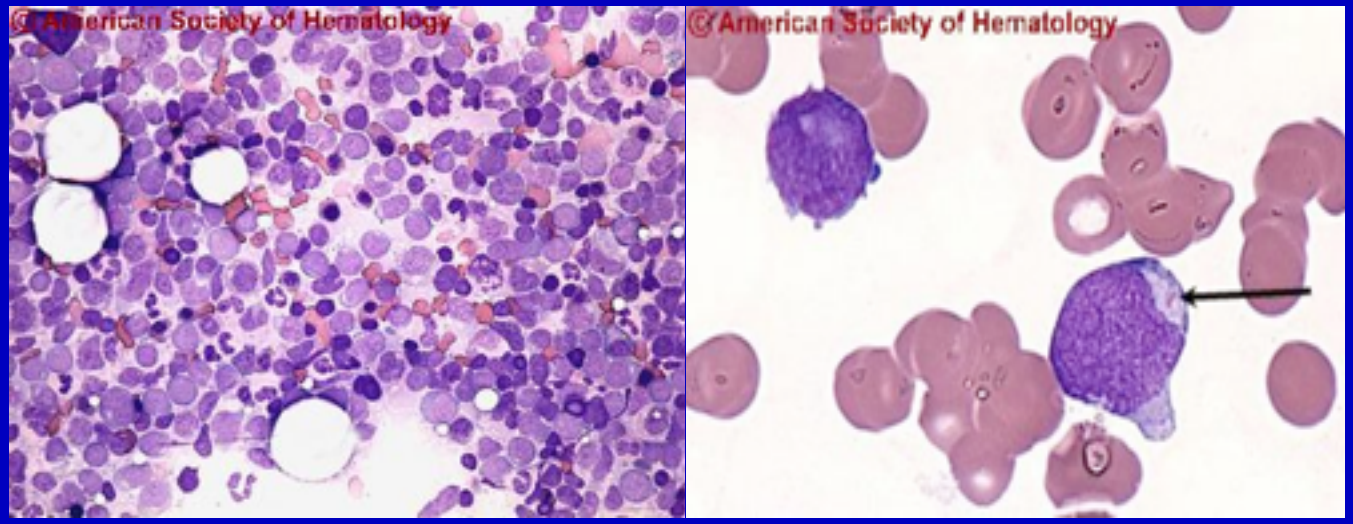
Hematologic Malignancies



Elizabeth A. Griffiths, MD
Leukemia Service, Department of Medicine
Roswell Park Cancer Institute
SUNY-UB School of Medicine

2013 Estimated US Cancer Cases*

Men	Women
841,390	843,820

Prostate	29%
Lung & bronchus	14%
Colon & rectum	9%
Urinary bladder	7%
Melanoma of skin	5%
Kidney & renal pelvis	5%
Non-Hodgkin lymphoma	4%
Oral cavity	3%
Leukemia	3%
Pancreas	3%
All Other Sites	18%

Source: American Cancer Society, 2012

29%	Breast
14%	Lung & bronchus
9%	Colon & rectum
6%	Uterine corpus
5%	Thyroid
4%	Melanoma of skin
4%	Non-Hodgkin lymphoma
3%	Kidney & renal pelvis
3%	Ovary
3%	Pancreas
20%	All Other Sites

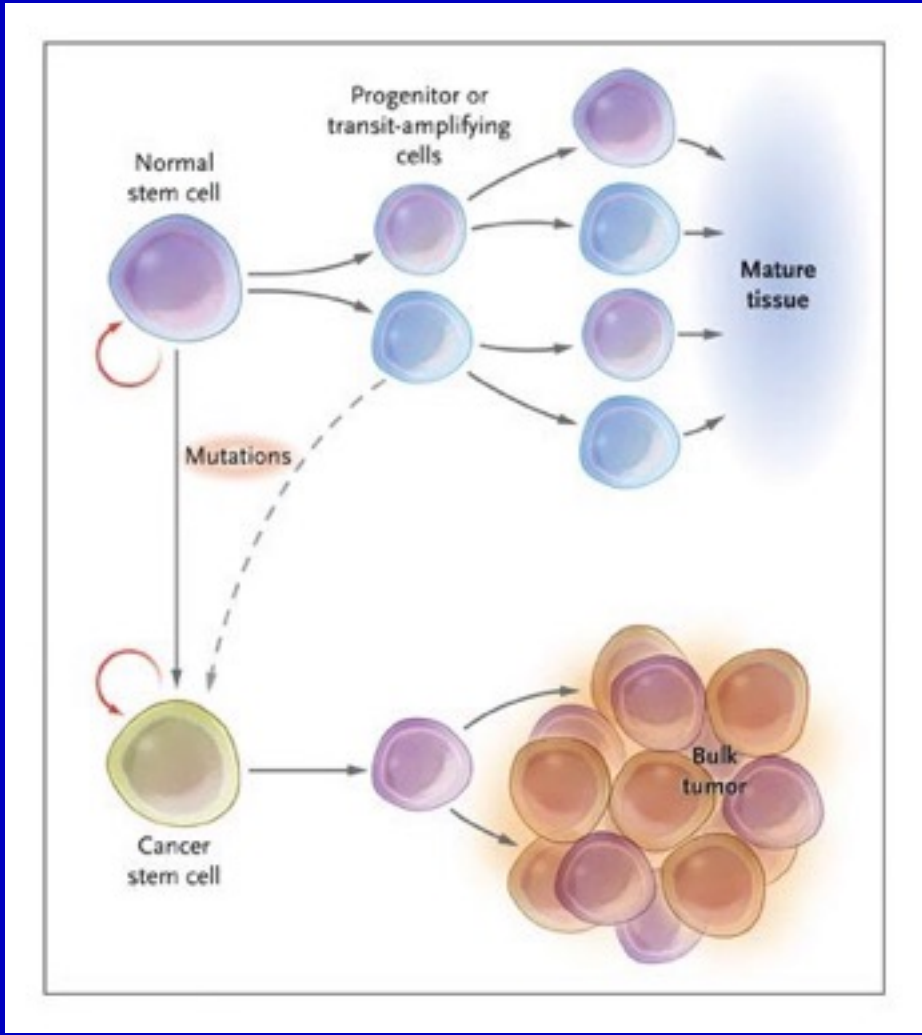
Source: American Cancer Society, 2012.

*Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.

2012 Estimated US Cancer Deaths

Men 301,820		Women 275,370	
Lung & bronchus	29%	26%	Lung & bronchus
Prostate	9%	14%	Breast
Colon & rectum	9%	9%	Colon & rectum
Pancreas	6%	7%	Pancreas
Liver & intrahepatic bile duct	5%	6%	Ovary
Leukemia	4%	4%	Leukemia
Esophagus	4%	3%	Non-Hodgkin lymphoma
Urinary bladder	3%	3%	Uterine corpus
Non-Hodgkin lymphoma	3%	2%	Liver & intrahepatic bile duct
Kidney & renal pelvis	3%	2%	Brain/other nervous system
All other sites	25%	24%	All other sites

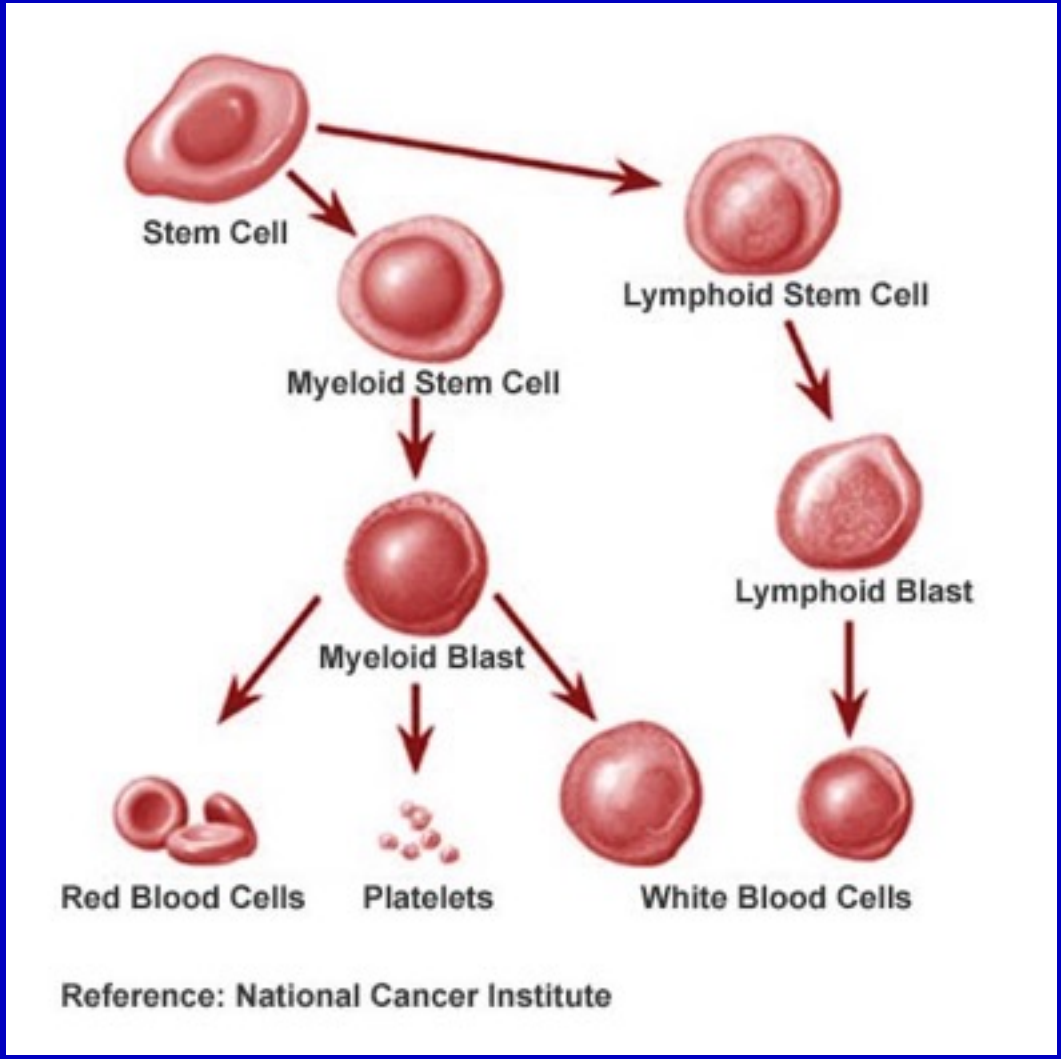
Blood cancers are normal blood cells gone “bad”



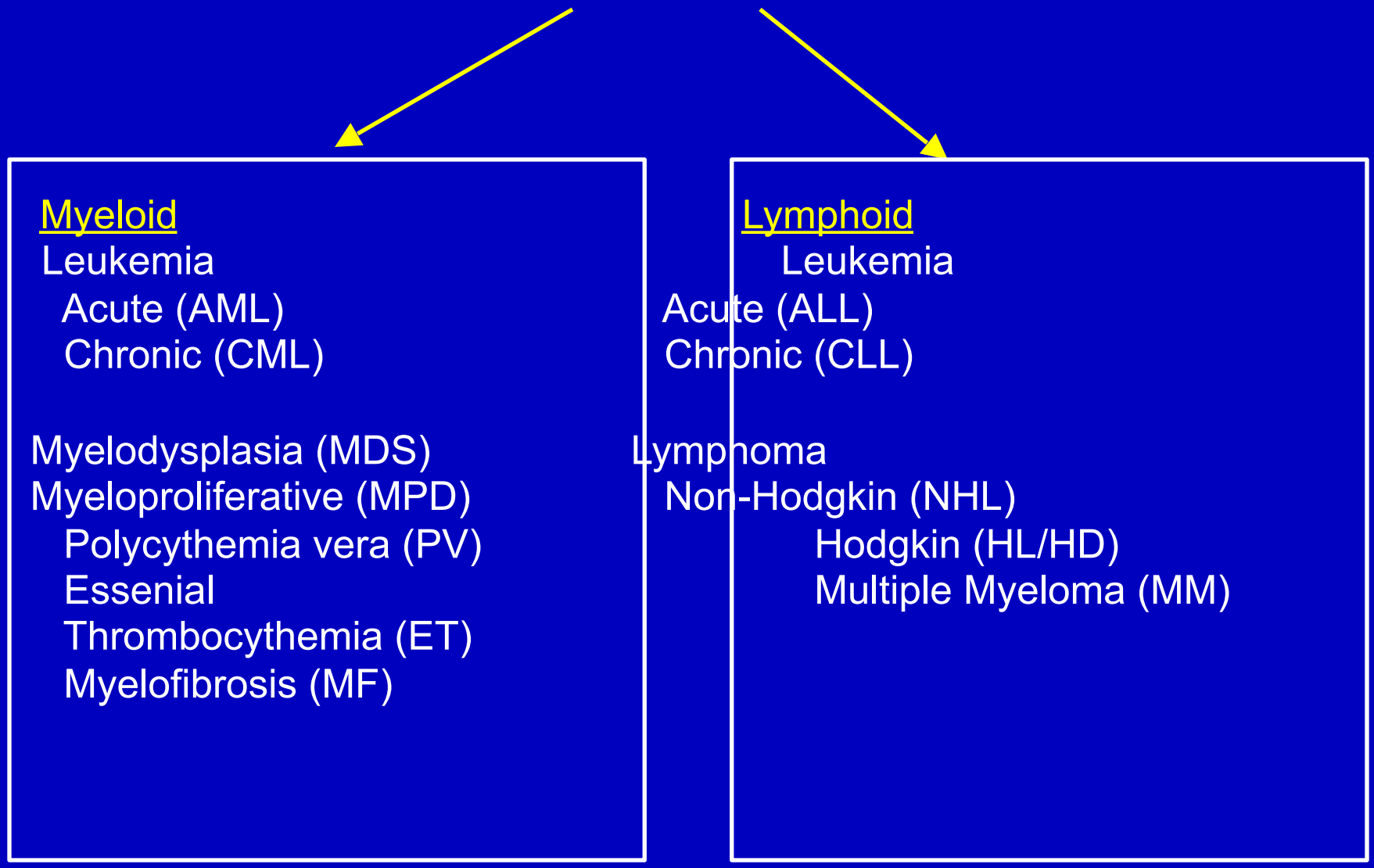
Jordan C et al. N Engl J Med 2006;355:1253-1261

The NEW ENGLAND JOURNAL of MEDICINE

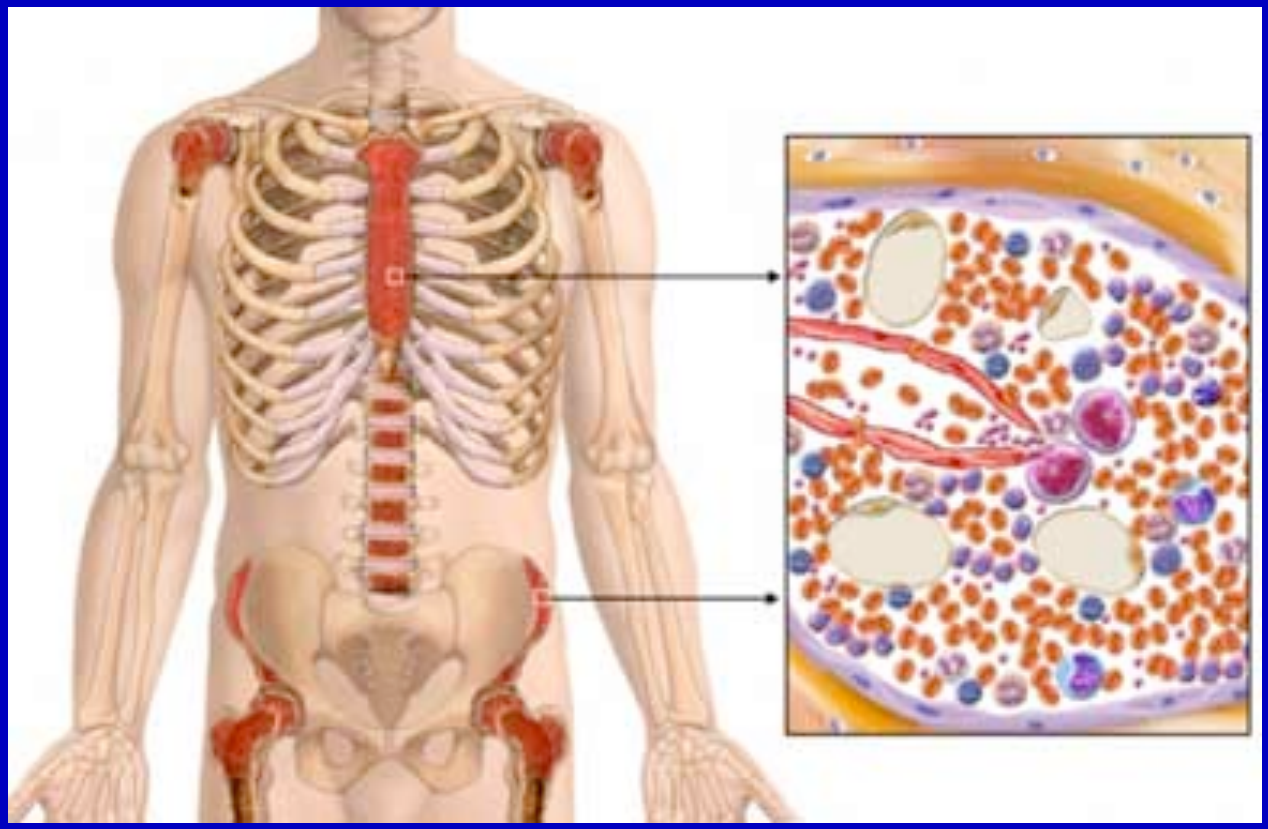
Hierarchy of Hematopoiesis

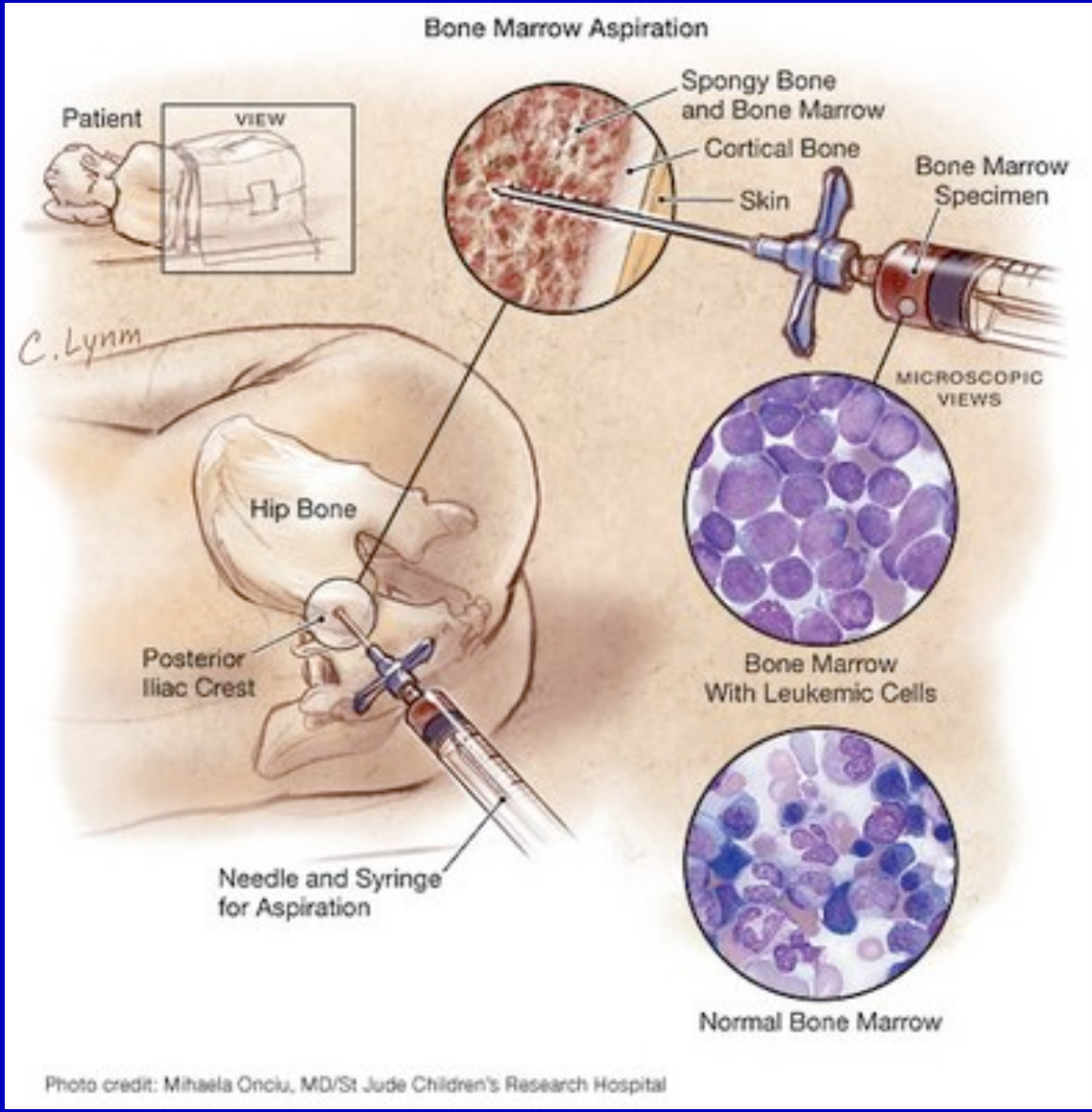


Types of Blood Cancers



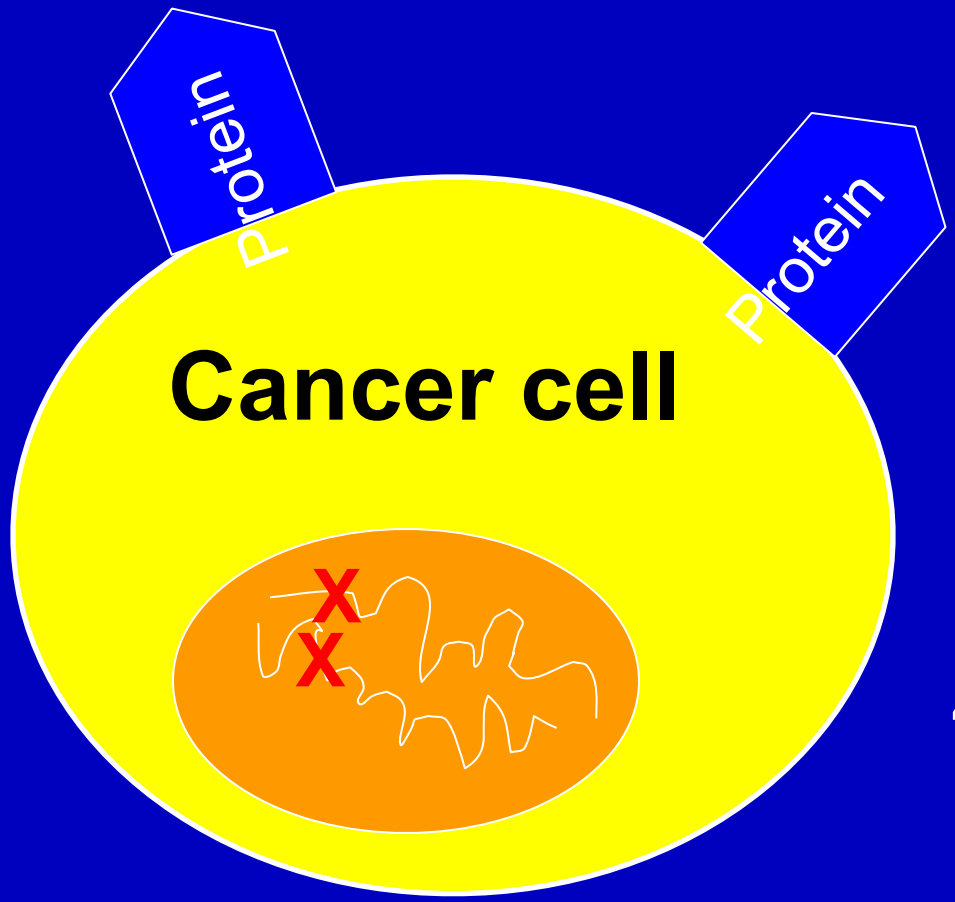
Bone marrow sites in adults




Bone Marrow Aspiration
Patient
VIEW
Spongy Bone and Bone Marrow
Cortical Bone
Skin
Bone Marrow Specimen
C. Lynm
MICROSCOPIC VIEWS
Hip Bone
Posterior Iliac Crest
Bone Marrow With Leukemic Cells
Needle and Syringe for Aspiration
Normal Bone Marrow
Photo credit: Mihaela Onciu, MD/St Jude Children's Research Hospital

