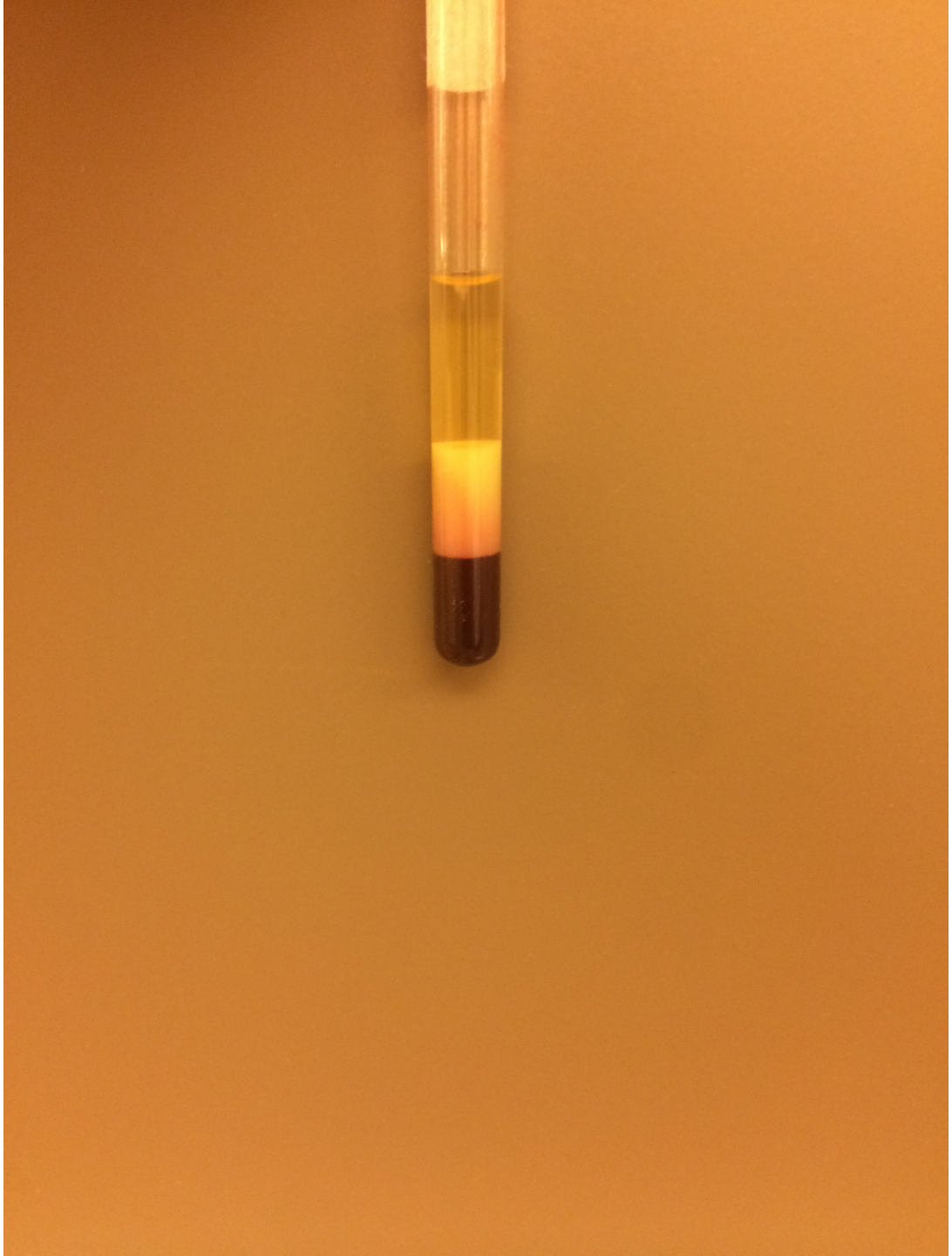
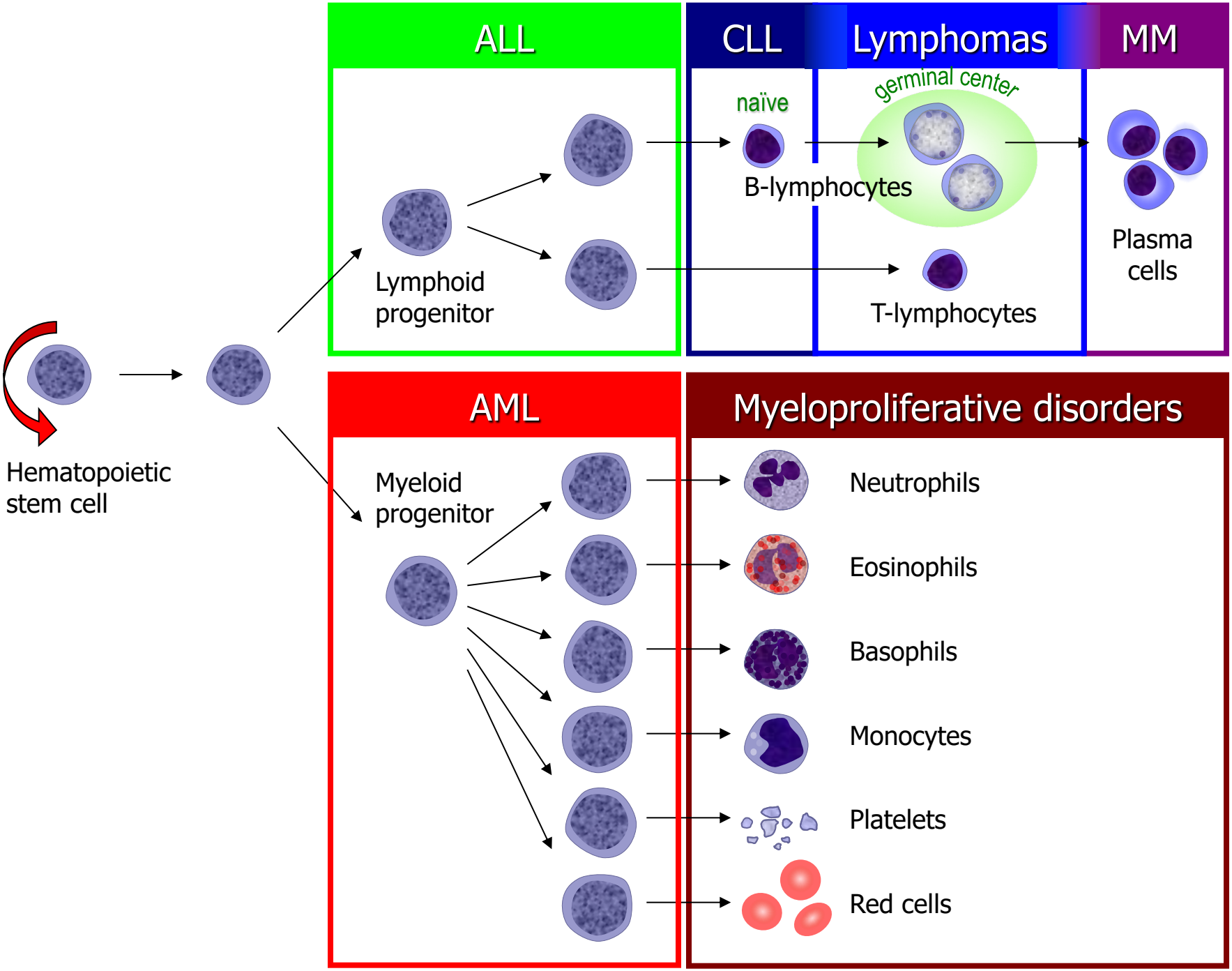
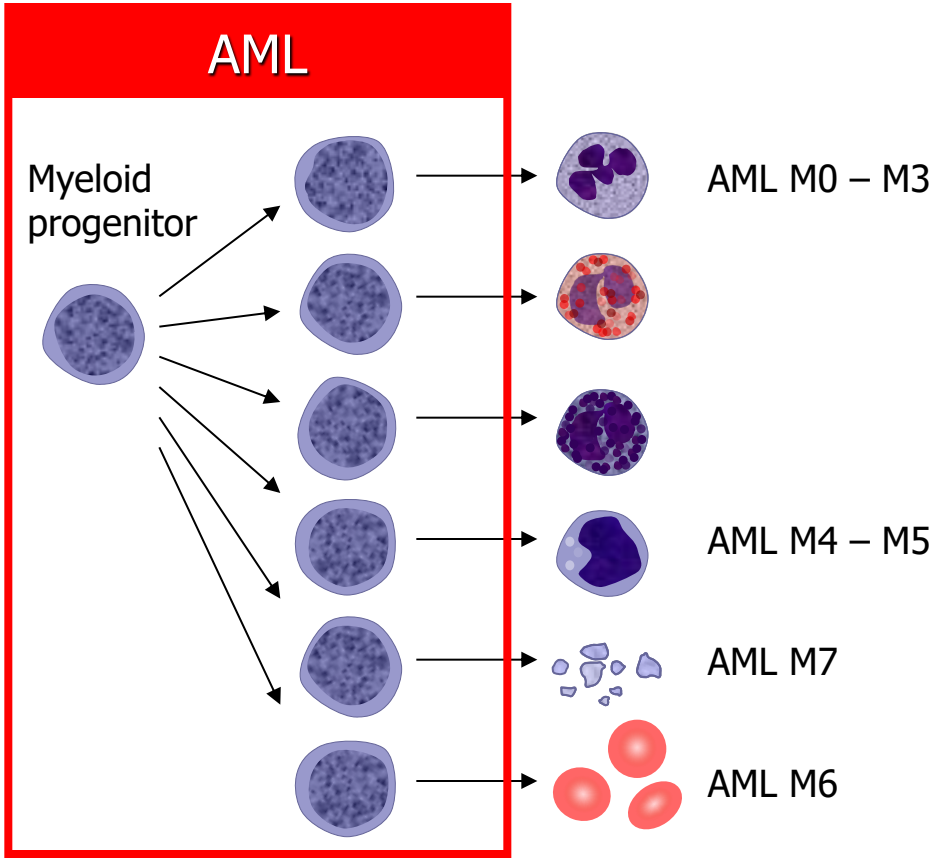
Akutte myelogen leukemi 13-02-2018

