Introduction to Acute Leukemia

Brigham and Women's Hospital
Internal Medicine Residency
Boot Camp 2024

Marlise R. Luskin, MD MSCE
Senior Physician, Adult Leukemia Program, Dana-Farber Cancer Institute
Assistant Professor, Harvard Medical School

Dana-Farber Cancer Institute

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Disclosures

- Ad Board: Pfizer, Novartis, Jazz, KITE
- Research funding: AbbVie, Novartis

Me: Marlise R. Luskin MD, MSCE

- **Hometown** – Edina, Minnesota
- **Medical School** – University of Pennsylvania
- **IM Residency/Chief Resident** – BWH
- **Heme/Onc Fellowship** – U of Pennsylvania
- **Senior Physician** – Adult Leukemia Group, DFCI
- **What do I do?** – Clinician, clinical research, education

Case

49-year-old man develops fatigue and dyspnea on exertion.

He visits his PCP who conducts a cardiac evaluation (EKG, exercise stress test, unrevealing). Subsequently checks a CBC which reveals leukocytosis, anemia, and thrombocytopenia.

Referred to the BWH ED and admitted to Oncology C team.

Vitals: **T** 98.8 **HR** 83 **BP** 117/66 **SpO2** 99% on RA

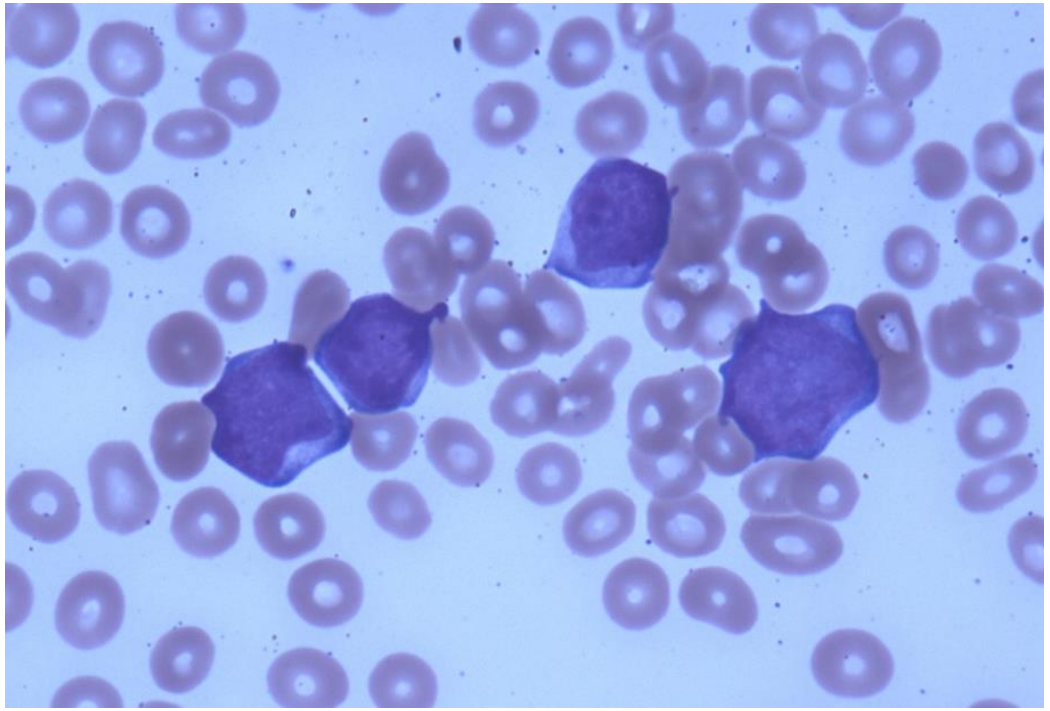
Case

WBC 6.7 Hgb 6.7 Plt 42

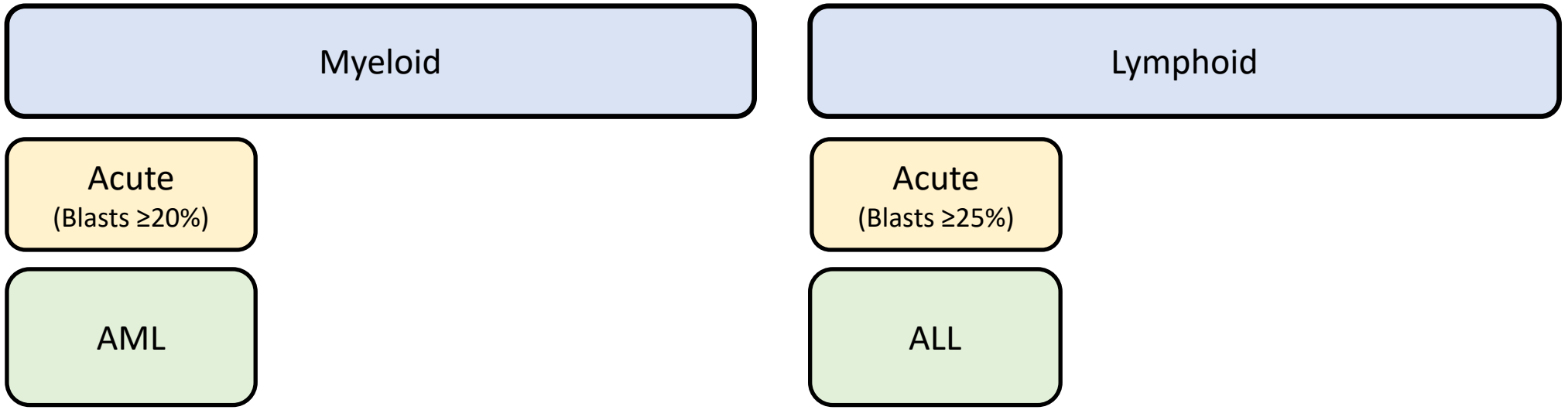
30% neutrophils, 23% lymphocytes,
26% monocytes, **17% others**

<u>Chemistries</u>
Electrolytes normal, Cr 1.1,
ALT 23, AST 33, Alk Phos 86, Tbili < 0.2

<u>Coags</u>
INR 1.2, fibrinogen 432, D-dimer 1494

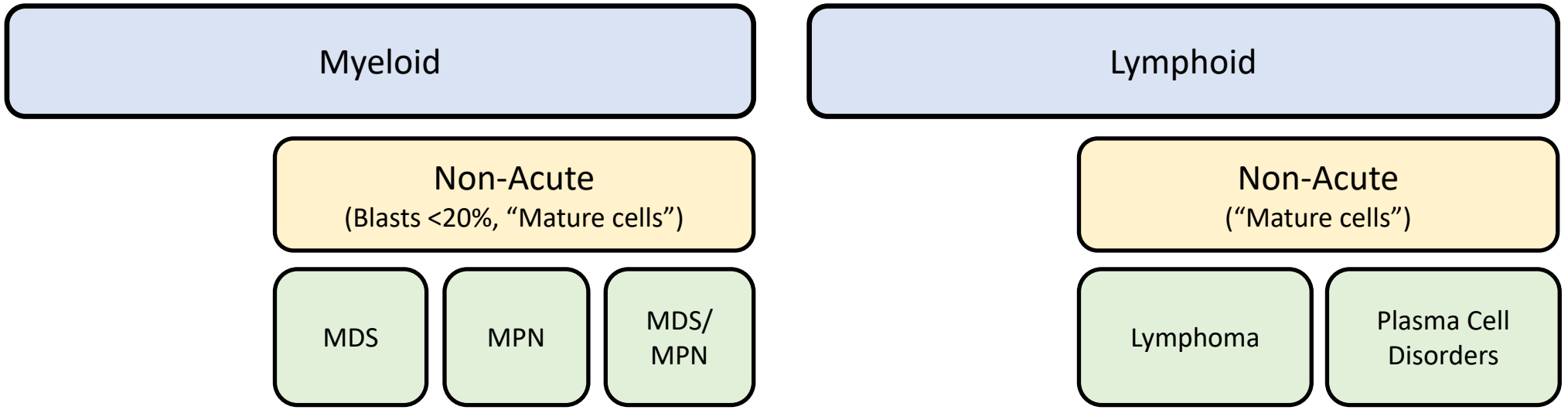


How I Think About Leukemia



- **"Acute" leukemias –** Proliferation of immature cells (blasts). Differentiation impaired.
- **"Chronic" myeloid leukemias, lymphomas, and plasma cell disorders –** Proliferation of differentiated myeloid and lymphoid cells; no or less impairment of differentiation.

How I Think About Leukemia



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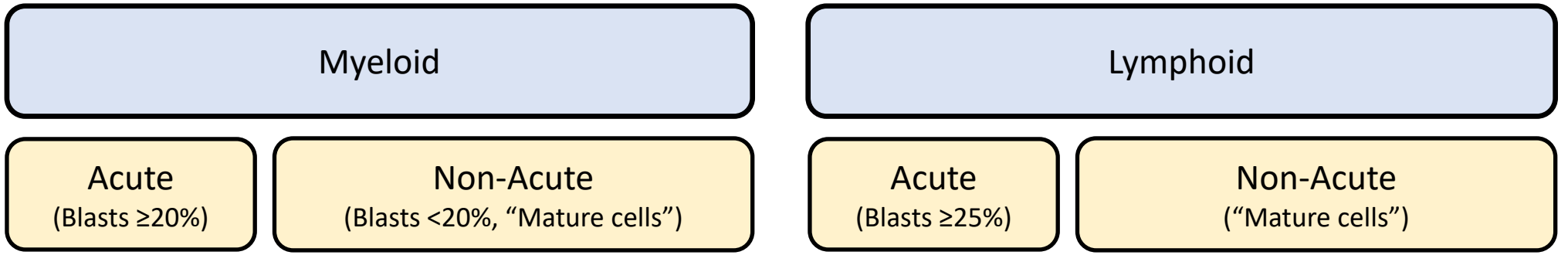

Lymphoblastic lymphoma (LBL) → acute leukemia that does not circulate.

Chronic lymphocytic leukemia (CLL), Hairy cell leukemia (HCL), LGL leukemia → mature *circulating* lymphoma

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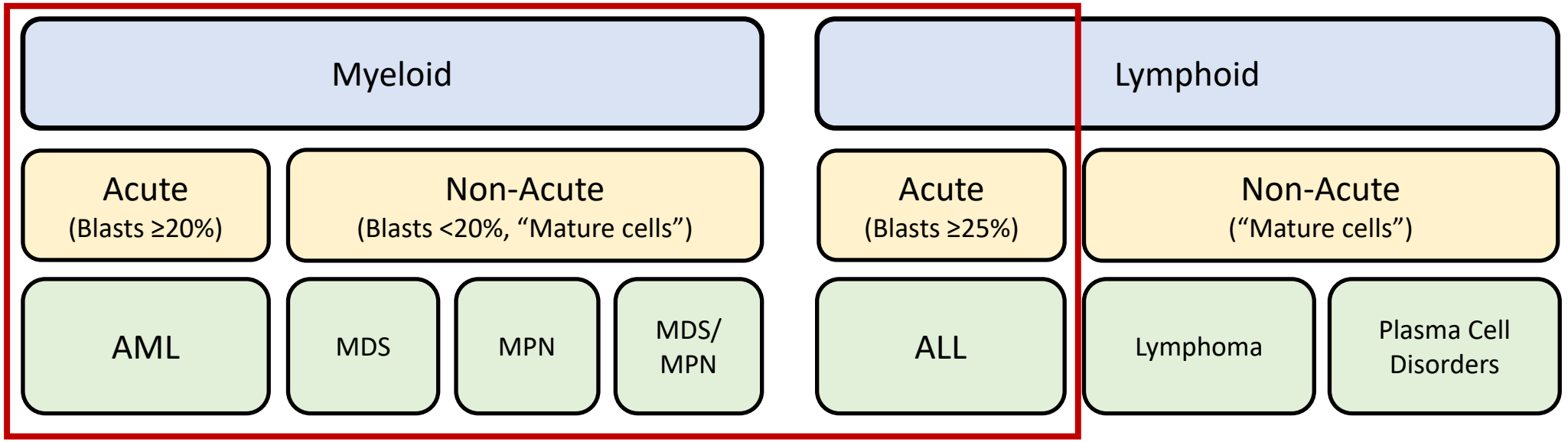
Note: Term "leukemia" may refer to any disease with a "circulating" component (i.e. lymphomas in "leukemic" phase).
Note: Term "lymphoma" may refer to a disease that accumulates in lymphoid structures (i.e. lymphoblastic lymphoma).

What I Treat



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Others!! What are they?

- **Are the "others" blasts? (i.e. concern for acute leukemia)**
  - Review smear! Blasts: large nuclei, nucleoli, open chromatin, scant cytoplasm (high N:C ratio). Look for Auer rods.
  - *Clues ("situational awareness")*: Abnormalities in other cell lineages (cytopenias – neutropenia, anemia, thrombocytopenia; **monocytosis**).

- **Lineage of blasts (i.e. lymphoid versus myeloid**)
  - Myeloid – Auer rods (confirmatory), "monocytic appearing".
  - Lymphoid – Smaller blasts, very little cytoplasm.
  - *Confirmation*: Flow cytometry, cytochemistry, immunohistochemistry – markers to identify developmental stage and lineage (myeloid vs lymphoid).

