Case SH2017-0359

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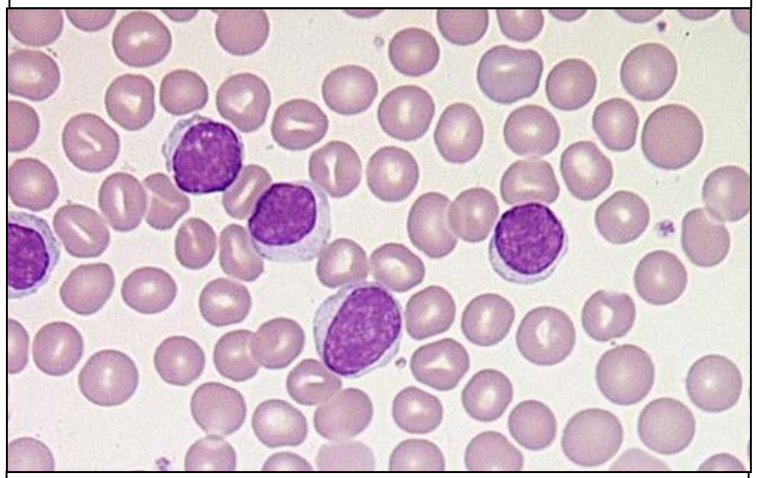
Initial Diagnosis and Treatment – 81 Male

2008

WBC 109 K/ul
HGB 12 g/dL
Plts 145 K/ul



95% monotypic B cell population:

KAPPA+
IgM+/IgD+, CD19+, CD20+ CD5+, CD23+, FMC7-

2009 - FISH

- *TP53* deletion negative
- Disomy for chromosome 12
- *ATM* (11q22.3) del. negative
- Chromosome 13 del/ loss neg
- IGH translocation negative

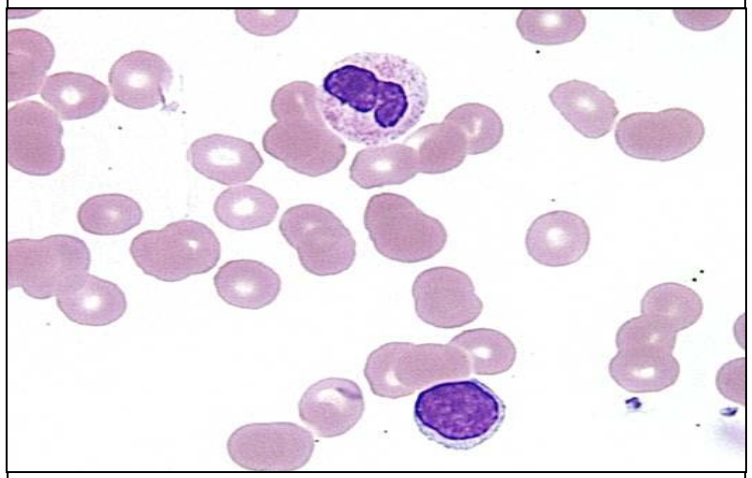
2010-2011

<u>FCR (2010)</u>
Fludarabine
Cyclophosphamide
Rituximab

<u>BR (2011)</u>
Bendamustine
Rituximab

2012

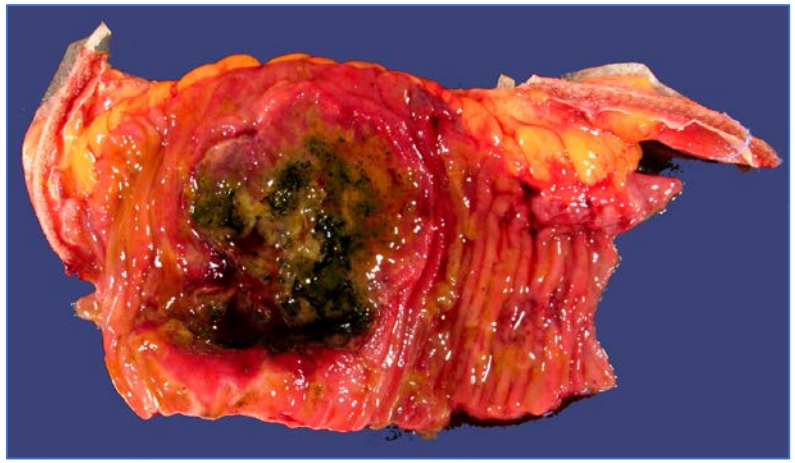
WBC 3.6 K/ul
HGB 9.6 g/dL
Plts 115 K/ul

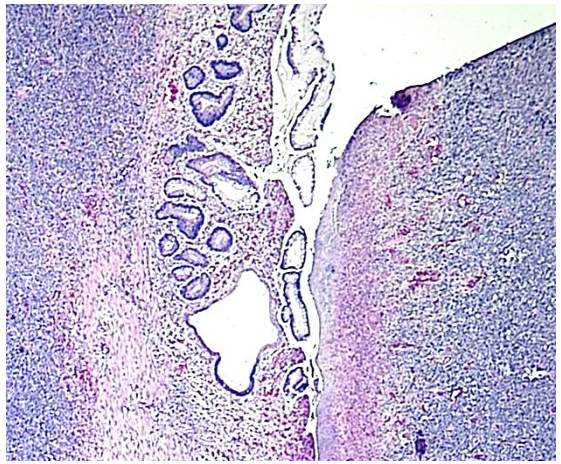


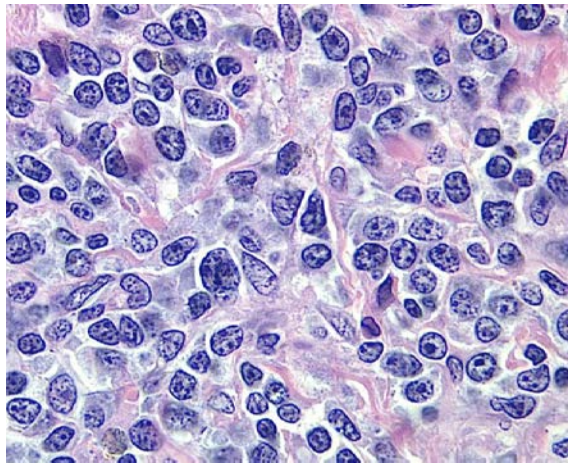
57% monotypic B cell population:

