



Speakers:

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**Bart Scott, MD:** Thank you very much. It's a pleasure to be here. We had over 90 patients registered to attend this even. So, it's a very good turnout and I appreciate that.

So, this is going to be a general view about MDS. We're going to talk about some of the therapeutic interventions. We have a lot of excellent speakers lined up today. I typically save thank you's for the end, but I'm going to start with thank you's now just in case some of the people that I need to thank are not here at the end, but Joan (inaudible 0:37) thank you very much for helping to organize this and put this together. Joan works with me at the Fred Hutch and she keeps me on schedule and keeps me on time and make sure that I do everything that I need to do in order to be a functioning person. So, I greatly appreciate that.

(Applause)

And then Dr. Deeg is here and he basically founded this program of MDS and the truth is none of this would be happening without him. So, thank you for organizing everything and putting things together. It's obviously really taken off in a positive way.

(Applause)

And then Kim Varney, she's one of our research coordinators. Many of the patients know her that are on clinical trials. She's managing two very important trials right now and helps patients with any questions they may have regarding the studies and is, obviously, very important to making sure that the studies operate in an efficient way. So, thank you.

(Applause)

And Kate Duran is sitting beside her and many of the patients know her as well. She's also managing some of our MDS clinical trials in the same way research coordinator and keeps every one of the patients on the trials informed of what's going on and make sure that we're up to taking all the clients. So, thank you very much.

(Applause)

Alright. So, with that I'll get started and my topic is what is MDS and so we'll start with that and I can just tell you that it's not a straightforward answer. So, it's not a one sentence type thing and

the truth is that MDS is a collection of diseases with multiple different causes and not every single patient is a little bit different and it's not one single disease. It's a collection of different diseases. It's characterized by bone marrow dysfunction. So, inside your bones are what we call stem cells and these stem cells give rise to several different other cells that's circulating in your body that have very important roles in making sure that your body is functioning normally and red blood cells which are the erythrocytes gives you energy. The megakaryocytes which make platelets prevent bleeding and bruising and then you have these white blood cells that helps fight off infections. So, primarily that would be the neutrophils and patients with MDS can have dysfunctional production of one, two or all three of these cells and some people have problems with neutrophils and get infections, some people have problems with red blood cells and feel really tired and fatigued and other people have problems with platelets and have a lot of bleeding and bruising.

So, this is a Zen diagram showing MDS and MDS does overlap with some other diseases like myeloproliferative neoplasms and actually Dr. Salit's going to be speaking about that between 1:00 and 1:30 today and it also overlaps (inaudible 3:44) aplastic anemia. There's an entity called hypoplastic MDS that has a lot of features that are shared with aplastic anemia and then, of course, there's a progression into acute leukemia and there is some overlap between the MDS and acute leukemia people who have what we call high bone marrow blast counts. So, there's 9,700 new cases per year of MDS. It's actually more common than acute myeloid leukemia or AML. Overall, the median survival is two to three years and the (inaudible 4:15) burden is likely underestimated and there has been studies looking at this and many patients over the age of 70 with anemia is not really evaluated. So, they're not being diagnosed and we've done some outreach programs to community practice physicians to try to get them to be more aggressive in their diagnostic workup. I think there's a feeling that people of an older age group don't necessarily need to be worked up for their anemia because there's not really interventions that they could receive that would be a benefit and hopefully this talk today will prove that to be untrue. It's predominately a disease of older aged patients and the median age is about 72. It's more common in men than women and the incidence does increase with age. So, it's about 1.5 higher incidence in men than women. This survival curve was taken from the old diagnostic model and I'll go through our new diagnostic model as part of this talk today. So, this is looking at age related incidence. This is just one study. There have been many studies looking at age related incidence and there's a clear association with risk of getting MDS and increasing age.

So, what causes MDS? Well, the truth is we don't know. So, there are a lot of theories and there are many different causes. Now, for some people there are inherited forms of MDS. That is a small, small, small minority of patients with MDS and it's usually a well-defined family history and we do have some patients that we follow that have an inherited form of MDS, but the vast majority of patients with MDS have it acquired and there's different stages that they go through. Early stage MDS is characterized by low blood counts and a low risk of progression to MDS, but higher staged... I'm sorry, AML, but higher staged MDS is characterized by increased blast counts in the bone marrow and a higher risk of going into acute leukemia.

So, one of the things that has been coming out over the past five years is this increased reliance on what we call cancer genomics and historically when MDS was kind of first looked at there wasn't a great understanding of what we call cancer genomics, but inside your cancer cells there are chromosomes and these chromosomes have your genetic code in them and about 50 percent of patients with MDS have a type of cytogenetic abnormality. So, half don't and when we do what's called a karyotype and you may have heard about that we're actually looking at your chromosomes and we're looking to see if there's any major changes and this is useful for prognosis and also for diagnosis, but I've had a molecular level. So, when you're looking at the actual genes themselves so this is a very microscopic level. We can also do mutational profiling. So, some of you may have heard that term 'mutations,' but it's really looking at single point mutations within these chromosomes within the cancer cells and if you look at some series of patients with MDS almost all patients with MDS either have some type of cytogenetic abnormality or some type of underlying mutational abnormality and that's helpful for risk stratification and eventually we're hopeful that it will be helpful for therapeutic interventions and that's kind of where we hope that things go because then the treatment would be targeted for the patient's individual specific disease.

So, right now in order to diagnose a patient with MDS they have to have at least 10 percent of the cells in the bone marrow showing dysplasia. Now, dysplasia is a term that refers to abnormal growth. So, that's what MDS is basically abnormal growth of cells inside the bone marrow that results in low blood counts. They also have to have at least one blood count that's low so that would be red blood cells or platelets or white blood cells. You need to make sure that there's not a secondary cause of dysplasia. So, that's usually things like vitamin B12 deficiency, hypothyroidism, alcohol use and copper levels and then there are some patients that you can diagnose just based off their chromosomes. So, if they have certain characteristic chromosomal abnormalities that would be diagnosed with MDS.

This is the current WHO classification of MDS. It's basically divided into two groups of patients. This top part here are patients with a low blast count and that would be a bone marrow blast count of less than five percent and that's very helpful from a prognostic perspective. These patients generally have issues with low blood counts. They may need blood transfusions, but they generally have a lower risk of going into leukemia and the bottom part here are those patients who have increased blasts usually greater than five percent and these patients would have a worse prognosis and a higher risk of going into leukemia.

One of the things that has happened over the last five years is an increased reliance upon cytogenetics or looking at outcomes. So, when you have your bone marrow done there's two very important pieces of information as a physician that I would want to know from that bone marrow and one of them is what is the blast count. So, that was kind of reviewed on the previous slide, but the other one is what is the cytogenetics and you can look at these cytogenetics and the blast count and it helps us to determine your prognosis. So, if you're a patient with MDS,

hopefully, you would know what your blast count is and what your cytogenetics show because that would be information that your physician should have and if you ask that question you should be able to get that answer from them.

So, this is the current prognostic system that we use. It's called the revised IPSS or the IPSS-R. IPSS stands for International Prognostic Scoring System and it looks at the following factors, but the blast count is one of them and so you can see these different blast percentages. A normal person would have a blast count of less than five percent, but the lower it is the better the prognosis and then we look at your blood counts. So, what's your hemoglobin? That refers to your red cell counts. What's your neutrophil count? That's kind of from the white cell counts and what's your platelets and remember the platelets are what helps to prevent bleeding and bruising and then the last category there is your genetic code, the cytogenetics. So, we look at all of these different pieces of information and we're able to come up with a scoring system and we would place you into one of these risk groups and this does predict median survival. Now, no one can tell you you're (inaudible 11:45). People don't have that power and each person is an individual. So, these prognostic models are based on what happened to other people not necessarily what's going to happen to you. The other thing about these prognostic models is that most of them did look at intervention. So, many of these prognostic models and this one in particular patients were treated with growth factors and with transfusion support, but not necessarily disease altering medications.

(Inaudible 12:18) this idea about mutations and mutations are becoming more important characteristics in MDS and we're using it more and more to determine prognosis and also additionally hopefully with therapeutic interventions, but one of the types of mutations that you can see with patients with MDS is what's called spliceosome mutations and about 85 percent of patients with MDS have some type of spliceosome mutation and we're actually finding that there's certain types of MDS that are defined by certain mutations like SF3B1 which is strongly associated with patients who have refractory anemia with ring sideroblasts. So, we tend to see that type of mutation in patients with what we call RARS or refractory anemia with ring sideroblasts.

So, as I said we're learning more things about MDS all the time and one of the things that we have found is that there is clonal evolution model. So, people start out with what's called a founding mutation and then they develop subclone and these subclones may potentially increase the risk of them going into leukemia. So, this is basically looking at your genetic code and not at a chromosome level, but at a very small mutational level we're able to define and determine in patients with MDS what we call founding mutations that we believe are important in the pathogenesis of why people get MDS. So, this would be the founding clone and then over time people develop new mutations that then increase the risk of going into leukemia and they can also have subclones that may be more resistant to different types of treatments, but if we can target this founding mutation that would be a good way potentially to get rid of all of these different subclones have developed in a patient and would hopefully do a better job in treating

people. So, this is showing what would be considered founding mutations and secondary mutations as developed over time. These mutations can have a prognostic impact. So, these mutations in red have a negative prognostic impact and mutations in green have a positive prognostic impact. So, all of this is relatively new information and I wouldn't necessarily say that it's standard of care for everyone to have mutational testing at this point in time, but it is expected that in the future our prognostic models will incorporate these underlying mutations. So, this is kind of a look at what the future holds in regards to MDS. This is just one prognostic model that uses mutational abnormalities and I just put this up here to show that this is kind of what we plan to do in the future. Gene mutations can also be helpful in trying to distinguish between someone who has MDS and someone who has leukemia and that's basically shown in this and can be helpful in determining that.

