IOR
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Sviluppo di Prognostic Scoring Systems

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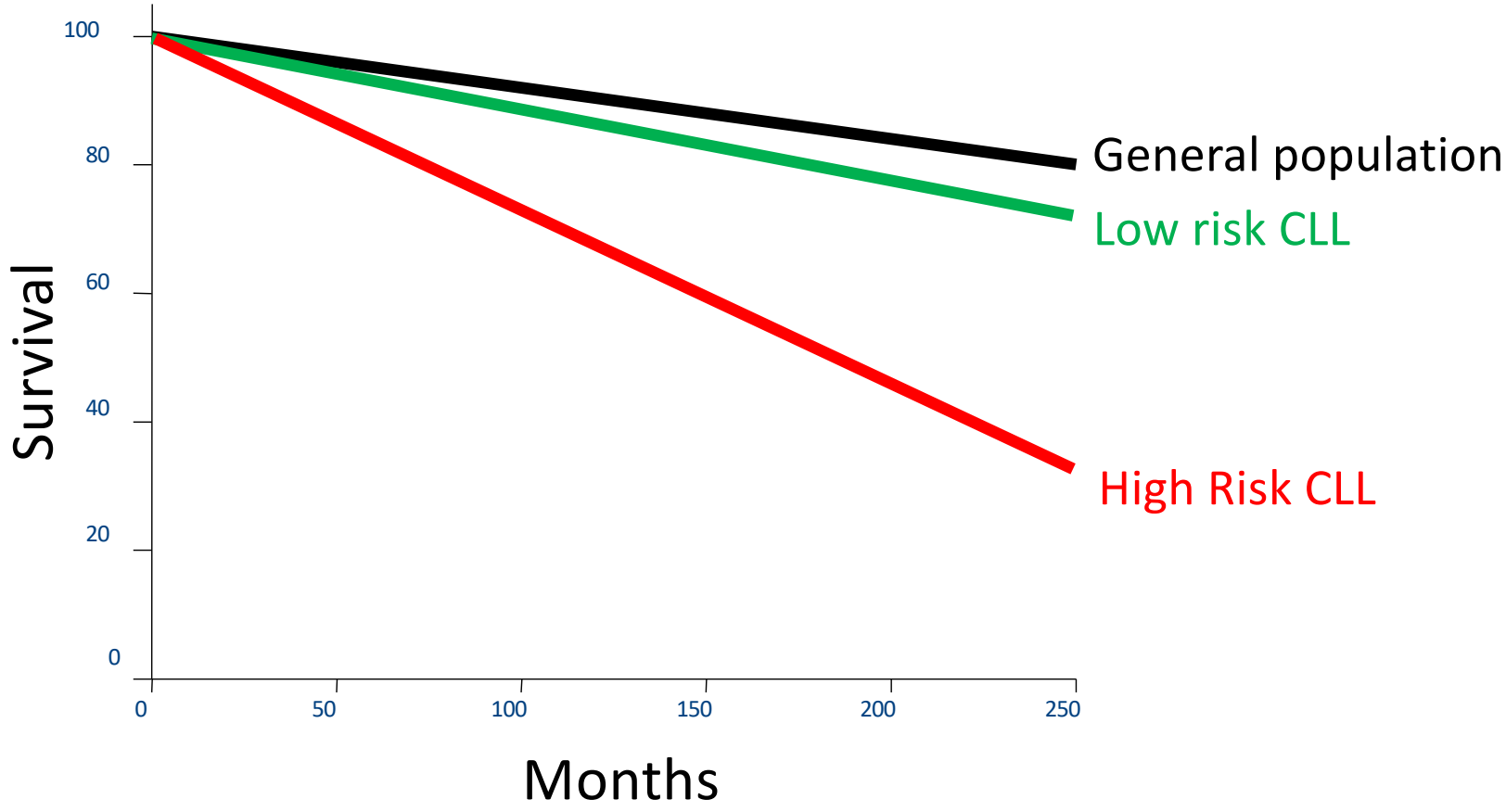
Overall survival

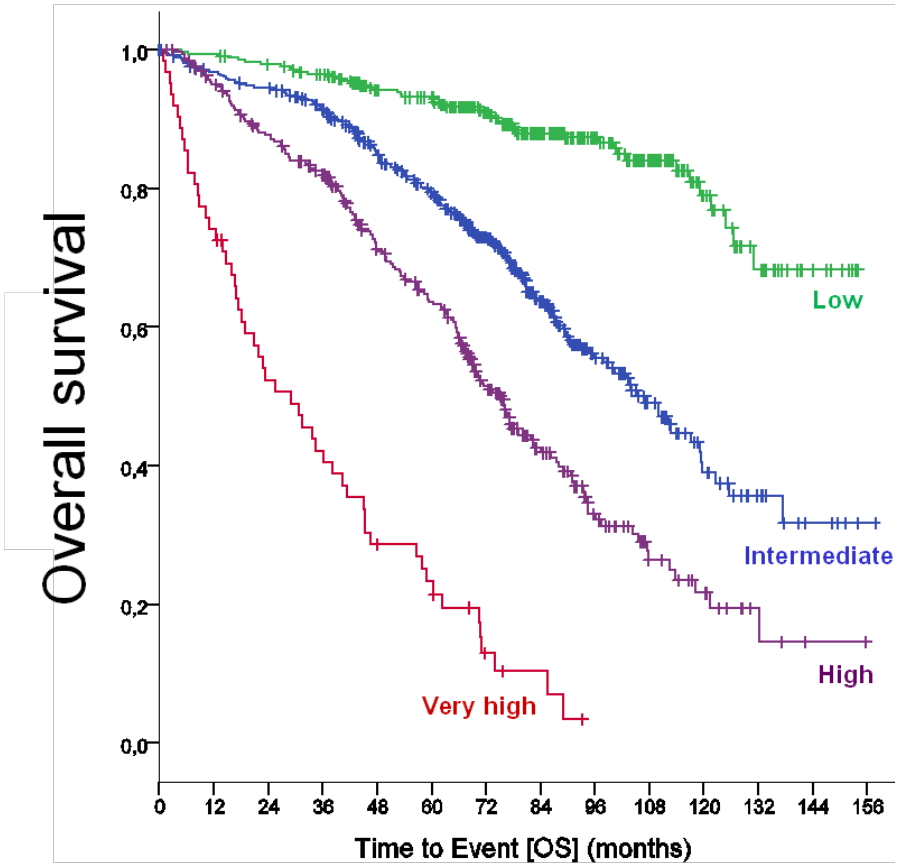
CLL: Homogeneous phenotype but heterogeneous clinical course



