Eytan M. Stein, MD
January 19, 2016

Slide 1: Strategies for Treating AML
Operator:
Greetings, and welcome to the **Strategies in Treating AML** Telephone and Web Education Program. It is now my pleasure to introduce your moderator, Lizette Figueroa-Rivera.

Slide 2: Welcome and Introductions
Ms. Lizette Figueroa-Rivera:
Hello, everyone. On behalf of The Leukemia & Lymphoma Society, a warm welcome to all of you. Special thanks to Dr. Eytan Stein for sharing his time and expertise with us today.

Before we begin, I'd like to introduce The Leukemia & Lymphoma Society's Executive Director of Research and Strategy, Dr. Amy Burd, who will share a few words. Amy, please go ahead.

Dr. Amy Burd:
I'd like to add my welcome to the patients, caregivers and healthcare professionals attending the program today. The Leukemia & Lymphoma Society exists to find cures and to ensure access to treatment for blood cancer patients. Our vision is simple: a world without blood cancer.

For more than 60 years, LLS has helped pioneer innovation, such as targeted therapies and immunotherapies that have improved survival rates and the quality of life for many of our blood cancer patients. To date, we have invested over $1 million in research to advance therapies and save lives.

In addition, as this program demonstrates, we are the leading source of free blood cancer information, education and support, and we touch patients in their communities through our 58 chapters across U.S. and Canada.

LLS acts as the voice for all blood cancer patients. We advocate for patients and survivors and their families, helping them navigate their cancer treatments and ensuring that they have access to quality, affordable, and coordinated care.

We're fortunate to have our presenter today, Dr. Eytan Stein, one of the nation's leading experts in acute myeloid leukemia. We appreciate his dedication to supporting our mission and his commitment to caring for patients living with blood cancers. I'd like to thank him for taking the time today to share important information on AML. Thank you, all. And now, I'll turn the program back to Lizette.

Ms. Lizette Figueroa-Rivera:
Thank you, Amy. And we would like to acknowledge and thank Stemline Therapeutics Inc. for support of this program.

Slide 3: Disclosure for Dr Stein
I am now pleased to introduce Dr. Eytan Stein. On behalf of The Leukemia & Lymphoma Society, thank you for volunteering your time and expertise today with us. Dr. Stein, I am now privileged to turn the program over to you.

Slide 4: Acute Myeloid Leukemia
Dr. Eytan Stein:
Thank you very much. I'm really delighted to be able to participate in this webinar. One of the things I love doing is talking to patients and their caregivers and really helping to explain what acute myeloid leukemia is and our current treatment strategies and how we can make treatments better.

Slide 5: Leukemia – United States
I think many of you on the call know that leukemia in general means cancer of white blood cells. And leukemia comes in a few different flavors. You can have acute leukemia, or you can have a chronic leukemia.

Acute leukemias come in two flavors also. There's acute myeloid leukemia, which represents about 19,000 cases per year in the United States. And there's acute lymphoid leukemia, which represents about 6,000 cases per year in the United States. And of those, about 4,000 of those cases are pediatric cases.

Of the chronic leukemias, there's also lymphoid leukemias, which represent about 15,000 cases, and chronic myeloid leukemia, which represents about 6,000 cases per year in the United States. Of course, what we're going to be talking about today is acute myeloid leukemia.

One other thing is that there are some rarer leukemias, which we're not going to talk about today because it would require a whole conversation in and of itself. One of those is known as blastic plasmacytoid dendritic cell neoplasm or BPDCN, which is the easier way of saying it. There's also something called acute promyelocytic leukemia, which is a subset of acute myeloid leukemia but is treated differently, and we're not going to really touch on that much today.

Slide 6: Hematopoiesis: Maturation and Differential Chart
Dr. Eytan Stein:
In order to understand what acute myeloid leukemia is, you really have to understand what a normal blood system does and how a normal blood system operates. If you look at this chart, this is normal hematopoiesis, which means normal development of the blood system.

So, in your bone marrow and all of our bone marrows, we all have these baby stem cells called myeloid stem cells. And what they do when they're acting normally is they mature down these arrows into neutrophils and platelets and erythrocytes, which are red cells.

What happens in acute myeloid leukemia is pathologically actually quite simple. And that is that the myeloid stem cell matures and becomes a myeloblast, which is the first step here. But, then it gets stuck at the myeloblast stage of development. So, the myeloblast cannot mature down those arrows into a healthy normal neutrophil, which is an infection-fighting cell.

And not only can that myeloblast not mature, but those myeloblasts accumulate, and that crowds out the other normal cells, like platelets and red cells. And that is why patients' blood counts become abnormally low, and they require blood transfusions and platelet transfusions.

Slide 7: Basic Facts
Most patients with acute myeloid leukemia are diagnosed over the age of 60. And that's because the incidence of this disease really dramatically increases as patients' age. You can see from the chart or from the graph on the right, that between the ages of 55 and 64, the incidence of the disease in the United States per 100,000 goes from somewhere around 3 per 100,000 up to 20 to 25 per 100,000. So, this is generally a disease of older adults in the United States and around the world.

Slide 8: Overall Survival in AML
When we talk about the overall survival in acute myeloid leukemia, one of the things that I think is very satisfying is that, over the past 40 years, for younger adults, the overall survival really has dramatically improved.

Looking at this survival curve, if you just look at the top graph, each different color is a different five years of treatment for the treatment of AML. You can see, again, in the top graph, that between 1970 and '79, that's actually nine years, the overall survival at 10 years for patients with AML was quite poor at about 5%.

