Il Linfoma Mantellare

Varietà Indolente: approccio terapeutico e risultati

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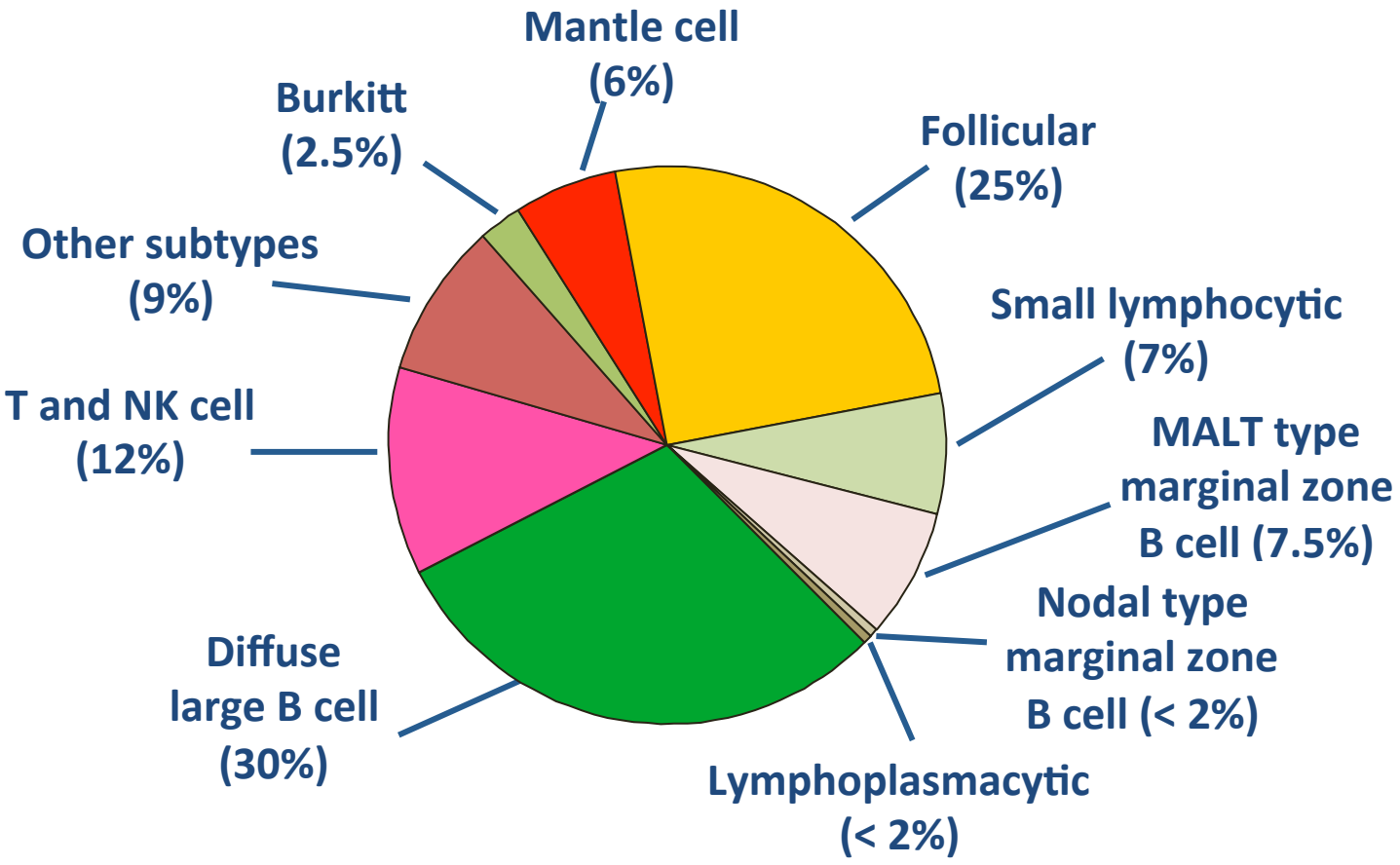
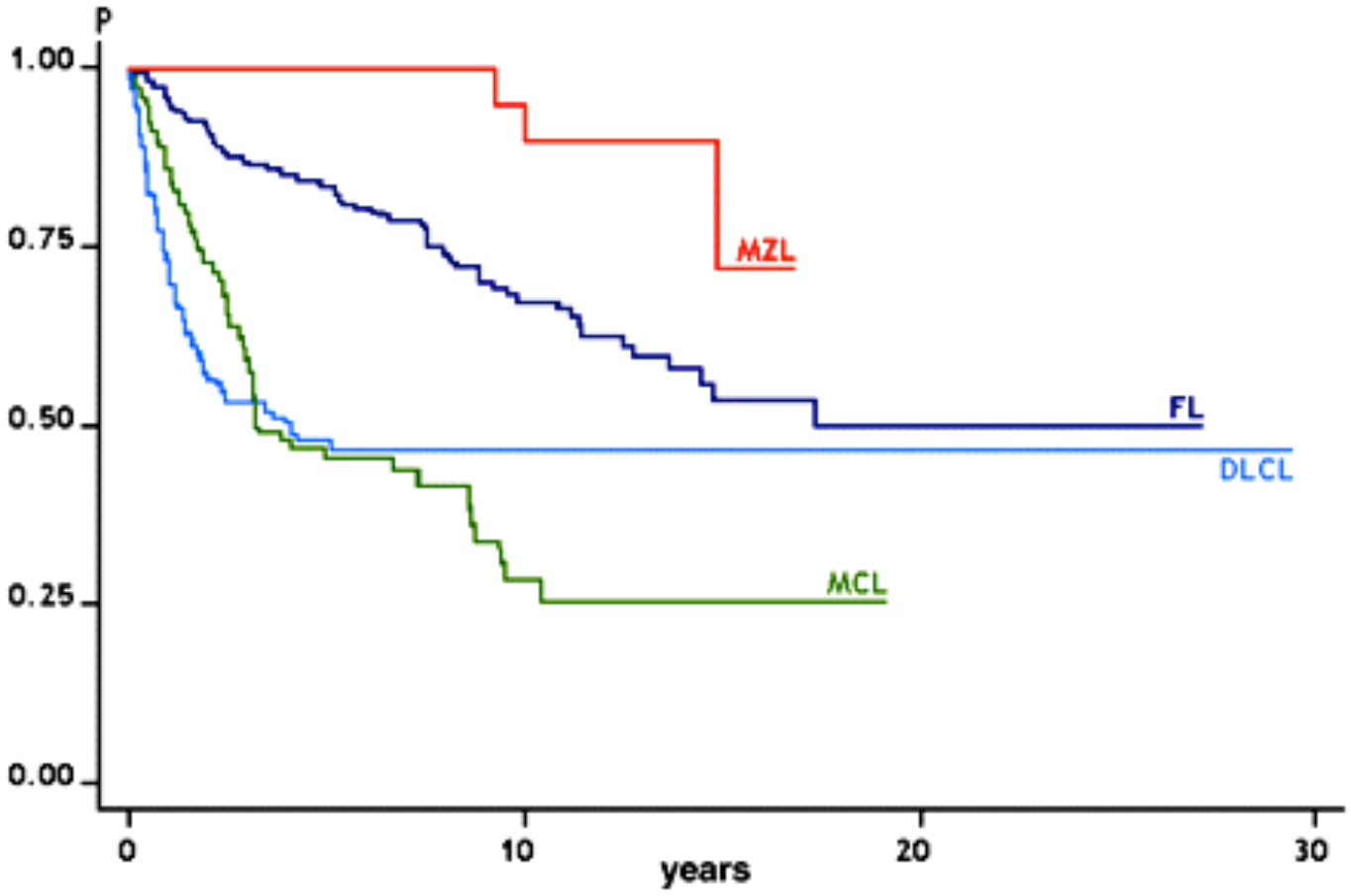
Mantle cell lymphoma: 6% of NHL cases



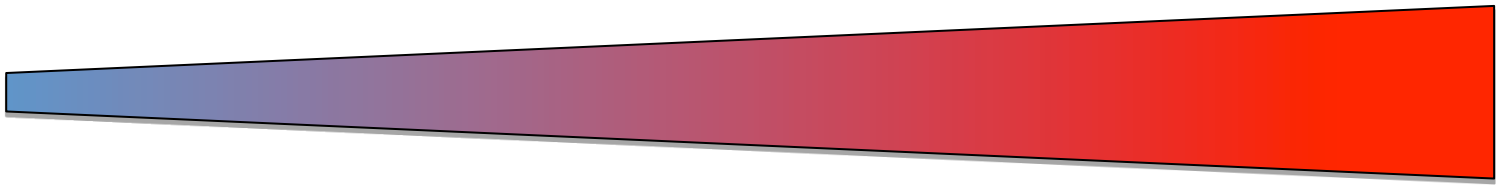
Lichtman. Williams Hematology, 7° Edition. 2006; 1408.

