Speakers:
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Audrey Hassan: Good morning, everyone, and welcome to our MDS patient and family forum today. I'm Audrey Hassan, the patient liaison with the Foundation. I think most of you met Janice. Janice was a recent hire at the MDS Foundation. She's actually from Miami. So, we're both happy to be here today and we want to thank you for choosing to spend this Saturday with us. It's an honor and pleasure to have as our guest speakers today Drs. Swords, Xu, Nimer, Komanduri, Nurse MacIntyre and Vanessa Ruiz from Sylvester Cancer Center today. So, without further ado let's get our program started and please join me in welcoming our first guest speaker, Dr. Ronan Swords.

(Applause)

Ronan Swords, MD: Thanks for taking the time out of your Saturday mornings to come and listen to us this morning and it's my great privilege to come and give you an overview about MDS, how we make the diagnosis, some of the common treatments that we use and some of the ways that we're making those treatments more effective. So, you're going to hear throughout the morning from some of our faculty and Dr. Xu is a researcher in the area of MDS and he's pioneering some very exciting work here at Sylvester. Dr. Nimer will talk about the importance of clinical research in this disease and you'll hear later on then from Dr. Komanduri who leads the bone marrow transplant program here. So, we have a particular interest in caring for patients with Myelodysplastic Syndromes and we have a group of very, very talented people in the lab and in the clinic and we have a lot of patients who get diagnosed with disease in our community in South Florida. This tends to be a disease of elderly patients and this tends to be a disease of patients who are older than the age of 60. I won't use the term 'elderly.' I've got in trouble for that term before. I don't like either myself, so apologies and so that gives us an opportunity really to study patients and study new treatments in terms of clinical trials and what I do is I lead the adult leukemia program here at Sylvester and I'm an MD PhD. So, I see patients in the clinic one part of the week and then for the rest of the week I'm mainly involved with research.

So, what I'm tasked with this morning is basically to skate a very big pond as quickly as possible. So, I got 30 minutes to tell you about what it is that we understand by MDS, how we make the diagnosis and the importance of making a correct diagnosis and then some of the treatment options that we commonly think about and some of the clinical research that's ongoing right now and profiling some very exciting new treatments.

So, just to begin with, I mean, what is MDS? MDS is a problem with your bone marrow such that the bone marrow doesn't make blood properly. Now, if you think about the bone marrow as an organ that makes blood cells. In the bone marrow there are lots of different cells and… but the most important cells in the bone marrow are what we call stem cells. So, stem cells in the bone marrow can do one of three things. They can sit there and do nothing, they can make other stem cells or they can divide and mature into adult blood cells – red cells, white cells and platelets and so you've got an early stem cell here that matures and develops as you go from left to right into an adult blood cell here and as we go along the cell changes its shape and size and it looks different as it gets more and more mature. So, you have an early stem cell here and a mature cell here. Now, the problem in Myelodysplastic Syndromes is that in normal bone marrow, this is a regulated process when we go from here to here, but in Myelodysplastic Syndromes that process breaks down so that the stem cell here on the left loses its ability to make enough adult blood cells and the blood cells that they make that don't function properly. So, if a doctor does a blood count that's literally what we do. We count blood cells – red cells, white cells and platelets and the very first thing that goes wrong in patient with MDS is the blood count drops and so when you see a low blood count whether isn't a good explanation otherwise in terms of having a low iron level or a low B12 level we think about a problem with the bone marrow and that will lead in many cases to a bone marrow aspiration and biopsy and we can make a diagnosis of Myelodysplastic Syndrome by seeing funny looking cells affecting mainly myeloid bone marrow cells. So, that's what the name means myelodysplasia. Dysplasia means funny looking and myeloid means that the cells that are particularly affected by the process. So, in myelodysplasia all these cells that emerge from this damaged cell here look funny and they look different and those abnormalities are very, very key in terms of making the diagnosis.

Now, what causes the disease? Well, these stem cells get damaged. The DNA in the cell gets damaged. So, if you think about DNA as to a cell as Windows is to a PC. The DNA will instruct the cell how to behave, how to function, when to divide and where to hang out in the body. Now, if the DNA in a cell gets damaged the cell can change its identity from a normal cell into a cancer cell and that's exactly what happens in patients with myelodysplasia. The genetic damage that occurs in the stem cell means that the cell loses its ability to make a proper adult blood cells and that damage over time can get worse. So, the analogy I use for patients is it's almost analogous to buying a brand new car. So, you buy a brand new car. It will run fine for five years, but if you don't service it regularly you may have problems with the piston, there'll be problems to the gasket and all of a sudden your car is chugging along and it's not behaving like a car anymore. So, the point being that 1) the damage will lead to other damage over time and the disease will get worse and then over time the stem cell actually loses its ability completely to make out blood cells and what it does it makes early immature cells we call blasts or leukemic blasts. So, the goal in everyone who's got Myelodysplastic Syndrome is to protect them from the disease transforming into something more serious.

So, as I mentioned Myelodysplastic Syndromes are more common in patients older than the age of 60. We have some ideas as to why that might the case and in the bone marrow the cells divide

very quickly and sometimes the cells when they divide into two daughter cells can make mistakes and those mistakes can turn into a cancerous cell and the ability of younger patients to be able to repair those mistakes essentially protects them from cells turning cancerous. As patients get older, the cells lose their ability to correct mistakes and those mistakes can accumulate in rapidly dividing cells and that's why we see the disease more commonly in older patients. The cells in the bone marrow divide quickly, they make mistakes. Older patients that don't have the same ability to repair those mistakes and those mistakes get transmitted into a disease that we call Myelodysplastic Syndrome.

Now, sometimes we have an explanation for why patients have MDS, but the vast majority of the time when patients come to the clinic they say I've been healthy all my life. How can I possibly have this disease? It's a surprise to patients when they go to their annual physical to have a blood count and I'm sure you're very familiar with the story to have a blood count and the doctor tell you your blood count is abnormal and it's a surprise to patients because they feel great and they have no symptoms and that's a very common story.

If you go through the history you can't find anything in the history that might link the disease with something in the past. So, for example, we know that there are some patients who get chemotherapy or radiation therapy and that can damage bone marrow stem cells and then over time that damage can manifest itself as a disease and they're what we call therapy related Myelodysplastic Syndromes, but in the vast majority of cases we don't have a good explanation for why the patients have the disease and I end up saying look, we're very good at telling what's wrong with patients. We're very bad at telling them why they got the problem to begin with. So, that's the subject of a lot of research right now, but it's this slide just makes the point that sometimes patients are born with diseases that increase their risk for getting Myelodysplastic Syndromes or patients over time something happens like a course of chemotherapy or some radiation treatment or exposure to industrial chemicals or pesticides that could damage the stem cells such that they no longer function and you get this disease called MDS.

Now, I'm putting this slide up here because this is important. Myelodysplasia can look a lot like other diseases. So, it can look a lot like a disease called aplastic anemia, a myeloproliferative disease, this rare type of leukemia and some autoimmune diseases. There are lots of things both in the bone marrow and outside the bone marrow that can cause the bone marrow cells to look funny and give the appearance of Myelodysplastic Syndrome where that's not the case at all. So, for example, if a patient has infection or takes particular medicines. The size and shape of the red cells and the white cells and platelets in the bone marrow can change and a pathologist who may be less experienced might make a diagnosis of MDS when that's not the case at all. So, the point being you need a really experienced pathologist to be able to make the diagnosis and the key thing in terms of getting the right outcome is to match the right diagnosis with the right treatment and if any of you start with the wrong diagnosis you're immediately behind the eight ball in terms of getting the best possible results. So, it's always worth being at a center where there is expertise on the pathology side and on the clinical side.

So, that leads to the next slide how do we diagnose and classify the disease. So if you understand a little bit about the biology of the disease what causes the disease and the importance of looking down the microscope and seeing cells that look like MDS and you can understand a little bit about what we need to make the diagnosis. So, the very first thing as I mentioned that goes wrong in MDS is the blood count changes and it generally goes down. In the early phases of the disease patients get anemic. So, they don't make enough red cells and then over the course of time the anemia will get worse and then the white cell count might change and the platelet count might change and at that point then the physician gets nervous that there might be something going on and that usually leads to a bone marrow aspiration and biopsy and there's lots that we can learn about the bone marrow in characterizing patients with MDS. So, we can see the abnormal looking cells, but we can also do a test call cytogenetics. So, cytogenetics is a test where we get a direct measurement of the amount of damage that has occurred in stem cells and that measurement gives us information about the diagnosis and it also gives us information, in some cases about prognosis and in other cases about selecting treatments. So, based on this test there are certain treatments we consider for one patient and certain treatments we consider for another based on the abnormalities we discover in the cytogenetics test. These are additional tests as well. There are lots of other reasons as I mentioned why your blood count might be abnormal. The bone marrow needs building blocks to make enough blood cells, for example, B12, iron, folic acid and if these ingredients are low in your blood then the bone marrow doesn't have the building blocks it needs to make sufficient blood cells and the blood count can drift down. So, it's always important to exclude other reasons which are a lot more benign in making the diagnosis and we've had patients come to Sylvester where a diagnosis of myelodysplasia has been made. The patient gets myelodysplasia directed treatment and nothing happens to the blood counts and we discover that, in fact, the problem was iron deficiency anemia to begin with as opposed to myelodysplasia. The patient goes in iron tablets and the blood counts normalized. So, very, very important in making the diagnosis correctly.

Now, these are some of the questions that you might want to ask your physician to get a sense of their experience and their expertise in making a diagnosis and in treating patients with MDS and we're going to cover some of these topics over the course of the next few minutes. Make sure that the physician has categorized the disease. So, like any human disease there are mild forms, there are moderate forms and there are severe forms and it's the patient with the sort of moderate to severe forms, they're the patients that need treatment. Patients with mild disease in some cases don't require any treatment at all and we've ways to prognosticate. There are elements that we looked at in the bone marrow and the blood counts that would allow us to put patients into categories and that gives us a sense of who needs to be treated and who doesn't. So, were cytogenetic tests carried out? Was there an EPO level done? So, many of you are familiar with drugs called Procrit or Aranesp and these are hormones that you get every week or every three weeks that stimulate the marrow to make more red cells and this is a level called the EPO level and that will give a sense of whether or not a priority injection is going to be effective. So, patients with EPO levels less than 500 who've got mild disease, the EPO is more likely to be

effective. It's also important to make sure if you think EPO is going to work that patients have enough iron in their body because remember you're getting the bone marrow to make more red cells. If it doesn't have the ingredients to do that nothing's going to happen. So, iron levels are important and always consider whether or not and this may or may not be appropriate depending on your age and other medical problems, but have patients been considered for a bone marrow transplant? That's really the only curative therapy that we know of today for this disease although having said that I've had patients who have been on non-transplant based treatment for many many years and so it's not fair to say that a bone marrow transplant is the only curative treatment. There are some patients who are alive and disease free for years with non-transplant alternatives, but it is important to consider because it is curative treatment.

Now, this next slide is the way we classify the disease. As I said, you got mild forms, intermediate forms and more severe forms and in the old days, in the 1980s the first classification systems were published and that basically classified disease patients according to how the cells looked and stained under the microscope and so you've got these patients here who got very mild disease and you've got these patients here in the bottom where the disease is a bit more severe.

Yes?

Q1: The classification system the way it was developed (inaudible 17:53) treatment does the classification system (inaudible) may be success along the way the treatments that may affect basically where one would fall in a category?

Ronan Swords, MD: That's a great question. I think you've predicted my next couple of slides. So, the question is this is an old system, we've learned more about the disease. We have more modern diagnosis techniques we use in the clinic. How do those techniques then change the way we classify the disease in 2016 because this classification was published first in the early 1980s and the field clearly has moved on. So, to answer your question we have now incorporated modern diagnostics into assigning prognosis for patients with MDS. So we rely on blood count abnormalities, we rely on how the cells look and stain, but we also incorporate the cytogenic test into the classification system. Now, if you think about MDS as a disease where you've got damaged stem cells or that damage gets worse with time and in the early phase you've got a little bit of damage and mild anemia and that's essentially what we refer to as myelo displeasure syndrome. It's not really Myelodysplastic Syndrome, but patients have to be reminded about the disease because they got to come into their doctor every three to six months and they have to have blood count checks and so on, but really for those patients the problem exists on paper. They don't have any symptoms, they feel great and so on, but once that damage starts it gets worse over time and the anemia gets worse and then other components of the blood count get worse and then start… the patient starts needed to need transfusions. So, red blood cells and platelets and so on and the disease moves on. Now as the disease gets worse the blood counts drift down, you need transfusions, but some of the stem cells are beginning to lose their identity

and they're turning into early leukemia cells and the percentage of early leukemia cells begins to grow in the bone marrow and so this is how we think about prognosis and the key things that are important in assigning prognosis are the percentage of early leukemia cells in the bone marrow. We basically… there's a related leukemia to MDS that you may or may not be familiar with. It's called acute myeloid leukemia and as the MDS begins to get worse the percentage of acute leukemia cells increases and once that percentage goes beyond 20 percent we call that disease acute myeloid leukemia. Ten years ago we used to… you need to have at least 30 percent leukemia cells in the marrow to make the diagnosis of AML. So, really it's just like changing speed limit on the freeway. There's very little difference between a car that's going 69 per hour and a car that's going 71 miles per hour. They're still going pretty quickly and so really the difference between someone who's got MDS with 19 percent blasts and someone who's got 21 percent blasts is just the title of the disease on paper. I just want to make that… put a red flag there because people really get nervous when they hear the term acute myeloid leukemia and then people want and something to happen yesterday because yesterday I had MDS and now I have AML and I'm in more serious trouble when really it's just a very gradual spectrum of the same disease.