But, if you then scan your eye up to the purple line, you can see that between 2005 and 2009, the overall survival increased by almost 50%, such that the overall survival in that

Dr. Eytan Stein:
five-year period was 53%. And I suspect that over the past five to six years, the overall survival has improved even more.

If you look at the bottom survival curve, you can see that the survival for older adults with AML, that is patients older than age 60, has also improved between 1970 and 2009, going from less than 5% to about 23%. But, we still have work to do with the older adult population to try to match the successes we've made with patients younger than age 60.

Slide 9: Bone Marrow Biopsy
Anyone that is diagnosed with AML, the first procedure that they undergo to confirm the diagnosis and to make the diagnosis is a bone marrow biopsy. And that's because you really need to look at the engine or under the hood of the patient to take a look and see where the problem lies.

And when we do this bone marrow biopsy, a needle is inserted into a place where a lot of bone marrow is produced. And in this case, that's the patient's pelvic bone. The bone marrow is extracted. It's placed under a microscope. And this is what it looks like under the microscope.

All of these cells on the right-hand side are blasts. These are all the bad cells. And this actually came from a patient with acute myeloid leukemia.

The next thing the doctor will do after taking this big view of all the blasts that are in the bone marrow is look and see if there are any changes in those blasts that portend either a favorable risk of disease relapse or an unfavorable risk of the disease relapsing more quickly.

Slide 10: Chromosomes
And one of the ways we do this is we look at the patient's chromosomes. You probably know that all of us have 46 chromosomes, two pairs of 23. They're numbered from 1 to 22. And then women have two X chromosomes. And men have one X chromosome and one Y chromosome.

And what you're seeing here is the normal complement of chromosomes in a patient without leukemia. But, what happens in many patients, especially older patients with leukemia, is that these chromosomes get messed up. And the easiest way to put this is, if you imagine taking a piece of, let's say, chromosome 1 and switching with a piece of, let's say, chromosome 20, or you take a piece of chromosome 8 and switch it with a piece of chromosome 9, which then again switches with a piece of chromosome 16, for example, that can tell us whether a patient has a favorable prognosis or an unfavorable prognosis. And it helps guide us in our therapies.

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Slide 11: Where Have We Made Definite Progress?
Dr. Eytan Stein:
And what we've been doing over the past 10 years is taking even a deeper look into the genetic makeup of a patient's leukemia. And this is the place where we have made definite progress.

So, if you remember the chromosomes I just showed you on the previous slide, you can see that we can even look in greater detail at those chromosomes at specific genes that reside on those chromosomes. The chromosomes are made up of DNA. We can look at genes that are sitting on those chromosomes. And we can see if there are any specific mutations, like the ones I've listed here, again, that helps guide us with how a patient might do with standard treatment for their AML. And in addition, if a patient is not doing particularly well, it helps guide us with clinical trials that might target these specific gene abnormalities.

In addition, it gets even more complicated because most people don't just have one gene abnormality, but as is depicted on the right-hand circle, which is called a Circos plot, you can see that the ribbons that connect the different words of gene abnormalities show co-occurring mutations. That is, most patients with AML have more than one mutation. And the question becomes, when you're thinking of targeting a specific mutation on a clinical trial, which one do you have to go after, or should you go after all of them at once?

Slide 12: Advances in the Treatment of AML
I would say that there have been four big advances in the treatment of AML up until about 2015. The first is when allogeneic or stem cell transplants were initially developed in the late 1970s. The second is when we realized that giving strong chemotherapy called 7 plus 3, which we'll talk about in a second, became something that improved patient outcomes. The third is when we saw that giving patients consolidation chemotherapy after their incomplete remission can also improve outcomes and cure patients. And finally, we've been making tweaks on our chemotherapy regimens, such that, if we increase the dose of one of the drugs that is used for induction chemotherapy, called daunorubicin, there's a suggestion that patients younger than age 60 do better and are cured at a greater rate when they have higher doses of daunorubicin.

Slide 13: Current Paradigms for Treating Newly Diagnosed AML
When I see a patient in my office who is referred to me for a new diagnosis of AML, the first thing I'm looking at is, number one, what is their age? And number two, what other medical problems do they have? And this tends to correlate with the patient's age.

Dr. Eytan Stein:
Most folks who are over the age of 65 or 70 will have some other medical problem, maybe some high blood pressure, high cholesterol. Maybe they've had a heart attack in the past, while patients who are younger than age 60 or age 50 or certainly age 40 often don't have a lot of medical problems or maybe have never even been hospitalized before.

So, I look at a patient, and I try to assess what other medical problems they have besides having newly diagnosed leukemia and also their age. And the way we typically think about treating patients is as follows: For patients without comorbid medical conditions who are between the ages of about 18 and 70 or 75, we think about giving them intensive induction chemotherapy with this regimen called 7 plus 3.

For patients who are older than, let's say, age 73 to 75, or if they have comorbid medical conditions, we think of doing what's called a low-intensity strategy with drugs in the class called hypomethylating agents. There are two that are approved, at least in Europe, called decitabine and azacitidine.

And then there is a group of patients, unfortunately, who are either very elderly or very infirmed. And those patients, unfortunately, really can't tolerate any therapy against their leukemia. And we aim to do things to keep them going by giving them blood and platelet transfusions and giving prophylactic antibiotics to try to prevent infections.

