# FISHing for Acute Leukemia

Matthew Ulrickson, MD
Banner MD Anderson Cancer Center
September 20, 2016

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

# *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

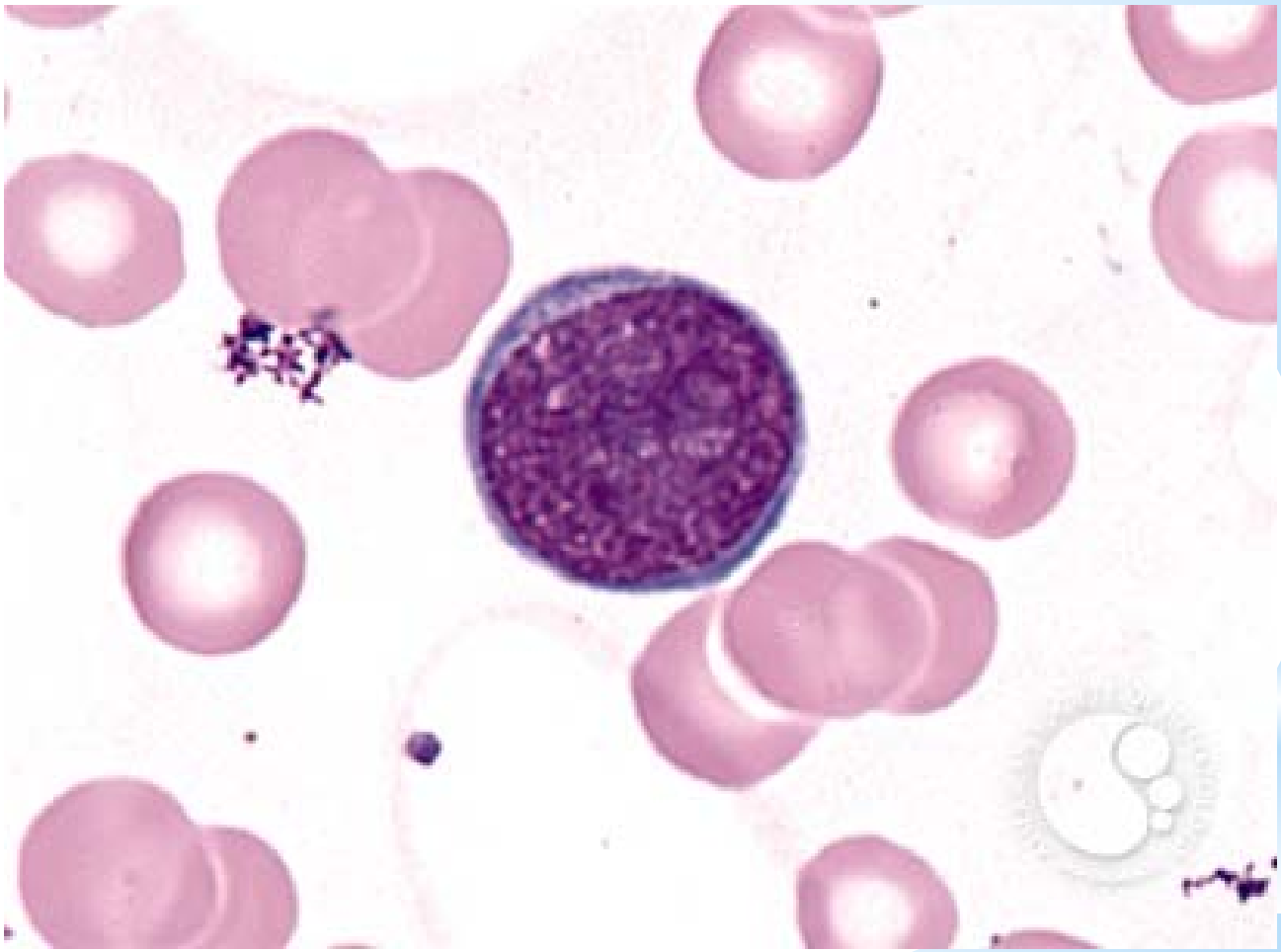
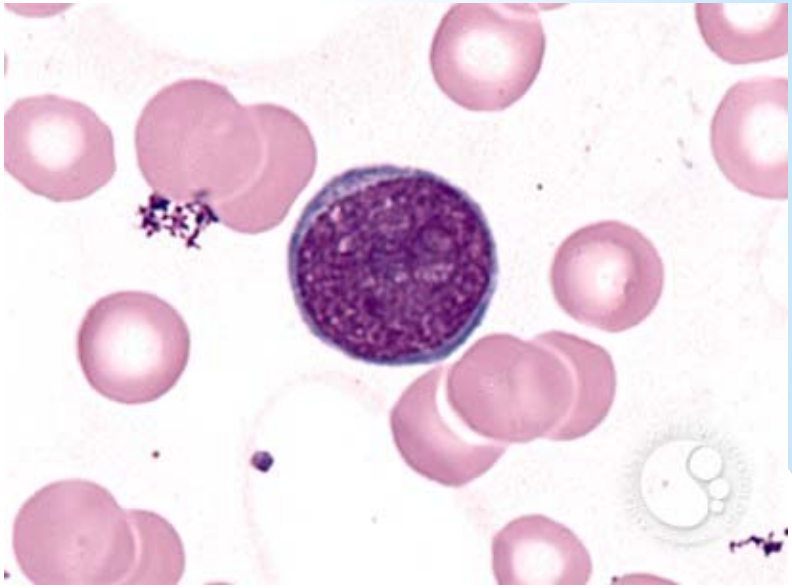


Image courtesy of Peter Maslak

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

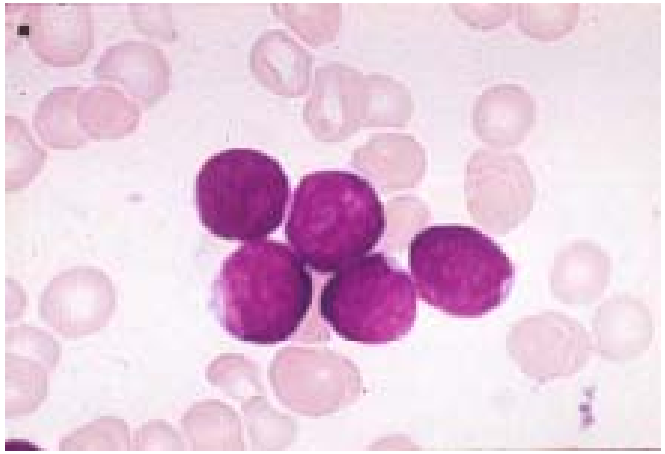
- Exam: Temp 37.3, HR 117, BP 107/54, RR 24
- Conjunctival rim pallor noted, tachycardic with systolic murmur present at the apex. No LAD or HSM

# Initial testing

* CBC: 6.9>2.6<79 MCV 100

# 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



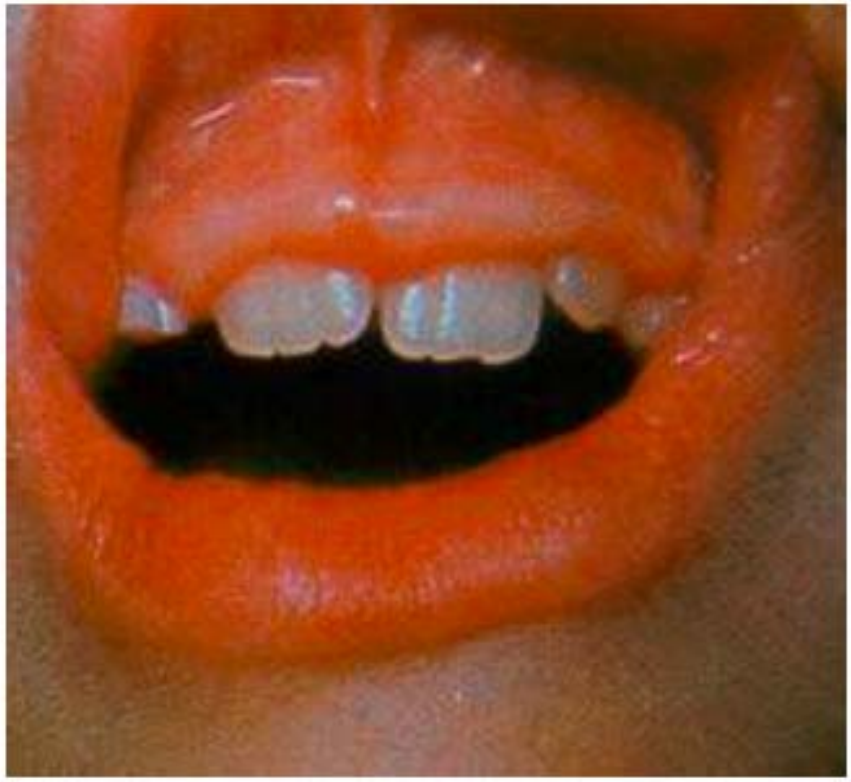
- Reticulocyte 0.3%; absolute 2000/µl
- Cr 0.8, total bilirubin 0.4, LDH 392, albumin 3.7, AST 45, ALT 145,