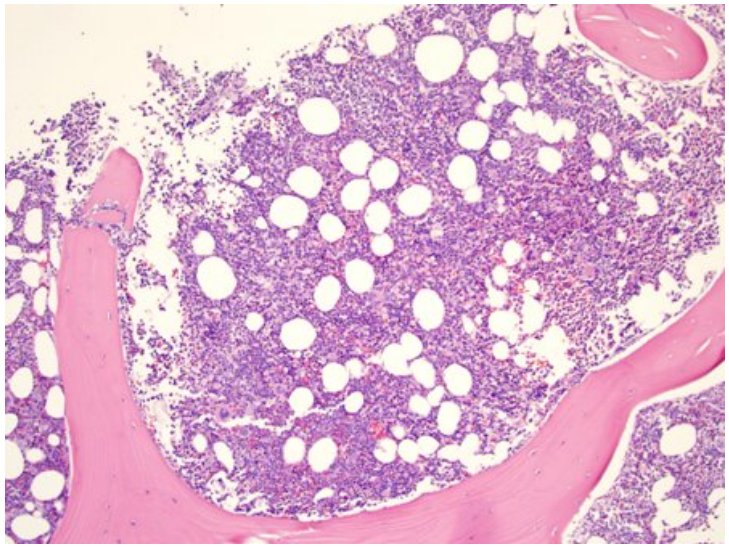
Yngvar Fløisand, Avdeling for blodsykdommer, OUS - Rikshospitalet

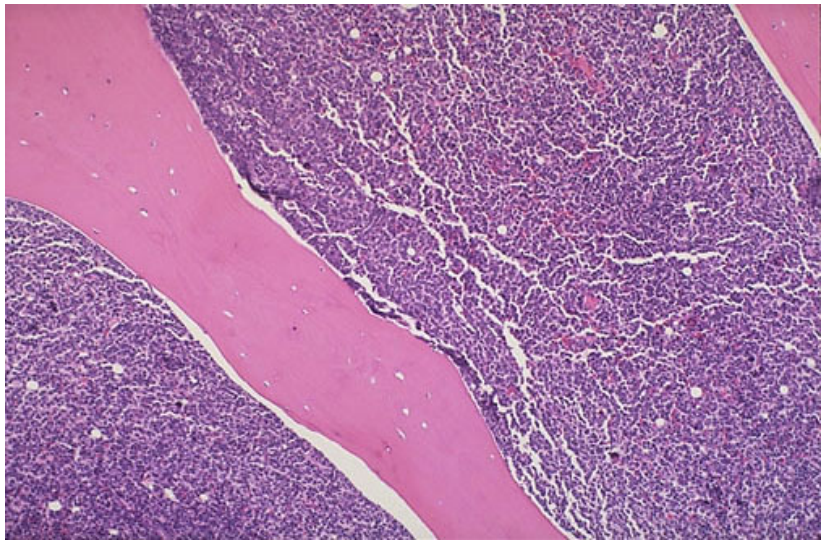


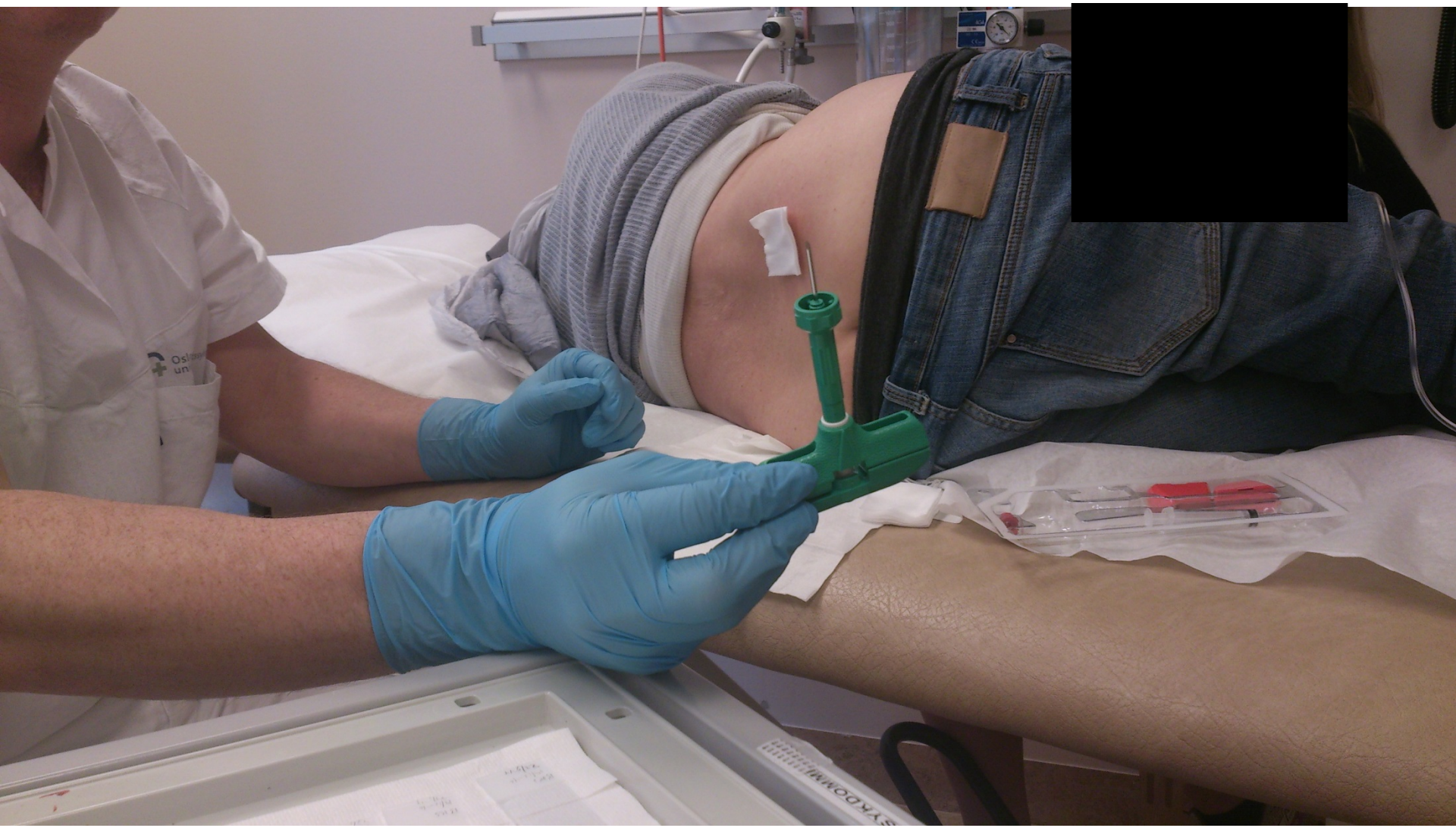

ALL
CLL
Lymphomas
MM
germinal center
naïve
B-lymphocytes
Plasma cells
Lymphoid progenitor
T-lymphocytes
Hematopoietic stem cell
AML
Myeloproliferative disorders
Myeloid progenitor
Neutrophils
Eosinophils
Basophils
Monocytes
Platelets
Red cells

