Translating Guidelines and Clinical Trial Data to Improved ALL Management and Outcomes

Learning Objectives

- Outline the current classification system for ALL and the differences in biology and treatment strategies between pediatric and adult patients with ALL
- Review current evidence for induction, consolidation, maintenance, and transplant strategies in the treatment of ALL in pediatric and adult patients
- Summarize current guideline recommendations for the treatment of both Ph–negative and Ph–positive ALL patients
- Outline strategies for the treatment of patients with refractory or relapse ALL
- Identify emerging treatments and the role of currently available targeted agents in the management of ALL

ALL = acute lymphoblastic leukemia; Ph = Philadelphia chromosome.

Acute Lymphoblastic Leukemia

- 6050 new ALL cases in the United States annually
- ALL accounts for 20% of adults with acute leukemia and ~80% of all childhood leukemia cases
  - 60% of ALL patients are younger than 20 years-of-age
  - ALL accounts for 25% of all childhood cancers
  - ALL is more common in males: 62%
- Greatest incidence in the United States among Hispanics
  - Higher incidence in whites vs blacks
  - Peak incident rate: 2-5 years-of-age; >50 years-of-age

American Cancer Society. http://www.cancer.org/Research/CancerFactsFigures/CancerFactsFigures/cancer-facts-figures-2012. Accessed January 4, 2013. Jemal A, et al. *CA Cancer J Clin*. 2004;54(1):8-29.

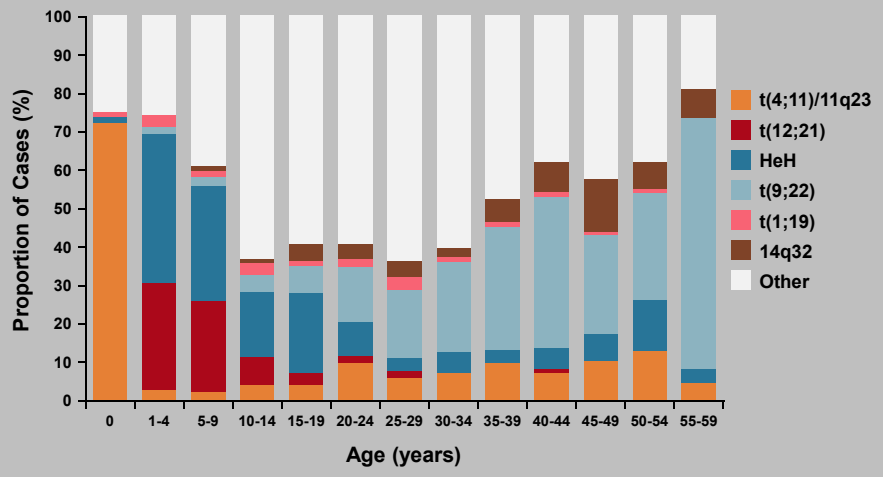
Risk Stratification and Classification of ALL at the Time of Diagnosis

- NCI risk factors for pediatric ALL (BCP>TCP)
  - Age
    - Standard risk: >1 year-of-age; <10 years-of-age
  - WBC
    - ≥50,000 vs <50,000
- Immunophenotype classification (BCP and TCP)
- Genetics of leukemia cells
  - rMLL, hypodiploidy (<45), iAMP21—**Unfavorable**
  - Double trisomy 4+10, ETV6-RUNX1 fusion gene—**Favorable**
  - BCR-ABL fusion gene—**Requires special treatment**

NCI = National Cancer Institute; BCP = B-cell precursor; TCP = T-cell precursor; WBC = white blood cell; rMLL = Mixed-Lineage Leukemia gene rearrangement; iAMP21 = intrachromosomal amplification of chromosome 21; BCR-ABL = breakpoint cluster region-Abelson.

Kanwar VS, et al. http://emedicine.medscape.com/article/990113-overview. Accessed January 14, 2013. Bhojwani D, et al. *Leukemia*. 2012;26(2):265-270. Harrison CJ. *Clin Lab Med*. 2011;31(4):631-647.

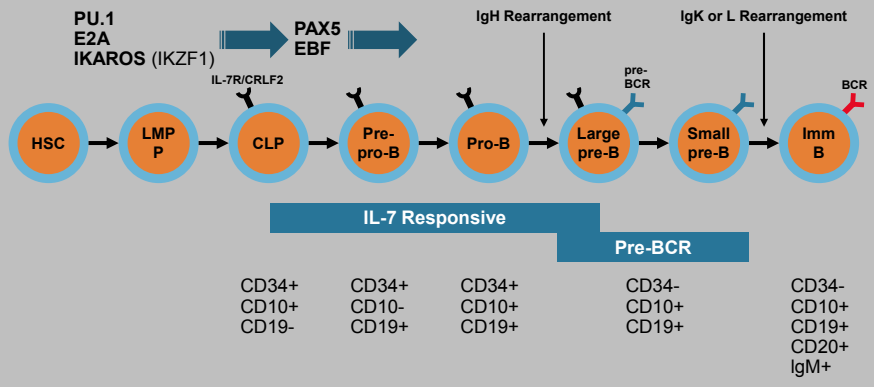
Distribution of the Common Chromosomal Abnormalities According to Age



HeH = high hyperdiploidy.
Harrison CJ. *Clin Lab Med.* 2011;31(4):631-647.

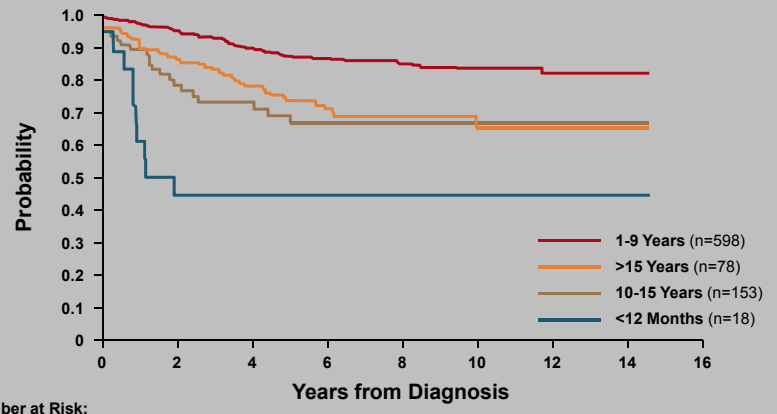
Genetic Abnormalities Are Not Random

B-Cell Development Stages, Immunophenotype, Major Transcription Factors, and Signaling Molecules



EBF = early B-cell factor; Ig = immunoglobulin; HSC = hematopoietic stem cell; LMPP = lymphoid-primed multipotential progenitor; CD = cluster of differentiation; IL = interleukin.
Zhou Y, et al. *Human Pathol.* 2012;43(9):1347-1362.

Age at Diagnosis Correlates with Outcome



Number at Risk:

<12 Months	18	11	8	8	6	1	1	0	0
1-9 Years	598	528	378	295	213	149	85	31	4
10-15 Years	153	130	100	77	50	26	11	6	1
>15 Years	78	60	40	29	20	7	1	0	0

Pui CH, et al. *Lancet*. 2008;371(9617):1030-1043.

Diverse "Associated" Chromosomal Abnormalities

Frequency of Genomic Amplifications and Deletions in Pediatric ALL

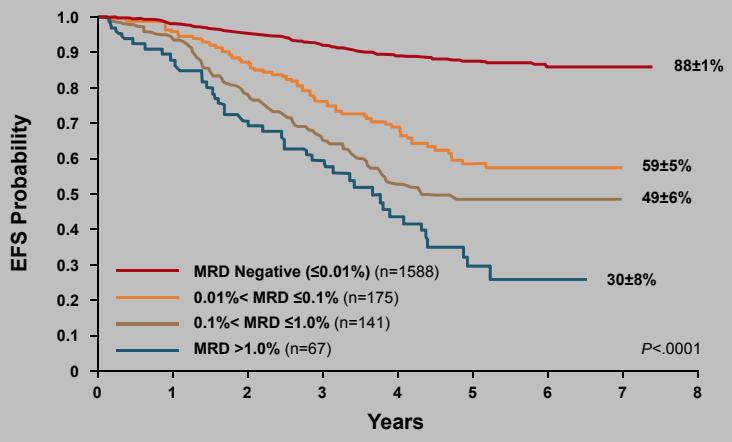
Group	Subtype	N	Amplifications (mean±SD)*	Deletions (mean±SD)*	All Lesions (mean±SD)*
B-ALL	Hyperdiploidy with >50 chromosomes	39	9.56±3.59 (5-20)	1.59±2.49 (0-11)	11.13±5.0 (5-27)
B-ALL	TCF3-PBX1	17	1.59±0.62 (1-3)	2.12±1.17 (1-4)	3.7±1.53 (2-7)
B-ALL	ETV6-RUNX1	47	0.89±1.51 (0-8)	6.0±4.63 (1-21)	6.68±4.8 (0-21)
B-ALL	rMLL	11	0.09±0.3 (0-1)	0.91±1.81 (0-6)	1±1.79 (0-6)
B-ALL	BCR-ABL1	9	4±5.3 (0-12)	4.2±4.15 (0-12)	6.8±4.52 (0-13)
B-ALL	Hyperdiploidy with 47-50 chromosomes	23	1.70±1.55 (0-7)	3.5±3.12 (0-12)	5.1±4.31 (0-15)
B-ALL	Hypodiploid	10	1.1±1.91 (0-6)	6.0±4.42 (3-18)	7.1±6.12 (3-24)
B-ALL	Other	36	1.06±3.21 (0-19)	4.64±5.14 (0-20)	5.58±6.57 (0-23)
B-ALL	Total	192	2.97±4.28 (0-20)	3.83±4.2 (0-21)	6.63±5.56 (0-27)
T-ALL		50	0.9±1.98 (0-9)	4.9±6.21 (0-30)	5.8±7.12 (0-39)
All Cases		242	2.54±4.0 (0-20)	4.06±4.69 (0-38)	6.46±5.90 (0-39)

