Acute and Chronic Leukemias and MDS

- Acute Leukemias
  - Acute Myeloid Leukemia (AML)
  - Acute Lymphoblastic Leukemia (ALL)
- Chronic Leukemias
  - Chronic Myeloid Leukemia (CML)
  - Chronic Lymphoid Leukemia (CLL)
- Myelodysplastic Syndrome (MDS)

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Disclosure Information

The following relationships exist related to this presentation:

- Dr. Richard Stone has served as a consultant for Abbvie, Amgen, Agios, Arog, Celgene, Cornerstone, Jazz, Karyopharm, Novartis, Orsenix, Pfizer,

Off-Label/Investigational Discussion

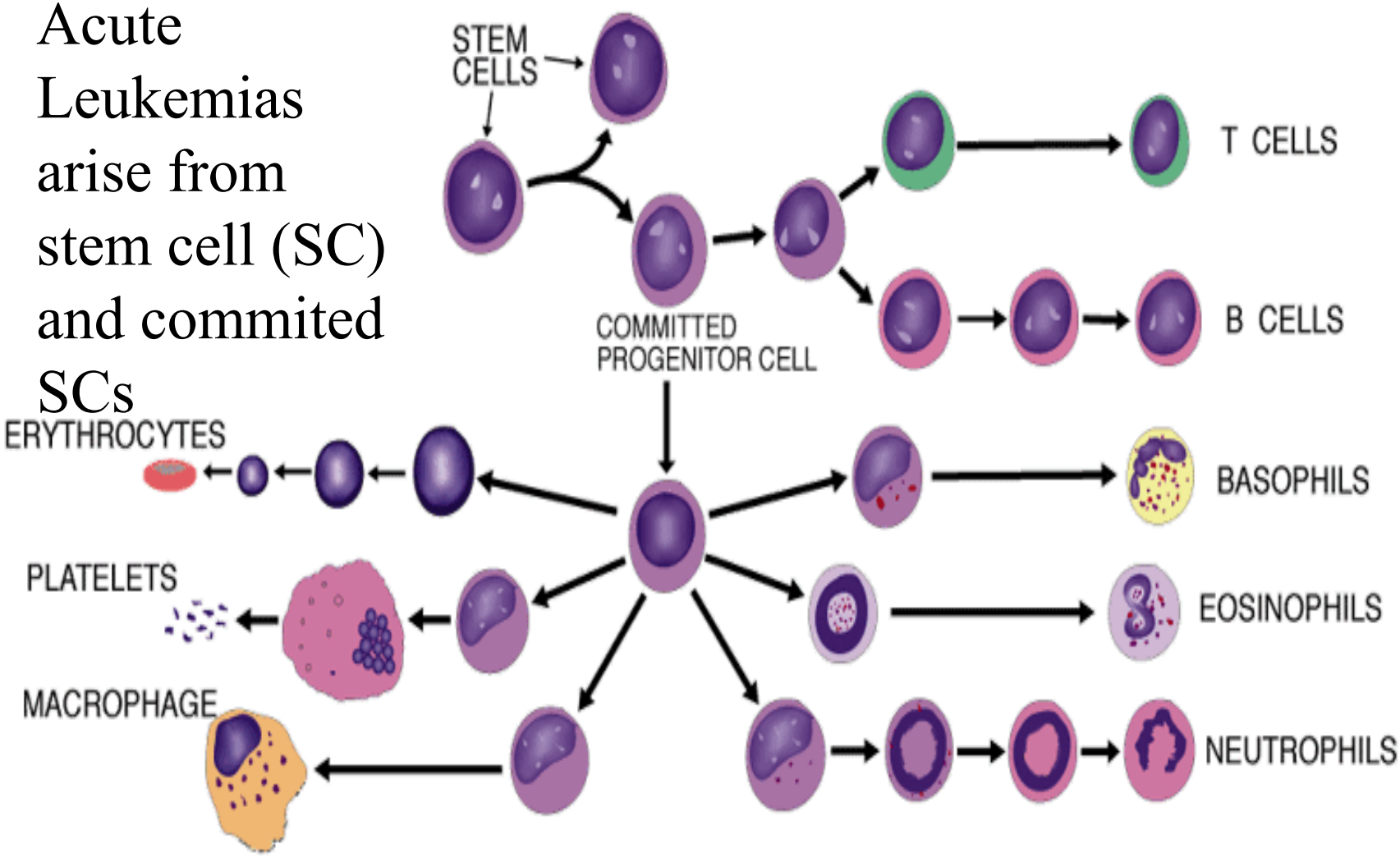
In accordance with CME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

Leukemia: Definition

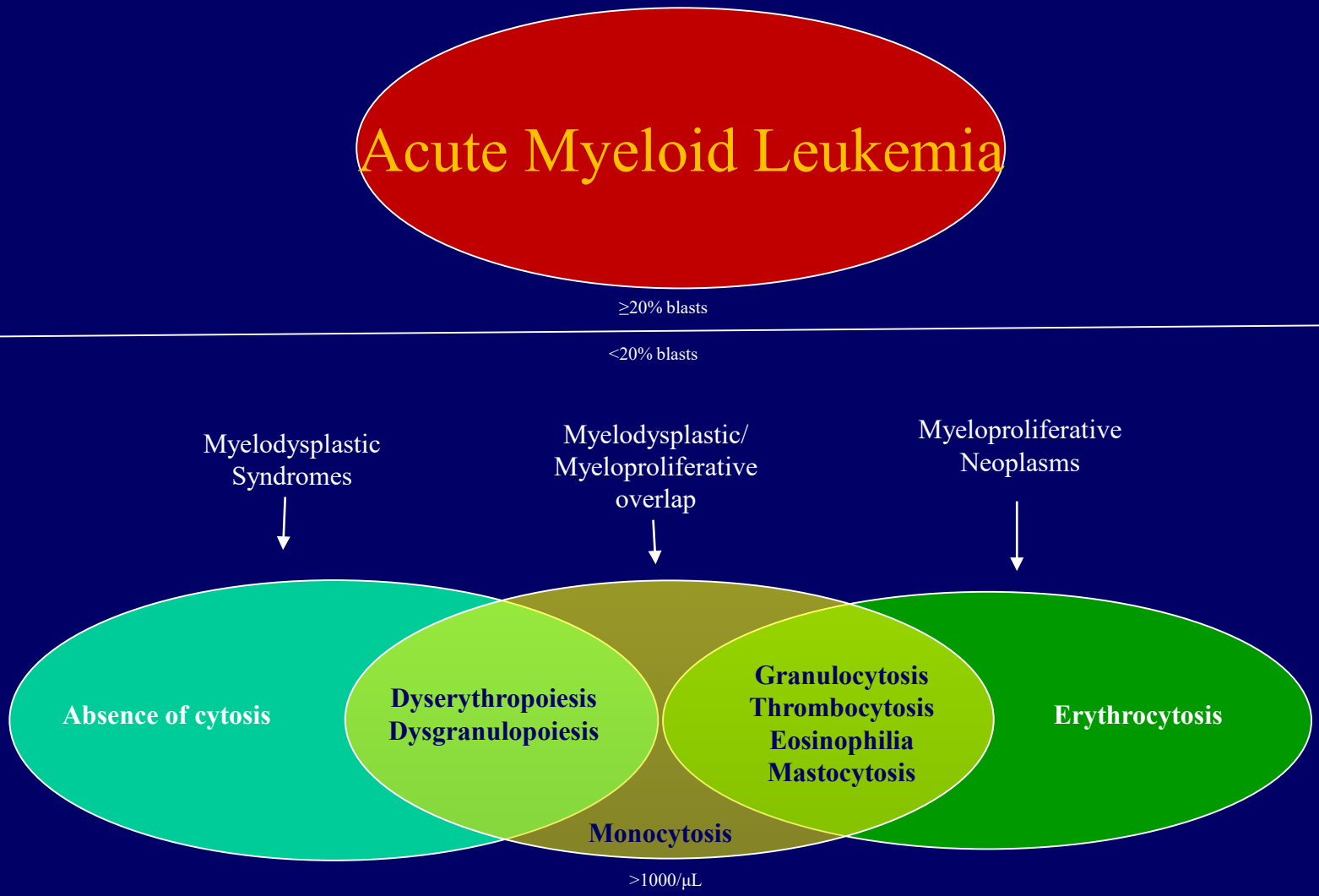
- **Overabundance of white blood cells in peripheral blood**
  - **If Immature (like stem cells) then acute leukemia**
  - **If mature (like normal cells) then chronic leukemia**

HEMATOPOIESIS

Acute Leukemias arise from stem cell (SC) and commited SCs



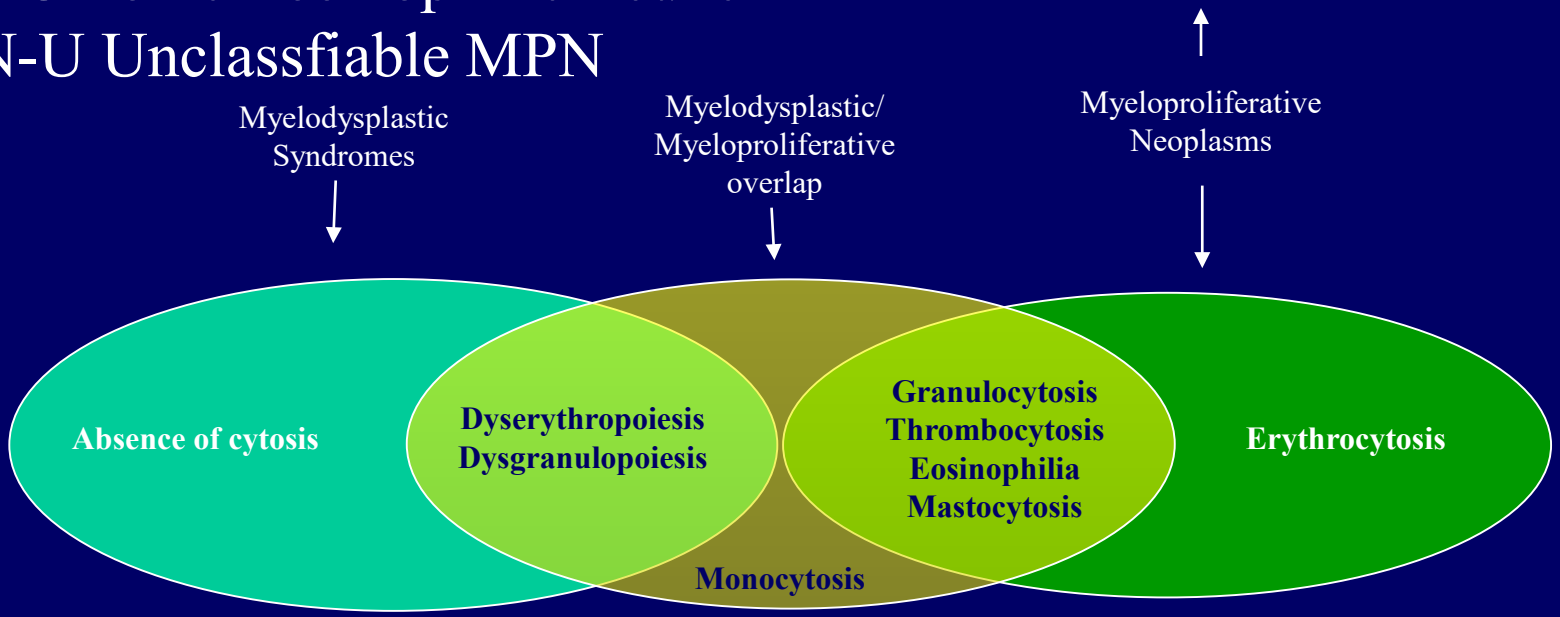
Myeloid Malignancies



Chronic Myeloid Malignancies

PV-polycythemia vera
ET-Essential thrombocytosis
PMF- Primary Myelofibrosis
CNL-Chronic Neutrophilic Leukemia
SM- Systemic Mastocytois
CEL-Chronic Eosinophilic Leukemia
MPN-U Unclassfiable MPN

