ACUTE LYMPHOBLASTIC LEUKEMIA (ALL): DIAGNOSIS, TREATMENT AND SIDE EFFECTS MANAGEMENT

LEUKEMIA & LYMPHOMA SOCIETY

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LEARNING OBJECTIVES

- Describe the various types and subtypes of acute lymphoblastic leukemia (ALL)
- Identify tests used to diagnose disease and monitor treatment of ALL
- Explain the overarching goals of treatment for ALL
- Explain approved and emerging treatment options for ALL, including stem cell transplantation, and the role of clinical trials
- Describe strategies to manage treatment side effects as well as potential long-term and late effects of treatments for ALL
- Describe the healthcare professional's role in managing patients with ALL

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FACULTY

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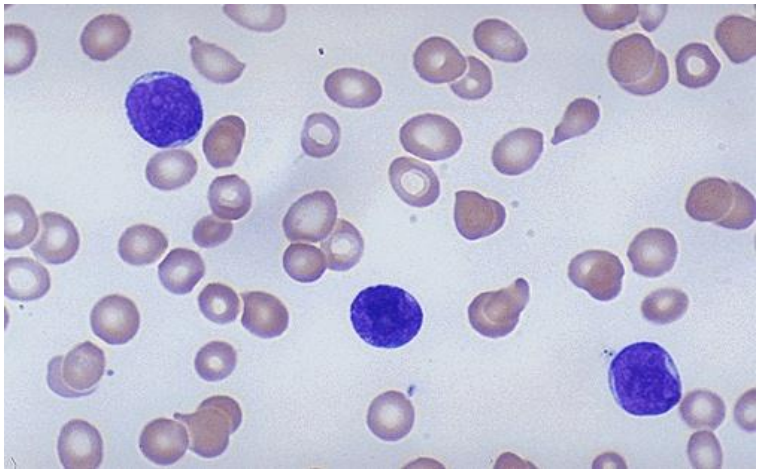
ALL Morphology



Clonal expansion of immature lymphoblasts

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EPIDEMIOLOGY

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Estimated Incidence of ALL in 2024

New Cases	6550
Deaths	1330

Age Group	5-year Overall Survival (OS)
Pediatric (< 18 yo)	89%
Adults and young adolescents (19-39 yo)	61%
Adults (40-60 yo)	40%
Elderly adults (> 60 yo)	20%

[1] American Cancer Society: Cancer Facts and Figures 2018. Last accessed October 23, 2018.

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ALL Statistics

	Incidence per 1,000,000 person-years
Peak age of 1-4 years	78.7
Nadir age of 40 – 59 years	8.1
Race	
Hispanic	24.9
Non-Hispanic White	16.6
Asian and Pacific Islanders	14.8
Black	10.2

Dores et al. *Blood* . 2012;119:34-43.

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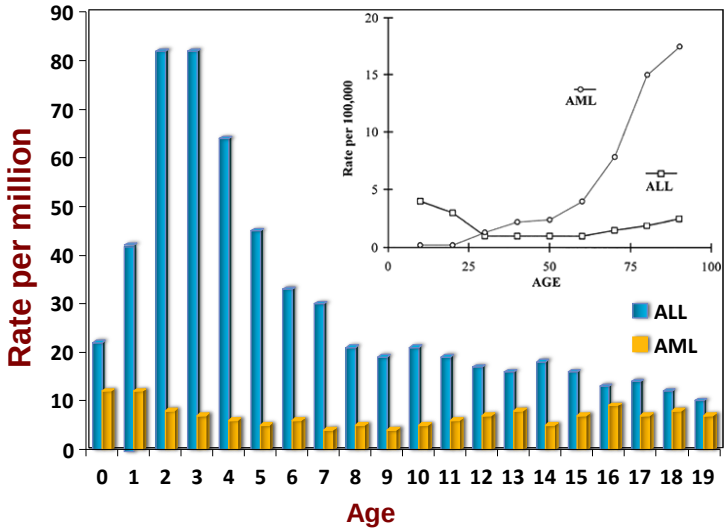
Age-Related Incidence of ALL



Dores et al. *Blood* . 2012;119:34-43.

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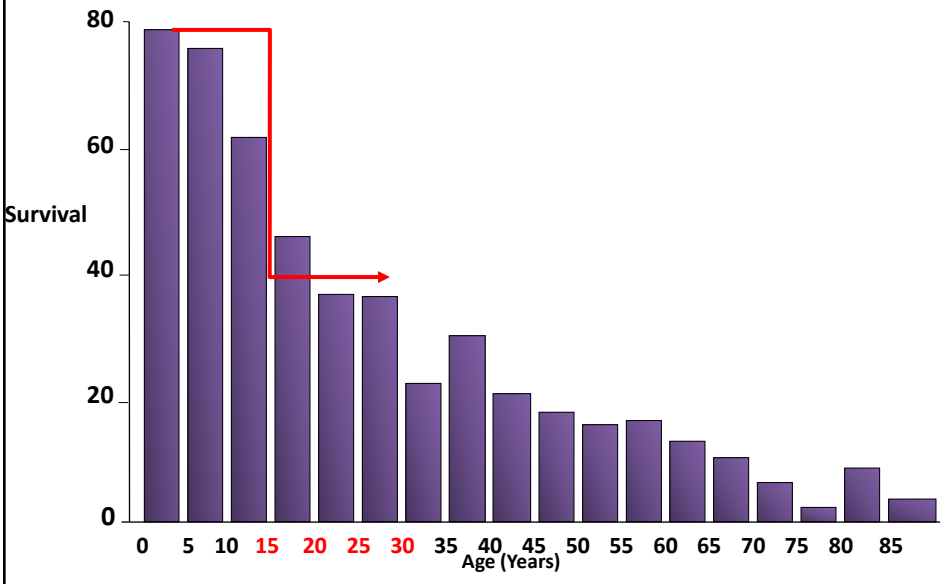
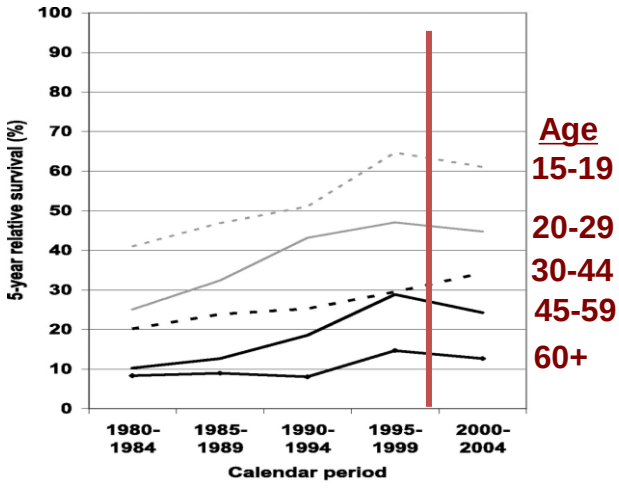
ALL 5-Year Survival



http://seer.cancer.gov/statfacts/html/alyl.html-see

9

5-Year Survival of ALL by Major Age Groups: 1980-1984 to 2000-2004



Pulte D et al. Blood 2009;113:1408-1411

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DIAGNOSIS

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WHO Classification 2008 Revisions

- **B lymphoblastic leukemia/lymphoma (L/L)**
  - B lymphoblastic L/L, NOS
  - B lymphoblastic L/L, recurrent genetic abnormalities
- **T lymphoblastic leukemia/lymphoma**

Vardiman et al. Blood. 2009;114:937.

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Diagnostic Work-Up

- Bone marrow biopsy with:
  - Cytogenetics
  - Flow Cytometry
  - FISH for major recurrent abnormalities
  - PCR testing for BCR-ABL if t(9;22) is suspected
- Lumbar puncture to assess CSF
  - Usually not done while circulating blasts are present
- Testicular exam
  - Especially in T-cell ALL

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Diagnosis

- Morphology
  - Wright-Giemsa-stained BM aspirate smears
  - H&E-stained core biopsy and clot sections
- Immunophenotype
  - Comprehensive flow cytometric immunophenotyping
- Cytogenetics
  - Karyotyping of G-banded metaphase chromosomes
- Molecular Characteristics
  - FISH for major recurrent genetic abnormalities
  - RT-PCR for fusion genes (ie, *BCR-ABL1*)

Terwiller,T. Blood Cancer J. 2017 Jun 30;7(6):e577.

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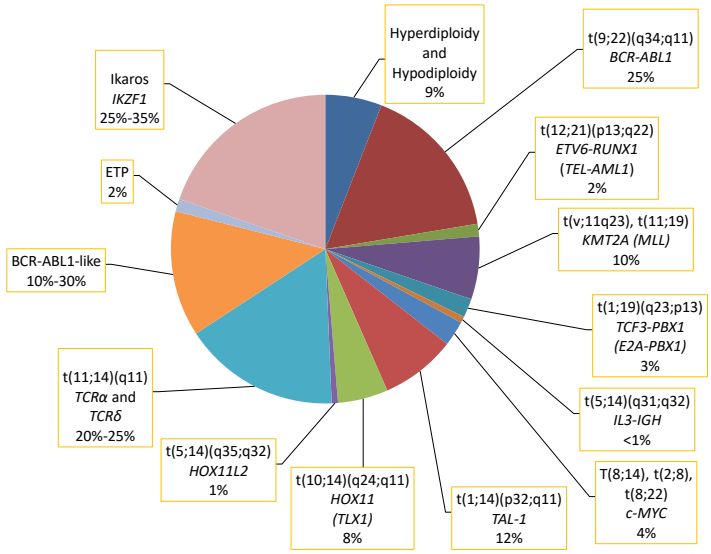
Cytogenetic Abnormalities Adult ALL



Roberts, K. Hematology, 2018 137-145

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Key Genetic Alterations in ALL

ALL subtype	Alterations/Mutations
T-lineage	PHF6, CNOT3, RPL5, RPL10, Notch/FBXW7
ETP	Loss of function (GATA3, IKZF1, RUNX1, ETV6) Gain of function (Ras, FLT-3, IL7R) Inactivating (EZH2, SUZ12, EED, SETD2, DNMT3A)
BCR-ABL1-like	Rearrangement CRLF2 in 50%; activating JAK mutations in 50% CRLF2r Rearrangement kinase genes ABL1, ABL2, EPOR, PDGFRB
Hypodiploid	Ras (NF1, PTPN11, NRAS, KRAS) IKZF2/IKZF2 TP53, commonly germline
Burkitt	TCF3/ID3 , CCND
Relapsed	CREBBP , NT5C2 enriched
Familial	TP53 low hypodiploid; PAX5 pGly193Ser in autosomal dominant
Ph+	IKZF1 deletion

Mullighan et al. *Blood*. 2013;122:3899.

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Cytogenetic Risk Groups

- Good risk (rare in adults)
  - Hyperdiploidy
    - 51-65 chromosomes
    - Trisomy of chromosomes 4, 10, 17
  - t(12;21)(p13;q22): *ETV6-RUNX1* (*TEL-AML1*)
- Poor risk
  - Hypodiploidy
    - <44 chromosomes
  - *KMT2A* rearranged (t[4;11] or others)
  - t(v;14q23)/IgH
  - t(9;22)(q34;q11.2): *BCR-ABL1* (defined as high risk in the pre-TKI era)
  - Complex karyotype (≥5 chromosomal abnormalities)
  - Ph-like ALL
  - Intrachromosomal amplification of chromosome 21 (iAMP21)

Roberts, K. Hematology, 2018 137-145.

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BCR-ABL1- Like ALL

- 10% –30% cases B-lymphoblastic leukemia
  - Associated with poor prognosis
  - Responsive to TKIs
- *IKZF1* alterations
  - IKAROS for lymphoid lineage development
- *CRLF2* rearrangements
  - Receptor for thymic stromal lymphopoietin
- JAK/STAT pathway
- Other alterations
  - *ABL1*, *ABL2*, *EPOR*, *JAK2*, *IL7R*, *PDGFRβ*, *EBF1*, *FLT2*,*NTRK3* and *SH2B3*

Pagliaro, L,et al. Nature Reviews Disease Primers 10, 41(2024).

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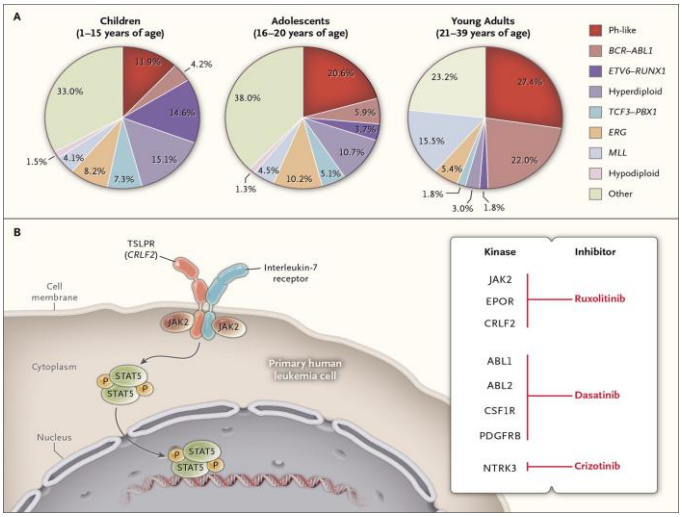
Actionable Genetic Lesions in Philadelphia Chromosome–like (Ph-like) Precursor B-Cell Acute Lymphoblastic Leukemia (ALL)



Graubert TA. N Engl J Med 2014;371:1064-1066.

