FISHing for Acute Leukemia

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Banner MD Anderson Cancer Center
September 12, 2017

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Objectives

* Discuss the clinical presentation and diagnosis of acute leukemia
* Discuss the impact of molecular features on prognosis and management
* Discuss the treatment of AML in the elderly
* Discuss up front management of APL and ALL

*Case Presentation

*32yo resident presents with sore throat and fever

*Cervical adenopathy is present on exam

*CBC: 35>35%<35k

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*Peripheral Smear

*92% Other
*4% Lymph
*4% Neutrophils

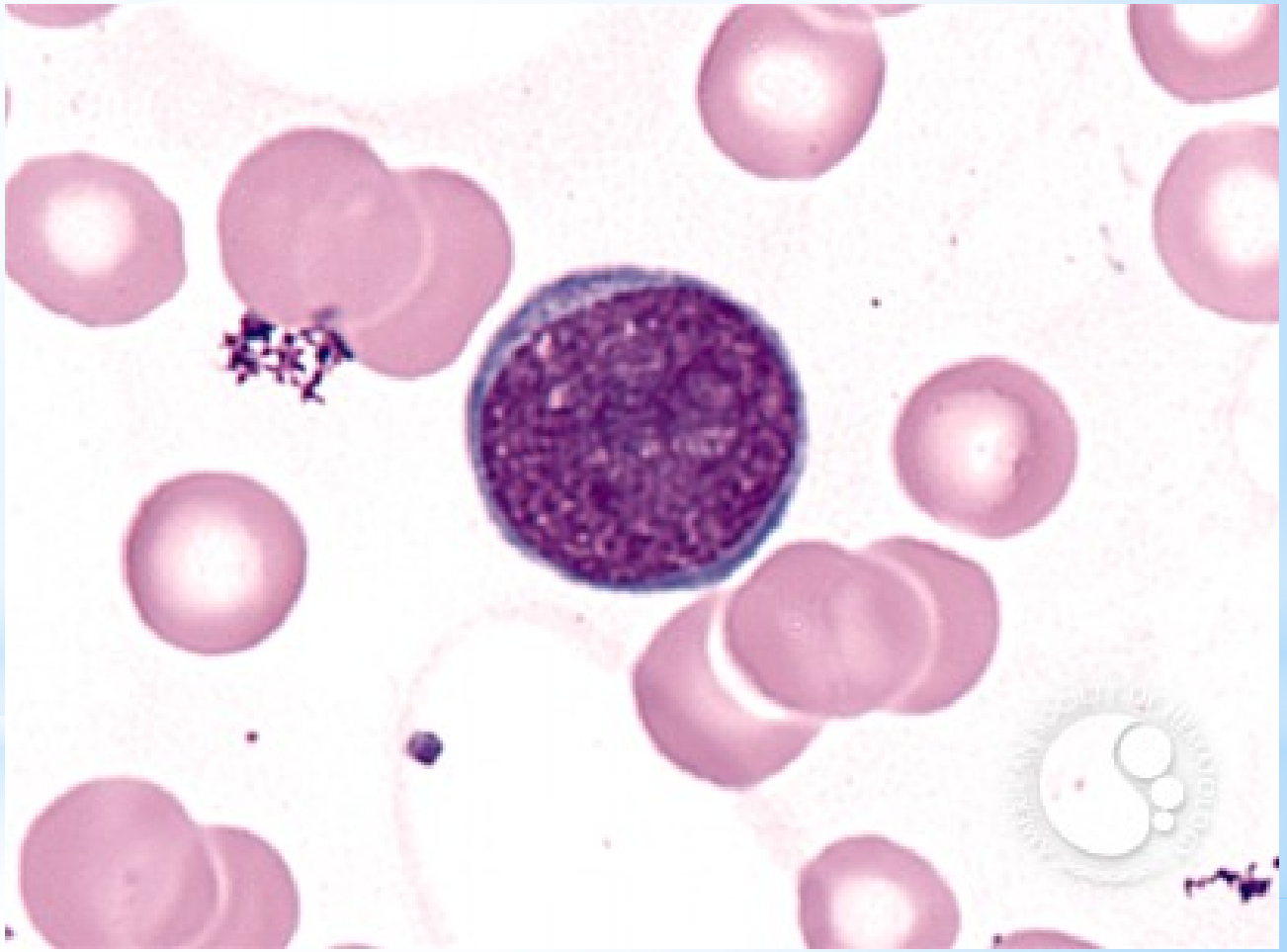
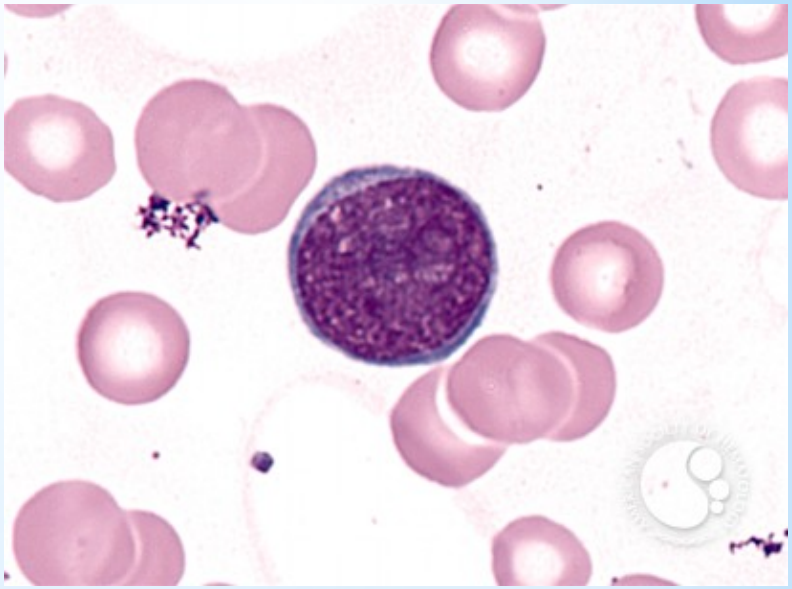


Image courtesy of Peter Maslak

American Board of Internal Medicine®

*Peripheral Smear



- *92% Blasts
- *4% Lymph
- *4% Neutrophils

- *He was diagnosed with Ph+ Acute Lymphoblastic Leukemia

- *Induction chemotherapy plus dasatinib was recommended

Image courtesy of Peter Maslak

Case Presentation

* 52yo man develops intermittent fevers x 2 weeks
* Later, chest pain, dyspnea on exertion, followed by marked fatigue.
* No other B symptoms and no bruising or bleeding.
* No other PMHx, never smoker, rare EtOH
* 1 full brother, 1 full sister

* Exam: Temp 37.3, HR 117, BP 107/54, RR 24
* Conjunctival rim pallor noted, tachycardic with systolic murmur present at the apex. No LAD or HSM

Initial testing

* CBC: 6.9>2.6<79 MCV 100

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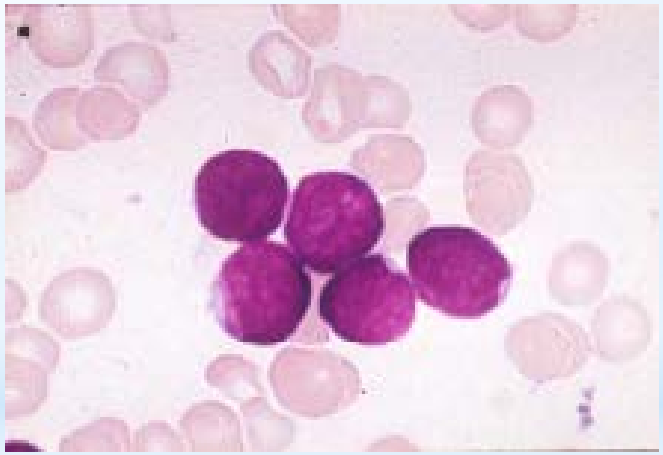
Initial testing

- CBC: 6.9>2.6<139 MCV 100
  - 32% neutrophils, 6% bands, 2% lymphocytes, 1% monocytes, 1% metamyelocytes, 1% myelocytes and 53% 'other' cells.
- Peripheral smear
  - Atypical immature cell population with high N:C ratio, nucleoli



- Reticulocyte 0.3%; absolute 2000/µl
- Cr 0.8, total bilirubin 0.4, LDH 392, albumin 3.7, AST 45, ALT 145,

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Clinical Symptoms of AML

* Bone Marrow Failure (Cytopenias)
  * Anemia - dyspnea, pallor, chest pain
  * Neutropenia - infections
  * Thrombocytopenia - bleeding, petechiae
* Coagulopathy
  - esp APL, Acute myelomonocytic leukemia
* Tissue invasion

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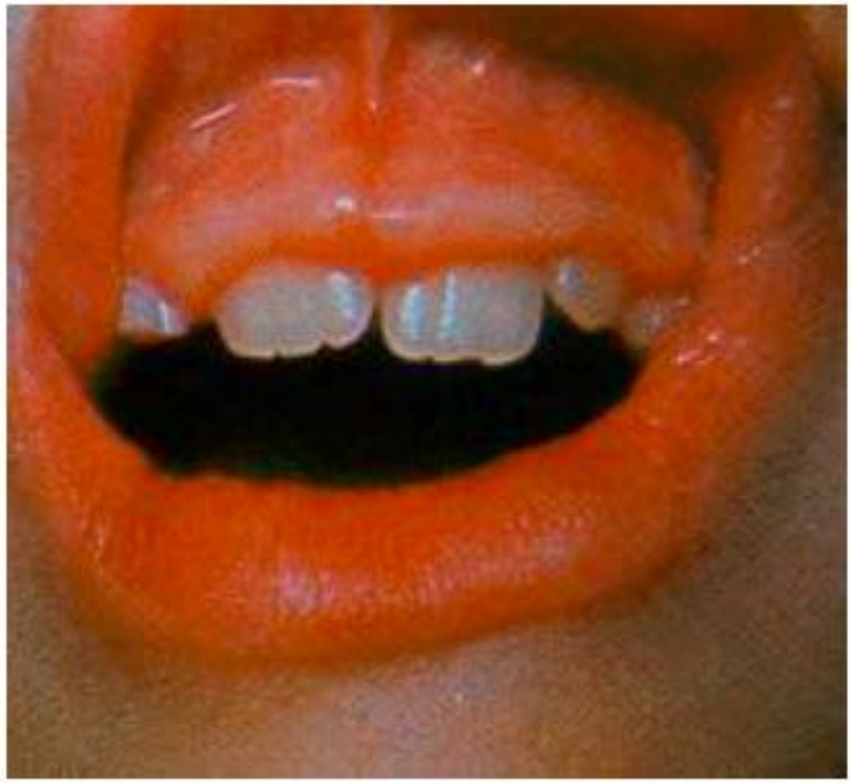
Tissue Invasion in AML

* Associated with high WBC, monocytic subtypes, CD56+
* Can Involve
  - spleen
  - gums
  - perianal
  - skin
  - renal
  - lung



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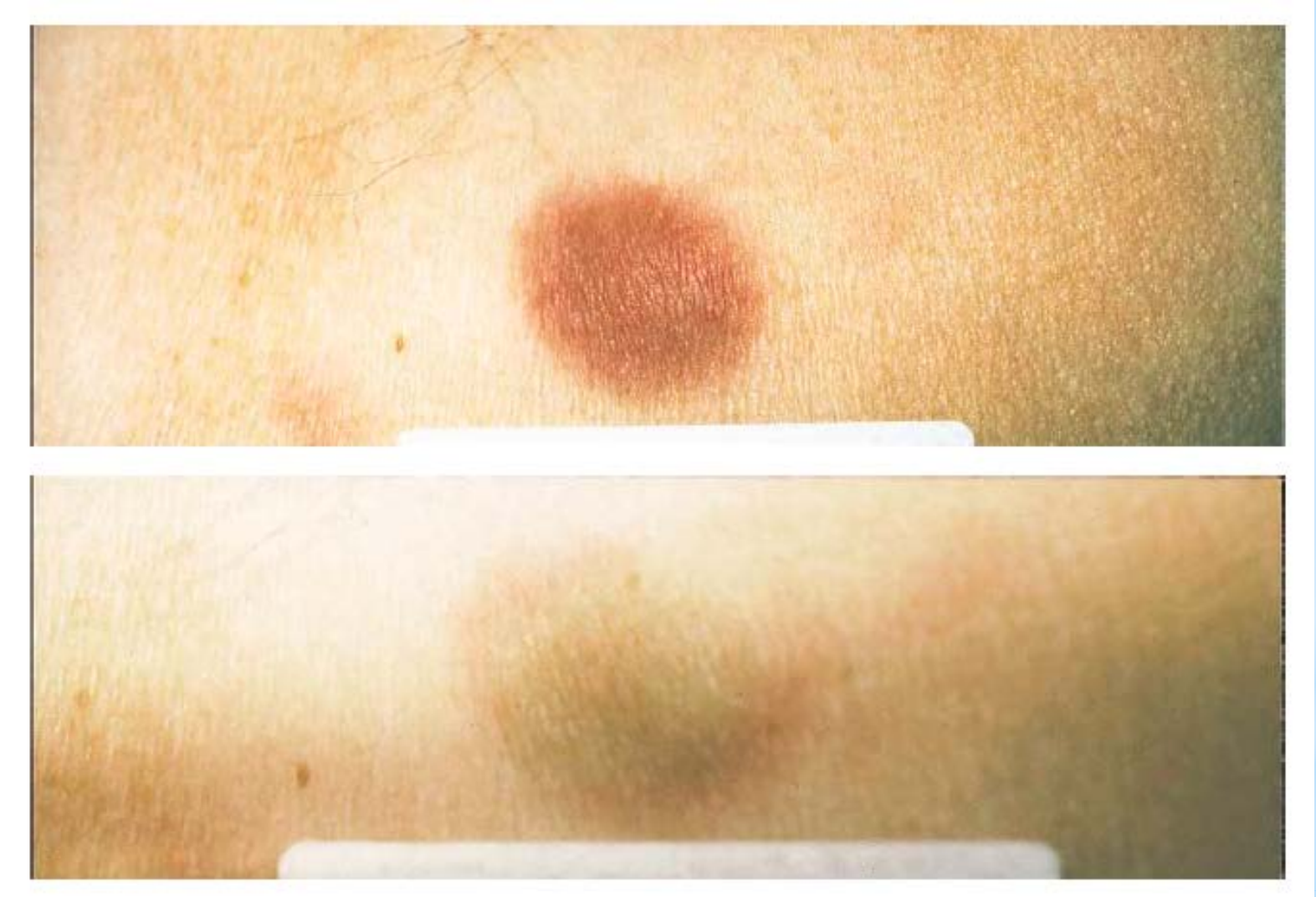
* Chloroma



