Hello, everyone. On behalf of The Leukemia & Lymphoma Society, I would like to welcome all of you. Special thanks to Dr. Elizabeth Raetz and Dr. Wendy Stock for volunteering their time and expertise with us today. Before we begin, I’d like to introduce Dr. Louis DeGennaro, The Leukemia & Lymphoma Society’s President and Chief Executive Officer, who will share a few words.

Dr. Louis DeGennaro:
I’m Dr. Louis DeGennaro, President and CEO of The Leukemia & Lymphoma Society. I’d like to welcome all of the patients, caregivers and healthcare professionals attending the program today.

At The Leukemia & Lymphoma Society, our vision is a world without blood cancers. Since we started in 1949, LLS has invested more than $1.2 billion in breakthrough research to advance lifesaving treatments and cures. We’ve played a pioneering role in funding many of today’s most promising advances, including targeted therapies and immunotherapies that have led to increased survival rates and improve the quality of life for many blood cancer patients.

Though LLS is known for funding groundbreaking research, we do so much more. As this program demonstrates, we are the leading source of free blood cancer information, education, and support for patients, survivors, caregivers, families, and healthcare professionals. We also support blood cancer patients in their local communities through our chapters across the country, and we advocate at the state and federal level for policies to ensure that patients have access to quality, affordable, and coordinated care. We’re committed to working tirelessly toward our mission every single day.

Today you’ll have the opportunity to learn from esteemed key opinion leaders. They each have volunteered their time and we appreciate their dedication to supporting our mission, their commitment to caring for patients living with blood cancers. Thank you for joining us.

Lizette Figueroa-Rivera:
Thank you. And, we would like to acknowledge and thank Pfizer and Takeda Oncology for support of this program.

I am now pleased to introduce our first presenter, Dr. Elizabeth Raetz from NYU School of Medicine in New York, NY, who will speak first on pediatric ALL. Dr. Raetz, I’m privileged to turn the program over to you.
Dr. Elizabeth Raetz:

Thank you so much for the opportunity to join you today to discuss recent advances in the treatment of childhood ALL.

Disclosure:

Elizabeth Raetz, MD, has affiliations with Pfizer (Grant Support).

Wendy Stock, MD has no affiliations to disclose.

Slide 3: Disclosures

As a way of disclosures, I do receive research funding, a grant for a clinical trial from Pfizer.
Leukemia is the Most Common Childhood Cancer

Leukemia is the most common childhood cancer, representing approximately one-third of all malignancies in children from birth to 14 years of age.

Slide 5: Leukemia Epidemiology: Children vs. Adults

This pie chart here shows the relative frequency of major hematopoietic malignancies in children on the left, compared
to that in adults on the right. And you can see that while ALL is the most common blood system cancer in children, it is
relatively infrequent in adulthood where lymphomas and chronic leukemias predominate.

Slide 6: Childhood ALL Outcomes

This slide shows the tremendous improvements in childhood ALL outcomes over the past 5 decades, with survival rates
now exceeding 90%.
Slide 7: Improvements in ALL Survival: 2006-10 vs. 2000-05

This has raised the question as to whether we’ve reached an outcome plateau. However, in looking more closely at survival rates among children treated on Children’s Oncology Group (COG) trials, we’ve continued to see improvements in more recent eras. This has been particularly notable for T-ALL, where there’ve been 10% improvements in overall survival rates in the recent decade.
Curative Strategies in Childhood ALL

- Delivery of multiple chemotherapy agents to prevent drug resistance
- Recognition that sanctuary sites need focused treatment (CNS)
- Identification of risk groups at diagnosis to determine intensity of therapy
  - NCI risk group and clinical features
  - Sentinel genetic lesions
  - Early response to therapy (MRD)

Slide 8: Curative Strategies in Childhood ALL

These outcome improvements have been attributed to a number of different factors that include the delivery of multiple chemotherapy agents to prevent drug resistance; the recognition that sanctuary sites need focused treatment, so particularly the central nervous system and testicular area; and also the identification of risk groups at diagnosis to determine the appropriate intensity of therapy. And, some of the key factors for risk assignment are an NCI (National Cancer Institute) risk group, so a child’s age at their initial diagnosis and their white blood cell count, and other clinical features of their disease, such as whether they have a central nervous system involvement. Another key factor for determining risk is the presence of sentinel genetic lesions in the blast population. And then, another critical factor is how quickly their leukemia responds to treatment. And, this is now measured most accurately by determining something called MRD or minimal residual disease.
### Key Clinical Prognostic Factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>&gt; 1, &lt; 10 years – favorable</td>
</tr>
<tr>
<td></td>
<td>≤ 1 and ≥ 10 years – unfavorable</td>
</tr>
<tr>
<td><strong>White Blood Cell Count</strong></td>
<td>&lt;50,000/μL – favorable</td>
</tr>
<tr>
<td></td>
<td>≥50,000/μL – unfavorable</td>
</tr>
<tr>
<td><strong>Immunophenotype</strong></td>
<td>B-precursor – favorable</td>
</tr>
<tr>
<td></td>
<td>T-cell – requires more intensive therapy</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>Female – favorable</td>
</tr>
<tr>
<td></td>
<td>Male – historically required longer treatment</td>
</tr>
<tr>
<td><strong>Extradullary Disease</strong></td>
<td>Absent – favorable</td>
</tr>
<tr>
<td></td>
<td>Present – unfavorable</td>
</tr>
</tbody>
</table>

**Slide 9: Key Clinical Prognostic Factors**

This table here summarizes some of the key clinical prognostic factors that we use in childhood leukemia. You can see that age is important, so that children over 1 year of age and less than 10 years of age tend to have a more favorable prognosis, whereas infants less than 1 and children over 10 years of age generally require stronger treatment. White blood cell count at diagnosis is also prognostic with a count of less than 50,000 being favorable and more than 50,000 placing children in the higher risk group. The immunophenotype of the leukemia is also important. A B-precursor immunophenotype is most common in about 85% of children with leukemia and associated with generally favorable outcomes, where T-ALL outcomes, I've now shown you, have approached those in B-ALL and are outstanding, but T-cell leukemia requires more intensive therapy. A child's gender is also important. Females have a more favorable prognosis than males. And, the presence of extradullary disease, most commonly in the central nervous system, is also an adverse prognostic feature.
In addition to clinical features and measurements of early treatment response, the presence or absence or specific genetic changes in leukemic blasts plays an essential role in determining prognosis and stratifying ALL therapy as well. This pie chart shows the breakdown of common cytogenetic findings, and you can see that about 50% of children have genetic changes in their blast population that are associated with a favorable outcome, so high chromosome content or alternatively the presence of the ETV6-RUNX1 translocation.

In contrast, relatively rarely, children will have unfavorable genetic features in their blast population, so iAMP21, the BCR-ABL fusion, which is referred to as the Philadelphia chromosome, or MLL gene rearrangements.
Minimal residual disease response at the end of induction is the single most important outcome predictor in childhood ALL. And, you can see that those children who are MRD-negative have much higher chances for long-term survival than those who have persistent disease that remains at the end of induction.
Approach to Genetic Testing and Classification

- **Children’s Oncology Group classification studies**
  - POG 9900 (12/13/00-2/28/05, n= 3762)
  - AALL03B1 (12/29/03-9/6/11, n=11,206)
  - AALL08B1 (08/09/10-7/23/18, n= 17,372)

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**Slide 12: Approach to Genetic Testing and Classification**

As an example of how this information is used to assign risk group to each child with ALL, the Children’s Oncology Group has conducted a series of 3 different classification studies, enrolling thousands of children, where genetic and MRD testing has been performed uniformly in approved laboratories and used for treatment stratification. Other treating groups use similar classification systems as well.
Risk Classification in Childhood ALL

- NCI Risk Group & Extramedullary Disease Status
- Sentinel Genetic Lesions
  - Trisomies 4, 10, & 17
  - ETV6-RUNX1
  - BCR-ABL1
  - KMT2A-R
  - iAMP21
  - Chromosomes <44
- Rapidity of Response
  - Morphology day 8/15
  - Day 29 Flow MRD

Low Risk (29%)
Standard Risk (33%)
High Risk (34%)
Very High Risk (4%)

Slide 13: Risk Classification in Childhood ALL

This slide shows an overview of the most recent risk classification system used by the Children’s Oncology Group. And, you can see here that at the time of diagnosis children with ALL were enrolled in the study and then initiated induction therapy according to their risk group, so their age and white blood cell count. So, if they were age between 1 and 10 and had a low white blood cell count, they began a standard risk induction regimen with 3 different medications, whereas if they were high risk, with an age greater than 10 or a high white blood cell count, they began induction therapy with 4 drugs. Then during induction information about the genetic features of their leukemia population became available and their response to treatment during the first month was assessed early at day 8 and 15 of induction, and also at day 29 by flow cytometry based MRD. All this information was then integrated during induction and at the end of induction they were assigned to either a low, standard, high risk, or very high-risk group for their subsequent treatment beyond induction.
Many Relapses Occur Unpredictably