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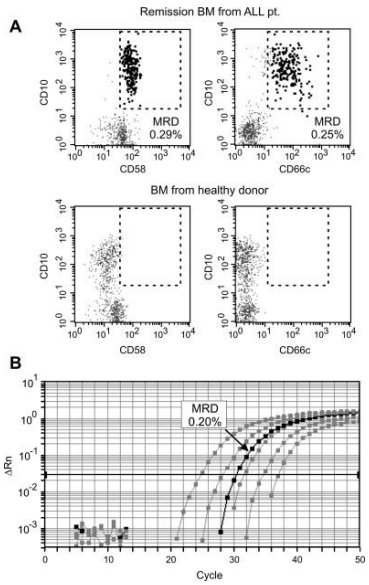
Minimal Residual Disease (MRD) in ALL

Two methods of MRD detection

1) **Flow cytometry**
   - Looks for ALL-specific immunophenotype or abnormal antigen expression

2) **PCR**
   - Looks for clonal rearrangement of immunoglobulin and T-cell receptor genes unique to the leukemic clone



Campana D. *Hematol Oncol Clin Am* 2009; 23:1083-98.

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RISK STRATIFICATION AND PROGNOSTIC FACTORS

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Adult ALL Risk Categories

Prognostic factors	Standard Risk	Adverse Risk
Age	≤ 35 years old	>60 years old
WBC at diagnosis	<30K	>100K
Immunophenotype	Precursor B-cell	Early/mature T-cell
Cytogenetics	---	t(9;22)/BCR-ABL1, t(4;11), Hypodiploid <44, t(1;19) Complex (≥ 3 abnormalities)
Mutations	---	IKZF1
Minimal residual disease after induction	<0.01%	≥ 1%
Time to CR1	≤ 4 weeks	> 4 weeks
Cycles to obtain CR	1 cycle	> 1 cycle

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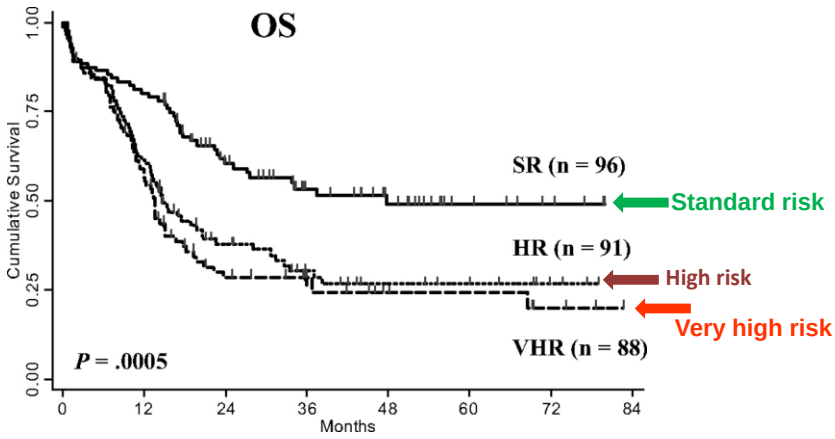
Overall Survival by Risk Class



Bassan R et al. *Blood* 2009;113:4153-4162©2009 by American Society of Hematology.

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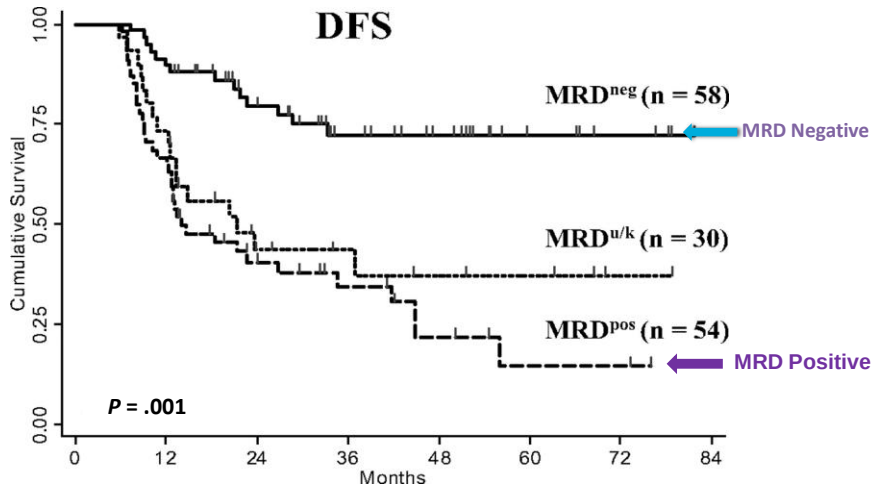
Disease-Free Survival According to MRD Status



Bassan R et al. *Blood* 2009;113:4153-4162©2009 by American Society of Hematology.

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Factors Affecting Treatment Decisions

- Age
- Comorbidities
  - Liver disease, transaminitis, or high bilirubin
  - Congestive heart failure
  - Neuropathy
- Immunophenotype and risk stratification
- BCR-ABL
- Time point and cutoff for minimal residual disease (MRD) will be dependent on the induction regimen used

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PRINCIPLES IN ADULT ALL THERAPY: FRONT-LINE THERAPY

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Adult ALL
No Clear Standard of Care

- Multiple chemotherapy regimens and no comparable trials
  - NCCN guidelines: clinical trial or pick your favorite
- Very wide age range
  - AYA 15-39 yrs.
  - Younger Adults 40-65yrs.
  - Older adults 65+
- Uncertainty about the role of alloHSCT
- Relapse/ refractory – ??? (bridge to alloHSCT)

Malard, F., Mohty, M.,Lancet 2020; 395: 1146–62

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CNS Prophylaxis in Adult ALL

- All ALL treatment regimens include CNS prophylaxis
- Regimens without cranial irradiation effective
- High-dose systemic therapy for low-risk disease
- Intrathecal MTX alone or alternating with ara-C effective
- Early IT therapy + high-dose systemic therapy effective for high-risk disease
- **Risk-oriented approach optimal**

Malard, F., Mohty, M., Lancet 2020; 395: 1146–62

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Role for Allogeneic Stem Cell Transplantation in ALL

- Allogeneic HSCT may be considered for:
  - High risk disease
    - Poor risk cytogenetics/molecular changes: Ph-like or Ph+ w/ IKZF1, ETP T-cell, MLL,KMT2A, tp53 and complex karyotype
    - High WBC at diagnosis
    - Central nervous system disease
  - Relapsed disease
  - Primary induction failure (delayed CR)
  - MRD positive disease after induction chemotherapy

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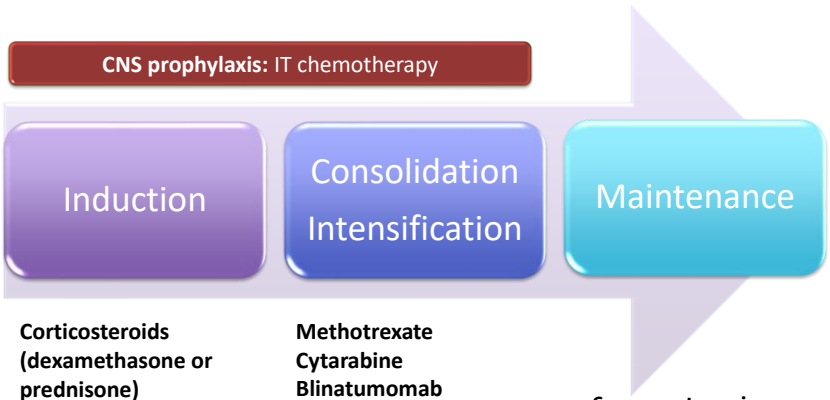
Principles of ALL Therapy



Malard, F., Mohty, M. Lancet 2020; 395: 1146–62

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Role of Oncology Pharmacist

Chemotherapy Selection
- Dose modifications (age, organ function, toxicities)
- Chemotherapy counseling

Medication Review
- Toxicity checks
- Drug interactions
- Dose adjustments

Supportive Care
- Side effect management
- Therapeutic drug monitoring
- Antibiotic recommendations

Discharge Preparation
- Prior authorization
- Discharge counseling

Holle LM, et al. Oncology pharmacists in health care delivery: vital members of the cancer care team. J Oncol Pract. 2014 May;10(3):e142-5.

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Pharmacological Considerations

- Vinca alkaloids
  - Vincristine
- Anthracyclines
  - Doxorubicin
  - Daunorubicin
- Topoisomerase 2 inhibitor
  - Etoposide
- Alkylating agents
  - Cyclophosphamide
- Tyrosine kinase inhibitors
  - Imatinib
  - Dasatinib
  - Nilotinib
  - Ponatinib
- Antimetabolites
  - Methotrexate
  - Cytarabine
  - Nelarabine
  - Mercaptopurine
  - Thioguanine
- Enzyme
  - Asparaginase (pegaspargase)
- Corticosteroids
  - Dexamethasone
  - Prednisone
- Monoclonal antibody
  - Rituximab
  - Inotuzumab ozogamicin
  - Blinatumomab

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ALL Therapy "Personalized Therapy"

Entity	Management
Burkitt	HCVAD-R x 8; ITx16; Rituximab+brief high-intensity chemo with filgrastim
Ph-positive ALL	HCVAD + TKI; TKI maintenance; allo SCT in CR1
T-ALL	HD CTX, HD ara-C, Asp; nelarabine?
CD20 – positive ALL	ALL chemo Rx+ rituximab
AYA	Pediatric-inspired therapy; HCVAD-R
MRD by FCM	Prognosis; need for allo SCT in CR1

Malard, F., Mohty, M. Lancet 2020; 395: 1146–62

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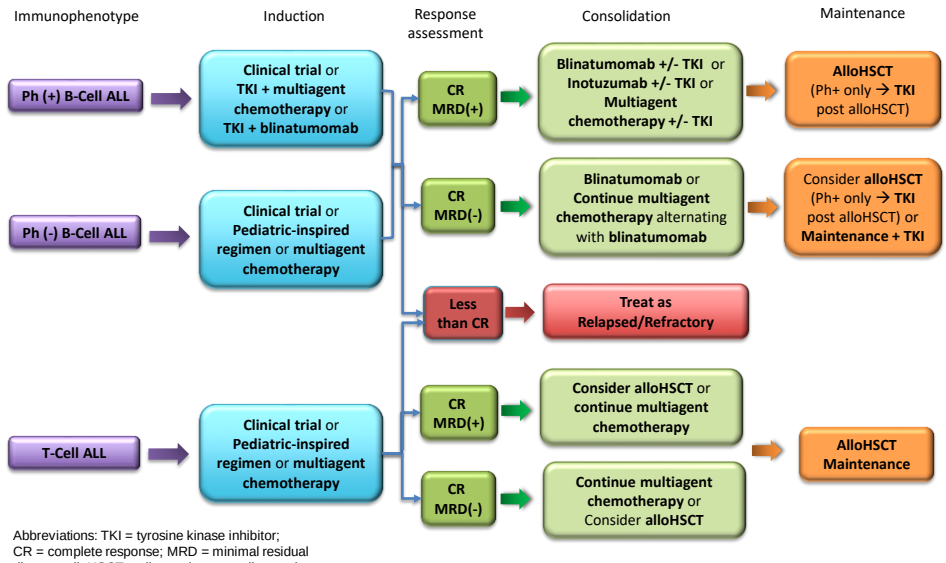
AYA (18-39 years old) Treatment Algorithm



Abbreviations: TKI = tyrosine kinase inhibitor; CR = complete response; MRD = minimal residual disease; alloHSCT = allogeneic stem cell transplant

Malard, F., Mohty, M. Lancet 2020; 395: 1146–62

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Adolescents & Young Adults with ALL

Country	Regimen	Age	No.	%CR	% 5-yr EFS
U.S.	CCG CALGB	16 – 21	196 103	96 93	64 38
France	FRALLE 93 LALA94	15 – 20	77 100	94 83	67 41
Holland	DGOG HVON	15 – 18	47 44	98 91	69 34
UK	ALL97 UKALLXII	15 – 17	61 67	98 94	65 49
Italy	AIEOP Gimema	14 – 18	150 95	94 89	80* 71*

***2-yr event-free survival (EFS)**

Stock et al. *Blood.* 2008;112:1646-54; Boissel et al. *J Clin Oncol.* 2003;21:774-80; de Bont et al. *Leukemia.* 2004;18:2032-2035; Testi et al. *Blood.* 2004;104:1954a; Ramanujachar et al. *Cancer.* 2006;48:254-61.

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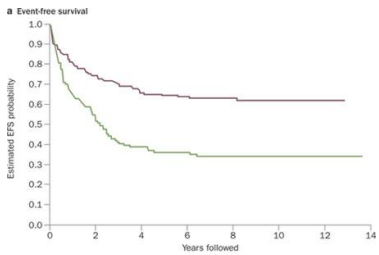
Comparison of EFS and OS CALGB or CCG

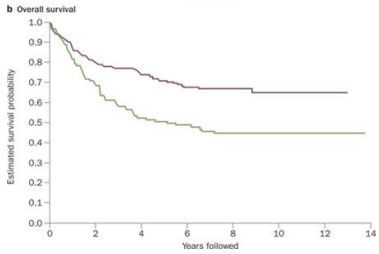
EFS



Peds at 7 yrs: 63%

Adult at 7 yrs: 34%

OS



Peds at 7 yrs: 67%

Adult at 7 yrs: 46%

Schafer E & Hunger S. *Nat.Rev.Clin.Oncol.* 2011.

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Why Do AYA Have a Better Outcome on Pediatric Protocols?

- Patients?
- Treatment team?
- Clinical trials?
- Treatment?

