# Pediatric Leukemia:

## *an overview of where we are and what's to come*

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# Disclosures

I have no conflicts of interest to disclose.

# Our Objective

Review common presentations, diagnosis, management, and off-therapy principles for pediatric leukemia

# Why should I care about pediatric leukemia?

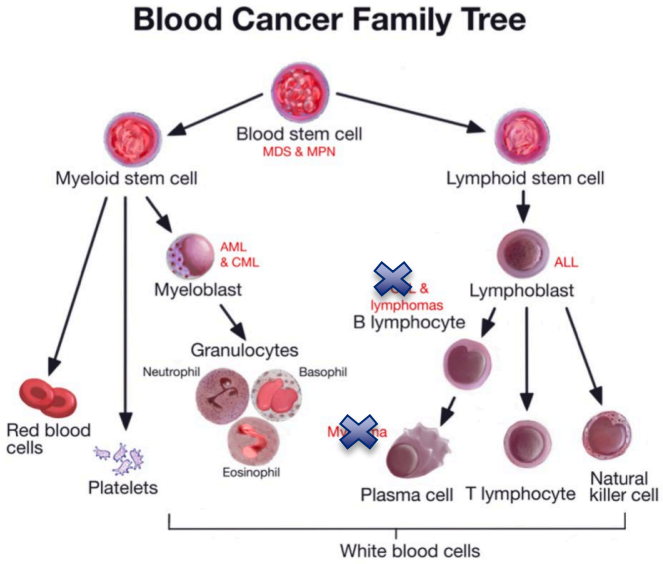
- Prevalence: Represents the most common childhood cancer
- Progress: Area of very active research with rapidly evolving diagnostic and management strategies
- Hope: Many patients will be long-term survivors!

