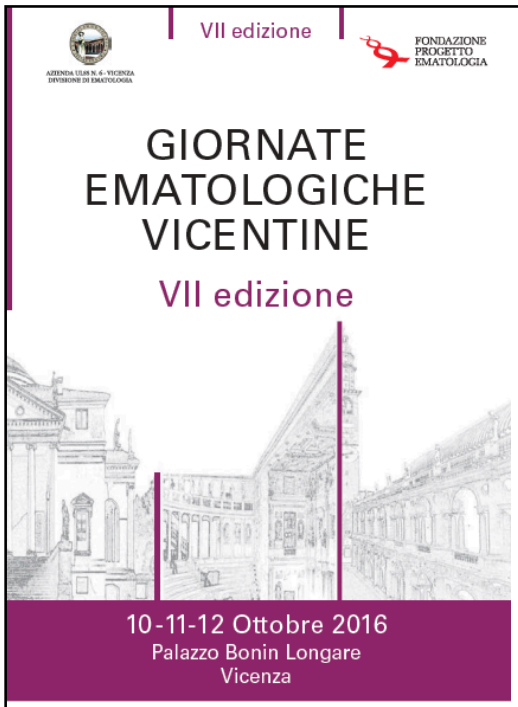

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E' POSSIBILE UN APPROCCIO MIRATO NELLA SCELTA DELLE NUOVE MOLECOLE IN AMBITO EMATOLOGICO?

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Disclosures

Roche (Advisory Board)

Janssen (Advisory Board)

Gilead (Advisory Board)

Amgen (Advisory board; research support)

Novartis (Advisory Board)

Celgene (research support)

GSK (Advisory Board)

Karyopharm (Advisory Board)

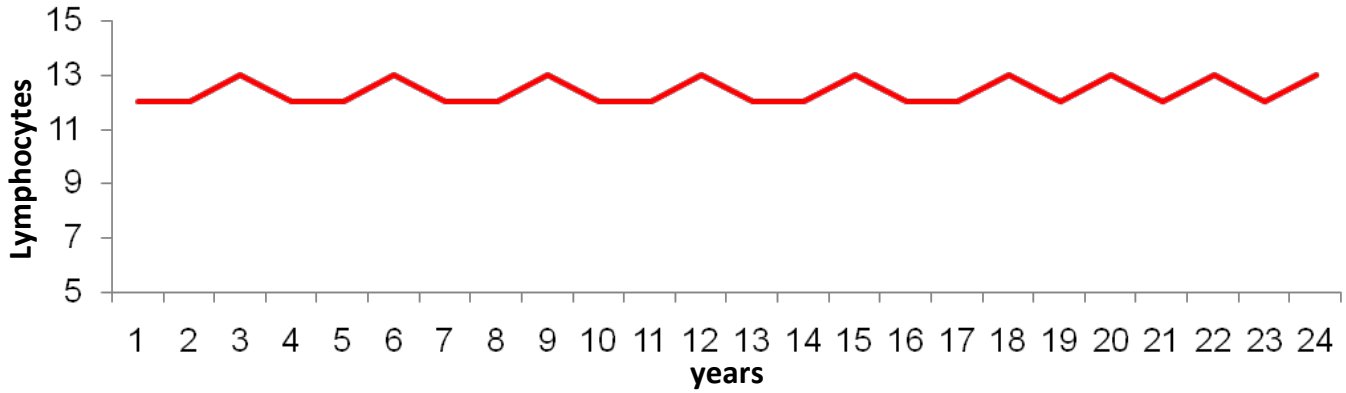
Morphosys (Advisory Board)

Outline

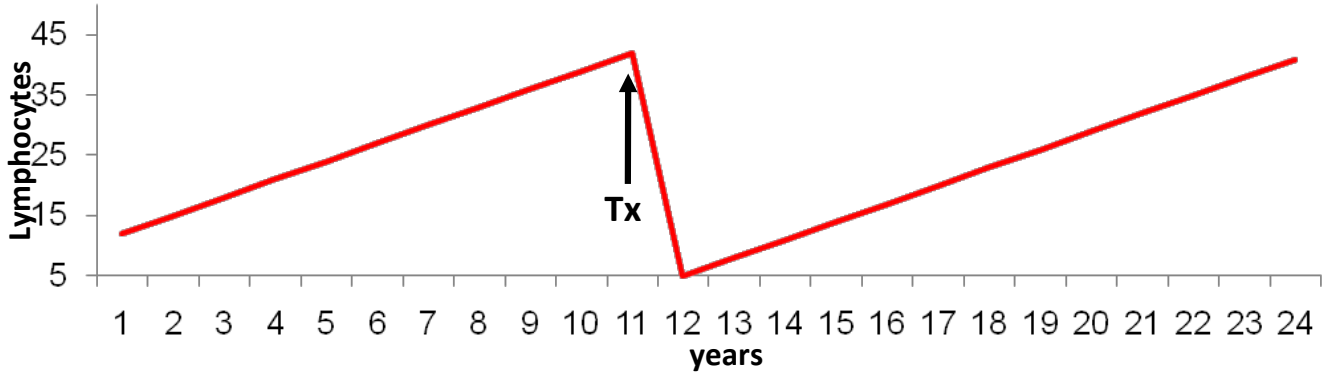
- CLL as a ***clinical practice*** model for precision medicine
    - Predictors ***for choosing*** a novel molecule
    - Predictors ***for not choosing*** a novel molecule
- DLBCL as a ***potential*** model for precision medicine

CLL: Homogeneous phenotype but heterogeneous clinical course

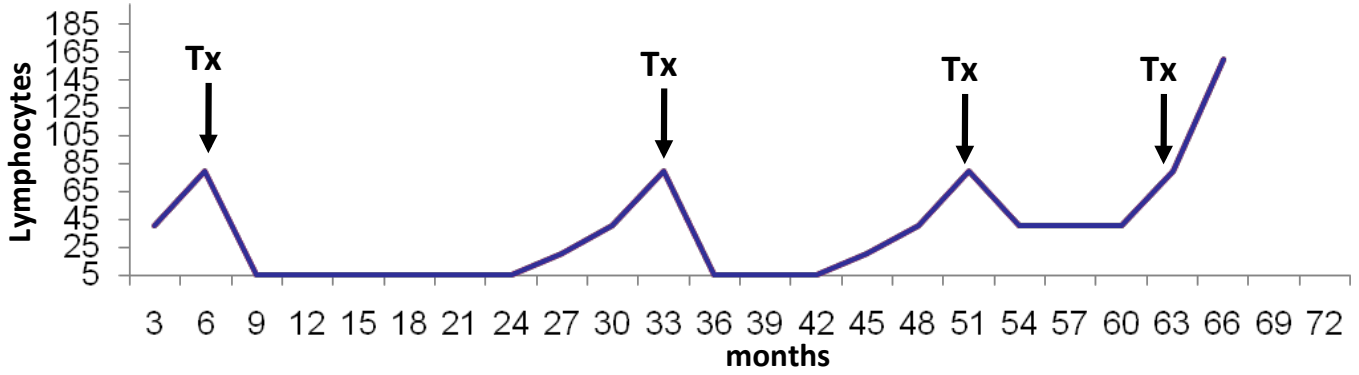
Highly stable



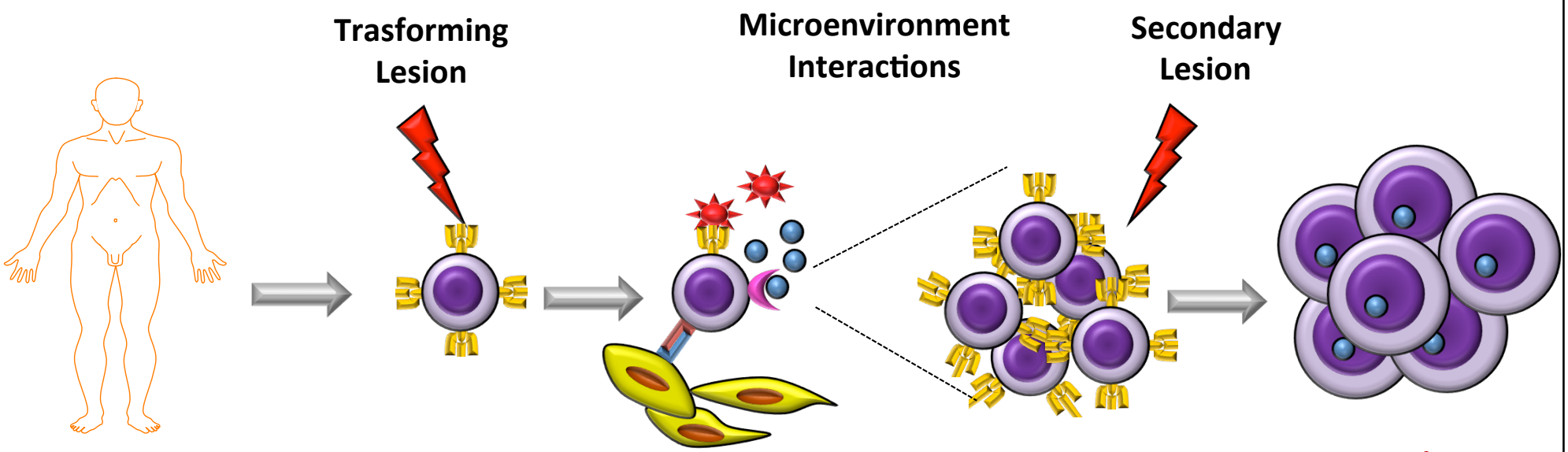
Slowly progressive



Rapidly progressive



Pathogenesis of CLL



Predisposition

Polygenic
IRF4
IRF8
MYC
Other

Initiation

del13q
+12

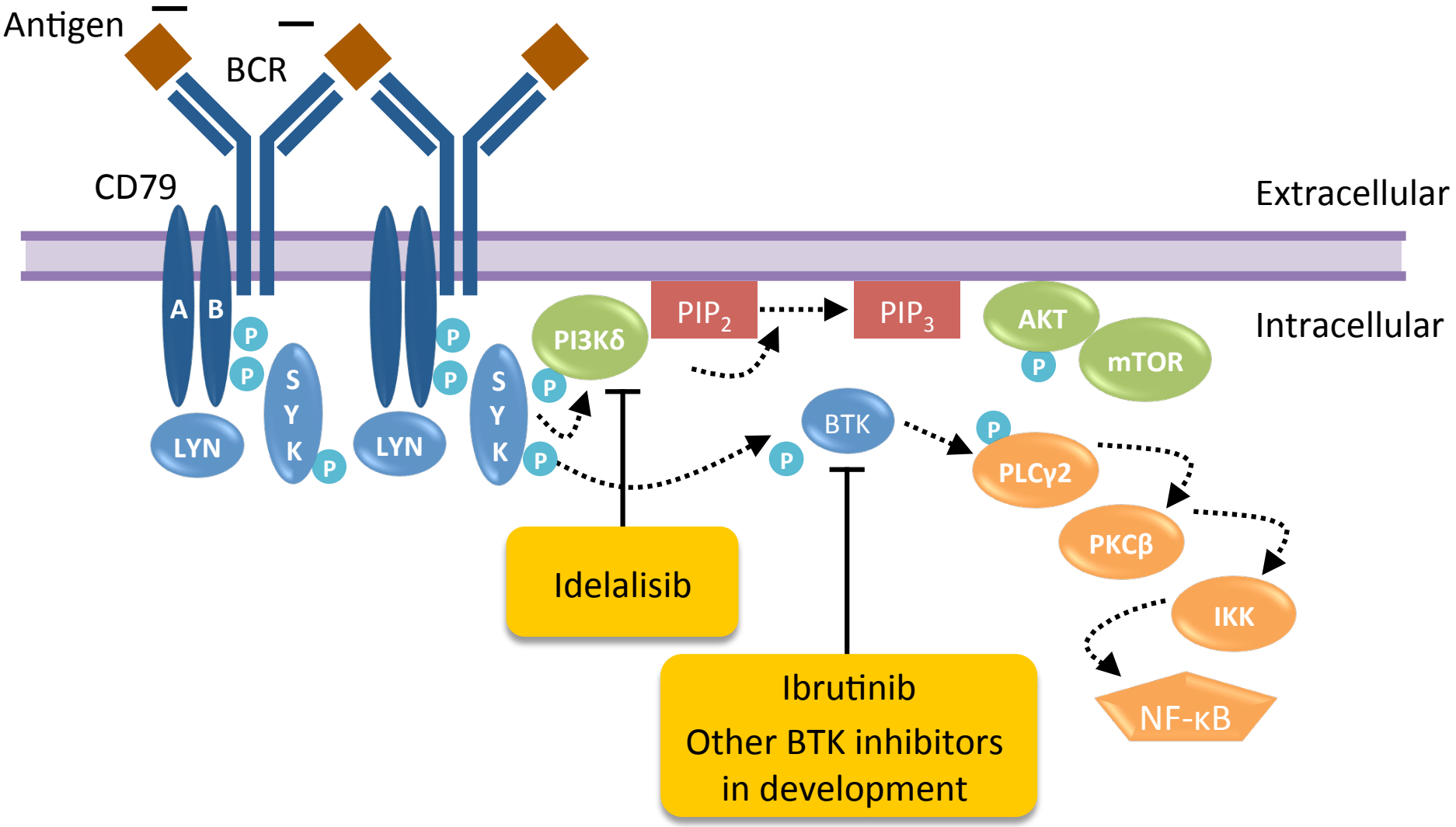
Promotion/Accumulation

Signaling pathways
BCR
NF-kB
TLR
CD38
VLA-4 integrins
NOTCH
CXCR4

Progression
Chemorefractoriness
Transformation

TP53
NOTCH1
SF3B1
BIRC3
ATM
MYC
CDKN2A

Therapeutic targeting of BCR signalling



BCR: B-cell receptor; CML: chronic myeloid leukaemia

Wiestner A. *J Clin Oncol* 2013;31:128–130.