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Allogeneic Stem Cell Transplantation MRC/ECOG UKALLXII/E2993 Trial Ph- Negative ALL

	Overall survival		Relapse		Non relapse death	
	Donor	No donor	Donor	No donor	Donor	No donor
High risk	41%	35%	37%	63%	36%	14%
	NS		P<0.0005		P<0.05	
Standard risk	62%	52%	24%	49%	20%	7%
	P<0.02		P<0.05		P<0.05	

High risk any of : Age ≥ 35 years

WBC > 30,000/μL (*B Lineage*)

> 100,000/μL (*T Lineage*)

Time to CR > 4 weeks

Goldstone *Blood*. 2008;111:1827.

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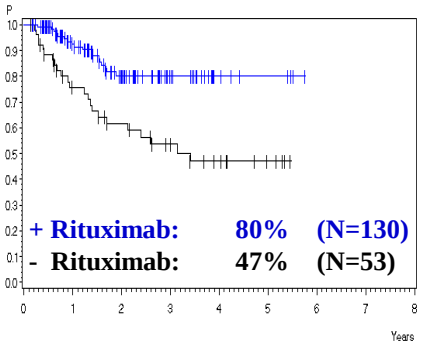
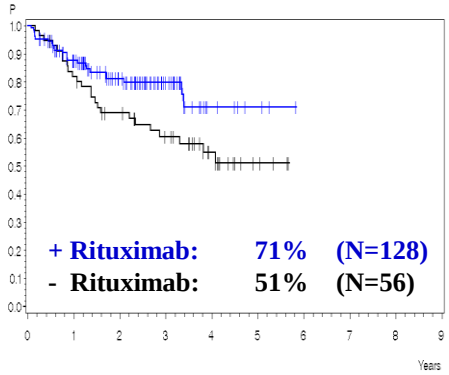
Remission Duration and Overall Survival CD20 pos. Standard Risk < 55 yrs

GMALL 07/2003

Remission Duration



Overall Survival



Hoelzer. 2010.

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Childhood vs Adult ALL: Disease Biology

	Children	Adults
Peak incidence	5 years of age	50 years of age
% of all leukemias	80-85%	5%
T cell	10-15%	20-25%
Mature B cell	1-2%	3-5%
Ph positive ALL	3%	20-30%

Sallan SE, et al. *Haematology* 2006; 128-132.

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Asparaginase Intensification Pediatric and Pediatric-"Inspired" Regimens

	Asparaginase	Upper age	OS @ 3-7 yrs.
True Pediatric			
DFCI[1]	E. Coli	50	74%
CALGB 10403	Pegaspargase 2,5000	39	73%
Pediatric "Inspired"			
PETHEMA[2]	E. Coli	30	69%
GRAALL-2003 [3]	E. Coli	45/60	64%/47%
USC[4]	Pegaspargase 2,000	57	58%
Princess Margaret[5]	E. Coli (retrospective)	60	65%
Asparaginase Intensification			
GMALL 7/03[6]	PEG 500/1000 → 2,000	55	67%

[1]DeAngelo ASH 2007; [2]Ribera JCO 2008; Abst # 587; [3]Huguet JCO 2009. [4]Douer ASH 2012 abstract # 1495; Storring J, [5]Br J Haematol. 2009 [6]Goekbuget ASH 2010 Abstract # 404.

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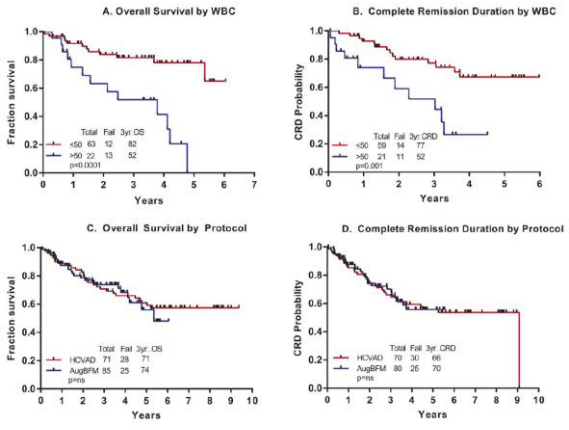
Augmented Berlin-Frankfurt-Münster Therapy in Adolescents and Young Adults With Acute Lymphoblastic Leukemia

- **Objective**: Compare ABFM and hyper-CVAD treatment in AYA patients
  - 85 patients (ages 12-40) with Ph-negative ALL received ABFM regimen
  - 71 historic AYA patients with ALL who received hyper-CVAD regimen
- Patient and disease characteristics, as well as MRD status, were analyzed for their impact on outcomes



Cancer. 2014 Dec 1; 120(23): 3660–3668. Published online 2014 Jul 17.

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Augmented Berlin-Frankfurt-Münster Therapy in Adolescents and Young Adults With Acute Lymphoblastic Leukemia

- ABFM tolerable in AYA patients with ALL, but not associated with significant improvements in CRD or OS
- Shift to pediatric-based therapy for AYA patients with ALL (notably those ≥ 21 years) may need further assessment
- The toxicity profiles between the two groups differed significantly
- High WBC count at baseline remained an independent predictor of OS in multivariate analysis

Cancer. 2014 Dec 1; 120(23): 3660–3668. Published online 2014 Jul 17.

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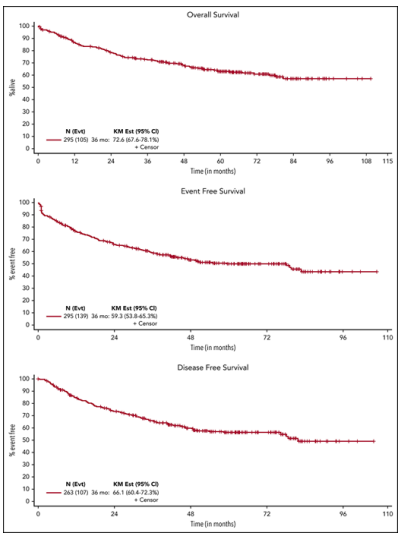
CALGB 10403 "Pediatric Inspired" Regimen

- Objective: assess feasibility and safety of pediatric-inspired regimen in older adolescents and young adults (AYA)
- Median age: 24 years (range: 17-39)
  - B-cell (Ph+ excluded): 76%
  - T-cell: 24%
  - CNS disease: 11%
- Results (n = 295):
  - Median OS: not reached
  - Estimated 3-year OS: 73% (95% CI 68-78%)
  - Median EFS: 78 months
  - Median DFS: 36 months
  - Bone marrow response after induction: 89%
  - Pretreatment factors associated with worse treatment outcomes: obesity, Ph-like disease



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CALGB 10403

Remission Induction (Course I)
- **Allopurinol** –300 mg/day (unless allergic), to continue until peripheral blasts and extramedullary disease are reduced
- **IT-Ara-C** – Ara-C 70 mg IT on D 1.
- **Pred** –60 mg/m^2/day PO or IV in two divided doses on D 1-28
- **VCR** –1.5 mg/m^2 (maximum dose 2 mg) IV on D 1, 8, 15, and 22
- **DNR** –25 mg/m^2 IV on D 1, 8, 15, and 22
- **PEG** –2500 IU/m^2 IM or IV D 4
- **IT-MTX** - 15 mg IT on D 8 and D 29 (also administered on D 15 and 22 for patients with CNS3)

Extended Remission Induction (if required)(Course IA)
- **Pred** –60 mg/m^2/day PO or IV (methylprednisolone) in two divided doses on D 1-14
- **DNR** –25 mg/m^2 IV on D 1
- **VCR** – Vincristine 1.5 mg/m^2 (maximum 2 mg) IV on D 1 and 8
- **PEG** –2500 IU/m^2 IM or IV D 4

Remission Consolidation (Course II)
- **CTX** –1000 mg/m^2 IV on D 1 and 29
- **Ara-C** –75 mg/m^2 IV or SC on D 1-4, 8-11, 29-32, and 36-39
- **6-MP** –60 mg/m^2 PO on D 1-14 and 29-42
- **VCR** –1.5 mg/m^2 (maximum 2 mg) IV on D 15, 22, 43, and 50
- **PEG** –2500 IU/m^2 IM or IV on D 15 and 43
- **IT-MTX** -- 15 mg IT on D 1, 8, 15, and 22 (omit doses on D 15 and 22 for patients with CNS3)

Interim Maintenance (Course III)
- **IV-MTX** –starting dose 100 mg/m^2 IV (escalate by 50 mg/m^2 /dose on D 1, 11, 21, 31, and 41
- **VCR** – 1.5 mg/m^2 (maximum dose 2 mg) IV on D 1, 11, 21, 31, and 41
- **PEG** –2500 IU/m^2 IM or IV on D 2 and 22
- **IT-MTX** - 15 mg IT on D 1 and 31

Delayed Intensification (Course IV)
- **VCR** – 1.5 mg/m^2 (maximum dose 2 mg) IV on D 1, 8, 15, 43, and 50
- **DEX** – 10 mg/m^2 PO (or IV) divided BID on D 1-7 and 15-21
- **DOX**- 25 mg/m^2 IV on D 1, 8, and 15
- **PEG** – 2500 IU/m^2 IM or IV on D 4 (or D 5 or D 6) and D 43
- **CTX** – 1000 mg/m^2 IV on D 29
- **Ara-C** – 75 mg/m^2 IV or SC on D 29-32 and 36-39
- **6-TG** – 60 mg/m^2/day PO on D 29-42
- **IT-MTX** -- 15 mg IT on D 1, 29, and 36

Maintenance (Course V)*
- **VCR**–1.5 mg/m^2 (maximum dose 2 mg) IV on D 1, 29, and 57
- **DEX**– 6 mg/m^2/day PO (or IV) in 2 divided doses every 4 weeks on D 1-5, 29-33, and 57-61
- **6-MP**– 75mg/m^2/day PO on D 1-84
- **IT-MTX** -- 15 mg IT on D 1(also is given on D 29 of the first 4 courses of maintenance)
- **PO-MTX** – 20 mg/m^2 PO weekly on D 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78 (held on D 29 of the first 4 courses of maintenance when IT-MTX is given)

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Asparaginase

- Mechanism of action:
  - Acts by hydrolyzing serum asparagine, inhibiting protein synthesis through amino acid depletion. Normal cells can synthesize their own asparagine and therefore are spared the cytotoxic effects.
- Dosing & Administration:
  - Given either intravenously (preferred) or intramuscularly

Medication	Bacterial Origin	Dosing & Frequency	Half-Life
Pegaspargase (Oncospar®)	E. Coli	≤ 21 yo: 2500 units/m2 > 21 yo: 2000 units/m2 ~ every 2 weeks or per protocol	5.5-7 days
Calaspargase (Asparlas®)	E. Coli	2500 units/m2 ~ every 3 weeks or per protocol	16 days
Erwinia recombinant asparaginase (Rylaze®)	Pseudomonas fluorescence engineered Erwinia chrysanthemi	25 mg/m2 q48 hours OR 25 mg/m2 Mon & Wed, and 50 mg/m2 Fri	16 hours

Oncospar (pegaspargase) [package insert]. Boston, MA: Servier; November 2021.
Asparlas (calpaspargase pegol-mkhl) [prescribing information]. Boston, MA: Servier; December 2021.
Erwinaze (asparaginase) [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals; March 2016.

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Asparaginase Toxicities & Monitoring

- Hypersensitivity reactions
  - Infusion reactions vs anaphylaxis
  - Silent antibodies
- Hepatotoxicity: AST, ALT, bilirubin
- Pancreatitis: amylase, lipase, triglycerides
- Coagulopathy (venous thromboembolic events > bleeding): platelets
- Myelosuppression: CBC
- Minimal nausea/vomiting, diarrhea
- Glucose intolerance: blood glucose, A1c
- Fatigue and malaise

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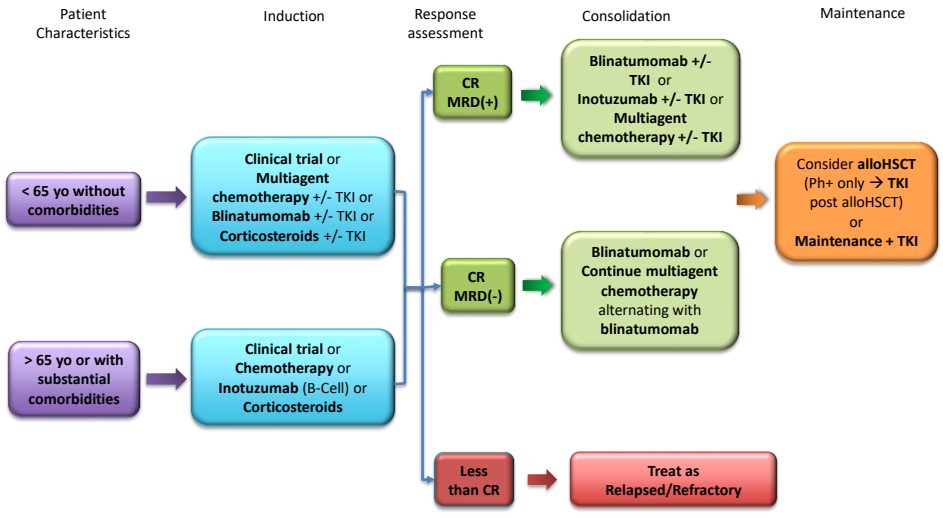
Adults (40+ years old) Treatment Algorithm



Abbreviations: TKI = tyrosine kinase inhibitor; CR = complete response; MRD = minimal residual disease; alloHSCT = allogeneic stem cell transplant

Malard, F., Mohty, M. Lancet 2020; 395: 1146–62

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ALL Induction Regimen Examples