CML	*-BCR-ABL1*	*100%*
PV	*-JAK2*	*99%*
ET	*-JAK2/MPL*	*60%*
PMF	*-JAK2/MPL*	*70%*
CNL	*-CSF3R*	*90%*
	-SETBP1	*33%*
SM	*-KITD816V*	*90%*
CEL		
MPN-U		



Acute Leukemia : Clinical Presentation

- Bone marrow failure
  - neutropenia- infection/fever
  - anemia- fatigue/SOB
  - thrombocytopenia- bleeding
- Metabolic abnormalities
  - hypokalemia- renal tubular damage from myeloblasts
  - hyperkalemia, hyperphosphatemia, hypocalcemia, hyperuricemia- tumor lysis syndrome

Acute Leukemia : Selected Clinical Issues

- Infection
  - Do not delay antileukemic therapy while infection resolves
  - Early use of antifungals
  - Raw fruit and vegetables probably OK
- Thrombocytopenia
  - Platelet transfusion threshold of 10K/ul
  - Obligate use of single donor platelets is contoversial
- Tumor Lysis Syndrome
  - Hydration, allopurinol, and judicious use of sodium bicarbonate is effective
  - Single dose of recombinant urate oxidase can be considered if pt cannot take po

Acute Leukemia: Blasts on Wright stain

feature	myeloid	lymphoid
cytoplasm	ample	scant
granules	a few	absent
chromatin	open	less so
nucleoli	many	few
Auer Rods	in 50%	no

Cytochem: perox-AML, NSE-AMo/ML; PAS-ALL

Acute Leukemia: Immunophenotypic Diagnosis

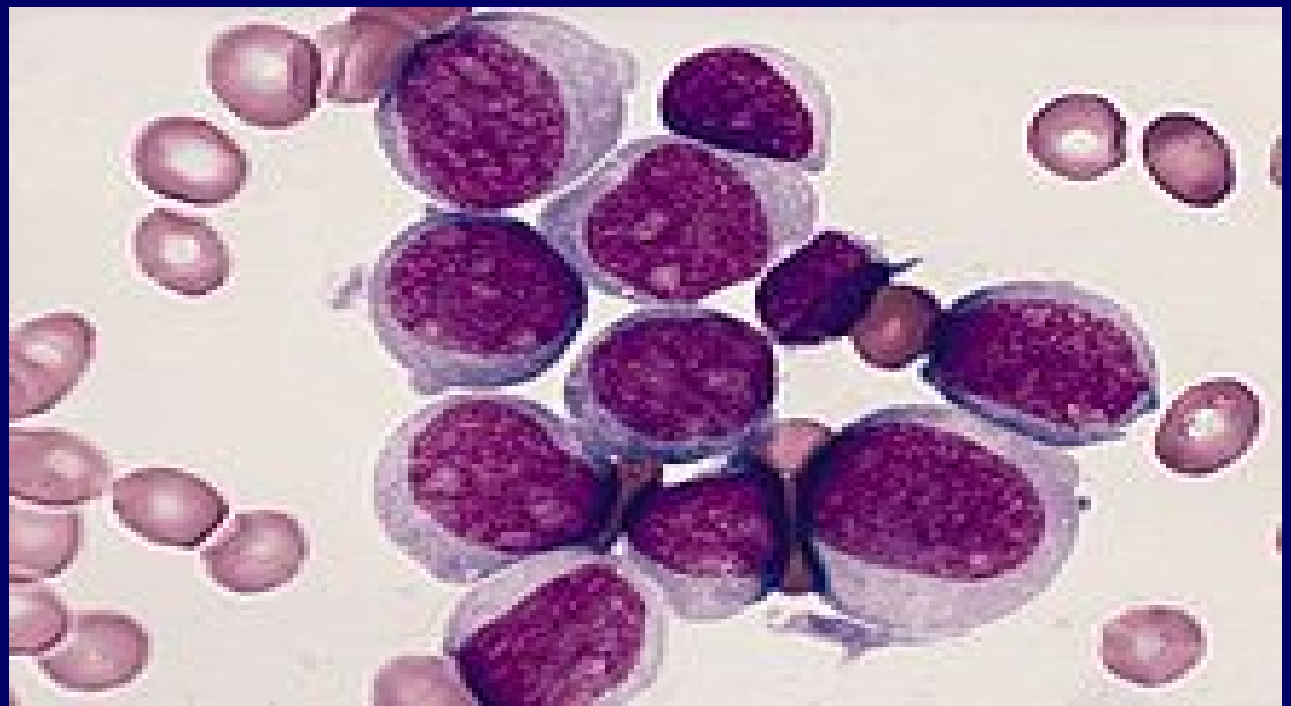
- AML: CD33 (in 90%), CD15, CD117 (c-kit); CD14, CD11c- monocytic
- ALL:
  - pre-B cell: CD19, CD20, CD10 (CALLA) in most
  - B-cell: CD19, surface immunoglobulin
  - T-cell: CD2, CD7, CD3

AML: FAB Classificaton

- M0: Cytochem neg; myeloid Ag on flow
- M1: Peroxidase pos.
- M2: Perox pos.; some differentiation
- M3: Acute Promyelocytic Leukemia
- M4: Acute Myelomonocytic Leukemia (perox and NSE pos.)
- M5: Acute Monocytic Leukemia (NSE pos)
- M6: Acute Erythroleukemia
- M7: Acute Megakaryocytic Leukemia

AML: What is it and how did it get there?

- Unbridled proliferation of hematopoietic stem cells (myeloid lineage) resulting in marrow failure and patient death unless successfully treated
- Risk factors: AGE, prior chemo for other cancers, ionizing radiation, industrial solvents (last 3 probably <10% of incidence=15K new US cases annually)



Key Points from de novo AML genome atlas-1

- **AML genomes have fewer mutations than most other adult cancers (n=13, 5 of which are aomg the 23 recurrently mutated genes)**
- **9 Key categories:**
  - **transcription-factor fusions (18%)**
  - **nucleophosmin (*NPM1*) (27%)**
  - **tumor-suppressor genes (16%)**
  - **DNA-methylation–related genes (44%)**
  - **signaling genes (59%)**
  - **chromatin-modifying genes (30%)**
  - **myeloid transcription-factor genes (22%)**
  - **cohesin-complex genes (13%)**
  - **spliceosome-complex genes (14%).**

The Cancer Genome Atlas Research Network
N Engl J Med 2013; 368:2059-2074.

Current Risk Assessment in AML

Key Prognostic Data in AML in 2017

Patient **age**	
Cytogenetics / karyotype	
Primary versus **secondary** disease (secondary = post-antecedent hematologic disorder, or therapy-related)	
Molecular studies:	
• *FLT3* ITD (internal tandem duplication) mutation	*Unfavorable*
• *NPM1* mutation	*Favorable*
• *CEBPA* biallelic mutation	*Favorable*
• *ASXL1, RUNX1, TP53; KIT (in CBF)*	*Unfavorable*

Of Future Importance: mutation status of ***IDH1/2, DNMT3A, TET2***, etc.

Acute Leukemia: General treatment principles

- **Goal 1:** Induction rx to reduce gross leukemia to undetectable levels (2-3 log cell kill)

- **Goal 2:** Reduce 10^9 - 10^{10} cells, undetectable by standard means, present at CR, to a level low enough to achieve prolonged disease-free survival ('cure')

Older Patients With AML Continue to Have Inferior Outcomes

Age group	Complete remission rate (with "3&7"-like regimens)	Early mortality	Disease-free survival	Long-term overall survival	Median survival
<60 years	70%	10%	45%	30%	24 months
≥60 years	45%	>25%	<20%	10%	10 months

•**Data are based on CALGB & MRC trials for which adults of all ages were eligible**

AML in > 60 yo: Lack of Effect of induction chemo choice on DFS- HOVON AML-9

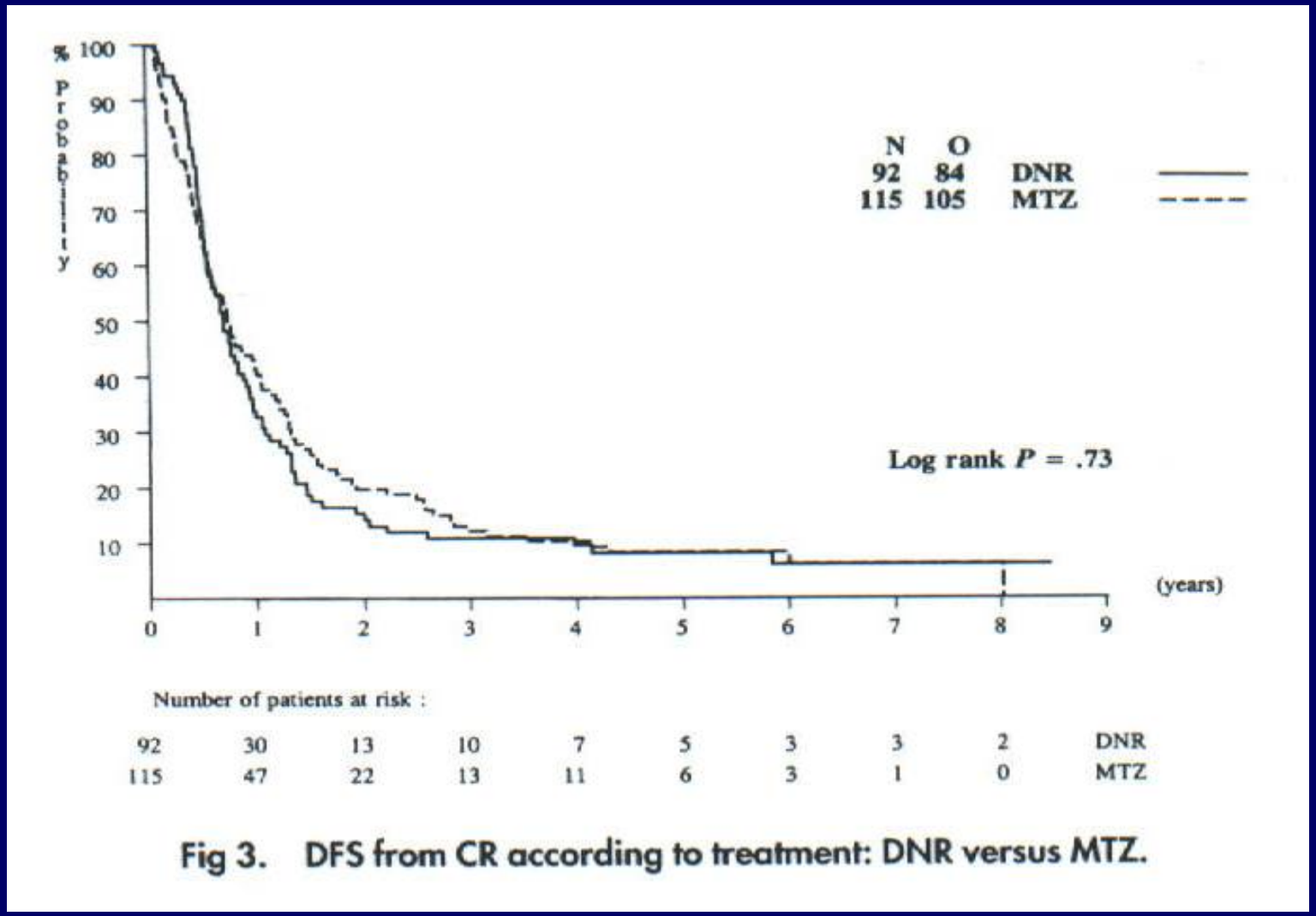


Fig 3. DFS from CR according to treatment: DNR versus MTZ.

