Adult Acute Leukemia:
Rocky Mountain Blood Cancer Conference Overview

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Today's Agenda

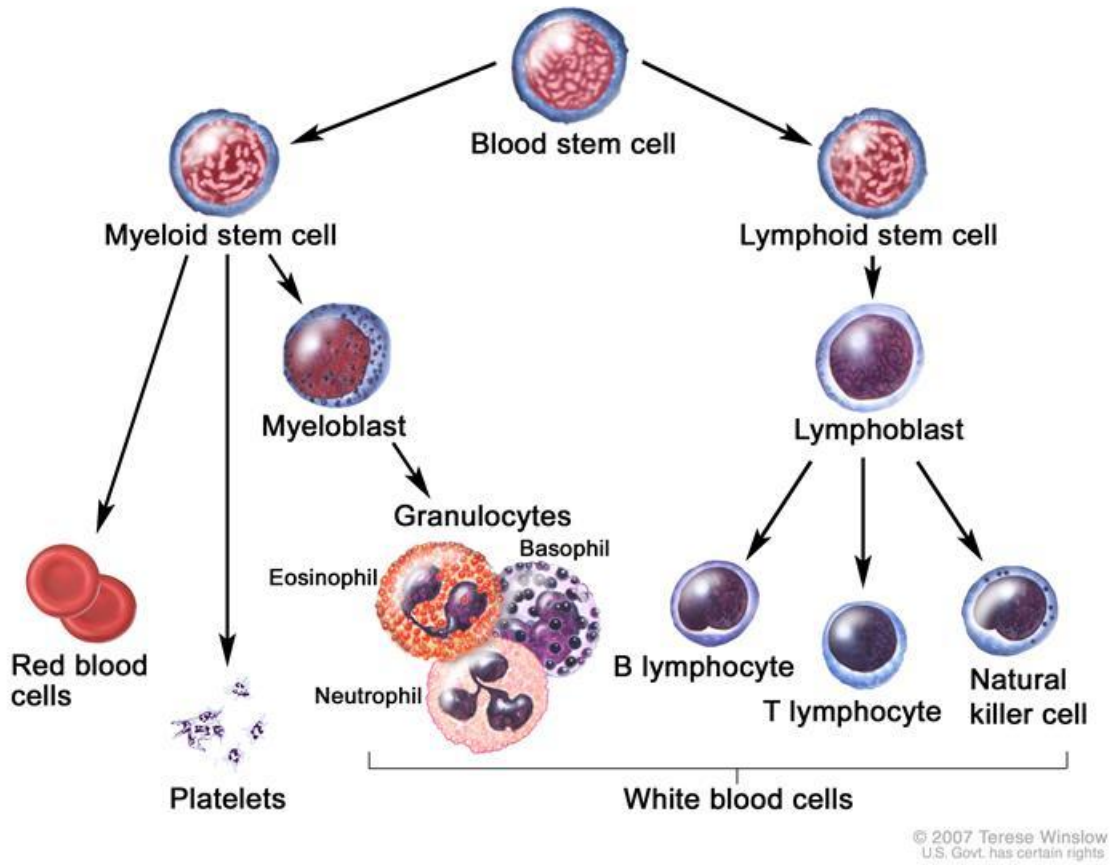
1. Basic Principles of Acute Leukemias

2. Acute Myeloid Leukemia (AML)
   a. Prognosis
   b. Treatment

3. Acute Lymphoblastic Leukemia (ALL)
   a. Prognosis
   b. Treatment

What is acute leukemia

- Uncontrolled growth of a primitive hematopoietic cell leading to ineffective hematopoiesis



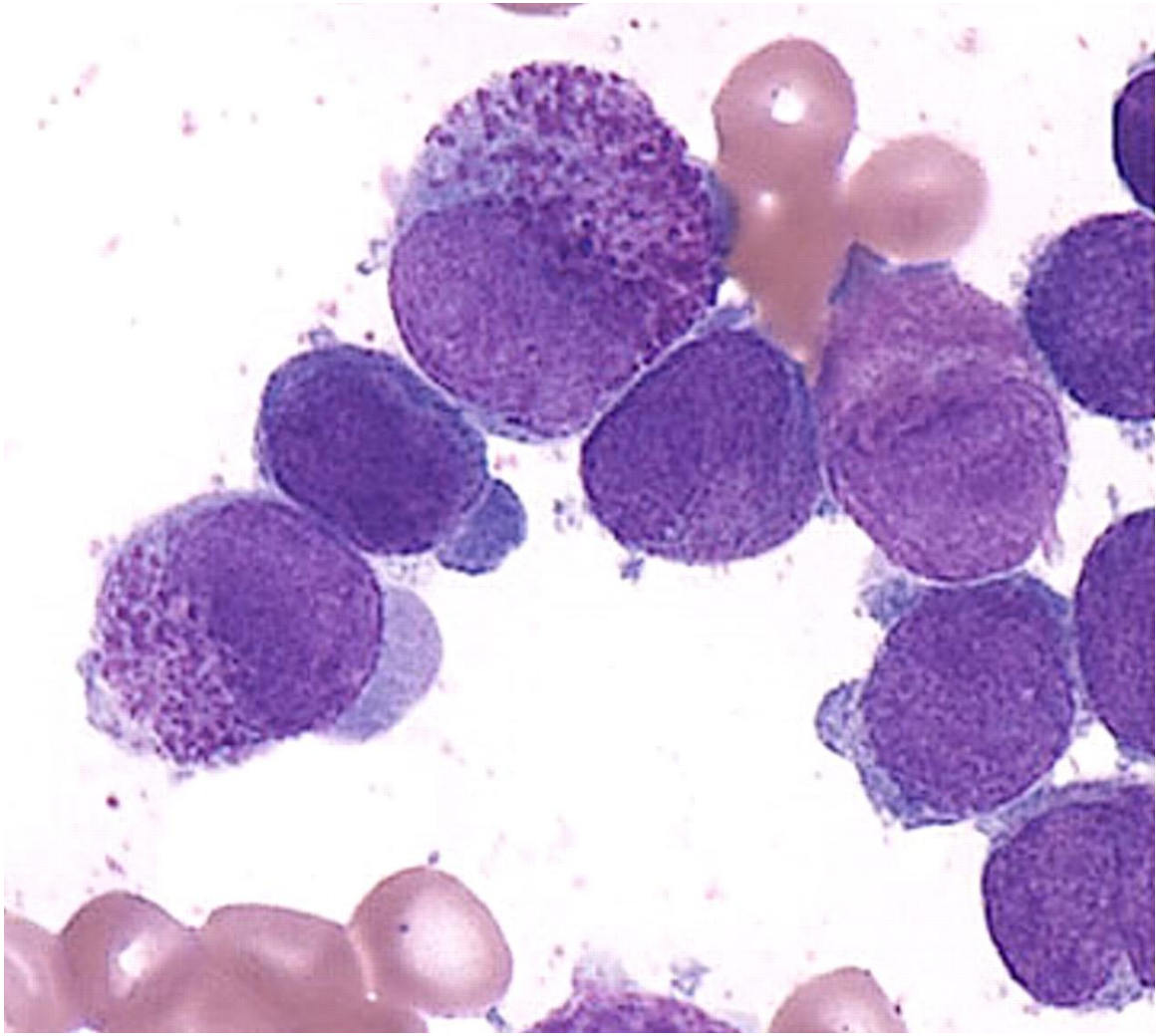
What is acute leukemia

- Syndrome – not a disease (… increasingly recognized to be true of most cancers)
  - Phenotypic manifestation of any of a number of genetic abnormalities causing maturation arrest and growth advantage
    - Phenotype:
      - Low red blood cells (decreased energy)
      - Low platelets (bleeding)
      - Ineffective white blood cells (infection)
      - Enlarged lymph nodes (ALL)
      - Rapidly fatal (weeks) if untreated

