Dan Douer, MD
January 14, 2014

Slide 1 – Welcome and Introductions

Operator
Good afternoon, and welcome to "ALL: Understanding Diagnosis & Treatment for Adults," a free telephone web education program. It is my pleasure to introduce your moderator, Lauren Berger.

Ms. Lauren Berger
Thank you and hello everyone. On behalf of the Leukemia & Lymphoma Society, a warm welcome to all of you, and special thanks to Dr. Dan Douer for sharing his time and expertise with us today.

We have over 500 individuals participating from across the United States and several countries around the world, including Barbados, Canada, China, Guatemala, Norway, and Peru.

We'd like to acknowledge and thank Amgen Oncology for their sponsorship of this patient education program. Continuing education is sponsored by the Leukemia & Lymphoma Society.

You should have received or downloaded program materials, including a biography for Dr. Douer and slides for his presentation. If you have not already accessed the slides, you can view or print them from our website at www.lls.org/programs. Following the presentation, we will take questions from the audience.

We are audiotaping and transcribing this program for future posting on our website at lls.org/leukemiaeducation. This provides an opportunity to read or listen again to today's program.

Before we begin, I'd like to introduce the Leukemia and Lymphoma Society's President and CEO, John Walter, who will share a few words with you today. John, please.

Mr. John Walter
Thank you, Lauren. I'd like to add my welcome to the patients, caregivers, and healthcare professionals on the program today.

The Leukemia & Lymphoma Society (LLS) exists to find cures and ensure access to treatments for blood cancer patients. We have one goal, a world without blood cancer. For more than 60 years, LLS has helped pioneer innovations such as targeted therapies and immunotherapies that improve survival rates and quality of life for many blood cancer patients. To date, we have invested nearly $1 billion in research to advance therapies and save lives. Until there is a cure, LLS will continue to fund promising research from bench to bedside.

Mr. John Walter
LLS is the voice for all blood cancer patients. We are the leading source of free cancer information, education, and support. We touch patients in their communities through our 61 chapters across the United States and Canada.

And we advocate for all blood cancer patients, survivors, and their families, helping them navigate their cancer treatments and ensuring they have access to quality, affordable, coordinated care.

We are fortunate to have as our presenter today, Dr. Dan Douer, one of the nation's leading experts in acute lymphoblastic leukemia. We appreciate his dedication to supporting our mission and commitment to caring for patients living with blood cancers. I would like to thank him for providing us today with important information on ALL.
Thank you, and I'll turn the program back over to Lauren.

Slide 2 – Dan Douer, MD

Ms. Lauren Berger
Thank you, John. I am now pleased to introduce Dr. Dan Douer, Attending Physician, Leukemia Service at Memorial Sloan-Kettering Cancer Center in New York City. On behalf of The Leukemia & Lymphoma Society, thank you for volunteering your time and expertise today. Dr. Douer, I am now privileged to turn the program over to you.

Slide 3 – ALL Topics

Dr. Dan Douer
Thank you, Lauren, and hello to everyone wherever you are.

I will be talking on several topics related to acute lymphoblastic leukemia, or ALL; how do we diagnose it and assess its risks, and based on the risk assessment, how we design treatments plans, and recommend treatment options. We will discuss the role of clinical trials, and the advancements in ALL in the treatment of patients.

A very important point which I discuss at the end of the lecture, is communication touch-points among patients and healthcare providers, which is particularly important in managing this disease.

On a large scale there are two different forms of acute leukemia. Acute myeloid leukemia, AML, which you can see on the right, is mostly a disease of adults. And the other form is acute lymphoblastic leukemia, ALL, on the left side, which is mostly in children, although more than 40 percent of the patients are adults, age more than 20. This presentation is only ALL.

Slide 4 – Epidemiology: Age Specific Incidence Per 100,000 Population

Dr. Dan Douer
ALL is not a very common disease, with only 6,300 patients diagnosed annually in this country. It's a little more common in patients of Hispanic ethnicity. It is the most common cancer in children, although one of the rare cancers in adults. Pediatric ALL is the most curable cancer.

Slide 5 - ALL - Not Just a Pediatric Disease: Treatment Age Groups

Dr. Dan Douer
So, ALL is not just a pediatric disease. Historically, patients are stratified by age into children, which are about 60 percent of ALL, with an upper age limit that varies by country or institution, but generally ranges up to the age of puberty or age of 21. And then there is the age of the adults, and then there are patients who are older adults above age 60.

Recently, a new group has been identified and is called adolescents and young adults, AYA, with an upper age limit of 39 years, and includes adolescents and young adult patients, ages between 15 and 39.

There are patients that are treated by pediatricians; an overlap group - patients who are treated by pediatricians or adult physicians; and as we move into adulthood, patients treated by adult physicians.

Slide 6 - Survival by Age at Diagnosis: 2 Year Age Intervals, 2000-2007, SEER17

Dr. Dan Douer
One of the most important findings in ALL is the high cure rate in children. But, in adolescence, somewhere around age 15, there is a drop in the survival of ALL patients to a rate of 40 percent or less. So, this is an important slide, because of the question, "Why is that drop?" We'll discuss it more.

Slide 7 - Acute Leukemia Clinical Features (I)

Dr. Dan Douer
But, before that, a few words about acute leukemia, in general, and it applies also to ALL. Most of the patients present acutely. Since leukemia is a disease that involves the marrow, and originates in the marrow, the symptoms are related to the inability to produce blood cells.

Dr. Dan Douer
A lack of red cells causes anemia, weakness, and tiredness; low platelets can cause bleeding; and low neutrophils can cause infections. With time, the leukemia cells emerge out of the bone marrow into the blood, increasing the number of white cells in the blood.

The diagnosis can be made in the blood, but we always do the bone marrow tests where we see these leukemic cells that we call blasts. The normal bone marrow is suppressed or not detectable.

Slide 8 - Acute Leukemia Clinical Features (II)

Dr. Dan Douer
Some patients may have disease outside of the marrow, most commonly in the spleen, liver, and lymph nodes, and other non-hematological tissues, particularly in the central nervous system (CNS), but other organs as well.

