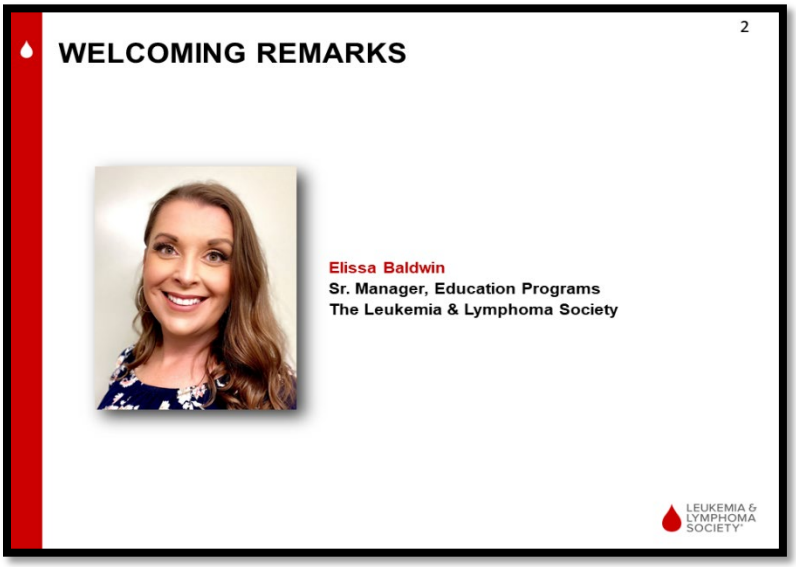
CAR T-Cell Therapy In Patients Of Advanced Age
Speakers: Peter Riedell, MD and Mariam Nawas, MD

Elissa Baldwin: Hello, everyone, and welcome to CAR T-cell Therapy in Patients of Advanced Age.



My name is Elissa Baldwin with the Patient Education team at The Leukemia & Lymphoma Society and I will be your moderator today.

We will have a question and answer session after the presentation, where our speakers will answer questions that came into our LLS Information Specialists and online Community.

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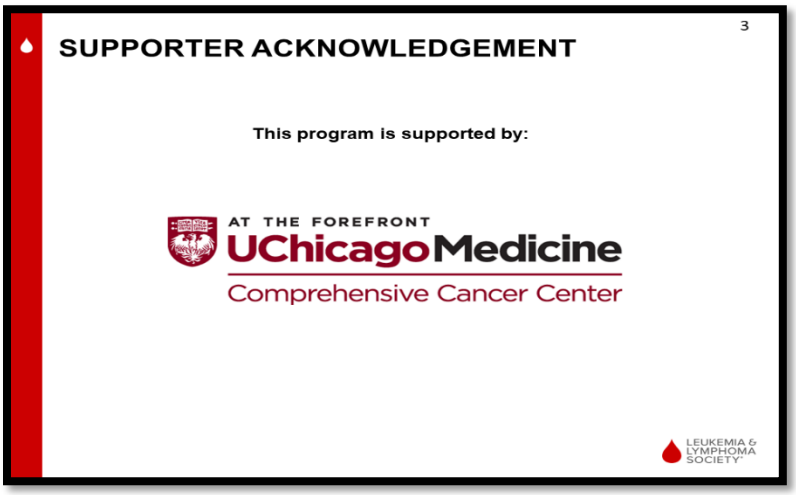
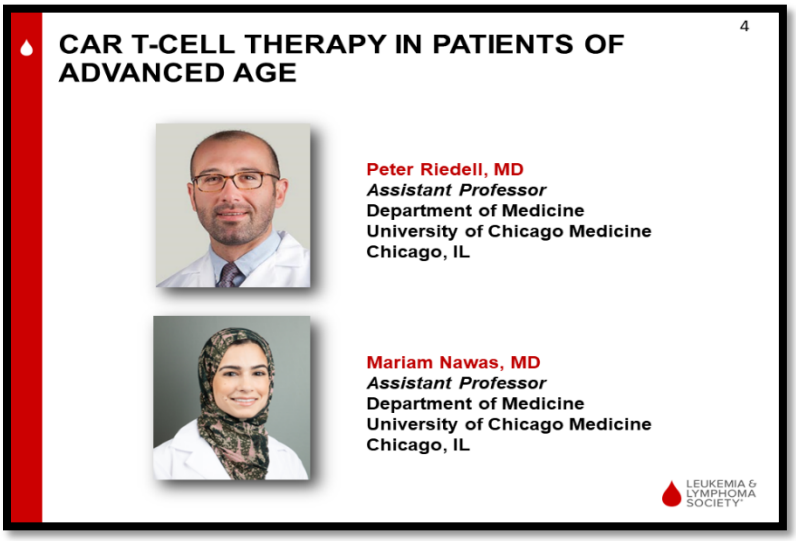


We would like to acknowledge the University of Chicago Medicine for their support of this program.



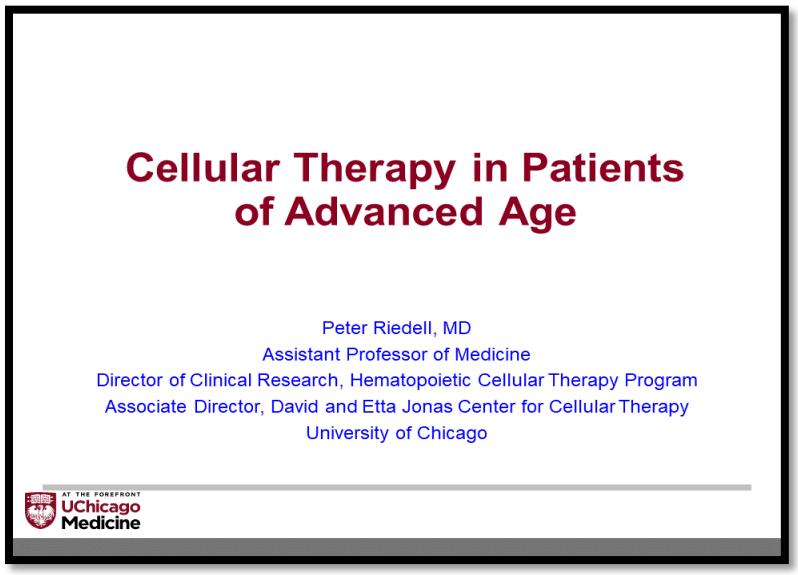
I am now pleased to introduce our speakers for this lecture.

Dr. Peter Riedell is a hematologist/oncologist and Assistant Professor of Medicine at the University of Chicago. He specializes in the care and treatment of adults with all types of Hodgkin and non-Hodgkin lymphoma and is an active clinical researcher for several ongoing clinical trials to treat aggressive lymphomas. As the Director of Clinical Research for the Hematopoietic Cellular Therapy Program, he leads the University of Chicago's efforts in stem cell transplantation and CART T-cell therapy for lymphoma.

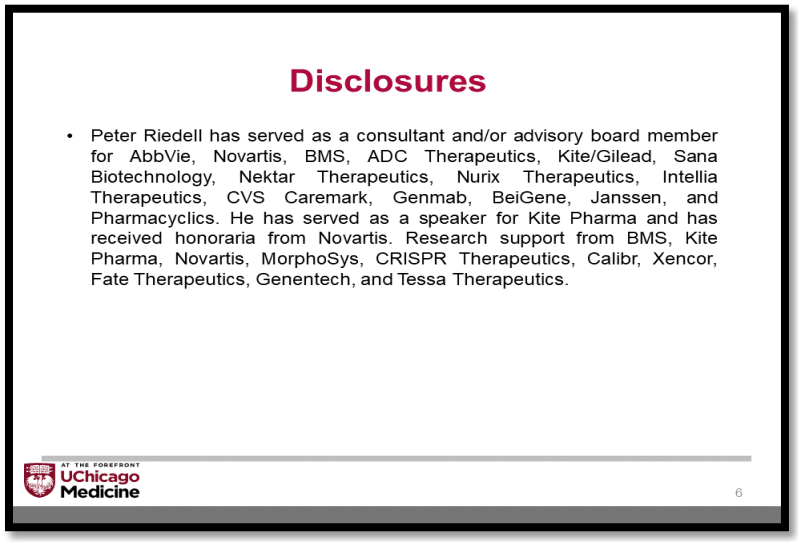
Dr. Mariam Nawas is a hematologist/oncologist and Assistant Professor of Medicine at the University of Chicago, who specializes in the treatment of leukemia and myelodysplastic syndromes (MDS), as well as in allogeneic hematopoietic cell transplantation. Her research focuses on improving patient-reported outcomes and survival of older adults undergoing transplantation and cellular therapy.

On behalf of The Leukemia & Lymphoma Society, thank you both for volunteering your time

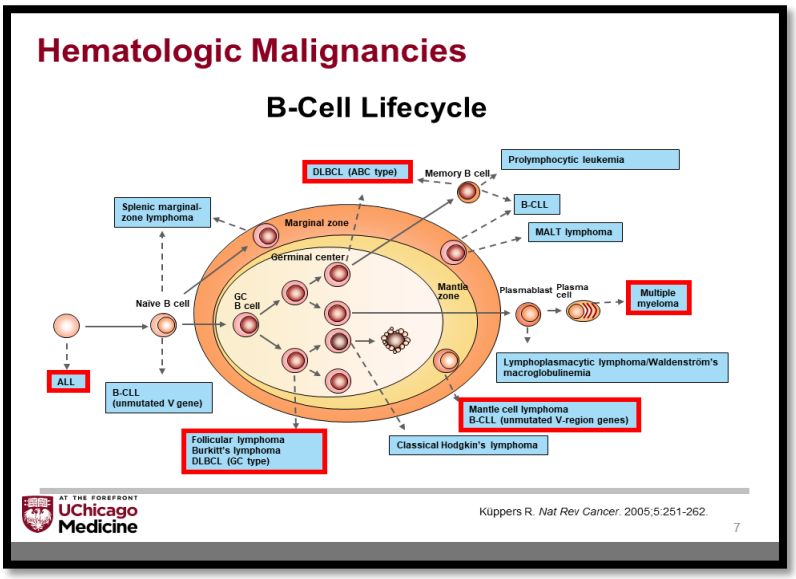
and expertise. Dr. Riedell, I am now privileged to turn the program over to you.



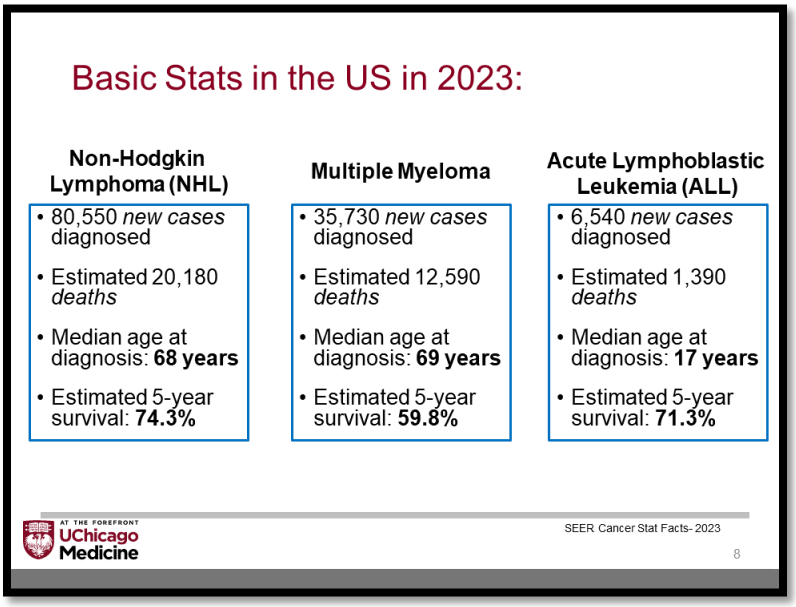
Dr. Peter Riedell: All right, so today we'll talk about cellular therapy in patients of advanced age.



These are my disclosures.

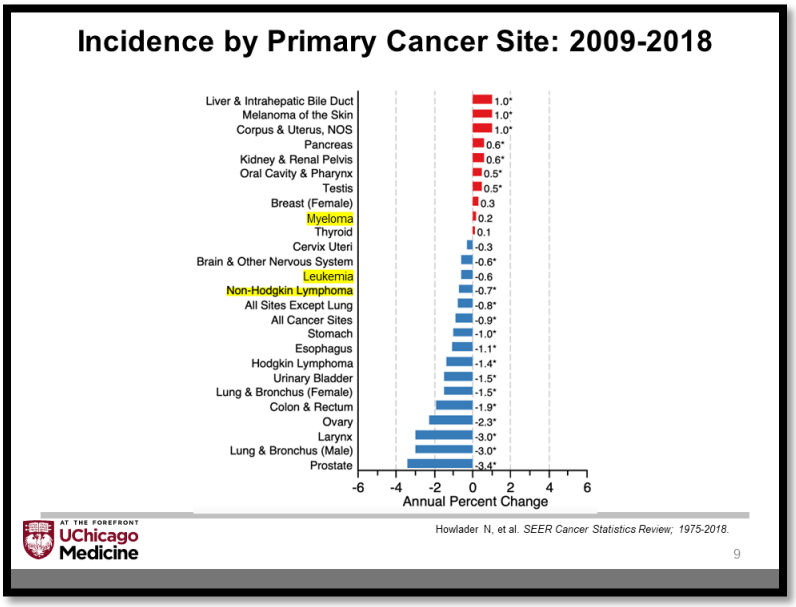


So, when we think about hematologic malignancies, I wanted to just sort of set the stage for where the different blood cancers kind of fall in. The cancers that we'll be discussing today are all from, essentially, a type of the immune system called the B cell. And it really depends on where within the life cycle of that B cell, it develops mutations or other issues that leads to development of different malignancy types. You can see here on the bottom left of the figure here, that if it happens early in the life cycle of a B cell, that leads to a disease called acute lymphoblastic leukemia. And we can also see as that B cell matures, that it may develop other abnormalities separate from the initial that leads to other subtypes of hematologic malignancies such as lymphoma and also multiple myeloma. And that'll kind of set the stage for what we'll talk about today.

