Speakers:
Azra Raza, MD
Jayshree Shah, APN-C, RN, MSN, BSN, BS

Tracey: Thank you so much for attending today. We're really excited about the nice, big turnout and we may even have a few others coming in and out. So, my name's Tracey. I'm a director with the MDS Foundation. I'm here with my colleagues, you've probably already met Lea Harrison and Debra Murray. If there's anything that you need throughout the course of today, don't hesitate to hunt us down. We're happy to help. Some housekeeping… Actually, I'll start with the MDS Foundation. I don't know how familiar you are with the Foundation. We've been in existence for 22 years. So, that's a really long time helping patients and professionals and we're happy to do it and to continue. The bathrooms are right outside where you came in kind of across the steps. We are audiotaping today's presentation. So, if you could speak in the microphone that would be great. We're going to have the audiotape up on our website after the event and we're also transcribing, so it will be available in print probably within the next couple of weeks. We're expecting a very casual atmosphere. If you're hungry get up and help yourself. If you want something to drink, if you just need to walk around. It's all very comfortable. We're also having another additional educational opportunity after our event. It's not an MDS Foundation educational presentation. It's on transfusion specifically and that will be in the room… actually a little bit down the hall on your left. We'll help direct you if you decide that you want to stay. That should only be probably less than 30 minutes after we're done here. I'd like to thank our sponsors as always, Celgene, Novartis, Onconova, Baxter, our generous donors, patients, professionals, everyone because of the donations we're able to have programs like this one.

Now, Tuesday, October 25 was MDS World Awareness Day. We had a big online presence for World Awareness Day, but I was hoping I think Debra handed out some flyers for World Awareness Day. If you all wouldn't mind kind of holding them up for me we can take a couple of pictures and then that's something that we can also put on our website and kind of expand. So, do you mind if I take a quick photo with that right now? Great. On my very fancy phone. So, if everyone could just hold the flyer up… Wonderful. Thank you. It's in your package and then Debra passed some extras out. Great. Are we ready? There we go. There in the packet and I think there are some extras as well. Wonderful. Wonderful. I'm going to take a couple of photos, so bear with me. That's great. Thank you so much. We have quite a few.

Just a quick question today. Do we have any AML patients here with us today? I'm asking only because if you'd like we have someone looking to interview AML patients to collect some information. If you may be interested in doing an interview you can come find me. That would be great at any point throughout the day.

Also to introduce our speakers. You know, we have Dr. Azra Raza. Dr. Raza will speak first followed by Jayshree Shah from Hackensack University Medical Center. Dr. Raza's from

Columbia University Medical Center. So, we don't want to take up any more time. So, I'd like to introduce Dr. Raza. Thank you so much.

(Applause)

Azra Raza, MD: Thank you, Tracey. Thanks to the MDS Foundation for giving met his opportunity to come her in front of you today.

Many of you in this room come and see me in clinic and those who don't I just want you to know that we truly believe that we have to combine our passion for wanting to cure MDS and acute myeloid leukemia with compassion and unless we involve our emotions, we really don't own something. I thought I knew a lot about MDS because I already dedicated already 20 years of my life to it, but I realized that hard truth and facts are all great, but if they're not combined with emotions then it's like a jockey without a horse. It's like a bird without flight and it wasn't until my own husband got leukemia and he was the head of the cancer center and got the very leukemia that he's trying to dedicate his life to cure since he's 15 years old and so I had also a chance to stand on the other side of the bed for five years and take care of him myself and the most important lesson I learned was how we must have a very open dialog all the time with our patients because not only knowledge is power, but I all the time I learned from all of you who come into clinic and many times we'll sit and just talk about other things besides science and medicine. We try to avoid politics because both sides feel heartburn, but generally our conversations are very pleasant and we try to get to know each other and work together because this is a journey. This is a chronic, Myelodysplastic Syndromes is a chronic disease and acute leukemias which arise from MDS are also more or less smoldering kind of chronic slowly progressive disease. So, it's so important for the two of us to have that feeling that we are there for each other. It's not just I'm there for you. We are all there for each other and while I'm speaking here alone today, I have to say that the entire staff that we work with in Columbia University or anywhere else, Dr. Stuart Goldberg is here, Jayshree Shaw. They have their own amazingly dedicated staff and so I want to also complement our colleagues who help take care of all of you. I give many talks all the time, but the one that I really, really look forward to is always this one because it allows me to speak in English. I don't have to speak in scientific jargon anymore. So, what I thought I'll do is really take you to the forefront, the cutting edge of what's happening, in English, but really not leave anything behind. So, you just stay with me and we will take a case history and start progressing.

First of all, why MDS? Why MDS is very simple for me. When I was 28 years old I was seeing a patient with acute myeloid leukemia. That's what I wanted to specialize in and as I saw more and more leukemia patients I realized that many of them gave a history of having had a disease prior to leukemia and those days we used to just call it preleukemia. I said wow, this is great. We can study two stages of the same disease – preleukemia as it progresses to acute leukemia and that's why I began to study both diseases and then slowly I realized that preleukemia is a real challenge

all by itself and so more and more of my life got dedicated to MDS, but of course we treat patients through their diseases.

So, I thought the best thing is let's take the example of a hypothetical 61 year old man who's just discovered to have a very borderline anemia. I mean, many MDS patients have they have a hemoglobin of 11 would be proclaiming it from the rooftops it's so good, but it is a borderline anemia. Now, the white count and platelet counts are low. So, we do a bone marrow and the bone marrow doesn't look terribly abnormal just like the blood count didn't look terribly abnormal. So, we couldn't really diagnose what this patient has. We see these kind of patients all the time and now we call them well, you have ICUS. ICUS actually means I'm ignorant, I don't know, but it stands for idiopathic cytopenia of undetermined significance. It means there are meaningful cytopenias which means low blood counts, but they don't meet the minimal diagnostic criteria for MDS. So, what happens to these patients who have ICUS? Well, almost 3,000 patients were followed at Mayo Clinic for 13 years and 59 percent ended up having MDS, 18 percent developed some other cancer, 20 percent never developed anything. So, the question I wanted to answer here is it is not good to have ICUS because 80 percent patients will end up with either MDS or a non-MDS cancer. So, what happens to our case? Patient is followed for a year. We do periodic blood counts and then the generic sequencing studies becomes available from the blood. So, we did that and we found suddenly the presence of a mutation in this gene splicing factor 3 beta 1 and this now changes the patient's diagnosis from ICUS to CHIP. Well, what is CHIP? CHIP is clonal hematopoiesis of indeterminate potential. So, that means there is a clone or a certain population of cells in the bone marrow which now has that mutation SF3B1, but what is the mutation going to do? What are these cells containing the mutation? How are they going to behave? It can vary from patient to patient. So, that's why we call it indeterminant potential. We don't know its potential.

