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Sue Hogan: Thank you Dr. Nimer. Again, welcome officially. My name is Sue Hogan. I'm Operating Director of the MDS Foundation. We're located in Yardville, New Jersey, but we have patient forums throughout the country and internationally. Debra Murray is also here. You might have spoken to her on the phone or through E-mail. She's our patient coordinator. She's outside signing you in.

We have a very full agenda today and I'd like to thank Dr. Nimer and the Sylvester Comprehensive Cancer Center for inviting us, for providing the space and the team of experts that are going to present. I hope you'll have found the information very helpful. In addition, we have another great guest speaker. Her name is Sandra Madden. She's going to talk about from the caregiver perspective right after lunch and I'm not sure whether you recall Sandra was married to Dave Madden. You might recall him better as Rueben Kincaid from "The Partridge Family." He was the manager on that show, the TV series, and Sandra was his caretaker throughout his illness and she was graciously offered to give her perspective and her experience in caretaking. We're honored to have you with us, Sandra. Thank you.

Really quick also, today happens to be Rare Disease Day for 2015 and if you would like right before lunch we had these flyers outside and to commemorate the day, we'd like to take a picture, a photo, of each of you holding up the picture. We're going to blast it through an E-blast, have it on our foundation website just to show that we're aware and this is, of course, Myelodysplastic Syndrome is a rare disease. So again, thank you. Just a quick warm welcome to you all and lunch will be… we're pretty much on schedule. Lunch will be at 12:00. We'll take it from there and if you have any questions about the foundation itself, I'll be around throughout the day. I'll be happy to answer them and I'll turn the program over now to Dr. Watts, our first presenter. Thank you again.

(Applause)

Justin M. Watts, MD: Thanks. Good morning Thanks for being here. It's a pleasure to see you all. I recognize some of you. So, I'm Justin Watts. I'm a physician, a hematologist, here at Sylvester. I had trained at Sloan Kettering and recently came down to join Dr. Nimer here at Sylvester and I see exclusively MDS and leukemia patients and my research is focused on

clinical research developing new drug therapies for MDS on clinical trials working with Dr. Nimer and others here at Sylvester.

So, my assignment was to talk to you guys about what is MDS and then Dr. Nimer is going to speak some more on treatment and then I'm happy to answer more questions about treatment and clinical trials at the end of his talk, but first I'm going to talk about what is MDS and so MDS is Myelodysplastic Syndrome. Myelo means marrow or bone marrow and dysplasia means that the cells are abnormal, broken or fragmented and that's what the word means. I'm going to review the definition a little bit more with you and talk about the epidemiology of MDS, how common is it, etc., what are the common symptoms, how do patients present, how do we diagnose MDS and what is the prognosis and then we'll talk more about treatment after that, Dr. Nimer's talk and then I can answer more questions about clinical trials specifically and then Dr. Pereira is going to speak to you as well about bone marrow transplantation for MDS later this morning.

So I wanted to start with a case and I made this up and some of this is doctor speak, but I think you guys can all follow it I'm sure and this is kind of how we process information and data about a patient and how a patient will commonly present. So, a 70 year old man who has a history of high blood pressure and some heart disease, but is otherwise healthy and fit and asymptomatic and has controlled medical problems then develops slowly progressive fatigue and shortness of breath over several months and because his symptoms are getting worse he sees his primary care doctor who does a blood count and his hemoglobin is 7.2. So, he's very anemic and a year ago his blood counts were normal. The white blood cell count are also a little bit low, but not as low as the hemoglobin and he has routine testing done for B12, folate, other things and there's no explanation for the anemia and then that prompts him to see a hematologist and he has a bone marrow aspirate and biopsy which shows MDS with something called multilineage dysplasia and six percent blast cells and we'll talk more about that in a minute. Chromosome analysis shows that he has something called Trisomy 8 or an extra copy of chromosome 8. You should have two chromosomes in each cell. He has three in his leukemia cells and he also has a mutation in a single gene called TET2 on mutation analysis which is something we do now as well and with all that information he comes back to his hematologist to discuss treatment options and we'll come back to the case at the end, but that's commonly how a patient will present.

So, what is MDS and Dr. Nimer was talking about this earlier. It's been a little slippery to define and to understand for some patients. It is a cancer. It's a bone marrow or blood cancer. It's a lower grade or more indolent blood cancer than leukemia, than acute leukemia. Sometimes it's called a preleukemia and that's not really correct because it is a blood cancer and it's not technically a leukemia. It can be thought of maybe a pre-acute leukemia because it can turn into AML which is what we call leukemia, acute myelo leukemia but it is a blood cancer, but it's not acute leukemia. Some patients can transform into leukemia. Most don't, but that is a risk and definitionally what MDS is it's low blood counts in the circulating or peripheral blood. One more of the blood counts are low, white cells, red cells, platelets and they would look at the bone marrow under a microscope, we see dysplasia and that means the bone marrow cells are

abnormally appearing. They're broken and fragmented and sometimes there's too many of them. Usually, there is too many of them, but they're not leukemia cells. There may be a small number of leukemia cells anywhere from none up to 19 percent. Usually, it's one percent, five percent, 10 percent, in that range. You can see if you get closer to 20 percent, 20 percent is when we call it acute leukemia and it fluxes between 19 and 21 percent. Nothing really. So, it becomes semantics once you get close to AML, but many patients will stay with a low blast count for the duration of their disease and most patients don't transform to acute leukemia. You can still have problems with very low blood counts even without it becoming acute leukemia and it can still require treatment, of course, which many of you know. Usually, we'll find a genetic change or a mutation in the MDS cells as well. Usually, more than one and that can be very important data to know both for a different prognosis and for potential treatment options down the line and we'll talk more about that and the outcome of having MDS is hearing many of your stories you can see that it can be very variable. Some patients do very well and don't need treatment. Some patient need treatment right away and this can depend on a number of different risk factors that we can detect at your initial diagnosis and more on that in a minute.

So, MDS overall is a rare cancer, but it's one of the more common blood problems or blood cancers in older adults and there are at least 10,000 cases a year in the US. There may be many more as older patients with unexplained anemia, for example, especially if they're very old and they go undiagnosed because they never have a bone marrow biopsy and if the MDS is mild, we never know they have it and blood counts decrease with age. We know that as well. Not all those patients will have MDS, but some probably do. So, the precise incidence is not known, but at least 10,000 new cases a year in the US. It's the disease of older adults. Younger patients can certainly get it, but the average age is about 65 to 70 years old and there's a slight male predominance and it can be associated and this is important with chemotherapy or radiation received for a prior cancer and it's important for your doctor to know that and that can be your risk factor as well.

So, common symptoms of MDS. So, the symptoms of MDS are almost always related to low blood counts and in MDS one or all the blood counts can be low and many patients won't have any symptoms depending on the severity of the decrease in blood counts, but there are three types of blood cells and if one of them is low, you're going to have different symptoms based on what that type of cell is. So if your red cells are low and you're anemic, you're going to have symptoms related to decreased oxygen delivery to tissues. Red cells carry oxygen in your body. So, you can have fatigue commonly, shortness of breath, possibly chest pain or dizziness if you're very anemic and that's related to low red blood cells and we can fix that easily with transfusions, but then we have to find something else to fix it long term when a patient has MDS. If the white blood cell count is low, patients are predisposed to infection. Fevers, chills and specific infections also sometimes mouth sores or poor wound healing. Those can all be signs of a very low white blood cell count and if the platelets are low which form blood clots in the blood, if you cut yourself, for example, you can have bleeding problems. So, those are how patients sometimes present with one of those symptoms related to one of those problems with the

blood count, but usually it's fatigue related to anemia. Many patients aren't symptomatic at all and the MDS is just picked up on a routine blood count. The blood counts are low, that prompts a bone marrow biopsy can and we'll find it early.

So, when any patient has unexplained low blood counts, they should have a bone marrow biopsy with a hematologist and we diagnose MDS based on what we see morphologically. That means what we see under the microscope in terms of what the cells look like and there has to be dysplasia present by definition in at least one of the cell lines. A cell line is the cells in the bone marrow that produce one of the three types of cells in the blood, either white cells, red cells or platelets and we see abnormalities in some of the precursor cells to one of those types of blood cell and that defines MDS. Some patients will have an increase in leukemia cells or blast cells, but not all and in many patients most really will find either a chromosome change or a mutation and that can help confirm the diagnosis of MDS if it's subtle or if it's in question. Other diseases are ruled out when you first present. B12 deficiency, different nutritional deficiencies that can mimic MDS, other types of blood cancers or disorders and also rarely some medications can mimic MDS and those things will be reviewed and ruled out by your doctor.

So, I just wanted to show you a few pictures of what these cells look like under the microscope, MDS cells. So, these are red blood cells and a red blood cell making cells in the bone marrow and this is peripheral blood, circulating blood, and you see these red cells are all different shapes and sizes and that's not normal. That's dysplastic. This huge cell down here is a very abnormal megaloblastic it's called, red cell precursor. It's way too big. There's too much cytoplasm around the nucleus. Cells have a nucleus and the cytoplasm around it and these clusters of cells here are red cell precursors that are very abnormal looking and you shouldn't have two nuclei like this and this is a cluster of dysplastic red blood cell making cells in the bone marrow and this little connection here, bridge, you shouldn't see that. So, we see these kind of things and we say this is dysplasia in the red cell lineage in the bone marrow and if there's enough of it that can mean you have MDS and then the same thing with the white cells. This is a neutrophil, the important type of white cell that fights bacteria. There should be granules in it. So, you should see these purple dense little dots and there's none here and that's a dysplastic feature and you can imagine if your white cell count is low and they don't have granules, then you're going to have a hard time fighting infection and these other pictures. There should be multiple lobes through the nucleus and there's just one big one here and two here. These are all abnormal repeaters. We can see just so you have an idea of what we see. These are platelet producing cells in the bone marrow. They're called megakaryocytes and these are way too small and the nucleus is off to the side. Other just kind of changes that we see that are dysplastic that tell us that a patient has MDS. This is what a normal platelet (inaudible 13:36) cell looks like. It's very big. There's multiple nuclei here. There's little platelets budding off here and this is a normal functioning platelet making cell in the marrow and you see these are abnormal ones here. They're much smaller. So, sometimes it's very clear cut. Sometimes it's more subtle. And I wanted to mention this briefly because I talk about chromosome changes and what we mean by that and this is a picture of the 5Q- syndrome, a rare type of MDS, and you should have two copies of each chromosome in your

cells and in MDS there is an acquired abnormality. You're not born with it, but there's an acquired abnormality in your bone marrow stem cells that creates the MDS cells and this is an example of what we see. So, this is… You should have two copies of chromosome 5. This patient has two copies and this is the full copy, but this copy part of it's missing and it's truncated there and so all that genetic material is lost in those MDS cells and some of those genes must be important for preventing cancer or MDS and that material is lost and patients then go onto develop MDS and we can see that under a high powered microscope when we look at the chromosomes.

Q1: How does this (inaudible 14:48)?

Justin M. Watts, MD: We don't know. So, it almost certainly the patient wasn't born with it. Rarely there are inherited MDS syndromes, but at some point in that patient's life there was a genetic change when a stem cell was dividing. It's random. So, there are millions of divisions of your stem cells a day and if that happens enough and you live long enough the chances of something happening randomly, even though small, increase to the point where some patients will get MDS. If this patient had gotten chemotherapy or radiation therapy for prostate cancer or breast cancer, that can increase the risk slightly, but enough to make it more likely that a (inaudible 15:30) like that will occur, but most patients with MDS had have been treated with chemotherapy or radiation and it just happens randomly, but we don't really know.

Q2: So, it's typically a(inaudible 15:42).

Justin M. Watts, MD: It can be.

Q2: As in (inaudible 15:45).

Justin M. Watts, MD: It can be. Possibly. Certain toxins, especially drugs we give to treat other cancers or radiation exposure can predispose patients or increase the risk. I'm not talking about a large increase in risk. It goes .01 percent chance to .1 or 1 percent chance the patient gets MDS, but we treat a lot of patients for breast cancer or prostate cancer and you cure these diseases and then there is some risk down the line that from that treatment MDS will develop later.

Q3: (inaudible 16:21) just by virus like a (inaudible 16:24) virus or…

Justin M. Watts, MD: Yeah.

Q3: … before… either that or the vaccines (inaudible 16:28).

Justin M. Watts, MD: That's a really good question. MDS, no not that we know of. Some of them form as some other blood or bone marrow diseases or cancers can be caused or indicated by viruses, but to our knowledge not MDS. So, there may be a temporal relationship there, but

there's no causality with the shingles or the shingles vaccine and the development of MDS. It's probably just coincidence as far as we know.

