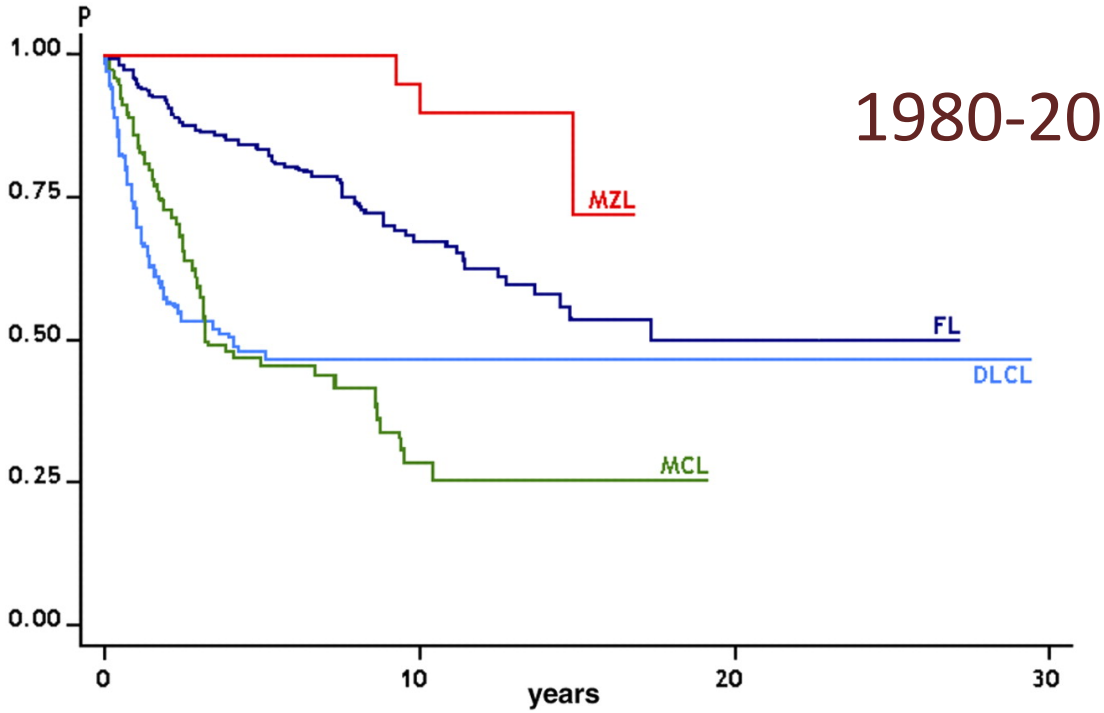
MCL varietà aggressiva: approccio terapeutico e risultati

Francesco Zaja, Udine

Rimini, 16 aprile 2016

Cause-specific survival of the main B-cell lymphoma subtypes

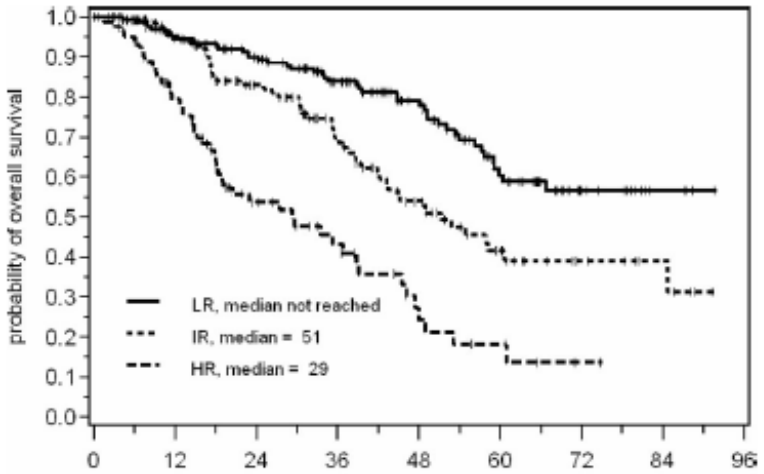


1980-2006

Oncology Institute of Southern Switzerland, Ghielmini and Zucca, Blood 2009

MIPI Index: historical data

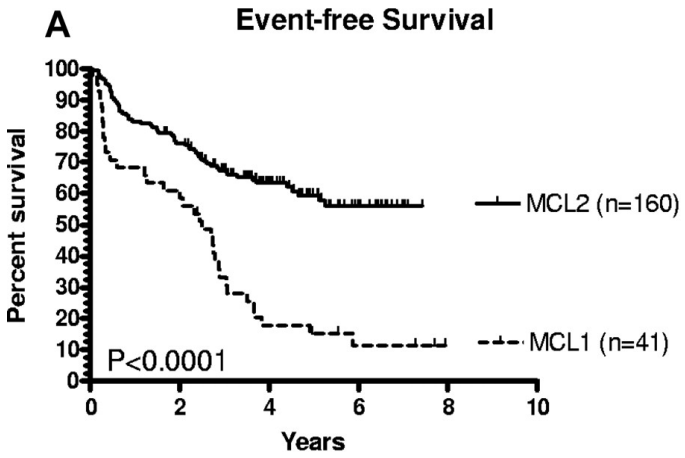
Age x 0.03535)
+ 0.6978 (if **ECOG** >1)
+ [1.367 x log10(**LDH**/ULN)]
+ [0.9393 x log10(**WBC** count)]

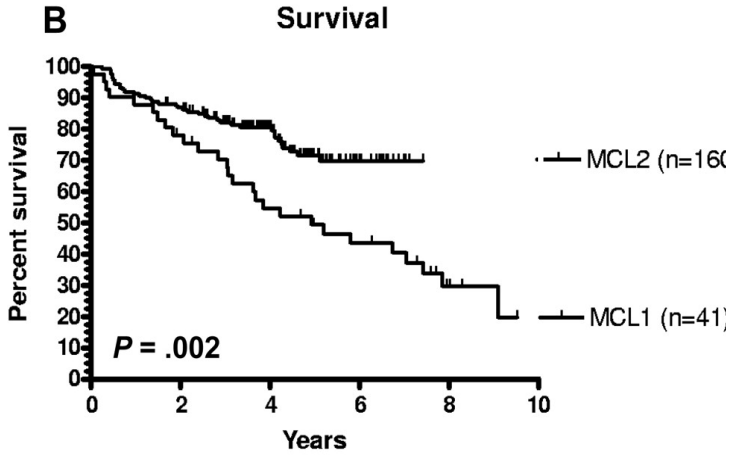


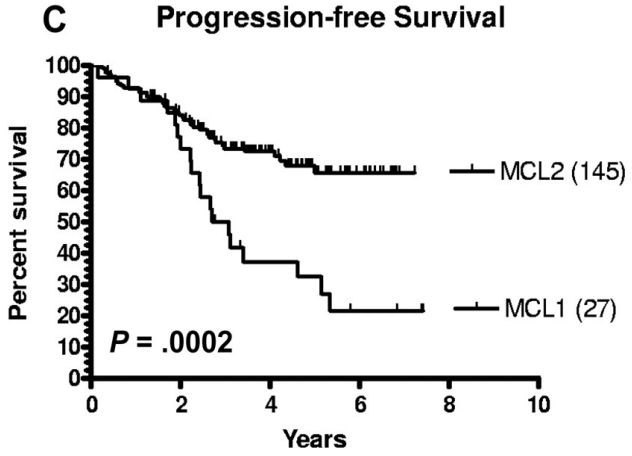
	Score	Patients (%)	Median OS (months)	5-years OS (%)
Low	< 5.7	44	NR	60
Intermediate	5.7-6.2	35	51	40
High	> 6.2	21	29	15