Diagnosis of blood cancers

1. Appearance (morphology)



2. Abnormal protein expression (flow cytometry) (histochemistry)

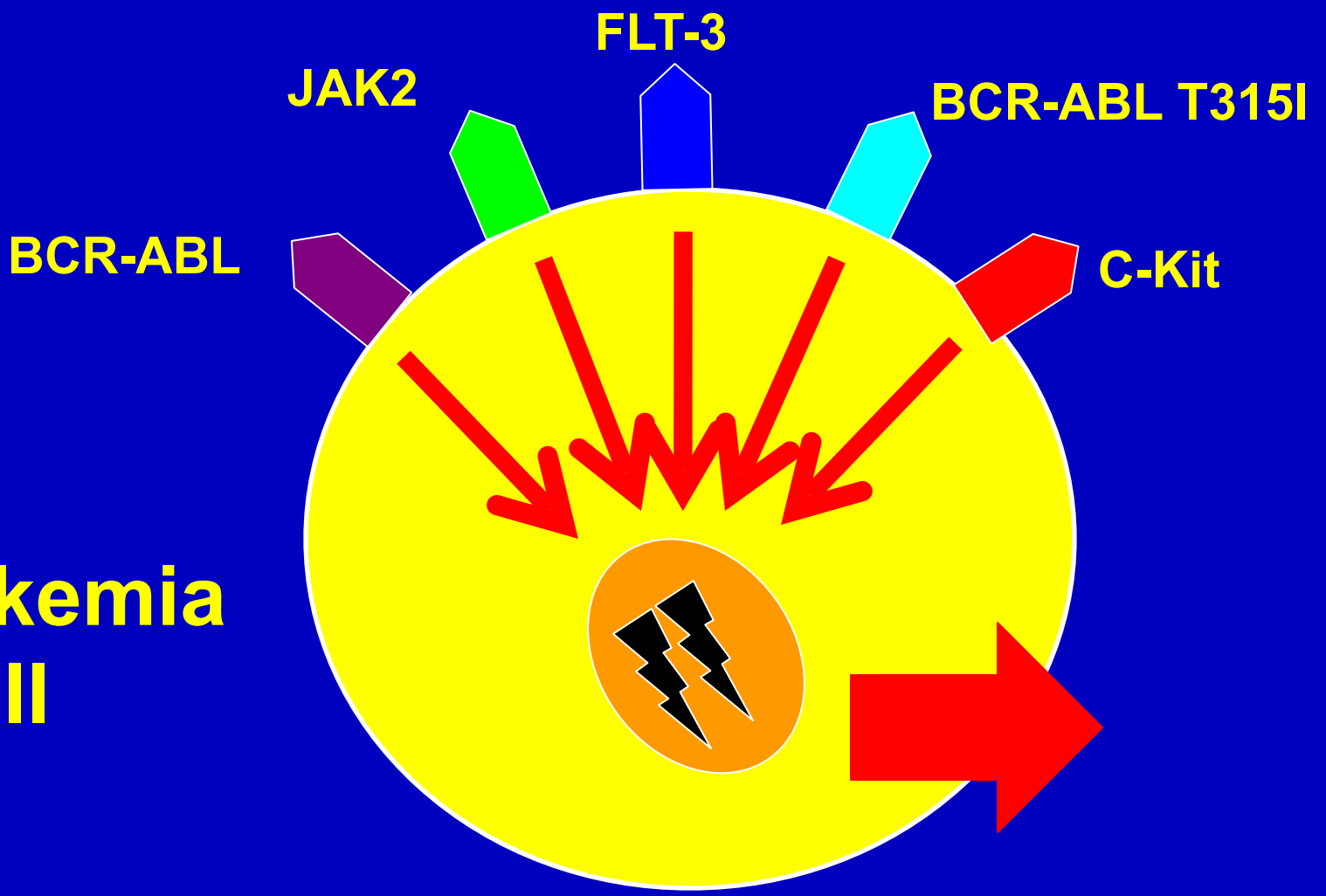
3.Chromosome abnormalities (cytogenetics)

4. Specific gene mutations

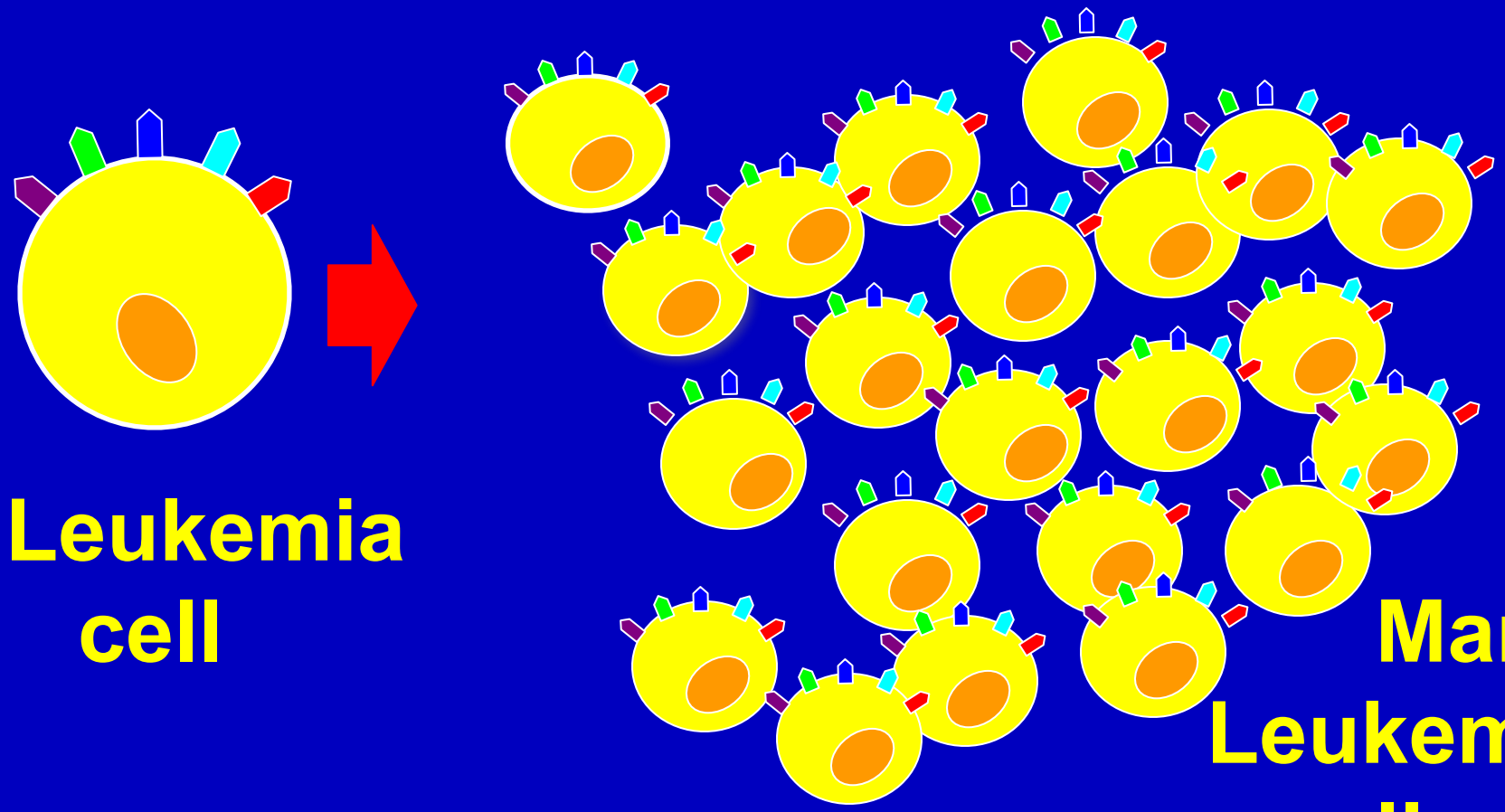
Treatments for Blood Cancers

- Cytotoxic chemotherapy
- Stem cell (bone marrow) transplantation
- Biological therapies (some experimental)
  - Receptor tyrosine kinase inhibitors
  - Antibodies
  - Immunomodulating agents
  - Differentiating agents

Leukemia cells express many abnormal receptors which promote growth



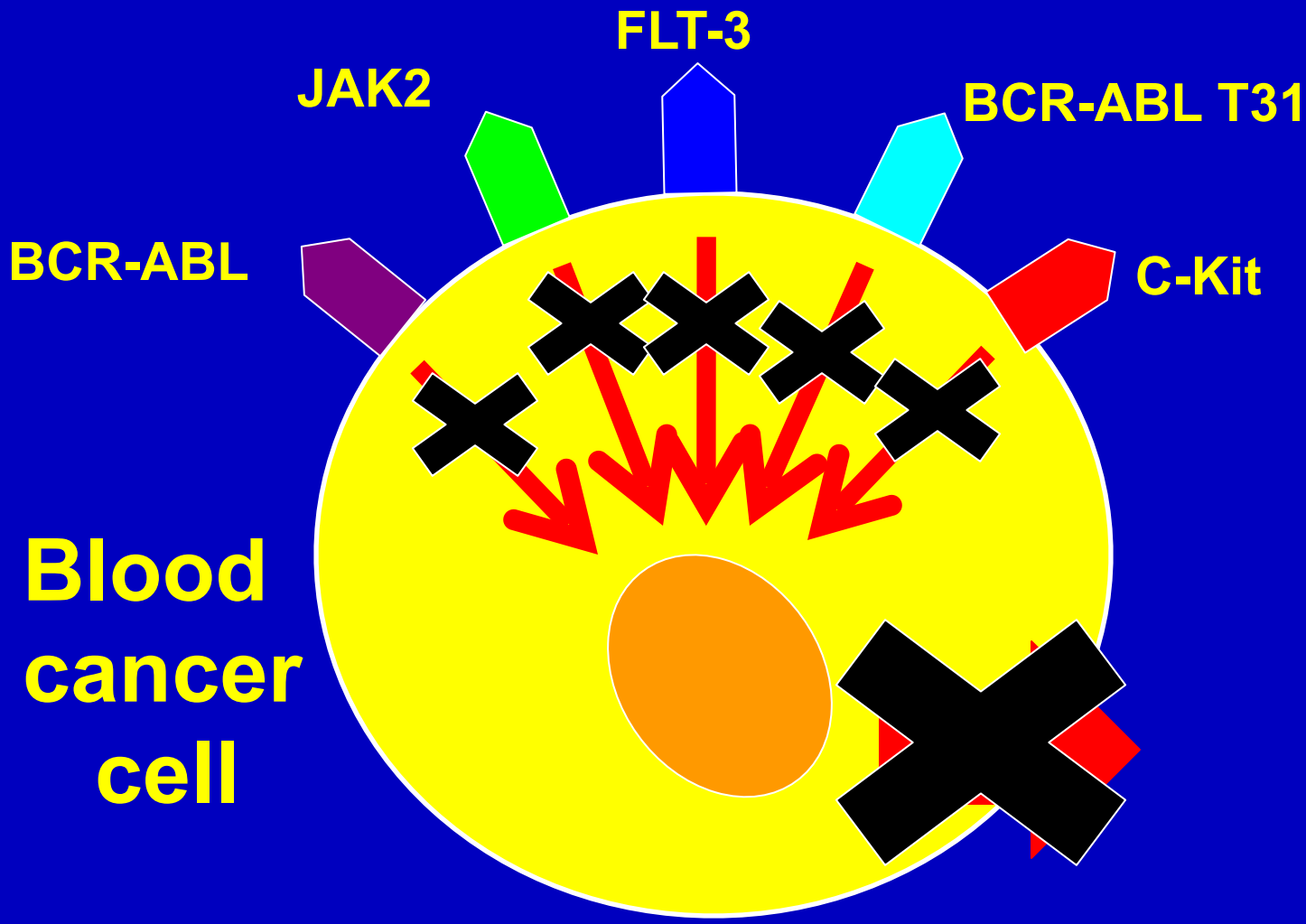
Leukemia cells express many abnormal receptors which promote growth



Leukemia cell

Many Leukemia cells

Inhibitors of tumor-specific receptors can inhibit leukemia growth



Specific kinase receptor inhibitors for different leukemia patients

Leukemia	Abnormal receptor	Inhibitor name
AML (FLT-3 mut)	FLT-3	Sorafenib, Midostaurin, AC220, et al.
ALL (Ph+)	BCR-ABL	Imatinib, Dasatinib (Sprycel), nilotinib (Tasigna)
CML	BCR-ABL	Imatinib, dasatinib, nilotinib
CML (resistant)	BCR-ABL T315I mutation	Ponatinib
Myelofibrosis (MF)	JAK2	Jakafi

Stem Cell Transplantation

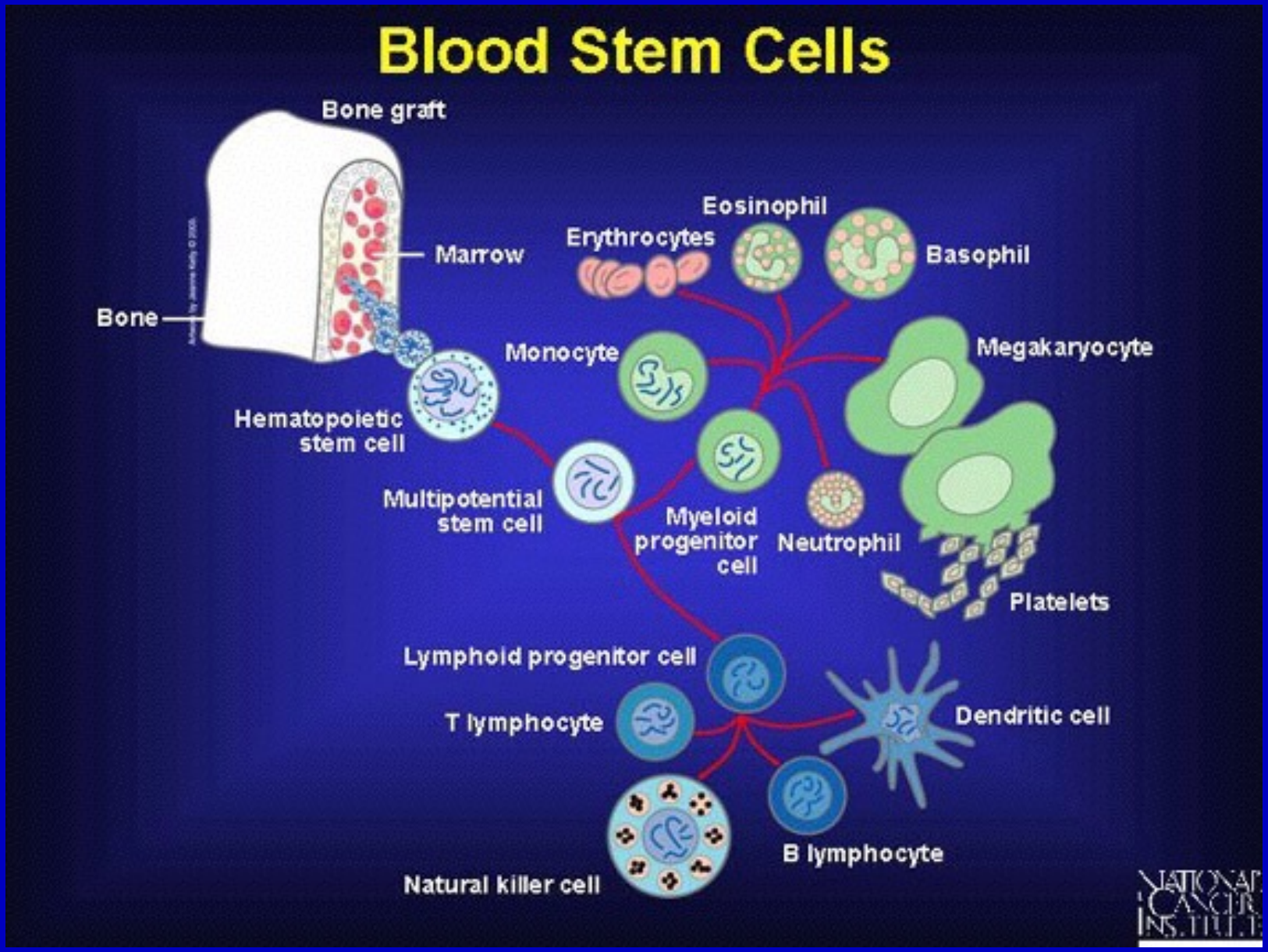
Requires compatible donor stem cell source:

- Allogeneic, autologous, syngeneic,
- Marrow vs. blood vs. cord blood cells

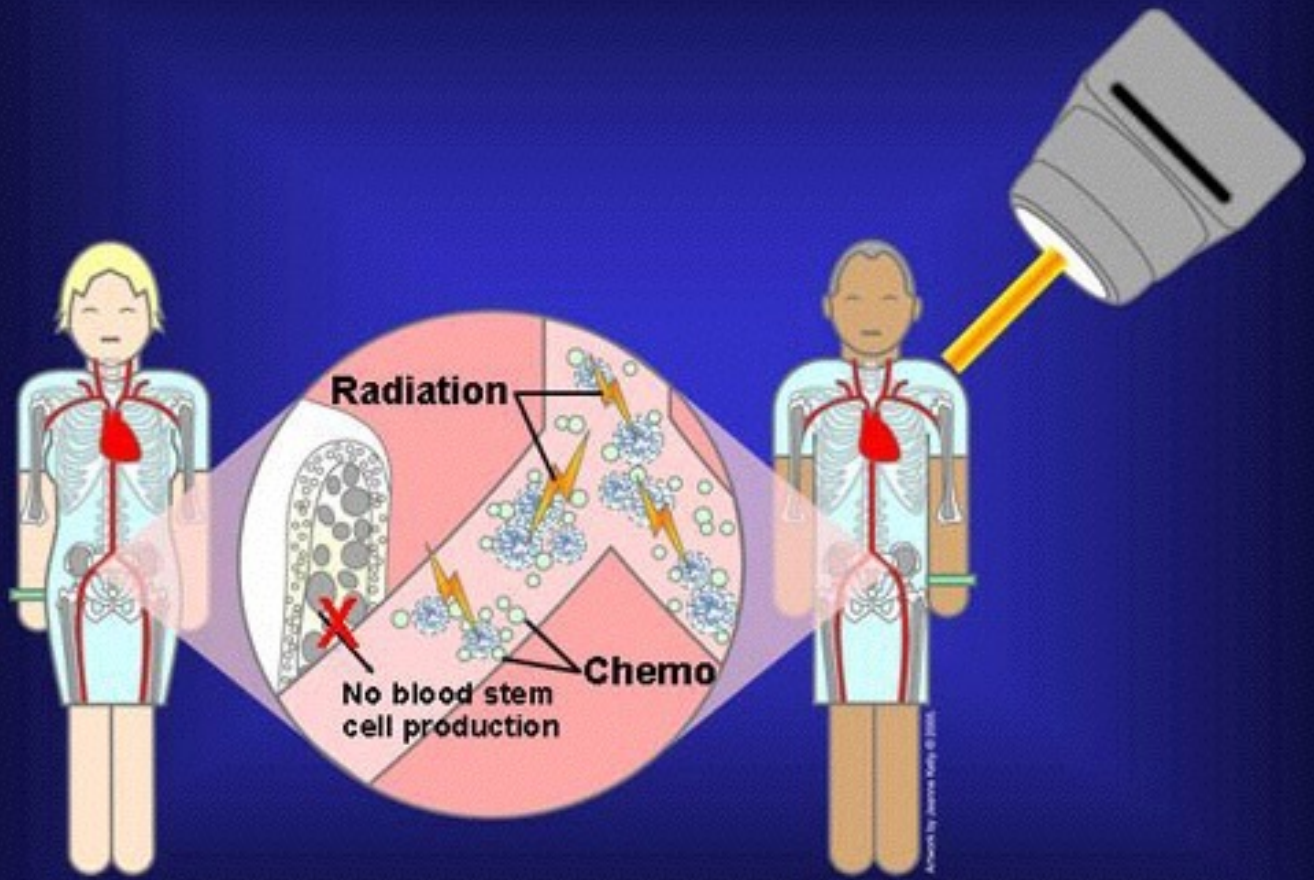
Pre-SCT chemotherapy/immunosuppression (termed conditioning) to prepare BM for new stem cells

