

**Adult Acute Lymphoblastic Leukemia (ALL):  
Update on Diagnosis and Treatment**



# Welcome & Introductions

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# Adult Acute Lymphoblastic Leukemia (ALL): Update on Diagnosis and Treatment

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Rochester, MN

Tuesday, February 17, 2015

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## Disclosure

**Mark R. Litzow, MD**

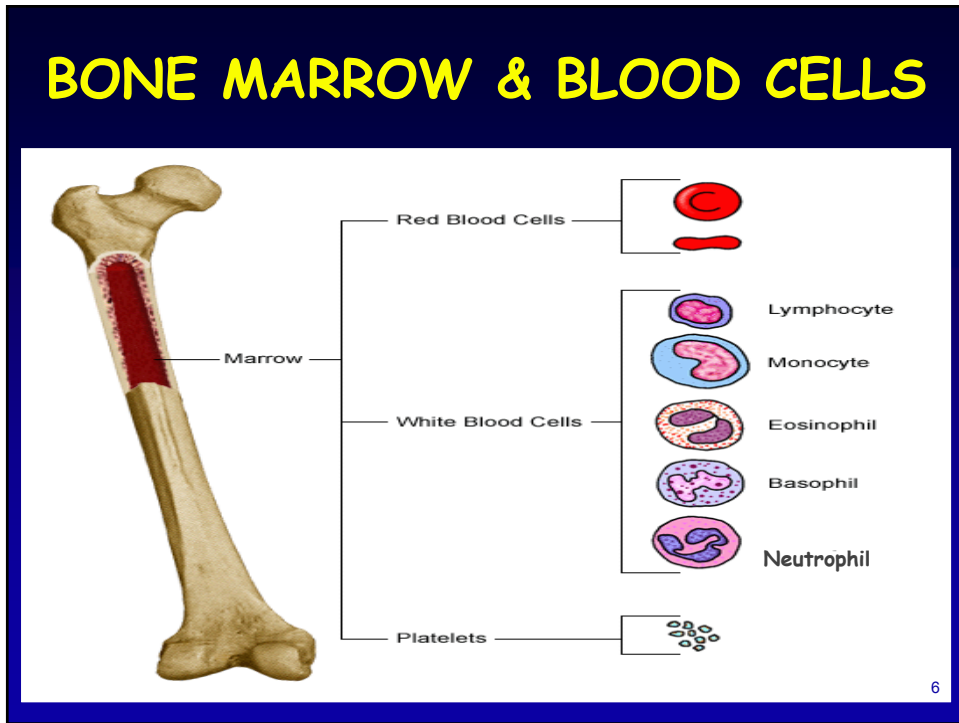
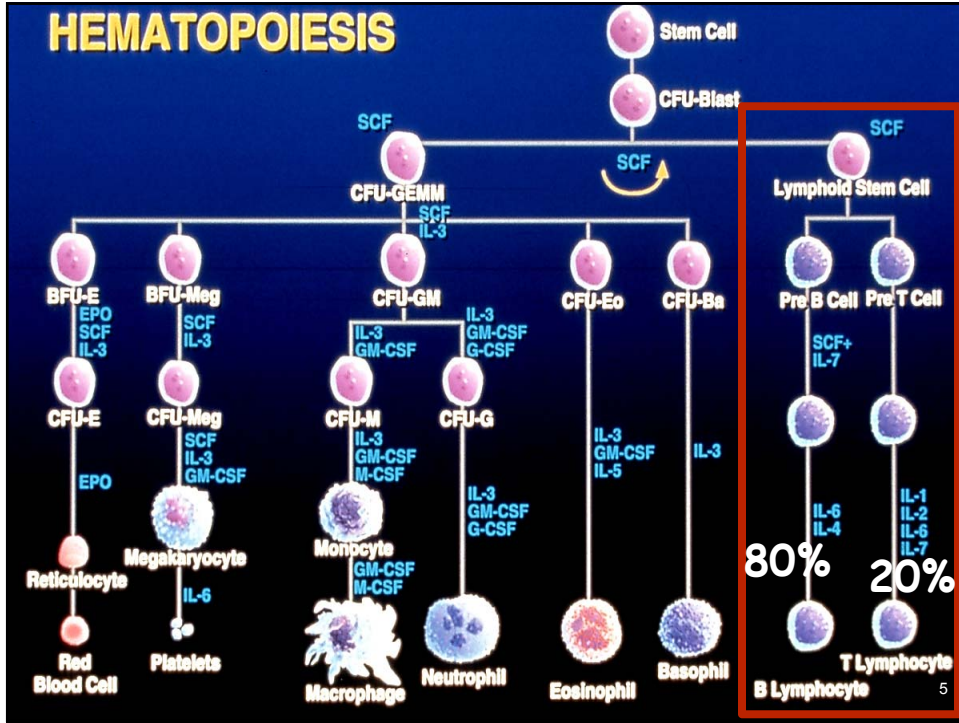
*Consulting: Amgen Inc., Sigma-Tau Pharmaceuticals, Inc.*

