AML – Basics

• Myelo – Bone marrow
What does bone marrow do?

Blood Cells

- Stem Cell
- Red Blood Cells
- White Blood Cells
- Platelets
Differentiation

Transformation

Neutrophils -> Low neutrophil means Neutropenia
Lymphocytes
Monocytes
Eosinophils
Basophils

Normal
Red
Platelets
White

Slide borrowed from Dr. Rafel Bejar
Etiology of AML

Familial or Congenital Predisposition

Often early onset and part of a larger syndrome

Topoisomerase II inhibitors
- Ionizing radiation
- DNA alkylating agents

Peaks 1-3 or 5-7 years following exposure

“De novo” (idiopathic, primary)

Median age ~67 years; increased risk with aging

Slide adapted from Dr. David Steensma
Secondary AML

Myelodysplastic Syndromes (MDS)

Myelodysplastic syndrome/Myeloproliferative Neoplasm

Myeloproliferative Neoplasms
Genetics - Basics

[Diagram showing DNA, chromosome, cell, and gene structures.]

Adapted from National Human Genome Research Institute
Genetics - Mutations
Mutations accumulate and Get fixed
When We are Young
Mutations accumulate and get fixed
(Less well as we age)
Mutations may occur in CRITICAL areas of our genes.
Age related Clonal hematopoiesis
Clonal hematopoiesis is associated with increased risk of hematologic malignancy
Diagnosis

In some genetic abnormalities, this cut off may not be applicable.
• Most common acute leukemia in adults
• Estimated incidence in 2017: ~21,400 new cases (1.3% of new cancer cases)
• Estimated mortality in 2017: ~10,600 deaths

Incidence of AML 2010-2014

Pathogenesis and Biology of AML

200 clinically annotated cases
23 genes commonly mutated
237 genes mutated in 2 or more cases
FLT3-ITD Mutations

- Mutated in approx 30% AML patients with normal cytogenetics
- Receptor tyrosine kinase with important roles in hematopoietic stem cell survival and proliferation
- Associated with an aggressive disease phenotype (increased relapse rates and worse survival)
Nucleophosmin (*NPM1*) Mutations

- Incidence in normal karyotype-AML ≈ 50%
- Commonly associated with *FLT3* mutations
- Favorable impact on prognosis if $NPM1^{\text{mut}}/FLT3\text{-ITD}^{\text{neg}}$
- Favorable impact on prognosis if $NPM1^{\text{mut}}/FLT3\text{-TKD}^{\text{pos}}$

References:

A  Total Cohort

<table>
<thead>
<tr>
<th>Gene</th>
<th>Overall Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLT3 (ITD, TKD)</td>
<td>37 (30, 7)</td>
</tr>
<tr>
<td>NPM1</td>
<td>29</td>
</tr>
<tr>
<td>DNMT3A</td>
<td>23</td>
</tr>
<tr>
<td>NRAS</td>
<td>10</td>
</tr>
<tr>
<td>CEBPA</td>
<td>9</td>
</tr>
<tr>
<td>TET2</td>
<td>8</td>
</tr>
<tr>
<td>WT1</td>
<td>8</td>
</tr>
<tr>
<td>IDH2</td>
<td>8</td>
</tr>
<tr>
<td>IDH1</td>
<td>7</td>
</tr>
<tr>
<td>KIT</td>
<td>6</td>
</tr>
<tr>
<td>RUNX1</td>
<td>5</td>
</tr>
<tr>
<td>MLL-PTD</td>
<td>5</td>
</tr>
<tr>
<td>ASXL1</td>
<td>3</td>
</tr>
<tr>
<td>PHF6</td>
<td>3</td>
</tr>
<tr>
<td>KRAS</td>
<td>2</td>
</tr>
<tr>
<td>PTEN</td>
<td>2</td>
</tr>
<tr>
<td>TP53</td>
<td>2</td>
</tr>
<tr>
<td>HRAS</td>
<td>0</td>
</tr>
<tr>
<td>EZH2</td>
<td>0</td>
</tr>
</tbody>
</table>
Clinical Presentation