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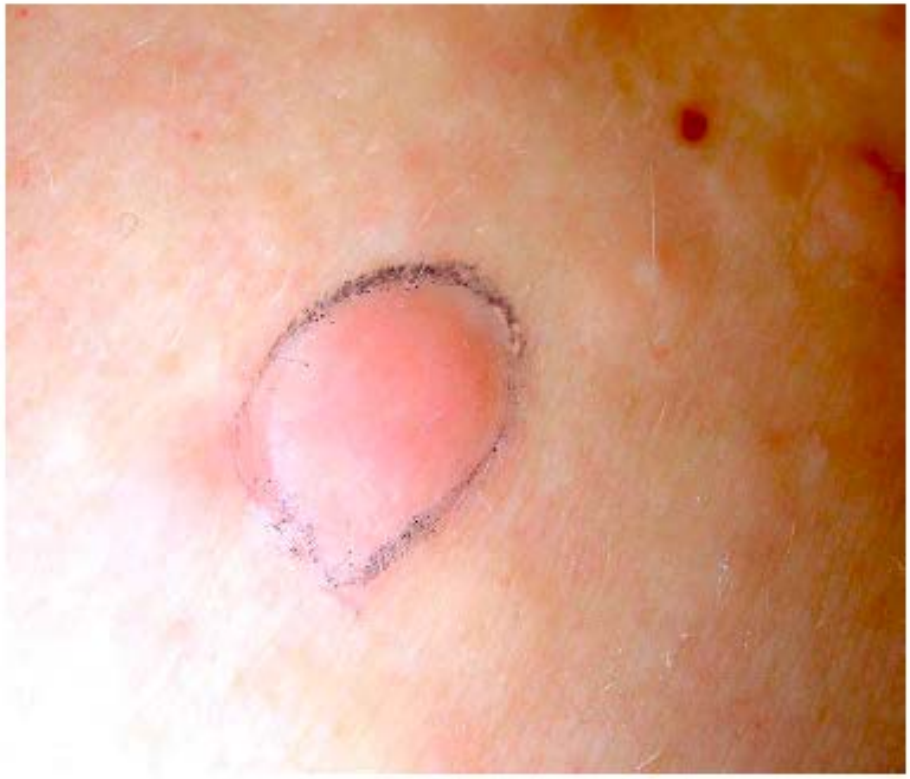
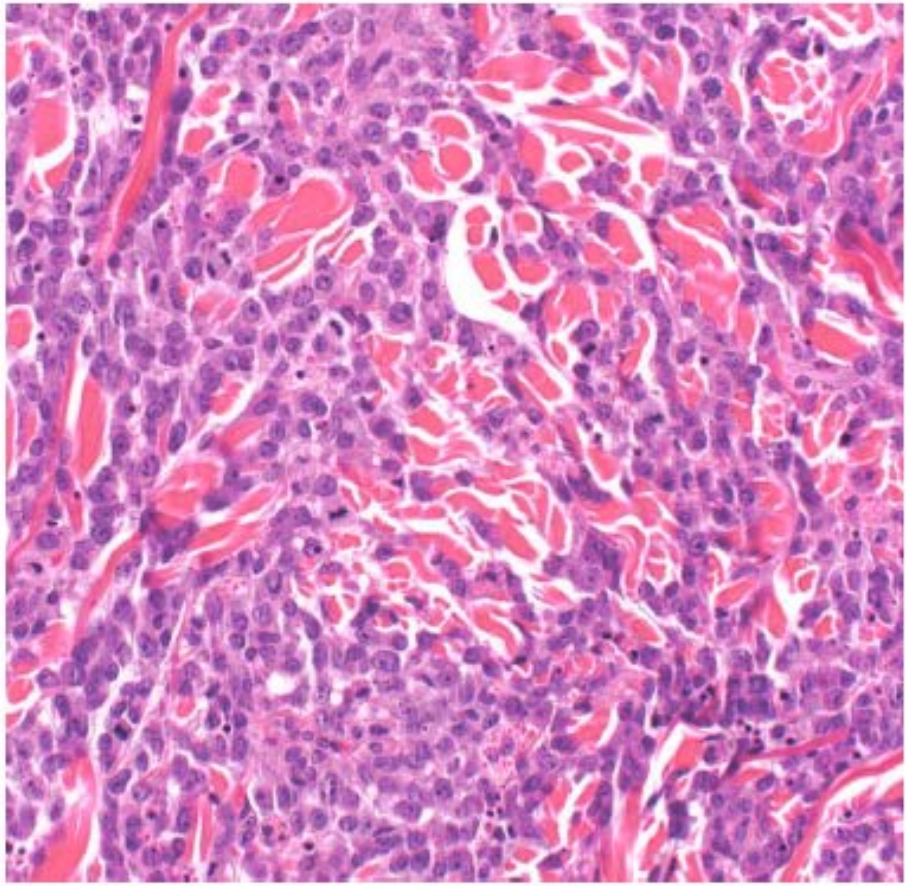
Leukemia Cutis





Sauter and Jacky *NEJM* 1998. 338:969

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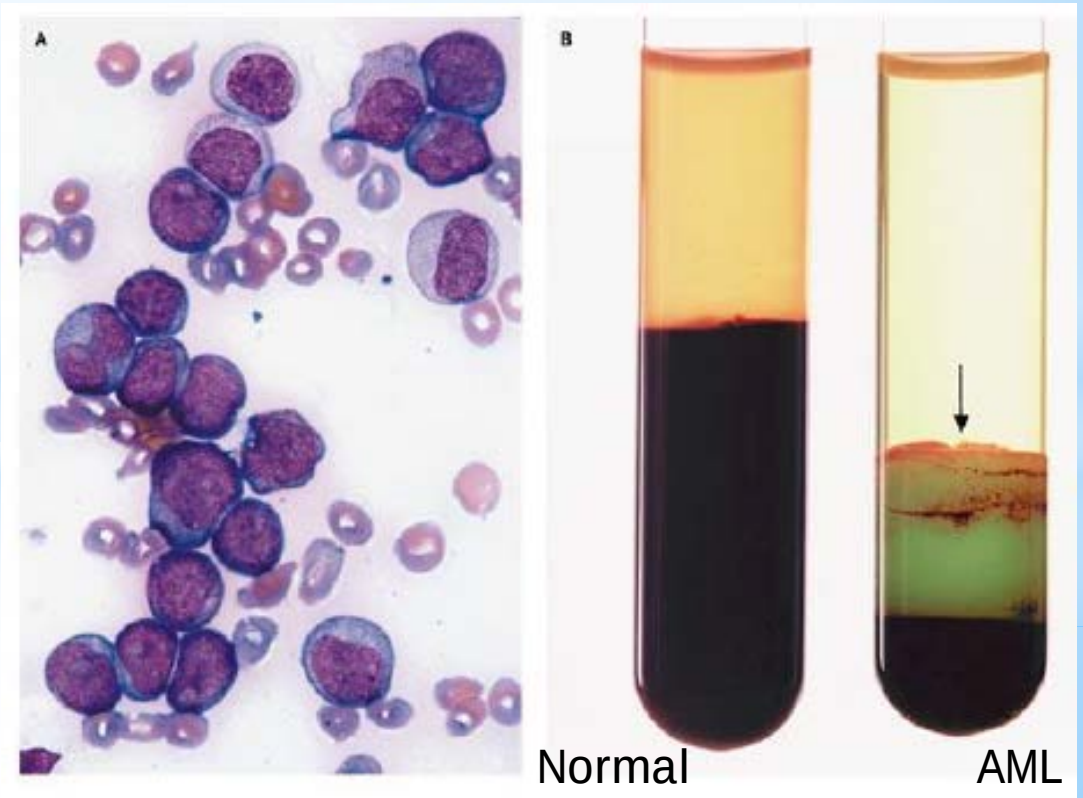
High Circulating Blasts

- Hypoglycemia
- Hypoxia
- Hyperkalemia
- Elevated Lactate

Mauro MJ NEJM 2003. 349:767



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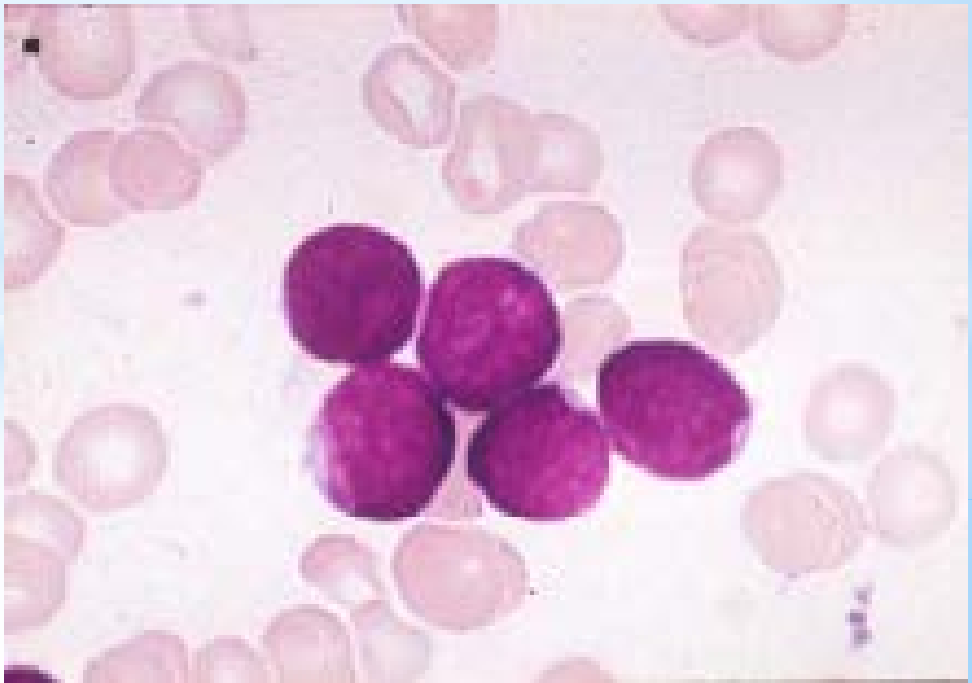
Evaluation of patient with AML

- Initial triage
  - History and Physical
  - CBC with differential (look at the peripheral smear)
  - BMP, LFTs, uric acid, ABO type and screen
  - PT, PTT, fibrinogen



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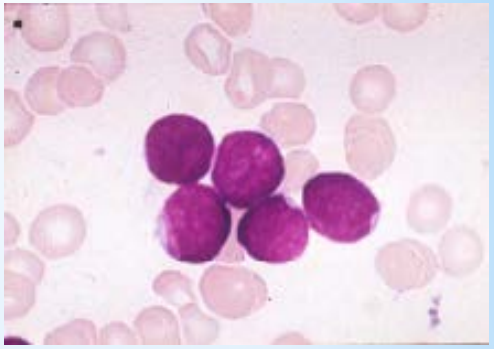
Evaluation of patient with AML



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  - History and Physical
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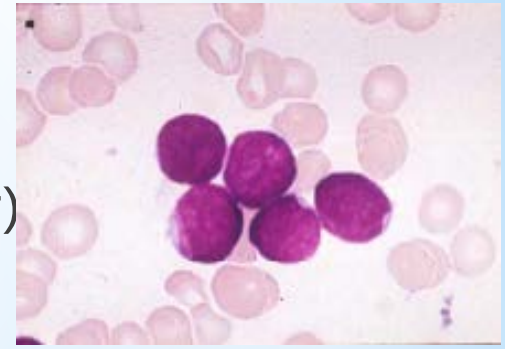
- Diagnosis
  - Bone marrow biopsy
  - FISH and cytogenetics, flow cytometry
  - Molecular: FLT3, NPM1, CEPBA, IDH, ckit (can be sent on PB)
  - If circulating blasts, send peripheral blood for flow cytometry (STAT) to make dx

