european research initiative on CLL

Clinical impact of gene mutations in CLL

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ERIC/Harmony mutation project in CLL

- Evaluate 10 of the most frequently mutated genes in CLL and assess their prognostic and clinical relevance

  TP53, *NOTCH1*, *SF3B1*, *BIRC3*, *XPO1*, *NFKBIE*, *MYD88*, *ATM*, *POT1*, *EGR2*

- ~4700 cases (pre-treatment samples) from 21 participating centers

Participating centres

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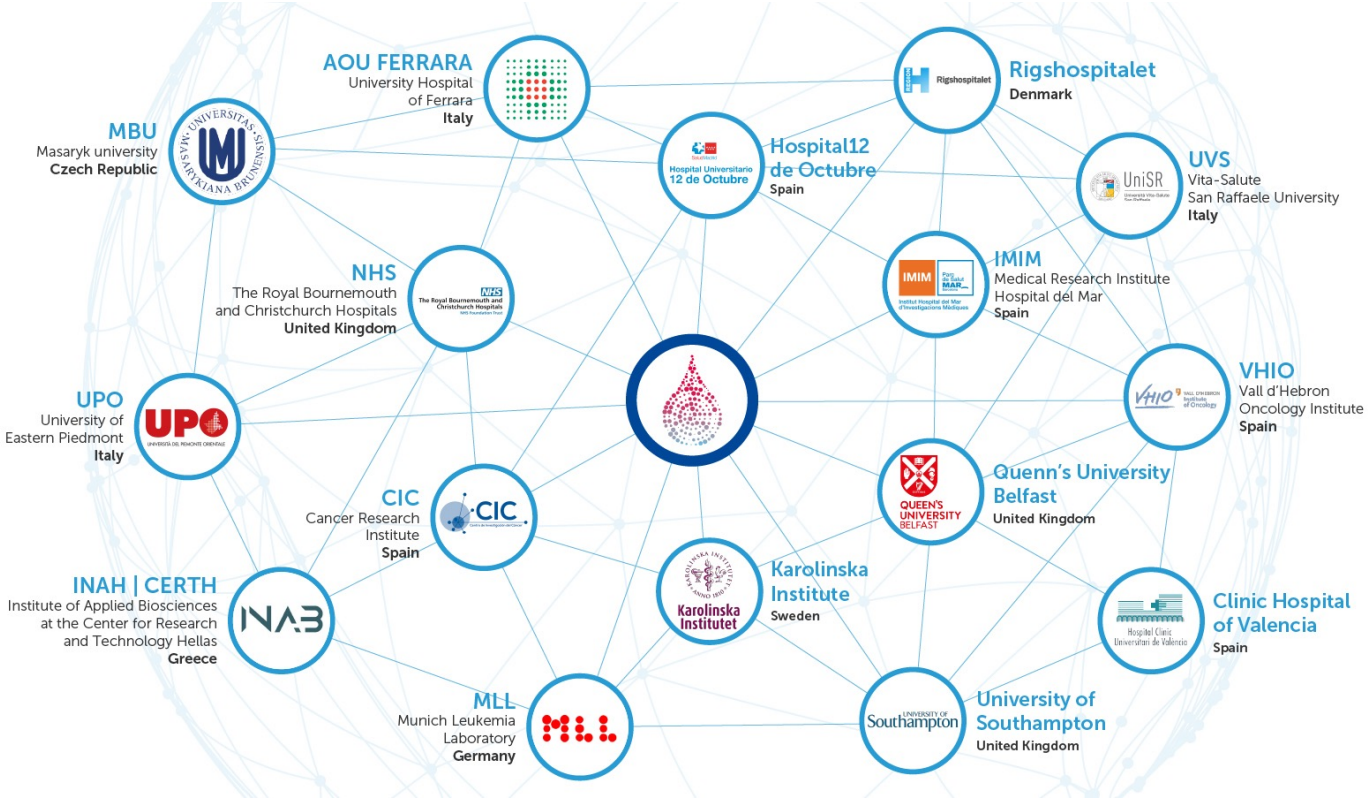