Q4: Just going back to that broken (inaudible 16:57), so could that have happened to someone when they were young and it effect the break shows up 40 years later or did it happen sometime recent?

Justin M. Watts, MD: Probably recently. We know that you need, at least for most types of MDS, you need more than one mutation or chromosome change. So, it's possible that some patients may have one change very early and they never had MDS and then 20 years later they acquire a second mutation that tips the balance and the MDS develops and we're still sorting a lot of that out.

Q4: (inaudible 17:31) mutations going on right now while we're sitting here.

Justin M. Watts, MD: Probably and most of them don't take hold because the cell can't survive. Most mutations aren't compatible with the cell surviving at all and if you have the sweet spot where this mutation and the cell can survive it and then grow into a cancer cell that's when we get cancers. Sometimes our immune system can eradicate it early, but if it can't then the cancer will grow out.

So, I don't want to belabor this, but these are the different subtypes of MDS per the most recent WHO classification and the most common type is called RCMD or refractory cytopenia with multilineage dysplasia. That's the most common type, 70 percent of patients. What that means is one or more of the cells is low in the blood and one or really two or more of the cell lines in the marrow are dysplastic appearing. So usually, more than one blood count is low in most patients with MDS. Rarely just one blood count will be low and that's refractory cytopenia, but unilineage dysplasia and there's also one called refractory anemia with ring sideroblasts which is also pretty rare where we see this unique type of cell, the ring sideroblast. These are less common and these are a very low grade usually. This one is also usually low grade because there's no increase in blast cells. The blasts are less than five percent, but depending on the chromosomes, sometimes they can be more aggressive and these are the subtypes of MDS where we see blast cells or leukemia cells, a small number, so we don't call it leukemia, but we see with the RAB1 or RAB1 between five and nine percent and then between 10 and 19 percent is RAB2 and if you hit 20 percent we call it AML. So, these are the ones that have the higher risk of transformation to AML, but you can see it's still not in most patients, about 20 to 40 percent and there are some rarer subtypes as well.

So, we use those classifications to predict prognosis to an extent, but we also have other methods that do it to help us predict prognosis that incorporate a lot of different variables and this is the IPSS score. Some of you may have heard of it. It's the International Prognostic Scoring System score and there's a revised one as well, but they're essentially the same and they take into

account the number of low blood counts, how many blast cells are in the bone marrow and what the chromosomes look like and then we add all those points up and calculate a score and it can be low risk or high risk or intermediate risk. Intermediate is split into 1 and 2 with 2 being closer to high risk and based on these scores, we can predict how a patient might do. Lower risk patients usually live several to many years with MDS and it never effects their lifespan. Higher risk patients without treatment with no treatment we know from older studies from the '80s and '90s that they may only live a few months without treatment and that's on average and there of course outliers and these are population studies and I'll show you some more data on those in a second, but importantly we have new approved drugs that have come out since those studies were done. There's three approved drugs for MDS in the past 10 years or so. Many of you have been on them and then there are newer therapies as well available in clinical trial many of which are targeted therapies that are very exciting and we can talk more about those in a minute and also we have the capability now to do stem cell or bone marrow transplantation in MDS patients when used to we didn't with reduced intensity transplantations and all these things can improve quality of life and survival of MDS patients and we'll talk more about the specific treatments in a few minutes.

I just wanted to show this table so you see what we talk about when we say your IPSS score and we look at three variables – the number of blasts, the chromosomes and the blood counts and then you get a score. We add a numerical score up and you fall into one of these categories and low, Intermediate 1/2 and high risk and these are older data, but it's what we have to work with and you see that even without any treatment, without therapy, lower risk patients can live six years on average. Many live much longer than that. Higher risk patient without treatment behave more like a leukemia and the average survival is not nearly as long, but it definitely unique to each patient and sometimes we're surprised.

One last point I wanted to make. In addition to looking at the chromosomes which contain thousands of genes, we now look at specific gene mutations. One gene and we know that there are some genes that if they're mutated can cause or drive MDS and these are lot of letters and numbers but they mean something to us. These are different genes that are commonly mutated in MDS, TET2 for example, Rdh1 and Rdh2 and the reason these are important is because they can help us predict prognosis, if a patient has normal chromosomes or if we're not clear where they fall into in terms of a risk group. Some lower risk patients behave more aggressively and having these mutations can help us predict if that's going to happen or not and more importantly probably is that some of these mutations are targetable with new drugs. Many of these drugs are pills and they can block the mutant protein and keep it from working or the mutant gene and we have one such drug here, or really two drugs, one that targets IDH1 and one that IDH2. What you're seeing at about five or 10 percent in MDS patients and even more leukemia patients and those drugs are on clinical trial and we have them here and they're showing very promising results, but this is targeted therapy. You have to have the mutation to respond to the drug and we're developing more of these drugs hopefully to eventually target every one of these mutations and the other thing these mutations do is give a better sense of prognosis. Some we know are bad

to have, some are good and some are neutral or unclear and in addition to the IPSS score, the blast, the chromosomes, the blood counts, at specialized centers we're doing these mutation tests which can help further refine and characterize your specific MDS in terms of what mutations you have and can help us get a sense of how it's going to behave and maybe offer open avenues to new treatments on clinical trials.

Q5: How is a mutation (inaudible 24:14) is it part of (inaudible 24:16)?

Justin M. Watts, MD: It can be done on the blood. Usually, we like to do on the bone marrow because it's more accurate and so it's another test we're doing on the bone marrow cells.

So, in conclusion, so MSD is a common blood problem in older adults. It can happen in younger patients, but the median age is around 70 or the average age of getting MDS. It causes low blood counts which depending on the severity can cause no symptoms at all, minor symptoms, require transfusions or in some cases EPO or growth factors and in some cases they're very low can be life threatening. They can transform to AML which is a more aggressive blood cancer, but even by itself MDS can cause significant problems with low blood counts and require treatment and your doctor can predict your prognosis based on different risk factors that are best assessed at initial diagnosis when you're first diagnosed, which we can assess later as well even after treatment, but these numbers are based on averages. So, it's important to remember that and each patient is unique and like you said, we don't always know how someone's going to do, but we can give you a good sense and with newer treatments, the survival and the quality of life with MDS is improving with standard therapies that have been recently approved as well as many promising new therapies being developed on clinical trials and with reduced intensity bone marrow transplantation which can cure MDS and is now available in patients up to age 70 or even older. Here we transplant patients in their early 70s and some centers we transplant patients even in their later 70s depending on their overall fitness, etc.

Q6: I was told that I'm too old for that. The risk is higher. What are the risks?

Justin M. Watts, MD: So, no one is technically too old for a transplant just based on their age, but you have to consider all of the variables. Your age, the type of MDS you have, how much treatment you've had for the MDS already, how low the blood counts are, do you have any other medical problems and you have to put all of that into an algorithm and decide does the potential benefit of a transplant outweigh the risk and the risk of a transplant, Dr. Pereira will talk about more later, sometimes the transplant itself, that first month there is a risk of death with that and we have to factor that in and sometimes there are complications even if a patient is cured. It's something called graft versus host disease. So, we have to kind of weigh the risk and benefits. What are the chances of curing the MDS with a good quality of life and what are the chances of something bad happening from the transplant and then discussing with the patient, sometimes it's a no-brainer, but if it's kind of neck and neck we have to have a conversation with the patient and kind of decide as a group.

Q7: (inaudible 27:29) bone marrow transplant (inaudible 27:31) stem cell bone marrow.

Q6: You said something the chances of being cure (inaudible 27:36)

Justin M. Watts, MD: We don't usually think of it as a curable disease without a transplant, but what does cure really mean because if a patient lives 20 years on Vidaza or on EPO treatment or other treatments and they were 70 when they got MDS and they live until they're 90 or older and die from something else, they may have had a little bit of MDS left, but essentially they're cured in terms of their disease is controlled and it doesn't affect their life, the quality of life is good and it's not the cause of their death, but it may still be there, but transplant can cure MDS in the sense that we can't find any evidence of it even with very sophisticated molecular test looking for mutations left behind. So, transplant is usually thought of as the only truly curative option, but there are many treatments we have that control MDS for a long time and it may be essentially cured for some patients.

Q8: You're saying there's no chronological limitation to… if you are serviced strictly by the VA and you hit 60 you are out of luck.

Stephen D. Nimer, MD: Not being an expert on the medical care provider that the VA… I don't think we can comment. What I'd like to do again, some of you were here before 10:00 and heard that I have a very hard stop. I need to get on a plane. Dr. Watts is going to be here after, so I wanted to give a short presentation, answer a few questions and then leave things to him what we found in these session is the questions virtually are endless and we want to give everyone as much time as possible to answer questions to have things answered only I can't answer them after about 11:02.

So, Dr. Watts and my talk hopefully will be complementary. I was asked to speak about approaches to therapy and this is a bone marrow from a patient with MDS and oftentimes when we show these to physicians even if they're not a hematologist on the left side is the normal and then on the right side is the MDS bone marrow and if you're not a hematologist who's used to looking at these, you can't really tell the difference and that's part of the problem with this disease that the dysplasia means sort of funny looking and what's funny looking depends on who's doing the looking and so that's why sometimes it's a very difficult diagnosis to make in people.

So, what are the treatment options? So, there's three FDA approved drugs – 5-Azacitidine, Decitabine, Lenalidomide. There were all approved between 2004 and 2006. So, in the last nine years there aren't new drugs that have been FDA approved, but there's a number of drugs some of which you may actually be taking that are out there to treat the disease. As Dr. Watts said, really this is not a curable disease without a bone marrow transplant. Our hope is that people will… my assumption is everyone's going to die at some point and hopefully you die with MDS

and not from MDS, but we're not there yet and so the advanced forms of MDS often are the things that take peoples' lives.

So, to deal with anemia and the low platelet count, you can get transfusions. People are transfused sometimes for a decade, harder to get platelets for that long as opposed to red blood cells and if people get a lot of transfusions in particular of red blood cells, there can be a buildup of iron in the body and so it is rare that people have complications from the buildup of iron, but there are drugs available now to prevent that from happening and it's called iron chelation. The body does not have a way to get rid of iron in the body, the excess iron, and so it has to be removed with some kind of a drug and that's what… there're are several out there.

Hematopoietic growth factors. There are drugs… There's a drug called call Eltrombopag which is approved to treat the low platelet count of aplastic anemia. It's been tried in MDS and there's trials of that. There is drugs that are known as Erythropoietin or Procrit or Aranesp and these stimulate the red blood cells and there's drugs like Neupogen and Neulasta that can stimulate the white blood count and for some people these are even combined and patients get two of these. There's no evidence that these are dangerous except for a few situations where if people forget that the patient… the doctor forgets the patient has MDS because the blood counts get much better and ignores the patient when the patient is developing an infection, but short of that these are useful for people with certain types of anemia. They don't correct the disease. They don't make the disease go away, but they make the blood counts much better. The hypomethylating agents change the disease. They treat the underlying cause whatever it may be and there's people whose disease can disappear completely for a while with these agents. Low dose chemotherapy has been used now often for… The FDA when it approves a drug, it wants a comparator. So, once there's a treatment, you can't compare your treatment to no treatment anymore. So, you have to compare your treatment to something and so the drugs are often compared to low doses of chemotherapy. Low doses of chemotherapy are minimally effective, but they are used particular in the UK. They're used more often than in the United States and so these drugs like 5-Azacitdine that have been compared to low dose chemotherapy, the 5-Azacitdine comes out the winner.

Intensive chemotherapy. Before we had these drugs, we used to either wait until people were on the verge of leukemia or we treated them as though they had leukemia with intensive chemotherapy involving a four to five week stay in the hospital and what happened is many of those patients after going through the intensive chemotherapy still had MDS there and so there are situations where that's very important because having MDS and good blood counts is better than having MDS and lousy blood counts, but sometimes it's a lot to go through for a modest improvement.

Marrow and stem cell transplantation. I have some slides in here. I didn't know if you were going to ask a lot of questions about it. I will get to those slides and then there's a huge effort right now to modulate the immune system. For the first time ever we can unleash the immune

system against peoples' cancers. You may have seen this against melanoma and now there's some lung cancer patients and other cancer patients. There are drugs that are being approved to do this. They've not really been tested much against MDS, but they're now beginning to be tested and then investigational agents and there's a variety of them. None of them are almost about to be approved and so they're still quite early.