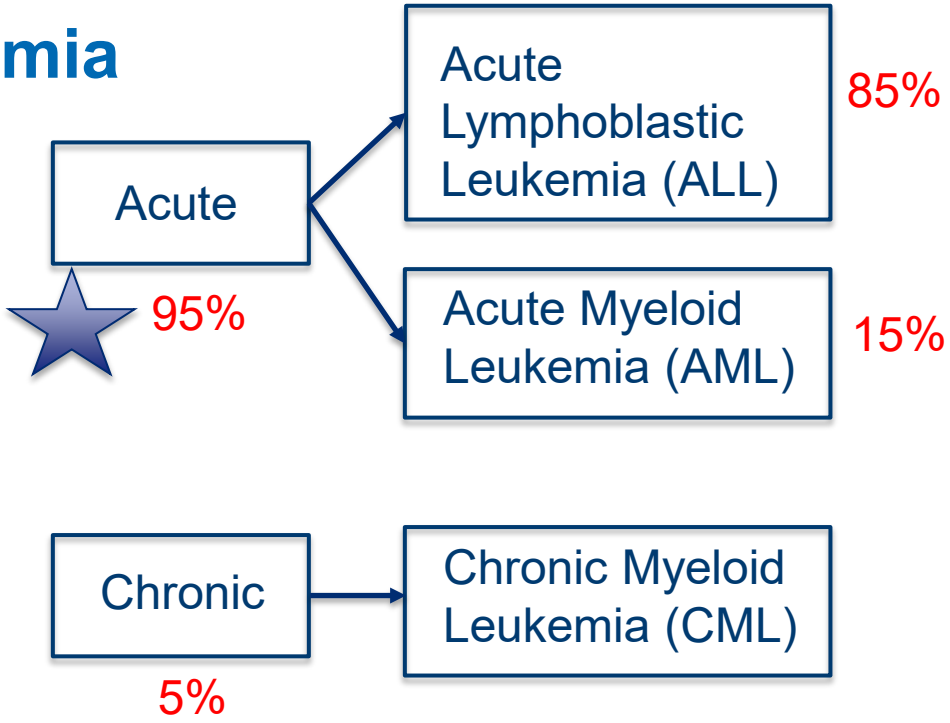
# Overview: Pediatric Leukemia

1. Presentation/Diagnosis
2. Overview of therapies
3. Off-therapy considerations

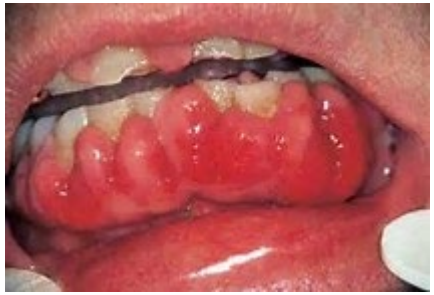
# Presentation/Diagnosis

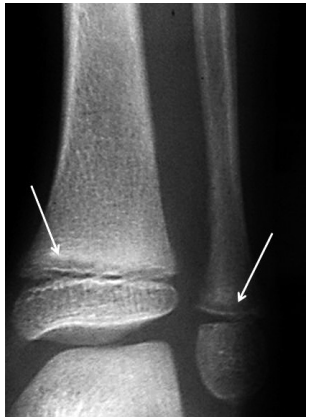
# Types of Childhood Leukemia

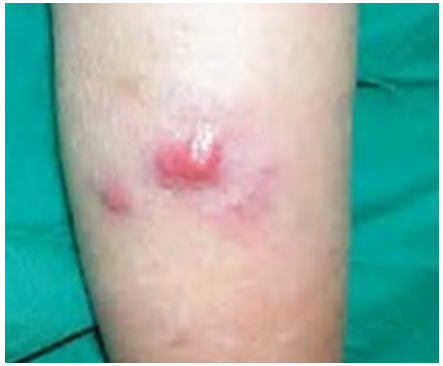


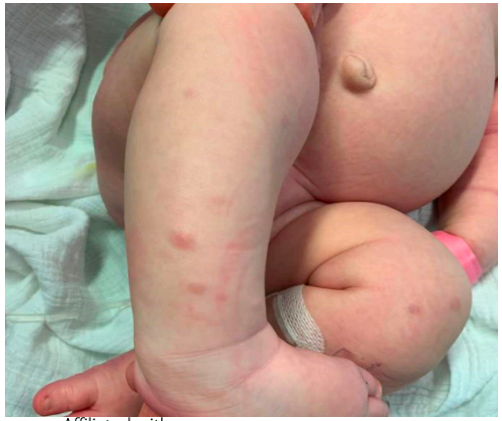



# Presentation



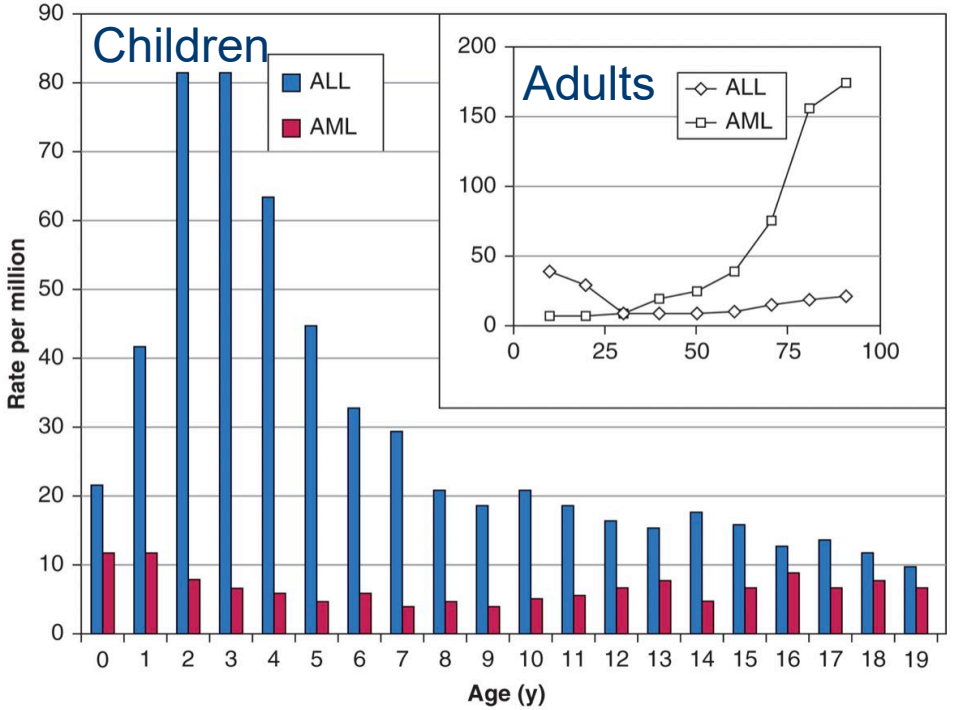






| Symptom/Sign | Frequency |
|---|---|
| Fatigue | 50% |
| Fever | 60% |
| Bone pain | 25% |
| Bleeding | 50% |
| Lymphadenopathy | 25-50% |
| Hepatosplenomegaly | 70% |
| Gingival hyperplasia | 10% AML |
| Petechiae or purpura | 25% |
| Leukemia cutis (AML>ALL) | 5% |
| Chloromas (AML>ALL) | |
| Hyperleukocytosis | 10-20% |
| Cytopenias | 25-50% |
| Coagulopathy/DIC (APML) | |

# Epidemiology




ALL: ¼ of all childhood cancers

- Nearly 5,000 kids diagnosed/year in US
- Peak 2-5 years old, M>F

AML:

- 500 kids diagnosed/year in US
- No distinct peak age incidence in childhood

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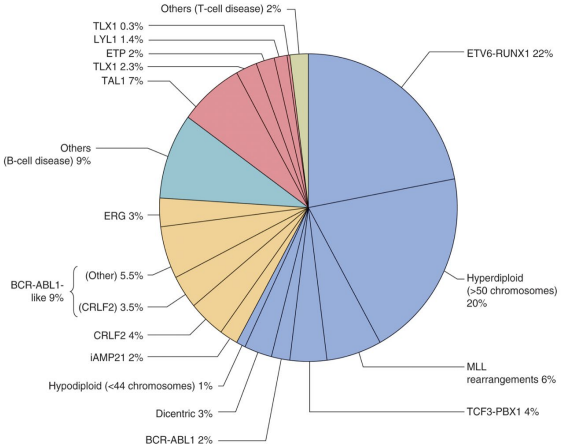
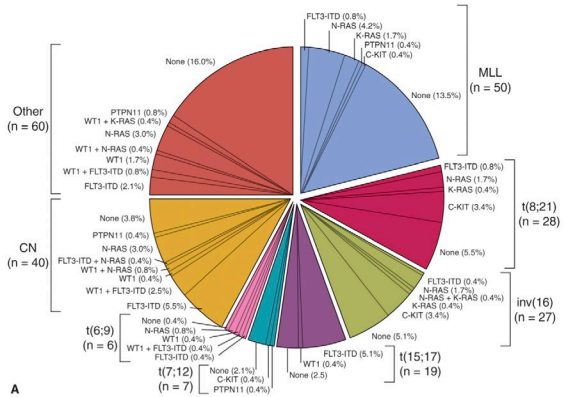
Pizzo & Poplock, Principles and Practice of Pediatric Oncology 7th Edition
Brown & Hunger, Acute leukemia in children

# Genetics of Leukemia

Proposed to arise from (1) susceptibility loci and (2) somatic mutations in genes critical to hematopoietic cell development

- Sporadic (95%)
- Specific inherited syndromes (<5%)
  - Down Syndrome: 10-20x more likely to develop leukemia than non-DS
    - ALL>AML (except infants)
  - Li-Fraumeni
  - Neurofibromatosis
  - Bloom, Nijmegen breakage, Shwachman-Diamond, Diamond-Blackfan, Ataxia telangiectasia syndromes

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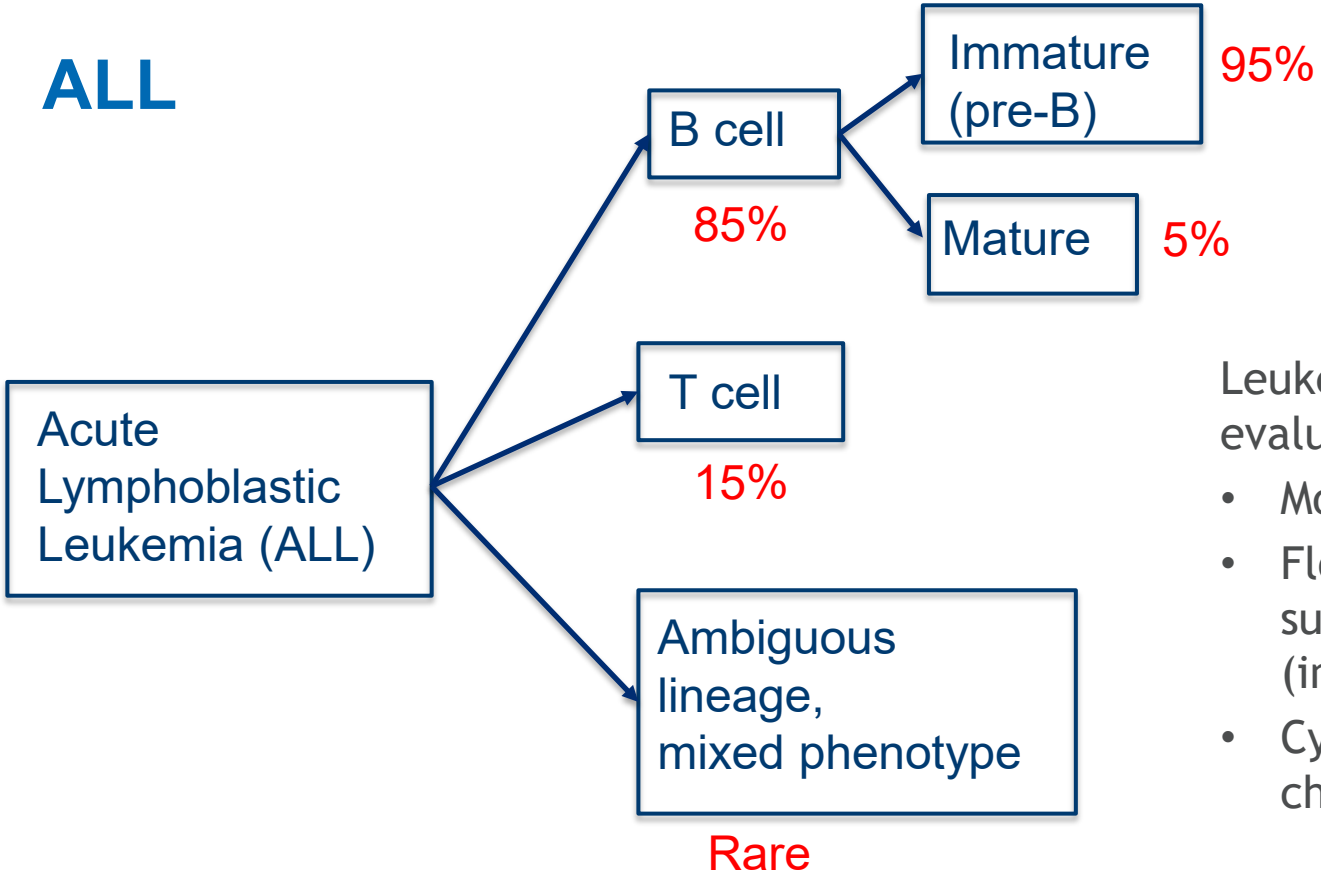
Pizzo & Poplack, Principles and Practice of Pediatric Oncology, 7th Edition

