Speakers:
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Jamile Shammo: Good morning everyone. How is everyone? It's a beautiful day in Chicago and that by itself is worthy of celebration. So, my name is Jamile Shammo and I am one of the attending hematologists at Rush University not too far from here. I have been in charge of the MDS program and Myeloproliferative Neoplasm program as well a little over a decade. So, I remember when I took over the MDS program, we had really two options at that time, to transplant or not. That was the main decision at that time when someone had that diagnosis because truly there were very few options that we had for patients, but now I think in each and every step when it comes to MDS there's something new that's going on. So, I think in that sense this will be very timely to sort of give you an update, but before I talk I would like to hear from each one of you as to what is your connection to MDS and what it is that you hope to get out from this gathering. So, maybe we'll start with you.

Q1: I've been diagnosed with MDS about a year and I was wanting to get more information that was current.

Q2: My name is *(Attendee)* from Florida and I had MDS for 17 years with RARS and I go to at least 1 or 2 of these a year and I find them very, very beneficial and I will have a couple of questions. I'm here to learn. Thank you.

Q3: I'm with *(Attendee)*.

Q4: Good morning. I'm *(Attendee)* here in Chicago. I just help to support one of the specialty pharmacies that actually helps to dispense a lot of (inaudible 1:58) medication.

Q5: (inaudible 2:01) my father actually is diagnosed with MDS in January. Fairly (inaudible 2:09) and round three of chemo. (inaudible 2:19) working on things (inaudible 2:20).

Jamile Shammo: You wanted to understand about it. Of course.

Q6: Hi. My name is *(Attendee)* and my husband has MDS and we've been dealing with this for 12 years now.

Q7: I'm the husband. I was diagnosed in March of 2002 with RARS. I get supportive therapy and Darbepoetin and although I've had no blood transfusions, I've had iron overload, which they're not really sure, so I take Exjade and I've had some damage done to my heart and liver, but now my ferritin levels are probably average to about 150 during the past year where it was over 1,000.

Jamile Shammo: Do you know if you were checked for a hemochromatosis?

Q7: Yes.

Jamile Shammo: And negative?

Q7: I had… that's iron overload isn't it?

Jamile Shammo: I meant the genetic hemochromatosis.

Q7: No. I had the… Yeah…

Jamile Shammo: Got it. So timely.

Q8: I'm *(Attendee)* and I work with the MDS population and I'm with the (inaudible 3:32).

Q9: Hi. My name is *(Attendee)*. My cousin is the patient. So, I'll defer to him, but I might ask you if you could hold the mic closer to your mouth because it's very difficult to understand the wording. It's not clear at all and apparently I would assume the sound engineer can tell you better. It's because of all the wood in here and those monitors just bouncing off the wood. It's very difficult when you use the level mic.

Jamile Shammo: Is it difficult for you guys sitting on this…?

Q10: It is hard.

Jamile Shammo: To hear me. Well, help.

Q11: I guess I didn't hear the first part of whole statement.

Q9: I think if you just hold the leveler mic closer to your mouth that will overcome it.

Jamile Shammo: Is this better?

Q9: A little.

Jamile Shammo: Awesome. Bring the volume up then.

Q9: Volume will make it worse.

Jamile Shammo: Yeah. Go ahead.

Q12: Diagnosed with MDS a year ago. Gone through eight sessions of Vidaza. Red, whites and platelets are all over the ballpark although the reds have been pretty steady, but below the bottom range. Been taking booster shots in addition. So, (inaudible 4:54) progression to acute myelo leukemia I believe. (Inaudible 5:00) who the hell knows.

Jamile Shammo: And that's why you're here to kind of…

Q12: That's why I'm here. I want to find out what the hell's (inaudible 5:06)

Jamile Shammo: What to do.

Q13: Good morning. I'm *(Attendee)* and I'd like to thank you so much for coming out. I was diagnosed two years ago with early stage MDS and we're just watching it at this point.

Q14: I'm *(Attendee)* and this is *(Attendee)*. We're here because her mother was diagnosed in 2010.

Q15: I'm *(Attendee)*. I'm here with my husband, *(Attendee)*, who has Myelodysplastic Syndrome.

Q16: My name is *(Attendee)*. I've got MDS and numerous other stuff, but I'm here to try to learn everything I can.

Q17: I'm *(Attendee)* and I was diagnosed 18 months ago and right now I'm not getting any treatment. My hemoglobin is 9.2 and it keeps dropping, but just been watching and waiting.

Q18: I'm *(Attendee)*. I'm *(Attendee)*'s wife and I'm a caregiver.

Q19: My name is *(Attendee)*. I've been with the MDS subtype CMML for a year. I took six months… six cycles of Vidaza and it failed and the blood transfusion went from once every two weeks to once every week. So, I'm looking for options, clinical trials, also transplant. So, I'm just undergoing this transition period trying to figure out what is best and what (inaudible 6:57) would I have with these treatments. It was that one doctor told me I have two to three years to live, so I have to do something about it so I'm here to figure it out.

Q20: I'm *(Attendee)*. I have MDS. I've had it for almost three years. I get weekly shots of Aranesp and periodic blood transfusions and I'm here to learn more about the treatments.

Jamile Shammo: Well, welcome. I'm sure everybody has their challenges when it comes to this disease. Now, can you hear me better?

Q21: (inaudible)

Jamile Shammo: Let's try it. So, ah. You were right. Thank you. It would be a shame if I'm here and you guys couldn't hear a word whatever I'm saying. So but if it's too loud also please let me know.

So, let's talk a little bit about MDS. So, here we go… It's a little… there's a little lag. I love etymology. So, myelos… myelodysplastic, right. You want to know where the word comes from. So, myelos means marrow, dys means bad, plasis means formation. So, it's simply bad formation of the bone marrow and you have to realize that some of the dilemmas that we have with diagnosis dates back to when the disease was initially noted. Some people noted that prior to leukemia, some patients had anemia or certain blood abnormalities. So, but it had such various presentation at that time that they simply called it refractory anemia. Some people called it preleukemia and truly the very first attempt in classifying MDS was not too long ago in '76 and then right after that came the more recent classification in 2008. So, you're going to find me pointing basically to some of the new and updated information as we go elective to diagnosis, classification and treatment.

So, the definition of MDS sometimes can be problematic for patients because in a way it's abstract. There's a lag or a bone marrow failure in generating blood elements. On the other hand, there's a subset whereby you start having blast formation and blasts are the bad cells that at some point when they accumulate beyond 20 percent either in the bone marrow or in the blood mean that this is simply progression to leukemia. So, you have to get used to the blast count and how much blasts are there in the marrow. The incidence is not very high. This is what's been estimated and as far as progression to leukemia, I know one of you wondered about this. Simply, it's about 30 percent. I think it's a little bit higher in the higher risk disease than 30 percent maybe 50 percent, but in general whether or not people progress to leukemia the main issue that people deal with is simply consequences of bone marrow failure be it anemia, neutropenia or thrombocytopenia.

So, why does this happen? Yes?

Q22: I have to sit here because I cannot hear you back there.

Jamile Shammo: Still even with the thing. I'm sorry. There's not much I can do about it I guess. So, is this any better by the way like when I…? You're fine.

Q23: (inaudible 10:48)

Jamile Shammo: I know. I wonder if I will try without it.

Q24: You might be better without it.

Jamile Shammo: How about this? Better? You guys want to maybe just (inaudible 11:02) closer so that way. So, I could try to yell. Is this better?

Q25: Yes.

Jamile Shammo: Better than the muffled… Alright. Let's just do that and if you want to move closer, be my guest.

(No audio 11:26 – 13:00)

Jamile Shammo: And then I also ask about genetic predisposition whether or not somebody has their family member, but also if they hadn't had an evaluation with the bone marrow biopsy there is no way to know. Often, we ask people have you been exposed to certain environmental (inaudible 13:23), etc. and a lot of times I hear, "Yeah, I was in work in the print shop," or, "I was exposed to certain chemicals for many years," but I'll be honest with you with the exception of certain like benzene or chemotherapy for that matter these types of associations are not truly well studied. I think maybe we need better epidemiological studies to identify what might be get exposed to that might result in this disease.

