Institute of Pathology,
University of Tübingen Germany

Case SH2017-0086

Leukemic, non-nodal MCL with complex Karyotype and *TP53* deletion and mutation with rather indolent clinical behaviour

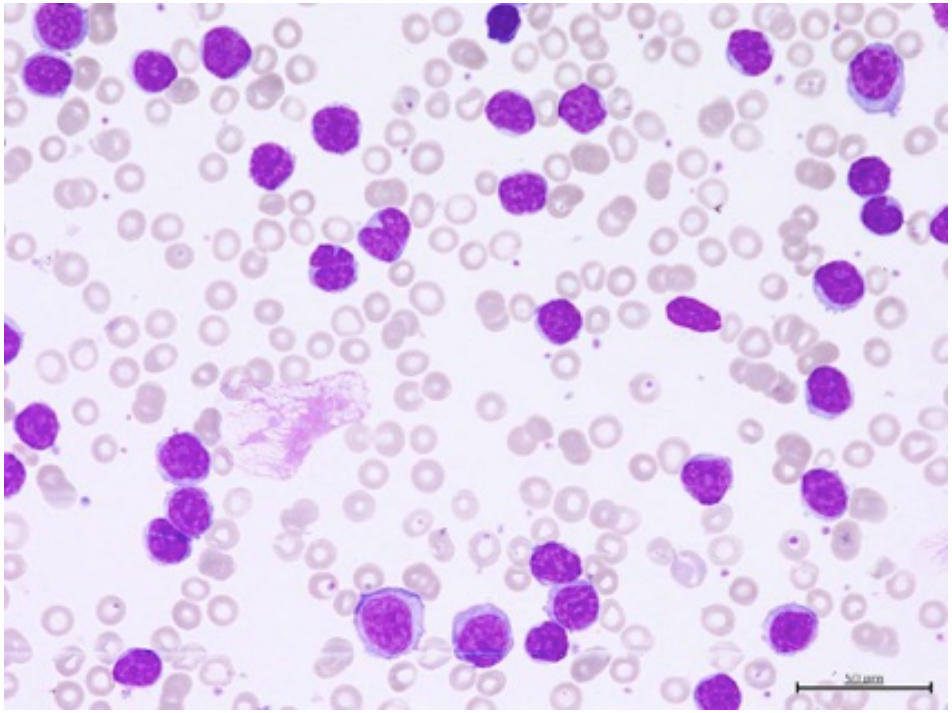
Leticia Quintanilla-Fend

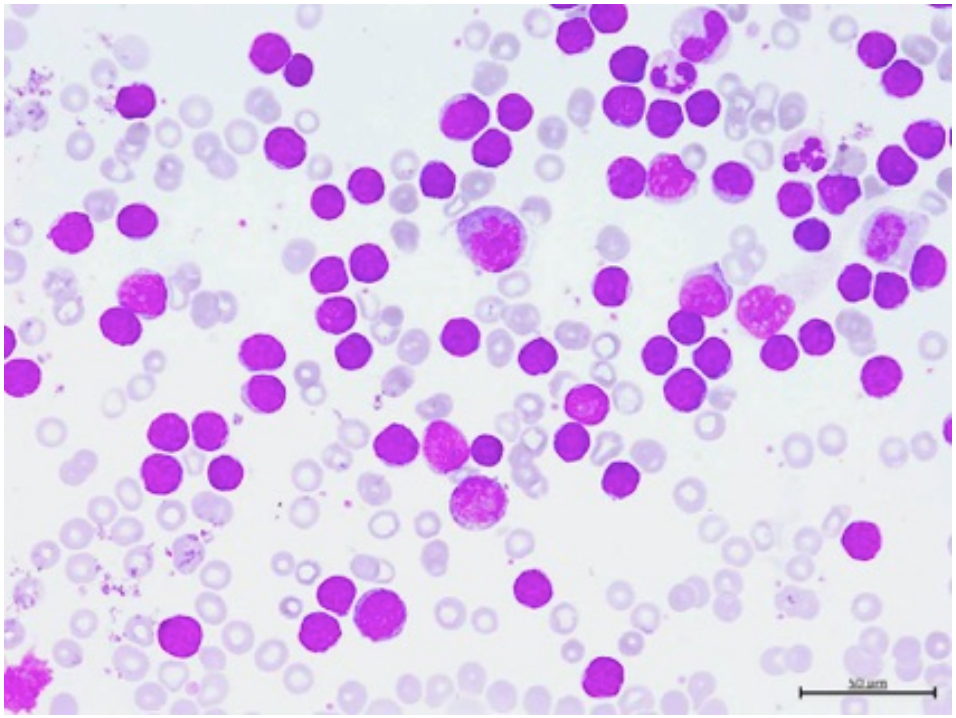
Clinical history

- A 76 year-old female with high blood pressure and otherwise asymptomatic was found to have mild leukocytosis in September 2016.
- In November she developed broncho-pneumonia and was hospitalized.
- Her leukocytes were over 300 000 /µl with 94.2% being lymphocytes. Hb 8.6 g/dl and platelets 268 000.
- Physical examination revealed mild splenomegaly

Peripheral blood smear

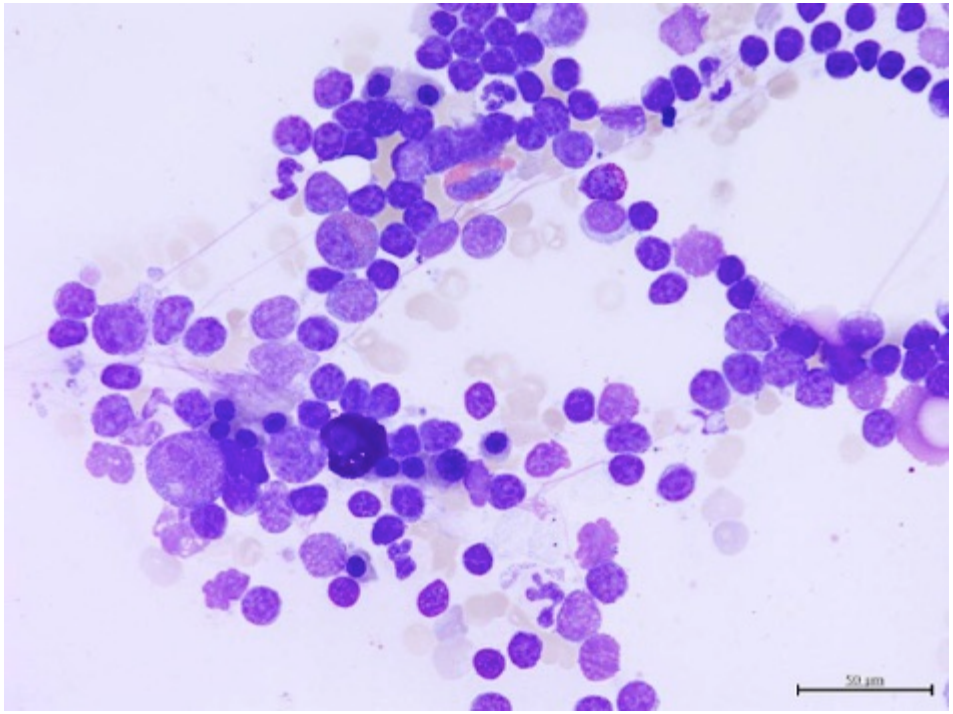
- Increased numbers of small lymphocytes,
- Hypochromic anemia with anisocytosis
- Reduced number of platelets
- Few segmented granulocytes

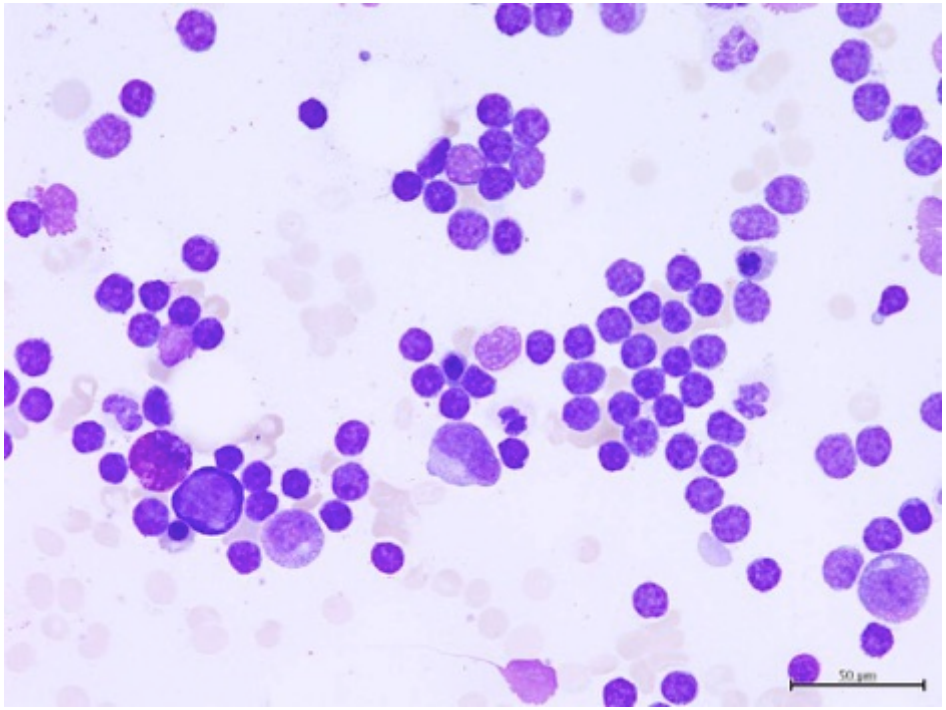




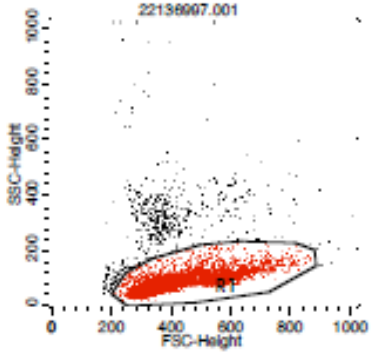
Bone Marrow aspirate

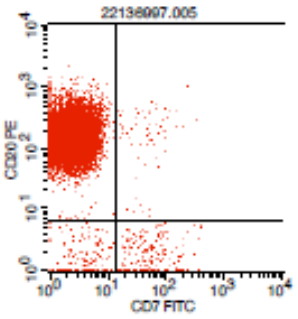
BM aspirate showed infiltration by the same small lymphocytes





