ACUTE (AND NOT SO CUTE) LEUKEMIA

Matthew Ulrickson, MD

Banner MD Anderson Cancer Center

September 11, 2018

Banner MD Anderson Cancer Center

Making Cancer History®

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

Banner MD Anderson Cancer Center
Making Cancer History®

CASE PRESENTATION

- 32yo resident presents with sore throat and fever
- Cervical adenopathy is present on exam

- CBC: 35>35%<35k

Banner MD Anderson Cancer Center
Making Cancer History®

PERIPHERAL SMEAR

- 92% Other
- 4% Lymph
- 4% Neutrophils

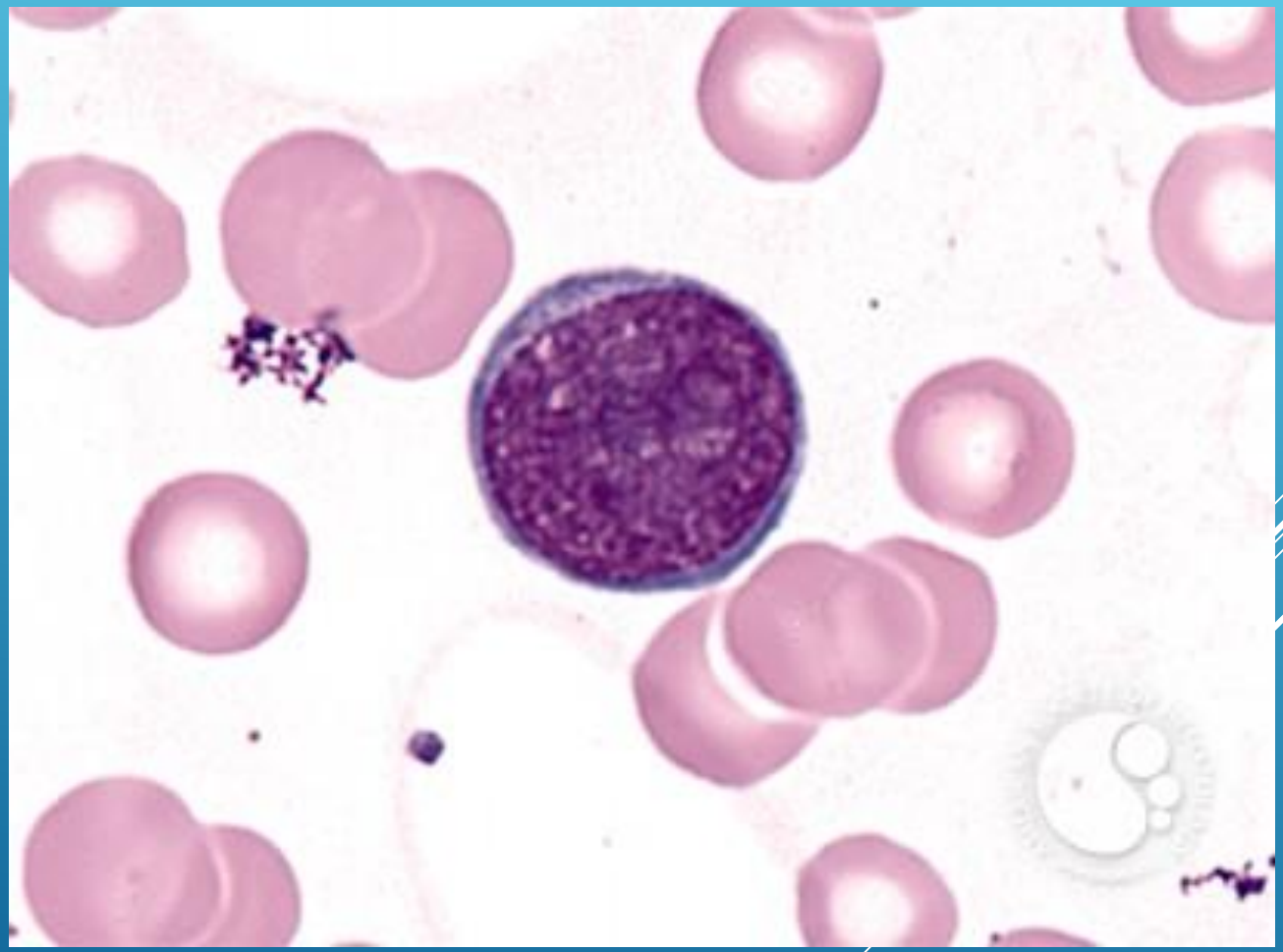
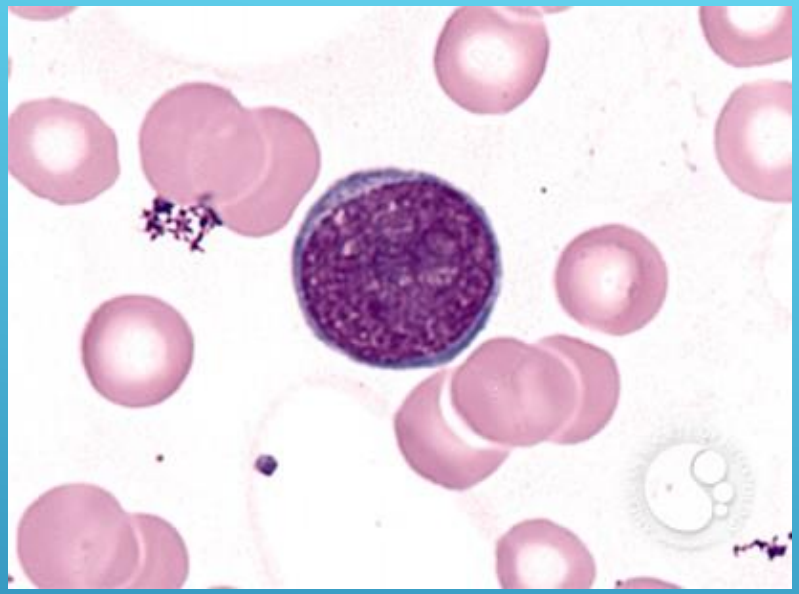


Image courtesy of Peter Maslak

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

Banner MD Anderson Cancer Center
Making Cancer History®

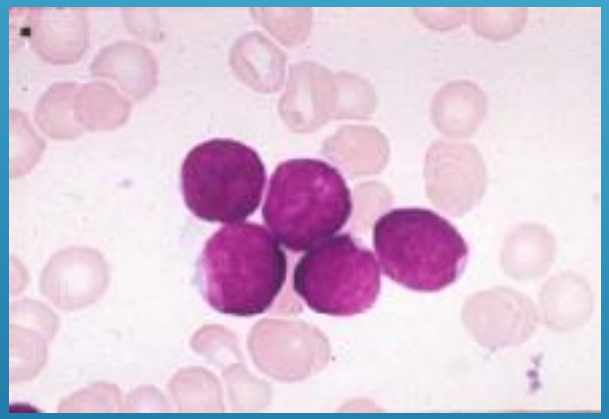
INITIAL TESTING

- CBC: 6.9>2.6<79 MCV 100

Banner MD Anderson Cancer Center
Making Cancer History®

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

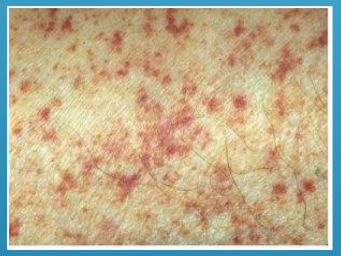


- Reticulocyte 0.3%; absolute 2000/µl
- Cr 0.8, total bilirubin 0.4, LDH 392, albumin 3.7, AST 45, ALT 145,

Banner MD Anderson Cancer Center
Making Cancer History®

CLINICAL SYMPTOMS OF AML

- Bone Marrow Failure (Cytopenias)
  - Anemia - dyspnea, pallor, chest pain
  - Neutropenia - infections
  - Thrombocytopenia - bleeding, petechiae