IDIBAPS
Institut D'Investigacions Biomèdiques August Pi i Sunyer

Cohort characteristics

(4674 patients)

Gender	
Male	2692 (63.3%)
Female	1982 (36.7%)
Median age at diagnosis	64.5 years
IGHV status	
M-CLL	2498 (56%)
U-CLL	1927 (44%)
unknown	(247)
Recurrent aberrations	
del(13q)	1868 (41%)
trisomy12	571 (13%)
del(11q)	503 (11%)
del(17p)	249 (5.5%)
Binet stage	
A	3369 (74%)
B	827 (18%)
C	387 (8%)
unknown	(64)
Treatment status	
treated	2745 (58%)
untreated	1929 (42%)

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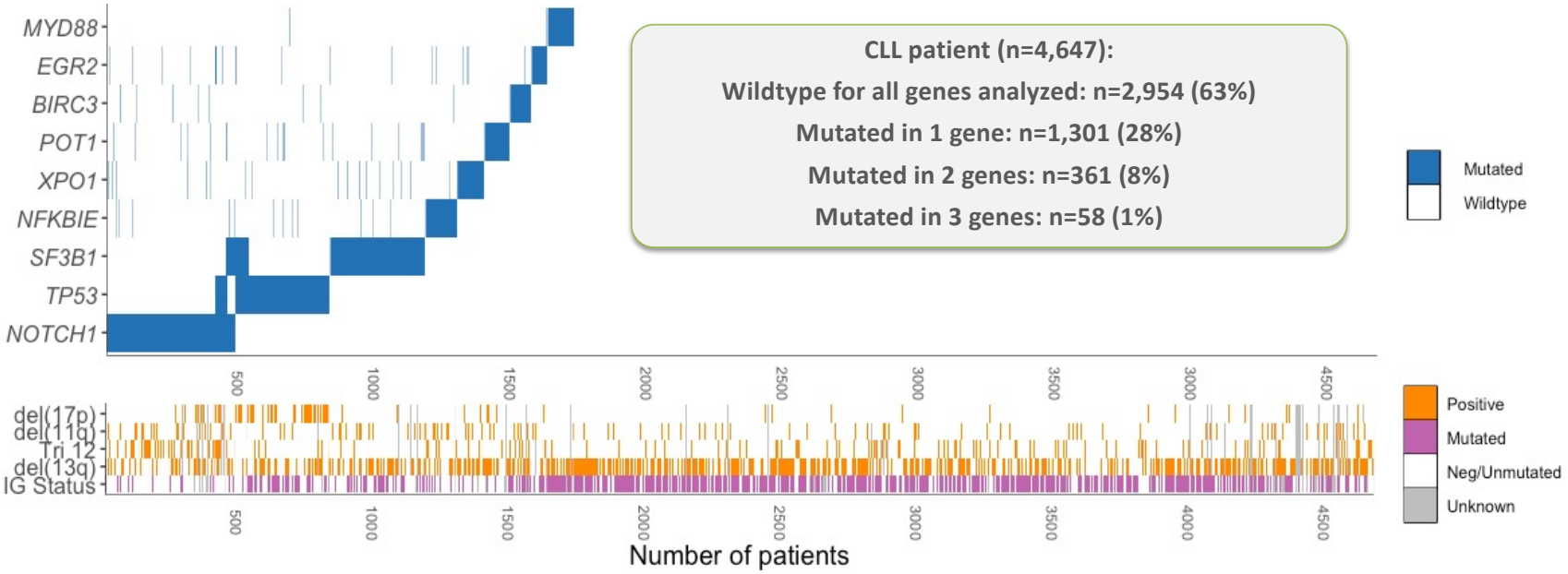
Mutational landscape



