Marien Hospital Düsseldorf VKKD

State of the art Diagnostik der MDS

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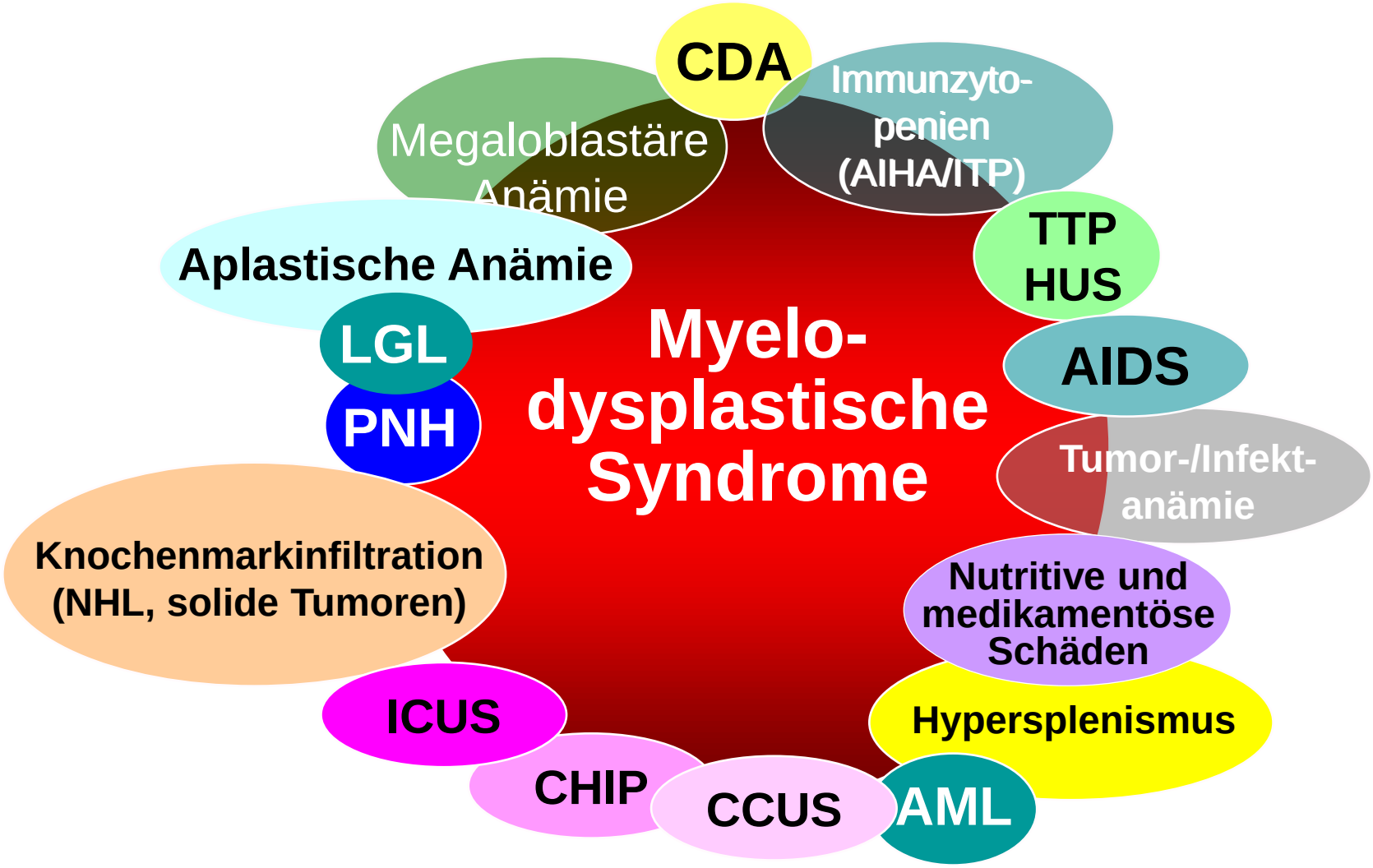
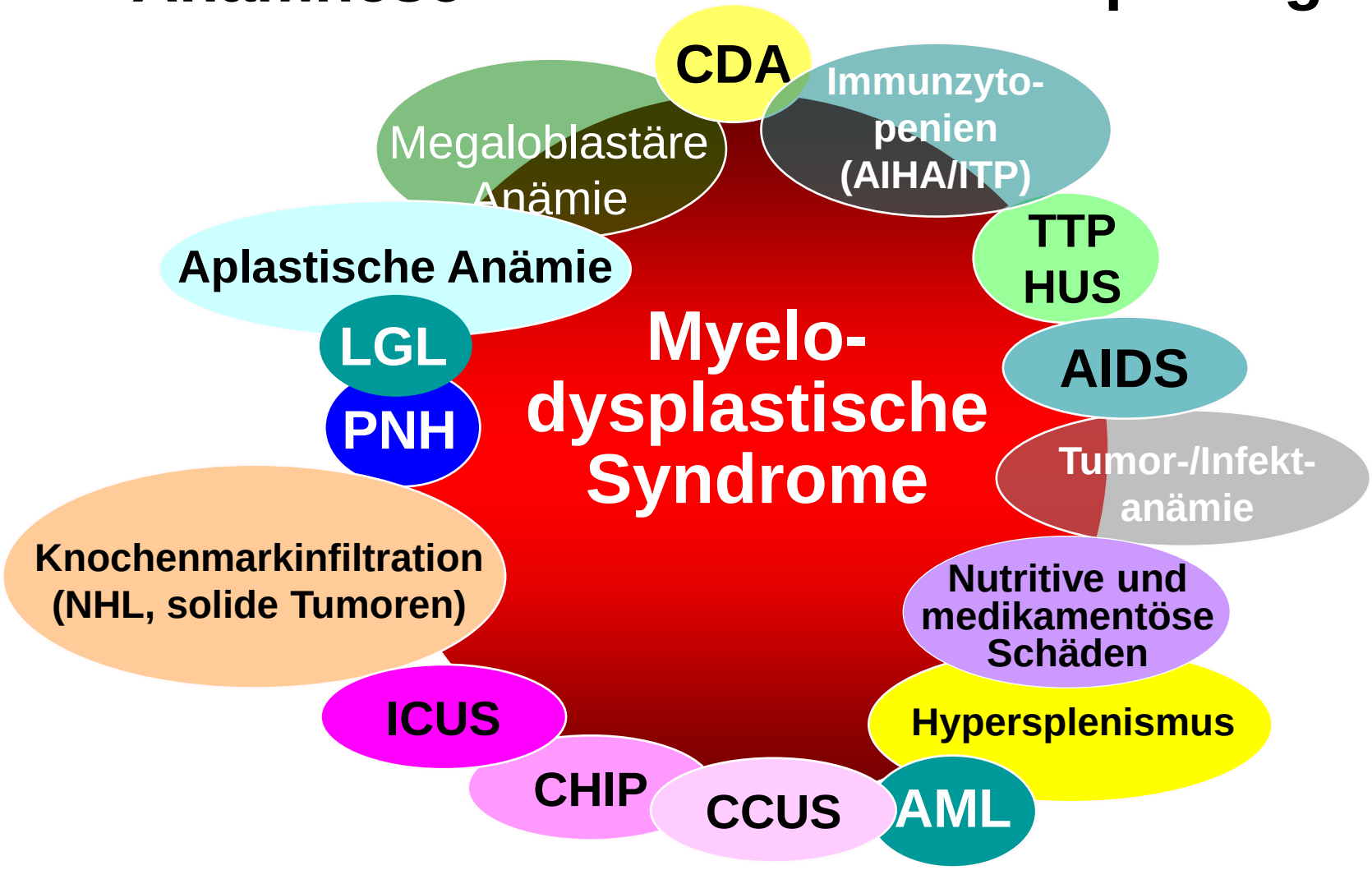
Differentialdiagnosen der MDS



Differentialdiagnosen der MDS

Anamnese Labor Morphologie



Rationelle Diagnostik bei MDS

Anamnese:

- Medikamentöse und nutritive Noxen (Alkohol, Drogen)
- Berufliche Exposition (Farben, Lacke, Benzol, Radioaktivität)
- Frühere Behandlungen (Chemotherapie, Radiotherapie)
- Autoimmunerkrankungen
- Familienanamnese

Rationelle Diagnostik bei MDS

Körperliche Untersuchung:

- Infektionen
- Hinweise auf Autoimmunerkrankungen (z.B. Arteriitis temp.?)
- Lymphknotenvergrößerungen
- Splenomegalie

Rationelle Diagnostik bei MDS

Blutentnahmen:

- Großes Blutbild (Erythrozytenzahl, MCV, MCH, RDW)
- Retikulozyten
- Differentialblutbild von Hand
- Infektionsserologie (Hepatitis, HIV)
- Vitamin B12/ Folsäure, Ferritin, Transferrin, LDH
- Kupferspiegel, Zinkspiegel

Minimal diagnostic criteria

www.impactjournals.com/oncotarget/ Oncotarget, 2017, Vol. 8, (No. 43), pp: 73483-73500

Priority Review

Proposed minimal diagnostic criteria for myelodysplastic syndromes (MDS) and potential pre-MDS conditions

Peter Valent[1,2], Attilio Orazi[3], David P. Steensma[4], Benjamin L. Ebert[5], Detlef Haase[6], Luca Malcovati[7], Arjan A. van de Loosdrecht[8], Torsten Haferlach[9], Theresia M. Westers[8], Denise A. Wells[10], Aristoteles Giagounidis[11], Michael Loken[10], Alberto Orfao[12], Michael Lübbert[13], Arnold Ganser[14], Wolf-Karsten Hofmann[15], Kiyoyuki Ogata[16], Julie Schanz[6], Marie C. Béné[17], Gregor Hoermann[18], Wolfgang R. Sperr[1,2], Karl Sotlar[19], Peter Bettelheim[20], Reinhard Stauder[21], Michael Pfeilstöcker[22], Hans-Peter Horny[23], Ulrich Germing[24], Peter Greenberg[25] and John M. Bennett[26]

Minimal diagnostic criteria

A. Prerequisite Criteria (both must be fulfilled)

- Persistent (4 months) peripheral blood cytopenia** in one or more of the following lineages: erythroid cells, neutrophils, platelets (exception: in the presence of a blast cell excess and MDS-related cytogenetic abnormalities the diagnosis of MDS can be established without delay)

- Exclusion of all other hematopoietic or non-hematopoietic disorders as primary reason for cytopenia/dysplasia***

B. MDS-Related (Major) Criteria (at least one must be fulfilled)

- Dysplasia in at least 10% of all cells in one of the following lineages in the bone marrow smear: erythroid; neutrophilic; megakaryocytic****

- ≥15% ring sideroblasts (iron stain) or ≥5% ring sideroblasts (iron stain) in the presence of *SF3B1* mutation

- 5-19% myeloblasts on bone marrow smears (or 2-19% myeloblasts on blood smears)

- Typical chromosome abnormality(ies) by conventional karyotyping or FISH*****

C. Co-Criteria (for patients fulfilling A but not B, and otherwise show typical clinical features, e.g. macrocytic transfusion-dependent anemia; two or more of these co-criteria must be fulfilled for considering a provisional diagnosis of MDS)

- Abnormal findings in histologic and/or immunohistochemical studies of bone marrow biopsy sections supporting the diagnosis of MDS****

- Abnormal immunophenotype of bone marrow cells by flow cytometry, with multiple MDS-associated phenotypic aberrancies indicating the presence of a monoclonal population of erythroid and/or myeloid cells

- Evidence of a clonal population of myeloid cells determined by molecular (sequencing) studies revealing MDS-related mutations******

Valent P, Oncotarget 2017, 8:73483ff.

Annäherung an die schwierigen Differenzial-diagnosen

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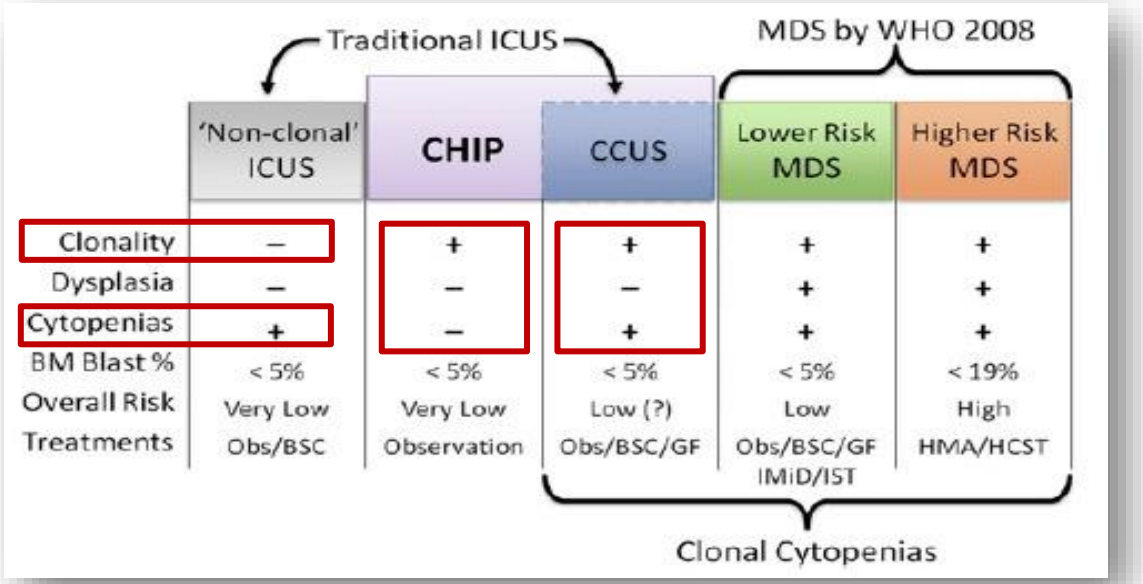
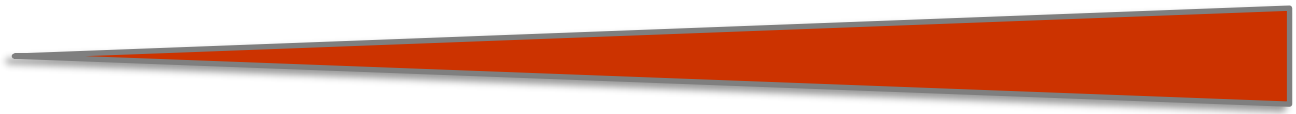


	CHIP Unselected Population	CCUS At Diagnosis	CCUS Prior to MDS/AML Progression	MDS All Risk Groups
Mutated Genes	*DNMT3A, TET2,ASXL1, JAK2, TP53 …*	*TET2, DNMT3A,ASXL1, SRSF2, TP53, …*	*TET2, SRSF2, ASXL1, U2AF1, DNMT3A, …*	*SF3B1, TET2, ASXL1, SRSF2, DNMT3A, …*
# of Mutations	~1	~1.6	~2	~2.6
Typical VAF	9-12% (>10% with ↑ risk)	30-40%	~40%	30-50%
Mutation Rate	~10% of 70 year-olds	About 35% of ICUS	About 90% of ICUS	About 90% of MDS

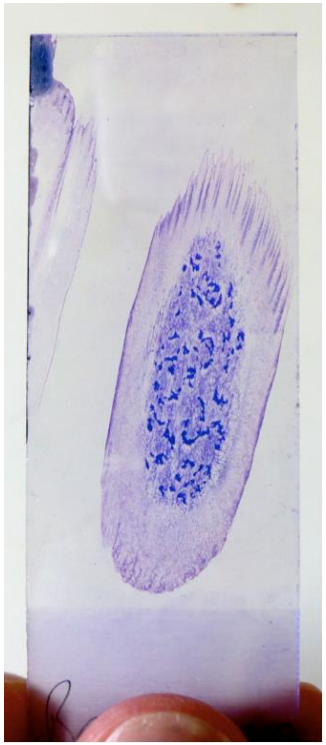


VAF ≥ 10
Number of mutations

Rationelle Diagnostik bei MDS

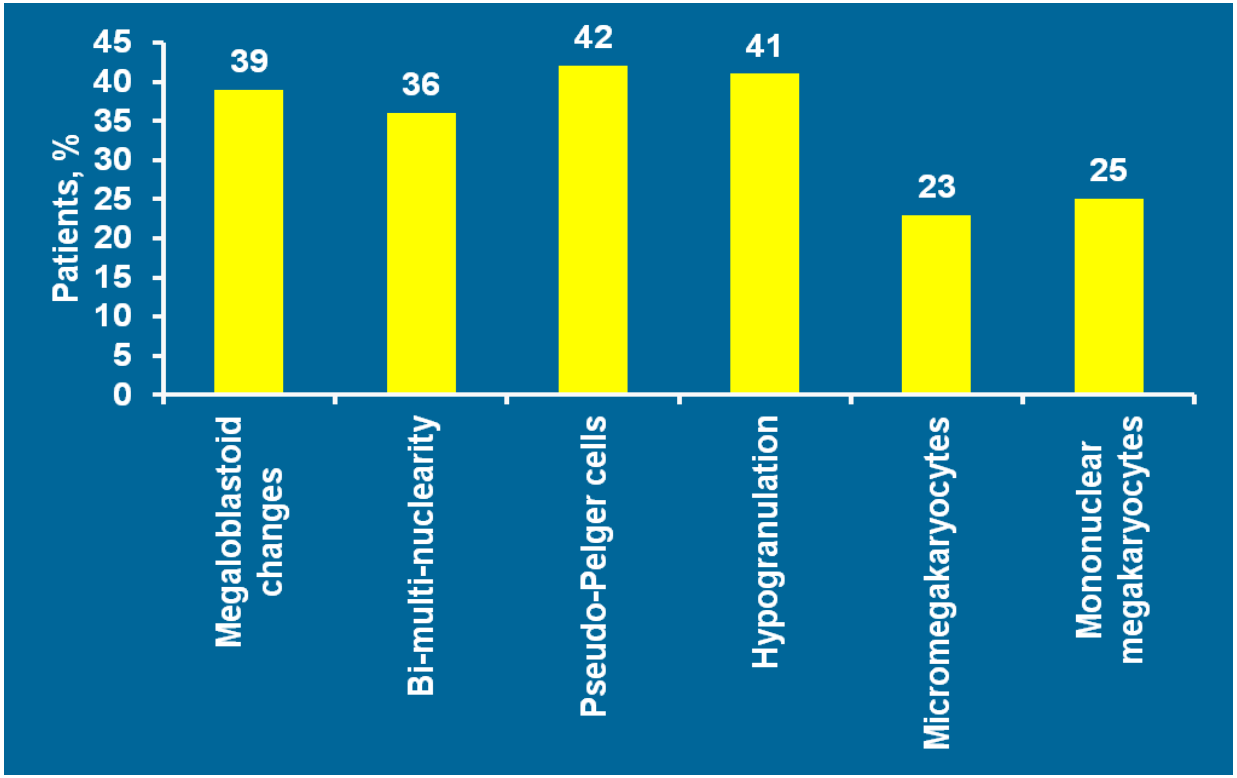
- KM-Punktion:
- Spina iliaca posterior superior
- Kein Heparin als Antikoagulans
- Ausstrich- oder Bröckel-Quetsch-Präparate
- Falls Immunphänotypisierung: 1 – 2 ml reichen, diese zuerst aspirieren
- Keine sonderliche Blutungsneigung (Thrombozytopenie, Antikoagulation)

