
# ADVANCES IN ACUTE MYELOID LEUKEMIA

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LEUKEMIA & LYMPHOMA SOCIETY®

## DISCLOSURES

Advances in Acute Myeloid Leukemia

**James M. Foran, MD, FRCPC, has affiliations with Actinium, Agios, Boehringer Ingelheim, H3B Biomedicine, LLS, NOHLA Therapeutics, Takeda Millennium, Trillium, Xencor *(Research);* Astellas, Boston Biomedical, Jazz Pharmaceuticals (*Honoraria).***

## Advances in AML in 2018
## Learning Objectives

i. Evaluate the optimal incorporation of newly-approved therapies in AML

ii. Understand the role of mutations and deep sequencing in determining prognosis and selection for AML therapy

iii. Consider the role of Allogeneic Transplantation as consolidation therapy after AML therapy

iv. Optimize collaborative & supportive care

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## What is Leukemia?

- Greek: “White Blood”
- Cancer of bone marrow (blood-producing) cells
  - Immature/primitive BM cells, proliferative - ***acute***
- Abnormal Complete Blood Count
- Short-term survival without therapy
- Prognosis varies greatly
  - Requires detailed pathology review & diagnosis

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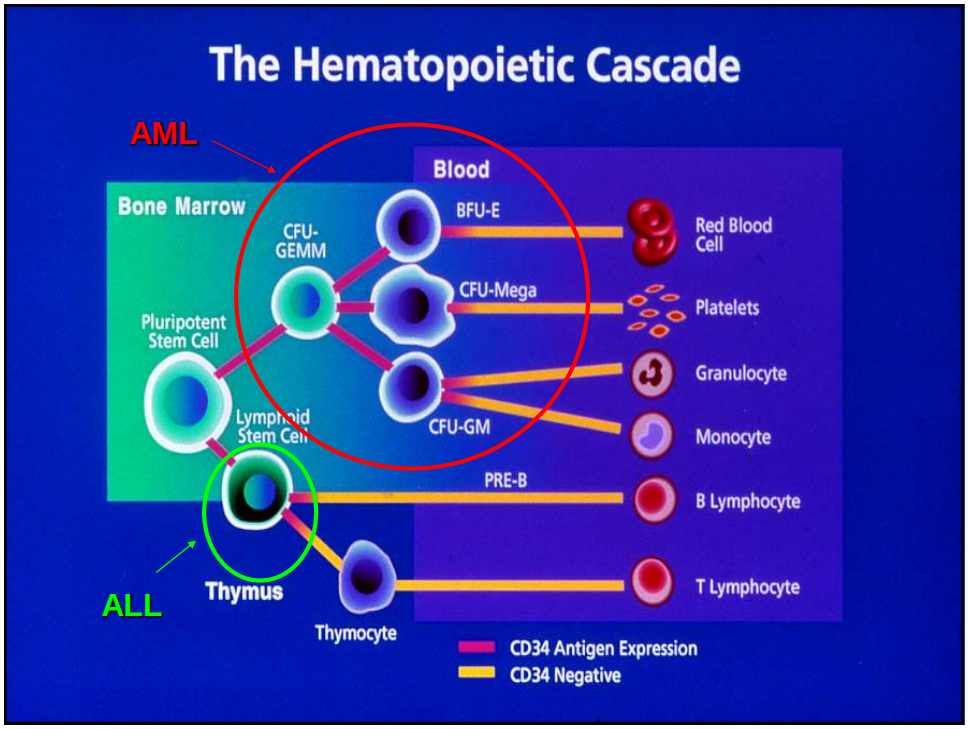


**Estimated New Cases**

| | | | Males | Females | | | |
|---|---|---|---|---|---|---|---|
| Prostate | 164,690 | 19% | | | Breast | 266,120 | 30% |
| Lung & bronchus | 121,680 | 14% | | | Lung & bronchus | 112,350 | 13% |
| Colon & rectum | 75,610 | 9% | | | Colon & rectum | 64,640 | 7% |
| Urinary bladder | 62,380 | 7% | | | Uterine corpus | 63,230 | 7% |
| Melanoma of the skin | 55,150 | 6% | | | Thyroid | 40,900 | 5% |
| Kidney & renal pelvis | 42,680 | 5% | | | Melanoma of the skin | 36,120 | 4% |
| Non-Hodgkin lymphoma | 41,730 | 5% | | | Non-Hodgkin lymphoma | 32,950 | 4% |
| Oral cavity & pharynx | 37,160 | 4% | | | Pancreas | 26,240 | 3% |
| Leukemia | 35,030 | 4% | | | Leukemia | 25,270 | 3% |
| Liver & intrahepatic bile duct | 30,610 | 4% | | | Kidney & renal pelvis | 22,660 | 3% |
| **All Sites** | **856,370** | **100%** | | | **All Sites** | **878,980** | **100%** |

**Estimated Deaths**

| | | | Males | Females | | | |
|---|---|---|---|---|---|---|---|
| Lung & bronchus | 83,550 | 26% | | | Lung & bronchus | 70,500 | 25% |
| Prostate | 29,430 | 9% | | | Breast | 40,920 | 14% |
| Colon & rectum | 27,390 | 8% | | | Colon & rectum | 23,240 | 8% |
| Pancreas | 23,020 | 7% | | | Pancreas | 21,310 | 7% |
| Liver & intrahepatic bile duct | 20,540 | 6% | | | Ovary | 14,070 | 5% |
| Leukemia | 14,270 | 4% | | | Uterine corpus | 11,350 | 4% |
| Esophagus | 12,850 | 4% | | | Leukemia | 10,100 | 4% |
| Urinary bladder | 12,520 | 4% | | | Liver & intrahepatic bile duct | 9,660 | 3% |
| Non-Hodgkin lymphoma | 11,510 | 4% | | | Non-Hodgkin lymphoma | 8,400 | 3% |
| Kidney & renal pelvis | 10,010 | 3% | | | Brain & other nervous system | 7,340 | 3% |
| **All Sites** | **323,630** | **100%** | | | **All Sites** | **286,010** | **100%** |