Tuesday, February 17, 2015

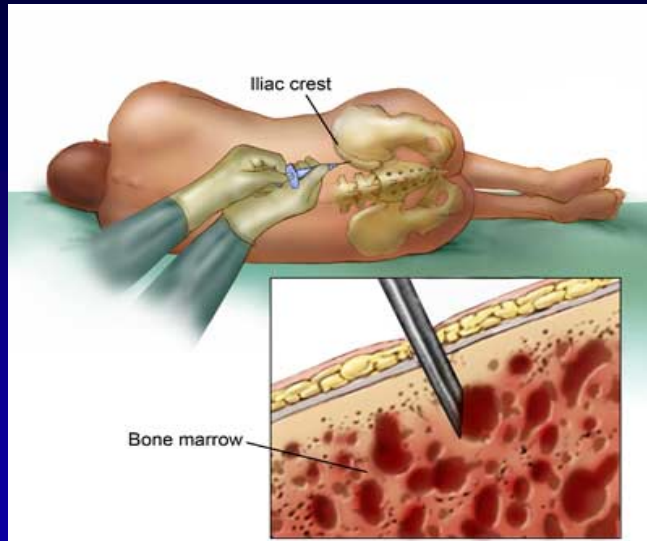
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## Presentation Objectives

- Describe how ALL is diagnosed
- Delineate the role of cytogenetics in treatment planning
- Review the current treatment options for newly diagnosed and relapsed/refractory patients
- Discuss the role of clinical trials in the advancement of ALL treatment
- Review the types of side effects and their management
- Assess the importance of open communication with your healthcare team

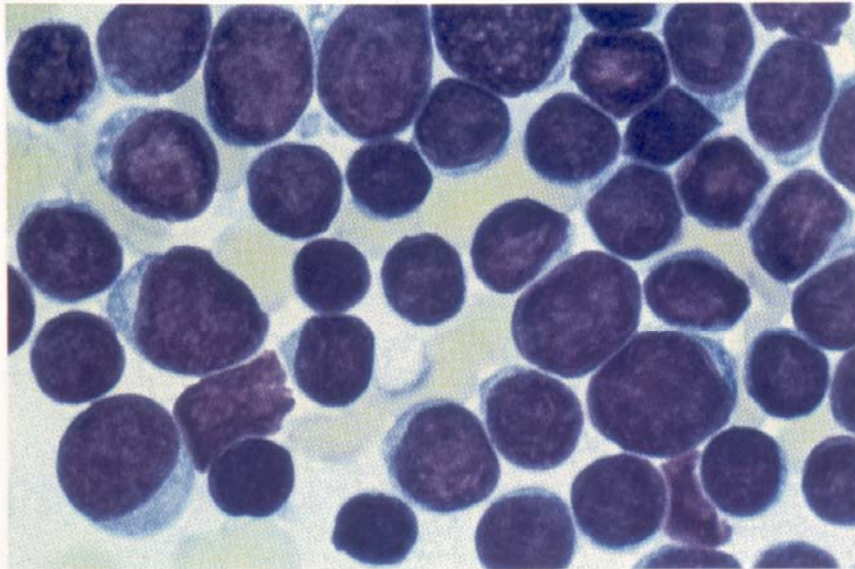


# BONE MARROW BIOPSY



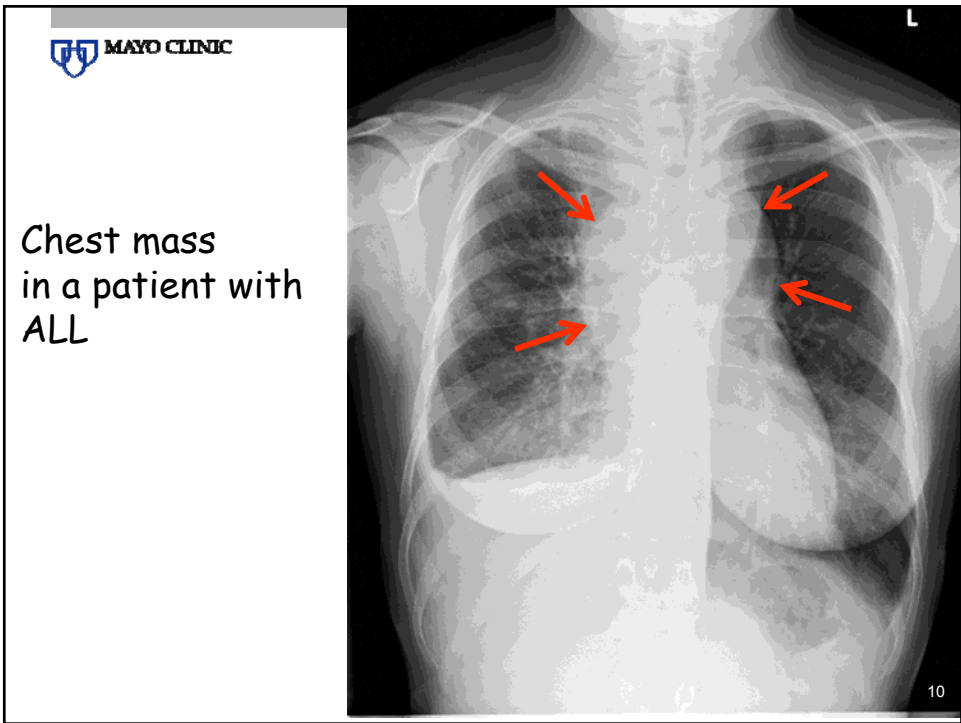
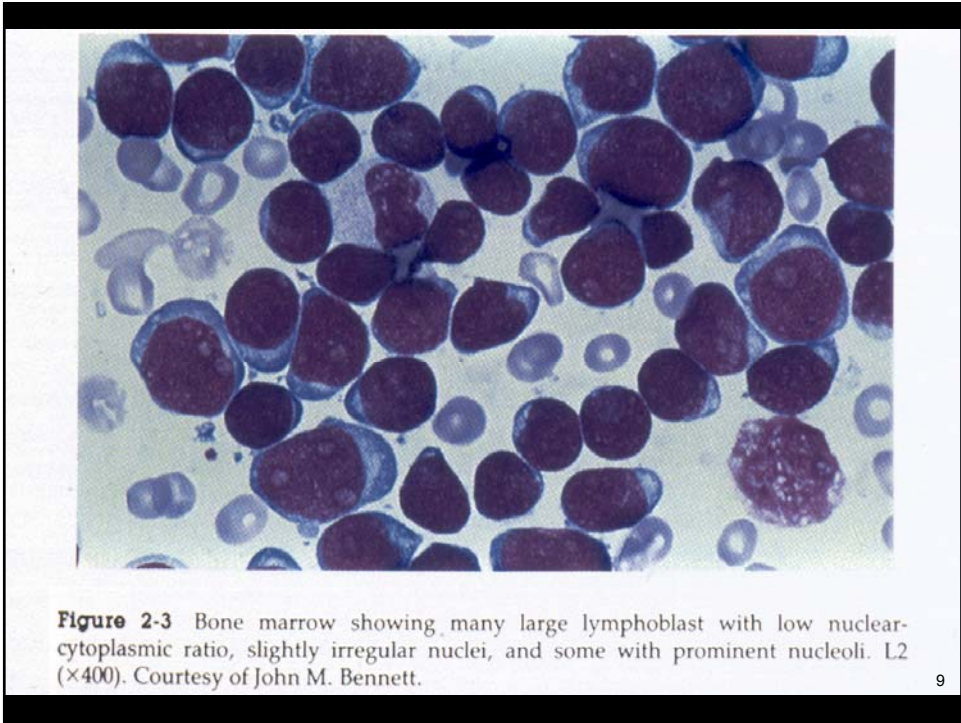
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**Figure 2-2** Bone marrow showing predominantly small lymphocytes with high nuclear-cytoplasmic ratio and indistinct small nucleoli. L1 ( $\times 1000$ ).

