Speakers
Jamile Shammo, MD, FASCP, FACP
Jean Ridgeway, MSN, APN, NP-C, AOCN

Dr. Shammo: I'd like first of all welcome all of you to the MDS Symposium and I like to thank the MDS Foundation to make this possible basically. So, I want to welcome you again to Rush University Medical Center and say that this meeting is very special. Special for me as much as it is for you because this is all about you. This is isn't the time when we just talk for three hours telling you about MDS. I'd like to hear from you what you have to say, what were some of the purposes for you coming actually to a symposium like that and I certainly hope that by the end of the meeting that you would walk out of here with having the purpose that you attended this meeting fulfilled. So before we start, actually, since we're waiting, I'd like each one of you to maybe introduce themselves, tell us a little bit about who you are, what is the connection with MDS and you can share whatever information you'd like to share about your disease and some of the reasons why you would like to attend this symposium and what you want to learn from doing this basically. So, start with you.

Ken: I'm Ken Helmzer. My wife here is Sandy. I'm here to support my wife. She has MDS. Sandy.

Sandy: I have MDS. I was diagnosed in 2010. It's low risk MDS. I had a clinical trials and… within. Actually, it was Dr. Shammo's trials and now I'm… don't give any treatment at the moment and kind of holding my own.

Rich Megaly (sp? 1:51) is the patient. I'm his significant other and we're going 60 treatments of Vidaza, was diagnosed in October of 2007. He's had 3 (inaudible 2:07) and it's been working. We've been very fortunate since Vidaza has been doing the job and so we just wanted to come here because it was MDS patients. Rather we went to a leukemia (inaudible 2:23). It was very technical and really didn't help us a lot. So, we figured that this would be a good place to learn.

Dr. Shammo: More helpful.

Glenn: Good morning. Glenn Anderson. My wife, Marlin, from the middle part of Wisconsin up by the Green Bay Packers area. My treatment was diagnosed down here in Chicago. Dr. Meta at Northwestern Memorial. I was diagnosed as high risk. I'm in my 21st treatment. I'm basically at low risk. One of my questions is to find out why do I stay at high risk when all my test results show that I'm in the low risk, but I'm still classified as high risk, but I feel great living an active normal lifestyle at this time. I am on Vidaza. I start my 21st treatment next Wednesday for 7 days.

Barbara: My name is Barbara (inaudible 3:21). My husband was diagnosed with MDS about eight months ago. Right now, he's, I guess, just holding his own. The doctor really hasn't prescribed anything because so far it's only affected his red blood cells. His white blood count and his platelets are fine. So, he'd like to know what…

Dr. Shammo: What to do.

Barbara: What to do and we are trying to live a normal life and our daughter's here to support us.

Dr. Shammo: Excellent.

Rich: I think he said everything that I would have said. My name is Richard Arnot (sp? 4:06).

Barbara: We're from Indiana.

Richard: Indiana.

David: I'm David Hensel. This is my wife Judith. We're from Chicago. I was diagnosed with MDS 11 years ago and I've been Revlimid for 10 years and if there's a condition of remission that's me and I have a completely normal blood workup and I'm feeling great and have no problems. (inaudible 4:42)

Judy: My name is Judy Hensel. I'm his wife and he originally has started at the University of Chicago in a study and he was put on Revlimid because he had the 5Q- so and he's been doing, knock on wood, very well.

Bob: My name is Bob Ritell (sp? 5:07) and I was diagnosed with MDS in 2011 and I just had 6 treatments and chemo and the doctor's holding back, Dr. Avina Kapal (sp? 5:17), who is at Rush University and he probably say he'll keep me on a maintenance program and blood transfusions and chemo every 5, 6 weeks, something like that. This is my daughter, Eileen.

Maria: My name is Maria and I was diagnosed with MDS in 2012 in the spring and at this time we're just watching… I'm having blood taken every couple of weeks and it's the white count is very low and the platelets are low. So, holding my own. A bit fatigued, but just, you know, doing whatever they say. Thank you.

Mary Ellen: I'm Mary Ellen Kelly. I live in the Northwest suburbs and I have low risk MDS. I was diagnosed in the fall of 2011 and I receive weekly injections of Aranesp. So, I'm here just to find out other treatments.

Dr. Shammo: Okay.

Linda: I'm Linda Berger, here from Indiana and I'm here to support for my husband, Steven.

Steve: My name is Steve Berger. I'm from Indiana. I have… I don't know what I have. It's either low risk or high risk. They're keeping me on a maintenance program right now, which to me might… just testosterone improved. In conjunction with that and with other conditions I do have, so I'm kind of just holding my own. Thank you.

Paula: Hi. My name is Paula Quintero. We're coming from… I'm coming from Cincinnati with my mother. She has MDS. She's coming from Venezuela, South America just to know more

about this illness. It's (inaudible 7:20). I'm also (inaudible 7:22) our country. So, why we're come here to hear more about this illness and to understand what to do if the thing that we're doing now is the correct thing. So, I appreciate all the help of everybody here. Her name is Angela and my name is Paula.

Dr. Shammo: Welcome.

Tom: I'm Tom Besandrea (sp? 7:46). I come from Lincolnshire, Illinois. I'm on watch for MDS and I was put on watch in 2011 and I'm just here to get educated.

Linda: Hi. My name is Linda and I was diagnosed with MDS about a little over a year ago. I think I'm intermediate. They haven't done anything and I don't feel sick and so at this point I'm just trying to find about it and learn about it and what can I do, what can I expect. I'd like to meet other people with this. So…

Dr. Shammo: Welcome.

Ann: I'm Ann Albert and I'm just here to support my friend, Linda.

Linda: This is my husband, Patrick.

Linda: My name is Linda Heller, Linda also and my daughter from Bristol, Wisconsin and my son from Minnesota and my granddaughter is here with me to support me today and I have the 5Q deleted and I was on one… or I was diagnosed in 2005 and I have… What was I going to say? I have 1 treatment with Revlimid for 1 month and it was very strong. It was a very strong dose and I couldn't handle it because I have other things going on with me too, so… but I don't whether I'm still at… what kind of risk I am. I don't know whether I'm low, medium or high.

Dr. Shammo: Or high risk. Right. Well, we're going to be talking all of that. Actually, (inaudible 9:25) low risk (inaudible 9:26). Okay. Who else hasn't had the opportunity to speak? Go ahead.

David: My name is David Zeff. I'm from Southaven Michigan and I was diagnosed at the University of Michigan in July of 2011. I was on Vidaza through the end of February doing very well and all of a sudden it quit working. So right now, I'm on maintenance with Aranesp and Neupogen and blood transfusions when I need it because they're afraid to move me to the next drug because I've had 2 bouts in the hospital with infection and they're afraid I'm not going to make the third. So, I'm here to learn today and again my doctors are trying to build me up to go into Dacogen or whatever the next step is in chemo therapy and my…

Dr. Shammo: Dacogen?

David: Dacogen. Yes. And my son, Steve, is here with me to support me. Thank you.

Dr. Shammo: Hello, Steve. Michelle, want to introduce…

Michelle: I'm Dr. Shammo's, clinical research nurse, so I take care of all the patients on the clinical trial that we have. So, I'm just here to speak about what trials are and it looks like no one is really going to fit that, but at least you'll know, you know, what your other options are if progression happens or if things change. So, I'm just talking a little bit about that and the trial that we have here at Rush.

Dr. Shumal: Everyone knows Deborah and we have representative from (inaudible 11:17) and of course, Jill, who has been the hero of the meeting, right? Who, Gene, from University of Chicago and she's going to be talking to you a little bit later about trials and more on MDS to come. So, I think the very segment that we'd like to do is an overview on this disease because I realize that there's a lot of educational need, if you will. You have to forgive me because MDS is a very complex topic. No mater how much I try to make it, you know, easier to understand, there's still a lot of technicalities in there. So, I decided that I'm going to use the same slide deck that I normally use for physicians, but I want to alter that so that I can make it patient friendly. So, I'd like you to pay your attention to the figures and the numbers that I'm going to show you on those slides. Don't mind the complexity of it. Okay? But I need to get myself a laser pointer. So, I know I have one in my purse. I will be right back. (12:17 – 12:55).