***Range is shown in parentheses.**
B-ALL = acute B-lymphoblastic leukemia; T-ALL = acute T-lymphoblastic leukemia.
Mullighan CG, et al. *Nature*. 2007;446(7137):758-764.

The Importance of Early Response to Treatment

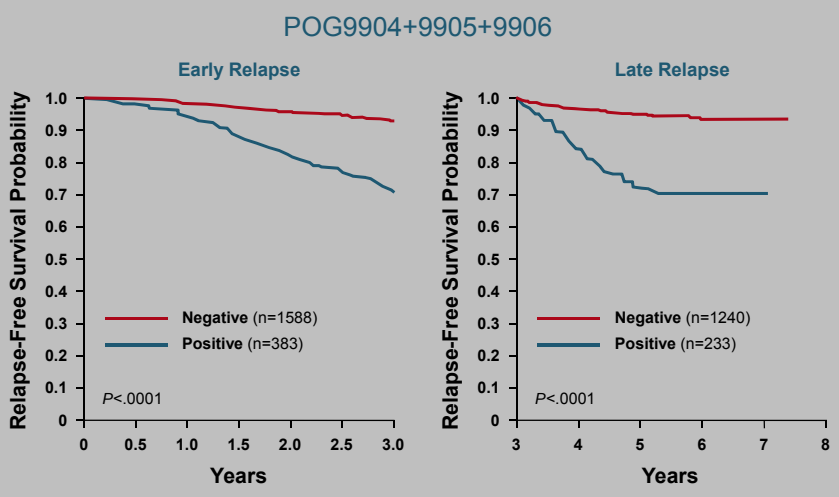
Early Response Predicts Outcome

MRD on Day 29 of Induction by Flow Cytometry



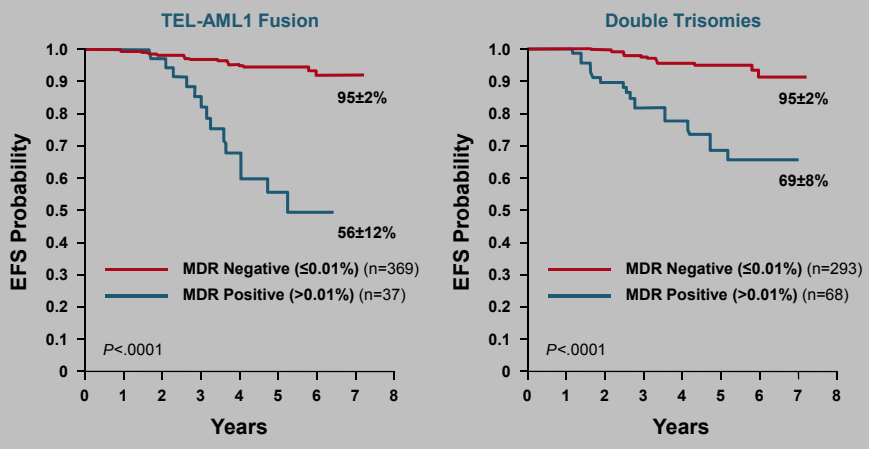
MRD = minimum residual disease; EFS = event-free survival.
Borowitz MJ, et al. *Blood.* 2008;111(12):5477-5485.

MRD on Day 29 of Induction Predicts Both Early and Late Failure



POG = Pediatric Oncology Group.
Borowitz MJ, et al. *Blood.* 2008;111(12):5477-5485.

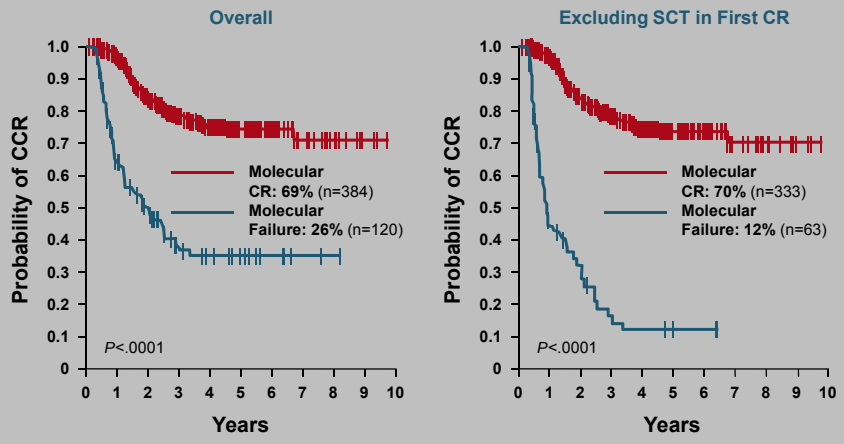
EFS of NCI SR Patients With Favorable Genetic Features



SR = standard-risk.
Borowitz MJ, et al. *Blood.* 2008;111(12):5477-5485.

CCR for Patients in the SR and HR Groups According to Molecular Response Status

Week 16 in Adult ALL Patients

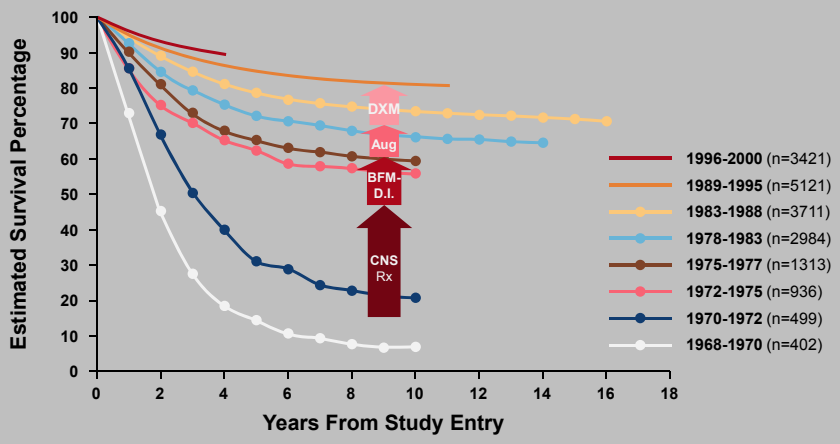


CCR = complete continuous remission; HR = high-risk; SCT = stem cell transplantation; CR = complete response.

Gökbuget N, et al. *Blood.* 2012;120(19):1868-1876.

Current ALL Treatment Methods and Strategies

Therapy is the Most Important Prognostic Factor!

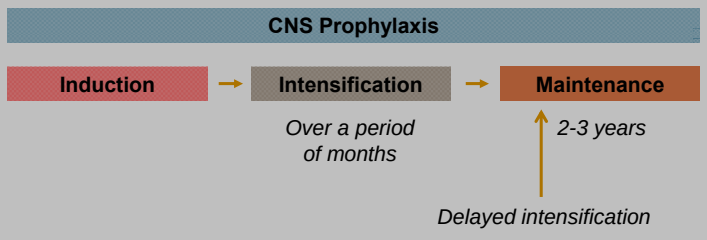


DXM = dexamethasone; Aug = augmentation; BFM-D.I. = Berlin-Frankfurt-Munster-delayed intensification; CNS = central nervous system.

Bleyer A. Evolution of ALL therapy in infants, teenagers, and young adults. Presented at: Enzon Oncology Team Meeting; May 31, 2006; Atlanta, Georgia.

ALL Treatment

- Induction
- Post-induction intensification
- Delayed intensification
- Maintenance phases
- CNS prophylaxis



Induction Therapy

Treatment Options	Agents
Pediatric	
New York	Vincristine, prednisone, daunomycin, asparaginase, CPM
COG/SR	Vincristine, DXM, prednisone, asparaginase
COG/HR+T-cell	Vincristine, DXM or prednisone, prednisone, asparaginase, daunomycin
Adult	
Linker	Vincristine, DXM or prednisone, asparaginase, daunomycin
UKALL XII	Vincristine, DXM or prednisone, asparaginase, daunomycin
HyperCVAD	Vincristine, DXM, doxorubicin, hyperfractionated CPM

CPM = cyclophosphamide; COG = Children's Oncology Group; UKALL = Medical Research Council Acute Lymphoblastic Leukemia; HyperCVAD = hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone.