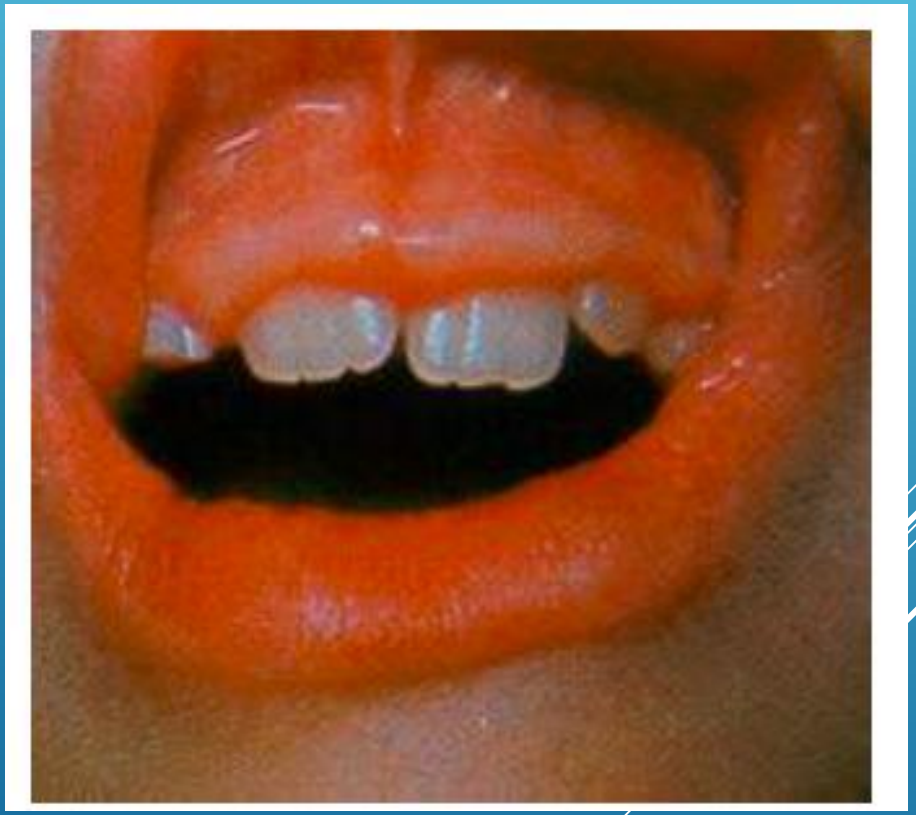


- Coagulopathy
  - esp APL, Acute myelomonocytic leukemia
- Tissue invasion

Banner MD Anderson Cancer Center
Making Cancer History®

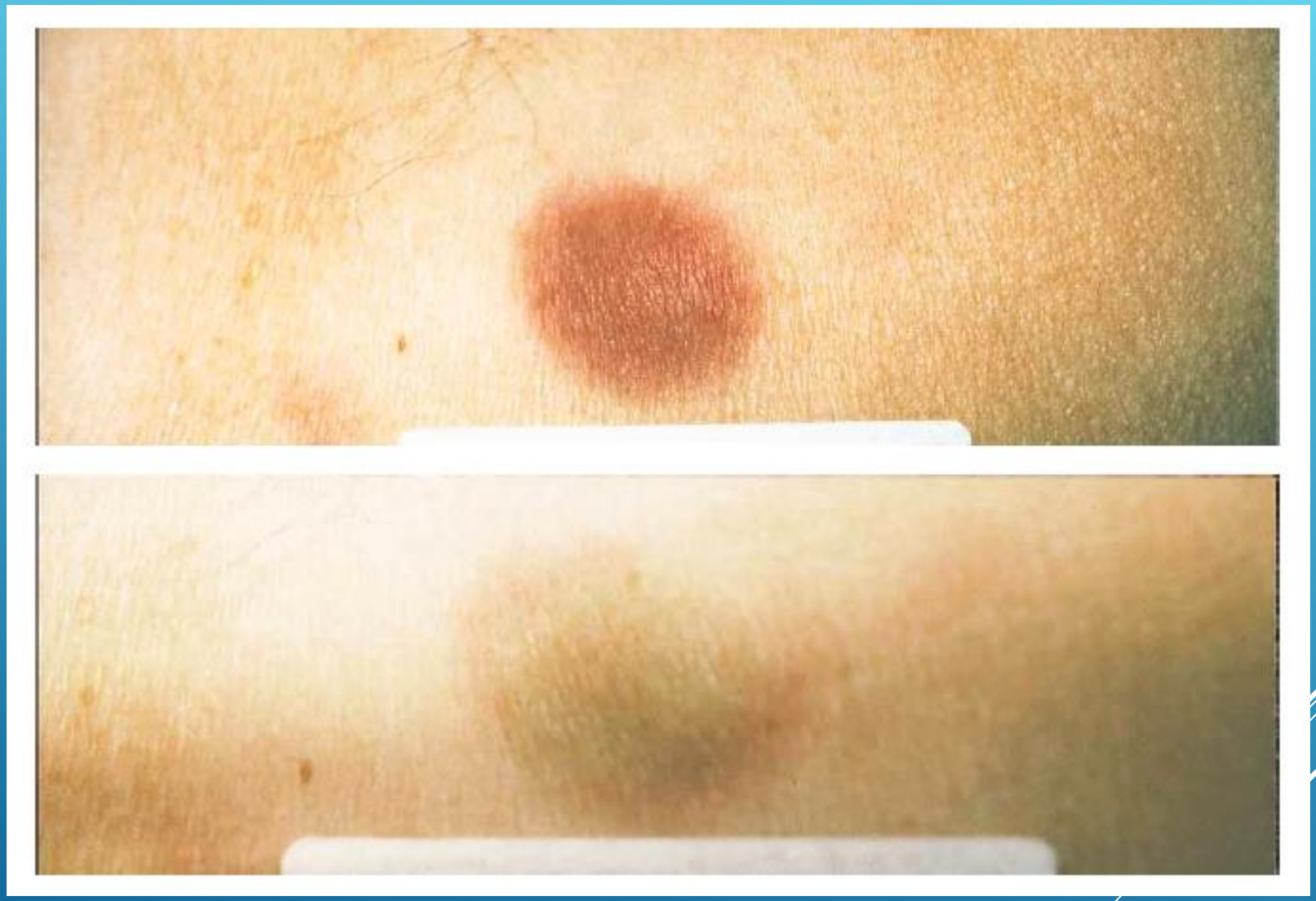
TISSUE INVASION IN AML

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



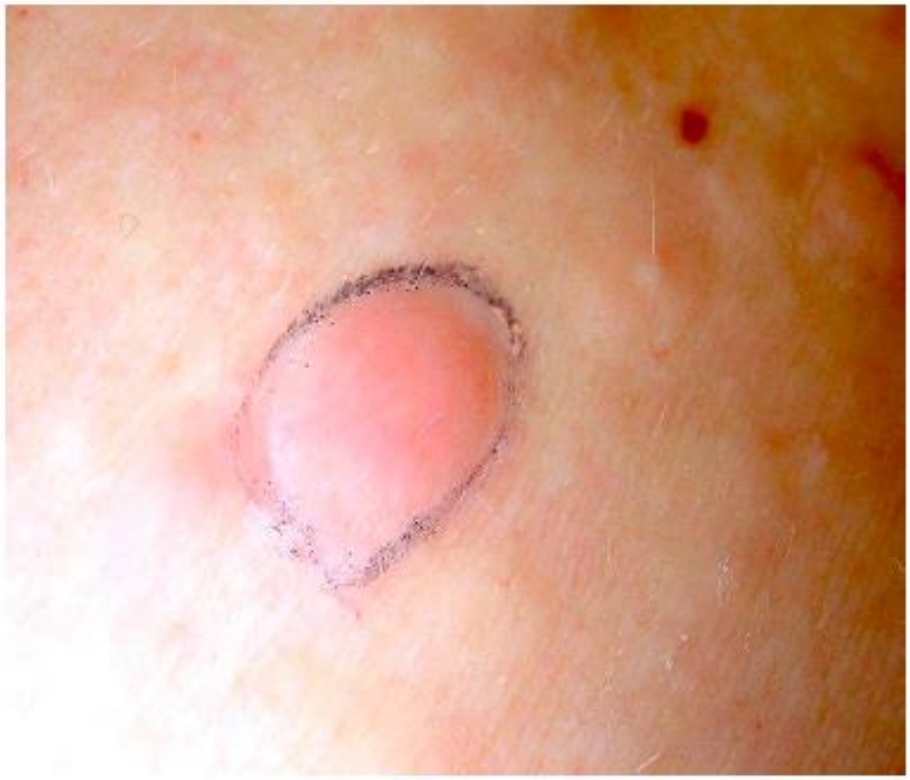
Banner MD Anderson Cancer Center
Making Cancer History®