MCL: the NHL I'd like not to have



Ghielmini E. and Zucca E. Blood 2009

MCL: Clinical Presentation



Indolent — **Very Aggressive**

Recent observations
Variable clinical course (1)

↓

Clinical characteristic this patients ??

↓

There is diagnostic criteria for the identification of these patients ??

↓

Risk adapted management

Historically
Low rates of CR with standard therapy
Median OS: 3-4 yrs (1)
15% long-term survivors (2)

1. Pèrez-Galàn P. et al Blood 2011; 117:26-38
2. Dreyling M. et al Hematology Am Soc Hematol Educ Program 2009: 542-551

Outcome of Deferred Initial Therapy in Mantle-Cell Lymphoma

Peter Martin, Amy Chadburn, Paul Christos, Karen Weil, Richard R. Furman, Jia Ruan, Rebecca Elstrom, Ruben Niesvizky, Scott Ely, Maurizio DiLiberto, Ari Melnick, Daniel M. Knowles, Selina Chen-Kiang, Morton Coleman, and John P. Leonard

Martin P. et al JCO 2009; 27:1209-1213

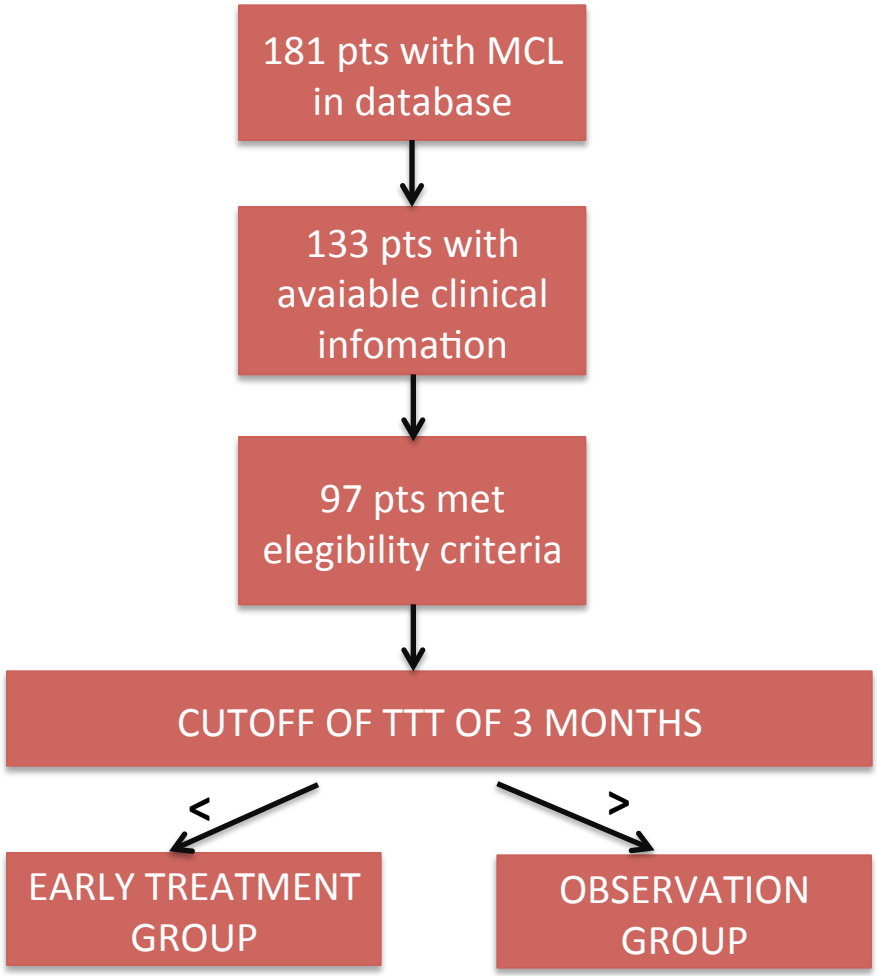
JOURNAL OF CLINICAL ONCOLOGY

Time to Treatment Does Not Influence Overall Survival in Newly Diagnosed Mantle-Cell Lymphoma

Eve HE, a. JCO 2009;27(32):189-90.

Patients and Methods

- ✓ Retrospective analysis
- ✓ Inclusion criteria were: a diagnosis of MCL between 1997 and 2007 and known date of first treatment
- ✓ Patients were divided into **early treatment** and **observation** groups, on the basis of time from diagnosis to first systemic therapy (TTT).



Martin P. et al JCO 2009; 27:1209-1213

Results (1)

Characteristic	Early Treatment* No.	%	Observation* No.	%
Total patients	66		31	
Age, years				
Median	65		58	
Range	44-89		40-81	
Sex				
Male	58	88	21	68
Female	8	12	10	32
Stage				
I-II	0/50	0	5/20	25
III-IV	50/50	100	15/20	75
Elevated LDH	20/39	51	3/12	25
Elevated WBC count	9/41	22	3/17	18
WHO performance status				
0	15	39	12	86
> 0	23	61	2	14
Extranodal involvement	38/40	95	12/14	86
Bone marrow involvement	33/44	75	13/17	76
Mantle Cell International Prognostic Index				
Low	12/37	32	6/13	46
Intermediate	10/37	27	3/13	23
High	15/37	41	4/13	31
International Prognostic Index				
Low	1	3	4	36
Low-intermediate	12	34	3	27
High-intermediate	12	34	2	18
High	10	29	2	18
Ki67 > 30%	11/34	32	5/15	33
p53 > 20%	4/31	13	1/13	8