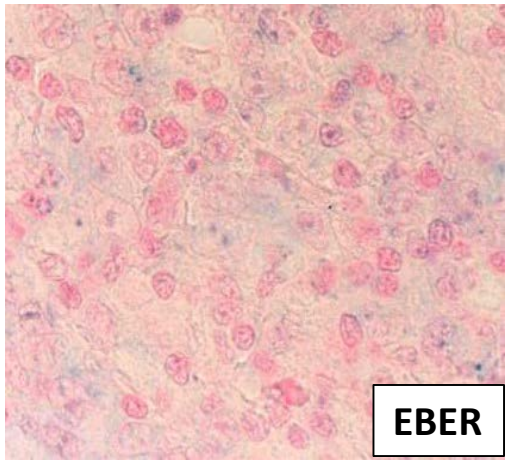
KAPPA+
IgM+/IgD+, CD19+, CD20+ CD5+, CD23+, FMC7-

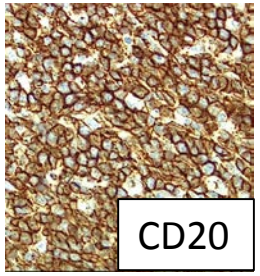
2012 – 1st Richter Transformation

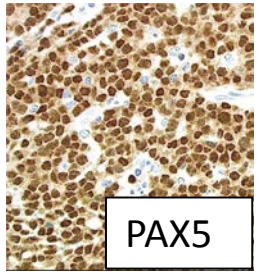


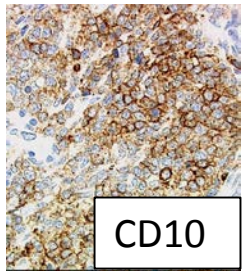


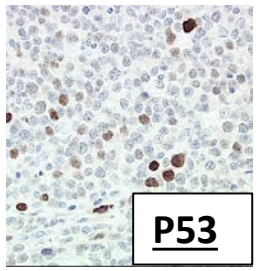


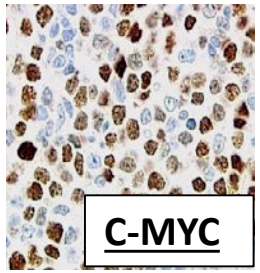


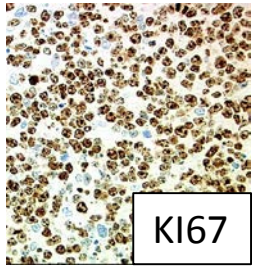


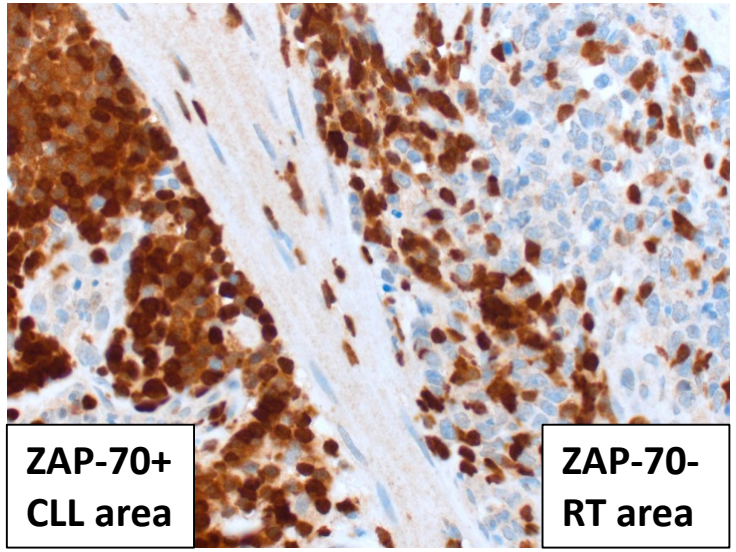












LAMBDA+
C-MYC+

IgM+/IgD+,
CD19+, CD20+,
CD10+, CD5-,
CD38+, BCL2+,
BCL6+

Cytogenetics:
Complex karyotype
with **t(8;22)**

FISH:
Positive for
***MYC* rearrangement**

Treatment with EPOCH-R

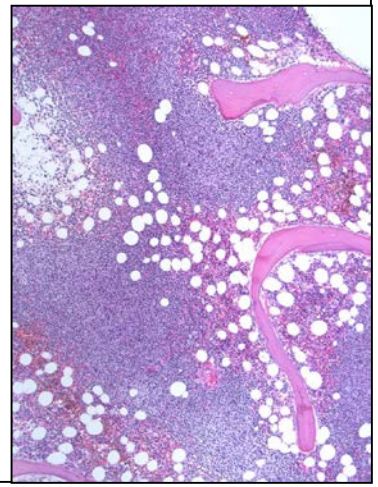
CLL Progression and Ibrutinib

2013 - CLL Progression

BM bx: Extensive CLL involvement
KAPPA+
CD38+
ZAP-70+

FISH
- ***IGH* translocation positive**
- **Trisomy 12 positive**
- ***TP53* deletion positive**
- *ATM* deletion negative
- Chr13 deletion and loss negative

NGS and SNP analysis
- **TP53 mutation**
- **Trisomy 12**
- 17p deletion
- 18p deletion