Despite the strength of our current risk classification algorithms, there’re really many challenges that remain. And, one of the most significant challenges is if you look at children who relapse, about 50% of those children who ultimately relapse fell into what we would assume to be one of the most favorable risk groups. So, these relapses are still occurring unpredictably. And, this highlights the need for continued refinements in risk classification.
Another challenge is where I showed you that the outcomes overall for children with ALL have been quite good and have continued to improve. This hasn’t been true at the end of the age spectrum, so here you can see the outcomes for infants less than a year of age, are clearly inferior, as well as those for the adolescents and the young adults.
I want to shift directions next and talk about the current landscape and future directions in ALL therapy.
Overarching Goals for ALL Therapy

- **Improve cure rates**—Identify patients who will fail current therapies and alter approaches
  - Specific genomic subsets
  - High minimal residual disease (MRD) burdens
  - Adolescents and young adults (AYAs)
  - Infants
- **Decrease acute and late effects**
- **Optimize medication adherence**

**Slide 17: Overarching Goals for ALL Therapy**

So, overarching goals for ALL therapy are first and foremost to improve cure rates by identifying patients who have failed current therapies and altering their approaches. So, there have been a number of efforts to refine therapy for children with specific genomic alterations, those who have high minimal residual disease burdens, the adolescents and young adults, and infants. Other overarching goals for ALL therapy are to decrease acute and late effects and to optimize medication adherence.
Targeted Therapy for ALL

Recently there’s been a great deal of enthusiasm about adapting therapies that directly target genetic changes in leukemia cells.
Philadelphia Chromosome-like (Ph-like) ALL

- Ph-like ALL comprises 15-20% of high-risk B-ALL occurring in children and adolescents and 20-40% of B-ALL in adults
  - Driven by genetic alterations that activate kinase signaling
  - High rates of MRD and relapse with conventional chemotherapy

Slide 19: Philadelphia Chromosome-like (Ph-like) ALL

One subtype of ALL where this has been particularly relevant has been Ph-like ALL. Ph-like ALL was defined in 2009 by both Dutch and US groups and it’s a very unique subtype of leukemia. It was initially discovered because the leukemic blasts had a gene expression profile that looked nearly identical to that in Ph-positive ALL, but it left the underlying BCR-ABL fusion. We’ve now learned that Ph-like ALL comprises about 15 to 20% of high-risk B-ALL occurring in children and in adolescents, and up to 20 to 40% of B-ALL in adults. We know now that this type of leukemia is driven by genetic alterations that activate kinase signaling, and this is a challenging type of leukemia to treat, with high rates of minimal residual disease and relapse when treated with conventional chemotherapy.
Genetic Subtypes of Ph-like ALL

Elegant studies have shown the specific subtypes, genetic subtypes of Ph-like ALL, and you can see on this diagram here that most commonly, individuals with Ph-like ALL have rearrangements in a gene called CRLF2. Other subtypes of Ph-like ALL involve ABL-class alterations, JAK2 and EPO rearrangements, and other JAK-STAT signaling pathway abnormalities, as well as Ras pathway abnormalities. Despite the genetic diversity in Ph-like ALL, the majority of these cases have alterations that converge on 2 common pathways, the ABL-class pathway and the JAK-STAT signaling pathway.
Spectrum of Recurring Genetic Alterations in Ph-like ALL

- ABL-class fusions
- EPOR or JAK2 rearranged
- CRLF2 rearranged
- Other JAK-STAT pathway
- Ras pathway
- Misc or no kinase activation


Slide 21: Spectrum of Recurring Genetic Alterations in Ph-like ALL

And this is notable because we would predict then that the majority of individuals with Ph-like ALL would have underlying genetic lesions that would be predicted to be amenable to treatment with FDA approved ABL-class inhibitors and JAK inhibitors.
Can We Build on the Success of TKI + Chemotherapy in Ph+ ALL?

In thinking about how to design optimal treatment for individuals with Ph-like ALL, we asked if we could look back at the experience in treating Philadelphia chromosome positive ALL. Here you can see on the left, these are the results from a clinical trial where imatinib, the tyrosine kinase inhibitor, was added to conventional chemotherapy, and with the addition imatinib disease-free survival rates went from 20% to about 70% with the addition of this targeted treatment. So, this has become the paradigm that people have modeled for treatment of Ph-like ALL.

Nagar et al. *Cancer Res* 2002: 4236-4243

COG AALL0031: 7-yr DFS 71.7% vs. 21.4% for historical controls treated without TKIs
Importantly, there've also been some anecdotal clinical reports of responses to tyrosine kinase inhibitor therapy in Ph-like ALL. This case was reported of a 10-year-old boy who had refractory B-ALL with 70% blasts remaining at the end of induction. His cytogenetic analysis showed that there was an abnormality in the long arm of chromosome 5 at the location of the PDGFR beta gene. This child was later found to have a fusion that activated that gene, an EBF1-PDGFR beta fusion. He failed multiple rounds of aggressive chemotherapy and then was started on imatinib once the cytogenetic findings were confirmed, and had immediate clinical improvement. Within 2 weeks, he achieved a morphological remission with some residual disease and the detection of the chromosomal abnormality was gone. He has sustained a long-term remission. So, this is one example that would suggest that this is good to be studying this class of agents in Ph-like ALL.
I wanted to shift next to talk a little bit about immunotherapy for childhood ALL, which has been another area where there has been significant promise.
Promising New Immunotherapies for B-ALL

<table>
<thead>
<tr>
<th>Immune Therapy</th>
<th>Mechanism of Action</th>
<th>Patient Population Studied</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inotuzumab</td>
<td>CD22-directed humanized moAB conjugated to calicheamicin</td>
<td>Adults with CD22+R/R B-ALL</td>
<td>80.7% CR/CRI</td>
</tr>
<tr>
<td>Blinatumomab</td>
<td>Bispecific T cell receptor engager (BITE) that redirects CD3+ T cells to CD19+ blasts</td>
<td>Adults with R/R Ph- B-ALL, Children with R/R B-ALL</td>
<td>39% CR, 39% CR</td>
</tr>
<tr>
<td>CAR T cells</td>
<td>T cells transduced ex-vivo with chimeric anti-CD19 receptor</td>
<td>Children with CD19+ R/R B-ALL</td>
<td>83% CR/CRI</td>
</tr>
</tbody>
</table>


Slide 25: Promising New Immunotherapies for B-ALL

So, over the past decade there have been published trials that have shown the benefits of immunotherapy in many populations of children and adults with recurrent and newly diagnosed disease. So, one agent that has been promising, has been inotuzumab. Inotuzumab is a monoclonal antibody that’s directed to CD22 that’s commonly expressed on leukemic blasts. This antibody is conjugated to a cell poison called calicheamicin. Another agent that has been promising has been blinatumomab. Blinatumomab is also an antibody that binds to both a child or adult CD 3 positive T-cells, so healthy immune system cells. And, simultaneously binds to blast cells, leukemic blast cells that express CD19. And, a final drug that’s been very promising has been CAR-T cells. So, these are T-cells that have been transduced outside of an individual to express a receptor that will target CD19 on blast cells.
Inotuzumab Ozogamicin (IO)

- CD22 is expressed in >90% of pediatric pre-B ALLs
- Humanized IgG4 anti-CD22 antibody conjugated to calicheamicin, a potent cytotoxic anti-tumor antibiotic
- Rapid internalization upon binding


Slide 26: Inotuzumab Ozogamicin (IO)

And, just sometimes because a picture is more helpful, this is a diagram showing a depiction of inotuzumab. So, CD22 is expressed in over 90% of children with pre-B-ALL. And, inotuzumab, as I mentioned, is an antibody that’s conjugated to calicheamicin, a potent cytotoxic anti-tumor antibiotic. So, when inotuzumab binds to CD22 on the cell surface, it’s internalized rapidly and then delivers the calicheamicin poison to the cell replication machinery.
Slide 27: Blinatumomab

This next slide shows a depiction of blinatumomab. So, blinatumomab is what we term a bi-specific antibody that binds to both a child’s CD3 positive T-cells, so there’re T-cells in their body that fight infections and are good for tumor surveillance. And, it also simultaneously binds to CD19 on the surface of blast cells. So, in effect, brings a child’s immune system in contact with our tumor cell to initiate tumor cell lysis.
Slide 28: Chimeric Antigen Receptor (CAR)

And finally, the next slide is a depiction of chimeric antigen receptor T-cells. So, chimeric antigen receptors are engineered, and they’re expressed on the surface of a patient’s own T-cells. These constructs consist of a single antibody chain that specifically targets a tumor antigen, so in this case CD19 on the surface of blast cells.
Chimeric Antigen Receptor Therapy

The process of manufacturing and administering CAR-T cells is shown here. Chimeric antigen receptor therapy is similar to an autologous bone marrow transplant procedure. T-cells are collected from a child by apheresis and then the T-cells are expanded and genetically modified to express a CAR construct in a manufacturing lab. And then, they’re administered back to the patient in a process that takes about a month to complete.