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## Acute Lymphoblastic Leukemia- Epidemiology

- 6,000 case per year diagnosed in USA
- Two thirds occur in children
- Represents 75% of all cases of acute leukemia in children and 10-20% of all cases of acute leukemia in adults
- In children the peak incidence occurs at age 4 and in adults at >age 65



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## World Health Organization CLASSIFICATION OF LYMPHOID NEOPLASMS

- PRECURSOR LYMPHOID NEOPLASMS
  - **B lymphoblastic leukemia** with
    - NOS
    - t(9;22)(q34;q11.2); *BCR/ABL1*
    - t(v;11q23); *MLL* rearranged
    - t(12;21)(p13;q22); *TEL-AML1 (ETV6-RUNX1)*
    - hyperdiploidy
    - hypodiploidy
    - t(5;14)(q31;q32); *IL-3-IGH*
    - t(1;19)(q23;p13.3); *E2A/PBX1 (TCF3-PBX1)*



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## PHILADELPHIA CHROMOSOME t(9;22)(q34;q11)




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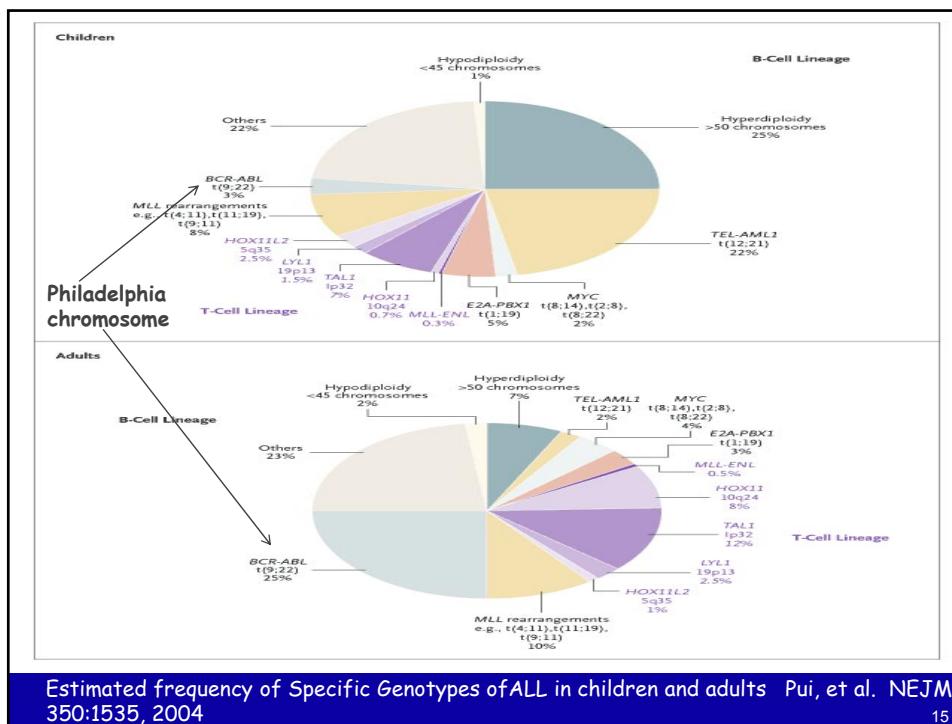
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## WHO CLASSIFICATION OF LYMPHOID NEOPLASMS

- PRECURSOR LYMPHOID NEOPLASMS
  - **T lymphoblastic leukemia/lymphoma**
    - Pro T sCD3-, cyCD3+, CD7+
    - Pre T CD7+, CD2+, CD5+
    - Cortical T CD1a+
    - Mature T CD1a-
  - **Burkitt-cell leukemia** (now classified with Burkitt lymphoma as a mature B cell neoplasm) 

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## ADVERSE PROGNOSTIC FACTORS FOR ADULT ALL

- Age >35 years
- WBC > 30K/ $\mu$ L (B cell); 100K/ $\mu$ L (T cell)
- Cytogenetics t(9;22), t(4;11), +8, -7, complex, hypodiploid/near triploid
- Time to CR >4 weeks
- Minimal residual disease: >10<sup>-3</sup> to 10<sup>-4</sup> after induction, >10<sup>-4</sup> or increasing after consolidation



Hoelzer, D. ASCO Education Book, 2002, p. 49.