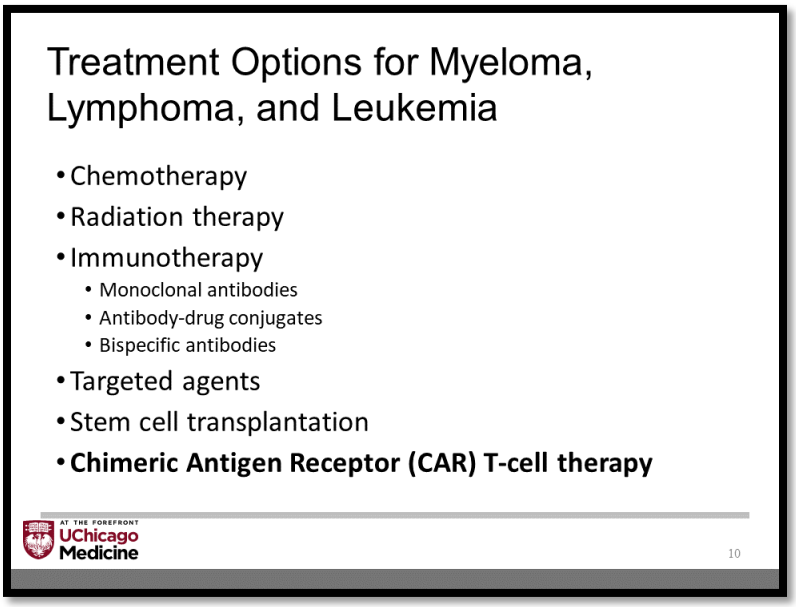


So, in terms of basic statistics, today we'll be reviewing essentially three different hematologic malignancies, including non-Hodgkin lymphoma (NHL), multiple myeloma and acute lymphoblastic leukemia (ALL), and specifically looking at cellular therapy treatments in these different diseases. And in order to kind of get a better understanding of these, I thought it was important that we went through the statistics. And so non-Hodgkin lymphoma, of the three diseases that we'll discuss today is the most common, with approximately 80,000 new cases

diagnosed with around 20,000 patients, unfortunately estimated to pass away from their disease. This is a disease along with multiple myeloma that is typically diagnosed in the late 60s. If we look at multiple myeloma, it's less common than non-Hodgkin lymphoma. And additionally, the outcome unfortunately is not as rosy as we see with non-Hodgkin lymphoma, at least with our current therapies. Acute lymphoblastic leukemia is a disease, which is seen both in young adults and adolescents along with older patients, though the median age at diagnosis is 17 years.

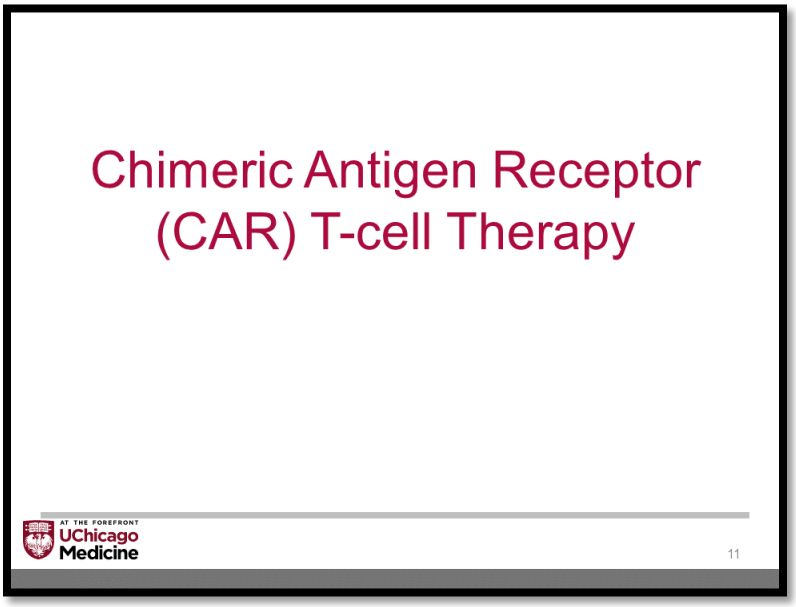


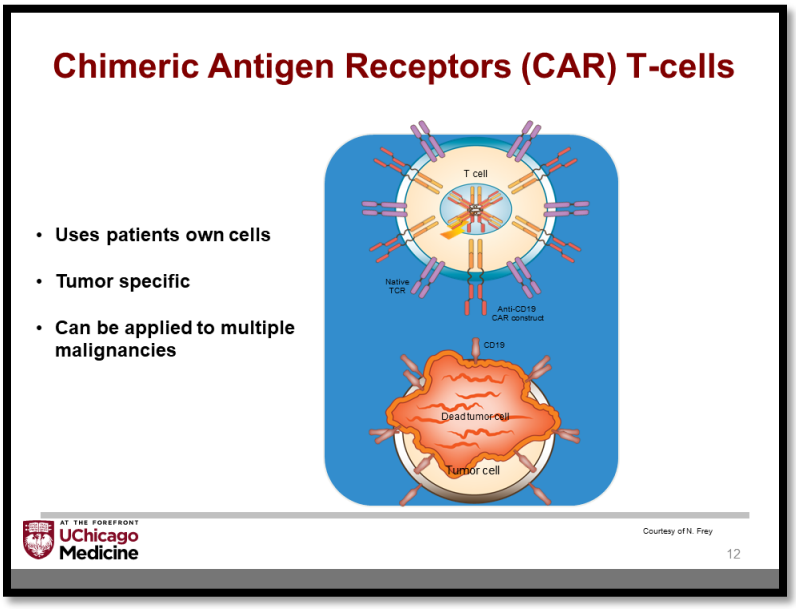
When we think about these three diseases, we look at the incidence through time, the incidence of leukemia and non-Hodgkin lymphoma has actually been decreasing with time, although myeloma has had a slight uptick over the past nine years.



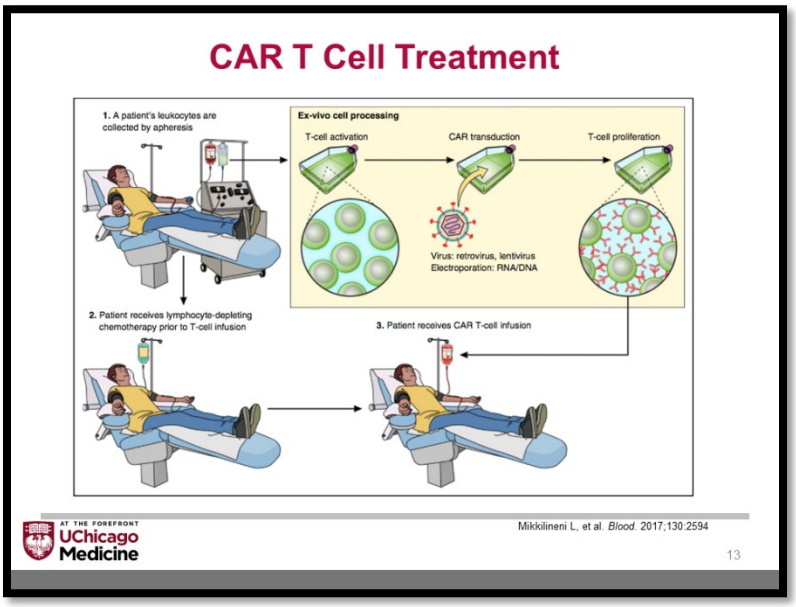
In terms of treatment options for these different diseases, it can be varied. Many of them we utilize frontline chemotherapy or immunotherapy approaches, and additionally, other treatment options such as stem cell transplantation are an option. But today we'll be focusing for the

discussion here on a novel type of treatment, which is chimeric antigen receptor T-cell therapy or CAR T-cell therapy.

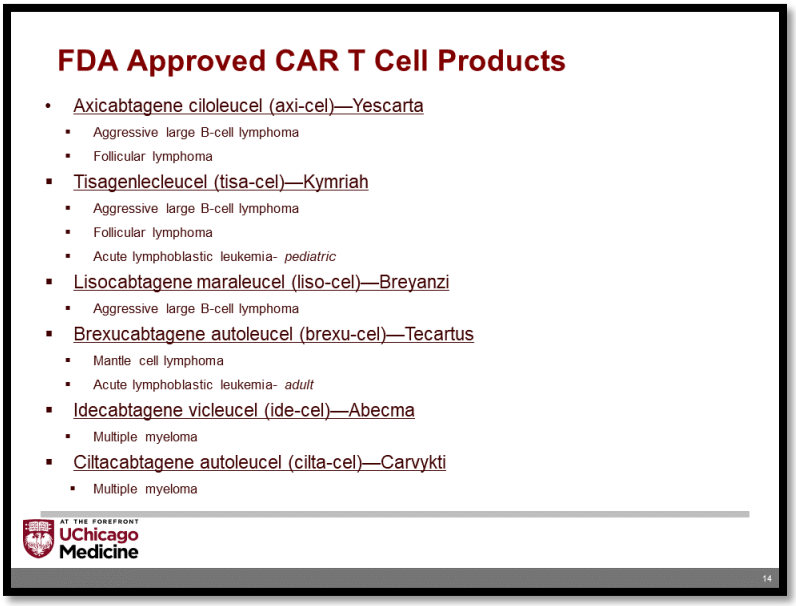




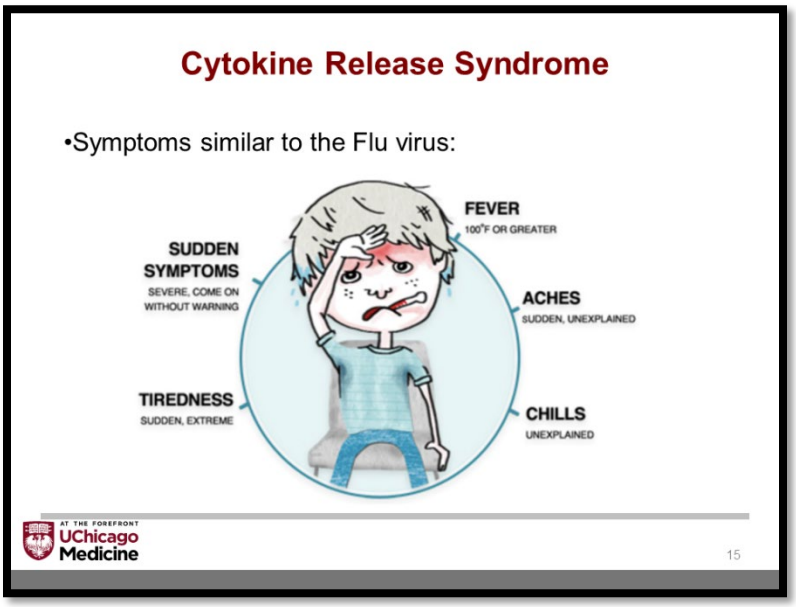
And so with CAR T-cell therapy, this really utilizes a patient's own T cells in order to identify and to attack cancer cells. These CAR T cells can be tumor specific and be engineered in order to attack different proteins which are expressed on cancer cells. And this in theory could be applied to multiple malignancy types. This starts with taking a patient's own T cells and exposing them to a viral vector, which essentially leads to expression of this construct or chimeric antigen receptor on the surface of these T cells. And then upon infusion of these CAR T cells, they bind to tumor cells and lead to destruction of the cancer cells.



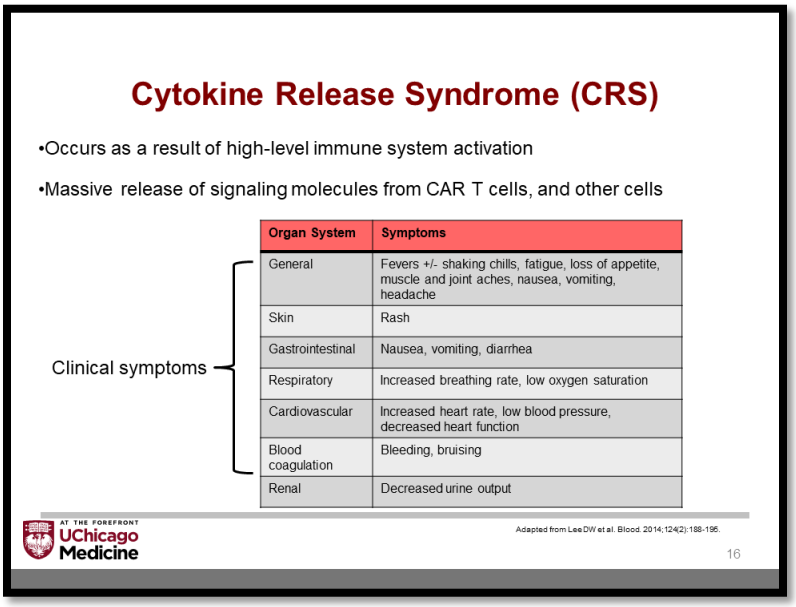
This process starts by us collecting a patient's T cells through a process known as apheresis, and that's done as an outpatient. Following apheresis, those cells are then sent to the manufacturing facility where they undergo processing and eventually become CAR T cells. Following their appropriate manufacturing, the cells are then returned to the treating center and the patient receives chemotherapy, followed by the CAR T cell infusion. And that's the typical workflow for this type of treatment.