Alright. How about how MDS patients present. Well, some patients present asymptotically. They go to their local doctor and they get a CBC and their doctor says, oh, your blood counts are low, come back in a month and let's see if they're still low and sometimes it is and then eventually the physician will say okay, we need to do a bone marrow to try to figure out why your blood counts are low and the patient may say well, jeez, I feel fine, doc. I don't really have any problems, but then they may be diagnosed with having MDS. The majority of patients do have some symptoms related to their low blood counts and anemia by far would be the most common low blood count with fatigue, shortness of breath, chest pain and heart failure. Infection can also be seen. So, patients may present this. Retrospectively, it is the principle cause of death in patients with MDS and then bleeding. So, people can have bruising, they can have nose bleeds and this could be a presentation of MDS. When we work up the patient we check their blood counts. We check their iron levels. I mentioned that we rule out other causes of MDS like low folic acid levels and low B12 levels. We check to make sure they're not hemolyzing and then we also would do what's called a serum (inaudible 16:55) to turn the role for growth factor therapy which we'll go into and in order to diagnose MDS you need to do a bone marrow and the first time we would do both an aspirate and a biopsy. So, what's the difference between that? Sometimes the terms are used interchangeably, but there is a difference between them. An aspirate is just taking out fluid. A biopsy is actually taking out a piece of bone chip and when you do a biopsy you can look for things like cellularity and whether or not there is scar tissue present and that's hopeful to us as a prognostic marker because if there is scar tissue present then patients typically have worse outcome and then cytogenetics is usually done on the aspirate material, so the fluid that you take out. So, for the first bone marrow we like to make sure that we get a bone chip and also the fluid, but you don't have to have that done every single time. Sometimes we'll just take the fluid out and when we do this bone marrow we look at what's called the cellularity and then as I said in order to diagnose MDS you need to have dysplasia involving at least 10 percent of any single cell line or you have to have these characteristic cytogenetic changes. We'll look to see what the blast count is. We'll look to see if they have what's called ring sideroblasts because that's a certain type of MDS that has a better prognosis. That's the one that has the association with the SF3B1.

So, this is an example of a patient with MDS and what you're supposed to notice here is that there's a lot of empty spaces in their bone marrow and so we would call this low cellularity because of these empty spaces and we would say that this is hypocellular MDS which has that overlap with aplastic anemia.

This is a patient who has ring sideroblasts. So, you basically see rings of blue around their immature red blood cells. So, this is a very characteristic finding of a certain subtype of MDS called refractory anemia with ring sideroblasts. So, you see the rings are blue and when we do your bone marrow we do different stains on them and we look at them. So, that's why we can't tell you anything the very first day you get your bone marrow because these stains have to be... the slides have to be paired and stained and have to be evaluated and looked at and it can take up to three days for that to occur. This is another example of a ring sideroblast where you see these blue dots forming around an immature red blood cell.

This is a megakaryocyte. So, mega is another term that means big and karyocyte means cell. So, this is a big cell and it's dysplastic because of the formation of what you call the nucleus that you see here. It's very deformed. So, this would just give you an example of what we call a dysplastic megakaryocyte and so when the pathologist looks at this they would say okay, here's one cell that's abnormal and as I mentioned you need to have at least 10 percent of these cells that are abnormal in order to diagnose MDS.

This is a red blood cell precursor that has what we call nuclear-cytoplasmic dyssynchrony. So, basically that's just telling you that there is this evidence of dysplasia that's there. It's not maturing in a normal way.

There's a certain subtype of MDS called Del 5Q. So, that typically has a very good prognosis. They have these unusual type of megakaryocytes that you see here. Their nucleus is not very condensed as you see here. It has a lot of what we call open chromatin. So, this is just another example of what the pathologist would be looking at.

Here is the ring sideroblast. This is an abnormal neutrophil in the peripheral blood. We call that a pseudo Pelger-Huët anomaly. So, when you have your bone marrow done they typically draw blood as well and then look at the blood smear to see if there's any abnormal cells there in the blood smear. By way of example this would be considered to be more of a normal neutrophil and this, obviously, has a very abnormal appearance. Sometimes we call this the bar dumbbell because it looks like that.

These are what we call hypolobated micromegakaryocytes. Megaloblastoid (inaudible) you may have heard that term. If you'd heard the term megaloblastoid anemia that can be seen in MDS as well, but it's another example of dysplasia.

So, I'll put these slides up not necessarily to give you a full education of looking at dysplasia in

MDS, but basically just to give you some idea of what we look at when we view your bone marrow and when we view your peripheral blood and also to convey to you that there is some subjective nature to this. So, as a patient you would like your physicians to be definitive, but this type of determination just looking at it you can see that it could be somewhat subjective and sometimes when pathologists review your marrow there may be disagreement about what's considered to be dysplasia and what's not considered to be dysplasia which is why I think it's important to have your marrow evaluated at least at some point at a center of expertise because those pathologists are very used to looking at patients who have MDS. They're very good at looking at the different types of dysplasia and you may get additional information that's helpful for a prognosis and treatment if you have your marrow reviewed by someone who's an expert in reviewing marrows for MDS.

So, MDS is difficult to diagnose. The clinical and diagnostic studies are imprecise. Many of these bone marrow cellular entities overlap like with aplastic anemia and cytogenetics and molecular testing has become increasingly important and certainly everyone with MDS should have cytogenetic testing and I think in the near future the same would be said of this molecular testing.

So, I'd be happy to take any questions that you guys may have about what is MDS. So, if you have any questions about this talk. Yes?

**Q1:** You were saying it's good to have an evaluated bone marrow in a center. In Hutch, just where they have the person who could really evaluate well.

**Bart Scott, MD:** Yes.

**Q1:** Okay. So, we're fine with that.

**Bart Scott, MD:** Yes.

**Q1:** Okay. Just wanted to get (inaudible 23:31)

**Bart Scott, MD:** And there are centers of excellence defined that are (inaudible 23:36) the MDS Foundation. So, it doesn't necessarily have to be us and I think it's great if it's us, but there are many centers of excellence throughout the United States.

Yes?

**Q2:** My husband was diagnosed in 2009 and he had extra blasts and he basically had 9 months to live without a transplant. Has there been significant changes as to what the plan is for as to how you handle and prognosis and is it still the same as having a transplant or/// just curious on that.

**Bart Scott, MD:** Right. So, Dr. Deeg is going to be speaking about transplants and when it's indicated and when it's not indicated. So, I think he'll be able to answer that question. One thing I will say is that the mutational analyses that I mentioned is becoming a more important part of when we made that decision to go forward with transplant and so we're not only looking at the blast count, we're not only looking at the cytogenetics but that's another aspect that we're looking at to determine prognosis, but in general transplantation is reserved for those patients who are of good health, who are the relatively younger age and who have a poor prognosis.

Yes, sir?

**Q3:** On the cytogenetic and molecular testing is that (inaudible 25:05) down in the bone marrow itself?

**Bart Scott, MD:** Interesting question. It would... for cytogenetics it's preferred that it's done on a bone marrow, but the mutational testing can be done on the bone marrow or the peripheral blood. It doesn't necessarily have to be done on the bone marrow. In order to do the cytogenetics you have to capture the cells and stay the division and it's typically hard to do that on the peripheral blood, but the mutational testing can be done on peripheral blood or marrow.

**Q4:** Another question. You had a slide that talked about the minimal (inaudible 25:43) had all the different components. It was like 10 percent of the cells have to be dysplastic and then something about blasts and something else.

**Bart Scott, MD:** So, you need at least 10 percent of any single cell line that has dysplasia or you could have the bone marrow blast count that's greater than five percent or you could have a characteristic cytogenetic abnormality and all of these would be diagnostic of MDS. Right now mutations alone are not sufficient to make a diagnosis of MDS right now.

Other questions? Yes, sir.

**Q5:** What's the line we're making considered on your blasts? It's gone from Myelodysplastic Syndrome to AML.

**Bart Scott, MD:** Twenty percent. Now, that's somewhat arbitrary. I mean, what's the difference between 19.9999 and 20 percent? That's the number that people have agreed on and that's the number that we use. I think that it would be naïve to think that something special happens until 19 and 20 to make you completely different.

Okay. Yes, sir?

**Q6:** In the handouts are there notes here on your presentation?



**Bart Scott, MD:** Yeah. You know, I think that it's being recorded and it'll be available online. Is that right?

**MDS Foundation:** We can make that happen. Yes. So, just if you'll check back to the MDS Foundation website and to Audrey, some of you came out a little late, Hassan is our patient liaison. She can arrange that for you.

**Q6:** Thank you.

**Bart Scott, MD:** Yes, sir?

**Q7:** How often do you have to have a bone marrow in this process?

**Bart Scott, MD:** Yeah. So, that's individualistic and I wouldn't make a statement that would be... that should universally applied to every patient. So, that's a question that involves a complex set of parameters and risks, the patient age, all of these things that are quality of life are all considered the type of intervention that they're getting. So, that's not a question that I would be able to answer broadly. It's very individualistic per patient per individual.

Okay. So, move onto the next topic which is non-transplant therapy for MDS.

So, when we're considering treatment for MDS one of the major things that we look at is what their blast count is and in general the higher the blast count the more aggressive we are with treatment like with giving a transplant and the lower the blast count the less aggressive we are with treatment by giving observation or growth factors. We also look at transfusion support. If patients are heavily transfusion dependent we would give more aggressive treatment. If they have good bone marrow function and they don't need as much transfusion support and they have a low blast count sometimes observation alone is an appropriate choice for patients with MDS. So, it's obviously a very complex algorithm that one goes through in determining the best treatment for an individual patient.

So, in regards to lower risk patients transfusion support, growth factors, Lenalidomide also known as Revlimid, Azacitidine also known as Vidaza, our enrollment into a clinical trial are all potential appropriate treatment options. So, the patient primarily has anemia. That'll be a low red cell count characterized by fatigue, shortness of breath, possibly having chest pain. The principle treatment would be packed red blood cells. So, when we transfuse blood we don't transfuse whole blood anymore. The blood is divided into different elements and there's three main elements. There's red blood cells, there's white blood cells and there's platelets. So, with the red blood cells there are side effects of getting a transfusion. You can get activation of the immune system. So, people can get a lot of inflammatory symptoms after the infusion of red blood cells. So, things like hives, fevers, chills, they can have accumulation of fluid into their lungs. They can get volume overload with swelling in their feet, fluid that gets into their lungs as well and

then these red blood cells do have they have iron in them and so the iron can build up over time and it can cause damage to the heart and the liver over time. So, no therapeutic intervention is absent of side effects and that includes transfusion support.

