Predictive biomarkers

Davide Rossi, M.D., Ph.D.

Hematology
IOSI - Oncology Institute of Southern Switzerland
IOR - Institute of Oncology Research
Bellinzona - Switzerland

CLL subgroups

- **Newly presented pts**
- **First line pts**
- **Relapsed pts**

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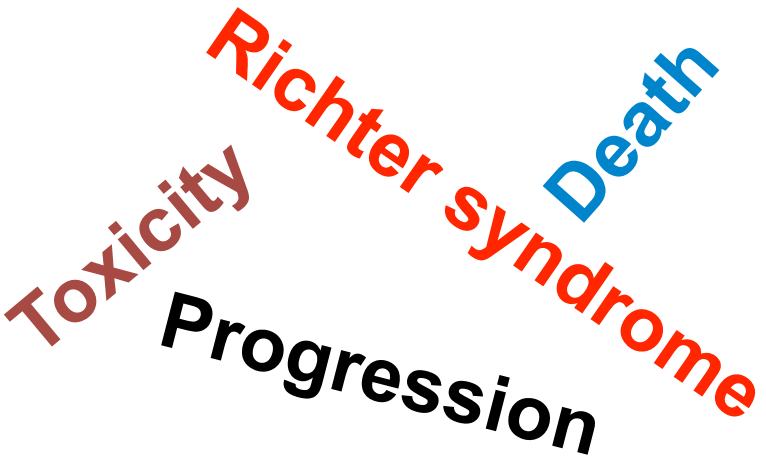
Clinical applications of predictive and prognostic biomarkers in CLL

Predictive biomarkers

Prognostic biomarkers



Treatment tailoring

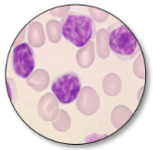
Patient counseling

Frequency of follow-up

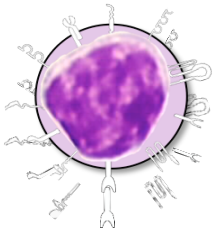
Identify those apropriate for early intervention trials

Biomarker: variable that associates with disease outcome

Host Factors: ***Age***, ***sex***, *etc*

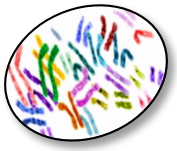


Disease Markers: ***Stage***, *lymphocyte count,* ***LDT***, *etc*

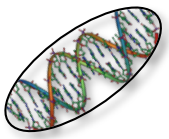


Ag expression: *CD38, Zap70,* ***CD49d***, *etc*

Serology: ***β2M***, *TK, LDH, sCD23, etc*



Genetics: ***del17p***, ***TP53 mutation***, *del11q22, del13q14, trisomy 12, NOTCH1 mutation, SFRB1 mutation, etc*

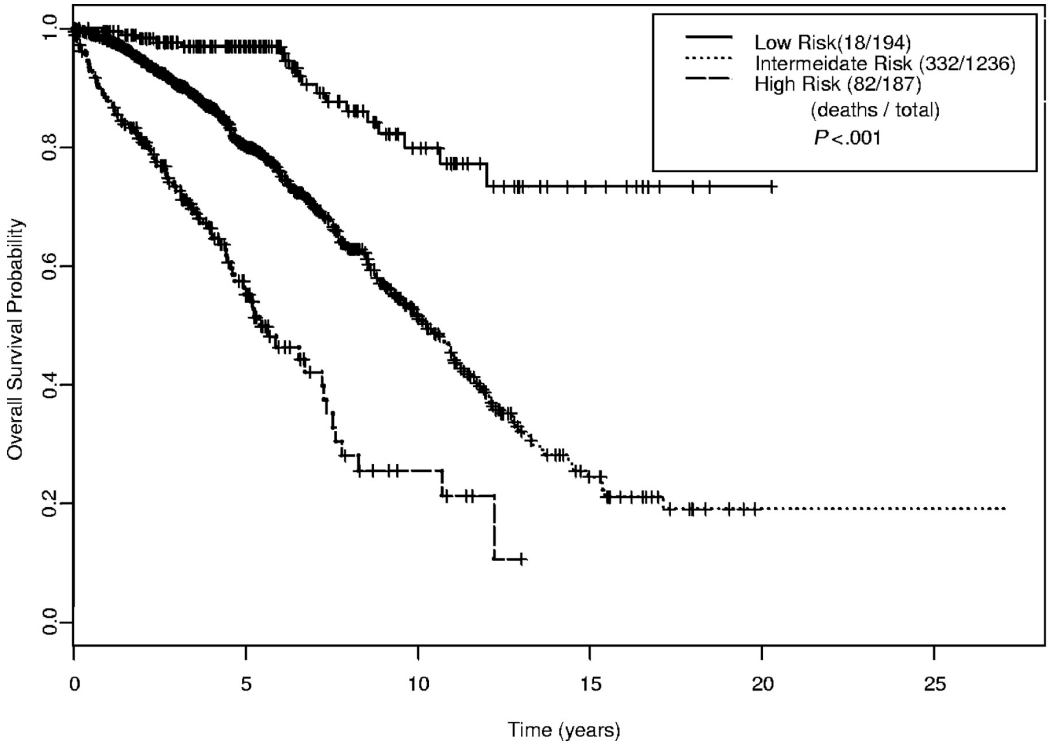


Biology Markers: ***IGVH-sequence***, *BCR-structure*

MDACC score

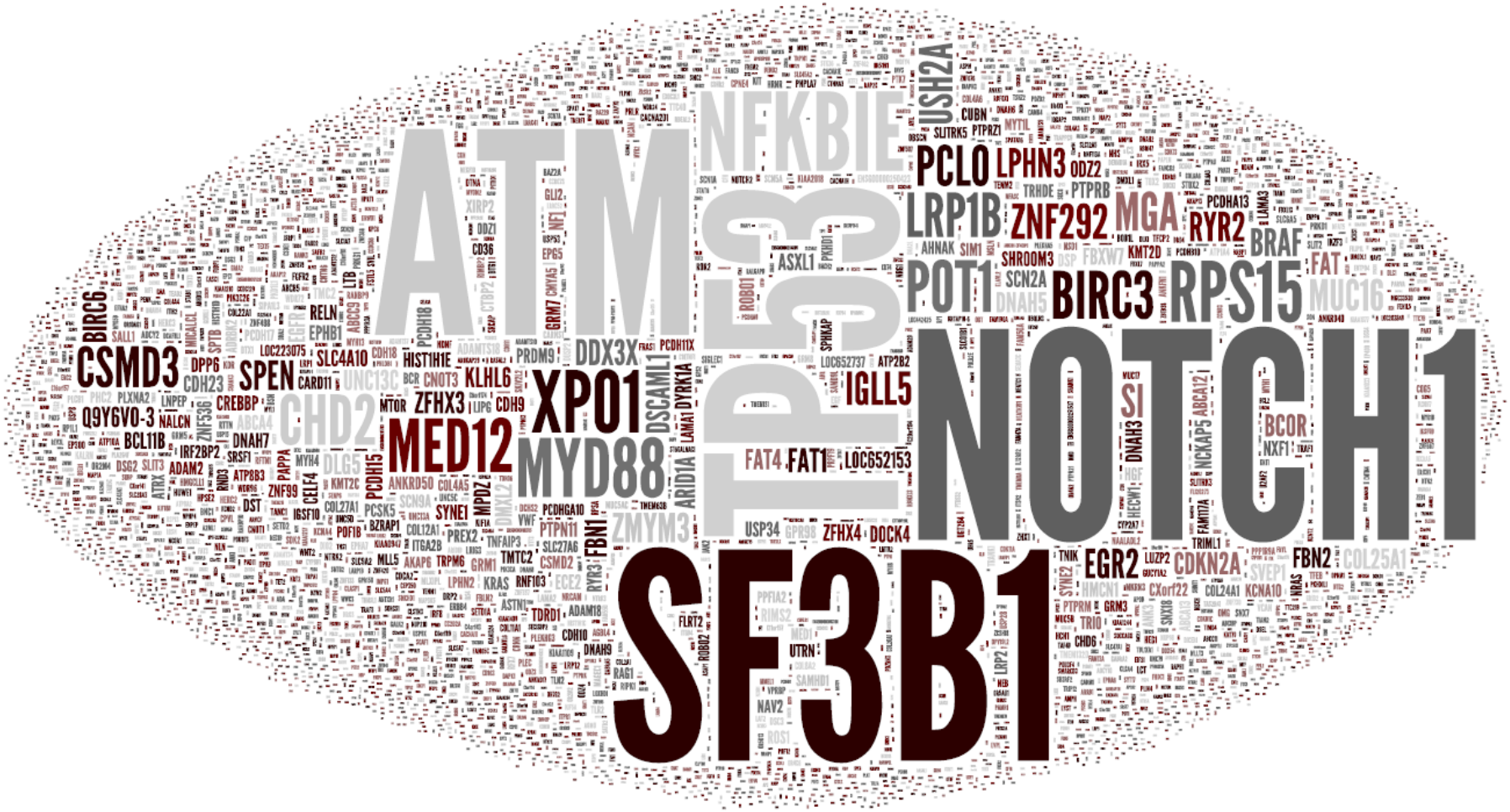
Biomarker	Score
Age	
<50 years	1
50-65 years	2
>65 years	3
Sex	
Male	0
Female	1
Rai stage	
0-II	0
III-IV	1
Involved nodal areas	
≤3	0
3	1
Lymphocyte count	
<20x10^9/L	0
20-50x10^9/L	1
>50x10^9/L	2
β2-microglobulin	
<ULN	0
1-2xULN	1
>2xULN	2