So, now what I'm telling is that if in the bone marrow we have normal stem cells then ICUS, then CHIP, then MDS and then AML. This is how really the bone marrow problems progress. So, what happens to our patient? Now, after another year he was noted to have worsening anemia. We repeated a bone marrow and now we are seeing dysplastic changes plus slightly increased blasts, but 15 percent cells were ring sideroblast. We'll talk about this in a minute, but and the mutation SF3B1 which we had previously noted is found in 35 percent of the cells. Cytogenetics also now show a deletion in chromosome 5 long arm. So now, the patient's diagnosis goes from ICUS to CHIP to MDS, but RARS, refractory anemia with ring sideroblasts. Many of you have seen this slide with me, but let's just go over it.

When we do a bone marrow the marrow is inside the bone. So, we take a piece of the bone and we look at it under the microscope. What we see first are these background cells called the microenvironment of the bone marrow. On top are these stem cells and it is these stem cells which make blood in a healthy adult by first making copies of themselves and then in addition to dividing they undergo maturation into white cells, red cells, platelets and then they enter blood and in any given 24 hours a healthy adult makes a trillion cells which go from the marrow into

the blood. What happens with MDS is that we have the background cells. We have the stem cells. One of these stem cells gets damaged. So, the first thing for you to know is that your MDS begins in a single cell. We have 37 trillion cells in our body. Out of that one cell is damaged. This is not a congenital damage. It is not something you were born with. It is an acquired damage, a somatic mutation has occurred. The consequence of this damage to the cell is that by the time these normal stem cells divide into two this one will divide into 100. In other words it is proliferating very, very rapidly. Its daughters overwhelm the bone marrow very quickly and now in the MDS patient everything which comes out of the marrow is red. It's daughters of that cell. Here you see they're multicolor. Right? Because they were coming from different stem cells. Now, everything is coming from that one parent cell whose daughters entered but they're able to mature. They just look abnormal and when something looks abnormal we call it dysplastic. So, myelodysplastic means white cells, red cells, platelets together are called myeloid cells as opposed to lymphoid cells and myelodysplastic means these cells are looking abnormal, but they're able to become fully mature white cells, red cells, platelets except before entering blood many of them drop dead and that's why now the number of cells entering blood is decreased and the patients present with anemia, neutropenia, thrombocytopenia. It depends on which cells are dying faster in which patient. So, the patient we began with only had anemia first. So, only his red cells were low but then we noticed the cells were low meaning now these cells started to die a lot more and then platelets also can come down.

Another thing which can happen, now before I go on I wanted to point out that you have these fully mature white cells in the blood. We can look for every genetic mutation that we want to find in the stem cell in these fully mature cells because you see they're all daughters of that cell. That's why for genetic mutations we can always use the blood. Bone marrow is not necessary, just remember that. Now, another thing that can happen to MDS patients is that in when they are undergoing maturation one of the daughters now stops maturing and remains immature. It is called a blast. Up to five percent blasts are normal in the marrow, but when that marrow reaches 20 percent it is called acute myeloid leukemia. So, here is the trajectory of a normal healthy adult making a trillion cells every day and then we have damage here and then as a result of that we have clonal hematopoiesis, clonal bone marrow formation. That means one clone of cells is responsible for all this. What happens to the normal stem cells? They become… they go to sleep. They are quiet now because they're over whelmed by this population.

So, the question we always ask when a patient… our patient is diagnosed, we are following the patient. Now, we made the diagnosis of MDS. The question now I'm asking is what is the prognosis because as I told you some patients can develop acute leukemia. What is the chance for our patient to develop acute leukemia? Why is that important? Because that is a serious turn as MDS is going along that's okay. So, traditionally, we have used the International Prognostic Scoring System for finding patients who are at low risk or high risk of developing leukemia and in this system you take into account these three variables. What are the percentage of blasts in the marrow, what is the cytogenetic and how many blood counts are low and based on this a score is assigned and if the score is low, the patient's chance of progression to leukemia is low

and if it's high then it's high. The problem is that it accurately predicts prognosis in only a subset of patients. Why? Because you can't take a curve of survival like this and apply it to an individual patient sitting across the table from you because what we can say is that I saw 100 pateints like you then a third will behave like this, median, a third will very quickly develop leukemia or die and a third can live up to 20 years. So, this is the problem. It's a nightmare to try and apply these survival curves to individual patients. So, do not let anyone tell you when you walk into a doctor's office and you have 2.7 years to live. No. Absolutely not because you could very well live 20 years. So, I really am allergic to those kinds of… for this reason. We can't. We can't be so accurate about biology, but recognizing some of the pitfalls, an attempt was made to revise this IPS which was published in 2012 and, again, the same three parameters, cytogenetics, percentage blasts and number of blood counts which are low. The same three were taken into account, but looked at more closely. Cytogenetics divided into more groups, blast count and not just how many blood counts are low, but how low are they? Is the hemoglobin more than 10? Eight to 10? Less than eight? And platelets less than 50,000 and so on. So, let's see what our patient's IPSS-R was. Remember he had now a hemoglobin of 10.5, absolute neutrophil count 1,500, platelets normal still. Bone marrow blasts were six percent. Cytogenetics were good because they were deletion 5Q. That's a good cytogenetic. So, the IPSS Revised score according to the calculator is three and the category would be low risk MDS. Now, it turns out that some patients who have low risk MDS may not do as well as other patients even though they have low risk MDS because they are older, hemoglobin is much lower, platelet counts are lower or blasts are higher or they didn't have the good cytogenetics or some minor changes like scarring in the bone marrow, etc. and it turns out then when MD Anderson Cancer Center people looked at their experience, they found three categories of patients and they called it lower risk prognostic scoring system that within the lower risk of MDS patients are also additional categories of people who will do well and who will not do well. So, what they found was after looking at 865 patients with Low or Intermediate 1 risk by International Prognostic Scoring System, they found three categories. Category one, the median survival is 18 months; category two, 27 months; category three; 14 months. Now, compare 14 months to 18 months. Where were are calling both patients as having lower risk MDS, but one is surviving 14 months another 18 months, median meaning half of them are surviving more and half less. So, this is why I'm trying to explain the pitfalls of these systems that they're not etched in stone. So, now MD Anderson's system became raised a big question. How can we call 100 patients low risk MDS when some will progress in 14 months and some in 18 months. So, then what they did is looked at IPSS-Revised scoring as compared in these patients with lower risk MDS and this is a very nice study that was published from Spain. They looked at 371 lower risk patients whom they followed for 6.6 years and they found the same thing that three categories, category one the survival is 9 years, 6 years and 2 ½ years. What a difference between 2 ½ and 9 years and then how about progression to survival. Here, 5 percent progressed to acute leukemia, here 25 percent progressed. So, you see there is a difference in lower risk MDS and that is now very well recognized. We know that if we can identify who this patient is who's at risk of developing leukemia early or dying early then we can try to intervene early for that patient.