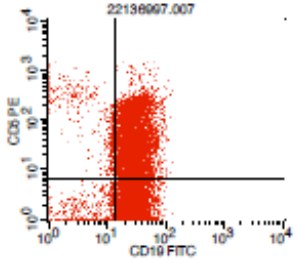
FACS analysis in Peripheral blood





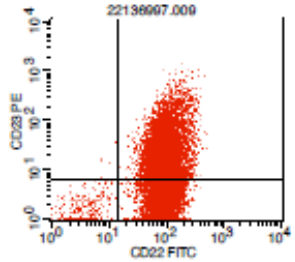
Gated Events: 14754 Total Events: 15000

Quad	Events	% Gated	% Total
UL	14337	97.17	95.58
UR	64	0.43	0.43
LL	160	1.08	1.07
LR	193	1.31	1.29



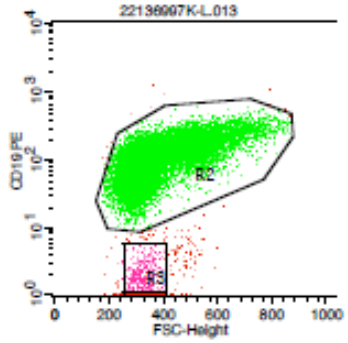
Patient ID: Wurster, Ilse*02.11.1940
Total Events: 15000

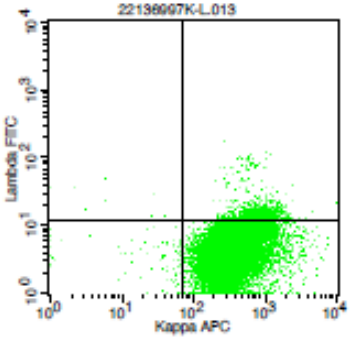
Quad	Events	% Gated	% Total
UL	452	3.11	3.01
UR	6411	44.07	42.74
LL	464	3.19	3.09
LR	7221	49.64	48.14



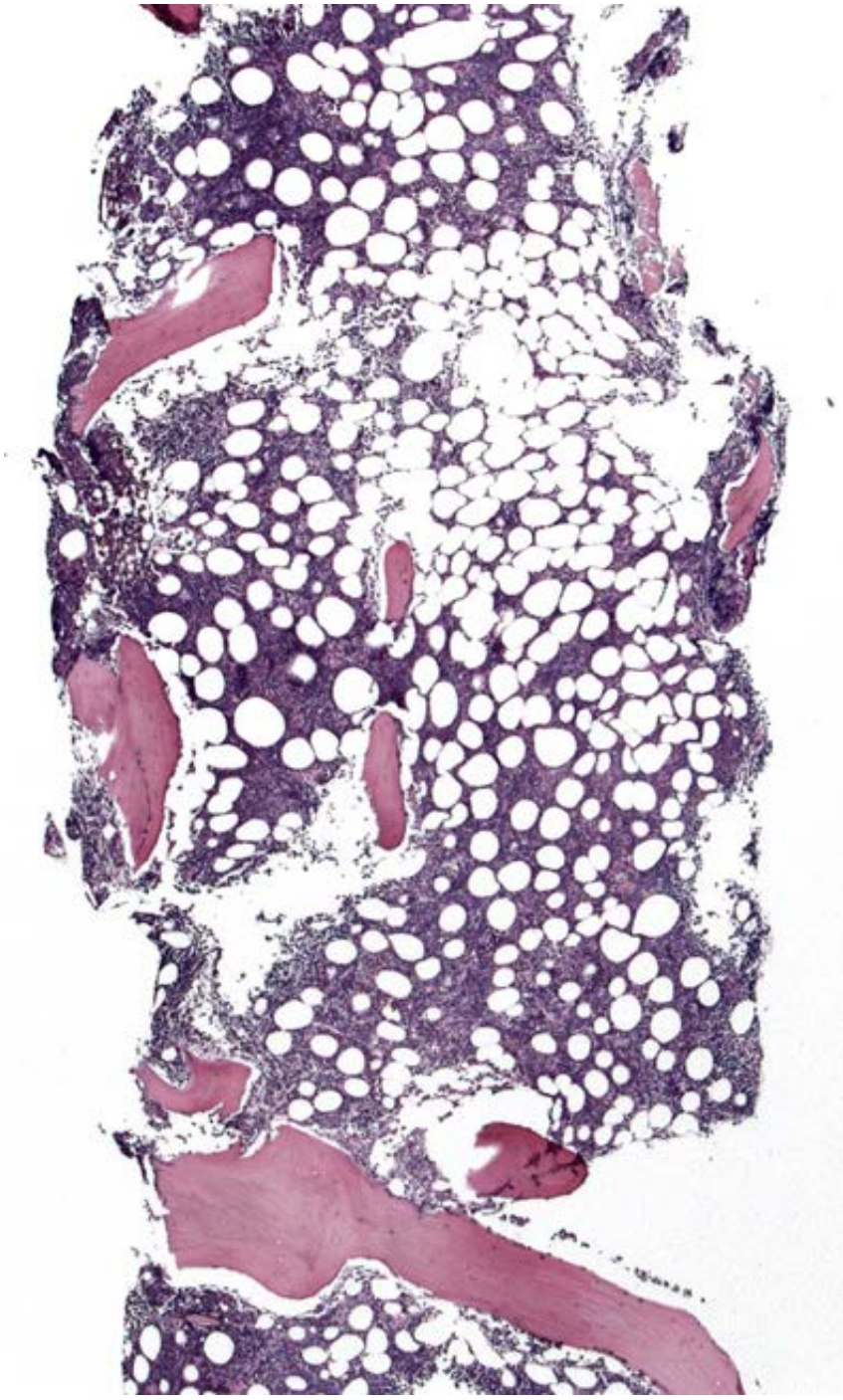
Gated Events: 14449 Total

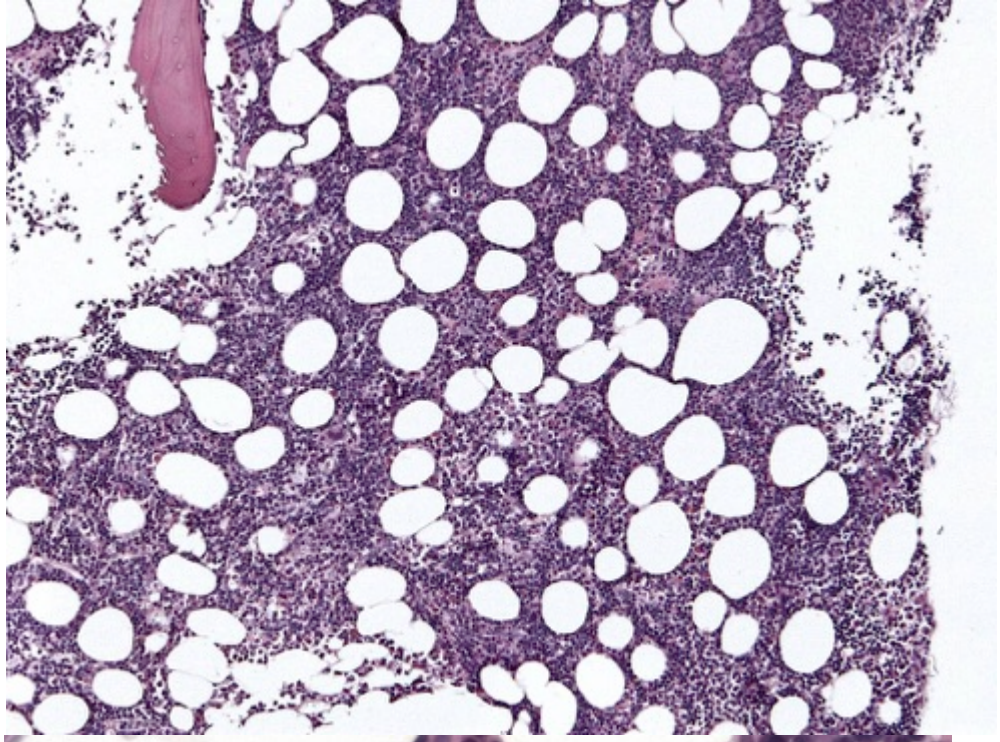
Quad	Events	% Gated	% Total
UL	4	0.03	0.03
UR	7153	49.51	47.69
LL	283	1.96	1.89
LR	7009	48.51	46.73