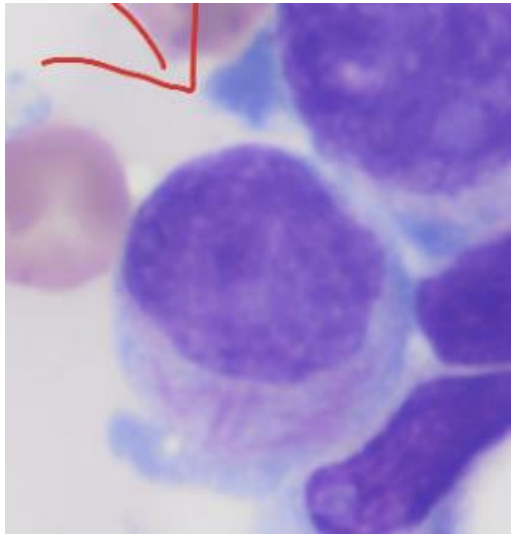
- **Leukemia fake outs**: Atypical lymphs (mononucleosis); lymphoma in "leukemic phase."

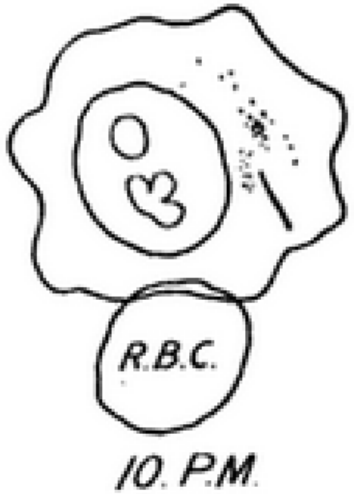
Auer rods

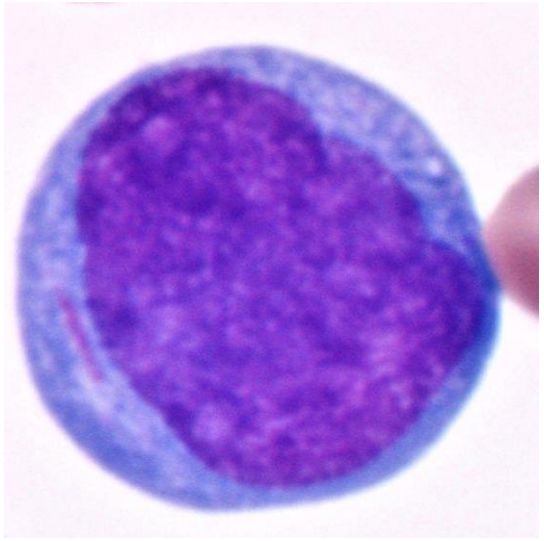
SOME HITHERTO UNDESCRIBED STRUCTURES FOUND IN THE LARGE LYMPHOCYTES OF A CASE OF ACUTE LEUKÆMIA.

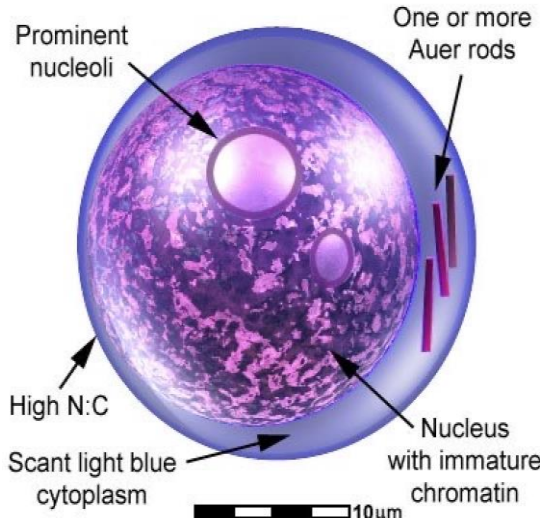
By John Auer, M.D.,

FORMER HOUSE OFFICER OF THE JOHNS HOPKINS HOSPITAL; FELLOW OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH.



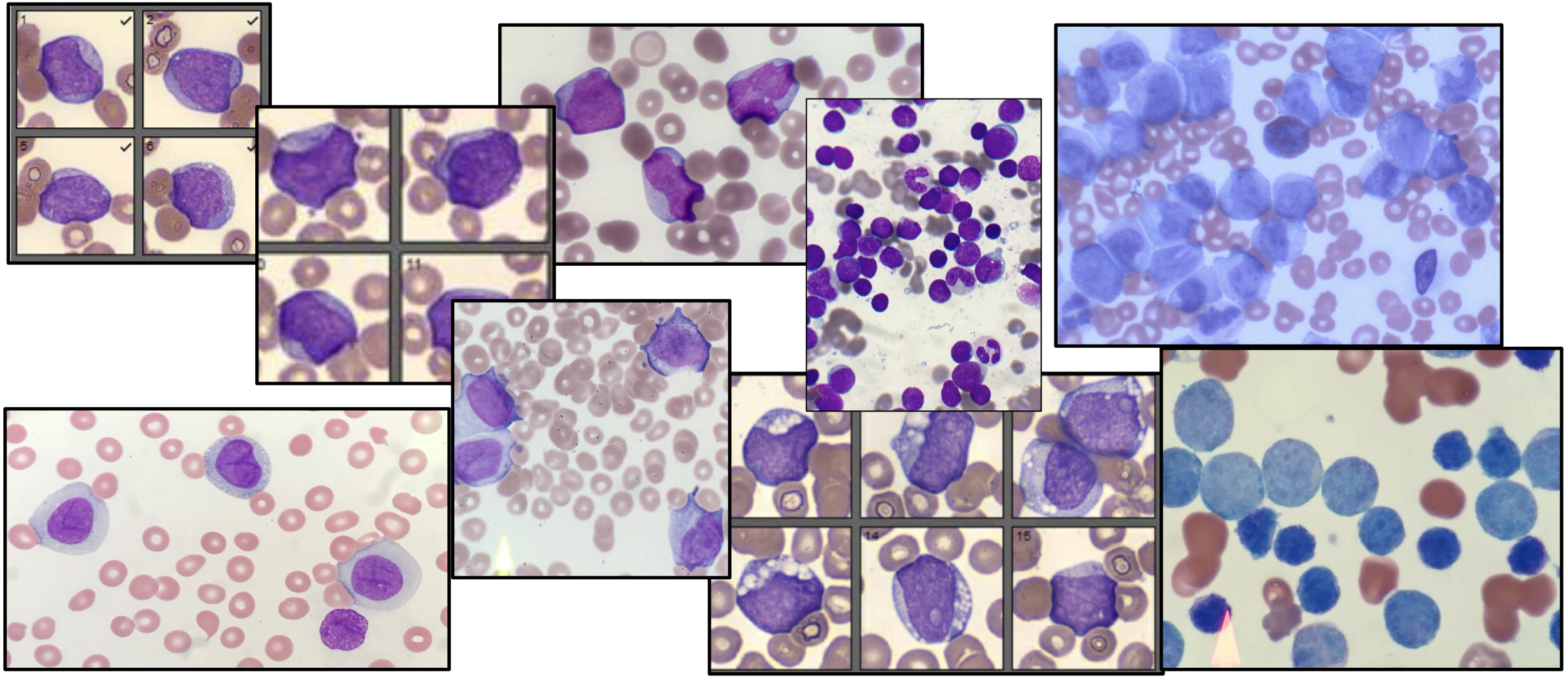




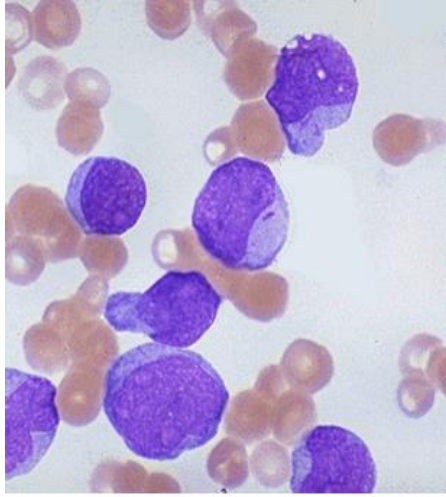


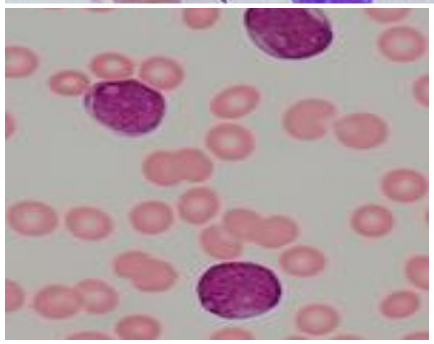
- Rod shaped crystalline structures from primary granules of myeloid blasts.
- Auer rods = confirm myeloid, and confirm malignancy..
- John Auer (1875-1948) who described and illustrated them in 1906 in a patient admitted at Hopkins under William Osler. (He thought they were lymphoblasts!).

Acute Leukemia – Lets Have a Blast! …



Blast Immunophenotype





- **Immaturity**: CD34 (myeloid or lymphoid), TdT (lymphoid).
  - Not all blasts will express.
- **Acute myeloid leukemia**:
  - MPO
  - Myeloid: CD13, CD33, CD117
  - Monocytic: NSE, lysozyme, CD11, CD14, CD64
- **Acute lymphoid leukemia:**
  - B-cell: CD10, CD19, CD20, CD22, (sIg negative)
  - T-cell: CD2, CD3, CD7

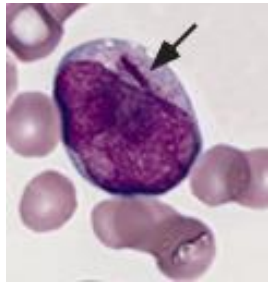
Acute Leukemia:
Are blasts ≥ 20% on blood, aspirate, core, other tissue?

Pearl: Can see "aberrant" expression of lineage markers.

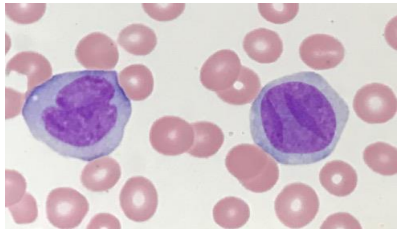
Lineage specific markers:
MPO, or **2+ myeloid/ monocytic markers** for **AML**
CD3 for **T-ALL**
CD19 + additional (CD10, CD22, CD79a, PAX5) for **B-ALL**

Acute Myeloid Leukemia (AML) – Diagnosis

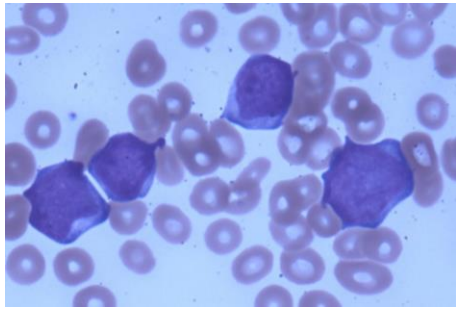
- **Myeloid blasts ≥ 20% of total cells of bone marrow aspirate or blood.**
  - Disease MAY be found outside medullary space.
    - *Myeloid sarcoma = chloroma = granulocytic sarcoma = extramedullary AML.*
  - t(8;21), inv(16), t(15;17), *NPM1* = think AML regardless of blast %.



- **Blasts can be identified morphologically (previous slide).**

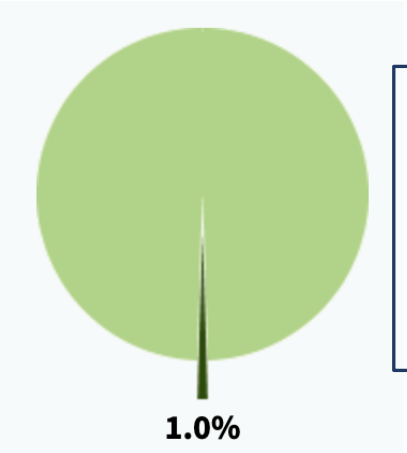


- **Lineage (myeloid vs lymphoid) assignment requires additional tests: cytochemistry, immunophenotyping (flow cytometry, immunohistochemistry), unless Auer rods are present (myeloid).**
  - Blasts identified by "immaturity" markers (i.e. CD34, CD117).
  - MPO expression confirms myeloid but is not universally positive.
  - Most cases: CD34, HLA-DR, CD117, CD13, and CD33.
    - Monocytic: CD34-; APL (and APL-like/*NPM1*): CD34-, HLA-DR-.