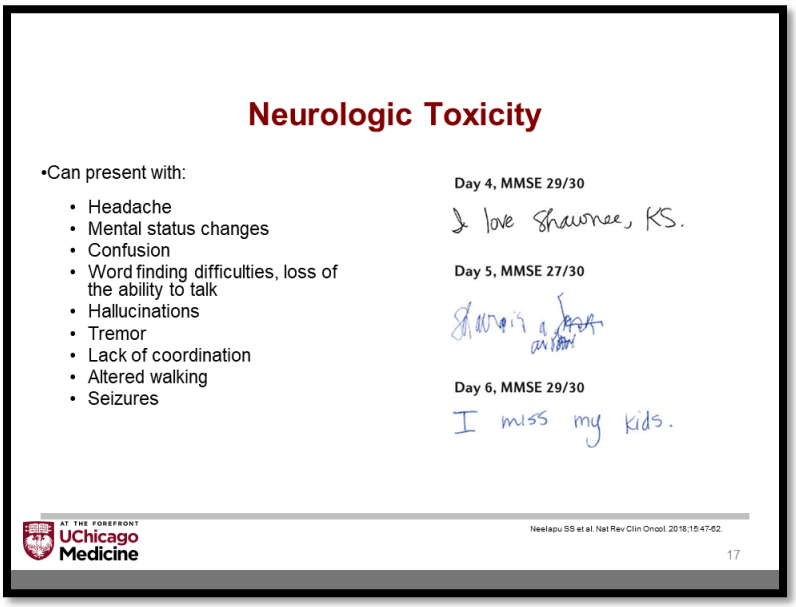
Currently, we have several FDA approved CAR T cell products, with four of the products being approved for various types of non-Hodgkin lymphoma, including aggressive large B cell lymphoma, follicular lymphoma, along with mantle cell lymphoma. More recently, we also have two new drugs which are approved for multiple myeloma, including idecabtagen vicleucel and ciltacabtagene autoleucel. Additionally, two of the agents are also FDA approved for acute lymphoblastic leukemia, including tisagenlecleucelal and brexucabtagene autoleucel.



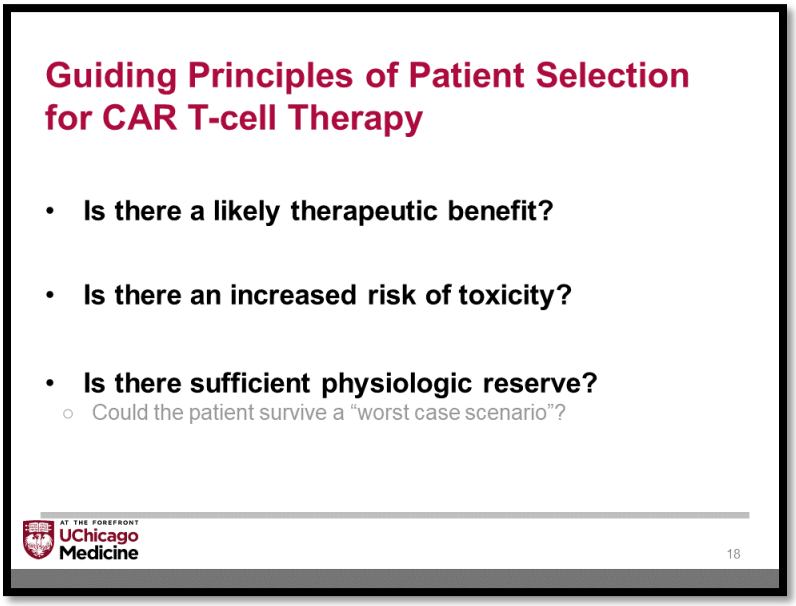
When we think about CAR T-cell therapy, this is a treatment that may be associated with development of side effects, and one of those is known as cytokine release syndrome (CRS). And this is really a constellation of symptoms which occur as a consequence of the immune system becoming activated, engaging the cancer cells and leading to this sort of storm and development of symptoms. And this can kind of be likened to the flu, where patients may demonstrate things like a fever, sometimes chills and muscle aches, feeling tired or lethargic. And that's sort of how we think about this. Is it's really the immune system reacting against the cancer cells.



When we see this high level of immune activation, it may result, as I mentioned, in many different symptoms which can affect different organs. And I think this is really relevant specifically when we're talking about the use of this therapy in patients, that it may be of advanced age and may have other medical comorbidities, including things like cardiac dysfunction or pulmonary abnormalities or decreased kidney function. And you can see here in the table some of the clinical manifestations of cytokine release syndrome and how they may impact different organ systems.

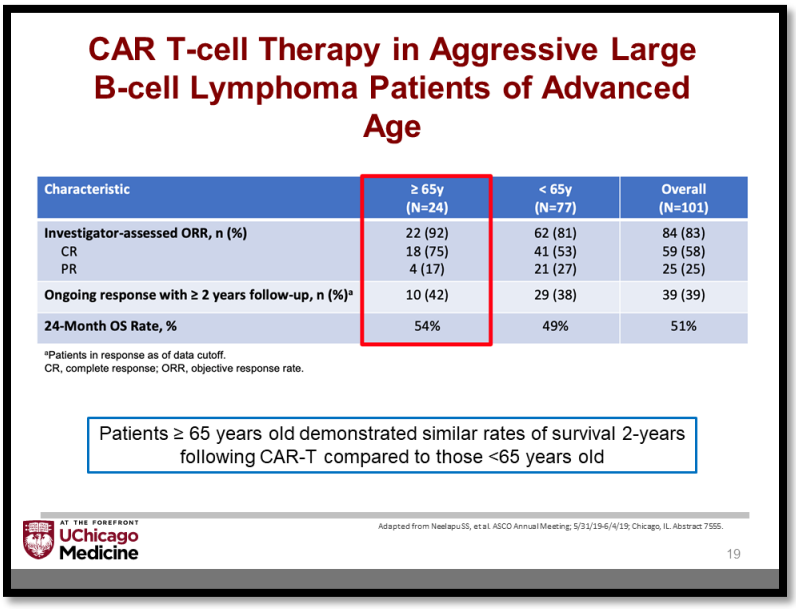


One of the other toxicities that we also discuss with CAR T-cell therapy is neurologic toxicity. And this can present with things like headaches, sometimes confusion, potentially seizure activity. On the right here, you can see a writing sample from a patient that underwent CAR T-cell therapy. And on day four, the writing sample appears very clear and legible, although on day five, the patient developed neurologic toxicity. And you can see that the writing is nearly illegible, though on day six, after treating their neurologic toxicity, you can see that their writing is really back to their baseline. And this is important, as we can see, these changes evolve very quickly in patients that are undergoing CAR T-cell therapy. And it's something that we monitor for very closely.

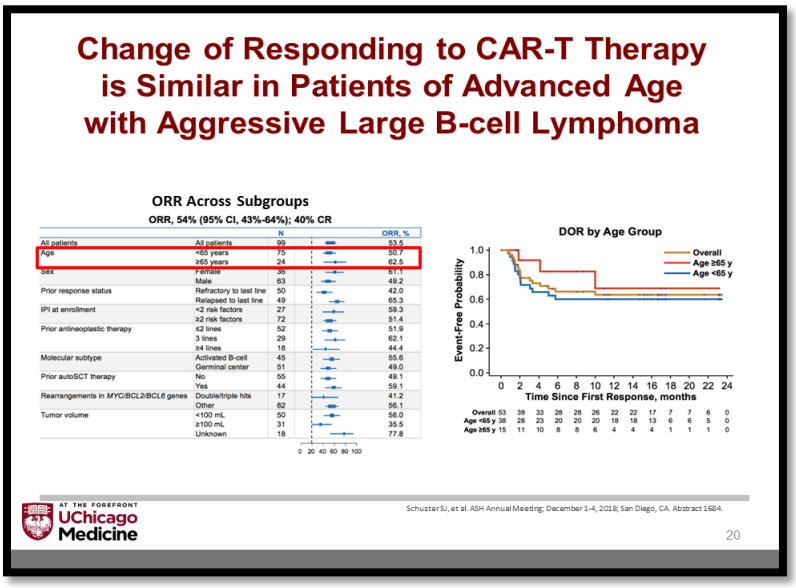


When we think about CAR T-cell therapy, there's really three things that we want to identify when we're trying to select adequate candidates for this type of therapy. And there's really three. What I would say guiding principles that we look at. Is there a likely therapeutic benefit of CAR T-cell therapy in the patient? Does that patient's own medical problems and potential other comorbidities lead to a potential increased risk of toxicity from this type of treatment? And overall, does that patient possess sufficient reserve in order to undergo this therapy? And really

what that boils down to is, does this patient have the ability to potentially sustain what we would know as a worst case scenario where they may develop severe cytokine release syndrome or neurologic toxicity?

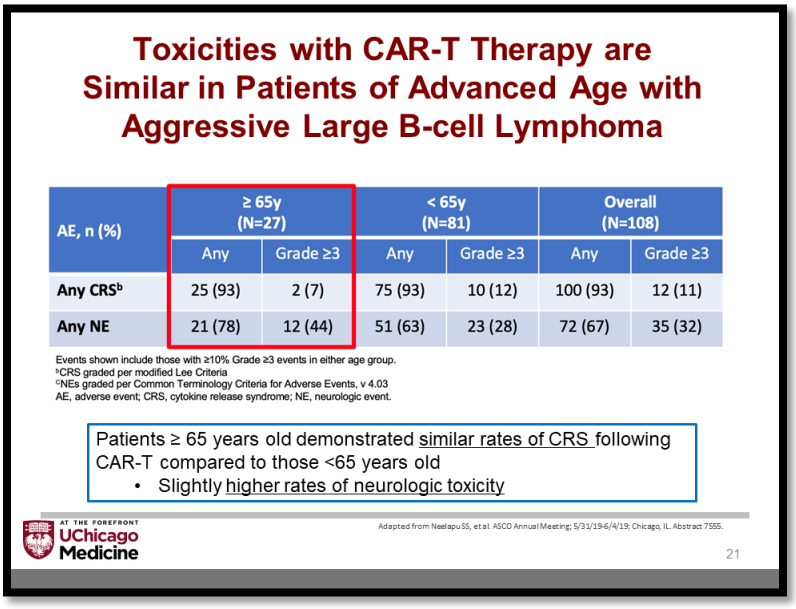


So, when we look at CAR T-cell therapy, this has been investigated now in a wide range of patients. But one of the more recent things that has been sort of evaluated in the data is this therapy in patients that are of advanced age. And comparing that to patients who are less than 65 years of age. And I think some really important things have been noted through this investigation. What we've been able to tell is actually the use of CAR T-cell therapy in patients of advanced age. Age 65 years of age and older, appears to yield very similar outcomes compared to their younger counterparts. Where we see at two years following CAR T-cell therapy we see a very similar proportion of patients who are alive and still doing well.

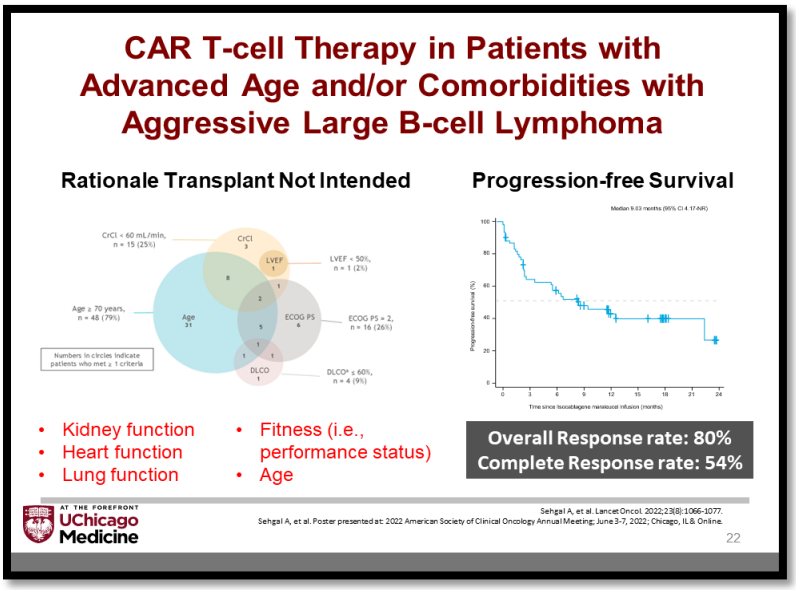


Additionally, this was also demonstrated with another CAR T cell product in a different clinical trial. And so again, that gives us even more confidence that the use of this therapy inpatients of advanced age is safe but, also yields similar responses and similar outcomes. And that's demonstrated in the table on the left there along with the duration of response curves on the

right. And we can see that really those patients that are age 65 years and older do very similar to those patients that are less than 65 years of age.



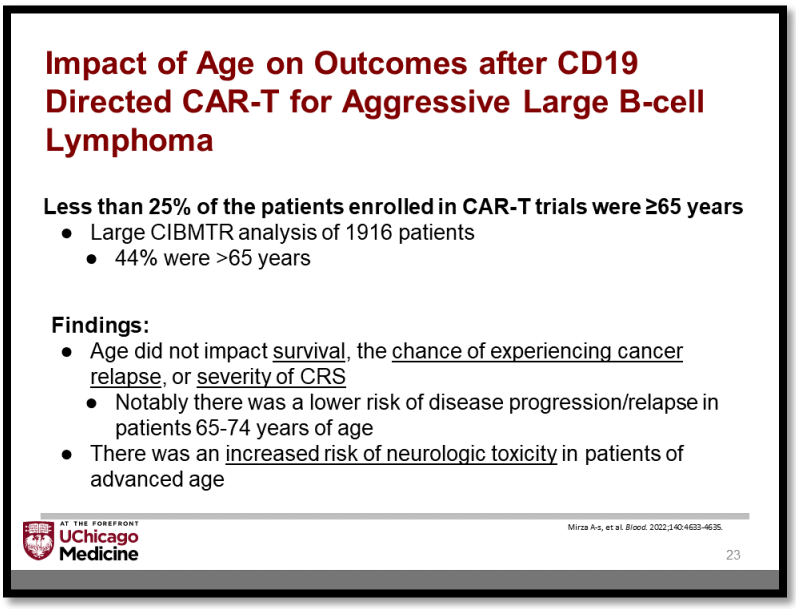
One of the other things of course, to be very mindful of when using CAR T-cell therapy in patients of this age range, is how do these patients fare in terms of toxicity? Are the toxicities greater in this age group compared to patients of a younger age? And this is an analysis that specifically looked at that and was able to demonstrate that patients of advanced age actually showed very similar rates of cytokine release syndrome compared to patients who were younger. There was though a hint that there may be slightly higher rates of neurologic toxicity in patients of advanced age where we can see here that the incidence of neurologic events of any grade was 78% compared to younger patients where it was lower at 63%.