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**AML (2018)** **Cases: 19,520** **Deaths:10,679**

Siegel R: CA Cancer J Clin 68:7, 2018

## Epidemiology of Leukemia
## Relevance in the Clinic

- The causes of cancer are largely unknown in individual patients
- Deeply relevant to patients and their families
  - "Why did this happen to me?" [1]
  - Impact of the cause on the disease course
  - Risk of recurrence
    - Interventions, appropriate lifestyle changes, etc.
- Recognition of Familial Risk
- *Impact of specific leukemia risk factors on genetics, prognosis and outcome after diagnosis largely unstudied*

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[1]Dizon DS: ASCO Connection, 09 April 2015



## AML Epidemiology
## Exposures Identified in Case-Control Studies

| | Relative Risk of developing AML |
|---|---|
| Obesity | 2-fold |
| Acetaminophen | 1-2 |
| Aspirin | Lower risk ? |
| Smoking | 2 |
| Farm/Rural habitat | 2 |
| Benzene | 2-10 |
| Ulcerative Colitis | 4 |
| Chemo/Radiation for other cancer | 2-10 |

**Some risk factors that have been associated with AML development identified in Population-Based Case-Control Studies**

- **Not proof of causality, but suggests increased risk**
- **Further studies ongoing**

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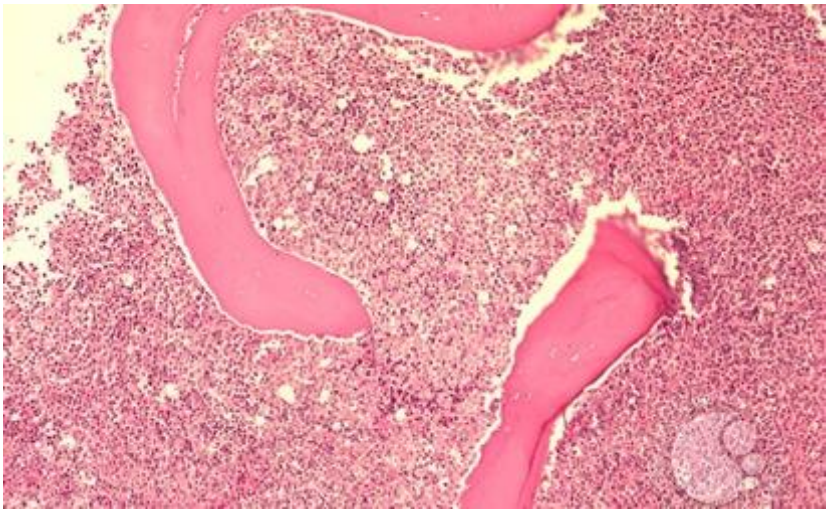
Ross, Cancer Epidemiology Biomark & Prev. 13:1810, 2004.
Sinner, Cancer Epidemiol Biomark & Prev. 14:2446, 2005.
Ross, Cancer Epidemiol Biomark & Prev. 20:1741, 2011.
Sandler, JNCI 85:1994, 1993
Natelson, Am J Hematol 82:826, 2007
Johnson, Ca Caus. & Contr. 23:1083, 2012