Platelet transfusions is done for thrombocytopenia and this slide is showing a patient with thrombocytopenia. These little dots here are what we would call the platelets and patients who receive platelets can receive transfusion... can develop transfusion reactions with fevers, chills and hives and they can also develop (inaudible 31:03) which means it becomes more and more difficult over time to find platelets for them. Platelets are more aneugenic than red blood cells. So, they stimulate an immune reaction more than red blood cells. We can support people with red blood cells for many, many years, but for platelets it becomes difficult to support them greater than a year because they develop antibodies to the platelets and it becomes harder and harder to find appropriate platelets for a given individual over time.

I saved the middle one for last because it's probably the... well, it's definitely the most controversial and there actually may be no benefit for anyone assigned transfusions. So, there's a lot of different studies that have looked at this, but I can tell you that we would really only consider granulocyte transfusions in the setting of an active, severe infection in a patient with a low white blood cell counts. It's laborious and it has a short lived effect and usually those cells stick around very, very, very long. It's not widely available and the clinical utility is unproven. So, there's some studies showing potential benefit, there's other studies showing no benefit. So, it is a controversial area.

Growth factor areas. This is the actual most common therapeutic intervention that's used for MDS. There's no FDA labeled indication for MDS for any of these growth factors at this point in time, but with that being said they are still the most commonly used medication. So, there's growth factors that primarily stimulate red blood cell production and that would be Procrit, Aranesp. These are given as a subcutaneous injection. There's other growth factors that stimulate white blood cells, Neupogen and Neulasta. These are also given as an injection and then there's platelet growth factors, Romiplostim also known as Nplate that's given as an injection and then Eltrombopag also known as Promacta is given as a pill and these would stimulate platelet production. The Romiplostim and Eltrombopag are approved for IAT which is what we call immunity aided thrombocytopenia. Eltrombopag is also approved for aplastic anemia which as I said is really related to MDS and so these are the currently available growth factor treatments. Generally, these types of interventions are used for early stage MDS.

There are things that we can look at that predict response to red blood cell growth factors and one of those is the EPO level and EPO level refers to Erythropoietin and that's what this is. Erythropoietin and Darbepoetin are basically erythropoietin. So, if you already have a very high EPO level giving extra EPO is not necessarily beneficial. So, before we would start you on growth factors for red blood cells we would check that EPO level before starting you on that treatment and that can help us to decide if it would be of any benefit.

This is a trial looking at different growth factors therapy versus supportive care for patients with MDS. So, this was actually a randomized trial. They allow a crossover after four months. So, patients were randomized to either get Erythropoietin with or without GCSF versus supportive care and the supportive care arm is in a solid line and the EPO arm is in the dashed line and there was no difference in survival. So, there was no survival benefit seen in this trial for the people who got growth factors, but it should be noted that this study allowed for crossover after four months. So, it's hard to show a difference in survival if everyone gets the same treatment. So, that I would say wouldn't necessarily persuade me from using these medications. There is no difference in leukemic transformation. They did find that the erythroid response rate which was the primary end point of the study was higher in those patients who got Erythropoietin. So, it made their hemoglobin better and they needed less transfusions if they got treatment with Erythropoietin. So, there are a group of patients that can benefit from that. There is some data to indicate a potential benefit with survival. This is a comparison of two different groups of people. The Nordic group primarily from Sweden and the Italian group, obviously, from Italy, but the practice at that time was in the Italian group they were basically not given Erythropoietin and GCSF whereas the Nordic they would as they basically show that the people who were in the Nordic group lived longer than the people in the Italian group, but that may not necessarily be due to the Erythropoietin. Italians like to smoke and drink and (inaudible 36:01) so that (audience laughter) of worse survival. One of the things they did look at and this was going into leukemia and you can see it looks about the same. So, getting EPO does not increase your risk of going into leukemia.

ATG. So, that stands for anti-thymocyte globulin and that's basically horse serum that's directed against your own immune system. So, there are a subset of patients with MDS who have it because their immune system is basically attacking their own bone marrow and it's typically this kind of MDS group of patients that overlap with aplastic anemia and so there are some characteristic findings you can see in their bone marrow. It tends to be people of a younger age. They have a certain immune system type and it tends to be people who have a shorter duration of red cell transfusion dependence that benefit from ATG therapy. This is one group that looked at predictive factors of response to ATG. Other groups have looked at these factors and have shown that you can have responses here in an older age group. So, I'll just say that there's a lot of things that we look at when we determine whether or not a patient would benefit from ATG and it includes a variety of factors including their cellularity in their marrow and their age, but if you do respond to ATG you have a much better prognosis than if you don't. Now, what this is getting at is basically this is a different cause of why people have MDS and people have MDS as a result of an immune mediated attack on their bone marrow just have a better prognosis.

Patients who receive ATG and in a retrospective trial had a better survival, but this may not be because they got that ATG. It may be because they were selected to get that ATG. So, I already told you that one of the things that people look at is age. So, a critic could say that this study showed that younger people lived longer than older people. (audience laughter) A critic could

say that, but you'll notice here that they did try to eliminate age bias by limiting it to people less than 60, but that wouldn't completely correct for an age bias. So, let's just say that patients who get ATG are typically a select group of patients who are more likely to respond and typically have a better prognosis and typically have an underlying cause that's immune mediated and thus do have a better prognosis.

Lenalidomide also known as Revlimid. It's made by Celgene. It is an analog of Thalidomide and it's structurally related to Thalidomide and you can see that there's just one change here. So, you don't have to be a chemist to look at these two shapes and compare them and see that they're very similar. So, Lenalidomide is derived from Thalidomide, but it has less toxicity and it has a greater response rate in MDS patients. There have been lots of trials looking at Lenalidomide or also known as Revlimid. When these trials are done they are divided up into two main groups – those patients with deletion 5Q and those patients without deletion 5Q. Now, what is deletion 5Q? That refers to the chromosomes, the cytogenetics remember, 5Q refers to chromosome 5 and the long arm of chromosome 5. Basically these patients are missing part of their genetic code, but if they have that abnormality they're more likely to respond to Lenalidomide also known as Revlimid. So, there were two phase two trials that were done at the same time. Phase two trials are early trials where you will get whether or not a drug works. This trial enroll people with both deletion 5Q and without deletion 5Q. So, the MDS-003 trial was only deletion 5Q and the MDS002 trial was everybody else and on the basis of this trial Lenalidomide was approved for patients with deletion 5Q. The starting dose is 10 milligrams a day, either 21 or 28 days. In order to be eligible you have to be red cell transfusion dependent and for the MDS-003 part you have to have deletion 5Q. The major side effects of the Lenalidomide or Revlimid was lowering of the platelets. That's thrombocytopenia and the neutrophils. That's part of your white cell count. If you had deletion 5Q you are more likely to have lowering of your blood counts, but you're also more likely to have a response and there is a relationship between lowering of the blood counts and response and actually we now know that people who have lowering of their blood counts with Lenalidomide ultimately are people who are most likely to respond to the drug. So, this is looking at the two different trials. Both are phase two. These are early trials and the MDS-003 was the deletion 5Q and the 002 was the non-deletion 5Q and basically what they've seen is you have deletion 5Q you're more likely to become transfusion independent and you're more likely to have a long duration of transfusion independence whereas if you have non-del 5Q you're literally... you're less likely to become transfusion independent and you have a shorter duration of transfusion independence. So, if you look at the deletion 5Q the transfusion independence rate was 67 percent and in the non-Del 5Q it's 26 percent and the duration of transfusion independence was approximately two years for deletion 5Q and about 41 weeks for non-deletion 5Q.

So, do we have anyone in the room that's currently on Lenalidomide or Revlimid?

**Q8:** For 12 years.

**Bart Scott, MD:** Fantastic and you have deletion 5Q?

**Q8:** (Agreement sound)

**Bart Scott, MD:** Excellent. Another person back there on it as well?

**Q9:** Yes.

**Bart Scott, MD:** How long have you been on it?

**Q9:** Six months.

**Bart Scott, MD:** So, these deletion 5Q patients can have a really good benefit from this drug.

So, as I said the drug was approved...

Yes, sir?

**Q10:** Well, I was on it but I swelled up and I had a reaction to it.

**Bart Scott, MD:** Sometimes people do have immune system reactions to it. It does modulate the immune system and so people can have really bad rashes. They can have swelling and things like that. So, it's not for everyone that's for sure.

So, on the basis of the phase two trial the drug was approved, but is approved by the FDA and they said okay, if we approve this you have to go back and do a phase three trial. So, that's what they did and remember a phase three is basically a randomized trial. So, this MDS-004 was the recognized trial in deletion 5Q and the MDS-005 was the randomized trial in non-deletion 5Q and they're basically comparing Lenalidomide to placebo. This MDS-004 also looked at two different doses – five milligrams and 10 milligrams. Because it lowered the counts so much, 79 percent of the people who got Lenalidomide had to have their dose reduced because their blood counts went down or their neutrophil counts went down. Their hemoglobin and hematocrit go up. They didn't need transfusions any more, but their neutrophil counts and platelets would go down and as I said 79 percent needed a dose reduction. So, given that information they wanted to see what would happen if you had a lower dose. So, that's why you see this five milligram arm on this Lenalidomide trial.

So, when you look at your data this is the deletion 5Q, but the patients who got 10 milligrams had a higher transfusion independence rate compared to placebo and the 10 milligrams did better than the five milligrams. So, in general the recommended starting dose of the Lenalidomide is 10 milligrams a day unless people have preexisting low blood counts or kidney dysfunction or liver dysfunction.

This is the trial looking at non-deletion 5Q and only about 27 percent of patients with non-deletion 5Q became transfusion independent. So, it does have a lower response rate, but this is a randomized trial showing that Lenalidomide is significantly beneficial in patients compared to the placebo with non-Del 5Q when looking at transfusion independence and this was significantly different. The FDA label indication for Lenalidomide remains deletion 5Q not non-deletion 5Q.