Evaluation of immunologic consequences

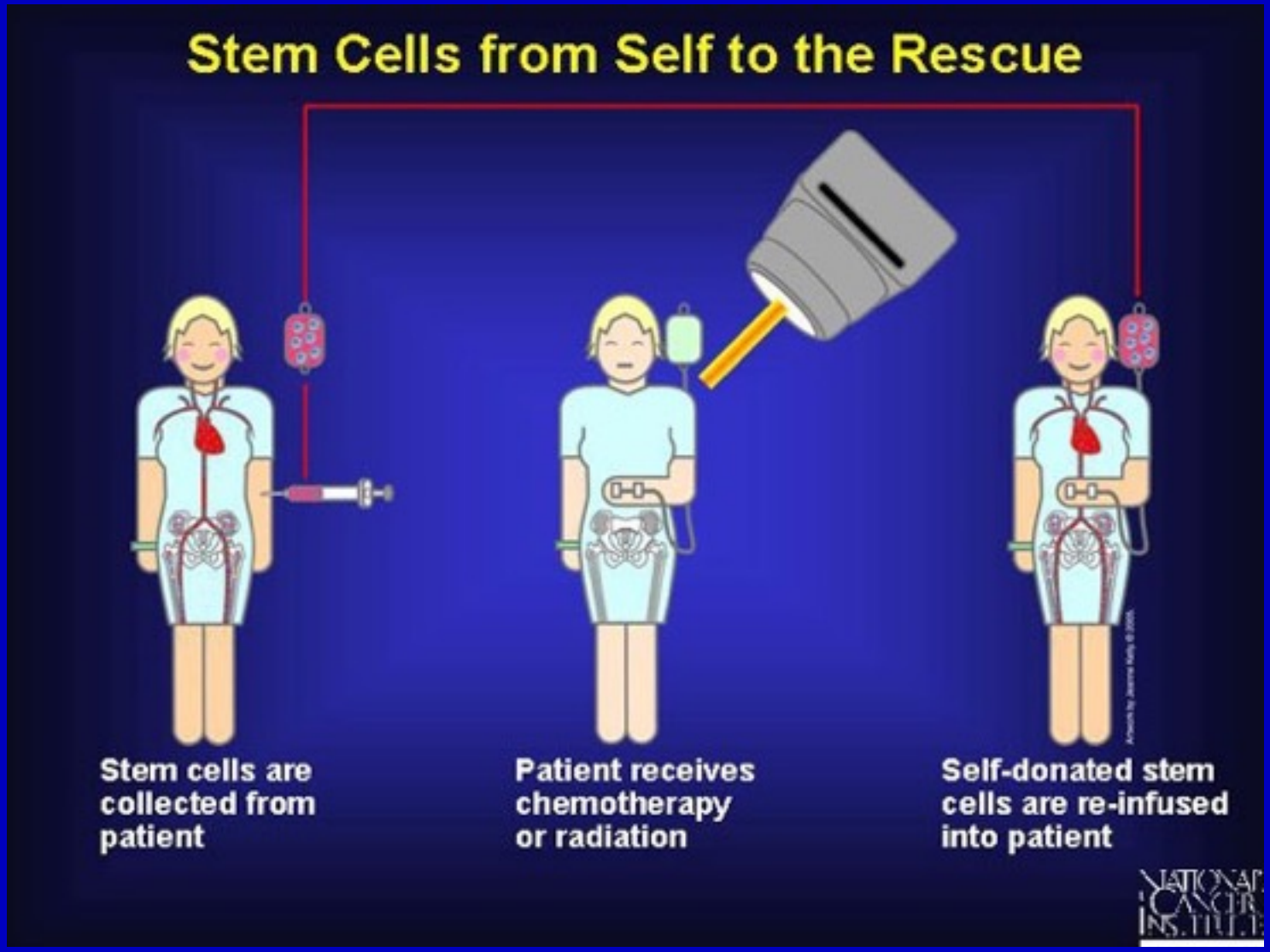
-Graft vs. Host, Graft vs. Leukemia


Blood Stem Cells
Bone graft
Marrow
Bone
Eosinophil
Erythrocytes
Basophil
Monocyte
Megakaryocyte
Hematopoietic stem cell
Multipotential stem cell
Myeloid progenitor cell
Neutrophil
Platelets
Lymphoid progenitor cell
T lymphocyte
Dendritic cell
B lymphocyte
Natural killer cell

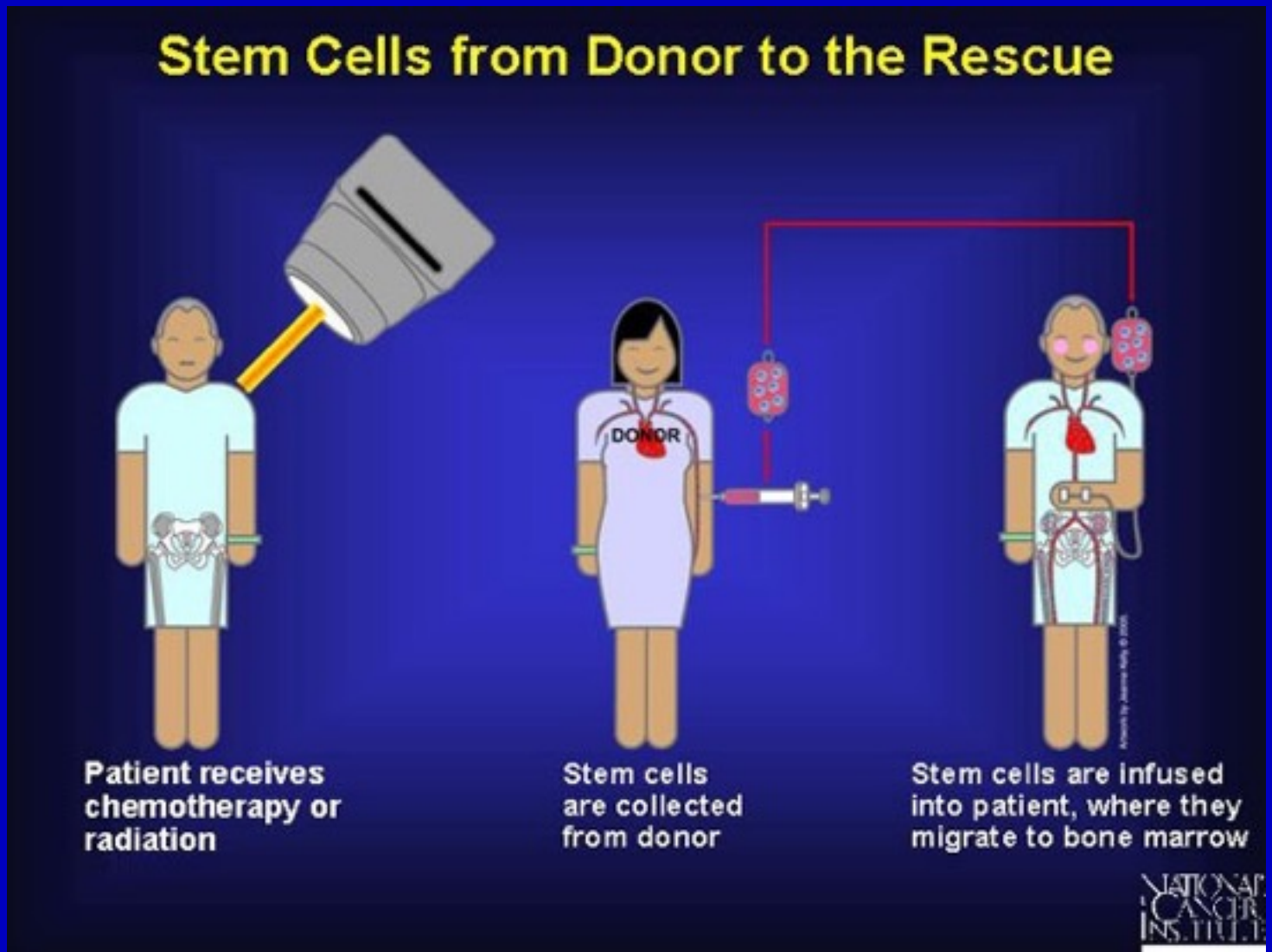
Blood Stem Cell Transplants: When?



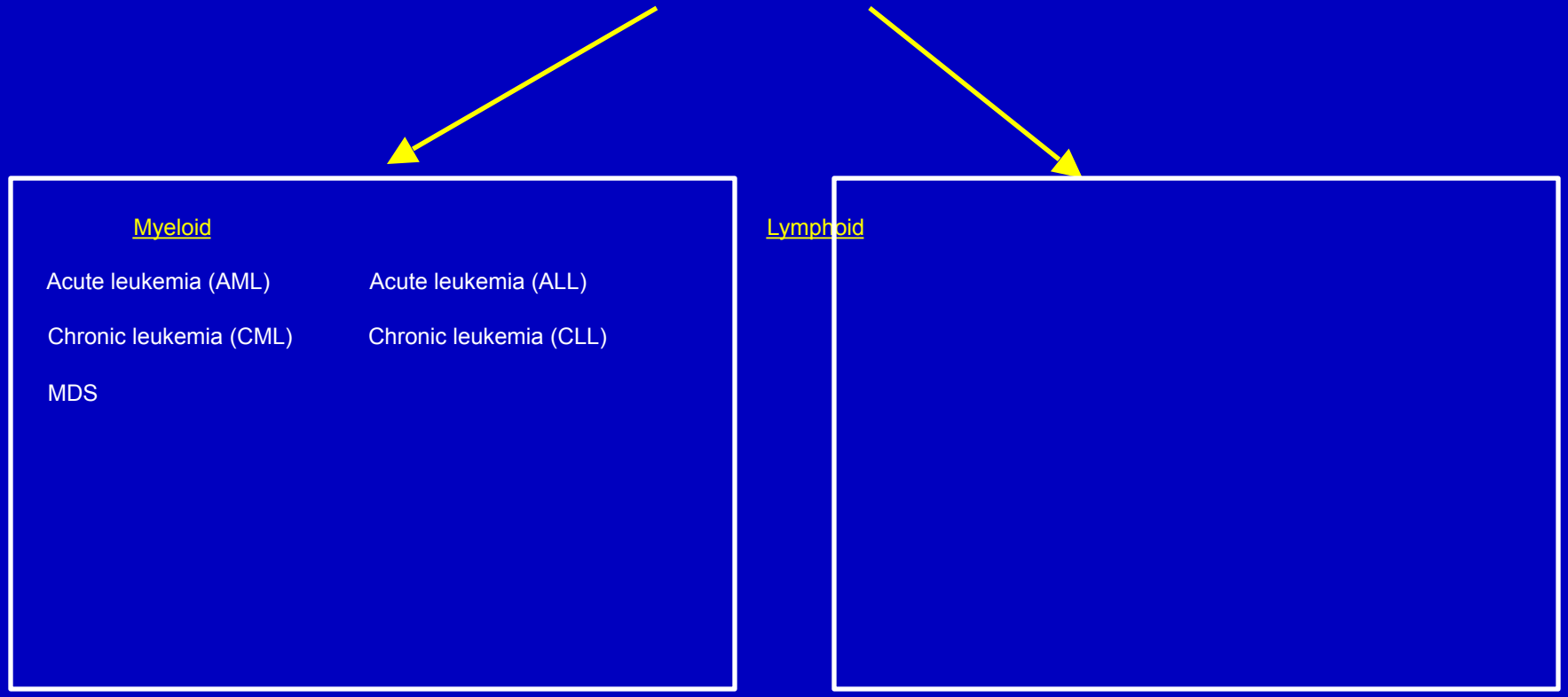
Autologous Stem Cell Transplant= Means for High dose Chemotherapy



Allogeneic Stem Cell Transplant= Immune/Blood System Replacement



Types of Leukemias

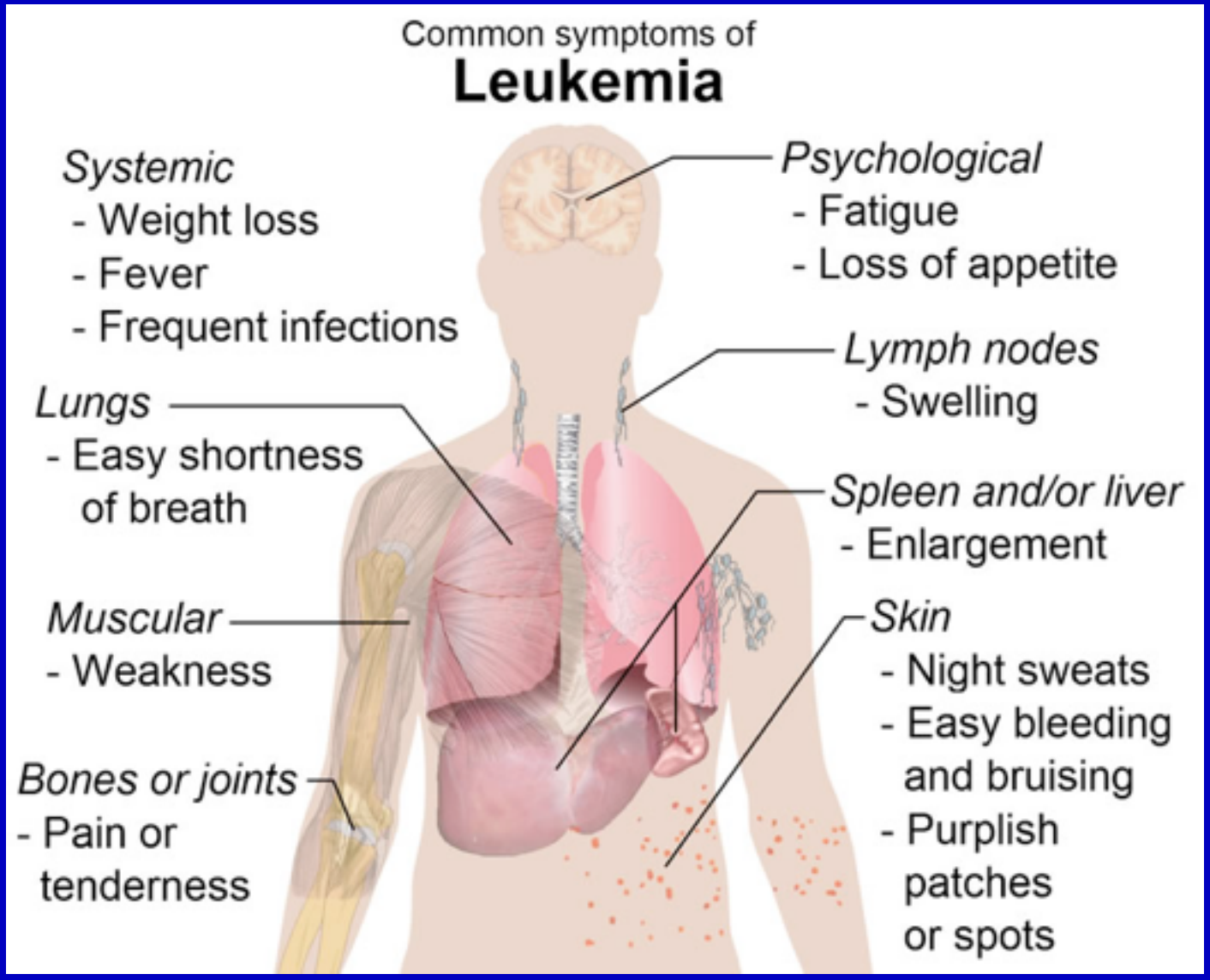


Acute= fast growing (days-weeks)
Chronic=slow growing (months-years)

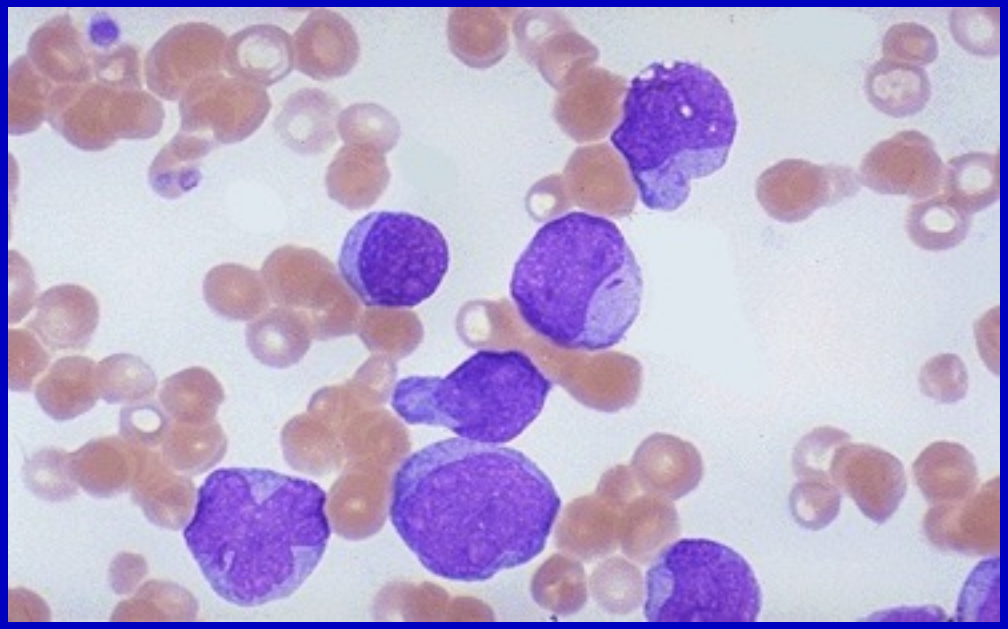
Acute leukemias

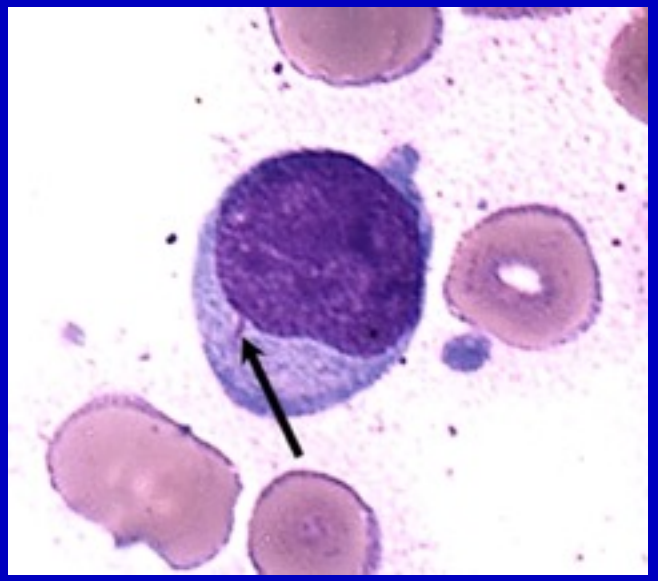
- “Leukemia is cancer of the white blood cells- cancer in one of its most explosive, violent incarnations…… Its pace, its acuity, its breathtaking, inexorable arc of growth forces rapid, often drastic decisions; it is terrifying to experience, terrifying to observe, and terrifying to treat. The body invaded by leukemia is pushed to its brittle physiological limit…..”

Siddartha Mukherjee. The Emperor of all Maladies: A Biography of Cancer. Scribner (2010).