# 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

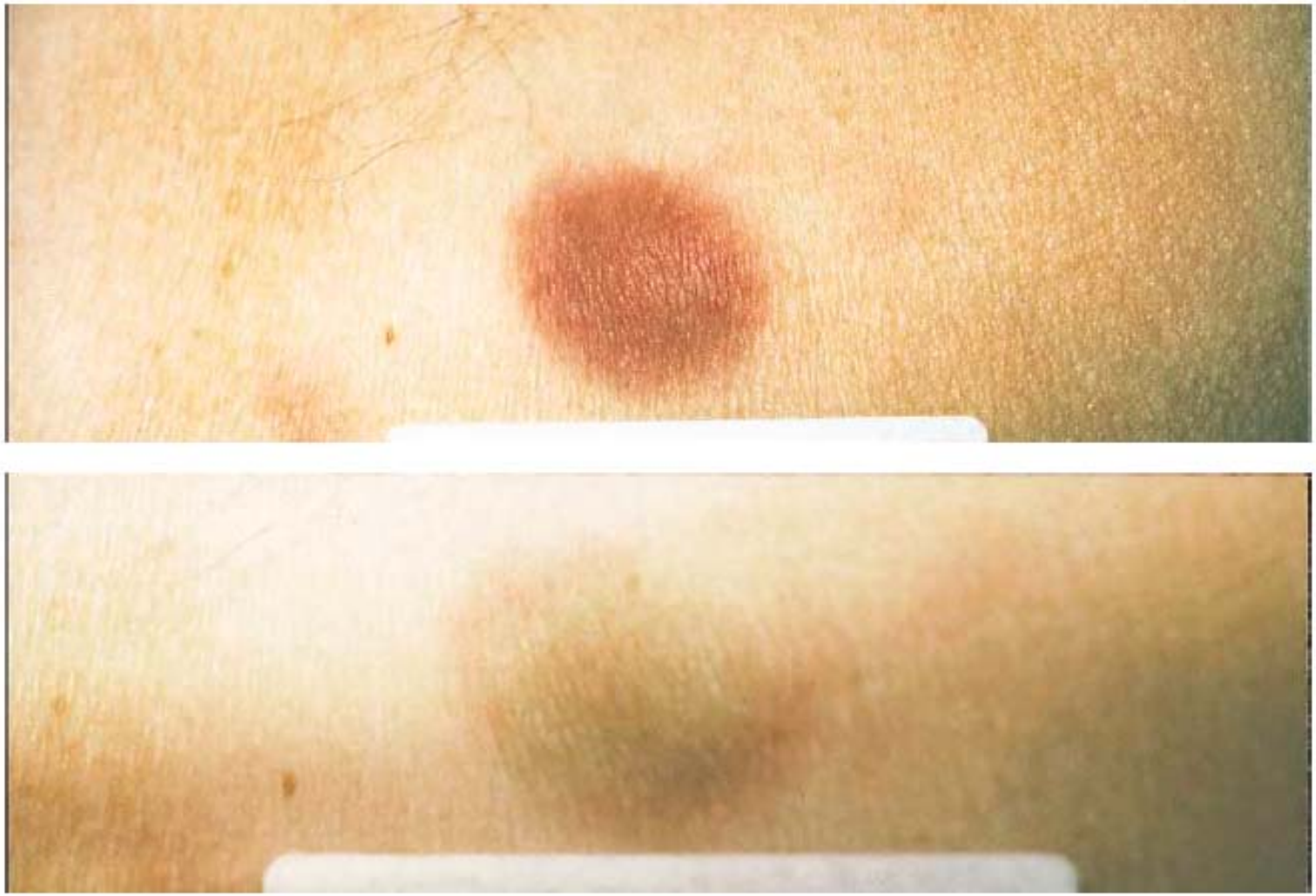
# Tissue Invasion in AML

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



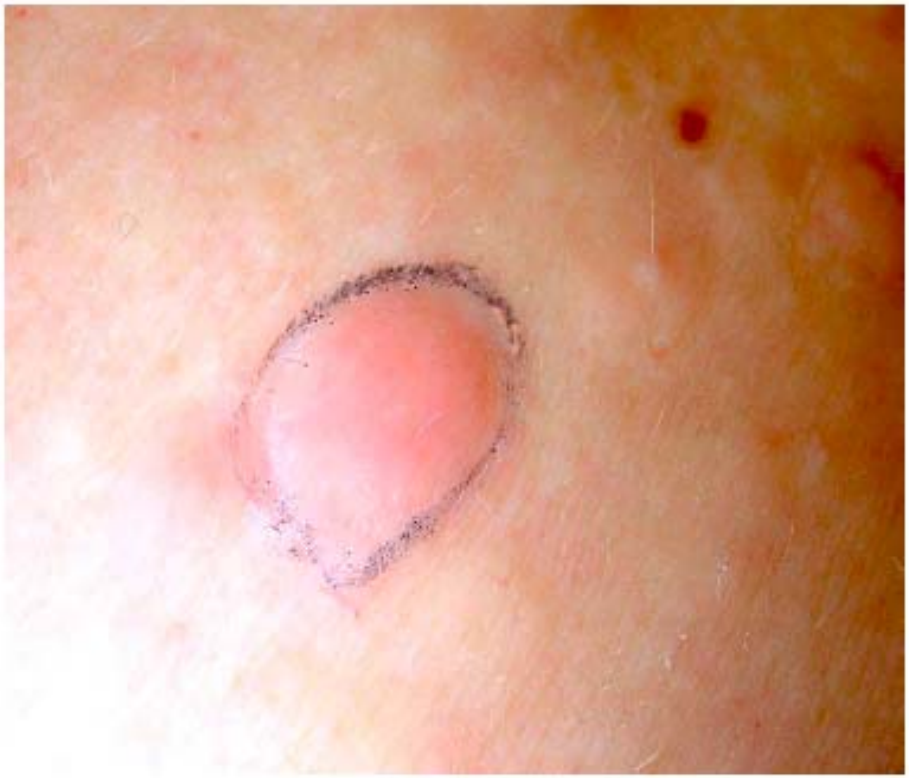
Banner MD Anderson Cancer Center
Making Cancer History®

