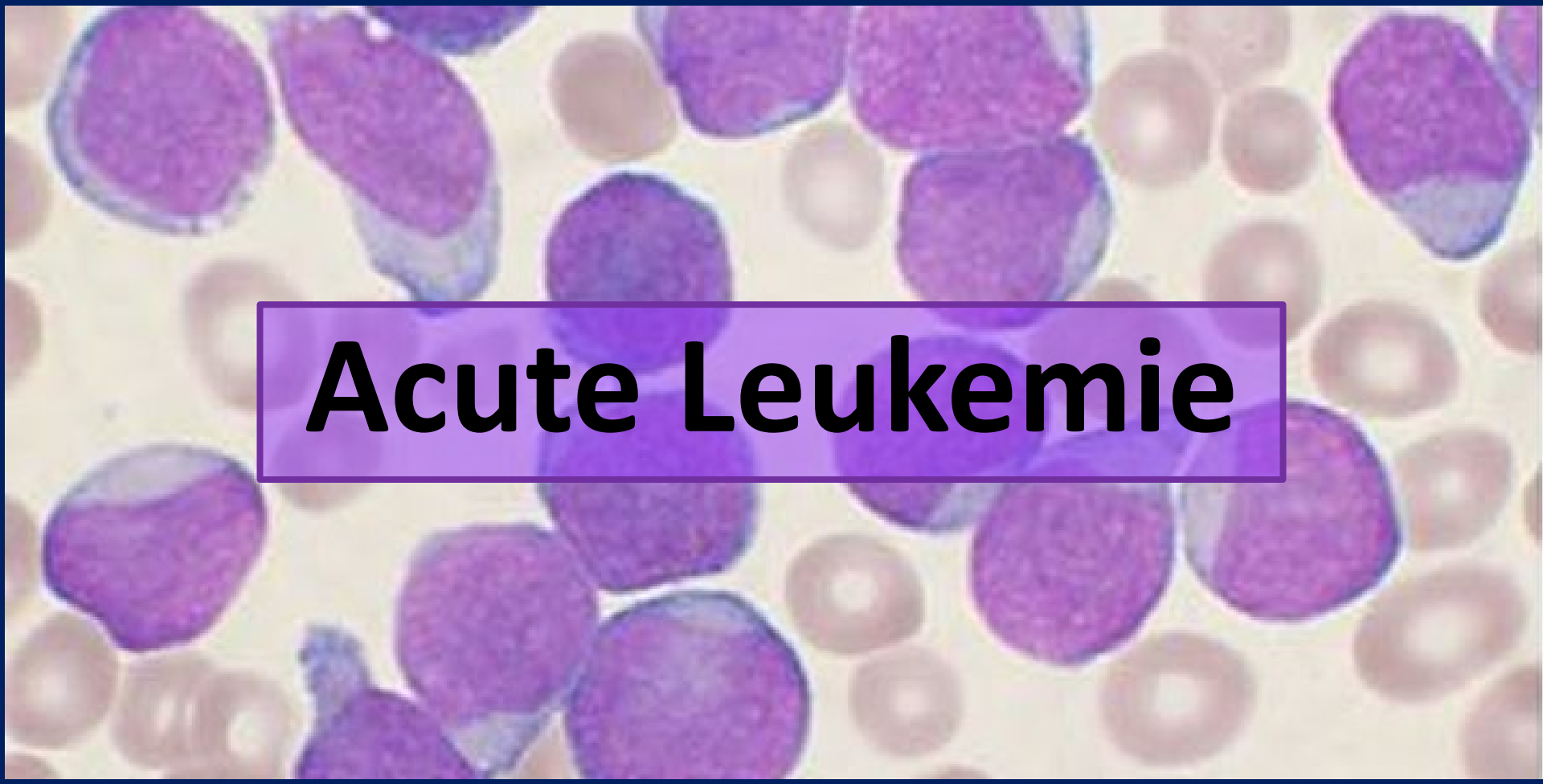


Acute Leukemie

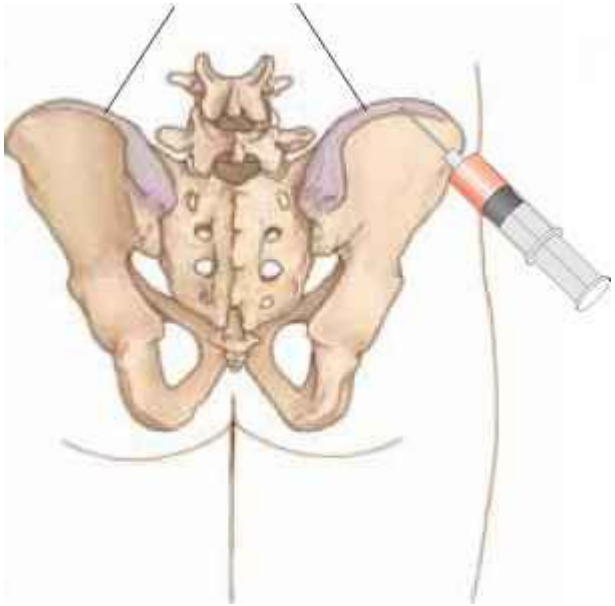
Goda Choi / C.W.Choi@umcg.nl

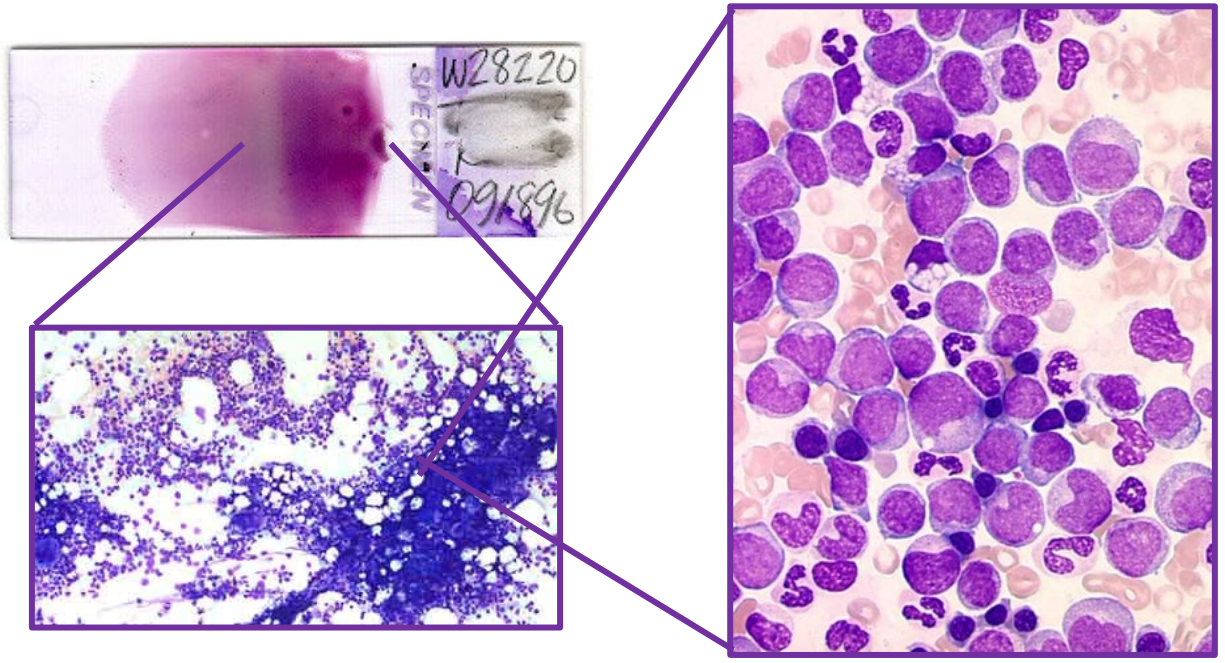
Leerdoelen dag 3

1. Update nieuwe criteria bij de diagnosen (MDS en) acute leukemie.
2. Identificeren van blastaire kenmerken passende bij APL (AML-M3).
3. Moleculaire diagnostiek met de microscoop!

Stelling (niet te verwerpen)

Cytologie / morfologie is de hoeksteen van de diagnostiek van acute leukemie.





Gebruik morfologie voor diagnose en classificatie

umcg

Tellen van 500 cellen

- % blasten versus alle kernhoudende cellen

cytochemie

- myeloperoxydase (MPO) of Sudan black B kleuring (SBB)
- non-specifieke esterase (NSE) reactie