So, I want to infuse a little bit of entomology in there. If you ever thought about why the words myelodysplasia or MDS is utilized it's because of these combination of word. Myelo which means marrow and then plastic… or dys means bad. plasis formation. So, bad formation of the marrow and actually it's not a very old disease. It's a relatively recent disease that we've identified. For example, in the earliest 20th century, people, hematologists in particular, noticed that a subset of patients who ended up developing leukemia had a phase before they did so where they had abnormal blood counts, either anemia, neutropenia or cytopenia. So everyone sort of realize or recognize that there is a pre-leukemia phase which is where the word pre-leukemia sometimes comes from. Well, now we know today that not everybody who develops this disease ends up with leukemia and that we have certain prognostic features that help us or certain features, if you will, that allow us to identify the subgroup. Okay? So, hence that term that was used in '53. So again, not a very old… You're not talking about something like syphilis or recognize hundreds of years ago. So, the early identification of this disorder because of the vague nature of it has been somewhat problematic and that's why we'd reason why it's represents such a challenge, you know? You have to believe me when I tell you that there's a lot of people out there who do have MDS yet they don't have that diagnosis. They've been referred to hematology. They've never seen someone who would actually give a reason why someone has anemia or low counts and they might say, "Oh, you know, of course, they're 75. They're entitled to a little bit of cytopenia." So, there's a relatively present or prevalent age bias, but in my opinion I think everybody deserves a diagnosis. Okay? And in '76 was the very first attempt to actually sit together, a bunch of doctors, pathologists and statistician, to say, "Well, you know? Let's just define this as categories, pathological categories, and come up with a classification," which was what was known as the French, American and British classification or the FAB classification, but again, realize that this was in 1976. In fact, the most recent WHO classification is 2008. So, you can imagine that there's so much flux of information about this entity in recent years and I don't know how you guys feel, but every time I sit with a patient in the room and to try and explain what MDS is, it's one of the most difficult things to explain and I think when there are blasts in the marrow, it becomes a little bit more understandable. Okay. So,

these are collection of immature cells that are in the marrow. They have a very good definition of what a blast is, but anything that's low risk, that's problematic. Why? Because then you have to rely on something called dysplasia or the bad formation of the marrow that we talked about.

Well, so how do you define dysplasia? This is basically the most logical diagnosis. So, pathology or the pathologist, sits, looks at the computer or at his own microscope and they have to look at cell and tell themselves whether or not these cells are dysplastic meaning do they look normal or abnormal and there are certain definitions for each one of those lineages, red cells, white cells and platelets as to what dysplasia is. Now, what makes it a little bit more complicated is that sometimes you can have dysplasia in things not related to MDS. For example, if someone has hepatitis. They will have dysplasia in the bone marrow. If someone develops HIV, any kind of a viral infection and you decided you want to perform the marrow now. Guess what? You're going to see dysplasia. So, a lot of it depends on timing, contaminant diseases that are happening at the same time and putting the clinical data together. So, low risk MDS in particular tends to be relatively harder to diagnose. Having said that, if you have someone that doesn't have a lot of blast, but they tend to have genetic abnormalities meaning the side of genetic abnormalities you've all heard about meaning when they take a little sample of the marrow and they kind of grow it to see what kind of genetic abnormalities there are. If you see that, that would be more proof that this, indeed, is MDS like in deletion 5Q situation, bonafide MDS and clearly the bone marrow even though it appears to be packed hypocellular, you know… what does that word mean? What is hypocellular? Does anyone know?

?: The blast amount of the cells.

Dr. Shammo: Yes, very good, and usually the people estimate cellular and I'm going to teach you a little trick and when you go back to your doctors they will be impressed. Wow. They know… So, it's usually 100 – age. So if someone is 50 or let's say 60 years of age, their cellularity should be 40 percent. So, if the 60 year old has a bone marrow biopsy and now their cellularity is at 80 percent that's considered abnormal. That's considered hypocellular enhanced. Obviously, your bone marrow is on overdrive. Now, the irony in that is that even though the bone marrow is on overdrive, you don't have normal peripheral blood counts. Right? So, there's a block in maturation. The marrow is going on and on and on and on producing or trying to and yet in the peripheral blood you don't have a lot of (inaudible 18:52) coming out and the reason behind that is that at least it has been shown that there's a lot of cell deaths that happens in the bone marrow. We don't understand some of the blocks, what is it exactly that happens that causes those cells to not develop and go out into the peripheral blood, but that's coming and finally only about 30 percent of the patients who have this disease will evolve onto leukemia, not everyone. Having said that, the problems that they face be it leukemia, be it MDS are consequences of what we call bone marrow failure states. So, bone marrow failure means when the bone marrow fails. Now you all know what heart failure is. Right? The heart not working. Kidneys don't work, etc. So, this is the closest thing to a bone marrow that doesn't function. It's bone marrow failure and clearly like many of you have talked about is that there gradations to that. Someone may live with a hemoglobin of 8 not needing transfusions, just staying like this for a long time. Adult patients who had the diagnosis made and I've been following them. Actually, some of them had deletion 5Q with a hemoglobin of 12. Okay. No need to do anything about it.

So, when you say bone marrow fail, I like to qualify it as to the degree of severity. Everybody has a different number.

What are the causes? I'm sure you all heard about Robin Roberts fight with MDS. In her case, I think it's clear she's gotten toxic injury from chemotherapy and it is too bad and we don't know how to identify those patients. Actually, there's one of my research interests is to identify the reason and the cause behind why do 5 percent of the patients who get breast cancer, sometimes 1 percent, 1 to 5 develop this. What is it about her that was different? I'm sure she got the same kind of chemo that many other women got and yet she developed this disease. So, that's, I think, is the next step that we need to understand with this entity. So clearly, exposure is something that we need to understand a little bit better. What about genetic predisposition? Many times people ask will I be giving this to my family members and the answer is no. In 90 percent of the cases, it's probably not related to that. I mean, certainly there are entities whereby genetic predispositions to MDS does occur and it could be transmitted like if you think about Fanconi's anemia and (inaudible 21:31) Aldridge and some of the strange way our genetic abnormalities that the pediatricians tend to see a lot more than adult hematologists, yes, but in general this is not a disease that's transmittable to offsprings.

We sort of touched upon that secondary offset cyto… we call it cytopenia related MDS and there are two different types. I don't think any of you had received… Although I would like to ask how many of you think, at least, that they've had something called toxic exposure to either chemical, benzene, radiation of any sort. Put your hands up. So, two of you. Do you care to share what type of exposure it was?

?: Benzene.

Dr. Shammo: Benzene and…?

?: Well mine was (inaudible 22:19) chemical and also (inaudible 22:22) small (inaudible 22:25) radiation part of it.

Dr. Shammo: Tonsil?

?: No, no (inaudible 22:29) the doctor said well, a lot of people was in that (inaudible 22:37).

Dr. Shammo: This is a disease of older individuals, so you can see the incidents rising. As the older you get, the higher the chances are, but you can see there's a small percentage of patients that tend to be less than 50 years of age and it can happen as well. Clinical presentation. I'm sure you're all familiar with might happen. Fatigue, infections, fevers, bleeding, bruising and all because of this anemia. Neutropenia and (inaudible 23:11) cytopenia are low (inaudible 23:12).

So, let's talk a little bit about how doctors think about those parameters. So, anemia, obviously, is the most common, 90 percent of the patients will have that. Neutropenia which is a decrease in the neutrophils, the cells that fight infection and like I said, it's gradation of severity. The normal is 1,500 and above, but your risk of infection, actually, won't be high unless you hit this… unless you have severe neutropenia. Anything less than 500… In fact, anything less than 100 that's

what poses the risk of infection. Okay? So, if I have someone who sits between 1,000 and 1,500, you know what? Their risk is probably like mine in contracting the infection, but if you develop more than 3 infections a year even though your disease may be low risk and you happen to have neutropenia, then I'm going to start thinking about well, maybe we need to put this under control. Okay?

Why this is sometimes difficult is because of tremendous overlap with leukemia, myelographic neoplasms, P&E, aplastic and LGL. Realize that all of you know that, but you'd be amazed sometimes physicians don't realize it. MDS is a diagnosis that has to involve doing a bone marrow biopsy and doing all the appropriate tests that come with that.

This is just to show you the frequency of some of the genetic abnormalities that can happen. Division 20 and 5 are considered good risks, 8 is intermediate, Y is good. Actually, 17 and 11 are considered… and 7 are not considered good cytogenetic subtypes. This is the 2008 classification and you know I know some of you said we don't understand low risk, high risk. What does that mean? Well, it's the because of the way it's interpreted. So for example, if one of you happened to have something called RCUD or refractory cytopenia with unilineage meaning that you had the low counts with only 1 lineage affected with dysplasia. That would explain to you what it means. That's low risk. Someone has a refractory anemia with ringed sideroblasts, low risk. You go to RCMD. So, that may be considered low risk, but because the dysplasia is involving 3 different lineages then that's not very low risk. The behavior of RCMD then don't even maybe considered low risk may not be so low risk. Okay? So, there's some variations on the (inaudible 25:41) when you come trilineage dysplasia. Deletion 5Q is considered low risk and then once you start to get blast, blast mean that now you started to have abnormal myeloid forms that will only accumulate. We don't know how to get rid of those myeloblasts and I guess some of the reasons behind that is that they're so educated, they're smart cells, they know how to exist. You give them chemo, you give them… They just stick around. Okay, but we're learning and you've heard some of the examples in patients had been receiving (inaudible 26:20) and things like that that there is a way to put them under control.

?: What it's saying there.

