Leukemias: Review for Boards and General Practice

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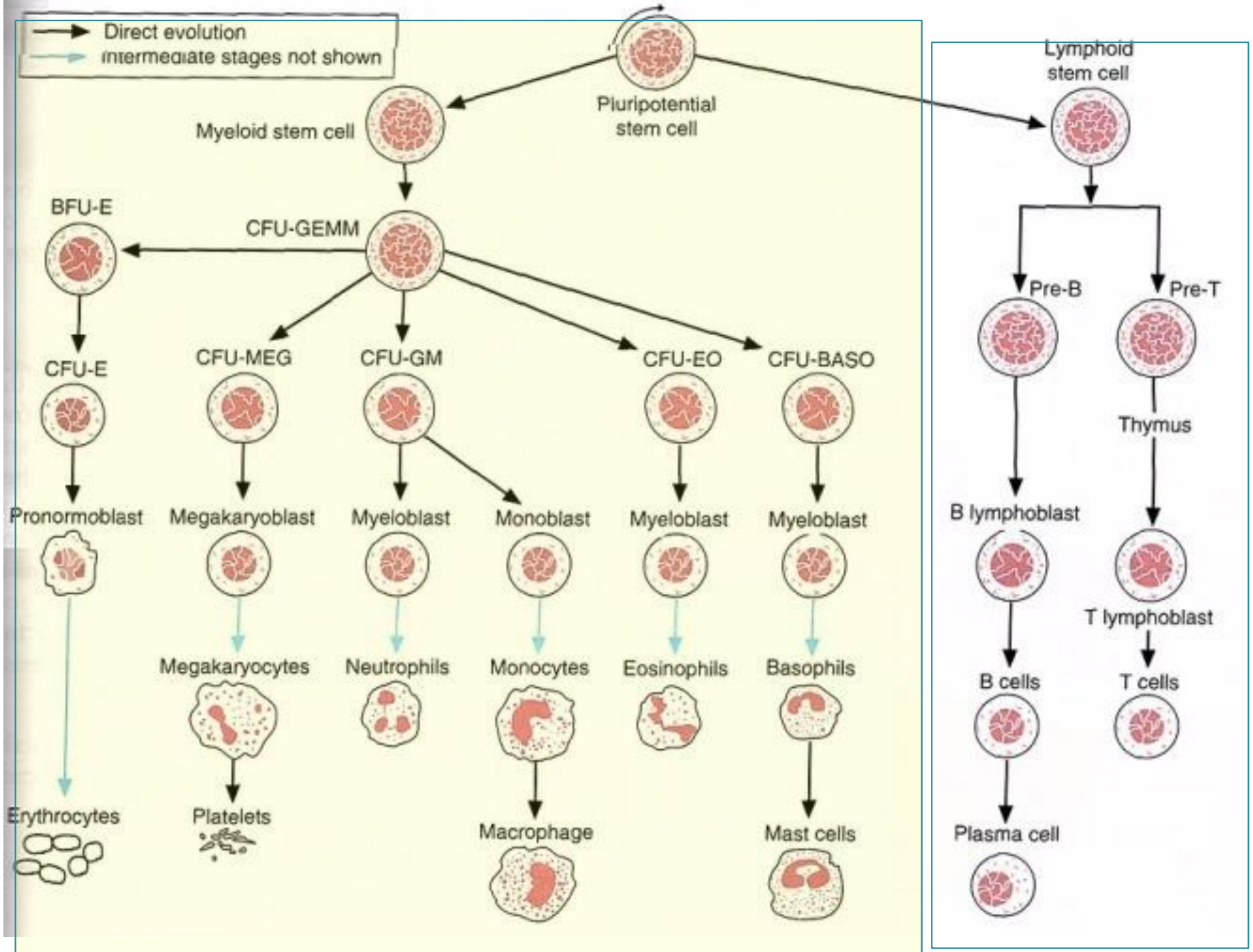
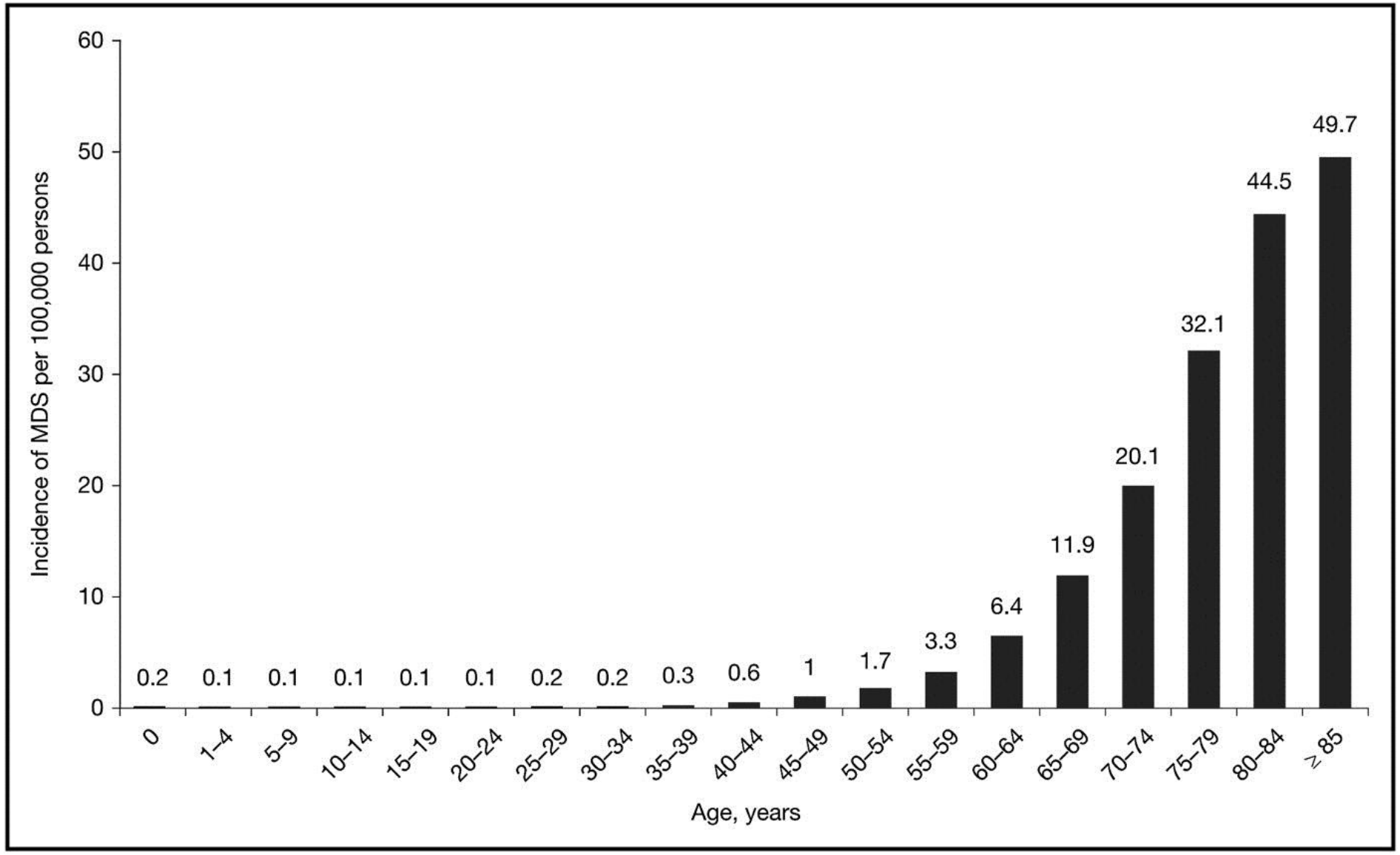
Leukemias: Outline

- Myelodysplastic syndrome and acute myeloid leukemia
- Acute lymphoblastic leukemia
- Chronic lymphocytic leukemia
- Chronic myeloid leukemia
- Hairy cell leukemia


Direct evolution
Intermediate stages not shown
Pluripotential stem cell
Myeloid stem cell
Lymphoid stem cell
BFU-E
CFU-GEMM
CFU-E
CFU-MEG
CFU-GM
CFU-EO
CFU-BASO
Pre-B
Pre-T
Thymus
Pronormoblast
Megakaryoblast
Myeloblast
Monoblast
Myeloblast
Myeloblast
B lymphoblast
T lymphoblast
Megakaryocytes
Neutrophils
Monocytes
Eosinophils
Basophils
B cells
T cells
Erythrocytes
Platelets
Macrophage
Mast cells
Plasma cell

Myelodysplastic syndrome

- Spectrum of clonal (neoplastic) myeloid disorders characterized by:
  - Ineffective hematopoiesis
  - Cytopenias
  - Qualitative disorders of blood cells
  - Chromosomal abnormalities
  - Variable predilection to evolve to acute myelogenous leukemia



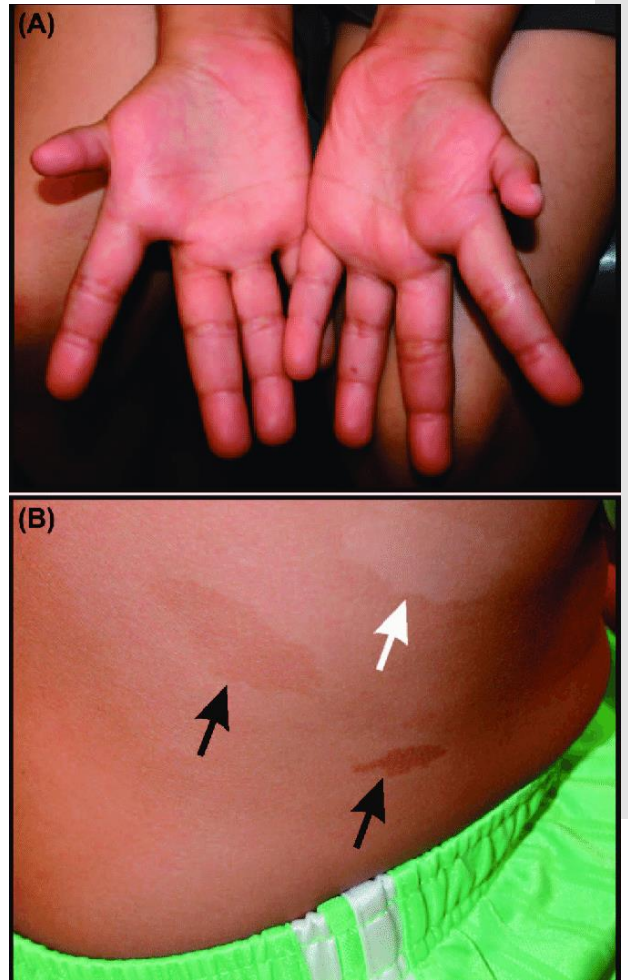
NCI SEER Database 2001-2008

MDS: Epidemiology

- Uncommon in people <50 years of age
- >10,000 new cases annually in US
- Mostly Caucasian men

