UPDATE ON PLASMA CELL NEOPLASMS

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DISCLOSURES

Research support from Stemline

Speaker honoraria from Stemline and EUSAPharma

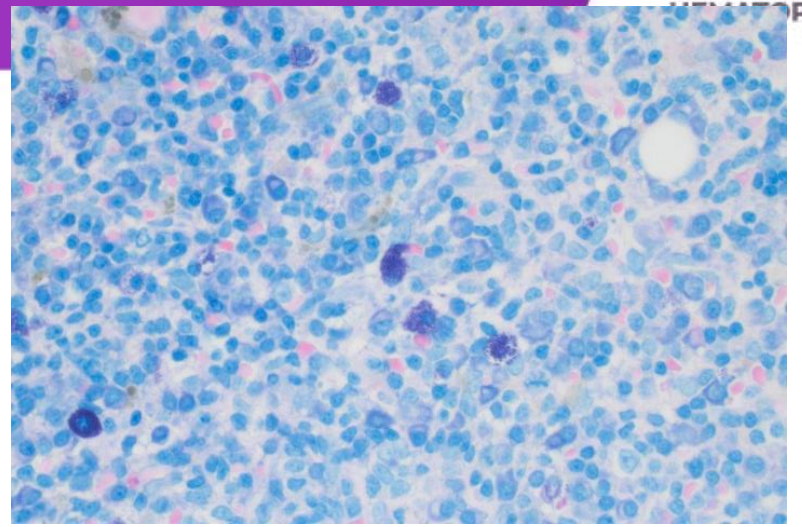
PLASMA CELL NEOPLASMS

Plasma cells are the dominant and proliferating neoplastic population, +/- monoclonal immunoglobulin (M-protein)

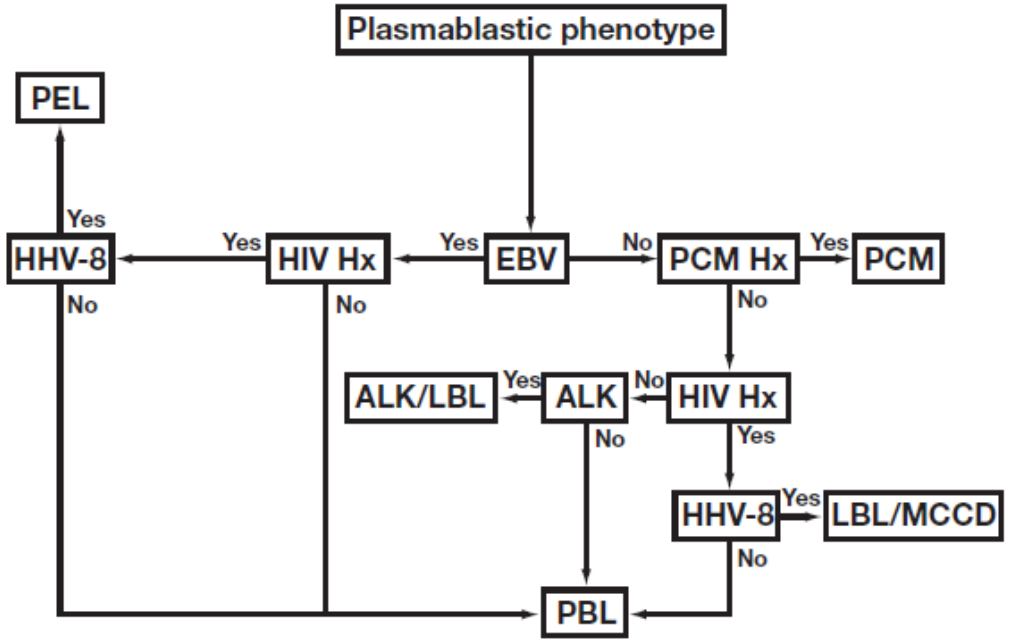
Plasma cell tumors need to be differentiated from

- Small B cell neoplasms with plasma cell differentiation
- Terminally differentiated aggressive B-cell lymphomas with plasmablastic phenotype (PBL, PEL, ALK+ LBCL)

Multiple myeloma 10% of all hematological neoplasms, 1% of all cancers

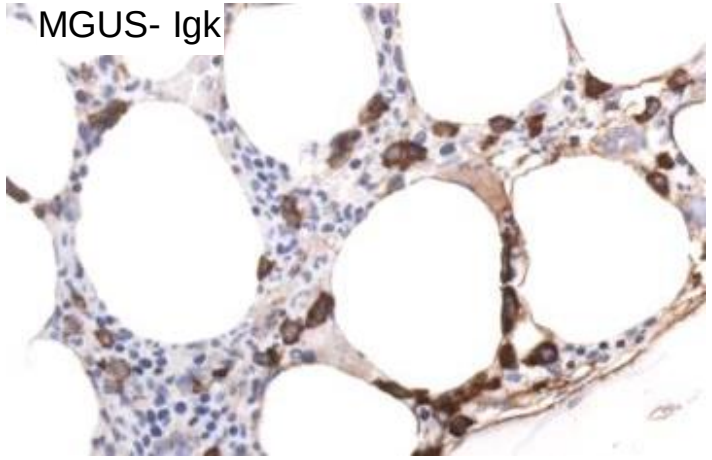


LPL



Hsi et al, AJCP 2011

SYSTEMIC PLASMA CELL DISORDERS SHOW STEPWISE EVOLUTION

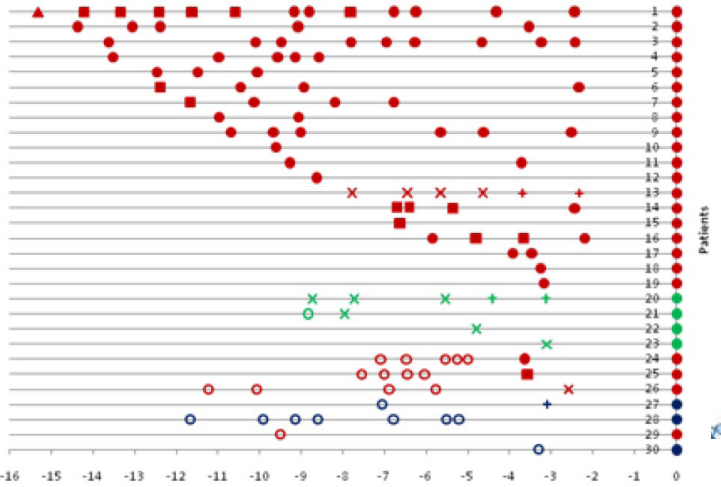


MGUS → Smouldering MM → Intramedullary MM → Extramedullary MM and Plasma cell leukemia

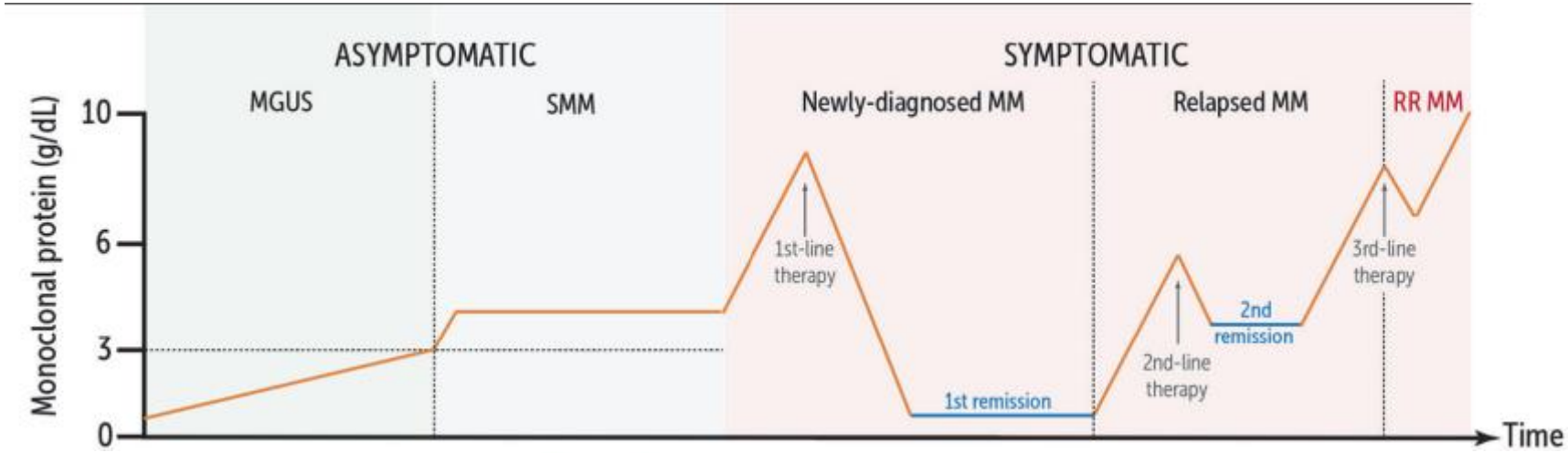
Genetic evolution

Microenvironment

MGUS is (virtually) universal precursor to MM – progression rate 1%/year



Weiss et al, Blood 2009

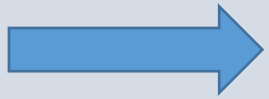


Ho et al, Leukemia 2020

CLASSIFICATION OF PLASMA CELL NEOPLASMS

Evolution from clinically inapparent precursors through an indolent (smoldering) disease phase to manifest organ damage

Alternative occurrence as localized disease (plasmacytoma)



Integration of clinical, laboratory and imaging parameters for diagnosis

International Myeloma Working Group (IMWG) consensus criteria form basis for classification plasma cell neoplasms in both ICC and WHO classifications

SLIM-CRAB CRITERIA FOR DEFINING ACTIVE DISEASE

Clinical symptoms caused by end organ damage (**CRAB**) and biomarkers of malignancy (**SLiM**)

Hyper**C**alcemia (>0.25 mmol/L (>1 mg/dL) above normal or >2.75 mmol/L (>11 mg/dL))

Renal insufficiency (creatinine clearance <40 mL or serum creatinine>177 µmol/L (>2 mg/dL))

Anemia (Hb >20g/l below normal or <100g/L)

Bone lesions (one or more lytic lesions on Rx, CT or PET-CT)

Sixty % BM plasma cells

Serum free **Li**ght chain ratio ≥100

>1 focal lesion on **M**RI

*Rajkumar et al, Lancet Oncol 2014

IMWG CONSENSUS CRITERIA FOR PLASMA CELL NEOPLASMS

3° CONGRESO LATINOAMERICANO DE HEMATOPATOLOGÍA
SÃO PAULO | 2023

Non-IgM MGUS

- Monoclonal serum protein <30 g/L
- <10% plasma cells in BM
- No PCM-related end-organ damage

Incidence 3-4% >50y, >5% >70y
Progression risk 1%/year (1.5% for IgA, 0.3% for LC)

Smouldering (asymptomatic) myeloma

- >10% and <60% plasma cells in BM and/or paraprotein >30 g/L
- 500mg/24h urine
- Absence of myeloma-defining events or amyloidosis

Symptomatic myeloma

- >10% plasma cells in BM (or plasmacytoma)
- Monoclonal protein in serum or urine
- Myeloma-defining events
  - End organ damage
  - Biological markers of malignancy

*Rajkumar et al, Lancet Oncol 2014

Determination of PC count by cytology (not FCM!) and histology, higher value counts

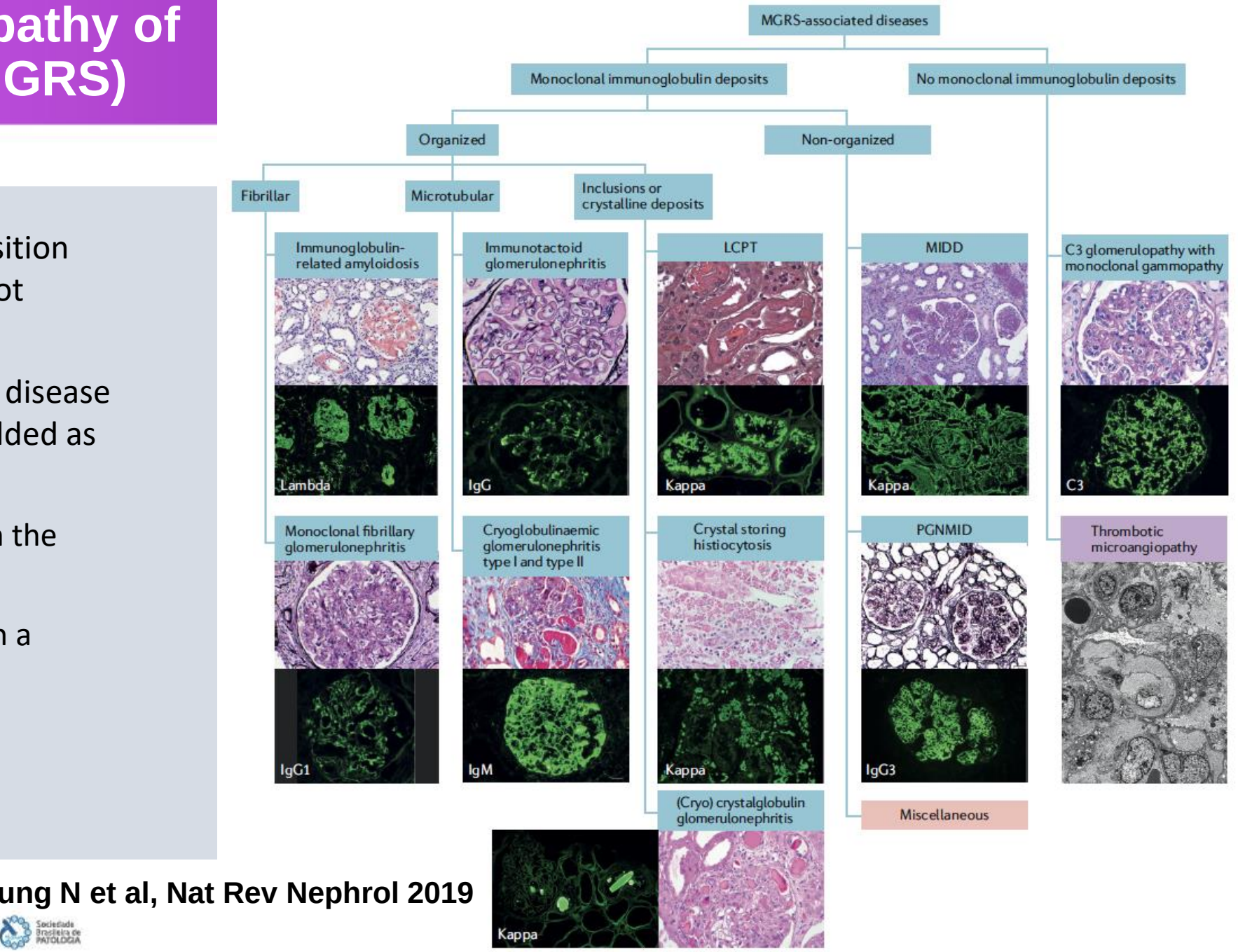
Monoclonal Gammopathy of renal significance (MGRS)

Renal damage caused by IG deposition due to clonal B/PC proliferation not fulfilling criteria for malignancy

MGRS not introduced as separate disease entities in 2022 ICC, but can be added as qualifier

- ICC nomenclature focused on the neoplastic process
- MGRS and MGCS can occur in a variety of B cell neoplasms

Extended concept MG**Clinical**S



Leung N et al, Nat Rev Nephrol 2019

IMWG CONSENSUS CRITERIA FOR PLASMA CELL NEOPLASMS

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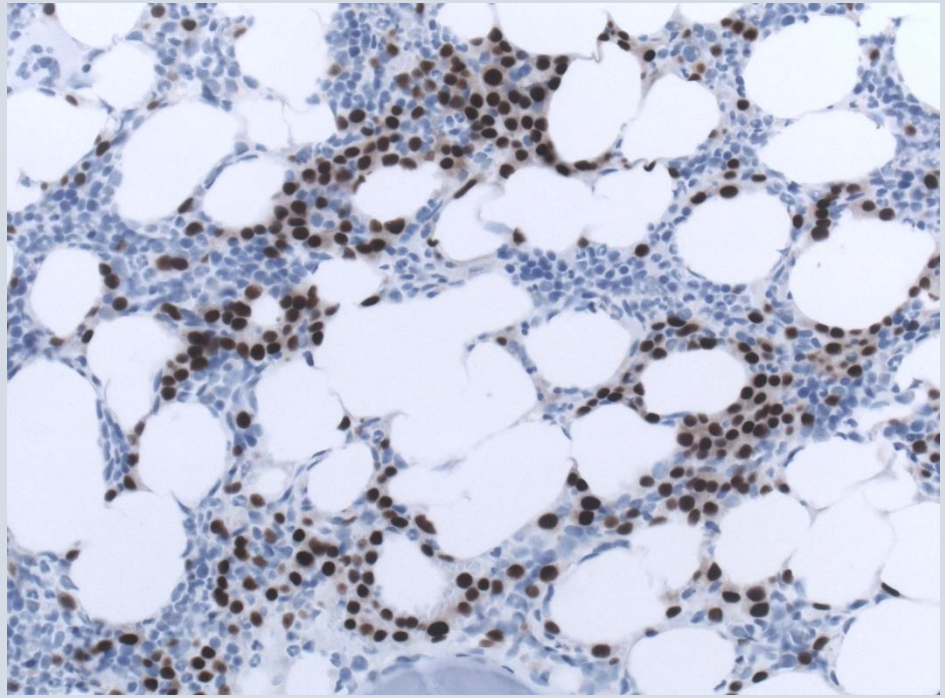
*Rajkumar et al, Lancet Oncol 2014



MUM1

ASSESSMENT OF RISK FOR PROGRESSION IN SMM

Mateos MV et al, BCJ 2020

SMM shows highly divergent evolution

Definition of progression risk criteria for SMM patients for early therapeutic intervention

