ESMO Preceptorship Programme

Lymphoma – Lugano, Switzerland – November 27 and 28, 2015

Small lymphocytic lymphoma with del(17p)

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Third year of the Hematology fellowship training program

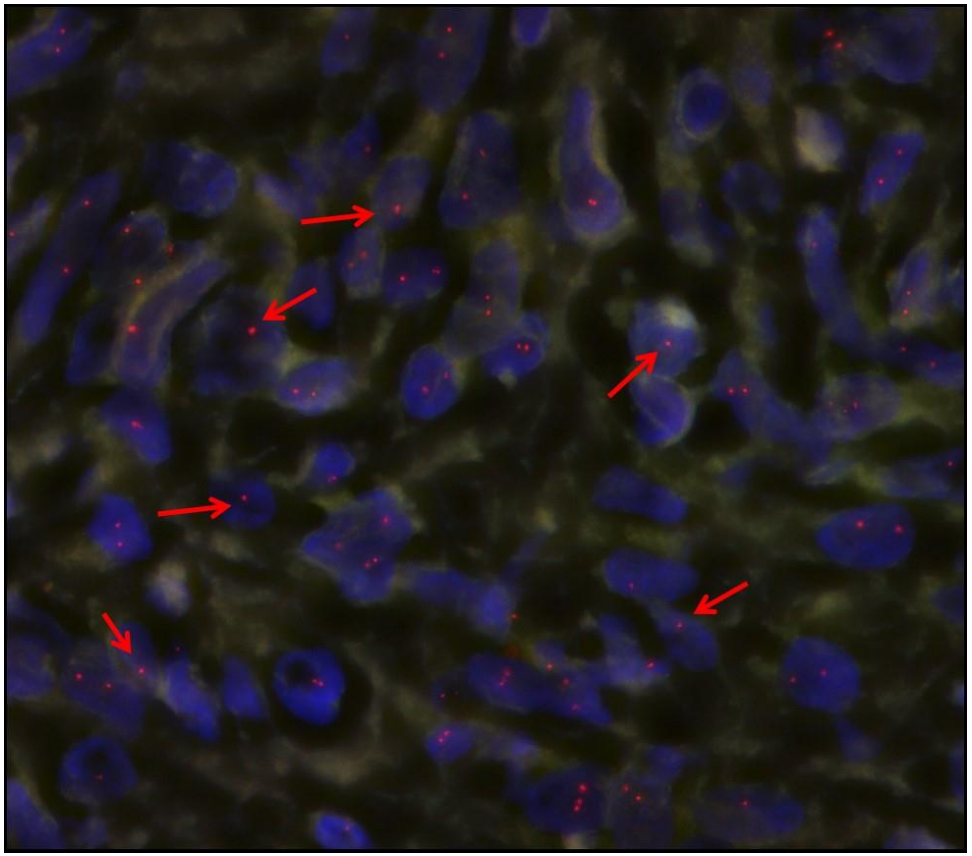
Hospital Clínic, University of Barcelona, Barcelona, Spain

CLINICAL CASE

- 40 year-old woman
- Past medical history: without relevance
- December 2012
  - Cervical and supraclavicular lymphadenopathy (< 3 cm)
  - B symptoms absent
  - No organomegaly
  - Lab tests: without relevance (no lymphocytosis)
  - CT scan: multiple cervical, supraclavicular, axillary, retroperitoneal and inguinal lymphadenopathy

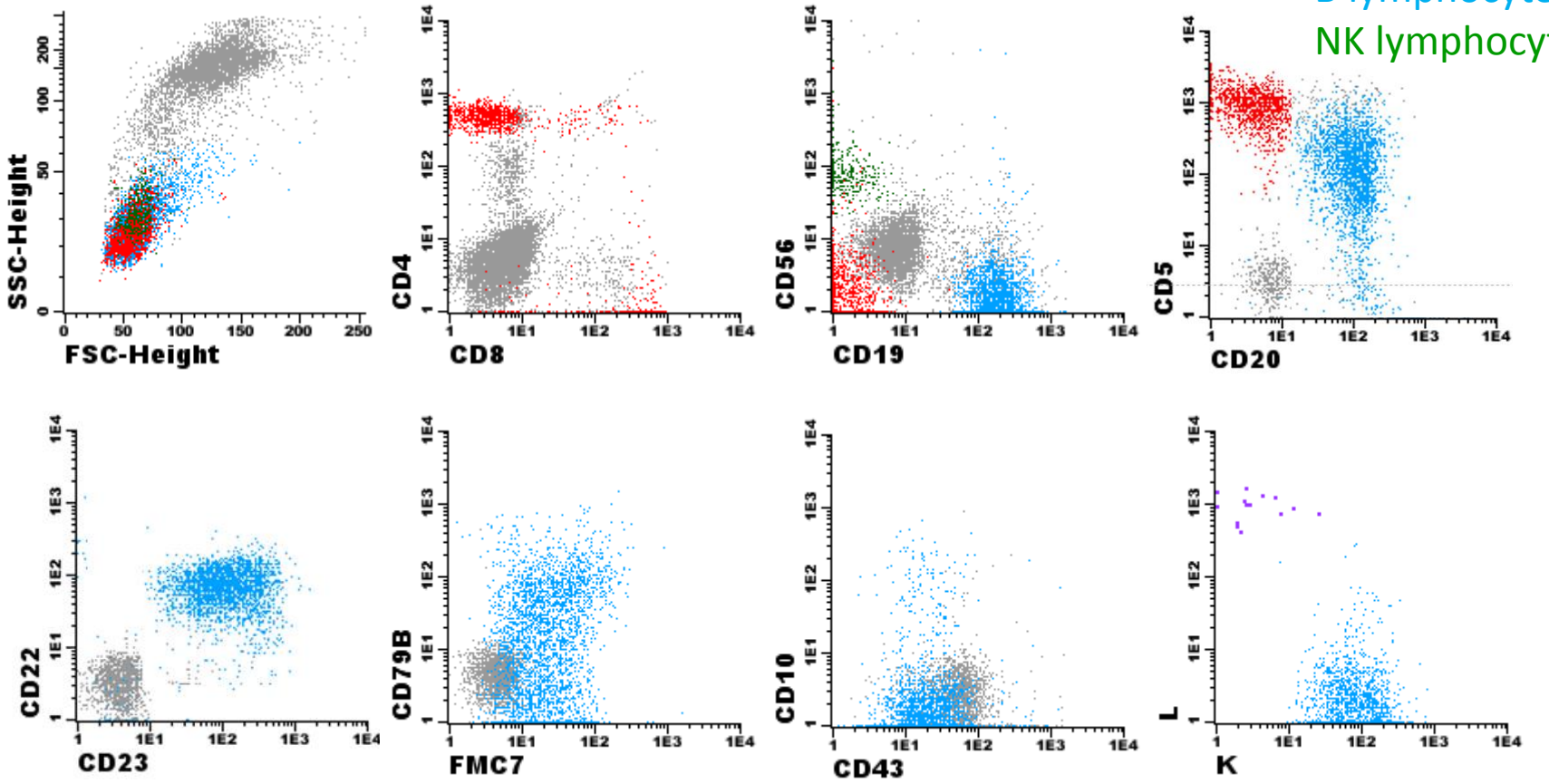
CLINICAL CASE

- Cervical lymph node biopsy:
  - Small lymphocytic lymphoma (SLL)
  - FISH: heterozygous deletion of *TP53* in 60% cell nuclei



IMMUNOPHENOTYPE (peripheral blood)

T lymphocytes
B lymphocytes
NK lymphocytes



Clonal B-cell population: CD5+, CD23+, CD43+, CD10-, Kappa+, CD20^{dim}, CD79^{dim}, FCM7-, CD22+, ZAP-70 and CD38 < 20%

CLINICAL CASE

- Cervical lymph node biopsy:
  - Small lymphocytic lymphoma (SLL)
  - FISH: heterozygous deletion of *TP53* in 60% cell nuclei
- Immunophenotype (peripheral blood):
  - Clonal population: < 5,000 CLL-phenotype B-cell lymphocytes / mm^3
- Diagnosis:
  - SLL del(17p)
- Treatment: watchful waiting strategy

- September 2013: progressive disease (lymphadenopathy)

FCR

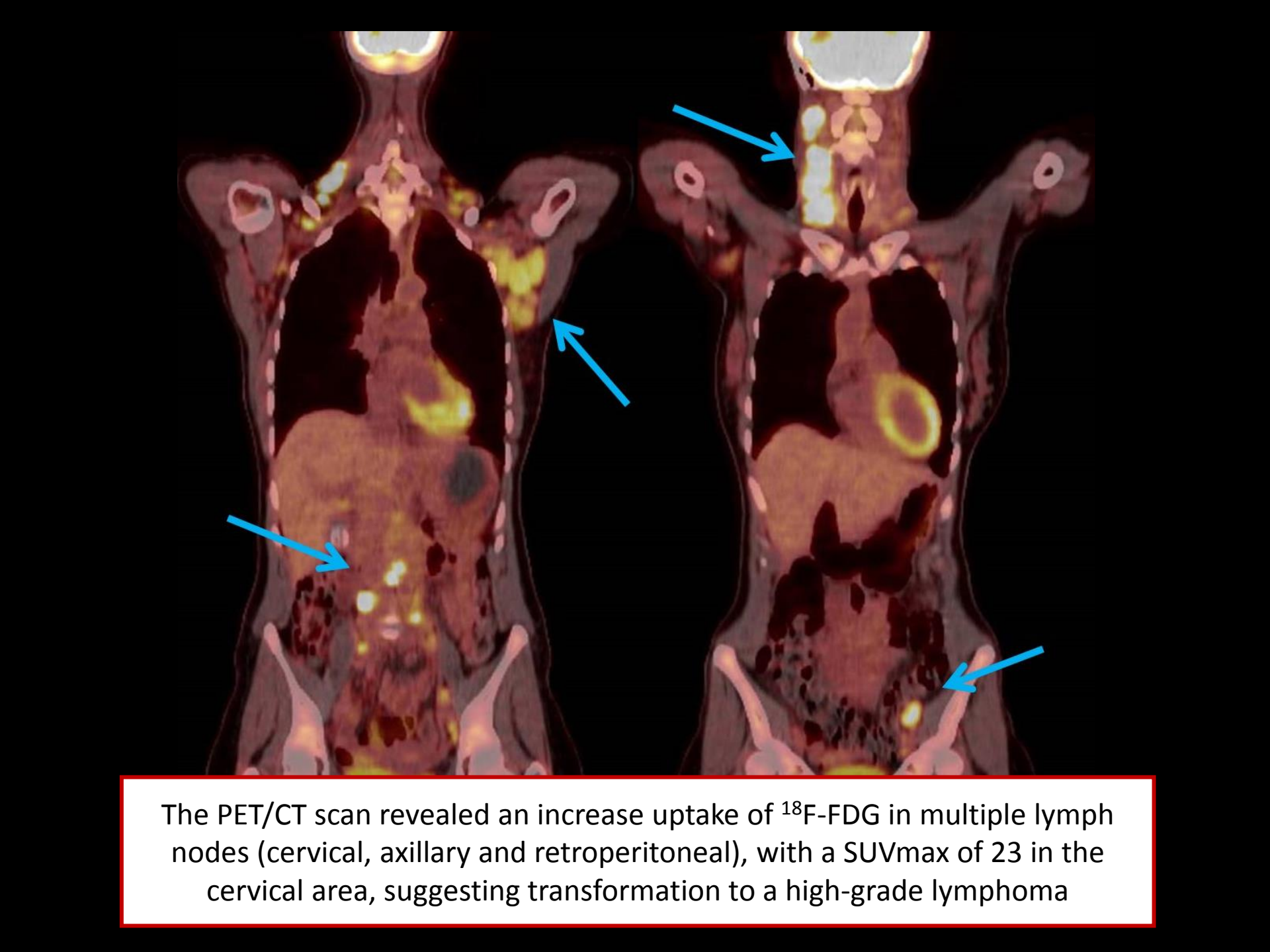
- October – December 2013 (2 cycles)
- Without response

Rituximab + bendamustine +/- idelalisib

- Clinical trial: Feb – Jul 2014 (6 cycles)
- Revaluation of the disease: complex karyotype
- Progressive disease (lymphadenopathy)
- Randomized to the placebo group
- HLA identical related donor: not found