National Cancer Institute. http://www.cancer.gov/cancertopics/pdq/treatment/childALL/HealthProfessional/page4. Accessed January 14, 2013. NCCN Clinical Practice Guidelines in Oncology. http://www.nccn.org/professionals/physician_gls/pdf/all.pdf. Accessed January 4, 2013.

Presymptomatic CNS Therapy (CNS Prophylaxis)

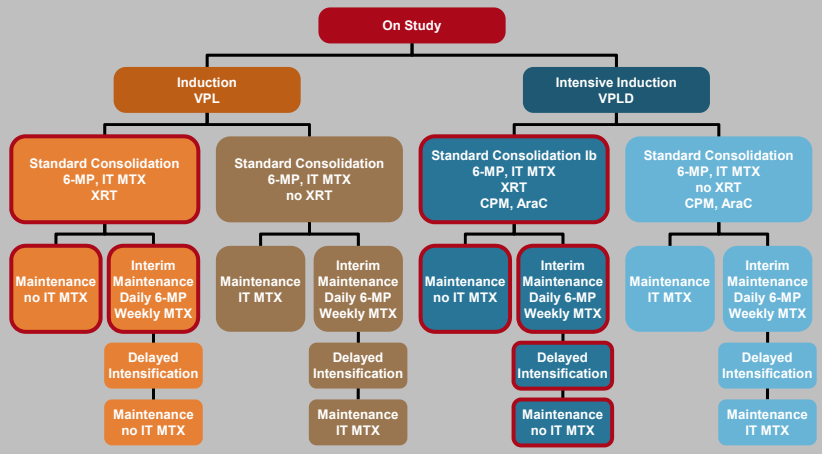
- Effective systemic chemotherapy
  - HD MTX, DXM, asparaginase, thioguanine
- Early intensification and optimization of intrathecal therapy
  - Triple IT therapy vs IT MTX
- Cranial irradiation
  - A central role in the 1960's but employed less because of serious long-term sequalae

HD = high dose; MTX = methotrexate; IT = intrathecal.

Pui CH, et al. *Semin Oncol.* 2009;36(4 suppl 2):S2-S16.

Post-Induction Intensification (Consolidation)

CCG-105: Average (Standard) Risk

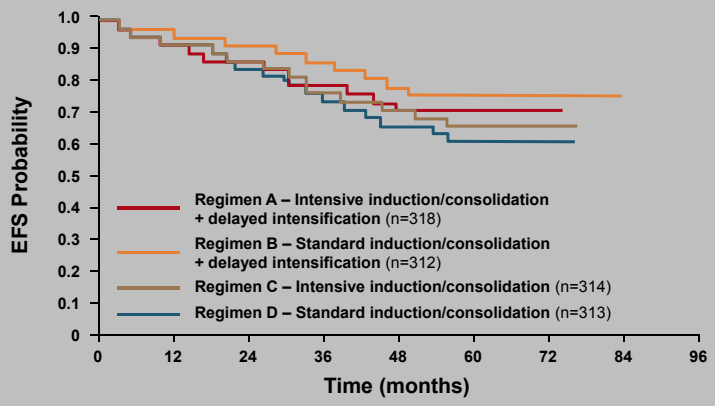


CCG = Children's Cancer Group; VPL = vincristine + prednisone + L-asparaginase; VPLD = vincristine + prednisone + L-asparaginase + daunomycin; AraC = cytosine arabinoside; 6-MP = 6-mercaptopurine; XRT = external-beam radiation.

Tubergen DG, et al. *J Clin Oncol*. 1993;11(3):520-526.

CCG-105—Average (Standard) Risk, Early vs Delayed Intensification

EFS for Randomized Patients <10 Years-of-Age on Regimens Containing Delayed Intensification



Tubergen DG, et al. *J Clin Oncol.* 1993;11(3):527-537.

CCG-Modified Standard BFM

Induction (5 weeks)	Consolidation (8 weeks)			
VPLD	CPM AraC 6-MP	2 week delay	CPM AraC 6-MP	2-week delay

16 weeks of intensive therapy including
6 weeks of delay for count recovery

Interim Maintenance (8 weeks)	Delayed Intensification (8 weeks)		
Oral 6-MP/Oral MTX	Vincristine/DXM/ Doxorubicin/ L-asparaginase	CPM AraC 6-MP	2-week delay

Nachman JB, et al. *N Engl J Med.* 1998;338(23):1663-1671.

Augmented BFM

Induction (5 weeks)	Consolidation (8 weeks)			
VPLD	CPM AraC 6-MP	Vincristine- L-asparaginase	CPM AraC 6-MP	Vincristine- L-asparaginase

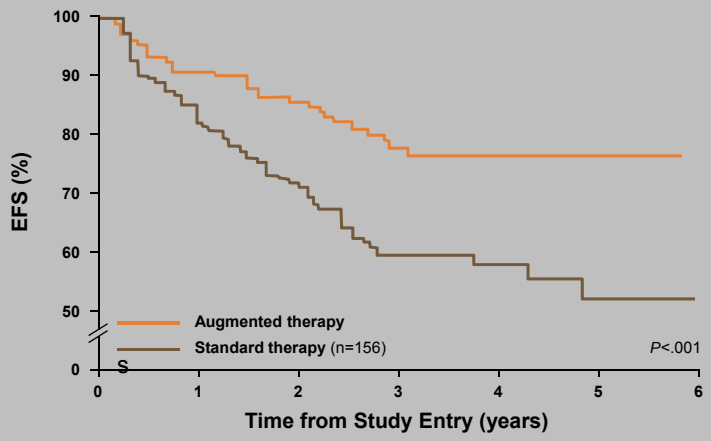
No delays—40 weeks of intensive therapy

Interim Maintenance #1 (8 weeks)	Delayed Intensification (8 weeks)		
Vincristine/Capizzi MTX + L-asparaginase	Vincristine/DXM/ Doxorubicin/ L-asparaginase	CPM AraC 6-MP	Vincristine- L-asparaginase
Interim Maintenance #2 (8 weeks)	**Delayed Intensification (8 weeks)**		
Vincristine/Capizzi MTX + L-asparaginase	Vincristine/DXM/ Doxorubicin/ L-asparaginase	CPM AraC 6-MP	Vincristine- L-asparaginase

Nachman JB, et al. *N Engl J Med.* 1998;338(23):1663-1671.

Longer and Stronger PII

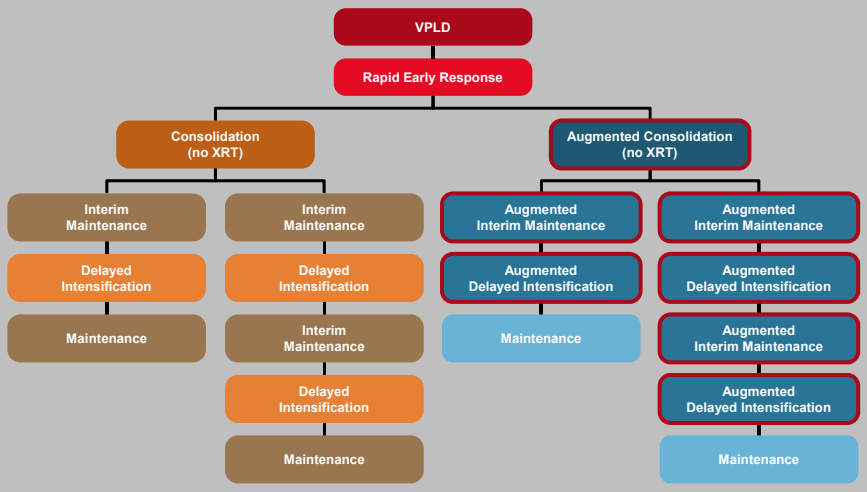
CCG-1882



PII = post-induction intensification.
Nachman JB, et al. *N Engl J Med.* 1998;338(23):1663-1671.

Length and Strength of PII

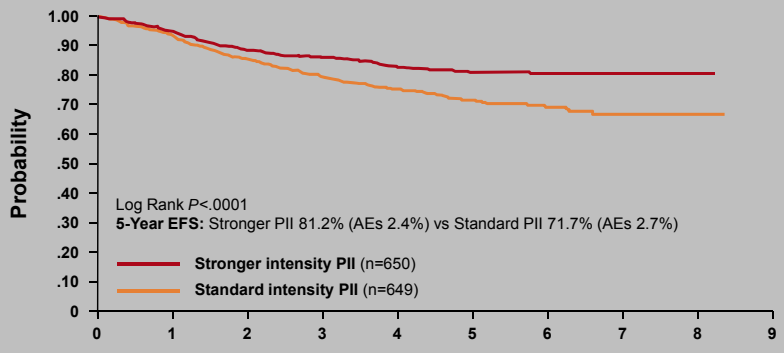
CCG-1961: Higher Risk



Seibel NL, et al. *Blood.* 2008;111(5):2548-2555.