CLL mutations

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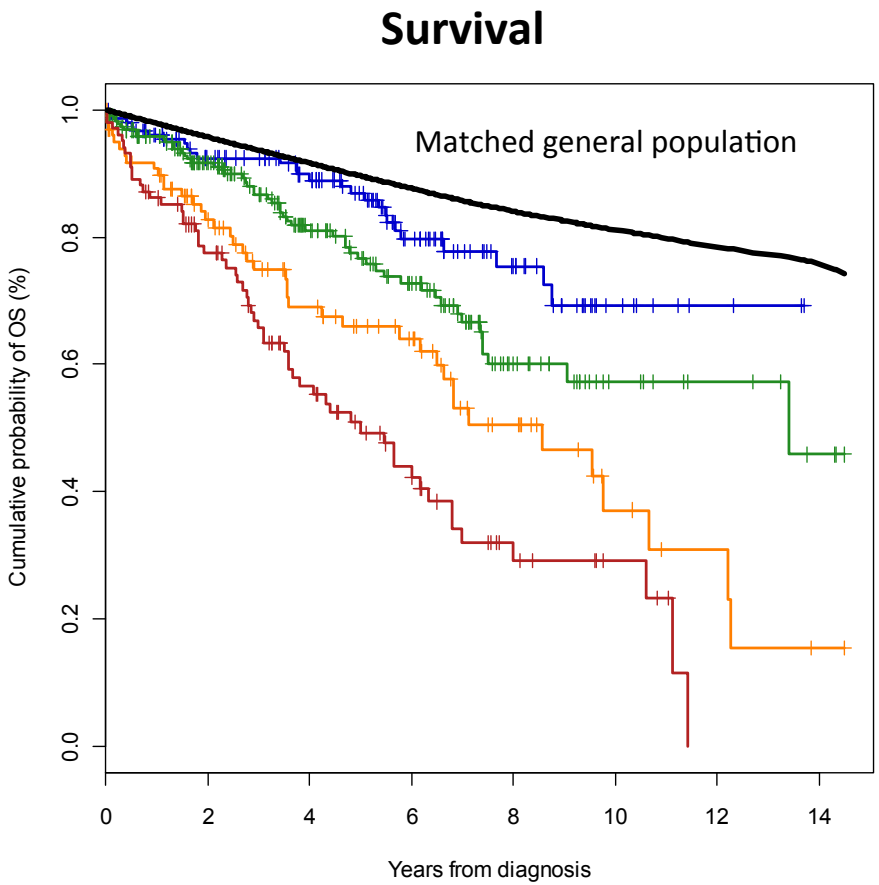
Font size according to gene mutation prevalence

- **One of the tumors with the lowest background mutation load (0.6 per Mb)**
- **No unifying gene mutations**

Fabbri, J Exp Med 2011; Puente, Nature 2011; Rossi, Blood 2011; Quesada, Nat Genet 2011; Wang, N Engl J Med 2011; Rossi, Blood 2012

Integrating mutation and cytogenetics for CLL survival prognostication

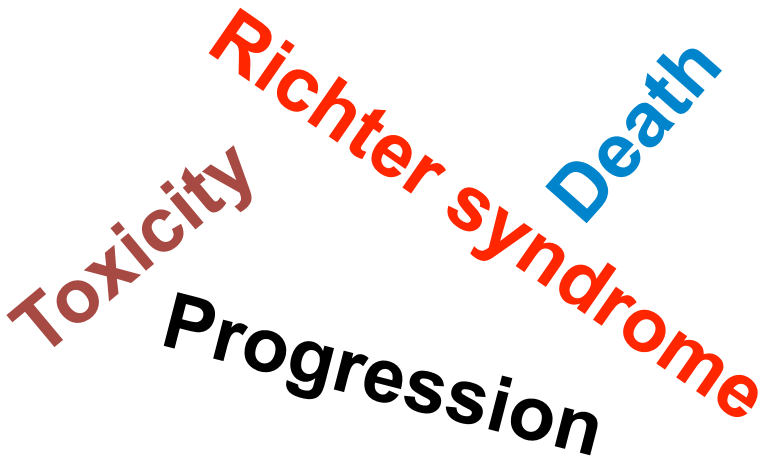


	N	10-year OS	10-year relative OS
del13q	26%	69%	84%
Normal/+12	40%	57%	70%
NOTCH1 M/*SF3B1* M/del11q	17%	37%	48%
TP53 DIS/*BIRC3* DIS	17%	29%	37%

Rossi et al, Blood 2013

Clinical applications of predictive and prognostic biomarkers in CLL

Prognostic biomarkers



Provide information on the likely outcome of CLL independent of treatment

Patient counseling

Frequency of follow-up

Identify those apropriate for early intervention trials

Predictive biomarkers

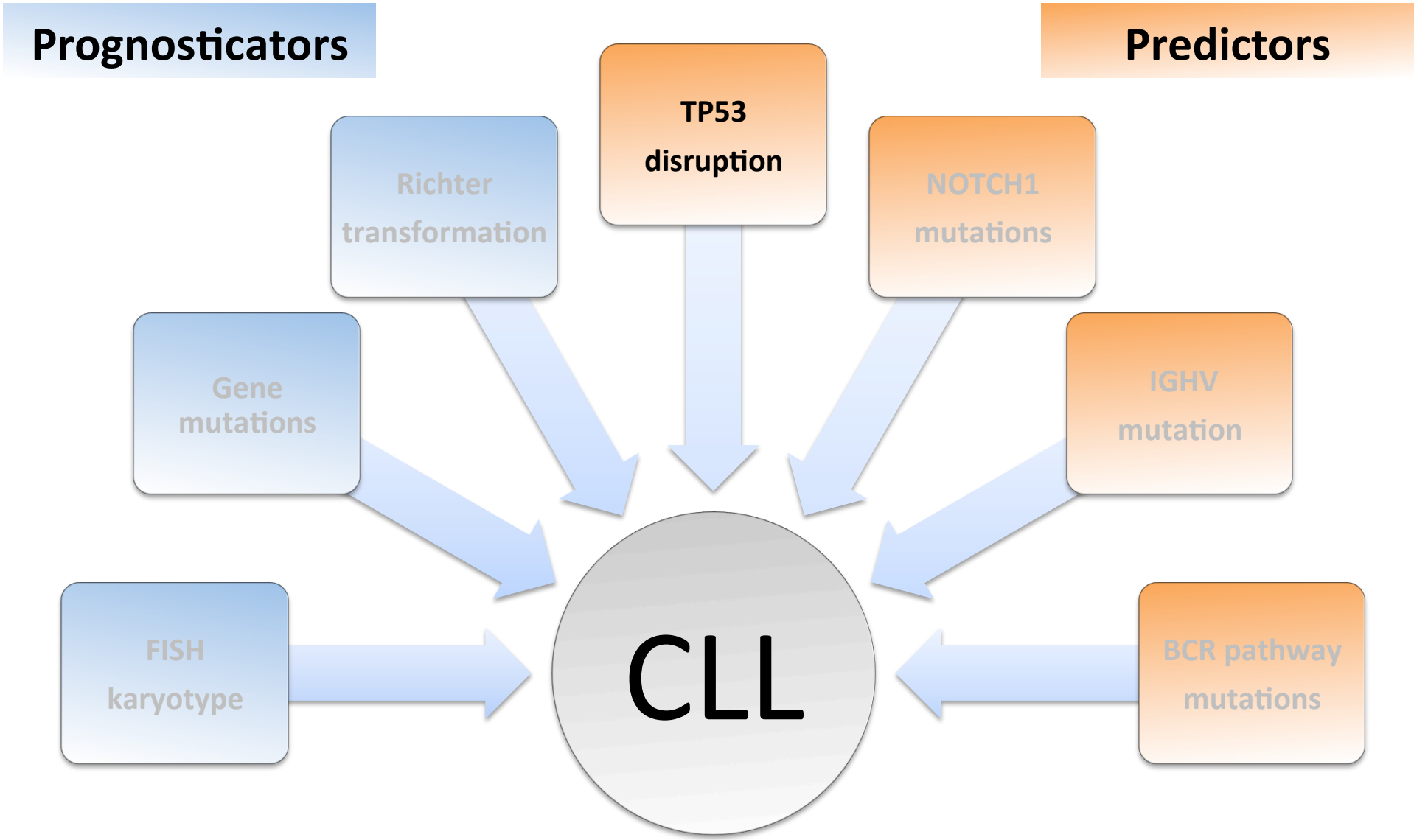
Provide information on the likely benefit from a specific CLL treatment

Treatment tailoring

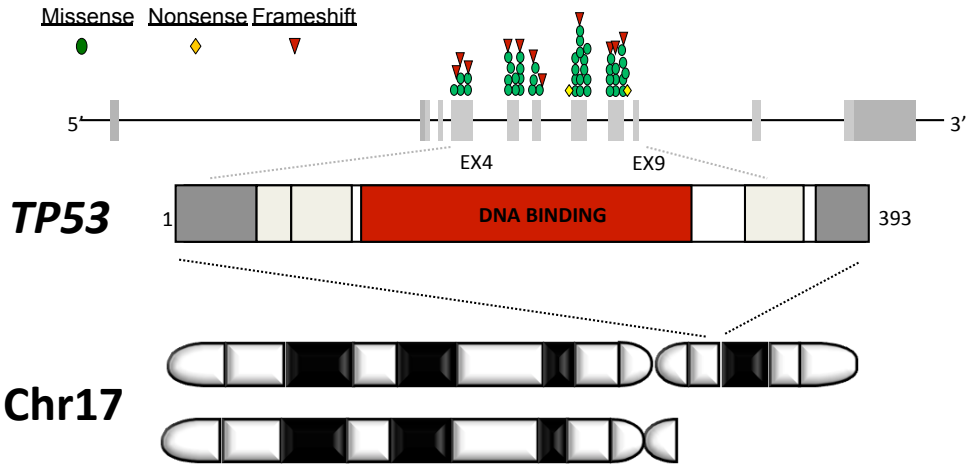
Outline

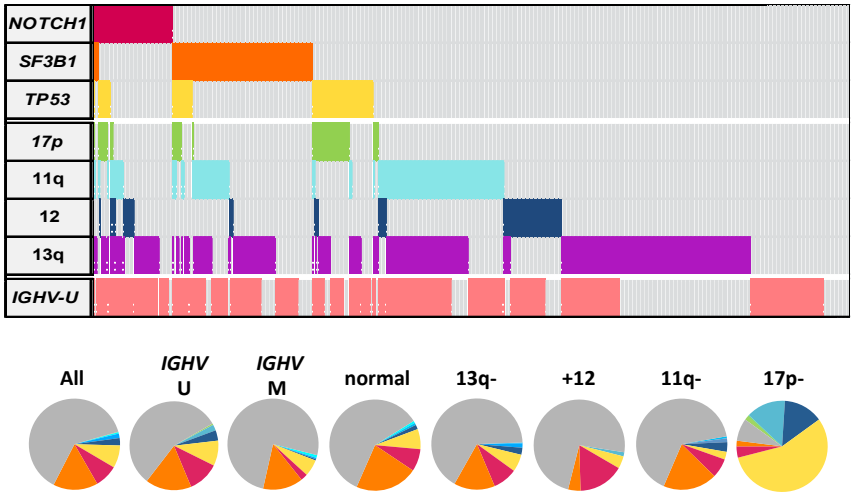
- CLL as a ***clinical practice*** model for precision medicine
  - Predictors ***for choosing*** a novel molecule
  - Predictors ***for not choosing*** a novel molecule
- DLBCL as a ***potential*** model for precision medicine