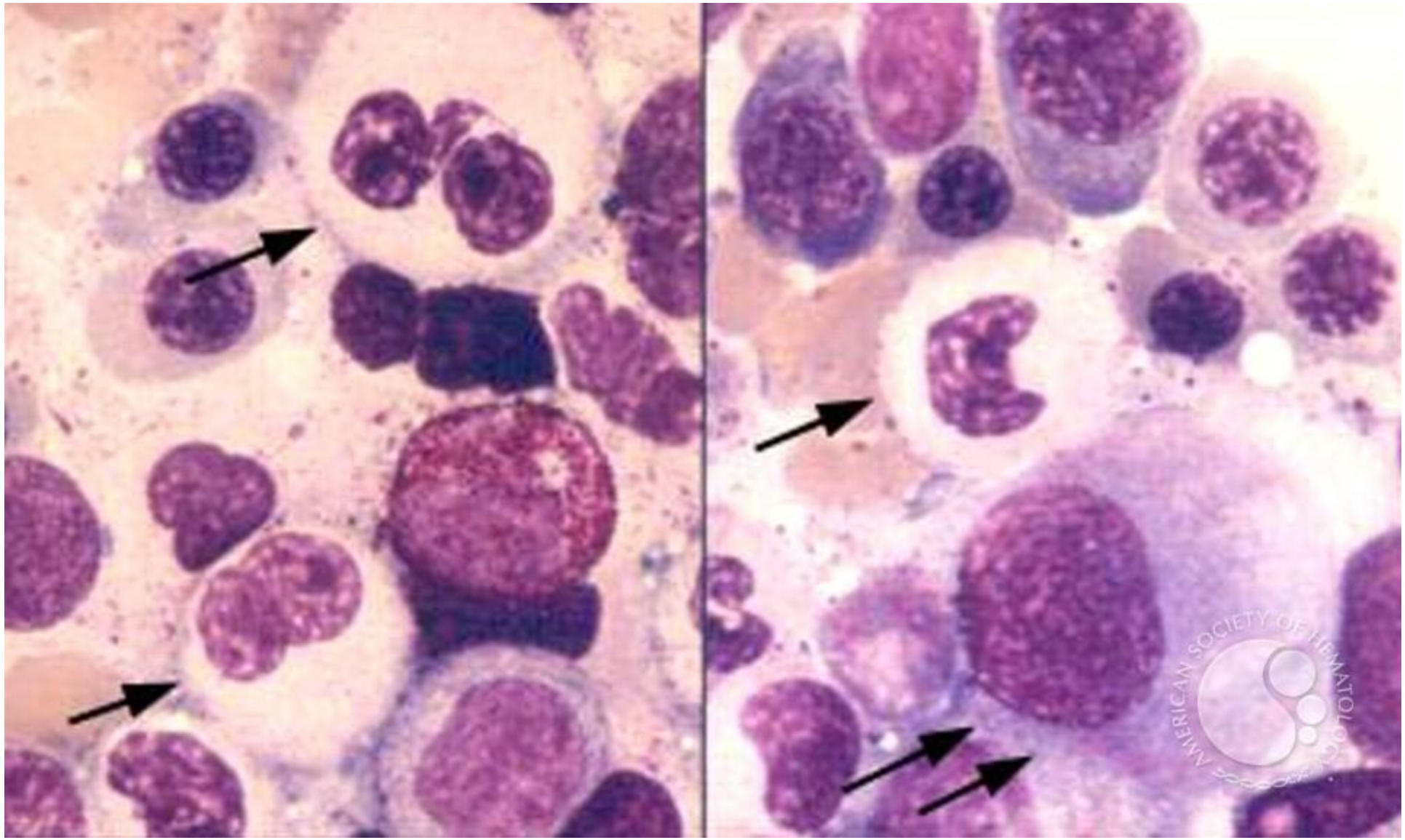
MDS: Risk Factors

- Ionizing radiation
- Exposures
  - Secondary or treatment-related MDS
  - Benzene
- Congenital disease
  - Fanconi anemia, Down syndrome



MDS: Diagnosis

- Peripheral blood
  - Morphology
  - Flow cytometry
  - Cytogenetics
  - Molecular markers
- Bone marrow
  - Same as with peripheral blood
  - Most accurate assessment of marrow cellularity, topography, stromal change, maturation pattern; measuring residual disease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MDS: Clinical symptoms

- Pallor
- Weakness
- Increased infections
- Bleeding
- Arthralgias
- Asymptomatic…

MDS: Diagnostic criteria

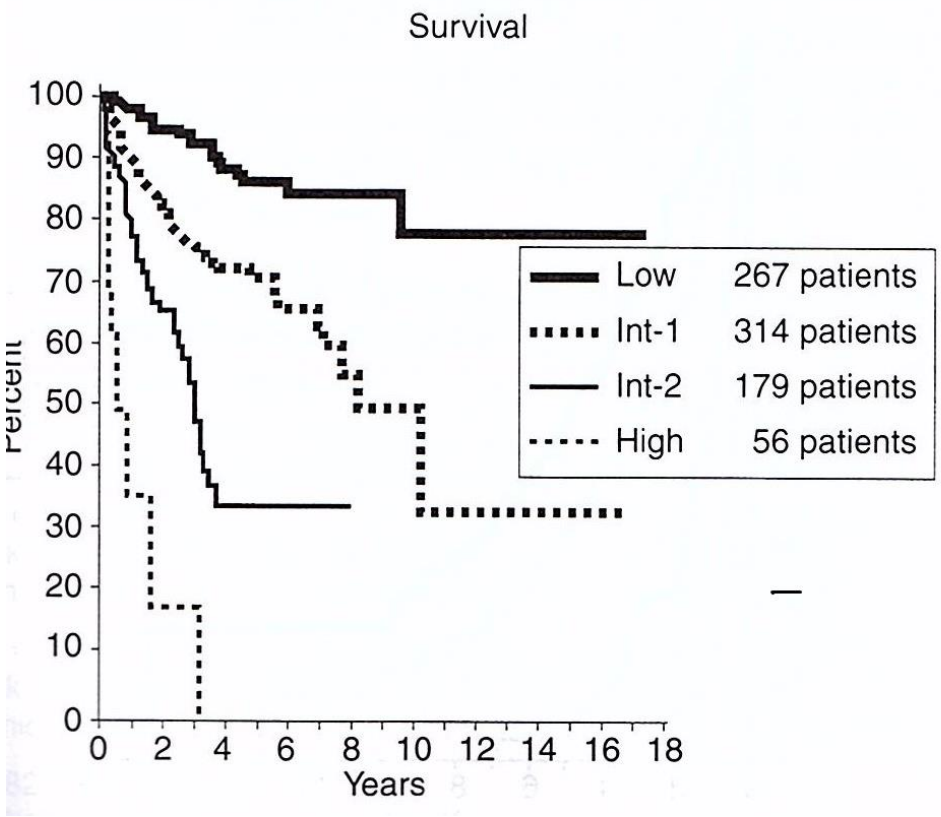
- At least 10% of cells of at least one myeloid BM lineage (erythroid, granulocytic, megakaryocytic) must show unequivocal dysplasia.
- Causes of secondary dysplasia should be excluded
- If morphologic features inconclusive, presumptive dx can be made if a specific clonal abnormality present
  - Del(20q), +8, -Y

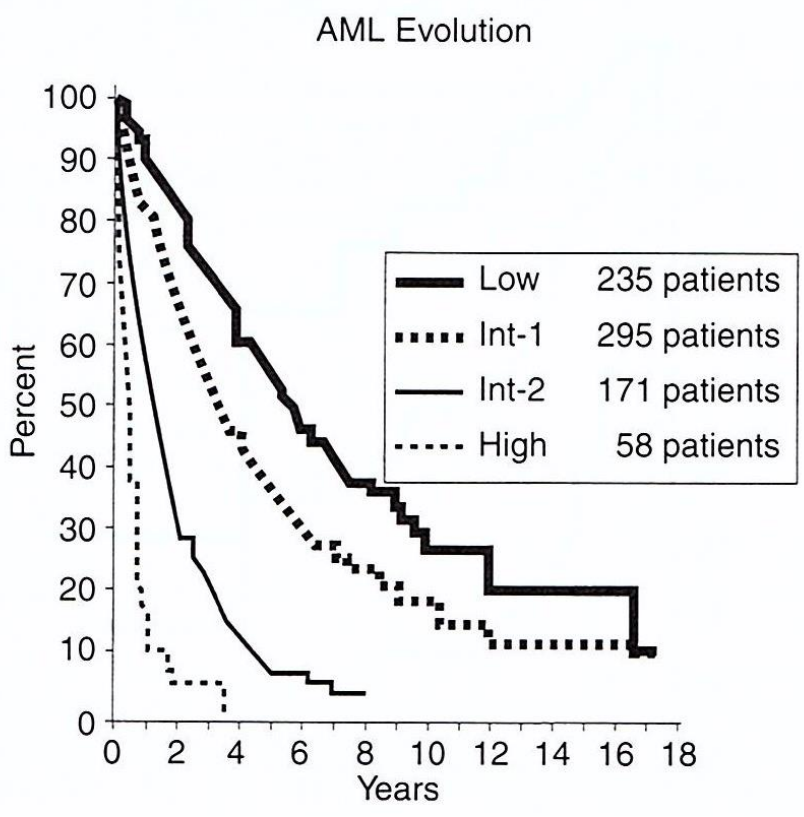
MDS: Prognosis

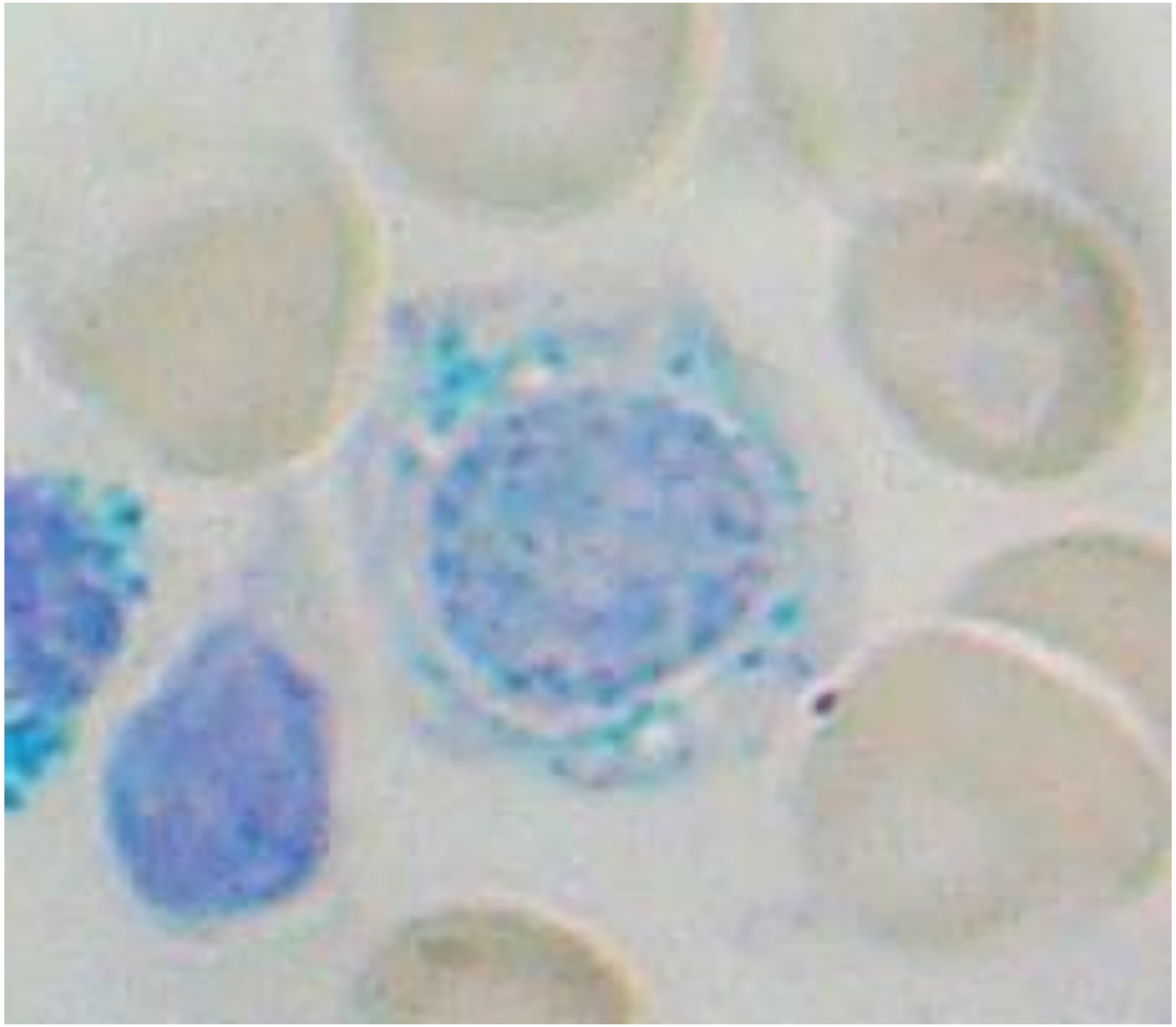
International Prognostic Scoring System for MDS

Prognostic variable	0	0.5	1.0	1.5	2.0
Marrow blasts	<5	5-10	--	11-20	21-30
Karyotype	Good	Intermediate	Poor		
Cytopenias	0-1	2-3			

Risk Category	Combined score
Low	0
INT-1	0.5-1.5
INT-2	1.5-2.0
High	>/= 2.5


Survival
Percent
100
90
80
70
60
50
40
30
20
10
0
0 2 4 6 8 10 12 14 16 18
Years
Low 267 patients
Int-1 314 patients
Int-2 179 patients
High 56 patients


AML Evolution
Percent
100
90
80
70
60
50
40
30
20
10
0
0 2 4 6 8 10 12 14 16 18
Years
Low 235 patients
Int-1 295 patients
Int-2 171 patients
High 58 patients



MDS: Treatment

Supportive care
- Erythropoietin
- G-CSF
- Transfusion
- Iron chelation
- Transfusion
- Antibiotics