Treatment Principles

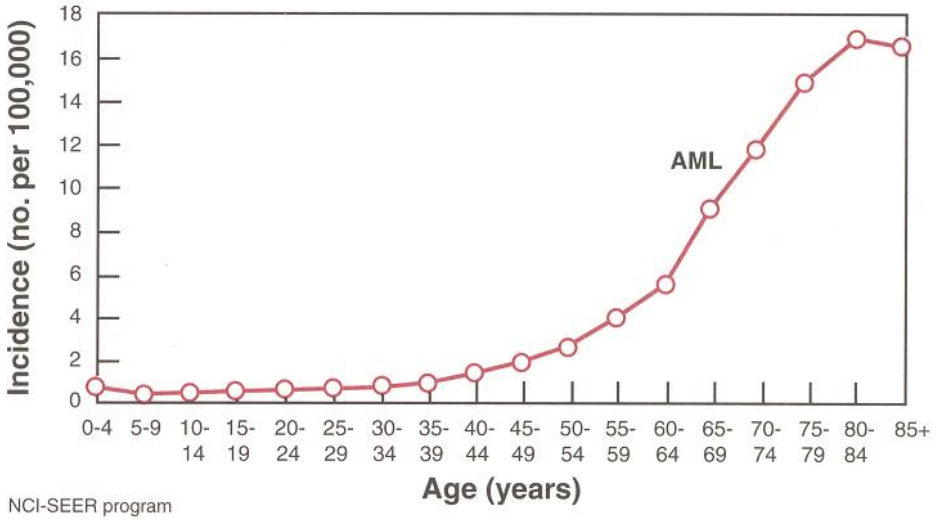
- Treatment options depend on a variety of factors: age, comorbidities, patient wishes, specific abnormalities associated with disease
- Initial goal is to induce remission
- Next goal is consolidate remission and hopefully cure
- Tools include conventional chemotherapy, stem cell transplant, immunotherapy, novel and targeted agents

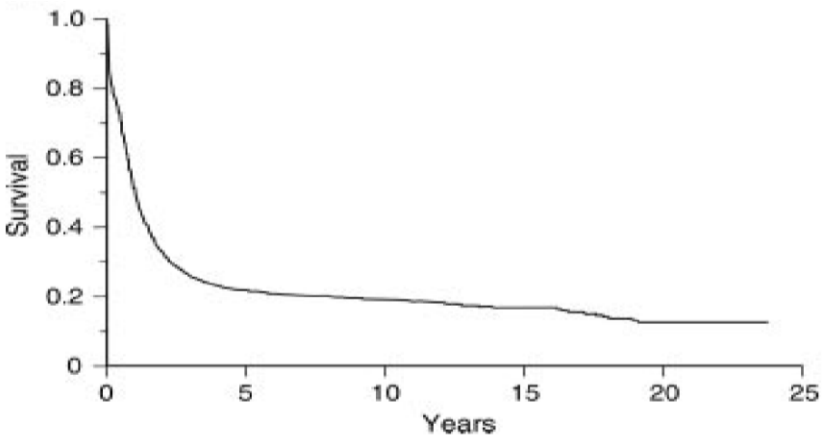
Acute Myeloid Leukemia



Demographics and Outcomes

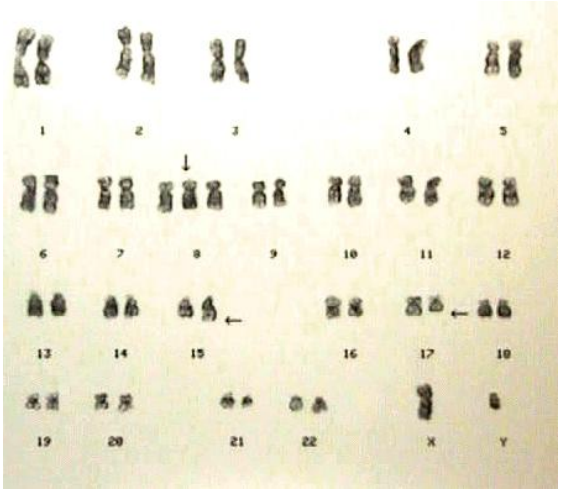
- About 13,000 new diagnoses/yr; 9,000 deaths
- Affects all ages, but incidence increases among older pts