Common symptoms of
Leukemia
Systemic
- Weight loss
- Fever
- Frequent infections
Psychological
- Fatigue
- Loss of appetite
Lymph nodes
- Swelling
Lungs
- Easy shortness of breath
Spleen and/or liver
- Enlargement
Muscular
- Weakness
Skin
- Night sweats
- Easy bleeding and bruising
- Purplish patches or spots
Bones or joints
- Pain or tenderness

Acute myeloid leukemia (AML)

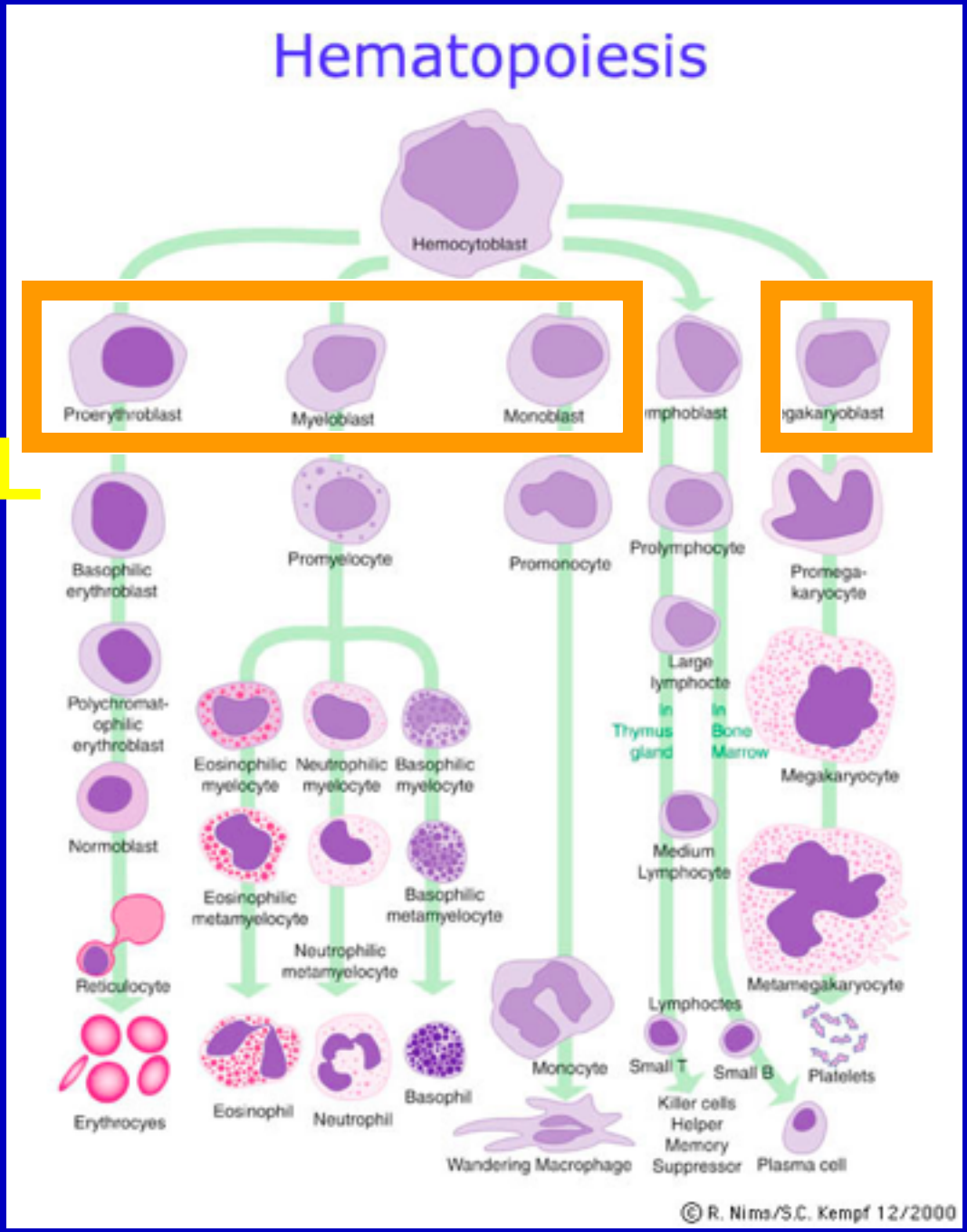




Immature myeloid blasts
Auer rods (coalesced granules)

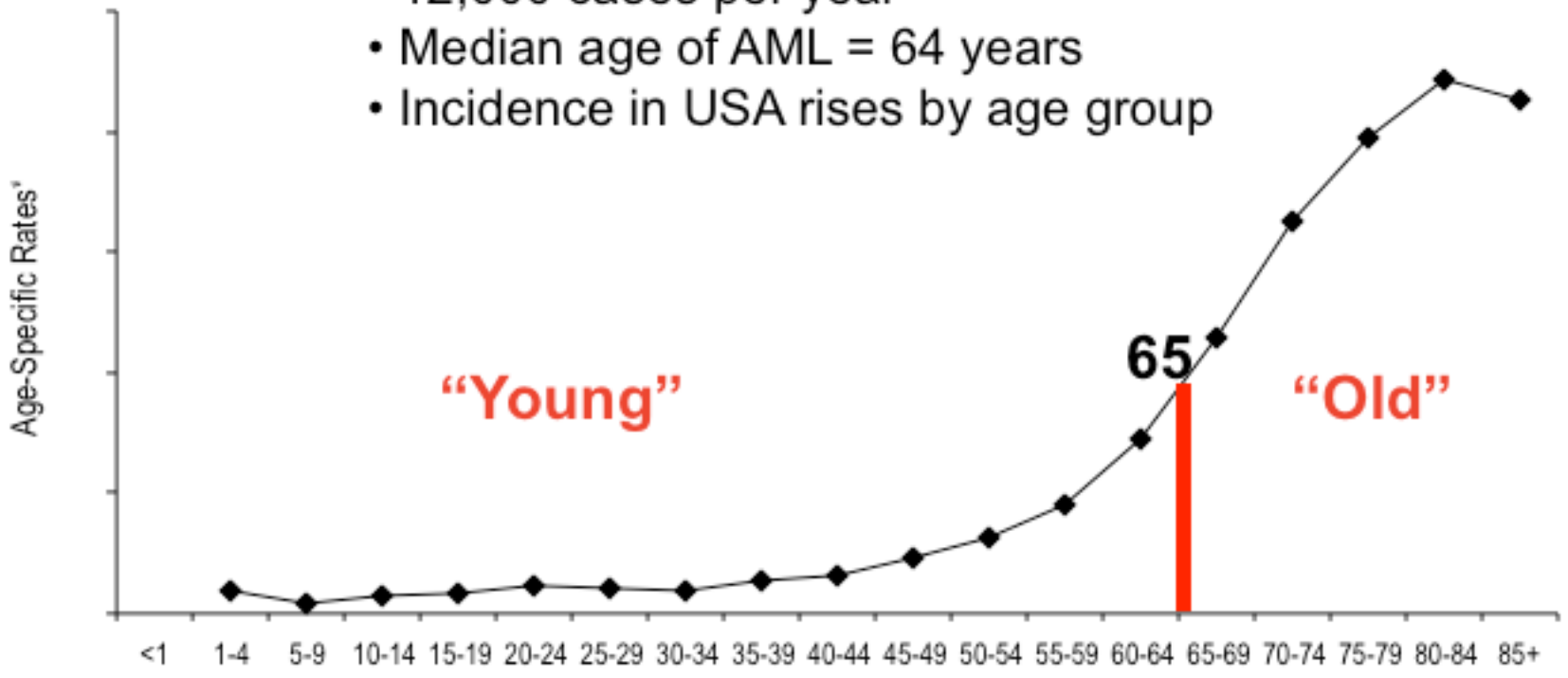
AML ←

→ AML


Hematopoiesis
Hemocytoblast
Proerythroblast
Myeloblast
Monoblast
mphoblast
gakaryoblast
Basophilic erythroblast
Promyelocyte
Promonocyte
Prolymphocyte
Promega-karyocyte
Large lymphocte
Polychromat-ophilic erythroblast
Eosinophilic myelocyte
Neutrophilic myelocyte
Basophilic myelocyte
in Thymus gland
in Bone Marrow
Megakaryocyte
Normoblast
Medium Lymphocyte
Eosinophilic metamyelocyte
Basophilic metamyelocyte
Neutrophilic metamyelocyte
Metamegakaryocyte
Reticulocyte
Lymphoctes
Monocyte
Small T
Small B
Platelets
Erythrocyes
Eosinophil
Neutrophil
Basophil
Killer cells
Helper
Memory
Suppressor
Wandering Macrophage
Plasma cell
© R. Nims/S.C. Kempf 12/2000

Acute Myeloid Leukemia

- 80% of acute leukemia in adults
- 12,000 cases per year
- Median age of AML = 64 years
- Incidence in USA rises by age group



Rates are per 100,000 and are age-adjusted.
National Cancer Institute. SEER Cancer Statistics Review 1995-2000.

Acute myeloid leukemia (AML): Clinical features

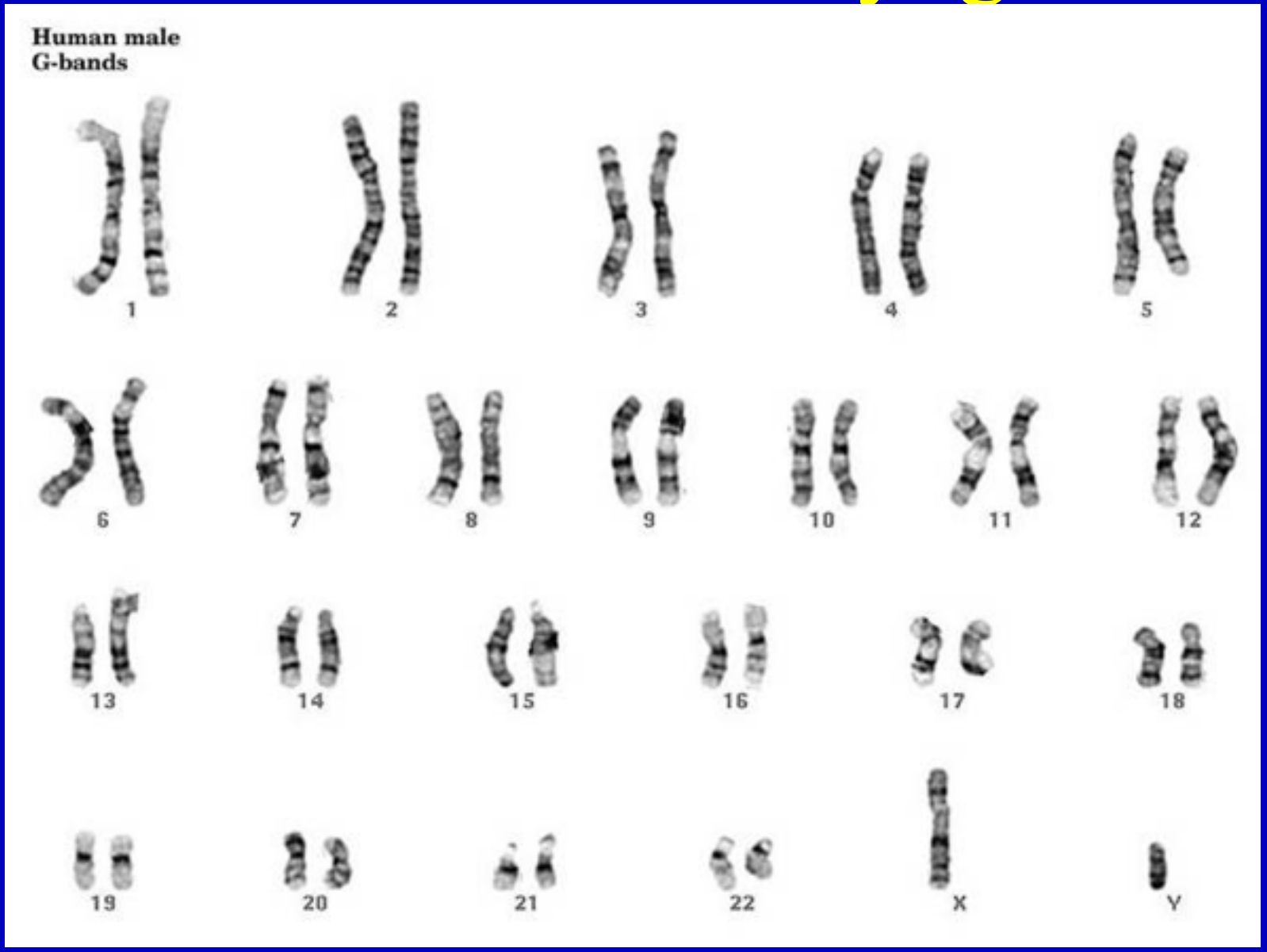
- Most common acute leukemia in adults (median age 67 y)
- Projected incidence 19,950 cases in 2016, mortality rate 50%
- Rapidly growing over days-weeks
- Presents with infection, bleeding or bruising, fatigue due to high or low white blood cell counts, low hemoglobin and low platelets
- May arise from prior hematologic disease such as myelodysplasia, myeloproliferative disorders, or prior chemotherapy/radiation for other cancers

Prognostic Factors in AML

- Disease Biology:
  - Cytogenetics (Critical!)
  - Gene mutations (*FLT-3, NPM1, CEBP*α mutations)

- Clinical Features:
  - Age > 65 years old
  - Performance status
  - Prior hematologic disorder
  - Therapy-related AML
  - High white blood cell count at diagnosis

Normal Male Karyogram



Risk Categories In AML: European LeukemiaNet Guidelines

Favorable risk

- t(8;21), inv(16) or t(16;16) (Core Binding Factor)
- Normal Karyotype, $NPM1^{mut}$ /$FLT3\text{-}ITD^{neg}$
- Normal Karyotype, $CEBPA^{mut}$

Intermediate-I

- Normal Karyotype, $NPM1^{mut}$ /$FLT3\text{-}ITD^{pos}$
- Normal Karyotype, $NPM1^{wt}$ /$FLT3\text{-}ITD^{pos}$
- Normal Karyotype, $NPM1^{wt}$ /$FLT3\text{-}ITD^{neg}$

Intermediate-II

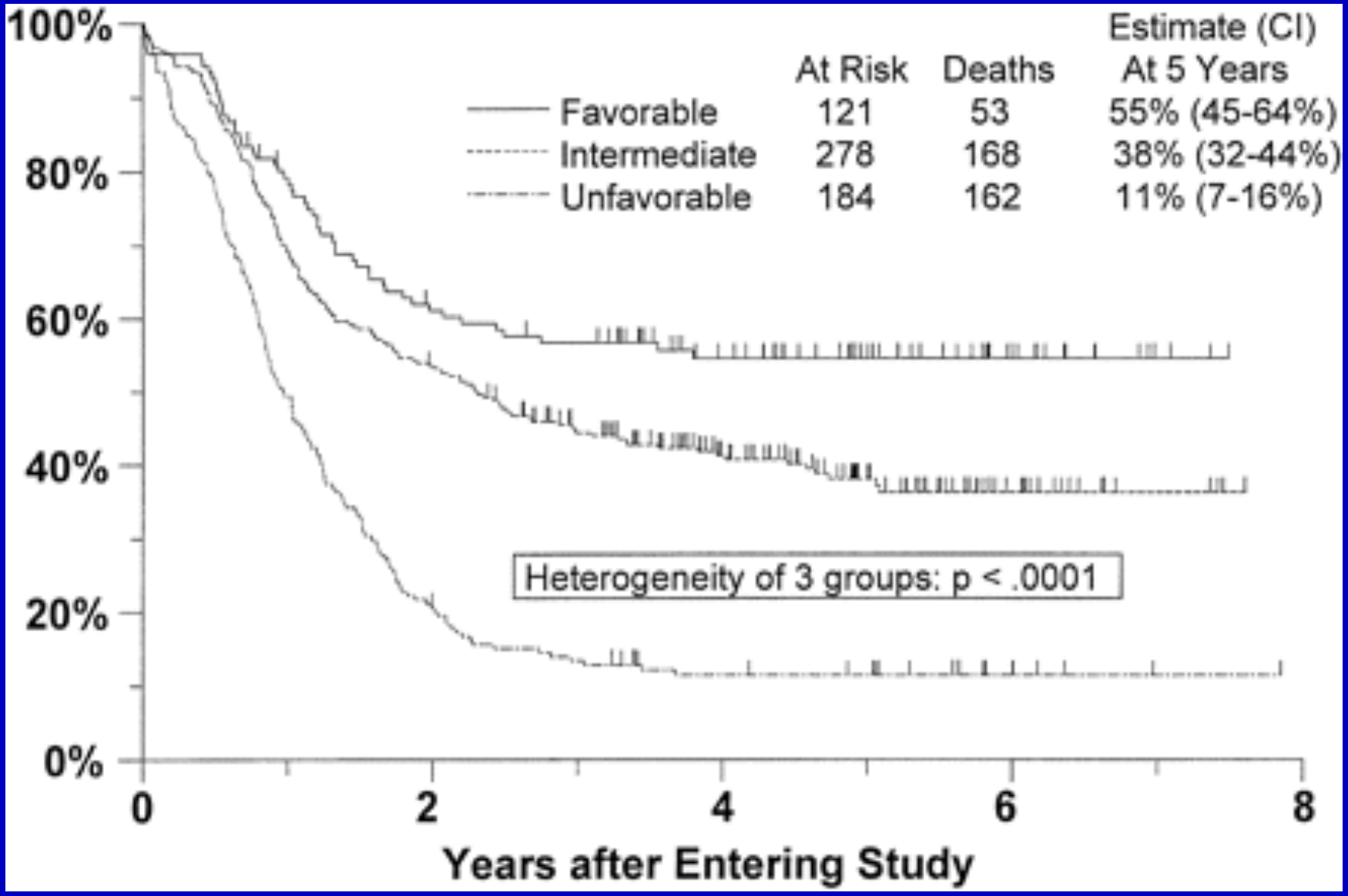
- t(9;11)(p22;q23); MLLT3-MLL
- Cytogenetic abnormalities not classified as favorable or adverse

Adverse Risk

- inv(3), t(6;9), *MLL* rearranged, –5 or del(5q), –7, abnl(17p)
- Complex karyotype

Intermediate

Overall Survival by Cytogenetic Group



Slovak ML et al. Blood, 2000; 96: 4075-83.

AML Treatment Goals

Diagnosis: stabilize pt, treatment decision (high/low/no go)

Induction: achieve CR and normal hematopoiesis

Post remission: prevent relapse
- Consolidation chemotherapy
- Allogeneic vs. Autologous stem cell transplantation

Refractory/relapsed disease: prolong survival/QOL
- Clinical trials
- Ara-C/anthracycline based re-induction
- Allogeneic vs Autologous SCT
- Supportive care, hospice

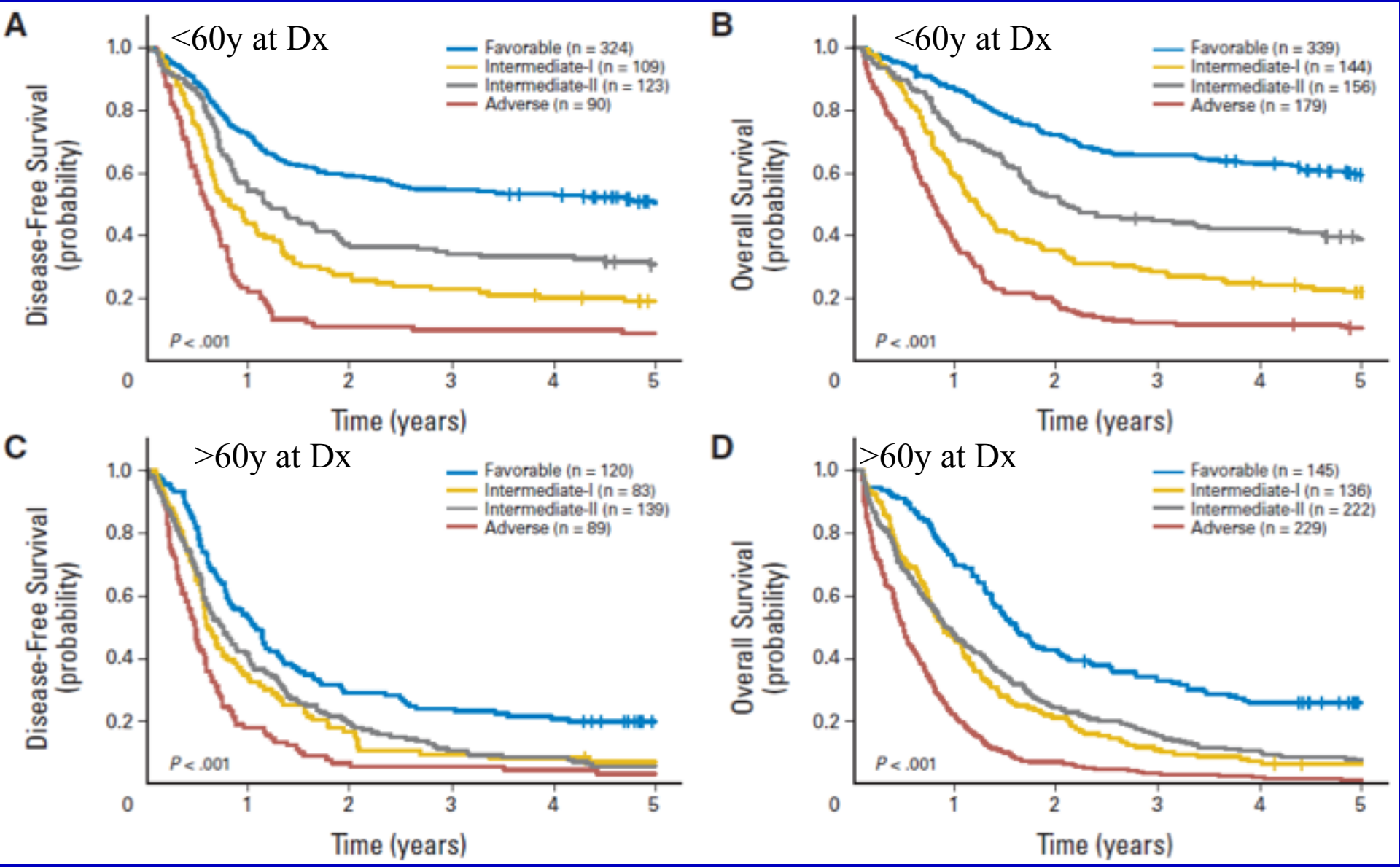
Standard AML therapy

- Induction: Admission to hospital for inpatient chemotherapy with two drugs: cytarabine (7 days) and anthracycline (3 days); requires a 30 day inpatient stay for chemo, antibiotics, transfusions until normal blood counts recover

- Remission= absence of leukemia on BM; does not equal cure (disease gone forever)

- All Pts in remission will require consolidation chemotherapy (1-4 shorter rounds of chemotherapy) OR stem cell transplantation for long term cure

Survival w/ Chemotherapy for Patients with AML



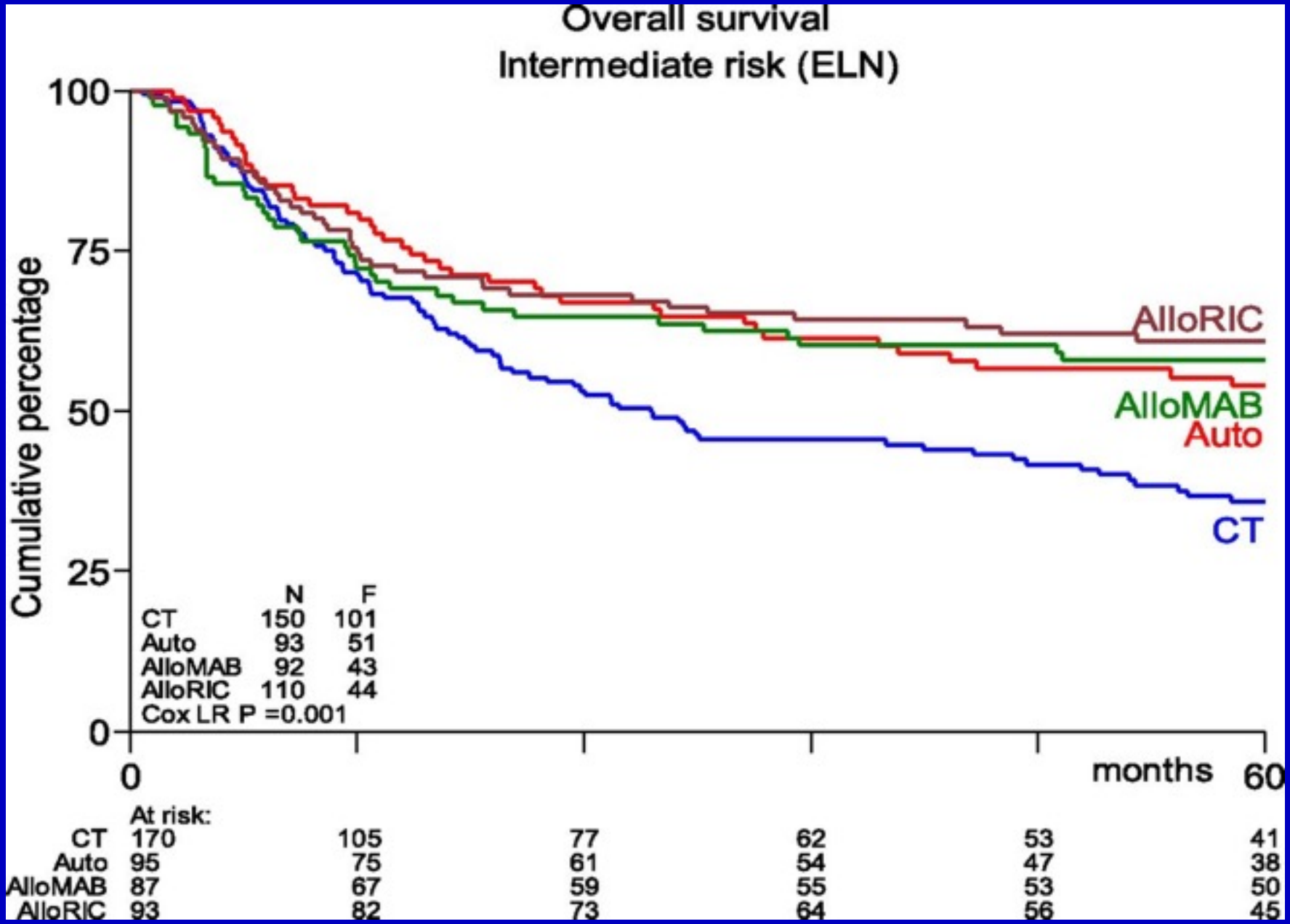
Mrozek et al. JCO 2012; 30:4515-23.