Dr. Shammo: So, I'm going to skip that. Okay. So, here's the IPSS. So, I showed you the risks by pathology, but the doctors the minute they see you they will do something called International Prognostic Scoring System. That's the most commonly utilized tool. So if you look at this and you know your disease, you could actually estimate your risk. I give you a couple minutes to do that. So if you know the bone marrow blast percentage, you can give a score. Let's say someone has 6 percent blast. They get a .5. Carry a 5, let's say deletion 5. So, it's a zero. Let's say they only have anemia. That's another 0. So, the only score that they gotten is the 0.5 which puts them at intermediate 1. Okay. That is where you are. So anything up to 1 is intermediate 1. Anything up to 2 is intermediate 2 and anything over 2.5 is considered high risk MDS. Usually, anomaly and I'm going to show you the graph. People consider low and int 1 as 1 entity and int 2 and high as another. Why? Because when they follow the survival of those patients and by the way, this is without treatment. Just because they didn't have any treatments available. So, this is what you're looking at is the natural history of MDS. This is what happens when you don't treat someone. Alright? But so then you begin to understand if you have someone who has low risk disease,

look at how so many of them lived up to work. What is that number? Sixteen years no treatment. It's ridiculous. Right? So, but by the same token, some people who have low risk disease actually passed away at 2 years. So, what you can infer from that is that the IPSS is not perfect. Right? Because you… somebody may appear that they are low risk at the outset, but in time they may progress very quickly and others, you know, may just hang out without treatment.

So what is in there that we are missing and I will show you what is missing in that scoring system. So but generally speaking, like if you… the way doctors read that is that they look at what median survival which is how long did half of the patients live. So here's the 50 percent. Okay? Chance and then you can draw that. So, the 50… half of the patients that have low risk disease live at about 6 years, but the other half lives longer. Alright. And for me as a doctor, just looking at the IPSS, this is very difficult to know which group do you belong to even if you have low risk disease, but like I said, we have better ways to guestimate the diagnosis and for example because of many you from what I understand have low risk disease. This is something that Dr. Garcia-Manero from MD Anderson put together because of his… this observation that I just explained to you that some people even with low risk disease have different outcomes. So what he did he said, "You know what? If have someone who has low risk disease and I know one you said I'm not sure why am I called even though I'm told low risk. I'm told I'm high." So, it could very well be because of the cytogenetics. If you happen to have an unfavorable karotype like complex carrier type, deletion 7 and any deletion 7 abnormalities, I don't alone or as a complex karotype makes it unfavorable. If someone has very low platelet count, that's also not good. So if you're satisfied low risk MDS patients according to this prognostic model then you're going to see this. You're going to see people who actually go on to live what, 6 – 7 years, half of them and the others that are told they have low risk disease and you can see that they don't make actually the 2 year mark. Okay? So, there are certain prognostic schema that we use to further stratify low risk disease.

Okay. So then I told you the IPSS was no so perfect. It's not perfect because it doesn't take into account transfusion dependency. For example, everybody who has a hemoglobin less than 10 falls in the same category. Well, that's not really right. If you have someone who has hemoglobin 9.8 not requiring transfusions versus someone who has a 6 gram hemoglobin, every time they come they're exhausted. They need transfusion. They're not in the same risk group. Wouldn't you agree? So, that's the problem with the IPSS is that doesn't take the severity of cytopenias in account and also that's where it gets complicated, but I just wanted you to know that doctors are thinking about the cytogenetic abnormalities in different terms. So, you have very complex gradation of what those abnormalities are. Be it as it may, deletion 5 is considered good and 7 is not very good. Complex when it's more than 3 abnormalities is actually the worst possible category and here's the revised IPSS. Again, you could look at it and see how you might fit in that. Again, notice that people who have hemoglobin less than 8 get a higher score. People who have platelets less than 50 are also distinguished. People who have neutrophils less than 800 also get a higher score which is only reasonable and so now we have 5 different groups with the highest possible group getting a score of 6. So that might be changing, but you know what? There's so much you can make out of prognostic schema. Right? In reality, I think it's the bunch of things that figure into it. Now, understanding that it's not just the cytogenetics. There's a little bit more to that. So that there was a fascinating paper that came out of Dr. Bahar from San Francisco, Stanford, and they looked at actually… you know, have you ever heard of the Geno

Projects? The Human Geno Project where they basically sequenced the entire geno so they know what the normal sequence of gene is and so what they did is that they went and took over 400 patient samples, right, and then they studied them extensively to see what's different about their DNA from normal DNA, right, and then they came up with a bunch of point mutations. For example, many of them and you see the zeros here. That means that they are very statistically significant, but likely to survival. So, the ASXL1, Valez 1, PPP3, names don't mean anything to you but the point is that when patients with MDS had those mutations, they didn't do well. So, maybe it's not just the IPSS. Maybe it's a little bit more to that than what we're learning about. Now, often people will ask me, "So, should we be doing this? Is this something that's commercially available?" It's commercially available, but to tell you the truth, I don't know what to do with the information because do I know that if my patient that had this, does that mean I have to treat them earlier and if I treated them earlier will they have a better outcome? We don't have data to support that. So, I tend to be very skeptical about… I mean, it's interesting. I think it should be pursued. I think everybody maybe on a clinical trial platform should be tested for these things and then followed prospectively to see what happened to those who got it and those who don't, but we don't have that kind of data yet and Dr. Bahar said, "Look. If you have someone that has low risk in blood like you see here that doesn't have the mutation, for example, the mutation is absent then their behavior is this, but if you happen to have a present mutation then all of a sudden actually look here. If they happen to have the mutation, now their behavior is a little bit worse." Okay. So, but I like to see these data confirmed perspectively meaning if we took 100 patients and then we look at the mutation and say now those who have the mutation, we were going to be treating them sooner or do something or intervene in some way, is this better and I don't know that.

The other exciting development we need to know about that for people who RARS is that there was a discovery, a very interesting discovery, actually, in the way the cells process some of the proteins as there was this mutation that was discovered specific to RARS where 65 percent of this patients who had this had this mutation and this was in 2011. So, I am sure that there will be some development in this disease entity where we will be targeting what is known as splices zone mutations in a way, the way your bodies splice the RNA and package it and get it transcribed. So for the longest time really, we didn't know how to make buckets out of MDS but I think we're starting, right? Deletion 5 is one, potentially RARS is going to be another, high risk maybe with point mutation will be the other part. So, a lot has been happening and this is just to show you this is the location of that mutation where it intervenes with the way the MRNA gets spliced. So, something happens and you get a mutation. All of a sudden you don't get transcription. There's interference with the way iron is metabolized and people end up with RARS.

Okay. Now onto to treatment. Before I move on, questions about diagnosis and risk stratification? Let's move on.

So when I see a patient in my clinic, the question is to transplant or not. That's what it is and today I'm going to tell you my own personal bias on transplant because if you don't transplant which presumably the transplanters would like to say, "Ah, this is the curative option," and I agree with that. It's curative but with a price and I want to show you what that price is. Now if you do opted not to go for a transplant then you will fall onto non-curative approaches and we'll

talk about those. So, that's the notation that's… and this is a transplanter by the way. Corey Cutler put this together to show that look if you don't transplant people this is what happens but if you transplant you will lose some at the outset but then some will go on disease free. Okay. So, but you're losing some at the very beginning even though they may not have disease on board and that's the price I was talking about. Plus, you don't know where their point is. It could be 16 years for some of the people who have low risk disease.

What are the data? This is data from the International Bone Marrow Transplant Registry looking at some 450 patients. Some had low risk, some had high risk. The bottom line 40 percent are alive, not 100 percent and when transplanters say and we always had this debate, so they know my opinion. I wish there was a transplanter. It would be a lively discussion but nonetheless. Twenty-three percent relapsed. So, then where's the cure? How come this is not an entirely curative treatment option? You still have relapses. Okay? So, here's another one. People said, "Well, what about reduce intensity transplant?" meaning when because usually if you give someone myeloablative, if you have older patients, they can't tolerate that and people won't recommend that to begin with, but if you have someone who's older and you introduce this idea of reduced intensity transplantation meaning that you don't give them massive doses of chemo, a little bit of chemo, to allow space for this new marrow that they're going to be getting. What happens? Here's what happens. So, the 4 year overall survival was 31 percent… 30 percent. That's your cure rate. Okay? And there were some patients that relapsed and there were some patients that died not from relapse but from other complications. It's about 30 percent. So, 30 percent relapsed, another 30 percent of this non-relapsed. It's leaving you with 31 percent of… you know. It's not stellar. Here's another one that just came from 2012, this ASH meeting and it looked at 700 patients. Look at who was the oldest that was transplanted. Seventy-eight years old. That was one gutsy transplanter. Seventy-eight years old. I mean that's remarkable you have to admit, right? So, bottom line, 65 percent of them had advanced disease meaning that they had more than 5 percent blast in the bone marrow and some of them actual gutsy enough to say, "You know what? We're not just going to do matched related," which means like a sibling that has the exact same interlay typing, "but we're going to do unrelated donors," but they're a perfect match from some marrow registry, okay, and some of them where actually slightly mismatched and, again, those are the numbers. People die from transplants, 30 percent of the cases, and higher, actually, if it's someone that's not related. People realize 32 percent if it's from their sibling. A little bit less if you have an unrelated donor. Again, survival between 38 to 47 disease free and you're going to probably ask me, well, what is the difference between survival and disease free survival. Anyone? Survival versus disease free survival. What's the difference? Survival means that they're all alive, but some of them may be living with disease whereas disease free meaning that they're alive and disease free. So, this is the ultimate outcome, right, and, again, you're talking about 40 percent at best. So the next time you think about trans… and I'm not… believe me. I'm not trying to say don't go for a transplant. By all means, but when you do go for it you need to know the data. You want your transplanter to tell you what are my odds and what am I going to be faced with and what's my life going to be like after I have the transplant. Very important, but if you decided not to do that then we have a variety of options. We have EPO or Aranesp. They're both the same. Aranesp lingers in the circulation a little bit longer. It has a longer half life. There's Neupogen which I don't give to people just because they're neutropenic. I give it if they have an infection maybe and especially if they're

getting like myelosuppressive treatment like Vidaza or Lenalidomide, Aza, Dacogen, of course, transfusions, antibiotics and likely trials.

