IOR
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Predictive biomarkers

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Conflict of interest

Research Support:	Gilead, Abbvie, Janssen, Cellestia, Xeneticbio
Employee	No
Consultant	No
Major Stockholder	No
Speakers Bureau	No
Honoraria	Gilead, Abbvie, Janssen, Roche, AstraZeneca, Loxo
Scientific Advisory Board	Gilead, Abbvie, Janssen, AstraZeneca, MSD, Loxo

CLL subgroups

- **Pts with lymphocytosis**
- **Newly presented pts**
- **In need of treatment pts**

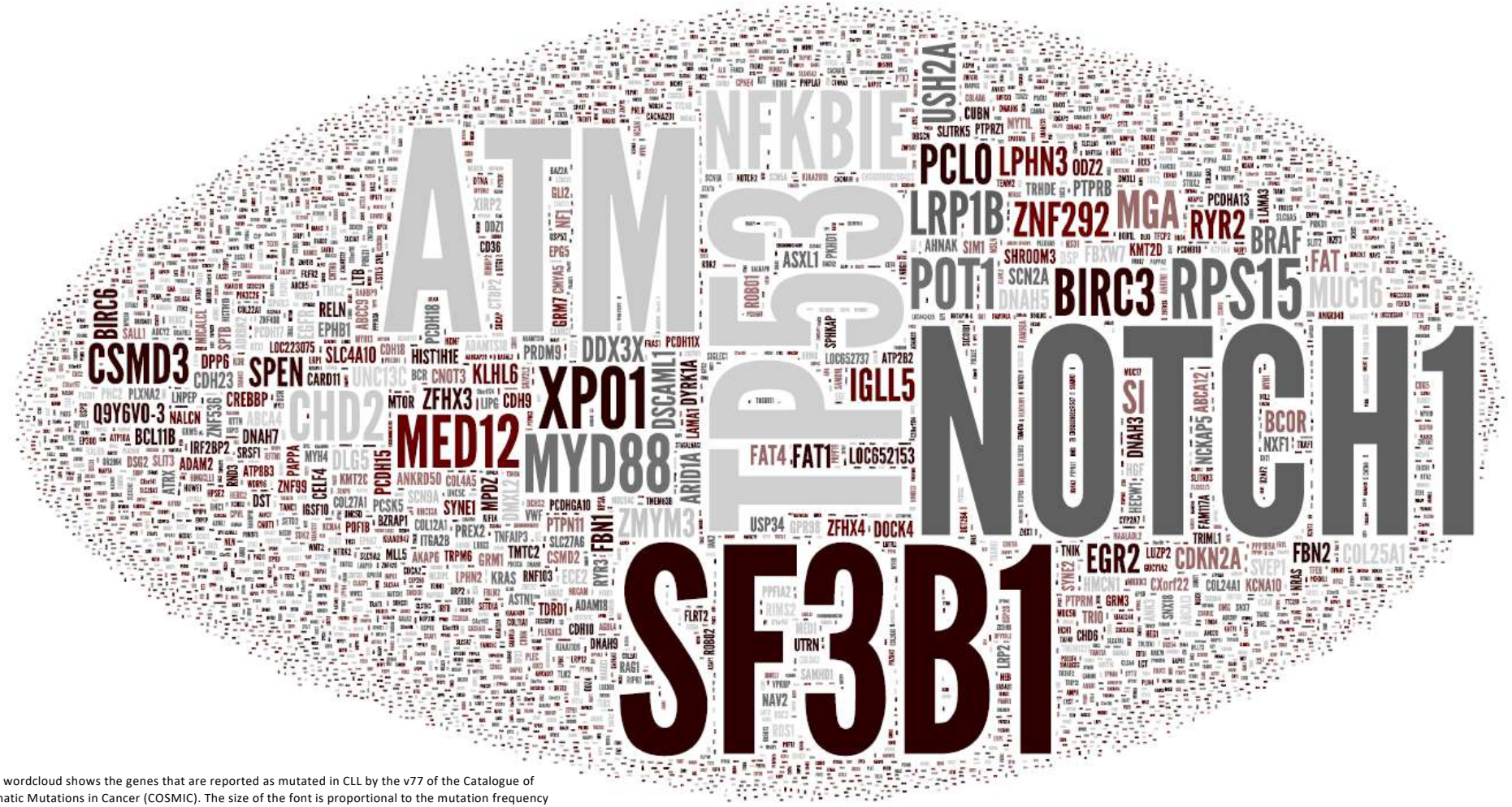
Establishing diagnosis

Diagnostic test	General practice
Tests to establish the diagnosis	
CBC and differential count	Always
Immunophenotyping of peripheral blood lymphocytes • A panel of CD19, CD5, CD20, CD23, CD23, kappa and lambda is usually adequate to establish the diagnosis • Borderline cases: CD43, CD79b, CD81, CD200, CD10, or ROR1 may help refine the diagnosis	Always

CBC, complete blood counts

Hallek M, et al. *Blood* 2018;131(25):2745–2760.

The mutational landscape of CLL

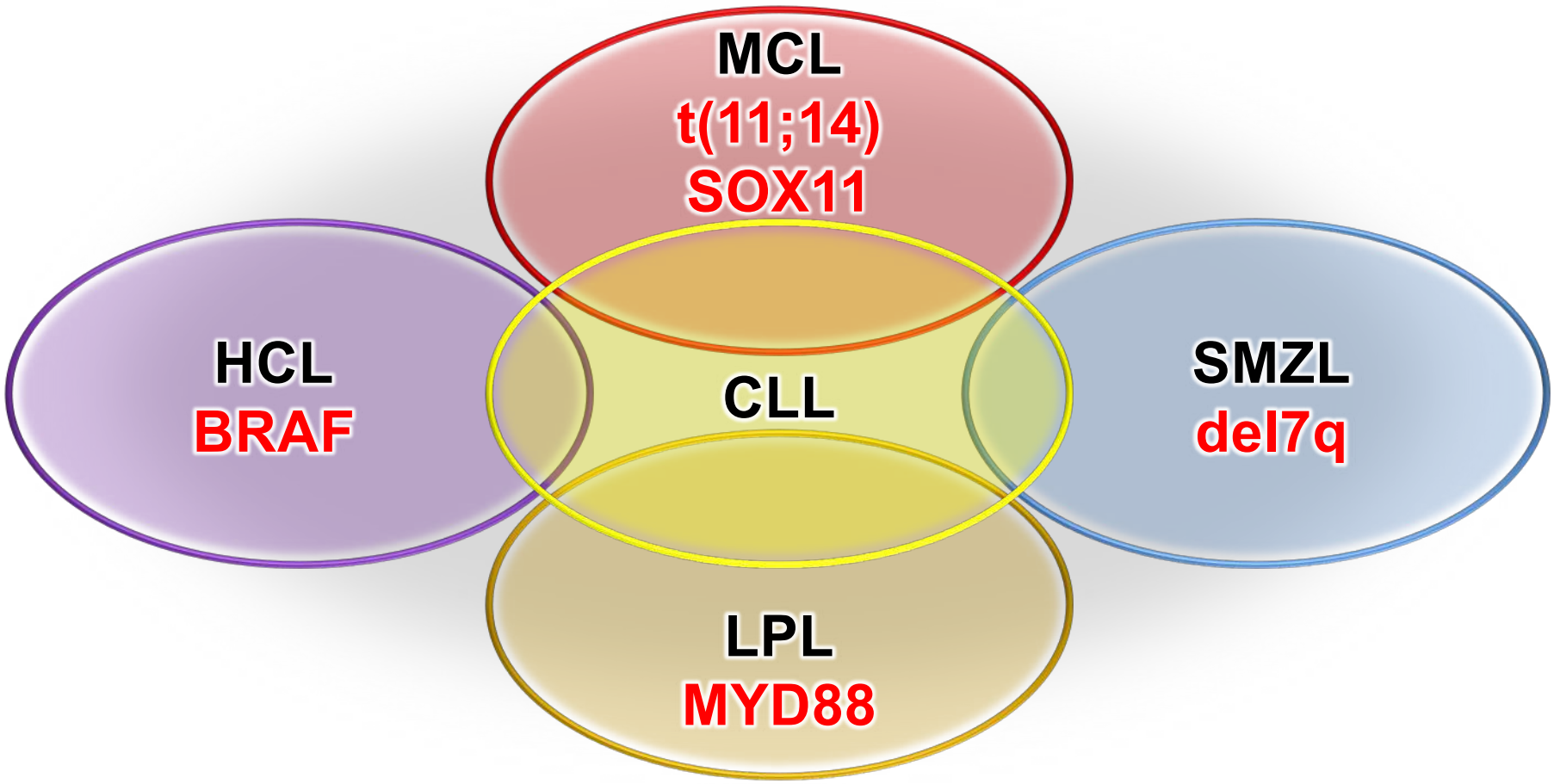


The wordcloud shows the genes that are reported as mutated in CLL by the v77 of the Catalogue of Somatic Mutations in Cancer (COSMIC). The size of the font is proportional to the mutation frequency

Fabbri, et al. J Exp Med 2011
Puente, et al. Nature 2011
Rossi, et al. Blood 2011
Wang, et al. New Engl J Med 2011
Lamdau et al. Nature 2015
Puente et al. Nature 2015

Gaidano G, Rossi D. Hematology Am Soc Hematol Educ Program. 2017 Dec 8;2017(1):329-337

Differentiating CLL from mimicking B-cell lymphoproliferative diseases



CLL, chronic lymphocytic leukaemia; **HCL**, hairy cell leukaemia; **LPL**, lymphoplasmacytic lymphoma; **MCL**, mantle cell lymphoma; **SMZL**, splenic marginal zone lymphoma.

Swerdlow SH, et al. WHO classification of tumours of haematopoietic and lymphoid tissues. In: World Health Organization Classification of Tumours. Lyon, France: IARC. 2017;
Swerdlow SH, et al. *Blood*. 2016;127(20):2375–2390.