What happens to MDS patients? I took this chart from the IPSS-Revised paper. They took over 7,000 patients from the MDS Foundation registry and they divided them 1,313 according to IPSS Revised system had very low risk disease 722 had very high risk disease and then these in between. Now, look at the survival of patients with very low risk disease, the median survival meaning half the patients will live longer than this is 8.8 years. Many of you in the room have had MDS for eight years, 10 years. I have patients I have been following for over 20 years and look at the very high risk. Half of them are dead within six months. So, what are these people dying of? Even the very low risk patient eventually if they die what do they die of and what about these patients who are dying very fast? It turns out that between 20 to 30 percent patients at most will die with acute myeloid leukemia. Those dying without leukemia are really 70 to 80 percent. It means there's not such a big difference between lower risk and high risk where acute leukemia is concerned, but they die faster. What are they dying of? That's what I want you to really appreciate. So, I'm saying to you MDS patient no matter how long they take to die, it's a chronic disease. It can go on for a very long time, but eventually when patients die they die only 30 percent of the time with leukemia, 70 percent of the time they die of bone marrow failure.

What is bone marrow failure? Lowering of the blood count. More and more increasing profundity of their cytopenia counts keep following lower and lower. You get more and more transfusions. Platelets start to fall then white count starts to go down and eventually the counts become so low we can't keep up with transfusions. So, 70 percent patients will die of infection or bleeding. Infection from low white count, bleeding from low platelets whereas only 30 percent will die of leukemia, but there is a difference between… so, this is what you need to appreciate that the bone marrow gets filled up with blasts in acute myeloid leukemia which happens 30 percent of the time because as I told you these people will have more than 20 percent blasts. In MDS, the blasts are not high necessarily. They are never more than 20 percent because then the patient becomes leukemic. The blood will contain more blasts, more cells here and here the blood contains less cells because they are dying more and more. Bone marrow failure is the problem here. The reason I'm making this distinction is the following. When we say a patient has MDS, the high risk MDS could be because the patient had 19 percent blast or it could be because the patient had bad cytogenetics and bone marrow was failing, so the counts were very low. Now, the treatment we design has to be very different. In the patient with 19 percent blasts, we need to control that expanding population of blasts. Right? We need to give anti-leukemia therapy, but in the patient whose marrow is failing, we have to try and protect the cells from dying. Just the opposite. This is the difference. This is why we cannot simply substitute the word AML for MDS to AML and say it's the same disease. They're two very different diseases really. This is what I said here you need to design acute leukemia, anti-leukemia therapy and here it's anti-apoptosis which means cell death. Apoptosis is cell death and so the reason I'm trying to make this very fine distinction is why MDS patients have to be characterized, their marrow has to be studied and all we have to determine if they're high risk why are they high risk? Is it because they're going to develop leukemia or is it that their marrow is going to fail because for the same high risk patient the treatment I design will be totally different. I hope I'm making this

clear. If I'm not, ask me later. I'm happy to… I try to do it in this slide, but I feel like it didn't do justice. Sorry.

Now, let's follow our patient. We follow him for another six months. Now, the anemia worsens and hemoglobin is now 7.6. So, we have to start transfusion the patient. Clearly, he is starting to require treatment. So, the first treatment for anemia is always recombinant erythropoietin which is a normal hormone produced in the body by kidneys and it causes maturation of the stem cell to where it's red blood cells. Fifteen to 20 percent patients will respond to Procrit or Aranesp. They are the same thing. They are erythropoietin. Procrit just lasts is short half-life, one week it has to be given weekly, Aranesp every two weeks. Not many patients respond. The ones who respond are the ones whose base line serum EPO level was less than 500 and who were not getting too many transfusions and most of the responses will occur within eight to 12 weeks. So, our patient did not respond to EPO, becomes transfusion dependent and is now requiring two units of blood every three to four weeks. Getting transfusions is not a good thing because survival is affected. Patients who are transfusion independent tend to have a better survival than patients who are transfusion dependent, but I want you to know that a good number of patients getting lots of transfusions are going to live for a very long time as long as we are able to give them transfusions safely and that's what we need to talk about. Now, it also depends on much blood they are getting. Zero, one unit, two units every month, three or four units every month. So, survival gets shorter as patients get more blood. What is the problem with blood transfusions? It can lead to chronic iron overload because with every unit of blood we directly put into the blood 200 milligrams of iron and the body has no mechanism of removing this iron. So, after as few as 20 units or 10 transfusions and the ferritin level of more than 1,000, adult patients may be at risk for chronic iron overload and when extra iron is produced what will happen is that it's… sorry… it just gets deposited into all these organs – pituitary, thyroid, heart, liver and the deposition occurs very silently. So, the organ can be 90 percent replaced with iron before developing any abnormality in function. That's the scary part. This is why we have to be vigilant and keep count of how many transfusions have we given. If we have given more than 20 units or 10 transfusions, we need to try to remove the excess iron.

Now, what happened to our case? We repeated a bone marrow and did a molecular profile. No change in cytogenetics, but blast count is seven percent now and genetic profiling shows that in addition to the mutation the patient had he has now developed the second mutation in eight percent cell. So, it's a small clone, p53 mutation. Our patient had refractory anemia with ring sideroblasts. What are ring sideroblasts? They're just red blood cells before they have exuded their new place. So, it's an (inaudible 31:13) blast, but here iron gets trapped in mitochondria and makes a circle around the nucleus like a ring. So, sideroblasts simply means red blood cell containing iron. Sidero means iron. What I want you to appreciate is this cell is showing you poverty in the midst of plenty. There's plenty of iron present, but it cannot be used to make hemoglobin. That's the one step missing in RARS patient. If only we can discover that one step, we will cure your disease instantly. So, everybody and their grandmother is now really on the

race. Why? Because almost 90 percent patients can have a mutation in this gene, SF3B1. So, we know it's that one gene causing this. These ring sideroblasts do appear.