Bone marrow smear



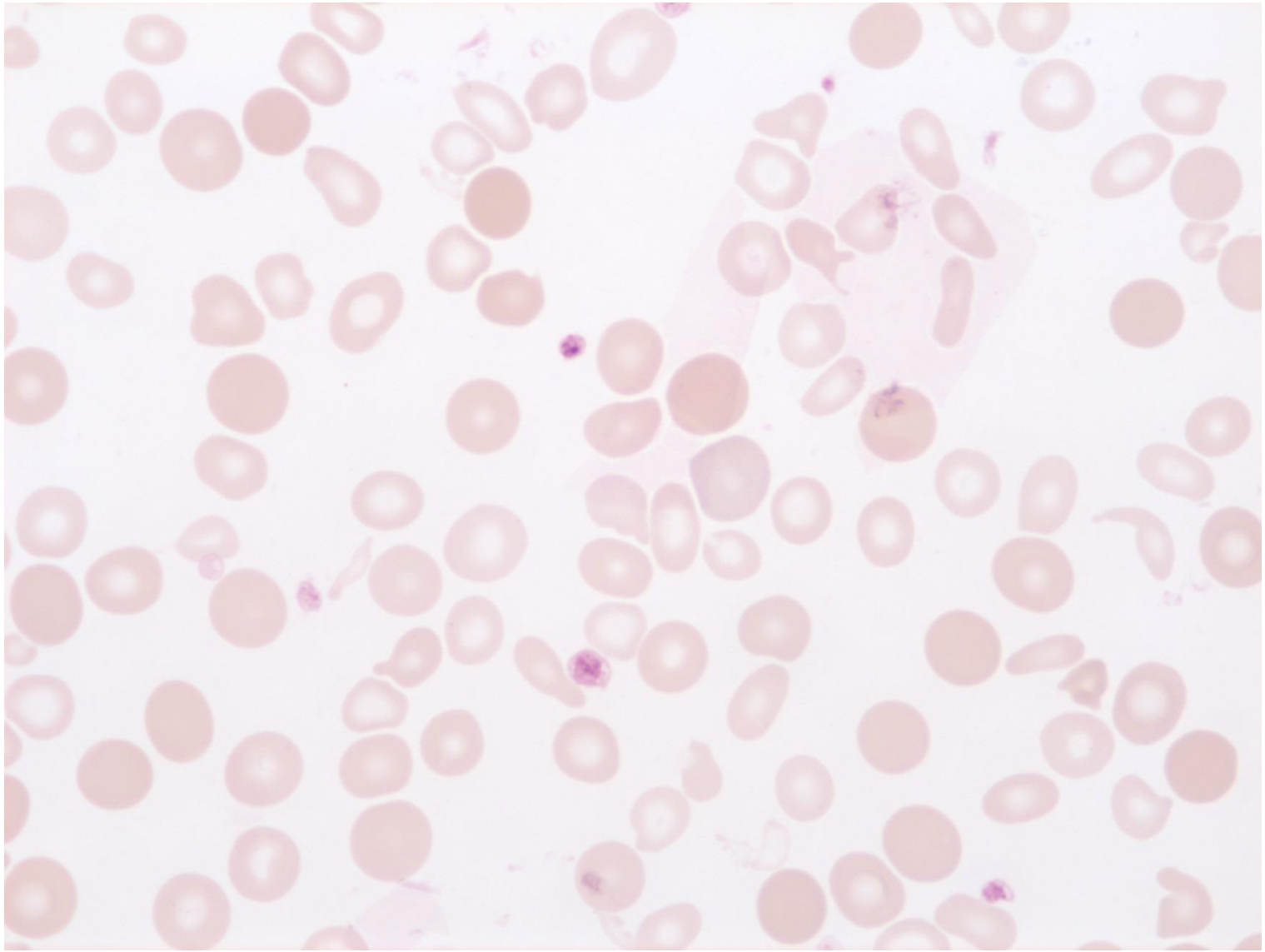
Bone marrow film

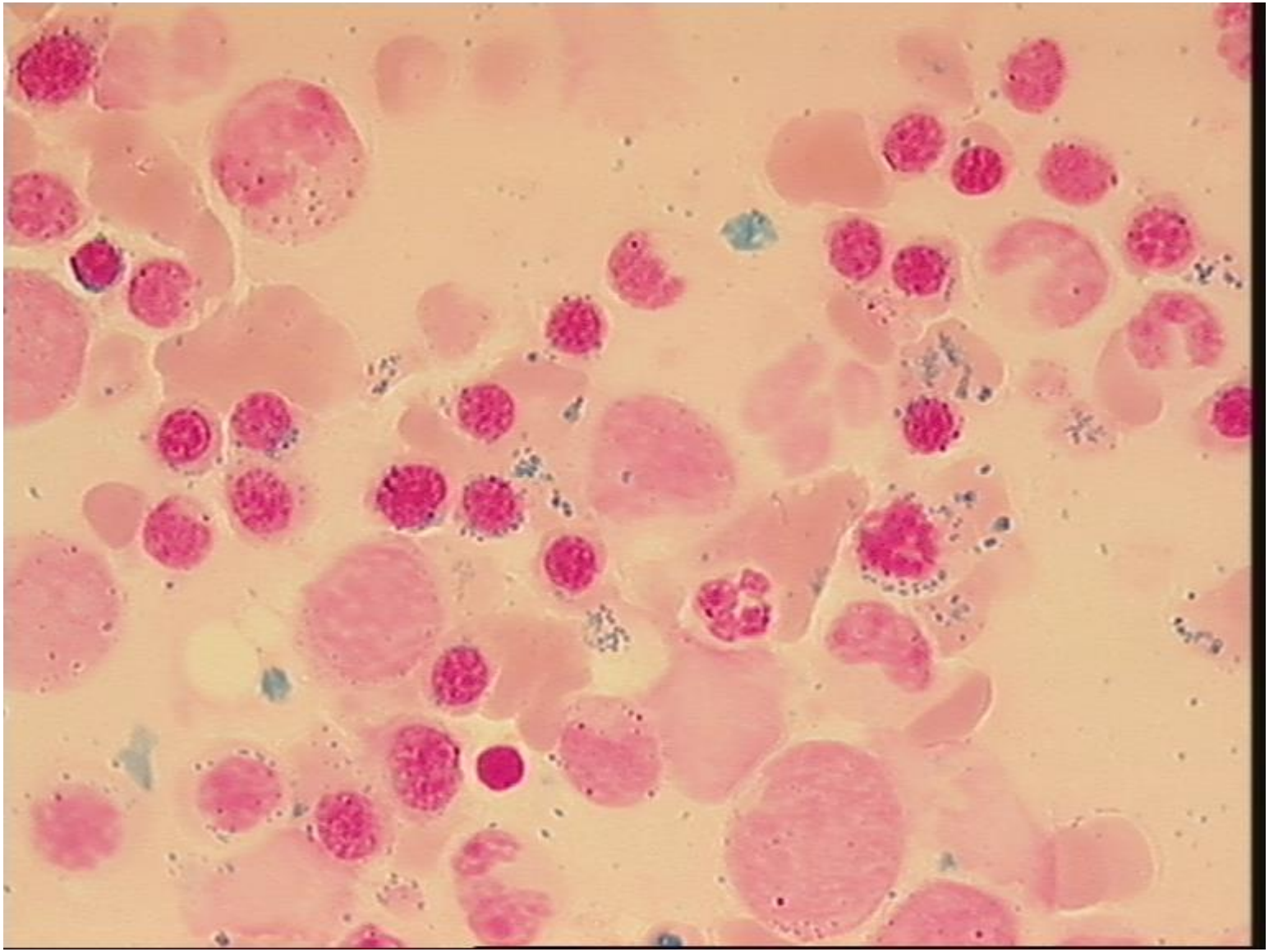
Häufigste Knochenmarkdysplasien bei MDS

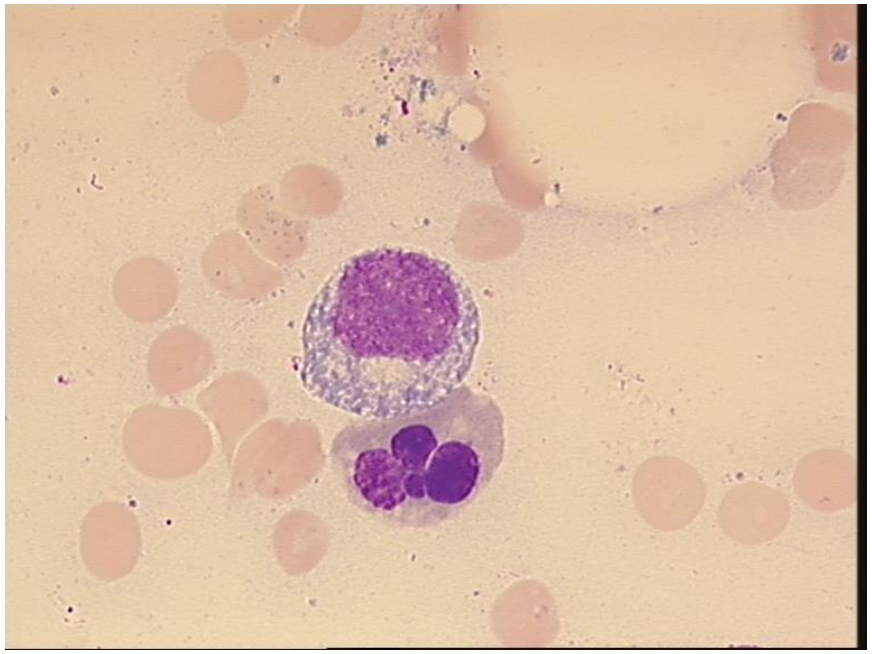


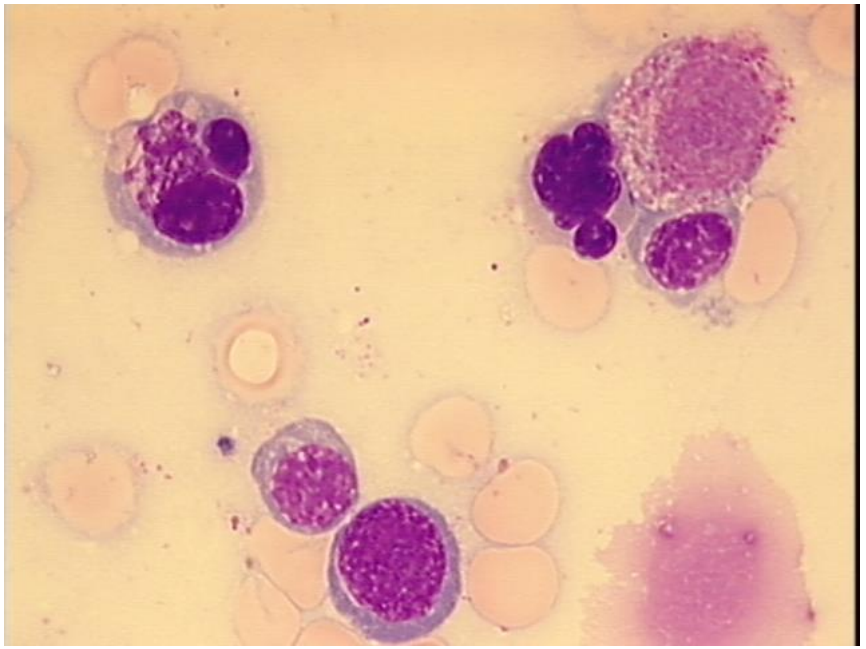
Most frequent signs of dysplasia in 3,156 patients with MDS

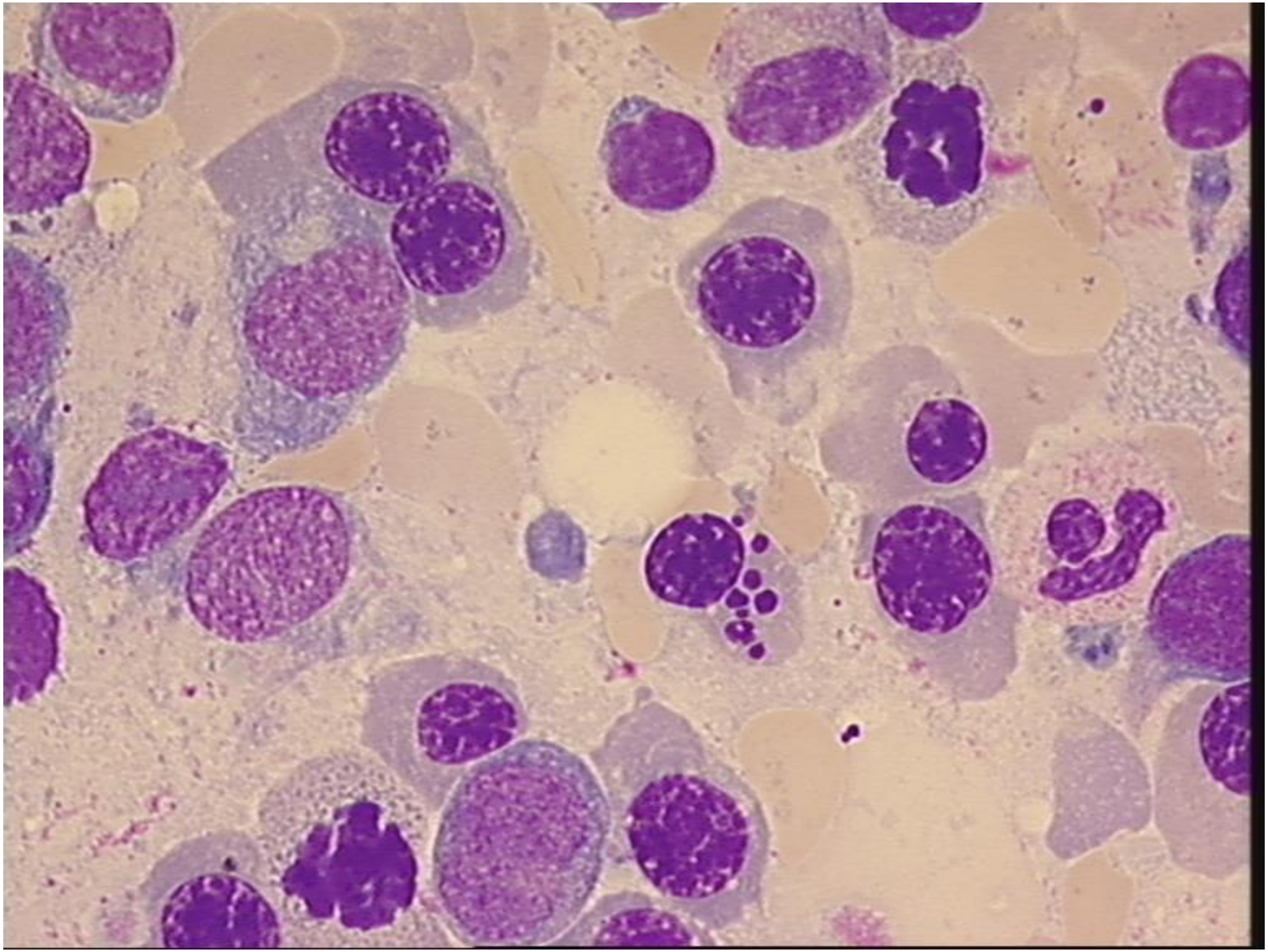
Germing U, et al. *Leuk Res* 2012;36:727–34