Evaluation of patient with AML



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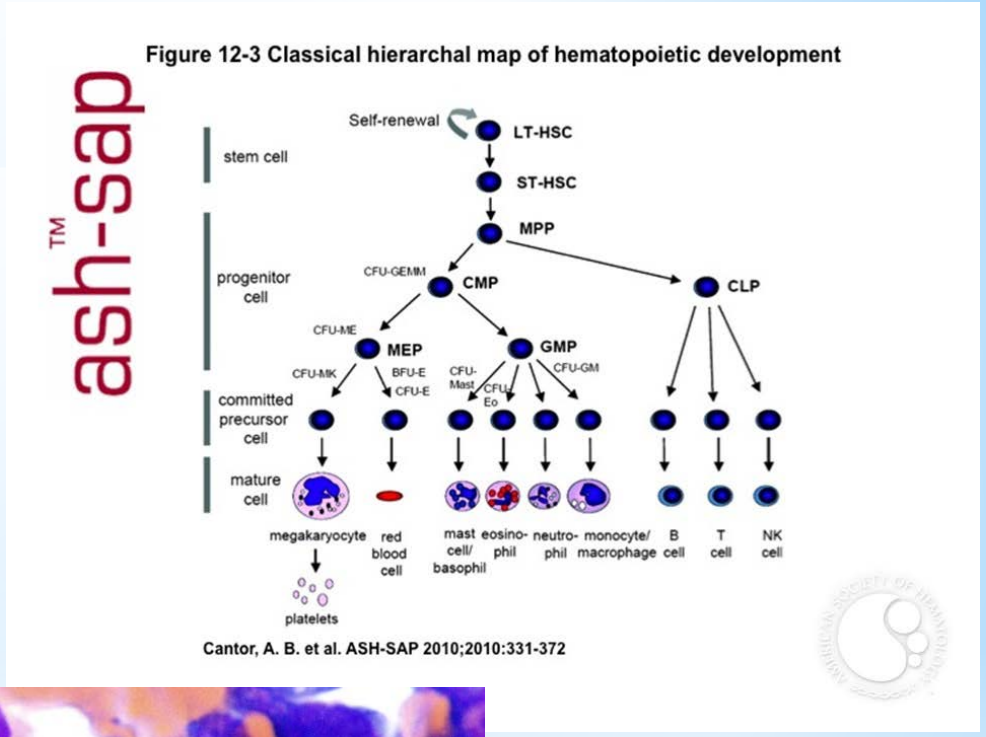
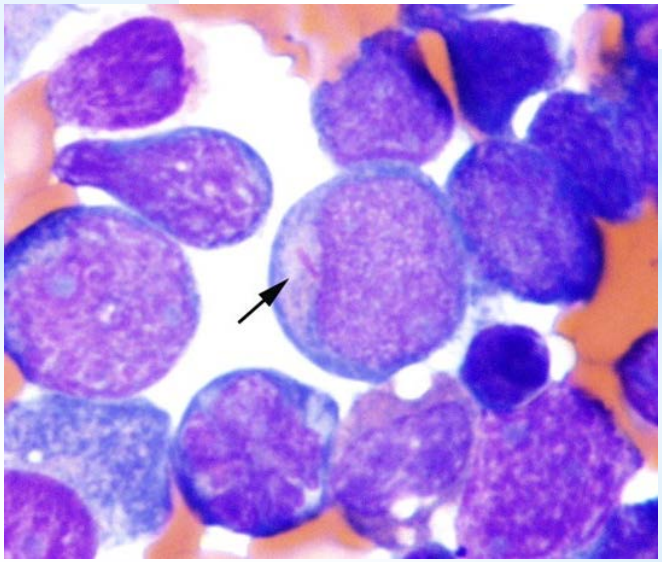
  - If circulating blasts, send peripheral blood for flow cytometry (STAT) to make dx
- Plan ahead
  - HLA typing (Type I for platelets, Type I and II for SCT)
  - Identify siblings and brief health history, CMV serostatus
  - Consideration of future fertility

* Differentiate AML vs ALL

* Rarely, can see Auer Rods
  - Only in myeloid blasts
* Flow cytometry
* Cytogenetics - t(8;21), inv16, t(9:22)





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Immediate Emergency?

- Leukostasis (leukapheresis)
  - Pulmonary or neurological symptoms related to increased serum viscosity
  - Can occur
    - when myeloid blast count >50-100k
    - When lymphoid blast count >400k
    - very rare in CLL
- DIC (esp APL and monocytic)
  - Aggressive product replacement
- Initial treatment can trigger SIRS
- Tumor lysis syndrome

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How soon to treat the others?

* Sekeres et al Blood 2009. 113:38
  - No increase in mortality when treatment started within 5 days for patients >60yo.
  - In younger, earlier the better
* Obtain necessary diagnostic information prior to selecting regimen
  - Echocardiogram
  - Central line (anthracycline is vascular irritant, extravasation toxicity)

AML vs ALL with flow cytometry (or IHC)

Myeloid	*B-cell (lymphoid)*	*T-cell (lymphoid)*
CD13	***CD10***	***CD2***
CD33	***CD19***	***CD3***
c-kit	***CD20***	***CD4***
CD14	***CD22***	***CD5***
CD64	***Surface Ig***	***CD7***
Glycophorin A		***CD8***
CD41		
MPO		

CD34 marks these cells as immature blasts (rare exceptions of CD34-negative blasts) The same marker as for HPC

Day 1

- Only day 0 in transplant
- Day 1 = first day of chemotherapy
  - Knowing how long since last chemo lets us anticipate and interpret

7+3 = 3+7

- Induction
  - Anthracycline (3 days)
    - Daunorubicin 60-90mg/m2 better than 45mg
    - Idarubicin 10-12mg/m2
    - Mitoxantrone 12-15mg/m2
  - Cytarabine (ara-C) - 7 days continuous infusion
    - 100mg/m2 better than 200mg/m2

Berman et al. Blood 1991. 77:1666
Ohtake et al. Blood 2011. 117:2358
Rowe et al. Blood 2004. 103:479
Wiernik et al. Blood 1992. 79:313

* 3+4 = ?

* 3 days of anthracycline (same as 7+3)
* 4 days of cytarabine at 1gm/m2
  - Burnett et al. JCO 2013
  - High-dose AraC benefits <45yo (FLAG-Ida)
* No data yet published on this regimen
  - Extensive experience in Houston
* Day 21 marrow with this regimen

*Trials of Induction therapy in AML

Table 1 Results of selected trials of therapy for adult AML

Table 1 | Results of selected trials of therapy for adult AML

Trial	Regimen	*n*	CR total (%)	CR cycle 1 (%)	Early death (%)	Resistant disease (%)	OS 3-year (%)
PALG[3]	DA	211	56	51	10	34	33
	DAF	219	59	55	9	32	35
	DAC	222	67.5	62	11	21	45
SWOG[6]	DA	300	69	50	1	29	55
JALSG[7]	DA	525	77.5	61.1	2	20	48
	IA	532	78.2	64.1	5	17	48
ECOG[5]	D45A	293	57.3	41.1	4.5	39	33
	D90A	289	70.6	58.8	5.5	25	40
MRC[2]	DA	240	83	NA	6	11	41*

*5-year overall survival. Abbreviations: CR, complete remission; D45A, DA 45 mg/m² per day; D90A, DA 90 mg/m² per day; DA, daunorubicin and cytarabine; DAC, daunorubicin, cytarabine and cladribine; DAF, daunorubicin, cytarabine and fludarabine; IA, idarubicin; NA, not applicable; OS, overall survival.

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Nat Revw Clin Onc doi:10.1038/nrclinonc.2012.98

AML in the elderly

* Increased resistance to chemotherapy (MDR1 expression)
* More likely to have unfavorable cytogenetics
* More likely secondary to MDS
* More comorbidities

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Appelbaum et al. Blood 2006. 107:3481

* Mortality from 7+3 induction at 30 days

	Age			
	< 56	**56 - 65**	**65 - 75**	**> 75**
Patient #	364	242	270	79
ECOG PS				
0	2%	11%	12%	14%
1	3%	5%	16%	18%
2	2%	18%	31%	50%
3	0%	29%	47%	82%

Appelbaum et al. Blood 2006. 107:3481

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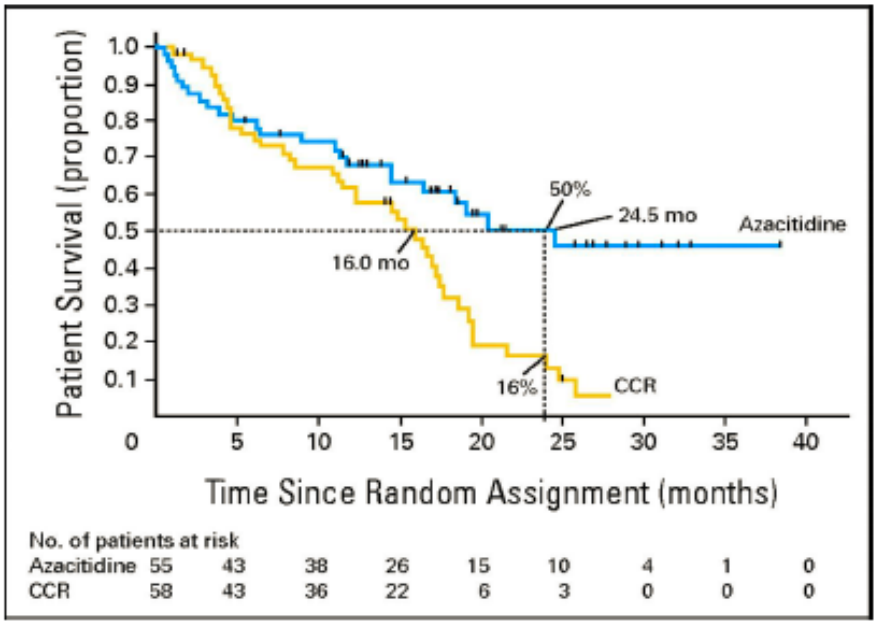
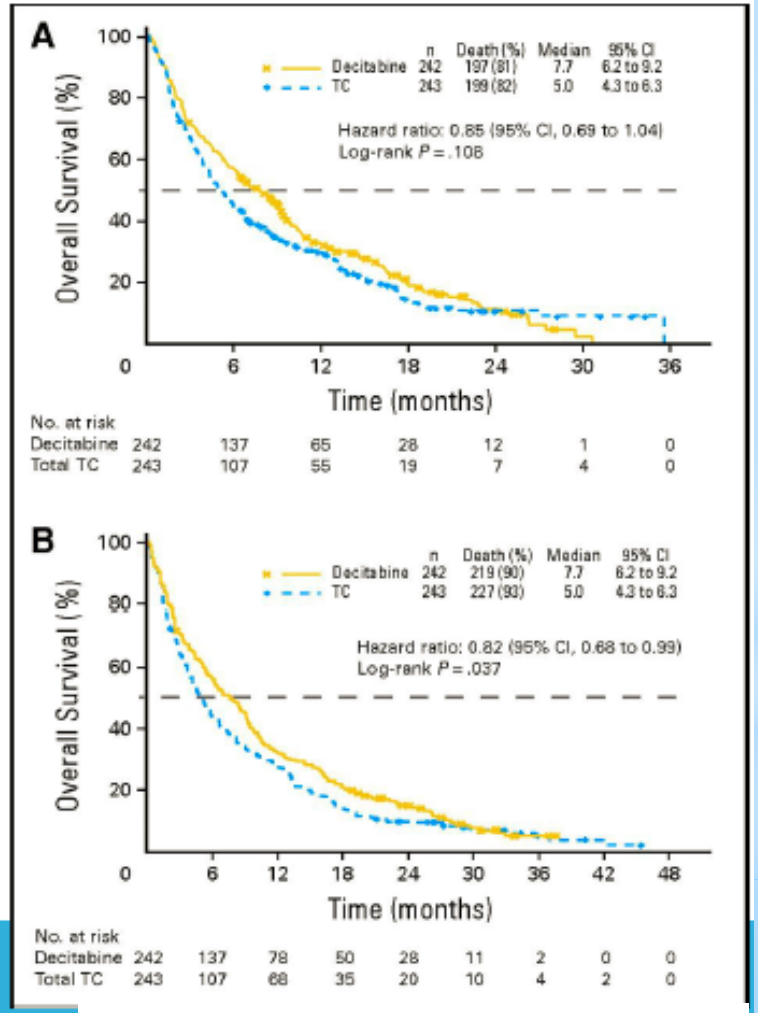
* Hypomethylating agents in AML

Med Age 70
Aza 75 mg/m² daily X 7 days q 4 weeks
CCR=BSC(27),LDAC (20), IC (11)



Age ≥ 65
Dec 20 mg/m² daily x 10 days q 4 weeks
TC=SC(28) +/- LDAC (215) 20 mg/m² daily x 10 days q 4 weeks



Fenaux P et al. *J Clin Oncol* 2010;28:562-569

Kantarjian H M et al. *J Clin Oncol* 2012;30:2670-2677

Day 3-7

- The pathology results begin to return
  - inv16 by FISH, confirmed by cytogenetics
  - cKIT mutation added = negative
  - FLT3 ITD, NPM1, CEPBA, IDH negative

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Day 3-7

- The pathology results begin to return
  - inv16 by FISH, confirmed by cytogenetics
  - cKIT mutation added = negative
  - FLT3 ITD, NPM1, CEPBA negative

- So what?!?