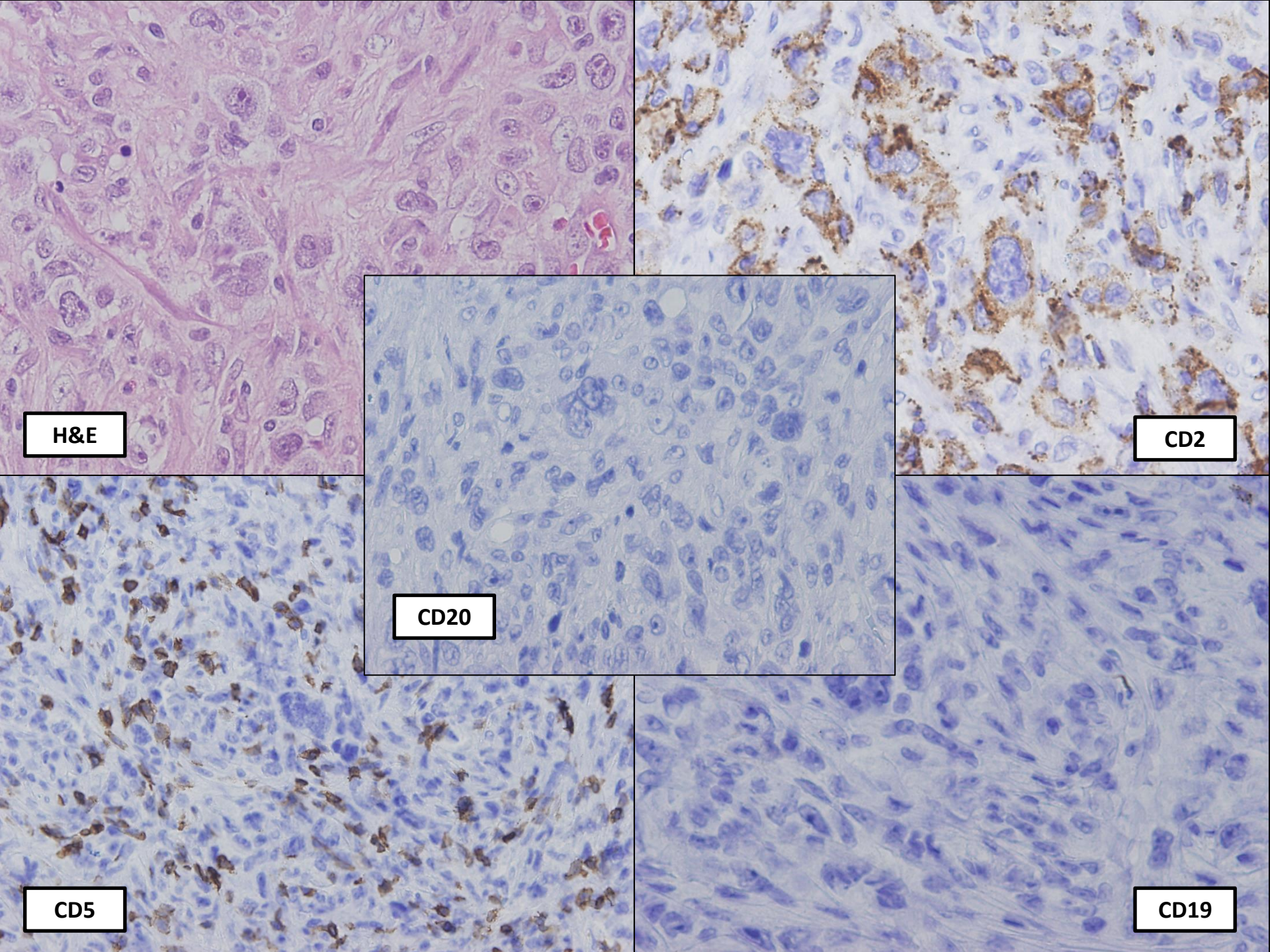
Duvelisib *vs.* ofatumumab

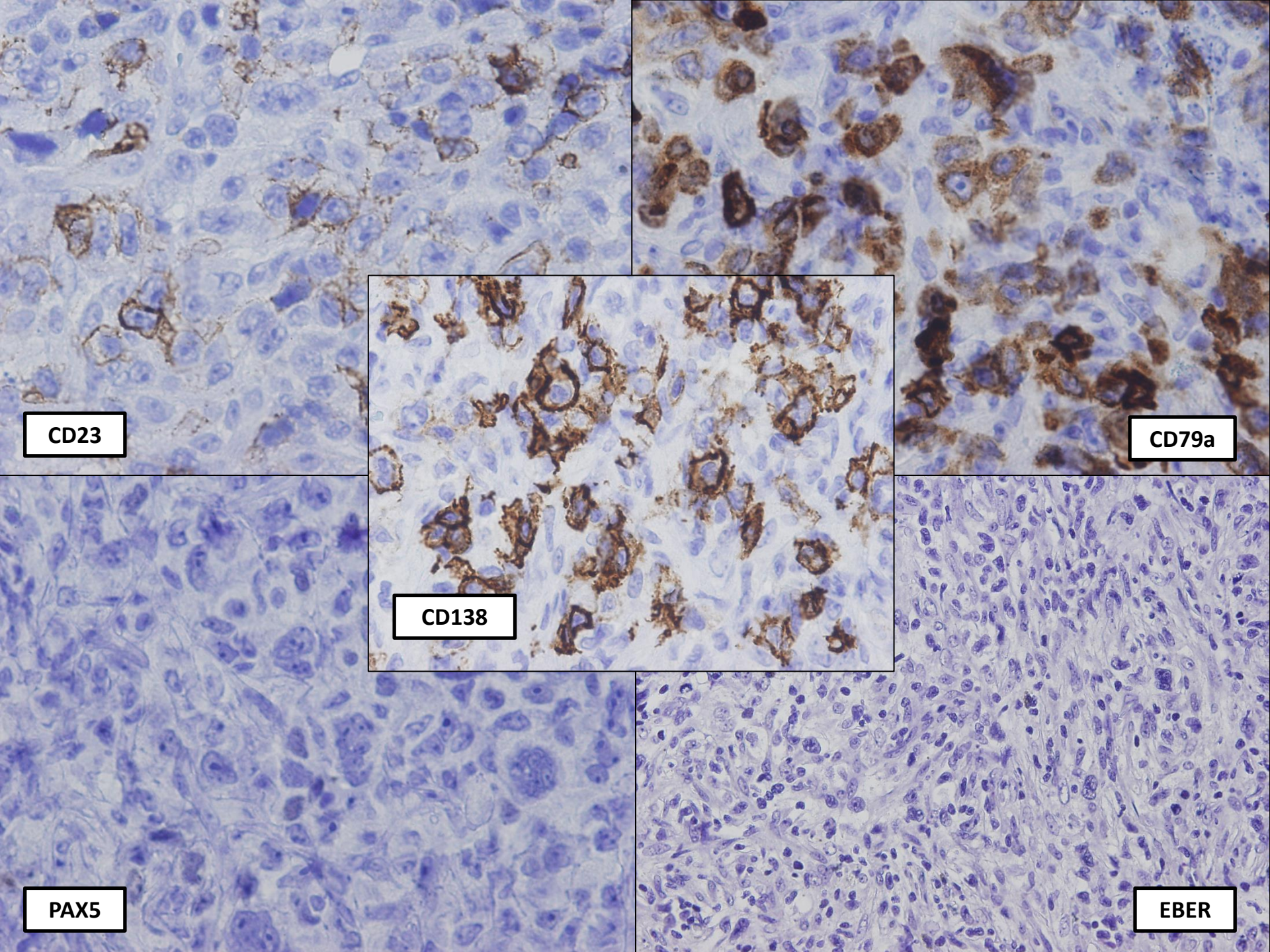
- Clinical trial: Oct 2014 – Feb 2015
- 5 cycles (duvelisib group)
- Progressive disease, with B symptoms, and LDH increase
- Matched unrelated donor (HLA 10/10)

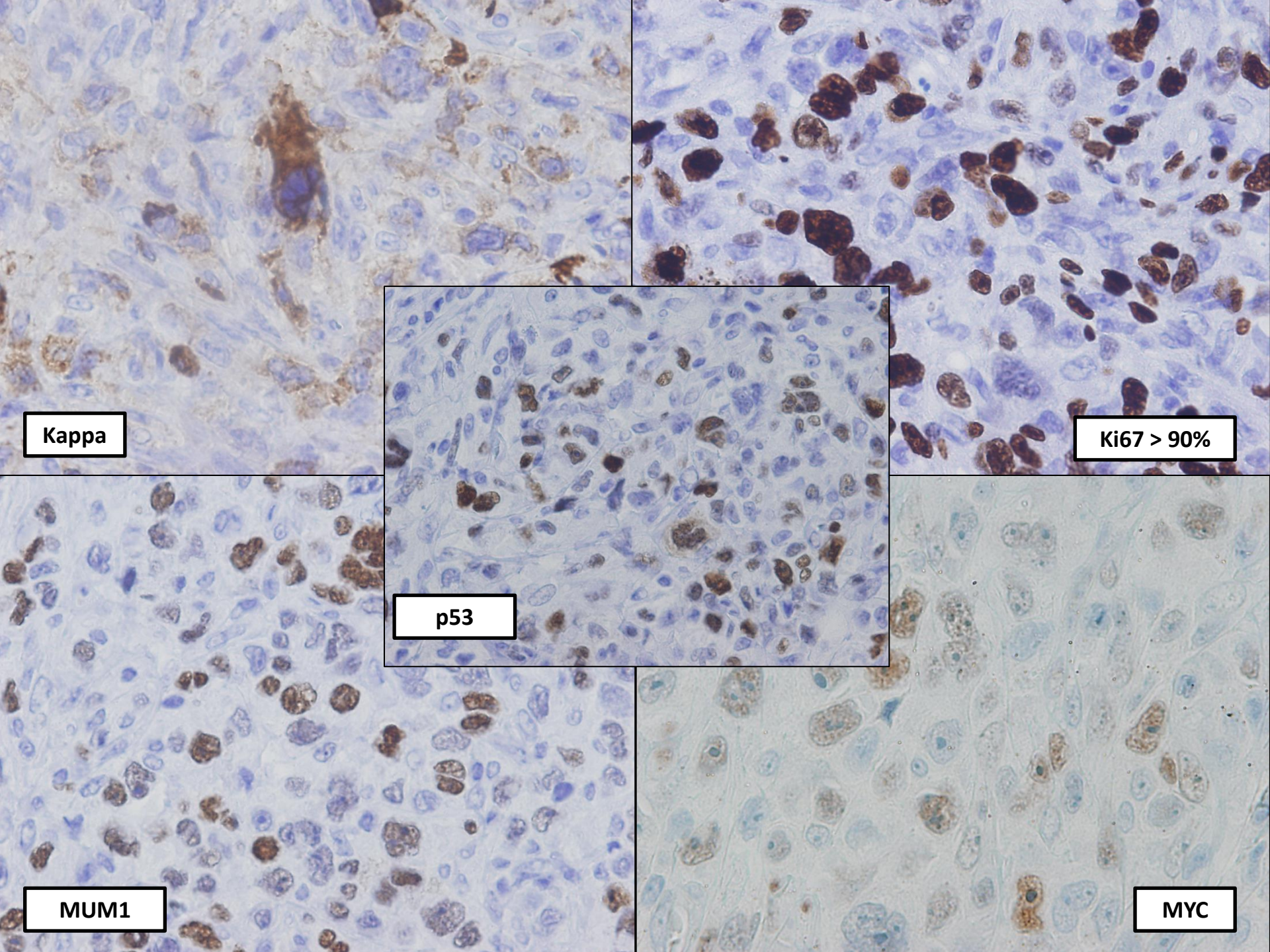


The PET/CT scan revealed an increase uptake of ^{18}F-FDG in multiple lymph nodes (cervical, axillary and retroperitoneal), with a SUVmax of 23 in the cervical area, suggesting transformation to a high-grade lymphoma

CERVICAL LYMPH NODE BIOPSY


H&E
CD2
CD20
CD5
CD19


CD23
CD79a
CD138
PAX5
EBER


Kappa
Ki67 > 90%
p53
MUM1
MYC

CLINICAL CASE

- Cervical lymph node biopsy:
  - Positive: CD2, CD79a, CD23, IRF-4/MUM-1, cIg Kappa LC, CD138
  - Negative: PAX-5, CD19, CD20, CD30, EBER
  - Ki-67 > 90%, p53+, MYC (weak nuclear staining)
- FISH: 3-5 copies of *MYC* in 78% cell nuclei
  - Without rearrangement

Plasmablastic transformation of small lymphocytic lymphoma EBV (-)

DHAP

- March – April 2015 (2 cycles)
- Progressive disease (lymphadenopathy)

Selinexor

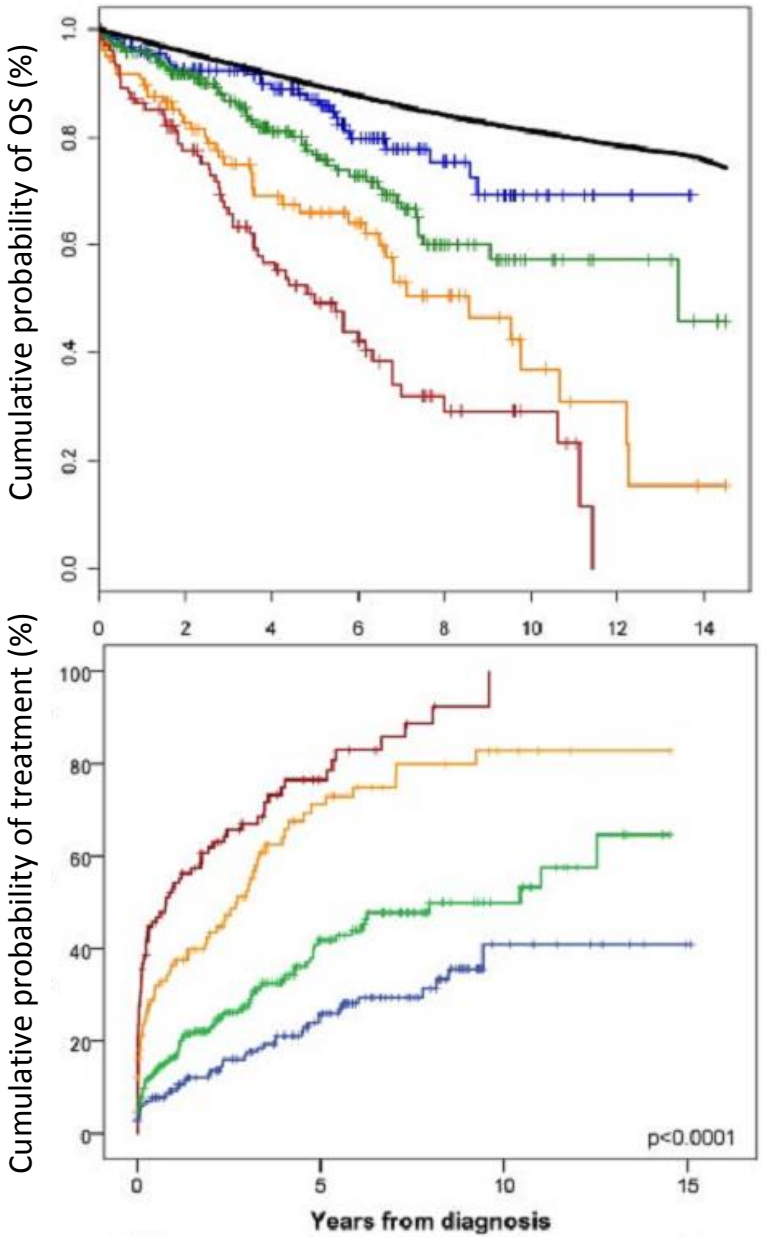
- Phase II clinical trial: June 2015
- Selective inhibitor of nuclear exportin
- Progressive disease
- ECOG performance status: 4

