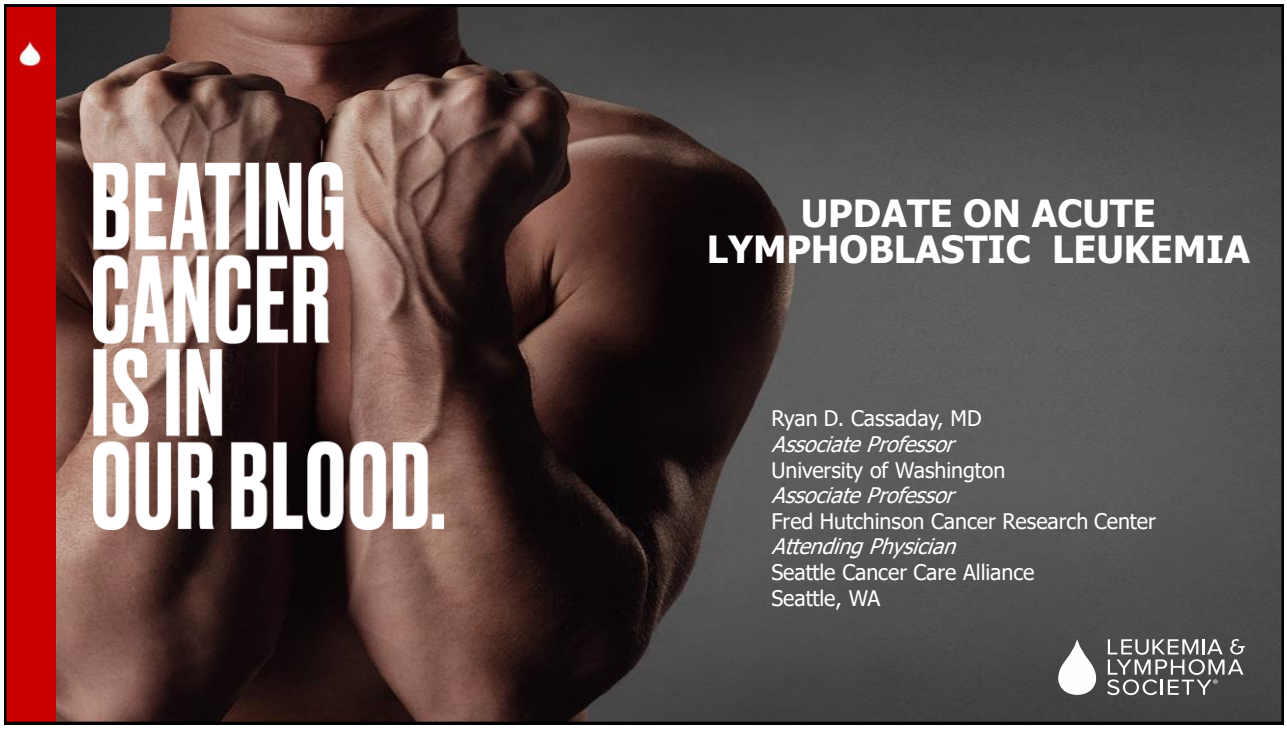

UPDATE ON ACUTE LYMPHOBLASTIC LEUKEMIA

Ryan D. Cassaday, MD
Associate Professor
University of Washington
Associate Professor
Fred Hutchinson Cancer Research Center
Attending Physician
Seattle Cancer Care Alliance
Seattle, WA

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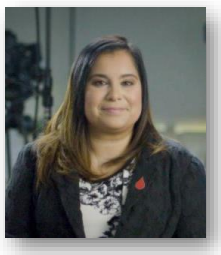
WELCOMING REMARKS

Update on Acute Lymphoblastic Leukemia



Lizette Figueroa-Rivera
Sr. Director, Education & Support
The Leukemia & Lymphoma Society

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DISCLOSURES

Update on Acute Lymphoblastic Leukemia

Amgen: grant support, honoraria/consultation fee
Kite/Gilead: grant support, honoraria/consultation fee
Pfizer: grant support, honoraria/consultation fee