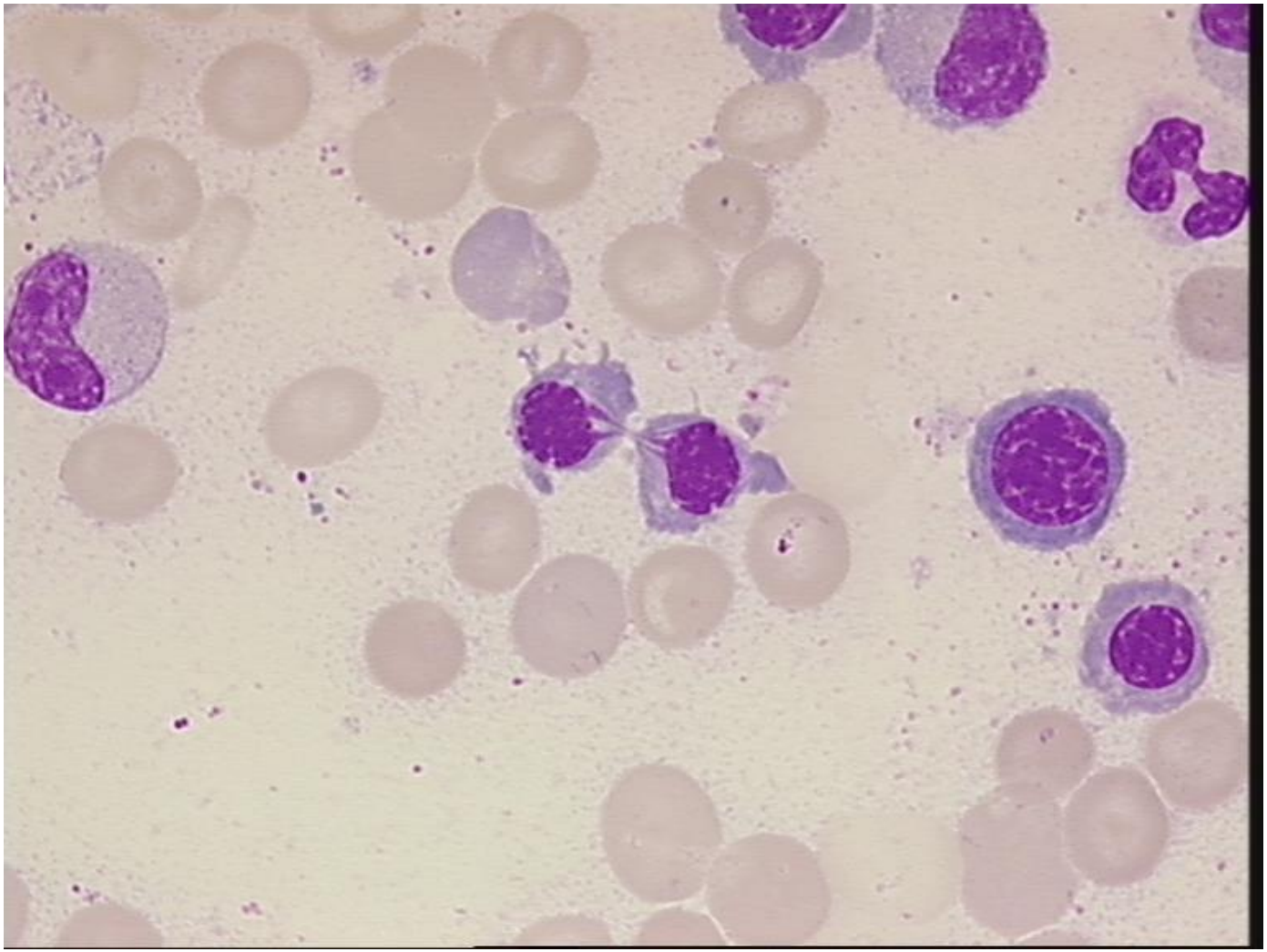


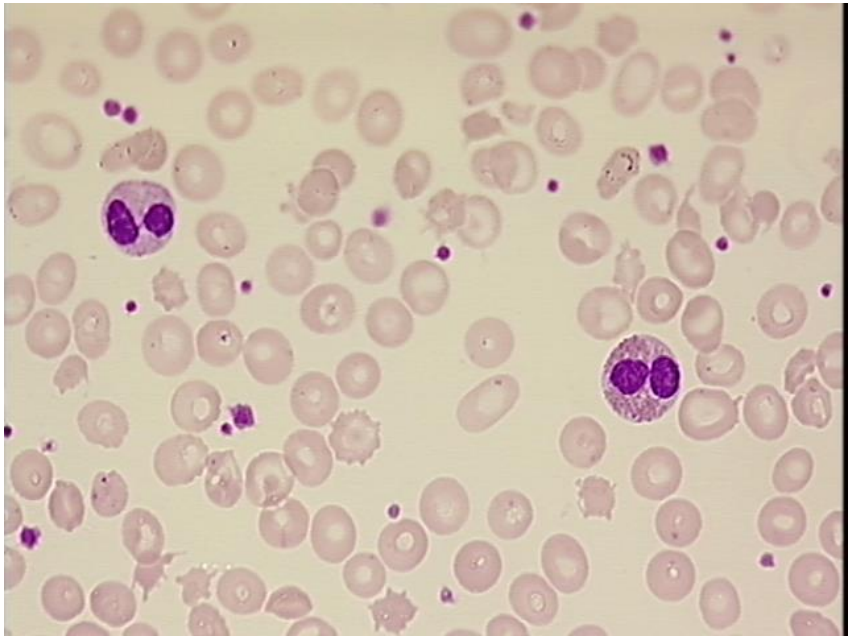


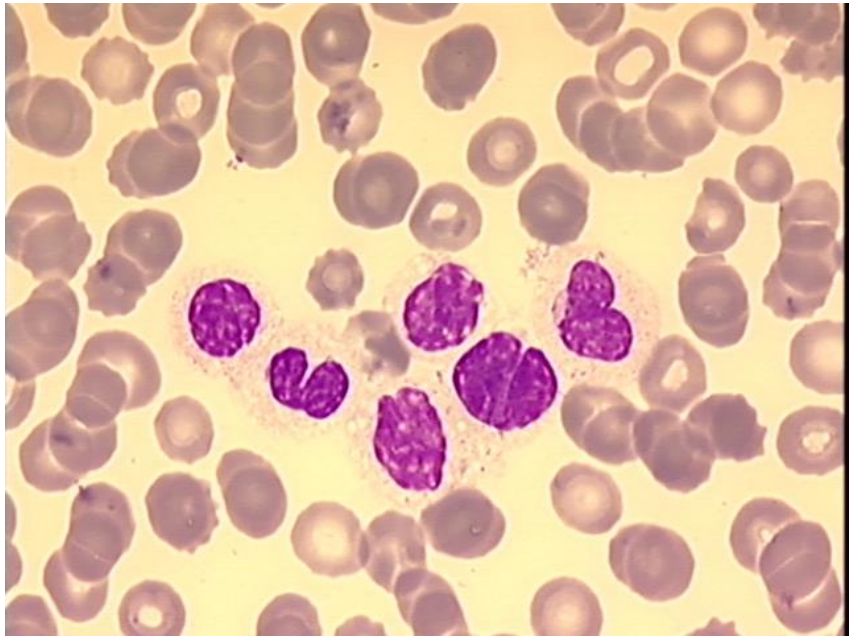


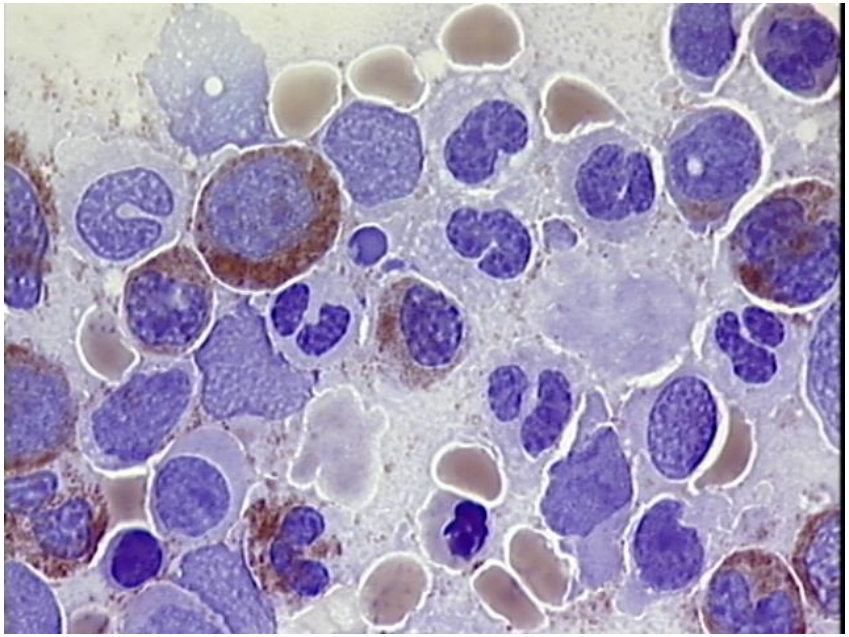


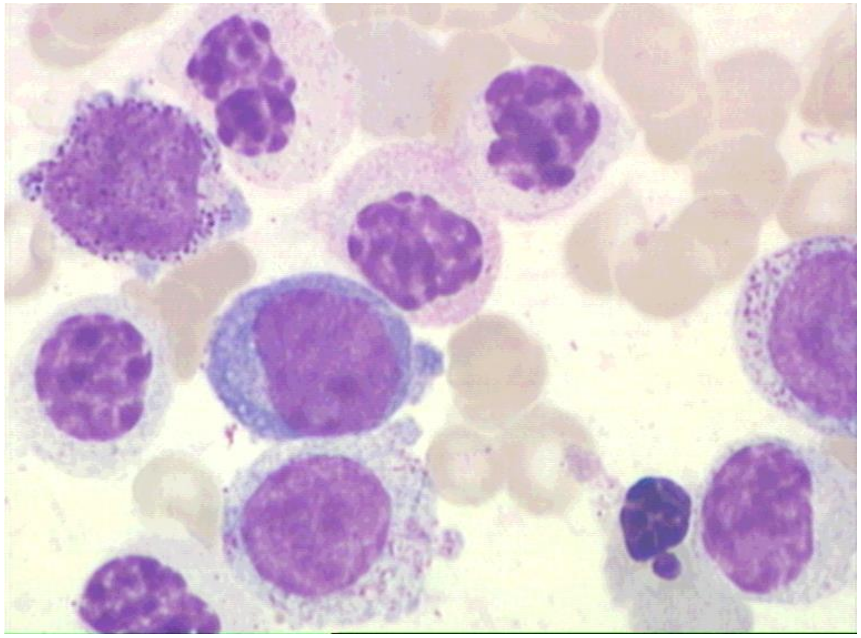


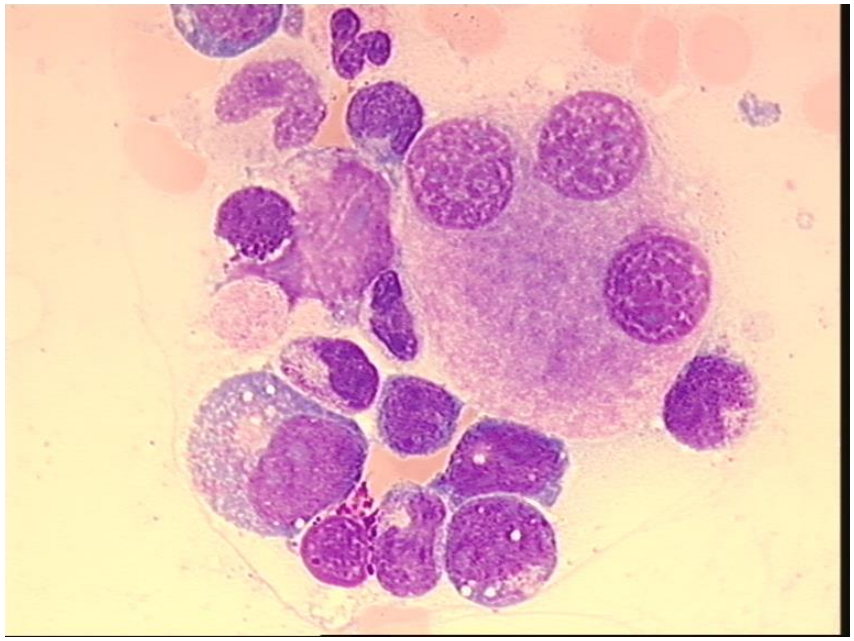


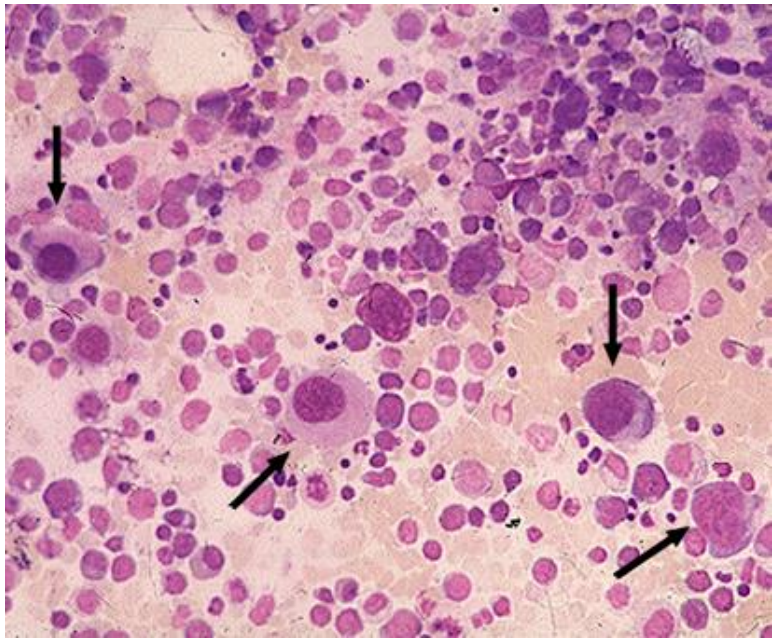


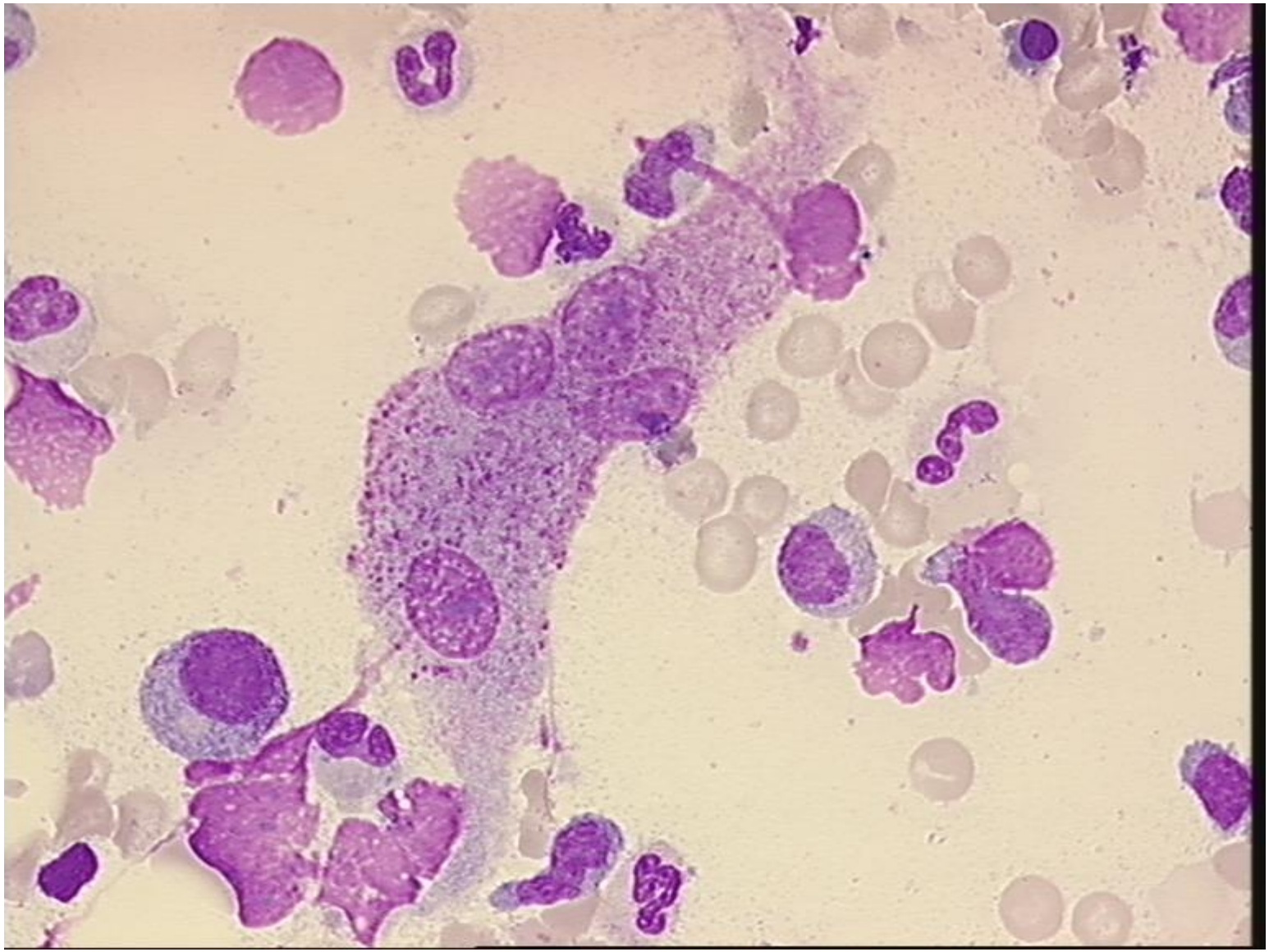


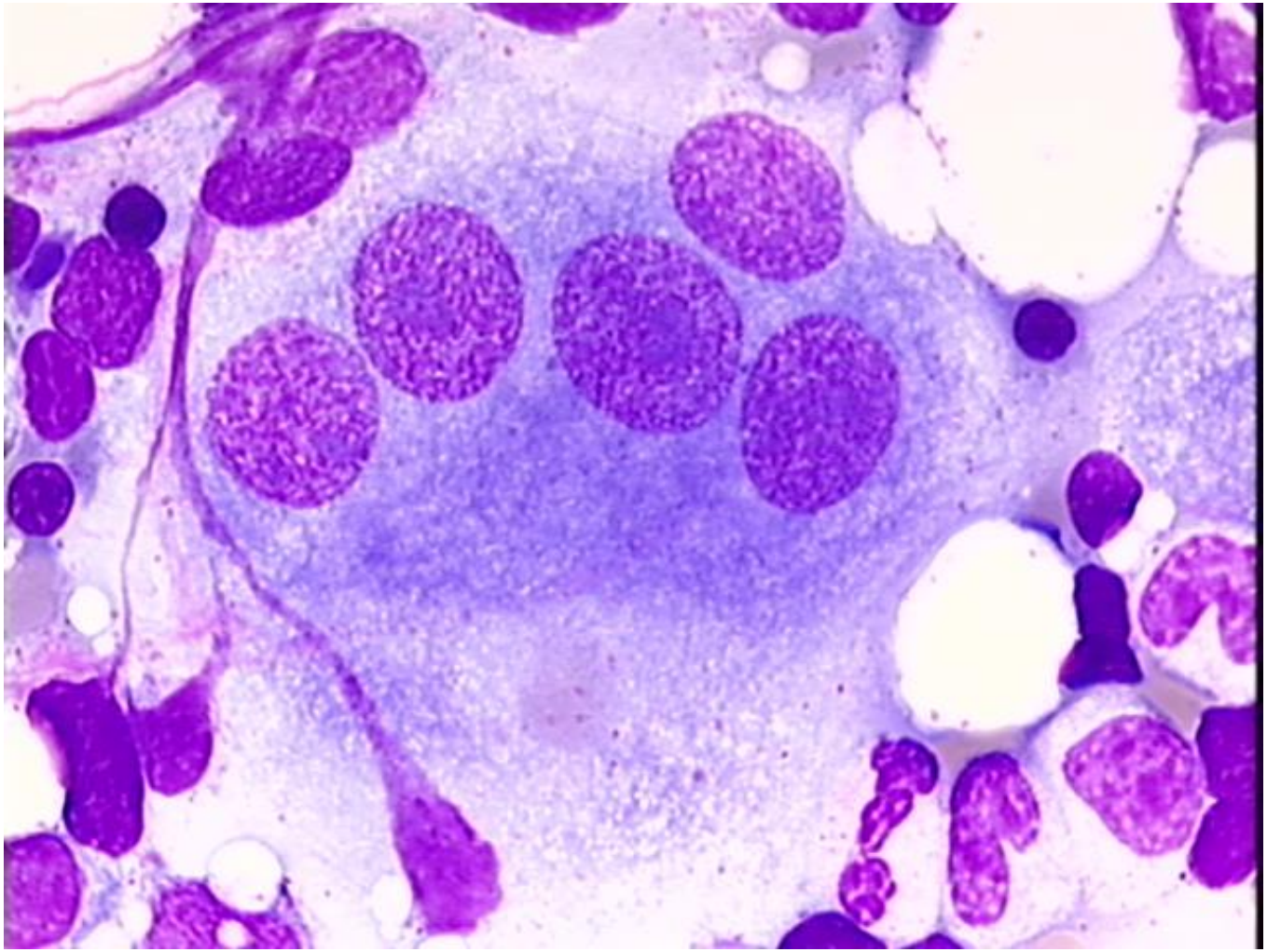






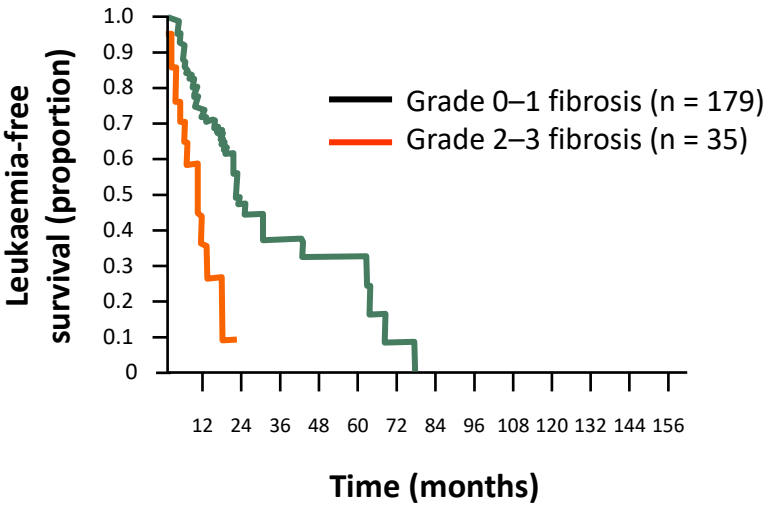




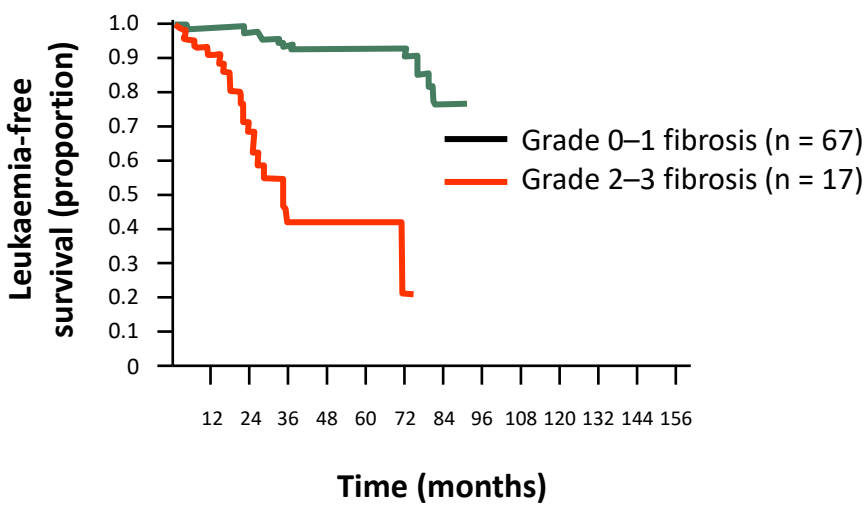


Knochenmarkhistologie

Patients with RA/RARS/RCMD ± RS (n = 214)



Patients with RAEB-1/-2 (n = 84)



Patients with grade 2–3 fibrosis had reduced leukaemia-free survival compared to patients with grade 0–1 fibrosis

Della Porta MG, et al. *J Clin Oncol*. 2009;27:754-64.