+/-

Hypomethylating agents
- 5-azacytidine
- decitabine

Immunotherapy
- Cyclosporin
- Antithymocyte globulin
- Lenalidomide

Chemotherapy
- cytarabine

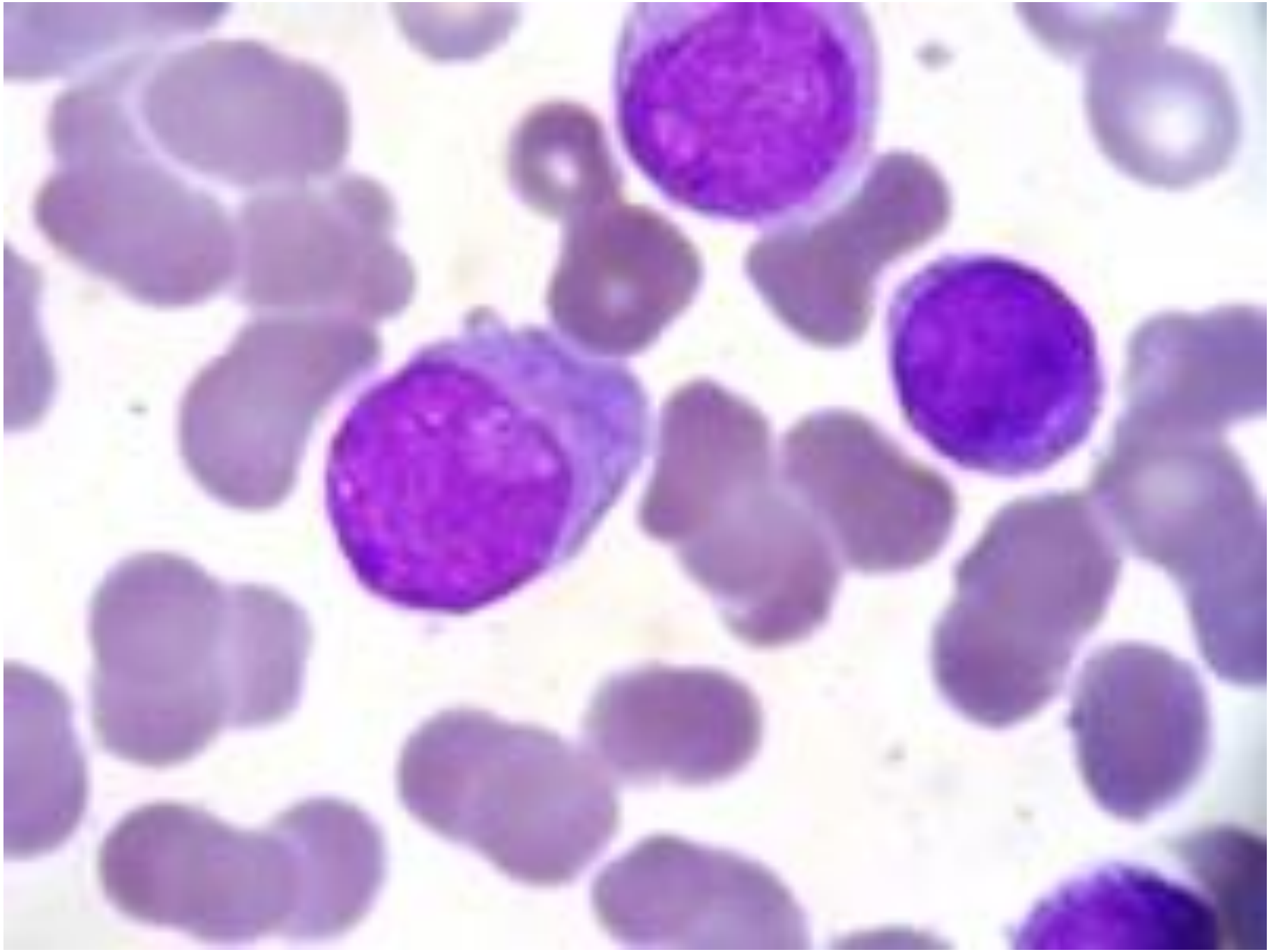
+/-

Stem cell transplant

AML: Pathophysiology

- Accumulation of abnormal myeloblasts in blood, bone marrow, or organs
- Diagnosis:
  - >/= 20% myeloblasts in marrow or blood
  - <20% in cases of "core binding factor" AML (t(8;21), inv[16], t[16;16]) or acute promyelocytic leukemia, t(15;17)

AML



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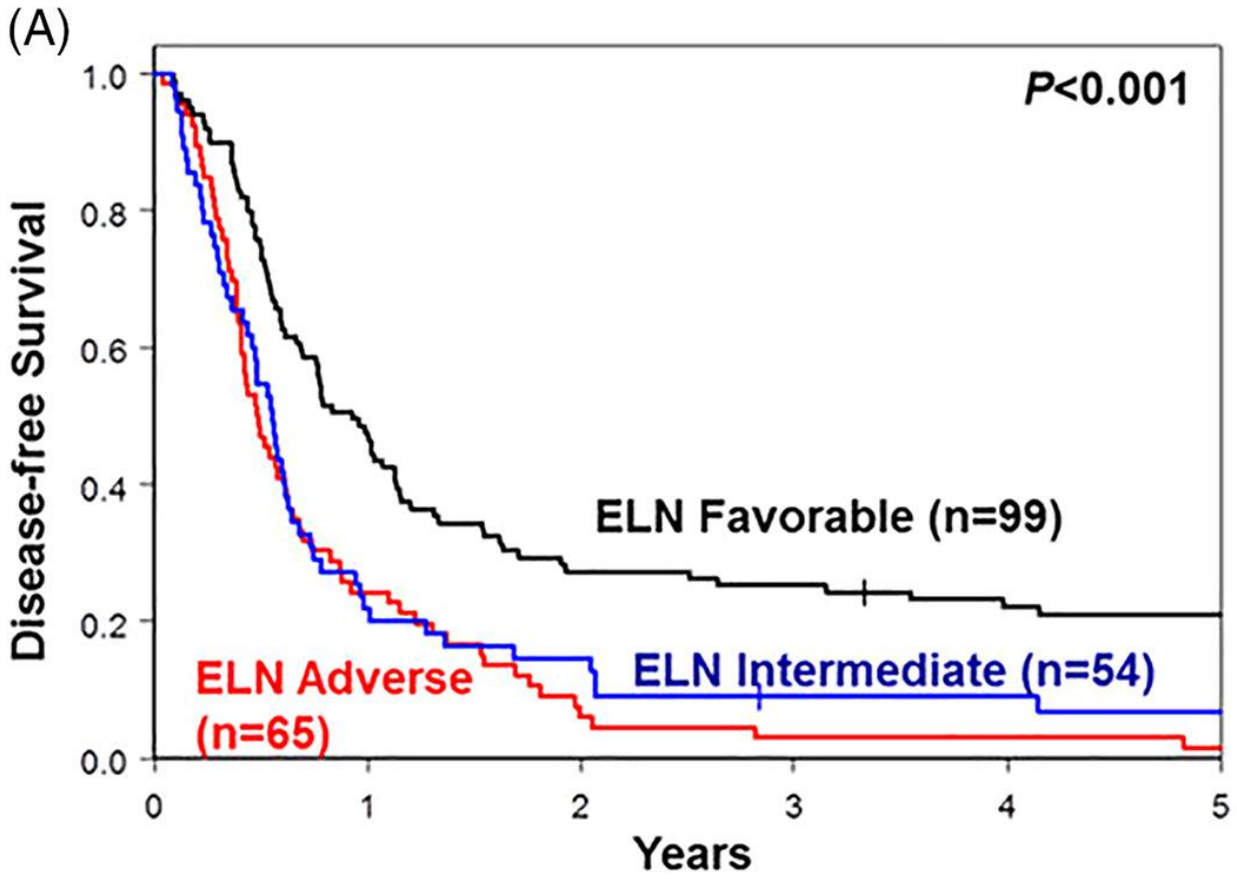
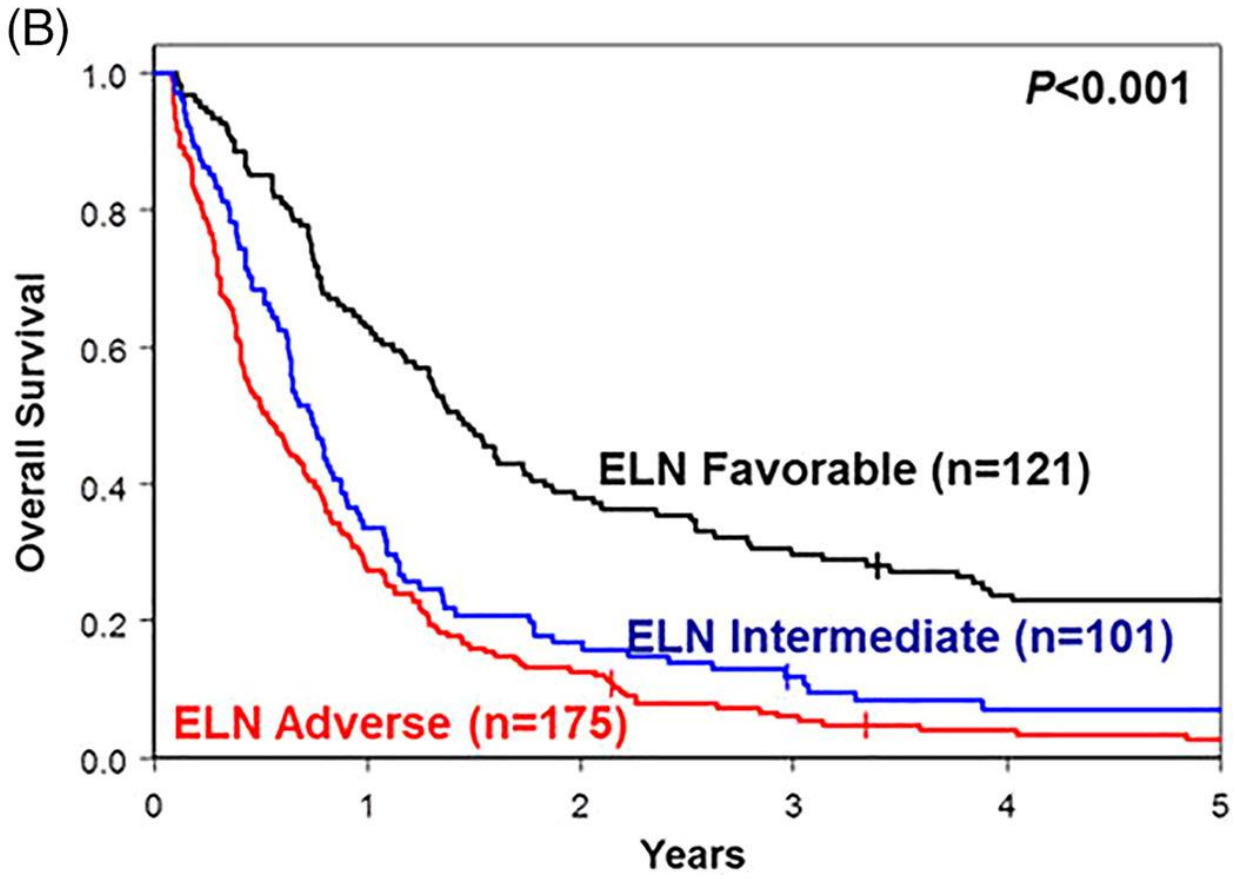
AML: Risk stratification

- Age
  - "Young" </= 65
  - "Old" >65
- Treatment related mortality based on age, socioeconomic status, comorbidities, social support
- AML resistance
  - Genetics – cytogenetics/mutation status of genes

AML: Risk stratification

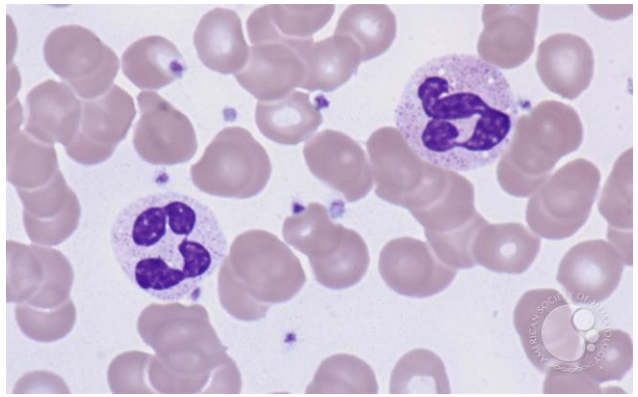
- Favorable
  - t(8;21)
  - T(15;17)
  - Inv(16) or t(16;16)
  - Mutated NPM1 without FLT3-ITD or with FLT3-ITD low (allelic ratio <0.5)
- Intermediate
  - Mutated NPM1 with FLT3-ITD high
  - Wild type NPM1 without FLT3-ITD or with FLT3-ITD low
  - t(9;11)
  - Cytogenetic abnormalities not classified as favorable or adverse
- Adverse
  - t(6;9), t(11;23), t(9;22), inv(3) or t(3;3), del 5q, del 7, abnormal 17p, complex karyotype, wild type NP<1 and FLT3-ITD high
  - Mutated RUNX1
  - Mutated ASXL1
  - Mutated TP53