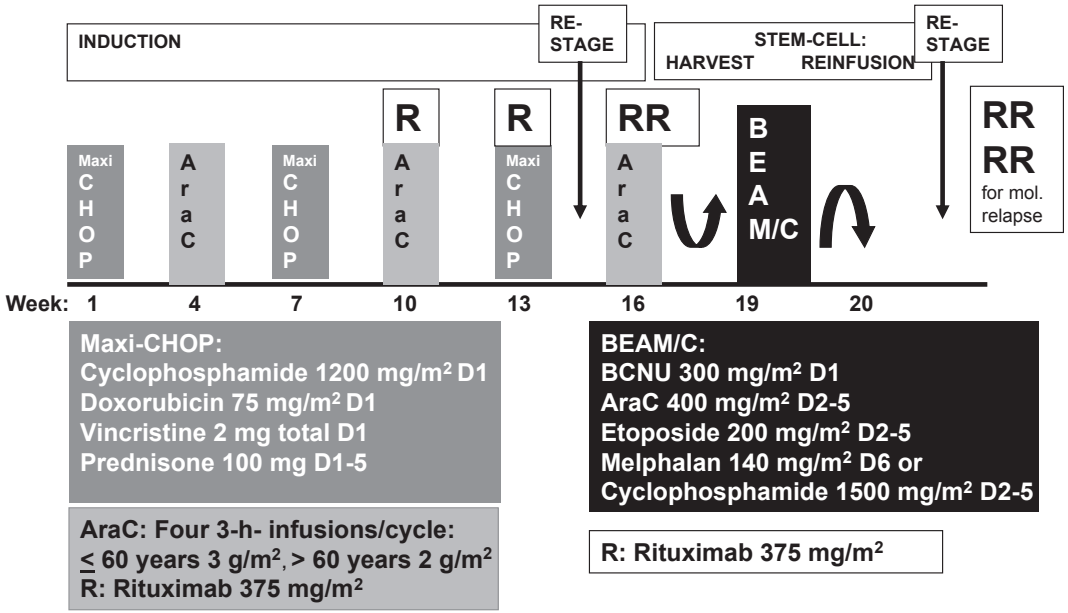
Hoster et al, Blood 2008

Nordic Lymphoma Study Group
MCL1 vs MCL2









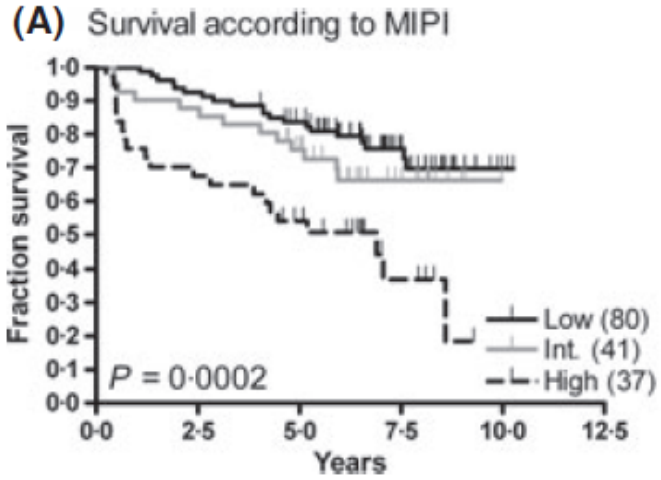
Significant improvement in OS in the last 10 years:
-introduction of new strategies upfront in younger patients
-availability of novel agents in older patients or in the R/R setting

Geisler et al, Blood. 2008

Nordic MCL2 trial update

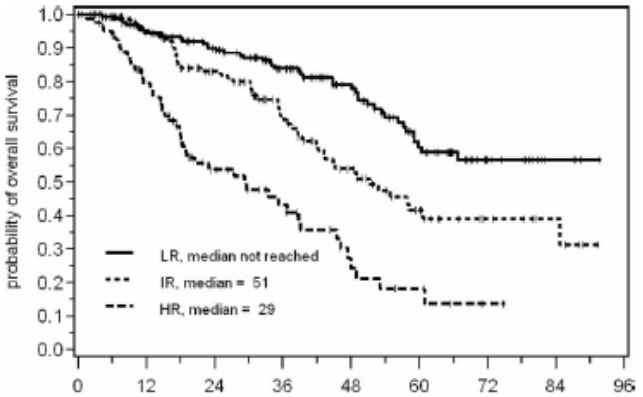
Median observation time of 6·5 years. Median EFS of 7·4 years

Geisler et al, BJH 2012



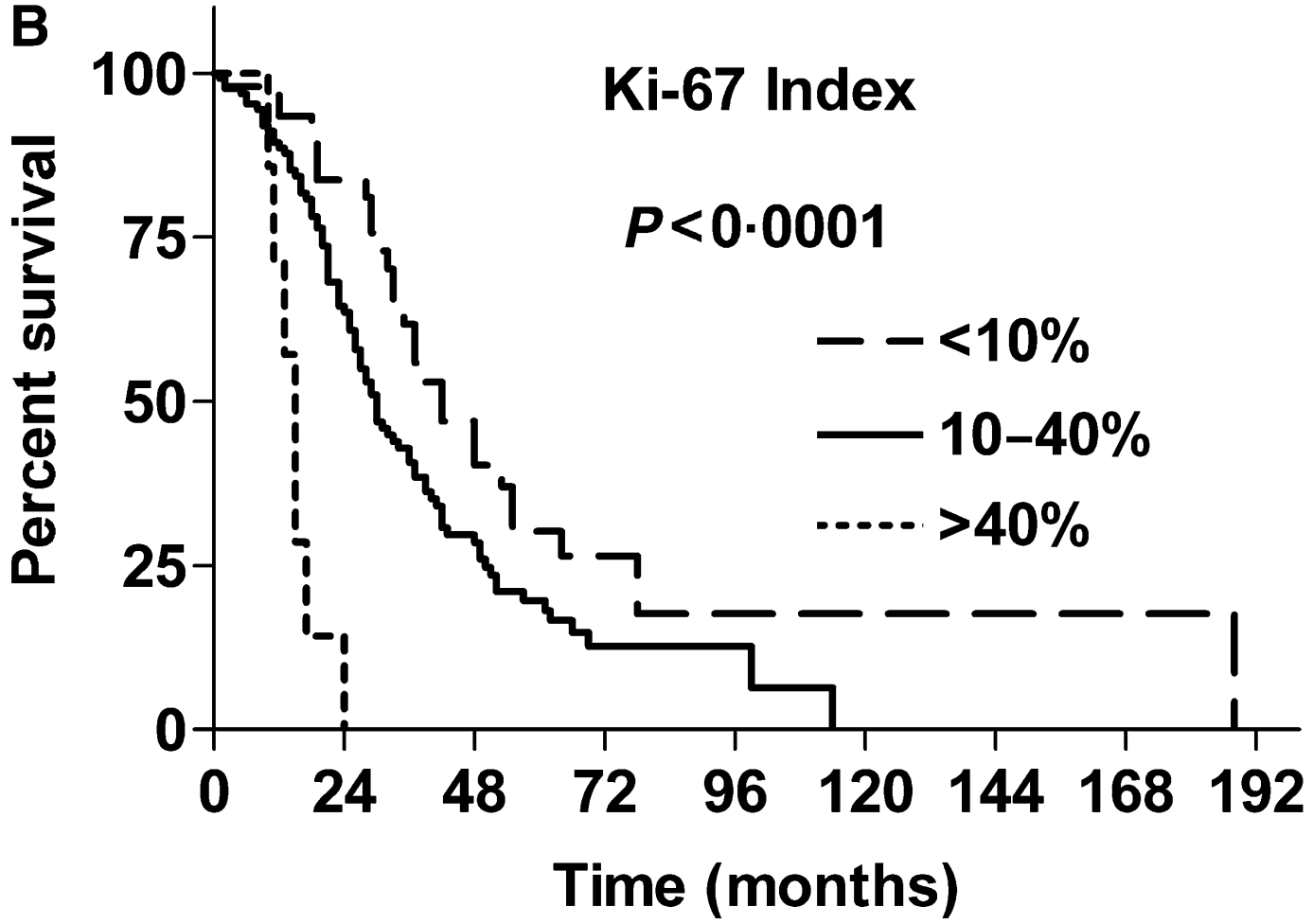
	Median OS (months)	5-years OS
LOW	NR	85%
INT	NR	75%
HIGH	29	55%

