Speakers:
Michael R. Savona, MD
Denise McAllister, MS, ARPN, AOCNP

?: Today we have our guest speakers Denise McAllister, a member of our nurse leadership board and Dr. Michael Savona, hematologist oncologist here at Vanderbilt. Dr. Savona has dedicated his career to MDS and transplant research. His post grad training includes a fellowship at the University of Michigan and other work at the National Institutes of Health in Bethesda, Maryland, The University of California and the United States Air Force. In 2010, Dr. Savona served the US Department of Defense in Iraq as part of Operation Iraqi Freedom joining other physicians in a theater intensive care unit to provide care for coalition forces, contract workers and host nationals. He has earned several awards and grants and has extensive experience writing, teaching and speaking on topics related to the research and treatment of blood cancers. I'd like you to help me welcome Denise McAllister. She's donated her time to coming today on a Saturday and I'll have Dr. Savona come in as well.

Denise McAllister: Good morning everyone and thank you for being here. It's a pleasure of being part of the MDS Foundation Nurses Leadership Board. It's also a pleasure for me (inaudible 1:42). Just to go over the agenda. Dr. Savona's presentation will come first talking about what is myelodysplasia and therapies. Then we'll take probably just a brief break, maybe five minutes or so to change slides and that's when we'll have a quality of life discussion about living with myelodysplasia then we will break for lunch at approximately 12 o'clock and then from 1:00 to 2:00 we'll finish up with the discussion on tips on how to live each day especially (inaudible 2:20) with myelodysplasia. So, I'm very proud that you're here. Just housekeeping ideas. There's restrooms around the corridor. If you have cell phones, will you please put those on vibrate. This is an open discussion. This day is meant for you. It's devoted to you and we're here to help and just to give a shout out to the MDS Foundation. I'm very proud (inaudible 2:51) very proud to be a part of this group. This organization is really very (inaudible 2:55) and devoted to the care of patients with myelodysplasia and they're also very devoted to healthcare providers and sharing that we have what we need to help deliver our care to patients, education support as well as grants, having leaders that have devoted their career to myelodysplasia and talking about the science of the disease and what learn especially each year through the American Society of Hematology (inaudible 3:29). So, thank you very much. Dr. Savona.

(Applause)

Dr. Michael Savona: Thank you, Denise. So, I try not to wear a suit and tie much anymore, but I do for this crowd. So, I'm really grateful to be here. It's real flattering to see you show up on a Saturday during the (inaudible 3:55) tournament listen to me talk about my passion of (inaudible 4:01) and to Denise and to Tracy and Aubrey and Dee from the MDS Foundation. This is a really wonderful group and I've worked a lot with them over the years and it's just been a very

gratifying relationship and I hope you that you find you can take advantage of some of the offerings they have for patients because I think they can really help you and your families.

I had talked to scientists who are developing new therapies and I give talks to my seventh grade science class and so and everything in between and when I speak to people in the community, these groups are always a very wide variety of backgrounds and knowledge that comes into this room. I really expect that both that you interrupt me because I'm going to talk to you about the science behind some of the new therapies and it's fairly complex, but I find that sometimes patients come with me in understanding everything about new molecules and I certainly don't want to skip over something for the sake of trying to make it understandable. I think in the course of this talk I can get the point across and hopefully if you are at a point where you are not following, please interrupt.

Denise and I are not going to spend too much time talking about the ideology or pathogenesis of MDS. I'm just going to spend in the beginning a few moments and Denise will follow up some more about how we categories different types of MDS. I'm really going to focus on what the treatment is now and what we're trying to do in the future. Dr. Mohan is my partner at Vanderbilt and he's here today and he also takes care of people with MDS and we're a Center for Excellence for the MDS Foundation. We have many clinical trials with people with MDS and I'll talk to you about those in a moment.

I do have some disclosures. I sit on several different advisory boards. The reality is 99 percent of the drugs these days are developed in pharma. So, it's very important to have good relationships with industry and I'm unabashedly participating in such a fashion because that's what's important for the patients, but I pursue what's interesting and if the drug is not interesting, I have no allegiance to working with one group or the other, but they support some of my work and you should know that (inaudible 6:24).

So, what I tell a lot of patients that come into my office for the first time about MDS is the two take home points. One, it's Myelodysplastic Syndromes. It's not syndrome. It's many, many, many diseases and we're just not smart enough to break it out into what those diseases are yet. We just say MDS. So, that's an important first take home point. The second part of that and the corollary to that is that it ranges from something that is annoying enough to bring you into the doctor's office and something that you'll die with all the way through acute leukemia where if we don't do something, it's something you can die from. So, it's a real wide variety of different types of diseases. Everyone understands, the heart people have done such a good marketing job. Everyone understands heart attacks. Everyone understands the idea of your heart not beating. Some people can understand it very well. Your heart not beating at the right rate. Over your whole life when you run up a flight of stairs, your heart beats faster, you go to sleep it slows down. It's amazing the heart can figure that out and do that right, but sometimes you need a pacemaker. Sometimes the heart doesn't quite beat right or sometimes it stops beating. You need the defibrillator and you probably know people that have a defibrillator or a pacemaker in their

chest and that's to take care of the ticker that's not quite meeting the demands that it did when the… many years ago.

Well, the bone marrow is much more amazing. The bone marrow can make white cells when you have an infection. It makes more white cells. When you are cut and you're bleeding, your bone marrow makes more platelets. When you rise up to a high elevation and the oxygen is thin and you have to make more red blood cells to carry oxygen, the bone marrow can do this and it can do the opposite in the reverse situation. In your whole life, your bone marrow is balancing this in homeostasis and sometimes just like people need a pacemaker because their heart is not beating the right way, sometimes the bone marrow stops functioning right. Unfortunately, we don't have a pacemaker for the bone marrow and what myelodysplasia is, it's essentially a pacemakerless atrial fibrillation in the bone marrow and sometimes that can spin out and become in your bone marrow's effort to repair a more aggressive disease like acute myeloid leukemia.

I'll show you some pictures here. This is an example of (inaudible 8:48) which is where the platelets… what the platelets look like in MDS and the cells that make platelets, that make karyocytes and this erythropoiesis which is the red cells and you'll take my word for it that these are funny looking cells. You can see this one, the (inaudible 9:03) nucleated cell here, but you can see on this slide with normal granulopoiesis. These are white cells being made in the bone marrow. This is what they should look like. Precursor white cells and in this granulopoiesis over here, you see hyper segmented neutrophils. You see what's called (inaudible 9:24) cells. You see these multilobulated cells and what happens it just makes total sense. The bone marrow is trying to a job. It can't do any more so it overdoes the job or it underdoes the job and the assembly line, parts get put on the chassis in the wrong order.

So, the other kind of analogy I tell patients is think of it upper Detroit. So, this works for me, but think of an auto factory. You need iron, you need erythropoietin, you need B6, you need B12, you need AC Delco to send in your spark plugs, you need a batter, you need a windshield. You need all those pieces to make the vehicle. So, all those pieces are there and you still can't make it. That's a problem with the factory. So, when you go into your doctor, we're going to check your B12, your B6, your iron, your folate, your erythropoietin and if all those pieces are there and you still can't make cells, well that's a problem with the factory, the bone marrow. That analogy works for me anyway. Sometimes I carry that analogy a little far. In a worst case scenario, that… Here's an example of that. That factory, all the pieces are there, but there's only one guy in the assembly line and he's just slapping pieces on the chassis and in the end the chassis goes off the assembly line with no windshield and no wheels and that is what AML is. It's basically an under formed… the precursor cells, unfinished blood cell which has been arrested and replicated by these clonal molecular abnormalities and has no death programming. So, it lives forever. It's immortality of the white blood cell.

MDS is typically a disease of those in the mature age category, but I have patients in my clinic, unfortunately, who are 25 years old with MDS and I have patients who are 90 and doing fine

with no treatment in my clinic with MDS. There's a male preponderance although I certainly have female patients with MDS. Usually, the cardinal feature is anemia, but sometimes people come in with infections and their white cells are low and sometimes people come in with low platelets and they're bleeding and these have different prognostic ramifications that are nuances that Dr. Mohan and I have to sort out and help us in our planning for therapy.

Everyone asks what causes MDS. We don't know. We know radiation. So if you worked on a nuclear submarine or you're exposed to benzene. We know that these things are carcinogenic and can lead to bone marrow changes. We know that from the Hiroshima and Nagasaki in Japan post nuclear explosion radiation therapy science that's been done there and benzene which most of the people are older than me in this room. So, you probably been exposed to benzene. When I was young, benzene was easy to get and now it's fairly regulated. So hopefully, the carcinogens associated with benzene is a thing of the past and hopefully people don't have the exposure, but some of the people in this room who are young in the 30s, 40s and 50s, benzene was available at your hardware store as a solvent and a lot of people were exposed to this. When I was deployed to Iraq, they were using it to wash off the side of buildings. It's unfortunate that it's still around and MDS is associated with chromosomal changes and Dr. Mohan and I are used to looking for these things and we know that some of these chromosomal changes are really bad and that will help us adjust our therapy and we know some of these chromosomal changes are actually a good risk. So, that will help us a devise a therapeutic plan as well.

Q1: I have a question. I guess one of the ways to get it is exposure to carcinogens or toxins?

Dr. Michael Savona: Yes.

Q1: And I was also told high dosages of chemo made prior.

Dr. Michael Savona: Yes. Sorry. So, that's my… I neglected to talk about chemotherapy, but radiation, benzene and chemo and specifically chemo that damages DNA and the typical story is breast cancer and I can't tell you as a young oncologist and fellow when I would go to these meetings and hear about how we continue to include anthracyclines for the care of breast cancer and how the risk of AML was so low we should still do it. Yet I was the one seeing AML in the clinic for all those people who had cured breast cancer. So, it may be low, but if you get it it's devastating. So yes, there is a treatment related MDS and AML that could be caused by chemo and it's specific chemotherapies that damage DNA.

So, this is just kind of an overview slide that talks about our general strategy in MDS. When we think about lower risk disease with low blasts, well, we try to think what's the least invasive therapy that can guarantee the best quality of life for as long as possible without toxicity and we think growth factors. Sometimes when people have hyper classic MDS, for example, because they have low cell count in their bone marrow we give them steroids or immunosuppression. That can be very beneficial. For an isolated 5Q-, there's something called 5Q- syndrome where

people have just the 5Q-, just the fifth chromosome is missing a piece and if the fifth chromosome is missing a piece on the bone marrow, those people tend to benefit from this drug called Lenalidomide or Revlimid and Revlimid is a funny drug. It's an immunomodulatory agent and we're not sure exactly how it works, which is a little bit scary, but it's extremely well tolerated in most people and then there's a small number of people have a lot of trouble with that drug. I don't know if anyone's taken Lenalidomide in here before. How did you do with it?