Importance of IGHV mutational status

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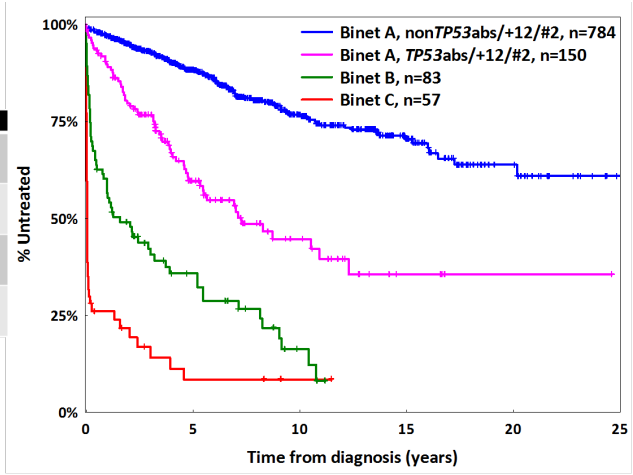
Prognostic index for TTFT in M-CLL

Risk group	5-yTP	10-y TP
Very high risk 5% of M-CLL mTTF: 0.1 years	92%	92%
High risk 8% of M-CLL mTTFT: 1.5 years	64%	84%
Intermediate risk 14% of M-CLL mTTFT: 8 years	40%	55%
Low risk 73% of M-CLL mTTFT: nr	12%	25%

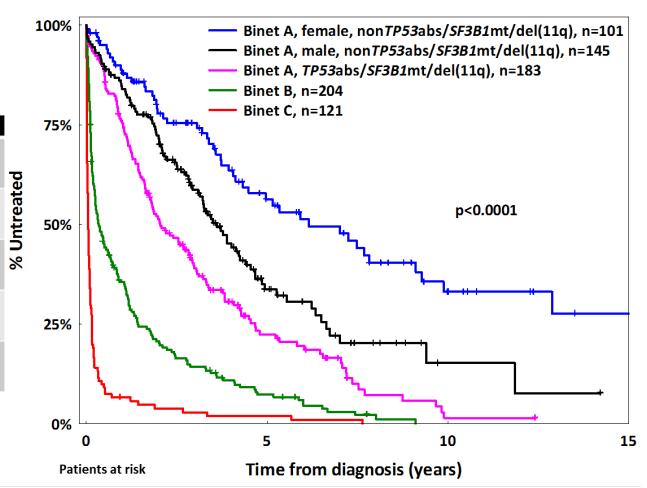


Patients at risk

Very high risk	57	3	1	0	0	0
High risk	83	16	1	0	0	0
Intermediate risk	150	40	9	1	1	1
Low risk	784	417	150	47	10	3

Prognostic index for TTFT in U-CLL

Risk group	5-yTP	10-y TP
Very high risk 16% of U-CLL mTTF: 0.1years	100%	100%
High risk 27% of U-CLL mTTFT: 0.4 years	90%	100%
Intermediate risk 24% of U-CLL mTTFT: 2.1 years	78%	98%
Low risk 19% of U-CLL mTTFT: 3.6 years	65%	85%
Very low risk 13% of U-CLL mTTFT: 6.1 years	45%	65%



Patients at risk

Very high risk	121	2	0	0	
High risk	204	9	0	0	
Intermediate risk	183	24	1	0	
Low risk	145	11	3	1	
Very low risk	101	38	14	4	