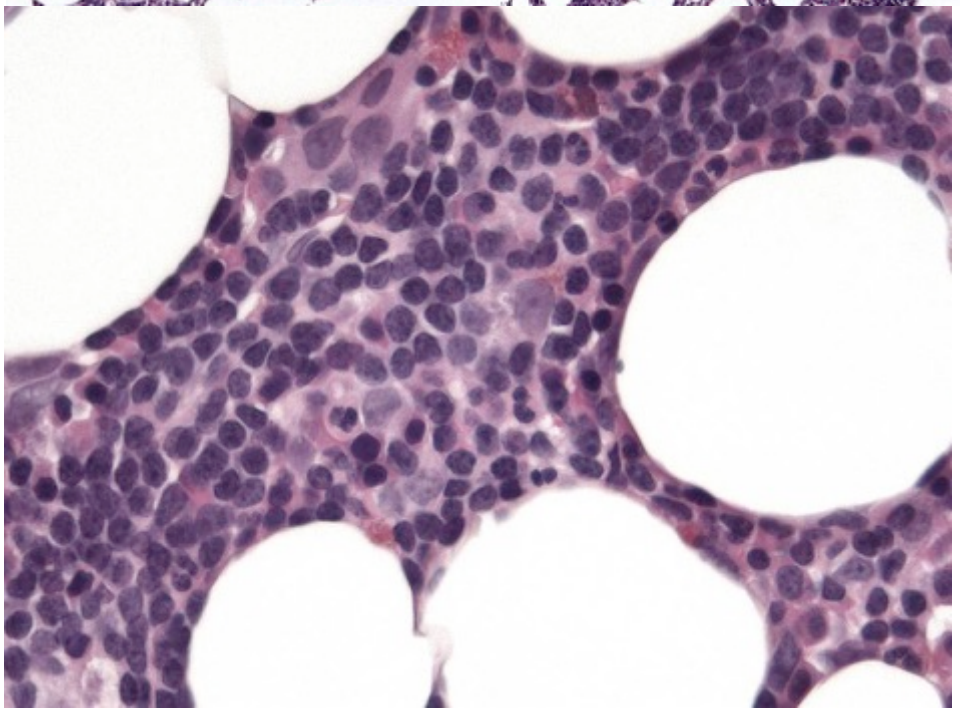


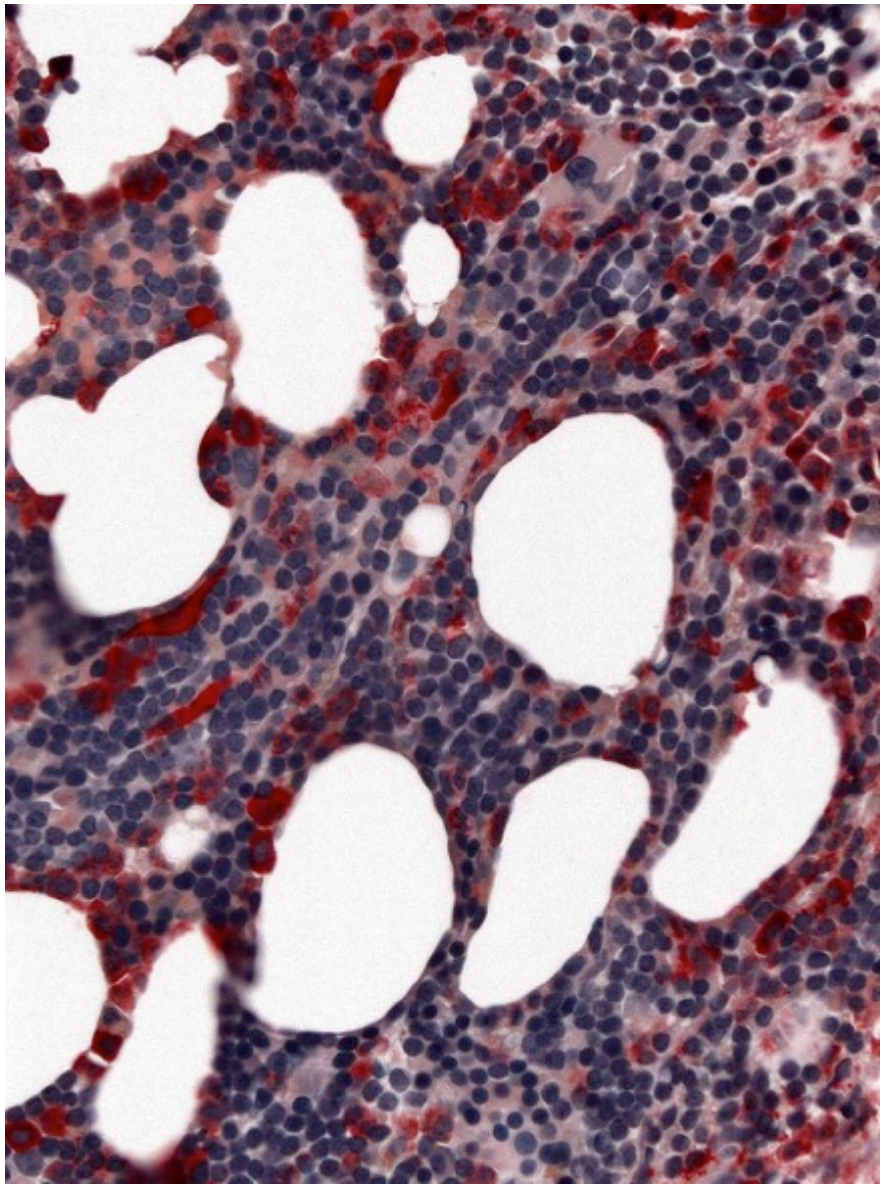


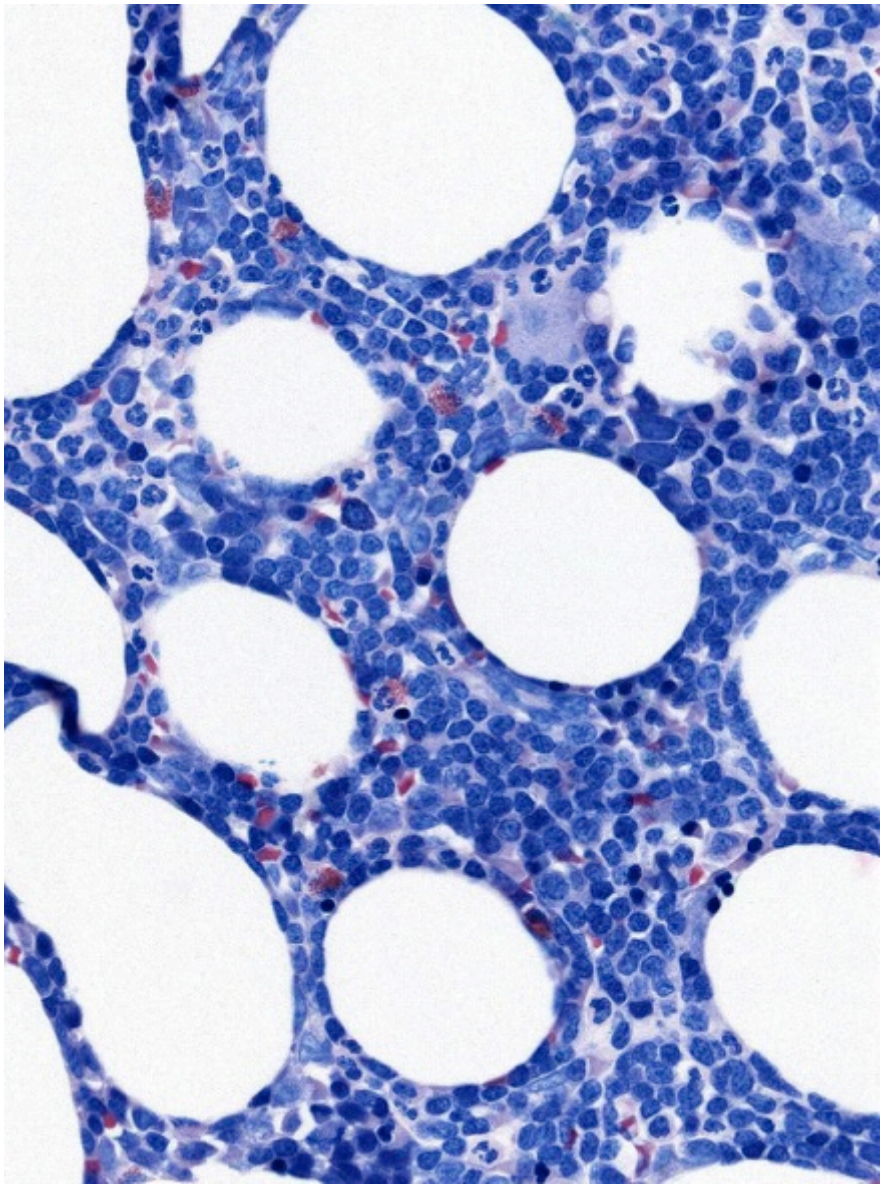
96% monoclonal B-cells with CD19+, CD5+, CD20+, CD22++, CD23 partially expressed and sKappa++.