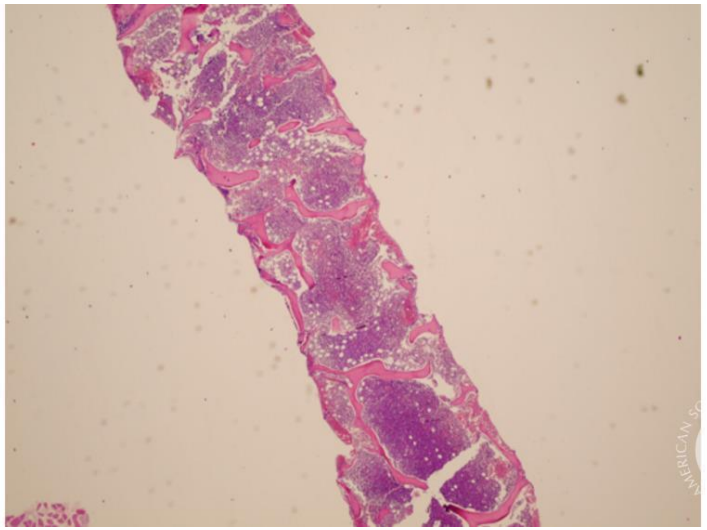




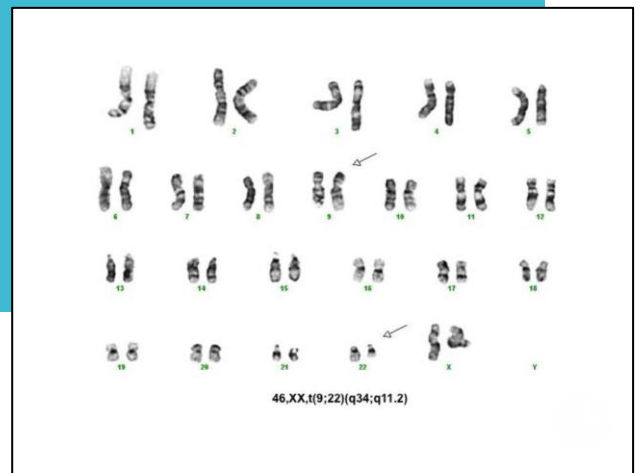
American Journal of Hematology, Volume: 93, Issue: 10, Pages: 1267-1291, First published: 16 October 2018, DOI: (10.1002/ajh.25214)

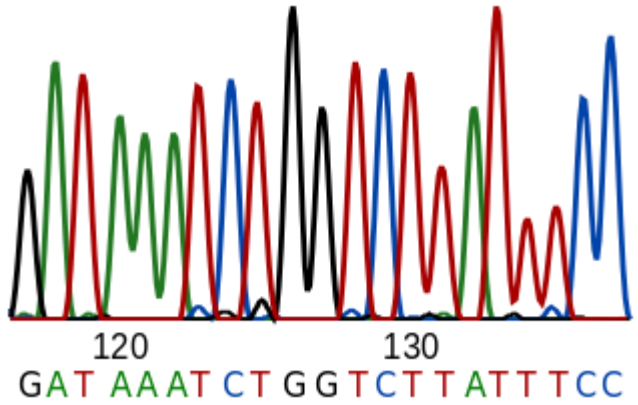
AML: Diagnosis

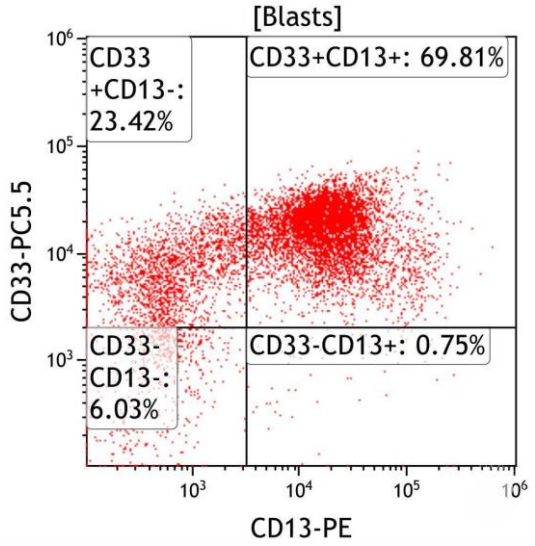




- Peripheral blood smear
- Bone marrow biopsy
- Flow cytometry
- Cytogenetics
- Next generation sequencing







AML: Treatment

- Induction therapy goal
  - Achieve complete remission without measurable residual disease

- 7+3 (7 days of cytarabine, 3 days of anthracycline)
  - +midostaurin for FLT3 + AML
  - +gemtuzumab ozogamicin for CD33+AML
- Vyxeos

Fit, low TRM

- Azacytidine/decitabine + GO
- IDH2 inhibitors: enasidenib, ivosidenib
- Venetoclax
  - +azacytidine or decitabine
  - +low-dose cytarabine

Elderly/unfit, high TRM

- Clinical trial

AML: Treatment

- Consolidation therapy goal
  - Maintain disease remission
- Stem cell transplant
  - Fit patients, age <70, with intermediate and adverse risk disease
- Intermediate/high dose cytarabine

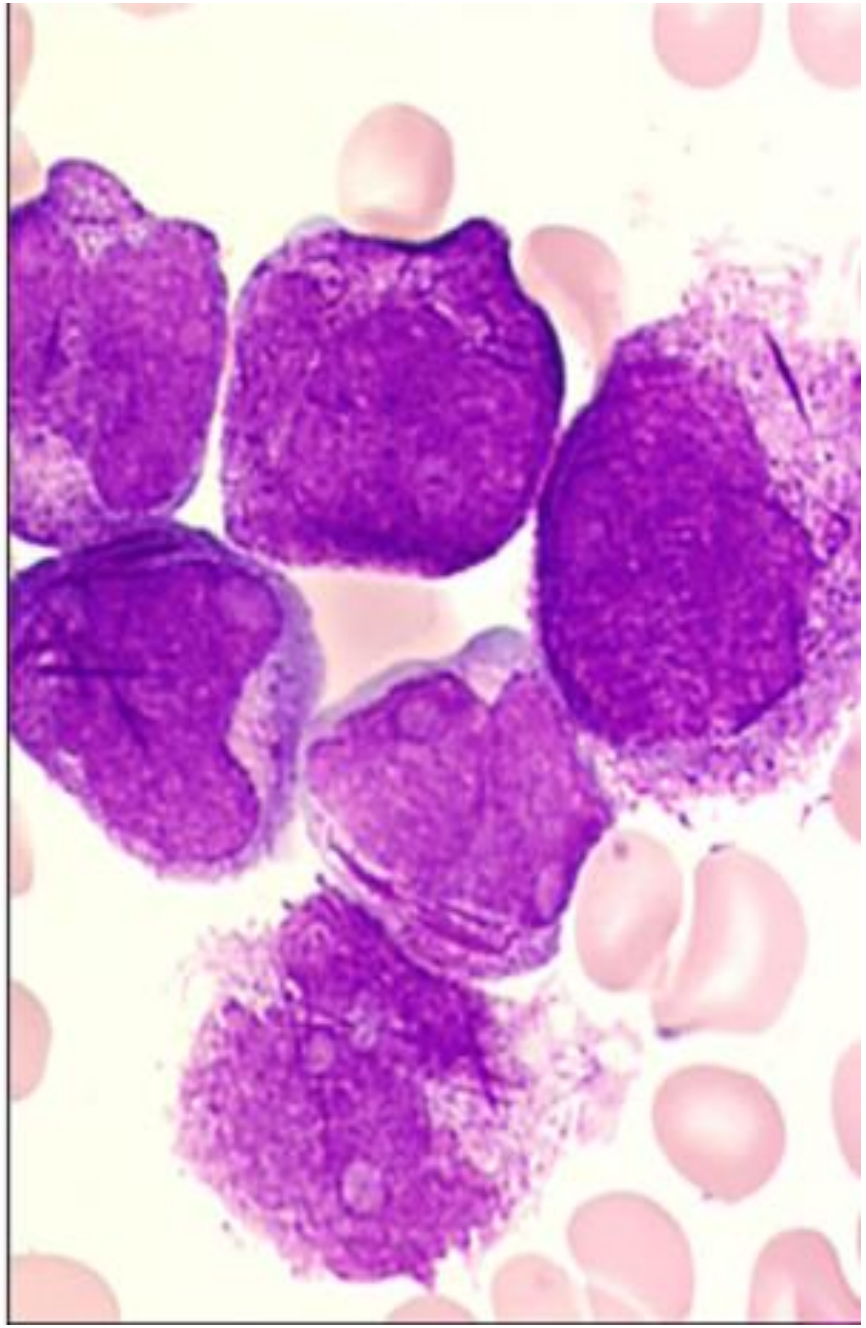
AML: Treatment

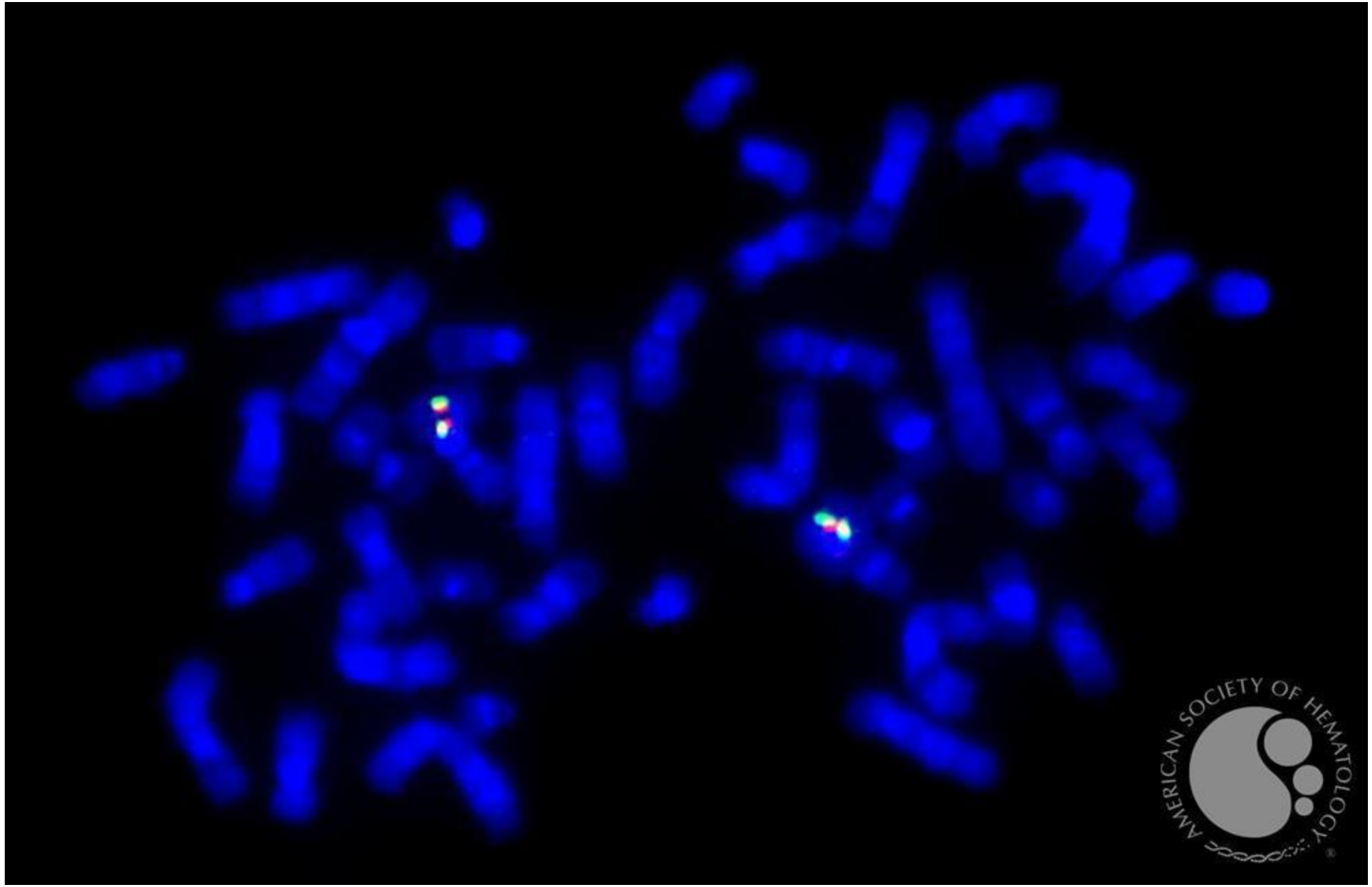
- Salvage therapy
  - For relapsed/refractory AML