Introduction of Molecularly or Immunologically Targeted Therapy in B-ALL

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Projected 5-yr DFS</th>
<th>Therapeutic Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>SR-Favorable</td>
<td>&gt;95%</td>
<td>Standard therapy with 2 year duration</td>
</tr>
<tr>
<td>HR-Favorable</td>
<td>&gt;94%</td>
<td>Blinatumomab</td>
</tr>
<tr>
<td>SR-Avg &amp; High</td>
<td>~89%</td>
<td></td>
</tr>
<tr>
<td>High Risk</td>
<td>~80%</td>
<td>Inotuzumab</td>
</tr>
<tr>
<td>Very High Risk</td>
<td>&lt;50%</td>
<td>CAR T-cell therapy</td>
</tr>
<tr>
<td>Ph+, Ph-like</td>
<td>60-85%</td>
<td>Molecularly targeted therapy</td>
</tr>
</tbody>
</table>

So, then looking ahead to the next planned Children’s Oncology Group trials in the front-line for children newly diagnosed with ALL, which should be opening later this year, there’ll be a lot of efforts to bring some of these new promising immunotherapeutics to the front-line to investigate their role in this group of patients. So, standard-risk favorable and high-risk favorable children have genetic features and response characteristics that would predict they have outstanding outcomes with disease-free survival rates that exceed 94%. So, these children will receive standard chemotherapy with a 2-year therapy duration for both boys and girls. The standard risk average and high patients have a projected disease-free survival rate of close to 90% and these children will be eligible for a randomization on the clinical trial to receive blinatumomab. The high-risk disease patients with a projected disease-free survival rate of about 80% will be eligible to participate in a trial where this randomization that includes inotuzumab. And, children with very high-risk disease with projected disease-free survival rates of less than 50%, will be eligible to enroll on a companion trial where they’ll receive CAR-T cell therapy. Children with Ph-positive and Ph-like disease will have the opportunity to receive molecularly targeted therapy.
So, if you look at the distribution in the predicted risk groups, the distribution is shown here, so in essence about 50% of children on this next generation of trials will be eligible to participate in a clinical trial that offers an immunotherapeutic agent.
Slide 32: T-cell ALL Outcomes: COG AALL0434

I wanted to shift next to discuss some recent updates in the treatment of T-cell ALL. So, significant outcomes of improvements have been seen, as I showed you in one of the first slides, so that overall survival rates for children with T-ALL now exceed 90%. The AALL0434 Children’s Oncology Group trial had 2 different randomizations that looked at 2 different schedules of methotrexate during the inner maintenance phase of treatment, and this trial showed that lower-dose methotrexate in an escalating schedule with asparaginase was superior to high-dose methotrexate. Of note, the timing of radiation on those 2 arms of the protocol did differ, so that children who received the lower-dose methotrexate had their radiation therapy earlier. And then, this trial also looked at the addition of a drug called nelarabine. There were six 5-day cassettes of nelarabine that were administered to patients who participated in the randomization. And, those children, nelarabine also showed a benefit in this patient population.
And finally, I think it's fair to say that the development of targeted therapy and immunotherapy in T-ALL has lagged a bit behind that in B-ALL. But, there've been some very exciting advances in understanding the biology of T-ALL in recent years and there're several pathways that have been shown to be activated and are potentially targetable. And right now, there are early phase trials that are investigating BCL-2 inhibitors, such as venetoclax, the anti-CD38 antibody daratumumab, and CDK4/6 inhibitor, such as palbociclib in children with refractory and relapsed T-ALL. So, more information should be available soon about these new classes of agents.
Decreasing Acute and Late Effects and Optimizing Adherence

And finally, I'll finish with a brief discussion of some ongoing efforts to decrease acute and late effects of treatment and measures to optimize medication adherence.
Slide 35: Why is it Important Not to Over Treat ALL?

There’s been growing recognition how crucial it is to assess the quality of survival when measuring the overall success of therapy and there’s a balance. While cure rates are now high for many childhood tumors, this does not come without an expense in terms of short- and long-term side effects from treatment. For example, the US Childhood Cancer Survivor Study of close to 15,000 childhood cancer survivors showed that 69% of ALL survivors have a serious chronic health condition at 30+ years. Efforts are now underway to determine if there’re certain side effects that children experience during treatment that will place them at a high risk for later chronic health conditions, so prevention strategies can be implemented. Carefully assessing how this impacts a patient’s perception of their quality of life over the continuum of treatment and survivorship is also essential.
Slide 36: Two Loci Associated with 6MP Tolerance at Genome-wide Significance Level

One example of an effort to identify children who are at high risk of developing low blood counts from 6MP is shown here. Very elegant studies from investigators at St. Jude Children’s Research Hospital have shown that children who have variants in either the TPMT gene or the NUDT15 gene are very likely to have intolerance with regular doses of 6MP. They’re likely to develop cytopenias. So, if you know that a child has an alteration or a variant in one of these genes from the get-go, their therapy can be modified so they receive a lower dose of this chemotherapy and can tolerate it better.
Slide 37: Natural History of Osteonecrosis

Another unwanted side effect that significantly impacts quality of life in children and particularly teenagers receiving ALL therapy is osteonecrosis, which is a term for death of a segment of bone, most particularly the hips and the knees. To try to understand this better in the most recent COG high-risk trial, the 1131 trial, MR screening, MRIs of the hips and knees, were performed at 3 time points during treatment. And, in addition to that levels of different drugs, so dexamethasone, methotrexate and asparaginase were measured and will be correlated with the risk for developing osteonecrosis. It's hoped that from these studies, if we can identify those children who are at most risk for developing this complication, that we can implement prevention strategies or alter their therapy up front.
And finally, there’s been a lot of interest in better understanding the neurocognitive side effects of ALL therapy. While most children don’t experience a decline in IQ or school performance, about 25% of children can experience difficulties with attention and processing speed. And so, within the most recent COG high-risk ALL 1131 trial, there was a neuropsychological testing battery called Cogstate that was performed at multiple time points in treatment. And then also, a more traditional battery of neuropsychological testing was performed. And, we hope from analyzing these data that we’ll understand what the course of neurocognitive function is over the trajectory of treatment and again be able to identify those children who are at most risk for having impairments long term.
Low Adherence to Oral 6MP Significantly Increases Relapse Risk

And finally, I'll finish with a discussion of adherence to daily 6-mercaptopurine. One of the most significant challenges with ALL therapy is the need to take daily 6MP and methotrexate weekly for a prolonged period of time. Available evidence suggests that a substantial proportion of teenagers and young adults don't adhere to therapy with nonadherence rates of about 60% that have been observed. If you look on the left you see that adherence rates definitely drop as children get older and nonadherence, which is defined as not taking 95% or more of daily scheduled 6MP has significantly been associated with about a 3-fold increase in relapse risk.
Slide 40: Assessing Adherence to Oral 6-Mercaptopurine

To address this concern, there’ve been several initiatives that have been underway mainly by Smita Bhatia and her group at the University of Alabama. So, within their work there have actually used a MEMS cap, which is a special cap for 6MP bottles, that can track when the bottle is opened, and you can see a tracing that’s been downloaded from an adherent patient on the left compared to a nonadherent patient on the right. In future clinical trials there will be an option for children to participate in studies to improve adherence, where this MEMS cap will be used. And then, there’ll be text message reminders to take 6MP, there’ll be special educational videos and modules and customized calendars that are provided to see if any of these measures will increase medication adherence going forward.
So, in summary, improving ALL outcomes requires addressing unique aspects of the host and tumor biology, as well as refining therapy, and the next generation of Children’s Oncology Group trials will strive to do this in several ways. So, molecularly targeted therapy will be incorporated for Ph-positive and Ph-like disease. There’ll be a risk-based introduction of immunotherapy. Efforts are underway to improve medication adherence and to identify predictors for toxicity. And, it will be essential to assess the quality of survivorship.
Slide 42: Acknowledgements

And with that, I’d like to finish by first and foremost thanking all the incredible children and families. Your partnership is essential on the treatment journey, and you are an inspiration. Second, I’d like to acknowledge all my wonderful colleagues in many disciplines in our division at NYU, and my many colleagues within the Children’s Oncology Group Disease Committee. It definitely takes a village and I feel very honored to be a part of this community.

Thank you very much. This concludes my presentation.
ALL in Adults: Promising Times for Our Patients

Wendy Stock, MD
Anjuli Seth Nayak Professor of Leukemia Research
University of Chicago Medicine

Lizette Figueroa-Rivera:
Thank you so much, Dr. Raetz, for your very clear presentation. And, due to a change in travel plans, you will now hear a prerecorded presentation from Dr. Wendy Stock at the University of Chicago in Chicago, IL, who will speak on adult ALL.
Slide 44: Objectives

**Objectives**

1) Highlight treatment challenges and recent progress in treatment of adults with ALL

2) Review novel therapies for patients with relapsed ALL, focusing on recently approved agents

3) Overview of strategies to introduce new agents into the frontline setting to optimize outcomes

Dr. Wendy Stock:

Good afternoon, everyone. I’m sorry that I’m not here live, but I know that my colleague Dr. Emily Curran will do a wonderful job answering the additional questions that you may have, and my heart is with all of you.