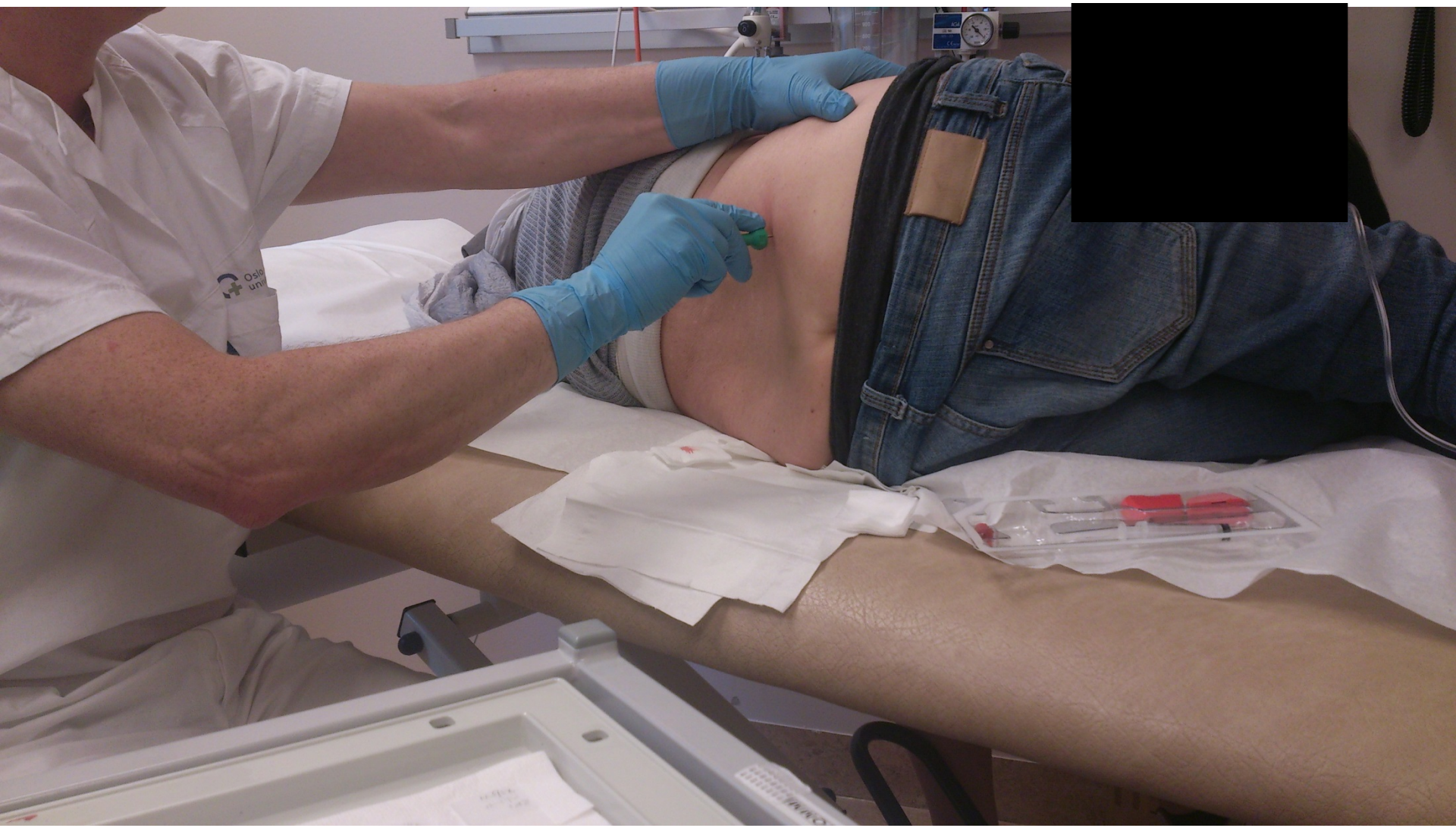

AML
Myeloid progenitor
AML M0 – M3
AML M4 – M5
AML M7
AML M6

Symptomer på akutt leukemi skyldes infiltrasjon av benmargen med benmargssvikt

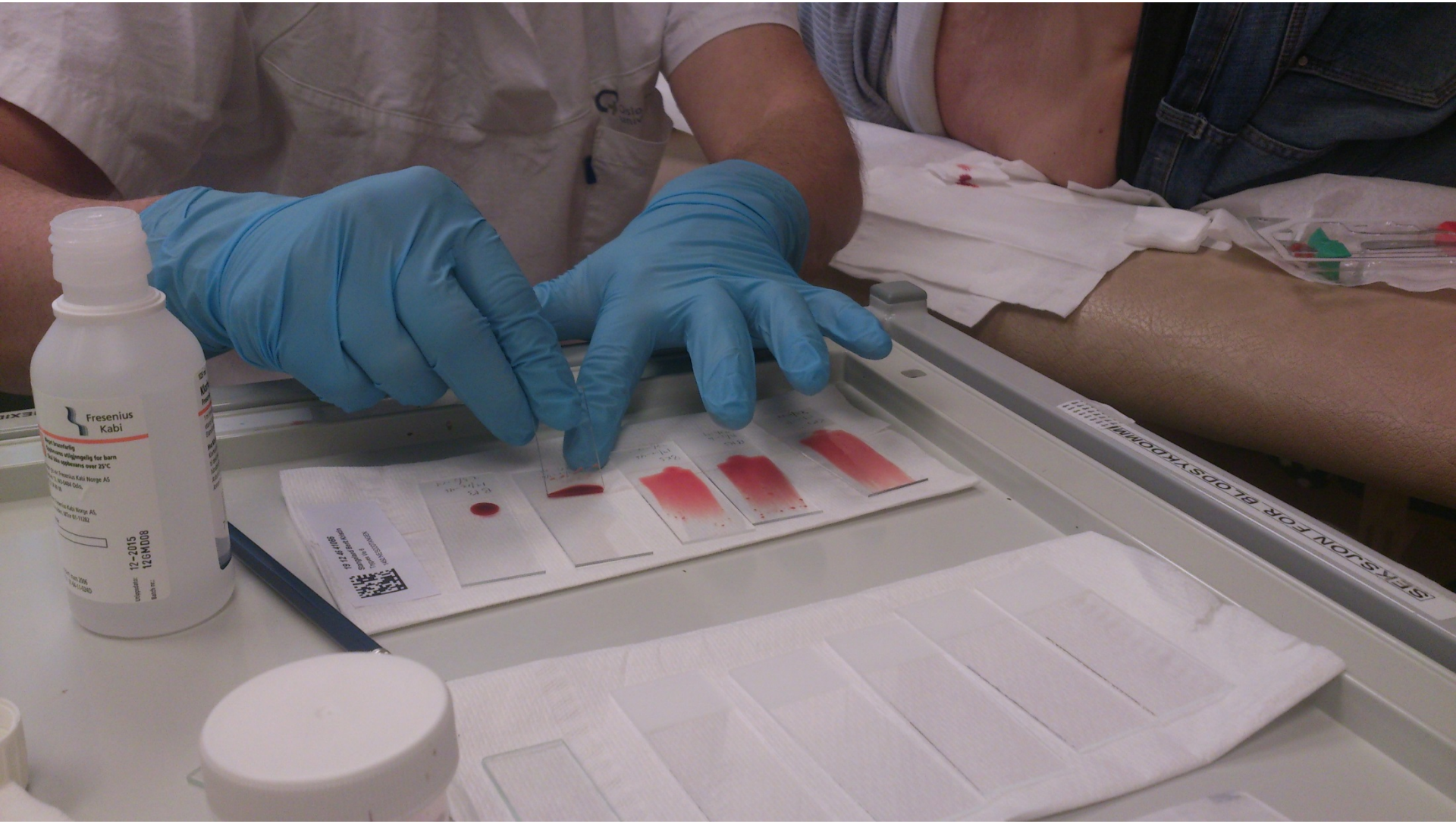


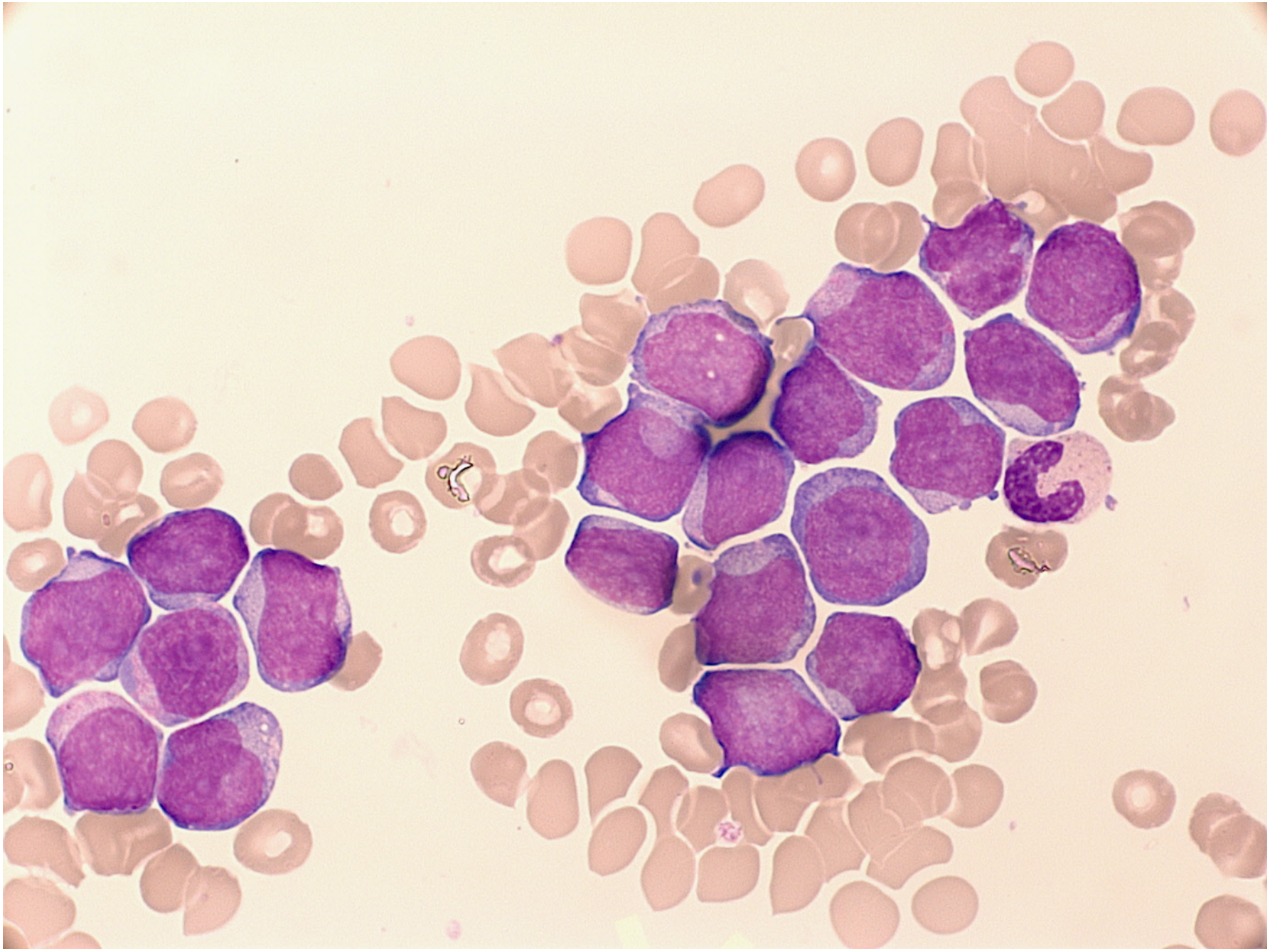