AML: Allogeneic Stem Cell Transplantation

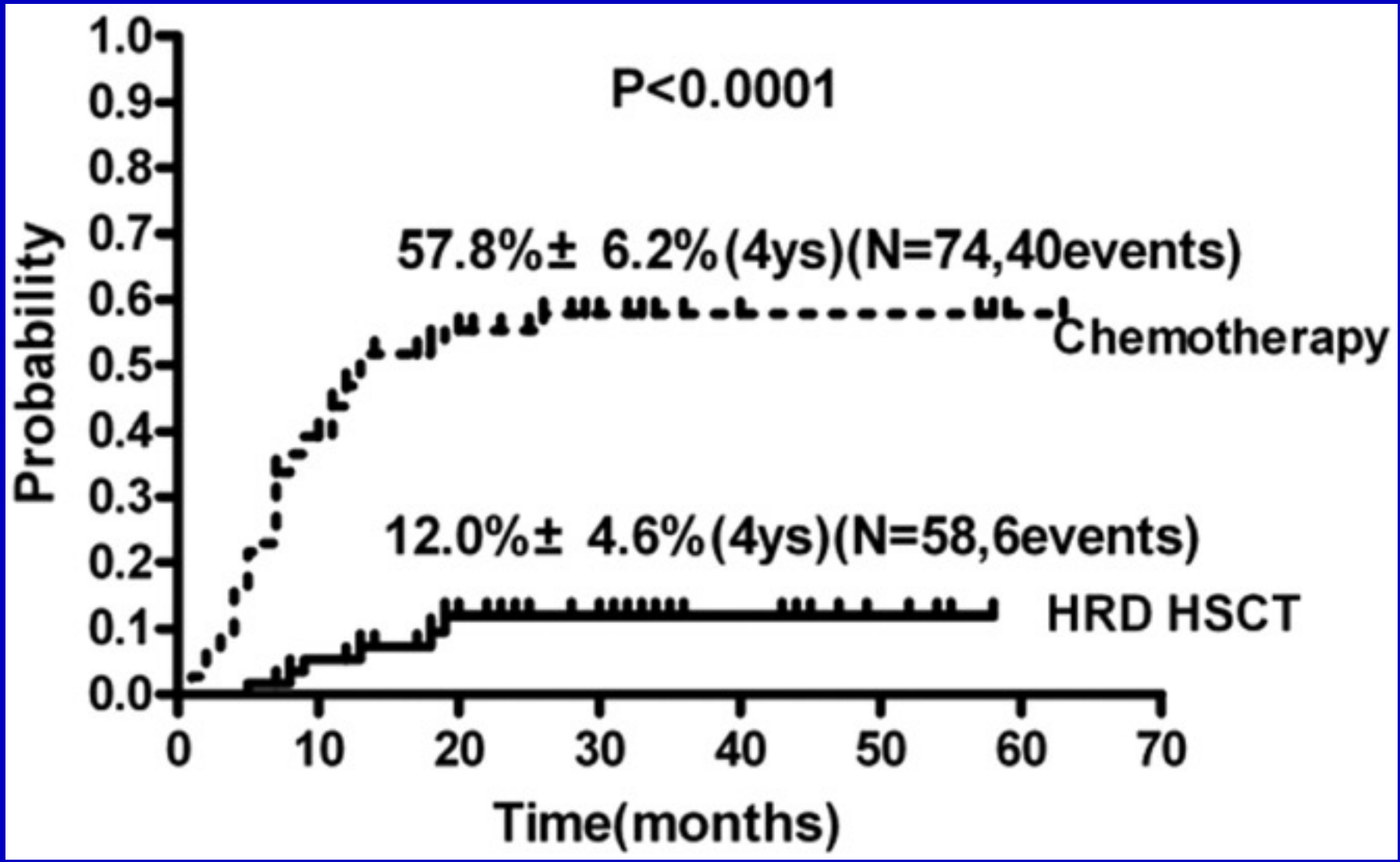
- Need HLA matched donor (sibling vs. unrelated)

- Only cure for many pts (generally <75 yo)
  - High risk leukemia
  - Refractory to initial chemotherapy
  - Relapsed leukemia
  - Second remission after relapse

- Mortality/morbidity with SCT: 25-30%

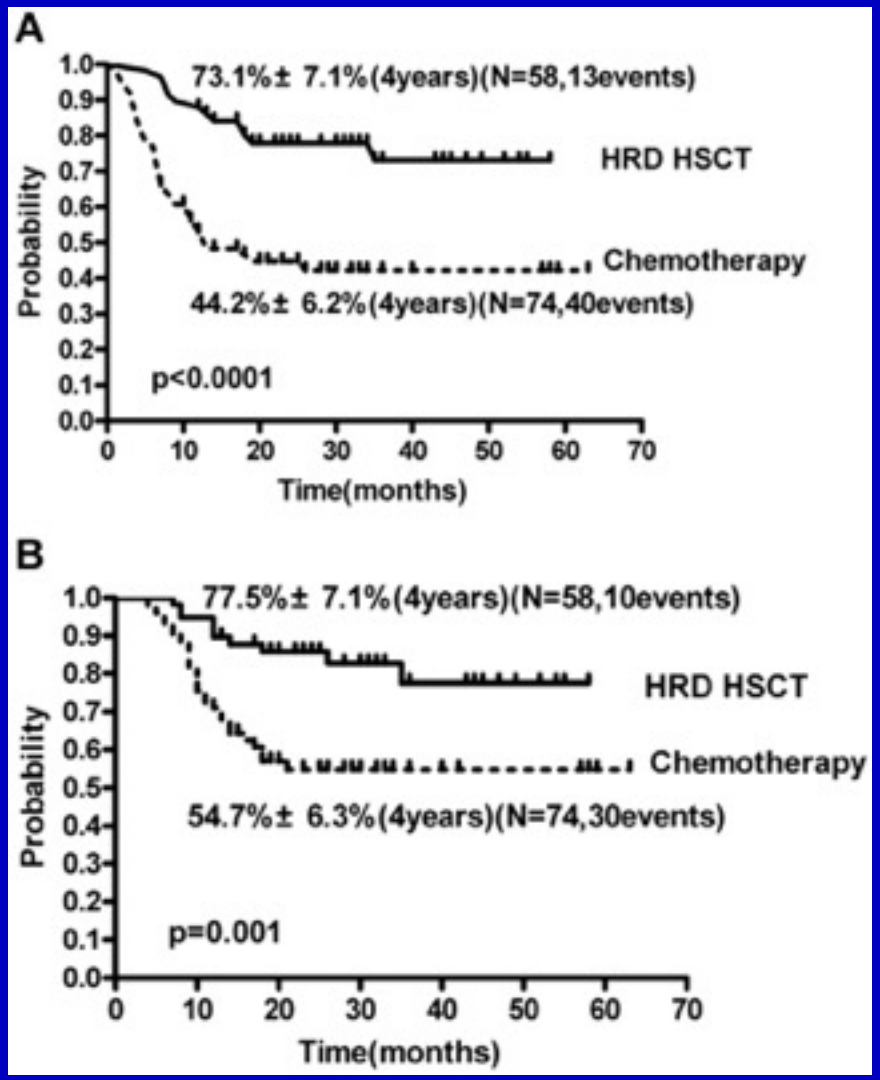

Overall survival
Intermediate risk (ELN)
Cumulative percentage
100
75
50
25
0
AlloRIC
AlloMAB
Auto
CT
N F
CT 150 101
Auto 93 51
AlloMAB 92 43
AlloRIC 110 44
Cox LR P =0.001
0
months
60
At risk:
CT 170 105 77 62 53 41
Auto 95 75 61 54 47 38
AlloMAB 87 67 59 55 53 50
AlloRIC 93 82 73 64 56 45

Risk of Relapse:
Chemotherapy-alone vs. Allo-Transplant for Intermediate/high-risk AML



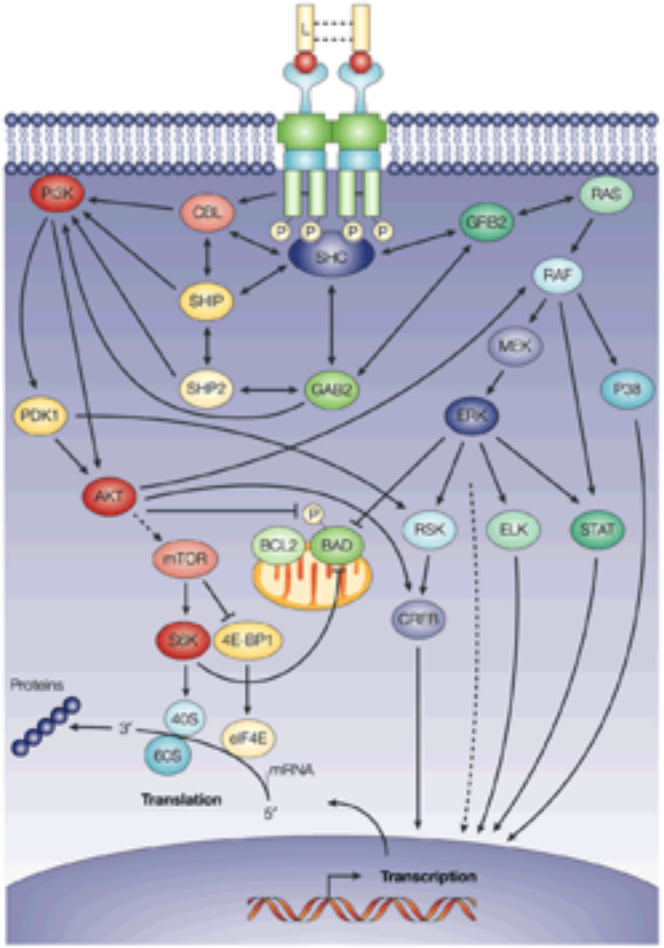
Xiao-Jun Huang et al. Blood 2012;119:5584-5590

DFS and OS for Int/High risk AML Patients: Chemotherapy vs Allogeneic Transplant



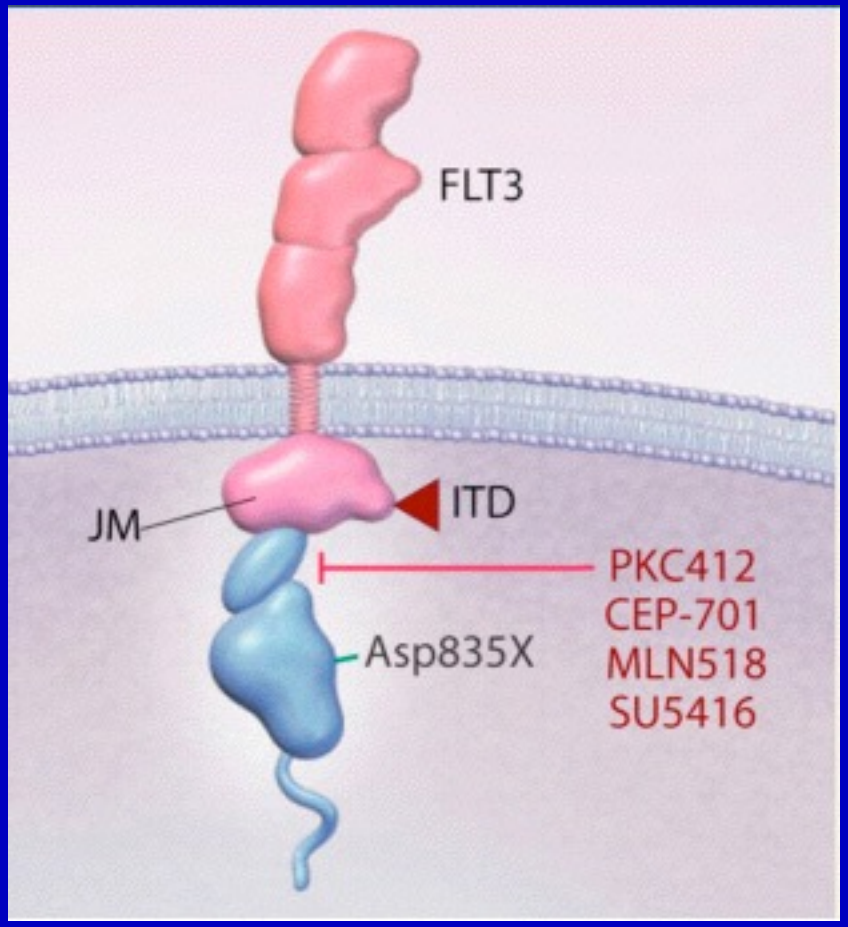
Xiao-Jun Huang et al. Blood 2012;119:5584-5590

FLT-3 kinase receptor in normal hematopoietic stem cells



FLT-3 kinase activation in hematopoietic cells results in stimulation of myriad downstream (PI3K, ras, Stat) pathways promoting growth

FLT-3 Mutations in AML

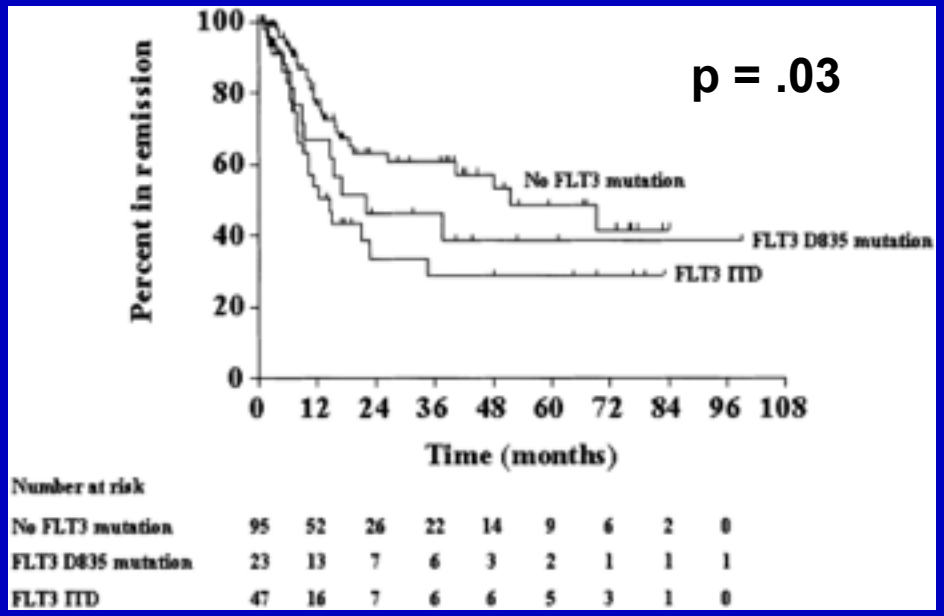


- Result in constitutive activation of FLT3 kinase
- Activation of growth-related signaling pathways
- FLT3 inhibitors (CEP-701, PKC412, MLN518, SU4516) block receptor kinase activity

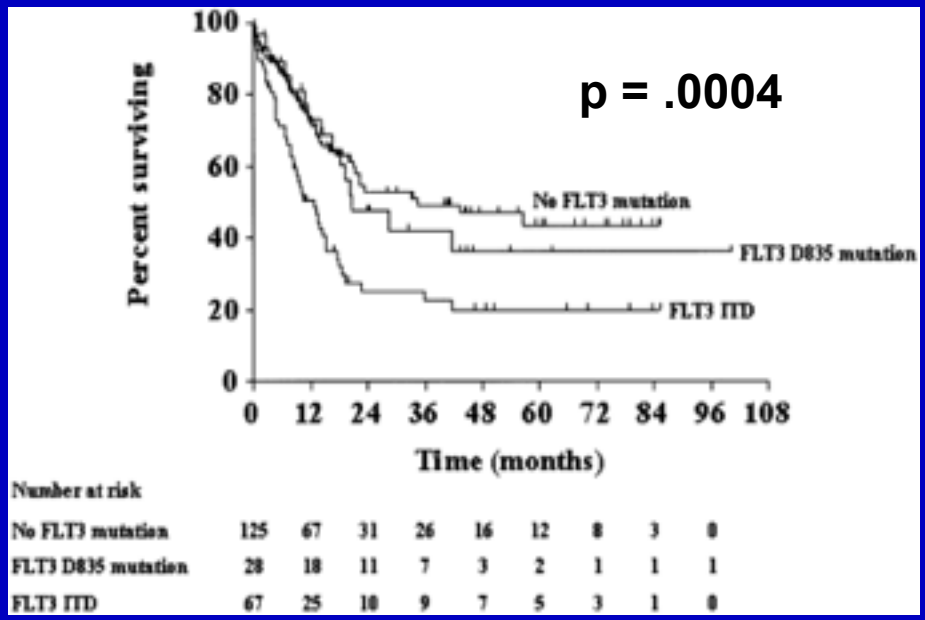
FLT-3 mutated AML is associated with worse clinical outcomes