Topics

- Basic Information
- High-Risk Features
  - Measurable residual disease (MRD)
- Treatment Approaches
  - Chemotherapy
  - Immunotherapy
  - Blood & Marrow Transplantation

BASIC INFORMATION

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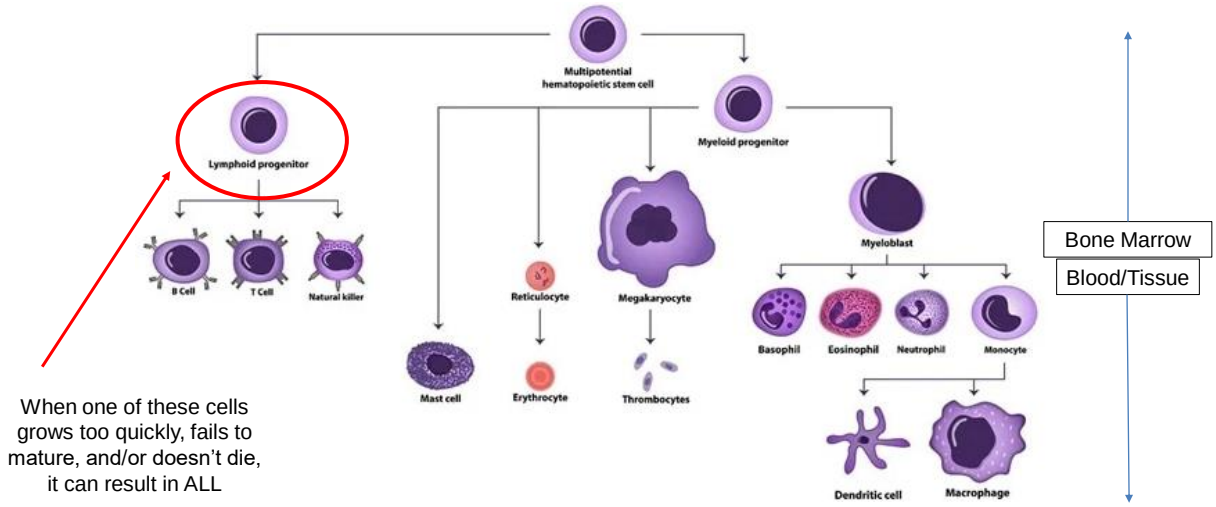
Leukemia = Cancer of Blood Cells



When one of these cells grows too quickly, fails to mature, and/or doesn't die, it can result in ALL

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Modified from: https://www.news-medical.net/life-sciences/What-is-Hematopoiesis.aspx

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Changes in the Blood Caused by ALL