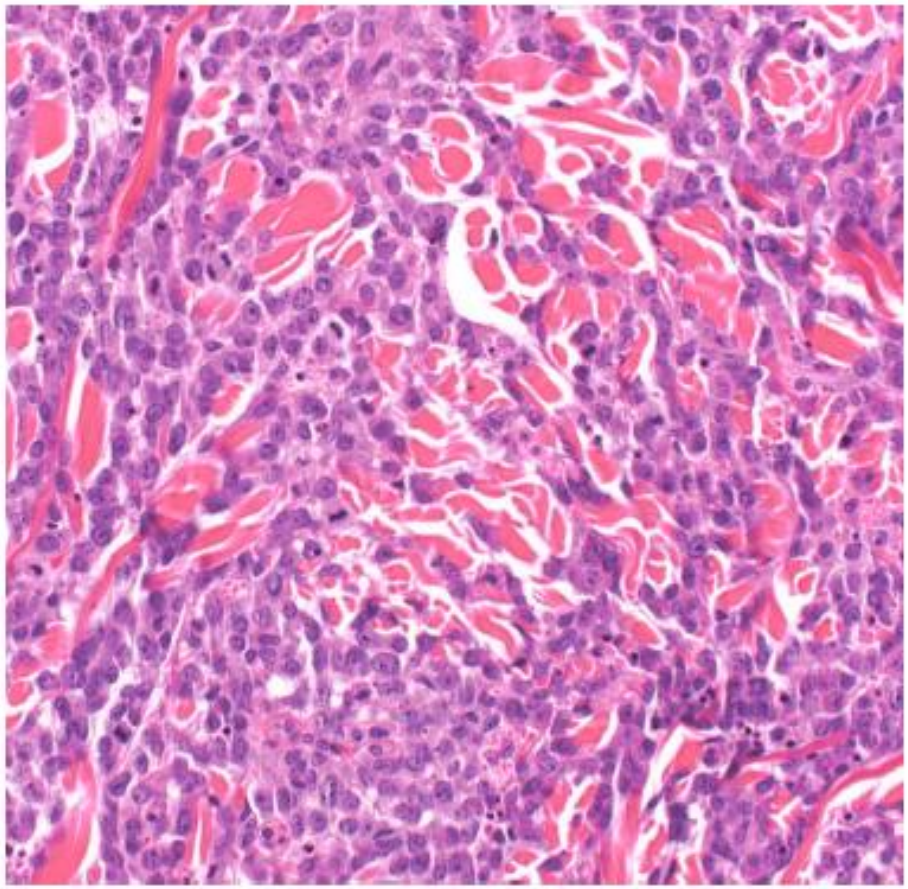
CHLOROMA



Banner
MD Anderson
Cancer Center
Making Cancer History®

LEUKEMIA CUTIS





Banner MD Anderson Cancer Center
Making Cancer History®

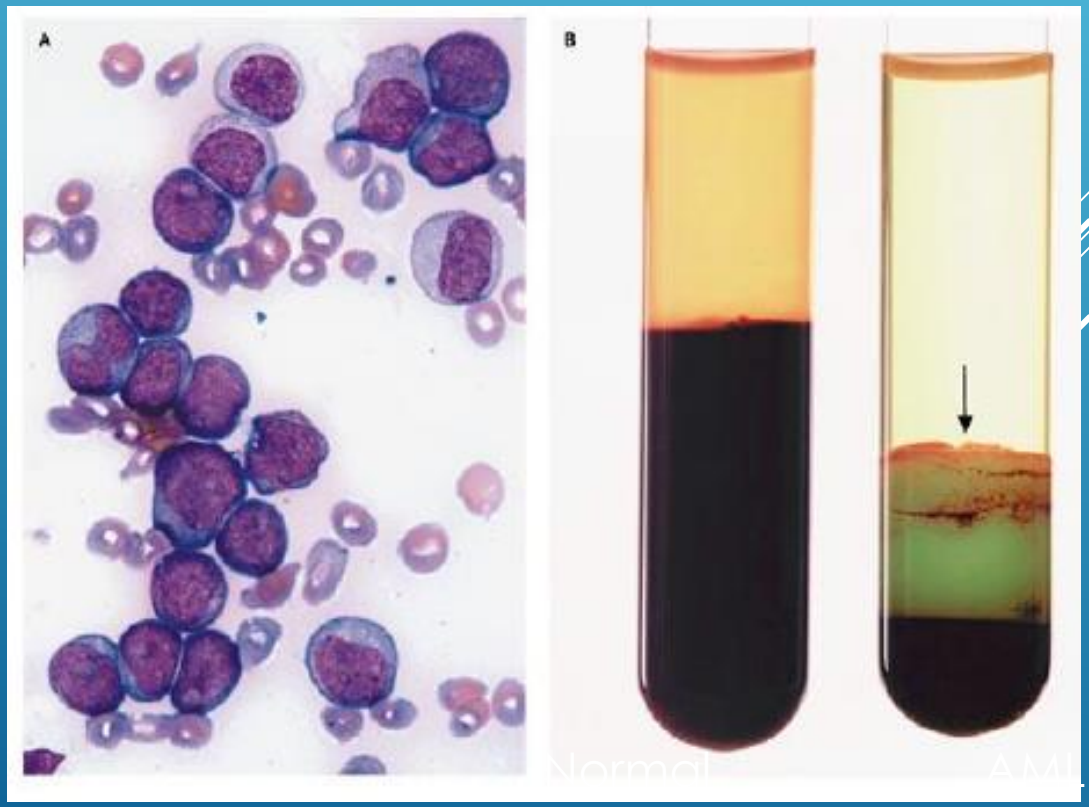
Sauter and Jacky *NEJM* 1998. 338:969

HIGH CIRCULATING BLASTS

Pseudo:

- Hypoglycemia
- Hypoxia
- Hyperkalemia
- Elevated Lactate

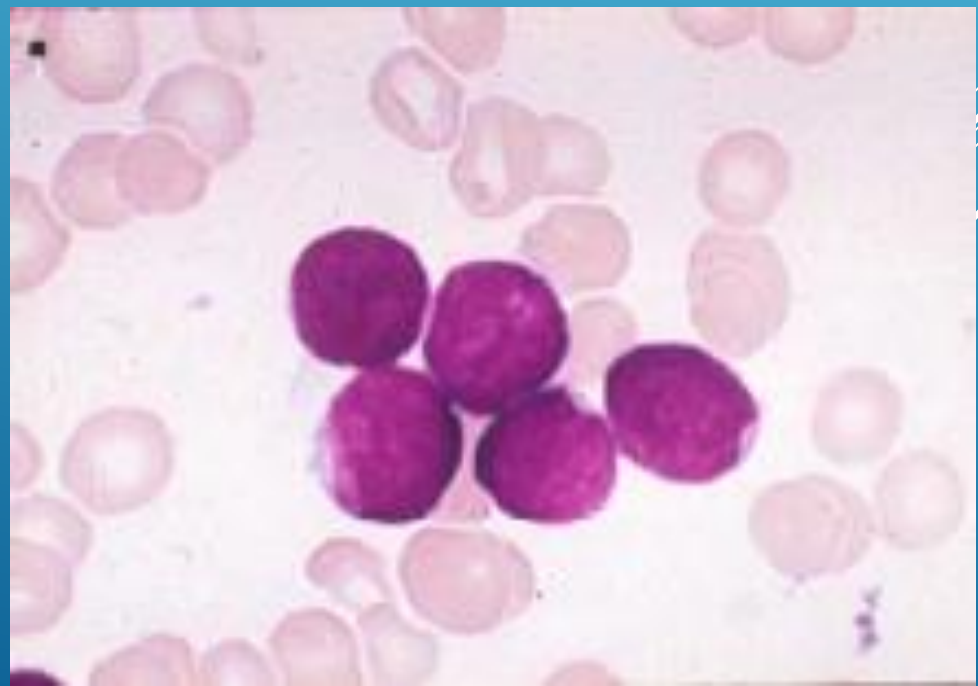
Mauro MJ NEJM 2003. 349:767



Banner MD Anderson Cancer Center
Making Cancer History®

EVALUATION OF PATIENT WITH AML

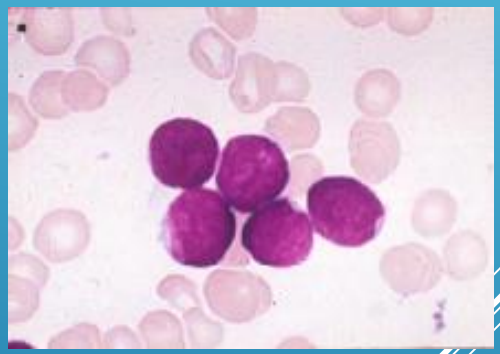
- Initial triage
  - History and Physical
  - CBC with differential (look at the peripheral smear)
  - BMP, LFTs, uric acid, ABO type and screen
  - PT, PTT, fibrinogen



Banner MD Anderson Cancer Center
Making Cancer History®

EVALUATION OF PATIENT WITH AML

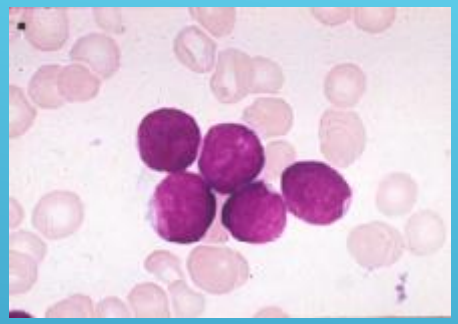
- Initial triage
  - History and Physical
  - CBC with differential (look at the peripheral smear)
  - BMP, LFTs, uric acid, ABO type and screen
  - PT, PTT, fibrinogen



- Diagnosis
  - Bone marrow biopsy
  - FISH and cytogenetics, flow cytometry
  - Molecular: FLT3, NPM1, IDH, Myeloid/Lymph molecular panel
    - (can be sent on PB)
  - If circulating blasts, send peripheral blood for flow cytometry (STAT) to make dx

Banner MD Anderson Cancer Center
Making Cancer History®

EVALUATION OF PATIENT WITH AML



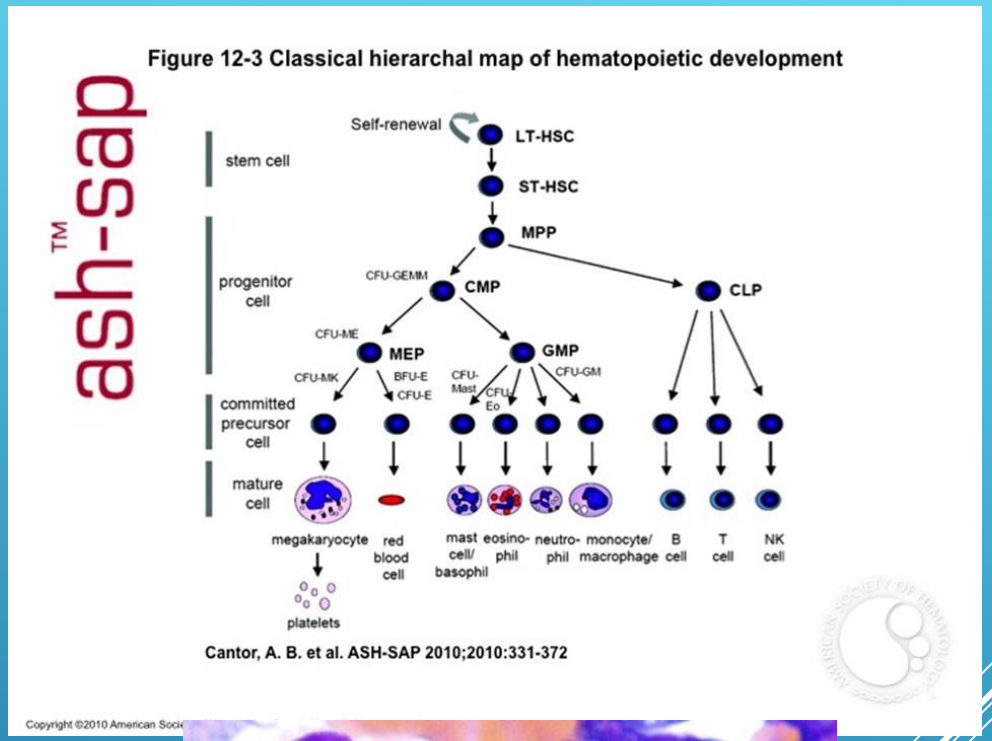
- Initial triage
  - History and Physical
  - CBC with differential (look at the peripheral smear)
  - BMP, LFTs, uric acid, ABO type and screen
  - PT, PTT, fibrinogen
- Diagnosis
  - Bone marrow biopsy
  - FISH and cytogenetics, flow cytometry
  - Molecular: FLT3, NPM1, CEPBA, myeloid molecular panel (can be sent on PB)
  - 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