2013

Ofatumomab

2014-2015

Ibrutinib

↓

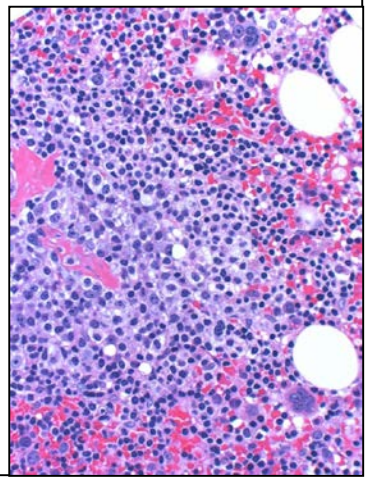
Disease Improvement

2015 – Post-Ibrutinib Therapy

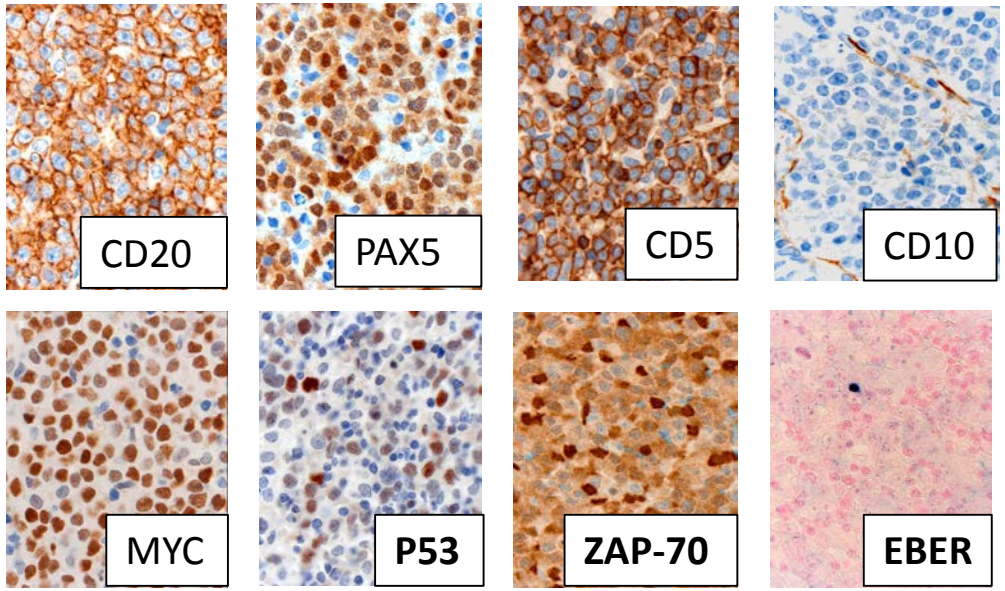
BM bx: Morphologic progression of CLL
KAPPA+
CD38+
ZAP-70+