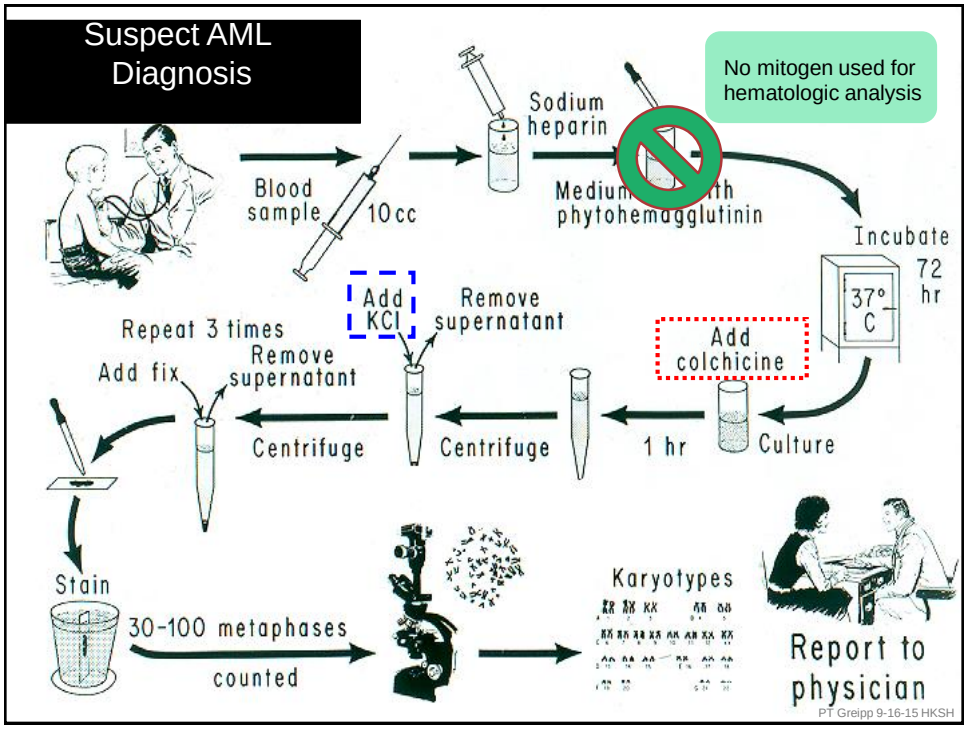
## AML BM biopsy





## Acute Leukemia

- Complications of Leukemia:
  - Infection — Rapid onset, esp. if neutropenia
  - Bleeding — Low platelets, low fibrinogen ***DIC***
  - Clotting — Hypercoagulable, even if low platelets
  - Fatigue — Anemia, transfusions
  - Leukostasis — "Sludging" - confusion, stroke, bleed, cardiopulmonary symptoms
- Importance of coordinated clinic evaluation & hospital care
  - **Acute Leukemia** Must see in 24-48 hours whenever possible
  - Frequently direct hospital transfer , or being admitted for urgent evaluation and initiation of treatment
  - ~4 week intensive "*remission induction*" therapy

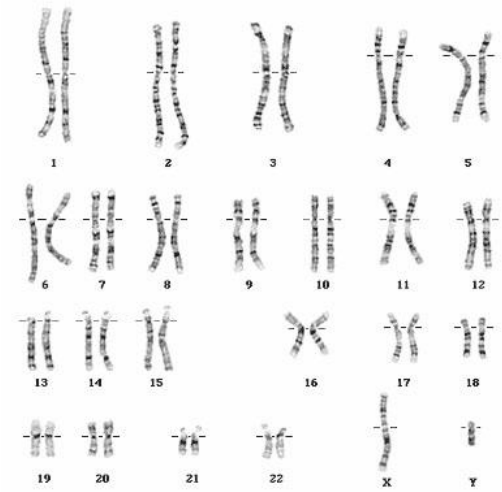



# Cytogenetic Testing

**Chromosome analysis**
- requires dividing cells
- whole genome coverage
- low resolution (~5 Mb)

**FISH analysis**
- does not require dividing cells
- site-specific
- higher resolution (~100 Kb)

**Microarray analysis**
- does not require dividing cells
- whole genome coverage
- 2.6M copy number markers
- 750k SNPs
- high resolution (~25-50 Kb)

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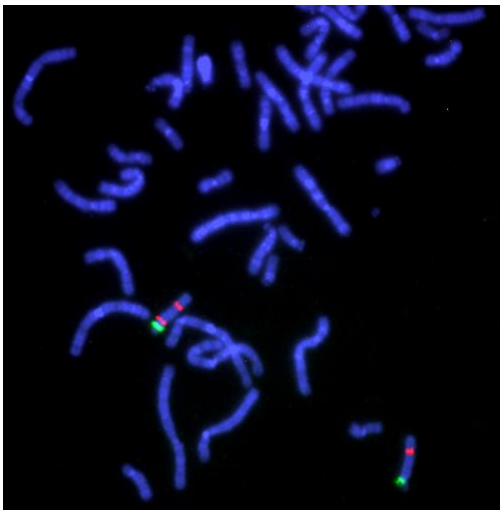

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## Mutations

- *A change that occurs in our DNA sequence, either due to mistakes when the DNA is copied, or as the result of environmental factors (e.g. UV light, or cigarette smoke)*
  - Typically 'acquired' in certain cells
    - Can be inherited ('germline')
- May disrupt normal gene activity and cause diseases, like cancer
- Can contribute to prognosis with standard therapies
- * Some gene mutations that involve a unique cell process can be targeted

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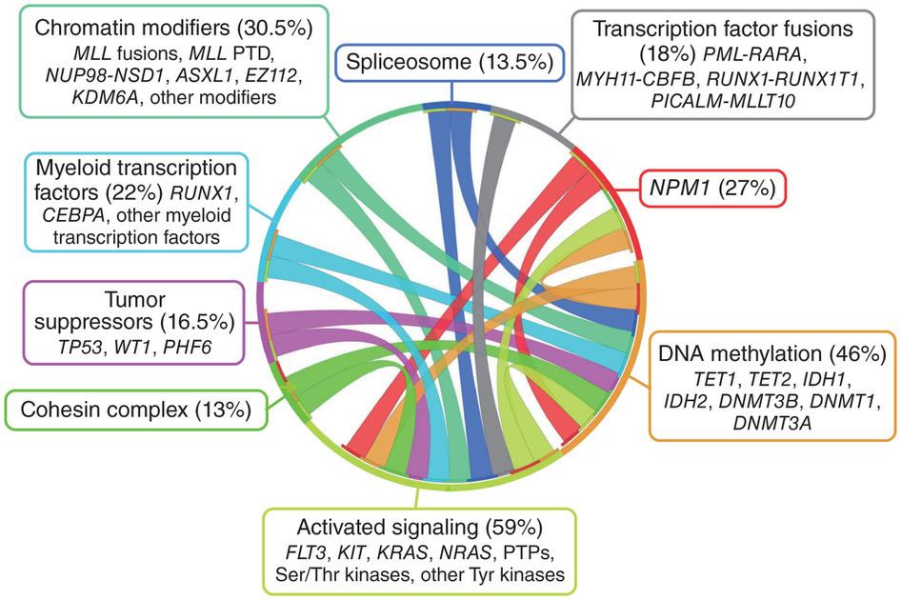
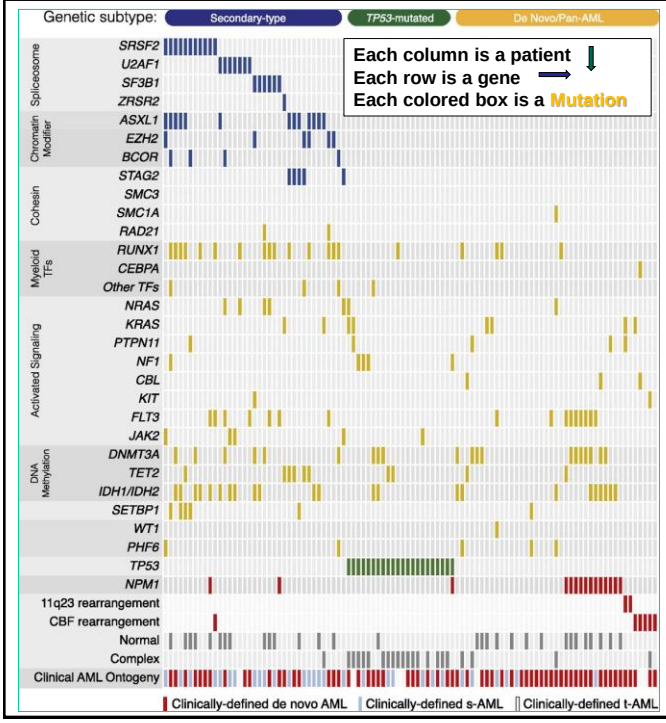
## AML is a complex biological disease