Lowenberg, B et al , *J Clin Oncol* 16: 872, 1998

Selected Lower-Intensity Approaches in Older, Poor Prognosis Patients With AML

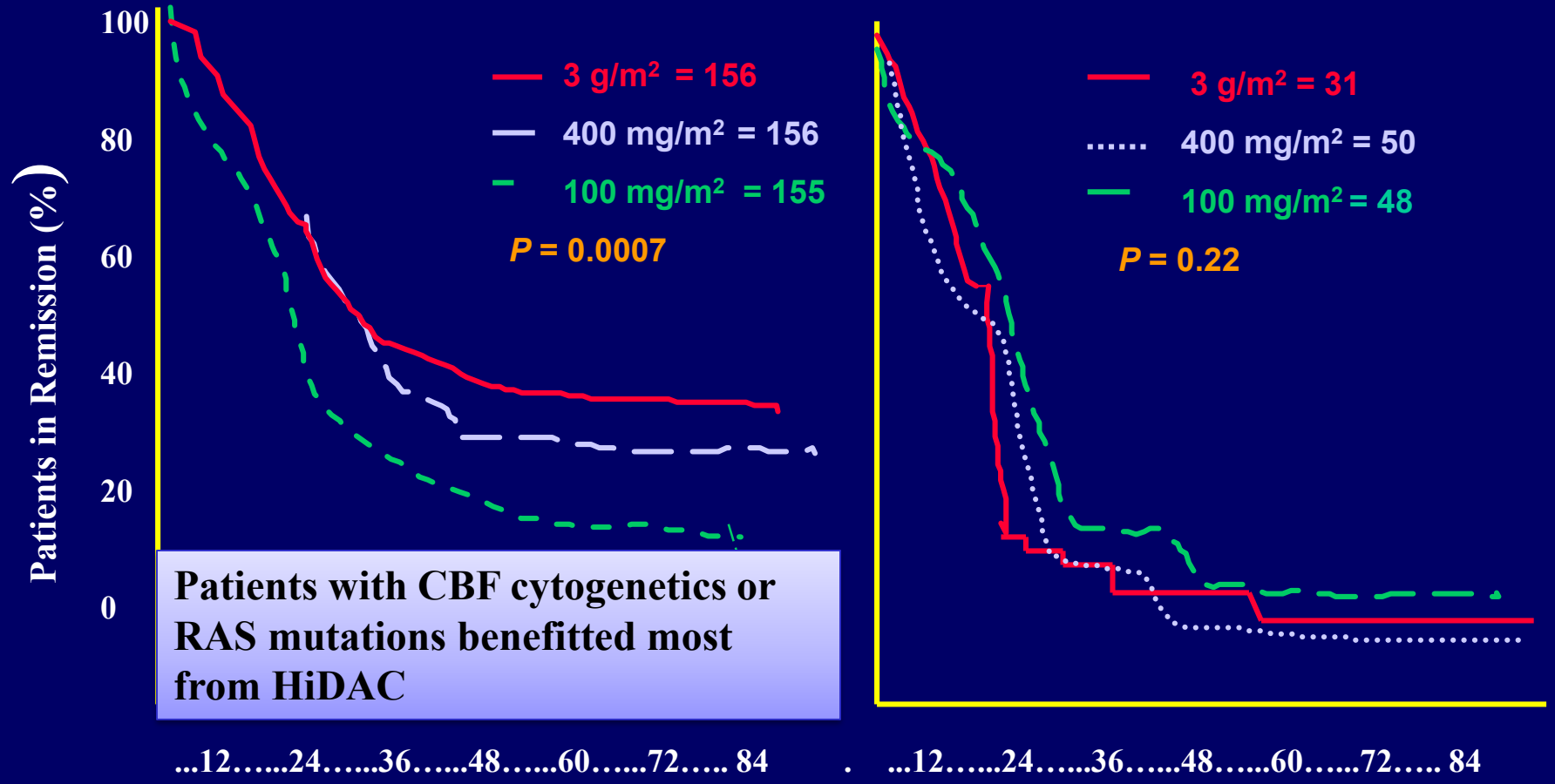
- **Clofarabine 30 mg/m^2/d x 5d (n = 112) (nucleoside analogue)[1]**
  - Median age 71 years, 36% with prior MDS
  - 38% CR, 8% CRp (seen even with several risk factors)
  - Early death rate = 10%
- **Decitabine 20 mg/m^2/d x 5d (n = 55) (DNAMTi)[2]**
  - Median age 74 years, 42% had secondary AML
  - 24% CR, 2% CRp
  - Early death rate = 4%
  - Ph III v lowdac: 18% v 8% CR, 7.7v 5.0 mo med OS (missed primary EP; n=485; Kantarjian et al, JCO, 2012)
- **Decitabine 20 mg/m^2/d x 10d (n = 53)[3]**
  - Median age 74 years, 36% had secondary AML
  - 47% CR, 64% CR + CRi
  - Early death rate (8 weeks) = 15%
  - Higher levels of miR-29b associated with increased likelihood of response

1. Kantarjian H et al. *J Clin Oncol.* 2010;28(4):549-555.
2. Cashen AF et al. *J Clin Oncol*. 2010; 28(4):556-561.
3. Blum W et al. *PNAS* 2010; 107 (16):7473-7478

AML: Treatment of those under age 60 (non-APL)

- Induction
  - anthracycline (3d) plus cytarabine (7d, IV continuous infusion)
- Post-remission Therapy
  - intensive chemo
  - autologous Stem Cell Transplant (SCT)
  - Allogeneic stem cell trnasplant

Consolidation: DFS Benefit Only in Patients < 60 Years Receiving High-Dose Ara-C



Bloomfield CD, et al. *Cancer Res.*1998;58(18):4173-4179; Neubauer A, et al. *J Clin Oncol.* 2008; 26(28):4603-4609;

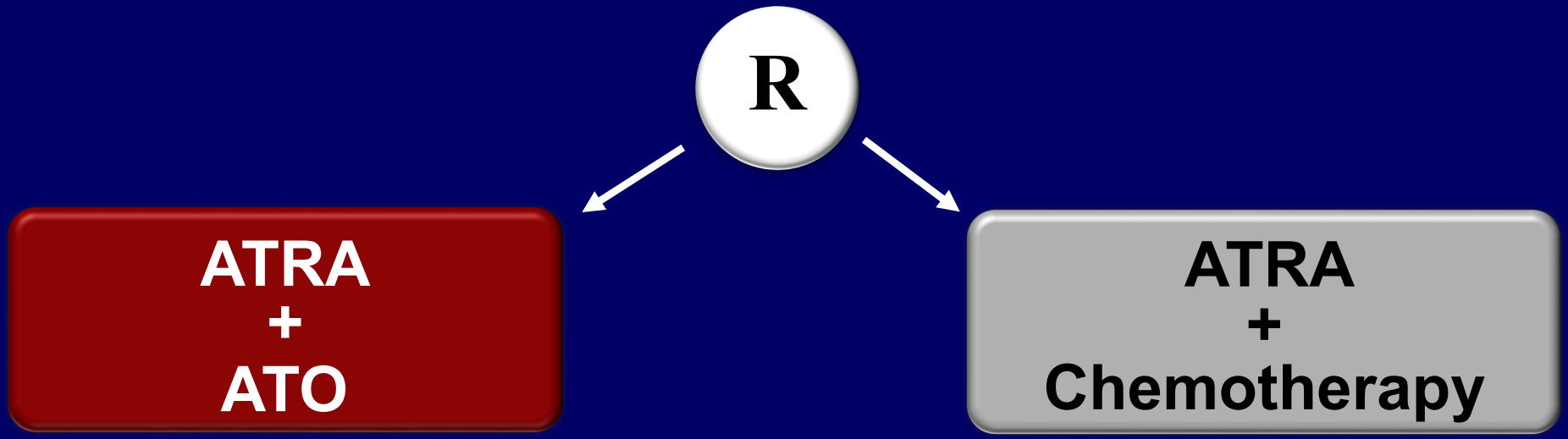
Mayer RJ, et al. *N Engl J Med.* 1994;33(1):896-903.

Treatment of Acute Promyelocytic Leukemia

Key Principles of APL Management
Suspect the disease!
• Risk of death is greatest in the first two weeks after diagnosis, especially if ATRA initiation is delayed…
• So, if the clinical setting suggests the possibility of APL (e.g., clefted blasts, strong CD33+, DIC) **do not wait** for molecular confirmation to start ATRA
Document disease
• Use cytogenetics or FISH for t(15;17), or RT-PCR for *PML-RARA* fusion
• Variant translocations are rare, but important to know about, since several do not respond to ATRA
Assess risk
• If WBC >10 x 10^9/L: <u>high risk</u>
• If WBC ≤10 x 10^9/L: <u>standard risk</u> (lowest risk if platelets also >40 x 10^9/L)
Is the patient an anthracycline candidate?