EFS During 5 Years of Follow-Up in ALL Patients

EFS According to the Type of Post-Induction Chemotherapy



Number at Risk:									
Stronger PII	650	611	559	473	340	220	138	42	2
Standard PII	649	598	536	448	325	196	111	37	3

AEs = adverse effects.

Seibel NL, et al. *Blood.* 2008;111(5):2548-2555.

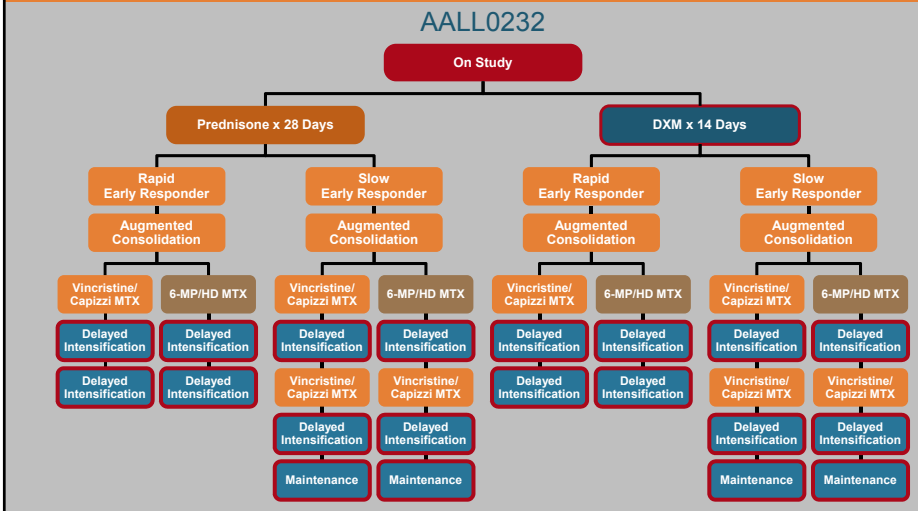
High-Dose MTX with Leucovorin Rescue

Study	Population	IV MTX Dose	EFS Advantage
CCG-139	IR	0.5 g/m^2	No
CCG-144	SR	33.6 g/m^2	No
CCG-5971	Lymphoblastic lymphoma	5 g/m^2	No

IR = intermediate risk.

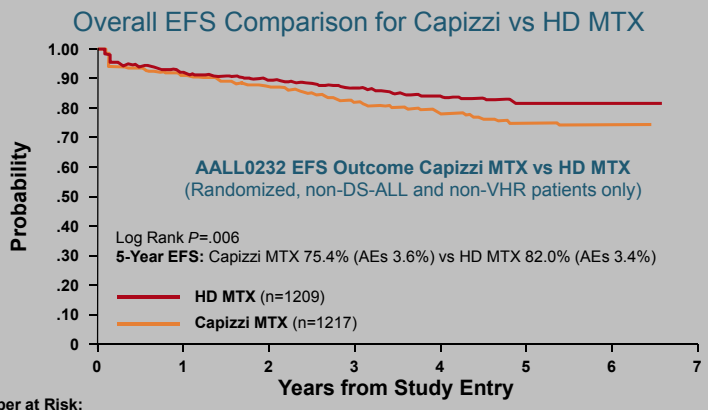
Lange BJ, et al *Med Pediatr Oncol.* 1996;27(1):15-20. Nathan PC, et al. *Leuk Lymphoma.* 2006;47(12):2488-2504. Abromowitch M, et al. Presented at: American Society of Hematology Annual Meeting; December 6-9, 2008; San Francisco, California. Abstract 3610.

DXM vs Prednisone; HD vs Escalating IV MTX



AALL0232 = high-risk precursor B-ALL protocol.
Larsen EC, et al. Presented at: 2011 American Society of Clinical Oncology Annual Meeting; June 3-7, 2011; Chicago, Illinois. Abstract 3.

AALL0232—Excluding Ph+, Hypodiploid, MLL; Including RER and SER



Number at Risk:

Capizzi MTX	1217	883	679	460	288	105	10
HD MTX	1209	895	689	483	305	103	12

MLL = Mixed-Lineage Leukemia gene; RER = rapid early response; SER = slow early response; DS-ALL = Down's syndrome and ALL; VHR = very high-risk.
Larsen EC, et al. Presented at: 2011 American Society of Clinical Oncology Annual Meeting; June 3-7, 2011; Chicago, Illinois. Abstract 3.

Maintenance

- Daily mercaptopurine + weekly MTX since the 1960s
  - Full dose is more effective than half dose
  - CPM and cytarabine add toxicity but no benefit
  - Childhood ALL is unique in requiring prolonged therapy
    - 2 years>18 months; 3 years>2 years
    - L92-13 study with 1 year of intensive therapy
      - 60% EFS for HR and 60% EFS for SR
  - Vincristine/steroid pulses
  - Parenteral vs oral MTX

Pinkel D. *Cancer.* 1979;43:1128-1137. Tsuchida M, et al. *Leukemia.* 2010:24(2):383-396. Eden T, et al. *Br J Haematol.* 2010;149(5):722-733. Wehinger H, et al. *Klin Padiatr.* 1982;194(4):214-218. Koizumi S, et al. *Cancer.* 1988;61(7):1292-1300. Brandelise S, et al. *J Clin Oncol.* 2010;28(11):1911-1918.

COG Treatment Allocation

Pediatric BCP Risk Stratification

AALL0932/AALL1131

Day 8 PB MRD	<.01%	0.01%-1%	>1%	
Day 29 BM MRD	<.01%	<.01%	<.01%	>.01%
Subset/MRD				
Age <1 year	Infant			
BCR-ABL	Ph+			
CNS 3	VHR			
Age >13 years	VHR			
Induction failure	VHR			
Hypodiploid, iAMP21, rMLL	VHR			
NCI SR, TEL-AML1 fusion, Trisomy 4+10	LR	SR		HR
NCI SR, Other	SR		HR	VHR
NCI HR, Age <13 years	HR			VHR

AALL0932 = newly diagnosed standard-risk precursor B-ALL protocol; AALL1131 = newly diagnosed high-risk precursor B-ALL protocol; PB = peripheral blood; BM = bone marrow; LR = low-risk. Hunger SP, et al. *Pediatr Blood Cancer*. 2012 December 19 [Epub ahead of print]. Hunger SP, et al. J Clin Oncol. 2012;30(14):1663-1669.

COG B-Cell Precursor Subsets

Subset	Subsets	Percent	Expected EFS
Infant	1	3%	50%
Ph+	1	3%	75%
VHR	8	22%	<80%
HR	3	23%	88-90%
SR	2	34%	90-95%
LR	1	15%	>95%

Hunger SP, et al. *Pediatr Blood Cancer*. 2012 December 19 [Epub ahead of print]. Schultz KR, J Clin Oncol. 2009;27(31):5175-81. Gaynon PS, et al. Leukemia. 2010;24(2):285-97.

Risk Stratification: Pediatric, T-Cell

AALL0434

Presenting Features	M1 on Day 8 or 15 Day 29 MRD <.1%	M1 on Day 29 Day 29 MRD .1%-1%	M2/3 on Day 29 or Day 29 MRD >1%
Age 1-9 years WBC <50,000 No Testes disease CNS 1	LR	IR	HR
Age >10 years WBC >50,000 Testes disease CNS 3	IR		HR

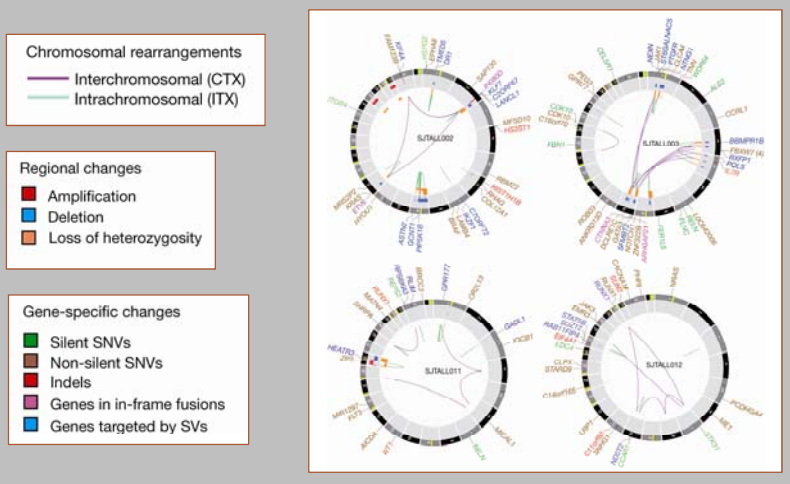
- No validity of conventional age/WBC
- End consolidation MRD (day 85!)
- Adverse ETP

M1, 2, 3 = bone marrow morphology stages; ETP = early T-phenotype.