CLL subgroups

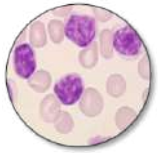
- **Pts with lymphocytosis**
- **Newly presented pts**
- **In need of treatment pts**

Patients ask advice on…

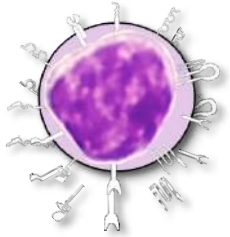
Life expectancy

Biomarker: variable that associates with disease outcome

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



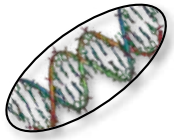
Disease Markers: ***Stage***, *lymphocyte count,* ***LDT***, *etc*



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*

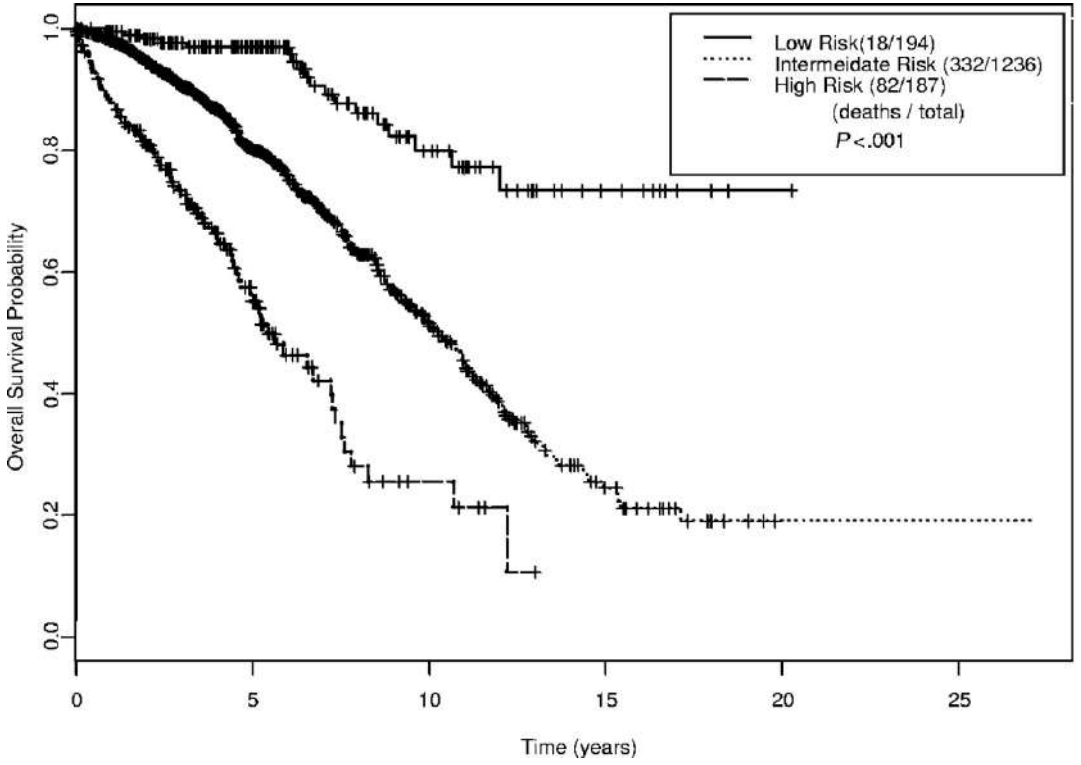


Biology Markers: ***IGVH-sequence***, *BCR-structure*

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

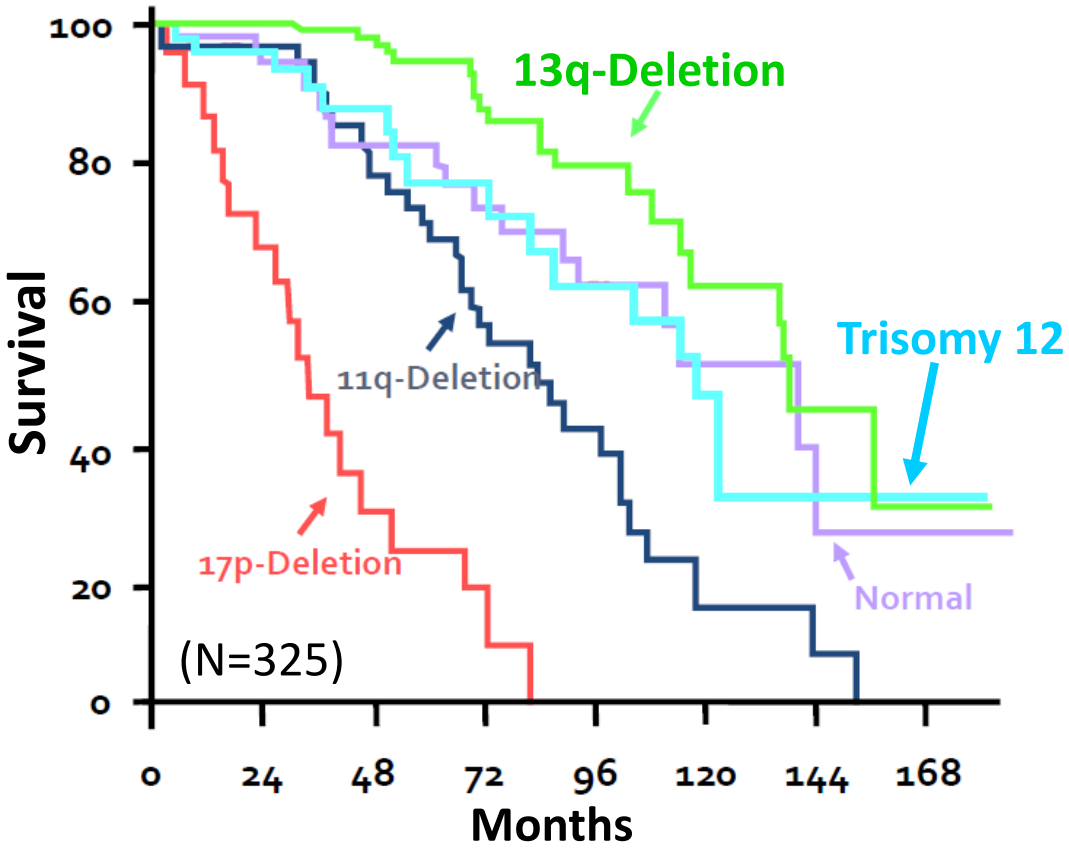
Risk group	Score	5-year survival
Low-risk	1-3	97%
Intermediate-risk	4-7	80%
High-risk	>7	55%



Wierda et al, Blood 2007

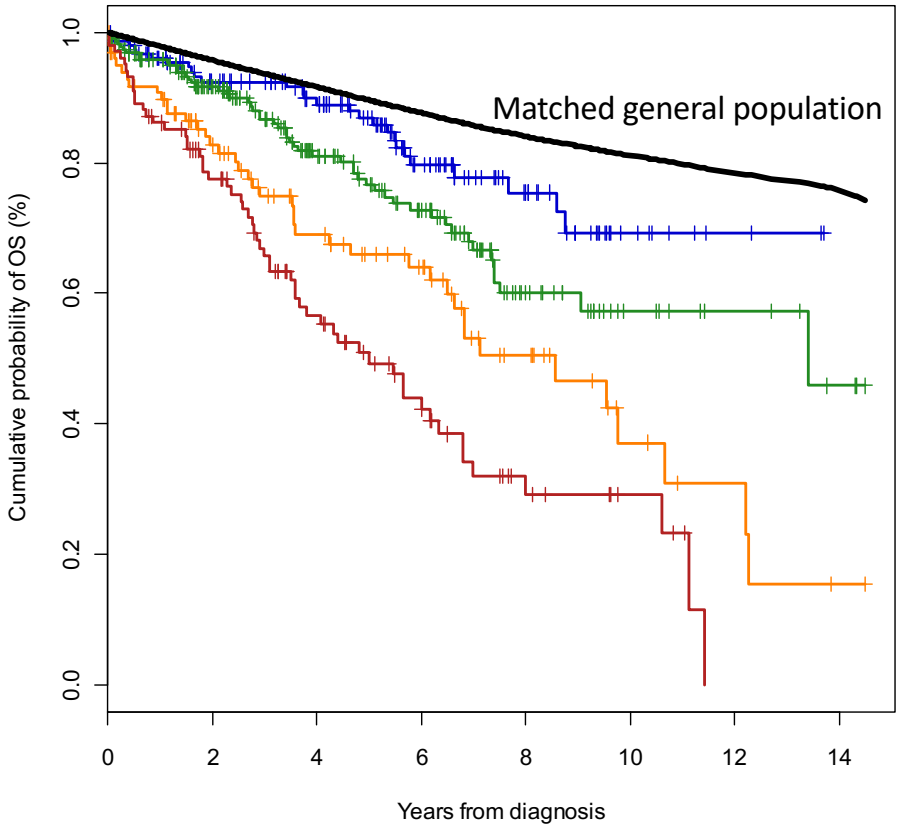
Patient counseling on survival: genetic-based models

Cytogenetic model



Döhner H, et al. N Engl J Med. 2000

Cytogenetic-mutational model



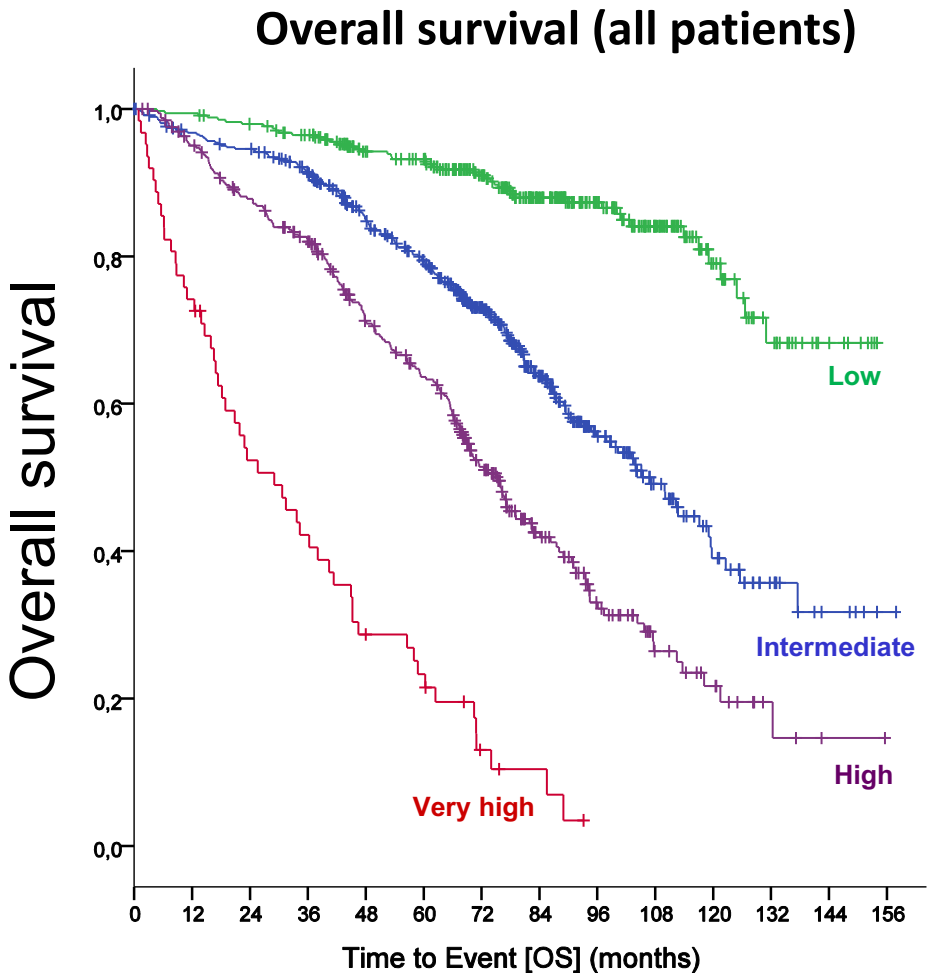
	N	10-year OS
del13q	26%	69%
Normal/+12	40%	57%
NOTCH1 M/*SF3B1* M/del11q	17%	37%
TP53 DIS/*BIRC3* DIS	17%	29%