Fallbeispiel 1

- 60 jähriger Mann, asymptomatisch
- Vor 2 Jahren noch normale Blutwerte

  Hgb 14,2 g/dL, ANC 2100/µL, PLT 238.000/µL
- Seit 2 Jahren, langsam fallender Hb-Wert auf 10,1 g/dL
- Auffallend: Mikrozytose (MCV 66 fL) und Hypochromie (MCH 19 pg/RBC)
- GI: keine Blutung
- Ferritin normal, Transferrinsättigung normal
- Löslicher Transferrinrezeptor erhöht, RDW 30% (11%-15% normal)

Peripherer Blutausstrich
Warum Schießscheibenzellen?

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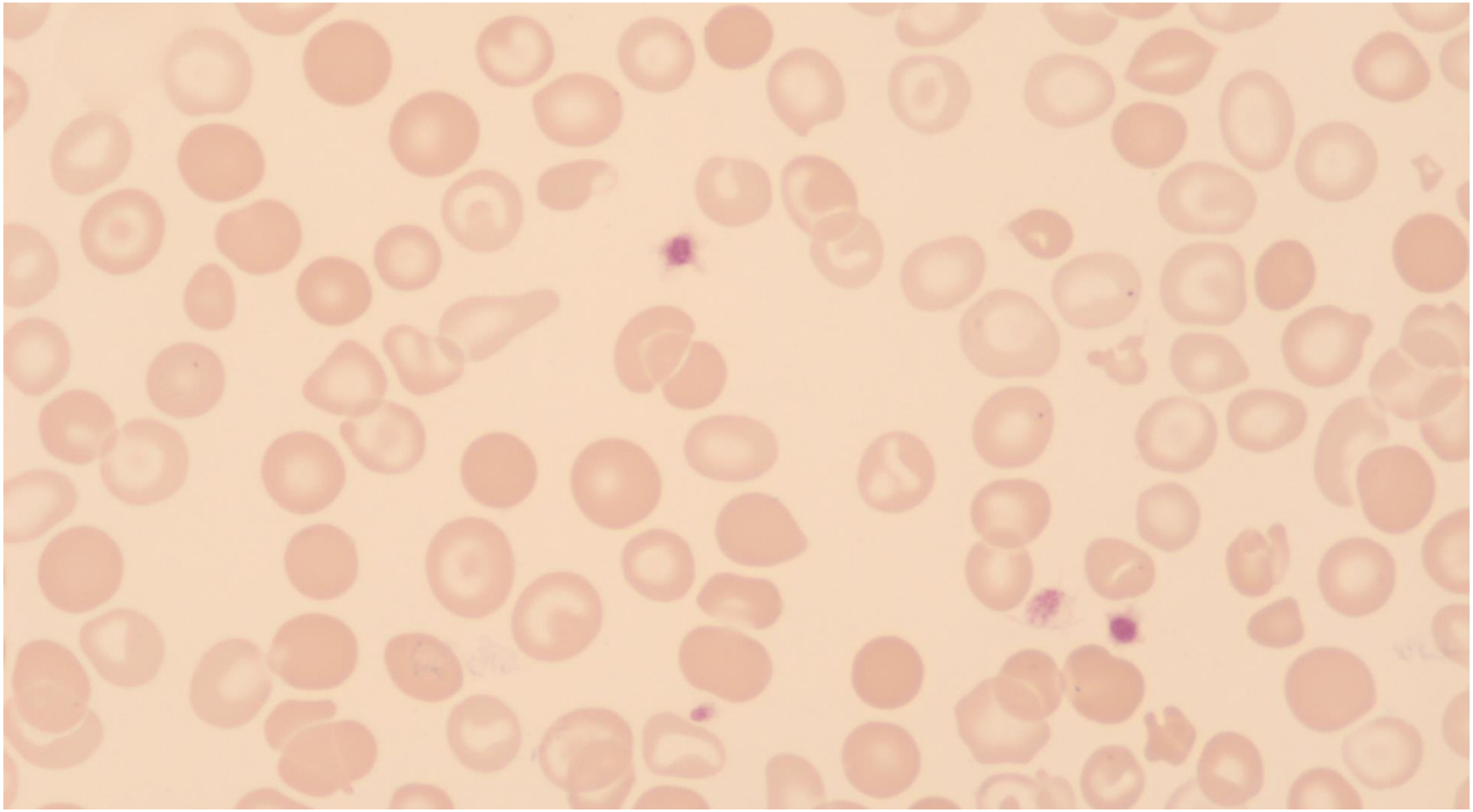