Regimen (NCCN Guidelines 2024)	Ph (+) B-ALL	Ph (-) B-ALL	T-Cell	AYA (High Intensity)	Adults (Moderate-High Intensity)	Elderly (Low Intensity)
TKI + Blinatumomab	X (+ TKI)			X	X	X
CALGB 10701	X (+ TKI)			X	X	X
Dose-adjusted HyperCVAD	X (+ TKI)	X	X	X	X	X ("mini")
EsPhALL	X (+ TKI)			X		
Corticosteroid +/- vincristine	X (+ TKI)	X	X	X	X	X
EWALL	X (+ TKI)	X				X
CALGB 10403		X	X	X		
DFCI ALL (based on 00-01)		X	X	X		
PETHEMA-ALL		X	X	X		
Dose-adjusted CALGB 8811 Larson		X	X		X	
Inotuzumab ozogamicin + miniCVD		X			X	X
MRC UKALLXII/ECOG 2993		X	X		X	
ECOG 1910		X		X	X	X
GRAALL-2005		X	X	X	X	
USC/MSKCC ALL (CCG-1882 based)		X	X	X	X	
Linker 4-drug regimen		X	X	X	X	
AALOLD07		X	X			X
GMAALL		X	X			X
DFCI 91-01		X	X			X
CALGB 9111		X	X			X
COG AALL 0434			X	X		

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Comparison of Standard Adult Ph- ALL Regimens

Table 3. Acute Lymphoblastic Leukemia Induction Regimens

Regimen	Induction	Consolidation	Maintenance	CR Rate, %	5-Year DFS Rate, %
LALA-94; Thomas & Fiere 2008[51]	P, V, C, D, or Ida	Ara-C, MTZ, or C, Ara-C, 6-MP based on risk	HSCT or MTX/6-MP or additional chemotherapy based on risk	84	30
Hyper-CVAD; Kantarjian 2004[40]	Hyper C, V, A, and D alternating with MD MTX and Ara-C × 8 cycles	See induction	Allo HSCT or 6-MP, V, MTX, P	92	38
UCSF 8707; Linker 2002[52]	P, V, D, and L-Asp	V, P, D, A, Ara-C, VM-26, MTX	6-MP, MTX	93	52
GMALL 05/93; Gokbuget & Hoelzer 2009[49]	Induction 1: P, V, D, MTX, L-Asp; Induction 2: C, Ara-C, 6-MP	HD Ara-C, MTZ, HD MTX, L-Asp, 6-MP	6-MP, MTX	83	35-40
CALGB 8811; Larson 1995[48]	P, V, C, D, L-Asp	C, subq Ara-C, 6-MP, V, L-Asp	6-MP, MTX	85	39 (Ages 30-59 y); 69% (aged <30 y)[a]

Faderl et al, Cancer 2010.

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HyperCVAD Schema

A	B	A	B	A	B	A	B

A (Odd Cycles): 1, 3, 5, 7

Chemotherapy Agent	Day 1	2	3	4	5	6	7	8	9	10	11	12	13	14	…21 or 28
Cyclophosphamide IV	xx	xx	xx												
Vincristine IV				X							x				
Doxorubicin IV				X											
Dexamethasone PO or IV	x	x	x	x							x	x	x	x	
Intrathecal (IT) chemotherapy during lumbar puncture		x													
Filgrastim daily SQ injection (alternative: pegfilgrastim x1)					x	x	x	x	x	x	x	x	x	x	x

B (Even Cycles): 2, 4, 6, 8

Chemotherapy Agent	Day 1	2	3	4	5	6	7	8	9	10	11	12	13	14	…21 or 28
Methotrexate IV	x														
Cytarabine IV		xx	xx												
Intrathecal (IT) chemotherapy during lumbar puncture		x													
Filgrastim daily SQ injection (alternative: pegfilgrastim x1)					x	x	x	x	x	x	x	x	x	x	x

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Corticosteroids

- Agents: prednisone, dexamethasone
- Destroys leukemia cells, alleviates symptoms, and prevents chemotherapy-induced nausea and vomiting
- Side effects:
  - Short term: hyperglycemia, hypertension, heart burn/acid reflux, insomnia
  - Long term: mood changes, osteoporosis, joint necrosis

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Vincristine

- Mechanism of action:
  - Binds to tubulin and inhibits microtubule and mitotic spindle formation; causes cell cycle arrest between M and S phases
- Dosing and Administration:
  - Weight based (1.4-1.5 mg/m2) or flat dose 2 mg IV infusion over 5-10 minutes (number of doses depend on protocol)
  - Should NEVER be given intrathecally (can cause paralysis and death)
  - Avoid administration on the same day/time as other intrathecal medications
- Drug interactions:
  - Major CYP3A4 substrate: Avoid administration of strong or moderate CYP3A4 inhibitors or inducers
- Toxicities:
  - Gastrointestinal (constipation, paralytic ileus, intestinal perforation)
  - Neurotoxicity, peripheral neuropathy
  - Extravasation
  - Loss of appetite/weight loss

Vincristine sulfate [package insert]. Lake Forest, IL: Hospira Inc; March 2013.

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Vincristine Neurotoxicity

- Neuropathies are a common occurrence with vinca-alkaloid therapy
  - Dose-dependent and dose-limiting with vincristine
    - Most protocols cap dose at 2 mg
    - May require dose reductions or discontinuation for severe toxicities
    - Use caution in patients with pre-existing neuromuscular disease and/or with concomitant neurotoxic agents
  - Sensory: paresthesia, numbness, impaired touch sensitivity or temperature recognition, neuropathic pain, jaw pain
    - Peripheral neuropathy can also be treated with other medications (e.g. gabapentin, pregabalin, duloxetine)
  - Motor: extremity weakness, walking difficulties, impaired balance, deteriorated reflexes and fine motor abilities, muscle cramps
  - Autonomic: constipation, paralytic ileus, incontinence, urinary retention, orthostatic hypotension
    - Constipation caused by hypomotility of gut and injury of myenteric neurons in colon
      - All patients should be given a prophylactic bowel regimen (e.g. polyethylene glycol, senna) and stay well hydrated
      - Avoid other constipating medications when possible
      - For persistent constipation, other laxatives and rarely enemas are used

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Daunorubicin & Doxorubicin

- Mechanism of action:
  - Anthracyclines that inhibit DNA replication and induce DNA strand breakage through several mechanisms including intercalation of DNA strands, inhibition of DNA polymerase, and topoisomerase II inhibition
- Dosing / Administration:
  - IV push over ≤ 15 minutes or IV infusion over 15-30 minutes
- Common toxicities:
  - Myelosuppression
  - Gastrointestinal (nausea, vomiting, diarrhea, mucositis)
  - Extravasation
  - Red/orange discoloration of body fluids
  - Alopecia
  - Cardiotoxicity

Daunorubicin [package insert]. Bedford, OH: Bedford Laboratories; June 2013.
Idarubicin [package insert]. Schaumburg, IL: APP Pharmaceuticals, LLC; December 2008.

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Anthracycline Cardiotoxicity

- Increased reactive oxygen species formation and targeting of topoisomerase 2 in cardiomyocytes; can be acute (rare) or chronic (more common)
  - Risk factors: cumulative anthracycline dose, history of cardiovascular (CV) disease, reduced LVEF, radiation, age, CV risk factors (smoking, hypertension, diabetes, hyperlipidemia, obesity)
- All patients should have an echocardiogram prior to anthracycline administration to confirm adequate left ventricular heart function (LVEF)
  - Caution in patients with LVEF ≤45% or those with ≥10-15% drop from baseline
- Several cardiotoxicity prevention and treatment strategies have been studied:
  - Cumulative lifetime anthracycline monitoring
  - Continuous or extended infusion, dose fractionation
  - Dexrazoxane administration (can also be used for extravasation)

Drug	Maximum Lifetime Dose
Daunorubicin	550 mg/m^2
Doxorubicin	450-550 mg/m^2
Epirubicin	900 mg/m^2
Idarubicin	150 mg/m^2
Mitoxantrone	140 mg/m^2

Volkova M, et al. Anthracycline Cardiotoxicity: Prevalence, Pathogenesis, and Treatment. *Curr Cardiol Rev*. 2011;7(4):214-20.
Bubalo J, et al. Anthracycline-Induced Cardiotoxicity in Adults. *JHOP*. 2018.

56

BCR-ABL1 Tyrosine Kinase Inhibitors

	Imatinib (Gleevec®)	Dasatinib (Sprycel®)	Nilotinib (Tasigna®)	Ponatinib (Iclusig®)
Generation	1st	2nd	2nd	3rd
Dosing	400 mg once daily	100 mg once daily	400 mg twice daily	30-45 mg once daily
Strength	100 & 400 mg tablets	20, 50, 70, 80, 100, & 140 mg tablets	50, 150, & 200 mg capsules	10, 15, 30, & 45 mg tablets
Administration	With or without food	With or without food	Empty stomach (-2/+1 hours)	With or without food
Side effects	Fluid retention Pleural or pericardial effusions GI upset Muscle cramps Rash	Fluid retention Pleural or pericardial effusions Myelosuppression GI upset Rash Rare: pulmonary arterial hypertension	Qtc prolongation Hepatotoxicity Hyperglycemia Pancreatitis Myelosuppression Rash Rare: peripheral arterial occlusive disease	Arterial occlusive events or venous thromboembolic events Hepatotoxicity Pancreatitis Rash Hypertension Fluid retention Cardiac arrhythmias Hemorrhage Rare: heart failure

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BCR-ABL1 Tyrosine Kinase Inhibitors Drug Interactions

- Review all prescription, over-the-counter, herbals, and supplements with the pharmacist to check for drug-interactions!

Medication	Imatinib (Gleevec®)	Dasatinib (Sprycel®)	Nilotinib (Tasigna®)	Ponatinib (Iclusig®)
Proton Pump Inhibitors (PPI) [e.g. pantoprazole, omeprazole]	✓	✗	✗	✓
Histamine 2 Receptor Antagonists (H2RAs) [e.g. famotidine, ranitidine]	✓	Take once daily 2 hours AFTER TKI	Take once daily 2 hours AFTER TKI	✓
Antacids	✓	Take +/- 2 hours from TKI	Take +/- 2 hours from TKI	✓
Fluoxetine, bupropion, citalopram	Qtc monitoring	Qtc monitoring	✗	Qtc monitoring
Amiodarone, diltiazem, verapamil	Consider alternative	Consider alternative	✗	Consider alternative
Azole antifungals [e.g. fluconazole, voriconazole, posaconazole]	Monitor, dose adjust, or consider alternative	Monitor, dose adjust, or consider alternative	Monitor, dose adjust, or consider alternative	Monitor, dose adjust, or consider alternative
Fluoroquinolones	✓	Qtc monitoring	Use with caution	✓

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Chemotherapy-Free Regimen to Treat Ph+ ALL

- Phase 2 single-group trial of chemotherapy free regimen to treat Ph+ B-ALL consisting of dasatinib plus glucocorticoids followed by two cycles of blinatumomab.
- The primary endpoint of the trial was sustained molecular response in the bone marrow after treatment.
- Strategy was based on using a targeted and immunotherapeutic strategy to improve outcome and reduce toxicity of treatment.

Foa et al, Dasatinib-Blinatumomab for Ph-Positive ALL in Adults, NEJM OCT 20,(383)17, 1613.

59

Clinical Characteristics

- 63 patients
- Median age 54, range 24-82
- Male 29, female 34
- Wbc median 13,000, range 600-88,000
- Fusion protein p190--41, p210--17, p190 and p 210--5

Foa et al, Dasatinib-Blinatumomab for Ph-Positive ALL in Adults, NEJM OCT 20,(383)17, 1613.

60

Results

- Complete Remission 98%
- 29% had a molecular response, percentage increased to 60% after the second cycle of treatment with blinatumomab
- Percentage of patients with molecular response further increased after additional cycle of blinatumomab
- Median follow up at 18 months, OS 95% and DFS 88%
- DFS was lower among patients with an IKZF1 deletion plus additional genetic aberrations. ABL1 mutations were detected in 6 patients who had increased MRD during induction

Foa et al, Dasatinib-Blinatumomab for Ph-Positive ALL in Adults, NEJM OCT 20,(383)17, 1613.

61

Results

- Those with ABL kinase mutations had clearance of disease blinatumomab
- Six relapses occurred
- 21 events grade 3 or higher were recorded
- 24 patients received a stem cell allograft, and 1 death was related to transplantation
- Regimen effective with high rate of molecular response and survival and few adverse events grade 3 or higher
- May become the standard of care for Ph+ B-ALL

Foa et al, Dasatinib-Blinatumomab for Ph-Positive ALL in Adults, NEJM OCT 20,(383)17, 1613.

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CONSOLIDATION

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Methotrexate

- Mechanism of action:
  - Folate antimetabolite that interferes with DNA synthesis, repair, and replication by irreversibly binding to and inhibiting dihydrofolate reductase
- Dosing and Administration:
  - Varies based on protocol (IV bolus, IV continuous infusion, or oral tablets)
  - Renal excretion
- Common toxicities:
  - Nephrotoxicity (acute kidney injury, usually reversible)
  - Gastrointestinal (nausea/vomiting, diarrhea, stomatitis)
  - Hepatotoxicity
  - Myelosuppression
  - Dermatological reactions
  - Neurotoxicity

Methotrexate [package insert]. Lake Zurich, IL: Fresenius Kabi; June 2015.