What about therapy related? Often we are treating certain diseases to achieve cure. Unfortunately, 2, 3, 5 years after the chemo, people develop myelodysplasia. So, we know that by giving chemotherapy and radiation, you could cause damage to the stem cells like I'm sure you all remember Robin Roberts and her MDS and the fact that she underwent transplantation. So, that's the other area of challenge that I think we need to study a little bit better to understand a) what is exactly the driving event beyond exposure to chemo because obviously not everybody who gets chemo develops MDS. Right? We looked at it at our center and out of 150 patients that had lymphoma, only 5 percent developed MDS with certain follow up and this is sort of similar to what we have seen also in the literature. So, it varies from less than 1 percent with breast cancer to maybe up to 15 percent in certain lymphoma patients. Now, what's interesting is that maybe we're going to be moving away further and further from chemotherapy in the future because we're developing biological agents for the treatment of disease and maybe this will bring that risk down.

Well, you know, for example for lymphoma, right now certain patients don't get chemotherapy. They get something called Rituximab. Well, Rituximab isn't necessarily chemo and I realize at some point they will be requiring chemotherapy but with more inventions of drugs that aren't toxic to the stem cells. So, this is all in the works. It's not all perfect yet. When it comes to the type of chemotherapy, we have various forms of the MDS that develops after chemo. So to me, this is very interesting because this isn't like a random generic event. This is something that's actually predictable like you give people certain types of chemo, they develop certain genetic abnormalities. You give them a different kind of chemo, you can expect a different type of genetic abnormality. So, there is a lot to be learned about that process, but… and I know that the

University of Chicago consortium did a study looking at specific genetic alterations that happen in therapy related and I think the heterogeneity that incorporates in that is massive. So, we need to understand a little bit more about the genomes and mutations so that we can come up with better treatments.

So now, that was the epidemiology. What about the diagnosis? Very important to go to a center that has a pathologist that's very comfortable with MDS diagnoses. I can tell you over the years, we've had people who had B12 deficiency that were told they had MDS. Right? I've had people who had autoimmune disease that were told they had MDS. You treat the autoimmune disease, the MDS goes away. That was not MDS. Okay. That was not MDS. It was B12 deficiency. So, you have to be very careful about what changes are they seeing that makes this disease what it is. So, sometimes dysplasia, which is the name that's in MDS, is something that happens with viral infections. I've had people who have hepatitis C and had dysplasia in the bone marrow. Does that mean they have MDS? No. You treat the hepatitis C, all the dysplasia or most of it goes away. So, be very careful with that and to some extent, MDS is a tough disease to pinpoint. Why? Because it shares a lot of similarities with other diseases. For example, with AML, with aplastic anemia and many others. Again, your pathologist and clinician that you're seeing extremely important in making this diagnosis. Sometimes for my patients, I may have to do another bone marrow like a few months or several… couple of years later just to be certain that this is the disease I'm telling my patients they have. So…

This is just to show you like in case you wondered what does dysplasia look like, here is what it is. For example, this is what they see in the bone marrow. A lot of nuclei in one cell or very large cells or cells here that a couple of you had ring sideroblasts and this is how they look like with iron stain. All those little blue granules are iron deposits that are killing those cells that they don't eventually mature. So, there's a certain subset that's called 5Q- syndrome and actually just the other day we had a bone marrow that we looked at and it had classic features that I predicted that it would be deletion 5Q before the cytogenetics came back. So, that's why this is called 5Q- syndrome because it's typically affecting older women and it has specific features to the bone marrow and that's why I say that there are certain predictable reason for this entity that we should be able to identify beyond what we already know today.

And this also to show you… How many of you know what cytogenetics look like? Have you ever seen a karyotype? That's the reason why I put this here. So when people do something called cytogenetics on the bone marrow of the MDS cell, they look at the 22 sets of chromosomes. You know, you see one from mom, one from dad. That's how we inherit things and they're basically graded or numbered by size. So number 1 is the largest, 22 is the smallest and here are the sex chromosomes. So, 2 Xs means that this is a female. If it were 1X 1Y, it would have been a male. So, this is normal. You can see how both sets of chromosome look perfect. Perfectly identical. So, what happens when you have cytogenetic abnormalities? This is what the chromosomes look like and here's why you have to have a very good cytogeneticist to also identify the genetic abnormalities that can be seen. If you don't have someone who knows

what they're doing, clearly and I've seen that, too. Certain illnesses could be called a different disease all together. If they missed the type of translocation or chromosomes. So in this setting, you could see that there's a whole part of chromosome 5 is gone. So, this is what makes it myelotomy 5 and here, again, your 7… the duplicate is gone. There's a little piece missing from chromosome 8 rather or 1 other piece that's attached onto chromosome 8 and there's many others that are missing that are conglomerate. You see them at the bottom. So again, this is representative of what the blasts or the clone of MDS might look like under cytogenetic testing.

And just wanted to show you the classification. That's the most recent one that we abide by and, again, the pathologist should be comfortable with that. Okay. So now that we've made the diagnosis, how do you go about risk stratification? What do your doctors do to say here is what we're going to be doing to tell you about your risk? So, the IPSS is what we typically apply and it does have a combination of blasts, karyotype or cytogenetics and then the degree of cytopenias and this is the survival. So, like let's take an example. Does anyone want to apply their numbers to this? We can make it sort of interactive if you feel like it or I can just come up with a patient on my own. So anyway, no takers, huh? Go for it.

Q26: (inaudible 22:38). You want to know the bone marrow blasts…

Jamile Shammo: The blast count.

Q26: Less than 5 percent.

Jamile Shammo: Okay. So, you get a 0 there.

Q26: And the karyotype is 26 normal. (Inaudible 23:12) cytopenia is 3.

Jamile Shammo: So, you had normal cytogenetics. So, that's another 0 and then you had 3…

Q26: Actually, I cannot say cytogenetics are normal. There is abnormalities on Q11 and Q3. One is transcripted and one is deleted.

Jamile Shammo: So, the 11 is deleted?

Q26: 11. Q11.

Jamile Shammo: So you had… I would call it somewhere in between although I wouldn't want to know what kind of 3 because in the new classification in version 3 is considered is poor risk, but let's assume 3 abnormality and with the 11. So, that's not good and not based either. So, let's call it intermediate So, you get .5 and you said you have 3 cytopenias?

Q26: (inaudible 23:57) cytopenia. Hemoglobin of 8.5, (inaudible 24:01) less than 3.5, platelet count around 80,000.

Jamile Shammo: Eighty thousand and what's the neutrophil count?

Q26: Neutrophil count is… absolute neutrophil count I don't recall. I want to say it is always hanging around… I'm talking about the (inaudible 24:18) diagnosis and they're hanging around between… less than 1,000.

Jamile Shammo: So, you're right because anything less than 1,800 count. So basically, you have Int 1 because the .5 for the cytogenetics and the cytopenia is another point. So, you're at Intermediate 1. Now when we talk about the median survival of patients with Intermediate 1, that's basically with nothing but supportive care and this is something that's drawn from years of following those patients and now you know that nowadays those numbers don't apply because we have other treatments that may have not been figured into those survivals.

And just to graph to show the reason for these types of numbers basically some… and I like to show the graphs only to tell you that there's so many variations on the scene and changes that pertain to each patient that we cannot glean that cause someone who has low risk disease or likely take care… think in your case, the Int 1 for example in green. Some people don't make it in the first 2 years and yet others are alive by 16 years. So, think of the difference between 2 and 16 years. It's ridiculous. Right? And even for people who have Intermediate 2. Again, some people didn't make to the first 2 years and yet some are alive by 8 years. So, why? So, there's a lot more that goes into it than just the IPSS and just keep that in mind.

When it comes to low risk disease, we're realizing that we're just lumping too many patients in one category that may not necessarily be very discerning. So then Dr. Manero decided to look into it a little bit further. Let's say someone had an IPSS with low risk disease. What he did is that he went one step further and said, well, let's look at those people by their age, cytogenetics and the platelet count and he split those patients into three categories. So, the bottom line if you tend to be older with the lower platelet count and a bad cytogenetics, this isn't necessarily low risk disease and so those are all things that we look at when we're evaluating patients that are seemingly low risk. So, that is a problem of any classification schema that you might have.

So, what's new in the MDS classification world is the IPSS revised. So, I think it would be good to maybe take you case and apply that to the IPSS revised to see what we come up with. So in this case, I think let's see if we have all the data that we need. We have a blast count less than 5 percent, so you get 1. We have a hemoglobin which was 8.something. So, you get another 1. So, that means we have 2 so far. Platelets were 80. So, that's 2.5. Absolute neutrophil count was over 800. Yes? Well, usually it's applied at the beginning anyway and then the cytogenetics, let's assume that it's intermediate although, again, in version 3, you have to look at the exact type, but that would be two. So, you have 2, 3, 4.5 we decided. So, 4.5 is still in the intermediate category

in here, but I can tell you that when they took that prognostic score and applied it to everybody that had the IPSS, you could see the changes that were made in that we probably were down scoring some patients that we should have been more cognizant of.