Baliakas et al. Haematologica 2019

Gene mutations and time to first treatment

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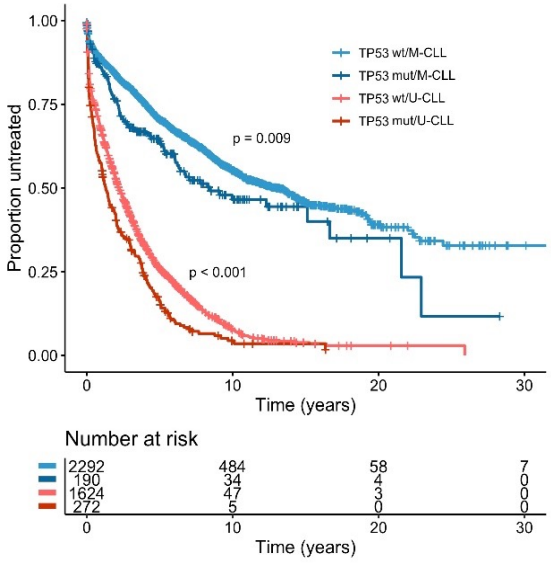
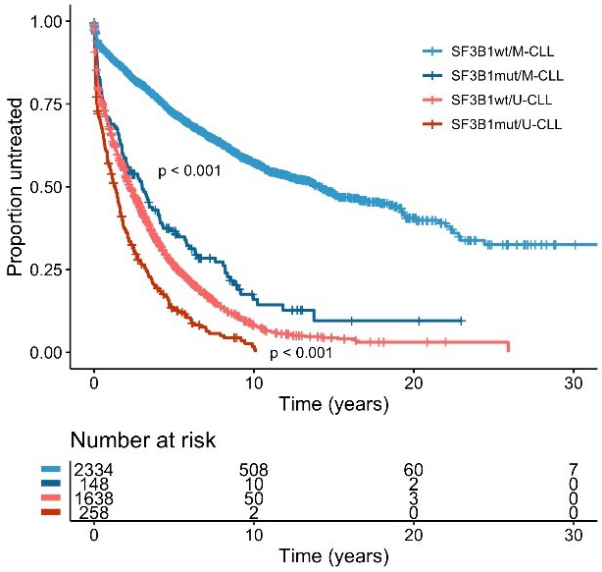
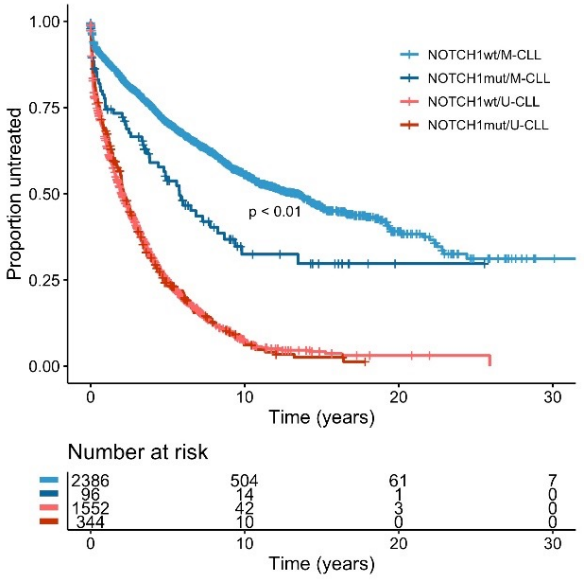
TP53