Rossi et al, Blood 2013
Baliakas et al, Leukemia 2015

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**

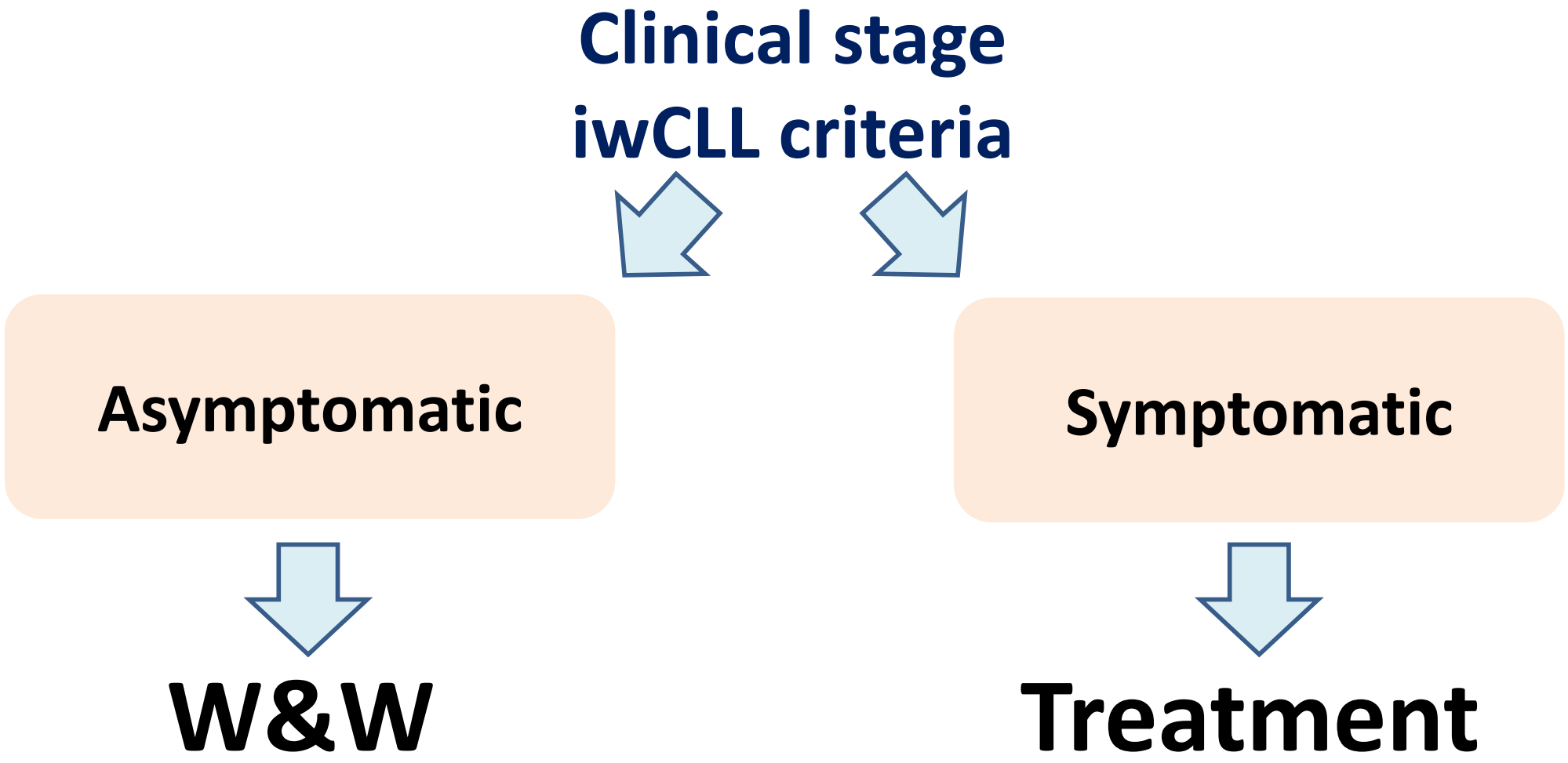
Risk group	Score	Patients N (%)	5-year OS, %
Low	**0 – 1**	340 (29)	93.2
Intermediate	**2 – 3**	464 (39)	79.4
High	**4 – 6**	326 (27)	63.6
Very High	**7 – 10**	62 (5)	23.3