• Signs and symptoms mainly due to high white blood cells and/or severely low blood counts
• General fatigue, pallor, and weakness
• Bone pain, discomfort, and tenderness
• Fever and infection
• Enlarged Lymph node & organ enlargement
• Involvement of oropharynx and teeth
Other Clinical Issues

- Petechiae, purpura, ecchymosis, and mucosal bleeding
- Disseminated intravascular coagulation
- Leukemic involvement of the skin
- Myeloid sarcoma
- CNS involvement
- Hyperleukocytosis and leukostasis
- Tumor lysis syndrome
- Neutropenic infections

AML: Diagnosis and Prognosis

- History and physical
  - Age and performance status
  - Previous treatment history?
  - Antecedent marrow disorder
  - Disease outside the bone marrow???
  - White blood cells at presentation
Diagnostic Tests for AML

- Complete blood count and differential count
- Bone marrow aspirate
- Bone marrow biopsy
- Immunophenotyping
- Cytogenetics
- Screening for gene mutations including: NPM1, CEBPA, RUNX1, FLT3, TP53, ASXL1
## 2017 Risk Stratification by Genetics

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Genetic Abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Favorable</strong></td>
<td>t(8;21)(q22;q22.1); RUNX1-RUNX1T1</td>
</tr>
<tr>
<td></td>
<td>inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11</td>
</tr>
<tr>
<td></td>
<td>Mutated NPM1 without FLT3-ITD or with FLT3-ITDlow</td>
</tr>
<tr>
<td></td>
<td>Biallelic mutated CEBPA</td>
</tr>
<tr>
<td><strong>Intermediate</strong></td>
<td>Mutated NPM1 and FLT3-ITDhigh</td>
</tr>
<tr>
<td></td>
<td>Wild type NPM1 without FLT3-ITD or with FLT3-ITDlow (w/o adverse-risk genetic lesions)</td>
</tr>
<tr>
<td></td>
<td>t(9;11)(p21.3;q23.3); MLLT3-KMT2A</td>
</tr>
<tr>
<td></td>
<td>Cytogenetic abnormalities not classified as favorable or adverse</td>
</tr>
<tr>
<td><strong>Adverse</strong></td>
<td>t(6;9)(p23;q34.1); DEK-NUP214</td>
</tr>
<tr>
<td></td>
<td>t(v;11q23.3); KMT2A rearranged</td>
</tr>
<tr>
<td></td>
<td>t(9;22)(q34.1;q11.2); BCR-ABL1</td>
</tr>
<tr>
<td></td>
<td>inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2,MECOM(EVI1)</td>
</tr>
<tr>
<td></td>
<td>-5 or del(5q); -7; -17/abn(17p)</td>
</tr>
<tr>
<td></td>
<td>Complex karyotype, monosomal karyotype Wild type NPM1 and FLT3-ITDhigh</td>
</tr>
<tr>
<td></td>
<td>Mutated RUNX1</td>
</tr>
<tr>
<td></td>
<td>Mutated ASXL1</td>
</tr>
<tr>
<td></td>
<td>Mutated TP53</td>
</tr>
</tbody>
</table>
**Effect of Mutational Profiling**

<table>
<thead>
<tr>
<th>Cytogenetic Classification</th>
<th>Mutational Analysis</th>
<th>Integrated Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable: 19% of cohort (3-yr OS: 58%)</td>
<td>3-yr OS: 85%</td>
<td>Favorable: 26% of cohort (3-yr OS: 64%)</td>
</tr>
<tr>
<td>Intermediate: 63% of cohort (3-yr OS: 36%)</td>
<td>3-yr OS: 42%</td>
<td>Intermediate: 35% of cohort (3-yr OS: 42%)</td>
</tr>
<tr>
<td>Unfavorable: 18% of cohort (3-yr OS: 11%)</td>
<td>3-yr OS: 13%</td>
<td>Unfavorable: 39% of cohort (3-yr OS: 12%)</td>
</tr>
</tbody>
</table>