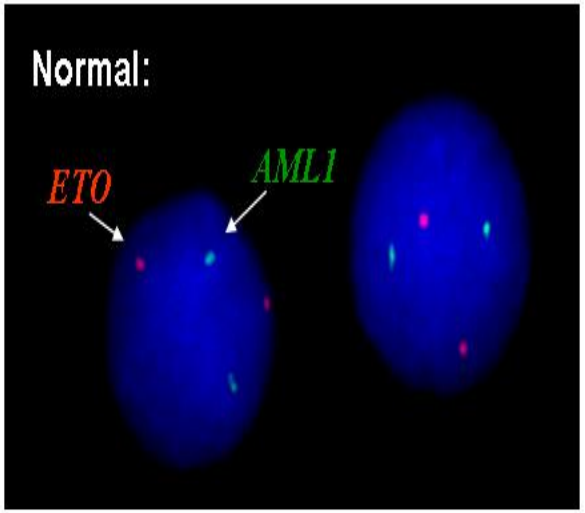


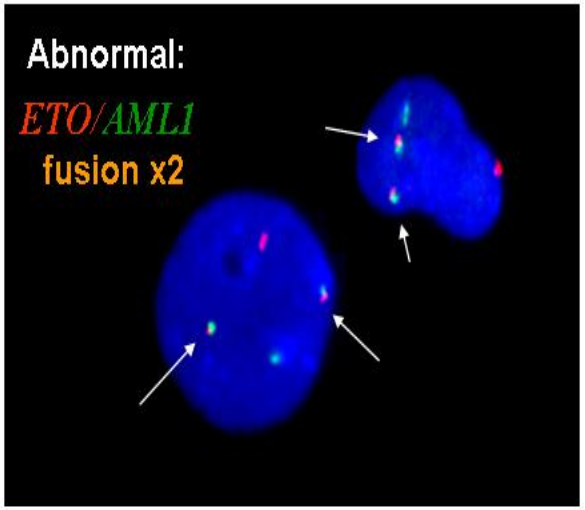


Modern Disease Classification

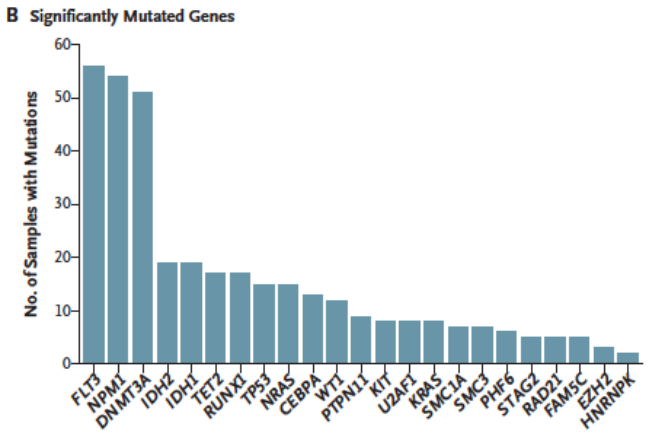
Cytogenetics/FISH

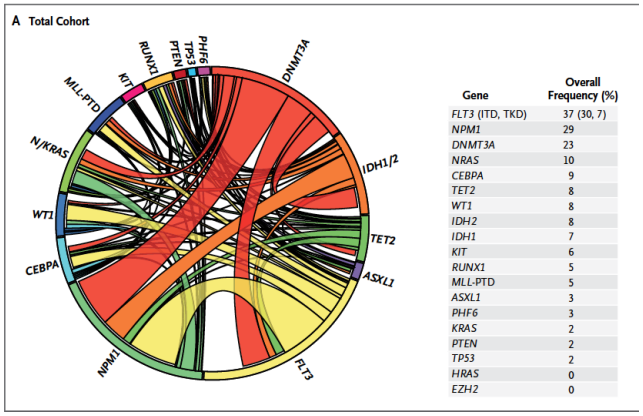




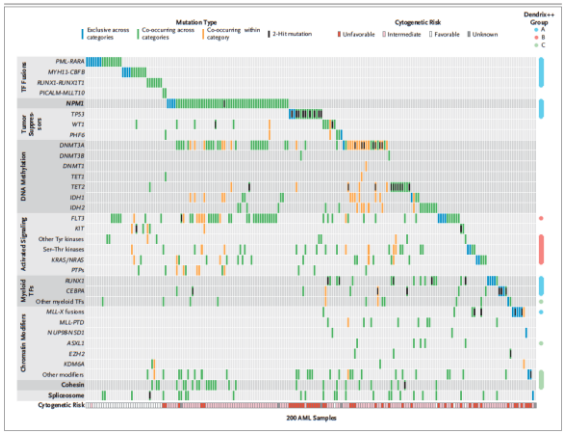


Molecular testing



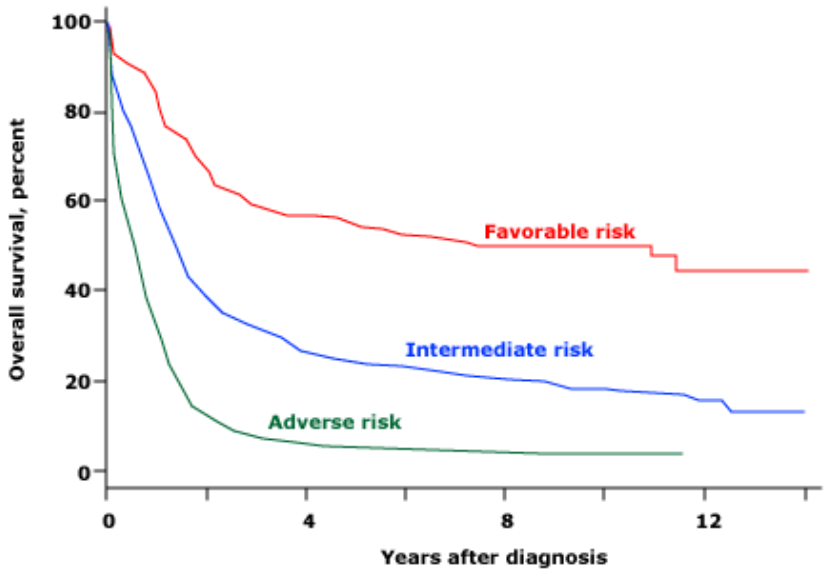


Gene	Overall Frequency (%)
FLT3 (ITD, TKD)	37 (30, 7)
NPM1	29
DNMT3A	23
NRAS	10
CEBPA	9
TET2	8
WT1	8
IDH2	8
IDH1	7
KIT	6
RUNX1	5
MLL-PTD	5
ASXL1	3
PHF6	3
KRAS	2
PTEN	2
TP53	2
HRAS	0
EZH2	0



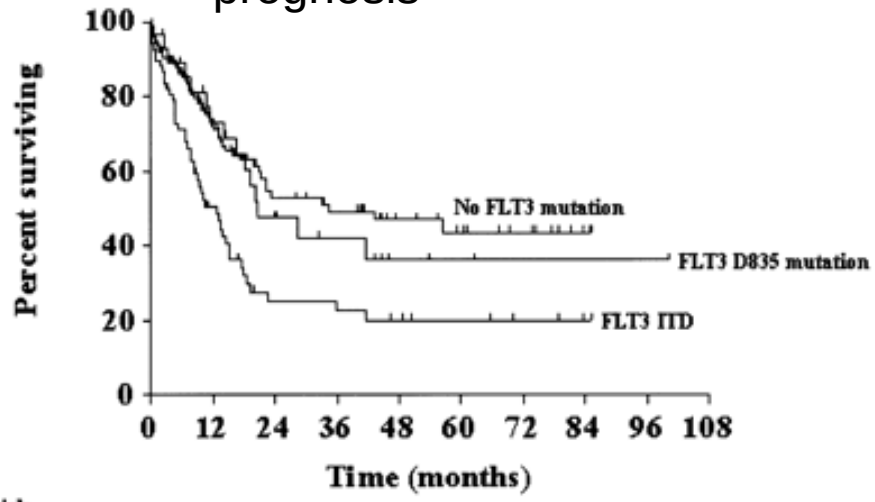
Recurrent cytogenetic abnormalities

Good Risk (Favorable)	
MRC[12]	inv(16)/t(16;16)/del(16q) with or without other abnl t(15;17) with or without other abnl, t(8;21) with or without other abnl
CALGB[14]	t(8;21), inv(16)/t(16;16)
SWOG/ECOG[13]	inv(16)/t(16;16)/del(16q) with or without other abnl t(15;17) with or without other abnl t(8;21) without del(9q) or complex karyotype
Intermediate Risk	
MRC	Normal, 11q23 abnl, +8, del(9q), del(7q), +21, +22, all others
CALGB	Normal, -Y, del(5q),* t(9;11), t(6;9),* del(9q),* loss of 7q, t(6;11),* +8 sole,* +8 with one other abnl,* –7,* +11, del(11q), +13, del(20q),+21, t(11;19)(q23,p13.1)*
SWOG/ECOG	Normal, +8, +6, –Y, del(12p)
Poor Risk (Unfavorable)	
MRC	Complex karyotypes (≥ 5 unrelated abnl) del(5q), –5, –7, abnl (3q)
CALGB	Complex karyotypes (≥ 3 unrelated abnl) inv(3)/t(3;3), –7,† abnl (12p), +21,† t(6:9),‡ t(6;11),‡ –7,‡ +8 sole,‡ +8 with one other abnl,‡ t(11;19)(q23;p13.1)‡
SWOG/ECOG	Complex karyotypes (≥ 3 unrelated abnl) del(5q), –5, –7/del(7q), abnl 3q,9q, 11q, 20q, 21q, 17p, t(6;9), t(9;22)