Today, I have the pleasure of talking about the promising new treatments and our current state of affairs for adults with acute lymphoblastic leukemia.

The objectives of this talk are to highlight treatment challenges and recent progress in the treatment of adults with ALL; to review novel therapies for patients with relapsed ALL, focusing particularly on the recently approved agents, and a little bit on CAR-T cells; the overview of strategies to introduce new agents into the front-line setting, which we’re now doing to optimize outcomes.

I am not going to have time today to discuss Philadelphia chromosome positive acute leukemias in particular, but I’m sure that if there are additional questions about that subset in specific at the end during the question and answer period, my colleague, Dr. Emily Curran, will be happy to do that.
So, I’m going to start by framing the problem and reviewing a little bit about the survival of adults with acute lymphoblastic leukemia during the last several decades.
ALL in Adults: The “Old” State of Affairs (circa 2005)

- Multi-drug regimens “similar” in design to pediatric trials
  - But traditional adult regimens have lower intensity dosing of steroids, vincristine, asparaginase; less CNS prophylaxis compared to pediatric regimens
  - “one size fits all”
- High rates of remission in adults (80-90%)
- Post-remission therapy dictated largely by age/ cytogenetics
  - Limited options for targeted therapy except for Ph+ ALL
  - High risk patients receive allogeneic transplant if donor available
    - Lower relapse rates but...Survival benefit questionable due to transplant related mortality
- Long term survival: 30-40% overall


ALL in adults, as of about a decade ago, had a very unsatisfactory outcome. We used, in general, multi-drug regimens that were very similar in design to pediatric trials, but the traditional adult regimen had lower intensity dosing of steroids, vincristine, asparaginase, less central nervous system prophylaxis, which is a key component of treatment of ALL compared to pediatric regimens, and generally we were using for all adults, regardless of subset or age, one-size-fits-all treatment, that is one kind of regimen for all adults. There were high rates of remission, which was very good, but we didn't do very well long term, where survival was only 30 to 40%, and that's because the post-remission therapy was really limited in terms of the options, except for the Philadelphia chromosome positive ALL patients, where even a decade ago we were already adding in targeted agents and improving outcomes. In general, our approach at that time was to give or recommend an allogeneic stem cell transplant for high-risk patients. And, as I said, the outcomes were not particularly satisfactory with only 30 to 40% of patient's long-term survivors. But that is changing and I'm going to review that in the next few slides.
Slide 47: Survival of 759 adults with ALL treated on CALGB studies from 1988-2006

This slide represents the outcome of our adults with acute lymphoblastic leukemia who were treated over a 2-decade period in the late 1980s through the mid thousands on CALGB, which is now known as the Alliance for Clinical Trials in Oncology Cooperative Group. And, you can see here that our overall survival was about 41% and particularly where that white arrow is, is the very, very unsatisfactory outcome for our older adults over the age of 60 with acute lymphoblastic leukemia. And, this is all changing for the better, happily.
ALL in Young Adults: Adoption of Pediatric Regimens Has Become the New Standard

CALGB 10403
- 2019, Ages 16-39

Historical CALGB vs CCG
- 2000, Ages 16-21

Blood, 2019: 133, 1548-1559
Blood, 2008: 112, 1646-54

Slide 48: ALL in Young Adults: Adoption of Pediatric Regimens Has Become the New Standard

Next slide shows that in fact, the outcome in young adults with acute lymphoblastic leukemia has significantly improved and we have a new standard of care. We have now learned that we can successfully adopt pediatric regimens into the care of our young adults with ALL and improve outcomes compared to our historical control. On the right of this slide, as you can see here, this was a comparison that we did many years ago, showing that young adults with ALL fared much better when they were treated on a Children’s Oncology Group trial, the CCG, compared to when they were treated on the adult trial, the CALGB trial, as shown here. And, as I just mentioned, the reason for that is many-fold, but one of them was that even though we thought we were using similar treatments, they weren’t identical. And so, as we moved forward, we performed a large national study called CALGB 10403, which is shown here. It included all young adults with ALL, both B-precursor and T-precursor ALLs, from the ages of 16 to 39 years, and it was just published about 2 weeks ago with the final results, which are in fact extremely encouraging because we now have an overall survival rate of about 73%, which is a more than 30% improvement compared to our historical controls from the late 80s to the mid-thousands, simply by adopting a pediatric regimen and using it faithfully and committing to a very complicated and long-term treatment protocol that was very feasible and doable by centers throughout the United States. So, this is now, for this study and a number of others, one of which I’m going to show you in a second, that this is not just one study that shows the outcomes have improved with pediatric treatment for young adults with ALL.
The next slide here shows a beautiful study that was done by the NOPHO, which is the Northern European Group for treatment of patients with leukemias, and they did an amazingly interesting study where they treated all patients from the age of 1 year old to 45 year old's with acute lymphoblastic leukemia on the exact same treatment trial. And, here too, they showed that using their intensive pediatric approach and only stratifying treatment based on biological features of the disease, not by age, the outcomes were improved for all age groups compared to historical controls. And, even though, as you can see here in the green, the older patients, the 18 to 45-year-old patients, didn’t do quite as well as the very youngest patients on the trial, they did exceedingly well with an event-free survival of 74%. The reason that younger adults don’t do as well as children still has to do with many issues that we’re trying to tease out, including biological features of the disease, and biological features of even aging in the young adult population, compared to children, were just not as hearty as little children, even by the time we reach age 18 in terms of treatment tolerability of some of the drugs that we use.
Slide 50: Progress: Addition of Rituximab Improves Outcomes

On the next slide, I also show that one of the new agents that’s already been introduced into front-line therapy. Rituximab is not actually a new agent, it’s been around for about 15, 20 years now, and used extensively in the treatment of lymphoma, but we had never used it intensively in the treatment of all patients with acute lymphoblastic leukemia. Rituximab is directed against the protein on the surface of the lymphoblast called CD20 and this is an antibody that targets or attaches to CD20 on the surface of the leukemia cells and then results in the leukemia cell death. And, the French Group here in this study that’s shown on the slide, showed that patients with acute lymphoblastic leukemia, adult patients, whose leukemia cells express CD20, which is only about a third of patients with ALL, with B-cell ALL, did in fact have a very significant improvement statistically in their survival rate, when the addition of this antibody was made. This gives us the idea that if we had a truly more comprehensively effective antibody that might do the same thing. And, I’ll come back to that in a little bit because that’s exactly how we’re approaching things now as we move forward.
Slide 51: Historical Survival Rates after Relapse

On the next slide, now I begin to talk about how some of these new agents have improved outcomes for our patients with relapsed leukemia and how these then new agents, which have now been approved for relapsed leukemia, are being incorporated into front-line treatment. So, we’re going to go full circle.

In the past our outcomes for patients with relapsed acute lymphoblastic leukemia here were extraordinarily poor. And, you can see the survival rate for patients were really, really low, only about 5 to 10%. So we didn't have good tools to get patients whose diseases have relapsed back into a remission. Once they were back in remission, we could take them to an allogeneic transplant, a stem cell transplant, which could then result in their prolonged survival. But, you can see from this slide that it was very difficult first of all to get patients back into remission and for that reason we had very poor outcomes because we weren’t able to recommend transplant if the disease wasn’t in remission. That has changed dramatically in the last 5 years.
Slide 52: Blinatumomab

One of the drugs that has helped to change that is a very, very interesting antibody, it’s called blinatumomab. It’s actually called a BiTE, which stands for bi-specific T-cell engaging antibody. And, it’s shown here in this diagram. In the diagram you can see that this BiTE has a component that attaches to the T-cells, a normal T-cell, and a component that engages the malignant leukemia B-cell. And, it brings this T-cell into contact with the malignant leukemia cell and results in the killing of the leukemia cell. Now, that’s pretty fascinating and it’s very similar to what we’re going to talk about when we talk about CAR-T cells in a little while. But, this is an antibody that is given by vein, by continuous infusion, and it’s a way of harnessing the patient’s normal T-cells to kill B-cells. Not all ALLs are B-cell ALL. Twenty percent are T-cell ALL. And, this antibody only works for patients with B-cell leukemias, which are the majority of ALL in both pediatric and adult patients.
Blinatumomab: Relapsed/Refractory ALL

- 189 pts Rx with blina x 4 wks Q 6 wks

<table>
<thead>
<tr>
<th>Response</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-CR</td>
<td>63(33)</td>
</tr>
<tr>
<td>-CRh</td>
<td>18(10)</td>
</tr>
<tr>
<td>-CR+CRh</td>
<td>81(43)</td>
</tr>
<tr>
<td>-No marrow blasts</td>
<td>17(9)</td>
</tr>
</tbody>
</table>