Risk group	Score	5-year survival
Low-risk	1-3	97%
Intermediate-risk	4-7	80%
High-risk	>7	55%



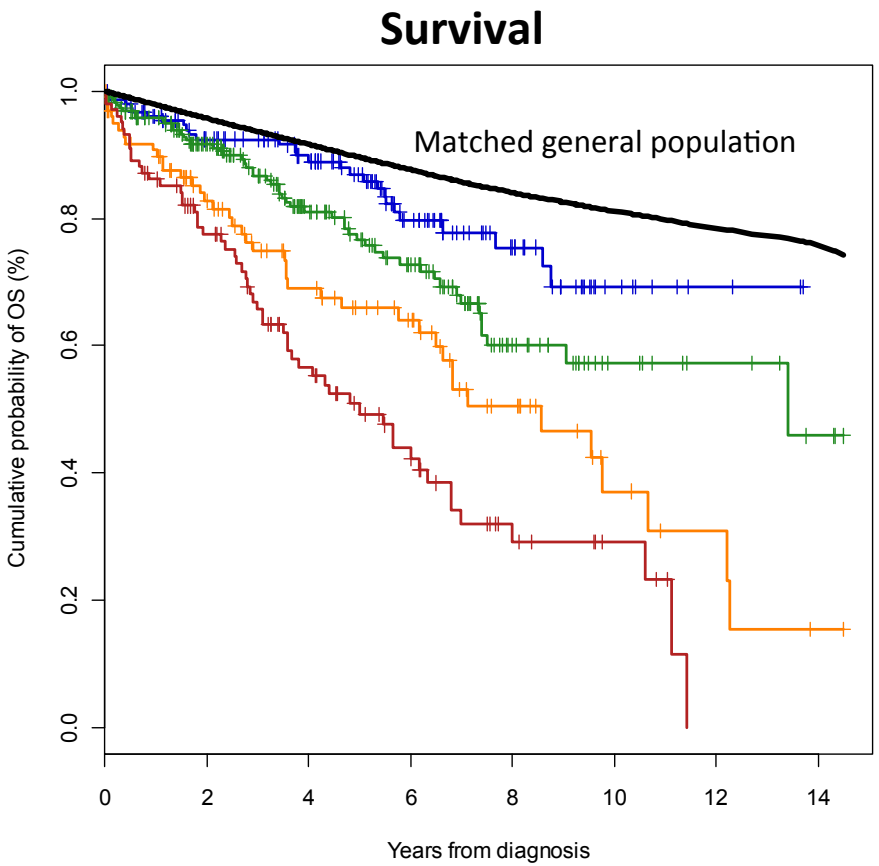
Wierda et al, Blood 2007

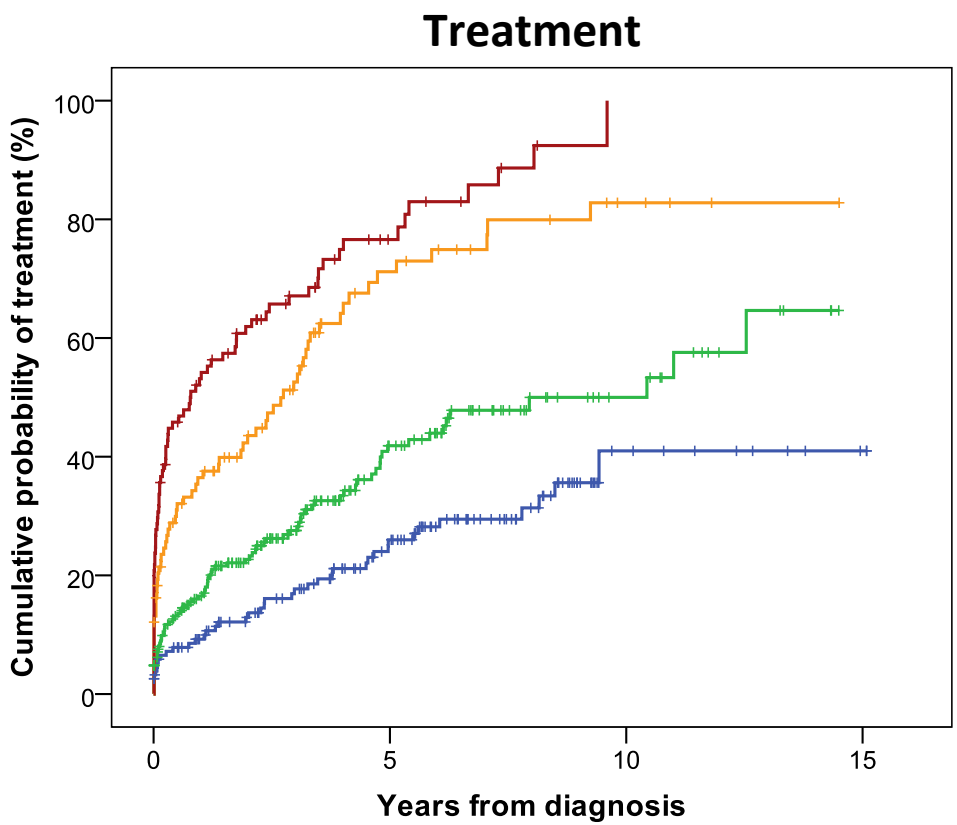
The mutational landscape of CLL



The wordcloud shows the genes that are reported as mutated in CLL by the v77 of the Catalogue of Somatic Mutations in Cancer (COSMIC). The size of the font is proportional to the mutation frequency

Integrating mutation and cytogenetics for CLL survival prognostication





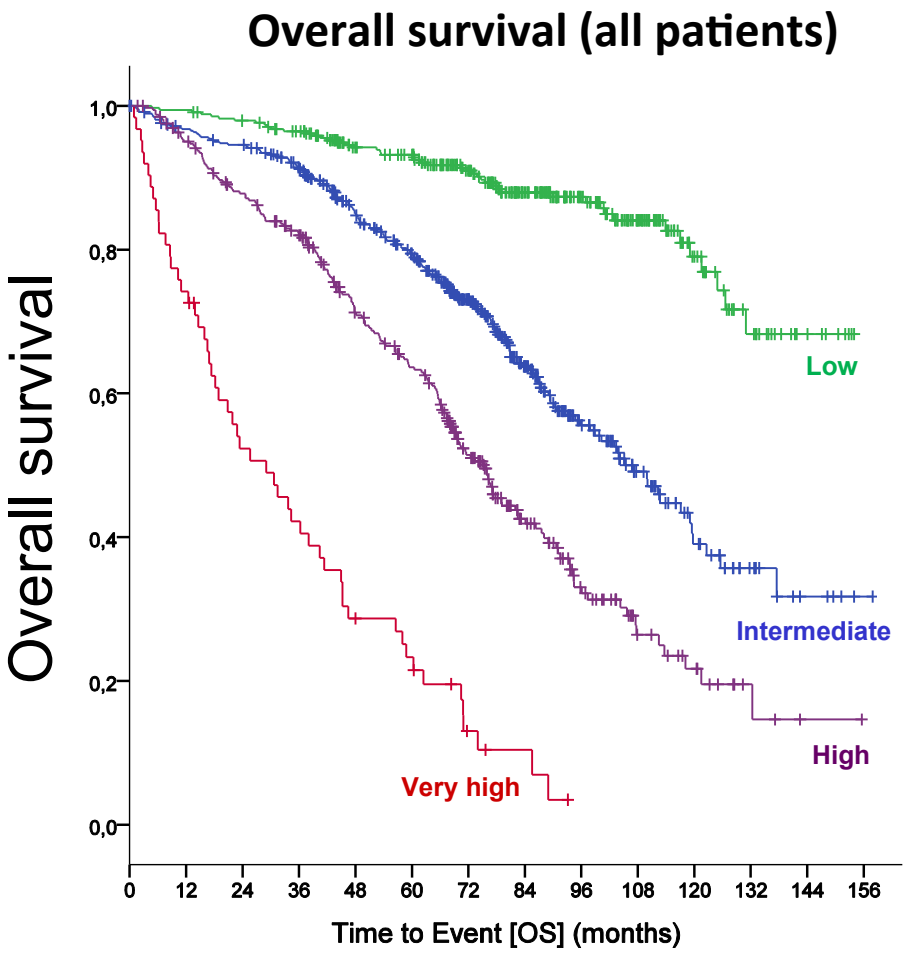
	N	10-year OS	10-year relative OS	Terated at 10 tears
del13q	26%	69%	84%	41%
Normal/+12	40%	57%	70%	50%
NOTCH1 M/*SF3B1* M/del11q	17%	37%	48%	83%
TP53 DIS/*BIRC3* DIS	17%	29%	37%	100%

