TRANSCRIPT

WELCOME AND INTRODUCTION

Lauren Berger, MPH

[Slide 1 – Title Slide] Good afternoon. On behalf of the Leukemia & Lymphoma Society (LLS), thank you for joining us this afternoon. **[Slide 2 – Welcome and Overview]** I'm Lauren Berger, Senior Director, Professional Education and Engagement at the Leukemia & Lymphoma Society.

[Slide 3 – The Leukemia & Lymphoma Society] We are committed to improving patients' quality of life through research, education, support and advocacy. LLS advocates for funding to accelerate the discovery and development of blood cancer therapies and to ensure that patients have coverage through insurance for their care. To date, LLS has invested more than $1 billion in research to advance therapies and save lives.

[Slide 4 – Individual Support Resources] We are pleased to offer individual support resources such as disease-specific booklets, comprehensive information on our website, patient and professional education videos and webinars for which you can earn CEs (continuing education) and **[Slide 5 – Individual Support Resources cont'd]** financial support for our patients.

We have a new online community which is a social network for healthcare professionals and patients to seek answers and share information.

[Slide 6 – Individual Support Resources cont'd] Our Information Resource Center, staffed with nurses, social workers and health educators talk to patients, caregivers and professionals about disease and treatment, including clinical trials, and provide financial and psychosocial support on a daily basis.

We know that you are key to supporting patients through day-to-day treatment, education and support. As we hear from patients, you're the ones that they go to with their questions to help them understand their disease and their treatment and to discuss and to help manage side effects and other complexities of their care, such as access to treatment. We know that you are there for them at every point in their care. Thank you for the very important role that you play in each patient and caregiver's journey.

Today our presenters will discuss new and evolving treatment strategies, including how the heterogeneous nature of blood cancers dictates treatment and prognosis, the role of clinical trials and the evolving role of CAR (chimeric antigen receptor) T-cell therapy. Treatment and side effect management and communication with patients about clinical trials will be highlighted. Our case studies will focus on acute myeloid leukemia (AML) and on diffuse large B-cell lymphoma.

To receive continuing education credits for your participation today, please complete the evaluation, including your license and the state that you're from. A certificate of completion will be issued to you within 30 business days.

I would like to very much thank our supporters and to acknowledge Kite Pharma, Novartis Pharmaceuticals and Stemline Therapeutics for their support of today's program.

I'm now honored to introduce our speakers. Margaret McCormick is the lead for the Clinical Trial Support Services at The Leukemia & Lymphoma Society national office. She will talk about supporting patients through education and personalized clinical trial searches. Margaret Green is not able to be here today. I am pleased to introduce Monica Kwari, Research Nurse Supervisor in the Department of Leukemia at the MD Anderson Cancer Center. Monica will discuss the role of clinical trials in treating patients with acute myeloid leukemia. Brenna Hansen, Research Nurse Specialist at the Center for Cancer Research, National Cancer Institute at the National Institutes of Health, will discuss the evolving role of treating patients with CAR T-cell therapy for diffuse large B-cell lymphoma. Special thanks to each of you for volunteering your time and expertise with us today.

Peg, I am now honored to turn the program over to you.

SUPPORTING PATIENTS THROUGH EDUCATION AND PERSONALIZED CLINICAL TRIAL SEARCHES

Margaret McCormick, RN, BSN, MA, MBA

[Slide 7 – Supporting Patients Through Education and Personalized Clinical Trial Searches] Good afternoon. You're in for a treat today. You're going to be introduced to four patients throughout our program, and each patient has a special message to share.

We're going to provide information about clinical trials throughout the program, the place they take in treatment, the hope they instill in our patients, and the responsibility that we, as members of the healthcare team have to provide patients with realistic expectations about the possibility of success.

I'm Peg McCormick and I head up the Leukemia & Lymphoma Society's clinical trial services. We engage patients in a conversation about the role of clinical trials in their treatment and assist them in their efforts in finding a clinical trial and overcoming the obstacles to enrollment.

Early in my work with these patients, I personally struggled with balancing the hope and optimism that our patients feel when they contact us with a realistic potential for success. In fact, for a time, I think I was so intent on not giving them false hope that I went a little too far the other way. So, I went in search of some answers of a way to speak with my patients about the role of clinical trials.

[Slide 8 – The Anatomy of Hope] If you weren't familiar with Dr. Jerome Groopman, I encourage you to pick up his book, the *Anatomy of Hope*. I hung on every word that Dr. Groopman wrote in this book. He takes us on a journey through the experience of a few of his patients who had very, very little chance of success in a clinical trial or a treatment and they survived; and some had every hope that this treatment would succeed, and who didn't survive.

But his message to us was clear - who are we to determine ahead of time what that hope is? His book gave me a lot of confidence in speaking with patients and walking them through the process and allowing what happens to happen.

Speaking of hope, I want to introduce you to one of my patients who is sitting in a hospital room in Boston right now. She's a nurse. She sends you her greetings. She wishes she could have been here.

Her name is Jamie. She's a NICU (neonatal intensive care unit) nurse. **[Slide 9 – Treatment]** She was diagnosed when she was age 30 with diffuse large B-cell lymphoma, and was successfully treated. She was in remission for a number of years, and in 2009 her diffuse large B-cell returned to her right eye. She had that eye removed, and was again treated successfully and was in remission for that disease for quite a while. In 2014, she was diagnosed with triple-negative breast cancer. She chose to have a bilateral mastectomy for treatment, and continued remission of her large B-cell lymphoma.

[Slide 10 – Treatment cont'd] She came to us in 2015, about a year ago, struggling with whether she should have an allogeneic transplant or an autologous transplant. We helped her work through those issues, and at that time we brought up the possibility of a clinical trial. During this discussion,

we introduced the concept of CAR T. She underwent autologous transplant; but unfortunately, her diffuse large B-cell returned. At this time, she was intent on finding a CAR T-trial.