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WHO AML Categorization

- >20% blasts in PB or BM required
  - except for *

Acute myeloid leukemia with recurrent genetic abnormalities

- *AML with t(8;21)(q22;q22); *RUNX1-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)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*
- AML (megakaryoblastic) with t(1;22)(p13;q13); *RBM15-MKL1*
- *Provisional entity: AML with mutated NPM1*
- *Provisional entity: AML with mutated CEBPA*

Acute myeloid leukemia with myelodysplasia-related changes

Therapy-related myeloid neoplasms

Acute myeloid leukemia, not otherwise specified

- AML with minimal differentiation
- AML without maturation
- AML with maturation
- Acute myelomonocytic leukemia
- Acute monoblastic/monocytic leukemia
- Acute erythroid leukemia
  - Pure erythroid leukemia
  - Erythroleukemia, erythroid/myeloid
- Acute megakaryoblastic leukemia
- Acute basophilic leukemia
- Acute panmyelosis with myelofibrosis

*Myeloid sarcoma

Myeloid proliferations related to Down syndrome

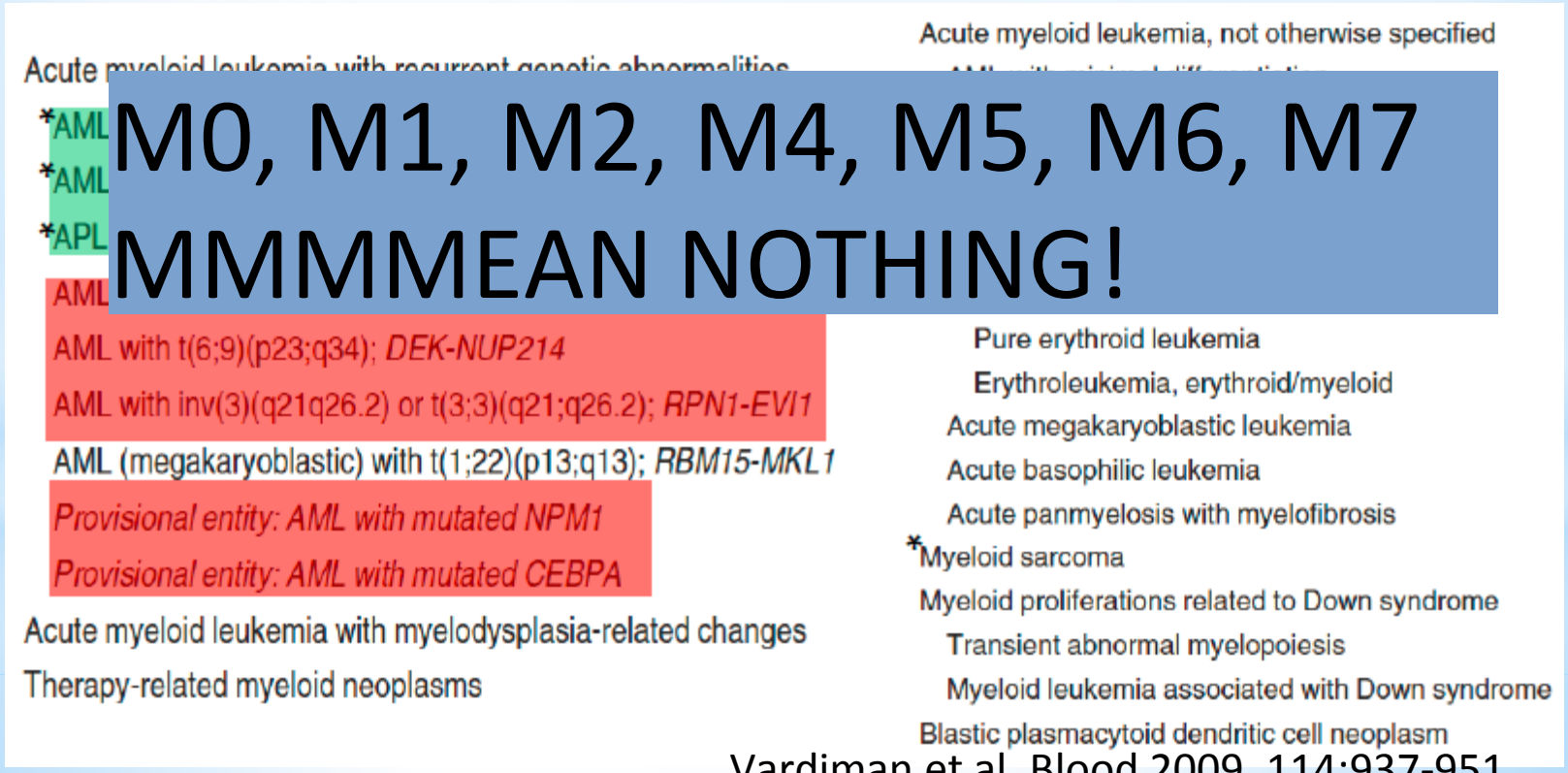
- Transient abnormal myelopoiesis
- Myeloid leukemia associated with Down syndrome

Blastic plasmacytoid dendritic cell neoplasm

Vardiman et al. Blood 2009. 114:937-951

* WHO AML Categorization

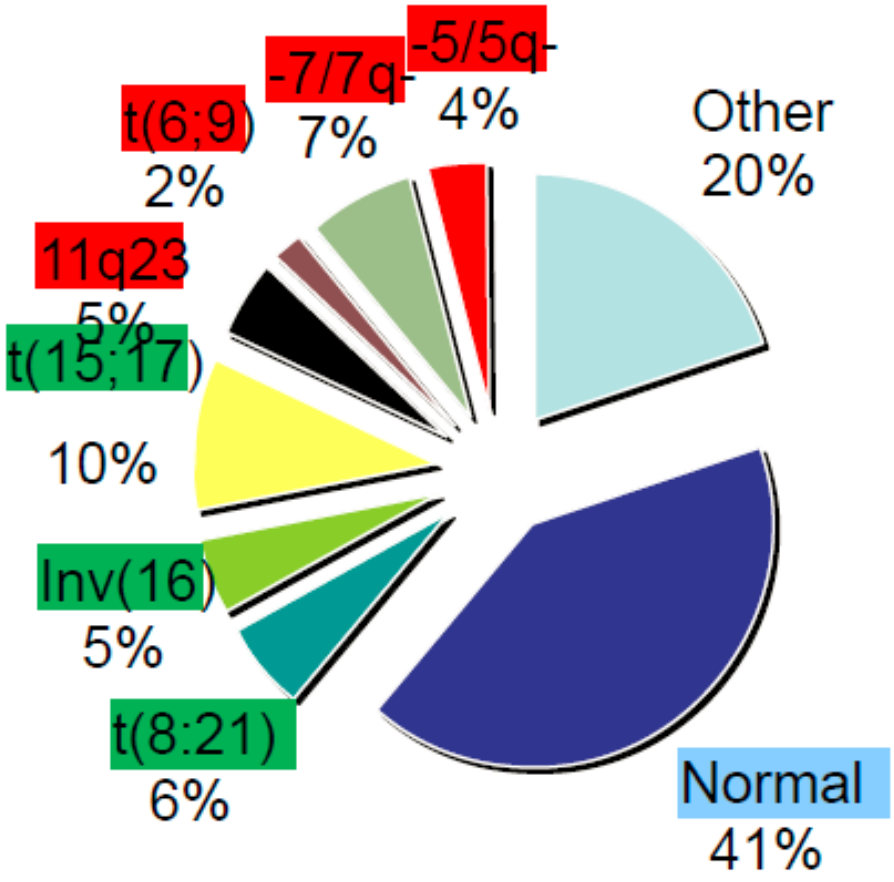
* >20% blasts in PB or BM required
  - except for *

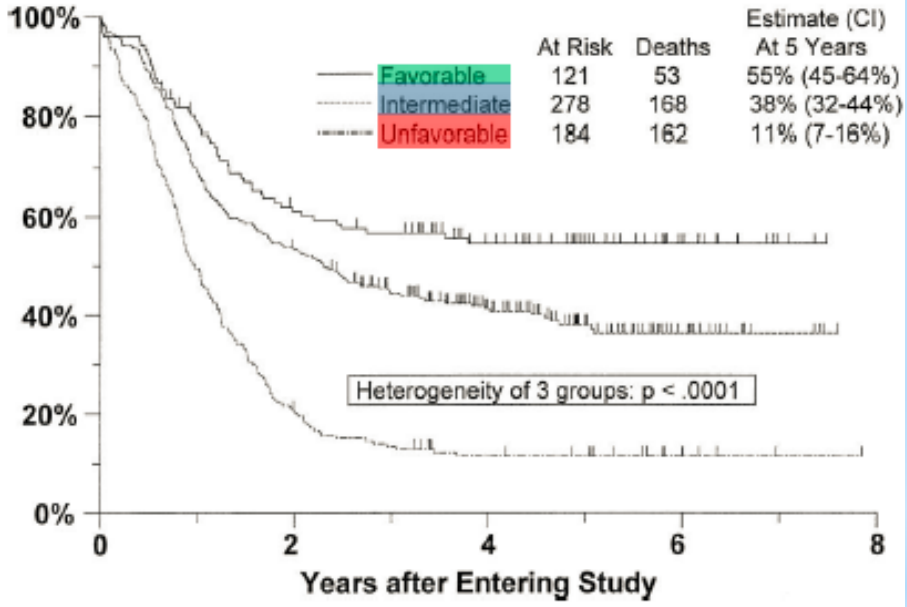


M0, M1, M2, M4, M5, M6, M7
MMMMEAN NOTHING!

Vardiman et al. Blood 2009. 114:937-951

Clonal Cytogenetic Abnormalities in Adult AML





t(16:16), del 16q

-Y, +8, +6, del 12p

Abn 3q, 9q, 11q, 20q, 21q, 17p, t(9;22), complex

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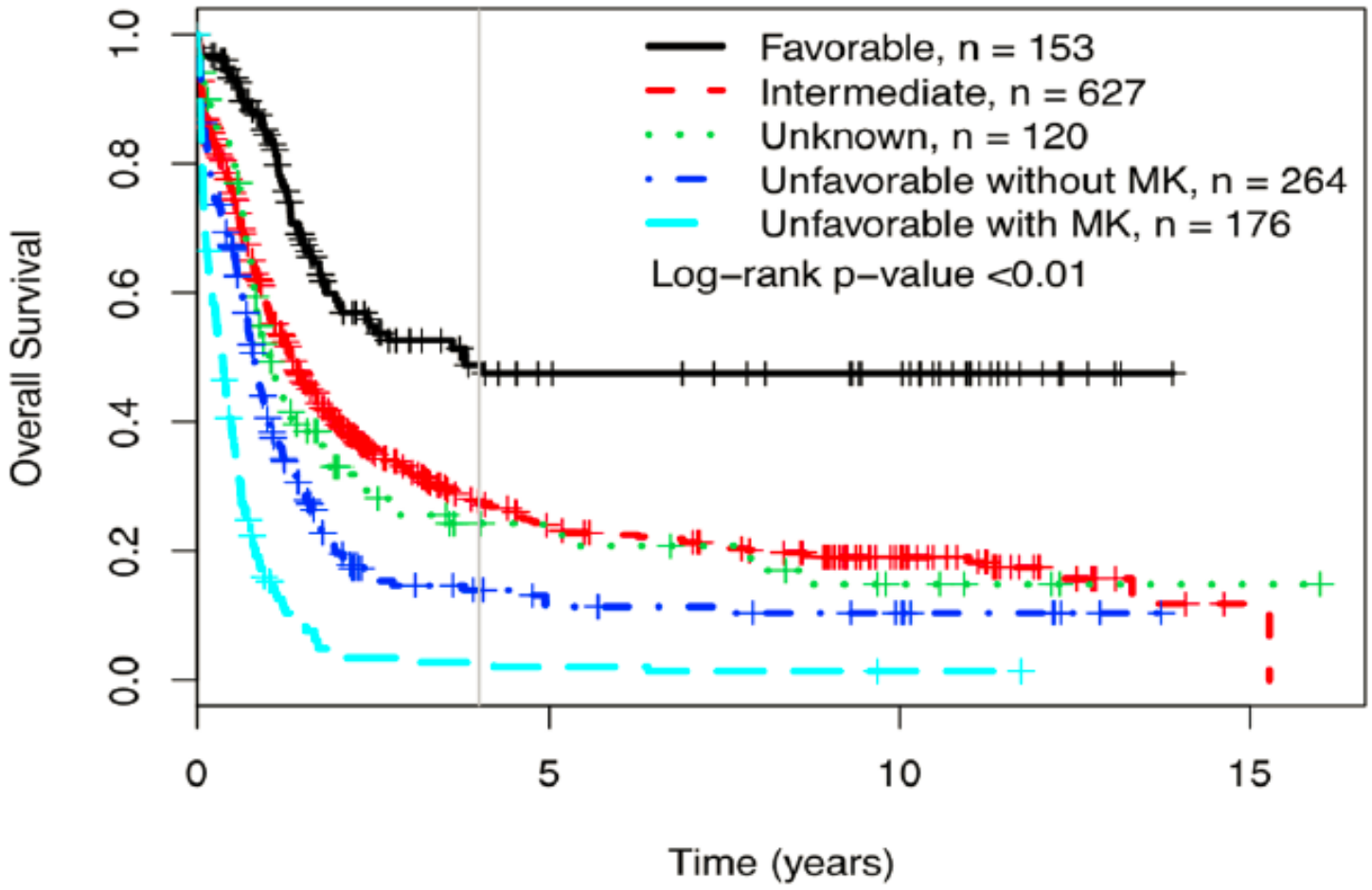
Slovak et al. Blood 2000. 96:4075