- Median OS 5.9 mo; Median RFS 6.1 mo
- Toxicities: CNS
- 64/81 (79%) responders achieved CR or CRh in cycle one

Topp. Lancet Oncology 2015;1:57

Slide 53: Blinatumomab: Relapsed/Refractory ALL

Now, when this antibody, blinatumomab, was used in patients with relapsed leukemia, we had quite a nice response rate, which is shown here in the black, of 43%. And, that is much higher than the 5 to 10% that you saw with our other regimens that we had in the past. And, of those patients who were treated and achieved remission, the majority of them responded within one cycle of treatment, which is a 4-week treatment that, as I mentioned, goes continuously by vein and patients are actually outpatients and wearing a little pump that is changed once-a-week to deliver the antibody continuously.
Slide 54: Blinatumomab Phase III (Tower): Higher CR, EFS and OS

Next slide shows that once we saw these good results, we then went on to do what’s called a randomized Phase III trial, where we compared the new antibody, blinatumomab, to our best chemotherapy regimens that we had for relapsed leukemia. And, this series of figures here, shows that over 400 patients were randomized in a 2-to-1 fashion, that is twice as many received blinatumomab as received the standard of care chemotherapy, and it showed that in patients with very, very resistant relapsed ALL, blinatumomab was superior to SOC, which stands for standard of care, in the primary endpoint of survival, with a 7.7 months improved survival versus only 4 months for the standard of care, 34% of those patients entered complete remission, and had superior event-free survival. And, this trial resulted in the final approval of blinatumomab because then we were able to have a 34% survival remission rate, which then allowed us to take those patients on to potentially curative stem cell transplant and/or additional treatment. So, this was very exciting, and this was just, as you can see, published just 2 years ago.
There’s another very interesting antibody that has also been approved in the last 2 years. It is called inotuzumab ozogamicin. These names are incredibly complicated, but I’m going to refer to it from now on as inotuzumab or ino. And, what inotuzumab is, is it’s actually an antibody that is carrying a little missile. The missile is represented here in red and this antibody attaches to a different protein on the surface of the B leukemia cells called CD22. And, when inotuzumab binds to the CD22 protein that’s present on B lymphoblasts, it attaches and then this little missile, which is actually a poison called calicheamicin, is internalized into the cell, gets into the nucleus of the cell, binds to DNA and kills the leukemia cell, prevents it from replicating or dividing.
Slide 56: International Phase III: Ino vs Standard of Care

This drug was shown to be very, very effective in relapsed patients and then in order to get approval, similar to the blinatumomab, a randomized Phase III study that was an international study was performed. And, this international study again showed that inotuzumab compared to standard of care therapy, just like with the blinatumomab, had an improvement in outcome. This slide just shows you what the inotuzumab schedule was. This drug is actually given once-a-week for 3 weeks in a row in the outpatient clinic and it’s very, very well tolerated in general. And, these were the standard of care chemotherapy drugs that we used to compare with the inotuzumab. These were patients again with relapsed acute lymphoblastic leukemia of the B-cell subset.
Inotuzumab superior to standard of care

<table>
<thead>
<tr>
<th>CR/CRi % (95% CI)</th>
<th>InO</th>
<th>SOC</th>
<th>1-Sided P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>80.7 (72–88)</td>
<td>33.3 (24–44)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CRi</td>
<td>35.8 (27–46)</td>
<td>19.8 (12–29)</td>
<td>0.0056</td>
</tr>
<tr>
<td>CRi</td>
<td>45.0 (35–55)</td>
<td>13.5 (7–22)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

MRD-negativity among responders, n (%) [95% CI]

<table>
<thead>
<tr>
<th>CR/CRi</th>
<th>InO</th>
<th>SOC</th>
<th>1-Sided P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>69/88 (78.4%) [68–87]</td>
<td>9/32 (28.1%) [14–47]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CR</td>
<td>35/39 (89.7%) [76–97]</td>
<td>6/19 (31.6%) [13–57]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CRi</td>
<td>34/49 (69.4%) [55–82]</td>
<td>3/13 (23.1%) [5–54]</td>
<td>0.0034</td>
</tr>
</tbody>
</table>

Slide 57: Inotuzumab superior to standard of care

In the next slide, there’s a diagram here that shows you the outcomes of the patients. And, what I want to highlight are the things that are highlighted in red. Inotuzumab resulted in an overwhelmingly high response rate of nearly 81%. You remember that the blinatumomab resulted in about a 40%, 45% response rate. This drug, 81% compared again to about a 30% response rate, 33% in this case, of patients with the standard of care regimen. So again, a highly statistically significant improvement for the inotuzumab-treated patients in terms of remission rates.

And importantly, and we haven’t talked much about this yet, but minimal residual disease or measurable residual disease is an important component of prognosticating or predicting outcome in ALL. And, we know what MRD stands for is measurable residual disease, that’s disease that you can no longer see when you do a bone marrow biopsy and look for the leukemia, but you can still detect it at a very sensitive molecular level. And, we know that even subclinical disease or MRD positive disease is worse than having no detectable disease. And, we know that’s very important. And in fact, what we saw in this study, and in the blinatumomab study, that patients who responded had extremely high rates of eradication of minimal residual or measurable residual disease. And, that is a good thing because that’s an even more powerful tool for eradicating leukemia.

So, we have 2 drugs and because of this study, this drug inotuzumab, was approved for treatment of patients with relapsed ALL of the B-lineage subset, and those leukemias almost always express CD22, just like the blinatumomab, where it was directed against CD19, another protein on the B-cell leukemia surface.
Slide 58: Duration of Remission, Progression-Free and Overall Survival: Favors Inotuzumab

Here are the survival rates on this slide of the patients. And, you can see, similar to the blinatumomab, that the patients who got inotuzumab had improved outcome compared to the standard of care, but patients were still relapsing. And, the idea, as I mentioned earlier, is to try to take these relapsed patients, once they’re back in remission, where the remission rate was 81%, to a bone marrow transplant. And in fact, a paper was just published in the last couple of weeks, showing that patients who got inotuzumab went into remission and were able to go to transplant, actually had extremely good long-term disease-free survival of over 50%. So, compared to 5%, we now are able to hopefully rescue and cure potentially 50% of the patients who respond to inotuzumab. And, that’s very exciting. So, we are really moving the bar upwards in terms of survival for our relapsed patients.
In Relapse, How do we choose?

<table>
<thead>
<tr>
<th>Unique treatment related toxicities</th>
<th>Blinatumomab</th>
<th>Inotuzumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologic toxicity:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6% blinatumomab vs none in control group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRS:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5% of blinatumomab vs none in control group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Veno-occlusive disease:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11% inotuzumab vs 1% control (SOC)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease status</th>
<th>Lower disease burden, T cell function?</th>
<th>High or Low disease burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment options</td>
<td>CAR-T? Loss of CD19 with Bina?</td>
<td>CAR-T? CD22 (early studies ongoing)</td>
</tr>
<tr>
<td>Administration</td>
<td>Continuous IV infusion X 4 weeks</td>
<td>Short IV infusion weekly X 3</td>
</tr>
<tr>
<td>Cost [drug cost only at UChicago]</td>
<td>$88,984/cycle</td>
<td>$89,760/cycle</td>
</tr>
</tbody>
</table>

**Slide 59: In Relapse, How do we choose?**

How do we choose between these excellent new treatments that we have? Well, there are a number of considerations and that's more up to the doctors really to sort of figure out, along with the patient, but it really has to do with certain considerations about the type of disease, the amount of disease that's present at the time of relapse, and the other treatment options that are available. And this slide, which I’m not going to go into in any great detail, shows some of the ways that I try to think about which of these drugs to use, in which order. And, both of them are effective, both of them can be used, and again it just depends on certain factors about the disease biology and the patient's overall plans for going forward with transplant.