The problem for Jamie was that her platelets were low as a result of her treatment, she was on steroids to keep her blood counts up, and her diagnosis of a cancer within two years made her ineligible for most of the CAR T trials that were open. We were able to find one CAR T trial she qualified for. She got her blood counts in order. On the 20th of April, she received her T cells back. I spoke with her this morning, she's feeling fantastic; and she probably will be discharged in a day or two from the hospital.

[Slide 11 – Jamie] So, what Jamie wants to tell you from her hospital bed in Boston is keep trying, don't give up, find resources. She clearly is a woman who never gives up.

[Slide 12 – Impending Crisis in Cancer Clinical Trials] Despite the hope that clinical trials offer our patients, there is an impending crisis in cancer clinical trials. Before I started researching this aspect, I didn't realize that 40% of NCI (National Cancer Institute) sponsored clinical trials fail to accrue and a full third of Phase III trials close because of poor accrual. So, what does this mean for our patients? That potentially life-saving drugs either don't get to market or they get to market much later than they could. And then just think of all those patients who offered themselves for a clinical trial whose data will not count for anything.

[Slide 13 – Question] So, I'm going to ask you to pick up your ARS (audience response system) and let us know your perception of what percentage of patients with cancer participate in clinical trials. So, most of you answered B, 8 to 10%. **[Slide 14 – Answer]** And the answer is 3 to 5%. So, more if you're looking at children, much more and we're edging up. It used to be 3%, it's now 5%.

[Slide 15 – Most Interested; Few Enroll] A national survey in 2003 was conducted among adults without cancer. The survey asked participants ‘if you had cancer, would you be willing to participate in a clinical trial’? 32% said, "Yes, absolutely." Another 38% said, "Yes, if I had some questions answered, I'd be very interested in participating in a trial." But we know that only 5% of people with cancer are enrolled in a trial. **[Slide 16 – Patient Barriers]** Why is this? Clearly, you encounter the barriers in your practices every day.

[Slide 17 – Most Not Told of Possibility of a Trial] The biggest barrier is actually that physicians don't refer patients to clinical trials. In a study with a group of four community-based oncology practices in Northern New England where they had an active clinical trial program, only 44% of eligible patients were even told about a trial. And only 20% of patients eligible for Phase II and III trials in their particular practice were referred to the trial. So, clearly, there's an education element here.

[Slide 18 – Physician Barriers] Why don't physicians refer? Certainly they care deeply about their patients' well-being, but they have obstacles to overcome as well. The biggest concern is physicians’ impressions of the trial's scientific merit are not high. There are time and economic constraints as well. Clearly, it takes more time to work with a patient in a trial than outside of a trial. If they're referring outside of their practice, there's the issue that they might not come back to their practice for care. Perhaps one of the biggest obstacles is it takes a lot of time to talk about trials and the risks and

benefits of specific trials. Physicians want to make sure their patients understand and they're not quite sure they do.

[Slide 19 – LLS: Personalized Search Services] So, given the significant challenges that both researchers and patients have in overcoming obstacles to enroll in a clinical trial, two years ago the Leukemia & Lymphoma Society instituted a program to provide deep personalized help to patients who were interested in trials. The Information Resource Center fields about 40,000 calls a year from patients with blood cancers, family members and healthcare professionals. Callers are educated about their disease, about resources available to them, including financial resources. When it becomes clear that those patients are in need of in-depth help to access a trial, the Specialist will refer them to LLS's Clinical Trial Services.

We first take an intake, much like you would take in your practices. We'll take a history; we'll understand their current physical condition because they need to be in fairly good physical condition to participate in most trials. We'll try to understand their financial and insurance situation. For example, we do not want to recommend a trial in another state if somebody has Medicaid and they have no chance of being able to go outside of their state. We'll try to understand their support services, and then we'll get a very deep disease history, including markers, mutations and anything else that will help guide us to an individualized search.

Then, and only then, do we do a search for them. We prepare a very targeted list of clinical trials for callers to bring that back to their healthcare team – which helps facilitate a detailed conversation about those opportunities.

If physicians are unable to do that due to time constraints, then we will do that for them. We'll talk callers through the list of trials. We'll personally call the trial site and make certain there's an opening for them before we connect the research team with the patient to have a more extensive conversation about that trial. They're either enrolled or they're not enrolled. And if they're not enrolled, they come back and we start the process over again.

You may be surprised that 50% of the patients that we work with around clinical trials, eventually get into a clinical trial. So, compare that to the 3 to 5% of patients with cancer that join a trial, we're pretty pleased with that number.

I'm going to turn the presentation over to Monica who will take you through AML and a unique clinical trial for AML.

THE ROLE OF CLINICAL TRIALS IN TREATING PATIENTS WITH (AML): A CASE STUDY

Monica Kwari, RN, BSN, CCRP

[Slide 20 – The Role of Clinical trials in Treating Patients with (AML): A Case Study] Good afternoon and welcome. I'd like to thank you for attending this presentation and appreciate you spending your time with us. My name is Monica Kwari.

[Slide 21 – Question] Okay, before we start, there's questions. What percentage of your patients are being treated for blood cancer? Answer is A to D. You have seven seconds. **[Slide 22 – Answer]** Wow, D is 76 to 100 and then almost the same, actually. It's not too many significant on A, B, and D. Nice to know. Thank you.

[Slide 23 – Overview of AML] AML or acute myeloid leukemia is a heterogeneous hematologic malignancy group of diseases. It is a myeloid cell cancer characterized by rapid growth and accumulation of abnormal white blood cells in bone marrow and peripheral blood and/or other tissues. These malignant cells interfere with the normal production of other cells, which are red blood cells, platelets which cause anemia and bleeding. AML is caused by genetic changes that result in increased cellular growth and proliferation and impaired maturations.

[Slide 24 – Overview of AML cont'd] This year, according to SEER (Surveillance, Epidemiology, and End Results), it is estimated about 20,000 people in the US will be diagnosed with AML. More than half of them will die from the disease. About 27% of them will survive up to five years while receiving effective treatment.