So, the first thing is does everybody need to be treated with this disease and the answer is no and so we tend to put people at the high risk and low risk disease. High risk can mean either you have very low blood counts, so it's dangerous or you have a high likelihood of developing leukemia and for those people that as soon as they come in to see the doctors we recommend they get on some treatment. There are other people who have low risk disease. Sometimes your platelet counts is 100,000 and that's the only evidence that you have MDS. There's nothing dangerous about a platelet count of 100,000 and so we would just observe people. So, lower risk patients can be either observed or in some situations they will be treated as well and in the intensity of the treatment depends on the risk of having a bad outcome whether it be leukemia or death from low blood counts and so we generally don't treat people with low risk disease with a bone marrow transplant unless there's something compelling about that and every patient is different and then the people with higher risk, they are more commonly treated with transplant than the low risk patient and, again, if you have high risk disease, you rarely get a drug like erythropoietin which the only thing that tends to do is raise your hemoglobin and so if you have very bad diseases that's not enough and so the treatments tend to modulate based on the type of disease and so 5-Azacitidine and Decitabine are referred to as hypomethylating agents and what that means is that the DNA can exist in one of two states. Actually now we know it's five or six states, but either methylated or un-methylated and when the DNA is methylated it changes the configuration of the DNA and in MDS there's too much methylation going on and so these drugs reduce the amount of methylation and that either kills the cells or makes them behave better and so 5-Azacytdine and Decitabine are DNA hypomethylating agents. High intensity chemotherapy, or IC, allogeneic transplants. So although for lymphoma patients whose bone marrow may be normal, they could use their own bone marrow for a transplant. For MDS patients you need somebody else's bone marrow and then the other treatment options here include watch and wait, immunosuppression, Lenalidomide, Erythropoietin and clinical trials.

So, this is some history. Lou Silverman from Mt. Sinai in New York led the CALGB which stands for the Cancer and Leukemia Group B Trials. This is a trial that enrolled patients all over the United States. It took forever to complete this trial, way longer than they thought because MDS just wasn't on too many peoples' radar screens. There were not so many people studying it and so when a patient came in with MDS, the doctors didn't even talk about a clinical trial. So, this was extremely… This took forever to accrue these patients and what it did is this shows not the survival of the patients, but the time to developing AML and you could see here this is… I don't know how many of you are familiar with these curves. This is generally they're called a survival curve. So, there's time in months here and there's something happening and it's either something good happening or something bad happening. In this case, it's the probability of

remaining event free. No one wants an event. Events are not good and so if you start out everyone's event free and then over time more and more people are having events and so if you look at 24 months down here if you just get supportive care, there's only about 25 percent of the people haven't had a problem. If you get 5-Azacitine it's more like 40 percent of the people haven't had a problem and so this is evidence that the drug is working. Now if you look at the survival here, this is the survival, the probability of being alive. You can see that there's not that much difference here and the reason is is the way the study was designed is if you were getting supportive care. So the patients, the doctors didn't know. You got one or the other and then if you got supportive care and you weren't doing well, the doctor could give you the 5-Azacitidne. So, this isn't 5-Azacitidine versus nothing. This is early 5-Azacitidine versus late 5-Azacitidine and so then they do what's called a landmark analysis. They look at everyone who go the drug before six months and everyone who got the drug after six months and if you do a landmark analysis, it shows that there is a benefit to getting 5-Azacitidine in terms of survival and the FDA looked at this data and in two years later they approved this drug. The Europeans at the same time they looked at this data and they said, "We're not interested in the landmark analysis. That's not the way we do trials here," and they didn't approve it and so what the company did and this is a trial I was involved in this trial, but this was a European study led by Pierre Faneau who's in France, Lou Silverman was involved and they did the study comparing 358 patients. Half received 5-Azacitdine and the other were randomized to receive conventional care and that was without doctor's choice. So, the doctor had to say… they have envelopes. Really, it's not exactly like the Oscars, but for these patients it probably was equally important. So, the doctor had to decide to what the patient would get if they didn't get 5-Azacitidine and they could either just get transfusions and antibiotics and they can get low dose chemotherapy or they could get intensive chemotherapy and so then the 179 that got the Aza were compared to the 179 that didn't and this is what the data looked like. So now, you're looking at the proportion of patients that are surviving and you can see here that the patients who got the Aza did much better than the patients who got any of the other three options and this to us is pretty impressive. It's almost a doubling of the survival time with the 5-Azacitidine and so they then look and see who benefits from 5-Azacitdine. So here I don't know… hopefully, you can see a little bit. What about age? So, this line here is one. So, if you don't derive any benefit then it's one. You're the same if you go the Aza or you didn't get the Aza and so you can see that everything is here on this side of the line with a couple of exceptions and so basically this says favors Azacitidine. So if you're female or male, if you're young or older, depending on the FAB and the IPSS and all these things almost everybody benefits from 5-Azacitidine. This trial was done largely in Europe and so after this trial was done the European agencies approved 5-Azacitidine there. 5-Azacitdine, I don't believe is approved yet in Japan and I think that Decitabine is not approved in China. So, there's still countries in the world where you can't get access to these drugs.

One of the other interesting things is to look at patients who over age 75. One of the things that I'm heavily involved with, heavily involved, is what we call age bias and that is… I have a picture of my college roommate's grandmother on my phone. I went to her 100th birthday party in Boca Raton. I treated her when she was at Sloan Kettering 10 years ago at age 90 for

lymphoma. Most doctors wouldn't have treated her. They would have said, "You know, you're 90. What do you need?" and so the same thing happens with MDS patients. Somebody's 75 years old. The doctors don't even give them the drugs. These drugs are very well tolerated, 5-Azacitidine, Decitabine, Revlimid. To me, I can't say it's a crime, but whatever the non-legal term is to have people who could benefit from these drugs who aren't even treated and so that's one of the things. So, this shows for the people in that trial who are over the age of 75 and there were 87 patients here and so the patients who got Azacitidine did so much better than the others. So, there's no reason not to treat people over age 75. Then there are people who were right on the verge of leukemia. They also did better with 5-Azacitidine and so these two drugs, Azacitidine and Decitabine, are also now used to treat people with leukemia if it's not a very aggressive form of leukemia. So, people with smoldering leukemia are also getting these drugs with benefit.

You heard about the 5Q- syndrome. The thing about this is that we understand a lot about this disease and so these patients usually aren't given 5-Azacitidine or Decitabine and they're put on Revlimid or Lenalidomide. Based on a trial that was published again in 2006, FDA moved very rapidly to approve this drug in 2006 based on this data and so this drug is approved for treating del 5Q MDS. So all the patients required red blood cell transfusions. Sixty-six percent of the patients no longer needed a transfusion on this drug and so… and the rise in hemoglobin. So, people who get Erythropoietin to call it a response the hemoglobin has to go up one point. So if you go from seven to eight, that's a response. Here the average response in the patients was five grams. So if you started out with a hemoglobin of seven, your hemoglobin goes up to 12 which is extraordinarily meaningful. The responses last two years or more. On average, the responses to that drug in 5Q- are two years and the 5Q-… There are people who have a complete response. Their chromosomal abnormality goes away and… there's at least one of my patients from Sloan Kettering still on this drug. She started 2003. Twelve years. She's been on the drug 12 years and so it's a remarkable drug that works in 5Q-. If you don't have 5Q-, about a quarter of the patients who are red cell transfusion dependent become independent.

Q10: You said something about two years.

Stephen D. Nimer, MD: The average… So, the people with 5Q- who respond, on average their response is two years long and so…

Q10: You can't take it in advance?

Stephen D. Nimer, MD: Well, then people are trying to figure out what happens when you lose the response and so for the most part when you give it again it doesn't work. So, we have to figure out a new strategy for that. 5Q- is considered a low risk MDS and so there are people who have the same chromosome abnormality but their disease is much worse and so here you can see that if you have isolated 5Q-, you have a 67 percent chance of responding, but if you have a 5Q- and multiple other abnormalities the chance of your responding is zero and so when you have

the… This whole thing I was asked whether you need to see a hematologist who knows a lot about MDS. The fact is everything's in the details and so if you don't have the complete story, someone calls you on the phone and they say is 5Q-, you say a 67 percent chance of responding and then later in the conversation they say, "Oh, they also have a chromosome 7 abnormality and chromosome 20 abnormality," and then you'd say, "Oh. Well, if they have three abnormalities this drug's not going to work."

Q11: So, you wouldn't use that drug in that particular case. You would opt for the more advanced…

Stephen D. Nimer, MD: Exactly.

Q11: … and now we're going (inaudible 48:31).

Stephen D. Nimer, MD: Unless the patient failed the drugs that were more likely to work. The way we give drugs tends to be on the percent. So if one drug works 80 percent of the time and another works 20 percent, we'll give the drug that works 80 percent, but there are some patients who may not respond to the first drug who will respond to the second drug and we're trying to figure that out before we have to give the patients the drug, but at the moment we aren't there.

So, what I'm going to do 1) there's an oral version of Vidaza. It seems like it's very effective. The response rate in previously untreated patients is 73 percent. That's about the same as the injections of Azacitidine. If you've received the injections, it seems to work in some people also. Again, the devil's in the details whether these people had not yet responded to the IV form or had actually progressed despite the IV form, but this drug is probably… it works. It's the same drug as you take in the shot form. If the pill is absorbed, it should work as a pill.

What I'm going to do only for the sake of time… Actually, let me go back one slide. So, these drugs are usually given every month, every four… doctors say every four weeks or every month. So, you get 5-Azacitdine let's just say seven days every four weeks and then what happens is we have a patient who's been on the drug for five or six years or eight years and then they say, "Doc, it's Christmas Eve. I don't want to come in. I want to wait an extra week." Things happen. So, how do you advise somebody? How important is it take the drug every four weeks and the answer is nobody knows, but this is some data that I find a bit compelling. The drug works by demethylating your DNA. So, here's where you start out. You take the drug. The methylation goes down and then about 30 days the methylation has gone back up. Now, it's not exactly where it was before, but you could imagine if you wait longer, it's going to be back to where you were and so there is a time when if you wait long enough you're not getting any benefit from the cycle before and so when I start these drugs I give them pretty religiously every four weeks because I think you want to take advantage of each cycle. Then someone's two years out and they say, "My daughter's getting married," and… "Okay. Take another week." I mean, life is

more important than this graph here of hypomethylation of the DNA, but it's important to realize that we don't have these answers.

Decitabine. How many of you have gotten Decitabine? So, Decitabine is less commonly used. If you use it, you get five days… five days a time? Some of the data it can be a little bit more difficult to tolerate because it can lower the blood counts. It tends to work a little faster than 5-Azacitdine. The trials have so far not shown the same thing in terms of survival. So, that we look at these things called p-values. They're probability values and what they tell us is whether the result could have happened by chance and so we like that whatever the result should occur less than five percent by chance. Here although the Decitabine looks better, the possibility that that's just by chance and if you did the study again, it wouldn't see the benefit is 38 percent. So, this doesn't mean that this is better than 8.5 months. It may be the same is 8.5 months and so we often use this drug as a bridge to stem cell transplant because it works very quickly. So people with very high risk disease we try to lower the risk before the transplant and we give this drug. We don't really know whether that works as a strategy, but we think that if patients have better counts going into the transplant they may do better, but we really don't know the answer to that and then who gets induction chemotherapy and it's very rare. Look at these studies – 2001, 2006, 2007 because most people don't get chemotherapy for their disease anymore.

Let me go back to new agents here. There's a lot of new agents and some of them are old agents and new agents. Rigosertib, SGI-110, vosaroxin, Eltrombopag, the ABT. So, there's a lot of things going on. Unfortunately, there's pretty strict criteria and without knowing the best thing is to go to clinicaltrials.gov. Type in MDS and you'll find every MDS trial that's going on in the nation.

Stephen D. Nimer, MD: And what I'm going to do for the sake of time is tell you about this. This is the MDS Foundation. Every other year people come from all over the world. I think the meeting in 2013 which was in Berlin attracted people from 64 different countries and so all the MDS experts in the world get together. So, if you ask us do we talk to each other and do we know what each is doing? The answer is for sure we don't wait till every other year to do that. We talk to each other all the time and so but this is a chance and we have nursing forums and things for patients. This is the first time in a while it's been held in the United States and so it is an opportunity for people to be aware of that.

Okay. Timing of the transplant. Again, I think rather than me lecture you too much. Transplants. It's curative therapy. So, we don't want people… I think someone said that only the creator knows how long we're going to live, but the other thing is nobody knows how long your disease is going to stay stable. So, if you have a curative option for your disease, we don't want people kind of hoping for the best and postponing indefinitely because sometimes the disease suddenly changes and if then you your chance for being cured goes down. So, everyone's disease is different. We can't say it's not applicable to everybody here, but the fact is is that if you have a cure waiting for you, we're much more concerned that you be able to be alive when you're 75

than that you get an extra couple weeks in before your bone marrow transplant. We encourage people to take a vacation, added time, but the fact is that we like to cure people of their disease and so when people have a curative options, we like to make sure that they understand how important it is to be cured.