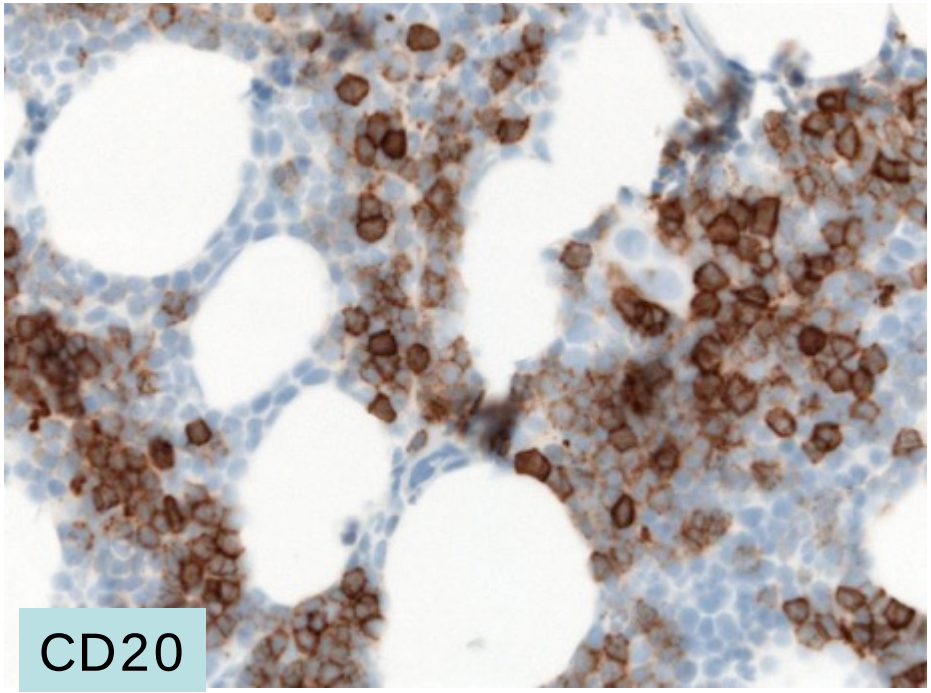


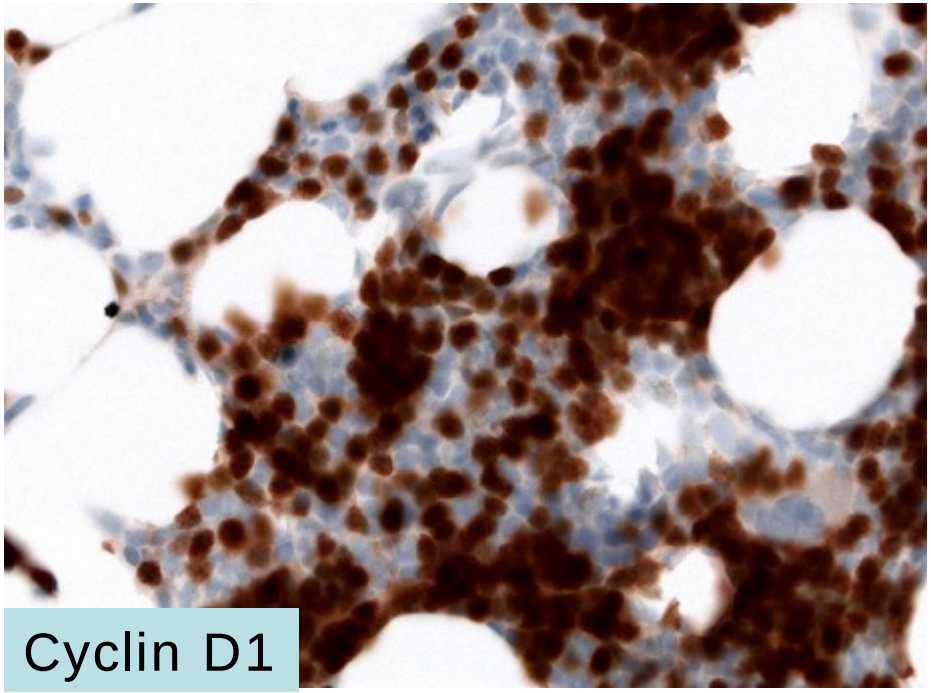


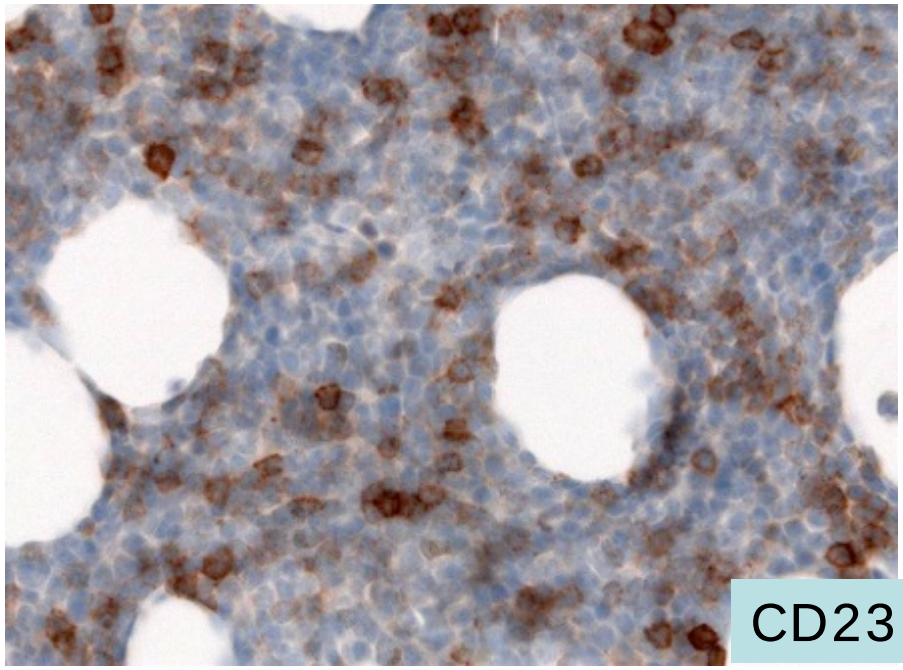


ASDCL 40x

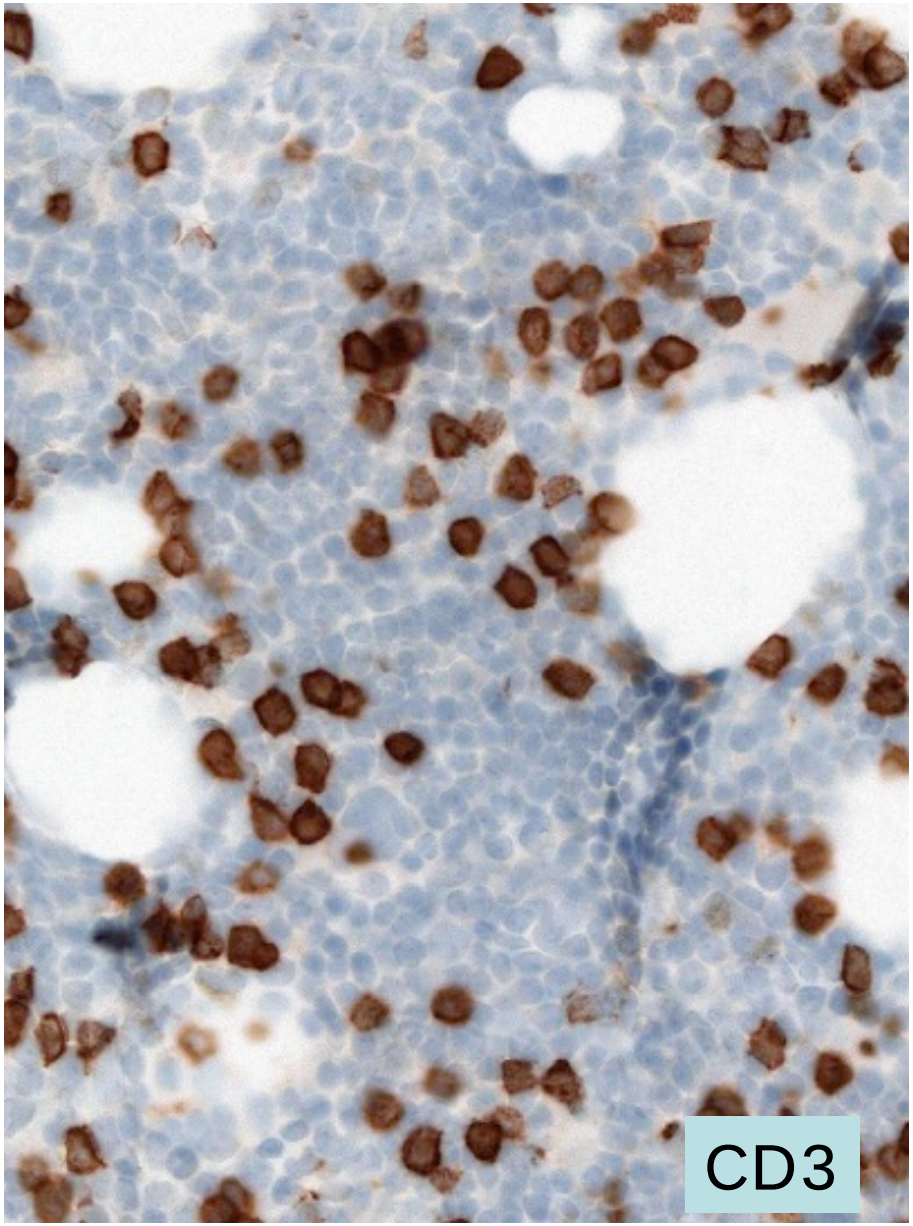
Giemsa 40x

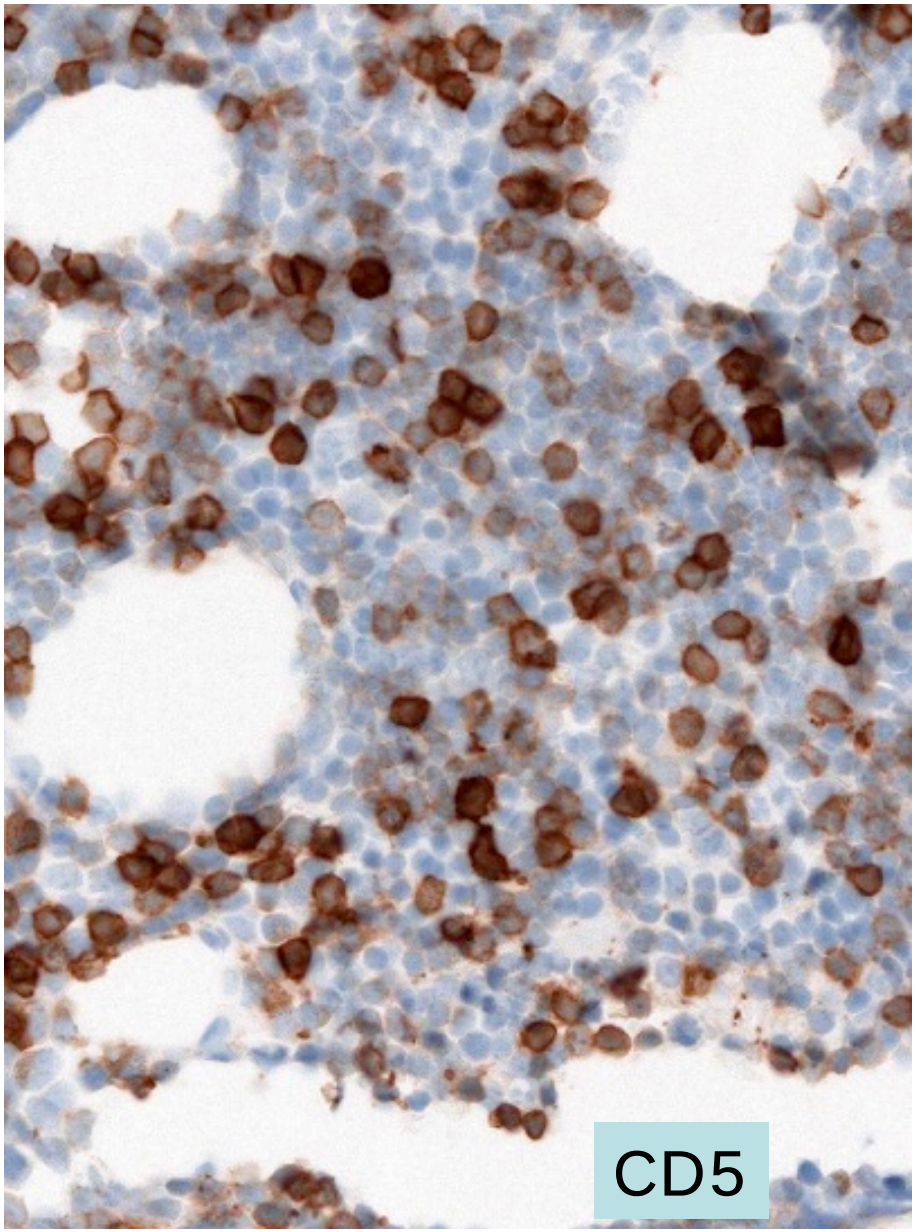






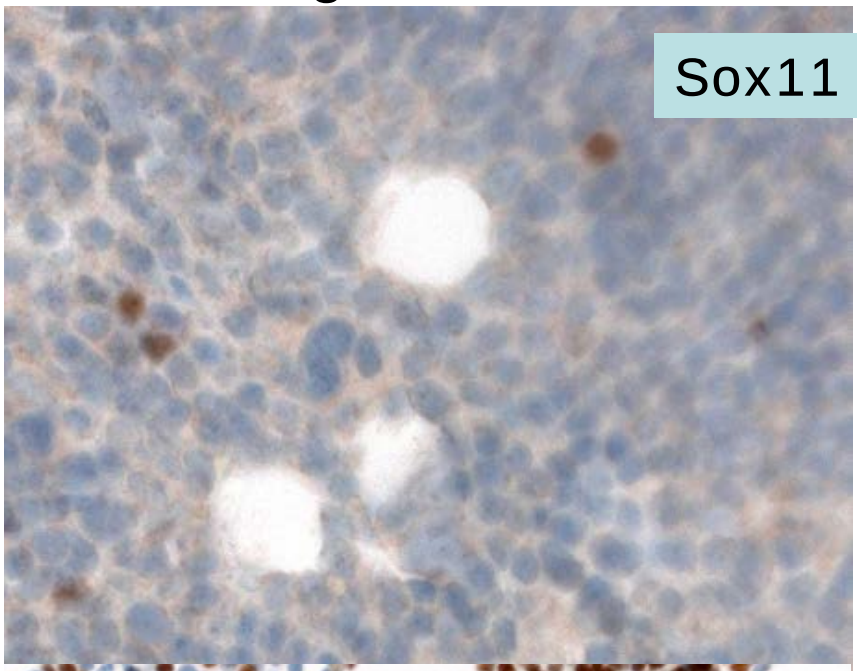