Schultz KR. *J Clin Oncol.* 2009;27(31):5175-81. Krampera M, et al. *Br J Haematol*. 2003;120(1):74-9. Willemse MJ, et al. *Blood.* 2002;99(12):4386-93.

Early T-Cell Phenotype: Molecularly Heterogeneous

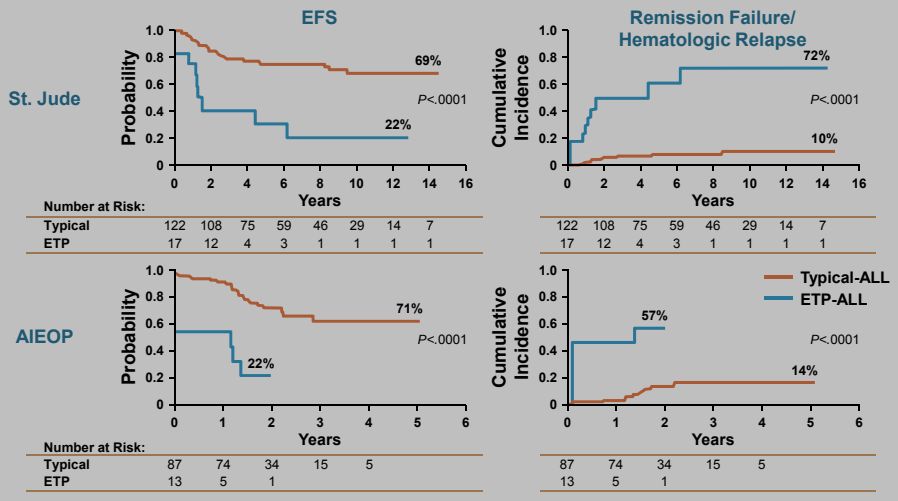
CD1a(-), CD8(-), CD5(weak) with Stem-Cell or Myeloid Markers



Zhang J, et al. *Nature*. 2012;481(7380):157-163.

Early T-Cell Phenotype: Molecularly Heterogeneous

CD1a(-), CD8(-), CD5(weak) with Stem-Cell or Myeloid Markers



AIEOP = Associazione Italiana Ematologia Oncologia Pediatrica.
Coustan-Smith E, et al. *Lancet Oncol*. 2009;10(2):147-156.

End Consolidation MRD in T-ALL

Relapses by Risk Group

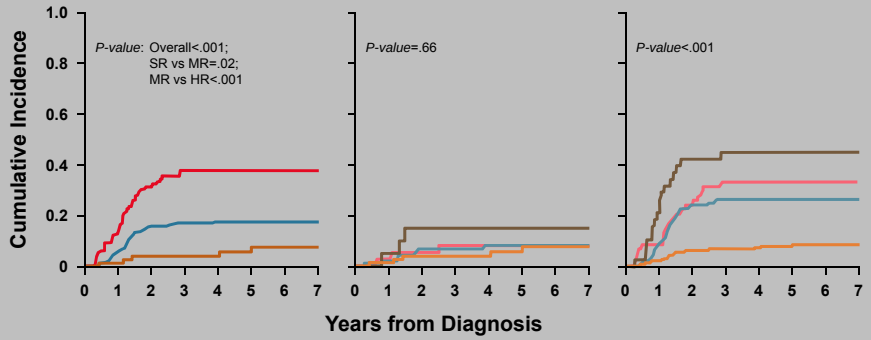
	Number Patients	Number Relapse	7-Year CI
SR	75	5	7.6% (3.3)
IR	292	51	17.6% (2.2)
HR	97	36	37.7% (5.0)

MRD Negative at TP2 Relapses by MRD at TP1

	Number Patients	Number Relapse	7-Year CI
Negative	75	5	7.6% (3.3)
<10E-3	90	7	8.0% (2.9)
10E-3	37	3	8.2% (5.0)
>10E-3	20	3	15.0% (8.0)

Relapses by MRD at TP2

	Number Patients	Number Relapse	7-Year CI
Negative	222	18	8.5% (1.9)
<10E-3	145	38	26.3% (3.7)
10E-3	59	19	33.0% (6.2)
>10E-3	38	17	44.7% (8.1)



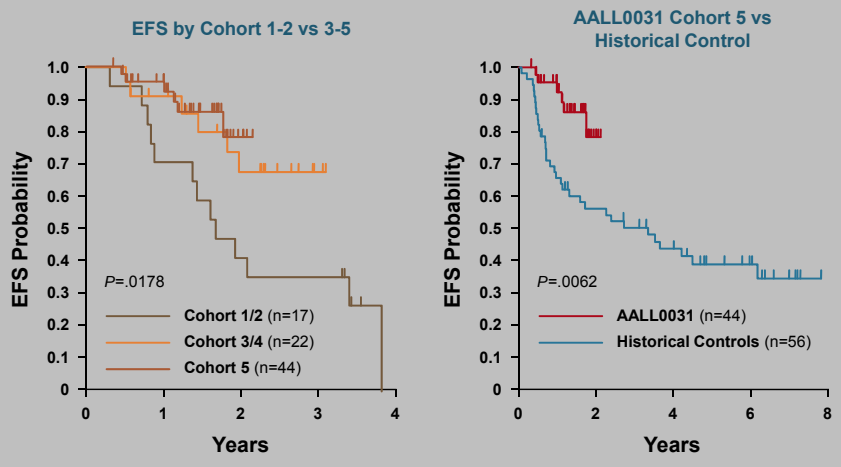
TP1 = time point 1; TP2 = time point 2; CI = confidence interval; MR = medium-risk.
Schrappe M, et al. *Blood.* 2011;118(8):2077-2084.

"Targeted Therapy" Ph+ ALL in Children; Pre-Imatinib

Study Groups	Years of Study	N	Percentage	CR	EFS	Reference
Dana-Farber	1981-89	15	3.5	80	0	Fletcher et al (1991)
POG	1981-89	58	2.3	78	7	Crist et al (1990)
St. Jude	1984-94	23	3.6	87	33	Ribeiro et al (1987)
BFM/AEIOP	1986-95	61	1.3	75	38	Schrappe et al (1998)
NOPHO	1986-97	17	1.3	NA	41	Forestier et al (2000)
CCG	1988-95	30	2.3	97	20	Uckun et al (1998)
UKALL	1990-97	25	2	NA	27	Hann et al (2001)
Dana-Farber	1991-95	6	1.6	100	50	Silverman et al (2001)
St. Jude	1994-98	6	2.9	89	29	Pui et al (2004)
AEIOP	1995-99	30	2	86	46	Arico et al (2002)
UKALL	1997-2002	42	2.3	86	52	Roy et al (2005)

AEIOP = Associazione Italiana Ematologia Oncologia Pediatrica; NOPHO = Nordic Society for Pediatric Hematology and Oncology.
Jones LK, et al. *Br J Haematol.* 2005;130(4):489-500.

Imatinib + Chemotherapy Improves Outcome for Childhood Ph+ ALL (AALL0031)



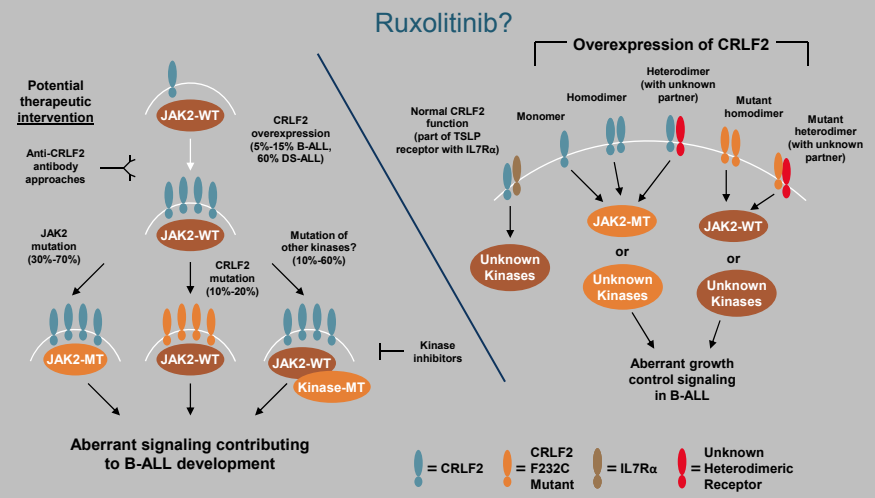
AALL0031 = Evaluation of imatinib mesylate into an intensive chemotherapy regimen for children with Ph+ ALL.
Schultz KR, et al. *J Clin Oncol.* 2009;27(31):5175-5181.