When you're over 65, the risk of the transplant goes up. So, we say we transplant somebody that's 75 years old, 80 years old and we do, but it's unusual and the upside has to be high because at age 80 if you go through one of these transplants, the chance of you getting back to the same life you had before the transplant is low. It's tough. It takes a lot of energy. One of my patients with leukemia, he sends me a daily E-mail. He is 4 ½ years out from his transplant. He's almost 77 years old. It starts out every day. I know what his blood pressure is, his pulse is, how much time he spent on the exercise machine, but every single day he sends me this thing and he had a rough time. He's alive. He's cured. He's great, but this is not a light undertaking when you're over age 70 or 75 years old and so the modeling is different. So even though it is a curative option that if the chance of being cured and going back to your normal life is three percent, that's… no one should say to you, "Well, look. You got to take this. It's the only chance to be cured," because as Dr. Watts said there are people who are alive either with their disease or their disease is in remission. We may not use the word 'cure,' but if you're feeling fine, that's a great condition to be in.

What else can I say? This is the most important thing. This disease… Every disease is heterogenous, but if you have a low thyroid and you go to see the doctor, the doctor is going to put you on thyroid pills and that will be the same everywhere in the world. You have a low thyroid, they give you thyroid pills and that's the end of the story and you can stay on that forever. Everyone's disease is different. We encourage people to see experts and the presentation is different at the beginning when you see the doctor and the course, what happens after you see the doctor for the first time can be different in every patient, and so doctors have to 1) we have all these scoring systems and stuff. There's nothing like talking to the patient and finding out what the patient wants to do and trying to give the best advice you can.

So, I'm going to stop. I'm going to look at my iPhone just to see 10:59. So, I have… You have me for three more minutes and thank you for your attention. Yes?

Q12: I just want to say, my daughter is 33. (inaudible 58:57)

Stephen D. Nimer, MD: Fifteen years.

Q12: Which she was fine. We are from South America (inaudible 59:07)

Stephen D. Nimer, MD:: So, 1) we assume you have great doctors and as…

Q12: (inaudible 59:19)

Stephen D. Nimer, MD: We're happy to offer our services here if you're in the vicinity or we can recommend you to the MDS Foundation Center of Excellence and MDS is we probably both skip… it's not common in children, but it is seen in children and, again, without knowing the details, but bone marrow plantation in children is much better. We consider children kind of up to age 16 and 17. So, I think in your 20s you're not a child anymore. With these histories, usually people a lot of times still see the pedestrians. Pedestrians like…

Q12: Her last bone marrow shows that one of her chromosomes is (inaudible 1:00:09)

Stephen D. Nimer, MD: Which one?

Q12: I'm trying to think. It's BCL2ITH T (inaudible 1:00:23) 242 (inaudible)

Stephen D. Nimer, MD: Rather than it would take quite some time to go through all that. Maybe during the break we can talk about that. It's not a common thing for MDS. Yes?

Q13: Just a quick question. Is Vidaza considered chemo?

Stephen D. Nimer, MD: Yes.

Q14: You mentioned that your prognosis of when people who have high grade MDS are not treated is only month to month, but what is it for people who are treated?

Stephen D. Nimer, MD: So again, it depends what the treatment is and what the situation is. If you look at the IPSS, there's a range of survivors and so the first IPSS says all those survivors were for patients who were never treated. There were no treatments at the time of the first IPSS. So very recently there's the revised IPSS and the revised IPSS are for people who got some treatment. So if you look at the survival stage by stage it's much better now than it was in the original, but there's a huge range. So, there are patients that says your survival is anywhere between eight months and eight years and so, it's hard to say. I'm going to let Dr. Watts come up to the podium and answer some more questions and hope you enjoy your day.

(Applause)

Justin M. Watts, MD: Go ahead.

Q15: What is your experience when the patients that have MDS with (inaudible 1:02:15)?

Justin M. Watts, MD: She asked about patients with MDS who have fibrosis in the marrow. We see that sometimes. It's relatively uncommon. It's a disease called myelofibrosis where there's a lot of fibrosis in the marrow which there can be some overlap or dysplastic features in

myelofibrosis or you can have MDS. We're excluding MDS, but there is some component of fibrosis. I think if there is... There are newer drugs that we're studying on clinical trials that may be able to reverse fibrosis. Usually, those are reserved for patients who have already had other treatment, but there are some exciting therapies that can maybe effect the fibrosis. Having a transplant with myelofibrosis or MDS with fibrosis is done. It can make it a little more difficult because the fibrosis or scarring may still be there or may be hard to get rid of with the transplant even if you get rid of the MDS cells or the leukemia cells, but it can definitely be done. It may be a little bit more of a difficult transplant, but for… and MDS with fibrosis, the fibrosis is important but the other features of the MDS in terms of the blast cells, the blood counts, your symptoms, the chromosomes, they're still going to be a kind of the driving factor in determining if and when you should have a transplant.

Q16: (inaudible 1:03:53) clinical trials (inaudible)

Justin M. Watts, MD: I don't think so at this time. I think it's still too new. So, standard treatment with Vidaza or something like that followed by a transplant would probably be more appropriate. There are some transplant protocols that may be more tailored to patients with myelofibrosis or fibrosis. That would be on a transplant trial, but I don't think an MDS specific trial prior to a transplant if you're young and you have a transplant option would be… it could be done depending on the details, but I think a standard treatment like Vidaza would probably be more appropriate in that situation and if you needed that other therapy later or didn't respond to the Vidaza or we needed to get the blast cells down a bit or the counts up a bit before the transplant then the trial could be an option, but we can talk about that later if you want.

Q17: What is the difference in terms of what you actually do between a bone marrow transplant and (inaudible 1:04:59) transplant or is it the same thing?

Justin M. Watts, MD: So, it's the same thing. So an allogeneic meaning from a donor transplant, we use stem cells. Usually, we collect those from the blood or the donor. We give them Neulasta or Neupogen shots to stimulate the cells to come out of the marrow and collect them from the blood. Sometimes we'll go into the bone marrow itself and take the stem cells out of the bone marrow itself. The patient has to be under anesthesia for that. So usually, we use stem cells from the circulating blood after we've stimulated the bone marrow. It's the same thing. Stem cell bone marrow transplant, you're given… at least in terms of allogeneic, you're giving a donor's stem cells whether you get it from the blood or from the bone marrow it's the same thing. Was that your question?

Q17: So, a patient would receive the stem cells or the marrow out. Is that a surgical thing?

Justin M. Watts, MD: No, it's like a blood transfusion. So, the patient… The donor donates the cells first either from the blood or from the bone marrow usually from the blood after we've stimulated the bone marrow to release these stem cells into the blood. Then we have the cells.

We can freeze them or we can have them fresh if depending on the timing. The donor gives the cells. The patient meanwhile is admitted to the hospital, given the preparative chemotherapy regimen to get them ready to receive the cells and then the cells are in a bag and they're transfused through a vein, through a line, just like a blood transfusion and then they're circulated in your blood and then over a few days to weeks they engraft in the bone marrow and produce new blood cells and admits the new immune system from the donor cells. So, the cells are given. It's pretty straightforward actually given the cells. It's not a surgical procedure. They're given through an intravenous line like a blood transfusion. Sometimes it's just one bag, sometimes it's more than one bag.

Q17: Okay. Then the patient… What chemo… is that like the Dacogen or…?

Justin M. Watts, MD: So, Dr. Pereira may speak more on this, so the transplant process includes separate from Dacogen, Azacitidine. We may give those drugs before the transplant, but the transplant process includes a high dose of chemotherapy as part of the transplant given first and then a few days later the cells are infused, the donor cells, and then the cells eventually grow back into a new blood system for you and immune system. So, the high dose of chemo given before the transplant is part of the transplant and that's to get rid of any residual MDS and to prepare your body to receive the new cells, so you don't reject those cells. Yes?

Q18: Dr. Watts, could you and also Dr. Nimer are Sloan alumnus so to speak. Are you aware in the New York City area (inaudible 1:08:02) trials that are going on?

Justin M. Watts, MD: At Sloan Kettering a lot of the trials they have there we've opened here because we know them well and we're working on a lot of the same kind of cutting edge drug therapies. Some of the kind of exciting new treatments in MDS and AML 1) are the IDH inhibitors which they have open there and we open here. These are drugs that inhibit a specific mutant enzyme or protein in MDS or leukemia cells that about 10 to 20 percent of patients will have and these are still in phase one trials, but the data we're presented at our big conference called ASH last year in 2014 and they were very exciting, early data. That's one example of the trial they have there and we have here. So I think in terms of clinical trials for MDS and AML, every center is going to have a lot of trials and they're going to have different ones, some are the same ones. In terms of a trial, there's kind of… There are multiple different types. In general, I think the ones that are going to be most successful are ones that are targeted to something specific about your MDS or leukemia like a specific mutation that you have or pathway that's dis-regulated and there's a drug that we know targets that, but if only 20 percent of patients have that mutation, that may be great for them, then what about the other 80 percent. So, another type of trial that we're working on in MDS and leukemia is immunotherapy and immunotherapy approaches which are different than targeting a specific abnormality. That may stimulate your own immune system to attack and eradicate the MDS and they may be a more global approach. There's something called a PD-1 inhibitor and these have been really revolutionized melanoma and other solid tumors and we're studying those now in MDS and leukemia and they have a

study open at Sloan Kettering and we're trying to open one here as well in the next few months using this type of immunotherapy and there are other types of immunotherapy as well using modified T-cells. You may have heard of those to treat different types of leukemia and Sloan Kettering is very involved in that and we're bringing those studies here, too. In terms of specific studies, we can talk afterwards, but Sloan Kettering… There are lot of good centers in New York, but Sloan Kettering is probably where I would go first if you live near there or go back and forth to see exactly what trials they have. Yeah?

Q19: I'm wondering is the only way to catalyze the test, the bone to see what chromosome of the blood (inaudible 1:10:55) were effective. Is it a spinal tap or would you do something else?

Justin M. Watts, MD: No, we can do all those tests from a blood draw.

Q19: Not from a spinal tap.

Justin M. Watts, MD: You mean the bone marrow?

Q19: Yeah.

Justin M. Watts, MD: So, we can do it from the blood. It's better to do it from the bone marrow because we get MDS cells, but we can do it from the blood and usually find something. So if we do it from the blood and we find something, that's great. There's not going to be a false positive. If it's there, it's there, but if we do it from the blood and we don't find a mutation it doesn't mean for sure you don't have one. We have to do a bone marrow to be certain, but if we start with the blood if you've already had a lot of bone marrows or you had problems with them and you don't want another one, we could start with the blood.

Q19: You don't collect at the bone marrow through the spine.

Justin M. Watts, MD: No. You would do it… We usually do it in the hip. So, it's kind of like to the side of the spine. You lay on your belly and we kind go into the big flat bone. Sometimes with leukemias, we'll do spinal tap which is different which is going into the fluid around the spine to see if there's leukemia in there, but that doesn't happen with MDS. So with MDS, you should just be having a bone marrow biopsy. Yeah?

Q20: There was mention about the treatment of infections if you've have MDS making sure (inaudible 1:12:15) what is the difference (inaudible 1:12:18) treating infections if you have MDS versus you don't?

Justin M. Watts, MD: There's no difference per se, but we're much more diligent watching for infections because we know MDS patients are predisposed to them. So if you have MDS and you're neutropenic meaning you have a low white blood cell count and you have a fever, it's not

like if you have a fever and you don't have MDS. So if you have a fever with MDS if your blood counts are low that could be an emergency and you'd have to call your doctor right away and you may be admitted to the hospital for IV antibiotics. If that keeps happening, sometimes we'll put patients on prophylactic oral antibiotics to try to prevent infection. We don't always do that upfront because then you end up on a lot of different medicines that you may not need. So really, we take infections much more seriously, but we don't really treat them differently except more aggressively sometimes when we don't know what… We try to identify the infection, but we're waiting to see what infection it is sometimes we'll be aggressive and admit you to the hospital and give you IV antibiotics to prevent a severe infection from developing, but you wouldn't do it a patient without MDS. Yeah?

Q21: You mentioned (inaudible 1:13:29). My wife is hoping to become a candidate (inaudible 1:13:34)

Justin M. Watts, MD: Yeah. It's more of an anemia directed there.

Q21: Can you explain how it works or (inaudible 1:13:43)?

Justin M. Watts, MD: We don't have that trial here. I don't know exactly how that one works. It's more of an anemia directed therapy to improve the red blood cell count. It may have some effects on the underlying MDS itself, but it's more designed for patients with severe anemia and is not responding to other treatments.

Q21: They've also found that by putting patients on this it does increase the red blood cells (inaudible 1:14:12), but you have to take a lot of it.

Justin M. Watts, MD: Yeah. So yeah…

Q21: (inaudible 1:14:17) it's supposed to be very good for people.