Hoster et al, Blood 2008



	Median OS (months)	5-years OS
LOW	NR	60%
INT	51	40%
HIGH	29	15%

Clinicopathological study from the European MCL Network



Tiemann et al BJH 2005

J Hematopathol (2009) 2:103–111
DOI 10.1007/s12308-009-0036-x

ORIGINAL ARTICLE

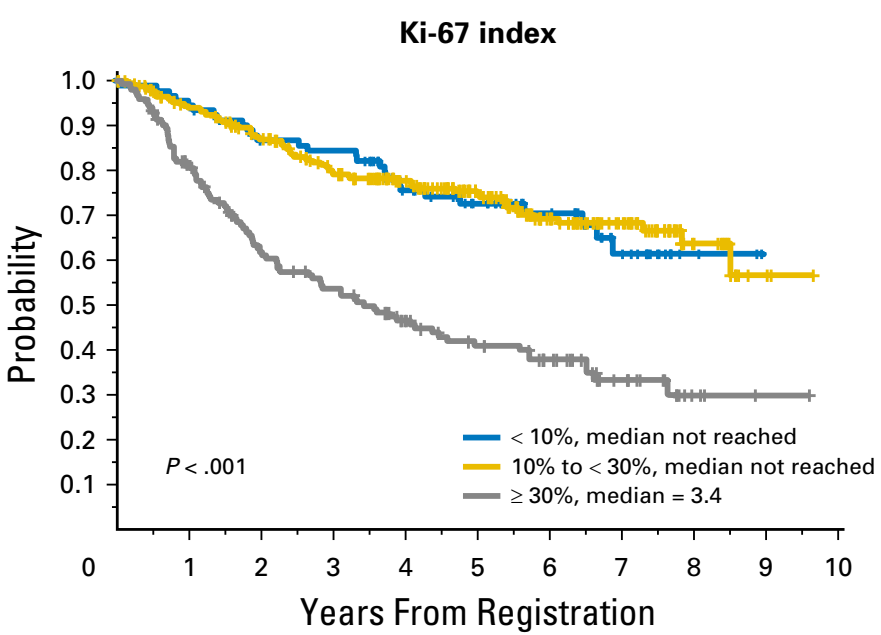
Ki-67 as a prognostic marker in mantle cell lymphoma—consensus guidelines of the pathology panel of the European MCL Network

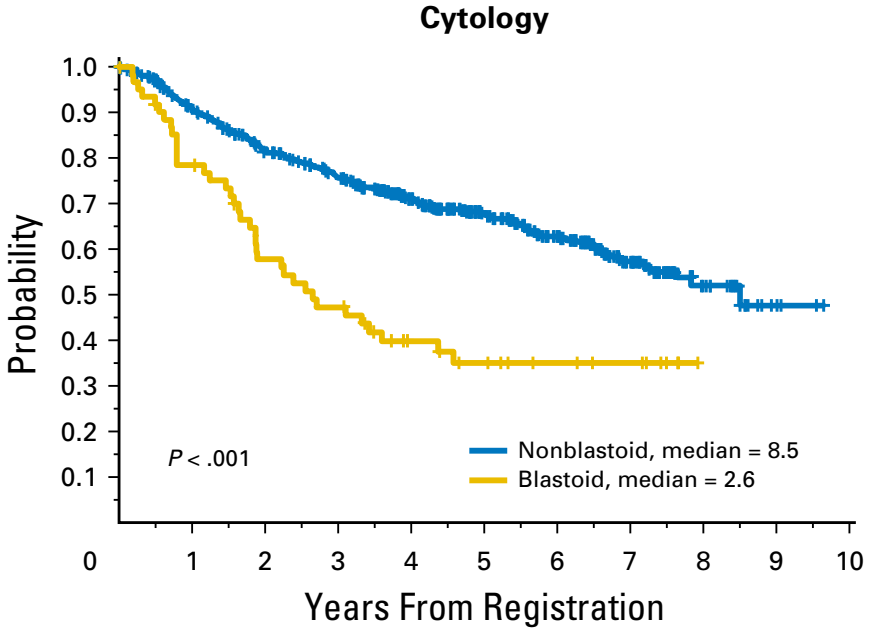
Wolfram Klapper · Eva Hoster · Olaf Determann · Ilske Oschlies · Jeroen van der Laak · Françoise Berger · Heinz Wolfram Bernd · José Cabeçadas · Elias Campo · Sergio Cogliatti · Martin Leo Hansmann · Philip M. Kluin · Roman Kodet · Yuri A. Krivolapov · Christoph Loddenkemper · Harald Stein · Peter Möller · Thomas E. F. Barth · Konrad Müller-Hermelink · Andreas Rosenwald · German Ott · Stefano Pileri · Elisabeth Ralfkiaer · Grzegorz Rymkiewicz · Johan H. van Krieken · Hans Heinrich Wacker · Michael Unterhalt · Wolfgang Hiddemann · Martin Dreyling · for the European MCL Network

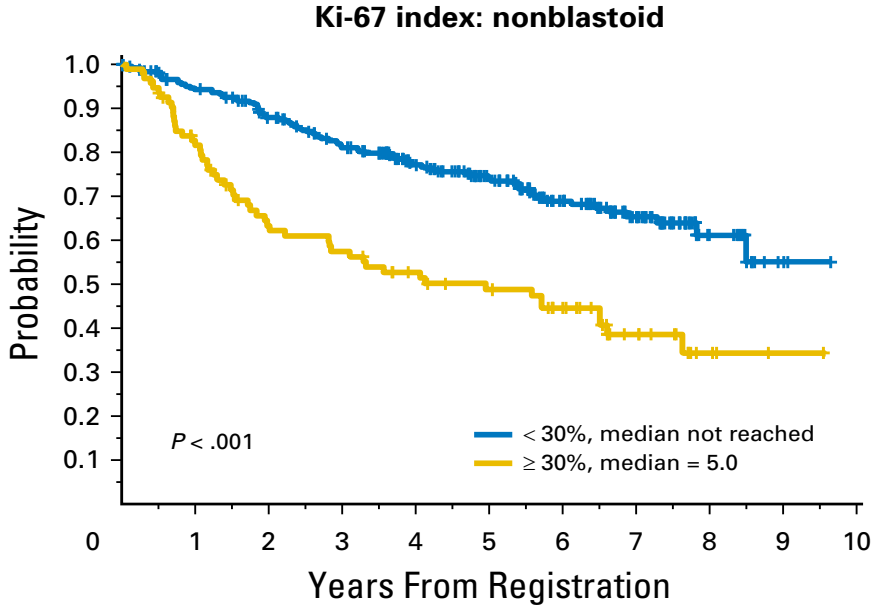
Prognostic Value of Ki-67 Index, Cytology, and Growth Pattern in Mantle-Cell Lymphoma: Results From Randomized Trials of the European Mantle Cell Lymphoma Network