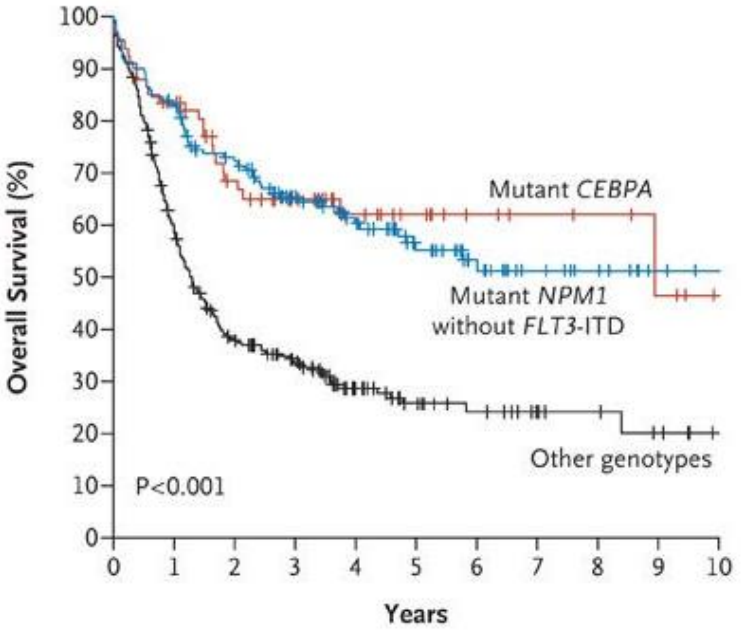
Molecular testing

FLT3 ITD carries negative prognosis



Number at risk									
No FLT3 mutation	125	67	31	26	16	12	8	3	0
FLT3 D835 mutation	28	18	11	7	3	2	1	1	1
FLT3 ITD	67	25	10	9	7	5	3	1	0

CEBPA and isolated NPM1 carry favorable prognosis



No. at Risk											
Other genotypes	266	153	90	68	39	22	15	9	7	4	0
Mutant *NPM1* without *FLT3*-ITD	150	123	101	75	56	38	25	14	10	4	2
Mutant *CEBPA*	67	54	39	30	19	13	8	6	5	3	0

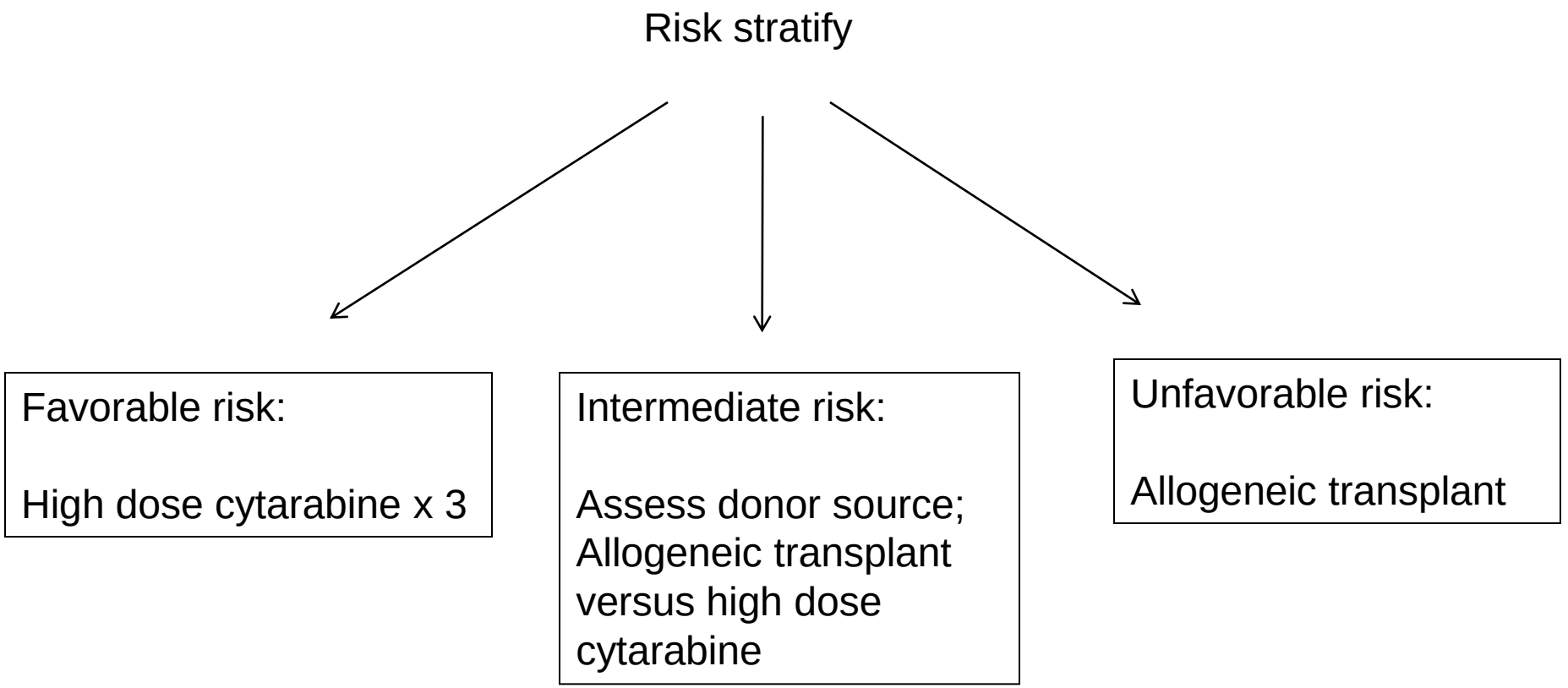
Schlenk RF, NEJM 2008

AML in the young (<60-65): Induction

- 7 + 3 standard induction regimen for decades
  - 7 days cytarabine
  - 3 days anthracycline (daunorubicin, idarubicin, or mitoxantrone)

- Numerous studies comparing alternative agents and novel combinations of agents have not improved survival, though investigations continue

AML in the young: Consolidation



AML in the young: Relapse

- Attempt reinduction with any of a variety of regimens, including novel agents

- Allogeneic transplant if possible

AML in the elderly (>60-65)

- More nuanced

- Assessment of performance status, prognostic characteristics of AML, patient goals

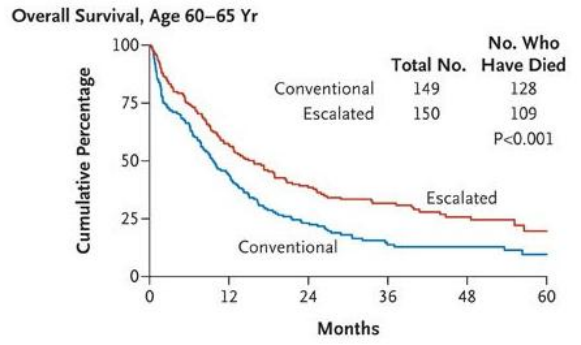
Why else do older patients do more poorly

- More multidrug resistance phenotypes
  - (33% < age 56, 57% > age 75)
- More often out of MDS
- More often poor cytogenetics
- Comorbidities – less able to tolerate chemo

