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WELCOMING REMARKS

CHILDHOOD ALL: A ROADMAP TO THE FUTURE

Lizette Figueroa-Rivera, MA
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Childhood Acute Lymphoblastic Leukemia (ALL): A Roadmap to the Future

June 2024

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Disclosures

- Stock ownership
  - Amgen
- Honoraria/Consulting fees
  - Amgen, Jazz, Novartis, Servier

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Learning Objectives

- Advances in treatments for ALL in children
- Side-effect management
- Advocating for your child's needs with the healthcare team

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Acute Lymphoblastic Leukemia (ALL)

- ALL is the most common pediatric cancer, accounting for about 25% of all cancers that occur in children
- About 6000 total ALL cases/year in US
  - Half occur in children and adolescents <20 years old
  - Incidence peaks at 2-4 years of age, with incidence of 80 cases/million at that age
- ALL was incurable until the early 1960s
- Long-term survival rates for children with ALL now approach 90%
  - Survival is inferior for adolescents and young adults (AYA) and gets progressively worse for older patients

Hunger and Mullighan, *N Engl J Med,* 373: 1541-52, 2015

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Children's Oncology Group ALL Trials

- Only US National Cancer Institute (NCI) sponsored pediatric cooperative group
- ~220 members institutions in US, CA, AUS, and NZ
  - 90-95% of enrolled patients reside in US
- About 2000 newly diagnosed ALL patients/year enroll in COG ALL trials
- About two-thirds of US ALL cases among those 0-19.99 years old enroll in a COG ALL trial
  - ~70% of those 0-14.99 years old
  - ~50% of those 15-19.99 years old

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The world's childhood cancer experts

Hunger, *J Clin Oncol,* 30: 1663-69, 2012

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Clinical Trial Terminology

- Remission: <5% ALL cells in the bone marrow based on morphology (microscope) with no leukemia outside the bone marrow (extramedullary)
  - CR1=first remission; CR2=second remission; etc.
- Molecular remission: <0.01% MRD in the bone marrow
- Event-free survival (EFS): percentage of patients alive and in remission without having relapsed at a given timepoint (usually at 3 or 5 years)
- Overall survival (OS): percentage of patients alive at a given time point (they may have relapsed and may or may not be in remission)

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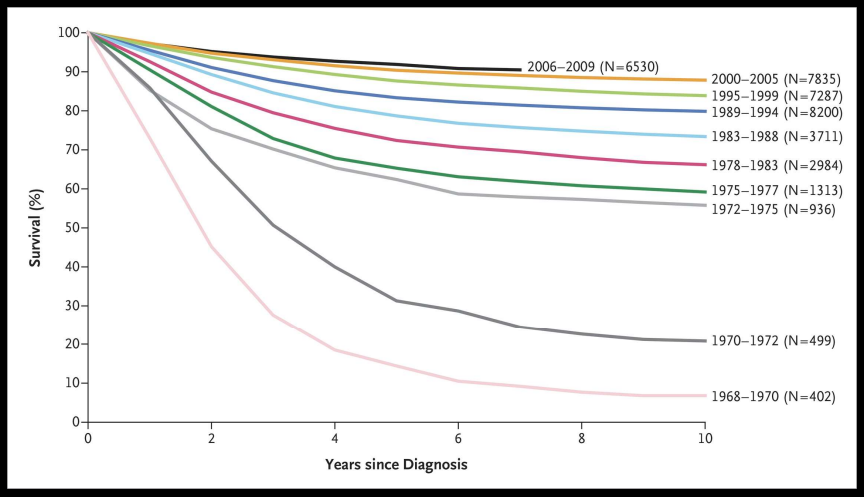
Improved Survival in Childhood ALL
CCG/COG Trials 1968-2009 (n=39,697)



Hunger SP, Mullighan CG. N Engl J Med 2015;373:1541-1552

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Chemotherapy Agents Used in Childhood ALL: Year of FDA Approval