Slide 14: When Does 7+3 Not Equal 10?
So, if we talk about induction chemotherapy, I think this is the only case where 7 plus 3 does not equal 10. And what is 7 plus 3?

Slide 15: Cytarabine and Daunorubicin
So, 7 plus 3 is when patients who are candidates for intensive induction chemotherapy are given seven days of a drug called cytarabine continuously. And that overlaps with three days of a drug called daunorubicin.

So, the 7 plus 3 is really seven days of chemotherapy, but three of those days are concomitant with the cytarabine that they are getting.

Slide 16: Calendar
And patients who get intensive induction chemotherapy, at least in the United States of America, typically are admitted to the hospital for about a month. If you look at this calendar, you'll see that, for example, a patient might get admitted to the hospital with newly diagnosed AML.

If they are going to get induction chemotherapy on January 2nd, in this case, it's of 2011, they would get their treatment for seven days. In general, the next two weeks or the

Dr. Eytan Stein:
week of the 9th and the 16th, their blood counts would become very, very low, and they would require transfusions with blood and platelets.

And then around the week of the 23rd, which would be the fourth week, what we hope is that all of the leukemia cells have gone away, and the only things that grow back are the good healthy cells that are maturing correctly.

Slide 17: Garden
So, this is akin--what I always tell my patients--to a garden, normal--all of us have our garden full of flowers, which is our bone marrow.

Slide 18: Barren Field
But, when someone develops leukemia, the garden gets overgrown with weeds. We give induction chemotherapy. And what that does is that not only kills the flowers, but it also kills the weeds.

Slide 19: Flowers
And what we hope is that, when the garden grows back, all that grows back are the flowers.

Slide 20: After Complete Remission…
One of the things we know, though, is once we give induction chemotherapy, and once patients have gone into remission, in general, if you don't do anything after a patient is in remission, the chance of relapse is relatively high.

So, the first hurdle is getting a patient into remission. And the second hurdle is keeping the patient in remission. And this is how we think about what to do once a patient is in remission.

We look at those things that I showed you before, the chromosomes and specific gene mutations, to try to come up with, what is the risk of the AML coming back?

So, in patients who have better-risk AML, and those are these chromosome abnormalities, we think about just giving further courses of chemotherapy after they're in remission. And that's called consolidation chemotherapy.

In patients with poor-risk leukemia, we think about giving, instead of consolidation chemotherapy, we think that probably the best way to get patients to stay in remission is to pursue a stem cell transplant, an allogeneic stem cell transplant.

But, then there's this large group in the middle, of patients who have intermediate-risk AML. And for those patients, it's unclear exactly what to do. And it really becomes an

Dr. Eytan Stein:
individual decision based on the patient's genetic profile and the risks associated with a bone marrow transplant, whether that patient would have a bone marrow transplant or whether we would recommend not having a bone marrow transplant.

Slide 21: Approach to AML Treatment
So, again, just fast forwarding to how I approach the treatment of AML, it's really fairly straightforward with the standard treatments that we have now. I see a patient with acute myeloid leukemia. We make a determination jointly whether they would benefit from induction chemotherapy.

If we don't think they would benefit from induction chemotherapy, we ask whether they might benefit from a hypomethylating agent, like decitabine or azacitidine, which I call a low-dose approach, or either the patient doesn't want to pursue a low-dose approach or induction chemotherapy, or perhaps they are very elderly or very infirm, and they just get blood and platelet transfusions.

In those patients who've gotten induction chemotherapy, the next decision point is, should we pursue a bone marrow transplant, or should we pursue further episodes of further chemotherapy, which is called consolidation chemotherapy.

Slide 22: New Directions to Treat AML
What I want to move onto now is really to talk about some very exciting new directions to treat AML. All of the things I'm going to talk about right now are recent clinical trials that have either been presented or are currently being conducted. But, I'm very hopeful that some of the treatments I'm telling you about will find their way into how we treat AML over the next five years and improve the survival for this disease.

Slide 23: FLT3 Inhibitors in the Treatment of Acute Myeloid Leukemia
The first thing I want to talk about is FLT-3. FLT-3 mutations are found in approximately 30% of patients with acute myeloid leukemia. And one of the things that happens when patients have a FLT-3 mutation is abnormal bone marrow blasts, so that blasts that can't mature start proliferating. And you get this overabundance of blasts, maybe even more so than you would in regular old acute myeloid leukemia.

And because of this and because we know that FLT-3 is abnormally mutated in 30% of patients and portends, in general, a less favorable prognosis, we've been trying for many years to target FLT-3.

Slide 24: A Phase III Randomized Double-blinded Study of Chemotherapy +/- Midostaurin (PKC412) in Newly Diagnosed Adults Aged 18-60 with *FLT3* Mutated Acute Myeloid Leukemia (AML)

Dr. Eytan Stein:

And this year at the annual meeting of the American Society of Hematology (ASH®), a big Phase 3 trial was presented randomizing patients to either get induction chemotherapy with a FLT-3 blocker, a FLT-3 inhibitor called midostaurin, or randomizing patients to get induction chemotherapy with a placebo. And this is the way the trial was set up. This trial was conducted by one of the big cooperative groups in the United States called the Alliance for Clinical Trials in Oncology and was led by Dr. Richard Stone and Dr. Hartmut Döhner.