# Overview of Therapies

# ALL

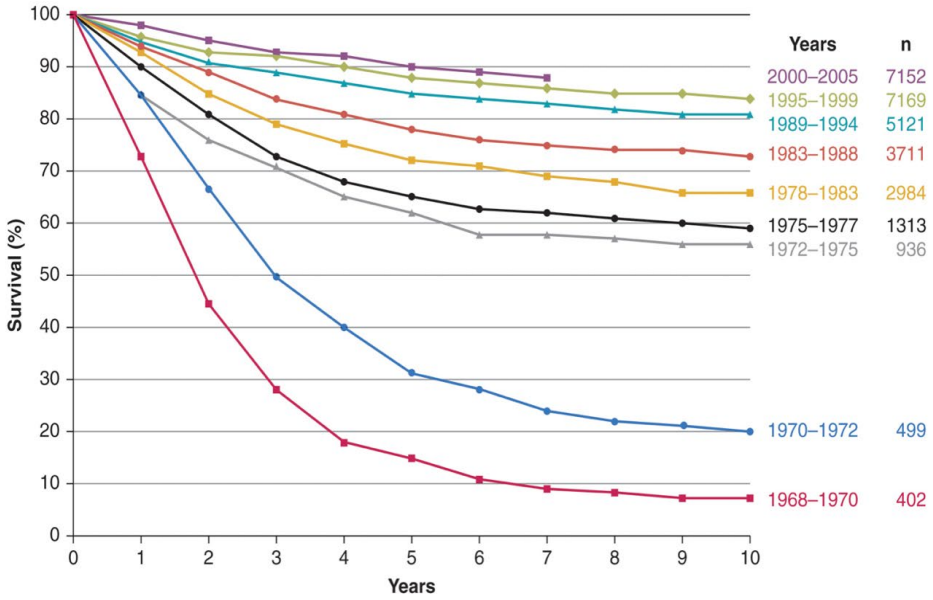
# ALL




Leukemia predominantly evaluated by…

- Morphology: L1, L2, L3
- Flow cytometry: for cell surface markers (immunophenotype)
- Cytogenetics: FISH & chromosomes/karyotype

# ALL: Historical context, our poster child




1940-50s: single agents (antifolates)

1954: first patient cured (9 yo F)!

1960s: combination therapy (added vincristine and steroid) + CNS radiation; cooperative groups formed and provided protocols for treatment

1970s: early classification, discovery of cytogenetics and development of risk-based treatment

1980s+: ongoing risk stratification



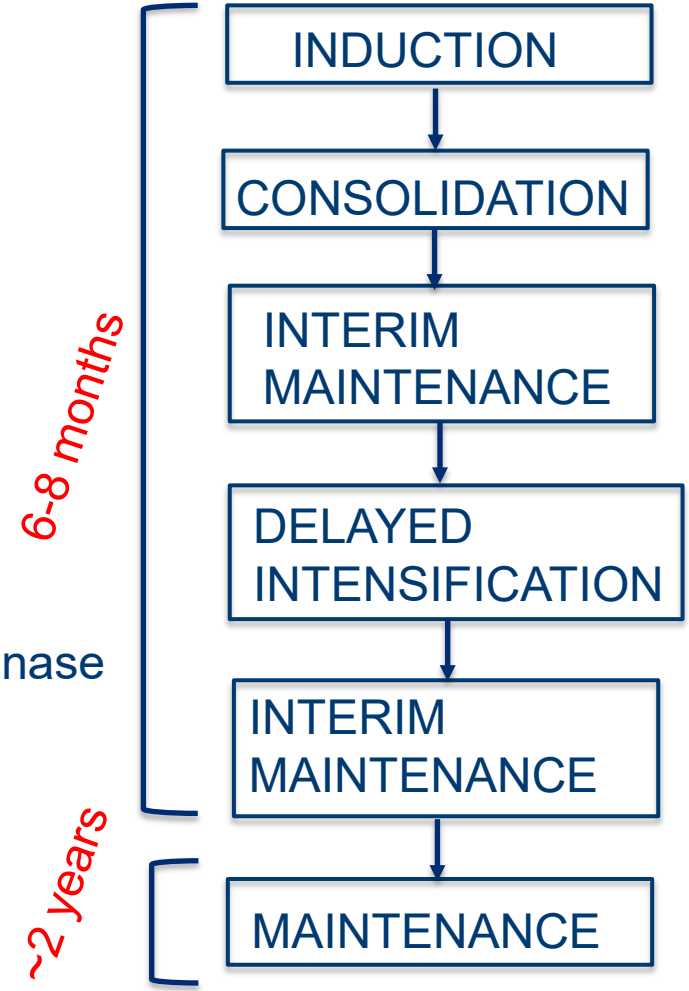
Hunger et al, JCO, 2012
Pizzo & Poplack, Principles and Practice of Pediatric Oncology, 7th Edition

# ALL: Therapy Basics

- Multi-agent chemotherapy (predominantly outpatient)
- Risk-adapted therapy
- Preventative CNS therapy
- Post-remission intensification & maintenance

<u>Differing chemo "backbones":</u>

- Standard risk B ALL
- High risk B ALL
  - Ph+ (BCR-ABL) ALL (add tyrosine kinase inhibitor)
  - T ALL (add nelarabine)
- Infant B ALL

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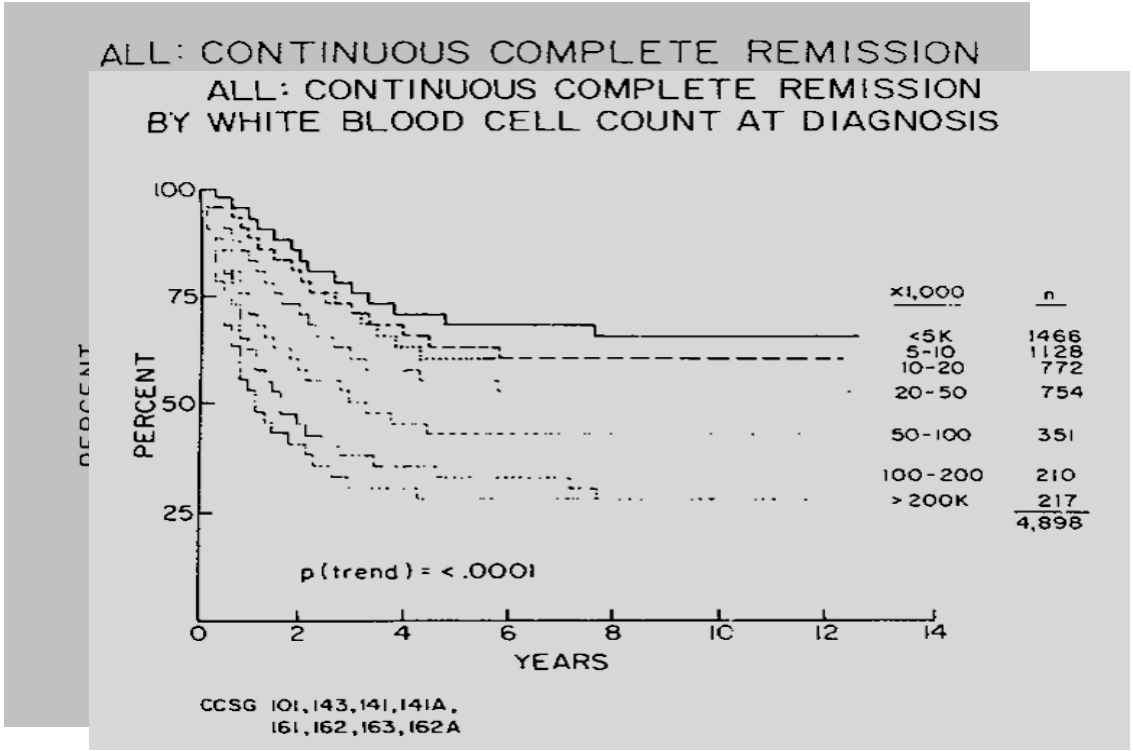
# ALL: Risk Stratification