Prognostic scoring system of survival for CLL treated with chemoimmunotherapy

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

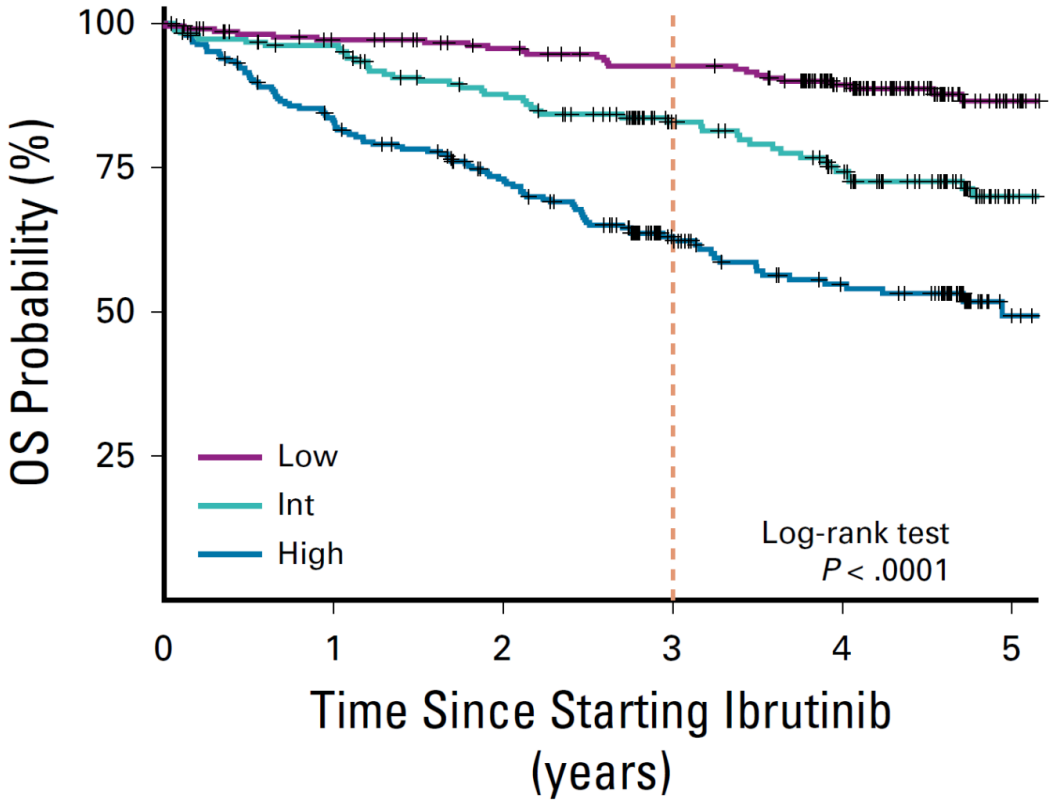


International CLL-IPI working group. Lancet Oncol 2016

Prognostic scoring system of survival for CLL treated with ibrutinib

Variable	Points
TP53 aberration	1
Prior treatment	1
B2M ≥5 mg/l	1
LDH ≥250 U/l	1

Risk group	Score
Low risk	0-1
Intermediate risk	2
High risk	3-4

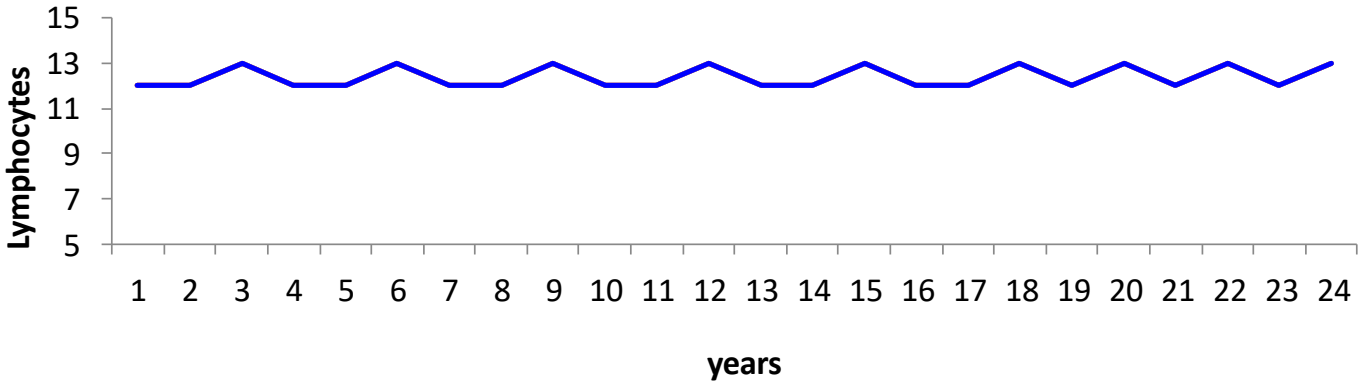


Ahn IE, J Clin Oncol. 2020

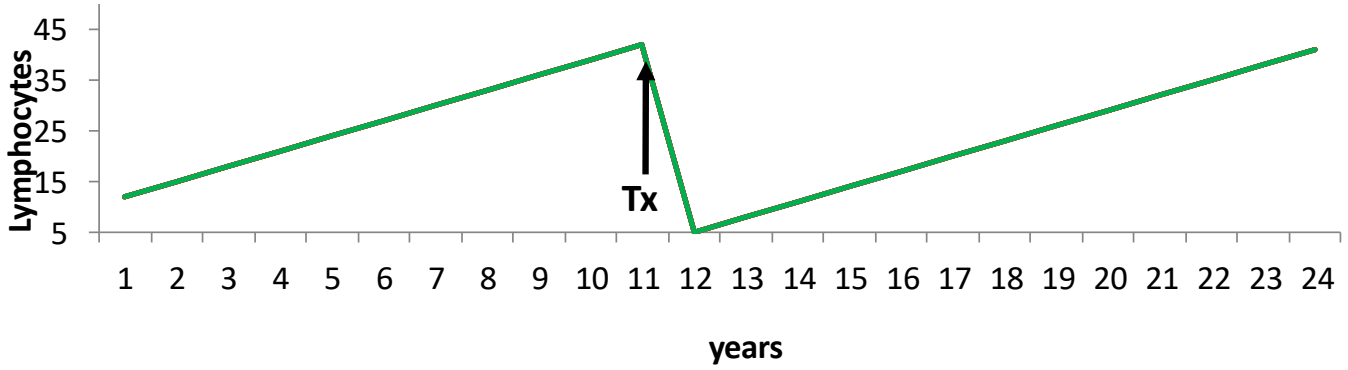
Time to first treatment

Binet A CLL: Homogeneous phenotype but heterogeneous clinical course

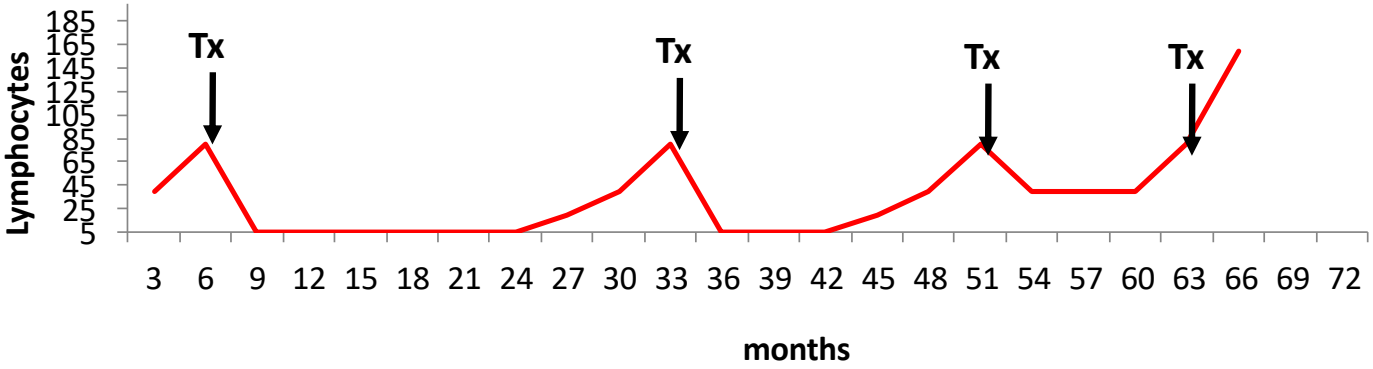
Highly stable
1/3



Slowly progressive
1/3

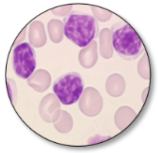


Rapidly progressive
1/3



Biomarker: variable that associates with disease outcome