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High Dose Methotrexate (HD-MTX)

- Delayed clearance of HD-MTX (≥1,000 mg/m^2) is associated with several toxicities including acute nephrotoxicity, hepatotoxicity, and neurotoxicity
- Strategies to efficiently clear HD-MTX and reduce the risk of toxicity should be employed
  - Temporarily stop medications that interact with HD-MTX
    - Sulfa drugs (trimethoprim/sulfamethoxazole)
    - Proton pump inhibitors (pantoprazole, omeprazole, esomeprazole)
    - Penicillins (piperacillin/tazobactam, amoxicillin, ampicillin)
    - NSAIDs (aspirin, naproxen)
    - Others: Vitamin C, probenecid, tetracyclines
  - Hydration and urine alkalinization with continuous IV sodium bicarbonate + D5W
    - Increases HD-MTX solubility and reduces crystal formation
    - Maintain urine output > 100 ml/hr and urine pH > 7
    - May also receive oral sodium bicarbonate and/or acetazolamide
  - Therapeutic drug monitoring
    - Antidote (marked delayed HD-MTX clearance + impaired renal function): glucarpidase
  - Administer leucovorin 24-36 hours after starting HD-MTX, and continue until methotrexate is cleared from the blood
    - Doses > 25 mg should be given IV for better absorption

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Cytarabine

- Mechanism of action:
  - Pyrimidine analog that is incorporated into DNA chains, as well as inhibition of DNA polymerase, resulting in decreased DNA synthesis and repair
- Dosing and Administration:
  - IV infusion or SQ injections
- Common toxicities:
  - Gastrointestinal toxicity (nausea, vomiting, diarrhea)
  - Hand-foot syndrome
  - Hepatotoxicity
  - Cytarabine syndrome (fevers, myalgias, bone/chest pain, rash)
  - Corneal toxicity
  - Neurotoxicity

Cytarabine [package insert]. Rockford, Il: Mylan Institutional; December 2013.

66

High Dose Cytarabine

- High-dose cytarabine (≥1,000 mg/m^2) is associated with several toxicities that require unique prophylaxis and monitoring
  - Conjunctivitis
    - Can present as itching, irritation, burning sensation, rare: mild-moderate temporary vision loss
    - High cytarabine concentrations in the aqueous humor or deposits in the corneal epithelium can trigger inflammatory cascade and result in conjunctivitis
    - Patients should receive prophylaxis with dexamethasone 0.1% eye drops (alternative prednisolone or artificial tears), administered as 2 drops in each eye every 6 hours until 48 hours after the last cytarabine dose
  - Neurotoxicity
    - High-dose cytarabine readily crosses the blood-brain barrier, and can result in cerebellar toxicity which presents as difficulty with speech, confusion, tremors, gait instability, somnolence, and rarely seizures
    - Risk factors for the development of cerebellar toxicity include age >50 years, renal impairment, and higher cytarabine doses
    - Patients should be assessed for cerebellar toxicity prior to every dose

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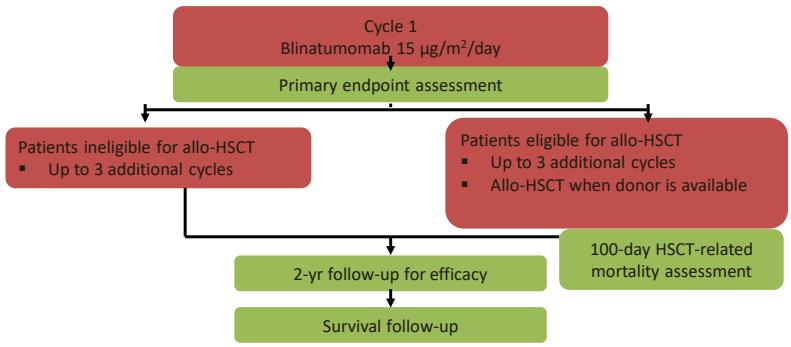
BLAST: Blinatumomab in MRD+ Patients With ALL in Hematologic CR

- Open-label phase II study (N = 113)



- Blinatumomab was given by continuous IV infusion, 15 µg/m^2/day x 28 days per cycle, for 4 wks on/2 wks off (one cycle) for a maximum of up to 4 cycles
  - All eligible patients received HSCT after the first cycle
  - Primary endpoint: complete MRD after 1 cycle (MRD- with no PCR amp)

Gökbuget N, et al. ASH 2014. Abstract 379.

68

BLAST Conclusions

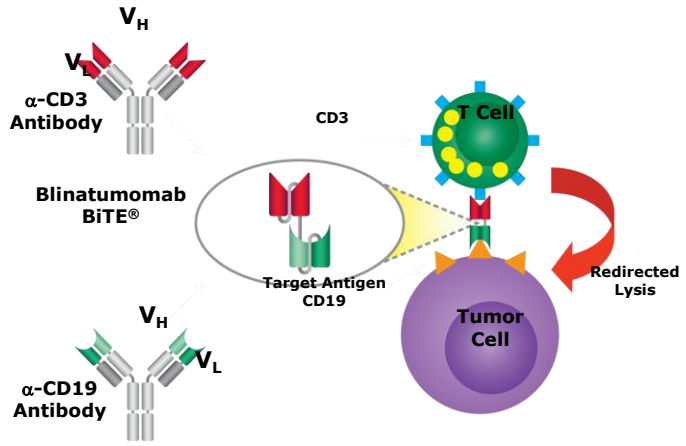
- Blinatumomab induced **complete MRD response in 80% of patients** with ALL who achieved hematologic CR but had persistent or recurrent MRD
  - Complete MRD response rate after 1 cycle: 78%
- Treatment interruptions due to treatment-related AEs in 28% of pts
- Primarily neurologic events, influenzalike symptoms
  - Most neurologic AEs grade 2 or less

Blinatumomab approved 3/29/2018 to treat pts with ALL MRD+ with hematologic CR

Gökbuget N, et al. ASH 2014. Abstract 379.

69

Blinatumomab Mechanism of Action



- Bi-specific T-cell engager (BiTE) antibody designed to direct CD3 expressing cytotoxic T-cells to CD19 expressing B-cells

Bargou. *Science* 2008;321:974.

70

Blinatumomab Dosing and Administration

- Continuous infusion for 4 weeks, followed by a 2-week break
  - Short half life (~ 2 hours)
  - Can be prepared as 24-hour, 48-hour, and 168-hour bags
  - After required hospitalization and confirmation of no toxicities, patients can continue treatment outpatient through infusion center or home infusion
- Premedication with dexamethasone (or prednisone equivalent) required:
  - Prior to first dose of each cycle
  - Prior to step up dose (R/R only)
  - When restarting therapy after infusion interruption ≥ 4 hours
- Blinatumomab should be given through a dedicated lumen / line with no other medications, fluids, or blood products running through it
- Bags may contain overfill, do NOT flush the infusion line when changing bags or finishing an infusion

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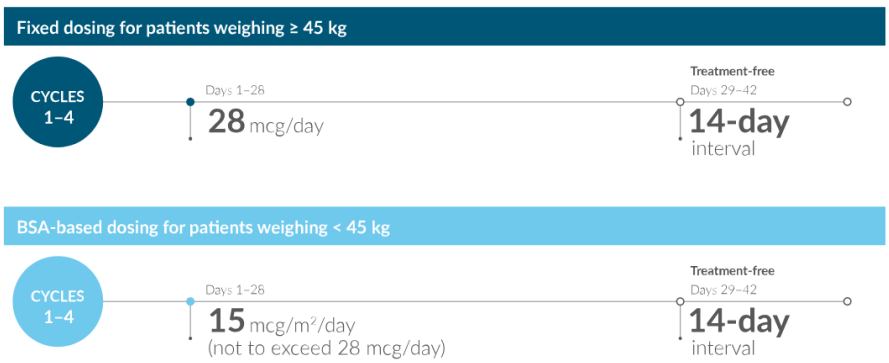
Blinatumomab Dosing: MRD+ B-ALL

- Hospitalization is recommended for first 3 days of Cycle 1 and 2 days of Cycle 2 to monitor for toxicities
- Pharmacists are critical for coordinating and transitioning patients to outpatient blinatumomab therapy



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Blinatumomab Toxicities

- Boxed warning: Cytokine release syndrome (CRS) – 7-15%
  - Systemic inflammatory response triggered by T-cell activation and associated with high levels of cytokines and inflammatory markers
    - Risk factors: degree of disease burden, initial starting dose
  - Presentation: fevers, chills, capillary leak, hypoxia, hypotension, fatigue, myalgias, tachycardia, flu-like symptoms
  - Median onset: ~ 2 days; median time to resolution: ~ 5 days
    - More common with first cycle of blinatumomab treatment
  - Treatment
    - Supportive care: acetaminophen, IV fluids, oxygen
    - Interrupt infusion and give dexamethasone for severe (grade $\geq$ 3) or persistent grade 1-2 CRS
    - Tocilizumab given to refractory CRS patients
    - Blinatumomab infusion may be restarted once CRS resolves

Blincyto (blinatumomab) [prescribing information]. Thousand Oaks, CA: Amgen Inc; March 2018.
Kantarjian H, et al. N Engl J Med. 2017;376(9):836-847.

73

Blinatumomab Toxicities

- Boxed warning: Neurotoxicity (20-53%)
  - Disruption of blood brain barrier by activated T cells and cytokine release; binds to CD19+ B-cells in central nervous system
  - Presentation: headache (most common), dizziness, confusion, somnolence, slurred speech, tremor, imbalance, rare: seizure, aphasia
  - Onset: usually within first 7 days; time to resolution: ~ 5 days
  - Management: interrupt infusion and give dexamethasone
    - Can restart at lower dose once neurotoxicity resolves
    - Discontinue permanently if seizures occur
- Other toxicities
  - Minimal nausea / vomiting or diarrhea
  - Hepatotoxicity (transient transaminitis)
  - Myelosuppression
  - Lymphopenias

Blincyto (blinatumomab) [prescribing information]. Thousand Oaks, CA: Amgen Inc; March 2018.
Kantarjian H, et al. N Engl J Med. 2017;376(9):836-847.

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HyperCVAD Schema

A	B	A	B	A	B	A	B

A (Odd Cycles): 1, 3, 5, 7

Chemotherapy Agent	Day 1	2	3	4	5	6	7	8	9	10	11	12	13	14	…21 or 28
Cyclophosphamide IV	xx	xx	xx												
Vincristine IV				X							x				
Doxorubicin IV				X											
Dexamethasone PO or IV	x	x	x	x							x	x	x	x	
Intrathecal (IT) chemotherapy during lumbar puncture		x													
Filgrastim daily SQ injection (alternative: pegfilgrastim x1)					x	x	x	x	x	x	x	x	x	x	x

B (Even Cycles): 2, 4, 6, 8

Chemotherapy Agent	Day 1	2	3	4	5	6	7	8	9	10	11	12	13	14	…21 or 28
Methotrexate IV	x														
Cytarabine IV		xx	xx												
Intrathecal (IT) chemotherapy during lumbar puncture		x													
Filgrastim daily SQ injection (alternative: pegfilgrastim x1)					x	x	x	x	x	x	x	x	x	x	x

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HyperCVAD → Blincyto

HyperCVAD x 8 cycles

Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8
A	B	A	B	A	B	A	B

HyperCVAD x 4 cycles followed by blinatumomab

Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8
A	B	A	B	Blina	Blina	Blina	Blina

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MAINTENANCE

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Maintenance

- Ph+ ALL
  - Maintenance regimen + TKIs (imatinib, dasatinib, nilotinib or ponatinib)
  - Monthly vincristine/prednisone pulses (2-3 years)
  - Weekly methotrexate + daily 6-MP as tolerated
  - Example: POMP
- Ph- ALL
  - Weekly methotrexate + daily 6-MP + monthly vincristine/prednisone pulses (duration based on regimen)

Malard, F., Mohty, M. Lancet 2020; 395: 1146–62

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PRINCIPLES OF ADULT ALL THERAPY: RELAPSED OR REFRACTORY ALL

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Adult ALL

- Primary refractory (resistant) disease
  - Patients who fail to obtain a complete response (CR) with induction therapy
    - Failure to eradicate all detectable leukemia cells (>5% blasts) from the bone marrow and blood with subsequent restoration of normal hematopoiesis
- Relapsed disease
  - Reappearance of blasts in the bone marrow or peripheral blood (>5%)after the attainment of a complete remission

Terwiller, T., Abdul-Hay, M. Blood Cancer Journal (2017) 7, e577;

80

Relapsed ALL Facts

- CR rates with initial induction are 85-90%
- The 5y-OS is now 40-50%
- However, 1/3rd of standard risk and 2/3rd of high risk ALL patients will eventually relapse
  - CR rates after 1st salvage are 31-44%
  - CR rates after 2nd salvage are 18-20%

O'Brien et al. (2008). *Cancer,* 113:3186-3191; Gokbuget et al. (2012). *Blood,*120:*JCO,*29, 532-543; Gokbuget & Hoelzer. (2009). *Semin Hematol,* 46:64-75; Thomas et al (1999). *Cancer,*86:1216-1230: Tavernier et al (2007). *Leukemia,*21:1907-1914: Felding et al (2007). *Blood,*190, 944-950: Orior et al (2010). *Haematolog,* 95:589-596: Jeha et al (2006). *JCO,* 24:1917-1923: Berg et al (2005). *JCO,*23:3376-3382: DeAngelo et al (2007). *Blood,* 109:5136-5142.