If you happen to have low risk disease, this is how most of the patients in the United States think about treating you. First of all though, you need to require therapy meaning if you have a hemoglobin over 10, you have no symptoms, platelet count is reasonable, no issues with bleeding or infection. Why treat? I wouldn't treat. I would watch. So, you need to have a reason for therapy. For example, people who have low platelet count, have you had bleeding complications? What is your platelet…? Have you had transfusions then yes, you need to be treated so that you can reverse that possibility of that trend. For people who have anemia, what's your hemoglobin level? Are you tired? Have you required transfusions? You have to have a reason because treatment itself does come with symptoms and adverse events. You have to have a reason to start that, right?

So here's the algorithm. So when you have someone whose identified with delete 5Q, Lenalidomide? It's a slam dunk period and I'll show data as to why. If you don't have deletion 5Q then you're going to do something called EPO level and EPO by the way some of you may be getting that is a hormone that is produced in the kidneys. That's something we make. A little bit in the liver, but for the most part, it's made in the kidneys. So you know, it's a natural product that we give back. Here's the caveat. If you're body is already making too much of it and the trigger would be anemia. If you're anemic the kidneys go oh, we need EPO. Let's put EPO out. Maybe we can make some blood. So if you had so much of it onboard maybe over 500 because that's the number that's been adopted from clinical studies, you're not going to respond. Your body is already reacting to the anemia. You're not going to need EPO and even if you got it, it's going to be money wasted because there's really a low chance of response. Now, if your EPO level is… Okay and this is the over 500. If your EPO level is less than 500 and you don't require a lot of (inaudible 43:46) then maybe there's a chance because then you're looking at the normal bone marrow compartment and you're giving it a kick in the butt. Come on already. Make some more. Okay. So, that would be the 1 reason why I might use what we call urethral poetic stimulating agent, okay or EPO RNS. Sometimes especially in people who have RARS, people have noticed that if you give a little touch of EPO together with Neupogen, those patients respond better. We don't know why. It may be simply synergy between Neupogen and Aranesp for EPO to have a better, at least (inaudible 44:31) response improvement in the anemia. Okay. So, that would be the only instance what I would say not just EPO, but I'll add a little touch of Neupogen and that's not because of neutropenia. That's because I want people's hemoglobin to improve. Okay?

So, what do you do with someone who has low risk disease, very high EPO and doesn't have deletion 5Q? Now what? Well, what's available is what we call hypomethylating agents meaning Dacogen or Azacitidine or what we call immunosuppressive therapy and I'll tell you what that means. Something like cyclosporine or ATG. Hypomethylating agents are actually, again, the same decision point has to be made. Does the patient need to be treated? And realize once you start therapy with hypomethylators there's no stopping. You've heard someone… who was the longest? Sixteen (inaudible 45:27) I mean, so that has to be an understanding that once you begin there's no stopping, so you have to choose a very good time to say this is what I want to start and Revlimid we talked about that. So, this was a study that we actually had at Rush as well as it

sounds like University of Chicago and people got 6 months of Revlimid at which time you can see how… look at their hemoglobin increase. Five grams. Imagine someone starting, for example, at 8 because this was the median hemoglobin when they entered the study, going up by 5 grams to 13. That's incredible. So and that's why this drug became first line for deletion 5Q. Here's what happened to 1 of the patients I put on the study. So, this was an OC3, she was getting transfusions actually every so often. This is her hemoglobin and this is when she got the drug right here in November. Look what happened to her neutrophils and platelets. Precipitous drop and that's to your point about, you know, having the low counts and especially if your kidney function is not so perfectly normal, this would be even more pronounced. Okay? But ultimately, she recovered and bam, she's never received transfusion. I can tell you my last contact with her was about 5 years after this study then we sent her back to her state and she was getting drug and everything went well. So, that's the reason I say that's a very good treatment action if you have deletion 5Q. If you don't, that's a little trickier, okay, because look at the response rate. Here is response rate in terms of coming off transfusion completely is about 1 in 4. So, 1 in 4 would come off transfusion if they don't have deletion 5Q and hemoglobin increase is real when it happens but we really don't know. We don't understand what is it about this drug that and who are those 25 percent of patients. Wouldn't it be nice to identify them? There was some work that looked at microchip (inaudible 47:42). Again, the genomic stuff to see if we could predict responses to that, but I don't think this has become, again, available in the clinic. What about amino suppressive therapy? Like I have some young patients that I have used in cyclosporine. You have to have a reason to amino suppressive therapy and what happens there is that your own T cells, your own immune system, becomes activated because of the presents of the MDS clone and attacks your bone marrow. So, this is an immune mediated destruction, okay, of the cells. So if you in essence suppress your immune system then maybe the normal marrow would recover. That's the point of using immunosuppressive therapy. So, normally people who have (inaudible 48:30) people who have hypoplastic I hadn't told you about that. There are even though most of the patients will have a very active marrow, 10 percent will have a marrow that's relatively empty, you know, and so those will be the people that might benefit from that.

Next, transfusion. So, transfusion dependence is actually not a very good thing to have. If I had a patient that started developing transfusion, I would like to reverse that trend and that would be time to treat them because usually the survival of people who develop transfusion is usually a little bit less than who don't require it. What about iron chelation? How many of you are on XJ or on some form of chelation to take out some of the iron? If you don't care to share that, that's okay, too, but there are certain recommendations that you should be aware of for those of you who are transfusion dependent and there are some differences. Like the MDS Foundation says anything over 1,000 of ferritin you need to chelate. Whereas the (inaudible 49:32) says 2,500. In reality, I think we all need to wait for the clinical trials, the randomized clinical trial between XJ or no XJ in low risk MDS to see actually does it matter really or do you just need to it before you get the study results. I want to wait even though my guess really tells me that maybe chelation beyond 2,500 of ferritin is a good idea. There are some clinical find… This is a study I'm telling you about. It's basically XJ versus not and then you see what happens in time and this is still ongoing. It's going to be years before we know.

There are certain drugs that stimulate platelet production for people who have low platelet count. That is also being studied in low risk disease. Again, (inaudible 50:21) versus not to see does it

have any impact on platelet count and then I won't go through that. There's something called ARRY-614 and this drug basically suppresses some of the cytokine that get generated in the bone marrow and there are some degree of responses and this is being explored more in the future. Now, combination treatments have become interesting. This is a study that Dr. Vasa did. I did the study which Sandy alluded to with Revlimid and Vidaza in low risk disease and it proved to be a little bit difficult. So, the combinations are not very easy to do. Okay. Especially in low risk because to me the risk is… the space are too high. I don't want to put people at risk just because I want to learn if this combination is feasible and I was hoping it would be a little bit easier to perform, but it turned not to be, but that's the reason why you do studies basically.

There's an oral Vidaza. So, those of you who have been Vidaza for a long time would love to hear that there's a potentially oral formulation that might become available, but we're still doing the studies with that. So, I don't know in reality. There's another drug that was recently approved to initiate phase 1 studies and it's called Aproset (sp? 51:43). This is going to start in Europe, I think, as a phase 1 and again if there are interesting, presumably stimulate a risk for paresis and these are the hypomethylating agents. This is the a Prosidene. This is the Dacogen. Very similar in composition, similar to 1 of the nucleotide in the DNA and I'm going to go just quickly on the responses. Here, so this is a Vicidomine. The initial study and about 44 percent of the patients responded. So, not 100 percent. When you go on it, you need to know that this isn't 100 percent that deal and then you should probably know that this drug also improves survival which I'm sure you've heard that people who were randomized to a Vicidomine versus conventional care regiments lived longer. So, that would be my drug of choice anyhow. Dacogen is the other alternative and it's a drug that was also approved based on the very, very similar study design. The responses are also very similar to what you have in a Vicidomine. Very similar, but the trial that they've conducted actually did not show a difference in outcome. It showed improvement in progression pre-survival, but so people who lived a little bit longer without progression of their disease, but there was no difference in survival. So after people fail hypomethylators, my recommendations is clinical trials. I don't like to go from 1 drug to the other. It just… there's no responses. No responses that had been documented. Is it not worth trying? I suppose, but my hope for success is not so high, I'll be honest with you. So, I like to choose 1 therapy and stick with it for as along as possible because most of the patients will respond to Aza after 6 cycles of therapy, not most, but those who are about to respond, let's say 50 percent. You have to do 6 cycles before you determine and that's what was done. Any response assessment before that is too soon unless it's frank progression and that's why I say it's very nice when people go on investigational therapies because you know what? This is how all of those drugs were approved. This is how Revlimid, Aza and Dacogen were approved. Why? Because people were on trials. So, thanks to all of you because of your contribution or potential contribution.