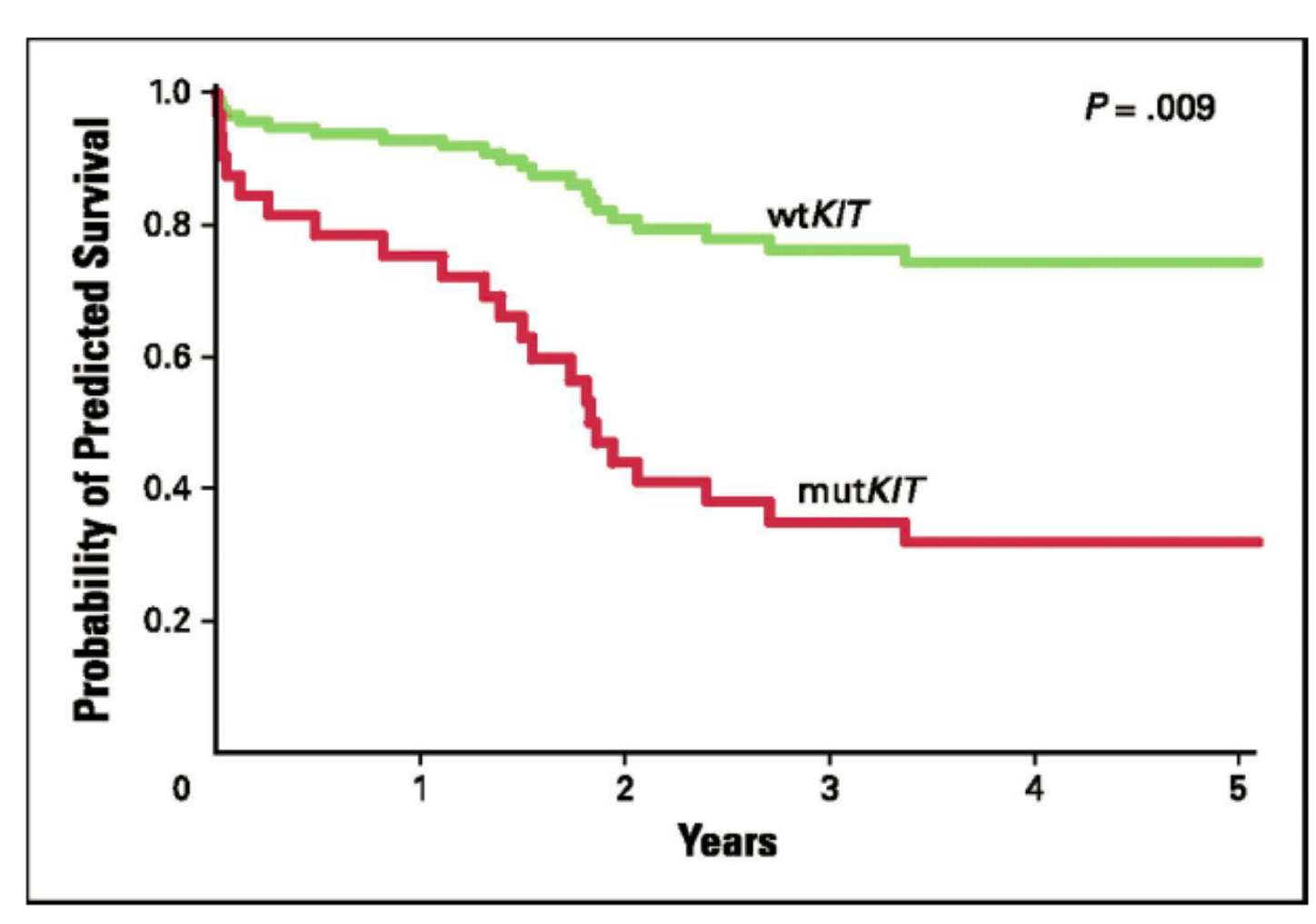
Cytogenetics and Survival in AML



MK=2 or more monosomies or 1 monosomy with structural abnml

Medeiros et al. Blood 2010. 116:2224

* Survival inv(16) AML based on KIT



Paschka P et al. JCO 2006. 24:3904

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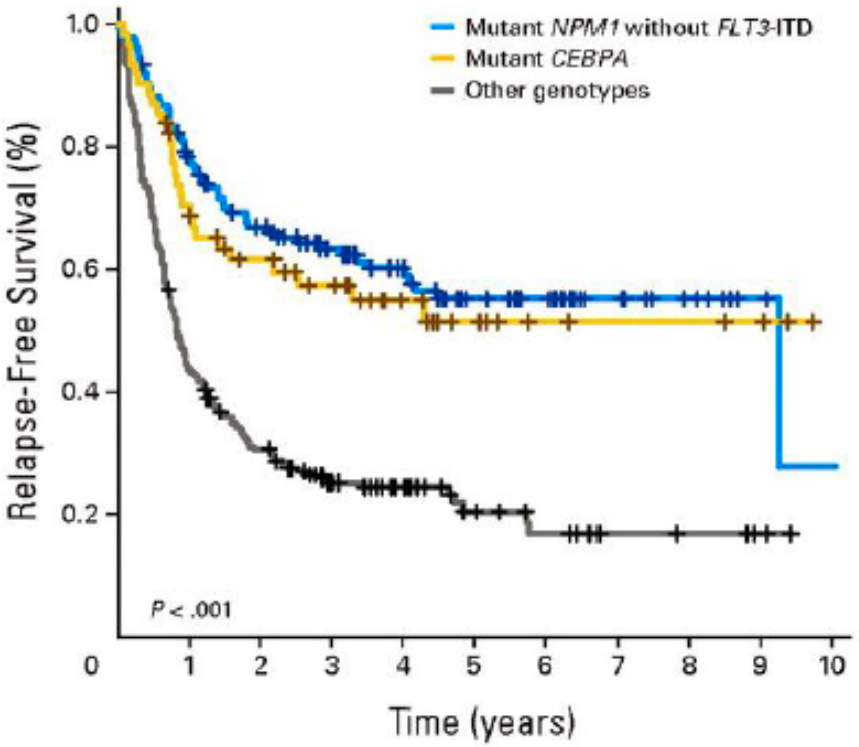
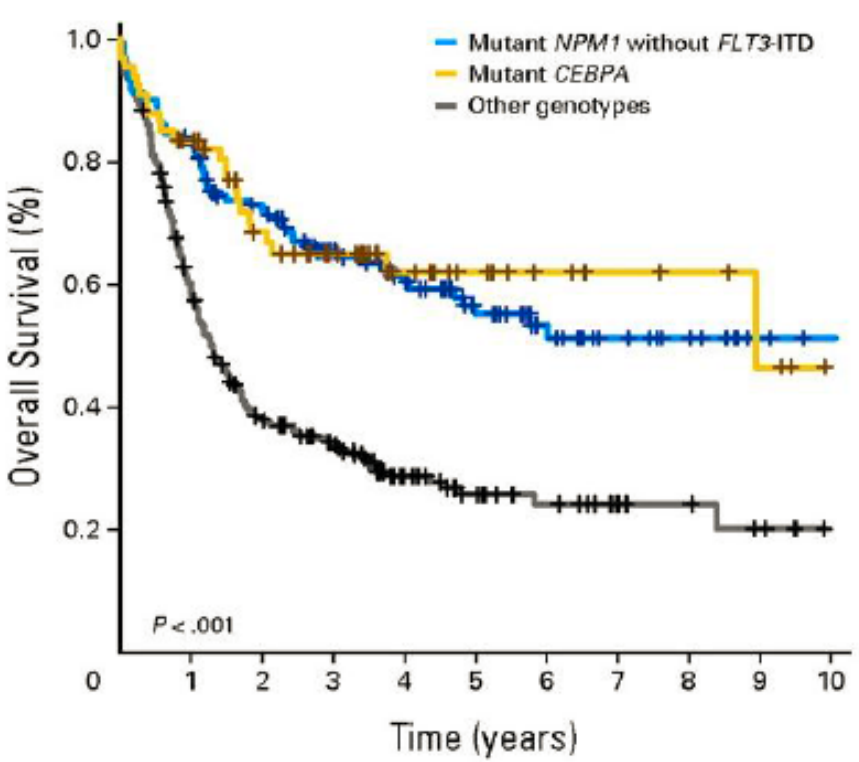
* AML with normal cytogenetics





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Schlenk et al. NEJM 2008. 358:1909

* **On target**
  Mutations help optimally treat AML

* Current targeted medicines available:
  * FLT3 + = midostaurin
  * IDH + = enasidenib
  * Many other in clinical trials

Stein, EM et al. *Blood*. 2017 Aug 10;130(6):722-731. Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia.
Stone, RM et al. *N Engl J Med*. 2017 Aug 3;377(5):454-464.
Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a FLT3 Mutation.

So what is next?

* Need to achieve complete remission (CR)
  - <5% blasts by morphology AND Plt >100k and ANC >1.0
  - Day 14 or Day 21 marrow tells us some, but not all of CR definition
  - CR is one of the best predictors of OS for individual patient
* If not in CR - next line therapy
  - Minimal residual disease = CR, but with detectable disease by flow/FISH/molecular
* If in CR - not done yet…

* AML in CR1

* Consolidation with Cytarabine x 3-4 cycles
  - Burnett et al JCO suggests total of 4 (3 consolidation) is just as good as 5

- Hematopoietic Stem Cell Transplant (HCT)

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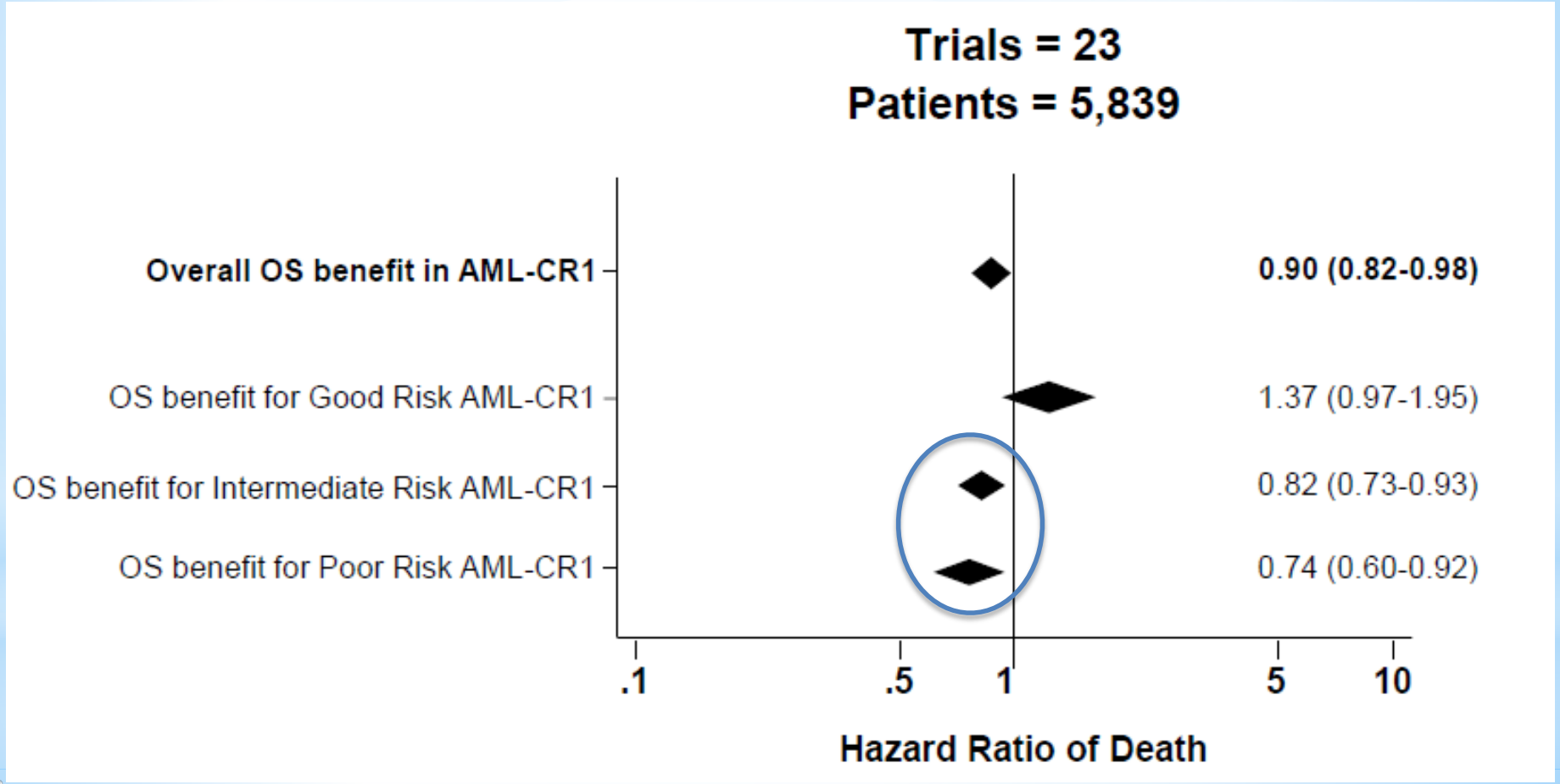
This document is a facsimile from an official text (law, regulation, etc.) published in the *Journal officiel de la République Française*, the official gazette of the French Republic.