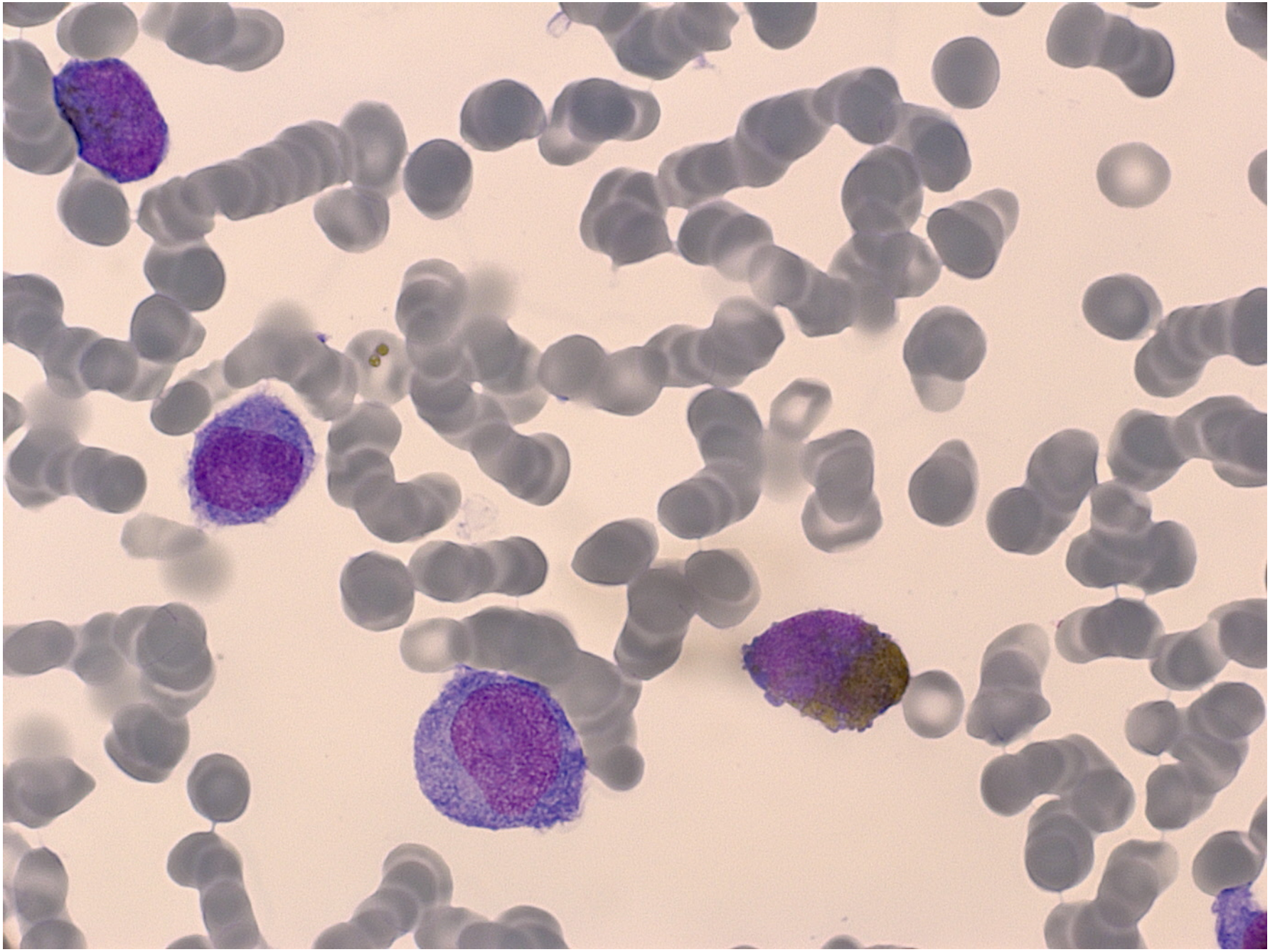


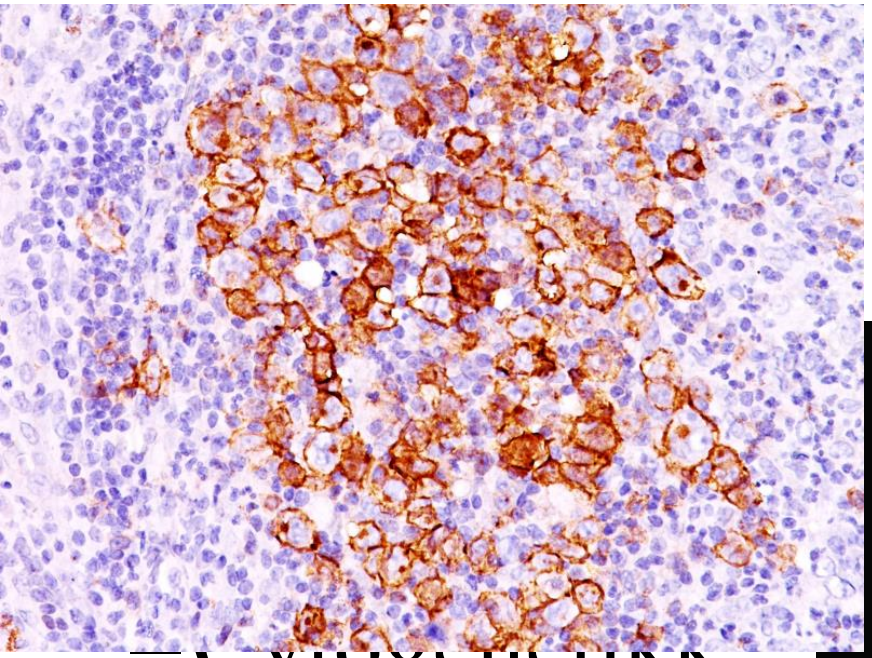


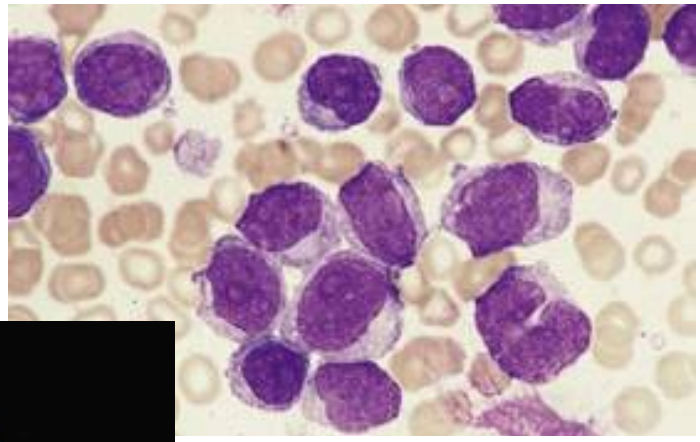

Fresenius
Kabi
12-2015
12GMD08
SEKSJON FOR BLODSYKDOMMER


Fresenius
Kabi
12-2015
12GM008
SEKSJON FOR BLODSYKDOMMER



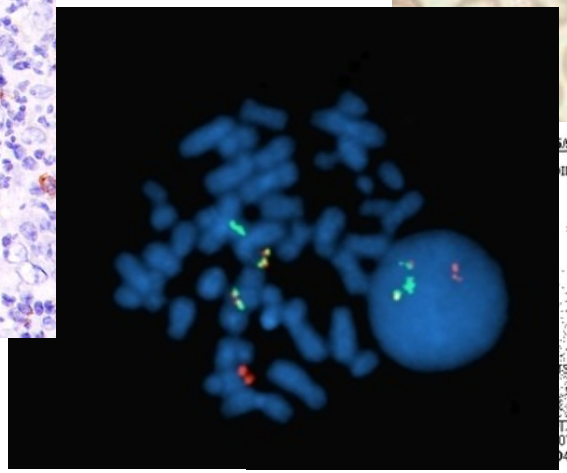