Rossi et al, Blood 2013

CLL-IPI

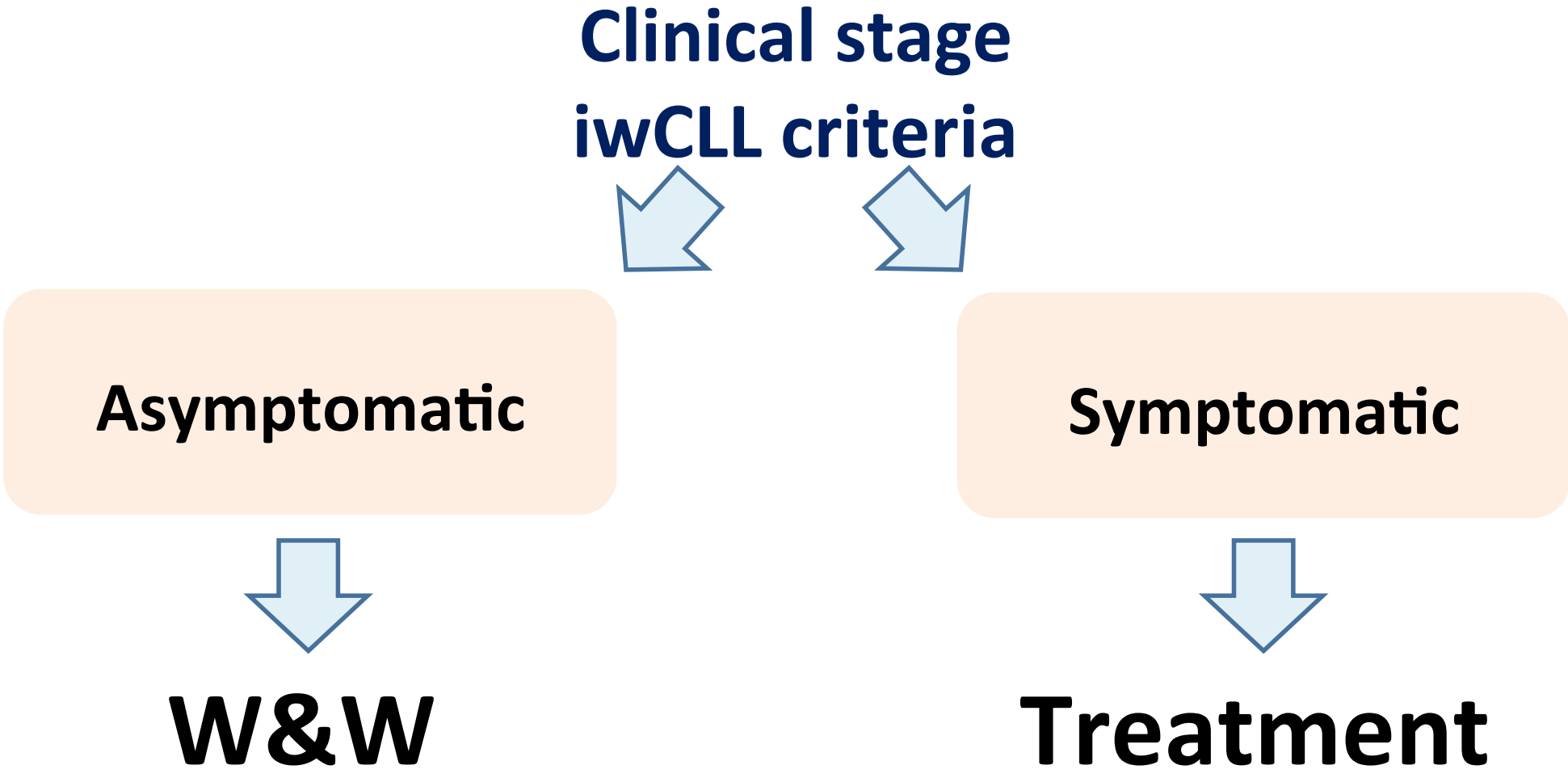
Variable	Adverse factor	Coeff.	HR	Grading
***TP53* (17p)**	deleted and/or mutated	**1.442**	**4.2**	**4**
***IGHV* status**	Unmutated	**0.941**	**2.6**	**2**
B2M, mg/L	> 3.5	**0.665**	**2.0**	**2**
Clinical stage	Binet B/C **or** Rai I-IV	**0.499**	**1.6**	**1**
Age	> 65 years	**0.555**	**1.7**	**1**
Prognostic Score				**0 – 10**

Risk group	Score	Patients N (%)	5-year OS, %
Low	**0 – 1**	340 (29)	93.2
Intermediate	**2 – 3**	464 (39)	79.4
High	**4 – 6**	326 (27)	63.6
Very High	**7 – 10**	62 (5)	23.3



International CLL-IPI working group. Lancet Oncol 2016

Clinical applications of biomarkers in CLL

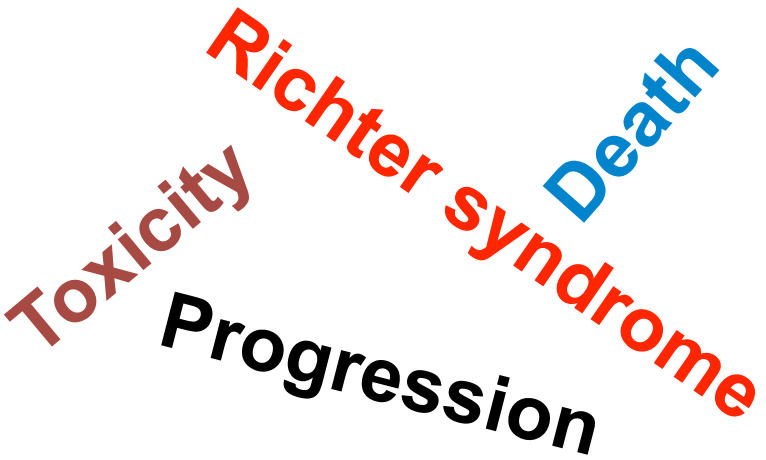


Hallek iwCLL 2017

Clinical applications of predictive and prognostic biomarkers in CLL

Predictive biomarkers

Prognostic biomarkers



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CLL subgroups

- Newly presented pts
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Outline

- **Predictive biomarkes in the 1st line setting**
  - **Pts fitness**
  - ***TP53***
  - ***IGHV***

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  - **Remission duration**
  - ***TP53***
  - **Histology**

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Biomarkers that identify unfit patients

MDACC	↑ myelosuppression/dose reductions in patients >60 yrs[1] ↑ early treatment discontinuations in patients ≥70 yrs[2]
CLL8	↑ hematological toxicity in patients ≥65 yrs[3] ↑ adverse events in pts with increased CIRS[4]
CLL10	↑ infections in patients >65 yrs[5]
REACH	↑ adverse events in patients with decreased CrCl[6]

[1]Keating et al. J Clin Oncol. 2005; [2]T Ferrajoli A, et al. Leuk Lymphoma. 2005: S86; [3]Hallek et al. Lancet. 2010 ; [4]Goede et al. Haematologica (EHA meeting abstracts). 2012; [5]Eichhorst et al. Blood. 2014 (ASH meeting abstracts) ; [6]Robak et al. J Clin Oncol. 2010

SIOG recommendation for the identification of pts **less fit for FCR**:

- Older age (e.g. **≥65 years**)
- Higher comorbidity burden (e.g. **CIRS >6**)
- Impaired renal function (e.g. **CrCl <70 mL/min**)