**Figure 2.** Revised risk stratification of patients with AML on the basis of integrated genetic analysis. Prognostic algorithm and survival curves with integrated mutational profiling are shown (used with permission from Patel et al\textsuperscript{21}).
# Prognostic Features in AML

<table>
<thead>
<tr>
<th>Cytogenetics</th>
<th>Molecular genetics:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• FLT3 ITD mutation</td>
<td>Generally unfavorable except in older patients</td>
</tr>
<tr>
<td>• NPM1 mutation</td>
<td>Favorable if isolated</td>
</tr>
<tr>
<td>• CEBPA biallelic mutation</td>
<td>Favorable</td>
</tr>
<tr>
<td>• KIT mutation [in ~25% of t(8;21) or inv(16) AML]</td>
<td>Generally unfavorable</td>
</tr>
<tr>
<td>Primary vs secondary disease (antecedent hematologic disorder, or therapy-related)</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>Age</td>
<td>&gt; 60 years</td>
</tr>
<tr>
<td>Performance status</td>
<td>&gt; ECOG 1</td>
</tr>
<tr>
<td>Medical Comorbidities</td>
<td></td>
</tr>
</tbody>
</table>
Treatment

Comorbid Medical Conditions

Age:
18

Intensive Induction “7+3”

65

Low-intensity strategy

75

Supportive Care

95
Intensive Treatment

- **Induction**
- **Primary Induction Failure**
- **Post Remission**
- **More Chemo or Transplant**
Intensive Treatment

Standard Non-Protocol Therapy for Acute Myeloid Leukemia (AML)

Induction (Goal: achieve complete remission)

3 & 7 Regimen

Cytarabine (Ara-C) -- 7 day continuous infusion

Day 1

Daunorubicin -- daily IV x 3 days

Approximately Day 14:
Bone marrow aspirate/biopsy

Day 21

Recovery of healthy blood cells usually occurs after Day 21

If persistent leukemia, retreatment may be necessary
If no persistent leukemia, wait for recovery of healthy cells

Conditions for hospital discharge:
Absolute neutrophil count >500/mm³ (>0.5 x 10⁹/L)
Any infections are controlled (e.g., no fevers)
Adequate oral intake

Slide adapted from Dr. David Steensma
The 7+3 Regimen in AML

Complete remission rate in younger pts: 60% to 75%
Complete remission rate in pts older than 60 yrs of age: 35% to 50%

Mortality rate 10—30%

Vyxeos OR CPX-351 (Cytarabine:Daunorubicin) Liposome Injection:

- 100 nm bilamellar liposomes
- 5:1 molar ratio of cytarabine to daunorubicin
- 1 unit = 1.0 mg cytarabine plus 0.44 mg daunorubicin
Overall Survival Was Greater in the CPX-351 Arm Compared to the 7+3 Arm
Midostaurin

Oral targeted therapy

Added day 8-21 after the result of blood test for FLT-3 is positive (FLT3-ITD or TKD)

Nausea, Vomiting, skin rash
Intensive Treatment

- Median overall survival: midostaurin 74.7 months (range 31.7 – not reached) versus placebo 26.0 months (range 18.5–46.5)

Overall Survival
Censored at time of transplant

Arm | 4-year Survival
--- | ---
MIDO | 63.8% (95% CI: 56.71)
PBO | 55.7% (95% CI: 47.63)

1-sided log-rank p-value*: 0.04
Hazard Ratio*: 0.75

<table>
<thead>
<tr>
<th>time (months)</th>
<th>number at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIDO</td>
<td>360</td>
</tr>
<tr>
<td>PBO</td>
<td>357</td>
</tr>
</tbody>
</table>

Medians not reached
* controlled for FLT3 subtype (TKD, ITD-Low, ITD-High)
Overall Survival - Post-transplant
Treatment with Mido increases OS after SCT in CR1

- SCT in CR1: HR 0.61
- SCT outside CR1: HR 0.98

% alive vs. time (months)