Agent	Year Approved by FDA
6-Mercaptopurine	1953
Methotrexate	1953
Prednisone	1955
Dexamethasone	1958
Cyclophosphamide	1959
Vincristine	1964
Cytarabine	1969
L' Asparaginase	1978
Daunorubicin	1979

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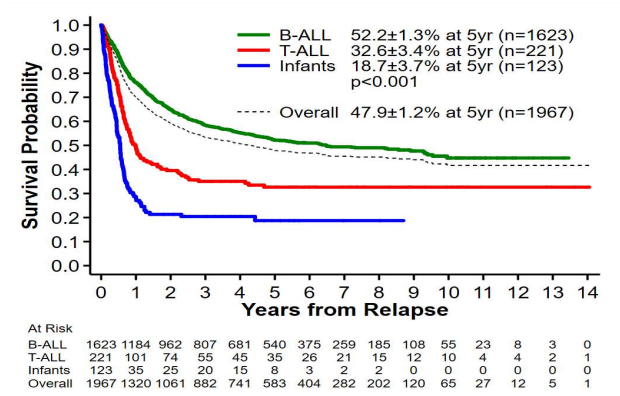
ALL: Survival Following Relapse



- **15,874 pts enrolled in 10 COG trials between 1996-2004**
- **1967 (12%) of these pts relapsed**
- **Graph shows survival post-relapse**
- **Don't have details of therapy, but given the years involved, it was likely chemotherapy +/- HSCT**

Limited improvement over time with chemotherapy intensification and HSCT

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Rheingold, *J Clin Oncol* 37, 2019 (suppl; abstr 10008)

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Major Questions in Pediatric ALL Therapy in 2024

- How do we increase cure rates for those not cured today?
  - 10-12% of children with ALL will relapse
  - Only about half of children who relapse are cured
- How to we optimize therapy for ultra low risk ALL?
  - Subgroups of children with ALL with >95% EFS and >98% OS can be identified
  - How do we treat them to have the fewest short- and long-term side effects?
- How do we improve cure rates for children with ALL diagnosed in low and middle income countries worldwide, where most children live?

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ALL: Risk Factors and Treatment Stratification

- Clinical
  - Age, initial white blood cell count (WBC), central nervous system (CNS) status
- Immunophenotype
  - Children: 85% B-ALL and 15% T-ALL
- Treatment response
  - Assessed by minimal residual disease (MRD) levels at end induction (EOI) and end consolidation (EOC)
  - COG uses multi-parameter flow cytometry (flow) to measure MRD
  - Emerging more sensitive technologies assess MRD by Next General Sequencing (NGS) or High Throughput Sequencing (HTS)
- Sentinel genetic lesions
  - Chromosome number (ploidy) and structural rearrangements, particularly chromosome translocations
- COG risk stratification systems use a combination of clinical features, immunophenotype, MRD and sentinel genetic lesions to classify patients into different risk groups
  - Different treatment backbones for different groups
  - Different randomized questions in different groups
  - Identify small high-risk patient subsets to test precision medicine therapies

Clinical Risk Groups in Childhood B-ALL: NCI Criteria

- Standard risk: ~65% patients
  - Age 1.00-9.99 years and initial white blood count <50,000
  - Current 5-year EFS ~92%, OS ~97%
- High risk: ~35% patients
  - All others
  - Current 5-year EFS ~75%, OS ~85% for non-infants
    - Achieved with more intensive therapy
  - Outcome still poor for infants < 1 year old
    - ~3% of patients; generally treated on different trials
- NCI risk criteria do not apply to T-ALL
  - All treated with more intensive therapy similar to that for HR B-ALL

Hunger and Mullighan, *N Engl J Med*, 373: 1541-52, 2015

Survival Improvements 1990-2010: COG Trials T-ALL vs. B-ALL

Immunophenotype	5-year OS%: 1990-94	5-year OS%: 2006-10	Reduction in death rate
B-ALL	84.9 +/- 0.5 (n=5068)	91.7 +/- 0.4% (n=7397)	45.0%
T-ALL	70.7 +/- 1.7% (n=748)	90.6 +/- 1.7% (n=676)	67.9%