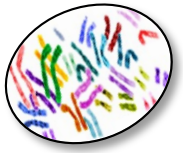
Host Factors: ***Age***, ***sex***, *etc*



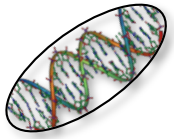
Disease Markers: ***Stage***, *lymphocyte count,* ***LDT***, *etc*

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

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

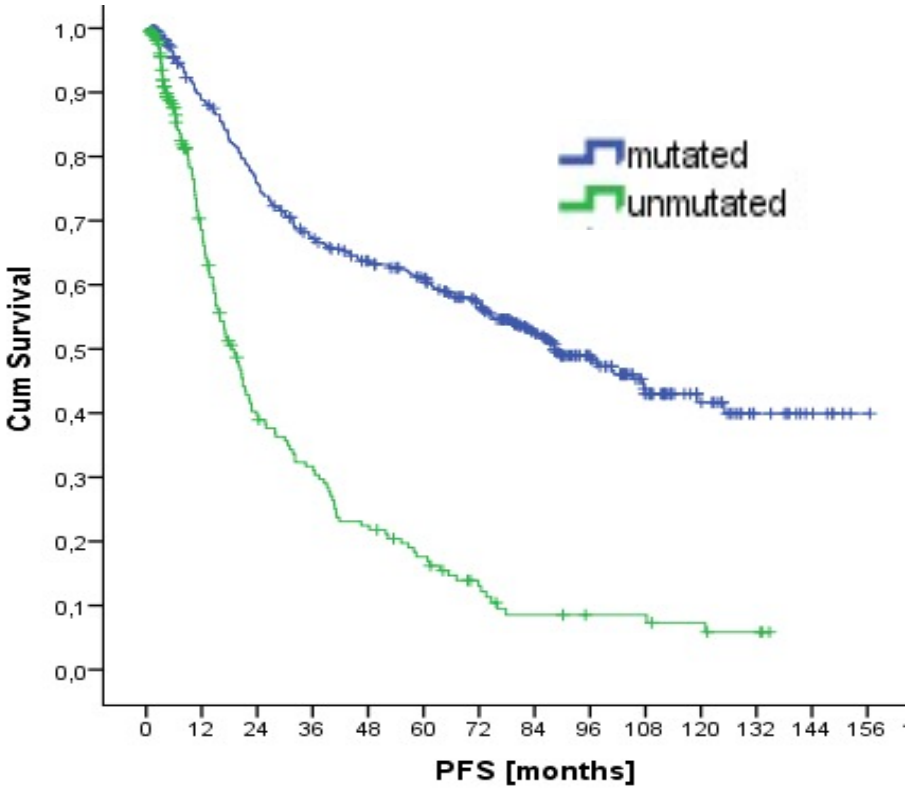


Genetics: ***del17p***, ***TP53 mutation***, *del11q22, del13q14, trisomy 12, NOTCH1 mutation, SFRB1 mutation, etc*

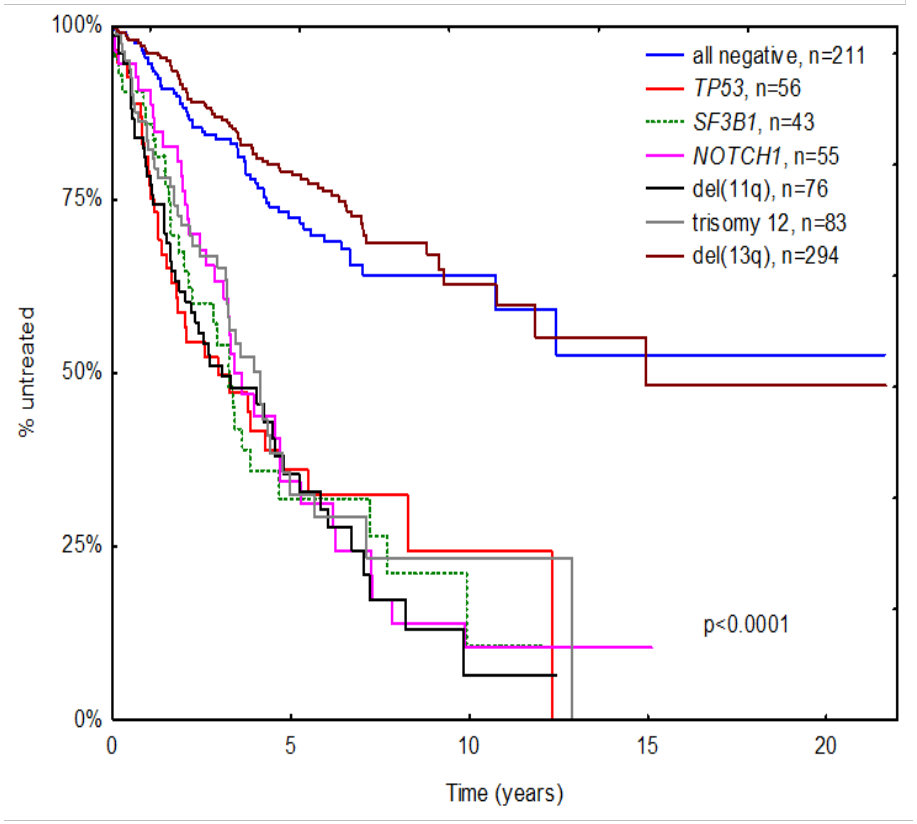


Biology Markers: ***IGVH-sequence***, *BCR-structure*

Patient counseling on risk of progression: genetic-based models



GCLLSG CLL1 study



Baliakas et al, Leukemia 2014

Patients with *TP53* disruption and IGHV mutated status show indolent clinical course: a study on 1,327 CLL

Table: Time to treatment (TTT) and overall survival (OS) according to *TP53* disruption and *IGHV* mutational status.