* Meta-analysis of RCTs of HCT for AML in CR1



Koreth et al. JAMA 2009. 301:2349

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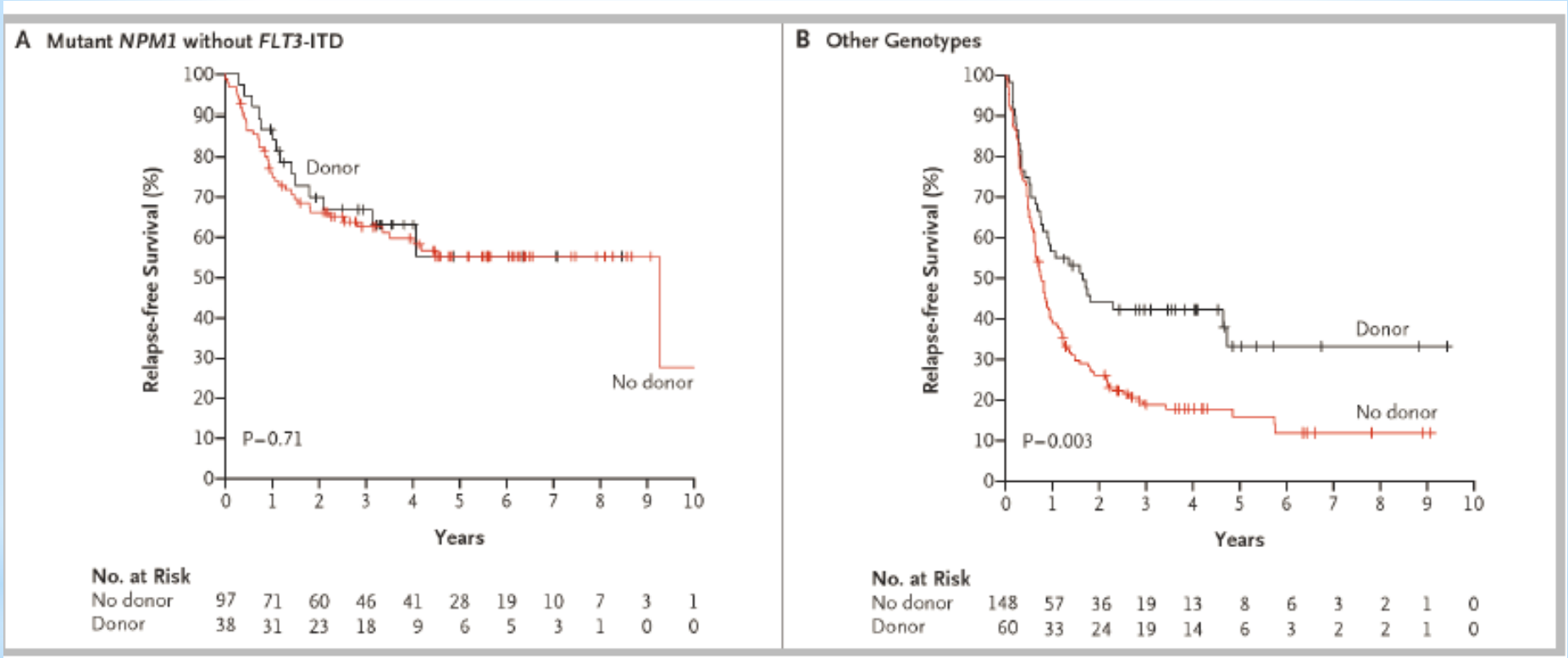
HCT for AML with normal cytogenetics



Schlenk et al. NEJM 358:1909, 2008

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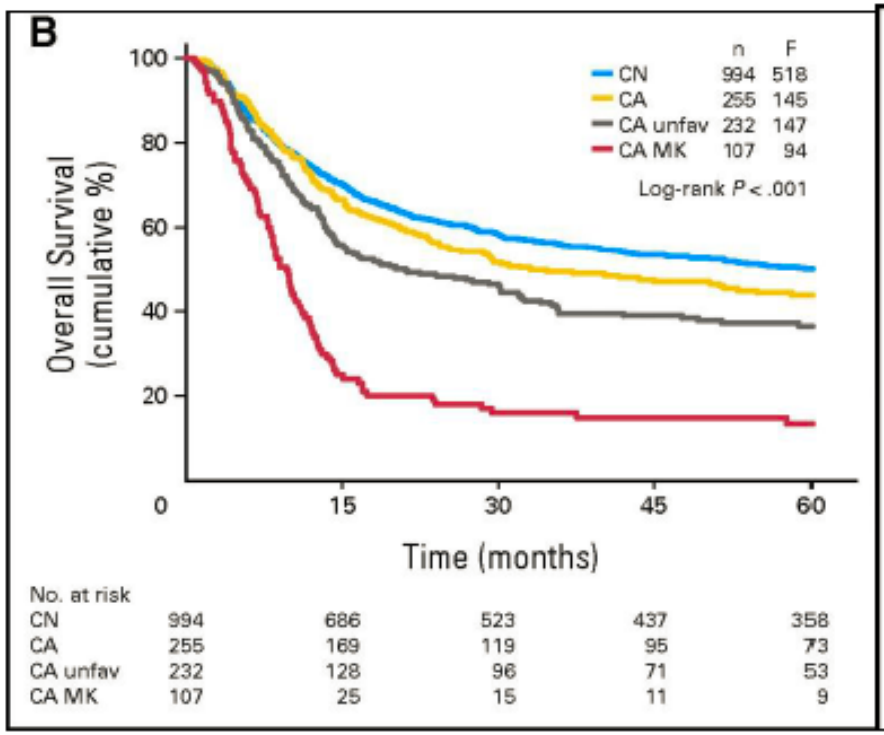
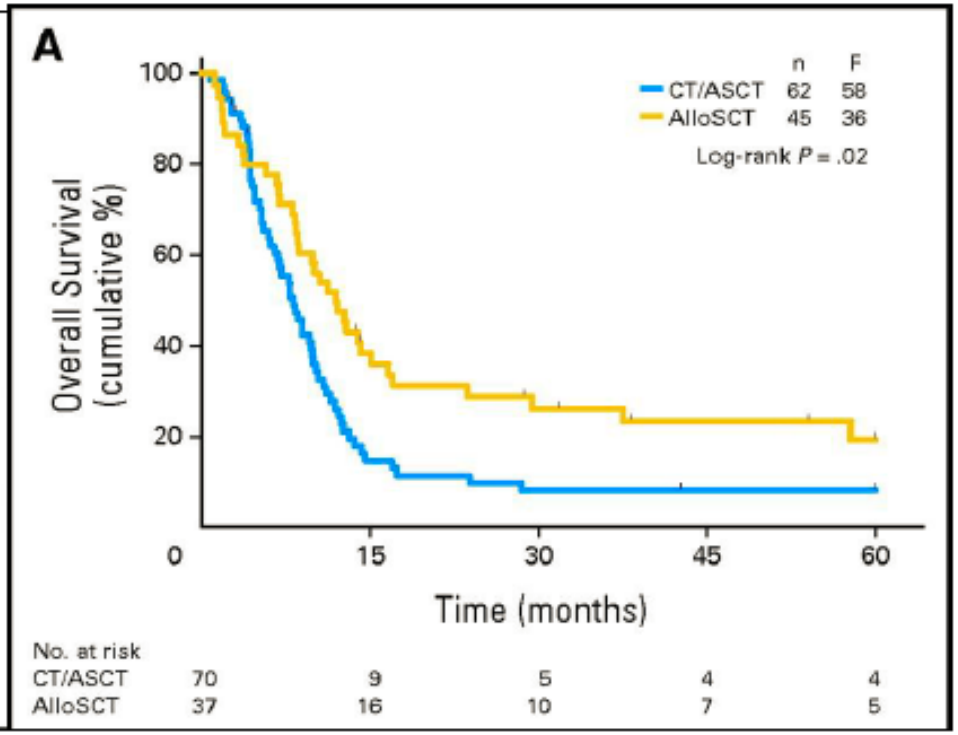
HCT for MK AML





Cornelissen et al. *J Clin Oncol* 2012;30:2140-2146

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Indications for Allogeneic SCT in AML

- Primary Induction Failure (Primary Refractory)
- Second (CR2) or later remission
- Relapsed disease
- CR1
  - Intermediate risk
  - Adverse risk cytogenetics
  - Secondary AML (MDS, prior chemotherapy)

Our Patient

- Enters a complete remission after induction
- Completes 3 additional cycles of consolidation
- Currently remains in remission, back at work, with regular follow up

Our Patient

* Enters a complete remission after induction 3+4
* Completes 3 additional cycles of consolidation
* Currently remains in remission, back at work, with regular follow up

* But what if the disease comes back?

When is enough?

* Estey Blood 1996
  - 206 pts, median age 56yo
  - Received chemotherapy for relapsed/refractory AML and did not go to transplant (1991-1994)

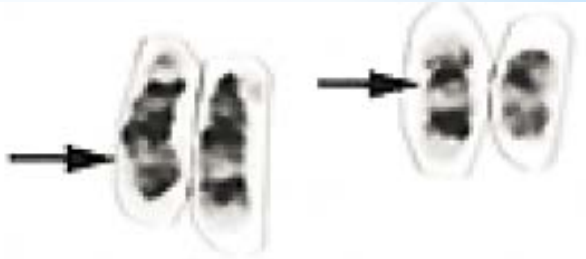
First Salvage (n = 206)	***68% Conventional 32% investigational (topotecan, 2Cda, taxol)***	***CR rate 23%***
Second Salvage (n = 93)	***43% conventional 57% investigational***	***CR rate 11%***
Third Salvage (n=40)		***CR rate 10%***
Fourth salvage (n=17)		***CR rate 6%***

* Duration of CR1 and likelihood of response

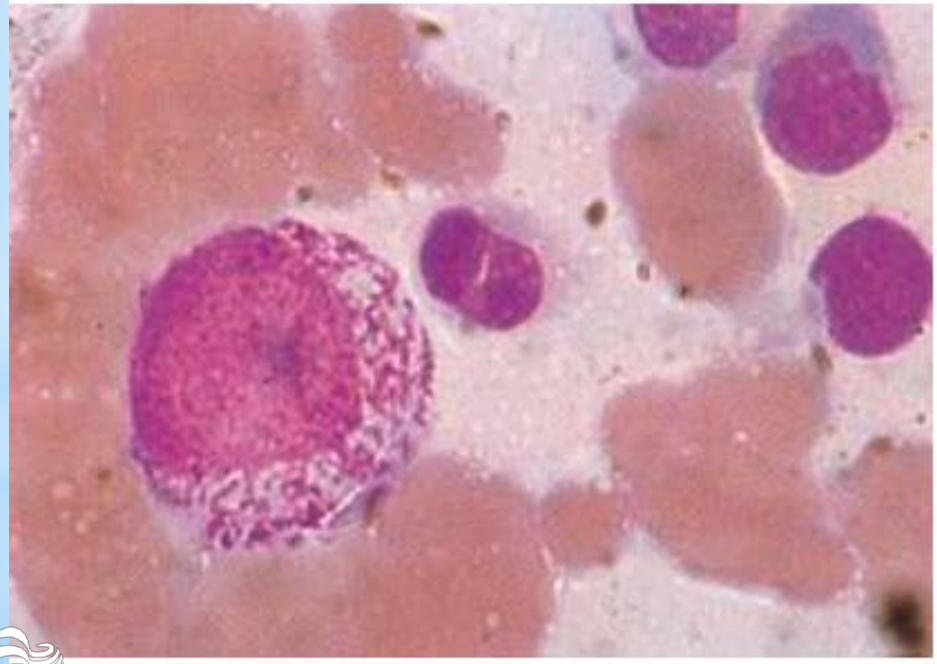
Treatment	*Likelihood of CR*
CR1 >2yrs, 1st salvage n=15	*73% (45-92%)*
CR1 1-2yrs, 1st salvage n=30	*47% (28-66%)*
CR1 <1yr or no CR, 1st salvage n=160	*14% (8-21%)*
CR1 <1yr or no CR1 2nd - 4th salvage n= 58 (96 tx)	*0% (0-4%)*

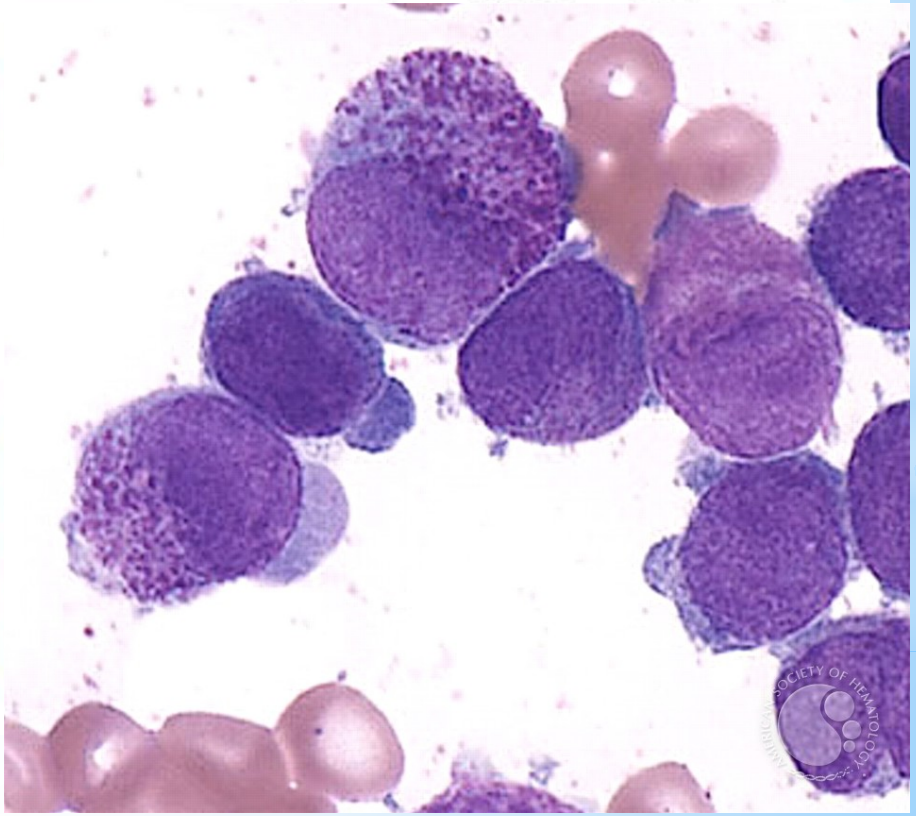
* Acute Promyelocytic Leukemia (APL)