Cytogenetics
- Abnormal mosaic male karyotype

NGS
- *KRAS* mutation
- *BCOR* deletion
- *BCORL1* deletion
- ***BTK* mutation**



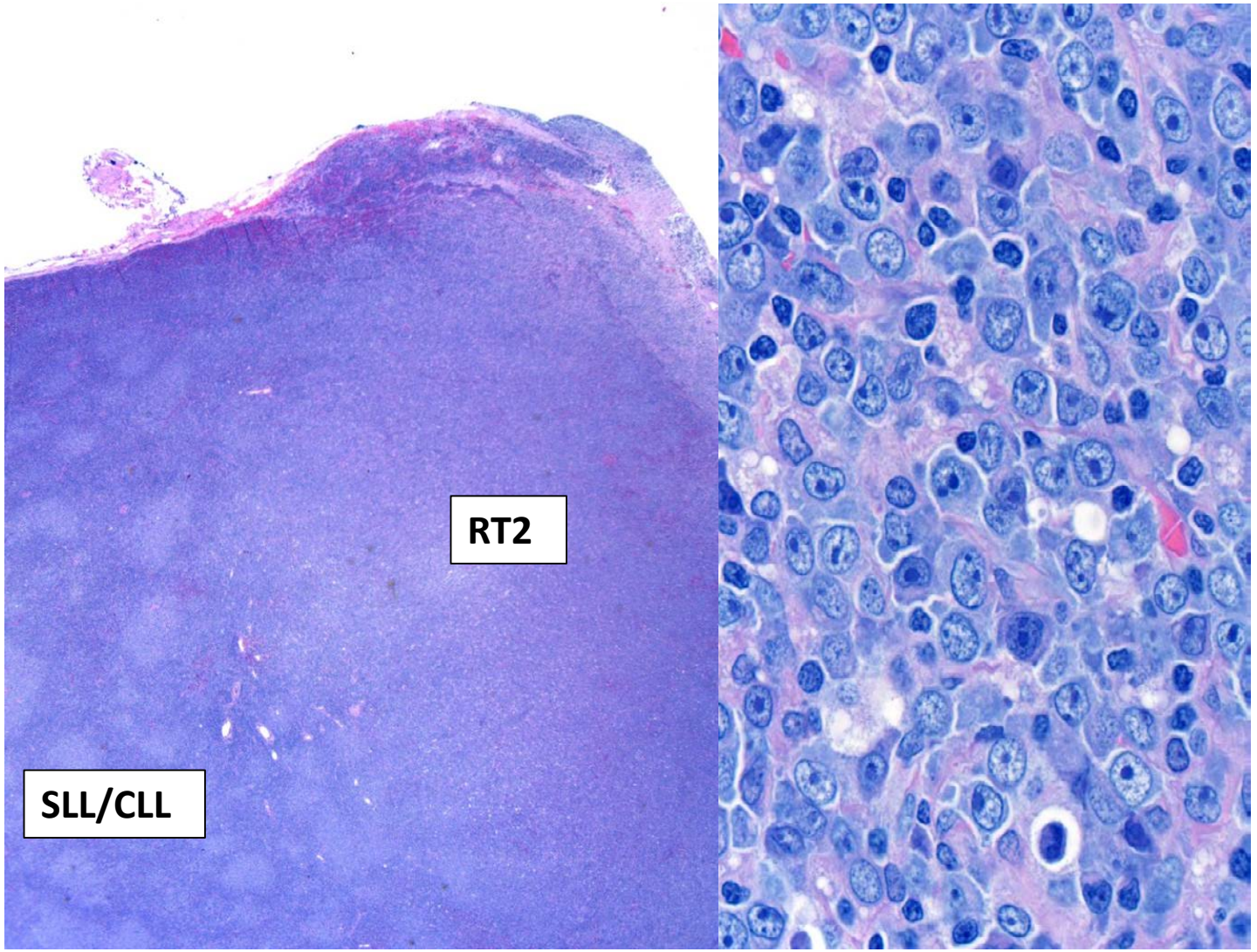
2015 – 2nd Richter Transformation



KAPPA+ C-MYC+
CD10-, BCL2+, BCL6+, MUM1+, BCL2+,, ZAP-70+,
~100% KI67, P53+, EBER-

Cytogenetics:
Complex Karyotype with **t(8;14)**

FISH:
Positive for ***MYC* rearrangement**



Entospletinib (GS-9973 – SYK inhibtor) - Early 2016

Our Proposed Diagnosis:

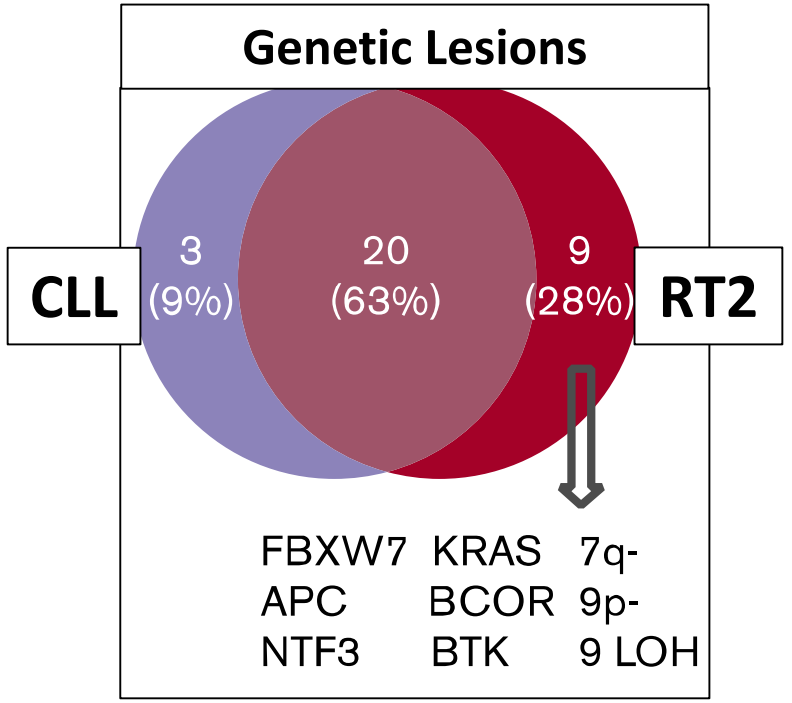
Chronic Lymphocytic Leukemia and Two Richter Transformations with MYC Rearrangement

Panel Requested Points

- Clonal relationship between CLL and two Richter transformations in our patient based on *IGH* gene rearrangement studies
- Clonal evolution of CLL and mechanism of Richter transformation
- Mechanism of disease recurrence or transformation associated with small molecules inhibitors used to treat this patient (Ibrutinib, GS-9973 and ofatumomab)
- Clinical significance of clonally related vs unrelated Richter transformation to preceding CLL

Clonal Relationships Between CLL and Two RTs in Our Patient

IG Heavy and Light Chain Gene Rearrangement Analysis (Biomed-2)					
	IGH A mix	**IGH B mix**	**IGH C mix**	**IGK A mix**	**IGK B mix**
RT1 2012	316 bp	~248 bp	**114 bp**	**139 bp** **286 bp** 190 bp	250bp 280bp
RT2 2015	**300 bp** **+** **318 bp**	**~250 bp**	**114 bp**	**139 bp** **286 bp**	400 bp
CLL 2015	**300 bp** **+** **318 bp**	**~250 bp**	**114 bp**	---	---