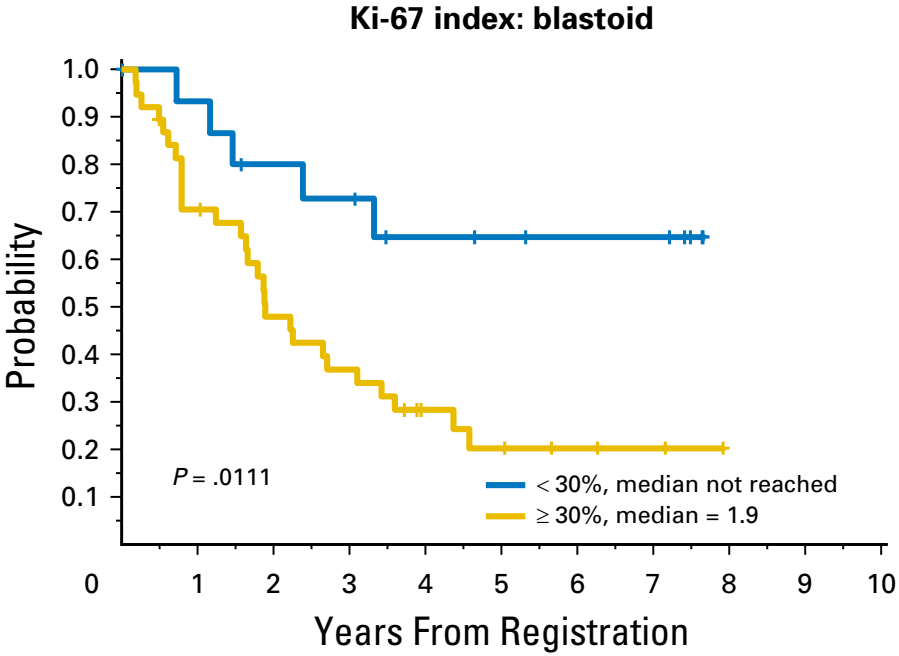
Patients with Ki-67	508
Patients from MCL younger trial - elderly trial	52% - 48%
Age, median (range)	62 (30-83)
Stage III-IV	15-80%
ECOG PS 2-4	6%
Elevated LDH	36%
MIPI: low intermediate high	41% 35% 24%
Ki-67, median (range)	20% (2-97%)
Morphology classic blastoid small cell	88% 10% 2%

Hoster et al, JCO 2016









Hoster et al, JCO 2016

MIPI-c risk group	MIPI	Ki67
Low (0)	Low	< 30%
Low intermediate (1)	Low (0) Intermediate (1)	≥ 30% (1) < 30% (0)
High intermediate (2)	Intermediate (1) High (2)	≥ 30% (1) < 30% (0)
High (3)	High (2)	≥ 30% (1)

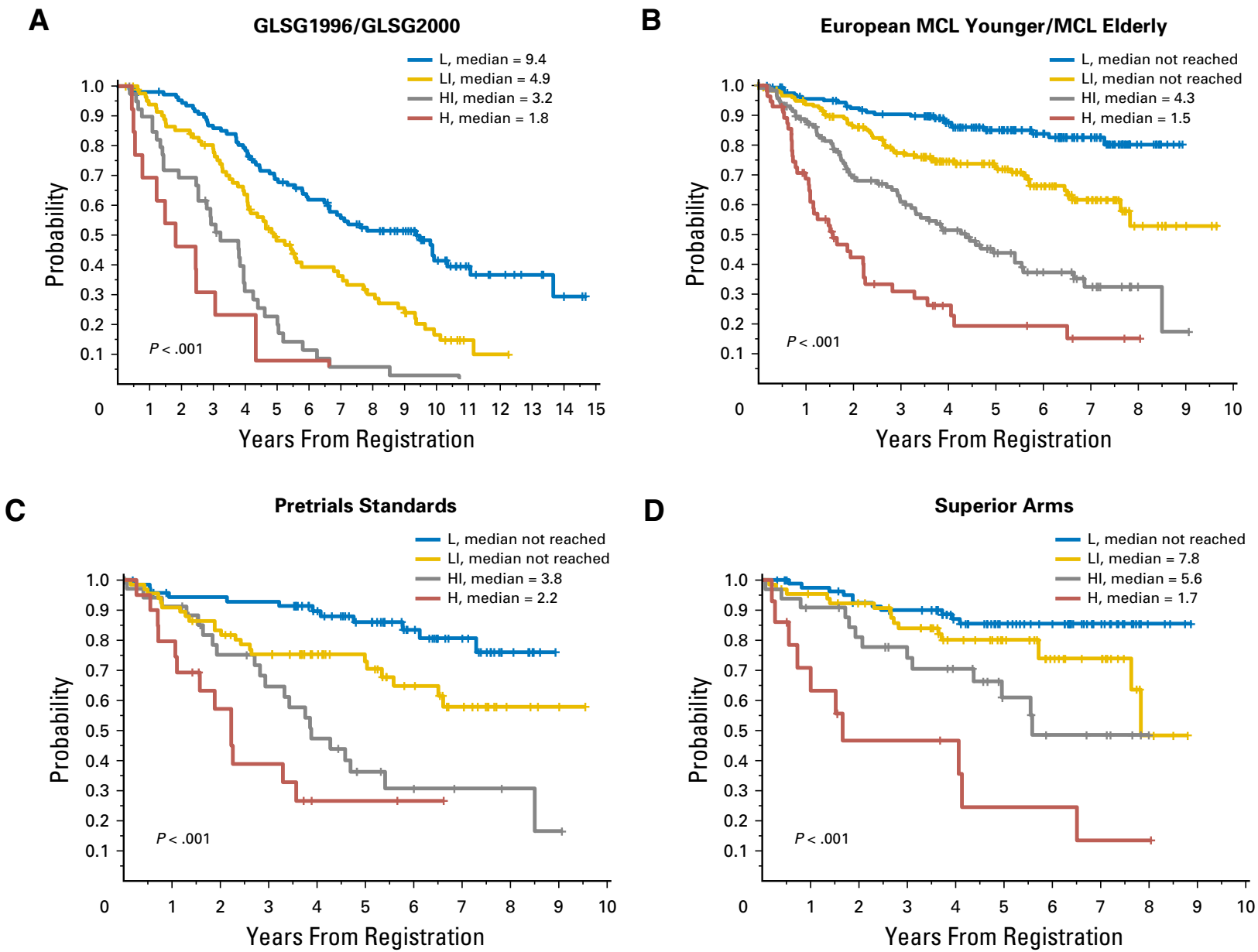
Hoster et al, JCO 2016

Studies of European MCL Network

- CHOP vs MCP (GLSG1996)
- CHOP vs R-CHOP (GLSG2000)
- R-CHOP → ASCT vs R-CHOP/R-DHAP → ASCT (NCT00209222)
- R-CHOP → R vs R-FC → R (NCT00209209)

GLSG1996/GLSG2000	% of patients	5-year OS
Low	44	70%
Low intermediate	34	45%
High intermediate	16	15%
High	5	5%

MCL Younger/MCL Elderly cohorts	% of patients	5-year OS
Low	32	85%
Low intermediate	34	72%
High intermediate	23	43%
High	11	17%



Hoster et al, JCO 2016

Our results also show that:

- Ki-67 index is a better prognostic factor than cytology and growth pattern
- Ki-67 should be used together with MIPI
- the modified combination of Ki-67 index and MIPI integrates the most important clinical and biologic markers currently available in clinical routine
- the currently applied treatment strategies have not overcome established prognostic factors, emphasizing the need for new treatment approaches.

