WELCOME AND INTRODUCTION

Operator
Greetings, and welcome to the ***Update on T-Cell Lymphomas*** telephone and web education program.

It is now my pleasure to introduce your moderator Lizette Figueroa-Rivera. Thank you, Ms. Figueroa-Rivera. You may begin

[Slide 1 – Welcome and Introductions]
Lizette Figueroa-Rivera, MA
Thank you and hello everyone. On behalf of The Leukemia & Lymphoma Society (LLS), a warm welcome to all of you. Special thanks to Dr. Andrei Shustov for sharing his time and expertise with us today. We have over 400 people participating in today's program from across the United States and several countries around the world, including Canada, China, Colombia, Guatemala, Italy, Libya, South Korea, Sweden, and the United Kingdom.

Before we begin, I'd like to introduce The Leukemia & Lymphoma Society's Senior Vice President of Partnerships, Carson Jacobi, who will share a few words. Carson, please go ahead.

Carson Jacobi, MPH
Thank you so much, Lizette. 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 ensure access to treatment for blood cancer patients, and our vision is a world without blood cancer. For more than 60 years, LLS has helped patients; and it's helped to pioneer innovation such as targeted therapies and immunotherapies that have improved survival rates and quality of life for many blood cancer patients. To date, we have invested over $1 billion in research to advance therapies and save lives; and until there is a cure, LLS will continue to fund promising research from bench to bedside.

In addition, as this program demonstrates today, we are the leading source of free blood cancer information, education and support and we touch the lives of patients in their communities through our 61 chapters across the United States and Canada. And LLS also acts as the voice of blood cancer patients for all blood cancer patients; and we advocate for patients, survivors and their families, helping them navigate their cancer treatments and ensuring that they have access to quality, affordable and coordinated care.

We're very fortunate to have as our presenter today Dr. Andrei Shustov, one of the nation's leading experts in T-cell lymphoma. 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 providing us today with important information on T-cell lymphoma. I thank you all. Have a fantastic program, and now I'll turn it back over to Lizette.

Lizette Figueroa-Rivera, MA

Thank you, Carson, and we would like to acknowledge and thank Celgene Corporation for their support of this program. Following the presentation, we will take questions from the audience.

[Slide 2 – Andrei Shustov, MD]
I am now pleased to introduce Dr. Andrei Shustov, Associate Professor of the University of Washington, and attending physician, hematologic malignancies at Seattle Cancer Care Alliance in Seattle, Washington. On behalf of The Leukemia & Lymphoma Society, thank you for volunteering your time and expertise. Dr. Shustov, I am now privileged to turn the program over to you.

[Slide 3 – Disclosures]
PRESENTATION
Thank you very much. Good afternoon everyone on the East Coast, and good morning to everyone west of the Great Lakes. This is Dr. Shustov from the University of Washington.

[Slide 4 – T-Cell Lymphomas: Overview]
Andrei Shustov, MD
Today, I will give you an update on a very specific type of lymphoid malignancy cell lymphomas called T-cell lymphomas.

In order to understand the specific topic or very rare type of problem, it is better to first put in the context of the larger picture. So it is very, very useful to talk about T-cell lymphomas in the context of lymphoma in general. And in order to understand lymphomas, one has to look at what lymphomas are; and they are tumors of the immune system. So, first, I would like to look and introduce the immune system that will allow us then to zoom in into lymphomas and then specifically into T-cell lymphomas.

[Slide 5 – Lymphoma Basics – Immune System]
Again, T-cell lymphomas are tumors of the immune system. The immune system consists of hundreds and hundreds of lymph nodes that all of us have, and they're distributed throughout our body from head to toes. Shown on this slide is the lymphatic system, represented by little green nodules; and these are lymph nodes that all of us have in the neck, collarbone area, armpit area, inside our body, groin, etc. You can also appreciate that all these lymph nodes are connected by green lines that also represent part of the immune system. They are lymphatic ducts.

[Slide 6 – Lymphoma Basics – Lymph Node]
Why is it important? It is important to understand how the immune system functions. Inside the lymph nodes, we have immune cells. If one takes the lymph node out, makes a slide and looks in the microscope, one would see thousands and thousands of different cells. That's what's inside the lymph node, and these are immune cells.

There are different varieties of them. When I talk to my patients, I frequently compare immune system to the family of ants. Even though it's simplistic, it's very useful. Imagine the anthill, that part of the forest where the ant family patrols and surveils that part of the forest from top to bottom: every tree, every bush, every part of the ground is patrolled by little ants. And if there are intruders, they attack and eliminate them.

Andrei Shustov, MD
The immune system is very similar to that. There are billions and billions of cells that run around your body every second of your life. And what they do, they reach out to every corner of the human body and try to make sure that there's no intruder, there is no infection, there is no bacteria, virus, or fungus that enters your body.

Also similar to the ant family, the immune system has different types of immune cells. And by and large, what's important for today's discussion is that there are B-cells and T-cells, and both of them are lymphocytes. In fact, the word lymphoma comes from the word "lymphocyte." So it's a tumor of the lymphocyte or tumor of the immune cell.

Any cell in the human body can undergo mutation, and I'm not going to detail what reasons cells can mutate. Some of the mutation cause transformation into the cancerous process, so muscle cell can become cancerous. The intestinal cell becomes cancerous. Similar, lymphocytes can mutate and lead to the development of cancer that we call lymphomas.

Now let's go back to the notion that there are T-cells and B-cells. Therefore, we recognize T-cell lymphomas and B-cell lymphomas. Interestingly, amongst the T-cells and amongst the B-cells, there are different subtypes that carry different functions. Some of them are soldier cells or killer cells that eliminate bacteria or even fight cancer cells. Some of them are regulatory cells. They tell other parts of the immune system where to go, how to work, and when to shut down the immune response if necessary. And there are some cells that produce little weapons that attack bacteria or attack viruses and help other members of the immune system to work together. It is easy to understand now, or better to understand now, that there are several dozen types of lymphomas because any of those cells can mutate.