Slide 25: Schema

And this is the way the trial was set up. If you were diagnosed with acute myeloid leukemia, the doctor would check and see if you had a FLT-3 alteration. If you had a FLT-3 alteration, patients would be randomized to either receive induction chemotherapy with the FLT-3 inhibitor or induction chemotherapy with a placebo.

If they went into remission, they could go on and continue to receive the FLT-3 inhibitor, both during consolidation chemotherapy and during the maintenance phase of the study.

Slide 26: Overall Survival (Primary Endpoint): 23% Reduced Risk of Death in the Mido Arm

And the results that were presented last month were pretty remarkable in that this is the first time in acute myeloid leukemia that a targeted agent, that is the blue line and that's the FLT-3 inhibitor midostaurin, has been shown to improve overall survival in patients with FLT-3-positive acute myeloid leukemia.

You can see that the degree of improvement in overall survival is modest. It's about 7% at five years. But, it's real, and it's there.

Midostaurin, I believe, is going to be presented to the Food and Drug Administration (FDA) in the near future. And if it does get approved by the Food and Drug Administration, I suspect that the combination of induction chemotherapy with midostaurin will become the standard of care for patients with newly diagnosed FLT-3 positive acute myeloid leukemia.

Slide 27: IDH in AML

So, the next drug I want to talk about are inhibitors of a mutation in a gene called IDH, or isocitrate dehydrogenase. I'd say about 15% of patients with acute myeloid leukemia have a mutation in this gene called IDH. And when you have a mutation in this gene called IDH, what happens is that this mutated gene produces too much of a substance

Dr. Eytan Stein:
called 2-HG. When you have too much 2-HG, it blocks those blasts from maturing into normal healthy infection-fighting neutrophils.

So, the idea is that, if you block mutant IDH, you can lower the levels of 2-HG. And what happens is that those blasts can then flourish and start maturing into neutrophils.

Slide 28: Garden and Flowers
So, instead of what I told you before, where we would give patients chemotherapy that would kill everything in the bone marrow, both the good cells and the bad cells, this is an example of what's called a differentiation therapy, where you take the weeds, and instead of killing them, you cause them to bloom into flowers. It transforms the leukemia cell into a normal healthy cell in theory.

Slide 29: Phase 1/2 Study Design
There's a clinical trial that is currently being conducted, both of an inhibitor of mutant IDH2 and of an inhibitor of mutant IDH1. I'm going to talk about the IDH2 study just for a second.

This is a study that started out as a Phase 1 study. A Phase 1 study is done to see what the best dose of a drug is. This Phase 1 study was given to a number of patients. And the best dose of the drug was found to be 100 milligrams a day.

And after the dose escalation was completed, dose expansion was started in four different groups of patients, older than age 60, younger than age 60, and patients who had never been treated with AML before. That part of the trial has now completed.

And we've moved onto a Phase 2 trial looking at 125 patients with relapsed and refractory acute myeloid leukemia with an IDH2 mutation to see whether giving this drug, this oral pill, as a single agent can help these patients get rid of their leukemia.

Slide 30: Response
These are the results that were presented at the American Society of Hematology annual meeting. And what I want to draw your attention to is this column that is highlighted or that is boxed off in red. And this is in the relapsed and refractory AML population. So, these are patients who have either not responded to any chemotherapy or patients who had AML and then relapsed.

Almost 40% of patients getting this oral pill have gone into either a complete or a partial remission. And I would say that that is really, really quite amazing for a single agent in a group of patients with acute myeloid leukemia.

Dr. Eytan Stein:
There are now studies that are being developed to combine this treatment with chemotherapy with the idea that, if you give induction chemotherapy with this treatment in patients who have this IDH2 mutation, you could make the outcomes even better than they would be with chemotherapy alone.

Slide 31: Antileukemic Activity and Tolerability of ASP2215 ≥80 mg in FLT3 Mutation-Positive Subjects with Relapsed or Refractory Acute Myeloid Leukemia: Results from a Phase 1/2, Open-Label, Dose-Escalation/Dose-Response Study
Another agent that is being developed to target the FLT-3 abnormality that we talked about before is a drug that has been known previously as ASP2215 and is now known by the name gilteritinib. And this is another oral drug that is being tested in a clinical trial for patients with relapsed and refractory AML and also in patients who have a FLT-3 abnormality.

Slide 32: Overall Survival by Response in FLT3+ Subjects Treated with ≥80 mg Gilteritinib
And over here are some results of those patients who went on this clinical trial. And you can see in the blue line that there were a large group of patients that went into a complete remission. And there were also patients who went into a partial remission.

Of those patients who went into a complete remission, the median duration of response was 111 days, so almost three months. And again, this is a drug that is now being tested for relapsed and refractory patients with FLT-3-positive acute myeloid leukemia. And interestingly, this drug, gilteritinib, is a stronger FLT-3 inhibitor than midostaurin.

So, you could conceive of a situation where, if you gave gilteritinib with induction chemotherapy, you may actually get a survival benefit that exceeds what was seen with midostaurin and chemotherapy.

Slide 33: SGN-CD33A Plus Hypomethylating Agents: A Novel, Well-Tolerated Regimen with High Remission Rate in Frontline Unfit AML
So, both of the previous or the three previous drugs are examples of small molecule inhibitors of mutations that are found in patients with acute myeloid leukemia. There's another class of drugs called antibody drug conjugates. And these classes of drugs aim to target specific things that are sticking off of the leukemia cells. That is, it's a way of bringing chemotherapy directly to a leukemia cell rather than pumping chemotherapy throughout a patient's body.

