ACUTE LEUKEMIA

Matthew Ulrickson, MD
Banner MD Anderson Cancer Center
September 17, 2019

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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

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CASE 1

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

- CBC: 35>35%<35k

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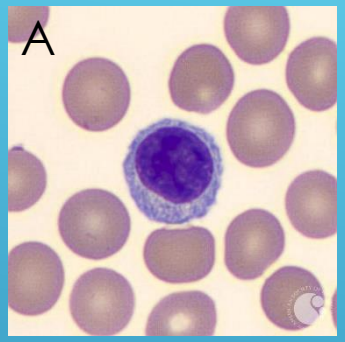
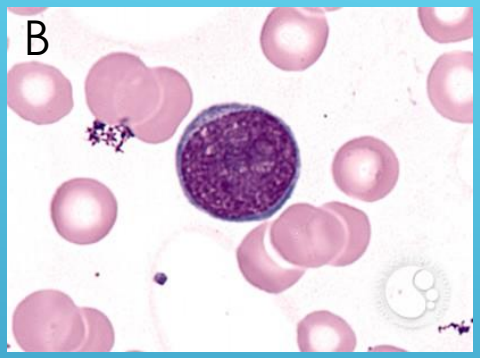
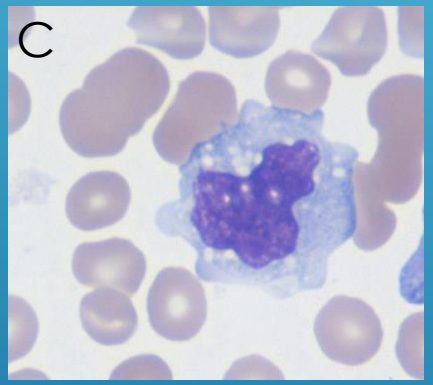
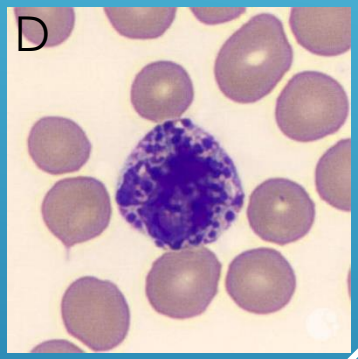
WHICH OF THE FOLLOWING IS A BLAST?

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









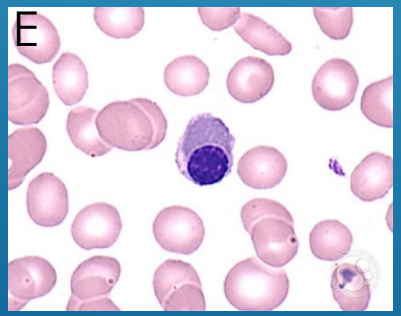
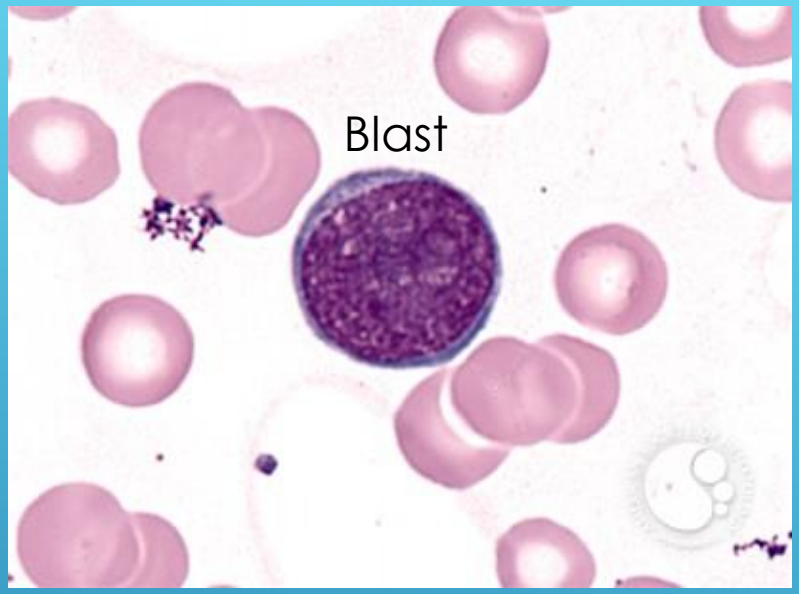


Image courtesy of Peter Maslak

PERIPHERAL SMEAR

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



- He was diagnosed with Ph+ Acute Lymphoblastic Leukemia

- Addition of which of the following medications to Induction chemotherapy is recommended?
  - A. Ruxolitinib
  - B. Gilteritinib
  - C. Dasatinib
  - D. Rituximab
  - E. Blinatumomab

Image courtesy of Peter Maslak

CASE 2

- 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
- 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

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INITIAL TESTING

- CBC: 6.9>2.6<79 MCV 100

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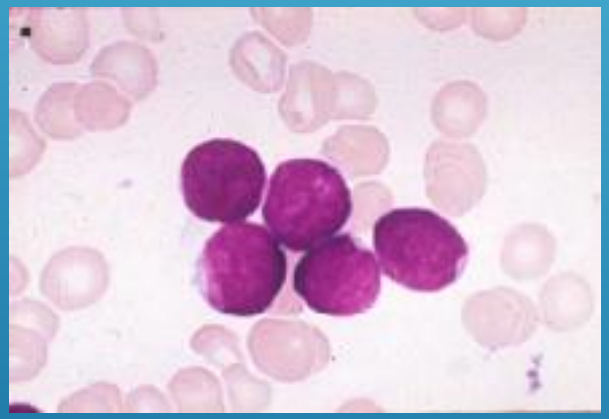
INITIAL TESTING

- 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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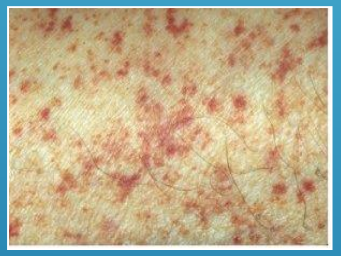
CLINICAL SYMPTOMS OF AML

- 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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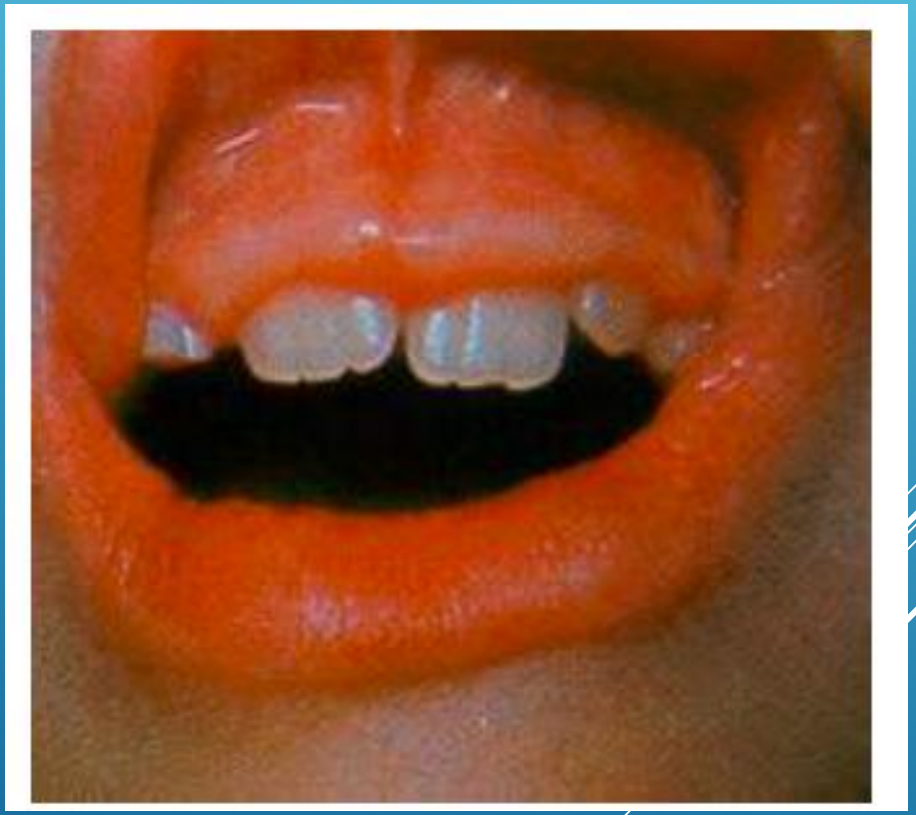
TISSUE INVASION IN AML