International CLL-IPI working group. Lancet Oncol 2016

Treatment indication

Clinical applications of biomarkers in CLL



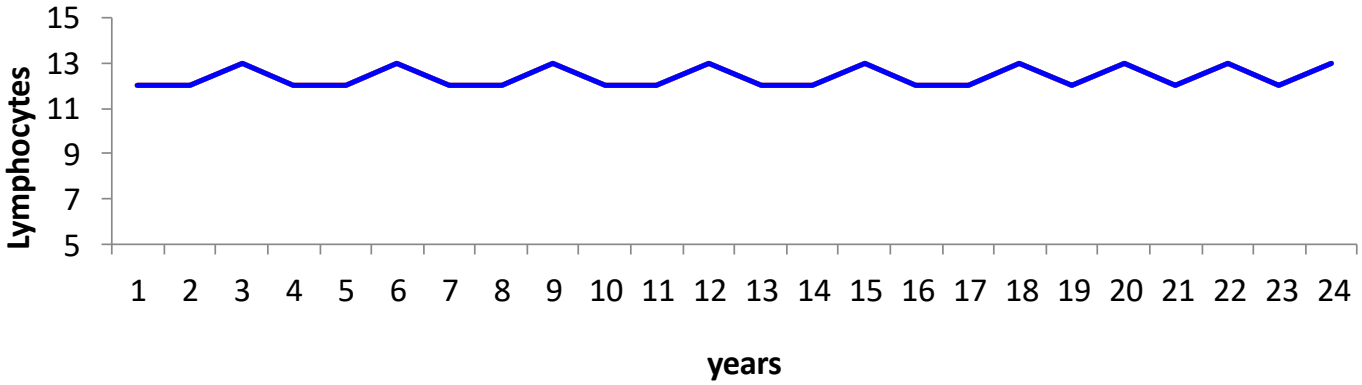
Hallek iwCLL 2017

Patients ask advice on…

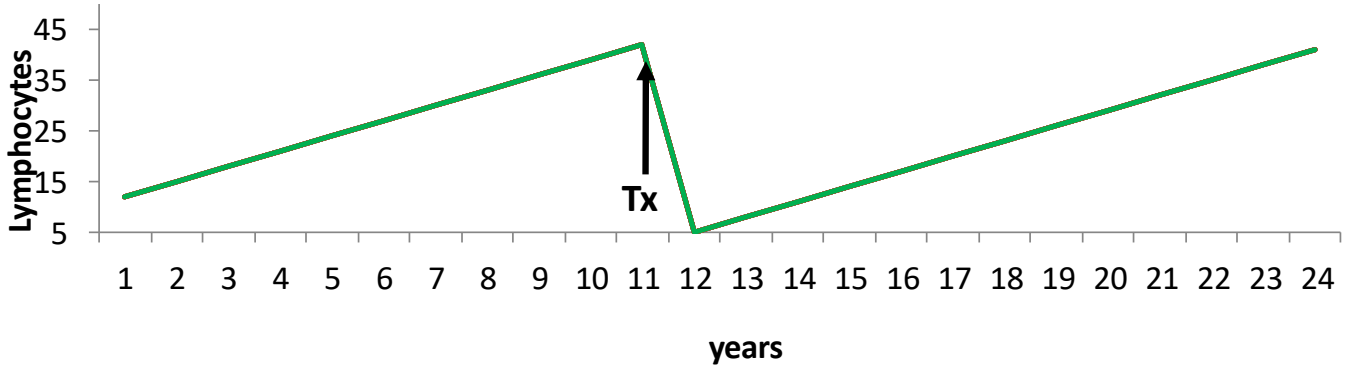
Probability of treatment need

Binet A CLL: Homogeneous phenotype but heterogeneous clinical course

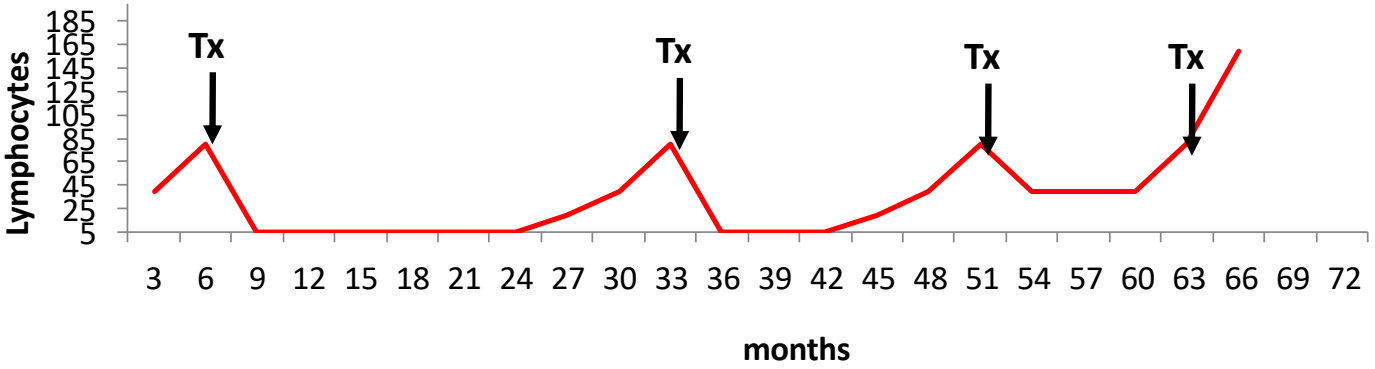
Highly stable
1/3



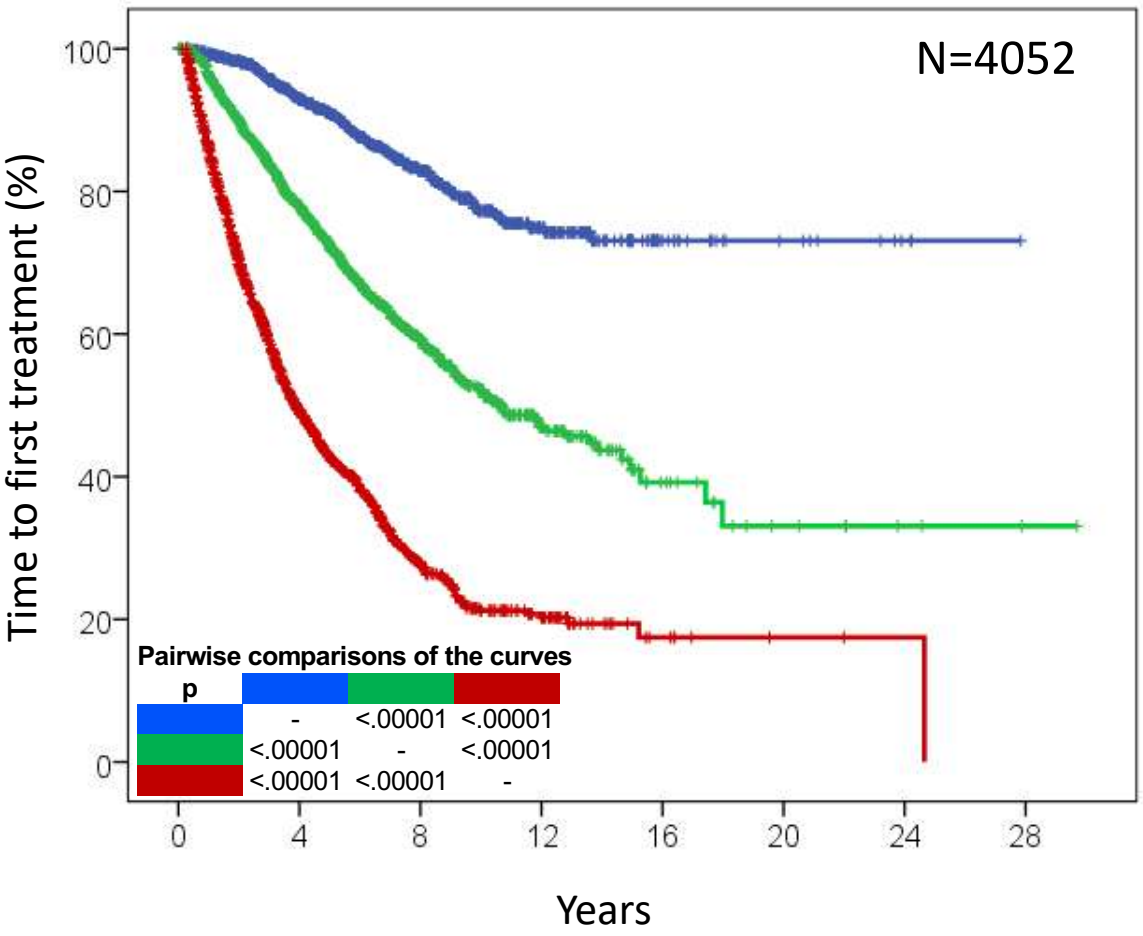
Slowly progressive
1/3



Rapidly progressive
1/3



Time to first therapy: IPS-E



Variable	Grading
IGHV unmutated	1
Lymphocytes >15x10^9/L	1
Nodal involvement	1

Risk group	Score
Low risk	0
Intermediate risk	1
High risk	2-3

Cumulative incidence of treatment

	1 year	5 years
Low risk	<1%	8%
Intermediate risk	3%	28%
High risk	14%	61%

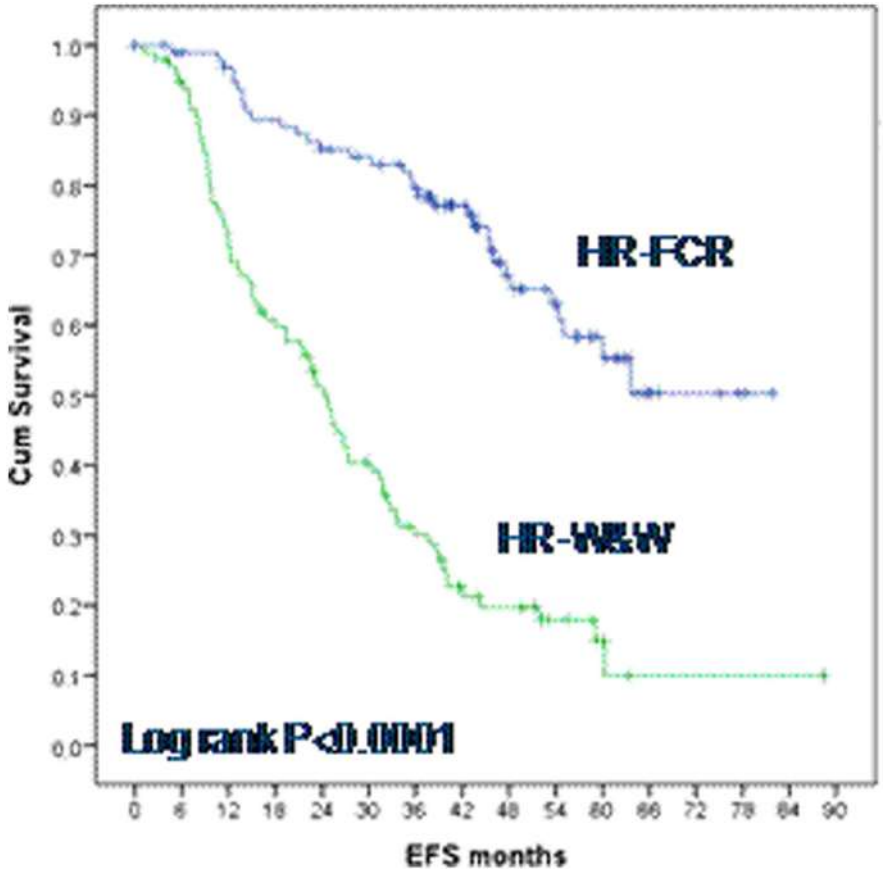
Conduluci A, et al. ICML 2019

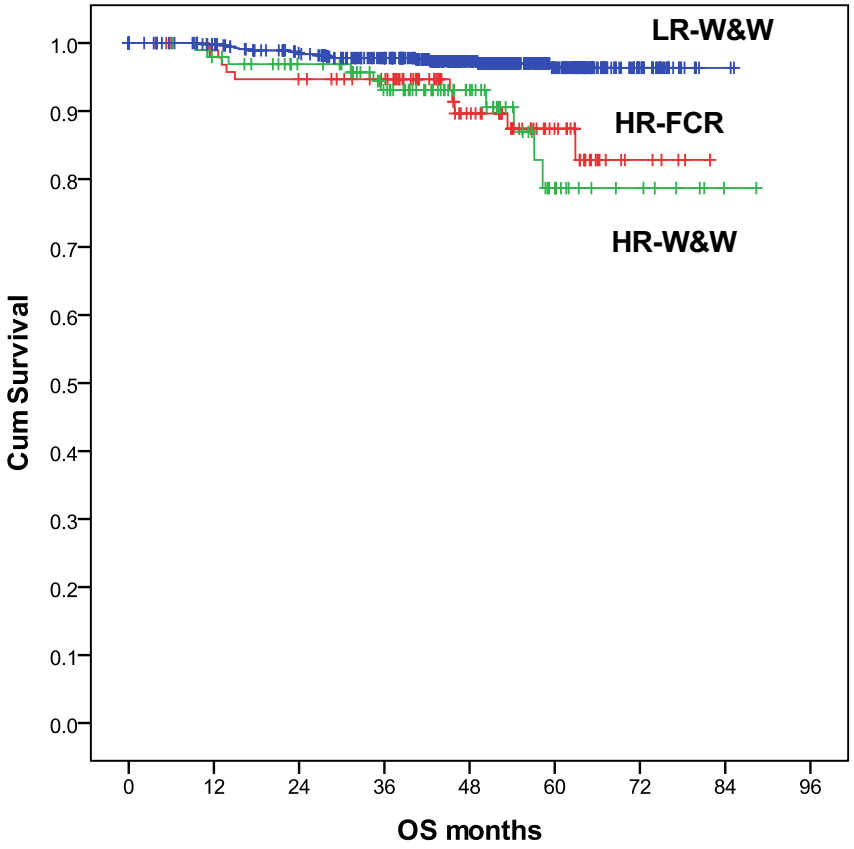
Early intervention with FCR in high risk Binet A CLL

CLL7: 800 patients

103 HR-CLL defined by genetics

- Gender
- Age
- ECOG performance status
- del(17p)
- del(11q),
- IGHV mutation status
- β2-microglobulin
- thymidine kinase