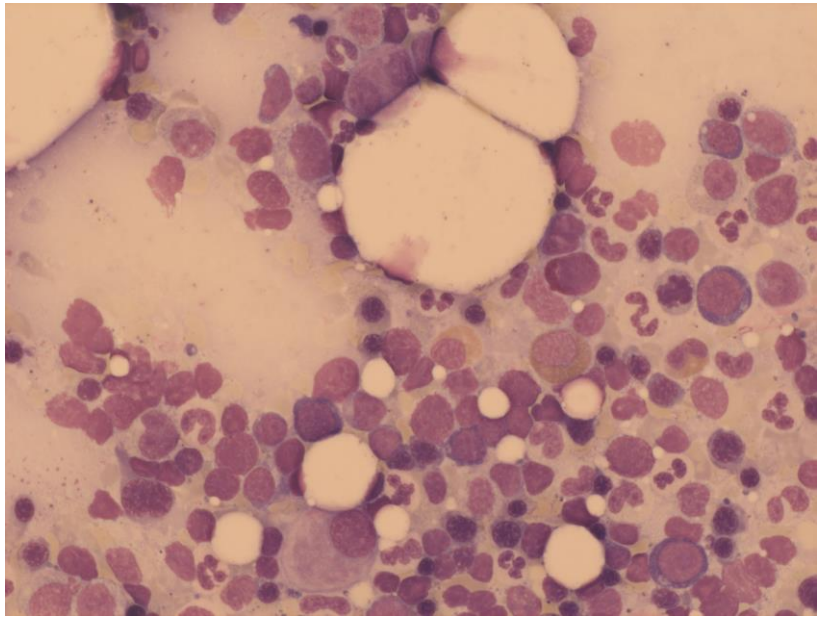

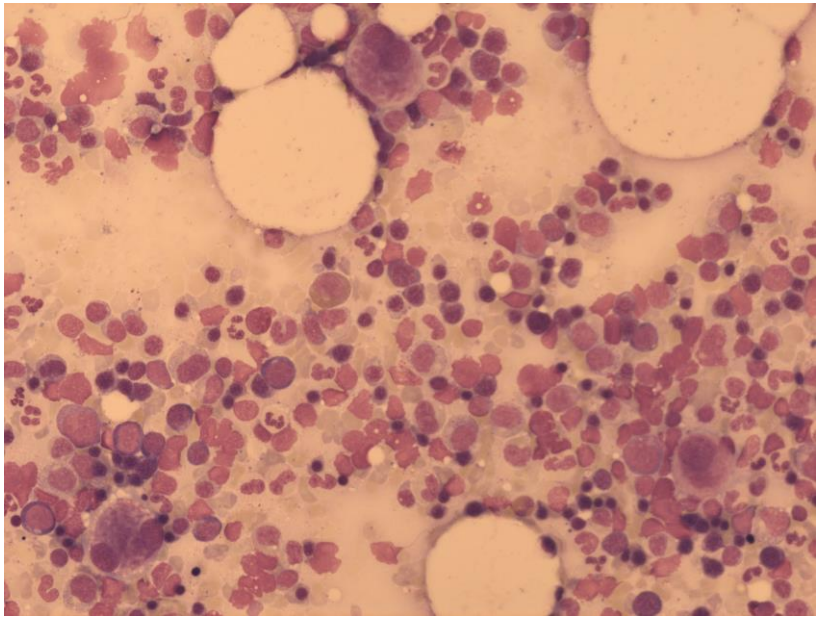

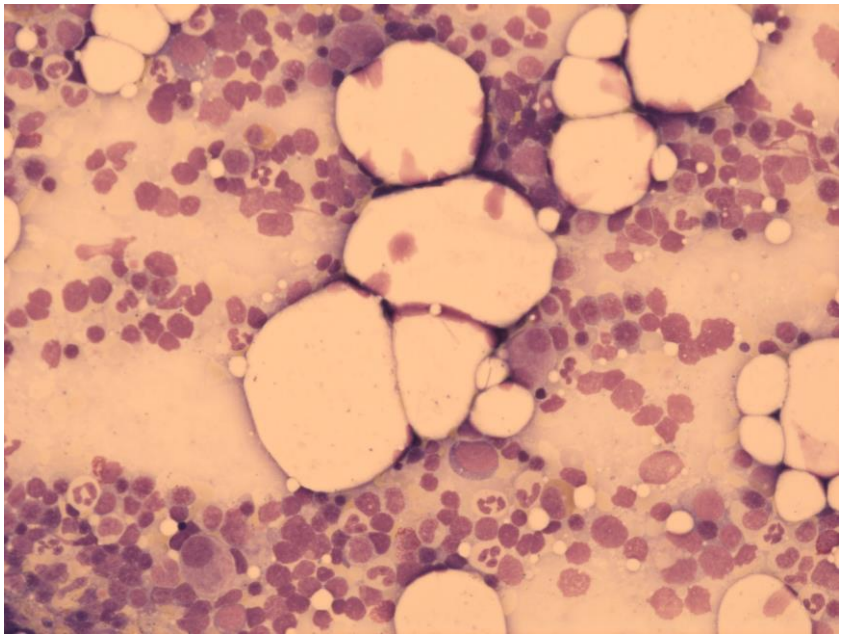

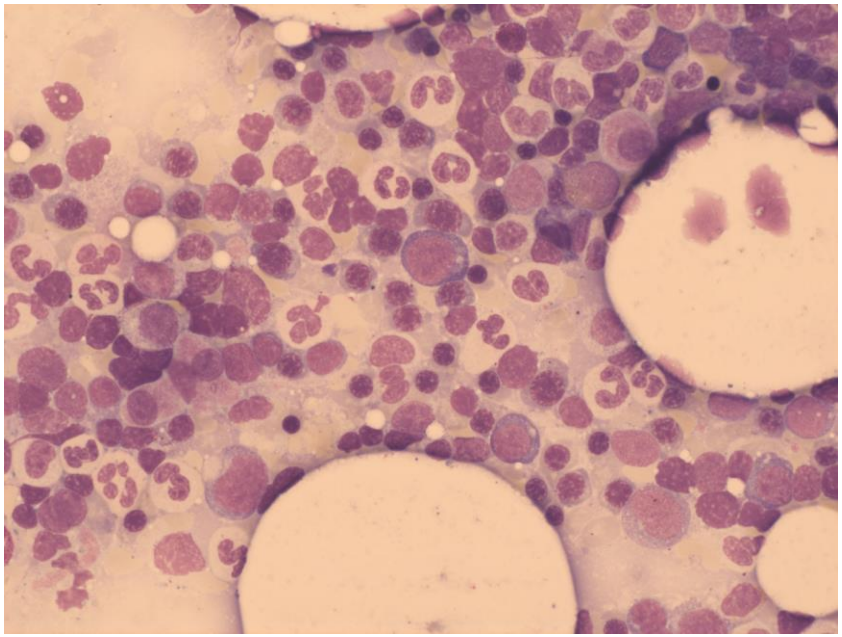

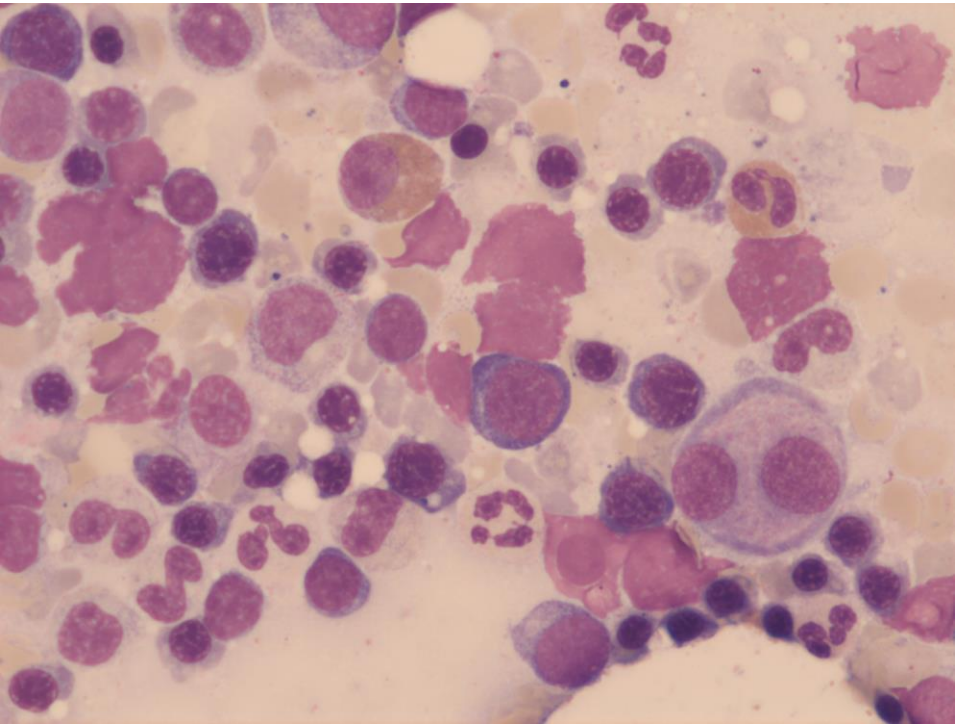

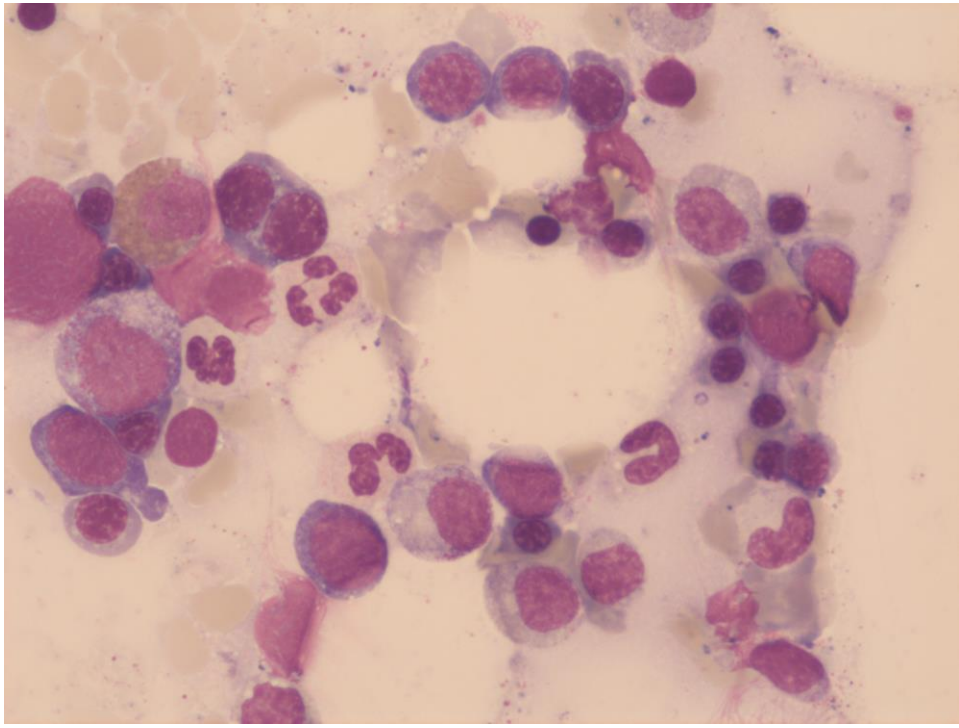

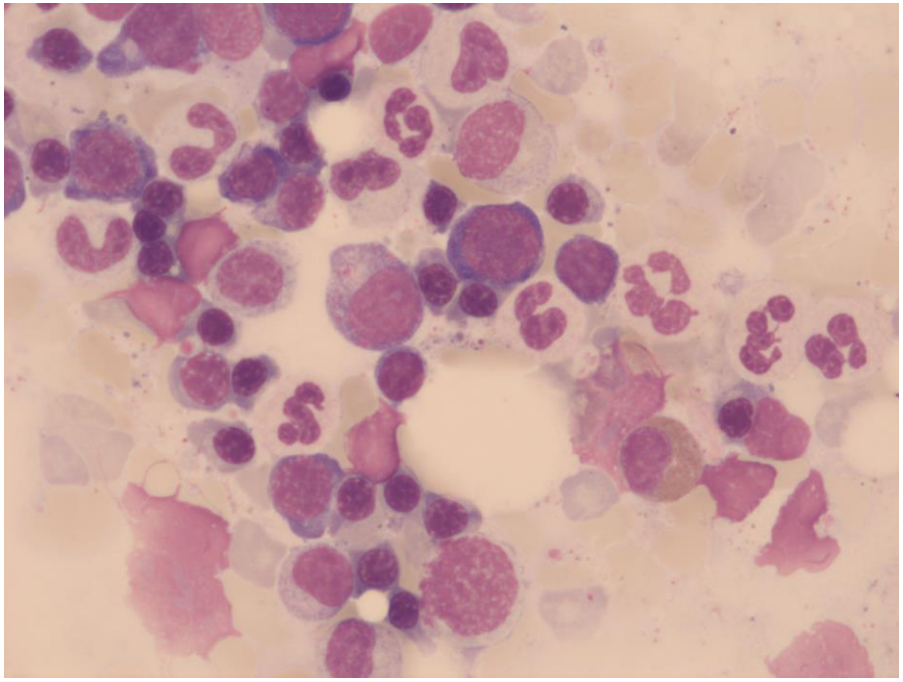

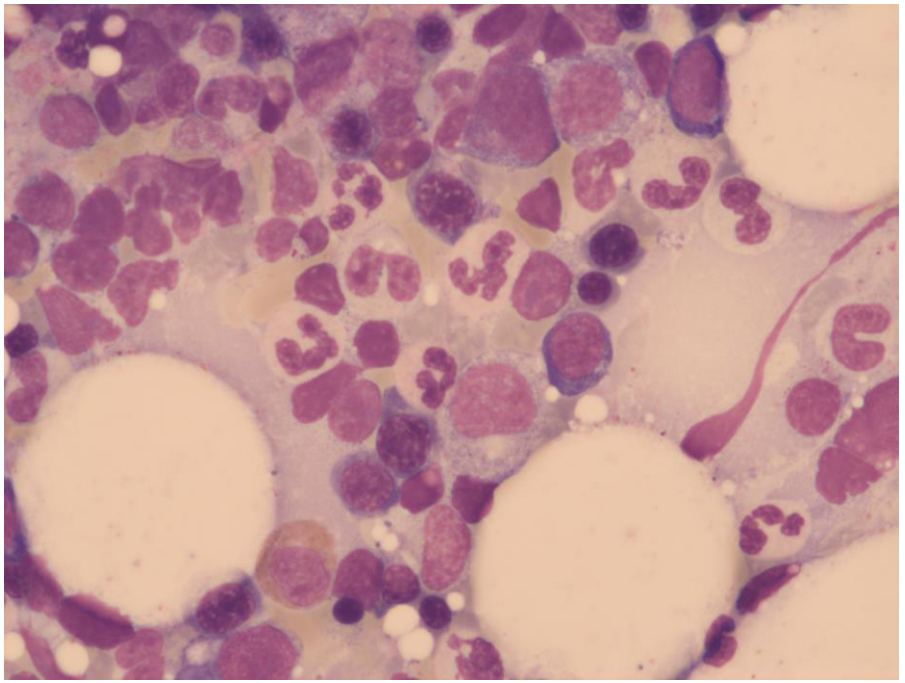

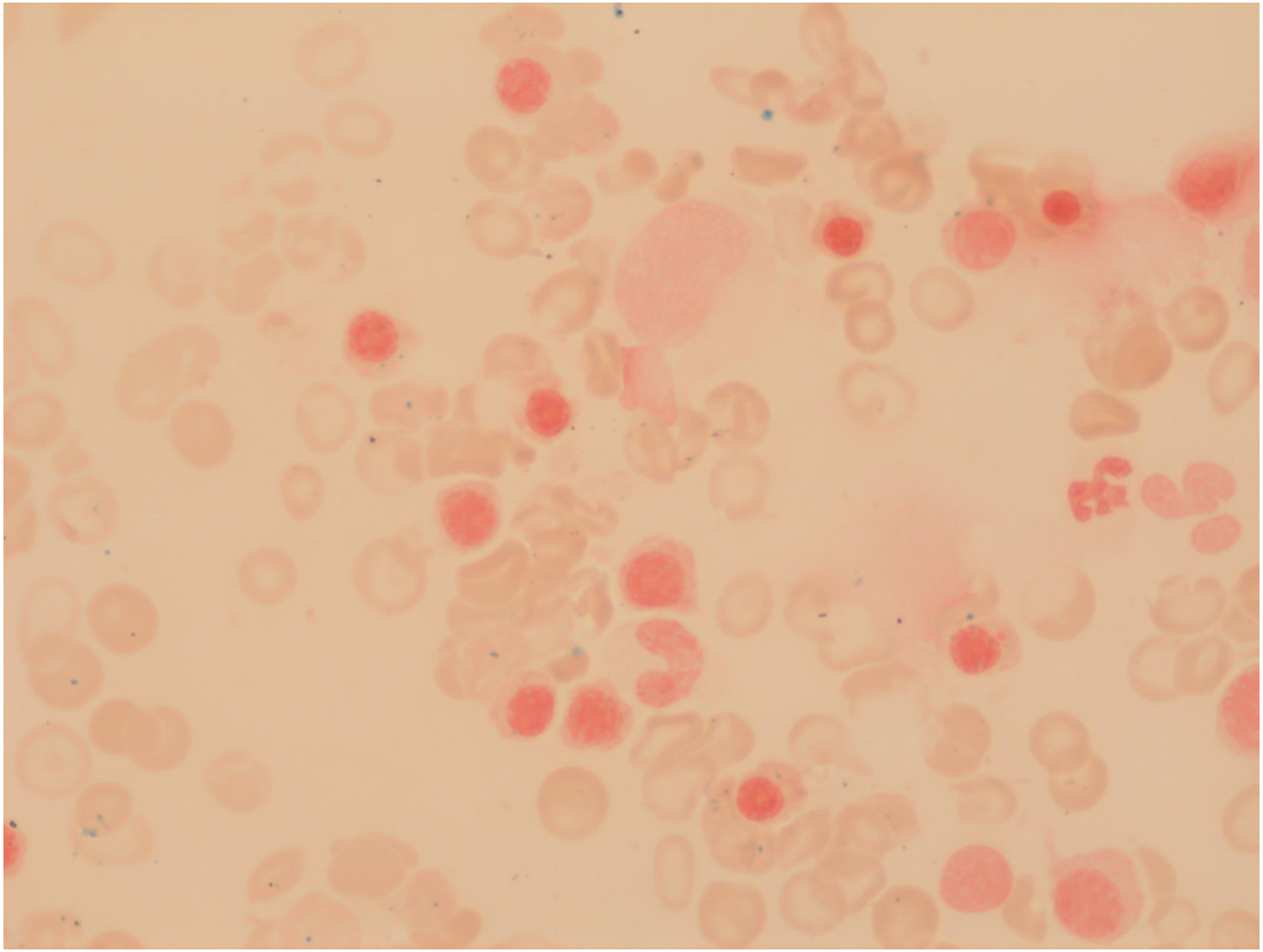

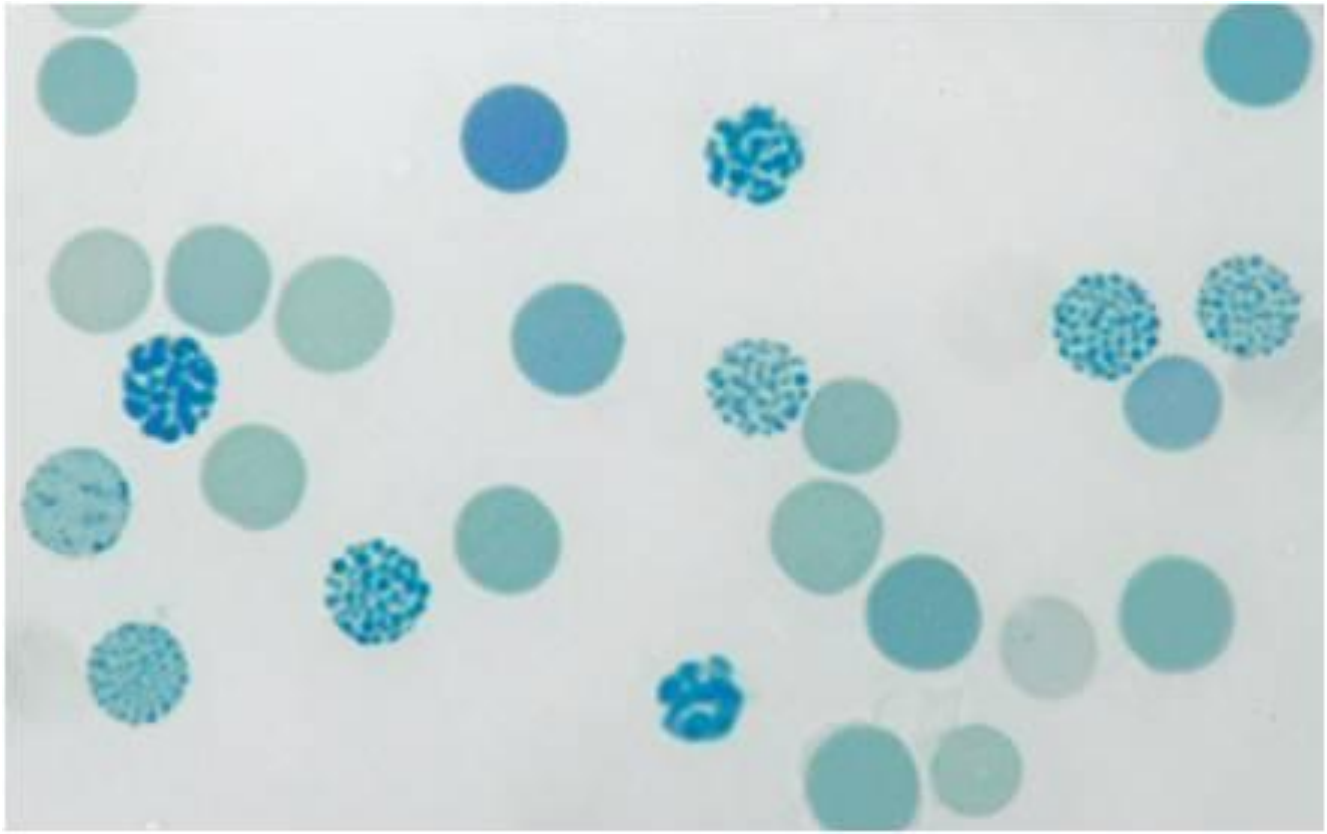

Molekularbiologie

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Veränderungen (Tier 1 oder 2)[1]

Gene	Exon	DNA/cDNA	Protein	VAF[2]	Bewertung	Material	
ASXL1	13	c.1900_1922del	p.Glu635Argfs*15	23	Tier 1	KM	DNA
ATRX	35	c.7219C>T	p.Arg2407*	81	Tier 1	KM	DNA
EZH2	08	c.866G>T	p.Cys289Phe	34	Tier 2	KM	DNA
PHF6	10	c.1024C>T	p.Arg342*	77	Tier 1	KM	DNA
U2AF1	06	c.470A>G	p.Gln157Arg	41	Tier 1	KM	DNA

[1] Tier-Bewertung siehe Legende zur Tabelle „Durchgeführte Analysen".
[2] VAF: Varianten Allel Frequenz, % mutierte/(mutierte+Wildtyp reads) mittels NGS.

Durchgeführte Analysen

Gen	Bewertung[1]	Analysierter Bereich	Ensembl transcript ID	Methode	Sensitivität		Material	
					Screening	MRD		
ASXL1[2]	**Tier 1**	**E13**	**ENST00000375687**	**NGS**	**mind. 3%**	**1,000%**	**KM**	**DNA**
ATRX	**Tier 1**	**Komplett**	**ENST00000373344**	**NGS**	**mind. 3%**	**1,000%**	**KM**	**DNA**
CBL	Wildtyp	E08, E09	ENST00000264033	NGS	mind. 3%	1,000%	KM	DNA
DNMT3A	Wildtyp	E07-E23	ENST00000264709	NGS	mind. 3%	1,000%	KM	DNA
EZH2	**Tier 2**	**Komplett**	**ENST00000320356**	**NGS**	**mind. 3%**	**1,000%**	**KM**	**DNA**
JAK2[3]	Wildtyp	Komplett	ENST00000381652	NGS	mind. 2%	1,000%	KM	DNA
PHF6	**Tier 1**	**Komplett**	**ENST00000370803**	**NGS**	**mind. 3%**	**1,000%**	**KM**	**DNA**
RUNX1	Wildtyp	Komplett	ENST00000344691	NGS	mind. 3%	1,000%	KM	DNA
SF3B1	Wildtyp	E13-E16	ENST00000335508	NGS	mind. 3%	1,000%	KM	DNA
SRSF2	Wildtyp	E01	ENST00000392485	NGS	mind. 3%	1,000%	KM	DNA
TET2	Wildtyp	Komplett	ENST00000380013	NGS	mind. 3%	1,000%	KM	DNA
TP53	Wildtyp	Komplett	ENST00000269305	NGS	mind. 3%	1,000%	KM	DNA
U2AF1	**Tier 1**	**Komplett**	**ENST00000291552**	**NGS**	**mind. 3%**	**1,000%**	**KM**	**DNA**
ZRSR2	Wildtyp	Komplett	ENST00000307771	NGS	mind. 3%	1,000%	KM	DNA

[1] **Wildtyp/Negativ/Normalexpression:** kein Nachweis von Veränderungen.
Positiv/Überexpression: Nachweis von Veränderungen.
Tier 1: molekulargenetisch pathogene Veränderung. Relevanz für Therapie, Diagnose oder Prognose ist vom Krankheitsbild abhängig.
Tier 2: ein somatischer Ursprung der Veränderung ist wahrscheinlich, die molekulare Pathogenität der Veränderung ist nicht eindeutig zu belegen. Relevanz für Diagnose oder Prognose je nach Krankheitsbild möglich.
Tier 3: Variante unbekannter Signifikanz (VUS); bei Mutationslasten > 30% (siehe Spalte VAF in der Tabelle im Anhang) kann zur Unterscheidung zwischen einer Keimbahnveränderung und einer somatischen Veränderung eine Abklärung aus Normalgewebe (MSH/Nagel) sinnvoll sein. Somatische Veränderungen wären ein Zeichen für Klonalität der Hämatopoiese und als Verlaufsmarker geeignet.
(**Tier 4:** gutartige oder mit hoher Wahrscheinlichkeit gutartige Veränderungen (Polymorphismen), die hier nicht explizit aufgeführt werden.)
[2] Die Mutation c.1934dup im Homopolymerbereich des *ASXL1* Gens weist eine Sensitivität von etwa 5% auf.
[3] MRD für Hotspot-Mutation (p.V617F) mit einer Sensitivität von 0,03% möglich.

Sequenzierte Bereiche mit geringer coverage (< 400 reads)

Gen	Region
PHF6	c.730-2 - c.730-1 (E08, 394x, 1.8%)
ATRX	c.595-2 - c.595-1 (E08, 390x, 2.8%), c.2439 (E09, 333x, 0%), c.5698-2 - c.5715 (E24, 287x, 21.5%), c.6217+2 (E27, 393x, 0.9%), c.6508 (E30, 392x, 0.5%)

Genspezifische Region HGVSc (Betroffenes Exon, minimale Coverage, prozentualer nicht ausreichend abgedeckter Anteil des betroffenen Exons)

Diagnose ?

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- Trilineäre Dysplasie +++
- Schießscheibenzellen im peripheren Blut
- Red cell distribution width +++
- Normale Eisenhomöostase
- Erythroide Hyperplasie
- Karyotyp: 46, XY

$\sum$: acquired alpha thalassemia MDS (AT-MDS)

Immunphänotypisierung bei MDS

(C) Co-criteria

(for patients fulfilling „A“ but not „B“, and otherwise show typical clinical features, e.g. macrocytic transfusion-dependent anemia)

Abnormal phenotype of bone marrow cells clearly indicative of a monoclonal population of erythroid or/and myeloid cells, determined by flow cytometry

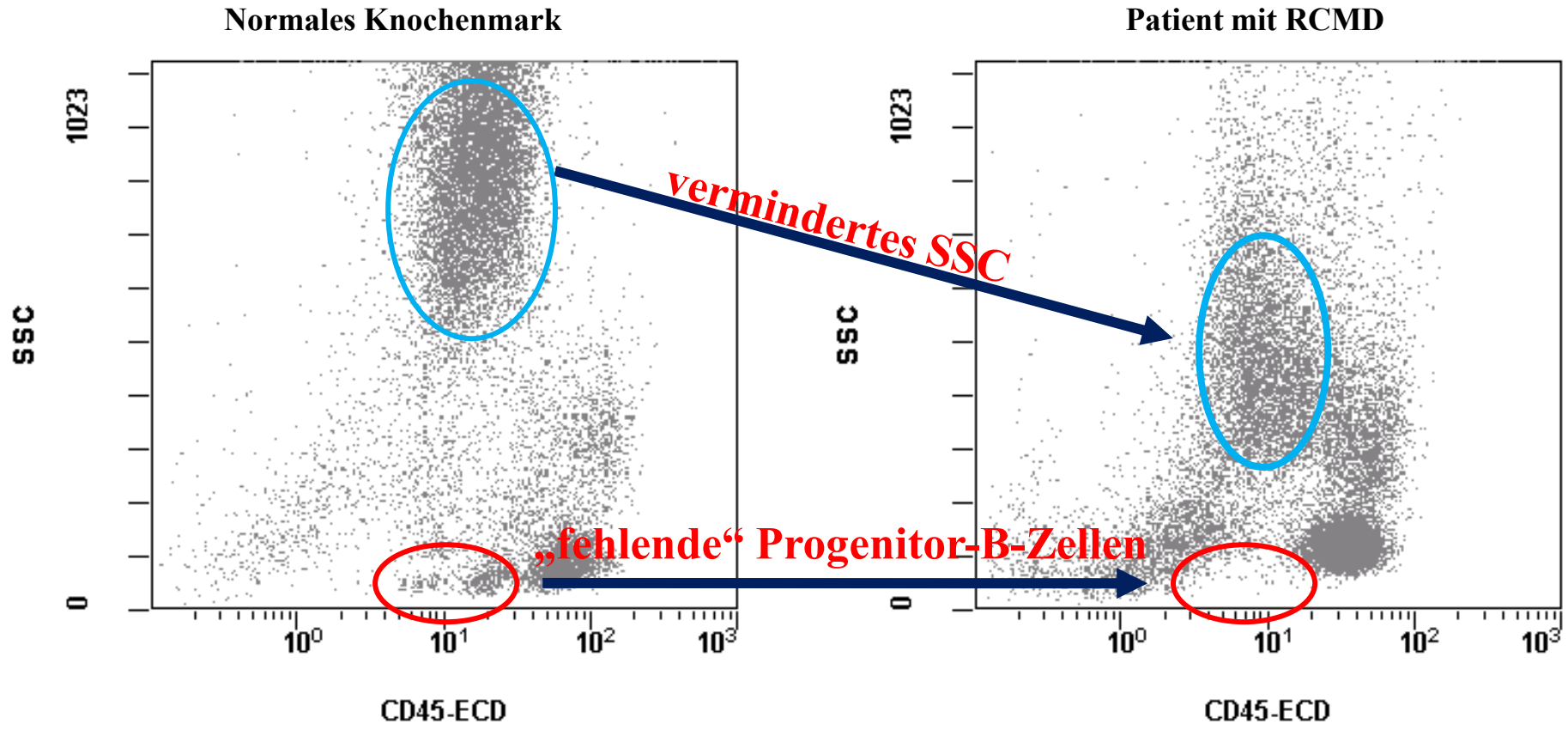
Clear molecular signs of a monoclonal cell population in HUMARA assay, gene chip profiling, or point mutation analysis (e.g. *RAS* mutations)

Markedly and persistently reduced colony-formation (±cluster formation) of bone marrow or/and circulating progenitor cells (CFU-assay)

Valent P, Leuk Res 2007, 31:727-736

Immunphänotypisierung bei MDS

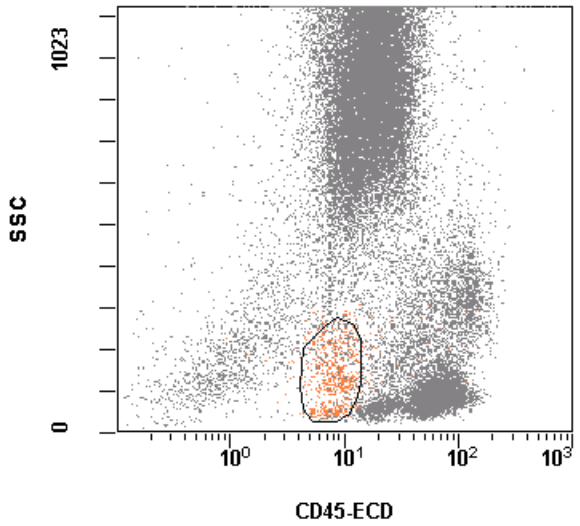
Marien Hospital Düsseldorf VKKD



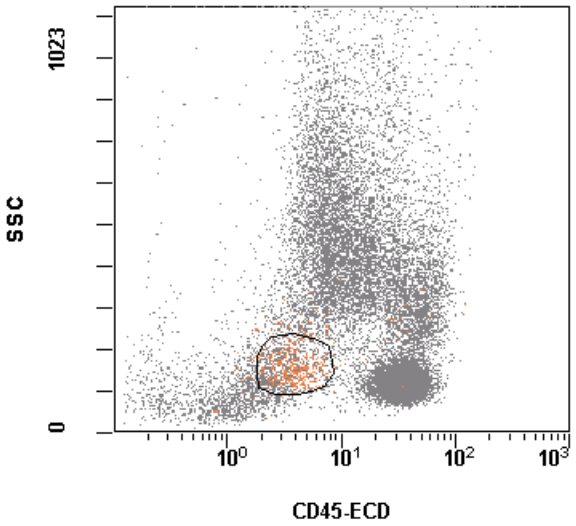
M. Heinsch, Duisburg

„Pathologisch differenzierte Blasten“

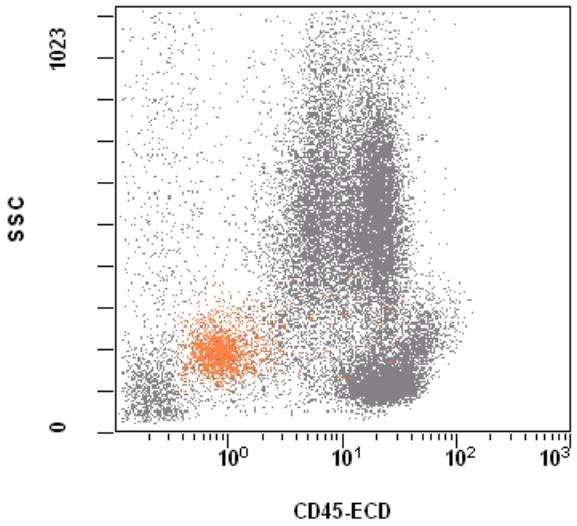
Normales Knochenmark



RCMD



RAEB-I



M. Heinsch, Duisburg

Immunphänotypisierung bei MDS

Progenitor-AG: CD34, HLA-DR, CD38, CD10,CD117, TDT,
Aktivierungs-AG: CD90,CD133, CD135, CD45, CD71, CD9, „7.1“

Myeloische-AG: CD13, CD14, CD15, CD33, CD41, CD61, CD64, CD65, CD66b, CD235a, MPO, LF

Lymphatische-AG: CD2, CD3, CD4, CD5, CD7, CD16, CD19, CD22, CD56, cCD79a,

Adhäsions-AG: CD11b, CD36, CD123

Zytogenetik in der MDS-Diagnostik

Risikoklassen (n; %)

Very good (81; 2.9)	Good (1,809; 65.7)	Intermediate (529; 19.2)	Poor (148;5.4)	Very poor (187; 6.8)
Single del(11q) –Y	Normal Single del(5q) del(12p) del(20q) Double Double incl. del(5q)	Single Del(7q) +8 +19 +21 iso(17q) Any others Double Any other	Single Inv(3)/t(3q)/ del(3q) –7 Double Incl. –7/del(7q) Complex 3 abnorm.	Complex >3 abnorm.