Azacitidine. So, Vidaza, also known as Vidaza, is FDA approved for low and intermediate 1 and intermediate 2 and high risk MDS, but this was a trial looking at different dosing of Azacitidine and so many people with MDS live in communities where they don't have a cancer clinic that's open every day. So, we are. The SCCA is open every day. So, we have patients over there now who are getting treatment. We're open till ten o'clock on the evenings on the weekdays and around 5:00 to 7:00 on weekends, but community cancer centers are not open over the weekend. So, they can't give seven days in a row of treatment unless the patient is admitted to a hospital and this, obviously, causes a lot of increased burden on the patient. So, for that reason this was a study looking at alternative dosing schedules because the way Azacitidine was approved was a seven day regimen and so this looks at five days on, two days off, two days on. So, you take the weekend off. This looks at five days on, two days off, five days on. So, you take the weekend off. This just gives it for five days and the people in this study basically have lower risk MDS and what they found was that there wasn't a difference in regards to response rates between the different dosing therapies. So, it's okay to get it for five days in a row if you have lower risk MDS. So, if you're out of the community and can't come in and be admitted to a hospital to get it over a weekend it is okay to get it for five days in a row.

This is taken from the current algorithm, the NCCN Guidelines for Management of Anemia, but if you have deletion 5Q Lenalidomide would be the first choice of treatment. If you do not have deletion 5Q and you got a low EPO level then growth factors would be the best first choice of treatment. If you have non-deletion 5Q and you have a high EPO level and you have these factors that are listed here that some people think predicts their response to ATG then you should get that. ISG means immunosuppressant therapy. That's basically ATG. If your EPO level is high and you don't have these factors that would predict response to ATG then you should get hypomethylating therapy Lenalidomide or a clinical trial.

Alright. Transfusion dependence. So, is transfusion dependence an issue in MDS? The answer is yes. Those retrospective studies have shown that if you are transfusion dependent and this is red cell transfusion dependence you have a worse outcome. So, needing red blood cells is associated with a shorter survival. Now, there's a difference between association and cause. Okay? So, just because something happens after something else doesn't mean that that something caused it and so there may be other reasons why people who are transfusion dependent have a worse survival and it could be just because they have worse disease and it really doesn't have anything to do

with them getting red blood products. So, that is an issue right now in MDS and there are disagreements about whether the transfusions itself is causing the worse survival in MDS.

If you look at the number of transfusions that people get the more transfusions you get the worse the survival is. If you look at ferritin. Ferritin is a marker for iron overload.

Do we have any transfusion dependent people in the room? Okay. And do you guys know what your ferritin level is? I always like to see who has the highest ferritin level. Does anyone want to blurt one out?

**Q11:** It fluctuates. It's between 1,500 and 1,800.

**Bart Scott, MD:** Eighteen hundred?

**Q11:** Yes.

**Bart Scott, MD:** Does anyone beat 1,800?

**Q12:** I think mine's higher.

**Bart Scott, MD:** Yours is higher. Yours is around 3,000. So, you got around 3,000.

**Q12:** Yes.

**Bart Scott, MD:** Alright, but in high ferritin is associated with a worse survival, but again that doesn't mean that the iron overload is causing the worse survival. So, we have to be careful about how we assign cause.

This is a study that prospectively looked at people who are chelated versus people who are non-chelated and the chelated patients had better survival. Now, this is honestly somewhat misleading because when you look at the reasons why we would chelate someone. One big reasons is that they have a long survival because you don't typically see problems with iron overload until five to 10 years after the iron overload. So, if I'm seeing a person and they've got iron overload, but I anticipate they're going to have a short survival that's not necessarily a person that I would chelate. So, this type of study can be misleading unless it's randomized because what I'm telling you is that the people who are chosen to get chelation were chosen to get it because they were likely going to live longer. So, critics had looked at this and say physicians are very good at selecting who will live longer and will live shorter. Okay. So, getting chelation doesn't necessarily mean you're going to live longer.

This is a trial looking at giving chelation to try to improve hemoglobin. Now, that may sound weird, but these iron, this iron can build up and can also get inside your bone marrow and can

cause damage to the stem cells. So, the idea is that if we can remove some of this excess iron we can actually improve the marrow function in patients with MDS and iron overload and so this is looking at patients who have a response with hemoglobin in receiving an iron chelation and basically the argument that this is making is that iron chelation can improve hematopoiesis, improve cell production in patients with MDS and so I want to point this out because we do have a clinical trial that's open right now for people with iron overload who are red cell transfusion dependent looking at aggressive iron chelation. So, if you're someone who's within the area and you're interested in participating let them know, but we do have a trial right now that's open looking at iron chelation for people with iron overload.

So, this is looking at MDS patients who are likely to benefit most from iron overload and different recommendations from the MDS Foundation which is the group that's sponsoring this event and also the National Cancer Center guidelines and you'll see here life expectancy greater than one year and no comorbidities that limit progress. So, people who are selected to get iron chelation typically have a better prognosis. So, in order to answer the question of whether iron chelation is beneficial or not you would need a randomized trial and there is a randomized trial that has completed approval. It's called a TELESTO Trial and we're all eagerly awaiting the results of that study, but it's going to be a while before we know the results, but that very nice trial has completed accrual.

Alright. Moving on to higher risk MDS. Dr. Deeg is going to be speaking about transplants. So, my focus will be on these two hypomethylating agents and a clinical trial and clinical trials.

So, hypomethylating agents. That's Vidaza and Dacogen also known as Azacitidine or Decitabine. Show a hands in the room who's receiving any of those two medications, Azacitidine or Decitabine? Okay. So, small number of people are getting that. So, that these drugs are FDA approved for patients with MDS and one of them has shown a benefit in regards to survival, but these drugs are believed and I'm going to emphasize believed. They're believed to work by actually changing gene expression in your DNA and so what they do is they basically make the cancer cells more sensitive to death and that's a good thing. We call it programmed cell death or apoptosis. So, a scientific term would be that they potentiate apoptosis in cancer cells. Basically, what that means is they increase the sensitivity of the cancer cells to die and they do that by altering gene expression.

So, this is the randomized trial done for Azacitidine. It's called the AZA 001 trial and to date it's the only study, only randomized study showing the survival benefit in MDS. So, it was an interesting design. Patients would come into their doctor's office and their doctor would choose one of three therapies for them. That would be best supportive care, low dose Cytarabine or induction chemotherapy. So, the doctor would say okay, you got advanced MDS. I'm going to choose this treatment for you. Why would they choose a certain treatment over another? Well, best supportive care to (inaudible 54:41) the people with a lot of comorbidities who are older that they can tolerate induction chemo and induction chemo to the people who are younger who have



good performance status who they thought could tolerate induction chemo and then the low dose Ara-C which is called LDAC would be between the two. So, the physician would choose okay this is what I'm going to give you and after the physician made that choice they would then be randomized to either physician's best choice or Vidaza also known as Azacitidine. So, this trial essentially compared Azacitidine to what the physician thought was best and you look overall it's going to be balanced between what the physician thought was best which is called CCR. It stands for conventional care regimen versus the Vidaza. Now, when we look at these different groups of the conventional care regimen, you're going to see that the people who got induction chemo were younger than the people who got best supportive care and the people who got induction chemo had more advanced disease.

Now, wait a minute. AML, I thought this was an MDS talk. Well, it used to be that MDS was up to 30 percent blasts, but they changed the definition of it after this trial had already started approving. So, this trial was approved based on the old definition of 30 percent. So, these AML patients had 20 to 30 percent blasts. So, that's why there's some AML people in here. When you look overall there is a benefit in median survival of approximately nine months. So, patients who received Azacitidine lived nine months longer than people who did not. Now, I don't think there's anyone in the room who would volunteer to be on either one of these curves. Right? I'll take the curve that stays up here around 100 percent. So, I think it's important to keep in mind that while Azacitidine does prolong overall survival it is not curative and that's why we have... we're looking at different types of treatments trying to improve response rate and that's why I think that a clinical trial would be indicated for any patient with MDS for which they are eligible because the truth is we do not have curative therapy for MDS at this point in time outside of a stem cell transplant.

This is looking at blood count improvements. So, this is anything to (inaudible 57:11) your improvement and this E stands for erythroid. That's red cells, P for platelets and N for neutrophils. That's white blood cells. So, in this trial about 39 percent of patients who got Azacitidine had an improvement of red cells, about 32 percent had an improvement in their platelets and about 20 percent had an improvement in their neutrophils and then this CCR is the conventional care regimen which could have been inductive chemo, it could have been best supportive care or it could have been low dose Cytarabine.

Adverse events. So, what kinds of toxicities do you get with Vidaza? Well, it depends what ones are low blood counts and the low blood counts are worse during the first two months of treatment and the median response time to Azacitidine is four months and the majority of people who respond, over 90 percent of people who respond do so by six months. Now, I have to tell you that this is a mistake that is frequently, all too frequently made that a drug is discontinued early and I see that many times. I've seen that in people treated with Lenalidomide and I've seen that in people treated with Vidaza. This drug, Azacitidine, will make your blood counts worse. It's expected to do so before it gets better. So, getting two cycles of Azacitidine means you get all... and then you stop it. It means you get all the toxicity, but none of the benefit. So, if you're

going to start treatment with this it's important to stick with it, to accept the fact that your blood counts may go lower, but to get patients through that and then continue the treatment. Now, if you get to six months of treatment and you're still not having the benefit that would mean, of course, then the drug has not worked. Now, with Lenalidomide, I mentioned with Lenalidomide that 80 percent of people get lowering of their blood counts during the initial phase of treatment and that's usually the first eight weeks. So, Lenalidomide it's recommended that you stay on it for three months before you know whether or not it's working and with Vidaza/Azacitidine that would be six months. So, if you stop the drug too soon you're not going to know if it works or not.

This is a trial done with Decitabine. In this study it wasn't compared to physician best choice. It was compared to supportive care. So, patients were actually randomized between Decitabine and supportive care. This trial did have a design flaw and the basic design flaw was that if you responded they stopped the treatment. So, they didn't continue on treatment. This is in contrast to the Azacitidine trial and the Azacitidine trial patients who responded stayed on it. In this trial if you responded you were taken off and so that's why many people feel there was no survival benefit with Decitabine. So, there is a debate right now why there was no survival advantage with Decitabine and people have different feelings about this. It could be that they were taken off which is this first bullet. It could be because it was different populations. It could be how the drug was given. So, this Decitabine in this clinical trial in the survival study was given in honestly a weird way, not the typical way that you give it, but then the final point that there actually could be a true difference between Azacitidine and Decitabine. Azacitidine may have effects on different types of molecules than Decitabine does which is probably too extensive to go into it, but I will tell you that that this is kind of an unsettled question, but the fact that Decitabine showed no survival advantage is true. So, I think in general it's preferred to use a drug that does show a survival benefit over a drug that does not. There are some potential benefits with Decitabine. There's a quicker response time. So, that's a potential benefit and it may have increased responses compared to Azacitidine and anyone in the room in Decitabine/Dacogen? No.