myelodysplasie

- % binnen cellijn
- multi-lineage / uni-lineage

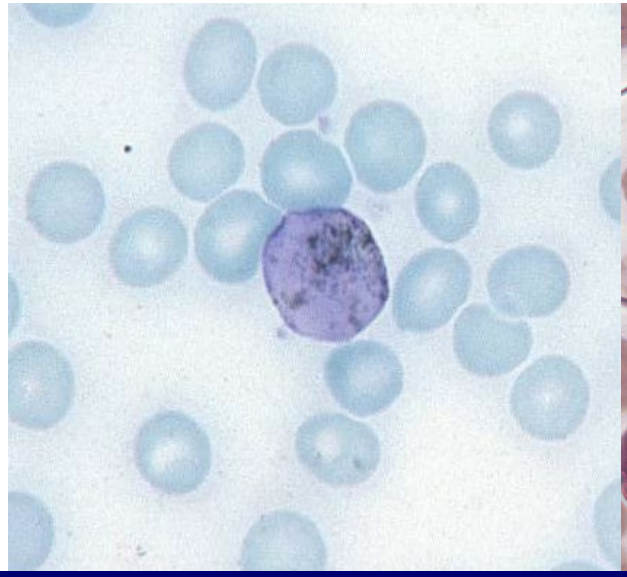
ijzerkleuring

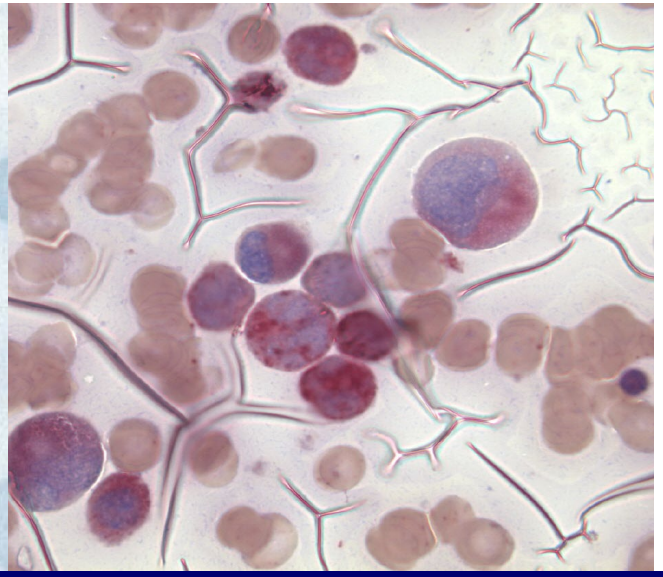
- ring sideroblasten

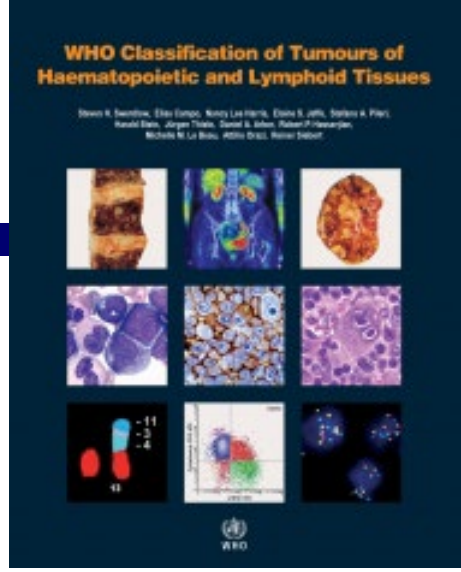
Cytochemie

myeloperoxydase reactie of Sudan black reaction is positief in myeloide cellen (sterk) en monocyten (zwak)

non-specifieke esterase reactie is positief in monocytaire cellen (diffuus in cytoplasma)







Leukemia

REVIEW ARTICLE OPEN

The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms

Joseph D. Khoury[1✉], Eric Solary[2✉], Oussama Abla[3], Yassmine Akkari[4], Rita Alaggio[5], Jane F. Apperley[6], Rafael Bejar[7], Emilio Berti[8], Lambert Busque[9], John K. C. Chan[10], Weina Chen[11], Xueyan Chen[12], Wee-Joo Chng[13], John K. Choi[14], Isabel Colmenero[15], Sarah E. Coupland[16], Nicholas C. P. Cross[17], Daphne De Jong[18], M. Tarek Elghetany[19], Emiko Takahashi[20], Jean-Francois Emile[21], Judith Ferry[22], Linda Fogelstrand[23], Michaela Fontenay[24], Ulrich Germing[25], Sumeet Gujral[26], Torsten Haferlach[27], Claire Harrison[28], Jennelle C. Hodge[29], Shimin Hu[1], Joop H. Jansen[30], Rashmi Kanagal-Shamanna[1], Hagop M. Kantarjian[31], Christian P. Kratz[32], Xiao-Qiu Li[33], Megan S. Lim[34], Keith Loeb[35], Sanam Loghavi[1], Andrea Marcogliese[19], Soheil Meshinchi[36], Phillip Michaels[37], Kikkeri N. Naresh[35], Yasodha Natkunam[38], Reza Nejati[39], German Ott[40], Eric Padron[41], Keyur P. Patel[1], Nikhil Patkar[42], Jennifer Picarsic[43], Uwe Platzbecker[44], Irene Roberts[45], Anna Schuh[46], William Sewell[47], Reiner Siebert[48], Prashant Tembhare[42], Jeffrey Tyner[49], Srdan Verstovsek[31], Wei Wang[1], Brent Wood[50], Wenbin Xiao[51], Cecilia Yeung[35] and Andreas Hochhaus[52✉]

blood®
Special Report

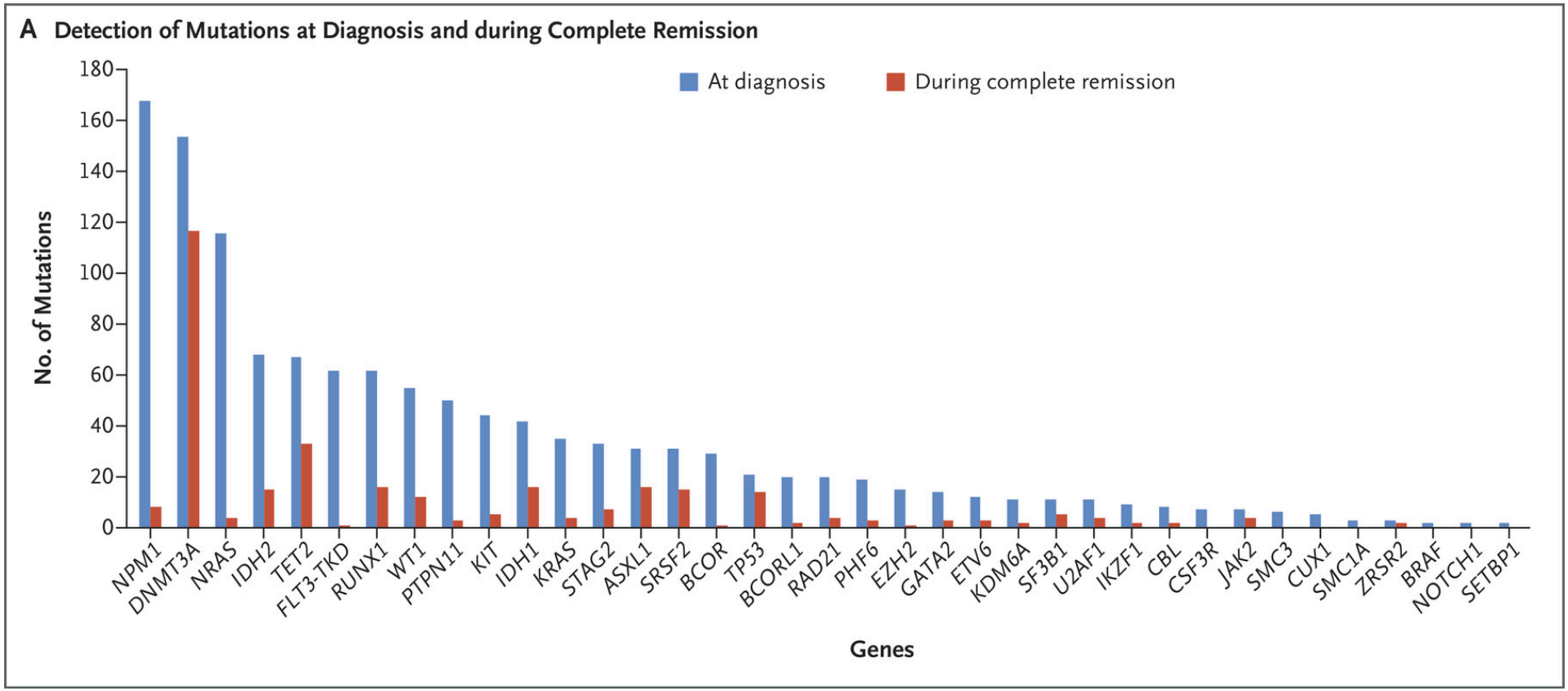
International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data

Daniel A. Arber,[1] Attilio Orazi,[2] Robert P. Hasserjian,[3] Michael J. Borowitz,[4] Katherine R. Calvo,[5] Hans-Michael Kvasnicka,[6] Sa A. Wang,[7] Adam Bagg,[8] Tiziano Barbui,[9] Susan Branford,[10] Carlos E. Bueso-Ramos,[7] Jorge E. Cortes,[11] Paola Dal Cin,[12] Courtney D. DiNardo,[7] Hervé Dombret,[13] Eric J. Duncavage,[14] Benjamin L. Ebert,[15] Elihu H. Estey,[16] Fabio Facchetti,[17] Kathryn Foucar,[18] Naseema Gangat,[19] Umberto Gianelli,[20] Lucy A. Godley,[1] Nicola Gökbuget,[21] Jason Gotlib,[22] Eva Hellström-Lindberg,[23] Gabriela S. Hobbs,[3] Ronald Hoffman,[24] Elias J. Jabbour,[7] Jean-Jacques Kiladjian,[13] Richard A. Larson,[1] Michelle M. Le Beau,[1] Mignon L.-C. Loh,[25] Bob Löwenberg,[26] Elizabeth Macintyre,[27] Luca Malcovati,[28] Charles G. Mullighan,[29] Charlotte Niemeyer,[30] Olatoyosi M. Odenike,[1] Seishi Ogawa,[31] Alberto Orfao,[32] Elli Papaemmanuil,[33] Francesco Passamonti,[28] Kimmo Porkka,[34] Ching-Hon Pui,[29] Jerald P. Radich,[35] Andreas Reiter,[36] Maria Rozman,[37] Martina Rudelius,[38] Michael R. Savona,[39] Charles A. Schiffer,[40] Annette Schmitt-Graeff,[41] Akiko Shimamura,[15,42] Jorge Sierra,[43] Wendy A. Stock,[1] Richard M. Stone,[15] Martin S. Tallman,[44] Jürgen Thiele,[45] Hwei-Fang Tien,[46] Alexandar Tzankov,[47] Alessandro M. Vannucchi,[48] Paresh Vyas,[49] Andrew H. Wei,[50] Olga K. Weinberg,[51] Agnieszka Wierzbowska,[52] Mario Cazzola,[28] Hartmut Döhner,[53] and Ayalew Tefferi[19]