APL 0406 Study

Acute Promyelocytic Leukemia
Low/intermediate risk patients
(WBC $\leq 10 \times 10^9$/L, AGE 16-70)



LoCoco et al *NEJM* 369: 111-121, 2013

Treatment

ATO arm

Induction

ATO

ATRA

Until CR

Consolidation

ATO ATO ATO ATO

4 weeks on / 4 weeks off

2 weeks on / 2 weeks off

Estey *et al*, Blood 2006

Chemo Arm

Induction

IDA

ATRA

Until CR

Consolidation

IDA MTZ IDA

ATRA ATRA ATRA

3 monthly cycles

Maintenance

MTX + 6MP

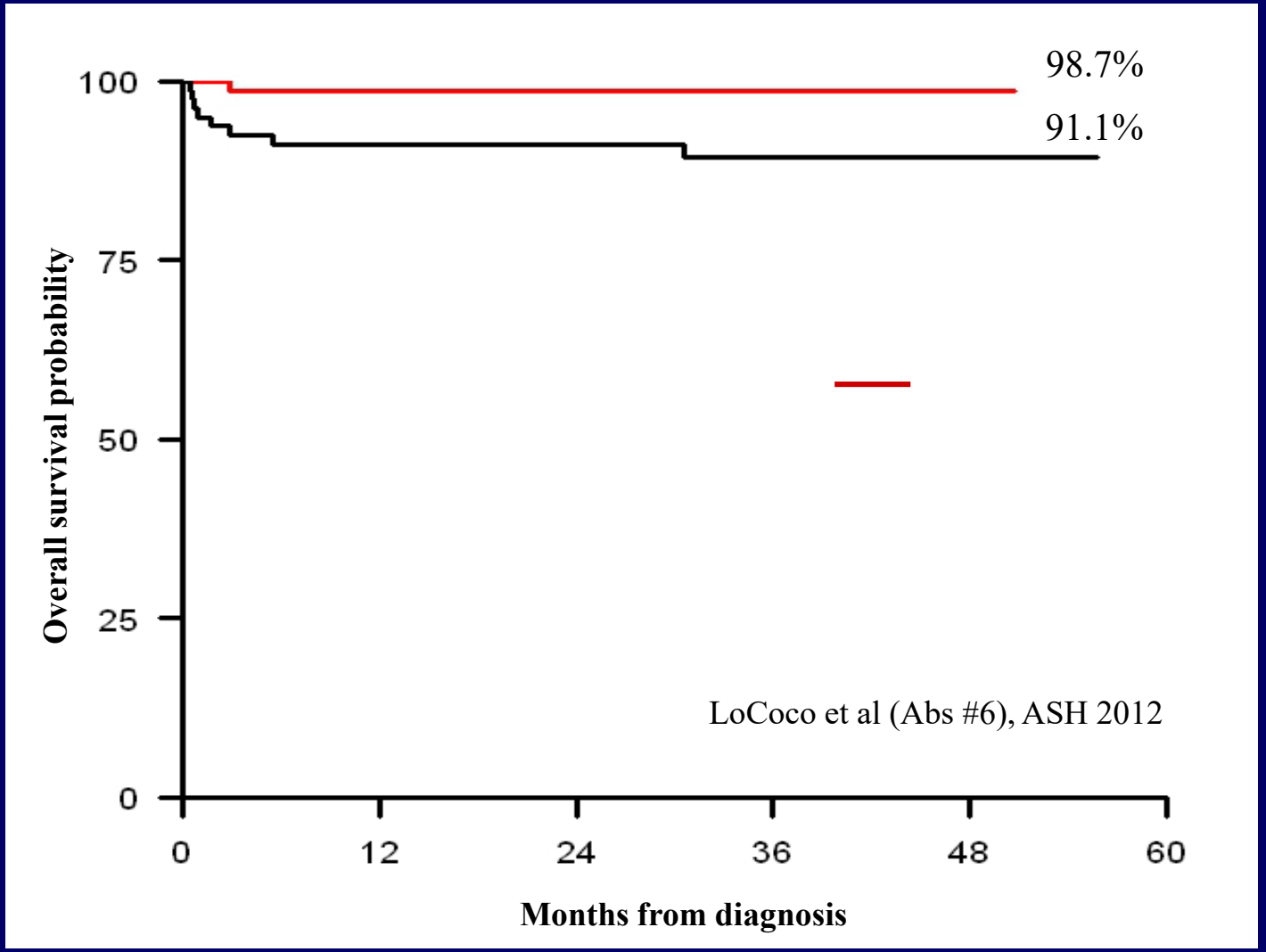
ATRA

2 years

Lo-Coco *et al*, Blood 2010

LoCoco et al NEJM 2013

Overall Survival



ALL: Therapy

- Childood ALL-85% cured: The great success story based on anthracycline, vincristine, steroid, L-asp induction; CNS prophylaxis; intensification; and POMP maintenance
- Adult ALL-35% cured: More difficult biology (inrceased inc PH+), but perhaps therapy could be improved even with available agents
  - Ongoing trial lead by DFCI adult leukemia team: almost exact pediatric rx to adults

ALL: Therapy in Children

- Successive steady improvements in recent past such that even high risk children are doing well; DFCI studies

	EFS
– 1981-5 (hd MTX , no L-asp ind'n)	74%
– 1985-7 (ld MTX, L-asp ind'n)	78%
– 1987-91 (no CNS XRT, SR)	78%
– 1991-5 (hd MTX,L-asp ind'n, 30 wk intens dexamethsone)	83%

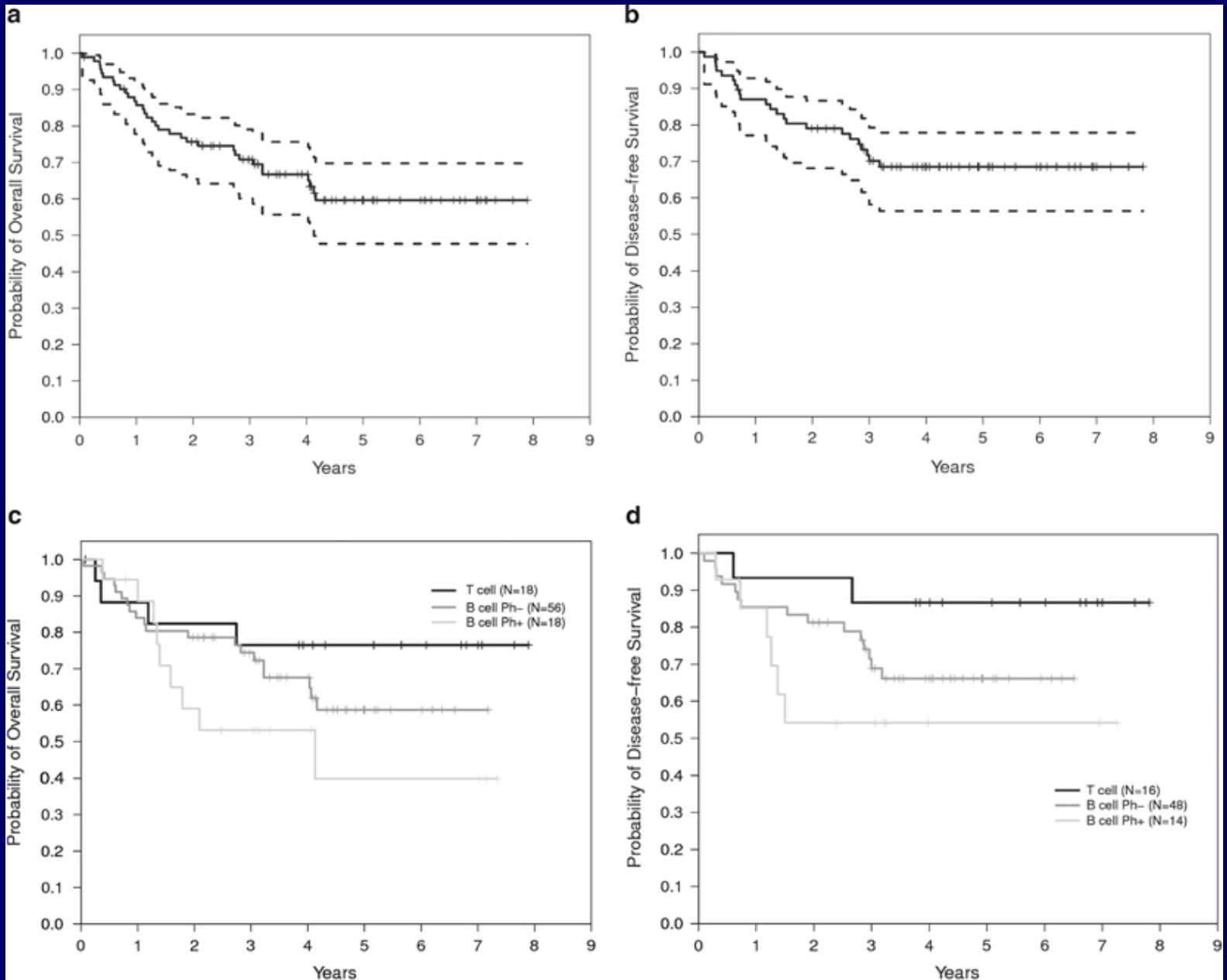
Childhood ALL: Late Complications of Therapy

brain Tumor	Cranial XRT
AML	topo II drugs (teniposide, anthracylines)
cardiomyopathy	anthracyclines
encephalopathy	Cr XRT, steroids, MTX
AVN of bone	steroids
osteoporosis	steroids, Cr XRT, ametab
short stature	Cr XRT, steroids, h.d chemo
obesity	Cr XRT
hypothyroidism	Cr XRT, h.d. chemo

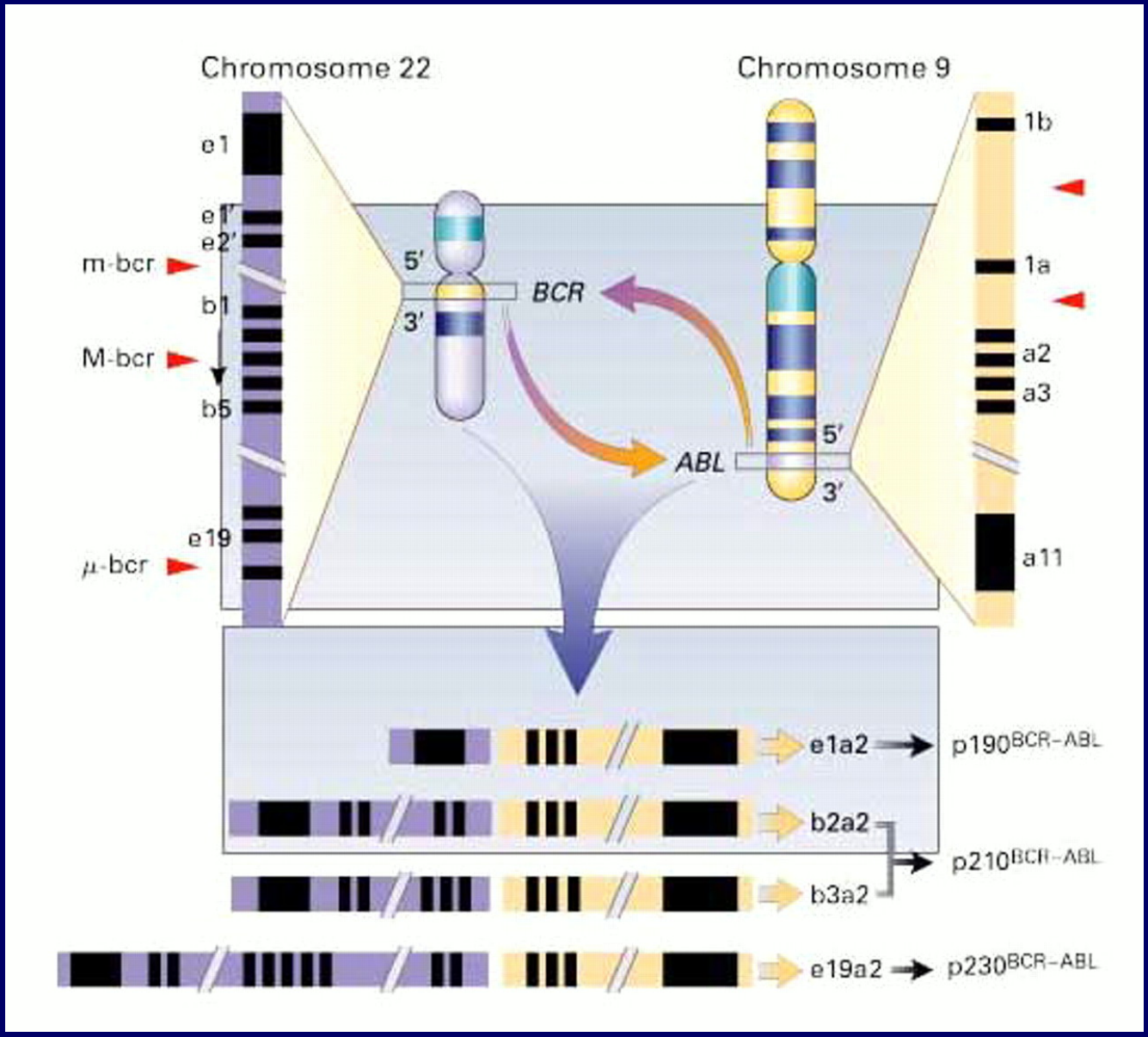
Outcome Comparison of Adolescent/Young Adults with ALL on Pediatric vs. Adult Clinical Trials