SF3B1



NOTCH1



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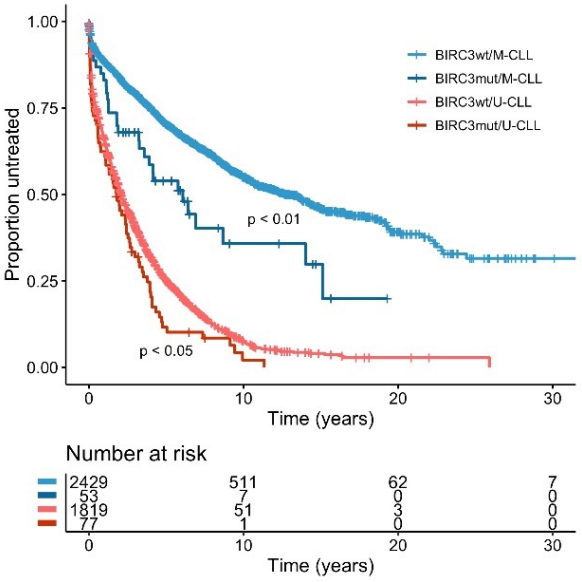
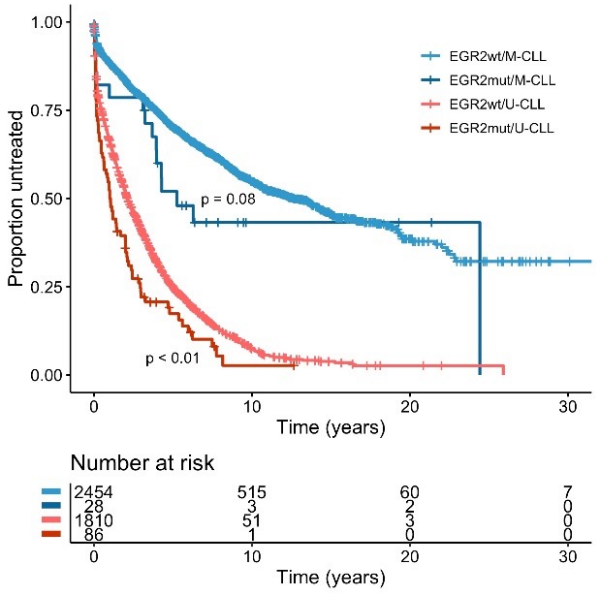
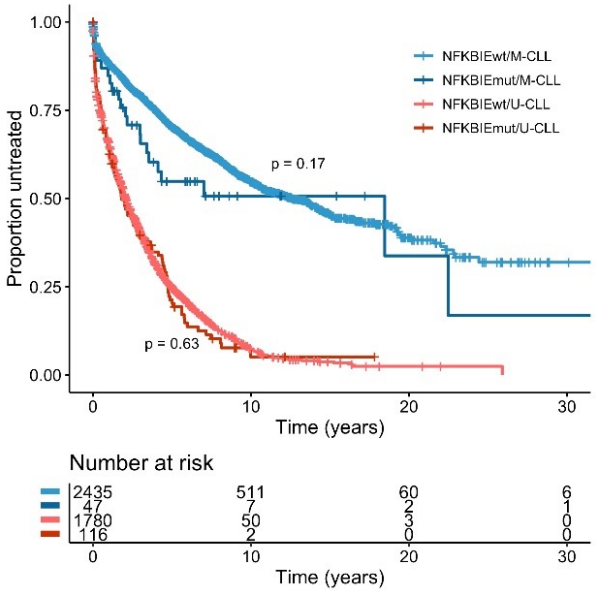
BIRC3