Normal

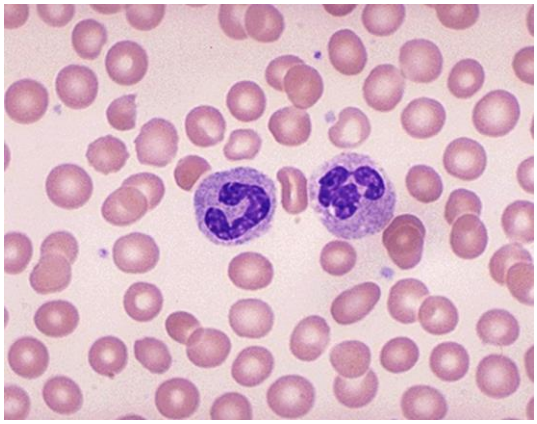

Image Courtesy of Univ. of Utah:
https://library.med.utah.edu/WebPath/

ALL

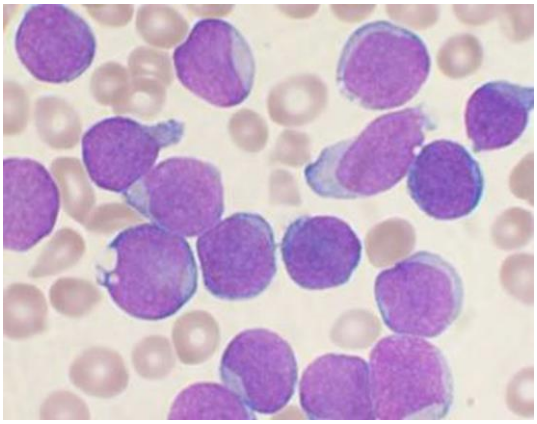

Image Courtesy of Wikipedia:
https://en.wikipedia.org/

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Leukemia in the U.S., 2021

	New Cases	Deaths
ALL	**5,690**	**1,580**
CLL	21,250	4,320
AML	20,240	11,400
CML	9,110	1,220
Other	4,800	5,140
Total	60,530	23,100

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Siegel, *et al. CA Cancer J Clin* 2021;71:7-33.

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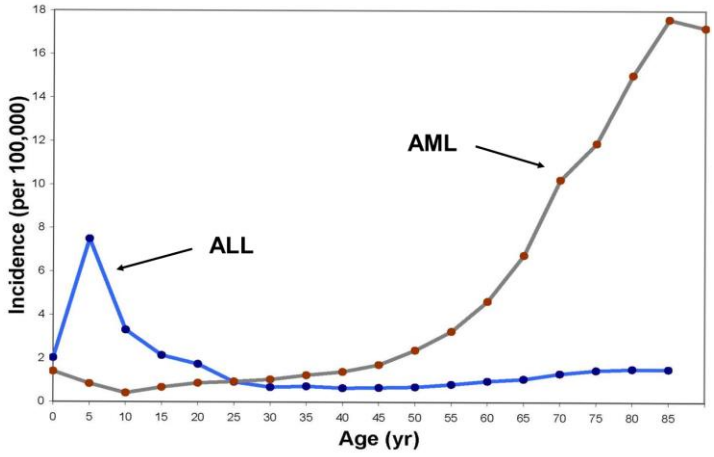
Acute Leukemia Incidence by Age



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Is it Leukemia or Lymphoma?

Lymphoblastic Lymphoma

Lymphoblastic Leukemia

Enlarged Lymph Nodes
Tumor Mass in Chest, Testicle, etc.

Cancer Cells in Blood and/or Bone Marrow

- Official name: lymphoblastic *leukemia/lymphoma*
- Generally treated the same way regardless of how it presents

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Subgroups of ALL

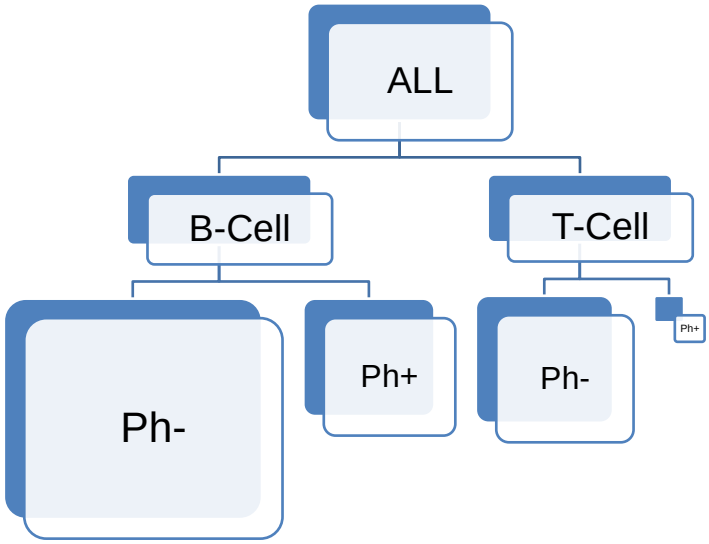
~80% is B-cell, ~20% T-cell

- RARELY can see features of both in the same case

Ph = Philadelphia chromosome

- Found in ~20% of cases (Ph+)
- VAST majority are B-cell
- (More on this later!)