Overall Survival difference for B-ALL vs. T-ALL
1990-94: 14.2%
2006-09: 1.1%

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Hunger, *J Clin Oncol,* 30: 1663-69, 2012
Raetz, *Pediatr Blood Cancer*, 65: e27057 (S222), 2018

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"New" Treatments for Childhood ALL

- "Targeted" or precision medicine therapies
  - Tyrosine kinase inhibitors (TKIs) such as imatinib and dasatinib
    - Directly inhibit mutant proteins fundamental to ALL development
    - Standard of care in Philadelphia chromosome positive (Ph^+) ALL
    - Currently being tested in Philadelphia chromosome like (Ph-like) ALL
- Immunotherapies
  - Blinatumomab
  - Inotuzumab
  - Chimeric antigen receptor (CAR) T-cells

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Newly Diagnosed ALL: Current COG ALL Trials

- AALL1731: Standard Risk B-ALL
- AALL1732: High Risk B-ALL
- AALL1631: Ph+ and Ph-like ALL

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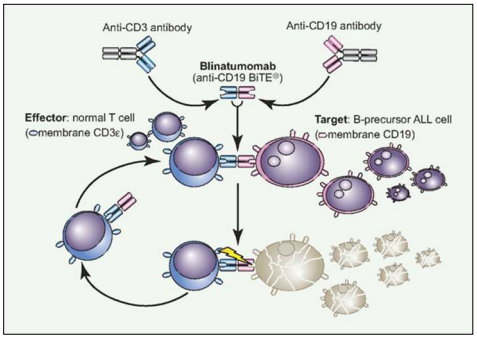
Blinatumomab



Adapted from *Brown, Blood, 131: 1497–98, 2018*

- Bi-specific T-cell engaging (BiTE) antibody that links CD3+ T-cells to CD19+ cells, enabling killing of the CD19+ cells by the patient's own cytotoxic T-cells
- Given by continuous 28-day infusion
- Side effect profile very different from cytotoxic chemotherapy
  - Causes lymphopenia but little anemia, thrombocytopenia or neutropenia
  - Very low incidence of serious infections
  - Unique CNS toxicities including hallucinations and seizures
- Improves EFS and OS in relapsed ALL

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COG AALL1731: Blinatumomab in Newly Diagnosed ALL

- NCI standard risk B-ALL
  - All patients receive an identical "3-drug" (dexamethasone, calaspargase, vincristine + intrathecal chemotherapy) induction for 28 days and are then assigned to different risk groups
- The major study question is to determine if adding two 4-week cycles of blinatumomab to standard therapy improves EFS
  - Blinatumomab given by 4-week continuous infusion
  - Start in the hospital and continue at home
- Separate treatment approaches for children with Down syndrome and ALL due to higher rates of toxicity in these children

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Study Chairs: Sumit Gupta and Rachael Rau

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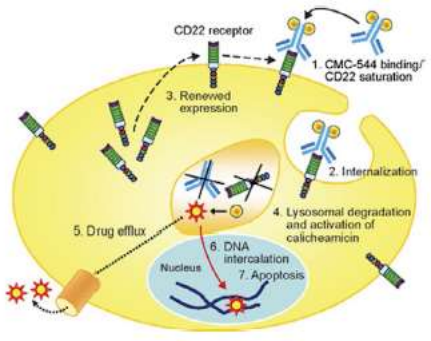
Inotuzumab Ozogamicin (InO)



- CD22 expressed universally on B-ALL
- InO is a humanized IgG4 anti-CD22 antibody conjugated to calicheamicin
- Binds to CD22, internalized and calicheamicin is released
- Given via IV infusion over one hour on day 1, 8, & 15 of a 4-week cycle
- Improves EFS and OS in adult relapsed ALL; induces remissions in pediatric relapsed/refractory ALL

Thota and Advani, *Eur J Haematol*, 98: 425-34, 2017

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COG AALL1732: Inotuzumab in Newly Diagnosed ALL