AML gedefinieerd door differentiatie

AML met minimale differentiatie	MPO- of SBB-expressie van twee of meer van myeloid geassocieerde antigenen zoals CD13, CD33, CD117
AML zonder uitrijping	myeloïde uitrijping < 10%, ≥ 3% blasten positief voor MPO of SBB, expressie van twee of meer van myeloid geassocieerde antigenen zoals MPO, CD13, CD33, CD117
AML met uitrijping	myeloïde uitrijping > 10%, ≥ 3% blasten positief voor MPO of SBB, expressie van twee of meer van myeloid geassocieerde antigenen zoals MPO, CD13, CD33, CD117, < 20% van de cellen is monocytair
acute myelomonocytaire leukemie	monocytaire uitrijping ≥ 20%, myelocytaire uitrijping ≥ 20%, ≥ 3% blasten positief voor MPO
Acute monocytaire leukemie	Monoblasten, promonocyten en/of monocyten ≥ 80%, myelocytaire uitrijping <20%. Blasten en promonocyten hebben expressie van tenminste twee monocytaire markers zoals CD11c, CD14, CD36, CD64 of positiviteit voor NSE
Acute erytroïde leukemie	≥ 80% kernhoudende erytocytaire cellen met ≥ 30% proerytroblasten (< 80% kernhoudende erytrocytaire cellen sluit deze AML niet altijd uit)
acute megakaryoblasten leukemie	MPO- of SBB-expressie van een of meer van de markers CD41, CD42b, CD61
acute basofiele leukemie	Blasten en onrijpe basofielen met metachromasie bij toluidine blauw kleuring, blasten zijn negatief voor MPO, SBB en NSE en geen sterke CD117 expressie ter uitsluiting van mestcelleukemie

AML is not *one* disease



Jongen-Levrencic. *N Engl J Med* 2018;378:1189-99.

Acute leukemie ≥20% blasten *van alle cellen*

Uitzonderingen:

AML met veelvoorkomende genetische afwijkingen

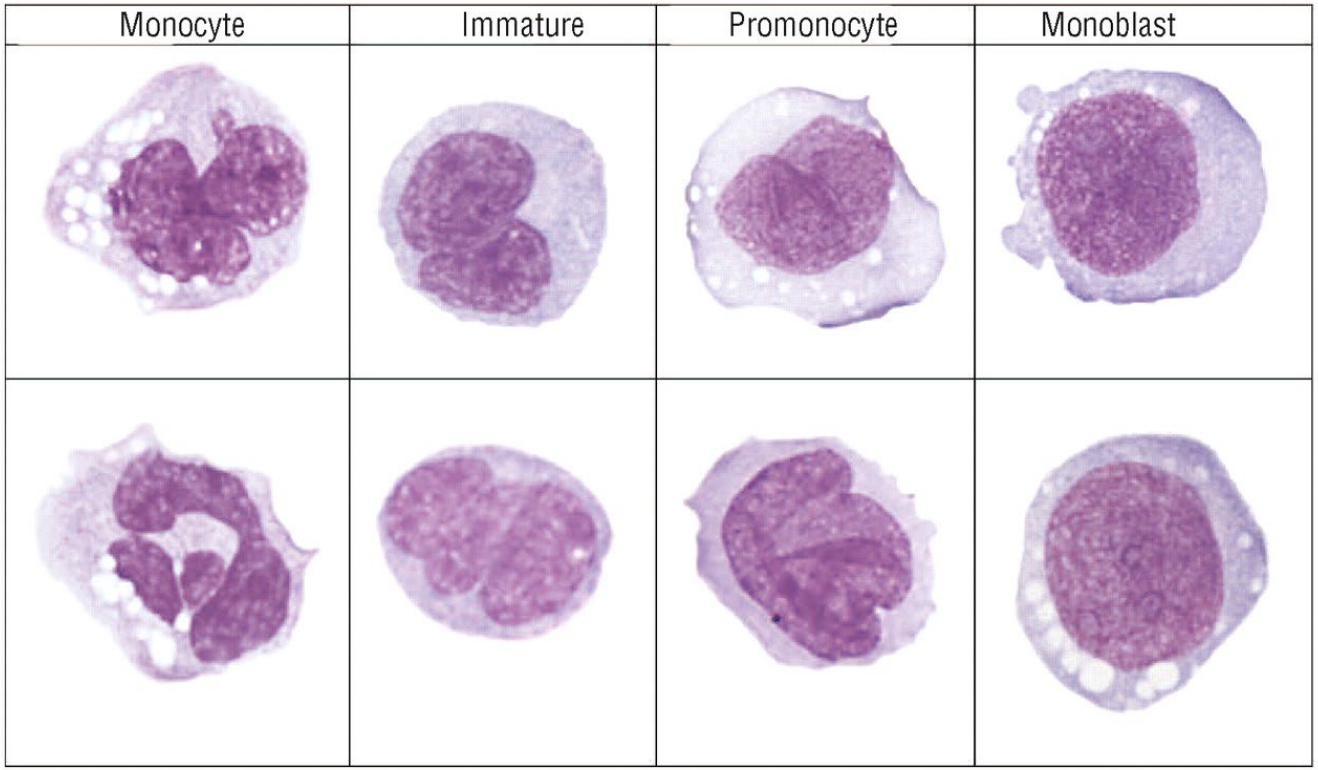
Acute myeloid leukaemia with defining genetic abnormalities
Acute promyelocytic leukaemia with *PML*::*RARA* fusion
Acute myeloid leukaemia with *RUNX1*::*RUNX1T1* fusion
Acute myeloid leukaemia with *CBFB*::*MYH11* fusion
Acute myeloid leukaemia with *DEK*::*NUP214* fusion
Acute myeloid leukaemia with *RBM15*::*MRTFA* fusion
~~Acute myeloid leukaemia with *BCR*::*ABL1* fusion~~
Acute myeloid leukaemia with *KMT2A* rearrangement
Acute myeloid leukaemia with *MECOM* rearrangement
Acute myeloid leukaemia with *NUP98* rearrangement
Acute myeloid leukaemia with *NPM1* mutation
~~Acute myeloid leukaemia with *CEBPA* mutation~~
Acute myeloid leukaemia, myelodysplasia-related
Acute myeloid leukaemia with other defined genetic alterations

Khoury *et al. Leukemia* 2022

Acute leukemie ≥20% blasten *van alle cellen*

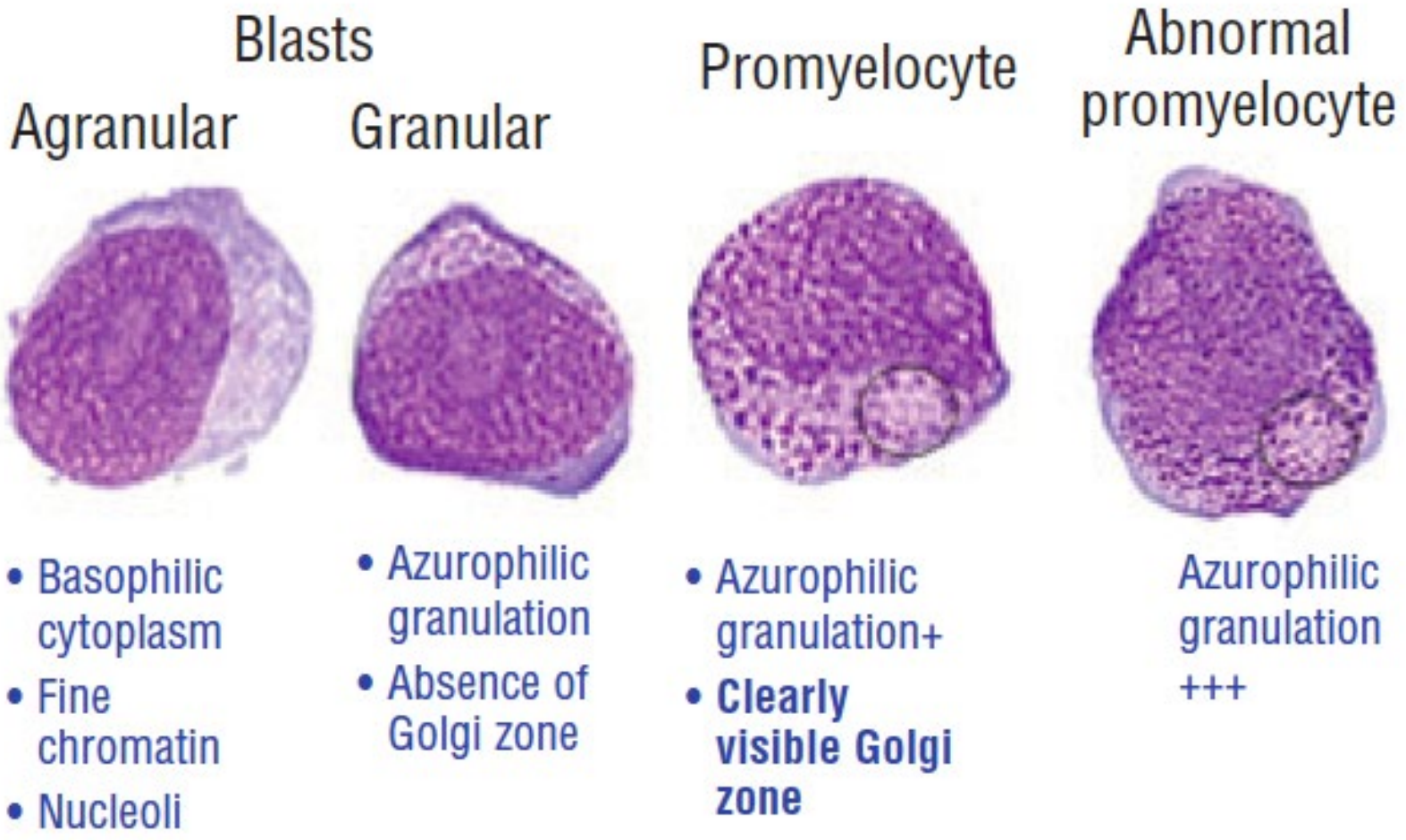
Uitzonderingen:

AML, monocytair (monoblasten + promonocyten)



Goasguen. *Haematologica* 2009

Blasten en (afwijkende) promyelocyten



Mufti. *Hematologica* 2008;93:1712-17.