## CHEMOTHERAPY OF CHILDHOOD ALL: HISTORICAL PERSPECTIVE

SINGLE AGENTS	FREQUENCY OF CR(%)
Prednisone	57
Vincristine	55
Methotrexate	21
COMBINATION AGENTS	
Pred+VCR	85
Pred+6-MP	81
Pred+VCR+6-MP+MTX	94

CR=Complete Remission, Pred=Prednisone, VCR=Vincristine, MTX=Methotrexate,  
6-MP=6 Mercaptopurine



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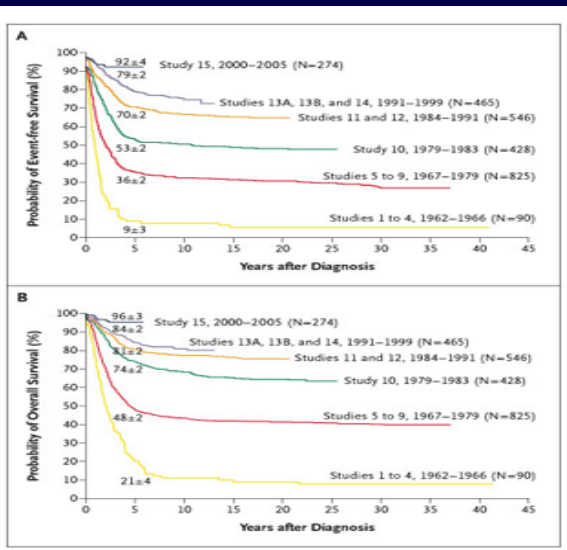
## CHEMOTHERAPY OF CHILDHOOD ALL: HISTORICAL PERSPECTIVE

- Total therapy: 4 Phases (Pinkel, JAMA, 1971)
  - Induction of complete remission with Pred+VCR
  - High doses of antimetabolites IV qd for one week
  - Cerebrospinal irradiation
  - Prolonged maintenance therapy with combination of agents over 2 to 3 years



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## Improvements in Outcome of Pediatric ALL in 2255 Pts. At St. Jude's 1962-2005



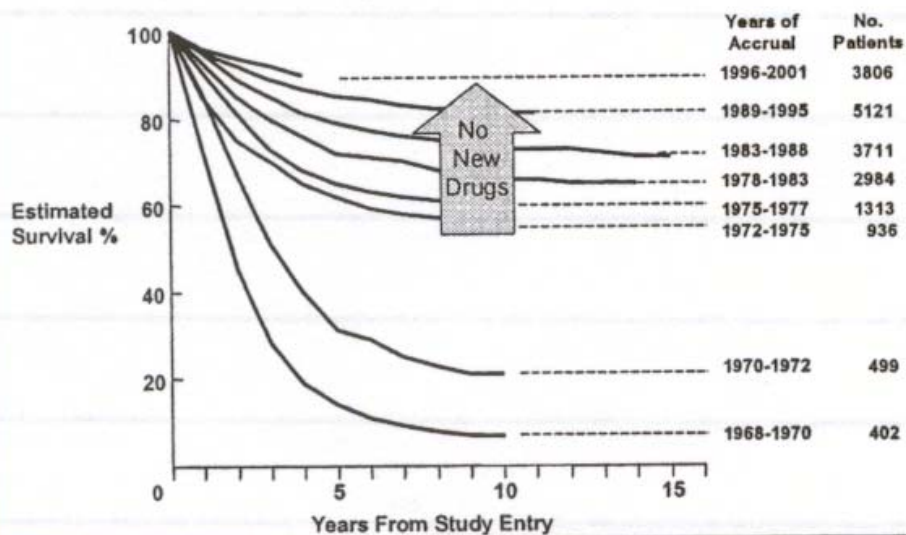
Kaplan-Meier Analyses of Event-free Survival (Panel A) and Overall Survival (Panel B) in 2628 Children with Newly Diagnosed ALL.

Pui and Evans, NEJM 354:166, 2006



### Survival of 18,772 Pediatric Patients with ALL Treated on Sequential CCG Clinical Trials over Three Decades

Tubergen DG, Bleyer A: The Leukemias. Nelson's Textbook of Pediatrics. 17th Ed, 2003, Saunders, Philadelphia, pp. 1694-8.



## THERAPY OF ADULT ALL

- Built on pediatric experience
- Followed outline of 4 phases of "total therapy"
- Incorporated new drugs as they became available, e.g., daunorubicin (1967), cytarabine (1968), asparaginase (1970)
- Intensified consolidation therapy with alternating cycles of non-cross-resistant drugs