Slide 34: Vadastuximab Talirine (SGN-CD33A; 33A): Proposed Mechanism of Action in Combination with HMA

Dr. Eytan Stein:

The way these drugs are designed are as follows. Basically, you have this antibody, which is in the upper left corner. And this antibody attacks something called CD33, which is sticking out of many acute myeloid leukemia cells.

On this antibody is this little bit of chemotherapy. And when you combine the antibody with the chemotherapy and then give it to a patient, the antibody goes directly to the abnormal cell. It gets internalized or swallowed by the abnormal cell. The chemotherapy gets cut off of the antibody and does its thing to kill the abnormal cell. And one of the things that researchers asked was whether combining this antibody drug therapy with one of the low-dose therapies called azacitadine or decitabine, whether that would improve the outcomes in patients over one of the hypomethylating agents, azacitadine or decitabine, alone.

Slide 35: Best Clinical Response per Investigator

And when you look at the early results of this study, I think it's also, again, remarkable that, if you look at the right-hand bottom corner, the remission rate in 23 patients that were treated with this combination with newly diagnosed AML is 65% in this older patient population. This was a trial in general for patients who were older. And that is really a remarkable result and something that we wouldn't expect to see in patients who are getting azacitadine or decitabine alone.

Slide 36: A Phase 1b Study of Venetoclax (ABT-199/GDC-0199) in Combination with Decitabine or Azacitidine in Treatment-Naive Patients with Acute Myelogenous Leukemia Who Are ≥65 Years and Not Eligible for Standard Induction Therapy

Finally, I want to talk about one other trial that had pretty spectacular results. And that's a trial using a drug called venetoclax, also known as ABT-199, again, in combination with decitabine or azacitadine in patients with AML who had never been treated before, who are older than 65 years of old and not eligible for induction chemotherapy.

Slide 37: Venetoclax: Selective BCL-2 Inhibitor

The way this drug works is as follows. We all have in our cells a substance called BCL-2 that allows cells or specifically cancer cells in this case or leukemia cells to survive. Basically, our body has the ability, if it notices that there is a cell that is abnormal, that cell, when it works correctly, when the body thinks that cell is going to turn into cancer, there's a switch that goes on that causes that cell to self-destruct and die.

But, when that switch is malfunctioning, you can imagine that a cell gains an abnormality that might cause cancer. The switch that causes the cell to self-destruct is not working. And that cell then develops into a full-fledged cancer cell. And that switch

Dr. Eytan Stein:
is BCL-2. So, when BCL-2 is not functioning correctly, it allows those cancer cells to survive. The idea then is that, if you block this BCL-2, you can restore the switch that causes the leukemia cell, the cancer cell, to die and cause patients to go into remission.

Slide 38: Best Responses in All Evaluable Patients in All Cohorts
So, again, if you look at the bottom right here, where it says 26 and 24, so these are the responses in patients who are treated with a combination of ABT-199, this drug venetoclax, with either azacitadine or decitabine. And the numbers in parentheses are the percent of patients who went into remission.

And you can see the overall remission rate with the combination is 76%, while the complete remission rate or the complete remission rate with what we call incomplete count recovery is 71%. So very similar to what we saw with the antibody drug conjugate SGM and one of the hypomethylating agents, as shown on the previous slide. But again, much better than what we would expect with one of the hypomethylating agents alone.

Slide 39: The Future is Bright
In summary, when I'm thinking about AML, I think the future is actually quite bright. I think we increasingly understand the genetics of acute myeloid leukemia. We understand what's causing this disease. And we're developing novel targeted therapies that are oral. They're well tolerated. And they really lead to impressive response rates.

We're developing wonderful inhibitors of FLT-3 with one of them that shows an overall survival benefit in a randomized Phase 3 trial. We're developing wonderful inhibitors of IDH1 and IDH2. We're developing the antibody drug conjugate from Seattle Genetics and other antibody drug conjugates that bring chemotherapy directly to the leukemia cell rather than giving the chemotherapy that sort of swims throughout patients' bodies. And we also have this inhibitor of BCL-2, which I showed you before, that has an over 70% response rate in newly diagnosed older patients when combined with one of the hypomethylating agents.

Slide 40: Future Paradigm for Treating Newly Diagnosed AML
So, in the future, I think that our treatment paradigms are going to be as follows. Instead of just giving intensive induction chemotherapy or a hypomethylating agent, that's what HMA is here, I think we're going to be giving a targeted agent with chemotherapy and a hypomethylating agent or maybe an antibody drug conjugate with a targeted therapy.

Dr. Eytan Stein:
And in those patients who can't tolerate chemotherapy or induction chemotherapy, the strong chemotherapy, I think we're going to be giving targeted agents alone. And specifically for those patients who are a little bit older and they have just gotten supportive care, that is no active anti-leukemia treatment, I think that is a patient population that is really ripe to get these targeted agents, because most of these targeted agents have very, very few toxicities. They have few side effects. And this older group of patients or this infirm group of patients are a group we think that will potentially derive really a lot of clinical benefit from these drugs.

Slide 41: Thank You!
So, thank you very much. This is just a picture of New York City. This concludes my presentation.

Slide 42: Question & Answer Session
Ms. Lizette Figueroa-Rivera:
Thank you so much, Dr. Stein, for your very clear and informative presentation. It is time for the question-and-answer portion of our program.

Doctor, we'll take the first question from Brenda. Brenda asks, "What new steps are being taken to protect the heart from current AML treatments?"