1. NCI Risk Grouping
    - Age
    - Presenting WBC



# ALL: Risk Stratification

1. NCI Risk Grouping
   - Age
   - Presenting WBC

2. Extramedullary disease
   - CNS and testicular

**TABLE 19.5**

**Definitions of Central Nervous System (CNS) Disease Status at Diagnosis Based on Cerebrospinal Fluid Findings**

| Status | Cerebrospinal Fluid Findings |
|---|---|
| CNS-1 | No lymphoblasts |
| CNS-2 | <5 WBCs/μL with definable blasts on cytocentrifuge examination |
| CNS-3 | ≥5 WBCs/μL with blast cells (or cranial nerve palsy) |

WBC, white blood cell.

# ALL: Risk Stratification

1. NCI Risk Grouping
   - Age
   - Presenting WBC
2. Extramedullary disease
3. **Leukemia genetics**

FAVORABLE CYTOGENETICS FOR B-ALL PATIENTS

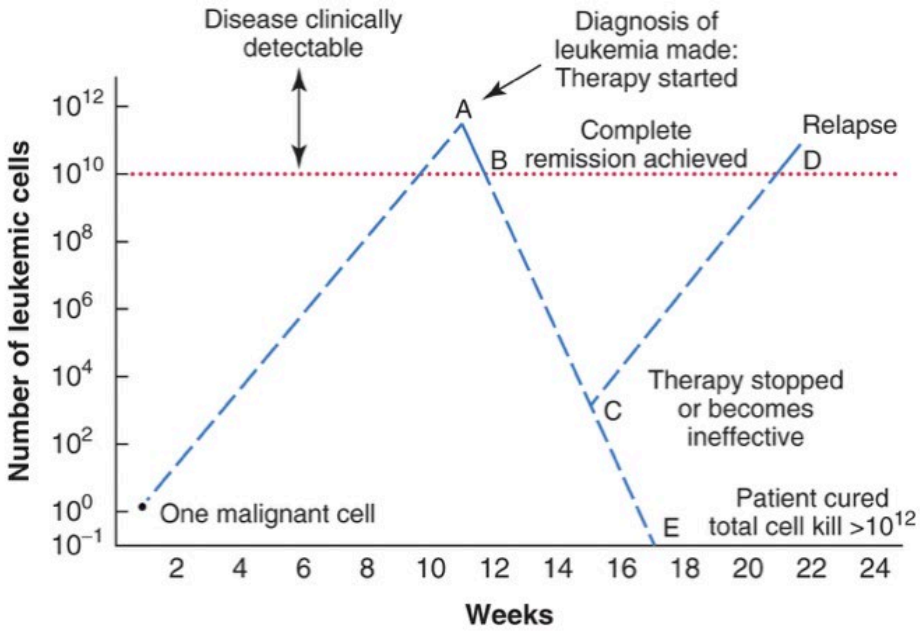
1. *ETV6-RUNX1* as identified by cytogenetics, fluorescence in-situ hybridization (FISH) or molecular studies
2. Double trisomies 4, 10 (DT) as identified by cytogenetics, fluorescence in-situ hybridization (FISH), or molecular studies

UNFAVORABLE CYTOGENETICS FOR B-ALL PATIENTS

1. iAMP21 as identified by central cytogenetic review (fluorescence in-situ hybridization (FISH) or SNP array).
2. *KMT2A* (formerly *MLL*) rearrangements as identified by cytogenetics, fluorescence in-situ hybridization (FISH), or molecular studies.
3. HYPODIPLOIDY: Fewer than 44 chromosomes and/or DNA index < 0.81, or other clear evidence of a hypodiploid clone.
4. t(17;19)(q21-q22;p13.3) or resultant *E2A-HLF* fusion transcript determined by cytogenetics, fluorescence in-situ hybridization (FISH), or molecular studies.
5. PHILADELPHIA CHROMOSOME POSITIVE (Ph+) ALL:
   a) *BCR-ABL1* fusion transcript determined by FISH or RT-PCR
   b) t(9;22)(q34;q11) determined by cytogenetics

# ALL: Risk Stratification

1. NCI Risk Grouping
   - Age
   - Presenting WBC
2. Extramedullary disease
3. Leukemia genetics
4. **Response to therapy**
   - Minimal/measurable residual disease (MRD)



# ALL: Risk Stratification

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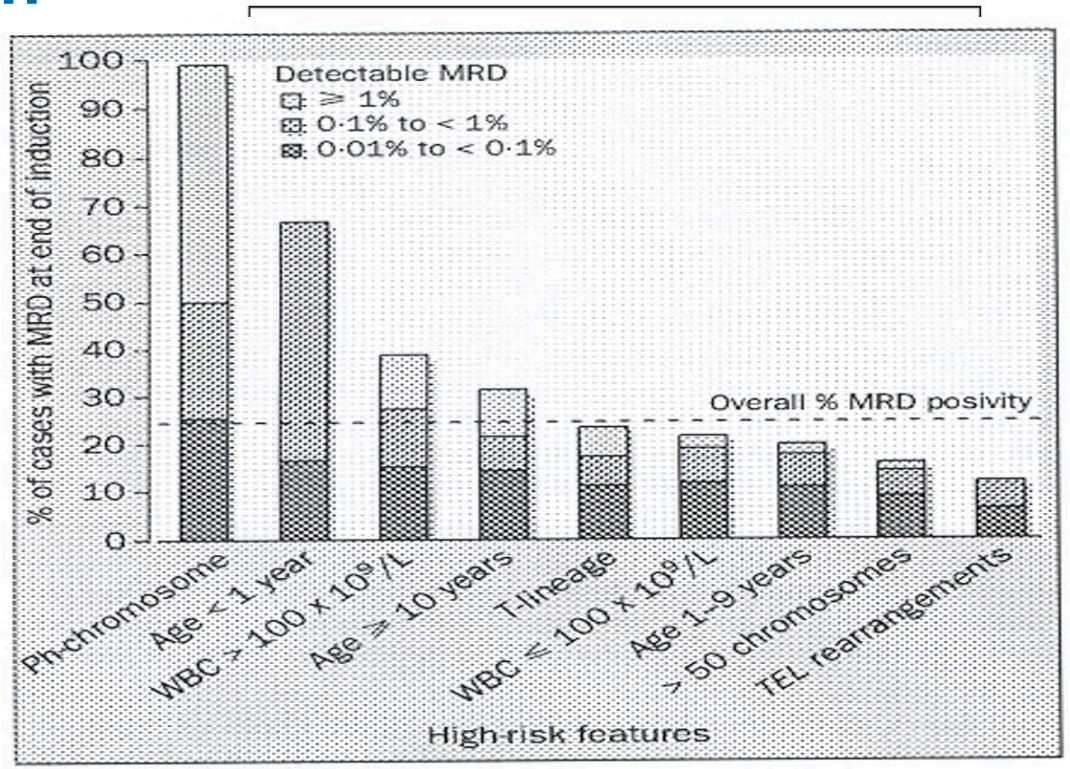