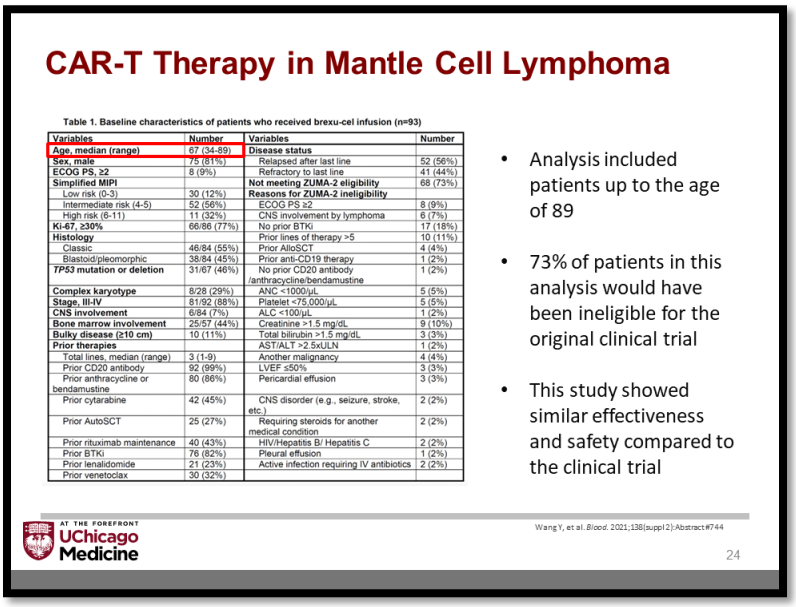
CAR T-cell therapy has also been explored in patients who may not have been typical candidates for autologous stem cell transplant, which is one of the therapies that we use in patients both with multiple myeloma along with large B cell lymphoma. And this is a study which specifically looked at CAR T-cell therapy in that patient population. And we can see on the left are some of the reasons why patients who were enrolled in this study would not have qualified

for something like a stem cell transplant. And it was because they had impaired cardiac function or impaired kidney function or impaired lung function, or they were just of an advanced age where the use of something like stem cell transplant wouldn't be felt to be very safe.

In additionally, and last of all, would be that those patients may not have had an intact performance status or they may not have really been felt to be fit enough for transplant. And if we take that patient population, those patients that classically would not have been candidates for a stem cell transplant, we see that the use of CAR T-cell therapy is actually a viable option, and we see here that the chance of responding to CAR T-cell therapy in that population was close to 80%.The overall response rate and specifically the complete response rate was close to a 54%, which is really encouraging, again for patients who may not have stem cell transplant as an option or may not be appropriate candidates for typical, more aggressive treatments.



This was also demonstrated in another analysis in a larger group of patients, close to about 1900 patients, of which close to about 40% of those were greater than the age of 65.In this analysis, it was able to demonstrate that age did not have an impact on survival of patients, it did not have an impact on the chance of experiencing cancer relapse, nor did it have an impact on the development of cytokine release syndrome. And in fact, notably, there was actually a lower risk of disease progression or relapse inpatients who were of advanced age. And again, as noted in the prior slide, there was a slightly increased risk of neurologic toxicity in this population.



CAR-T Therapy in Mantle Cell Lymphoma

Table 1. Baseline characteristics of patients who received brexu-cel infusion (n=93)

Variables	Number	Variables	Number
Age, median (range)	67 (34-89)	**Disease status**	
Sex, male	75 (81%)	Relapsed after last line	52 (56%)
ECOG PS, ≥2	8 (9%)	Refractory to last line	41 (44%)
Simplified MIPI		**Not meeting ZUMA-2 eligibility**	68 (73%)
Low risk (0-3)	30 (12%)	**Reasons for ZUMA-2 ineligibility**	
Intermediate risk (4-5)	52 (56%)	ECOG PS ≥2	8 (9%)
High risk (6-11)	11 (32%)	CNS involvement by lymphoma	6 (7%)
Ki-67, ≥30%	66/86 (77%)	No prior BTKi	17 (18%)
Histology		Prior lines of therapy >5	10 (11%)
Classic	46/84 (55%)	Prior AlloSCT	4 (4%)
Blastoid/pleomorphic	38/84 (45%)	Prior anti-CD19 therapy	1 (2%)
***TP53* mutation or deletion**	31/67 (46%)	No prior CD20 antibody /anthracycline/bendamustine	1 (2%)
Complex karyotype	8/28 (29%)	ANC <1000/µL	5 (5%)
Stage, III-IV	81/92 (88%)	Platelet <75,000/µL	5 (5%)
CNS involvement	6/84 (7%)	ALC <100/µL	1 (2%)
Bone marrow involvement	25/57 (44%)	Creatinine >1.5 mg/dL	9 (10%)
Bulky disease (≥10 cm)	10 (11%)	Total bilirubin >1.5 mg/dL	3 (3%)
Prior therapies		AST/ALT >2.5xULN	1 (2%)
Total lines, median (range)	3 (1-9)	Another malignancy	4 (4%)
Prior CD20 antibody	92 (99%)	LVEF ≤50%	3 (3%)
Prior anthracycline or bendamustine	80 (86%)	Pericardial effusion	3 (3%)
Prior cytarabine	42 (45%)	CNS disorder (e.g., seizure, stroke, etc.)	2 (2%)
Prior AutoSCT	25 (27%)	Requiring steroids for another medical condition	2 (2%)
Prior rituximab maintenance	40 (43%)	HIV/Hepatitis B/ Hepatitis C	2 (2%)
Prior BTKi	76 (82%)	Pleural effusion	1 (2%)
Prior lenalidomide	21 (23%)	Active infection requiring IV antibiotics	2 (2%)
Prior venetoclax	30 (32%)		

- Analysis included patients up to the age of 89
- 73% of patients in this analysis would have been ineligible for the original clinical trial
- This study showed similar effectiveness and safety compared to the clinical trial

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Wang Y, et al. *Blood*. 2021;138(suppl 2):Abstract #744

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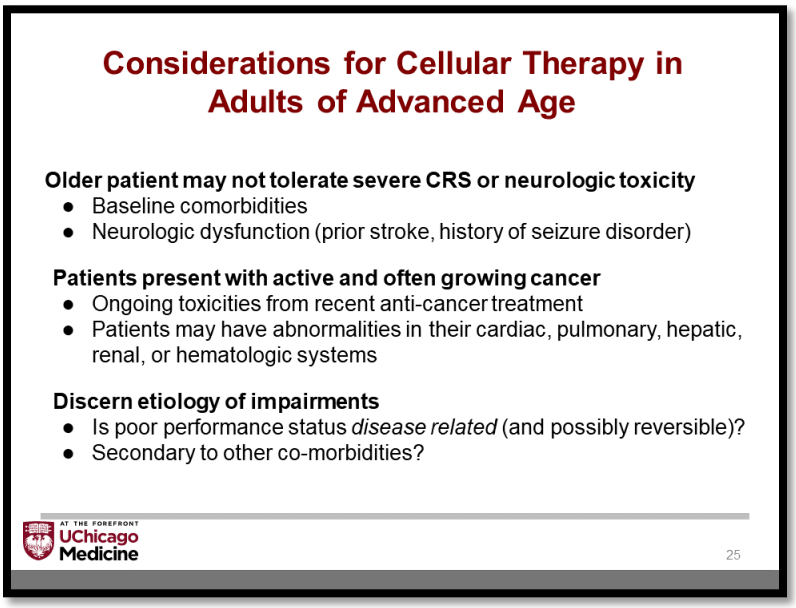
This is also looking at the use of CAR T-cell therapy in a different subtype of lymphoma, known as mantle cell lymphoma (MCL). And I think the important thing to understand here is that in a lot of the clinical trials that eventually led to FDA approval of CAR T cell agents, the inclusion and exclusion criteria, the sort of strict guidelines that were needed in order to be enrolled on that study, often hindered or limited the inclusion of patients of advanced age. While in the commercial setting, we're not hindered or have to deal with those guardrails. And so, this was an analysis that looked at use of CAR T-cell therapy and mantle cell lymphoma in the commercial setting where patients were treated up to the age of 89. And we can see here that close to about three quarters of patients who were in this analysis actually would have been ineligible for the pivotal clinical trial that led to approval in mantle cell lymphoma. Though, importantly, this treatment in the commercial setting showed very similar outcomes in terms of how safe it was and also how effective this treatment was.



Considerations for Cellular Therapy in Adults of Advanced Age

Older patient may not tolerate severe CRS or neurologic toxicity
- Baseline comorbidities
- Neurologic dysfunction (prior stroke, history of seizure disorder)

Patients present with active and often growing cancer
- Ongoing toxicities from recent anti-cancer treatment
- Patients may have abnormalities in their cardiac, pulmonary, hepatic, renal, or hematologic systems

Discern etiology of impairments
- Is poor performance status *disease related* (and possibly reversible)?
- Secondary to other co-morbidities?

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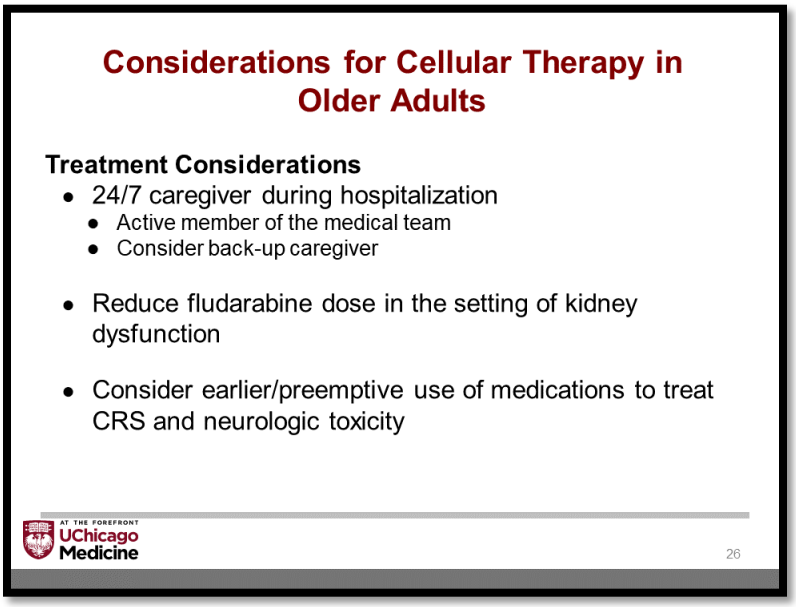
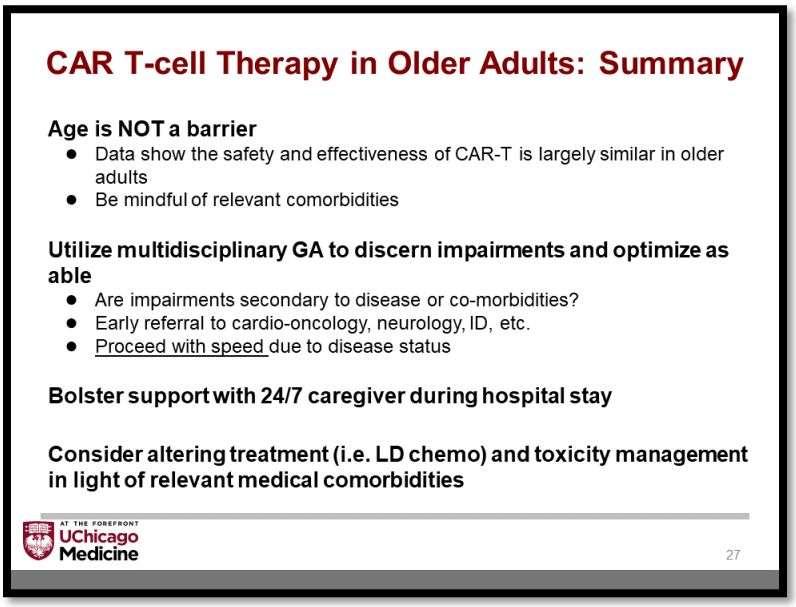
And so, when we use CAR T-cell therapy and other cellular therapies in patients of advanced age, there's a few things that we need to be mindful of. Older patients we know may not tolerate things like severe cytokine release syndrome or neurologic toxicity based on their

baseline comorbidities. Patients often in this age range may have neurologic complications at baseline, such as a prior stroke or a history of seizure disorder, which may put the mat risk for additional toxicities with CAR T-cell therapy. Also, patients may have active and often growing cancer which therefore may yield impairments in their cardiac, pulmonary, hepatic or renal function at baseline just due to the cancer itself. And so, it's important as clinicians that we discern and understand what the etiology or what's the cause of these underlying impairments. Is it because of the patient's disease or is it because of just their normal history and is it a prior condition and not related to the cancer? And we think that those impairments that maybe related to lymphoma will likely improve with treatment of their cancer as opposed to impairments that may be at baseline and already part of the patient's own medical history.