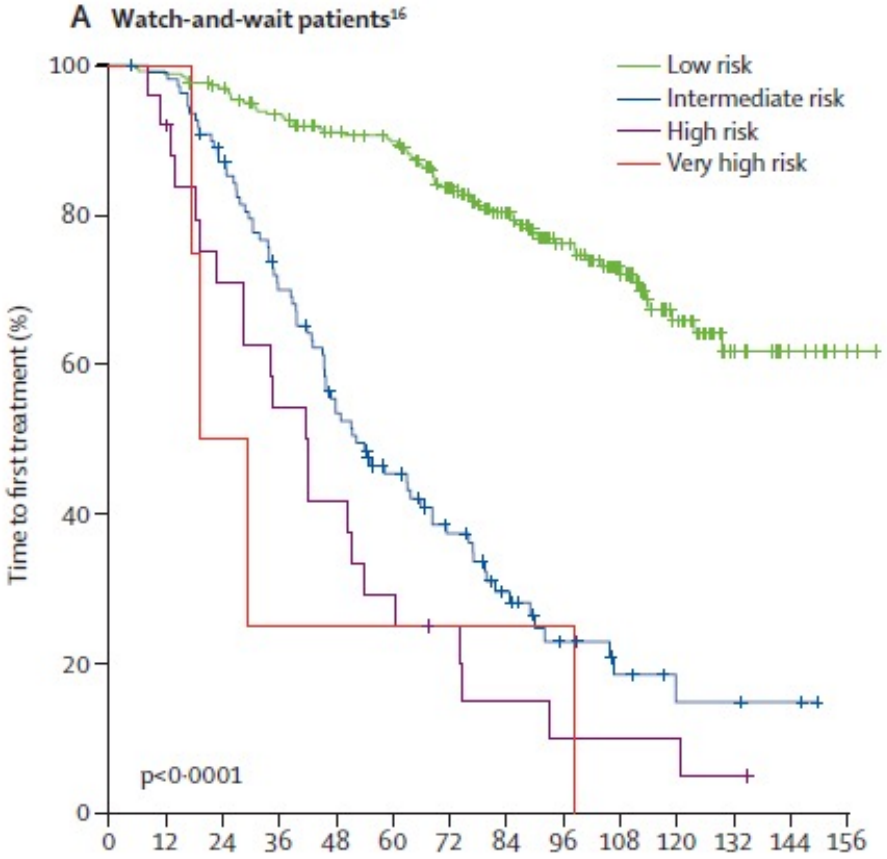
	n	TTT (years)	*TP53*wt/ *IGHV*-M	*TP53* disruption/ *IGHV*-M	*TP53*wt/ *IGHV*-U
		5-year OS			
***TP53*wt/*IGHV*-M**	669	14			
	674	91%			
***TP53* disruption/*IGHV*-M**	33	10	n.s.		
	35	76%	0.009		
***TP53*wt/*IGHV*-U**	370	4	<0.001	<0.001	
	381	81%	<0.001	n.s.	
***TP53* disruption/*IGHV*-U**	51	2	<0.001	<0.001	n.s.
	53	57%	<0.001	0.006	<0.001

Jeromin S, et al. ASH 2016,

Validated prognostic score system for CLL prognostication

CLL-IPI:

- Based on clinical trial CLL
- Developed for OS as endpoint
- Secodarily assessed in W&W CLL
- Multiple biomarkers (Age, clinical stage, B2M, IGHV, TP53)
- Complex scoring requiring a calculator



International CLL-IPI working group. Lancet Oncol 2016

IOSI-EMA-005 study

Multicenter, international, retrospective, observational study (NCT03436524)

Study inclusion criteria:

- flow cytometry confirmed diagnosis of CLL after 1996[1,2]
- early stage at diagnosis as defined by blood cell count and physical examination[1,2]
- active surveillance as initial management after diagnosis