***Sai-Juan Chen, Nature Genetics 45,586, 2013***




## Mutations & Genetic Subtypes in AML

- Guide prognosis and therapy
- Targetable mutations
  - Multiple mutations common
- Insights into biology and epidemiology of AML

**Lindsley et al, Blood 125:1367, 2015**

## AML biology predicts response to cytarabine + anthracycline chemotherapy

| Risk status | Cytogenetics | Molecular abnormalities |
|---|---|---|
| **Better risk** | inv(16) or t(16;16) or t(8;21) without *c-KIT* mutation, t(15;17) | Normal karyotype with ***NPM-1* mutation** in the absence of *FLT-3* ITD or Isolated biallelic *CEBPα* |
| **Intermediate risk** | Normal karyotype<br>Trisomy 8 alone<br>t(9;11)<br>Other not defined | t(8;21), inv(16), t(16;16) with ***c-KIT* mutation** |
| **Poor risk** | Complex (≥3 clonal abnl)<br>Monosomal karyotype<br>-5, 5q-, -7, 7q-<br>11q23 (not t(9;11))<br>Inv(3), t(3;3)<br>t(6;9), t(9;22) | Normal karyotype with ***FLT-3 ITD*** mutation |

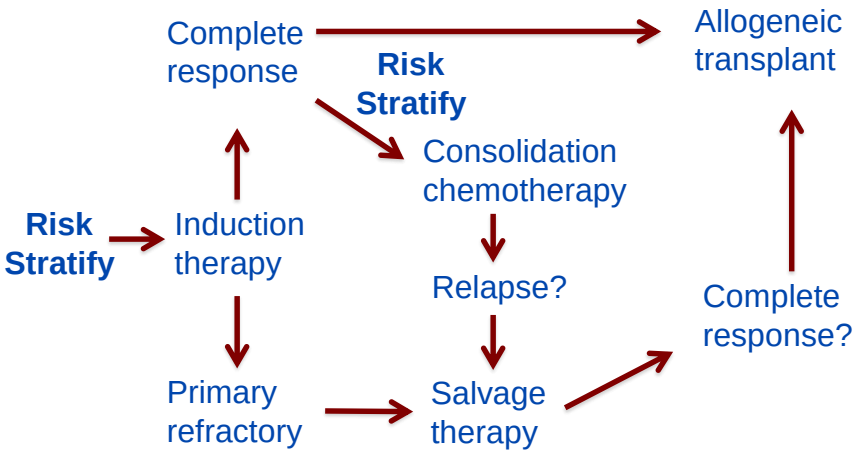
*Adapted from NCCN Guidelines. Acute Myeloid Leukemia*

## Principles of AML Treatment

- Improve symptoms and suffering from AML
- Cure whenever possible
- Treatment is better than no treatment for almost all patients
- Allogeneic transplant



## Modern Treatment Paradigm of AML with Intensive Therapy (Fit)



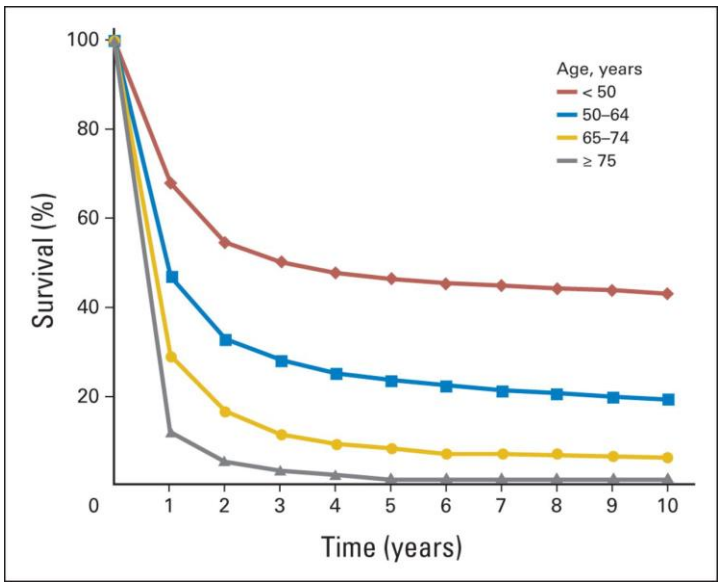
## Treatment of Acute Myelocytic Leukemia: A Study by Cancer and Leukemia Group B