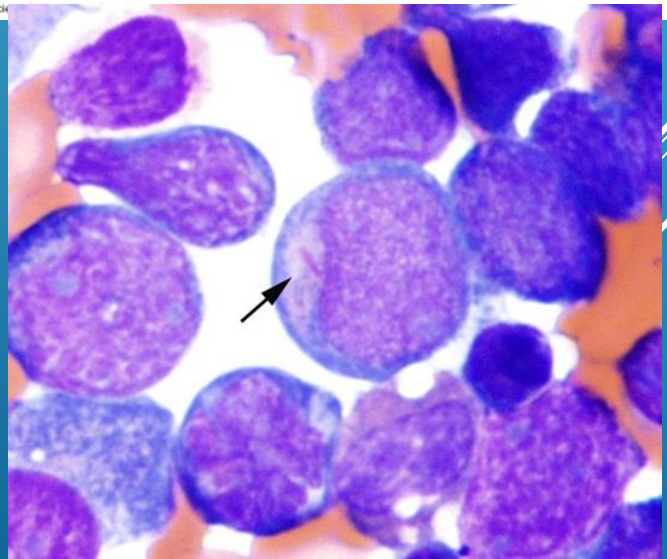
DIFFERENTIATE AML VS ALL

- Rarely, can see Auer Rods
  - Only in myeloid blasts
- Flow cytometry
- Cytogenetics - t(8;21), inv16, → AML

  t(9:22) → ALL

  t(15;17) → APL





Banner MD Anderson Cancer Center
Making Cancer History®

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
    - rare in CLL, CML
- DIC (esp APL and monocytic)
  - Aggressive product replacement
- Initial treatment can trigger SIRS
- Tumor lysis syndrome

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

Banner MD Anderson Cancer Center
Making Cancer History®

7+3

- 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

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.

Banner MD Anderson Cancer Center
Making Cancer History®

Nat Revw Clin Onc doi:10.1038/nrclinonc.2012.9

AML IN THE ELDERLY

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

Banner MD Anderson Cancer Center
Making Cancer History®

Appelbaum et al. Blood 2006. 107:3481

MORTALITY FROM 7+3 INDUCTION AT 30 DAYS

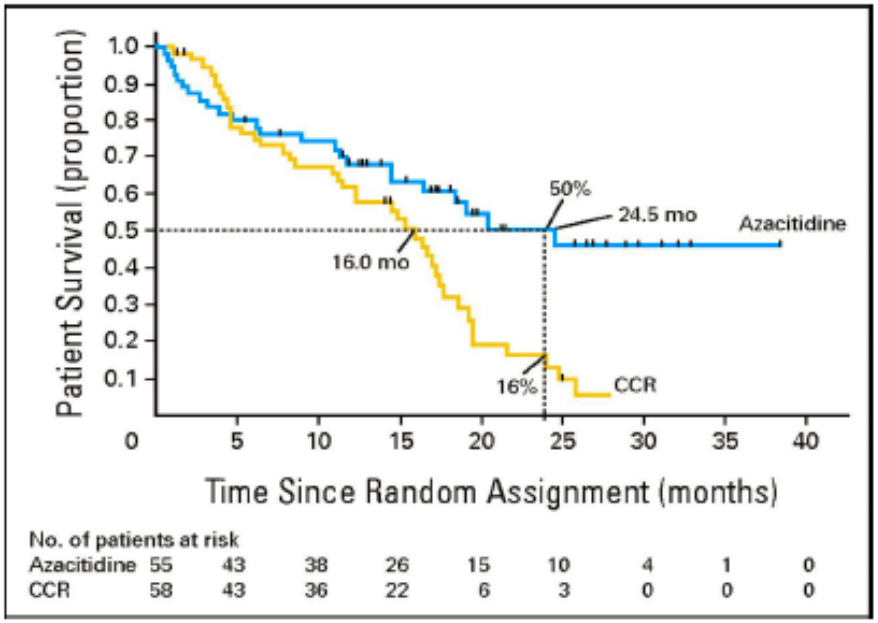
	Age			
	< 56	**56 - 65**	**65 - 75**	**> 75**
Patient #	364	242	270	79
ECOG PS				
0	2%	11%	12%	14%
1	3%	5%	16%	18%
2	2%	18%	31%	50%
3	0%	29%	47%	82%

Banner MD Anderson Cancer Center
Making Cancer History®

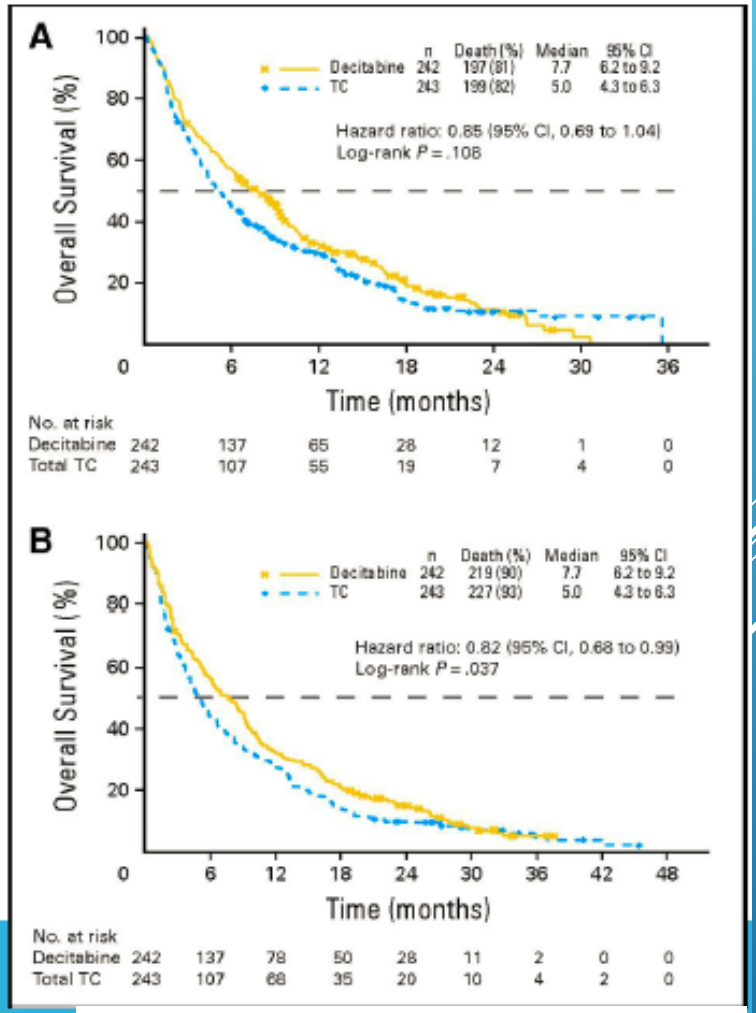
Appelbaum et al. Blood 2006, 107:3481

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

Banner MD Anderson Cancer Center
Making Cancer History®

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?!?

WHO AML CATEGORIZATION

Acute myeloid leukemia (AML) and related neoplasms
AML with recurrent genetic abnormalities
AML with t(8;21)(q22;q22.1);*RUNX1-RUNX1T1*
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);*CBFB-MYH11*
APL with *PML-RARA*
AML with t(9;11)(p21.3;q23.3);*MLLT3-KMT2A*
AML with t(6;9)(p23;q34.1);*DEK-NUP214*
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM*
AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);*RBM15-MKL1*
Provisional entity: AML with BCR-ABL1
AML with mutated *NPM1*
AML with biallelic mutations of *CEBPA*
Provisional entity: AML with mutated RUNX1
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
AML, NOS
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monoblastic/monocytic leukemia
Pure erythroid leukemia
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
Transient abnormal myelopoiesis (TAM)
Myeloid leukemia associated with Down syndrome