+ Censor

Gemtuzumab Ozogamicin: Anti-CD33 Antibody–Drug Conjugate

- Conjugated toxin: calicheamicin
- Approved in 2000 based on 30% CR rate in relapsed AML
  - Voluntarily withdrawn in 2010 after addition to frontline chemotherapy shown to increase mortality
- Subsequent studies demonstrated survival benefits, particularly in pts younger than 60 yrs of age and/or with favorable risk
  - Combinations with chemotherapy[^2]
  - 5-trial meta-analysis showed benefit of GO addition to induction[^3]
  - DFS benefit in pediatric AML[^4]
  - OS benefit in pts older than 60 yrs and ineligible for chemotherapy[^5]

- Risk of veno-occlusive disease (Liver problem)

MDSC targeting with Gemtuzumab ozogamicin restores T cell immunity and immunotherapy against cancers
Livingstone FultangaSilviaPanettiAMargaretNgbPaulCollinsaSuzanneGraefaNagyRizkallaaSarahBoothaRichardLentonaBorisNoyvertcClaireShannon-LoweAGaryMiddletonaFrancisMussaia2CarmelaDe Santoa2
## AML Postremission Therapy

<table>
<thead>
<tr>
<th>Better-risk karyotype</th>
<th>HiDAC 3g/m² over 3h q12 d 1,3,5 x 4 * OR HiDAC x 1-2 ⇒ auto HSCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate-risk karyotype</td>
<td>Matched sibling or auto HSCT OR HiDAC 3g/m² over 3h q12 d 1,3,5 x 4 * OR Clinical trial</td>
</tr>
<tr>
<td>Poor-risk karyotype AHD t-AML</td>
<td>Clinical trial OR Allo HSCT/alternative donor HSCT</td>
</tr>
</tbody>
</table>

Consolidation (Goal: lower risk of relapse)

High-dose or Mid-dose Cytarabine (Ara-C) -- “HiDAC” or “MiDAC” (May be repeated up to 4 times, with 2-6 week break between cycles after count recovery)

6 Cytarabine (Ara-C) doses total, each dose is a ~3 hour infusion
1 dose in AM and 1 dose in PM on days 1, 3, and 5 (no chemotherapy on day 2 or day 4)

Most patients can be safely discharged from the hospital on day 6, but about one-half will need to be readmitted later, usually due to fevers during the period of low white counts (neutropenia)

*First Consolidation treatment (“cycle”) usually begins 2-6 weeks after recovery of blood counts following Induction chemotherapy
* For some patients, the first Consolidation cycle may be “2 & 5”, a shortened version of 3 & 7, instead of HiDAC or MiDAC
* Some patients will go to stem cell transplant during or instead of Conservation (depends on patient age, risk of relapse, and donor availability)
Consolidation: DFS Benefit Only in Patients Age <60 Years Receiving High-Dose Ara-C

Patients with CBF cytogenetics most benefit from HiDAC

AML in Older Adults
Treatment Rates over Time (2000-2009)
(SEER-Medicare Analysis, n=8,336)

Non- Intensive Treatment

- Older patients are likely to have other medical problems
- Less favorable and more unfavorable cytogenetics
- Higher incidence of preceding MDS
- Increased chance of therapy related morbidity and mortality
- Lower rates and duration of complete remission and shorter median survival
- Less likely to be eligible for transplant
# CR, Early Death, and Survival Rates in Older (≥ 55 years) AML

<table>
<thead>
<tr>
<th>STUDY</th>
<th>N</th>
<th>Induction / Consolidation</th>
<th>CR</th>
<th>ED</th>
<th>OS (3-5 year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB</td>
<td>388</td>
<td>DA/A or MA</td>
<td>52%</td>
<td>25%</td>
<td>15%</td>
</tr>
<tr>
<td>ECOG</td>
<td>348</td>
<td>D or I or M (each) + A/A</td>
<td>42%</td>
<td>17%</td>
<td>10%</td>
</tr>
<tr>
<td>SWOG</td>
<td>328</td>
<td>DA or ME/DA</td>
<td>43%</td>
<td>7%</td>
<td>19%</td>
</tr>
<tr>
<td>MRC</td>
<td>1,314</td>
<td>DAT or ADE or MAC/DAT Or COAP, DAT, COAP</td>
<td>55%</td>
<td>19%</td>
<td>10%</td>
</tr>
<tr>
<td>Kantarjian H, et al.*</td>
<td>466</td>
<td>Various cytarabine-based intensive chemotherapy regimens</td>
<td>45%</td>
<td>-</td>
<td>4 weeks = 26% 8 weeks = 36% 1 year = 28%</td>
</tr>
</tbody>
</table>