Stauder R et al. Ann Oncol 2017 28: 218-227

CrCl, creatinine clearance
CIRS, cumulative illness rating scale

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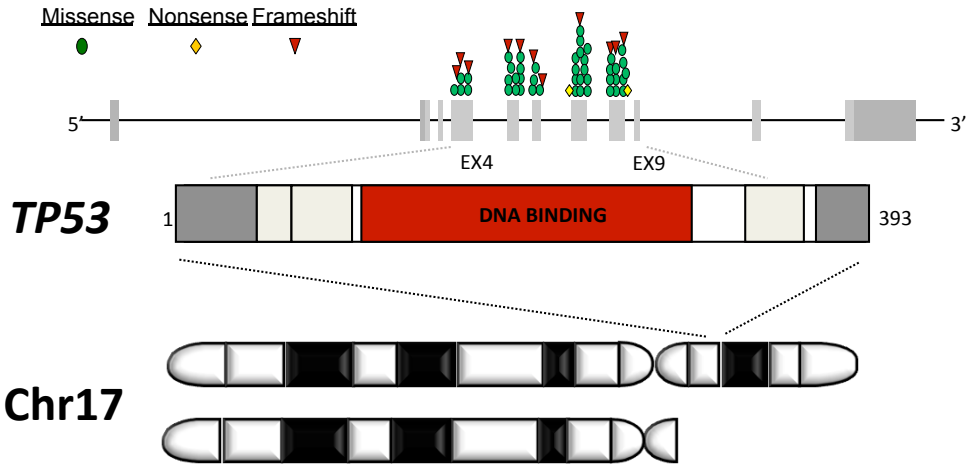
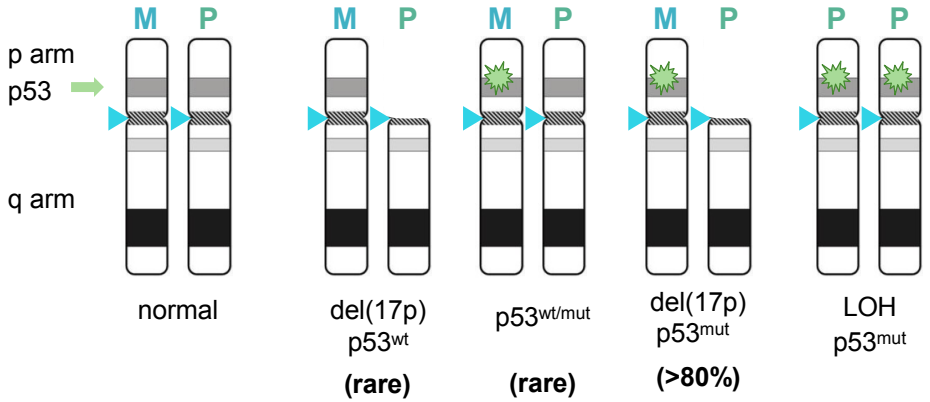
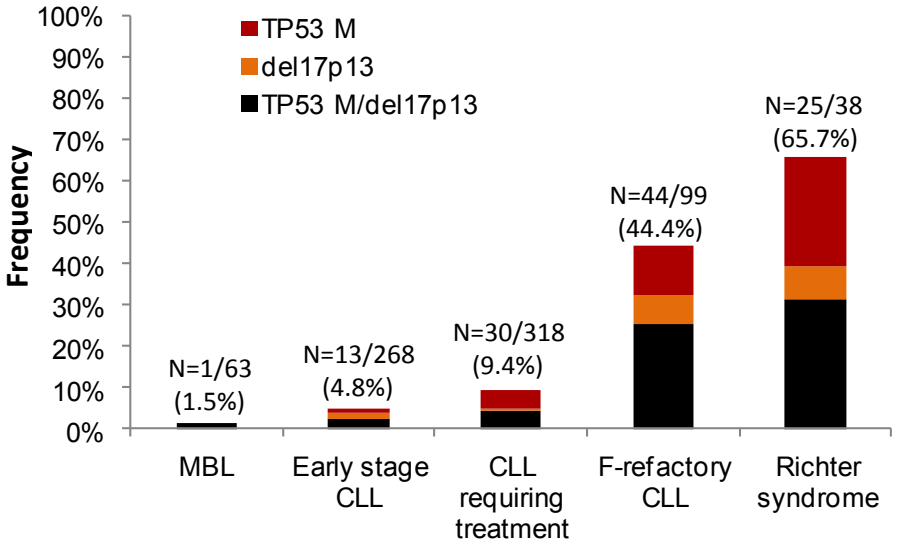
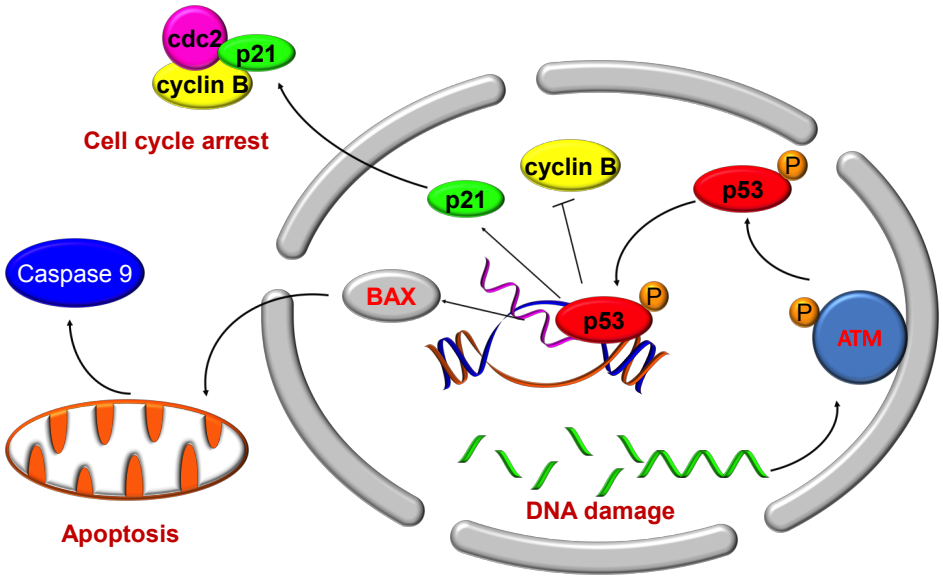
TP53 abnormalities in CLL







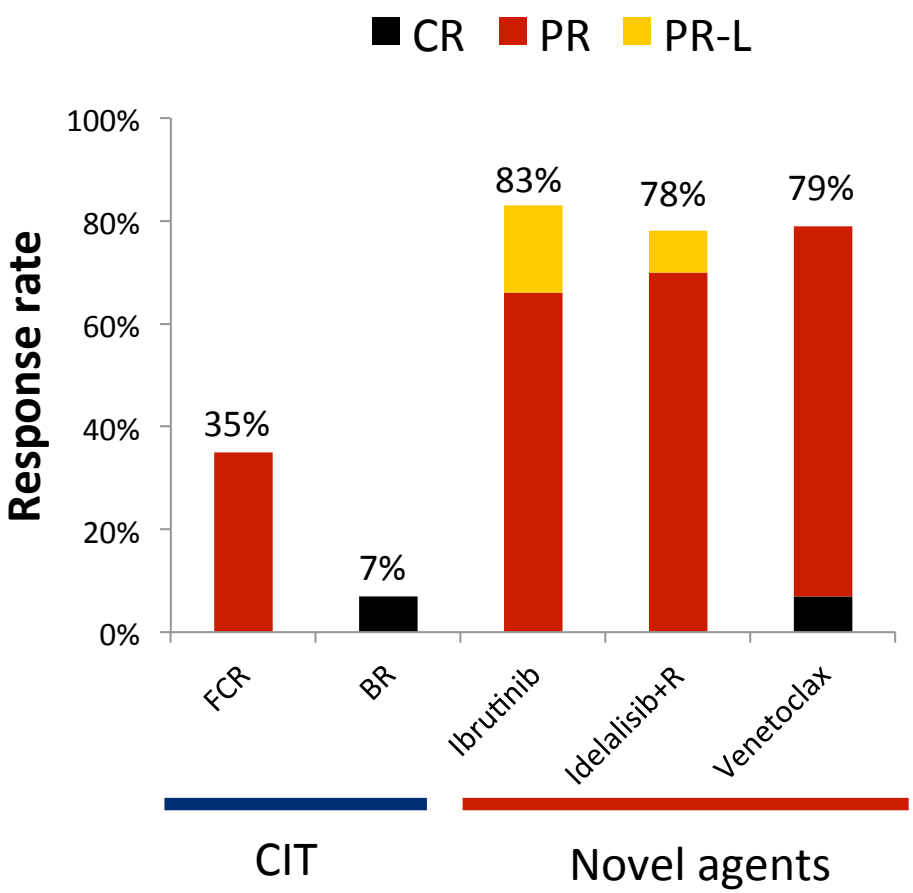


Dohner et al, New Engl J Med 2000 ; Rasi et al, Haematologica 2012; Zainuddin et al, Leuk Res 2011; Zenz et al J Clin Oncol 2010;Rossi et al Blood 2011; Rossi et al Blood 2014

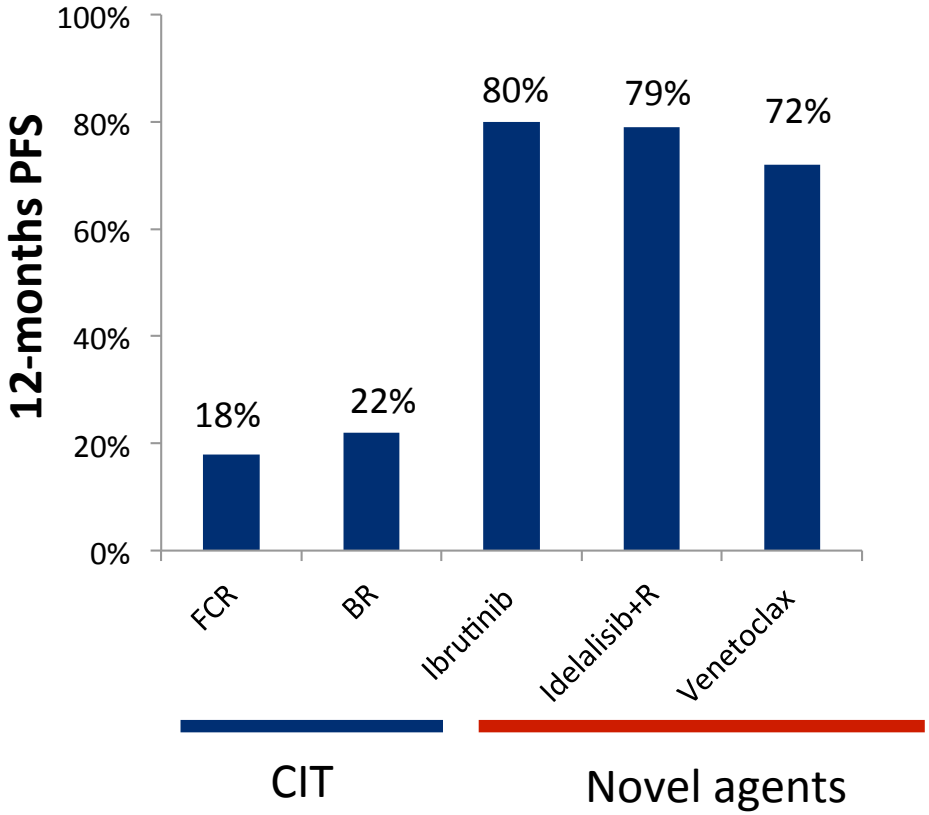
Chemoimmunotherapy (CIT) vs novel agents in *TP53* disrupted CLL ‡