Abnorm. = abnormalities

Schanz J, et al. J Clin Oncol 2012

Zytogenetische Risikoklassen der MDS

Multizenterregister von 2,754 patients

Medianes Überleben der fünf zytogenetischen Subklassen

1. Schanz J, et al. J Clin Oncol 2012

MDS: Molekulargenetik

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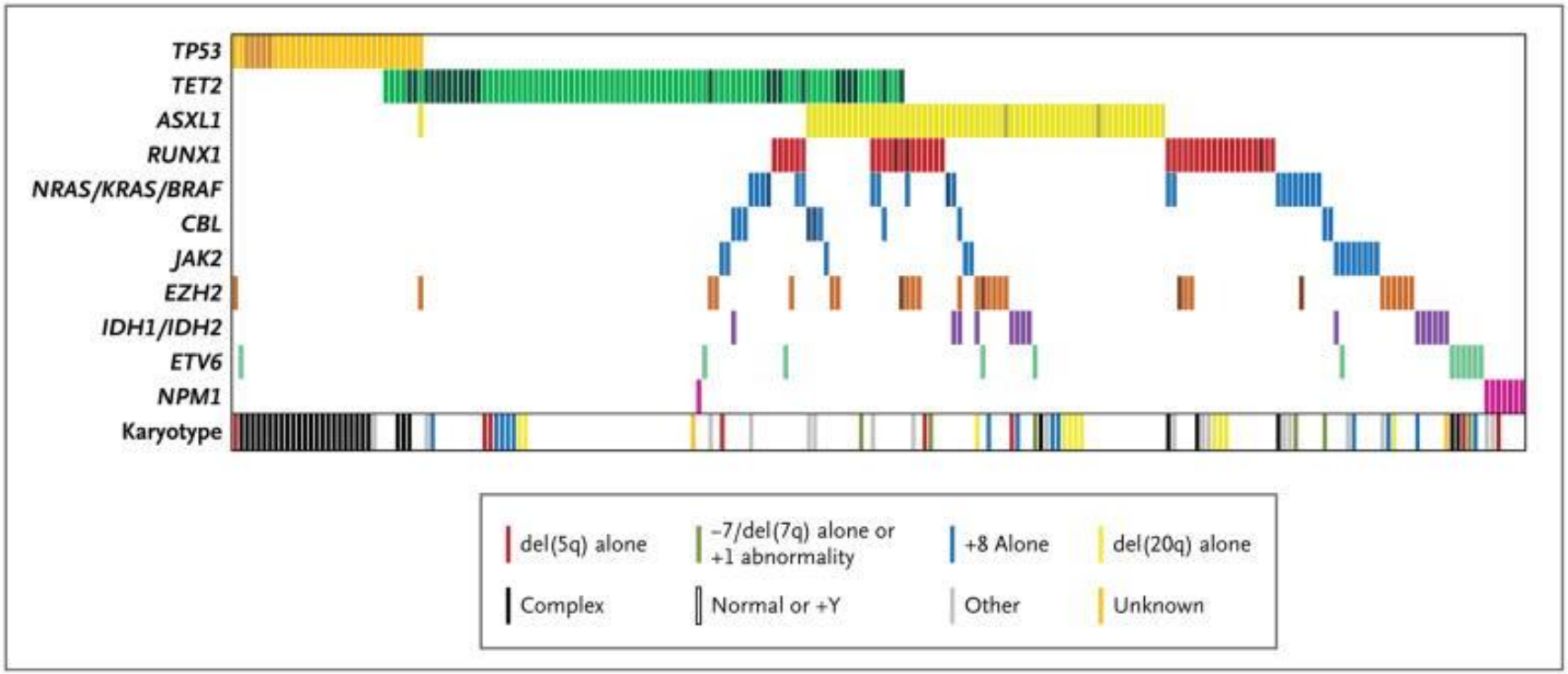
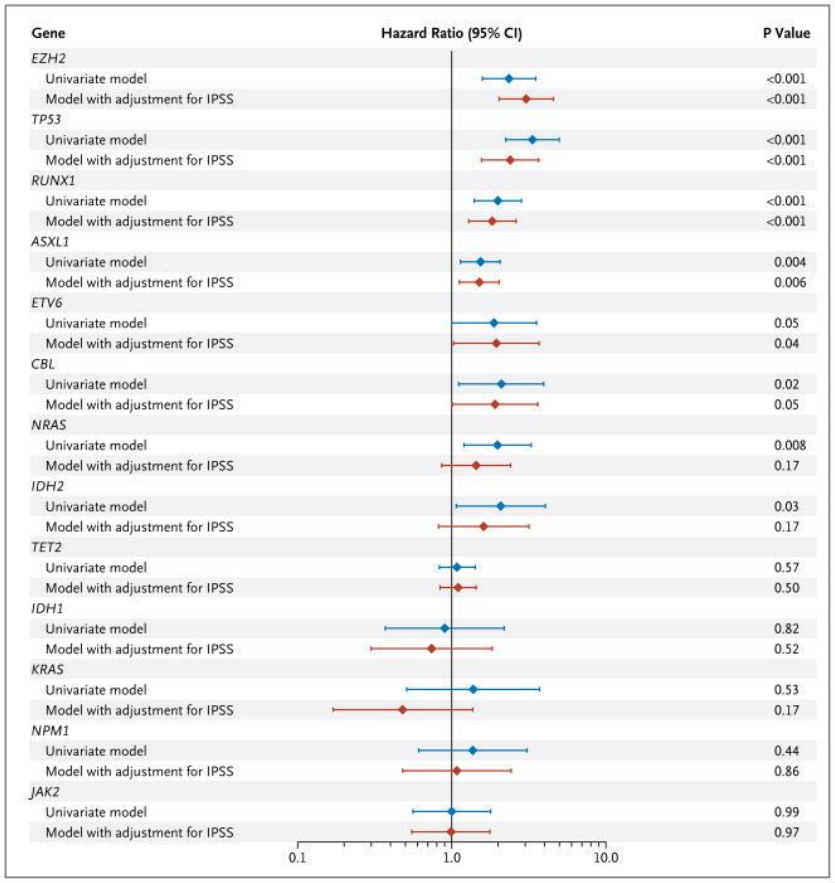
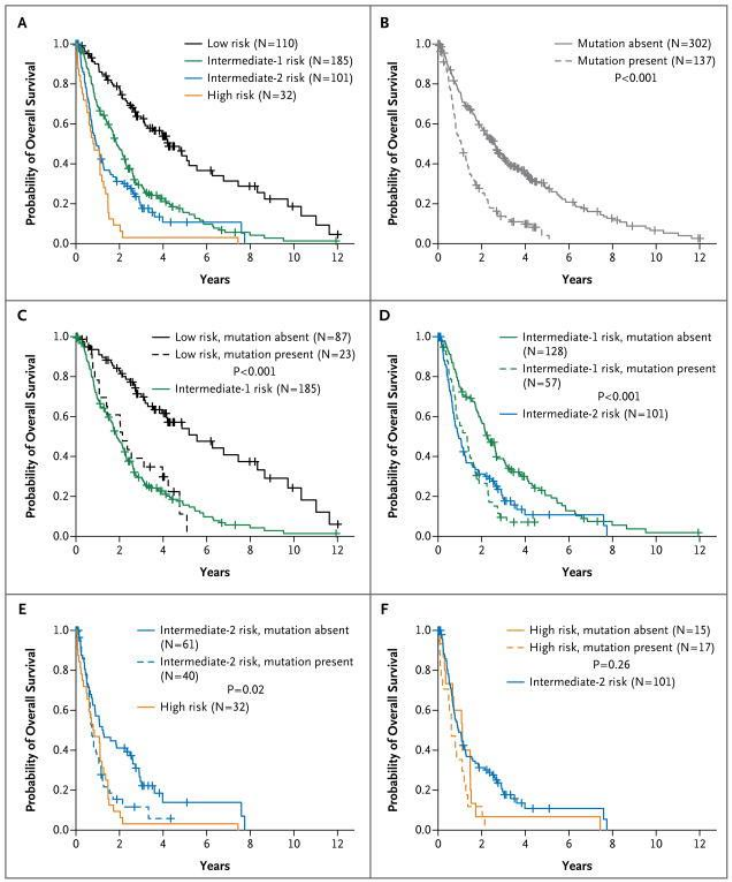


Untersuchung von 439 Patienten mit MDS (Knochenmark)
18 relevante Gene identifiziert

Bejar et al., 2011

MDS: Molekulargenetik



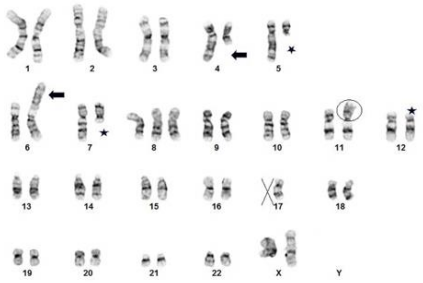


Mutationen in TP53, EZH2, ETV6, RUNX1 und ASXL1 sind mit ungünstiger Prognose assoziiert und unabhängig von etablierten Risikofaktoren

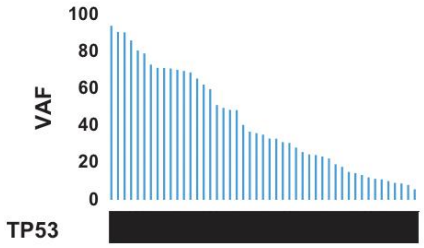
Bejar et al., 2011

Clinical implications of *TP53* mutations in MDS

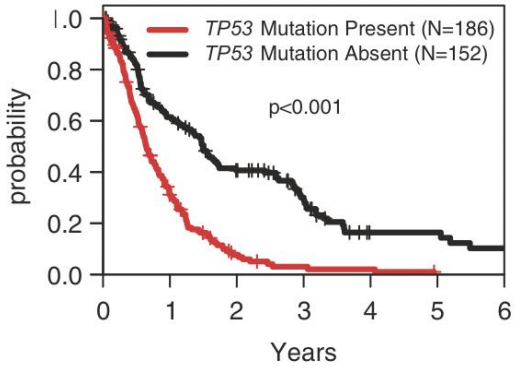
Complex karyotype



LOH at 17p



Adverse outcomes

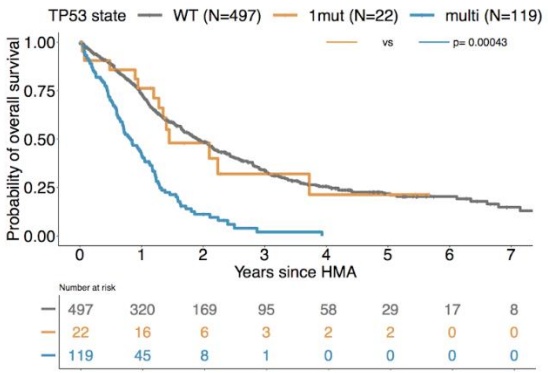


Miesner et al, 2010; Salman et al, 2016; Haase et al, 2019

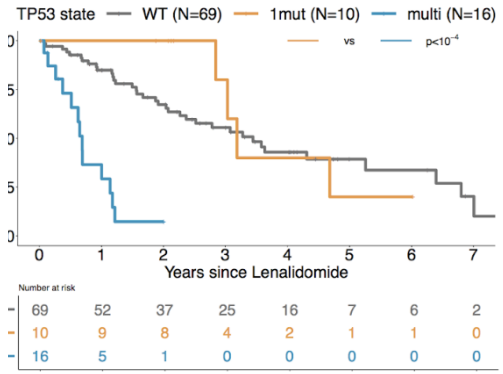
TP53: ALLELHÄUFIGKEIT

Marien Hospital Düsseldorf VKKD

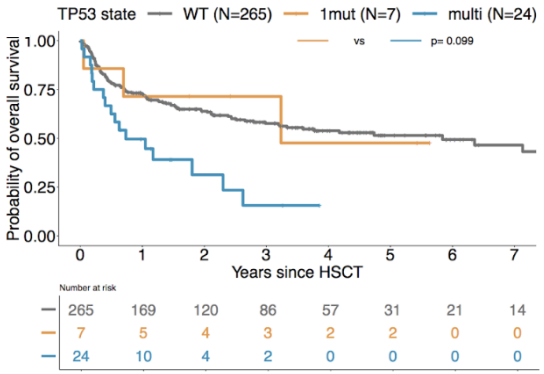
Hypomethylating agents



Lenalidomide



HSCT



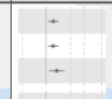
Consideration of *TP53* allelic state in correlative studies of treatment response

E. Bernard, ASH 2019

The IPSS-M model

Model fit with a robust Cox multivariable regression adjusted for confounder variables

Category	Variable	Multivariable model: hazard ratio[#] (95% CI)	Weight w	Scaling x^{mean}
confounder	$^{1}/_{10}$ **Age**, in years	1.23 (1.05 - 1.43)	N/A	N/A
	Sex:Male	1.22 (1.06 - 1.41)	N/A	N/A
	Type:Secondary/Therapy-related	1.36 (1.10 - 1.68)	N/A	N/A
clinical	% **Bone Marrow Blasts**, in %	1.42 (1.30 - 1.55)	0.352	0.922
	$^{1}/_{100}$ min(**Platelets**,250), in x10^9/L	0.80 (0.72 - 0.89)	-0.222	1.41
	Hemoglobin, in g/dL	0.84 (0.81 - 0.88)	-0.171	9.87
cytogenetics	**IPSS-R category vector**[&]	1.33 (1.21 - 1.47)	0.287	1.390
gene main effects	***TP53***^{multi}	3.27 (2.38 - 4.48)	1.18	0.0710
17 variables, 16 genes	***MLL***^{PTD}	2.22 (1.49 - 3.32)	0.798	0.0247
	FLT3$^{ITD+TKD}$	2.22 (1.11 - 4.45)	0.798	0.0108
	SF3B1^{Sq}	1.66 (1.03 - 2.66)	0.504	0.0166
	NPM1	1.54 (0.78 - 3.02)	0.430	0.0112
	RUNX1	1.53 (1.23 - 1.89)	0.423	0.126
	NRAS	1.52 (1.05 - 2.20)	0.417	0.0362
	ETV6	1.48 (0.98 - 2.23)	0.391	0.0216
	IDH2	1.46 (1.05 - 2.02)	0.379	0.0429
	CBL	1.34 (0.99 - 1.82)	0.295	0.0473
	EZH2	1.31 (0.98 - 1.75)	0.270	0.0588
	U2AF1	1.28 (1.01 - 1.61)	0.247	0.0866
	SRSF2	1.27 (1.03 - 1.56)	0.239	0.158
	DNMT3A	1.25 (1.02 - 1.53)	0.221	0.161
	ASXL1	1.24 (1.02 - 1.51)	0.213	0.252
	KRAS	1.22 (0.84 - 1.77)	0.202	0.0271
	SF3B1^{wt}	0.92 (0.74 - 1.16)	-0.0794	0.186
gene residuals[$]	min(**Nres**,2)	1.26 (1.12 - 1.42)	0.231	0.388
1 variable, 15 genes	Possible values are 0,1 or 2			



^residual genes*: BCOR, BCORL1, CEBPA, ETNK1, GATA2, GNB1, IDH1, NF1, PHF6, PPM1D, PRPF8, PTPN11, SETBP1, STAG2, WT1*

Continuous clinical parameters
Marrow blasts, platelets, hemoglobin

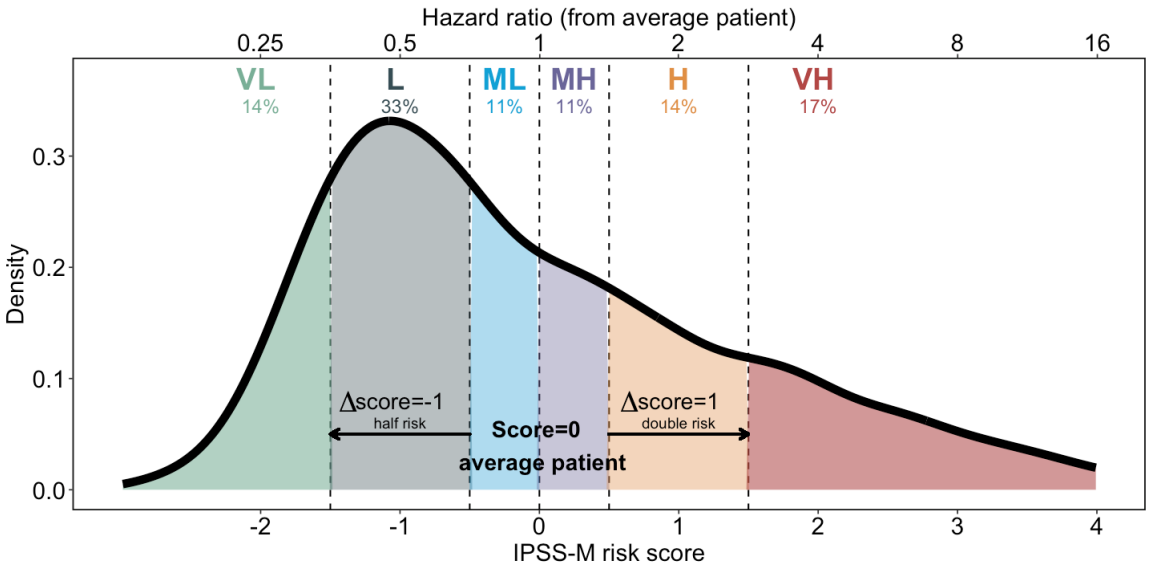
IPSS-R cytogenetic categories

17 genetic variables from 16 main effect genes
Individual weights attributed to each variable