APL: Overview

- Rare subtype of AML (<10% of all AML's)
- Characterized by distinctive blast morphology, coagulopathy, high curability if early death can be prevented
- Fusion of PML on chromosome 15 to RARα on chromosome 17 results in PML:RARA fusion protein => uncontrolled cell proliferation and inhibition of cell differentiation

APL: Morphology

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APL: Treatment

- Prevention of early death
  - Empiric all-trans retinoic acid (ATRA) while awaiting confirmation of dx
  - Manage coagulopathy/DIC
    - Monitor PT/PTT, fibrinogen, FDP
    - Transfuse cryoprecipitate, platelet, FFP with goal of maintaining fibrinogen >100-150, plts >30-50, INR <1.5

APL: Treatment

- Non high risk patients (WBC</= 10x10^9/L)
  - ATRA + arsenic trioxide
- High risk patients (WBC>10x10^9/L)
  - ATRA + chemotherapy (idarubicin or cytarabine+daunorubicin)
  - ATRA+ ATO +chemotherapy

ALL: Overview

- 6000-7000 new cases per year
- Bimodal distribution
  - First peak in childhood
  - Second peak around age 50
- Long term remission
  - Pediatric population – 90%
  - Adults – 30-40%

ALL: Pathophysiology

- Risk factors
  - Down syndrome, Fanconi anemia, Bloom syndrome, ataxia telangiectasia, Nijmegan breakdown syndrome
  - Radiation, pesticides, solvents, EBV/HIV
  - De novo most common
- Pathophysiology
  - Abnormal proliferation and differentiation of clonal population of lymphoid cells
  - Chromosomal aberrations
    - Philadelphia chromosome (up to 50% prevalence, has prognostic and therapeutic implications)

ALL: Classification

- Classification
  - French American British criteria (L1,L2, and L3)
  - World Health Organization
    - B-lymphoblastic – 75%
    - T-lymphoblastic – 25%
    - Burkitt-cell leukemia

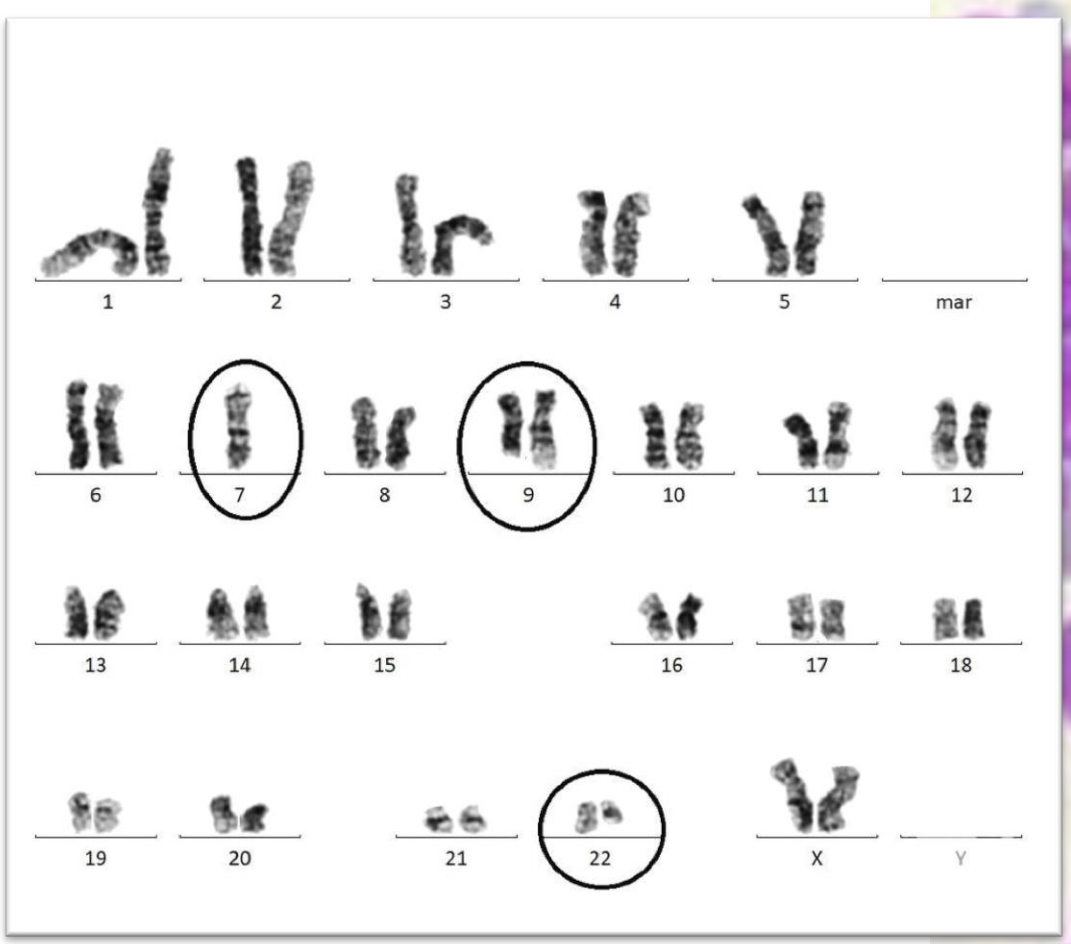
ALL: Prognosis

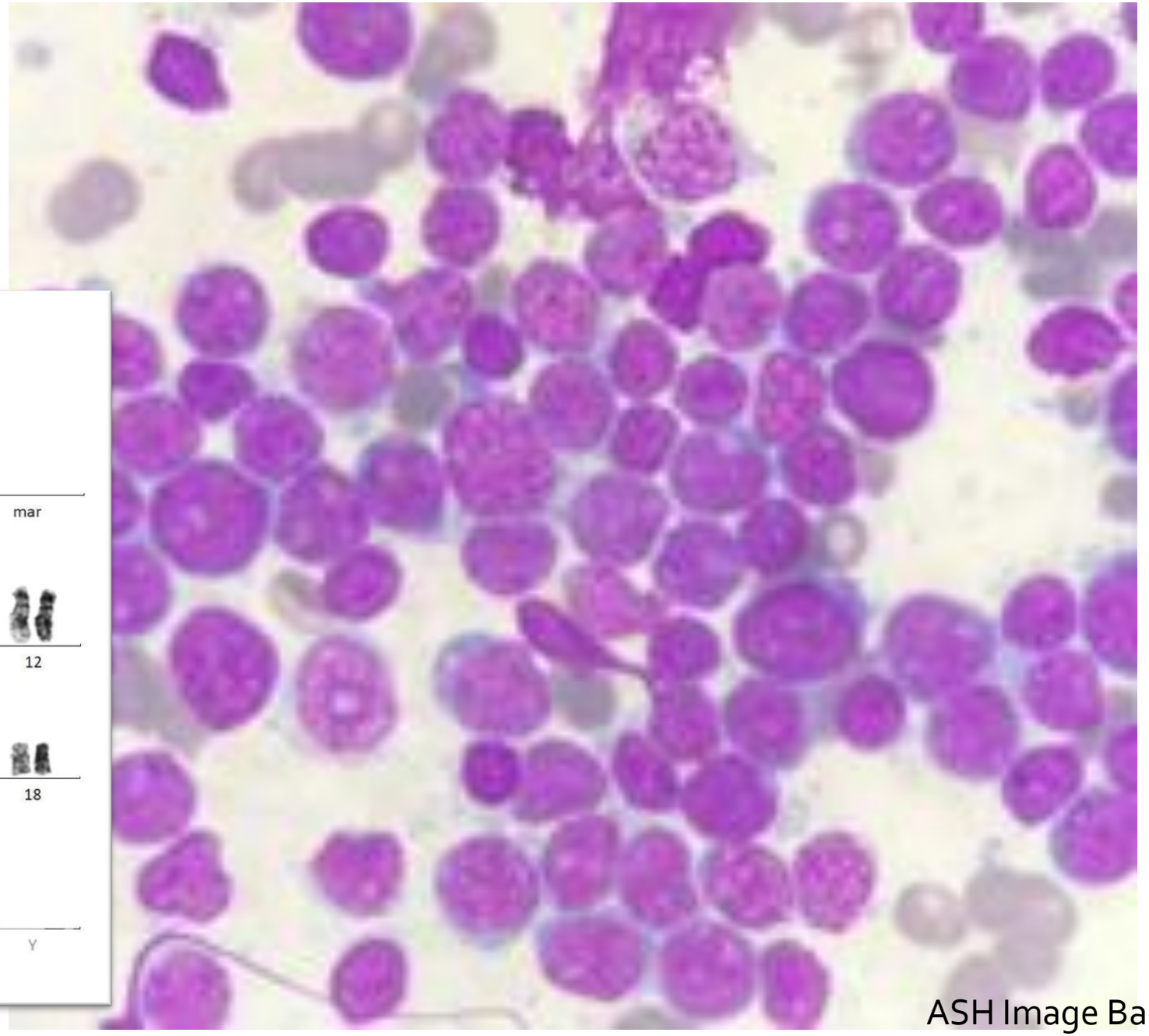
- Prognostic factors

-Ph chromosome negative
-WBC<30

-Age >60
-Ph chromosome positive
-Hypodiploid
-Complex karyotype

ALL





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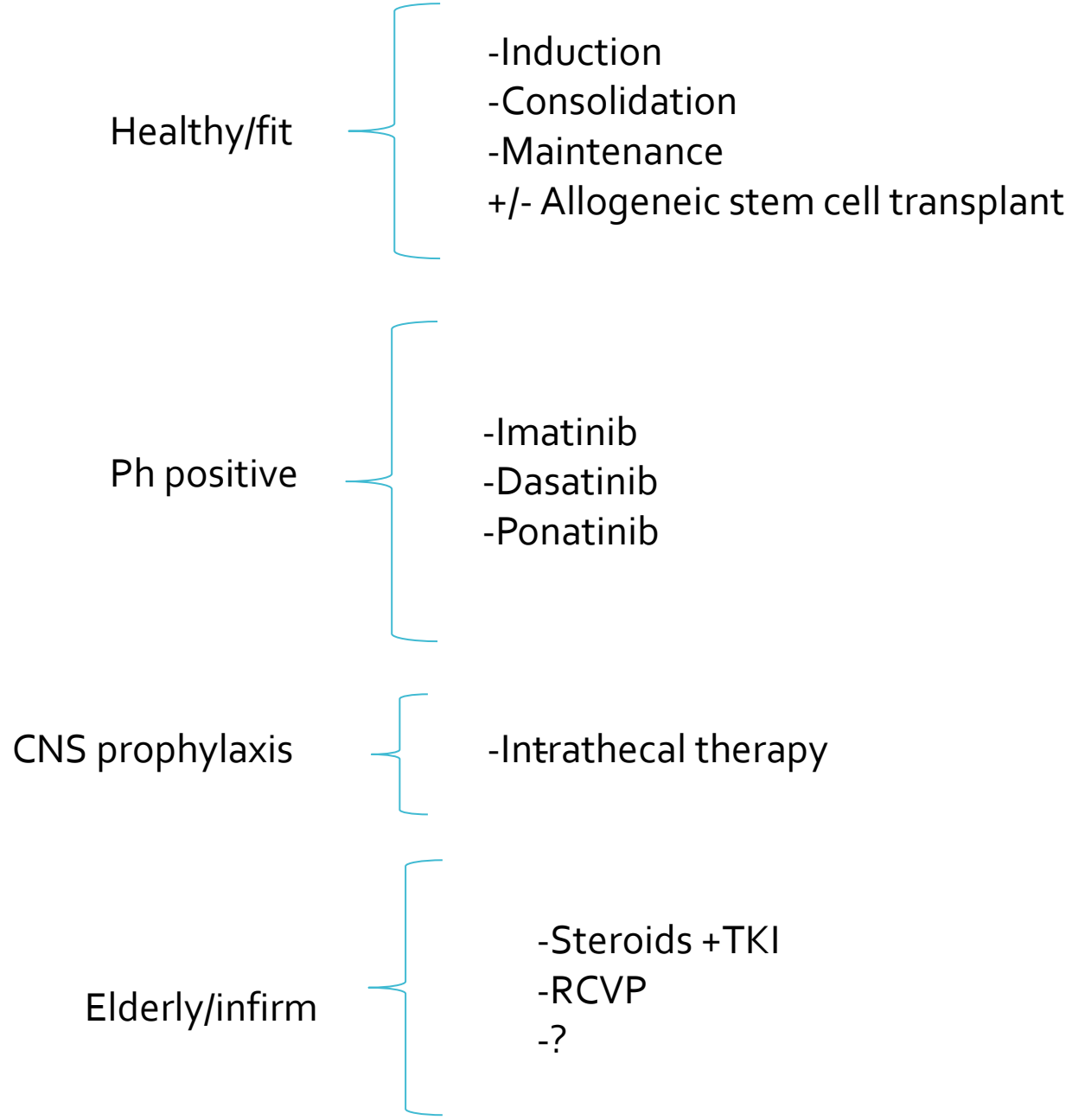
ALL: Treatment