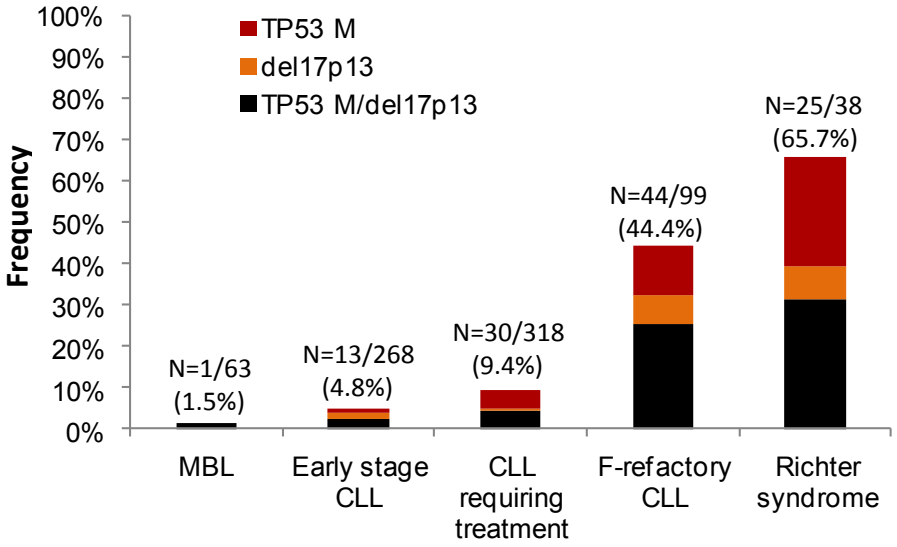
Prognosticators and predictors in CLL

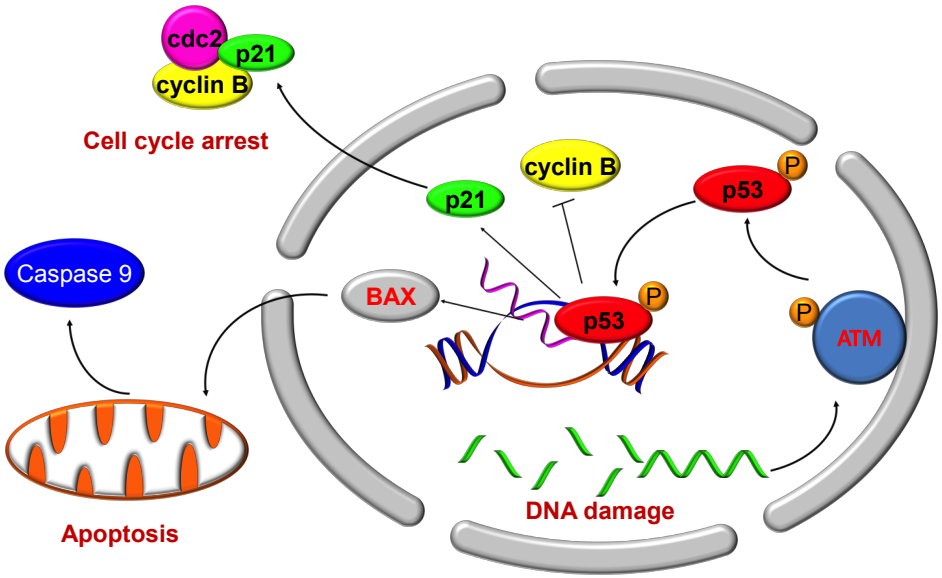


TP53 abnormalities in CLL



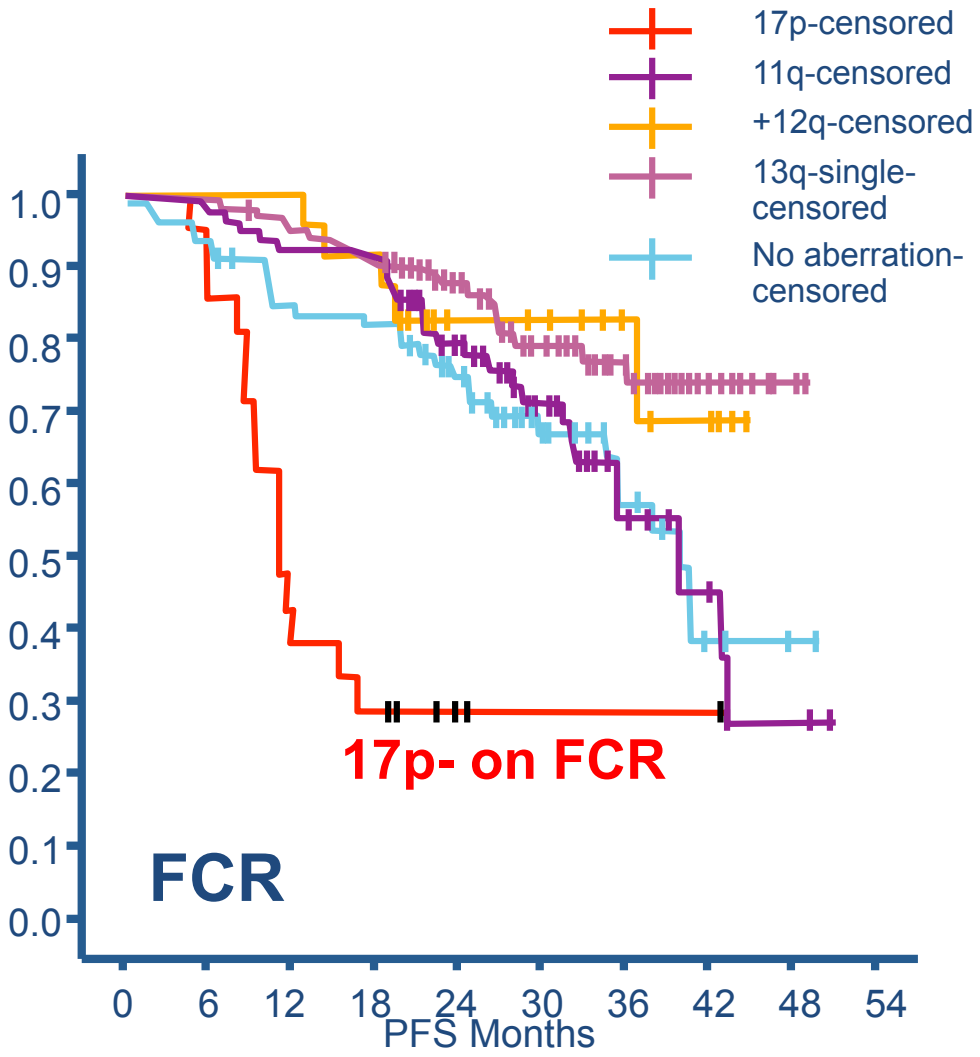




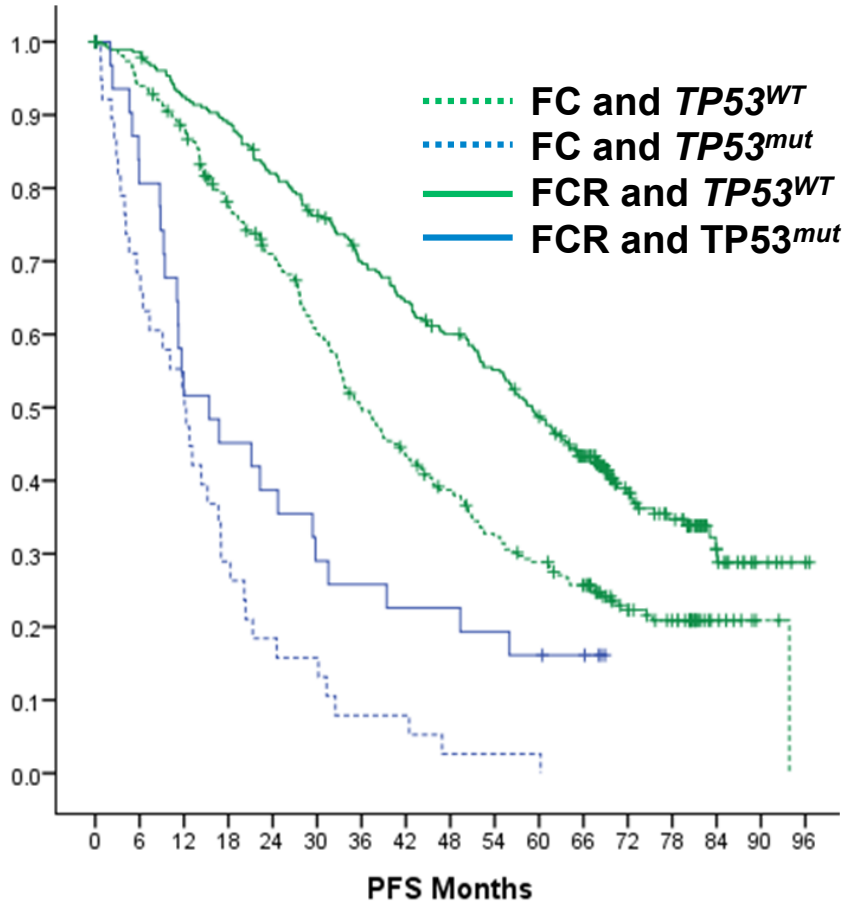


Dohner et al, New Engl J Med 2000 ; Rasi et al, Haematologica 2012; Zainuddin et al, Leuk Res 2011; Zenz et al J Clin Oncol 2010; Rossi et al Blood 2011, Stilgenbauer, Blood 2014

TP53 abnormalities in CLL



Hallek et al, ASH 2009



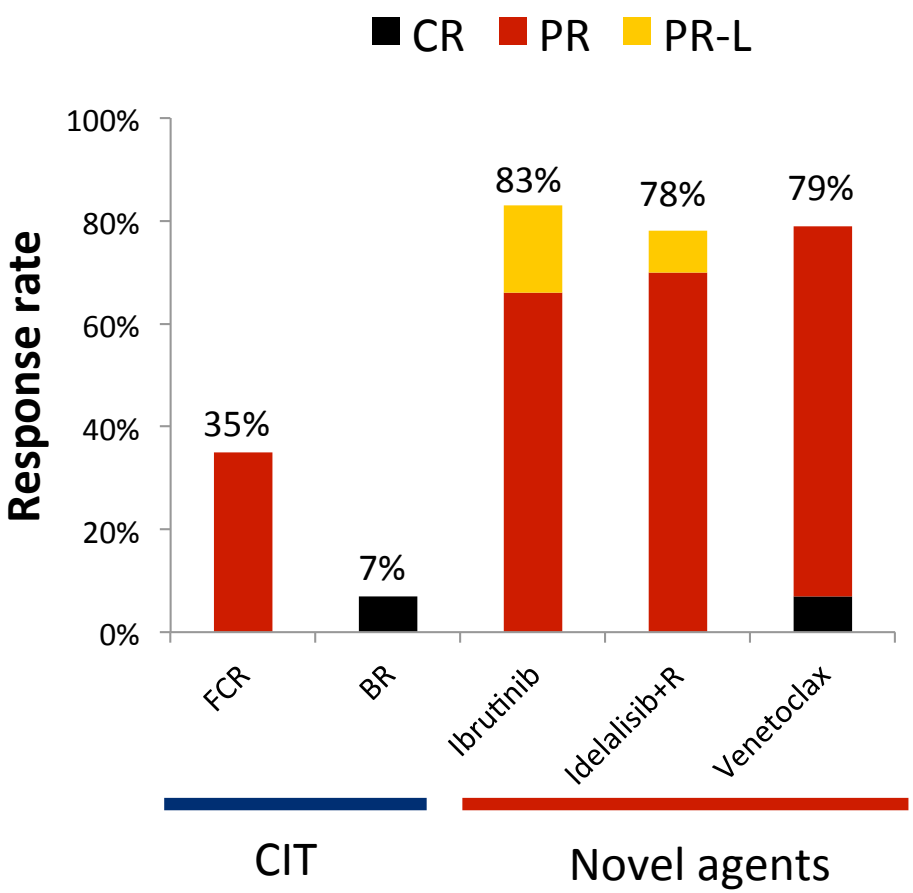
Stilgenbaueret al, ASH 2012

EHA-20: Ljungstrom S121; Tausch LB2070 (novel FCR prognosticators)

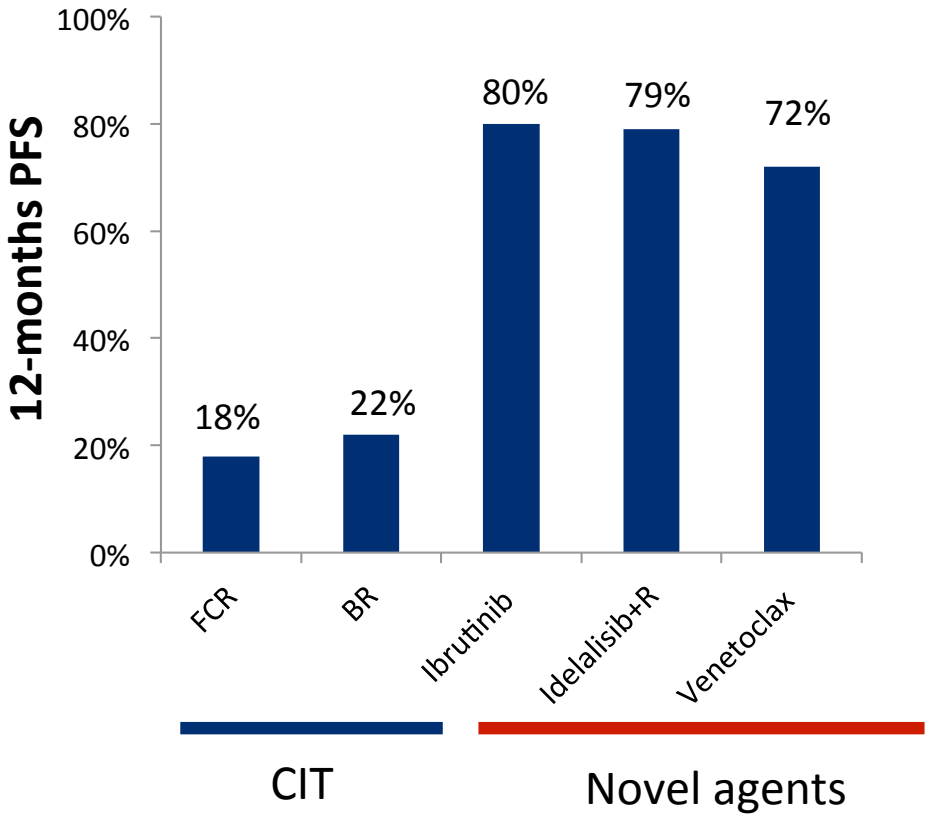
Chemoimmunotherapy (CIT) vs novel agents in *TP53* disrupted CLL

Relapsed/Refractory CLL

Response rate



PFS



Badoux Blood 2011; Fisher J Clin Oncol 2011; O'Brien, ASH 2014; Sharman ASH 2014; Byrd ASH 2015; Stilgenbauer, ASH 2015

Guideline recommendations for *TP53* analysis in clinical practice

	When	What
iwCLL	Before treatment	17p deletion
ERIC	Before treatment	*TP53* mutation
BCSH	Before treatment	17p deletion and *TP53* mutation
NCCN	Before treatment	17p deletion and *TP53* mutation
ESMO	Before treatment	17p deletion and *TP53* mutation

Hallek et al. Blood. 2008;
Oscier et al. Br J Haematol. 2013
Pospisilova et al. Leukemia. 2012
Zelenetz et al J Natl Cancer Inst 2015
Eichhorts et al, Ann Oncol 2015.

Clonal architecture of *TP53* mutated CLL

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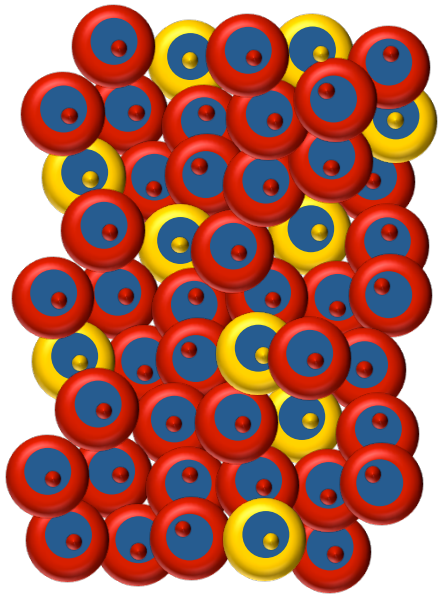
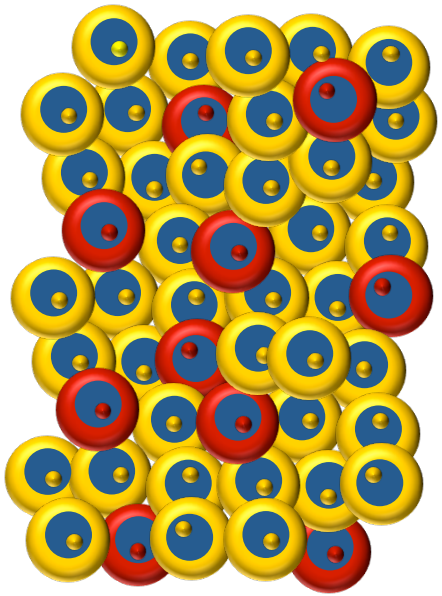
Scenario 1