Analysis of 1996 patients

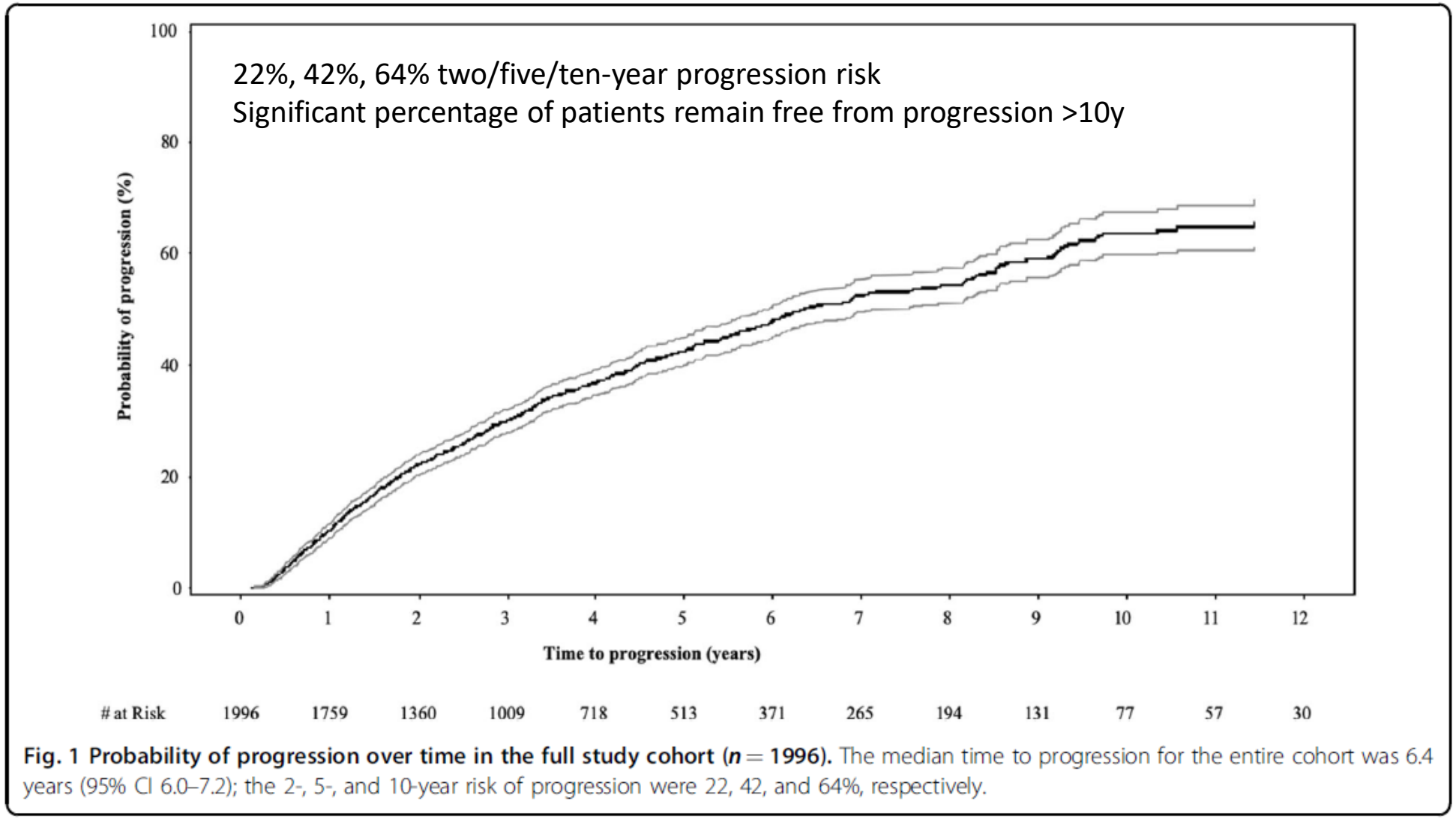


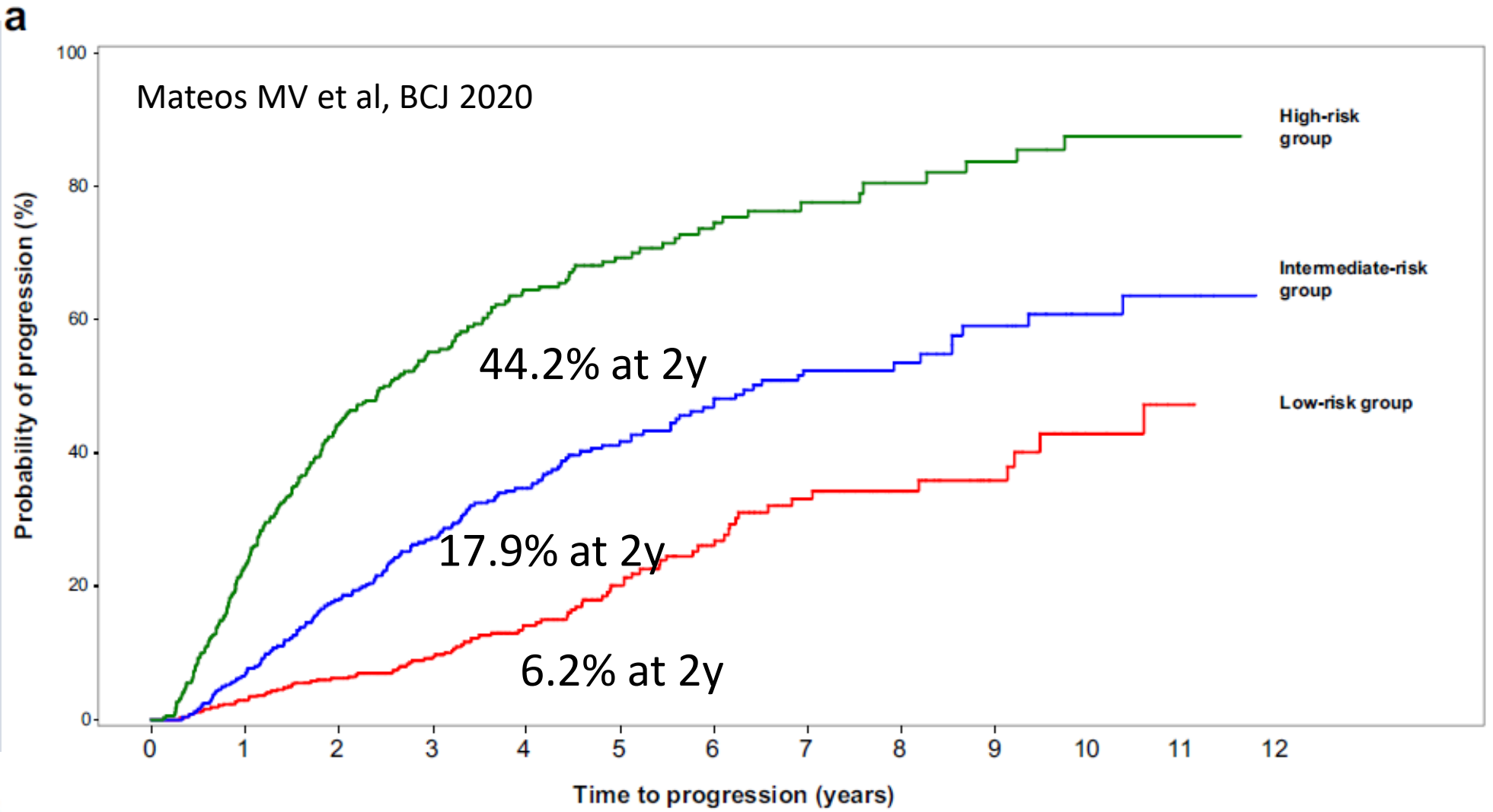
Fig. 1 Probability of progression over time in the full study cohort ($n = 1996$). The median time to progression for the entire cohort was 6.4 years (95% CI 6.0–7.2); the 2-, 5-, and 10-year risk of progression were 22, 42, and 64%, respectively.

3 PARAMETER MODEL (2/20/20) FOR DEFINING HIGH RISK SMM

Serum M protein >2g/dL

Free light chain ratio >20

BM plasma cells >20%



IMWG CONSENSUS CRITERIA FOR PLASMA CELL NEOPLASMS

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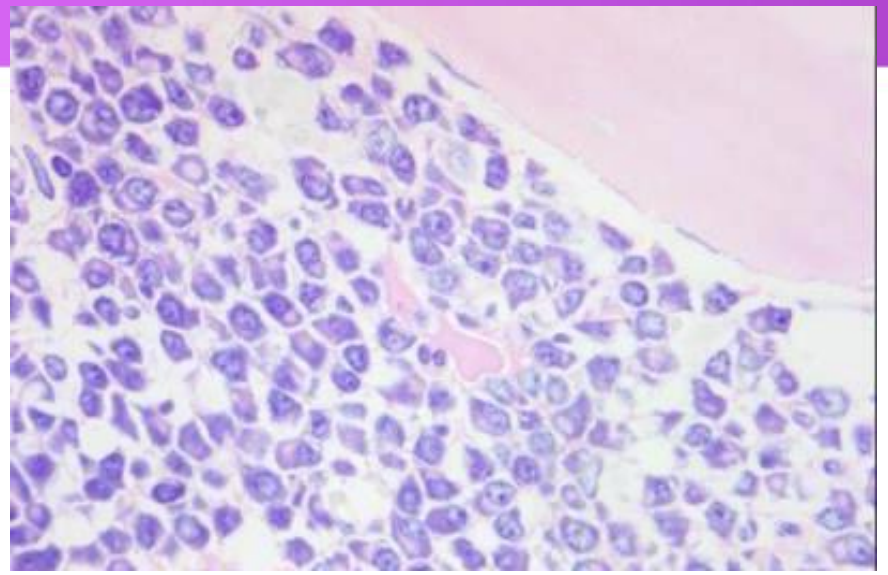
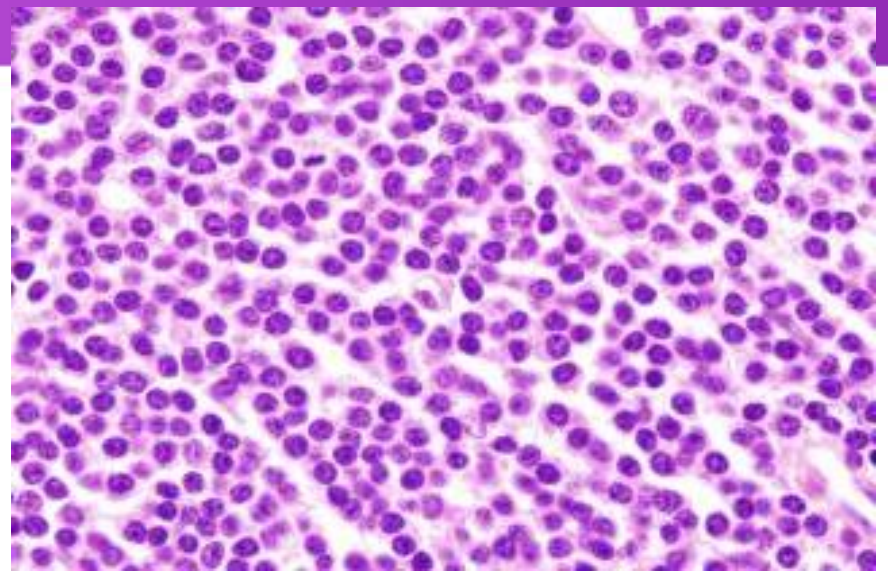
AND
Myeloma-defining events
End organ damage
Biological markers of malignancy

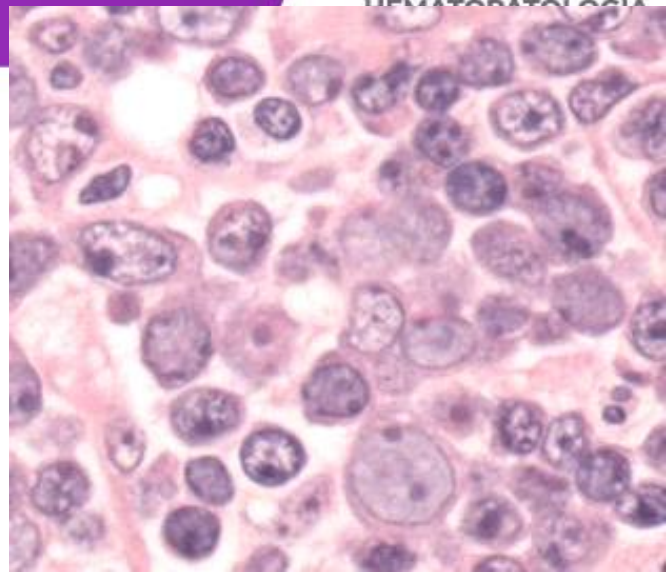
} SLiM-CRAB criteria

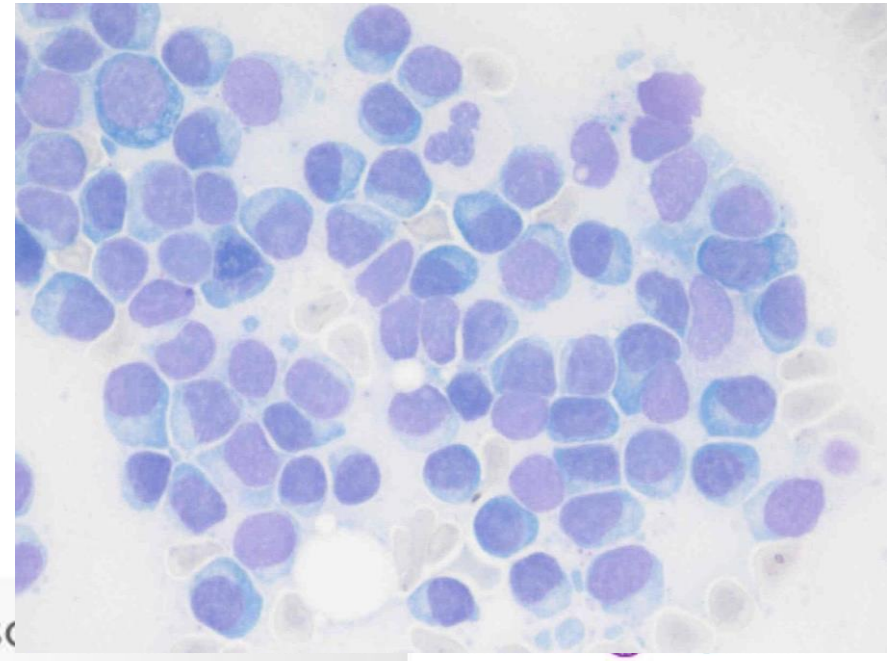
*Rajkumar et al, Lancet Oncol 2014

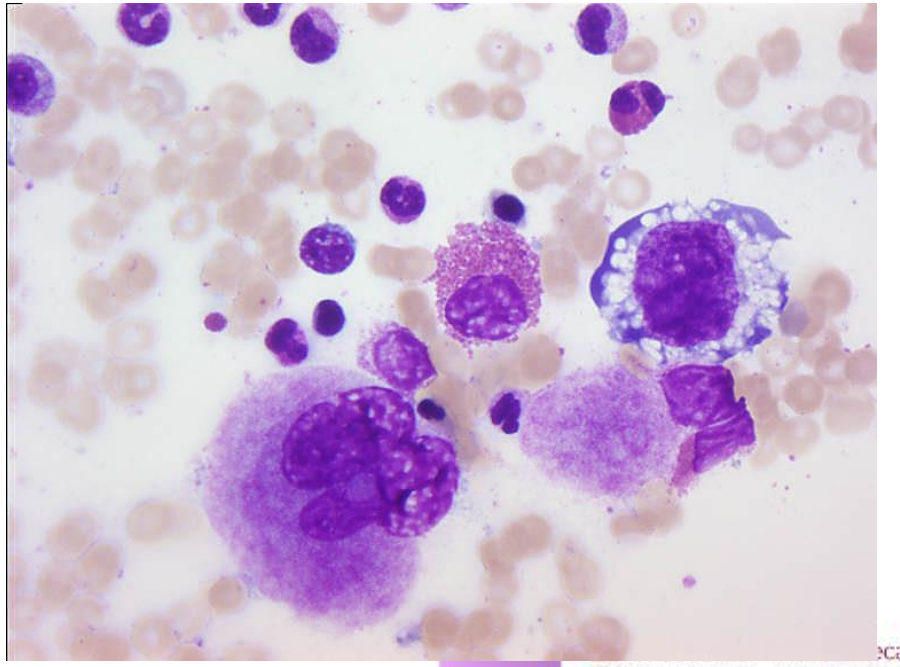
MM DIAGNOSIS IN PATHOLOGY – ALWAYS EASY?