Heterogeneous expression of CD23 as demonstrated in FACS analysis

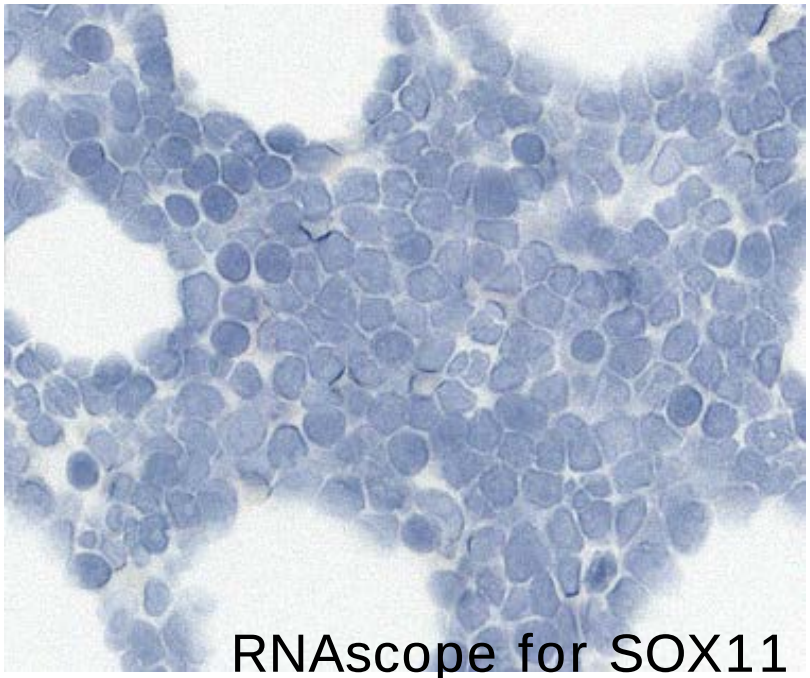




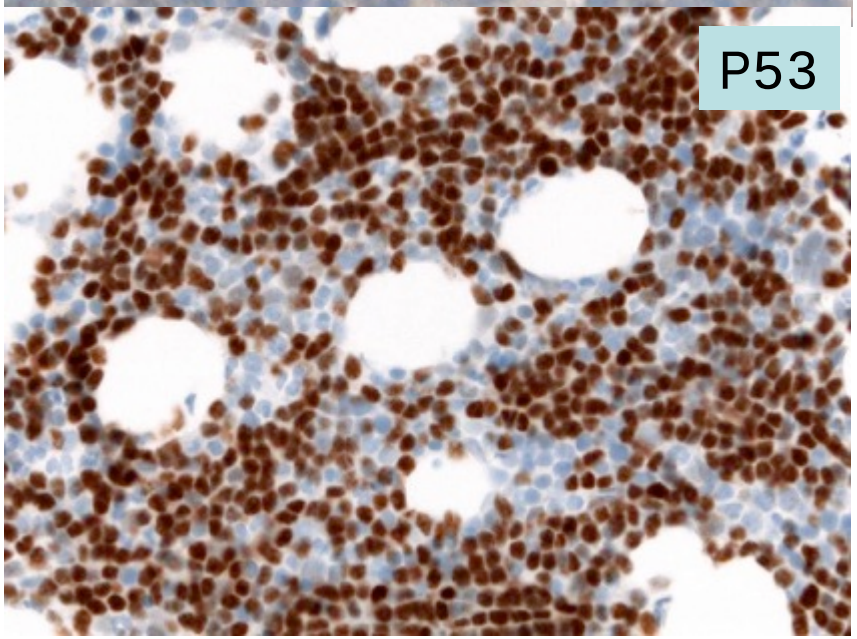
CD5 expression also heterogeneous

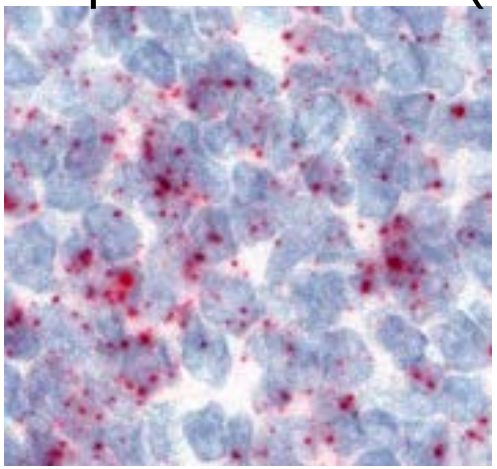
Sox11 negative both with IHC and at mRNA level