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



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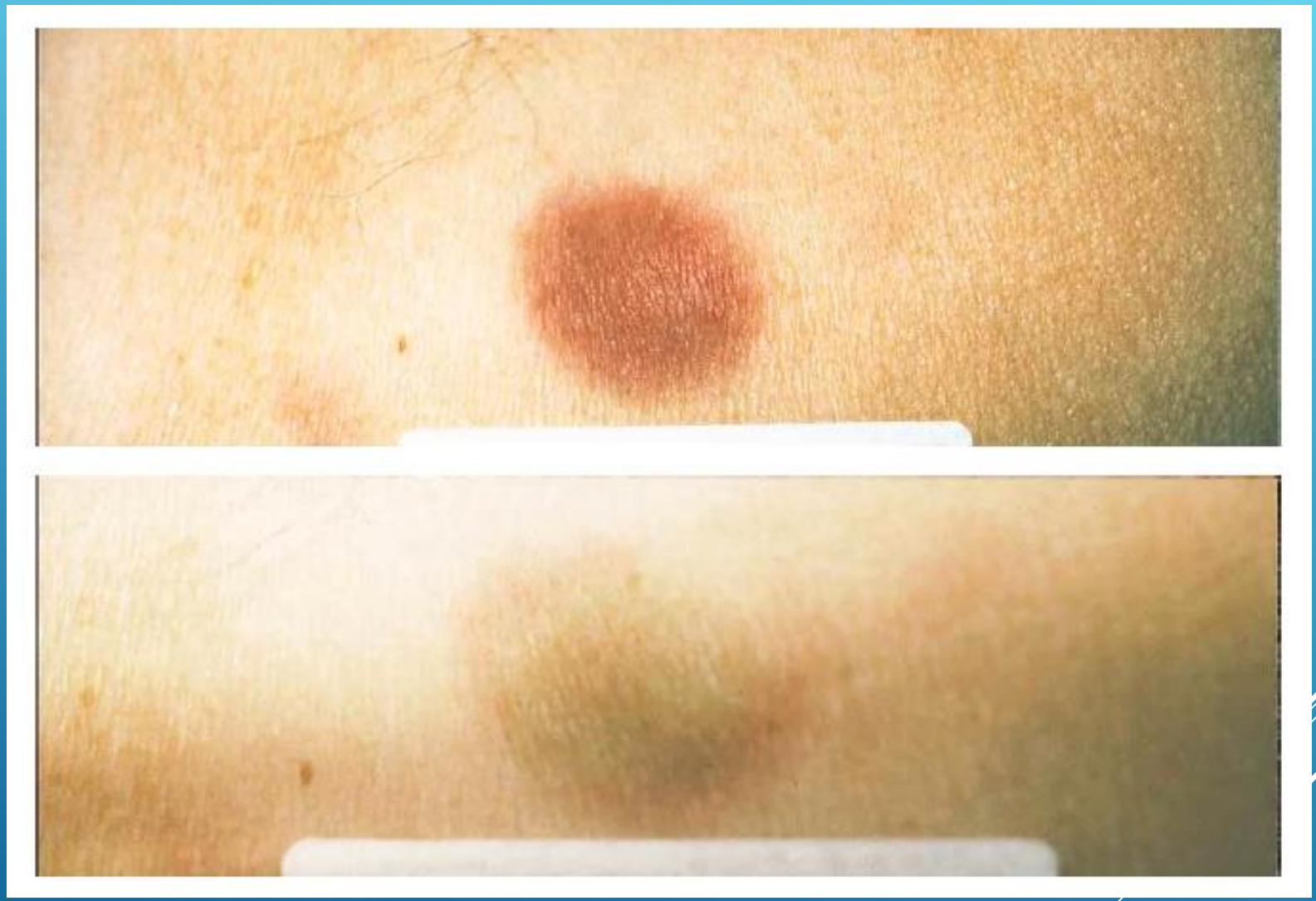
CHLOROMA



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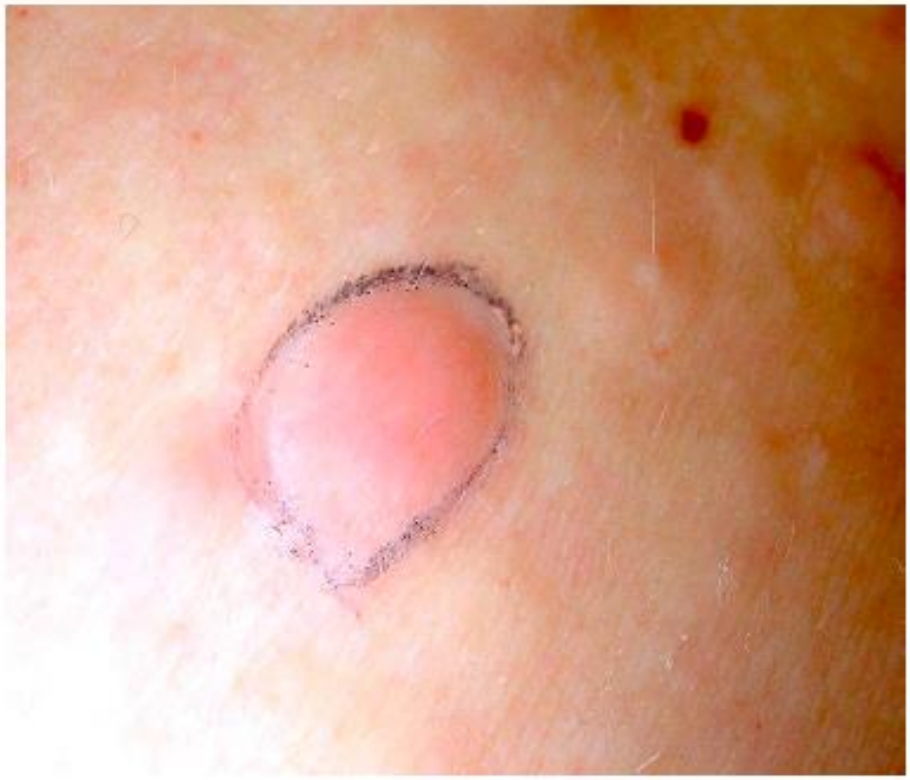
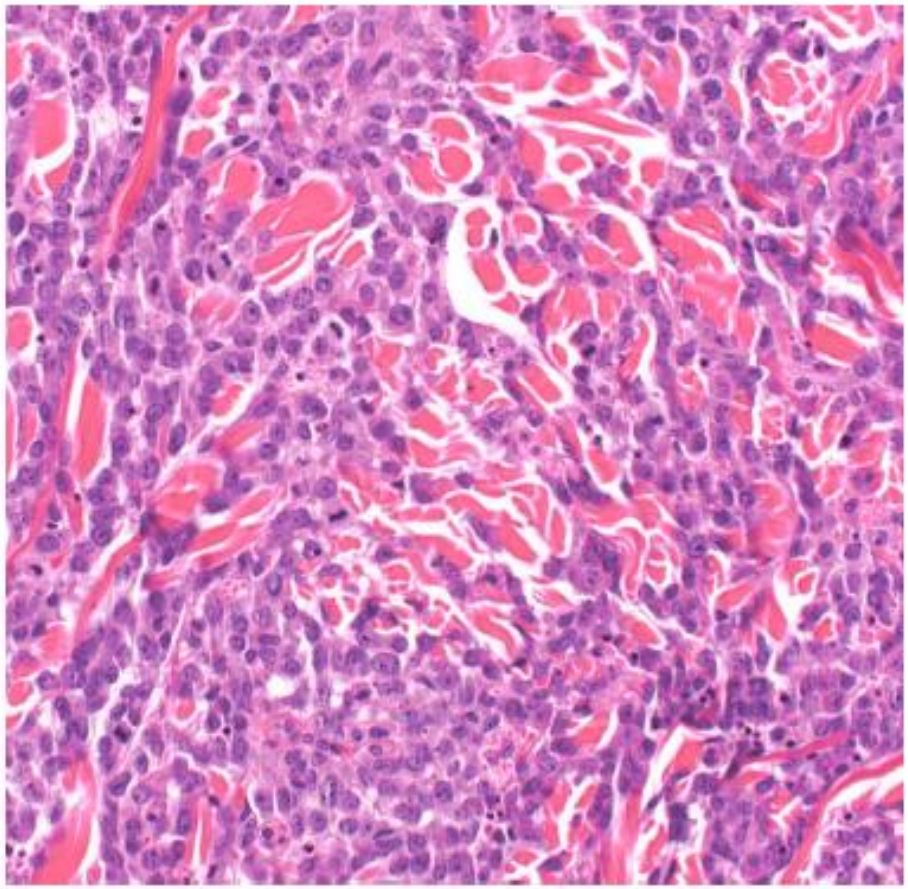
LEUKEMIA CUTIS