Palliative care

- Decease: July 2015
- We could never perform the HSCT

Thank you…

Integrated mutational and cytogenetic model for CLL



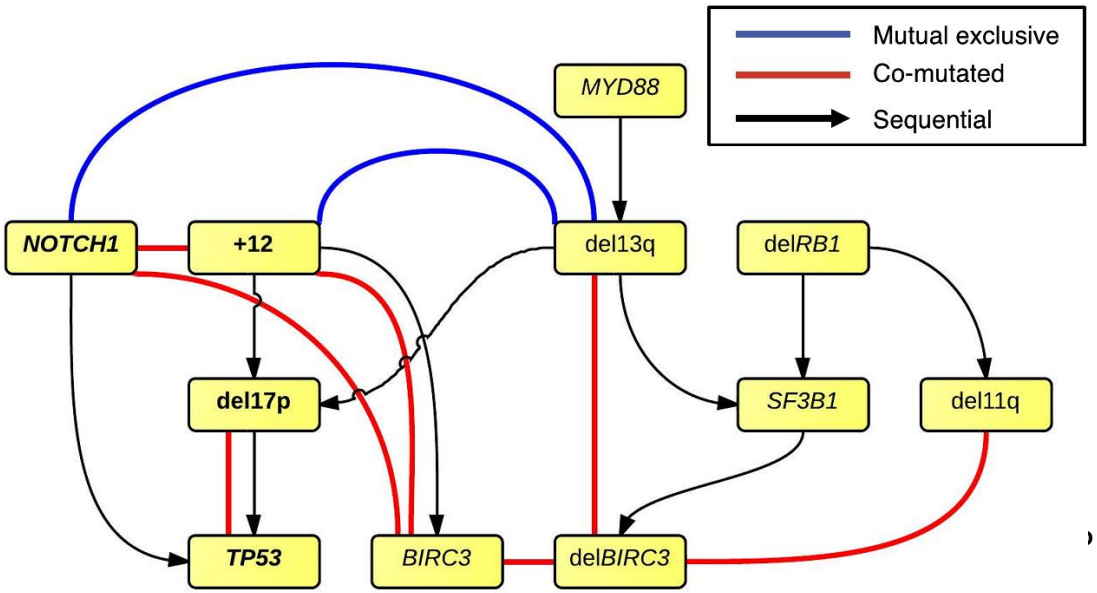
Category	Associated genetic factors
Very high risk	del(17p)*/*TP53* mutation and/or *BIRC3* mutation
High risk	del(11q)*/*ATM* mutation and/or *NOTCH1* mutation and/or *SF3B1* mutation
Intermediate risk	Trisomy 12 Normal karyotype and FISH
Low risk	Isolated del(13q)*

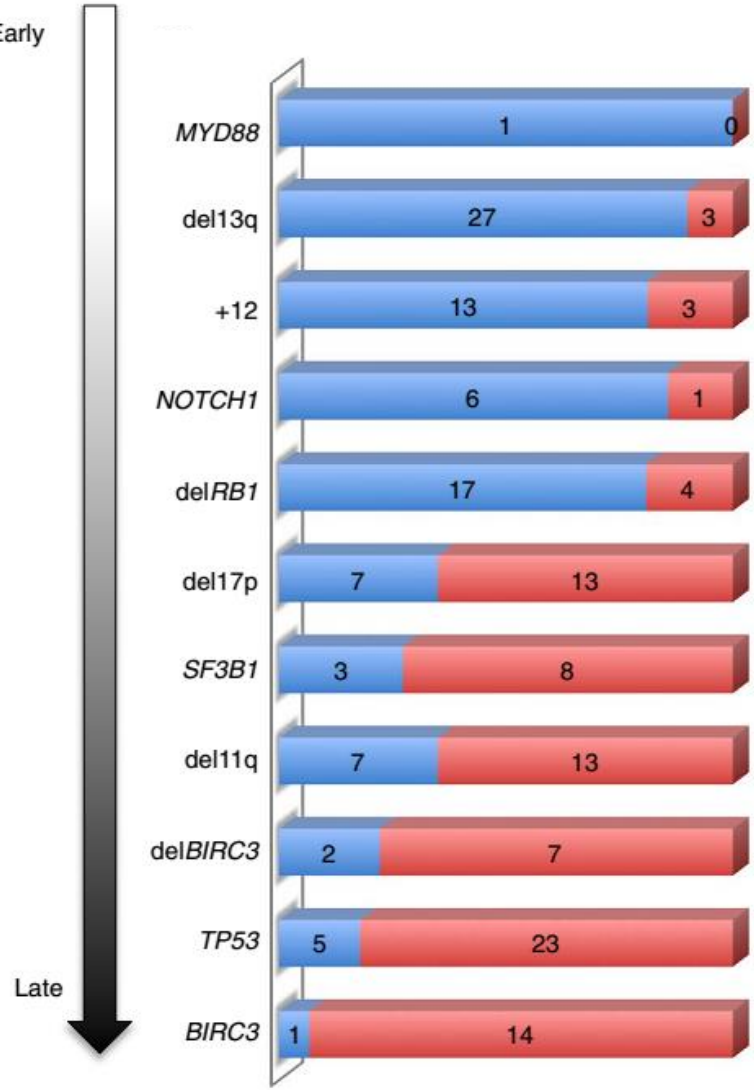
- Matched general population
- del13q14
- Normal/+12
- *NOTCH1* M/*SF3B1* M/del11q22-q23
- *TP53* DIS/*BIRC3* DIS

Rossi D, *et al*. Blood 2013
Puiggros A, *et al.* Biomed Res Int 2014

Evolution pathways in CLL

- N = 70 patients, 12 years
- Evolution of CLL follows a time-ordered process
  - Co-occurrence:
    - Del(17p13) and *TP53* mutations
    - Del(11q22-q23) and *BIRC3* mutations
    - +12 and *NOTCH1* mutations
    - *BIRC3* abnormalities, +12 and *NOTCH1* mutations
    - Del(13q14) and *BIRC3* deletion
  - Mutually exclusive relationships
    - Del(13q14) and +12 / *NOTCH1* mutations
- Two distinct and mutually exclusive evolutionary paths



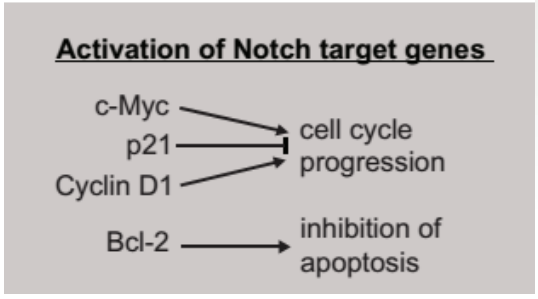


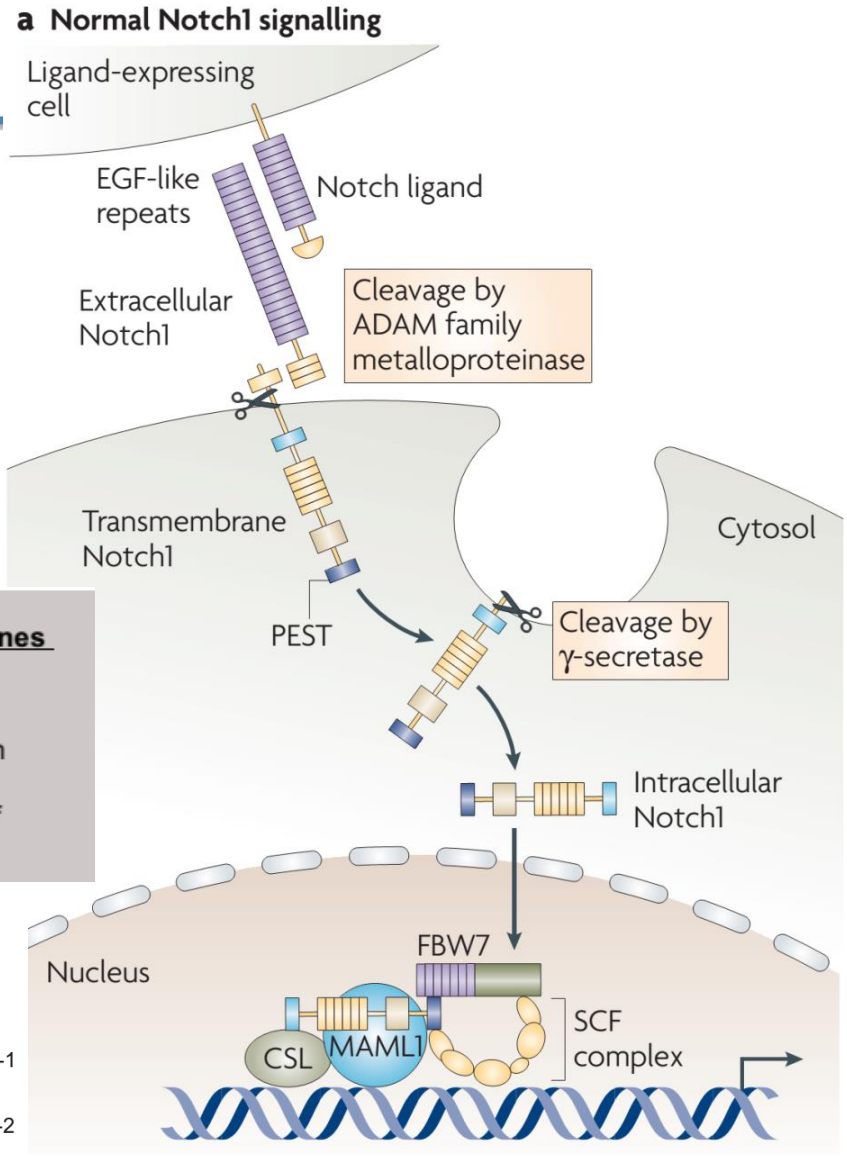
PROGRAM

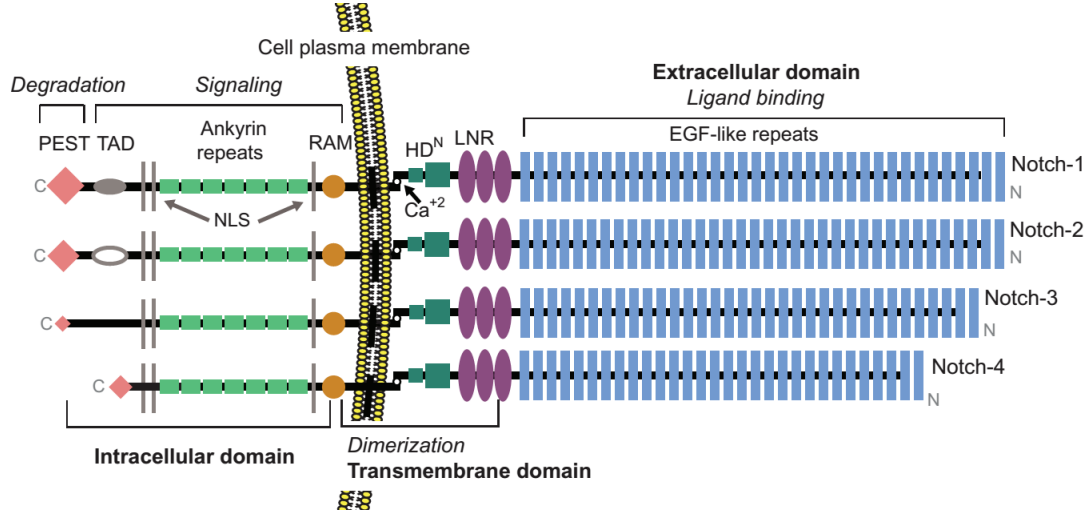
Wang J, *et al*. eLife 2014

NOTCH1

- Notch1: transmembrane glycoprotein
  - Heterodimeric receptor
- Three domains: extracelular, transmembrane and intracelular
- PEST domain (proline, glutamate, serine, threonine) Degradation signals
- Cleavage:
  - Metalloproteinase
  - γ-secretase
- Transcription factor