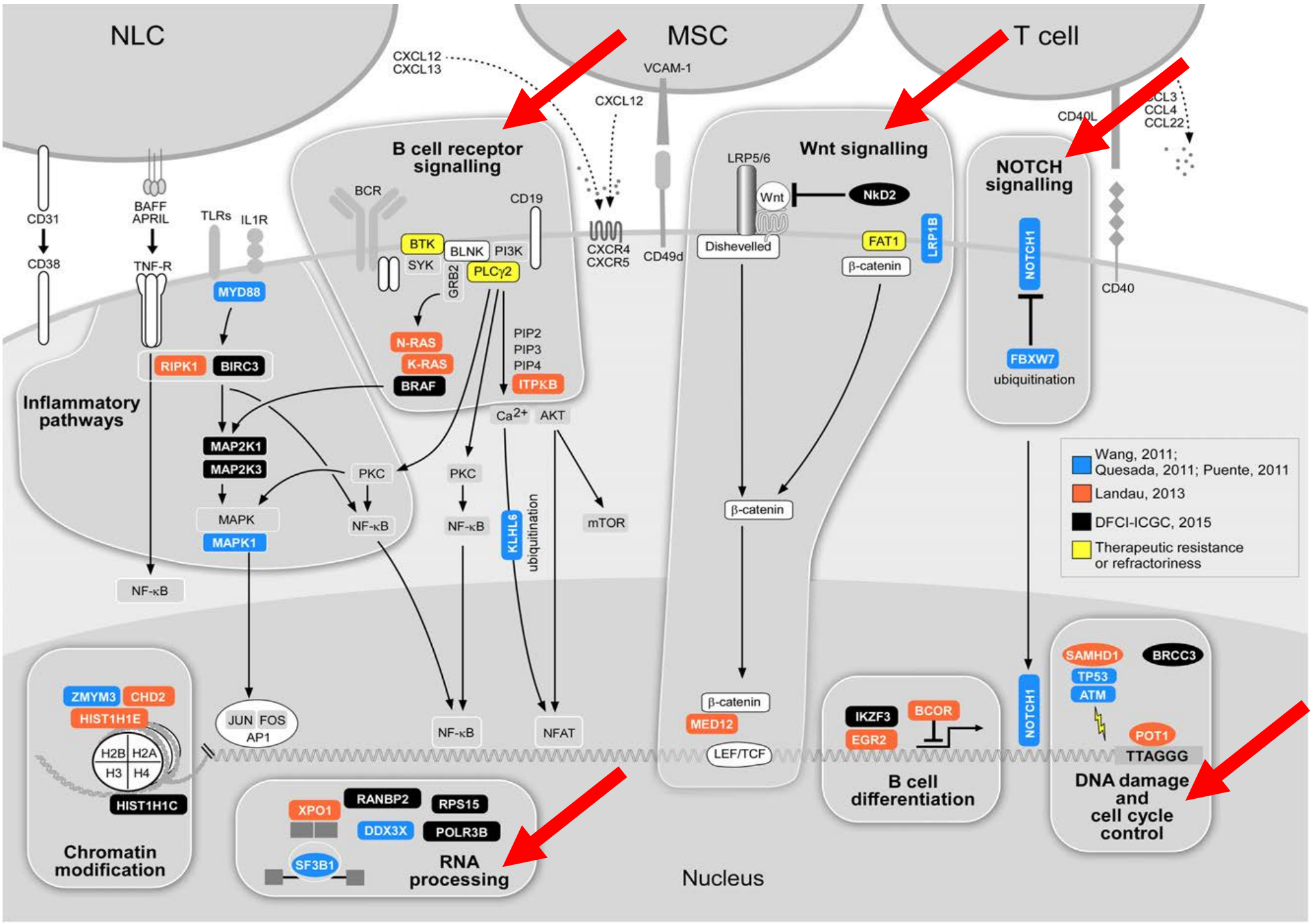


NGS & SNP:

***Same BTK^{C481S}* mutation present in both CLL & RT2**

Richter transformation 2 (RT2) is clonally related to CLL

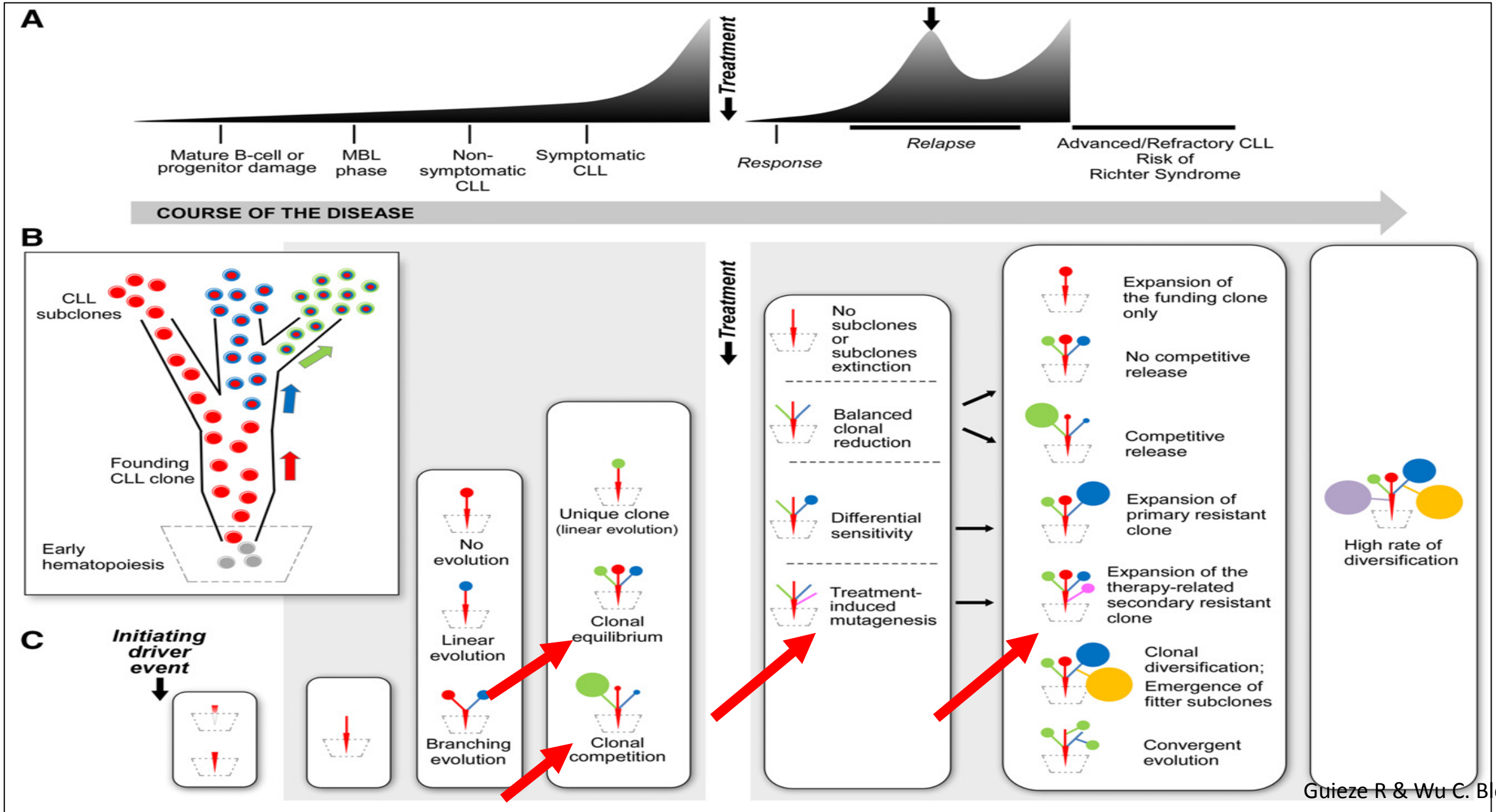
Richter transformation 1 (RT1) is partially related to CLL and RT2