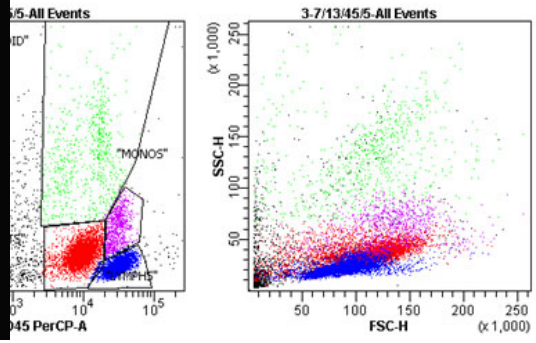


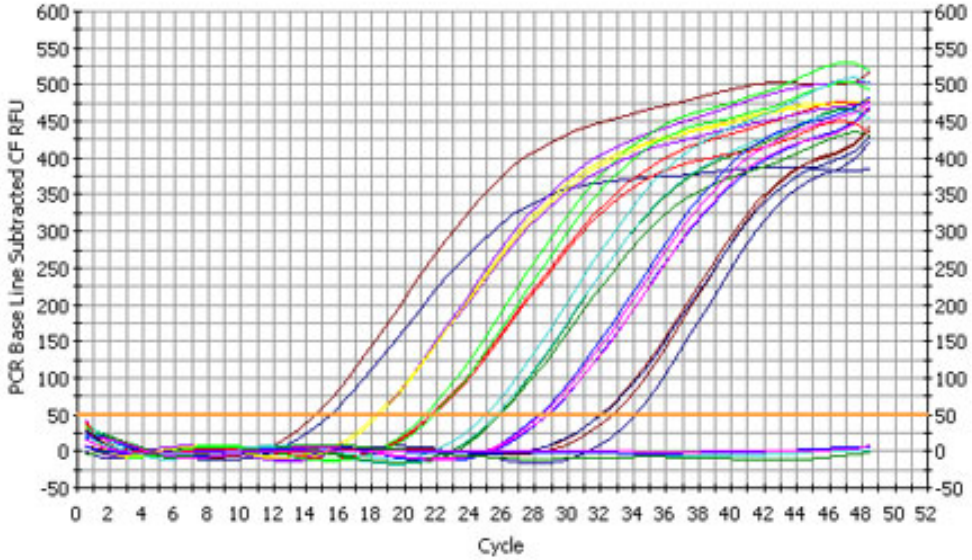


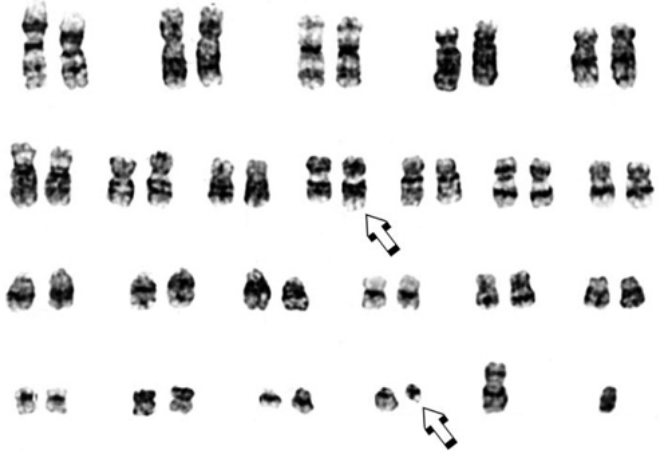
– Cytogenetikk

– FISH









AML

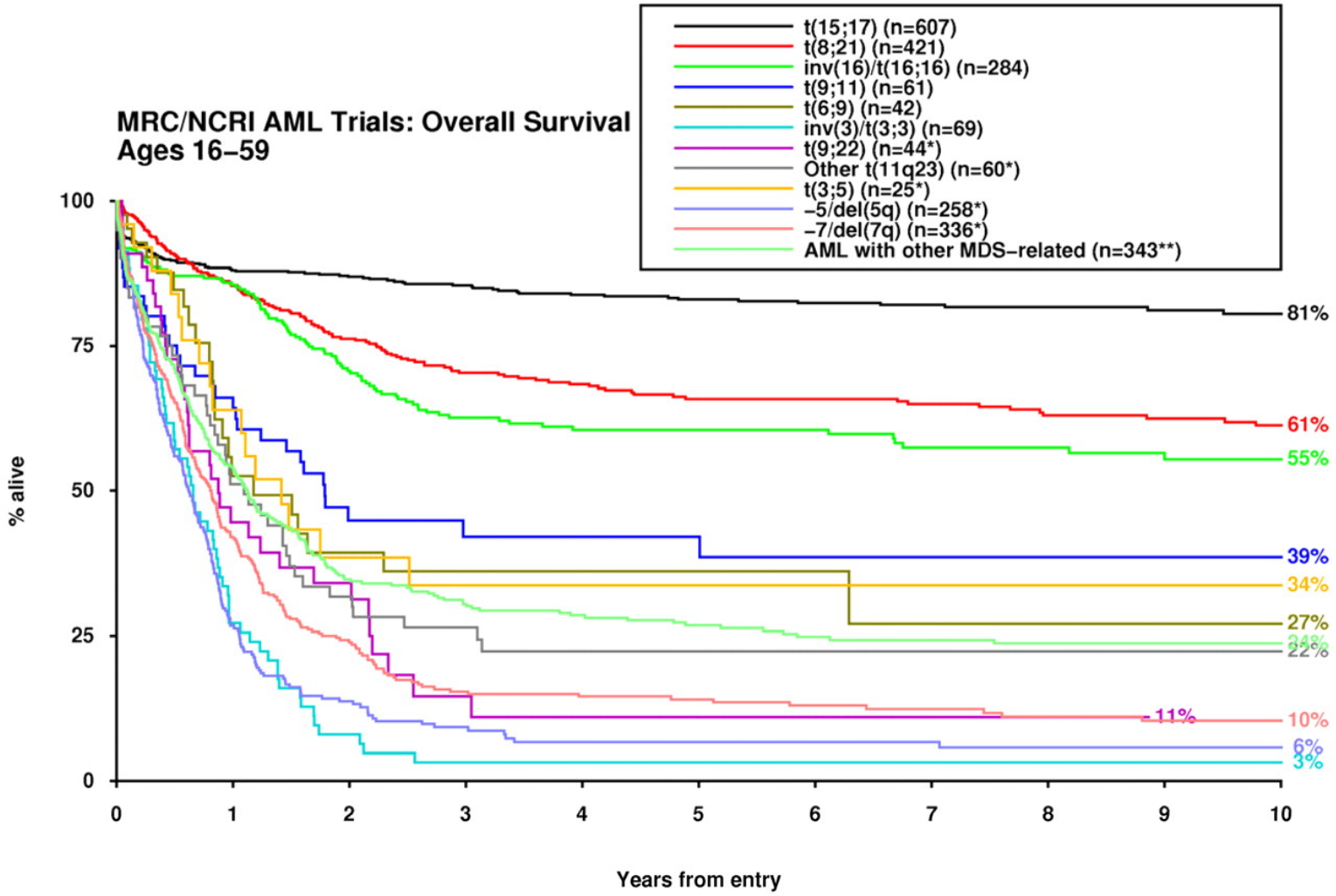
Akutte myelogene leukemier er en heterogen gruppe sykdommer