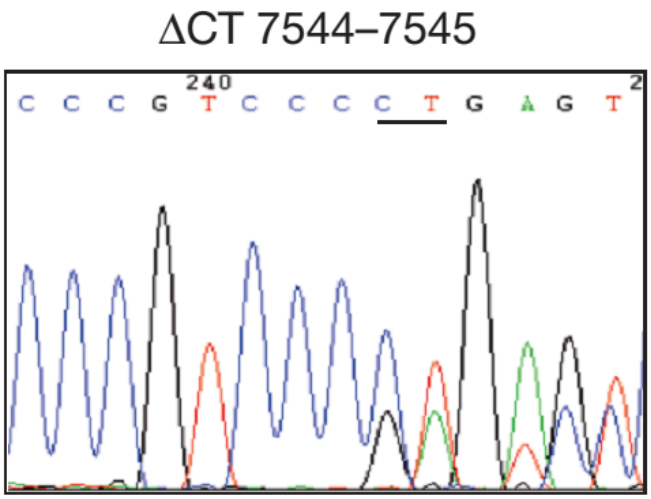


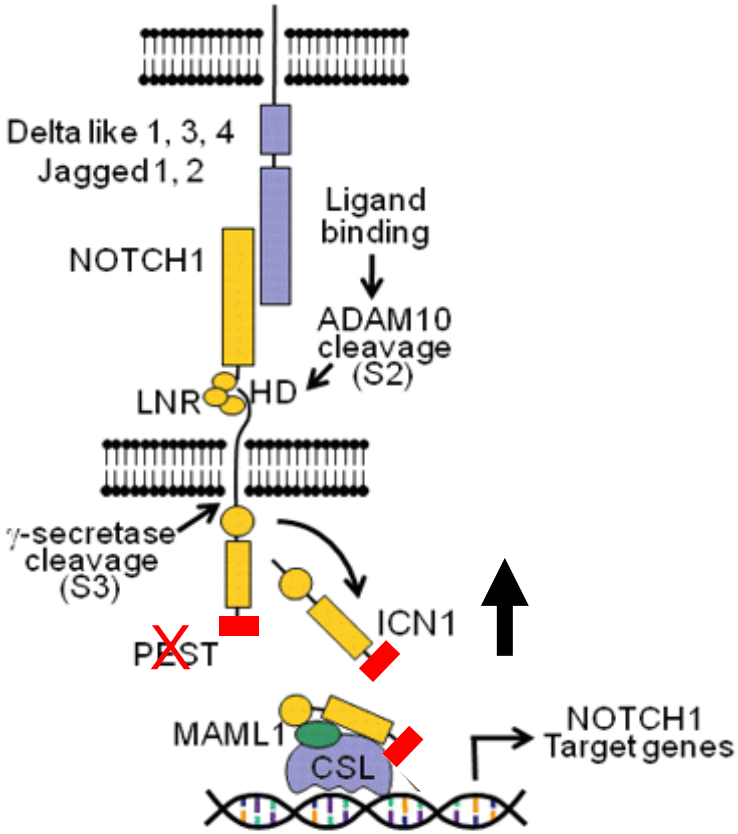
IP PROGRAM

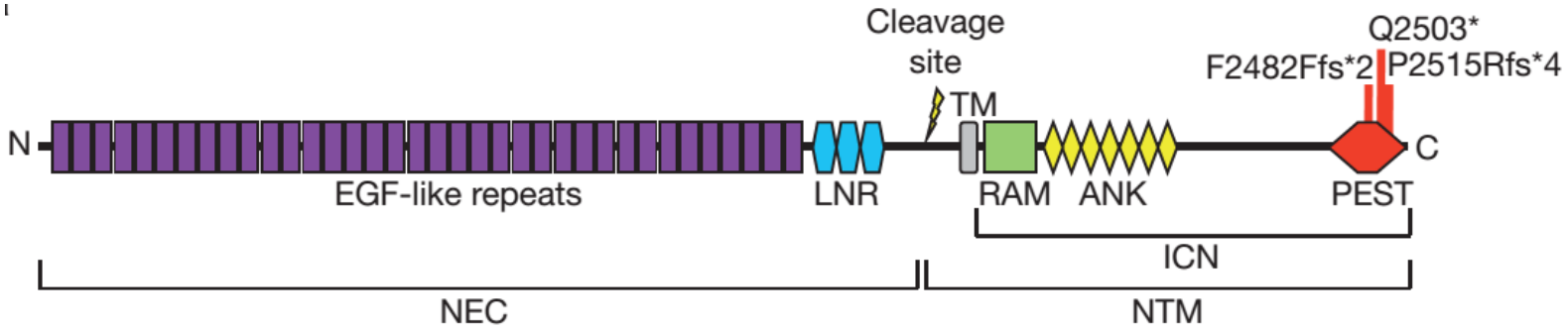
Aifantis I, *et al*. Nature 2008;
Olsauskas-Kuprys R, *et al*. Onco Targets Ther 2013

NOTCH1 mutations in CLL

- Activating mutations
  - P2515Rfs*4 (ΔCT 7544-7545)



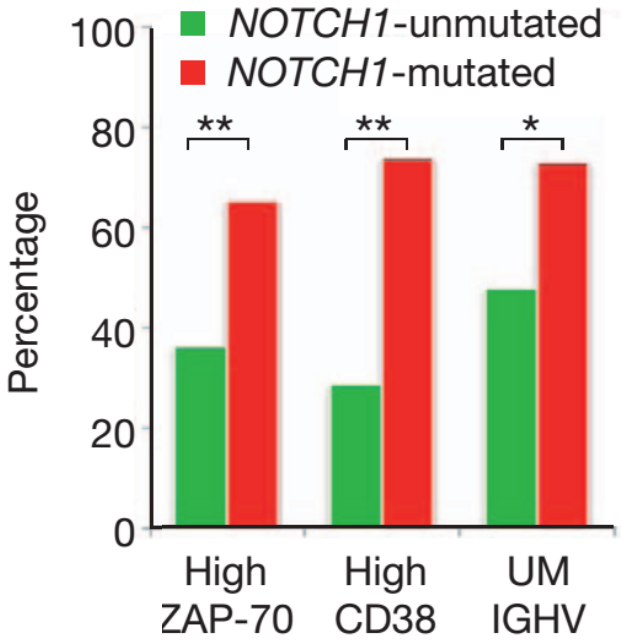


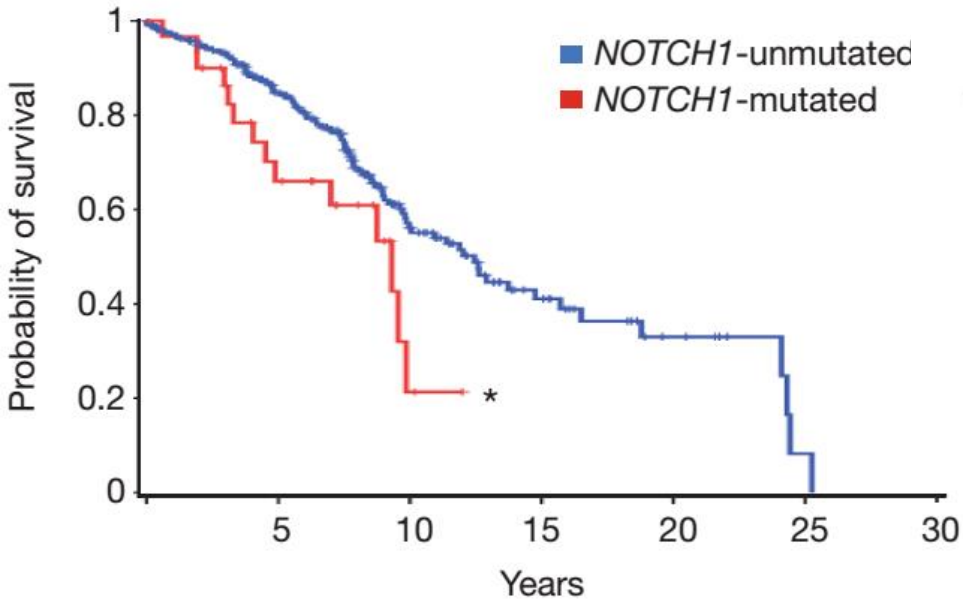


Puente XS, *et al.* Nature 2011;

NOTCH1 mutations in CLL

- Clinical implications
  - Frequency: 10% of al CLL
  - Associated with trisomy 12
  - More aggressive clinical course
    - ZAP-70, CD38, UM *IGHV*
  - Shorter survival
  - Higher risk of transformation

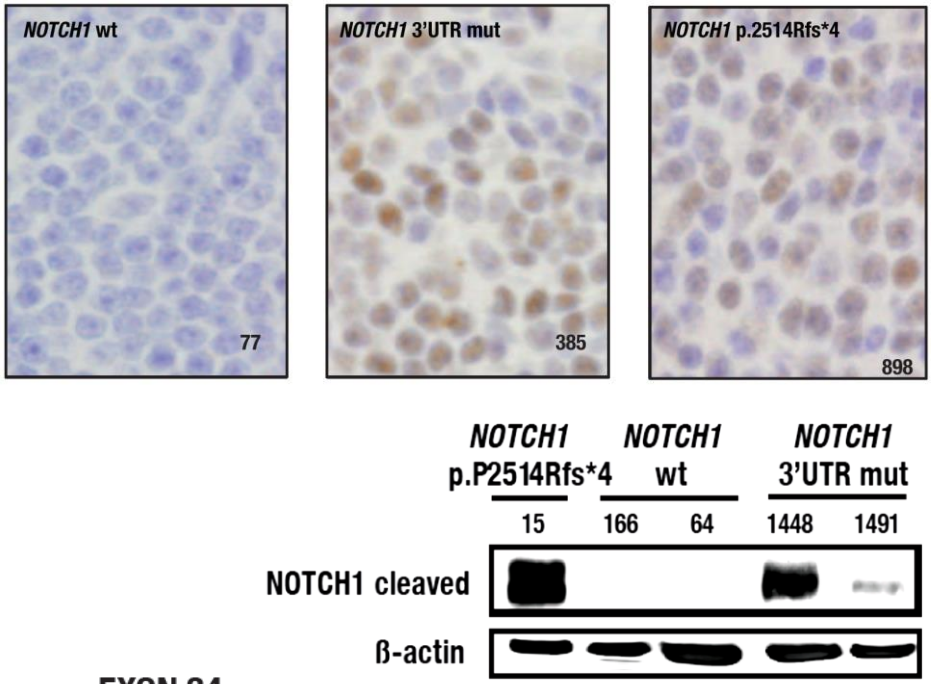




Puente XS, *et al.* Nature 2011;
Fabbri G, *et al*. J Exp Med 2011;
Rossi D, *et al.* Blood 2011;

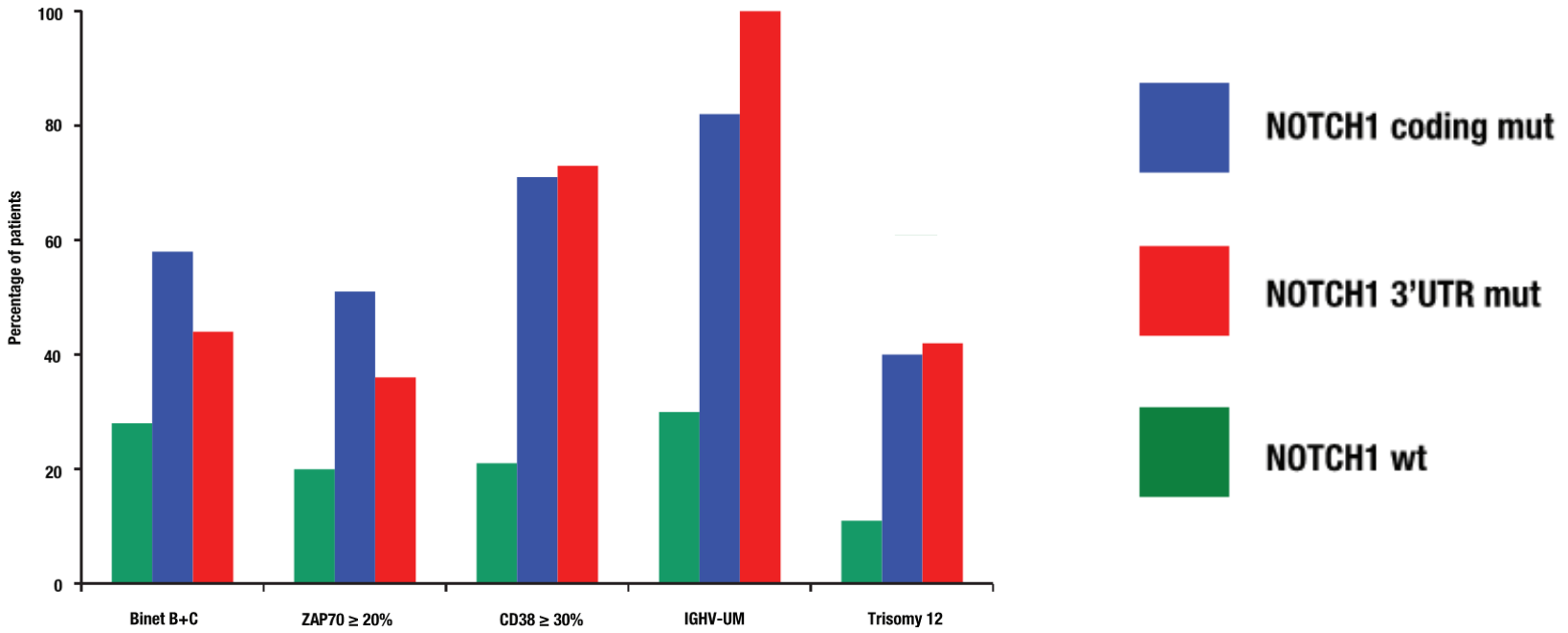
NOTCH1 mutations in the 3'UTR domain

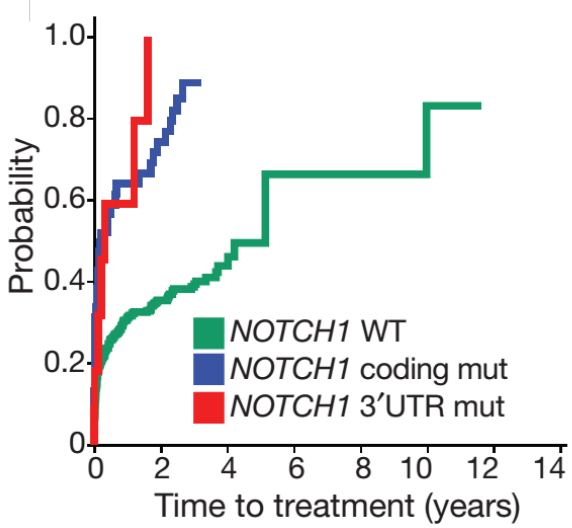
- Mutations in no-coding regions
  - 3'UTR of *NOTCH1* (Chr 9 exon 34)
  - Novel splicing event
  - Between a cryptic donor site and a new created acceptor site in the 3'UTR
  - Deletion of the last 158 coding bases
  - This within-exon splicing remove a PEST domain and increase protein stability and expression