Q2: (inaudible 15:31) short time before I had a bone marrow transplant.

Dr. Michael Savona: You did. So unfortunately, Lenalidomide doesn't work for a lot of patients and we've tried it sometimes in patients who have the 5Q- but also have other abnormalities and for patients who have 5Q- and other abnormalities in their cytogenetics, it doesn't work as well. The standard therapy, I'm going to spend a little bit of time talking about Decitabine and 5-Azacytidine is to give this epigenetic therapy and that's for people who have lower risk disease, but they have a transfusion demand and… or we're preparing them for transplant or if they have high risk disease and I can talk a little bit about strategy on there in a moment. For younger patients sometimes we'll give chemotherapy with the intent of taking them directly to an allogeneic stem cell transplant and then, of course, my role is to try to push the envelope forward with new therapies because what we have isn't good enough. I have lots of… I have a couple slides and a planned discussion around allotransplant and if it's okay with you I'd like to save that till the end if that's okay because there were a lot of good questions about allogeneic stem cell transplant that came with the registration.

Q3: I'm sorry. I have to ask another question. If you just talked about it and it kind of went over my head, but can explain what the blasts are?

Dr. Michael Savona: Yes and this is important. Bring this up because sometimes I think I'm saying something that I'm not. So, blasts are those… Those are those chassis without the wheels and windshields that are going out. The blasts are in the series of development. Imagine AML being a condition where your body is ruled by two year olds. So, that's a problem. Right? They don't have any (inaudible 17:30). So your cells in development go through a stepwise fashion where they become more and more fit to carry out their end job. Red cells carry oxygen. The white cells fight infection. So your cells in development go through a stepwise fashion where they become more and more fit to carry out their end job. Red cells carry oxygen, the white cells fight infection, make karyocytes and platelets to keep you from bleeding. (Inaudible 17:45) to control your immune response to antigens in the air, allergies and so forth. If those cells are not developed and they stop developing and they make unauthorized copies of themselves that's leukemia and what we say is those cells are blasts. That's what we call them. So, I'm sorry I didn't make that clear. So, thank you for asking, but that's the general idea and what happens in that state is that not only do you not have normal neutrophils, but you can start to develop a problem where you have too many two year olds. You have too many nonfunctional cells and sometimes people as we get their blood vessels become so filled with these cells we have to put

them on a machine and take the cells out. That's lymphopoiesis. People can have heart attacks and strokes and thromboembolic events secondary to all these cells crowding up in the blood vessels.

Q4: The amount of blasts that put you into the lower or the higher risk (inaudible 18:55)?

Dr. Michael Savona: Yeah. So, this is something that Denise is going to talk about a little bit, but I'll spend a moment on this. So, the risk stratification in MDS is based on three main things – what your cell counts are, how low your red cells, your white cells and your platelets are and that's nuance, but just low counts; what your cytogenetics are. So, what are the chromosome abnormalities in your blood cells and actually we understand and this is too much detail, but we actually look for not just cytogenetic, but we look for molecular…little mutations and the number of these mutations is growing, so you can imagine the information we're trying to keep straight here, but just think genetic abnormalities in the blood cells and then the third thing is blasts. So, if the blasts are high, you get extra points for that and there's all kinds of different systems that have been developed to prognosticate for MDS. You probably heard of IPSS. There's now IPSS-R. There's WPSS. The bottom line is that we're looking to try to best put people into risk categories so we can say, you know, I can't say what's going to happen with you, but 1,000 people like you did like this or they did like this and that's how I speak to patients. I have no idea what's going to happen you. I'm not God. You're your own person. This is you gone wrong, but people who have cell counts like yours, this is how they traditionally did and actually the board members, a couple of the board members of the MDS Foundation, are world renowned in our little nerdy circle for developing these systems. Peter Greenberg whose basically one of the leaders of the MDS Foundation at Stanford is a professor emeritus and he developed this system for IPSS which has been extremely valuable and helps us decide who to give Azacitidine to or who to give Decitabine to or who to take the stem cells transplant. So, it's really been kind of defining.

Q5: So, the only way to determine blasts is through the bone marrow biopsy. Right?

Dr. Michael Savona: Well, we can cheat a little bit and look in the peripheral blood if you got blasts floating around, but when we say number of blasts, we're talking about the bone marrow and when I was a fellow, I knew I was going to be doing this to people. So, I actually had them do it on me and it wasn't fun. I would not do it on a Saturday night for a good time, but I also think it's not that big of a deal if the information is going to be important. I guess the challenge I would ask you to bounce back to your physician is is the information we're going to get for this going to change what we do? Is it going to affect how we move forward because if you're just doing it because that what it says to do in the book, I don't want to deal with (inaudible 21:37). So, I'm apathetic to this, but unfortunately we get a lot of information from the bone marrow and we really need it. Not to mention this is a plug for our tissue repository, but I do a lot of research from bone marrow samples that are drawn at the same time as the standard of care bone marrow. I don't do it for research. I do the bone marrow for clinical care and I ask patients if they're

willing to let me have some anonymous bone marrow stored anonymously so we can do laboratory based experiments and that's how we're pushing the bar ahead.

Iron chelation. Iron chelation is tricky. So, you can iron chelation through a subcutaneous method where you can sleep with a needle in your arm. How many of you think you can tolerate sleeping with a needle in your arm. Very few people can. Some people can pull it off. Have you done it?

Q6: I have done it.

Dr. Michael Savona: How'd it go?

Q6: Well, it's not chelation. It's just a needle that I've been getting (inaudible 22:38). So, it's not iron chelation.

Dr. Michael Savona: But you've had a needle in there. Okay. So if you can… I don't mean a port. I mean an actual needle. So if you only sleep… just sleeps like this. I'm all over the place, but if you're a sleeper who can just sleep like this and sometimes subcutaneous chelation is a great way to go. It's relatively harmless and over eight hours, you get the iron off. The other modes of chelation are a little different. One is IV three times a week. Nobody wants to go to the doctor's office for three hours three times a week to get chelated and then the third are these oral drugs and one is Deferasirox and Deferasirox is a great drug. What's the problems? It's upsetting to one's GI. Has anyone ever taken Exjade or just Deferasirox before?

Q7: Yeah. She takes it every day.

Dr. Michael Savona: How does she do with it?

Q7: Pretty good.

Dr. Michael Savona: Some people do great. Some people kind of get roughed up and interacts with a lot of medicines. So, we got to be careful and it complicates things a little bit. It's metabolized in the liver and it actually can't be taken in renal failure or when people have renal insufficiency. So if you're a diabetic and you already have a little renal insufficiency, you can't take this medicine or it can make it worse.

We also think that there's a couple of… There's some debate about this, but we also think that taking the iron off actually stimulates hematopoiesis. So if people have lots of transfusions and their iron level goes up we think that taking the iron off is important to protect their organs, but we also think taking the iron off might actually stimulate hematopoiesis and there's some clinical… there's an empiric clinical trial that it's now to show this. It has to do with stimulation of the hormones that actually contribute to hematopoiesis. Let's just leave it at that.

Q8: I get my chemo through shots. Are we covering that? Is there anything to…

Dr. Michael Savona: We're going to talk about that in a second. So, epigenetic. So, this is my challenge. So, this is a really tricky concept, but the idea of epigenetics is that you have DNA which encodes for all of your genes and in MDS what happens is and some of those genes, there's a mutation and those genes are made and they make proteins when they shouldn't. To get those genes to be made, there has to be made there has to be some influence from the outside. It can be done in a variety of different ways – methylation, ubiquitination, simulation, histone deacetylation. Don't worry about that. Think of it like this. There's policing of the genome and one kind of way of policing the genome is the city cops, the demethylating agents or the methylators and in MDS we know we can take off those methyl groups and we can change the way genes are transcribed and I'm going to talk more about the county cops, Internal Affairs and some of the other… the FBI and some of the other polices that are little bit different but still affect transcription of genes.

So, DNA methyltransferase inhibitors or hypomethylating agents are genes that basically change in expression, but they're happening from outside of the coded DNA at the outside genome DNA. There's lots of ways this is done. I mentioned DNA methylation and that is what your shots probably are. Unless you have EPO, you're probably getting Azacitidine shots five days a week or seven days a week?

Q8: Five. One week a month.

Dr. Michael Savona: Yeah. A week a month. So, what happens in MDS and in AML and a lot of cancers is that this protein has miniscule (inaudible 26:57) actually helps as an enzyme helps add a methyl group to part of the DNA. All this is is just a nitrogen ring that's part of the DNA. DNA is made up of four nucleotides, five if you count uracil but cytosine, guanine, thymidine, adenosine. So four nucleotides and they're basically just nitrogen rings that are added to a sugar group and that whole thing is that's what DNA is. Well, what happens in these tumors is that this… there's additions or changes to these that actually single the gene to turn off or turn on. So, this cytosine is methylated here and the way you can think about this is that you could think of what I'm going to show you here and then a reverse of it. So at the top, there's no methylation and that gene will be expressed. That's a cartoon that basically shows that there's no police turning this on or off. Down here there's methyl groups on what's called promoter region before the gene is transcribed and that gene never gets transcribed. So, it's silenced and if you think about MDS or any cancer… MDS is a little different, so let's think about any cancer because it's part of MDS, but just think about cancer a dysregulation of the growth and the depth. You should have in normal cells a hemostasis your whole life, a balance. There's cell turnover. There's cells that are dying and new cells are being created and what happens is cancer. You go like this. So, the genetic program is all towards making more cells. Does that make sense? So if you have a gene that makes more of itself, it'll be turned on and if you have a gene that tells a cell hey, it's

time for you to die. You need to program cell that gene is turned off. So, the bet with hypomethylating agents is that by giving the drug, Azacitidine or Decitabine and taking the methyl groups off that most of the genes affected are actually the pro-growth ones and will get back into a normal hemostasis and sometimes that works. So, these are the two drugs – 5-Azacitidine and Dacogen which 5-Aza-2'-deoxycytidine. They're kissing cousins. Now, the reason we use Azacitidine is because my friend Pierre (inaudible 29:45) published it in *JCO 2006* a phase three study which show patients who got Azacitidine did better than people who didn't. There's a 9.4 survival benefit. Well, scientists get excited about a statistically significant 9.4 month survival benefit. I know that's good, but if 50 percent of the people are still gone in two years that's not good enough. That's what that means. So, 50 percent of the people on this Kaplan-Meier curve over time with standard therapy are going here. You add this drug, this extends the life from an epidemiologic standpoint of people by nine months and that's why we give this drug because we know it's better than the standard of care. There's a bell curve. Some people do much better. Some people don't do as well. The bottom line is that it's a step, but it is way not good enough and for anyone who has MDS, who's happy with 24 months?