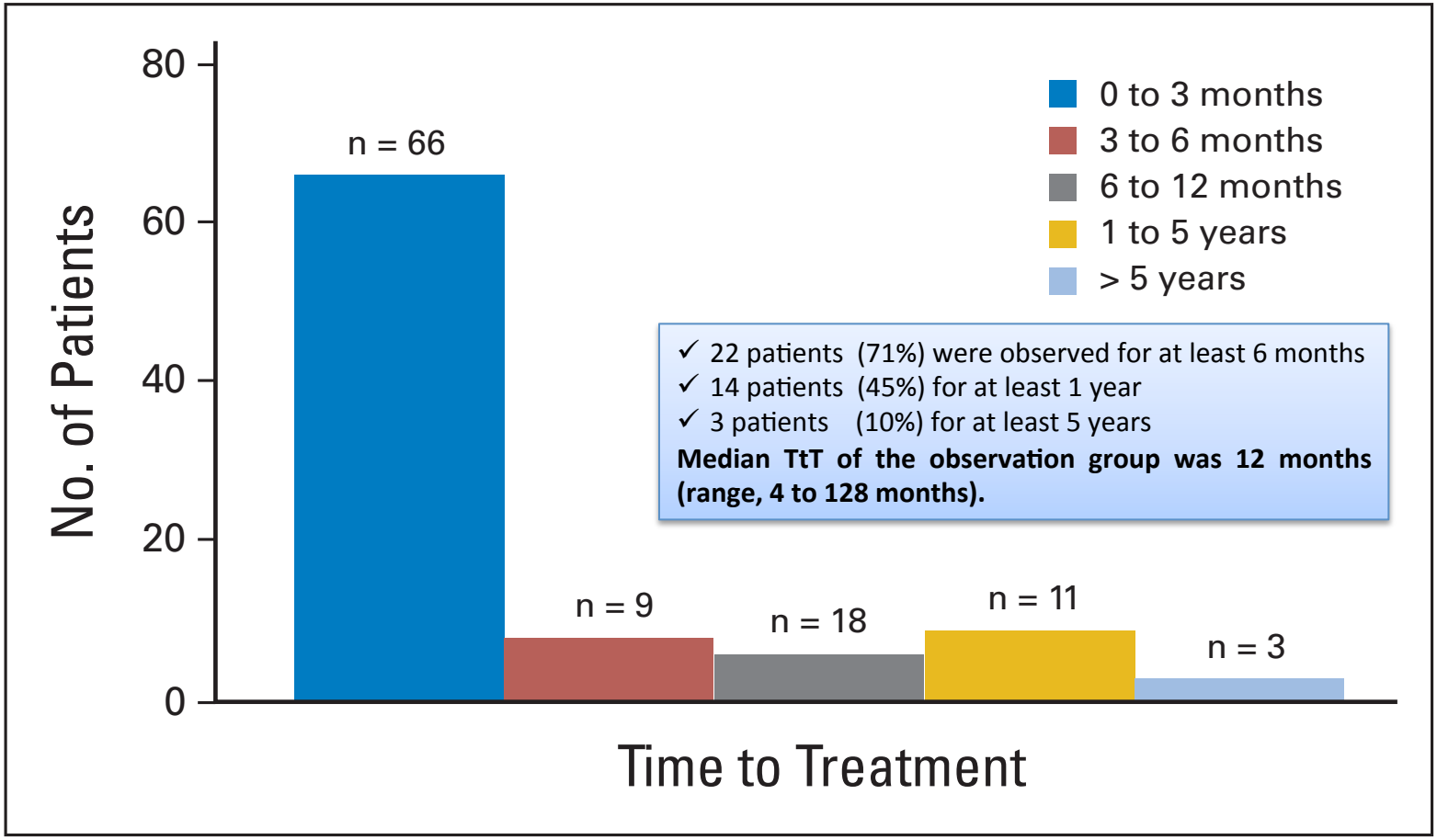
Abbreviation: LDH, lactate dehydrogenase.
*No. of patients varies according to available data.

Table: Patient Characteristics by Treatment Group

- ✓ **Adverse PS** was correlated with early treatment on univariate logistic regression (*P* . 008);
- ✓ **All early-stage** patients were in the observation group, perhaps relating to less complete staging in absence of symptoms;
- ✓ As a single variable, **the MIPI** failed to predict treatment group (odds ratio 0.73, *P* .40)
- ✓ Neither Ki-67 or p53 status by immunohistochemistry associated significantly with treatment;
- ✓ All seven patients with **blastoid MCL** were in the early treatment group.

Martin P. et al JCO 2009; 27:1209-1213

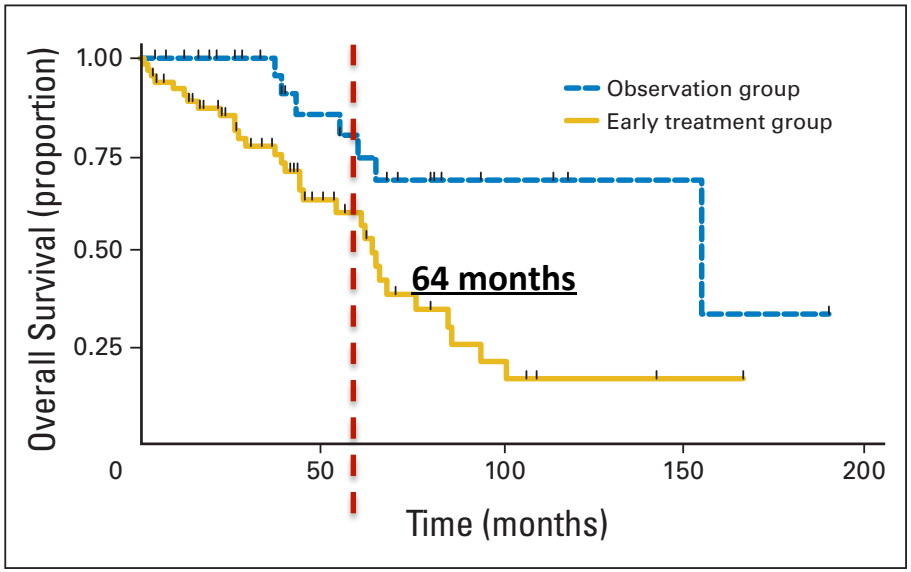
Results (2)



Martin P. et al JCO 2009; 27:1209-1213

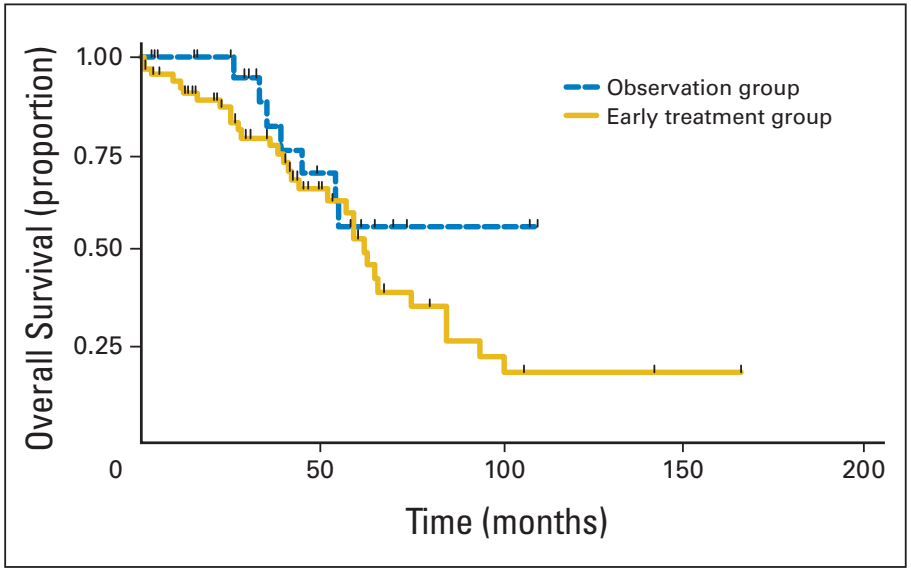
Result (3)

OS from diagnosis



- ✓ With a median follow-up of 41.5 months, the median OS was 64 months in **the early treatment group**
- ✓ With a median follow-up of 55 months the median OS of **observation group** was not reached AND IS SIGNIFICANT SUPERIOR TO THAT OF EARLY TREATMENT (p=.0038)

OS from treatment



- ✓ OS difference between groups disappeared when measured from date of first therapy rather than from diagnosis, suggesting that longer time until death occurred before treatment and is not attributable to greater chemo- therapy sensitivity.

Martin P. et al JCO 2009; 27:1209-1213

Time to Treatment Does Not Influence Overall Survival in Newly Diagnosed Mantle-Cell Lymphoma

Table 1. Patient Demographics and Clinical Characteristics

Characteristic	Treatment Group: Early Treatment (n = 33) No.	%	Observation (n = 16) No.	%
Age, years				
Median	68		59	
Range	39-87		43-90	
Sex				
Male	27	82	9	56
Female	6	18	7	44
Ann Arbor stage				
I-II	4 of 30	13	0 of 14	0
III-IV	26 of 30	87	14 of 14	100
ECOG performance score				
0	14 of 29	48	14 of 16	88
1	7 of 29	24	1 of 16	6
≥ 2	8 of 29	28	1 of 16	6
Bone marrow involvement	21 of 30	70	10 of 13	77
Elevated LDH (> 450 iu/L)	12 of 25	48	4 of 9	44
Lymphocytosis (> 4.0 × 10^9/L)	8	24	8	50

Abbreviations: ECOG, European Cooperative Oncology Group; LDH, lactate dehydrogenase.