[Slide 5 – Lymphoma Basics – Immune System]
Now before I go any further, I would like to jump back to the previous slide and make a notion that when lymphomas arise, when those mutations happen, they can happen at any one of those lymph nodes. And now it's better understood that lymphomas can start growing in any part of a human body. That separates lymphomas from any other type of cancer. Lung cancer can only start in the lung. Breast cancer can only start in the breast. Prostate in the prostate. But immune cells travel all over the body. That's why the lymph nodes can transform in the armpit, in the intestines, in the groin, in virtually anywhere. It is also easier to understand why we cannot just surgically cut the lymphoma out. Very, very frequent question that comes from patients who are diagnosed with early stage, why cannot we just take it out? And the reason is when you look at this map of a human body, you would appreciate that there are hundreds of lymph nodes; and those cells that transform into one of them start traveling immediately to different parts. So, virtually, it is impossible to pick every single lymph node in a certain area of the body. That is why surgery is very rarely a part of the lymphoma treatment.

Before I leave this slide, I'll make a last statement. Those lymphatic ducts that are highlighted by green lines, that's how lymphomas usually spread. I call them country roads. They go from one lymph node to another, from one to another. Now occasionally lymphocytes, normal immune cells, but also lymphoma cells can also jump in the bloodstream; and that's a highway, and it takes them a whole different direction, unknown part of the body, and that is why sometimes it's really bizarre, at least

Andrei Shustov, MD
initially, when the person can have enlarged lymph nodes in the neck and then a single lymph node in the groin. Totally disconnected, but lymphomas can present that way.

[Slide 6 – Lymphoma Basics – Lymph Node]
And, again, going back to the lymph node, I will also point out that there are different types of cells there besides T- and B-cells. And those cells help, lymphocytes help immune system, help immune cells to function. But in the process of lymphoma development, they also become something we call microenvironment. They become the supporting structure for lymphoma growth.

Now that we know what the immune system is, we know what a lymph node is, and how many lymph nodes we have, we understand better that there are two families of lymphomas, T-cell lymphomas and B-cell lymphomas, and there are dozens of different subtypes.

[**Slide 7 – T-Cell Lymphomas are Rare]**
By and large in adults, B-cell lymphomas are most common. And if you were to compare the proportions of all the non-Hodgkin lymphomas between T-cells and B-cells, one would realize that for every person with T-cell lymphoma, there are at least ten patients with B-cell lymphoma. So T-cell lymphomas are rare. That's the first and important thing to understand.

[Slide 8 – T-Cell Lymphomas are Rare Cont'd]
Now from our previous discussion a minute ago, we know that T-cell lymphomas are a family. Now we recognize multiple different types of T-cell lymphomas. Some of them are more common. Some of them are very rare. But in the context of all the lymphomas, you can now appreciate that those little circles become smaller and smaller; and, therefore, they become even smaller proportion of all the lymphomas. This is all to demonstrate that for every particular individual diagnosed with a specific type of T-cell lymphoma, these diseases are very rare.

[Slide 9 – T-Cell Lymphomas are Rare Cont'd]
Furthermore, we now recognize that some of them we have to divide even further. We started looking into gene expression, into chromosomal function in those T-cell lymphoma cells. And we are realizing that every individual has very specific type of T-cell lymphoma. So in the future, we will probably be surprised that there are more subtypes we thought of; but, again, the reverse side of the coin is that for a particular individual diagnosed with T-cell lymphoma, it is very, very rare.

[Slide 10 – Many Types of T-Cell Lymphomas]
This slide demonstrates the same statement in a different way. These are the names of T-cell lymphomas that all of us now can recognize and treat individually. There are four different subfamilies. We call them leukemic, nodal, extranodal, and there's a very special subtype of T-cell lymphomas called cutaneous or skin T-cell lymphomas. Again, once scientists started looking into how different they are from each other, they recognized that their genetic profile, the way they respond to chemotherapy, the way they behave, is very unique. If you look at the second from the left family, say as an example we take NK/T-cell lymphoma nasal type and go all the way to the right and look at adult T-cell leukemia lymphoma. These tumors, these cancers have nothing in common. Yes, we call them lymphomas. Yes, we call them T-cell lymphomas, but now we are recognizing they're so different that the treatments have to be very different. In fact, as you will see at the end of my presentation, now we started to develop medicines, develop agents, develop specific targeted

Andrei Shustov, MD
treatments that are applicable, can be used for a specific subtype of T-cell lymphoma and not for others.

So in the next five, ten years, it is my vision that we will be treating all of these lymphomas differently and we'll have specific protocols. By the way, we are already doing this for B-cell lymphomas for over a decade. When I see a patient with B-cell lymphoma, or my colleagues in the country see patients with B-cell lymphomas, there is no doubt that they're so unique that every B-cell lymphoma, in general, has a different approach. We are getting there with T-cell lymphomas, and this will certainly improve our efforts and improve our success and hopefully we will come to the point where the overwhelming majority of these tumors will be cured in every patient.

[**Slide 11 – Diagnosis/Staging]**
Once lymphoma is diagnosed, the next step, is trying to find out how widely it is spread in the human body. First of all, diagnosis is made based on the same principle we diagnose any illness. We ask patients about their symptoms, how long they persist, and it is very important because some of the T-cell lymphomas look under the microscope like noncancerous conditions. Some of them look like lupus. Some of them might look like infection. Some of them might look like a reaction to the medication. So the history is very, very important.

This might include history of travel. This might include a history of recent foods. This might include a history, how long this node was present, and this really helps both clinicians like myself and pathologists make a precise, accurate and final diagnosis.