[Slide 25 – Overview of AML cont'd] Diagnosing a specific AML classification can be done using immunophenotyping, cytogenetics, and now gene sequencing. With the advent of gene sequencing, mutational profiling can help to detect risk assessment, prognosis and ultimately interventional decisions.

[Slide 26 – FAB Classification] As you know, in the 1970's, a group of French, American, and British leukemia experts (FAB) divided AML into subtypes, M0 through M7, based on the type of cell from which the leukemia develops and how mature the cells are. This was based largely on how the leukemia cells looked under the microscope after routine staining.

In the last few years, blastic plasmacytoid dendritic cell neoplasm or BPDCN was added to part of the classification. BPDCN is a rare disease recently recognized as a neoplasm derived from plasmacytoid dendritic cells. There are not too many treatment options available yet. Treatment for BPDCN that I am aware of is biologic targeted therapy in clinical trial. If you may need information about this, contact the LLS. They can help.

[Slide 27 – AML Subtypes Based on the WHO Classification] FAB classification system is useful and is still used to group AML in subtype, but it doesn't take into account many factors that are now known to affect prognosis. The World Health Organization (WHO) has developed a newer system that includes some of these factors, to try to better classify AML. The WHO system classification divides AML into several groups.

- AML with certain genetic abnormalities
- **[Slide 28 – AML Subtypes Based on the WHO Classification cont'd]** AML with myelodysplasia-related changes
- AML related to previous chemotherapy or radiation, **[Slide 29 – AML Subtypes Based on the WHO Classification]** myeloid sarcoma (also known as granulocytic sarcoma or chloroma or extramedullary myeloblastoma)
- Undifferentiated and biphenotypic acute leukemia, which are leukemias that have both lymphocytic and myeloid features, sometimes called ALL (Acute Lymphoblastic Leukemia) with myeloid markers, AML with lymphoid markers, or mixed phenotype acute leukemias.

[Slide 30 – Molecular Information: Next Generation Sequencing] By using a molecular diagnosis test, we are able to analyze an individuals' genetic code and how their cells express their genes as proteins. The test provides a wide range of critical information in making the right medical decision based on a certain mutation such as NRAS, KRAS, FLT3, IDH1, IDH2, etc.

[Slide 31 – Isocitrate Dehydrogenase (IDH) Mutations as a Target in AML] Isocitrate dehydrogenase or IDH mutation, as a target in AML, IDH is an enzyme of the citric acid cycle. Mutant IDH2 produces 2-hydroxyglutarate which alters DNA methylation. Mutation in IDH has been found in approximately 15% of AML patients.

[Slide 32 – Current Treatment] Current standard of care for chemotherapy for the young AML patient is an induction regimen with cytarabine and daunorubicin, followed by consolidation with high-dose cytarabine for one or two cycles. This treatment regimen could be a little strong for elderly patients who may already have a few underlying comorbidities. For elderly patients, the treatment choice is using hypomethylating agents such as decitabine, either five or ten days of treatment. For patients with a poor-risk prognosis, they may be considered for stem cell transplant options. Some patients with relapsed or refractory AML, clinical trials may be an option such as Phase I or Phase II, which some of them combine in standard known chemotherapy with an investigational study drug.

CAR T-cells for AML is still new in the clinical trial. This may become a breakthrough as more trials are coming and later when they get more mature with data and results. Compassionate use or expanded access for non-FDA-approved drugs may also be considered.

[Slide 33 – Therapies Under Investigation] Investigational therapies such as FLT3 inhibitor, IDH1, and IDH2 inhibitor, targeted antibody agents, second- and third-generation drugs, vaccines, or checkpoint inhibitor immunotherapies.

[Slide 34 – Question] Now the second question. How likely are you to bring up the topic of clinical trials for newly diagnosed patients? Answer is A to D, you may choose, and you have seven seconds.
[Slide 35 – Answer] C, not very likely. I would use the same thing too for newly diagnosed. But for the second, after relapse, I'll do clinical trials. However, like you said, there is a gene mutation with molecular diagnosis. We can also personalize the treatment based on a mutation. So, it can be used also as an induction treatment for newly diagnosed, but depending on the situation too. What availability, what is the mutation, and most of them are in the clinical trial actually too. Okay, very good.

[Slide 36 – Case Study] All right, a 80-year-old [*sic* 68] male diagnosed with ET (essential thrombocythemia) since 1999. His JAK2 (Janus kinase 2) status was unknown due to unavailable molecular testing at that time. Treated with Hydrea, then transformed to AML with JAK2-positive in 2015 and found to also have complex cytogenetics and IDH2-positive.

[Slide 37 – Treatment] He received an AML induction regimen with high-dose cytarabine and mitoxantrone in August 2015. On day 12 of this induction, his bone marrow shows 80% blasts. In September 2015, he was re-induced with high-dose cytarabine and etoposide. On day 14 his bone marrow showed disease improvement but still had residual disease.

In October 2015, he received ruxolitinib and then ATRA (all-trans retinoic acid). And after one month of the treatment, his bone marrow showed disease progression. During November and December 2015, he received decitabine for ten days, and bone marrow in January 2016 showed continued disease progression.

[Slide 38 – Complications During Treatment] During these treatments, he had complications with pulmonary hypertension, secondary to history of multiple PEs (pulmonary embolism) and DVTs (deep vein thrombosis), ischemic stroke which required rehabilitation on this right hand. Then his performance status improved, and he was able to transfer as an outpatient. He was also neutropenic and had infections.

[Slide 39 – Clinical Trial: IDH2 Inhibitor Study] During his last bone marrow, it showed that he had IDH2-mutation. He consented, screened, and deemed eligible for IDH2-inhibitor study. He started on IDH2 inhibitor study on January 12, 2016. During the study, he improved clinically; and his bone marrow in March 2016 showed 7% blasts with normal cytogenetics.