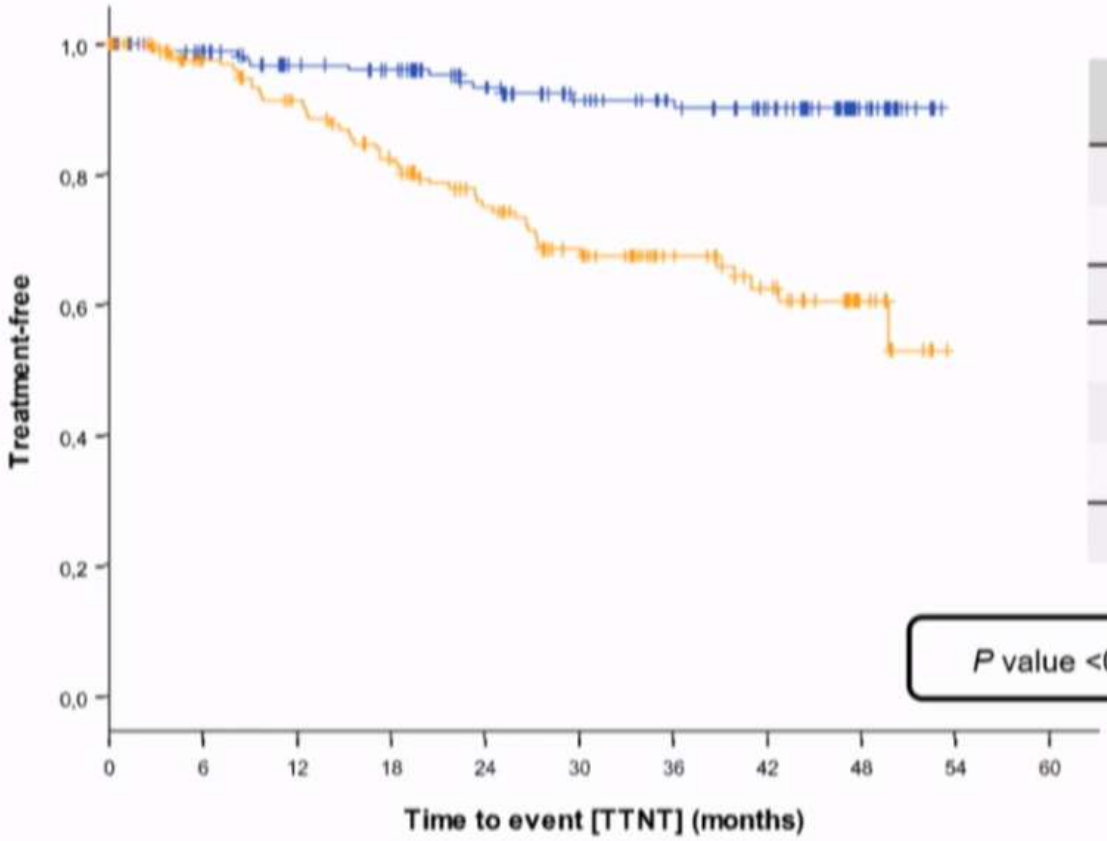


Schweighofer et al., submitted

Treating HR early stage CLL – Results from CLL12 trial

TIME TO NEXT TREATMENT

DEUTSCHE STUDIENGRUPPE



Subsequent treatment	Ibrutinib (n=15)	Placebo (n=57)
Chemoimmunotherapy	9	30
Chemotherapy	1	5
Anthracycline-based		2
Ibrutinib-based	3	13
Venetoclax-based		6
Idelalisib-based	2	
Missing		1

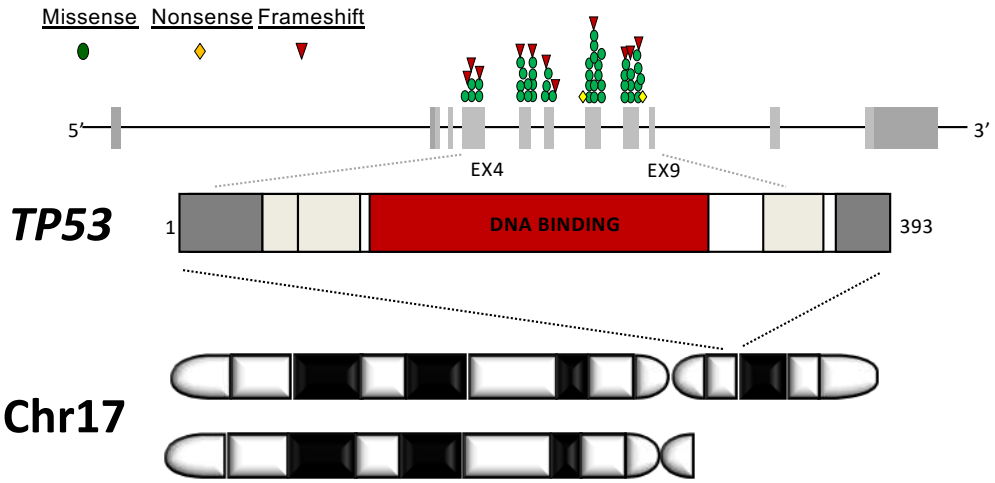
P value <0.0001, HR 0.205

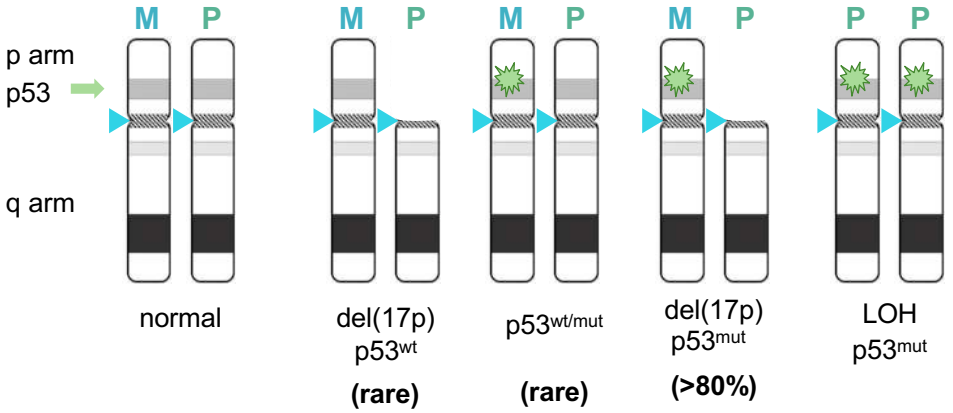
CLL subgroups

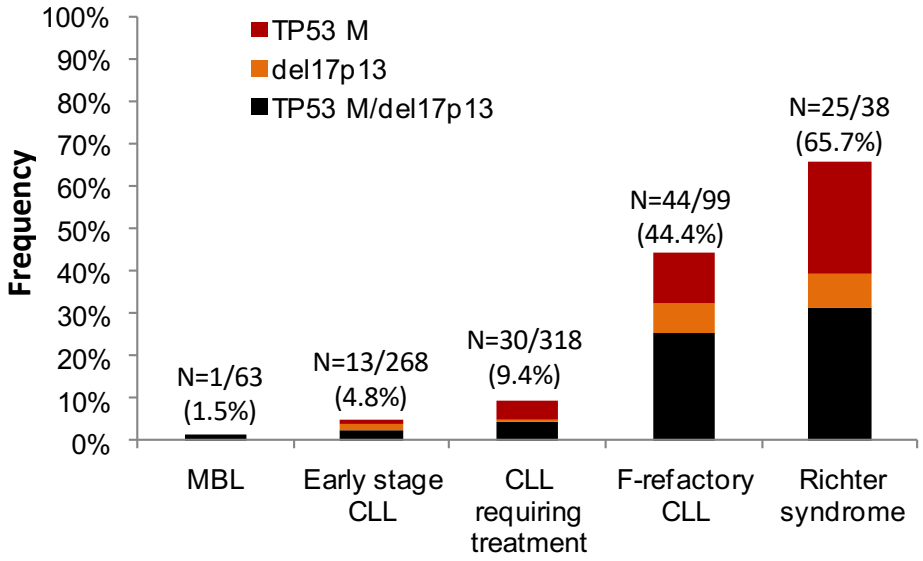
- **Pts with lymphocytosis**
- **Newly presented pts**
- **In need of treatment pts**