By Kanti R. Rai, James F. Holland, Oliver J. Glidewell, Vivian Weinberg, Kurt Brunner, J. P. Obrecht, Harvey D. Preisler, Ismat W. Nawabi, David Prager, Robert W. Carey, M. Robert Cooper, Farid Haurani, J. L. Hutchison, Richard T. Silver, Geoffrey Falkson, Peter Wiernik, H. Clark Hoagland, Clara D. Bloomfield, G. Watson James, Arlan Gottlieb, S. V. Ramanan, Johannes Blom, Nis I. Nissen, Arthur Bank, Rose Ruth Ellison, Faith Kung, Patrick Henry, O. Ross McIntyre, and Sze K. Kaan

**In a randomized study of acute myelocytic leukemia (AML), 352 patients of all ages were treated for remission induction by one of the four regimens: 7 days of cytosine arabinoside (ara-C) by continuous intravenous (i.v.) infusion or bolus injection every 12 hr, together with daunorubicin (DNR) by rapid i.v. injection on days 1, 2, 3; or 5 days of ara-C by infusion or bolus injection and DNR for 2 days only. The regimen of 7 and 3 infusion was significantly superior to the other 3 regimens, resulting in 56% complete remission (CR). For remission maintenance, ara-C was given for 5 days every month and each month one of the following four drugs added on a cyclic rotational basis: thioguanine, cyclophosphamide, CCNU, or DNR. Although ara-C dosage each month was the same, the route of ara-C administration by random allocation was either rapid i.v. bolus or subcutaneous (s.c.) injection. The median duration of CR was significantly longer for s.c. ara-C group: 14 mo for patients less than 60 yr old (versus 8 mo for i.v.) and 31 mo for 60 or older age group (versus 9 mo for i.v.). Patients who received a combination of the best of the four induction regimens (7 and 3 infusion) and the better of the two maintenance schedules (s.c. ara-C) had a median remission duration of 22 mo and a median survival of 35 mo (the longest reported in a prospective randomized trial of therapy for AML). These results establish the validity of an intensive chemotherapy to produce rapid marrow aplasia followed by a sequential maintenance therapy for achieving prolonged disease-free survival in AML.**

- First large randomized study
- Established '7&3' (Daunorubicin & Cytarabine) as the standard remision induction therapy in younger adults

Rai et al, Blood 58:1203, 1981




***Relative survival by time and age for Acute Myeloid Leukemia based on SEER data.***

Klepin H et al; *Journal of Clinical Oncology* 32:2541, 2014

## Advances in 1st line Intensive Treatment

- **Vyxeos**™ - New chemotherapy formulation for 'secondary AML' (arising after prior chemo or radiation, or prior BM disease such as MDS)
- **Mylotarg**™ – Antibody targeting a common leukemia cell surface marker called CD33, linked to a toxin -'immunotoxin'
- **Midostaurin** (**Rydapt**™)– oral inhibitor for FLT3 mutations

**Applies to younger (<75 yrs) and 'fitter' patients*

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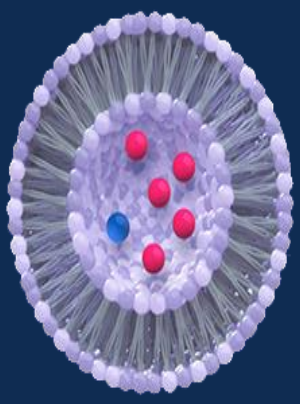
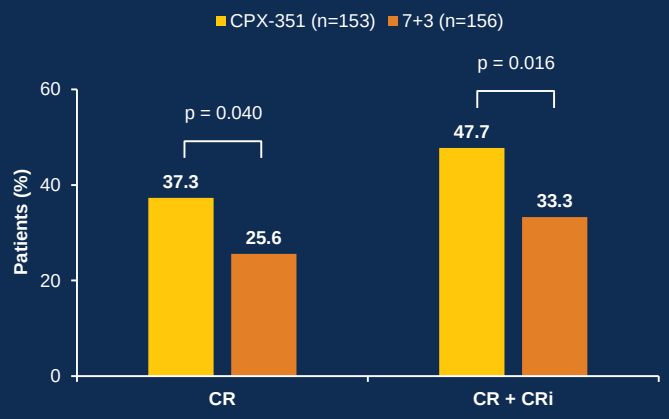
## CPX-351 Uses a Nano-Scale Delivery Complex



- 100 nm bilamellar liposomes
- 5:1 molar ratio of cytarabine to daunorubicin
- 1 unit = 1.0 mg cytarabine plus 0.44 mg daunorubicin

## Patients Treated With CPX-351 Exhibited Statistically Significant Improvements in Response Rate

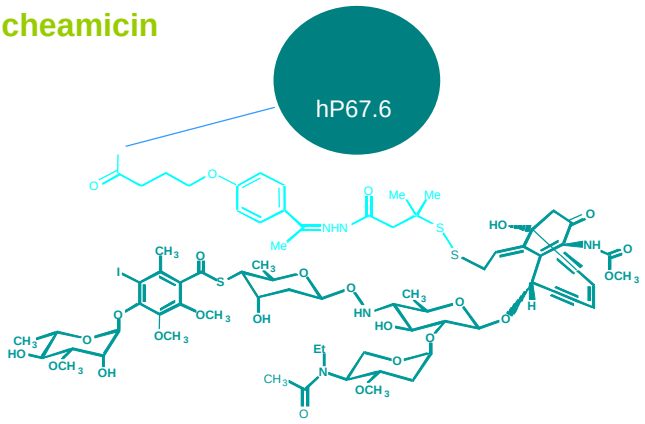



- **Higher Remission rate**
- **Better survival**
- **Higher rate of successful BMT**