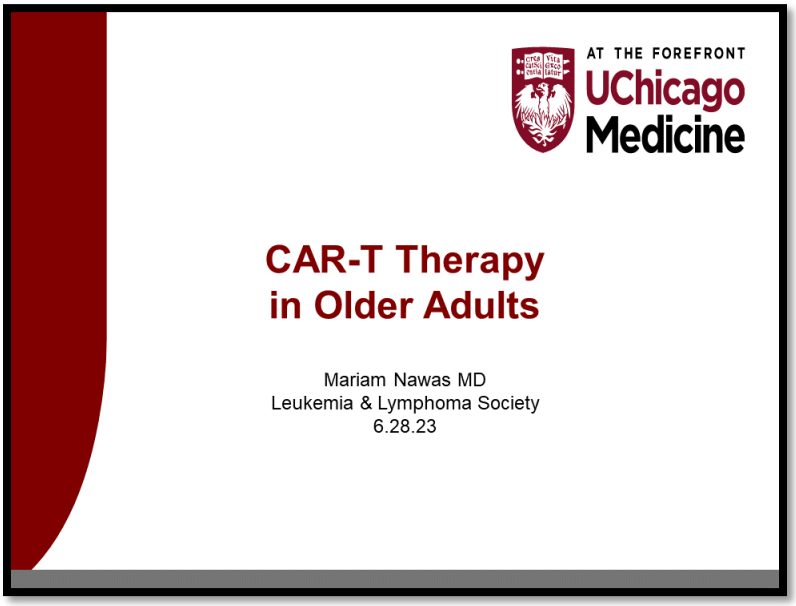
We also want to make sure when we're providing CAR T-cell therapy that we're doing this in a very safe manner. And so, at our medical center and frequently at other medical centers around the country, we do require 24-hour caregiver support. And we really emphasize that that caregiver support starts at the time of CAR T-cell infusion and of course that certainly continues after their CAR T-cell inpatient treatment course or outpatient management. The caregiver in this setting is really an active member of the medical team and it's also important in many instances to identify a backup caregiver should the primary caregiver not be available or themselves have medical problems that require caring for. Patients often of advanced age do have decreased kidney function, and so it's important to be cognizant of that and potentially reduce doses of medications like fludarabine, which is used in the CAR T-cell treatment process. Also, in these patients we often try to be a little more aggressive with our management of toxicities in order to prevent more serious or severe grades of things like neurologic toxicity or cytokine release syndrome.



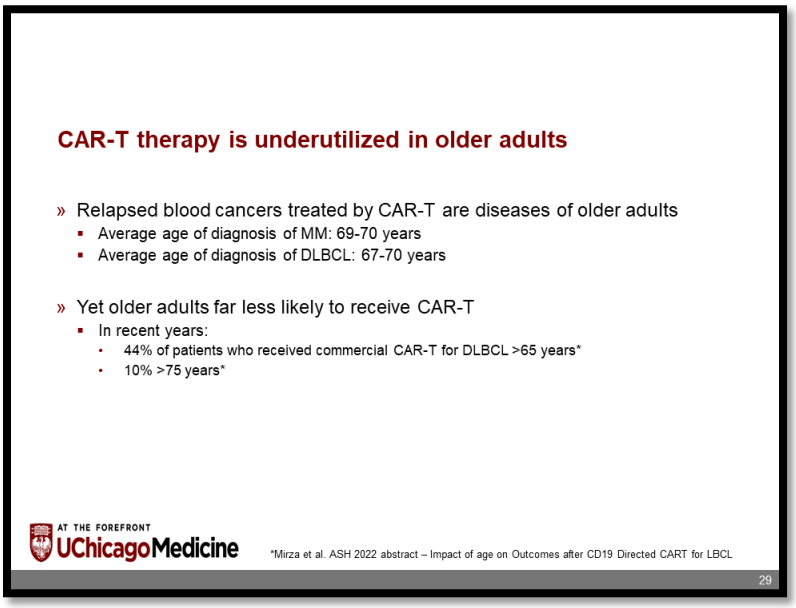
And so, in summary, with the use of CAR T-cell therapy in older patients, age is actually not a barrier. And data has really shown that this therapy can be safely provided in patients of advanced age, and it seems to be equally effective in patients of older age compared to their younger counterparts. Though, that being said, we do need to be mindful of patients' relevant comorbidities and potentially adjust and provide this treatment in a very nuanced manner.

We try to utilize at our medical center a multidisciplinary geriatric assessment in order to discern impairments and optimize patients as much as able. And Dr. Nawas will get into this with a little bit more detail in the upcoming lecture. We also try to bolster support, as I mentioned, with having a 24-hour caregiver during their hospital stay and then, additionally, consider altering their treatment through the use of different chemotherapy platforms for lymphoid depletion, or using different toxicity management strategies in order to allow patients to get through this treatment safer.

Thank you.

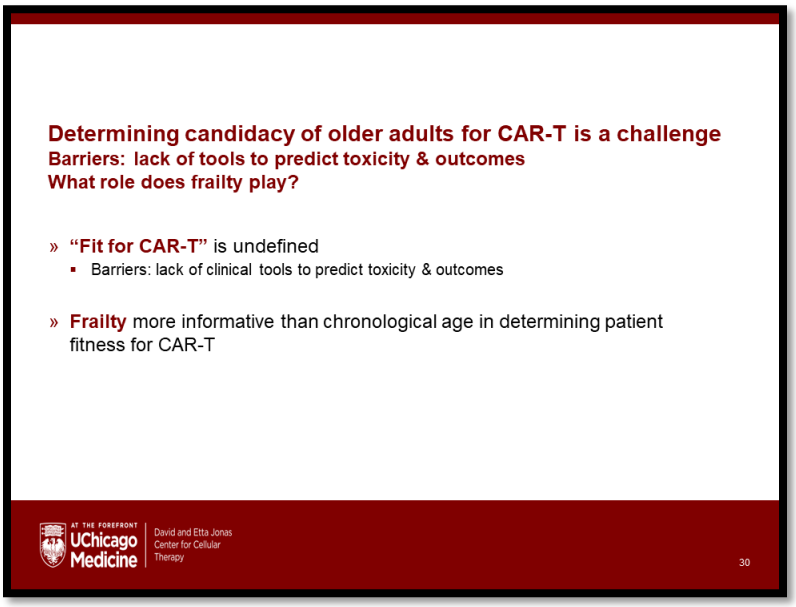


Dr. Mariam Nawas: Hi. So, I'm Dr. Nawas. I will be following up Dr. Riedell's talk by speaking a little bit more about CAR T in older adults and specifically how we evaluate older patients for CAR T-cell therapy, what constitutes a CAR T candidate and how age plays into these considerations.

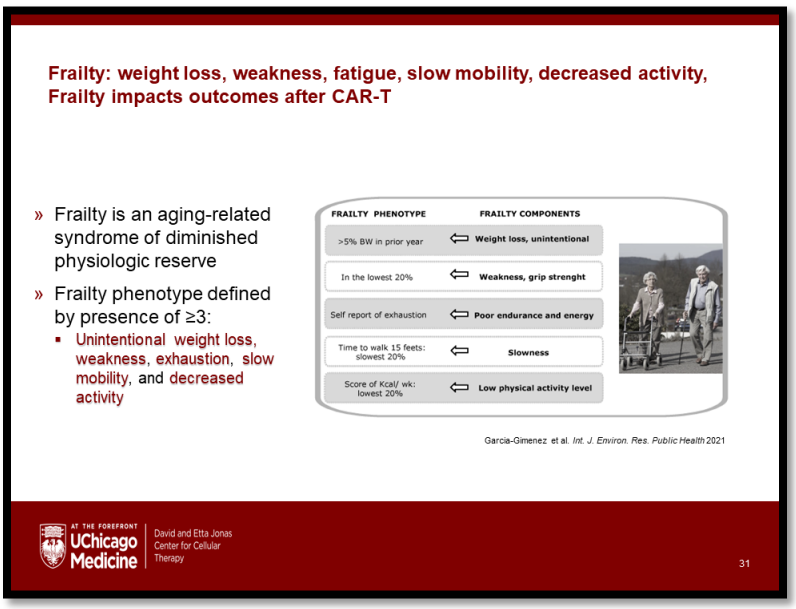


So, as we heard already, the main disease indications for CAR T therapy are diseases of older patients. So, multiple myeloma and large cell lymphoma are diseases of older patients. The average age of onset, as we can see, is generally in the late 60s or about age 70. And so, if older patients or if CAR T was being used equitably based on need and indication, we would expect that most recipients of CAR T therapy are older patients. But that's actually not what we see. What we find instead is that CAR T therapy is being underutilized in older patients.

There was a recent analysis that pulled together data from CAR T centers across the country, and they looked at patients with large cell lymphoma who had received CAR T therapy commercially. Meaning that these patients were treated with CAR T not on a study protocol that may have limited their eligibility based on age or comorbidities, but they received CAR T as standard of care. And so, that's what we call real world data that really reflects practice patterns across the country. And what they found was that a sizable minority, but a minority of patients who received CAR T for large cell lymphoma were over age 65, and only10% of patients were over age 75. And so, that is not really congruent with the demographics of these diseases. and it tells us that for some reason, older patients are not being considered for or being offered CAR T therapy at the same rates as younger patients.

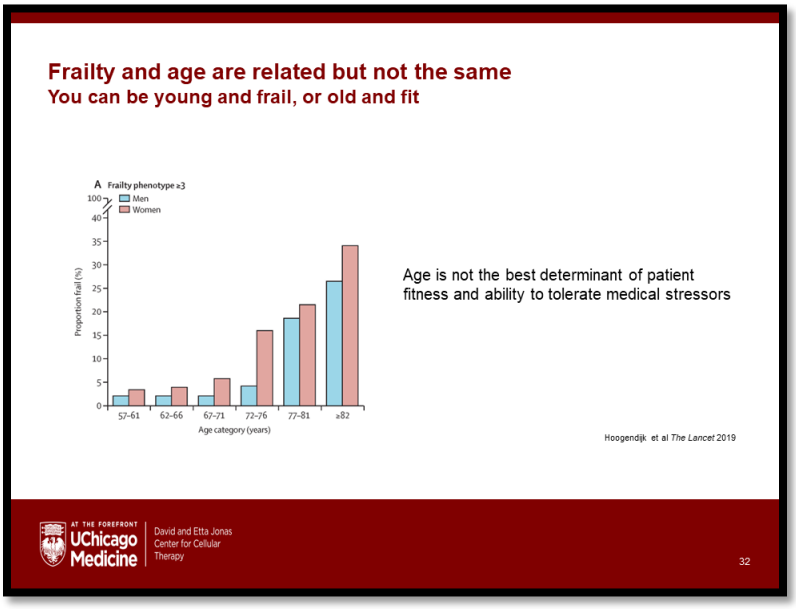


So why is this? One of the barriers is that physicians are not always sure about who is an appropriate candidate for CAR T therapy. There is a common perception that older patients may do worse with therapy or may not benefit from therapy the same way that younger patients do. And this whole construct of what it means to be fit for CAR T therapy is really not well defined. So, physicians lack really clinical tools to predict who will and will not benefit and who will and will not experience toxicities with CAR T. And so, in the absence of clinical tools, often providers will rely on something like chronological age, even though, as we've seen, based on Dr. Riedell's data, that he shared evidence really does not support this approach. And so, we believe that frailty is a lot more informative than chronological age in determining patient fitness for CAR T.

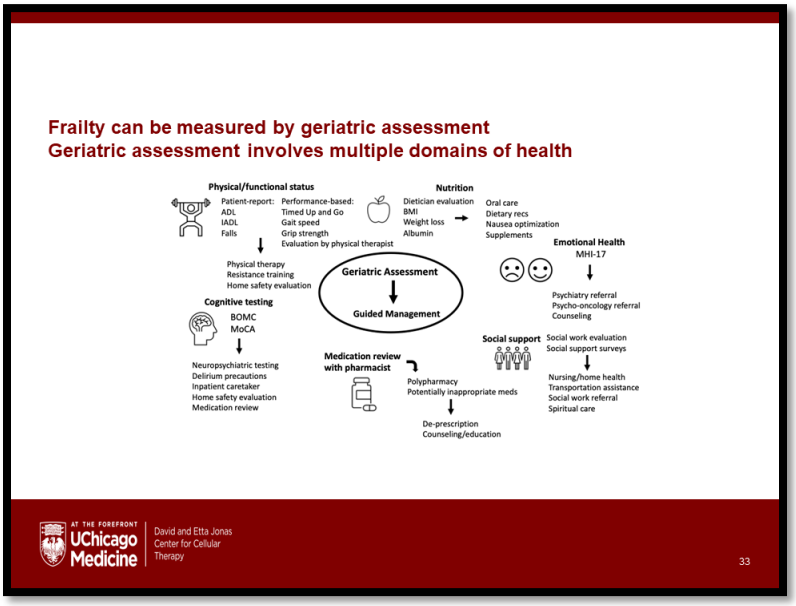


So, frailty is an aging related syndrome of diminished physiologic reserve. When a frail patient is faced with a medical stressor such as CAR T therapy, they don't have a lot of reserve, and they may be more susceptible to poor health outcomes. One of the ways of defining frailty is something called the Fried frailty phenotype, and that is defined by the presence of three or more of the following. So unintentional weight loss, weakness, which often is measured by tests

of grip strength, feelings of exhaustion or fatigue as reported by patients, slowness, which could be measured by gait speed, and then just overall decreased physical activity.