Okay. So, clinical trials. I'd like to review some of the clinical studies that we currently have open and one of those studies is investigating a new class of medications that were called immune checkpoint inhibitors. So, this is a very interesting class of medications. They're being used for a variety of different cancers and actually there's more literature to support their use in people with solid cancers than in people with blood cancer. So, MDS is a blood cancer, but we're kind of borrowing from people who treat solid cancers, but that whole idea behind these immune checkpoint inhibitors is that we stimulate your own immune system to recognize the cancer and kill it. That's basically what we're trying to do with these immune checkpoint inhibitors and that's what this graph is showing. You have a tumor specific T cell that's a part of your own immune system that's attacking a cancer cell. That's a good thing. We want to encourage that, but these cancer cells are tricky and they express things on their surface that weaken your immune system and prevent it from attacking the cancer and so these class of medications these

immune checkpoint inhibitors basically prevent that from happening. They prevent the cancer cell from decreasing your immune system and making it not attack the cancer. So, they promote your own immune system and they allow for your own immune system to attack the cancer. So, you can probably guess that as a side effect of these medications is basically overstimulation of your immune system. So, people can get those kinds of side effects with fevers, rashes, chills, increased inflammation. These are one of the major side effects of these class of medications, but they are being used increasingly in patients with MDS and one of these medications is called Natalizumab and we have a trial right now that is looking at Natalizumab which is this immune checkpoint inhibitor. It stimulates your own immune system and we're combining it with Azacitidine as upfront treatment for MDS and this trial's currently opened and is accruing patients. In order to be eligible you have to be basically newly diagnosed or untreated with hypomethylating therapy. So, these are people who have not received previous treatment with hypomethylating therapy. In case... this (inaudible 1:03:58) right now is the coordinator for that trial. So, if you're interesting you can speak to her about that, but it's basically for people who have not been treated with hypomethylating treatment yet. Now, we just found out, what was it yesterday or maybe two days ago that they're opening up another arm of the study for people who have failed Azacitidine. So, it's now going to use both upfront and also for people who have failed Azacitidine. So, if you've been getting the drug and it doesn't appear to be working or maybe you've been getting it and it never worked you're potentially eligible for that as well.

The reason why failing Azacitidine is important is because historically it has a very short survival. So, one of the areas of active investigation is what are we going to do for these people who get hypomethylating therapy and fail it. So, if you look overall the median survival for people who have high risk MDS that fail Azacitidine is only about six months. So, this is a group of people that we really need to come up with better treatments for. If you look retrospectively the best outcomes in this group of people were seen with transplantation or enrollment into a clinical trial. So, this is really a group of people that should either be transplanted or go into a clinical trial if possible. If you have low risk MDS and you failed Azacitidine the median survival was about 17 months. So, again, a relatively short survival for patients with low risk MDS.

So, one of the drugs we're looking at for people who have failed Azacitidine is a drug called Guadecitabine and you're probably thinking boy that sounds kind of familiar because it is similar to Decitabine and so this is the structure of Azacitidine. This is the structure of Decitabine and this is the structure of Guadecitabine also known as S110. So, Decitabine and Azacitidine have a very similar chemical structure and so does Guadecitabine because this part is basically the same as this part. So, you don't have to be a chemist that these this looks like this, this and this, but what they've done is they added an extra component and this right here this is the extra component and it's guanosine and it inhibits the enzyme that breaks these drugs down. So, Guadecitabine is basically a modified form of Decitabine that sticks around in your body longer and we think that improves response rates.

So, right now we had a clinical trial looking at patients who have previously failed hypomethylating therapy. It could have been Decitabine or Azacitidine and they're randomized between Guadecitabine and physician choice. So, it's similar to that AZA 001 trial and Kim is the coordinator for that setting. So, if you failed Azacitidine or you're not responding or you failed Decitabine and you're not responding then you are essentially eligible for this trial.

Rigosertib is another drug that's being tested in patients who have failed hypomethylating therapy and there has been a previous phase three randomized trial with Rigosertib comparing Rigosertib to physician choice basically which included low dose Ara-C which is a type of chemotherapy hydroxyurea growth factors or best supportive care. We participated in this study. This Rigosertib works by inhibiting some enzymes that we believe make the cancer cell resistant to death. So, by inhibiting these enzymes we basically make the cancer cells more likely to die which is obviously something we want to have happen. The Rigosertib is given as an IV infusion over three days. So, we actually give the patient an infusion pump that they keep with them for the three days. They're checked by a nurse every day over at the SCCA. The study does pay for housing. So, you can get and, by the way, most of these studies do support travel expenses including housing. Most of them do. So, if that's a concern don't necessarily include from going into the study or not basis, but the Rigosertib is given as an IV infusion over three days and this was the primary endpoint of the trial and there was no difference unfortunately. So, this data was not sufficient to submit to the FDA for approval, but they looked at a certain subset of patients and they found that in a certain subset of patients there was improved responses and that were patients who were younger and patients who had a smaller amount of time between the Azacitidine and failure. So, there is a subsequent phase three randomized trial looking specifically in that group of people who are less than 82 and who are on hypomethylating therapy for less than nine months. So, that trial is also open and Kevin is also the coordinator for that study and if you're interested we'd love to get you enrolled. In order to be eligible, patients must have failed prior therapy with hypomethylating agents.

So, moving onto a summary. This is a study actually done in conjunction with the MDS Foundation. So, the MDS Foundation has done some important studies with patient surveys and things along those lines, but if you look at people with MDS who are treated in the US, by far the most common treatment they get is growth factors. Around (inaudible 1:09:47) percent. Vidaza around 16 percent and then if you look at GCSF which is a certain type of growth factor around 10 percent, Lenalidomide around eight percent, Decitabine around two percent, Thalidomide around one percent. These are all recently diagnosed patients. So, it just goes to show you first of all that EPO brought back one of the most commonly used medication, but also a minority of patients with MDS are actually treated which is pretty surprising. We have other epidemiologic data that shows that. So, MDS is not only underdiagnosed it is also undertreated.

So, in conclusion for non-transplant therapy, transfusion support plus supportive care is an appropriate choice for some patients with MDS. Growth factors remain the most common treatment choice. Immunosuppressant therapy is an appropriate choice for some patients. That

would be ATG. Lenalidomide, that's Revlimid is indicated for people Del 5Q who are transfusion dependent. Vidaza has been shown to improve overall survival and the role iron chelation remains controversial. Any results of a randomized control trial, TELESTO, and I will just also say that there are several clinical trials that are available for patients with MDS not only here, but I know we have some people who are from Portland OASSU has a lot of active clinical trials as well and I would encourage you as someone who has a diagnosis of MDS if you haven't been seen at a center of excellence, I would strongly encourage to really do that not only for accurate diagnosis and prognosis, but also for consideration of enrollment into clinical trials because it's only through a clinical trial participation that we're able to advance the field.

So, this portion of the talk was scheduled to last till 11:00. It was a really long talk and I realize that. I'm not going anywhere. So, I'll be here and available for questions, but I'm going to (inaudible 1:11:46) forth my colleague, Dr. Deeg, who will talk about transplantation.

(Applause)

**Joachim Deeg, MD:** Good morning. Thank you, Bart, for the introduction. It's a pleasure to be here and certainly very pleased to see a tremendous turnout. We're tracking (inaudible 1:13:04) through portals of staying updated on what is happening in the field with this disease.

As Bart indicated by assignment is to talk to you about transplantation. I will be coming back repeatedly, however, for his presentation since it goes without saying basically is very important for in a non-transplant and transplant therapy. I will also say (inaudible 1:13:32) introduction that as all science like Bart already the decision of many here is controversies and the decisions are often difficult. Just a few weeks ago I did a transplantation actually on (inaudible) uncertainty on both physician's and the patient's part in the decision making process and I may refer to that in between as we go through this presentation.

So, in the MDS spectrum, Bart showed to you what we currently consider MDS making the strong point that this is not one disease but a broad spectrum of various diseases and we are learning very quickly actually (inaudible 1:14:15) and this has been further expanded just over the last year or two by mutational clonal analysis. Everybody's familiar now with the term clone if not already before from (inaudible 1:14:34) and what is important to recognize is that as we grow older we seem to have a tendency to evolve abnormal cells and normal bone marrow and these abnormal cells may carry or do carry the potential that may lead to the development of a clinically recognizable disease. So, that's one entity called (inaudible) as explained down here. (Inaudible) poesies of indeterminate potential which obviously quickly are recognized only by doing mutational analyses and there is something called non-clonal ICUS idiopathic cytopenia of underdetermined significant. Again, what is the meaning and the prognosis with that and then the CCUS for clonal cytopenias of underdetermined significance.

Now, this is not... So, these by (inaudible 1:15:50) in the red are entities that are not considered MDS, but we are increasingly recognized may be precursors of MDS, which I'll summarize to you in the right two columns, low risk and high risk as Bart very nicely presented. So, we classify as he also pointed out the disease on the basis of blast count essentially for most cytopenias and most importantly the cytogenetics that I trust one to repeat what was already we have currently a five classification of (inaudible 1:16:33) classification from very good to very poor and just to make the point that if a patient presents with a very good cytogenetic risk the median life expectancy all these are statistics and uncertainty when talking to you as an individual patient the median life expectancies of our five tiers if you're on the higher highest risk group is about five months. So, very important difference and that needs to be taken into consideration when (inaudible 1:17:02) is made and when we start talking about what therapy should be advised. You have seen this before as well. Just to make a point in how important the cytogenetics are. There is currently no officially accepted classification scheme that has been overrated the mutations yet, but that works ongoing and we will have one before too long. I will not repeat all the other factors that Bart has presented already.