So, what do we do? We try to improve upon what we know. So, I'm going to talk about new research in this area of epigenetics and some other areas starting with what we know. So, I just talked to you about Decitabine and 5-Azacitidine. Well, we know those drugs work. What if we can make them work better the same kind of drugs? So, Dr. Mohan is running this trial at Vanderbilt with this drug and I participated in the phase one trial where basically they take Decitabine and they add this bulky deoxyguanosine group to it. This is chemistry. So, don't worry about it. Just think big bulky group. So, it's harder for the body to digest. You get a shot of this and it sticks around for a while and it turns out when we did the study, I don't really have a pointer, I apologize. This is a very complicated study and the first part we didn't know how to give it. We though, "Boy, it would be nice for patients if they just had to have it once a week." It turns out that didn't work as well. So, we got stuck with the days one through five and then we went further and put more patients on days one through five at one of these two doses and it turns out that these two doses are full (inaudible 32:07) doses and enough to get the action that we want to get. Now, let me show you experimentally how we show that. So this is TK. So the only thing I want to show you about this is if you think about Decitabine and this going off on this axis is how much Decitabine there is and this is how much time after you get it. So, you get your shot. In two hours later, you got that much floating around at that dose. At that dose, you got that much floating around. If you have this drug, same equivalent dose, you got that much floating around in two hours. Because of that bulky group, it's just harder for the body to get rid of it. So, your cells are exposed to that drug longer. It's almost dumb it's so simple, but if it works who cares. If it works and it's not toxic then who cares? So, the half-life's a little bit longer and we just think if increasing the half-life for a drug that already works maybe we can make this study. So, remember I told you pulling off those methyl groups is what these drug do, a hypomethylating agent? Well with the test, this is way complicated test, but there's a way we can actually measure where the methyl groups are pulled off and there's a dose dependent. These are going higher, higher doses. There's a dose dependent demethylation. So the more drug you

get, the more methyl groups you pull off. That's important to know. That's called pharmaco dynamic endpoint and that tells us we're actually doing what we think we're doing with the drug.

Q9: Is this applied with Vidaza?

Dr. Michael Savona: This is kind of like that. This is the cousin of Vidaza, Dacogen, but Dacogen or Decitabine has that extra group on it now that makes it bigger and harder to get rid of, but the principle is the same. So now, we look to see does that demethylation actually correlate with a response because it's fine if you pull the methyl groups off of it, but if it's not helping anybody who cares. So, the complete responders, the people who had the drug and the disease completely went away which is what we're really aiming for, those people all have these 10 percent demethylation. I have a lot that looks like this.

Q10: And the disease goes away?

Dr. Michael Savona: (inaudible 34:34) the disease goes away. It doesn't mean it's cured, it means we can't see it. Complete remission. Questions about this? Don't be afraid to ask these question because I don't want to…

Q11: Repeat your last (inaudible 34:48) about CR.

Dr. Michael Savona: So, a CR, or complete remission, means we don't see any evidence of the disease. There's no cytogenetic abnormalities, no blasts. The counts are back. The marrow looks normal. Has anyone had a CR of their MDS?

Q11: I went from eight to almost zero the last… on Vidaza, but I'm going through the next bone marrow biopsy to see.

Dr. Michael Savona: Congratulations.

(Applause)

Dr. Michael Savona: That's wondering and I wish we had more of that and that's what this is about. We don't have enough. There's one person who's got a CR in this room I hope, knock on wood, but we need to have two and then three and then hopefully everybody gets a CR.

Q11: I didn't stop Vidaza. I still do it.

Dr. Michael Savona: You can't stop it.

Q11: (inaudible 35:37).

Dr. Michael Savona: Can't stop it. And I'll talk about can't stop in a minute. This business that I'm showing you so you understand the science behind why we do these things. This is an example of a pharmaco dynamic endpoint. So, this is showing that that methyl group is pulled off and it's also showing that pulling the methyl group off is essential to have response because the only people who had complete response had the methyl groups pulled off. That's the only take home note. That's not that complicated. We did the science to prove that the drug was working in the people that it worked because if it works that's great. We sure like to know why. Jake, are you following this?

Q12: Yeah.

Dr. Michael Savona: Well, that's great, but it's still five days a week. I still have to drive from Jackson into Nashville. I have to sit in the (inaudible 36:31) waiting room for two hours before I get Dr. Mohan to see me. Do I take this medicine by mouth that would be nice. Well, here's the problem. Normal Decitabine or Azacitidine if you just swallow the medicine, you got an enzyme in your belly called (inaudible 36:56) and it will just eat up the medicine and your cells will never see any of the medicine. A bummer. So, what are the strategies to get around that? Two strategies. The first strategy is you take Azacitidine and you make a new molecule called CC46 which is a super dose of that 5-Azacitidine. So, just basically overwhelm that enzyme. So, what's the problem with giving so much of the drug that you overwhelm the enzyme? Toxicity. So, people are sick and I developed that drug and I got people who failed Vidaza, but then they took oral Vidaza and they got response it was great, but then they were sick. So, the story to that drug remains to be determined. Another strategy and this is so stupid it's brilliant. Another strategy is just inhibit the enzyme. So, there's a new therapy with a drug called E7727 and E7727 is given with oral Decitabine in little doses, nontoxic doses, just inhibit the enzyme at the same time. Cool, right? Well, there's the preclinical evidence to show you why we think this works. This was done in monkeys. I didn't do it, but it was done in monkeys. Decitabine orally given at this low dose, the nontoxic dose, didn't do anything. We know have you to be in this range. You have to have that much floating around in your blood to actually do what you want it to do. This didn't do anything. We know history normal oral dose that's what you get, but guess what? You give this little itty bitty dose of E7727, you're already in range. So, we have six patients on this drug at Vanderbilt. We already have responses. It's a phase one trial, so it's a total pain in the butt. The patients have to come back all the time to have bloodwork and so forth, but after three months and we get all that blood work, they're free to go with five pills. So instead of coming in for five days in a row for shots, we give them their pills and say you look good, see you in a month. So, that's kind of the evolution of the therapy. It's not a home run. That's not a new kind of mechanism of action, but if you can get CR Vidaza or on Dacogen and I could give it to you in a pill, you don't have to come into the office. I'm speaking to patients and the families. Is that a bonus or not?

So, we're working very hard to get this passed… you got to go through hurdles. You got to get the safety stuff first. You got to make sure it's safe and then we got to see this really work as

good as we think it does in a systematic fashion and what it does then (inaudible 39:40) it gets approved and give it to you.

Q13: It's seven years?

Q14: So how many more years?

Dr. Michael Savona: That's shrinking. This is a little bit of diversion, but you asked and it's a good question. So during development it used to take 17 years from discovery to market. There's some people in this room that could probably do this better than me, but it used to be 17 years. Back in like 2010, there were a couple of drugs that were approved that were basically developed in 3 ½ years and now we're dealing with toxicities. So, the FDA said uh uh maybe we're doing this a little too fast. So, there's been a little bit of a… despite outcry from patients who want the drugs, it's been a little bit of a step back because there's been some toxicities because you go through that systemic approach too fast. I mean, I can see it both ways. Ponatinib is a drug that Dr. Mohan and I deal with all the time. It's the best drug for CML. It's the only drug that can treat people who have one mutation CML called T359. If you have the mutation and you don't have Ponatinib, you're in trouble. We had that drug and there was a press release 25 percent of patients on the trial had a vascular event. So, the FDA pulled the drug off the market and I had patients who were actively taking the drug who I couldn't give the drug to. Well, come on. It's a cost benefit analysis. If you're going to die from your leukemia, we'll take the risk of cardiac… We'll take the cardiac risk. Give the patient the… It turns out this all dose dependent. On the flip side of that is we should know more about this drug before we have it out there. It causes heart attacks and strokes in people who could do just as well on another (inaudible 41:27). So, that's the kind of plus/minus on that.

Alright. So, back to E7727. We have this trial open as (inaudible 41:36) Vanderbilt. We're the lead enroller. We're actually driving the genomic studies for this compounds development. So, we're kind of excited about this. Not as a new mechanism, but as a patient quality of life deal because if I can bring you Azacitidine and just give you pills and do that safely, to me that's a victory. Not a huge victory, but a small victory. Definitely an improvement in quality of life. Any questions?

On to Net 8. When we give lectures to scientists and other physicians, everyone's very interested in the mechanism and everyone's very interested in these pathways. This is what's known. This is what scientists have discovered. All I want you to concentrate on is there's another group of police. Now, these are the county police and instead of pulling off methyl groups, they ubiquitinate. They do other modification to the genome and by drugging up the pathway against Net 8, we can actually shut off ubiquitination. Well, this is a normal function. So, you don't want to shut off all ubiquitination and there's been some trouble with the development of this drug and this back to the speed of development question. This drug was working really well in acute myelogenous leukemia. People had no options. We're going up on the dose, we're going up on

the dose. We had people die from like a septic like syndrome. We stepped back and said, "Oh, wait a minute." That was at 180 milligrams. We went way back to 20 milligrams and at 20 and 30 milligrams we've basically been safe. We've had no troubles. This is a drug I've been developing with some colleagues around the country. You can see add this drug Azacitidine. This is AML now, but if you add this drug to Azacitidine in the red bar here, you actually get not just the best of Azacitidine, not the benefit of (inaudible 43:41) or LM494, but you get a synergistic benefit. It's more than adequate. It's actually synergistic. One plus one equals three. The purple line on the right is if you put tumors in animals, in mice, that purple line shows how the two drugs together work so much better than either of the drugs alone. See the purple one? So, that was enough to move forward for doing a study where we actually took patients who are over 60 who weren't eligible for the standard high dose chemotherapy that you had in the hospital. We gave them Azacitidine plus NLM494, (inaudible 44:17), and this is an AML study that has a lot of implications for MDS because this AML is like the AML that people get in the mature age category. It's molecularly more similar to MDS than AML that you see in a child, for example. This is an IV drug. It's given 1, 3 and 5. You're already in for AZ, just one more drug. Patient characteristics. We had some dose toxicities at 30 milligrams (inaudible 44:46). People had liver enzymes abnormalities. Because of the scare before it that high dose, we decided to just abandon that dose and go down. People did fairly well on this. There was quite a bit of… it says drug related. (inaudible 45:03) neutropenia. When you don't have any white cells, it's really tough to pin (inaudible 45:08) neutropenia on the (inaudible 45:10). You start here. This is normal and you start low and your drugs drive you down a little bit and we'll attribute those counts being low to the drug and that's how those toxicities get pinned on the drug and it is what it is, but here's the responses. We had half the patients go into a CR or a PR. So, complete remission or a partial remission where normalization of the blood counts and some of them are still in there and this is over a year and a half. So, this is kind of exciting and to that end, we're actually in the process of writing the study now… or finishing touches on the study now, bringing it to regulatory bodies to get a study approved and then open it at Vanderbilt sometime in the late spring. And this is for patients who haven't been treated with MDS for MDS yet.