Acute leukemie ≥20% blasten *van alle cellen*

<u>Uitzonderingen:</u>

AML, erytroid	bij	≥80%	erytroblasten
	met	≥30%	pro-erytroblasten
	en	≤20%	myeloblasten

WHO (2022) - overige leukemieën

Acute ongedifferentieerde leukemie (AUL)

MPAL (“mixed phenotype ambiguous lineage”)

met specifieke mutatie (b.v. *BCR::ABL1* of *KMT2A*)

MN post cytotoxische therapie (MN-pCT)

Khoury. *Leukemia* 2022

MPAL: lineage-defining markers

Myeloid

MPO of

≥2 van: NSE / CD11c / CD14 / CD64 / lysozym

B-lymfoid

$CD19^{bright}$ met 1 van: CD79a / cyCD22 / CD10

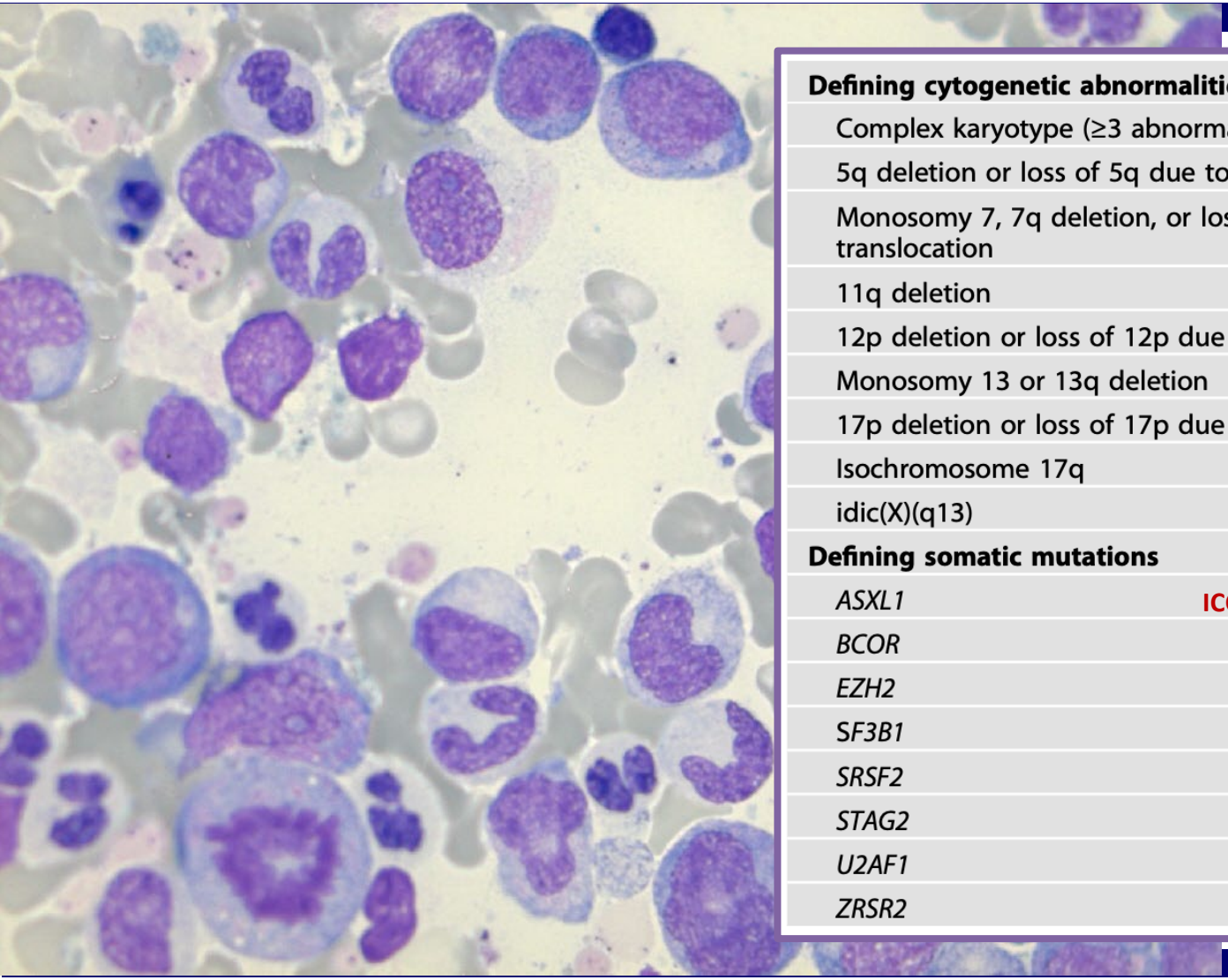
$CD19^{dim}$ met 2 van: CD79a / cyCD22 / CD10

T-lymfoid

$cyCD3^{bright}$ of mCD3

AML-MR (WHO) / AML-MR GM of CA (ICC)

cellijn(en) met =>50% dysplasia en/of…



Defining cytogenetic abnormalities	
Complex karyotype (≥3 abnormalities)	
5q deletion or loss of 5q due to unbalanced translocation	
Monosomy 7, 7q deletion, or loss of 7q due to unbalanced translocation	
11q deletion	
12p deletion or loss of 12p due to unbalanced translocation	
Monosomy 13 or 13q deletion	
17p deletion or loss of 17p due to unbalanced translocation	
Isochromosome 17q	
idic(X)(q13)	
Defining somatic mutations	
ASXL1	**ICC:** *RUNX1*
BCOR	
EZH2	
SF3B1	
SRSF2	
STAG2	
U2AF1	
ZRSR2	