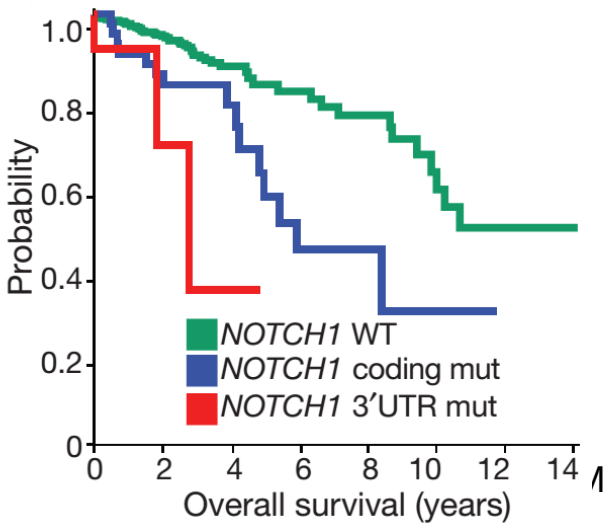


Puente XS, *et al.* Nature 2015

NOTCH1 mutations in the 3'UTR domain



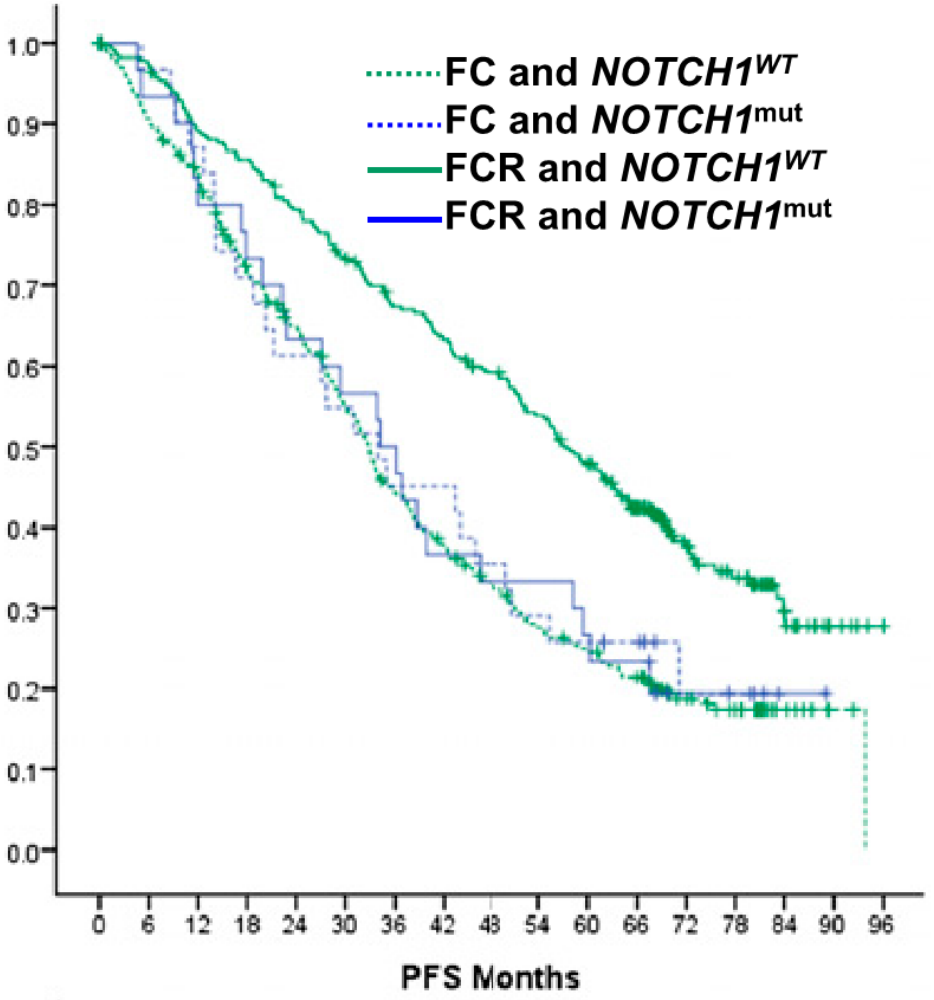




Puente XS, *et al.* Nature 2015

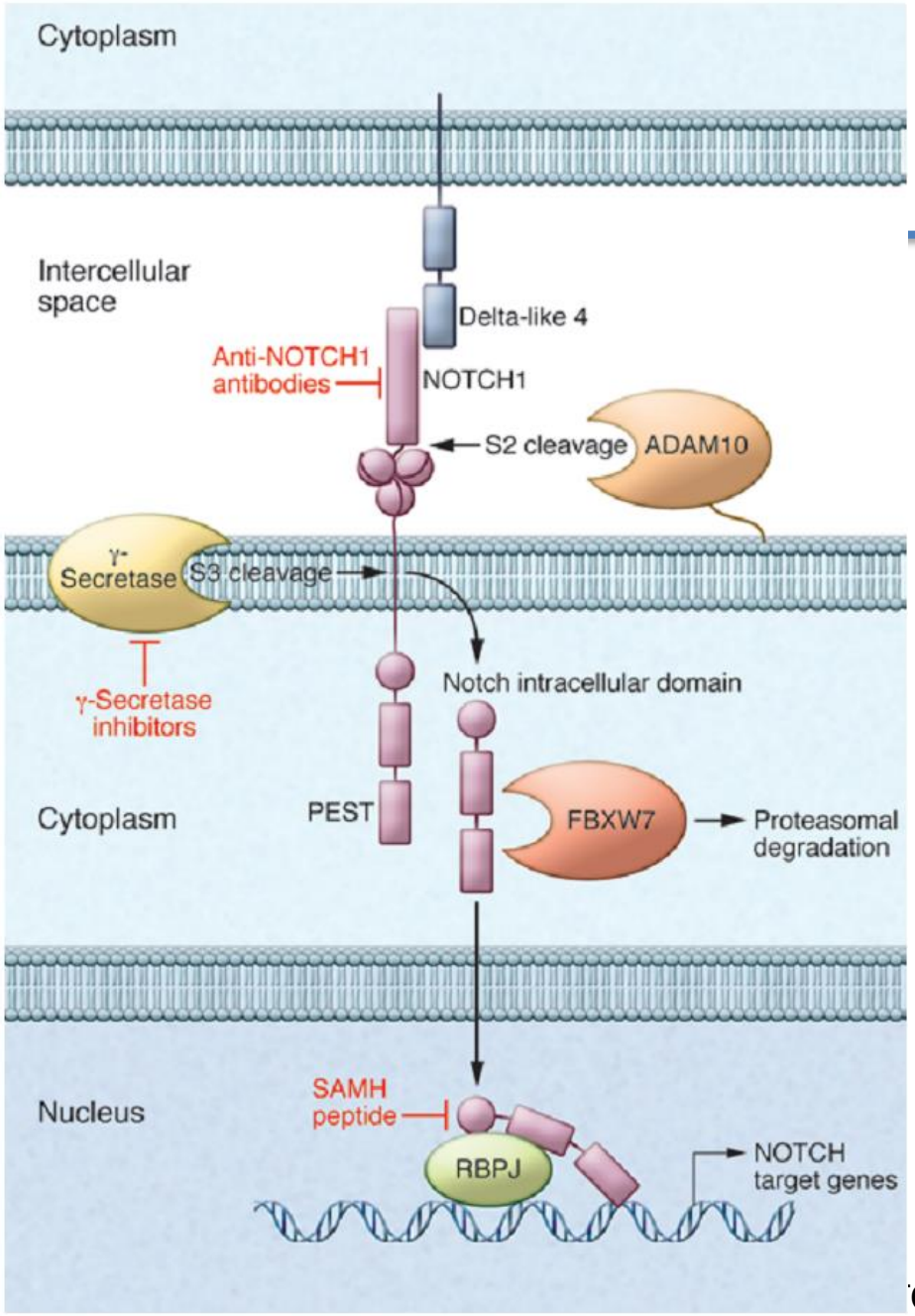
Rituximab in *NOTCH1*^{mut}

- Analyzed in the CLL8 study
  - FC vs FCR
  - *NOTCH1*^{mut} in 10%
  - Rituximab failed to improve response and survival in *NOTCH1*^{mut}
  - Decreased benefit from the addition of rituximab to FC



Stilgenbauer S, *et al.* Blood 2014

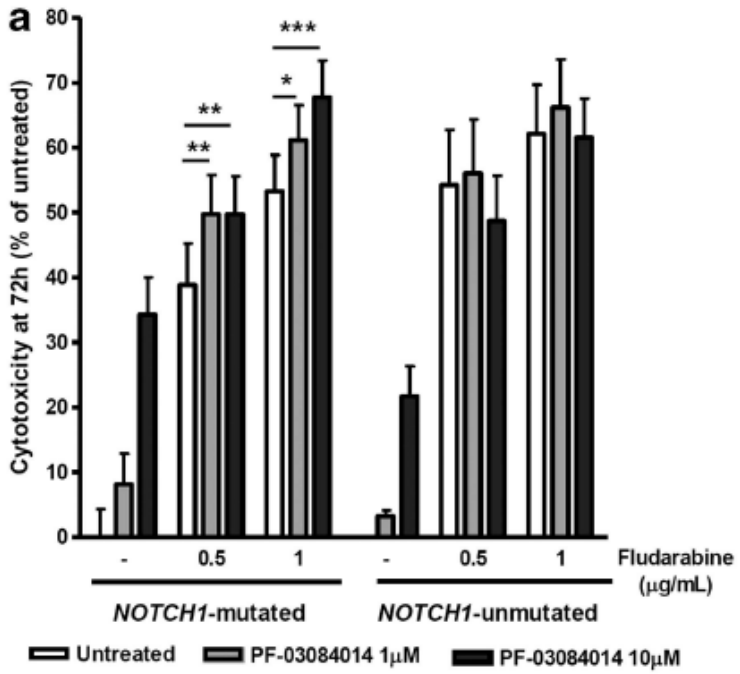
Approaches to block NOTCH1 signaling

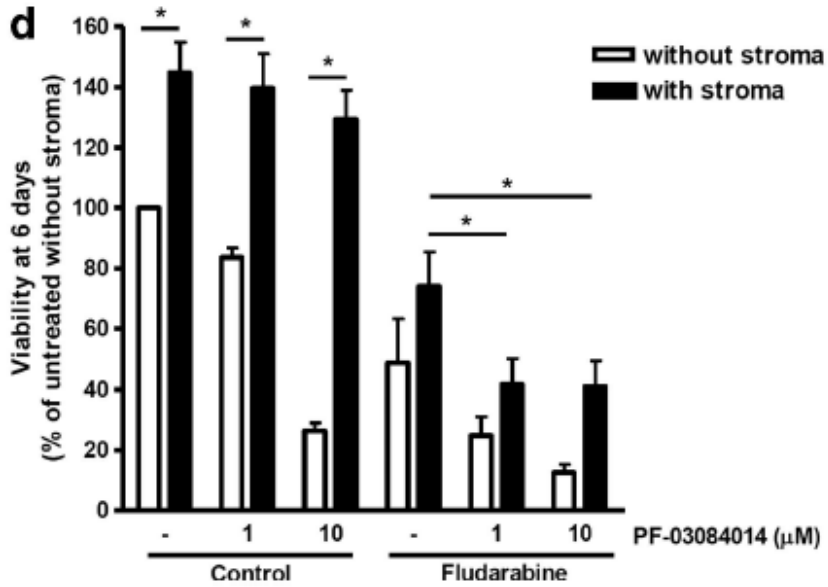


- Anti-NOTCH1 inhibitory antibodies: inhibition of ADAM10 cleavage
- Blockage of γ-secretase activity
- SAMH1 peptides: disruption of the NOTCH1 nuclear transcriptional complex

Van Vlierberghe P, *et al.* J Clin Invest 2012

Effect of γ-secretase inhibitor PF-03084014 in *NOTCH1*^{mut} CLL



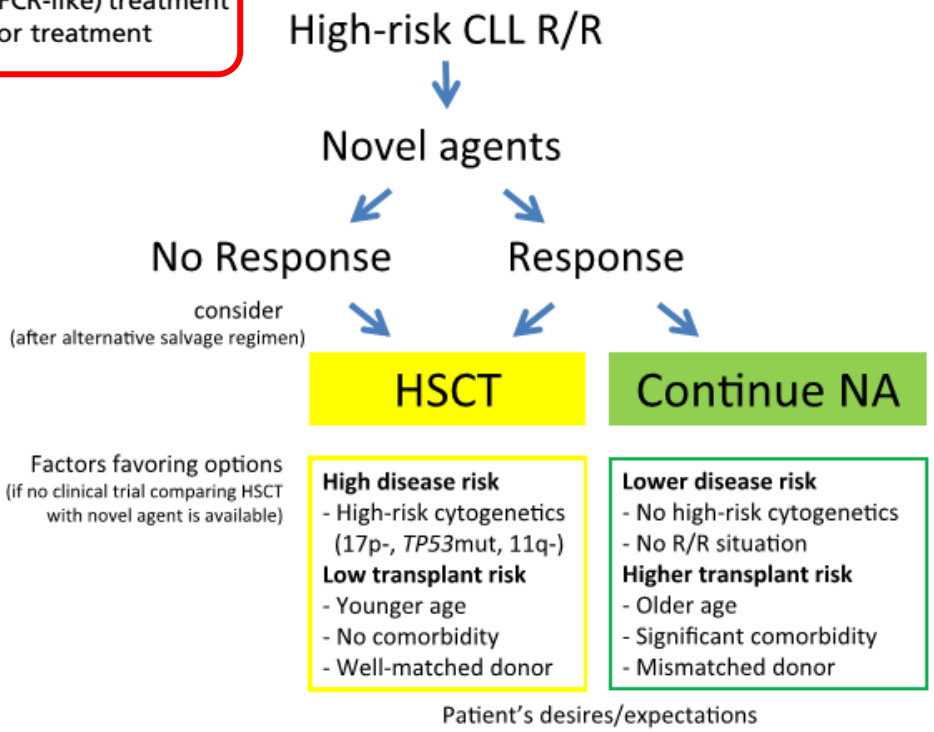


- PF-03084014 inhibits *in vitro* constitutive Notch1-activation and induces selective apoptosis in *NOTCH1*^{mut} CLL
- Synergistic action with fludarabine, even in presence of protective stroma