AML in the elderly: treatment

Initial treatment decision

Aggressive induction



Lowenberg B, NEJM 2009

Hypomethylator

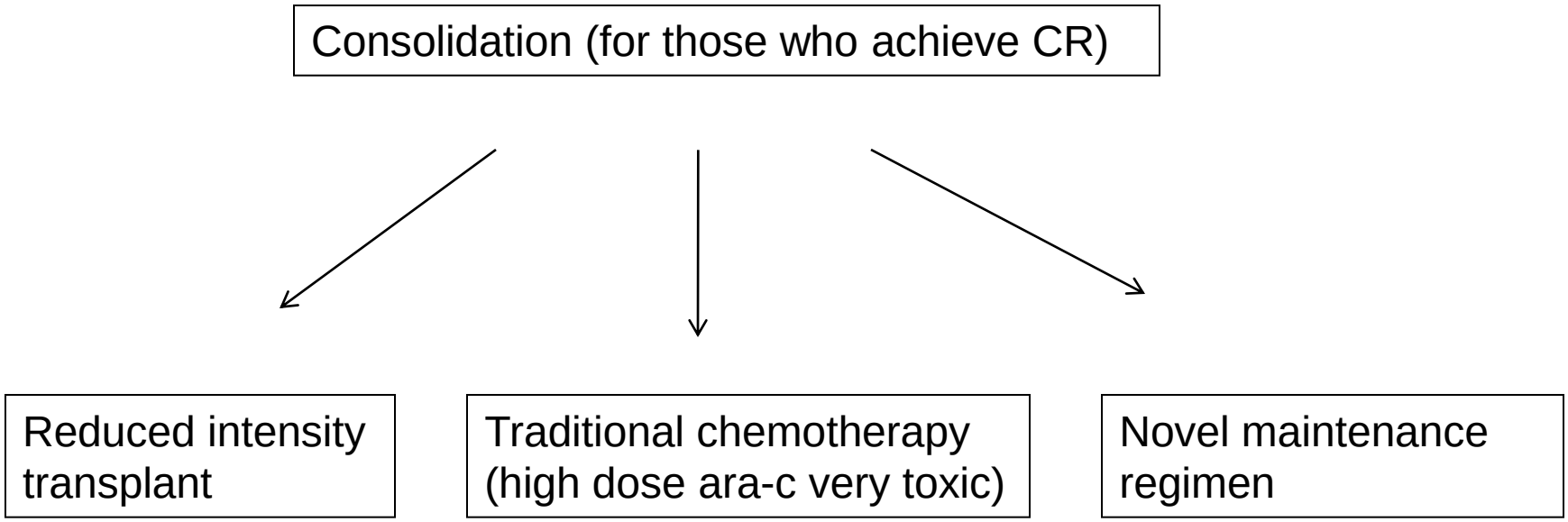
Novel therapeutic trial

Numerous targeted (or at least hopefully less toxic) regimens currently under investigation in various combinations and dosing schedules