… but not all the patients were treated with the most active agents…

Hoster et al, JCO 2016

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bortezomib-Based Therapy for Newly Diagnosed Mantle-Cell Lymphoma

	R-CHOP	VR-CAP
	m-PFS (months)	**m-PFS (months)**
Ki-67 < 30%	16	31
> 30%	9	15
MIPI low	17	50
intermediate	17	28.5
high	10	10.5

Robak et al. NEJM 2015

Rituximab, bendamustine and cytarabine (RBAC500) as induction therapy in elderly patients with mantle cell lymphoma: a phase 2 study from the Fondazione Italiana Linfomi

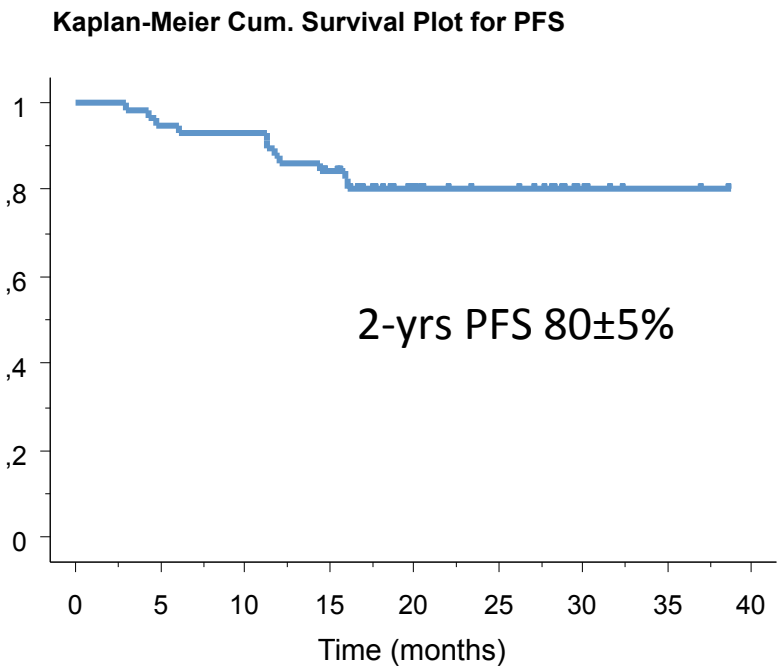
C. Visco[1], A. Chiappella[2], S. Franceschetti[3], C. Patti[4], S. Ferrero[5], D. Barbero[5], A. Evangelista[6], M. Spina[7], A. Molinari[8], L. Rigacci[9], M. Tani[10], A. Di Rocco[11], G. Pinotti[12], A. Fabbri[13], R. Zambello[14], S. Finotto[1], M. Gotti[15], A. M. Carella[16], F. Salvi[17], S. A. Pileri[18], M. Ladetto[17], F. Zaja[19], G. Gaidano[3], U. Vitolo[2], F. Rodeghiero[1].

Patients Demographics and Disease Characteristics at Baseline

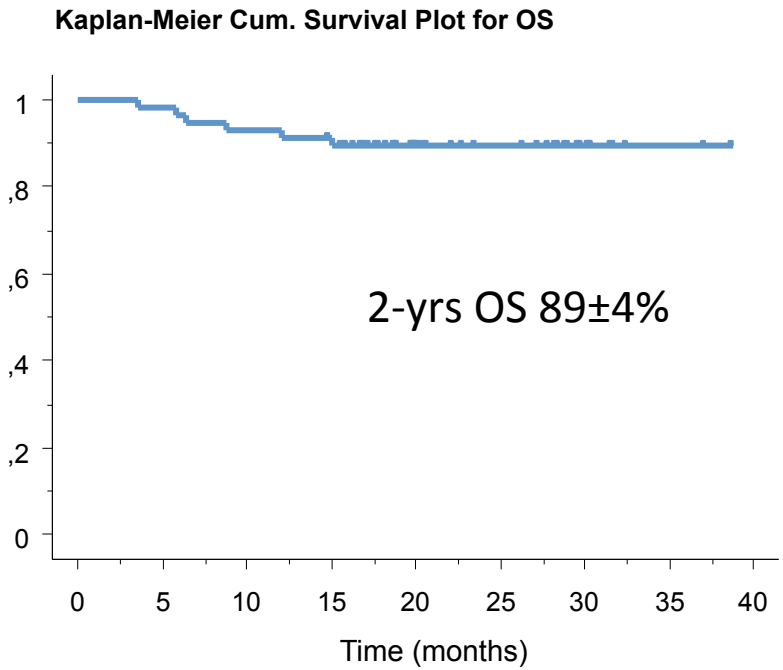
	Overall (57)	%
Age, years		
median (range)	71 (61-79)	
Gender		
male	43	75
Performance Status		
0-1	54	94
AAS		
III-IV	52	91
MIPI risk category		
low	9	16
intermediate	23	40
high	25	44
BM involvement	36	63
Elevated LDH	20	35
Histology		
Classic	43	75
Pleomorphic	8	14
Blastoid	6	11
Ki-67 (%)		
median (range)	20 (5-85)	