T-cell more commonly associated with "lymphoma" presentation



(Note: bottom row is approximately to scale based on incidence)

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High-Risk Features

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Estimating Prognosis in Adults with ALL

- Age
  - Generally, prognosis worsens as we age
  - Over age 35 = high risk
- Number of white blood cells ("WBC count")
  - Normal WBC count: ~4,000-10,000 cells/µL of blood
  - High risk B-cell: > 30,000/µL
  - High-risk T-cell: > 100,000/µL
- Cytogenetics = evaluation of chromosome structure, number, etc.
  - Normal: 23 pairs of chromosomes
  - Abnormalities can lead to better or worse prognosis
  - Philadelphia chromosome is an example (seriously, more on this later!)
- Research identifying newer groups: ETP-ALL, Ph-like ALL, etc.
- Regardless of any of these, ***cure is still possible***

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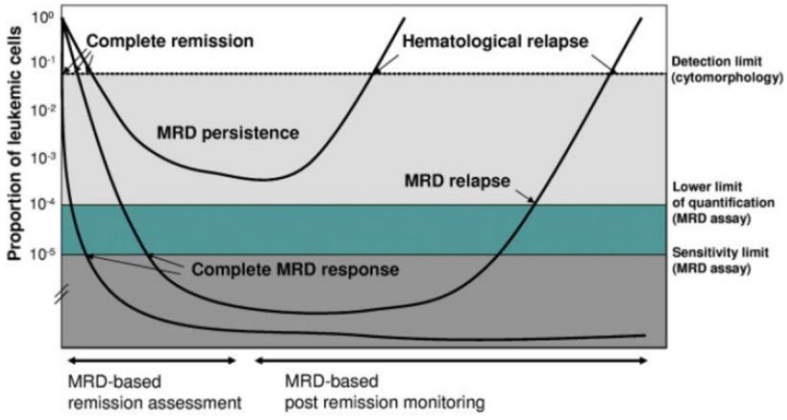
Conceptualization of Measurable Residual Disease (MRD)



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Bruggemann, *et al. Blood*. 2012;107:4470-81.

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Basics of MRD Testing

- Different methods available
  - Most common in US = flow cytometry
  - FDA-approved test called clonoSEQ uses gene sequencing from each patient's leukemia cells → more sensitive, longer turn-around
- Not all laboratories are the same
- Important role at different timepoints in treatment
  - End of "induction" (~3-4 weeks after starting)
  - End of "consolidation" (~2-3 months after starting)
  - Prior to transplant
- Specimen quality is important
  - Bone marrow is generally more reliable than blood
  - Needs to be the tested on a small volume from the first pull of aspirate

MAKE SURE YOUR HEMATOLOGIST/ONCOLOGIST PLANS TO DO MRD TESTING!
IF THEY AREN'T SURE HOW, THEY CAN CALL A SPECIALIST!

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TREATMENT APPROACHES

General Principles: Newly-Diagnosed

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A Few Words on Clinical Trials

- Designed to help us answer questions in our field
  - Is one treatment approach better than another?
  - Is a new drug effective?
  - Are there new mechanisms of action that we can explore?
  - Will laboratory testing help us understand more about the disease?
- Excellent medical care is an integral part of the experience
- Participants are not "guinea pigs"
- If a study includes randomization, it is because we don't know which option is best
- May permit access to exciting (but not yet approved) agents

Importance of Philadelphia Chromosome

Ph- ALL

- Still largely consists of multi-agent chemotherapy regimens
- Young adults may be treated with "pediatric" regimens
- Newer drugs may allow us to use less chemotherapy

Ph+ ALL

- Revolutionized by the use of oral medications that block its effects
- Latest approaches are using less and less chemotherapy
- Historically would include transplantation; maybe not anymore?

Where Does Transplant Fit?