Having said that, there is no substitute for looking under the microscope, doing specific tests and assigning the name to the lymphoma that will drive the rest of the treatment, the rest of the management and eventually lead us to victory and curing the disease.

Now I would like to point out something that we teach our fellows, our trainees and physicians in the communities that for lymphomas the biopsy has to be excisional. What does it mean? It means that the lymph node has to be taken out in its entirety. This is something different from other cancers because to diagnose lymphomas, we have to really look at the structure. Besides all the tests that we have, all the sophisticated technology, there is no substitute for a pathologist looking at the entire lymph node. Also remember that when somebody does the lymph node biopsy, the needle might pass through the area of the lymph node that is not affected by lymphoma or affected by something else. So the diagnosis can be erroneous. There is no substitute again for taking the whole lymph node out, and even when patients had needle biopsy and they come to me for consultation or my colleagues, we always send patients back for a full biopsy of that node.

Now, once the diagnosis is established, the next step is, again, to find out how far the lymphoma has spread because this will change therapy to some degree. Now we have sophisticated methodology called CT scans and PET scans, and two of those rely on different features of lymphoma growth. CT scan measures the size of the lymph nodes. A PET scan shows how active this node is that translates into what we call the bulk of the tumor.

We also do bone marrow biopsy because the bone marrow is part of the immune system, immune organ, and lymphomas can spread there.

Andrei Shustov, MD
Patients who have symptoms suggestive that lymphoma might have spread in a very unique compartment of our body, central nervous system, we might suggest doing the lumbar puncture, sometimes brain MRI. But these two at the bottom are not performed in every patient.

[Slide 12 – Clinical Symptoms I]
Now how do lymphomas present? What symptoms to pay attention to and bring up to the doctor, and this is also helpful. Somebody who is in remission, what do you watch for?

The constitutional symptoms. These are the same symptoms that a person has when he or she has a flu, and it is understandable. Fevers, body aches, headaches, sweats, loss of appetite. All of those things happen with systemic infection. And guess what, we have those symptoms not because of the virus but because of the immune system fighting. It is not surprising then that when lymphomas arise, these are immune system tumors. They do the same thing. They produce the symptoms. So all of those constitutional symptoms listed here are very important to pay attention to.

Based on that human body map that I presented, localized symptoms are also important to pay attention to because lymph nodes can start enlarging anywhere in the body; and they can apply pressure to say bile ducts or the urinary tract, and may present with symptoms of a gallbladder attack or a kidney stone or anything that lymphoma can mimic based on where the pressure is applied.

[Slide 13 – Clinical Symptoms II]
Again, when the pressure is applied to specific parts of the body, lymphomas can have so many faces; and that is why on one side it's a fascinating disease, on the other side you have to pay attention to pretty much everything that happens in your body. And I ask my patients always call me, even though you think it is something that it's unrelated to your disease.

[Slide 14 – Clinical Symptoms III]
Lymphomas can spread to the bone marrow, as I pointed out a couple of slides ago. And what does the bone marrow do? The Bone marrow is responsible for making our blood cells. And if it gets out-crowded by lymphoma, it is understandable that it can lead to low blood counts. So what symptoms do you watch for? If platelets become decreased or patients have low platelet count, platelets are responsible for making clots. So you have to pay attention to increased bruising or unexpected bleeding like nosebleeds or gum bleeds, etc. so that bleeding symptoms are important to pick out and report to your doctor.

If red blood cells become low, it is called anemia. Red blood cells are also made in the bone marrow, and symptoms related to that are shortness of breath, fatigue, dizziness; and those things can, again, happen in lymphomas if bone marrow is involved.

White blood cells that fight infection, are also produced in the bone marrow. So if white blood cells are low, the patient's at risk of infections. So all of those things are to be paid attention to, and lymphomas can present with any or several of the symptoms we just looked at.

[Slide 15 – Clinical Symptoms IV]
Finally, T-cell lymphomas might have very specific syndromes; and I will point out the most striking ones.

Andrei Shustov, MD
So-called angioimmunoblastic T-cell lymphoma. These are lymphomas of the regulatory T-cells. Remember, I mentioned those cells that regulate the whole immune response, and I call them the government of the immune system. So angioimmunoblastic T-cell lymphoma is a tumor of those cells. It is understandable then that when patients have this lymphoma, they can have symptoms of excessive immune activation or something we call autoimmune syndrome. And think about it. What can be happening when people have excessive immune response, and this is the whole area of rheumatology.

Remember diseases like lupus, rheumatoid arthritis, multiple sclerosis, all of those are related to hyperactive immune system or misfiring immune system, if you wish. So angioimmunoblastic T-cell lymphomas frequently present with symptoms that are reminiscent of lupus. Joint pain and stiffness, skin rash, hives, itching, excessive fluid in the chest or stomach. The patient can have generalized body aches, anything that the immune system can attack and those symptoms that are observed in rheumatoid arthritis and such can be part of the angioimmunoblastic T-cell lymphoma.

Another example of a unique clinical presentation is nasal NK-cell lymphoma or lymphoma that originates in the nasal or nose cavity. And, not surprisingly, that the unique feature of this is sinus or nose pain or pressure, discharge, bleeding, etc.

There is a unique T-cell lymphoma or leukemia called T-cell prolymphocytic leukemia. It is a T-cell lymphoma that presents in a liquid form. That's why we call it leukemia. And part of that presentation is enlargement of the spleen, so patients can have excessive pressure in the spleen area.

I'm showing you this just to demonstrate how diverse T-cell lymphomas can be, and it really takes experience and knowledge of subtypes to be able to suspect and drive the investigation into the right direction to make the correct diagnosis but also apply proper therapy.