- ✓ 52 patients consecutively diagnosed with MCL between 1994-2008
- ✓ 49 patients avaiable for analysis
- ✓ Cut of of TTT 3 months

Trend in the **Observation group**:

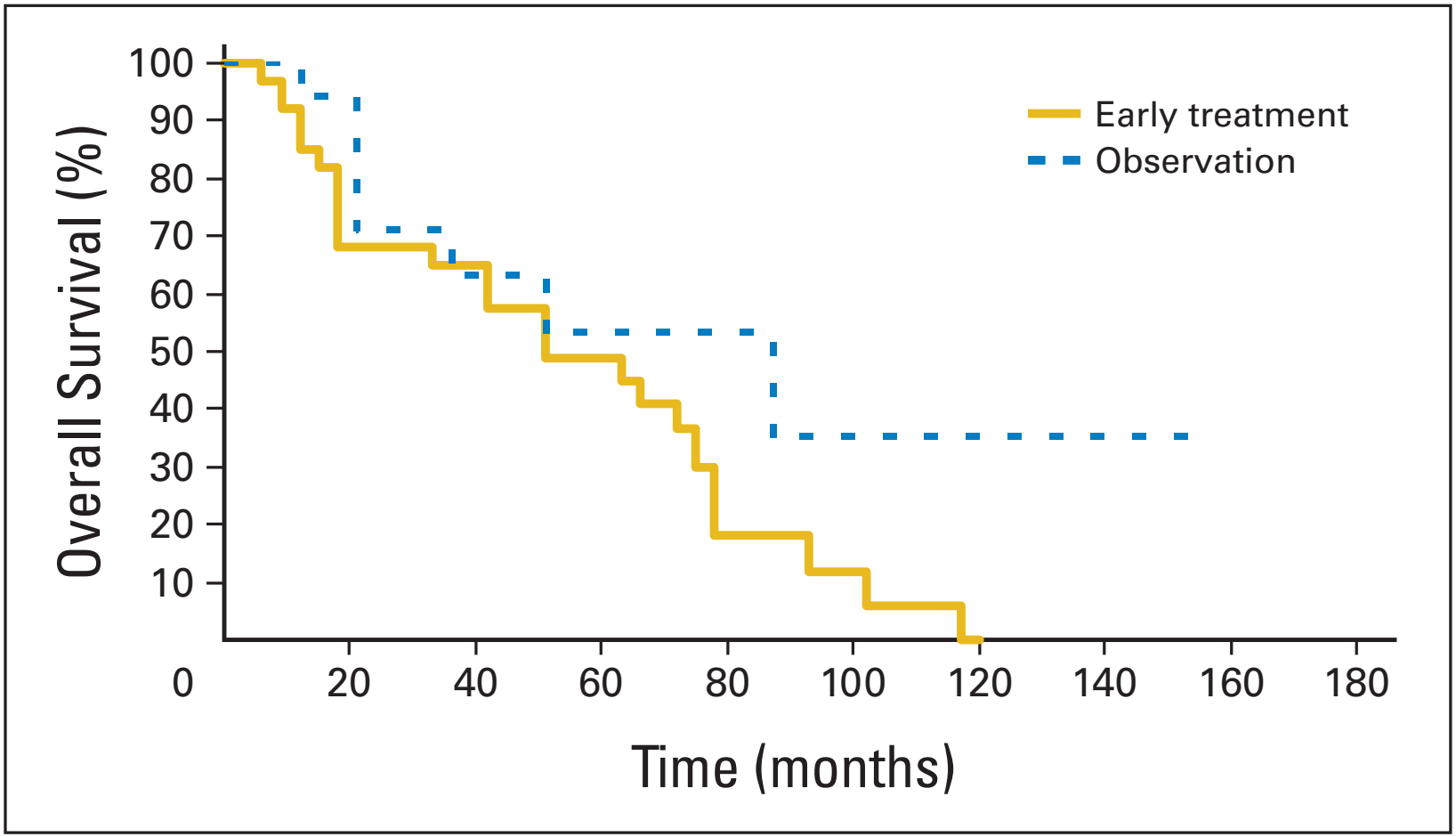
- ✓ Lower age 59 vs 68 years old
- ✓ ECOG score 0-1 (94% vs 72%)
- ✓ Higher % with **lymphocytosis 50%** vs 24%

- ✓12 patients (75%) were observed for at least 6 months
- ✓ 8 patients (50%) for at least 1 year
- ✓1 patients (6%) for at least 5 years

Median TTT of the observation group was 11.1 months (range, 3.7 to 131.1months).

Eve HE, a. JCO 2009;27(32):189-90

Results



Overall survival of observation versus early treatment groups

Eve HE, a. JCO 2009;27(32):189-90

Conclusions: They EXIST

- ✓ Two groups have reported on separate cohorts of patients who did not receive up-front chemotherapy at the time of diagnosis but were instead managed with a 'watch and wait' approach

- ✓ Both groups found that this approach did not have adverse effects on survival outcomes, suggesting that if such patients can be reliably identified, chemotherapy for this group, with its attendant morbidity, could reasonably be deferred

- ✓ Although diagnostic criteria for the identification of these patients are not currently available, there is evolving recognition of clinico- pathological differences identifying this group from the group of patients with classical MCL.

Furtado M. et al al. Haematologica 2011; 96(8)1086-1988

Features of iMCL

Clinical

Biological

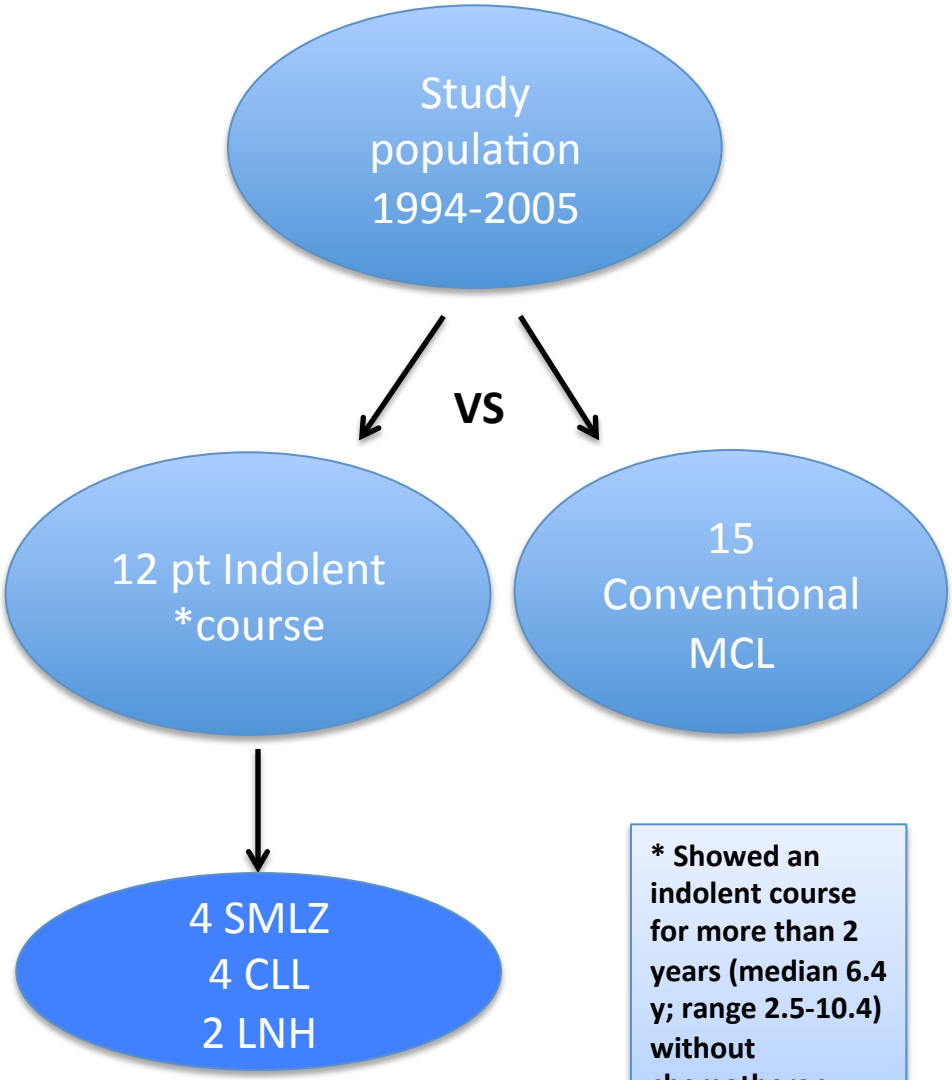
Molecular and Cellular Pathobiology

Cancer Research

Genomic and Gene Expression Profiling Defines Indolent Forms of Mantle Cell Lymphoma