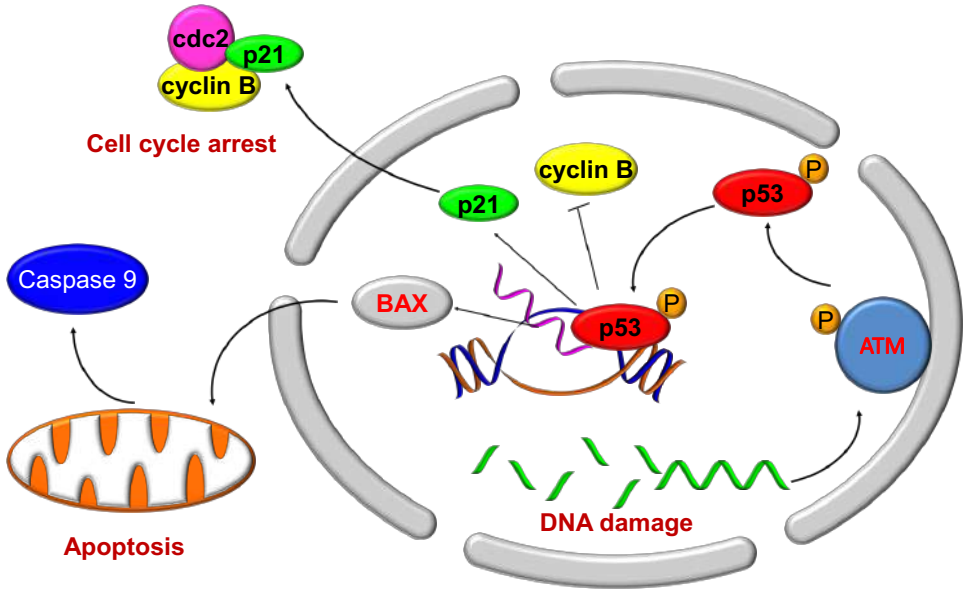
TP53 status

TP53 abnormalities in CLL



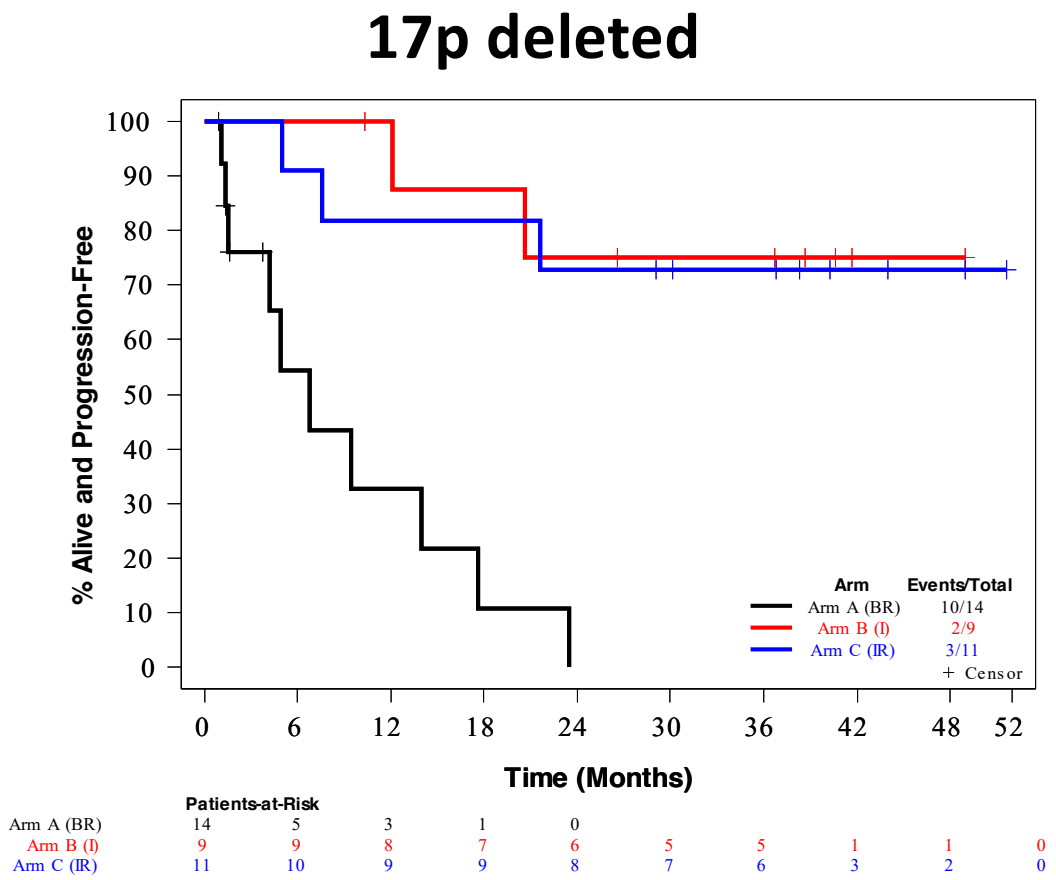






Dohner et al, New Engl J Med 2000 ; Rasi et al, Haematologica 2012; Zainuddin et al, Leuk Res 2011; Zenz et al J Clin Oncol 2010;Rossi et al Blood 2011; Rossi et al Blood 2014

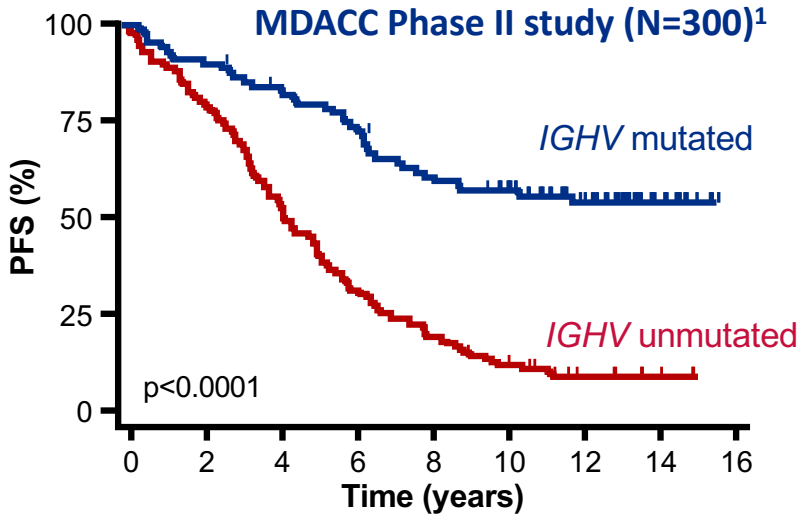
Patients with 17p deletion

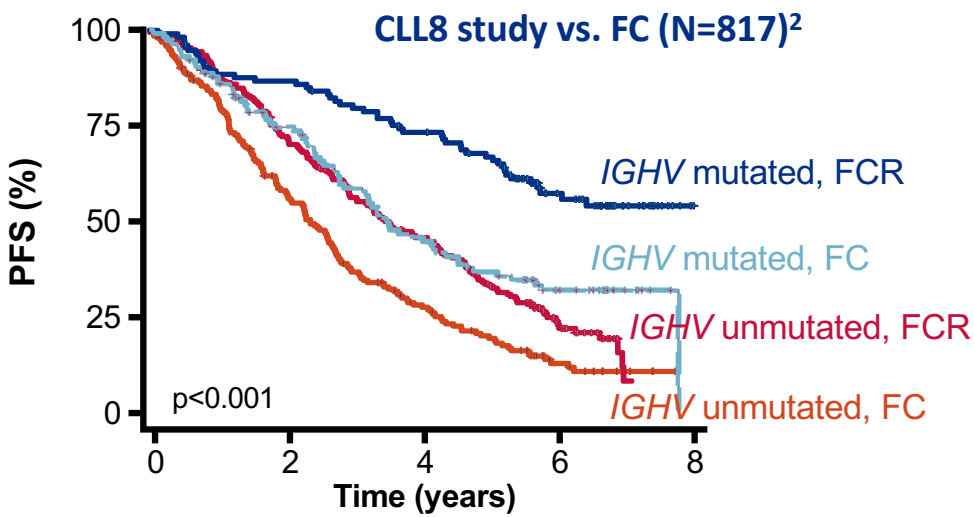


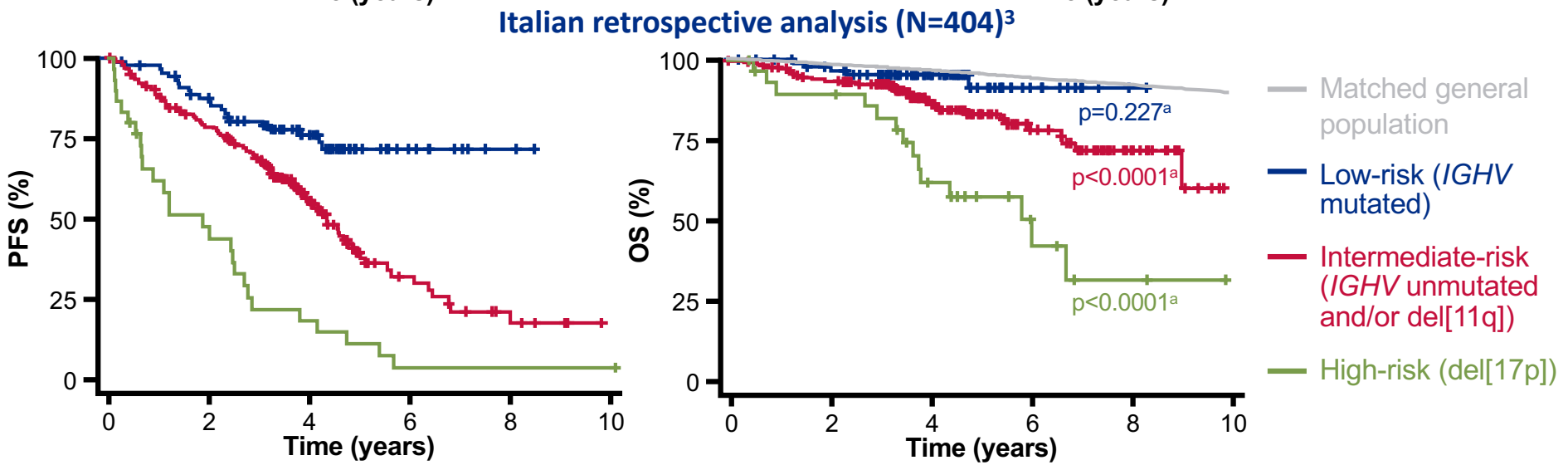
Woyach J et al, ASH 2018, #6

IGHV status

Patients with *IGHV*-unmutated status and/or del11q and/or del17p do not benefit from chemoimmunotherapy





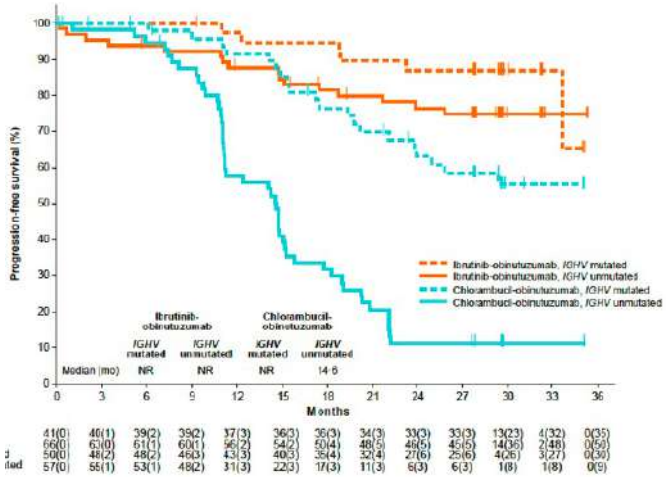


[a] p-value vs. matched general population
FCR: fludarabine, cyclophosphamide, rituximab; MDACC: MD Anderson Cancer Center; OS: overall survival; PFS: progression-free survival

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.

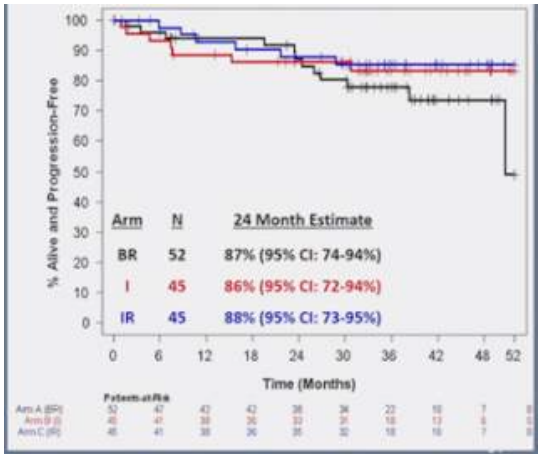
PFS in IGHV unmutated CLL

iLLUMINATE (Moreno #691)
Included high risk



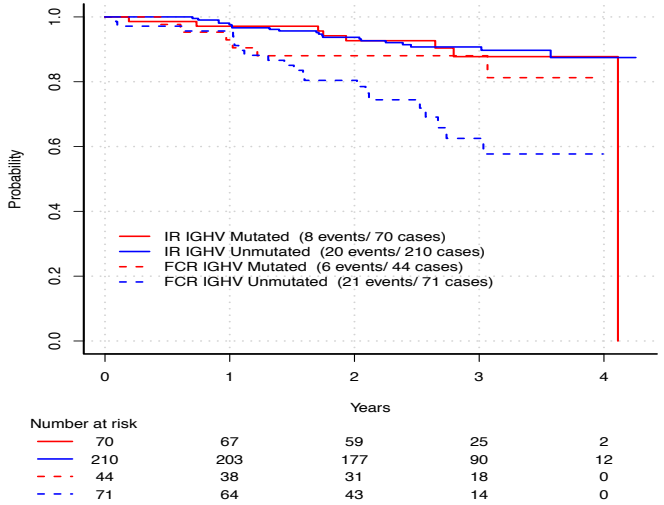
uIGHV: HR 0.15 (0.08 – 0.27)
mIGHV: HR 0.30 (0.12 – 0.75)