[Slide 16 – Diagnosis: Antigens on T-Cells]
Shown here is the basis of how we make the exact final diagnosis. Every cell in our body has specific molecules that stick out of the surface. We call them receptors. The purpose of those molecules is for cells to communicate. Immune cells or any other cells in our body, they do not have eyes or ears or they cannot speak; so the way they communicate is by extending the special molecules, you can call them arms, and they touch each other and they communicate, and they also can sense chemical signals.

Now why is it important for us? It is important to understand then how pathologists can say exactly that first you have a T-cell lymphoma even though it's very rare and they see it rarely, but also pinpoint what type it is. Every cell in our body, different lymphomas or different lymphocytes have a specific set of those arms. And many of you might have read the pathology reports for your specific diagnosis, and you have seen these very long statements, very long descriptions when pathologists add that the cells are CD3-positive, CD4-positive, CD5-positive, CD7-negative, etc., etc., etc. And the reason I'm showing you this slide is so you understand now what that means. It means that the cells have CD3 that sticks out of the cell, CD4, CD5, and they do not have CD7. So every type of lymphoma has a specific signature associated with this, and then once the signature is determined and there's a very specific test for it called flow cytometry, there is very, very little doubt in diagnosis.

Andrei Shustov, MD
I spent a minute explaining this because this is a very frequent question that newly diagnosed patients ask me, is it really true? Do they really know 100% that I have lymphoma? And this is the answer that I discuss with patients, how we make it and to point out that there is very little doubt when the diagnosis is made correctly.

[Slide 17 – CT-PET Imaging]
This is to demonstrate how staging works. You see the picture of a patient who just had a PET scan, and the PET scan is based on lymph nodes lighting up after absorbing sugar, radioactive sugar. And you can see in the right side of the neck or left side if you just look at the picture, actually, both sides of the neck as well as throughout the body there are these bright yellow, almost electric bulbs lighting those areas. That's how lymphoma looks in the PET scan. That's how we stage the disease when it presents for the first time.

[Slide 18 – Staging]
And to understand how staging works, we go from I to IV; and the human body is divided in the middle by the diaphragm; you see that red line across the human body

[Slide 19 – Staging Cont'd]
If the person has lymph node area involvement like in this circle, just one area, we call this Stage I.

[Slide 20 – Staging Cont'd]
If there are multiple areas, but one side of that line, we call this Stage II.

[Slide 21 – Staging Cont'd]
If people have lymphoma involvement on both sides of the diaphragm, it becomes a Stage III.

[Slide 22 – Staging Cont'd]
And Stage IV is assigned to the patients where lymphoma breaks out of the lymph nodes and goes to other organs, and it can be any organ like liver, spleen, bone marrow, etc.

[Slide 23 – Staging Cont'd]
We also talk about A and B, and those designate having those constitutional symptoms we discussed or no symptoms. That's how we stage it, and when you look at your medical records or your doctor tells you, you have Stage IIIB, now you understand how that works.

[Slide 24 – T-Cell Lymphomas: Therapy]
In the next several minutes I will tell you the news, the very significant advances that we achieved in T-cell lymphoma science and therapy in the last seven years. I will not talk much about initial treatments because we are still working on establishing the best therapy and incorporating these new drugs now in frontline treatment. I'll just make the one statement that's very, very important for newly diagnosed patients that the best way to treat the disease at this day and age is participate in clinical trials because all the agents that I'm going to mention in the next five minutes are now being investigated in newly diagnosed patients. And all of us in T-cell lymphoma science, clinical science are very excited that these studies are now open that allows patients to get access to these new drugs in the setting of disease that was just diagnosed.

Andrei Shustov, MD

[Slide 25 – New FDA-Approved Agents in PTCL]

Five years ago if you asked me if we have any drugs for T-cell lymphoma approved in the United States, I would say, "Unfortunately, no." We have dozens for B-cell lymphomas, nothing for T-cells. Five years later we are all very excited and very proud that we have four drugs that just entered research and were approved in the United States to treat peripheral T-cell lymphomas. And they're listed here, and I will show you one by one very briefly how they work and how active they are in patients whose T-cell lymphoma failed to respond to any other treatments.

The first agent ever approved for PTCL or peripheral T-cell lymphomas, all the subtypes, was pralatrexate. How does it work? If I have to summarize it in a couple of sentences, I would say pralatrexate, just like its little brother methotrexate, is a vitamin blocker. All it does, it blocks the folic acid, the essential vitamin that our cells need to grow. Remember that all the pregnant women are required to take excessive doses of folic acid. Why is that? Because the baby is growing really fast, and the cells that divide rapidly need folic acid.

Now if we take this knowledge and apply it somewhere else, we can look at the tumor cells, lymphoma cells. They do need folic acid to grow because tumor grows all the time. And if we deprive tumor cells of folic acid, all they can do is die out. It turned out that when pralatrexate was investigated in animals first and then early human studies that the most sensitive tumors to this agent were T-cell lymphomas. We still don't understand why, but we don't ask questions. When we see a signal like this, we move on and we conducted a large clinical trial where patients were treated with pralatrexate. And these were patients who received multiple prior treatments. Some of them received bone marrow transplant and the lymphoma still came back.

[Slide 26 – Pralatrexate: Mechanism of Action]

So pralatrexate enters the tumor cell through these pumps called RFC-1 that are circles in the green membrane. And then undergoing transformation inside the cell, it blocks the specific molecule or enzyme called DHFR. Without going to chemistry of this, I will just say that completely blocks the folic acid function in the cell.

[Slide 27 – PROPEL: Key Data]

So let's see what happens with the patients who failed multiple prior treatments. This study was called PROPEL, and we enrolled more than 100 patients with T-cell lymphomas. And now you understand that being so rare, this was a huge achievement in clinical science. We were able to put together a study with over 100 patients. These patients failed multiple prior treatments, some of them had transplant, some of them had as many as seven different types of treatments, including multi-agent, several chemotherapy drugs combined together.