ALL: Treatment

- Hematopoietic stem cell transplantation
  - Relapsed/refractory disease
  - High risk patients
  - Standard risk patients with detectable "MRD" (minimal residual disease)

CLL: Overview

- Most common type of leukemia in western countries
- 15,000 new cases per year
- Median age of diagnosis ~ 72
- Male>female cases

CLL: Pathogenesis

- Clonal proliferation and accumulation of mature monoclonal B-cells within the blood, bone marrow, lymph nodes, and spleen
- Initiated by loss or addition of large amounts of chromosomal material followed by additional mutations that may render more aggressive biology

CLL: Prognosis

Prognosis

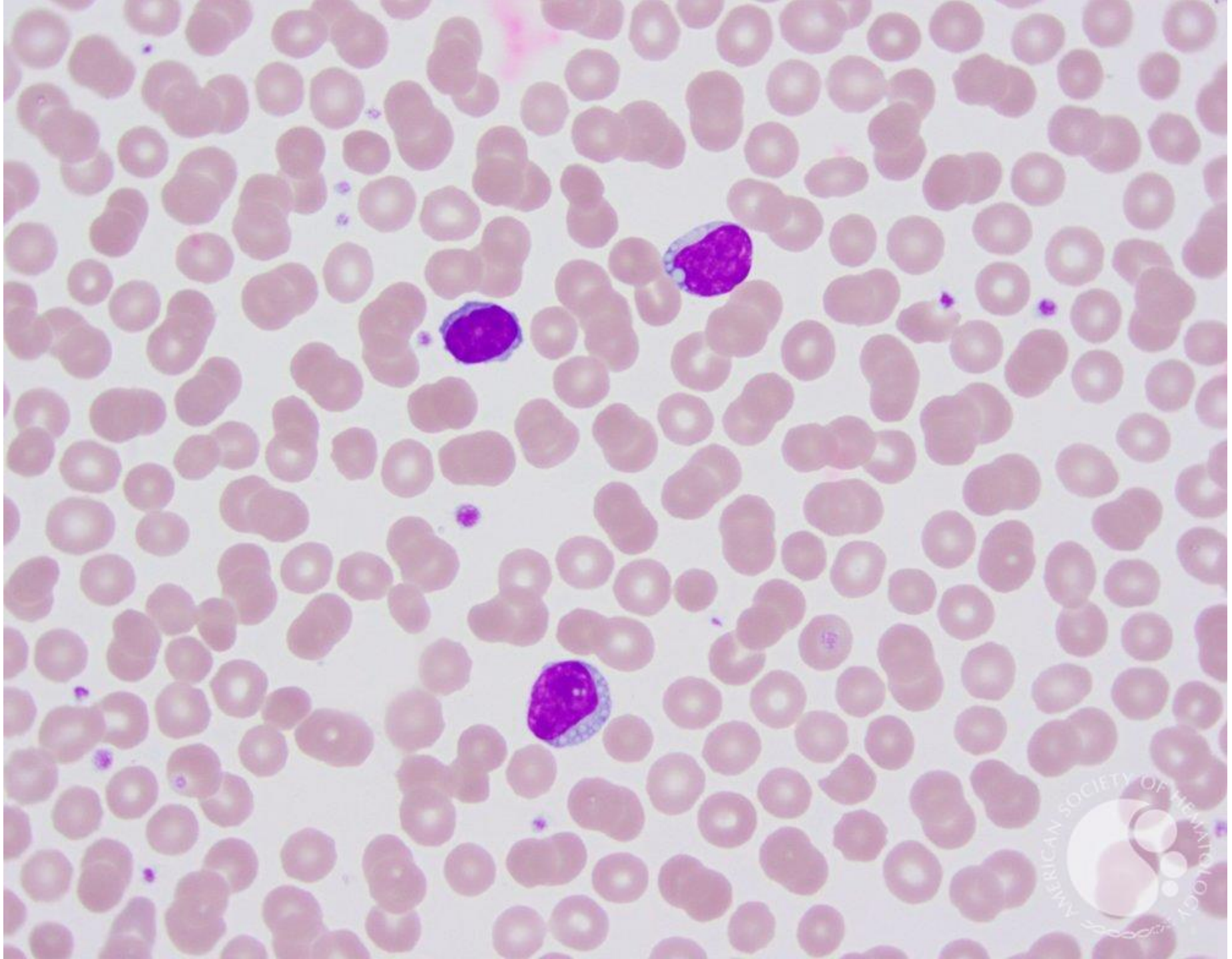
Chromosome aberration	Genes affected	Prevalence	Prognostic significance
Del 13q14	miRNA-15a and 16-1	55%	Favorable
Del 11q	ATM	25%/	Poor
Trisomy 12	?	10-20%	?
Del 17p	TP53	5-8%	Very poor

Role of microenvironment/cell signaling pathways

CLL: Diagnosis

- Requires presence of >/= 5000 B-lymphocytes/uL in peripheral blood for duration of 3 months
- Cells in blood smear typically small, mature lymphocytes with narrow border of cytoplasm and dense nucleus
- Confirm clonality by flow cytometry
  - CLL typically expresses CD5, Cd19, CD20 (low), and CD23

CLL



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CLL

Distinguish from….

- Prolymphocytic leukemia (T-cell PLL)
  - Presence of excess prolymphocytes
- Small lymphocytic lymphoma (SLL)
  - <5000 B-lymphocytes per uL blood
  - Morphologically/therapeutically similar as CLL
  - Lymphadenopathy
  - Absence of cytopenias
- Monoclonal B-lymphocytosis (“MBL”)
  - <5000 B-lymphocytes per uL blood
  - Absence of cytopenias, lymphadenopathy, or organomegaly
  - Risk of progression to frank CLL – 1-2% per year

CLL: Risk Stratification

Rai

- Low risk
  - Lymphocytosis only
- Intermediate risk
  - Lymphocytosis PLUS lymphadenopathy and/or splenomegaly
- Poor risk
  - Disease-related anemia (<11 g/dl) or thrombocytopenia (<100x10^9/L)

Binet

- Based on number of enlarged lymph node regions >1 cm, organomegaly, presence of anemia or thrombocytopenia
- Stage A
  - Hb>/= 10 g/dl
  - Platelets >100x10^9/L
  - 2 involved regions
- Stage B
  - Hb>/=10 g/dl
  - Platelets >100x10^9/L
  - 3 or more involved regions
- Stage C
  - Hb<10 g/dl
  - Plts <100x10^9/L

CLL: Risk Stratification

- CLL International prognostic index (CLL-IPI)
  - Weighs 5 prognostic factors: TP53 dysfunction, IGHV mutation status, B2-macroglobulin, clinical stage and age

CLL – IPI category	OS at 5 years	Clinical consequence
Low-risk	93%	Do not treat
Intermediate-risk	79.3%	Do not treat unless sx's
High-risk	63.3%	Tx indicated unless no sx's
Very high-risk	23.3%	Novel agents/clinical trial

Treating early stage disease does not result in survival benefit

CLL: Treatment indications

- Progressive marrow failure
- Massive/symptomatic splenomegaly
- Massive/progressive/symptomatic nodes
- Progressive lymphocytosis >/= 50% increase over 2 months or lymphocyte doubling <6 months
- Autoimmune complications, poorly responsive to steroids
- Symptomatic extra nodal involvement
- Unintentional weight loss, significant fatigue, fevers, night sweats

CLL: Treatment

- Chemotherapy
  - Chlorambucil
  - FCR
- Monoclonal antibodies
  - Anti-CD20 – Rituxan, ofatumumab, obinutuzumab
  - Anti-CD52 – Alemtuzumab
- Agents targeting cell signaling pathways
  - Ibrutinib/acalabrutinib – Bruton tyrosine kinase inhibitor
  - Idelalisib – PI3K inhibitor
  - Lenalidomide – immunomodulatory
  - Venetoclax – Bcl2 inhibitor
  - CART - Immunotherapy

CLL: Treatment

- Selection of therapy depends on clinical stage, symptoms, fitness of concomitant diseases of the patient, genetic risk of leukemia, line of therapy

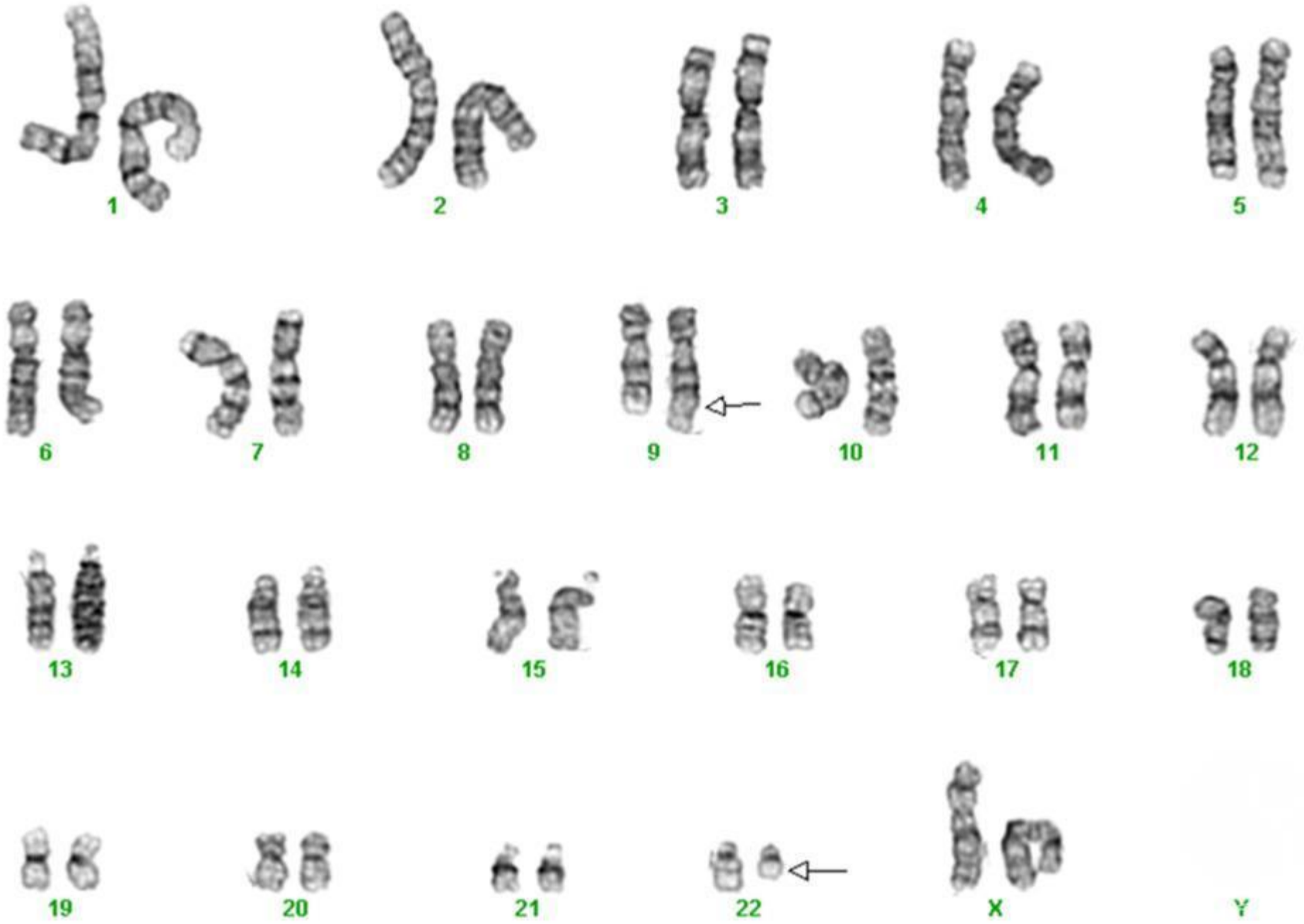
CML: Overview

- Myeloproliferative neoplasm
- Accounts for 15% newly dx'd cases of leukemia
- 9000 new cases/year