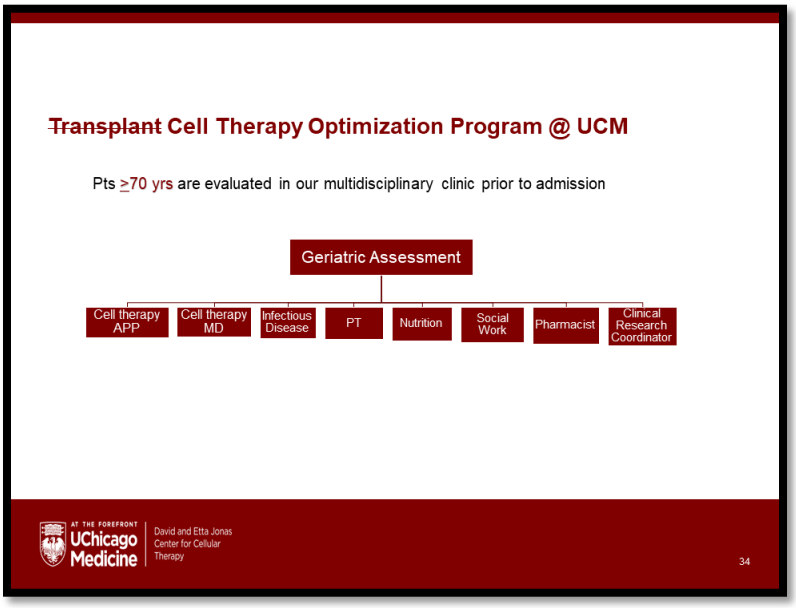


So, frailty and age are certainly related, but they're not the same, meaning that you can be young and frail or old and fit. And one, number one, chronological age is not going to tell you the full story. This figure came from a study of thousands of community dwelling adults. And this was done in Amsterdam. So they looked at patients, or not patients, just community dwelling people who were age 55and older, and they monitored them over time. And they also applied a frailty assessment, the same one that we just described, to see what the prevalence of frailty was in different age populations. And what you can see is that frailty definitely increases with age. But there's still a substantial portion of patients, even patients in their seventies and eighties, who don't meet that criteria for frailty. And then also you can be under age 65 or under age 60 and still be frail. So in summary, age is not the best determinant of patient fitness and ability to tolerate medical stressors.



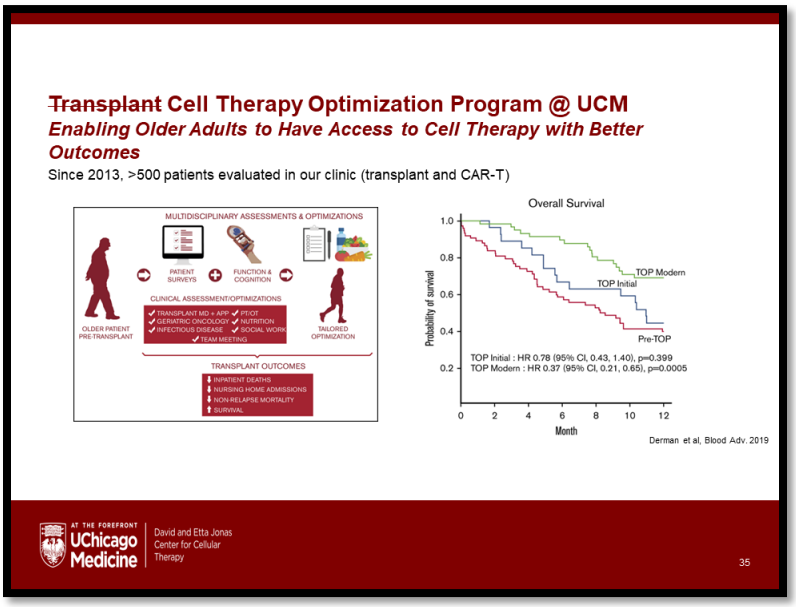
So, frailty can be measured by something called the Geriatric assessment. The geriatric assessment is a comprehensive way of evaluating different domains of health, and it often ends up being a multidisciplinary assessment. So the idea is that there is a lot more to someone's health than just their cancer history, their medical problems, and their age. The domains of health include things like physical and functional status, nutrition, cognition, emotional health, social support, et cetera. And so, what we strive to do with a geriatric assessment is try to figure out how a patient is doing in each of these different domains, because we know that deficits in any one of these domains can increase the susceptibility to poor outcomes.

So in the context of a geriatric assessment, often a patient will meet with multiple different providers. So for example, they may meet with a physical therapist who will do performance based tests such as, again, a gate speed to see how fast a patient can walk, something like grip strength. To test the strength of a patient, they would meet with a dietitian who would go over the patient's diet, caloric intake, what they're eating, and provide education optimization around that. They would meet with a social worker who would figure out what the patient's caregiver plan is. Whether they have good safety at home, what their transportation plan is, how well supported they are, and they would meet with a pharmacist to go over medications, make sure there's no inappropriately prescribed medications, et cetera. So, the geriatric assessment really achieves two things. It tells you how fit or frail a patient is or where they fall on that scale, and it also identifies deficits in these domains if they exist. And that gives you the opportunity to intervene upon these deficits. I like to think of it as, by figuring out what these deficits are, we can optimize the patient for the treatment, and we can also optimize the treatment for the patient. And what I mean by that is that, for example, if we were to do this testing and see that there were deficits in physical strength or nutrition. We could assign the patient a home exercise program or a physical course of physical therapy to get them stronger. We would identify what the barriers are to better nutrition. Is it nausea, taste changes? Poor appetite? We would try to intervene on those things. And then, for example, if a patient tested as having some cognitive impairments, then we would know that puts them at risk for things like confusion or delirium in the context of a long hospital stay. And so, we would then instate something called delirium precautions to try to prevent that from happening.



So, at the University of Chicago, we have something called the Transplant Optimization Program, which is a way of applying a geriatric assessment in older patients undergoing cellular

therapy. It used to be that, so when this was created about a decade ago, it used to be that we only saw patients under consideration for stem cell therapy. But now with the advent of CAR T therapy, we also see patients who are older, defined as 70 years or older, who are under consideration for CAR T therapy. So really the name should be updated to something like Cell Therapy Optimization Program. And this is a half day clinic in which a patient undergoes a geriatric assessment. The way that it works is that the patient comes into clinic and they stay basically in one room, and it's a revolving door of providers. So, the patient will meet with a cell therapy doctor and nurse practitioner who will provide education around the CAR T process. They will meet with an infectious disease doctor to make sure that they're not at increased risk of some type of infection or reactivation. And again, they would do the testing with a physical therapist, a nutritionist, and they would speak with a social worker, a pharmacist, and finally a clinical research coordinator. So again, it is very comprehensive testing.

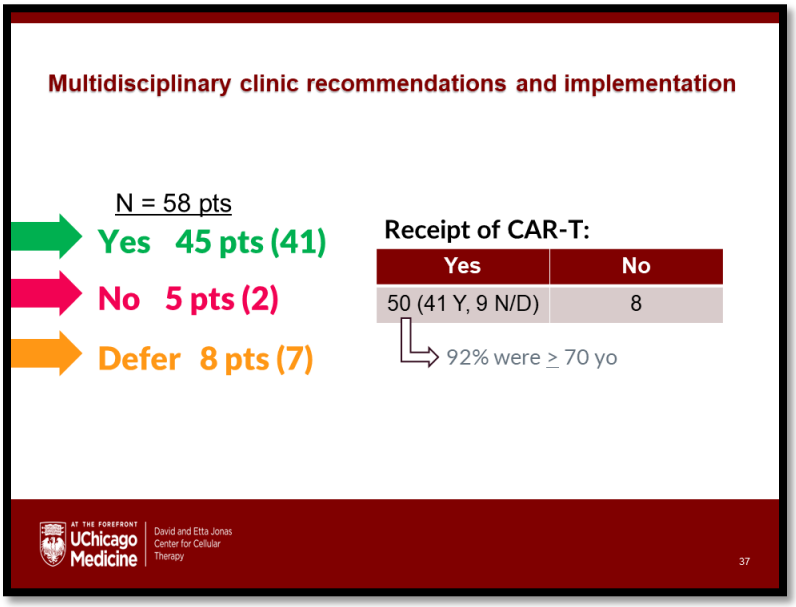


So, since the inception of this clinic in 2013, we've seen over 500 patients come through this clinic. And this includes patients who were under consideration, again, not just for CAR T, but also stem cell transplant. And so, these two figures I pulled from a paper that our group had published about our experience with this clinic in the context of older patients under consideration for donor stem cell transplant, to sort of give you an idea of the value that we feel this clinic brings.

So over here on the right is a survival curve. And if you have not looked at these before, basically this is a way of tracking patient survival over time. And so, the ideal survival curve would actually just be a straight line from one, meaning that no patient has passed away over time. But as patients pass from disease or complications, obviously the curve will trend downward. So, the higher the curve is to being just a straight line, the better survival is. So, what is shown here is that this red curve shows what survival was like in older adult patients undergoing transplant before the implementation of this program. And then with the first iteration of the program, you can see the survival seems to improve. And then with the most modern iteration that we have implemented now, survival really improved a lot. And the reason for that is because we feel we were able to better select patients for this therapy. So, unlike CAR T, transplant can be a lot more rigorous. And it is really crucial to make sure that the patient that you're selecting for transplant is someone that you feel can get through it safely. So by doing the assessment, it gave us again, just a much better sense of patience and enabled

better patient selection and it also enabled optimization of the transplant and making the transplant a little bit safer.

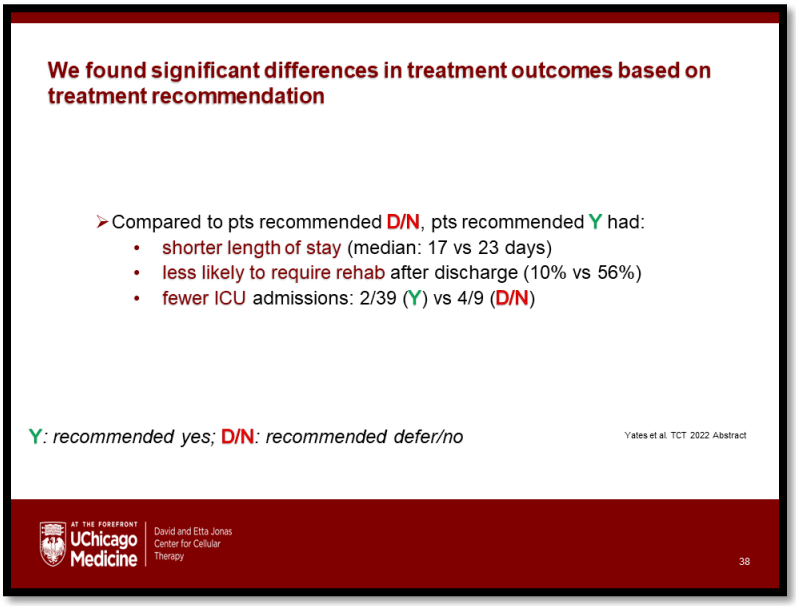
So, you know, that's in the setting of transplant. But what's the value and what is the data regarding the value of a geriatric assessment in older patients treated with CAR T therapy? So, I'm going to show you first data again from our own clinic at the University of Chicago in this regard. And then I'll share some data from a couple of other studies at other institutions looking at the prognostic value of frailty in CAR T.



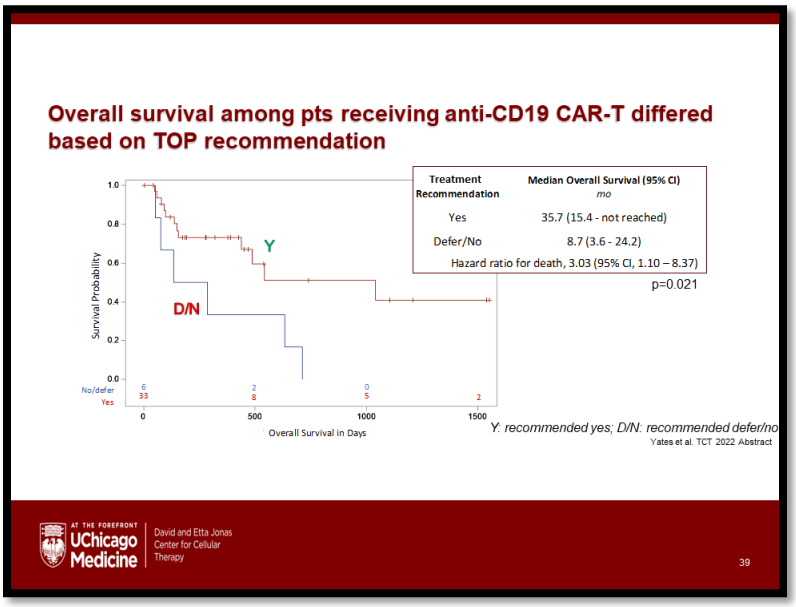
So, this is just a recap of our experience in the clinic with CAR T patients. So since, from 2017, really since the beginning of when we started doing CAR T until, I would say the end of 2022, is when we cut this off. We had seen about 58 patients who were under consideration for CAR T therapy. And the vast majority of these patients were age 70 or older. And when patients go through the clinic, we assign them basically a treatment recommendation. And it's one of three things. It's basically a green light saying that we feel that this patient is not at any type of increased risk for toxicity or safety issues and that we feel this patient is safe to proceed.

Rarely, but occasionally, we will meet a patient that we think has some type of red flag that we think will put them at a very high risk of complications. And we say we don't think that this patient should proceed. And then sometimes, there are patients that we feel could use a little bit of optimization of different elements of their health before they should proceed onto CAR T. And importantly, these treatment recommendations are not binding. Sometimes patients will ask me like, am I going to delay or prevent them from going on to CAR T? And that's not the intention. This is just guidance provided to the referring doctor. And ultimately, the decision about proceeding is made with the referring doctor who knows the patient the best and with the patient.

But what we were curious in knowing is that, did patients who were given a green light from us, did they have better outcomes than patients that we had recommended against CAR T? But who ended up going to CAR T regardless. So, that's what these numbers represent. Of the 58 patients that we evaluated, most of these patients we said yes to, most of whom went on to CAR T. Again, there were a few patients we said no to, a couple of whom went on to CAR T nonetheless. And then eight patients that we had a deferral recommendation for most of who went on to CAR T and often without carrying out the full optimization recommendations because time was just a barrier. And so again, we wanted to compare the outcomes of this group with this group to see if we were actually any good at predicting how people were going to do.