Slide 9 - Diagnostic Evaluation for Acute Leukemia

Dr. Dan Douer
When we have a patient with acute leukemia, we need first to differentiate between AML and ALL. We do a blood count and look at the leukemic cells and blood chemistry, but the most important diagnostic tests are checking the blasts by immunophenotyping, cytogenetics, and molecular genetics.

Slide 10 - Diagnostic Tests

Dr. Dan Douer
The first test is immunophenotyping. Several cell markers on the leukemic cells can distinguish AML, as you can see by myeloid monocyclic markers. And then, in the middle of the slide in yellow, are markers that characterize ALL. Sometimes, it's not so easy, and there are some very rare cases that are a combination of myeloid and lymphoid, and I will not discuss them.

Within ALL, we divide the patients into pre-B ALL, which are most of the patients, and T-cell ALLs, with special characteristics as you see here.

Slide 11 - T-cell ALL: 25% of Adult ALL

Dr. Dan Douer
T-cell ALL accounts for about 25 percent of adult ALL. It's mostly in young adults, usually between the ages of 20 to 50. Many patients present with a large mediastinal (chest) mass, with or without bone marrow disease.

Dr. Dan Douer
This is important to understand, because in my experience almost every patient has a mediastinal mass. And if you don't see the disease in the blood or the marrow, the diagnosis is made by biopsy of the mass. In some patients, this mass is very big, causes pleural or pericardial effusion, or sometimes, obstructions of veins. T-cell ALL is more often an emergency. But in fact, they respond very well to treatment, and the mass and related symptoms quickly disappear. T-cell ALL has a little better prognosis than the pre-B. They also have a higher rate of CNS relapse, which we'll talk later about how to prevent.

Slide 12 - ALL: Karyotype and Outcome

Dr. Dan Douer
The next tool in evaluating ALL is cytogenetics-checking the chromosomes of the leukemic cells (we don't check the normal cells). Some chromosomal abnormalities imply a favorable prognosis, and others are unfavorable, as you can see in the list.

The most common chromosomal abnormality in adults is Philadelphia chromosome ALL; we will speak about this ALL subtype later on in this lecture. Now, the most unfavorable chromosomal abnormality is translocation between 4 and 11.

Slide 13 - Other Poor Prognostic Indicators

Dr. Dan Douer
Other more general prognostic indicators that we use: increasing age reduces survival; a higher white cell count at diagnosis is an unfavorable sign-above 30,000 for pre B-cell ALL and 100,000 for T-cells (although these are arbitrary cut-offs).

Children respond very fast, in about two weeks. In adults, those who respond by four weeks have a better outcome than those who respond only after eight weeks.

We also use very sensitive techniques to detect what is called minimal residual disease, or MRD--disease that we cannot see under the microscope. If one is MRD positive at the end of the four weeks or eight weeks, it usually indicates an unfavorable outcome. It is routinely used in children, but is now beginning to be used in adults as well.

Slide 14 - Specific Recurrent Genetic Abnormalities

Dr. Dan Douer
More recent and newer information is the finding of recurrent genetic information. There are many--some for the pre-B-cells, and some for the T-cells. This list just gives you a "flavor", since this will be a major advancement in the field. The information is mostly from children and young adults with ALL, but soon there will be also data in older adults.

Dr. Dan Douer
We will probably begin to stratify patients to different treatments using these genetic abnormalities. I should emphasize that they are not yet in routine clinical use and are still under investigation.

Slide 15 - ALL: Treatment Elements

Dr. Dan Douer
There are four elements in ALL treatment. First, induction, with the goal of achieving a complete remission in about one month. Next, consolidation, which is several cycles of rather intensive chemotherapy over a period of months, and then, two to three years of mild chemotherapy called maintenance.

In addition, ALL has a high risk to relapse in the central nervous system (CNS). If we don't prevent it, half of the patients will relapse in that site. Therefore, CNS prophylaxis is necessary, starting it very early, continuing during consolidation, and now even in maintenance. I'll talk about CNS prophylaxis in a minute.

Slide 16 - Challenges in Establishing "State-of-the-Art" Treatment

Dr. Dan Douer
One challenge in treating ALL is establishing an agreed upon standard or the state of the art in treatment. Several reasons are involved. First, there's a wide age range, as I showed you earlier, and it is likely that patients at different ages will be treated by different regimens. Second, we have multiple chemotherapy regimens by few comparable trials, so it's hard to select. Third, there is uncertainty about the role of bone marrow transplantation or allogeneic transplantation. I'll talk about it later.

And also, we'll talk about the new regimens. And therefore, the NCCN guidelines that physicians use just list a number of regimens and allow the physician to pick their favorite one, or enroll in a clinical trial.

Slide 17 - Principals of Adult ALL Protocols

Dr. Dan Douer
What regimens are used in ALL? As I said, there are many ways of treating it and all include maintenance and CNS prophylaxis, and they can be divided into two general models.

One treatment model is called the BFM or its variants, which has been studied by all large groups in this country and Europe. It has been derived from children.

Dr. Dan Douer
The other approach is a regimen called Hyper-CVAD. It was developed at M.D. Anderson and mostly in this institution. It is the most commonly used regimen in adults in this country, especially in the community, probably since it is simpler; but much less in Europe.

Hyper-CVAD has some disadvantages. Each treatment cycle has to be given as an inpatient for a few days. It's more myelosuppressive. And asparaginase cannot be given, a drug which is included in the BFM model, which we think is a very important drug. However, the outcome of these two models is similar.

Slide 18 - Adult ALL: Recent Large Front-line Clinical Trials

Dr. Dan Douer
For illustration, you can see a list of several regimens. The regimens are the names on the left side. Despite different approaches, many of them are based on the BFM model, but you can see also the Hyper-CVAD regimen. The complete remission rate is high - about 90 percent. It's even higher than in AML. But, with all these regimens, the overall outcome is 40 to 45 percent, which is not satisfactory.

Slide 19 - Central Nervous System Prophylaxis

Dr. Dan Douer
A few words about CNS prophylaxis that is mandatory. We use a small dose of methotrexate given intrathecally (into the spinal fluid) for about 12-16 injections throughout the treatments. Also, we use systemic high-dose methotrexate that penetrates the CNS. We have almost stopped using radiation to the brain if we use the first two approaches.