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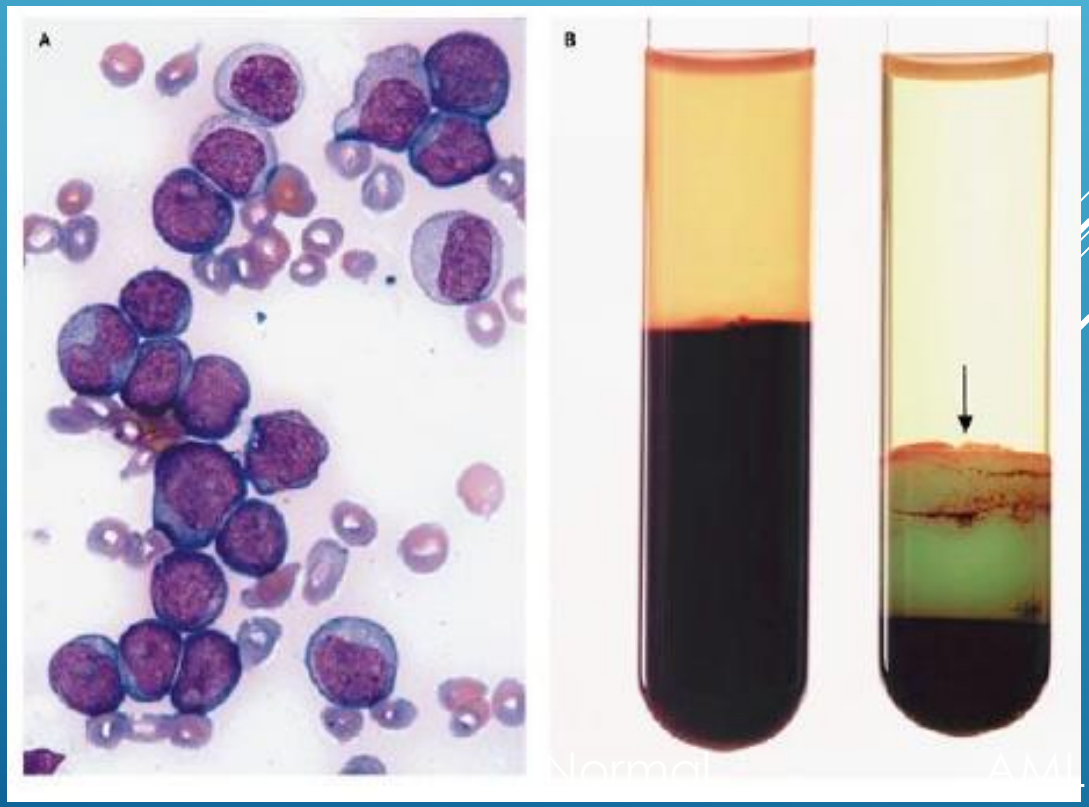
Sauter and Jacky *NEJM* 1998. 338:969

HIGH CIRCULATING BLASTS

Pseudo:

- Hypoglycemia
- Hypoxia
- Hyperkalemia
- Elevated Lactate

Mauro MJ NEJM 2003. 349:767



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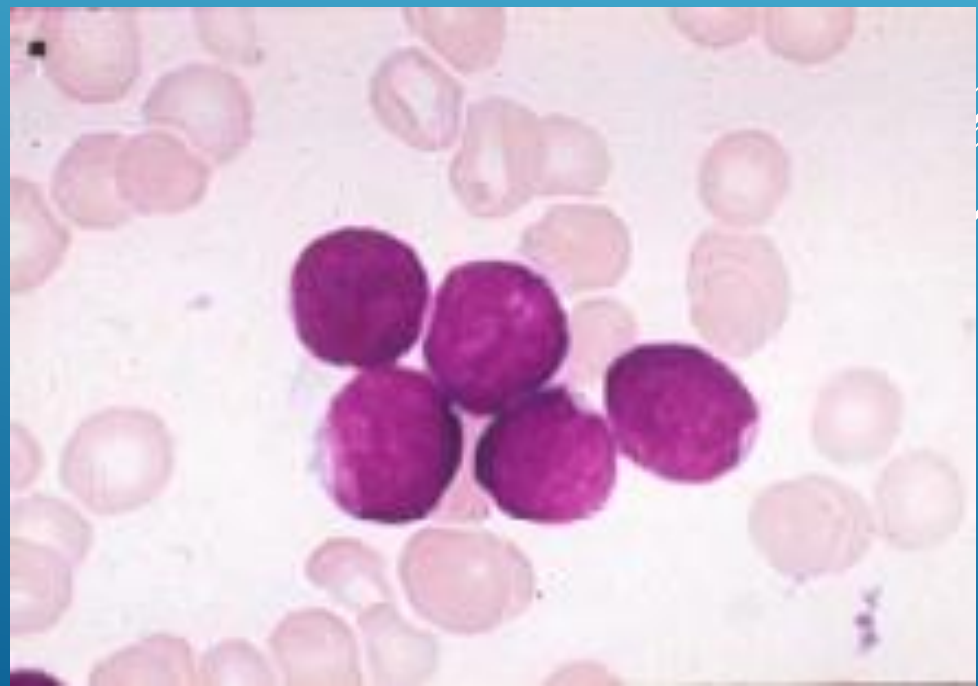
EVALUATION OF PATIENT WITH AML

- 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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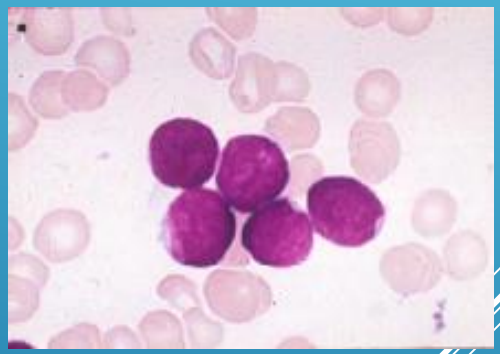

- Diagnosis
  - Bone marrow biopsy
  - FISH and cytogenetics, flow cytometry
  - Molecular: FLT3, NPM1, CEPBA, IDH, Myeloid/Lymph molecular panel
    - (can be sent on PB if circulating blasts)
  - If circulating blasts, send peripheral blood for flow cytometry (STAT) to make dx

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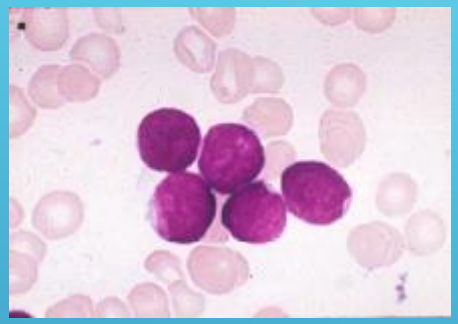
EVALUATION OF PATIENT WITH AML



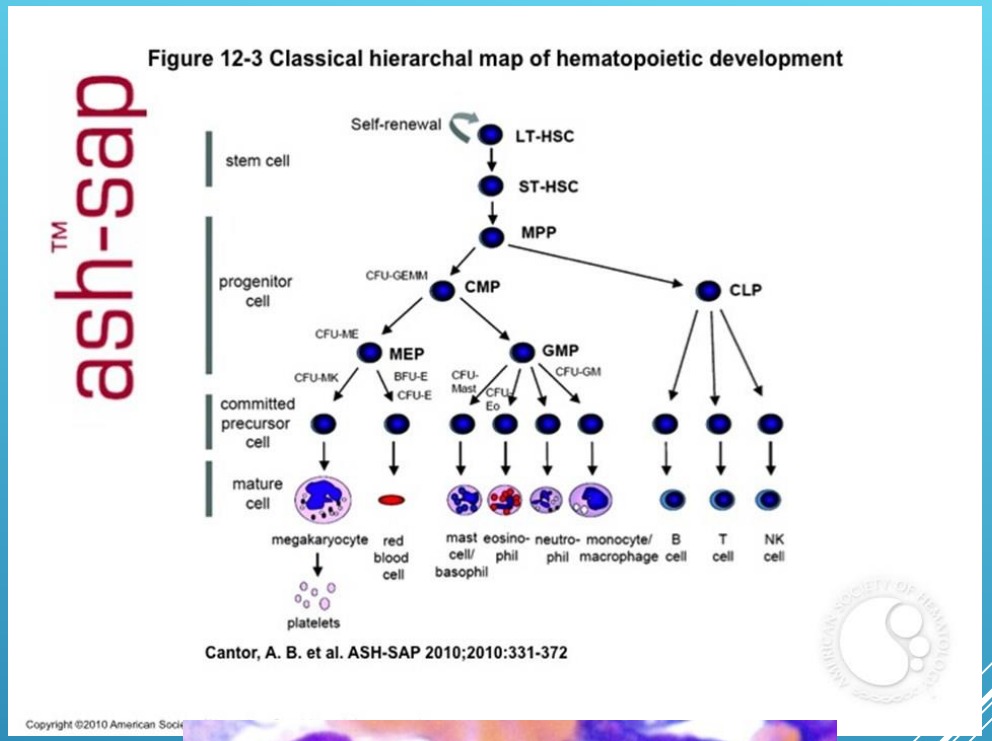
- Initial triage
  - History and Physical
  - CBC with differential (look at the peripheral smear)
  - BMP, LFTs, uric acid, ABO type and screen
  - PT, PTT, fibrinogen
- Diagnosis
  - Bone marrow biopsy
  - FISH and cytogenetics, flow cytometry
  - Molecular: FLT3, NPM1, CEPBA, myeloid molecular panel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

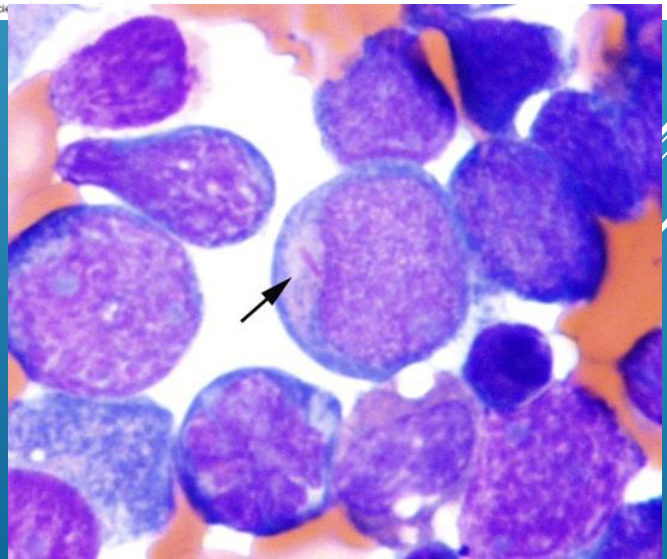
DIFFERENTIATE AML VS ALL

- 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





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IMMEDIATE EMERGENCY?