[Slide 40 – Communication With Patient] When a patient is on this clinical study, you want to have close communication with the patient during the study and provide necessary information related to the study drug. It is important. Copy of the signed consent, stating test procedures and expected side effects of the study drug. When screening procedures can be performed, and what needs to be met for protocol eligibility prior to starting treatment.

If the trial is requiring patients to be randomized, let the patient know how and when this will be done. Dose and schedule treatment, provide a pill diary for patient to document the study drug administration. Inform the patient to remember to return the filled out pill diary and bring the unused or leftover study drug, including the empty bottles for drug accountability documentation.

[Slide 41 – Communication With Patient cont'd] Ask how the patient feels. Ask if the patient is experiencing side effects. Most patients forget to mention them during follow-up visits, but they may mention a few weeks later that they do have a few side effects.

Provide a schedule calendar for lab tests during study and follow-up visits. This will help with patient compliance.

Again, ask if they have experienced any side effects and how they manage their side effects. If they do have side effects, you may need to educate them on how to manage the side effects such as

anticipating taking antiemetics for nausea or vomiting, encourage notifying study team first if another provider is planning to prescribe new medication that may be prohibited during the study.

Provide a card with a clinical trial number, study drug name, contact information of the primary care team, and protocol study team such as the physician, PI, research nurse, clinic, and emergency room so the patient knows how and who they need to contact if they have questions or are having an emergency.

[Slide 42 – Psychosocial/Support Issues] Being there, providing emotional support for the patient and their family members is a huge help for them. Sometimes they just want you to be there to listen. We are all busy running around doing our work, but please remember a few minutes listening to them, it will have an impact on this patient that somebody cares for them.

Be honest. If you could not help with their issue, let them know and help them out to find other resources which can. Insurance. Having cancer is bad already. A problem with insurance is even worse.

It was mentioned earlier some patients who received standard of care treatment but it didn't work may be told that there is no other option for them. Perhaps there is a possible option for compassionate use drugs that could be considered when the patient is not eligible or no clinical trial is open.

[Slide 43 – Question] Now before I turn the presentation over to Brenna Hansen, a research clinical specialist at NCI, who will explore the role of CAR T-cells in a treatment of diffuse large B-cell lymphoma, I have one more question. If your patient needs a drug that is only being offered in a clinical trial and that trial is closed, what would you do? **[Slide 44 – Answer]** So, the answer is B and D. B, seek out compassionate use. Okay, good, thank you.

TRANSCRIPT

THE EVOLVING ROLE OF TREATING PATIENTS WITH CAR T-CELL THERAPY: A CASE ON DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

Brenna Hansen, RN, BSN, OCN®

[Slide 45 – The Evolving Role of treating Patients with CAR T-Cell Therapy: A Case on Diffuse Large B-Cell Lymphoma [DLBCL]] Hello, my name is Brenna Hansen. I'm a Clinical Research Nurse Specialist at NCI over at NIH. Today I'm going to be presenting **[Slide 46 – Diffuse Large B-Cell Lymphoma]** a case study about diffuse large B-cell lymphoma and CAR T-cell therapy.

[Slide 47 – Diffuse Large B-Cell Lymphoma DLBCL] So, first, an overview on diffuse large B-cell lymphoma. Diffuse large B-cell lymphoma is cancer of mature B-cells. It's the most common subtype of non-Hodgkin's lymphoma with about 25% of non-Hodgkin's lymphoma cases being diffuse large B-cell lymphoma.

[Slide 48 – Diffuse Large B-Cell Lymphoma DLBCL cont'd] Diffuse large B-cell lymphoma is a very diverse category of different risks. Depending on what type you have, there's ten different subtypes that are in general classification. And also, approximately 60% of patients have advanced disease at diagnosis, while 40% have a more localized disease.

There is a five-year overall survival rate for non-bulky disease of 95%. That's people who are diagnosed that have masses initially less than 7.5 centimeters. For patients that have larger masses, also called bulky disease, there's only a 60% five-year survival rate for those patients. And then on top of that, patients that have first-line therapy but then progress beyond that, only 10% experience disease-free survival with the second-line treatment regimens.

[Slide 49 – Diagnosing DLBCL] So, to diagnose diffuse large B-cell, the first thing is when patients first present, they will come in with night sweats, general complaints, weight loss, and sometimes if the mass is large enough, they'll complain of abdominal pain. The mass is a rapidly growing mass, and the most common presentation is in the neck and the abdomen; and that's when you really get that abdominal pain as a part of the initial symptoms. But you can see it's such general symptoms, like other cancers, you can see that delayed diagnosis and you could have advanced disease at that time.

When they really find out what's going on is when they do a biopsy of the tumor. They'll go in there and they'll take an excisional biopsy. It's usually up here in the neck, and they'll just have the pathologist look over the slides; and they can actually tell that it is diffuse large B-cell lymphoma.

Another way they kind of monitor progression is they'll do a PET (positron emission tomography) scan, and you can see the large tumors actually light up on the PET scan; and it'll monitor their disease response through them throughout, so you can actually see the tumors grow and shrink throughout.

[Slide 50 – DLBCL Treatments] So, treating diffuse large B-cell, the first-line therapy is R-CHOP, which is systemic chemotherapy of cyclophosphamide-doxorubicin-vincristine-prednisone plus rituximab. A lot of times they'll actually pair that, especially if there's only one site of disease, with local radiation. And then also R-CHOP-14, which is just basically a modification of the previous

regimen and EPOCH-R, which is etoposide-prednisone-vincristine-cyclophosphamide-doxorubicin and rituximab. These are all the basic general guidelines.

So, the second-line therapy, there's a lot of them; and it's going to be dependent on what type of diffuse large B-cell we have. An example is GEMOX, which is gemcitabine and oxaliplatin.

Another therapy for diffuse large B-cell is autologous stem cell transplants. However, most places have to have you in remission before they're willing to do that for you, and also clinical trials.