Targeted Therapy

- Every agent has molecular targets
  - MTX and DHFR
- Targeted therapy requires a patient population for whom the molecular target is critical
  - ATRA → acute promyelocytic leukemia
  - TKIs → chronic myelogenous leukemia
  - Abnormal gene product (BCR-ABL; RARα)
  - Over-expression?
- Target should clonal—not sub-clonal
- "Early" vs "late" disease
  - Chronic myelogenous leukemia vs Ph+ ALL

DHFR = dihydrofolate reductase; ATRA = all-trans-retinoic acid; TKIs = tyrosine-kinase inhibitors; RARα = retinoic acid receptor-alpha.

CRLF2 and JAK2 in B-Cell Progenitor ALL: A Novel Association in Oncogenesis



WT = wild-type; MT = mutated; TSLP = thymic stromal lymphopoietin; IL7Rα = interleukin 7 receptor alpha.

Roll JD, et al. *Cancer Res.* 2010;70(19):7347-7352.

Adolescents and Young Adults

Trials	Age (years)	Induction Rate		EFS	
		Adult	Pediatric	Adult	Pediatric
FRALLE-93/ LALA-94	15-20	83%	94%	41%	61%
DCOG/HOVON	15-18	91%	98%	34%	69%
NOPHO92/ Swedish Group	15-18/15-20	90%	99%	39%	74%
ALL97/UKALL XII	15-17	94%	98%	49%	65%
CCG/CALGB	16-20	90%	90%	34%	63%
NOPHO/Finnish Group	10-16/16-25	97%	96%	60%	67%

FRALLE = French Acute Lymphoblastic Leukemia Group; LALA-94 = Leucemies Aigues Lymphoblastiques de l'Adulte-94; DCOG = Dutch Childhood Oncology Group; HOVON = Dutch Haemato-Oncology Association Studies; CALGB = Cancer and Leukemia Group B.
McNeer JL, et al. *Curr Opin Oncol*. 2012;24(5);487-494.

Treatment Allocation—Adult

The Best Management of Any Patient Is a Clinical Trial

Ph- ALL

- Age 15-39 or >65 years and no substantial comorbidities
  - Chemotherapy as in pediatrics
  - Allogeneic BMT if MRD+ or HR
- Aged >65 years or comorbidities
  - Multiagent chemotherapy
    - Dose reductions
  - Corticosteroids

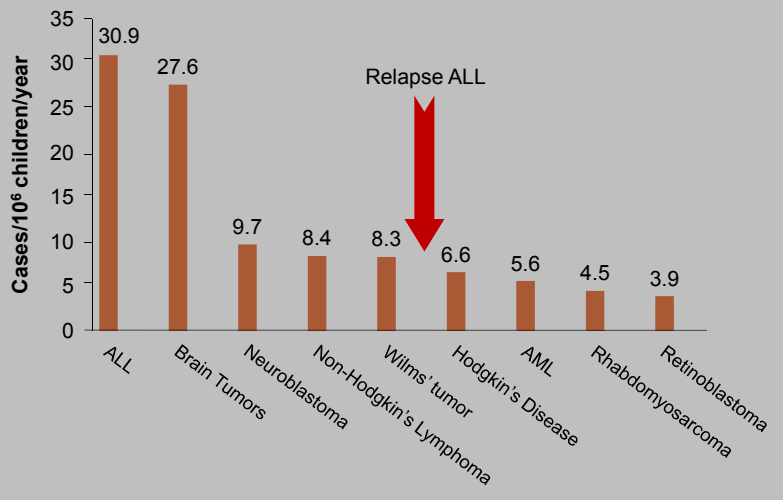
Ph+ ALL

- Aged 15-64 years, no comorbidities
  - Chemotherapy + TKI
  - Allogeneic BMT (donor)
- Aged >65 years or comorbidities
  - Corticosteroids + TKI

BMT = bone marrow transplantation.
NCCN Clinical Practice Guidelines in Oncology. http://www.nccn.org/professionals/physician_gls/pdf/all.pdf. Accessed January 4, 2013.

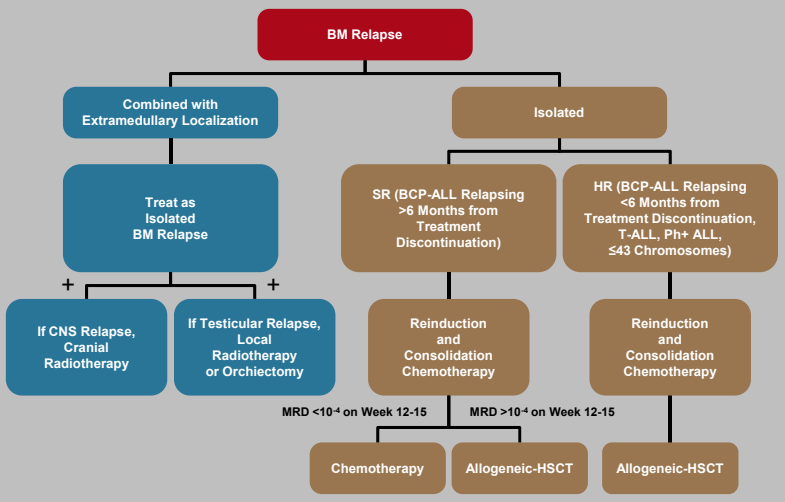
ALL Relapse and Its Affect on Patient Survival

Relapsed ALL is the 7th Most Common Childhood Malignancy



AML = acute myeloid leukemia.
Adapted from: Gaynon PS, et al. *Cancer.* 1998;82(7):1387-1395.

Algorithm for Treatment of BM Relapse ALL in Children



IEM = isolated extra-medullary relapse; HSCT = hematopoietic stem cell transplantation.
Locatelli F, et al. *Blood.* 2012;120(4):2807-2816.

Despite Successful Remission, Induction, and BMT, Most ALL Patients Who Relapse Die

CCG-1900 series trials—Survival after 1st Relapse

Site of Relapse (n)	5-Year Survival
Isolated BM(1123)	24%
Combined BM (264)	39%
Isolated CNS (409)	59%
Isolated testes (104)	58%
Average	35%

Nguyen K, et al. *Leukemia.* 2008;22(12):2142-2150.

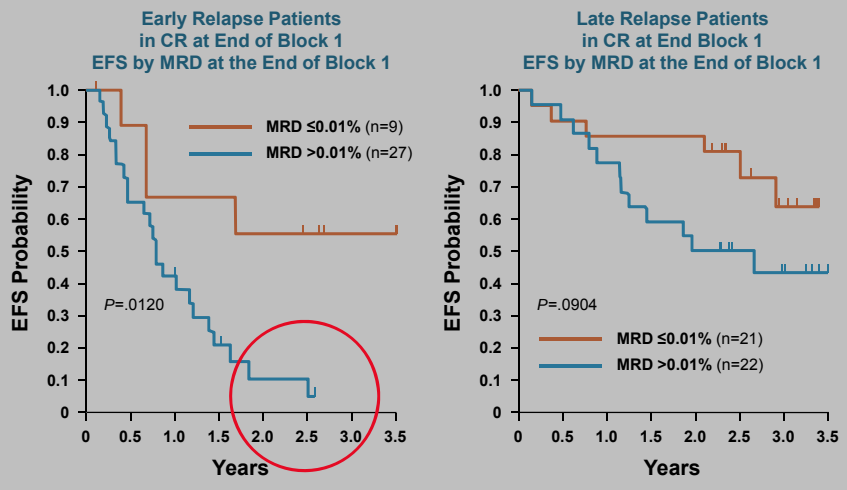
BM Relapse

		1983-1987 6-Year Survival N=3712, (n)	1988-2002 5-Year Survival N=9585, (n)
Very Early CR1 <18 months	Isolated	6% (233)	11% (412)
	Combined	6% (34)	12% (86)
Intermediate CR1 18-36 months	Isolated	11% (193)	18% (324)
	Combined	11% (26)	40% (54)
Late CR1 >36 months	Isolated	43% (215)	43% (387)
	Combined	49% (60)	60% (124)

No differences from 1989-1995 vs 1996-2002

Gaynon PS, et al. *Cancer*. 1998;82(7):1387-1395. Nguyen K, et al. *Leukemia*. 2008;22(12):2142-2150.