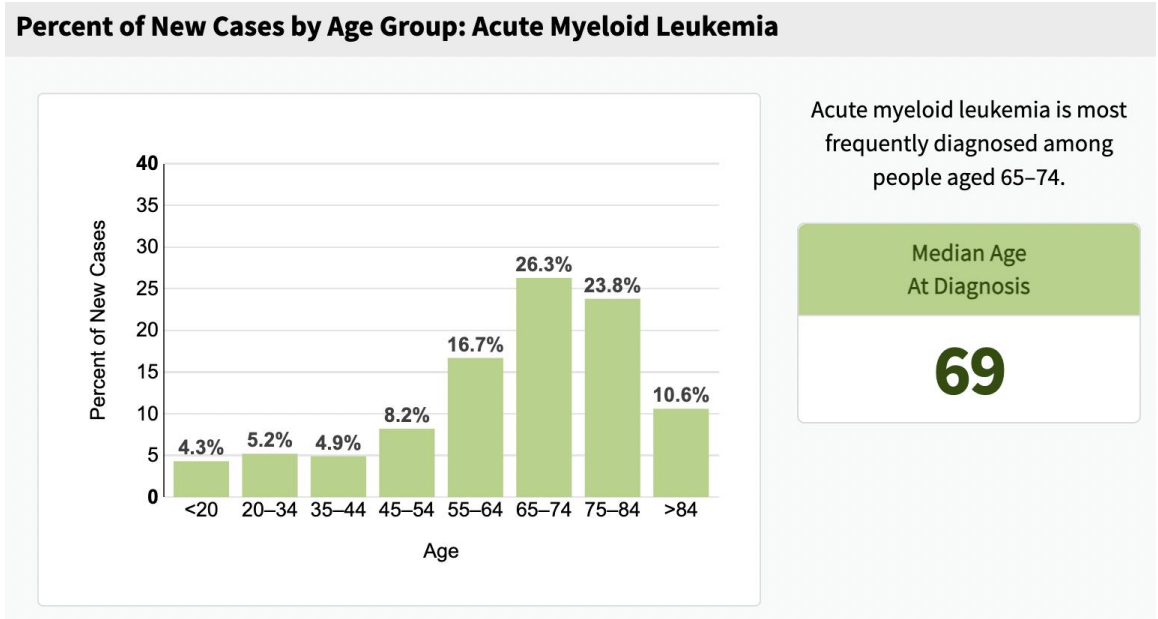


AML – Epidemiology and Demographics

Estimated New Cases in 2024	20,800
% of All New Cancer Cases	1.0%



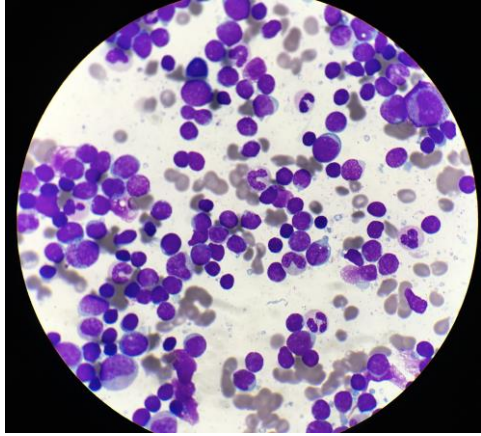
BUT these patients spend a lot of time in the hospital…it will feel like much more than 1% at BWH.



Risk factors: Age, exposure to radiation/chemotherapy, antecedent myeloid neoplasm, bone marrow failure disorders (inherited, immune mediated).

https://seer.cancer.gov/statfacts/html/amyl.html

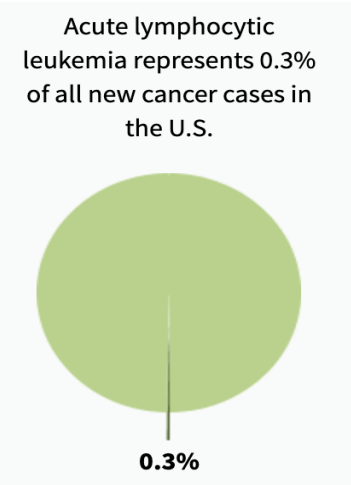
Acute Lymphoblastic Leukemia (ALL) – Diagnosis



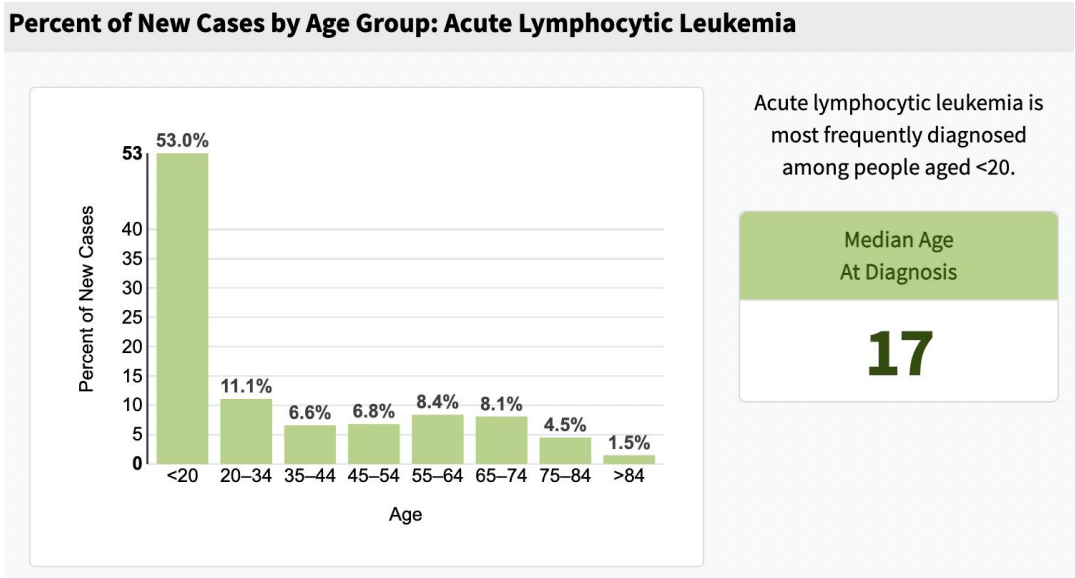
- **Aggressive hematologic neoplasm of B- or T-lymphoblasts**
  - Acute lymphoblastic leukemia (ALL) /Lymphoblastic lymphoma (LBL)
- **Clinical Presentation**
  - Cytopenias (bone marrow failure), adenopathy, mediastinal mass (T-cell), hepatosplenomegaly, central nervous system.
  - Constitutional symptoms (fatigue, fevers, sweats, weight loss, bone pain).
- **Diagnosis: Morphology (blasts) and immunophenotype (flow cytometry/IHC) to determine lymphoid (B or T) and maturity stage.** *Aggressive lymphoma can mimic.*
  - B-lymphoblasts: CD10, CD19, CD20 (some), and CD22; Ig negative
  - T-lymphoblasts: cCD3 and other T cell antigens.

ALL – Epidemiology and Demographics

Estimated New Cases in 2024	6,550
% of All New Cancer Cases	0.3%



BUT these patients spend a lot of time in the hospital…it will feel like much more than 0.3% at BWH.



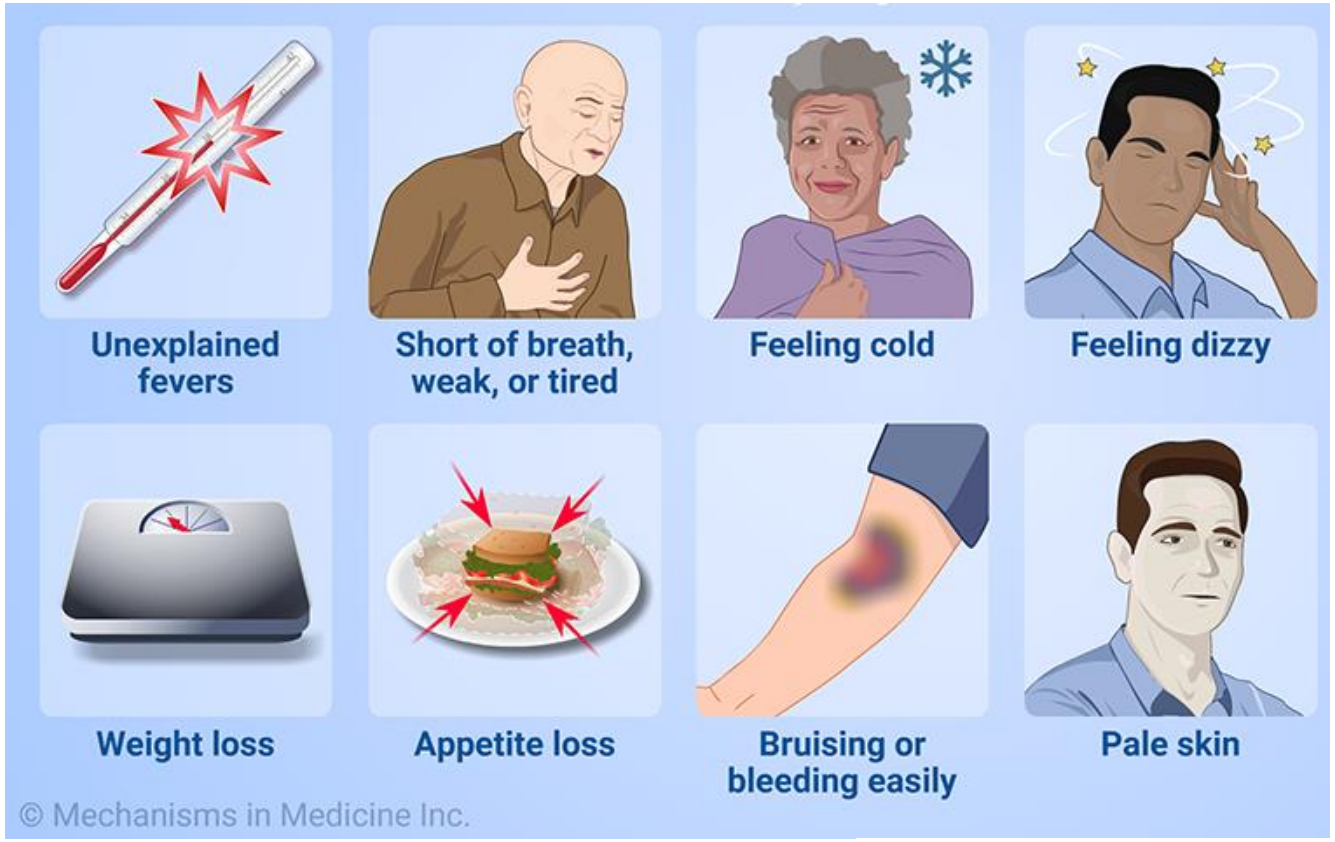
- Most common leukemia in children.
- Adults comprise ~50% of ALL diagnoses, but majority of deaths.
- Risk factors: Down syndrome, prior chemo/radiation (myeloma).
- In adults, ~1/3 are Philadelphia-chromosome positive

https://seer.cancer.gov/statfacts/html/alyl.html

Acute Leukemia - Diagnosis

Acute **L**eukemia

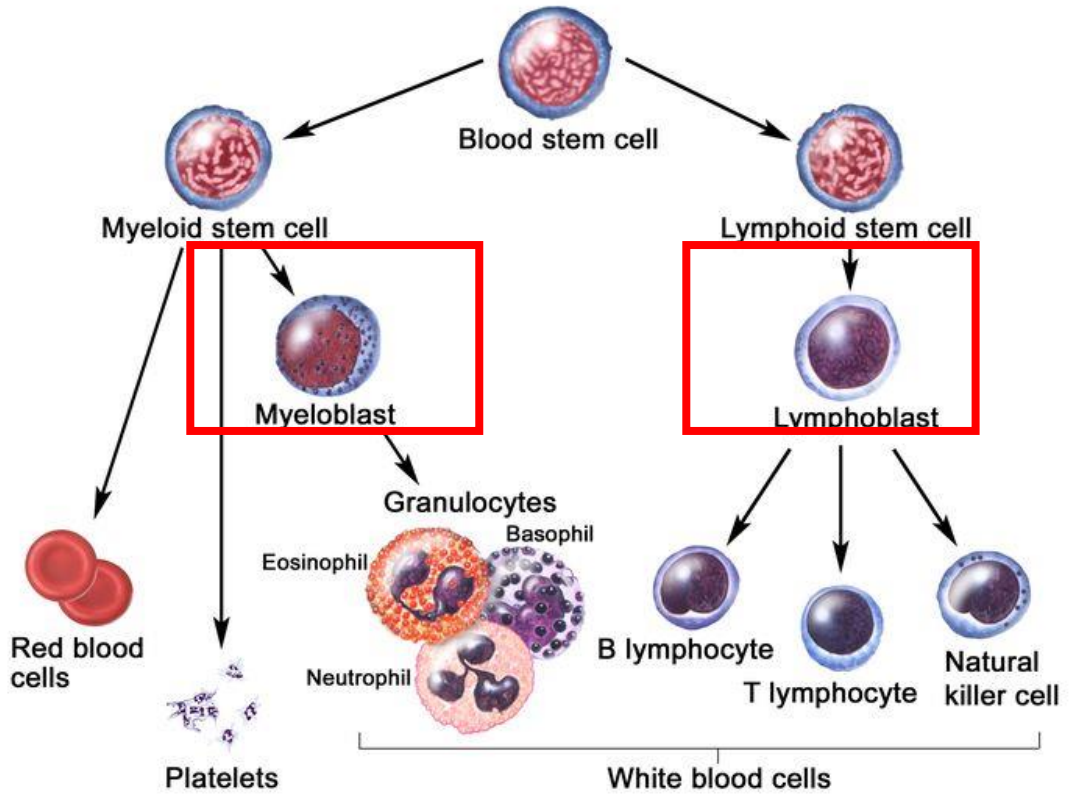
Develops over a few weeks



Acute Leukemia - Diagnosis

Acute **L**eukemia

Increased number of immature ”baby” cells called blasts:

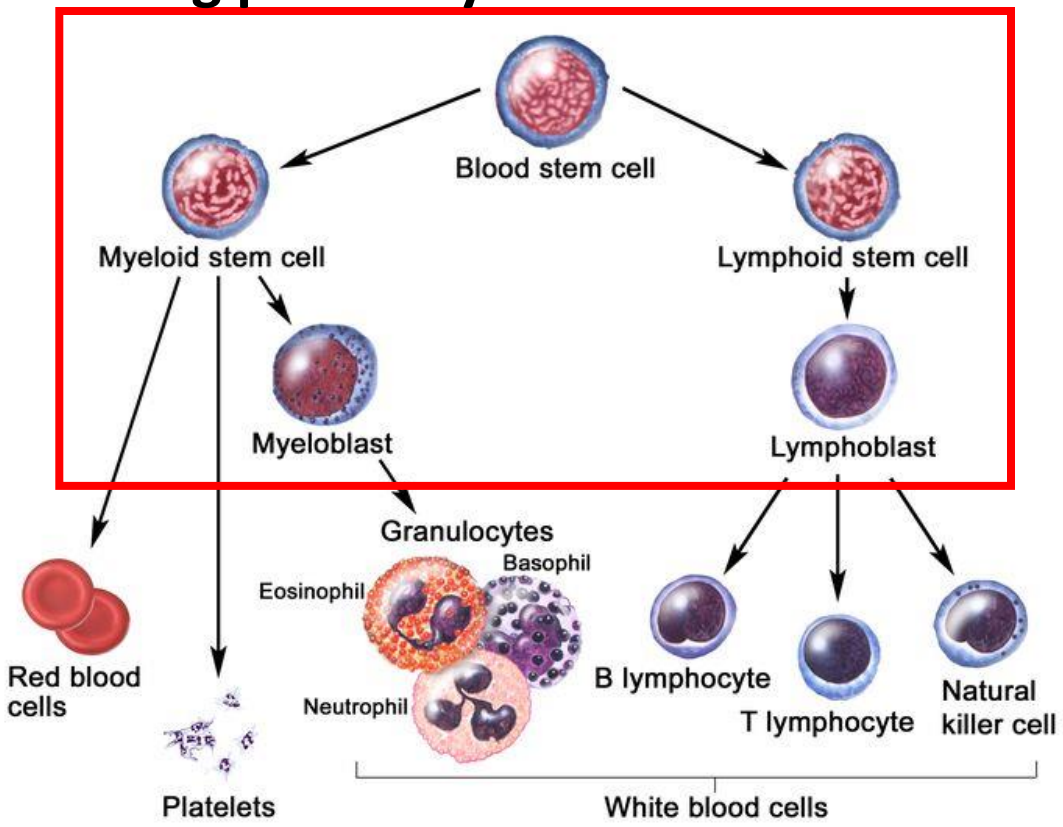


National Cancer Institute, 2007

Acute Leukemia - Diagnosis

Acute Leukemia

Taking place in your bone marrow:



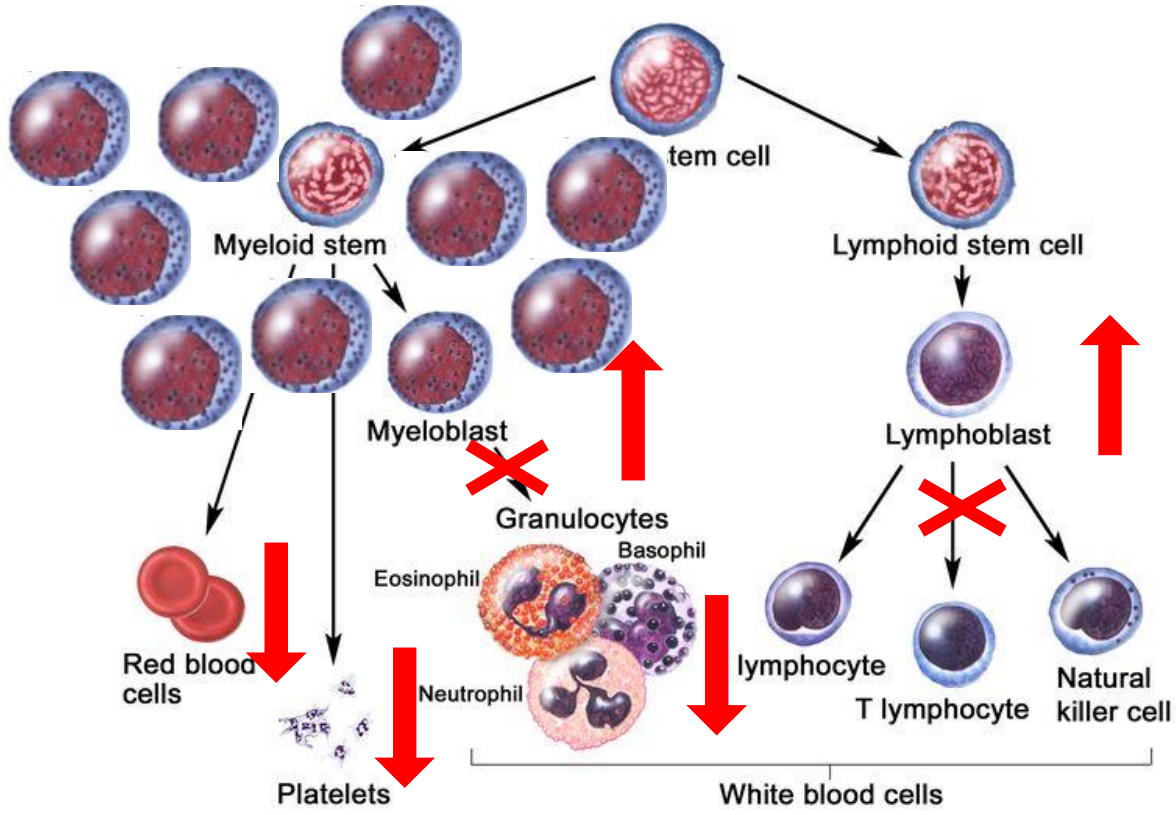
National Cancer Institute, 2007

Acute Leukemia - Diagnosis

Acute **L**eukemia

The problem: Too many blasts (>20%)

↓ White blood cells = ↑ Infections
↓ Red blood cells = ↑ Fatigue
↓ Platelets = ↑ Bleeding/Bruising



National Cancer Institute, 2007

Leukemia Differential Diagnosis…

Acute leukemias (with ≥ 20% blasts) – blood, aspirate, or core biopsy

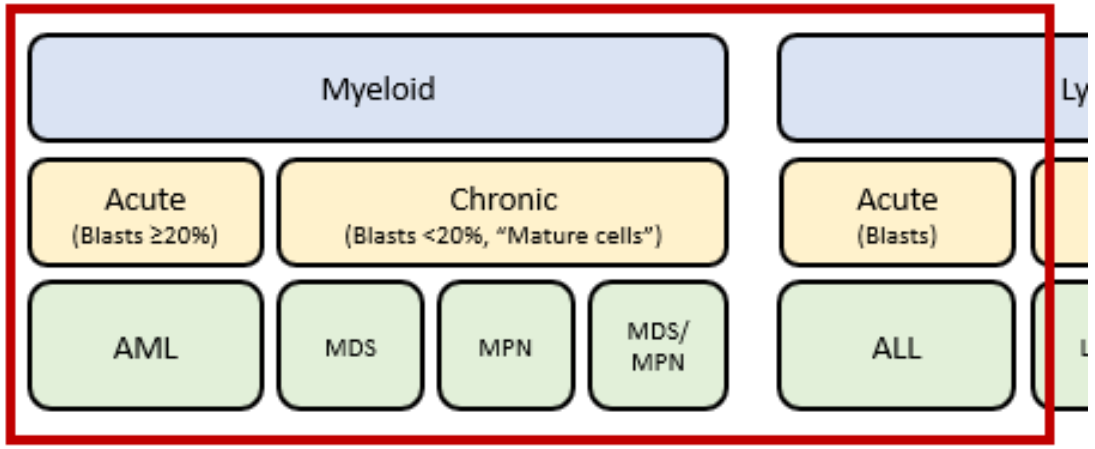
- Acute myeloid leukemia (AML)
- Acute lymphoblastic leukemia (ALL)
- Mixed phenotype acute leukemia (MPAL)
- CML in blast crisis (myeloid or lymphoid)

“Mature” myeloid neoplasms (<20% myeloblasts)

- Myelodysplastic syndrome
- Myeloproliferative neoplasms (Ph+ CML, Ph-)
- MDS/MPNs (e.g. CMML)

Aplastic anemia

Circulating “blastoid“ lymphomas



Back to the Case: AML Confirmed

Flow of the PB confirmed lineage – did not finalize diagnosis (<20% blasts)

Peripheral blood:

Immature cells (**15% of total events** by CD33 and CD13 expression) that is positive for CD45(dim), HLA-DR, CD123, CD38, **myeloid markers CD13, CD33, CD117** (large subset), CD15(dim), and is negative for CD34, CD56, and other monocytic, B and T lymphoid markers, consistent with **MYELOBLASTS**."

Bone Marrow:

Aspirate**:** Blasts**: 33%;** rare Auer rods

Core**:** Markedly hypercellular (<5% fat), about **50%** of the cellularity is composed of large blasts dispersed chromatin, prominent nucleoli, occurring in large clusters.

Bone marrow aspirate / biopsy will allow further characterization of extent of disease (% blasts).

Leukemia and IM Residents

- **Opportunity to be part of the initial diagnostic process and clinical decision making of a new cancer diagnosis.**
  - YOU could make the diagnosis – go look at the blood smear! *Do you see blasts? Did you find an Auer rod?*
- You will need to use your knowledge of cardiology, pulmonary, infectious disease, endocrinology, rheumatology, critical care, GI/hepatology, nephrology, palliative care, geriatrics, etc. etc. on our service! *Leukemia = internal medicine with a twist.*
- Prelims too! Anesthesia, dermatology, radiation oncology, etc. **You will see these patients in your future practice!**
- You are the first doctors our patients meet in the middle of the night, early in the morning, and when the road gets tough – *they need you, and we need you!*

A New Leuk! Outline of the Admission

- **Oncologic emergencies** – What complications of disease need urgent or emergent management?

- **Preparation for chemotherapy** – What assessments need to be completed to prepare patient for chemotherapy, and help determine treatment?
  - Attending/fellow: Disease specific (disease subtype/"targetable" features)
  - Resident: Patient specific (organ function, performance status, etc.).

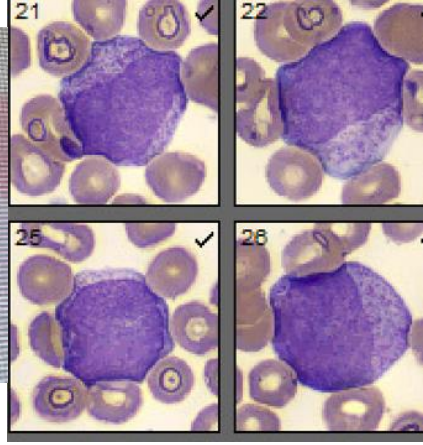
- **Diagnostics** – What information is needed to confirm diagnosis and determine a treatment plan (guided by attending/fellow)?

Oncologic Emergencies

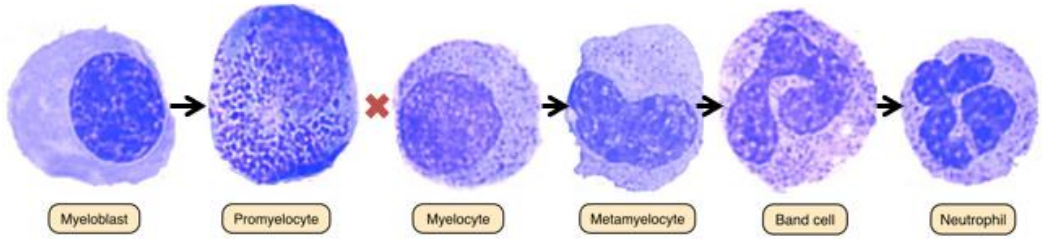
Neutropenic fever/infection
Hyperleukocytosis/leukostasis
TLS
Cytopenias
DIC
Is there a reason to suspect APL?