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

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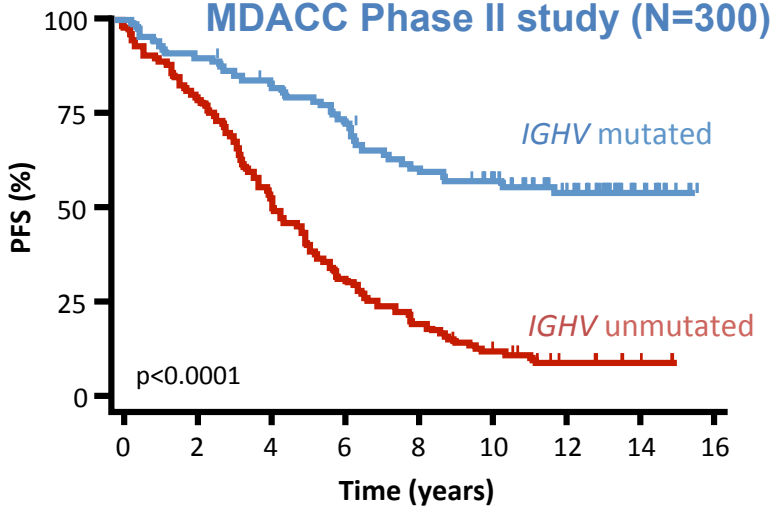
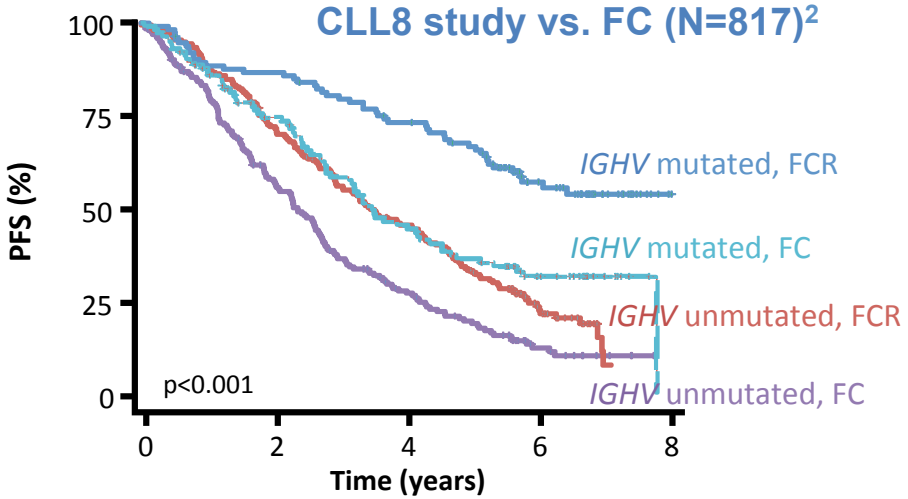
IGHV mutated patients gain the greatest benefit from FCR

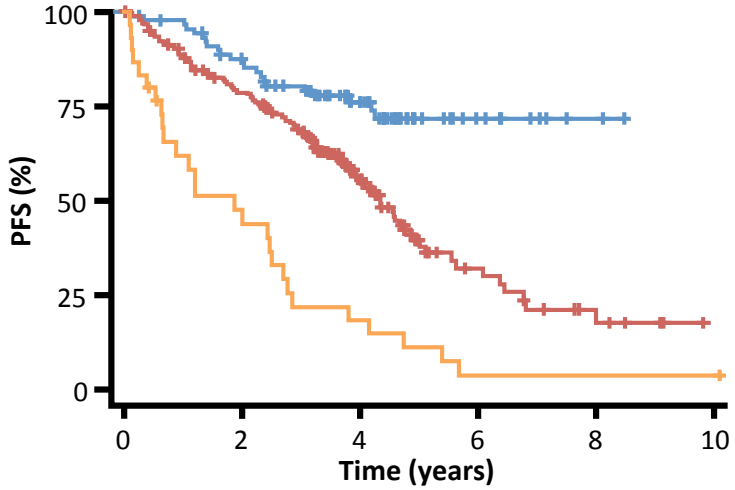
MDACC Phase II study (N=300)[1]



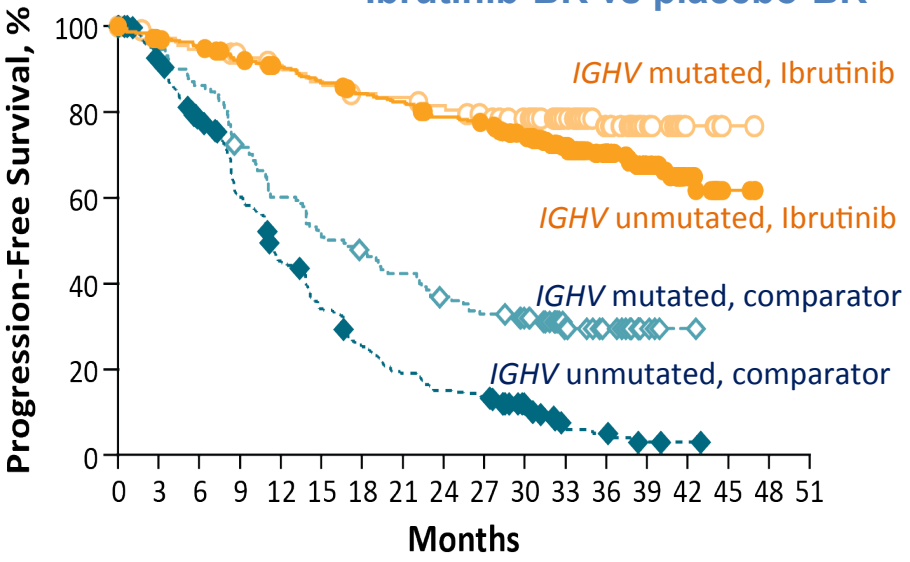
CLL8 study vs. FC (N=817)[2]



Italian retrospective analysis (N=404)[3]

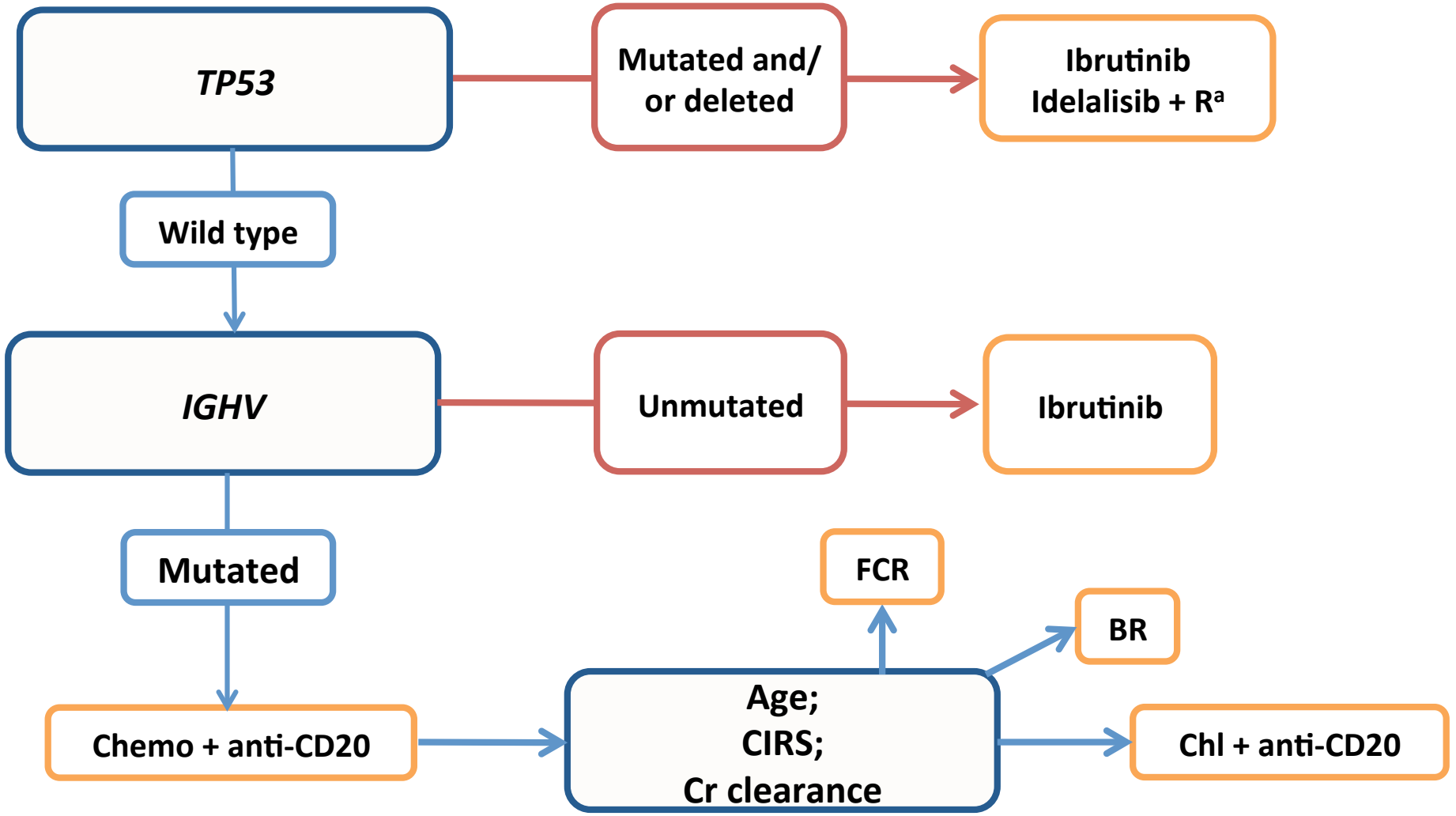


ibrutinib vs ofatumomab
ibrutinib vs chrlorambucil
Ibrutinib-BR vs placebo-BR[4]



1. Thompson PA, *et al. Blood* 2016; 127:303–309. 2. Fischer K, *et al. Blood* 2016; 127:208–215. 3. Rossi D *et al. Blood* 2015; 126 1921–1924, 4. Kipps T et al. ICML14

Can first line treatment be informed by biomarkers?