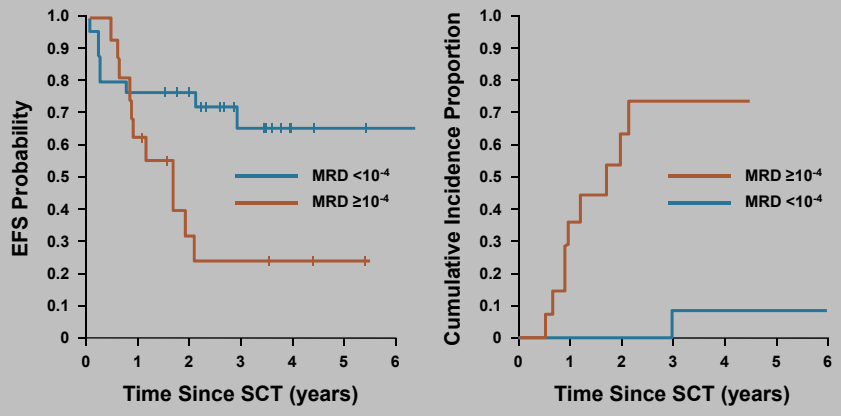
AALL01P2—First BM Relapse Outcomes in MRD Positive vs Negative



AALL01P2 = intensive induction therapy for children with ALL who experience a BM relapse.
Raetz EA, et al. *J Clin Oncol.* 2008;26(24):3971-3978.

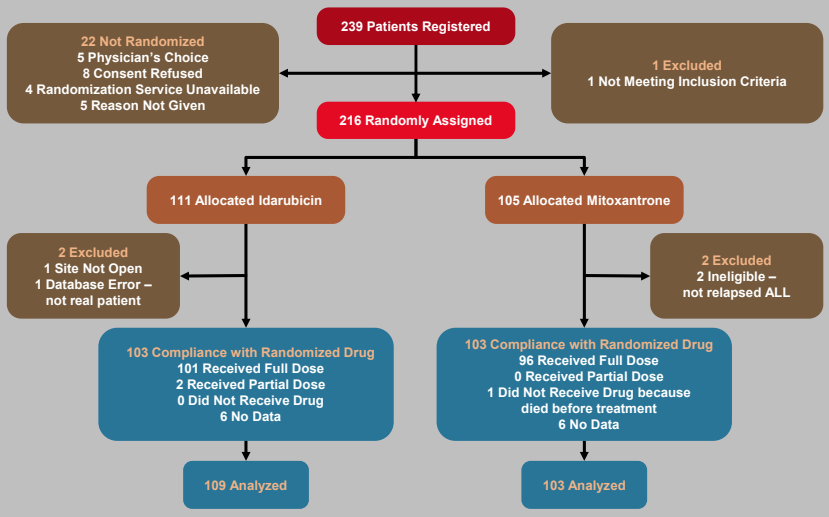
Pre-BMT MRD Predicts Post-BMT Relapse

EFS Probability and Cumulative Incidence of Subsequent Relapse in Intermediate-Risk Patients with ALL



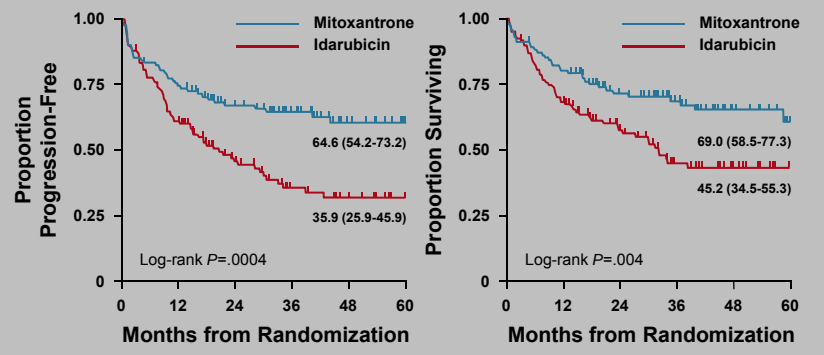
Bader P, et al. *J Clin Oncol.* 2008;27(3):377-384.

MRC R3: Mitoxantrone vs Idarubicin



Parker C, et al. *Lancet.* 2010;376(9757):2009-2017.

MRC R3: Mitoxantrone vs Idarubicin



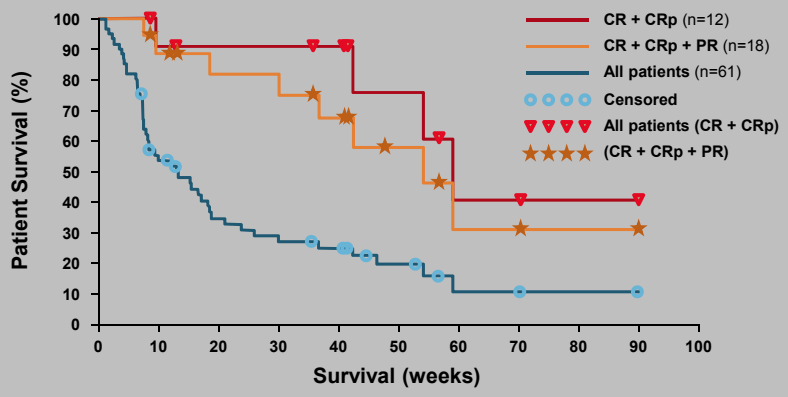
Number at Risk:						
Mitoxantrone	103	76	54	40	21	10
Idarubicin	109	66	36	20	13	5

103	82	58	43	23	10
109	74	46	27	16	6

No difference in reinduction rates or MRD

Parker C, et al. *Lancet.* 2010;376(9757):2009-2017.

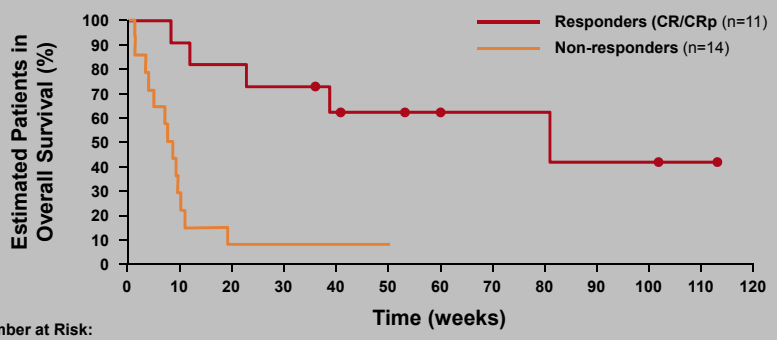
Clofarabine in Pediatric Patients with Refractory or Relapsed ALL



- An open label, multicenter study
- Pediatric patients with refractory or relapsed ALL received clofarabine 52 mg/m^2 IV daily for 5 days, every 2-6 weeks for up to 12 cycles

CRp = CR with incomplete platelet recovery; PR = partial response.
Jeha S, et al. J *Clin Oncol.* 2006;24(12):1917-1923.

Clofarabine, Etoposide, and CPM in Pediatric Patients with Refractory or Relapsed ALL



Number at Risk:												
Non-Responders	14	3	1	1	1	0	0	0	0	0	0	0
Responders	11	10	9	8	6	5	3	3	3	2	2	1

- Multicenter study
- Pediatric patients with refractory or relapsed ALL received clofarabine 40 mg/m^2, etoposide 100 mg/m^2, and CPM 440 mg/m^2 given daily for 5 days in induction and 4 consecutive days in consolidation

Hijiya N, et al. *Blood.* 2011;118(23):6043-6049.

Indications for Allogeneic BMT

Pediatrics

- 1st remission
  - Hypodiploidy?
  - Ph+?
  - Induction failure?
  - rMLL infants, <6 months-of-age and slow response?
  - MRD >0.1 after 3 months?
- Early marrow relapse
- Late marrow relapse
  - MRD positive at end induction/consolidation (~1 month/~3 months)

Adults

- 1st remission—medically fit
  - Aged <39 years
    - High WBC
    - Unfavorable cytogenetics
    - MRD positive
  - Aged 40-65 years—medically fit
- 2nd remission—medically fit

Oliansky DM, et al. *Biol Blood Marrow Transplant.* 2012;18(7):979-981. NCCN Clinical Practice Guidelines in Oncology. http://www.nccn.org/professionals/physician_gls/pdf/all.pdf. Accessed January 4, 2013.

Candidate Agents

Chemotherapy

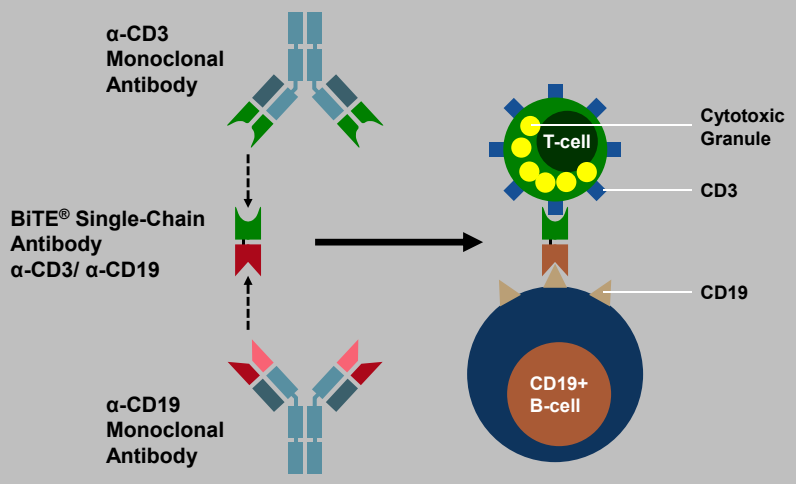
- Antipurines
  - Clofarabine, nelarabine
- Liposomal vincristine
- Flt3 inhibitors
  - Lestaurtinib*, quizartinib (AC220)*
- Proteosome inhibitors
  - Bortezomib, carfilzomib
- mToR inhibitors
  - Temsirolimus, evrolemus
- Aurora kinase inhibitors*
- BCL-2 inhibitors – obatoclax*
- Notch inhibitors
- Survivin inhibitors – EZN3042*
- Epigenetic strategies
  - Vorinostat/decitabine
- Toll-like receptor 9 agonists
- CXCR4 inhibitor – plerixafor

Immune directed therapies

- Monoclonals
  - Rituximab, Epratuzumab*
- Immunotoxins
- Moxetumomab*, SGN3419*, Inotuzomab ozogamicin*, SAR19a*, Combotox*
- Immune constructs
  - Blinatumomab*

***Investigational drug not currently FDA approved.**

Blinatumomab



Nagorsen D, et al. *Leuk Lymphoma.* 2009;50(6):886-891.