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Assessment of Relapsed ALL

- **Type of relapse**
  - Flow cytometry for immunophenotype: is it like the original disease or has there been a lineage switch?
  - Is this secondary leukemia, especially if late relapse?
- **Site of relapse**
  - Isolated relapse: bone marrow (BM), central nervous system (CNS), extramedullary (EM) relapse
  - Combination
- **Timing of relapse**
  - Early (< 18 months from diagnosis) or primary refractory: re-induce with novel therapies
  - Late (> 36 months from initial diagnosis): can consider re-treatment with the same induction regimen
  - Duration of complete response (CR)

Gokbuget, N., et al Blood (2024) 143 (19): 1903–1930

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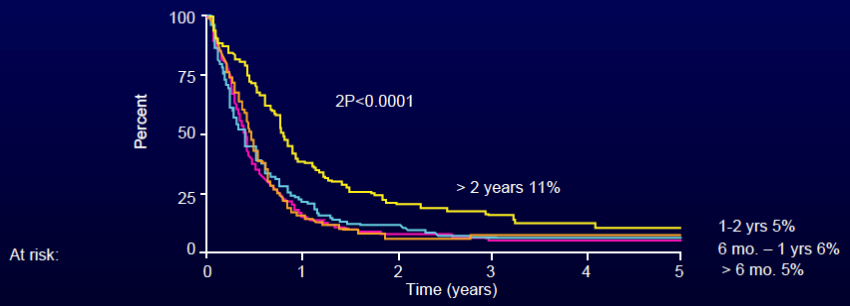
Outcomes Are Poor For Adults with Relapsed ALL Following Frontline Therapy (MRC UKALL/ECOG 2993)

- **Median OS after relapse was 4.6 months; 1-year OS was 22%**
- **With nearly 4.5 years of follow-up, only 42/609 (7%) patients are alive and disease free; 5% of patients died during induction therapy**
- **Patient age, sex, time to relapse (below), site of relapse, and type of therapy in CR1 were associated with OS**



At risk:						
<6 months	153	24	12	7	6	5
6 m – 1 yr	177	27	11	10	9	6
1-2 yrs	163	34	16	10	7	6
> 2 yrs	116	40	19	13	7	4

Fielding A, et al. *Blood*. 2007;109(3):944-950.

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Relapsed/Refractory (R/R) ALL Treatment

- Treatment decisions affected by:
  - Age / performance status / comorbidities
  - Initial induction treatment
  - Immunophenotype and Ph status
  - Duration of CR / time from initial diagnosis to relapse
- Treatment is challenging because these patients have very poor prognosis
- There are no established preferred standard of care for salvage therapies, but HSCT is the only potential curative modality
- After CR2 with a salvage regimen, allogeneic HSCT should be considered as soon as possible. The role of allogeneic HSCT following cellular therapy unclear
- For patients that relapse after an initial allogeneic HSCT, other options may include a second allogeneic HSCT and/or donor lymphocyte infusion.

DuVall, A., et al, JCO Oncology Practice, Vol 18; 7

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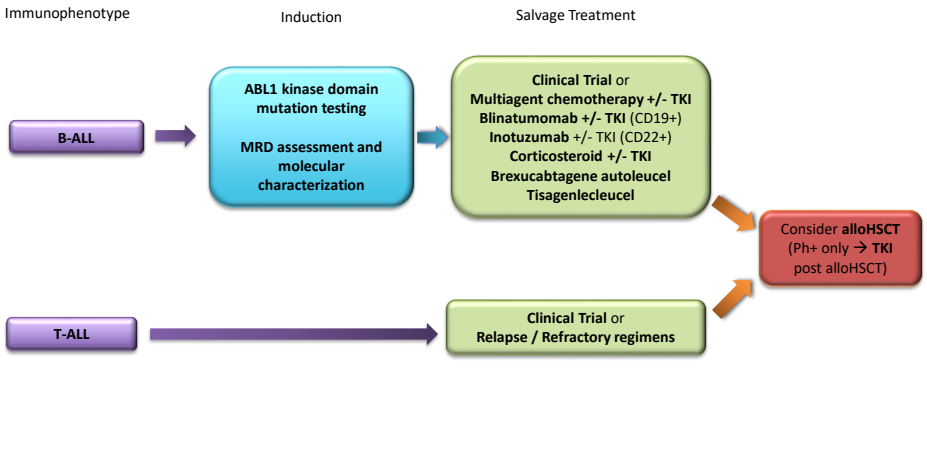
Relapsed or Refractory (R/R) Treatment Algorithm



Abbreviations: TKI = tyrosine kinase inhibitor; CR = complete response; MRD = minimal residual disease; alloHSCT = allogeneic stem cell transplant

Molina, J., Carraway, H. Current Treatment Options in Oncology (2024) 25:993–1010

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Relapsed/Refractory Ph+ ALL Treatment Options

- Mutation testing for the *ABL1* kinase domain is recommended
- TKIs (imatinib, dasatinib, nilotinib, bosutinib, or ponatinib) are options if not administered during initial induction
- For second- and third-generation TKIs, relevant *BCR-ABL1* mutations should be considered

Molina, J., Carraway, H. Current Treatment Options in Oncology (2024) 25:993–1010

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R/R ALL Treatment Options

B-Cell Only	B or T-Cell	T-Cell Only
• Blinatumomab (CD19+) +/- TKI • Inotuzumab ozogamicin (CD22+) +/- TKI • Inotuzumab + miniCVD +/- blinatumomab • Brexucabtagene autoleucel (CD19+) • Tisagenlecleucel (CD19+, age < 26 yo)	• Clinical trial • Augmented HyperCVAD • Clofarabine +/- etoposide + cyclophosphamide • MOpAD • FLAG-Ida or FLAM • Cytarabine-containing regimen • Alkylator combination regimen	• Nelarabine +/- etoposide + cyclophosphamide • Bortezomib or Daratumumab-containing regimen • Mitoxantrone + etoposide + cytarabine • Venetoclax-containing regimen (+ decitabine, HyperCVAD, miniCVD, or nelarabine)

Consider HSCT

***Augmented hyper-CVAD**: hyperfractionated cyclophosphamide, intensified vincristine, doxorubicin, intensified dexamethasone;, pegaspargase; alternating with high-dose methotrexate and cytarabine; **FLAG-IDA**: fludarabine, cytarabine, granulocyte colony-stimulating factor ±idarubicin; **MOpAD:** methotrexate, vincristine, pegaspargase, dexamethasone

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TOWER STUDY
Blinatumomab for R/R Salvage Therapy

Design:
- Phase 3 multicenter trial
- Randomized 2:1

Patient population (n = 405):
- Adult Ph(-) B-ALL:
  - Refractory to primary induction / salvage therapy
  - 1st relapse (remission < 12 months)
  - 2nd or greater relapse
  - Relapse post alloHSCT

Blinatumomab	
Induction (C1)	9 mcg x 7 days, then 28 mcg x 21 days
Consolidation (C2-5)	28 mcg x 28 days
Maintenance (C6-9)	28 mcg x 28 days

Standard of Care (Investigator's Choice)	
FLAG +/- anthracycline	HD-MTX-based
HiDAC-based	Clofarabine-based
Maintenance until alloHSCT, toxicity, or relapse	

Dombret H, et al. *Leuk Lymphoma* 2019; 60(9): 2214-22.

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TOWER STUDY
Blinatumomab for R/R Salvage Therapy

Table 3. Best hematologic response and minimal residual disease response within 12 weeks of treatment initiation.

	First salvage							Second or later salvage						
	Blinatumomab ($N = 104$)			Chemotherapy ($N = 63$)				Blinatumomab ($N = 167$)			Chemotherapy ($N = 71$)			
Response category	No.	%	95% CI	No.	%	95% CI	p^a	No.	%	95% CI	No.	%	95% CI	p^a
Best hematologic response														
CR	46	44.2	34.5, 54.3	18	28.6	17.9, 41.3	.050	45	26.9	20.4, 34.3	3	4.2	0.9, 11.9	<.001
CRh	6	5.8	2.1, 12.1	2	3.2	0.4, 11.0		18	10.8	6.5, 16.5	4	5.6	1.6, 13.8	
CRi	1	1.0	0.0, 5.2	3	4.8	1.0, 13.3		3	1.8	0.4, 5.2	3	4.2	0.9, 11.9	
CR/CRh/CRi	53	51.0	41.0, 60.9	23	36.5	24.7, 49.6	.069	66	39.5	32.1, 47.4	10	14.1	7.0, 24.4	<.001
MRD responses among patients with CR/CRh/CRi														
Any MRD response	33	62.3	47.9, 75.2	13	56.5	34.5, 76.8	.70	41	62.1	49.3, 73.8	3	30.0	6.7, 65.2	.031
Complete MRD response	26	49.1	35.1, 63.2	9	39.1	19.7, 61.5	.53	32	48.5	36.0, 61.1	1	10.0	0.3, 44.5	.008

Dombret H, et al. *Leuk Lymphoma* 2019; 60(9): 2214-22.

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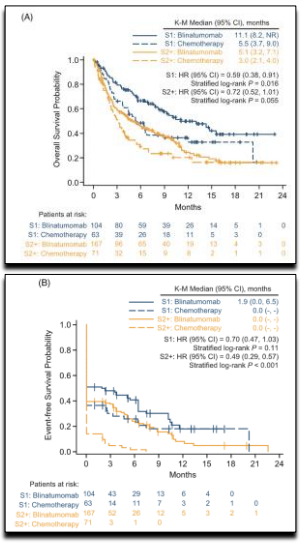
TOWER STUDY
Blinatumomab for R/R Salvage Therapy

- Median OS
  - 1st salvage: 11.1 vs 5.5 months (HR 0.59, 0.38-0.91)
  - 2nd or later salvage: 5.1 vs 3 months (HR 0.72, 0.52-1.01)
  - Similar results after censoring for allogeneic HSCT
- EFS @ 6 months: 41% vs 26%



Dombret H, et al. *Leuk Lymphoma* 2019; 60(9): 2214-22.

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Blinatumomab Dosing: R/R B-ALL

- Hospitalization is recommended for the first 9 days of Cycle 1 and 2 days of Cycle 2

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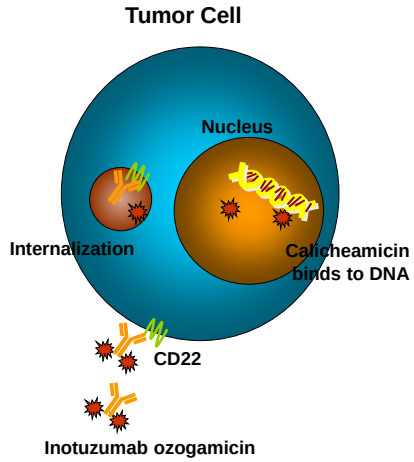
Inotuzumab Ozogamicin Mechanism of Action

- Humanized antibody-drug conjugate: CD22 antibody, cytotoxic calicheamicin, and acid-cleavable linker
- Antibody-antigen complex rapidly internalized upon binding to CD22
- Calicheamicin released inside the tumor cell, binds to DNA, and induces double-stranded DNA breaks and subsequent cell cycle arrest

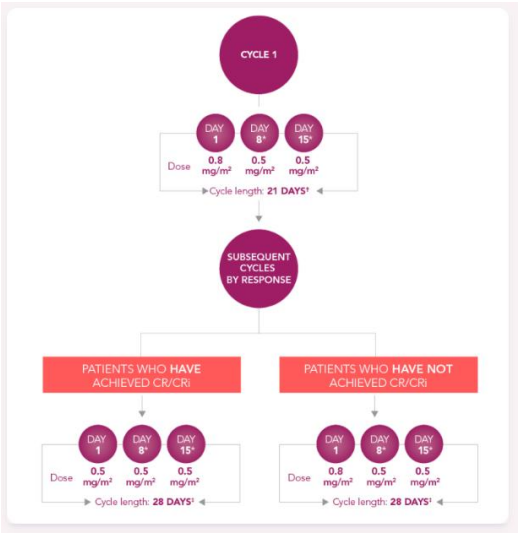


Ricart. *Clin Cancer Res*. 2011;17:6417-6427.

92

Inotuzumab Ozogamicin Dosing and Administration

- Premedication with acetaminophen, diphenhydramine, and hydrocortisone 30-60 minutes prior to infusion
- Administered over 1 hour (protect from light)
- Number of cycles based on goal to proceed to HSCT
  - HSCT: 2-3 cycles
  - No HSCT: 6 cycles



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Inotuzumab Ozogamicin Toxicities

- Boxed warning: Hepatoxicity
  - Severe, life-threatening, and sometimes fatal sinusoidal obstructive syndrome (SOS)/veno-occlusive disease (VOD) has been seen
  - Risk factors:
    - Greatest risk in patients who received HSCT after inotuzumab ozogamicin treatment
    - 2 alkylating agents, high total bilirubin at baseline, history of VOD/SOS, liver disease
  - Median time to onset:15 days (range: 3-57 days)
  - Prevention:
    - Some providers may start ursodiol
    - Minimize number of cycles to 2 before proceeding to HSCT
- Other toxicities:
  - Infusion reactions
  - QTc prolongation
  - Myelosuppression
  - Nausea, vomiting, constipation, abdominal pain
  - Headache or fatigue
  - Infection

Besponsa (inotuzumab ozogamicin) [prescribing information]. Philadelphia, PA: Wyeth Pharmaceuticals Inc; March 2018.
Kantarjian HM, et al. NEJM. 2016;375:740-753.