- >20% blasts in PB or BM required

Arber et al. Blood 2016. 127:2391-2405

WHO AML CATEGORIZATION

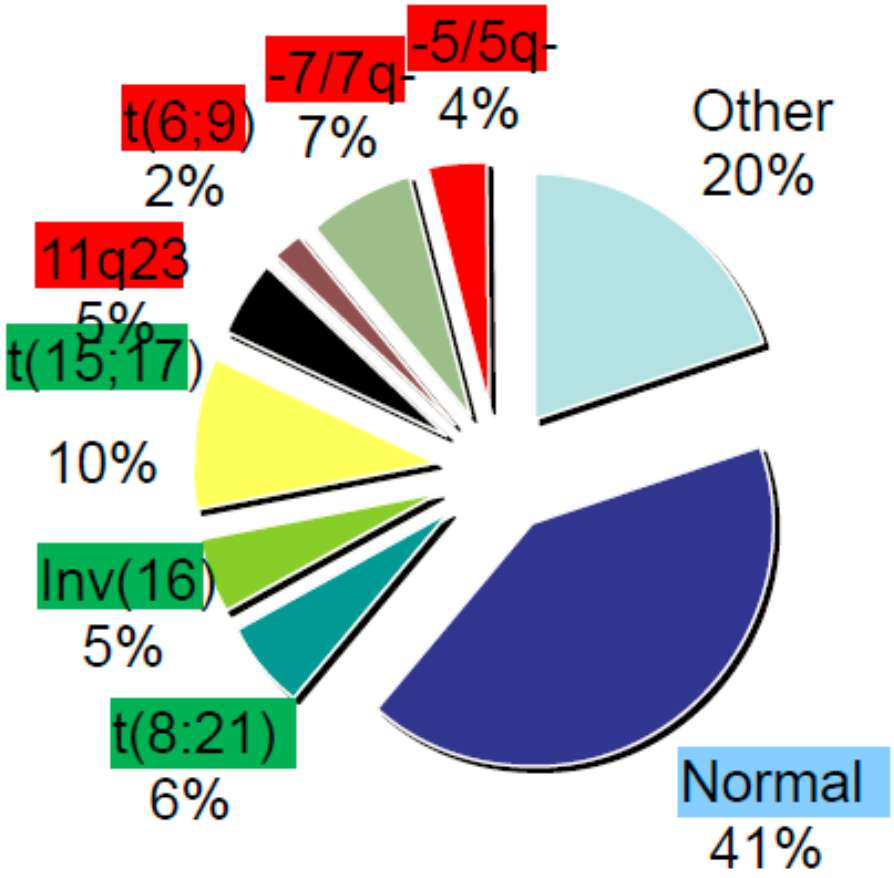
Acute myeloid leukemia (AML) and related neoplasms
AML with recurrent genetic abnormalities
AML with t(8;21)(q22;q22.1);*RUNX1-RUNX1T1*
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);*CBFB-MYH11*
APL with *PML-RARA*
AML with t(9;11)(p21.3;q23.3);*MLLT3-KMT2A*
AML with t(6;9)(p23;q34.1);*DEK-NUP214*
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM*
AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);*RBM15-MKL1*
Provisional entity: AML with BCR-ABL1
AML with mutated *NPM1*
AML with biallelic mutations of *CEBPA*
Provisional entity: AML with mutated RUNX1
Acute myelomonocytic leukemia
Acute monoblastic/monocytic leukemia
Pure erythroid leukemia
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
Transient abnormal myelopoiesis (TAM)
Myeloid leukemia associated with Down syndrome

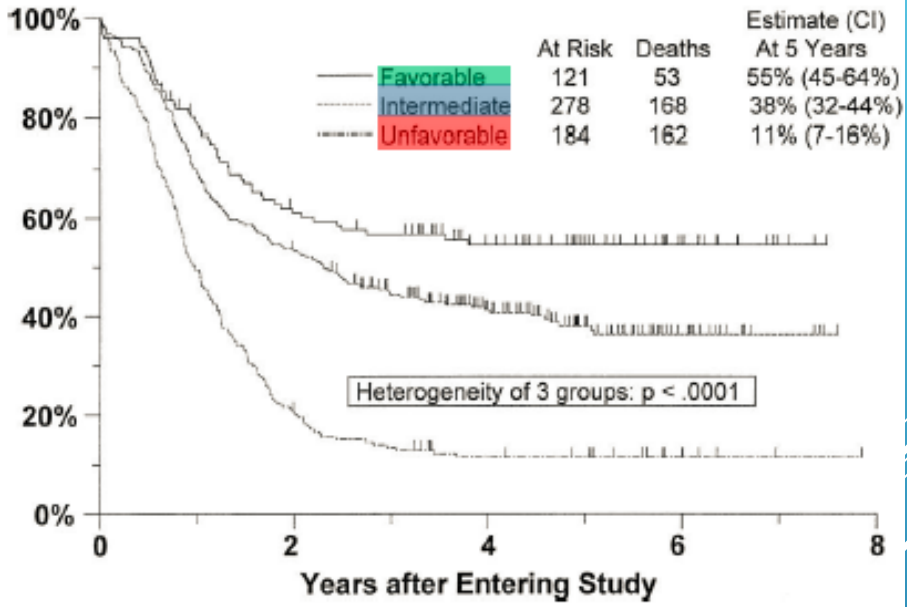
M0, M1, M2, M4, M5, M6, M7
MMMMEAN NOTHING!

- >20% blasts in PB or BM required

Arber et al. Blood 2016. 127:2391-2405

Clonal Cytogenetic Abnormalities in Adult AML





t(16:16), del 16q

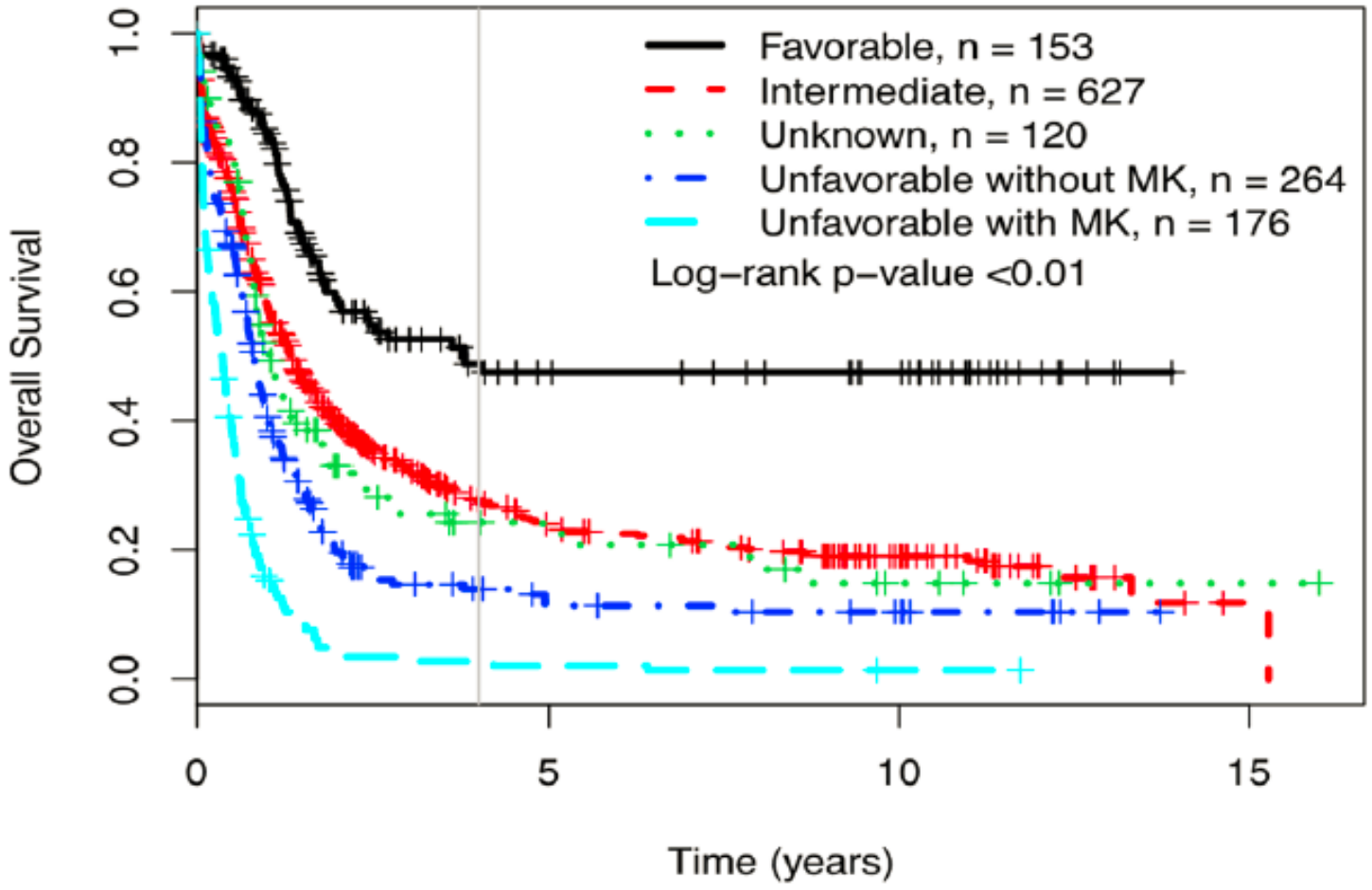
-Y, +8, +6, del 12p

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

Banner MD Anderson Cancer Center
Making Cancer History®

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

ON TARGET MUTATIONS HELP OPTIMALLY TREAT AML

- Current targeted medicines available:
  - FLT3 + = midostaurin
  - IDH2 + = enasidenib
  - IDH1 + = ivosidenib
  - CD33 = gemtuzumab
  - Many others 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 marrow tells us some, but only part 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…