Core Cellular Pathways Affected by Significantly Mutated Genes in CLL

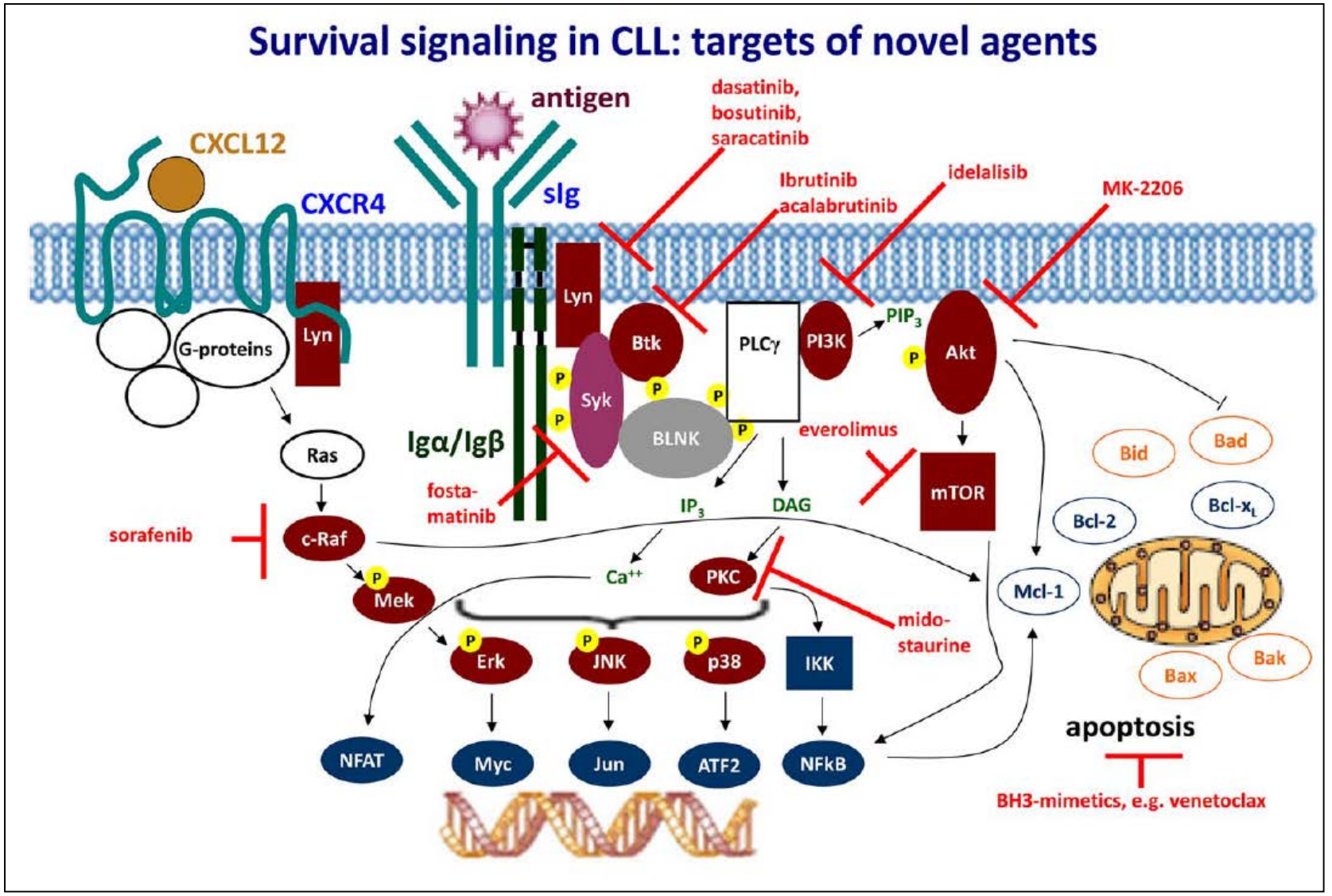
Guieze R & Wu C. Blood 2015

Clonal Evolution of CLL and Mechanism of Richter Transformation



Guieze R & Wu C. Blood 2015

Small Molecule Inhibitor - Ibrutinib

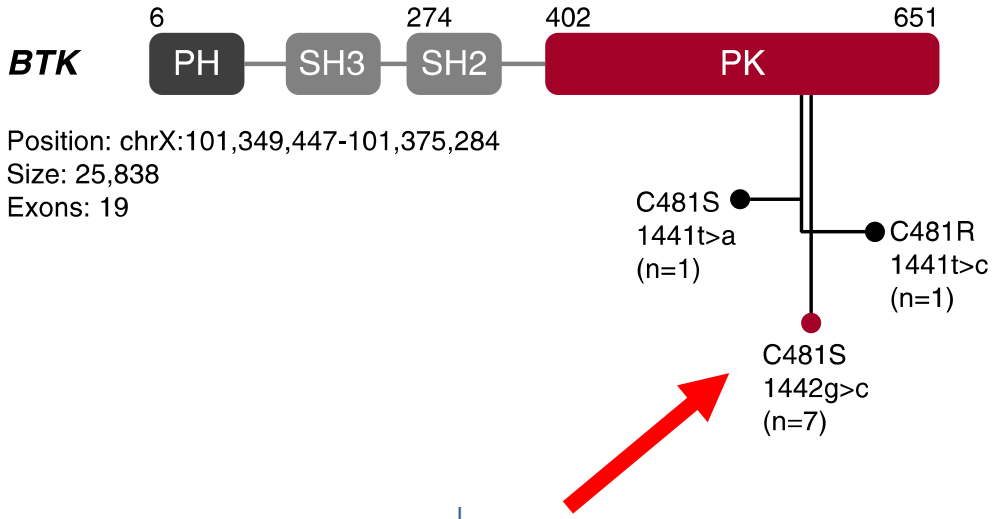


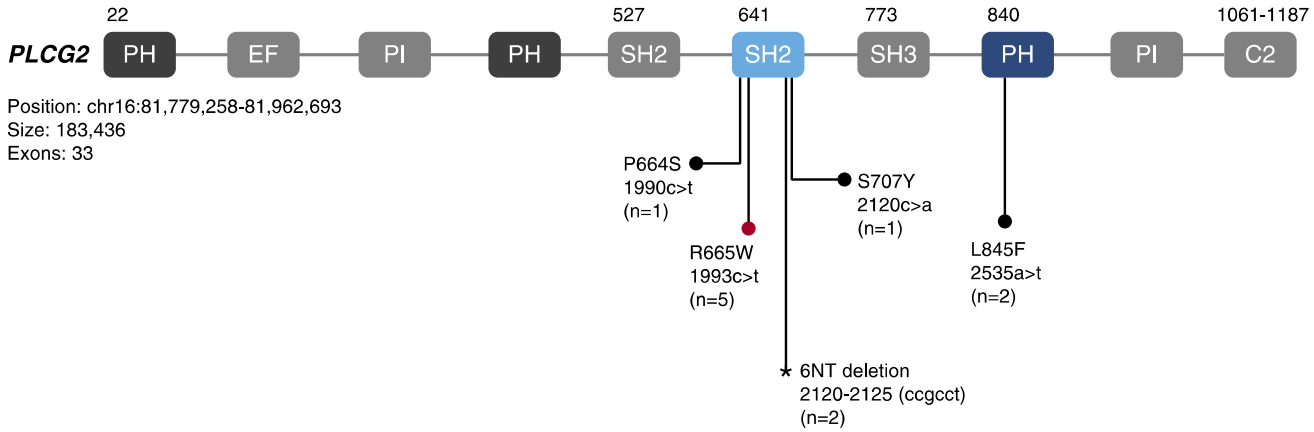
- Bruton's tyrosine kinase (*BTK*)
  - Downstream activation of survival pathways: NF-kB and MAP kinases
- Ibrutinib is orally active, small molecule *BTK* inhibitor that induces apoptosis in CLL cells
- Two different patterns of progression:
  - Primary refractory disease or early progression → histologic transformation