So, and percentage blasts or percentage of leukemia cells important. Karyotype abnormality. That sort of direct measurement of the amount of damage, genetic damage, in the stem cells and then cytopenia. Cytopenia is just a fancy word for peripheral blood count abnormalities and so you might imagine a patient who's got 19 percent leukemia cells who needs transfusions all the time who's got very low blood counts and who's got a lot of genetic damage might be more advanced than someone who's just has got mild anemia.

By separating patients into those categories then we can predict how quickly the disease is going to move and which patients need to be treated. So, what we want to know is for everyone who makes… where we make the diagnosis we know that that there are some patients where the problem, as I said, exists on paper and lasts years. Those patients don't need to be treated, but there are other patients and that we know that something the disease is going to transform quickly those are the patients we need to get treatment. Patients are coming in and out of the hospital all the time for blood transfusion support, those patients needs to be treated.

And so what Im showing you here is the difference in survival and the difference in the risk of transformation to acute leukemia based on the categories. So, you'll hear about this system called the IPSS score and you got what's called a low score, an Intermediate 1 score, an Intermediate 2 score and a high score and that's based on looking at these three important parameters and we can calculate a score and put patients into a risk category and that gives us a sense of who needs to be treated and this is what we call risk adapted treatment. Now, the score as you mentioned is evolving all the time as we learn more and more about the disease. So, we know now, of course, that transfusion support is important and has prognostic information for us. That was ignored with the first iteration of the IPSS. The current iteration is the WIPSS and that incorporates transfusion support and as the prognostic systems get better and better we do a better job of

picking out patients that need to be treated and patients that don't. These are model systems and so sometimes the model will say this patient is going to have a bad outcome unless we intervene quickly, but in many cases for those patients they do just fine without treatment and the alternative is also true that the model might say this person has a very low risk disease, but six months later the patient has transformed into a more serious disease. So, the point is with these more accurate model systems we can identify the patients who needed to be treated more effectively. Does that make sense?

Now, so that leads us to a treatment. Now, what are the goals of treatment in patients with Myelodysplastic Syndrome? We want to… ultimately we want to cure as many patients as possible. We know bone marrow transplant is curative. You're going to hear all about the latest developments in bone marrow transplant from our transplant director, Dr. Komanduri, later on in the morning, but a bone marrow transplant isn't appropriate for everyone with this disease and therefore for patients where we don't think about doing a transplant we think about prolonging survival, putting patients into remission, improving blood counts, keeping patients out of hospital for as long as we can and with excellent quality of life. So, they're the key goals for treatment and once for everyone we start to treat one of the most important things that we can do for patients is to protect them from the disease transforming into acute myeloid leukemia and that's a disease that's much more challenging to treat compared to Myelodysplastic Syndrome.

So, you're probably familiar with some of the treatment options. Once we've made the decision to treat patients then the challenges of the available options which is the safest option to put patients into remission and to give them good quality of life to keep them out of hospital or of the available options is it appropriate to think about a bone marrow transplant, something more intensive. So, we have drugs like Azacitidine, we have drugs like Decitabine, we have drugs like Lenalidomide, we have drugs to support the bone marrow and making more blood cells, Procrit, Aranesp and so on. Now, there are certain types of MDS where we think about one treatment over another and I'll just give you an example of how we think about assigning treatment based on what we learned from the diagnosis. So, there is a subset of patients with MDS where the immune system is important, where the immune system is hyper activated and the blood cells of the bone marrow makes… come out into the blood and they get eliminated by the immune system. That's a particular type of MDS with particular types of features and so when we see that type of MDS we think about using some treatment to damp down the immune system and so the patients we think may benefit from this approach are patients with a particular blood test abnormality called a HLA-DR15 abnormality and we look for that and patients who are younger than 60 tend to do better with these types of approaches. There's a particular karyotype of cytogenic abnormality we see and usually patients have lower risk disease by the IPSS and they have a very brief transfusion history if they've been transfused at all. So then we think about a drug called ATG and we think about drugs like Cyclosporine and we think about drugs with steroids and rather than going into the details of these treatments it's… I just want to get the message out there that disabling the immune system for patients with this particular type of MDS is very effective.

Now, here's another example where we might use a particular type of drug for a particular type of disease. This is Lenalidomide or Revlimid. You may have heard about this drug and this is a drug that's very effective for patients with a disease called the 5Q- syndrome. Now, that's a particular type of MDS that tends to be more common in women than men. Interestingly, patients present with high platelet counts as opposed to low platelet counts. The cells when we look at the bone marrow have a very particular appearance and when we do the cytogenic test to measure the genetic damage in the cells, we see a very particular type of damage involving chromosome number five and we know that for those patients who get Lenalidomide which is a pill the patients take daily for three weeks with a break of a week. So, it's three weeks on, one week off, three weeks on, one week off, but that's a very effective treatment for patients with this disease and the vast majority of patients they would get benefit. The blood count will normalize and patients will avoid the need for transfusions. Now, the responses for Lenalidomide can last anywhere from months to years. Lenalidomide does not work as well for patients who have other abnormalities in addition to this particular 5Q problem and what we see in the community for doctors who may not be as experienced or may not see as much MDS as we do as Sylvester is that some patients get this drug for a particular type of MDS, but the drug doesn't work as well for and then for those patients what you end up doing is patients get side effects with a drug that doesn't work as effective as it should.

Now, the most commonly prescribed drugs that we see in… that we use that Myelodysplastic Syndromes are the DNA methyltransferase inhibitors. That's a bit of a mouthful. Azacitidine, but the other name for Azacitidine is Vidaza or Decitabine and the other name for Decitabine is Dacogen. Now, how do these drugs work? So, if you go back to the analogy I used for every cell in your body's got DNA. On the DNA you've got genes and there are 26,000 genes on a DNA. The genes make proteins and the proteins tell the cell what to do. There are genes that are switched on and there are genes that are switched off and it's the genes… it's what genes are on and off at any one time that will dictate what type of cell you are in the body. So, this is something we called gene expression. So, the gene expression, the gene's on and off in the bone marrow stem cell are totally different to the genes that are on and off in a heart cell, a kidney cell or a muscle cell. Even though the DNA in all of those cells is identical, it's what's on and off that will define the function. Now, similarly what's on and off that defines the difference between a normal cell and a cancer cell and we know in patients with Myelodysplastic Syndromes right across the length of the DNA there's a chemical called a methyl group and that… if you imagine a Post-it note. So, you got these Post-it notes that decorate the length of DNA from the start to the finish and those Post-it notes will change the way that genes… in other words the genes that are supposed to be on are off, the genes that are supposed to be off are on and so those changes change the identity of the stem cell and that's how patients get Myelodysplastic Syndrome. So, what do these drugs do? Well, they kind of remove these Post-it notes from the DNA and restore normal gene expression. So, you try and convert the identity of an abnormal cell into a normal cell. So, these damaged myelodysplasia stem cells you coerce them to change their identity into normal blood stem cells so that they do the job of making blood cells properly. Does that make

sense? So, these drugs are not chemotherapy drugs. Some doctors use the term chemotherapy I think more to remind patients that patients with Myelodysplastic Syndromes in over the course of time may end up with a cancer like acute leukemia, but in terms of how they work they don't work like chemotherapy and that's why we can give these drugs as an outpatient. Usually in the case of Vidaza, patients get seven days of treatment with a break of three weeks and we have a week on and three weeks off, a week on and three weeks off and it takes some time for the effect to happen and it usually takes in order to get a fair shake of Vidaza, you need to be on the drug for at least four months which is another important question that if your doctor takes you off the drug after a course or two courses or three courses really you haven't had a fair amount of treatment to be able to say whether the drug is effective or not. Now, about half of the patients that get this drug with Myelodysplastic Syndrome will benefit. Now, benefit means everything from restoring and improving the blood count to the point that you don't need transfusions anymore right up to achieving a normal bone marrow, putting the disease into remission and for the patients where that happens we basically continue treatment and the treatment continues indefinitely until the disease comes back or a bad side effect comes along. I have one or two patients in my clinic where we have a discussion for patients who've been on the drug for several years in terms of what can we do about reducing doses and reducing the frequency of treatment and we really don't have any good data on that because it is the exception of the rule to be sort of four or five, six years on the treatment and my approach has generally been if it's not broken don't fix it and if there are no problems with the treatment if you can get it every four weeks just continue getting it every four weeks, but over the course of time sometimes the blood counts can drift down meaning that you can't get it every four weeks and you sort of space out the doses and that's fine to do also.

So, the reason I'm talking more about Vidaza than Decitabine is because Vidaza is the only treatment other than bone marrow transplants that have been shown to improve survival. So, this is a big clinical trial called the AZA 001 trial and this is a randomized trial meaning lots of patients with Myelodysplastic Syndrome were randomly only assigned to get either Azacitidine or what we thought to be the best therapy at the time and the best therapy was supportive care. It was a drug called low dose Cytarabine and it was chemotherapy and for all the patients that were assigned to get Vidaza they did better in terms of the side effects, the chances of getting into remission and the chances of being alive longer. So, this is a very important drug for us and I'm going to tell you about some of the improvements that we've made with Vidaza as it relates to combining Vidaza with something else to make the Vidaza effect more potent.

I'm putting this slide up here and I think that the MDS Foundation are going to make these slides available to you. I hope they will. This is the www.nccn.org. So, these are the guidelines that physicians follow for what's for standard of care practice in MDS and these guidelines are constantly changing. These guidelines you will get in physician speak and in lay person speak as well. That's a web site that's worth visiting. There's tons of education there.

And what new agents do we have in the horizon? So, we're making huge ground now in developing better treatments for myelodysplasia. Now, there's a website called clinicaltrials.gov. If you're a clinical investigator or if you're running a clinical trial protocol you are obliged by the FDA to register your trial on clinicaltrials.gov. This is a search box here and if I type in myelodysplasia into the search box and I exclude all the studies that have been finished, I get this number here, 394. So, the point here is that there are dozens and dozens and dozens of studies ongoing for patients with MDS and that reflects the huge advances that we've made in the laboratory in terms of our understanding of the disease. So, if you know more about the disease, you're in a better position to design better and more effective drugs and all that knowledge is now being brought to bear in patients through a plethora of clinical trials. Don't forget that patients with Vidaza who are getting Vidaza now at one point in the past were on phase one or early phase clinical trials for Vidaza and we've had a number of success stories for patients where Vidaza has failed who get onto a clinical trial who get back into remission. So, the point here is that there are lots and lots of options for this disease.

Now, I'm not going to go through 394 individual clinical trials. So, I'm going to tell you what I think is exciting. So, we're presenting this study at ASH, the American Society of Hematology. It's the annual trade meeting we have. The major academic meeting on the calendar and it's going to be in San Diego this year. So, we've got 30,000 - 35,000 delegates will attend this meeting from all over the world to hear about the latest development in various diseases within hematology. So, we're presenting at an oral session and this drug called Enasidenib, AG-221. This is what we call a targeted treatment. So, in Myelodysplastic Syndrome we know that there are abnormalities in the cells that change their identity and there's a protein abnormality… there's a protein called the IDH protein that's activated in stem cells that impair the ability of the stem cell to make blood cells properly. If we attack that or hijack that protein with a drug treatment and switch the effect off, the stem cell begins to mature and develop into the adult blood cells it was supposed to be from the beginning. So, this is an example of targeted treatment. Mutations that are unique in the stem cell that the stem cell needs to grow and survive and function and if you switch off those mutations you essentially starve the cells to death.

Yes?