Cooperative Group	Study Period/ No. Pts.	Age (yrs)	CR (%)	EFS (%)
North America (Stock)	1988-1998	16-21		(6 year)
CCG (peds)	196 pts		96%	64%
CALGB (adults)	103 pts		93%	38%
French (Boissel)	1993-1994	15-20		(5 year)
FRALLE (peds)	77 pts		94%	67%
LALA (adults)	100 pts		83%	41%
Dutch (deBois)	1985-1999	15-21		(5 year)
SKION (peds)	47 pts		98%	69%
HOVON (adults)	73 pts		91%	31% / 46%
Italian (Testi)	1996-2000	14-18		(2 year)
AIEOP (peds)	153		94%	83%
GIMEMA (adults)	95		95%	55%

DFCI Pediatric-Inspired ALL for adults age 18-40



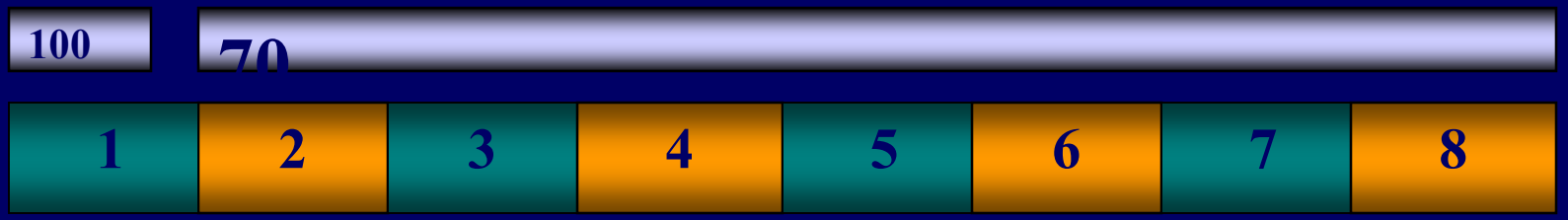
Deangelo et al Leukemia 2015



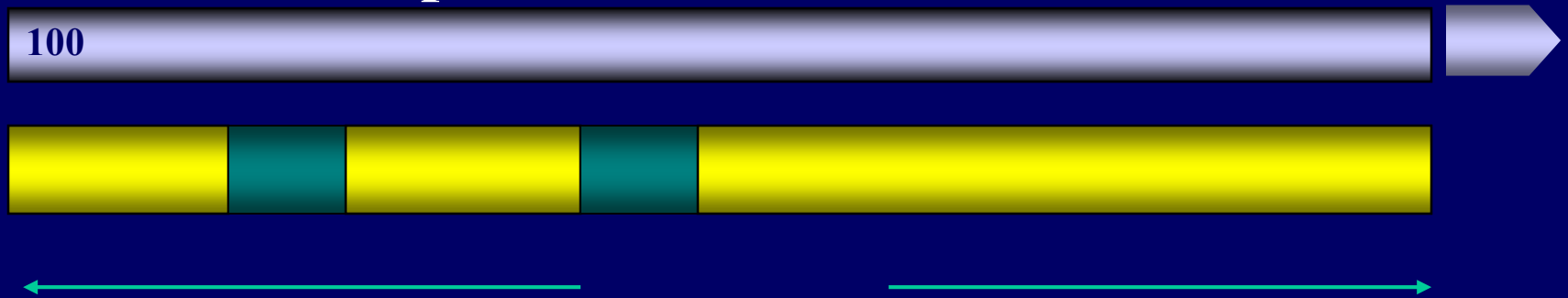
Faderl, S. et al. N Engl J Med 1999;341:164-172

SWOG S0805 – Chemo/dasatinib

Intensive phase



Maintenance phase

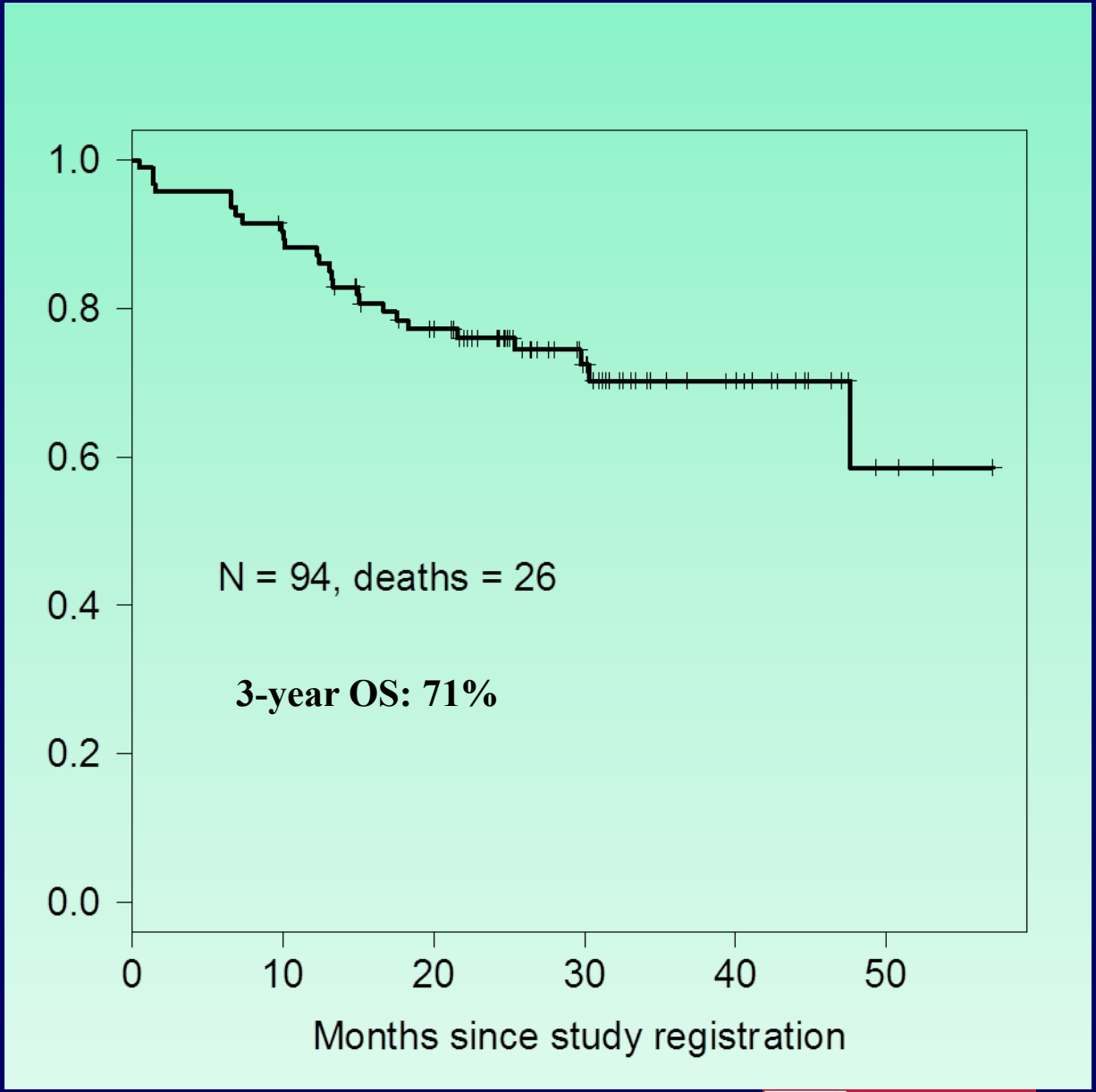


Risk-adapted intrathecal CNS prophylaxis

- Hyper-CVAD
- MTX-cytarabine
- Dasatinib 70 mg po daily
- Vincristine + prednisone