And the most important figure on the slide is the one on the bottom left. You see these blue lines going up and down, and if the blue lines go down, it means the tumor was shrinking. So if you take all of those lines that go down, you would see that in almost two-thirds of the patients, there was shrinkage of the tumor. And, again, these patients failed more than a dozen different drugs, some of them bone marrow transplant. And just one drug alone, in two-thirds of the patients, caused shrinkage of the tumor. And without going into too many scientific details of the study, I will just say that the first exciting development, the first exciting advancement in T-cell lymphomas and based on

Andrei Shustov, MD
this data, this drug was approved by FDA and now is available for patients who have failed multiple prior treatments.

One thing as far as toxicity I will point out, we are still figuring out how to deal with it; and it is mouth inflammation or mucositis. Roughly half the patients, maybe a little bit more, will develop soreness in the mouth or cold-like symptoms in the mouth or painful swallowing, just like you have when you have a strep throat. It is called mucositis or mucosal inflammation.

We have a study now that is enrolling patients that is trying to prove that if we use an antidote to pralatrexate, 24 hours after administration, it might completely abrogate its symptoms. But this is something that you have to be aware of, if you were to remember one side effect of pralatrexate, that would be mucosal or mouth inflammation.

[Slide 28 – Antigens on T-Cells]
Now remember that schema where we saw a lot of arms sticking out of the cells, and one of the directions we took this time is to see, well, if there are specific arms that stuck out of tumor cells, can we target it? And the answer is yes.

[Slide 29 – Antigens on T-Cells Cont'd]
One of the best candidates seemed to be a molecule that we called CD30, and it is present on a lot of T-cell lymphomas but most pronounced on so-called anaplastic large T-cell lymphoma.

[Slide 30 – SGN-35 is a CD30-Directed Antibody-Drug Conjugate]
So scientists in several different institutions early on decided to target that molecule, and they used the antibody, the very immune molecule that our immune system produces against bacteria but very specific for CD30. Not only they have done that, but they also attached a very toxic component. You see this in the red balls to the tail of that molecule. So now we have a targeted missile. You also have what I frequently call the war hats. You have those little explosives that are attached to it.

[Slide 31 – Brentuximab Vedotin: Mechanism of Action]
Now what happens with that, when this drug is infused into the human body, on this schema, you have to zoom in a little bit. You see on the surface of the cell those purple arms that stuck out, the antibody finds it and attaches directly to the target, right in the middle of the slide, on top of the cell, on top of the schema. Again, you see the purple almost-pyramid and the fork-like molecule attaches to it and that's the drug. It does not attach to anything else. It makes it very targeted, so what happens afterwards? It turns out that the CD30 molecule or receptor is the signal for the cell to engulf it, to swallow it, to suck it in, just like a jellyfish does. It puts it in a little bubble, and its little bubble is the cell stomach. It digests it and what happens? It liberates those toxic molecules. So now we have the system where it can deliver a toxic chemotherapy drug inside the tumor cells without affecting anything else. Very, very unique. Very slick science.

[Slide 32 – B-Vedotin in Relapsed/Refractory ALCL]
And let's see what happened. What happened was the drug activity that we very rarely see in oncology in general, I will point your attention again to the bottom left part of this slide. And now we see that every single one but one of the lines is going down. Ninety-seven percent of patients achieved tumor reduction. We rarely see responses like this in tumors, let alone T-cell lymphomas.

Andrei Shustov, MD
So this was a very huge success in targeted therapy in general, but we were lucky in T-cell lymphomas this was the first drug that showed that remarkable activity.

Now if you go back to the table part of that, it will show you that 86% of patients, almost everybody, achieved a pronounced response. And at the bottom right side of the slide, the only reason I put this graph there, is to demonstrate that plateau, meaning the horizontal part of the curve. What that means statistically is that these patients who are on that plateau are not relapsing anymore, years after receiving therapy. So this was a remarkable, clinical discovery in T-cell lymphomas; and the agent now called brentuximab vedotin, and it was approved in the United States to treat patients with specifically anaplastic large cell lymphoma that failed prior treatments.

[Slide 33 – HDAC Inhibition]
To save us time, I will quickly mention two other agents that belong to the same group of molecule. We call them HDAC inhibitors. What is HDAC inhibition? It sounds pretty scientific, and the reason I put this slide, it is very complicated. I'm not going to walk you through all these little circles, but to demonstrate how many effects these drugs can have on the tumor cell: it decreases the motility of how fast they spread, it slows down the proliferation or the division of tumor cells, it slows down the growth of the blood vessels into it. How does it do it?

When I tried to explain to my patients how HDAC inhibitors work, I ask them to imagine a very thick book. And in that book there are only several pages that need to be read on a daily basis. So the rest of them are glued together, and that's how our chromosomes work. We do not need all the genetic code that is buried in there. We just need several pages. But it turns out that tumor cells are capable of opening those glued pages or they glue together their own pages. So what HDAC inhibitors do, they let us reopen the pages that's necessary to access information on how to kill the tumor cell. In a different way, they reprogram the tumor cell computer or their DNA and tumor cells start dying. So these are not toxic drugs that damage the DNA, chop it up; they reboot the whole computer.

[Slide 34 – Romidepsin in Relapsed/Refractory PTCL]
And this unique mechanism of action allowed us to treat patients with disease that failed to respond to pretty much most of the chemotherapy that's active in lymphomas and still achieve responses in approximately a quarter of the patients, those who would never respond to any other chemotherapy agents.

What's unique about romidepsin, if you go down on the bottom right part of the slide, you get, as I already pointed out with brentuximab, you see the horizontal part of these curves. It means that if patients get response to romidepsin, it is very likely that this response is going to last a very long time. And in my experience, patients who shrink their lymph nodes very well, and when I treat patients who failed a lot of prior treatments, transplant didn't work, the chief response to romidepsin, it is very likely that you can maintain it for months and months and months. And that is a very exciting moment for patients like that.