TP53 mutation representation
80%

Detectable by Sanger sequencing

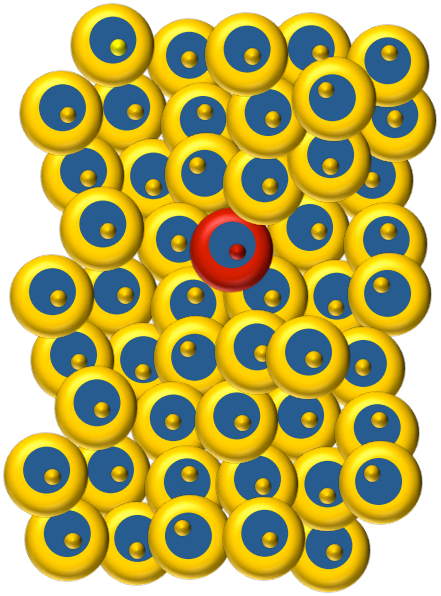
Scenario 2



TP53 mutation representation
20%

Barely detectable by Sanger sequencing

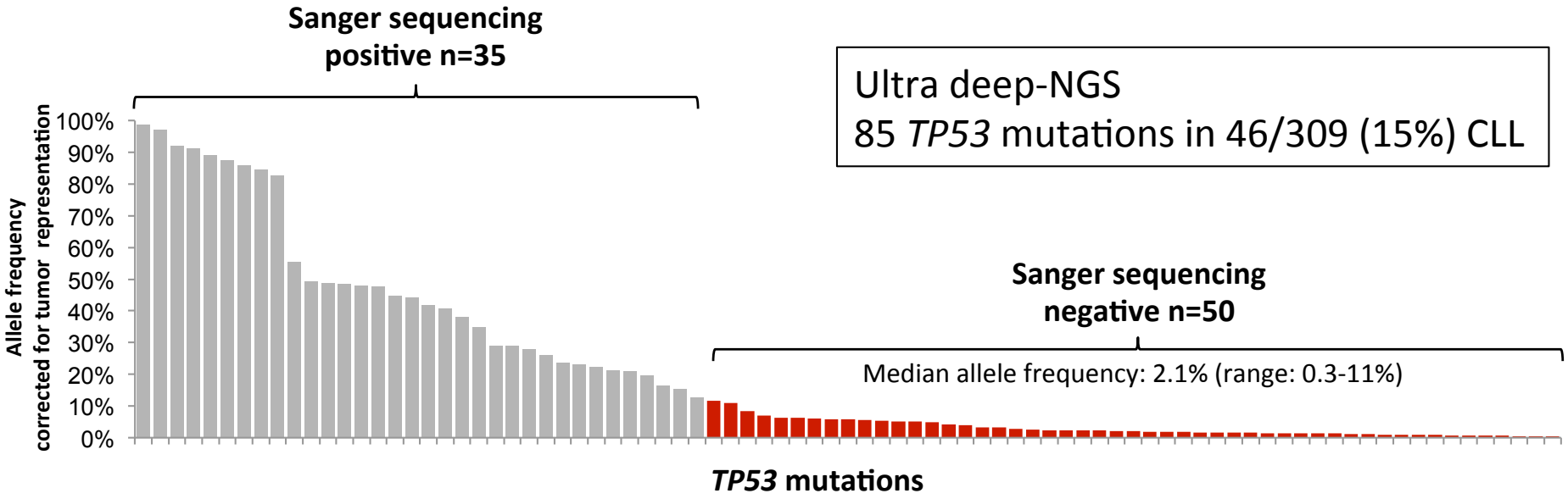
Scenario 3



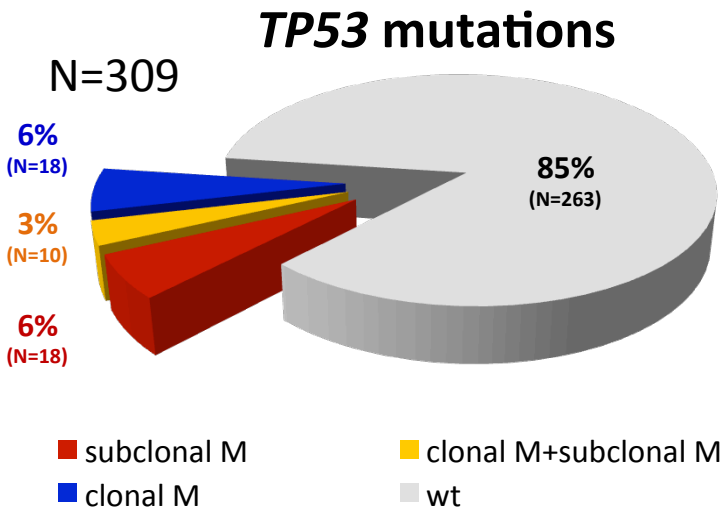
TP53 mutation representation
1%

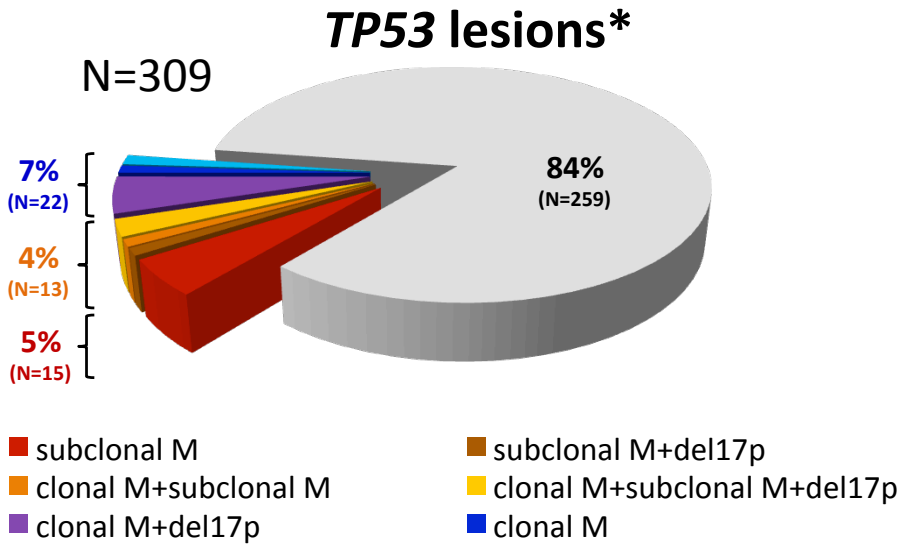
Not detectable by Sanger sequencing

Small *TP53* mutated subclones account for ~30% of all cases harboring *TP53* defects



Ultra deep-NGS
85 *TP53* mutations in 46/309 (15%) CLL

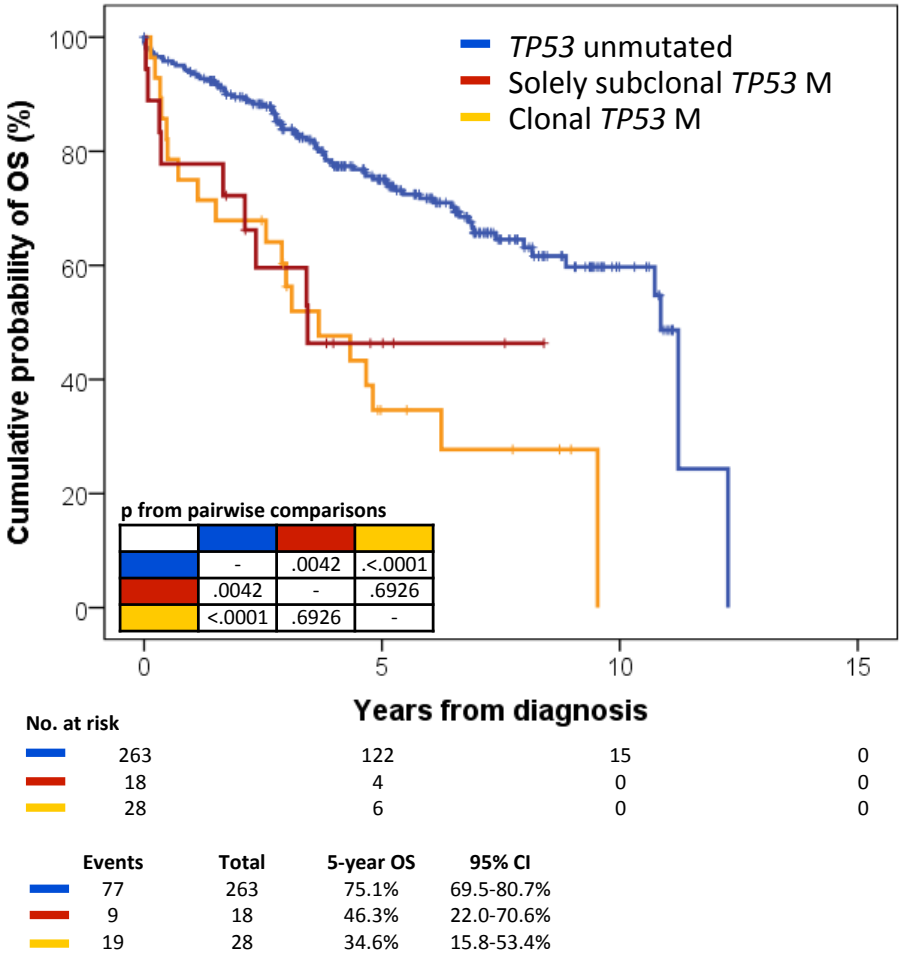


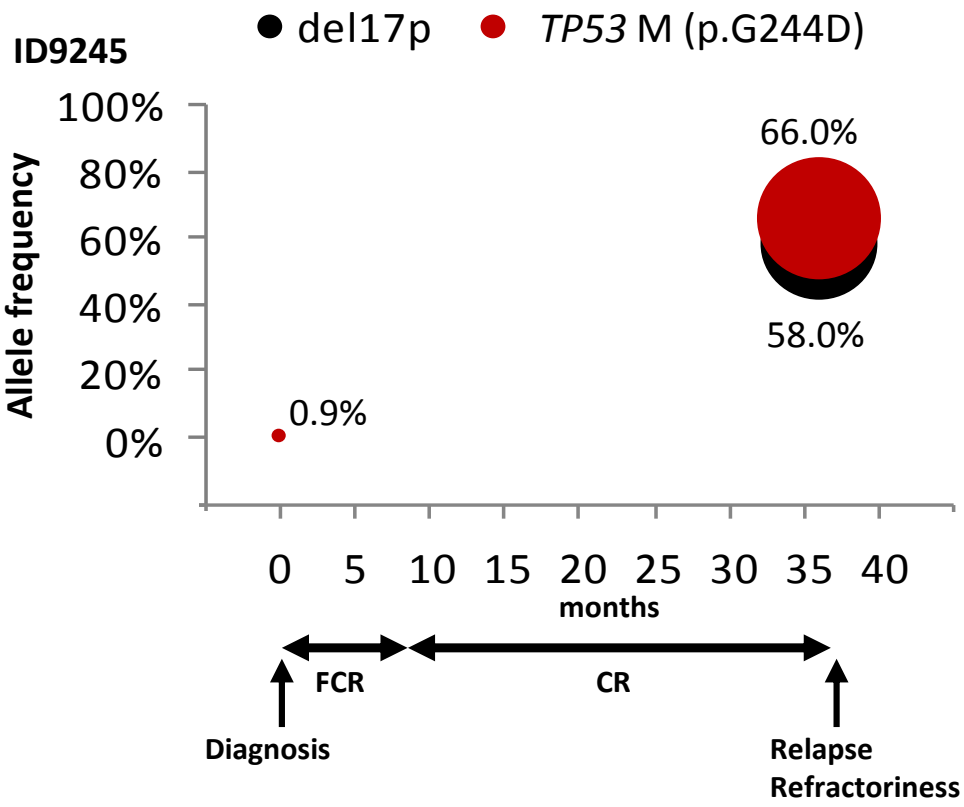


* *TP53* mutations and 17p13 deletion

Rossi, Blood 2014

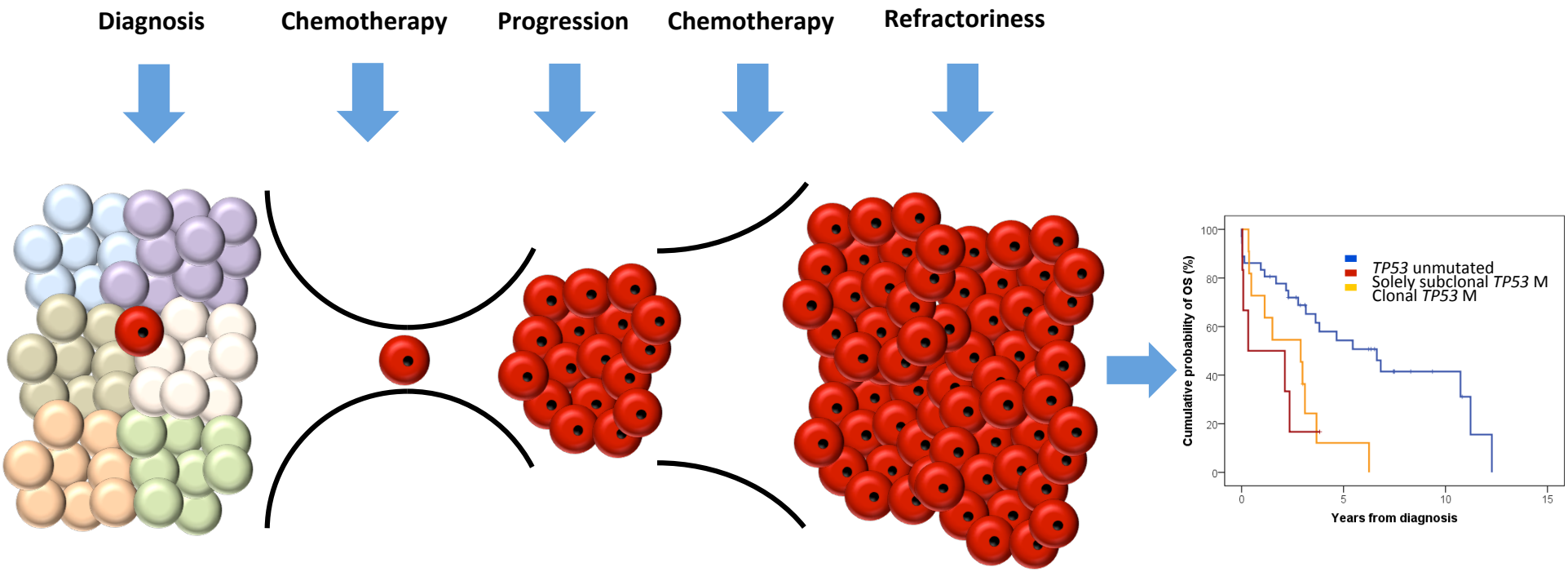
Small *TP53* mutated subclones have the same unfavorable prognostic impact as clonal *TP53* defects





Rossi, Blood 2014

Small *TP53* mutated subclones are selected by treatment because of their chemoresistance