Slide 20 - 5-year Survival of ALL by Major Age Groups: 1980-1984 to 2000-2004

Dr. Dan Douer
This epidemiological slide shows that although the outcome is better with lower age, it highlights that in adults of all ages, the outcome has not improved over the years; in fact it may have slightly worsened between 2000 and 2004.

Slide 21 - Adult ALL – First Relapse: Survival

Dr. Dan Douer
When patients relapse, the outcome is very poor, regardless of the age of diagnosis, on the left of the slide, or the type of treatment. The overall long-term survival in relapsed ALL is less than 10 percent. So, one really would like to get a higher cure rate on your first-line of treatment, because once relapsed, it becomes very difficult to treat.

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Slide 22 - Strategies to Improve Outcome of Adult ALL

Dr. Dan Douer
How can we improve the outcome which I have shown? What are the strategies that we can use? One approach is allogeneic bone marrow transplantation (from a donor). A second approach is learning from pediatricians, and treating with what we call "pediatric-inspired regimens", which I will explain later.

Another approach is identifying special subtypes for different treatments. This is where molecular analysis will help. The best example is Philadelphia positive ALL, which we now treat totally different, and I will speak about it separately, and finally, new drugs.

Slide 23 - Bone Marrow Transplantation: CIBMTR Recommendations

Dr. Dan Douer
First is the issue of bone marrow transplantation (BMT). The standard recommendations are allogeneic transplantation for high-risk patients in first remission, although there are various ways of defining high-risk patients or all patients in second or subsequent remission. When patients relapse and then enter a complete remission, the only way for cure is allogeneic transplantation. The role in standard-risk adult patients is less clear, but it is often not recommended.

Slide 24 - Allogeneic Stem Cell Transplantation: MRC/ECOG UKALLXII/E2993 Trial Ph Negative ALL

Dr. Dan Douer
However, a very large study conducted through collaboration of the American ECOG group and the British Medical Research Counsel showed, in high-risk patients, no difference if they were transplanted or not transplanted, while in standard-risk patients, there was a small benefit for patients who were transplanted; as you can see, 52 percent versus 62 percent, which is highlighted in red.

The main reason for transplant failure is because of the complications of the procedure, although less nowadays, but, there is still mortality related to transplantation. If we can find ways to get the same results without transplantation in standard risk patients, that would be preferable. Remember this 62 percent number with transplantation, which we will return to later. Autologous transplantation has no role.

Slide 25 – Outcome: Adults vs. Childhood ALL

Dr. Dan Douer
The second approach is the pediatric-inspired regimen. In adults, the leukemia-free survival is about 40 percent as opposed to a much better outcome curing 80 percent of children with ALL.

Slide 26 - Survival of 18,772 Pediatric Patients With ALL Treated on Sequential CCG Clinical Trials Over Three Decades

Dr. Dan Douer
What is the reason for this gap? First, the pediatricians have, over the years, improved the outcome of patients from about 10 percent in 1966 through the 2000s to 80 percent. This was done by a series of clinical trials, each one designed on the basis of results of previous clinical trials. Over the years, the treatments have been modified and improved. Some of the key changes were the discovery of the need for CNS prophylaxis and adding delayed intensification or augmentation of some drugs, like dexamethasone. But, you will notice that all this significant improvement has occurred without adding new drugs. This has never been studied systematically in adults.

Slide 27 - Adolescents and Young Adults: Retrospective Comparison Pediatric vs. Adult Protocols

Dr. Dan Douer
Second, as you see in this slide that compares the outcome of adolescent ALL patients (ages usually 16 to 20), who were either treated by pediatricians on pediatric protocols or by adult physicians on adult protocols. The patients were of the same age and similar disease characteristics. The only difference was one group was treated by pediatricians and the other by adults.

In the United States, the cure rate of pediatric protocols by pediatricians is 63 percent compared to 34 percent treated by adult protocols; almost double, in the same type of patients. This has been shown in almost every other country in the world. So, this has brought age as a difference between the treatment of adults and children to the center of the discussion.

Slide 28 - Age - A Complex Prognostic Factor

Dr. Dan Douer
Age is a more complex prognostic factor. Per se, children have better cytogenetics and are likely to do better because they have a “better” leukemia. They also tolerate chemotherapy better than adults. However, young adults tolerate the chemotherapy similarly to adolescents.

Dr. Dan Douer
There are also differences in treatments regimens that are given to adults. They are less intense as opposed to pediatric protocols. In adults, we also have a problem of compliance.

In children, it can be called "the mother factor"; a child or an adolescent is usually brought by the mother. Adults come on their own and usually tend to have a lower compliance. Also, pediatricians are more adherent to the treatment plan than adult oncologists. So, it's not only the age itself; it's the treatment and the way the treatment is given.

Slide 29 - Pediatric Treatment Approaches: Principals

Dr. Dan Douer
The next approach of improving the outcome of adult ALL is by using the principles adapted from pediatric protocols. Usually, they involve more intense, non-myelosuppressive agents, which means drugs that do not suppress the bone marrow, especially using asparaginase, and we will talk about it a little more. Allogeneic transplantation is only for very, very high-risk patients.

A few words about asparaginase, which is a chemotherapy drug active as a single agent that is used only in ALL and almost never in other diseases.

Slide 30 - Asparaginase Activity in ALL: Summary

Dr. Dan Douer
In children, several randomized clinical trials showed that asparaginase alone improved the outcome. When the patients received the same combination chemotherapy, with or without asparaginase, those that got asparaginase had a better outcome.

Clearly, asparaginase is a critical or key element in the treatment of pediatric ALL and is included in every regimen and given for five or six cycles. That means several months of treatment. Historically, in adults, because of toxicity concerns, it was either not used or given for a short period of time. This is one of the key differences between the treatments between children and adults.

Slide 31 - Unique Toxicities of Asparaginase

Dr. Dan Douer
The reason that there was a reluctance of using it in adults is that the drug has unique toxicities. The drug toxicities include allergic reactions, pancreatitis, clotting, liver dysfunction, diabetes, and some neurological problems.