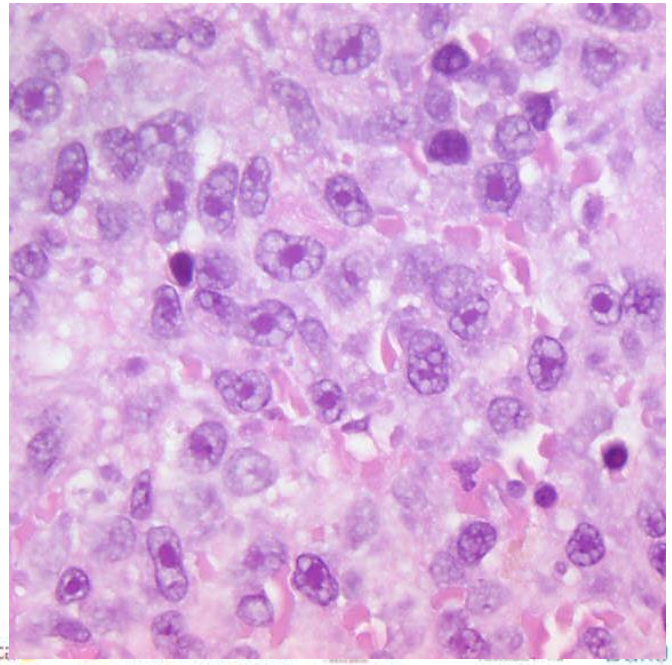


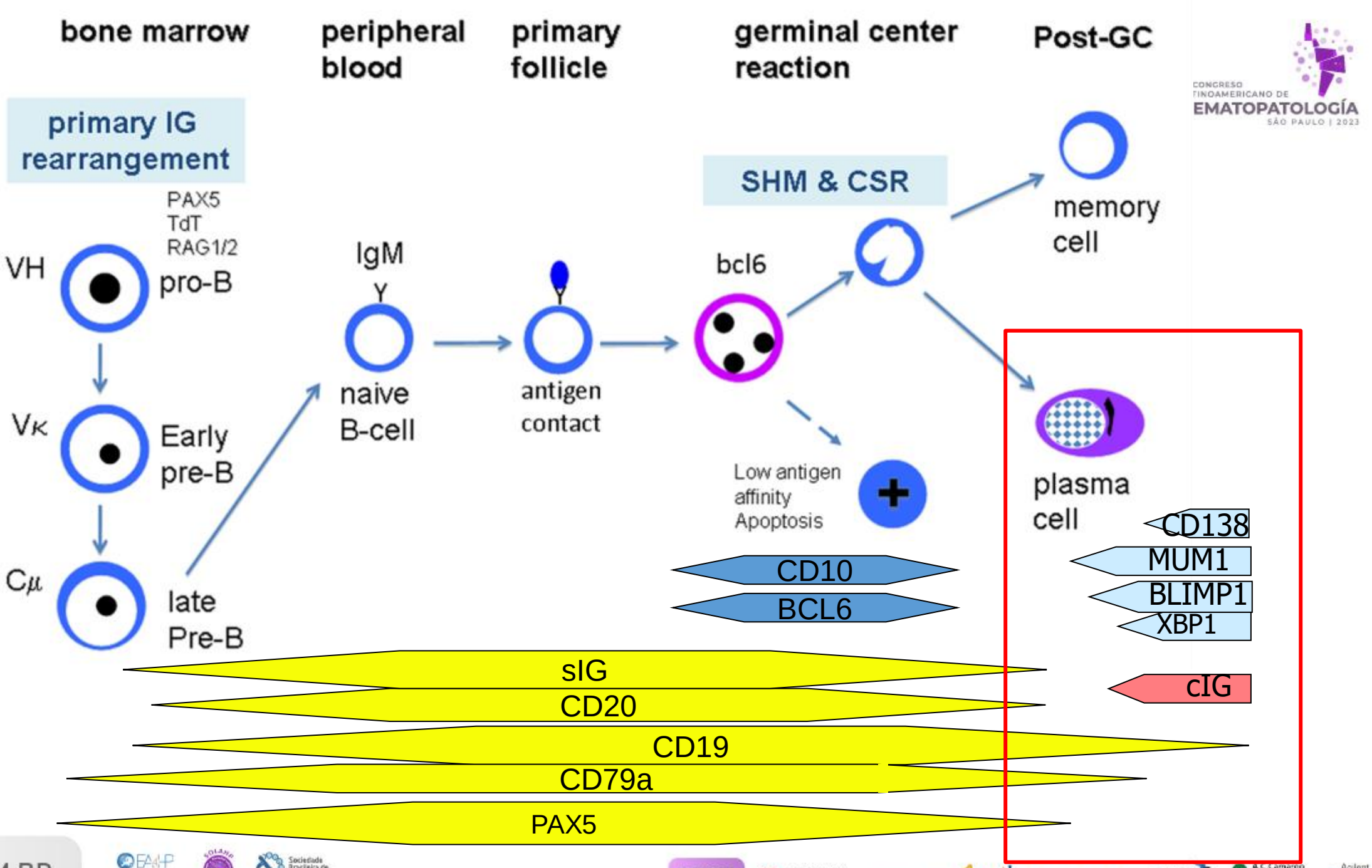










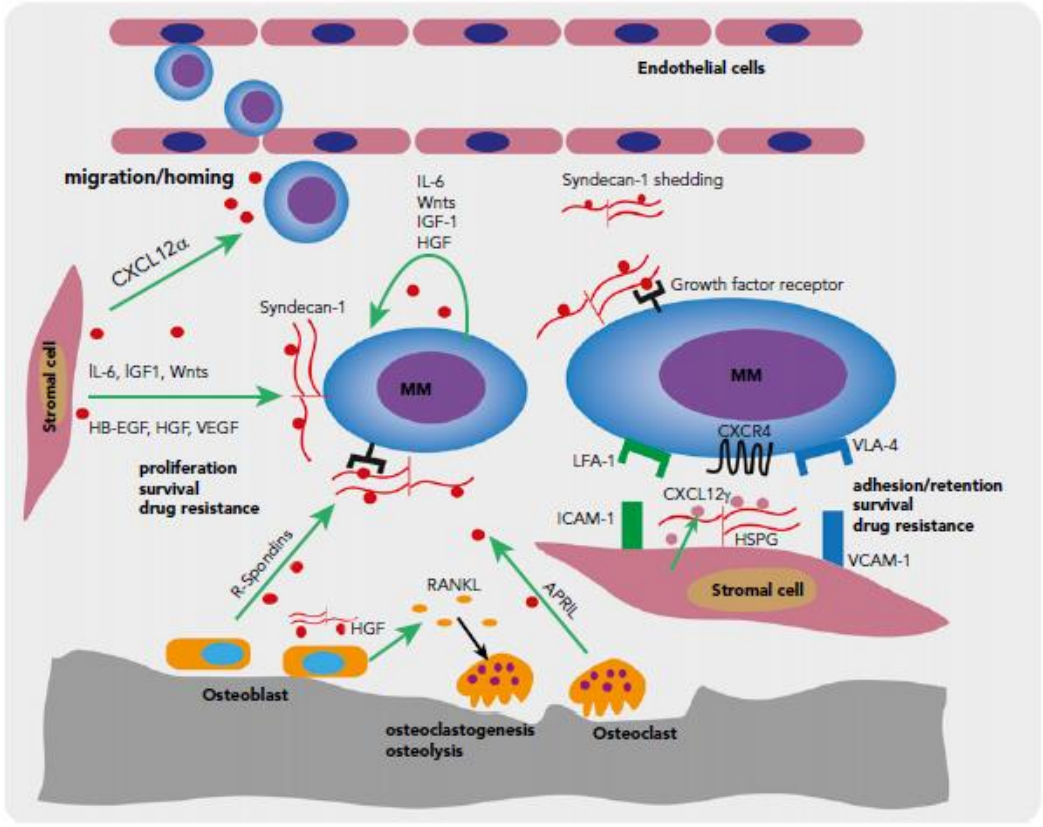

bone marrow
peripheral blood
primary follicle
germinal center reaction
Post-GC
primary IG rearrangement
PAX5
TdT
RAG1/2
VH
pro-B
Vκ
Early pre-B
Cμ
late Pre-B
IgM
naive B-cell
antigen contact
SHM & CSR
bcl6
memory cell
Low antigen affinity Apoptosis
plasma cell
CD138
MUM1
BLIMP1
XBP1
CD10
BCL6
sIG
CD20
CD19
CD79a
PAX5
cIG

Relevant markers of plasma cell differentiation

CD138 (syndecan)

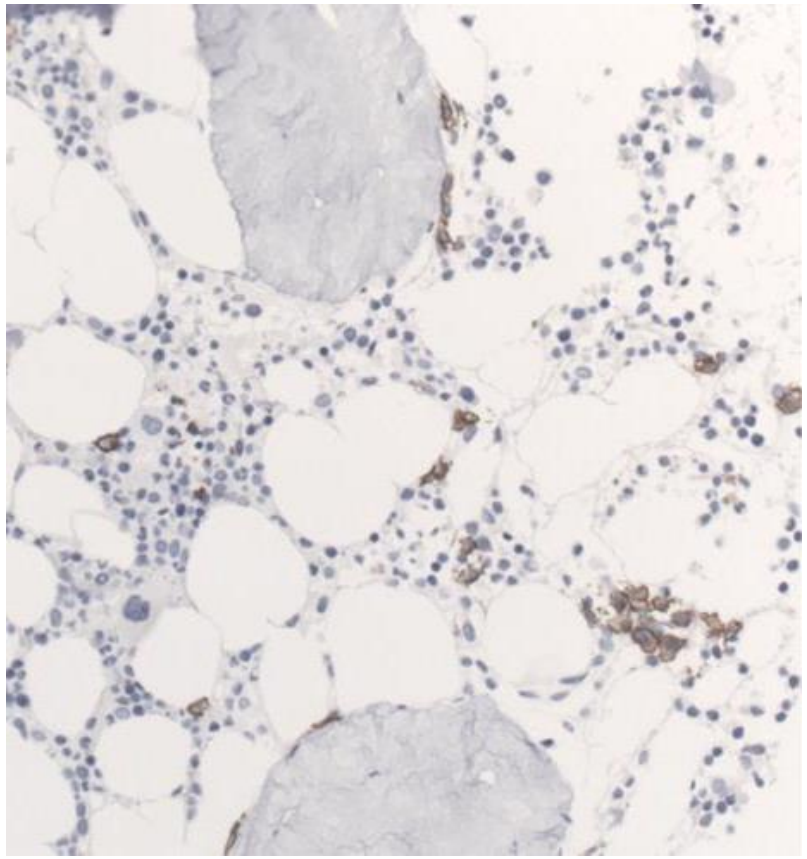
Transmembrane heparan sulfate proteoglycan (HSPG)

Provides alternative mode of interaction with microenvironment in the absence of BCR signalling



Ren Z et al, Blood 2021

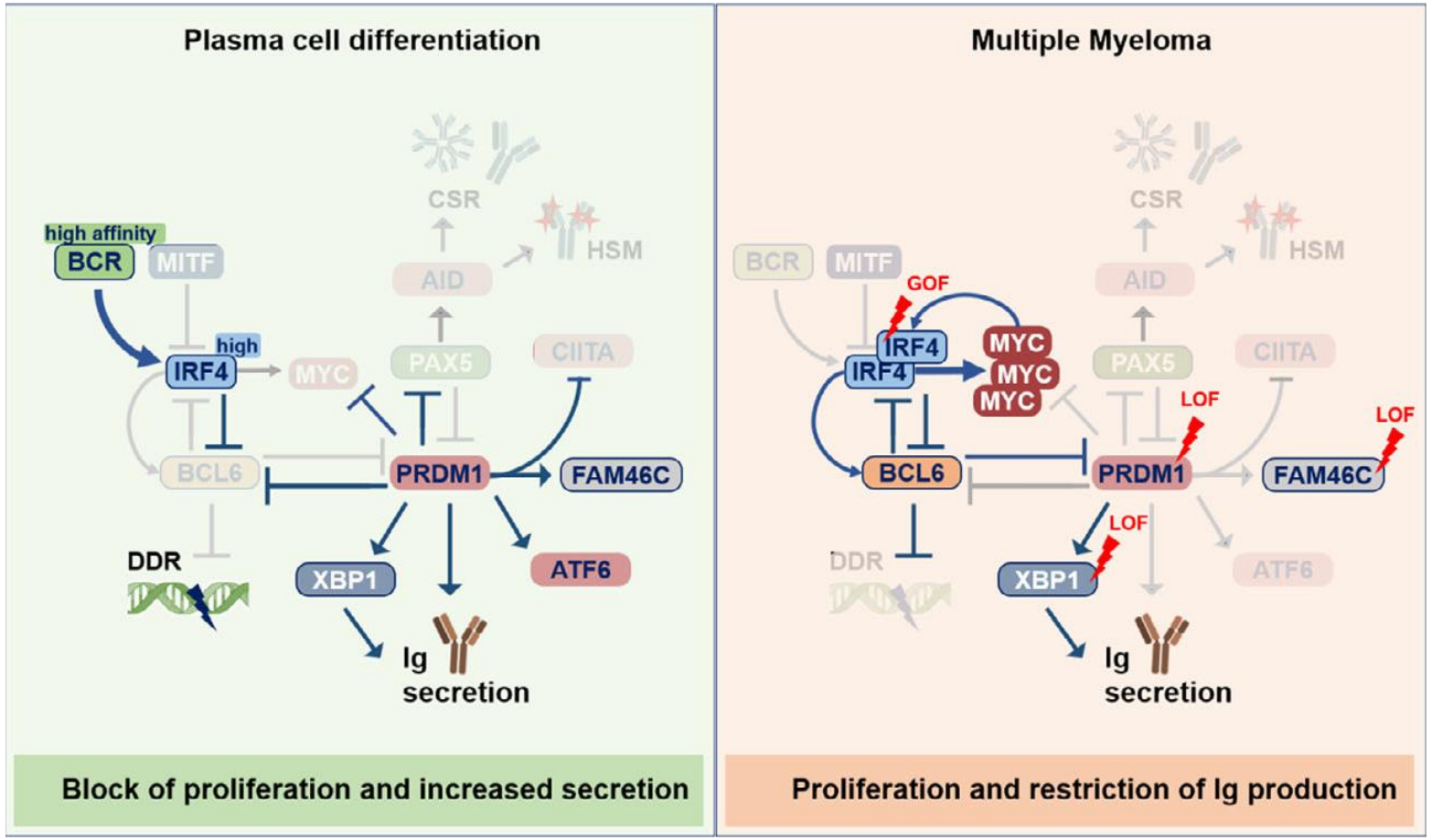
CD138



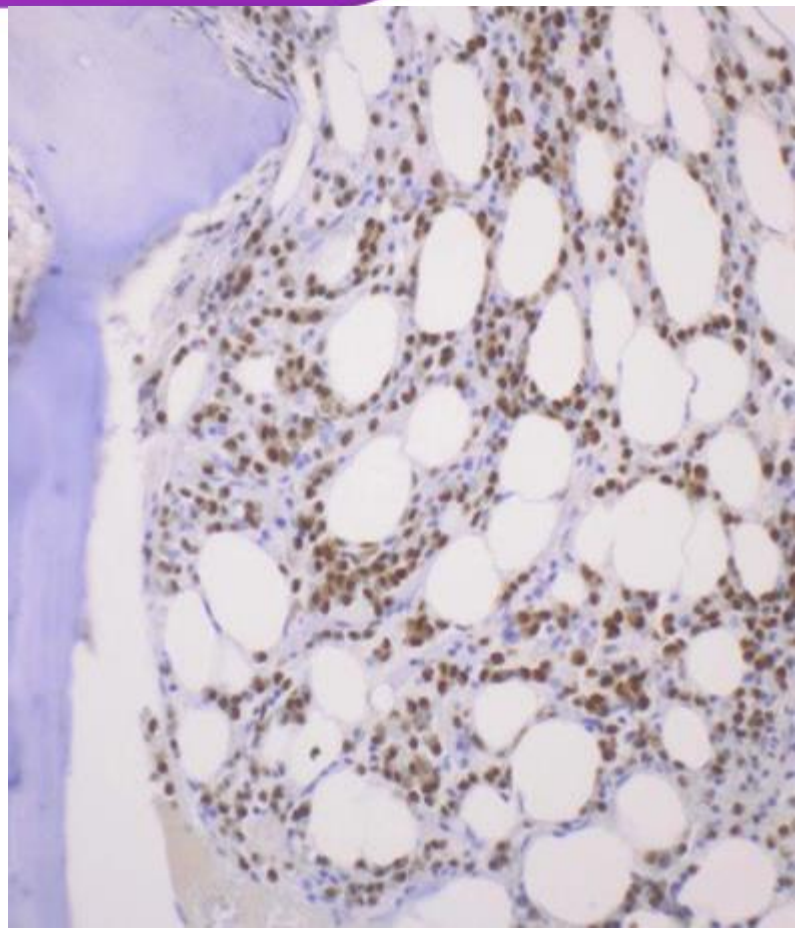
Sometimes variable intensity
Expressed by epithelial cells

MUM1/IRF4

Master regulator of PC development and key survival factor



Perrini et al, FEBS J 2021



Very reliable PC marker
Expression in terminal diff. B cell neoplasms and ALCL

Gain of function mutations in *IRF4* and loss of function mutations in XBP1 and PRDM1 shift from secretion to proliferation

Immunoglobulin light and heavy chains

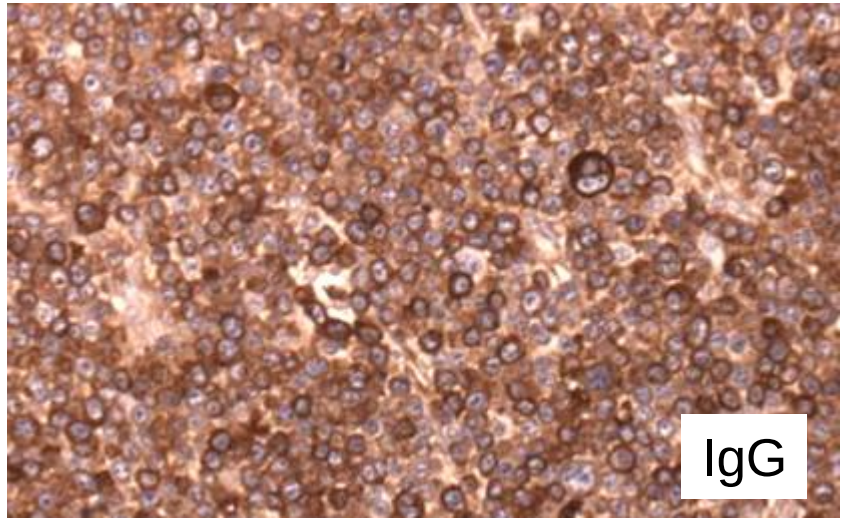
Monoclonal light chain expression by virtually all neoplastic plasma cells

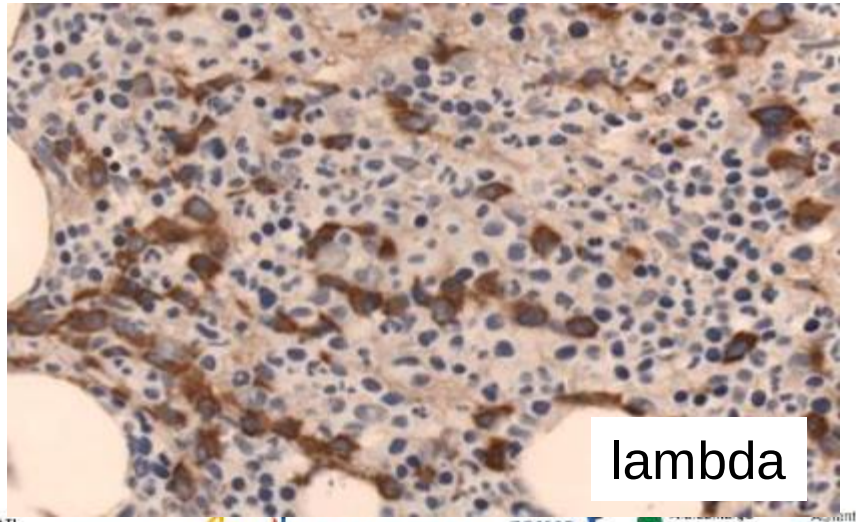
- Expression levels often much lower than in normal PC, interpretation may be difficult – CISH as alternative

IgG 50-60%, 15% IgA, 15-20% light chain only

Rare MM express IgD, IgM or IgE

- Biclonality (including both light chains) common in MGUS (5%) §, but rare in established MM (0.91%)*
- Likely suppression of second clone similar to immunoparesis (reduction in polyclonal IG)