WHO 2016

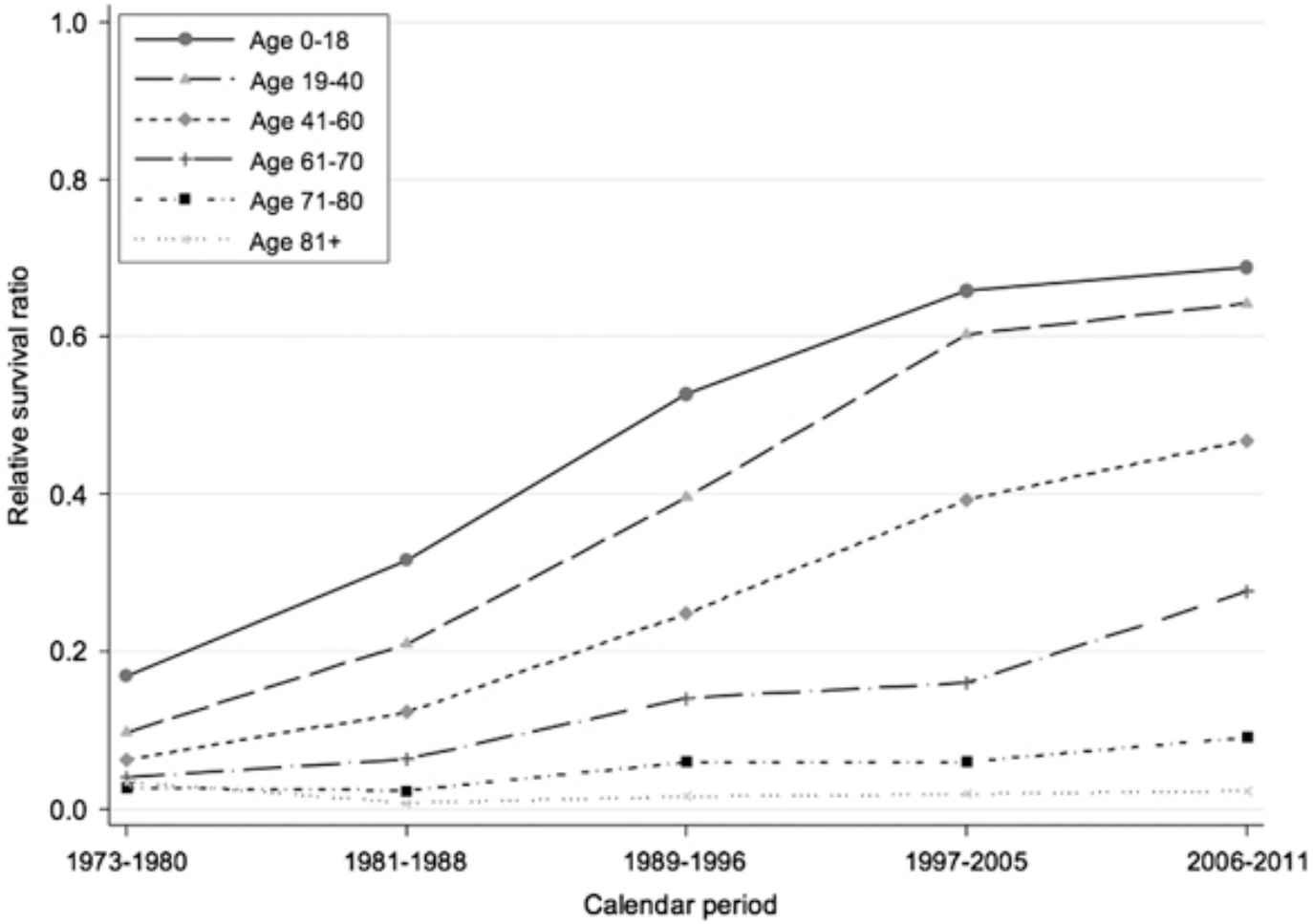
FAB

M0	Udifferensiert leukemi
M1	Uten modningstegn
M2	Med modning
M3	Hypergranulær promyelocyttleukemi
M4	Myelomonocyttleukemi
M5	Monoblastleukemi
M6	Erytroleukemi
M7	Megakaryoblastleukemi

Acute myeloid leukaemia with recurrent genetic abnormalities
AML with t (8;21)(q22;q22): RUNX-RUNX1T1
AML with inv(16)(p13;1q22) or t(16;16)(p13.1;q22): CBFB-MYH11
APL with t(15;17)(q22;q12): PML-RARA
AML with t(9;11)(p22;q23): MLLT3-MLL
AML with t(6;9)(p23;q34): DEK-NUP214
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*
AML (megakaryoblastic) with t(1;22)(p13.3;q13.3); *RBM15-MKL1*
AML (megakaryoblastic) with t(1;22)(p13;q13): RBM15-MKL1
Provisional entity: AML with BCR-ABL1
AML with mutated NPM
AML with biallelic mutations of *CEBPA*
Provisional entity: AML with mutated *RUNX1*
Acute myeloid leukaemia with myelodysplasia-related changes
Therapy-related myeloid neoplasms
Acute myeloid leukaemia, not otherwise specified
AML with minimal differentiation
AML without maturation