Verònica Fernàndez[1], Olga Salamero[2], Blanca Espinet[3], Francesc Solé[3], Cristina Royo[1], Alba Navarro[1], Francisca Camacho[4], Sílvia Beà[1], Elena Hartmann[5], Virginia Amador[1], Luis Hernández[1], Claudio Agostinelli[6], Rachel L. Sargent[7], Maria Rozman[1], Marta Aymerich[1], Dolors Colomer[1], Neus Villamor[1], Steven H. Swerdlow[7], Stefano A. Pileri[6], Francesc Bosch[2], Miguel A. Piris[4], Emili Montserrat[2], German Ott[8], Andreas Rosenwald[5], Armando López-Guillermo[2], Pedro Jares[1], Sergi Serrano[3], and Elías Campo[1]

Materials and Methods



Validation cohorte

112 patients with MCL from 1986-2007

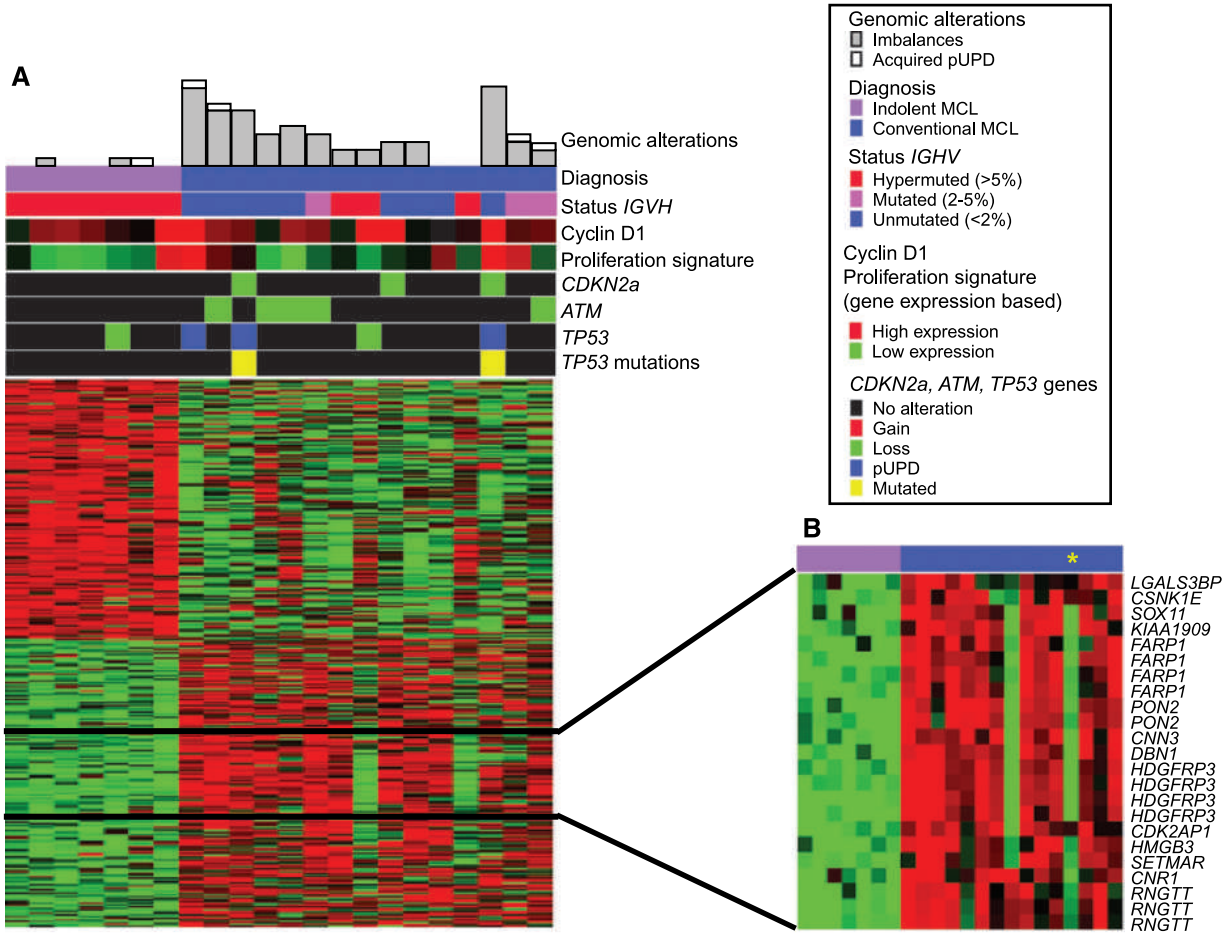
Fernandez V. et al Clin Canc Res 2010; 1408-1418

Conventional vs Indolent MCL Clinical Characteristic

	iMCL (*n* = 12)	cMCL (*n* = 15)	*P*
Clinical and pathologic data*			
Median age (range)	58 (41–75)	67 (30–83)	NS
Sex (male/female)	9/3	11/4	NS
B symptoms (%)	0	33	0.03
ECOG ≥2 (%)	0	70	0.01
Nodal presentation (lymph nodes >1 cm), %†	17	93	<0.001
Palpable splenomegaly (%)	50	60	NS
Gastrointestinal involvement (%)*	100	50	NS
Bone marrow involvement (%)*	92	91	NS
WBC count >10 × 10^9/L (%)*	33	82	NS
Lymphocyte count >5 × 10^9/L (%)*	44	82	NS
Atypical lymphocytes (%)	92	91	NS
High serum LDH (%)*,†	0	46	0.03
High serum β_2-microglobulin (%)*	20	80	NS
Intermediate or high-risk MIPI (%)*	0	46	0.016
Morphology			
Small cell (%)	67	13	0.007
Classic	33	74	
Blastoid	—	13	
$CD5^+$ (%)*	64	93	NS
IGHV gene hypermutations (>5%)*	70	20	<0.04
Genomic profile*			
0–1 imbalance	100	13	<0.001
≥2 imbalances	0	87	
Evolutive data			
Splenectomy (%)	42	20	
Chemotherapy at any time (%)	17	100	
Median follow-up, y (range)‡	6.4 (2.5–10.4)	3.3 (1.5–5.1)	NS
Dead patients (%)	0	47	<0.001
5-y OS (%)	100	49	0.03