RNAscope for SOX11 (-)

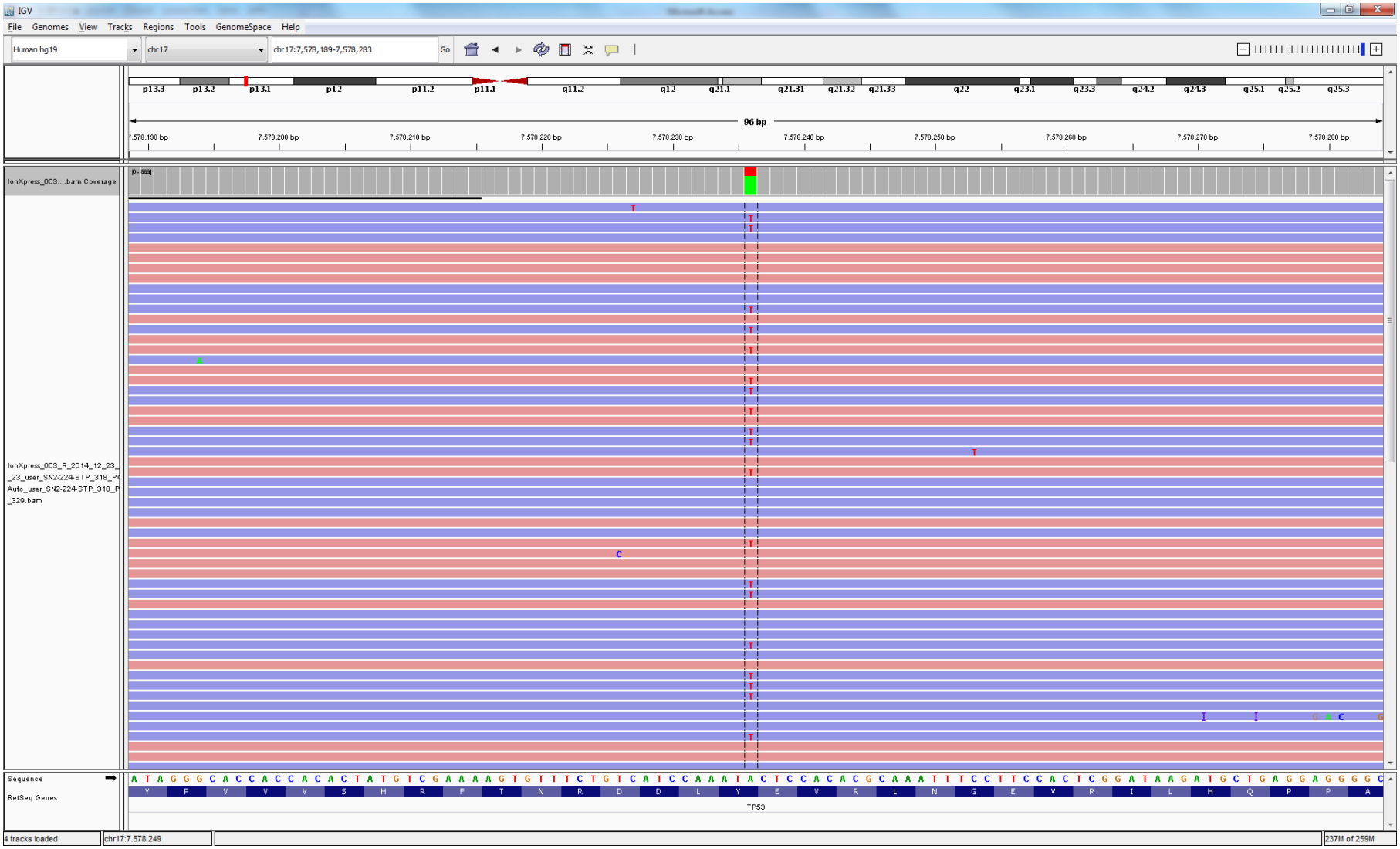




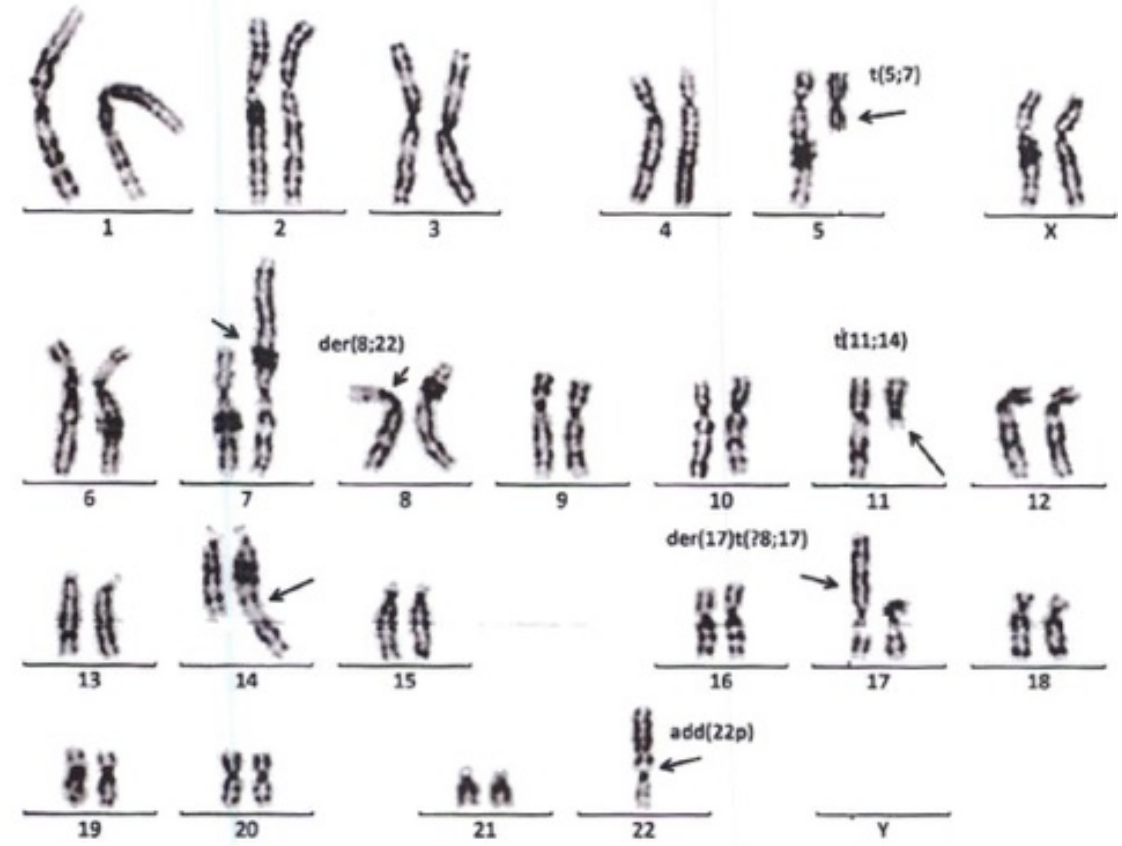
RNAscope for SOX11 control
In a classic MCL

TP53 NGS analysis

_TP53_: p.Y205N, c.613T>A (VAF 32%)



Cytogenetics



FISH analysis showed deletion of 17p13.1 (*TP53* deletion)

Complex karyotype:

45,XX, t(5;7)(q12-13;p21-22), der(8;22)(q10:q10), t(11;14)(q13;q32), der(17) t(?8;17), add(22)(p?)

Clinical follow-up

1st cycle R-Bendamustin 2nd skipped 2nd 5th 6th

Steroids ↓ ↓ ↓ ↓ ↓ ↓

	23.11.16	24.11.16	25.11.17	29.12.16	04.01.17	01.02.17	18.05.17	03.07.17
Leukocytes/µl	324 540	387 000	11 830	8 810	7 380	2 710	6 520	1150
Lymphocytes absolute	305 730	280 000	4 960	2 190	0.65	0.29	0.30	0.18
Lymphocytes (%)	94.2	72.0	41.9	24.9	8.8	10.7	--	--
Hemoglobin (g/dl)	7.8	8.5	8.5	8.8	8.0	8.8	10.0	10.5
Platelets/µl	268 000	89 000	89 000	287 000	204 000	180 000	168 000	148 000

Interesting features of submitted case

- This is an interesting case of leukemic, non-nodal MCL with an indolent behaviour that was accelerated by an acute infection but that responded very well to control of the infection and one cycle of chemotherapy.