[Slide 35 – Belinostat in PTCL]
Most recently belinostat is another HDAC inhibitor that we tested in patients with T-cell lymphomas that failed multiple prior treatments, and we have seen the same thing. Again, let's go down to the left bottom slide, and every bar that points down indicates patients that responded to treatment after

Andrei Shustov, MD
nothing else worked pretty much. And you see that two-thirds of the patients achieved shrinkage of the tumor. Again, very exciting developments in peripheral T-cell lymphomas; and all the drugs that I just named were approved in the United States for treatment of relapsed/refractory T-cell lymphoma.

[Slide 36 – Recently FDA Approved Drugs – T-Cell Lymphoma]
This slide summarizes all four of them: pralatrexate, romidepsin, brentuximab vedotin, and belinostat. And an interesting observation is that we still have to work to figure out how to combine them, how to bring them to combination treatment because at the top yellow bar or row, you see that their responses, except for brentuximab vedotin, are still in the order of 25 to 30%. So a third of the patients will achieve response. About two-thirds will have tumor shrinkage. And the duration of response, that is the second row in black from the bottom is about a year, meaning that half the patients, at about a year, will start progressing; and we have to do something else.

Now, is it bad news or good news? The good news about this is that now we have the drugs that produce responses in patients that we would not expect anything else to work, even after transplants fail. The bad news is we need to do more work, and we are doing it. And I'm going to go back to my statement that I made a couple of minutes ago that what we're doing now, we're trying to bring all of these agents into the frontline treatment so we don't have to wait for patients to relapse and use them but we start incorporating them into the frontline treatment.

At this juncture, it is happening in the context of clinical trials; and there are at least two studies in the United States enrolling patients that combine frontline chemotherapy with brentuximab vedotin, and there is another study that combines chemotherapy with pralatrexate. We just completed the study of chemotherapy with belinostat and romidepsin plus chemotherapy is done in Europe. So if you or your family members, your friends are diagnosed with T-cell lymphoma, it is very, very important to try to find out what studies are open in your area because this is the only chance you can get these new agents without waiting for the lymphoma to relapse.

[Slide 37 – Treating a Disease is Science, Treating a Patient is Art]
After all the studies are done, the art of treating T-cell lymphoma or any type of cancer remains an art. Science is science. Look at the numbers. But when I see patients with T-cell lymphomas, we do a lot of homework with a lot of discussion. We go into details of all the treatments in patient disease because how do you decide which one of the drugs to use if the lymphoma comes back? We don't have a good study that compares all of them together, being lined up and comparing which one is first, which one should be second, would one should be third. Instead, it is really an art to pick the best drug the physician feels is for your particular disease, based on what type of T-cell lymphoma it is, what is your medical condition/background, what is your preferred schedule of traveling for treatments? So it is truly an art, how we treat T-cell lymphomas at this juncture. And it probably will remain art, not only for T-cell lymphomas but cancer medicine in general.

[Slide 38 – T-Cell Lymphomas: Clinical Trials]
And I will finish by summarizing the advantages and risks associated with clinical trials.
Clinical trials are very important for patients with rare diseases, with diseases where the majority of patients are still not cured with the first go.

Andrei Shustov, MD
[Slide 39 – Clinical Trials: Enroll or Not Enroll]
It is important because it gives you the chance to receive therapy that might not be approved for another two, three years. Remember, when they do clinical trial tests, investigators, we see that the drug is really useful, it's very effective. But it has to pass all the scrutiny and then reviewed by FDA and has to be voted on, so the process that takes two, three, four years from the moment that we say that, or we feel that a drug might be very, very effective. So the way to take advantage of that is participation in clinical trials that, for some patients, might change lives.

We monitor patients very, very closely on clinical trials because we still don't know what side effects these drugs might cause; and it is an advantage because we bring patients more frequently to clinic. We watch for all the side effects. We do additional tests, and sometimes we find something that otherwise would be hiding from the physician and the patient if we did not look.

Now clinical trials aren't without risks. Until the study is completed, we don't really know how well the drug works. So you might be receiving treatment that at the end of the day, we look at the results, and say this study was not effective. The drug didn't work. Yes, there is a risk. But, again, it is really an accurate assessment by patient and physician whether the risk is justifiable and whether disease is rare enough or scary enough that we have to take this risk and try something new.

Side effects will not be fully described until several studies are done, so potentially patients can have side effects that we are not aware of using new drugs. But, again, everybody's body is different. You can have unexpected side effects with regular chemotherapy. It goes back to accurate risk assessment and looking at benefits of participation of clinical trial.

Finally, think of personal or health information, this is not different from every time that you come to a physician or your dentist office when you sign the HIPAA (Health Insurance Portability and Accountability Act) form where we do collect information about your disease and background. It is very well-protected. When you're in a clinical trial, there is more information that's collected in the research file, and there is always risk. And there's something to consider and discuss with your doctor, but this risk is extremely small.

And I will finish right there to leave a couple of minutes to think about T-cell lymphomas and answer any questions that some of you may have. Thank you very much for your attention, to present this exciting development that me and my colleagues were working on so hard on in the past five, seven years.

QUESTION-AND-ANSWER SESSION

[Slide 40 – Question & Answer Session]
Lizette Figueroa-Rivera, MA
It is now time for the Question-and-Answer portion of our program. We'll take the first question from our Web audience. The first question comes from Winnie. It says, "My oncologist prescribed folic acid supplements for me to take during my chemotherapy treatment for immunoblastic T-cell lymphoma. Is this okay? I had anemia and bone marrow involvement as well."

Andrei Shustov, MD
Yes, thank you for that question, and it is very appropriate and timely because I get asked this question very frequently with any type of lymphoma.