Survival curves

PFS

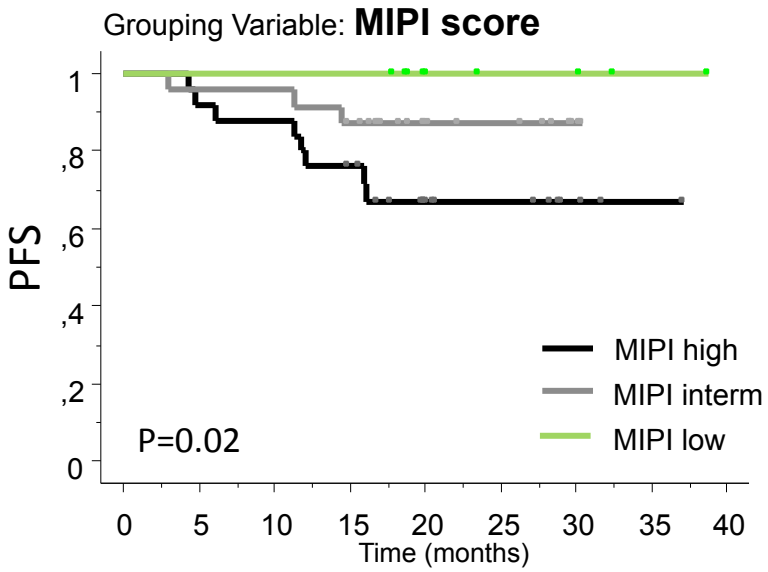


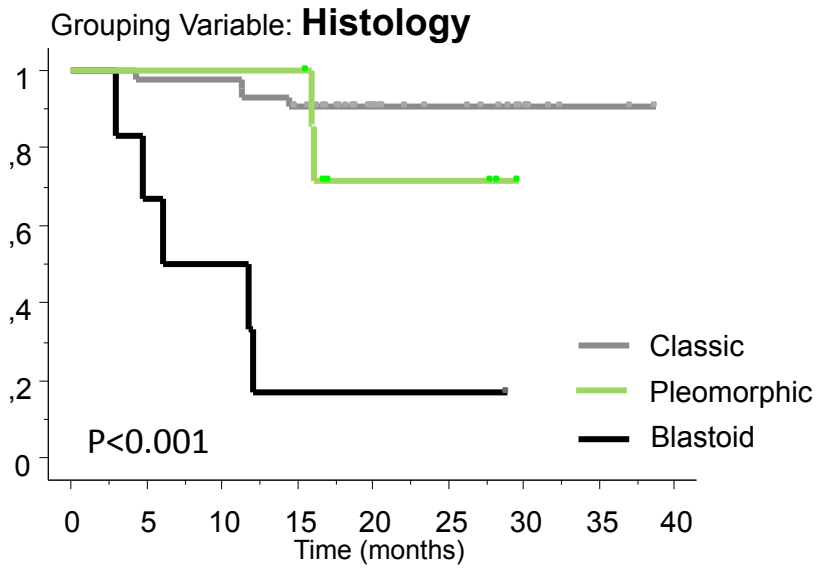
OS

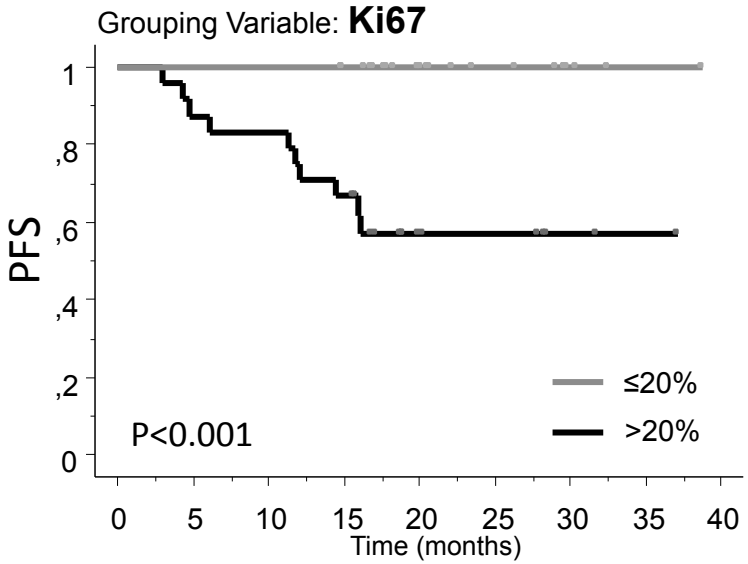


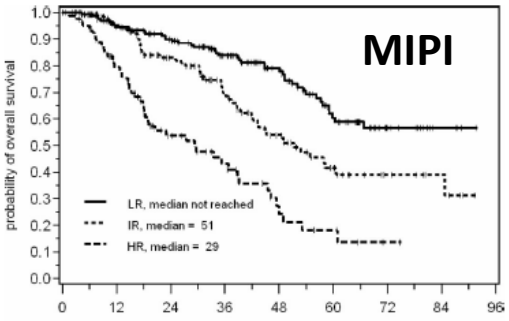
Median follow-up 22 months (15-38)

Survival curves

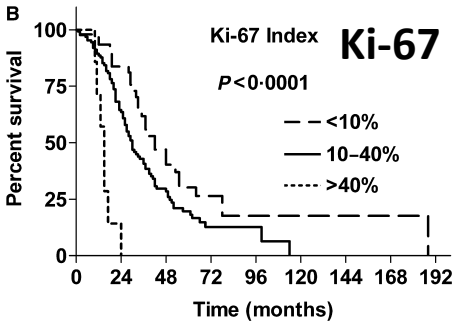








Hoster et al, Blood 2008



Tiemann et al BJH 2005

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lenalidomide plus Rituximab as Initial Treatment for Mantle-Cell Lymphoma

Jia Ruan, M.D., Ph.D., Peter Martin, M.D., Bijal Shah, M.D., Stephen J. Schuster, M.D., Sonali M. Smith, M.D., Richard R. Furman, M.D., Paul Christos, Dr.P.H., Amelyn Rodriguez, R.N., Jakub Svoboda, M.D., Jessica Lewis, P.A., Orel Katz, P.A., Morton Coleman, M.D., and John P. Leonard, M.D.

Characteristic	Patients (N = 38)
Sex — no. (%)	
Male	27 (71)
Female	11 (29)
Age — yr	
Median	65
Range	42–86
ECOG performance status — no. (%)*	
0–1	37 (97)
>1	1 (3)
Ann Arbor stage III or IV — no. (%)	38 (100)
Lactate dehydrogenase level — no. (%)	
Normal	23 (61)
Elevated	15 (39)
Bone marrow involvement — no. (%)	
Yes	34 (89)
No	4 (11)
MIPI score — no. (%)†	
<5.7	13 (34)
5.7 to <6.2	13 (34)
≥6.2	12 (32)
IPI score — no. (%)‡	
0–1	6 (16)
2	18 (47)
3	10 (26)
4–5	4 (11)
Ki-67 index — no. (%)	
<30%	26 (68)
≥30%	8 (21)
Unavailable	4 (11)

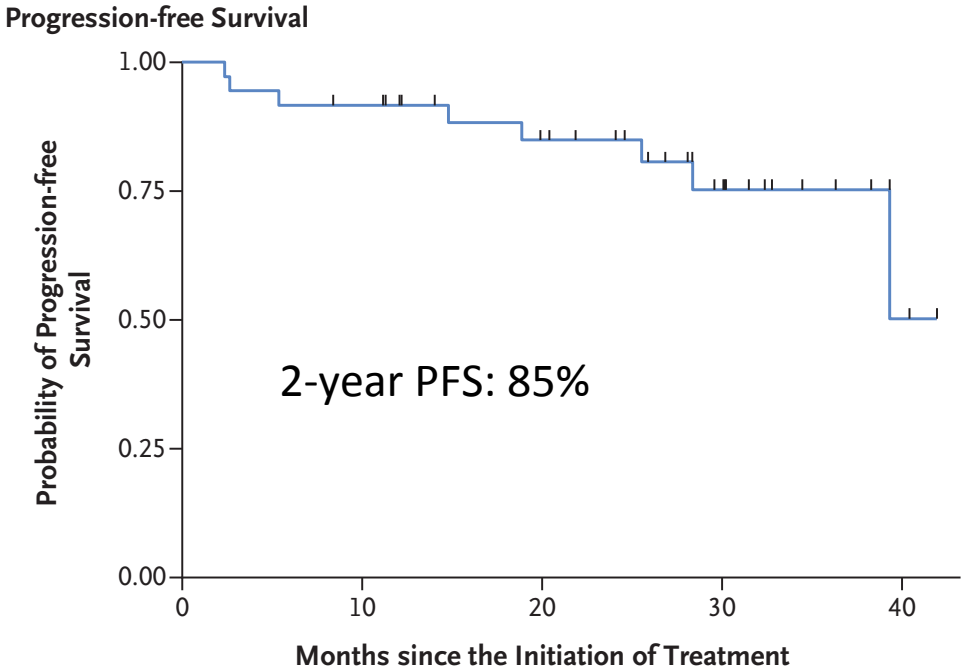
Table 2. Rates of Best Response at the Median Follow-up of 30 Months.