*Age 70 years or older.
• 446 patients ≥ 70 years; treated with cytarabine-based intensive chemo between 1990 -2008
• CR was 45%,
• 4-week mortality was 26%, and 8-week mortality was 36%.
• The 1-year survival rate was 28%.
• A multivariate analysis of prognostic factors for 8-week mortality identified age ≥ 80 years,
complex karyotypes,
poor performance (2-4 ECOG),
Elevated creatinine > 1.3 mg/dL.

• Patients with none, 1, 2, 3, or ≥ 3 factors (9%) had estimated 8-week mortality rates of 16%, 31%, 55%, and 71% respectively.
Overall survival of older AML patients treated with decitabine or azacitididine

**DACO-016**

<table>
<thead>
<tr>
<th>N</th>
<th>Death (%)</th>
<th>Median, mo</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decitabine</td>
<td>242</td>
<td>197 (81)</td>
<td>7.7 (5.2, 9.2)</td>
</tr>
<tr>
<td>Total TC</td>
<td>243</td>
<td>183 (82)</td>
<td>5.0 (4.3, 6.3)</td>
</tr>
</tbody>
</table>

**AZA-AML-001**

<table>
<thead>
<tr>
<th>N</th>
<th>Death (%)</th>
<th>Median, mo</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azacitidine</td>
<td>241</td>
<td>174 (72)</td>
<td>10.4 (8.0, 12.7)</td>
</tr>
<tr>
<td>CCR</td>
<td>247</td>
<td>159 (68)</td>
<td>6.5 (5.0, 6.9)</td>
</tr>
</tbody>
</table>

Survival improvement was similar with decitabine vs azacitidine:

- Median OS in DACO-016: decitabine 7.7 months, TC 5.0 months (p=0.108); 54% improvement with decitabine vs TC
- Median OS in AZA-AML-001: azacitidine 10.4 months, CCR 6.5 months (p=0.101); 60% improvement with azacitidine vs CCR
Hypomethylating Agent vs Induction in Older Adults (Age >70) With AML

TP53 and Decitabine in AML

- Bone marrow blast clearance in 67% unfavorable risk vs 34% intermediate and favorable risk
- 100% patients with TP53 mutations had ORR
- Generally needs at least 2 cycles
- Responses short, remissions < 1 year

Venetoclax plus HMA or LDAC combination

60 % complete remission or complete remission with incomplete blood count recovery

Median time to CR or CRi was 1 month

Median duration of response 8.4 months

Low blood counts, fatigue, risk of infections, risk of tumor lysis syndrome
Glasdegib LDAC combination

Hedgehog pathway inhibitor

Oral medication along with low dose Ara-C

CR 17%

Survival 8.8 months

Side effects: low blood counts, fatigue, nausea
Relapsed/Refractory AML

- No standard therapy
- Example salvage regimens:
  - MEC (mitoxantrone, etoposide, cytarabine)
  - CLAG (cladribine, cytarabine, GCSF)
  - FLAG-IDA (fludarabine, cytarabine, GCSF, idarubicin)
  - High-dose cytarabine
  - Hypomethylating agents (off label)
- If CR1 > 12 mos, > 60% chance of CR2, ok to re-induce with same treatment as original induction
- If CR1 < 12 mos, <20% chance of CR2
- Allo transplant in CR2 needed for long-term survival
- CLINICAL TRIALS
IDH pathway

2-HG, 2-hydroxyglutarate; α-KG, α-ketoglutarate; IDH, isocitrate dehydrogenase; KDM, lysine (K)-specific demethylase; TET2, tet methylcytosine dioxygenase 2.
Enasidenib (AG-221; *IDH2* inhibitor)