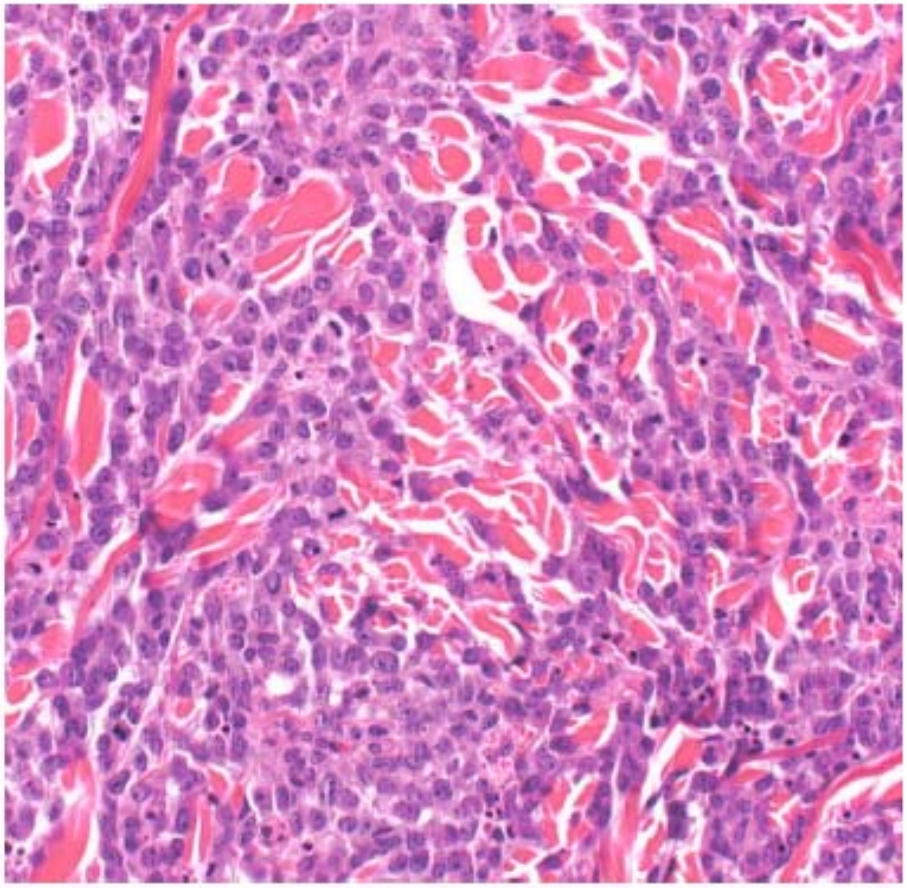
# * Chloroma



Banner MD Anderson Cancer Center
Making Cancer History®

# * Leukemia Cutis



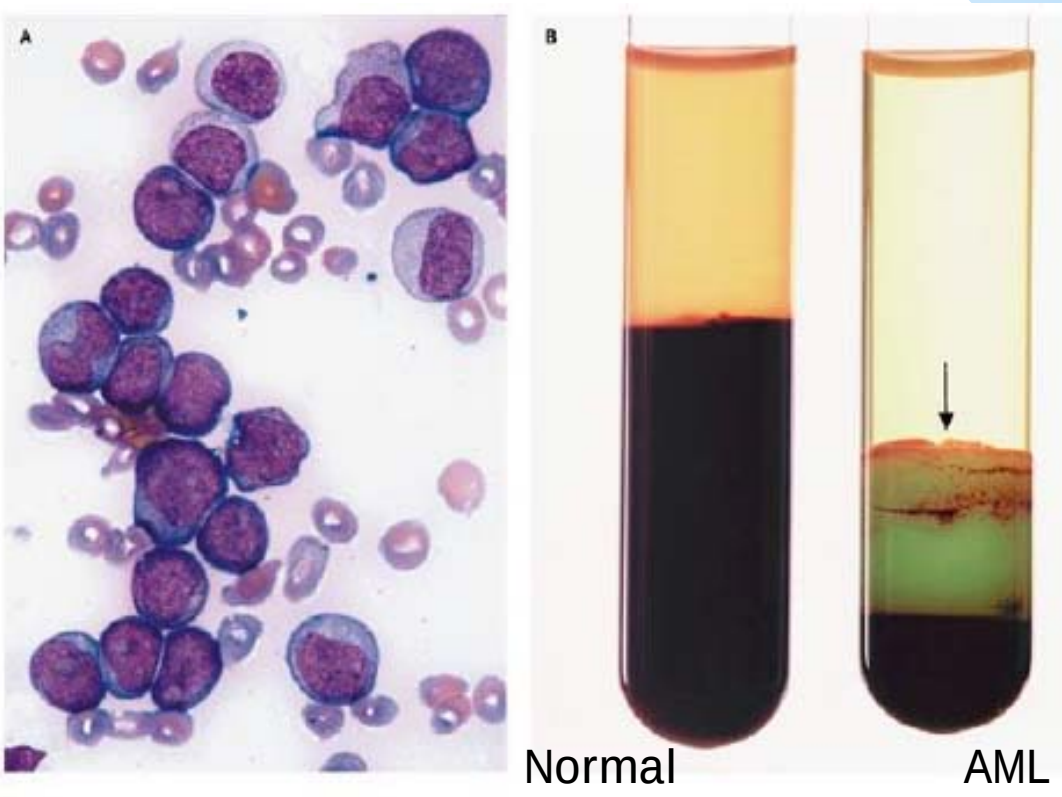


Sauter and Jacky *NEJM* 1998. 338:969

# * High Circulating Blasts

* Hypoglycemia
* Hypoxia
* Hyperkalemia
* Elevated Lactate

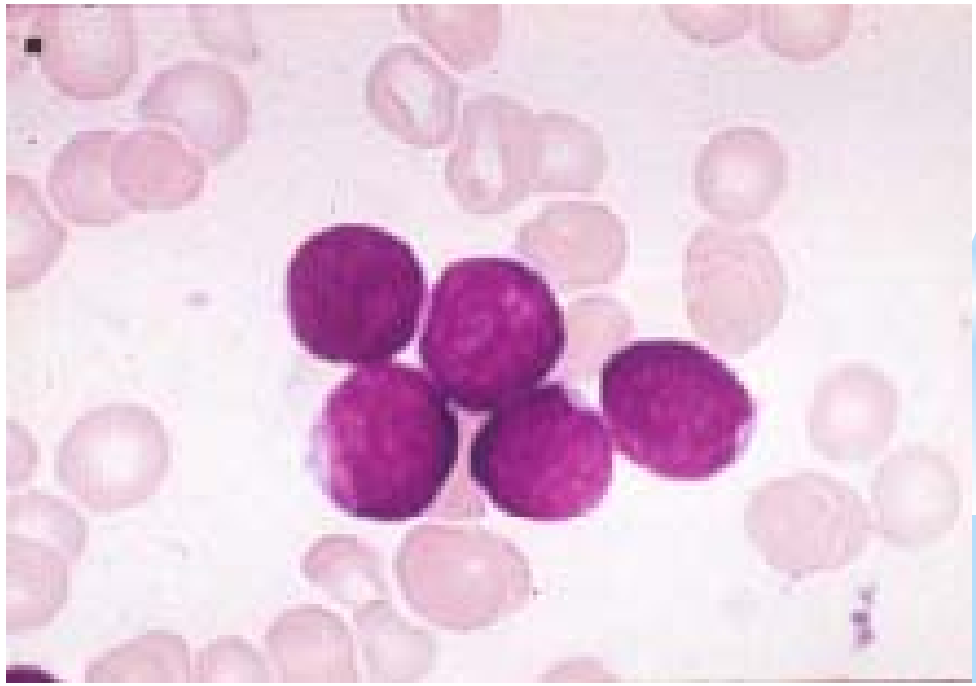
Mauro MJ NEJM 2003. 349:767




Banner MD Anderson Cancer Center
Making Cancer History®

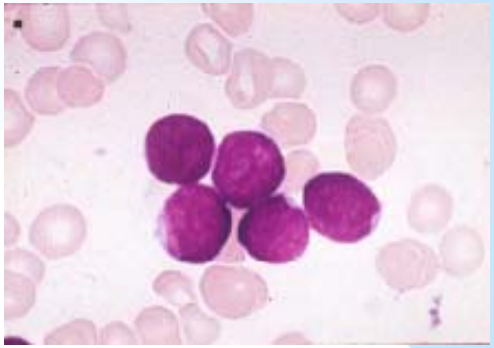
# Evaluation of patient with AML

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



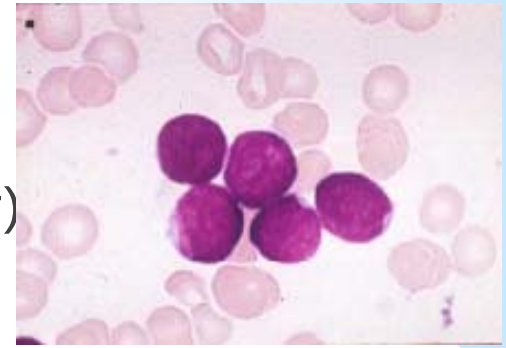
Banner MD Anderson Cancer Center
Making Cancer History®

# 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, 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



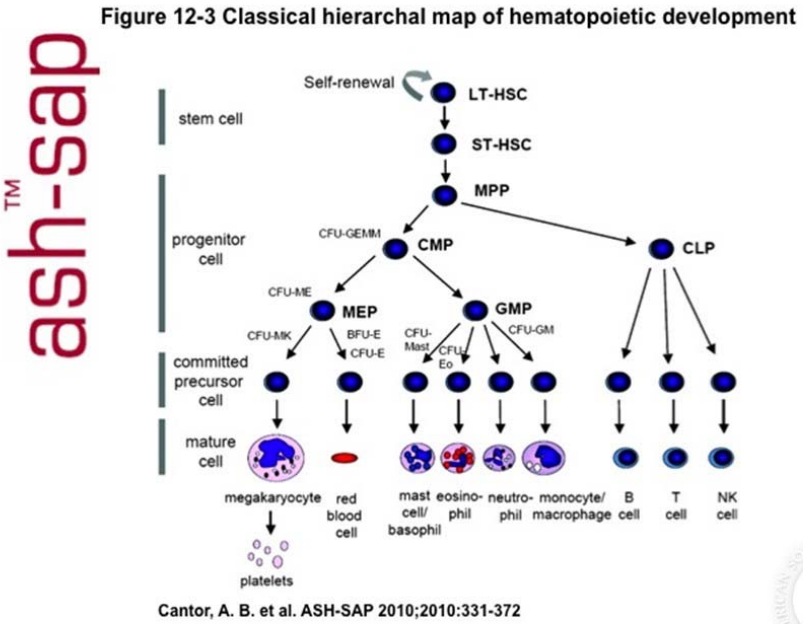
- Initial triage
  - History and Physical
  - CBC with differential (look at the peripheral smear)
  - BMP, LFTs, uric acid, ABO type and screen
  - PT, PTT, fibrinogen
- Diagnosis
  - Bone marrow biopsy
  - FISH and cytogenetics, flow cytometry
  - Molecular: FLT3, NPM1, CEPBA, ckit (can be sent on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

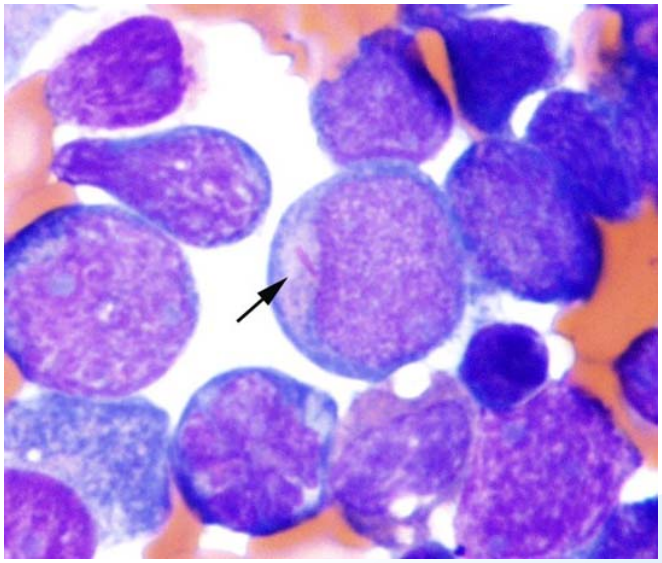
# * Differentiate AML vs ALL

* Rarely, can see Auer Rods
  - Only in myeloid blasts

* Flow cytometry

* Cytogenetics - t(8;21), inv16, t(9:22)



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
    * very rare in CLL
* 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 = 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.

Banner MD Anderson Cancer Center
Making Cancer History®

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

Banner MD Anderson Cancer Center
Making Cancer History®

Appelbaum et al. Blood 2006. 107:3481

# * Mortality from 7+3 induction at 30 days

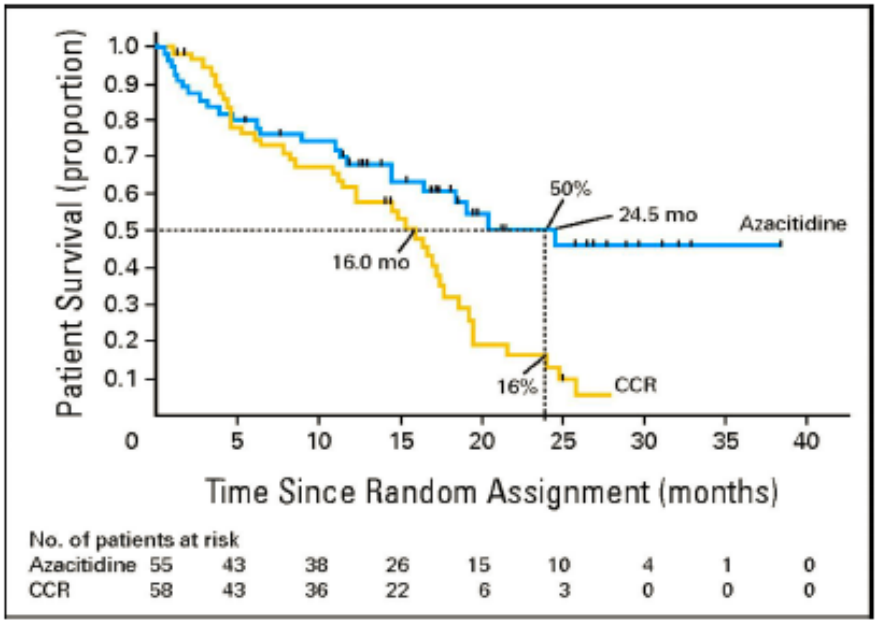
| | Age | | | |
|---|---|---|---|---|
| | **< 56** | **56 - 65** | **65 - 75** | **> 75** |
| **Patient #** | 364 | 242 | 270 | 79 |
| **ECOG PS** | | | | |
| **0** | 2% | 11% | 12% | 14% |
| **1** | 3% | 5% | 16% | 18% |
| **2** | 2% | 18% | 31% | 50% |
| **3** | 0% | 29% | 47% | 82% |

Banner MD Anderson Cancer Center
Making Cancer History®

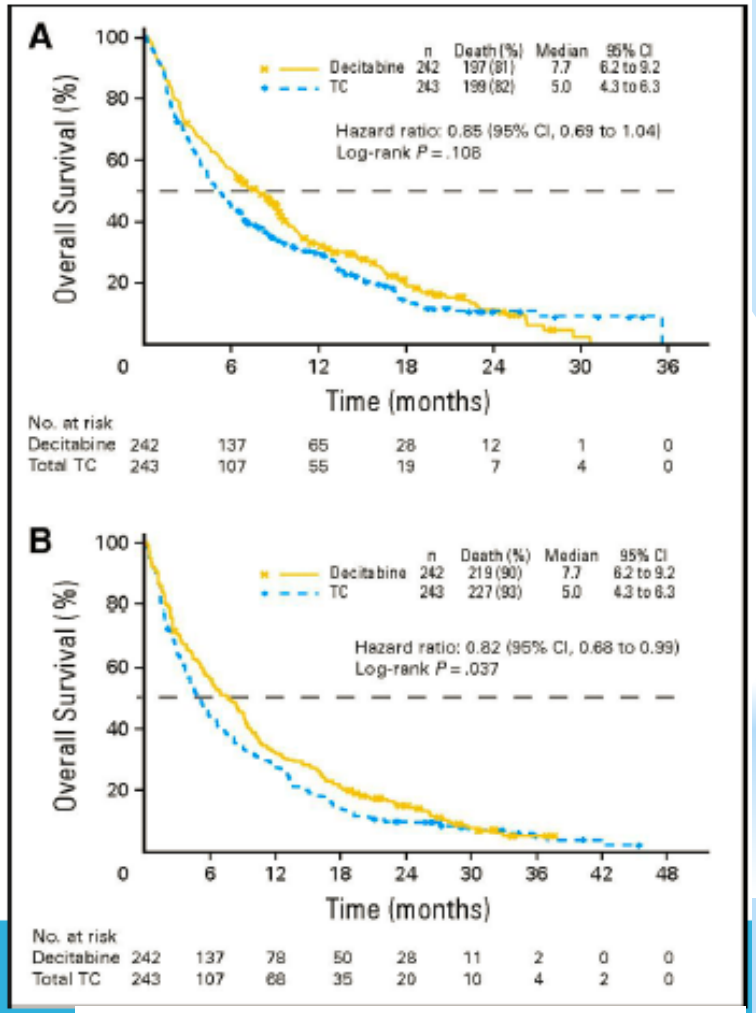
Appelbaum et al. Blood 2006. 107:3481

# * 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

# 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

* >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 *

Acute myeloid leukemia with recurrent genetic abnormalities

*AML

*AML

*APL

AML

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

M0, M1, M2, M4, M5, M6, M7

MMMMEAN NOTHING!