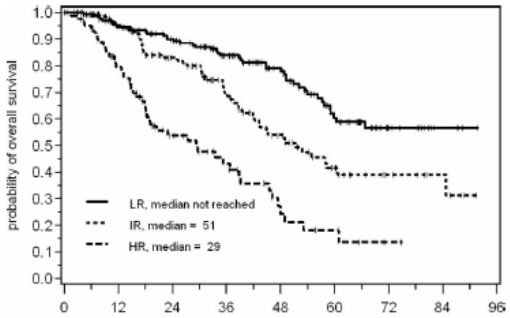
Response	Patients	Intention-to-Treat Population (N = 38)	Patients Who Could Be Evaluated (N = 36)
	no.	%	
Overall response	33	87	92
Complete response*	23	61	64
Partial response	10	26	28
Stable disease	1	3	3
Progressive disease†	2	5	6
Could not be evaluated‡	2	5	

Table 3. Survival and Follow-up Data.

Variable	Value
Median progression-free survival	Not reached
2-Yr progression-free survival — % of patients (95% CI)	85 (67–94)
2-Yr overall survival — % of patients (95% CI)	97 (79–99)
Follow-up time — mo	
Median	30
Range	10–42
Time to partial response — mo	
Median	3
Range	3–13
Time to complete response — mo*	
Median	11
Range	3–22

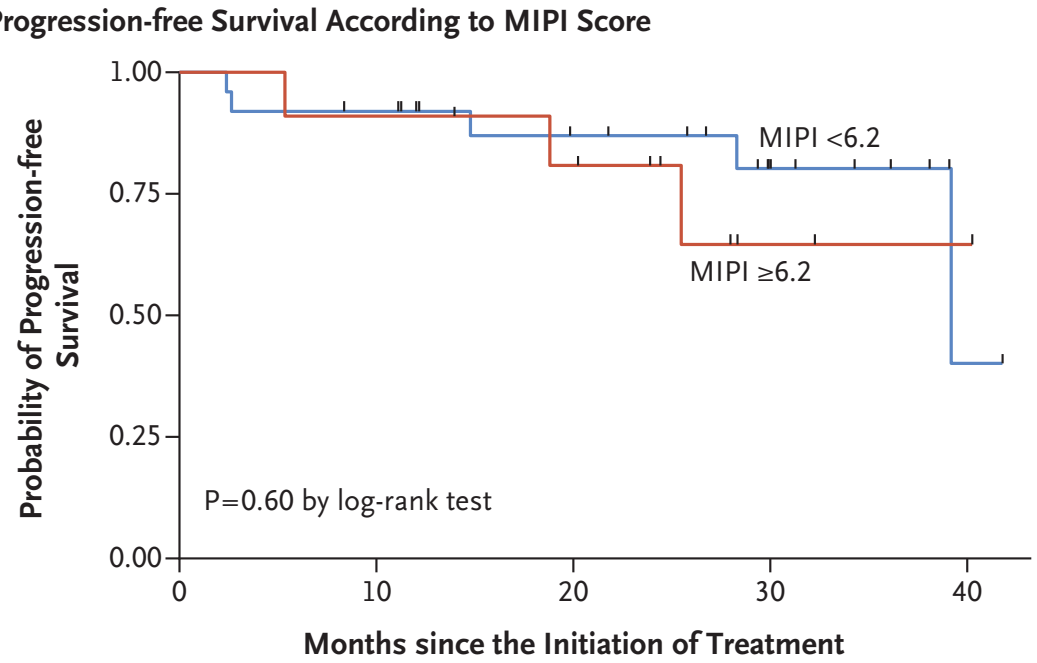
Ruan et al NEJM 2015





Hoster et al, Blood 2008

Neither the MIPI and IPI scores nor the Ki-67 index measurements were correlated with response to treatment or progression-free survival.



Ibrutinib in combination with rituximab in relapsed or refractory mantle cell lymphoma: a single-centre, open-label, phase 2 trial *Lancet Oncol* 2015

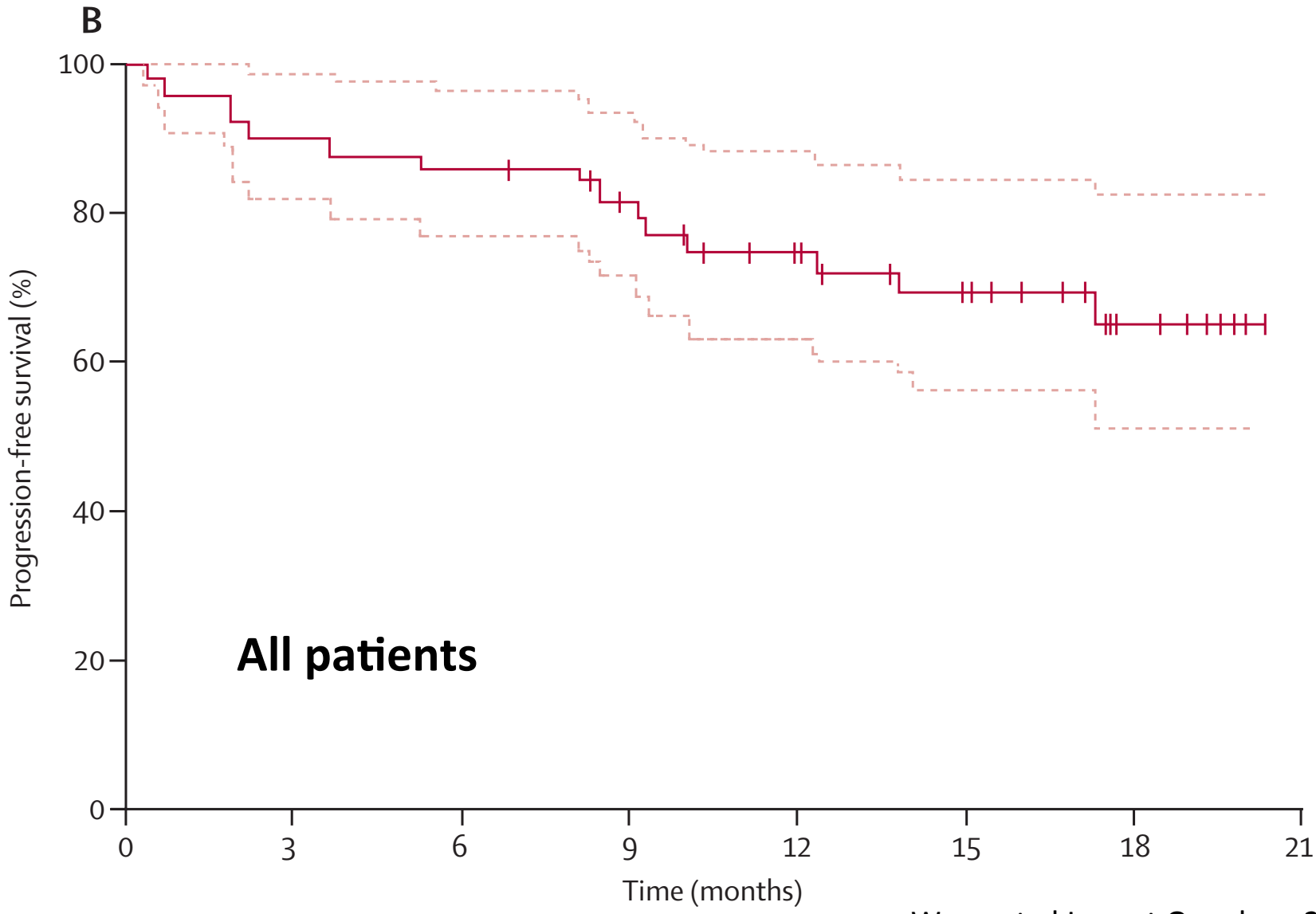
Michael L Wang, Hun Lee, Hubert Chuang, Nicolaus Wagner-Bartak, Frederick Hagemeister, Jason Westin, Luis Fayad, Felipe Samaniego, Francesco Turturro, Yasuhiro Oki, Wendy Chen, Maria Badillo, Krystle Nomie, Maria DeLa Rosa, Donglu Zhao, Laura Lam, Alicia Addison, Hui Zhang, Ken H Young, Shaoying Li, David Santos, L Jeffrey Medeiros, Richard Champlin, Jorge Romaguera, Leo Zhang