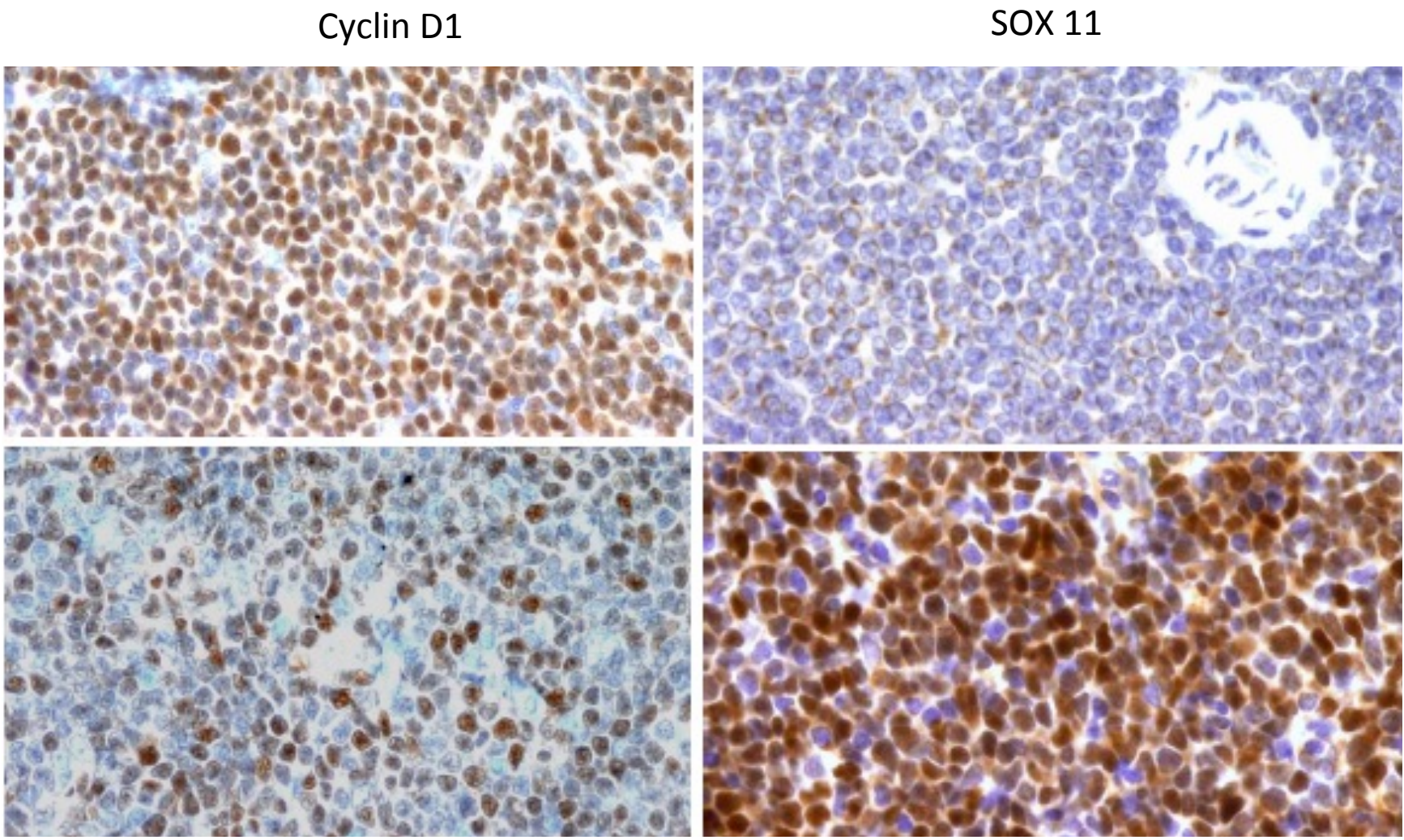
Fernandez V. et al Clin Canc Res 2010; 1408-1418

iMCL: Molecular and Genetic Features



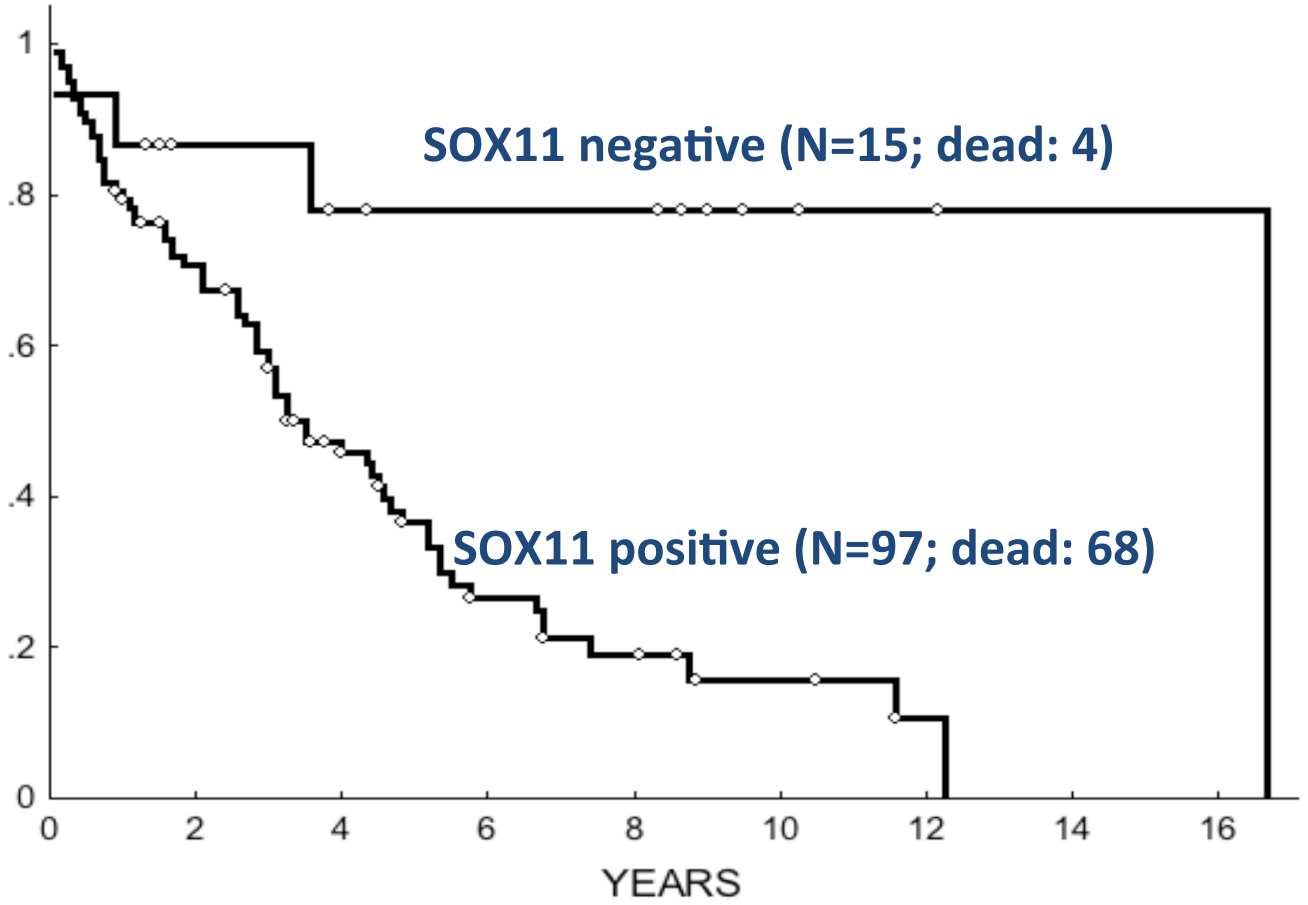
Fernandez V. et al Clin Canc Res 2010; 1408-1418

Sox 11 Protein Expression in MCL



Fernandez V. et al Clin Canc Res 2010; 1408-1418

OS in MCL validation cohort according to SOX 11 expression



Fernandez V. et al Clin Canc Res 2010; 1408-1418

Conclusions: iMCL is a specific subtype

Features of iMCL

Clinical

1. Predominant non-nodal disease
2. Asymptomatic presentation stable disease

Biological

1. High rate of IGVH gene mutations;
2. Lack of genomic complexity
3. Absence of expression of several genes, including SOX11 and other transcription factor of the high-mobility group family

This clinical presentation and SOX11 negativity identify patients with MCL that do well without aggressive chemotherapy and may benefit from management strategies more adjusted to the biology of the disease.