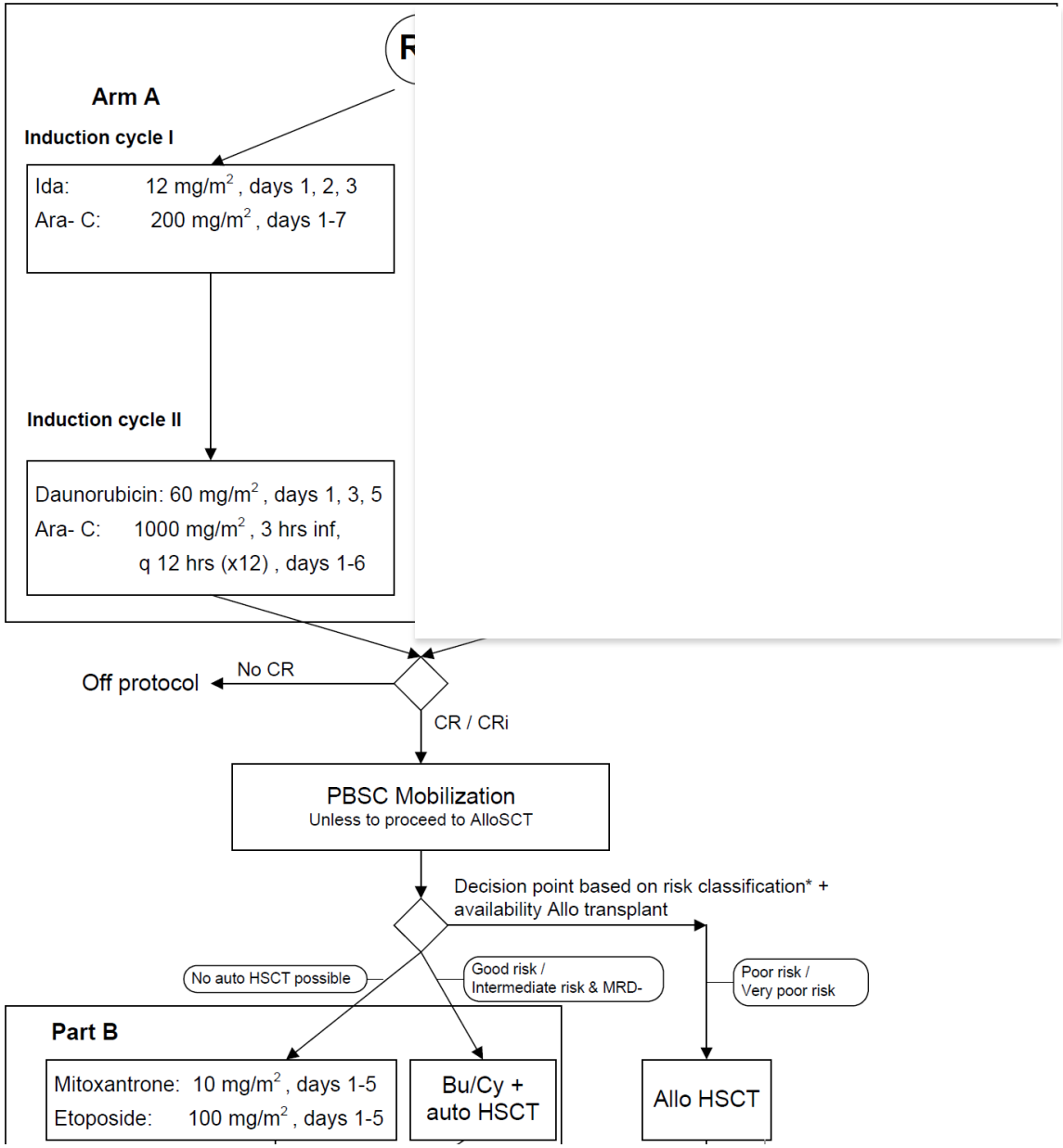
David Grimwade et al. Blood 2010;116:354-365

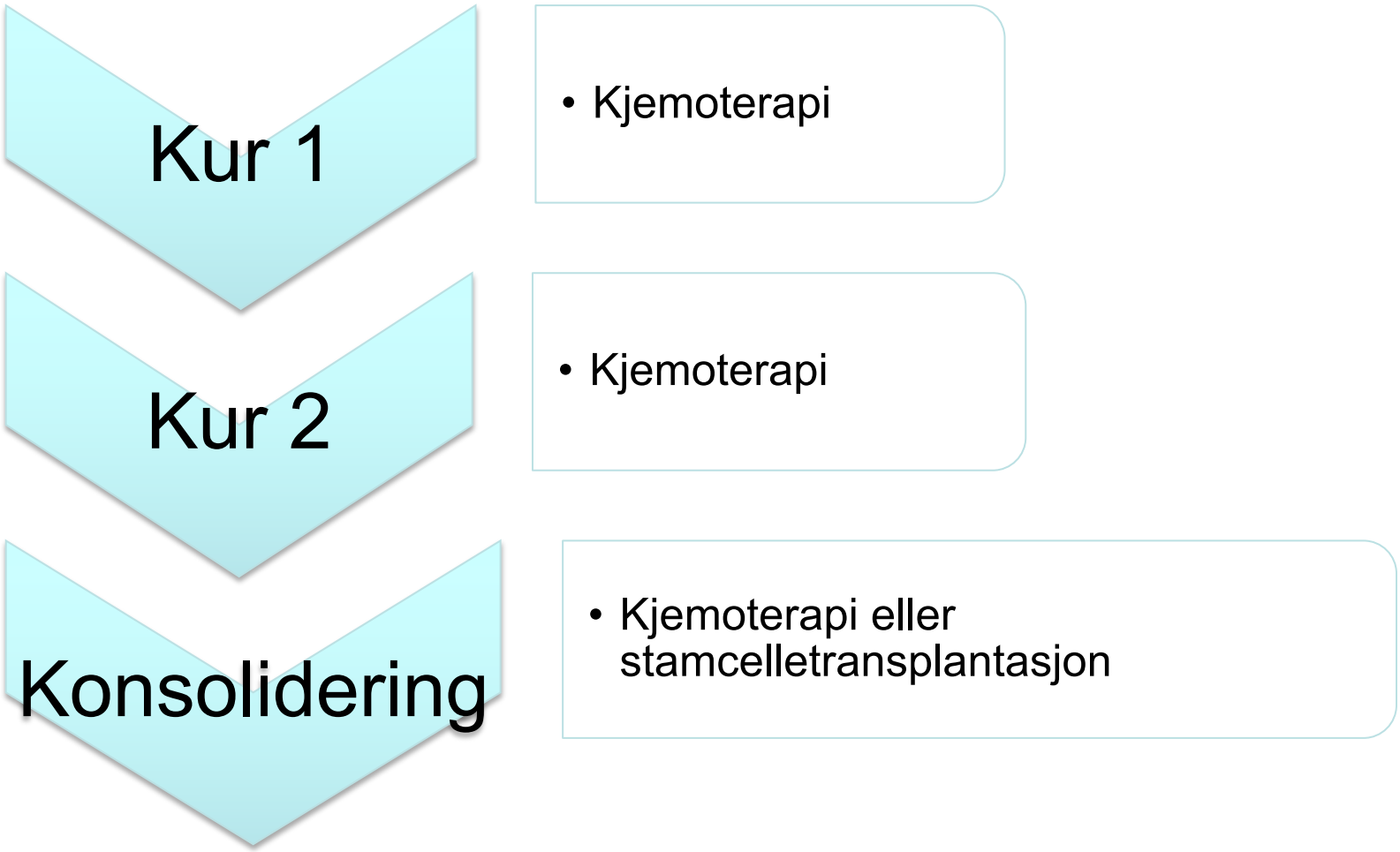


Age category (years)	1973-1980 (95% CI)	1981-1988 (95% CI)	1989-1996 (95% CI)	1997-2005 (95% CI)	2006-2011 (95% CI)
0-18	0.17 (0.10,0.25)	0.32 (0.23,0.62)	0.53 (0.42,0.62)	0.66 (0.57,0.73)	0.69 (0.58,0.78)
19-40	0.10 (0.06,0.14)	0.21 (0.15,0.27)	0.40 (0.33,0.46)	0.60 (0.53,0.67)	0.64 (0.54,0.72)
41-60	0.06 (0.04,0.09)	0.12 (0.09,0.16)	0.25 (0.21,0.29)	0.39 (0.35,0.43)	0.47 (0.41,0.52)
61-70	0.04 (0.02,0.06)	0.06 (0.04,0.09)	0.14 (0.11,0.17)	0.16 (0.13,0.19)	0.28 (0.23,0.33)
71-80	0.03 (0.01,0.05)	0.02 (0.01,0.04)	0.06 (0.04,0.08)	0.06 (0.04,0.08)	0.09 (0.06,0.12)
81 and older	0.03 (0.01,0.09)	0.01 (0.00,0.04)	0.02 (0.00,0.04)	0.02 (0.01,0.04)	0.02 (0.01,0.05)

Standard behandling av AML 2018

1 Scheme of study

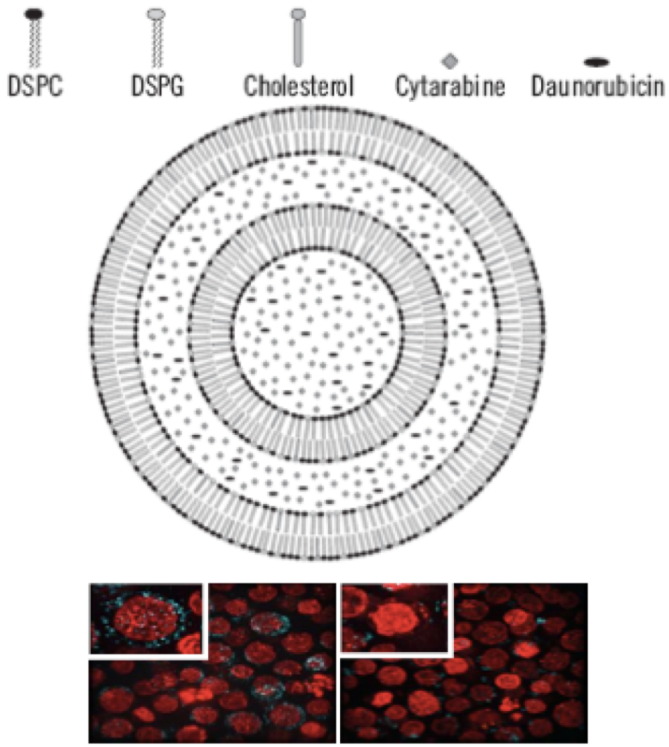



Kur 1
• Kjemoterapi
Kur 2
• Kjemoterapi
Konsolidering
• Kjemoterapi eller stamcelletransplantasjon

Hva kommer?