**Lancet et al, J. Clin Oncol 2018**

## Gemtuzumab-ozogamicin (Mylotarg™)

- **hP67.6 - humanized anti-CD33 antibody**
- **Linker**
- **Calicheamicin**



## Gemtuzumab Ozogamicin (Mylotarg™)

- Benefit in significantly lowering the relapse rates by approximately 10-15%
  - Day 1,3,5 added to 7&3 intensive chemotherapy
- Most benefit in patients with 'Better' or 'Intermediate' risk cytogenetics
  - Probably not helpful in 'Adverse' cytogenetics
- Must watch for Liver toxicity, especially in patients who may ultimately go to allogeneic transplant
  - 'VOD' – veno-occlusive disease, a post-BMT complication

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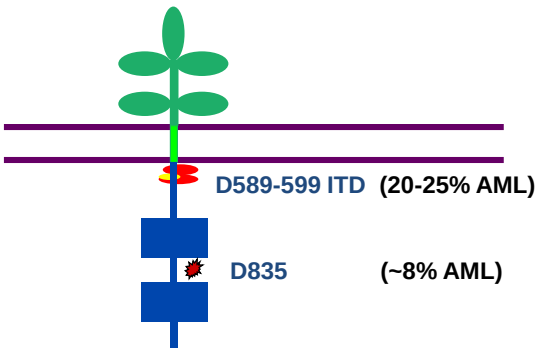
## What is FLT3?




- FLT3 is an important growth factor receptor
- Necessary for normal signaling and growth of bone marrow stem cells

- **Flt3 mutations**: approximately 30% of AML patients
  - Causes abnormal leukemia signaling &proliferation
- Independent adverse prognostic factor, contributes to relapse

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Gilliland, Blood 100:1532, 2002
Nazha, Haematologica 97:1242, 2012

## FLT3 Inhibitors

- Bind to mutated FLT3 receptor to 'shut down' signaling
- ***Midostaurin*** - ~10% advantage in survival in large randomized study if FLT3 mutation
  - *FDA-approved* in 1st line with 7&3 chemotherapy
- **Sorafenib** - possibly helpful with low intensity chemo
  - Not FDA-approved in AML
- In development for ***relapsed*** AML with FLT3 mutation
  - **Quizartinib** - superior survival to chemotherapy alone, targets the most common FLT3 mutations
  - **Gilteritinib** – complete remissions, targets both FLT3 mutations

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## Principles of Incorporating New Agents

- Patients should be receiving new drugs, but it should be *on label*, and we must be thoughtful and selective
- New agents should not be routinely combined until there is data showing safety and superior outcomes
  - allowing for exceptional case-by case scenarios
- There is still a group for whom standard 7&3 is appropriate
- If possible, await FLT3 status and cytogenetics whenever possible ***before*** starting therapy
  - Not always possible to expedite these tests, therefore sometimes must start therapy with 'best guess'

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## Proposed Mayo Clinic Treatment Guidelines incorporating new agents

| | Age | Population | Cytogenetics | Dosing | BMT Candidate |
|---|---|---|---|---|---|
| **Midostaurin** | Any | FLT3 mutation | Any | D8-21 | Yes |
| **Vyxeos™** | Any (60-75 years) | Therapy-related or secondary AML, prior MDS | MDS-related cytogenetics | D1,3,5 | Yes |
| **Gemtuzumab** | Any | CD33+ve | Any (not 'adverse') | D1,4,7 | Yes |
| **Standard 7&3** | Any | CD33-neg | Adverse; or if CD33-negative | | Yes |

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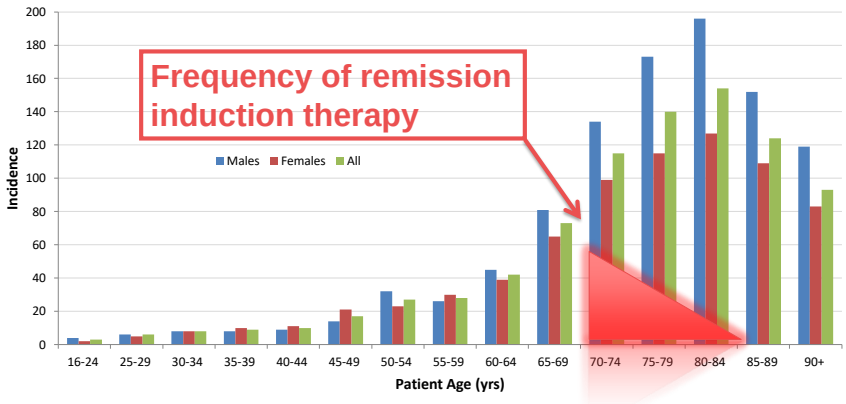
## Age-Specific AML Incidence Rates

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Juliusson, Blood 2009.

## Low Intensity Therapy for AML

- Older patients (>75), or those who are not fit for intensive therapy due to comorbid disease
- Represents the largest proportion of patients with AML
  - Survival often short without therapy, ~4 months
- Low-dose cytarabine (LDAC) - advantage over BSC
  - Azacitidine or Decitabine - possibly better
    - Newer oral versions in development
    - Possible role in maintenance
- Improve survival, but not curative
  - Convert AML into a more *chronic* or subacute course
  - Occasional remissions but stable AML is meaningful

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## Low Intensity Combination Therapies

- How to improve outcome?
- Many clinical trials ongoing, HMA combination
- Novel targets:
  - HDAC inhibitors
  - NEDD8 inhibitors
  - Monoclonal antibodies (e.g. CD33-based)
  - Mutations (e.g. *IDH1*, IDH2, FLT3)
  - Apoptosis (BCL2)
  - Immune [BiTE's, Checkpoint inhibitors]
    - **Many others**….!