- Procedure that gives the patient (recipient) a new blood and immune system
  - Can help keep some patients in remission
  - Complications make it too risky or unavailable to some
- Historically recommended for younger fit adults with high-risk disease features
- Now being used more selectively
  - Still an important option for some patients while in first remission
  - For others, may be reserved in case disease comes back → only treatment that has established curative potential in this situation

TREATMENT APPROACHES

Newly-Diagnosed Ph- ALL

Pros and Cons of Pediatric Regimens

Pros

- Some studies of past experiences ("retrospective") suggest outcomes are better
- May require fewer hospitalizations

Cons

- No definitive ("prospective") studies have proven these are better
- More lumbar punctures
- Not all doctors/clinics are comfortable with them

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Example of a Pediatric Regimen for ALL: VERY Complex

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 01-28
- **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 & D 29 (also administered on D 15 and 22 for CNS3 patient)

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/m2 (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 & 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 & 22 for CNS3 patients)

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
- **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, 43, and 50
- **DEX** – 10 mg/m^2 PO (or IV) divided BID on D 1-7 and 15-21
- **PEG** – 2500 IU/m^2 IM or IV 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, & 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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Stock, *et al*. *Blood*. 2019;133:1548-59.

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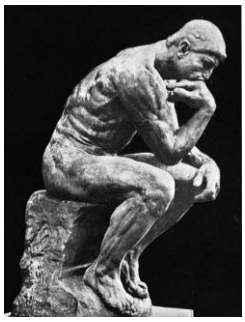
Approaches for Less-Young Adults

HyperCVAD

Linker

DFCI



CALGB 8811

GMALL

ECOG 2993

Mini-hyperCVD + InO

- None are known to be superior
- Often determined by comfort of the doctor and/or center—rare disease, so stick with one approach

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ALL in Older Adults

- Standard regimens can be very toxic
- Older adults often have other medical issues, which can make them more susceptible to complications
- Much higher rate of serious complications (even death) when standard approaches are tried
- If we aren't aggressive enough, disease won't respond
- Newer strategies are trying to reduce/replace chemotherapy without sacrificing efficacy

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Treatment Approaches

Newly-Diagnosed Ph+ ALL

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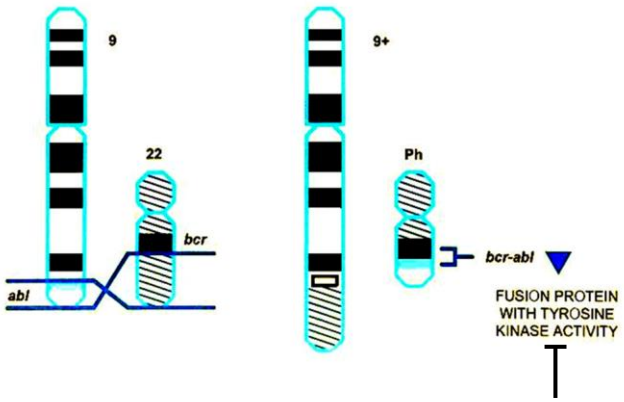
What is the Philadelphia Chromosome?!?!



Targeted drugs (imatinib, dasatinib, ponatinib, etc.) are designed to BLOCK this activity—
Referred to as “tyrosine kinase inhibitors” (TKIs)

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Treatment of Ph+ ALL: Summary

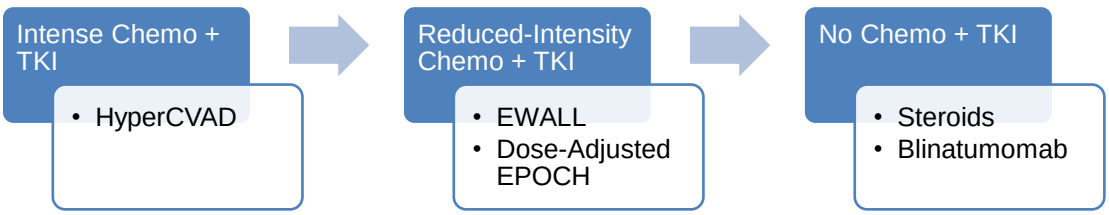
The basics:

- Include TKI with chemotherapy

Controversial topics:

- How much chemotherapy is necessary?
- Is one particular TKI superior?
- Should transplant be recommended for all patients?