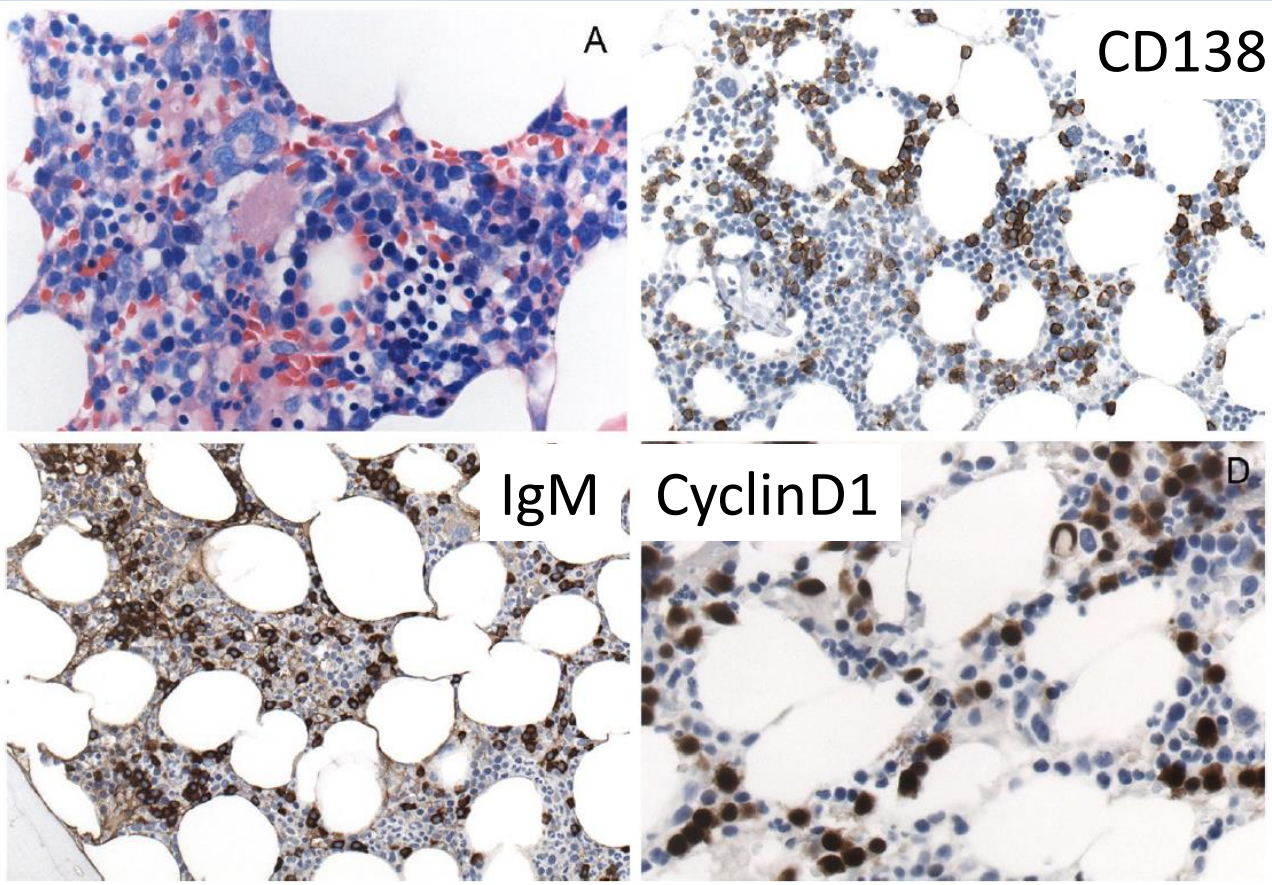


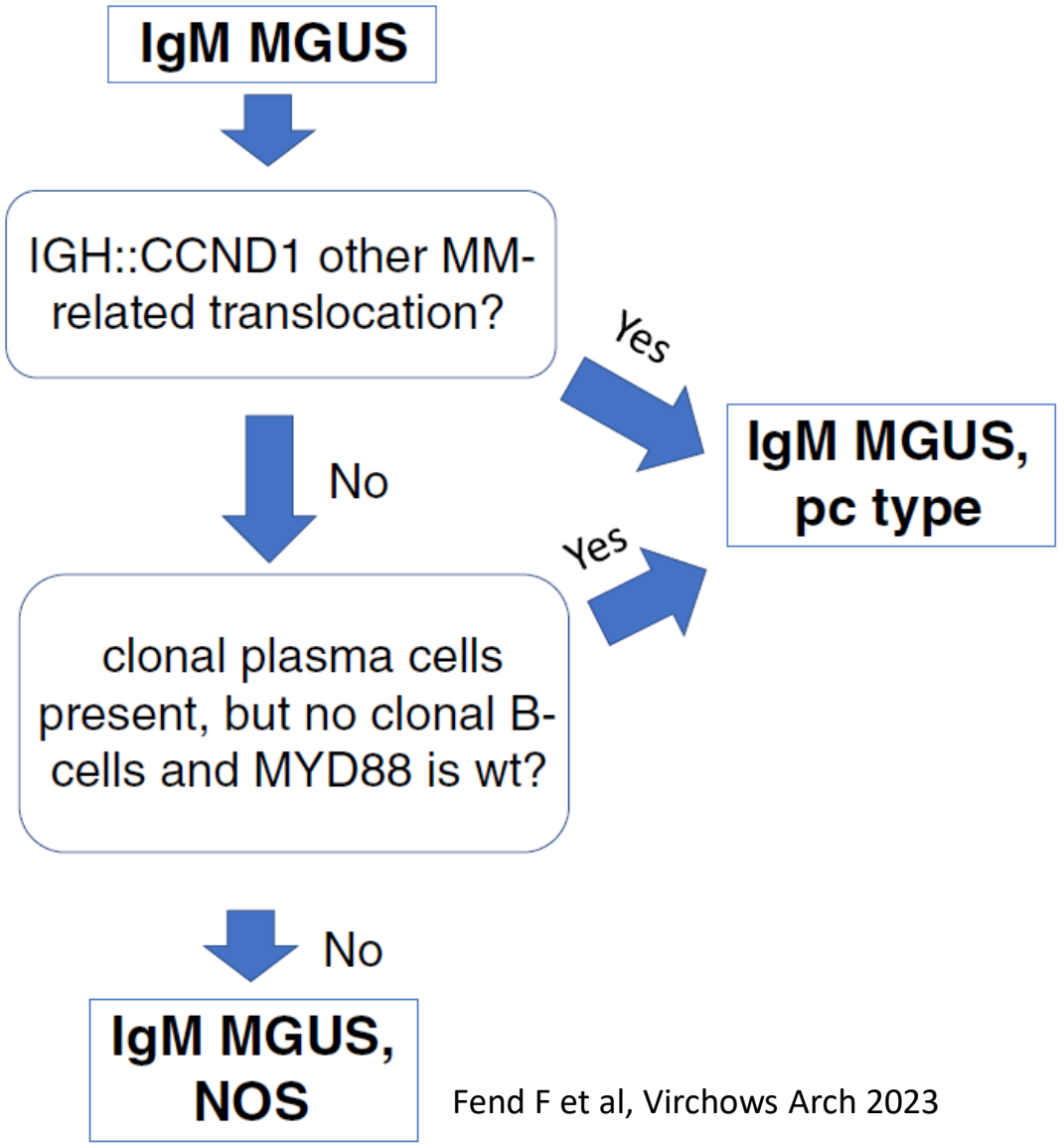
- § Landgren et al 2014; *Campbell et al, BJC 2017

IGM MGUS AND IGM MM

Higher frequency of t(11;14)

Separation from LPL by lack of MYD88^{mut,} presence of clonal B cells and aberrant immunophenotype of PC





Fend F et al, Virchows Arch 2023

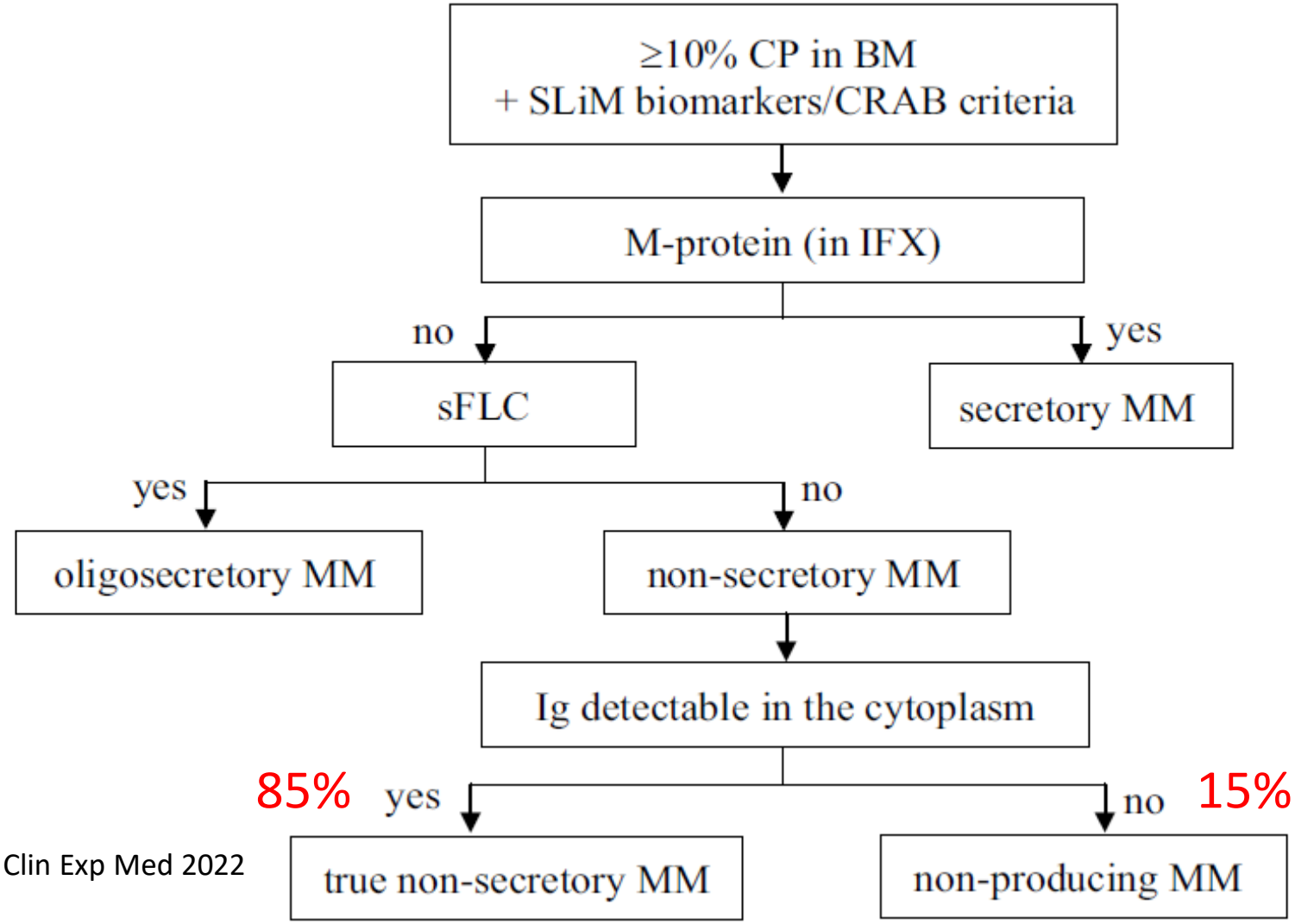
NON-SECRETORY MM

True non-secretory MM rare (<1-2%)

Frequency decreased due to increased sensitivity of diagnostic tests (FLC)

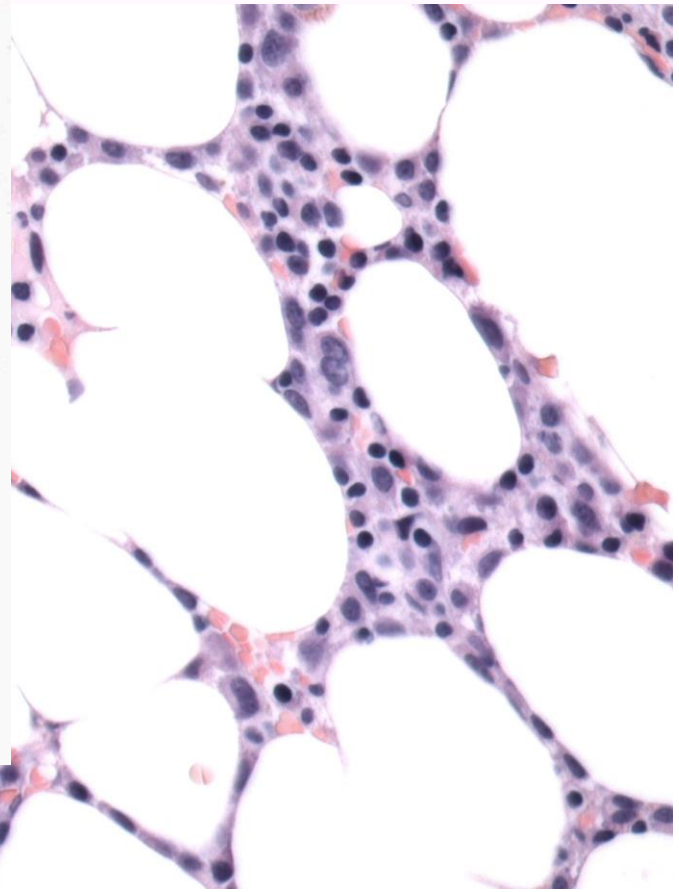
Diagnosis of non-secretory MM requires determination of serum free light chain ratio

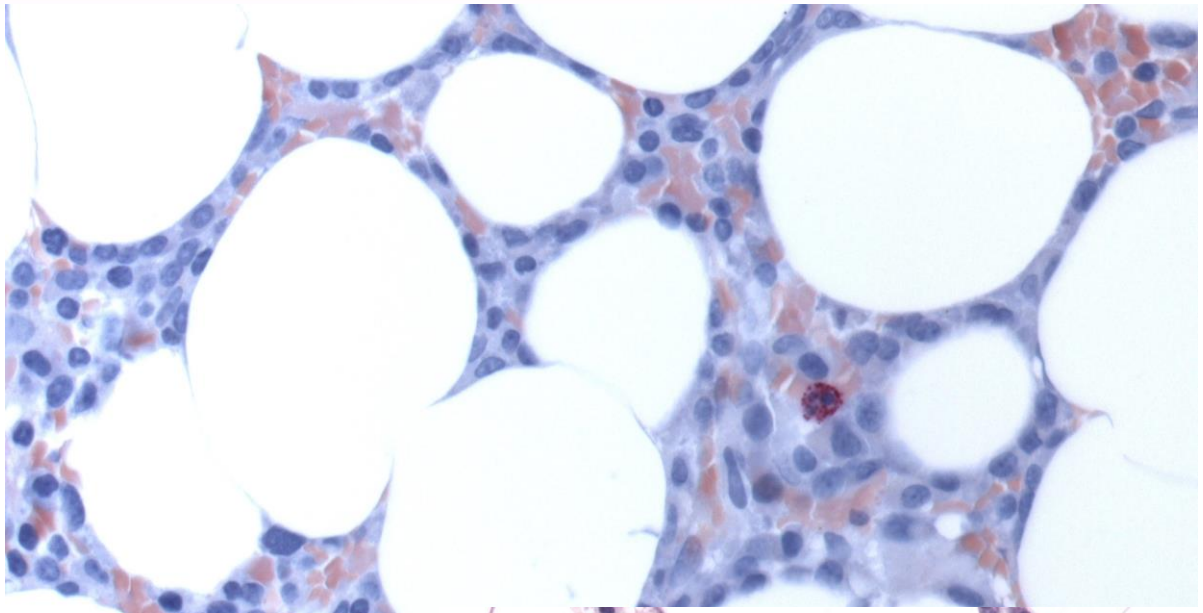
Lower frequency of renal complications and paraneoplasia

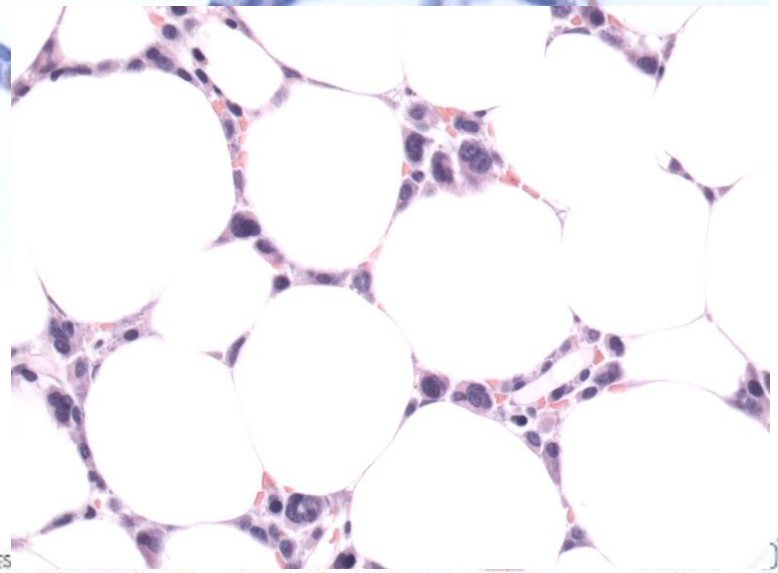


Charlinski et al, Adv Clin Exp Med 2022

THE GOOD, THE BAD AND THE UGLY

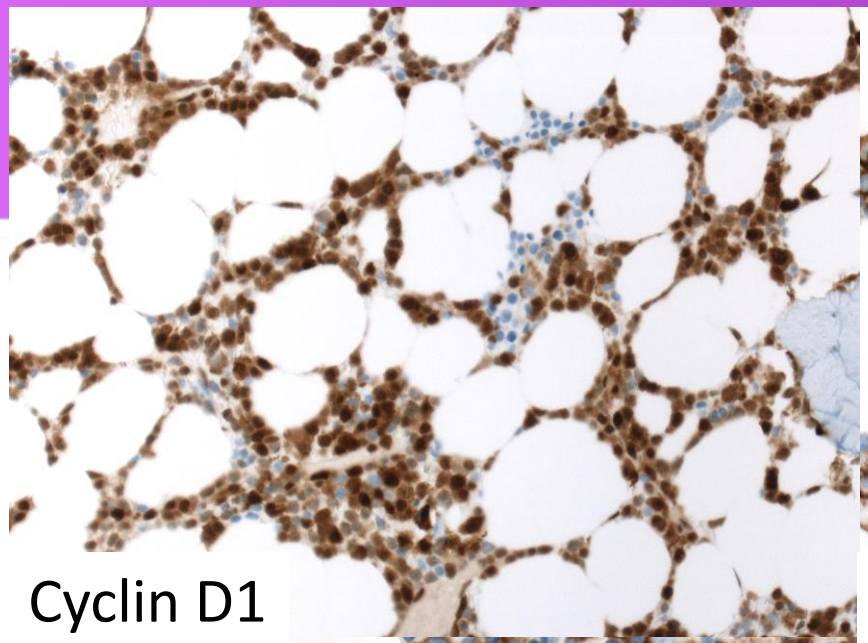




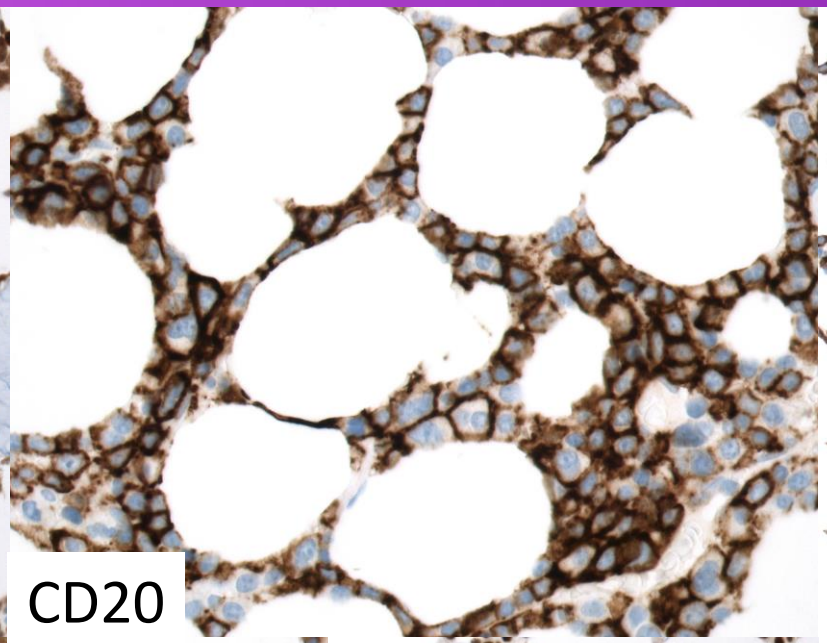


- 54-year-old male
- Pancytopenia and 2% blasts in PB
- MDS? AML?