What is this mutation doing to the red cell that it cannot use the iron anymore? And if it can't use the iron it dies and hemoglobin is not made. That's the problem. The issue here is so our lab was the first to establish this exciting crisper technology because we thought we could just cut out the motion in stem cells of that we obtained from our patients and I'll talk about that in a minute, but I wanted you to appreciate the complexity of nature. SF3B1 mutation if it is present in the bone marrow, 100 percent patients, 100 percent, will have the presence of ring sideroblasts in their marrow, but 10 percent pateints with breast cancer have SF3B1 mutation in their breast cancer cells and there no ring sideroblasts there. Ten percent patients with pancreatic cancer can have SF3B1 mutations. Now, these kinds of splicing factor mutations are turning up in diseases like amyotrophic lateral sclerosis, neurologic diseases. So, what I'm trying to say is the same gene if it is mutated in the bone marrow it leads to RARS. If it's mutated in breast cells, leads to breast cancer and they don't have anything in common if you look at them except they are both cancer. This is why we feel that if we find the answer in MDS for something it can be applied to 10 percent patients with pancreatic cancer, 10 percent with breast cancer. It's a huge thing and this was one of the main reasons I dedicated my life to study this preleukemia because I felt that if we can define the milestones which a cell has to cross before it goes from preleukemia to acute leukemia then the same thing could be applied to other cancers and the complexity that comes with it also is that the treatment we develop for ring sideroblasts will not work for pancreatic cancer because they don't have ring… but even though they have the same mutation.

These are issues that somehow are all coming together. So, I want to… I hope I leave you with a wave of optimism that we all feel we are on the verge of all these 100 years of work I feel is coming together to bring us some sudden breakthroughs and we really, really beginning to see a lot of patterns emerging because we are all connected so much better through the cyberspace that if one doctor in Fargo, North Dakota discovers something and puts it on the net, within 10 seconds I have access to it through the public domain sitting here. We have a very exciting time and that is really accelerating the progress that's going on.

So, in honor of tissue bank, we looked at 202 patients with refractory anemia ring sideroblast and we found that 60 percent had the mutation SF3B1, 40 percent did not and those who had the mutation had a better survival. What about p53? This is associated with complex cytogenetics which means chromosomes are damaged. Here are patients with multiple damage chromosomes and a mutation in p53 and their survival is pretty bad, but here are patients with the same kind of damaged chromosome, but no mutation in this single gene and many of them are living for eight years. So, you see the difference that genetics trumps cytogenetics, the cytogenetics meaning the chromosomes were damaged equally. A single gene mutation was the difference. So, in the past when we saw a patient who had multiple damaged chromosomes we'd get very concerned that maybe this is an unstable genome and this patient is going to progress to leukemia. Well, now we have learned our lesson. Until we do look for this one genetic mutation, we shouldn't be giving

bad news to our patients, but if we do see p53 mutation with the damaged chromosome, then we become concerned. Let's plan something early intervention of some more aggressive treatment.

So, another place where this mutation and this gene is important is in patients who present with an isolated deletion of long arm of chromosome 5. These patients are supposed to have a long survival and low risk of transformation to leukemia, but a good 20 percent can have a mutation in that gene and if they do they progress to leukemia fast and need a transplant sooner. So, once again don't give good news to the patients until we know what is their mutational status and this is why I called my talk MDS and the era of genomics because see what I'm saying that we thought we knew deletion 5Q patients do well generally, but some are not doing so great, 20 percent. That's one out of five. Turns out we can tell what those 20 percent are through the genomic studies and that's why MDS has changed in the era of genomics. Not just diagnosis but our management of the patient.

Now, I don't want to go too much over this, but just wanted to say that recurrent mutations are seen just in about 40 genes. So whenever we send… we tell you oh, we are going to do a genetic profile we are really sequencing only 40 genes and splicing factor mutations and epigenetic genes account for about 70 percent of the mutations, but there are problems. Problems are like our patient had two mutations. This is associated with very long survival, but I just told you this is bad news. So, now the patient has two of these. Is it a good… is the patient going to do well or no? First, look at how many cells have the good mutation, how many cells have the bad mutation. It turns out that with p53 even if it is in 10 percent or less cells is not so good. So, just remember that in terms of mutational profiles the dominant clone has different implications than a small subclone, but all mutations may not have the same consequences. Favorable and unfavorable cannot occur together like in our patient these two are occurring together, but basically I'm saying to you is that if an unfavorable mutation occurs it trumps the favorable mutation. This will be the bad one.

Let's see what happened to our case. What treatment options for this patient whose now transfusion dependent? Remember patient had ICUS, CHIP, lower risk MDS with deletion 5Q becomes anemic more and more anemic. We try Procrit. It didn't work. We go to now giving the patient transfusions. So, what is next? Well, the approved treatment for patients with deletion 5Q is Lenalidomide. Sixty-seven patients can have a complete transfusion independence and 26 percent patients even without deletion 5Q can have complete transfusion independence. So, the patient who had become transfusion dependent we started him on Lenalidomide or Revlimid and he becomes transfusion dependent, but after two years of response the hemoglobin starts declining and once again starts requiring transfusions. So, the question is, I mean, we had a perfect treatment for this patient. He had a complete response. Why do they stop responding? And this is not just a problem of MDS. It's a problem why we are failing to cure cancer in general just be with me for one minute. I told you that what happens in MDS and in most cancers is that one cell becomes abnormal and expands its population. Well, the problem is at the same time it gives birth to little daughter cells each of which have the same founder mutation of this

original cell, but pick up some passenger mutations which differ slightly from the dominant clone. Let's say we now come in with treatment and the dominant clone of cells were sensitive and dies, the patient will enter complete remission, all the blood counts improve, but like our patient did we gave the patient Revlimid, had a complete response, was doing well until one of these daughter clones rears its ugly head and fills up the marrow again. So in other words, no cancer is one cancer. There are thousands and thousands of these clones waiting to take their turn sequentially to populate and this is why the problem we see let's say BRAF mutation in melanoma. Look at this patient's horrible melanoma. Well, we give the treatment BRAF inhibitor, an oral drug and has a complete, beautiful response, but then it all comes back. Why? Because another clone now took over and the fact that that new clone took over means it was resistant. So, it's not one disease. It's a diaspora (inaudible 42:18), many cells are involved. I don't want to make you pessimistic. You see, the question I ask always is what disease have we cured ever that we are except infectious diseases that we keep demanding cancer be cured. All we have to do is make cancer into a chronic disease that people can live with like they live with diabetes, high blood pressure. We don't cure those diseases, but we make them livable and we can do that with cancer, too. I mean, all these clones can be controlled, can be kept in check. So, that's why I wanted to explain this.