NCI National Clinical Trials Network
a National Cancer Institute program

SWOG S0805 – Overall Survival (OS)(Whole



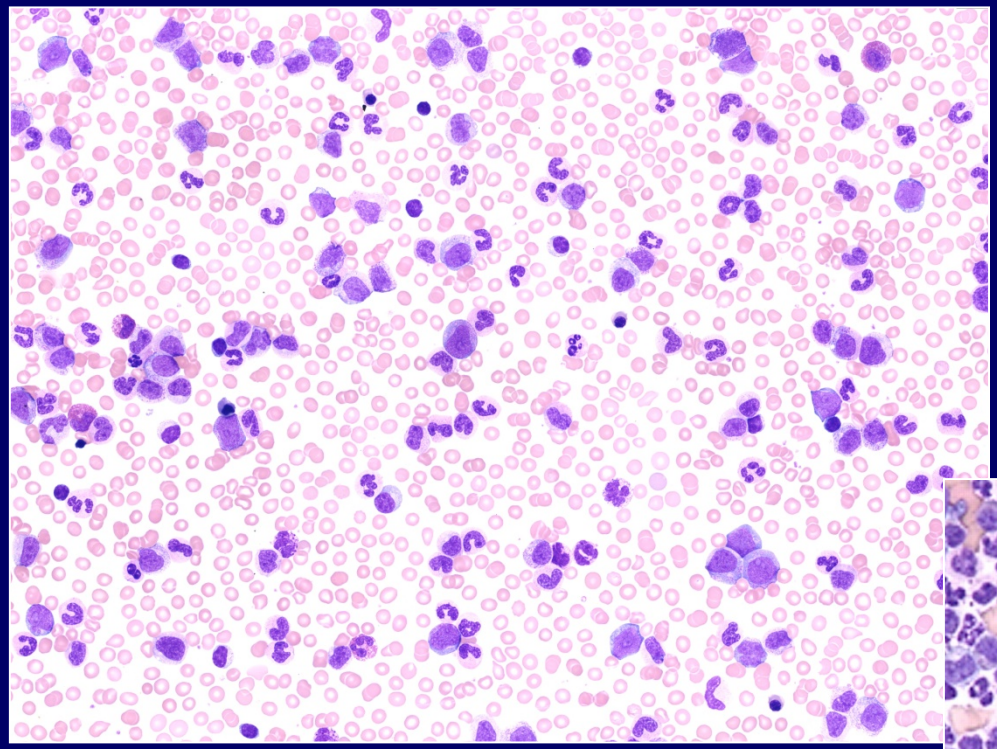
Ravandi, ASH 2015

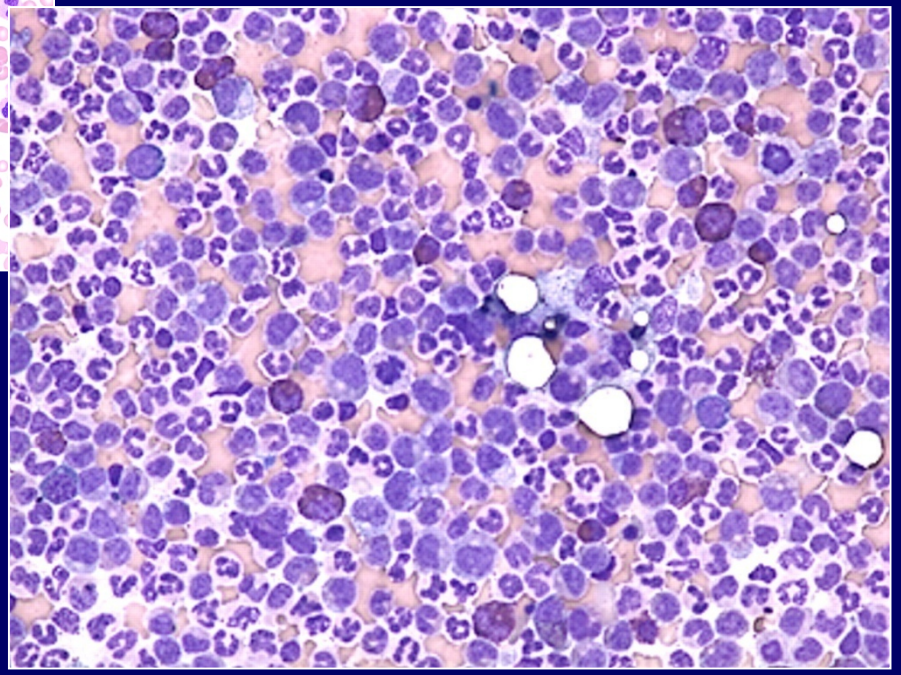
NCI National Clinical Trials Network
a National Cancer Institute program

Monoclonal Antibodies and Their Targets in ALL

Antigen Target	Antibodies
CD19	Blinatumomab SGN19a SAR3419 Combotox
CD20	Rituximab Ofatumumab
CD22	Epratuxumab Inotuzumab Combotox BL22, HA22
CD52	Alemtuzumab

CML Stable Phase



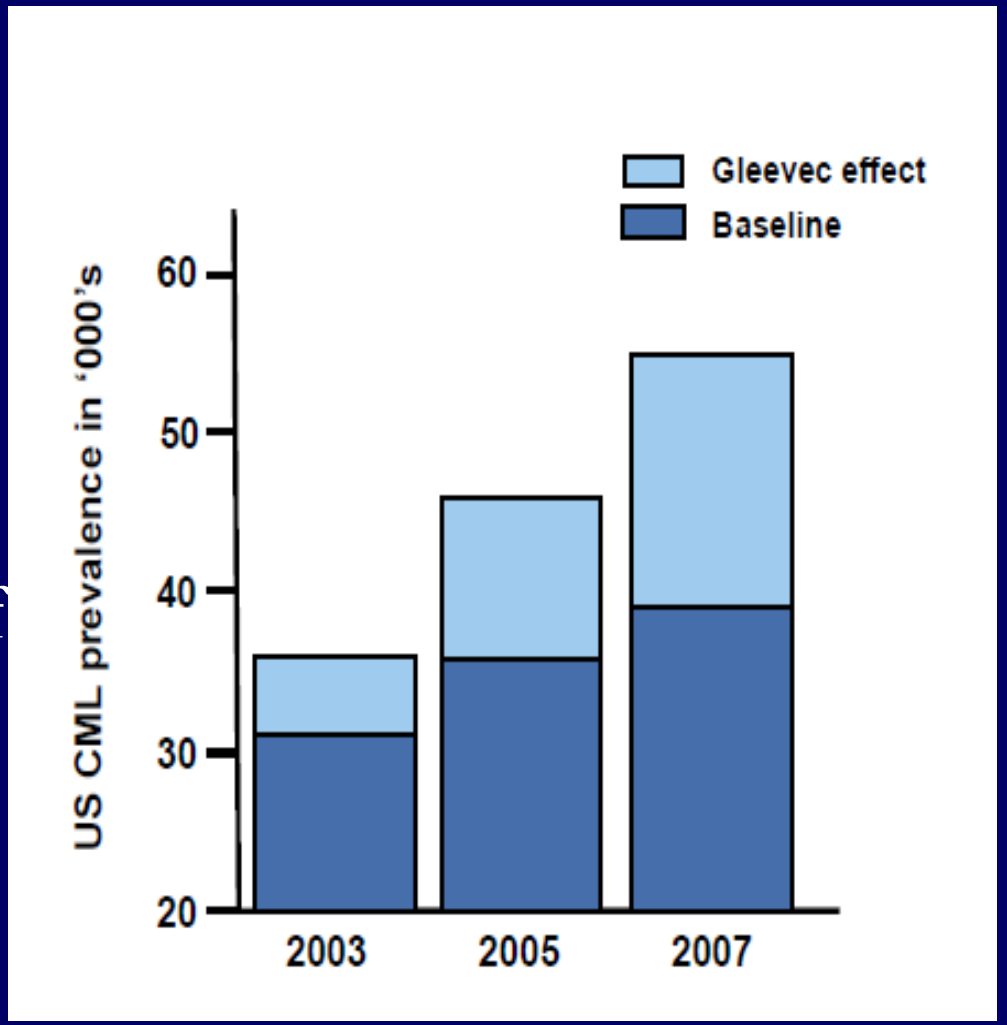


Presentation and Clinical Course Chronic Phase

- 85-90% present in chronic phase
- 50% asymptomatic at presentation
- symptoms are often non-specific
  - fatigue 80%
  - weight loss 60%
  - abdominal discomfort 40%
  - easy bruising 35%
  - leukostasis, priapism, thrombosis are unusual

CML Prevalence

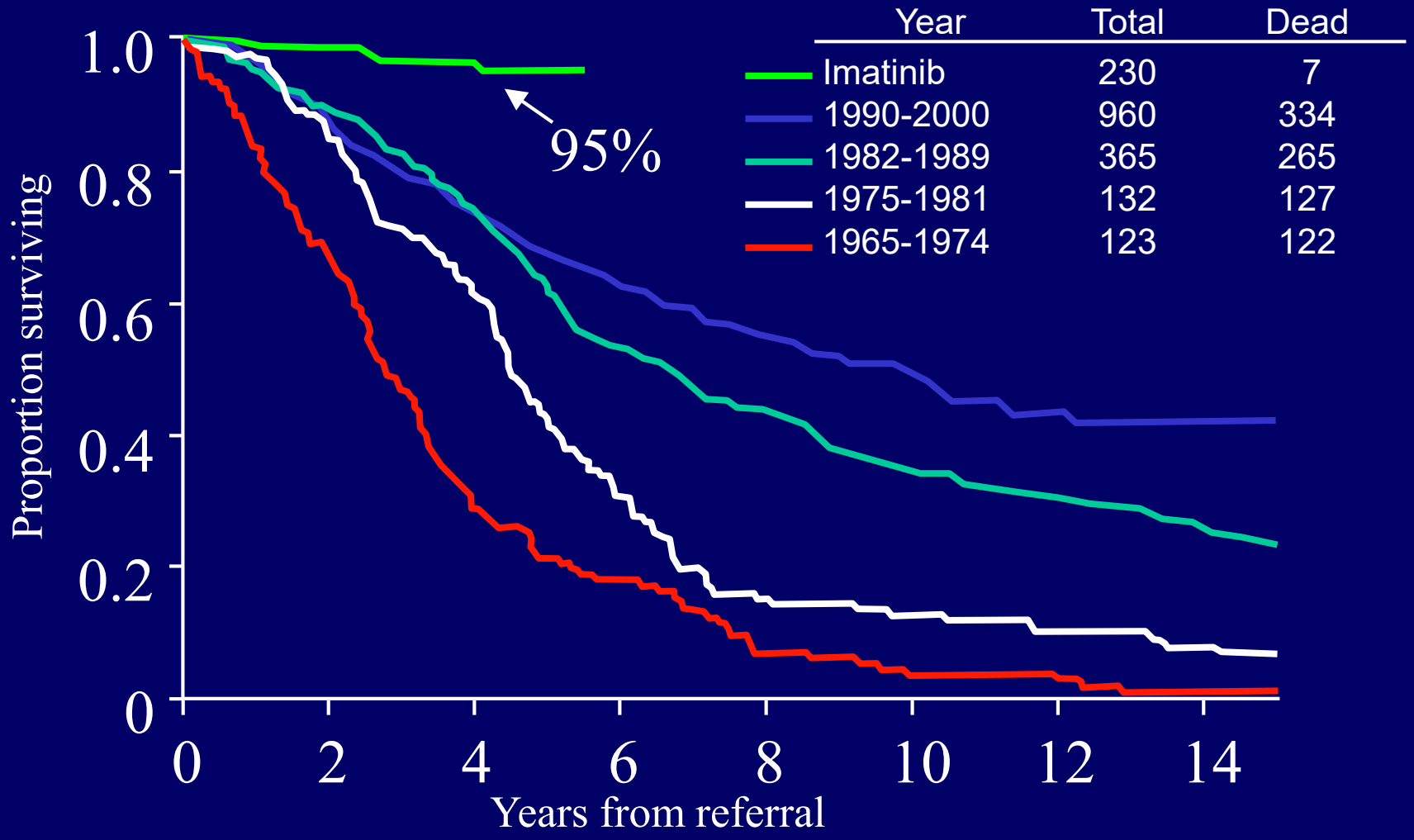
- US Prevalence is currently 40-50,000 patients with ~4600 new cases per year.
- Anticipated increase of >10% per year.