Khoury. *Leukemia* 2022 // Arbor. *Blood* 2022

WHO 5 (2022) - overige leukemieën

B-LBL / ALL

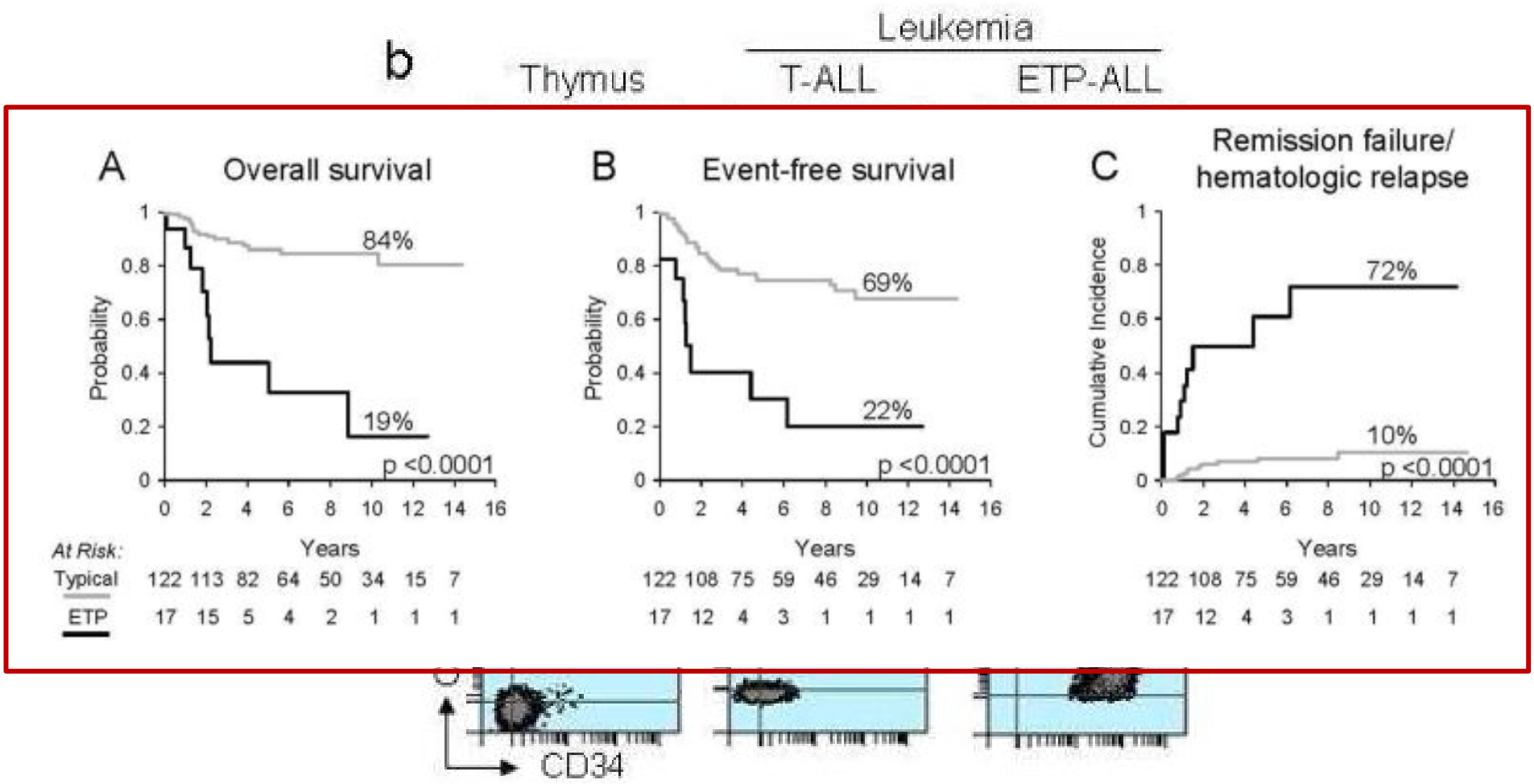
BCR::ABL1

T-LBL / ALL

Early T-cell Precursor Lymphoblastic Leukemia

Khoury. *Leukemia* 2022

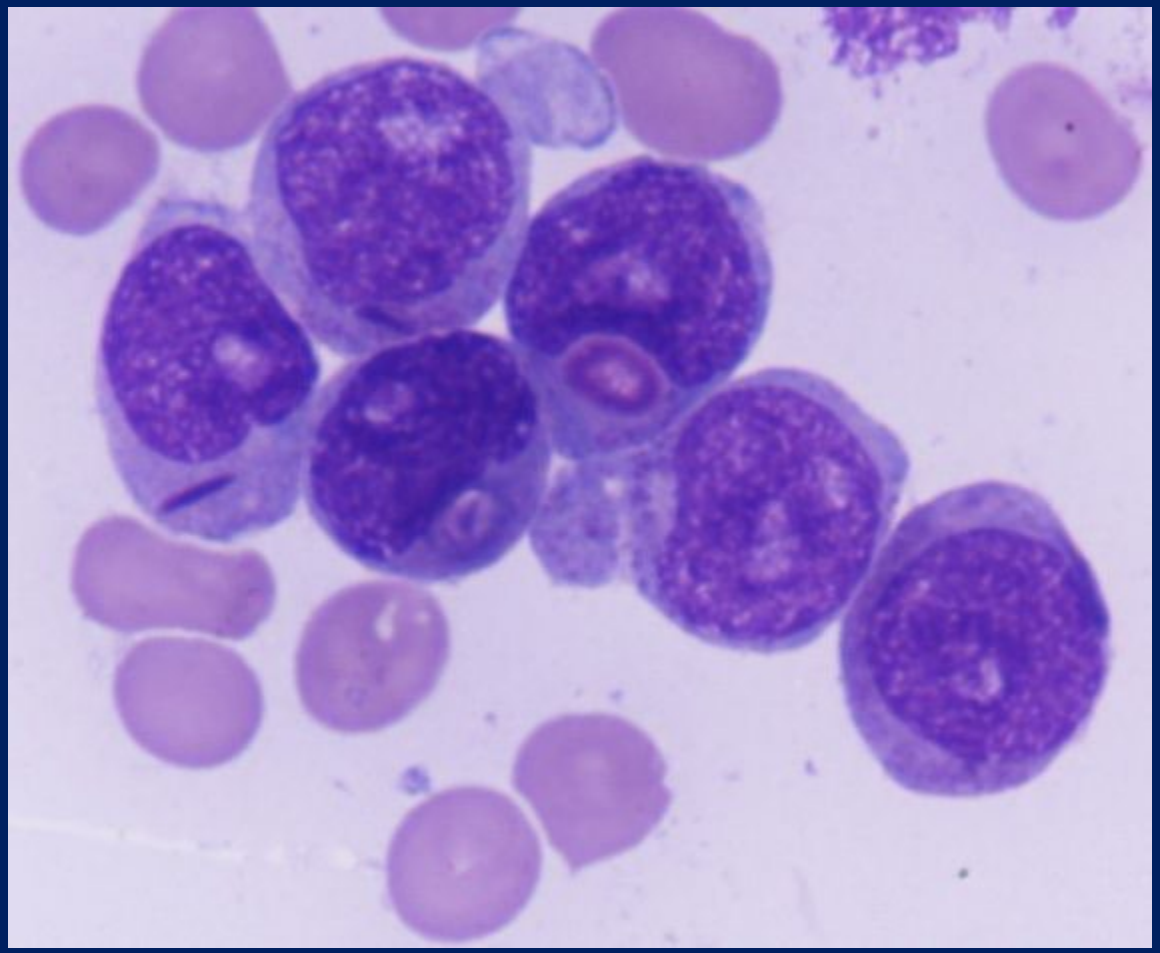
Early T-cell Precursor (ETP) ALL



Coustan-Smith. *Lancet Oncol* 2009;10:147-56.

Opwarmen voor het practicum…

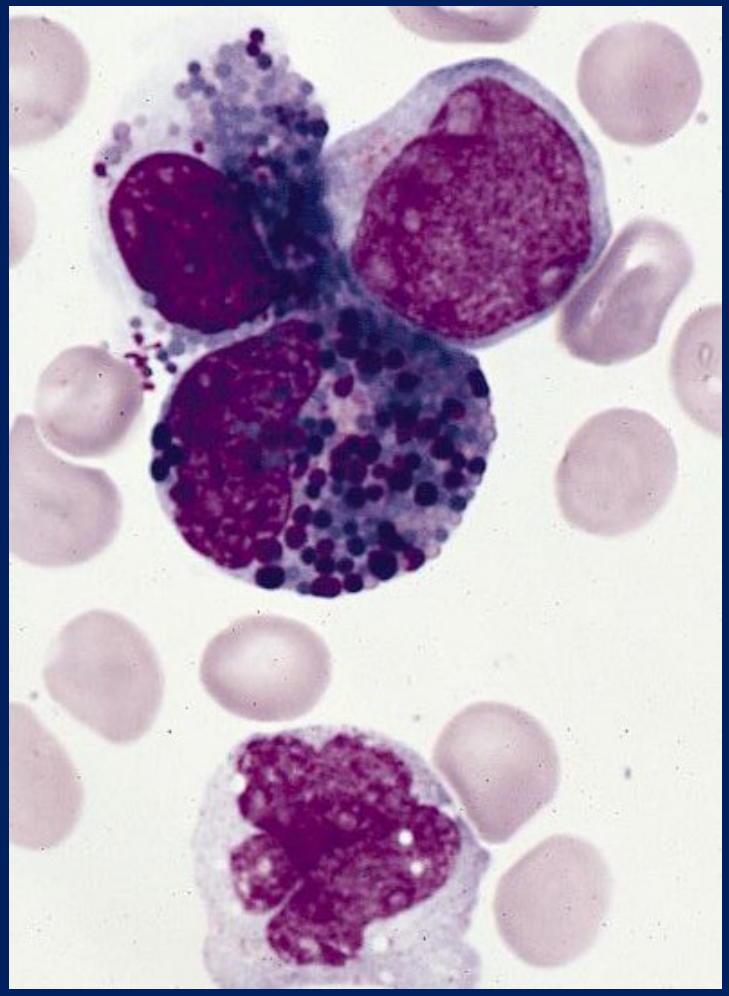
AML met t(8;21)