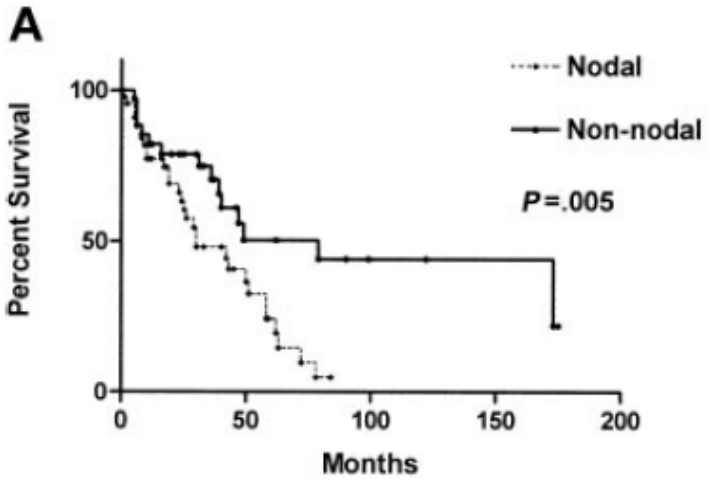
- The most interesting feature in this case is the presence of *TP53* deletion *and* mutation with complex karyotype.

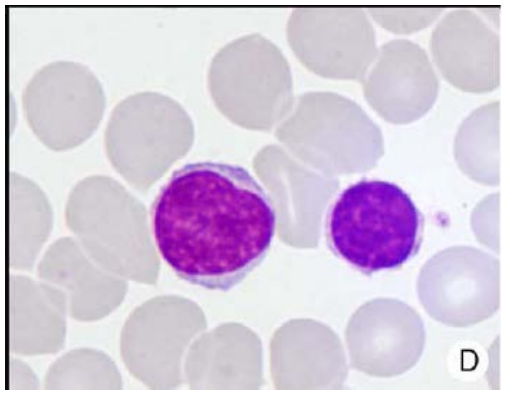
- The differential diagnosis with CLL since this group of MCL often show round-cell cytology and CD23 expression.

Leukemic, non-nodal MCL

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



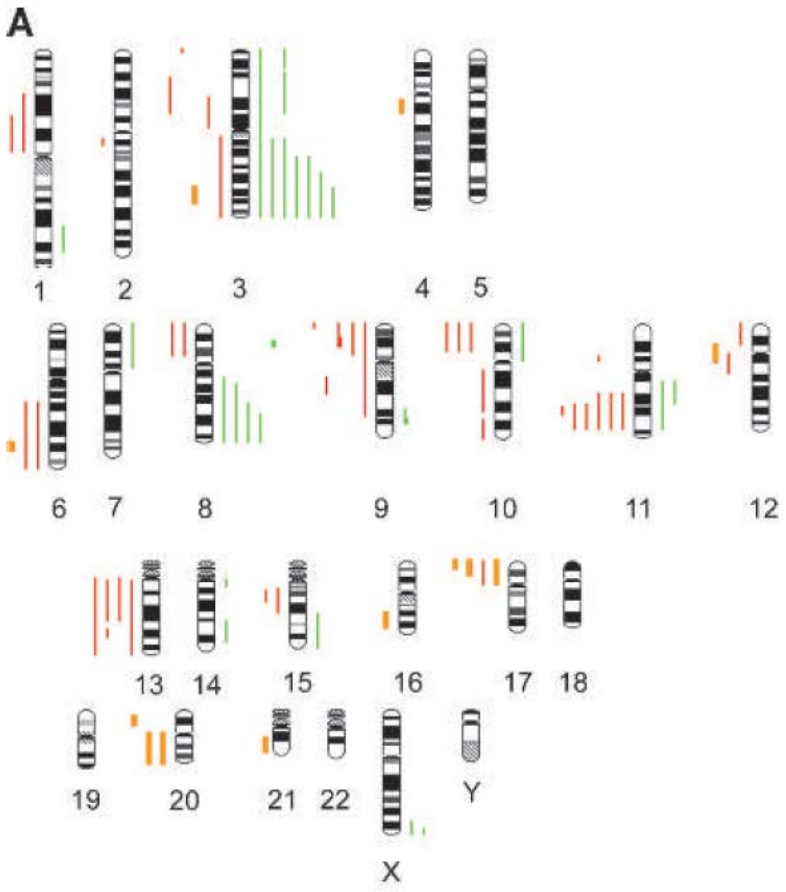


- Lymphocytosis, splenomegaly, mutated IgVH genes and often CD5- and t(11;14)

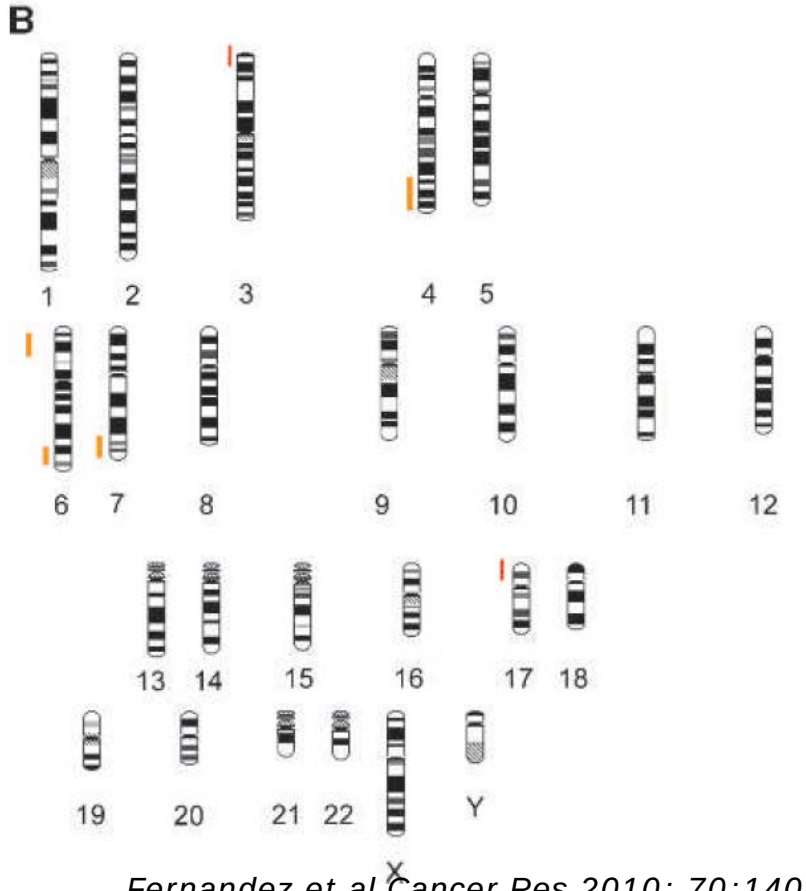
BLOOD, 15 JUNE 2003 • VOLUME 101, NUMBER 12

Mantle cell lymphoma

Aggressive MCL



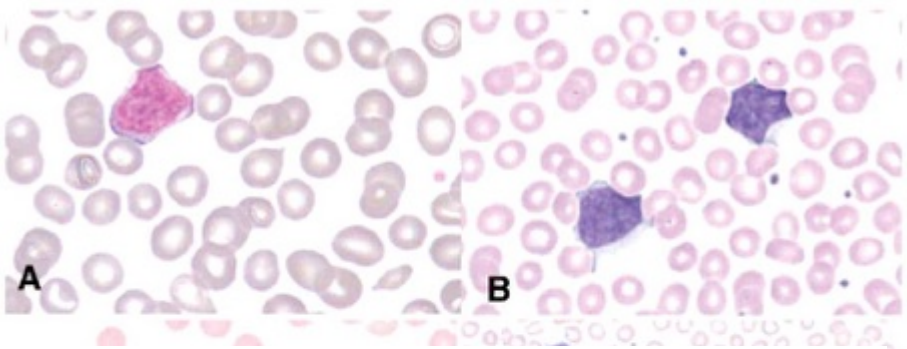
Indolent MCL

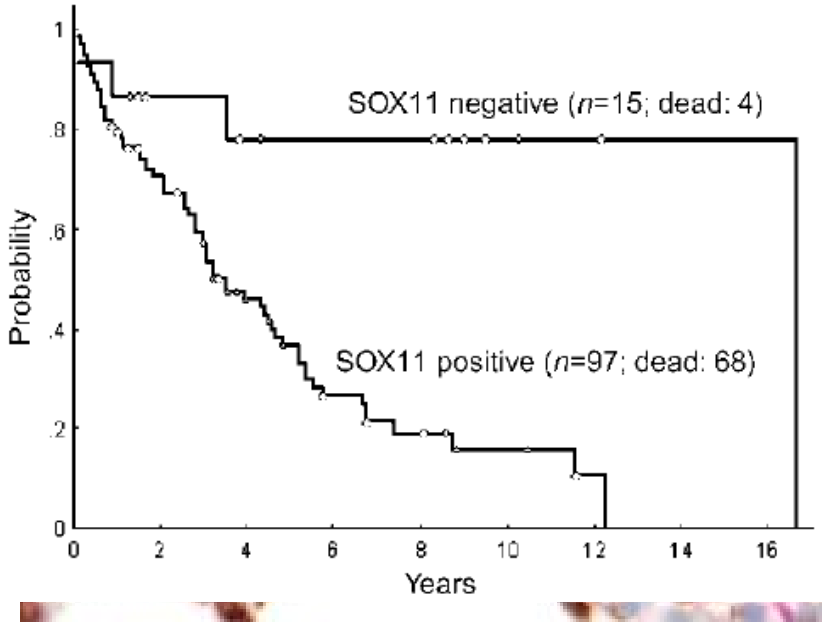


Fernandez et al Cancer Res 2010; 70:1408

Leukemic, non-nodal MCL

- Indolent clinical behaviour
- No treatment at diagnosis
- Non-komplex karyotype
- GEP signature shared with aggressive MCL except for 13 genes
- SOX11 negative