Dr. Dan Douer
However, recently we have been using asparaginase in adults more frequently and are able to detect these side effects earlier and treat them. The reluctance that has historically been there in using it in adults, especially in young adults, is decreasing.

Slide 32 - Asparaginase Intensification: Pediatric and Pediatric - "Inspired" Regimens

Dr. Dan Douer
This next slide shows several examples of true pediatric or pediatric-inspired regimens given to adult patients. All of them have asparaginase intensification.

Some that are true pediatrics--exact copy of a pediatric regimen, for example, is CALGB 10403, which is a national study that has just closed. We don't know the results.

Other regimens are pediatric-inspired; they are similar pediatric protocols, but with some adjustments for adults; other studies, mostly intensification of asparaginase.

If you look at the right side, you can see the survival is much higher, in the 60 or 70 percent range. This is about the outcome we would see with transplantation. It is higher than the 40 percent with our historical adult regimen.

One question of these more intense treatments is, "What is the upper age limit? The national study, CALGB 10403, is limited to patients between 15 and 39 years of age. Others treated patients up to 60.

We are not sure what is the upper age limit in which one can use these pediatric or pediatric-like treatments, but we think it is somewhere between the age of 50 and 60. For patients who are over 60 years, there is no standard treatment and asparaginase is too toxic in this age group.

This is the direction that we are moving: treating, especially young adults, with these pediatric protocols. As you can see, the preliminary data is very promising.

Slide 33 - USC II Modified CCG Augmented Pediatric Arm (BFM)

Dr. Dan Douer
This is one example--these are very complex--of one of these regimens recently published. It is very complicated, with multiple treatment cycles with many drugs, including several doses of a long acting asparaginase called pegylated asparaginase. One problem with these regimens is they are extremely complicated and physicians have difficulty in remembering them. There are calendars that we give the patients to

Dr. Dan Douer
follow these complex treatments. However, you see the results. The outcome appears to be better.

Slide 34 - Ph+ ALL in CR1 – Pre-imatinib Era: MRC UKALLXII/ECOG 2993

Dr. Dan Douer
I want to move on and talk about Philadelphia positive ALL. Before the imatinib era we treated this with chemotherapy, and as you can see historically, only 19 percent were cured. I remember those days when less than 10 percent were cured with chemotherapy. At that time the only way to cure these patients was to perform BMT, either from a sibling or from a matched unrelated donor, resulting in about a 40 percent cure rate. The only way to cure Philadelphia positive ALL was by allogeneic transplantation. And even then only the minority were cured.

Slide 35 - Philadelphia Chromosome (Ph^+) ALL

Dr. Dan Douer
What is Philadelphia positive ALL? This ALL has a specific chromosomal abnormality in which two genes, one from chromosome 9 and another from chromosome 22, switch places and form one new fusion gene. It is almost always a precursor B-cell. Interestingly, it is rare in children and the incidence increases with age. After age 55 or 60 years, about half of the patients have Philadelphia positive ALL.

The change in the outcome of this disease was adding the new tyrosine kinase inhibitors (TKI), which are standard treatment in chronic myeloid leukemia, but are also active in ALL. The first generation TKI is a drug called imatinib, and the second generations are dasatinib and nilotinib. In brackets, you see the commercial names. A new TKI is ponatinib, reserved for patients resistant to all other TKIs.

Slide 36 - Northern Italy Leukemia Group Protocol (Ph^+ ALL)

Dr. Dan Douer
In this slide you can see studies where patients were given imatinib together with chemotherapy, with or without BMT. You can see in the yellow, adding imatinib increased the survival and reduced the relapse rate. In Philadelphia positive ALL, we can say the TKIs, for example imatinib, have single agent activity. One can get complete remissions with these single agents, but they are not durable. They also need to receive chemotherapy, and together the survival increases to about 30 to 50 percent (even without BMT).

Dr. Dan Douer
One of the problems we have is that we are not sure what is the ideal chemotherapy. There are studies that have shown steroids and a TKI can produce complete remission in all patients.

Slide 37 - Treatment of Ph+ ALL: Summary

Dr. Dan Douer
So, we may not need the pediatric or intensive treatments that we have been using for other ALL. But, we don't exactly know which chemotherapy. It's clear, however, that adding a TKI has improved the outcome.

In fact in children, although Ph positive ALL is rare there, treatment has improved to such an extent that no BMT is needed.

In adults, we do recommend still performing an allogeneic transplantation in remission, because it will further improve the outcome. If patients become resistant to imatinib, we can switch to second and third generation TKIs. These drugs have dramatically changed the outcome of Philadelphia positive ALL, from a disease that was the worst ALL to one of not so bad. In fact, if we have a 60 year old patient, we hope for the Philadelphia positive disease, because now we have better and more effective treatment.

Slide 38 - New Agents (Immunotherapy) Targeting B-cell ALL

Dr. Dan Douer
I will move on to discuss new agents. I divided this part into two sections. First, immunotherapy, and then we'll talk about new agents.

Immunotherapy is a method of using antibodies that target the leukemic cells. There are certain known targets on ALL cells such as CD20, CD19, and CD22.

Rituximab, which is a standard drug in lymphoma, can target the CD20, and by itself, has little activity. But, some studies have shown that adding rituximab to chemotherapy slightly improves the outcome. It is not accepted by everybody yet. There are other antibodies that are directed to another antigen--to CD22. All are in clinical trials.

One is epratuzumab, which is the naked anti-CD22. The second one is inotuzumab, that is an anti-CD22 antibody that carries a toxin, and like a targeted missile, it is directed to leukemic cells. It is showing promising results. Another antibody has a different toxin.

Dr. Dan Douer
Highlighted in red are the therapies that target CD19 on the leukemia cells. One drug is called blinatumomab, and the second approach, you may have read about this in the newspapers, is called CAR, or Chimeric Antigen Receptor, targeting autologous T-cells.

Slide 39 - Mode of Action of BiTE® Antibody Blinatumomab

Dr. Dan Douer
Blinatumomab, also called BiTE is a smart fusion antibody. At one side, it contains the part that targets CD19 on the leukemia cells. The other side of blinatumomab binds to the normal T-cell. In this way the drug engages the T-cells and directs them to tumor cells and is able to kill the tumor cells. It directs the normal T-cells to affect and kill the tumor cells.