Evolution of New Approaches for Ph+ ALL



- Less chemo generally means fewer side-effects, but not necessarily better outcomes
- Less experience with newer strategies
  - Will early results hold up over time?
  - What happens if/when leukemia relapses?

Treatment Approaches

If Initial Treatment Fails (a.k.a., Relapsed/Refractory ALL)

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Approvals for Relapsed/Refractory ALL

- Traditional Chemotherapy Agents:
  - Nelarabine (T-ALL)
  - Clofarabine
  - Liposomal vincristine
- TKI for Ph+ ALL: ponatinib
- CD22 antibody-drug conjugate: inotuzumab ozogamicin
- CD3-CD19 bispecific T-cell engager: blinatumomab
- CD19 CAR-T cells: tisagenlecleucel

Approved Most Recently

Most Excitement

Only for B-Cell ALL

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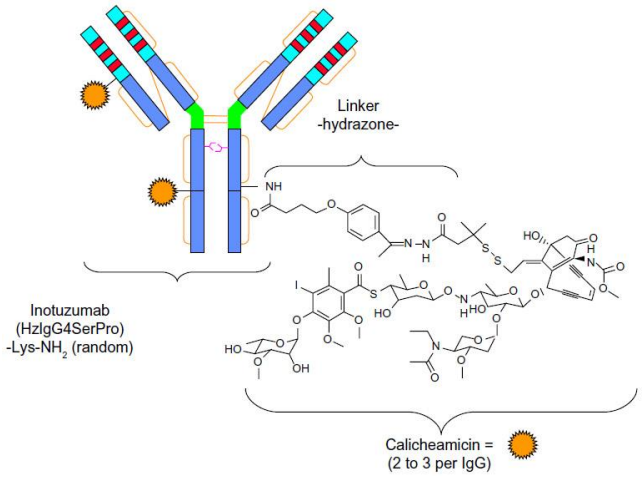
Inotuzumab Ozogamicin (InO) = Antibody-Drug Conjugate



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Thomas. *Blood Lymph Cancer: Targets and Therapy*. 2014;4:1-8.

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Notable Features of InO

- Relatively easy to administer
- Side-effects are analogous to chemo
  - Low blood counts
  - Liver toxicity, severe in some cases (VOD/SOS)
- Results may improve with addition of low-dose chemotherapy ("mini-hyperCVD + InO")
- Unlikely to work for long by itself—generally followed by transplant

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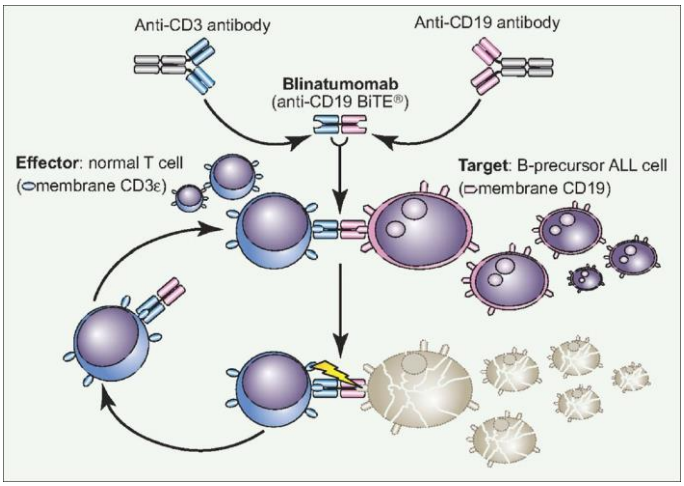
Blinatumomab (Blin/Blina) = Bispecific T-Cell Engager

