2nd edition

Unmet challenges in high risk hematological malignancies: from benchside to clinical practice

Turin, September 13-14, 2021

Starhotels Majestic

Scientific board:
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Biological identification of high risk Mantle Cell Lymphoma

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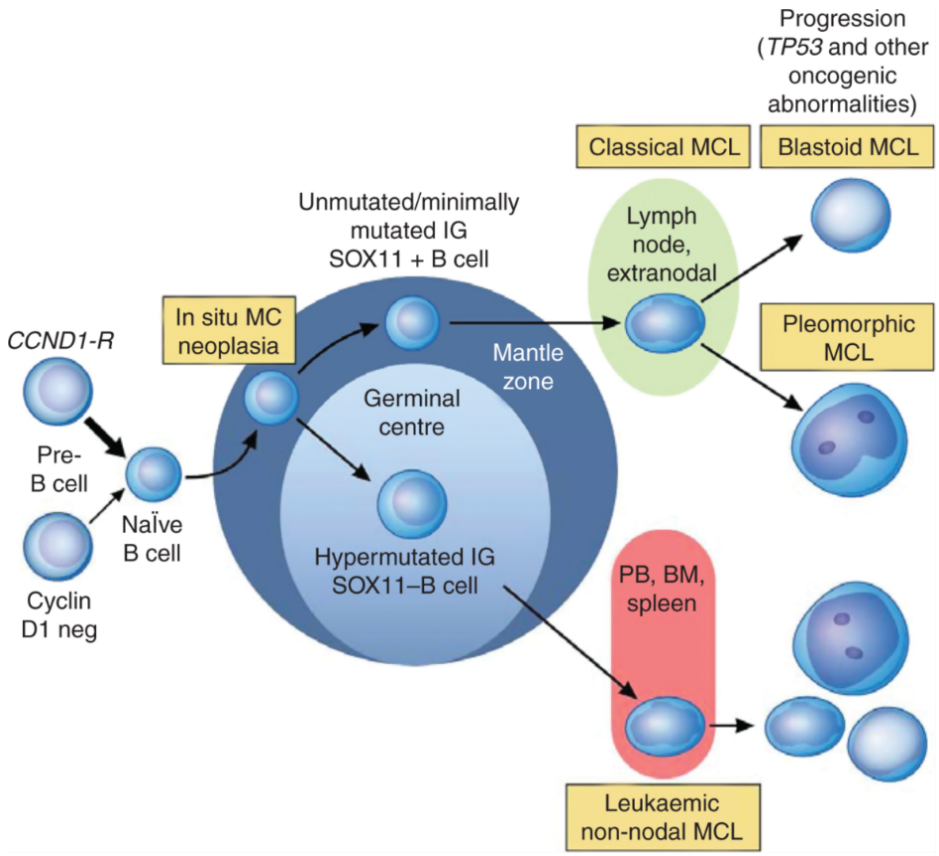
Conflict of interest

- No conflict of interest

Model of molecular pathogenesis in MCL

genetic hallmark
t(11;14)(q13,q32)
98% +

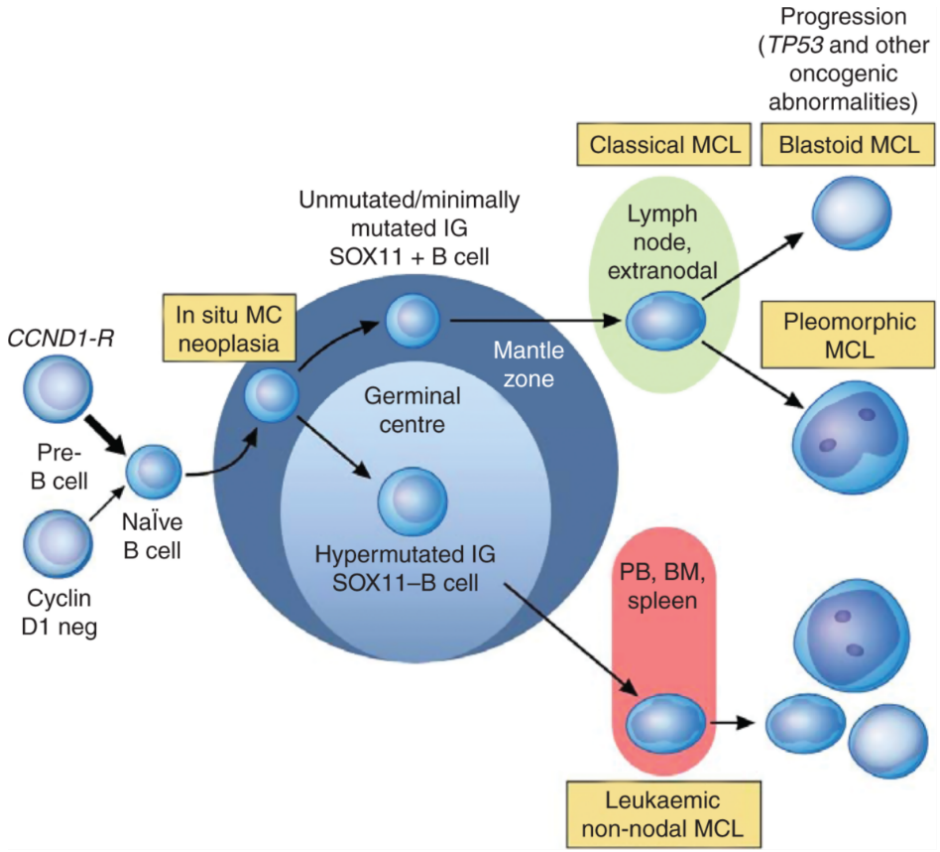


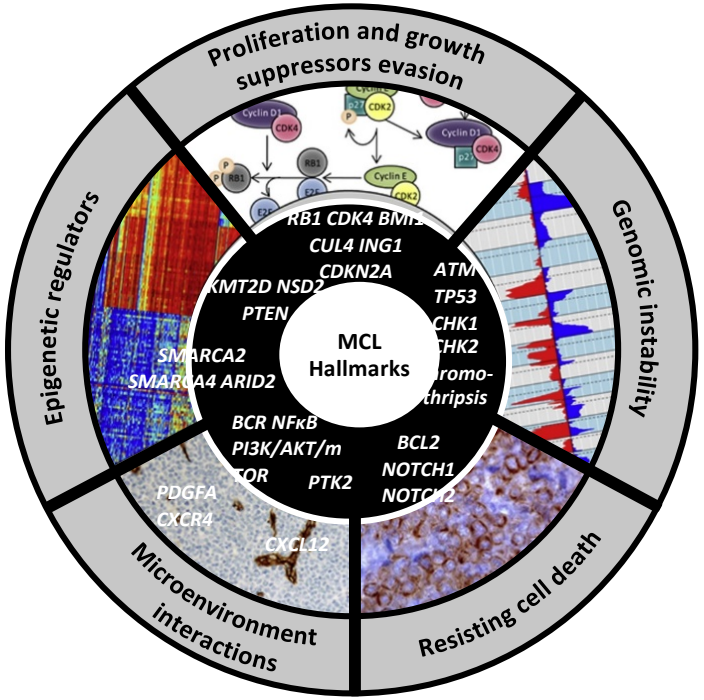
main pathogenetic factors:
- Cyclin-deregulation
- Sox11-deregulation

Swerdlow S.H. et al WHO 2018

Model of molecular pathogenesis in MCL

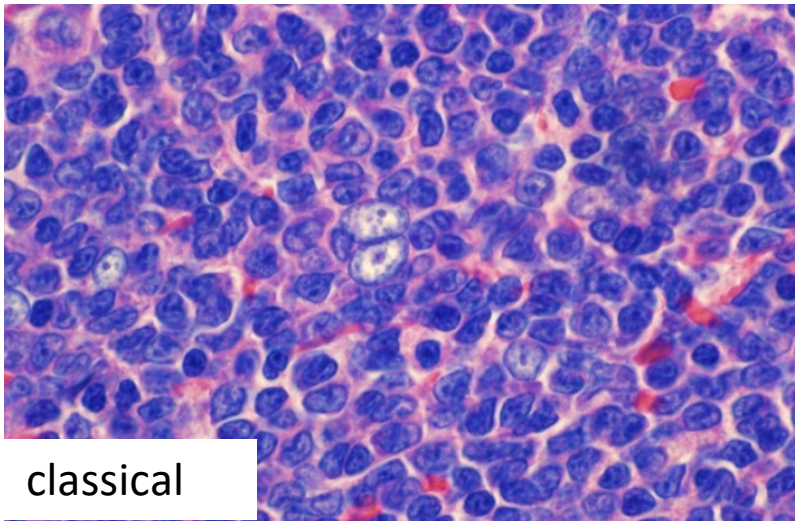
genetic hallmark
t(11;14)(q13,q32)
98% +



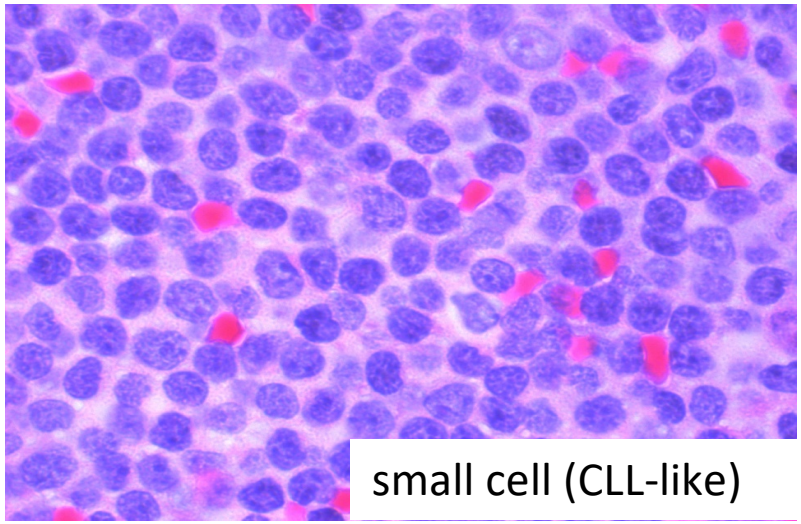


Swerdlow S.H. et al WHO 2018

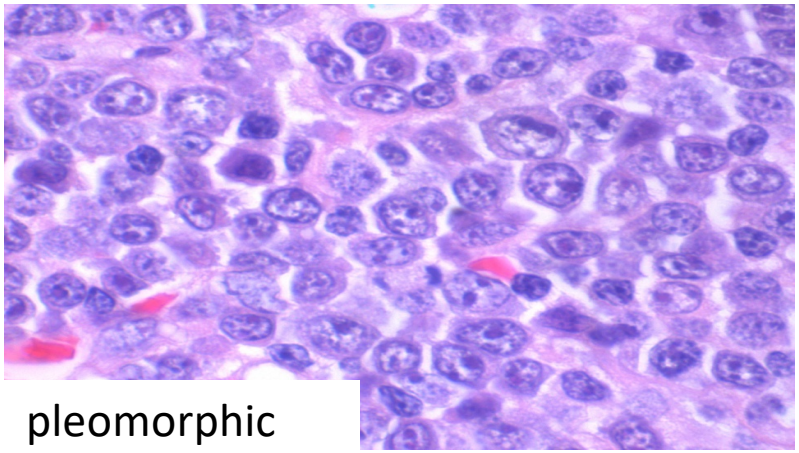
Cytology of MCL



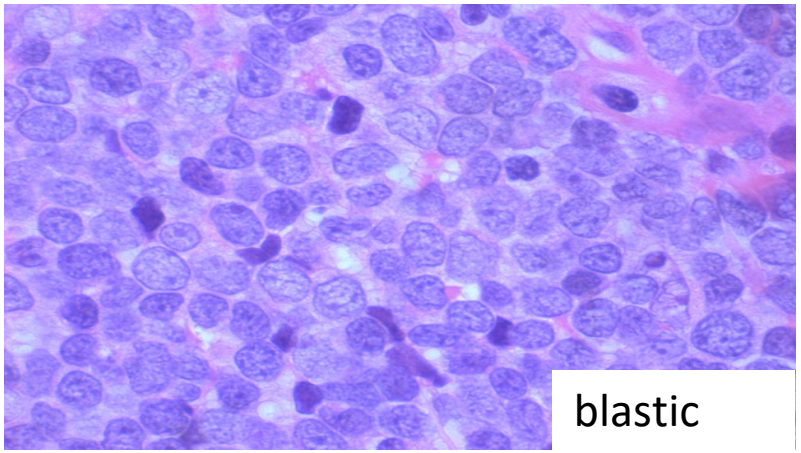
classical



small cell (CLL-like)



pleomorphic



blastic

MCL: two major subgroups (WHO 2016)