94

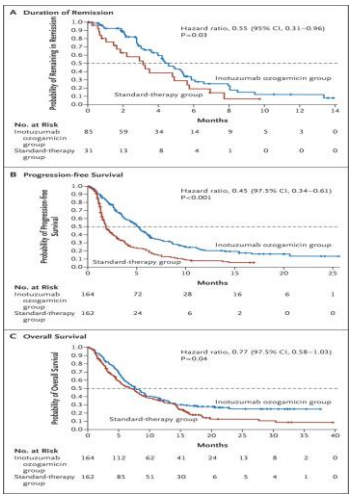
Intotuzumab Ozogamacin vs. Standard Salvage Chemo in Relapsed B-ALL

- 326 patients randomized to receive intotuzumab vs standard induction chemo
- 218 included in intention to treat analysis
- CR IO 80.7% vs SCT 29.4% p<.001
- MRD negative in 78.4% vs 28.1% p<.001
- Major complication of IO, VOD in 11% vs 1% in SCT group

Kantarjian et al, NEJM 2016, 375 (8).

95

Intotuzumab Ozogamacin vs. Standard Therapy for Relapsepd CD22 Postive B-Cell ALL



Kantarjian HM et al. N Engl J Med 2016;375:740-753.

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IO
Relapsed/Refractory ALL Response

Response	Monthly, N=49 No. (%)	Weekly, N=40 No. (%)
CR	9 (18)	7 (18)
CRp	14 (29)	12 (30)
CRi (marrow CR)	5 (10)	4 (10)
Resistant	19 (39)	15 (38)
Death < 4 wks	2 (4)	2 (5)
OR	28 (57)	23 (58)

Kantarjian H, et al. *Cancer.* 2013;119:2728-36.

97

IO in Relapsed/Refractory ALL
Minimal Residual Disease

Parameter	Monthly, N=27 MRD Negative No. (%)	Weekly, N=20 MRD Negative No. (%)
CR	8/9 (89)	6/7 (86)
CRp	9/14 (64)	7/10 (70)
CRi (marrow CR)	0/4 (0)	1/3 (33)
MRD negative	17/27 (63)	14/20 (70)

Kantarjian H, et al. *Cancer.* 2013;119:2728-36.

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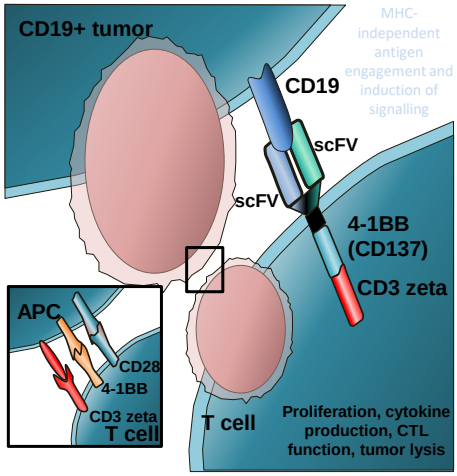
Chimeric Antigen Receptors MOA

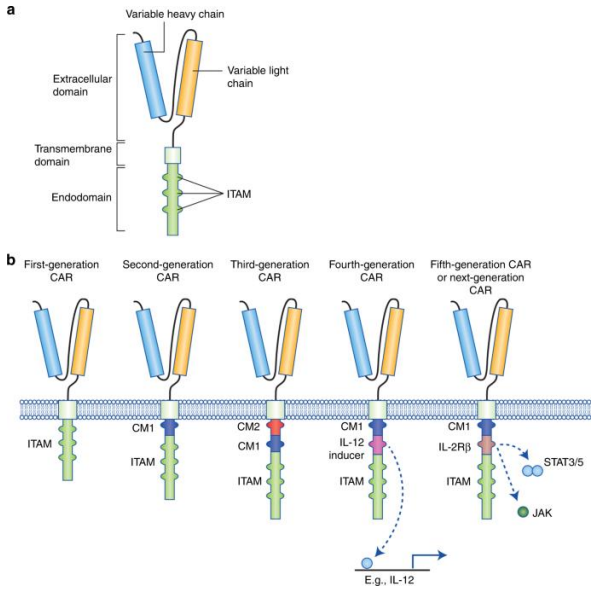
- Genetically engineered receptors that combine anti-CD19 single chain variable fragment of an antibody with intracellular signaling domains of T cells
- With the use of lentiviral-vector technology, CTL019 T cells express a CAR with CD3 zeta and 4-1BB (CD137) signaling domains
- Tisagenlecleucel is approved for patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse
- Brexucabtagene Autoleucel is approved for the treatment of adult patients with relapsed or refractory B-cell precursor ALL



1. Grupp S, et al. ASH 2014. Abstract 380.
2. Maude SL, et al. N Engl J Med. 2014; 371:1507-1517.

99

Chimeric Antigen Receptors



Tokarew N et al. Br J Cancer. 2019; 120(1):26-37.

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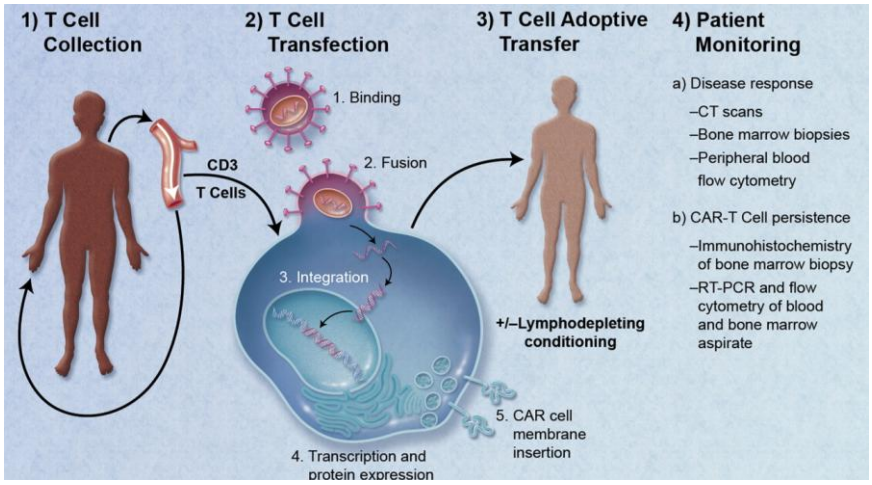
Chimeric Antigen Receptor–Modified T Cells



- Patient specific T-cells engineered to attack cells that express CD19
- In vivo expansion and robust antileukemic effects of CTL019 (formerly CART19) cells was previously demonstrated in 3 CLL patients

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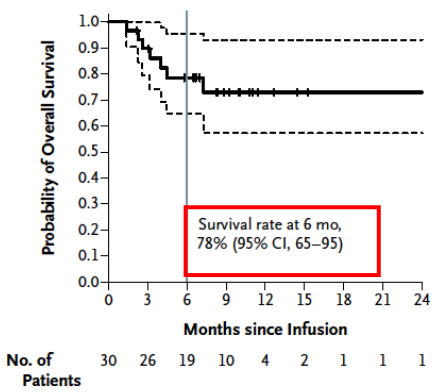
CAR T-cells (CTL019) Lead to Sustained Remissions in ALL Patients

30 pts with relapsed/refractory ALL with 2 years of follow-up

Characteristics
- Ages 5-60 yrs old
-18 (60%) had prior alloHSCT
-3 (10%) had refractory ALL
-22 (73%) had ≥ 2 relapses

Responses
- **27 pts (90%) achieved CR** one month after T-cell infusion
- 2 of 3 prior blinatumomab Rxed pts responded

Median f/u= 7 mos
Range: 2-24 mos



Maude et al NEJM 2014; 371: 1507-1517.

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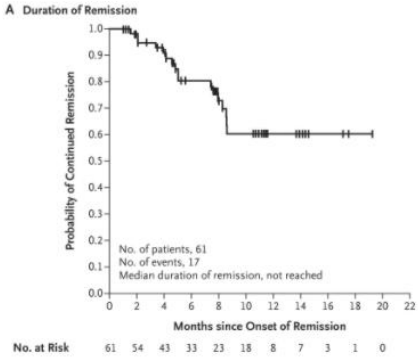
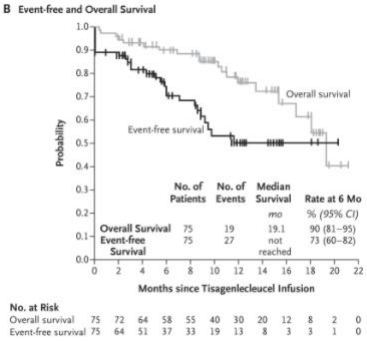
Efficacy of Tisagenlecleucel: Overall Remission Rate of 81%





N Engl J Med 2018; 378:439-448.

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Safety of Tisagenlecleucel

Table 3. Adverse Events of Special Interest within 8 Weeks after Infusion, Regardless of Relationship to Tisagenlecleucel.*

Type of Event	Any Grade (N=75)	Grade 3 (N=75)	Grade 4 (N=75)
	number of patients (percent)		
Any adverse event of special interest	67 (89)	26 (35)	30 (40)
Cytokine release syndrome	58 (77)	16 (21)	19 (25)
Neurologic event	30 (40)	10 (13)	0
Infection	32 (43)	16 (21)	2 (3)
Febrile neutropenia	26 (35)	24 (32)	2 (3)
Cytopenia not resolved by day 28	28 (37)	12 (16)	12 (16)
Tumor lysis syndrome	3 (4)	3 (4)	0

N Engl J Med 2018; 378:439-448.

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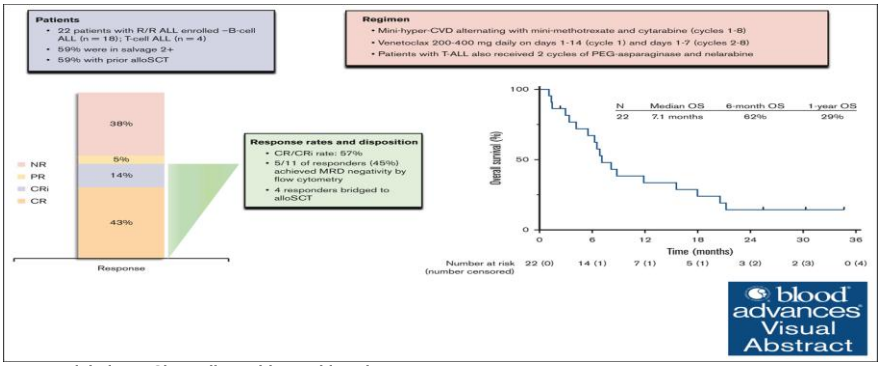
A phase 1/2 Study of Mini-Hyper-CVD Plus Venetoclax in Patients with Relapsed/Refractory Acute Lymphoblastic Leukemia



Nicholas J. Short,Elias Jabbour,Nitin Jain,Jayastu Senapati,Lewis Nasr,Fadi G. Haddad,Zhenhua Li,Yu-Chih Hsiao,Jun J. Yang,Naveen Pemmaraju,Maro Ohanian,William G. Wierda,Guillermo Montalban-Bravo,Gautam Borthakur,Lina Han,Lianchun Xiao,Xuelin Huang,Regina Abramova,Min Zhao,Rebecca Garris,Marina Konopleva,Farhad Ravandi,Hagop Kantarjian, A phase 1/2 study of mini-hyper-CVD plus venetoclax in patients with relapsed/refractory acute lymphoblastic leukemia, Blood Adv, 2024,

American Society of Hematology
Helping hematologists conquer blood diseases worldwide

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Zuma-3: Brexucabtagene Autoleucel (KTE-X19) for R/R B-ALL

- Phase 2 single arm open label multicenter international study (n = 55 patients)
  - Median age: 40 years (28-52)
  - 47% received ≥ 3 previous therapies
  - 42% received previous allogeneic HSCT
- Results
  - Complete remission: 71%
  - MRD negativity: 76%
  - Median duration of remission: 14.6 months
  - Median time to allogeneic HSCT: 98 days
  - Median OS: 18.2 months (15·9–not estimable) in all treated patients and not reached in responders

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Zuma-3: Brexucabtagene Autoleucel (KTE-X19) for R/R B-ALL

- Safety data:
  - 95% of patients experienced at least 1 Grade ≥ 3 adverse event

	Any Grade	Grade ≥ 3
CRS (Median onset: 5 days)	89%	24%
Neurological Events (Median onset: 9 days)	60%	26%
Anemia	53%	49%
Neutropenia	27%	27%
Thrombocytopenia	33%	30%
Alanine aminotransferase increased	22%	15%

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Cytokine Release Syndrome (CRS) Treatment Algorithm

Grade	Fever (≥ 38°C)	with Hypotension (SBP < 90 mmHg)	and/or Hypoxia (requires oxygen for O2 sat > 90%	Management
1	Yes	No	No	Monitor fluid status Empiric treatment for febrile neutropenia & sepsis screen Supportive care (antipyretics, analgesics) Consider tocilizumab in absence of improvement within 3 days
2	Yes	Yes - does not require vasopressors	Requires low-flow nasal cannula	Closely monitor all organ function Supportive care (fluids, antipyretics) If older/considerable comorbidities: tocilizumab +/- corticosteroids
3	Yes	Yes – requires vasopressor +/- vasopressin	Requires high flow nasal cannula, facemask, or nonrebreather)	Tocilizumab +/- corticosteroids Supportive care
4	Yes	Yes – requires multiple vasopressors	Requires positive pressure (CPAP, BiPAP, intubation, mechanical ventilation)	Tocilizumab +/- corticosteroids Supportive care

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Neurotoxicity Treatment Algorithm