[Slide 51 – DLBCL Case Study] So, here's a case study just to kind of go over what's been talked about. Sara is a 36-year-old woman who goes to her doctor complaining of persistent night sweats, swollen lymph nodes in her neck and upon examination several unusual lumps are noted on her head. She eventually has a PET scan that shows high metabolic activity in her abdomen, neck, and the palpable masses on her head. She also had one behind her orbital, but the one that was very apparent was the one on the back of her head.

So, they biopsy the mass on her head, and they confirm that she has double-hit diffuse large B-cell lymphoma, which is very high risk. She immediately begins R-CHOP, but after two cycles, she has no sustainable response; and they really know that doesn't really help these people anyway, so they move on to two different lines of, second lines of therapy, and she still has no response.

She has an eight-year-old child and wants to see him grow up, knowing from the start that double-hit diffuse large B-cell lymphoma has a poor prognosis. She has been researching clinical trials. She has read promising articles on the Internet about CAR T-cell therapy.

[Slide 52 – CAR T-Cell Immunotherapy] So, a quick question, based on the case study, how confident would you be referring this patient to a clinical trial? Okay, these patients really have very little options if nothing else is working with the standard care.

So, CAR T-cell immunotherapy, so she wants to give it a try. Have any of your patients asked you about targeted immunotherapies? Just a kind of general view to see what everyone's exposure is. I'm actually a little surprised it's that high. But I guess it's about equivalent to people who are interested in CAR T cells, so it makes kind of sense with the crowd.

[Slide 53 – What are CAR T Cells?] So, first off is what are CAR T cells? So, CAR T cells have a chimeric antigen receptor T-cell. So, basically a chimeric antigen receptor is an immune receptor that's engineered from parts from different sources. The CAR itself, which is the receptor on the outside of the T cell, is engineered. It's a monoclonal antibody that is modified to recognize a very specific target. So, that's kind of why it has many different categories here in the media, so it's precision therapy, meaning it's targeted towards you. And it’s gene therapy because that's how they make the cells, and it's adopted therapy because it is cells that are from your body modified and placed back in.

[Slide 54 – How are CAR T-Cells Made?] So, how are CAR T cells made? So, basically, the CAR cells are collected from the patient through apheresis; and then they are genetically modified by inserting a gene into the cell itself. And it forces them to express that receptor that was previously talked about. And in that case, it can actually target the cancer cells. That's why it's really important to

kind of understand what targets are available and what disease you have and what targets are on what disease.

[Slide 55 – How are CAR T Cells Made? cont'd] So, the cells are collected. They activate the T cells and the cytotoxic T cells. They do transfection, which is when they insert the gene and make the T-cell. And then they put in the culture, and this is when the cells will replicate and expand where you get the dose that you really need to infuse in the patient. So that can be a shorter time period or a long time period, but it's usually around seven to ten days. And that is because you don't want them to be in culture too short because you want them on a cell as you need, and you also don't want them to be in culture too long because they become less effective.

And after that, those cells are cryopreserved and purified for the patient, and then they are also administered later on. So, sometimes they are done as fresh infusions, meaning they come right out of culture to a patient; but a lot of times they're cryopreserved, and that's just because with the pharmaceutical companies involved, they'll come in and they'll manufacture the cells off site; and you really want to be able to make this a more standardized treatment that eventually we can give to the general population versus having it done at a research hospital, which really is where you do the fresh culture infusions.

So, one of the things, let's talk about as a target of the CAR T cells, so this is very difficult to explain to patients because they hear in the media that this new therapy is really going to cure me, it's going to cure cancer, and they really have to understand that the CAR cell can only help you if you carry the target.

[Slide 56 – Types of CAR T Cells] So, there are different CAR T-cell targets, depending on different proteins that are expressed on the cancer. So, different cancers will express different proteins, which the antibodies are forced to target with these new T cells that are manufactured. And that can be extra confusing because even though you have the right type of cancer that should be carrying this target, your cancer still might not carry the target. Sometime during treatment you may have lost it, and that's very, very difficult news to give to a patient because we ask them to send in biopsy slides just to make sure that they have this target. And then to tell them that even though you have this disease, you cannot qualify for the study; and you really have to explain to them it's not because we don't want to treat you. It's because it just really won't work for you, unfortunately.

And one of the things with this target too, especially with these, because new targets are coming out all the time, and people really ask why are there early trials, early phase trials? Because we have to make sure that these are safe targets. So, we have to have a target that's on the cancer and nowhere else in the body that's going to hurt you because if you can find a target on the cancer of the target but then it's also on your heart, that's not going to help you if you can't survive the treatment.

[Slide 57 – CAR T-Cell Immunotherapy Treatment Schema] So, when a patient's going to have CAR T-cell immunotherapy, this is the general schema they follow. First they have to come into an eligibility visit, and that's kind of important to emphasize because they really want to come and be treated. They really have to understand these are clinical trials. They have to come and be evaluated and make sure it's safe. They have to have good cardiac function. They have to be in good shape in general to survive the potential side effects from these CAR T cells, which I'll go over, but can be fairly extreme.

Then they have to go under apheresis where we collect the cells from them. And then on top of that, depending on if they're at a research site where they do the infusions there, or if they're doing a pharmaceutical study where they're sending them away, it can take four to six weeks to make those cells in that case. And so you really have to be able to, it's not a fast treatment; and that's really hard to explain to them also.

And on top of that, they're on a clinical trial. There's a time period between treatments that you have to wait for safety, and so you can only treat so many patients a month at a site, on a protocol even. And so, after the cells are collected and they're expanding and doing what they need to do, and they're ready to be infused, you have to do a baseline evaluation so you can make sure the patient is still eligible for the trial and for research, because it is research, because you have to know how they respond. Then they'll start a lympho-depleting chemotherapy. And the reason for this chemotherapy, it's not like a stem cell transplant. It's a much lower dose. It's that we lower the T cells down a little bit to allow the T cells to come in, to expand better. So, it's not the high doses that they would usually have for other types of cellular therapy necessarily.