So, what's the future when it comes to risk stratification? The future, I think, is this: In point mutations. So, I showed you the cytogenetics, but point mutations is the hot topic in MDS. Why? Because it's looking at very small changes that happen into the chromosome and I'll show you an example. So, this isn't MDS. This is sickle cell, but just to give you the idea about the point mutation. So, here's your DNA. That's our genetic material that makes us who we are and usually every protein or every amino acid in the protein is coded for by three different nuclear type. Look what happens here. If you have one change, just one in that gene what happens is that you get a different protein that's put on all together and you end up with a huge disease called sickle cell with anemia and people die at earlier age and it's a single point mutation. So, you're going to ask me, well, did they do this in MDS? Absolutely. Some people… actually some of the samples were taken from Rush, Dr. Raza who was at Rush had a lot of samples and her and other people did genetic screening on all those patients that had MDS and found that you have actually a variety of very interesting mutations in various genes inside our genome that might actually portend for worse survival. So, you have ASXL1, each one of them and it's very… I don't want to go through that, but they figure into the way that the cell grows, matures, proliferates or dies for that matter. So, they get that single mutation in there then that what causes the cell to just live forever. So, if we could figure out a way to shut this process down, we've got it made. So, that's the next step, but I think one word of caution before you move forward on this is to say what happens when you get someone who develops those lesions from the get go versus those who have it later on and what about other disease entities? Do people have these kinds of mutations? I mean, the point is that there's a lot of excitement about this, but that also means you have to do a lot of work to understand where do those mutations fit in a diagnosis, prognosis and possibly treatment of MDS. I do think that that's very interesting lead that we need to work on, but nothing thus far though.

Now, we're jumping into the treatment. As I told you before, the main concepts of treatment haven't really changed. It's either curing somebody with transplant or deciding who needs to be basically evaluated for transplant versus someone who you would say, well, I don't know that I'm going to cure you, but I will treat you and often I'll tell my patients we can't cure diabetes. We can't cure hypertension, but we do treat them. So, that should be thought of in the same fashion.

Well, let's talk a little bit about transplants since some of you are interested in that. So, these are relatively old set of data, but it's a large study that looked at the median age. The oldest patient in the series was 64. Most of those people had very advanced MDS. Only 40 percent had lower risk and the majority of those people actually had completely myelo ablative transplants and the transplant related mortality meaning people who died simply because of transplant related issues was reported at 37 percent at 3 years. Twenty-three percent of those people relapsed meaning

that even though we do say this is cure, it truly isn't 100 percent promise of cure because some people still relapse and that left you with a 40 percent disease free survival and about 40 percent of those people at 3 years were alive. I think it's important to realize that this is, obviously, a different patient population, relatively older study. So, let's see what the newer studies showed. So, here's another paper that were published in 2010 and look at the size of this patient population. Almost over 1,300. Those people were all over 50 years of age and some of them had transplantation that was from their sibling and some had matched transplant, but not from their own sibling - from somebody in the registry and also 40 percent of them had… so fewer patients had fully ablative transplant which means you got very high doses of chemo that completely wiped out their bone marrow whereas others, 60 percent, had something called reduced intensity which means that you're getting some chemo to create some space for the new marrow, but you're not completely wiping it out and why is that important is because now we can take older patients that would not be able to tolerate that fully ablative transplant and offer them that option because they can tolerate it or we think they can tolerate it. So, what were the data, the outcome? So, the paper showed that actually at 4 years about 31 percent of the patients were alive. So, that's not very hot is it? So, I think that the issue that comes with transplant is a difficult notation to target because I can't tell you sitting with a patient who I think is a very good candidate for transplantation if he's going to be from the 31 percent. I can't even in the best of intentions it's hard to say. Yes?

Q27: (inaudible 34:46).

Jamile Shammo: Well, I think that we don't think of age necessarily as a (inaudible 34:59) indication for transplantation. I mean, you can say physiologic age. If they have low comorbidity scores, etc. There's certain ways to evaluate them, but I have patients who are in their 70s that I think that transplant may be the way to go, but fewer though than the norm, but what I'm trying to say is that we need improve the outcome of transplantation in MDS. Thirty-one percent is not a very good number. We need to make it better.

And then here's the newest paper basically on transplantation in 2013 and this is looking at older people between 60 and 70 to your question that had undergone reduced intensity transplantation which without we wouldn't be able to put those people through transplant to begin with and his conclusion was that basically people who are between 60 and 70 if they underwent reduced intensity transplantation, you're better off doing it right away if it's Intermediate 2 or high risk disease, but if you have low risk disease, you're better off waiting. So now, I think this was sort of the result of an older study, too, but this is sort of came as a confirmatory study. I don't transplant people who have low risk disease. Okay? I don't, but if they progressed, if they showed me that they didn't respond to the agents I have, they happen to be young. If they started to develop infectious complications, if they started to become transfusion dependent and I don't have anything to control their disease with, you better believe I would be putting them through a transplant. So, I think the timing for it and I think the type of disease that the patient had has to be evaluated in a very detailed way before this decision is made and what you don't want to do is

miss the window of opportunity. When someone already progressed to acute leukemia, that's difficult to get with outcomes. It's not impossible. Certainly possible, but we shouldn't be waiting to that point. You should do it prior to that point if you can.

What about other therapeutic options other than transplant? A couple of you said that you get supportive care with EPO Aranesp. We have Lenalidomide, Aza, Decitabine, supportive care, clinical trials that I would like to discuss very briefly.

So, here's the algorithm for low risk disease and you can see that we go by EPO levels. Often patients come without baseline erythropoietin level and it's surprising, but in general people have low risk disease or refractory anemia with ring sideroblasts should be treated with EPO. You should get at least 12 week trial before somebody pulls the trigger and said it's not working. So timing of it is also important. Now, if they have happen to have deletion 5Q then Lenalidomide is a very reasonable choice. If they happen to be older and happen to have high EPO level then you can consider immunosuppressive therapy. We don't really use much ATG cyclosporine in this country although the NCI looked into it for a certain subset of patients. It's something that I might entertain for some of my younger patients with something called hypoplastic MDS. Once they fail all of the above, then things like Azacitidine or Decitabine may be considered. Why? Because for lack of other choices. Should we have different clinical trials for this patient population? Absolutely and there are certain trials that are going on but with not very exciting results if you will. These are data on who might be a good candidate for erythropoietin and we have certain algorithms that we chose and I can talk to you guys later on as to who may be a better candidate. Basically, people who have low EPO level, low transfusion need benefit best.

And here's Lenalidomide. Probably one of the most exciting drugs in the area of MDS and it works very well for people who have deletion 5. It's approved based on results of a small phase 2 study. It's not that proved in Europe you should know and they're looking into a randomized trial to see does it actually cause leukemic progression. That's why it's not yet approved there. And in people who don't have deletion 5Q, it's also tried, but the results there are not so hot and, again, it's difficult to say who's likely to respond.

What about transfusion dependency? I thought I heard one of you say that they were being chelated. Now, that's another important piece that we have to think about that in people who have transfusion dependency in yellow and this is their survival, you can see how their survival is a little bit worse than those who are transfusion independent and that actually didn't matter what their IPSS risk score is and I think this is the other piece that we need to have better data on. Should we be chelating everybody? What should the level be of the ferritin when you try to chelate someone and if you do chelate them appropriately and kept their ferritin really low, are they going to do better than someone who isn't? Unknown and so that's where the clinical trials are also on to prove this, but in general and you all should know this there are guidelines or recommendations for iron chelation. Some in the NCCN guidelines suggested 2,500 whereas the

MDS Foundation suggest that anything over 1,000 merits initiation of iron chelation. So, that's basically the guidelines that you could adopt one and go with it.

So, what are some of the trials in low risk MDS? I think the most important one if you ask me is that (inaudible 41:17) study which is looking at exactly what I just told you whether or not chelation with this agent makes people… has a positive impact on peoples' lives. So, this is taking people who have low risk disease that get randomized to either nothing or to chelation. Once they hit a certain point of their ferritin in the study, it's 1,000, and then they're following them not just for chelation purposes or toxicity of the drug, etc., but they're looking at cardiac events, heart. Is it possible that just by giving so much transfusions we are affecting the heart in a certain way and maybe if we paid attention to that there wouldn't be that many effects on the heart? This is what we're trying to find out basically. Does it matter if we chelated somebody and what would happen at five years? So, they're being followed for a long period of time and I think it's going to be very interesting to see what happens there.