Q2: (inaudible 40:48 – 41:18)

Ronan Swords, MD: Yeah. That's a great question. The question is that say, for example, someone has the 5Q- syndrome who gets Revlimid and Revlimid works great for two – two and a half years and the disease returns. How effective would a treatment like this, for example, be for that population of patients? When we talk about targeted treatment it's a big challenge for us in cancer in general because we know in cancer there are about 40,000 to 50,000 mutations that have now been described. About 500 of these mutations are what are called driver mutations. In other words the causes for cancer, but we only have maybe about 20 or 25 what's called targeted treatment. So, really of 50,000 mutations what you have to do is separate out what the driver

mutations are and what the passengers are. If you got a big bus with 50,000 people whose driving the bus? That's the person you need to go after and that's how we think about developing targeted treatments in cancer. Now, this is an effective drug for the vast majority of patients that have a mutation in this particular protein, not everyone with myelodysplasia will have a mutation in this protein and so the drug will only work if you have the mutation and so this is an oral treatment and the point of this presentation is to get the message out is that if you have this mutation with myelodysplasia and no other therapy has worked that in the majority of cases this oral treatment that you take once or twice a day will work. The patient numbers aren't that big, but this is a trial that because it's working so effectively in a small number of patients we expect that with larger numbers we won't see a huge difference in terms of the efficacy. So, we think this may be a drug that's going to be approved for myelodysplasia very soon.

This is another drug that we're profiling. This is another oral session that we have at ASH and this is some of the work that we're doing here at Sylvester. So, Azacitidine is a very good drug for patients with myelodysplasia in about half of the patients. So, if you've got a good drug what are the ways that you can make a good drug better? Well, you could add something. Now, we've done a lot of work with a drug called Pevonedistat and this is a drug that works very well on its own but in a minority of patients and when we go back into laboratory models of myelodysplasia that Dr. Xu is going to talk about and we combine Azacitidine with this new drug Pevonedistat we get a much more potent effect. So, it's two plus two equals five. The drugs when they're combined are much more effective in MDS than when they are given on their own in mice and so we went into the clinic then and we did this combination study and we were able to over double the response rates when we add this drug to Azacitidine. Now, the challenge is every time you add a drug you may increase the risk of side effects occurring and that's been a challenge with designing combination treatments in myelodysplasia and we think we've solved that problem now because this drug Pevonedistat virtually adds no new side effects. So, what are the side effects of Vidaza you may or may not be familiar with these – constipation, fatigue and low blood counts. When we add this drug we still get the same side effects, but the responses are over doubled. So, this is a study that we're excited about and is now going into a randomized study. So, what we want to do is really decide if this combination is actually better than Vidaza on its own. We randomly assign patients to get the true drugs together versus Vidaza on its own and if the combination comes out on top then the FDA will approve this new drug for the treatment of myelodysplasia.

The last drug that I'll just mention briefly is a drug called Luspatercept and that's a new drug that's based on an understanding that in myelodysplasia stem cells there are proteins that accumulate that prevent the stem cell from making normal adult blood cells and those patients run into problems with anemia and they need blood transfusions all the time. This medicine is designed to get inside the MDS cells and to soak up these proteins essentially. They bind with these proteins, inactivate them and the cells' ability then to make enough adult blood cells returns. And this was a study that was designed for patients who are on the low risk of the spectrum, but who needed blood transfusions all the time and so this is a drug that's given every

three weeks subcutaneously in a way similar to the way Aranesp is given. So, it's almost like Aranesp, but the good thing about it is that when Aranesp and Procrit and drugs like it stop working this drug will work in the majority of patients.

So, I think just to take some questions, maybe I'll stop talking here and but I want to get the message loud and clear that this is a disease where we've made huge improvements in terms of understanding the biology of the disease and in terms of improving the models of the disease in the laboratory. The way we develop drugs for human diseases is that we've got models of the disease in the lab. So, you can give Myelodysplastic Syndromes to mice, you can give leukemias to mice, you can give all sorts of bad things to mice and test new drugs and then move those drugs into the patient. So, if you got a very, very acute model of the human disease in the laboratory if your drug works in that model then there's a good chance it might work in patients. So, we've made some improvements with the MDS models that we have and Dr. Xu will tell you about those, but improving the model systems, improving the understanding of the disease and testing more drugs, I think's, very apparent now when you have nearly 400 clinical trials ongoing for this disease. So, I'm happy to take any questions and thank you for your time and thanks for listening.

Yes?

Q3: I went to (inaudible 48:30) Dr. (inaudible 48:40) at Sylvester and when she was giving me my diagnosis she said I would recommend if you're young enough, healthy enough to just get the stem cell transplant and not introduce any type of therapy and she said it's not something that is emergent but why not go that route? Why introduce and I found that rather confusing. I mean, I don't think that would change your chances or I mean, I didn't really question her because (inaudible 49:19).

Ronan Swords, MD: That's a good question and so if you have Myelodysplastic Syndrome and you're a candidate for a bone marrow transplant if you get treatment before the transplant does that increase your chances of the transplant being more successful or potentially fatal. It is true that if a transplant is being considered for patients with more advanced phase disease. So, if you're a week or two weeks away from getting acute myeloid leukemia then it makes sense for those patients where the disease is moving quickly to give some type of chemotherapy to put the disease into remission so as that at the time of the transplant you're in remission and for those patients it's true that there's a better outcome and that's almost intuitive. If your disease is moving quickly and you have MDS one week and you turn off your stem cell transplant two weeks later but now you have acute myeloid leukemia your transplant isn't going to work as well. Now, for the patients who have low risk disease by IPSS we don't see any advantage for transplanting those patients when the disease is early in its course and for those patients a transplant may do more harm than good. The last thing you want to do and Dr. Komanduri will be answer this in a more knowledgeable way than me, but the last thing you want to do is for a patient with low risk disease who may be alive for three to five years without any therapy you

don't want to transplant those patients if there's a 15 to 20 percent chance that the transplant won't work or worse that the transplant will result in a serious complication, possibly death. The last thing you want to do is cut someone's life short and so we really need to… you pick your battles when it comes to a transplant and it's always an issue of risk and benefit. What is the risk of the disease from not doing the transplant versus the risk of the transplant if you do and so it's all about balancing risk and really it depends on lots of different variables. It depends on how advanced the disease is, it depends on your age, it depends on the availability of a good donor and so on and so where does the chance to avoid the transplant? We'll take that chance first and if the disease moves on and the only curative option is a transplant then it may be more reasonable to do the transplant at that time, but it can be quite challenging because if you're 70 and you've low risk disease and now you're 75 and the disease has moved on you may not be as healthy for the transplant and so it often boils down to a very thoughtful and a discussion with the transplant doctor and with patients and what patients want. Any decision I make with patients is… there has to be an agreement with the doctor and the patient before we decide on any treatment, but our role… the best thing we do for a patient is make sure that they're making an informed decision and that we've all the information we need to be able to make an informed decision and the correct decision.

Q4: Question with referenced to different types of doctors, I guess. We're from the Naples Marco area. Do we work with a general practitioner in our local community or do you have a recommended doctor in your field that's working research with you in that Naples Marco community market or what are some of the procedures? I started out with a general practitioner who was also a cancer doctor and he has me on Revlimid now for about two weeks and the numbers are going down and they were down. They're going further down, but I understand you go down and you get right up, but who follows up on the whole process and maybe some of the other folks here have ideas.

Ronan Swords, MD: That's a good question. I mean, sometimes it's not practical for patients based on geography or largely based on geography to come to Sylvester for regular appointments. What I think patients will often find valuable is if they come to a center like Sylvester who has a lot of expertise both in the diagnosis, management and research of MDS to get the diagnosis fully characterized, to get the knowledge that you've been seen in an expert center, you got the right diagnosis and you got the right management plan and then for that management to be supervised by a hematology oncology doctor in the local area. Now, we do that very effectively here. I co-manage lots of different patients with some excellent community doctors and that's important because once the therapy starts you have to know at what point to switch therapy if it's appropriate. Don't switch too early, don't switch too late and that requires regular follow up and so once my experience has been that patients will come if they want to travel or if they want to link with the local doctor in the area we'll have a conversation with that doctor in the local area and make sure that the management plan is very clear and that if patients have any concerns or queries regarding decisions that are taken my door is open and we can communicate quite closely. So, as I mentioned to get the best outcomes maybe it's better to see a

doctor who does nothing but treat MDS as opposed to see a doctor who treats a variety of other different problems and I think that gives a lot of comfort to patients in the knowledge that the diagnosis is correct, the treatment is correct and if things don't work out it's not because the diagnosis wasn't correct. It was maybe largely because the treatment that was either was effective for it is no longer effective and so on. That would be my recommendation for a diagnosis that's rare and that can be confused with other things better to get characterized in a Center of Excellence at the beginning.

Q5: (inaudible 56:05)

Ronan Swords, MD: Yes. So, the disease will change its colors all the time. Some patients go into remission and stay in remission for a long time. Sometimes the remission doesn't last so long. Sometimes the remission doesn't come with your first attempt. It may require another attempt and there are not many community practitioners who have clinical trial options available for this disease. Some community doctors don't think about screening for these targets. So, for example, for everyone who's got this disease we will check for an IDH mutation to see if we can get them on the IDH inhibitor trial or at least to see if that's an option. Every single patient or at least the majority will get seen by Dr. Komanduri's group and for a transplant assessment. We do bone marrow transplants on patients with this disease up to the age of 75 and the transplant options are becoming broader and safer and we're getting better and better at supportive treatments and protecting patients from complications from transplant. So, we can offer more intensive therapy to older patients more commonly now than we were able to 10 years ago. So, these are all the things a specialist center can offer patients that maybe community can't.

Q6: This is your field, MDS (inaudible 57:34).

Ronan Swords, MD: Yeah. So, I see patients on Monday mornings and the majority of patients in my clinic have MDS and related diseases. Yes. And the basic scientists that I work with are particularly interested in epigenetic defects in this disease. These are enzymes that go wrong and when they go wrong they reprogram the gene expression in DNA. So, they change the genes that are on and off because they're mutated and the idea would be to target those enzymes, restore their function, restore a normal expression to the cells and return them to having a normal identity. Those types of enzymes are very commonly mutated in myelodysplasia and we have lots of basic scientists who are particularly interested in targeting those enzymes with better treatments.

Q7: Does it move slower (inaudible 58:41) or faster? Is there anything related in that way?

Ronan Swords, MD: Yeah. It can vary. One of the most valuable things to us and I think it's something that's ignored from the current prognostic systems is historical blood counts. In other words, the patients who are older than 60 often go for annual physicals and it's very useful to trace back a blood count abnormality over the course of time and so if you see a low hemoglobin

today and you see the same low hemoglobin five years ago without a huge difference then that type of MDS is moving quite slowly versus the type of MDS where the blood count abnormalities are very low, but six weeks ago or six months ago the blood counts were normal. So, that gives predicting what's going to happen in the future is largely based on what's happening in the past, but we don't always have the luxury of historical blood counts and that's why these prognostic scoring systems are important for us. So, if we pick up the disease and we don't know what phase the disease is at or how quickly it's been moving or how long it's been in the bone marrow then we need to be able to make some determination at that time point in terms of how the disease is going to move going forward.

Q8: (inaudible 1:00:13) determine this disease is something that is in all like general physicals when you get a physical with bloodwork?

Ronan Swords, MD: Yeah. So, usually you'll get a CBC, some chemistries, your cholesterol checked, your blood sugar is checked and your prostate, your PSA level checked if you're a man and a full physical exam and so as I said the very first thing that goes wrong in MDS is the blood count. So, you screen for it and you'll pick it up just from a routine physical and most patients, most patients don't have any problems. They don't have any symptoms at the time the diagnosis is made. There are other patients who do get symptoms and sometimes symptoms are helpful in deciding when the disease came along. So, if someone comes in with a low blood count who's never had blood counts before who felt great six months ago but then over the course of six months it gets more and more tired then maybe the disease merged six months ago caused a low hemoglobin the (inaudible 1:01:22) came along and then that's what precipitated the referral to the doctor who discovered the anemia.

Audrey Hassan: I think that we can move forward with Dr. Xu. Thank you Dr. Sword so very much.

Ronan Swords, MD: Thank you.

(Applause)

Audrey Hassan: We'll have plenty of time to ask as many questions as you like. We won't end the program until you get all your questions answered. So, don't worry. I also wanted to mention Dr. Sword's touched on clinical trials. In fact in your information packets today we have information on the Provanda (sp? 1:01:57) Stat trial and they're doing the trial in the Miami area. So, in your packets will be information flyers on new clinical trials in this region. So, please help me in welcoming Dr. Xu today. Thank you.

Mingjiang Xu, PhD: Hi, everyone. It's very nice to come here to represent the MDS research community at Sylvester. So, I try to do my best to use the lay terms to try to explain it better and how we approach to try to basically improve the treatment of MDS.

So, it's basically… so what we do the ultimate goal is try to find the prevention. So, that's the best if before it happened we don't want the disease to happen and if it's happened we want its early intervention. So, as early as possible to try control the disease and don't let it progress to more ugly disease or for instance secondary AML for MDS cases. So, my research is focusing on several particular genes and those genes they are mutated in patients with MDS and today I'm going to focus on while the gene is called TET2. So, this is an enzyme. It's an enzyme. I'm going to talk about how this enzyme dysregulation leads to MDS and how we are going to target this enzyme, try to improve the therapy for specifically for the patient who have this mutation.