Justin M. Watts, MD: It sounds like if the anemia… So people with MDS, patients with MDS, usually they have one thing that's kind of their main problem whether it's they keep getting infections or they have really bad anemia or their platelets are really low. Sometimes everything's off, but sometimes it's just one thing. So if anemia is your main problem and EPO and other agents haven't worked and you have MDS that is appropriate for a trial like that meaning it's not on the verge to being leukemia then that sounds like it would be a good option.

Q21: Hers is (inaudible 1:14:53) different hospitals are experimenting with (inaudible 1:15:00).

Justin M. Watts, MD: Yeah.

Q21: Is that being done in this area at all?

Justin M. Watts, MD: We don't have that trial here. We have about six or seven or eight trials for MDS and leukemia, but there are hundreds of trials across the major centers in the US and it sounds like it may be a good option for you guys.

Q22: If you go to a clinical trial for (inaudible 1:15:25), do you have a 50 percent chance of getting a placebo rather than the (inaudible 1:15:31)?

Justin M. Watts, MD: So, the trials we're talking about not usually. So, you're talking about a randomized placebo controlled trial. So, for someone with… So, there are different kinds of trials. Phase one and two trials usually aren't randomized and there's no placebo. So everyone gets the drug that we're studying and we're studying safety and we're studying to make sure the drug is well tolerated and we're studying early signs that it's effective. Then the final stage is usually to compare the investigational treatment to something else in a randomized fashion, but in someone with MDS or leukemia unless it's a very early MDS, you can't compare a treatment to nothing because patients need treatment. So, you wouldn't get a placebo. You would get standard of care treatment versus the new treatment. So, no MDS study should you get nothing, but in most of the MDS studies that we're talking about studying novel agents that are in phase one or two trials, earlier phase trials, everyone gets the drug. Phase three trials is sometimes randomized, but you'll get some treatment for the MDS, but it could be Azacitidine which you could get off the trial, but you have a chance of getting randomized to that standard of care drug, Azacitidine. Yeah?

Q23: I'm transfused every two weeks (inaudible 1:16:59) blood and my doctor (inaudible 1:17:04) that the bone marrow is not (inaudible 1:17:07) and how long can I continue that and (inaudible 1:17:13)?

Justin M. Watts, MD: So, red blood cells, we can transfuse indefinitely. There's no limit to how many you can get.

Q23: I have iron…

Justin M. Watts, MD: Iron overload. So iron overload isn't usually a problem in adults with MDS. Iron overload can be a problem in kids who have sickle cell anemia or other inherited anemias because they're getting transfused over decades and when they're 50 they might have a problem with iron overload. So usually unless the patient is very young when they get MDS and usually those patients get a transplant or do something else, iron overload you shouldn't really worry about too much. There are drugs that can bring it down if the iron level is very high, but even with very high iron levels it doesn't usually affect your organs like your heart or your liver unless it's been high for many years, but there is drug called Exjade that's a chelater that can bring it down.

Q23: I've been taking it (inaudible 1:18:20), but it hasn't been bringing it down. It keeps going up. It's (inaudible 1:18:25) now.

Justin M. Watts, MD: So, that's high, but it can be higher. So, I think if you're getting blood every two weeks, that's just a big iron load. I wouldn't worry and the Exjade can't keep up with it and if you increase the dose you might have side effects. I wouldn't worry too much about the iron. It's usually not a problem and it's monitored, but the more important thing is for you to get the blood transfusions. Now if we could minimize the need for blood transfusions somehow by either giving you EPO or Aranesp or…

Q23: I've had them.

Justin M. Watts, MD: And then didn't work yet.

Q23: (inaudible 1:18:59)

Justin M. Watts, MD: So sometimes those drugs stop working with MDS and other treatments like Vidaza…

Q23: I've been on Vidaza only for 10 months and (inaudible 1:19:09+-)

Justin M. Watts, MD: So you're at the point now where it would be an option potentially to consider a clinical trial to reduce the transfusion requirement if you could find something that works well for you or just continuing with the transfusions but only getting them when you really need them and not if you're not symptomatic, wait another few days until you need to be transfused and minimize how many total you're getting.

Q23: I've been told two things (inaudible 1:19:40). I was told not to let it go (inaudible 1:19:49) goes low below eight and (inaudible 1:19:53).

Justin M. Watts, MD: There's no magic number there. Usually, below seven or eight we'll transfuse. If you're not symptomatic with a hemoglobin of 7.5 and we can wait till it's below seven.

Q23: Below seven?

Justin M. Watts, MD: It depends on your symptoms and how quickly it's going down. There's no magic number, but less than seven or eight. So if you're getting so many transfusions that it's cumbersome and you're going all the time we may kind of relax the threshold a bit. In some patients, we'll use seven instead of eight. There's no magic number there. It's more about how quick we think it's going to go down and if you're symptomatic and how you're feeling. If you

don't feel well with a hemoglobin of seven then we'll transfuse you before it gets there, but there's no limit to how many transfusions you can get.

Q23: I've been going to seven.

Justin M. Watts, MD: It depends on all of the details a bit and a conversation with your doctor, but if some patients we use seven as the threshold. Some patients we use eight. Some patients we use nine or 10 if they have heart disease or something and they need a higher hemoglobin. So, it can depend. Yes?

Q24: Would a chemo give you (inaudible 1:21:06) regimen interfere in any way with the chemo?

Justin M. Watts, MD: What was the question?

Q24: Supplements.

Justin M. Watts, MD: It depends on what they are and I think a multivitamin or vitamins are okay in reasonable doses but you want to be careful with some of the supplements because we don't always know what's in them and they may interact with drugs you're getting for the MDS and they can affect the liver sometimes. So, I would just make sure your doctor knows what you're on and make sure you know what's in the drugs that you're getting, but supplements are drugs.

Q25: Is there a diet regimen for someone who has MDS?

Justin M. Watts, MD: Not really. If someone… There's not really any magic diet. If someone's very neutropenic or their white blood cell counts are very low, we advise them not to eat certain kinds of foods like raw foods, sushi, things like that given risk of infection, but there's not… as long as it's a reasonably well balanced diet and you're getting enough calories in and not losing weight and that kind of thing, there's no special diet and a multivitamin is good to be on to make sure you're getting enough B12 and folate and things like that, which you should be getting from your diet, but you don't want to take a multivitamin with iron. Most MDS patients do not need any extra iron because they already have too much iron from getting blood transfusions.

Q26: I heard something about turmeric and ginger.

Justin M. Watts, MD: I don't know anything about that. Sorry. So, we can do more questions later, but I think we have more presentations. I'll be around we can chat.

Feng-Chun Yang, MD: Thank you for sitting here for so long time, but I'm going to switch gears to like the lab research. So, the reason I'm talking about this topic is just to let you know so

what really we can understand more of this disease and identify the new treatment because this disease as you have heard from the previous two doctors is a heterogeneous disease. Response to the treatment are different. So, the reason is because the cause are different. So, it's really case by case and so I'm going to show you what really this means.

So although in the terms of the cell biology for MDS is really well understand. However, the (inaudible 1:24:24) is not well established and for example since 2007 and due to advance in new novel genetic technics being established. So, scientists have been found there are dozen of the new mutation, gene mutations, in the MDS patient and then so those mutations, as you can see, for example, is really covers like 50 patient on this side and then the other 40… up to 45 patient on this side which means like almost every single patient you will have a mutations in the after 2007 new identified the genes, but however what those genes are doing is really under study right now and so I'm going to give you one example. The ASXL1, which this is a gene how we investigate this gene. This, for example, this gene is identified in 2009 and then so… in 2009 December and then our laboratory start this gene models start from 2010 and the reason we pick up this gene to study it is because it's really associates the mutation of the gene. If you have a like a change of the gene, we call this a mutation. It will lead to early death and then so also if you have this gene mutation and you're transformed to leukemia rate is much higher than the non-mutated patient. So which means this gene is a driver gene. However, for this gene molecular level and it's really understanding and so but our research goal is to establish a model to study this one and later I will tell you why we establish a model and then also once we establish the model, we can use the model to study the cellular and the molecular more detailed deep levels mechanism. So, then we can talk about to identify to find the new target, new treatment and then really the goal is really to find a novel treatment for the MDS.

So the first… I'm going to tell you why we choose to use the mouse model is because human cells we have limited like access and then so but mouse because it's really high (inaudible 1:27:35) and then easy to manipulate and also the similarity to human in many ways. For example, the genetics and atomically and physiologically. So, for that reason we pick up to establish a mouse model and then so with the establishing model we can find if it's true can recapitulate the human disease. If so, we will do the molecular study and then so once we identify the new molecular or new target, we can test the new compound in the established model, which we call it's preclinical platform or preclinical model and then so next step is we will validate our finding in a humanized mouse model. So, the reason we call it humanized mouse model is if you transplant human cells into generally mice it will reject. However, if we remove the mouse the killing cells and make it acceptable for the human cells. So, then we can use the in vivo in the body system to find the new… to test a new compound, new drug and then so that's basically what is ongoing in my laboratory.

And then so this is just showing how we establish the model and when we establish model we have to know what the gene look like and then we will make the target… make it mark so to a green fluorescent, the green light so we can follow those cells and try to see are those cells

changed to the diseased just like a human. So for example, this is the mouse with the human ASXL1 like the phenotypes like mouse model is cell is smaller, the mice are smaller and then they survive really short and then so those mice we can see as the Dr. Watt and Dr. Nimer mentioned it's dysplastic feature. So, you have really altered or changed the cell morphology which is similar as we can see in the human. So then we will track each individual mouse to see what disease they can develop and then just like what we're doing in the human, but we will have totally the pathologic of the doctors, everything is working on the animal.

So once we make sure we set up this mouse model and then so the next goal for us is just to see the molecular level what we can find. Why if you have this gene you will suffer the disease and then so to do this one, we will do… we're doing a lot of different levels, experimental study in the laboratory. For example, we have to do like the protein level and to see what's really going on and to put in to the cells and to see if they can occur for the bridge like what has occurred in the patient and what causes and then so one thing I can tell for this last four years, the progress in the laboratory is we identify the protein where it can lead to the bridging. So once we identify that one, the next step we're doing is can we target this protein. Can we make it better? So, the next the step we're doing, but then in the laboratory we have six… actually it's two laboratory collaborative work and six post doc fellow who have PhD or MD doctor or and another two laboratories with another two fellows. So, all this people are extremely focusing on one study. Only four focus on the ASXL1. So, they will look at the protein level, DNA level, RNA level, every single level to pick up a single molecule to see if we can target it and then so, for example, one study is that we know for the patient if they have this mutation the end of the protein it's gone. So, can we make it back? How can we pick it up? For example, there is a novel treatment we called it (inaudible 1:32:46). So the reason we called (inaudible 1:32:49) is for the… generally we have this a full protein. However, if you have the ASXL1 mutation, your protein changed to really tiny bit smaller protein and this protein is really bad. It won't have all your cells function normally. So, that's why you can see the dysplastic feature and the bridging or is really the (inaudible 1:33:17) the dead early. So, then we identified new technique to really allow this become a normal protein. So, what we're doing… the progress right now is in the cells, not in the body, in the cells we can make the small protein become full, normal functioned protein in the cells and the next step what we're doing is that we will establish a new model, actually we already established this new mouse model where it have this short protein and then so we're doing right now is giving the mice the new treatment and then make the protein become full functioning in the body and then we will see if those mice still have the same phenotype. Can we treat it? Can we restore it? So, that's in the laboratory is what we generally do is find a new gene, find a new gene and establish a model and from this model we will test a new like… find a new target, find a new… like the molecule which contribute to the disease and then so we will find a new way to target this molecule and then to make it function normally. So, this is like… it's a manpower in the laboratory is also very extensive too for this one. So as I mentioned earlier, and then so that's the four step and establish a model, identify target, drop testing in the mouse and then next we will validate in the human and then so as I mentioned, the mouse won't accept the human transplanted stem cell and then so but scientists made a way to allow those mice to

receive the human cells. So, what we're doing is we find the human samples like Dr. Watts said and we do the peripheral blood and then found the mutation is ASXL mutation and then from this mutation… mutated patient and we collect the stem cells. We mark them with the fluorescence, the dye, and then so we will inject into the mice and as you can see the mouse become with the human cells and then so what we're doing is after two weeks of the reconstitution of the human cells and we start to treat the mice with a new compound and then so we will follow up how those human cell behave. Can we make it normal? So, that's what we are at the moment and then so but the laboratory research is really the goal is bring the bench work to the bad side to really benefit to all the patient who suffer from this disease and then so that's where the last sentence I wrote is translate our findings into the highly effective or curative therapies for most patient suffering from MDS. The reason I'm saying that most patient because as I mentioned earlier, not everyone has the same reason and then because of that the 20 percent of this MDS patient with ASXL1 mutation, this specific gene mutation, which means if successful it could be benefit to this 20 percent. However, the other people like TET2 at the beginning… I'll go back to the first slide. So as you can see, at the beginning this slide, there's some of the gene also have the similar like a phenomenon. We might be applied with the same strategy to see if we can apply this technique to cure this like phenotypes, the disease.