Acute myeloid leukemia, not otherwise specified

Pure erythroid leukemia

Erythroleukemia, erythroid/myeloid

Acute megakaryoblastic leukemia

Acute basophilic leukemia

Acute panmyelosis with myelofibrosis

*Myeloid sarcoma

Myeloid proliferations related to Down syndrome

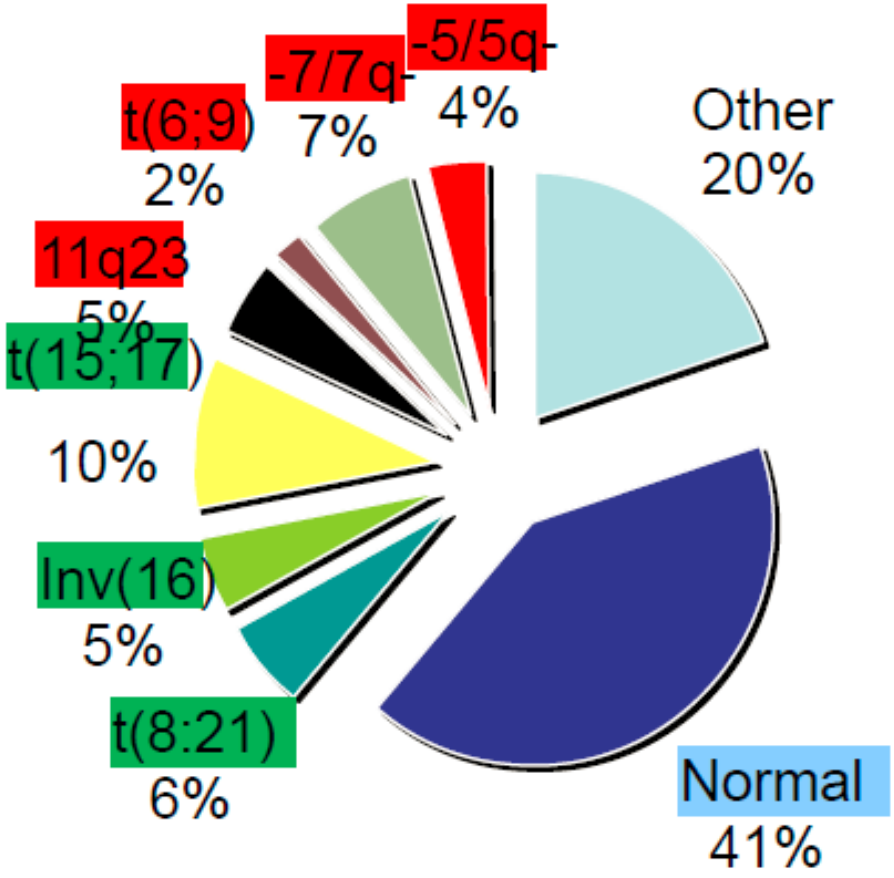
Transient abnormal myelopoiesis

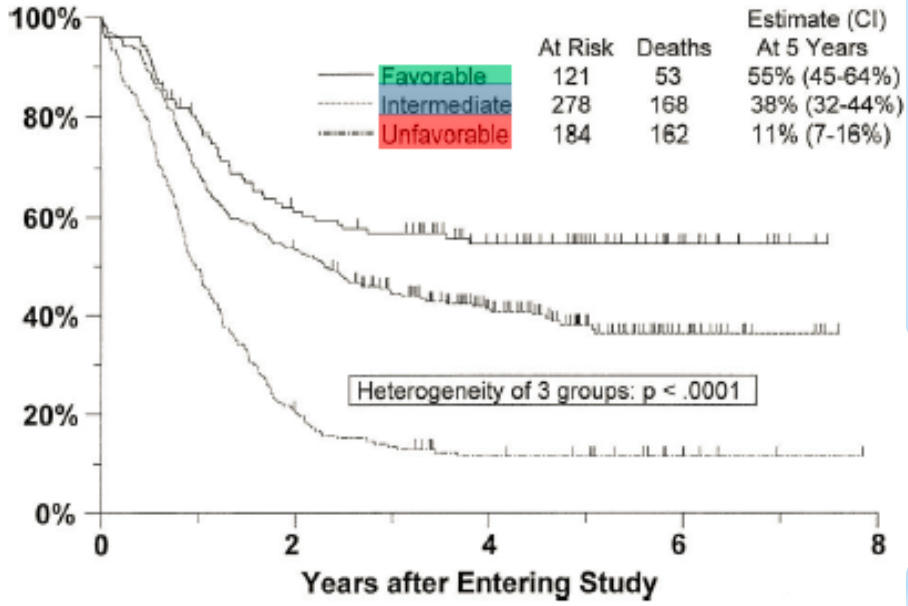
Myeloid leukemia associated with Down syndrome