Fernandez V, et al., Cancer Res 2010;70:1408
Ondrejka SL, et al., Haematologica 2011;96:1121
Navarro A, et al., Cancer Res 2012:72:5307

Prognostic role of SOX11 in a population-based cohort of mantle cell lymphoma

*Lina Nygren,[1,2] *Stefanie Baumgartner Wennerholm,[3] Monika Klimkowska,[1] Birger Christensson,[1] Eva Kimby,[3] and Birgitta Sander[1]

BLOOD, 3 MAY 2012 • VOLUME 119, NUMBER 18

Table 3. Clinical and pathologic features in SOX11⁻ and SOX11⁺ tumors in the whole cohort of patients with MCL

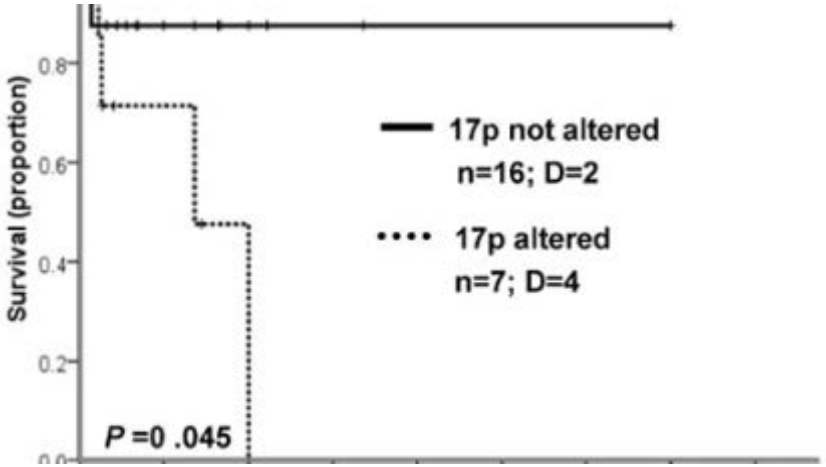
Clinical and pathologic features	SOX11⁻ cases, n = 13 (%)	SOX11⁺ cases, n = 160 (%)	P
Median age, y (range)	71.4 (48.4-89.9)	69.7 (36.2-89.2)	
Male sex	10/13 (77)	108/160 (68)	NS
Age > 65 y	11/13 (85)	101/160 (63)	NS
B symptoms	6/13 (46)	59/154 (38)	NS
ECOG score ≥ 2	1/12 (8)	6/152 (4)	NS
Nodal presentation (> 4 nodal sites)	6/12 (50)	99/157 (63)	NS
Splenomegaly	5/10 (50)	73/146 (50)	NS
Ann Arbor stage IV	13/13 (100)	129/159 (81)	NS
WBC count > 10×10^9/L	7/13 (54)	47/154 (31)	NS
Lymphocyte count > 5×10^9/L	7/13 (54)	38/153 (25)	.045
High serum LDH level	9/12 (75)	58/149 (39)	.029
MIPI high risk	6/8 (75)	57/126 (45)	NS
Ki-67 high (≥ 30%)	5/12 (42)	54/142 (38)	NS
Ki-67 very high (≥ 50%)	1/12 (8)	25/142 (18)	NS
Blastoid structure	2/12 (17)	15/145 (10)	NS
p53 positivity > 20% of cells by IHC	9/13 (69)	24/152 (16)	< .001
CD23 positivity by flow cytometry	7/12 (58)	64/137 (47)	NS
Indolent disease*	2/13 (15)	15/157 (10)	NS
Intense treatment without ASCT	1/12 (8)	3/160 (2)	NS
ASCT	1/12 (8)	31/160 (19)	NS
Median overall survival (days)†	494	1180	.014

Non-nodal type of mantle cell lymphoma is a specific biological and clinical subgroup of the disease

Cristina Royo[1,13], Alba Navarro[1,13], Guillem Clot[1], Itziar Salaverria[1,2], Eva Giné[3], Pedro Jares[1], Dolors Colomer[1], Adrian Wiestner[4], Wyndham H. Wilson[4], Maria Carmela Vegliante[1], Veronica Fernandez[1], Elena M. Hartmann[5], Nicola Trim[6], Wendy N. Erber[7], Steven H. Swerdlow[8], Wolfram Klapper[9], Martin J.S. Dyer[10], Manuel Vargas-Pabón[11], German Ott[12], Andreas Rosenwald[5], Reiner Siebert[2], Armando López-Guillermo[3], Elías Campo[1,14], and Sílvia Beà[1,14]

Leukemia 2012;26:1895

- Cases with *TP53* alteration
- Complex karyotype
- Aggressive behaviour



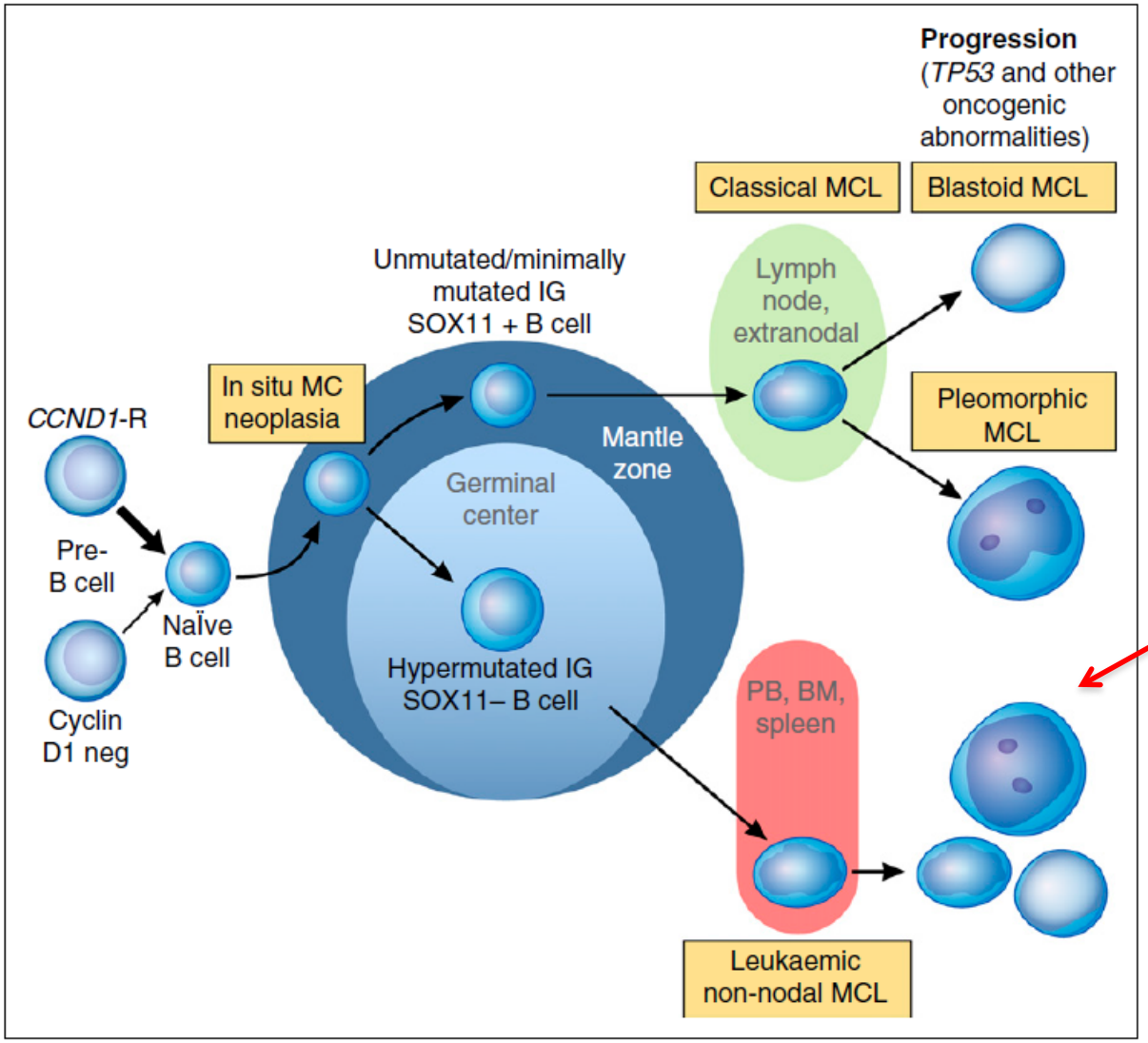
Progressive leukemic non-nodal mantle cell lymphoma associated with deletions of *TP53*, *ATM*, and/or 13q14☆,☆☆

Jennifer Chapman-Fredricks, MD [a], Jose Sandoval-Sus, MD [b], Francisco Vega, MD, PhD [a], Izidore S. Lossos, MD [b,c,*]

[a] Division of Hematopathology, Department of Pathology, University of Miami, Miami, FL.
[b] Division of Hematology-Oncology, Department of Medicine, Sylvester Comprehensive Cancer Center, Miami, FL.
[c] Department of Molecular and Cellular Pharmacology, University of Miami, Miami, FL.

Annals of Diagnostic Pathology 2014;18:214

Mantle cell lymphoma



TP53 mutation

BLOOD, 19 MAY 2016 • VOLUME 127, NUMBER 20

Final diagnosis

- Leukemic, non-nodal MCL with complex karyotype and *TP53* deletion and mutation with rather indolent clinical behaviour