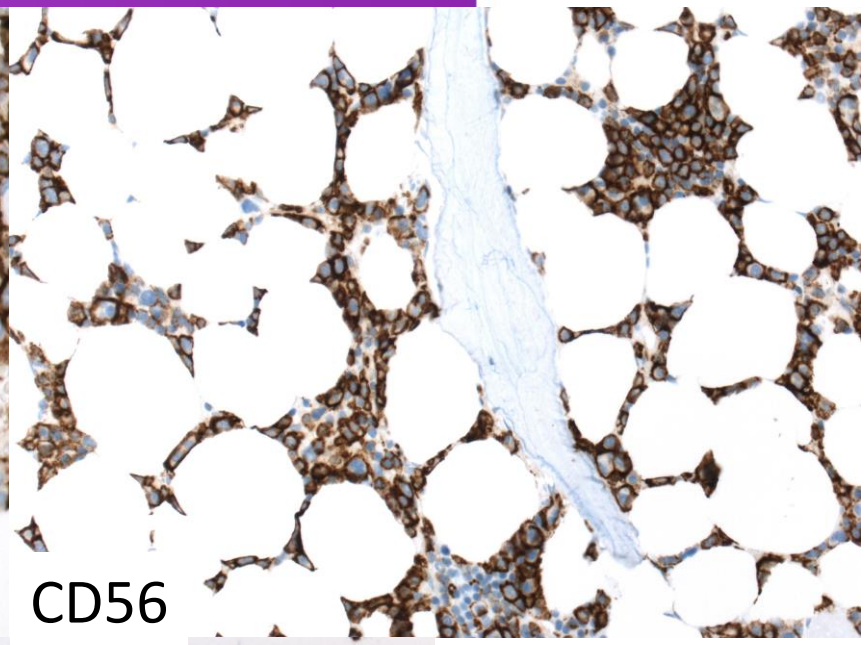
ASDCL



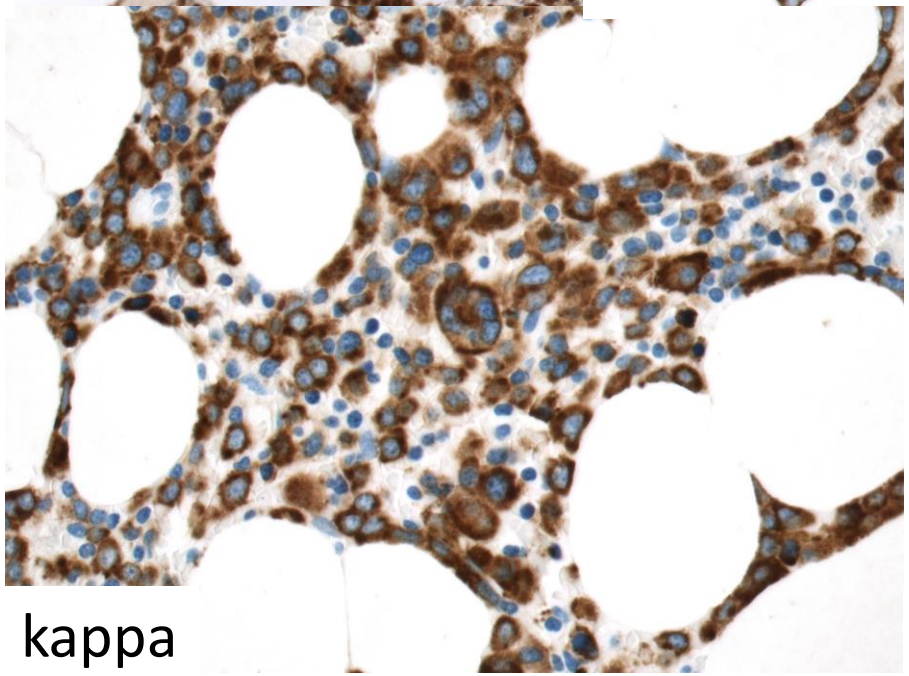
Cyclin D1



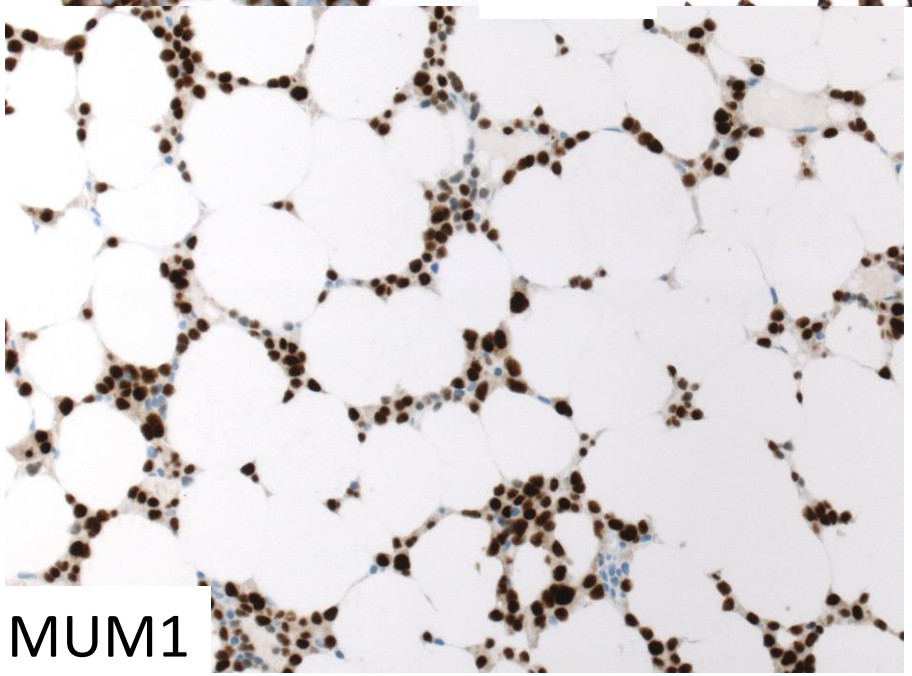
CD20



CD56



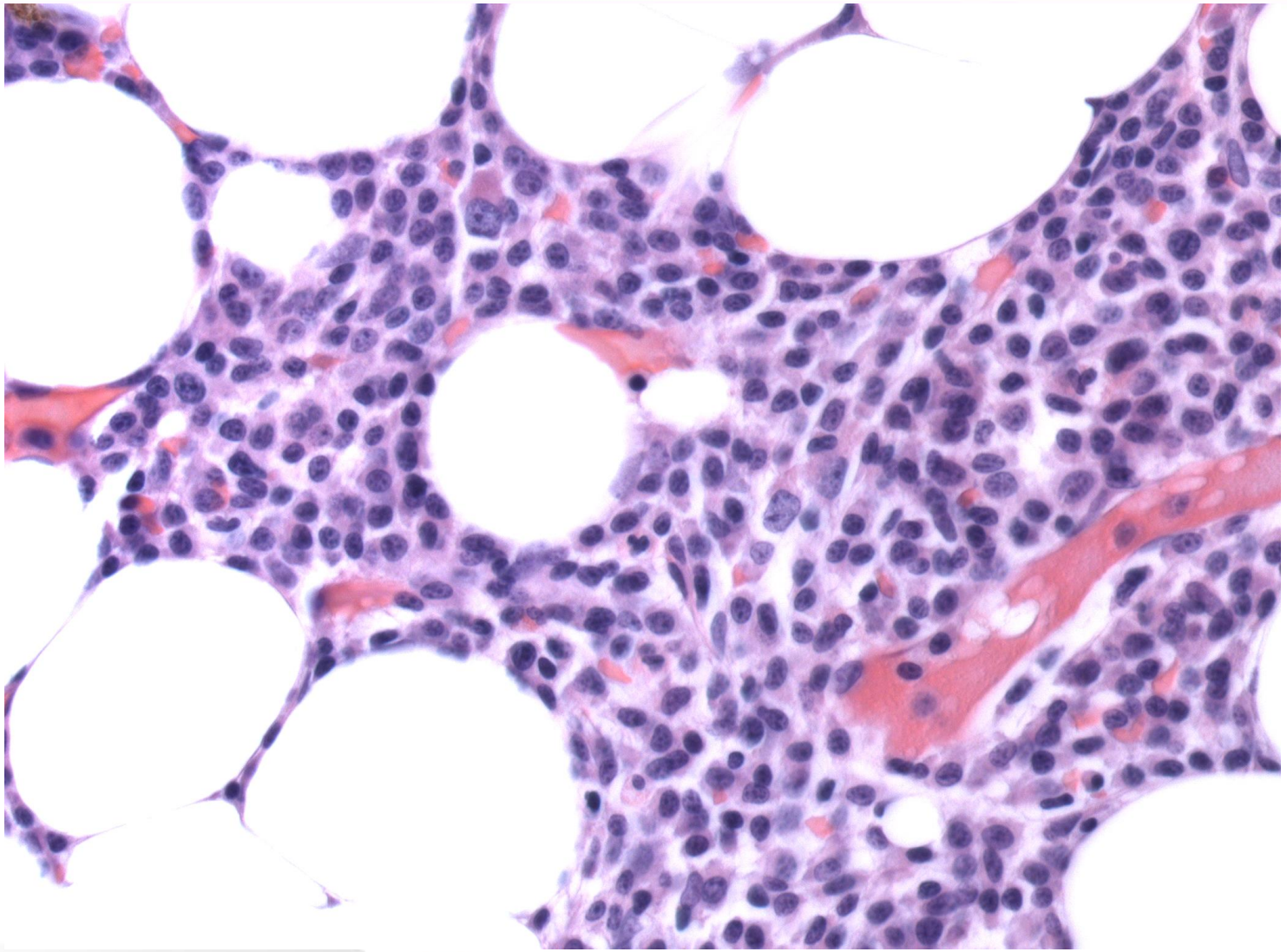
kappa

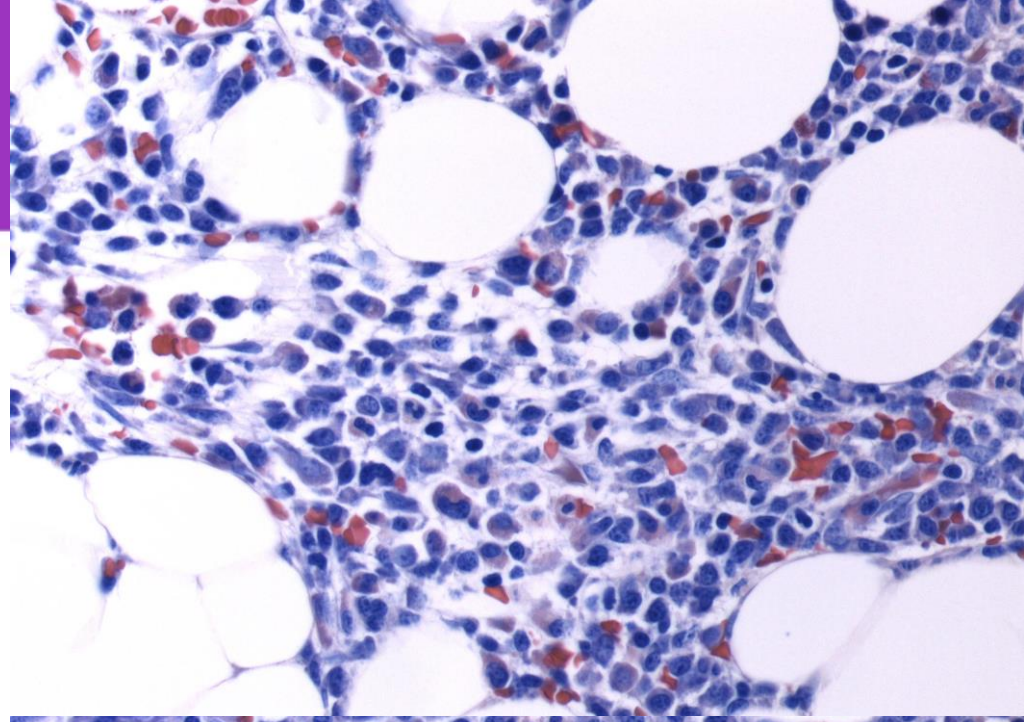


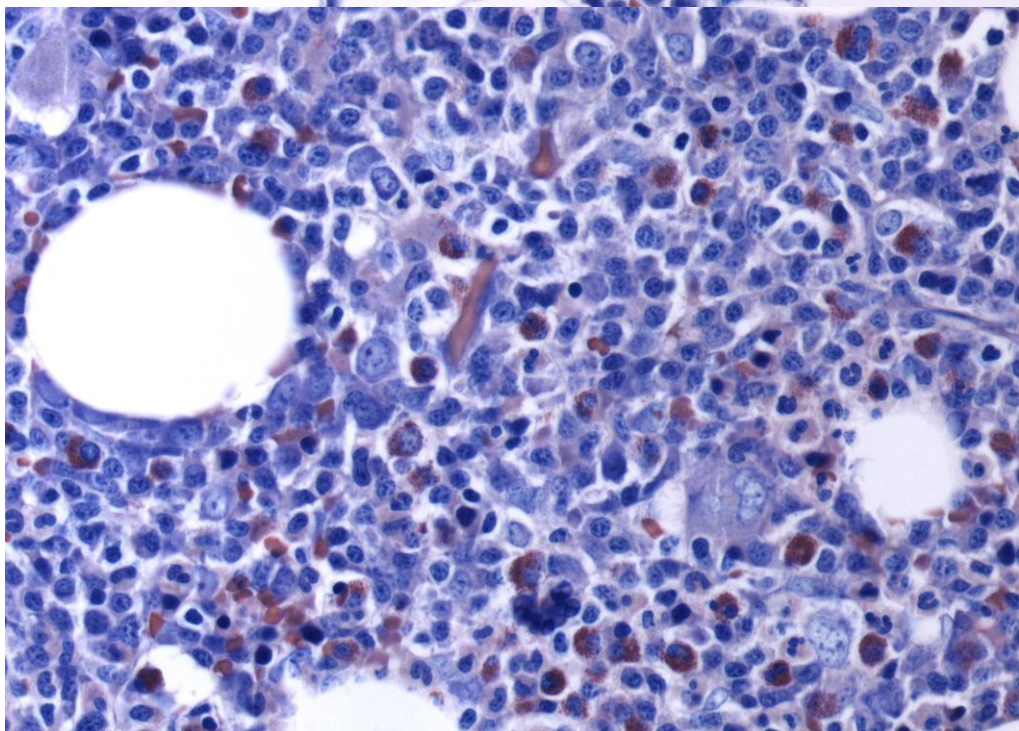
MUM1

MM with CD20 expression and t(11;14), Aplasia of granulopoiesis

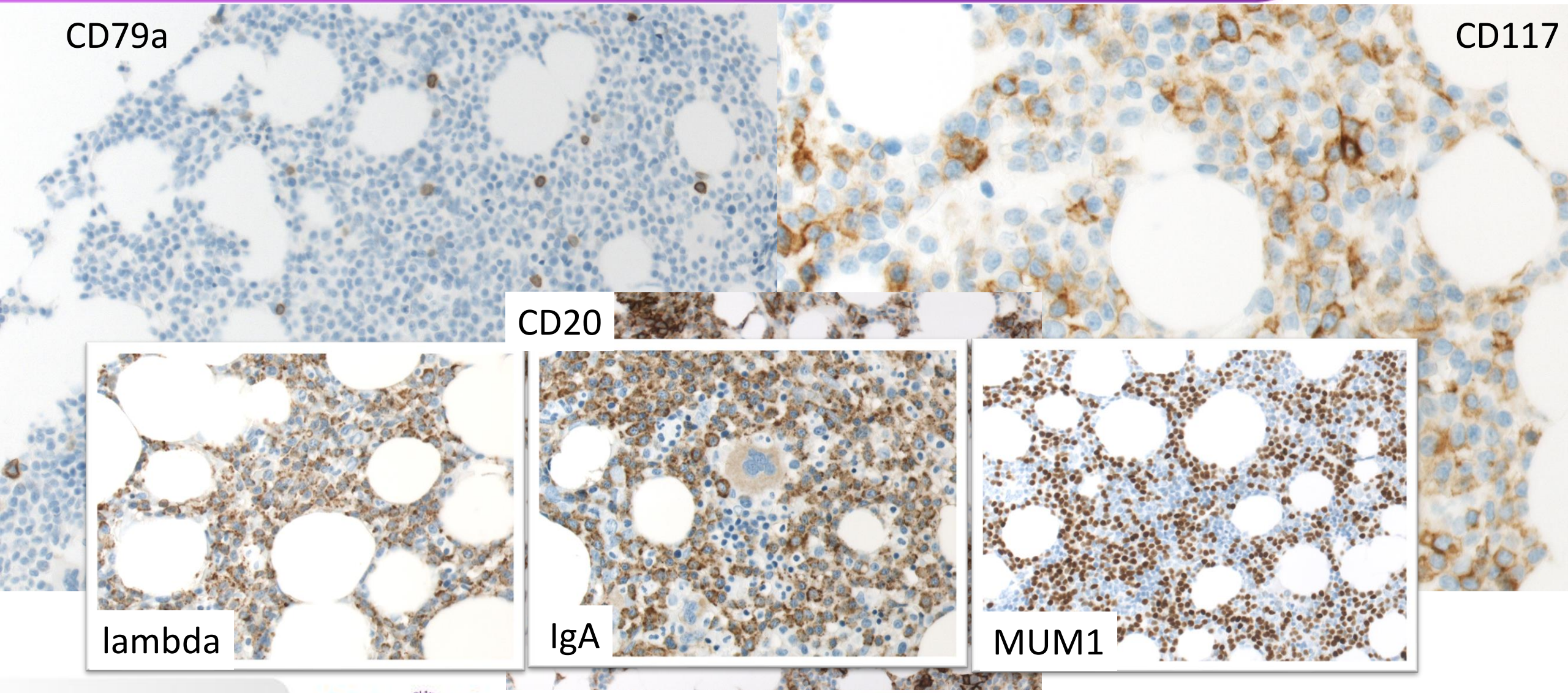
69-YEAR-OLD FEMALE, SPLENOMEGALY, THROMBOPENIA – HCL?