Blastic plasmacytoid dendritic cell neoplasm

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

# Clonal Cytogenetic Abnormalities in Adult AML




t(16:16), del 16q

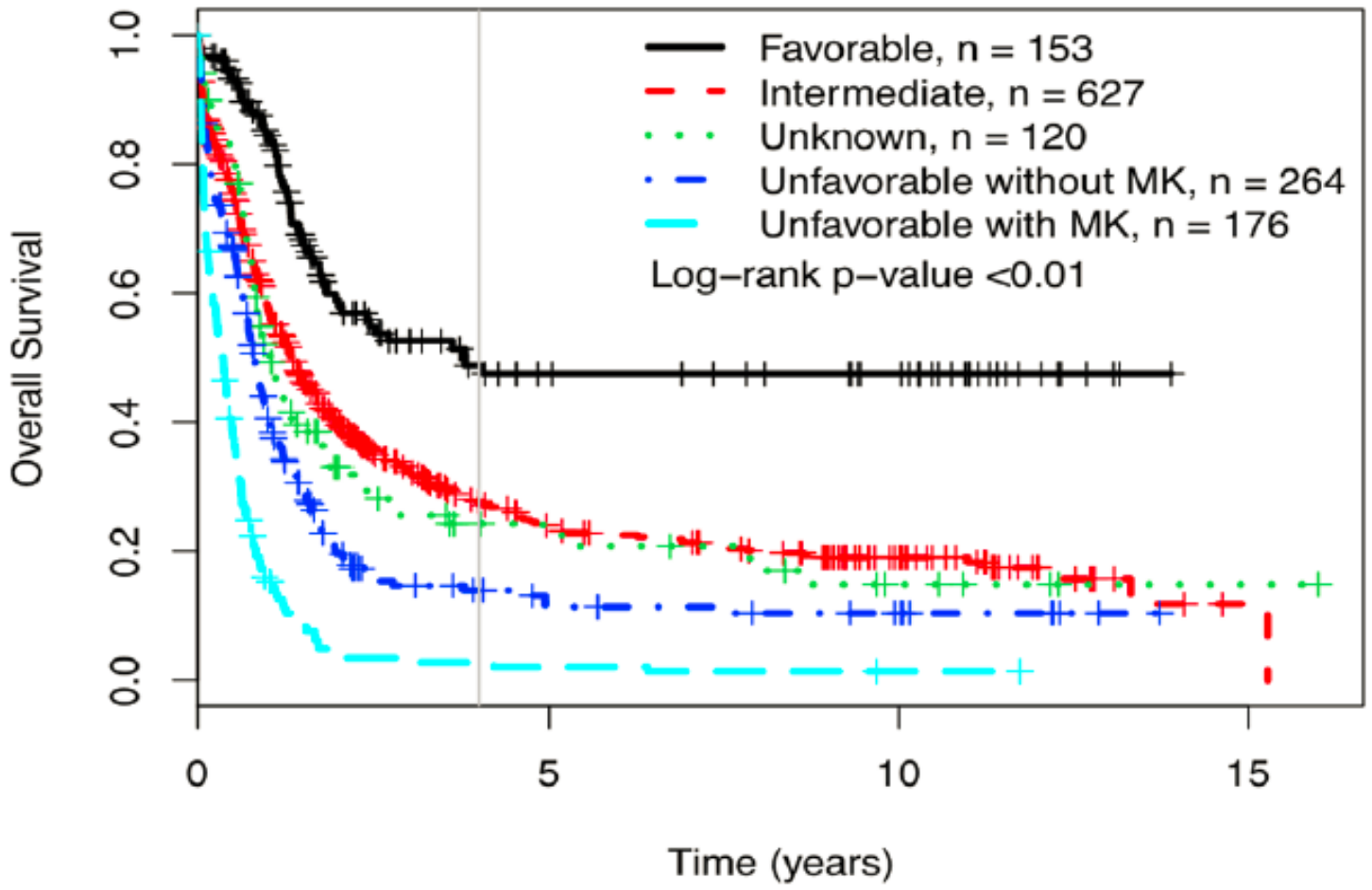
-Y, +8, +6, del 12p

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

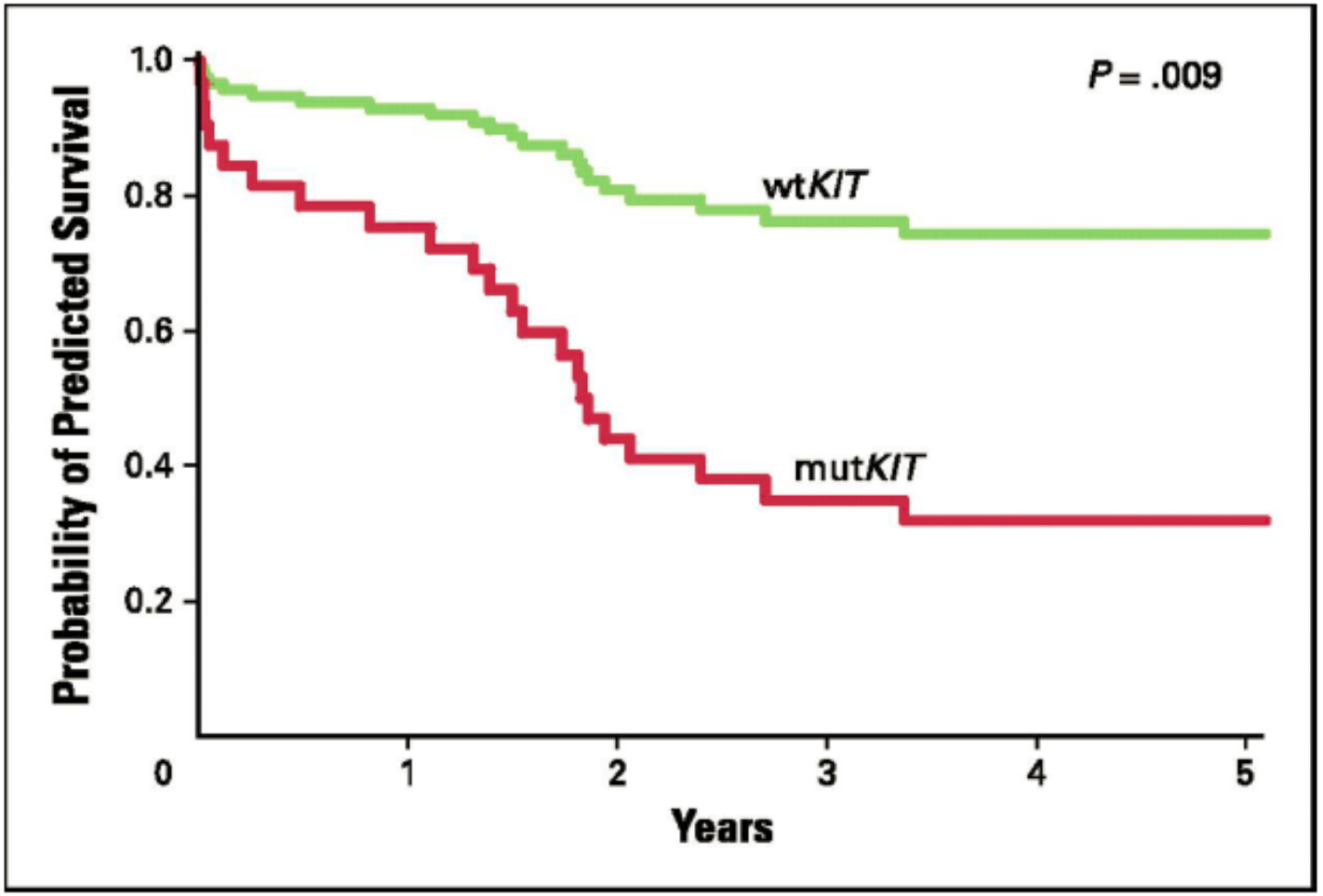
# Cytogenetics and Survival in AML




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

Medeiros et al. Blood 2010. 116:2224

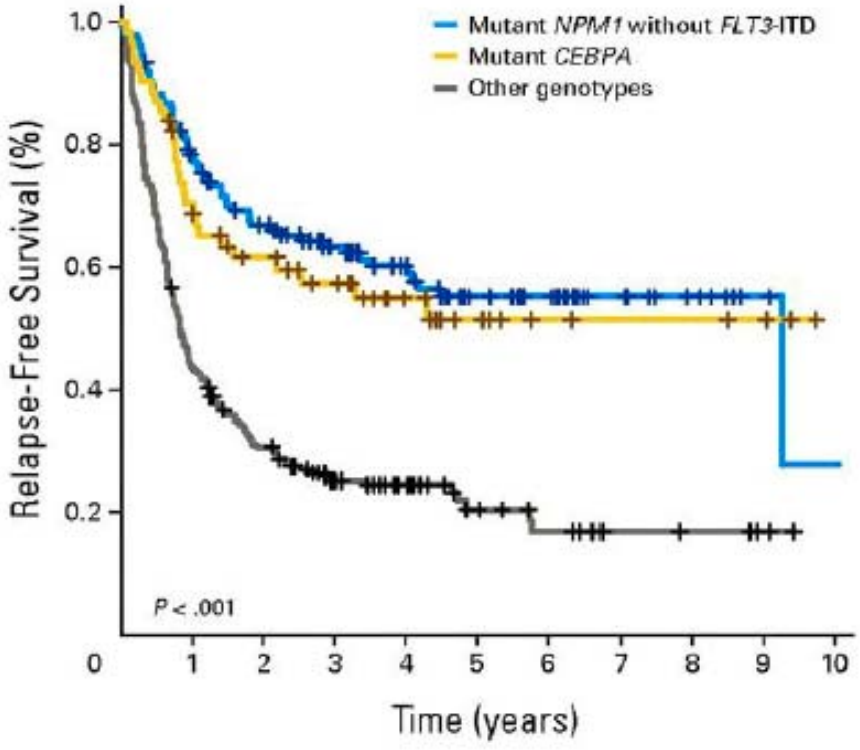
# * Survival inv(16) AML based on KIT

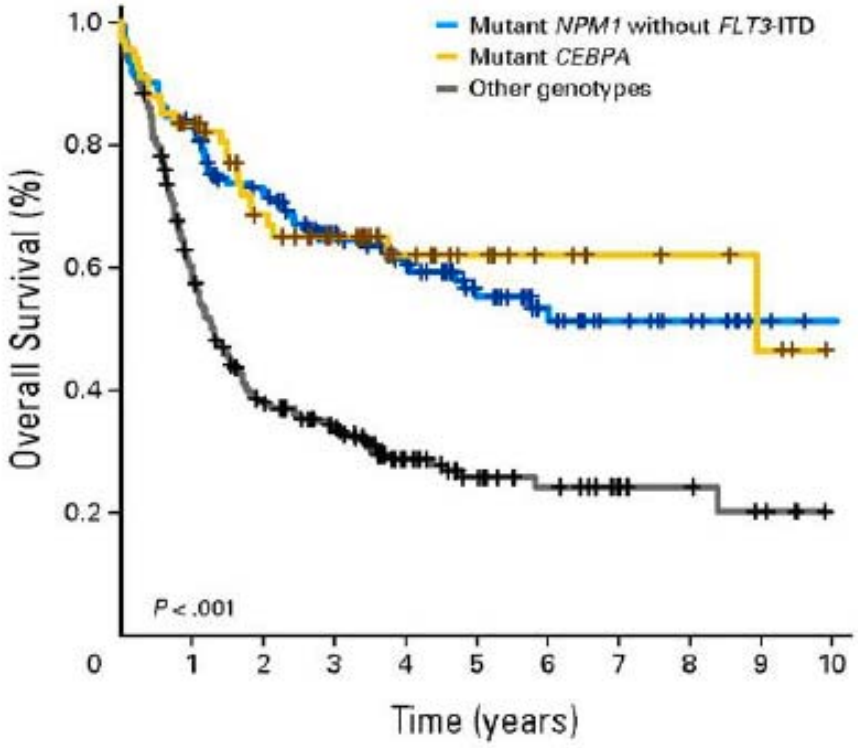



Paschka P et al. JCO 2006. 24:3904

Banner MD Anderson Cancer Center
Making Cancer History®

# * AML with normal cytogenetics




Schlenk et al. NEJM 2008. 358:1909

# 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

# Prognosis: European Leukemia Net

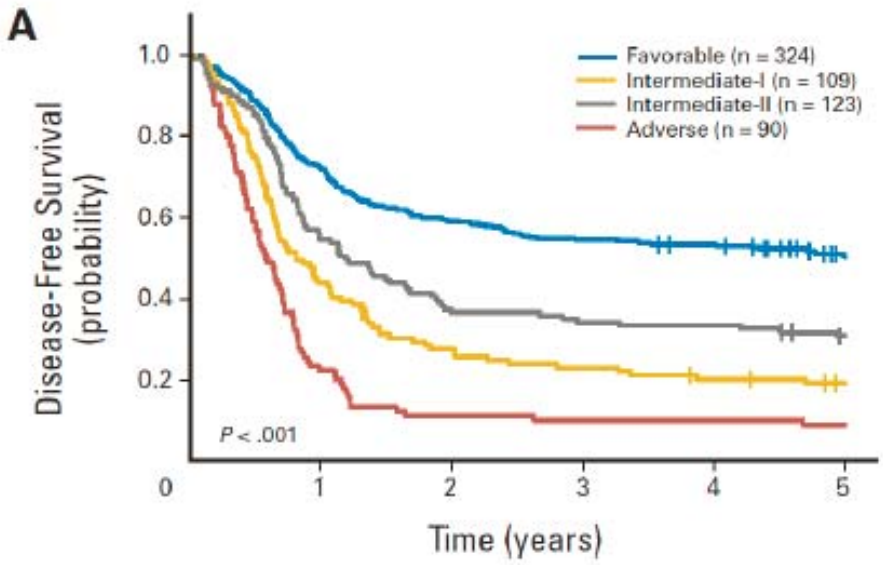



**Table 1.** European LeukemiaNet Standardized Reporting System for Correlation of Cytogenetic and Molecular Genetic Data in AML With Clinical Data[12]

| 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 _____

# So what is next?

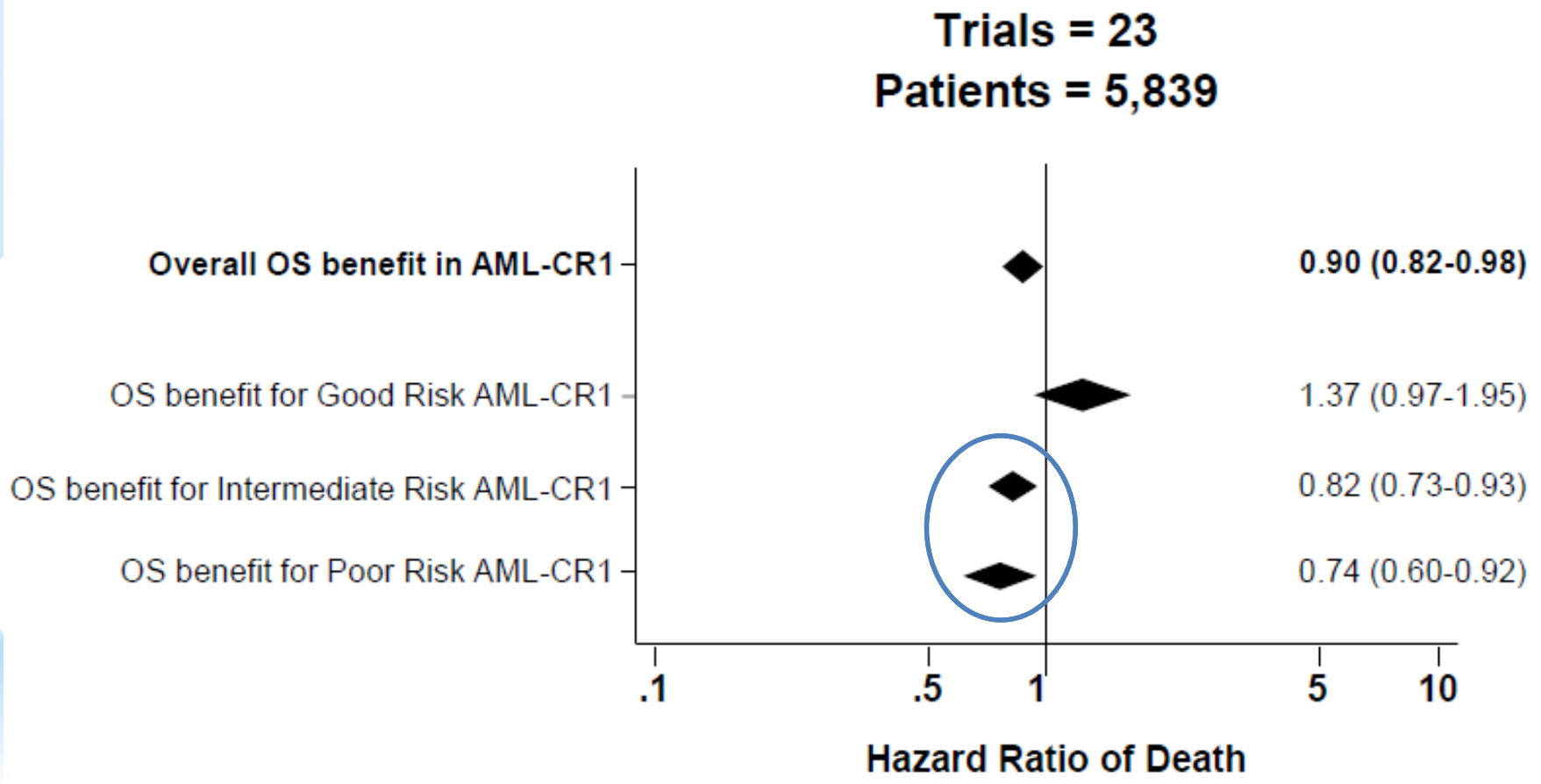
* Need to achieve complete remission (CR)
  - <5% blasts by morphology AND Plt >100k and ANC >1.0
  - Day 14 or Day 21 marrow tells us some, but not all of CR definition
  - CR is one of the best predictors of OS for individual patient
* If not in CR - next line therapy
  - Minimal residual disease =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