- Leukostasis
- Pulmonary or neurological symptoms related to increased serum viscosity
  - Which of the following patients is most likely to have leukostasis?
    - A. CML with WBC of 300k
    - B. ALL with WBC of 180k
    - C. CLL with WBC of 500k
    - D. AML with WBC of 120k
    - E. Cdiff with WBC of 70k

IMMEDIATE EMERGENCY?

- Leukostasis
- 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

IMMEDIATE EMERGENCY?

- Leukostasis
- 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

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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*
MPO	*CD20*	*CD4*
	CD22	*CD5*
	Surface Ig	*CD7*
		CD8

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

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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

5+1

- Mitoxantrone/AraC (high dose) at BMDACC
  - Lower Therapy-related mortality in older patients vs 7+3
  - Other AML trials show better CR rate with high dose AraC in young patients

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Am J Heme 2019

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%

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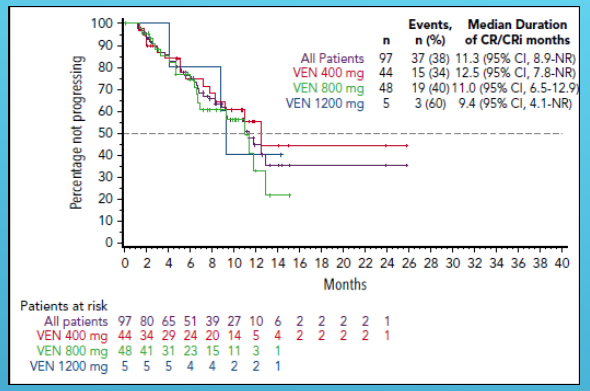
Appelbaum et al. Blood 2006, 107:3481

HYPOMETHYLATING AGENTS WITH VENETOCLAX IN AML



- Phase 1b study, n= 145
- >65yo and ineligible for induction chemotherapy
- Venetoclax plus azacitidine or decitabine (HMA)

- Median age 74yo, poor risk cytogenetics in 49%
- 67% = CR (37%) or CRi (30%)
- Median duration of response 11.3 months, mOS 17.5m
- 8% (n=11) death within 60 days unrelated to AML

DiNardo, et al. *Blood* 2019; 133(1):7-17

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
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- So what?!?

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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

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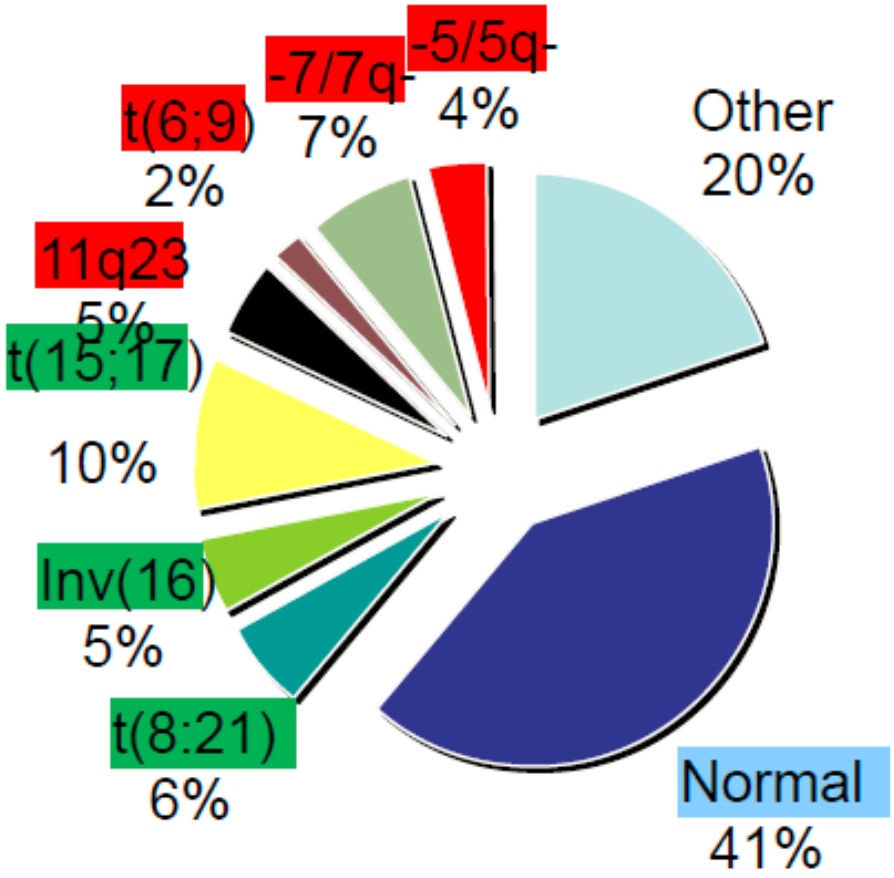
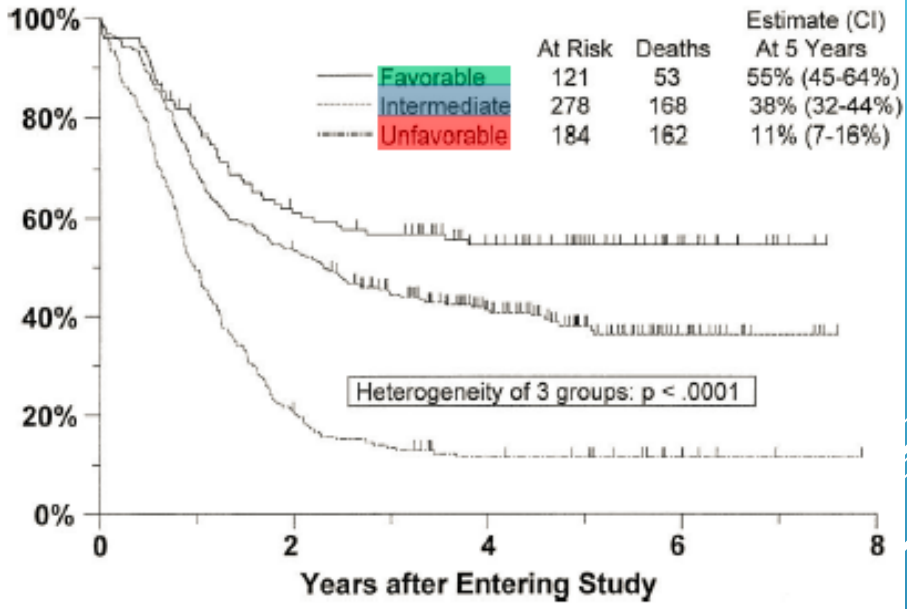
M0, M1, M2, M4, M5, M6, M7
MMMMEAN NOTHING!

- >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

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Slovak et al. Blood 2000. 96:4075

ON TARGET MUTATIONS HELP OPTIMALLY TREAT AML

- Current targeted medicines available:
  - FLT3 + = midostaurin, gilteritinib
  - 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…