What happens to our patient? Now, he stops responding to Revlimid and is transfusion dependent again. So, now what? Well, now we consider the hypomethylating agent. There are two FDA approved hypomethylating agents. They have established role in high risk MDS, but limited role in lower risk disease. In fact in transfusion dependent, lower risk MDS resistant to Procrit. Hypomethylating agents like these two, the response rate is only 17 percent and that's what happened to our patient. After six cycles of receiving hypomethylating drugs the patient still had not responded. So, basically the unmet need of lower risk MDS is that majority of patients remain transfusion dependent either chronically or episodically. Episodically because like in our patient he responded for two years to Lenalidomide. So, he didn't require transfusion, but then again became transfusion dependent. So, anemia diagnosis is present in 87 percent of patients, 29 percent are transfusion dependent, 40 percent receive transfusions as the only form of intervention and because of chronic anemia dependence on transfusions and subsequent iron overload survival is shortened and risk of developing leukemia is increased.

So continuing our case based on one year history of transfusions, I advised the patient to start iron chelation therapy. He did not take the treatment regularly. Eventually, presents the emergency room in acute heart failure, now has received between 50 to 70 units of blood. Ferritin is over 5,000, admitted to intensive care unit for six weeks fighting for his life. Look at his CAT scan before and after. Can we dim the lights maybe? So, the lungs here are completely black. This is the liver which looks white. This is the spleen and these are the kidneys. Now, this was the before CAT scan. After he has received all those units of blood and we repeat the scan, look at the liver now. It was white here. It is darker than the lungs now because 90 percent of this liver has been just replaced with packed with iron and yet there were no liver function abnormality. That's the scary thing that we need to be aware, we need to be proactive, we need

to keep count on our patients how many transfusions have they gotten. So, I had to begin both intravenous and oral chelation aggressively, but after four weeks in the hospital, six weeks in the intensive care unit, patient is finally back to work actually and has now even improved his hemoglobin and reduced transfusions. Patient failed erythropoietin, Lenalidomide, 5-Azacitidine or Vidaza, remains transfusion dependent, but now experiences worsening white count and lowering platelets and repeat bone marrow now shows 17 percent blasts, deletion 5Q but a new cytogenetic abnormality, one whole chromosome 7 is missing and mutations in both these genes, but p53 that was 8 percent is now 70 percent of the cell. So, that clone has expanded from eight percent to 70 percent.

What are the next steps for treatment? Well, the patient now has high risk MDS. So, we think of experimental trials. Patient is my patient, so the experimental trial we give to our patient is with a very exciting new drug called Rigosertib. It interacts with the RASP binding domain. It's a small molecule which means it is not chemotherapy and it is available both in intravenous and oral formulations. So, there was a phase two study on the basis of which we developed, my colleague, Dr. Louis Silverman developed a very nice combination trial of giving Azacitidine with the Rigosertib in patients who had failed Azacitidine alone and he showed that if they fail one drug, but now you combine it with Rigosertib, patients can do much, much better and 62 percent patients here and 85 percent patients who had never received Azacitidine or Dacogen and look at the response rate. Eighty-five percent. That's unbelievable. So, in combination with Azacitidine even for Azacitidine failure this is a very good approach. Eight-five percent patients had an overall response. Now, there is a phase three trial going on with the drug alone which is what we put our patient on. That is called the INSPIRE trial. In this trial it depends upon the previous trial which was an on time trial in which 299 patients were treated either with placebo, best supportive care or with Rigosertib and it turned out that the patients who did the best who more than doubled their survival were patients who were primarily failures of hypomethylating drugs and who had very high risk disease. So, the current trial, INSPIRE, that is going on at many institutions but in New York we are one of those institutions, very exciting trial. This is with the intravenous Rigosertib for patients who have failed hypomethylating agents as primary failures and who have high risk disease. That's exactly our kind of patient and this is the description of the inspire trial. I'm happy to leave my slides if you want to look at it.

So, the patient was given IV Rigosertib and did very well, actually. Had a great quality of life, but after about nine months, his blood counts began to deteriorate again and had to be taken off the study. Now, remember he started when he was 61. Now, he's 67 years old. So, what… now we are pushed into a corner. We have tried the supportive care. We tried FDA approved drugs. We tried experimental drugs. Now what? Well, now think about transplant. The transplant data here that in lower risk MDS if you transplant the patients they live 38 months median. If you don't transplant, it's twice as good. Why? Because any time we recommend a treatment for a disease we first ask ourselves what is likely to kill the patient the disease or the treatment? Lower risk MDS is not going to kill the patients, but if we try to cure it it's like bringing a tank to kill a mosquito. We will end up killing the patient. So, no. The recommendation is that you wait for

lower risk to transplant them only when you have tried everything else and for higher risk patients, well, then it's for higher risk it is the first option. If patients are young enough and have a match and can tolerate chemotherapy, high doses for the preparative regimen then this is the first option for high risk patients because 20 percent can have a long term cure or long term survival. So, the current recommendation is that patients who have lower risk MDS, patients should only be transplanted when there are no other options left and disease is progressing and for high risk patients immediately on diagnosis.

So in summary, what I showed you for low risk MDS patients ask the question is there a deletion 5Q? If yes then treatment is Lenalidomide. If no, what is the EPO level? Is it less than 500? Yes, try Procrit or Aranesp. If not then you can try Revlimid, Vidaza, Dacogen, some immune suppressive therapies or clinical trials. For high risk MDS, first ask the question is a donor available? Yes, then can the patient tolerate transplant? If yes, then that is the first option. If the patient cannot tolerate transplant or no donor is available, then hypomethylating agents and then after that really nothing except experimental drugs and that's the problem.

What is the goal for treatment? It differs from individual to individual in MDS patient. We want better long survival for our patients, but with the best quality of life. I have some patients sitting in this room who achieved complete transfusion independence with a drug, but opted to stop it because it made them feel so blah. They said if I have no quality of the life what's the point? I'd rather take blood than be able to play golf and so it is really depends on individual and really depends on so important to have the right quality of life.