# ALL: Risk Stratification

| Standard Risk | High Risk |
|---|---|
| Age 1-9 yo | Age < 1 or ≥ 10 yo |
| WBC < 50K | WBC ≥ 50K |
| CNS 1/2 and no testicular disease at diagnosis | CNS 3 or testicular disease at diagnosis |
| Favorable or no adverse cytogenetics | Adverse cytogenetics |
| Good response | Poor response |
| | T cell |

# ALL: Current Prognosis

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HR

T A

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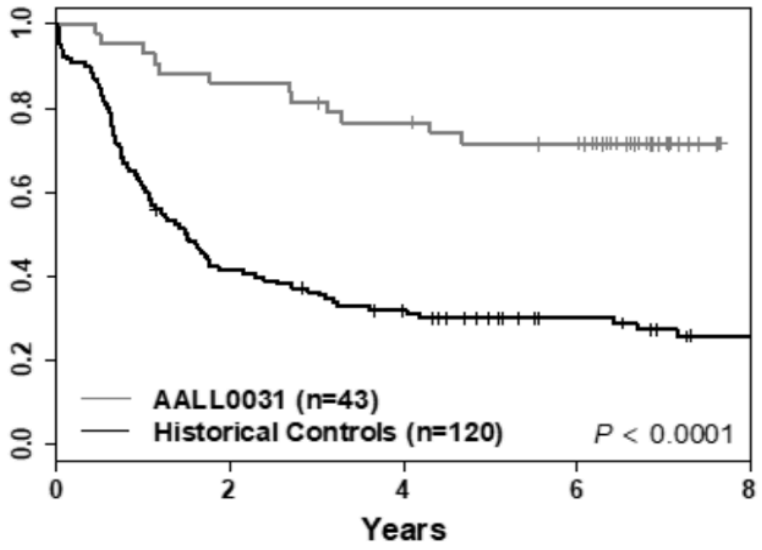


Addition of imatinib to chemo for Ph+ ALL

**7-yr EFS**

| | |
|---|---|
| **AALL0031c5:** | **72%** |
| **POG ALinc 14-16:** | **27%** |

Schultz JCO 009, Leukemia 2014

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need it,
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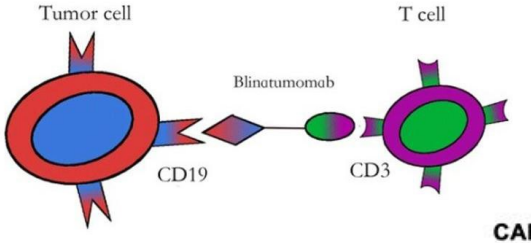
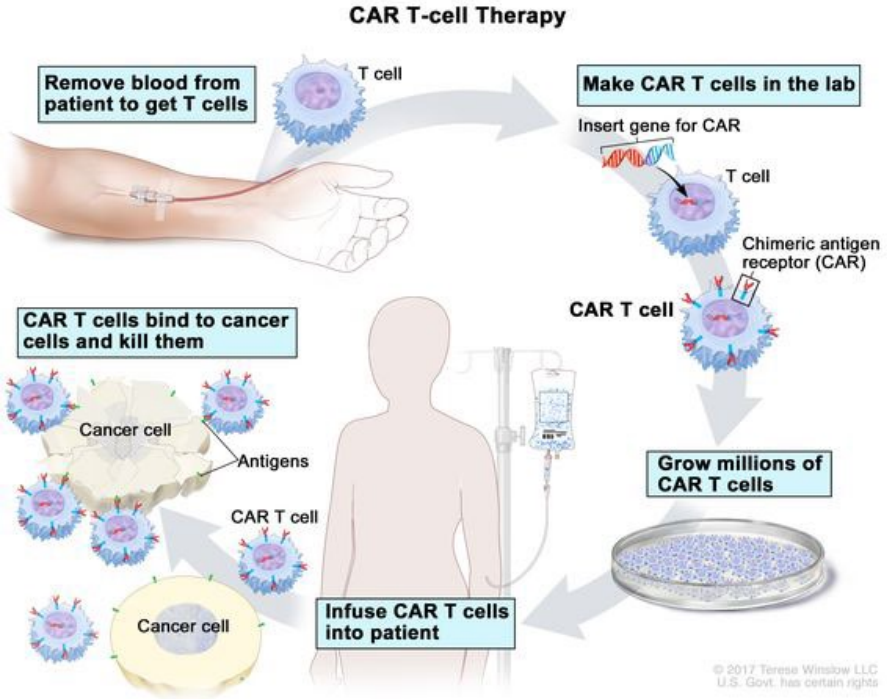
# ALL: New Agents

- Nelarabine (T cell)
- Blinatumumab (CD19 targeted)
- Inotuzumab (CD22 targeted)
- CAR-T Cells (CD19, 22…)
- **Working on targeted agents for T ALL and infants

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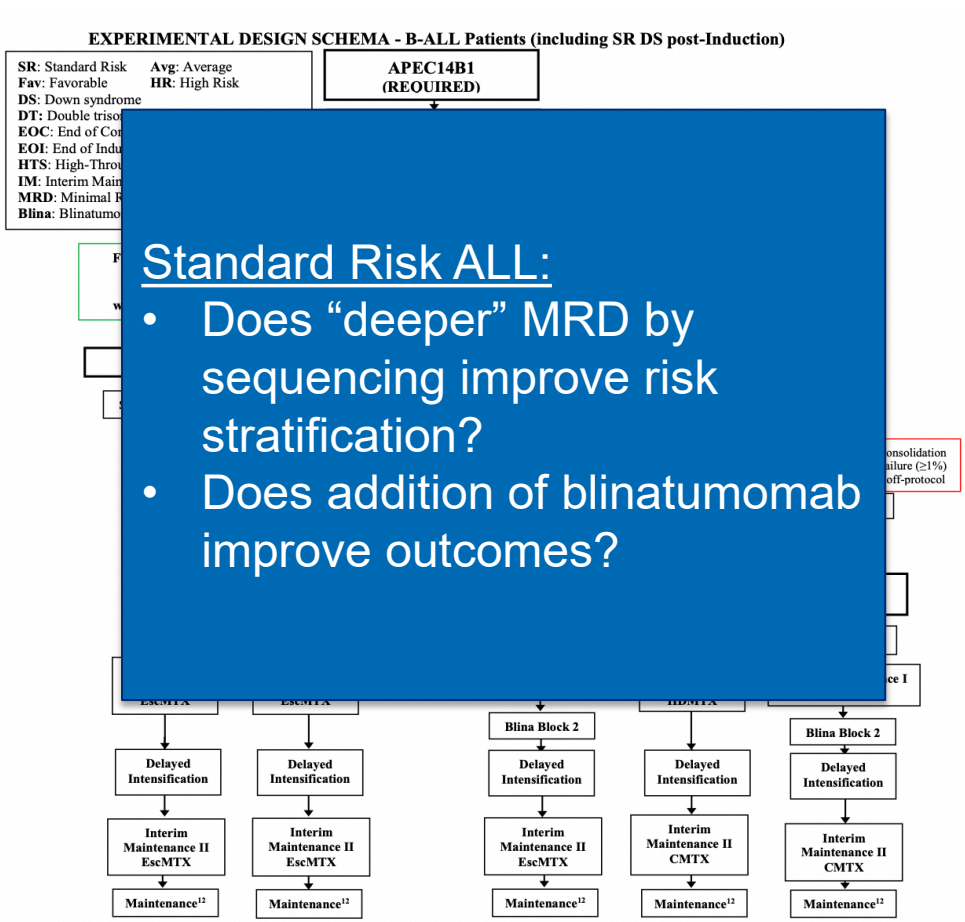
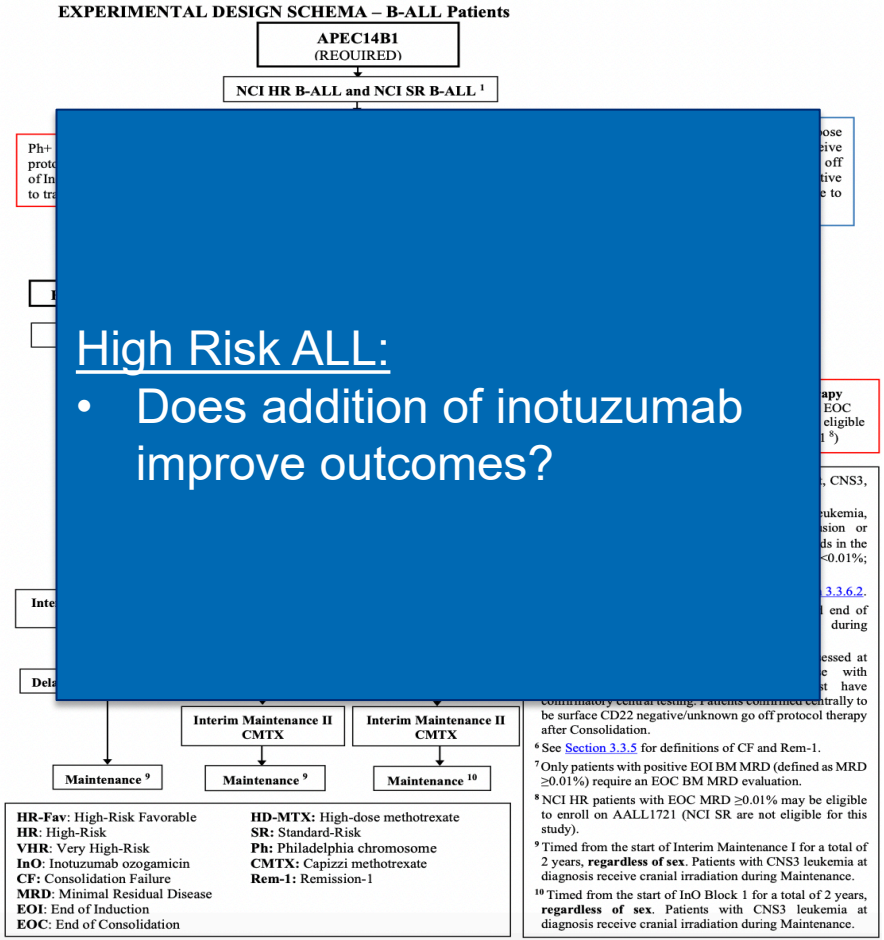
# ALL: Current Protocols