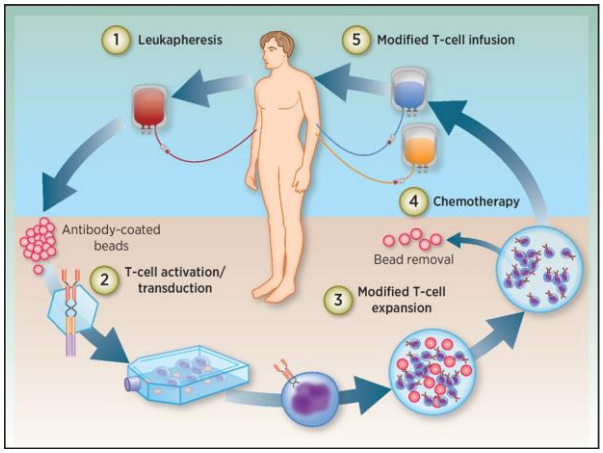


Kapoor, *et al. Clin Cancer Invest J*. 2014;3(6):577-8.

Notable Features of Blinatumomab

- More challenging to administer
  - Continuous IV infusion for 4 straight weeks
  - Breaks between cycles last 2 weeks
  - Ongoing study of a subcutaneous form
- Unique side-effect profile
  - Cytokine release syndrome (CRS): inflammatory response caused by drug
  - Neurologic toxicity: probably related to inflammation or direct effect on brain tissue
- Seems to work better when the amount of leukemia in the body is lower (including MRD)
- Some patients MAY stay in remission without transplant

How Chimeric Antigen Receptor (CAR)-T Cells are Produced



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Maus & June. *Clin Cancer Res*. 2016;22(8):1875-84.

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Notable Features CAR-T Cells

- Currently only approved for patients age 25 years or younger
  - Recent study of a different product in adults over age 18
  - May become FDA approved this year
- Only offered at specific medical centers
  - May need to relocate for 2+ months with a caregiver
- Does require some chemotherapy
- Unique side-effect profile
  - Similar to blinatumomab (but probably more severe)
  - Chemotherapy given prior to infusion also can cause toxicity
- Some patients MAY stay in remission without transplant

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How Do We Choose Between These Options?

- Disease Burden
- Prior Treatment(s)
- Other Medical Issues
- Logistics
- Caregiver Availability
- Transplant?

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Even Though These Are All Good Options…

CLINICAL TRIALS ARE STILL IMPORTANT TO CONSIDER

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Summary and Concluding Remarks

- Our understanding of biology and behavior of ALL is improving
- This has helped generate new treatment approaches
  - New laboratory testing
  - New drugs
  - New combinations
- Despite these advances, ALL in adults remains a challenging disease to treat
- Clinical trials and support from organizations like LLS are helping to advance our field and improve outcomes for everyone

THANK YOU

Questions?

Q&A SESSION

Update on Acute Lymphoblastic Leukemia

- **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:

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: infocenter@LLS.org
All email messages are answered within one business day.

CLINICAL TRIAL SUPPORT CENTER
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

NUTRITION CONSULTATIONS
Our registered dietitian has expertise in oncology nutrition and provides free one-on-one consultations by phone or email.
www.LLS.org/Consult.

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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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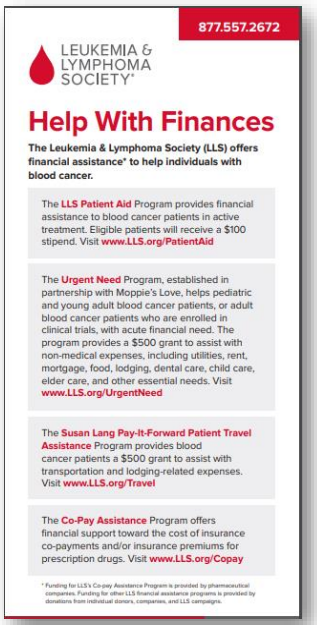

The Leukemia & Lymphoma Society (LLS) offers the following financial assistance programs to help individuals with blood cancer: **www.LLS.org/Finances**

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

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THANK YOU
We have one goal: A world without blood cancers
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