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**clinicaltrials.gov**

## Venetoclax

- Oral BCL2 inhibitor
  - FDA-approved in CLL, chronic leukemia that is BCL2-dependent
- Targeting BCL2 (and possibly MCL1) expression is important in some patients with AML
  - Remission in ~20% with relapsed AML
- **Addition** to low intensity therapy (azacitidine) appears to increase complete remission rate and improve survival in 1st line setting

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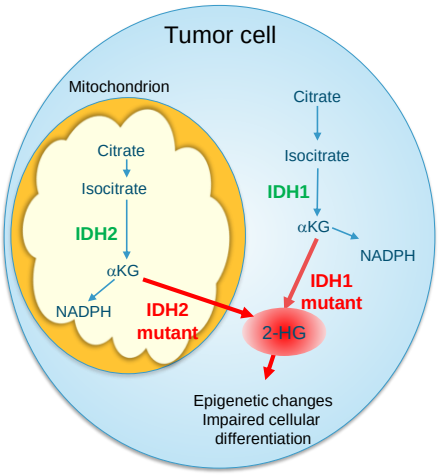
## IDH Mutations as a Target in AML

- **Isocitrate dehydrogenase (IDH)**
  - critical enzyme of citric acid cycle
- IDH2 mutations: 9–13% of AML
- IDH1 mutations: 6–10% of AML
- **IDH mutations:**
  - Aberrant methylation
    - i.e. DNA not 'read' properly
  - Impaired cellular differentiation
    - i.e. cells 'stuck' as blasts
  - Drives leukemia

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[1]Based on literature analysis. Estimates will continue to evolve with future data.
[2]Dang et al. *Nature* 2009;462:739-44.

## Targeting **IDH** mutations in Relapsed AML

**Enasidenib** (IDH2) and **Ivosidenib** (IDH1)

- Oral agents that bind to mutated IDH
- Induce remission in about 30% of patients with relapse AML
  - Improve blood counts, decrease transfusions
- Impact in 1st line being studied, in combination
- Can cause *'Differentiation syndrome*' side effect
  - Large number of leukemia cells that were *stuck* as immature 'blasts' begin to differentiate and mature, and to flood blood/system, causing high WBC, and pulmonary and organ dysfunction

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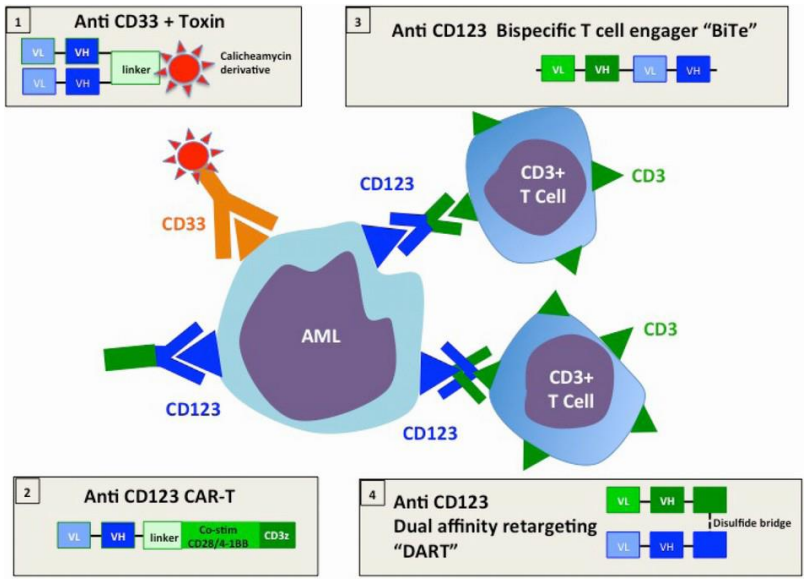
## Antibody-based therapeutic strategies for AML

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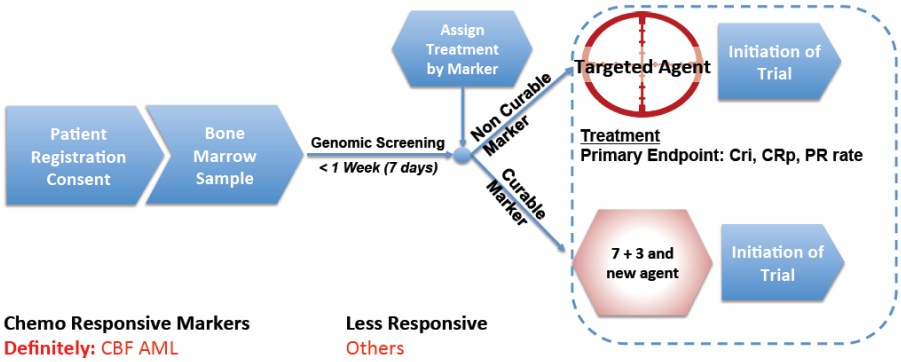
**Role of immune 'checkpoint' inhibitors remains uncertain in AML**

**Barrett, Ann Transl Med, 2017**

## CLINICAL TRIAL DESIGN: PATIENT IDENTIFICATION

**Phase 2, newly diagnosed AML patients, > 60 yrs**




**Chemo Responsive Markers**
**Definitely:** CBF AML
**Maybe:** NPM1+/FLT3-

**Less Responsive**
Others

Beat AML

LEUKEMIA & LYMPHOMA SOCIETY fighting blood cancers someday is today

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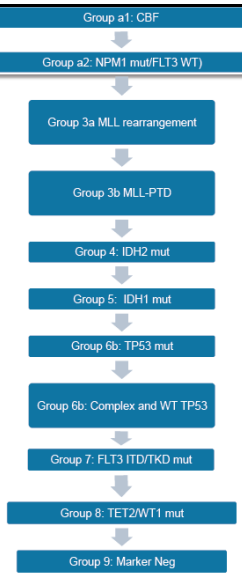
## How is Therapy Assigned