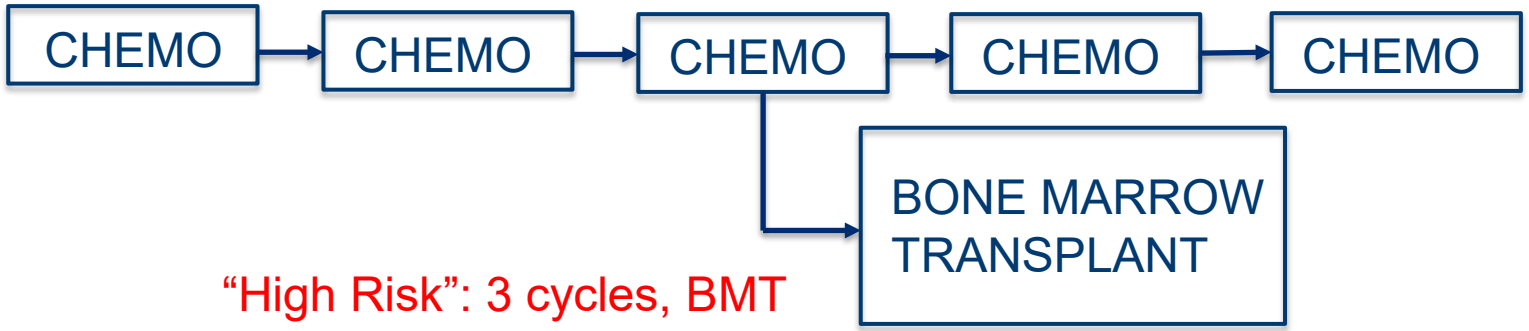



# AML

# AML: Therapy Basics

- Multi-agent chemotherapy (all inpatient) +/- bone marrow transplant
  - Risk-adapted therapy
  - Newer addition of targeted agents for all patients (anti-CD33; gemtuzumab) and specific genetic subgroups (FLT3 mutations; FLT3 inhibitors)
  - No maintenance (did not improve outcomes)

"Low Risk": 4-5 cycles of chemo (4-6 weeks each)




"High Risk": 3 cycles, BMT



Pizzo & Poplack, 7th ed (2016)
Bailliere's Clinical Hematology, Vol 9, No 1 (1996)

# AML: Risk Classification

1. Leukemia genetics
    - With modern therapy, morphology (FAB classification) does not correlate with prognosis

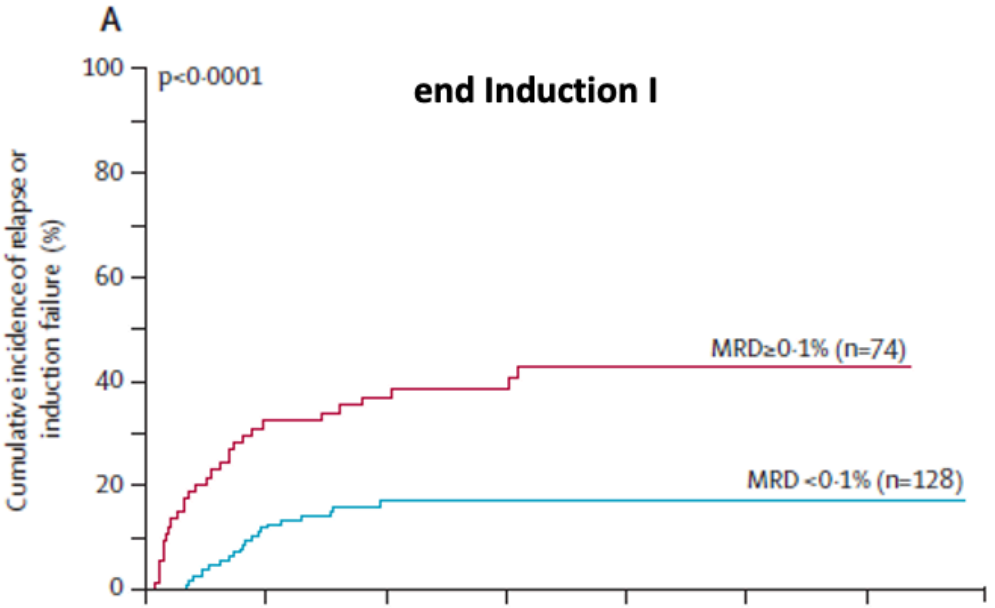
| UNFAVORABLE PROGNOSTIC MARKERS | |
|---|---|
| **Cytogenetics** | **Genes** |
| t(3;21)(26.2;q22) | *RUNX1-MECOM* |
| t(3;5)(q25;q34) | *NPM1-MLF1* |
| t(6;9)(p22.3;q34.1) | *DEK-NUP214* |
| t(8;16)(p11.2;p13.3)<br>(if 90 days or older at diagnosis) | *KAT6A-CREBBP*<br>(if 90 days or older at diagnosis) |
| t(16;21)(p11.2;q22.2) | *FUS-ERG* |
| inv(16)(p13.3q24.3) | *CBFA2T3-GLIS2* |
| t(4;11)(q21;q23.3) | *KMT2A-AFF1 (MLL-MLLT2)* |
| t(6;11)(q27;q23.3) | *KMT2A-AFDN (MLL-MLLT4)* |
| t(10;11)(p12.3;q23.3) | *KMT2A-MLLT10* |
| t(10;11)(p12.1;q23.3) | *KMT2A-ABI1* |
| t(11;19)(q23.3;p13.3) | *KMT2A-MLLT1(MLL-ENL)* |
| 11p15 rearrangement | *NUP98-any partner gene* |
| 12p13.2 rearrangement | *ETV6- any partner gene* |
| Deletion 12p to include 12p13.2 | Loss of *ETV6* |
| Monosomy5/Del(5q) to include 5q31 | Loss of *EGR1* |
| Monosomy 7 | No associated gene |
| 10p12.3 rearrangement | *MLLT10- any partner gene* |
| No associated cytogenetic abnormality | *FLT3/ITD* + with allelic ratio > 0.1% |
| RAM phenotype as evidenced by flow cytometry | |