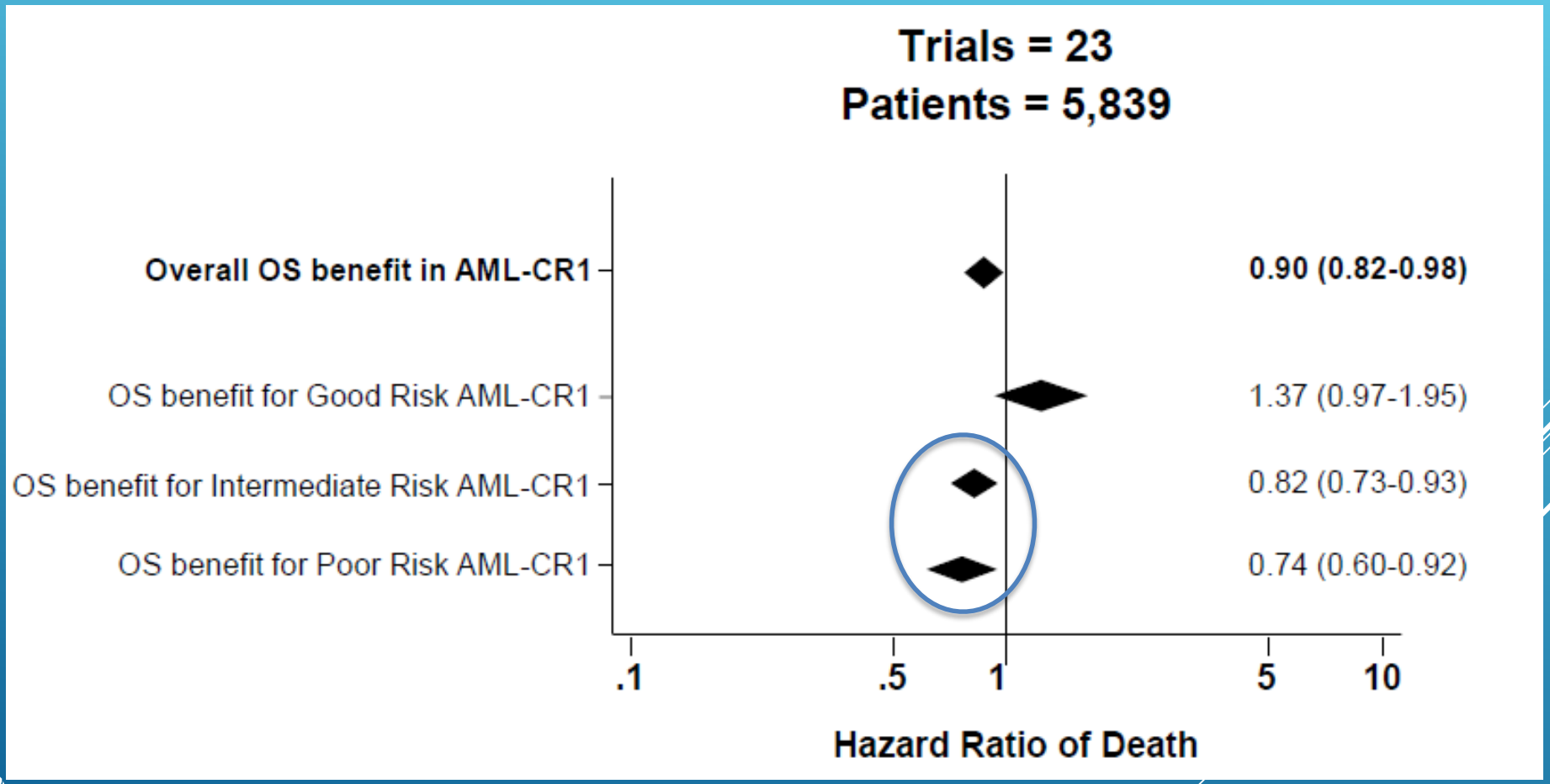
AML IN CR1

- Hematopoietic Stem Cell Transplant (HCT)

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

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



Banner MD Anderson Cancer Center
Making Cancer History®

Koreth et al. JAMA 2009. 301:2349

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)

Banner MD Anderson Cancer Center
Making Cancer History®

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

Banner MD Anderson Cancer Center
Making Cancer History®

OUR PATIENT

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

- But what if the disease comes back?

Banner MD Anderson Cancer Center
Making Cancer History®

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%***

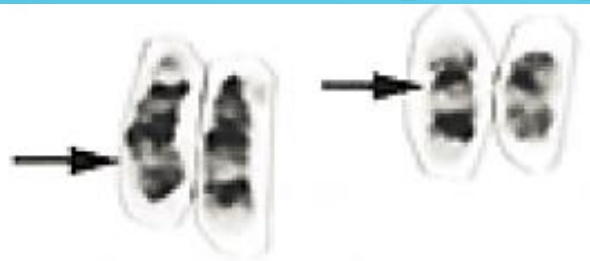
DURATION OF CR1 AND LIKELIHOOD OF RESPONSE

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%)*

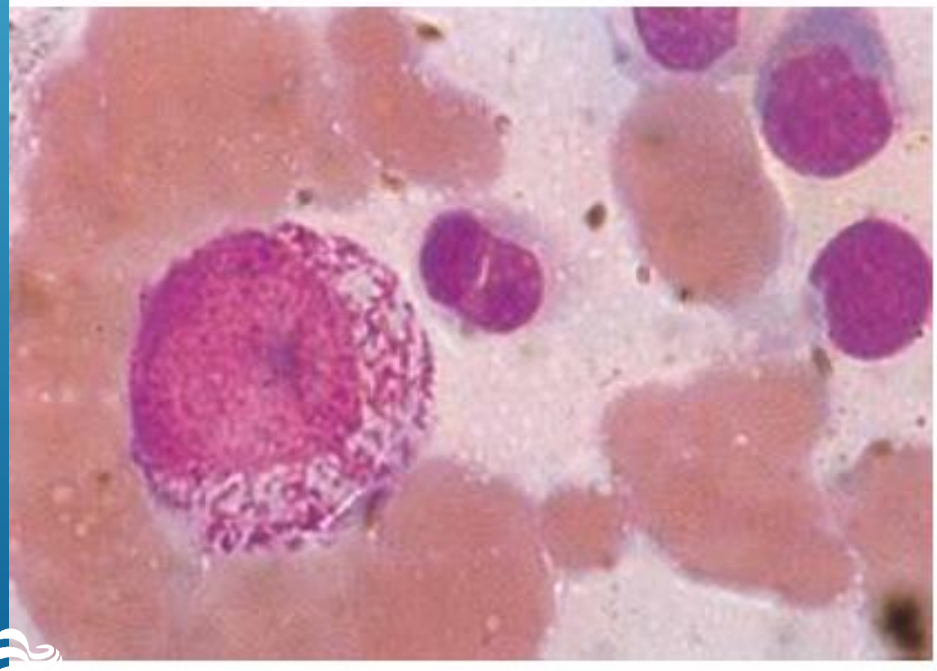
Banner MD Anderson Cancer Center
Making Cancer History®

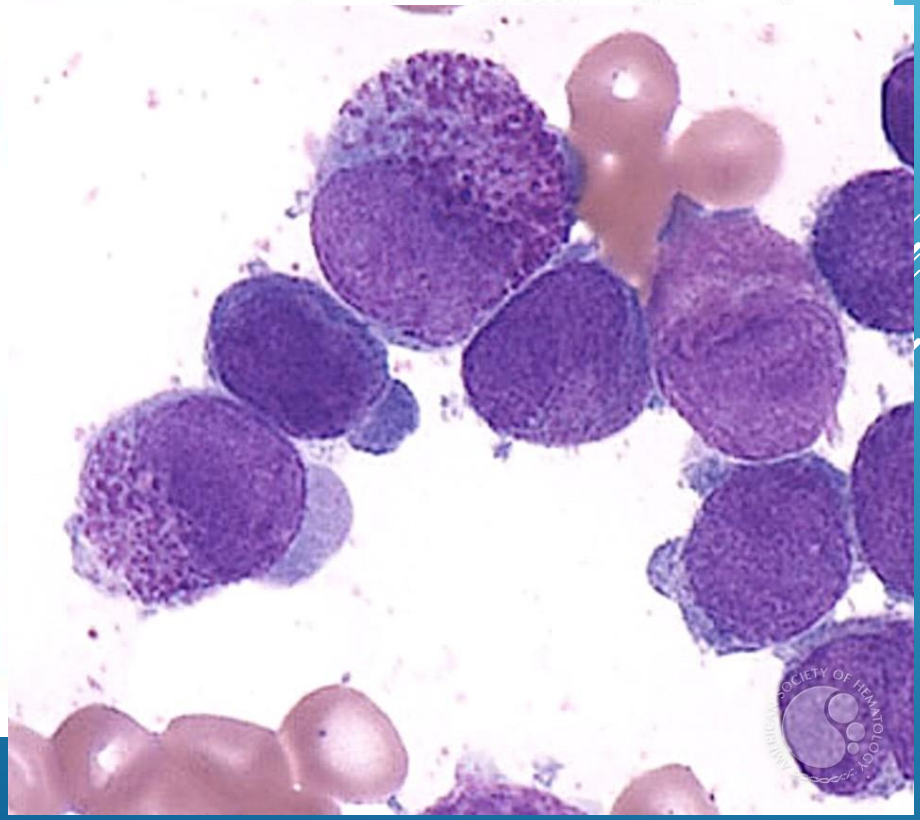
ACUTE PROMYELOCYTIC LEUKEMIA (APL)

APL



t(15;17)(q22;q12)