IGA PARAPROTEIN, DETECTION OF T(14;16) AND 13Q-

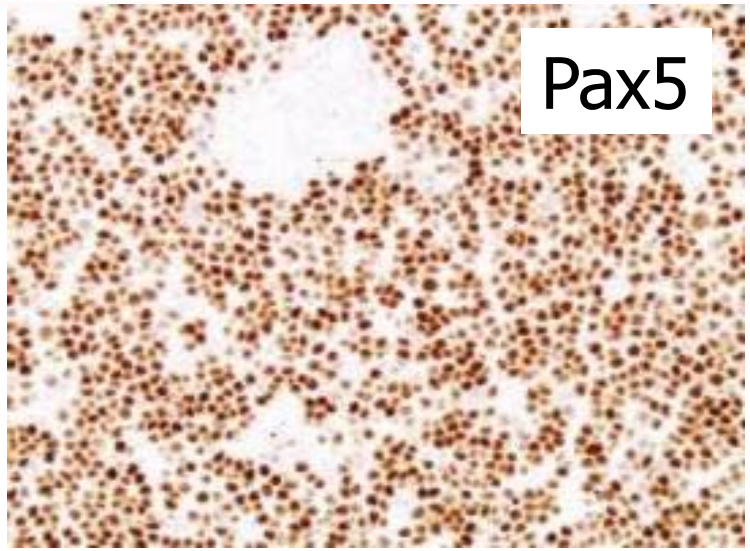


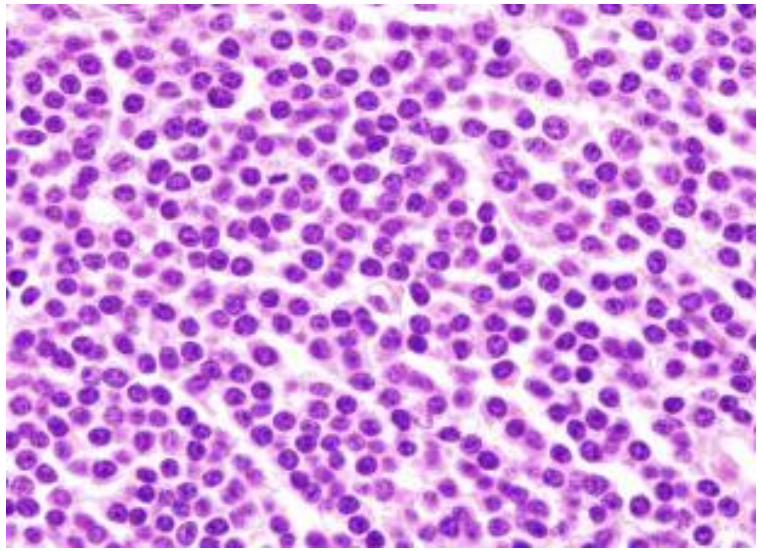
MM IMMUNOPHENOTYPE

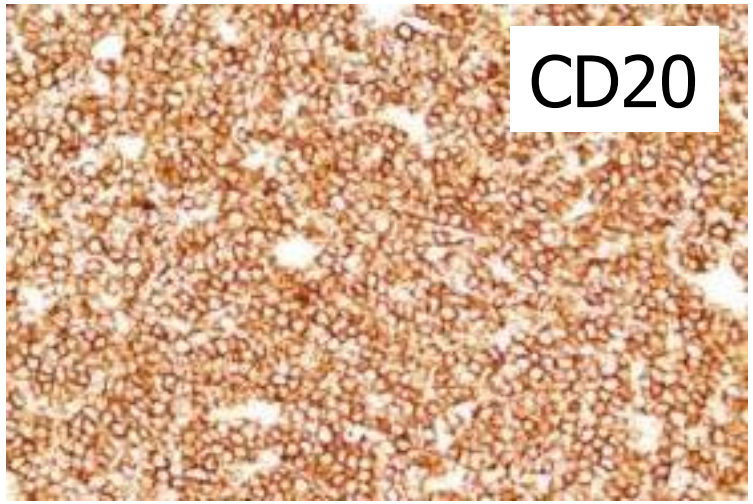
Normal PC
Negative: PAX-5, CD22, CD20
Positive: CD19, CD138, CD38, CD79a, cIG, CD45+/-, EMA

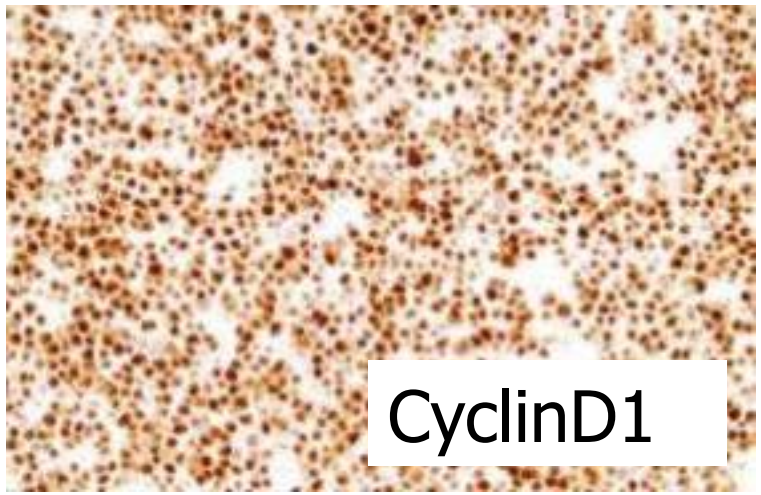
Malignant PC lack CD19
CD56 (75%), CD117 (3-30%), CD20 (20-30%), CyclinD1 (50%, 20% strong), PAX5 (rare), CD10, MYC

Partial preservation of B-cell program especially in t(11;14)+ PCM – sometimes in primary plasma cell leukemia



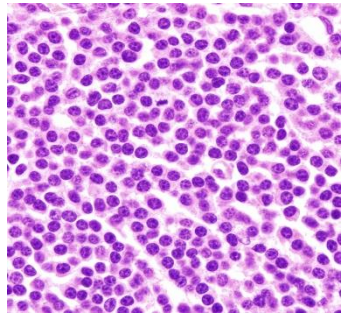






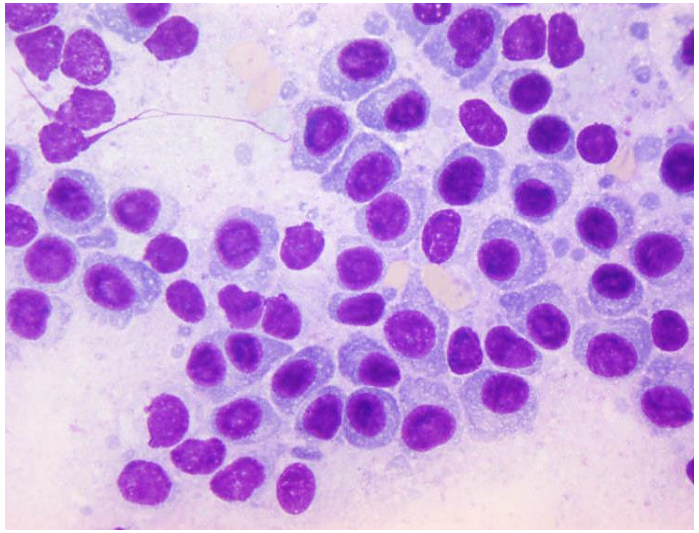
Lorsbach et al, AJCP 2011

BORDERLANDS OF MM



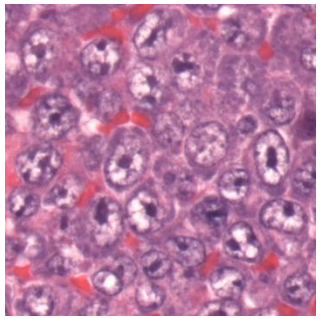
Lymphoplasma-
cytic morphology
B-cell markers
IgM MM

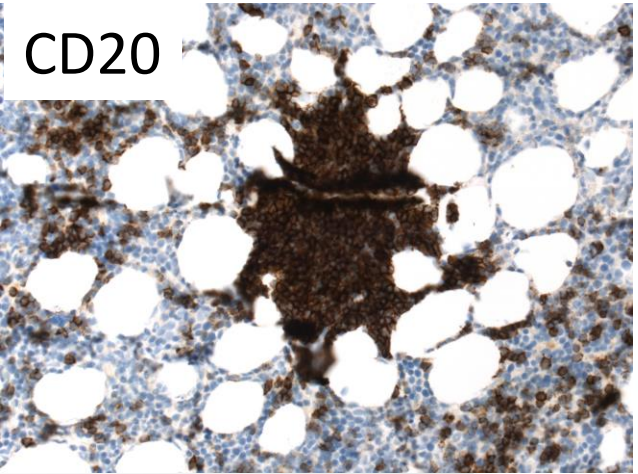
Lymphoplasmacytic
lymphoma (non IgM)
Mantle cell lymphoma
Co-occurring B-NHL

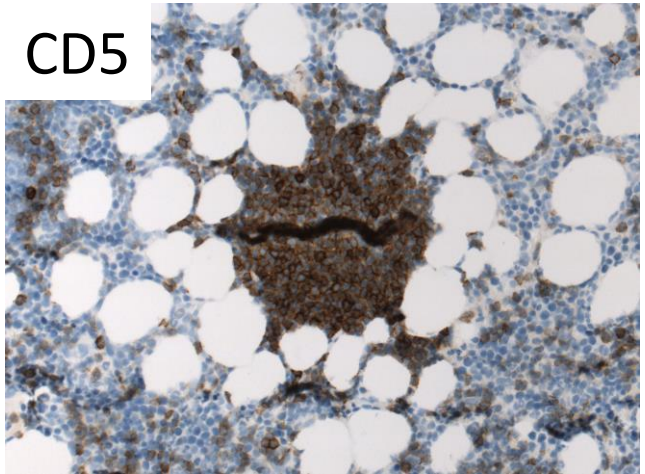


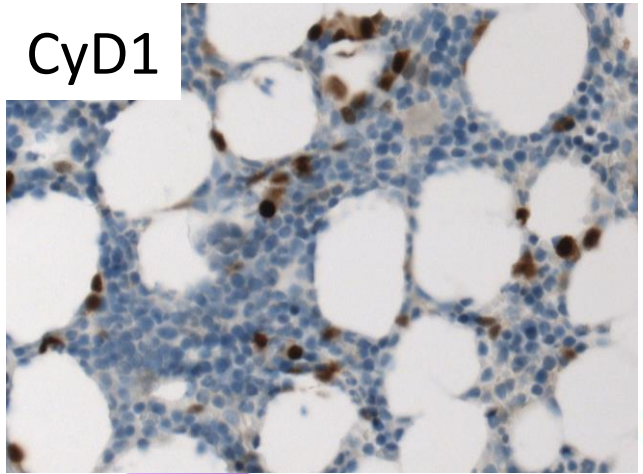
(Plasma-) blastic morphology
High proliferation
Loss of PC markers
EBV positivity

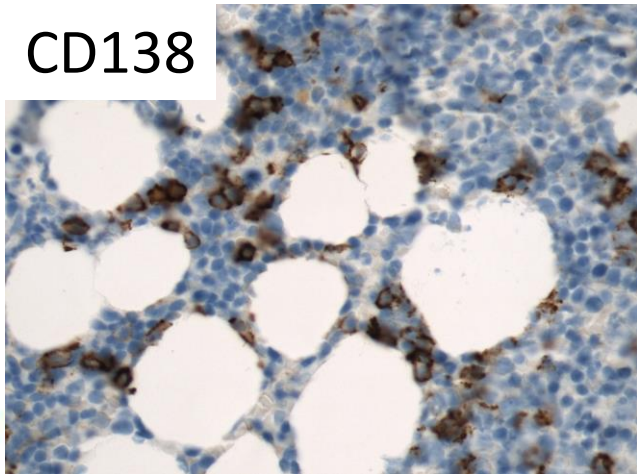
Plasmablastic lymphoma
Other high grade B-NHL
Non-lymphoid neoplasms





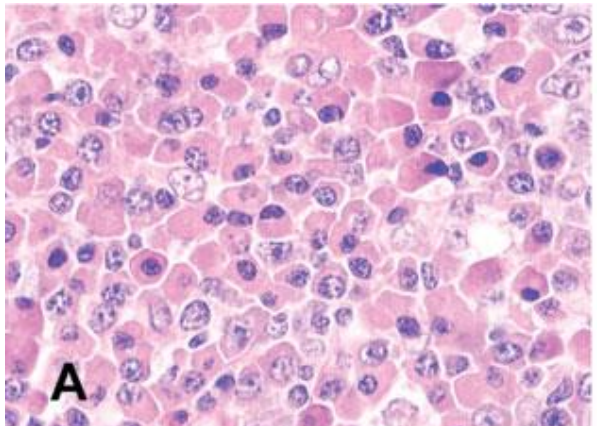




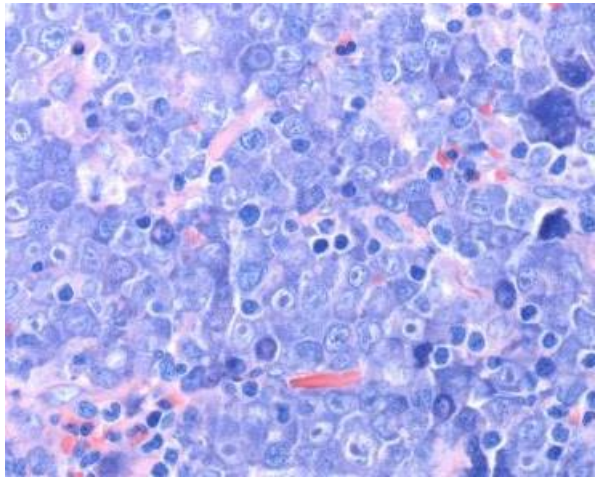


BORDERLANDS OF MM – EXTRAMEDULLARY PROLIFERATIONS OF PLASMACYTIC/PLASMABLASTIC MORPHOLOGY

	Plasmablastic MM	Plasmablastic lymphoma	Extraosseous plasmacytoma
Location	Any site, occ. leukemic	Extranodal, oral cavity	80% head & neck
Morphology	Plasmablastic/plasmacytic	Plasmablastic large cell /immunobl.	Usually mature
M-protein	Most cases	Rare	30%, low level
Osteolytic lesions	Common	Rare	Occasionally (skull)
Bone marrow	Yes	May occur	No or at MGUS level
CD56	CD56+	-/+	-/(+)
Cyclin D1 / t(11;14)	15-20%	Neg.	Neg.
MYC rearrangement	common	common	rare
EBV	Rare	60-70%	rare
Genetics	MM-type tx. and trisomies, RAS, P53	MYC translocations, JAK/STAT3 pathway, TP53	Trisomies and IGH-translocations, no t(11;14)



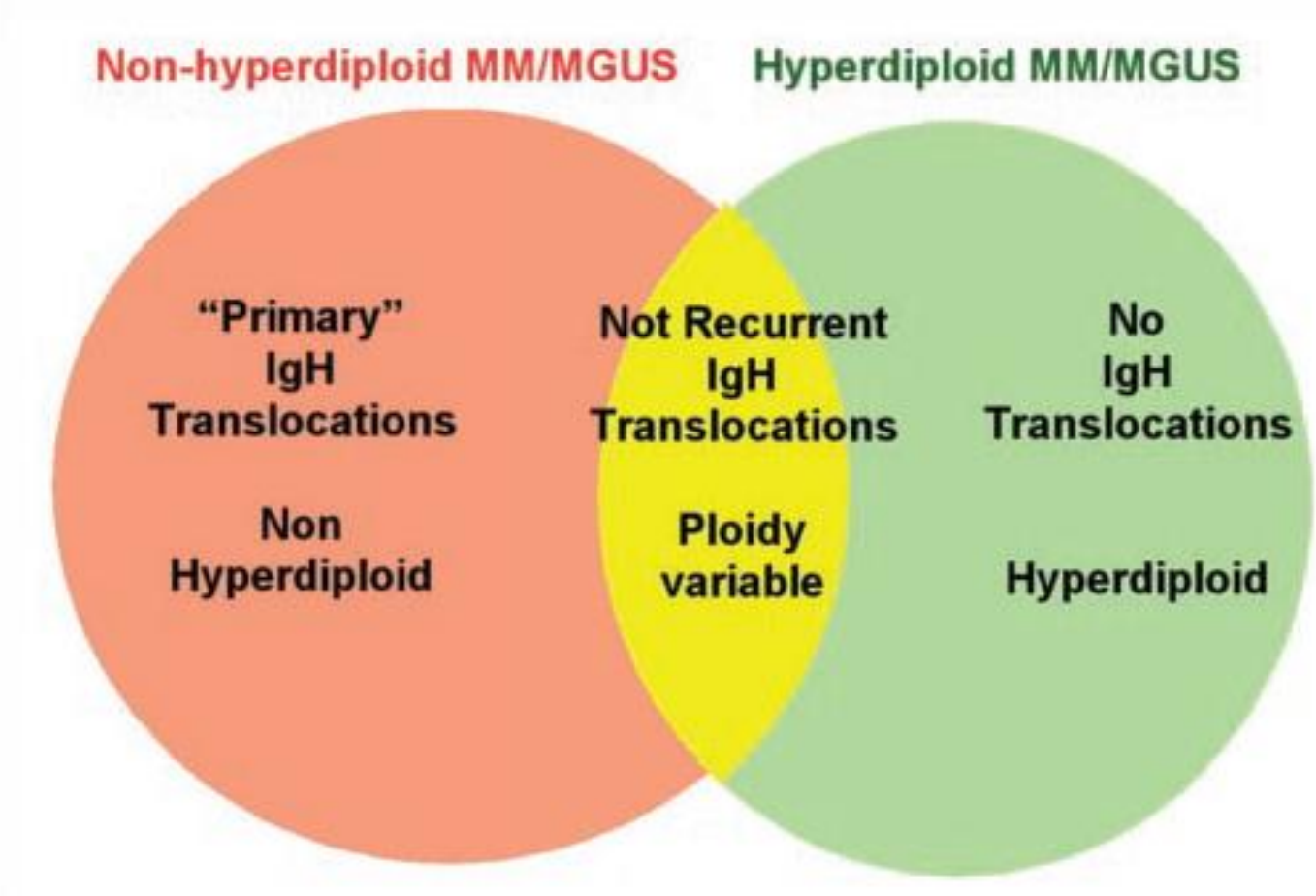
Primary extraosseous plasmacytoma



Plasmablastic lymphoma

GENETICS OF MULTIPLE MYELOMA

- MM is a genetically heterogeneous disease
  - 40-50 % show recurrent translocations
  - 45% show trisomies of uneven chromosomes (3,5,7,9,11,15,19,21)
- These primary alterations are already present in MGUS

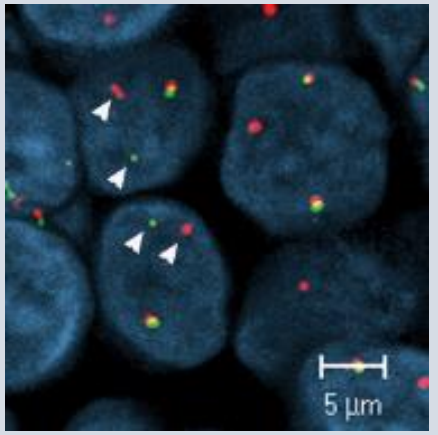


Fonseca et al, CCR 2004

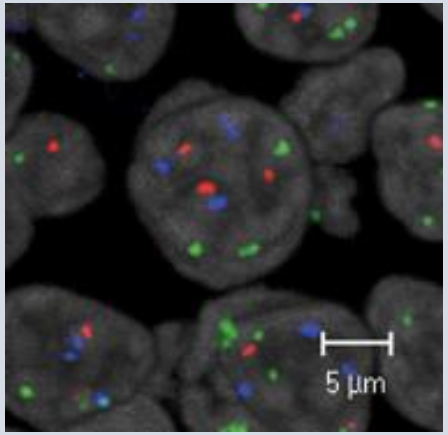
IMWG cytogenetic classification of MM

Hyperdiploid	45%
Non-hyperdiploid	40%
Cyclin D translocations	**18%**
t(11;14) cyclin D1	16%
t(6;14) cyclin D3	2%
t(12;14) cyclin D3	<1%
NSD2/MMSET translocation t(4;14)	**14%**
MAF translocations	**8%**
t(14;16) MAF	**5%***
t(14;20) MAF-B	**2%***
t(8;14) MAF-A	<1%
Unclassified (other)	9%

Fonseca, Leukemia 2009



Break 14q32



Trisomy 9 and 15

Minimal Panel
t(4;14) *FGFR3/NSD2*
t(14;16) und t(14;20) *MAF*
Del 17p *TP53*

Comprehensive Panel
t(11;14) *CCND1*/cyclin D1
Del 13
Ploidy
Chromosome 1 alterations

VOLUME 33 · NUMBER 26 · SEPTEMBER 10 2015

JOURNAL OF CLINICAL ONCOLOGY

Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group

Integration of high risk cytogenetics provides improved stratification in MM and SMM