ALLIANCE (Woyach #6)
Included del(17)p



mIGHV HR: not reported

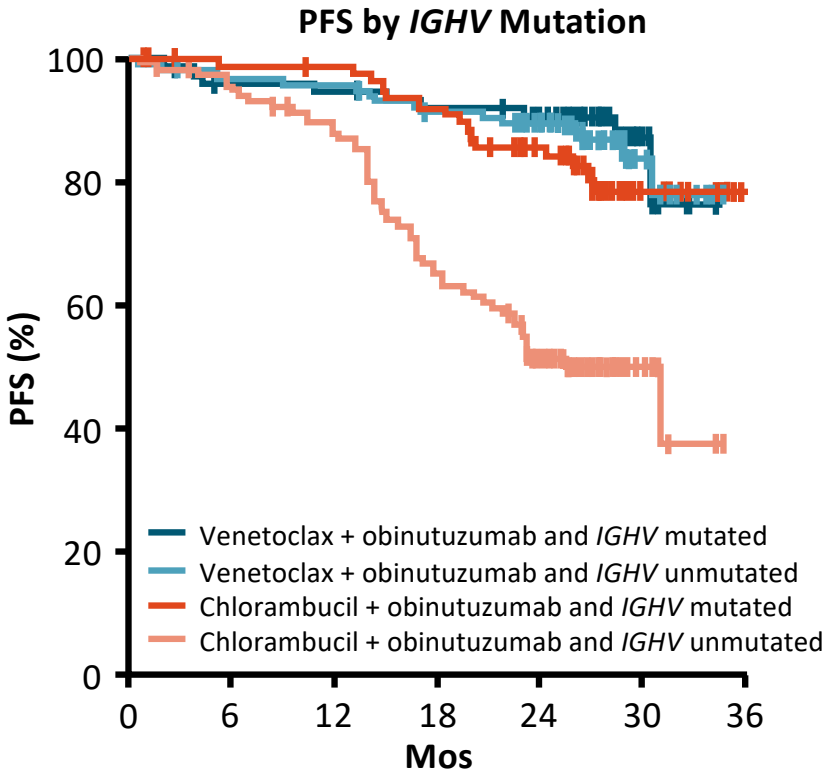
E1912 (Shanafelt LBA-4)
No del(17)p

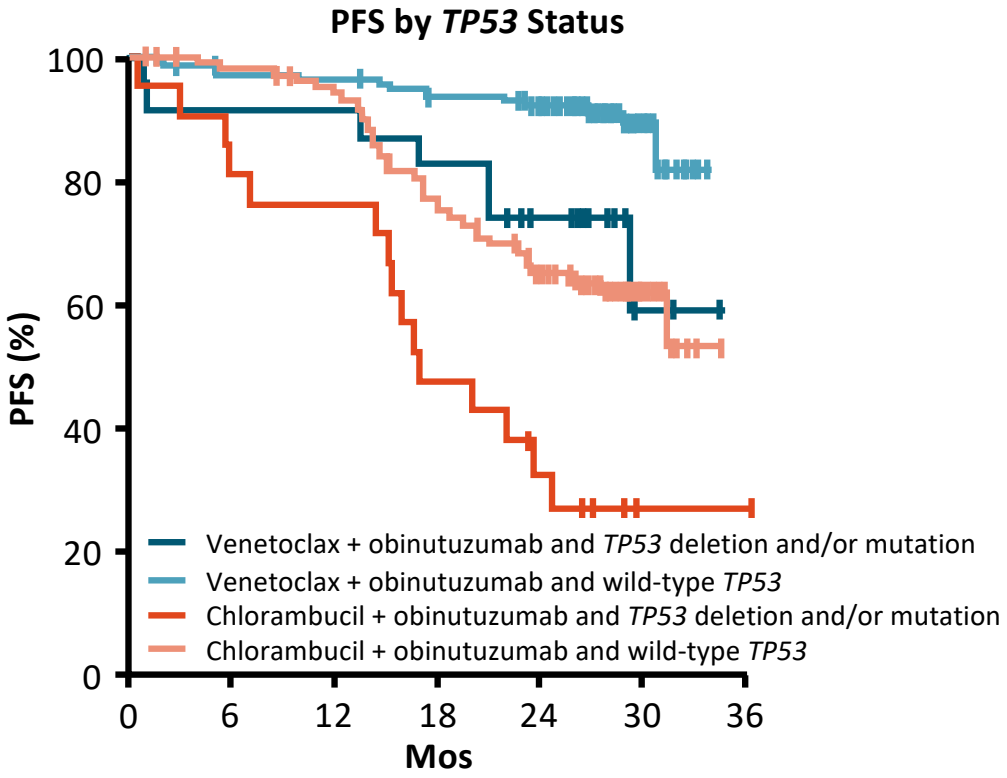


uIGHV: HR 0.26 (0.14-0.5; p < 0.0001)
mIGHV: HR 0.44 (0.14-1.36; p = 0.07)

Moreno et al. ASH 2018. Abstract 691. Moreno Lancet Oncol 2018 (Suppl. App.)
Woyach et al., NEJM 2018 (Suppl. App.)
Shanafelt et al. ASH 2018. Abstract LBA-4. NCT02048813. (Presentation)

PFS by IGVH Mutation and *TP53* Status





Fischer. ASCO 2019. Abstract 7502. Fischer. NEJM. 2019;380:2225. NCT02242942.

Histology

WHO 2016 Classification
Richter syndrome

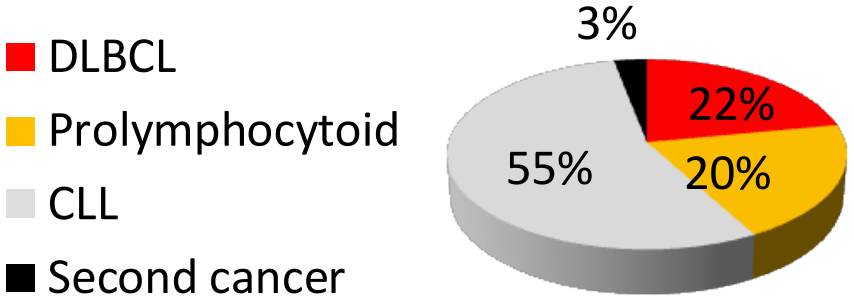
Clinical suspicion of transformation

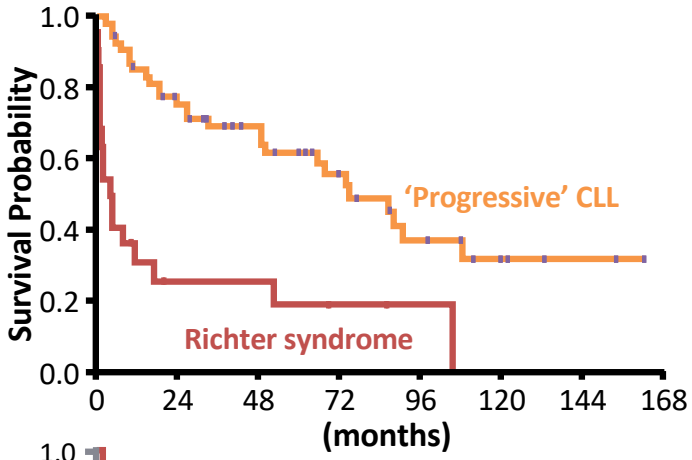
- Asymmetric growth of localized lymph nodes
- Bulky disease
- B symptoms
- Sudden and excessive rise in levels of LDH

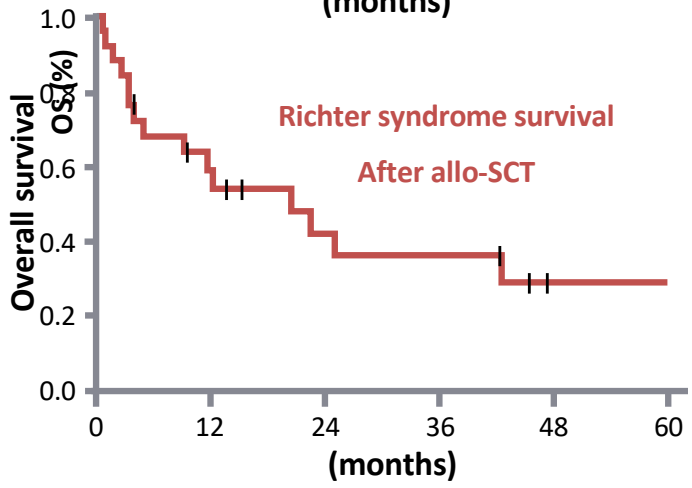
PET/CT in Richter syndrome diagnosis

	RS
Sensitivity	91%
Specificity	80%
Positive predictive value	53%
Negative predictive value	**97%**