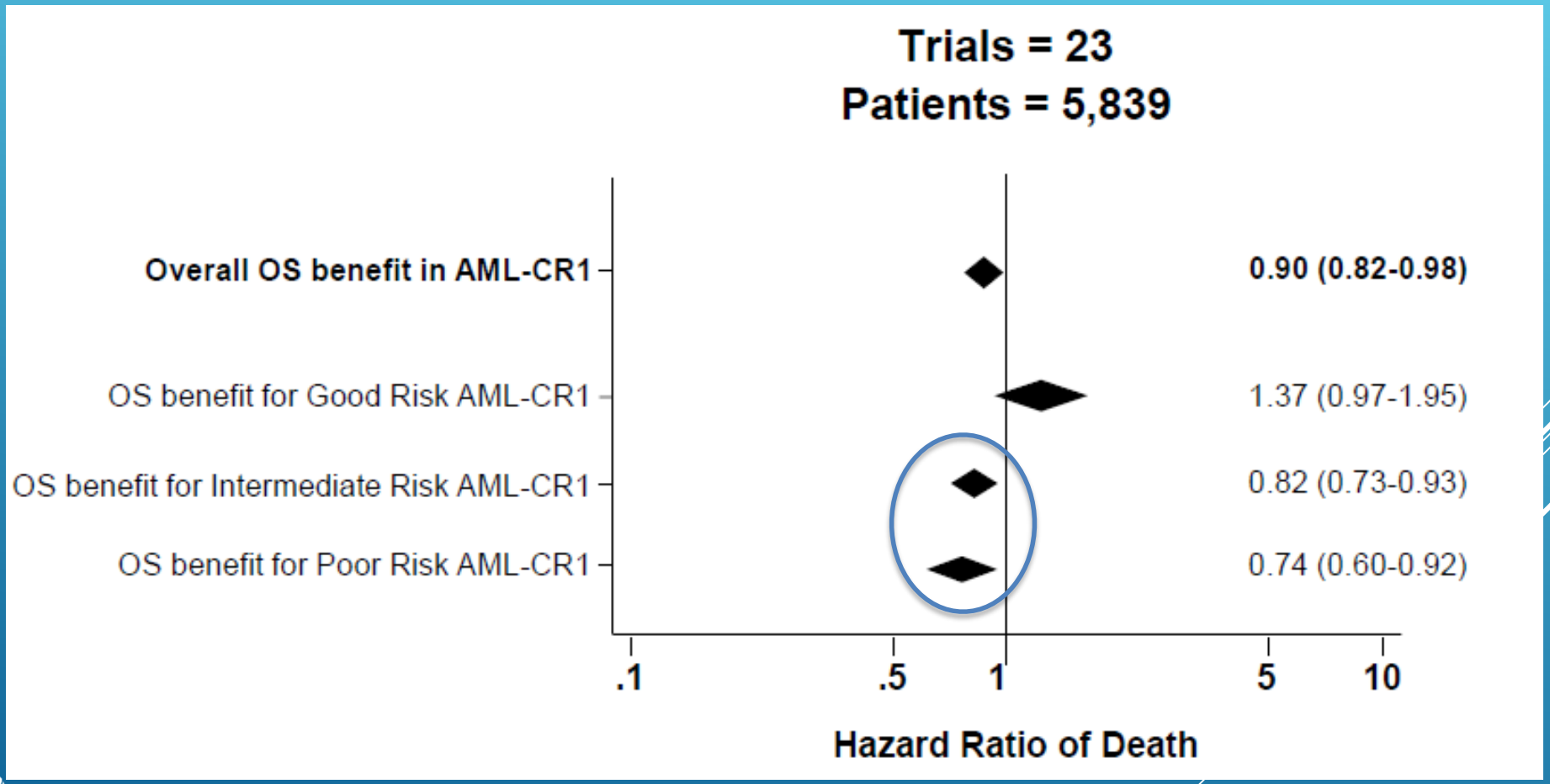
AML IN CR1

- 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



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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)

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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

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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?

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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%)*

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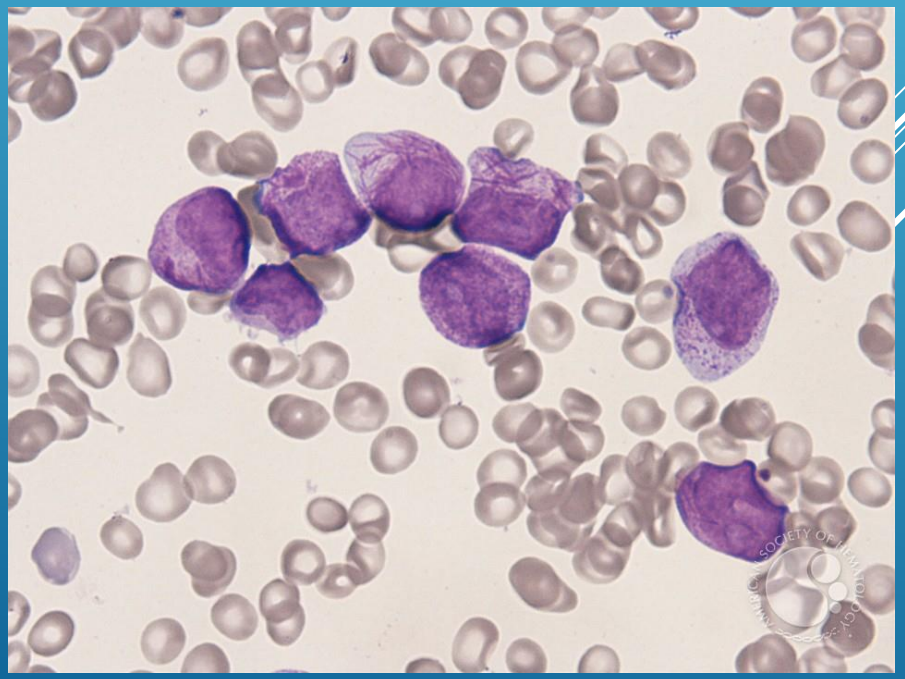
CASE 3

- 44yo woman presents to the ED with bleeding gums and a non-blanching erythematous rash. Labs as follow:
- CBC: WBC 1.9>7.2<5
- INR 2.6 PTT 48 Fibrinogen 113
- Peripheral smear is below.

- Which of the following medications do you recommend?
  - A. Doxycycline
  - B. ATRA
  - C. PCC
  - D. Dasatinib
  - E. Aminocaproic Acid



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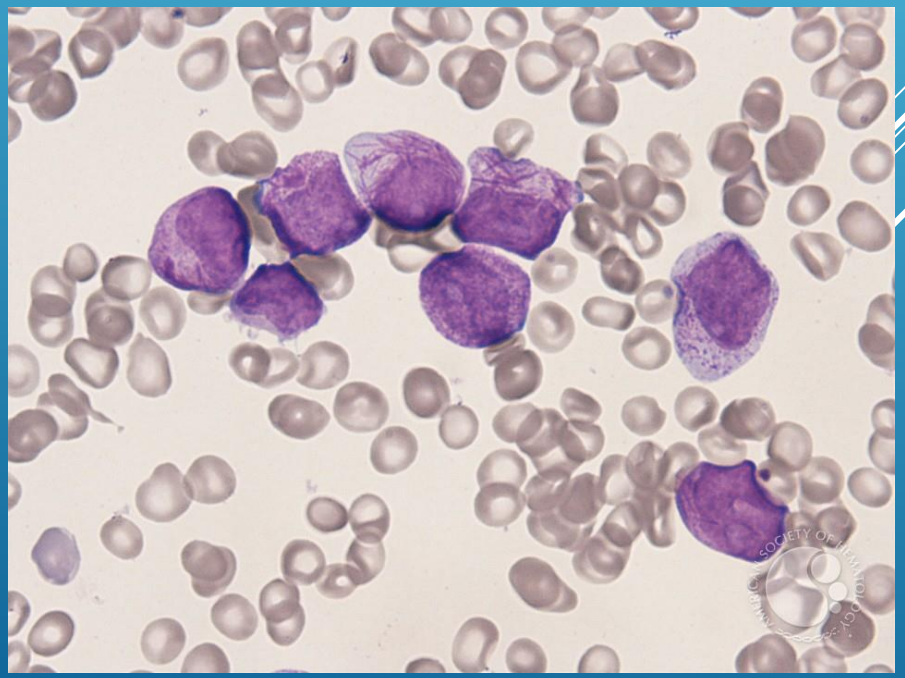
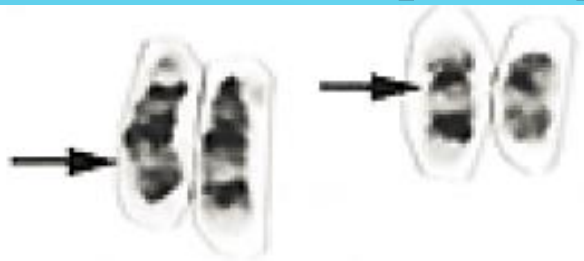
  - B. ATRA (Tretinoin)
  - C. PCC
  - D. Dasatinib
  - E. Aminocaproic Acid