APL



t(15;17)(q22;q12)





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* Aggressive early care for APL

* Early mortality (within days of diagnosis) ~5-10%
  - Bleeding
  - Bleeding
  - Intracranial bleeding
* Start ATRA as soon as suspected
  - If wrong, no harm done
  - Do not wait for testing results to start (t(15;17))

- Long-term cure rate >95%
  - ATRA/Arsenic
- Aggressive blood product transfusion to decrease bleeding risk

ATRA = All trans retinoic acid

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* All-Trans Retinoic Acid

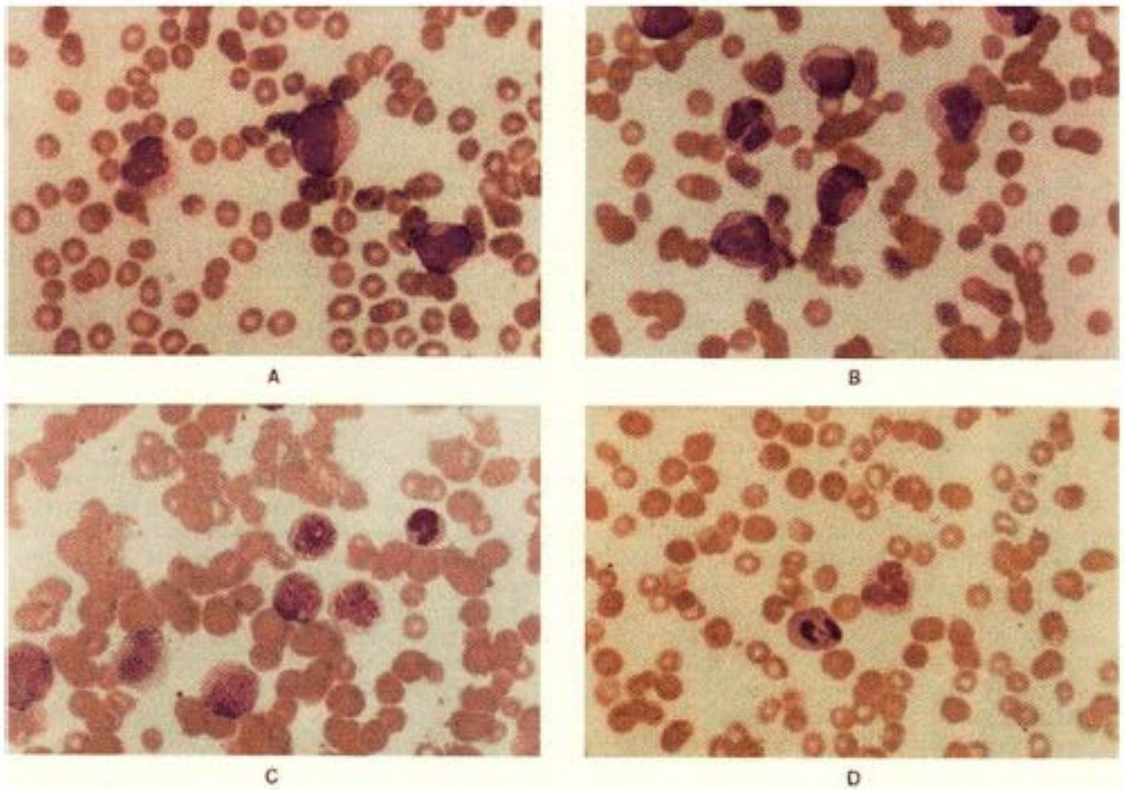
Tretinoin

Clinical response

- Associated with maturation of leukemic clone
- Expression of PML/RAR-α decreased

WBC increases

Reduced relapse



Warrell, R. P. et al. *N Engl J Med* 1993;329:177-189

ATRA Toxicity

"APL Differentiation Syndrome"

- Effusions, edema, ⇑ Wt., fever, ⇓BP
- Chemotherapy if WBC ⇑
- Dexamethasone if symptoms

Consider prophylactic if WBC > 10

Pseudotumor Cerebri (venous thromboses)

Dry Skin, Mucus Membranes

Hearing Loss

Acute lymphoblastic leukemia/lymphoma (ALL)

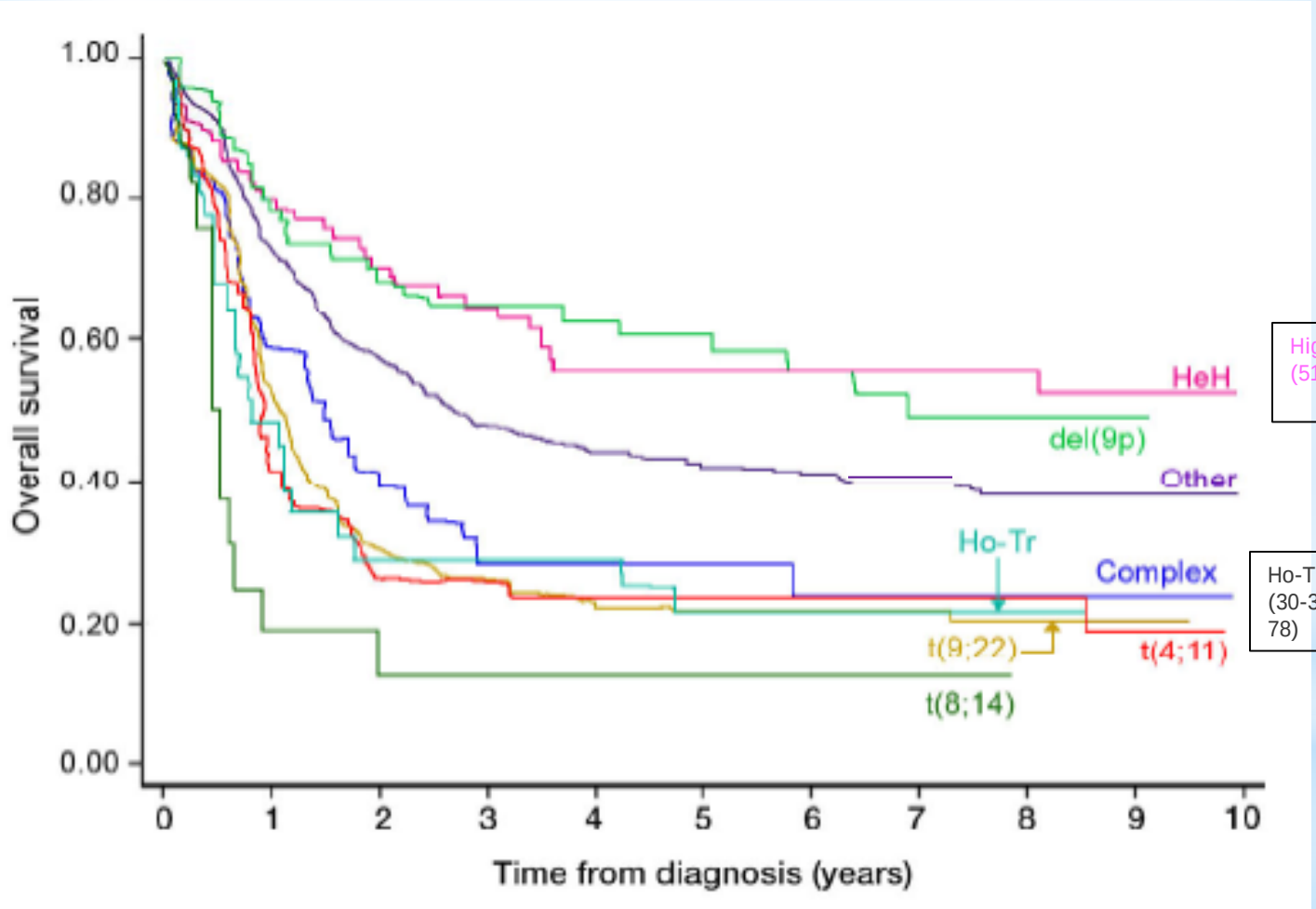
- Peak age at diagnosis 7yo
- But diagnosis possible throughout life

- Adolescent and young adult ALL
  - Treat with a ‘pediatric regimen’
    - Anthracycline, steroid, asparaginase, vincristine, 6-MP, cyclophosphamide
- Must administer intrathecal chemotherapy
  - Without this – 50% have CNS relapse

Back to Philly

- ALL can also have the Philadelphia Chromosome t(9;22)
  - p190 instead of p210
  - Respond to Imatininb/Dasatinib/Nilotininb/Ponatinib
    - So always use these in Ph+ ALL

*Survival by Cytogenetic Subgroup: MRC UKALL XII/ECOG 2993



High Hyperdiploid (51-65 csomes)

Ho-Tr = Low Hypodiploid (30-39), near triploid (60-78)

Moorman AV. et al. Blood 2007. 109:3189

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*What to do with the rest?

- *Cytogenetic changes without clear prognostic information
- *Standard-risk patients that respond in nonstandard manner
- *Risk stratification in UK ALL XII (adverse features)
  - *Ph+
  - *>35yo
  - *WBC >30k B cell or >100k for T cell
  - *More than 4 weeks for cytologic CR (MRD)

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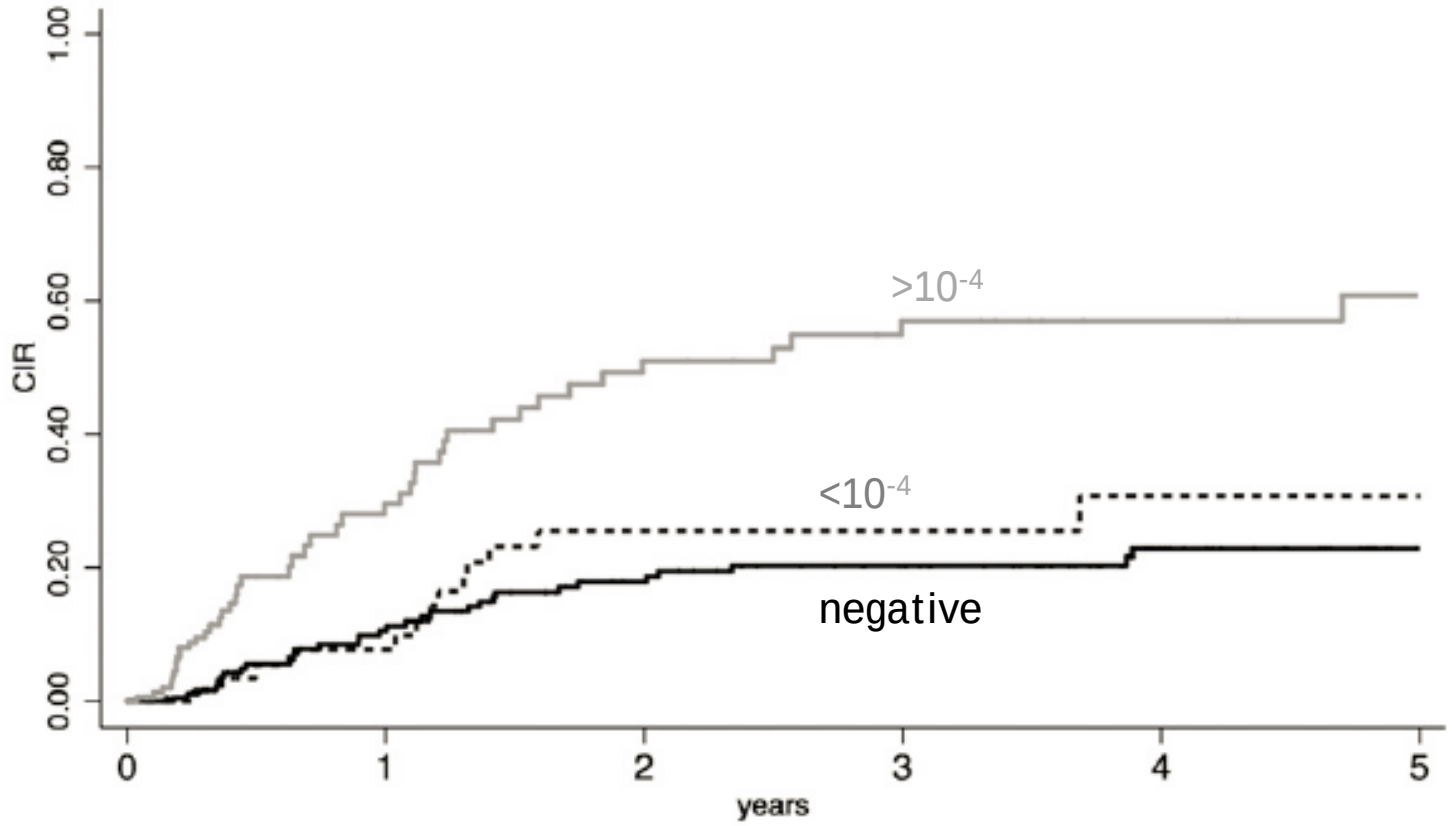
Moorman AV. Et al. Blood 2007. 109:3189