So one of the agents that we discussed, pralatrexate, is a blocker of folic acid; and it might sound counterintuitive when we ask patients to take folic acid during treatment or sometimes for anemia, etc. It is important to remember that folic acid itself is not promoting the tumor growth. And the way it's processed inside the tumor cells makes it possible to take folic acid and also be treated with folic acid blocker at the same time.

To answer the question very briefly, yes, it is absolutely safe and okay to take folic acid if your oncologist feels that your anemia recovery might depend on folic acid supplementation. But in the context of T-cell lymphomas, it is actually required if you are treated with pralatrexate to take folic acid and vitamin B12 because it might prevent that oral or mucosa inflammation as we talked about.

Lizette Figueroa-Rivera, MA
Thank you, Winnie for the question. The next question will come from the telephone audience please.

Operator
Thank you. This question comes from Richard calling from North Carolina. Please state your question.

Richard, calling from North Carolina
“What type of T-cell lymphoma is treated by the regimen CHOP, C-H-O-P, which I was told is kind of a gold standard for what I have?”

Andrei Shustov, MD
So thank you, Richard, for asking the question. So CHOP (cyclophosphamide-doxorubicin-vincristine, prednisone) chemotherapy, C-H-O-P, is a regimen that was developed originally and worked very well in B-cell lymphomas. Because we did not have specific protocols for T-cell lymphomas, all over the country in academia and clinical private practice, CHOP was used to also treat T-cell lymphoma and still remains one of the options for newly diagnosed disease.

So the generic answer I can give you, that CHOP can be used for any type of T-cell lymphoma, even though we all in the academic world believe that it's not the best regimen. It does produce responses in general in the order of 60-70%, however, a lot of patients will relapse. That is why we try to encourage patients to seek clinical trials with newly diagnosed disease because what we're doing now is we're taking CHOP as a backbone and adding those new drugs on top of CHOP and hoping that CHOP is going to become a better protocol.

To sort of more directly answer your question, CHOP works better in anaplastic large cell lymphoma than other types of T-cell lymphomas; but it does not mean that it cannot be used. There are some other conventional chemotherapy or traditional chemotherapy drugs that can be added to CHOP. However, one has to keep in mind that it also increases side effects. So for younger patients, we sometimes use the regimen called CHOEP, which is CHOP plus another drug. But for older patients, it poses the risk of excessive side effects, including serious side effects.

Andrei Shustov, MD
Again, to circle back and give you a shorter answer after this explanation is CHOP can be used for any type of T-cell lymphoma, but it works best for anaplastic large cell lymphoma, to the best of our knowledge.

Lizette Figueroa-Rivera, MA
Thank you, and we'll take the next question from our Web audience. Doctor, Peg asks, "With the understanding that CAR (chimeric antigen receptor) T uses T-cells to fight B-cell disease, is there an immunotherapy agent such as CAR T for T-cell diseases?"

Andrei Shustov, MD
Yes, thank you for asking that question. It's very appropriate and timely at this day and age. As some of you or many of you might know, one of the biggest breakthroughs in cancer therapy in general, but in lymphoma and leukemia treatment in particular, was to find out how to teach a person's own immune system to fight cancer. And the most potent cells, most effective cells to do so are normal or competent T-cells, noncancerous T-cells.

So what scientists have done, they took the T-cells out of a person's body who has cancer or has lymphoma and taught them how to attack their own tumor. And after that, they were stimulated and reinfused into the patient's blood stream; and they go in and they wipe out the lymphoma. So these are called CAR T-cells, C-A-R. At this day and age, the only technology that is widely used, still in the research level, is CAR T-cells against B-cell lymphomas and B-cell leukemias. There are only a couple of research groups. They took it upon themselves to develop this for T-cell lymphomas. This research is in the very early stage; and one group is working on this in Houston and another group at NCI (National Cancer Institute) or NIH (National Institutes of Health), and they are targeting so far the same molecule that I discussed in my presentation, CD30. So the CAR T-cells against CD30 is being developed. And, obviously, a lot of groups are looking for more potential targets than T-cells.

Now this question comes up very frequently in my clinic. One has to be very careful with T-cells, and that's where the challenge is. People can live without B-cells for a very, very long time. We don't understand why, and I personally am puzzled. I have an immunology background. I'm puzzled by how can you eliminate B-cells for years and people do okay? But T-cells are a different story, and in order for us to be able to treat T-cell lymphoma with CAR T-cells, we have to first figure out what antigens or what receptors, those arms on the surface of T-cells, can be safely targeted. So when we come up with very potent, very effective CAR T-cells, they do not wipe out the immune system itself.

But, again, to answer your question in a brief manner, there are two groups that are working on developing CAR T-cells that target CD30; and hopefully will be used in the near future to treat, again, anaplastic large cell lymphoma or T-cell lymphomas that have CD30 on their surface.

Lizette Figueroa-Rivera, MA
Thank you and we'll take the next question from the telephone audience please.

Operator
Our next question comes from Kathy, calling from Kentucky. Please state your question.

Kathy, calling from Kentucky
"Good afternoon. I was wondering what the doctor's opinion is on having immunization after a stem cell transplant."

Andrei Shustov, MD
Okay. Yes, so very good question, and there is a lot of complexity associated with that. I practice/treat lymphomas in a large transplant institution. And at our center, as well as pretty much every center in the United States, there are specific protocols that guide us how to do immunizations after both autologous and allogeneic bone marrow transplant. And as a general statement, and I can pretty much speak for every transplant center in the country, we do immunizations at the year mark after both transplants when we think immune system is reestablished and is capable of reading that vaccine and mounting the immune response, just like normal immune system. So one year after the transplant, be it autologous or allogeneic. We conduct a whole series of vaccinations because those treatments pretty much wipe out all the childhood immunizations. If you're asking about the usual or annual vaccinations like flu vaccines or zoster vaccines or pneumonia vaccines, we do those at any time in post-transplant period because the benefits outweigh the risks. Even though we think that during chemotherapy or post-transplants those vaccinations might not work as well as a normal immune system, not being vaccinated might post more risks. And even weak immune response that person develops might be life-saving or might be sufficient to fend off the flu or pneumonia or other infectious agents that the vaccination is designated to.