López-Guerra M, *et al*. Leukemia 2015

CLL

Patients and subgroups that should be considered for hematopoietic stem cell transplantation	
EBMT criteria Dreger et al,[44] 2007	• Relapse within 24 mo after having achieved a response with intensive treatment (purine analogue combinations, autoSCT) • Detection of p53 abnormality and indication for treatment • Fludarabine resistance: nonresponse or early relapse (<12 mo after purine analogue-based therapy)
iwCLL criteria Hallek et al,[45] 2008	• Resistant disease: failure to achieve CR/PR • Relapse within 6 mo of last treatment • Detection of del(17p)-
Highest risk in risk category model Zenz et al,[46] 2012	• Fludarabine refractory CLL • Early relapse (within 24 mo) after FCR (or FCR-like) treatment • *TP53* deletion/mutation and indication for treatment



Dreger P, *et al.* Blood 2014
McClanahan F, *et al.* Hematol Oncol Clin N Am 2014

Transformation in CLL – Richter's syndrome (RS)

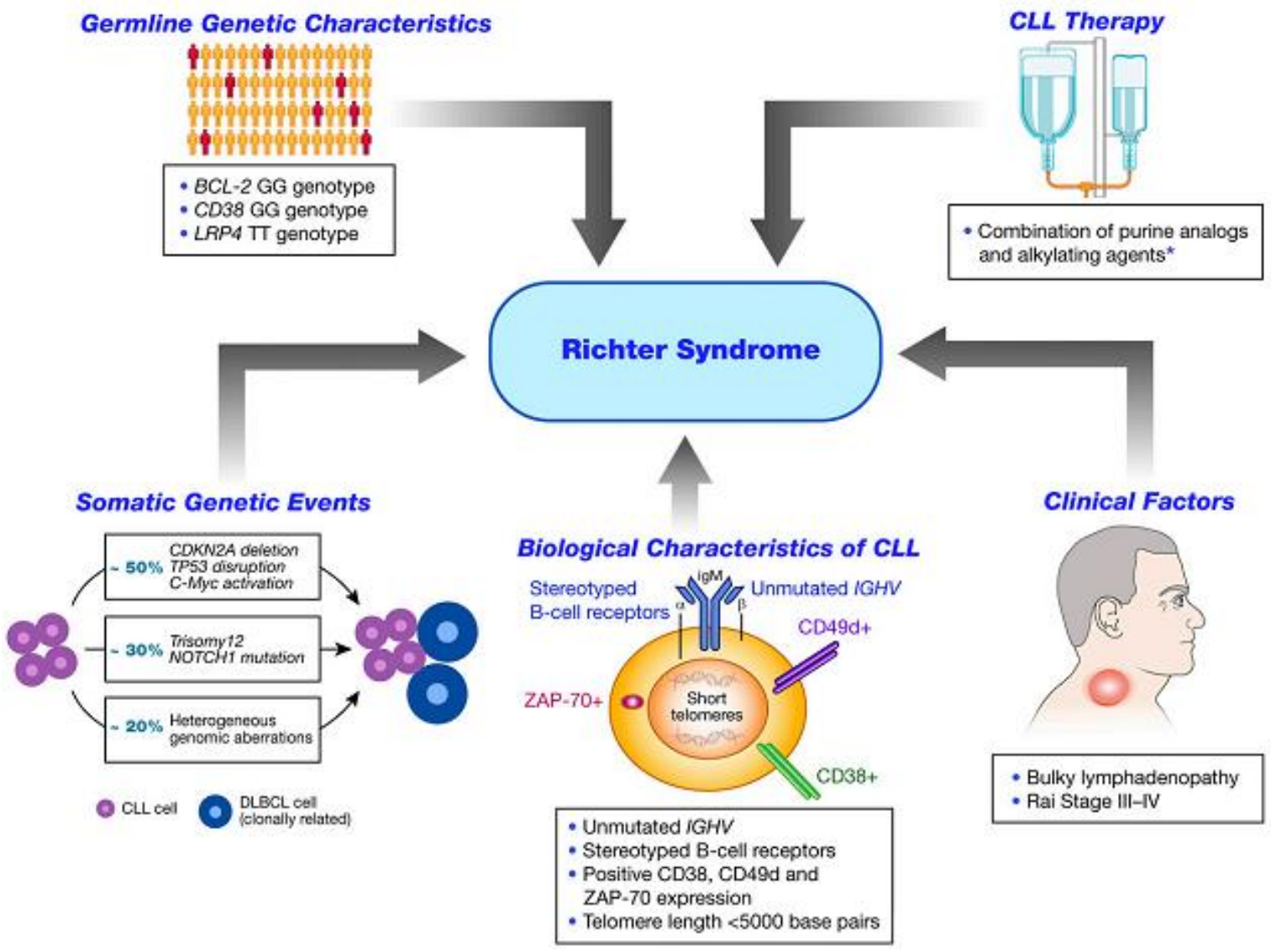
- Histological transformation of SLL/CLL to an aggresive lymphoma

- Prevalence: 1-11%
- Incidence: 0.5-1.0%
- Median presentation: 1.8-5 years

- Clinical features
  - B symptoms
  - Elevated LDH levels, hipercalcemia
  - Rapid enlargement of lymph nodes, extranodular involvement

Rossi D, *et al*. Br J Haematol 2008
Rossi D, *et al*. Adv Exp Med Biol 2013

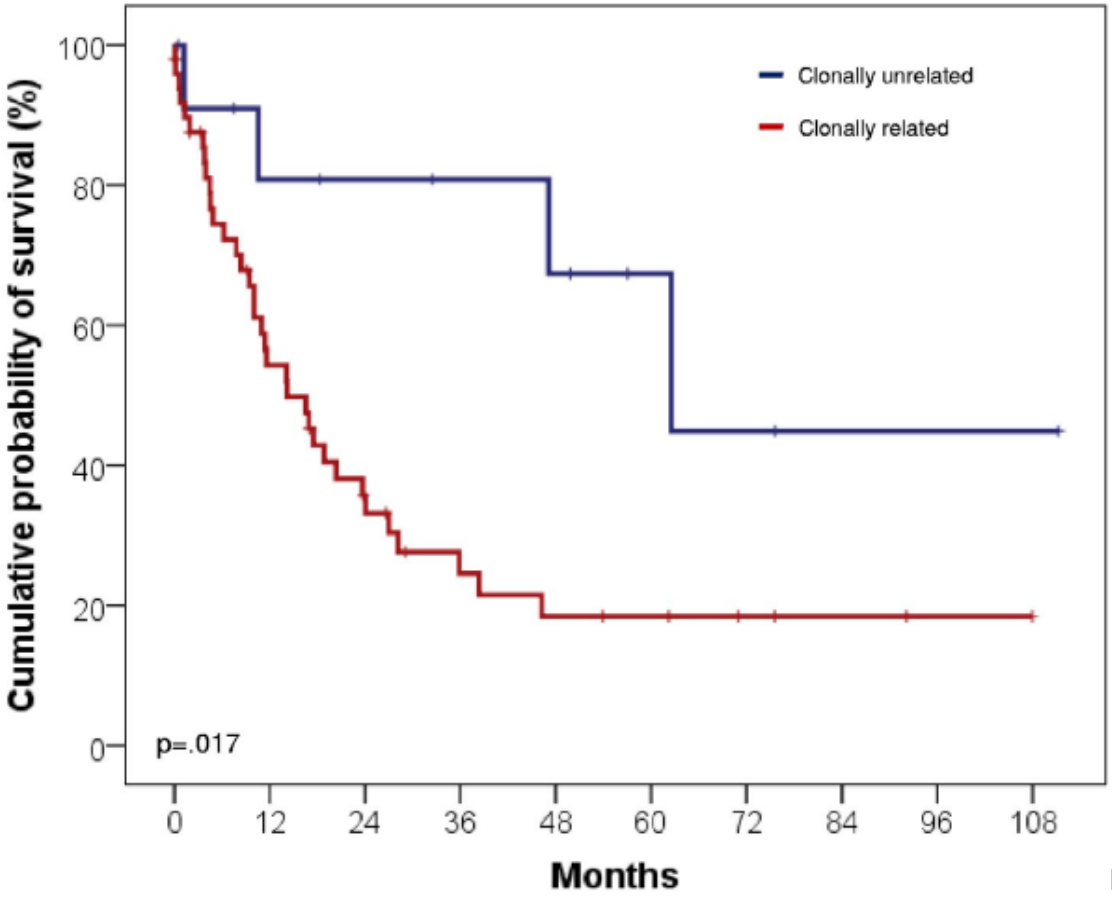
RS: risk factors



Parikh S, *et al*. Blood 2014

Clonally related and unrelated RS

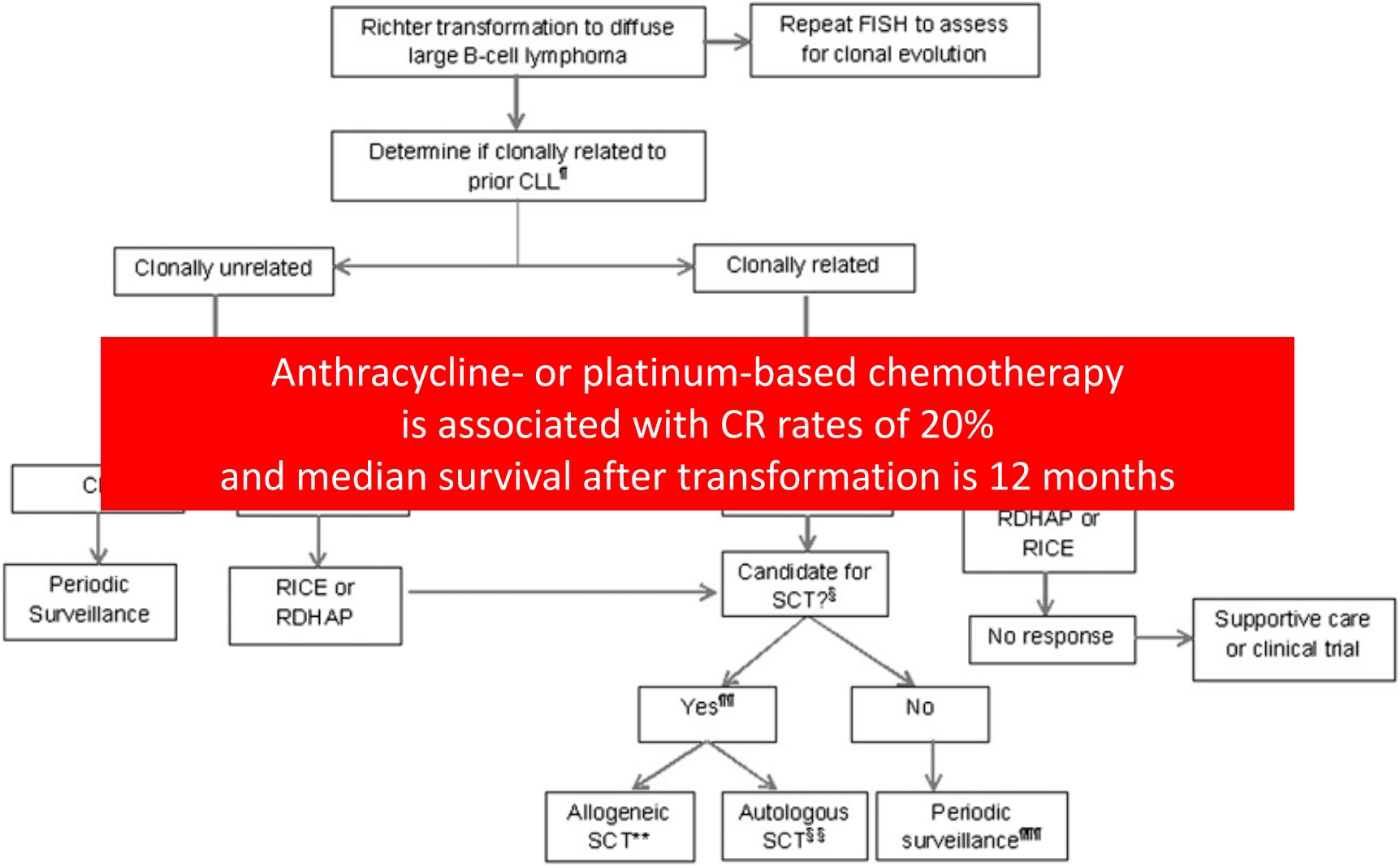
- Clonally related: 80%
- The molecular profile and the pronostic are clearly differents
- Clonally unrelated RS showed a longer survival (62 months) *vs* clonally related RS (14 months); p = 0.017



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
European Society for Medical Oncology