CML: Pathogenesis

- Philadelphia chromosome - Fusion of ABL1 gene on chromosome 9 with BCR gene on chromosome 22
- Results in BCR-ABL1, a constitutively active tyrosine kinase that promotes growth and replication

t(9;22)



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CML: Clinical symptoms

- Many are asymptomatic
- Symptoms stem from anemia and splenomegaly
  - Weight loss
  - Malaise
  - Early satiety
  - LUQ fullness/pain

CML:
3 phases

- Chronic phase (90-95%)
- Accelerated phase
- Blast phase

CML: Diagnosis

- Confirming Ph chromosome (or variant) by FISH or molecular studies
- Bone marrow biopsy
  - Confirms dx
  - Staging/prognostic information – blast%

CML: Differential dx

- Leukemoid reaction usually has WBC<50x10^9/L
- Other myeloproliferative neoplasms

CML: Treatment

- Imatinib
  - Competitive inhibitor of ATP binding site of BCR-ABL1 oncoprotein
  - Reduced annual CML mortality from 10-20% to 1-2%
- Dasatinib
- Nilotinib
- Bosutinib

More rapid achievement of cytogenetic and molecular remission than imatinib

Therapy discontinuation in exceptional responders

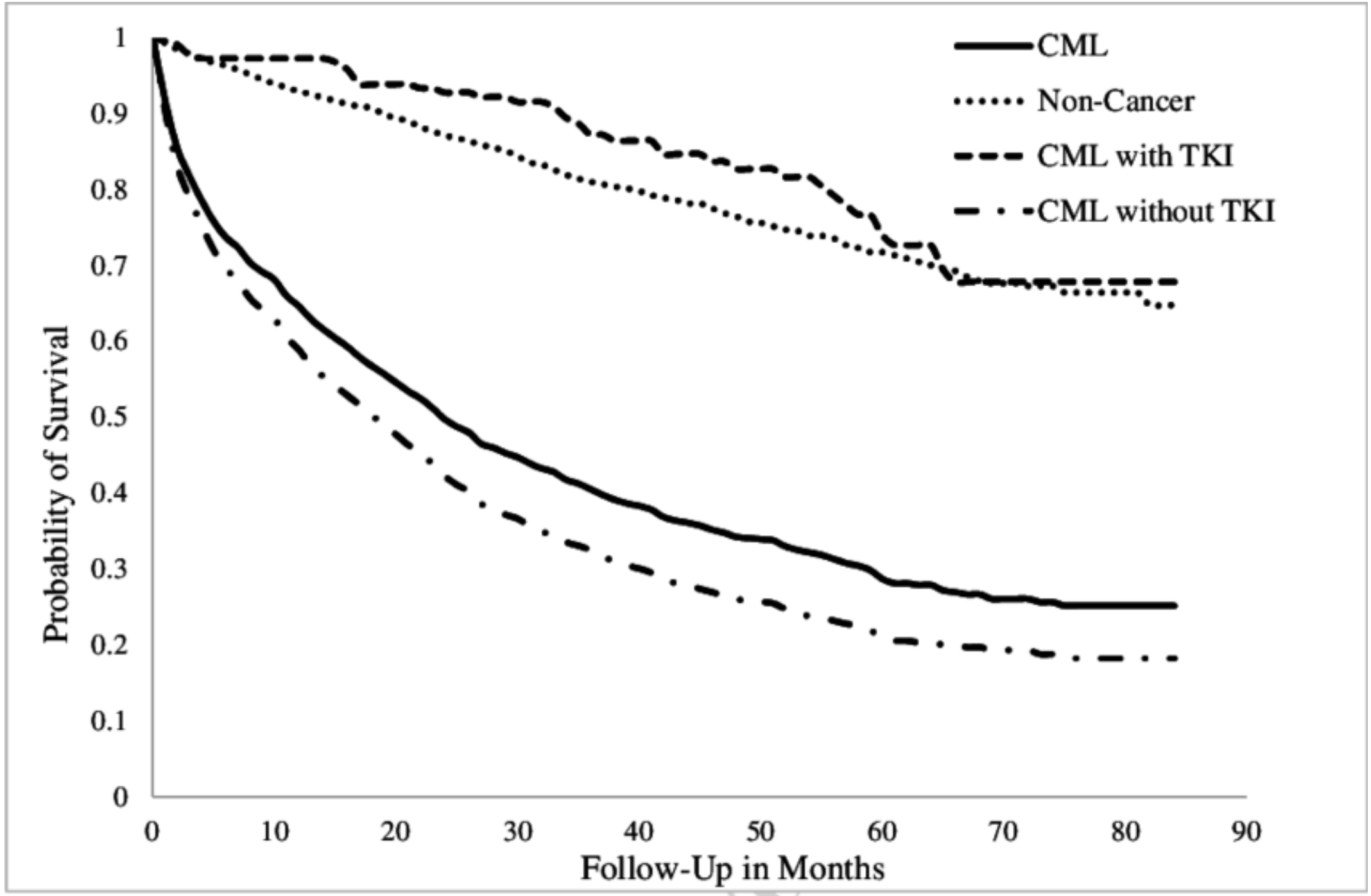
- Ponatinib – Effective in T315I mutations (drug resistance)
- Stem cell transplant
  - Accelerated/blast phase
  - After failure of 2 TKIs
  - T315I mutation after trial of ponatinib

CML: Potential Treatment Toxicities

- Imatinib
  - Weight gain
  - Fatigue
  - Peripheral/periorbital edema
  - Arthralgias/myalgias
  - Nausea
- Sprycel
  - Pleural effusions
  - Pulmonary arterial hypertension
- Nilotinib
  - Hyperglycemia
  - QT prolongation
  - Vaso-occlusive events

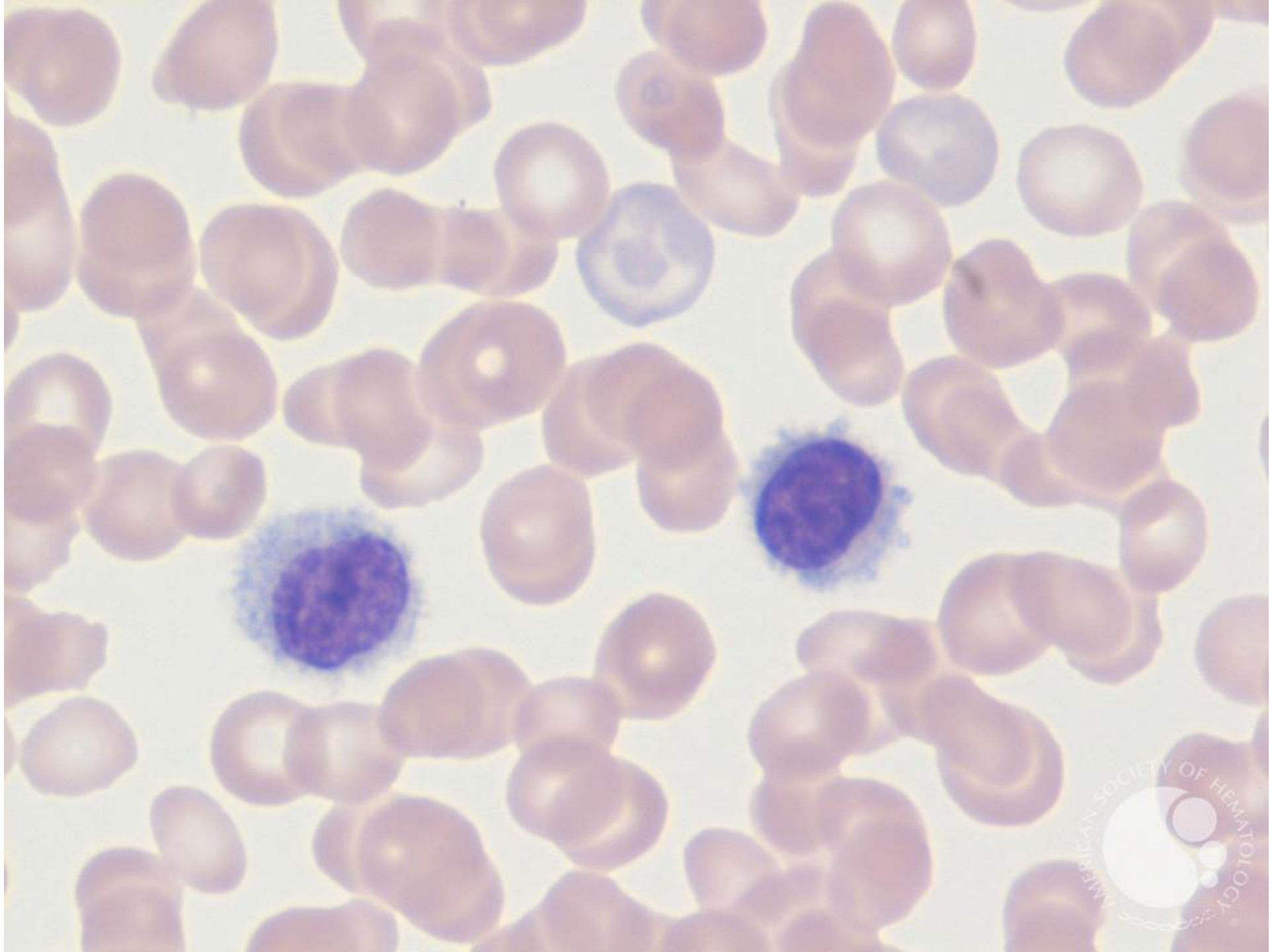
CML: TKI response evaluation

- Optimal
  - 3 months – Ph+<35%, BCR-ABL </=10%
  - 6 months – Ph+ 0%; BCR-ABL<1%
  - 12 months – BCR-ABL </=0.1%


CML
Non-Cancer
CML with TKI
CML without TKI
Probability of Survival
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
10
20
30
40
50
60
70
80
90
Follow-Up in Months

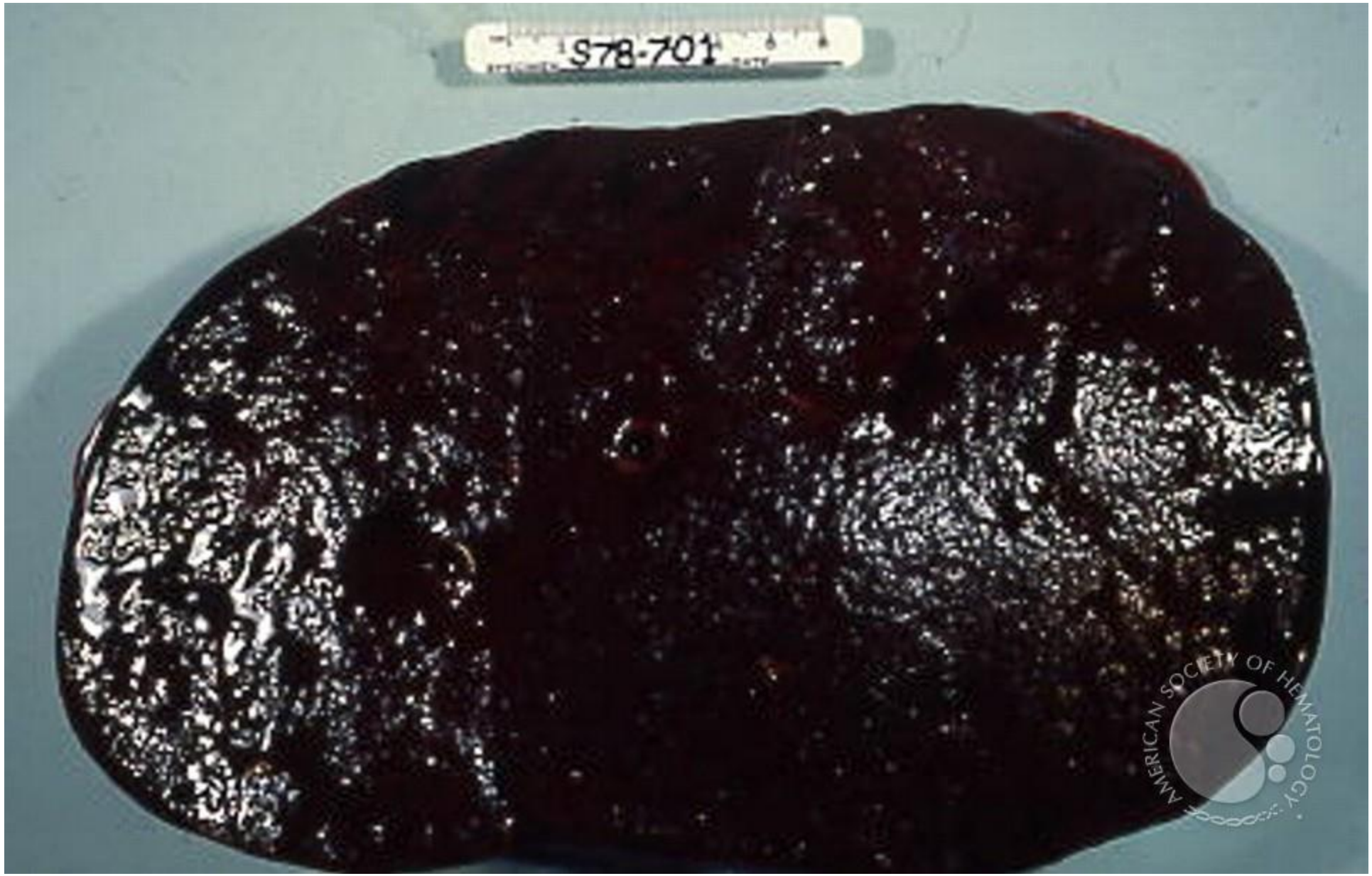
Hairy Cell Leukemia: Prevalence

- Accounts for 2% of all leukemias
- Occurs 4-5 times more frequently in men than women