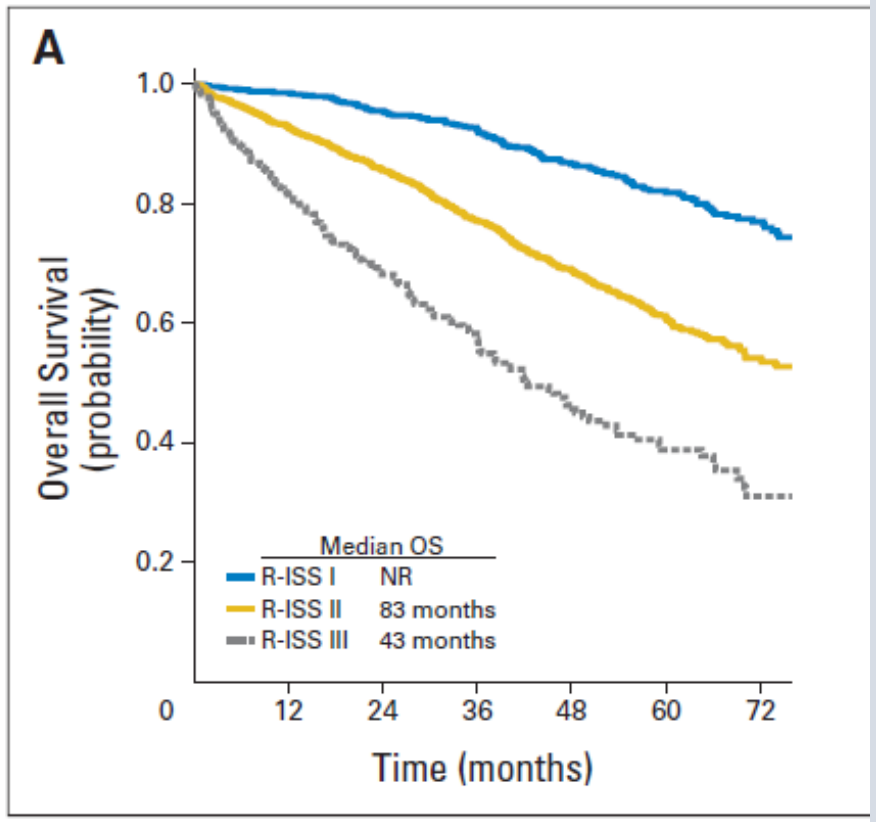


Table 1. Standard Risk Factors for MM and the R-ISS

Prognostic Factor	Criteria
ISS stage	
I	Serum β_2-microglobulin < 3.5 mg/L, serum albumin ≥ 3.5 g/dL
II	Not ISS stage I or III
III	Serum β_2-microglobulin ≥ 5.5 mg/L
CA by iFISH	
High risk	Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16)
Standard risk	No high-risk CA
LDH	
Normal	Serum LDH < the upper limit of normal
High	Serum LDH > the upper limit of normal
A new model for risk stratification for MM	
R-ISS stage	
I	ISS stage I and standard-risk CA by iFISH and normal LDH
II	Not R-ISS stage I or III
III	ISS stage III and either high-risk CA by iFISH or high LDH

High risk:

del 17p (TP53)

t(4;14)

t(14;16)

PFS:

I: 55 mo

II: 36 mo

III: 24 mo

Palumbo et al JCO 2015, Mateos et al, BCJ 2021

Mutational Spectrum, Copy Number Changes, and Outcome: Results of a Sequencing Study of Patients With Newly Diagnosed Myeloma

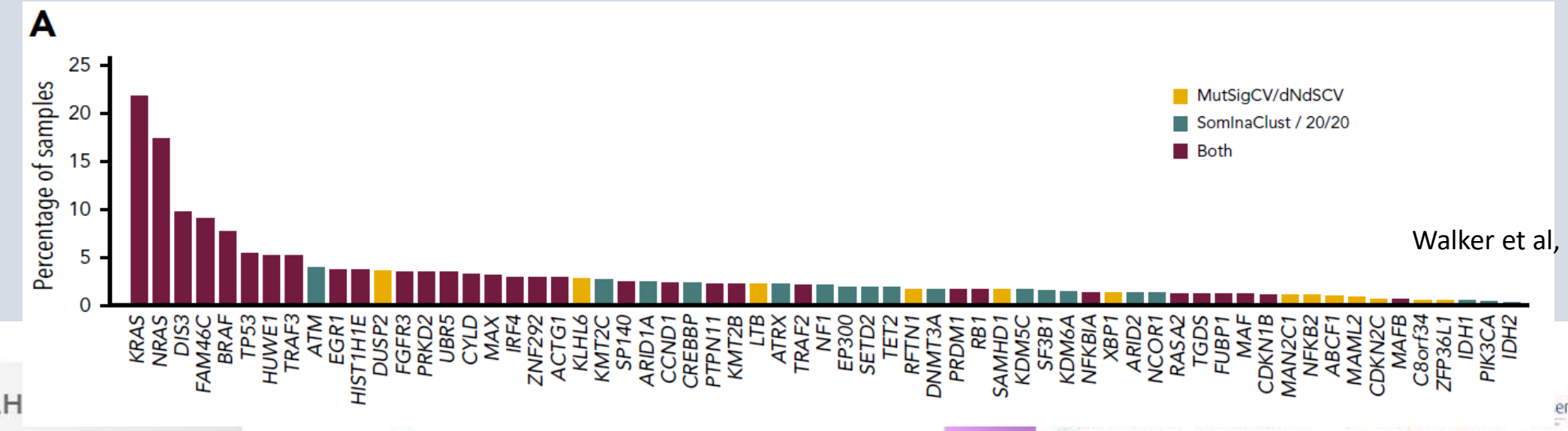
Walker et al, JCO 2017

WES in 463 patients with newly diagnosed MM showed 15 significantly mutated genes

- RAS pathway (43%)
- NFkB pathway (17%)
- G0/G1 cell cycle transition and epigenetic regulators

} Prognostically neutral

Mutations in *CCND1, TP53, ATM* associated with poor, *IRF4* and *EGR1* good prognosis



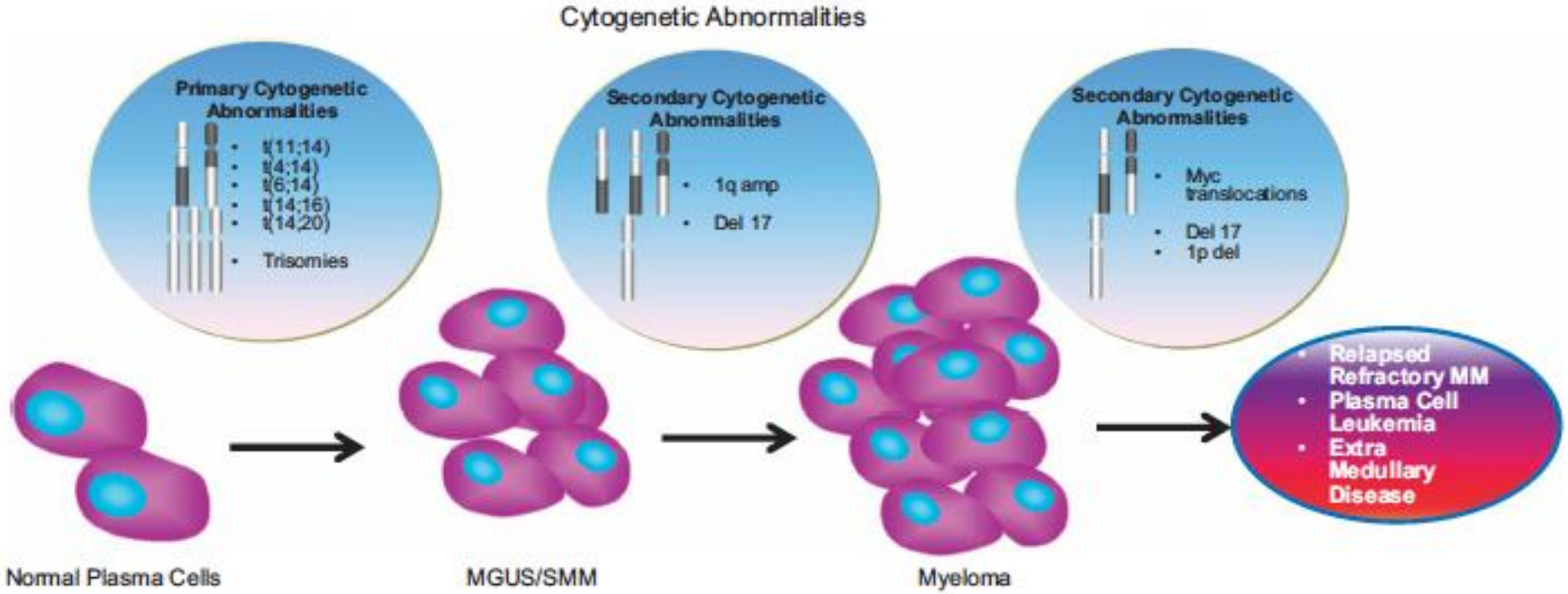
Walker et al, Blood 2018

GENETIC EVOLUTION OF MULTIPLE MYELOMA

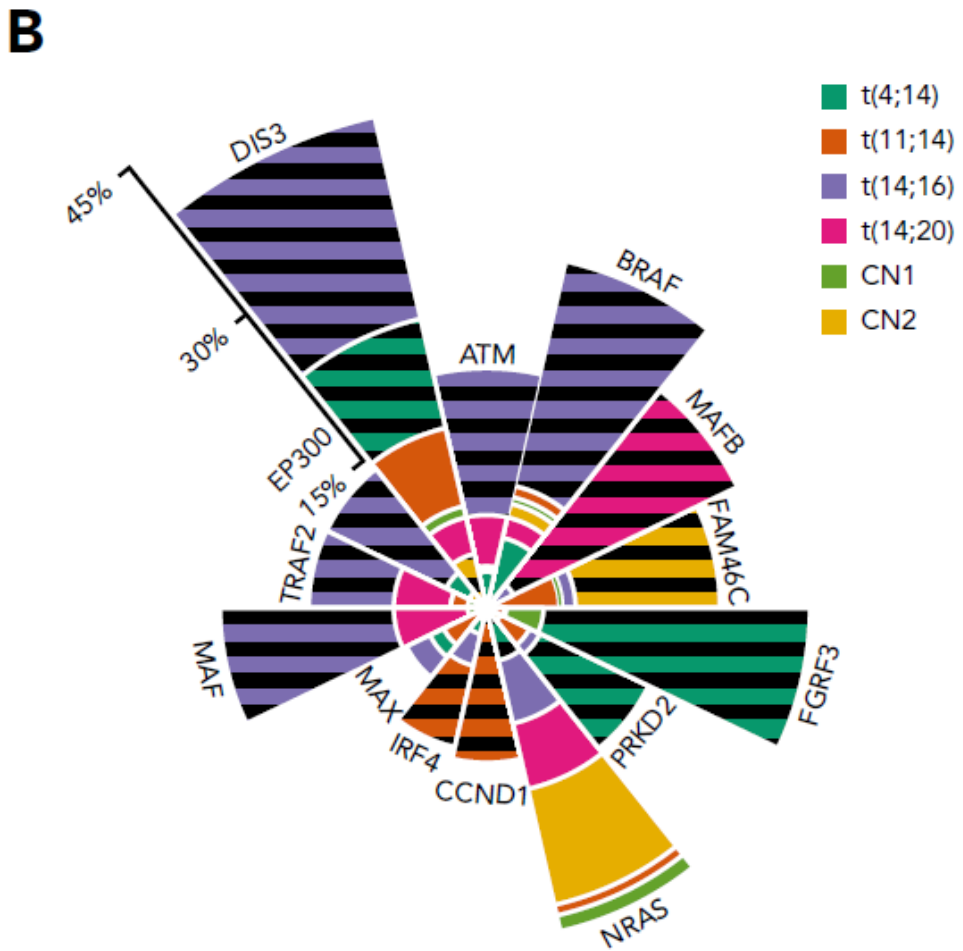
Initial Alterations establish the malignant clone (non-overlapping)

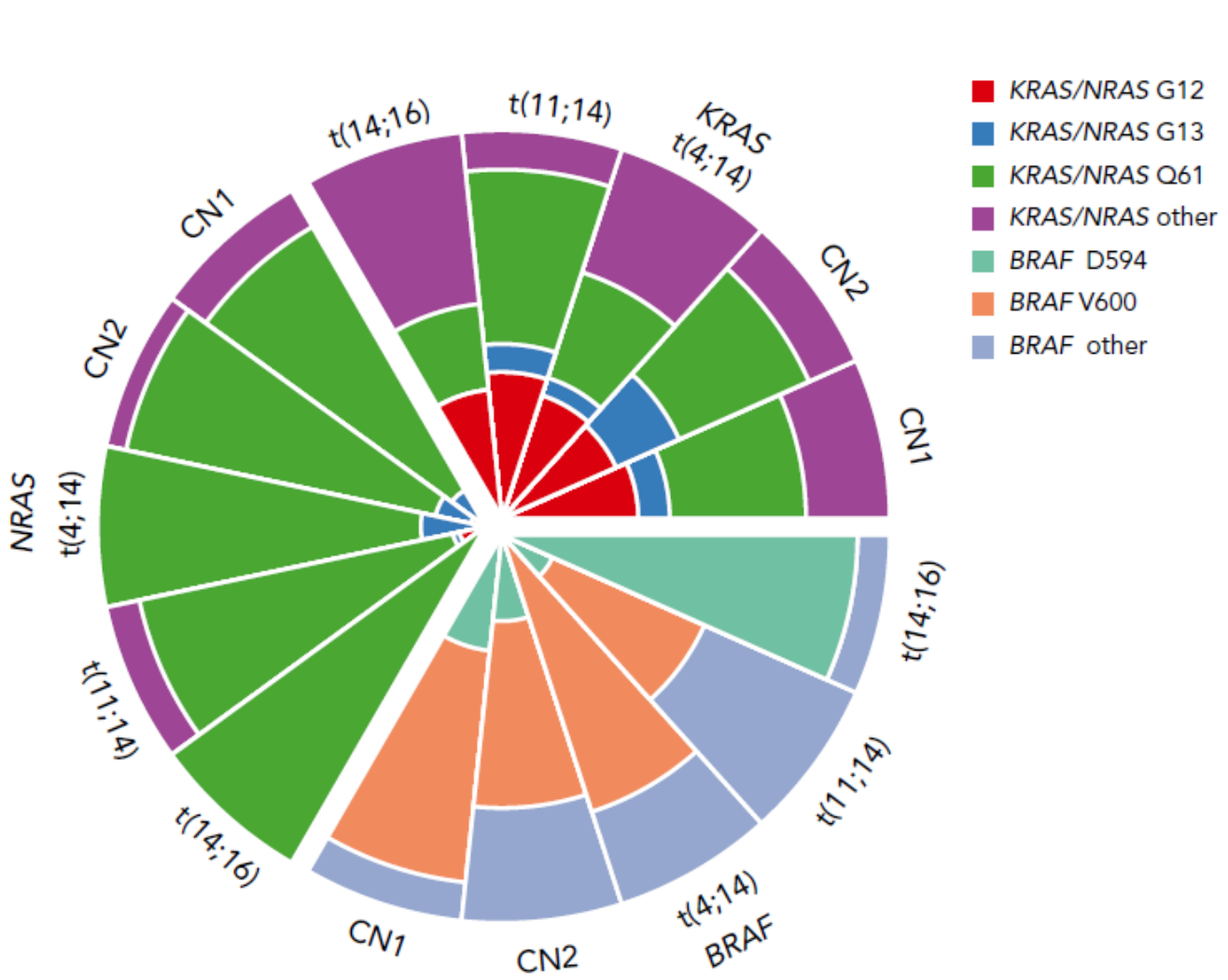
Rajan & Rajkumar, Boood Cancer J 2015

Secondary Alteration



STRONG ASSOCIATIONS OF PRIMARY AND SECONDARY GENETIC ALTERATIONS INDICATE ONCOGENIC DEPENDENCIES

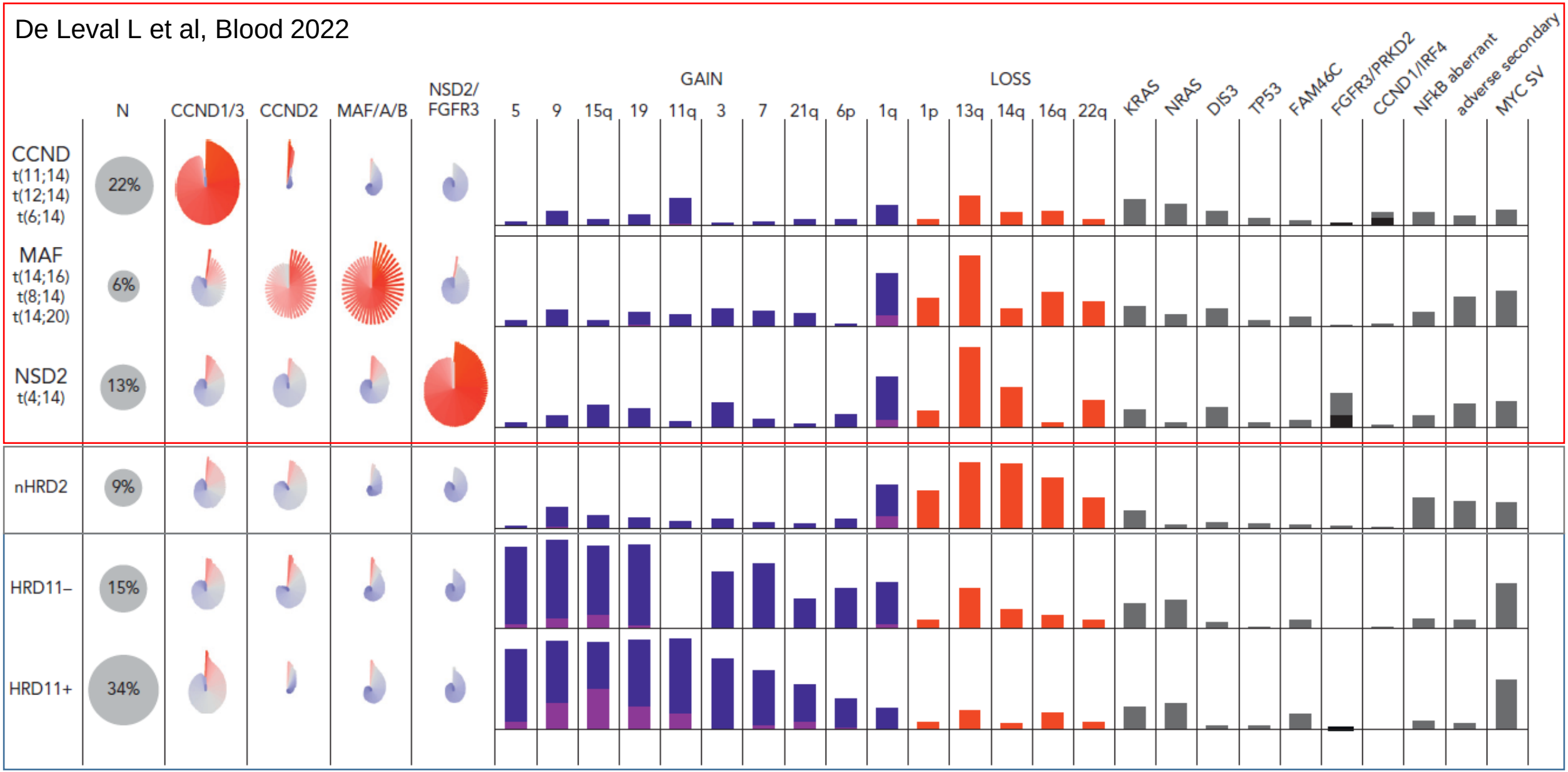




Walker et al, Blood 2018

MOLECULAR CLASSIFICATION OF MM

De Leval L et al, Blood 2022



WORK-UP OF MM GENETICS

FISH (or NGS-) based detection of recurrent translocations required for genetic subtyping according to ICC and relevant for risk stratification