There's another study that's looking at low risk disease patients sort of like in your case scenario where they get randomized to either supportive care of to something called Eltrombopag and Eltrombopag is a drug that brings on platelet production in the same way EPO brings on red cell productions. If you ask someone who has low platelet count and we're talking about really low, less than 75,000, and that's their main problem, well, then that's the person that you would randomize this study because we want to know is there any positive result of utilizing this agent compared to just nothing or transfusion. So, more on that to come.

Moving onto the drugs that we use for high risk disease. You have, as you know, there's Azacitidine and Decitabine and you can see their shape is the reason why they work because they go into the DNA. So, this drug actually that you're getting or some of you are getting gets into the DNA and causes alteration to the cell whereby it probably dies and that's how it controls some of the clones, the malignant clones. So, this was approved in a study that basically randomized patients to Azacitidine or something else and people were included in that trial, included a whole variety and I think this is something a lot of people don't know actually. What kind of people were enrolled on the study that lead to Azacitidine approval? Well, here they are. They had refractory anemia, refractory anemia with ring sideroblasts all the way to actually AML. A subset had CMML. In fact, 10 percent when that bone marrow was taken and was looked into under some other pathologist, a central lab for the trial, were deemed to have AML actually saying this is at that time they had to have blast count of over 30 percent and even though those people were included. So basically, the outcome of this study is what led the FDA to approve the agent and as you know the next study looked at the impact on survival. So, it's not just the efficacy, but also the survival and we know that this has basically been shown to result in a modest, but a real maybe 9 months in terms of survival and what's interesting is that people who were randomized to the agent lived longer and actually doubled the number of people who were alive by that age… by that time, 24 months.

Decitabine is the other agent, very similar to Aza, also approved for the same patient population, but 2 studies went on to show if there was survival and that didn't pan out. It's not to say it's not effective. It is, but for whatever reason maybe it was the patient population or the mode of administering Dacogen there was no discernable survival advantage.

So now, what happens if people had a good trial of Azacitidine or Dacogen and then they're not responding then what do you do? Well first, we need to understand what happens when they failed. So, this is basically the outcome of people who had a very good trial of those agents and were deemed to be nonresponders. What happened to them? So you could see that there were several trials that addressed that issue, one at Moffet, one by the French and one at MD Anderson and you can see that that's the median overall survival from 4 to 8 months. So, it's a difficult disease to have, but here's the interesting part about it. This wasn't like a prospective study. This is looking backwards and seeing what happened. What's interesting is that people who had investigational therapies and those who underwent Allo transplant look at their median overall survival. It's the best of all of those other subsets whereas people who just had transfusions were basically in the lowest possible category in terms of survival. So now, this suggests that going after clinical trials or undergoing transplantation may give you a better outcome and while this may be true, but I like to argue that those people were taking onto trials and transplant because they had the good performance trial. They had good heart, good kidneys, good lungs. Someone looked at them and said, "You know what? I think you can undergo transplantation and you should have a better outcome," and so me that would be the interesting part. So, I encourage all of you to consider clinical participation in clinical trials and also making sure that you get evaluated for transplantation up front when the disease is already diagnosed because that may be very helpful at some point since response to hypomethylating agents is not something we can predict and not everybody responds.

Are there any questions so far or you guys want to leave it to the end?

Q28: (inaudible 47:55). … you going to touch about the side effects of that drugs? Later?

Jamile Shammo: No... clinical trials but I can answer questions about side effects. Absolutely.

Q28: That would be fine. Thank you.

Jamile Shammo: So, moving onto clinical trials…

Q29: Hello. Can I ask you a question?

Jamile Shammo: Yeah.

Q29: I had a bone marrow biopsy and CBC, but I'm not sure how to get the IPS as that account. They didn't give it to me actually.

Jamile Shammo: You said you had CMML.

Q29: Yeah.

Jamile Shammo: So, the IPSS excluded people who have CMML.

Q29: Oh.

Jamile Shammo: Yeah. So, that's not included in that. You know why? Because CMML is considered as part of this what we call overlap syndrome. So, it's not just MDS. It's MDS/MPN because you have certain proliferative cells, monocytes, which is…

Q29: Yeah. I have a chrome 7 monosomy. That's the only defect.

Jamile Shammo: There are certain prognostic models that we can calculate that later on, but you can't do the IPSS unfortunately nor can people who have secondary MDS because when what's done all those people were taken out.

Q29: Other thing is I took Vidaza for 6 month, 6 cycles and I failed. Actually, the blood transfusion went from once per two weeks to once per week. So, what options… I'm not a responder. So, what options do I need to take from (inaudible 49:48).

Jamile Shammo: (inaudible 49:49).

Q29: I'm 51.

Jamile Shammo: Have you looked for matches for you in the registry?

Q29: We are starting that now.

Jamile Shammo: So, I would say probably either transplant or some of the things that I will be discussing right now. In your case, and again, I don't know the details. It would seem to me that if you failed transplantation… failed Azacitidine after a judicious trial of it then maybe it would be time to think about transplant.

Q29: Okay.

Jamile Shammo: So, the clinical trials that have been and this is… let me not underestimate this. This is a difficult problem to have because you have a patient population that has already gotten some comorbidities potentially a lot of transfusion, potentially a lot of chemo that got them bombarded and tired and now you have a disease that has failed. Now, what do you do? So, this

is ground for investigation which is the reason why the options after you fail one or the other become relatively smaller, not to say that they're not existent, but they're smaller all of a sudden. So, people have looked at something called Clofarabine. It's your standard chemotherapy and there are some people that respond to it. People are looking at oral Azacitidine which is an interesting take on the standard drug that we know and maybe it works better for people who responded and then they can be maintained with a pill that they can take at home instead of having to keep coming back to the doctor for treatment. I just wrote down a chemo order for one of my patients. She's 92 and she's on her 40 some cycle of Aza and I feel sorry for her because she has to keep coming because the idea is that once somebody responds, you keep treating them and I wish there was a pill that I could give her so that she could take it at home. Nonetheless, we still don't have that yet. Rigosertib is a drug I'm going to talk to you about in just a second and Sapacitabine, both are options. Erlotinib and Dasatinib have been also explored, but the results are not very exciting. I can tell you.

So, what about Rigosertib? Rigosertib is a drug and I'll tell you what it is in just a second, but has been tried in people who have failed Aza or Dacogen and they were able to show that well, maybe 30 to 40 percent of those people would respond. So, was kind of exciting because we really don't have any drug for someone who failed Aza or Dacogen. So, this was sort of grounds for saying well, maybe we should look into this drug a little bit further and that's the reason why this study took place and we participated in that trial and what we did is that we took people who had high risk MDS including CMML who relapsed or were refractory to Aza and we stratified them to either Rigosertib or best supportive care looking at survival. This trial completed its accrual and the results will be out by ASKO (sp? 53:03). I can't share the results with you because that's proprietary, but I can tell you that the same agent is being studied at our center. Now, this is an extension of the trial I just shown you. This trial, everybody gets the drug. All patients that have failed Azacitidine will be enrolled onto this treatment and how we do it is that this 3 day continuous infusion once every 2 weeks for 8 cycles and then they move onto once a week. A very well tolerated agent. You might ask me how does it work? Well, it's what we call tyrosine-kinase inhibitor meaning it paralyzes the cell. It just stops the phosphor relation that leads the cell onto grow and proliferate and so that's what Rigosertib is and those are the inclusion criteria basically and the patients have to have had either Aza or Dacogen without any response and then they may become eligible.

We have another one with the Cyclacel. It's basically similar in composition to Azacitidine or Decitabine. It's a nucleus side analog and what we're doing is that it's a pill actually which is, again, very attractive for people who have logistical difficulty of coming back and forth. Of course when you're on trial, you have to come back and forth because you have to collect data and check safety, etc. So, this is also for people who have high risk MDS that had failed hypomethylating agents. So, you have 2 open trials for this patient population and then we have 2 more. One of them is looking at patients who have high risk disease plus Int 1, of course, and they happen to have low platelet count and what we're doing is that we're randomizing patients. This is upfront. This is people who had not yet seen Azacitidine for the treatment of their MDS.

They get randomized to either Aza by itself or Azacitidine plus Eltrombopag which is the drug that helps the platelets proliferate. So, this might actually be helpful in reducing need for transfusion because as you know, Azacitidine will bring the platelet count down. You were asking about side effect. Myelo suppression is one of the most important ones and maybe this will bring it on, but it's not actually the reason why I wanted to do this study. The reason why I wanted to do it is some very interesting data on Eltrombopag and the fact that it may actually modulate the leukemic cell. It's not just about platelets. So, that's the part that would be really interesting to see will people who get the Azacitidine and Eltrombopag do better, respond better than those who are just getting Azacitidine? So obviously, this is going to be opening very soon and we hope to have some data in the next year or so.