Small *TP53* mutated subclone admixed with *TP53* wild type clones

Removal of *TP53* wild type clones and selection of the *TP53* mutated subclone

Expansion of the *TP53* mutated clone

Poor outcome

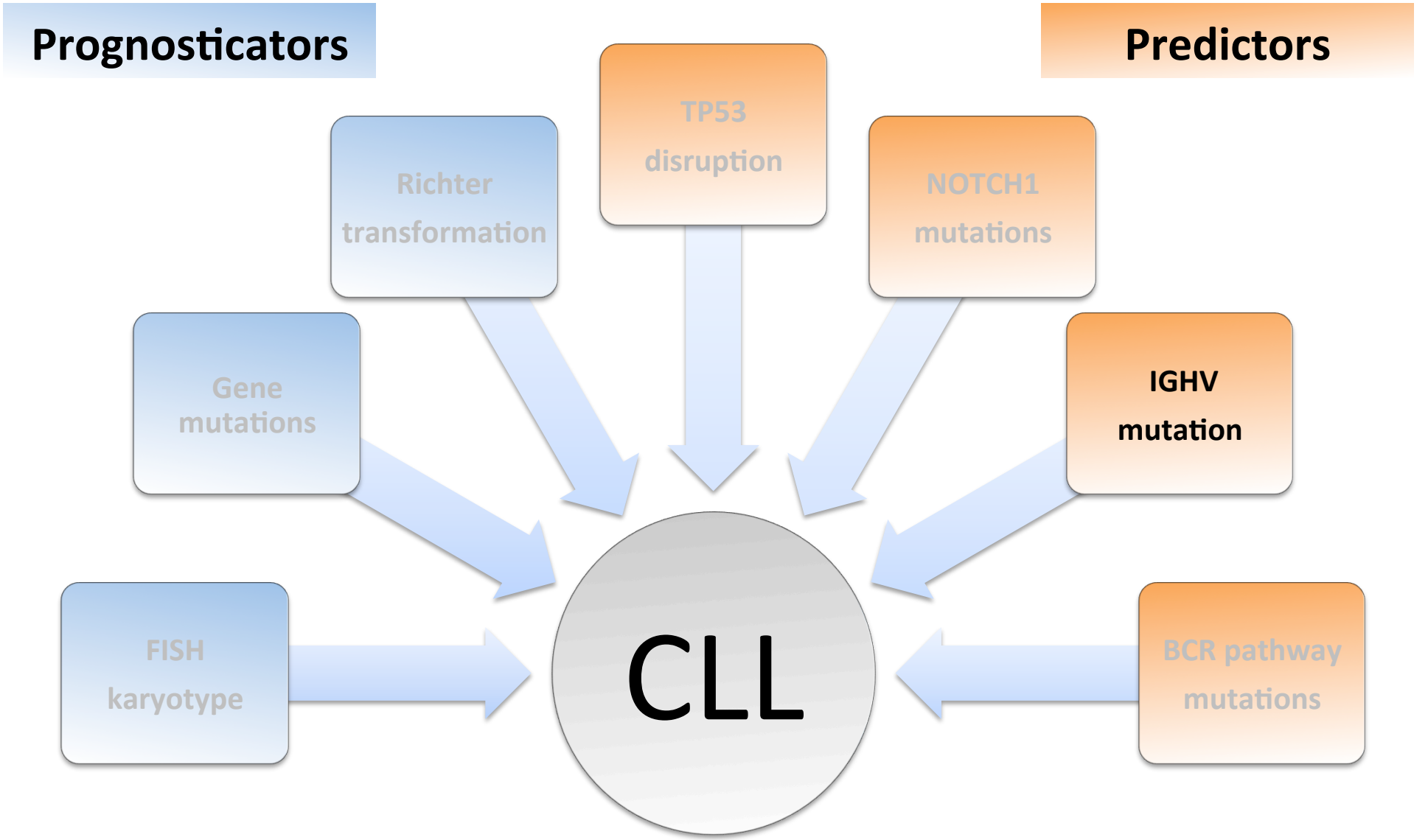
TP53 mutated CLL cell

Rossi, Blood 2014

Outline

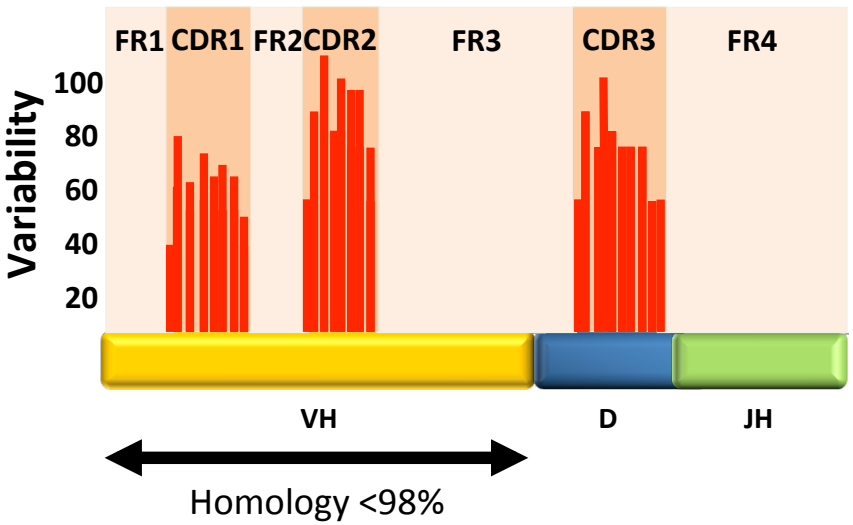
- CLL as a ***clinical practice*** model for precision medicine
  - Predictors ***for choosing*** a novel molecule
  - Predictors ***for not choosing*** a novel molecule
- DLBCL as a ***potential*** model for precision medicine

Prognosticators and predictors in CLL

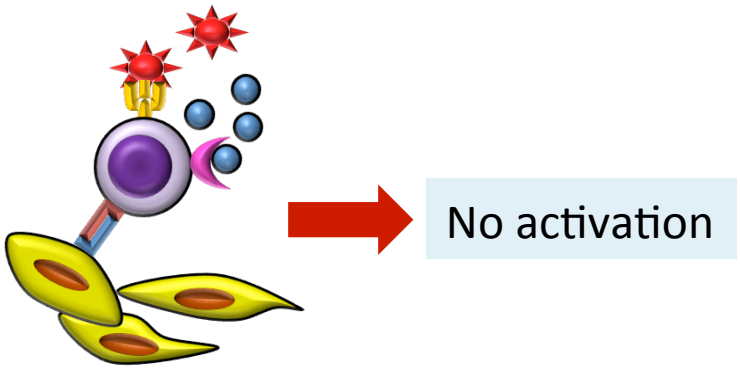


IGHV mutations in CLL

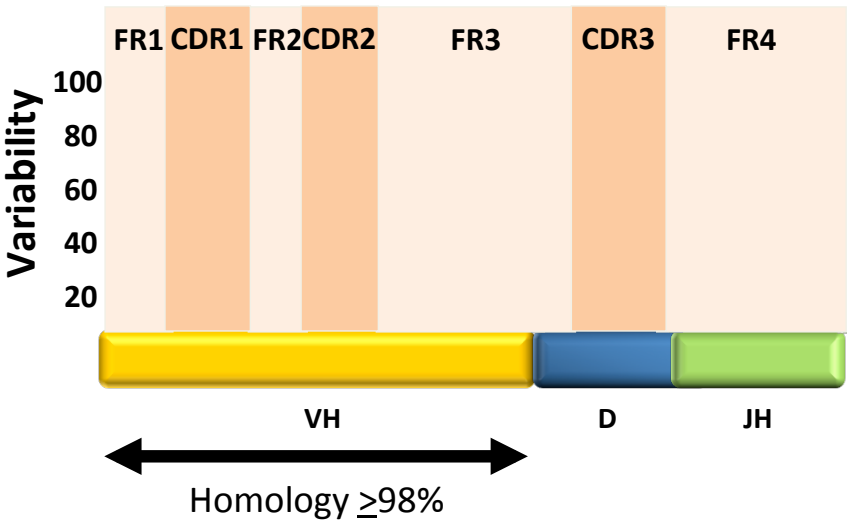
IGHV mutated



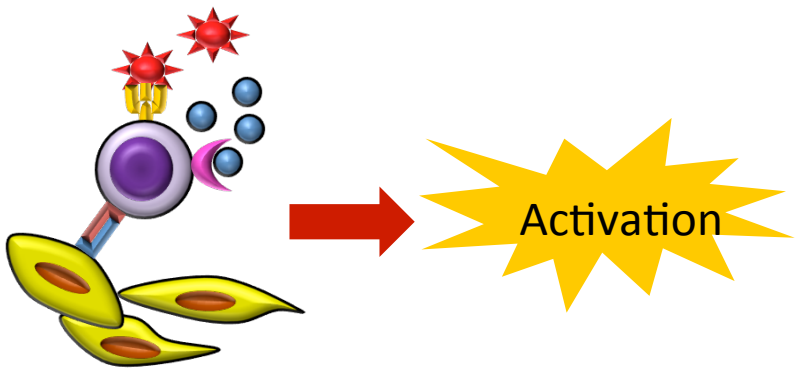
Newly diagnosed CLL: **~60%**
Progressive CLL: **~40%**
Relapsed/Refractory: **~20%**



IGHV unmutated

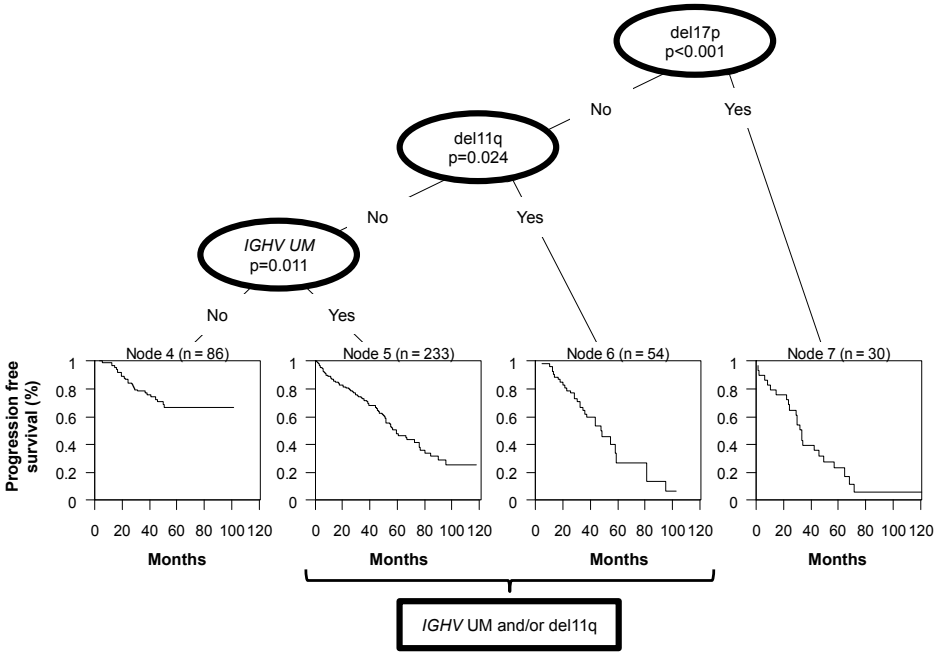


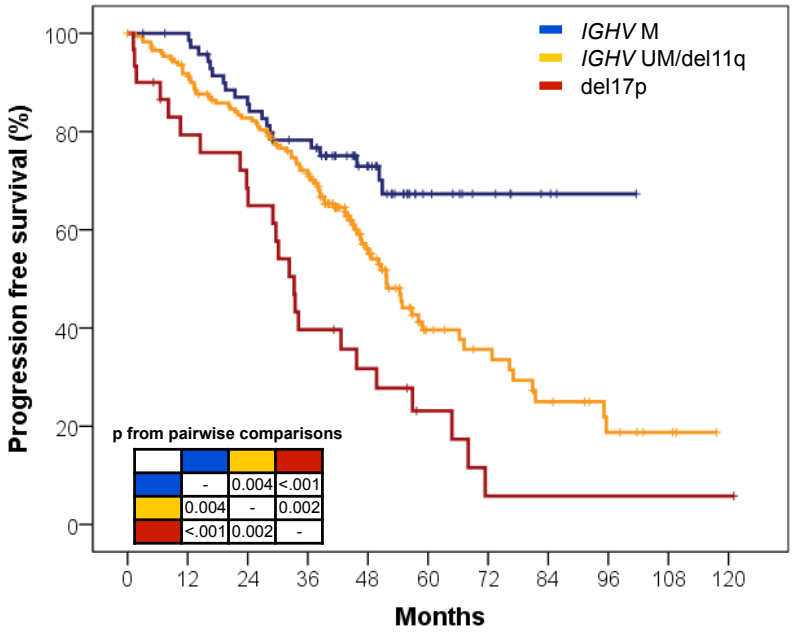
Newly diagnosed CLL: **~40%**
Progressive CLL: **~60%**
Relapsed/Refractory: **~80%**

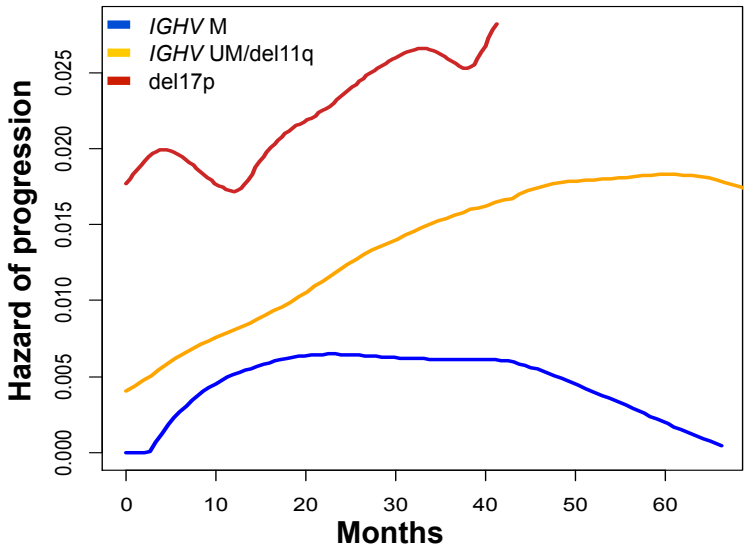


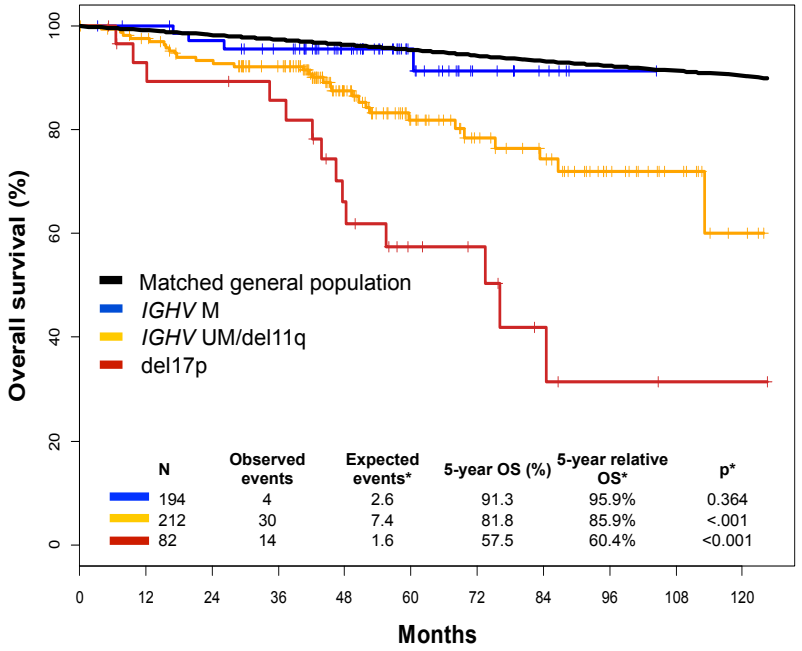
Chiorazzi et al. New Engl J Med 2005

IGHV mutated patients devoid of del17p and del11q gain the greatest benefit from FCR