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

Banner MD Anderson Cancer Center
Making Cancer History®

ALL-TRANS RETINOIC ACID

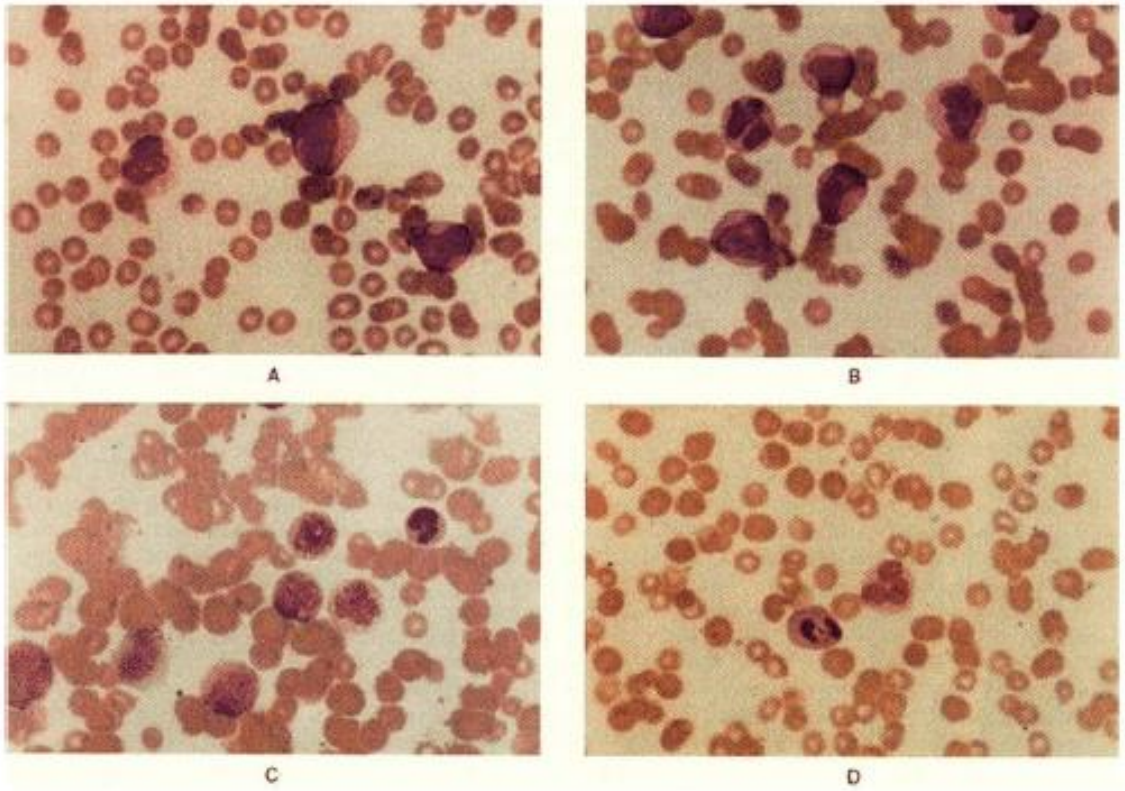
Tretinoin

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)

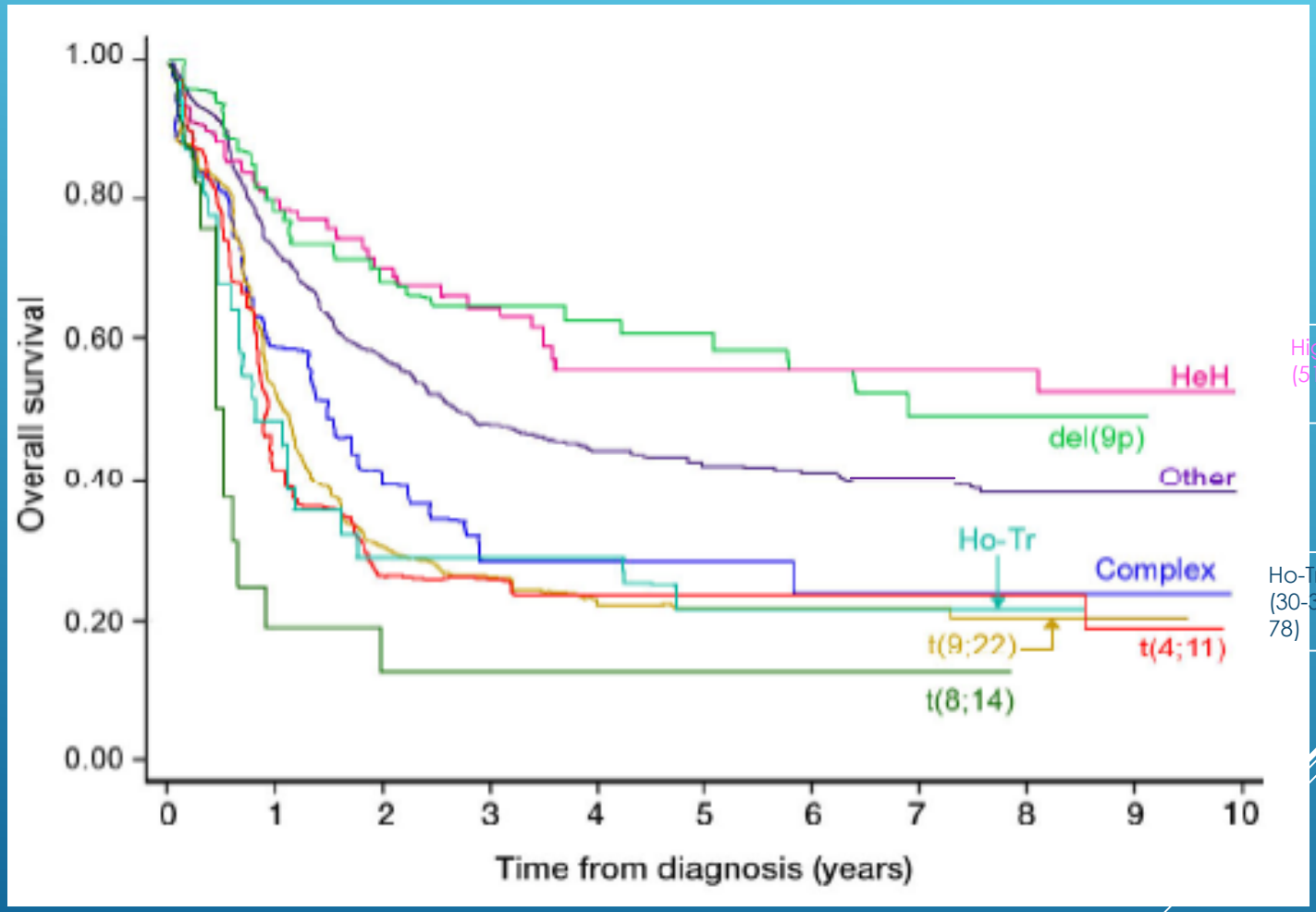
- Peak age at diagnosis 7yo
- But diagnosis possible throughout life

- Adolescent and young adult ALL
  - Often treat with a 'pediatric regimen'
    - Anthracycline, steroid, asparaginase, vincristine, 6-MP, cyclophosphamide
- Must administer intrathecal chemotherapy
  - Without this – 50% have CNS relapse
    - With IT chemo - ~5% CNS relapse

BACK TO PHILLY

- ALL can also have the Philadelphia Chromosome t(9;22)
  - 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)

Banner MD Anderson Cancer Center
Making Cancer History®

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

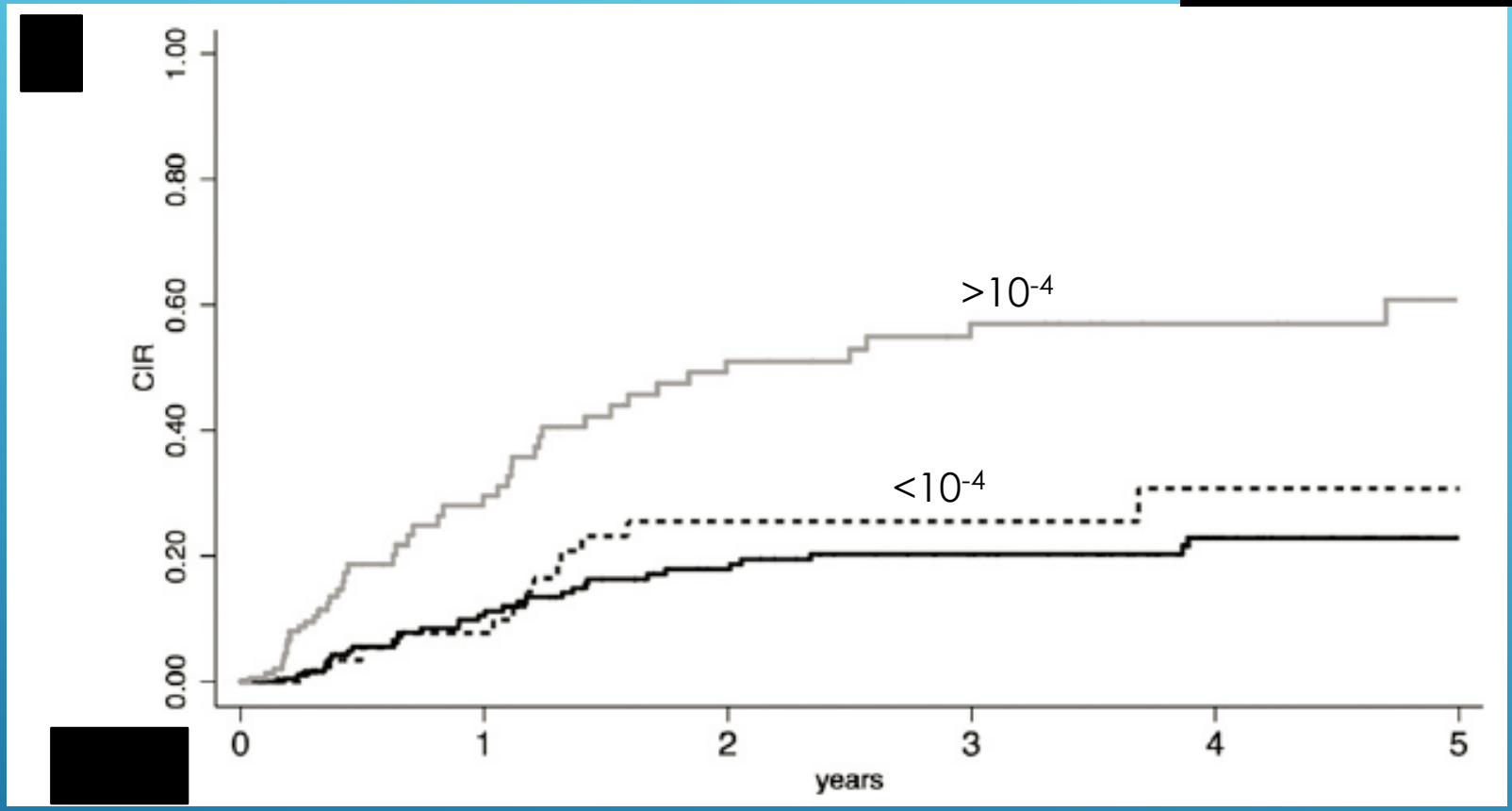
WHAT TO DO WITH THE REST?