So, this gets fairly detailed, but like I said before, there's the police that monitor the genome, the city police, there's the county police. This is like Internal Affairs. So, histone methyltransferase inhibitors are actually… Histone methyltransferase is actually a protein that decides how the DNA is going to make itself open for transcription. So, DNA is wrapped up in these little balls like pearls on a string kind of like this bottom down here in order to save size. DNA is billions of base pairs long, but inside your cells it's wrapped up around these little balls called histones and when it's wrapped up real tight, no genes can be made, but what it does it unravels and rolls up, it unravels and rolls up. There are proteins. I mean, Francis Collins who's the director of the National Geno Project once said in a lecture and he's an intelligent design guy and he's kind of very philosophical about this and he once said to a small group of us and I was a student or a fellow and I said, "If you don't believe after this…" It's so incredible how you couldn't be a believer. That's his thing, but then anyway the histones are all wrapped up DNA and these Internal Affairs cops come around and they open up... they control the opening up of the

chromatin for the other police to decide to turn on gene transcription or not. At this locus, there's… this is just an example, but there's a variety of different proteins that are all essential for transcription to happen and there are now drugs that target all different parts of the protein complex and it turns out in the lab if you block that one protein, you shut the whole thing down. So, I'm showing you this not because it's a promise or a home run it's very alluring from the standpoint of what we can learn in this area. So, I (inaudible 48:49) the development of this drug called 5676 with some people around the country and this a .1L inhibitor. So, it blocks that one of those proteins in that complex. It's very specific for just that protein. So, there's no off target to this. You give the drug. It's not like it cause you to turn blue or you to grown another horn or something. There's nothing else it does. It just affects that one molecule and we enrolled a ton of patients and nobody had any toxicities but we didn't have a lot of response which was very disheartening because we thought oh, we had a great target here and we're still trying to figure out why it didn't work, but in a couple patients it worked really well. This is a lady who had CMML which is an MDS type kind of disease that transformed into acute myelogenous leukemia and she had leukemia cutis which showed up at these bumps. It's all gone. It all went away with the drug. It's the only thing we (inaudible 49:44). No toxicities. It's amazing and I'm so thankful to you because it's amazing what people go through. She had to carry this fanny pack for 21 days with her port because the drug is a continuous infusion for 21 days and she did that for months, but her disease was (inaudible 50:00), her skin lesions went away. She's a beautiful woman. She was very conscious of these things and they all went away. So, it didn't cure her disease, but it took a disease that had a median survival of three months, multi-relapsed AML. A year later she's still alive. We're onto something. So, I'm showing you this because we're in the process of developing a variety of different agents that target this whole complex related to that internal affair cop and we think that there's some there there and then it specifically targets proteins which shouldn't be in action and it doesn't have any off target effects. This molecule, this (inaudible 50:46) we have antibody that beats that (inaudible 50:48) and it's opening April 1. I think the (inaudible 50:51) slide set.

Also in that complex is another molecule DRB4 controls… this one's a little more ubiquitous it's not just involved in cancer. It's involved in normal function, but there's a series of bet inhibitors or bromodomain inhibitors that are coming out and we're actually participating in a phase one first in human study for this bromodomain inhibitor 54329.

So remember I told you before I don't really care about one pharma company or another because I just want to pursue for my patients. I will disclose this is one I have stock in and I'm on the board. So, I do have an interest in the success of this company. I'd like to think that I'm without conflict, but because I have this interest I don't participate in any of the clinical trials because that would be an obvious conflict, but I do want to tell you about the science because I think it also express some of the themes I've been talking about and kind of branching out and now that we have the capacity and technology to do some of these things, we're exploring all these new mechanisms that we didn't (inaudible 51:50). So, SINE or selective inhibition nuclear export is very interesting. So, when proteins are in the nucleus that's when it's active. When they're out of

the nucleus that's when you turn them off and there's these shuttle busses taking them in and out of the nucleus and it turns out that the ones that are very important for cancer are all on the same bus line. They're all on the green line. So, they all get on the same bus line. It's called XP01 and in cancer guess what? What do you thank happens to XP01? There's a ton of it. Because cancer (inaudible) wants to get those tumor suppressors out of the nucleus. Tumor suppressors are here shutting down cancer. Cancer says I don't want tumor suppressors suppressing me. I want to get the tumor suppressors out. So, XP01 is revving up and there's extra shuttle rockets like there's an SEC tournament down town. Just shuttle everybody all those Kentucky fans out of there. So, this drug actually blocks… I mean, it's ingenious how people figure this stuff out. So, this drug actually fits in there and blocks the shuttle bus. It boots up all those shuttle buses. So, all those Kentucky fans can do all their good will down (inaudible 35:04). Spend money for our (inaudible 53:08) space. The point is that it's very interesting and it's intelligent design, but that shuttle bus is responsible for all of the tumor suppressor movement out of the nucleus. So, all those tumor suppressors sit on that same bus. So, people off the bus and they stay in the nucleus, there's some there there. Here's some mice. The vehicle is just mouse got injected with tumor. This is just leukemia, but it's in bone marrow mice and guess what happens. They end up dying from overwhelming amounts of leukemia. This is the science we do. I know it's not exactly the… I wish we didn't have to do this, but this is how we make things safe for patients and figure things out. I'm showing these slides because I want you to be in touch with at least part of the process.

This is the first drug which was inhibiting sign, but this is the drug that now have for people and when it's given for 15 days, no sign of the leukemia at all and when you stop the drug, you have to wait a week or two before you see anything about leukemia in the mouse. It's interesting. There's a variety of preclinical experiments and if you just kind of take a quick view at this that the bottom line is that not just hematologic cancers, but throughout cancer this blocking of that shuttle bus leads to improvement preclinically. So, this drug is being developed in a variety of different tumors, hematologic tumors like MDS and AML and myeloma, lymphoma and also in solid tumors.

And I want to just show you a picture because I think for people with cancer and people who know people with cancer this is the most valuable thing to see. Well, what did it actually do for the patient? How are they living? This is what happens this patient's tumor burn. This is a person who had a stem cell transplant, six different therapies, a year after starting treatment with no toxicity. The patient now has a complete remission. It's all… you can't see anything, but at the time of the slide, 93 percent reduction. Not everybody, but we need to figure out why this person responds so great and some patients don't respond, but at least we have the response. Just like the (inaudible 55:25) we can really study those people who respond and say what's different about that person and how can we make these other people who didn't respond more like them? (Inaudible 55:32)

This is lymphoma, but I'm making a point. In AML, good blast reduction. Again, why didn't it work in these people? No idea. I don't know what happened here and I want to replicate this. So,

we take a drug like this and we mix it with other drugs. We do genetic studies on the patient's cells that didn't do so well and genetic studies on the patient's cells who did really well and we compare them. We have a study now that Dr. Strickland, Dr. Mohan and I's partner who's not here is running at Vanderbilt. Again, I don't participate in that study.

So just to kind of tie this all together and this is kind of a segue of why people respond and why people don't respond and what we're starting to learn about inflammation and what's out there in cancer development and inflammation and the immune system and immuno-oncology and this whole new developing field. I don't know if you've read any of this or know anybody with melanoma or bladder cancer or seen the press, but there is a lot of excitement right now with manipulation of the immune system and tumors and MDS is like… MDS is the poster child and we're participating, I'm very excited about this, in new drug development that alters the immune milieu, if you will, in the bone marrow. You have to remember it's not just the clone and the red cells and the white cells and the neutrophils, the red cells and the platelets, but it's also a variety of different antibodies which I call Special Ops, your neutrophils fight infections. Your antibodies and your T-cells they're part of an immune system that's kind of special. Some of those immune cells, some of those T-cells, they're involved in seeking and destroying. As soon as they see something that they shouldn't see, they kill it. Some of those T-cells, they're involved with immune tolerance. So, they see an antigen and they interact with the antigen and they tolerate it and they kind of… it learns to be there and actually that's a very part important part of stem cell transplant. This is the basis of graft versus host disease where effector T-cell or the T-cells that are those destroying T-cells grow beyond regular T-cells which is the tolerance ones. So this is a very complicated analogy, but in short just think of T-cells being a 'gamish' of lots of different immune cells that regulate (inaudible 58:12).

It turns out that in MDS this is a very inflammatory state. This is an angry, angry state in the bone marrow. Interesting. Do you feel inflamed? You are in your bone marrow. If you have MDS, your bone marrow is inflamed and we have to figure out how we can change that synthesizer of different T-cells so that we adjust the amounts of those T-cells. This influence how those different T-cells are made to promote normal hematopoiesis. Let me say that a different way. When you have MDS, there's so much inflammation there and there's not bad T-cells, but there are T-cells that are behaving badly. It's like I tell my children, "You're not a bad kid. What you did is bad." So, the T-cells are your own, but they're behaving badly. They're encouraging the clone and what happens is if you have a mutation, that mutation sends a signal to make that T-cell behave badly. That tumor cell made that T-cell behave badly. That T-cell goes in there and inflames. It makes the tumor cell stronger. The tumor cell sends more signal, more T-cells come and they get more and more inflamed. It's a cycle. So, we have to kind of break that cycle. So, part of the strategy in treating MDS in 2015 – 2016 is actually lumping and adjusting the T-cell repertoire within the bone marrow with drugs. Everybody kind of grasp that at least? It's getting my son away from that poor influence. So, we have a variety of trials ongoing and this is the first part of like immuno-oncology I wanted to share with you that's kind of on the cusp with MDS.

The second part is completely the opposite and paradoxical. So, this is the hottest thing in lung cancer and melanoma and bladder cancer and renal cancer and maybe breast? What did I miss? Pancreas cancer. I mean, since the development of chemotherapy. This is an amazing development. Merck, Bristol Meyers Squibb, Genentech are battling right now, the three front runners for what they call a $20 billion market. It's disgusting, but this free market is what drives development. So, we have to kind of find a way to tolerate this. Speaking of tolerance.