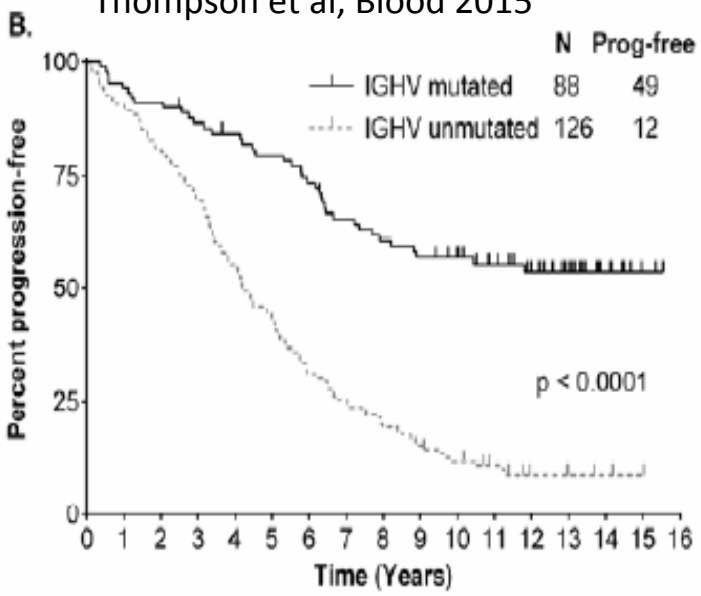




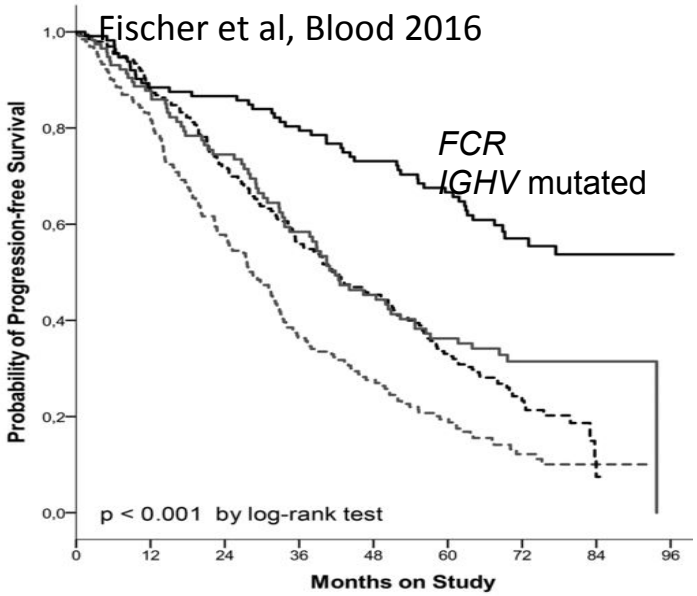


IGHV mutated patients gain the greatest benefit from FCR

Thompson et al, Blood 2015



Fischer et al, Blood 2016

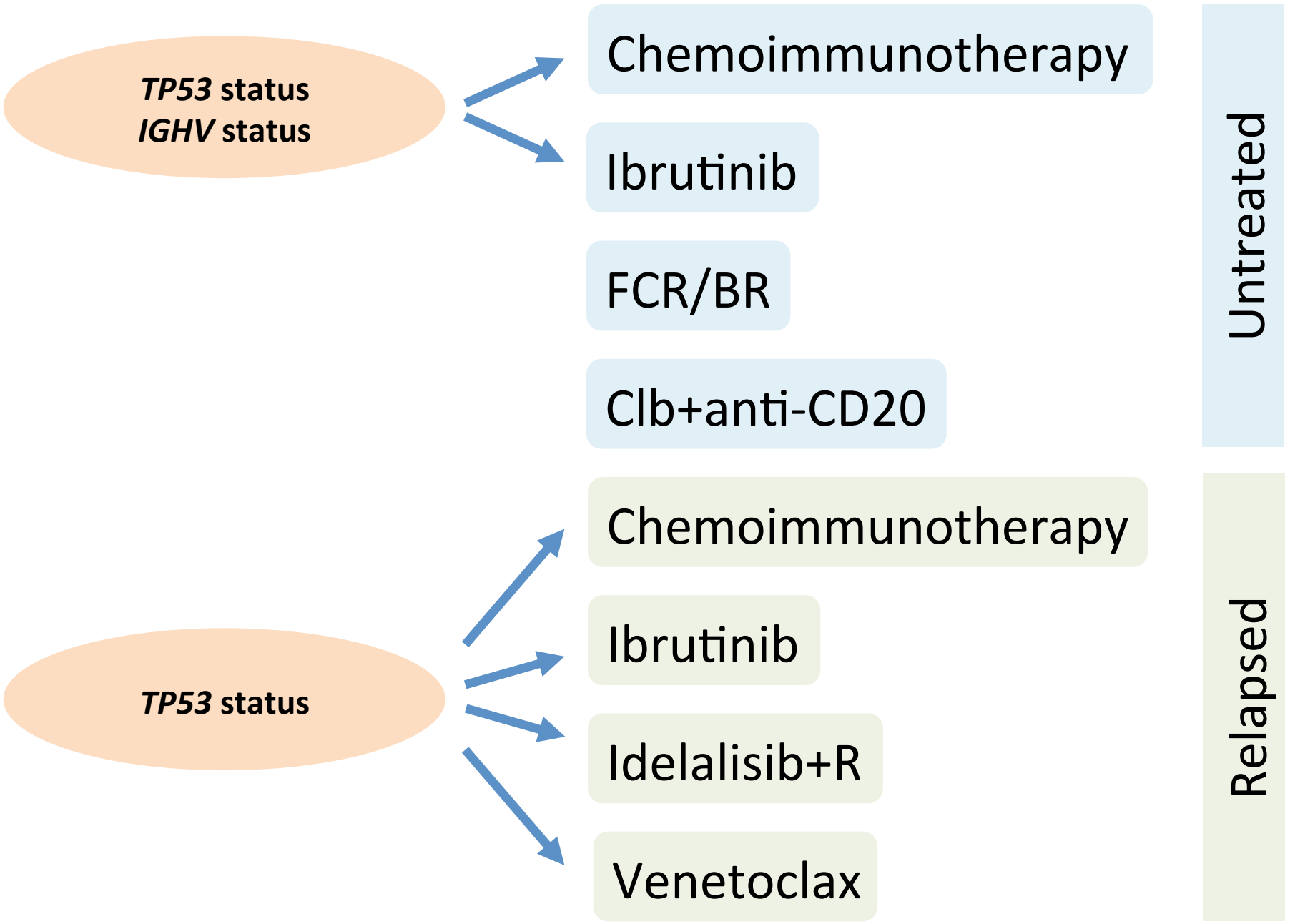


Guideline recommendations for *IGHV* analysis in clinical practice

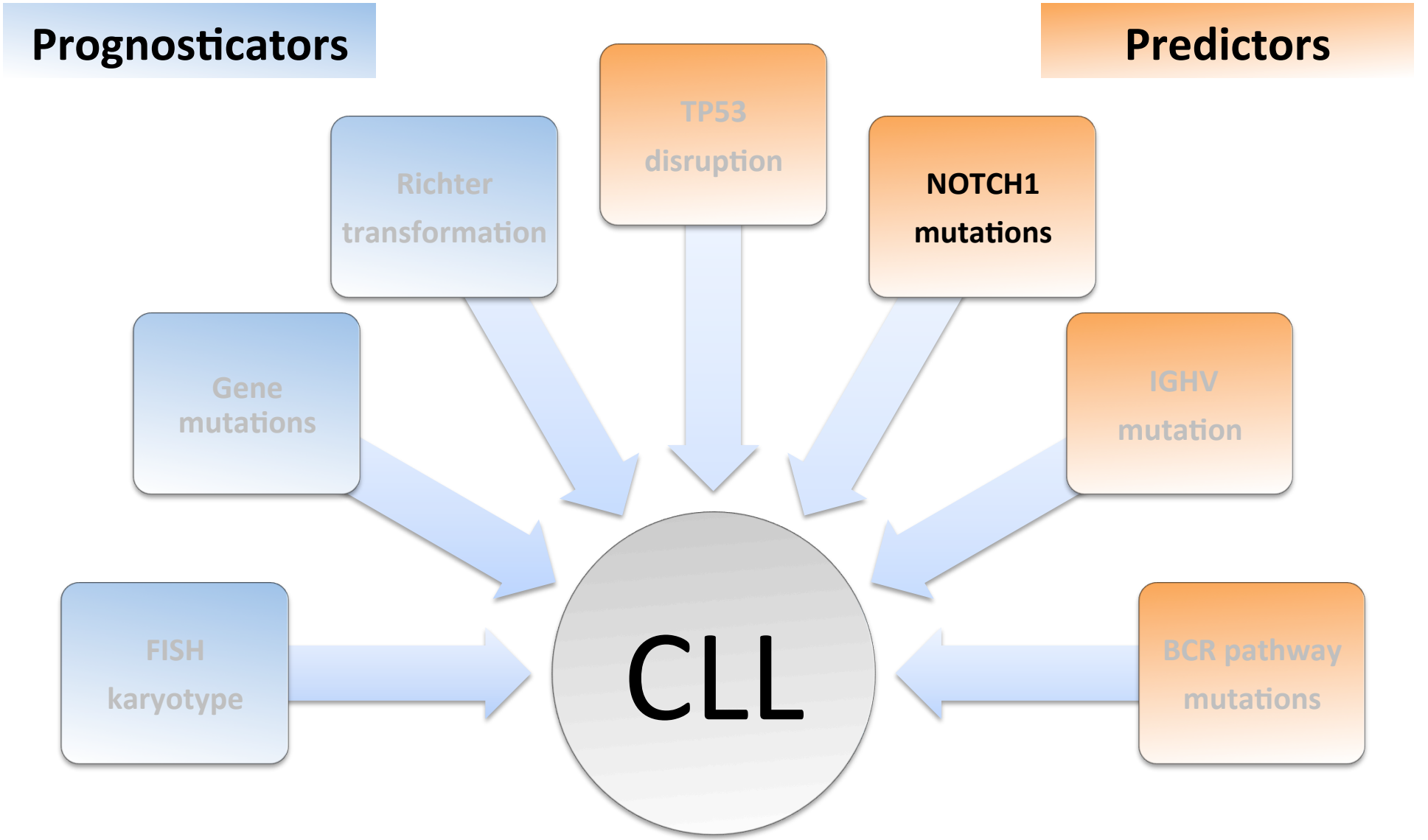
	Recommendation	When
iwCLL	Not generally indicated	-
BCSH	Not recommended	-
NCCN	Not generally indicated	-
ESMO	Desirable	Before treatment

Hallek et al. Blood. 2008;
Oscier et al. Br J Haematol. 2013
Zelenetz et al J Natl Cancer Inst 2015
Eichhorts et al, Ann Oncol 2015.

Can treatment decision be informed by biomarkers?

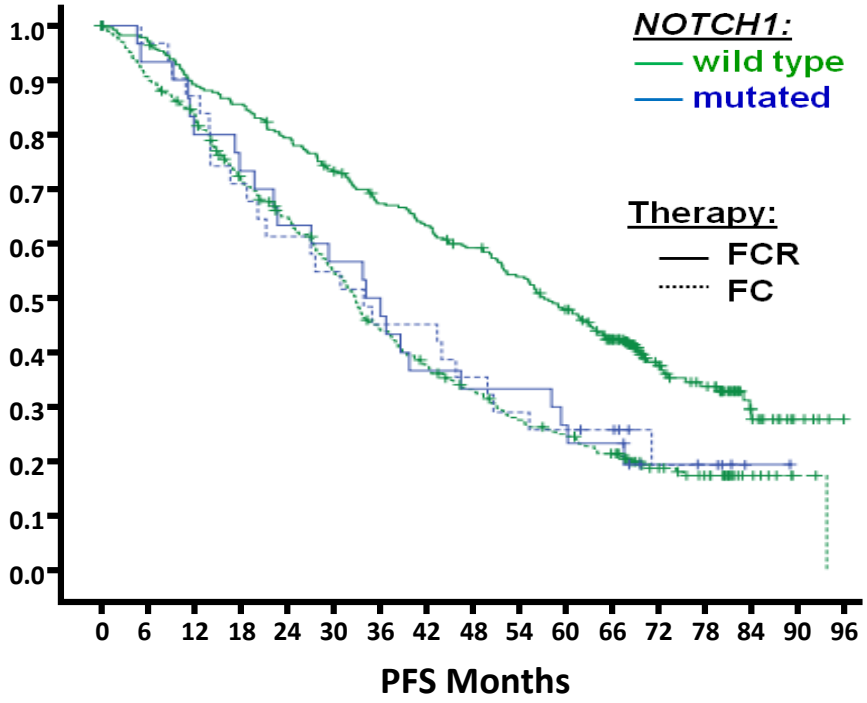


Prognosticators and predictors in CLL



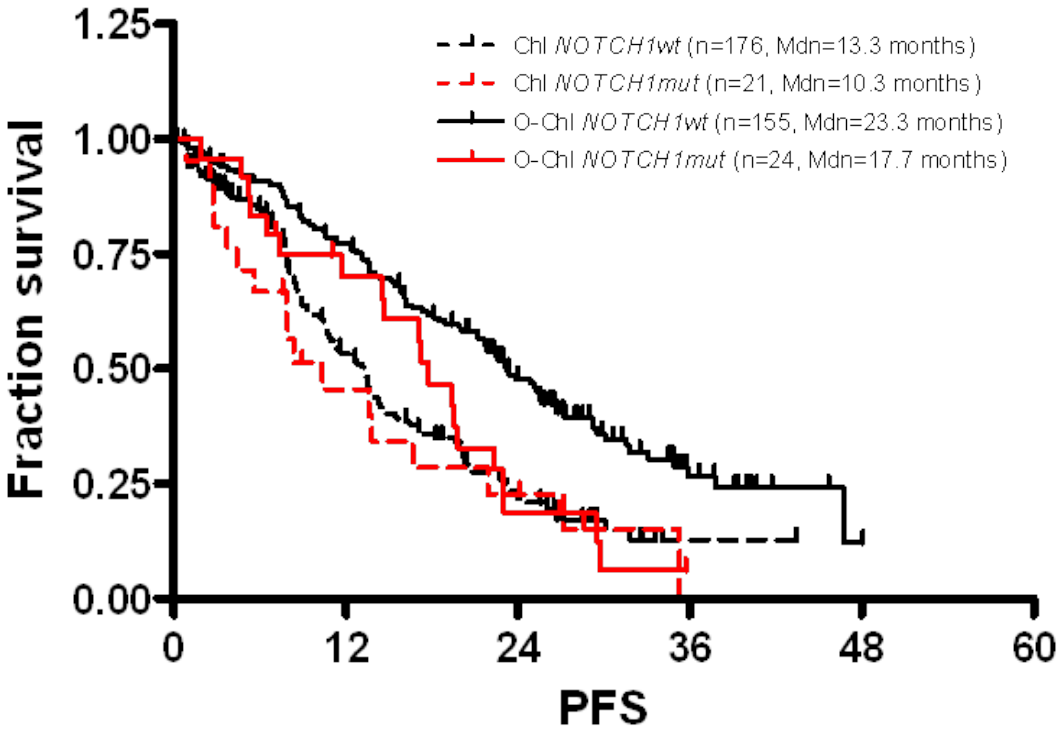
NOTCH1 mutations as predictive marker for no benefit from addition of anti-CD20 MoAb to chemotherapy