1 genetic variable from 15 residual genes^
Number of mutated genes (0, 1 or 2)

The IPSS-M risk categories

A six-category risk schema

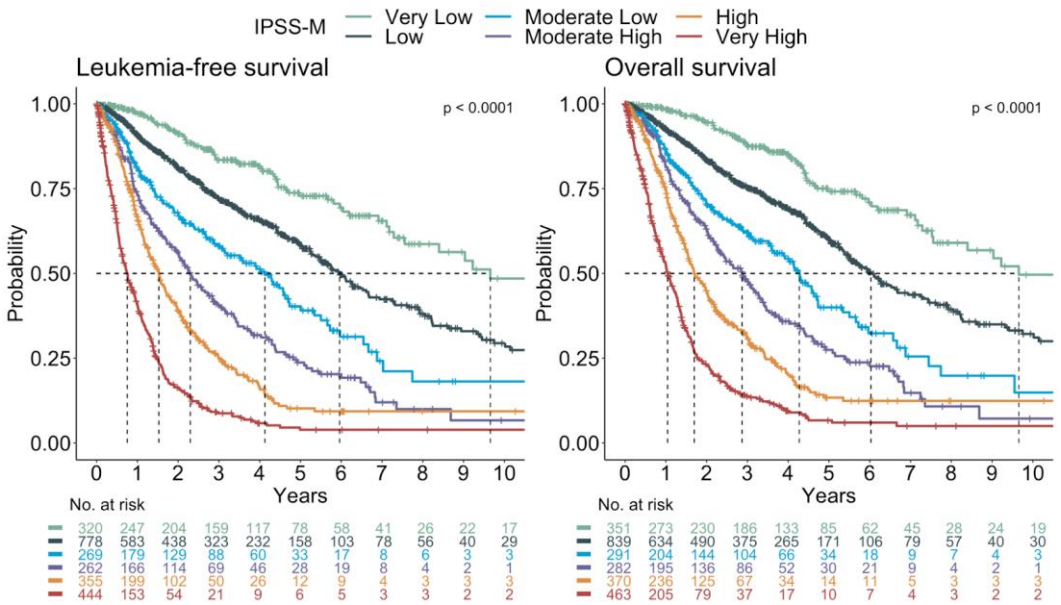


Very Low | Low | Moderate Low | Moderate High | High | Very High

The IPSS-M risk categories

A six-category risk schema

IPSS-M	Very Low VL	Low L	Moderate Low ML	Moderate High MH	High H	Very High VH
Patients, % (n=2,701)	14% (381)	33% (889)	11% (302)	11% (291)	14% (379)	17% (469)
Risk score	≤ -1.5	> -1.5 to -0.5	> -0.5 to 0	> 0 to 0.5	> 0.5 to 1.5	>1.5
Hazard ratio[#] (95% CI)	0.51 (0.39 - 0.67)	1.0 reference	1.5 (1.2 - 1.8)	2.5 (2.1 - 3.1)	3.7 (3.1 - 4.4)	7.1 (6.0 - 8.3)
Median LFS, yrs 25-75% LFS range, yrs	9.7 5.0 - 17.4	5.9 2.6 - 12.0	4.5 1.6 - 6.9	2.3 0.91 - 4.7	1.5 0.80 - 2.8	0.76 0.33 - 1.5
Median OS, yrs 25-75% OS range, yrs	10.6 5.1 - 17.4	6.0 3.0 - 12.8	4.6 2.0 - 7.4	2.8 1.2 - 5.5	1.7 1.0 - 3.4	1.0 0.5 - 1.8
AML-t by 1 yr, % 2 yrs 4 yrs	0.0 1.2 2.8	1.7 3.4 5.1	4.9 8.8 11.4	9.5 14.0 18.9	14.3 21.2 29.2	28.2 38.6 42.8
Death w/o AML by 1 yr, % 2 yrs 4 yrs	2.2 7.0 15.9	8.5 16.2 29.5	12.0 19.8 33.6	18.0 31.1 51.1	19.3 39.8 54.2	30.6 45.6 51.3



Very Low | Low | Moderate Low | Moderate High | High | Very High

Prognostic separation of the IPSS-M risk categories

Fallbeispiel 2: Zytogenetik

Marien Hospital Düsseldorf VKKD

Sehr geehrter Herr Professor Giagounidis,

bei Ihrer Patientin wurde eine Chromosomenanalyse durchgeführt.

Karyotyp (nach ISCN):

46,XX[20]

Kulturansätze: R24, R24+Thymidin, R24+Thymidin+Zytokine, R24+Thymidin+Zytokine HMF 24

Metaphasen karyotypisiert: 20
Bandendarstellung: G-Banden
maximale Bandenzahl (ca.):

Metaphasen nur ausgezählt: 0
Färbetechnik: GAG
normaldiploide Metaphasen: 250
aberrante Metaphasen: 0

Fallbeispiel 2: Molekulargenetik

Marien Hospital Düsseldorf VKKD

Gen	Bewertung[1]	Analysierter Bereich	Ensembl transcript ID	Methode	Sensitivität		Material	
					Screening	MRD		
ASXL1[2]	Wildtyp	E13	ENST00000375687	NGS	mind. 3%	1,000%	KM	DNA
BCOR	Wildtyp	Komplett	ENST00000378444	NGS	mind. 3%	1,000%	KM	DNA
BCORL1	Wildtyp	Komplett	ENST00000540052	NGS	mind. 3%	1,000%	KM	DNA
BRAF[3]	Wildtyp	komplett		NGS	mind. 3%	1,000%	KM	DNA
CALR	Wildtyp	E09	ENST00000316448	NGS	mind. 2%	1,000%	KM	DNA
CBL	Wildtyp	Komplett	ENST00000264033	NGS	mind. 3%	1,000%	KM	DNA
CEBPA	Wildtyp	Komplett	ENST00000498907	NGS	mind. 3%	1,000%	KM	DNA
CSF3R	Wildtyp	E14-E17	ENST00000373106	NGS	mind. 3%	1,000%	KM	DNA
CUX1	Wildtyp	Komplett	ENST00000360264	NGS	mind. 3%	1,000%	KM	DNA
DDX41	Wildtyp	Komplett	ENST00000507955	NGS	mind. 3%	1,000%	KM	DNA
DNMT3A	Wildtyp	Komplett	ENST00000264709	NGS	mind. 3%	1,000%	KM	DNA
ETNK1	Wildtyp	E03	ENST00000266517	NGS	mind. 3%	1,000%	KM	DNA
ETV6	Wildtyp	Komplett	ENST00000396373	NGS	mind. 3%	1,000%	KM	DNA
EZH2	Wildtyp	Komplett	ENST00000320356	NGS	mind. 3%	1,000%	KM	DNA
FLT3	Wildtyp	E20	ENST00000241453	NGS	mind. 3%	1,000%	KM	DNA
FLT3-ITD	Wildtyp	Duplikation	ENST00000241453	NGS	mind. 3%	1,000%	KM	DNA
GATA2	Wildtyp	Komplett	ENST00000341105	NGS	mind. 3%	1,000%	KM	DNA
GNB1	Wildtyp	Komplett	ENST00000378609	NGS	mind. 3%	1,000%	KM	DNA
IDH1	Wildtyp	E04	ENST00000345146	NGS	mind. 3%	1,000%	KM	DNA
IDH2	Wildtyp	E04	ENST00000330062	NGS	mind. 3%	1,000%	KM	DNA
JAK2[4]	Wildtyp	Komplett	ENST00000381652	NGS	mind. 2%	1,000%	KM	DNA
KIT[5]	Wildtyp	Komplett	ENST00000288135	NGS	mind. 3%	1,000%	KM	DNA
KRAS	Wildtyp	E02, E03	ENST00000256078	NGS	mind. 3%	1,000%	KM	DNA
MPL	Wildtyp	Komplett	ENST00000372470	NGS	mind. 2%	1,000%	KM	DNA
MYD88[6]	Wildtyp	Komplett	ENST00000396334	NGS	mind. 3%	1,000%	KM	DNA
NF1	Wildtyp	Komplett	ENST00000358273	NGS	mind. 3%	1,000%	KM	DNA
NOTCH1	Wildtyp	E26-E28, E34	ENST00000277541	NGS	mind. 3%	1,000%	KM	DNA
NPM1	Wildtyp	E11	ENST00000296930	NGS	mind. 3%	0,010%	KM	DNA
NRAS	Wildtyp	E02, E03	ENST00000369535	NGS	mind. 3%	1,000%	KM	DNA
PHF6	Wildtyp	Komplett	ENST00000370803	NGS	mind. 3%	1,000%	KM	DNA
PIGA	Wildtyp	Komplett	ENST00000333590	NGS	mind. 3%	1,000%	KM	DNA
PPM1D	Wildtyp	Komplett	ENST00000305921	NGS	mind. 3%	1,000%	KM	DNA
PRPF8	Wildtyp	Komplett	ENST00000572621	NGS	mind. 3%	1,000%	KM	DNA
PTEN	Wildtyp	E07-E08	ENST00000371953	NGS	mind. 3%	1,000%	KM	DNA
PTPN11	Wildtyp	Komplett	ENST00000351677	NGS	mind. 3%	1,000%	KM	DNA
RAD21	Wildtyp	Komplett	ENST00000297338	NGS	mind. 3%	1,000%	KM	DNA
RUNX1	Wildtyp	Komplett	ENST00000344691	NGS	mind. 3%	1,000%	KM	DNA

Fallbeispiel 2: Molekulargenetik 2

Marien Hospital Düsseldorf VKKD

SETBP1	Wildtyp	E04	ENST00000282030	NGS	mind. 3%	1,000%	KM	DNA
SF1	Wildtyp	Komplett	ENST00000377390	NGS	mind. 3%	1,000%	KM	DNA
SF3A1	Wildtyp	Komplett	ENST00000215793	NGS	mind. 3%	1,000%	KM	DNA
SF3B1	Wildtyp	E13-E16	ENST00000335508	NGS	mind. 3%	1,000%	KM	DNA
SMC1A	Wildtyp	Komplett	ENST00000322213	NGS	mind. 3%	1,000%	KM	DNA
SMC3	Wildtyp	Komplett	ENST00000361804	NGS	mind. 3%	1,000%	KM	DNA
SRSF2	Wildtyp	E01	ENST00000392485	NGS	mind. 3%	1,000%	KM	DNA
STAG2	Wildtyp	Komplett	ENST00000218089	NGS	mind. 3%	1,000%	KM	DNA
TET2	Wildtyp	Komplett	ENST00000380013	NGS	mind. 3%	1,000%	KM	DNA
TP53	Wildtyp	Komplett	ENST00000269305	NGS	mind. 3%	1,000%	KM	DNA
U2AF1	Wildtyp	Komplett	ENST00000291552	NGS	mind. 3%	1,000%	KM	DNA
U2AF2	Wildtyp	E02, E06	ENST00000308924	NGS	mind. 3%	1,000%	KM	DNA
UBA1	Wildtyp	Komplett	ENST00000335972	NGS	mind. 3%	1,000%	KM	DNA
WT1	Wildtyp	E07, E09	ENST00000332351	NGS	mind. 3%	1,000%	KM	DNA
ZRSR2	Wildtyp	Komplett	ENST00000307771	NGS	mind. 3%	1,000%	KM	DNA

Molekulargenetik 3

Sehr geehrter Herr Kollege Giagounidis,

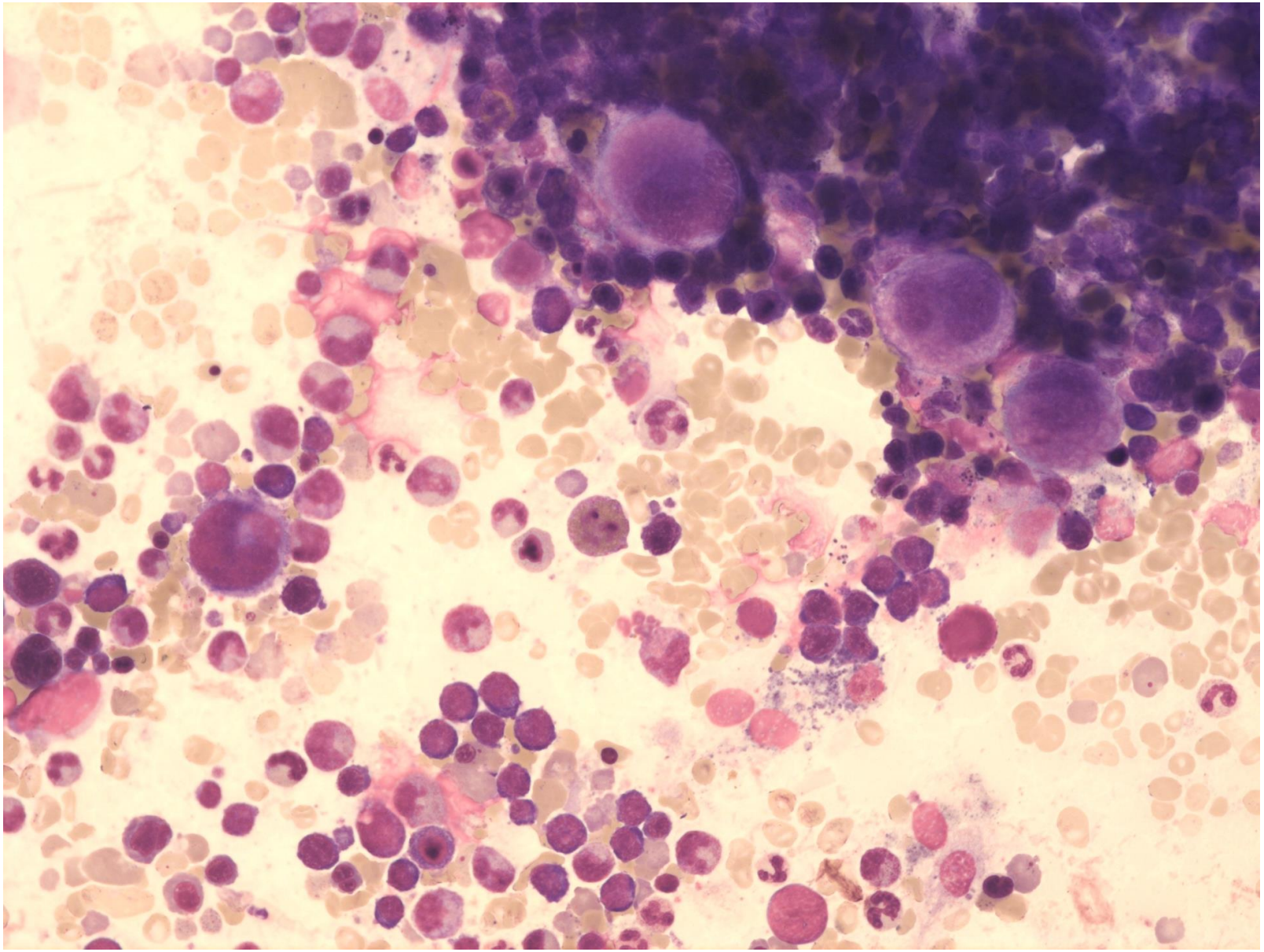
wir berichten über die Untersuchung der o.g. Probe(n).