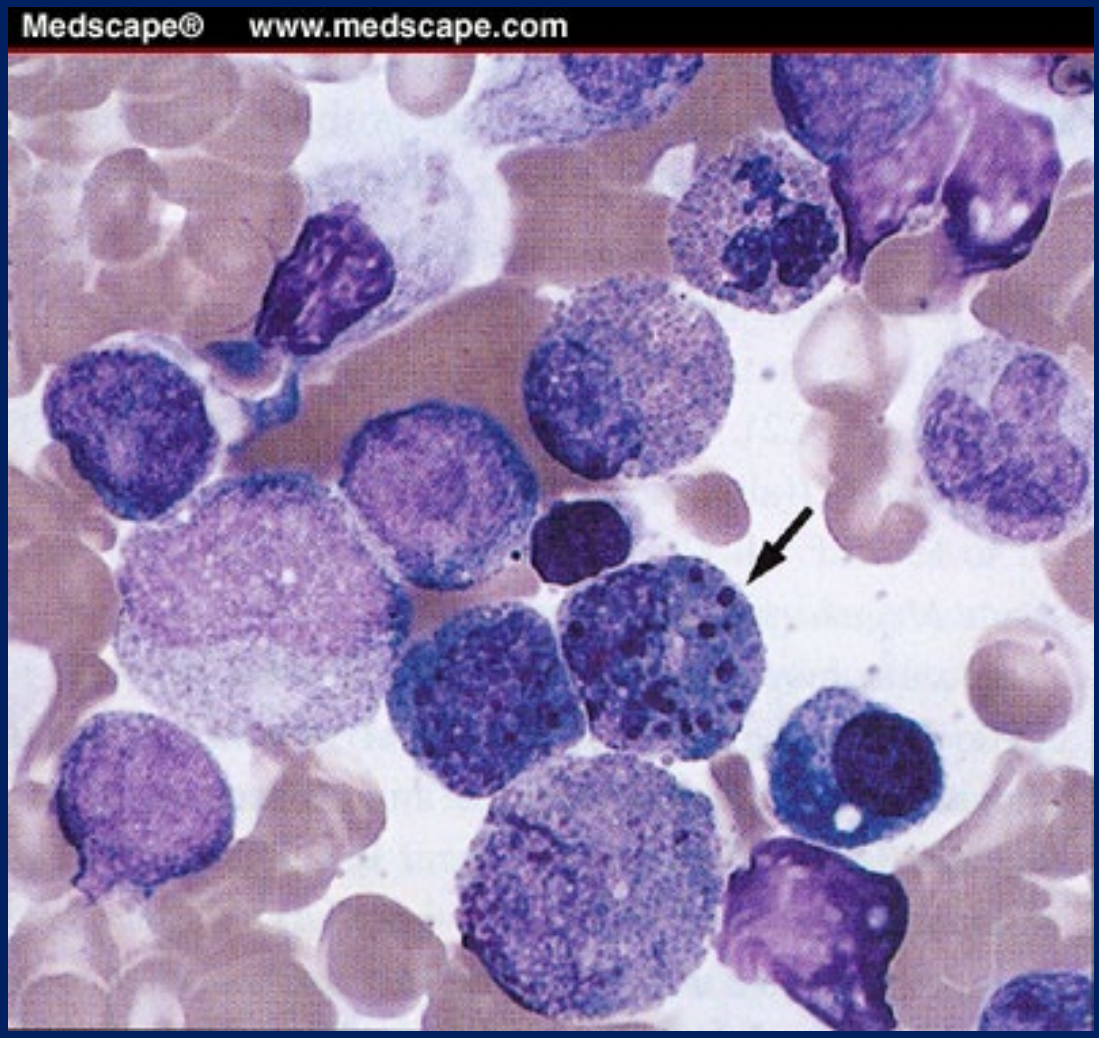


CD19
CD56

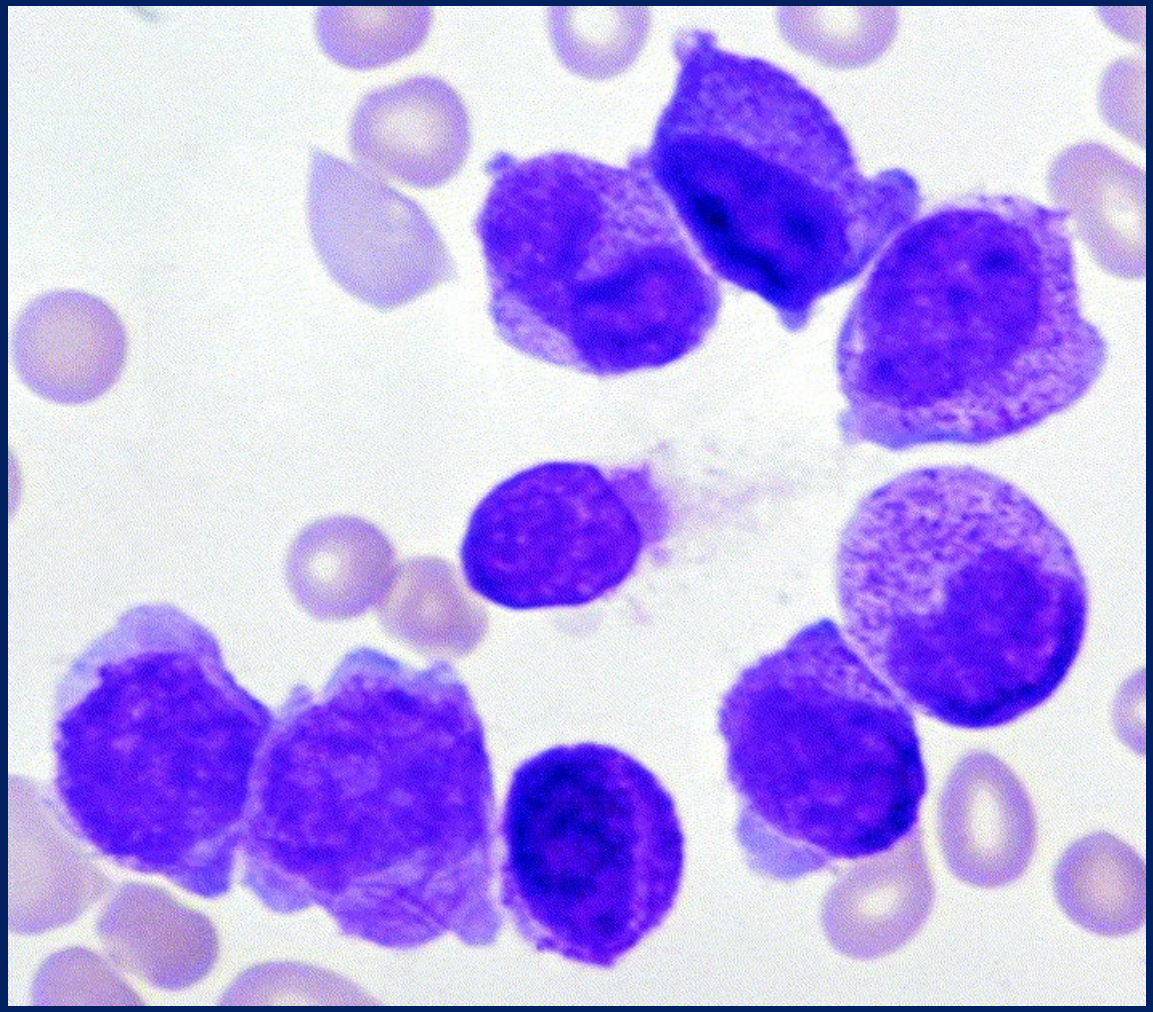
Abdusalam. *Acute Leukemia – The Scientist's Perspective and Challenge*

AML met inv(16) of t(16;16)



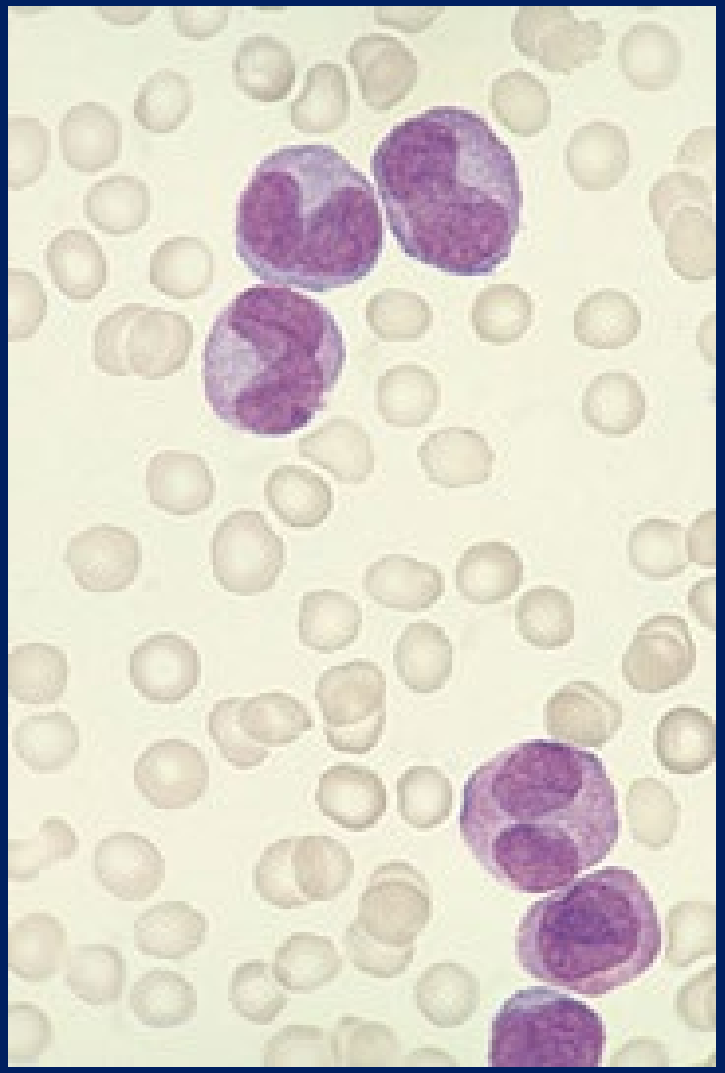


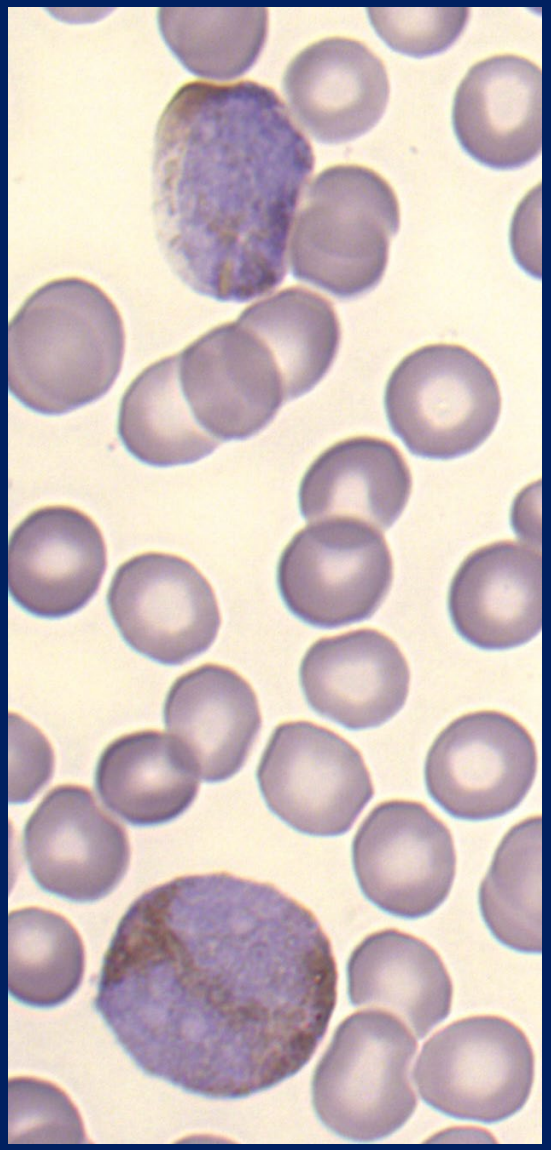
AML met t(15;17)