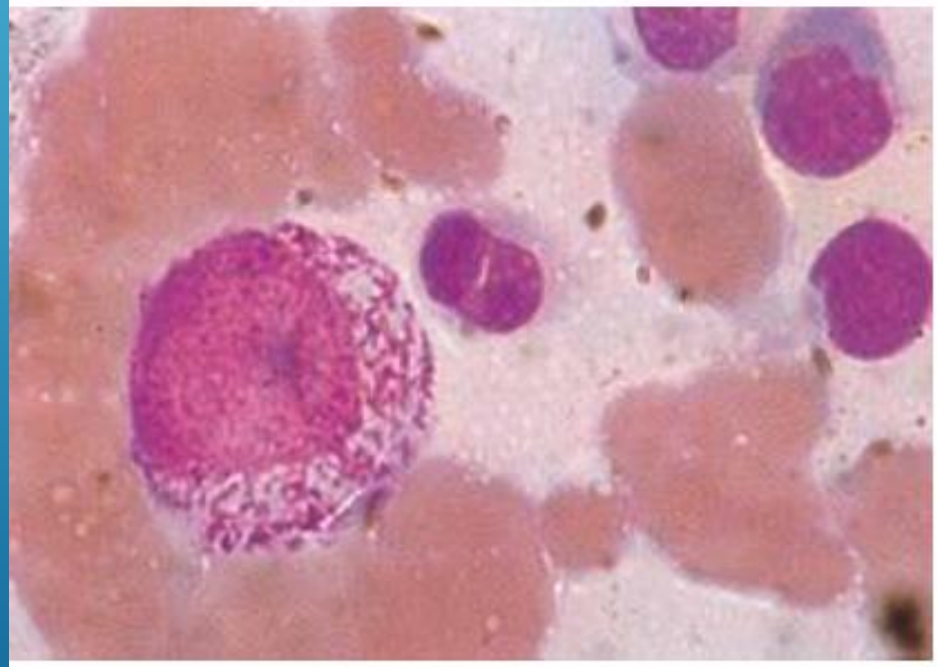


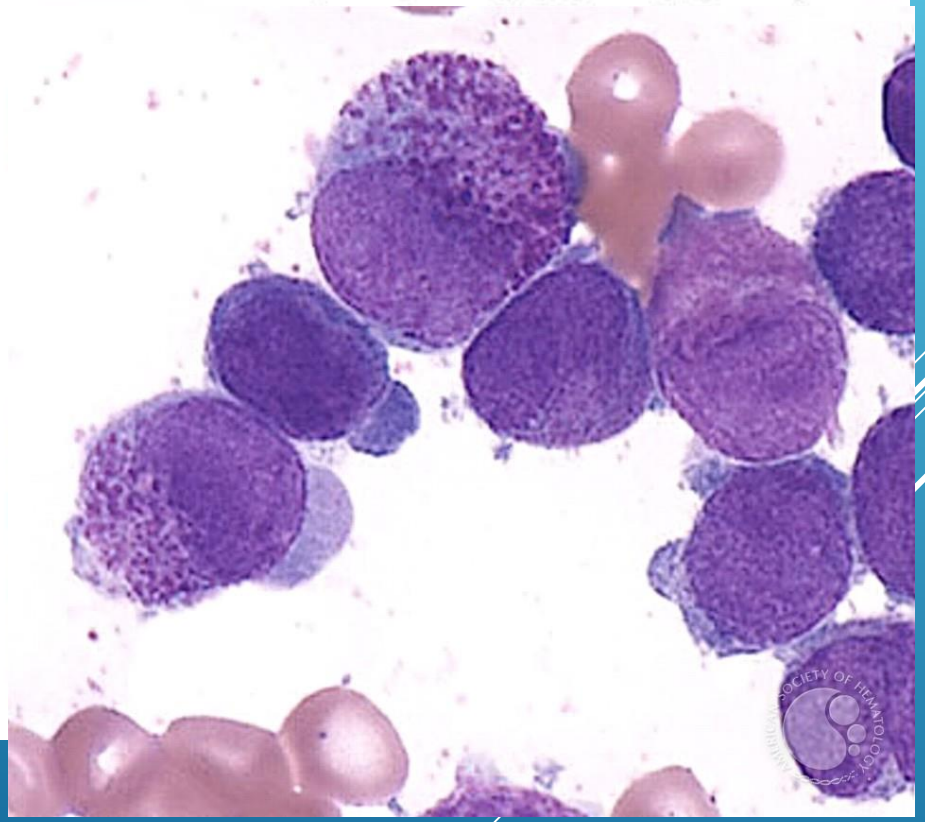
ACUTE PROMYELOCYTIC LEUKEMIA (APL)

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 (as long as HCG negative)
  - Do not wait for testing results to start but send 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

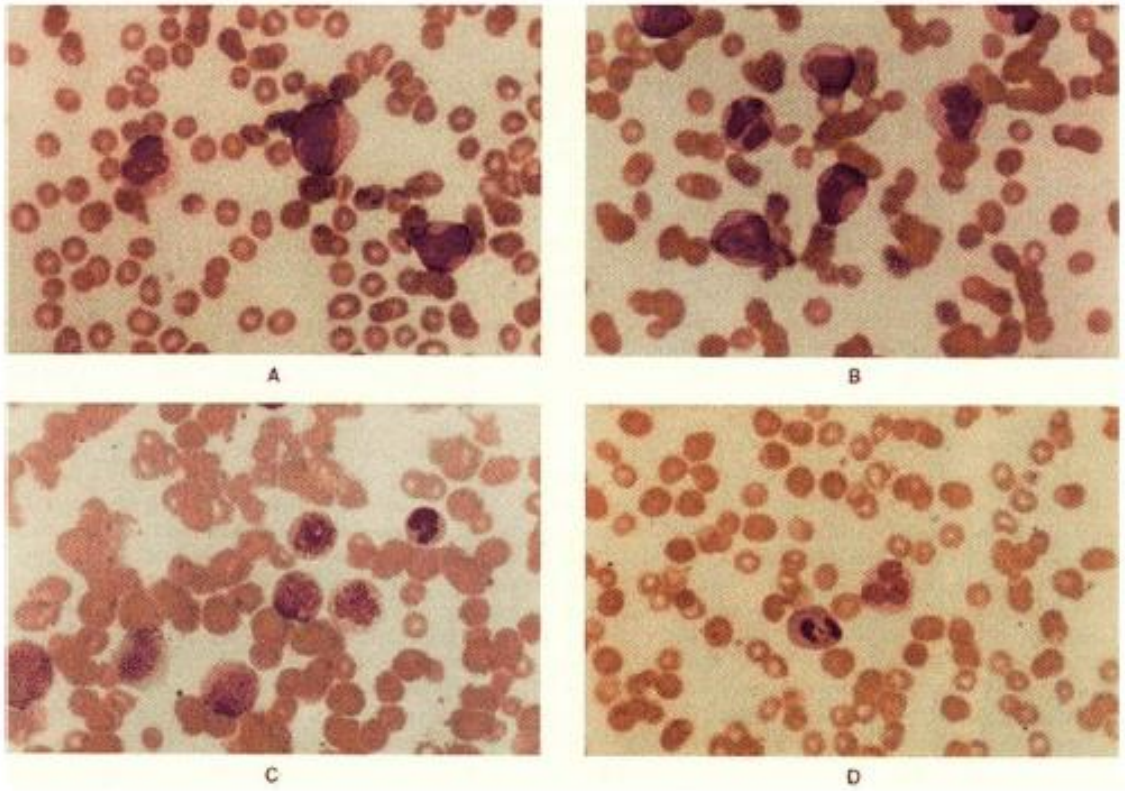
Tretinoin

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)

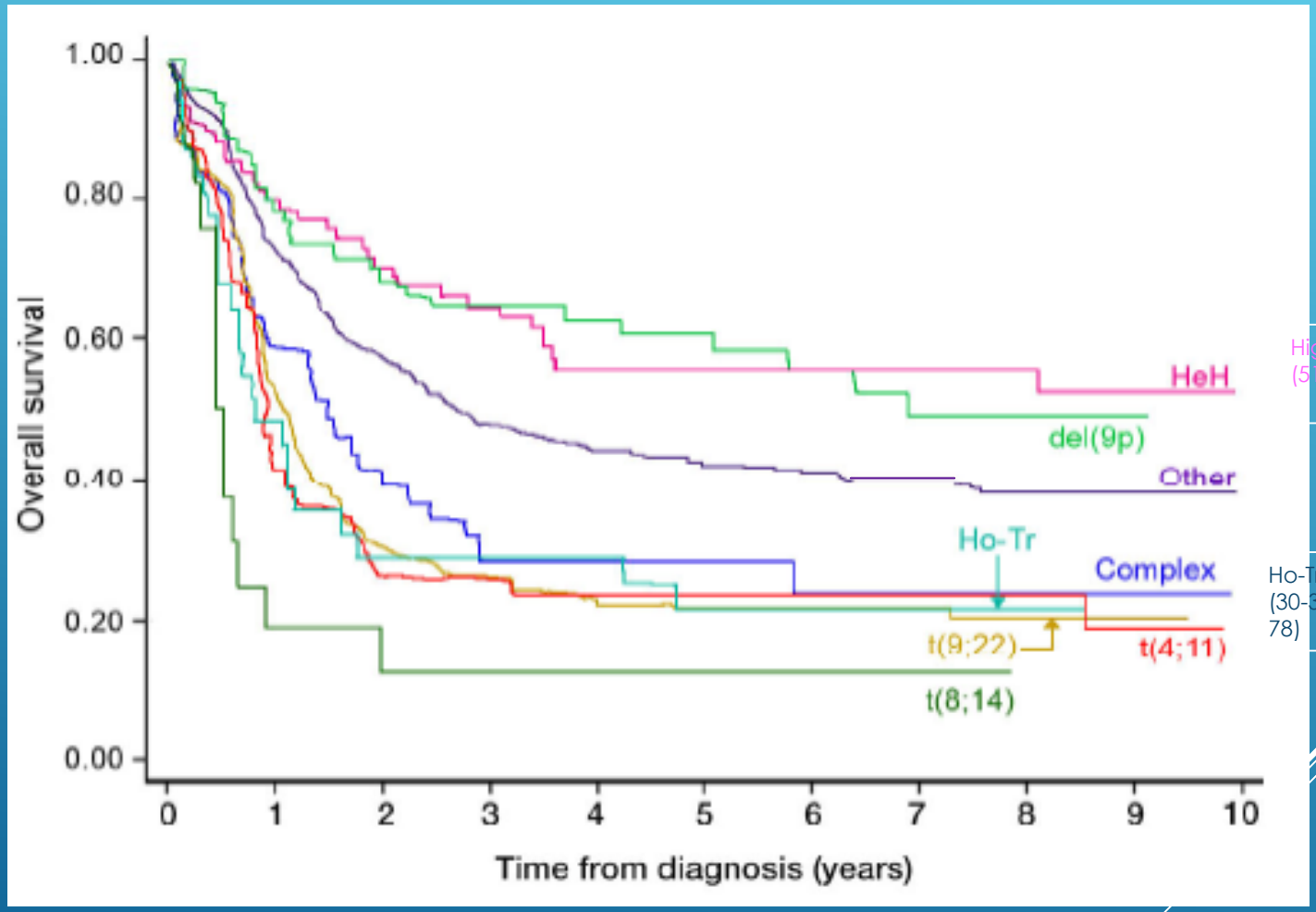
- Peak age at diagnosis 7yo
- But diagnosis possible throughout life