Toll-Like Receptors

- TLR are pattern recognition receptors
  - Part of our innate immunity
- Perhaps T-cells are capable of recognizing other leukemia-specific antigens
  - Support for a role of host immune responses in the maintenance of post-chemotherapy remission
  - Relapse ALL possesses changes consistent with evasion of immune effector mechanisms
- **CpG-oligodeoxynucleotide:** TLR agonist for MRD-positive leukemia

CpG = cytosine-phosphate-guanine.
Kanzler H, et al. *Nat Med*. 2007;13(5):552-559.

Another Approach: Chimeric Antigen Receptor

- Autologous chimeric antigen receptor
  - Extracellular domain derived from an antibody combined with the intracellular signaling domain of CD3
  - Allows tumor cells to be recognized in non-MHC manner
- 10 patients with CLL/ALL using CD19 as target
  - 4 CR
  - 2 PR in CLL

MHC = major histocompatibility complex; CLL = chronic lymphocytic leukemia.
Porter DL, et al. *N Engl J Med*. 2011;365(8):725-733. Porter DL, et al. Presented at: American Society of Hematology Annual Meeting; December 8-11, 2012; Atlanta, Georgia. Abstract 717.

The Right Stuff

The Right Drug

The Right Target

The Right Disease

The Right Context

The Right Schedule

The Right Dose

The Right Population

Gaynon P, et al. *Br J Haematol.* 2005;131(5):579-587.

Conclusions

- Substantial numbers of young people and adults are cured with current risk-adapted strategies
  - Various post-induction intensification schemes yield similar outcomes with similar prognostic factors
  - Allogeneic BMT remains important for adults
  - AVN in adolescents and TRM in adults
- Relapse remains the major barrier to cure
  - BMT is not the complete answer to the challenge of relapse
- Targeted therapy requires identification of 'molecularly' homogenous subpopulations

AVN = avascular necrosis; TRM = treatment-related mortality.

Translating Guidelines and Clinical Trial Data to Improved Acute Lymphoblastic Leukemia Management and Outcomes

Post-Activity Evaluation

To receive documentation of credit, please print and complete the evaluation and mail or fax it to NACCME

Location of Meeting _____ **Date of Meeting** _____

NACCME would appreciate your feedback on the quality and impact of this activity.
Please answer the following questions, some of which are rated on a 5-point Likert scale
(1 = strongly disagree/poor/very little; 5 = strongly agree/excellent/great deal).

1. **To what extent were you able to achieve each of the following learning objectives?**

Outline the current classification system for ALL and the differences in biology and treatment strategies between pediatric and adult patients with ALL	1	2	3	4	5
Review current evidence for induction, consolidation, maintenance, and transplant strategies in the treatment of ALL in pediatric and adult patients	1	2	3	4	5
Summarize current guideline recommendations for the treatment of both Ph–negative and Ph–positive ALL patients	1	2	3	4	5
Outline strategies for the treatment of patients with refractory or relapse ALL	1	2	3	4	5
Identify emerging treatments and the role of currently available targeted agents in the management of ALL	1	2	3	4	5

2. **Please rate the faculty in terms of their knowledge and expertise.** 1 2 3 4 5

3. **Please rate the faculty in terms of their teaching ability.** 1 2 3 4 5

4. **Please rate the following components relating to this activity:**

Content	1	2	3	4	5
Relevance to your practice	1	2	3	4	5
Educational format	1	2	3	4	5
Audience-participation portions (eg, Q&A, pre/post-testing)	1	2	3	4	5
Handouts and/or other materials supporting the activity	1	2	3	4	5
Overall	1	2	3	4	5

5. **How much did you learn as a result of this CE program?** 1 2 3 4 5

NACCME: 300 Rike Drive, Suite A, Millstone Township, NJ 08535; Phone: 609-371-1137; Fax: 609-371-2733

6. **Of the patients you see on a weekly basis, how many will benefit from the information you learned today?**

□ 10 or fewer □ 20 □ 30 □ 40 □ 50 or more

7. **Did this activity meet your educational needs?**

□ Yes □ No

8. **Did this activity increase your knowledge?**

□ Yes □ No

9. **Did this activity increase your competence?**

□ Yes □ No

10. **Did this activity increase your confidence?**

□ Yes □ No

11. **The therapeutic recommendations presented in this activity did not encourage inappropriate or excessive use of products/devices.**

□ Agree □ Disagree

12. **The information presented in this activity did not serve to advance a proprietary interest of any commercial entity.**

□ Agree □ Disagree

13. **How many patients with ALL do you impact on a weekly basis?**

□ 5 or fewer □ 10 □ 15 □ 20 □ 25 or more

14. **According to Nguyen et al, what is the average 5-year survival rate for children with ALL after a first relapse?**

a. Less than 25%
b. 25% to 50%
c. 51% to 75%
d. More than 75%

15. **How confident are you in your ability to optimize outcomes in children with ALL?**

a. Very confident
b. Confident
c. Somewhat confident
d. Not confident

16. **How do you rate your ability to appropriately treat patients with relapsed or refractory ALL?**

a. Excellent
b. Good
c. Fair
d. Poor

17. **How often do you intend to use novel chemotherapy for reinduction in children with more than 1 relapse of ALL?**

    a. Always
    b. Often
    c. Rarely
    d. Never

18. **Why do you plan to increase use of novel chemotherapy for reinduction in children with more than 1 relapse of ALL?**

    □ Because novel chemotherapy has demonstrated the potential to increase survival rates
    □ Because of challenges associated with treatment alternatives
    □ I do not intend to increase because I already adhere to this recommendation
    □ I do not intend to increase because I disagree with this approach
    □ I do not intend to increase because of barriers outside of my control

19. **Do you intend to make any changes to your practice?**

    □ Yes, please specify:_____

    _____

    _____

    □ No

20. **What barriers outside of your control prevent you from changing your practice and/or optimizing patient outcomes?** (check all that apply)

    □ Lack of available guidelines for ALL treatment
    □ Formulary placement
    □ Affordability concerns on the part of the patient or caregiver
    □ Patient adherence
    □ Lack of patient or caregiver education regarding disease/treatment
    □ Adverse effects of ALL therapies
    □ Lack of influence over treatment selection
    □ Other:_____

21. **How might future activities help you address those barriers?**

    _____

    _____

    _____

22. **Would you be interested in additional educational activities within this therapeutic area?**

- □ Yes – what topics would you like to learn more about?_____
- □ No

23. **In which of the following other therapeutic or practice areas do you have educational needs?** (check all that apply)

- □ Anemia
- □ Anesthesia
- □ Bacterial Infections
- □ Breast Cancer
- □ Colorectal Cancer
- □ Deep Vein Thrombosis
- □ Fungal Infections
- □ Hematologic Malignancies
- □ Hemostasis
- □ Law
- □ Lung Cancer
- □ Medication Errors/Safety
- □ Oncology Supportive Care
- □ Pain
- □ Prostate Cancer
- □ Psychiatry
- □ Transition of Care
- □ Transplant Medicine
- □ Other:_____

24. **In which of the following formats do you prefer to receive education?** (check all that apply)

- □ Live symposium
- □ Small-group meeting
- □ Phone teleconference
- □ Live web meeting
- □ On-demand web
- □ Handheld/mobile device
- □ Enduring print
- □ Other:_____

25. **How much time did you spend participating in this activity?**

_____

REQUEST FOR CREDIT
Please complete all sections to be eligible for credit and return to course registrar at the meeting site.

E-mail [REQUIRED] _____ **Degree** _____

Name _____ **Title/Specialty** _____

REQUIRED FOR PHARMACISTS: Date of Birth (MM/DD) _____ **NABP ID** _____

Address _____ **Affiliation** _____

City _____ **State** _____ **Zip** _____ **Phone**_____

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