So, MDS is really have a several related diseases. It's like the MDS is related to as Ronan has been talked about related to MPN and it can transform to AML and it's very similar to a patient with MDS and MP overlapping disease and those group of patients have a lot of overlapping features in terms of genetic abnormalities. So, that's why so actually our study is focusing on MDS, but often touch for other diseases, related diseases, such as the MDS-MP overlapping diseases and AML. So, as you can see that the myeloid malignancy as a whole they account for 30 percent of the blood cancers. So, the rest of the 70 they are linked for the cancers and as you can see for the table the incidents of the is about 12 patients every 100,000 population per year is newly diagnosis and MDS is about 4.4 this average. As you can see the five year survival. So, the five year survival for MDS average is about 32 percent. So, this is… I'm not satisfied for this survival rate and we want improve it and through research and through doctors and through the whole societies (inaudible 1:05:49).

Ronan Swords, MD: I'm going to hijack Dr. Xu's talk and we can pick up with where Dr. Xu left off. Dr. Nimer has an engagement at noon and I'm going to introduce Dr. Nimer as our cancer center director who's a Jedi Master essentially in the area of myelodysplasia and leukemias. He's going to talk all about clinical research and the importance of clinical trials and research in this area and what we've been doing in MDS. So, would that be okay?

Audrey Hassan: He's also Chairman of the MDS Foundation. (inaudible 1:06:35)

Stephen D. Nimer, MD: So, good morning everybody. I apologize. I just came from an engagement and I have this very crazy schedule today. So, what I wanted to do is several things and first and foremost is to welcome you all here to Sylvester. You've heard that I have at least two hats. One of them is being the head of the cancer center here and the other is being the chairman of the MDS Foundation and I'd actually like to start and talk about the Foundation itself. I think I've been a member of the Board of the Foundation for about 15 years and have been the chairman of the Board of the Foundation for about four years and it's an international foundation and it does a tremendous amount of good. Audrey, I think, probably has introduced both herself and the Foundation a little bit. The Board is made up of currently made up of physicians. There are a couple of nurses and the physicians pretty much cover around a dozen countries and the sort of the leading expert from every country on MDS is on our board and so

we have every other year a symposium coming up in May in Valencia, Spain and we also have a big presence in a symposium the first Friday in December at the American Society of Hematology meeting and it's usually attended by about 1,000 physicians and scientists from all over the world who come to hear an update on what's going on in MDS and so the mission of the Foundation is really threefold probably. One is to educate the public, maybe educate the public to help patients and families who have MDS or who may have MDS get to the right physicians and the right care. Third, is to teach professionals about MDS. Again, of the, 1,000 people who attend this symposium every year many of them are physicians in the community who see a lot of MDS and want to make sure that they're doing the right things for their patients and the fourth mission is to fund research. So, I've been a physician for a long time, actually. Every year I count at another year and I'm up to 37 years and so I've became interested in what we call bone marrow failure, aplastic anemia and MDS as a fellow and started doing research and for most of my career there's been no treatment at all for MDS and so only in the last 11 – 12 years have the treatments evolved and there's still far too few treatments and so even though there's three treatments, most patients are only would get two of them. They're not combined. They're generally given one after the other and then people run out of options. So, there's actually quite a lot in the pipeline. There are a few things that are exciting and most of what's in the pipeline is actually too early to know if it'll work at all. It's a difficult disease. In part, everyone's disease is different. It behaves differently and we're trying to understand how to predict what's going to happen.

So, you know that there are two things that happen to patients with… three things that happen. One is patients die with MDS. That's the goal so that you don't from MDS, but if the MDS is progressive either people get worsening bone marrow failure and lower counts. Sometimes the disease evolves to leukemia and what we've been doing, in fact, here we just recruited a woman named Ken Figueroa. We can take all morning to explain why she's called Ken, but Maria Figueroa and we recruited her very recently from the University of Michigan and she had been collaborating with my lab and with a group at Sloan Kettering which is where I came from before I was here to try to figure out if we can predict who's going to get worse and who's not. So, we have a project we're about to submit the manuscript describing the project and I'll just very briefly say that what we've done is we've taken serial blood or bone marrow samples from patients and we followed and seen what happens and then a year later we took 25 of the patients who had nothing happen over that year. So, they were diagnosed with MDS, none of them were getting transfused and they a year later none of them were getting transfused and then we took another 25 who were either minimally getting transfused but had a normal platelet count or a normal white count and then a year later they actually now were getting more transfusions or they had lower blood counts. So, one group was stable and the other group had progressed, but at the time they first presented to us they all looked the same and so we took their blood cells and we've done something called a study in the DNA methylation. Two of the three drugs that are available for treating MDS are called DNA hypomethylating agents which means hypo is less so they remove methylation and so we looked at these patients and what we found and what we're going to report is that we… there's a profile of people who are going to progress. So, even

though the doctor doesn't know if you're going to progress or not if you look at the DNA methylation there's one pattern that predicts in a year later the person's going to be fine and the other one predicts that a year later the person's not going to be fine and this is the sort of research that we think, we meaning me, meaning Sylvester, meaning the MDS Foundation although they haven't supported this research in any way financially that is 1) very important research, and 2) is the research that patients want to know about because what we do is currently we assess clinically what's happening sort of the blood counts, what the bone marrow looks like, what the genetics are and we tell people that your survival is most likely going to be somewhere between three and 12 years or your survival is going to be somewhere between this number and that number and with the genetics that we do when we send off for the gene mutational panels that helps us a lot in some mutations, but we really want to be able to understand how to stratify patients and how to advise patients and so for physicians and patients struggling with this disease, it's really what you want to know – what's going to happen. There are lots of patients I've taken care of patients who've been on Vidaza for 15 years. I've been taking care of patients before any of these drugs were available, that I've given transfusions for 14 or 15 years and so and then most of the time you go to the Internet, you read terrible things, everyone is wondering what's going to happen and so it's very nice to know that there are patients who do extremely well and that there are patients even who do extremely well and never need any chemotherapy for the disease. So, it's extraordinarily heterogenous disease and when you think about making progress with treating this is the real problem.

So, how do you decide if a treatment is going to work or not and so just to give you an example let's say you have two people and they look the same and one of them is going to live 15 years if you do nothing and one of them is… the one year if you do nothing. So, if you gave a patient who is going to live one year nothing and you gave the patient who's going to live 15 years drug A and that patient lived for 15 years suddenly you're going to think that drug A was a miracle and so because… so it's really very... the complexity of the disease makes it more difficult to make progress so that you have to… so what we do in part is we tend to treat people when it's very clear that they're in need of treatment as opposed to treating everyone when we make the diagnosis and so that's one area that we want to make a lot of progress and then the other area that we've made a lot of progress is the role of stem cell transplantation and so stem cell transplantation is curative. Most people who get this disease are right at the edge of the age where transplant is either possible or not possible. So, for younger patients it's curative and we try to transplant younger patients when the time is right and for older people we hope to see if they can get a transplant, but it's not always the case. When I learned to be a transplant doctor the cutoff age for a transplant was age 45. If you were over 45 no one in the United States would do a transplant and now probably around age 72 is when we start getting nervous about doing a transplant for this disease. The other problem which is that peoples' families are not as large as they were 50 years ago and so the transplants we did at the beginning you had to have a brother or sister that was a match and now there's so many other types of transplants that can be done including a parent or a child. So, a child that is half matched with the parent and vice versa and so now we can do transplants when there's only half matching. It doesn't have to be a full

match. However, if you're 70 we really don't like to do those transplants because they're still very risky, but if you're 60 it's sort of easy for us to do.

So, let me get back to the Foundation for a moment because what I've just told you is something that I think every doctor needs to hear and try to think about and every researcher needs to hear and try to think about and patients and their families. Things like this. So, everyone on the Board can talk like this and people who we've arranged for the patient forum today from Sylvester they can explain this to you, but if you live outside of a major city and you get one of these diseases it's very difficult and so Audrey can probably tell you how many phone calls she gets from people. They're at a complete loss. They go to see their doctor and they say I've been diagnosed with Myelodysplastic Syndrome. The doctor says, "Oh, I remember. I treated a patient like that four years ago. Why don't we get started?" Okay. Well, so the Foundation is across the globe. We have people on the Board from Brazil now and Japan recently. I was in China about a year ago. There's Centers of Excellence now in China. I went to a hospital just outside of Beijing. It was incredible. It's totally a hematologic cancer hospital. There's 750 beds and I was on the floor where they have 100 beds for Myelodysplastic Syndrome patients. It's two… actually sometimes more than two patients in a room, but room after room after room and so they're very interested in research and in interacting fully internationally and so the Foundation does all these things for patients.

How many of you are from either Broward or Palm Beach or Miami-Dade counties? Okay. And some of you are from Florida but a different county? So, we right now Sylvester we see more than 50 percent of all of our patients come from outside Miami-Dade County. So, we have these satellites and we have great expertise that we say we deliver locally but there's also certain types of diseases where it's still where the expertise like Dr. Swords or Dr. Xu is here in Miami and so we coordinate very well, but the fact is is that there's decisions to be made, many decisions and oftentimes even sometimes the decision is whether the diagnosis is correct.

So, I was relaying a story last week while I was in New York one of the doctors at Sloan Kettering retired and he was taking care of a young woman and she had just published a book that was what it was like as a young woman to live with a disease that nobody could diagnose and then when he retired, she was assigned to be my patient and so I looked over the records and I did a diagnosis. I mean, I did a bone marrow and looked at it and made a diagnosis and I told her, "You have Myelodysplastic Syndrome," and she learned about that and as I got to know here at some point I leaned over to her and I said, "You know, if I had been your doctor a while ago, you wouldn't have been able to write a book about how nobody could ever figure out what was wrong with you. You had myelodysplasia. Your doctor just didn't evaluate you for that," and so the book was a pretty good seller. She made some money on the book and it was good. So, the diagnosis of this disease itself is not that straightforward. Some people have what are called overlapped syndromes where not all some of the blood counts are high and some are low and so it is a difficult area. It's just a difficult area.

You're going to hear from Dr. Xu about some of the mice that we've made that can recapitulate the disease in humans, but it's difficult. One of the key things is there are other diseases that are much more common. Colon cancer, breast cancer, lung cancer, things like this. The number of researchers in MDS continues to get more and more. However, it's not that easy to capture in any one type of experiment the heterogeneity of disease and so we continue to make advances. There are several drugs that are being tested. Some in particular for anemia that look very good and then other ways of coming things and so we hope that we'll still have the ability to… I watch how the biotech stocks do and interesting, very interesting that with Donald Trump being the President Elect, the biotech stocks have really gone way up in the last week because the people feel that the Republicans are more inclined to allow biotech companies and pharma to investigate new treatments with less fear of lawsuits and things. Whether that's the right approach or not the right approach I'm not here politically. I'm not going to do that, but the fact is is that it's very important that the pharma companies that the biotechs be allowed to do things. The FDA, the head of the FDA, Rich Pazdur, his wife passed away recently of cancer and over the last few years he's changed his attitude about things. One was the focus on safety and the other is if you don't have anything that's available to treat you shouldn't you be allowed to take a gamble and should the federal government where they should be on that alignment. So, in MDS we need new drugs. We need… we have tremendous insight into this disease from biologically and the gene level, but we still have to translate that into things that help people and so to the extent that we can get more and more advocates among you to reach out and talk about the importance of this research there's a lot of famous people who have died of MDS and one of the problems, unfortunately, is that there are certain diseases where people are advocates, where the patients are advocates for a long time and so our best advocate right now is Robin Roberts and she's cured and she had MDS that came about from treating her breast cancer and she's "Good Morning America." Right? "Good Morning America." Okay. I don't watch too much TV in the mornings, but she's an amazing advocate and so that's what we all need and so I can assure you at Sylvester you have great advocates and we're very committed here actually in the State of Florida. The Moffitt Cancer Center up in Tampa, Alan List is another member of the Board and he is the CEO of Moffitt. He's an MDS expert and we're working together with them very closely on a lot of things to make advances here in Florida for the 20 million people who live in the state.

So, that's sort of… you're going to get much more detail from everyone else about some of the trials and what's available, but I wanted just to share with you the perspective. I'm looking at these two young guys who I helped recruit and things. I believe they may have been alive when I became a physician, but I'm not sure they were alive when I became a physician and so I can always use the age card here, but I'd be happy to answer any questions that you have and thank you for coming and hope you have a good day.

Yes?

Q9: (inaudible 1:27:37) program at Sloan Kettering (inaudible).

Stephen D. Nimer, MD: It's not as large as it was when I was there. There's a large leukemia program that there's one main physician who sees MDS, Virginia Klimek, and I don't know who the second one is, but there's also lots of people there who do leukemia. Marty Tallman is the head of their leukemia program. He's somebody I've known for a long time for decades and Virginia was actually a mentee of mine when I was there.

Yes?