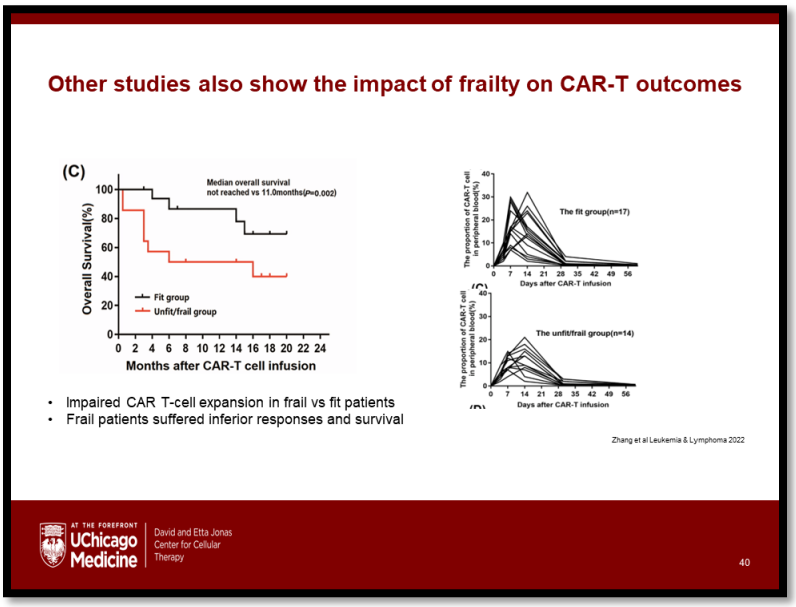


So, the first outcomes that we looked at were short term outcomes, meaning things like how long were patients in the hospital, did they need physical rehabilitation after discharge, et cetera. And if we compare the outcomes of these two groups, we saw that patients who were given a green light definitely had shorter hospital stays, 17 days versus 23 days. And that would presumably reflect a less complicated hospital course. These patients recommended yes, were a lot less likely to need physical rehabilitation to recover from the hospital stay for CAR T, and they were also a lot less likely to end up in the ICU during the course of their CAR T hospitalization.

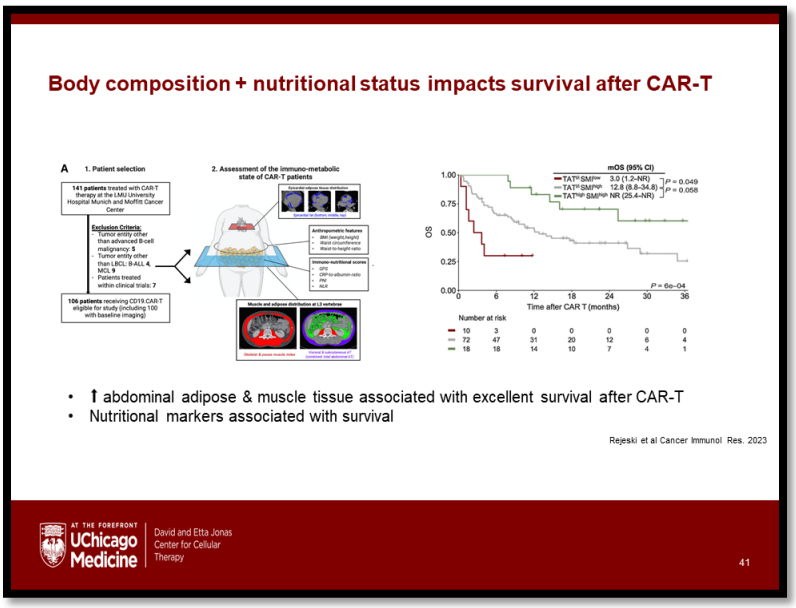


And then to look at survival. So again, this is another survival curve. What we can see here is that patients who received a recommendation of yes, had better survival than patients who were recommended defer or no. So, patients recommended yes, about half of them lived at least three years after CAR T therapy versus less than nine months in patients recommended defer or no. And again, the primary reason for this difference was toxicity and safety. So, it's not that we saw that the patients who were considered fit were less likely to relapse after CAR T. It was more so that we were actually very accurate in figuring out who would suffer major complications of CAR T therapy and specifically lethal complications. So, it is not something that happens often with CAR T, but it absolutely can happen. And the patients who passed away early or passed away of a treatment related complication were patients who had been recommended against.

So again, this is not to say that frailty, even on its own should be a barrier, but it definitely sort of gives you an idea of what to lookout for in the future and it's something to take into consideration when making the decision. And one thing I want to point out is that it wasn't that there was any single test on the geriatric assessment that was predictive of these outcomes. Meaning, as I showed you, we do many different types of tests physical tests, cognitive tests, et cetera. And on their own, no test had very significant predictive value of survival or any of these types of outcomes. But it was the treatment recommendation, which comes from gathering all of that data and basically putting that whole picture together. That sort of final treatment recommendation was the thing that did bring prognostic value.

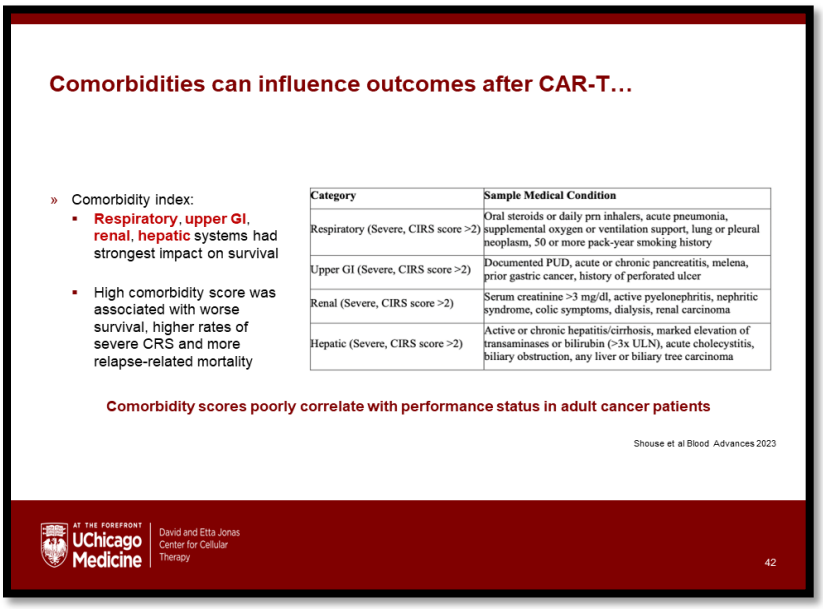


So, this is data from a different study that had a group of, I think 50 or so patients with large cell lymphoma who were undergoing CAR T. And they also did a type of frailty assessment on patients. And so, they classified patients who received CAR T based on whether they were fit at the time that they received CAR T or whether they classified more as frail. And so, what I want to show here is something that they saw that was different between those two groups. So, one thing that's important when we give a patient CAR T cells is that we want to see in those first couple of weeks that the CAR T cells are expanding, meaning that they are multiplying and proliferating. And the more that they expand, which is shown here based on this peak, the higher that expansion, the more likely the patient is to have a durable and sustained response to CAR T therapy. And what you can see is that for some reason in the frail patients, that expansion did not happen as well as it happened in patients who were fit. And that ultimately translated into, again, a survival difference between the two groups. And so, I thought that this was just very interesting and gave a little bit of a biological basis of maybe why we see differences in outcomes between fit and frail patients.



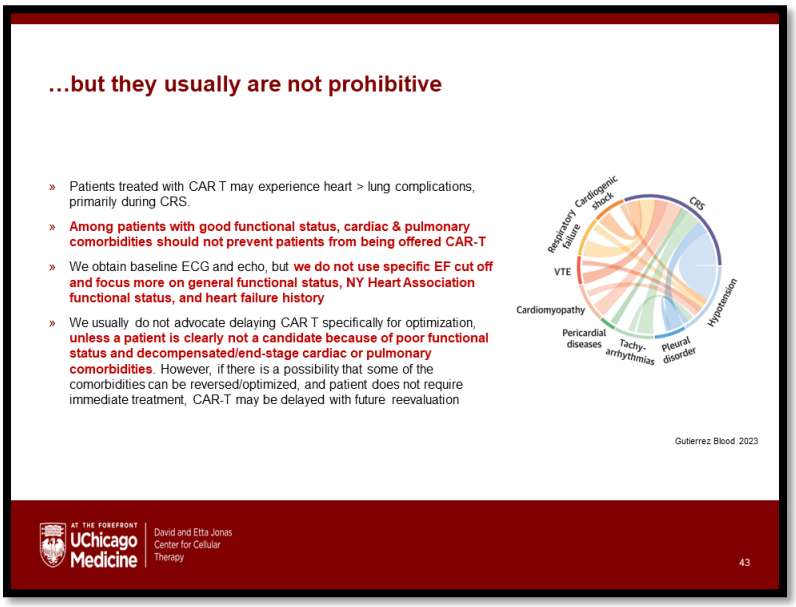
And then, this is one study that looked at the impact of body composition and nutrition in patients with large cell lymphoma who underwent CAR T therapy. So again, one of the

important domains of health is nutrition. And so, this was a study that used the baseline CT scans that patients undergo prior to CAR T therapy. And they took basically like a slice of the CT scan, as you can see here. And by looking at the CT scan, you can actually measure how much muscle tissue and how much fat tissue a patient has. And they wanted to see whether this body composition differences between patients, if this had anything to do with how patients did. And again, this really stratified outcomes very nicely. So patients who had the best outcomes and the best survival were patients who had a lot of muscle mass and a lot of fat tissue. Patients who really did not benefit very much from CAR T were patients who did not have… patients who had low muscle mass and low-fat tissue. And then here, somewhere in the middle is patients who had high muscle mass but not a lot of fat tissue. So again, there are just a lot of ways of predicting who will and will not benefit from CAR T that are a lot more informative than just chronological age. So these are host factors like nutrition, like frailty, et cetera.



And then I'm just going to talk quickly about comorbidities because this is of course a common question. Patients want to know if some of their medical issues may preclude them from getting CAR T. So, one thing I will say is that comorbidities definitely can influence outcomes after CAR T therapy. But in general, we really do our best to not let these comorbidities be prohibitive if they don't have to be. So, to just show you an example of how these things matter to outcomes, this was a study that looked at, I think, 600 or so patients, again with large cell lymphoma who had received CAR T, and they looked to see what other medical problems the patients had. And they found that specifically, these four medical issues with the respiratory status or lung function, upper GI problems, things like ulcers or pancreatitis, kidney issues and liver, issues had the strongest impact on survival after CAR T, and people who had more of these issues suffered worse survival, but they also suffered more toxicity, such as the cytokine release syndrome, and also were more likely to die of relapse after CAR T.

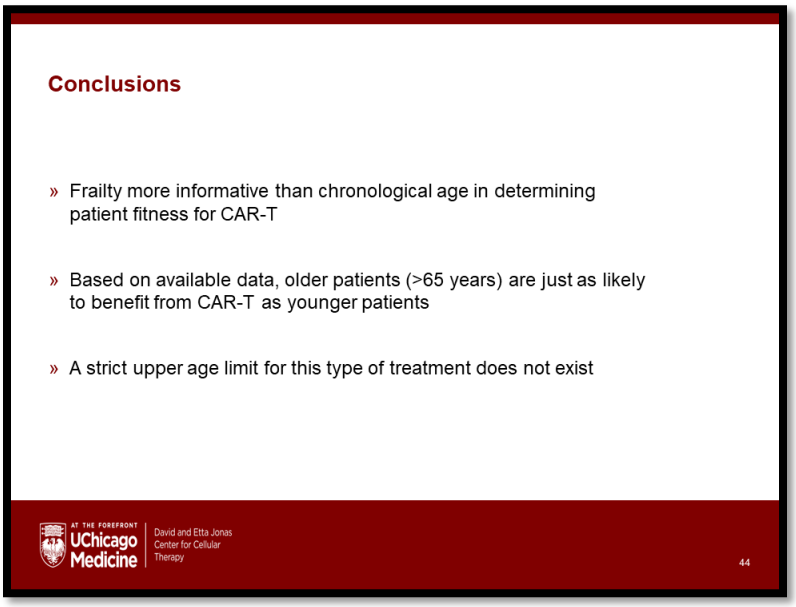
One thing that's important to know is that comorbidity scores do not correlate well with performance status in cancer patients. Meaning that, again, you can have a lot of medical issues and still be fit, or you can have very few medical issues and be frail. And so, understanding these things sort of separate of each other really helps give you the most information, again to make the best decision for the patient.



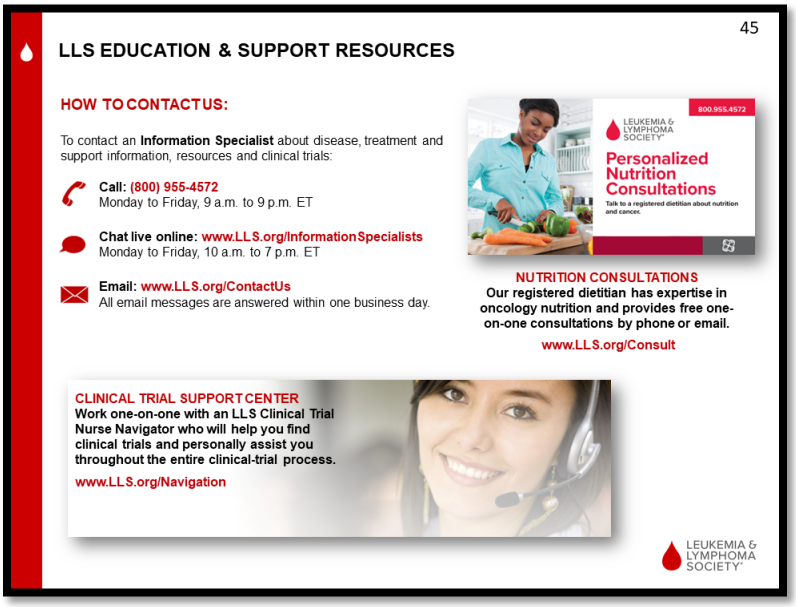
So this is a lot of text, but I feel like really summarizes our philosophy and our approach to how we handle comorbidities and CAR T patients. And I pulled this from a review article that was written by a cardiologist, a lung doctor, and a cell therapy doctor talking about how they think about comorbidity and CAR T patients.

