with colitis on IDELA +R also reported diarrhea; ** Includes 16 preferred terms

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Inactivation of PI(3)K p110δ breaks regulatory T-cell-mediated immune tolerance to cancer

Khaled Ali, Dalya R. Soond, Roberto Piñeiro, Thorsten Hagemann, Wayne Pearce, Ee Lyn Lim, Hicham Bouabe, Cheryl L. Scudamore, Timothy Hancox, Heather Maecker, Lori Friedman, Martin Turner, Klaus Okkenhaug & Bart Vanhaesebroeck

Nature, June 2014

Vall d'Hebron Hospital

ABT-199 (GDC-0199): Background

- Intrinsic apoptotic pathway dysregulated in CLL: overexpression of BCL-2 (+ deficiency in TP53)
  - Prolonged survival through evasion of apoptosis
  - Resistance to cytotoxic agents
- ABT-199 is a selective, potent, orally bioavailable BCL-2 inhibitor that binds BCL-2
  - >1000-fold higher affinity than BCL-X_L, BCL-W and MCL-1
  - ABT-199 acts as a BH3-mimetic, displacing the BIM from BCL-2 → apoptosis

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ABT-199 Treated Patients: responses

Responses	All n (%) n = 78	del (17p) n (%) n = 19	F-Refractory n (%) n =41	IGHV Unmutated n (%) n =24
Overall response	60 (77)	15 (79)	31 (76)	18 (75)
Complete response (CR/CRi)#	18 (23)	5 (26)	9 (22)	7 (29)
Partial response*	42 (54)	10 (53)	22 (54)	11 (46)
Stable disease	10 (13)	2 (11)	7 (17)	2 (8)
Disease progression	2 (3)	1 (5)	1 (3)	2 (8)
D/C Prior to first (W6) assessment	6 (8)	1 (5)	2 (5)	2 (8)

6/11 patients in CR had negative MRD in BM

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Adverse Events

All Grades ≥20% of pts	N=105 n (%)
Diarrhea	42 (40)
Neutropenia	38 (36)
Nausea	37 (35)
Upper respiratory tract infection	35 (33)
Fatigue	27 (27)
Cough	21 (20)
Grades 3/4 ≥ 5% pts	**n (%)**
Neutropenia	35 (33)
Anemia	10 (10)
Febrile neutropenia	7 (7)
Thrombocytopenia	7 (7)
Hyperglycemia	7 (7)
Tumor lysis syndrome (TLS)	7 (7)
Hypokalemia	5 (5)

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Summary

- Clinical and biological insights allow us to better stratify patients for prognosis and treatment
  - Fit patients → FCR
  - Not candidates for FCR
    - Bendamustine + rituximab
    - Obinutuzumab + chlorambucil
    - Rituximab + chlorambucil
  - High-risk CLL→ targeted therapies

- New TK inhibitors
  - Are changing the paradigm of treatment of CLL
  - Active in high-risk CLL
  - Challenging allogeneic transplantation
  - Lymphocytosis is not a problem (Do we need CR MRD-?)
  - Longer follow-up is needed (off-target effects, acquisition of resistances)

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