Nodal MCL

- nodal and leukemic involvement

- Cell of origin naive B-cell
- No germinal center reactions
- unmutated IGHV
- SOX-11 overexpression
- Higher degree of genomic instability (ATM, CDKN2A, chromotin modifier mutations

Leukemic non-nodal MCL

- Clinically leukemic presentation and splenomegally

- 10-20% of MCL
- Cell of origin is memory B cells with mutated IGHV
- SOX-11 negative
- genomic stability few epigenetic modifications
- germinal center experienced B-cell

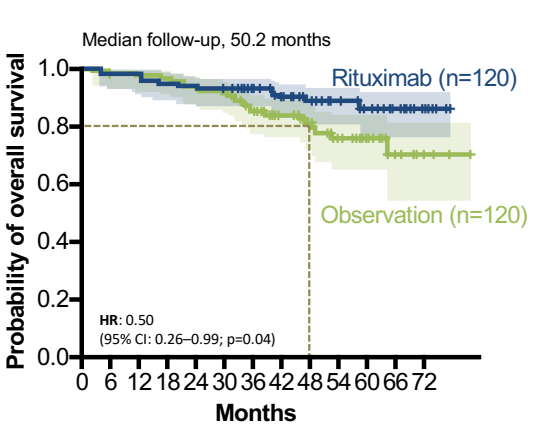
Swerdlow SH et al. The 2016 revision of the WHO classification of lymphoid neoplasms. Blood. 2016;127(20):2375-2390.

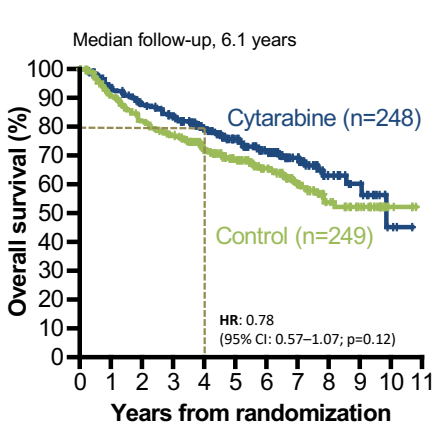
Treatment options: what did we achieve ?

Current treatment standards

Overall survival with ASCT ± maintenance

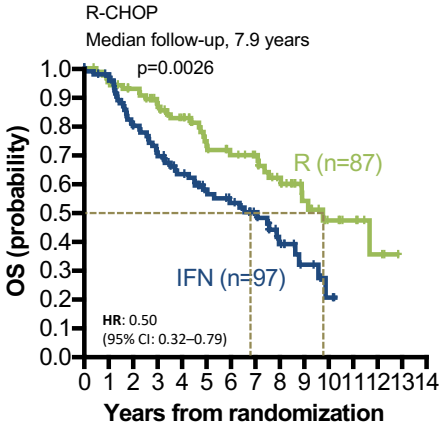
Survival rates from randomization following ASCT*[1,2]

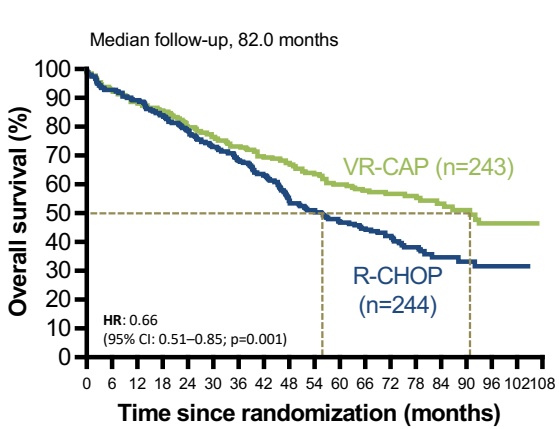




Overall survival without ASCT ± maintenance

Survival rates from second or first randomization, respectively*[3,4]



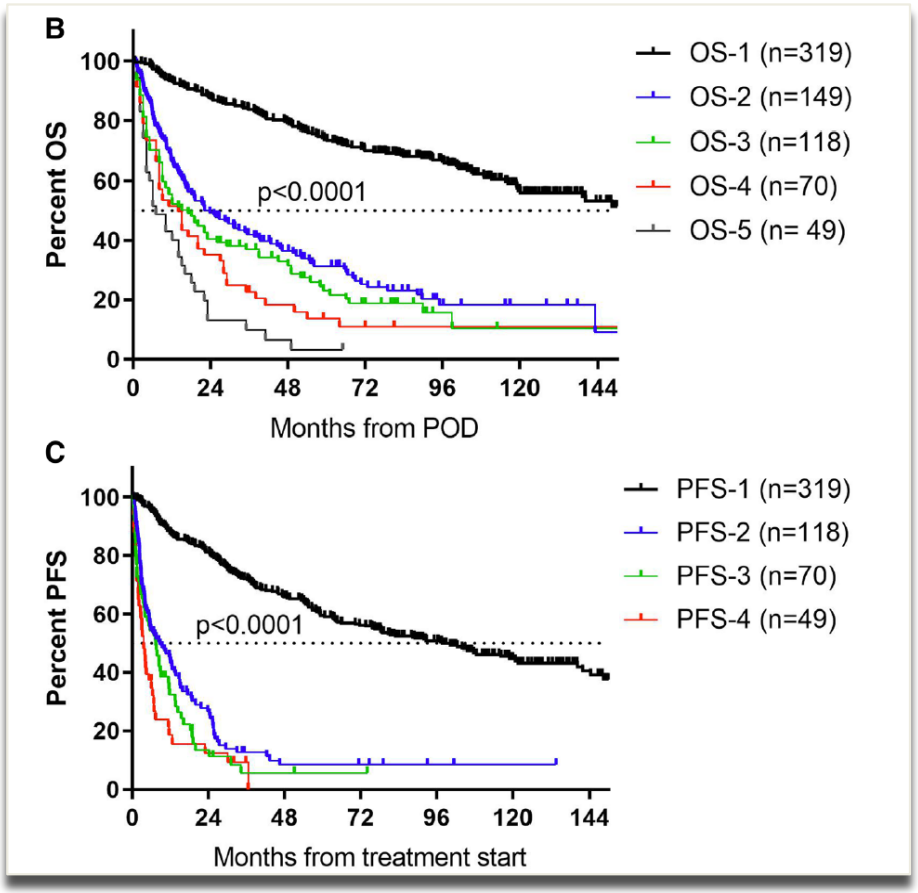


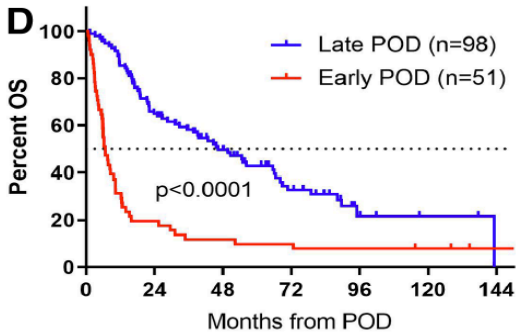
*Tick marks indicate censored data; shaded areas 95% confidence intervals.
IFN, interferon; R, rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; VR-CAP, rituximab, cyclophosphamide, doxorubicin, bortezomib, prednisone.

1. Le Gouill S, *et al. N Engl J Med* 2017;377:1250–1260;
2. Hermine O, *et al. Lancet* 2016;388:565–575;
3. Kluin-Nelemans HC, *et al. J Clin Oncol* 2019;38:248–256;
4. Robak T, *et al. Lancet Oncol* 2018;19:1449–1458.

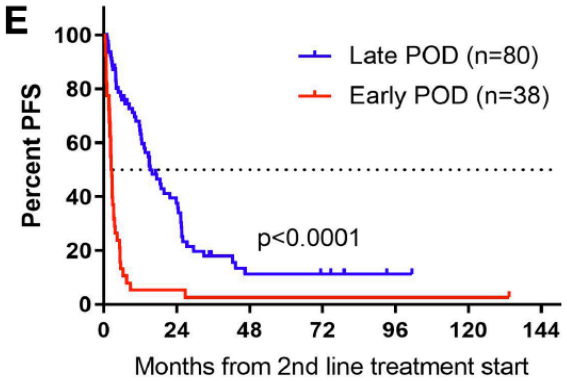
Unmet medical need in MCL - Younger patients -

Outcome of patients from the MCL2 and MCL3 trials after POD



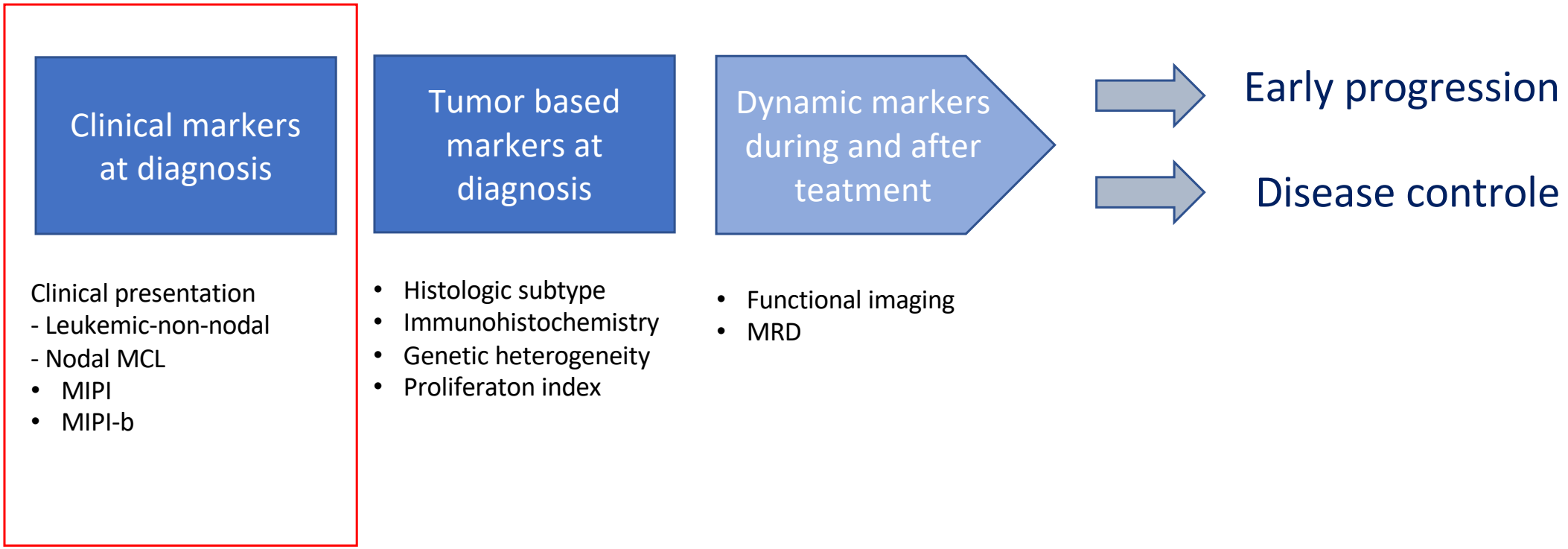


Late POD (n=80)
Early POD (n=38)