	Frequency	CR Rate*	
ITDs	71 (32%)	65%	
Asp835 Mutations	32 (14%)	82%	*vs. 76%

DFS

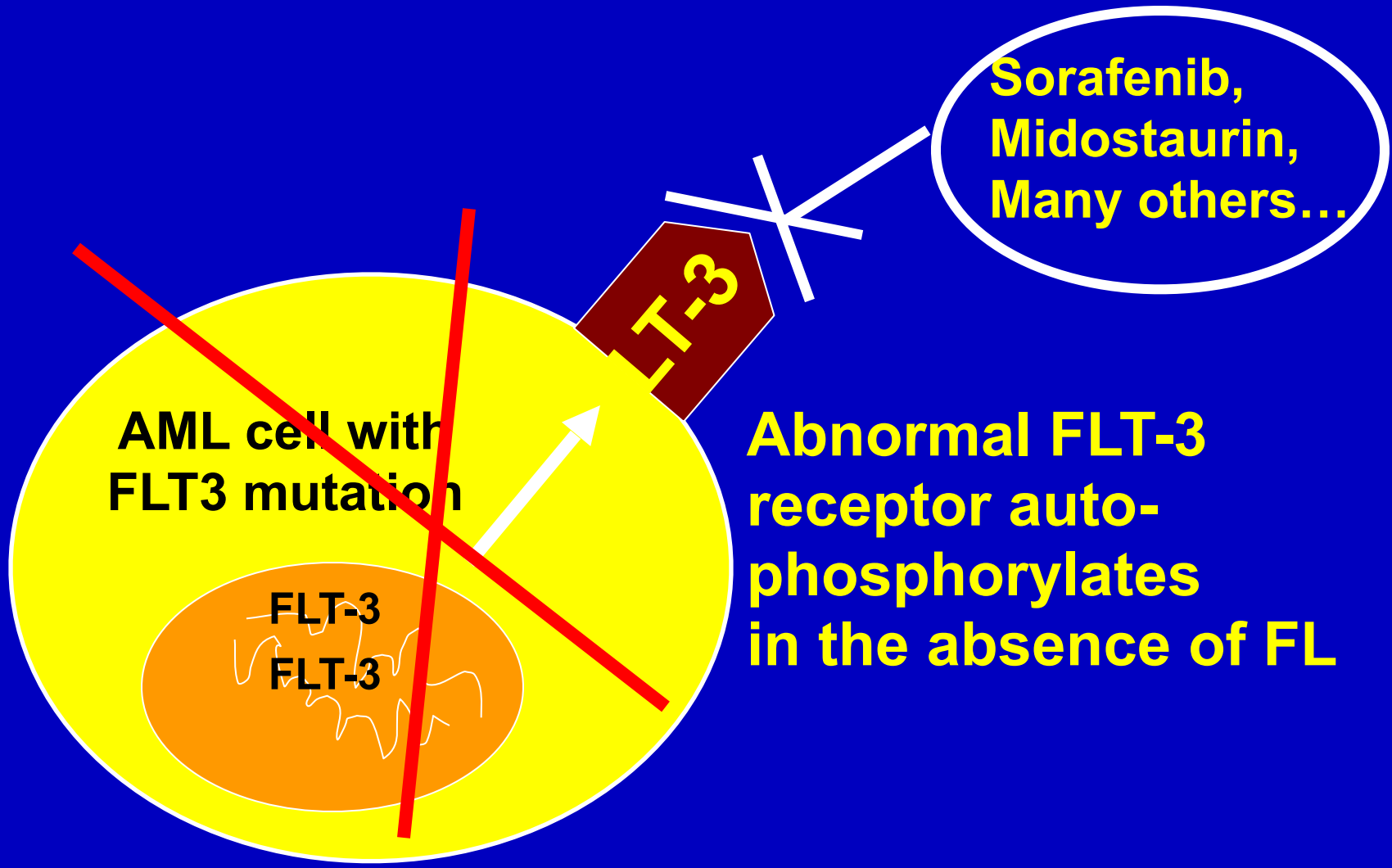


OS

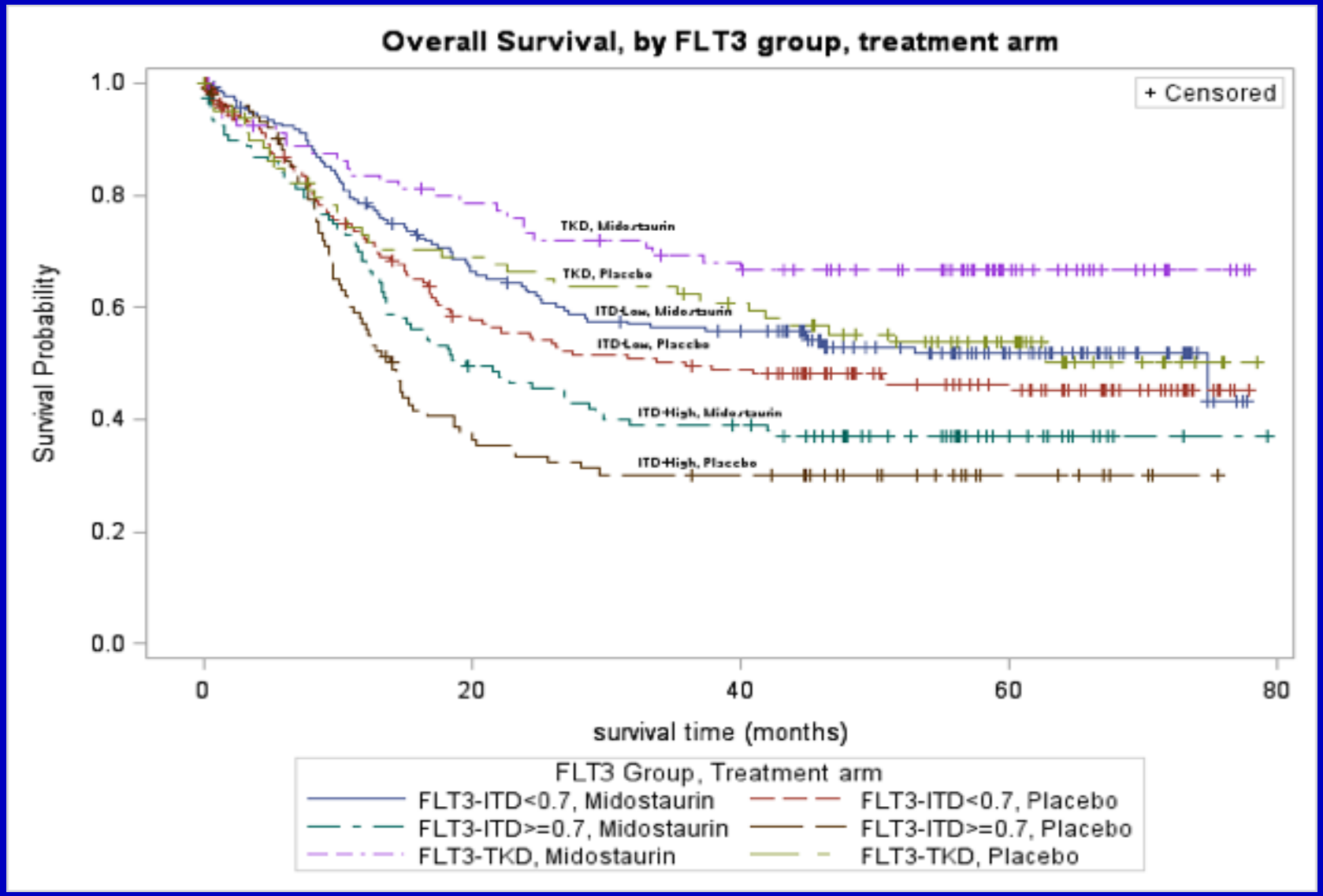


Frohling, et al., Blood 2002;100:4372

FLT-3 inhibitors in mutant FLT3 AML patients



Upfront FLT3 Inhibition Improves Survival in Pts w/ FLT3^{mut} AML



Stone RM et al. ASH 2015 Annual Meeting. Abst #6

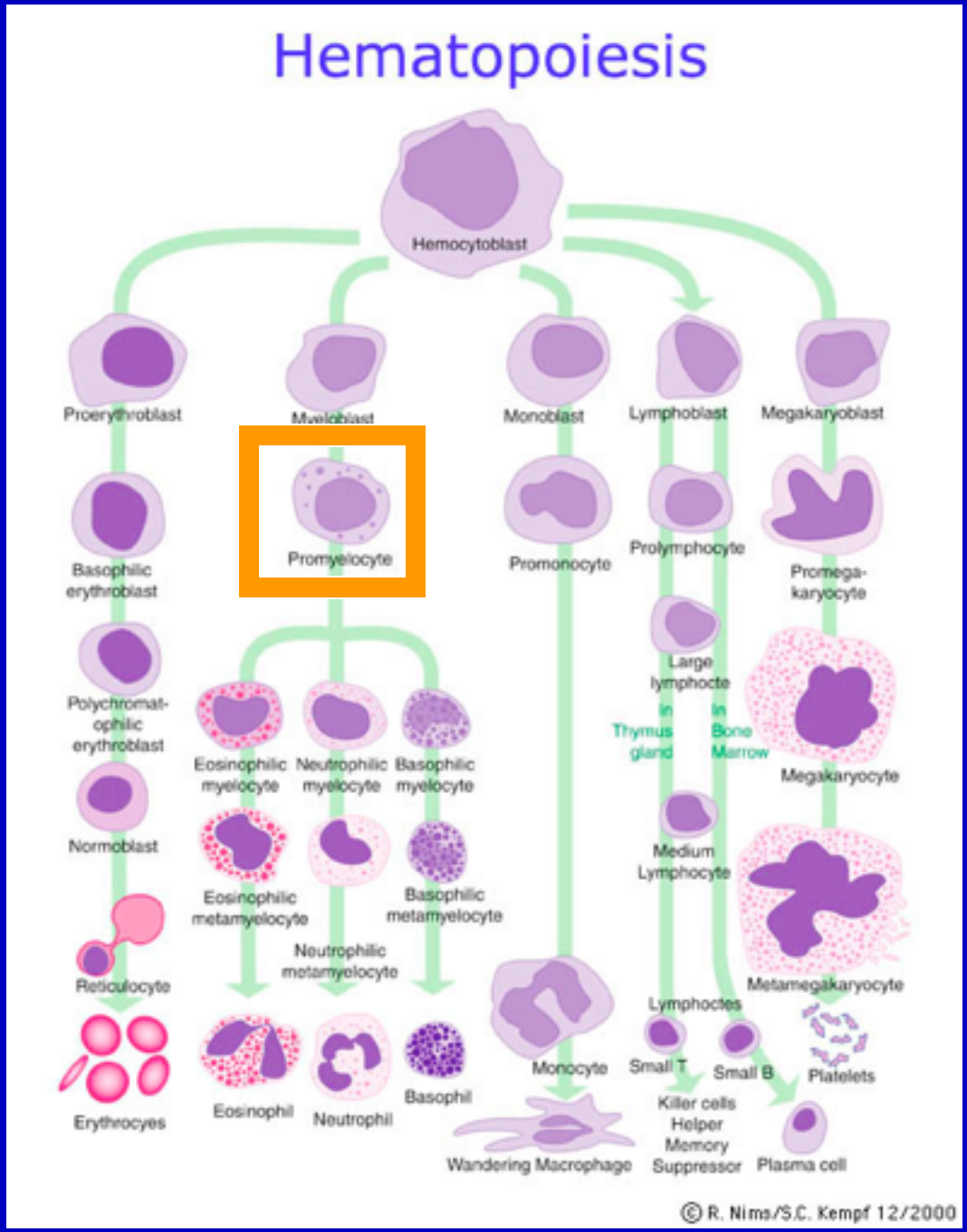
Acute promyelocytic leukemia (APL)

APL is characterized by the malignant proliferation of … immature promyelocytes….. the blood fills up with these toxin-loaded promyelocytes. Moody, mercurial, and jumpy, the cells of APL can release their poisonous granules on a whim- precipitating massive bleeding or simulating a septic reaction in the body……

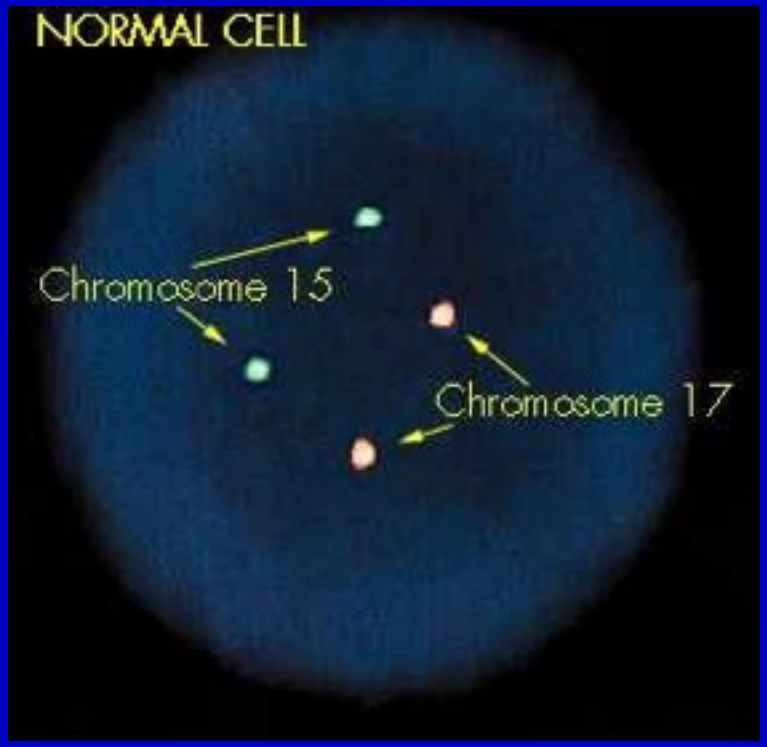
Most cancers contain cells that refuse to stop growing. In APL, the cancer cells also refuse to grow up….

Siddartha Mukherjee (The Emperor of Maladies)

APL ←

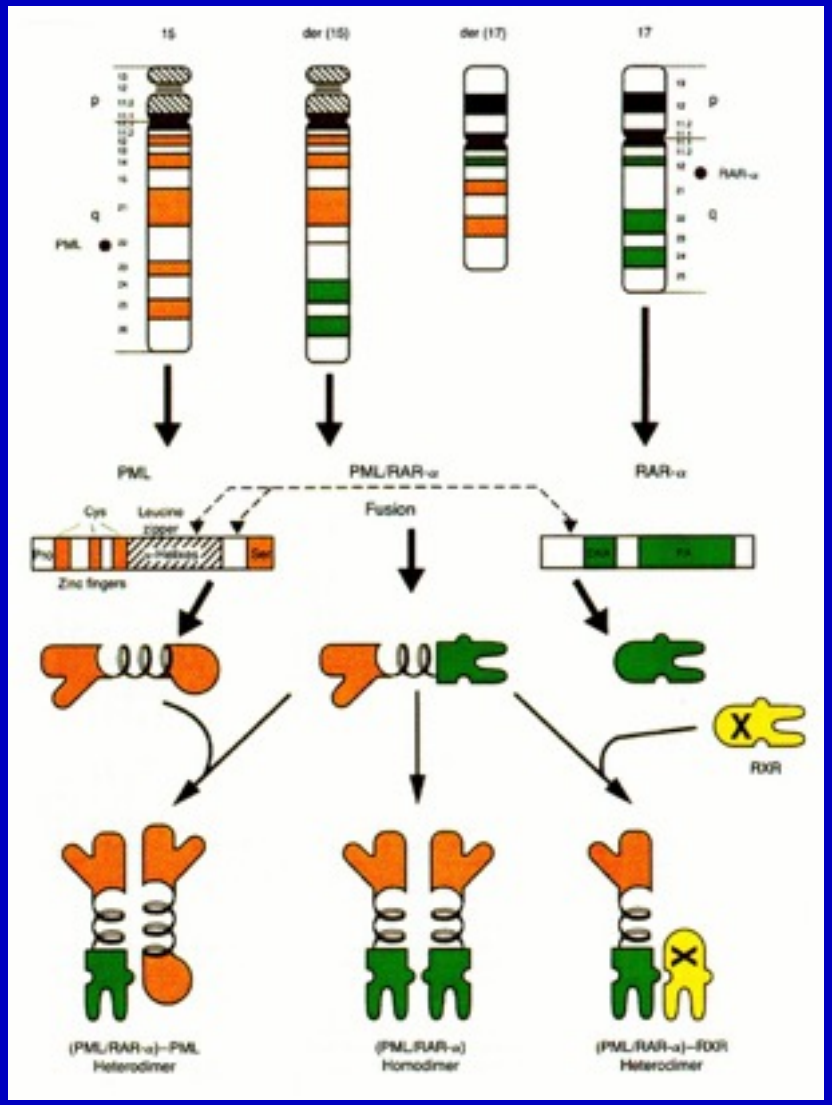

Hematopoiesis
Hemocytoblast
Proerythroblast
Myeloblast
Monoblast
Lymphoblast
Megakaryoblast
Basophilic erythroblast
Promyelocyte
Promonocyte
Prolymphocyte
Promega-karyocyte
Polychromat-ophilic erythroblast
Large lymphocte
Eosinophilic myelocyte
Neutrophilic myelocyte
Basophilic myelocyte
in Thymus gland
in Bone Marrow
Megakaryocyte
Normoblast
Medium Lymphocyte
Eosinophilic metamyelocyte
Basophilic metamyelocyte
Neutrophilic metamyelocyte
Metamegakaryocyte
Reticulocyte
Lymphoctes
Monocyte
Small T
Small B
Platelets
Erythrocyes
Eosinophil
Neutrophil
Basophil
Killer cells
Helper
Memory
Suppressor
Wandering Macrophage
Plasma cell
© R. Nims/S.C. Kempf 12/2000

Acute promyelocytic leukemia (APL)



APL cells contain a translocation between chr 15 & 17 (here seen by FISH)

APL: PML/RAR-alpha Fusion Protein



Balanced Translocation between Chr 15 and 17

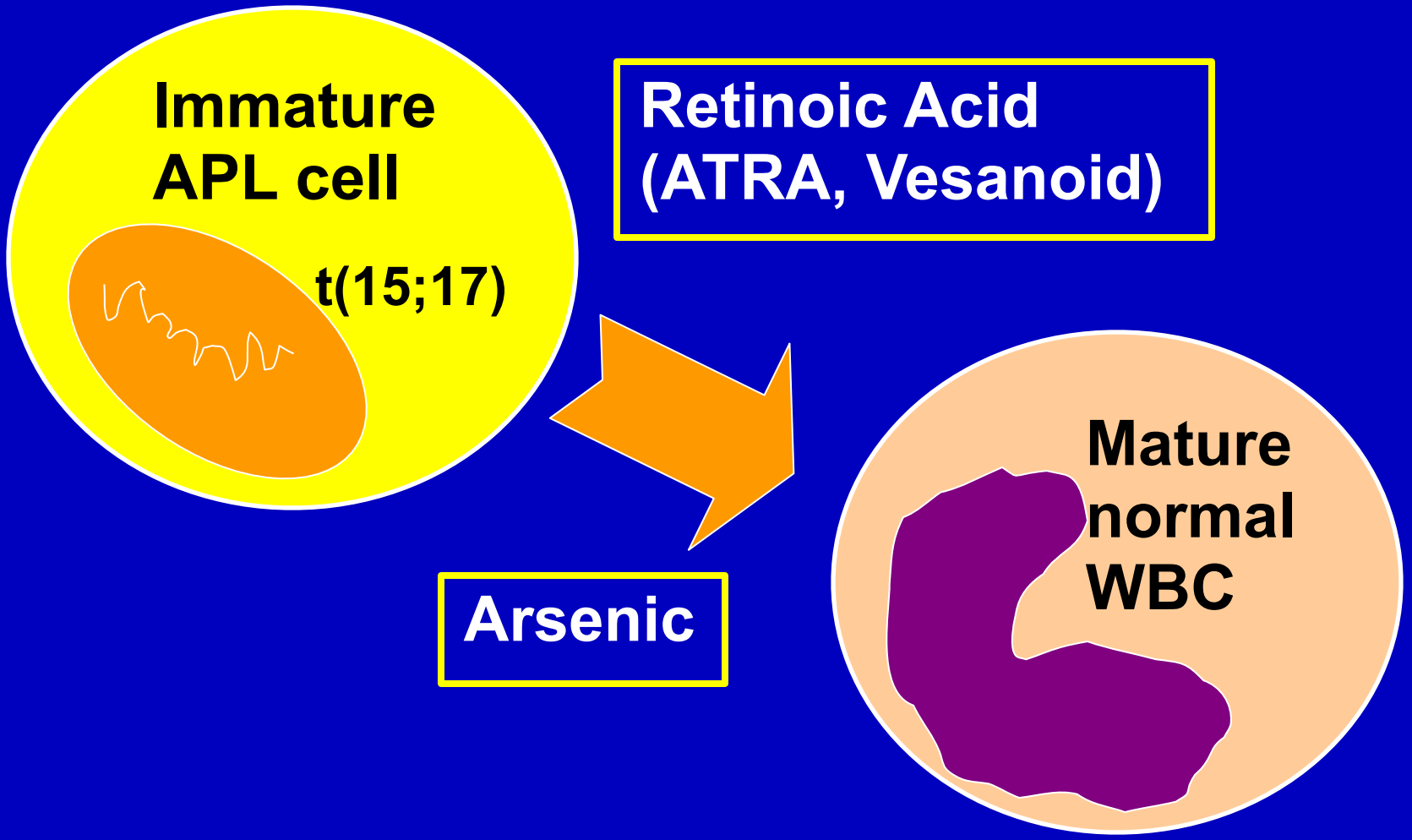
Results in a maturation arrest at the promyelocyte stage