Analysierte Gene: *CDAN1*, *CDIN1*, *KIF23*, *KLF1*, *RACGAP1* und *SEC23B*

Keine Veränderungen nachweisbar

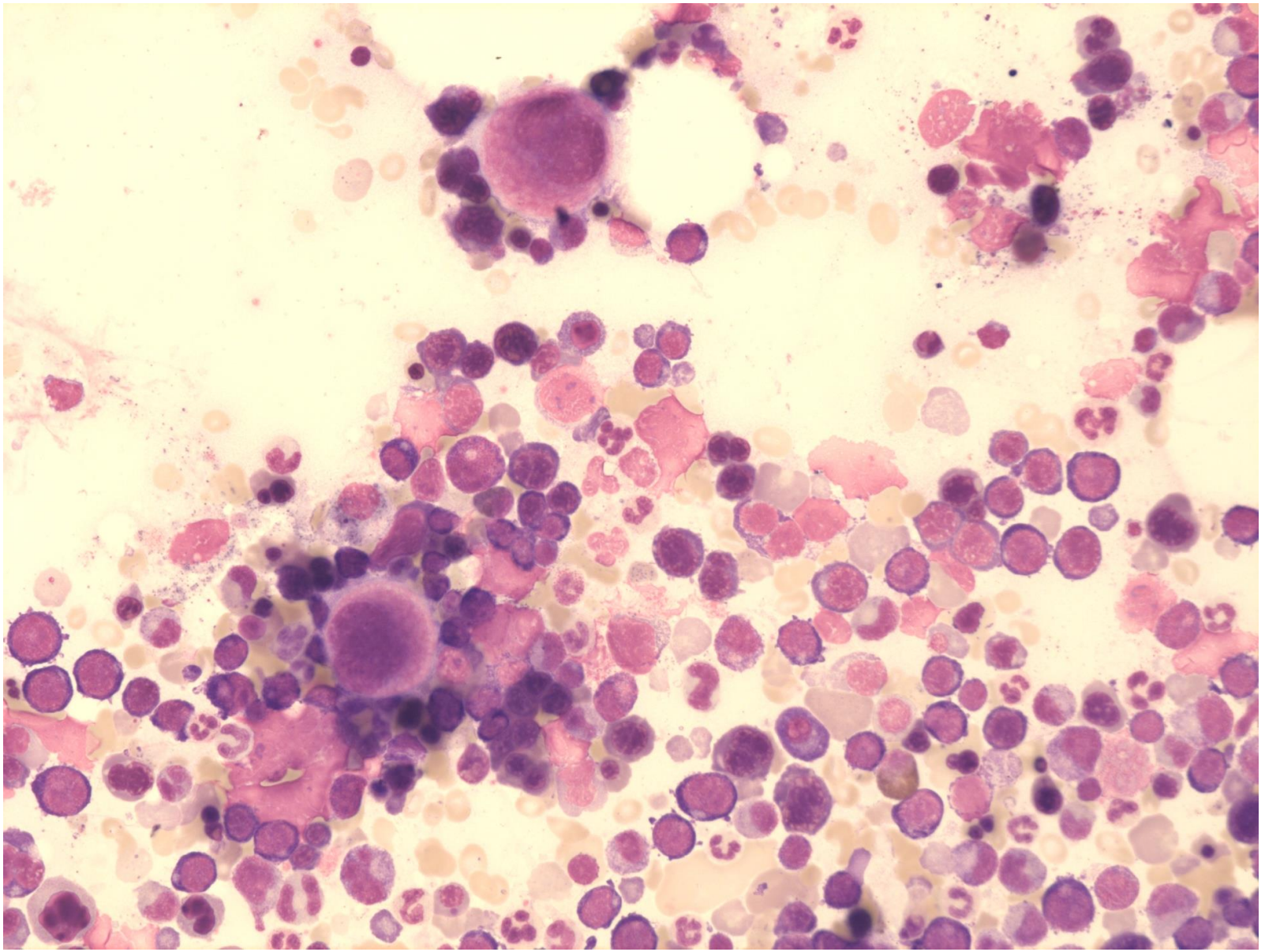
Fallbeispiel 2: Morphologie

Marien Hospital Düsseldorf VKKD



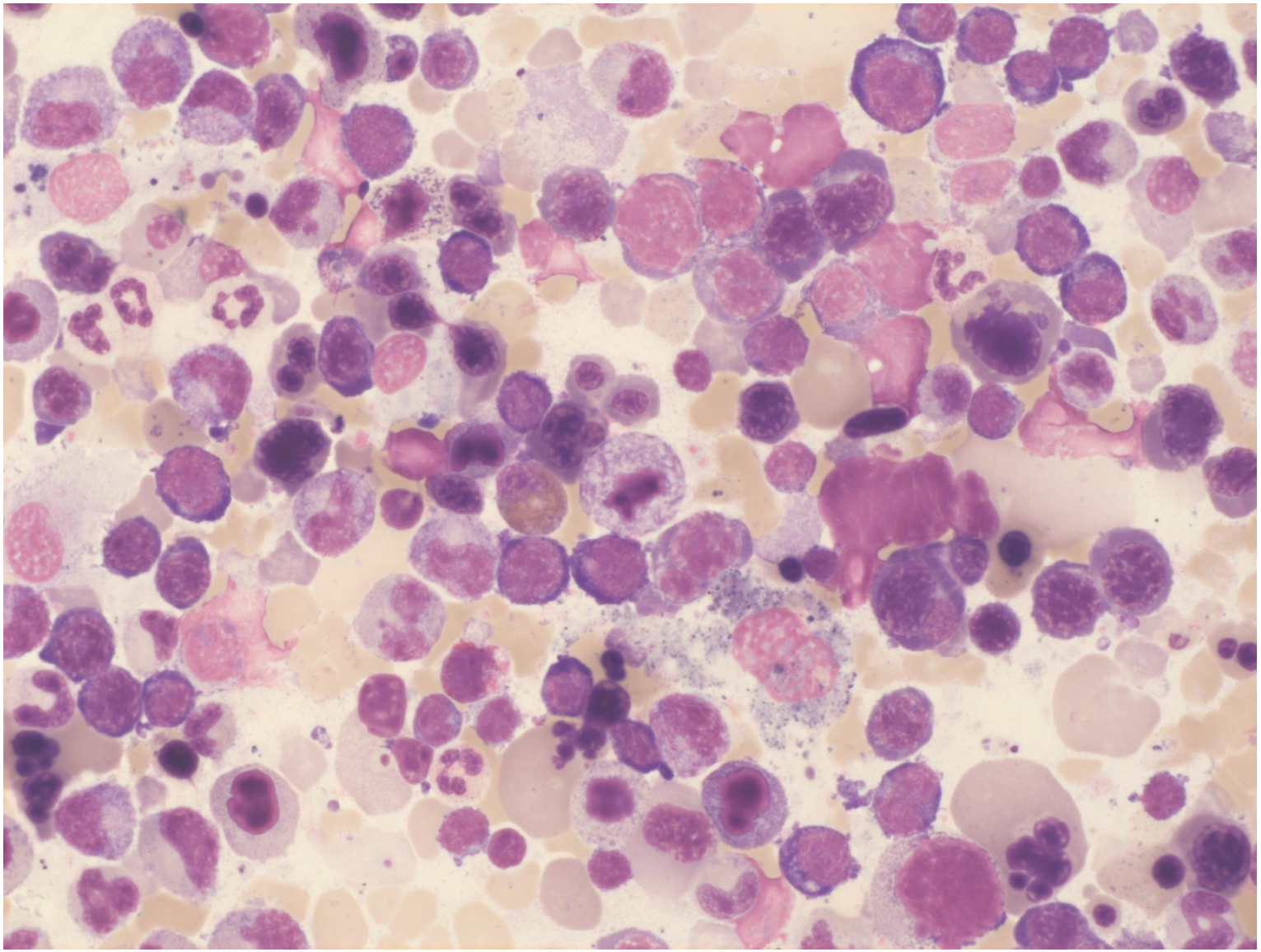
Fallbeispiel 2: Morphologie

Marien Hospital Düsseldorf VKKD



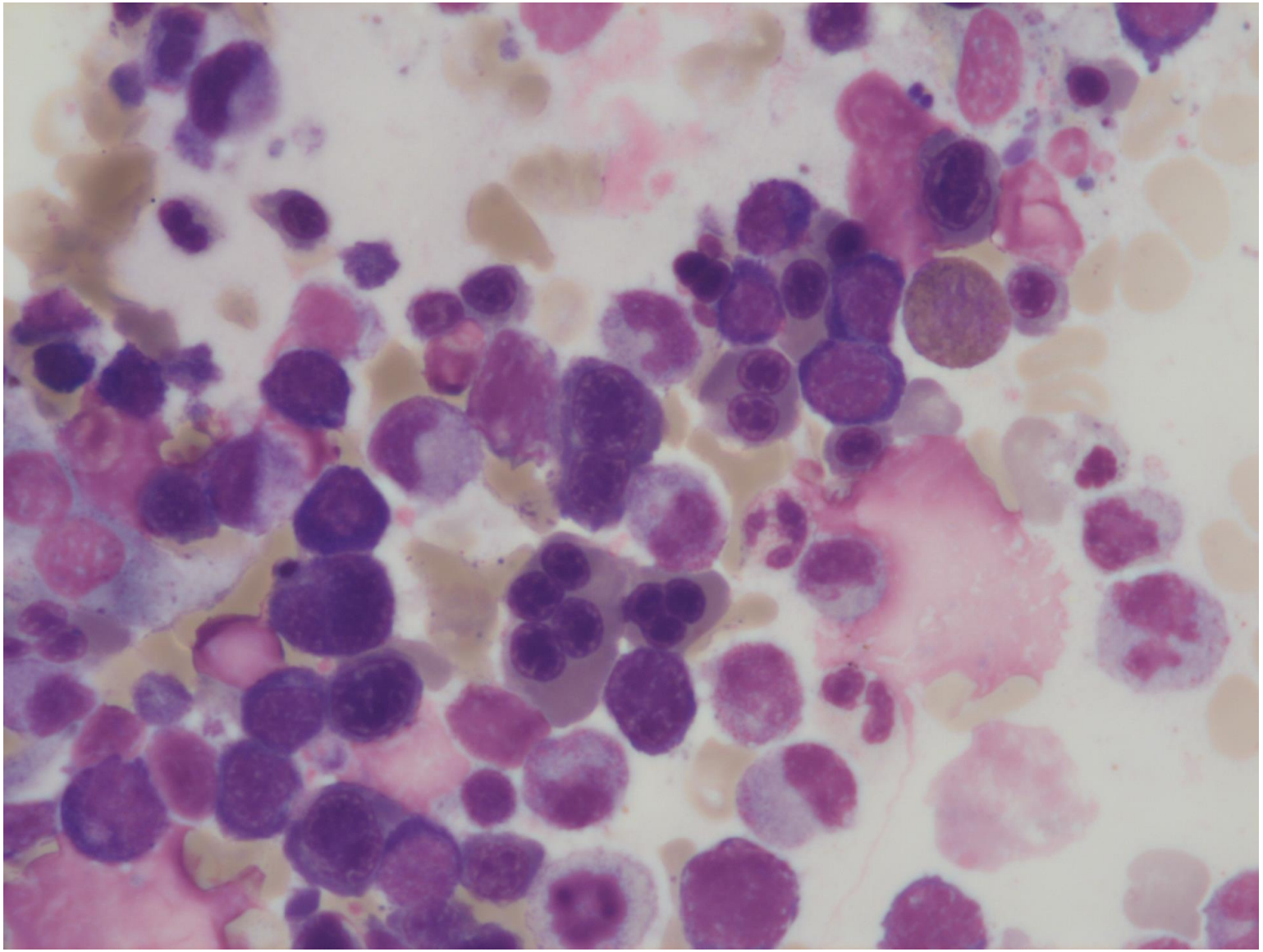
Fallbeispiel 2: Morphologie

Marien Hospital Düsseldorf VKKD



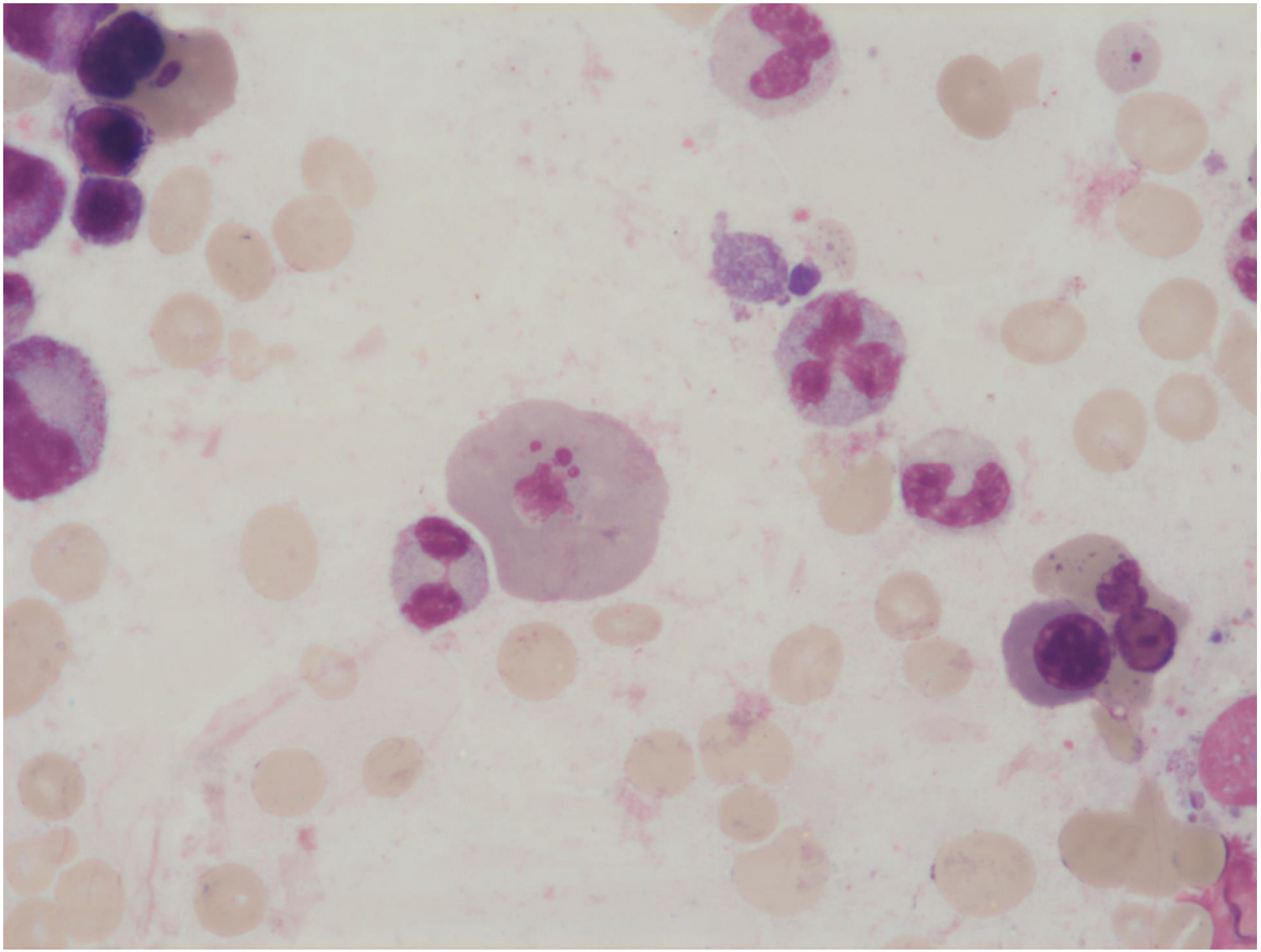
Fallbeispiel 2: Morphologie

Marien Hospital Düsseldorf VKKD



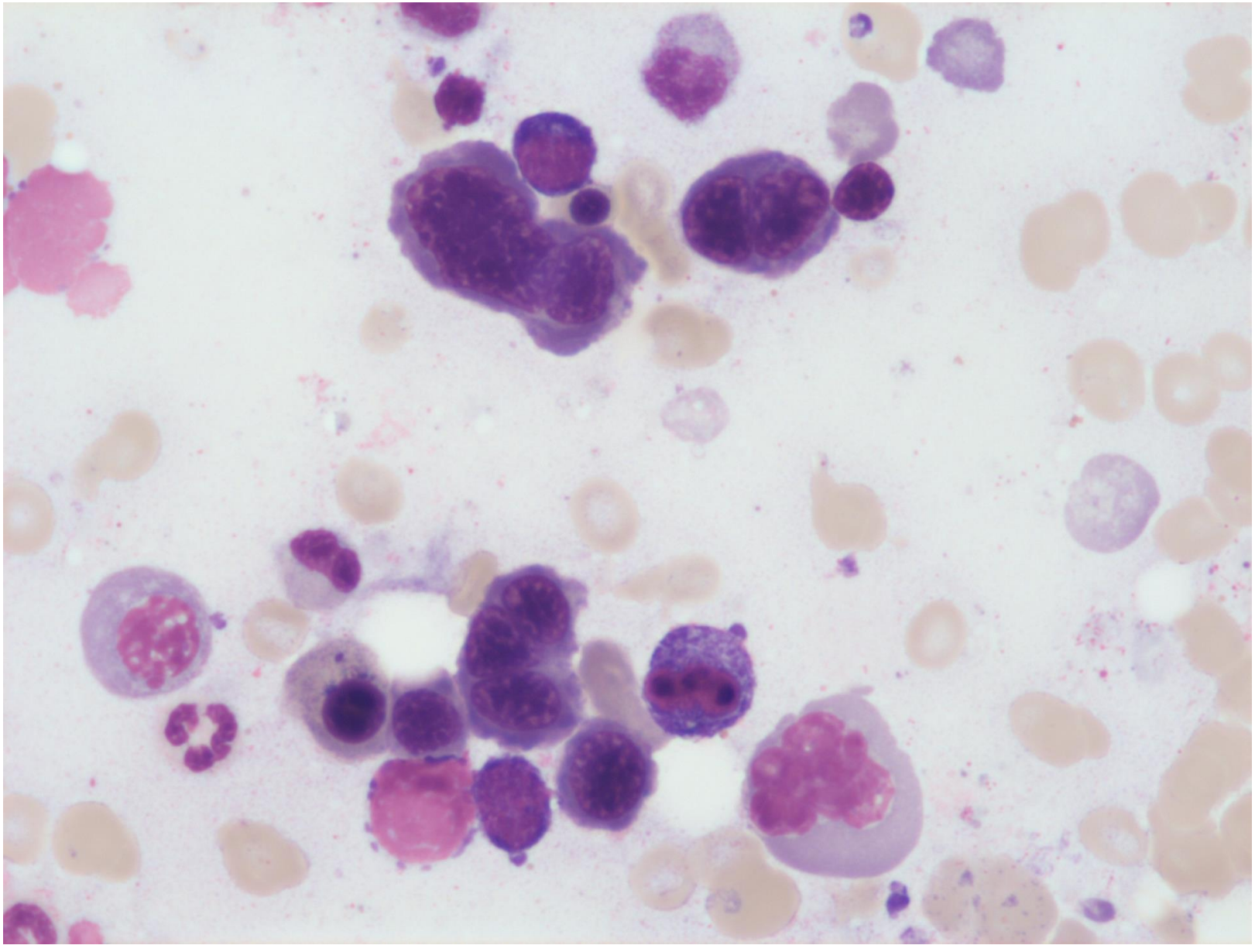
Fallbeispiel 2: Morphologie

Marien Hospital Düsseldorf VKKD



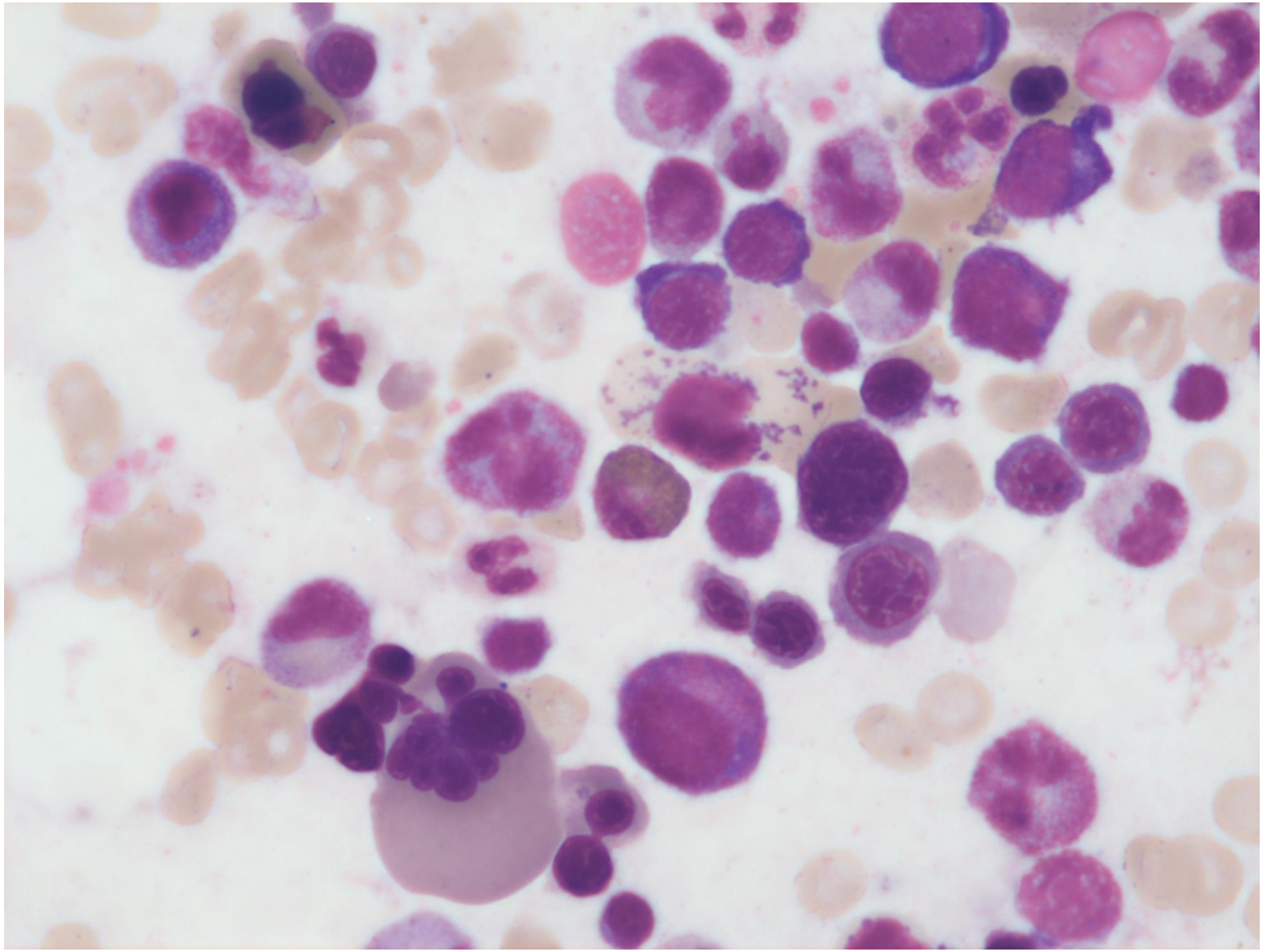
Fallbeispiel 2: Morphologie

Marien Hospital Düsseldorf VKKD



Fallbeispiel 2: Morphologie

Marien Hospital Düsseldorf VKKD



Diagnose?

Marien Hospital Düsseldorf VKKD

Congenitale dyserythropoetische Anämie Typ III

- bisherige molekulare Aberration noch nicht gefunden

- work in progress….