<table>
<thead>
<tr>
<th>Enasidenib 50 mg QD or 30 mg BID (highest 450 mg QD)</th>
<th>Total (N=181*)</th>
<th>R/R (N=128*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR, n (%)</td>
<td>30 (17)</td>
<td>23 (18)</td>
</tr>
<tr>
<td>CRp/CRi, n (%)</td>
<td>3+1 (2)</td>
<td>1+1 (2)</td>
</tr>
<tr>
<td>mCR, n (%)</td>
<td>15 (8)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>PR, n (%)</td>
<td>25 (14)</td>
<td>19 (15)</td>
</tr>
<tr>
<td>ORR, n (%)</td>
<td>74 (41)</td>
<td>52 (41)</td>
</tr>
<tr>
<td>Response duration</td>
<td>6.9 months</td>
<td>6.0 months</td>
</tr>
</tbody>
</table>

Side effects: Differentiation Syndrome, Jaundice from elevated Bilirubin
### Ivosidenib in R/R *IDH1*-Mutated AML:

<table>
<thead>
<tr>
<th>Primary Efficacy Outcomes</th>
<th>R/R AML 500 mg Set*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CR + CRh rate, % (95% CI)</strong></td>
<td>31.8</td>
</tr>
<tr>
<td>▪ Median time to CR/CRh, mos (range)</td>
<td>2.0</td>
</tr>
<tr>
<td>▪ Median duration of CR/CRh, mos (95% CI)</td>
<td>8.2</td>
</tr>
<tr>
<td><strong>CR rate, % (95% CI)</strong></td>
<td>24.0 (18.0-31.0)</td>
</tr>
<tr>
<td>▪ Median time to CR, mos (range)</td>
<td>2.8 (0.9-8.3)</td>
</tr>
<tr>
<td>▪ Median duration of CR, mos (95% CI)</td>
<td>10.1 (6.5-22.2)</td>
</tr>
<tr>
<td><strong>CRh rate, n (%)</strong></td>
<td>14† (7.8)</td>
</tr>
<tr>
<td>▪ Median duration of CRh, mos (95% CI)</td>
<td>3.6 (1.0-5.5)</td>
</tr>
</tbody>
</table>


Approved as single agent

Responses increases with time

Can cause increase in white blood cell and differentiation syndrome
Stem Cell Transplantation
EKG

ECHO

Pulmonary Function Tests

Dental exam

Bone Marrow Biopsy

Blood tests
Stem cells removed from donor

Patient receives treatment to destroy blood-forming cells

Patient receives stem cells

Courtesy: NCI
BMT CTN PROTOCOL 0901

A Randomized, Multi-Center, Phase III Study of Allogeneic Stem Cell Transplantation Evaluating Regimen Intensity in Patients with Myelodysplastic Syndrome or Acute Myeloid Leukemia
BMT CTN 0901: Randomized Phase III design

**MDS/AML < 5% blasts**
18-65 years PB/BM
HCT-CI ≤ 4 (-) CNS
MRD/MUD (7/8) (-) circ. blasts

**Randomization**

- **RIC regimens**
  - Flu/Bu2
  - Flu/Mel

- **GVHD Prophylaxis per Institutional guidelines:**
  - T-depleted and post-transplant Cy excluded