Q10: I have a question because you're the head of the Sylvester Cancer Center here just wanted to take the opportunity to tell you that you have a fantastic program here. My dad had a transplant with Dr. Komanduri's team a year and a half ago. So, for anyone whose new we did our research and we went to Cleveland Clinic in Ohio. We were going to go to Moffitt next and your team here not only saved his life but was the most caring, specialized nurses and transplant team that we could have wished for and before you leave we just wanted to tell you thank you because you have a fantastic team here.

Stephen D. Nimer, MD: Thank you. Thank you.

(Applause)

Stephen D. Nimer, MD: So, I think Krishna is going to, Dr. Komanduri's going to speak in a little bit. Krishna and I go back to I was one of his first attendings when he was an intern and he is going to be the President… in a couple months he'll be the President of the American Society of Blood and Marrow Transplantation. So, he will be the person. He's already heavily involved with government committees, with research planning meetings and things that we're very proud of him. He got his training at MD Anderson, is a transplanter and we've in the last… and I always hate to date things from when I got here. However, we just recruited our 90th new faculty member in the last four and a half years and they're really fantastic people, extraordinarily dedicated and the other thing which is wonderful here is that there's a lot of caring people. So, thank you so much.

Q10: (inaudible 1:30:20) to the doctors. Every level of every nurse, every lab technician just fantastic human beings.

Stephen D. Nimer, MD: Great.

Audrey Hassan: I want to thank Dr. Nimer for donating his time today and if we can get started with Dr. Xu. Thank you, Dr. Nimer, for coming.

(Applause)

Audrey Hassan: I just wanted to touch slightly on the MDS Foundation is very proud that we created our MDS Centers of Excellence program. We've identified over 160 Centers of Excellence that have qualified with our very strict criteria. Of course, Sylvester meets that… the very high criteria to maintain our integrity we are very strict with our… to qualify for that designation. So, anyone that would like to get an appointment at any one of our Centers of Excellence, they're listed in your packets and I'd be happy to if you need me to arrange a preferential appointment with any one of our contacts at any of our Centers of Excellence worldwide. Thank you, Dr. Xu, if you want to get started.

Mingjiang Xu, PhD: So, I'll continue with the… So, I think Dr. Sword have mentioned that it is MDS actually is really a cancer of old age. As you can see from this table right here this is updated in 2015. So, this is the most up to date. As you can see that as aging the incidence of MDS is increased sharply. So, it's increased. Actually, it's raised over 1,000 fold as aging. If you can see down here this from the lower panel this is the US population is divided by aging. As you can see that is 1973, it's 1980s and '90s as you can see that is right shifting. So, that means the US whole population is the older population is increasing. So, that means the MDS incidence will rise.

Q11: (inaudible 1:32:49) diagnosed more (inaudible) have it before?

Mingjiang Xu, PhD: I think it's definitely is right now the healthcare is getting better and people living is better and it's basically people live longer. So, the retirement age is now is 67 right now because before it was 65. It's gradually getting larger.

So, it's really there in the last five years there's a lot of advances in the genetics of MDS. Is largely thanks to the improved technology of the next generation sequencing. So, before the MDS the molecular basis is what encompass because right now if you can see from the pie chart the mutation there's more than 50 common mutations happening in MDS and actually every mutation have their unique characteristics driving to MDS. So, I never read that is Dr. Sword mentioned IDH1/2. So, this is Dr. Sword have doing a clinical trial specifically targeting this IDH2 which is five percent with MDS have this mutation. So, as my research in correlation with Dr. Nimer and Dr. Sword and other team members of the MDS research community here at Sylvester, we're dealing with the TET2 mutation right here as you can see that there's 20 percent of MDS patient have mutation in this particular gene and we're also working on the DDX41. It's basically less than five percent of the patient have this mutation and appear to have six down here. So, it is our team is studying several is key mutated genes in MDS. Our goal is try to basically studying those genes certainly as a basis from which we can find therapeutic target and eventually develop drugs to target those mutated genes which is the so called targeted therapy or it's called personalized therapy.

So, from now on I'll focus on the TET2 mutation. So, the TET2 mutational rate is about 20 percent in MDS. As you can see that this mutation is only happening on MDS and also other

related myeloid malignancies related to MDS including MDS/MPN, the mutational rate could as high as 50 percent and MPN between 10 to 20 percent and AML about 20 percent and for lymphoid malignancies the mutation could happen at a much lower rate and for solid tumor the TET2 mutation is pretty rare. However, the normal aging population over 70 years of age, they're about five percent of this population actually have a mutation. So, there's a recent report from is a by the studies of Harvard in England (?). It's showing that in those five percent of the aging population who had TET2 mutation be predisposed to MDS and other myeloid malignancies. So, if therefore that is the TET2 mutation is one of the early mutations happening is probably before MDS being developed. This is a very important gene happened early on. So, it's basically our research we want to target this gene, try to make… prevent MDS from happening as early intervention target in the therapeutics.

So, is what TET2 is? So, is the mutation has happened on the gene and the mutated gene there's a function. So, as long as you know the function you know how the mutation is leading to the protein is what basically characteristics of the cells is being dysregulated. So, this is a very complicated slide. I don't want to point to anything. It's basically the TET2 is enzyme is modifying whatever the base within DNA. In the DNA there is ATCG. So, there's a C. the C is cytosine can be methylated. The methylation of cytosine is very, very important. This is one of the hallmark of epigenetics regulating gene expression in the cells and also other functions of the cells. So, as you can see that the TET2 is specifically oxidized the 5hmC is making them 5hmC, FCCC and through a DNA repair machinery can carried off the methylation is returned to the cytosine. So, therefore is this gene is important regulators for gene for epigenetic regulation on the cells.

So, it's back to six years ago. So, as Dr. Sword said that is the trial mutation is important for disease. So, we want to prove if TET2 is really a driver mutation. So, you wanted to prove that as Dr. Nimer said that is we made animal models. Why we make animal models? Because the animal, the lifespan is two years. So, we can manipulate the genes in a mouse easily. So, it's basically we carried genes in the mouse. We make the TET2 now caught mice and we also have a mice which is only have one (inaudible 1:39:28) of half of the TET2 intact. So, as you can see from the lower table that if you lose TET2 genes the animal within two years all the animal die from a disease. If you lose one (inaudible) of TET half of the TET2, about 40 percent of the animal die within two years of their lifespan. So, what they die from? As you can see from the pie chart, majority of these animals they die from myeloid malignancies, over 90 percent and we think most of them they died from MDS or MDS/MP overlapping disease. So, basically we're proving that if you lose TET2 even a single (inaudible 1:40:18) is sufficient to cause MDS or other myeloid malignancies. We've proven that TET2 is a driver mutation. We should target it.

So, this is one of the example, one of the animal, as you can see that in a normal situation in the peripheral blood in the mice is the lower one is a situation of a TET2 (inaudible 1:40:44) mice. You have a lot of increased white blood cells and those cell types here there are neutrophils and monocytes and also this phenomena is happening in the bone marrow and we proved this using

histology and flow cytometry using antibodies. We show that in the animal there the dysregulation of hematopoietic cell populations and probably in the audience everyone know that is the myeloid malignancies they had poietic stem cell disease. So, it's basically why our animals they eventually develop myeloid malignancies. We first we look at the hematopoietic stem cells. As you can see from the flow cytometry that is we thought that before the animal went on to develop MDS or other myeloid malignancy the first thing the animal had they had a much larger hematopoietic stem cell pool in the animal, it three to four fold and also that when we take those stem cell out and to test their function, their hyperfunction, the more functional than compared with what it should be. So, they're hyperfunctional in terms of if (inaudible 1:42:10) more and when you transplant into other mice they're producing far more hematopoietic cells than the wild type. So, it's basically they have dysregulating the stem cell function by losing the TET2 genes.

So, we also found that is if you lose TET2, it's only in hematopoietic stem or progenitor cell level can cause the stem cell basically eventually initiating MDS. If you lose TET2 in the mature cell population, for example, neutrophils, monocytes, so on, you do not have the ability to cause the disease. So, this is telling us that when we target TET2, we should target hematopoietic stem progenitor cells rather than mature cells in order to prevent the disease from happening.

So as I said that it's TET2 is enzyme. So, we did one simple test. So, we have the TET2 (inaudible 1:43:12) cells. They do not have TET2 anymore. So, we can put TET2 back. As you can see that is when we put TET2 back the disease is being prevented. The stem cell function is being corrected, but if we put the catalytic domain in active, basically the TET2 other portions is intact. It is only do not have the catalytic function. If you put it back we cannot rescue the disease and the disease cells still happening is proving that the catalytic activity of TET2 is critical, is essential. So, where we should target. When we target TET2 we should target the catalytic activity. So, and this is a very complicated slide. It's basically when we prove TET2 catalytic activity important is how the catalytic activity is dysregulating the genome, epigenome at everything. So, cut story shot. If we found that the five hydroxyl methylation as I said that this is one of the product of enzymedic activity at this level in the genome is significantly decreased. So, it's basically we want to restore this using drugs and also we found that as the gene low side basically they have differential level of the so called 5hmC. The genes is being marked with this. They're concentrated with myelo cell differentiation and nucleogenesis stem cell regulate the genes. So, it's basically we want to correct this on the genome if you lose it with the hope to prevent all as early intervention strategy.

So, we also studied the patient. So, for this panel, this is we did the exome sequencing for over 300 patient with MDS and MDS/MPN. This is how the mutation is being discovered using exome sequencing and we analyze those data we divide it into the patient with TET2 mutation and result. We see that the patient who has TET2 mutation they have much higher mutational events as compared with the one do not have TET2 mutation indicating that the early occurrence of the TET2 mutation probably promoting the mutagenesis because they have more mutation happening in the cells of the MDS or MDS/MPN patient. So, we also proved that, indeed, in

cells if you lose TET2 you carried out TET2 the mutational frequencies increased by 24 fold. It's basically if you lose TET2 your cells is have more chance, 24 fold chance, to have mutation occur. It's basically if the mutation cannot be corrected then you have more chance to have other mutations and make your disease progress faster. So, and we also study the mechanism, indeed, this TET2. This implicated in the base (inaudible 1:46:46) repair and a mismatched repair this pathway is basically TET2 is participating in that two pathways probably as preventing the mutation from happening if you lose TET2 and you have higher chance to get mutations. It's now that is to come with our therapeutic hypothesis. As I said that is the TET2 is mutated in the patient. You can from the (inaudible 1:47:18) that is about 80 to 90 percent of the patient they only have one half of their TET2 is gone, is being lost. The other half is still intact. So, and basically this is in the... our term is called TET2 (inaudible 1:47:37) sufficient. You don't have enough TET2. So, what we do is that the patient still have one (inaudible 1:47:47) type TET2 earlier. So, how about we boost this remaining (inaudible). We make it better. We make it larger. We make it expression higher to try to prevent overcome the TET2 loss or the term is (inaudible) insufficiency. So, how we do it? So, it's basically one of the strategy that is we think vitamin C can increase TET2 activity. So, this is true because why the vitamin C can for the iron, the two plus iron is active for TET2 activity to be functional and the vitamin C can reduce the three plus iron to the functional two plus iron basically the increased iron (inaudible 1:48:36). The vitamin C can increase the TET2 activity and also vitamin A is also can improve the TET2 activity by increasing the TET2 transcription is basically the (inaudible 1:48:53) TET2 gene we can make more proteins out of it is by using retinoid acid. There's a recent report it showing that the vitamin C, the retinal which is metabolized retinoid acid can increase TET2 expression level therefore the activity. So, and also they're the co-enzyme is Alpha-Ketoglutarate is a co-enzyme of TET2. So, we can generally some of the alpha KG analogs which can boost TET2 activity to achieve that and also that is as Dr. Nimer and Dr. Sword mentioned they're the hypomethylating agent which has been approved as a drug to treat MDS and why combined with this drug because this drug is a hypomethylating agent. So, in the patient there's a dysregulation of the 5hmC and five methylation and this drug can reverse that of the phenotype at (inaudible 1:50:05) degree. So, this is using our TET2 animal model. So, in the TET2 (inaudible) mice when we give hypomethylating agent as you can see that the animal survival is being prolonged. They survive better, longer and they are phenotype, the disease phenotype is being onset is being delayed. So, we believe the hypomethylating agent can correct partial of the TET2 loss led dysregulation of the epigenome therefore can help the TET2 (inaudible 1:50:44) patient and also that we treated out TET2 (inaudible 1:50:49) mice was one year is we treated long time because the vitamin C is short term we probably don't see the favorable outcome. After one year as you can see from our analysis the disease phenotype in terms of myelo proliferation in the TET2 (inaudible 1:51:13) animal it dramatically improved as compared with the one you don't give vitamin C for one year. In terms of their spleen size is better and their monocytosis is getting better. So, it's basically in the aging population. So, for the aging population the vitamin C insufficiency this is as you cannot overlook the problem in the aging population. So, in the aging population there's more trend people have vitamin C insufficiency. So, we also perform the study we're still using (inaudible 1:51:50) mice because the human body we cannot synthesize vitamin C our self. We

have intake, take vitamin C from the fruits and basically to have enough supply to keep us do not have vitamin C insufficiency, but for the mouse, the mouse and guinea pig we can synthesize vitamin C. So, we made an animal model… not we made. We obtained an animal model who do not have the ability to synthesize vitamin C and by doing that we make the animal vitamin C insufficient then we start to give them different doses of vitamin C so using this method we can basically firmly confirm document that if the vitamin C's insufficiency can promote along with the TET2 loss promote the progression of MDS or initiation of MDS and if we're giving vitamin C supplement or correct the vitamin C insufficiency can then slow down the disease progression.