Finally, the last trial… The last trial that we are about to open is also one that looks at the chelation question. Like okay so you could chelate people who have low risk disease once they get to a certain seratin, but would the addition of Azacitidine matter if people were treated with the addition of Exjade or I should say Deferasirox. Does it add to people who are receiving Azacitidine because you know in the first two cycles of therapy with Aza, you'll probably need more transfusion than you ever did. You'll probably be wondering what have I done? I was okay and now look at this drug making more cytopenic, but the fact is this is expected. It's predictable and at some point when you start responding, those counts start to come up. So, this is looking at the question as to whether or not the addition of iron chelater to this patient population will be more helpful than not. Unknown and that's the reason why the trial is being done.

So in conclusion, I hope I have given you some update as to the challenge with the diagnosis, risk stratification, treatment and what is ongoing in this field and finally I want to show you my team and if I didn't have this good girls… Maybe we can see the last… Thank you. So, I have my Amy. Oh, that one. There you go. Oh, that's kind of odd. It's not letting you, huh? Anyway, my PA, Amy, is the person who coordinates what we call the MDS comprehensive clinic. We see patients together with the transplant or the pathologist, the cytogeneticist and we review everything about the patient So, she's the coordinator. Then I have my research staff that run the clinical trial, the coordinators and maybe… you don't have enlarge it. It's okay. So, Stephanie and… So, Kim and Stephanie are both research nurses, the 2… 3 data coordinator. Amy is my PA and that's myself. So again, and I want to take one moment to thank you all for coming and also thank all the patients that have participated in prior clinical trials that made the lives of people who have MDS today a little bit better. So, thanks for listening and if you have any questions, I'm happy to answer.

Q29: I have one question. I have been recommended for a clinical trial because I failed Vidaza, but then they have… that is with MEI Pharma and they have a Vidaza for people who fail Vidaza. They have Vidaza with the drug some research drug and for people who fail the Dacogen they have Dacogen with that drug. So now, the… that is a prescriptive pad, but my own, I'm just trying to think a little bit different. Since I failed Vidaza, why I need to take that

again with a new drug? Why not I take Dacogen with a new drug? Maybe will that be any… I'm just trying to be creative as a layman, but…

Jamile Shammo: So, a clinical trial with Dacogen and a new agent, some other agent.

Q29: Yeah because I failed Vidaza. They want to do Vidaza with the drug, but I'm like why do Vidaza? I already failed that. Why go that path again?

Jamile Shammo: I think the thinking is that probably the other drug which probably is an HDAC inhibitor. Did they tell you the name because my guess is that's probably what it is? That's the reason why they're doing the study because they're wondering if people who fail an agent now may respond to it if the tweaked it together with another agent and that has been described with certain drug combinations. You see? So, it's not unreasonable to do, but certainly it isn't your only option.

Q29: Yeah. If I switch from Vidaza to Dacogen with the research drug, would that be more hopeful than…?

Jamile Shammo: You know, I'll be honest with you. I mean, the data on CMML in particular when you switch from one to the other is really unknown because the only piece of data that I know, there's two clinical trials that were done. One was with people who had 3 cycles of Aza and then they're switched. Well, 3 cycles of Aza we all know is not enough. So, that study was not done well. The second one is the one I shown you when people failed and there were 16 or 17 patients that had failed Azacitidine and they were treated with Dacogen and nobody responded. So, am I saying that you shouldn't do it? I'm saying that the chances of a response after you failed the first hypomethylator is really small. So if you're going to do something, it's probably best on the clinical trial basis or consider transplantation which sounds like you're in the works for that.

Q29: Okay and even if I go undergo this trial because I have to do something in between transplant is not overnight. So, in the meantime go for this clinical trial, but what is the first… would it take a couple of months or two cycles to find out whether or not I am responding or not? What is the minimum time for the first reaction to respond?

Jamile Shammo: Usually, I mean, one cycle for anything is not enough. So, you have to have at least minimum of two cycles provided you tolerated the first one well and they do the second one and then they will evaluate you to see if you progressed. If you haven't they might move on continue that is.

Q29: Okay. So, if I don't respond then what happens in the two months? Should I cut it off or should I keep progressing till four or five months?

Jamile Shammo: Well, I think I'm sure if you're going to be enrolled on a clinical trial they have stopping rules. They will look at people… Nobody wants to give drug to people who aren't responding believe me. So, the trial procedures will be such that if you progressed, probably will be taken off study unless they have certain clause in there well if there's… I mean, it depends on the study, so that will be something you should ask the doctor that's enrolling you.

Q29: And then what do you have for a person in my case? I know you said something for people who fail the Dacogen. What does give… you have a clinical trial for ongoing…?

Jamile Shammo: Well, the one that I showed is the Rigosertib study for people that fail hypomethylators and that's the one that had open in our center right now and then there's that other oral pill I also told you about. So, it would be one of the two before transplant. Yes.

Q30: You said you had a 92 year old patient on the 42nd cycle of therapy, but I didn't get the agent.

Jamile Shammo: Azacitidine. I want to say 36. Thirty-six cycles.

Q30: Thirty-six cycles and the agent again was what?

Jamile Shammo: Aza… Vidaza.

Q30: Vidaza. Okay. Thank you.

Q31: Would you please tell me the correlation between bone marrow blasts and peripheral blood blasts?

Jamile Shammo: So, the bone marrow blast is the gold standard. That's what you should be relying on. The problem is…

Q31: Say that again.

Jamile Shammo: Bone marrow blasts… the bone marrow blasts is actually what you typically use as the gold standard. Now, the peripheral blasts can be a reliable only if they stay in your system for a minimum of eight weeks. Then they're reliable, but you know or maybe you don't what happens when you get an infection, blast count will (inaudible 1:04:38). You get a growth factor blast count goes up, but then it goes down to its baseline. That's why one value, one week, two weeks, not enough. You have to wait or even see what happens over eight weeks' time and then say okay that's reliable enough, but in reality, it's (inaudible 1:04:56).

Q31: In once instance I had Neulasta and Aranesp bone marrow… the blasts didn't do much in the peripheral. The next time, it just went out of site and been coming down very rapidly. Why?

Jamile Shammo: I'm not sure exactly what happened the first time or maybe when did they look at the blast count because the Neulasta lingers in your system for a while and maybe it took a while until those cells came up. So it depends on when they looked, but in general you get a growth factor. That's what happens. It pushes out whatever is in your bone marrow outside, but you cannot rely on that number though.

Q31: But the question is Neulasta and Aranesp would generally kick up your blasts.

Jamile Shammo: Neulasta more than Aranesp no doubt.

Q31: Thank you.

Q32: My diagnosis I have refractory anemia ring sideroblasts and I was diagnosed in February. This is (inaudible 1:06:01) Myelodysplastic Syndrome and I was put on Azacitidine, Vidaza. For the first 1 ½ year responded well except one time platelet count went to 17 and they (inaudible 1:06:16) with the platelet count transfusion responded very well. Now, I failed Vidaza. I failed Revlimid and left with all the masts like black pigmentation, nausea, vomiting, weight loss.

Jamile Shammo: (inaudible 1:06:36) Revlimid.

Q32: Yes and mostly diarrhea, severe weight loss and next one is… Next, I was evaluated at Sloane Kettering. In fact, I talked to you on the phone also for a transplant and initially they thought I'm a good case and we went on the registry. We got 9 out of 10 match. Meanwhile, there was some complication, which I don't have to go through and my performance score fell. In addition. Maybe I can answer indirectly have an answer the age makes the difference not by age alone. The comorbidities. I have a 2 valve surgery done and I have arrhythmia so I'm on coumadin. So, then I was decided not a candidate for bone marrow. So, I failed all therapies. Now, I am transfusion dependent, blood every 2 weeks. In your experience, my question, of the cases you know, how many transfusions a person can get total. What is the top you had a patient heard of (inaudible 1:07:59). Is there a number?

Jamile Shammo: (inaudible 1:08:02).

Q32: In the MDS, they have a newsletter on the patient. One patient more or less like my case, much younger than me. I wanted to say… never mind. I lost that particular paper (inaudible 1:08:23). He said he has (inaudible 1:08:25) 800 transfusions. The reason why I'm saying as a patient, I'm a physician. I'm retired now because of MDS alone and this gives a hope. You don't know how I hang onto that 800 number. I was devastated as I was coming up to near 200 transfusions, that 1 sentence reading okay I have… You know, it may look on paper oh 1 in 1,000 cases. I do not know. That's why I keep asking that question. Now, I passed 110 or 120, but I have that person's number. As a patient perspective, it's lot a lot of hope.