No home runs yet

Best supportive care

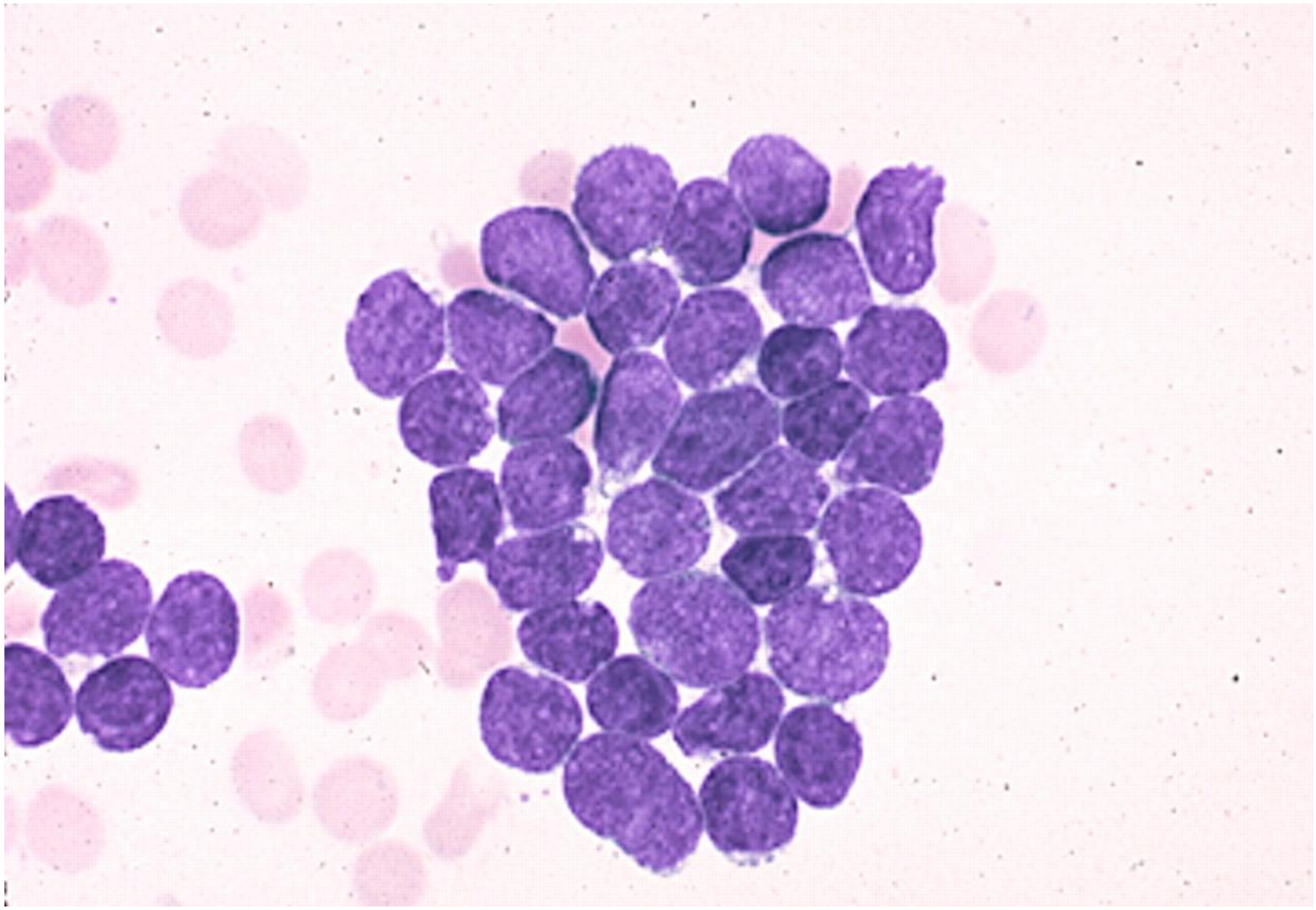
AML in the elderly: Consolidation



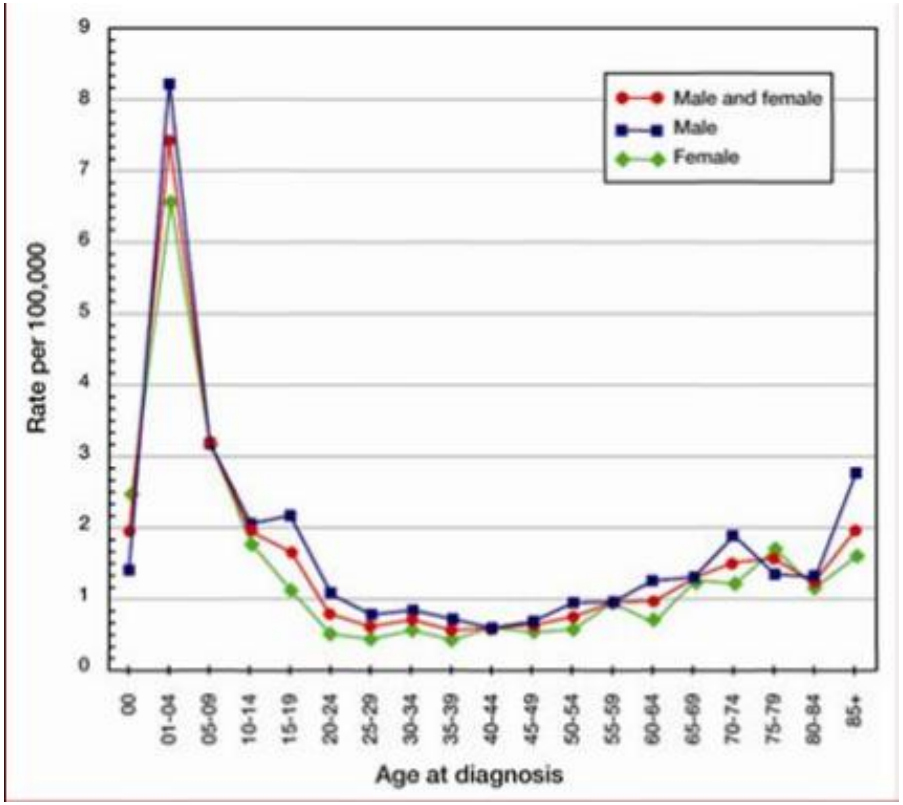
The newest drugs

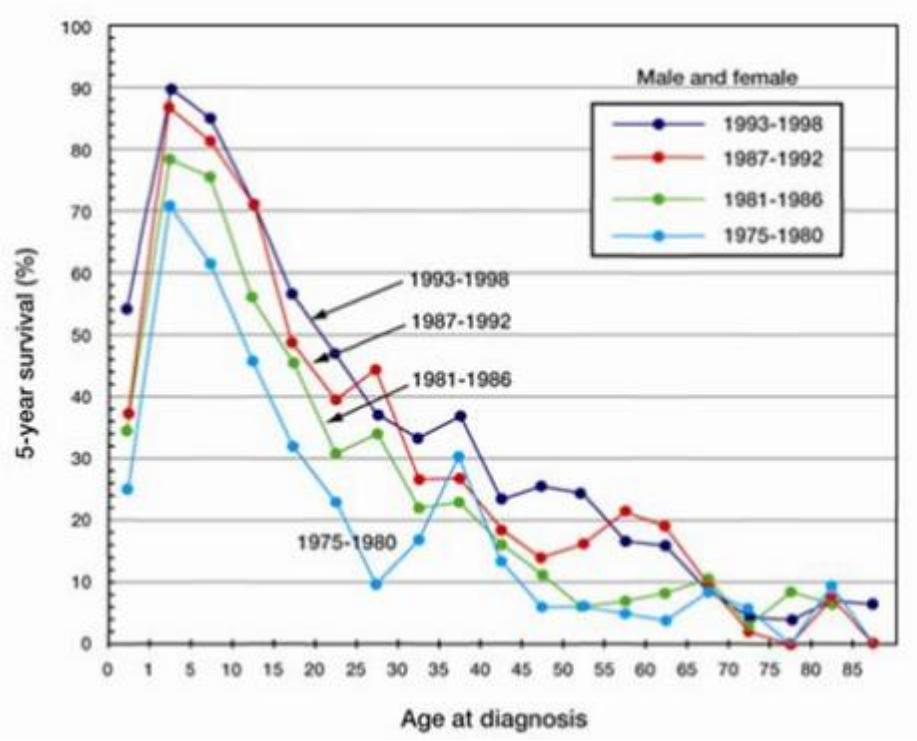
- CD33/CD BiTE antibody
- SGN-CD33a
- ABT-199
- Anti-IL3Rα/Anti-CD123
- DOT1L inhibitor
- IDH1 and IDH2 inhibitors