Zuckerman et al. *Blood* 2012;120:1993-2002

Acute Promyelocytic Leukemia

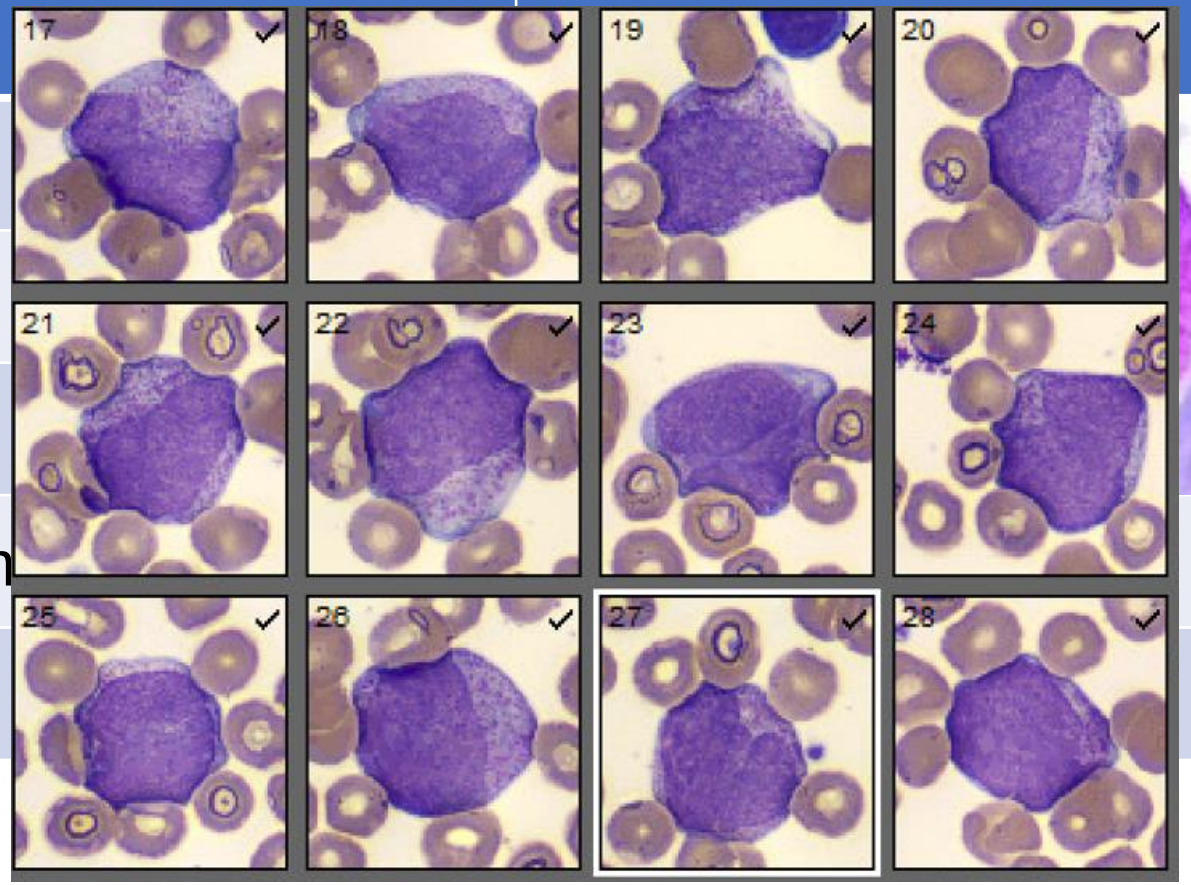


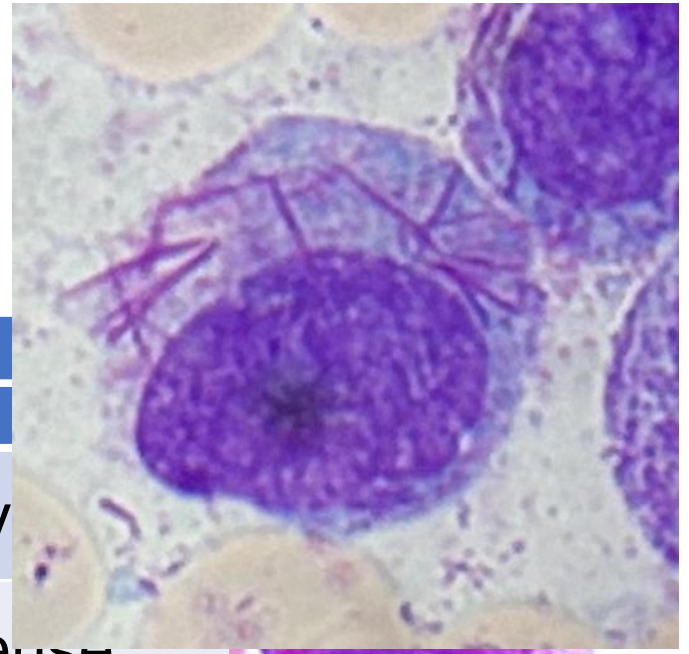
- RARE – MUST NOT MISS – DIAGNOSIS.
- AML subtype (~10%) defined by presence of t(15;17) translocation.
- Features: Younger (but not always), evidence of coagulopathy (DIC), pancytopenia, blasts: promyelocytes, bilobed nuclei, Auer rods, granules.
- HIGH EARLY MORTALITY – From coagulopathy (CNS hemorrhage).
- HIGH CURE RATES – If survive acute phase.
- Immunophenotype: CD34 neg, HLA-DR neg, CD33 pos.
- Confirm diagnosis: Cytogenetics t(15;17); RT-PCR *PML-RARA*.
- Treat:
  - Stabilize – transfuse (platelets, cryo, FFP), **all-trans retinoic acid (ATRA).**
  - Definitive – ATRA, arsenic, chemotherapy, gemtuzumab ozogamicin.



Abedin S, Altman JK. *Hematology Am Soc Hematol Educ Program* 2016;10-15;
Park et al. *Blood* 2011;118:1248-54

Acute Promyelocytic Leukemia





Onc Emergencies: Hyperleukocytosis and Leukostasis

- **Hyperleukocytosis:** lab abnormality that increases risk for →
- **Leukostasis :** clinical (confusion, hypoxemia, cardiac ischemia, AKI).
  - Leukostasis more likely when blast count >50-100K.
  - More common in myeloid/monocytic lineage (AML>>ALL).
  - Rare in ”chronic” myeloid (CML, MPN) and “lymphoid” leukemias (ALL, CLL).

- Monitor/assess**:** Trend WBC, clinical exam.
- Treat**:** Hydroxyurea (cytoreduction), consider leukopheresis.
- Prevent **:** Avoid/limit PRBC transfusions until WBC trends down.

Aqui N, O’Doherty U. *Hematology Am Soc Hematol Educ Program* 2014; 457-60

Preparation for Chemo / First Night Tips

- **Family Contacts** – Do confirm family contact info, put in Epic. Formal HCP? Decision-maker?
- **Pre-menopausal women** – Pregnancy test (can add onto serum).
- **Transfusions** – "Standard" oncology parameters; keep platelets higher if: DIC, active bleeding, very high fevers, hyperleukocytosis.
- **DVT prophylaxis** – Generally hold until decisions (may need procedures – lines, marrows, etc.).
- **Careful Medical History/Co-Morbidity Screening.**
  - **TTE, EKG, hepatitis exposure** (hepatitis B sAg, sAb, c Ab IgG or total, Hepatitis C Ab, HIV)
  - Medical problems, medications, allergies, names of key outside providers.
  - Code status: IF NOT Full, DOCUMENT reason/conversation.
- **Prophylaxis:** Mouth care (chlorhexidine and nystatin/clotrimazole troche) and acyclovir (400 mg TID)/valacyclovir (400mg BID). Allopurinol 300 mg daily for TLS prophylaxis.
- **Line:** Do not order until discuss with primary onc. If make NPO, discuss early whether necessary.
- **Support:** Social work consult. Nutrition and PT.
- *Sometimes challenging to complete all this overnight; carefully pass off unfinished work.*

What does the patient know?

Tread lightly.

Open ended questions –

- What have you heard from the doctors at the other hospital or in the ED?
- What is your understanding of why you were admitted/transferred to BWH?
- Who is supporting you and hearing information along with you?

Tailor your response to what the patient knows, what you know, etc.
Acknowledge uncertainty, fear, and questions – reassure that they are in the right place to begin addressing questions over the coming days.
DOCUMENT/PASS OFF patient understanding.

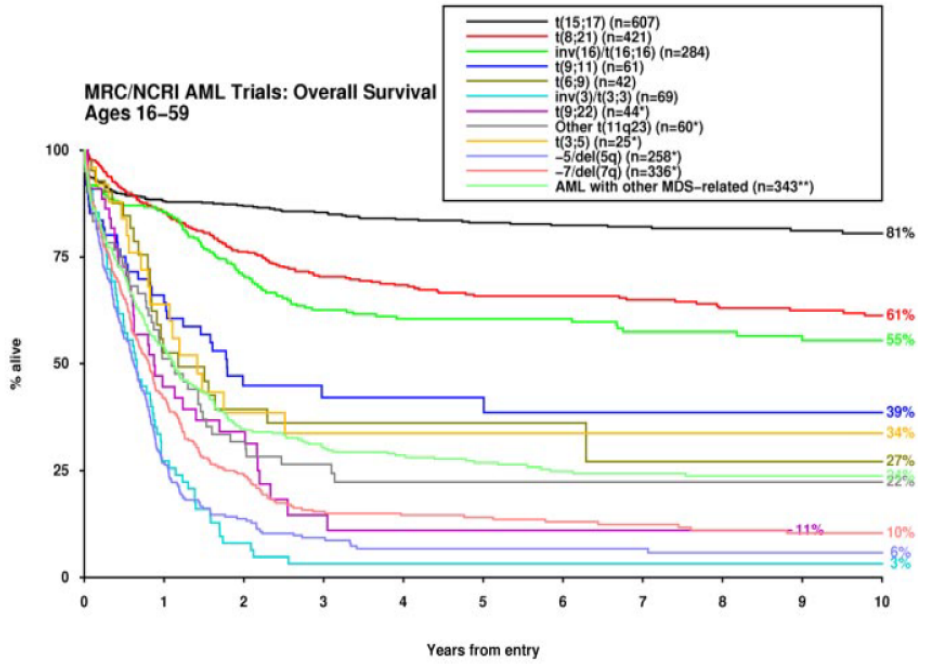
Acute Leukemia – Approach to Therapy

- **Induction Goal → Remission**
  - Reduce disease to morphologically undetectable levels → complete remission (CR). No blasts in blood. Fewer than 5% blasts in marrow.
  - Ideally with recovery of “normal” blood counts.

- **Consolidation Therapy Goal → Lengthen CR / Survival**
  - **Cure:** Reduce residual disease to prevent relapse (“cure”).
  - **Prolong remission/delay progression:** Maintain disease at a minimal residual disease state for as long as possible (extend survival, no cure).

AML – Prognostic Features

- **Age:** Older
- **Disease "context" (clinical ontogeny)**
  - Favorable: De novo
  - Unfavorable:
    - "Therapy-related" AML (prior chemotherapy/XRT).
    - "Secondary" AML (prior MDS/MPN).
- **Genetics (chromosomes and gene level mutations)**
  - Favorable:
    - *Chromosomes*: APL [t(15;17)];"core binding factor" AML: t(8;21); inversion 16.
    - *Molecular*: *NPM1* mutant without *FLT3*-ITD, bZIP in-frame mutated *CEBPA*
  - Unfavorable:
    - *Chromosomes*: Complex (3+), monosomal, 5 and 7 abnormality, inv 3*/MECOM*-r, *KMT2A-r*, etc.
    - *Gene*: *TP53*; "secondary-type" (*ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2*)

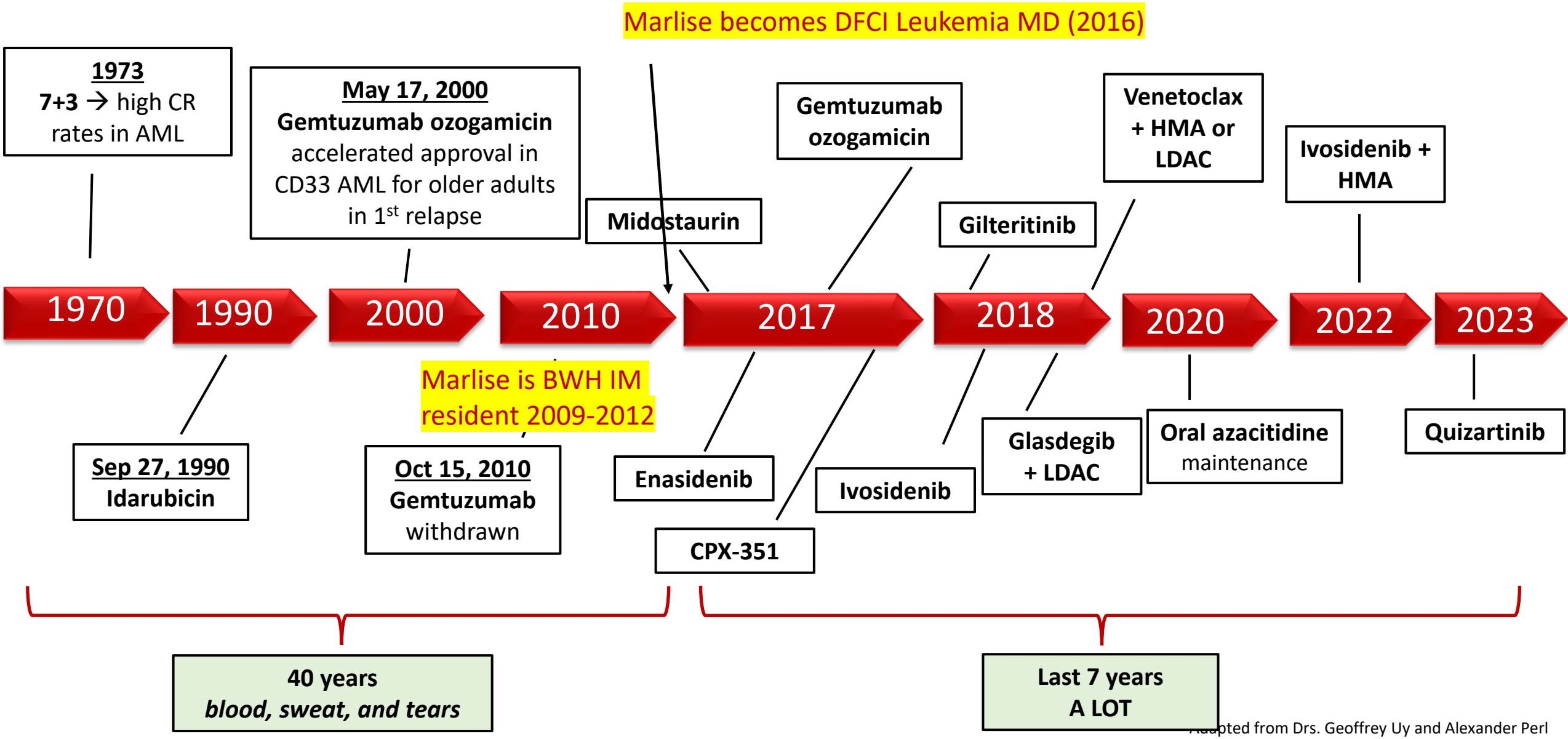


Grimwade et al. *Blood* 2010;116:354-65; Dohner et al. *Blood* 2022;140:1345-77

AML – Choice of Therapy

- **Determine "goal" of therapy** – curative or "palliative" intent.
- **Understand tolerability and likelihood of benefit of therapy.**
  - Tolerability
    - Patient: age, fitness/performance status, comorbidity
  - Expected response
    - Age
    - Ontogeny (clinical or genetic): therapy-related, secondary to MDS or MPN
    - Genetics (chromosomes and gene level mutations).
      - Predict responsiveness to chemotherapy.
      - Identify "targetable" mutations.
- Patient preferences and personal goals!