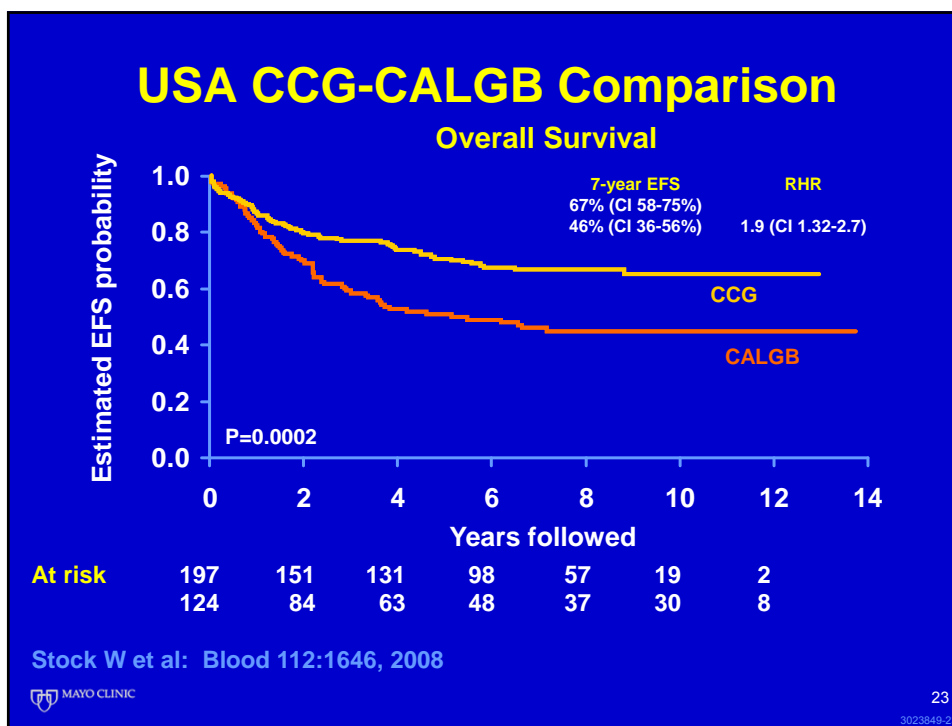
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## CONTEMPORARY ADULT ALL TREATMENT REGIMENS

- 1-2 months of induction with Daunorubicin, Prednisone (Pred), Vincristine (VCR), Asparaginase, Cyclophosphamide, Cytarabine, Methotrexate (MTX)
- Treat brain and spinal cord with MTX, Radiation
- Intensification/Consolidation with same agents as bullet #1
- Prolonged maintenance with 6-mercaptopurine, MTX, VCR, PRED



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## Specified Cumulative Postremission Doses

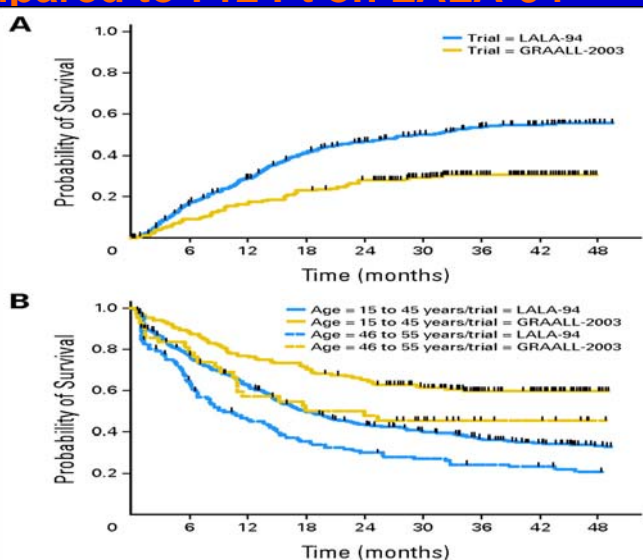
	CCG (2 trials)	CALGB
VCR (mg/m <sup>2</sup> )	22/45	14
Cytarabine (mg/m <sup>2</sup> )	1,800/2,400	1,200
DXM (mg/m <sup>2</sup> )	210/420	140
ASP (U/m <sup>2</sup> )	90,000/318,000	48,000
Doxorubicin (mg/m <sup>2</sup> )	75/150	90
CPM (mg/m <sup>2</sup> )	3,000/4,000	3,000
MTX (IV or oral) (mg/m <sup>2</sup> )	90/1,000	100
Intrathecal MTX/cranial RT	132 mg/1,800 cGy	105 mg/2,400 cGy

Stock W et al: Blood 112:1646, 2008

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## Pediatric Approach to Adult ALL Results of GRAALL-2003 in 212 Pt, Ages 15-60, Compared to 712 Pt on LALA-94



Huguet F et al. JCO 2009;27:911-918



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## Favorable Outcomes for Older Adolescents and Young Adults (AYA) with Acute Lymphoblastic Leukemia: Early Results of US Intergroup Trial C10403 Abstract #796

W Stock, SM Luger, A Advani, S Geyer, RC Harvey, CG Mullighan, CL Willman, G Malnassy, E Parker, KM Laumann, B Sanford, G Marcucci, EM Paietta, M Liedtkke, PM Voorhees, DF Claxton, MS Tallman, FR Appelbaum, H Erba, MR Litzow, RM Stone and RA Larson



On Behalf of the Alliance for Clinical Trials, the Eastern Cooperative Oncology Group and the Southwest Oncology Group

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## US Intergroup study for AYAs 16- 39 years old: C-10403