So what happens when tumor cells and T-cells interact is that there's a series of handshakes and what you could see here this is a tumor cell and this is the MAC complex that is kind of matching up with the TCR, gene complex, and there's a variety of these other, B71, P01, PD-1, PD-L1. These things all have to come together and when those things come together and the T-cell and the antigen this T-cell kind of promotes a tolerance. What happened in tumor cells? Again, brilliantly devious. The tumor cells make more of these kind of… these antigens that they know the T-cells will accept. It's subterfuge, propaganda. So, they're putting out these PD-L1s so that the T-cells will say, "Oh, that's okay. That's one of us." Cancer cells trying to say, "Hey, it's just me." It's just Michael. This isn't a foreign thing. You don't have to destroy me. I mean, isn't it just deviously brilliant or brilliant and devious and what these drugs do is actually block their antibodies to PD-L1 and again, so simple and such… It seems like a sledgehammer as far as specificity, but it works fabulously. There's spider pots that kind of show how people respond. Some people don't respond at all. Their tumor grows. Some people, their tumor doesn't grow and they stay like that forever, but here's the amazing thing on that spider pot. Some people get response and it stays there for years. So, we've got people who are treated for a year or three years out with lung cancer. Metastatic stage four lung cancer now have no disease. Why? Why do those people have that response and this guy not have that response? That's the question. So, the second part of this kind of inflammation and immuno-oncology discussion is not how we turn T-cells off, but how we should turn them on. This is why I didn't become an immunologist. It just made my head hurt.

Q15: You're not the only one.

Dr. Michael Savona: Sanjay and I are very interested in trying to exploit this understanding in solid tumors in MDS. We don't know how to do that yet. MDS is tricky. MDS is so tricky in the lab, we don't even have a model to study MDS in mice because MDS doesn't grow like leukemia. If you grow an aggressive MDS in mice, it turns into leukemia. They're related, but they're not really the same thing, but we're really trying hard to find the best model to study MDS, but guess what? You're the best model. There is no mouse model. There is no cell line for MDS. If you take your cells when you have MDS and I take them and put them in a dish, they don't grow. I can give them growth factor and make them grow and guess what and turn them into leukemia. It's a challenge, but I like a challenge.

So, just a kind of summary of the studies that we have. You can write these down. You can E-mail me. I can send you the slide. I can talk to you about these studies in more detail. This is what we're looking in MDS and AML and Dr. Mohan, Dr. Strickland and I run these studies and Vanderbilt. He's the one that I talked about for the most part. This is what's coming and this is really exciting. These are all coming in the next three to six months. This is a study of Panobinostat. I did talk about this. This is the JAK1 inhibitor manipulating those T-cells. This is BRD inhibitor manipulating T-cells again. This is AZD1775 which is a WEE1 inhibitor. Don't ask me to describe the mechanism. (Inaudible 10:04:54) is one of those police force that I was talking about. This is study with ABT-1999 and ABT-199 blocks BCL-2 which is part of the apoptosis pathway. So, patients who have tumors, the apoptosis is program cell death. So, they never die. They want to keep living in that tumor. So, ABT-199 helps them die.

So, we're very excited about what we're doing, but since I've come to Vanderbilt, my main focus has been trying to find a nice portfolio that suits the needs of our patients but not so big. Just big enough that we can actually take these compounds into the laboratory and really understand mechanistically what we're doing. It's fine (inaudible 1:05:41) for a lot of studies. It's much better to offer studies that we understand that we think have a chance of working. The old paradigm for phase one studies when I first started in this job, in this business, was this is where you go when you have nothing left and you want to leave a legacy. Kind of hard for a physician and harder for patients. I don't think this is going to work for you. It may help somebody else. Here's what's happening. The science has gotten so good that people come to phase one studies now and we have a precedent of singles, doubles, triples… my baseball hat. Singles, doubles, triples and home runs. We've had homerun. We've had this drug in (inaudible 1:06:23) while I was in training before entered this career. That drug is completely changed the landscape of the life people with CML. That's a homerun. We've had Azacitidine was kind of a single double with MDS. We haven't had a homerun yet. I want to be involved in a home run. So, I think early drug development is not what it used to be. I think the stakes are higher. I think the expectations of patients are higher. So, I would encourage you to have a thoughtful conversation about new drug therapy. In a way this is different than I would have encouraged your or I would have advised you 10 years ago when I thought that these things might not have much chance at all helping you. I think everything on this list we've selected because we think it has a chance of helping people not just a legacy.

Q16: So, does the local hematologist just call you or does the patient call you?

Dr. Michael Savona: So, you're welcome to do whatever you want. So, you can… it depends where people live. So if you live close by, we can see you as your primary hematologist. We can see you as a consulting hematologist. If you live in Jackson or you live in Murphy's Borough then… or Knoxville and a lot of our patients do then it's a conversation and we have excellent relationships with Kirkland Medical Center in Jackson and with Tennova Group in Knoxville and we work with those physicians and we advise and we respectfully agree or disagree and the patients can take all that information. I tell patients I'm just like… you're the boss and it's like I

go to my accountant. My accountant says, "Hey don't put your money there." I don't say, "No, I'll do whatever the hell I want." He's the accountant. He tells you what to do and ultimately I follow it but I'm the one who has to make the decision and it's just like any other professional advice you get. I try to advise you the best you can so you can make the best decision for yourself and quality of life is so important. You have to have that as part of your process. So, when Dr. Mohan and I talk to people, it's not just like, "Hey, this is a good study. You should come on this." This is a study that requires you to drive three hours from home three days a week. I think the chance of helping you is high enough you should do it or I think it's kind of a wash how much of an inconvenience or a hardship is it for you to drive? We've got patients who have to take an extra job to pay for gas money to come in. So, that's a different thing.

So, I'm just going to end and have time for questions. I can't thank you enough for your interest in this. It's very fulfilling to see so many faces, familiar faces in here and very gratifying to have this part of our job. I do this several times a year in different types of venues, so I love interacting with patients. Everything we do whether it's with mice, monkeys or petri dishes it's all to help you and please continue to be patient with us. We're trying the best we can. It's a challenge of gargantuan proportions.

I wanted to thank the research team at Vanderbilt we've really worked with and the myelo working group which is a group that I started at Vanderbilt. It meets weekly and includes clinicians, scientists, hematopathologists. Dr. Mohan, Dr. Strickland and I are the clinical leaders of that group and then we have a wonderful division. Of course, Tracy has been a friend and colleague at the MDS Foundation. You can't have enough friends in New Jersey, so that's a good thing. So, the MDS Foundation has been really a wonderful group and I encourage you kind of interact with them and take the material they've given you. These people are really heartfelt and dedicated to helping people in your position and, frankly, they're 40,- to 60,00 new cases of MDS a year. That's a lot more than a lot of solid tumor cancers that have a lot more attention. So, this is a group that's about you. Very unique.

I just want to kind of focus on a few questions and then take some open questions if that's okay time wise and what not. I am kind of running low on time, but these are some questions or rewording, my rewording of some of your questions when you came in.

Right now the standard of care is stem cell transplant for people who are eligible for stem cell transplant for people who have disease that's Intermediate 1 or higher on the IPSS. So basically, if you have high blasts or if you have cytopenias that really are effecting your quality of life or if (inaudible 1:10:55) and not getting the benefit that we expect you to get stem cell transplant is potential curative option. Stem cell transplant comes with baggage. Stem cell transplant is curative to some people, but we don't know which are going to cure up front and we know that it comes… We're transplanting someone else's immune system into you and we know that comes a (inaudible 1:11:21) of immortality. (Inaudible 1:11:23) has the lowest treatment related fatality in the United States, 10 – 15 percent. We're very proud of that. The lowest treatment related

mortality in the United States, 10 – 15 percent. So, that's still 10 – 15 percent of patients who in one year are not alive because of the transplant, but across the country the median is like 25 to 35 percent. So, some places are losing a third of their patients to their treatment. So, feel very good about the job that we're doing with the transplant, but we still are having relapses because the science is evolving.

Transplant and drug therapy are kind of a crash course where transplant's changing and the therapy's getting better and transplant is getting smarter and these things may not emerge and we didn't talk at all about our T-cells, but engineering of the immune system is kind of what transplant does in a very kind of forced way. We put someone else's immune system in you and give you drugs so that you tolerate this, but imagine if we could take your own immune system and just fix it and give it back to you and that's what a lot of the science is driving now. That's the (inaudible 1:12:29).

So people had asked about when you're candidates for stem cell transplant. There's no hard and fast rule. At Vanderbilt, we don't typically transplant people over 70 because we know that that transplant with mortality starts to go up. It's not because we're (inaudible 1:12:50). I'm a non(inaudible) . I take care of a disease of a mature age group. So, by definition I'm a non (inaudible), but I don't want to hurt people. I really don't want to subject people to something I think they can't tolerate and it's going to lead to a quicker death. Young people, kind of the (inaudible 1:13:08) choice, the paradox is always do I take the transplant when you're as well as possible or do I stretch out as much time as I can with you on Azacitidine so you can avoid whatever risk transplant there are and still be benefited and I run the risk of losing a response and part of transplant life. That's the balance. Some of you have been in that shoes where you kind of seen that time come and go. No right answer. You just do the best you can to be knowledgeable, find a good physician you can partner with and make the decision. Remember the decision you make is always the right decision. You can't second guess in this business. The stakes are too high. You may find somebody you have a good relationship with. You get the knowledge you need and the decision you make is the right decision. Whatever happens is the right decision because you can't go back.

Many stem cell transplants or reduced intensity transplants all of our MDS transplants with very few exceptions are reduced intensive and that helps our transplant (inaudible 1:14:11) mortality number to stay lower and that just means we give different drugs to prepare your bone marrow from taking someone else's immune system. I've done reduced intensity transplants people at 75 years of age. It has to be a real super star. Once in a while somebody will come in and they're 72, 73, 74 years old and they're running marathons and you say okay 75 (inaudible 1:14:34) if you really want to be aggressive we can pursue this for you. Sometimes people come in at 62 and they've already had a heart attack and they have heart failure and I can tell them they don't have… If we take them transplant there's an 80 percent you don't survive. I'm not going to offer this.

I just want to address this. I realize the sibling is the perfect way to give to go. It's not entirely true. This is an area of great debate, but siblings match at all of the HLA major (inaudible 1:15:09) compatibility antigens. So siblings match… If you're a sibling match, you match at all those antigens, but you also match at like the minor (inaudible 1:15:20). So, the chance that your immune system rejects a matched sibling, very low. The chance that your immune system from your sibling rejects you is lower than if it's nonrelated, but the chance that your sibling recognizes your tumor as foreign isn't as good as somebody else's. So, if you look at survival curves, unrelated matched donors, so if you got a 10 out of 10 lumberjack from British Columbia or Lakers from Miami is your donor, whoever they are, I always have fun with that. If your donor is 10 out of 10 match and they match at all those major (inaudible 1:15:57), but they mismatch at minor, you may get more of GVHD but you probably have a better chance of disease not coming back.

Q17: What's GVHD?