Dr. Eytan Stein:
That's a really good question. So, some of you may know that one of the drugs that we use for induction chemotherapy, the drug called daunorubicin, and that's in a class of drugs called anthracyclines, there are other drugs like that, like idarubicin. And then there's the drug actually used for breast cancer called doxorubicin, which is in the same class of drugs. All of those drugs at doses that are high can cause some heart damage, or in a patient who's had a previous heart problem, they can potentially be tricky to use.

One of the things that all of us do before we're treating someone with acute myeloid leukemia is we take a careful history to be sure the patient does not have a previous history of heart problems. And again, this is really only relevant in patients who are going to get one of these anthracycline drugs.

So, we take a careful history. Sometimes, we'll do what's called an echocardiogram or a MUGA (Multi Gated Acquisition Scan) scan to see if the heart is pumping strongly. And in those cases where those things are okay and the heart looks okay, the chances of having any sort of heart problem with these anthracyclines is very, very low.

Dr. Eytan Stein:
The other thing we do is, in a patient who's received chemotherapy, let's say, for some other cancer, let's say a patient who had breast cancer who got doxorubicin and, unfortunately, they now develop leukemia, we would calculate to be sure that the amount of anthracycline they had in the past did not exceed an amount where giving them more of the anthracycline could potentially cause problems.

But, ultimately, I think the best way to protect the heart is to hopefully get away from using a lot of anthracyclines with some of these new drugs that I described in my presentation.

Ms. Lizette Figueroa-Rivera:
Thank you, doctor. And we'll take the next question from the telephone audience, please.

Operator:
This question comes from Abraham calling from Connecticut. Please state your question.

Abraham:
Yes, doctor. Thank you. I have AML. And I had the induction therapy. It pushed it into remission. I'm in remission now. They started consolidation with decitabine. And the decitabine worked, but it kept on suppressing my white blood cells and my red blood cells and platelets. And I needed transfusions.

I also have a broken 20th chromosome. The large arm on it is broken. And so, my oncologist decided that we will just stop the consolidation chemo and just check to see whether or when I fall out of remission.

So far, it's been about six months. I have stayed in remission. I'm wondering whether, even though I'm in remission, I should start a new form of treatment?

Dr. Eytan Stein:
That's a great question. And it really gets to the more general question of, what can we do to keep patients in remission once they have achieved that initial remission with, let's say, induction chemotherapy?

The other thing is that abnormality of chromosome 20 that you describe does occur and is fairly common in patients of a certain age with acute myeloid leukemia. I don't know how old you are, but--.

Abraham:
I'm 76.

Dr. Eytan Stein:
Okay. So, in patients who are a little bit over the age of 70 with acute myeloid leukemia.

So, just to talk in general about this concept of whether giving any more therapy helps or doesn't help, unfortunately, one of our answers is that we don't completely know. We don't know whether giving further consolidation chemotherapy beyond what a doctor might initially give actually helps keep leukemia away or if it doesn't.

And the problem is that, if someone is getting consolidation chemotherapy or getting decitabine or getting something along those lines, and their blood counts get very low during that treatment, there's the potential for a significant complication to occur while the blood counts are low.

That is, although you might be keeping the leukemia away, and again, we have no trials to know whether that's actually helping or not. You might end up with some bigger problem, like a bleeding problem or a serious infection.

So, again, in general, in my patients who go into complete remission, I usually will give them some form of consolidation, depending on who the patient is. But, I don't generally keep it going. I usually stop because there is no clinical trial data to just sort of continue things indefinitely in a patient who's gotten induction chemotherapy that has gone into remission.

The situation is different if one started getting decitabine or a hypomethylating agent. In that situation, there is data that continuing those drugs as a maintenance therapy may be helpful. But, that's only if the initial treatment was decitabine or 5-azacitadine, not if the initial treatment was induction chemotherapy.

Ms. Lizette Figueroa-Rivera:
Thank you, Abraham, for your question. Doctor, the next question comes from the web. Kenneth is asking about his daughter. He states, "My daughter was diagnosed with AML in August, and it has been determined that she has an abnormality on her X chromosome, making her an unlikely candidate for certain treatment options. She is at the oncologist's office right now, and I'm anxiously awaiting to hear from her regarding whether she is in remission and can be scheduled for a cord blood tissue transplant as no marrow donor has been found yet, or if she has to seek a clinical trial. Do you know of any other options for her?"

Dr. Eytan Stein:
It depends a little bit on the specifics of the case. So, again, speaking more generally, in a patient with acute myeloid leukemia who has gotten initial induction chemotherapy and gone into remission, that's great then. And we think about doing the options I talked about in the presentation, which are either consolidation chemotherapy or a bone marrow transplant.

In a patient who has not gone into remission with the initial round of induction chemotherapy, we think about giving a second round of induction chemotherapy. And the reason is because, if you had AML, you did not go into remission, and then you give a second round of induction chemotherapy, about 40% of those patients who didn't go into remission the first time will go into remission with a second round of induction chemotherapy, again, speaking generally.

Patients who have not gone into remission after two rounds of induction chemotherapy, that's called primary induction failure. And those patients, I typically recommend that they seek some sort of clinical trial.

I am not aware of any clinical trials that are specific for mutations in the X chromosome. But, any of these other clinical trials, specifically the ones of the antibody drug conjugates and perhaps the BCL-2 inhibitor, and there are many, many other clinical trials out there, could potentially be effective. And I would recommend talking about that with your daughter's physician and really to hear what the best course of action might be.