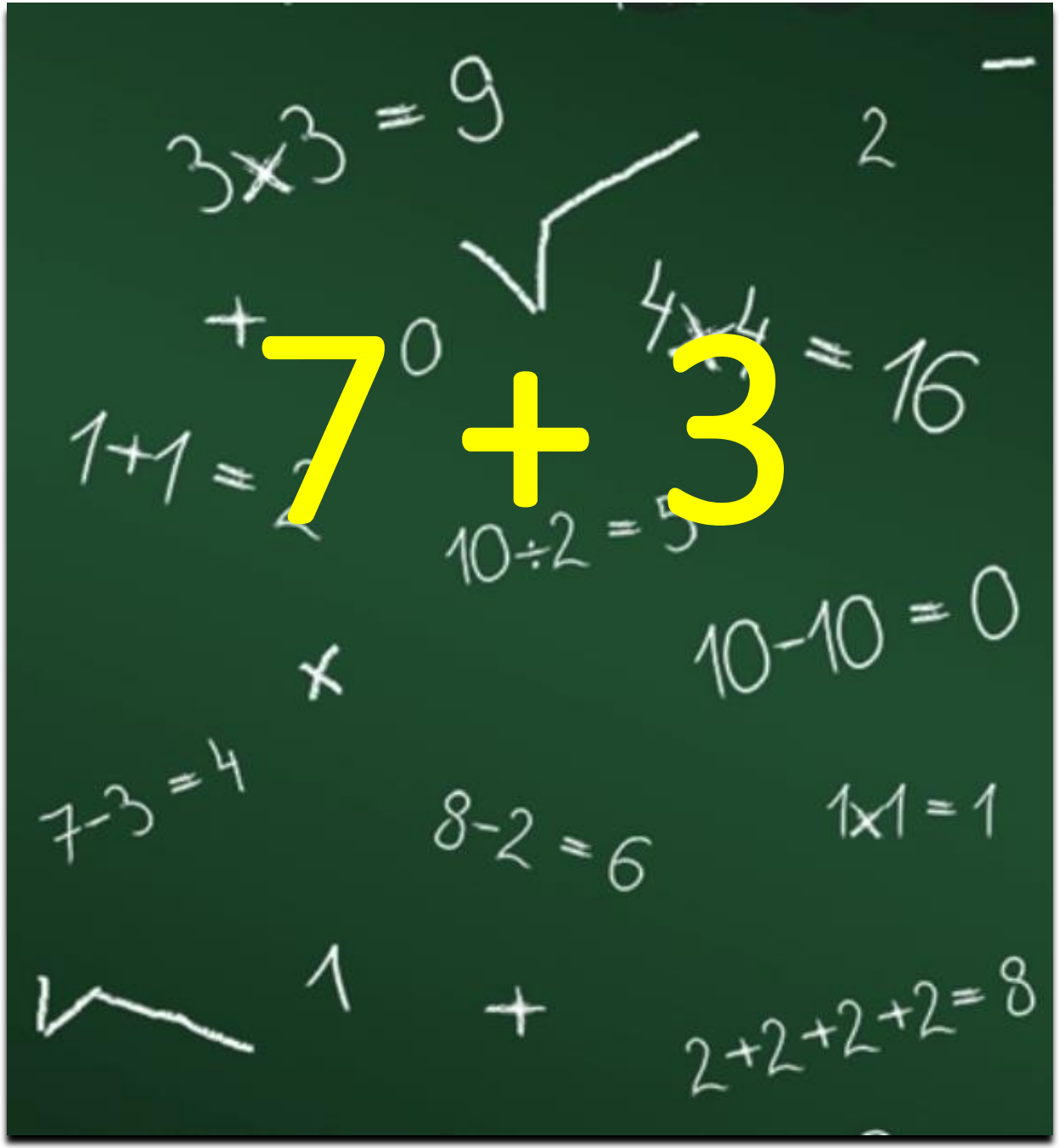
(Many) **New** FDA Approved Agents for AML



Adapted from Drs. Geoffrey Uy and Alexander Perl

Elementary!

That was then…



AML – This is NOW (2024). **CHOICE!**

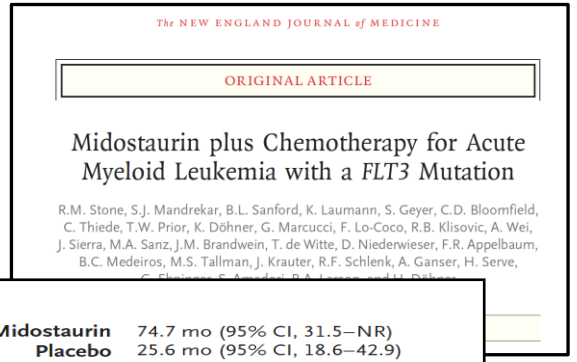
	Age < 60	**Age 60-75 "fit older"**	**Age >75 or "unfit"**
Intent	Curative (Regularly)	Curative (Sometimes)	Palliative
Initial Treatment (Induction)	daunorubicin + cytarabine (7+3) *+/-* midostaurin or quizartinib (*if FLT3*) +/- gemtuzumab ozogamicin (*if* CBF, ? *NPM1*)	7+3 +/- mido, quiz, GO CPX-351 (*if* secondary, therapy-related) HMA + venetoclax?	HMA + venetoclax HMA + ivosidenib Ivosidenib HMA (Enasidenib) Supportive care Hospice
Consolidation	Favorable: Cytarabine (HiDAC) Non-Favorable: Transplant FLT3 inhibitors	Chemo Cytarabine Oral azacitidine Transplant FLT3 inhibitors	

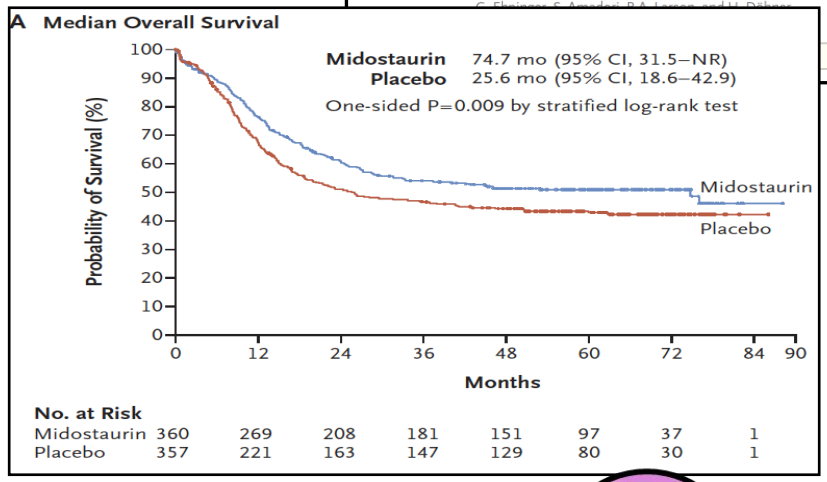
AML – Choice of Initial Therapy

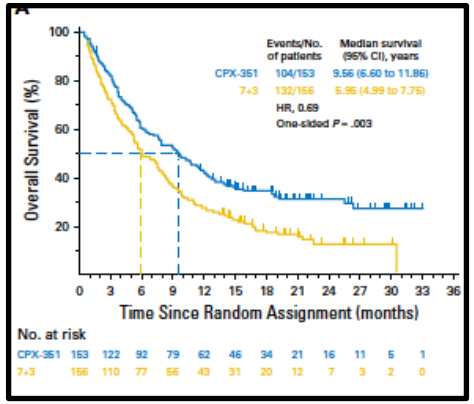
- **"Intensive" cytotoxic chemotherapy –** *fit, expected to be chemo-responsive, curative goal*
  - Daunorubicin and cytarabine ("7+3") – traditional AML induction.
  - CPX-351 (Vyxeos) – liposomal daunorubicin/cytarabine – for "high risk" AML *(prior chemo/radiation, prior MDS/MPN, high-risk karyotype).*
- **"Less-intensive" chemotherapy –** *older, unfit, not expected to be chemo-responsive, palliative goal*
  - Hypomethylating agents (decitabine, azacitidine).
  - HMAs plus venetoclax (BCL2 inhibitor), or ivosidenib (IDH1 inhibitor).
- **Targeted therapy**
  - FLT3 inhibitors (midostaurin, quizartinib) – in combination with 7+3.
  - IDH1 inhibitor (ivosidenib).
  - *Of note, gilteritinib (FLT3 inhibitor) and enasidenib (IDH2 inhibitor) only approved for relapsed disease.*

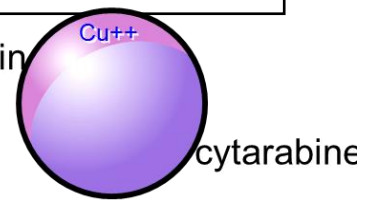
AML – 7+3 Basics

- **Daunorubicin (3 days IV push) plus cytarabine (7-day CI).**
- **Standard of care since the 1970s.**
  - Anthracycline intensification (60-90 mg/m^2 better than 45 mg/m^2 x 3) improves outcomes.
  - Increasing dose of cytarabine, adding 3rd cytotoxic chemotherapy no benefit.
- **FLT3 positive AML:** Add midostaurin, a FLT3 inhibitor, to 7+3 based on RATIFY trial (SHOUT OUT to Dr. STONE!); or – quizartinib (QuANTUM-First)
- **High Risk AML:** CPX-351 (Vyxeos) is a liposomal formulation of 7+3 at a fixed 5:1 molar ratio.
- **CBF, *NPM1?* AML:** Benefit from adding gemtuzumab ozogamicin









Fernandez et al. *N Eng J Med* 2009;361:1249-59; Lowenberg et al. *N Eng J Med* 2009;361:1235-48; Luskin et al. *Blood* 2016;127:1551-58 Stone et al. *N Eng J Med* 2017;377:454-64; Lancet et al. *J Clin Oncol* 2018;36:2684-92; Hills et al. *Lancet Oncol* 2014;15:986-96; Castaigne et al. *Lancet* 2012;379:1508-16, Erba et al. *Lancet* 2023;401:1571-83

AML – 7+3 Basics

- **First week:** Give 7 days of chemotherapy.
- **At day 14/15:** Check BMBx to check for chemoablation → if not chemoablated *(i.e. >5% blasts on cellularity of >20%)* → more chemo (”5+2” or “7+3” re-induction).
- **At count recovery (21-28 days from chemo):** Recovery marrow → assess remission status.

~70% of pts <60 years achieve CR with 1-2 cycles of induction.

~25% get re-induced (50% of which result in CRs).

Fernandez et al. *N Eng J Med* 2009;361:1249-59; Lowenberg *et al. N Eng J Med* 2009; 361: 1235-48; Luskin et al. *Blood* 2016; 127:1551-58
Stone et al. *N Eng J Med* 2017;377:454-64; Lancet et al. *J Clin Oncol* 2018;36:2684-92

AML – Hypomethylating Agents **+ Venetoclax**
VIALE-A

- Untreated patients, ineligible for standard induction therapy (median age 76 years).
  - Older Age (75 yrs or older).
  - Comorbid conditions
- Randomized, placebo controlled, endpoint OS.
- **Median OS:** 14.7 vs 9.6 months (HR 0.66)
- **CR:** 36.7 vs 17.9%
- **CR/CRi:** 66.4 vs 28.3%
- **AEs:** More cytopenias, F & N, and infection.

(Not yet compared to 7+3 in younger, fit adults, Randomized trial underway).

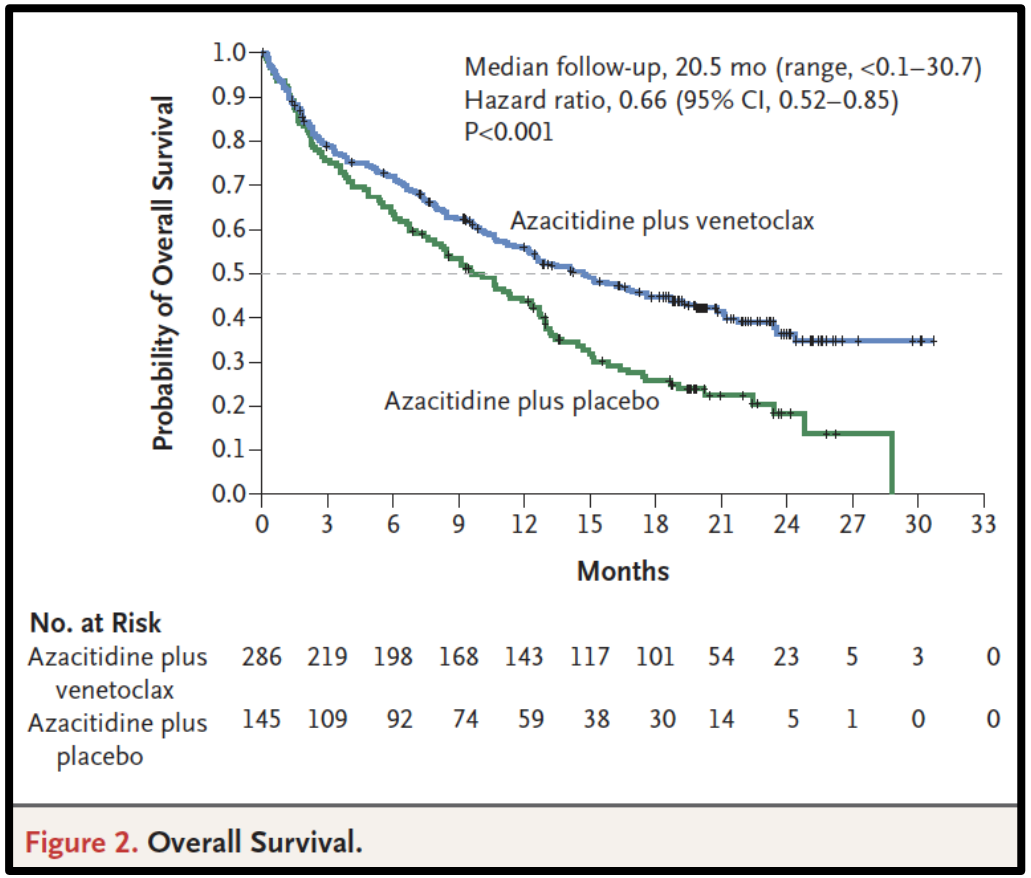


Figure 2. **Overall Survival.**

DiNardo et al. *N Eng J Med* 2020; 383:617-29 (Shout out to Dr. Garcia!)