- Adolescent and young adult ALL
  - 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)

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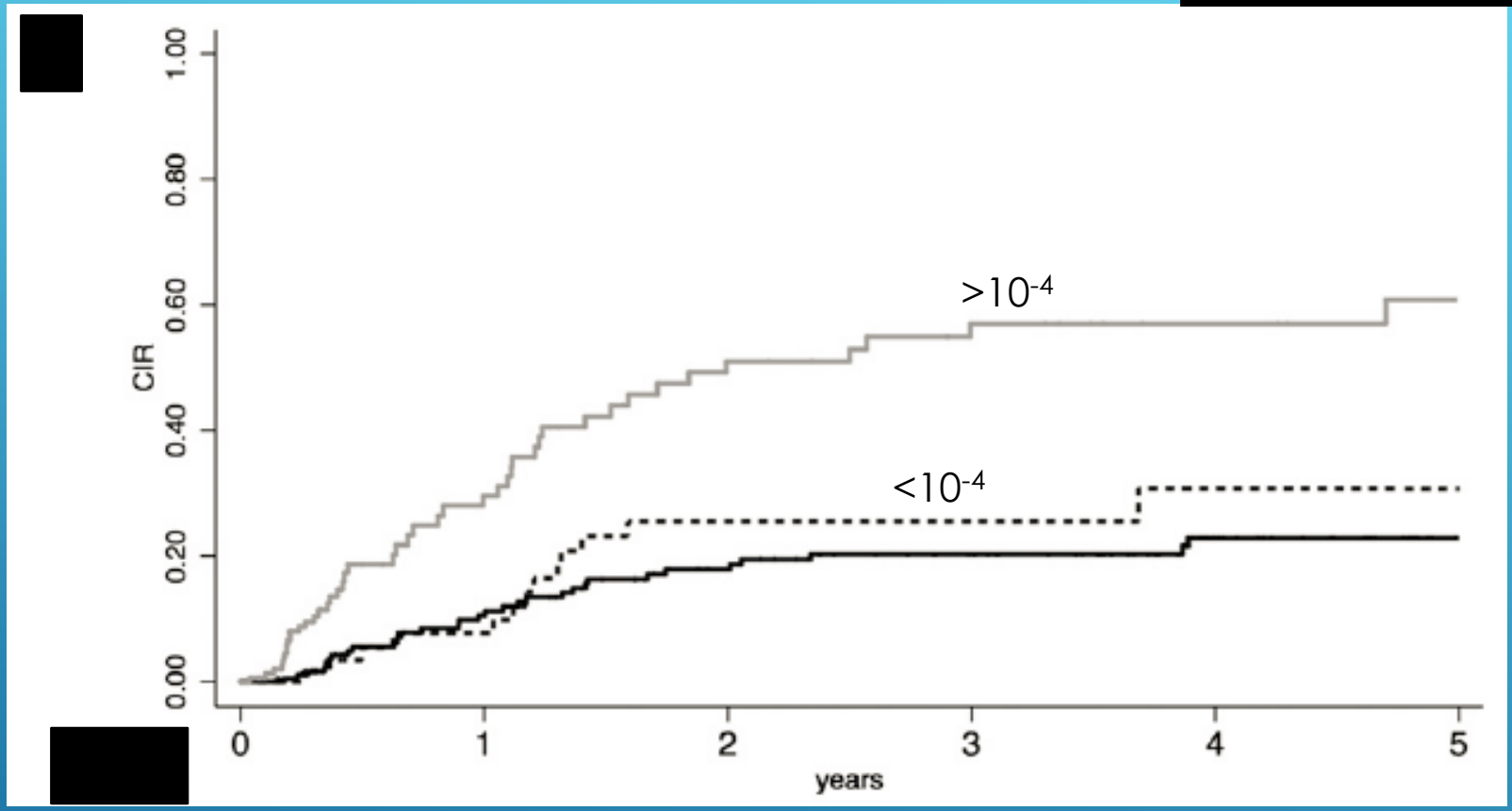
Moorman AV. et al. Blood 2007. 109:3189

MRD assessed at week 6; GRAALL 2003 protocol



MEASURABLE RESIDUAL DISEASE (MRD) AND RISK OF RELAPSE

PRESENCE OF MINIMAL RESIDUAL DISEASE (MRD) IS THE BEST CURRENT PROGNOSTIC FEATURE, GUIDING SCT VS NO SCT

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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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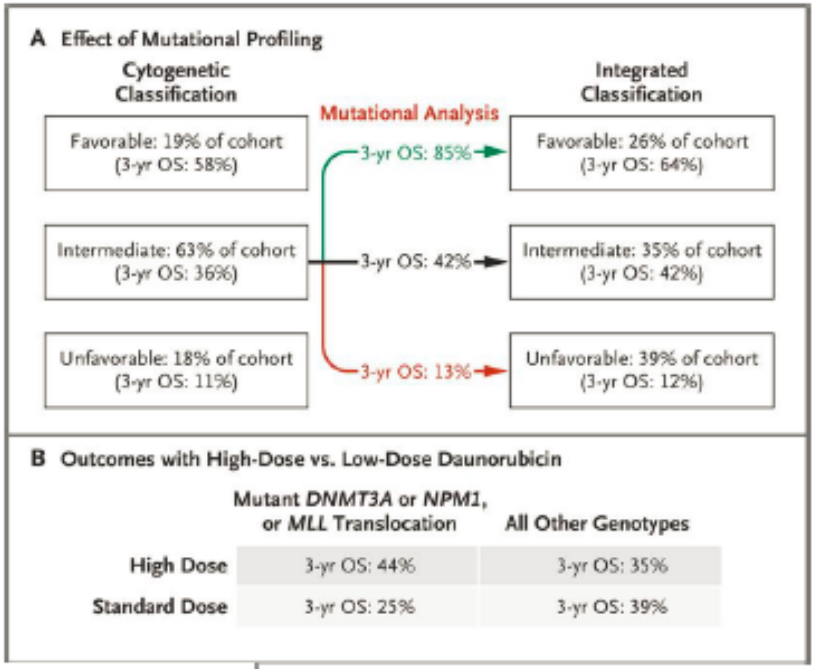
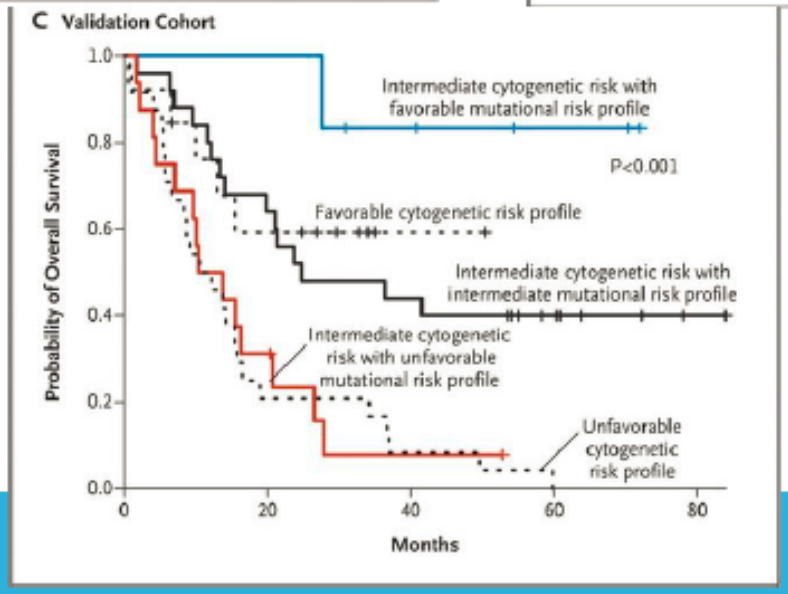
A Revised Risk Stratification

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.