GCLLSG CLL8



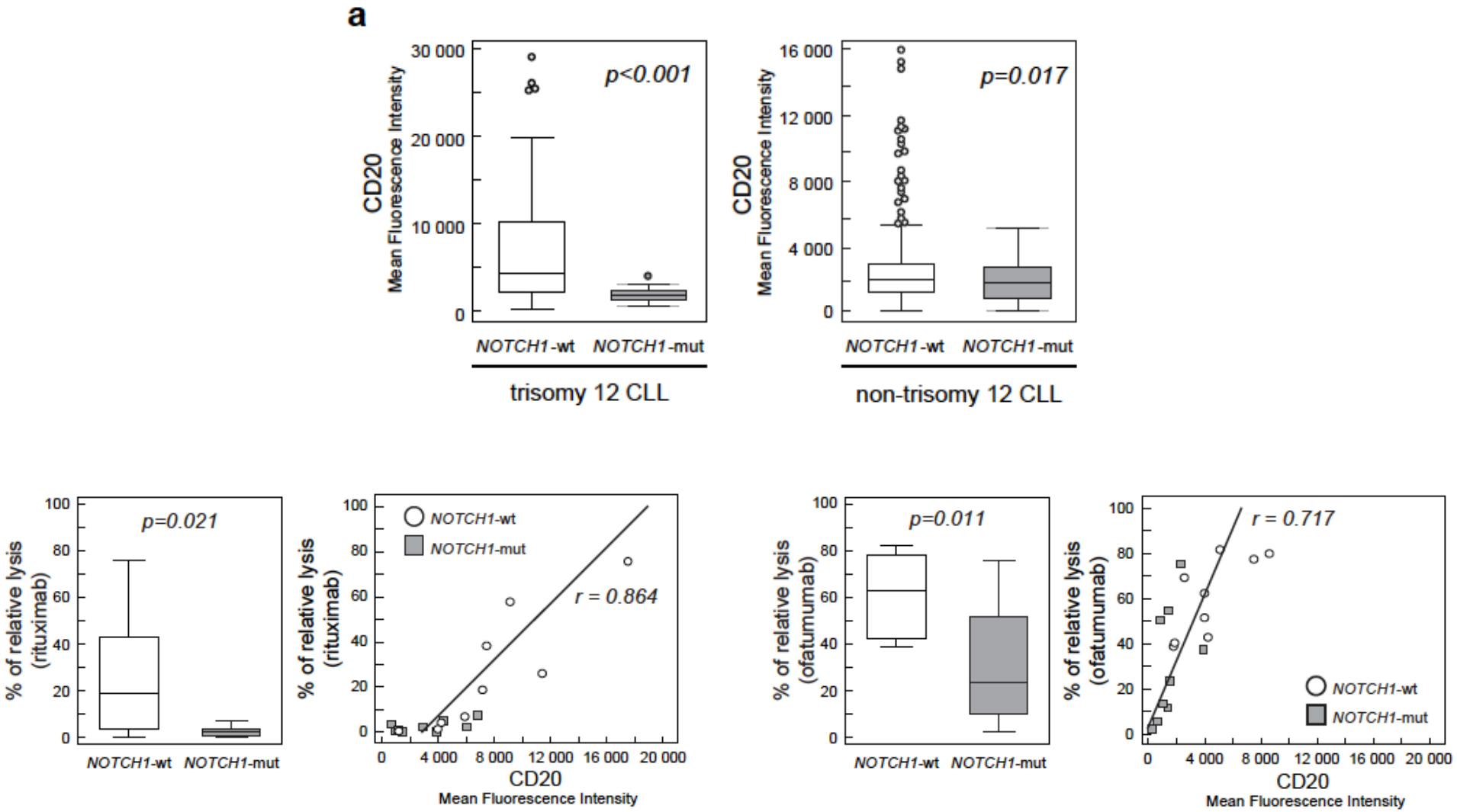
Stilgenbauer et al, Blood 2014

COMPLEMENT 1



Tausch et al, ASH 2013

NOTCH1 mutations associate with lower CD20 expression and reduced lysis by anti-CD20 mAbs

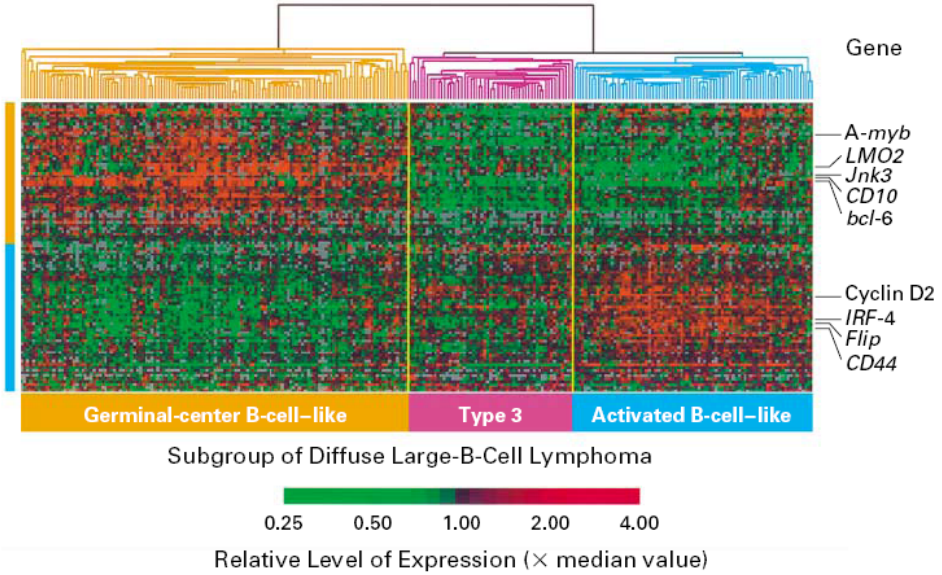


Pozzo et al, Leukemia 2016

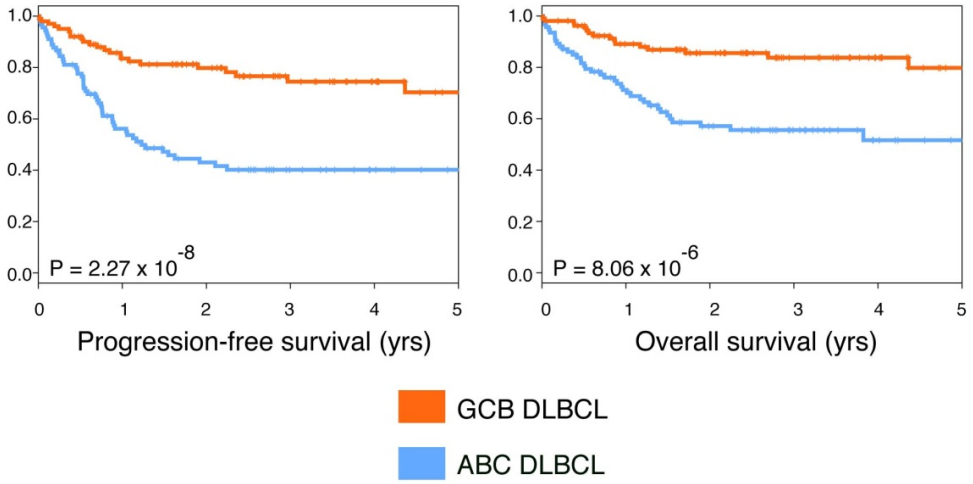
Outline

- CLL as a ***clinical practice*** model for precision medicine
  - Predictors ***for choosing*** a novel molecule
  - Predictors ***for not choosing*** a novel molecule
- DLBCL as a ***potential*** model for precision medicine

ABC-DLBCL is addicted of NF-kB

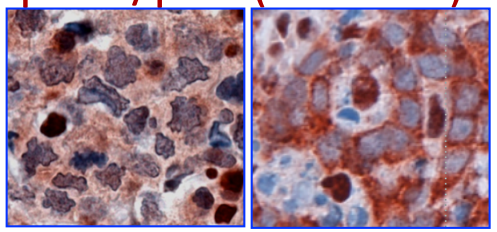


R-CHOP treated DLBCL

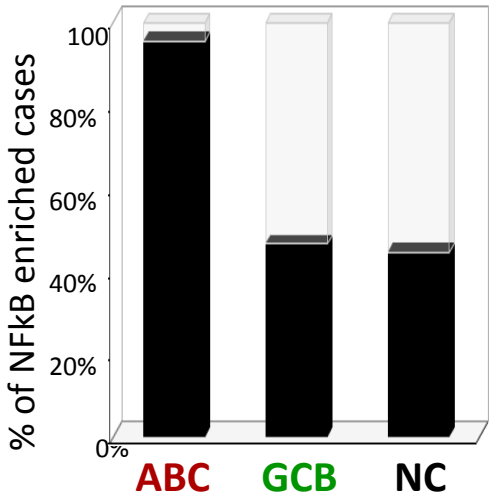


100% ABC-DLBCL have NF-kB activation

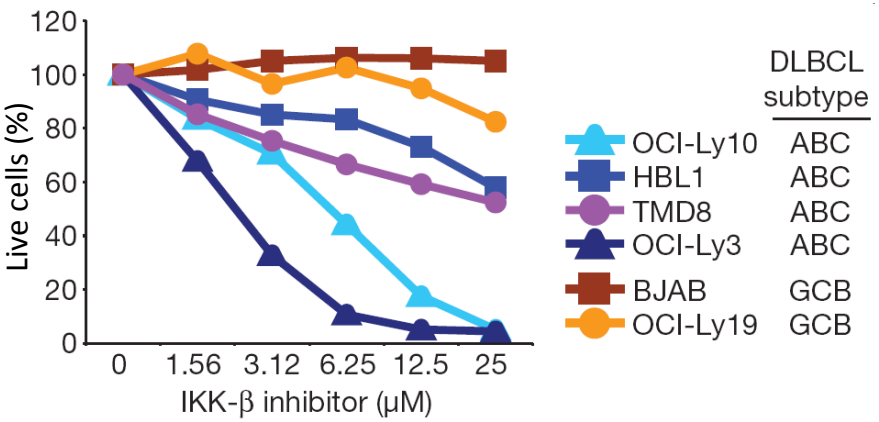
p105/p50 (classical)