Acute Lymphoblastic Leukemia



Demographics and Outcomes

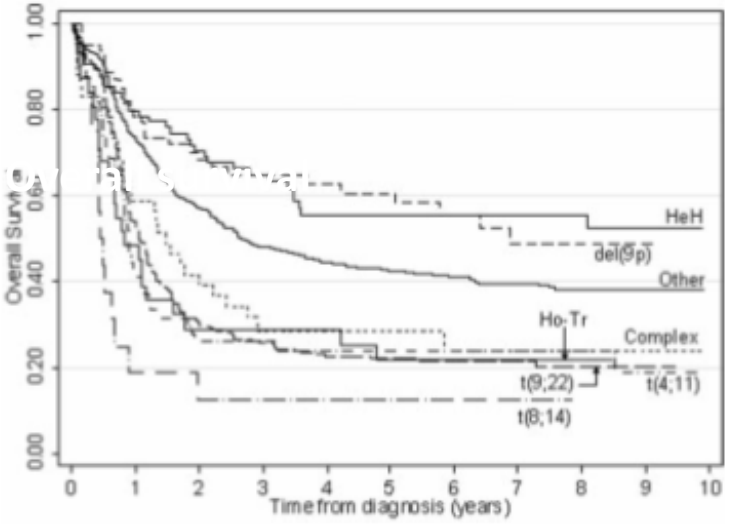


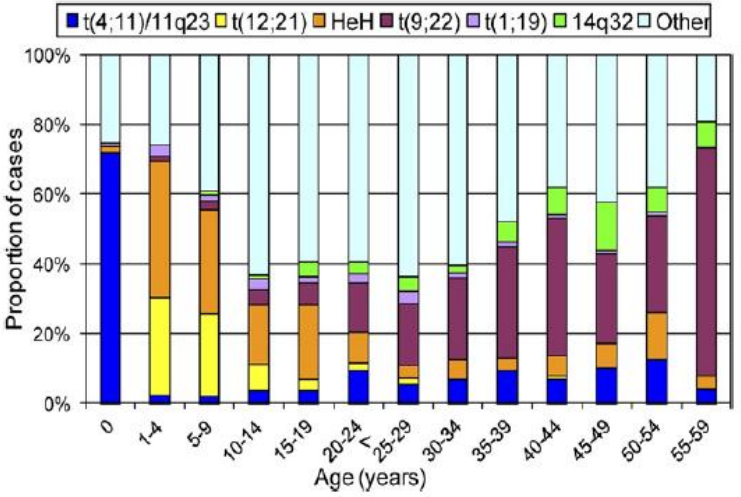


SEER data 2000-2003

Cytogenetics as Prognosticators

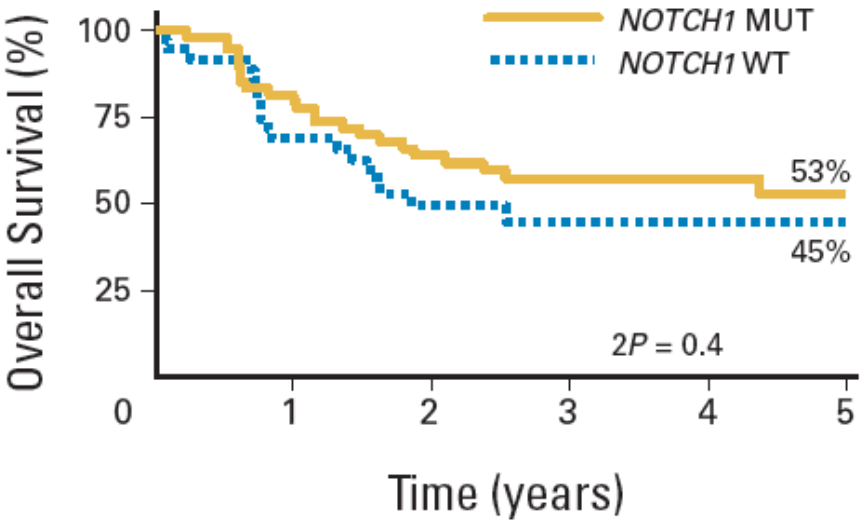
- 1,522 patients with ALL age 15-65
- Better prognosis:
  - Hyperdiploid
  - del(9p)
- Worse prognosis:
  - Complex karyotype
  - Hypodiploid
  - t(9;22)
  - t(4;11)
  - t(8;14)





Molecular testing

NOTCH



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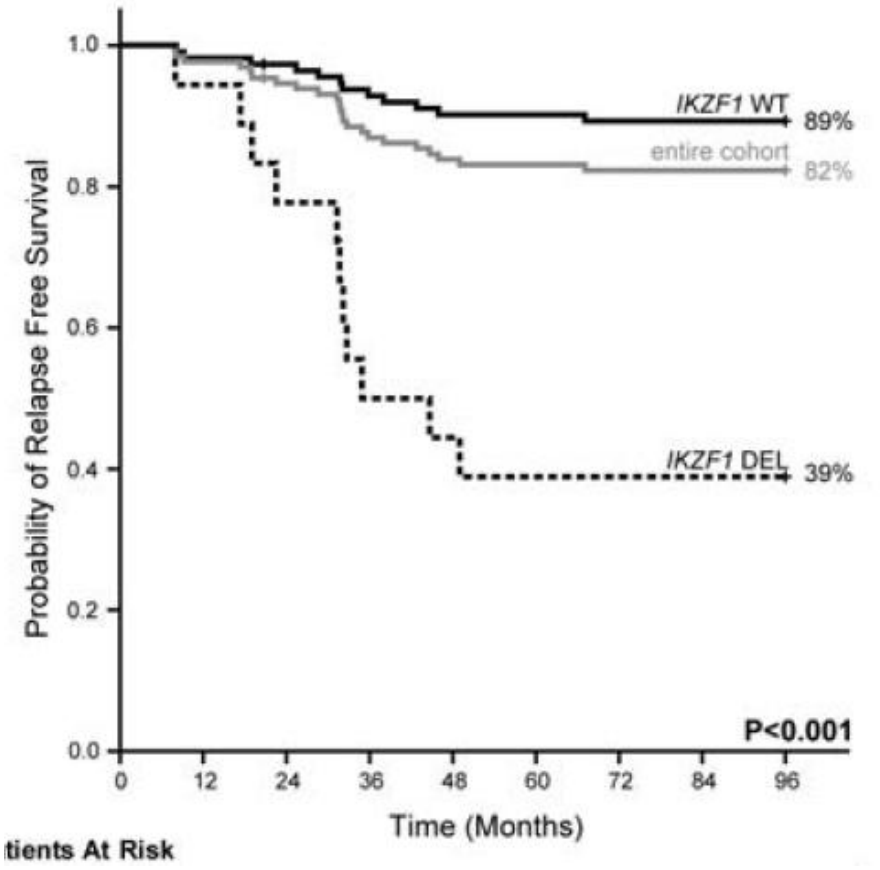
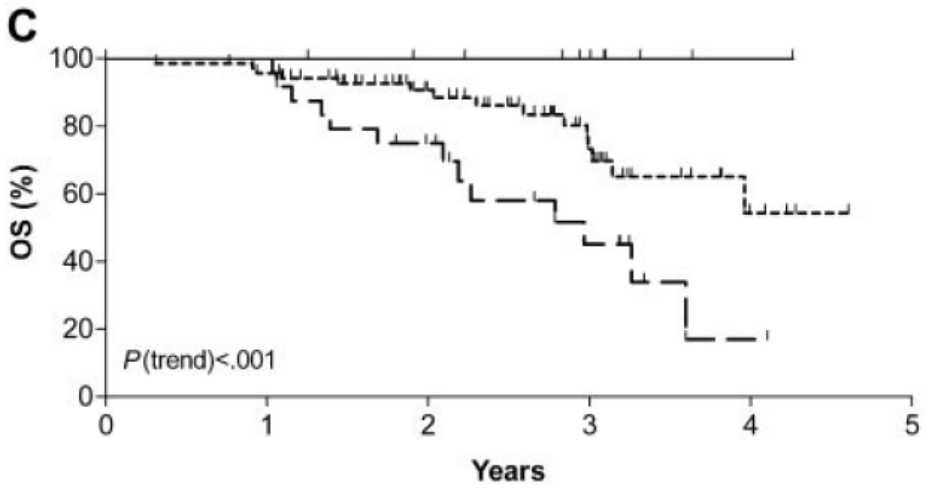


Minimal Residual Disease



Risk category	% of patients	3y relapse rate
Low	10%	0%
Intermediate	67%	47%
High	23%	94%