- 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)
- Presence of Minimal Residual Disease (MRD) is the best current prognostic feature, guiding SCT vs no SCT

Banner MD Anderson Cancer Center
Making Cancer History®

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

MRD assessed at week 6; GRAALL 2003 protocol



MRD AND RISK OF RELAPSE

Banner MD Anderson Cancer Center
Making Cancer History®

Beldjord Blood 2014 and Bruggemann Blood 2006. 107:1116

QUESTIONS AND THANKS

Matthew.ulrickson@bannerhealth.com

@MattUlricksonMD

APL: Sanz Prognostic Factors

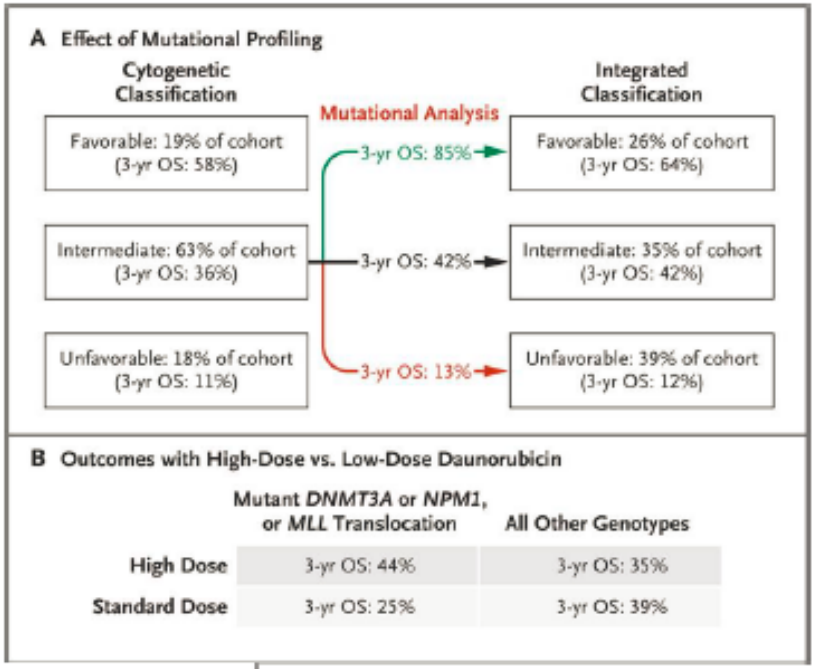
Low	WBC <10, Plt >40
Int	WBC <10, Plt <40
High	WBC ≥10

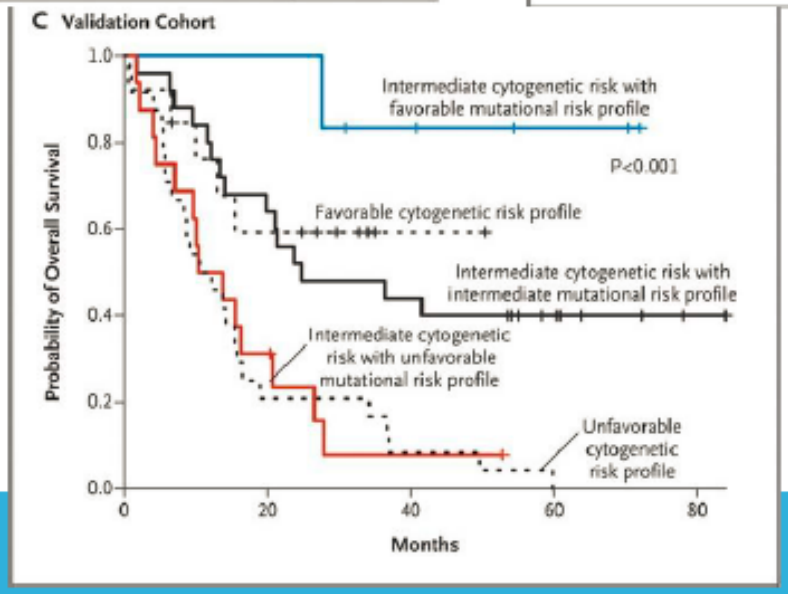
Sanz et al. *Blood*. 2010;115:5137-5148

Banner MD Anderson Cancer Center
Making Cancer History®

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.

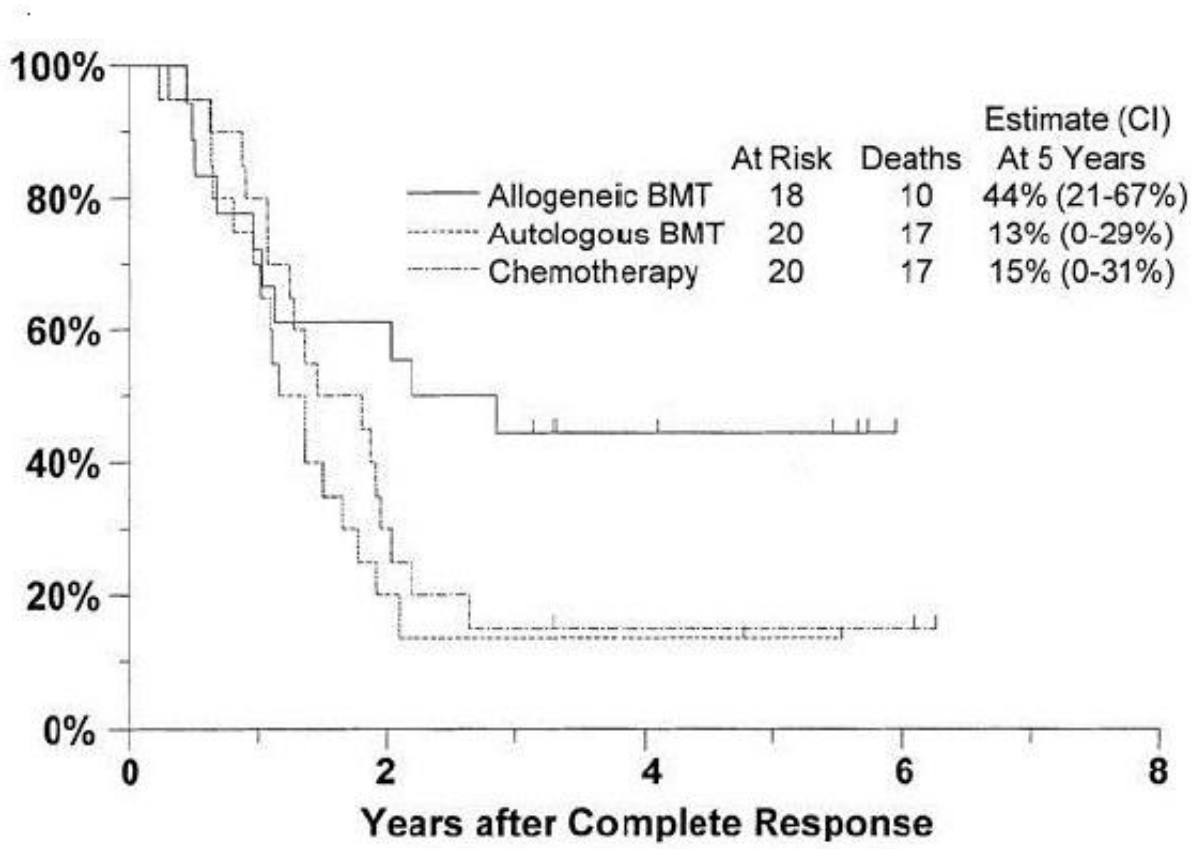
MOLECULAR MARKERS AND PROGNOSIS IN AML

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

Therapy of High Risk AML



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

Banner MD Anderson Cancer Center
Making Cancer History®

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

Banner MD Anderson Cancer Center
Making Cancer History®

Prognosis: European Leukemia Net

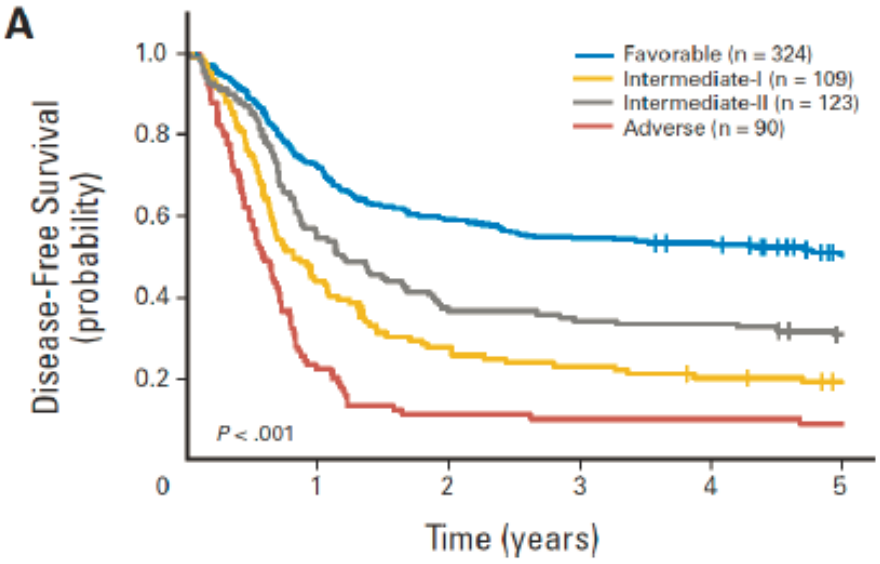


Table 1. European LeukemiaNet Standardized Reporting System for Correlation of Cytogenetic and Molecular Genetic Data in AML With Clinical Data[12]

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).

Banner MD Anderson Cancer Center
Making Cancer History®

Mrozek et al. JCO 2012 _____