EGR2



NFKBIE



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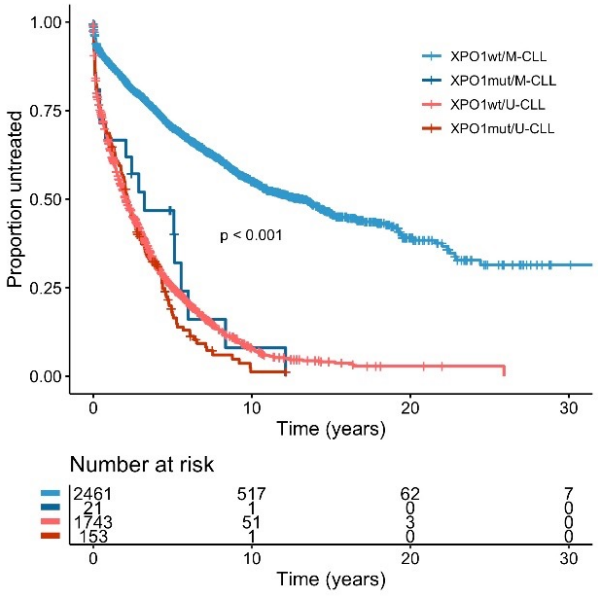
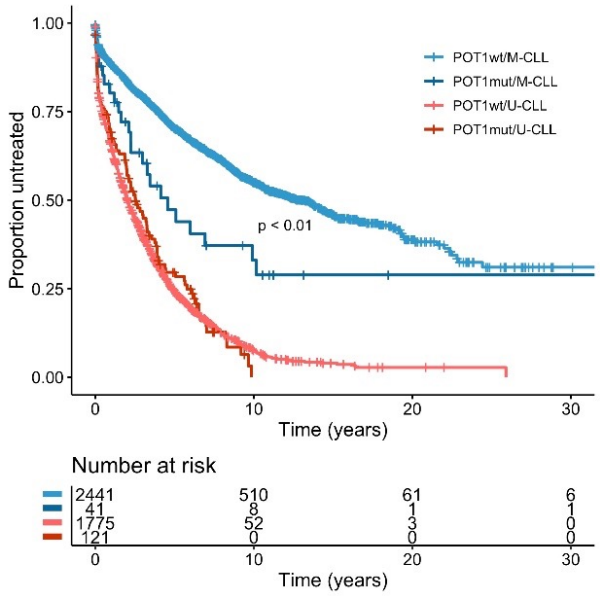
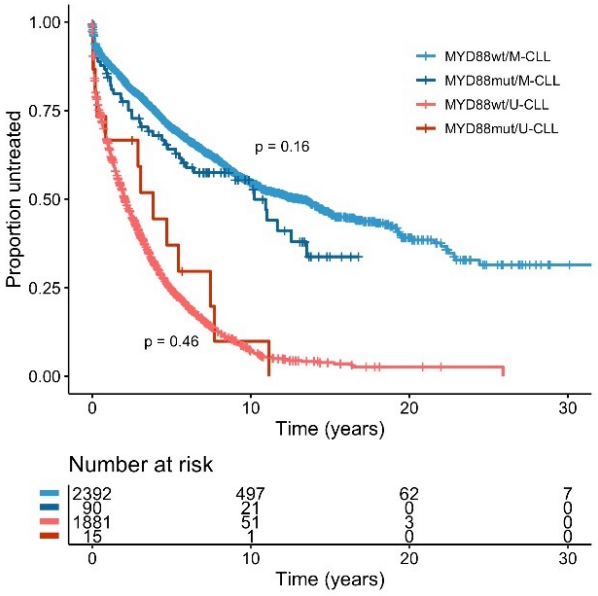
XPO1



POT1



MYD88



Multivariate analysis

Multivariable analysis of TTFT and recurrent gene mutations in CLL

N=4291	Hazard ratio (95% confidence interval)	p-value
Age > median (64 yrs)	1.02 (0.95-1.11)	0.566
Male	1.08 (0.99-1.17)	0.072
Binet B/C	3.73 (3.42-4.07)	<0.001
U-CLL	2.95 (2.69-3.23)	<0.001
SF3B1 mut	1.58 (1.41-1.78)	<0.001
EGR2 mut	1.39 (1.12-1.72)	0.003
TP53 ab	1.20 (1.06-1.36)	0.004
XPO1 mut	1.26 (1.07-1.49)	0.006
BIRC3 mut	1.25 (1.02-1.53)	0.031
NOTCH1 mut	1.11 (0.97-1.25)	0.085
POT1 mut	0.85 (0.70-1.04)	0.119
NFKBIE mut	1.15 (0.96-1.39)	0.139
MYD88 mut	0.95 (0.73-1.24)	0.699