| FAVORABLE PROGNOSTIC MARKERS | |
|---|---|
| **Cytogenetics** | **Genes** |
| t(8;21)(q21.3;q22) | *RUNX1-RUNX1T1* |
| inv(16)/ t(16;16)(p13.1q22.1) | *CBFB-MYH11* |
| No associated cytogenetic abnormality | *NPM1* mutation positive |
| No associated cytogenetic abnormality | *CEBPA* bZIP mutation positive |

# AML: Risk Classification

1. Leukemia genetics

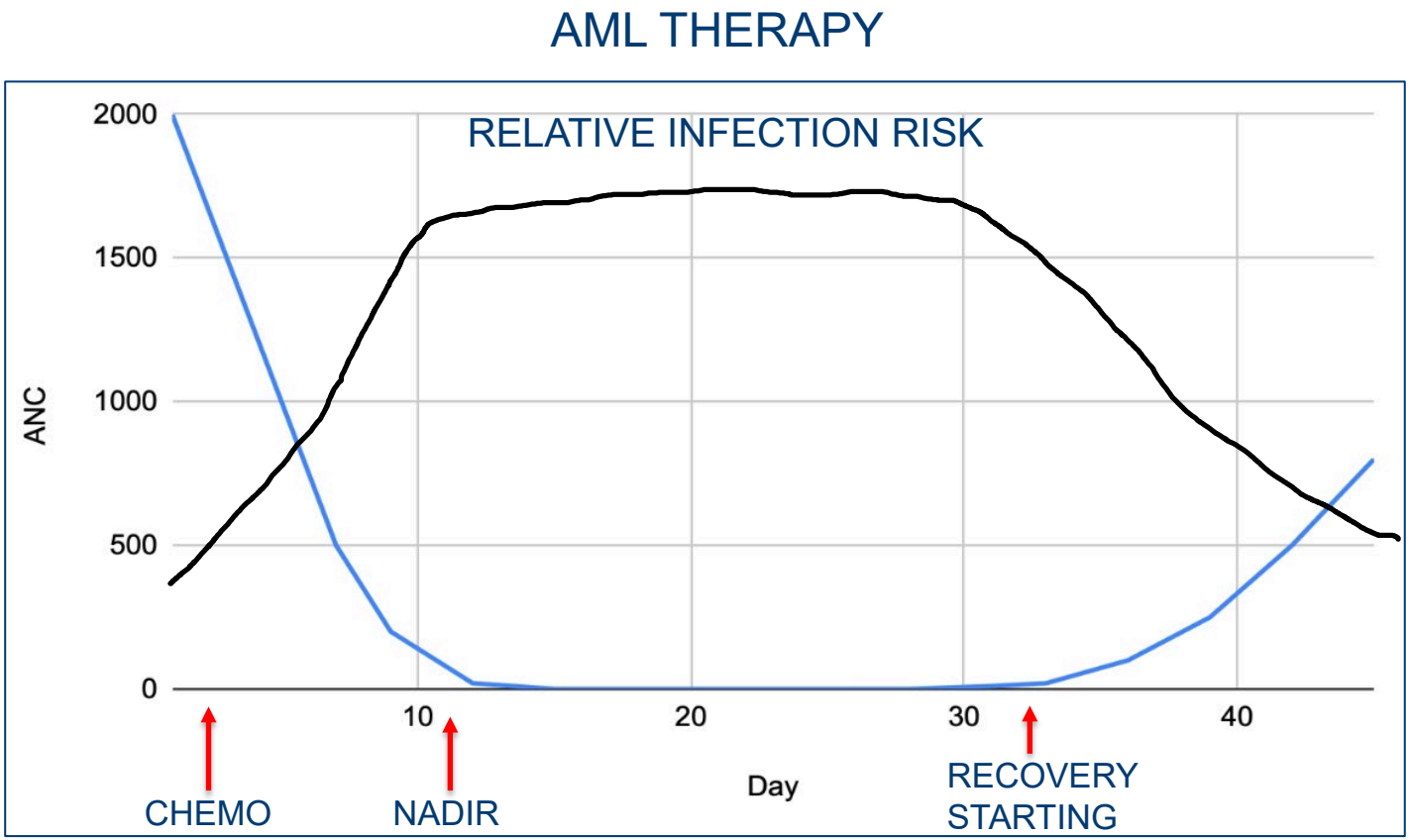
2. **Response to therapy**






Rubnitz et al, Lancet Oncol 2010

# AML: Importance of Supportive Care



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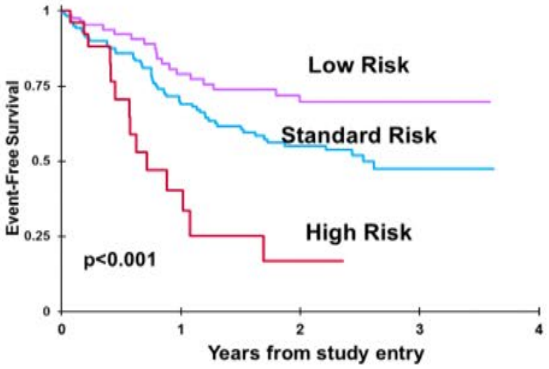
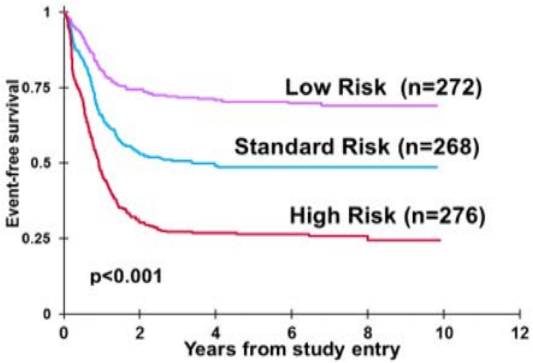
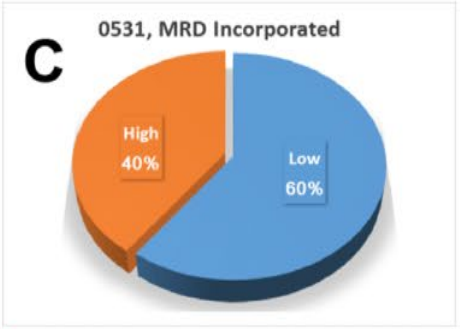
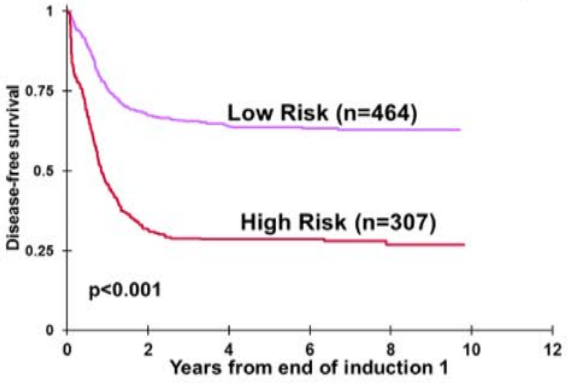
# AML: Current Prognosis