- NCI high risk B-ALL
  - All patients receive a "4-drug" (dexamethasone if <10, prednisone if ≥10; calaspargase; vincristine + intrathecal chemotherapy) induction for 28 days and are then assigned to different risk groups
- The major study question is to determine if inotuzumab improves EFS compared to chemotherapy alone
  - Inotuzumab arm replaces one cycle of chemotherapy (delayed intensification part 2) with inotuzumab and adds a 2nd cycle
  - Inotuzumab given by 1-hour infusion weekly x 3

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COG AALL1631: Chemotherapy + Imatinib in Ph+ ALL

- Patients with Ph^+ or Ph-like ALL with an "ABL class fusion" enter 2-4 weeks after diagnosis
- Receive chemotherapy + imatinib
- Testing two different chemotherapy backbones to determine if one is better than the other
  - "EsPhALL" regimen from Europe
  - "COG" HR B-ALL backbone
    - Less toxic and preferred if cure rates are the same

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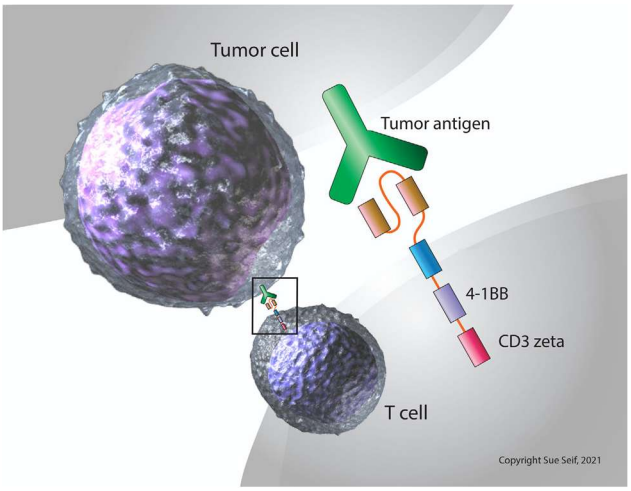
Chimeric Antigen Receptor (CAR) T-cells



- CAR T-cells are generated by stably transducing patient T-cells with a construct that leads to expression of a genetically modified T-cell receptor on the surface of T-cells
- Recognizes an antigen on the leukemia cell surface (CD19) and contains a co-activation domain (4-1BB for tisagenlecleucel) and the CD3 zeta domain that mediates target cell killing

Si Lim, *Pediatr Blood Cancer,* 68:e29123, 2021

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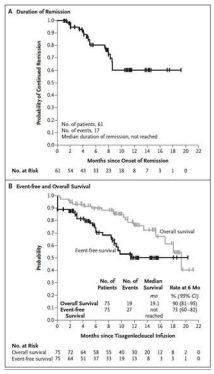
ORIGINAL ARTICLE

Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia

S.L. Maude, T.W. Laetsch, J. Buechner, S. Rives, M. Boyer, H. Bittencourt, P. Bader, M.R. Verneris, H.E. Stefanski, G.D. Myers, M. Qayed, B. De Moerloose, H. Hiramatsu, K. Schlis, K.L. Davis, P.L. Martin, E.R. Nemecek, G.A. Yanik, C. Peters, A. Baruchel, N. Boissel, F. Mechinaud, A. Balduzzi, J. Krueger, C.H. June, B.L. Levine, P. Wood, T. Taran, M. Leung, K.T. Mueller, Y. Zhang, K. Sen, D. Lebwohl, M.A. Pulsipher, and S.A. Grupp



- ELIANA was the first global, multicenter CAR T cell trial
- Treated patients had relapsed/refractory (r/r) ALL with a mean of 3 prior therapies (range 1-8) and 61% with prior HSCT
- CR + CRi (within 3 months) 82% (65/79 infused; 95% CI, 72-90)
- 98% (64/65) of responses were MRD-negative
- Duration of remission among responders
  - 60% at 12 months
- Event-free survival among infused patients
  - 50% (95% CI, 35% to 64%) at 12 months
- Overall survival among infused patients
  - 76% (95% CI, 63% to 86%) at 12 months
- *Results led to FDA approval of tisagenlecleucel in r/r ALL on 8/30/17*

Maude, *N Engl J Med*, 378: 439-48, 2018

CAR T-cells: Bridge to Transplant or Definitive Therapy?