And then there's also an inpatient admission involved, and that's because, again, the side effects are very severe. We want to look at you every second of the day during that high-risk time period to make sure you're safe.

Then you have the CAR T-cell infusion itself and then the patient monitoring for toxicities; and then even after discharge, because they're making these cells work better and last longer, we want you in the area to make sure you're okay so you can get to the hospital very quickly because if you start having symptoms, it can skyrocket fairly quickly, so we want you to be available and accessible for your safety or for the patient's safety. Then, hopefully, all goes well; and you have a disease evaluation to see what's going on.

[Slide 58 – CAR T-Cell Toxicities] So, we talked about CAR T-cell toxicities. So, one of the major CAR T-cell toxicities is cytokine release syndrome. Cytokine release syndrome is associated with the CAR T-cells actually having activity in the body. They'll go in and they'll release cytokines, and these cytokines are at such a high level that they can cause a little bit of havoc.

So, they can be very mild symptoms, but they also can be very severe symptoms. Very mild symptoms might be a headache, a fever for a few days. And if that's all you have, that's great. But these symptoms can get more severe where you start to see tachycardia, the heart rate going up. You can see hypotension with the blood pressure going down, and that could be as easy as fluid responsive for a couple of days or it could require resident ICU (intensive care unit) or the patients actually getting pressor support throughout this.

One thing that's very important to emphasize if you're a nurse taking care of these is early recognition of these symptoms. Low grade fevers that maybe you would ignore generally really have to be reported because that can be just the beginning of it. If the blood pressure is starting to trend down, you should have immediate response, and immediate management of the symptoms can really stop the severity from happening. Then on top of that, we may need to intervene if it gets too bad; and that might start steroids or give tocilizumab as something that can tamper down these T cells to stop the side effects. We don't want to do it right away because we do want the patient to have a response,

and this can interfere with it. But we do want the patient also to be safe, so that's a very important balance to maintain; and that's why these patients are admitted through those really risky time periods, which is immediately before the cells and usually about nine, ten days after the cells they stay admitted.

And that, in general, is the risk period, the highest risk period we look for. However, we're making changes on these CAR T cells. So, CAR T cells actually started around the late '80s. That's when they were first developed, but they started making improvements in different generations and changes and improvements to them to make them last longer or work harder. And when they did that, they didn't really start seeing good results in 2011, so you can see how new this therapy is. It's not something as established as sometimes people think, but when it works, it works really great. But they're still improving it. They're trying to make them last longer in the body. They're trying to stop them from being rejected from the body, and they're also trying to make them safer, which is a big thing when you have people who actually die in these trials. They die from the cytokine release syndrome. They can die from them just not working, because for whatever reason this is not going to work for patients, the patients are often very sick on this trial, so they'll just progress through.

And then other toxicities I kind of want to discuss. This is the big one you hear about, and there are also different toxicities associated with different CAR T cells. I do want to mention in particular though the anti-CD19 CAR T cells and their side effects because the big one they have is neurotoxicity. So this can be, again, very mild to very severe; but it can be mild tremors where the patient is just uncomfortable. It could be headaches. It could be confusion. We had patients that had aphasia for a few days, and this is all transient. So, as long as they have good support, they can recover for it; and they can have a good response and it's okay. But you really need early reporting, especially with the neurotoxicities because those really need to be intervened as soon as possible.

Another toxicity I just want to bring up real quick, the CD19 just to round it out, is B-cell aplasia, because CD19 is also on irregular B-cells; and it might take you a while to recover because it's going to take all the rest of them out with the cancer. And also tumor lysis syndrome. So if your patient has a very heavy disease burden and he's getting his T-cells and they work fairly quickly, your patient's going to be at high risk of tumor lysis syndrome.

[Slide 59 – Are CAR T-Cells a Good Option for a Patient?] So, are CAR T cells a good option for your patient? So, we talked about, does your cancer have the target that this T cell is targeting? So, that's the most important thing, again, to emphasize to the patient. Unfortunately, if you do not carry the marker, you cannot be treated. And it's not because we don't want to, again, it's because it just won't work. So, it's a lot to go through with no result.

The patient also must be able to tolerate apheresis. So, these patients are very heavily treated. They've gotten a lot of chemotherapy, and their counts in general just might not be great. So, if they can't maintain a platelet count high enough or a hemoglobin high enough, it's not going to be safe for them even to have their cells collected. They even have to have enough T cells to collect. Some of the patients are totally wiped out already.

They have to have adequate organ function and good performance status. So, if you're putting someone through cytokine release syndrome and you're putting them through all this hypotension

and pressors and all this trauma, if your baseline's not good, your chance of surviving is much slimmer. And it isn't experimental therapy. It's just not safe for you to go through it.

And then the patient must have measureable disease, and there's two reasons for that. It's because it's research but also because the target really has to be there because this treatment isn't a chemotherapy. It's immunotherapy, so it's living. So, the T cells go into the body, and they see the target, and they begin to replicate and really start having activity. So, if the target's not there, they just are not going to do anything.

And they also have to previously progress through standard therapy. This isn't something you want to give a newly diagnosed patient, especially since we saw earlier in the slides, especially with diffuse large B cell, there are a significant number of patients that respond to R-CHOP.

[Slide 60 – Are CAR T Cells a Good Option for a Patient? cont'd] Another thing that's good to emphasize is the patient has to tolerate being off their chemotherapy, and there's two windows where they have to do this. They have to be off their chemotherapy before the cell collection. Let's just let the body recover so we get good quality cells that are really going to grow in culture. And then the other part is that you want that washout time before the cell infusion itself.

And also to let the patient know that there's uncertain response. This is important, especially for the patients that come in hearing from other people how great this therapy is, which it's great. But they have to know that they might not have a response and it might not work for them.