We want to prevent the disease somehow from progressing, achieve complete remission, minimize side effects of therapy and this is my favorite slide. The point I'm trying to make is Myelodysplastic Syndromes, it's not one disease. It's a collection of disease. It is not one disease. If you look under the microscope there are all these types. If you look by a chromosome abnormality these are the recurrent abnormalities and these are the genetic abnormal. So, any combination is possible. So, no two patients are alike, but we still can find some similarities in patients. How? Because let's say we give a drug to the patient and the patient either responds or not respond and I always go to the opening lines of the novel, the great novel *Anna Karenina*. Happy families are all alike. Unhappy families are unhappy each in their own way. So, the responders are all alike. Nonresponders are different in their own way. One patient never took the drug, another one didn't absorb didn't absorb the drug, another one threw up the drug in all different reasons, but those who are responding to a drug must have something in common. So now watch this. My fellows call it my Wheel of Fortune slide. So, we can see patients who have, for example, RARS, normal cytogenic, SF3B1 mutation and respond and compare them to patients who have RARS deletion 5Q, p53 and don't respond. So, we can still find some similarities in patients and study them properly and identify and this is why since I was 27 years old I have received large amounts of funding for my research and have been a basic lab researcher all along, but I never lost sight of seeing patients. These younger people today either go into the lab or go into the clinic. They can't do the translational research, but I feel like it's so

important to do both because if we don't see patients we'll never even ask the right questions and if we don't ask the right questions what's the point of curing mice in the lab? I couldn't care less about that. I care about my patients and so I started a tissue repository because I look at this ICUS, CHIP, lower risk MDS, MDS MPN overlap, high risk MDS and then everything goes down to acute leukemia and the point is can we prevent that from happening? So, I was a naïve 28 year old when I decided to study MDS which is 100 years ago, but the first thing I said was let's save cells on my patients to study. Put them in a bank. I thought we'll be done with this in three years. Little did I know 30 years later we'll be still doing the same things, but amazingly we now have… been trying to intercept this from happening, these from becoming acute leukemia and the only way we can do it is study human cells. So today, a tissue repository that was started in 1984 by a 28 year old has 60,000 samples and do you know what? Every single cell has a story for me. I go open my freezer. I see those names and such things come back to me because everything represents a human being and I'm the only one whose patients are in that tissue repository. Not a cell comes from another second physician and that is truly a national treasure and I treat it like a sacred treasure so that when we move the tissue repository from Chicago to New York, I was driving behind that truck carrying it. This thing, if that doesn't reach I'm going to kill myself because I am waiting for technology to develop. Now, that we have cutting edge technology available, we have, as I said, for three decades 60,000 samples. We have all kinds of information on these patients. I don't want to bore you, but just to see when you give your bone marrow as so many of you know we take extra I ask and no one has ever refused me. So many of you in this room have so many times given to the tissue repository. I mean, once you give us the marrow somebody in my lab works for the next eight hours on that marrow separating DNA, RNA, pellets, proteins, CD34 cells and then we have a computerized data bank which contains everything. It's the ultimate in one click efficiency and so sometimes we don't get enough blood stem cells and I'm trying to fix the problem in the system cell. Stem cells can be found circulating in the blood or in the bone marrow. We separate them on a gradient and we get these CD34, but only a few thousand cells. The good thing is that MDS patients live long, come to clinic often. Many of you come… Every time you come to my clinic I ask you can I take your blood for tissue repository and you say yes. Why? Because each time you come we repeat blood draws, we isolate and freeze viable which means if I thaw them they will start growing your stem cells and my idea is if I can collect a bag of stem cells on each of my patients then when we have the technique of correcting that mutation, correct it and give you back your own cells. You don't need anything else. You don't need anything else for the… this is the exciting part. So, it's good for you who have given me so many of your cells to understand what we do with it actually and how critical it is and so now we can do many things in terms of cell.

Now, why do some patients with MDS continue with the disease for a long time and others progress rapidly? Our approach is we study freshly obtained cells directly from the patients. Let's say give the patient a drug… What… I'm not interested in developing new drugs. We have, let's say, a drug like Lenalidomide. We give it. We see who are the patients who are responding. Now, study the pre-therapy marrow using the latest technology. Genomics, epigenomics, metabolomics, proteomics, panomics which means that it's something like $50,000 per patient

and that's my problem. No one is willing to give that kind of grant to study. Our approach is we compare responders to non-responders using panomics, every cutting edge technology and now when we design the next trial we try to enrich it for patients who are likely to respond according to these studies. In other words, every next step must be informed by what we learned from our previous experience and then individualized therapy and this is the cutting edge cancer therapy treatment that even Republicans like. That's precision medicine. It's the end of one approach that we find druggable target identification. So, genome editing, I talked to you about it using molecular scissors to correct the defect in stem cells of the patient which we have collected and give them back to the patient. We've been doing this in the lab and we are really getting geared up in the first quarter of 2017 to rule this out.

I'm happy to talk about all these novel clinical trials. One of these is something I wanted to explain. This very exciting approach. So, every chromosome on its end have these areas called telomeres and when a normal cell divides into two it makes this telomere shortens each time that happens we can block the… So, telomere inhibitors is just an inhibitor of this enzyme which was going to prevent the shortening of the telomere and that drug is called Imetelstat and this Imetelstat was given to all types of solid tumors with zero response – zero, but when it is given to patients with myeloid malignancies 80 percent with essential thrombocythemia, 36 percent with myelofibrosis, 40 percent with lower risk MDS and RARS had a response. So, you see treatment of solid tumors very different than treatment of liquid tumors. That's one very important lesson here. We have an ongoing trial with this and they just completed the first phase. We are waiting for the phase two to… the second phase of the phase three trial to open.

I'll end by saying that we need to change our approach. We keep talking about curing cancer. No. We need to cure the body's immune system which allowed the cancer to appear in the first place. Something failed in the body's immune system to allow that original one cell to survive. You see damage. I told you than a trillion blood cells are produced every day. When cells are being produce they make mistakes. So, abnormal cells are produced, but those abnormal cells get removed very efficiently by our immune system, but as we age everything look… becomes decrepit. Everything becomes a little less efficient. I look in the mirror and I scream who is Phyllis Diller? What is she doing in my mirror! It's scary. How we change, but we are also changing internally. Things are giving up so that immune system doesn't remain as effective in removing those damaged cells and it is that one of those damaged cells just survive. So, my point is instead of this we have to make our immune system more efficient and that's why immune approaches are very exciting. I was just talking to you earlier about this antibody we have labeled radio labeled antibody. Very exciting. We have checkpoint inhibitors. In 2017, we are hoping by the mid of 2017 to have these natural killer cells available which take off the shelf, load them with the address by providing them the mutation that your particular MDS cells had. One patient had SF3B1 mutation, another had U2AF1 mutation. We put that address into the natural killer cell and let is loose and it only goes and kills that MDS cell. This is coming. This is right around the corner. I'm so excited about this.