?: It's comforting to find…

Q32: It is circumventing. This piece I wanted to express when it is diagnosed as physician we are rushing in the open society to give the survivor that number. Is it not necessary applicable to me or to each person. What number…? I don't want doctors to give false hope, but by the same time don't take away the hope at all, but that number I don't know rest of you feel that way. I'm not.

Q33: Yeah. I've had 457 units and anyway I've been transfusion for quite a while and I've been Exjade ever since it hit the streets and before that I was on Desferal and that was the injection in the stomach or you hooked to a pump 12 hours a day, take it out for 12 hours, put it back in. Did that for a year and a half. So, I was really happy when Exjade came around. Anyway, I do have a question about research. There was a Dr. Cogle at the University of Florida that is experimenting with the bark of a willow tree from South Africa he believes can help MDS patients. Are you aware of where that research is?

Jamile Shammo: I think that there's a lot of simple trials that are going on in this field. He'd probably the one to tell you which phase of his study is going on. Some of the information are not necessarily public (inaudible 1:11:01) clinical trial (inaudible 1:11:04) investigation that are ongoing. We know only what he has put out basically because there's a lot of proprietary information. So, has he offered you participation in that study?

Q33: No, I just went to a forum that was in Miami, over a year ago and he talked a little bit about it, but it was strictly…

Q34: They were just starting.

Q33: They were just starting.

Q34: Two years ago.

Q33: They were just starting, but I was just wondering if anything's been published about it or anything? Nothing.

Jamile Shammo: There's a lot of (inaudible 1:11:35) or even natural compounds that's been studied. Like I know years ago (inaudible 1:11:40) many things (inaudible 1:11:44) nothing themselves. But it's up to patients now there's always some good reason to continue.

Q33: I noticed you talked about Revlimid. I went through that trial down at Moffet with Dr. List and it didn't work for me either. In fact, I ended up with diarrhea and a few other things, but I went through the entire trial even though I knew half way through it wasn't working for me, but I went ahead and did the complete study because it may help someone else later on. So, I can

sympathize with you. I didn't have any genetic problems at all. I think that was for a 5Q negative, I believe that trial was.

Jamile Shammo: There were 2. One was for deletion 5 in which it worked and a (inaudible 1:12:29).

Q32: I am not non 5Q. I have other… cytogenic

Jamile Shammo: (inaudible 1:12:37)

Q32: Yes.

Jamile Shammo: You were on the MDS 002.

Q33: Right.

Jamile Shammo: And in the study, only border patients responded. I put a patient on (inaudible 1:12:47) and you can… it's amazing what (inaudible 1:12:53) to respond and let them say 1 out of 4 patients respond. She went from transfusion dependence every 2 weeks to 12. Tell me why…

Q34: And he went from six weeks…

Q33: I went from every six weeks down to three weeks for transfusions on that. So, it's worse. Plus the side effects.

Jamile Shammo: And it's not easy (inaudible 1:13:13) so you were probably (inaudible 1:13:16) but there was some work actually that was done there's like (inaudible 1:13:22) microchip (inaudible 1:13:23) a certain lab tool that you can look at to say people who have this profile that way it's not (inaudible 1:13:32).

Q33: Would RARS make any difference, refractory anemia with ring sideroblasts, which is what I have? Would that make any difference with that trial?

Jamile Shammo: (inaudible 1:13:46)

Q33: Yeah.

Jamile Shammo: Oh, does that make… you had RARS.

Q33: Right. I do have it.

Jamile Shammo: I don't think there's anybody… I think RARS is a different disease all together if you ask me. I think they identified the new mutation in processing protein in RARS maybe about a year ago (inaudible 1:14:06) something to do with processing a protein. I want to say that there should be drugs that target that specific mutation for RARS. The only thing that works well for RARS is EPO plus Neupogen, which is (inaudible 1:14:22) upfront anyway and then after that you go onto things like Aza and like there's nothing in the trials that suggested that RARS was bad from (inaudible 1:14:33) for response.

Q32: When do you start worrying about the ferritin levels?

Jamile Shammo: Well, I think that you see that there's some degree of (inaudible 1:14:46) where we should be worried like the MDS Foundation suggests 1,000 and (inaudible 1:14:53). I think 1,000 is too low and (inaudible 1:14:57) is too high. I had someone that has the (inaudible 1:15:00) 1,500 and beyond and I know that (inaudible 1:15:06) transfusion. I'm just (inaudible 1:15:09). So, we tend to (inaudible 1:15:11) when (inaudible 1:15:13) less than 500 which I say that 1,000 is a little too low.

Q32: But with the transfusion, it is like beating the odds. You are on chelating agent and you are getting transfusions. So again, we'll overload.

Jamile Shammo: Well, you could always modify the dose. The first (inaudible 1:15:33) is someone is tolerating it and then if there's a transfusion needs a little bit higher then when Exjade is needed, up the dose and utilize time because it takes about… In the ethics study where we looked at Exjade in people who have transfusional iron overload the end point was looked at 12 months. So, we all seem to be in that patient we want it out right now. Well, if you give a higher dose, people would have side effects and then they come off and they know that this happens. To me, lower doses more extended treatment is what prompted it. Did they start that on you?

Q32: Oh, yeah. I'm taking it…

Jamile Shammo: What was your level when they started?

Q32: It was already 2,000 and now it comes… then it went up to 3,500 and then it… it doesn't come down to 2,200 with the 1,000 milligram of Exjade daily.

Jamile Shammo: What was it at the time of diagnosis?

Q32: At the time of diagnosis it was not like in hundreds. I would say like 200 – 300 (inaudible 1:16:48).

Q35: To determine risk category definitively, bone marrow biopsy would be the preferable…

Jamile Shammo: Yes.

Q35: So when they throw in a CBCs and differentials and all that and throw those…

Jamile Shammo: Not enough

Q35: It doesn't mean a damn thing.

Jamile Shammo: And not enough which means something when you want to determine transfusion need or someone gets transfusion all you are worried about is (inaudible 1:17:16) then (inaudible 1:17:18) my patient didn't have any (inaudible 1:17:20). Now he has 10 percent and it's detected and he's not doing (inaudible 1:17:25) no reason for (inaudible 1:1728) then that will be a concern but it's not a diagnosis. He should never be utilized for that.

Q35: So but bone marrow should be the one way to go and you can have that as often as you can get it.

Jamile Shammo: So, there are…

Q35: I mean, I know…

Jamile Shammo: (inaudible 1:17:46) who ask me that. (inaudible 1:17:51)

Q35: I've gone from a 3 blast to a 9 blast. I don't know where the damn thing is right now.

Jamile Shammo: But you're getting Neulasta.

Q35: I'm taking Neulasta. Right. Not Neulasta, I'm taking Vidaza.

Jamile Shammo: Oh, that's what I'm saying.

Q35: And Neulasta and everything else that comes with it.

Jamile Shammo: Unless you have a blast count that has doubled and stayed like this for eight weeks without any causality then I think…

Q35: But you're talking about bone marrow.

Jamile Shammo: If I'm treating someone with Vidaza is getting their bone marrow biopsy on day 1 (inaudible 1:18:25) then maybe after 4 cycles with their worrying I'm going to give them 2 more cycles if they're progressing and (inaudible 1:18:35). If they're doing okay then maybe

after 6 cycles they might get (inaudible 1:18:41) so that I can set the response, but I'm not relying on blood blasts unless they're over 20 percent (inaudible 1:18:49) I wouldn't alter progression without (inaudible 1:18:54).

Q36: I didn't know if… I was waiting for his thank you. Do I need this or can you hear me? I know there's been studies in the past and I haven't seen anything recently as far as and to your knowledge has there been anything recent with the correlation between Crohn's disease and MDS?

Jamile Shammo: Well, I think the only thing that I can put the 2 together is if people with Crohn's had certain drugs that might be (inaudible 1:19:34) to the marrow possible. Some people had immunosuppressive therapies and things like Vitoxin. So, there are certain drugs that could cause MDS but from an epidemiological standpoint like do people have Crohn's have a higher risk of developing MDS, we don't have data to support it.

Q36: In the previous studies there were some that had been diagnosed with MDS first and then Crohn's and then some that had or vice versa and some diagnosed with both of them at the same time.