1. Cheson BD et al. Blood. 1996
2. Hallek M et al. Blood. 2008

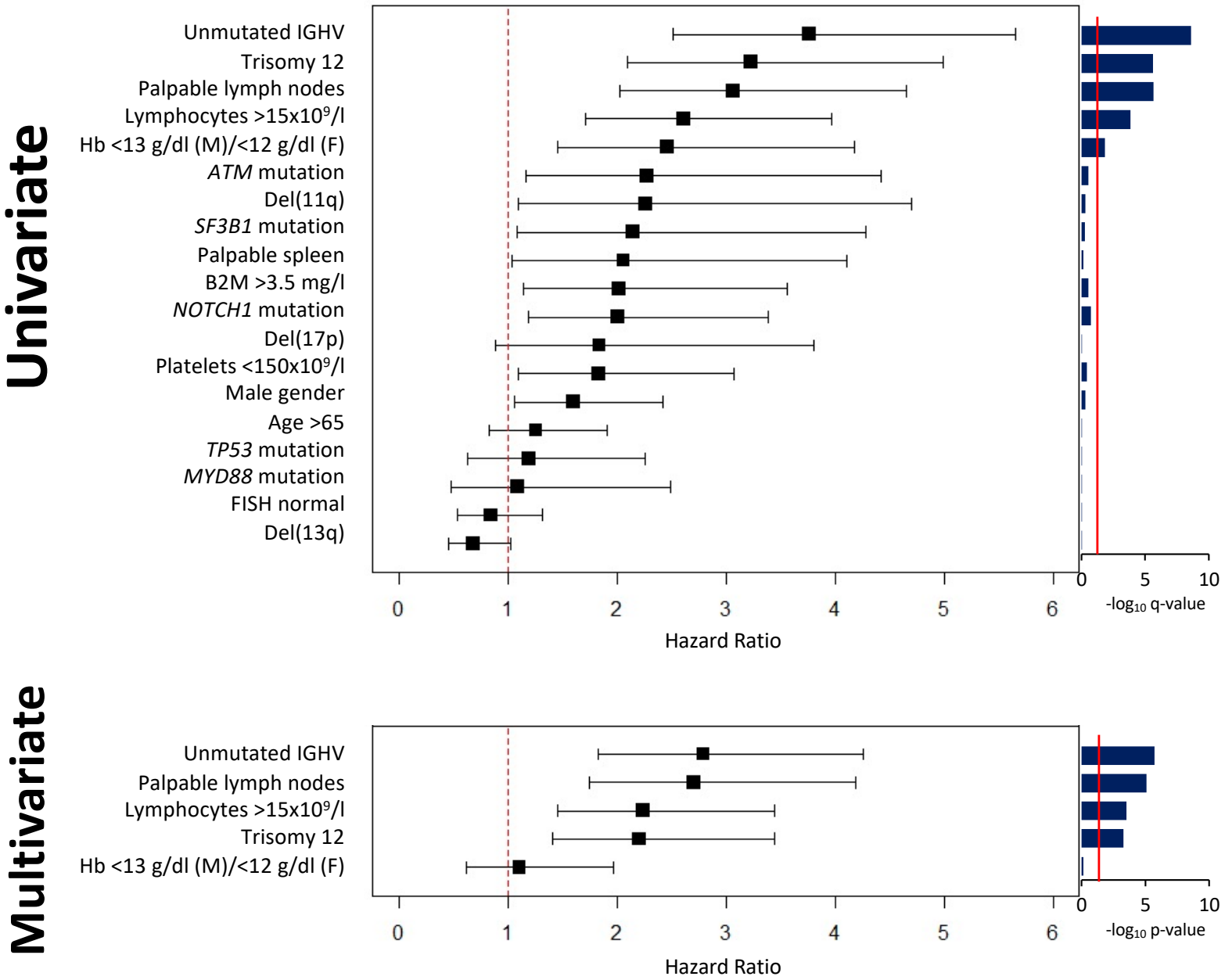
Characteristics of the study cohorts

	Training	Validation									
		Clinical trial series			Institutional series						Population based series
	UEP	CLL1	CLL7	O-CLL-1	MDACC	Mayo Clinic*	Barcelona	Brno	SU	Southampton	SCAN
	N=333	N=547	N=339	N=312	N=1225	N=881	N=355	N=269	N=223	N=226	N=223
Variable	%	%	%	%	%	%	%	%	%	%	%
Age >65	62	28	29	26	30	43	47	42	12	53	43
Male gender	53	61	63	61	59	67	57	62	56	59	59
Palpable lymph nodes	20	22	34	20	44	48	23	44	51	41	42
Lymphocytes >15x10^9/l	19	51	42	44	50	40	26	74	34	34	57
B2M >3.5 mg/l	10	8	2	1	10	10	11	12	4	21	7
Del 13q	50			46	45		50	58	44	67	41
Trisomy 12	18	9	8	9	16	18	16	11	10	11	7
Del 11q	5			7	9		9	15	10	9	5
Del 17p	6	3	2	3	6	5	4	7	4	4	2
Unmutated IGHV	28	29	22	34	39	45	39	50	31	31	25

Hb, hemoglobin; B2M, beta-2-microglobulin; FISH, fluorescence in situ hybridization; IGHV, immunoglobulin heavy variable gene
*early stage CLL according to Rai system (0-II)

N=4933

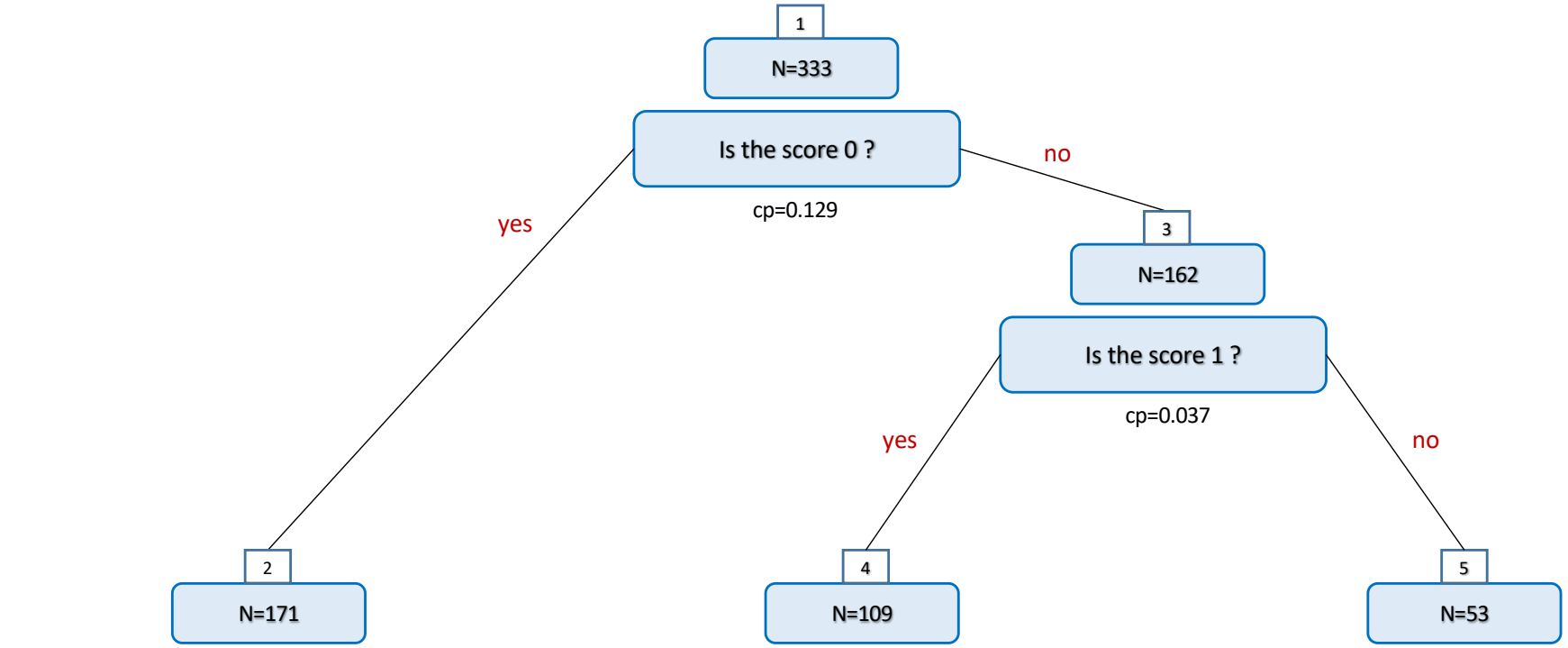
Univariate and multivariate associations and initial model for Time to First Treatment (TTFT)

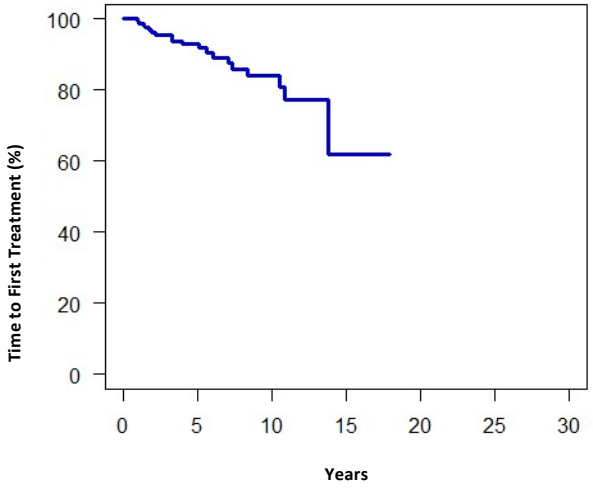


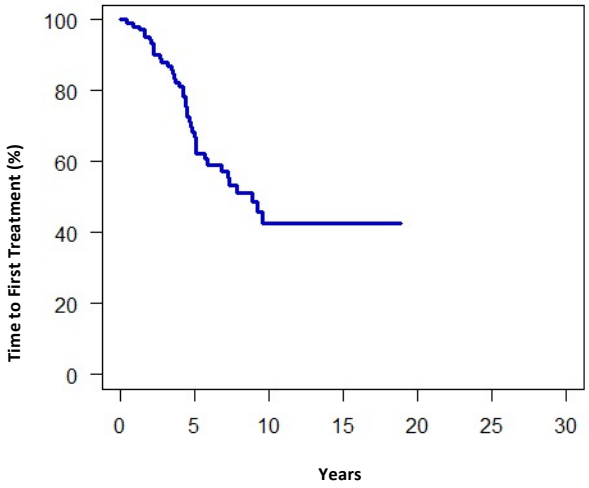
Characteristics consistently associated with TTFT