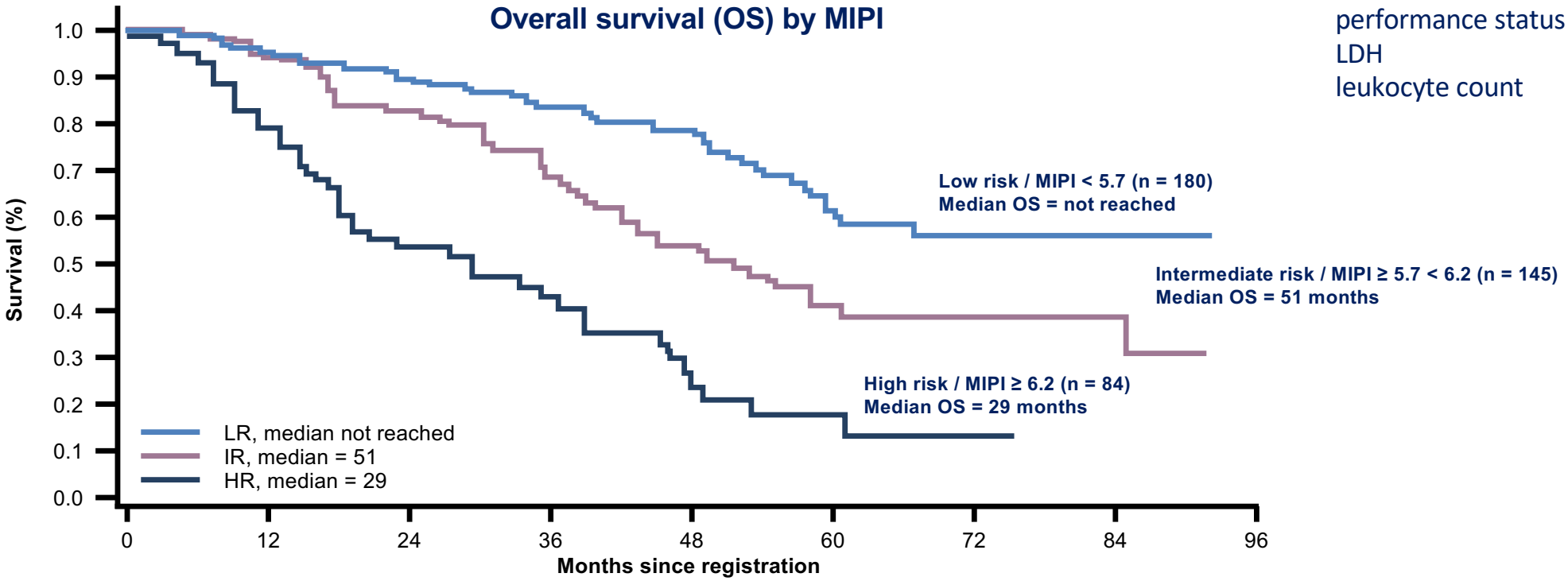
Eskelund Hemasphere 2020

Prognostic markers for MCL – identification of risk groups



MIPI is a strong indicator of prognosis and OS in patients with MCL

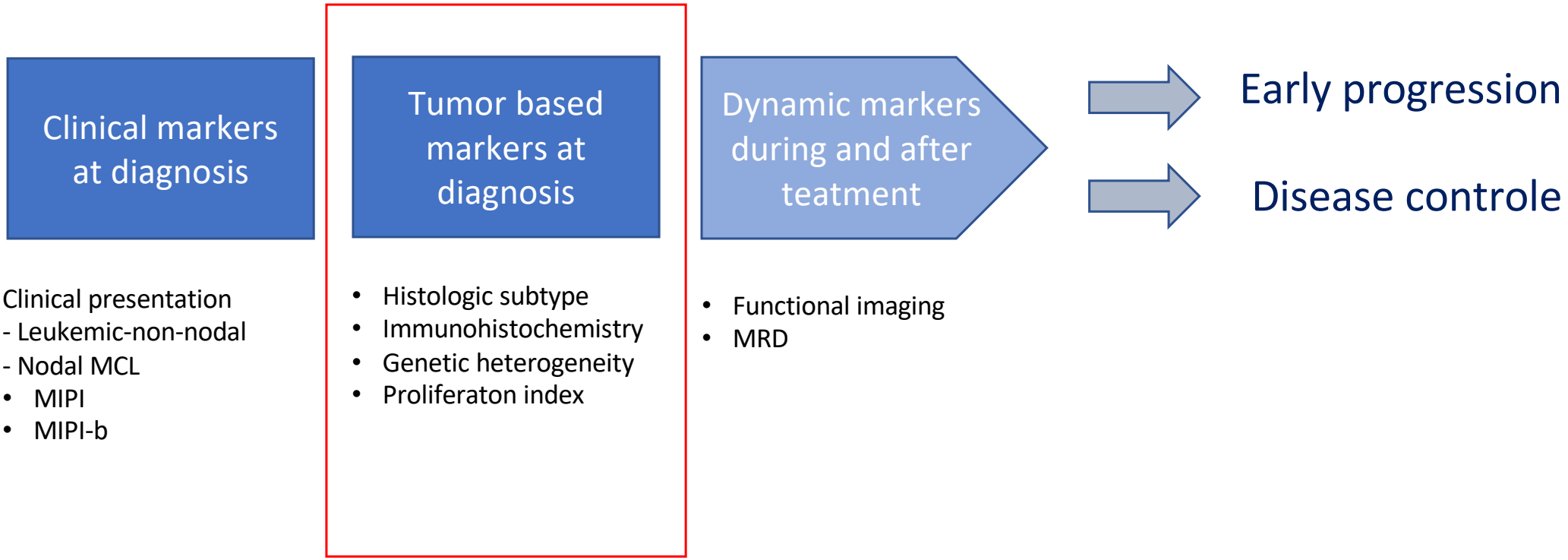
MIPI:
Age
performance status
LDH
leukocyte count



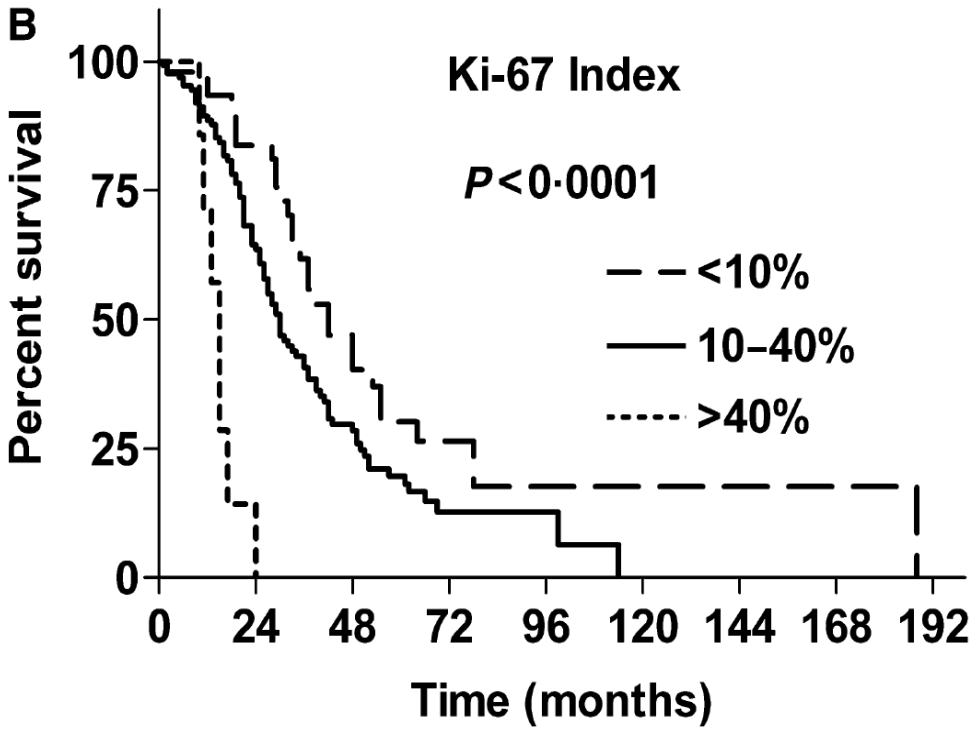
Median OS 29 months vs 51 months for high and intermediate risk, respectively

Hoster E, *et al. Blood* 2008;111:558–565.