Dr. Michael Savona: GVHD. Graft versus host disease. So, that's where transplant (inaudible 1:16:10) mortality kind of comes in when we're talking about transplant. Graft versus host disease is when the graft or the donor's immune system recognizes your tumor as foreign, but unfortunately recognizes you as foreign because remember you and your tumor are kind of all tied together. The tumor is you've gone bad and when I say your tumor a lot of people say I thought I had MDS. What I mean is your disease. So because your disease is you've gone bad, sometimes someone else's immune system just recognizes your disease… you've gone badly and also you and it's usually skin, liver, gut. It can be lungs and lung GVHD is tough. It's a very tough thing. We hate when this happens, but it does happen in some patients and it's doubly difficult because the drug that we use to kind of keep GVHD down, immunosuppressive drugs then puts you at risk for infection. So and that's where more of the transplant rate of mortality and morbidity comes in.

So, that's a little spiel on transplant. Maybe I can just end with that and if there's any questions I'd be happy to take them about transplant or about the drugs that we're developing or anything about MDS or there's something you think I can help you with or Dr. Mohan can help you with, we'd be more than happy to assist.

Q18: When you say that if they don't match because of the donor you don't know and you're going to have different complications and problems? Do you overcome that eventually or do you stay really sick?

Dr. Michael Savona: Well, you want to answer that?

Q19: You overcome it, but there's (inaudible 1:17:48) from it. It's like I'm cured from my MDS went into AML and I'm cured from that, but I (inaudible 1:17:59) in July, but now I have the complications from… I have the GVH which is the complications from the transplant and it was

recently doing good, but it attacked my lungs over a year ago and even though you're clear of cancer, but the side effects of the transplant kind of (inaudible 1:18:33) those two because it's we kick the cancer, but we can't kick the side effects.

Dr. Michael Savona: Thank you for sharing. (Inaudible 1:18:44) more powerful and more useful than anything I can tell you. We arrange and we enter this kind of deal we say we put (inaudible 1:18:54) but we can't take it out. We don't know. In some people the disease comes back and they have GVHD. That's a nightmare and happens in a small amount of people. Some people they get no GVHD and they're cured. I wish there were more of those, but most people they have some response either a complete remission or partial remission, but they have some GVHD. I don't want to see a little bit of GVHD. Do you know why? Because it shows me that the immune system, that donor immune system is working. It's doing something. It shows me that it's attacking something and it's the tumor itself, but I like to keep that in control and the problem is when it gets away from you it's very difficult. I tell patients it's like driving a boat in the wind. There's no stop button. It's very hard to get the set point.

Q19: Let me tell you, too, not everybody that has the graft versus host gets to (inaudible 1:19:47) minor and I have had some minor issues with this GVH, but there's everybody's case is different. So, that's one of the main… That (inaudible 1:20:00) is you can't look at one person and compare it. You can only… like he said was, (inaudible 1:20:08) only God knows what our future holds because I was told last year when it attacked, the graft versus host, my lungs I was given a year, February of last year it was the lung was going to get me and I'm still here. So, it hasn't got me yet. I may walk out of here today and be gone, but there's still hope.

(Applause)

Q20: Is there an age limit on donors?

Dr. Michael Savona: We don't want old marrow. (Laughing) I mean, this is part of the decision tree. So, if somebody… if it's the only matched donor is the 71 year old brother, I'll take it, but boy if I have an unrelated donor that was 22, those are fresh stem cells. This is where (inaudible 1:21:17). I prefer to give my patients that younger donor and because we find that sometimes that (inaudible 1:21:29) replace is (inaudible). There's not a hard and fast number. We have kind of standards of practice and we make exceptions to them all the time under the right circumstances.

Q21: Because on Be the Match, I think it's 40 something they didn't accept you after a certain age.

Dr. Michael Savona: Who said that?

Q21: On Be the Match.

Q22: I think it's 44.

Dr. Michael Savona: That's obviously not true. So, I think they're trying to do is trying to get more young people to donate, but maybe I'm (inaudible 1:22:10) their head the wrong way, but I think if the donor is 55 or 60 and that's the donor you have, that's the donor you have. What we're working on and I not personally, but we as a community are working on is alternative to donor transplants, haplo transplants and cord blood. Does everybody know what a haplo transplant is? So, a haplo transplant is when this is so everyone has a donor. So, the patient has no matched siblings, but their son or daughter or their parents who, if they're all blood relatives, are going to be half matched. Then you half match someone and you manipulate the donor source or you give the patient special chemo, so that he can tolerate those mismatches. They work because remember not only 5 out of the 10 major HLA complex will match, but you got all the minors will match. All the minors… but we don't check will match more if they only match (inaudible 1:23:07).

Q23: I have a (inaudible 1:23:09) people would use their own stem cells when they (inaudible 1;23:16). Could you go into that?

Dr. Michael Savona: I tried to avoid it, but I knew somebody would ask. She's asking about some using your own immune system and I alluded to briefly our T-cells. So (inaudible 1:23:33) is one of my heroes, from the University of Pennsylvania. He spent his whole career on trying to find ways to manipulate the immune system to fight this and over the past few years they cured some people, some kids, with refractory ALL. They cured them by taking their, the patient's T-cells and then reengineering these Frankenstein T-cells so that they have… the T-cells have antibody (inaudible 1:24:04). So, in ALL that antigen, CD19 that's just all T-cells that antigen. So what they do is they take the T-cells. They take them out of the body. They transfect the gene that makes CD19 so it grows, a CD19 antibody, so it grows in the T-cells. So, all the T-cells now go in like a heat seeking missile right with CD19. Well, half of those patients have no antibodies, but it cure the leukemia. Well, that's a low hanging fruit because there's an antigen on ALL that we can make an antibody that doesn't hurt you otherwise. Here's the problem in MDS. What's the antigen that they have? There is no antigen. We don't know what it is. The antigen that sits on MDS cells like CD33, well that's one that also sits on the neutrophil. So, what happens if you have a T-cell that lives in your body forever and now has an antibody CD33? It means you energy is going to be zero for the rest of your life. So, that's not so easy in MDS, but it's cool that they've done this and you can see how the science is moving towards developing T-cell, Frankenstein T-cells as you wish, for these other diseases and they're looking at this… and there's three companies – Juno is the combination that came out of… that is the company that works with MSK or Morrison Kettering Group did this. A guy I went to college with actually, his science and his post doc (inaudible 1:25:33) at Vanderbilt. Another group NIH, Steven Rosenberg been working on the immune system in renal cell cancer for 30 years. He formed a company called Kite Pharma and then the third is at Carl June's group out of UPenn paired with

Novartis which is a big pharmaceutical company. So, there's my stock tips for the day, but this is a big deal if you could imagine. Imagine treating one patient, taking your cells, taking them… putting them… getting all your T-cells, transfecting all those T-cells in a vat and then flying them back across the country. That's a process. So, imagine doing that for 1,000 patients. So, the facilities actually grow this up and to do this properly it's a big deal. It can't be done in the university. It's a pharma-university kind of partnership. So, that's why those companies were formed. So, that's, I think, an answer to your question.

Q24: So if you got MDS how can you use your own bone marrow?

Dr. Michael Savona: You can't. Not yet. Your bone marrow is broken. You don't want it, but there will be a way in the future, I hope, of taking T-cells and having them attack the bone marrow in a way to shut off all the nonsense that's happening, but we can find these unique antigen that sits on MDS that doesn't get on normal cells, we're going to go after that sucker and that's where we're going.

Q25: In your experience, how long does the drugs like Vidaza last in average patients?

Dr. Michael Savona: That's the million dollar question.

Q25: And the second question to your answer would be what do you do when it quits working?

Dr. Michael Savona: Can we talk about you since you're asking about you?

Q25: Yeah.

Dr. Michael Savona: So, you're probably the youngest guy with MDS in here, so let's talk about you. So, if it's working and it's working well, ride that horse.

Q25: Well, how long does the horse going to stay alive?

Dr. Michael Savona: I don't know. I mean, if that horse is to die in a year. You have horses that live for 10 years. I have patients (inaudible 1:27:44) and the longer you go and the more I say… I always tell people about General Hill. General Hill comes from military history and General Hill is one of my patients. General is a four star general and he was actually Jimmy's… "It's a Wonderful Life," Jimmy Stewart. It was Jimmy Stewart's copilot in World War II and Dr. Hill… or General Hill had MDS, a bad MDS, and I treated him in complete remission and his biggest complaint was coming into the "damn doctor's office. I got to play cards" all weekend long he wanted to play and he was in complete remission for three years and get this – he goes into… like he loses the response. He has a ton of blasts. He goes into AML. He's 82. I'm not going to give chemotherapy. He needed Decitabine and make… and not do anything, the kissing cousin of Azacitidine, he goes into complete remission again. He goes into remission for another year.

So, that's a super response. I've had patients that were on the drug for eight years. I've inherited some people that have been on for 10 – rare. Usually, we get people and depending on how bad the disease is to start off, usually get a response for a year or two. I would predict… I think the risk for you, you're a young man. So, I think the situation for you is it's a race between the science coming along and your need to go to stem cell transplant because the standard of care is when you start to have anything, loss of your response, first jump on that and to take the stem cell transplant, but if the standard of care and this is kind of an emerging new therapy, merged and can spare you that transplant of immortality risk because we don't know. We don't know if you're going to be one of these people who go through transplant and have complete remission and (inaudible 1:29:36) come and be a patient advocate and be the poster child or we don't know if you're going to end do fine and five years later end up on oxygen because you have lung GVHD. So, I think that the thing you need to be thinking about is just… Call your doctor and tell your doctor… Is he (inaudible 1:29:53).

Q25: I'm local.

Dr. Michael Savona: Who's your doctor?

Q25: Flynn.

Dr. Michael Savona: Oh, (inaudible 1:29:59). He knows kind of… He's a lymphoma specialist, but he knows what's happening in MDS. So, hold him to it. What's new? What's the status of our T-cells? What's appropriate for me? What's the status for T-cell manipulation? What's happening with science so that I may be able to get on that horse or I might have to jump on the transplant? That's your challenge. Everybody's got their (inaudible) because you're young, you're 63 and you have years before you need to go to transplant or not, but you're still eligible. Somebody else may be beyond the point where we transplant.

Q26: Are there circumstances where one could extend the interval between Vidaza treatment?

Dr. Michael Savona: Yes.

Q26: It's a selfish question because I'm particularly interested in the quality of survival is based on travel, overseas travel.