Ms. Lizette Figueroa-Rivera:
Thank you, doctor. And, Kenneth, we want to invite you to call our Information Specialists. They're master's level oncology health educators who can conduct an individual clinical trial search for your daughter once you get more information. I know that you are waiting for more information. And you can contact them by calling 1-800-955-4572, or you can e-mail them at infocenter@LLS.org. We want to be here for you.

And, doctor, the next question is from the telephone audience.

Operator:
Our next question comes from John calling from Kentucky. Please state your question.

John:
My question relates to reports that I've seen and read about, mainly coming out of the University of Pennsylvania, where they're using CAR-T stem cell work on leukemias. And I am just trying to determine if any of those, they're your own stem cells, are available for AML.

Dr. Eytan Stein:
Let me just very briefly describe what CAR-T cells are. And then I can chat about their use in AML. What the caller is referring to is a technology that's being developed both at the University of Pennsylvania and now at many other centers in the United States and Europe.

Primarily, right now, for the treatment of ALL, acute lymphoblastic leukemia, where what is done is a patient will have white blood cells taken out of their body. And the way that's done is sort of like giving a blood donation. And of those white blood cells, in the laboratory, a subset of white blood cells called T-cells are isolated.

And in the laboratory, you can actually take those T-cells and manipulate them so that they can start recognizing cancer cells that are in that same patient's body. The T-cells go to the lab. They get manipulated to recognize, for example, acute lymphoblastic leukemia, ALL. And then they get reinfused into the patient's body. And then those genetically modified or what we call chimeric antigen receptor or CAR-modified T-cells go off and find the cancer. And when it works, they kill the acute lymphoblastic leukemia.

So, that strategy has been, at least in the early clinical trials, really remarkably successful in patients with ALL.

In patients with AML, it is, I think, still really in its infancy. We are not 100% sure how well it's going to work in patients with AML. One of the reasons is that the target for this genetically modified T-cell in AML happens to also be found on normal cells in a patient's blood system.

So, you can imagine then, when you reinfuse these T cells, although they might kill the AML, they might kill normal cells also.

So, these are trials that are in their infancy. I think they're super exciting. And I'm eagerly awaiting to see what the results of them are. But, they're not quite as far along as the CAR-T cells for ALL.

Ms. Lizette Figueroa-Rivera:
Thank you, doctor. And thank you, John, for the question. Our next question comes from the web. We actually have two questions on APL, doctor. Rainbow asks, "What is the difference between AML and APL? I was diagnosed with APL and was told it was my 15th and 17th chromosomes that are abnormal."

And also, Lisa asks, "How often does APL relapse within one year of maintenance? And what is the treatment protocol at that point?"

Dr. Eytan Stein:
Great questions. APL, which is acute promyelocytic leukemia, is a subset of AML. And the abnormality in APL is as follows. Instead of getting too many myeloblasts, you actually get too many and a block in maturation at the next step. That is the myeloblast isn't the thing that stops maturing. It's the promyelocyte that stops maturing.

And that is caused by this characteristic abnormality, which is a flipping or a translocation between chromosomes 15 and 17. The good news about APL is that it has become one of, if not the most curable kind of acute leukemia that we have. And in acute myeloid leukemia, cure rates are higher than 90% with modern treatments. So, one difference is that sort of pathologically that's what the difference is.

The second difference is that the way we treat APL is completely different than the way we treat regular old AML. And that's because we have a couple of different drugs, one called ATRA, which is actually a vitamin A derivative, which is a pill, and one called arsenic, which when you give those one of those drugs or those drugs in combination to patients, it causes those abnormal promyelocytes to mature into normal healthy cells.

There was recently a clinical trial that was conducted a few years ago, maybe two years ago, and recently published, showing that, for patients with low-risk newly diagnosed APL, when patients like that get a combination of ATRA and arsenic trioxide, the overall survival rates, so the cure rates, are well up of 90%.

The relapse rates in patients who have gotten maintenance therapy are really low, I mean, extraordinarily low. And in those patients who, unfortunately, might relapse, there are good salvage options to try to get them back into remission.

So, I can tell you that the number of patients I have personally seen with really relapsed and refractory acute promyelocytic leukemia is very, very, very few. And the outcomes are truly remarkable. And I think what we're all aiming for is to make the rest of AML as good as the outcomes as we have for APL.

Ms. Lizette Figueroa-Rivera:
Thank you, doctor. And we'll take the next question from the phone audience, please.

Operator:
Thank you. Your next question comes from Celeste calling from New York. Please state your question.

Celeste:
Yes, hi. My 14-year-old son was diagnosed with AML. And he tested positive for the FLT gene. So, he just finished round one of IV chemo, which was a 10-day round with the cytarabine twice a day, daunorubicin three times, etoposide for five days. Then once he was done with that, he had oral sorafenib for 18 days. He took the last dose yesterday. What I was wondering is, listening to your talk, it really wasn't anything about the pediatric population. He's on a clinical trial with the sorafenib. And what is the standard of care for what he has, I guess, at his age with the AML with the testing positive for the FLT-3. Is that the standard of care, or are there other clinical trials?

Dr. Eytan Stein:
That's a really good question. So, I didn't really touch on the pediatric population for a couple reasons. One is that I'm an adult oncologist. But, the second reason is because you're right in that kids under the age of 18 are actually treated a little bit differently than adults. And one of the reasons is that kids actually can tolerate more chemotherapy than adults can.