Now, one important point, of course, is that the median age at the diagnosis when MDS is made is somewhere between 70 and 75 years. So, I contrast through some of the other diseases there's a median age range maybe only in the 50s or 60s and as I will try to emphasize as we reach the eighth decade of life our biological reserve clearly is no longer what it was when we were 25 or even 45 years of age and a lot has happened to our stem cells as indicated already on the first slide. There is precursor conditions that may make it more likely for us to develop MDS and how do we need to take that equation. These two pictures are taken from two publications just two years ago looking at very large numbers of patients in 18,000 to 19,000 patients and I will lead you through that once your (inaudible 1:18:44) I think it's very obvious. Shown at the bottom here is our age range and virtually the percent of individuals recognized with the certain (inaudible). Now, these were not patients or not individuals recognized as having a disease, but rather people considered to be healthy and what is shown here in that is patients who have a proportion of patients who had normal hemopoietic abnormality with both candidate drivers, mutations that are recognized now as being instrumental in propagating a disease and the curve in red shows a proportion of patients going up here as you can see to 15 percent. The patients who had normal hematopoiesis (inaudible 1:18:35) is shown, but the point is increasing age, increasing probability of those developments and the same was shown dependently in the other studies with a very high proportion of patients developing these clonal abnormalities.

And from the same research group actually (inaudible 1:19:57) in (inaudible) group a very recent just publication just a month or two old. They expanded on their work further and looked at transplantation as well showing that dependent upon age the type of mutations that we see will differ. On the left hand side is younger patients in red, younger than 40 years of age where the disease is much less frequent although it occurs and on the right hand side patients older than 40 years and the size of the dot indicates the frequency at which these mutations were observed and as you can see here most prominent TP53 which is the most frequent mutation (inaudible)

1:20:47) also here in the (inaudible) which has been (inaudible) methylation as Bart related to where we try to modify the expression of genes and the number of mutations that have been mentioned already. So, there is a pattern of mutations arising as we grow older and do these mutations matter. That's, of course, the important question.

Now in one very simple analysis done by Dr. (inaudible 1:21:19) he showed in a large number of patients as you can see here in parenthesis that if we look at patients who do not have any recognizable mutations, the black line here, this is the survival probability using median survival maybe around 5 ½ years. Now, if you have one adverse mutation the curve starts moving to the left and increasing numbers of mutations you get down to a survival probability that is maybe 1 ½ year. There was one single mutation that Bart pointed it as well. Through here SF3P1 (inaudible 1:22:05) splicing machinery which is responsible for transcribing the gene in terms of DNA and the RNA they had a slightly better survival, but clearly not only the type of mutation, but the number of mutations is relevant for the outcome of patients for an overall survival.

Now, how does it impact transplantation? Let's go through some aspects of transplantation. One more time, this slide summarizing the various parameters that (inaudible 1:22:44) in the (inaudible) scoring system in its revised version. The cytogenetics most people are marrow blasts and they are refined breakdown of the degree of cytopenias of low peripheral blood cell counts, anemias, thrombocytopenia and neutropenia are which the outcome and Bart emphasized already if a patient needs transfusions it may not be the transfusion that is responsible for a lesser prognostic analysis, but the cost that requires at least with a need for transfusion and so forth. Another factor is age by itself. That's to say that one more time for example if you here intermediate score, the score's are being made up here. The intermediate scores in a younger population the median life expectancy may be 5.3 years. In older population it may be only half that long, but that is important, of course, when we discuss how should we proceed, what treatment strategy should we develop for you and you and you as an individual patient, but again these are medians and I said before we are... we cannot be certain in any circumstance. These are statistics and when it comes to looking at individual patients there are already recognized in other currently uncharacterized factors that are relevant for how one given patient is going to do. We may have a patient who goes to transplantation, 75 years old, who has relatively high risk features and a history of transfusion needs and we may have a patient who is only 45 years old and doesn't have very high risk (inaudible 1:24:36) and may not be (inaudible) without transplantation. Now, our Italian colleagues have done a lot of work in this field and per the (inaudible 1:24:48) is IPSS and have added other factors that may impact the outcome after transplantation refer to it as the transplantation risk, the XTRI, that's shown here and so IPSS is our (inaudible 1:25:04) that some people call it a monosomal karyotype that Bart (inaudible 1:25:11) the cytogenetic. In detail this means would have a particular type of chromosomal abnormality. The most frequent one in MDS is the monosomy 7, (inaudible) may (inaudible) that abnormality in combination with another chromosome abnormality. That would be recognized as chromosome as a monosomal karyotype which really increases the risk meaning hence to speed up the progression

of the disease and unfortunately it's also associated with a high dose of (inaudible 1:25:46) transplantation.

Then we have HCTCI, the hemopoietic cell transplantation comorbidity index. In other words are there other diseases, other medical conditions present that may impact the overall (inaudible 1:26:05) of a patient and that could be hypertension, some other heart disease, diabetes, kidney disease, even (inaudible). These are all those (inaudible) here and then the refractory to induction chemotherapy and I can't say anything better than Bart (inaudible 1:26:26) before. It depends on our definition. We give certain type of chemotherapy. Does a patient respond or not respond and that includes Vidaza, have we selected already a patient on the basis of what we think the patient's risks are or are we really neutral in deciding. Well, for this presentation we will give this type of therapy and then if the patient does not respond is this non-responsiveness indication of the severity of the disease. In other words, we have select mutations, we have poor risk disease in both (inaudible) almost regardless of what we do. Anyway, the bottom line of their analysis and a very nicely done study is shown here. If you have a very low transplant risk index, you have an excellent outlook after transplantation. So, the long term survival drawing out here 10 years basically in the range of 75 percent. If you have a very high risk TRI there was no real long term survival. I personally I will say I do not like these more composite risk assessments since once we look at you and you as an individual patient all these fly out the window. It's you that will count and this is what makes the decision often very difficult.

Back to the mutations. This is one graph showing the results from this study I mentioned already which showed the different mutations in different age groups of patients and this slide shows the impact of the P53 mutation which was the most frequent one. Shown in black here are patients 40 years of age or younger and who did not have the mutation of whom somewhere along 60 percent survive after transplantation compared to... Sorry, I said that wrong. (Inaudible 1:28:41) patients without mutation (inaudible) the patients risk mutation, the upper curve shows the patient less than 48 years of age, no mutations, somewhat more than 60 percent survival, but they did have the mutation. This survival went down to 20 percent on this 30 percent. Older patients had the lower probability of survival even (inaudible 1:29:04) the mutations and in fact their long term survival was not different from that in younger patients if they did have the mutation. So, again, showing this very complex interaction with numerous factors the mutations as shown here the mutations and age and presumably additional factors that come into play.

Now, effect of long transplant therapy on transplantation and Bart showed you this slide already which is taken from the so called meta-analysis looking back on published data from a number of papers in patients who had been treated with Azacitidine for various presentations of MDS and then failed and failure was defined either as not tolerating the drug because of toxicity, of not responding to the drug or of having progressive disease while receiving the drug and this as Bart indicated the only really promising approach at that point was a transplant, but because without additional therapy the median survival is only about 6 months, but even with transplantation and this is, I think, still a very important piece of information to consider. Even with transplantation



the benefit was really remarkable only for patients who received the transplant with... before they had progression of the disease. Now, that is something we are (inaudible 1:30:51) and we are looking back. As I said, patients could have progressed. So, patients who did not progress by (inaudible) being stopped had stopped treatment because they didn't tolerate it or they simply didn't respond, did very well either got (inaudible) with a probability of long term survival in the range of about 30 percent. Patients who had continued to receive therapy and the disease was progressing and had a median survival that was not only prevented in patients who did not get a transplant, but was about a year and a half. So, it is important if you or anyone you know is on hypomethylating therapy and is interested in transplantation and is considered by the doctor a candidate for transplantation one should definitely look at transplantation as long as the disease is stable and not wait until the treatment is Vidaza fails.

So, that leads to the next question of condition intensity. Now if you had made the decision to go to transplantation. So you have heard about called me transplant. Forget it immediately again there is no me transplant. There are transplants of mini intensity of conditioning, but they are all transplants. So, since age is higher age is the (inaudible 1:32:17) of higher probability of developing the disease and we said we develop additional medical issues as we grow older, etc., etc. and get more (inaudible) the conditioning intensity remains a very important issue. Generally, we can give that higher intensity will kill more of the MDS cells and should therefore be more effective. These considerations led to a big study and (inaudible) or (inaudible) published that paper just recently to a study that was under the auspices of the (inaudible) BMPCN the Bone Marrow Transplantation Clinical Trials Network sponsored by the NIH where patients were randomized, many institutions across the US. Patients with AML or MDS who had less than five myeloblasts, again, these notorious blasts to receive a high intensity conditioning regimen or a low or reduced intensity conditioning regimen and what is shown in this graph is the probability of relapse, incidence of relapse and as you can see in yellow the results in AML and MDS patients who had received the reduced intensity conditioning regimen compared to patients who had received a high intensity conditioning regimen. Clearly, there was a substantially higher incidence of relapse with the reduced intensity conditioning regimens. We had hope that a lower probability of dying from causes other than relapse, the non-relapse modality as we say it would compensate for this higher relapse rate. So, that despite that we could possibly get the best outcome with very little consistency in mortality from non-relapse causes and so absorb a somewhat higher incident of relapse and thereby still improves survival. That was not the case even though this is, again, statistical the study did not reach the predetermined endpoint for overall survival. Nevertheless, the conclusion drawn from this study was that for patients who are able to tolerate high intensity conditioning regimens one should go for a high intensity regimen for the time being as the best strategy in this setting.