Jamile Shammo: See the problem is that, again, like it probably fits into what I was saying about dysplasia and the fact that if you have someone with an autoimmune disease they could have dysplasia in the bone marrow without it being MDS. You see? They had the (inaudible 1:20:19) so dysplasia is a sign of (inaudible 1:20:22) it persists then it's real. So, there's an art to it, but I'm not sure that I can say that (inaudible 1:20:33). I suppose you could argue that maybe people have autoimmune disease may have more of a predisposition for it but there's no solid proof to that.

Q36: Okay. Thank you.

Q29: I have a question about transplant. The doctor is saying that I have to respond to this chemotherapy either level 1 which is Dacogen, Vidaza or a clinical trial and disease must go under remission to qualify for a transplant, but I failed the Vidaza. So, should I just go right away for a transplant or should I go to clinical trial and what if I don't respond to the clinical trial. Then I go to through the transplant anyway regardless or…

Jamile Shammo: I think most transplanters do not function (inaudible 1:21:24) patients who have active ongoing disease because it would be really a waste of time and I know (inaudible 1:21:32) patient population all the time, but you saw the number actually who realize that (inaudible 1:21:38). Usually people who have a lot of diseases going into it, so they will go through the whole process and they've learned from (inaudible 1:21:46) only to see the disease come back because the reason for that is that it needs time until that graph that they've given you takes and kills all the MDS or the CMML cells, but you don't have that kind of time and the disease keeps

growing, the graph is going to be lost. I mean, it would be wasted. So, we don't like to take people who have active disease for transplantation. So if your disease has to show at least some degree of controllability and maybe that's what the trial will give you that edge so that you can go for transplant.

Q29: Now, let's assume that I go for a transplant. What is the hope with that? Am I getting a new life from it or is it just to pushing the longevity by a couple of years and the quality of life is kind of degraded?

Jamile Shammo: The notion behind the transplantation is cure. When we go for transplant, we're going (inaudible 1:22:45) the intent. We want to cure this patient.

Q29: Okay. So, it's a fresh new lease on life then kind of thing. And I'm from India originally. I heard that 70 percent of the people don't find a match at all for the bone marrow donors. So, what is like I find a match or…?

Jamile Shammo: Well, I think that I've known some patients who are from a certain ethnic groups and they have nobody in the registry that matches them. Caucasian (inaudible 1:23:18) most commonly found ethnic group in that registry. So, when I've had people do sometimes (inaudible 1:23:26) and get (inaudible 1:23:29) so that may be (inaudible 1:23:36)

Q29: I also had Crohn's disease and I took Imuran and the doctor one day said your blood count is low. Stop taking it. Stop taking it and one doctor at all these… I was diagnosed the MDS and can… and also gene 7 monosomy. So, can that ulcerated colitis, Crohn's disease and taking of the Imuran drug could that have caused…?

Jamile Shammo: (inaudible 1:24:05) cause of the colitis.

Q29: The drug caused the side effect. Is that a proven thing or is it a…?

Jamile Shammo: It's a proven (inaudible 1:24:13) MDS with (inaudible 1:24:15) MDS with the patient. So, there is some genetic disposition. There's a lot of people who take Imuran and they won't manifest with MDS. It could be a risk factor, but there's no certainty about this disease.

Q29: So then I was told that in the (inaudible 1:24:36) I had the autoimmune and lupus and all that stuff and then I think then they finally said you have MDS. So, is there a… Usually, the cure is related to the cause. So for the MDS people with Imuran damage, maybe it's called gene 7 monosomy. Is that a specific clinical trial? The origin, the different…

Jamile Shammo: When you have the disease like that transplant is the cure of all (inaudible 1:25:10) a new fresh one and getting a (inaudible 1:25:15) you keep that also (inaudible 1:25:17)

colitis or Crohn's under control now that the new situation (inaudible 1:25:22). That should take care of it. (inaudible 1:25:25) probably for the rest of your life (inaudible 1:25:28).

Q29: For the clinical trial, I'm assuming that trial is related to the cause which is in my case it's the Imuran drug and ulcerated colitis. Is there a clinical trial for those people and maybe the drug will just…

Jamile Shammo: (inaudible 1:25:46)

Q29: Okay. Nowhere in the world that is going on. (inaudible 1:25:50) trial.

Jamile Shammo: There are different trials who are secondary to MDS. Yes, absolutely. Some of them are (inaudible 1:25:56) and I'm sure others (inaudible 1:26:00) transplant but (inaudible 1:26:04) include that patient population is in the MDS patient population. (inaudible 1:26:14)

Q29: What is the secondary MDS?

Jamile Shammo: Secondary MDS is the MDS (inaudible 1:26:21) drug or radiation and (inaudible 1:26:30)

Q29: Thank you.

Q37: Doctor, is there anything on hereditary for MDS?

Jamile Shammo: That's a good question. Usually, if you had heredity MDS, like the young patient that manifests with that. So, the youngest I've had was a 26 year old woman (inaudible 1:26:53) anemia. So (inaudible 1:26:57) anemia patients can develop MDS and AML. So, there are certain genetic well defined genetic abnormalities that can affect the younger people ultimately developing MDS and leukemia at a much younger age. So, yes.

Q37: For their children.

Jamile Shammo: No, for their own. They would develop MDS which is an older patient disease at a much younger age. That would be hereditary. So like if you had someone in their 80s developing MDS, it would be hard to say that this a heredity. If they do have a gene predisposing them, they would manifest so much earlier.

Q37: Okay. Thank you.

Q38: Doctor, at what levels do you suggest that there be transfusions for the white blood cells, the red blood cells and then also the platelets?

Jamile Shammo: So, the easier ones. We don't transfuse white cells because there's a (inaudible 1:27:55). Red cells used to be that (inaudible 1:28:04) someone who doesn't have any cardiac disease less than 8, but (inaudible 1:28:08) in your blood (inaudible 1:28:09) less than 7. It's the younger patient, asymptomatic, (inaudible 1:28:14) usually less than (inaudible 1:28:16) patients or (inaudible 128:19). So most of them are older patients I find. They get to less than 7. They're just in bed. They can't (inaudible 1:28:27). So, (inaudible 1:28:28). Someone has cardiac disease and they may have (inaudible 1:28:31), but for in general, (inaudible 1:28:40) for older people (inaudible 1:28:42) let them (inaudible) younger and (inaudible)

Q38: And what about the platelets.

Jamile Shammo: The platelets. Let's say 10,000 in general unless they're (inaudible 1:28:50). Some people say well they have (inaudible 1:29:00).

Q38: And one more question. How long should we wait to see if Dacogen alone works?

Jamile Shammo: A minimum of three cycles and you know we (inaudible 1:29:16) and Vidaza is (inaudible 1:29:19) give up on the drug (inaudible 1:29:26). If someone is on Dacogen tolerating it (inaudible 1:29:30) I would be willing to go through more test to see just to give them the benefit of the doubt because (inaudible 1:29:37).

Q39: But she had started out on Vidaza and stopped responding after 30 cycles and then she went to Dacogen.

Jamile Shammo: That's interesting (inaudible 1:30:00).

Q38: What about the combination of the two?

Jamile Shammo: (inaudible 1:30:18). It's been (inaudible 1:30:21)

Q39: Thank you.

Q40: I have a question. How commonly do you see someone with MDS without any chromosomal abnormalities?

Jamile Shammo: Half the time.

Q40: When you see this diagnosed, he was at 15 percent blasts after 2 cycles because he's almost 76, Dana-Farber had stated that they wouldn't even consider a transplant after 76. So, his blasts had gone up a hair after 2 cycles and then he has another biopsy on June 3rd. He has STAT and they're considering a PDL1 blocker if the Vidaza doesn't work.

Jamile Shammo: I mean, PDL1 these are very interesting drugs in (inaudible 1:31:22) use. So, we're looking into starting a trial like that at Rush as well, but it's a trial. So, I would say that if they are certain that he's progressed actually responded to treatment (inaudible 1:31:38).

Q40: Alright. One more thing. They're fantastic at Dana-Farber, don't get me wrong.

Jamile Shammo: Who is it? Dr. (inaudible 1:31:46)

Q40: Yes and he is very matter of fact about things and my dad tends to take things very literally. So when he asked what the average life expectancy was, he said on average with where you're at about 2 years. So, my dad put a 2 year marker on his life and started his bucket list and we can't talk him out of it. He's like I'm going to be gone in 2 years and I don't know, I guess I was just kind of wondering because he has RAB.