Prognostic markers for MCL – identification of risk groups

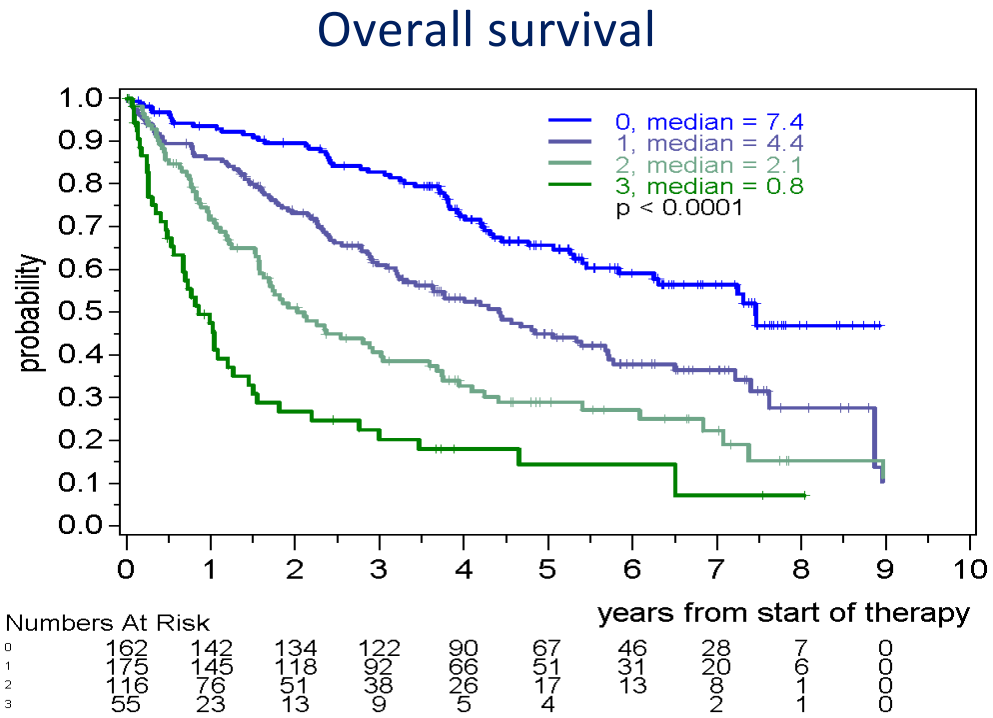


EU-MCL network study: Proliferation as predictor of outcome



Tiemann BJH 2005

EU-MCL network study: Modified combination of the Ki-67 index and MIPI



MIPI low, Ki67 <30%

MIPI low, Ki67>30%
MIPI intermediate, Ki67<30%

MIPI high, Ki67<30%
MIPI intermediate, Ki67>30%

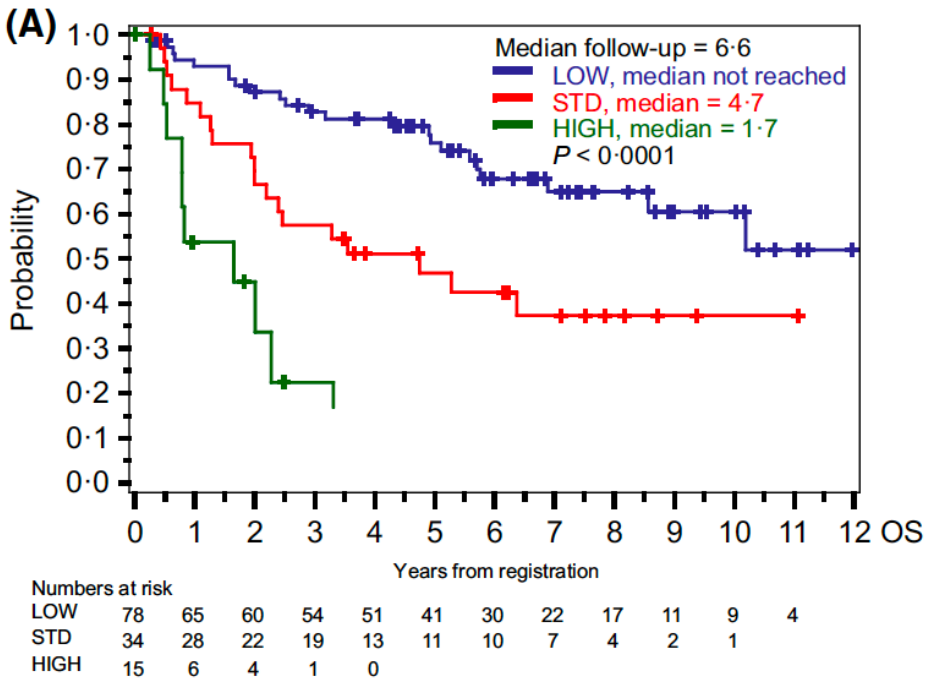
MIPI high, Ki67 >30%

Hoster et al, JCO 2016

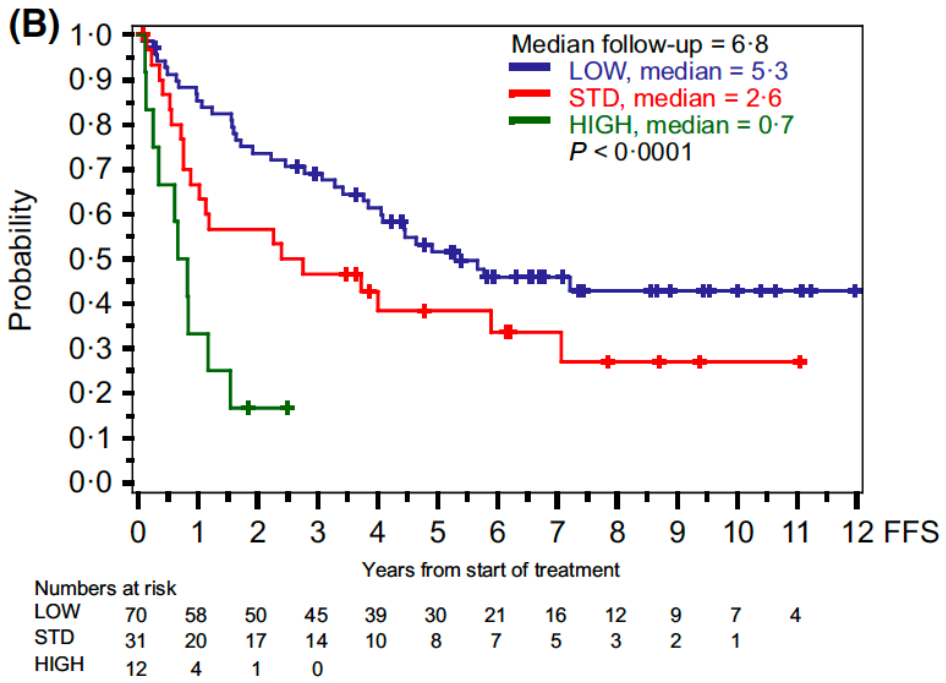
Proliferation: a key marker for outcome

Identifying subgroups via a proliferation signature-based score

OS



FFS

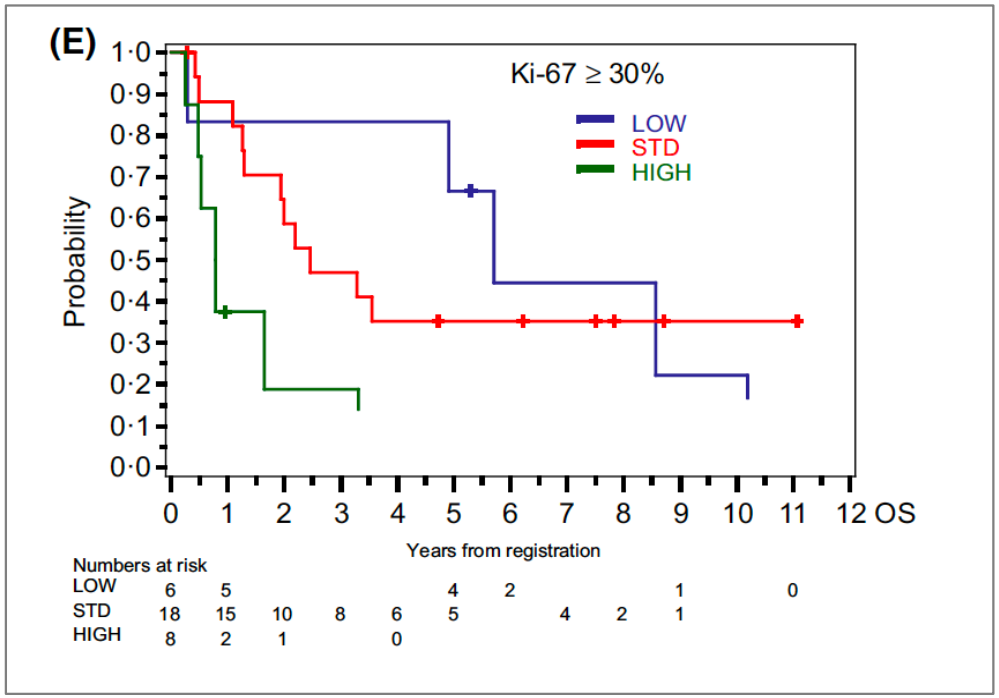


Rauert-Wunderlich Br J Haematol 2019

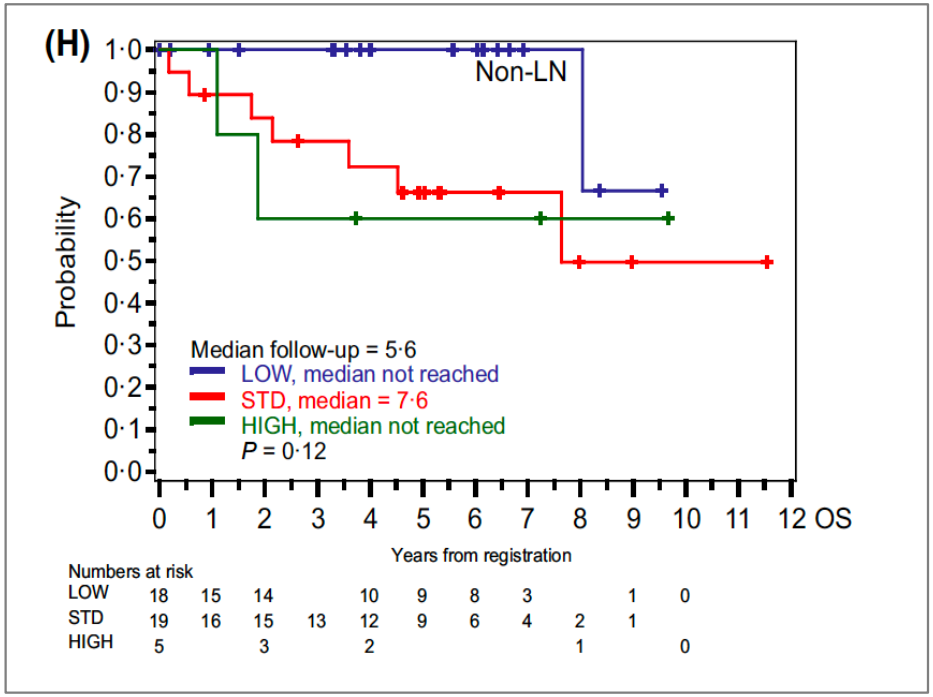
Proliferation: a key marker for outcome

Identifying subgroups via a proliferation signature-based score

Ki-67> 30%



Leukemic MCL

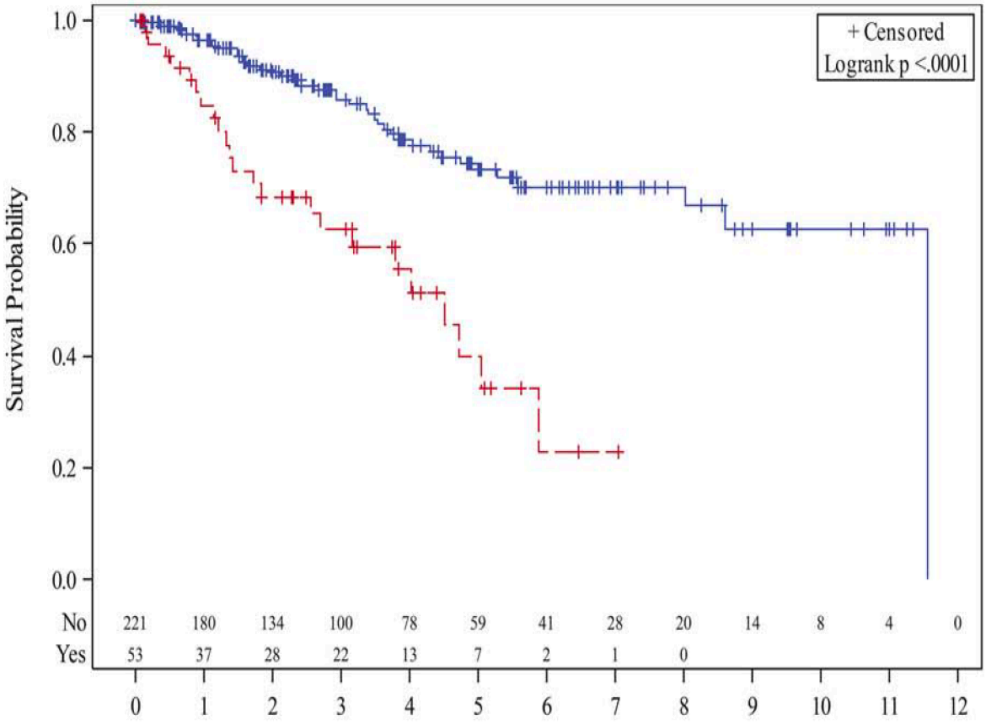


Rauert-Wunderlich Br J Haematol 2019

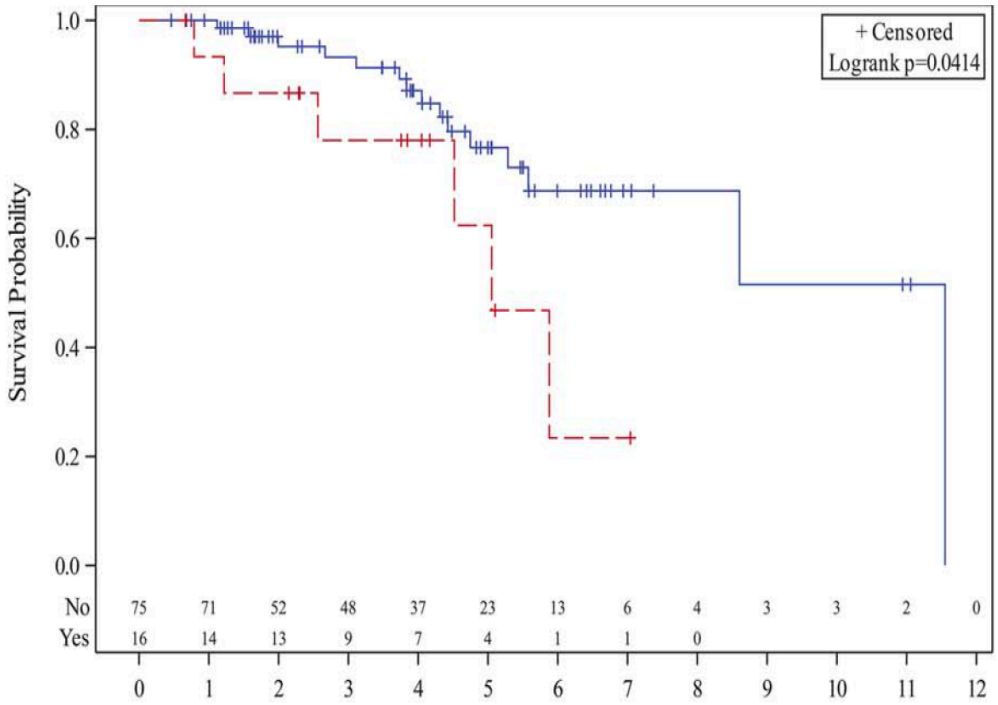
Genetic complexity: a keymarker for outcome