So, with that I'm… go to the last slide. So as I mentioned, there are two labs are really collectively working on this project and also we have collaborators like Dr. Steve Nimer and Dr. Zelin (inaudible 1:38:25) and the pathologist. So, like that's basically what I want to say to let you know what people are doing in the laboratory. Hopefully, you get some like information about to really understanding a disease to really be able to deliver effective treatment. Not only you have to work in the hospital, but also you have to work in the basic laboratory make it mechanism clear. Okay. Yeah?

Q27: You may have answered this question before I even asked it, but I might have missed it. About how long (inaudible 1:39:05) have some results of where we're (inaudible 1:39:11)

Feng-Chun Yang, MD: So the question is how long will this move from the beginning to deliver it to the clinic patient and then so this molecule identified in 2009 December and we started 2010 January and then so at the moment after this five full years what we got is to the point where we found a way to really make the protein bigger and also to be able to made two mouse model to test if it's okay, but if success, everything moves smoothly and hopefully within two years at least from the preclinic like I said, we will be done and then the next level is to see the trial, clinical phase one clinical trial. The whole process, hopefully, if there is another four or five years, it will be very optimistic. Yes?

Q28: So, is MDS hereditary? You're talking about genes or a gene that goes bad after…

Feng-Chun Yang, MD: So, the question is you are talking about the genes are the criteria or MDS is (inaudible 1:40:44)

Q28: MDS (inaudible 1:40:45) hereditary?

Feng-Chun Yang, MD: Okay. So, because the MDS cause of the MDS is heterogenous like a reason there is some many genes mutations as you can see the first slide I showed, almost every single patient will have this gene mutation, but the genes so far like seems to (inaudible 1:41:11) identified 12 genes and before that reported like around 10 genes also mutation can cause this one. Of course, there's some chemical stuff. There are other reasons, but for this genes not every single mutation genes are the driver gene. So for example, ASXL1, if you have this mutation and it will lead to the like a pure prognosis. So, is that the answer to your question?

Q29: The question is can she get it from her mother?

Feng-Chun Yang, MD: Oh, okay.

Q28: (inaudible 1:41:14) My mother has MDS. Do any of the children… we're talking about genes. Is it hereditary?

Feng-Chun Yang, MD: So for this mutations like some of the genes is not inherited. So, it's acquired later. So because MDS is like occurs in older generation most of them, but for the young people like for ASXL1 gene, it's always acquired. If it's like a born with it has a different disease. Okay.

Q30: Are you working on something for the 80 percent? I understand the need to work on the 20 percent because it's faster (inaudible 1:42:37) is there any work going on for the 80 percent?

Feng-Chun Yang, MD: Yes. So, the question is so ASXL only cover 20 percent of the patient. How about the other 80 percent of the cause of the genes, any one way we're working? Actually so in the United States and actually over the world there are many laboratories working on covered different genes, but one laboratory oftentimes is covered one or two genes.

Thank you.

(Applause)

Dr. Denise Pereira: So first of all, I'd like to thank you all for the opportunity to be here. My name Dr. Denise Pereira. I'm one of the stem cell transplant physicians at Sylvester Cancer Center. I do see some familiar faces here on the audience and it's always good to see our patients attending and I will primarily be talking with you today about the use of stem cell transplant as a methodology of therapy for patients with MDS. Now, the topic is very broad, so I will try to

achieve a couple of things on this next 20 minutes. The first one is to tell you what is the rationale behind the use of stem cell transplant and what subset and why would use on patients with MDS. We also will try to understand a little bit why transplant might or might not work and what are the positive as also the negative consequences of having a stem cell transplant and finally we'll discuss additional therapies that are on the horizon being given as a spinoff of transplant or as a complement to transplant in attempt to prove further the current transplant results. I also like to acknowledge that I had worked with Dr. Komanduri who is named on this slide to put together this slide set.

So, what is stem cell transplant and I thought it was very interesting because some of the questions that I heard Justin Watts taking is actually those are common questions that we hear when we talk about stem cell transplant and how did this whole thing started? Well this whole thing is started believe me or not more than 60 years ago initially as a way to replace a marrow that might have been lost or because the patient has a disease aplastic anemia, but also out of the fear during the Cold War that a nuclear attack might be placed and we would have as a result patients who'd be left without a bone marrow and the thought was could we then replace the marrow and restore normal hematopoiesis which pretty much restore normal blood counts. Now as this was further study, the idea of treating diseases who had their primary niche in the bone marrow came about and the question then became if we had a sick marrow, could we erase that marrow and then substitute with a now healthy marrow and once again reestablish normal blood counts and, indeed, go and cure patients. So, many of the initial studies done with patients with cancer were actually done on acute myeloid leukemia and acute lymphoid leukemia which are diseases of the bone marrow and one thing that became established which is what you see here on the second line is that high dose chemotherapy can indeed cure cancer by wiping out the bone marrow production of the blood cells. I must say also that a lot of the history of the chemotherapy dates back at about the same time, the '50s and '60s. So, we understood that giving chemotherapy could help and, again, the question is what if we give more and as I had mentioned here, you in fact can cure a cancer by doing so, but then the problem you are left with a situation that you have no bone marrow and you are left with a situation that you have no counts, you are left with situation that you have… you become transfusion dependent, a risk of infections and so on and so forth. So, what was found that the infusion of bone marrow cells could indeed do what we're looking for. So, by going to a patient bone marrow, extracting that thick material and then infuse… I should say going to the donor and then infusing a patient, indeed, you could achieve the goal of repopulating that marrow. Now over the years, we found out that we could mobilize, move the cells that normally reside on the bone marrow to the peripheral blood and that's why nowadays you hear this bone marrow transplant versus peripheral blood stem cell transplant. In all, they are equal in a way that what you're looking for is to give stem cells that will eventually repopulate a marrow that is in need, but there are slightly different properties of the cells depending where you gather them. So, the ones on the bone marrow are usually a little more slow growing than the one in the peripheral blood and that's why over the years peripheral blood stem cell transplant have become more and more of a standard of care in this field. Now, the patients that, again, were mostly seen to benefit from this

strategy were patients with high risk and relapsed leukemias and lymphomas and just to establish once again the difference between transplant from your own and from a donor. There are different reasons why you might choose to use one over the others. If you think about it that your marrow is the part that is sick, you really do not want your own bone marrow to (inaudible 1:49:13) attack you. You need a new one, but some other diseases like, for example, lymphoma where you really don't have the marrow involved, but you want the high dose chemotherapy to kill any other cells that might be floating elsewhere. You might even be able to use your own bone marrow to repopulate it after you received this high dose of chemotherapy.

What about patients with MDS? Where does this strategy apply? So first of all, patients with MDS because of the nature of the disease being on the bone marrow, it automatically implies that the kind of transplant that we commonly use is an allogeneic stem cell transplant, again, a transplant from a donor and in fact there's a strategy can be curative and there is nowadays and I'll follow up that we know that anywhere between 30 to 40 percent of the patients will get a transplant for MDS can be cured with this. Having said that though, the treatment is not without significant side effects and short of having a patient who is perceived to be high risk usually we are not offering a chemotherapy followed by a stem cell transplant on patients who have expected good prognosis and why is that? Well, this is because patients with MDS can live many years with an indolent form of the disease and can go about having pretty close a normal life provided they are not within the high risk category. So overall, the patients that are considered for immediate or a transplant within short period of time are patients who have higher risk disease. Those being patients with IPSS Intermediate 2 or above. Having said that because, again, I said to all that one can live many years with the disease, the possibility of the disease changing over time is real and exists and it is, indeed, a consideration to see a stem cell transplant doctor even shortly after diagnosis even if you don't have a high risk disease because at some point in the future this might become an option for you.

Now, you could see here this is a graphic with the total numbers of stem cell transplant that have been performed in the United States. That's from 2011 and nowadays the most common reason that someone will get a transplant is actually multiple myeloma and the kind of transplant that is given to those patients is autologous, but I will ask you to pay attention on the bars of AML, ALL, MDS, CML, aplastic anemia, CLL. You see that what those disease have in common is those are disease that affect the bone marrow. There are four primarily. What you see here is the blue color which is the color for allogeneic stem cell transplant.

What had happened over the last 10 to 15 years? Well, the outcomes have continued to improve and this is true across the board not only for younger, but now older patients. This is also true for patients who have a transplant from siblings, but also for patients who do not have a family donor end up having unrelated donor as a source of stem cells and while you can see that if you look at the orange line which would be the best group of patients, namely the younger patients with a family donor, over the last 15 years we have gone from an average survival (inaudible 1:52:47) that were 65 to now 80 percent, but even on the bottom line, the one with the green

where patients were older who have not had family donors are represented, you can see that over the last 15 years, we have gone for a survival of 40 percent to a survival of 60 percent. What this speaks of is progress, is that we are making strives even though, obviously, we all can recognize here that we still have a long way to go. We do all want these numbers to continue to improve.

Now, I know we start saying to you all about how the thought of transplant came about and how the idea was maybe you can cure patients by giving a lot of chemotherapy killing their disease and giving new cells and that's what we thought for decades on transplant, but as we try to deal with some side effects that comes from transplant, I'm going to say a name, graft versus host, which is basically a rejection, we learned that there is actually much more into transplant than we ever imagined 50 years ago. Indeed, when we get a patient… I shouldn't say a patient. I'm sorry. When we get a donor cells, they are to be infused on the patients, you do get more than the stem cells. What you actually getting along with it is the donor immune system. So in fact when patients get a transplant from a donor, they are not only getting the chemotherapy that will prepare and as Dr. Watts have said, lower the system, but, indeed, also kill the bone marrow to accommodate for the new bone marrow. They are getting the stem cells, indeed, but they are getting the donor immune system along and this can be rather beneficial because over the years we learn that the patient immune system kind of get accommodated with the cells, with the malignant cells and kind of live with it, but the donor immune system will not necessarily recognize those cells as normal and will go and attack the cells. So again, is a dual therapy. You get chemo, yes you do, but in addition you get immunotherapy along and that's why stem cell transplant can, indeed, cure patients when regular chemotherapy might not is because of this combination between chemo and immunotherapy that is provided by the stem cell transplant. Now even more interesting that is when you look the outcomes of the patient base who were their donors? So one would expect and I mention that to you all, but we do need a certain level of agreement between the donor and the patient so the transplant can proceed without a lot of complications. So, the natural thing is to think, hey, who else better than my identical twin to provide you the cells. Well, if you're looking to hear you see that if you use an identical twin as a donor the transplant can go initially well, but the probability of relapse is very significant and this is because you really don't have the immune component when you have an identical twin as your stem cell provider and again the provider of the new immune system and we can, indeed, remove externally the T-cells from the donor to the patients. Again, this was done primarily on the '80s with the hope to control the high incidence of rejection, but what we learn over the years by doing so is by doing the so called T-cell depletion. Again, you increase the probability of relapse. So, what become clear is that there is something about and I'm just going to say this is GVHD… no GVHD, no graft versus host. This is acute, this is chronic and it is both and what become clear is that some level of rejection seems to be associated with a protected effect on the donor… from the donor to the patient and decreasing significantly the odds of relapse. Relapse would being the disease coming back being this disease acute leukemia, MDS, so on and so forth.

So, who are those cells? Who are the cells that does allow this to happen and in humans and actually multiple other animals, those are T-cells. Now, we have a variety of different T-cells. They can do a number of things, but primarily when you get T-cells from a donor to a patient, there are some effects that are negative which are the graft versus host, the rejection part, but there are some cells that will indeed facilitate some positive things from happening. So, the negative things, again, would be when the T-cells from the donor will not recognize some tissue organs on the recipient being just the patient and will literally attack those organs and cause a lot of problems. Most commonly when this happen in acute phase namely within the first three months. This can affect the skin. This can involve the liver and also can go involve the gastrointestinal tract that we have depicted here on this picture, but on the other hand I said and I will reiterate there are some positive things that those T-cells from the donor can do and here you see that those T-cells can actually go and kill some of the tumor cells providing you of effect that as commonly known as graft versus tumor, graft versus leukemia depending on your disease effect and, again, this seems to be very important and is associated with a higher risk of chance of cure for the patients and besides that because those T-cells also are cells that have memory and have been in the past exposed to certain microbial organism like bacteria and virus. By giving the donor T-cells to the recipient you also provide the recipient, the patient, some degree of protection against some infections.