Jamile Shammo: I'll be honest with you. I try not to answer that question because… and I'll tell you why because every time I gauge the timeline based on (inaudible 1:32:30) I've always been wrong, not always wrong, but often (inaudible 1:32:36) to the point where I think I don't want to (inaudible 1:32:39) because of what I've shown you with the IPSS risk category. So, they… patients have the same risks for (inaudible 1:32:47) so the doctor… I mean, you're going to be wrong if you even attempt it. (Inaudible 1:32:56) I don't know (inaudible 1:32:59). That's how I will give it (inaudible 1:33:02) also but all my patients actually surprise me in an amazing way and that (inaudible 1:33:08) people who progress leukemia from transplant, low platelet counts and massive transfusion needs and they go on (inaudible 1:33:18) people who went on 2 years with simple supportive care. That certainly beats the numbers that I show you from 4 to 8 with the Vidaza (inaudible 1:33:29). So, I think we all have to sort of forget about the endpoint because I think the endpoint for all of this is somewhat known. Is it not? There's a very clear… Everybody got to have that endpoint at some point. So, what will be the point in belaboring that and worrying about when that's going to happen? So, that's how I…

Q40: Is there a certain percentage that they like to see the blasts down to before they will consider transplant?

Jamile Shammo: (inaudible 1:33:59)

Q40: Thank you.

Q41: I have a question for you. You mentioned Robin Roberts and her chemotherapy possibly being the cause of her… have there been any studies on radiation specifically?

Jamile Shammo: Radiation has been shown to be associated.

Q41: Is it the same percentage or is there a less…?

Jamile Shammo: I think when they're together, radiation and chemo, there's the highest risk. Chemo by itself and radiation increase the risk but not by much. I just want to respond with more than the other. I guess it depends on the extent of the radiation and the field of radiation.

Q41: I was going to ask that next question does it matter… I had targeted radiation. I am RT down in Houston for six weeks and so I was wondering if that is a… because it's a very targeted, very narrow band.

Jamile Shammo: There's a lot of… There's not a lot of data on that. Why? Because most likely people with radiation and MDS was mostly wider field, Hodgkin's, etc., but now if you look at the prostate cancer. I mean, people worry about (inaudible 1:35:07) getting (inaudible) or radiation (inaudible) study that came out of Cleveland Clinic (inaudible) would appear that there isn't an increase in the risk of MDS in older men that had prostate cancer and had evolved (inaudible 1:35:23). So and then the other piece is that you can't… this a patient population that already had malignancy.

Q41: Yeah. I could get hit by a truck.

Jamile Shammo: How much of (inaudible 1:35:39)

Q41: Thanks.

Q42: I have a question about hemochromatosis. I've had damage done to my heart and liver. Now with my ferritin levels of being low, is there any hope that any of that would be undone?

Jamile Shammo: That's a very good question and I think most of us feel that if you add a lot more iron to somebody's body… we've known from the thalassemia patients that developed problems with the heart and (inaudible 1:36:12) liver, etc. So, that's where the research is. I think it should work, but I don't have proof that it actually hasn't because if you chelate you're supposed to be obviously mobilizing the iron stores and hopefully is moving some of that iron stuff from the heart, etc. and that was (inaudible 1:36:33) fibrosis of the scar tissue that it comes from the iron. Unknown. Hopefully, maybe if you act upon it early enough that that should prevent the fibrosis from happening down the line, but we need the proof for that. That's why people are looking at echos and things like that after chelation to see okay (inaudible 1:36:53)

Q42: Would an echogram show that as opposed to an MRI because Medicare doesn't like to pay for…

Jamile Shammo: Well, that would be done on a study basis. That would be done in (inaudible 1:37:05)

Q42: Thank you.

Q43: (inaudible 1:37:11) last week I was worried although I know it would be (inaudible 1:37:31).

Jamile Shammo: In general those that we find in low risk stratification by Dr. Manera, but he had someone with a platelet count (inaudible 1:37:51), but in the middle of treatment and we all think that's important (inaudible 1:38:01) in certain populations (inaudible 1:38:10) that maybe also taken out and we know (inaudible 1:38:16) there's a lot of things that contribute to that. I would be very hesitant to look at one or two values and (inaudible 1:38:28).

Q44: If Aranesp doesn't really do much for fatigue I guess, what's the real advantage? My hemoglobin is 9.2 and it's been dropping for the last 18 months.

Jamile Shammo: You know, actually Aranesp (inaudible 1:38:44) agent has been shown to be associated with (inaudible 1:38:49) so if you respond to Aranesp (inaudible 1:38:55) and it has more, you should start to feel better. If you're not…this probably has nothing for your fatigue or whatever is going on it's probably is not related to your MDS. I shouldn't say it's not related to anemia (inaudible 1:39:10)

Q44: So, what's the response rate to Aranesp? I've heard like 30 percent.

Jamile Shammo: I mean, it depends. So if you take someone who had low EPO level and I don't know what your EPO level is and if you are transfusion dependent so let's say your EPO level is just at 100. You have a 70 percent chance of a response. If your EPO level is less than 100. If it's between 300 and 500 and you (inaudible 1:39:35). If your EPO level is bigger than 500 (inaudible 1:39:42). So, we need that number to figure it out.

Q29: I have a question. What is a good patient/support group forum for…?

Jamile Shammo: You're in it.

Q29: Yeah, but how do I interact with those people. Today is a good way to meet these people, but how do I otherwise exchange information with all my fellows here?

?: MDS Foundation.

Q29: I'm sorry.

Jamile Shammo: (inaudible 1:40:13)

Q45: Your second to the last slide you said SCT is the only curative option. Are you referring to transplants? Okay. And also do you recommend clinical trials for low risk MDS?

Jamile Shammo: (inaudible 1:40:42) my guess is that anytime you want to participate in the trial, it would be better (inaudible 1:40:53), but you have to weigh the risk and benefit

Q45: Right.

Q29: Will these slides be somewhere I can download? Your slides today?

Jamile Shammo: Oh, actually (inaudible 1:41:06)

Q46: Doctor, I just have a comment. If I was listening correctly, most people haven't had MDS too awfully long except the gentleman down there was 12 years. I just want them to know my husband has been diagnosed for 17 years. He is transfusion dependent and in iron overload, but he has a wonderful, positive attitude and I do believe that helps and there is a lot of hope. So, that's really why we're here. Well, he is here to learn, too, but I think it's good to share so that you all know and it'll give you hope.

Jamile Shammo: Thank you for sharing that.

Q47: Is there any… What's the latest studies on low risk as far as trials go?

Jamile Shammo: Oh, there's combination studies, too, so people are looking at sequential combinations of either Azacitidine with some like an HDAC inhibitor and there's people who are looking at erythropoiesis chelating agents like aposet (sp?1:42:11) other than the Aranesp that we have. People ar e looking for HDAC inhibitors. For example, it's in a variety of studies that looking (inaudible 1:42:20)

Q47: Yeah, but looking promising or is that hard to say?

Jamile Shammo: Not for me. You want the truth?

Q47: Yes.

Jamile Shammo: No. I don't see anything (inaudible 1:42:31). Not to say that it hasn't happened, but…

Q47: I know when I was first diagnosed there was a few studies on high risk none on low risk and it's just been the last few years that it's branched out.

Jamile Shammo: And I do think that there should be ones that are designed in a smart fashion and you need new targets, new drugs. So, I would find in those mutations, maybe you need drugs that find those mutation. That would be the smart way to go instead of saying, gee, when I found something in the lab… and I'm not saying that there's anything wrong with that, but I think that would be the proper, in my opinion, you could argue this (inaudible 1:43:10) like you identify the target. You found 5Q. You put Revlimid on that drug. Look what happened. Perfect. That's what you want. You found BCRABL. You got (inaudible 1:42:22). Perfect. That's what we need and the problem is heterogeneity. So, show me a mutation and a drug that works for it and I'm game for that clinical trial. That's my opinion.

Q48: (inaudible 1:43:33) 93 percent.

Jamile Shammo: Although the only thing with that is that in retrospect nobody knew upfront even Dr. List will tell you feel free to ask him. He didn't know that Revlimid was going to work in the 5Q. Right? So, it goes to show you. We luck out once in a while by mere luck. Anyway. So, thank you all for coming. Good luck.

Jean Ridgeway: So, you haven't met me yet but you will. Some people look familiar in this audience. My name is Jean Ridgeway and I'm a nurse practitioner. I'm going to be with you this afternoon. We have lunch scheduled starting at noon, but why don't we just start now and then we can finish up. Two o'clock is our end time. I like to be on time, so you will be out the door at 2:00 p.m. Okay? So, feel free. The lunch is up there and come on back to the table. I think if you don't mind just feel free to visit during lunch and we'll take our full hour. If you don't know where the restrooms are you got to walk down the steps a bit. Just a two little bits and then the men and the women's bathrooms are down the stairs or to the right and to the left. Thank you. Alright. Feel free and enjoy your lunch.