Complex karyotype in patients with MCL predicts inferior survival and poor response to intensive induction therapy

Overall survival

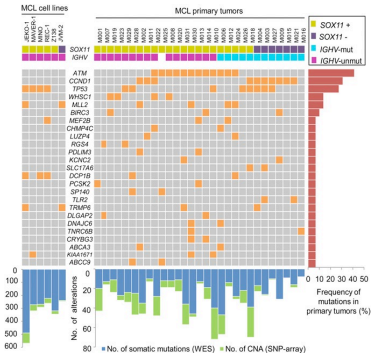


Overall survival after ASCT

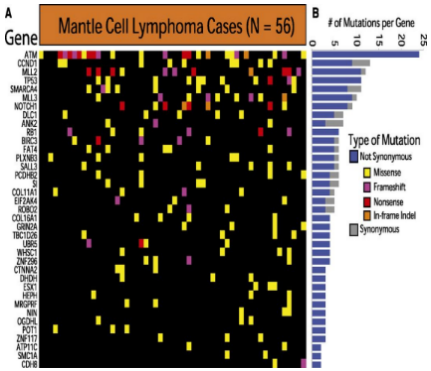


Greenwell et al. Cancer 2018, 124(11), 2306-2315

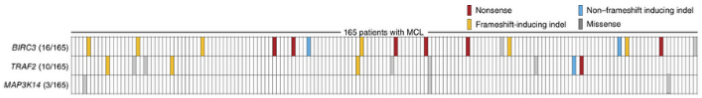
Recurrent mutations and SNV in MCL



Beà et al. *Proc Natl Acad Sci U S A*. 2013



Zhang et al. *Blood* 2014

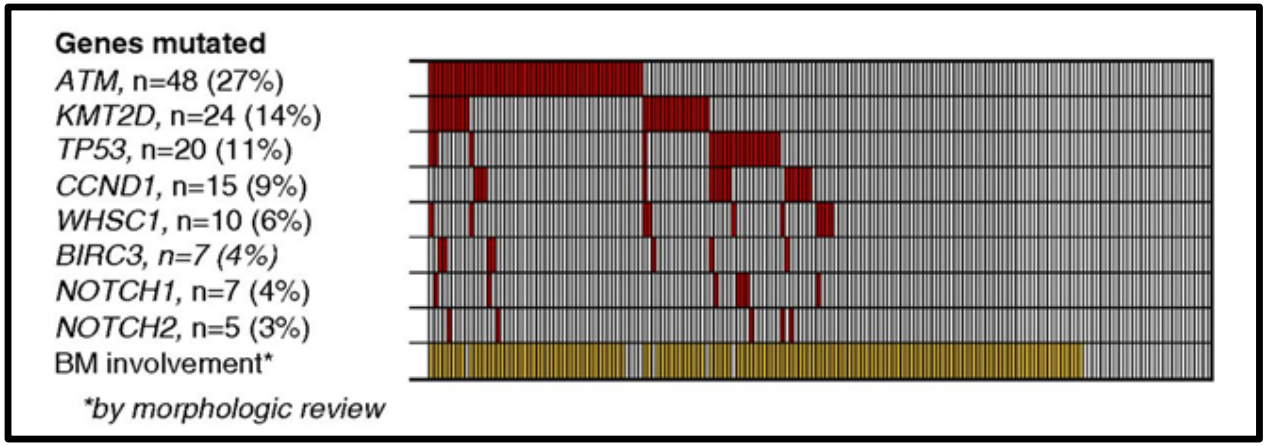


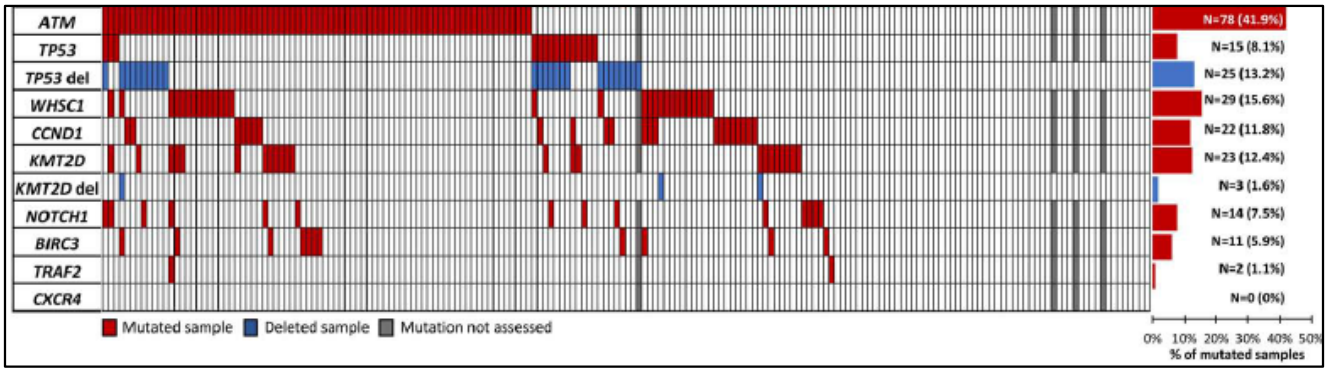
Rahal et al. *Nat Med* 2014

recurrent mutations in MCL >5%

- DNA repair genes and cell cycle regulators TP53, ATM, CCND1
- epigenetic regulation genes KMT2D, WHSC1
- cell-signaling pathways genes NOTCH1-2, BIRC3, TRAF2

Recurrent mutations and SNV in MCL



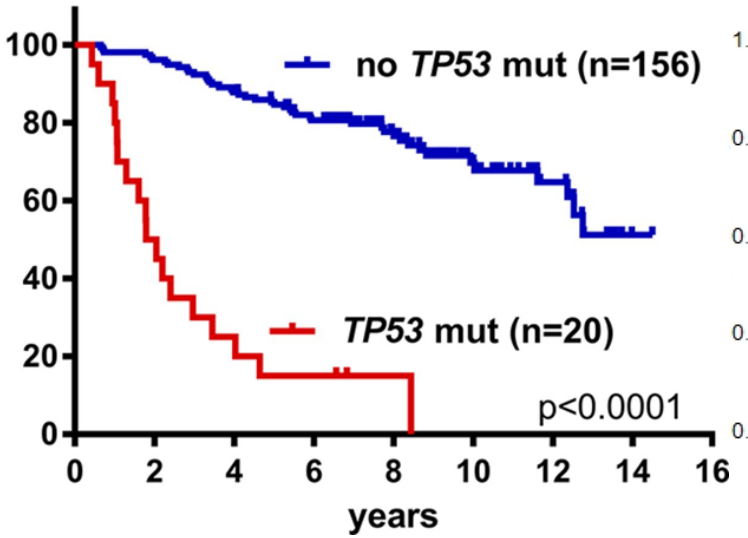


	MSKCC	Nordic	FIL
ATM	**49%**	**27%**	**42%**
TP53	**22%**	**11%**	**8%**
KMT2D	**20%**	**14%**	**12%**
CCND1	20%	9%	12%
WHSC1	12%	6%	16%
BIRC3	13 (8%)	4%	6%
NOTCH1	13 (8%)	4%	8%

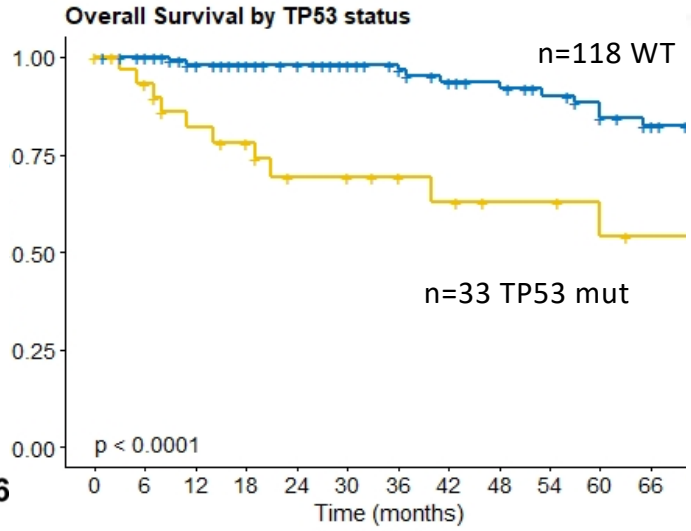
1. Joffe E Blood (2019) 134 (Supplement_1) : 22.
2. Eskelund, C. et. al. Blood Oct 26;130(17):1903-1910
3. Ferrero, S., et al. Haematologica, 2019

TP53 mutations: a keymarker for outcome

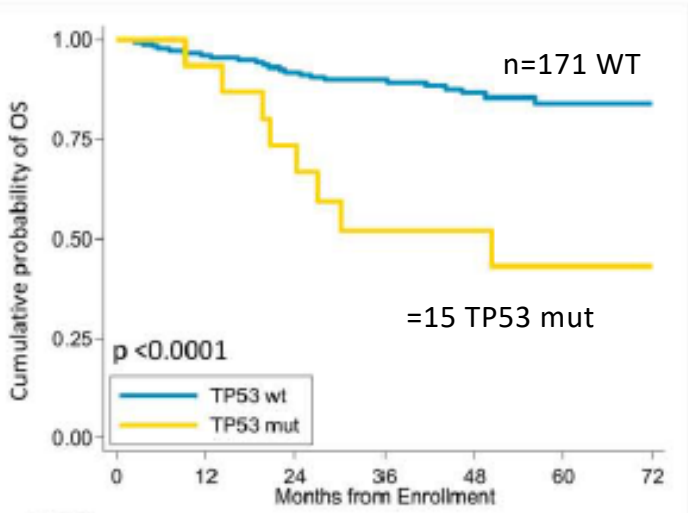
Eskelund, C. et. al.[2]



MSKCC[1]



Ferrero, S., et al. [3]



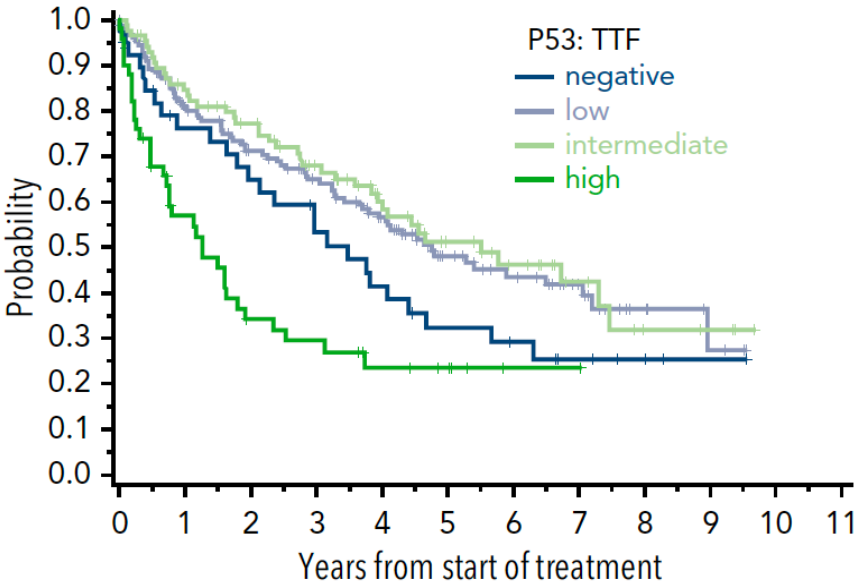
TP53 changes are significantly enriched in known high risk features:

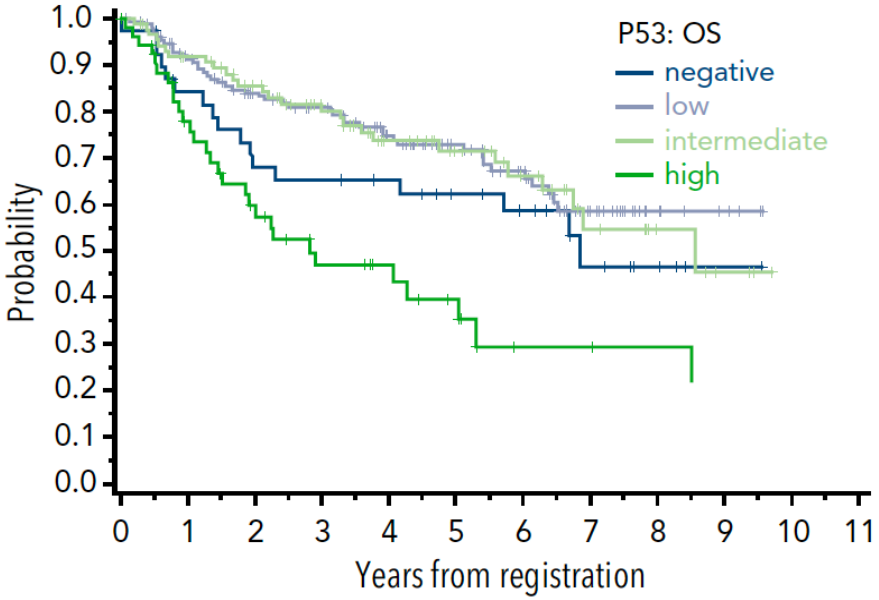
- 48.3% of the TP53 disrupted patients had Ki-67 ≥30%,
- 37.9% scored in the higher MIPI-c risk classes (i.e. “intermediate-high” and “high”
- 22.6% with blastoid morphology

1. Joffe E Blood (2019) 134 (Supplement_1) : 22.
2. Eskelund, C. et. al. Blood Oct 26;130(17):1903-1910
3. Ferrero, S., et al. Haematologica, 2019

Expression of TP53 is associated with outcome in MCL

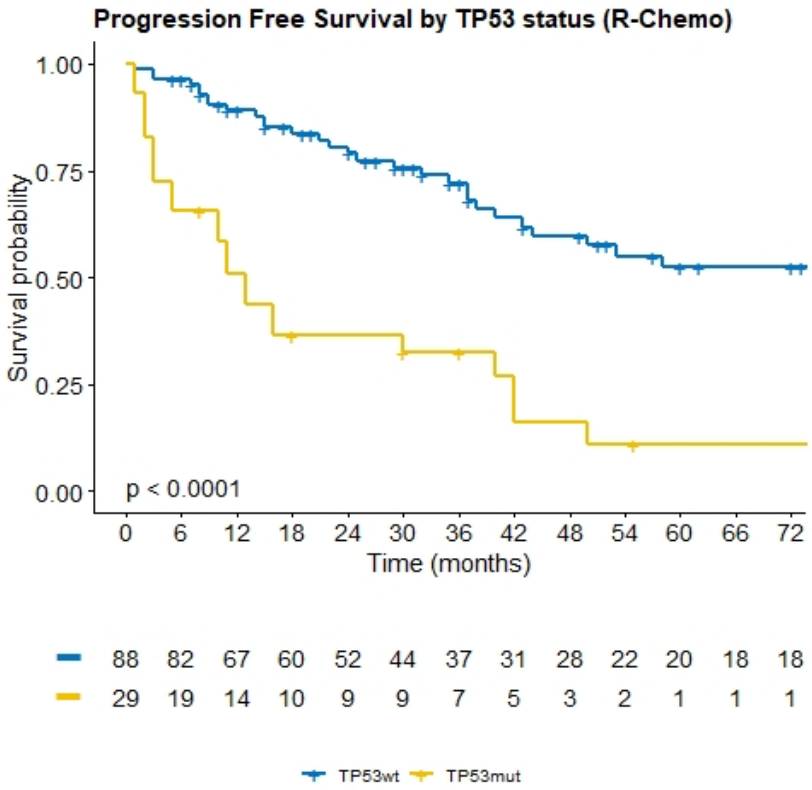
Results of the EU-MCL studies

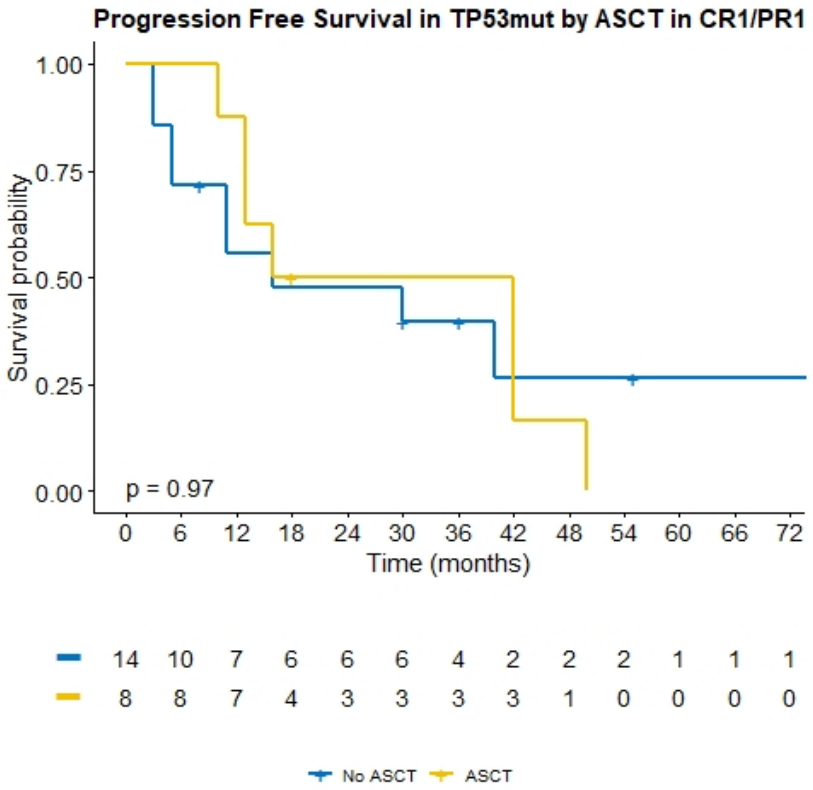




Aukema S Blood 2018

TP53mut patients experience early POD and may not benefit from autologous SCT



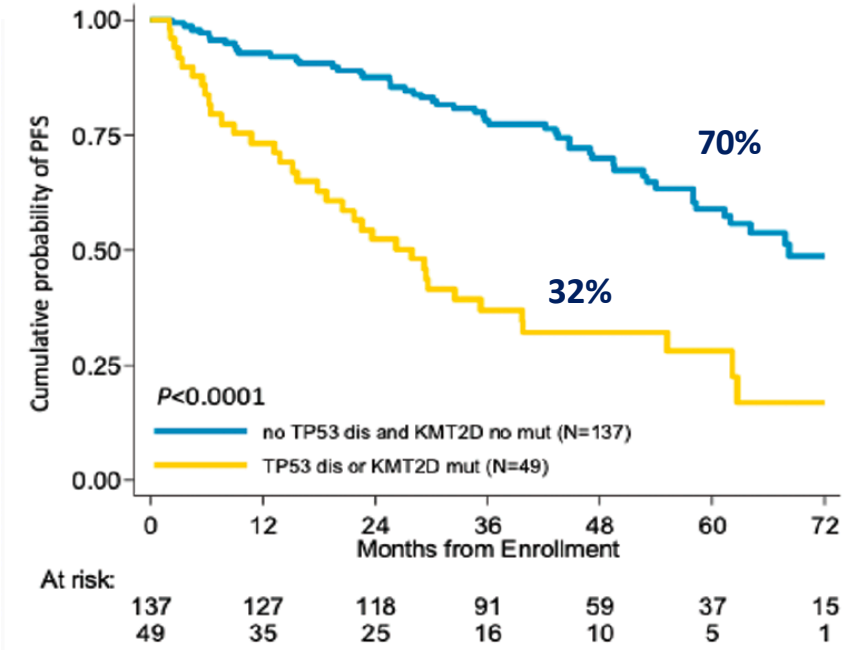


Joffe E Blood (2019) 134 (Supplement_1) : 22.

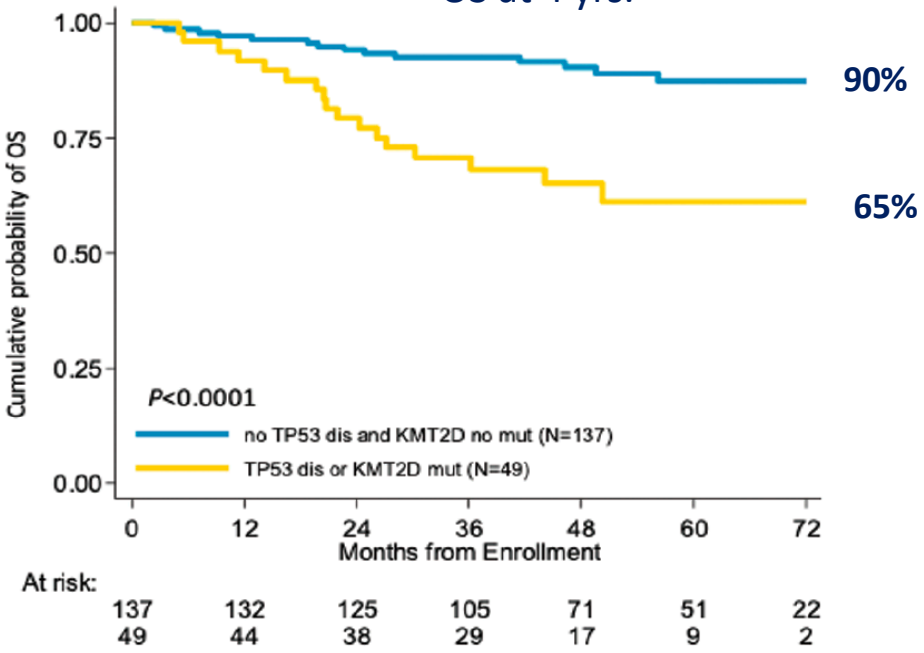
Prognostic impact of combined KMT2D/TP53 alteration

MCL0208 phase 3 trial

PFS at 4 yrs



OS at 4 yrs.

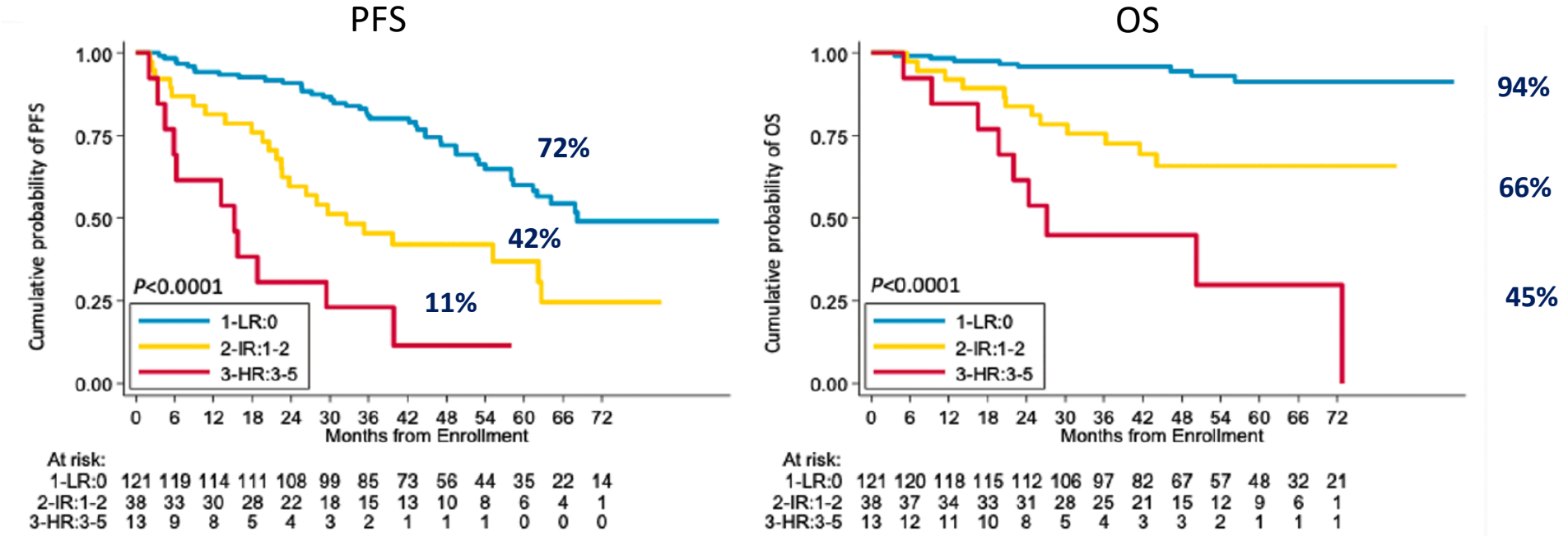


Ferrero, S., et al. Haematologica, 2019

MIPI+: the MIPI-g concept

Scoring of MIPI-c groups and KMT2D and TP53 disruptions and grouping into 3 risk classes