To underscore that further here are some data and I will walk you through that that one of our visiting fellows, (inaudible 1:35:08) from Italy, summarized for us and published last year. He looked at some, I think, 248 patients with MDS whom we had transplanted here at Hutch Cancer Center, the HCCA, and we looked at what we call minimal residual disease or he might call it

minimum identifiable disease. In other words we treat patients with something before transplantation and then the decision is made to proceed to transplantation. Does the patient at the time of the transplants being done have evidence of the disease or can we not identify any risks at all... evidence of the disease and there are various ways by which that can be done. The two methods that have been used pretty routinely for a number of years are by flow cytometry. So, the computer analysis compares our cells or the cytogenetics, again, in what is coming to use in our spot emphasize how the mutational analysis, which we did not analyze because we didn't have data of this. We analyzed flow cytometry computer analysis and the cytogenetics and what is shown on this slide on the left half of the slide results in patients who were negative by... in other words had no identifiable disease at the time of transplantation and on the right side patients who did have residual disease even though their marrow seemed to be in (inaudible 1:36:50) so only the particular analysis for cytogenetic or chromosome abnormalities revealed the presence of some disease and so the results show that if you were negative no residual disease whether you got a high intensity regimen or a low intensity regimen you and retrospectively the probability of survival is (inaudible) even though the low intensity is slightly higher relapse rate. However, if you did have evidence of disease at the time of transplantation then patients who had received a lower intensity regimen had a substantially lower probably of survival and if you have high intensity condition patients essentially you have a much higher relapse rate this low intensity. So again, underscoring this the importance of the disease versus how much disease is on board and how intensity can we prepare the patient, but this is, of course, one of the challenges because if we have a patient who we think cannot tolerate high intensity regimen because of those ATG SCI, the comorbidity index that shows other medical issues, how can we prepare that patient for transplantation if otherwise the patient is (inaudible 1:38:20) transplantation is interested in severe transplant. I don't think we have the definitive answer. We have basically every Wednesday morning conferences over at the Center discussions about those patients.

Now, we have recently done a series of trials using a new chemotherapy regimen that is investigational in this country. It has been approved in Europe for other reasons and (inaudible 1:38:49) in cancer for a number of years called (inaudible 1:38:54). It sounds very similar to Busulfan but is handled by our body very differently. It kind of bypasses the metabolism, the breakdown in the liver and is very well tolerated. We had done one study combining Fludarabine and other chemotherapy agents (inaudible 1:39:13) and then we followed it up with Fludarabine (inaudible) and added a low dose of radiation and intensifying the regimen. We had good experiences with Fludarabine combined with GI and since Fludarabine is very well tolerated very well we thought we could afford the addition of low dose (inaudible 1:39:31) to break. It may not mean a lot to you, but a high dose would be 12 or 14 (inaudible) and if you gave only that dose your bone marrow would recover eventually... I'm sorry. Would not completely (inaudible 1:39:46). So, this is the regimen three days of (inaudible), Fludarabine for five days and one dose of GPI and then in an effort to prevent this still challenging issue of graft versus host disease, GVHD, a combination of two drugs methotrexate and (inaudible 1:40:04) after transplantation and there were 96 patients in the study and we published it a couple of years ago

with our colleague. (Inaudible 1:40:17) who is now at Sloan Kettering in New York and this is a bottom line for patients with MDS. So, this is (inaudible) MDS and what we found that indeed this regimen seemed to have a very beneficial impact particularly in patients who have these high risk or poor risk chromosome abnormalities, cytogenetics and effect the relapse incidence in less one of (inaudible 1:40:44) patients among patients who had poor risk or high risk cytogenetics was not higher than it was for patients who had (inaudible) arrange cytogenetics and in fact the difference in survival had been mostly good and poorest cytogenetics was not significant. It was inferior 68 percent at two years compared to 82 percent survival which we thought was excellent, better than anything we had achieved prior to that, but it was not different and this led to a randomized phase two trial which we just completed and (inaudible 1:41:30) for publication which in 100 patients would basically confirm these results that we can improve the outcome in poor risk patients by a combination that includes (inaudible) with Fludarabine. So, the drug is not available currently, but efforts are underway to get it approved by the FDA for broader use and in fact it may be (inaudible) institutional (inaudible) study. A phase three randomized trial to confirm the data that we did obtain.

Now, there are other approaches to intensifying the conditioning regimen without significantly improving the toxicity which are logistically and technically more challenging. One is the use of (inaudible 1:42:37) immunotherapy. If when we get a total body radiation as I just mentioned in the previous study, we expose the patient, the total body, hence the name, to radiation from a radiation machine. It used to be cobalt in the past. It is now with linear accelerators, but it doesn't spare any part of the body. So one approach people for a while (inaudible 1:43:05) this magical bullets was to use the radioactive isotope, some of you may be familiar with it. In other words, various elements such iodine that consist in various forms and some of them are radioactive. Hence they are used for the treatment for thyroid diseases, for example, and couple those radioactive elements to an antibody that can recognize the tumor cell in the body. In our case, the MDS cell. There's an antibody that's recognized is what we call CD45, cluster of differentiation number 45 which is expressed from almost all MDS cells. (Inaudible 1:43:58) and so by having this conjugate, as we call it, isotope conjugated with the antibody. The antibody finds the target tumor cell and delivers the radiation charge through the tools and that does work indeed. It is not 100 percent. There are complications associated with it despite our efforts though (inaudible 1:44:25), but this is another promising approach, but as I said it is logistically and technically much more demanding than the other strategies and it is more difficult to make widely available. Nevertheless, both studies continue and they do hold promise.

Does age affect the outcome after transplantation? Well, basically I have said that already but just to illustrate that with a few pictures. This is by our colleague (inaudible 1:45:03) published in a big paper in the Journal American (inaudible) Association some five – six years ago and shown what he does here is comparing three age categories, not only MDS. This includes patients with other diseases as well, 64, 65 to 69 and 70 years of age or older at the time of transplantation and shown on the left is the probability of the non-(inaudible 1:45:28) mortality as I mentioned before making (inaudible 1:45:33) about 30 percent overall or percent (inaudible)

and on the right side the percent of patients, proportion of patients, surviving and, again, the statistics come in here. The statistics say there's no difference. The P value is higher than .05 It's .18 here, but you can... I would say particularly when I start trying to one patient that there is an indication that age has an effect even though these curves are not statistically significantly different and furthermore and that is most important when we make decisions about transplantation we are very careful in first reassessing how you any one given patient, how well you understand what we are getting into and what it means and whether, indeed, you are a patient I will take the risk. That's fine. Or whether you are a patient and we have many of those patients who come and say well, I want to have a transplant. Well, I say, okay, let's talk about it and then at the end of the discussion the patient will say well, I didn't know all that was involved. So, this is important. If you are well informed and you go into it knowing that transplantation definitely offers a potential of cure, no question about it anymore. We have patients now who are surviving more than 25 years after transplantation, but it does not guarantee. That is important to know.

So, Mohammad did a little more and he just emphasized it further. He added to this HCTCI that we have seen now a few times that stores various (inaudible 1:47:30) in an age. When you are older than 40 years of age you got one additional point and as you can see this one additional point brings your probability of long term survival stepwise down. If you had had a score of zero but were older than 40 you're probability of survival is by 15 percent lower than in a younger patient and so forth for one point up. So, age (inaudible 1:48:00).

Now, back to connected to what Bart presented as I said it is very important to keep both the non-transplant and the transplant playing fields together. Here on the left hand side you see the results of an analysis that (inaudible 1:48:21) from Germany did (inaudible) comparing to some of the data that you saw actually there (inaudible) in France presented and we met patients on the basis of their age, obviously, and disease manifestations and shown in red here is the survival curve of patients who had received Azacitidine/Vidaza and in black the survival curve in patients who went on to transplantation and as you can see for the first three years basically there was no difference. So, how do we... can we actually in an understandable way conveying to any one of you and convince ourselves who is the right patient to go to transplantation and who is not the right patient for transplantation. We don't know that yet. I think they're learning more with the areas with (inaudible 1:49:19) studies, but really until about two years your risk is lower from with a non-transplant approach. Yes, that is an advantage in the long run. Similarly here ignore this gray line here. This is a French study by (inaudible 1:49:35) showed patients who did have a donor who was matched for the antigens that we looked to be matched and patients who did not have such a donor and showed the same thing. Basically for two years these patients had similar outcomes. In other words whether you did go to transplantation or not for the first two years there was no difference between these two cohorts. Of course, there was a huge difference between 100 percent or zero percent for patients who did not make it, but did not know it beforehand and one last slide to make that point this was a study in which we collaborated with a number in this (inaudible 1:50:14) published by (inaudible) in Boston rating patients down by

their disease severity, again, using the IPSS it was before it was revised, the IPSS and the upper panels showing patients who had low risk disease who were not transplanted in yellow and who were transplanted in blue. So, if you had low risk disease you had no gain by undergoing transplantation and that is shown here in the red square within the yellow space looking at quality adjusted life years. If on the other hand you had high risk disease intermediate to high, yellow, again, no transplant. Blue is transplant. That is clearly similar to the two previous panels that I showed that managed for transplantation and the red square moves into the blue space showing there is an advantage in regards to quality adjusted life years with transplantation. We don't know beforehand and so two important studies are currently ongoing, one in Germany and one in this country and Bart is looking at for this one for our center here patients with MDS older than 50 years of age with intermediate or high risk disease, they have a donor versus no donor and they are assigned to these two arms respectively and the end point will be what is the best outcome. Should we/should we not transplant and can we identify factors beforehand that will help us in the decision-making process for or against transplantation and there is a cost to it, of course, not to beat that to death, but (inaudible 1:52:07) cell transplantation, comorbidity index and (inaudible) yet another modification of (inaudible) comorbidity index. He has added in this graph here to the comorbidities pre-transplantation the development of GVHD after transplantation which clearly shows a relationship between the comorbidity index and the development of more severe (inaudible 1:52:39) acute GVHD. So, that is important because GVHD, chronic GVHD, in fact, does increase with age. We've known that for a long time. Because of age, as I said earlier, we used a reduced intensity conditioning regimen all of them have unacceptable (inaudible 1:53:00) and to ensure engraftment with this reduced intensity regimen we use peripheral blood preferentially (inaudible) and bone marrow cells, but we do also know that this peripheral blood we have more chronic GVHD. Somewhat controversial issue currently whether we should change our policy again, but it's (inaudible) date. We use steroids, Prednisone, as front line therapy and steroids are poorly tolerated in older individuals. So, there are many areas that need further study. There's a lot going on in regards to the prevention of GVHD such as ATG. Bart mentioned that in a different setting. We use it for the treatment and prevention of GVHD. We give treatment after transplantation and you may hear Dr. (inaudible 1:53:56) about that a little later and there are various (inaudible 1:54:00) studies removing certain cell populations from the cells that we infuse from the donor to the patient to reduce the probability of GVHD, but if you have GVHD, chronic GVHD, you merely try a treatment for a year on average, 2.5 years in our studies and steroids can be there in there.