- CD19-redirected CAR T-cells approved for relapsed/refractory ALL
  - CD22 CAR and CD19+ CD22 CAR under active clinical investigation
- >90% attain a complete remission (CR), almost always MRD-negative
- What should you do next?
- In early CAR T-cell trials, most (2/3-3/4) patients had relapsed after prior HSCT and many patients who entered CR did not receive subsequent therapy
  - Clearly see a long-term plateau in survival, showing that CAR T-cells can be a curative therapy by itself
  - However, no clear guidelines on who "needs" HSCT post CAR and who might be cured with no further therapy
  - Substantial institutional variation
  - Prognostic biomarkers needed to help identify who should or should not undergo HSCT

Si Lim, *Pediatr Blood Cancer*, 68:e29123, 2021

Learning Objectives

- Advances in treatments for ALL in children
- Side-effect management
- Advocating for your child's needs with the healthcare team

Acute Side Effects of ALL Therapy: Common

- General
  - Low blood counts and mucositis
    - Need for transfusions of red blood cells (rbc) or platelets
    - Infection risk: hospitalization and IV antibiotics for fever and neutropenia (F+N)
  - Nausea and vomiting: risk is drug-specific
- Corticosteroids
  - Appetite changes and weight gain, hyperglycemia, mood changes
- Vincristine
  - Neuropathy, constipation
- Asparaginase products
  - Allergy or hypersensitivity reactions
  - May need to change to a different product (erwinia asparaginase)
- Hair loss: related to specific drugs

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Acute Side Effects of ALL Therapy: Uncommon but Can be Severe

- IV and intrathecal methotrexate
  - Stroke-like symptoms, seizures
- Asparaginase products
  - Bleeding or clotting (stroke or superior sagittal venous thrombosis)
  - Pancreatitis
- Anthracyclines
  - Heart muscle damage (cardiomyopathy); very rare with doses used for newly diagnosed ALL

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Side Effects: Prevention and Minimization

- Most centers have ”supportive care” recommendations
- Infections
  - Bactrim/Septra or pentamidine to prevent a rare pneumonia (PJP)
  - Centers may give prophylactic antibiotics or antifungal medications during specific phases of therapy
- Constipation
  - Stool softeners and laxatives during phases with vincristine
- Antiemetics to prevent or treat nausea and vomiting
  - Substantial patient to patient variability so make sure your treatment team knows what side effects your child has

“Normal” Life During ALL Therapy

- Different centers have different recommendations
- At our center we encourage school/preschool attendance and participation in normal childhood activities whenever possible for children with newly diagnosed ALL
  - Sport participation may depend on phase of therapy, especially for teenagers and contact sports
- 90% of children will be long term survivors and we want them to have as normal a childhood as possible

Long-Term Side Effects of ALL Therapy

- Risk depends on treatment received
- Much higher if undergo stem cell transplant (SCT) or need treatment for relapsed ALL
- Fertility issues
  - Uncommon unless have SCT or treatment for relapse
- Birth defects in children
  - No significant increased risk
- Learning and school performance
  - Higher risk with cranial irradiation or age <6 at initial diagnosis
  - Many centers offer formal neurocognitive evaluations after therapy completion

Learning Objectives

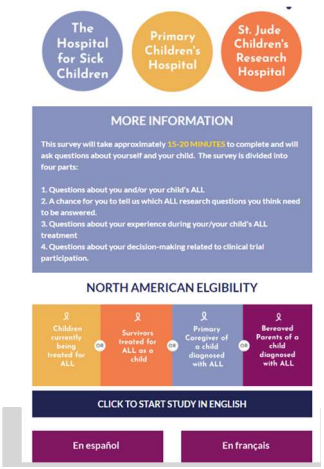
- Advances in treatments for ALL in children
- Side-effect management
- Advocating for your child's needs with the healthcare team