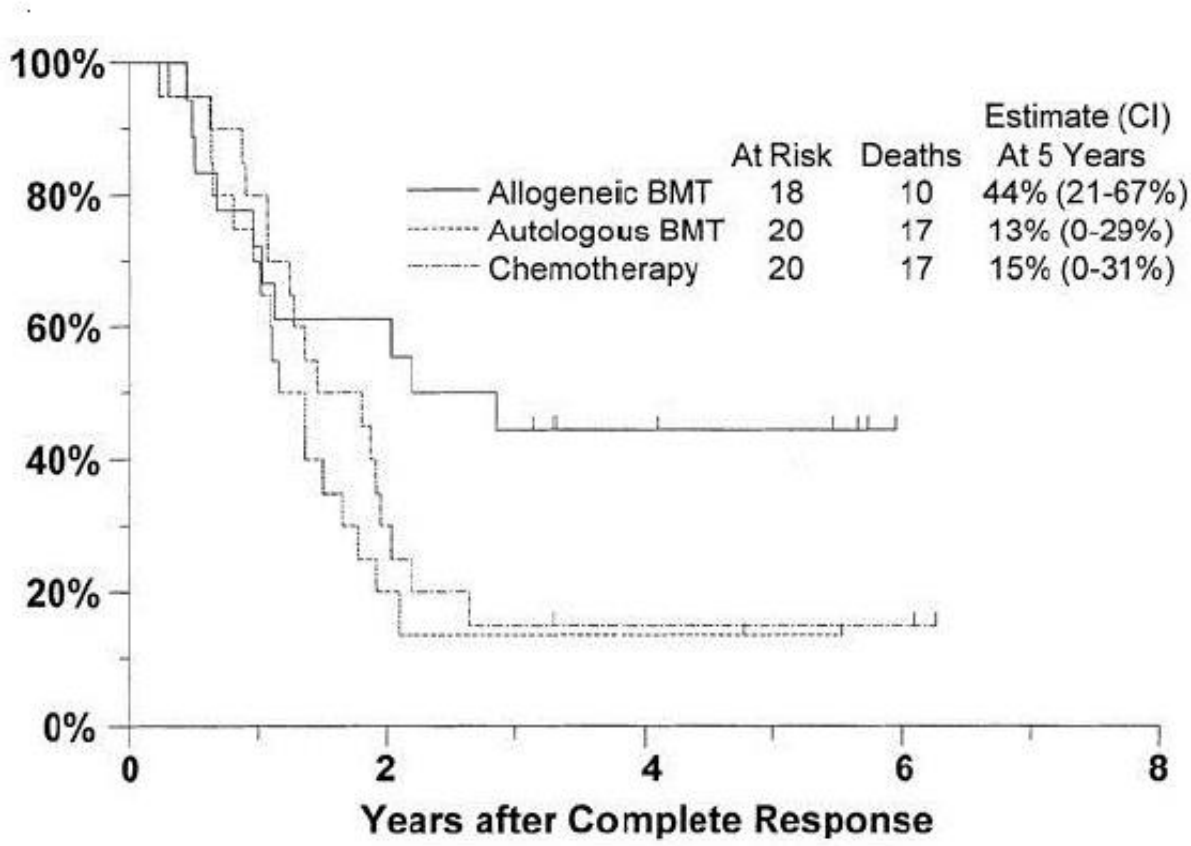
MOLECULAR MARKERS AND PROGNOSIS IN AML

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

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

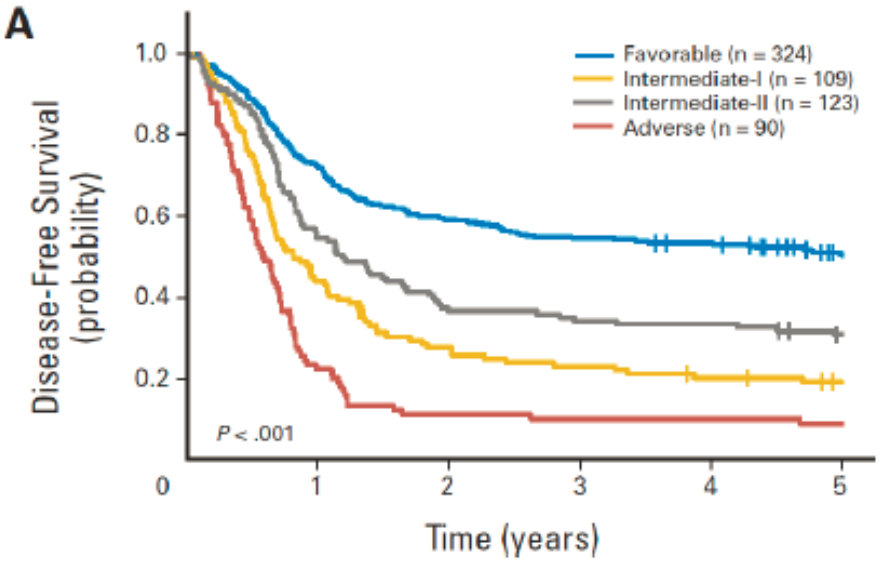

Table 1. European LeukemiaNet Standardized Reporting System for Correlation of Cytogenetic and Molecular Genetic Data in AML With Clinical Data[12]

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).

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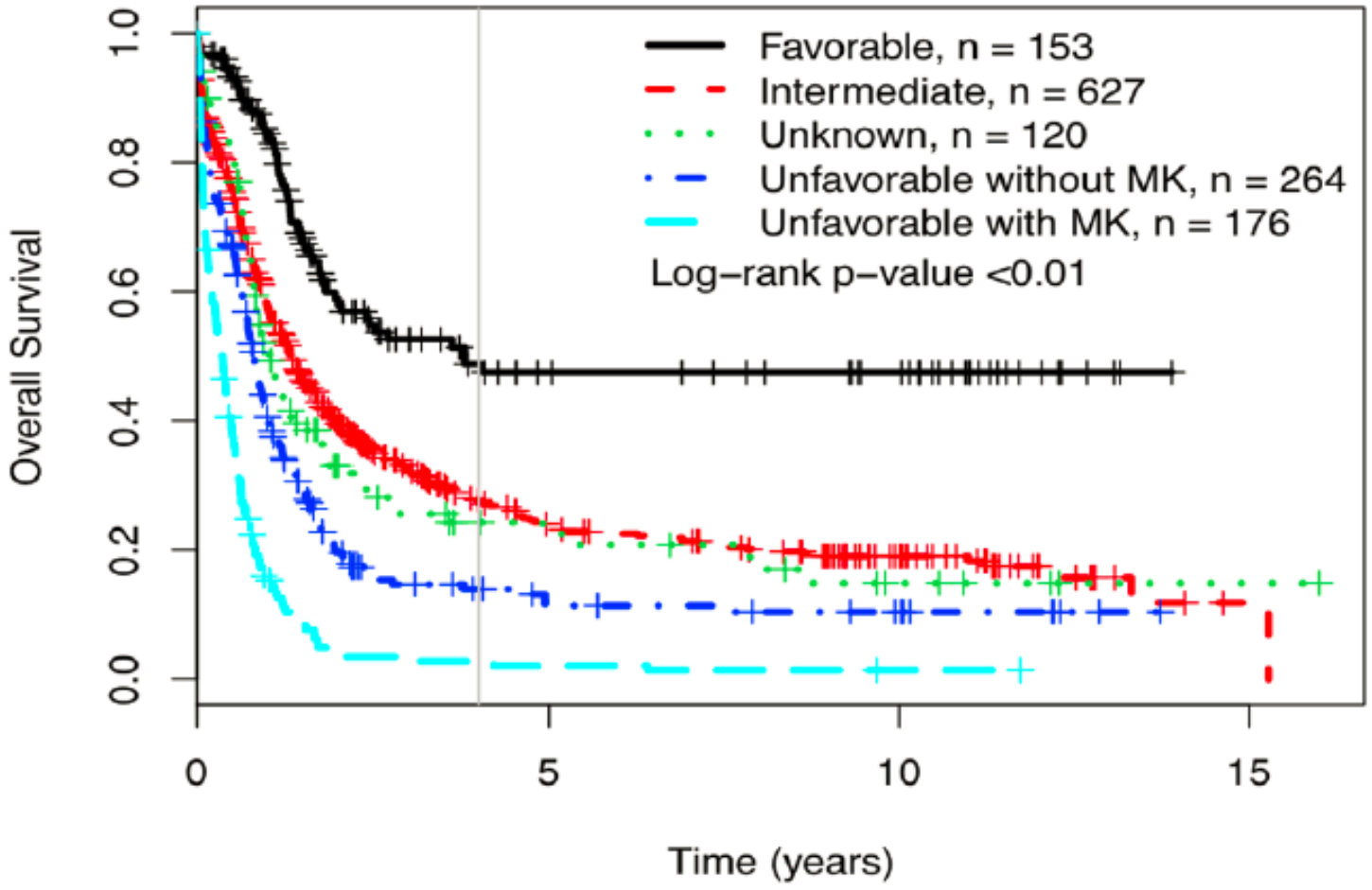
Mrozek et al. JCO 2012 _____

CYTOGENETICS AND SURVIVAL IN AML



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

Medeiros et al. Blood 2010. 116:2224

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

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