So, we are doing a lot of coast guard T therapies. You've been hearing a lot about it. Happy to explain this later if anyone wants to know. I don't want to take up too much time, but the ultimate design we have is that we combine targeted therapy and immune therapies and I'll end with saying this if I had the choice of saving the life of one MDS patient or a walk on the moon, I would never look at the moon again.

Thank you so much.

(Applause)

Thank you very much.

Happy to answer… Yes, please.

Q1: Does a routine bone marrow biopsy show whether or not you have that mutant gene such as the SFB31?

Azra Raza, MD: We do that from the blood actually. Remember I told you that even the sequencing is all done from the blood. So, yes.

Q1: (inaudible 1:05:52)

Azra Raza, MD: Yes. Yes?

Q2: About nine years I ago I used to hear them talk about saving (inaudible 1:05:59) had MDS then the past four or five years I heard MDS referred to as cancer. I was wondering about what (inaudible 1:06:12) at your institution what is the number at which you usually think about (inaudible 1:06:20) and what age is (inaudible 1:06:28)?

Azra Raza, MD: Before I won't forget I'll write your three questions. So, before MDS was called a preleukemia which seemed to say it's not cancer yet, but now we know we call it cancer. So, you're absolutely right. In 2002 it was decided that we are going to call define MDS even low risk MDS as a malignant disease and the basis for that is the clonality. If something is monoclonal, is descended from one cell that is an ultimate definition. So, it is a cancer, but very slow growing one. That's it. Your second question is what value of hemoglobin do we give transfusions? Onset of that is there is no fixed number of course, for anyone I tend to go by patient's symptoms. If they are getting symptomatic at 9.4 grams of hemoglobin and can't walk we will give them a transfusion, but if they can tolerate a hemoglobin of 7.5 grams without feeling symptomatic and doing their chores then we hold off the transfusions because for everything there's a risk and benefit. There is a risk of giving transfusions because we can overload with iron, but what is the risk of not giving transfusion? The hemoglobin going so low that the heart has to work twice as hard putting a strain on everything, not getting the right

amount of blood to anything, everything's slowing down, quality of life deteriorating. So, you always have to balance things and I think the best thing is what the patient's body tell us. No two patients will be alike. So, individualized therapy always, no fixed number. Now, in terms of transplant, again, we transplant patients at any age up to 75 even…

Q2: What age?

Azra Raza, MD: So, it's… up to 75 if their body has no comorbid conditions, if patients are otherwise in… they are 75 chronologically, but if you look at their physical age, it is like 69. What's the difference? So, any cutoff is artificial in situations like this, but after a certain age, yes, it will be more risky. So, while we individualize transplant with the older patients older than 75 for sure, we tend to recommend a nontransplant approaches only.

Yes?

Q3: (inaudible 1:09:12) with a patient who has hereditary hemochromatosis and low risk MDS?

Azra Raza, MD: Nothing very different than I would do with patients who have low risk MDS.

Yes?

Q4: I've been on Vidaza for 14 months. In 14 months, I've lost 22 pounds. Does the Vidaza cause the weight loss? No matter what I eat (inaudible 1:09:47) I'm 95 pounds now (inaudible 1:09:50).

Azra Raza, MD: No, but it is a symptom of disease by that the metabolism has changed and you can lose weight with cancer of any kind. So, it's more a symptom of the disease. Vidaza doesn't make you lose weight. No. You look beautiful.

Yes?

Q5: First, I want to say that I came here because a colleague of yours said that I should meet you, Gregory Mears.

Azra Raza, MD: Oh, yes.

Q5: I am very interested in getting involved with your trials in particular about the immune system thing that you just brought up (inaudible 1:10:40) I'm taking Vidaza and I'm in treatment for a while and now the Vidaza is failing. Very confused. I personally am very involved with holistic healing and praying and whatever I can… and helping other people. I've been a social worker, a teacher, I bring that with me and I'm hoping… and I'm (inaudible 1:11:06) an immune system (inaudible) So, I'm looking for other things to add to traditional medicine and I'm hoping

that I can find out from you how to get involved with other things besides Vidaza and the traditional medications.

Azra Raza, MD: Thank you so much. By the way, Dr. Mears and I were at a gala last night together.

Q5: He didn't tell me about that.

Azra Raza, MD: He's a mean dancer. (Laughter) So, to answer your question. If you're failing Vidaza, please come and see me. We have some very exciting alternatives to offer you. Second, your idea about all these other approaches to health. I have to say that I attended a patient's memorial service and at this service many people stood up and said, "Mrs. XYZ lived for 10 years with cancer because of her positive attitude." Somebody said, "Because of her willpower," and somebody else said, "Well, she lived for so long because so many people were praying for her." Then her husband got up and said… he's a professor of history. He got up and he said, "My wife lived for 10 years with cancer not because of prayers not because of willpower and not because of her positive attitude. She lived for 10 years because of her oncologist," and first I clapped because he said what are you saying about people who died early that they didn't have a positive attitude, that they nobody was praying for them. Is that what you're saying? He was angry, but I get thinking about this. Wouldn't (inaudible 1:12:53) and I realized that in the final analysis he was wrong that it does help to have a positive attitude, it does help to have a community that is there to support you whether it's through prayers, through encouragement, through any kind of support and I do think it matters very much to have a strong willpower and to try and build your rest of your body to help immune system – positive thinking, positive attitude, keeping engaged in life, all these things help your immune system. So in fact while in the beginning I felt good about the fact that he gave us some credit also that oncologists had a role to play, the more subtle answer to that is I completely agree with you that we need to pay more attention to a holistic care of patients and I'm happy to talk to you about this. Please come and see us. We can devise some ways of helping our patients – forming a group, doing things together. I'll be very happy to participate.

Q5: I really want to say I've had some very severe bouts with depression and I've been in standard treatments for, jeez, like I guess about 6 years and I went to the library looking for information because I felt I was very secluded and drawn into myself and they gave me information about MDS and I came home. I did some stuff on my little notepad. Within less than a week, I had information from MDS. It was a huge, huge breakthrough for me that I could sit here and cry. The people that I spoke to were just undying in support. The things that I read were loaded with information from other people who have MDS and I just can't thank the organization enough.

(Applause)

Azra Raza, MD: What a beautiful thing to say and this is the best proof of what you brought up that look, just finding that there are people to support brought you out of some kind of depression. I think this is very important also. This is why I think having a relationship with my patients that goes beyond being. I mean, the best way to treat a patient is for a patient not to feel like a patient, but to feel like a human being who's there and for me not to feel like a doctor, but to feel like yet another human being who's dealing with you and I think that is so essential and that just knowing that your doctor cares and that your patient trusts you. For both of us, that works beautifully and that gives us an inner strength which allows us then me to face my day going through tragic stories and patients to face their own daily hardships. I think you have brought up a very important point. Thank you.