AML – Induction Summary

- **Age <70-75 years and ”fit” enough to tolerate intensive induction?**
  - Yes: Daunorubicin + cytarabine (7+3), trial with intensive chemotherapy
  - No: HMA (decitabine/azacitidine) +/- venetoclax, +/- ivosidenib trial w/ HMA
- **Presence of a *FLT3*-ITD or *FLT3*-TKD mutation**
  - Add midostaurin (FLT3 inhibitor) to 7+3, trial with novel FLT3 inhibitors
- **Core binding factor leukemia**
  - Add gemtuzumab ozogamicin
- **Therapy-related or AML-MRC (known prior MDS, MDS-type cytogenetics).**
  - Consider CPX-351 (Vyxeos)
- **Presence of a *TP53* mutation?**
  - Consider HMA-based therapy.

Always Try to Enroll on Clinical Trial!

Case: Results, Initial Treatment, and Outcome

Diagnosed with **Acute Myeloid Leukemia**

Karyotype: Normal

Molecular: *NPM1* mutated, *NRAS* mutated, *FLT3*-ITD wildtype

Induced with daunorubicin and cytarabine (7+3). Nadir marrow was chemoablated.

Recovered counts ~day 24 and was discharged home.

Remission marrow assessment at follow up (~day 30) confirmed complete remission (CR), MRD negative.

AML – Consolidation Approach

- Allogeneic transplant is more effective anti-leukemia therapy.
- Allogeneic transplant has higher risk of morbidity and mortality than consolidation chemotherapy.
- Approach: Transplant patients when…
  - Benefit in cure rate with transplant felt to be significant enough to outweigh
  - Risk of toxicity/death from treatment.

AML – Choice of Consolidation

Curative intent

- Further cycles of “cytotoxic” chemotherapy (high dose-cytarabine)
- **Allogeneic transplant** - “Fit” patients with “high-risk” AML (Benefit / Risk)
  - Age 60 or greater
  - Intermediate or high-risk genetics
  - “Secondary” AML (prior MDS, MPN, MDS/MPN) or “therapy-related” AML
  - Primary refractory AML
  - *Approach: Transplant patients for whom improvement in cure rate outweighs risk of morbidity/mortality*

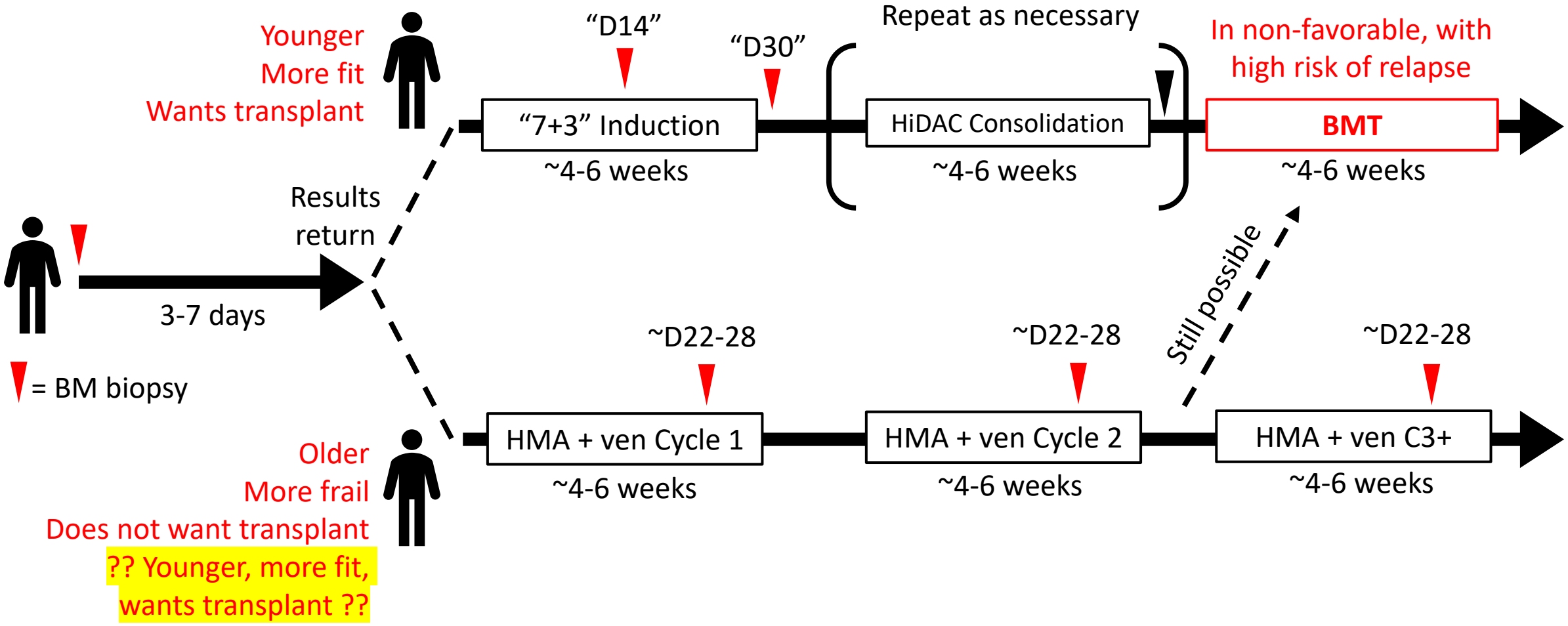
Non-curative intent

- Continue hypomethylating agent therapy or targeted therapy.

Hematopoietic Stem Cell Transplantation

- **Allogeneic:** from another person (not your own cells)
- **Concept:**
  - Chemotherapy before transplant to make room for donor cells
    - Myeloablative (ablates marrow, younger patients, more acute toxicities)
    - Non-myeloablative (older, comorbidities): rely on graft-versus-leukemia
  - Donor cells engraft and create new blood system (with new immune system) → graft versus leukemia (GvL).
- **Risks:**
  - Chemotherapy toxicities
  - Immune suppression: At risk for opportunistic infection
  - Graft versus host disease: Liver, skin, gastrointestinal
    - Steroids, escalate/add other immune suppressive medications.

How do we treat AML? Summary



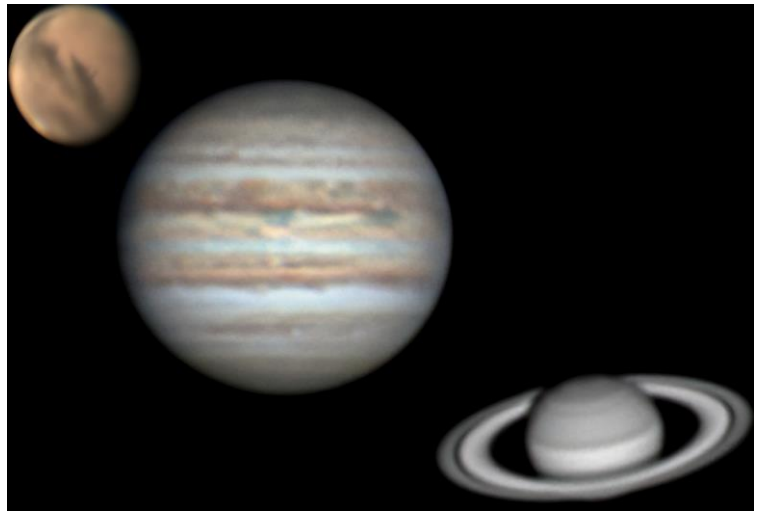
Case Follow-Up

Treated with 7+3 induction, achieved CR, then 4 cycles of high dose cytarabine consolidation chemotherapy (HiDAC).

Tolerated well. Admitted for GNR sepsis during cycle 4, recovered.

Working full time, raising teenage daughter, doing telescope photography.



ALL – A Pediatric Oncology Success Story

- **1948:** Sidney Farber described 5 children who responded (temporarily) to the folic acid antagonist **aminopterin.**

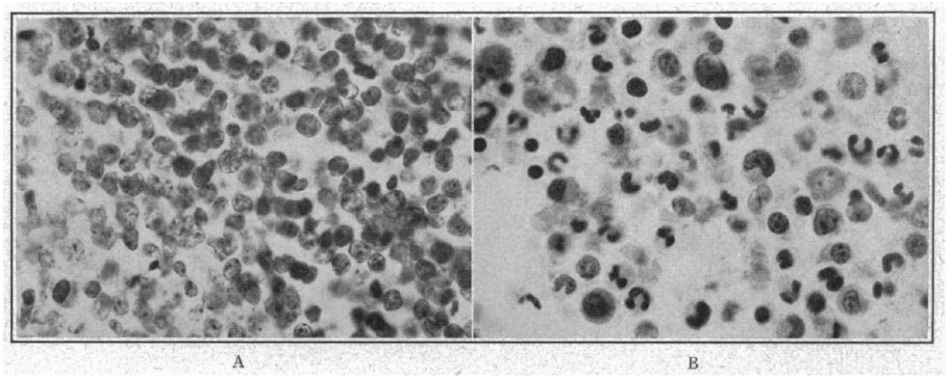
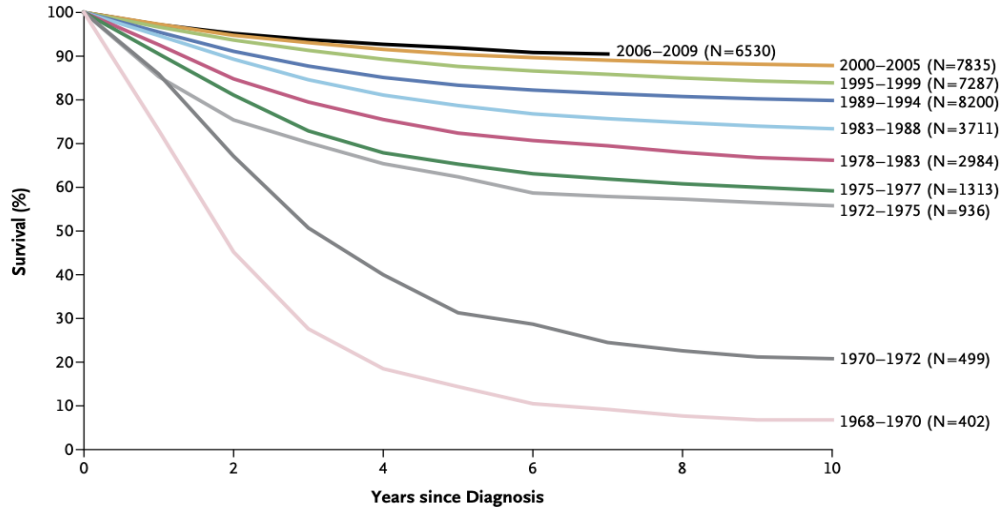


FIGURE 4. *Photomicrographs of the Sternal Bone Marrow in Case 3, Showing Giemsa-Stained Section on January 29, (A) and April 3 (B), 1948 (x1000).*

Note that the microscopical field is composed mainly of blast forms characteristic of leukemia (cell type undetermined) in the early section (A) and that a marked shift to mature cell forms, particularly of the polymorphonuclear series, with no leukemic cells, had occurred on the later examination (B).