You mentioned that your son had received 10 days of chemotherapy. And that's because kids generally can tolerate chemotherapy better than adults do. I don't think I can coherently tell you whether that is the standard of care in a pediatric population. But, I can tell you that sorafenib is also a FLT-3 blocker.

And in the adult population, there was a randomized study presented at the big hematology meeting two years ago showing that, if you add sorafenib to chemotherapy, at least in this brief initial look of the data, it improves what's called event-free survival. So, it keeps patients from relapsing. But, at least at the initial look at the data, it didn't make any of these older patients live longer. Having said that, I think that's because, probably, the data just hasn't had enough time. The trial hasn't had enough time to go on yet. And I think, in kids, it may be very different.

I guess what I would leave you with is that sorafenib is a FLT-3 blocker. And it would make sense to me, not knowing a lot about the case, it would make sense to me to use sorafenib in a patient with a FLT-3 abnormality.

Ms. Lizette Figueroa-Rivera:
Thank you, Celeste, for the question. And our next question comes from the web audience. Rishi asks, "How does the medication for AML affect fertility, especially among men?"

Dr. Eytan Stein:
That's a good question. It depends on the medication. And it depends how much of the medication you've gotten. In general, we certainly do not recommend that men father a child while they're getting chemotherapy because we don't know what the effects of the chemotherapy are on sperm.

In addition, in my practice, when I have a male who wants to have kids with newly diagnosed AML and I'm thinking of recommending induction chemotherapy, I will typically recommend that they sperm bank before getting that induction chemotherapy.

Having said all of that, I've seen plenty of cases where patients have gotten induction chemotherapy and then they go on to father children the old-fashioned way. And it's not uncommon for a patient to come back and say, "Hey, I didn't think that I was able to get anyone pregnant. And my wife and I are now expecting."

So, it certainly is definitely possible for men to maintain their fertility even after getting chemotherapy. And the best way to check that out is, after someone has gotten chemotherapy, if they haven't banked sperm, is to go to a urologist. And the urologist can tell them pretty quickly whether they'll be able to father kids, or what are the chances of them being able to father kids or not.

Ms. Lizette Figueroa-Rivera:
Thank you. And we'll take the next question from the telephone audience, please.

Operator:
Thank you. The next question comes from Michael calling from California. Please state your question.

Michael:
Yes, I wondered, what is the significance of an inverted 16th chromosome, which was something I had.

Dr. Eytan Stein:
So, inversion 16 is one of what we call the good-risk or the favorable-risk prognostic markers in patients with AML. What that means is that we think that many patients with inversion 16 can be cured with chemotherapy alone and do not need to have a bone marrow transplant. There are a few caveats to that, which are sort of beyond this telephone call. But, in general, that would be the approach.

The other thing that is positive about having inversion 16 is that, even in those patients with inversion 16 who do relapse, it is generally easier to get them back into remission, so that, at the time of their second remission, they can then go on to get a bone marrow transplant.

Dr. Eytan Stein:
So, in general, we think of inversion 16 as what we call a chemo-sensitive type of abnormality and that patients with inversion 16 have a very favorable prognosis.

Ms. Lizette Figueroa-Rivera:
Thank you, doctor. And the last question comes from Julie. She says that her "husband was diagnosed with AML and received his last chemotherapy consolidation treatment on December 16th, 2012. Now that he has been in remission for over three years, what is his risk of relapse? And how often should he be evaluated by his hematologist?"

Dr. Eytan Stein:
I can just tell you some of the data, and I can tell you what I personally do. Again, at our big annual meeting, which I keep talking about, the American Society of Hematology Annual Meeting, about three years ago, there was a talk given where the researcher looked at hundreds and hundreds of patients with acute myeloid leukemia. And in general, if you got to three years and did not relapse, the chances of relapsing were very, very small.

So, I know, with cancer, we often talk about five years. But, I think, in AML, if you get to three years, your chances of relapsing are really small. And at five years, the chances of relapsing are even less. So, I would say, in general, that at three years, the chances of relapse are pretty low.

What I typically do in a patient who is three years out and has had no signs of relapse is, I might have them get a blood count check every three to six months. And then maybe I'd see them every six months to every year.

As you get closer to five years, I lengthen out the time period to about every six months to one year that I see people and also with the same with the blood count. But, I think, really, the only monitoring that needs to be done in general in a patient who's three years without any relapse is checking blood counts, because really, one of the first indications that something might be going wrong is that the blood count will become abnormal.

Slide 43: Resources to Make Informed Treatment Decisions
Ms. Lizette Figueroa-Rivera:
Well, thank you all for your questions. And thank you so much, Dr. Stein, for your continued dedication to AML patients. You and your colleagues' research successes have made a positive impact on people's lives.

Ms. Lizette Figueroa-Rivera:
And we hope this information will assist you and your family in your next steps. If you were not able to get your question answered today, please call The Leukemia & Lymphoma Society's Information Specialists at 1-800-955-4572 from 9:00 a.m. to 9:00 p.m. Eastern Time, or reach us by e-mail at infocenter@LLS.org.

Information Specialists are available to answer your questions about treatment, including clinical trials, or answer other questions you might have about support, including financial assistance for treatment.

Dr. Stein, thank you, again, for volunteering your time with us today. On behalf of The Leukemia & Lymphoma Society, thank you all for joining us for this program. Goodbye and we wish you well.