ICANS Grade	ICE Score	Depressed level of consciousness	Seizure	Motor Findings	Elevated ICP / cerebral edema	Management Without CRS	Management With CRS
Grade 1	7-9	Awakens spontaneously	N/A	N/A	N/A	Supportive care	Tocilizumab
Grade 2	3-6	Awakens to voice	N/A	N/A	N/A	Supportive care Dexamethasone IV x 1 and reassess, repeat every 6-12 hours if no improvement	Tocilizumab +/- dexa methasone
Grade 3	0-2	Awakens only to tactile stimuli	Any clinical seizure that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	N/A	Focal/local edema on neuroimaging	Dexamethasone IV q6h or methylpred-nisolone then taper ICU care Consider repeat neuroimaging every 2-3 days	Tocilizumab + dexameth-asone
Grade 4	0 (un-arousable or unable to perform)	Unarousable or requires vigorous / repetitive tactile stimuli Stupor or coma	Life-threatening prolonged seizure (>5 min) or repetitive clinical or electrical seizures without return to baseline in between	Deep focal motor weakness (e.g. hemiparesis or paraparesis)	Diffuse cerebral edema on neuroimaging Decerebrate or decorticate posturing Cranial nerve VI palsy Papilledema Cushing's triad	High dose IV methylprednisolone every 12-24 hours x 3 days, then taper ICU care, consider mechanical ventilation Consider repeat neuroimaging every 2-3 days Treat convulsive seizures per protocol	Tocilizumab + methylpred-nisolone

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Conclusions

- Jury still out on efficacy and safety of pediatric style regimens in AYA and Adult ALL patients
- Clinical trials underway to incorporate antibody therapy in initial induction ALL treatment
- Elderly AML trials show efficacy of incorporation of inotuzumab in mini-hyperCVAD patients and are under investigation as a standard of care
- Trials underway to utilize blinatumomab in upfront setting in elderly patients with B-ALL
- The future of treatment: phase II study showed 98% CR rate using dasatinib and blina in ph + ALL patients

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Conclusions

- New agents such as venetoclax and navitoclax also show efficacy in ALL pts and are under investigation in the relapsed/refractory setting
- CAR-T is expensive and difficult to offer to broad population of patients. Many challenges remain in cost of therapy and insurance coverage
- Cellectis “off the shelf” CD 19 CAR-T may show promise in making this therapy more available
- Combinations of these new agents amongst themselves or with chemotherapy will be the next generation of treatment options for patients with ALL

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- For additional information review the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)– www.NCCN.org.

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NURSES' MANAGEMENT OF ALL

Kaitlin Rancani, CRNP, MSN
Nurse Practitioner
Thomas Jefferson University Hospital
Philadelphia, PA

LEUKEMIA & LYMPHOMA SOCIETY

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Diagnosis of Acute Lymphoblastic Leukemia

- Ensure patient understands diagnosis
- Provide emotional support
- Inquire about patient's social situation
  - Who do they live with? What do the do for work? Do they have transportation?
- Refer to Social Work

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Types of ALL

- Philadelphia chromosome positive (Ph+) B-ALL
  - Detected by BCR/ABL mutation
- Ph- B-ALL
- T-ALL
- Burkitts' Lymphoma

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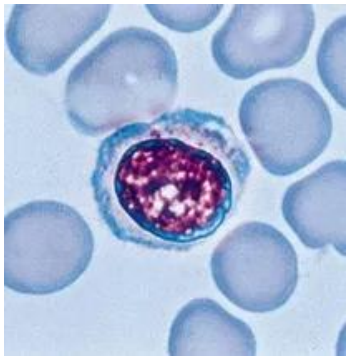
Blood Counts

- **Educate patient on Complete Blood Count**
- **Monitor labs 1-3x/week**
- **WBC**
  - Fight infection
  - Absolute Neutrophil Count (ANC) = WBC x neutrophils/100
  - Neutropenic when ANC <1000Hemoglobin
- **Hemoglobin**
  - Carries oxygen throughout our body
  - Transfuse Red Blood Cells when Hemoglobin <7.5 g/dL
  - Symptoms of low Hemoglobin include lightheadedness, fatigue, DOE
- **Platelets**
  - Allows our blood to clot to prevent bleeding
  - Transfuse for platelet count <15,000
  - Symptoms of low platelets include bleeding nose, bleeding gums, petechiae, headache
  - Risk for spontaneous brain bleed for platelets <10,000



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Abnormal Coagulation

- High risk for venous thromboembolism and bleeding before and during induction chemotherapy
- *Peg asparaginase* disrupts the anticoagulation pathways
- Fibrinogen needs to be monitored very frequently during induction
- Transfuse Cryoprecipate for Fibrinogen <120

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Treatment

- Induction chemotherapy usually requires hospitalization for initial days due to tumor lysis risk and abnormal coagulation
- Some treatments require hospital admission each cycle, eg. HyperCVAD
- Prepare for hospital stays and what to expect
- Provide education on chemotherapy drugs and side effects
- Make treatment calendar
- PICC line placement/care

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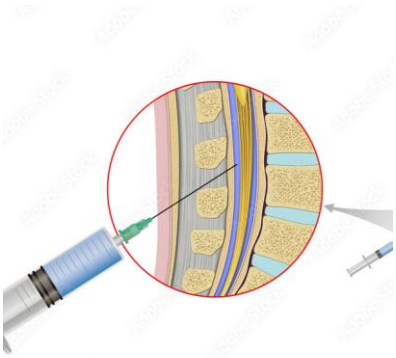
Intrathecal Chemotherapy

- Prepare patient for frequency of procedures
- Platelets >50,000 and fibrinogen >100
- Encourage hydration, caffeine, Tylenol
- For postural headache, treat with IVF and IV Compazine



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Medications

Prophylactic antimicrobials

- Acyclovir or Valacyclovir (antiviral, continuous)
- Levofloxacin or Ciprofloxacin (antibacterial, when ANC <500)
- Fluconazole (antifungal, when ANC <500)

Antiemetics

- Zofran
- Compazine

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Goals of Treatment

- Bone marrow biopsy usually performed after first cycle/course
- If in remission and MRD negative, continue treatment protocol followed by maintenance. Treatment is usually 2-3 years.
- If poor risk disease or MRD positive during treatment, proceed to bone marrow transplant

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Side Effects

- Nausea/Vomiting
- Headache
- Mucositis
- Peripheral Neuropathy
- Constipation
- Pancreatitis

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Neutropenic Fever

Fever >100.4 and ANC <1000

- Requires immediate medical attention and hospitalization

If able to begin outpatient workup:

- Blood cultures x 2, Urine Culture, Lactate, Respiratory Viral Swabs
- Administer, at least, 1L IVF
- Begin IV antibiotic as soon as possible, e.g. Cefepime
- If vitals and labs stable, direct admit to hospital

Emergency Room recommended if outpatient workup not possible

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Long Term Survival

- If Ph+ ALL, BCR/ABL testing every month for 1-2 years post maintenance
- Labs every 3 months until 3 years, then every 6 months until 5 years, then yearly
- Referral to survivorship clinic, support groups
- Ongoing emotional support

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Nurses' Impact

- High touch RN/APP care is imperative to the success of ALL patients.
- Clustering and coordinating care to keep patient safe while providing quality life is important.
- Collaborating with the full care team, including doctors, pharmacists, and nurses, allows for best practice and seamless care.

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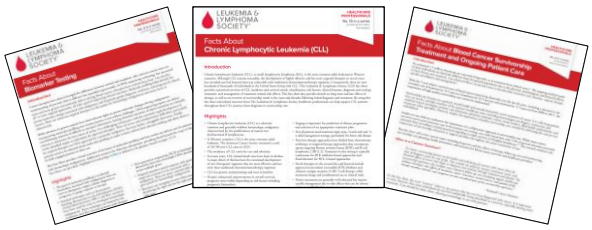
FREE LLS RESOURCES FOR HEALTHCARE PROFESSIONALS

- ❑ Free CME & CE courses www.LLS.org/CE
- ❑ Fact Sheets www.LLS.org/HCPbooklets
- ❑ Videos for HCPs www.LLS.org/HCPvideos
- ❑ Podcast series for HCPs www.LLS.org/HCPpodcast



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FREE LLS RESOURCES FOR PATIENTS

- **Information Specialists** – Personalized assistance for managing treatment decisions, side effects, and dealing with financial and psychosocial challenges (IRC)
  - www.LLS.org/IRC
- **Nutrition Education Services Center** – one-on-one consultation with a registered dietician for patients/caregivers of all cancer types (NESC)
  - www.LLS.org/Nutrition
- **Clinical Trial Nurse Navigators** – RNs and NPs provide personalized service for patients seeking treatment in a clinical trial, sift through and provide information to bring back to their HC team (CTSC)
  - www.LLS.org/CTSC
- **Reach out Monday–Friday, 9 am to 9 pm ET**
  - Phone: (800) 955-4572
  - Live chat: www.LLS.org/IRC
  - Email: infocenter@LLS.org
  - HCP Patient Referral Form: www.LLS.org/HCPreferral

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HERE TO HELP: LLS COMMITMENT

to providing education & resources to help patients access clinical trials

CLINICAL TRIAL SUPPORT CENTER

- A team of highly trained nurses and nurse practitioners experienced with hematological malignancies and clinical research.
- Provide education to patients about clinical trials, treatment options, and other disease specific information.
- Provide patients, families, and their caregivers with a professional, detailed, individualized search to discuss with their HCP.
- Provide guidance and serve as advocates throughout the clinical trial process. Help make connections between the patient and the trial site to facilitate enrollment as appropriate.
- Provide a personal connection and develop long term relationships to help better serve our patients.

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FREE LLS RESOURCES FOR PATIENTS AND CAREGIVERS

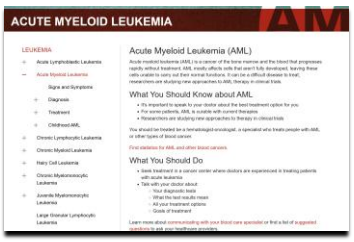
❑ **Webcasts, Videos, Podcasts, booklets**:

- www.LLS.org/Webcasts
- www.LLS.org/EducationVideos
- www.LLS.org/Podcast
- www.LLS.org/Booklets
- **www.LLS.org/Leukemia**

❑ **Support Resources**

❑ Financial Assistance: www.LLS.org/Finances
- Urgent Need
- Patient Aid
- Travel Assistance

❑ Other Support: www.LLS.org/Support
- LLS Regions
- Online Weekly Chats Facilitated by Oncology SW
- LLS Community Social Media Platform
- First Connection Peer to Peer Program



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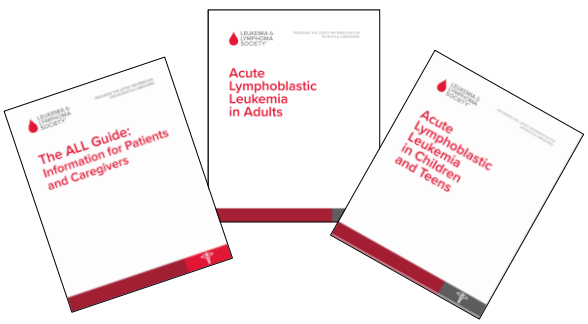
FREE LLS RESOURCES FOR YOUR PATIENTS



BOOKLETS AND FACT SHEETS

English – www.LLS.org/Booklets
Spanish – www.LLS.org/Materiales

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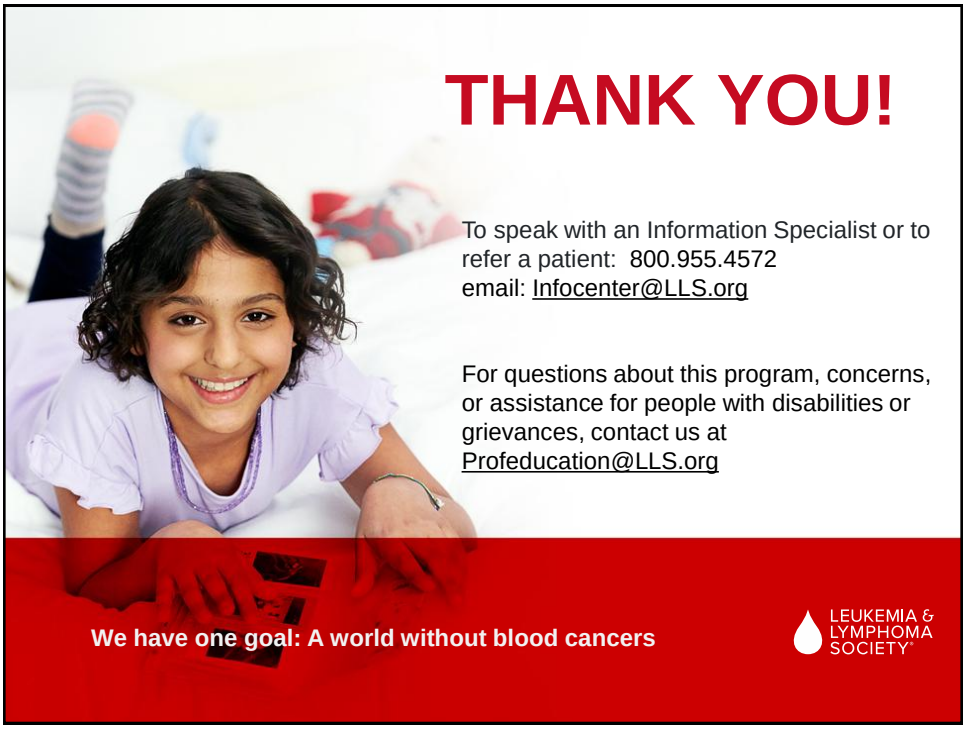
THANK YOU!
To speak with an Information Specialist or to refer a patient: 800.955.4572
email: Infocenter@LLS.org
For questions about this program, concerns, or assistance for people with disabilities or grievances, contact us at Profeducation@LLS.org
We have one goal: A world without blood cancers
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