[a] In patients who are not eligible for any other therapies
Chl: chlorambucil; CIRS: Cumulative Illness Rating Scale; Cr: creatinine

Personal communication.

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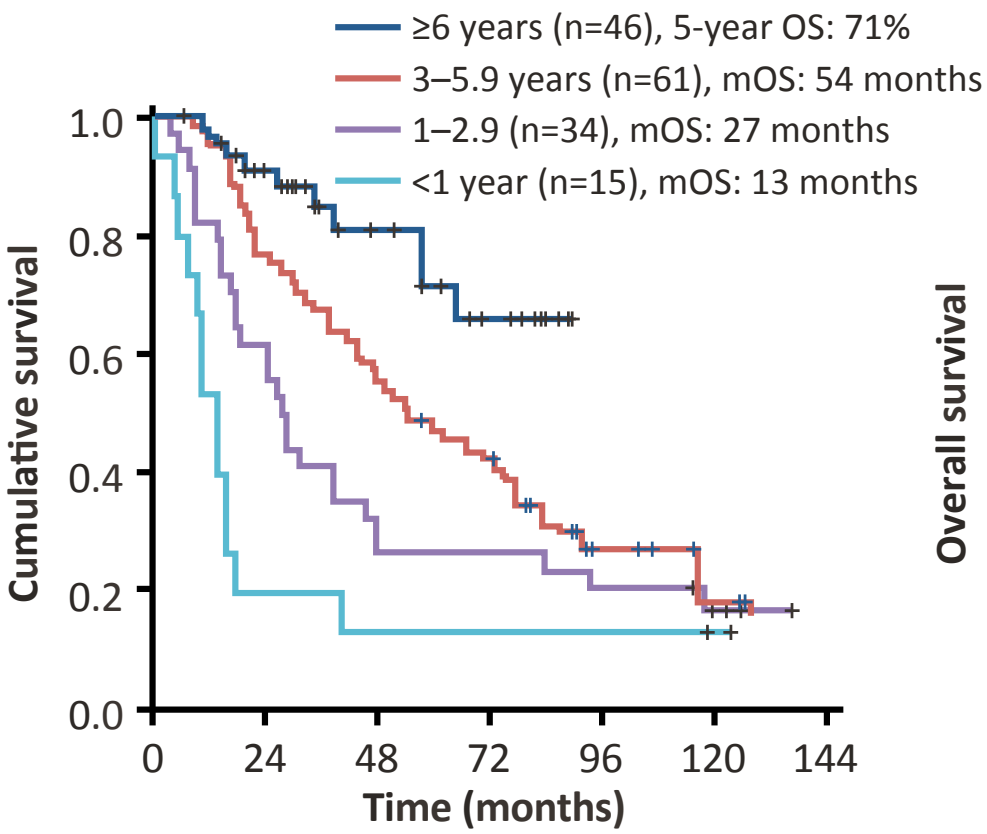
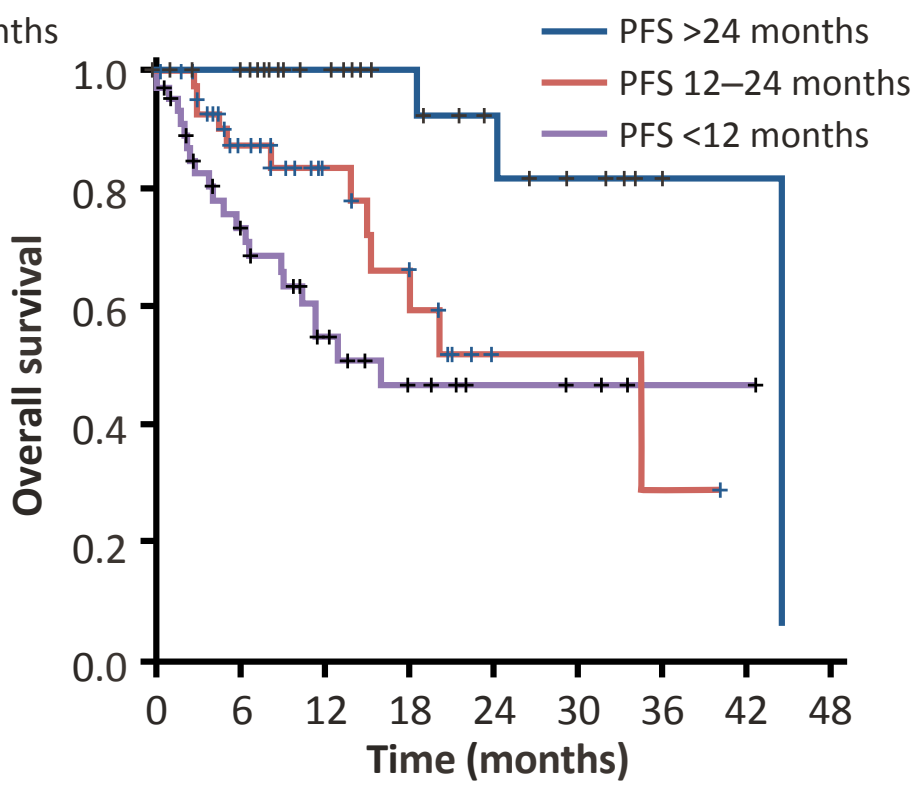
Late relapse after first-line chemoimmunotherapy supports maintained sensitivity

Survival after first salvage after FCR first-line failure: MDACC data[1]



36-month cutoff

Survival after first salvage after FC/FCR first-line failure: CLL8 data[2]



24-month cutoff

FC, fludarabine + cyclophosphamide; FCR, FC + rituximab;
MDACC, MD Anderson Cancer Center.

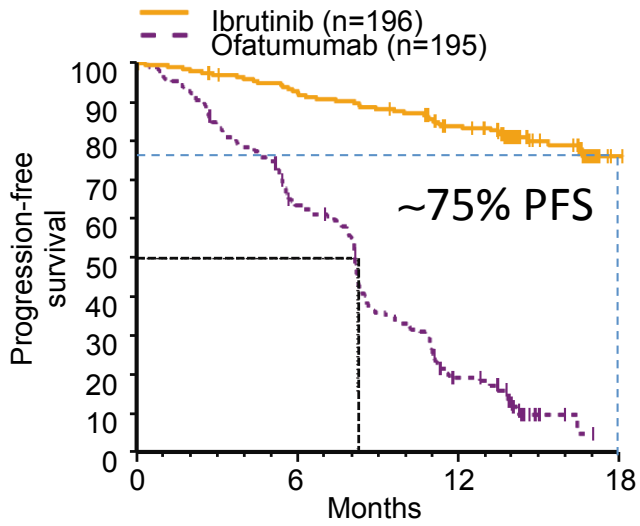
1. Tam CS, *et al. Blood* 2014; **124:**3059–3064;
2. Stilgenbauer S and Zenz T. *Hematology Am Soc Hematol Educ Program* 2010;**2010:**481–488

Salvage treatment in CLL not suitable for chemoimmunotherapy

Ibrutinib (RESONATE)

R/R CLL
Not suitable for F-based Tx
- PFS <36 mo
- del17p

ORR: 63%

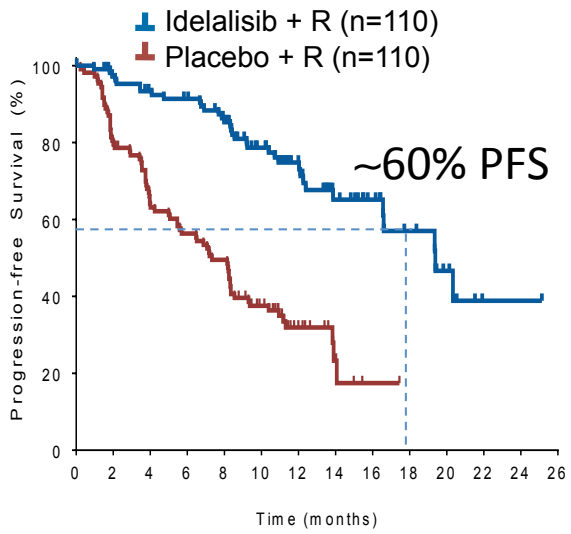


Byrd JC et al. New Engl J Med 2014 371:213-2

Idelalisib-R (116)