And also limited number of cell production slots. So, if you have a lot of people interested in this study, and it is a therapy that has to be tailored and made specifically for a patient, there is going to be less availability for that. It's not something that can be pulled off the shelf, and it takes a lot of time and coordination to get that going. So, there's usually very limited slots per trial.

And then on top of that, your insurance might not cover it. It's so new that a lot of patients say their insurance will not support them on the trials.

[Slide 61 – Supporting a Patient in a CAR Trial] So, if you have a patient that is on a CAR trial, they really need support through that. They need to maintain regular contact with their home oncologist, that's because they're going to need support through the trial in case they progress. They're also going to need support through the trial for side effects because they're going to come in, they're going to get this treatment, and they're going to do all the upfront monitoring, and then they're going to go home.

And then some of the side effects, like the low B-cell count, that's what I need support from the physician to make sure they stay safe and healthy. And also as the cells last longer in the body too, they might go home and have late side effects if this happens. So, it's very important that we keep the local physicians involved.

And then for social work concerns, the locations of these trials are fairly limited; and they might not be in a state where they live. So, it's a lot of money to travel to another state to get treatment and to stay locally in the area an extended time period. And then on top of that, bring a family member who can

help you and monitor you to make sure you stay safe. It's a big financial, potentially financial burden for them; and so they'll need help to find resources to make this a viable option.

And with that extended time away from their home, they're spending time away from work, they're bringing their partner away from their work; and they may have young children, and that's really difficult to do. So, having involvement with social work up front is very important.

And then psychological support. A lot of these patients have been through a lot, many different treatments, many different other trials. And I see a lot of patients that this is their last hope in their head, and they really just have no reserve for stress; and it's a very stressful trial because you do not know what's going to happen. And that probably applies to a lot of these trials out here.

[Slide 62 – Things to Consider] So, things to consider. So, CAR T-cell trials are early experimental trials, and this is very important to emphasize, I said, because in the media they talk about immunotherapy, how it's this miracle cure, and how it's going to change the face of cancer. And we really hope that it can expand so we get more targets and we have better, safer results; but at this time it's still an early trial. Disease response is not guaranteed. Enrolling and being treated on a CAR trial is a lengthy process, and all options and possible scenarios should be discussed with the patient and that's just general consenting, make sure they know all their options, but also let them know what happens if it doesn't work and if it does work what's going to happen. You still have to get long follow-up, come over to the site, and have checkups. You have to have gene therapy monitoring, so it's fairly extensive, and it's good that they know.

And then there are allogeneic stem transplants with CAR therapy. So, there are two types of people for CAR therapies. There are people who have never received an allogeneic transplant and patients that do. There are trials out there that can treat patients who have had a previous allogeneic transplant. What they'll do is they'll either use the cells from the donor or they'll use the cells from the patient themselves which are actually the donor's cells, and they can get that back to them and do the same therapy. The risk is higher for those patients because they're risking reoccurrence of graft-versus-host disease. So, there are extra things involved with that.

[Slide 63 – Revisiting the Case Study] Want to go ahead and revisit the case study? It says **[Slide 64 – Case Study]** Sara sends her records out and pathology to the clinical trial site, and she's deemed eligible because she expresses CD19. She travels out of the state to be evaluated, and she's confirmed to be eligible and has apheresis about two weeks later. Her cells are shipped to a facility and retains the CAR T cell. The treatment date is not for another five weeks, so in the meantime her home oncologist gives her a short-course chemotherapy to make sure she stays healthy enough for the treatment.

The chemotherapy will be complete in time for a pretreatment washout period, and she knows that she will be out of state for treatment for a month; and so she makes plans with her family that will allow her to have a caregiver without putting too much strain on them.

She is eventually able to start treatment and receives the anti-CD19 CAR cells. Four days post-infusion, she experiences fevers of 40.1 degree Celsius, tremors, and requires pressor support for three days in the ICU. Two weeks after the infusion, all CRS toxicities have been resolved completely and the masses on her head are no longer palpable.

[Slide 65 – Case Study cont'd] So, the CAT (computerized tomography) scans are actually a patient that I took care of, they were just completely wiped out. I actually had to go and feel, her head myself because I just couldn't believe it. And 99 days past infusion, she still maintained it; and I called her on the phone just a couple weeks ago, and she is still cancer free, walking her dog in the woods.

[Slide 66 – Acknowledgements] I just want to say thank you to my PI (primary investigator), James Kochenderfer, Jennifer Brudno, Caryn Steakley, Elizabeth Ness, and The Leukemia & Lymphoma Society for inviting me here. Thank you. **[Slide 67 – NIH Information]**

QUESTION & ANSWER

[Slide 68 – Question and Answer] Hello, this is Lauren Berger from The Leukemia & Lymphoma Society. We've received many questions from our symposium audience. Our faculty answered these questions, and I am pleased to share these questions and responses with you. Let's jump right in.

[Slide 69 – Question] Q: Have you found in clinical trials that they use the same apheresis line for the infusion itself or since these patients might require ICU care, are you using a different type of central line? And are they mainly taken care of in an inpatient unit or ICU setting?

Our faculty answered:
[Slide 70 – Answer] A: If a patient needs a central line for apheresis, they are going to need an apheresis line which is a larger line. You want to only use that for apheresis and use a central line such as a PICC line for the treatment itself. **[Slide 71 – Answer cont'd]** These patients can start their treatment on an inpatient unit with careful monitoring, with the good communication with the ICU so that a transfer can run smoothly if needed. Not all CAR patients end up in the ICU.

[Slide 72 – Question] Q: Can you speak more about the role of steroids in these patients because it seems a bit counterproductive to use those?

Our faculty responded:
[Slide 73 – Answer] A: Steroids are avoided before apheresis and again before CAR cell therapy and after because they do effect the effectiveness of T cells. However, steroids can be used if the side effects of the CAR cells are severe enough that the patient's safety is a concern. **[Slide 74 – Answer cont'd]** You would not want to use them unless that was the case. Another treatment that can be used is tocilizumab to control side effects of the CAR T cells. However, again the theory is that these drugs can also effect the anti-tumor effect of the CAR T cells so you would not want to use them unless the patient's safety requires it.