Dr. Michael Savona: So (inaudible 1:30:56) time. So, I have a patient who's also a physician who performed (inaudible 1:31:04) surgeries and he's fairly demanding and he insists to put off therapy and his neutrophils are low (inaudible 1:31:15), but before that he would say on huge point he's (inaudible) boundaries (inaudible) drop this guy off and he had no neutrophil. I'm like okay. He said, "Just give me my antibiotics and if I get sick I'll take them and I'll radio (inaudible 1:31:32)." So, we work with people all the time and, again, and I'm taking some of Denise's time, so we're going to shift into Denise. She'll talk to you more about this, but the

decisions we make treatment wise are always balancing or should always balance quality of life and this why this oral Decitabine, Vidaza I've been telling you about this is why this is kind of important when you develop here. A guy like you, it would be great if I could send you to (inaudible 1:32:00) with your five pills of A7727 or Decitabine and just make sure you have (inaudible 1:32:06) before you're going. Not (inaudible) that week to give you your shots. I think there are people who I say based on the trajectory of your counts and what happens when you're (inaudible), I think you should stay on 28 days or I think you should stay on a 42 day… but there are people that say, let's… and we have to be flexible. So, push your doctor whoever that is to consider that. I'm very adamant that the best (inaudible 1:32:35) is stage one through five and days eight and nine. So, either seven days in a row… this is Azacitidine now. Seven days in a row or skip a weekend and then Monday-Tuesday. I think that's a much better regiment that days one through five and there's evidence to prove that. For convenience, a lot of people just want to do Monday through Friday, but it's not as good. If you go on that regimen though I think you can stretch out the intervals. I don't think there's any harm and I think people actually have another nice week of benefit toward the end before their next cycle of therapy.

Q26: So, the seven day treatment is usually how long in between?

Dr. Michael Savona: Well, for Azacitidine anywhere from… God, I had one that was like 60 days once. I mean, we have people… We just play it by ear and we say the counts look like we can… and look in the marrow and the marrow is okay. It looks like you can wait another four weeks and then you just get in a system where you say okay this is a 42 day guy. This is a (inaudible 1:33:30). This is a 34 day guy. This is a 28 day guy. Decitabine is a little different. Decitabine is IV and that drug tends to have deeper and longer cytopenias. So, that drug can stretch out and that might be a consideration. Which ones you already take?

Q26: Vidaza, Azacitidine.

Dr. Michael Savona: Azacitidine is nice and you can go in the office and get your shots and you're out of there. Decitabine is IV. It's an hour and a half for those five days in a row, but it's only five days and in some cases… in some patients who are more elderly, I only give two or three days and we can stretch that interval to 40 – 50 – 60 days. This is the thing about and I'm a little bit biased because my area of fear… I mean, general oncology has got us up on end – breast cancer, anemia, but we study MDS (inaudible 1:34:20) neoplasm. This is our area. So, I think that that's the value that we add that you can say… we can fine tune those nuances and I think that's a value to patients who especially like you are traveling around and really can't be… get a benefit for not coming in monthly.

Q27: That is Vidaza and you can have it here versus Cincinnati versus Timbuktu. No?

Q26: Well, that's another question.

Dr. Michael Savona: You can have a Guinness at the bar on the street or in Dublin. I think it is different.

Q27: Oh, it is.

Dr. Michael Savona: The drug the same, but how you manage the nuances of the care are different.

Q26: You extend that. I want to get my Vidaza treatment this coming summer overseas.

Dr. Michael Savona: Boy.

Q26: How feasible would that be?

Dr. Michael Savona: You better talk to your insurer.

Q26: That will be the next question

Dr. Michael Savona: I think some of the best MDS docs and clinics are in Europe and it seems feasible. I've never had anyone ask me that question. I just don't know how prepared you go for that. Insurance is maybe a $5,000 a run. So, it's not insignificant, but if you're going to France or Italy, just E-mail me and I'll tell you who to go to.

Q26: I've already contacted the hematologists that's in the manual of the Center of Excellence. We have a residence in Switzerland. So obviously, I'm very interested in getting back there.

Dr. Michael Savona: So, people who are kind of back and forth across the pond I think this is less of an issue. I think for people who kind of go once, if you can establish a relationship with a guy there or gal there, but if you have a doc, great. If you need somebody let me know and I know a ton of people over there.

Q28: You're talking about stretching out intervals of the chemo to maybe longer instead of the first week of the month. What constitutes being eligible for that?

Dr. Michael Savona: So, I think like when you go get professional advice and you make a decision. So, you come to me and I'll take and I'll fly out all your hemoglobins (inaudible 1:36:43), but I'll get a printout of what happens with your hemoglobins and I'll look at this and I'll project and I'll say, "Boy, based on your disease and based on what happened with your hemoglobin, I think you really need to be treated here," or I'll say we can do this and we're used to kind of adjusting this for people based on their quality of life requests.

Q28: Because I've asked my doctor. I would have did this a few months. So, he keeps saying no.

Dr. Michael Savona: Local?

Q28: I have two oncologists, Dr. Reddy here and Dr. Young in Franklin.

Dr. Michael Savona: Okay. Good. So, I think that you can certainly keep asking those kind of… our responsibility is keep listing to these requests. At some point, Dr. Reddy is going to say okay she really wants to stretch this out. What's the potential harm and good of doing that in this situation? Everybody's situation is a little different. One more question and I get off the stage here.

Q29: My dad passed away last March and he it just happened so fast. He was always healthy until very last, I think it was… He only complained 25 days. So, it was no symptom except one day he said, "I am so exhausted," then they sent him to a hospital and they checked the blood test. You got MDS. So, he lives in China. This never come across our mind anyway. So, I'm thinking because of that do I need to pay attention to anything? Am I getting…?

Dr. Michael Savona: I'm very sorry for your loss. That's traumatic. It's always hard to lose a parent. It's traumatic in that fashion especially being 68,000 miles away. There are kindreds for MDS. There are familial inherited risks. Those are the vast majority very rare circumstance. Most of the time, this is sporadic. I mean, it just happens. Exposures in China may have been something you were exposed to as a child that he was exposed to. Maybe it had nothing to do… maybe your exposures are completely different (inaudible 1:39:14) and so forth. I think that it's much less likely that you have a related MDS type syndrome. Much more likely that this was his bone marrow breaking… whatever series of exposures he had. So, I wouldn't live your life any differently than just to say do your normal upbringing. Now if you told me, well, my sister had breast cancer and my brother has leukemia and my uncle… I mean, that's different. If you describe… I mean if you have a family history that's otherwise doesn't really matter (inaudible 1:39:48) one case. I would not be worried of that particular…

Q29: (inaudible 1:39:56) after he passed away kind of our families getting together for the funeral and the one thing my second cousin had said so basically, my dad's oldest sister die of similar symptom, but good to know if a medical situation.

Dr. Michael Savona: Yeah. It's time and place and so then the next question… So, I would (inaudible 1:40:27) the story but I don't know how in your situation, but I'll tell you a story that may help place it. So, I had a woman come from Colorado to see me and she had lymphoma, (inaudible 1:40:40) had MDS, her sister had MDS, her uncle had AML. It was a nasty kindred and I'm thinking Okay, I got to send her over to familial genetic counselor to see if it's something that's inherited and then she said, "Oh, yeah. He lived four miles from a uranium mining facility," and it turns out the cancer rates in that little community are like through the roof and that's awful and believe me I see… we're in a… I mean, there's no mine, but there's other

environmental risk here. So, I see people from an area and I'm not going to mention because I don't want to get into that here. I'm not an epidemiologist, but boy I know there's only 10,000 people that live in that town and I've seen 25 AMLs from there. Well if it's 1 in 10,000 people get the disease, that's a very high rate of AML in that town. I mean, I'm no statistician but that doesn't bode well. So, you wonder about some of the coal ash and stuff.

Q29: Since that I start pay attention to my blood counts. Since to me I'm always on the lower end of the red… white blood cell and the red blood cell, is that something…?

Dr. Michael Savona: And we think we can talk and I can look at it in more detail. Giving you flyby advice is probably not in your best (inaudible 1:42:00) and but maybe you're supersensitive because of what happened in your family and it's nothing… and maybe it's something to keep an eye on. Alright. One last question.

Q30: Has there been any association between high doses of Atorvastatin in MDS?

Dr. Michael Savona: I don't know. So Atorvastatin has been implicated in actually a reduction… or it's been in the lab duplicated as an anti-inflammatory reduction in some tumors and I've seen a lot of clinical trials being designed to look at this. I don't know if any of them been successful, but I haven't seen any lipid lowering agents as carcinogenic at all.

?: In fact, some of the statin cholesterol drugs are actually being used in combination with chemotherapy against acute leukemia, or at least it's being tested.

Dr. Michael Savona: That's the clinical trial that I was alluding to. So, we think it actually has an anti-inflammatory event that we don't know.

Q30: Did you mean to give me Mark Workman's card?

Dr. Michael Savona: Oh, God. Alright. Thank you very much.

(Applause)

?: Ladies and gentlemen, let's take about a 10 minute break while we change slides over. So, be back maybe at about 20 minutes till.

(Break and general chat 1:43:33 – 1:58:12).

Denise McAllister: Good morning again. My name is Denise McAllister as stated earlier and one thing that I didn't do really was tell you who I am. I'm not one to really talk about myself, so I understand why I easily glazed over that subject, but I am an oncology trained nurse practitioner and something that I don't know that anyone really knows about me in this room even my

colleagues from the MDS Foundation is that I am actually from Tennessee. I'm from a very small town that sits between Centerville and Dixon or it's the Pinewood Community. So, I'm born and reared about an hour west of here. So to return to Nashville and network with all of you and to meet all of you is really a pleasure for me. I have been in hematology care or really oncology care for almost 30 years and the bulk of that has been spent in hemalignancies starting out in the mid '80s under transplant unit at Emory University and that was really a groundbreaking time in transplant care. From there, I went to the Moffitt Cancer Center where I spent almost 20 years of my career and that really is where the bulk of my MDS experience has taken place. Dr. Savona did a very nice job in outlining really the progress of myelodysplasia through clinical trials and as a physician scientist what takes place in the laboratories that we're not even aware of or in the general public when you show up at your doctor's office. Working in the academic setting, I certainly have been exposed to the science of myelodysplasia throughout my career. I also had the privilege of working with one of those world renowned experts in myelodysplasia, Dr. Alan List, who is at the Moffitt Cancer Center today and he was very instrumental in getting Lenalidomide or Revlimid its FDSA approval in myelodysplasia and of course seeing Vidaza come to market with its FDA approval, see where we've come and what we know about a near doubling of survival with the use of that drug and then, of course, Decitabine.

When we look at myelodysplasia today and I hope that one of the key pearls that you'll take away from here is recognizing that we do have three FDA approved drugs, but also the passion behind the Centers of Excellence and the research that's going in the laboratory to truly make a difference in changing the natural history of this disease and bringing new therapies to all of us for use in patients who are diagnosed with MDS.

So, I'm going to spend probably just about the next 10 to 15 minutes talking about the Building *Blocks of Hope* which is what you all have in front of you and this is a list of the MDS National Leadership Board and Sandra Curtin is one of my colleagues. She is an oncology nurse practitioner who this was her vision, this book that you have in front of you and there have been folks from the MDS Foundation Leadership Board who worked on this with her, but it is the best tool that I have seen for folks with myelodysplasia as well as caregivers as far as a one resource that you can go to and get some additional information on a particular topic, but as well it will give you a list of resources to call or visit the website to get more information from.