R/R CLL
Not suitable for cytotoxic Tx:
- PFS <24 mo

ORR: 81%

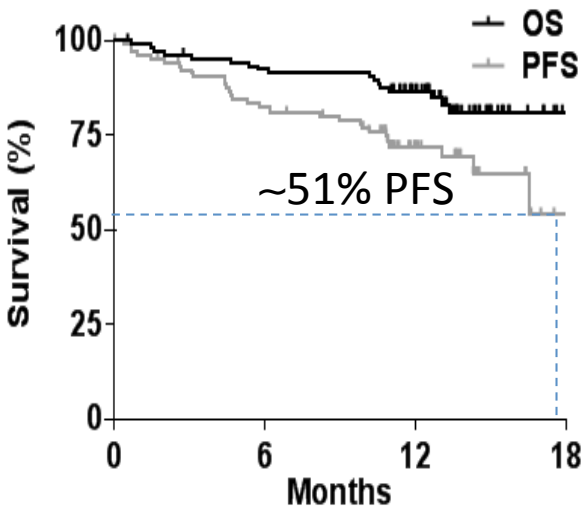


Furman R et al. New Engl J Med 2014 370:997-1007

Venetoclax M13-982

R/R CLL
Not suitable for cytotoxic Tx:
- del17p

ORR: 79%



Stilgenbauer S et al. Lancet Oncol 2016;17:768-78

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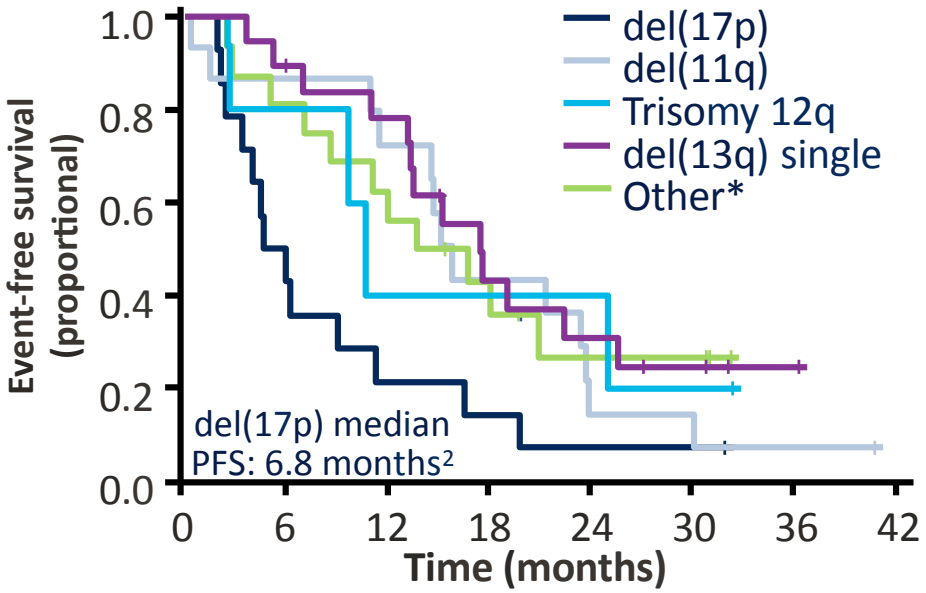
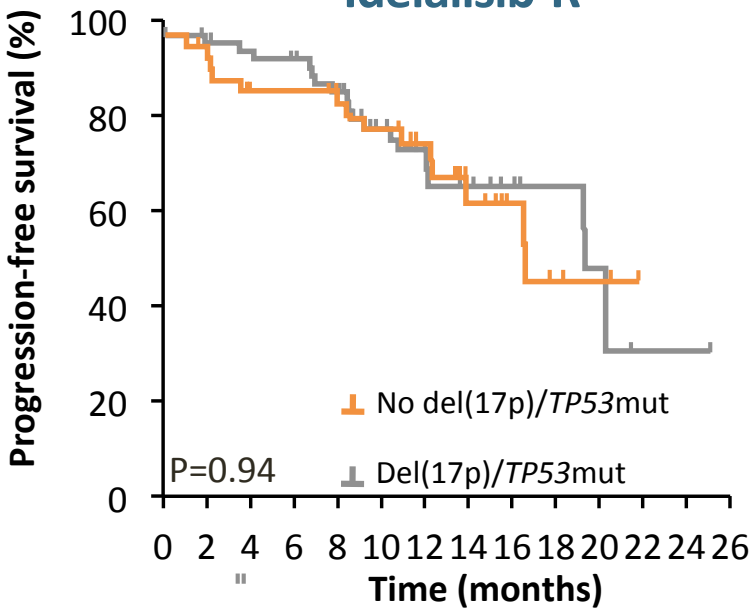
Event-free survival in relapsed *TP53* disrupted patients