And so, they wrote here so among patients with good functional status, heart and lung issues in general should not prevent patients from being offered CAR T. So, before CAR T, we do testing on things like cardiac status. We'll do an ultrasound of the heart, we'll do an echocardiogram, but in general, we're not really using any number or any kind of finding as a specific cut off to prevent someone from going on to CAR T. The only things that do really concern us is if a patient is very decompensated, meaning that they have heart failure that is just not well controlled, they're having many flares of congestive heart failure. Or again, functional status, meaning that these comorbidities are really impacting how a patient is able to function day to day and really impacting their fitness and frailty. And then they end the article by saying that they usually don't advocate delaying CAR T specifically for optimization unless, a patient is clearly not a candidate because of poor functional status or decompensated or end stage medical issues.

However, if there is not such a time crunch, and if you're offered the luxury of time, then there are certain things that maybe we would pick up on testing that would ideally be optimized before the patient moves onto CAR T in order to make the process safer. So, what this figure shows here, basically, is some of the specifically heart and lung issues patients might run into through the CAR T process that often are very closely related with the CRS complication. So, when patients experience CRS and a lot of inflammation, there can be changes to blood pressure, to heart function, there can be abnormal heart rhythms that develop, et cetera. And so often the way that I look at this is that if I see someone that I think is at a higher risk for these complications based on medical issues, then again, I'm not looking to get in the way of their treatment. But I do think about how can we make the treatment safer? How can we monitor them more closely, et cetera.



So, in summary, frailty is a lot more informative in chronological age in determining patient fitness for CAR T. As we saw based on available data, older patients are just as likely to benefit from CAR T as younger patients. And then finally, there is really no strict upper age limit for this type of treatment. And yeah, really, everyone, despite age, can benefit from this and can receive it safely. Thank you.



Elissa Baldwin: Thank you, Dr. Riedell and Dr. Nawas, for your very informative presentations. It is now time for the question and answer portion of our program. These are the most commonly asked questions that have come into our LLS, Information Specialists and online community. We'll get started.

So several questions have come in regarding CAR T being available for CML, CLL and AML. Do we see it becoming available for those diagnoses? And if not, why?

Dr. Mariam Nawas: So, I can speak a little bit to the AML, CML, sort of Myeloid diseases question. So, it is definitely something of interest. There are a lot of trials and a lot of work in

creating CAR Ts that are safe and effective for, especially acute myeloid leukemia. One of the barriers is that in order to create CAR T cells, what you're looking to do is you have to find a target that is present on the cancer cells so that those CAR T cells can recognize the cancer cells. But that target ideally, should not be present anywhere else because you want to be able to direct the CAR T cells to the cancer and not create toxicities and side effects where the CAR T cells might harm normal tissue.

And the issue with AML is that a lot of those markers on the leukemia blasts and on leukemic stem cells that cause leukemia to come back again in patients are also found on normal stem cells, normal hematopoietic tissue. And so, a lot of the issues so far have been really toxicity issues. Where we can certainly target a leukemia blast, but unfortunately, it's very hard to distinguish between normal blasts and normal hematopoietic tissue that is supposed to then be able to make healthy blood. And so there's a few other barriers, but I would say that's kind of the biggest one is figuring out what is the right target, and hopefully within the next few years we'll see something that's very effective and very safe in that space.

Dr Peter Riedell: And I can comment a little bit on CLL. So CLL is one of the other lymphoid malignancies, and actually we don't currently have CAR T-cell therapy that's approved for CLL, although there is certainly a good degree of experience using CAR T-cell therapy in that disease. Right now, it's still in the realm of clinical trials and in clinical development. But actually, recently we had a paper that was published demonstrating really encouraging results with the use of CAR T-cell therapy in that disease. And so I think this is something that we'll probably see more clinical trials utilizing CAR T in CLL and potentially in the years to come, an FDA approved product for that disease.

For next question, is CAR T-cell therapy better than stem cell transplantation?

Dr Peter Riedell: That's a great question. I'll maybe jump in. So, stem cell transplantation is a type of therapy that we use for different types of hematologic malignancies and that can come in a couple of different flavors. But for both multiple myeloma and for non-Hodgkin lymphoma, we're commonly using an autologous stem cell transplant. We have done some clinical trials which have evaluated and really compared the use of a typical treatment, which would be salvage chemotherapy and a stem cell transplant versus CAR T-cell therapy in a subtype of non-Hodgkin lymphoma known as diffuse large B cell lymphoma. And specifically, that question was evaluated in a population of patients that had more aggressive disease that either failed to initially respond to therapy or came back within a year after concluding initial therapy. And in that specific subset of patients, actually CAR T-cell therapy was found to be superior and actually offered an overall survival benefit, meaning that more patients live longer with CART - therapy than stem cell transplant. But that's in a specific clinical scenario and that's not something that we can necessarily apply across the board to all malignancy types and all subsets of hematologic malignancy.

So, there are now ongoing clinical trials actually in multiple myeloma to actually ask that same question of, can we replace stem cell transplant with CAR T-cell therapy? That's not data that we have currently, but we certainly are really eager to understand the answer to that question and to see if we can potentially replace stem cell transplant by CAR T-cell therapy in a range of blood cancers.

Elissa Baldwin: For our next question, we had a patient write in and say they have had both rituximab and CAR T-cell therapy. They still have no detectable B cells one year after CAR T. Will their body ever recover the ability to manufacture B cells?

Dr Peter Riedell: That's a really great question and one that I think historically we have shown that patients do largely recover their B cells, but sometimes it can take some time. A lot of it really depends on sometimes what their prior treatment was along with actually what type of CAR T-cell treatment they may have received. Some of our CAR T-cell therapies lead to persistence of the CAR T cells for sometimes months and even up to years. And in those instances, often we can have continued low B cell counts, but that's not always the case for every single patient. And we know that we don't need detectable CAR T cells forever to continue to remain in remission. And so, I would venture to say that in that particular situation, that likely there will be at a point in time B cell recovery in that patient.

Elissa Baldwin: Patients are asking will there be a CAR T option in the future that uses less chemotherapy and has less side effects, but maintains good efficacy.

Dr. Peter Riedell: So, certainly that's something that we're also actively exploring right now. The way that CAR T-cell therapy is provided is patients receive typically a three-day treatment with a cocktail of two chemotherapy agents followed a couple of days later by the CAR T-cell infusion. Although there's many efforts that are looking at how to more safely provide CART-cell therapy using less intensive chemotherapy backbones in order to potentially reduce toxicity. But one of the other important things that we're also doing is using different ways of manufacturing CAR T cells and even CAR T cells which sort of expand and do their activity, their job in a more effective but also safer manner. And that's something that we've been actively exploring in really a number of disease types that's still really in its infancy right now, but hopefully with more time and more experience, we should be able to bring some of those safer but similarly effective therapies to patients.

Elissa Baldwin: That's great. Now you discussed side effects in your presentation, but a lot of patients would like to know if side effects can appear several months to years after CAR T-cell therapy, or are they always just immediate?

Dr. Peter Riedell: That's a great question. When we've been doing CAR T-cell therapy, certainly in the clinical trials and now in the commercial setting, we do have a good understanding of the onset of toxicity and what toxicity is to expect certainly within the first 30 days and even in the first six months or a year now. But more long-term toxicities are something that's a little bit more unknown, and that's going to take really following patients for a lot longer in order to understand what potential toxicities may surface with continuing to follow patients.

The FDA does require that we follow patients for 15 years after their CAR T-cell infusion in order to really evaluate and to more clearly answer that question. And so, I think we do need more time to really fully understand the implications of CAR T-cell therapy long term. But one of the things that we have been seeing is slightly increased risk of infectious complications in patients that undergo CAR T-therapy. And that's kind of also played in with how we approach patients in terms of putting them on prophylactic antibiotics, or other antimicrobials, and giving them other medications such as intravenous immunoglobulins in order to potentially reduce their risk or to treat infectious complications.

Elissa Baldwin: A patient asked if their age may play a role in the severity of cytokine release syndrome and or neurotoxicity.

Dr. Mariam Nawas: So, there have been a lot of analyses looking to answer these questions. In general, it seems like toxicities are not worse in older patients, with maybe the exception of

neurotoxicity. Does seem like it can be a little bit more prevalent or a little bit more severe in older patients. So again, overall sort of survival expected to be the same response the same, but that particular side effect maybe a little bit more prevalent in older patients.

Elissa Baldwin: And our final question of the program patient wrote in and said they don't have any family or friends who could be their caregiver and they can't afford to pay a private caregiver. Are they still able to get CAR T-cell therapy?

Dr. Mariam Nawas: So, different institutions have different guidelines and requirements. At our institution, we do require a caregiver, at least in those initial weeks. And like Dr. Riedell said, it really starts during the time that they're in the hospital. One of the biggest advantages to having a caregiver there during the hospital stay is that, again, neurotoxicity, which seems to be a little bit more common in older patients, is something that can often be better or earlier detected by a family member or a friend than it can by us. So, during the course of the hospital stay, the patient will do testing a couple of times a day or a few times a day to make sure that they're answering questions appropriately, that there doesn't seem to be evidence of confusion. But, if you have a family member there or friend there who knows you much better than your care team knows you on a personal level, they could probably detect a little bit earlier than us. If there are behavioral changes or something to indicate that maybe that neurotoxicity is happening. And also, we're not able to be in the room 24/7. And so, for someone else to be there monitoring the patient more closely, that really helps us pick that particular complication up earlier. And the earlier we treat it often the easier it is to treat.

And then kind of more in the long term, when patients are discharged, there are certain restrictions like you can't drive in those first couple of weeks. So, there are a lot of things in which having a caregiver is advantageous. I would encourage this particular patient to speak with their care team, with a social worker. There may be a way of sort of patching together a care team. It doesn't have to just be one person the whole time, so there may be ways to make it work, but I do think a caregiver is really important.

Elissa Baldwin: A very special thank you to Dr. Peter Riedell and Dr. Mariam Nawas for sharing their expertise with us and their continued dedication to cancer patients. If we were not able to answer any questions you may have had during this program, please contact an Information Specialist at the Leukemia & Lymphoma Society at 1 (800) 955-4572 from 09:00 a.m. to 09:00 p.m. eastern time, or reach us at LLS.org/ContactUs.

CAR T-Cell Therapy In Patients Of Advanced Age
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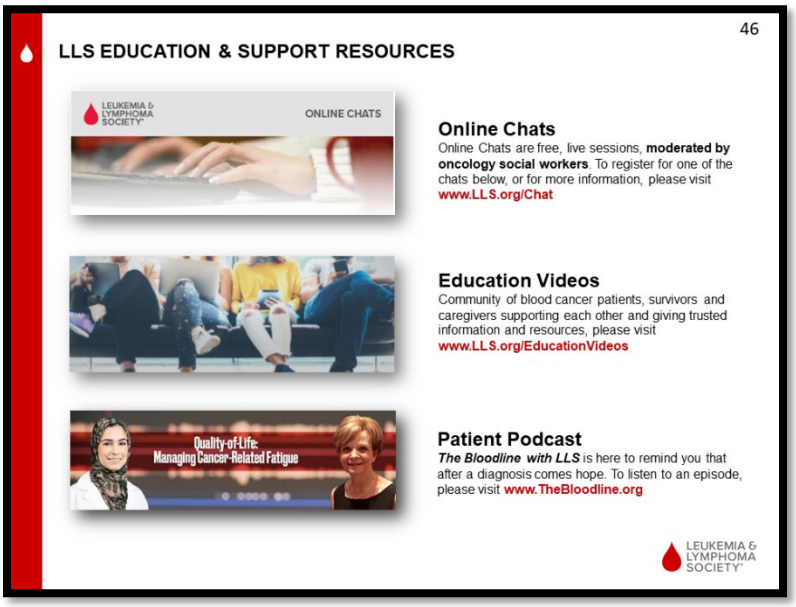

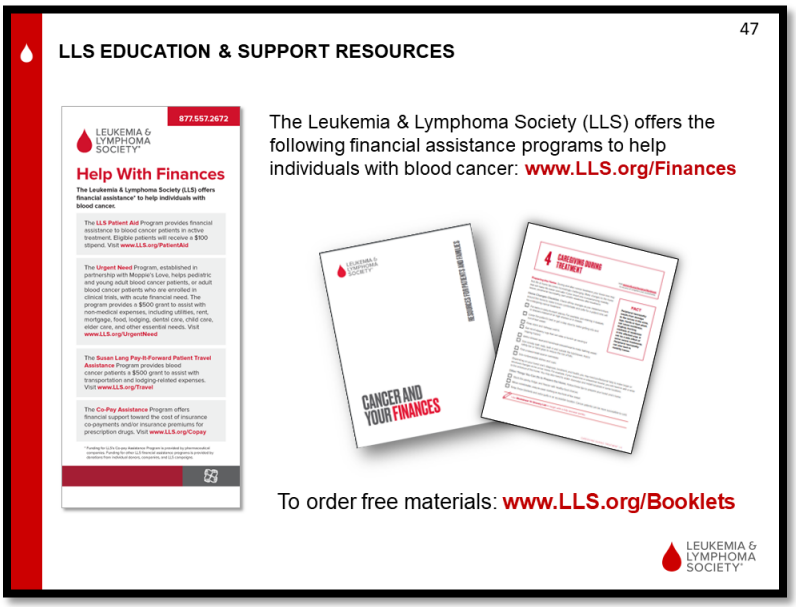

Please also take a moment to view the resources the LLS has available to you online chats, educational videos, podcasts, financial resources, booklets, and more.

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We also encourage you to please complete the program evaluation, which can be found at LLS.org/CARTeval or by scanning the QR code on your screen with your smartphone. Completing the evaluation will help us to continue to provide the engaging content and informative programming that would benefit you the most.

Dr. Riedell and Dr. Nawas thank you again for volunteering your time with us today, and on behalf of the Leukemia & Lymphoma Society, thank you all for watching this program. Take good care.