Slide 40 – Blinatumomab: Single Agent in Refractory/Relapsed Pre-B ALL

Dr. Dan Douer
Preliminary results show in patients with molecular disease (very little disease), that the response rate is high and of relatively long duration of response. In patients with overt relapse, complete remissions can also be achieved.

A large international study with blinatumomab with about 200 patients has recently been closed, and the data is being analyzed. This treatment is logistically difficult to administer because the drug is given as a 24-hour continuous infusion in a cycle of 28 days, and the treatment bags have to be changed every 48 hours.

Slide 41 - MSKCC CAR T-cell Protocol: Eligibility and Treatment Schema

Dr. Dan Douer
Another immunotherapy approach is what we call the CAR technology and Memorial Sloan-Kettering is one of the centers studying this novel treatment. Penn University also studies this. We first collect the patients' own T-cells from their blood. The T-cells are taken to the lab and then genetically engineered with a smart gene that directs these T-cells to the CD19 target on the ALL cells and at the same time activates the T-cells to kill the leukemia cells. This is a very sophisticated technology because it involves genetically engineering the T-cells.

As opposed to blinatumomab, the CAR approach uses the patient's own cells that can survive for months, and therefore, can provide long-term activity, while blinatumomab is an antibody, and it only works when the antibody is given.

Practically, the T-cells are collected and it takes about a month or two in the lab to introduce the CAR gene. The patient gets chemotherapy to reduce the disease volume,

Dr. Dan Douer
followed by reinfusing their own T-cells that are now genetically engineered to kill ALL cells.

Slide 42 - Adverse Events

Dr. Dan Douer
This procedure can be toxic, which I think the press has not emphasized. The side effects are fevers, drop in blood pressure, hypoxia, shortness of breath, and neurological changes. Many patients are treated in the intensive care unit to provide breathing support.

The cause of these side effects is what we call the "cytokine storm." The T-cells and the leukemic cells release a variety of molecules that cause these side effects. The patients can be very sick. The side effects can be ameliorated by steroids. The problem is that by giving steroids, the activity of the T-cells is blocked.

After three to four weeks, we often see the response. Patients often enter complete response. This is still experimental, but the results are promising.

Slide 43 - CAR T-cells Summary

Dr. Dan Douer
The Sloan-Kettering investigators reported results in 16 patients, 8 with overt relapse. The complete remission rate was 88 percent and it took 24 days to get there. Forty-four percent of the patients continued to allogeneic transplantation. We are not sure that this CAR T-cell technology cures the patients. The only thing we know that cures the patient in relapsed ALL is allogeneic transplantation.

In the few patients we have transplanted, we, so far, have seen no relapses. So, this is a very promising approach, although it needs much further investigation.

Slide 44 - Novel Targeted Agents

Dr. Dan Douer
A second group of new treatments is new targeted drugs, which are now in different experimental stages. I highlighted the Notch 1 inhibitor and the DOT1L inhibitor. These two are in clinical trials as single agents. We know they have activity, but they are very early in the development. Other drugs listed are in clinical trials.

This brings up again, the importance of the molecular analysis that I discussed earlier, because it can identify new future targets for drug development.

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Slide 45 - State-of-the-Art Therapy for Adult ALL: A Changing Landscape

Dr. Dan Douer
In summary, in adult ALL, the treatment landscape is changing, including: for young patients, we are switching to pediatric or pediatric-inspired approaches, though the upper age limit is unclear; and for Philadelphia positive ALL, we are already adding targeted agents, the TKIs. Unfortunately, we have no state-of-the art treatment for relapse and older adults.

Slide 46 - State-of-the-Art Therapy for Adult ALL: A Changing Landscape (continued)

Dr. Dan Douer
Future treatment changes will likely include new agents, immunotherapy, such as antibodies, including blinotumumab, or cell therapy. And maybe, in first complete remission, transplantation would be limited only for those with very high disease.

Slide 47 - Communication Touch Points Among Patients And Healthcare

Dr. Dan Douer
This is the last slide, which I think is extremely important that both patients and caregivers understand. The new pediatric approaches are complicated. We learned from pediatricians that adherence to the regimen is important for a better outcome.

We try to achieve the best patient compliance as possible, taking into account the side effects. Adults may have more side effects than in children. Better compliance is achieved in children who come with parents. It's very difficult with adults, due to practical factors such as time, work, family commitments, life events, or just wanting to go on vacation at a time when treatment is planned. This intensive treatment requires a time and effort commitment, which is challenging if we want to implement these new treatments.

We anticipate side effects and place great effort in teaching patients the side effects (in particular those related to asparaginase), so they report them to us as soon as possible and we can treat them earlier, which often mitigates the severity. In addition, there must be good communication between healthcare providers in such a complex treatment, for example, between major cancer centers and large community oncology practices.

These factors, which are mostly psychosocial and practical, are extremely important in implementing these new approaches.

Slide 48 - Thank You

Dr. Dan Douer
Thank you very much for your attention.

Slide 49 – Question & Answer Session

Ms. Lauren Berger
Thank you, Dr. Douer, for a very clear and informative presentation. It is now time for the question and answer portion of our program.

For everyone's benefit, please keep your questions general in nature without too many personal details so Dr. Douer can provide answers that are also general in nature.

We'll take this first question from the web audience. And this person asks, "Dr. Douer, you referred to event-free survival in several of your slides. What is considered an event? And who is included in a five-year, event-free survival?"

Dr. Dan Douer
We have different outcome measures (or metrics). Event-free survival is the strictest one. An event is anything, relapse, death, even death without a relapse. It's the most strict way of looking at long-term outcomes, since it not only measures the relapse rate, but also includes death during treatment from side effects of treatment, mortality from transplantation, and even deaths from unrelated conditions. An event-free survival of 60 percent has more significance than disease-free survival because this just tells us that they didn't relapse, but doesn't include deaths from other reasons. Overall survival is another parameter we measure and this may exclude transplantation deaths or treatment-related events.