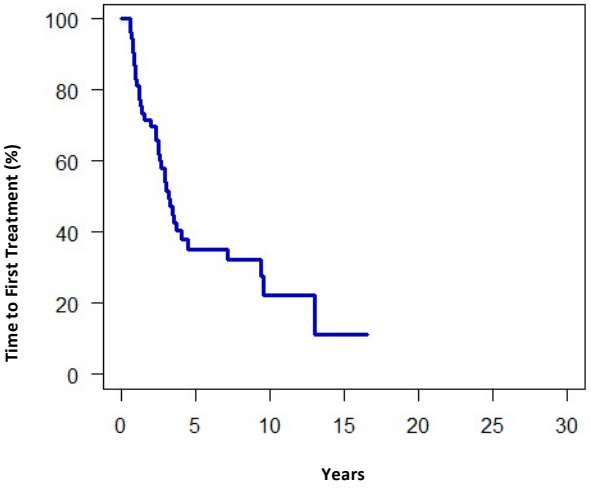
Variable	Percentage of selection in the final Cox model across the 10 Binet A study cohorts
Unmutated IGHV	100%
Lymphocytes >15x10^9/l	90%
Palpable lymph nodes	90%
Trisomy 12	40%

Risk group stratification and IPS-E generation





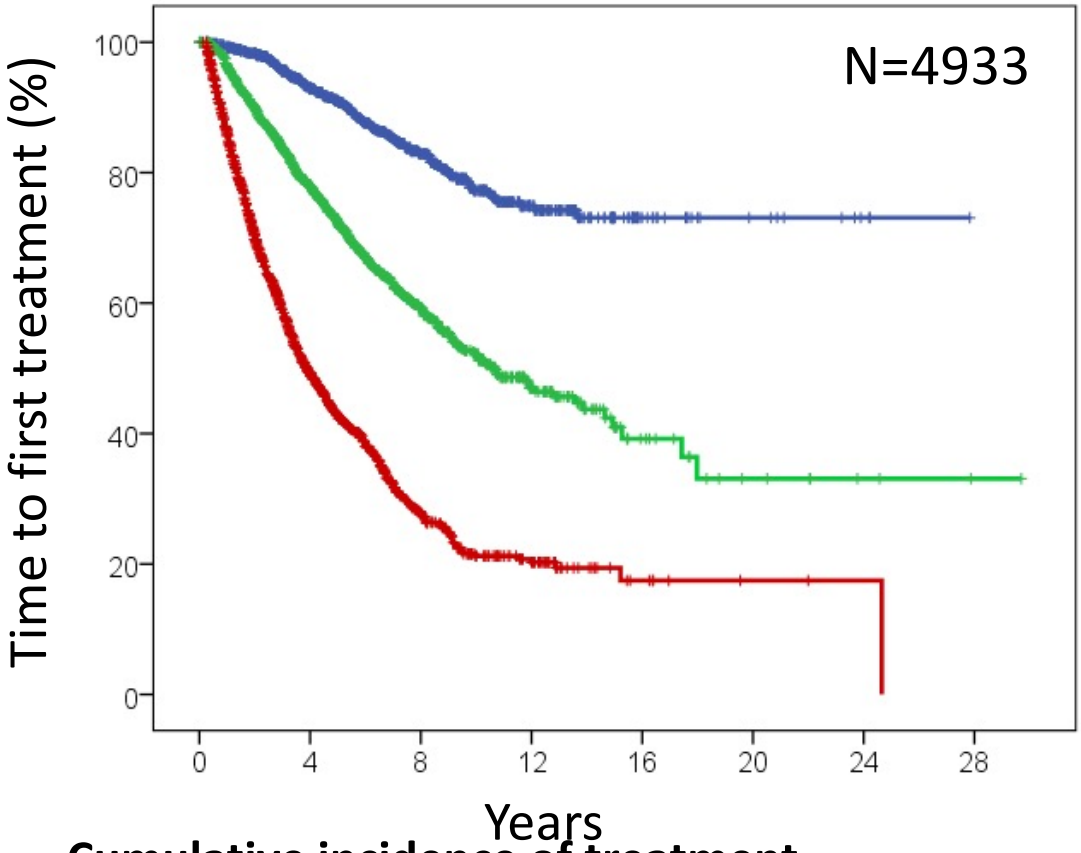




Risk group stratification and IPS-E generation

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

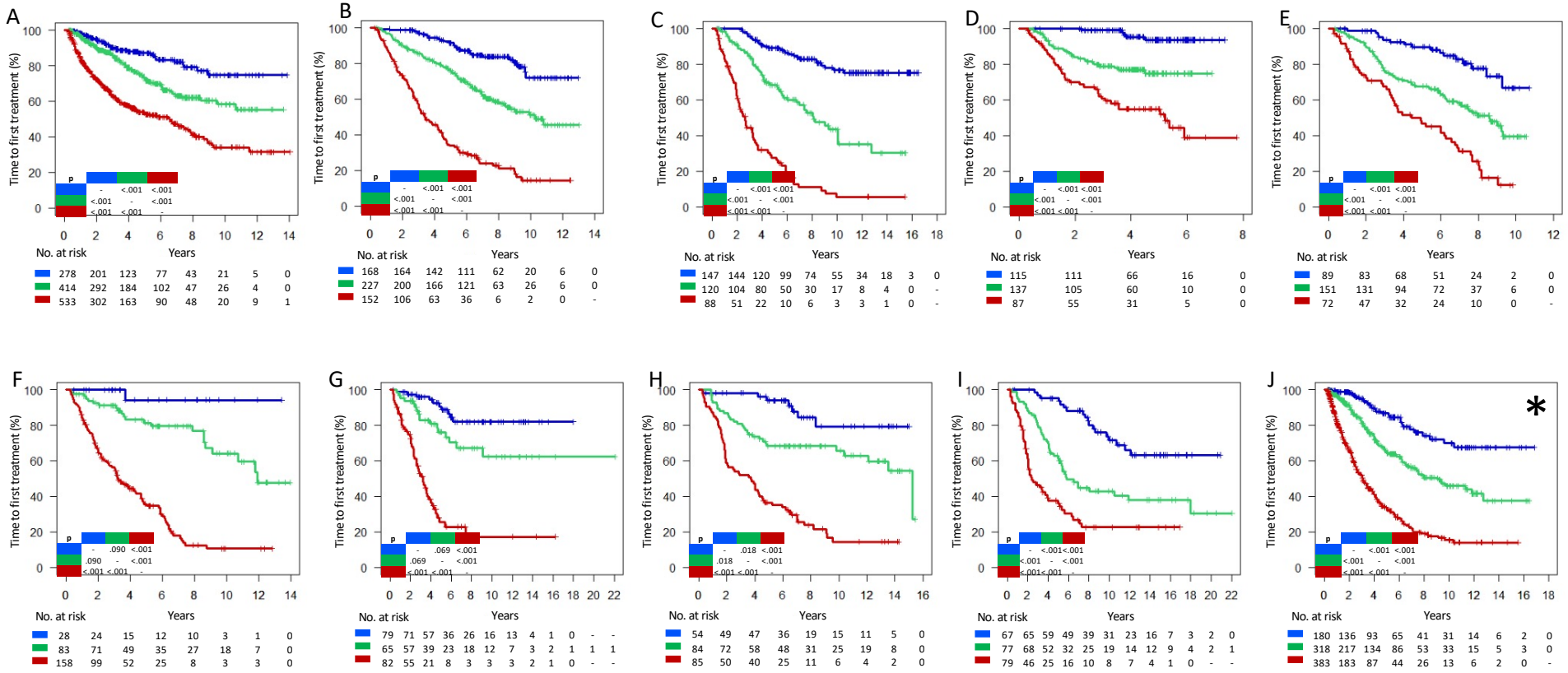
Risk group	Score
Low risk	0
Intermediate risk	1
High risk	2-3



Cumulative incidence of treatment

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

IPS-E in the validation cohorts

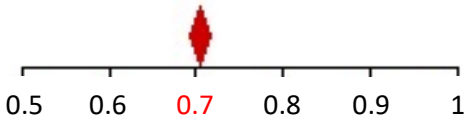


*early stage CLL according to Rai system (0-II)