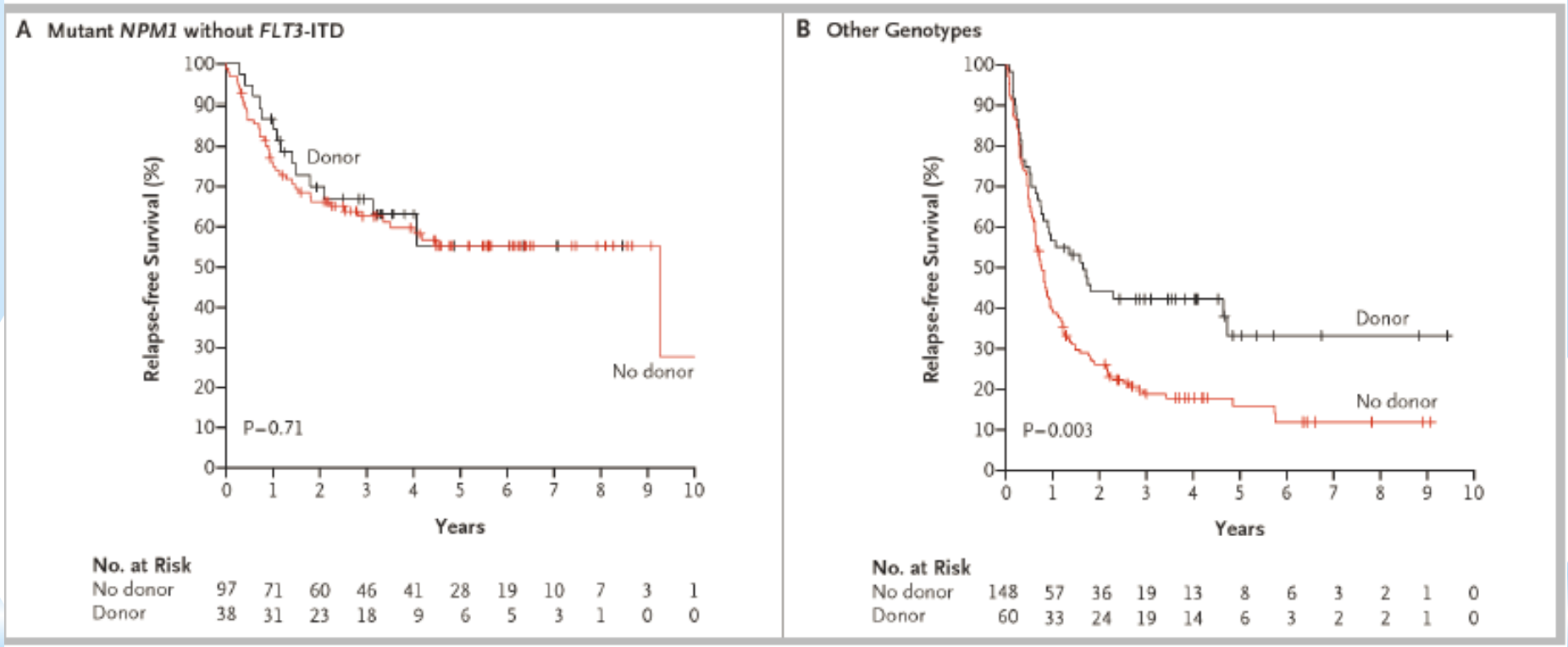
# * Meta-analysis of RCTs of HCT for AML in CR1




Koreth et al. JAMA 2009. 301:2349

Banner MD Anderson Cancer Center
Making Cancer History®

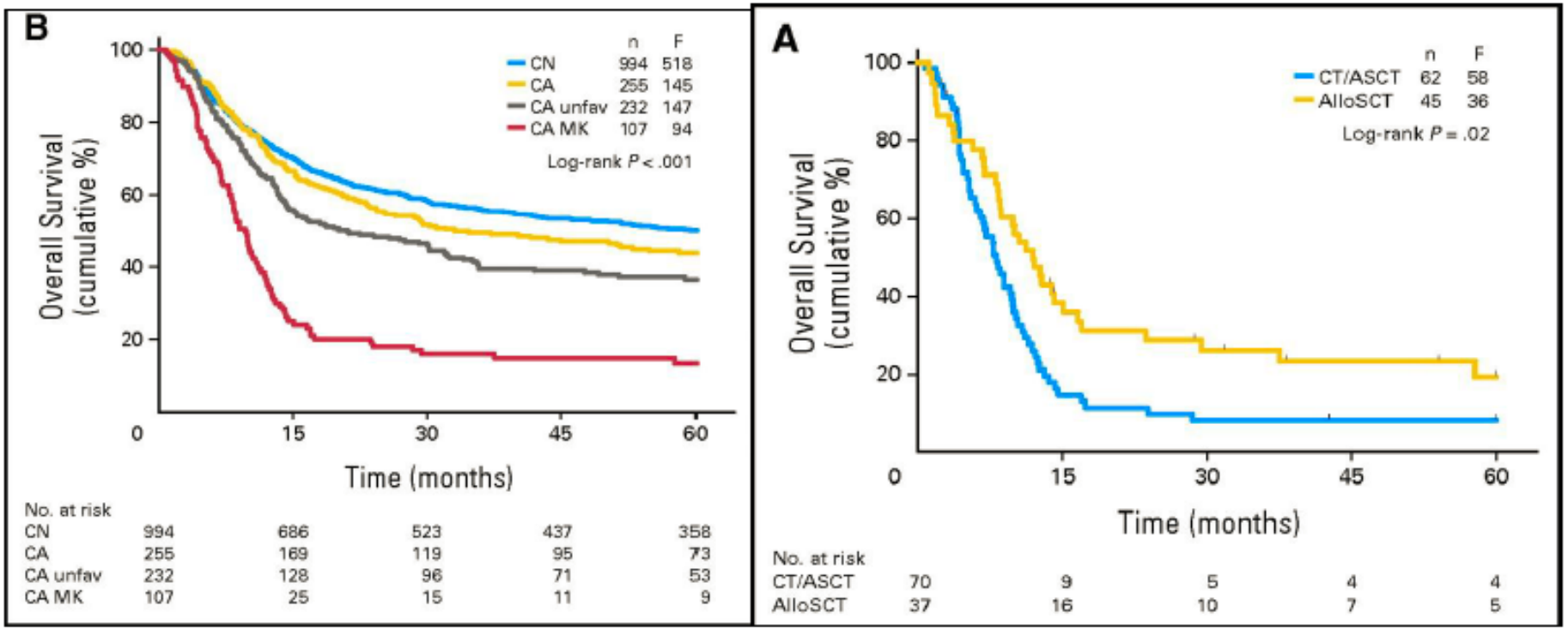
# * HCT for AML with normal cytogenetics




*Schlenk et al. NEJM 358:1909, 2008*

Banner MD Anderson Cancer Center
Making Cancer History®

# HCT for MK AML




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

Banner MD Anderson Cancer Center
Making Cancer History®

# 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 3+4
- 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)

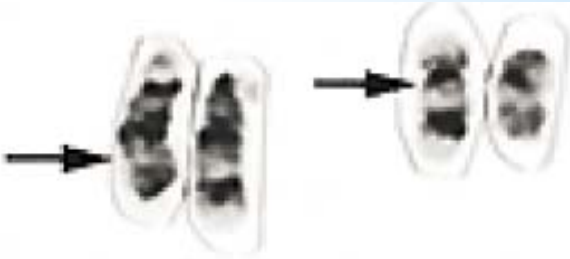
| | | |
|---|---|---|
| *First Salvage (n = 206)* | *68% Conventional 32% investigational (topotecan, 2Cda, taxol)* | *CR rate 23%* |
| *Second Salvage (n = 93)* | *43% conventional 57% investigational* | *CR rate 11%* |
| *Third Salvage (n=40)* | | *CR rate 10%* |
| *Fourth salvage (n=17)* | | *CR rate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