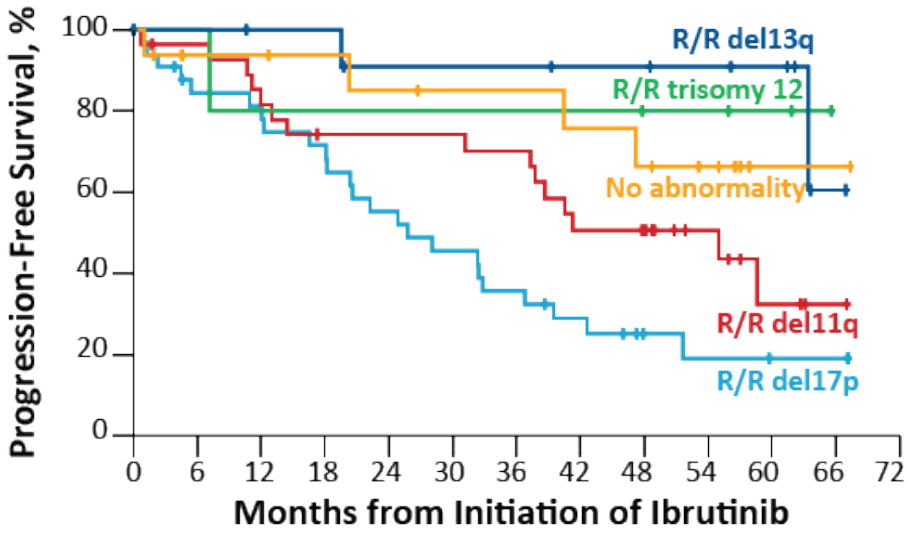
Bendamustine -R



Idelalisib-R



Ibrutinib



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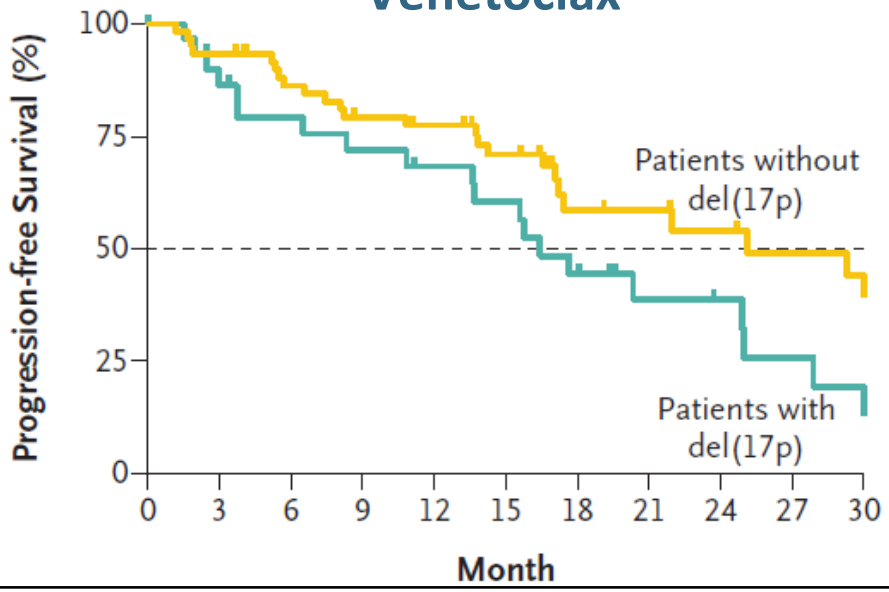
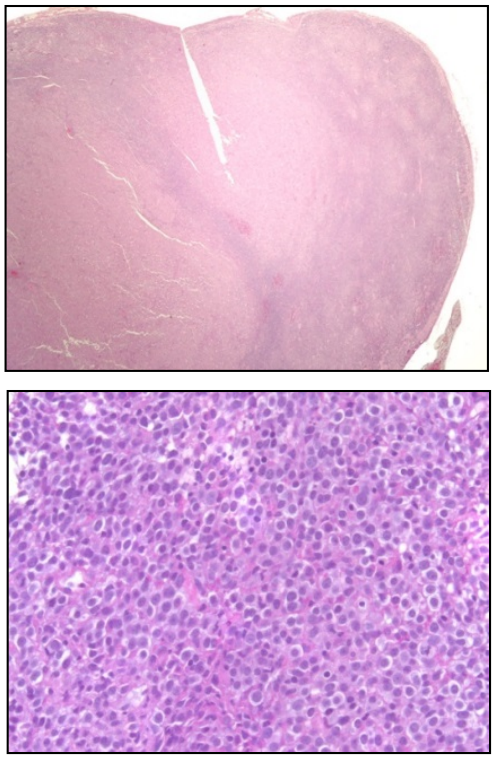
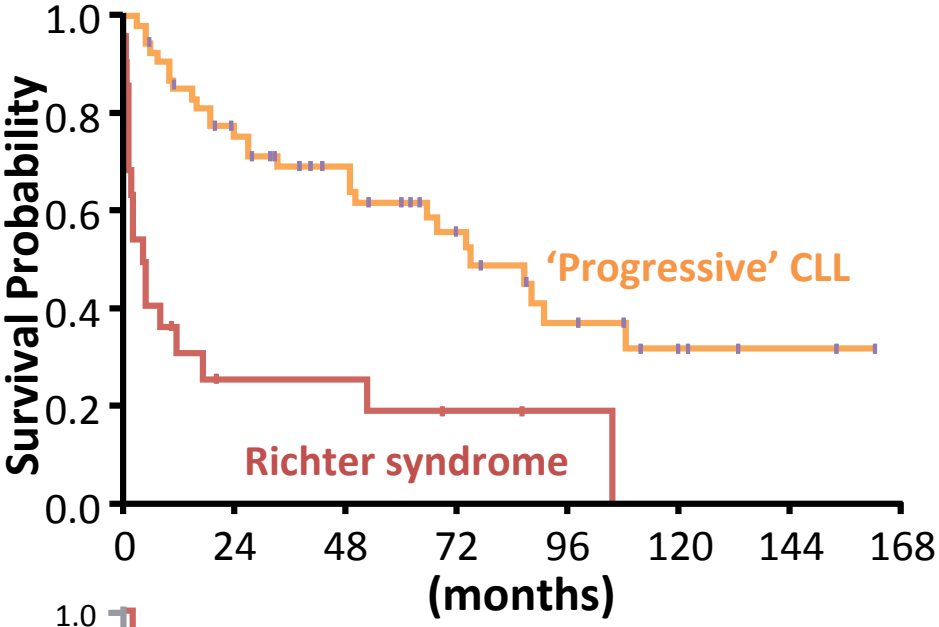
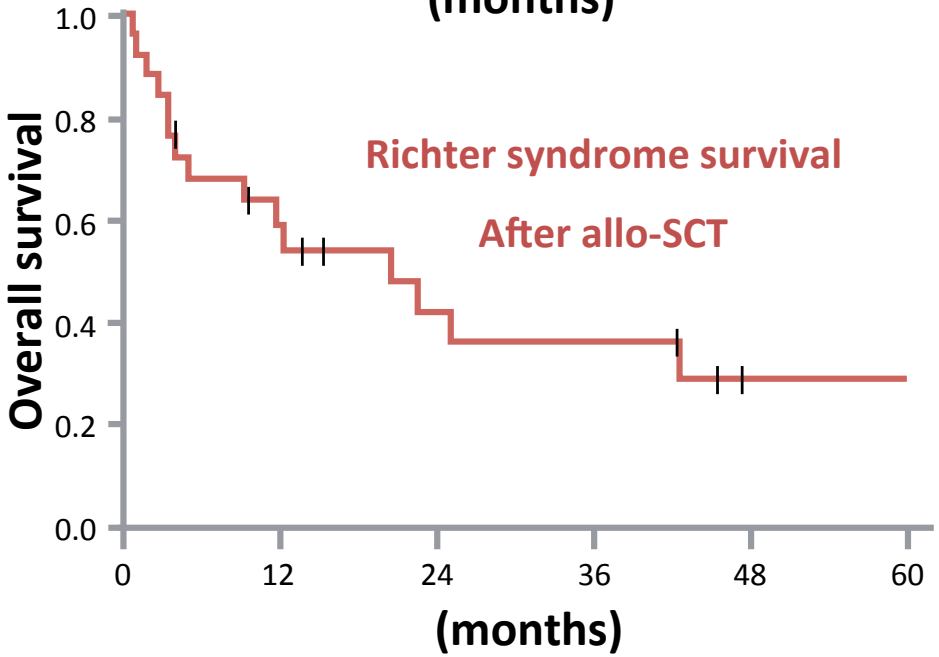


Histology of progressed CLL

Richter's syndrome
DLBCL variant



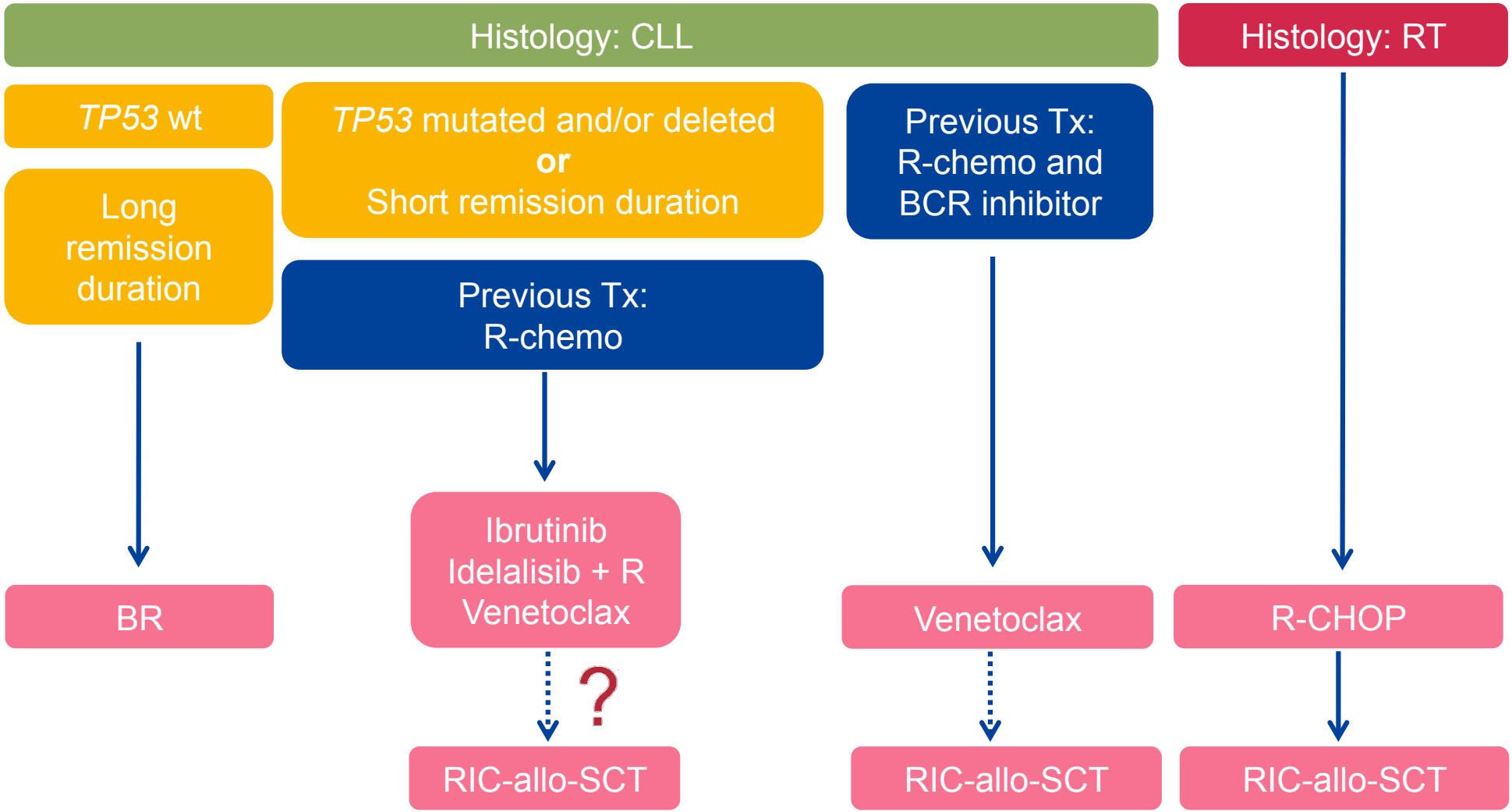




Cwynarski K, *et al. J Clin Oncol* 2012; **30:** 2211–2217.

Ginè E, *et al. Haematologica* 2010; **95:**1526–1533.

Can treatment of R/R CLL be informed by biomarkers?



BCR: B-cell receptor; R-chemo: rituximab chemotherapy; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; RIC-allo-SCT: reduced-intensity conditioning allogeneic stem cell transplant; RT: Richter transformation

Personal communication.

IOR Institute of Oncology Research

Experimental Hematology
Alessio Bruscaggin
Claudia Cirillo
Adalgisa Condoluci
Gabriela Forestieri
Francesca Guidetti
Lodovico Terzi di Bergamo
Valeria Spina

Lymphoma & Genomics
Francesco Bertoni

Franco Cavalli

OSI

Lymphoma Unit
Bernhard Gerber
Alden Moccia
Anastasios Stathis
Georg Stüssi
Emanuele Zucca

Nuclear Medicine
Luca Ceriani

Michele Ghielmini

UPO Università del Piemonte Orientale

Clara Deambrogi
Lorenzo De Paoli
Fary Diop

Gianluca Gaidano

Sapienza Università di Roma

Ilaria Del Giudice
Monica Messina
Anna Guarini

Robin Foà

FNSNF Swiss National Science Foundation

krebsliga schweiz Gemeinsam gegen Krebs

Fondation Nelia et Amadeo Barletta — Individualiser le traitement du cancer | Personalizing cancer treatment

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SAVE THE DATE: June 18-22, 2019