So, basically so what are we trying to do is we try to use combinations. So, we don't think vitamin C alone will correct the TET2 (inaudible 1:53:13) insufficiency. So, we want to use the DMKG which is can metabolize in our body to Alpha-Ketoglutarate can boost TET2 activity. We want to give retinoid acid basically this is metabolized from vitamins A. So, we want to give them all those together. Using the animal we find the right dosage can correct TET2 haplo insufficiency and eventually we want to take this to clinical trial. Hopefully, we can specifically prevent the MDS offset to AML for the patient lost one (inaudible 1:53:59) of TET2. It's basically benefiting the people who have the mutation, the aging people and also slow down their disease progression.

I'm going to stop here and take your questions. Thank you.

(Applause)

Q12: You say older patients. I'm here for my father who's 90 (inaudible 1:54:26) in the last six months his counts been going down and he's been diagnosed with a (inaudible) form of…

Mingjiang Xu, PhD: Oh, you mean people 90 years old.

Q12: Vitamin intake you're saying could be low.

Mingjiang Xu, PhD: I believe that is a take enough vitamin C, vitamin C you definitely will prevent a lot of things, make basically make everybody healthy. Basically, the food is to take a lot of fruits, vegetable and the vitamin nutritions.

Q13: (inaudible 1:55:01)

Mingjiang Xu, PhD: Yes. Yes. It's getting enough nutrition will definitely make a lot of things better.

Q13: (inaudible 1:55:10)

Mingjiang Xu, PhD: With dosage, I think if you go to Costco there's a lot of things. The daily supplemental thing for vitamin C, vitamin A. I think that will be the right dose. You don't want to get too much. If you have too much of vitamin C, it could cause certain problems and you don't want to vitamin A and vitamin C insufficient. So, you want to have enough.

Q12: Recommended (inaudible 1:55:40)

Mingjiang Xu, PhD: Yeah. I think it's, for example, if you have… if your eating habit is healthy enough you're eating enough fruits every day, I think that ought to be enough. For vitamin A the highest food is liver is what turkey liver or chicken liver. This has a lot of vitamin A and also sweet potato has a lot of vitamin A.

Q13: How about some of the (inaudible 1:56:17) beneficial for elderly person to take some of the supplements (inaudible 1:56:27)

Mingjiang Xu, PhD: I personally believe so. So, is eating healthy have enough this is particularly. Yes.

Q12: (inaudible 1:56:34)

Mingjiang Xu, PhD: It's basically is from the basic research is (inaudible 1:56:44) vitamin A and vitamin C they both can boost TET2 activity at a certain degree. So, it's (inaudible 1:56:52) if you lose TET2 you can cause MDS. So, why not boost it because you still have half of your TET2 in your body.

Q12: His eating habits going down so (inaudible 1:57:03).

Ronan Swords, MD: I just want to point out how important and significant the work that Dr. Xu has just presented is. So, he knows that there are a plethora of mutations that occur in patients with MDS. The mutation he's talking about is called a TET2 mutation. That happens more commonly in MDS than other disease meaning that it might be important in MDS in terms of how quickly the disease comes and how aggressively it behaves and so the way he tests that hypothesis is he depletes this TET2 protein in mice and the lower the level in mice the faster the disease comes and the more likely the mice are to die. So, the real challenge for us and when we look at mutations in cancer it's like if you go back to the analogy of the car. So, you get up in the morning, you turn on the ignition in your car and it doesn't work, you call AAA, you take it to the mechanic and the mechanic looks at your engine and he says you've got a problem with your carburetor, you have a problem with your pistons, your gasket is blown, your ignition doesn't work and he lists about seven or eight different problems with your engine and then he says had you checked your filter or your oil levels every three months you wouldn't have this problem anymore. So, that's the challenge in cancer is that we see all these mutation is which mutation came for it… it's the chicken and the egg situation. So, what Dr. Xu has discovered is that this

TET mutation that if the lower the level the worse the disease becomes and if there's a way to increase the level of this protein in the cells that you could protect the mice from getting a bad disease and you can raise the level of TET protein in mice by giving lots of vitamin A, lots of vitamin C and other drugs and so the notion would be that in patients where the TET protein is abnormal or mutated that you could take a similar approach by giving patients vitamin A and vitamin C and so on to attenuate the disease or delay the disease getting worse. So, as he's going through his slides I'm looking at the amount of work that's generated for each individual slides. So, you're looking at tens of thousands of dollars for a mouse experiment, paying salaries of scientists studying these mice, following mice for a year or two years. So, really it's quite remarkable and it's the type of research that we want to try and profile and showcase here because this is research that's essentially part of a bigger collaboration with the group in Memorial Sloan Kettering and it's really… it's cutting edge stuff, so it's very exciting.

Yes. Go ahead. Sorry.

Q14: The question it was kind of a reverse. You're studying what to do for it. I'm looking at a list of mediations I'm taking. Is there any medication that conceivably could induce MDS or could…? I don't who's studying that or is there anybody researching that as to what basically is causing it. In other words if you're taking 10 different prescriptions could any of those have an effect on it? Is there a possibility it's something we do to ourselves could be depleted?

Ronan Swords, MD: That's a great question. There's a caveat here because if you look at there's some diseases, for example, there's a rare leukemia called chronic lymphocytic leukemia or called CLL and where the cells have lots of vitamin C in them. That could mean that the cells like vitamin C and they need vitamin C to grow and survive and maybe giving vitamin C to those patients may not be the smartest thing to do because it could cause the disease to become worse and we know that in patients with, for example, prostate cancer who take lots of vitamin E prostate cancer can get worse. There are laboratory studies that show that giving vitamins along with chemotherapy can make chemotherapy less effective. So, I just want to be careful about the notion that vitamin C is kind of panacea or vitamin A is a panacea that will fix this problem. You have to be very, very careful in the patients that get lots of vitamins to make sure that the effect on the cancer cells is a negative one and not a positive one. So, in patients… in my patients in the clinic there has to be a very good reason for you to be on vitamins in the off chance that there may be… it is conceivable that the patients who may be taking lots of vitamins because of the "medicinal" benefits of vitamins where the cancer might be getting worse and the chemotherapy they're getting may be less effective.

Q14: (inaudible 2:02:17) aggregate your MDS. (Inaudible)

Ronan Swords, MD: That's a possibility, but a rare one. In other words, we don't go through the list of medications that patients might be on to say don't take this because your disease could get worse. We just don't have enough evidence to say to give that guidance with certainty.

Q14: (inaudible 2:03:02) personal matter.

Ronan Swords, MD: Well, it's a good question, but I don't want to sort of look at the strawman and say like you could be one whole bunch of things that could be making your disease worse, but you're right though. It's a possibility, but I think it's a remote one. I think it's a remote one.

Q15: What about information (inaudible 2:03:26) all those (inaudible) important for MDS patients, but you ask your own physicians and (inaudible) does it matter which (inaudible) that will build you white blood cells (inaudible), but then you will ask the physician about it and (inaudible)

Ronan Swords, MD: So, as long as you have enough iron, enough B12 and enough folic acid in your blood they're the critical building blocks you need to make blood cells. If all those levels are normal then taking more isn't going to improve your blood counts further.

Q15: You should look on the information when you get a blood test (inaudible 2:04:18)

Ronan Swords, MD: Yeah. Absolutely.

So, let me introduce to you to Dr. Komanduri who leads our transplant program and who is the president elect from the American Society of Blood and Marrow Transplantation who did his training in the MD Anderson in (inaudible 2:04:42) who knows everything there is to know about bone marrow transplantation and who's going to tell us all about the transplant program here at Sylvester, Krishna.

Krishna V. Komanduri, MD: Thanks, Dr. Swords. I am trained at MD Anderson though. I came from MD Anderson. Really my pleasure. Thanks to the Foundation and thanks to Dr. Swords and also Dr. Nimer for bringing me here. Clearly, a passionate smart group of people some of whom I know dearly and it's great to see that.

So, I'm going to talk about stem cell transplant for myelodysplasia and after seeing Dr. Xu's slides, I decided I'd put this slide in because he's talking to you about TET2 mutations and I thought okay, I'm giving you a different kind of a decidedly different talk which is a talk… this is slide that a photograph that Commander Chris Hadfield took from the International Space Station looking down at us. So, I'm going to give you… thi is not a 60,000 foot slide. This is a much, much higher than that slide. So, what I'm going to give you is the very, very broad high level overview. There's not going to be a lot of hard detailed science. If you want that there are plenty of times I'll be happy to have come back and I'll give you more of that, but that's not what we're going to talk about today because I want to address some very basic concepts about what stem cell transplantation is, how it applies to myelodysplasia and some very, very general terms what are the big issues that we're trying to deal with in the field and how's this evolving.

So, I have been here for about eight years now and I was at the University of Texas MD Anderson Cancer Center before that and before that at UCLA and UC San Francisco and it's been my pleasure and my privilege to work with Dr. Swords and Dr. Nimer and other clinicians who have expertise in leukemia and myelodysplasia and to lead the stem cell transplant program which as I'll show has really rapidly grown over the last several years.

So, I want to, again, really leave you some very basic fundamental concepts and I think that this is a very high level audience I may be talking below you because clearly you're a bright group of people, but I want to try and at least equalize the understanding in the room so that you all have some basic understanding of what stem cell transplantation is and how it applies to myelodysplasia.

So, what is it first of all? So, it is the primary curative therapy for many patients with high risk or relapsed leukemias and lymphomas. I didn't put MDS there, but MDS is on a spectrum of bone marrow diseases that can lead to acute myeloid leukemia and clearly it is a disease that can as you well know both from your own experiences and both your own reading can lead to bone marrow failure in some patients that leads to a need for transfusions and can lead to an inability to control infections and in other patients can lead to acute leukemia. I think it was sometimes inappropriately called preleukemia as though it always progressed to leukemia which is not true, but I won't go over the basic understanding of myelodysplasia because you've, obviously, had some phenomenal speakers who have done that already.

So, the historical rationale for what stem cell transplantation is and when I say stem cell transplantation and you hear the term bone marrow transplantation I'm really saying the same thing and, again, in the context of a short talk I'm not going to go over all of the evolution, but the bone marrows, of course, as you know from bone marrow biopsies is the factory for bone marrow for blood stem cells and the reality is most of what we call bone marrow transplants these days are not done using bone marrow anymore. So, it actually is confusing because most times people think when they hear bone marrow transplantation that when we do this we're taking cells out of the bone marrow by operations and we're sticking them in and then I'm a surgeon I'm going to come in with a green cap on. The reality is the vast majority of transplants that are done are actually done now collected from the stem cells that lived in the bone marrow that we only 20 years ago could get out of the bone marrow, but now and most often we can get them from the peripheral blood and they're infused like a blood transfusion where they go to the bone marrow. So, when I say stem cell transplantation we're still talking about blood forming stem cells that live in the bone marrow, but we don't usually get them from the bone marrow anymore. So, I think it's an outdated term to say bone marrow transplantation. So, when I use those terms just think of it in the same way.

So, the initial rationale and many people still come into my office thinking this is what we're doing today and it's partially true that high dose chemotherapy cures cancer that if there are

drugs that can treat cancer but can't cure it may be if we give a really high dose of chemotherapy we could wipe out the cancer and that can be true, but that if we use those high doses of chemotherapy we would wipe out the bone marrow production of blood cells and therefore that infusion of bone marrow stem cells can rescue patients and an analogy I sometimes give is weeds in a garden. If you have weeds in a garden and they're growing around your prized plants and you say well I want to use high doses of weed killer well, you might kill your prized plants, too. So, if you pull out those plants and you use the weed killer and then they'll come back either with those plants or you can get new plants then you might be able to kind of clean the garden and get rid of the weeds and those weeds being the abnormal stem cells that lead to blood cell production that's not normally myelodysplasia. This can be autologous which means that we can use the patient's own cells, something we don't do in the context of myelodysplasia because the patient's own primitive cells are themselves abnormal, but in the context of multiple myeloma which is a cancer of different types of cells in the bone marrow and Non-Hodgkin's Lymphoma we frequently do autologous transplantation that can either be life extending or in the context of lymphoma curative or we can talk about allogeneic transplants which are cells from another individual. These are the transplants that can be curative in myelodysplasia and I'll explain that's really going to be the focus of this talk.