Both of these drugs are not inexpensive, as you can see here. They’re extraordinarily expensive for each cycle of treatment. And, that’s something we have to think about as we move forward in healthcare in general. We have these beautiful new drugs, but they’re exquisitely expensive and we have to think about that, especially for people in the developing world, and how we’re going to incorporate these fantastic new treatments, will they be available to people because of this economic burden.
Slide 60: Anti-CD19 Directed CAR T cells
Slide 60: Anti-CD19 Directed CAR T cells

One of the other exciting areas in acute lymphoblastic leukemia, as well as for a lot of lymphoid malignancies now, is the development of CAR-T cell therapy. These are genetically engineered T-cells that are taken from the patients or from a donor. I’m going to talk about it in the sense that right now most of the trials are taking the T-cells from the patients and genetically engineering them. What does that mean? Well, the patients have their T-cells collected and a new gene is placed into that T-cell with a very fancy technique and that results in the production by this new gene of a new series of proteins that appear on the surface of the T-cell. And, what does all of this do? This allows the T-cell to have an additional little weapon for recognizing malignant B-cells. And, it's kind of similar to what I talked about with the blinatumomab. And, Dr. Curran and Dr. Raetz can answer additional questions that you might have. But this time we've actually taken the cells out of the patient in a process called leukapheresis or apheresis and the cells are then engineered, and they're shipped back after this new gene is introduced, that introduces this new protein. Once the cells are engineered and sent back to the center, patients are given a low dose of chemotherapy and then these new T-cells are infused, just like a blood transfusion, and they get to work. And, these new cells are very interesting. So, this diagram shows you that this is the vector, this is how the cells are genetically engineered to express this new gene. And this new gene then produces the message to produce these new proteins that then appear, as you can see here, on the surface of the T-cell. The cells are then sent back to the patient and then to the center where the patients are being treated. The patients are then admitted to the hospital and receive these engineered T-cells. And, what happens when they are infused is very similar to what I showed you with both inotuzumab and blinatumomab, only this is potentially more potent because the T-cells are long-living and maybe can provide a long-lasting effect. So, what happens is the T-cells are transfused into the patient, they find the malignant leukemia cell and they kill it. And, this is really quite amazing. And, this has been now tested and approved in a number of different settings and this approach is approved for children and young adults, up to the age of 25 with ALL. And, there are ongoing studies in older adults with ALL. And, I would presume that there will be approval of this approach in older adults in the near future.
CD-19 CAR-T cells: High Response Rates, Durability of Response Varies

<table>
<thead>
<tr>
<th>Ref</th>
<th>T cell Engager</th>
<th>Population</th>
<th>Response</th>
<th>CRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maude et al. NEJM 2014</td>
<td>Anti-CD19 CART 4-1BB</td>
<td>N=30 Peds&amp;Adults</td>
<td>CR=90%</td>
<td>100% CRS 27% Severe</td>
</tr>
<tr>
<td>Davila et al. SciTrMed 2014</td>
<td>Anti-CD19 CART CD28</td>
<td>N=44 Adults</td>
<td>CR=82%</td>
<td>43% Severe</td>
</tr>
<tr>
<td>Lee et al. Lancet 2015</td>
<td>Anti-CD19 CART CD28</td>
<td>N=21 Peds&amp;AYA</td>
<td>CR=67%</td>
<td>76% CRS 28% Severe</td>
</tr>
<tr>
<td>Turtle et al. JCI 2016</td>
<td>Anti-CD19 CART 4-1BB</td>
<td>N=30 Adults</td>
<td>CR=93%</td>
<td>83% CRS</td>
</tr>
<tr>
<td>Shah et al. ASH, 2017, Abstract 888</td>
<td>Anti-CD19</td>
<td>N=22 Adults</td>
<td>CR/CRi=82%</td>
<td>25%≥Grade 3 65% neurotox ≥ Grade 3</td>
</tr>
</tbody>
</table>

**Slide 61: CD-19 CAR-T cells: High Response Rates, Durability of Response Varies**

This next slide summarizes some of the studies and reports that have already been done using these CAR-T cells showing very, very high response rates, as you can see here in the 80 to 90% range in general. That is, that many patients go back into remission with this kind of treatment. But, one of the big problems has been, and here are the remission rates which are extremely high, one of the problems has been that infusing T-cells that are genetically engineered and get to work in a big hurry in a person can cause a lot of inflammatory proteins to be released as part of this killing process. And, that's called cytokine release syndrome or CRS. And, it can be pretty extreme and cause some really significant side effects. I don't have time today to go into all of this, but we are learning very quickly about how to both very quickly monitor and intervene to minimize the risk of this toxicity, but also potentially when might be the best time to treat patients to minimize that risk of it happening. And, that's for another discussion.
Long-term Follow-up MSKCC CAR-T based on Disease Burden at Time of Treatment

The long-term follow-up for adults with the CAR-T cell therapy still remains a little bit uncertain. That is, almost all patients again will go into remission, but only the patients who were treated, at least in the one published study now for adults with ALL who are treated with CAR-T cells, but the best results were achieved in terms of long-term benefit in patients who didn’t have that much disease in their bone marrow to begin with. So, probably for the patients who have high disease burden, the best thing to do would be once they are entering remission, where 80, 90% of patients do enter remission, to potentially consider moving forward with transplant once they’ve achieved remission after this CAR-T cell therapy. But, it does afford us a potential for maybe long-lasting cures after CAR-T cell therapy and that’s been shown there, our long-term survivors, particularly in the pediatric world and in some patients with lymphoma who were treated with CAR-T cells. We still don’t know that much about the durability in adults and that has to do with many factors, including the type of CAR-T cell that’s been manufactured. And, all of this is progressing at breakneck speed with huge progress, pretty much each month.

So, we have 3 great new techniques for getting people back into remission. Two of them are approved in adults, one approved in children and younger adults. And, now we can say, okay, if this is such a successful approach in the relapse setting, maybe we can prevent relapse altogether by introducing these drugs in the front-line of treatment.
Considerations for CAR-T in the Frontline

- Can very significant toxicities resulting from T-cell activation that occur in majority of patients (CRS, neurologic) be minimized?
  - Likely to be less frequent in setting of MRD
- Sequencing of CAR-T cells: May need to administered as final “consolidative therapy”
  - Concerns about CAR-T loss/depletion if additional immunosuppressive chemotherapy is used
- Durability of CAR-T cells? Resistance mechanisms
- Cost! - estimated at $475,000 for a single administration

Slide 63: Considerations for CAR-T in the Frontline

One of the things, and I’m just going to skip over this slide very quickly, thinking about the CAR-T cells, is that they’re yet thinking about this in the front-line, we still have a lot of work to do because we have to minimize the toxicities that occur. Once you have those CAR-T cells in there, you want them to persist for long periods of time. And, that may not yet be possible. And, we can’t think about treating patients again after the CAR-T cells with any drugs that we usually use for ALL treatment because they will maybe kill the CAR-T cells, the treatment. We’re still learning about why patients, even after this fancy treatment, relapse. And, if the other treatment was expensive, look at the expense for a single administration of CAR-T cells. So, these are all important considerations.
I'm going to focus in the last few minutes really about moving these other new drugs into the front-line of treatment. And, these drugs, blinatumomab and inotuzumab, which I mentioned, can be now incorporated into front-line therapies for patients with B-cell ALL. And, a drug that's an older drug called nelarabine, since we don't yet have fancy antibodies for the T-ALL patients, a drug called nelarabine can be used in the front-line of patients with T-cell ALL to also improve their outcome. And, I'm going to review a little bit about what's going on there.
Strategy: Incorporate new antibodies into multi-agent platform to eradicate MRD: Will it help?

So, as I mentioned earlier, getting rid of measurable or minimal residual disease is very important. Here I show you if patients are able to get rid of their minimal residual disease, even in this trial that I showed you at the very beginning of the talk, those patients who were able to, with very sensitive techniques, not have any evidence of measurable or minimal residual disease early in the treatment, did very, very well in terms of their outcome. They had an 85% survival rate. In contrast, those patients who entered remission, but still had at the molecular level detectable disease, didn’t do as well. So, our goal is to try to get these MRD positive patients MRD negative and maybe improve outcome for these patients and maybe even for these patients, by adding these new drugs into the front-line of treatment.
Slide 66: Testing Blinatumomab in Frontline: 2 studies in the US Intergroup

So, what are we doing about that? This next slide shows you 2 studies, one of which is still ongoing and the other of which has been just concluded that add blinatumomab into the front-line of treatment. The C1910 study is being done throughout the United States and Canada and it’s a Phase III randomized trial, testing the addition of blinatumomab to chemotherapy for adults ages 30 to 65. And the question is, as I just described, if adding that cool BiTE antibody to front-line treatment, in combination with chemotherapy, will improve the rate of patients who achieve MRD negativity and result in their improved outcome.
Slide 67: Inotuzumab in the “Frontline”

There’s another study that was done as a little pilot study that really used almost no chemotherapy, just blinatumomab, and a little bit of what we call maintenance therapy in older adults who have done really so far not very well with our standard approaches to treatment. And, this approach was just presented by my friend and colleague Dr. Anjali Advani at the recent ASH (American Society of Hematology) meeting a few months ago, that showed that this approach seems to have a very, very promising response rate and potentially durability.

So that, in our older adults who can’t tolerate treatment that well because of the toxicities of the treatment and whose disease may be more resistant to our traditional approaches, perhaps will be able to use very minimal chemotherapy and some of these new antibodies in the front-line of treatment to improve outcome.