Dominant negative to normal PML

Warrell R et al. N Engl J Med 1993;329:177-189

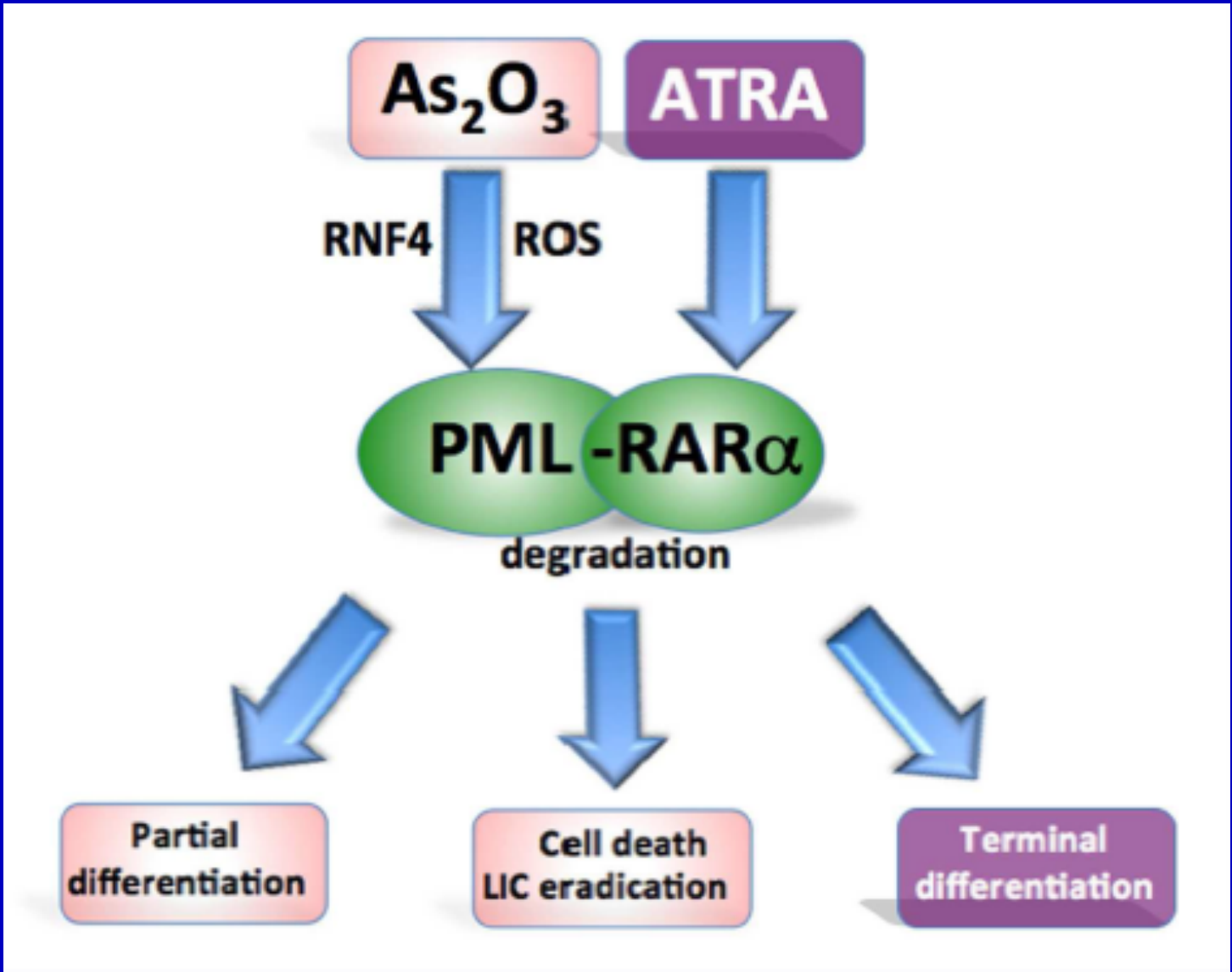
The NEW ENGLAND JOURNAL of MEDICINE

APL Therapy: Chemotherapy + Differentiation Therapy



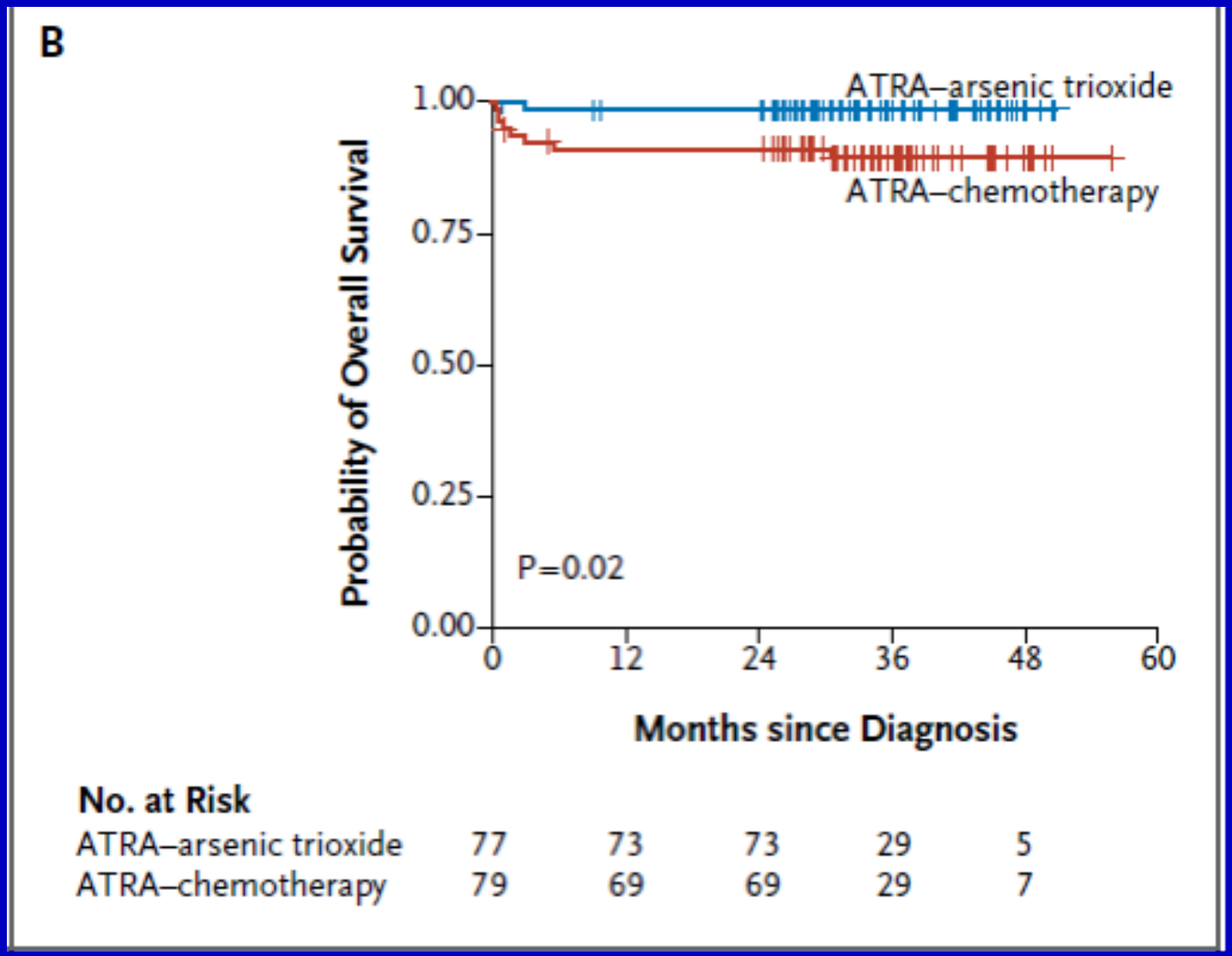
Arsenic treatment for APL

Mechanism of Differentiation Therapy



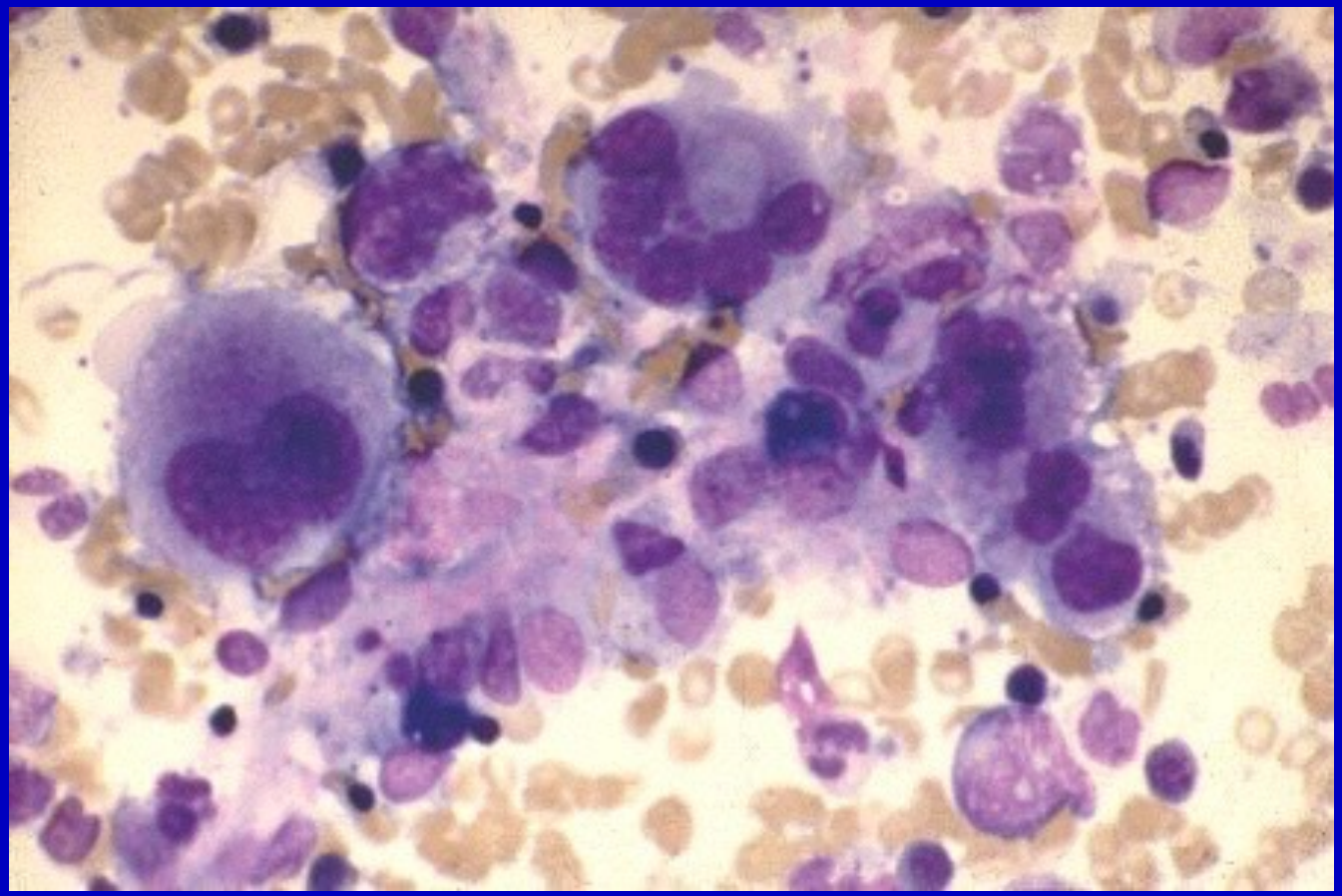
Wolyniec K. et al. Frontiers in Oncology 2013;3(124).

APL: Double Differentiation has Transformed Management and Outcome



LoCoco F et al. N Engl J Med 2013;369:111-21.

Myelodysplastic syndrome (MDS)



Myelodysplastic syndrome (MDS)

- Clonal hematopoietic stem cell diseases characterized by dysplasia and ineffective hematopoiesis in 1+ myeloid lineages

- Pancytopenia
- Infections, bleeding complications
- Transfusion dependence
- Risk of transformation to AML
- Less than 20% immature myeloid blasts in BM

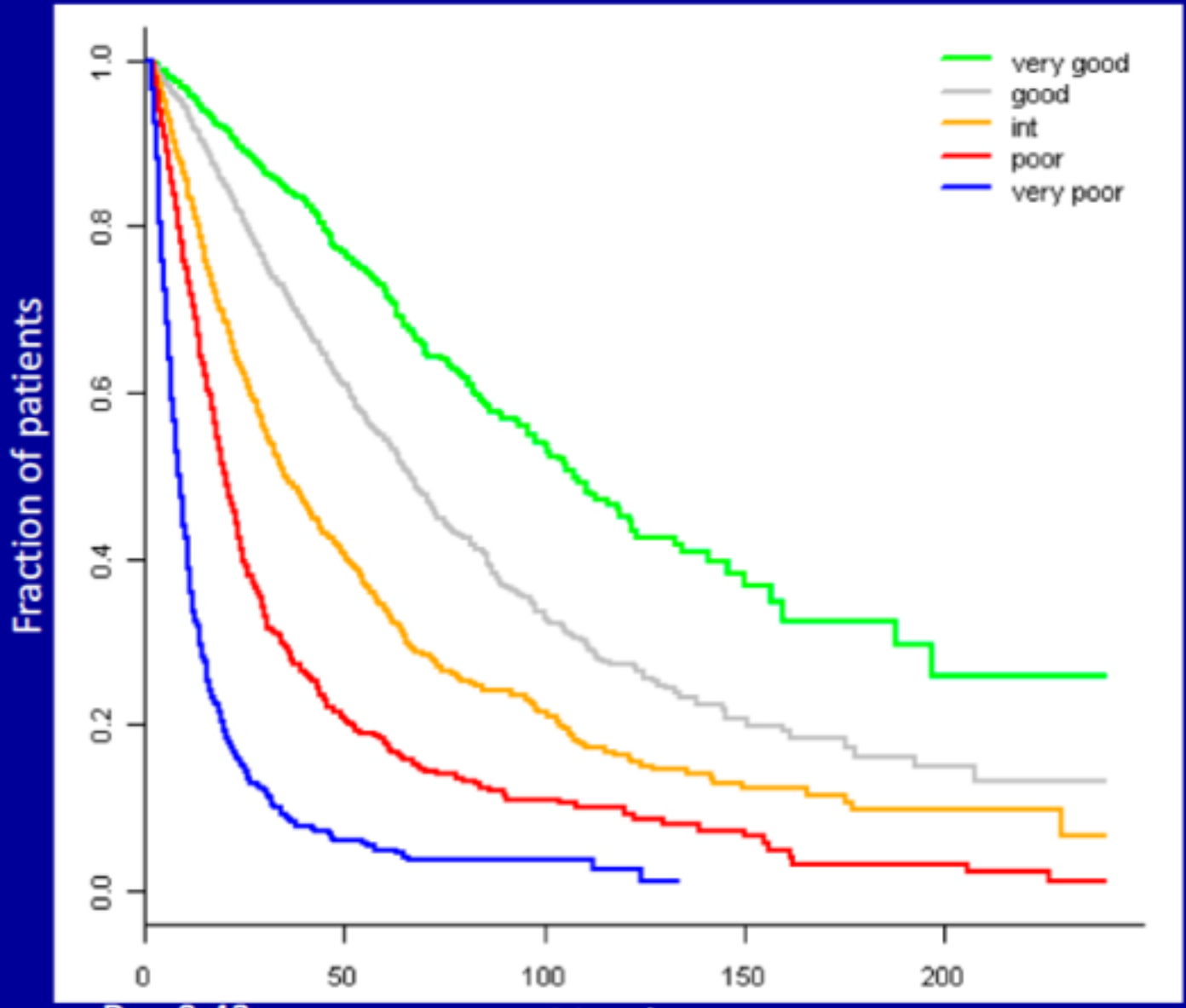
Prognosis in MDS: R-IPSS

Variable	0	0.5	1	1.5	2	3	4
Cytogenetics	VG		G		I	P	VP
BM blasts%	≤2		>2-<5		5-10	>10	
Hg	≥10		8-10	<8			
Platelets	≥100	50-100	<50				
ANC	≥0.8	<0.8					

Group	Cytogenetic Abnormality
Very Good	-Y, del(11q)
Good	NL, del(5q), del(20q), ≤2 w/del (5q)
Int	del(7q), +8, +19, i(17q), any other ≤2 clones
Poor	-7, inv(3)/t(3q)/del(3q), ≥2 w/ -7/del(7q), complex ≤3
Very Poor	complex> 3 abnormalities

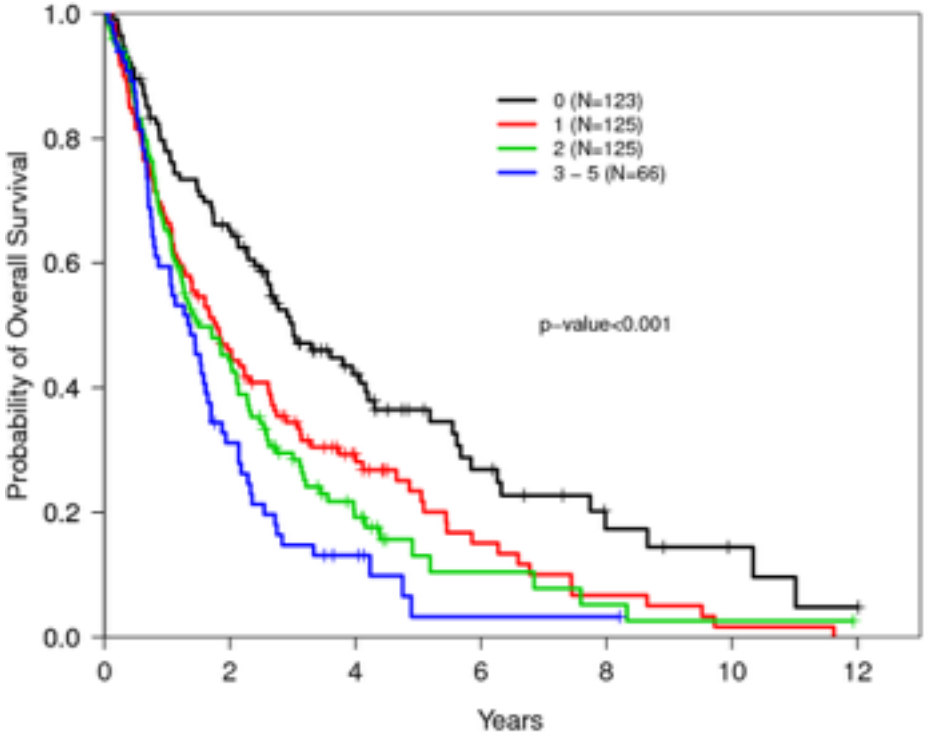
Risk Group	Score	Survival (y)	25% AML Tx (y)
V. Low	≤1.5	8.8	NR
Low	>1.5-3	5.3	10.8
Int	>3-4.5	3.0	3.2
High	>4.5-6	1.6	1.4
V. High	>6	0.8	0.73

IPSS-R Survival, n=7012



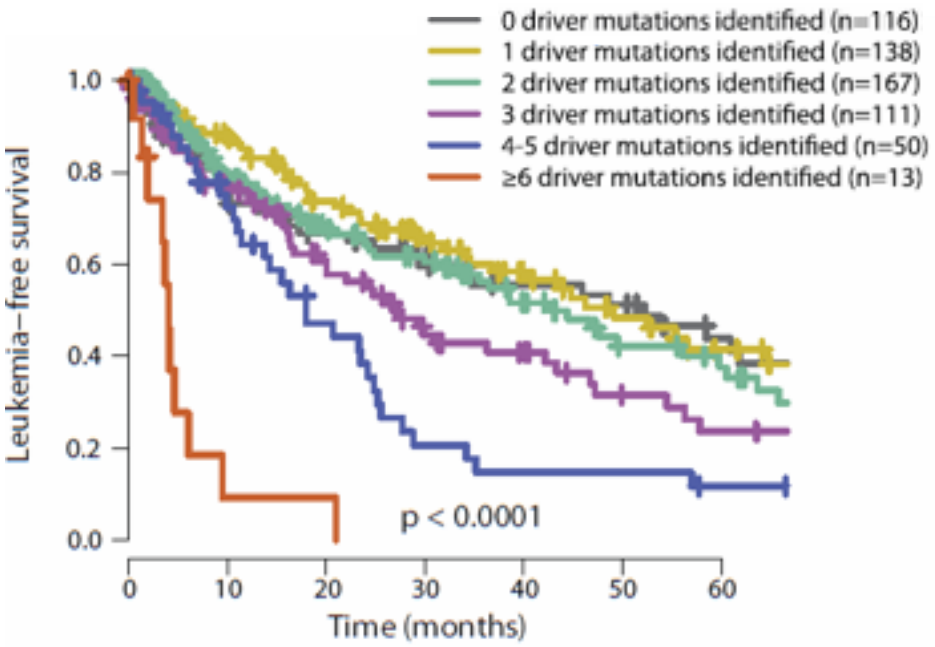
Greenberg PL, et al. Blood. 2012 Sep 20;120(12):2454-65

Mutations are also Prognostic in MDS



18 Mutated Genes

439 patients



43 Mutated Genes

595 patients

Bejar et al. *NEJM*. 2011;364:2496-506.
Papaemmanuil et al. *Blood*. 2013. (e-pub ahead of print)