So, what have happened over the last 10 years understanding some of the basics that we just discussed? Well, we have changed the way that we condition the patient to receive the transplant namely we have been able to cut down the amount of chemotherapy that we gave to allow the cells to settle in and we have by doing so given the T-cells more of a function of really eliminate every single last bad cell that might have been left behind by your chemotherapy. As a result of that, we can now transplant patients at a much older age than even when I started. I like to tell the stories to my patients that I'd be on this field since 1997. So, it's about 18 years. When I walked as a fellow to the unit for the first day, the so-called old patients were 50 to 55 years old and that was all. By the time I took my first job, we had patients in their 60s, but the end of the last decade, we had patients up to 70 years old and currently I have a patient right now in our unit that is above 70 and we have quite a few of them there between 60 and 70 years old and, again, this has been facilitated by the fact that we're able to change some of the preparative regiments after we understood that not what was important was not only the key but also the immune component of the transplant. As nowadays, peripheral blood is used more commonly than the bone marrow and the main reason why this happened is if you get peripheral blood, the cells tend to grow faster and by doing so you decrease the time that the patient remain with very low counts. Therefore, that is, again, the most common source of stem cells that we currently use and by, again, putting all those things together you can see that one day 100 day mortality which is a common benchmark for transplant patients have decreased from approximately 25 percent to less than 10 percent nowadays. The other thing that we want to acknowledge is that the National Marrow Donor Program has done an extraordinary job by enrolling potential donors and nowadays we have more than 20 million people worldwide that are on registries and available to provide stem cell to patients in need.

And you can see here is just, again, that will be in parallel with the improvement in results you see there has been a decrease in bone marrow as a source of the stem cells, an increase in use of peripheral blood because as I said the faster recover and hopefully less side effects, but even on patients who are not unfortunately don't come from large families where you would find more likely a sibling or have some rare genes that would be typical, very difficult to type, we have now alternative donor source include and I just will mention very briefly cord blood transplant.

I also will ask you to look into this. I actually love, love this picture which is what had happened over the last 15 years over transplantation in patient's age. If you see here in 2004, there barely any transplant being made… being done on patients that were over the age of 64, but nowadays, let me see if I can get the arrow back, is actually this represents the second highest group where volume of patients that we are currently transplanting. So, it's fascinating to me that in 15 years of this… the landscape have changed that much. Here at Sylvester what we have seen is very similar to the numbers that I have shown is a steady increase in volume and I'm very happy to say that within five years we're able to provide three times as many stem cell transplant procedures to the patients that we used to be even in 2008 a few years ago. Most of our patients as any other institutions are mostly autologous, but you can see that is a steady increasing number of allogeneic stem cell transplantations we are doing here.

So now that we said okay, we're doing better we have to ask ourselves what can we do to cure more patients, be able to transplant more people and really get to the next level? Well, there are a couple things that we think we still can improve upon it and some of them include being a little better in selecting patients and selecting patient by doing the patients who really need to be done, but, indeed, to not do patients that do not need this kind of strong and risky kind of therapy and to that we count with our license, with our leukemia MDS doctors who are fortunately bringing a lot of new drugs to the table. We can also develop better selective suppressive systems of the immune system and by doing so maybe we can get rid of the negative T-cell effect like the graft versus host but on the same token not eliminate the positive one which would be the graft versus leukemia versus MDS versus tumor. Very interested in number three here because it is more and more becoming our reality as we see is to modify the T-cells, the very ones that we said are important component of the immune response to specifically treat a given patient leukemia and lymphoma and we will talk a little bit about this on some clinical trials that are becoming more and more popular in transplantation and then in addition to that in MDS and leukemia patients, we also know that potentially by giving additional therapy after the transplant we might be faced with better outcomes and what more logic than to use a drug that we know can be helpful even before the transplant like, for example, Azacitidine.

So again, this is what we were just were saying can we inhibit this, but at the same time preserve this. So one way of doing that which is very revolutionary and is indeed becoming a reality as we speak is engineering the patient, now not the donor anymore, but the patient T-cells to identify certain proteins and to have them go after that leukemia, lymphoma, MDS cell and in fact this is

now derived a technology that exists to engineer those cells and the name that you'll be hearing I'm sure for years to come is CAR T-cells and those have been, indeed, tested in humans primarily with lymphoid malignancies namely ALL, namely lymphomas, but not yet that much done in myeloid malignancies, AML, myelodysplasia so on and so forth, but we do believe the time will come that this will also be available for myeloid malignancy patients and just a list here that there are a number of companies that are currently studying this in lymphoid malignancy and we are very proud that Sylvester is going to likely be one of only 10 sites in the country that will have the ability to use CAR T for patients with relapse, acute leukemia, lymphoid leukemia specifically and also diffused large B cell lymphoma and we expect those trials to be open by the spring 2015 and hopefully much more to come.

Now, let's talk a little bit about other strategies that we can currently use on patients who have had a transplant tried to decrease the incidence of relapse and I'm naming a drug that you folks have heard about it, Azacitidine is the brand… is not the brand name, is the chemical name for Vidaza. It is a drug as we all know that is used currently for treatment of MDS and can, in fact, be effective in a number of patients. So again, the question becomes if it can be helpful before can it be even further helpful after a transplant with the idea that if you have any little cell this behind that your immune system try… the immune system being the donor immune system is try to fight off can we give an extra help by giving a little bit of chemotherapy.

So, what have we learned about this strategy? Well, we have learned that, indeed, this can be performed and I'm going to give a little background on Azacitidine which is very interesting. This drug actually is known to exist and potentially be helpful since the early '70s, but in fact it took almost two decades to be able to bring this drug for (inaudible 2:08:05) in human studies all the way to the point that it was approved by FDA for the use of MDS. We, again, just want to reinforce that patients with the defense MDS, this drug can be effective in as many as 40 percent of patients and a small group of those can, in fact, achieve a complete response.

So, on trials they have attempt to use Azacitidine on the post-transplant. We're able to define that if you use it in lower dose, it can in fact be safe and well tolerated. It would work as a maintenance therapy after the patient received the allogeneic stem cell transplant and, in fact, it might contribute to further control of the patient MDS or AML and finally, there is also some very interesting data that some of those drugs that work with hypomethylating they can modulate the GVL versus GVH effect. As we had said before, this is something that we have an eye on it understanding that we'd like to promote the graft versus leukemia/MDS, but definitely inhibit the graft versus disease that can happen after a stem cell transplant. So even though this is not a standard of care, it is in fact very promising.

So in summary, I want to tell you all that stem cell transplantation provide evidence that immunotherapy can in fact cure cancer and people are being cured by other therapies including chemotherapy and this include curing MDS and AML. Outcomes have, indeed, improve significantly over the last decade and very much, indeed, over the last 15 years and this is very

important to keep in mind that we have to have a multidisciplinary team that care for those patients. We do a lot, but we would be nothing without our nurses, our pharmacists, our researchers that work alongside with us to provide the best possible care. Future trials in MDS and AML likely will combine transplant of some proposed strategies in attempt to improve further the numbers that we have review early on that slide and then I would like to leave you with a message that Sylvester is in the cutting edge of a lot of those approach. I'm going to stop now and I will take your questions. Thank you.

Q31: How long after post-transplant (inaudible 2:10:47)

Dr. Denise Pereira: Right. So, this is interesting. So, the question is how long does it take for you to feel like you're cured after you have a stem cell transplant? So, I will tell you for myeloid malignancies and MDS is within this group, it's about two years. What we have seen over and over is if the patient has not relapsed that means the disease have not returned within that window of time, it is will be very, very, very unusual that would so. If you ask me if I have seen, yes, I have. How many times over the last five years? One time, two times. So, we do believe that patients are cured if they had the myeloid malignancy namely AML or MDS if they have not relapsed within the first two years post-transplant.

Q32: Once you have identified a donor, how long… what is the process as far as (inaudible 2:11:46)

Dr. Denise Pereira: Donation, right? So it depends who the donor is. So, I'm going to step back a little bit and tell you that not so infrequently patients might think, "Oh, I have this sibling who he's the same blood type," or, "This person would like to donate because has the same blood type." The regular standard blood typing that we do really doesn't work for transplant. The typing for a transplant is a tissue typing and is a way more complex, but that's, again, having minded about the third of the patients will undergo transplant who have a sibling donor that in average take about six to eight weeks to happen because it takes some for us to do what we call clear the donor namely you have to have the patient typing. You have to have the donor typing. If the sibling happen to be a match, you do retype both of them. You want it to be as close to 100 percent sure as possible that this is truly a full match and then once you do that the donor have him or herself to go through a battery of test that does include a full physical, blood work, x-rays and so and so forth and we do so with two main objectives. One is to make sure that is safe for the donor to donate and under certain circumstance, you might choose to use bone marrow, again, is not what we commonly do, but that would require general anesthesia so many that the donor have to go through a very extensive clearance. On the other hand, you also do that because you want to protect the patient from getting anything that the donor might have. So, you don't want to… if you find out along the way that the donor has an infectious disease that can be transmitted through the stem cells like hepatitis, like HIV that donor should not be used and that's why it takes some time and then eventually you need to prepare the donor to donate. So, that's why the time… even on optimal circumstance is no less than six to eight weeks. Now once

you're talking about unrelated donor which is the most common case scenario that we face nowadays, we talk about at least two to three months because you have to understand the way that this works when I have a patient that I want to search for a donor and I know that patient does not have any siblings or the siblings have been typed and they are not found to be a match, I need to go to the registry and request donors that might be compatible. Now, how do we do that? Well, we have and this is true for any major transplant center you have nurses they're primarily trained on donor search and, again, this is all done through computer and you then identify say, I'm going to give a number, five patients, five potential donors. Once you have those potential donors identified, you have to go to the registry and tell the registry that you want to test donor 1, 2, 3, 4 and 5. You do not know where those donors are. You don't know their name. All that you know is their number and then the registry will reach out for the donor center, the center that might be closer to where the might live. It might live in the United States, it can be Australia and ask then that donor to come to the center or have blood draw and that blood is then forward back to us. When it's forward back to us, we have to sequence the donor in a very specific way the same way that the patient was originally sequenced to make sure that we, again, have a true match and that process in itself take time. This is a very laborious test and you want to make sure you get it right. Let's say then I found a donor. Then I have to depending where the patient in the process, estimate when my patient will be ready to get the transplant after he had or she might have had given therapy, after there was an infection complication that the complication is treated and so on and so forth. So, I give a set of possible dates not to the donor, to the National Marrow Donor Program who then goes to the donor again and run those dates by the donor and remember many of those donors are people who have their own life. They go to work, they go to school, they have families. So, they have to build in that time off on their life. So in average, two to three months. Initially when we say people like, "Oh, my God. That long?" but if you think about at that process is actually very easy to understand why does it take such a long time.

Q33: One thing identify the donor, the donor is going through the process by the transplant center. Is it weeks that they have be injected or it's days?

Dr. Denise Pereira: No, it's days and actually it's very interesting because you have really people that their job and we what we call transplant coordinator is to coordinate things so as the patient's undergoing something, the donor is undergoing something else on other side of the world up to a point that they were perfect match. You know, time, and for the donor, a majority of them, again, will be providing stem cell and for stem cell collection you use in average five days of a growth factor called Neupogen, but again, all the things that lead to that because you cannot start Neupogen unless you know you're going to use that donor, that is safe for that donor. So, you need to have the donor clearance and then to have the donor clear, you have to have the donor sing and clear you have to the blood work, the x-ray so on and so forth. So, that's the reason why.

Q33: They all have to be at (inaudible 2:17:24) transplant center.

Dr. Denise Pereira: So what happened there are donor centers they might not transplantations, but they are vested in the ability to do the clearance and the ability to collect the stem cell transplant that in which, again, I don't know if all of you would know, but the cell is assuming this is a patient… I'm sorry, not a patient, a donor that is not local. The process it takes place whatever the donor is. The donor is not transported back to the patient center. The donor has undergo the process where ever the donor is to be closest, again, to try to disturb the least amount of the donor's life as possible and the cells are then transported, not unusually by airlines. So, some of us will go on a given day to get cells, you name it, in California or Germany or other places. There are people who basically their role is to transport the cells.

Q34: They're frozen.

Dr. Denise Pereira: No. Not when you do the allogeneic stem cell transplant and even more if the cells are coming from far because as you can imagine those are young cells and they tend to die easily. So if you cannot transport them right away, even the process of freezing them becomes very challenging. So, there is a high level of coordination that is required. So, as things are happening on one side of the world, the donor is having other things. The other thing that I will tell you all nobody had asked me this yet, but you never admit a patient for a transplant unless the donor has been already clear. So, we never get the patient here and give them chemotherapy waiting for the donor to be clear. We don't do that because in case you can't clear the donor, the patient is left without a bone marrow. So, that's obviously we can't do it, but as I said it really require a very high level of coordination between the donor center, the national program and the patient center also.