So, in summary there's a lot more to be said, of course, but MDS is definitely curable by hemopoietic transformation even in patients older than 70 years if they are fit however we define that. The early post-transplant, of course, (inaudible 1:54:42) is not superior to no transplant therapies. So, what we need to work on identifying patients who will eventually benefit from the transplant. Age associated mutations may modify the behavior of the disease and thereby also affect the outcome after transplantation and that I just said in my (inaudible 1:55:05) slides is GVHD prevention is a major challenge.

I would like to thank all of our colleagues. Of course, (inaudible 1:55:15) and (inaudible) some of the people (inaudible) and, of course, all of our patients. Thank you very much.

(Applause)

Any questions? Yes?

**Q13:** I have a question. My husband had a transplant after... he's a high risk MDS and I need to find out he has ongoing GVHD. This been since 2009. Has there been any progress as to figuring out different types of... he was on steroids for a long time. What is the progress on trying to help out with this GVHD?

**Joachim Deeg, MD:** Let me try to be concise, but when you say nevertheless I just came in last night from a meeting in Chicago focusing on GVHD and (inaudible 1:56:18) particularly chronic GVHD for participation of a number investigators across the country and in conclusion there was that the best strategy is to prevent chronic GVHD. Once it is the trigger has been pushed, it is very difficult to control this very well, but more directly to your question I just mentioned a couple of those approaches. One, or a couple strategies that seem promising is to include ATG as part of the conditioning regimens and one is to (inaudible 1:56:58) after transplantation. As far as treatment is concerned for established chronic GVHD, there has been disappointingly little progress to be honest with you. We have been quite pleased by treatment with extra (inaudible 1:57:19) pheresis and you may be familiar with that. In other word, exposing... there are machines that have been developed exposing the patient's blood to ultraviolet irradiation, inactivating the T cells, reinfusing them and thereby not only activating them but that's basically it works like a vaccine. There are a lot of news about small molecules that are being tested. One that is at the focus of many people's attention right now is the TET2 (inaudible 1:57:48) that is used for treatment of other diseases, myeloproliferative diseases, and there are a number of similar molecules that are coming along. So, I don't probably familiar (inaudible 1:58:03) personally, but those are things to be considered. Some of the responses have been quite rewarding.

**Q13:** When you were talking about he's been on (inaudible 1:58:15) and they decrease it and then he has to get back on it. This has happened several times and he has not gone through the... it's where the blood goes through and you put the light on it.

**Joachim Deeg, MD:** Right.

**Q13:** Okay. He hasn't done that. Is that real promising as to curing the GVHD or is just kind of... will it maintain and then comes back.

**Joachim Deeg, MD:** Yeah. Well, as I tried to say already through whether any of the treatments that we currently have completely restores normal immune function has been questioned lately,

but on average patients whom we have treated here at our center for (inaudible) GVHD on average they require treatment for 2 ½ years meaning of course, (inaudible) much longer, but eventually the disease in many patients burns out so to speak. Does it mean normal immune function in regards to defense against infection and so forth? That is a somewhat different question. One of our former colleagues named (inaudible 1:59:20) published this study a number of years ago in patients who had been followed for as long as 20 years after transplantation and still showed some deficiencies in their immune events. However, not to be evasive in my answer, the goal, of course, is to stop the disease completely. Yes, absolutely, but by that time a lot of damage have been done on the thymus and other immune organs in our bodies. This is, as I was saying, this has remained quite challenging, but is he being treated here?

**Q13:** Yes. Fred Hutchinson and he... they did excellent work and they've been very good for him. He's still (inaudible 2:00:01) he's still seen at (inaudible) for the GVHD and that's the most frustrating part of it.

**Joachim Deeg, MD:** Yes. I agree.

**Q13:** We understand that he had a low survival rate and he had the Vidaza. He did that and then right before his transplant it did show that he had the blasts again, but since then he hasn't any... he's still in remission and it's very good, but it's just the GVHD...

**Joachim Deeg, MD:** (inaudible 20:00:33) we had (inaudible) all of our graft versus leukemia that one beneficial byproduct of this GVH is, of course, is that the graft also attacks not only the healthy part of the body, but also the disease and helps to eliminate the disease, graft versus leukemia (inaudible 2:00:53). The goal is to obtain that without having the graft versus host disease.

Other questions? Yes.

**Q14:** Dr. Deeg, is there any data yet that shows if there's a difference between the outcomes that you showed there from an HLA match, adult host versus adult (inaudible 2:01:12)? I know there's studies that (inaudible).

**Joachim Deeg, MD:** Another very good question. How can I most accurately answer that? So, this is where the front is moving right now comparing outcomes. Our policy currently is we look for an HLA match sibling. If we don't find one we look for an HLA matched unrelated donor. If we don't find one we look at either cord blood or a haplo identical. In other words, half identical. That would be a sibling possibly, but often child or parent and dependent upon the age since you by definition you would have 50 percent inherited from a parent and some 50 percent of the offspring. So, there are things that in our hands I mean, step wise, in our hands results with HLA matched unrelated donors are basically identical to results with HLA matched sibling donors. That's one aspect. Results comparing the cord blood to unrelated donors I think it is too early to

make a definitive statement and for some disease categories the results are very promising. The relapse rate tends to be somewhat lower and the GVHD incidence does not appear to be higher even though cord blood is in 95 percent of the transplants mismatched. We don't have fully (inaudible 2:02:52) finding (inaudible) poorly matched cord blood. That's why it's an interesting source of stem cells particularly for ethnic minorities of whom we have fewer represented in the registries. So, this is a very promising result and these are promising data and studies are going on comparing cord blood unrelated as well as HLA haplo identical (inaudible 2:03:19), but we'll have to wait for those results, but again those are studies and once it comes down to individual patient also depends upon factors such as honestly the size of the patient because if you use cord blood we have a limited number of cells that we infuse and they get diluted. It's easier in a trial than in a big adult who weighs 100 kilograms although it's being considered.

**Q14:** Thank you.

**Joachim Deeg, MD:** Yes, sir?

**Q15:** In all your studies have you noticed cases where chemotherapy of any type has kick started the bone marrow to develop its own quality blood?

**Joachim Deeg, MD:** You mean do we know whether chemotherapy can basically induce a remission so that the marrow comes back as normal cells?

**Q15:** Yes.

**Joachim Deeg, MD:** That happens and in many patients with acute leukemia that is our initial struggle actually. In patients with MDS that is much less frequent. There are some overall studies particularly from our colleagues at the MD Anderson Cancer Center in (inaudible 2:04:33) that show maybe about five percent, seven percent or so of patients that could have them. In other words, they have MDS, they are being treated with aggressive chemotherapy for a portion of patients who'll respond and some of those patients may eventually come back with normal marrow. It is possible. Yes.

**Q15:** Thank you.

**Joachim Deeg, MD:** Yes?

**Q16:** Have you checked the relapsed (inaudible 2:05:00) on patient the (inaudible 2:05:02) with matched donors and the mismatched donors. Have you compared those two groups because you showed the overall survival which is much worse, but it can related to other issues, again, of relapse of disease?



**Joachim Deeg, MD:** Right. Okay. If I understand your question correctly. There have been a number of studies looking... well firstly looking at matched versus mismatched outcome overall. Generally, the outcome has been inferior in patients who had a mismatched transplant.

**Q16:** I got it, but I ask about relapsed mortality or just relapse by itself and those two groups matched and mismatched.

**Joachim Deeg, MD:** I understand. So, the speculation was or even the hope was that based on what I just said a moment ago about a graft versus leukemia effect that if we use a mismatched donor that difference, HLA difference between the donor and patient, would lead to a more potent graft versus leukemia effect and therefore the relapse would be lower and in fact even though there may be some more proximity because of (inaudible 2:06:31) that normal relapse have this concern that may improve outcome. That has been going back and forth. I think where we stand right we won't have to say it does not result in an improved survival.

**Q16:** But this has not been studied as I understand.

**Joachim Deeg, MD:** It has been studied. I mean, in retrospect you can have what's looking at the last of the CIBMTR, The Center of Bone Marrow Transplant Research, has looked at that in large numbers of patients, but it's retrospective. It's not a prospective trial. That's correct.

**Q16:** One more question. What do we do for relapse after a transplant?

**Joachim Deeg, MD:** That is next to GVHD the other big problem and Bart is smiling. He actually did a study where we use an (inaudible 2:07:25) have done similar studies by design we used Vidaza after transplantation we started (inaudible 2:07:32) 28 and even if we had only minimal evidence of disease suggesting that the disease was coming back initiate treatment of Vidaza and that study was positive. It was published just a few months ago indicating that this is a beneficial approach and in a proportion of patients will certainly prolong survival and in a proportion of patients it will lead to complete remission. Other strategies are use of other agents that are coming around that are being tested. There are inhibitors that have been tested in AML mostly, but may be useful in MDS. We are infusing bone lymphocytes. You may have heard BLI, bone lymphocyte infusion, again, trying to enhance this graft versus leukemia effect. It works in a proportion of patients and we have done second transplants depending upon the patient's condition and when the relapse occurred. Most relapses, unfortunately, occur very early in the first nine to 12 months.

**Q16:** Thank you.

**Joachim Deeg, MD:** Yes, sir?

**Q17:** So, pre-transplant if the MDS impedes the transition to AML. Does that significantly change?

**Joachim Deeg, MD:** If the MDS has progressed to AML before transplantation. I think the short answer is yes. That is a negative factor definitely. What we are trying to do is we try to observe reset the (inaudible 2:09:15) the effect to a disease state that corresponds to MDS with it early analysis many years ago a large group of centers which suggested that if we succeeded in using a disease stage with less than five percent myeloblasts what we at the time refer to as refractory anemia that was unrelated over transplant. The long term success after transplantation from that starting point was not significantly inferior for patients transplanted for refractory anemia who had not progressed to AML, but there is in no other studies that have been done and some negative effect compared to the original MDS. Yeah.

If there are no further questions, I think, Bart, that was what you had meant for lunch break.

**Bart Scott, MD:** Yes. Lunch.

**Joachim Deeg, MD:** Thank you very much.

(Applause)

**Bart Scott, MD:** Lunch is ready from 12:00 to 12:30 and then 12:30 the next topic will be given. You can stay in the room, get your food over here.