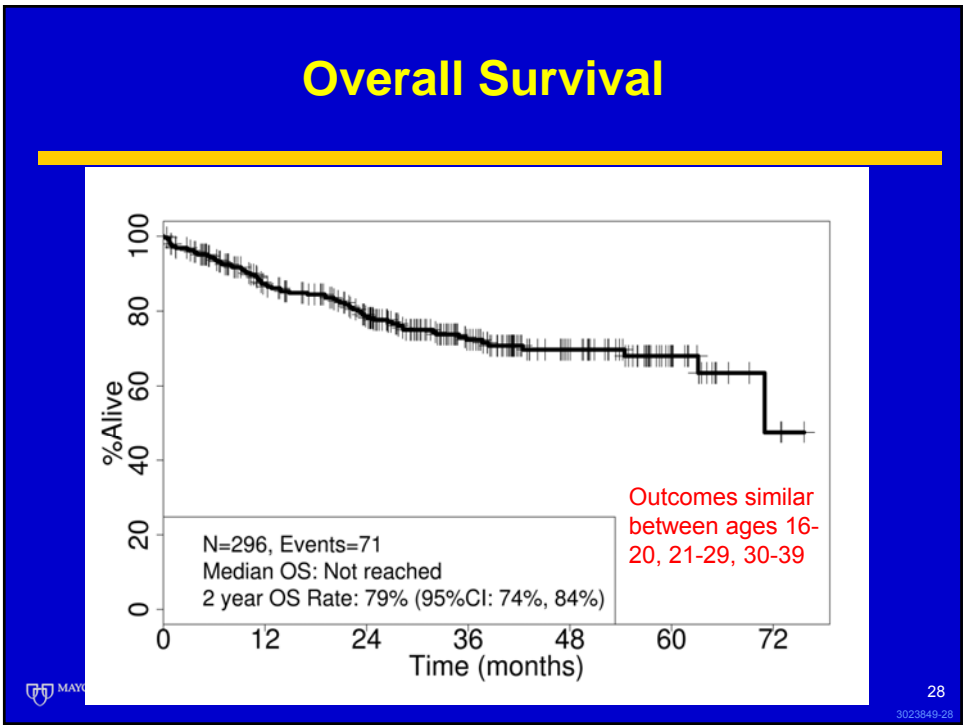
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Accrual completed on 9/15/12 (n = 300)

I	C	IM	DI	M
DNR	Cyclo	MTX	DOX	DEX
VCR	VCR	VCR	Cyclo	VCR
Pred	Dex	Peg-ASP	Dex	6MP
Peg-Asp	Peg-Asp	IT-MTX	Peg-Asp	MTX
IT-MTX	Ara-C		Ara-C	IT-MTX
IT-AraC	6MP		6-TG	
	IT-MTX		IT-MTX	

**T-ALL patients receive prophylactic RT after DI**  
**Maintenance therapy continues for 2 (F) – 3 (M) years**

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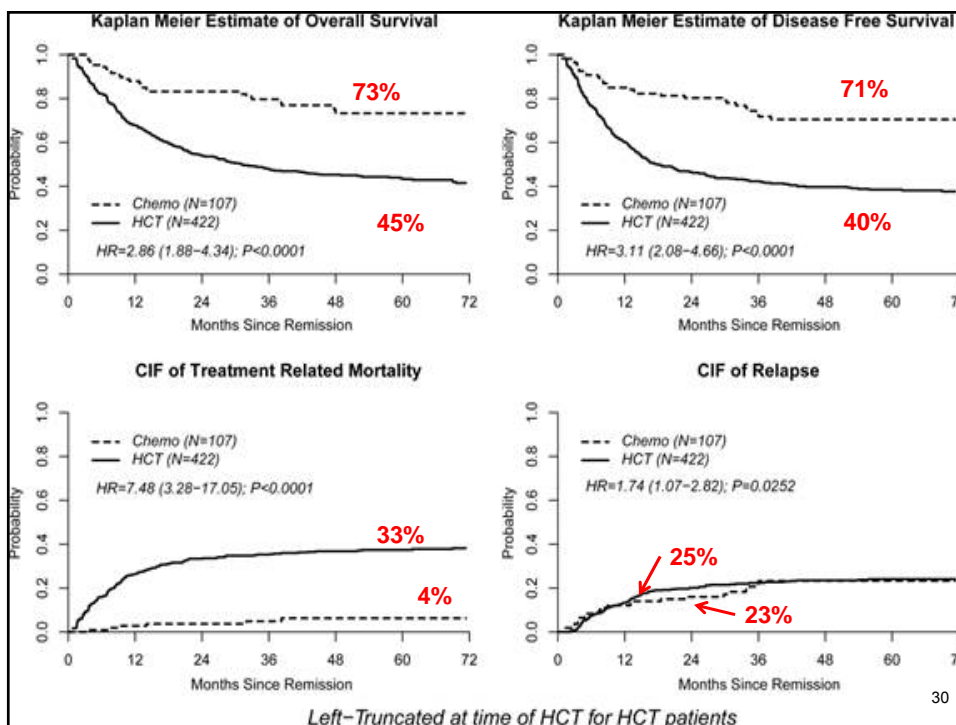
# Abstract #319 Superiority of Pediatric Chemotherapy (Chemo) over Allogeneic Hematopoietic Cell Transplantation (HCT) for Philadelphia Chromosome Negative Adult ALL in First Complete Remission: A Combined Analysis of Dana-Farber ALL Consortium and CIBMTR Cohorts