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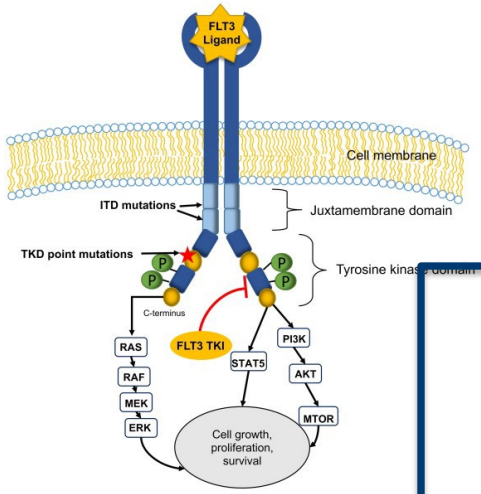
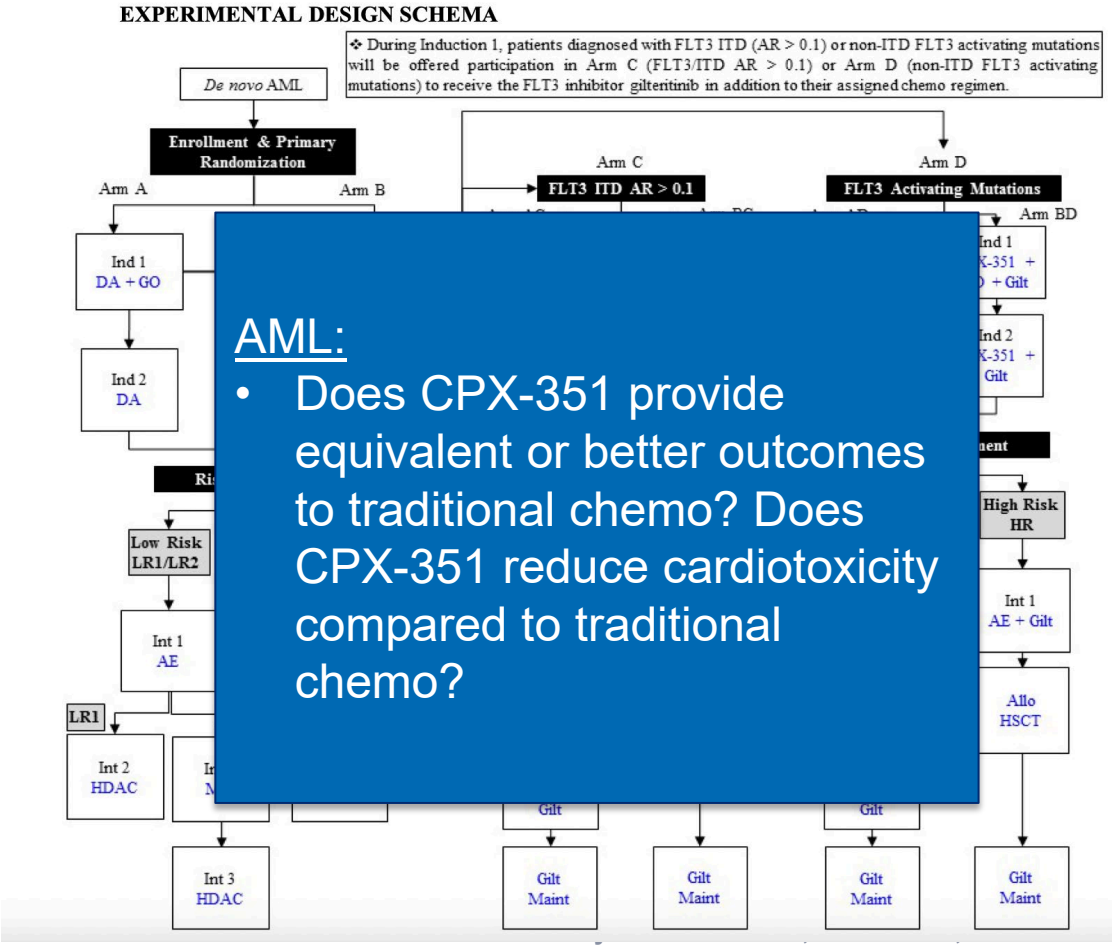
# AML: New Agents

- FLT3 inhibitors
- Gemtuzumab (anti CD33)
- CPX-351 (liposomal formulation combining cytarabine and daunorubicin)
- ***Working toward targeted immunotherapies




NEEDS:
*Improve outcomes for all, still lots of room for improvement
*Attention to reducing late effects where possible

# AML:
# Current Protocol



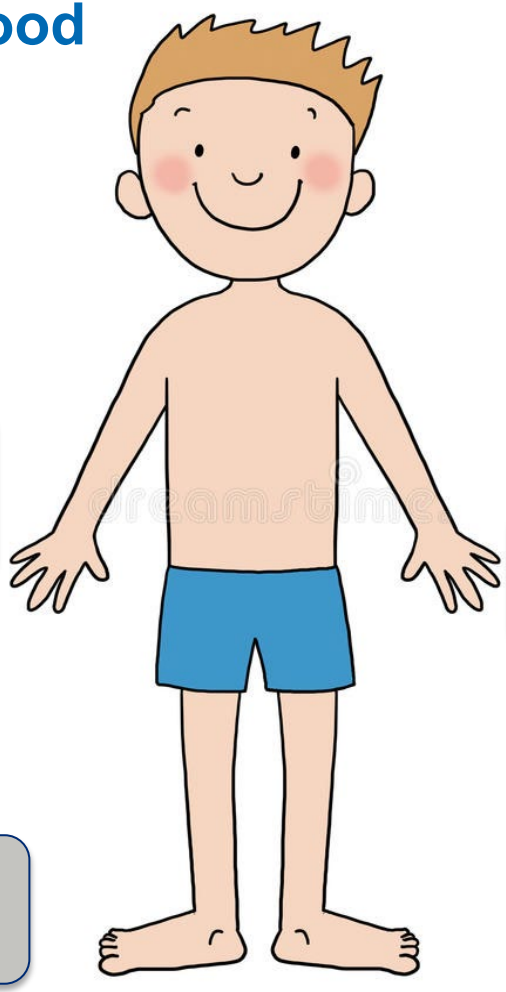
# Off-therapy Considerations

# Off Therapy

- Central lines typically out ASAP
- OK for routine vaccinations at 6 months off-therapy(new and catch-up from during therapy, s/p BMT requires full re-immunization schedule)
- Oncology off-therapy follow-up
  - Year 1 and 2: Monthly until CBC normalizes, then every 3 months
  - Year 3: Every 6 months
  - Year 4: Annually

  *These vary for pts who received bone marrow transplant
- HOPE & TACTIC survivorship clinics
- Great resource: www.survivorshipguidelines.org
  - COG Long-term Follow-up Guidelines

# Late Effects of Childhood Leukemia Therapy



- Endocrinopathies
- Obesity & Metabolic Syndrome
- Second Malignancies
- Osteopenia, AVN
- Neurocognitive Impairment
- Cardiomyopathy
- Infertility
- Psychosocial challenges

# Questions

**Feel free to contact me!**
**Kelly.Faulk@childrenscolorado.org**

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