Risk group stratification maintains also after adjusting for death as a competing risk

IPS-E validation

Cohort	N	Weight (%)	IPS-E c-index
Barcelona	355	8.8	0.75
Southampton	226	5.6	0.75
UEP	333	8.2	0.74
CLL7	339	8.4	0.73
CLL1	547	13.5	0.71
SU	223	5.5	0.71
SCAN	223	5.5	0.71
Brno	269	6.6	0.69
MDACC	1225	30.2	0.66
0-CLL1	312	7.7	0.66
Total	**4052**	**100**	**0.70**



Conduluci A, et al. ICML 2019

Meta-analysis of treatment requirement risk

1 year

- high-risk: 14.1%
- intermediate-risk: 2.1%
- low-risk: <0.1%

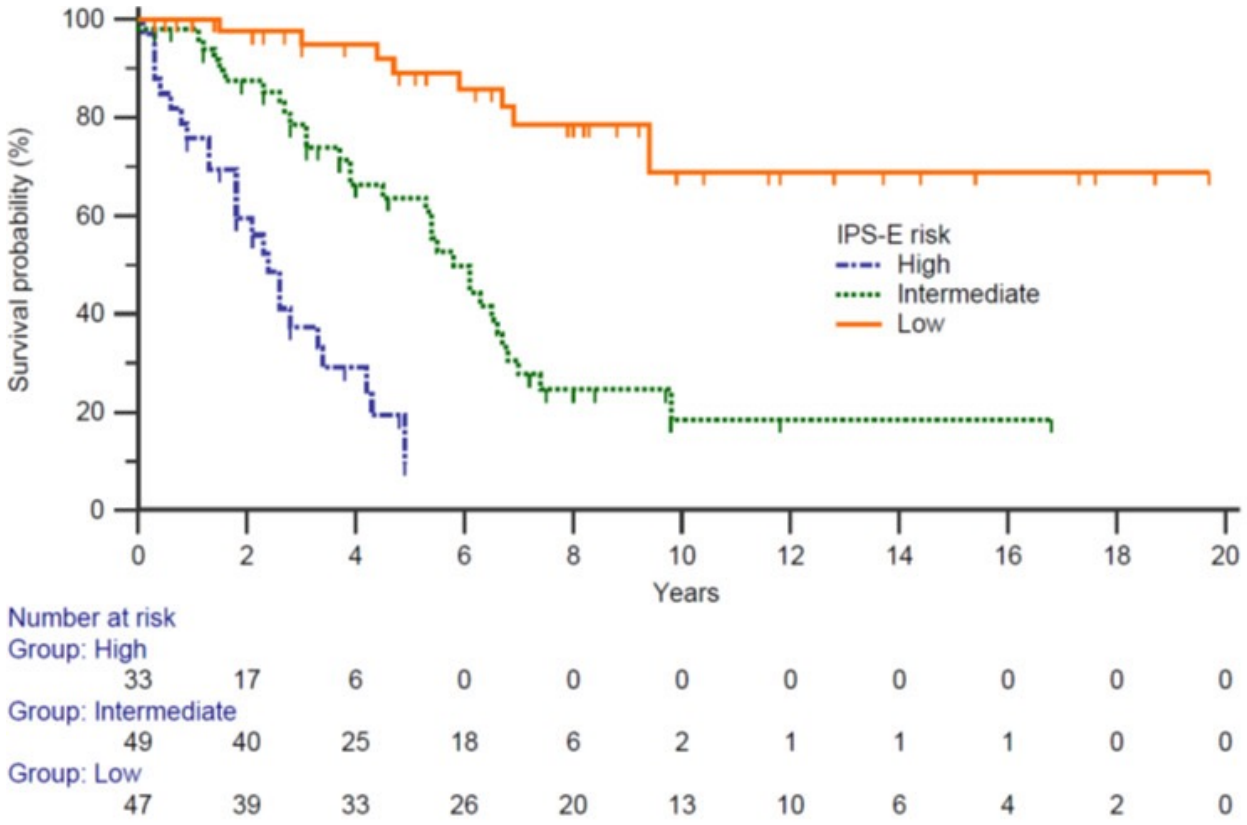
5 years

- high-risk: 61.2%
- intermediate-risk: 28.4%
- low-risk: 8.4%

Mayo cohort excluded to avoid heterogeneity (early stage CLL according to Rai system)

External validation of IPS-E (I)