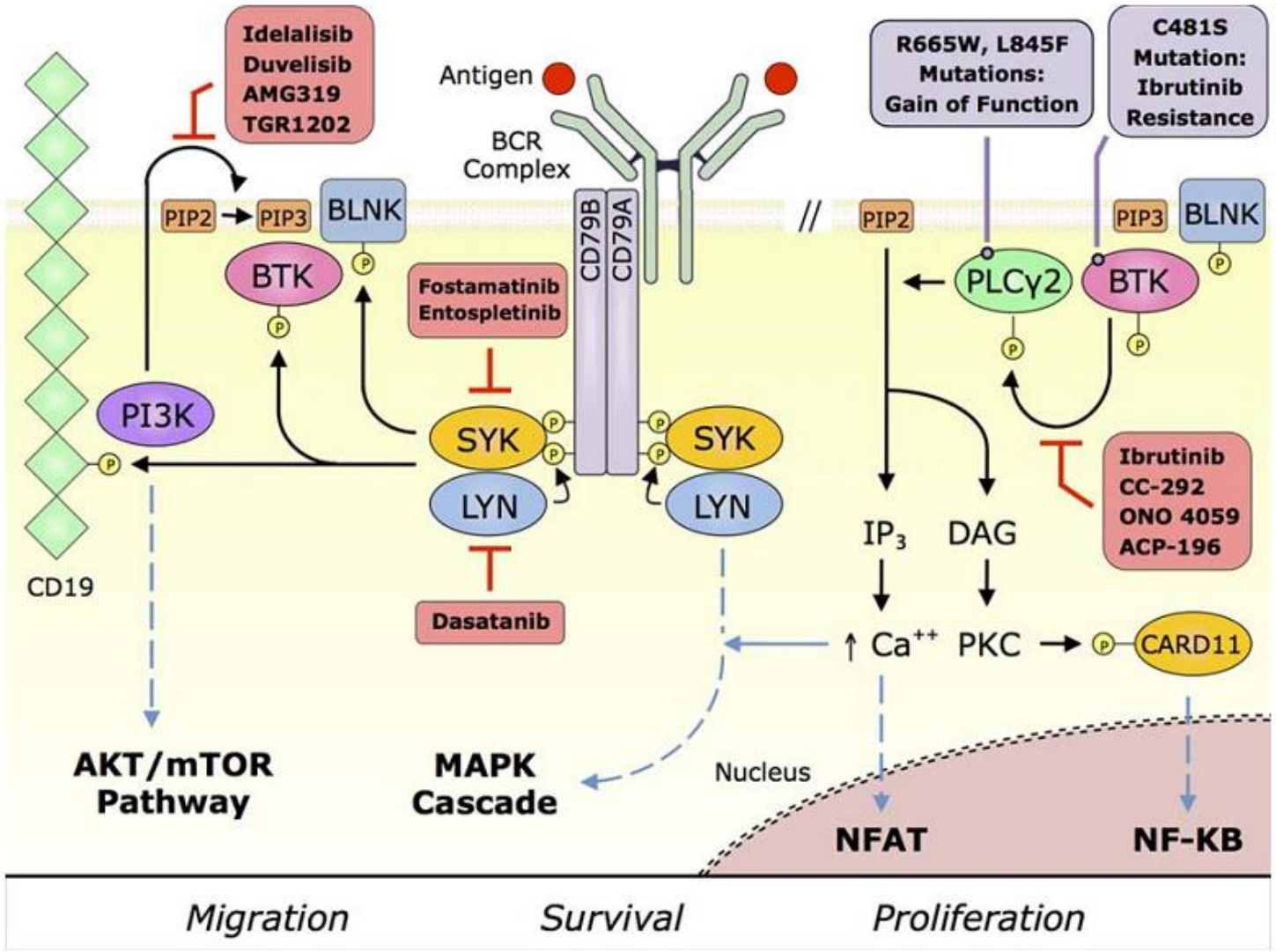
Rossi D, *et al*. Blood 2011
Fabbri G, *et al*. J Exp Med 2013

Management of RS



Parikh S, *et al*. Blood 2014

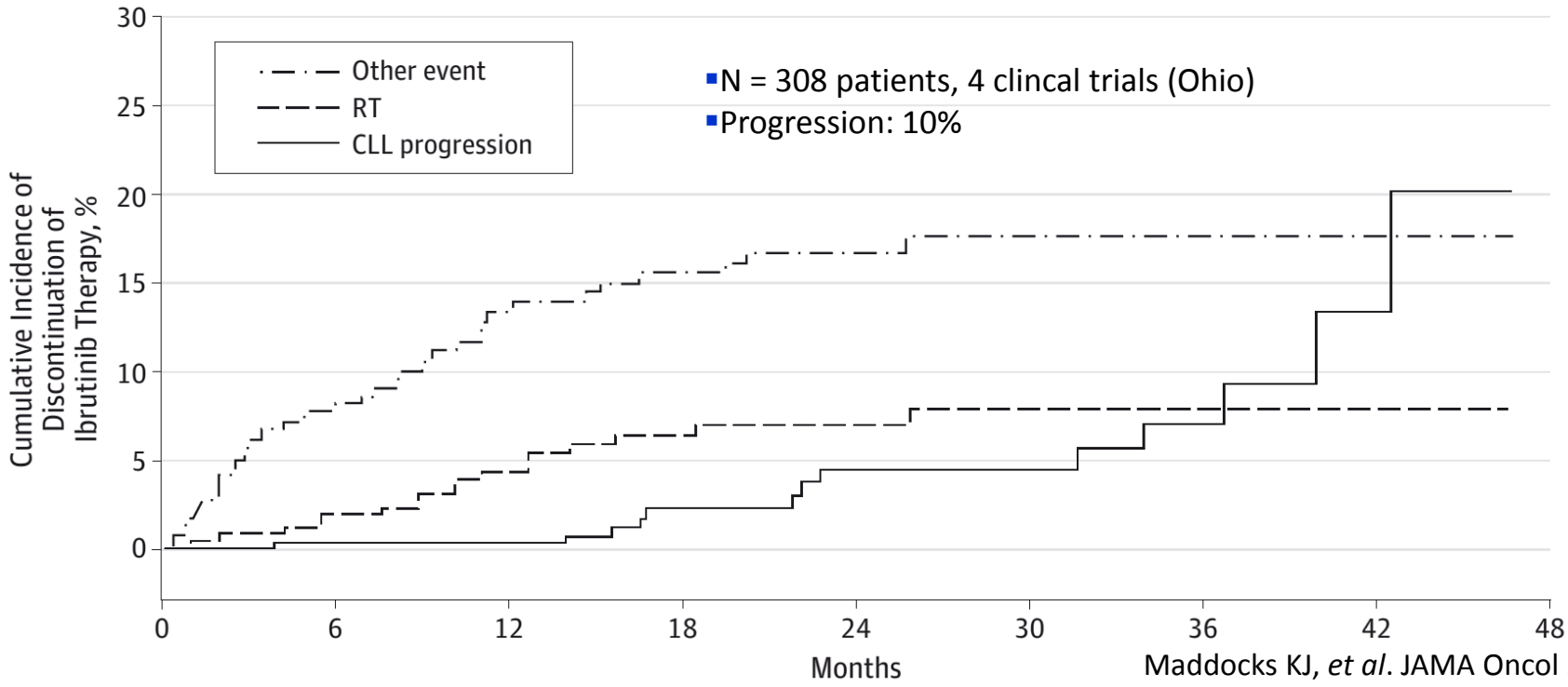
BCR inhibitors and RS



Mato A, *et al*. Am J Hematol 2015

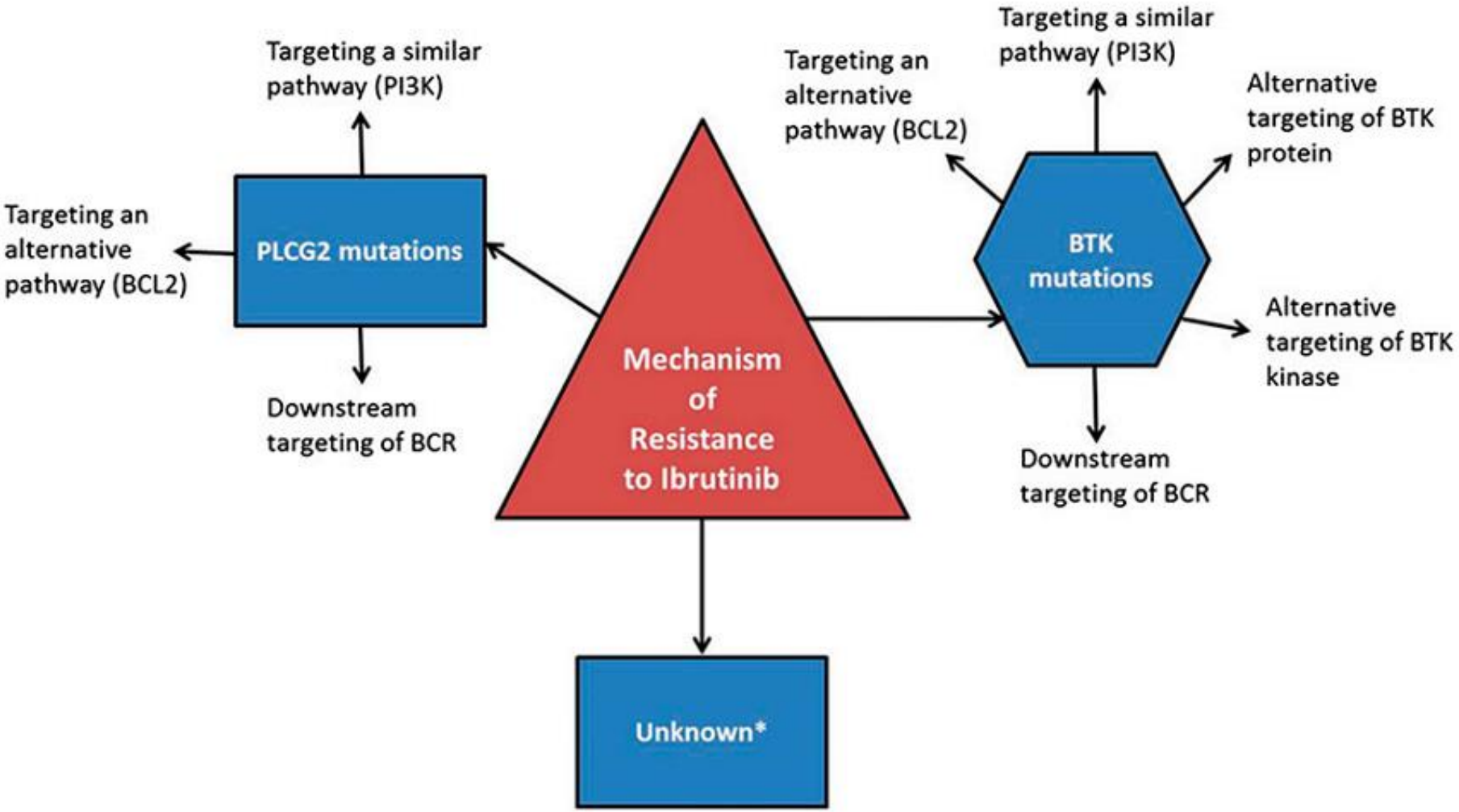
Stop ibrutinib?

N = 308	Richter's transformation (n=18)	CLL progression (n=13)
Progression with ibrutinib	Early	Late
Median survival	3.5 months	17.6 months
Mutations	BTK (2/8)	BTK o PLCγ2 (11/13)
Risk factors (multivariate)	BCL6 abnormalities and complex karyotype	