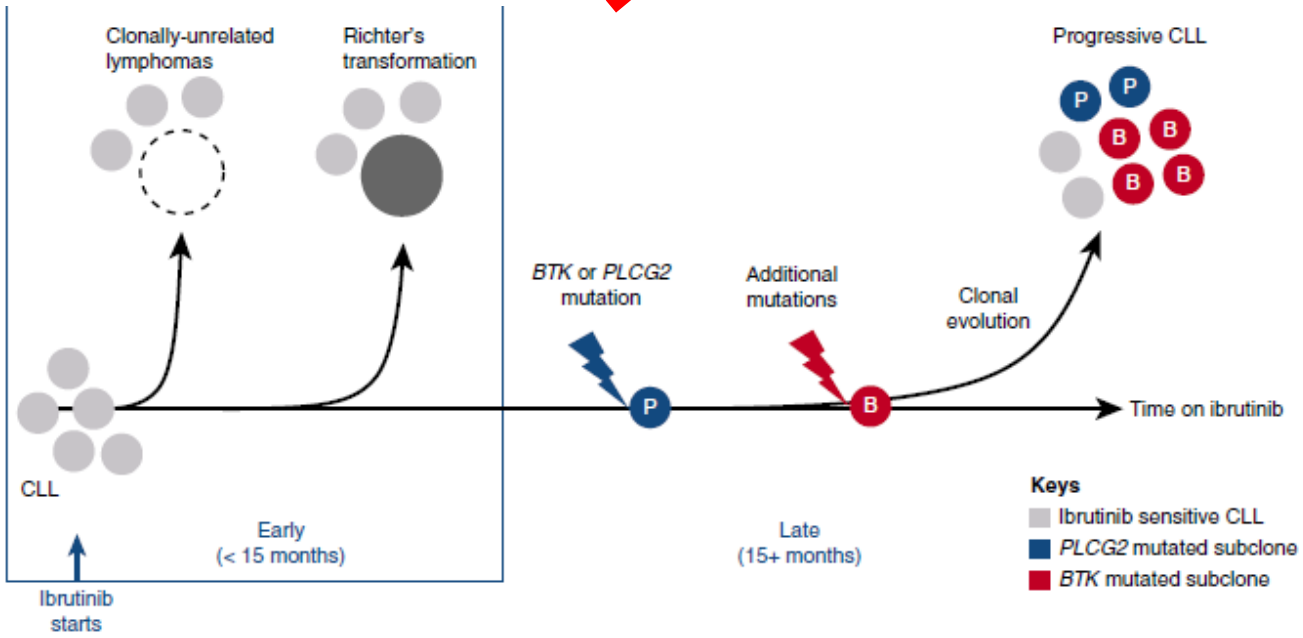
  OR
  - Delayed CLL progression

Hallek M. Am J Hematol 2017

Mechanisms of Ibrutinib Resistance and Transformation Events







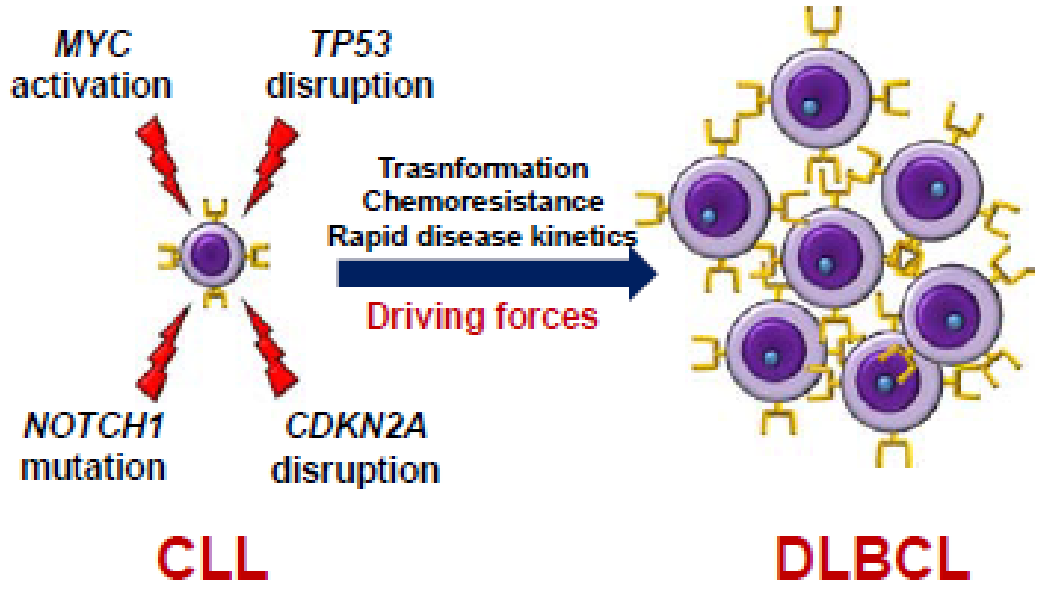
- Resistance to Ibrutinib
  - C481S mutation: Decreased Ibrutinib binding
  - R665W and L845F mutations in *PLCgamma2:* gain–of-function mutations leading to autonomous BCR activity
- Most cases of Ibrutinib-resistant CLL are often composed of multiple independent subclones

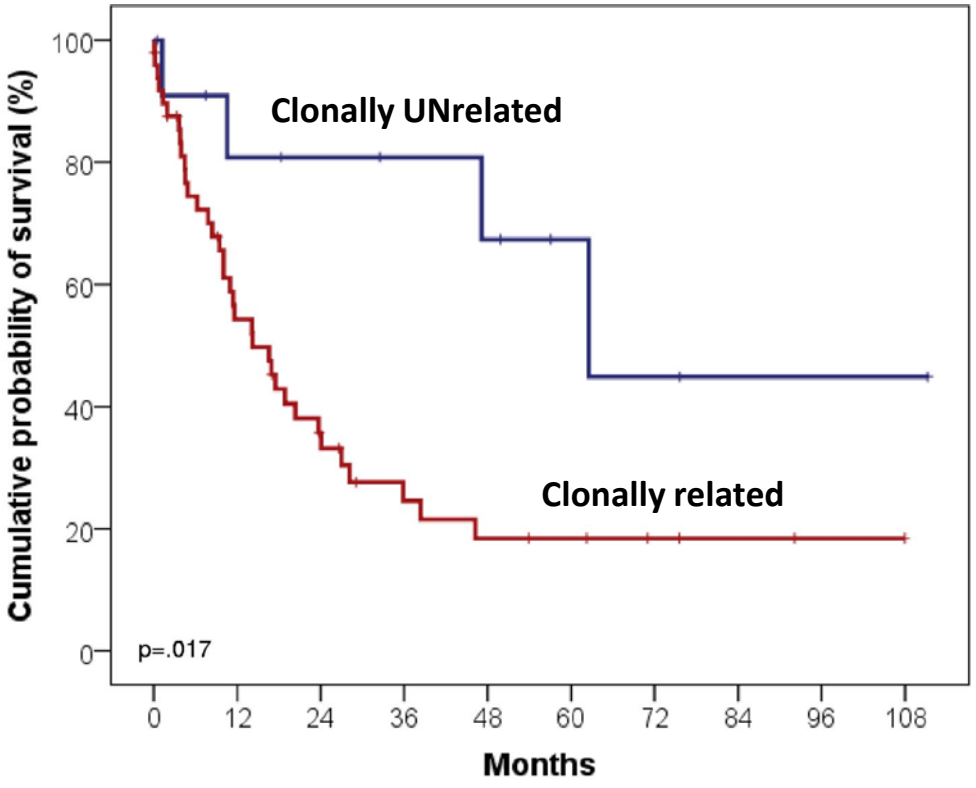
- Resistance mutations identified up to 15 months before progression
- Median survival following RT was 3.5 months and 17.6 months following CLL progression

Ahn IE et al. Blood 2017

Clinical Significance of Clonally Related vs Unrelated RT

- Clonal relationship between CLL and DLBCL suggests 2 types of Richter Transformations:
  - Richter transformation/DLBCL **clonally related to CLL(~80% cases)**
  - Richter transformation/DLBCL **clonally UNrelated to CLL(~20% cases)**
- **Clonally UNrelated RT** - clinically and biologically distinct - outcome similar to de novo DLBCL





- *TP53* disruption is one of the major factors affecting RT survival
- *TP53* disruption and *c-MYC* abnormalities are the most frequent genetic lesions in RT
- Analysis of sequential samples documented that *TP53* disruption and *c-MYC* abnormalities are frequently acquired at transformation

Rossi D . Blood 2011; Seminars Oncology 2016

Final Panel Diagnosis:

Chronic Lymphocytic Leukemia with Two Transformations to Diffuse Large B-cell Lymphoma

(Richter's transformation, with *MYC* rearrangements)

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Thank You

Questions?