Q6: (inaudible 1:15:57) I read that patients did not get (inaudible)

Azra Raza, MD: Okay. That's all voodoo. Forget it.

Q6: (inaudible 1:16:17) And I'm wondering if there's any relationship (inaudible)

Azra Raza, MD: It's a different disease, very different.

Q6: (inaudible 1:16:34)

Azra Raza, MD: One can lead to the other, but as polycythemia, where by itself is a different disease. It can develop into MDS and then that's a different MDS and polycythemia where is a different kind of disease. Yes.

Q7: We love you. I agree with you. My whole thing is family dynamics. (Inaudible 1:17:02). I think that's very, very important to have family (inaudible 1:17:13)

Azra Raza, MD: I couldn't agree more. When I try to tell my 22 year old daughter that families matter her answer is, "Mommy, whatever you are on I want to take it also," but I couldn't agree more. So important to have that support in the family, so important for families to support each other. I think that any of you who are willing to start these things, I mean, look at the MDS Foundation work. They have made a family out of all of you. Everybody in this room has something common with each other and I think that's a noble thing that you guys have done. Congratulations to Tracey and your team at MDS Foundation. Can we give just a few other people a chance? Yes?

Q8: (inaudible 1:18:08) Questions are how do you choose a proper doctor that does the genetic testing and if they are not is it something that we could suggest that (inaudible 1:18:24) us and do you have any suggestions on how do we start this path and (inaudible 1:18:33)

Azra Raza, MD: Yes. Very important question. So, when you're newly diagnosed in the past, we would say ask your hematologist, but now ask Google. Just Google and see MDS experts in the area. Talk to your hematologist. My advice is always work with the local hematologist, ask them directly and Google, take names. If you're not finding something if you put in MDS, you'll come up with MDS Foundation at least. You can always call them. They will help you. Where do you live? In that area these are the people who are dealing with MDS patients. I think it's very important to find an MDS expert because I see as an MDS expert 40 to 50 MDS patients every week and I've been doing this for 25 years. Whereas a regular hematologist in their practice will see maybe six patients a year. That is very different than seeing 40 to 50 pateints a week for years and years and science, medicine completely remains an art form. You can't read a book, cookbook, like and go and apply it to patients. No. It's an art form. It's very important to find someone who is or has handled a lot of MDS patients. Google, ask your hematologist, go to the MDS Foundation. Once you find the expert make sure they work for your hematologist locally so you only go to them as a tertiary care center for treatment decisions, but then everything is executed at the local level. That's my advice always. Now, there will be some experimental trials for which you have to go to special centers, but that's hopefully that comes much later and is a rare case, but not rare, but eventually when that happens you would have to do it, but for a long period of time you can continue with the local hematologist.

Can… (Attendee) go ahead.

Q9: Thank you for the informative presentation first. I would like to find out what the deposits. Is there any way to remove iron before the iron is transfused into the patient?

Azra Raza, MD: Good question, but you see the iron the way it is is iron combines with a protein called globin and that makes hemoglobin, hemoglobin which is as the heart of red cells. So, iron is not in the form of just iron there that we could remove. It is hemoglobin is iron. So when that red cell dies the iron gets released. Let's say I give a transfusion to a patient. Those red cells I give are going to live for a while and then they'll die. When they die they release their iron and when they release the iron that's the problem. So, no. The answer is no.

Yes, Mr. (Attendee).

Q10: Dr. Raza, thank you for your presentation. I was just wondering does health insurance including Medicare in any way dictate how you can proceed in the treatment of patients?

Azra Raza, MD: Never for us. Never.

Q11: As one of 10 children of grandchildren of an MDS patient, I need to ask what sort of family patterns have you found, if any, for inherited patterns?

Azra Raza, MD: Hereditary patterns are MDS is not a disease that's inherited but having said that I have regularly seen familial cases of MDS. I have a family, surprisingly, in which mother and two daughters have MDS, but now it turns out that the father who was not related at all to the mother has a first cousin with MDS also. So, this family got it double whammy from both parents and now two out four daughters have MDS and the third one we were going to use for her a transplant, turns out to have already bone marrow changes. So, it's very scary that in some families it is a familial thing, but that is not the usual case and when we see that familial MDS it doesn't really appear until after 50 years of age usually even in familial cases because if it was going to appear early it would be lethal disease and they wouldn't… the baby wouldn't survive anyway.

Yes?

Q12: Doctor, I want to thank you very much for your presentation. I came here with (inaudible 1:23:29) and your presentation really focused on that and your Wheel of Fortune, it's amazing to me (inaudible 1:23:43) because I'm a patient of yours and I'm low risk, but I do have multiple genetic mutations and you really have been down relatively to my condition and say you're low risk and where I'm watch and wait. So, it's amazing to me how your Wheel of Fortune spins and you're precise with it. So, I appreciate your presentation today very much.

Azra Raza, MD: Thank you very much. Right now, we only know about what are very favorable mutations. There's only one that I showed you, SF3B1. We know an unfavorable one is p53. Besides that we have only one other set of mutations, IDH1 and 2 for which we have treatments. That's 10 percent of cases. All other mutations are there, but we don't know what they exactly be for individual patients. So, that's why if you didn't have a particularly good one and a particularly bad one then we say just ignore these until we follow you and learn more about it.

Yes?

Q13: (inaudible 1:24:59) with a question about Medicare, it came from over here. (Inaudible 1:25:06) I'm on Procrit and the Procrit, the Medicare denied renewal of the prescription and then my hematologist got involved (inaudible 1:25:22) I don't know if I'm now am I? So, it's up to the hematologist to add his or her two cents, it's helped in my case.

Azra Raza, MD: Yes. Thank you.

Tracey: I'm a soft speaker so I'm just going to come up here. Thank you so much, Dr. Raza. That was wonderful.

(Applause)

Thank you very much. We're going to switch a little because I think we're running a little bit early. We're going to break for an early lunch and give everyone a little bit of a break and then we'll have Jayshree, our nurse, speak throughout the afternoon. Again, lunch is back there. We're just getting started uncovering everything. If you want to get a drink or use the rest rooms and then we're eating in this room also. So, in a little while we'll bring Jayshree out and we're also trying to control the temperature. I don't know if I'm the only one whose teeth are chattering, but I promise you we're trying to warm up the room. Okay? Thank you.