Lizette Figueroa-Rivera, MA
Thank you, doctor, and the next question comes from the Web audience. Jennifer says that she's read about a new immunotherapy that is being used for lymphoma called pembrolizumab or Keytruda®. She's asking if this new therapy is only utilized for B-cell lymphomas since there's a family member of hers with Sézary syndrome, and she's wondering if they can benefit from this new treatment.

Andrei Shustov, MD
Thank you for that question. It's very timely again, and I will comment. Pembrolizumab is a member of the very exciting new family of immunostimulatory drugs. They're called checkpoint inhibitors. Another agent that is approved in the United States, besides pembrolizumab, is nivolumab and the brand name might be more familiar to your patients called Opdivo®. They work in a similar manner. They activate the immune system to fight the tumor without taking T-cells out and educating them. There is a complex way that these drugs work; but they are, as a rule, antibodies, again, immune molecules, that block one of those arms that I talk about stick out of the cells.

And one of those arms that is extended from the tumor cell reaches out the on/off switch on the immune system cells and turns them off because the immune system always is trying to fight the tumor. So if you turn them off, the tumor is allowed to grow. So pembrolizumab (Keytruda) or nivolumab, these agents are blocking that off mechanism and unleash the immune system to fight the tumor. These are very exciting drugs, and they are very quickly expanding the trials in multiple, multiple cancers. Both of them are approved in the United States to treat solid tumors of the colon, lung cancer, renal cancer, melanoma; and they're being tested in lymphomas. As a matter of fact, to go to specifics of the question, we actually just completed the trial of pembrolizumab in Sézary syndrome and mycosis fungoides. Now the study just finished, and we reported very early results that are very, very encouraging. All I can say that there is a strong signal that pembrolizumab is active in

Andrei Shustov, MD
Sézary syndrome. We will need probably another 6, 12 months until we know how stable or how durable or how potent the response is; but all of us who were involved in the study have a feeling that it will be an effective drug.

Now I treat a lot of patients with Sézary syndrome, and I am familiar with the situation where you try multiple drugs and nothing else works. And then you start thinking about what else can I do. Pembrolizumab is absolutely not out of the question to try in patients with Sézary syndrome and might have a very high benefit with the challenge being that it is not approved to treat mycosis fungoides. So that would be what we call off-label use of the available medication. And there might be some obstacles, obstacles in terms of not having coverage for the drug. The insurances might not pay for it, or the physician would have to also accept the risk. Say, well, we don't have the solid data; that would be our clinical judgment call. And, again, I have used these type of drugs in my patients with Sézary syndrome; and I had very positive results. But one has to understand this is off-label use of medication, which means two things. The insurance might be a problem and we have to accept, both me and my patients or you and your physician, certain risks that the evidence is still not very solid. But I've been in a situation where nothing else works, and I think it is a clinical judgment call in those situations, and it's not the wrong choice.

Lizette Figueroa-Rivera, MA
Thank you and we'll take the last question from Glen. Glen asks “how effective is the romidepsin, and what is the recurrence rate of T-cell lymphomas since I've been fighting it since 2002? The longest I've been in remission is four years.”

Andrei Shustov, MD
Thank you for that question. Romidepsin is one of the HDAC inhibitors we discussed today. If you look at simple mathematics, when we analyzed the study the response rate of romidepsin in patients in whom many chemotherapies didn't work was 25%. It's a quarter of the patients. Now more than half of the patients who responded had a complete response. And you can look at this two different ways. One way to look at this, say, "Well, 75% of patients did not respond, and it's not a good drug for me." Or you can look at it a different way. By the time we think about using romidepsin, the physician that treats you has tried most likely one, two, three different types of therapies and all of them failed. And given the fact that romidepsin has a very tolerable side effect profile and the main thing to be concerned or to know about romidepsin is taste changes in most of the patients that sometimes can be very significant.

But given the fact that it does not have the toxicity or significant side effect of chemotherapy, it is one of the agents that it is not wrong to try in any situation because if you don't respond to it, you do not lose much in terms of side effects; and you can go into a different treatment. But if you're one of those patients who achieve complete remission, there's a very good chance that remission can last for years. The longest patients of mine who were on romidepsin in remission was almost five years without requiring anything else. Another patient had lymphoma that did not respond to any other treatment. And now I have probably a handful of patients like that. So the unique feature of romidepsin is complete response. The duration of response might be very, very long; and that's something that is worth exploring if your lymphoma did not respond to one, two, three or more treatments.

Lizette Figueroa-Rivera, MA
Thank you, Glen, for that question and thank you all for your questions.

CLOSING REMARKS

[Slide 41 – The Leukemia & Lymphoma Society Offers]
Lizette Figueroa-Rivera, MA
Please help me thank Dr. Shustov for volunteering his time with us today.

The Leukemia & Lymphoma Society offers online chats for non-Hodgkin lymphoma patients, for young adults, and caregivers. The chats provide forums for patients and caregivers, to share experiences and support one another. For information on how to participate, go to www.LLS.org/chat. If we were not able to get to your question today, please call a Leukemia & Lymphoma Society Information Specialist at 1-800-955-4572 between the hours of 9 AM and 9 PM Eastern Time or you can email us at infocenter@LLS.org.

To all of the patients, caregivers, and professionals participating in today's program, on behalf of The Leukemia & Lymphoma Society, thank you for sharing your time with us today. Goodbye and we wish you well.