# * Duration of CR1 and likelihood of response

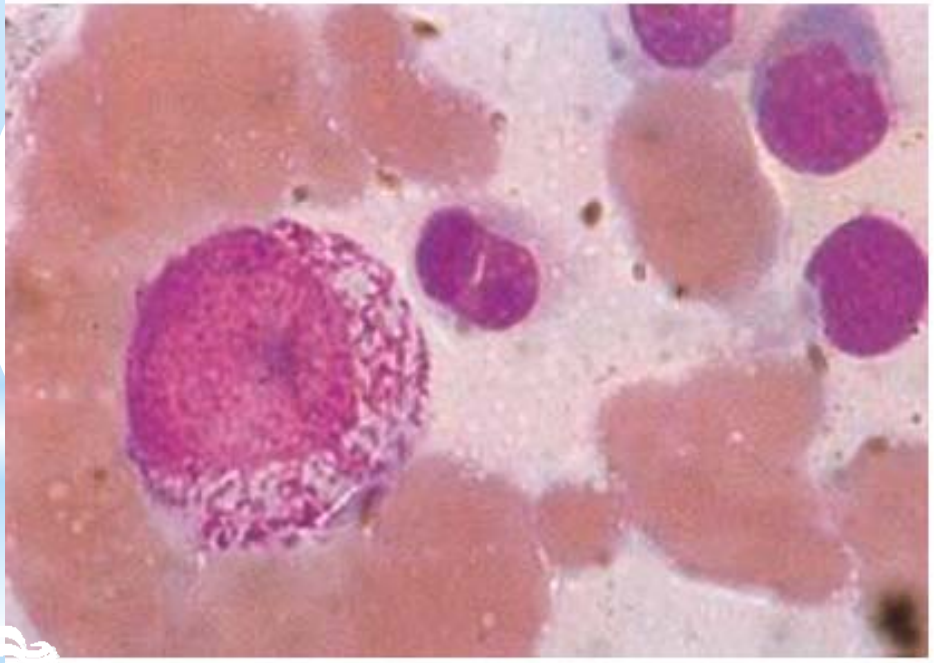
| *Treatment* | *Likelihood of CR* |
|---|---|
| *CR1 >2yrs, 1st salvage n=15* | *73% (45-92%)* |
| *CR1 1-2yrs, 1st salvage n=30* | *47% (28-66%)* |
| *CR1 <1yr or no CR, 1st salvage n=160* | *14% (8-21%)* |
| *CR1 <1yr or no CR1 2nd - 4th salvage n= 58 (96 tx)* | *0% (0-4%)* |

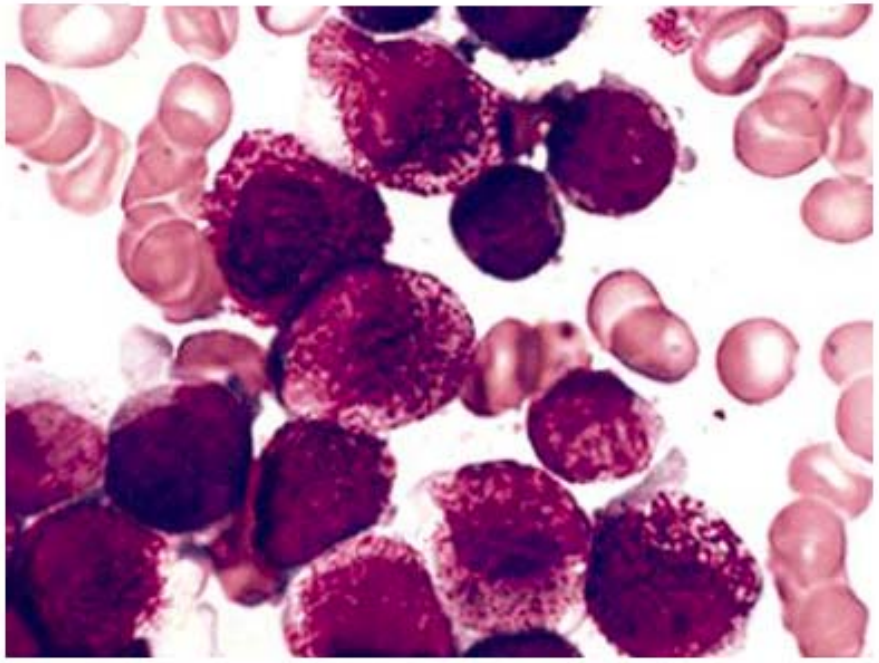
# * Acute Promyelocytic Leukemia (APL)

## APL



t(15;17)(q22;q12)





# * 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

# * All-Trans Retinoic Acid

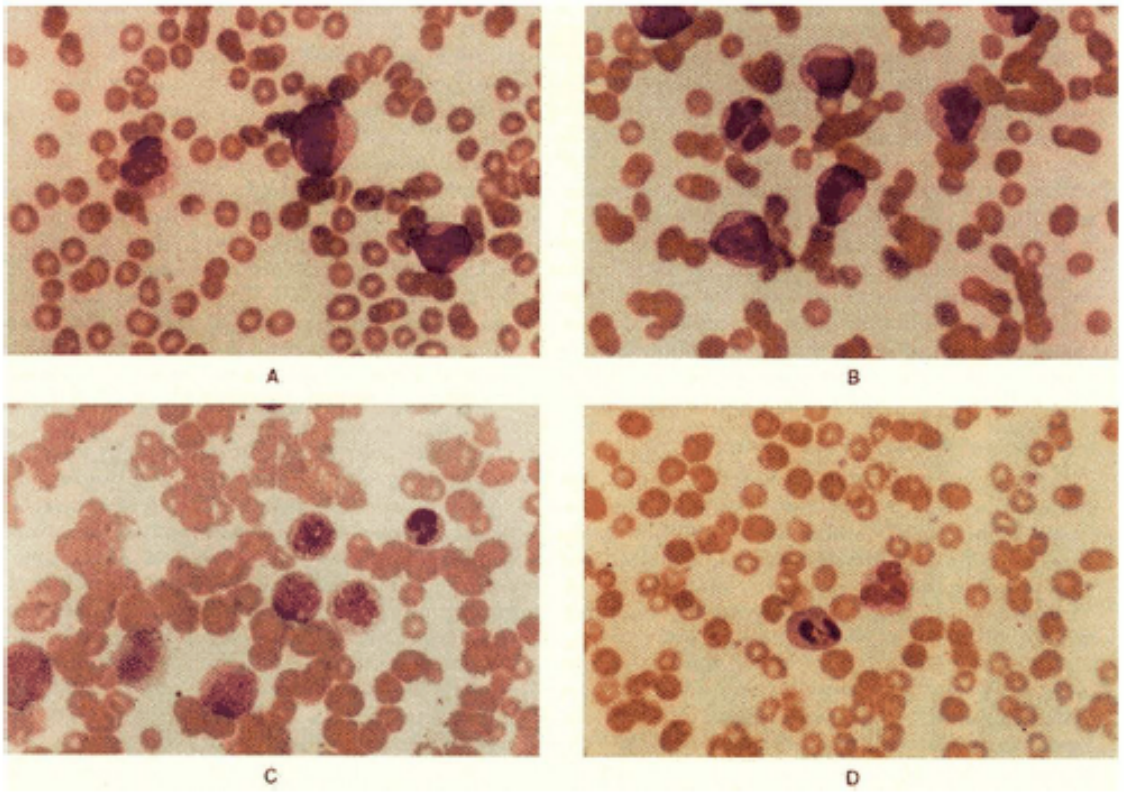
Tretinoin

**Clinical response**

- Associated with maturation of leukemic clone
- Expression of PML/RAR-$\alpha$ 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)

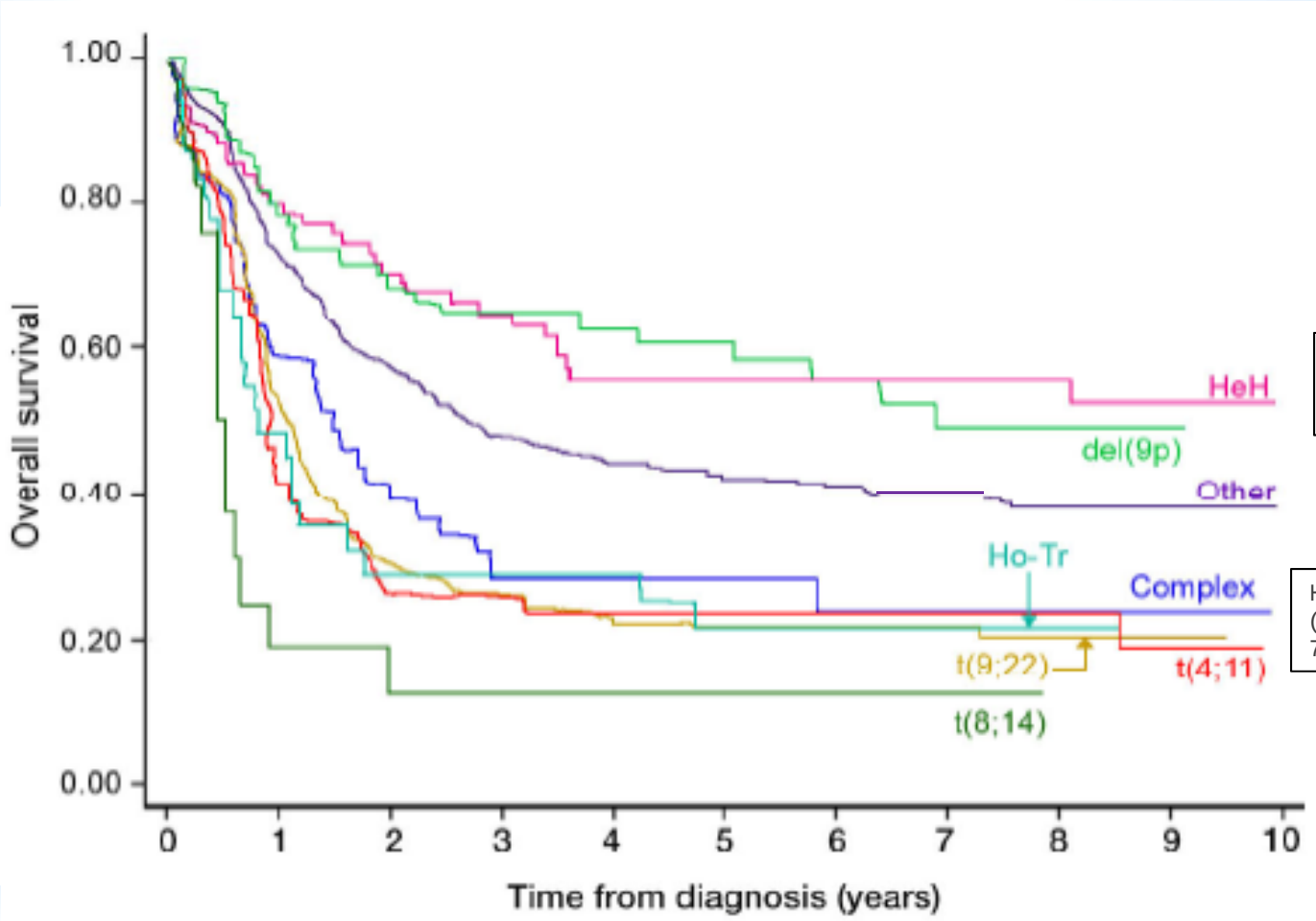
- Peak age at diagnosis 7yo
- But diagnosis possible throughout life