There's a bunch of other treatments that are under investigation for high risk disease called ferritin, I don't know how many of you have heard about this. Ricocertive (sp? 54:25) is the trial that we had here at Rush. I know Michelle is going to talk a little bit about that. We have certified to be now. It's not open anymore and there are many others that are being explored. None of that stuff is available yet in the clinic. There are some responses. You're talking about 33 percent. It's pretty much the failures. You're talking about 30 percent at best. Once you fail those drugs then your chances are 30 percent in all of the above and this is the Onconova compound. We had this randomized clinical trial and, again, no different. Response rate 30

percent. That's just the way it is right now. So, this is the study that we are going to. It's basically randomization to the Onconova versus the supportive care and this is the one that I closed just recently. We've been involved in many others. So, this low risk disease is going to be replaced by a combination of Azacitidine and an HDAC inhibitor. So, that's going to be the next clinical trial we're going to embark upon and then of course this one is still ongoing.

I told you about the combinations. We don't know if you really need them and if you do need them, which one is better. So, there's an ongoing study looking at Aza alone versus Aza and Lenalidomide versus Aza and an HDAC inhibitor and until we get the results of those trial, I will not use combination therapy outside of the clinical trial.

So, here's my conclusion. This is a difficult disease to doctors, to patients, but today we are far better than what we were 10 years ago and I'm hoping the next 10 years will be 100 times more than we have already achieved. So, thank you for listening and this is Aleppo. This is where I grew up and this is unfortunately the city that's under attack right now. So, this is like the old Suk (sp? 56:19) or the bazaar. This is the university. This is the citadel. This is like one of the citadels in the world.

?: Where's this?

Dr. Shammo: Aleppo in Syria and then that's part of the city center. So, I hope that those sites are preserved basically and I thought to throw something that's a little bit more colorful and now, I'm going to turn it over to Michelle who's going to talk to us about trials. Do you want to use the stand?

Michele: Oh, sure.

Dr. Shammo: Thank you.

(Applause)

?: We have a lot of time for Q&A and so stick around.

Michelle: Hi. I'm Michelle Balla and I'm Dr. Shammo's clinical research nurse. I've been working with her at Rush for like a year and a half and it's been nothing but a pleasure and I basically take care of the patients that we enroll on clinical trials. I don't actually give the treatment anymore. I used to be a chemo nurse for like 17 years and just like Dr. Shammo has said, I have a passion now for this because if you wouldn't participate in clinical trials or have them, we wouldn't have the drugs that we have today. So, I thought talking for a brief 15 minutes she wanted me to and I'm not a great talker like she is, but wanted to just maybe for you to understand what a clinical trial is and how I start talking to patients when Dr. Shammo refers them to me or gives me a heads up that this is someone we might want to participate in a trial.

So, I like to talk to patients and say kind of correct their misconceptions about clinical trials. So of course, here's the… when (inaudible 58:03) the developers of this drug can explain it, but its only side effect is that it causes your hard drive to crash and so the first thing when I meet with a

patient, I ask them what they think about a clinical trial and they say the first thing they say I'd say at least 50 percent of them, "I don't want to be a guinea pig. I don't want to be the guinea pig," and then there's a lot of terms in a lot of these consents that patients don't understand. So even though the consents are in a sixth grade reading level, I like to go over before I even hand the patient a consent. I like to go over a lot of terms. So, patients hear placebo in the consents a lot and they want to say what's a placebo and how are they used in a clinical trial. So, I guess if I explain the purpose of the trial and the structure and what the procedures are, it just doesn't seem to ominous or scary or the last ditch effort for a patient and then I… you know, we go through the benefits and then we go through the side effects of the drug and that usually makes them feel much more understanding about the trial and they bring the consent home and they start to understand what a clinical trial really is.

So, there's a lot of types of clinical trials. What we are going to be talking about is the treatment trial, but there's trials… all different types for screening. So, we try to find… the trial tries to find better ways for preventing diseases and diagnostic is basically for procedural and treatment is what we'll talk about and it basically is testing a study drug that is not FDA approved either by itself in combination with other drugs to treat cancer.

So when I first talk about clinical trials to patients, I say when they read the title, they're going to see it's what type of phase the trial is in. So, I like to explain what the phases mean. For the most part, I do mostly the phase 3 trials, but we do have all these phases at Rush with other disease types as well. So phase 1 is when you have a very, very small population of patients and you're actually just trying to determine what the side effects are and kind of where the dosing and what the dose would be along with the side effects. Phase 2, you get a bigger population and then you're actually trying to find what, you know, disease it works best in and then phase 3 is what trial I will be talking about afterwards with Dr. Shammo's trial and it basically is phase 3 is now knowing this is a drug that went through phase 1 and 2. So, we know what disease it works best in and we know the dose and now we're going to compare it to the standard of care. So, the standard of care being Vidaza, Dacogen and things like that and Revlimid.

There's me talking on the phone. A design study… All the studies have the same design. So when I first started doing clinical trials, it's 100 page document and I… I'm like this has got to be the most boring thing to read. So, I pick out all the terms that I want patients to understand because these are the basic things and structure of a trial. So when a patient says, "What is randomization?" When there are 2 arms of a drug. Arm means we're going to put patients on arm A, this drug or Arm B, this drug and what randomization means is basically I use the patient's ID number and put it in either the IVRS system, a phone, or I put it in the computer, so it's unbiased. I have no control over which arm the patient is getting. So, that's what randomized mean. So, people in the title of a study are always say a phase 3 randomized, nonrandomized. So, that's what that means.

They also talk about blinding and patients are like, "What does that quite mean?" So basically if it's a blinded study, that means that the patients don't know which treatment they're receiving and double blinded means that I don't know and either does the physician or the patient.

And then there's word placebo and basically when we use placebos, it's really showing what the side effects of that drug is going to be eventually when they unblind it and they know what patients were on that trial drug and which not so they can really follow the side effects of that.

Okay. So, what I do all day is I actually meet with the patients and Dr. Shammo has a clinic and she basically will identify patients for me and sometimes she calls me or sometimes she just calls… pages me and has me come meet them. So, the enrollment process is I get a hold of a patient's name who are thinking could be eligible for a trial and what we start to do is we prescreen them and so that's my job. I look at their history. I look how much chemotherapy they've had, I look at their labs, I look at their bone marrow and then after prescreening, we kind of see, okay, there's no red flags according to this trial that we have that would maybe exclude because I already find something that would exclude you, I wouldn't want to come talk to you and get you all excited about a trial and then not… you not be eligible. So, it's really important for me to make sure that I know this trial very well. So, that's my job and then I'll come to the patient and Dr. Shammo usually says, "You know, I'm sure I'll talk to you about a clinical trial." So, I take a consent with me. It's usually about 12 pages and it's pretty straightforward. It's pretty easy to understand, but what I do is just what I'm doing now. I tell them about the phases. I tell them all the study procedures and what you're expected to do in the clinical trial. A big thing I always tell patients is that it's voluntary. So, you sign a consent. Within 3 months of the treatment and all of a sudden, you say, "I'm not going to do this anymore." You have all the right in the world to withdraw your consent. So, it's completely voluntary. So, I'll sit down with the patient and go through the consent and then I have them take it home. The last thing I want you to do is not read the consent fully and not understand what you're getting into and then sign the consent for because that means you're enrolled. So, I usually follow up with calling the patient at home or Dr. Shammo follows up with them and they say, "I'm interested. I'm going to come in. What's my next plan? What do I do now?" So after a patient signs a consent, we go through something called the screening procedures and what that is… Clinical trials want a certain population of patients and mostly they want, obviously, pretty healthy ones. So, screen procedures are all the procedures that the patient has to go through and they're not saying that they're immediately going to have treatment and they're already on the clinical trial, but we're just screening them to make sure you're perfect for that population of… for the trial. So, things like chest x-ray, EKG, lab work, all that is after you sign the consent. So, I never do any of those procedures until after you sign the consent. Then Dr. Shammo and I, we sit down and we look over all the test results along with the protocol next to us and we say this person basically passed. They are eligible. Now if we notice that, say, you know, their heart test or something didn't come out exactly in the parameters that we'd like, you know, we have to deem them ineligible. That's something that I just have to just tell the patient that, "You know what? You don't qualify for this clinical trial." So even though you signed the consent, it doesn't mean that you're automatically enrolled in the clinical trial. You may be ineligible. I don't like those calls. So, once we deem them eligible then basically if it is a randomized trial which, you know, is with 2 arms then I actually then go into that computer system or the phone and I randomize the patient. So, I know what treatment you're starting and then I call the patient and we start when the treatment is supposed to start that day and then I follow you the whole entire time. So, I'm your nurse from start till when you say you don't want to do it anymore, till the trial finishes, etc.