Huang X, et al , *Cancer* 118: 3123-3127, 2012

Survival in Early Chronic Phase CML

Kantarjian H, et al, Blood 119: 1981-1987, 2012



CML: Current Status in 2017

Imatinib
Nilotinib
Dasatinib

Refractory response
Suboptimal response
Relapse
Intolerance

Nilotinib
Dasatinib
Bosutinib
Ponatinib
Omacetaxine*

SCT

* 2 or more TKIs

Goals of Therapy and Assessing Response

- Landmarks of response in CML:

Myelodysplastic Syndromes: Definition

- **Heterogeneous Marrow Stem Cell Disorder Characterized by Hypercellular Marrow and Peripheral Cytopenias**

Current "Standard" Therapy for MDS

Supportive care for all (transfusions and antimicrobials PRN, ?iron chelation)

Lower-risk MDS (*assessed using IPSS, etc.*)

Cytopenia(s)	Disease feature	First-line therapy
Anemia only	Del (5q)	**Lenalidomide**
	No del(5q), sEPO <500	**ESA** ± G-CSF
	No del(5q), sEPO >500	?Immunotherapy
Neutropenia or **thrombocytopenia** or both		None established; observation, growth factors, aza/decit reasonable

Higher-risk MDS

Partly based on 2014 NCCN guidelines; see www.nccn.org

Allogeneic SCT candidate?	Therapeutic approach
Yes	**Proceed to transplant ASAP**; a hypomethylating agent (HMA) or cytotoxic chemotherapy may be used as a "bridge"
No	**Azacitidine; decitabine** as alternate

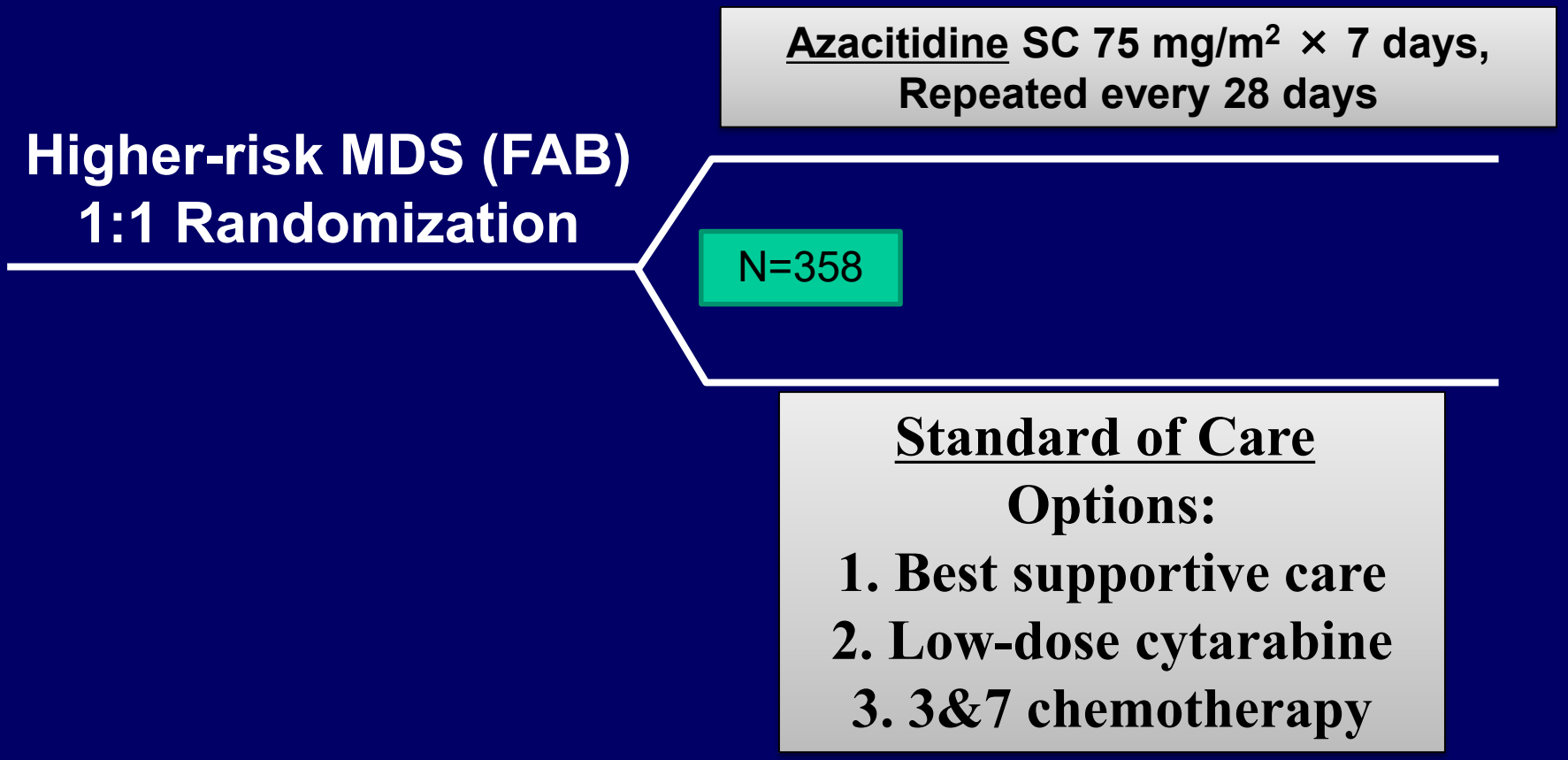
MDS: General Treatment Principles

Allogeneic Stem Cell Transplant: The only known curative modality, but practical only in a small subset (<10%) of patients.

Non-Curative Goals: Decreased transfusion needs, decreased infection, delay of disease progression, prolonged survival, increased quality of life

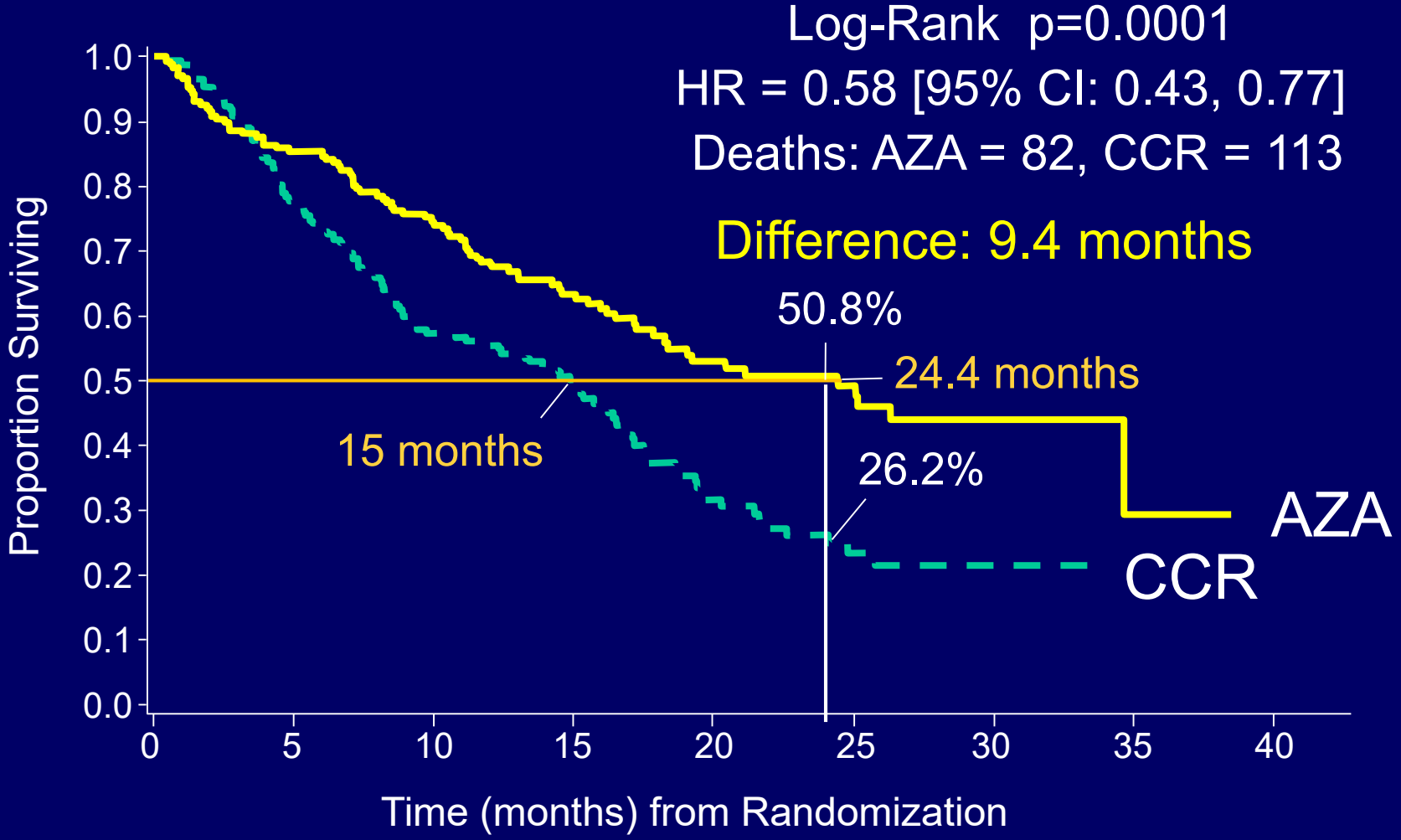
Azacitidine Survival Study

AZA-001 Survival Study Design



Fenaux P, et al. *Lancet Oncol.* 2009;10(3):223-232.

Overall Survival: Azacitidine vs CCR
ITT Population



Survival benefit seen even in non-CR pts.

Fenaux P, et al. *Lancet Oncology, 2009*

List et al, JCO 2010.