- 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

Banner MD Anderson Cancer Center
Making Cancer History®

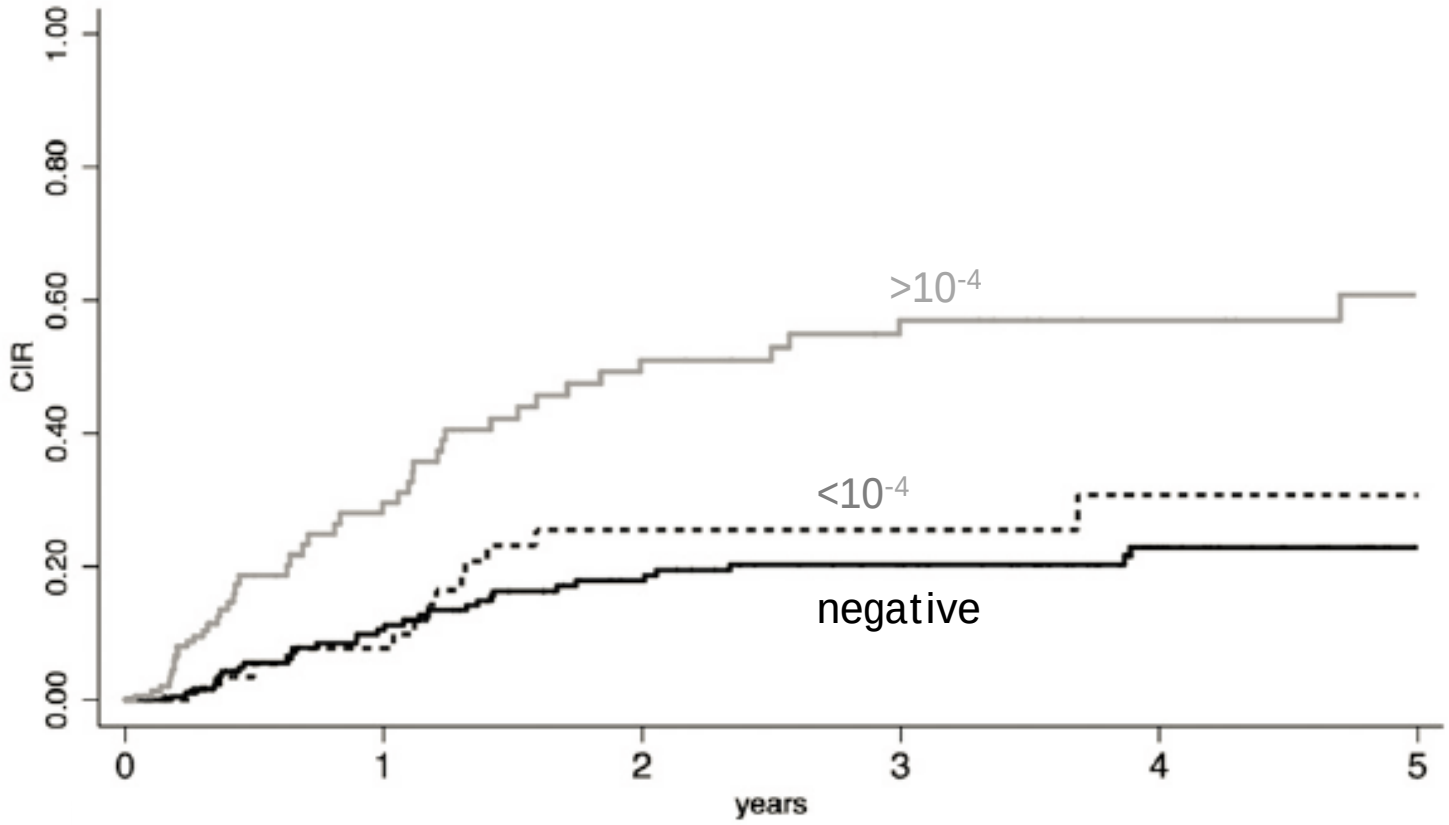
# What to do with the rest?

- 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)

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

# APL: Sanz Prognostic Factors

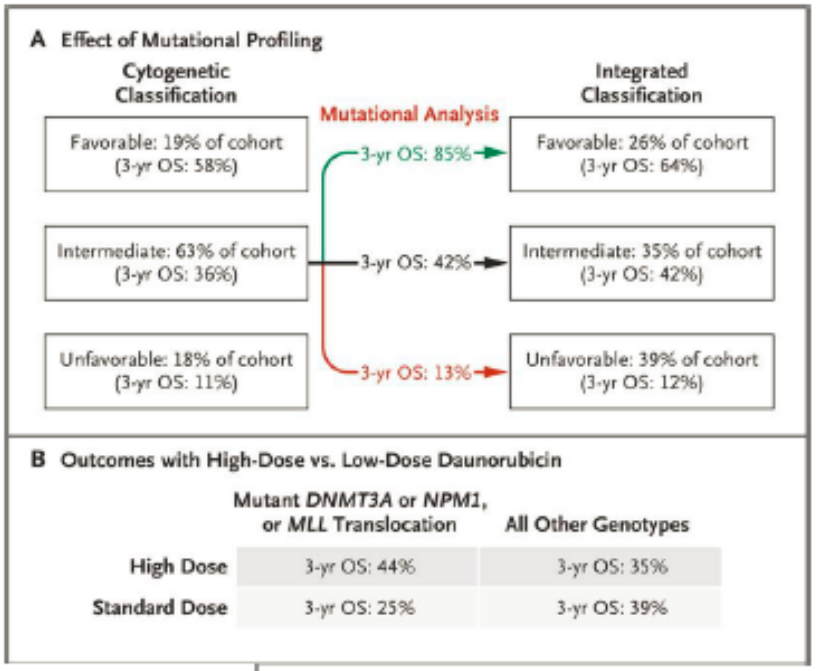
| | |
|---|---|
| Low | WBC <10, Plt >40 |
| Int | WBC <10, Plt <40 |
| High | WBC ≥10 |

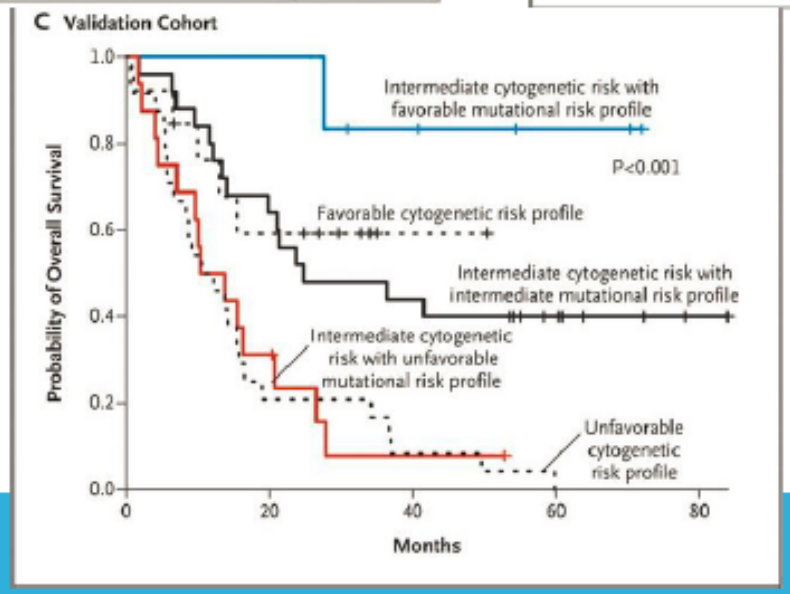
Sanz et al. *Blood*. 2010;115:5137-5148

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

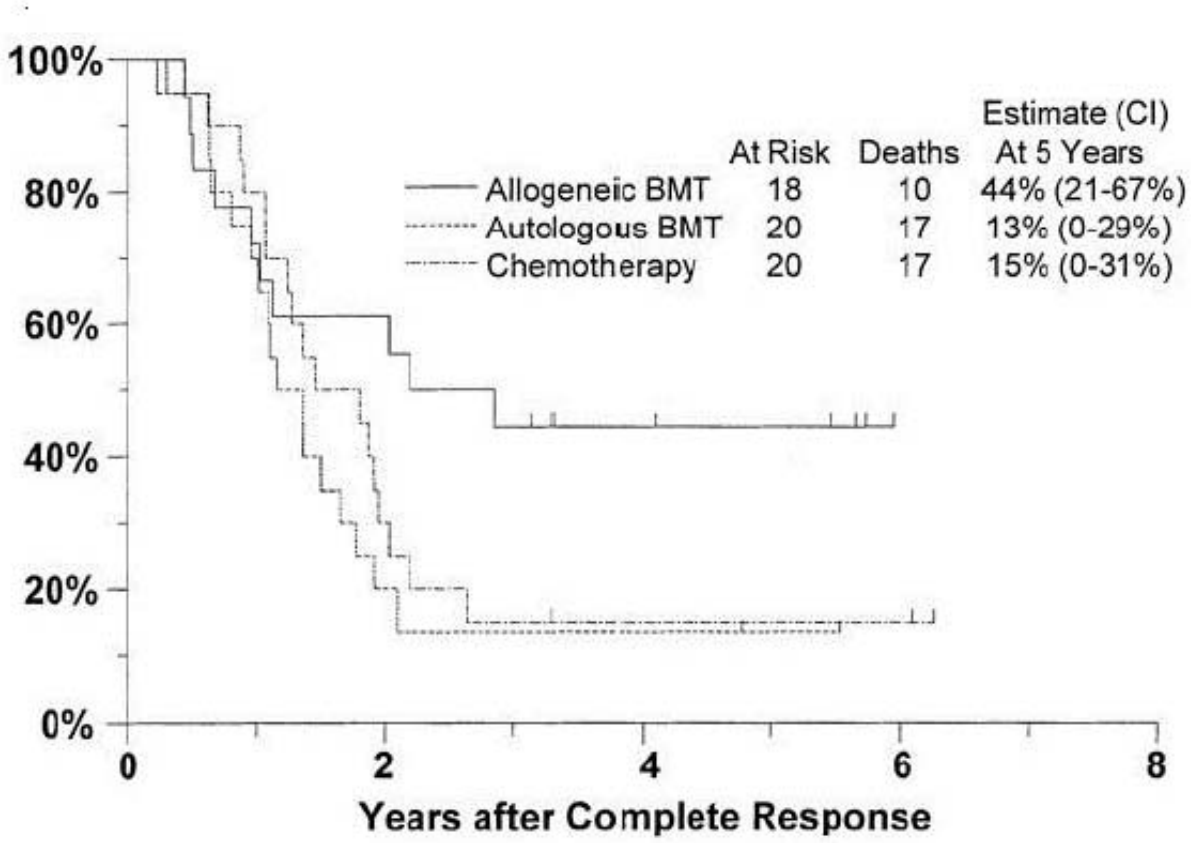
| Marker | Effect |
|---|---|
| NPM1 (33%) | fav |
| CEBPA (8%) | fav |
| Ras | fav (HDAC) |
| BRE | fav (MLL) |
| TET2 | unfav/fav |

| 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


Banner MD Anderson Cancer Center
Making Cancer History®

# Therapy of High Risk AML




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

Banner MD Anderson Cancer Center
Making Cancer History®