	Total (n=50)
Median age (years)	67 (45–86)
Men	38 (76%)
Women	12 (24%)
ECOG performance status 0–1	50 (100%)
Simplified Mantle Cell International Prognostic Index	
Low risk	22 (44%)
Intermediate risk	22 (44%)
High risk	6 (12%)
Tumour features	
Bulky mass	3 (6%)
At least one node ≥5 cm	17 (34%)
Refractory disease	35 (70%)
Stage 4 at diagnosis	50 (100%)
Bone marrow involvement at study entry	15 (30%)

	ALL	Ki-67 < 50%	Ki-67 ≥ 50%	Ibrutinib NEJM 2014
Patients	50	37	12	111
ORR	88%	100%	50%	67%
CR	44%	54%	17%	22.5%
DR	NR	NR	NR	17 months
mPFS	NR	NR	5.9	13 months

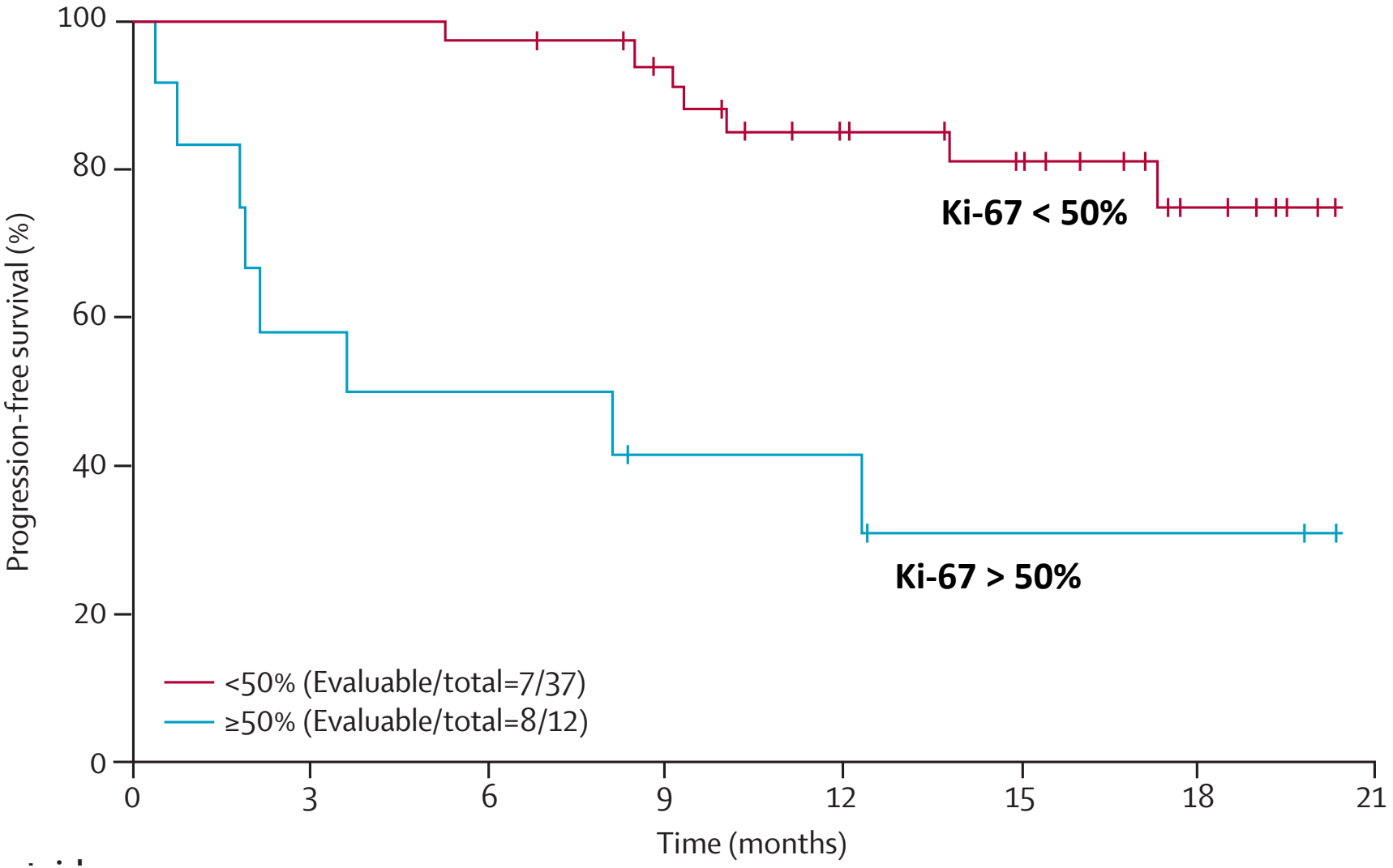
Wang et al Lancet Oncology 2015

R-Ibrutinib salvage therapy in MCL: PFS



Wang et al Lancet Oncology 2015

R-Ibrutinib salvage tx in MCL: PFS and ki-67



Wang et al Lancet Oncology 2015

Poor outcome for patients failing Ibrutinib therapy

Cheah C.Y. et al. Annals of Oncology 26:1175-1179, 2015

- 42 patients
- median age: 69 years
- median number of prior treatments: 2
- median number of 6.5 cycles (range 1-43).
- 31 patients experienced disease progression following Ibrutinib
- median OS among patients with disease progression: **8.4 months**

Martin P et al. 13 ICML, Hematol Oncol 2015:33, suppl.1:207

- 106 patients
- median age: 68 years
- median number of prior treatments: 3
- time on Ibrutinib: 4 months
- median OS following cessation of Ibrutinib: **2.9 months**
- 32.8% of patients surviving for at least 6 months and 17.2% of patients surviving for at least 12 months.

Take home messages

- Ruolo prognostico di:
  - Ki-67 (< vs > 30%)
  - Morfologia (classica vs blastoide)
  - MIPI (low vs intermediate vs high)
- Il nuovo c-MIPI deve essere validato in studi prospettici
- I nuovi programmi terapeutici: (RTX, ARA-C, ASCT, R-BAC, R2, R-Ibrutiinib) hanno migliorato globalmente la prognosi dei pazienti con MCL ed in parte superano il ruolo prognostico di MIPI e Ki-67