- 0 points, low risk group (LR 121 patients70.3%);
- 1-2 points, intermediate risk group (IR 38 patients, 22.1%);
- ≥3 points high risk group (HR 13 patients, 7.6%)



	MIPI-g	MIPI-c
PFS	**0.675**	0.592
OS	**0.776**	0.700

Ferrero, S., et al. Haematologica, 2019

FONDAZIONE ITALIANA LINFOMI

MCL0208 phase 3 trial

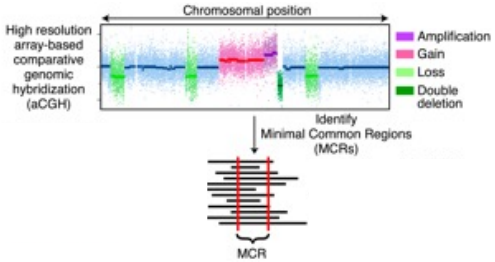
IOR Institute of Oncology Research

Genome-wide profiling

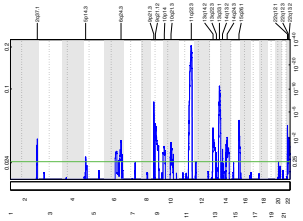
(Illumina HumanOmni2.5 array)

351 CNVs identified

Recurrently Altered Minimal Common Regions (MCRs)

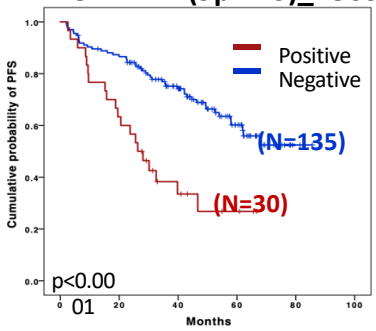


GISTIC

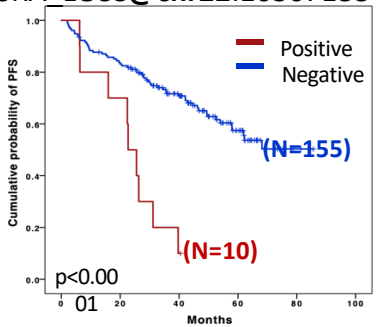


4CNVs associated with a shorter PFS after multivariate analysis

CDKN2A (9p21.3)_LOSS



SRA_**LOSS@chr22**:16367188-25447225



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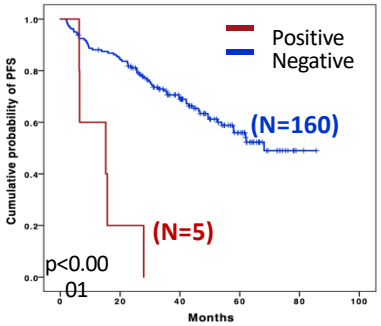
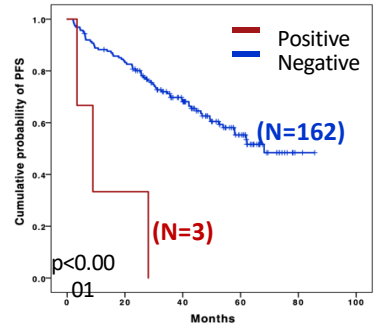


SRA_**HDEL@chr9**:22948787-24820658



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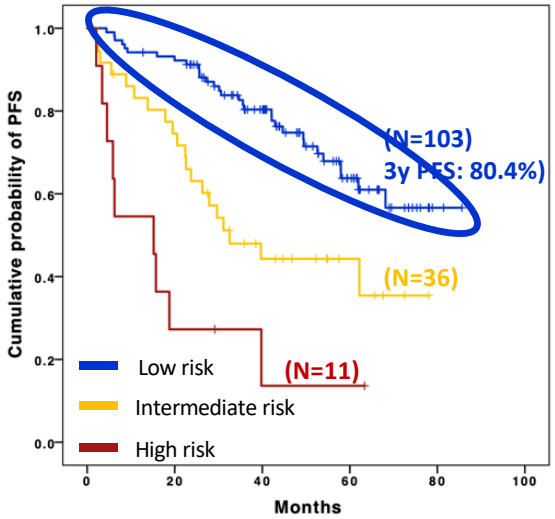
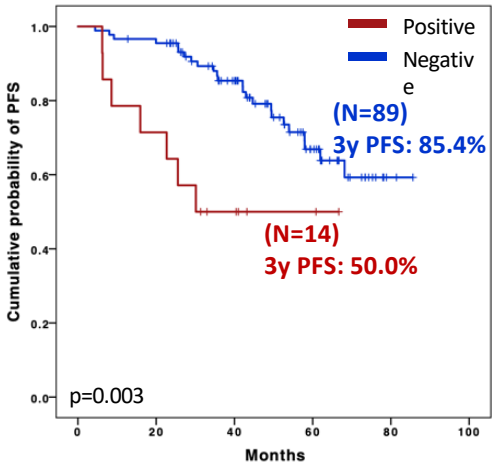
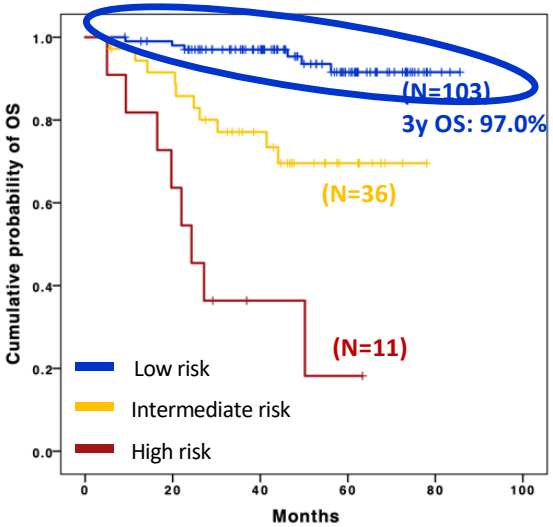
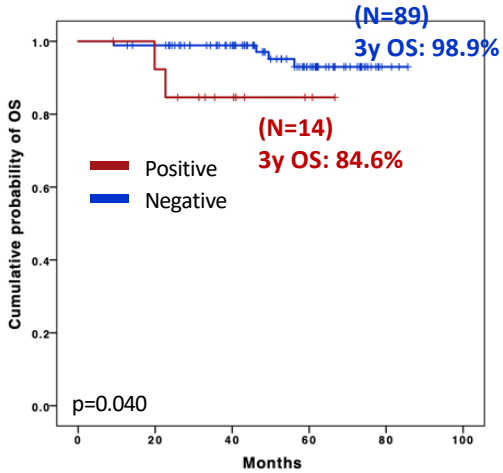
4CNVs split MIPI-g low risk patient









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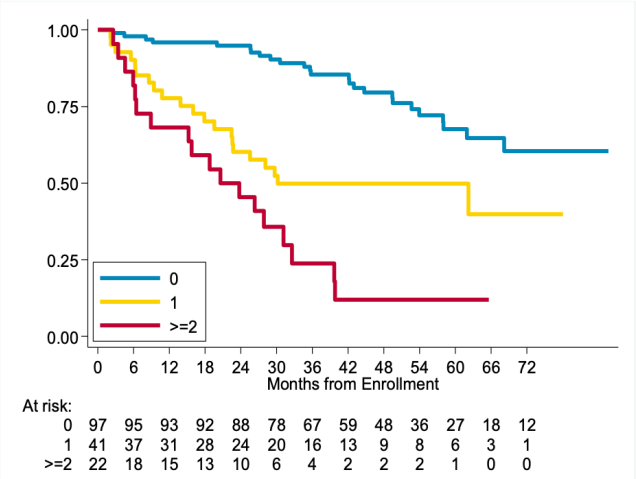
FONDAZIONE ITALIANA LINFOMI

A novel "genetics-only" score (MIPI-go)

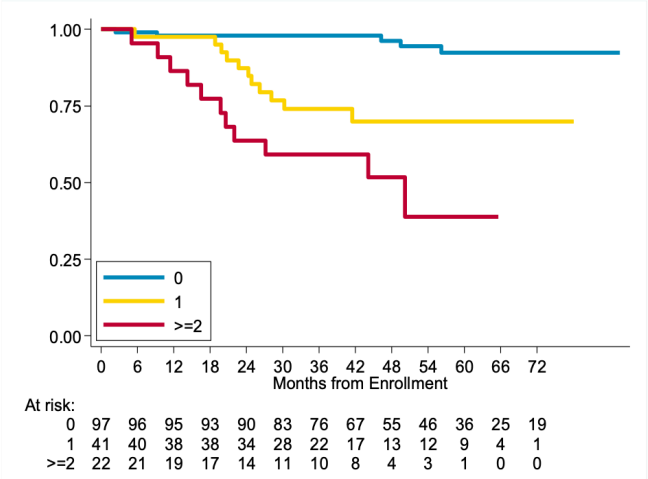
Variables	HR	p value	Point
***KMT2D* mutations**	2.43	0.012	1
***TP53* disruption**	2.63	0.003	1
MIPI-c high risk	1.42	0.382	0
4CNV	2.56	0.002	1

Low risk (LR)	0
Intermediate risk (IR)	1
High risk	≥2

PFS



OS



C-index

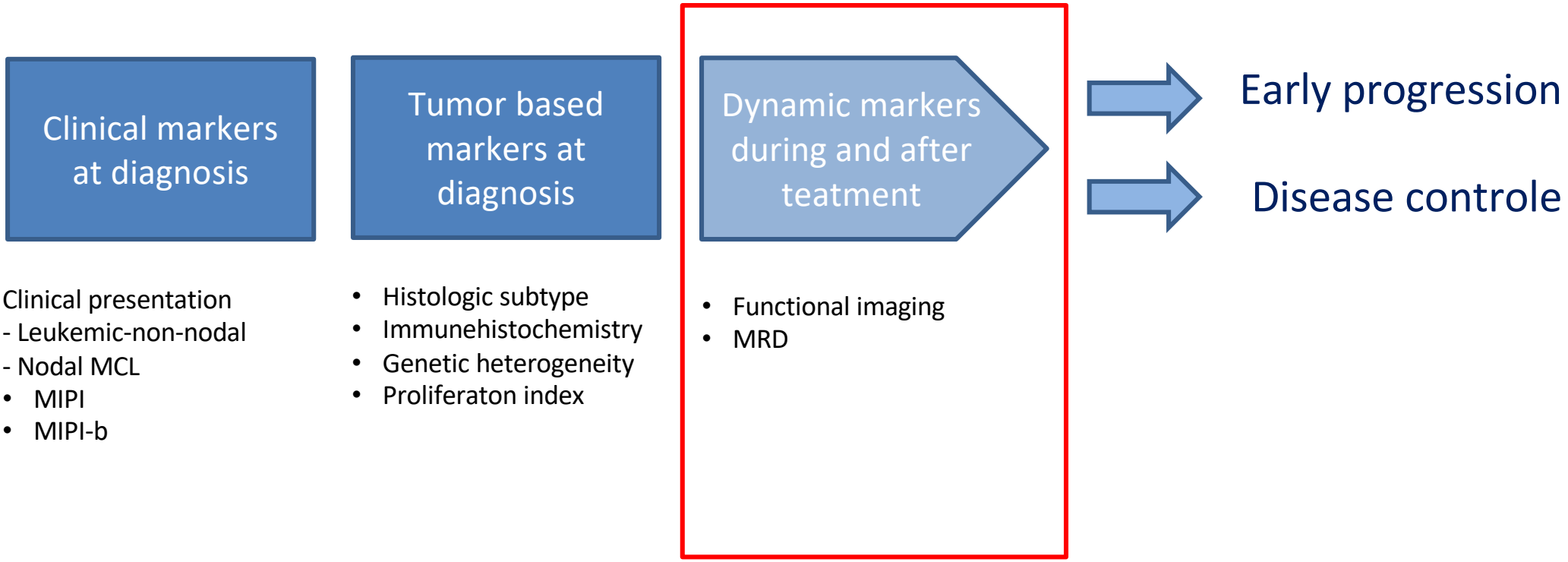
	MIPI-g	MIPI-go
PFS	0.675	**0.715**
OS	0.776	**0.782**