There’re similar approaches being used by the MD Anderson with inotuzumab in the front-line. And, they’ve combined inotuzumab with a mini dose of chemotherapy. And, they have very, very good outcome for that. I’m going to show you that on the next slide.
Can We Add Inotuzumab and Improve EFS to 80%? US Intergroup study for AYA: A041501

One of the things that we've done is that we have added inotuzumab now into the front-line of treatment for our younger adults with ALL. And, this study is ongoing and we're wondering whether we can improve event-free survival now from the 60% that we've already had to 80% by adding inotuzumab into the front-line of treatment. And, this study is ongoing in the United States now for adults ages 18 to 40 years old and with B-cell ALL. And, it's already accruing very nicely and we have some very exciting early responses in terms of measurement of minimal residual disease in the patients who are getting inotuzumab therapy. So, we're hopeful that this approach can be used in both younger and older patients.
Now, what about patients with T-ALL? The T-ALL patients don’t have these fancy antibodies to be able to be used yet. But, there is a drug that has been approved for the relapse of T-ALL that was recently added to the front-line of treatment and I think probably Dr. Raetz may be talking about that, and so I’m just going to gloss over it, but by saying that when nelarabine was added to combination chemotherapy in the front-line of treatment, the survival in children with ALL and young adults up to the age of 30 was almost 90% with the addition of the nelarabine. And, that showed a significant improvement to an already good rate of survival of 83%. And so, we’re thinking about in the older adult population whether we should now be incorporating nelarabine into the front-line therapies that we are already using for these younger adults.

Winter SS et al, J Clin Oncol 2018; 36, 2926
Dunsmore et al, Proc ASCO, 2018
Moving Forward with T-ALL

- Based on COG data, can/should we be incorporating nelarabine into frontline therapy for all AYAs?
  - Dose/schedule – should “adult” schedule be used?
- Other considerations: targeting survival pathways: Venetoclax/Navitoclax
  - Ongoing phase I has promising results in heavily pretreated patients (B and T with overall response rate of 50%)
- Immune targeting: CD 5 CAR-T trial initiated; others coming (gene edited CD7 CAR-T)
  - Daratumomab: Anti-CD38 Nice preclinical data in PDX precursor T and ETP ALL

*Bruehl et al. Blood 2018;131:995-999
Hanfei et al, SOHO abstract, 2018

Slide 70: Moving Forward with T-ALL

So, this summarizes what I just said about T-cell ALL. And, there are some other very interesting drugs that are being tested in the relapse setting right now that may soon move into the front-line treatment for young adults with ALL. So, as I said, should we add nelarabine? From the Children’s Oncology Group data, it suggests yes, we should into front-line therapy for all young adults with ALL. Should we add some new agents that are being tested? And, I don’t have time to go into them today, into the front-line of treatment, venetoclax and navitoclax combination are things that you may hear about in the near future. And, it has activity in the relapse of both patients with B and T-ALL and may be able to be incorporated into the front-line. And, there are actually some CAR-T cell approaches that are now being developed for patients with T-ALL that are soon to be in clinical trials.
Older Adults with ALL: Historical Data: 10-20% 3 yr Survival

This slide, as I showed you before, shows you the historical outcome of older adults with ALL, which was very poor.

Ino with low-intensity chemo for age ≥60

And I just want to show you one last time that the inotuzumab with low-intensity chemo for patients over the age of 60 results in a significant improvement in the outcome of those patients and so we're hopeful that these new antibodies will be able to be incorporated into the front-line of treatment successfully with very minimal chemotherapy.
And finally, I just want to add in terms of our talk about the new antibodies for older adults with ALL, by mentioning that we just opened in the U.S. Cooperative Group a new trial of no chemotherapy at all for older adults with ALL. They’re going to be getting both of the new antibodies in the front-line of treatment if they have B-ALL. And so, inotuzumab is going to be given, which as you may remember, had a very high response rate in the relapse setting, and then blinatumomab, which is very good at eradicating minimal residual disease, will then be given as post-remission therapy. This trial is just starting throughout the United States and I think it’s an extremely exciting direction that we’re moving, trying to remove some of the toxic chemotherapeutic drugs that haven’t worked very well in our older adults, and moving to a more targeted antibody-mediated approach.
Summary/Conclusions

- Survival Rates for both younger and older adults with ALL are improving
- Incorporation of new agents into frontline treatment is an exciting new approach
- Clinical trial participation is crucial for ongoing progress
- Thanks to all of you, patients, family and friends, for your courage, strength and grace!

Slide 74: Summary/Conclusions

So, in summary, I’d like to say that our survival rates for both younger and older adults with ALL are definitely improving. The incorporation of these new agents into the front-line of treatment is a very exciting new approach. And, we’ll see how this evolves over the next couple of years. But, it’s really important to remember that clinical trial participation is crucial to really evaluate the benefit of these new drugs, and we encourage anybody who’s able to participate if there is a trial open in one of these new trials for ALL patients.

And, I’d like to close by thanking all of you, all of you who are patients, your families and friends, for your courage, strength and grace and commitment to moving the field forward.
I finally want to acknowledge my colleagues here at the University of Chicago and around the country with whom I've been collaborating for many, many years to try to improve outcomes for young adults and older adults with ALL.
Slide 76: Thanks to our patients – they are our inspiration!

And, I thought I’d close with a very promising and exciting slide that demonstrates how much my own patients inspire me to do better. The beautiful bride in the middle of this picture was one of our first patients enrolled on the CALGB 10403 trial. She completed all of her treatment, she then got married, she finished her master’s degree, and she now is well and has 2 young children. And so, I thought I would try to close on a very bright and optimistic slide that makes me happy every time I see it and gives me great hope for the future.

Thank you all very, very much.
Lizette Figueroa-Rivera:

Thank you, Dr. Raetz and Dr. Stock. It’s time for our question and answer portion of our program. And as Dr. Stock mentioned, Dr. Emily Curran most graciously accepted our invitation to answer any questions today on adult ALL. Dr. Curran is one of Dr. Stock’s colleagues from the University of Chicago.

Lizette Figueroa-Rivera:

We'll take the first question from our web audience. Dr. Curran, Kenneth is asking about Ph-positive ALL. Can you speak to that and if it’s treated differently?

Dr. Emily Curran:

Yes. So, Ph-positive ALL, as Dr. Stock had mentioned and Dr. Raetz as well we’ve really seen a lot of improved outcomes with the introduction of tyrosine kinase inhibitors, like dasatinib and imatinib. And so, those are routinely now incorporated into treatment of Ph-positive ALL. Whether or not Ph-positive ALL needs standard chemotherapy as a backbone or, as we do here at University of Chicago, we actually use mostly steroids and the TKI such as dasatinib for treatment. And so, the introduction of those have really changed kind of how we treat Ph-positive ALL.

Lizette Figueroa-Rivera:

Thank you, Dr. Curran. And, Dr. Raetz, our next question from Krista and Neal, I know that you touched on this, they’re asking about the treatment protocol being shortened for boys with standard risk ALL from 2 to 3 years?

Dr. Raetz:

Yeah, so this is going to be a study question in the upcoming standard-risk and high-risk trial. So, historically as many of you might know, girls, the duration of treatment was 2 years from the start of interim maintenance and boys was 3 years from the start of interim maintenance because boys historically have had a little inferior outcome. When we look at the experience, though, worldwide, many other cooperative groups really have a standard treatment duration for both boys and girls, so our hope is with refinements in risk stratification, so being able to better ascertain which children really have the highest risk features that we can safely move to a 2-year therapy duration for both. I think this will be really a study question, though, as part of the clinical trial. So, the clinical trial will have a lot of monitoring built in to ensure the safety because we certainly don’t want to see any erosion in the cure rates that have been observed to date.
Lizette Figueroa-Rivera:
Thank you, Doctor. And, our next question Dr. Curran, Winston is asking what is the chance of getting ALL or other blood cancers after remission if you do have childhood ALL.

Dr. Curran:
Sounds you’re asking about secondary malignancies or relapse, and those are kind of 2 different things. In the setting of having childhood ALL, the chances of its relapsing later on in life are very low. The treatment of, I think Dr. Raetz kind of discussed this a little bit with the treatment of ALL in childhood, does put you at slightly higher risk of other cancers, which is why it’s important for monitoring and survivorship. There’s been some detailed survivorship plans where the long-term effects of chemotherapy are monitored. So, both of those are low, but it is important for long term monitoring.

Lizette Figueroa-Rivera:
Thank you. And, Dr. Raetz, Jonah’s asking will the treatment for ALL affect her child’s fertility.

Dr. Raetz:
That’s a great question. There’s a small chance that fertility can be impacted, but if you look at the regimens, the dose, one of the agents that we worry about most in terms of its impact on fertility is cyclophosphamide or Cytoxan. And generally, the doses that are administered in most ALL front-line protocols are relatively low, so most children in fact who receive ALL therapy don’t have issues with infertility, but there can be some risk of that. And certainly, it’s always good to have discussions with your healthcare provider about options for fertility preservation.

Lizette Figueroa-Rivera:
Thank you. And, Dr. Curran, Lisa is asking why relapses happen when everything seems to be successful and producing 100% donor cells, how can relapse happen and how can we help family members stay positive and hopeful while fear of relapse is still there.

Dr. Curran:
That is a good question. As Dr. Stock had mentioned, as well as Dr. Raetz, even when we see no evidence of leukemia, we know that occasionally there is still leukemia there, so-called the measurable residual disease and even at perhaps even levels below what we can measure. So, that’s typically why relapses happen, but that’s also why we’re using these other novel therapies with the hope of getting rid of those leukemia cells that are present but can’t be detected, with the hope that that will prevent those relapses that are unexpected.