1. Molecular and Cytogenetic Data Arrives with Top to bottom approach
2. Dominant clone at VAF > .3 chosen based upon classification
3. If no dominant clone at VAF > .3, go to .2 with top to bottom for assignment




Beat AML

LEUKEMIA & LYMPHOMA SOCIETY fighting blood cancers someday is today

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## Reasons to Evaluate for Allogeneic Transplantation

- Provides significant reduction in risk of relapse
  - Limitations of consolidation chemotherapy strategies
  - Currently must be in remission or 'leukemia-free"'
- Improved outcomes in *Modern Era*
  - High resolution/molecular HLA typing for URD's
  - Reduced intensity conditioning in older adults
  - Improvements in Supportive Care
    - *Older adults represent increasing proportion BMT recipients
- Increased availability of donors [unrelated, and alternative]
  - Haplo-identical – partially matched donors

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## Selection at BMT Center

- Patient-centered evaluation, discussion & decision taken together with BMT physicians
- Balance disease risks with risks/benefits of Allogeneic BMT
  - Leukemia risk & remission status
  - Patient eligibility
    - HCTCI, psycho-social assessment, consent
  - Donor availability, caregiver strategy/support, insurance
- Strict national standards, recognized indications[1]
  - FACT [Foundation for Accreditation of Cellular Therapy], reviewed and accredited every3 years
  - Stem Cell Therapeutic Outcomes Database *

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[1]Majhail et al, BBMT 21:1863, 2015

* http://bloodcell.transplant.hrsa.gov

## Patient Support & Palliative Care in Acute Leukemia

- Hospice and palliative care underutilized in leukemia
  - Patients often require more intensive support even near the end of life
    - Antibiotics
    - Transfusion support
    - Inpatient care needed more often as AML progresses
  - Pain uncommon

  *Nevertheless – effort to liaise with Hospice
- Caregiver support - who cares for the caregiver?
  - Social work initiatives – care for children of patients
  - Incorporate routine caregiver follow-up after BMT, and Post-BMT/CAR-T support groups

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## Pearls of Wisdom

- Almost all patients benefit from therapy
  - Set individual patient goals
    - Treat with intensive therapy and for '*cure*' whenever possible
- Current treatments still not adequate for many
  - We must work together to advance AML survival and outcomes
    - Clinical trials
      - Genomic tumor boards
        - Molecularly-targeted therapy

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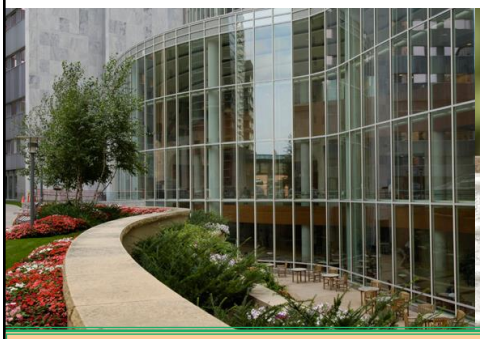

*"The best interest of the patient is the only interest to be considered, and in order that the sick may have the benefit of advancing knowledge, a union of forces is necessary."*

**1910: Dr. William J. Mayo**

Rush Medical College commencement address

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## Acknowledgments

NCI Comprehensive Cancer Center
A Cancer Center Designated by the National Cancer Institute


- Leukemia Clinical Team
  - Mayo Clinic Cancer Center

| | |
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Search '*leukemia*' at **www.mayoclinic.org**

## Q&A SESSION

Advances in Acute Myeloid Leukemia

- **Ask a question by phone:**
  - Press star (*) then the number 1 on your keypad.
- **Ask a question by web:**
  - Click “Ask a question”
  - Type your question
  - Click “Submit”

Due to time constraints, we can only take one question per person. Once you’ve asked your question, the operator will transfer you back into the audience line.

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## LLS EDUCATION & SUPPORT RESOURCES

- **Information Specialists**

  Master’s level oncology professionals, available to help cancer survivors navigate the best route from diagnosis through treatment, clinical trials and survivorship.
  - **EMAIL: infocenter@LLS.org**
  - **TOLL-FREE PHONE: 1-800-955-4572**
- **Free Education Booklets:**
  - **www.LLS.org/booklets**
- **Free Telephone/Web Programs:**
  - **www.LLS.org/programs**
- **Live, weekly Online Chats:**
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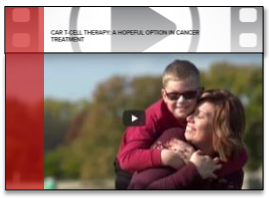
## LLS EDUCATION & SUPPORT RESOURCES




- **LLS Podcast, *The Bloodline with LLS***

  Listen in as experts and patients guide listeners in understanding diagnosis, treatment, and resources available to blood cancer patients: **www.thebloodline.org**

- **Education Videos**

  Free education videos about survivorship, treatment, disease updates and other topics: **www.LLS.org/educationvideos**

- **Patti Robinson Kaufmann First Connection Program**

  Peer-to-peer program that matches newly diagnosed patients and their families: **www.LLS.org/firstconnection**

- **Free Nutrition Consults**

  Telephone and email consultations with a Registered Dietitian: **www.LLS.org/nutrition**

- **What to Ask**

  Questions to ask your treatment team: **www.LLS.org/whattoask**

- **Other Support Resources**

  LLS Community, discussion boards, blogs, support groups, financial assistance and more: **www.LLS.org/support**