Hierarchical model for gene mutations

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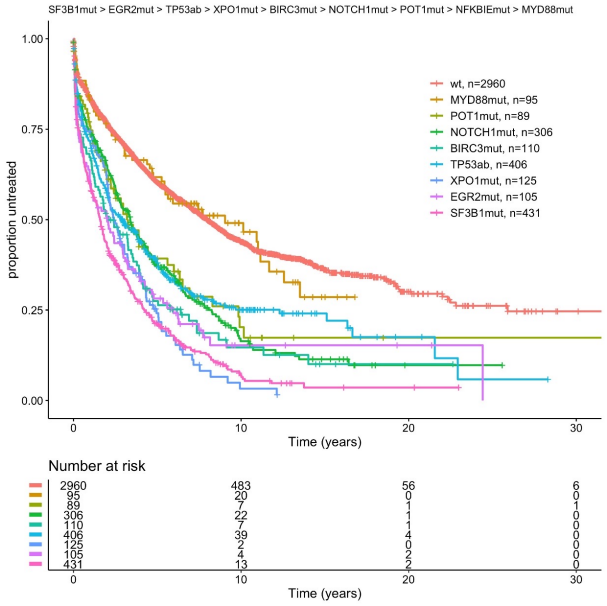

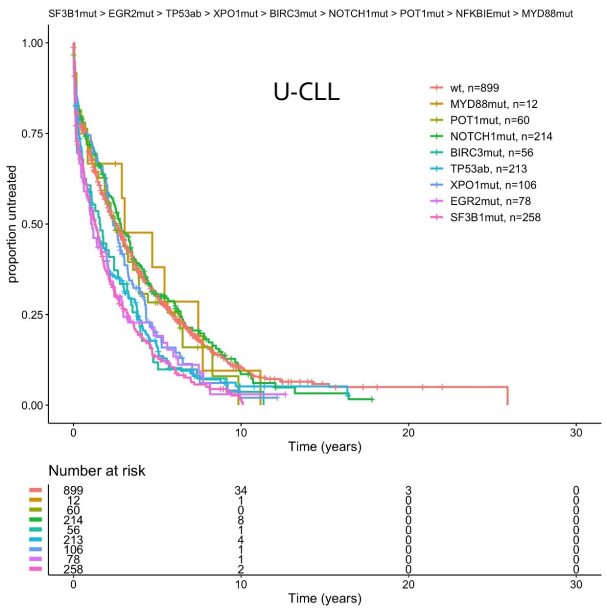

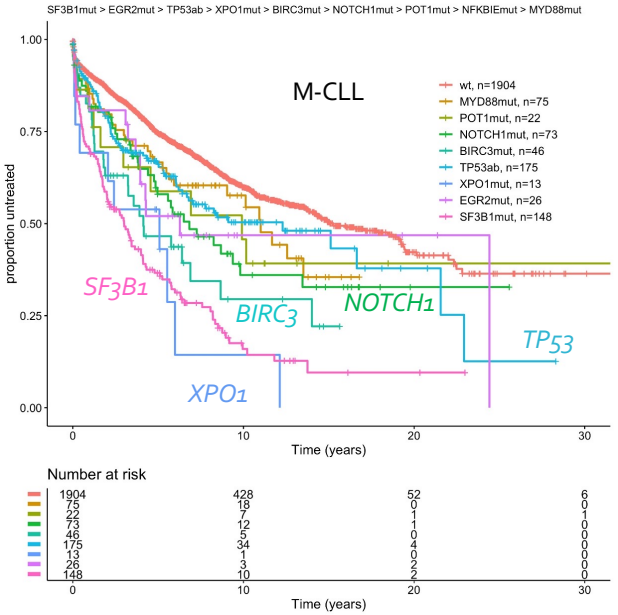

Conclusions

- Mutations in all genes analyzed, except *MYD88*, affected clinical outcome
- IGHV mutational status is important also in the context of recurrent mutations

Ongoing analysis:

- Impact of the number of genetic aberrations
- Co-occurring/mutually exclusive mutations
- Prognostic models in IGHV-mutated and unmutated CLL
- Overall survival as endpoint