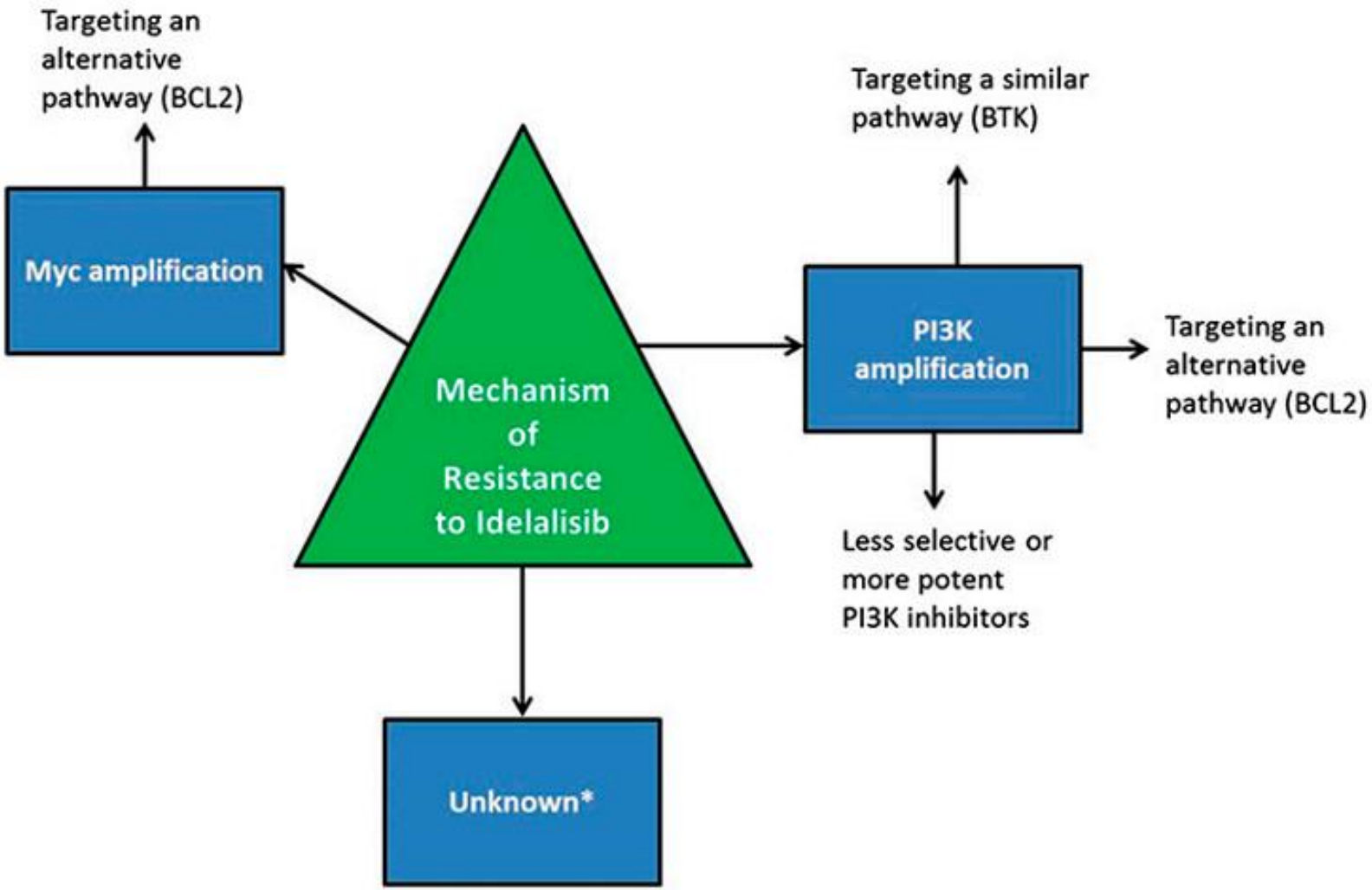
Maddocks KJ, *et al*. JAMA Oncol 2015

Ibrutinib: mechanism of resistence and treatment



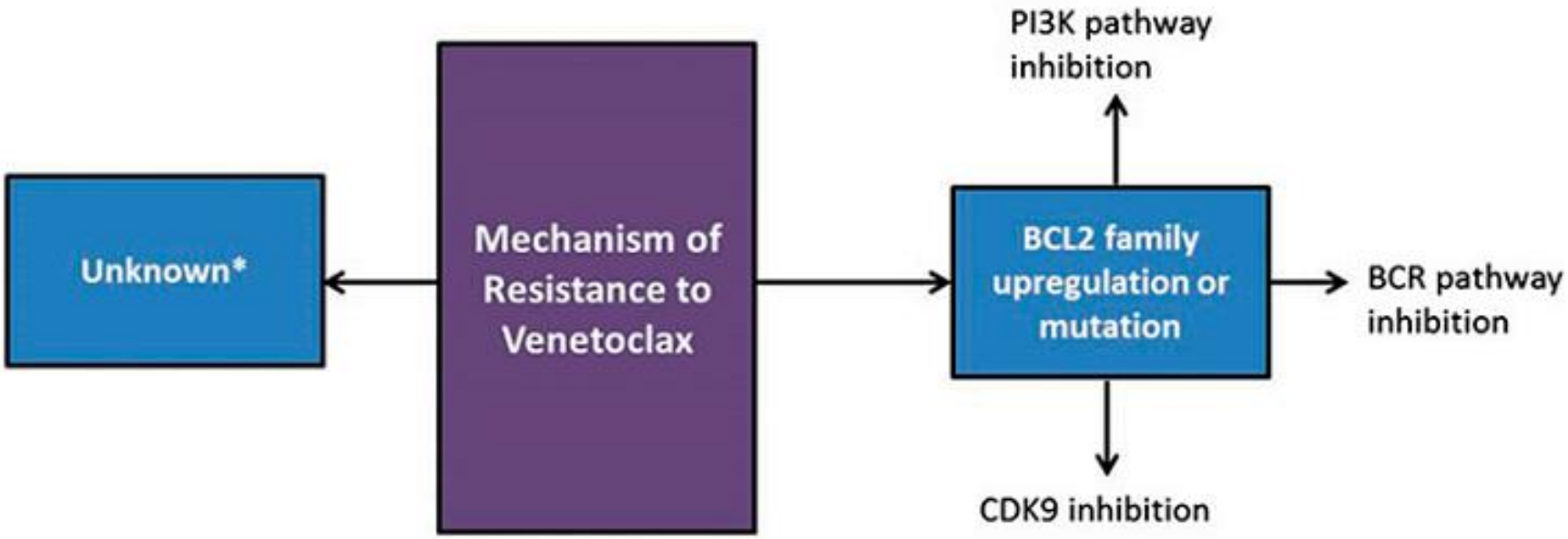
Woyach JA, *et al*. Blood 2015

Idelalisib: mechanism of resistence and treatment



Woyach JA, *et al*. Blood 2015

Venetoclax: mechanism of resistence and treatment



Woyach JA, *et al*. Blood 2015

Plasmablastic transformation in CLL

- Very rare
- N = 6, FL (50%), CLL (50%)
- Extranodal
- IHC:
  - CD20, PAX5, EBV, HHV-8 (-)
  - MUM1, CD138 (+)
- Del(13q) y del(11q)
- MYC rearrangement (2/3)
- BCL6 (3/3)

Case	#1 CLL	#2 CLL	#3 CLL
Age	70	52	57
Sex	Male	Male	Female
Time	0	85 mo	47 mo
Biopsy site	LN, mesenteric	Subcutaneous tissue	Mandibular
Bone marrow involvement	Yes†	Yes†	Yes†
Stage	IV-B	IV-A	IV-B
ECOG ≥ 2	Yes	Yes	No
High LDH	Yes	No	Yes
Bone lesion	No	Yes	No
M component	IgM-λ	λ	κ, λ
HIV	Negative	Negative	Negative
Prior treatment	No	Cysplatin Etoposide*	2-CdA‡
Treatment	R-CHOP × 2	R-CHOP × 6	VAD × 1 CHOP × 3
Follow-up	4 mo DwD	24 mo DwoD	6 mo DwD

	#1 CLL		#2 CLL		#3 CLL	
	CLL	PBL-T	CLL	PBL-T	CLL	PBL-T
CD20	+	–	+	–	+	–
CD79a	+	–	+	Weak	+	+
CD138	–	+	–	+	–	+
CD56	–	+	–	–	–	+
Blimp1	–	+	–	+	–	–
XBP-1s	–	+	–	+	–	+
IRF4	–	+	–	+	+/–	+
IRF8	+	–	+	–	+	–
PAX5	+	–	+	–	+	–
CD10	–	–	–	–	–	–
BCL6	–	–	–	–	–	–
BCL2	+	+	+	+	+	+
EBV	–	–	–	+	–	–
HHV8	–	–	–	–	–	–
ZAP70	+	–	+	–	–	–
Light chain	λ	λ	λ	λ	κ	λ

	#1 CLL		#2 CLL		#3 CLL	
	CLL	PBL-T	CLL	PBL-T	CLL	PBL-T
Cep12	Normal	Normal	Normal	Normal	Normal	Gains
13q	del 13q14.3	del 13q14.3	del 13q14.3	del 13q14.3	Gains	Gains
ATM	del 11q22	del 11q22	Normal	Normal	Gains	Gains
P53	Normal	Normal	Normal	Normal	Gains	Gains
MYC	Normal	Rearranged	Normal	Normal	Normal	Rearranged
BCL2	NE	Gains	Normal	Normal	Normal	Gains
BCL6	NE	Gains	Normal	Gains	Normal	Gains

Martínez D, *et al*. Am J Pathol 2013

RS treated with ibrutinib?

- Mayo Clinic experience
- N = 4 R/R CLL with biopsy-proven RS, refractory to R-CHOP
- Well tolerated, improvement of constitutional symptoms
- Median time on ibrutinib: 6.1 months

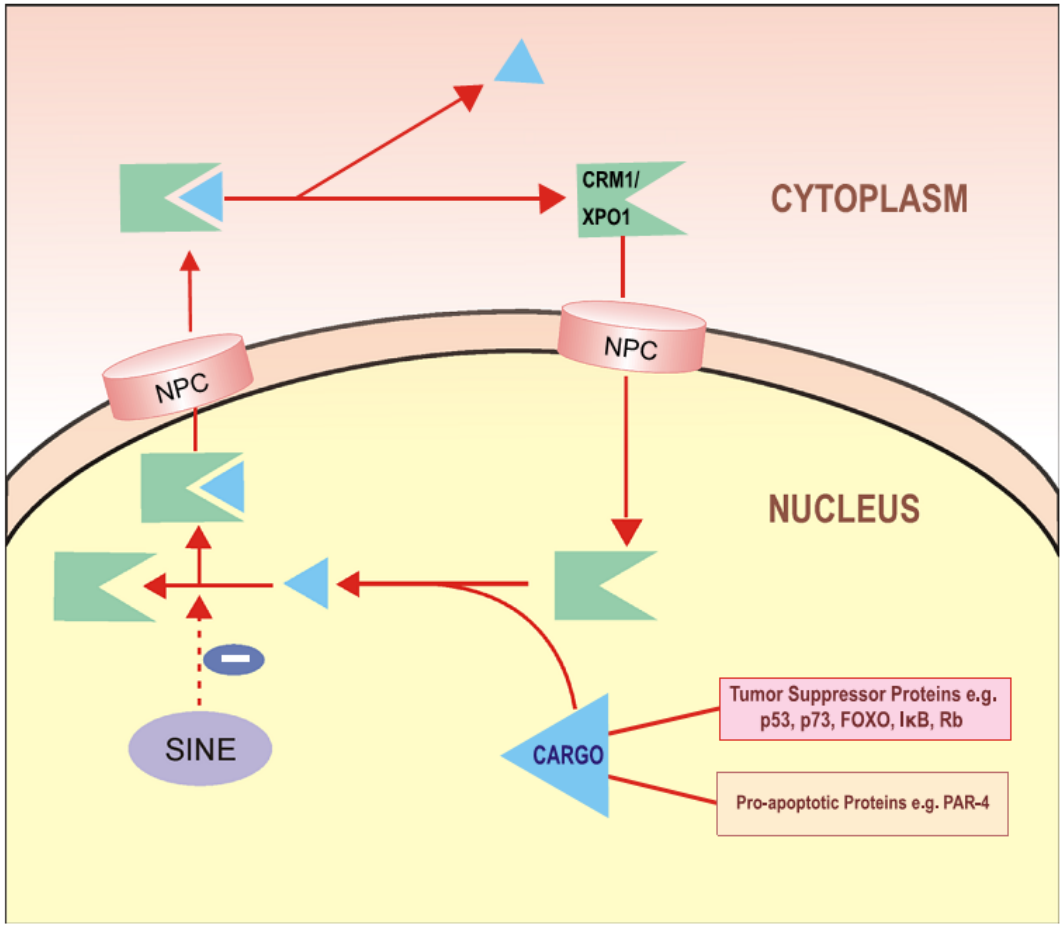
- Outcome:
  - n=1 CR (ongoing after 3 months of ibrutinib)
  - n=2 PR
    - n=1 progression of CLL (11 months)
    - n=1 progression of DLBCL (9 months)
  - n= 1 died (pulmonary mucormycosis after 4 months of ibrutinib)

- Caveats
  - Clonality available (n=1) clonally related RS
  - Concomitant high-dose steroids (n=2)

Tsang M, *et al*. Blood 2015

Selective inhibitors of nuclear exportin: selinexor

- Nucleo-cytoplasmic transport
- Transport of macromulecules “cargo” requires exportins (XPO1)
- Tumoral cells increment XPO1, transporting TSP into the cytoplasm
- Selinexor inhibits XPO1, retaining and activating multiple TSP
- Clinical trial phase II in RS
- Selinexor is effective in acquired resistance to ibrutinib (BTK C481S mutation)
- Selinexor + ibrutinib: synergistic cytotoxic effect in primary CLL



TSP: tumor suppressor proteins

Parikh K, *et al*. J Hematol Oncol 2014
Tsang M, *et al*. Blood 2015
Hing ZA, *et al*. Blood 2015
Das A, *et al*. Exp Hematol Oncol 2015

RIC allogeneic SCT in CLL

	Sorror et al*	Dreger et al†	Brown et al‡	Khouri et al§
No. of patients	82 (n = 64 with 5-y follow-up)	90	76	86
Median follow-up	5 y	72 mo	5.1 y	37.2 mo
Time period	1997-2006	2001-2007	1998-2009	1996-2007
Purine analog refractory disease, %	87	47	55	83
Cytogenetics	n = 7 (del17p), n = 7 (del11q), n = 9 (complex karyotype)	18% del17p, 36% del11q	17% del17p, 8% del11q	Not reported
Disease status SCT	55% refractory disease	21% refractory disease	43% SD/PD	17% refractory disease
Bulky disease SCT	24%	Not reported	21%	Not reported
Conditioning regimen	2-Gy TBI ± fludarabine (URD)	Fludarabine + cyclophosphamide ± ATG (URD)	Fludarabine + busulphan	Fludarabine + cyclophosphamide + rituximab
Donor status	37% URD	45% URD	63% URD	Not reported
Relapse rate	38% (5 y)	46% (6 y)	40% (5 y)	39% (3 y)
PFS	39% (5 y)	38% (6-y EFS)	43% (5 y)	36% (5 y)
OS	50% (5 y)	58% (6 y)	63% (5 y)	51% (5 y)
Chronic extensive GVHD	49% sib donor, 53% URD	53% (35/66)	65% (limited + extensive) at 2 y	56% (5 y)
NRM	23% (5 y)	23% (6 y)	16% (5 y)	17.4% (1 y)
Reported use of MRD monitoring/DLI	No	Yes	No	Yes
Impact of pre-SCT cytogenetics on SCT outcomes	No impact	No impact	No impact	Not assessed
Prognostic factors that influenced outcome	Model to predict 3-y inferior OS: LN size ≥5 cm, HCT CI score ≥1	Model to predict inferior EFS, OS, NRM: refractory disease at SCT, use of alemtuzumab prior to SCT	Model to predict inferior PFS: disease status at SCT, LDH, comorbidity, ALC	Model to predict inferior OS: hypogammaglobulinemia, CD4 <100/mm^3

Mato A, *et al*. Blood 2015

Anti-CD19 CAR therapy for CLL

Study	N	ORR	CR
University of Pennsylvania 2010*†	3	3/3	2/3
University of Pennsylvania 2014‡	24	10/24	5/24
National Cancer Institute§	4	3/4	1/4
National Cancer Institute‖	4	4/4	3/4
Memorial Sloan-Kettering¶	8	1	0

Mato A, *et al*. Blood 2015