Ms. Lauren Berger
Thank you, and thanks for that question. The next question is also from the web. "Can Ph-positive ALL be healed completely? And do I have to take a TKI medication, like Gleevec®, for the rest of my life?"

Dr. Dan Douer
This is one of the most important questions that we are asked; in CML, yes. In ALL, it is less clear. In Ph-positive we still recommend transplantation, but it is a debate in post-transplantation whether continuation with TKIs is needed.

Some studies suggest that it might be beneficial to continue with a TKI. However, the question also relates to patients that are not transplanted. But, most of the studies continue a TKI during the two to three years of maintenance, and if the patient is in a molecular remission, it is stopped. In contrast, in CML, it is given for life.

Dr. Dan Douer
Our approach now--and that is based on limited data—is to start a TKI such as Gleevec® at the moment ALL is diagnosed as Philadelphia positive, and continued throughout intensive chemotherapy, entire maintenance, and then stop it. And so far, it seems to be okay.

Ms. Lauren Berger
Thank you. The next question is also from the web, and this one's from Carolyn. And Carolyn asks, "What are the side effects of administering intrathecal methotrexate?"

Dr. Dan Douer
First is the discomfort of placing a needle between two lower vertebrae of the spine into the spinal fluid. Now it is often done by interventional radiology and the needle is directed by x-ray. Second, we inject a small amount of chemotherapy, which is a chemical which can irritate the brain, causing headache, and is the most common side effect. It often resolves in a day or two, but in some patients the headache lasts longer. A very rare side effect is seizures. We try to prevent the headache by asking patients to lay flat on the back after the procedure and drink more fluid.

Ms. Lauren Berger
Thank you for that question, Carolyn. We'll take the next question from the web, and this one's from Adriana. "Please talk about adult ALL maintenance drug protocols."

Dr. Dan Douer
This is an important question, since maintenance is mandatory, and we know that without it, patients relapse. Most maintenance regimens include four drugs. In maintenance, the treatment is long but not intense, avoiding drops in blood counts.

Every maintenance always includes the two drugs, daily 6-mercaptopurine and weekly methotrexate. Nowadays, we have learned from pediatric ALL, and add vincristine and prednisone, both very effective drugs. Vincristine is given once a month, followed by five days of prednisone. In summary, it's daily 6-mercaptopurine, weekly methotrexate. We often need to adjust and individualize the dose to avoid a drop in the blood count. Most patients tolerate it well without side effects.

Ms. Lauren Berger
Thank you for the question. The next question is from the web audience from Sarah. "I've heard that half-matched donor transplants for children with ALL is promising. Would this also be appropriate for adults?"

Dr. Dan Douer
So, that's not only in ALL. "Half-matched" donor transplants are called haploidentical transplants. We're talking about relapsed patients. This would not be as front-line, even in adults. Half-matched transplant in general, is very complicated, with much toxicity and a higher death rate because the donor and the recipient (the patient) are not well matched. It is still very experimental. Currently, there is a trend of using it in conjunction with umbilical cord blood transplant. The advantage of half-matched transplant is increasing the number of potential donors, since parents or children can be donors. Full matches are found among siblings, or in a bone marrow registry. Yes, it is done, but only in the context of a clinical trial.

Ms. Lauren Berger
Thank you. We'll take the next question from the web, please. And this one's from Chris. And Chris asks, "Is AVN, or avascular necrosis, a common side effect of ALL treatment?"

Dr. Dan Douer
That is a great question that we did not discuss today. What is avascular necrosis (AVN)? For those who don't know this, it is a bone that loses its blood supply, and as a result, bone tissue and structure is lost. The symptom is chronic pain. This usually happens in the hips, but occasionally in other bones. The only effective treatment is surgical hip replacement. This late toxicity is mostly seen in adolescence, and uncommonly in adults. It occurs in adolescent patients when the bones are still growing, but in adults, the bones don't grow anymore. AVN is probably related to the long treatment with steroids. Dexamethasone is more commonly used, and in one trial, the drug was stopped because those who got dexamethasone instead of prednisone had a higher rate of AVN.

Ms. Lauren Berger
Thank you for that question. We'll take the next question from the telephone audience, please.

Operator
Our first caller is Julie from New York. Please go ahead.

Julie
Thank you. When is it appropriate to use radiation treatment with this diagnosis?

Dr. Dan Douer
With ALL?

Julie
Yes.

Dr. Dan Douer
That is a good question. Historically, for central nervous system prophylaxis, radiation to the head was applied. This is no longer done because we give more intrathecal methotrexate, as well as very high doses of systemic methotrexate, which has brain penetration to prevent CNS relapse. In children it caused late, mild cognitive dysfunction as a side effect of radiation.

Radiation to the brain is used, however, in patients who relapse in the central nervous system. So, when you actually have disease in the brain, then we use radiation. Another area that could be considered is patients with T-ALL who have a large mediastinum. Such local tumor in the mediastinum disappears with chemotherapy, and we do not radiate this and have not noticed a higher rate of relapse.

Another situation where we use radiation is often as part of the regimen that prepares patients for transplantation and that is called whole body radiation.

Ms. Lauren Berger
Thank you for your question, Julie. We'll take the next question from the web, please, and this one's from Zog. Zog asks, "When on the maintenance phase, if you relapsed or if the maintenance isn't working as well as it should be, how would you know this, as your blood counts are up and down from one week to the next from the medication?"

Dr. Dan Douer
Yes, you are correct, that's difficult. In most cases such fluctuations are not from relapse but due to the maintenance treatment with methotrexate and 6-MP. In these patients we need to adjust the dose of these drugs and find a dose that keeps the blood stable. We try and keep the white cells at about 3,000. In most patients we manage to successfully individualize the dose. In relapse, the blood counts drop and do not go up. The only way to be sure that this is not a relapse is testing the bone marrow when we have a suspicion. In most patients dose adjustment helps. In general, a relapse would be a persistent drop and continuous, not up and down. But, when in doubt, we perform a bone marrow test. A relapse usually declares itself quickly. If it is not a relapse, after stopping the treatment for a few days and restarting with lower doses, the counts go back to normal.