Matthew D. Seftel, MD MPH  
 FRCPC for the CIBMTR



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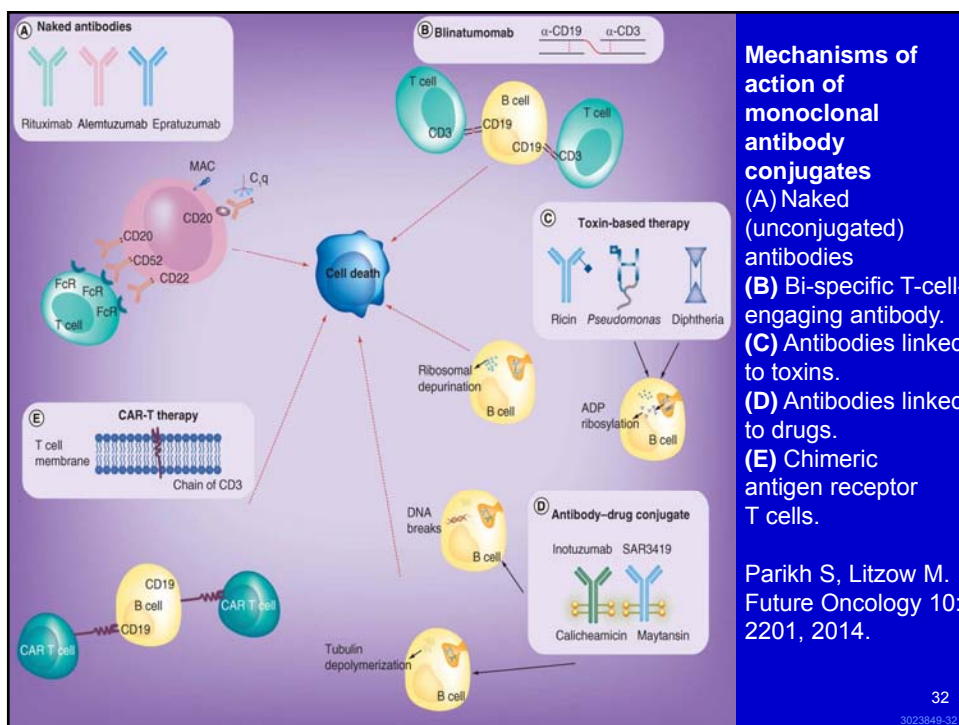
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## Treatment of Relapsed or Refractory ALL

- Different chemotherapy drugs and schedules
- Blood or Marrow Transplant
- Monoclonal Antibody Therapy





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FDA News Release

### FDA approves Blincyto to treat a rare form of acute lymphoblastic leukemia

First anti-CD19 drug to receive agency approval

For Immediate Release December 3, 2014

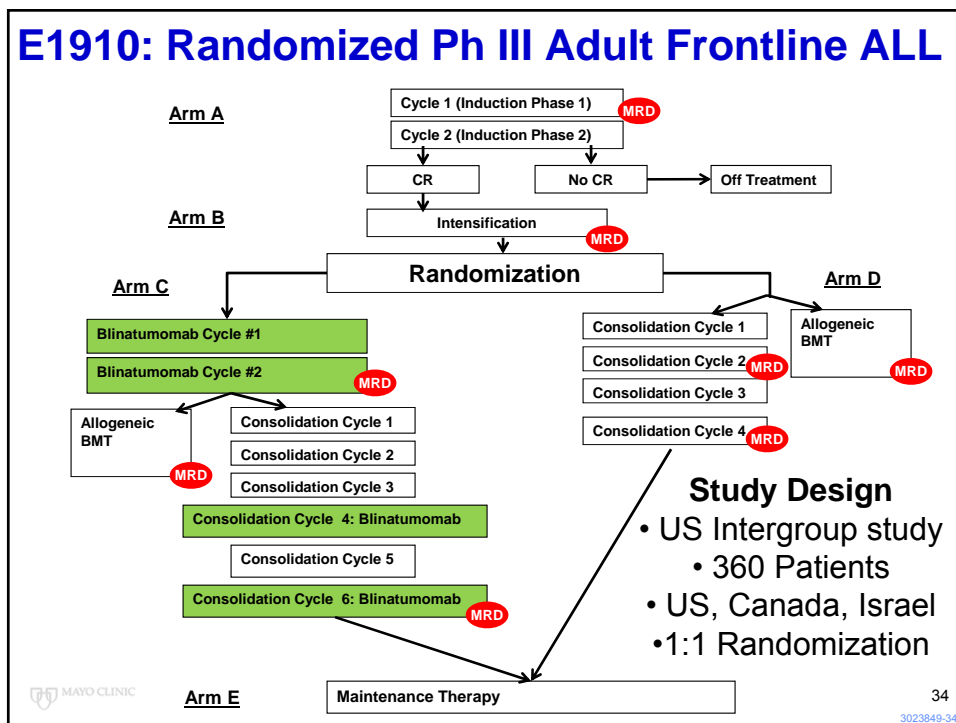
**Breakthrough therapy designation for Blinatumomab (5 mos ahead of schedule), REMS program**

- Requires confirmatory randomized trial
- **\$89,000** for one month of Rx

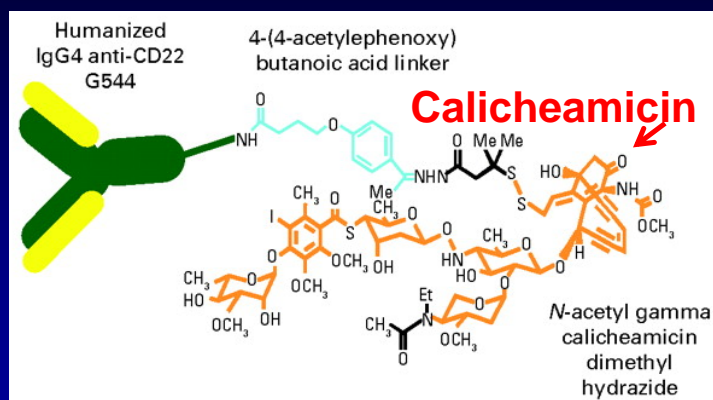


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## Inotuzumab ozogamicin



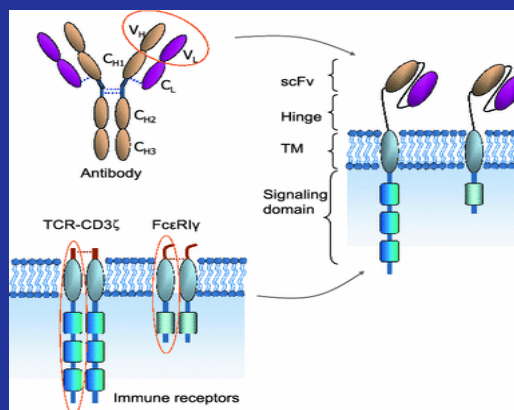
R/R ALL, Single agent activity - ORR 58%, Median survival of 6.3 mos