Fernandez V. et al Clin Canc Res 2010; 1408-1418

SOX 11 Expression

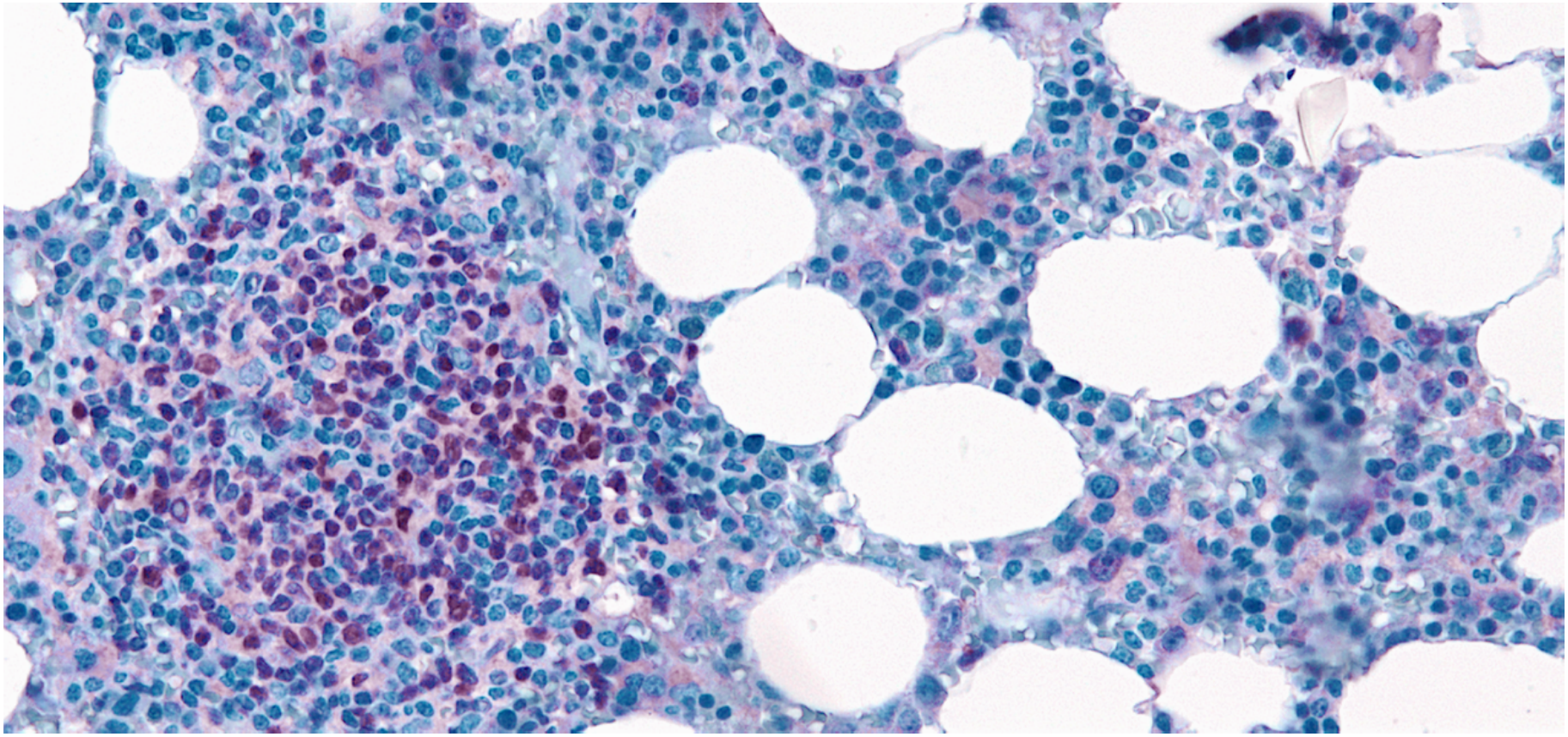
Patient	CD5	CD19	CD20	CD23	CD79b	FMC7	Light chain	Genetics	Bone marrow	SOX11
1	+	+	+ bright	+ subset	+	+	kappa bright	46,XY,t(11;14)(q13;q32)	1% single cell interstitial	Negative
2	+	+	+ bright	+ subset	+	+	kappa bright	N/A; +FISH	Not performed	N/A
3	+	+	+ bright	+	+	+	kappa bright	Complex karyotype* with t(11;14)(q13;q32); +FISH	Not performed at diagnosis**	Negative
4	+	+	+ bright	_	+	+	absent	N/A; +FISH	10% scattered interstitial aggregates	Low (20% of B-cells)
5	+	+	+	+	+	+	kappa	46,XX,t(11;14)(q13;q32)	1% single cell interstitial	Negative
6	+	+	+ bright	+ subset	+	+	kappa bright	46,XX,t(11;14)(q13;q32)	5% scattered interstitial clusters	Negative
7	+	+	+	_	+	+	kappa	N/A; +FISH	5% scattered interstitial clusters	N/A
8	+	+	+	_	+	+	kappa	N/A; +FISH	1% single cell interstitial	N/A

FISH: fluorescence in situ *hybridization for t(11;14)(q13,q32); N/A: not applicable. *complex karyotype detected 105 months after diagnosis: 43-36,XX,-X[4],del(1)(q25)[5] add(2)(p13)[12],add(6)(q13)[2]add(8)(p23)[15],t(11;14)(q13:q32)[16],-13[10],der(13)t(13;17)(p11.2;q21)[6],t15[3],-17[12],add(20)(q11.2)[3],t21[5],add(22)(p11.2)[16],+mar1[5],+mar2[6],+1-5mar[cp17]/46,XX[3]. **Bone marrow biopsy was performed after a dramatic response to a chemotherapeutic regimen and showed no residual disease. Bone marrow biopsy was repeated 105 months after diagnosis (relapsed) and lymphoma cells were negative for SOX11.*

- ✓8 patient asymptomatic with mild lymhocytosis
- ✓**Sox 11** was negative (4/5) or only weakly expressed (1/5)
- ✓5/8 MIPI High/Intermediate
- ✓Median follow-up: 27 months (range 5-109 months) and all pt, but one, are alive with no clinical evidence of disease.

Ondrejka et al. Haematologica 2011;96(8) 1121-1127

SOX 11



BONE MARROW BIOPSY: FIRST/ONLY SITE of BIOPSY
INTRAVASCULAR DIFFUSION
SMALL CELL CYTOLOGY

Conclusions about role of SOX 11

- ✓ Indolent MCL exist,
- ✓ well recognized within patients presenting with non-nodal, leukemic disease, it is likely that this is not the only clinical scenario
- ✓ *SOX11* and other genes are likely to become useful in the identification of these patients at diagnosis, also in bone marrow biopsy
- ✓ This will ultimately provide clinicians with the confidence to explore less intensive treatment approaches.

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Molecular and Cellular Pathobiology

Cancer Research

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CONCLUSIONS

iMCL is a specific subtype of MCL with a constellation of clinicobiological features that include a predominant nonnodal and asymptomatic presentation, stable disease, **high rate of IGVH gene mutations**, lack of genomic complexity, and absence of expression of several genes, including SOX11 and other transcription factor of the high-mobility group family

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5-y OS (%)	100	49	0.03

Fernandez V. et al Clin Canc Res 2010; 1408-1418

Immunoglobulin mutation status in iMCL

A subset of t(11;14) lymphoma with mantle cell features displays mutated IgV_H genes and includes patients with good prognosis, nonnodal disease

Jenny Orchard, Richard Garand, Zadie Davis, Gavin Babbage, Surinder Sahota, Estella Matutes, Daniel Catovsky, Peter W. Thomas, Hervé Avet-Loiseau, and David Oscier

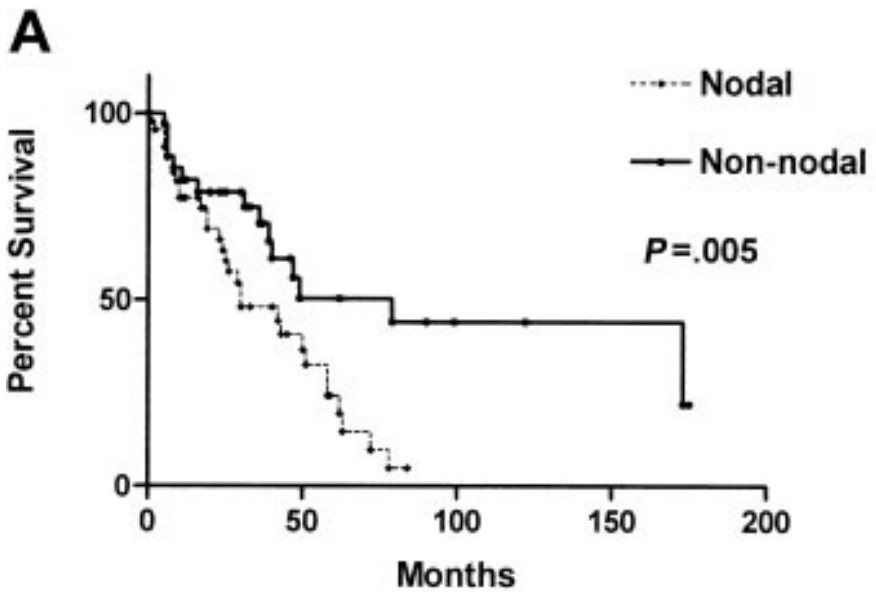
Table 1. Comparison of patient characteristics in nodal and nonnodal groups