In children, they are beginning to measure the levels of the drug. That might be helpful. Also, there's an enzyme that breaks down the 6-mercaptopurine, and patients that don't have this enzyme are more susceptible to 6-mercaptopurine, causing a drop in the blood. We often check if this enzyme is absent, as that already tells us to use less of the 6-mercaptopurine.

If it's a continuous drop in blasts and the patient feels bad, it suggests a relapse, but often this is not the case.

Ms. Lauren Berger
Thank you. Thanks for the question, Zog. We'll take the next question from the web audience. And this is from Michelle. "If 30 percent of the bone marrow was leukemic at the time of biopsy, can you determine how long one had the leukemia prior to diagnosis?"

Dr. Dan Douer
No. There is really no way that you can know. The leukemia population of cells is a clone, which means that they all developed from a single cell. These cells could've developed several years earlier, and it takes a few years for the cells to multiply. So, if the blasts are 30 percent today, you can't tell when the leukemia actually started.

Ms. Lauren Berger
Thank you for that question, Michelle. The next question is from the web audience, and it's from Paul. Paul asks, "Have any advances been made to avoid using very high dose of steroids to manage graft-versus-host disease in transplant patients?"

Dr. Dan Douer
I'm not a transplanter, and may not give you the best answer. For prophylaxis of graft-versus-host disease, we don't use steroids. We use other drugs that are T-cell suppressors. When graft-versus-host is active, steroids are an important treatment drug. Much of research is focused on better preventing and treating graft-versus-host disease.

Ms. Lauren Berger
Thank you. Next question is from the web. And this question is from Arden. "What is being done to minimize long-term and late effects such as cardiac function and neuropathy for patients with ALL?"

Dr. Dan Douer
This is an excellent question. This is important, especially in children, as most are cured and live many years, and most recently also in adults. These are cancer survivors, when late side effects can show up many years after being cured. Cancer survivors face a variety of problems, including fertility and psychosocial life adjustments. Cardiac toxicity is one of the late toxicities and is related to the anthracycline chemotherapy drugs. Most ALL regimens do not use much anthracycline, and cardiac complications are uncommon. This was studied mostly in childhood ALL survivors, but we have similar information in adults.

Neuropathy is caused by vincristine which is a chemotherapy drug always used in ALL. Neuropathy is seen more in older adults. It usually presents as numbness in fingers and toes, and occasionally as muscle cramps. In most patients it resolves with time but some experience this side effect longer.

Dr. Dan Douer
We may reduce the dose by half if we see that the neuropathy is persistent. Usually the neuropathy from vincristine disappears over the years. We also have better drugs now for neuropathy, things like Lyrica® or Neurontin®. Pain management clinics usually have a whole list of drugs that can help patients with neuropathy.

Ms. Lauren Berger
Thank you. And we actually have two questions on clinical trials, both from Steven and from Mark. So, I'll ask you them together. "What are the advantages and disadvantages of an adult ALL patient participating in a clinical trial? And also, how do we get our oncologists to consider them?"

Dr. Dan Douer
Historically, in this country, very few patients are enrolled on clinical trials, while in Europe almost everybody is.

Why should a patient go on a clinical trial? I think when you look at data on outcomes of patients on clinical trials--well, let's go the other way around. In patients who have relapse, the clinical trials are usually for new drugs.

And so, here, the advantage is when we no longer have good chemotherapy, the advantage is trying some new drug, and maybe it will work. So, there are the cases where there's nothing else. So, that's, for example, the CAR technology, the big advantage for patients who go on because other things didn't work so well.

The question is in front-line clinical trials. And there, we are trying to improve the information, and then the problem is the phase 3, where there is a randomization between a chemotherapy regimen with or without something. And you, by chance, will fall on one of the arms. There's a lot of monitoring of the trials. We do a phase 3 randomized trial where we really don't know if that new agent that is being added is better. It's probably that it might be worse. There might be side effects. Overall, patients on clinical trials statistically did better. All the new drugs came from clinical trials.

The second question is how to get your oncologist to consider them. Now, that's difficult. There's a website called clinicaltrial.gov, where you can see all of the clinical trials. But, every clinical trial has to have a principle investigator that is actually responsible to the FDA regarding conducting a clinical trial according to the regulations. And then, it has to get approval, most importantly, through what we call the Institutional Review Board, or the IRB.

So, you have to have all these mechanisms to follow the law when you do a clinical trial--I can't just do a clinical trial without following these regulatory pathways. Here, it takes

Dr. Dan Douer
about two to three months to open a clinical trial in order to comply with all of the regulatory requirements.

So, if a physician has a clinical trial, and a clinical trial is something that is approved by the Institutional Review Board. That's a clinical trial. It has to be approved by IRB. If you are giving a new drug just because you think it's better, that's fine, but it's not a clinical trial. If that physician has such a clinical trial, and many of the NCI groups have community physicians that participate in the clinical trials, and a lot of them will provide it. All large cancer centers always have clinical trials, and we always encourage them to come and explore. We have strict eligibility criteria because it's a clinical trial, we don't want to cause harm.

So again, the benefit to the patient is, in some cases, there's nothing else. In other cases, usually, there might be benefit. Now, if you find out that, after a certain number of patients, the new drug that we added is better than without it, we stop the clinical trial and this drug becomes standard.

So, there's a lot of monitoring and a lot of follow-up. So, you don't know how much regulatory effort we have put in to conduct them in a safe way. I mean, the safety is really important to us. And by that, patients are being followed much closer than any other patient because we really follow them. There's a nurse, there are data managers, there are a lot of visits.

So, it's much more, I mean, you should pay attention to every patient. We follow them very, very carefully because we want to get the data. So, there are several advantages for clinical trials.

We encourage our patients to go, if they are eligible, to clinical trials. In Europe, as I said, most patients go into clinical trials. In this country, unfortunately, only a minority go.

Ms. Lauren Berger
Thank you, Mark and Steven, for your questions. And if anyone would like more information about how to search for a clinical trial, or assistance to find, or to do a search, please call the Information Resource Center, and the Information Resource Center telephone number is in your packet, and I'll also mention it again at the end of the program.