Q35: Is there any (inaudible 2:19:40) the age of the donor are younger people and what about male (inaudible 2:19:45).

Dr. Denise Pereira: Yes. Absolutely. So, there is a hierarchy that we follow when we're looking for donors and there are donors that might be more 'desirable' or less 'desirable.' At the end of the day what is desirable is a donor that is 10 out of 10. So, we take almost everything, but in case that we have patients… Sorry, I should say donors multiple different donors you can then become picky. So, what do we use? We know that younger donors tend to be associated with a lesser risk of graft versus host and this is not very meaningful if you're talking about a difference of two or three years. So, a 22 years old is as good as a 25 and as good as a 27, but when you're talking about decades that makes a difference and this has been all very study and is already established. So if you have a donor that's 22 and your next donor up would be 35, you take the 22 years old. The other thing that you do is you try to match the patient and the donor sex. So as a general rule, if the patient is a male, you try to get a male donor to the extent that is possible. Again, there are patients that only will have one possible donor and it is what it is, but on the other hand the other thing interesting is even though if you may be looking first for females, females had had previous pregnancies are associated with higher risk of graft versus host if you use them as a donor. So, there will be times that all things equal a patient is a female, the donor is

a female with three prior pregnancies or you have a male about the same age. You then would take the male and it's very complex. There are many other things that we look. I mean, the biggest thing really is HLA typing. We always will take the higher match, but if you have more than one possible choice then that's when you go through the age, the sex, CMB status, A/B/O and you can go on and on and on.

Q36: (inaudible 2:21:49) how much is the probable outcome of the bone marrow transplant (inaudible 2:21:57)

Dr. Denise Pereira: About 10 percent for each number that you lose, if you will. So when you go from 10 to 10, to 9 to 10, you lose about 10 percent in a way of survival and cure rate.

Q36: At what point do they say you don't have a match?

Dr. Denise Pereira: So as a general rule, once you get anywhere below 9 to 10. So, being 8 to 10, 7 to 10, you don't do it. What you do nowadays is you use what we call alternative donor source which be cord blood or being a haplo transplant which is a whole different ballgame also and we do so because some cells, namely the cells from cord blood are more tolerant and they have… they cause less of a graft versus host in the chronic way. In others in the way of haplo transplant which you actually (inaudible 2:22:55) need is a half of a match usually from a family member. Not the cells, but the chemotherapy that we give to prepare can be manipulated to account for additional tolerance, but those alternative donor transplant. They can be done. We do them here at Sylvester, but they are not our first choice.

Q36: (inaudible 2:23:17) prior to transplant, how much research has been done to show that the end result of reoccurring (inaudible 2:23:27)

Dr. Denise Pereira: This is not settled at all. As you might know, the trial that has been published and I believe was presented ASH, believe two or three years ago comes from Moffitt and the numbers are small, about 20 something patients. So, it's very hard. Very hard to get to a conclusion with such a small sample. On that particular study, there was a suggestion that if you use Vidaza for the time that we're looking for the donor, we said, again, it takes two or three months for this to happen. You might have a benefit, a better outcome, but that in all fairness is too… the decision is not all there yet.

Q37: Is there any way that (inaudible 2:24:15) gets to know who the donor is (inaudible 2:24:17)

Dr. Denise Pereira: Yes. So, what happen is there are different registries have different rules about that. So, the American Registry would not allow you to have any direct contact with the donor for the first year. Some European registry, I want to say the French registry, actually I think is up to two years. So, you have to go to whatever registry would call for the longest. The patients and the donor can exchange messages even during the first year provide that there is no

identifier on the messages. So one thing that my nurse coordinator… an example that my nurse coordinator always uses you cannot say that there is a hurricane coming. I'm in the hospital, there is a hurricane coming. That will somehow allow the donor to get an overall sense where… which region of the country that you might be. That kind of communication will not be allowed, but well wishes and thank notes, those are definitely allowed even prior the first year. So, I have…

Q38: (inaudible 2:25:23) some of the stem cells can be (inaudible 2:25:29) can be saved

Dr. Denise Pereira: I'm sorry.

Q38: The stem cells when they're collecting them, you're getting (inaudible 2:25:38) can be saved in case in the future you have a relapse from the first (inaudible 2:25:44)

Dr. Denise Pereira: Right. So, this is a situation that does exist. The situation is more commonly if you have… much more common if you have an autologous transplant when patients donating for him or herself. This is actually pretty common in multiple myeloma. Now, one thing that we have to bear in mind is the donor being there's a family donor, a related sibling or an unrelated is actually undergoing medical procedures only because of the patient. There is not a medical need or indication for that donor to undergo. So, is a goodwill from the part of the donor and part of this ethically as physicians you cannot put the donor more than what is absolutely necessary to allow your patients to have the treatment that is needed. So, sometimes I have hard questions like since I have… Well, I'm fine. I don't need a transplant right now, but you tell me… which we'll tell possibly that I have a donor on the registry. Can I get the donor cells now and freeze them and then use when I need. The answer is no. That's not possible.

Q38: Is it sometimes excess collected and you have more (inaudible 2:27:01)

Dr. Denise Pereira: So, it used to be a thought that beyond a given dose of cells you actually could be more harm than anything else, but that though has been proved not true and in fact there is not a given cell dose that have been thought to be limited and in fact it looks like the more cells you get the better you do because also you tend to engraft faster. So, it's not our routine here to cap the donor cell dose and it is not our practice here to freeze any cells. Any more questions?

Q39: Yeah I have one. You gone around a very convoluted process of getting to the operating room, but not everybody in here realizes how easy it is to register to become a perspective donor.

Dr. Denise Pereira: Absolutely. I thank you for bringing this up. So, if anyone in the room being a family member who is like to contribute, if you go to Be The Match, just all you need to do is go Be The Match. They will give instructions, send you a swab that you can then put it back on the mail and it will then become a registered donor and you actually takes about… the

whole process take about two months, but that's true. The only thing… The only caveat that we tell patients and their families is if you want to do that please bear in mind that you're not there only for your family member. You are there for others because there's nothing more heartbreaking than knowing there is a donor somewhere in the registry and that person failing to respond because that person only register because they want to be on the registry for their sibling or cousin or so on and so forth. So please, bear this in mind we welcome absolutely the donors who are truthful and have the intention to donate to any and all, but if you are doing this only for one or two given person, it's just… like I said, to be on the other side as we are at a times as physicians is very hard knowing there's a donor out there and that that donor will not respond to our request. Thank you.

Q40: Is there an age limit on that?

Dr. Denise Pereira: So, there's an awesome question because we used to think like there is, but that's not really true and this is a moving target. Eighteen years ago when it started, the age limit was 50 years old. If I had a 52 – 53 oh my God this person is old. How are we going to get through this, but nowadays, I'm not going to tell you we have done someone in their 80s, but the older patient that I have I can remember us doing here it was… for allogeneic. For autologous is even a different ballgame. Autologous 75 – 76. Again, which is not the case for MDS patients, but for MDS patients, we have done patients that's 71 – 72 and currently like we have an AML patient in the unit right now that is 71 years old. Of course… of course, there is a whole array of tests that one have to go through because the numbers that I show you all are based on ideal workup namely when you go and you are transplant candidate, I just don't take your word or my word for it to say okay you can do this. We'll be fine. We have to go through about a very extensive pretesting that will prove to you and to me that you have a pretty decent chance of going through this and walking out of the unit in a chance of being cured. That's basically why we're looking at it. So, that include extensive heart testing, lung testing, kidney testing and there are times when the abnormality that is found is so significant that you will preclude you from safely getting the transplant and under no circumstance we will tell you your risk of doing this is higher than any potential benefit that you can derive. You're better off looking at other forms of therapy.

Q41: I'm just curious. The stem cells that are being transplanted in, do they get then to make sure… they must… to make sure there's nothing wrong with them like they don't have MDS or…

Dr. Denise Pereira: Right. So, the answer is no, but that's the reason why the donor go through an extensive testing. So, when I say the donor testing is performed to protect the donor. So, the donor if he or she is not healthy enough she will not undergo certain procedures, but is also done to protect the patient. So, the patient doesn't acquire a disease and I gave the example of hepatitis/HIV but that is also true for diseases associated with the blood. So for example, if you have a donor and the donor is found to have a low hemoglobin that might be a problem and that

donor is not necessarily going to be clear unless you find something easy to resolve like, for example, does a female that is menstruating and the iron is low and that's the reason why and you correct and if everything get better, okay you have the answer. It might suit you to use that donor, but on the other hand if there is a question, we just do not use the donor. We don't and this is true even within family members. So, that's why anytime we have a patient that is due to receive a transplant that family member, the potential donor is actually examined by a different physician than the patient's own physician because once you have a patient you're obviously vested and you have interest in your patient getting the transplant. So by assigning a different physician to the potential donor, again to your sibling, for example, we get away with this bias that the patient's physician might have.

Q42: After the extensive testing, what do you offer to the patients to improve (inaudible 2:33:15) candidate?

Dr. Denise Pereira: Sure. I would say that that's the reason why people should come to cancer centers. That's why you don't want to go to an isolated place where doctors practice in an isolated way. So, me and Justin, we have multiple patients in common. He will see someone that he might think can benefit. He will call me. He will mail me. He will see me in the hallway and say, "Listen. I like you to see this patient," and then after that not too infrequently we'll talk and we'll say, "Okay. This is the best thing. This is not the best thing." We interact. So what happen is if you find out that the patient is not to benefit from the transplant and you work with your colleagues so they can offer different opportunities this being standard of care or research opportunities to the patient.

Q43: How does the patient know where to find a clinical trial that suits his particular problem?

Dr. Denise Pereira: So, there is a website, the NCI list has entire list of all the clinical trials that are registering in United States and you can search by disease. You can search by how far out the trial… how mature the trial is. So as Dr. Watts was explaining, some of the trials are phase one or two. Those are earlier forms of trials. Other more mature phase three trials. So, you can choose all of this and you can get a list of trials if you go to the site of the NCI.

And I just want to make sure I'm looking here at the time. Because I apologize. I just want to make sure…

?: No problem. You definitely want to get all your questions in (inaudible 2:34:57). We'll have lunch right after this and then move onto the others, but if you could (inaudible 2:35:04) one more question…

Dr. Denise Pereira: You haven't had a question yet, so like I said I'm giving the opportunity to ones that haven't to ask.

Q44: (inaudible 2:35:17)

Dr. Denise Pereira: So, I would say that one of the most difficult things in transplant is timing actually and when do you decide to take the plunge, if you will. Sometimes it's very clear. Sometimes you have someone who comes to you with high risk disease that you know if you don't move first, you will lose the window of opportunity to perform that procedure. Other patients, you know they have been able to live with the disease, whatever the disease might be for such a long time that you don't want to rush the decision and I would say nothing better than follow up to help you on those cases. I do have a patient, just going to give an example, in the unit right now is getting her third transplant. So, she had two transplants for a different disease and over time she evolved into something that we believe is MDS even though we could never prove, but the bottom line is she has what we call a marrow failure state. Her marrow doesn't make cells to sustain safe blood count. On that patient between me and her took us… took us six months to decide. So, those things happen.

Q44: From the same donor?

Dr. Denise Pereira: From the same donor. She happened to have a sibling donor.

Q44: (inaudible 2:36:55)

Dr. Denise Pereira: It doesn't change. If you are… No, it doesn't.

Q44: (inaudible 2:37:04)

Dr. Denise Pereira: No, it doesn't change and we always just to also reiterate something that I didn't say. If possible, you always take siblings over unrelated donor with some exceptions. There are some exceptions. By a general rule, a young sibling is always the preferred donor over an unrelated donor.

Q45: Her sibling just had a child. What would be the advantage had been to him saving the cord?

Dr. Denise Pereira: That actually is a good question. I find it very hard to think for uses of the cord like… I have two kids I didn't save the cord on either of them because I kept thinking, you know, if I want… it happened to be that the disease is leukemia or lymphoma, I want a little bit of graft versus the leukemia or lymphoma. So, the cord from this child is not going to necessarily be helpful and then if it's from the sibling and the sibling was a match then the sibling, hopefully, will be able to donate and then you can use… I don't find it any immediate to use that I can't think of it. Alright. Last one.

Q46: I just want to (inaudible 2:38:28) note that she just made me feel good because today's my (inaudible 2:38:31) my second year of surviving (inaudible 2:38:39)

Dr. Denise Pereira: Congratulations.

Q46: Of MDS…

Dr. Denise Pereira: Happy birthday.

(Applause)

Q46: (inaudible 2:38:49)

Dr. Denise Pereira: Absolutely. Alright. I guess we're going to move on for lunch.