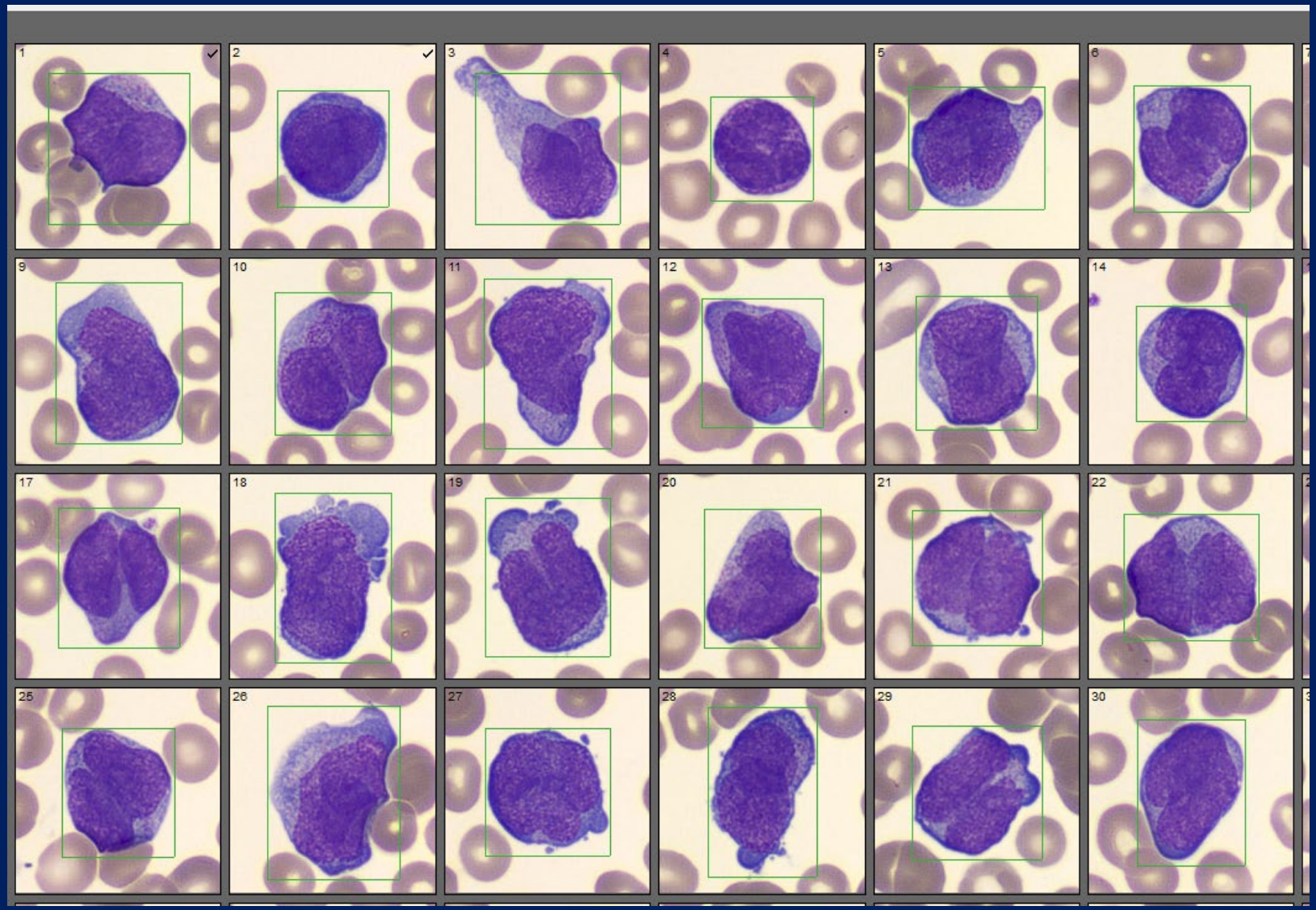
Liso & Bennett. *Best Pract Res Clin Haematol* 2003;16:349-55.

AML met t(15;17)

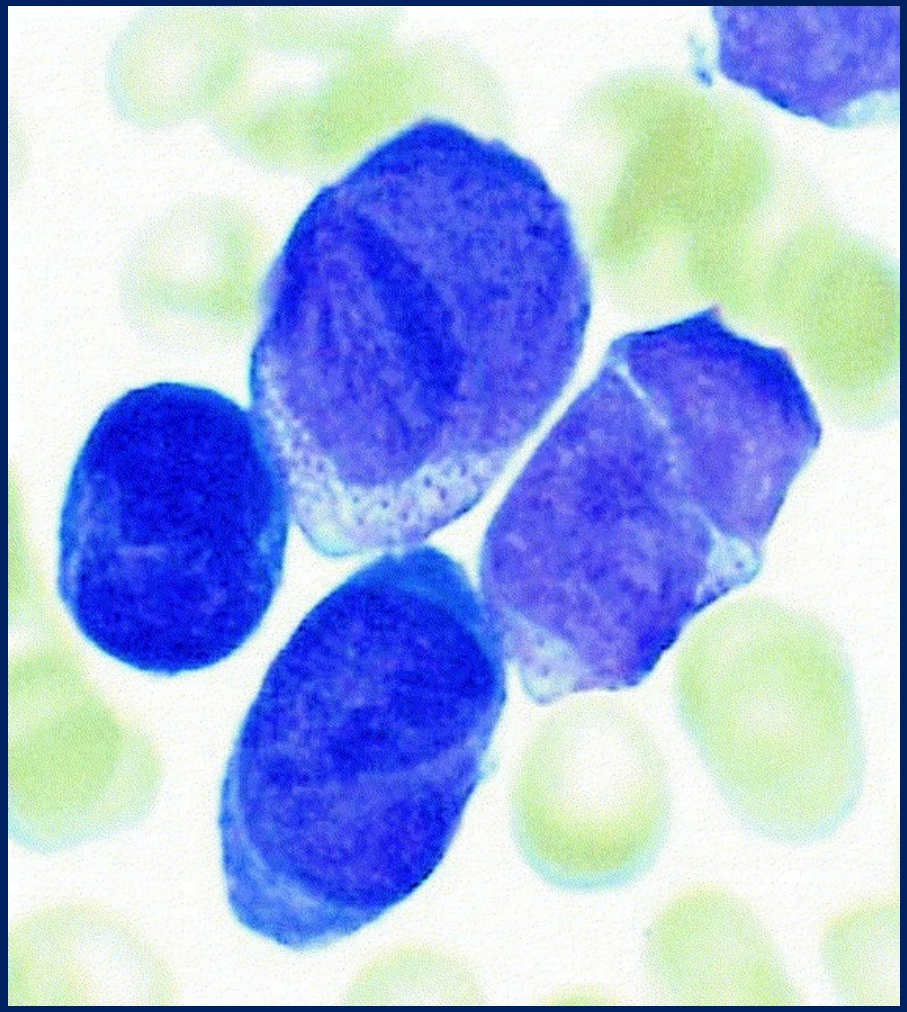




AML met t(15;17)