MRD assessed at week 6;
GRAALL 2003 protocol



*MRD and risk of relapse

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Beldjord Blood 2014 and Bruggemann Blood 2006. 107:1116

Questions and Thanks

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APL: Sanz Prognostic Factors

Low	WBC <10, Plt >40
Int	WBC <10, Plt <40
High	WBC ≥10

Sanz et al. *Blood*. 2010;115:5137-5148

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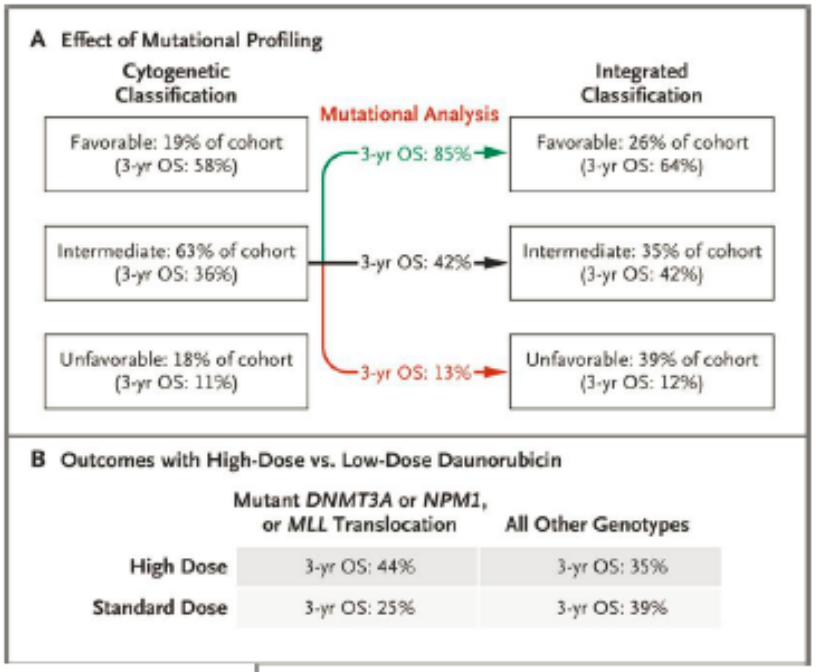
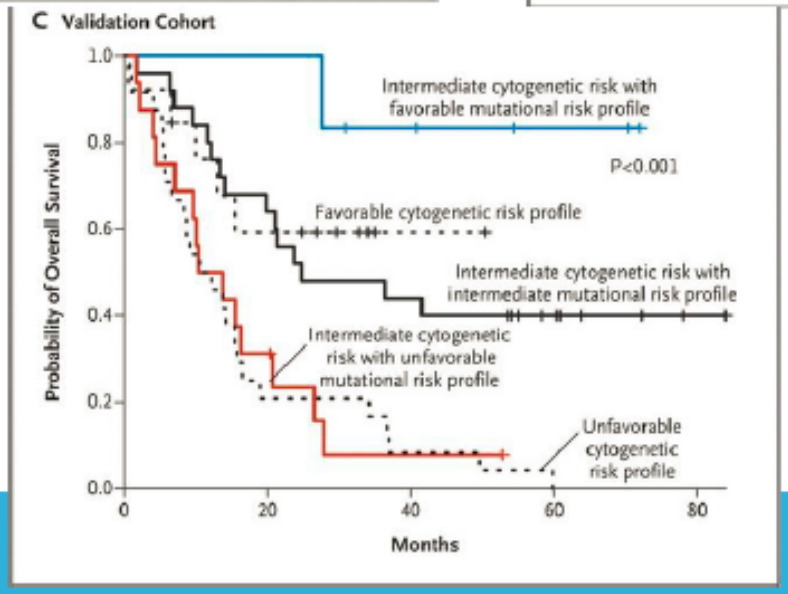
A Revised Risk Stratification

Cytogenetic Classification	Mutations		Overall Risk Profile
Favorable	Any		Favorable
Normal karyotype or intermediate-risk ctyogenetic lesions	*FLT3*-ITD-negative	Mutant *NPM1* and *IDH1* or *IDH2*	Favorable
	FLT3-ITD-negative	Wild-type *ASXL1*, *MLL*-PTD, *PHF6*, and *TET2*	Intermediate
	FLT3-ITD-negative or positive	Mutant *CEBPA*	Intermediate
	FLT3-ITD-positive	Wild-type *MLL*-PTD, *TET2*, and *DNMT3A* and trisomy 8–negative	Intermediate
	FLT3-ITD-negative	Mutant *TET2*, *MLL*-PTD, *ASXL1*, or *PHF6*	Unfavorable
	FLT3-ITD-positive	Mutant *TET2*, *MLL*-PTD, *DNMT3A*, or trisomy 8, without mutant *CEBPA*	Unfavorable
Unfavorable	Any		Unfavorable





Patel JP et al. N Engl J Med 2012;366:1079-1089.

Molecular Markers and Prognosis in AML

Marker	Effect
NPM1 (33%)	fav
CEBPA (8%)	fav
Ras	fav (HDAC)
BRE	fav (MLL)
TET2	unfav/fav

Marker	Effect
MLL	unfav t(9;11)
FLT3 ITD (Not TKD) (25%)	unfav
EVI1	unfav
IDH1/2 (33%)	unfav
MN1	unfav
WT1 (10%)	unfav
FL1	unfav
BAALC	unfav
CKIT	unfav (i16)
DNMT3A (18%)	unfav
ERG	unfav

Thol et al. J Clin Oncol 2011;29:2889-2896
Metzeler K H et al. J Clin Oncol 2011;29:1373-1381
Neubauer et al. J Clin Oncol 2008;26:4603-4609
Becker et al. J Clin Oncol 2009;28:596-604
Shen et al. J Clin Oncol 2011;118:5593-5603
Green et al. J Clin Oncol 2010;28:2739-2747

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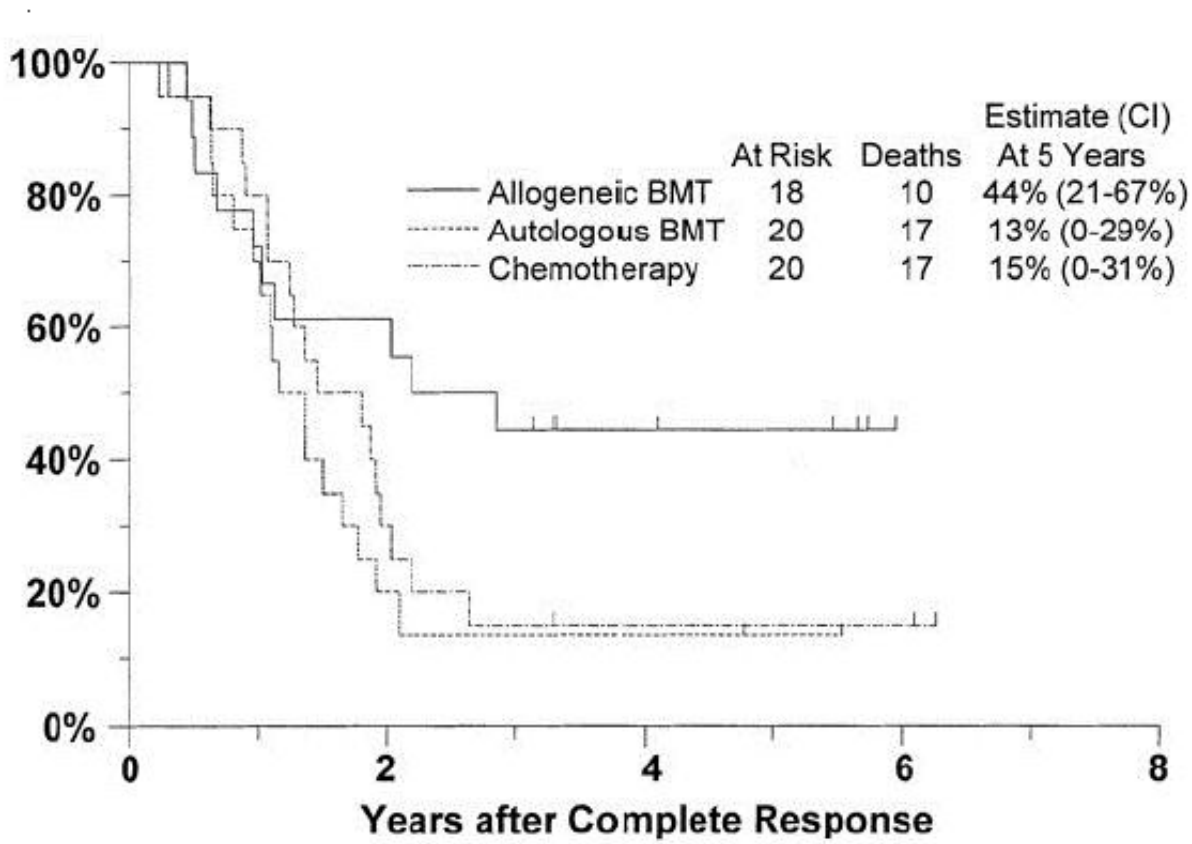
Therapy of High Risk AML



Slovak et al. *Blood* 2000;96:4080

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Integration of Cytogenetic & Molecular Data in Younger Pts

EFS > 75%

t (15;17)

Inv 16 , +22 Kit -

EFS 50-75%

Other inv 16, Kit -

T(8;21) with low WBC, Kit -

Normal karyotype, CEBPA +

Normal karyotype, FLT3-/NPM +

EFS 25-50%

Inv 16 , Kit +

T(8 ;21) with high WBC or Kit +

Normal karyotype FLT3-/NPM-

Normal karyotype FLT3+/NPM+

or –

Normal karyotype MLL1 PTD+

EFS < 20%

- Others except -5/-7 as sole abnormality w/o AHD

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Prognosis: European Leukemia Net

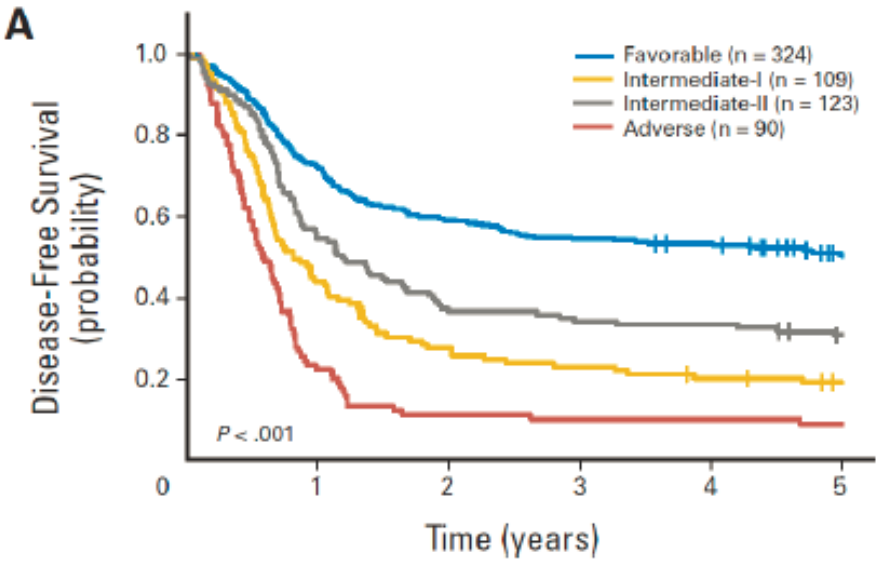

Table 1. European LeukemiaNet Standardized Reporting System for Correlation of Cytogenetic and Molecular Genetic Data in AML With Clinical Data[12]

Genetic Group	Subsets
Favorable	t(8;21)(q22;q22); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD (normal karyotype)
	Mutated *CEBPA* (normal karyotype)
Intermediate-I	Mutated *NPM1* and *FLT3*-ITD (normal karyotype)
	Wild-type *NPM1* and *FLT3*-ITD (normal karyotype)
	Wild-type *NPM1* without *FLT3*-ITD (normal karyotype)
Intermediate-II	t(9;11)(p22;q23); *MLLT3-MLL*
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*
	t(6;9)(p23;q34); *DEK-NUP214*
	t(v;11)(v;q23); *MLL* rearranged
	–5 or del(5q)
	–7
	abnl(17p)
	Complex karyotype*

Abbreviations: AML, acute myeloid leukemia; ITD, internal tandem duplication.
*Complex karyotype is defined as three or more chromosome abnormalities in the absence of one of the WHO designated recurring translocations or inversions: t(8;21), inv(16) or t(16;16), t(15;17), t(9;11), t(v;11)(v;q23), t(6;9), inv(3) or t(3;3).

Mrozek et al. JCO 2012 _____

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