	Nodal group	Nonnodal group	*P*
Patients			
No.	43	37	
M/F	2.3/1	2/1	1.0
Mean age, y (range)	65 (42-87)	63 (36-81)	.58
Clinical (%)			
Splenomegaly	25/43 (58)	28/37 (76)	.15
GI tract	8/43 (19)	2/37 (5)	.1
CD38, 30% or more positive (%)	32/34 (94)	16/33 (48)	< .001
IgV_H genes (%)			
98% or higher homology	28/31 (90)	15/34 (44)	
97% homology	3/31 (10)	3/34 (9)	< .001
Less than 97% homology	0/31	16/34 (47)	
Karyotype (%)			
Complex	11/11 (100)	9/17 (53)	.01
Single	0/11	8/17 (47)	
Median survival, mo (95% confidence limits)	30 (10-50)	79 (22-136)	.005

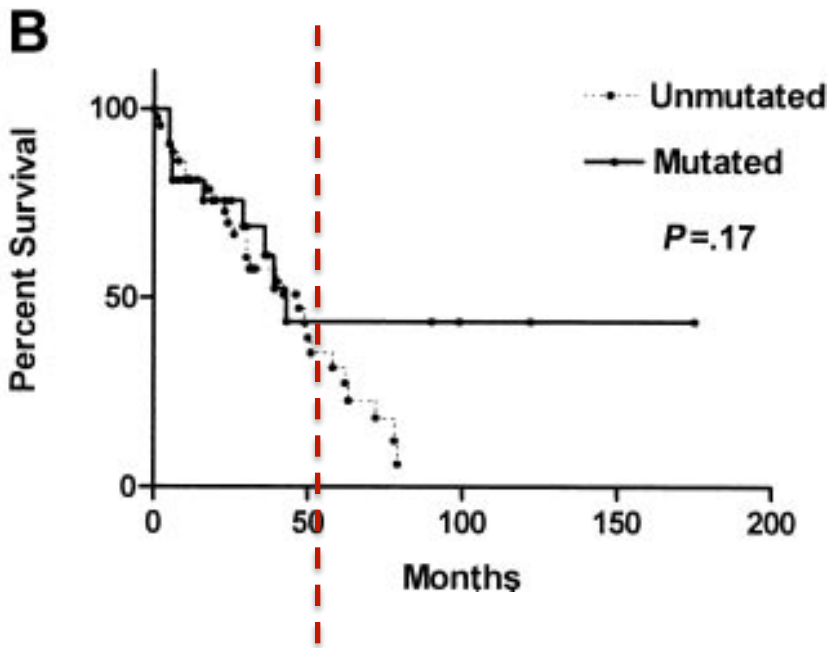
- ✓ **80 patients with peripheral blood lymphocytes carring t (11;14)**
- ✓ **Review the lymphocyte morphology, hystology, immunophenotype, IgVH gene status and clinical course**

Orchard J. Blood 2003 (101); 4975-4981

Immunoglobulin mutation status in iMCL



✓ Median survival nodal: 30 months vs nn nodal 79 months



✓ The effect of IgVh gene mutation status does not attain statistical significance.

Orchard J. Blood 2003 (101); 4975-4981

Back to practice……

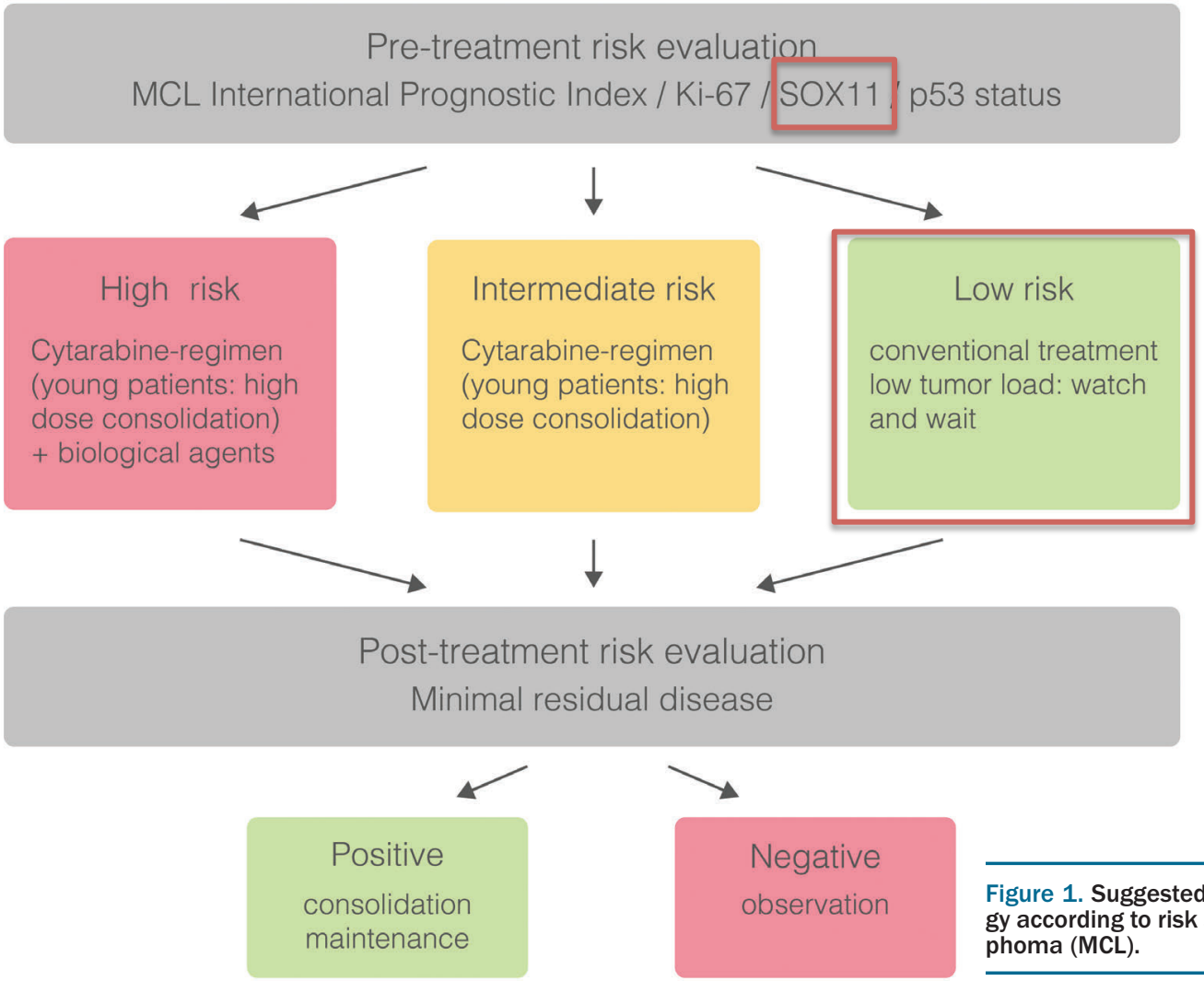


Figure 1. Suggested personalized treatment strategy according to risk stratification in mantle cell lymphoma (MCL).

Dreyling M. et al. Haematologica 2015, (100);706-708