Transfusion therapy results in iron overload

Moderate transfusion requirement:

- 2 units / month
- 24 units / year
- ~ 100 units / 4 years

High transfusion requirement:

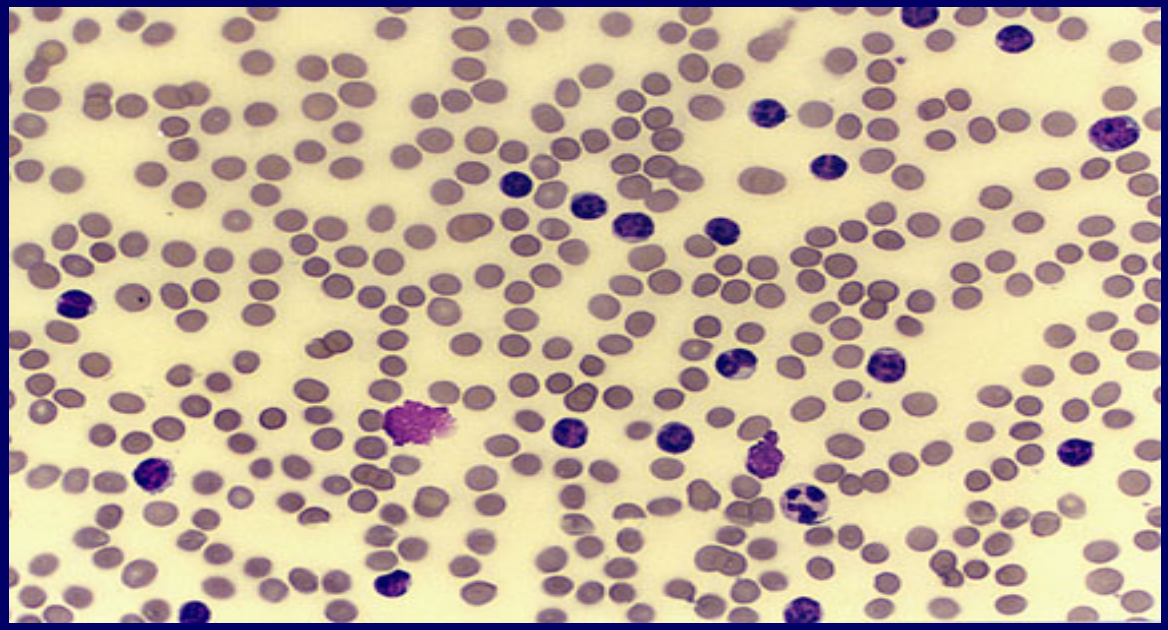
- 4 units / month
- 48 units / year
- ~ 100 units / 2 years

100 units: ≥ 20 g iron

Normal body iron: 3-4 g

Chronic Lymphocytic Leukemia

- **A lymphoproliferative disease of CD5 + mature B-cells.**
- **More a lymphoma (LN counterpart: small lymphocytic lymphoma) than a leukemia.**



Chronic Lymphocytic Leukemia: Clinical Features

- **May Present asymptomatically (typcially high absolute lymphocyte count in older adults)**
- **Other features in some pts: lymphadenopathy (LAN), splenomegaly, anemia, thrombocytopenia, systemic symptoms (fevers, et loss)**
- **Anemia or thrombocytopenia may be on the basis of auto-antibodies. Such pts respond to steroids.**
- **Hypogammaglobulinemia with associated infections with encapsulated bacteria (S. Pneumo, H. flu)**

Chronic Lymphocytic Leukemia: Diagnosis

- **Classically- send peripheral blood for flow cytometry, find CD5+, CC20+, CD23 + (MCL usually CD23-)**
- **Prognosis based on clinical staging**
- **Add in cytogenetics/FISH**
  - **13q- is good**
  - **11q- or 17p- bad**
- **Molecular studies: IgH rearranged- good, ZAP 70 bad**

Rai and Binet staging systems for classification of CLL

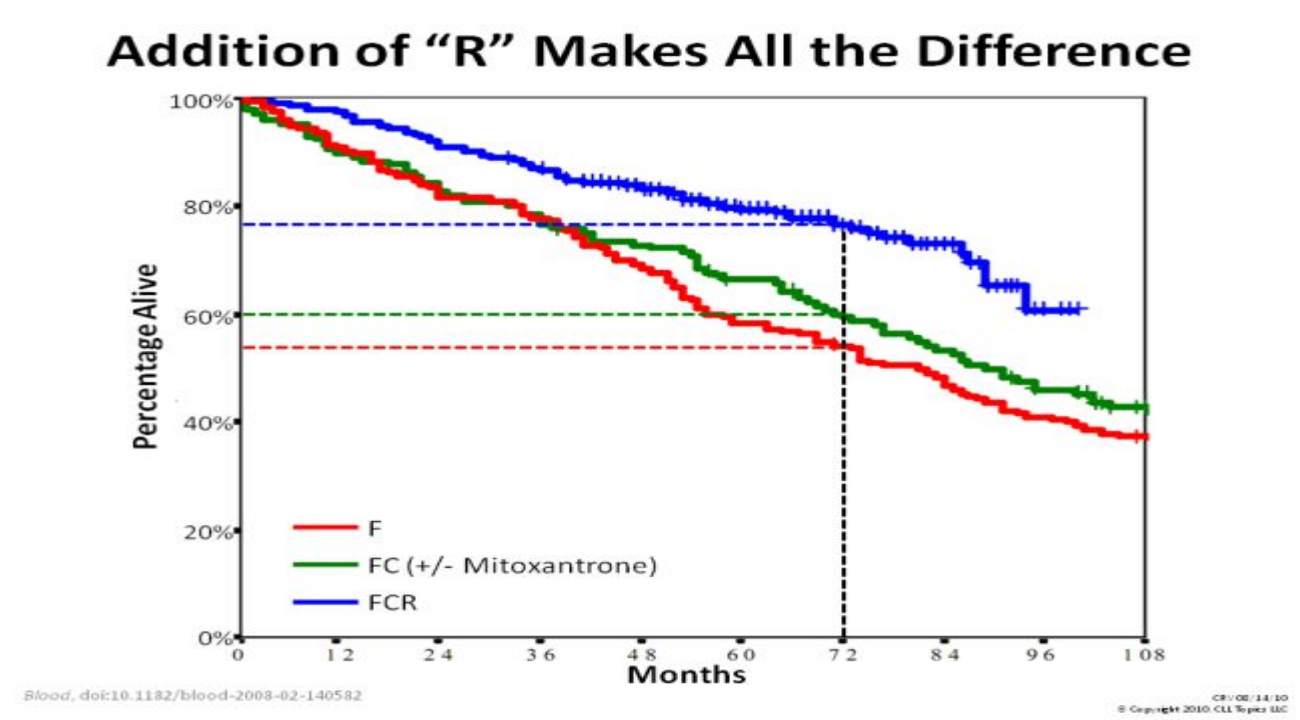
System	Stage	Definition	Median survival
Rai staging system			
	0 (low risk)	Lymphocytosis only	11.5 years
	I (intermediate risk)	Lymphocytosis and lymphadenopathy	11.0 years
	II (intermediate risk)	Lymphocytosis in blood and marrow with splenomegaly and/or hepatomegaly (with or without lymphadenopathy)	7.8 years
	III (high risk)	Lymphocytosis and anemia (hemoglobin <11 g/dL or hematocrit <33%)	5.3 years
	IV (high risk)	Lymphocytosis and thrombocytopenia (platelet count <100,000/mm^3)	7.0 years
Binet staging			
	A	Enlargement of <3 lymphoid areas (cervical, axillary, inguinal, spleen, liver); no anemia or thrombocytopenia	11.5 years
	B	Enlargement of ≥3 lymphoid areas	8.6 years
	C	Anemia (hemoglobin <10 g/dL or thrombocytopenia (platelet count <100,000/mm^3), or both	7.0 years

Chronic Lymphocytic Leukemia: Therapy

- **Disease is incurable, but many pts live for >8 ys**
- **Therapy indicated for a) clinical symptoms a) diffuse LAN, wt loss, profound fatigue b) cytopenias not due to autoimmunity c) rapid doubling of lymphocyte count**
- **Special situations**
  - **Steroids for auto-immune mediated cytopenias**
  - **IVIG for recurrent pyogenic infections**

Chronic Lymphocytic Leukemia: Therapy

- **Acceptable initial regimens**
  - **FCR (fludarabine, cyclophophamide, rituximab (anti CD20)**
  - **FR (fludarabine, rituximab)**
  - **BR (bendamustine, rituximab)**

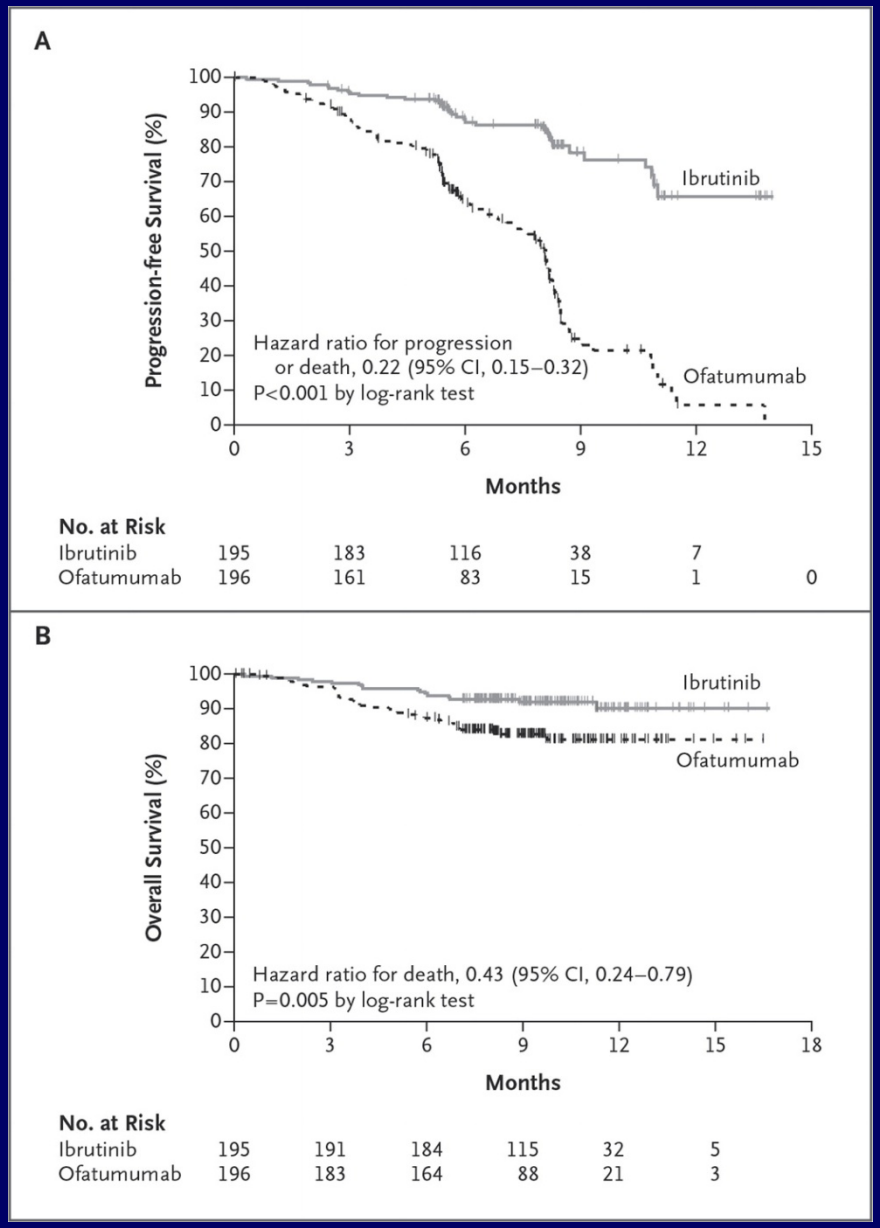


Badoux, X et al, Blood, 117: 3016-3024, 2011

Chronic Lymphocytic Leukemia: Therapy

- **Incredible new drugs for relapse (moving upfront)**
  - **Ibrutinib (sm mol inhibitor of Bruton's tyrosine kinase)**
  - **Idelalisib (sm mol inhibitor of PI 3 kinase)**
  - **Obinotuzumab (novel anti CD20 antibody)**
  - **Ofatumumab (novel anti CD20 antibody)**
  - **Venetoclax (ABT-199, sm mol inhib of bcl-2) (approved for 17p deleted)**

Ibrutinib is very active in previously treated CLL



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Patients and their families!!!!