Stakeholder Informed Priority Setting for Pediatric ALL Research

What: Investigator developed a patient/parent piloted survey

Purpose: To systematically capture parent and patient lived-experiences, perspectives, and preferences to better incorporate patient and parent voice into clinical trial design

Who: Partnership between Kellee Parker (pediatric oncologist), Lindsay Jibb (PhD RN researcher), Sarah Alexander (pediatric oncologist, chair of COG ALL cancer control group), Lisa Jacola (neuropsychologist, ALL-behavioral science liaison) and Kim Buff (ALL patient advocate/founder of Momcology®)



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Data captured

Demographic and ALL treatment information

Most difficult, disruptive and worrisome aspects of ALL treatment and experience

Acceptability of clinical trial with a de-escalation of therapy and preferences on design and consent support

Parent/Patient defined unanswered pediatric ALL research questions

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Dissemination, Utilization & Other Future Plans

- Results presented Children's Oncology Group Spring Meeting to inform development and design of future ALL clinical trials
- Momcology® webinar to share results back with the contributing community
- Future conference presentations and open access publications
- Stakeholder engagement symposium
- Continue to refine process to increase diversity of participants & apply to other disease groups

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Data for this study is not yet published

Please reach out to study team for questions!

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ASK A QUESTION
CHILDHOOD ALL: A ROADMAP TO THE FUTURE

Ask a question by phone:

Press star (*) then the number 1 on your keypad.

Ask a question by web:

Click "Ask a question"
Type your question
Click "Submit"

Due to time constraints, we can only take one question per person. Once you've asked your question, the operator will transfer you back into the audience line.

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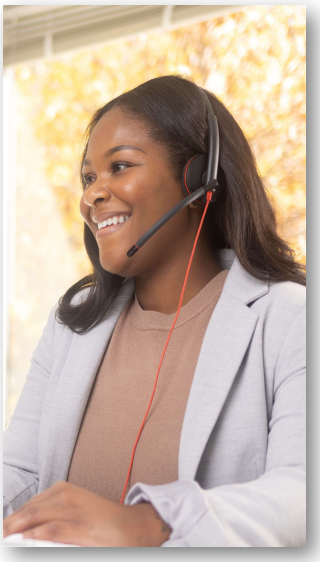
LLS EDUCATION & SUPPORT RESOURCES



HOW TO CONTACT US:

To contact an **Information Specialist** about disease, treatment and support information, resources and clinical trials:
www.LLS.org/InformationSpecialists

Call: (800) 955-4572
Monday to Friday, 9 a.m. to 9 p.m. ET
Chat live online: www.LLS.org/InformationSpecialists
Monday to Friday, 10 a.m. to 7 p.m. ET
Email: www.LLS.org/ContactUs
All email messages are answered within one business day.

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Work one-on-one with an LLS Clinical Trial Nurse Navigator who will help you find clinical trials and personally assist you throughout the entire clinical-trial process.
www.LLS.org/Navigation

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Our registered dietitian has expertise in oncology nutrition and provides free one-on-one consultations by phone or email.
www.LLSNutrition.org

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LLS EDUCATION & SUPPORT RESOURCES

Online Chats

Online Chats are free, live sessions, moderated by oncology social workers. To register for one of the chats below, or for more information, please visit **www.LLS.org/Chat**

Education Videos

View our free education videos on disease, treatment, and survivorship. To view all patient videos, please visit **www.LLS.org/EducationVideos**

Patient Podcast

The Bloodline with LLS is here to remind you that after a diagnosis comes hope. To listen to an episode, please visit **www.TheBloodline.org**

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LLS EDUCATION & SUPPORT RESOURCES

The Leukemia & Lymphoma Society (LLS) offers the following financial assistance programs to help individuals with blood cancers: **www.LLS.org/Finances**

To order free materials: **www.LLS.org/Booklets**

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THANK YOU
PLEASE PROVIDE US WITH FEEDBACK,
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