[Slide 75 – Question] Our next question:
Q: Is there one target that's shown to be more effective than other CAR Ts, like the CD19's better than the CD22 or have you seen better results with one target over another?

Our faculty responded:
[Slide 76 – Answer] A: No, but many trials are still in early stages and there are other parts of the treatment that can differ. A patient should ask these questions when they are interested in the study because the research is being constantly updated.

[Slide 77 – Question] Q: If they didn't require an apheresis line for collection, and they needed a line in the hospital, can the cells go through a PICC or a port or does it have to be a larger bore?

Response:
[Slide 78 – Answer] A: The cells themselves can go through any line that your hospital standard operating procedure (SOP) determines is appropriate for cell infusion. Small gauge peripheral IVs would not be appropriate. A protocol may indicate a preference that should be followed.

[Slide 79 – Question] Q: I'm just wondering what is the response rate for the CAR T cells of all the patients that you've seen?

Response:
[Slide 80 – Answer] A: This is constantly changing and updating especially since they are still early trials. I recommend looking at the most recent publications.

[Slide 81 – Question] Q: When you're cultivating these T cells, there's a virus used to get the gene into the T cells. What viruses do you typically see used, and is there a decision process that determines which virus?

Response:
[Slide 82 – Answer] A: The decision of what virus to use is all scientifically chosen, and so it's going to be dependent on the protocol. One that I have seen recently is a type of lentivirus.

[Slide 83 – Question] Q: What is the source of the gene that's inserted, and then how do you know if these target proteins are not expressed in other parts of the body besides the cancer?

Response:
[Slide 84 – Answer] A: The CAR complex is manufactured and can come from various sources. Early scientific studies are performed in early development of the CAR T cells, to make sure that the target protein is nowhere else in the human body that could harm any patient. New protein targets have to be tested very carefully.

[Slide 85 – Question] Q: How long after the CAR T-cell infusion can some patients exhibit cytokine release syndrome (CRS) or symptoms?

Response:
[Slide 86 – Answer] A: This is going to vary, and it's going to continue to change. I have seen in some, CRS symptoms within two hours after infusion. The patient had the CAR cells infused in the afternoon and was in the ICU before midnight. I have also seen patients who have had CAR T-cell side effects a couple of weeks after the infusion. **[Slide 87 – Answer cont'd]** As these cells are modified and improved, they can potentially become more potent and last longer in the body. This means that the general accepted four to ten-day range is going to change; and our practice and education will have to change around that to make sure that we stay updated.

[Slide 88 – Question] Q: The process before apheresis, are they mobilized with high-dose filgrastim (Neupogen®).

Response:
[Slide 89 – Answer] A: Filgrastim is used to mobilize stem cells into the peripheral blood stream. In this case they are just taking lymphocytes, so there are no drugs needed beforehand. **[Slide 90 – Answer cont'd]** You just have to have baseline good condition of your T cells and be able to tolerate apheresis. The apheresis is a much shorter apheresis procedure than you would have for a stem cell transplant collection.

[Slide 91 – Question] Q: You mentioned that chemo-conditioning was a lower dose. What are the drugs that you typically use for that?

Response:
[Slide 92 – Answer] A: At our site we use fludarabine and cyclophosphamide, but at lower doses since the chemotherapy is not used to fight cancer but lower the immune system to "make room" for the CAR T cells. **[Slide 93 – Answer cont'd]** Patients are more used to high-dose cyclophosphamide and the side effects that come with that, so the difference should be explained. At the lower doses, the most common subjective side effects are nausea and vomiting and in general, is well tolerated.

[Slide 94 – Question] Q: Assuming that a patient meets all the criteria for support, obviously, you're doing this in a big university setting. I'm wondering about community practice and if you have any advice as to how to help encourage patients to maybe just broadly sign up for clinical trials as well as the CAR T.

Response:
[Slide 95 – Answer] A: You can give them the information, content, and clinical site. They'll usually give resources on information about different facilities, a copy of the consent for the patient to look at and review to see if they're interested. But if they're just not interested you can't make them interested.

[Slide 96 – Answer cont'd] You can refer them to The Leukemia & Lymphoma Society, the telephone number is (800) 955-4572. Many times you don't have a lot of time in the clinic to talk to them about clinical trials and where they might fit in their treatment paradigm. **[Slide 97 – Answer cont'd]** Many patients are told that they should go to hospice and that there's nothing left that is available for them, which the physician really means there's nothing approved that's available for them. And sometimes they miss explaining that a clinical trial is a great option.

CLOSING REMARKS

Lauren Berger, MPH

[Slide 98 – Closing Remarks] Thank you. And let me close with a story that may not at first glance appear to be a success. **[Slide 99 – Margo]** Margo, who you see on the screen, was a 51-year-old woman who had been diagnosed with diffuse large B-cell lymphoma in October 2014. She was unsuccessful in having a second transplant approved, and she came to us at The Leukemia & Lymphoma Society looking for a trial. We were able to find a transplant for her; but, unfortunately, she succumbed to her disease on November 14, 2015, just one year after she was diagnosed.

But her husband wrote to us that the trial allowed Margo to see her son off to university and to see her daughter start high school and also for her daughter to make the varsity volleyball team. I ask you, was this clinical trial a success or was it a failure? And we think it was a success, but just take time to think about because each one of you in your role and each one of the patients that have participated in a clinical trial helps patients in the future. **[Slide 100 – Thank You]** To all of you who are working in clinical trials or are learning about clinical trials or are there to support your patients when they might be considering a clinical trial or referring them to the LLS if they have additional questions or needs for resources, we thank you. And we thank you for being here for today and for all the work that you do on a daily basis. Our applause to you.

Have a great day.