Max SUV cut off=5



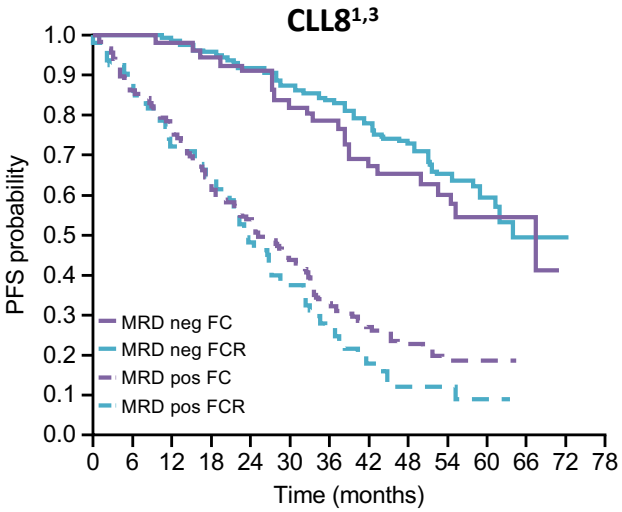


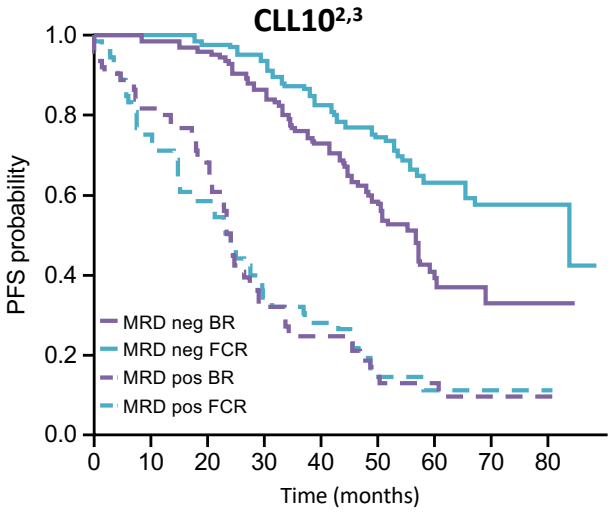


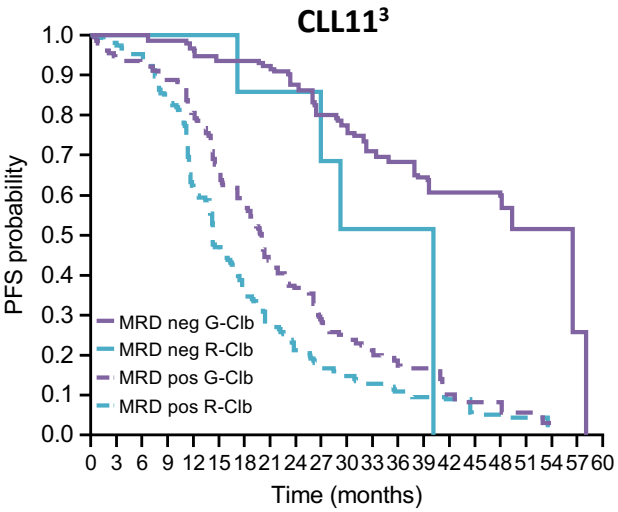
Rossi D et al. Semin Oncol 2016 43:311-9
Gine' E et al. Haematologica. 2010 95:1526-33
Buzzi JF et al. J Nucl Med 2006 47:1267-73
Mauro FR et al. Leukemia 2015 29:1360-5.

MRD

MRD is predictive of PFS with chemoimmunotherapy in CLL

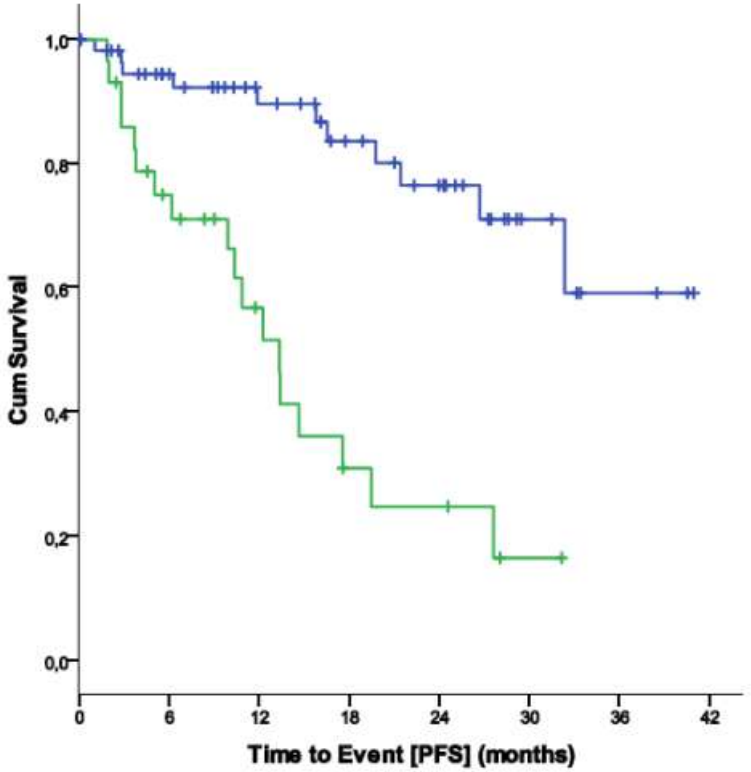


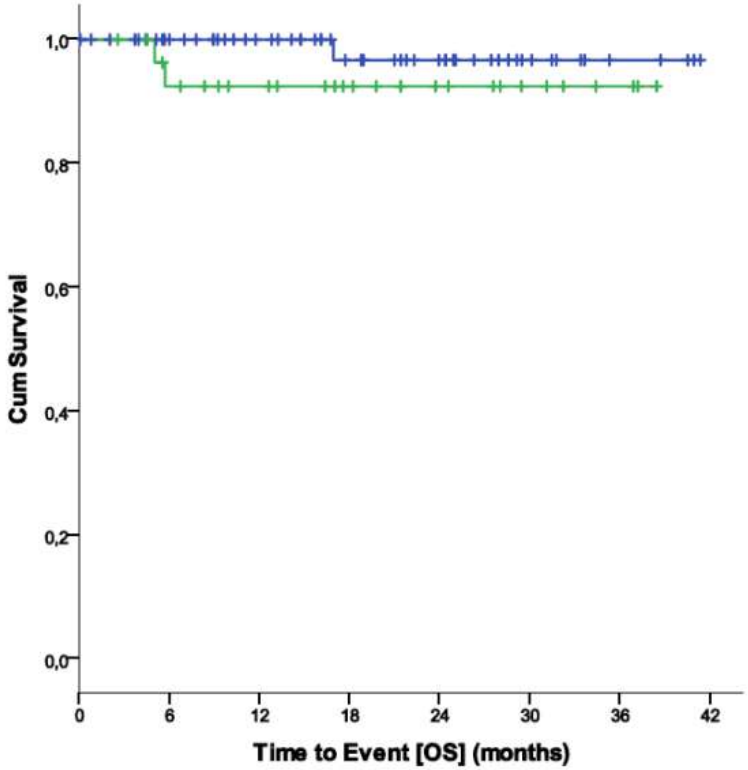




1. Böttcher S, et al. J Clin Oncol 2012;30:980–8; 2. Kovacs G, et al. J Clin Oncol 2016;34:3758–65
3. Dimier N, et al. Blood 2018;131:955–62; 4. Langerak AW, et al. Blood 2018:blood-2018-03-839688

Maintenance in MRD positive patients

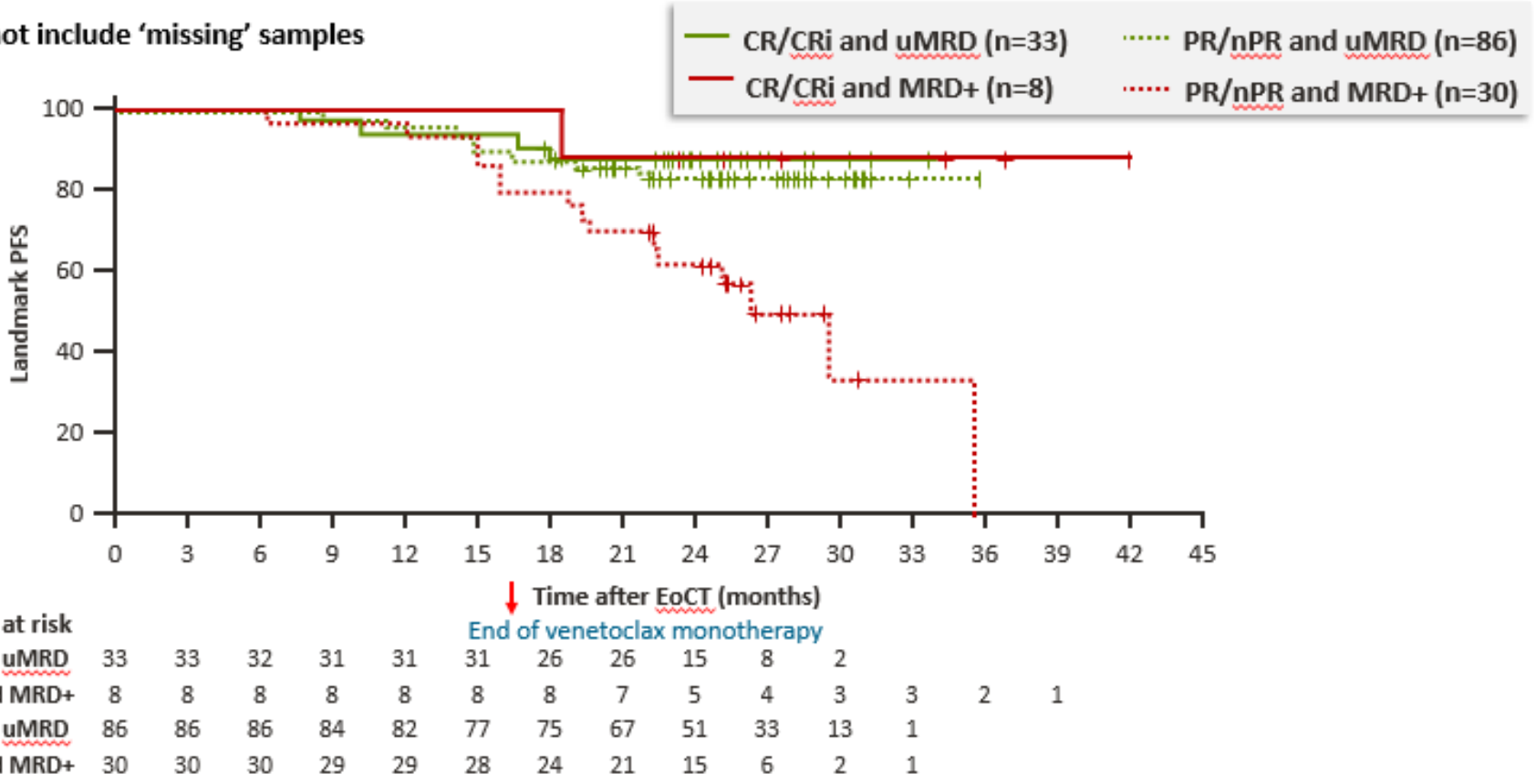




Fink AM, Lancet Haematol. 2017 Oct;4(10):e475-e486.

MRD negativity predicts response duration

MRD+ does not include 'missing' samples



No. of pts at risk														
CR/CRi and uMRD	33	33	32	31	31	31	26	26	15	8	2			
CR/CRi and MRD+	8	8	8	8	8	8	8	7	5	4	3	3	2	1
PR/nPR and uMRD	86	86	86	84	82	77	75	67	51	33	13	1		
PR/nPR and MRD+	30	30	30	29	29	28	24	21	15	6	2	1		

Kater et al. ASH 2018, Abstract 695

Conclusions

- Diagnostic biomarker: immunophenotype, morphology, CBC, PE
- Atypical phenotype: extend diagnostics to cytogenetics and BMB
- iwCLL criteria guide treatment initiation
- IGHV and *TP53* are guideline recommended molecular biomarkers for treatment tailoring
- Don’t forget RS
- MRD-guided treatment discontinuation?

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