So again, the principle of what we call myeloablative. So, what is meylo? Myelo means this refers to the production of healthy blood cells that normally protect us from infection like neutrophils and the myeloid cells are the cells that are abnormal in myelodysplasia and myeloablative means to wipe out or ablate the bone marrow. So, what we historically did in the 1950s and 1960s when this therapy was first used we used combinations at that point of chemotherapy and radiation, more commonly these days use just chemotherapy combinations alone to basically wipe out the recipient's blood cell production. So, if the recipient here just, again, simply is depicted as red cells in the bone marrow and then we give a graft which, again, could come from the bone marrow it could come from blood stem cells collected from the peripheral blood of the donor. There are other sources as well that I won't talk about then we basically kind of replant the garden and now the patient has these cells that come from the donor depicted as going from, again, red to blue in a very simplistic way here.

So, historically this approach because we were using very high dose of chemotherapy and radiation typically five to 10 times higher than, for example, Dr. Swords might give in the context of treating an acute leukemia putting it into remission. These regiments were toxic and associated with very high early mortality. So, when patients had stem cell transplants as many as 20 to 30 percent of patients would die in the first 100 days due to these toxicities, but what we realized was and this actually is a barrier to outcomes is that donor stem cell graphs were collected from the bone marrow or, again, were collected from the peripheral blood. They also had T cells and T cells are cells that protect us from infection. So, I had a flu shot earlier in the week and what that flu shot is doing is trying to boost my T cells that will allow me to have a more rapid response when I see the influenza virus. So, T cells protect us from foreign things, but if you infuse T cells from another individual even if well matched unless that person's an

identical twin so even a well matched brother or sister will still recognize differences in the recipient and cause a condition that is called graph versus host disease that occurs in 30 to 60 percent of recipients and that the frequency differs according to the matching of the donor and the recipient have. The prevention and treatment of graph versus host disease requires suppression of the immune system and so we suppress the donor's immune system actively just like if a recipient gets a solid organ transplant. Now, let's say I were to need a kidney and I were to get a kidney transplant. Well, immune system is healthy when that kidney is transplanted into me. So, we think about rejection which is my immune system attacking that foreign tissue, but in a stem cell transplant we're actually doing the opposite. The whole immune system, my immune system is being wiped out. So, the immune system of a donor is coming in and not only going to see my kidney but my whole body as foreign. So, we give immunosuppressive drugs and typically within three to six months kind of ween off those drugs and eventually in most patients and we hope that this happens that the immune system develops what we call tolerance that it learns to recognize that this is okay, I don't need to react to everything and I'm going to settle down and we can take patients off the immunosuppression, but this risk of what we call this graph versus host disease requires very close donor matching as we know from just I think the lay press. Well, when realize the T cells can cause this condition called graph versus host disease even though we started doing these transplants again the '50s and the '60s for acute leukemia by the mid-90s we had approaches that could take out the T cells from donor graphs and this seemed like the best of both worlds. If you could give healthy stem cells from donors but take out all the T cells well then you wouldn't get graph versus host disease and so a number of transplants were done in different centers either using the rare case of identical twins where an identical twin got a cancer like leukemia and received a transplant. Of course, there was no matching problems there or when the T cells were taken out actively to try to prevent graph versus host disease and the very surprising thing and, again, these are curves that are called cumulative incidence curves. So, as you go out more and more people will have an event. So, at the time of the transplant, of course, nobody has relapsed, but after transplant, unfortunately, despite doing everything right some patients will relapse with their disease and you can see here and I'll explain this is that this is a group of patients who got normal transplants with T cells and stem cells and they did not have graph versus host disease and you can see that the probability of relapse is about .25 which means about a quarter of those patients despite doing the transplant had their myelodysplasia or AML in this case, acute myeloid leukemia, come back. Well, patients who had a T cell depleted transplant, their risk of relapse was roughly double patients who didn't have graph versus host disease and got T cells. So, very simply if you take T cells out of a graph not only do you have the good effect of not causing graph versus host disease, but we found out a very surprising thing and that's that relapsed rate double. Remember these patients who got the T cell depleted transplants got very, very intensive therapy including the chemotherapy and radiation combination. So, that told us that the relapse is not just predicted by how they respond to that high dose of chemotherapy and radiation but that the immune system that we thought was really causing potentially a bad thing was really necessary for the maintenance of remission post-transplant and we now recognize that, indeed, it's that immune effect that we call a graph versus leukemia effect or, again, a graph versus malignancy effect that

allows us to cure patients who may have… we may not know what drugs to use because maybe we don't have those drugs yet, but the immune system of a donor has a very, very broad repertoire meaning that can see a lot of different things and can recognize abnormal cells in ways that drugs can't and we don't necessarily have to know that and, indeed, now after my studying this for 20 years when I went to UC San Francisco to train as a fellow there was literally nobody going cancer immunology in the institution and I went into an HIV immunology lab because HIV destroys T cells and we were learning a lot about immunology in the setting of HIV infection and it's shocking now because immunotherapy is the hottest thing that's developing in cancer therapy even in cancers like lung cancer that we thought would never respond in the immune system, but what we recognized, again, this is work that was published in 1990. So, more than 25 years ago was that the immune system of donors could cure leukemia and now I would say the rest of the cancer community is catching up to us and recognize that the immune system Is very powerful and can cure other cancers.

So, just very simply we now know that T cells can cause graph versus host disease. That is they can attack tissues like the skin and the liver and the intestines of the recipient, but they also have good effects that we call graph versus tumor effects or graph versus malignancy effects and, of course, the donor T cells can also protect the recipient from infection. The donor cells come into the recipient and protect the recipient from things like infection and other viruses, influenza and other viruses that are in the community or even inside the patient's own bodies. So, we call pathogen specific immunities. So, T cells really do good and bad things for us, again, with the good things including graph versus malignancy responses and pathogen specific responses. So because of this I need to update the slide. It's really about 15 years or so we recognized that a major goal of transplantation is to actually maximize the T cell effects. So, we now use less intense chemotherapy.

So, why does this matter? When I was in medical school we transplanted… we really didn't transplant patients over the age of 55 and then it became 60 and now we're routinely doing allogeneic transplants or donor transplants in individuals up to the age of 75 and as you well know, myelodysplasia tends to be a disease of older individuals. My wife's mother was diagnosed with myelodysplasia at the age of 71 and that's not unusual. So, when we were transplanting patients only to the age of 60, well we weren't really able to transplant many patients at all. There are unfortunate subsets of individuals who will get myelodysplasia at young ages, but most are in their 60s and 70s. If you can't transplant them because the therapy you have is too toxic well then you're not going to transplant any patient with myelodysplasia.

So, other things peripheral blood versus bone marrow as I talked to you about is commonly used as a stem cell source. The 100 day mortality has decreased from 25 percent to less than 10 percent and the brother or sister transplant setting it's around five percent. We have more graph sources and donors. I'm not going to talk about that today.

So, these are some curves of survival and I know it's not easy to look at these things especially or if you're a patient or if you have loved one, but these are transplant survival curves and with any therapy, of course, if you start looking at the moment that the treatment starts 100 percent of patients will be alive and over time patients will die. Now, some of those patients may be dying of other things. So, that does not necessarily mean that they're dying of myelodysplasia and, again, if you have a disease that affects patients and some who were diagnosed in their 80s that may actually be dyeing with myelodysplasia as opposed to of myelodysplasia, but I want to just show you a couple of… one take home message is that these are patients who are transplanted with earlier stages of myelodysplasia and these are patients who are transplanted with advanced stages of myelodysplasia and I want you to see that the survival six years after transplant is about 45 to 50 percent for patients with earlier stage disease and lower about little less than 40 percent for patients with advanced stage of disease. So, if we do a transplant in somebody who has more advanced disease we're less likely to cure them. So, the next one, again, here, again, this is early versus advanced age. This is… I'm sorry I'm going backwards here. The difference between these two things. So, this is years by disease status. These are unrelated donor transplants. I'm sorry. And these were brother and sister transplants. So, the unrelated donor transplants a little bit lower curves. So, slightly lower survival, but pretty similar. I was having a conversation about the impact of donors and how we do, but again with unrelated donors a little bit more tough transplant than when you have a matched sibling and, again, you can see probably a five to 10 percent less good outcome of transplants when we transplant patients with advanced disease and this is true for a lot of things, but there's a risk up front to transplant. So, if I were to summarize this it was clearly a curative therapy but associated with some risk of early complications and potential mortality. Typical age cutoffs are 70 to 75 depending on disease and health status. Obviously, the person who is running marathons at the age of 72 is different than the person who has had a triple bypass three weeks ago. So, that there's what we call comorbidities and other things and the longer we live the more medical baggage that we have.

Because some MDS patients will be stable for very long periods, early transplants shouldn't be done. If you're going to do something that's curative, but if you're going to do something that has an upfront risk, well you don't want to expose patients who are going to live for five to seven years to something, but again there's this paradox. If you wait too long so a stitch in time saves nine and the other hand if it ain't… so if it ain't broke don't fix it. On the other hand there's a stitch in time saves nine. These are two different opposing principles that a prostate cancer doc once told me. So, the issue is if you're doing well and you're likely to do well with supportive care with Azacitidine or another drug well, it might be better not to expose yourself to the potentially toxic risks and the early death related to transplant. On the other hand if you have high risk disease and the likelihood of your surviving more than a year or two or three is low well then it makes more sense to take the risk of doing a transplant. So, there's a risk to reward to everything.

So, there are staging systems. The International Prognostic System has these staging systems and INT2 is intermediate… there's an intermediate class and there's Intermediate 1 and Intermediate

2 which is worse. We have done studies that say well look the point at which you should do it is probably INT2 or above. So if you have earlier stage disease, low risk disease or intermediate risk that's kind of on the lower end of the intermediate risk you probably should not expose yourself to the risk of transplant, but if you're at higher risk, well, the chances are that not moving to transplant is actually going to be associated with higher risk, but it is recommended that even in lower risk MDS in patients eligible for transplant not necessarily 90 year old individuals that early referral to a transplant center could be considered to assess options at least to look at your donor status and to assess those things in case things progress because sometimes patients who seem to be doing well and tolerating therapy will go to their doctors and their counts will plunge or their bone marrow blasts or abnormal cells will increase and then you're scrambling sometimes. So, I think there's no harm in early consultation. We're certainly not going to do a transplant at any time that it's not appropriate and that the risk isn't outweighed… the risk outweighs the benefits. We're not, again, we not on commission here. So, we want to do what's best for you and supported by the medical literature.

So, the indications, again, look at myelodysplasia here. About 1,200 patients in 2013 were transplanted for myelodysplasia or myeloproliferative disease. This is a related group of diseases where, again, the marrow is slightly elevated and there are individuals who have a little bit of a cross. They have a little proliferative disease and myelodysplasia at the same time.

So, the next two slides are actually financial slides and this is important. Many patients with myelodysplasia are in Medicare years. Medicare. So, this is how Medicare covers stem cell transplantation. There is what's called an NCD or National Coverage Determination and the NCD is the official policy from the Center of Medicaid Services that outlines which disease indications for transplant are either covered. So, it says okay this is covered, it says this is not covered and then there's what's coverage with evidence determination which is kind of a trial period and it says we will cover it, but we want you to collect data that's submitted to a federal registry so we can see whether this is really cost effective, whether it's doing good or maybe doing more harm than good or maybe it's on a societal level it's not good enough that we think we should be devoting Medicare dollars to this as opposed to all the other important things that Medicare needs to cover. So, and if you don't have coverage under one of these three things we don't have any preauthorization. So, if we can do a transplant that may cost $300,000 or half a million dollars and we submit the bills and they say well, sorry, we decided not cover it we get paid literally zero. So, from a financial perspective and one of the things I'm doing in my role on the national level is really trying to address these financial barriers and that creates an access barrier. The bottom line is so unless somethings either covered or covered with evidence determination most transplant centers just can't afford to take that risk that they might do a transplant that might, again, cost hundreds of thousands of dollars or even $1 million and then get paid zero. That impairs our ability to do anything basically in a sustainable way. So, in 2009 and, again, with strong advocacy from the National Marrow Donor Program, Be the Match and the society I'm privileged to be leading soon, the American Society for Blood and Marrow Transplantation, the Center for Medicaid Services agreed to cover MDS under this coverage of

evidence determination. So, it means within a study so we have created a study basically so that if you get a transplant with Medicare we basically agree to report the data to a registry that says we're doing this stuff and we're collecting this. So, for seven years. So, the International Blood and Marrow Transplant Registry and I'm actually chairing a committee for them, too, has the approved study. So, you don't really have to know this, but this is what would happen if you're Medicare years and you're coming you would end up being transplanted under this study which isn't really a study. We're doing transplants the way that we always did. We know that they cure myelodysplasia patients. I just showed you data that suggests that it's curative and then just to show you in 2016 we expanded the coverage of allogeneic transplant to multiple myeloma, myelofibrosis and sickle cell disease, a blood cell disorder. We don't have transplant. We can't do a donor transplant for lymphoma, for example, even though we know that it can be curative. So, this is the kind of stuff that I'm doing on a national level in terms of advocacies.