So patients always ask me, "Well, where can I find the clinical trials for my disease?" So if you go onto clinicaltrials.gov, not only does it list the trial I'm going to talk about just for a brief few minutes, it lists all the trials that are available here at Rush.

Okay. So, Dr. Shammo's trial and the sponsor is Onconova and, see, now that you're learning what a trial is, how it says it's a phase 3 trial. So, what this Onconova trial is is it uses this drug Rigosertib. It's ON01910.NA. You don't have to know that, but it's given IV every other week through a little CADD pump. So, I'm the one who hooks up the patients and monitors them. So, the reason it's a phase 3 is because we're using Rigosertib as the study drug, the nonapproved… a non-FDA approved drug and we're comparing it to the standard of care which is Vidaza or Decitabine. We want to see does Rigosertib work better, just as good, not as good as the standard of care and it's for the MDS patients and all who are progressing, relapsing or just don't have a tolerance to Azacitidine.

So, that's why it doesn't fall into some of the people I've heard now. For people who are doing well, but just so you know this is out there in case the doctor comes and tells you, "You know what? You've had 6 cycles. It's just not working." So, that's when Dr. Shammo tends to say, "Michelle, this might be a good person for the Onconova trial."

Really quickly, it's IV treatment. You do have to have a central line. If patients don't have one, we put one in and it's a continuous infusion on the little CADD pump and I change the bag every 24 hours and it's for 3 days. So, we usually start on a Monday. It's Monday, Tuesday and Wednesday and I disconnect them on Thursday. Now, they can go basically on this clinical trial until we see progression. So, the goal of this trial is we keep the patient stable. Some patients require twice a week, once a week transfusions and slowly we're hoping we see less transfusion dependence on this clinical trial. So, that's a huge goal for quality of life for patients and thirdly, the biggest one is just so that we don't see those blasts creep up and then it's actually already a transformation into AML. So, I do have a few patients on this trial and one, she's been on it for like a year and 2 months and doing quite well. So, it's pretty well tolerated and it is very time consuming. You are spending some time with me. I get to know the patient very well, but… and that's it. Is there any questions?

(Applause)

And Sandy was on my other trial, so she's one of my patients. Thank you.

Jean Ridgeway: Two second intro about myself. I'm a nurse practitioner. I work at the University of Chicago. I happen to be on the Board, the Nursing Board for the Myelodisplastic Foundation and that's why I'm here because the Nursing Board put this resource together building on some other patient education materials that were available to patients and just needed some updating and some fine tuning and feedback that we had gotten from various patient forms said that how about we include these pieces? So, that's what this is all about and this is a resource that's available in a couple different forums. One is electronic. So, if you go to the website and you go to Patient tab, you can download this and keep it on your electronic device if you're so inclined or if your family is. The other is the hardbound copy. If you don't have one, all you have to do is give the MDS Foundation a call and they will mail it out to you or talk to

Dee. She'll be here until 1:30 and then she has to catch the shuttle to the airport and let her get your personal information to get you a copy of this. Okay? Clear enough?

So, I work down there at the University of Chicago, about 10 miles south of here. I did go to grad school here. I love this place. My daughter will graduate in 4 weeks from here with a graduate degree and so that's who I am. I live in the city. I have 4 great kids. I have a great husband. It's really nice out, so we're going to skip… stick to schedule. This is the piece that's supposed to complete at noon then we have lunch and then we've got some discussions. So, if you have questions, I would say write them down and we'll talk back and forth. I'm a stickler for time. We will end at 2 o'clock. Okay? I respect your time. That's important. Make sure that you get from Dee a parking validation so you get the reduced rate. If you need to get up and grab some more food or coffee, feel free to do so. Bathrooms are down the hallway and to the left. If you're wondering where in the world that is, that's where it is.

So, there's an interesting group of individuals who sit on a leadership board. Myself and another Chicago nurse, Sandy Curtin, is one of them, too. You'll see the list of our names, but we're an international group that work with patients and families just like you all who have been touched somehow by Myelodisplastic Syndrome. I have had the opportunity through the years to be involved with this for over 3 decades and seen quite a bit of evolution. I work with a great bunch of guys that you'll attest to and so that's what it is. So, this Building Blocks of Hope is really a resource for patients and families and it's put together to help people understand the whole gestalt of living with this illness. Sandy Curtin is a very right brain creative person and so there's some… If you look on the very front of it and you'll see this throughout the slides there's… you'll see that it has got Tucson teal… She lives in Arizona by the way. Navajo red and desert sand and for her very reminiscent of that Southwest landscape. She shows pictures when she does presentations of this beautiful scenery outside her back door with dessert sands, etc. So, but they form the building blocks of Hope logo constructed in a wavelike pattern. So, talking about the fluidity of life. I'm a total black and white person. I got to tell you this. This is way out of my comfort zone. Single band of red which continues up into the plants, symbolizes strength and improvement of the bone marrow function. So, I mean, she really put a quite a bit of thought into this and it's interesting if you think about it. With the idea of Hope and the future and extension coming out of the plant life itself. So, that's a little thing about the logo. She put a lot of time into it.

So, here's the folks who are on the Board and something interesting is that we're all over the globe. People from Switzerland, Australia, Poland, United States. So, all over the place. We're trying to pull in some of our Asian counterparts as well. As a group, we try to educate folks around the world. We tend to be fortunate enough in the US to have lots of education opportunities and live someplace where active clinical trials and treatments go on. So, we try to spread the wealth. That's who we are and there's lots of us. It's on the web page and what this looks at is a number of questions.

So, the Building Blocks of Hope really answers these questions and when you look at the different tabs, on this book you'll see it represented. So one of them is understanding MDS. You had a big talk about that, kind at a relatively high level, right? And that's okay. How's it diagnosed? You talked a bit about that. What are treatment options? Side effects? But it's at your

fingertips, this information. More… Just available to you to kind of refresh back and say what did they say about that? So, it's all down on print for you. What about new treatments? And again, ion overload is consequences of blood therapy. How about transplant centers? How do I pick a transplant center? That's one of the… So, there's a whole section in here in the book and it's called… What is it called? I can't see it in front of my eyes. They're going. *Quick Tips*. *Quick Tips* are about that and that answers kind of… It answers some very interesting questions and one of them is how to pick a transplant center and then how to keep yourself healthy. So if you go online, it's about 145 pages. It's formatted really well. If I have an Internet connection, I can play it maybe during lunch and show you it, but here it is. So, what we want to do is just introduce you to this concept and to the tool and help you understand it a bit. So, how to know about your disease, things that you've talked about already, the IPSS and the IPSSR scoring system, schedule, side effects, talking about being a partner and then an interesting component of this tool is helping you to have some ready access to tracking mechanisms. So, some people like a copy of their blood counts every week. Right? Some people who are savvy on the computer put together Excel spreadsheets and little graphs of their sheets. Other people like to write it down or just keep it together in a folder, but there's actually some templates in there of various different aspects of your treatment and care that are provided for you and if you download them on the Intranet then you can print out additional pages as well. So, that's part of it.

Now, this slide kind of looks familiar. Talking about what is MDS. Right? That it's a group of bone marrow cancers and that oftentimes becomes a question in this forum to I have a cancer or not? Is it a malignancy? And we know that MDS is something called a clonal disorder. So if you clone somebody, you have an identical representation and in this group of diseases that's exactly right. It's a clonal problem. One cell looks another, looks like another and it affects the blood. Stem cells are the hematological stem cells and it's not one disease. MDS really is a big umbrella term. Correct? Because your MDS is different than your MDS is different from your MDS. Very, very different with lots of variations and treatment recommendations that go along with it. So when you sit in a clinic next to somebody and they say if you get around to the small talk, "What are you here for? I'm seeing this doctor for MDS." "Well, I have MDS, too." "Really? What are you getting? I'm not getting that. Why am I not getting that?" So, a little bit of explanation.