nuclear cytoplasmic

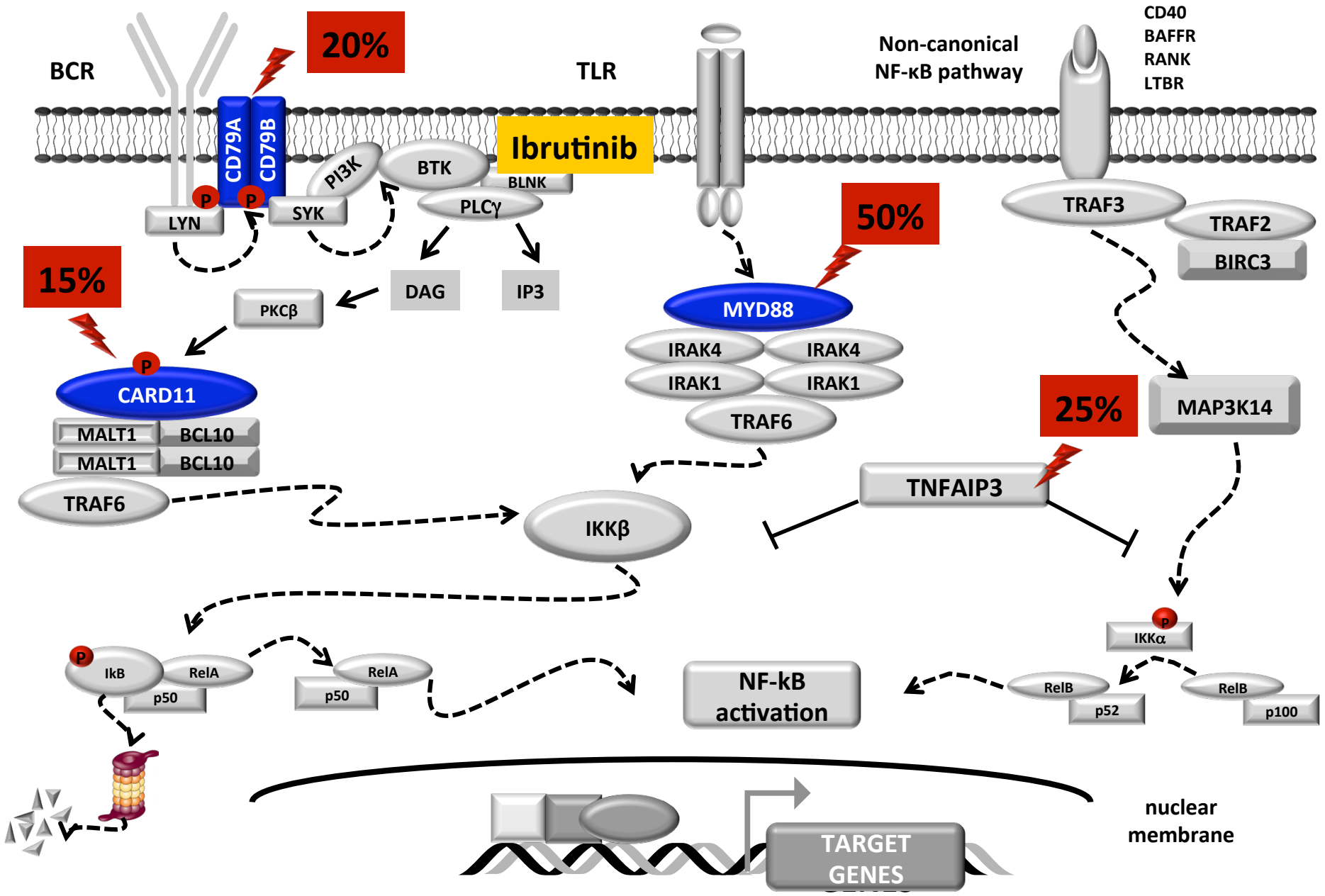


NF-kB inhibition is lethal for ABC DLBCL



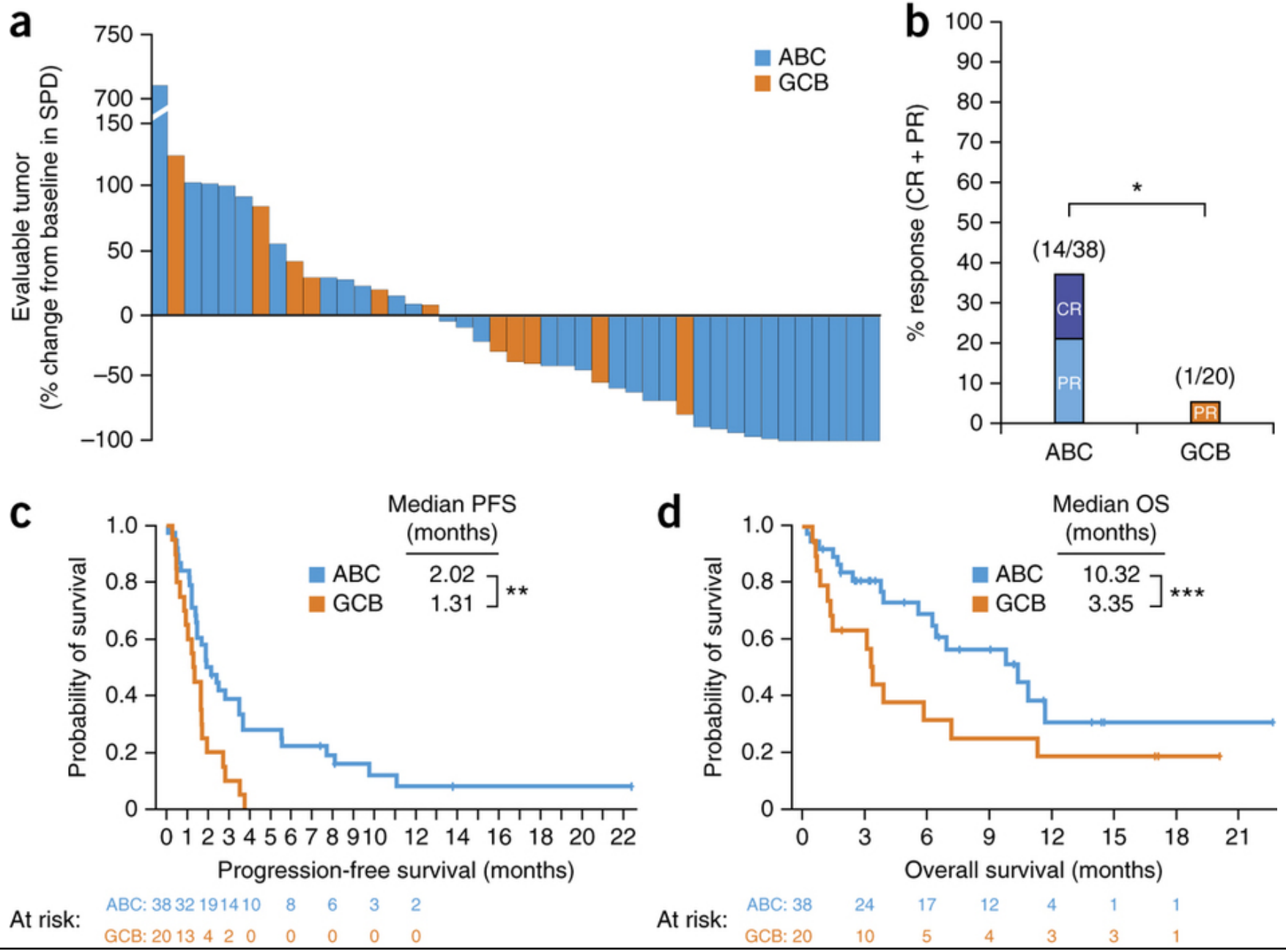
Lenz et al. NEJM, 2008
Compagno et al, Nature 2009
Davis et al, Nature 2010

Various alternative genetic mechanisms of NF-kB activation In DLBCL affecting the TLR and BCR pathways

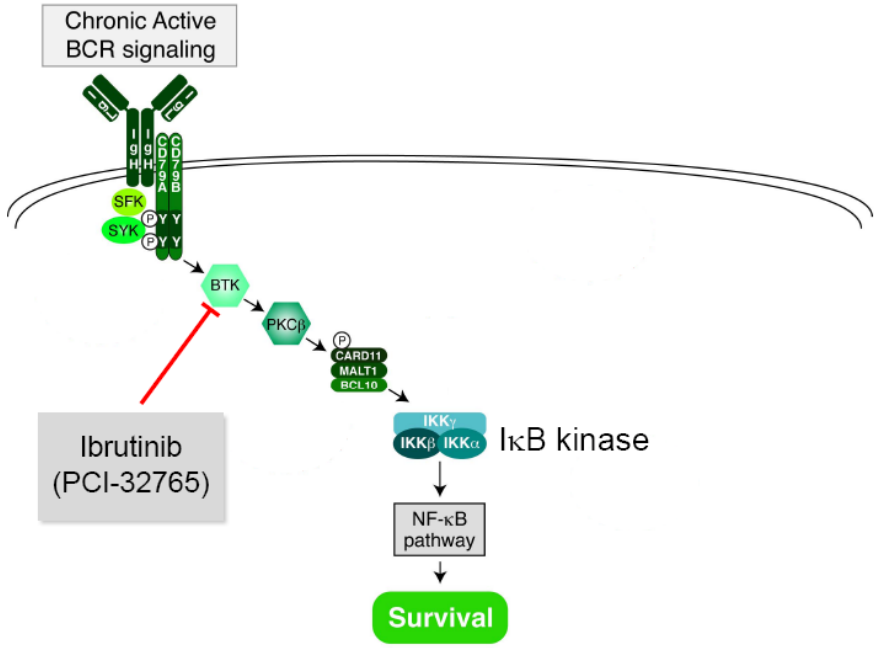


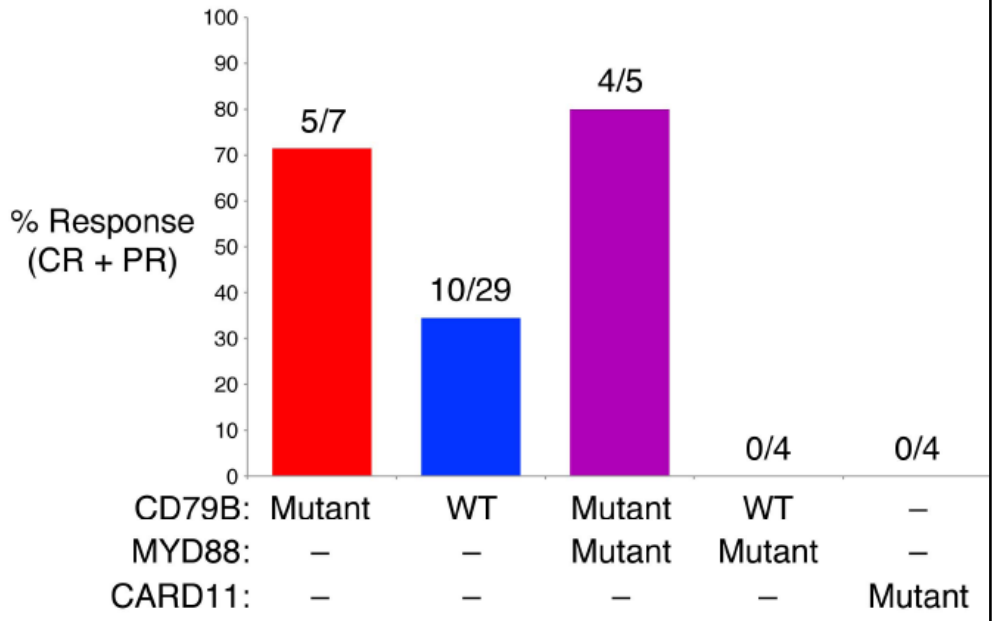
Ibrutinib in relapsed/refractory diffuse large B cell lymphoma

(Wilson et al, Nat Med 2015)

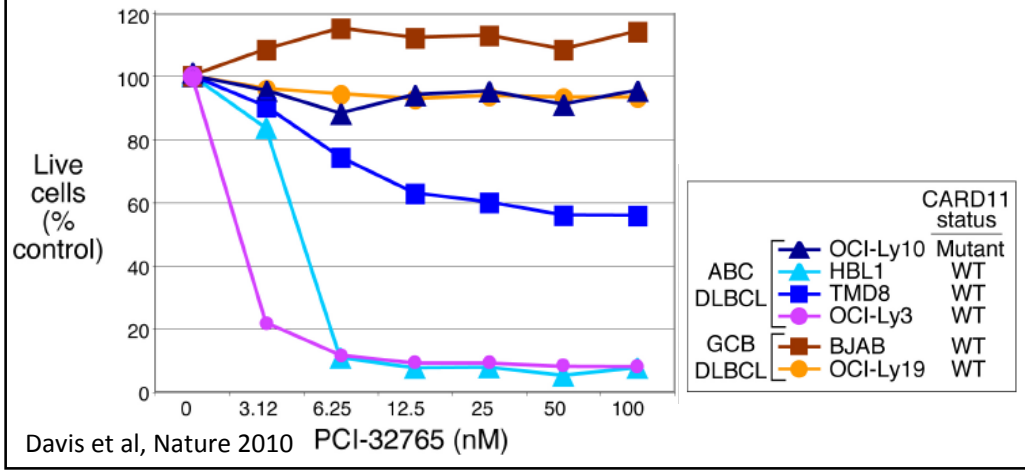


Blockade of BCR signaling in ABC DLBCL with Ibrutinib





Ibrutinib is toxic for ABC DLBCLs with BCR signaling



Davis et al, Nature 2010

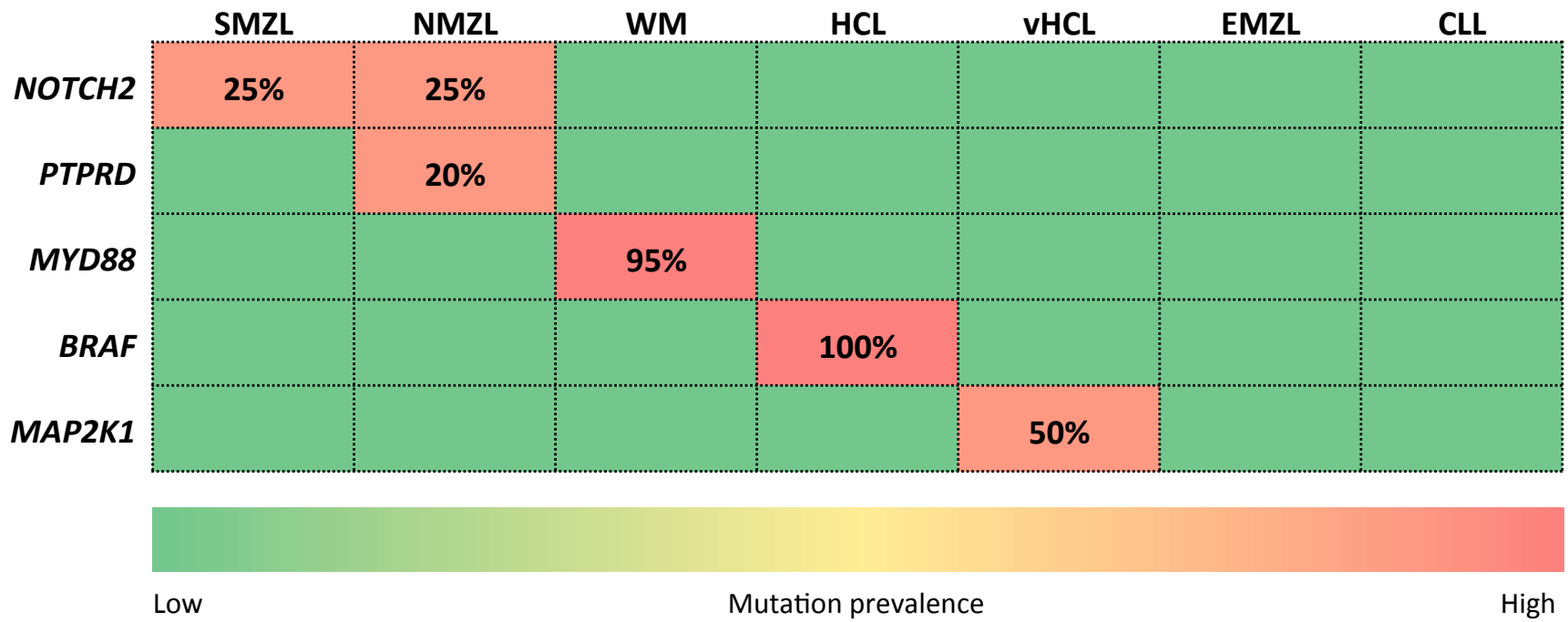
CD79B mutation predicts response

MYD88 mutation/CD79B wt predicts no response

CARD11 mutation predicts no response

Wilson et al, ASH 2012

Mutations in signalling pathway genes among indolent B-cell tumors



Tiacci et al, New Engl J Med 2011
Treon et al, New Engl J Med 2012
Landau et al, Cell 2013
Rossi et al, J Exp Med 2013
Rossi et al, ASH 2013
Waterfall et al, Nat Genet 2013
Spina et al, ASH 2014