So if you look at 2009 to 2010, less than 100 patients in the United States were transplanted over the age of 65 and these patients were almost certainly patients who had private insurance, not Medicare that said okay, yeah, we'll cover the several hundred thousand dollars of cost. The reason that the number of MDS transplants has increased now to over 350 this is an incomplete statistic for 2015 is because of this Medicare advocacy and effect that Medicare is now covering these transplants. Now, the reality is and for all of you who vote and lobby your congressmen, we actually lose probably $40,- to $100,000 in every Medicare transplant that we do. We still do them because it's ethically necessary and it's important, but Medicare, for example, when we do an unrelated donor transplant doesn't cover any of the cost, the typical cost, $45,000 to get a donor product and it doesn't cover it all. So, this is for the MDS Foundation can help us advocate on a national level for better coverage to at least even cover our costs. We're not looking to make a profit in academic medical centers. We're looking to have a sustainable academic mission, but the number of transplants done for MDS has dramatically increased primarily because in 2009 our society and others, again, were able to get it covered.

So, if you look at unrelated donor transplant. So, if you look at the arc of what I've talked to you about, we've realized now that it's not super high doses of chemotherapy that are critical. It's the immune system. So, we've lowered the dose of chemotherapy. We're doing older patients who are actually sicker and if you look at the number of transplants this 2004 to 2007. This is all diseases. This isn't just myelodysplasia. If you look at individuals under the age… over the age of 50 despite that this is the bulk of patients with cancer, we get cancers typically as we age, but there are fewer transplants over the age 50 than transplants done in the 18 to 50 year old group. Well, now appropriately the number of transplants that are performed these are unrelated donor transplants, more complicated transplants are actually now greater than the patients in 18 to 50. So, we're now actually just in the last several years have we gotten so good at doing transplants that we can do transplants in older patients, patients with heart problems or other things like that beforehand that we wouldn't have done before. If you look here, I think this is a really remarkable statistic. If you look at individuals over the age of 64. So, remember the majority of myelodysplasia patients are in this group. There are almost no transplants done. This is 2005.

Look here at this. This is the second highest bar now of all the unrelated donor transplants done by the National Marrow Donor Program and the highest bar is the individuals from the age of 51 to 64. So, we've had really a dramatic transformation in our ability to do stem cell transplants in older people and that's because we kind of changed the way that we do it. We're better at doing this. We're having better outcomes. So, despite the fact these statistics actually aren't as good as… they're better than they look because if you look at transplants that were done 1988 and 2002, one year survival for patients transplanted with myelodysplasia or myeloproliferative disorders was 42 percent. It was 36 percent at two years. Now, at 2012 to 2014, 50 percent of patients are alive at two years. These patients who were alive at two years are likely to be cured of their disease and most, 85 percent of them are off transplant related medications and are leading a high quality life. Some will have some chronic graph versus host disease and be seen, but by two years really most of the mortality related to transplant are there. Now, obviously, 50 percent means that half of the patients haven't survived. I'm not trying to paint this as a place that we want this eventually to be, but this is important because, again, most of the patients who are transplanted are actually patients with advanced disease who are not likely to live beyond two years at that point and the other thing that's critical is that these patients that we're transplanted before 2002 were under the age of 55 mostly if you look at the statistics and now these are… we have better survival with older patients who are much more sick to begin with and with more advanced disease.

So, our (inaudible 2:30:32) and what's happened here. So, I was recruited from MD Anderson Cancer Center 2008. We moved the inpatient unit from Jackson Memorial Hospital to Sylvester in 2011 and our volume has dramatically increased to the point where we're doing about 200 transplants a year. If you look at the number of transplants that we're doing from unrelated donors they're dramatically increasing to about 80 a year expected this year in 2016. So, we've been, I think, one of the fastest growing transplant centers in the country and I'm not going to show you the data, but our outcomes have been exceptional, better than predicted in national registries and I'm just going to show you a couple of conclusions from our inspectors from the transplant programs are highly regulated and we have our own very, very detailed accreditation process that we take months to prepare for and I'm just telling you this because I'm really proud of what we have at Sylvester. So, Dr. Komanduri and his team demonstrated a very cohesive and well-organized transplant center. Their transplant numbers have increased rapidly and the University of Miami has responded by providing increased inpatient and outpatient facilities. We have an experienced and knowledgeable team of transplant physicians, nurses and support staff that provides excellent care for their patients and I'm just fast forwarding to something we got a week a and a half ago. Dr. Komanduri and his team, this is from 2016, three years later, provided Miami with a much needed, large, high quality transplant center. The team is cohesive. The leadership administration has been very supportive by helping recruit well qualified physicians and staff to continue the growth of this program experience. The program has succeeded in keeping quality as a priority as evidenced by the quality management plan and the implementation of strict standards. I'm very proud of this because this is not something that I

was able to do. It was something like 65 individuals that we've added to this team have done together.

So, how can we improve transplant outcomes? I have a few more slides. Select patients that are likely to benefit. We don't want to pick patients who have great disease that are going to do fine without transplant because there are risks that can be very serious. Develop better ways of suppressing the immune system. I was talking to someone about this this morning. To me this is the heart of my research. How can we find patients to… the problem with graph versus host disease is we typically can suppress it but it leaves the patient's immune system decimated and at risk for fatal infections. Well, if we have better ways of targeting the immune system so that when patients develop graph versus host is we can suppress the immune system in more selective ways and this is true not only for transplant, but if you hear rheumatoid arthritis ads on TV you'll hear a beautiful ad that says here's what it can do to your freedom and then you'll hear 45 seconds of warnings about if you have tuberculosis, if you have this, if you have this and that's true. So, we don't have suppressive… we don't have ways to suppress the immune system that are selective and targeted. This is a critical area of research for me.

I'm not going to go into it today, but we are in some ways using unmodified T cells without transplant to try to treat leukemia. This is not really true for myelodysplasia yet. There's some really proof of principle ways. The problem is if we had T cell therapies that could destroy the myelodysplasia cells we would wipe out the bone marrow and still need a stem cell transplant. So, it's unlike diseases where the target is on a cell that doesn't produce bone marrow cells like leukemia and lymphoid leukemia and lymphoma where there's some dramatic advances. One of the things is to give post-transplant maintenance therapy. I showed you that unfortunately despite doing transplants that succeed up to 25 to 30 percent of patients will relapse afterward and that's really devastating. We think that we're doing something putting patients at this risk and hoping it will cure them, but then we still can see relapses. So, one of the things we can do is to take drugs that are known to work and are not curative from myelodysplasia up front but can be helpful like Azacitidine and give them afterward. So, many of you will know what Azacitidine is. Some of you will have been treated by it. It's a nucleoside analog. It's a hypomethylating agent which means that it affects the way the DNA makes proteins and it has immunoregulatory properties as well meaning it can affect the immune system. So, Azacitidine was approved to the US in 2004 for myelodysplasia. The first application was in 1971. By 1976 more than 800 patients had been treated with Azacitidine. I first saw patients being treated with Azacitidine in the mid-1990s when I was a fellow in San Francisco and, again, beginning in 1984 one of our major cooperative groups began a series of three studies from 1984 to 2002 examining the efficacy in advanced MDS patients. Around 15 percent of patients had again, there were about 40 percent response rates. So, a little less than half the patients who get treated with Azacitidine will respond with improved counts for longer survivals, but it's not curative in anybody though there are patients who can live long, long time with relatively stable counts. So again, 40 percent response rate. So, unfortunately, this was really one of the best advances that we've had. I say unfortunately

because 40 percent response rates are nothing that as academic physicians we should be content with.

I was part of a study conducted by Marcos de Lima who's now head of the leukemia and transplant program at Case Western in Cleveland but when Marcos and I worked together at MD Anderson giving low doses of Azacitidine. Typically, we give 75 milligrams per meter squared for patients who are being treated with Azacitidine in the non-transplant setting, but we gave lower doses after transplant at monthly intervals starting at about day 42 about a month and a half after transplant and the suggestion was that maintenance therapy may contribute to the treatment of patients with AML, MDS and to prevent relapses and that they might actually even be better and decrease the risk of graph versus host disease. There are some theoretical reasons to believe that and what we showed in a study that was already published in *Cancer* a few years ago was that it's not the standard of care, but it seems promising and it's something that at least when we… it was not what we call randomized control trial, but when we looked relative to other patients with similar risks, it appeared that fewer of those patients relapsed afterward and that they tolerated in these lower doses. So, just this year there was a paper published, Azacitidine has to be injected. It has to be given either under the skin or IV and there's no a study looking at the efficacy and safety of an oral Azacitidine compound in patients with lower risk Myelodysplastic Syndrome. This was a study that was led by Gabriel Garcia-Manero and again, another of my former colleagues at MD Anderson and basically 55 patients were treated in either 14 or 21 days, every 28 days and it was safe. There were a few deaths, but again in patients with myelodysplasia who we know bad things can happen for other reasons, 38 percent of the patients had clinical responses. So, not very different in terms of overall response rate, about the same as what we would expect from the traditional form of Azacitidine that's not for which there is no pill. So, given the prior safety of subcutaneous or injected Azacitidine following allogeneic transplant, we don't know about the efficacy. We haven't proven that that is better. We are very interested in the possibility of a clinical trial examining whether oral Azacitidine could decrease relapse rates following allogeneic transplantation and I'm very happy to say I was just in Germany last week at a meeting on relapse after allogeneic transplant and had this is a Celgene drug and had a very high level meeting with a very senior person who heads the drug development for myelodysplasia and the AML for Celgene and is very interested in doing a trial that will probably happen at here at Memorial Sloan Kettering, Case Western and a very large transplant center in the United Kingdom. So, probably just four sites and I'm very optimistic in that discussion. I don't want to speak for something that's not yet negotiated, but we'd hope that this might be something that we could open in the next six to 12 months and have patients be treated here with the notion would be we would do with a transplant inpatients who still had disease that needed to be transplanted, but then rather than just leaving them alone and hoping that they don't relapse and doing the other things that half of the patients who got transplanted in a randomized way would get oral Azacitidine and we would see whether those patients relapsed less than the others with no increased risks.

So, this is my last slide. Stem cell transplantation probably the first evidence that immunotherapy could cure cancers incapable of being cured including myelodysplasia and AML. The outcomes have improved dramatically through the development of multidisciplinary care models and academic cancer centers like Sylvester. This isn't something that can be done in the community. Future trials, I think, will combine transplant and pre and post-transplant approaches to improve outcomes. Obviously, we hope that non-transplant… I mean, I would love it if a non-transplant option was so wonderful that I would never have to do a transplant and put patients at risk of these things. I don't see that happening on the basis of what I see now, but if patients are in better shape and get treated before a transplant and then we can do a transplant and then improve outcomes and transplant and all the ways that we've been improving outcomes of that improvement continues to occur, I think we'll do better and better and I think I can honestly say that Sylvester's at the cutting edge of these approaches and I'll just say this is a Winston Churchill quote, "For myself I'm an optimist," and I think you have MDS then you're dealing with an incurable disease there is reason for optimism. It doesn't not seem to be much use being anything else and then another Winston Churchill quote, "I'm easily satisfied for the very best." I'm very convinced that we have a really wonderful group of clinicians and administrators that I'm proud to work with and at least we can work toward a brighter future together.

So, thanks for letting me spend some time with you. I'm happy to take some questions if any of you have them.

(Applause)

Audrey Hassan: Does anyone have any questions? I want to thank Dr. Komanduri. He actually has clinic today and so he's got to hurry back to his patients, but thank you so much for donating your Saturday to us.

Krishna V. Komanduri, MD: My pleasure.

Audrey Hassan: We appreciate it very much.

Krishna V. Komanduri, MD: Any other questions? Okay. Great. And I think the MDS Foundation can put you in touch with me by E-mail. I'm happy to answer questions if any of you have them and, again, thanks for your attention. Really, obviously, a bright group and I'm sorry I can't spend more time with you, but a pleasure to be here.

Audrey Hassan: Thank you.

Krishna V. Komanduri, MD: Thank you.

Audrey Hassan: I think there is one quick question.

Q16: My daughter (name) (inaudible 2:40:46)

Krishna V. Komanduri, MD: (Name). We love (name) and miss her. So, thanks. I told her that I couldn't… we couldn't spend a lot of time talk today.

Q16: (inaudible 2:40:51)

Krishna V. Komanduri, MD: She can give you my cell phone number. We can talk. I'm happy to help in any way.

Audrey Hassan: To keep on the schedule if you'd like to get yourselves lunch and we'll reconvene in here and then we can have Jessica MacIntyre who's a nurse from Sylvester Cancer Center speak during the lunch to keep on the program time if that's okay with everybody. Alright. Take your time. Do a bathroom break, bring your lunches back in and then we'll start with Jessica whenever you're back in here. Thank you.