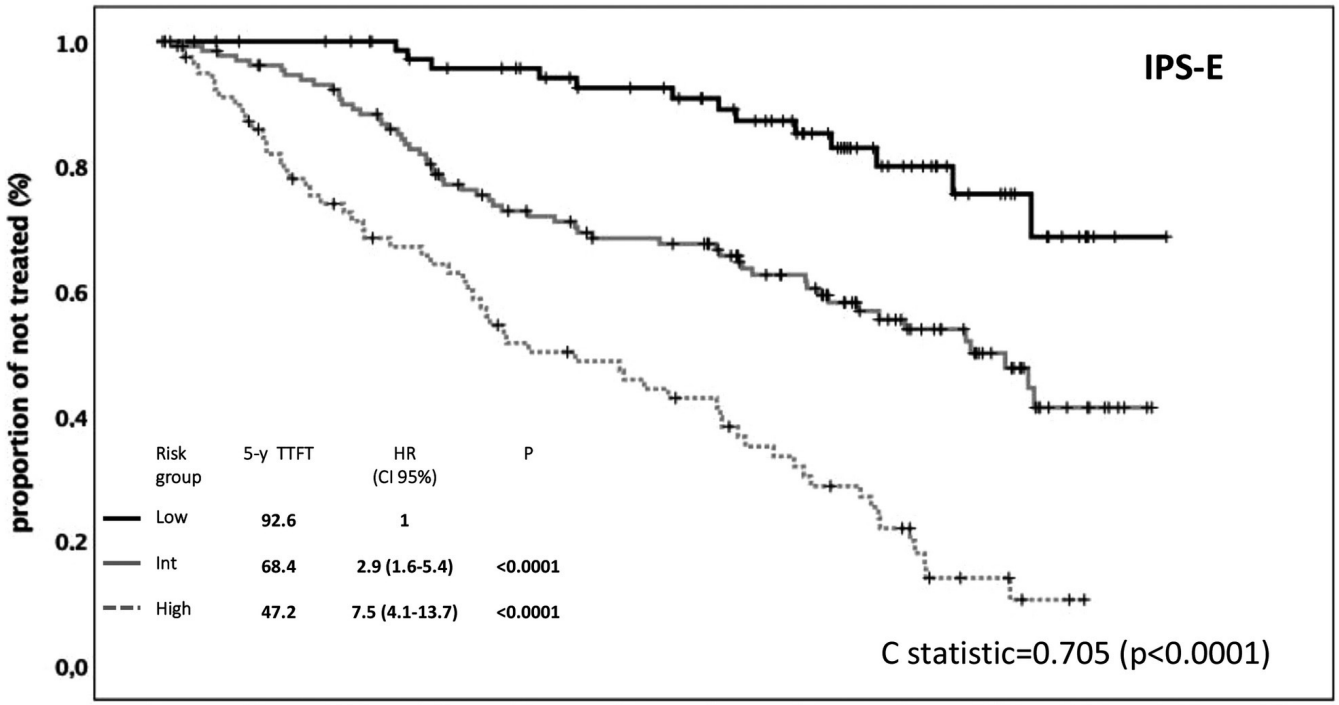
N=130 Binet A CLL



5-year TTFT of 8%, 28%, and 61%

Smolej L, Br J Haematol. 2020

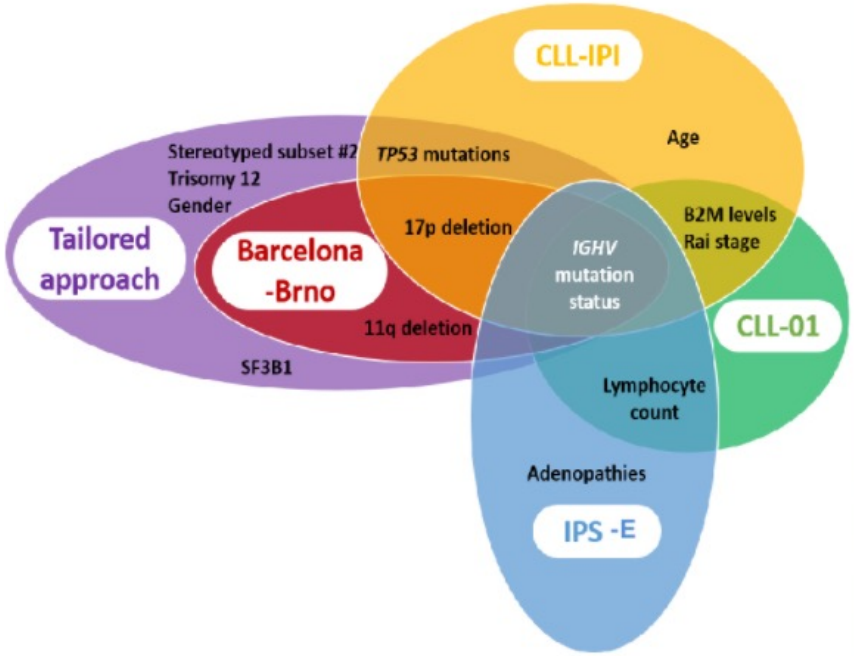
External validation of IPS-E (III)



No. of pts at risk													
Low risk	77	74	72	65	61	57	50	38	24	114	5	0	0
Int risk	135	125	114	95	83	75	70	56	36	21	7	0	0
High risk	80	67	54	44	35	31	27	18	12	5	0	0	0

Morabito F, et al. Eur J Haematol. 2021

External validation of IPS-E (II)



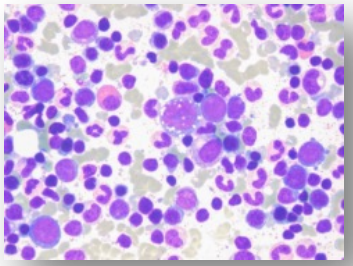
Score risk	Low			Intermediate			High			P	
	N	%	Median TTFT	N	%	Median TTFT	N	%	Median TTFT		C-index
CLL-IPI	265	62	188	133	31	52	30	7	27	<0.001	0.67
Barcelona-Brno	283	66	188	127	30	53	18	4	31	<0.001	0.67
IPS-A	185	43	NR	181	42	88	62	15	31	<0.001	**0.72**
CLL-01	231	54	188	160	37	61	37	9	31	<0.001	0.69
Tailored-M	265	92	188	24	8	60				<0.001	0.61
Tailored-UM	46	33	60	75	47	44	18	13	30	<0.001	0.58

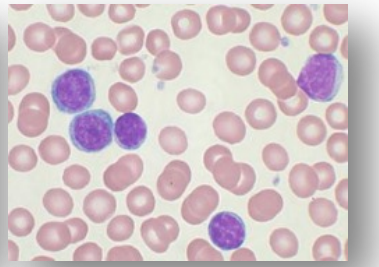
González-Gascón, EHA24; EP707

Benefits of an upfront risk definition

Upfront definition of the risk of treatment requirement can benefit:

- **patients**, who can be informed about the likely course of their disease
- **physicians**, who can allocate medical resources according to patients' risk
- **researchers**, who can design risk-adapted clinical trials





- Lymphoma
- Leukemia

Laboratory of experimental Hematology IOR

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	Simone Bocchetta PhD
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	Katia Pini BSc
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