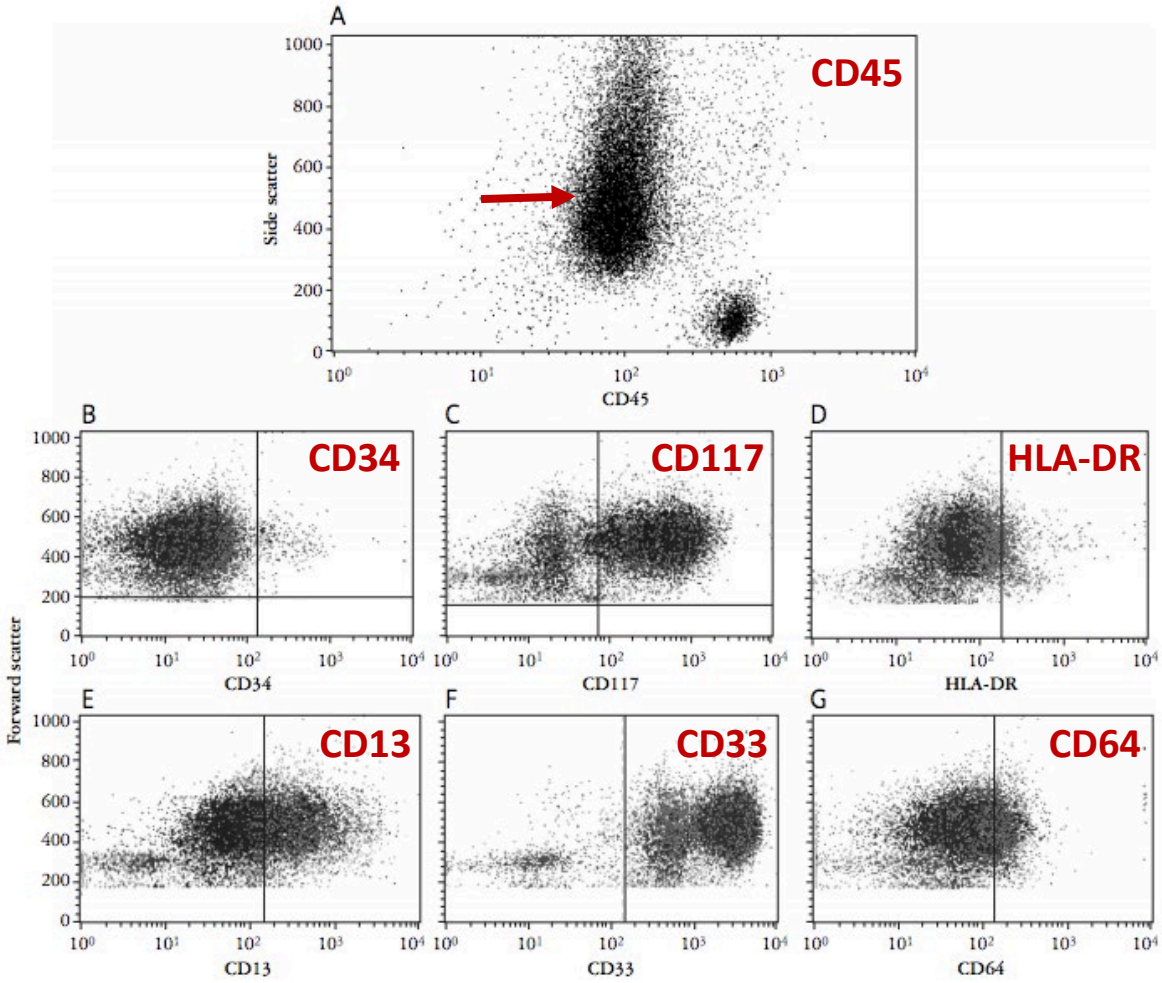


APL, microgranulaire variant (AML-M3v)



Liso & Bennett. *Best Pract Res Clin Haematol* 2003;16:349-55.

APL, diagnose heroverwegen…



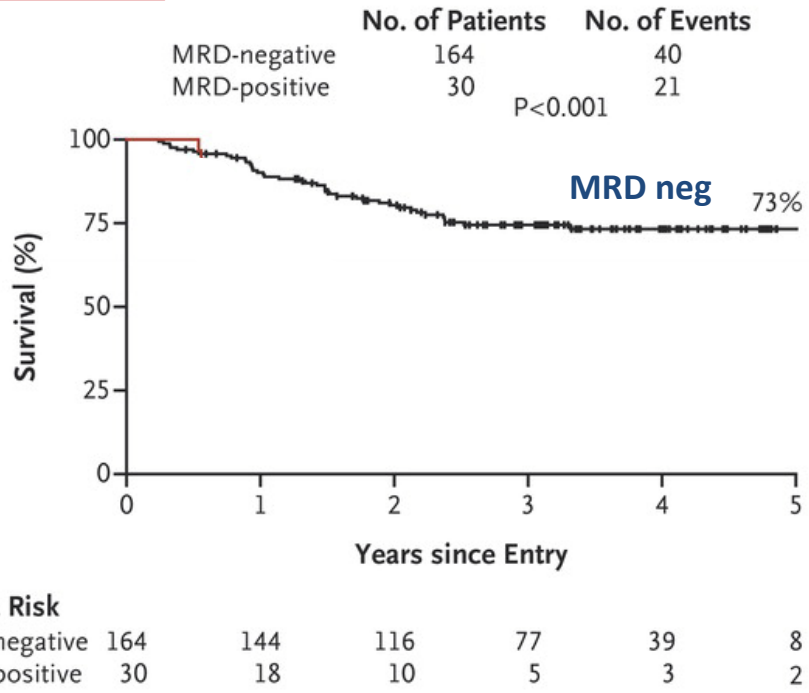
Gorczyca. *Pol J Pathol* 2012;1:8-17

AML met *NPM1* mutatie (± *FLT3* mutatie)

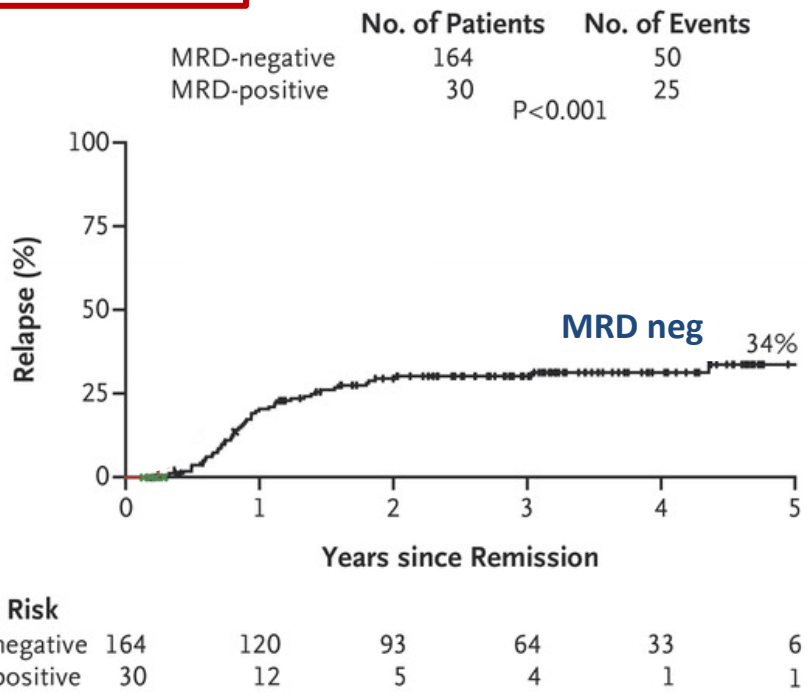
Vidholia & Menon. *Blood* 2015;125;889.

MRD: moleculaire diagnostiek (bv *NPM1*)

Overleving

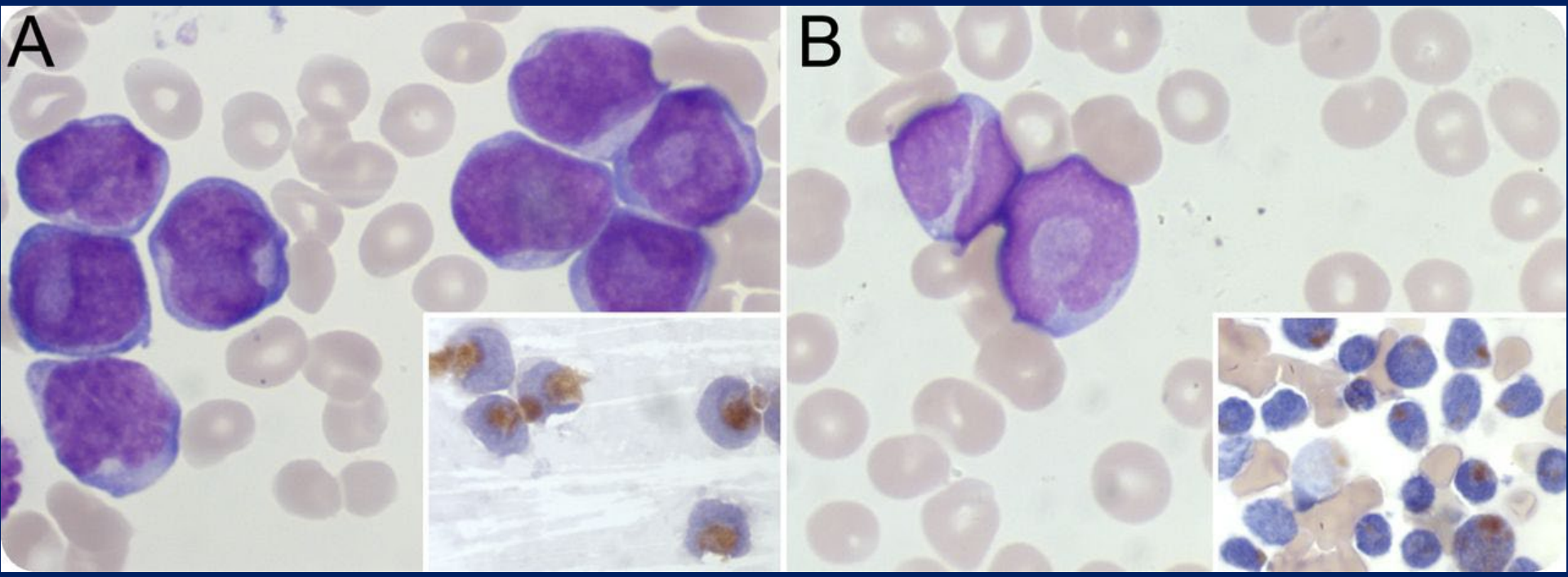


Recidief ziekte



Ivey. *N Engl J Med* 2016;374:422-33.

2 patiënten met vergelijkbare morfologie: ook dezelfde moleculaire afwijking?



PML-RARα
Flt3-ITD

NPM1 mut

Mikesch & Schliemann. *Blood* 2016;128:1309.

Take home messages

De morfologie *lijkt* zijn beste tijd te hebben gehad in AML diagnostiek met de moleculaire en cytogenetische diagnostiek en

De (definitieve) diagnose dient vaak uitgesteld te worden aan nieuwe bevindingen.

Thuis *nóg meer* indruk maken op de collega's:

- WHO 5 / ICC *updates en controverses*
- moleculaire afwijkingen voorspellen vanachter de mic