So what happens dysplasia is the hallmark. That's the D in MDS and dysplastic cells don't look normal. So if you were a trained pathologist and you looked at the cells up there, you'd say they're not normal. So, pathologists are able with a trained eye to look at a cell and know normal from abnormal. I, however, am not a pathologist. I spend some time with them, but a good example is that I drive a car just like a lot of other people in this room drive a car and when I go to my car and I look at the wheels, the wheels are always round. Right? So, I know my tires should be round. Now, somebody who thought they would pull a little prank on me would put tires on my car that were square or oblong. They wouldn't be the right shape. Correct? They would be the wrong shape. They would be dysplastic. Now, would the tires work on my car if they were oblong? Not as well as the round ones, right? Kind of get me there, but a lumpy ride. So and it's the same thing with dysplastic cells. Do they work? Somewhat but they don't give the same affect because they're just not composed correctly to give us the outcome that we need. So, they're dysplasia and that's really ineffective hematopoiesis as well and what happens? People get low blood counts. Right? That's called cytopenias. It's a great word if you play Scrabble. It gives you a lot of points. And what happens what we know is that some people do run the risk of

leukemic transformation with this disorder which is a difficult problem if it's occurs and what do we know that as the disease evolves that the bone marrow function becomes less. So, here's a fun little picture. So, this looks like a long bone but you've had a bone marrow biopsy and know that we get it from your posterior iliac crest, but it's a systemic organ. So inside the bone, what do we have? We have the hematopoietic stem cell. Right? That's the mother blood cell. When they do a stem cell collection, they're collecting those cells. Okay. And what do stem cells do? They have the unique ability to make a decision through a variety of prompters to become one of two major families. So, there's the myeloid family which you can track on the straight trajectory. So, you've got a myeloid progenitor cell and the myeloid family grows up to be either white cells, red cells or platelets. The lymphoid cells, the lymphoid progenitor those cells grow up to be B cells or T cells. So, those are the natural outgrowth of those families, but when things go awry, you have ineffective hematopoiesis and so somewhere along the trajectory, cells begin to stop growing up. So, they get halted in maturation and a very immature myeloid cell. It's called the blast cell. Correct? So normally, you can have a few blasts, less than five percent in your bone marrow, but above five percent, we know that that's abnormal. So when you have too many blast cells, what happens is that you begin to crowd out the normal cells. So, you've got these immature precursor cells and it takes effect and begins to crowd out the normal ones and as you do that then there's not maturation of the normal cells and so you begin to see a decrease in the normal cells that should be in the periphery like your red cells. So when your red cells you have anemia. Correct? Because the malignant cells are crowding out the normal production. So, you have peripheral cytopenias and when Dr. Shammo was talking about hypercellularity. We begin to see a very active marrow, but low blood counts.

So, how is diagnosed? How many people here… it took healthcare providers over a month to make your diagnosis? How many people took at least a month to make the diagnosis? How many people took two months? Three months? Four months? Five months? Six months? Not easily diagnosed is it?

?: Eighteen months.

Jean Ridgeway: Eighteen months to make the right diagnosis. A long time. Long, long time. For a lot of people, your presenting system… your presenting was what? What was happening with you? Why did you go to the doctor? Why did you go?

?: Nose bleed.

Jean Ridgeway: Nose bleeds. Who else? What made you go to the doctor?

?: I just went for a regular physical.

Jean Ridgeway: Regular physical. So, you were caught incidentally. They drew a CBC.

?: Exhaustion.

Jean Ridgeway: Exhaustion. Fatigue.

?: During a normal exam, a yearly, annual.

Jean Ridgeway: Caught on a yearly annual exam.

?: Same thing with me.

Jean Ridgeway: Same thing. So, what we're here… Heart problems?

?: Tired.

Jean Ridgeway: Tired. Fatigue. More fatigue. Fatigue is the most common. What we here most common complaint. Why do you think that is? Eighty-five percent of people who struggle with MDS have anemia. What do the red blood cells do? Carry oxygen. What does oxygen do? Makes everything go well. Right? Makes your brain work, makes your heart work, makes all your organs work. Give you energy. When you don't have that then you start having it and it's really difficult to get diagnosed. You know? It's really difficult. A month to 18 months. That's a big difference. So when we do… when we finally get it together and you get a CBC drawn and then you get referred to the oncologist. How many people just about fainted when they walked into hematology oncology? Anybody here go, "Oh, my God. I didn't know I was going to an oncologist? Like… I'm… They sent me to the wrong place? I shouldn't be here," because that's what we do. Hematology and oncology. You're laughing. That happened to you.

?: I can't hear.

Jean Ridgeway: You can't hear?

?: So, we're trying to tell him.

Jean Ridgeway: Sorry.

?: No, I can hear you pretty well.

Jean Ridgeway: So once you finally get there, what did we have to do? So, we did check your blood. Right? Checked of your CBC and then we checked lots of other things and then the dreaded bone marrow biopsy. Correct? Yes. So, that got done. Other things that we looked for were why else could you be anemic? Well, some people are anemic because they don't have the building blocks of the red cells. Iron. Right? Everybody says, "Why am I anemic? Do I have…?" Low iron, B12, B6, folate. Those are all the building blocks and so all those things were checked. Your thyroid was checked, your testosterone was checked. Not the ladies, though, and then your kidney and your renal function was checked. So, all those things get put together and then we come up with a diagnosis. Correct?

So, here's a busy slide about the classification systems. So, we have the old system which is the FAB, French, American and British. Those… That consortium of pathologists got together in the '70s and said, "We're all seeing the same thing. Let's call it uniformly the same thing so that when a pathologist from France, England or the US looks at somebody who has RARS, they all

say RARS. Okay. So, that was the first system. Then comes along the WHO, the World Health Organization, and they say the FAB is good, but now we have new tools and it can be better. The FAB had 5 classifications, 4 of the 5 have RA in it, Refractory Anemia, because what's the most common problem? Anemia. So, the WHO comes along and then it gets revised again in 2008 with more information, mostly cytogenetics and some of the more savvy molecular markers and it gets revised again. So, busy slide to tell you that from the beginning until now, we've had continual improvement in our understanding of the disorder and better testing to be able to tell folks what they have.

We talk about lines of dysplasia and how many blasts you have. Right? In the bone marrow. So, that all goes into classifying myelodisplastic syndrome. Now you talked a bit about this. This is the IPSS score and then now the IPSSR for revised. It's like the sequel to "Superman," right? Every good movie has a sequel. So, the IPSS has been under scrutiny and we know that it needs to be revised and it was revised. Peter Greenberg and all those folks did that for us and how many people in here know their IPSS score when they got diagnosed? You guys know that? Are you book worms? A couple? Little? No one's going to admit it.

?: With me the other IPSS, is that life expectancy?

Jean Ridgeway: So, the IPSS score is the International Prognostic Scoring System and it's done when you get diagnosed.

?: Right and that (inaudible 1:26:37) screen off like your DNA test.

Jean Ridgeway: So, it's a combination of three things. It's what are your blood counts, how many blasts you have in your bone marrow and what are your cytogenetics.

?: Well, seven years ago, they said I had four to seven years to live. They said that with medications.

Jean Ridgeway: Exactly. Exactly. So one of the criticisms of the IPSS scoring system is first of all it looks at life expectancy without treatment. So, that was a big discussion point that it looked back at data. It didn't take into… because it just didn't exist. So now, more of this information exists and the therapies exist. So, we've come up with the IPPSR and what it does is it gives the clinician a tool into picking an appropriate treatment for you. Okay?

So, here's the IPSSR and what has changed… there are two components that have changed. One is the cytogenetics. So, there used to be a different schema of what you looked at and we also didn't look at if you needed transfusions or not. So, the IPSSR blends that into the scoring system as well and so here's the various different cytogenetic groups with "estimate survivals" and so the thing about estimations and numbers are they're just numbers. Right? And you can… I wouldn't take them to heart. I think they're okay to use as a guideline, but don't plug yourself in because seven years ago you got diagnosed, right?

?: Yeah.

Jean Ridgeway: Then they said five to seven years…

?: Yeah. Four to seven.

Jean Ridgeway: … here you are and you're looking pretty good. So, that's the IPSS scoring and here's the categories. In the IPSS there were three… four categories, zero, one, two… zero, one, two and three. So, you were low risk, intermediate one or two or high risk. That was the previous scoring system and now here they've expanded it because they include the blood counts, the hemoglobin and platelets and ANSI and have changed the variability of the cytogenetics. Now, they're looking at five different categories. So, expanding and understanding that a little bit better. Now remember, if you really want to take notes that's okay, but if you go online all this stuff is written down and in the book, it's all there. So, like don't… You're not going to miss a thing. Trust me. So, I mean if… that's fine if you want to do that, but it's all there. All this information is here and it's here for you to use and to kind of understand. So, this looks at the risk of transformation as well and survival, but, again, this is estimated without any treatment. So what happens if you choose not to do any treatment? People can kind of predict looking back on data. So, still the same theory of low risk. Do these folks have a better long term survival than people who are diagnosed with a higher risk disease. Right? That's what this is telling us. Alright.