Hairy cell leukemia: Clinical manifestations

- Splenomegaly
- Infections
- Anemia/fatigue
- Thrombocytopenia/easy bruising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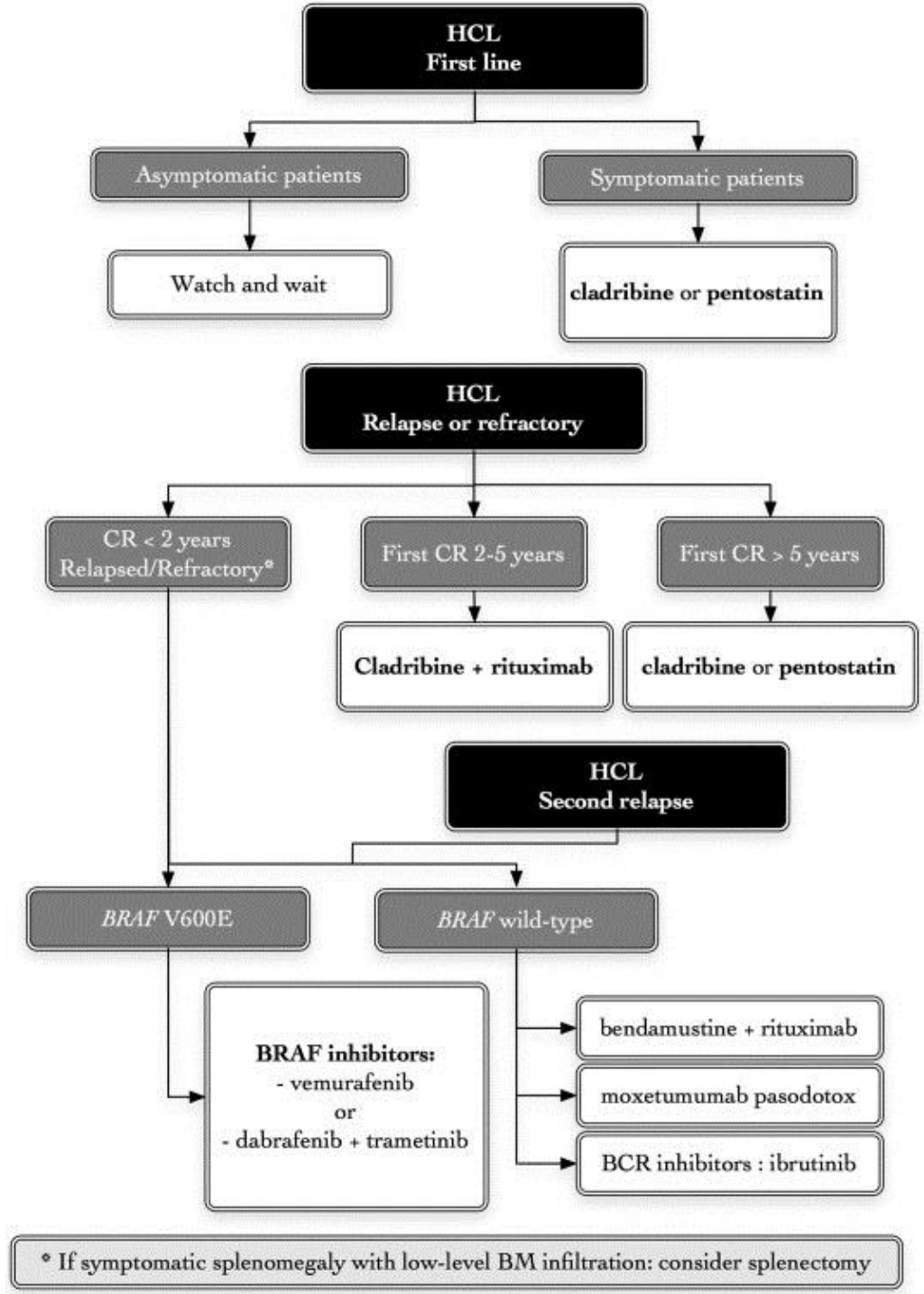
Hairy cell leukemia: Diagnosis

- CBC
- Peripheral smear
- Flow cytometry
  - Establishes B-cell clonality with CD11c, CD103, CD123, and CD25 expression
- Bone marrow biopsy
- 80-90% BRAF V600E mutation positive

Hairy cell leukemia: Prognosis

- Similar to CLL
- Poor prognosis associated with CD38 expression, unmutated IgVH, VH4-34 mutations


HCL
First line
Asymptomatic patients
Symptomatic patients
Watch and wait
cladribine or pentostatin
HCL
Relapse or refractory
CR < 2 years
Relapsed/Refractory*
First CR 2-5 years
First CR > 5 years
Cladribine + rituximab
cladribine or pentostatin
HCL
Second relapse
BRAF V600E
BRAF wild-type
BRAF inhibitors:
- vemurafenib
or
- dabrafenib + trametinib
bendamustine + rituximab
moxetumumab pasodotox
BCR inhibitors : ibrutinib
* If symptomatic splenomegaly with low-level BM infiltration: consider splenectomy

Q#1:
A 35 yo male presents to ER with fever and epistaxis. He has been experiencing malaise for several weeks and fever, chills, and anorexia for several days. Today, he developed epistaxis. He takes no medications.

On physical exam, temperature is 38.8 C, blood pressure is 105/70, pulse is 110, and respiration rate is 24. He is diaphoretic. Dried blood is noted in the nares, and gingival bleeding is present. No lymphadenopathy or hepatosplenomegaly is noted. He has petechiae bilaterally on the legs.

Labs:
PTT 60 s
Hb 9.8 g/dl
WBC 3.6 x 10x9/L with 20% neutrophils, 3& bands, 35% lymphs, 23% monocytes, and 18% atypical cells
Plt 17
PT 24
Fibrinogen 93

Peripheral smear shows immature leukocytes with prominent granules in the cytoplasm.

Which is the most likely diagnosis?
A. Acute promyelocytic leukemia
B. Aplastic anemia
C. Chronic granulocytic leukemia
D. Immune thrombocytopenic purpura

Q#2

A 35 yo man presents with a 6 month h/o night sweats, malaise, and 25# weight loss. He reports no fevers or other localizing symptoms. His only medication is acetaminophen.

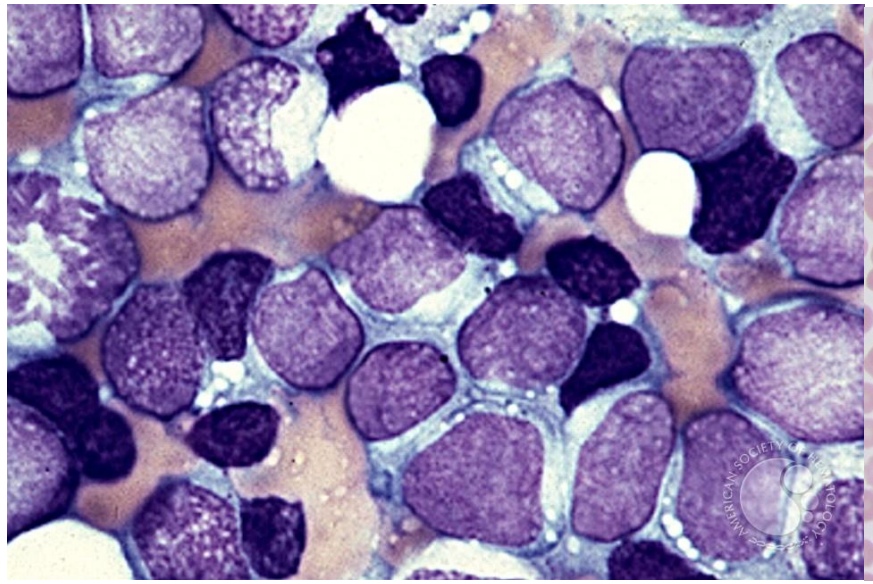
On exam, vital signs are normal. Abdominal exam reveals splenomegaly. Remainder of exam is noncontributory.

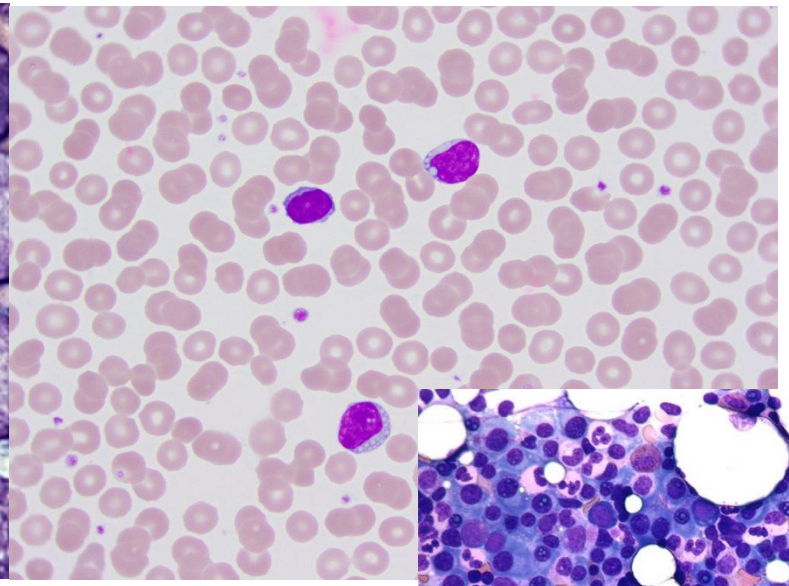
Labs show:
WBC 55K/uL (87% neutrophils, 2% myelocytes, 1% metamyelocytes, 0.5% basophils, 7% lymphocytes, 2.5% monocytes
Hb 12.5 g/dl
Plts 450K/uL

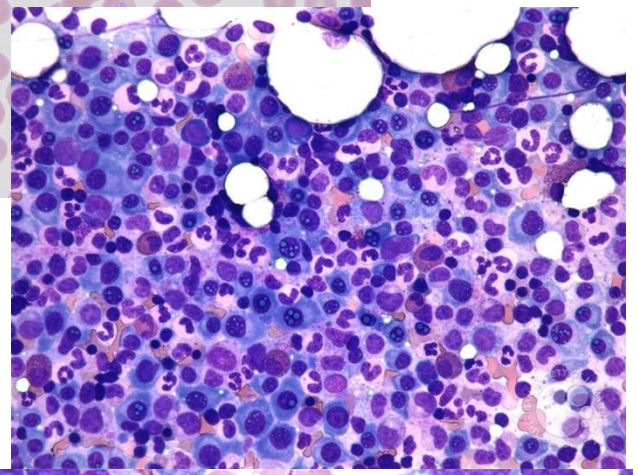
PCR for BCR-ABL is positive. BMBx shows hypercellular marrow with myeloid hyperplasia and 1% myeloblasts.

Which of the following is the most appropriate treatment?

A. Bone marrow transplant
B. Idarubicin and cytarabine
C. Imatinib
D. Vancomycin and levofloxacin







The End