Advani et al. JCO 2010 35

## Chimeric Antigen Receptor-Modified T Cells

CARs consist of:

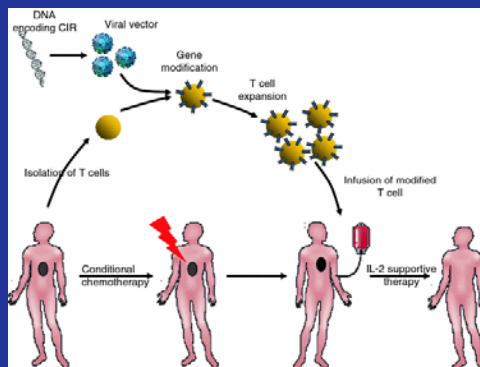
- scFv
- hinge region
- transmembrane & signaling domain – usually CD3 $\zeta$  or Fc $\epsilon$ R1 $\gamma$ , also CD28 and CD137 (41BB)



Lipowska-Bhalla, et al. Cancer Immuno Immunother 61:953-62, 2012

## Chimeric Antigen Receptor-Modified T Cells

- T cells are collected from a patient
- Retrovirally transduced with CAR genes
- Expanded ex vivo
- Infused back to the patient



Lipowska-Bhalla, et al. Cancer Immuno Immunother 61:953-62, 2012



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## Summary of Clinical Outcomes

	Number of Patients, N=27
Overall CR Rate	24/27 (89%)
MRD Negative CR Rate	21/24 (88%)
Median Time to CR (range)	22.5 days (9 – 33)

- **Median follow-up: 6 months**
- **12 patients remain disease-free**  
7 patients w/o subsequent HSCT
- **10 patients proceeded to allo HSCT**
- **9 patients relapsed during follow-up**
- **T cells persisted 1 – 3 months post T cell infusion**



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## Side Effects Management

- Nausea and vomiting – anti-emetics
- Fatigue-Exercise
- Anemia-Red Blood Cell Transfusions
- Low Platelets (Thrombocytopenia)-  
Platelet Transfusions
- Infections-Antibiotics
- Neuropathy-Anti-seizure medication,  
pain medication
- Complementary/Alternative Approaches



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## Early Survivorship Issues

- “Being cancer free does not mean being free of cancer”

Lingering side effects

Neuropathy

Fatigue

Cognitive dysfunction

Joint issues

Lymphedema

Sexual dysfunction



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## Long-Term Medical Issues

- Secondary Malignancies
- Cardiovascular Disease
- Endocrine Issues
- Cognitive Dysfunction
- Fatigue
- Lymphedema
- Fertility

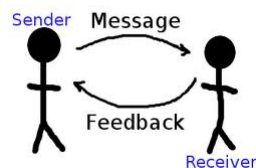
## Open Communication with your healthcare team

- Make a list in advance of the things you want to discuss at your appointment.
- If you don't understand something your doctor is saying, ask questions until you do understand.
- Take notes, or get a friend or family member to take notes for you.
- Being honest about symptoms can help doctors order the right tests and make the right diagnoses



## Open Communication with your healthcare team

- Ask your doctor to write down instructions for you.
- Ask your doctor for printed material about your condition or suggestions for where you can get more information.
- Don't forget that other members of your health care team, such as nurses and pharmacists, can be good sources of information.  
**Talk to them, too.**



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Adult Acute Lymphoblastic Leukemia (ALL):  
Update on Diagnosis and Treatment

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is today**  **LEUKEMIA &  
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## Question and Answer Session

Dr. Litzow's slides are available for download at  
[www.LLS.org/programs](http://www.LLS.org/programs)

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**Adult Acute Lymphoblastic Leukemia (ALL):  
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**The Leukemia & Lymphoma Society (LLS) offers:**

- **Live, online chats** that provide a friendly forum to share experiences with others.
  - Living with Acute Leukemia Chat* held on Thursday nights, 8:00-10:00 pm ET,
  - Caregiver Chat* held on Tuesday nights from 8:00-10:00 pm ET,
  - Young Adults Chat* held on Tuesday nights, from 8:30-10:30 pm ET.
  - **WEBSITE:** [www.LLS.org/chat](http://www.LLS.org/chat)
- **What to ask:** For a list of suggested questions to ask about certain topics, download and print any of the following guides.
  - **WEBSITE:** [www.LLS.org/whattoask](http://www.LLS.org/whattoask)
- **Free education materials:** [www.LLS.org/publications](http://www.LLS.org/publications)
- **Past ALL education programs:** [www.LLS.org/leukemiaeducation](http://www.LLS.org/leukemiaeducation)
- **Information Resource Center:** Speak one-on-one with an Information Specialist who can assist you through cancer treatment, financial, and social challenges.
  - **EMAIL:** [infocenter@LLS.org](mailto:infocenter@LLS.org)      **TOLL-FREE PHONE:** (800) 955-4572