1. MLL-translokasjon:
2. IDH1 mutasjoner: flere i utvikling
3. IDH2 mutasjoner:
4. Hemming av kinaser som er aktiverte ved AML
5. Hemming av ”Immune evasion”
6. Antistoffer mot overflateantigener ved AML
7. Hypermetylering/epigenetikk: mange kandidater
9 Nye cytostatika:
    - 9 Liposomalt Daunorubicin og Cytarabin, CPX 351. 5:1 molar ratio av Cytarabin og Daunorubicin i 100 nm liposomer. I en enhet er det 1 mg Cytarabin og 0,44 mg Daunorubicin.

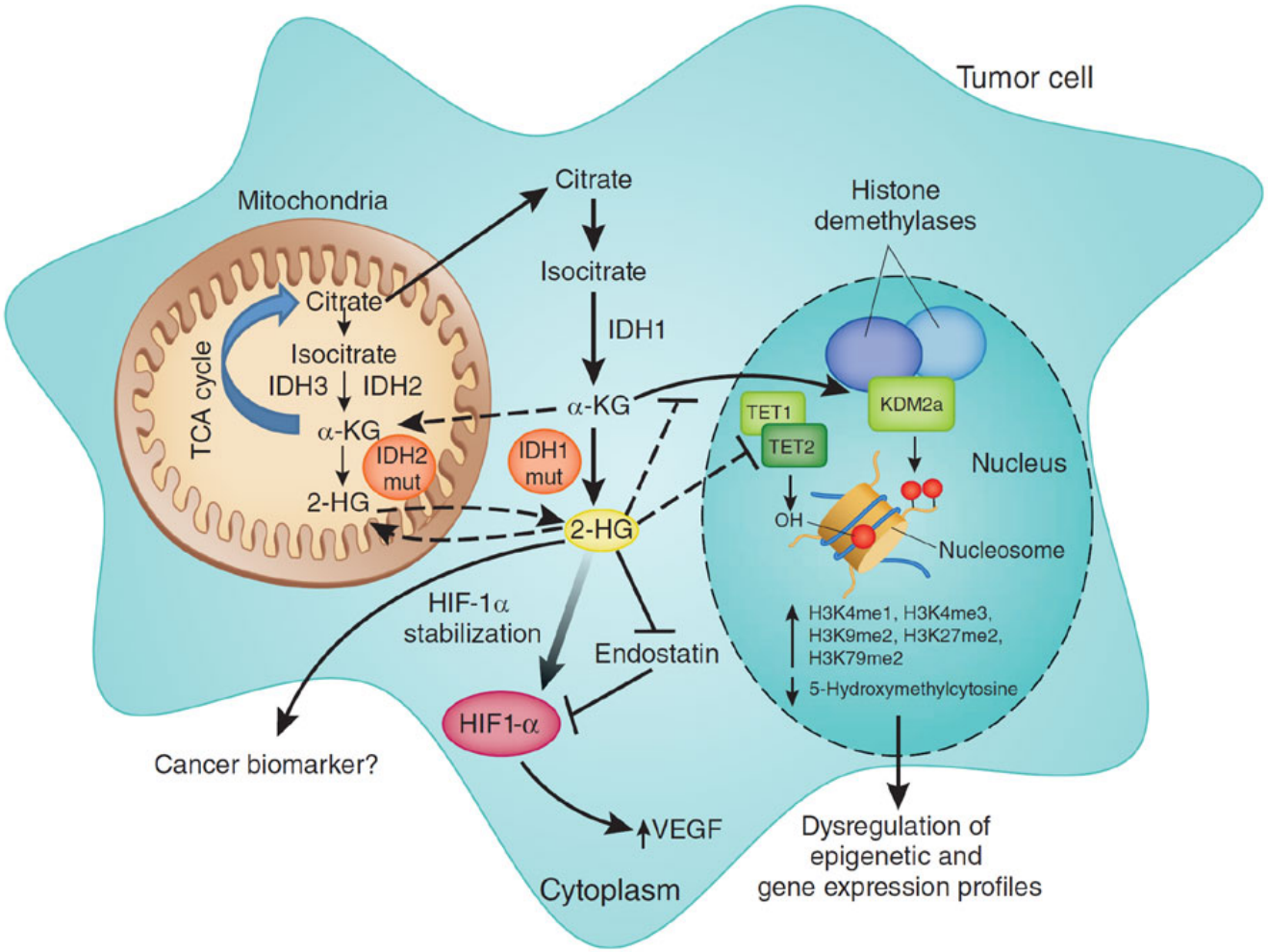
Cytarabine/Daunorubicin Liposome: CPX-351[1]



- 5:1 molar ratio of cytarabine to daunorubicin is optimal in in vitro and in vivo AML models
- 100-nm bilamellar liposomes
- CPX-351 accumulates and persists in the bone marrow
- Selective uptake of CPX-351 by leukemia blasts and intracellular drug release
- 1 unit = 1.0 mg cytarabine plus 0.44 mg daunorubicin

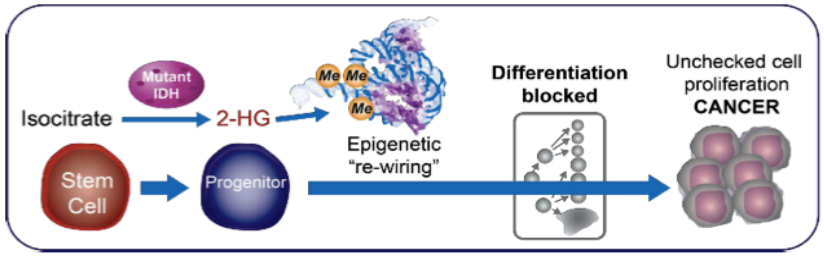
1. Lancet JE et al. *Blood*. 2014;123:3239-3246.

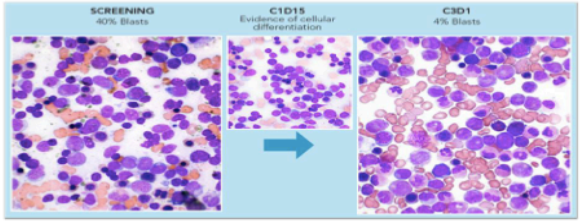
IDH mutert AML



IDH mutert AML

AG221: Differentiation Activity





@PeerView

AG-221 Phase 1/2: Clinical Response[1]

	RR-AML (n = 159)	Untreated AML (n = 24)	MDS (n = 14)	All (N = 209)
Overall response (CR, CRp, CRi, mCR, PR) (%) [95% CI]	59 (37%) [30%-45%]	10 (42%) [22%-63%]	7 (50%) [23%-77%]	79 (38%) [31%-45%]
CR	29 (18%) [CI: 13%-25%]	4 (17%) [5%-37%]	3 (21%) [5%-51%]	37 (18%) [13%-24%]
CRp	1 (1%)	1 (4%)	1 (7%)	3 (1%)
CRi	3 (2%)	0	0	3 (1%)
mCR	9 (6%)	1 (4%)	3 (21%)	14 (7%)
PR	17 (11%)	4 (17%)	0	22 (11%)
SD	72 (45%)	9 (38%)	6 (43%)	96 (46%)
PD	10 (6%)	1 (4%)	0	11 (5%)
Not evaluable	18 (11%)	4 (17%)	1 (7%)	23 (11%)

- Overall response by IDH mutation type: R140Q 36% / R172K 42%

1. Stein et al. ASH 2016.

@PeerView

FLT3-mutert AML

Figure 1. Overall Survival in Newly Diagnosed FLT3 mutant AML