It sounds like they’re wanting to know about post-transplant relapse as well, same thing. Post-transplant relapses can occur. Again, because perhaps there’s some leukemia that either the immune system is not getting rid of for a variety of different reasons or, that perhaps was there at the time of transplant. And so, these cells can reemerge. We hope that they don’t and we’re hopeful that with these, again, these newer therapies that are emerging, such as the targeted antibody therapies and the CAR-T that we can prevent that.

And, I would say that as far as supporting family members, it can be stressful and concerning to think about the possibility of relapse, but I would encourage everyone, as we heard today, that there are so many new and effective therapies now for ALL that are really quite encouraging.

Lizette Figueroa-Rivera:
Thank you, Doctor. And, Dr. Raetz, Christine asks my 8-year-old grandson has ALL and has gained a lot of weight from steroids I believe. Is this okay, will it last?

Dr. Raetz:
Yeah, that’s one of the things unfortunately with steroids, it’s one of the most common side effects. Most often that’s temporary but we have lots of programmatic support with nutrition and exercise intervention and I think with physical therapy sometimes those sorts of interventions can really help to minimize the weight gain so that it isn’t a long-term effect.

Lizette Figueroa-Rivera:
Thank you. And, Dr. Curran, Nanette is asking when do you think CAR-T 19 immunotherapy will be FDA approved for adults?
Dr. Curran:
That is a very good question. As Dr. Stock mentioned, we’ve seen some very encouraging results from the various different CAR-T cell trials in adults. And so, we’re hopeful that these will be approved soon. Exactly when is hard to predict. But again, the results have been very encouraging and so we’re hopeful that these will have approval soon.

Lizette Figueroa-Rivera:
Thank you. And, Dr. Raetz, Ali is asking is there any study on the classification of childhood ALL? My daughter was moved to high risk solely based on her 8-day residual. How accurate is this classification, considering the increase in the chemo dose for higher risk?

Dr. Raetz:
Yes, so the classification, I mean I think it is a little bit of a moving target as we learn more about new different genetic lesions and their importance. And, sometimes we have to interpret MRD within the context of the whole big picture, what other clinical features a child has and what sort of genetic changes in the leukemia population. But, sort of the approach that the Children’s Oncology Group has taken in developing classification studies is to look at the prior generation of classification studies and to really look at all the different combinations and how it impacted a long-term outcome. And, I think in the Children’s Oncology Group the studies, the treatment trials on a given classification study, there’ve been almost up to 10,000 children, so we do our very best to take all of our current information and really to analyze that and pick out those features that look like they would place a child a little higher risk. You certainly don’t want to augment treatment unless you have to but that’s sort of been the approach that’s been taken. I think if we look to the future, it’s going to become more sophisticated I think as we can do more advanced sort of genetic testing and learn more about the unique features of each child’s leukemia, my prediction will be as our ability for risk prediction will become more and more refined in the future.

Lizette Figueroa-Rivera:
Thank you. And, this question is for both doctors. Maggie is asking about any nutritional recommendations for ALL while on treatment and maintenance.

Dr. Curran:
So, I guess I’ll start. So, the general nutritional recommendations are to try to maintain a healthy diet. The steroids can, as previously discussed, can increase appetite and cause weight gain. We don’t encourage patients to actively go on diets, but just maintaining a healthy, well-balanced diet to the extent that they can is probably the most important from our standpoint.

Dr. Raetz:
And, I would second that. I agree with all of those suggestions. I think it can be hard because the cravings with steroids, particularly in young children, can be overwhelming. But, I think as much as you can encourage just a healthy balanced diet to offer, you know, the healthiest versions of things that, that children and adults crave. And, you know, certainly to take advantage of all the nutritional resources that most programs have available and exercise interventions as well is what I would recommend.

Lizette Figueroa-Rivera:
Thank you both. And, for Dr. Curran, Tammy is asking do health insurance companies cover this new approach with antibodies? I believe she’s speaking about CAR-T cell as well as the newer treatments.

Dr. Curran:
The FDA approved indications for blinatumomab. It is now, as Dr. Stock mentioned, FDA approved both for in the relapse setting as well as in the setting of minimal residual disease and therefore generally covered by insurance. So, inotuzumab, it is not currently approved for the front-line, so the newly diagnosed setting, but it is approved for relapsed leukemia and therefore covered by insurance. The trials that Dr. Stock described where inotuzumab is given earlier in treatment, those are given through the context of a clinical trial and that’s how the cost is managed. CAR-T cells are not yet approved for adults or older adults, and so that those are only given currently through the context of a clinical trial in which case the clinical trial helps support the cost of that treatment.
Lizette Figueroa-Rivera:

Thank you. And, Dr. Raetz, Paul is asking do we call the oncology team for routine illnesses and well childcare? If not, how is that care managed?

Dr. Raetz:

It’s a good question. I think there’s no right answer here, it sort of depends on the relationship with the primary care team and I know most primary care pediatricians really love to maintain all the contact with our children. I think it is, from a practical standpoint, for routine care when a child’s undergoing leukemia therapy, a lot of it we will see as an oncology practice just because some of the implications of routine illness are different and, you know, children with a fever, with a central line, might need a blood culture and different interventions than can be offered in a general pediatric office. So, I think our approach is that we do tend to see most children while they’re undergoing ALL therapy for all of the things that they develop during their treatment and then we also try to, you know, frequently update their pediatricians who always want to know how they’re doing, too. And, when children complete their therapy, they’ll have a lot of scheduled visits with the oncology team, but also will be at a point where they are transitioning to their pediatricians to resume immunizations and we feel like, you know, really close communication with the pediatric providers and their communities is essential at that time, too.

Lizette Figueroa-Rivera:

Thank you. And, we do have questions for you in regards to what can I do to protect my child from infection during and after treatment?

Dr. Raetz:

So I think, you know, it’s hard because most children are exposed to many different infections and I think, you know, we think it’s really important to have a normal life balance and to have all of those supports that are essential for children and for their development as well. So our policy, I mean there’s not a right or wrong answer, would be to encourage children to go to school to the extent that they can and to, you know, be connected in their communities and to participate in all the activities that they love, and then just to use the general, you know, measures of very good handwashing and usually I’ve found that teachers in the classroom are wonderful if they know that a child might be more prone to infection, are very good at alerting families if there’s something that’s going through the classroom that might put a child at particular risk. But, you know, for the most part, I think, you know, being exposed to routine common childhood illnesses isn’t that dangerous if just standard precautions are taken and children, if they do develop a fever, can be evaluated quickly by a medical provider. And, after therapy usually the infection risk, I mean it can take a while to restore immunity completely after a child completes their treatment, but again, the risk isn’t so significant, so we just generally recommend good handwashing and being alert if there are outbreaks of a particular illness in the community, but not restricting activity too much.

Lizette Figueroa-Rivera:

Thank you. And our last question today is for both doctors. We’ve gotten a lot of questions about supports for survivorship, for children survivorship and I know that, Dr. Curran, you also work with a lot of young adults with ALL. So, is there any type of survivorship support services for children and young adults with ALL? Dr. Curran, do you want to go first?

Dr. Curran:

So, as I mentioned before, survivorship after completing treatment is very critical. There are specialized survivorship clinics where physicians can evaluate the treatment that you received and discuss the risks and the follow-up that is needed. And, there’s clear guidelines for that as well that can often be communicated to even your primary care physician for longer term follow-up and to making sure that again you’re screened for all of the long-term toxicities from the treatment.

Dr. Raetz:

I think in the pediatric setting we often take the philosophy that survivorship even begins on day one and we rely on a multidisciplinary team approach, so, you know, in most pediatric clinics and settings I think you’ll find that there are people with expertise and really helping to maintain the well-being of children and their families, so we have, you know, educational support professionals, child life specialists, social workers, and we encourage anyone to make sure that their child and their family can take advantage of all those different services that provide a wonderful perspective. And then, in terms of the medical follow-up, just like Dr. Curran said, I think there’re well established guidelines now that, based on a regimen that a child received, are very good at, you know, making recommendations for any sort of particular medical follow-up that a child will need after they’ve completed their treatment.
Slide 79: Thank You

Lizette Figueroa-Rivera:

Well, thank you both for your presentation. Dr. Curran, thank you so much for getting on the line with us last minute. We do appreciate that.

We would like to acknowledge and thank Pfizer and Takeda Oncology.

As a reminder you can download and print the slides as well as listen to the audio of today's program from our website at www.LLS.org/programs.

If we were not able to get to your question today or want more information, you may speak to an LLS Information Specialist at 1-800-955-4572 from 9 AM to 9 PM Eastern Time, or reach us by email at infocenter@LLS.org. Information Specialists are available to answer your questions about treatment, including clinical trials, and answer other questions you may have about support, including financial assistance for treatment.

Again, Dr. Raetz, Stock, and Dr. Curran, thank you for volunteering your time with us today. And on behalf of The Leukemia & Lymphoma Society, thank you all for joining us. Goodbye and we wish you well.

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