Prognostic impact of cytogenetics modified by therapy regimen

Entity	Genetic alteration: test	Diagnostic use	Clinical impact	Future assays
Multiple myeloma (MM) MM-NOS MM with recurrent genetic abnormality MM with CCND family translocation MM with MAF family translocation MM with *NSD2* translocation MM with hyperdiploidy	t(4;14) *NSD2*::IGH; t(14;16) IGH::*MAF*; t(11;14) *CCND1*::IGH;*,§ gain of odd numbered chromosomes: FISH on bone marrow plasma cells (CD138-positive selected sample strongly recommended)*	Diagnostic of the ICC subtypes of MM	t(11;14) predictive of response to venetoclax[134]	WGS for subtype assignment, risk stratification, and decision making MRD using HTS for decision making
	t(4;14) *NSD2*::IGH; t(14;16) IGH::*MAF*; amp(1q); del(1p), del(17p)*; *TP53* mutations[464] For SMM: t(4;14) *NSD2*::IGH; t(14;16) IGH::*MAF*; 1q gain/amplification; del(13)[145] and *MYC* rearrangement[139]: FISH and HTS	Risk stratification at diagnosis and relapse	The adverse prognosis of high-risk genetics is partially overcome by the addition of a proteasome inhibitor[131] and/or anti-CD38 MoAb[132] to first-line therapy	

De Leval L et al, Blood 2022

CHANGES IN CLASSIFICATION – ICC 2022

IgM MGUS separated into

- Plasma cell type with *MYD88* WT and MM-type cytogenetics (e.g. t(11;14)), precursor to IgM MM
- IgM MGUS NOS

Name change back to multiple myeloma

Formal separation into cytogenetic groups

Emphasis on the presence of minimal BM infiltration in SPB and EMP

Name change to IG light chain amyloidosis

Introduction of localized AL amyloidosis as new category

Immunoglobulin M (IgM) monoclonal gammopathy of undetermined significance (MGUS)

★ IgM MGUS, plasma cell type*

IgM MGUS, not otherwise specified (NOS)*

Plasma cell neoplasms

Non-IgM MGUS

★ Multiple myeloma (plasma cell myeloma)*

Multiple myeloma, NOS

Multiple myeloma with recurrent genetic abnormality

Multiple myeloma with *CCND* family translocation

Multiple myeloma with *MAF* family translocation

Multiple myeloma with *NSD2* translocation

Multiple myeloma with hyperdiploidy

Solitary plasmacytoma of bone

Extraosseous plasmacytoma

Monoclonal Ig deposition diseases

★ Ig light chain amyloidosis (AL)*

★ Localized AL amyloidosis*

Light chain and heavy chain deposition disease

WHO CLASSIFICATION 5TH EDITION (PRE-VERSION)

Plasma cell neoplasms and other diseases with paraproteins	
Monoclonal gammopathies	
Cold agglutinin disease	*Not previously included*
IgM monoclonal gammopathy of undetermined significance	(Same)
Non-IgM monoclonal gammopathy of undetermined significance	(Same)
Monoclonal gammopathy of renal significance	*Not previously included*
Diseases with monoclonal immunoglobulin deposition	
Immunoglobulin-related (AL) amyloidosis	Primary amyloidosis
Monoclonal immunoglobulin deposition disease	Light chain and heavy chain deposition disease
Heavy chain diseases	
Mu heavy chain disease	(Same)
Gamma heavy chain disease	(Same)
Alpha heavy chain disease	(Same)
Plasma cell neoplasms	
Plasmacytoma	(Same)
Plasma cell myeloma	(Same)
Plasma cell neoplasms with associated paraneoplastic syndrome -POEMS syndrome -TEMPI syndrome -AESOP syndrome	(Same) Except AESOP syndrome *not previously included*

ICC AND WHO CLASSIFICATION OF PC NEOPLASMS

ICC 2022

Minor adaptations

Based on IMWG criteria

Increased importance of genetics

Relevance of minimal BM infiltration in solitary plasmacytomas

WHO 5th Edition

Minor adaptations

Re-organisation of categories based on type of paraprotein and IG deposition

Introduction of clinical syndromes caused by paraprotein

Overall, differences seem minor between the two classifications

NOVEL BIOMARKERS FOR MM

Gene expression analysis

UAMS 70 signature

EMC 92 signature

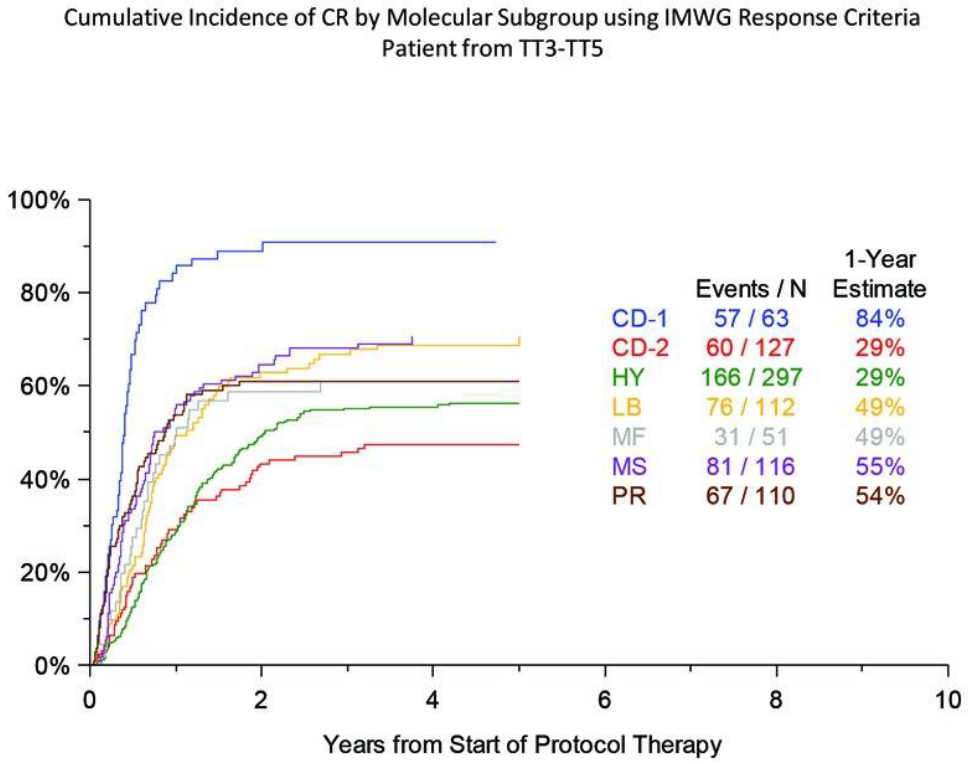
Mutational analysis

Epigenetics

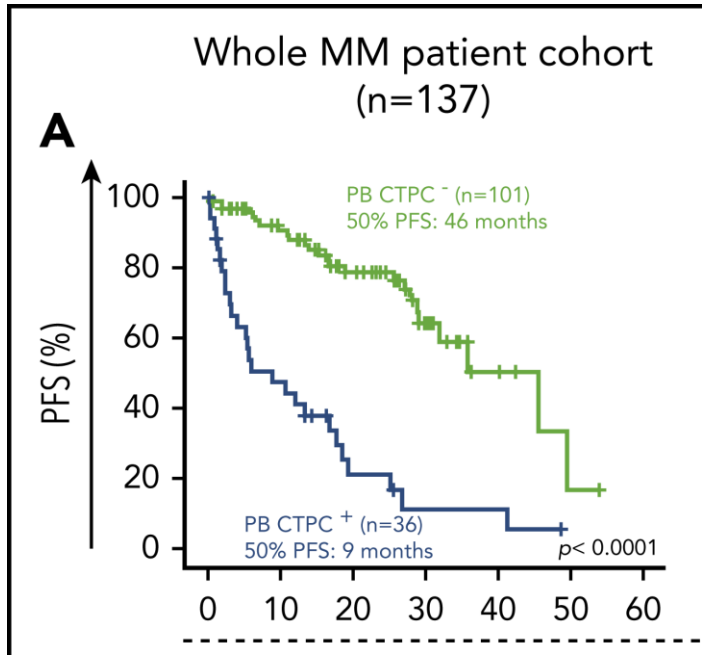
ctDNA

Circulating tumor cells

Exploration of role of **microenvironment**



UAMS 70 - Schinke et al, Haematologica 2017



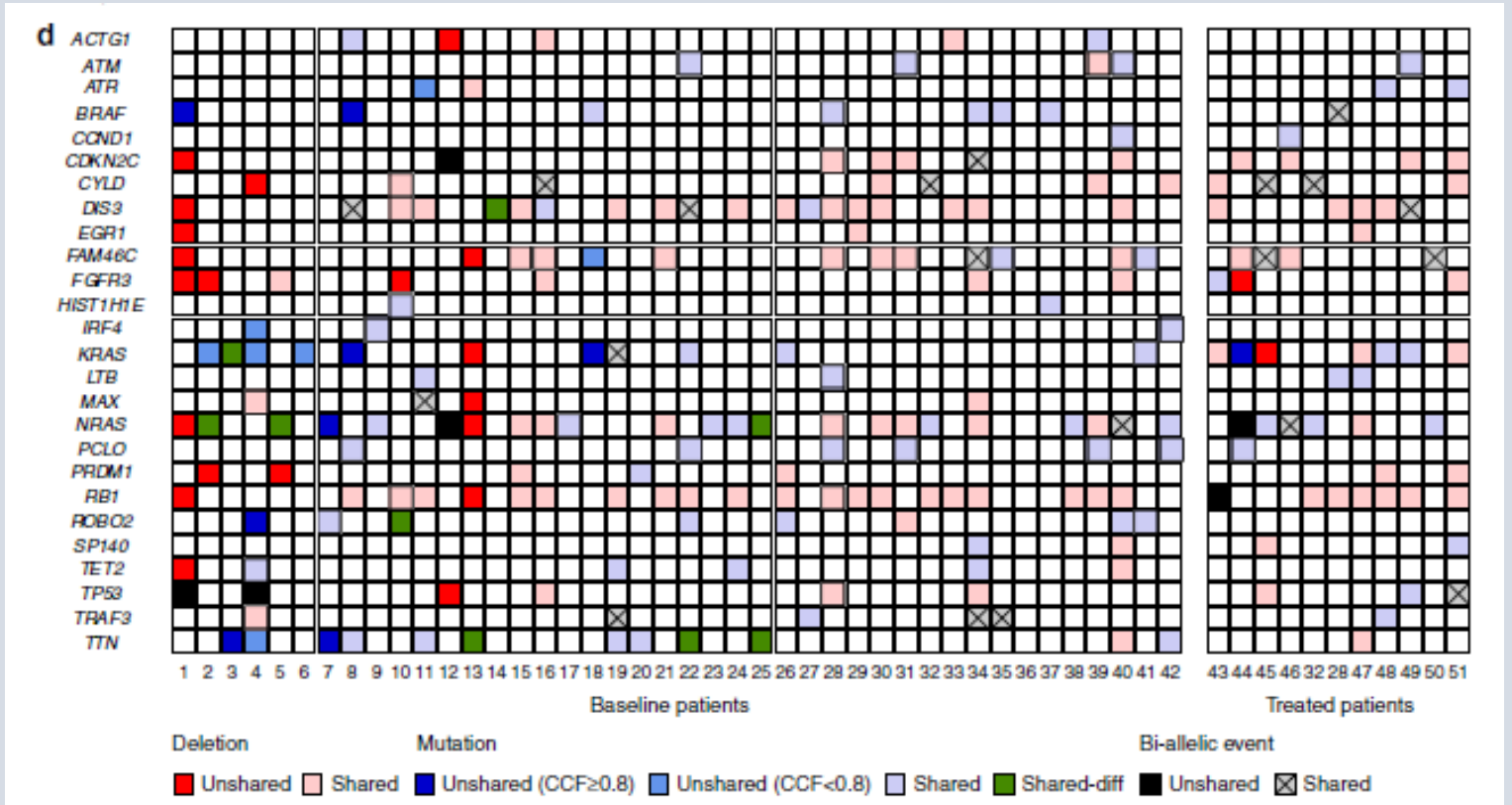
circulating PC with FCM post therapy
Sanoja-Flores L et al, Blood 2020

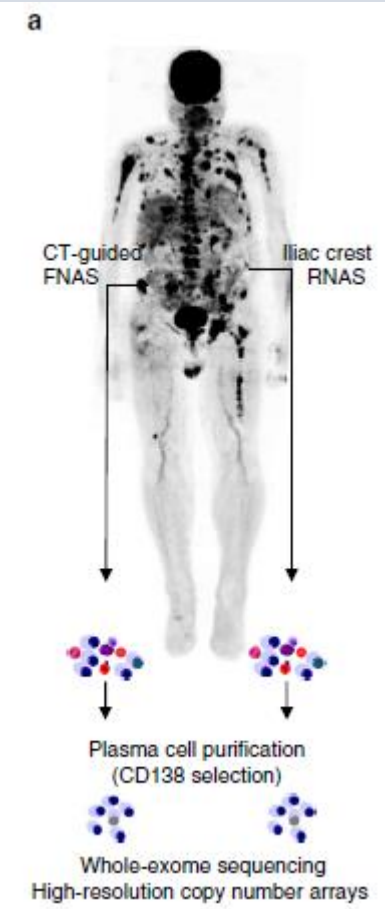
Spatial genomic heterogeneity in multiple myeloma revealed by multi-region sequencing

L. Rasche[1], S.S. Chavan[1], O.W. Stephens[1], P.H. Patel[1], R. Tytarenko[1], C. Ashby[1], M. Bauer[1], C. Stein[1], S. Deshpande[1], C. Wardell[1], T. Buzder[1], G. Molnar[1], M. Zangari[1], F. van Rhee[1], S. Thanendrarajan[1], C. Schinke[1], J. Epstein[1], F.E. Davies[1], B.A. Walker[1], T. Meissner[2], B. Barlogie[1], G.J. Morgan[1] & N. Weinhold[1]

75% of patients show clonal heterogeneity, especially with large lesions (>2.5 cm)

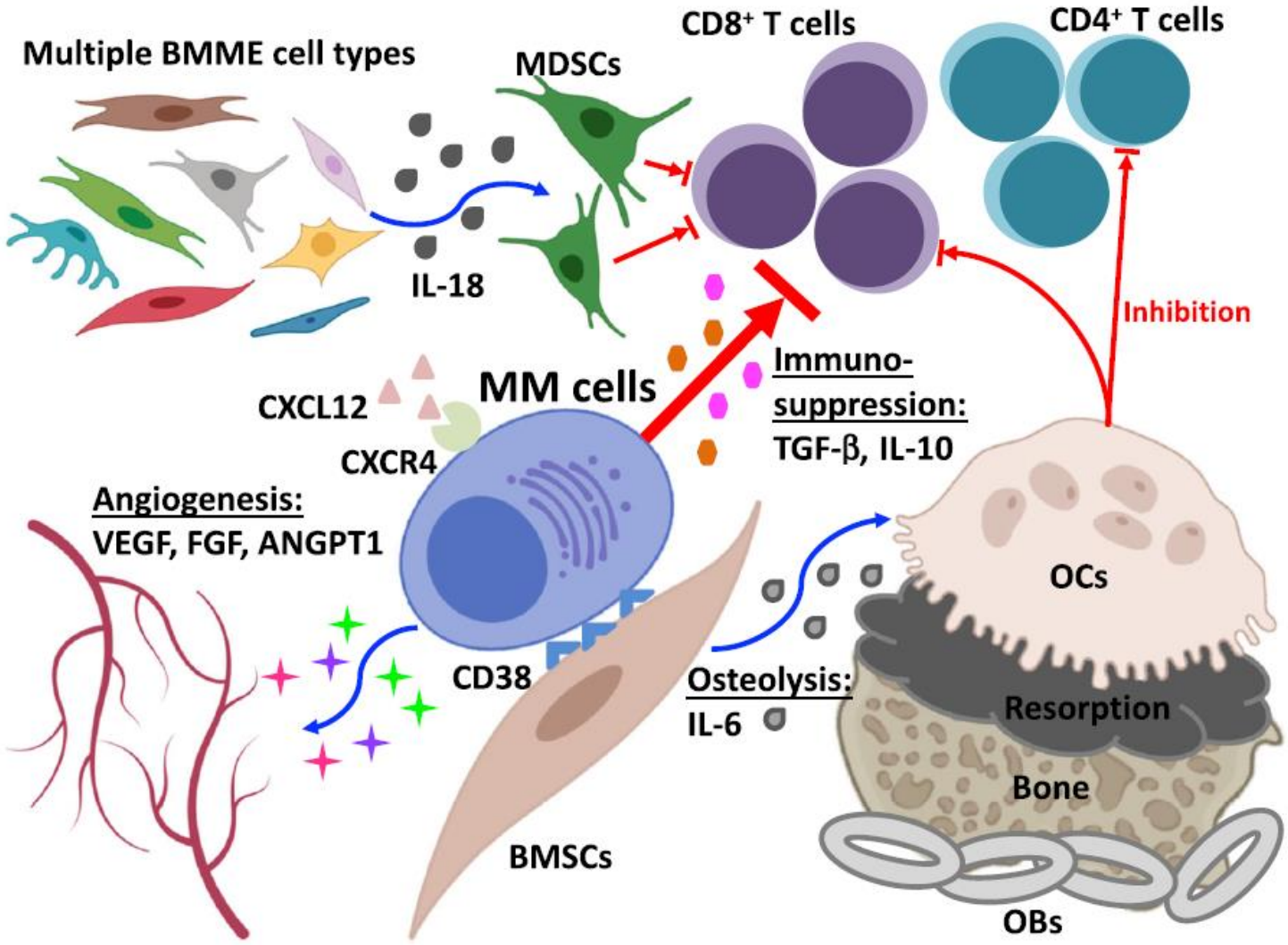
Initial (founder) alterations detectable in all tumor cells





MM AND THE MICROENVIRONMENT

- Complex interaction with BM microenvironment through adhesion molecules, cytokines/chemokines
- Induction of angiogenesis, Immunosuppression/-evasion and bone disease
- With progression increasing independence from BM ME development of extramedullary disease and PC leukemia
- Therapeutic targets



SUMMARY

Diagnosis of plasma cell neoplasms requires integration of clinical, laboratory and radiological findings

Precise quantification of plasma cells is essential

Unusual morphological and phenotypical features provide pitfalls, which can be avoided by a limited number of immunostains

Cytogenetic profile is an integral part of the current classification of plasma cell disorders

3° CONGRESO
LATINOAMERICANO DE
HEMATOPATOLOGÍA
SÃO PAULO | 2023

REALIZACIÓN

SOLAHP Sociedad Latinoamericana de Hematopatología

Sociedade Brasileira de PATOLOGIA

EA4HP European Association for Haematopathology

APOYO

RECORDATI RARE DISEASES GROUP

AstraZeneca

NOVARTIS

Janssen PHARMACEUTICAL COMPANIES OF Johnson & Johnson

A.C.Camargo Cancer Center Especializado em Vida

Agilent Dako