OS

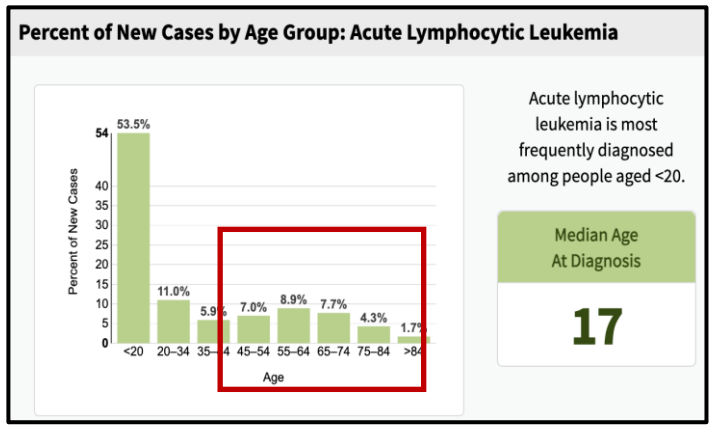


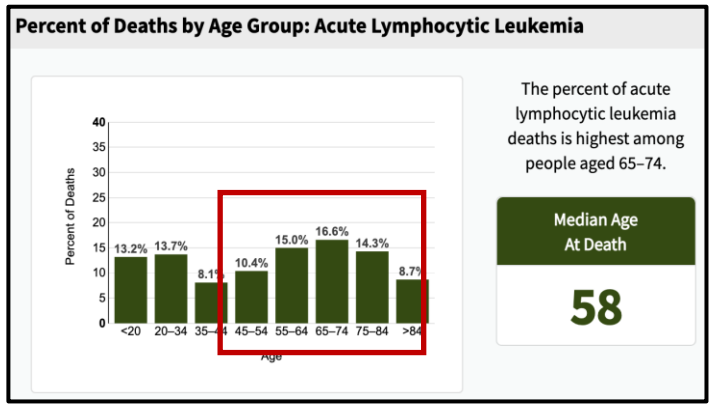
CCG and COG trials, 1968-2009

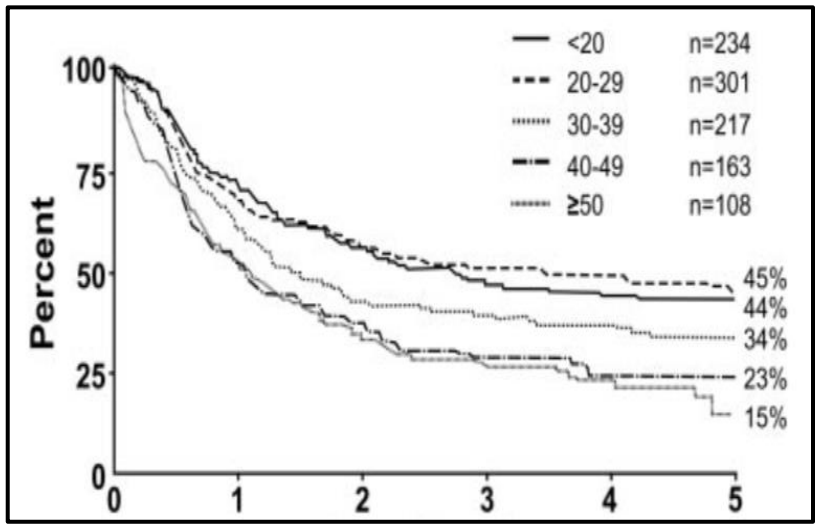
- **2023:** 75 years later, most children cured.
- How? Intensive, multi-agent, asparaginase-based, chemotherapy regimens, developed cooperatively and iteratively (with risk-based intensification).

Farber et al. *N Eng J Med* 1948;238:787-93; Pui et al. *J Clin Oncol* 2015;33:2938-48; Hunger and Mulligan *N Eng J Med* 2015;373:1541-52

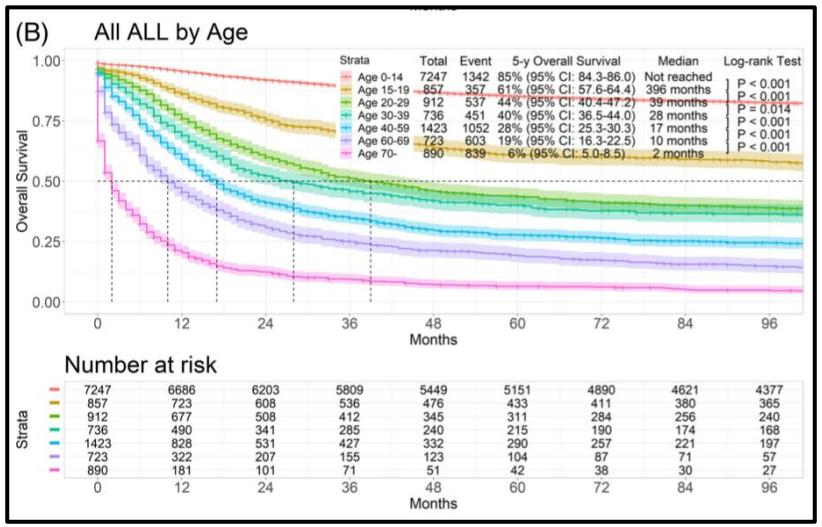
ALL – In Adult, More Work to be Done







ECOG 2993



SEER Analysis 1980-2017

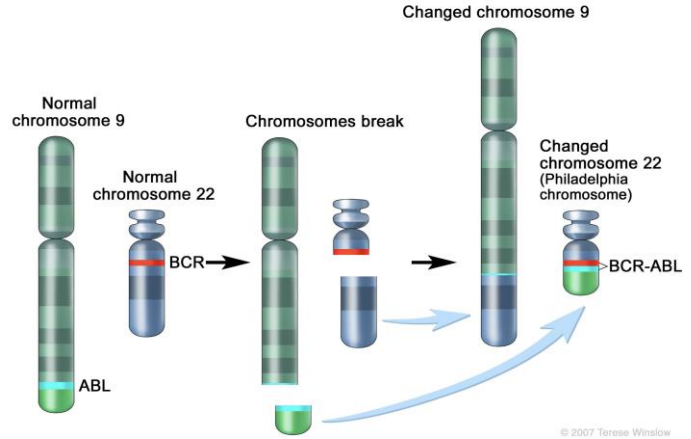
- Outcomes worsen with increasing age.
- Particularly impacting older adults.
- Higher risk disease plus poor tolerability of conventional chemotherapy.

https://seer.cancer.gov/statfacts/html/alyl.html; Rowe et al. *Blood* 2005;106:3760-67; Gokbuget N *Hematology Am Soc Hematol Educ Program* 2016;573-79; Luskin MR *Hematology Am Soc Hematol Educ Program* 2021; 1:7-14; Sasaki et al. *Am J Hematol* 2021;96:650-58

ALL – Framework for Treatment

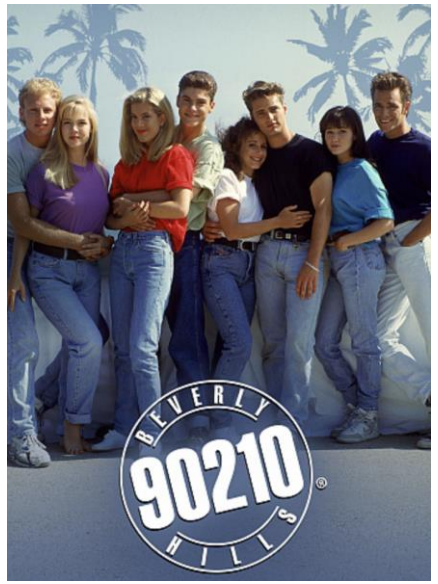
Therapeutic decisions guided by:

1) Philadelphia-chromosome status



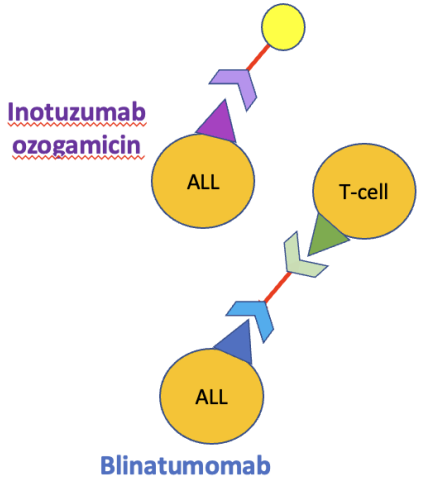
2) Age/fitness for chemotherapy

- AYA: Pediatric-inspired
- Adult: Standard intensity
- Older/comorbidities: Less intense, *novel investigational approaches showing promise*



ALL – Improvements on the Horizon

- For young adults, intensive, pediatric-inspired regimens (asparaginase-based).
- Novel immunotherapy (blinatumomab, inotuzumab ozogamicin) adding to, or replacing, conventional chemotherapy.
- For Ph+ ALL, novel TKIs and novel immunotherapies (blinatumomab).
- For relapsed patient, CAR-T therapy.
- MRD-guided treatment.



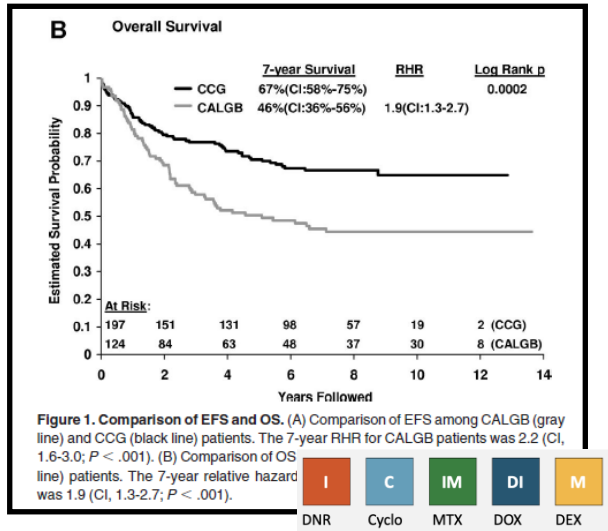
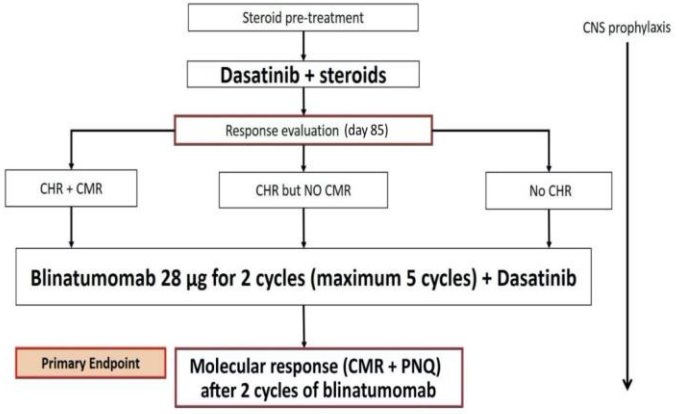
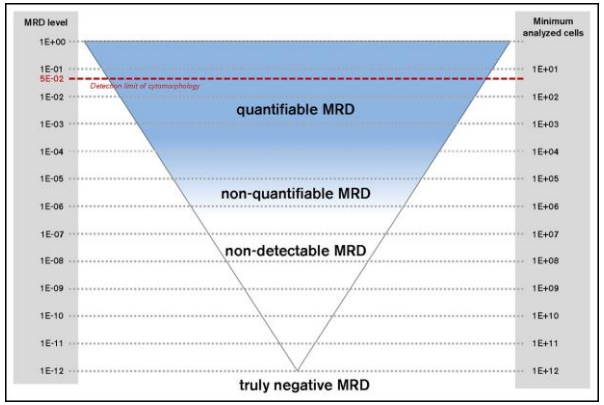


Figure 1. Comparison of EFS and OS. (A) Comparison of EFS among CALGB (gray line) and CCG (black line) patients. The 7-year RHR for CALGB patients was 2.2 (CI, 1.6-3.0; $P < .001$). (B) Comparison of OS line) patients. The 7-year relative hazard was 1.9 (CI, 1.3-2.7; $P < .001$).

I	C	IM	DI	M
DNR	Cyclo	MTX	DOX	DEX
VCR	VCR	VCR	Cyclo	VCR
Pred	Dex	Peg-ASP	Dex	6MP
Peg-Asp	Peg-Asp	IT-MTX	Peg-Asp	MTX
IT-MTX	Ara-C		Ara-C	IT-MTX
IT-AraC	6MP		6-TG	
	IT-MTX		IT-MTX	





Stock et al. *Blood.* 2008;112:1646-54; Stock et al. *Blood* 2019;133:1548-59; Kantarjian et al. *N Engl J Med* 2017;376:836-47; Kantarjian et al. *N Engl J Med* 2016;375:740-53; Bruggemann and Kotrova *Blood Adv* 2017;25:2456-66; Berry et al *JAMA Oncol* 2017;3:e170580; Foa et al. *N Eng J Med* 2020;383:1613-23

Acute Leukemia Conclusions

- Acute leukemias are aggressive cancers of immature hematopoietic cells ("blasts"). Acute leukemia can be myeloid (AML) or lymphoid (ALL).

- Initial management of acute leukemia focuses.
  - Identifying and controlling "oncologic emergencies."
  - Evaluating patient comorbidities, social context, and personal goals to determine therapy.

- Prognosis and treatment of acute leukemia related to
  - Patient age and comorbidities
  - Disease ontogeny (de novo vs secondary vs therapy-related) and genetic features
  - Availability of effective and/or targeted therapy.

- Patients with acute leukemia need excellent internal medicine.

DFCI Adult Leukemia Team

- Richard M. Stone MD
- Daniel J. DeAngelo MD, PhD
- Martha Wadleigh MD
- Jacqueline S. Garcia MD
- Eric S. Winer MD
- Rahul Vedula MD
- Maximilian Stahl MD
- Gregory Abel MD
- Lachelle Weeks MD
- Christopher Reilly MD
- Evan Chen MD
- Andrew Hantel MD
- Virginia Volpe MD
- Shai Shimony MD

- Andrew Lane MD PhD
- R. Coleman Lindsley MD PhD
- Zuzana Tothova MD PhD
- Mark Murakami MD
- Anthony Letai MD PhD
- Ilene Galinsky NP
- Mary Gerard PA-C
- Theresa Nguyen NP
- Kelly Ling PA-C
- Patrice Osullivan NP
- Ryan Osborn PA

Find a field of medicine you love, a patient population you love caring for, and a team you love being a part of!