So, let's look at things a little bit simpler. What are some simple facts about MDS? So for those of you who fall outside of this, most people are about 73 when they get diagnosed with this disorder. Okay. So, unfortunately as I think the target of older Americans comes into play, this is kind of an older person's disorder. Right? Seventh decade. We're all comfortable with saying it's an older person and that's okay. It's an incurable malignancy. There is one cure, right, that allogeneic stem cell transplant. Transplants are done here at Rush. We do transplants down at UOC. It's a rigorous therapy. Allogeneic means that you're getting cells from somebody else, a sibling perhaps, maybe an unrelated donor, but it's someone else. The leading cost of demise really in MDS is the disease itself and when we look at how to treat people, the risk stratification strategies are a good to help us understand what's going to be best for the person because you don't want to over treat someone but you don't want to under treat them. So, I heard a number of you saying 16 cycles of therapy. You've been on treatment for really… Mr. Hentzel's been on treatment for a long time. Like what are the triggers for therapy? Sometimes clinical trials a little different. Right. They may take a low risk person who might not need some of these parameters and looking at does it really improve, but basically having to need transfusions, being transfusion dependent. If you're having worsening cytopenias, more blasts or if you have high risk disease, high risk disease is an indication for treatment even upfront. So, your physician group helps individualize your treatment strategy. You guys discuss and we put all these things together. In your performance status… Do you know what performance status is? Performance status is taking how well you're functional. So, I use somebody who goes for a walk every morning, you do your own bills, you're pretty active then we say you have a good performance status. If you're feeling unwell and spending a half day in bed because you just really don't have the energy, you're just feeling very poorly then you have kind of a moderate performance status. If you spend all day in bed all the time then we would say you have a poor performance status and what we know is that performance status somebody who's up walking around and independent is going to do better regardless of the treatment than somebody who's in bed all the time. That's

just the truth. Then we look at comorbidities. Comorbidities are do you have hypertension, diabetes, chronic kidney disease? All those other types of pieces of health disorders, how do they factor in if you have MDS? And then looking at your cytogenetics. Do you have dunovo (sp? 1:32:43) MDS or do you have that therapy related? I heard Dr. Shammo talking about a therapy related MDS. Perhaps you had prostate cancer and you were radiated to the pelvis or breast cancer and now you have a therapy related MDS. So that's it and then your lifestyle. What are you looking for? What are your goals of therapy? So, that all plays in.

She talked a bit about this, right? Different therapies. People feel pretty comfortable? You know that there are a few FDA approved therapies. Correct? There are two hypomethylators, an oral agent called Lenalidomide or Revlimid, transplants and investigational agents or the clinical trials. So, what we try to do is maximize this.

This is a busy slide and what's listed up there and it's in the book and it's on the webpage is just what was available when this article was written. What was available at this time. So, different types of agents. Like Dr. Shammo was talking about looking at different sites of activity within the malignant cells trying to block that pathway that's giving activity. So, all different types of clinical trials with different agents. You know the key principles are really, again, we know that a transplant is the only cure. Age alone doesn't include folks from active therapies. If you're 40 or 70, eligible for treatment then that's… We treat people 80, 90. We have a 91 year old we're actively treating. He's doing fine. He's kind of a spry 91. But all of the therapies for MDS if you've received therapy you know that it's true that it takes a little time to get it to work. So, 4 to 6 cycles regardless of the therapy type that you have are going to be needed and we're going to look at this just a little bit closer. We got 5 minutes till lunch. Okay.

So, why is it happening? Okay. So, this is going to be a series of slides to get an understanding, hopefully, of what's going on in the bone marrow. So before treatment begins, this is taking a look at kind of snapshot of a slide of your bone marrow. Okay? So beforehand, your blood counts are dropping and the MDS is… you and the physician decide now it's time to start treatment. We're going to go ahead and do this. So, you've got a lot of abnormalities in your cells and so we're going to go ahead and start treatment and what's going to happen is that that graph down the side. So, your blood counts are going to start here, but with active therapy your blood counts are going to drop and probably during this first four to six weeks, they're going to get way worse before they get better and plateau out. So, that's what this graph is trying to tell you that. Within that first four to six weeks, your absolute neutrophil count is going to dip down before it comes up and gets better and you can see this slide on the bottom is showing us those larger cells, the malignant cells, are getting cleared out and as the therapy continues and your bone marrow begins to recover, now what the bone marrow is making are more healthy cells and that your blood counts are recovering even further and then as things really progress forward and a number of cycles have been done that people can even be weaned from "supportive care" the amount of transfusions that you need as you improve through it. So, that's just a little picture and a graph to go with it.

The challenge is both for the patient, the caregiver and the staff is getting through those first 4 to 6 cycles and sometimes when people start therapy it's been awhile since the diagnosis and then you start therapy and you really… you don't feel really well. Right? It's a lot of trips back and

forth to the clinic. It's a lot of trips for transfusions. Maybe you got an infection. You might end up in the hospital. So, you know, those first couple weeks during treatment can be a little rough. Right? That's for sure and it can be really discouraging and a lot of people need to rally around you and say, "Let's give it the full 4 to 6 cycles to see," because you can't truly make a decision until you get through those cycles and it can be… and that's very challenging. So, the key principles for therapy is that time is really needed for the best response. A minimum of 4 to 6. We've got somebody here who's been on it… He's been an oral agent for years and years. We have other people going through a cycle 16. Somebody over here said cycle 16. I forget who it was, but to get through it. So, sometimes things need to be delayed. Correct? Sometimes you need more supportive care and so just working together with your practitioners to get you through that time and this a slide. This is from one my colleagues, Sandy Curtin. She has a… I don't know how she attracts these people who make graphs of their slides, but she does and this is somebody who… this is looking at the pink dots are the hemoglobin, the yellow triangles are the platelets and the blue triangles are the white blood cell count. So, this is a patient who comes in and starts… this is actually somebody's blood counts. So, they came in and at the very beginning you can tell that the hemoglobin was about 12 grams per deciliter and they dropped down to about 8. So, things are kind of getting worse before better and same with the platelets. The platelets were higher and they dropped down and as things began to get realigned, a lot of talk about that. The bone marrow represents a factory and so the factory needed some tune ups in getting fixed. So, as the factory is getting fixed things are getting a little worse. They're not as efficient until they're all the way fixed and then they get better and this patient actually went through 4 cycles and so you can see the gradual improvement of the hemoglobin. Right? The pink line is continuing to trend up and the platelets take a big jump in cycle 4 as well as the white blood cell count and then this person does go for a transplant and so they're transplanted and then on the other side of that box 3 months after transplant, their blood counts are very, very much in the normal range. So, a good success story depicted graphically. Do the men in this group… The girls, we're not so impressed by graphs, but the boys, a lot of times they like the graphs.

So, this is somebody who's been on Lenalidomide for 10 years. This is 1 of Sandy's patients and so the same thing. You look at the pink line when this person started way back in 2002. This gentleman has been tracking his blood counts for Sandy ever since 2002 on an Excel spreadsheet and so there are his counts getting better and better and better and you can see along the line there's been some ups and downs, a couple little dips here and there and I'm sure he required… Maybe he was got (inaudible 1:39:45) whatever, but you can see the trend over time is to continue with therapy and this gentleman remains on therapy and continues to do quite well.

Other questions people ask are what can I do to stay healthy as I'm going through treatment? Eat a well balanced diet and fad diets are just that. They're fad diets. If there was anything magical in juicing and doing all that other stuff, we'd all be doing it. So, stick to a well balanced diet. You want to go ahead and stay active. For different people that means different things. Walks, bike riding. You want to try avoid to getting infections. So, you need to be able to get your flu shot that comes around October. People are sick then you kind of… you need to avoid them a bit. Avoid bleeding. Getting your teeth pulled when your platelets are low, if it needs to be done you got to do some coordination of care with that. Enjoy the things that you love. Continue to live

your life and get enough rest. There's a lot of resources. This is one of them. You need to ask for help and then be an active participant.

So, these are actually the tabs on the book. So if you look, tab number 1 is talking about understanding MDS. So, a lot of the slides that we went through are written in this book under tab number 1. Describing the disease process of MDS and answering some questions. Answers the question, gives you the answer in this first little section. The second part talks about looking at treatment and outlining various treatments that are recommended based on the type. Number 3 is the quick tips. So, quick tips are what do I do about constipation? How about diarrhea? What about a skin rash which can happen for a lot of folks. So when we wrote those, those are all based on evidence based medicine. So, it's not grandma's recommendation. It's recommendations based in science and data. So things in there are robustly written which is important when there's so much information on the Internet. You have to be a little cautious about what you read and where you get it from and what people are recommending. The next section talks about iron overload. That's a really nice section. Gives you lots of great pictures and then tab number 5 are those resources and tools for you to use about your MDS plan. So, you can keep track of appointments, keep track of medications, you can write down your pathology reports, etc. So, that's all in there and then the last tab is just the MDS Foundation and it gives some information about the Foundation itself and how to access it. So… and these are really about the folks that put this together. We had both patient and caregiver contributors. So, we asked patients what do they want and a couple patients are actually on the Board of Directors for this foundation and then a number of our physician colleagues as well and then the Nursing Group wrote quite a bit of this and Sandy helped really put this together. So, I stuck to time. It's 12 o'clock. Lunch is at 12 o'clock, right, Dee? And are they bringing it here? Is it set up out there?