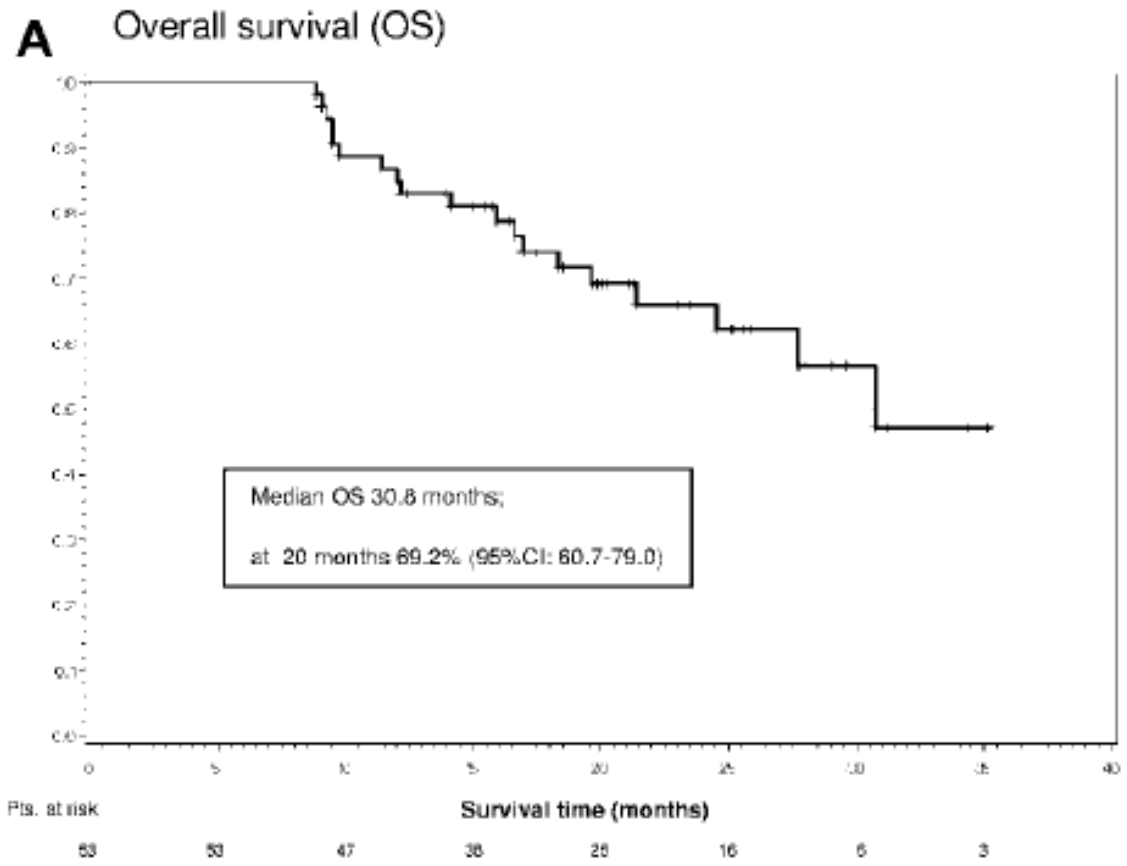
Principles of ALL therapy

Induction	• Vincristine/steroids • Anthracyclines • Asparaginase • Cyclophosphamide	CNS-prophylaxis
Consolidation Intensification	• Chemotherapy • Allogeneic transplant	CNS-prophylaxis
Maintenance	• Vincristine/steroids • Mercaptopurine • Methotrexate	

Treatment regimens

Group	N	Age	Ph+ %	T-cell %	CR %	DFS %
MRC/ECOG 2993	1826	31 (15-65)	19	20	91	38 at 5 y
CALGB 8811	197	32 (16-80)	27	28	85	33 at 5 y
GIMEMA 0288	778	27.5 (12-60)	22	26	82	29 at 9 y
GMALL 05/93	1163	35 (15-65)	24	-	83	35-40 at 5 y
HyperCVAD	288	40 (15-92)	17	25	92	38 at 5 y
LALA-94	922	33 (15-55)	23	38	84	36 at 5 y
UCSF 8707	84	27 (16-59)	16	33	93	53 at 5y

Ph+ ALL: Prednisone + Dasatinib



100% complete hematologic remission

Relapsed Disease

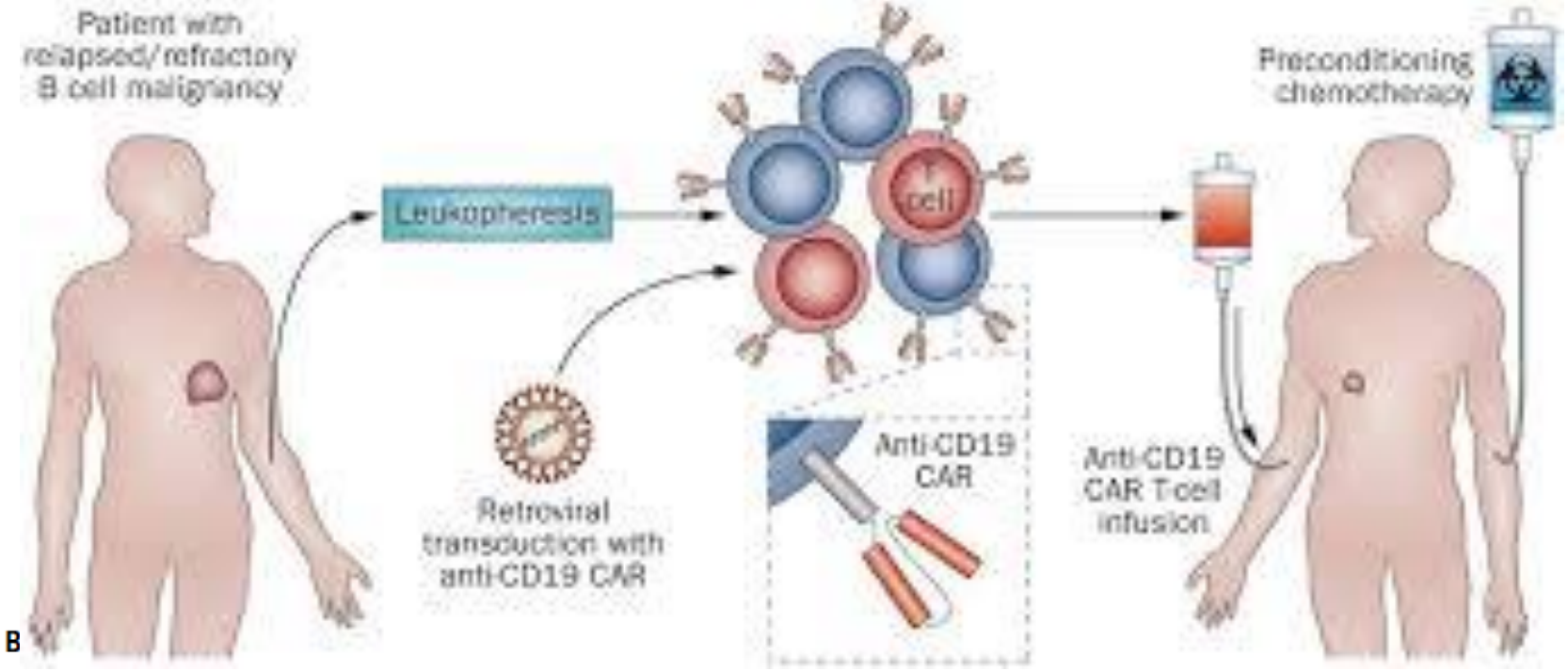
- Attempt reinduction with any of a variety of regimens, including novel agents

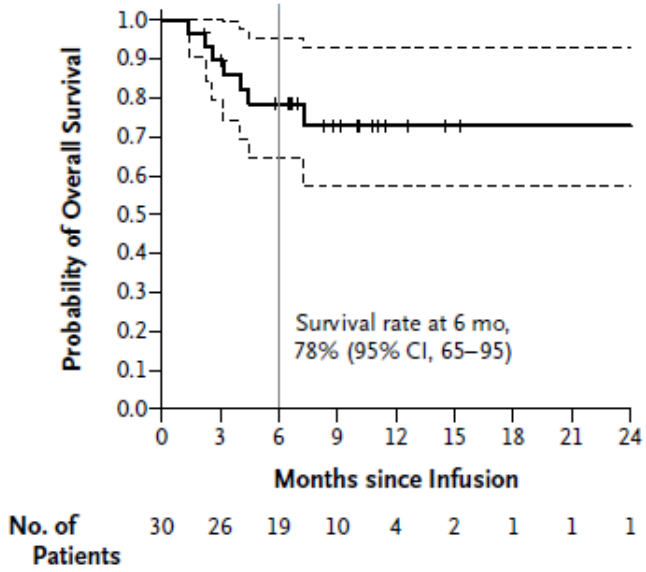
- Allogeneic transplant if possible

Newer drugs

- Monoclonal antibodies
  - CD19/ozogamicin (inotuzomab)
  - CD22 (epratuzumab)
- Nelarabine
- Clofarabine
- Liposomal vincristine
- Blinotumomab

CARs





27/30 (90%) complete remission rate