Clinical, molecular and histological features of MCL at diagnosis

	Ultra-high-risk MCL	High-risk MCL	Standard risk classic/nodular MCL	Non-nodular indolent MCL
Molecular features	*TP53* mutated with other high-risk gene mutations (*KMT2D, NSD2,CCND1, NOTCH1, CDKN2A, NOTCH2, SMARCA4*)	High karyotype complexity *TP53* mutated with high variant allele frequency (>10%) or del(17p) by FISH	Normal karyotype	Low karyotype complexity
	Few or no mutations of *IGHV*			Hypermutated *IGHV*
	High expression of *SOX11*	High expression of *SOX11*	High expression of *SOX11*	Very low or no expression of *SOX11*
Histology	*De novo* blastoid/pleomorphic histology K-i67 >30% issues with blastoid/ pleomorphic histology	Blastoid/pleomorphic histology Ki-67 >30% in classic histology	Classical histology Ki-67 <30%	Restricted to mantle zone of lymphoid follicles However, blood and spleen involvement may be noted
Clinical features	Bulky disease, clinically aggressive course	Bulky disease, clinically aggressive course	Bulky or non-bulky disease	Low-risk MIPI Leukemic non-nodal disease

1. Jain P, Wang M. *Am J Hematol* 2019;94:710–725;
2. Fernandez V, *et al. Cancer Res* 2010;70:1408–1418;
3. Sakhdari A. *Ann Diagn Patho* 2019;41:38–42.

Prognostic markers for MCL – identification of risk groups



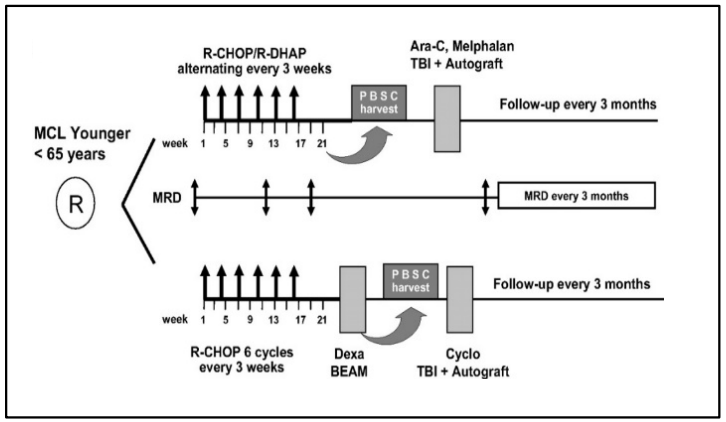
Prognostic impact of MRD in MCL

European MCL Younger trial:

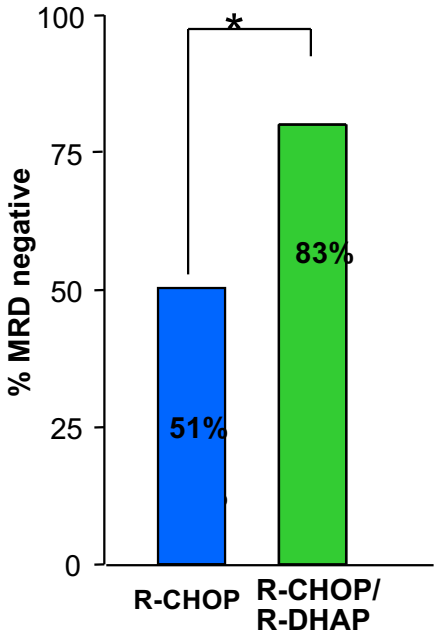
Remission Duration according to MRD Status after ASCT

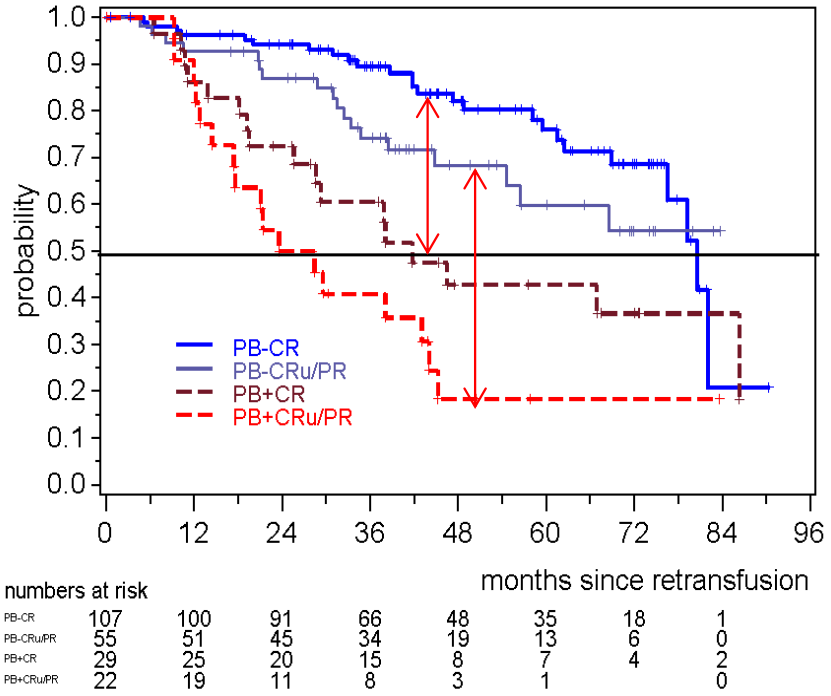
n = 231

Study flow



*p = 0.0013



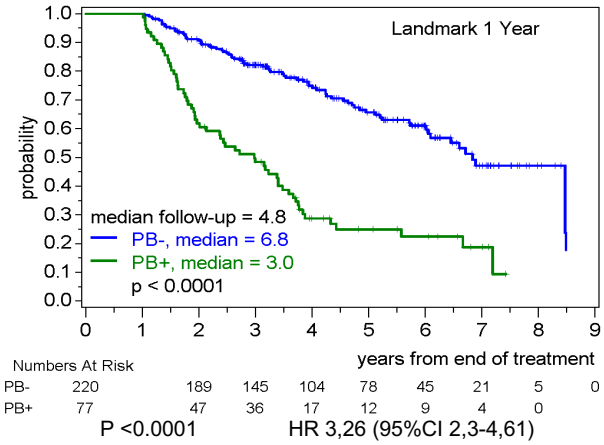


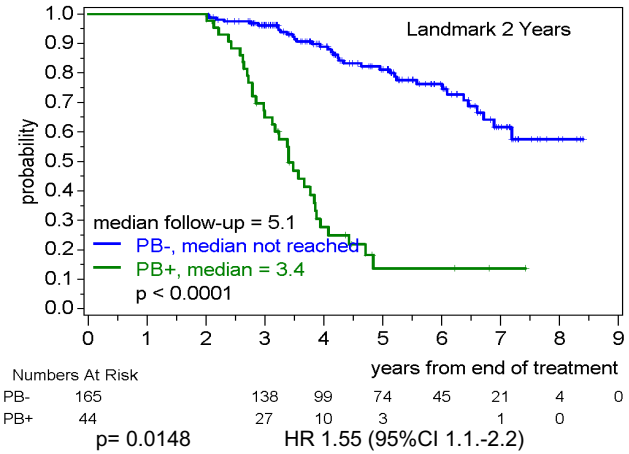
Hermine Lancet 2016

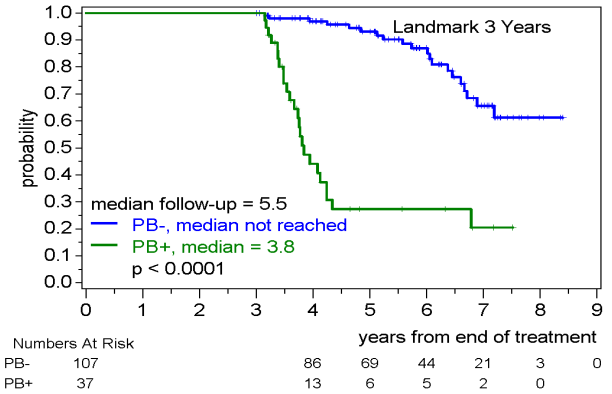
European MCL trials: Landmark Analysis: **PFS and OS** of patients in remission after ASCT (MCL Younger) or postinduction (MCL Elderly).

406 pats. In first remission 406 (67%) 225 Younger and 151 Elderly.

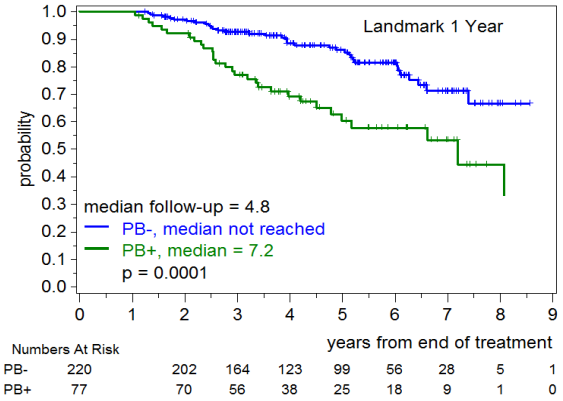
Cox regression: independent of MIPI, trial and treatment arm

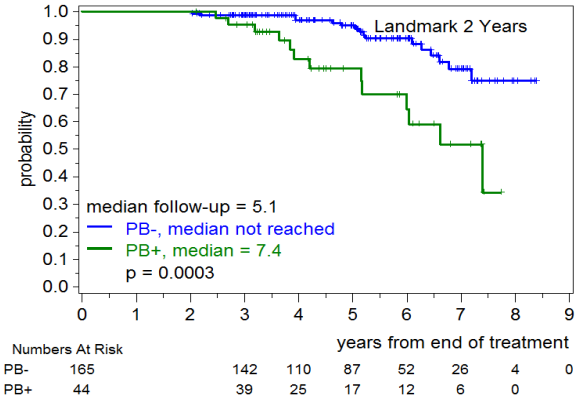


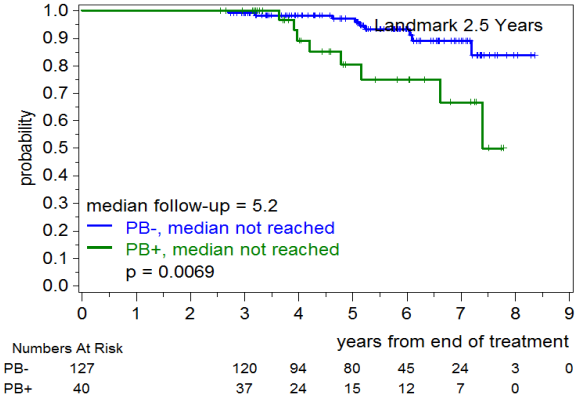




PFS







OS

Summary

- Pretherapeutic risk stratification is well established in MCL
  - Ki67 >30%, blastoid histology, TP53 alterations have been validated in clinical studies
- The MIPI- **+** concept defining clinico- biological subroups should be refined as basis for clinical trials
- Harmonization of diagnostic methods is needed for clinical trials
- MRD is an independent prognostic factor indicating early relapse after treatment
- Clinical trials focussing on high risk MCL are needed
  - Critical: turn around time, validated methods

Thank you!

EuroMRD

NGS EuroClonality

EU-MCL study group

Hämatologie Labor Kiel