- **MAC Regimens**
  - Flu/Bu4
  - Bu4/Cy
  - Cy/TBI

**18 Month Overall Survival**

BMTCTN.net
Overall Survival by Treatment Arm

MAC 77.4%
RIC 67.7%

P=0.07 (18 month pointwise)
9.7% difference (95% CI: -0.9%, 20.3%) MAC vs. RIC

Overall Survival by Disease Group

**MDS (N=54)**
- Survival Probability: P=0.71 (18 month pointwise)

**AML (N=218)**
- Survival Probability: P=0.027 (18 month pointwise)

**Survival Rate by Disease Group**
- **MAC**: 81.5%
- **RIC**: 85.2%
- **MAC**: 76.8%
- **RIC**: 63%

---

<table>
<thead>
<tr>
<th>Months</th>
<th>MAC 27</th>
<th>25</th>
<th>25</th>
<th>23</th>
<th>22</th>
<th>22</th>
<th>21</th>
</tr>
</thead>
<tbody>
<tr>
<td>RIC</td>
<td>27</td>
<td>26</td>
<td>26</td>
<td>25</td>
<td>23</td>
<td>22</td>
<td>20</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Months</th>
<th>108</th>
<th>105</th>
<th>101</th>
<th>91</th>
<th>87</th>
<th>77</th>
<th>67</th>
<th>62</th>
</tr>
</thead>
</table>
Relapse/Progression by Disease and Treatment Arm

For MDS:
- MAC: 3.7%
- RIC: 37%

For AML:
- MAC: 16.5%
- RIC: 50%

Incidence of Relapse

<table>
<thead>
<tr>
<th>Disease</th>
<th>Months</th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>15</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS</td>
<td>27</td>
<td>25</td>
<td>25</td>
<td>23</td>
<td>22</td>
<td>21</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>MDS</td>
<td>27</td>
<td>23</td>
<td>18</td>
<td>17</td>
<td>16</td>
<td>15</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td>105</td>
<td>96</td>
<td>88</td>
<td>84</td>
<td>79</td>
<td>69</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td>106</td>
<td>73</td>
<td>57</td>
<td>52</td>
<td>51</td>
<td>46</td>
<td>43</td>
<td></td>
</tr>
</tbody>
</table>
Treatment-related Mortality

MAC 132       121      113       107       101         90         75
RIC   133       96        75         69          67          61         56

MAC 15.8%
RIC 4.4%
P=0.02  (18 month pointwise)

What’s New on the Horizon

• We are improving our understanding about the biology of AML
• FDA approvals of new drugs
• New clinical trials with novel agents
• Transplant donor availability is improving
Acute Promyelocytic Leukemia

- 5-15% of all adult acute leukemias in the US

  - More common
    - Young / middle age adults
    - Hispanics and obese (BMI $\geq 30$)

- Incidence worldwide: 0.6 per $10^6$ people

- FAB: AML M3

- Caused by balanced translocation, usually t(15;17)
Model of APL Pathophysiology

![Diagram showing the model of APL pathophysiology. Corepressors are repressed by RA receptors, leading to differentiation block. Treatment with retinoic acid (RA) activates coactivators, promoting differentiation.](https://example.com)
Risk Stratification

Table 1. Acute Promyelocytic Leukemia Risk Groups

<table>
<thead>
<tr>
<th>Measure</th>
<th>Low Risk</th>
<th>Intermediate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC, /L</td>
<td>&lt; 10,000</td>
<td>&lt; 10,000</td>
<td>&gt; 10,000</td>
</tr>
<tr>
<td>Platelets, /L</td>
<td>&gt; 40,000</td>
<td>&lt; 40,000</td>
<td></td>
</tr>
<tr>
<td>Distribution, %</td>
<td>24</td>
<td>53</td>
<td>23</td>
</tr>
</tbody>
</table>

Data adapted.\textsuperscript{11}
North American Intergroup Protocol I0129

CT = Daunorubicin + cytarabine
Kaplan–Meier Estimates of Event-free and Overall Survival among Patients with Acute Promyelocytic Leukemia.
Treatment Algorithm for Newly Diagnosed APL

Suspect APL based on:
1. Presence of DIC
2. Atypical promyelocytes
3. Flow negative for HLA-DR

Start ATRA while waiting for cytogenetic and/or molecular confirmation

No t(15;17) or no PML-RARα
Stop ATRA
Treat AML

APL confirmed

Low- or Intermediate-Risk APL
- No QTc prolongation
- ATRA plus ATO
- Prednisone for prophylaxis
- Hydroxyurea if WBC increases to > 10,000/L

High-Risk APL (Options)
- ATRA plus ATO plus GO (if available)
- ATRA plus ATO plus idarubicin
- Follow C9710