Mutational Data is Additive with Clinical Models

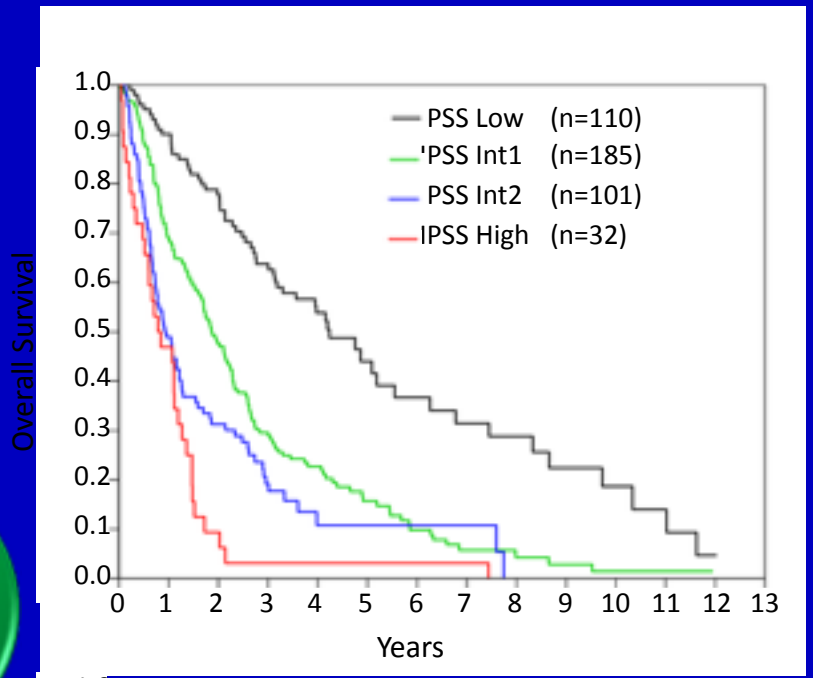
TP53

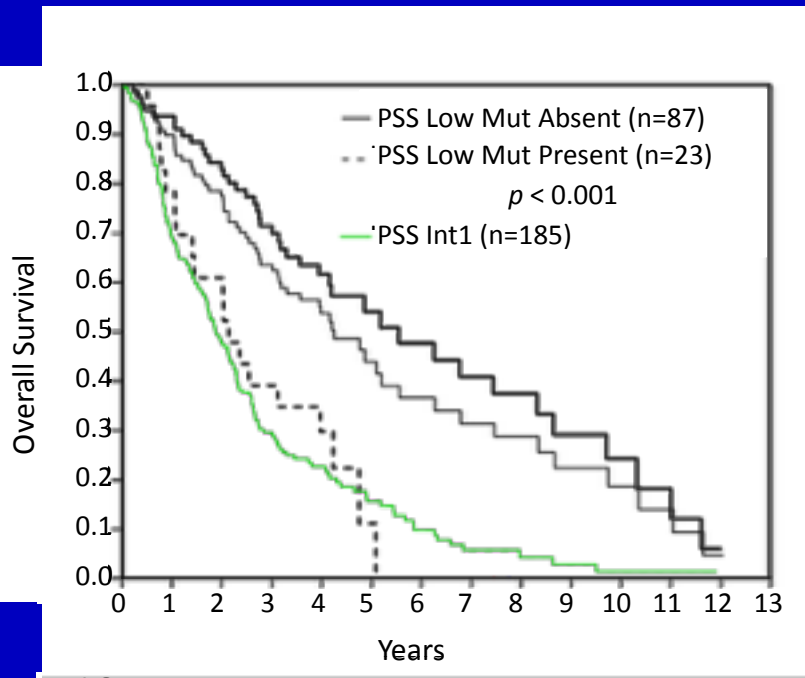
ETV6

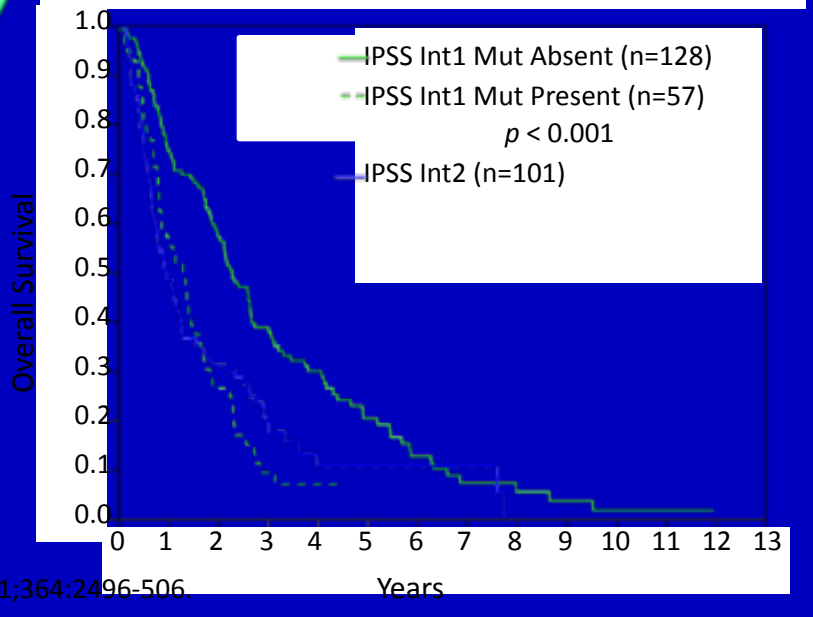
ASXL1

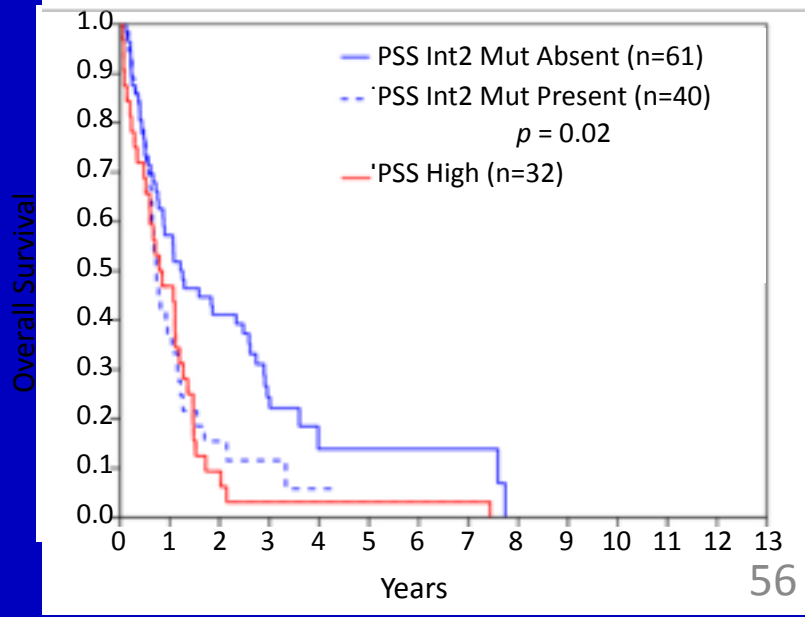
EZH2

RUNX1





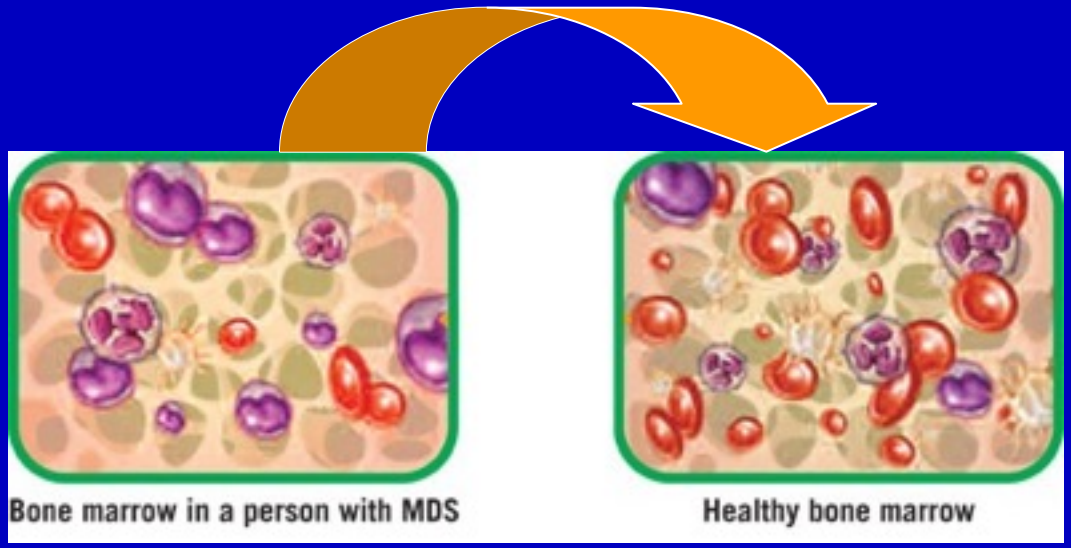




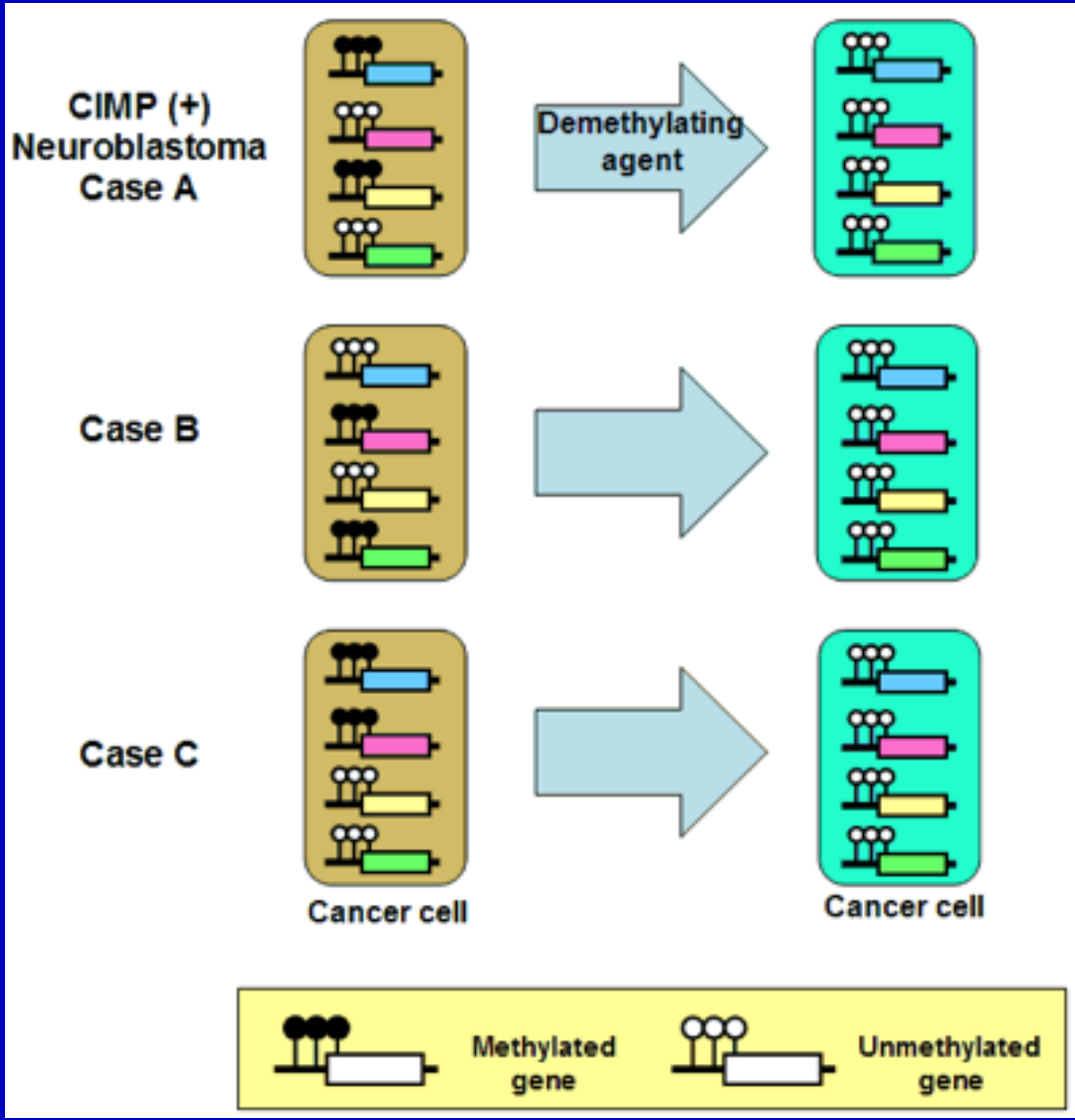
Bejar et al. *NEJM*. 2011;364:2496-506.

Treatment options for MDS

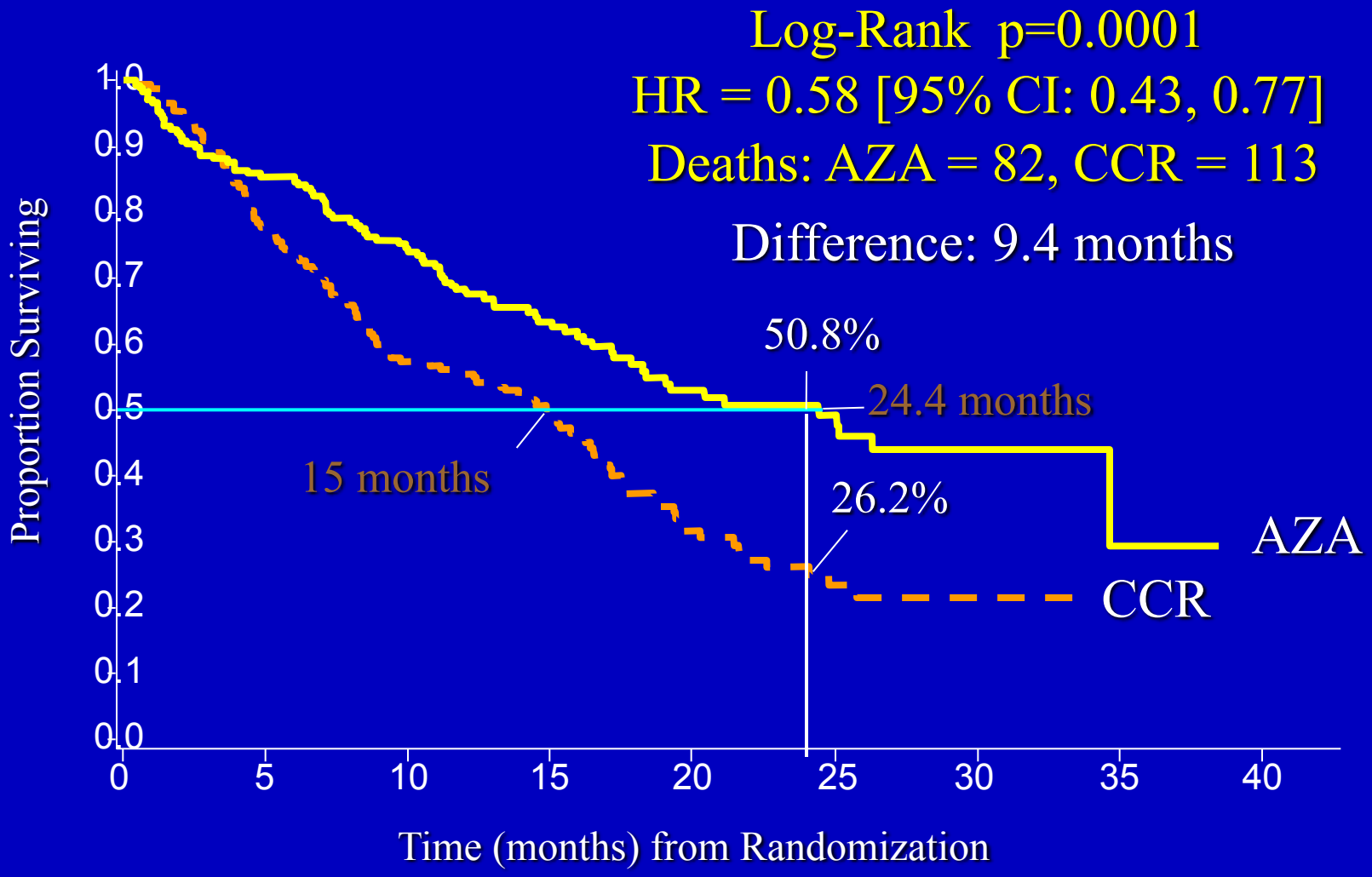
- Supportive care: transfusions, growth factors
- Hypomethylating agents
  - 5-azacytidine
  - Decitabine
- Allogeneic stem cell transplantation



Hypomethylating Agents



Azacitidine treatment Improves MDS survival



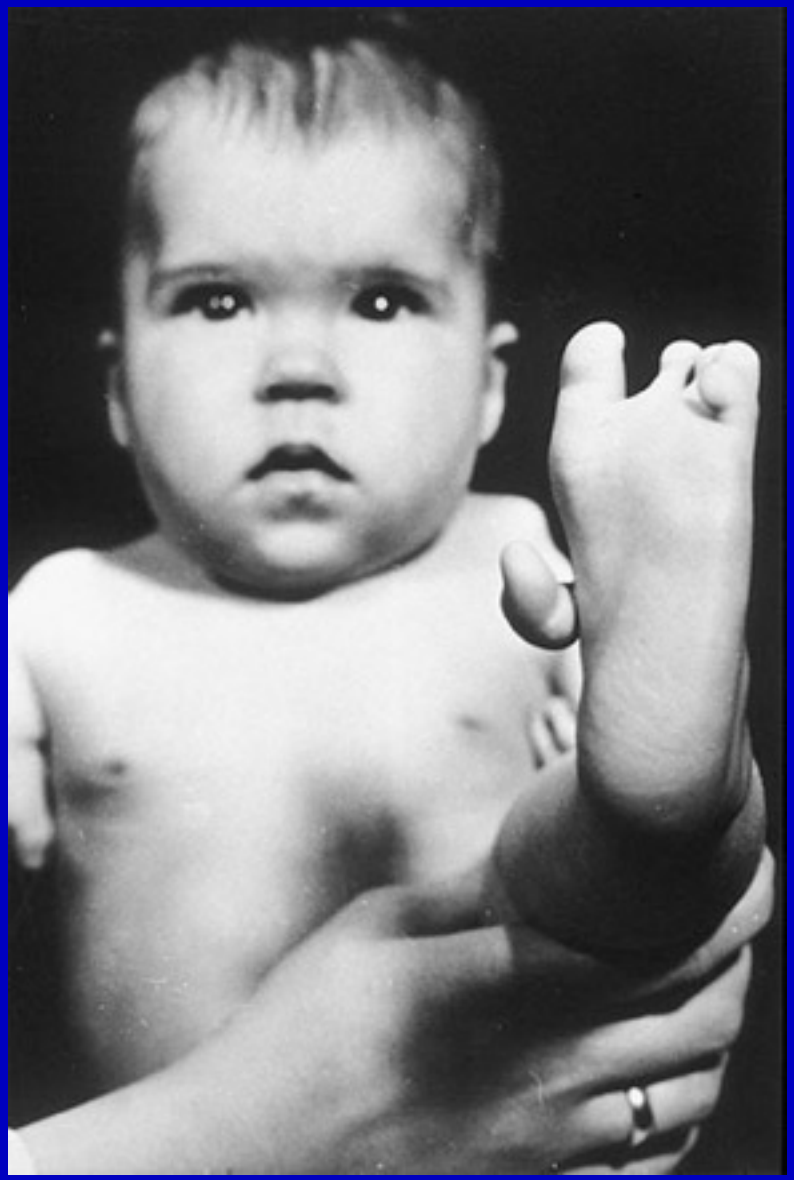
Fenaux P et al. Lancet Oncology 10: 223-232, March 2009.

Lenalidomide for MDS therapy

Derivative of *thalidomide*, a morning sickness pill associated with birth defects

Effective for therapy of MDS with chromosome 5 abnormality

Inhibits interactions between MDS cells and the local microenvironment

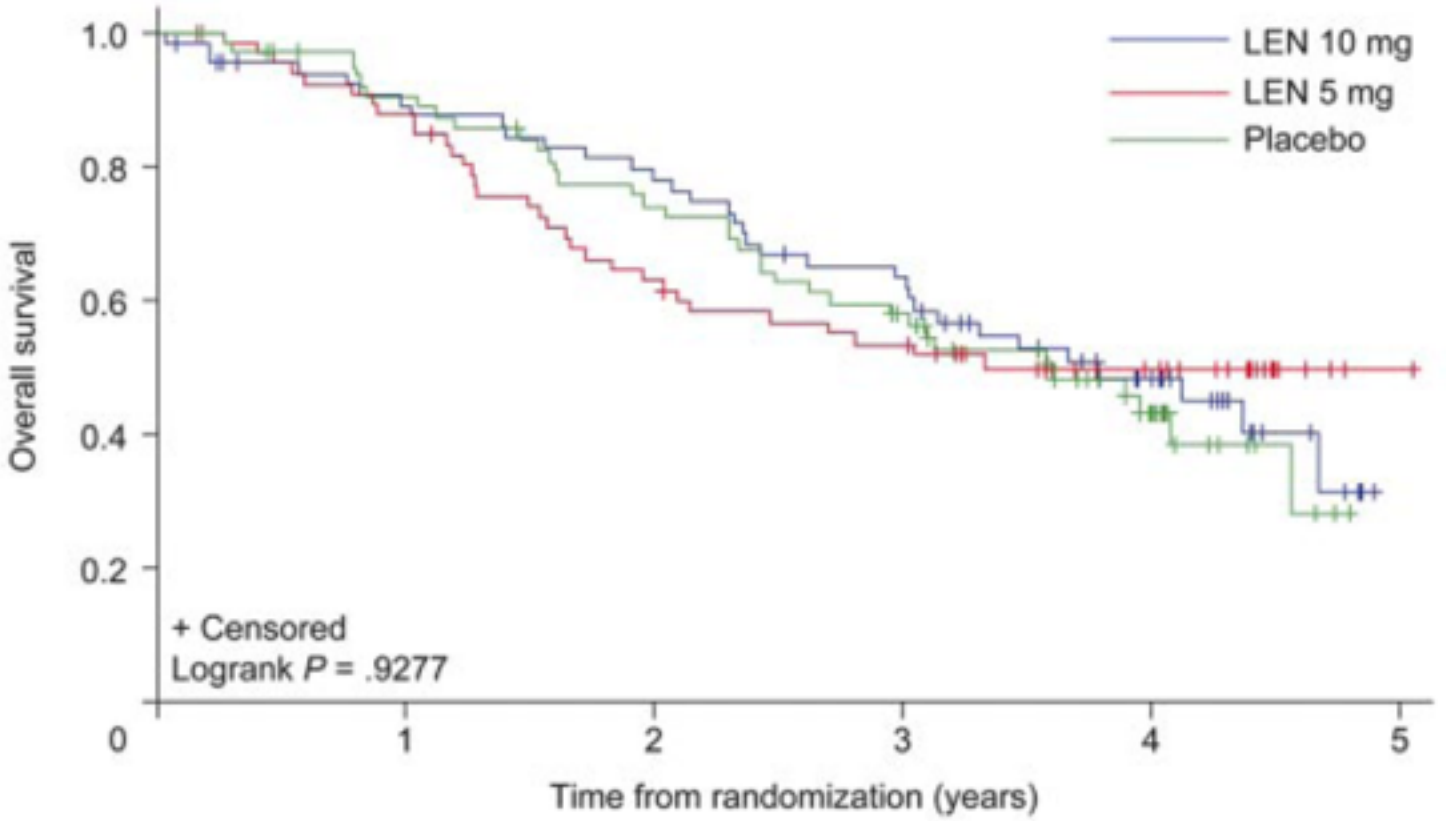


Phase III Study

- Three arms, well matched for age, sex, IPSS, transfusion needs, karyotype
- 205 pts treated
  - Len (2/3) vs placebo (1/3)
- Endpoint: RBC TI≥26 weeks
  - reached in 43-56% of Len pts and 6% for placebo
- Toxicity: myelosupression (90%) and DVTs (2-6%)
- No survival benefit

Fenaux et al. Blood 2011.

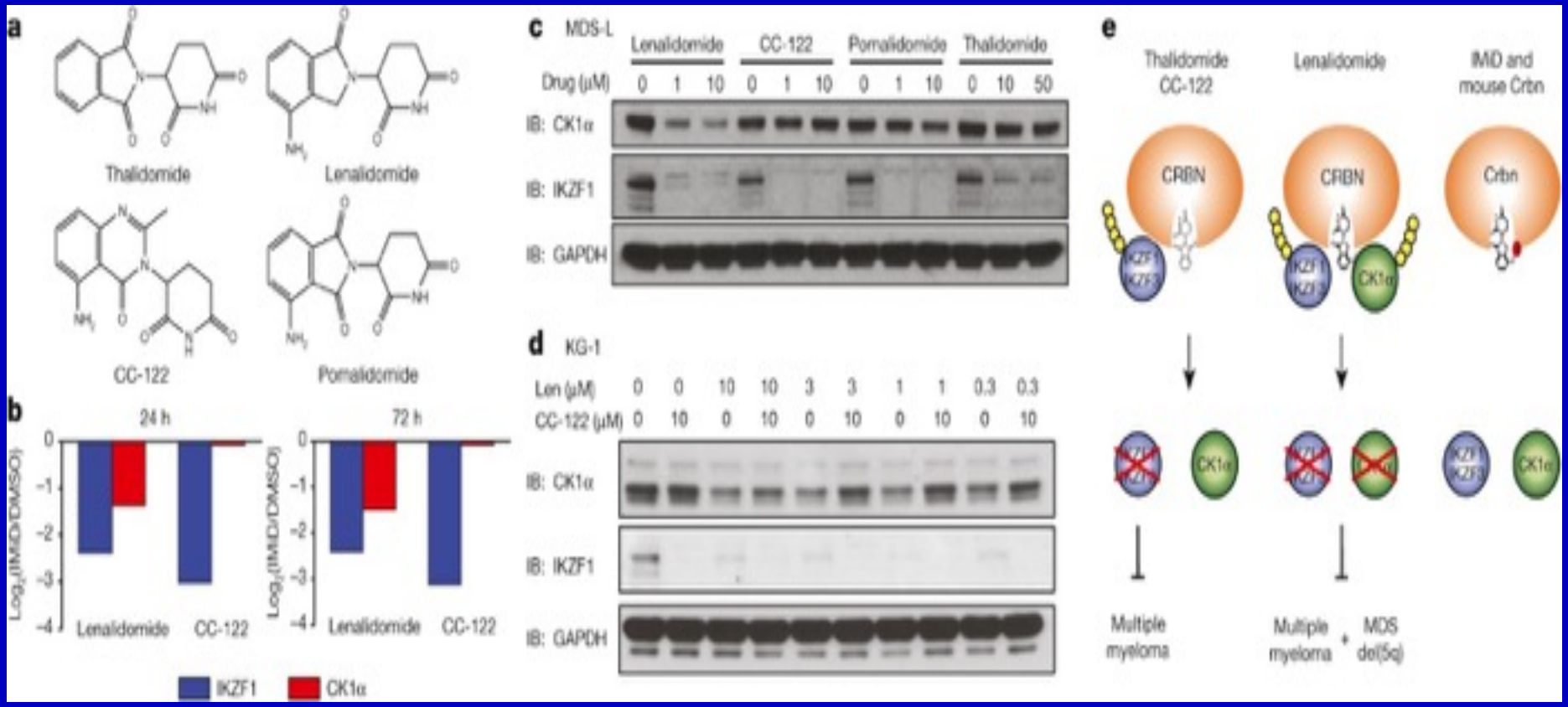
Phase III Lenalidomide OS



Patients at risk, n						
LEN 10 mg	69	57	50	35	15	0
LEN 5 mg	69	60	40	31	15	0
Placebo	67	58	46	32	8	0

Fenaux et al. Blood 2011.

Substrate specificity of thalidomide analogues.



J Krönke *et al. Nature* 000, 1-6 (2015) doi:10.1038/nature14610

Summary

- We still have much to learn
- Better understanding of the underpinning of leukemia have resulted in improved treatments
- Bench to bedside collaborations have improved outcome, but there is still plenty to do!

Questions??

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