The next question is from the web, and it's from Jay. And Jay asks, "Is it possible to ever be considered cancer-free from ALL, or will patients have to be tested for relapse for the rest of our lives?"

Dr. Dan Douer
Okay, that's a very good question. No need to be tested for relapse for the rest of their lives. When you say cancer-free, you mean cure. A remission is not cancer-free. Some people confuse a remission, when you don't see the disease, as cancer-free. A remission is not a cure. In remission, you don't see the cancer, but it can come back. When one says cancer-free, it means cured; it will never come back.

We know that most of the relapses happen early, within the first 18 months. As time passes, the relapse rate drops. Very few relapses occur after three or four years of being in remission. There are certain very rare cases that relapse after many years, but these are very rare cases.

But, as I said, most of the relapses are early. When you get to three or four years, the chance of relapse drops. It's not to zero, but it drops significantly. And you don't need to be followed or do anything; you just have to do blood counts, basically, that's all, from time to time. So, we follow the patients, but at that time, we don't do bone marrows every year. We just follow the blood.

Ms. Lauren Berger
Thank you for that question, Jay. We'll take the next question from the web, and this is from Lilly. "How important is Minimal Residual Disease, and can you provide a little bit more of an explanation about that?"

Dr. Dan Douer
I didn't have time to talk about it, so I thank you for this very important question. It allows me a little more time to discuss.

A complete remission is determined by looking at bone marrow samples with a microscope and not seeing leukemia cells. If the bone marrow has less than 1% leukemia (1 leukemia cell among 100 normal cells), they cannot be seen under the microscope. However, with more sensitive methods it is possible to identify fewer cells still remaining in the bone marrow. The observation of leukemia below what can be seen by the microscope is called "Minimal Residual Disease" (MRD). For example, MRD of 0.1% means one leukemia cell among a 1,000 normal cells or lower. The lower the MRD percentage, the better is the response, since few leukemia cells remain in the marrow. MRD tells us the depth of the response to the treatment. We have several sensitive laboratory techniques to measure MRD, which include PCR and flow cytometry. In children, if at day 28 of treatment, the MRD is 0.01% or higher (one leukemia cell per 10,000 normal cells), they are considered MRD positive (MRD+) and the prognosis of these patients is not as good as those who have less residual disease, i.e., MRD lower than 0.01% have a much better prognosis. Checking the MRD level is an excellent tool for prognostication and based on the degree of response to treatment.

Dr. Dan Douer
MRD positivity is probably the most important factor in predicting failure of treatment.

In adults we have less information about when to measure MRD and what are its parameters, and it has not yet become standard in this country, because the technology has not been standardized. In a year or two MRD checking in adults will also be routine.

To answer the question directly, MRD is important, especially early on in the treatment. For example, MRD positive would suggest changing the course of treatment, including consideration of a bone marrow transplant in first remission.

Ms. Lauren Berger
Thank you for that question. We'll take the next question from the web audience, and this is from Rima. "Did you say earlier that TKI plus prednisone while in CR1 is better either with or without chemo maintenance?"

Dr. Dan Douer
No, I think that there's some confusion. I'm sorry if it wasn't clear. We need to discuss two points.

First of all, TKI drugs in front-line treatment of Philadelphia positive ALL are active on their own, yet chemotherapy is needed for a better outcome. But we are not sure what is the optimal chemotherapy to add. There are studies that show that very good remission can be achieved with a TKI plus steroids without any other chemotherapies. In fact, 100 percent achieve a remission, but it is not a molecular remission, so, therefore, we recommend transplantation. We use such an approach in elderly patients with Philadelphia positive ALL because it is less toxic.

There was another aspect, a completely different one in your question, which is the issue of maintenance with TKI. Every patient has to get maintenance, but in Philadelphia positive patients, TKI is added as part of the maintenance.

Ms. Lauren Berger
Thank you for that clarification. The next question is from the web from Floris. She says, "Do I understand correctly that for a relapsed adult ALL patient, the only chance is still transplantation? My mother is 63, and she just relapsed."

Dr. Dan Douer
The answer is yes, to cure. If a relapse occurs, a second complete remission should be achieved, which is followed by transplant, which at this time is the only curative approach. At this point, transplant is still considered the only way to cure ALL that has relapsed.

Ms. Lauren Berger
Thank you for that question. The next question is from the web from Silas. "Is there is a specific number of months that's typical for the maintenance protocol you just talked about?"

Dr. Dan Douer
We give it for 30 months, 2 ½ years; others give it between 2 to 3 years. We start counting from the end of the consolidation.

Ms. Lauren Berger
Thank you for that question. The next question is from Mary on the web, and Mary asks, "What do longitudinal data show for ALL survivors who were three years old when diagnosed, only received chemotherapy, and are now in their early 20s?"

Dr. Dan Douer
The pediatricians have done a lot of work on long term survivorship in children who had ALL and were cured. One of the long term problems is that chemotherapy drugs by themselves can cause leukemia or AML. This is not common, but could occur any time up to 10 years from treating the cancer.

Usually fertility is not affected by the time the cured children become adults. There's an interesting point here, also. The question is, "What happens to the offspring of these patients that had leukemia in their early childhood?" There's no higher risk for their children to get cancer because the parents received cancer treatment. There are psychological problems because these children have cancer when their personality is developing. This normal development process is totally disrupted when one has a potentially fatal disease. The 2 or 3 years that is taken out of their lives during this important developmental stage is causing later psychological problems

Ms. Lauren Berger
Thank you for that question, and thank all of you for your questions. We hope this information will help you and your family in your next steps.

Slide 50 – LLS Contact Information

Ms. Lauren Berger
If you were not able to get your question answered today, please call The Leukemia & Lymphoma Society's Information Specialists at 800-955-4572, or you can reach us by email at infocenter@lls.org. We can provide you with information about ALL research,

Dan Douer, MD
January 14, 2014

Ms. Lauren Berger
clinical trials, questions you may have about treatment, and also questions about financial assistance for treatment.

Please help me thank Dr. Douer for volunteering his time and expertise with us today. And thanks also to Amgen Oncology for their sponsorship. On behalf of The Leukemia & Lymphoma Society, thank you for sharing your time with us today. We wish you well.