Something about MDS care is that it certainly is about individualizing treatment of what people need and there's certainly has been discussion here this morning where someone may be on Vidaza for five days versus someone being on Vidaza for seven days or someone who may have be getting treatment where the standard or the FDA approval is every 28 days. Some people may be getting their treatment at five weeks, some may be getting their treatment every six weeks. So part of that is certainly individualizing care. So, when we think about when do people need treatment and that is certainly when they become symptomatic. If someone requires blood products to survive or whether that's blood or platelets, someone needs blood products to get

them by or if someone is at risk for developing infection or they are developing recurring infections and those symptoms are not going to get any better until treatment begins to try to change what is going on in the bone marrow.

Dr. Savona has spoken about increasing blasts and those blasts are those very immature white blood cells and they do not go on to be fully functioning cells. They hang out in the bone marrow. They do nothing but take up space and they cause trouble and as we've gone along and revised definitions of various subtypes of myelodysplasia, today what we call acute myelogenous leukemia is if someone has 20 percent blasts in their marrow. So, that's why if someone is looking like they are progressing toward acute myelogenous leukemia then that certainly is an indication for treatment and, of course, when we look at the categories of myelodysplasia the general category is low risk, intermediate risk or high risk and certainly if someone does have a category of high risk myelodysplasia then that tells us they are at high risk for transforming to acute leukemia and our goal is to delay that for as long as we possibly can. So, that's a trigger to treat or an indication for treatment.

When it comes to deciding the therapies for folks or what's in peoples' best interest, certainly their performance status was talked about earlier. Are people independent? Are they able to care for themselves? With myelodysplasia primarily affecting an older population of folks, people can be in their 80s and still driving to the grocery store, still going to church. They may cook for themselves and cook for other people. So, you could have someone in their 80s who's very robust. You could have a younger person as was mentioned earlier where their heart function may not be the best, the liver function may not be the best, kidneys are not the best. So, treatments need to be tailored toward the individual person based on how well they function every day and what types of health problems they may have, if any at all.

Then there's the International Prognostic Scoring System and as Dr. Savona mentioned earlier, there's quite a discussion about what's the best prognostic scoring system for healthcare clinicians to use and certainly what is important to us is it's one that's validated that we recognize that we can go to that scoring system and it's going to tell us how aggressive is the myelodysplasia and give us some hint how it should be treated and as I was looking through the booklet again that you have in front of you in chapter two, page six it gives an example of what two of the International Prognostic Scoring Systems. One is the original and that's chapter two, page six where it says 'Seeking Treatment' at the bottom. Low risk it gives a score of zero and it's based on a point system meaning how many low blood counts do people have in their peripheral blood. Is their neutrophil count low? Are they neutropenic? Are they anemic? Are they thrombocytopenic? What cytogenetic abnormalities do people have? And that's listed here. Do people have, for example, a deletion 5Q and, of course, we have Lenalidomide that can target that abnormality and that one, of course, is considered a lower risk, but unfortunately in our practice and maybe even with some of you and people who we see every day, people can have quite a lot of chromosome abnormalities whether it's none or they have one or three or greater is considered complex and unfortunately and I'm sure Dr. Savona can speak to this as well. We see

people whose chromosome abnormalities may be a paragraph long. So, that is important when it comes to helping us with their International Prognostic Scoring System which is a point system.

If you'll also notice on this page, it tells us what the goals of therapies are for people. So, people who do have low risk disease, the goal is to help them have as best production of blood cells that we can with therapies. Reduce the number of blood product transfusion whether it's red blood cells or platelets, improve the quality of life as well as extend survival and if you'll notice at the higher risk which we call Intermediate 2 risk or high risk, you'll see here it's listed that the goal is survival and it certainly is to delay the time to leukemic transformation as we talked about earlier, improve the quality life as a result of the disease and the treatment and, of course, improve survival.

So, something about Dr. Savona that was also mentioned that or not mentioned, but certainly when I recognize that I've spent the bulk of my career in academia and I'm now in a community practice to have Centers of Excellence or to have physicians like him where you have access to who can help you determine what is your International Prognostic Score, but that all should be something that your community physician should be able to help you with as well. So, both physician groups have access to that information. So if you don't know what your score is, I think it's an important question to ask.

When we look at "Key Principles in Therapies," certainly what we know today is that we do not have a cure and the best option for cure is transplant which was discussed earlier and particularly allow transplant. Also, I think what we talked about in detail is that age is somewhat going by the wayside. It's more of how people function, what are their comorbid conditions, but also if you do have an older adult where transplant may not be the best options for them because of the comorbidity that is involved or the morbidity that is involved and people may do better to live out whatever life expectancy they have without transplant.

Patience is key when it comes myelodysplasia. It's a bone marrow that has many, many defects to it that is clearly been identified earlier. You have inflammatory cytokines that are a problem, you have cells that are dying off before they should, you have hypomethylation that's causing tumors, important tumor suppressor genes to become silent. So, that protection against cancers or MDS just isn't there anymore. So, therapies may not be so quick to turn all of that around and some of the therapies are very specific in what they target and if those targets are responsible for other clones it just may not be quick to turn it all around. Lenalidomide, for example, we can see in some a response as early as with their second cycle. Vidaza, it's the same. I've had patients on Vidaza where we didn't see their best response for a year and people can develop a new normal as time goes along, but it truly is about patients and not giving up too quickly on a therapy that may prove to work very well in the long run.

In hemalignancies, as was mentioned earlier, because the defect is in the bone marrow, blood counts do get worse before they get better and that's a given. So in myelodysplasia, someone

may start out with a beautiful white blood cell count, excellent infection fighting ability based on the CBC. Hemoglobin is terrible with requiring blood product transfusions. Platelet count may not be necessarily the best, but not platelet dependent. When therapy start, the white blood cell count can plummet putting people at risk for developing an infection. The red blood cell need may get worse and someone who perhaps has not required platelets before may suddenly require platelets. Sometimes people find that so frightening, patients living with the disease or people living with myelodysplasia as well as family members that they fear sometimes that the therapy is worse than the disease and I ask you to try to not think that way and know that these low blood counts are to be expected as we're cleaning out or trying to cleaning out the defect that rest in our bone marrow and you certainly saw the slides with the science behind these therapies and to the average person getting these medicines probably don't really have a good understanding or a good grasp of their importance and why it's important to continue to take these therapies to try to turn around the abnormalities that truly exist within us.

Proactive Management of Side Effects. That's key and that is true on behalf of healthcare providers as well as you who are at home. Our goal is to make a difference with myelodysplasia. Our goal is to try to turn this disease around as best we can with the therapies that we have available and our goal is also to allow you to live the best day that you can every day with myelodysplasia and with treatment and if side effects are occurring up front, we need to address them. One, we need to educate you on what you can expect. We also need to educate you on when to call or if you're ever in doubt if something should be going on or if it's a side effect that really puts you in a position where you don't want to receive treatment anymore then that needs to be talked about and it needs to be talked about early on. These therapies can make a difference and, again, I'd like to think that there's very little that we can't accomplish when it comes to side effect management and at least trying to make a difference in turning around an (inaudible 2:13:57) side effect and making things better, so people can be successful. So, good communication is key.

This slide depicts really the blood cells and what happens. This is before treatment begins. Here, things are well and then suddenly the blood counts start to drop off and it's almost like your blood counts are often in a ravine and sometimes people probably feel like they're in a ravine as well. Once treatment is initiated, you'll see here the blood counts go lower and the bone marrow is more empty of even normal cells and if when we look at data that was actually published by Michael Secris out of the Cleveland Clinic, he went back and looked at the data that gained Revlimid or Lenalidomide its FDA approval in myelodysplasia and something that came out of that particular study was that people who had a 50 percent decrease in their platelet count and people who had a 75 percent decrease in their neutrophil count were actually the ones who gained the best response from treatment. So, in cases like that we welcome those blood counts to drop, but at the same time it can certainly be quite worrisome to the person who's taking the medicine, showing up at the doctor's office feeling weak and also showing up disappointed that their blood counts are not better. If anything, they're worse. So just recognize that that this is a normal finding for us and working in oncology hematology care, you certainly have an expert

team of people who are accustomed to working with low blood counts whether it's in the solid tumor experience or in the hematology experience.

And our goal is that with therapy the bone marrow is going to recover to being normal or being near normal or the blood counts are where that people can live with them every day where it's not causing any troubles. And you'll see with the last block shows how the bone marrow is more active. There's more cells that are in there.

So, early toxicities can be discouraging and I, again, just to reiterate. Do not view that as things are getting worse. View it as something that is to be expected and that it's a partnership with the healthcare team and how to manage that.

So, strategies for making a difference. One, I was telling a gentleman the other day whose blood counts just repeatedly dropped down. We've had to bring him in instead of once a week for labs, we'd bring him in twice a week, Mondays and Thursdays, to see what his transfusion needs ar going to be and I told him when he's down in that gully, we're down in there with him and we're all going to climb out together and that's how it should be. Your healthcare team will support you through it whether it's modifying the dose of the chemotherapy… or not chemotherapy, but the drugs that are given or allow more time between treatments. We talked about going maybe from every four weeks to perhaps every five weeks. Whatever it takes to help people gain the best response. So, delay therapy is not always bad either and, of course, supportive care and letting people know up front that low blood counts are to be expected. So, setting that expectation.

This is a graph of someone who's had four cycles of Vidaza or Azacitidine and you'll see here the hemoglobin is in the purple, the platelets are in the yellow and the white blood cell count, well, maybe the hemoglobin pink. I'm sorry and the white blood cell count is in purple. So, you see here this person has a white blood cell count total of about 1,500 and Dr. Savona and I were talking earlier about the seesaw effect. So, blood counts can wax and wane and as the bone marrow starts to recover from treatment, you want to see them recover to a more normal range and, of course, with treatment they can drop again, but if you'll notice for example, look here at this white blood cell count, they started out at 1,000 and you look after four cycles of Vidaza where that white blood cell count went. It looks like between 5,000 and 6,000 and you see truly the change in the platelet count where their platelet count also a dramatic improvement and along with their hemoglobin and this shows the same graph of someone who has been on Lenalidomide or Revlimid for 10 years or over 10 years and you see that seesaw effect where blood counts can wax and wane, but they can wax and wane to the extent that no one is blood product dependent and are not suffering from repeated infections.

So, someone living with myelodysplasia. What are some tips for staying healthy and these are things that I know you know this already, but here it is in print and that's 1) is a balanced diet. Trying to eat as best as you can. Daily activity or exercise. I had this… Let me see. She was 91.

This very sweet 91 year old lady, extremely robust, myelodysplasia. She is someone who walks every day. She cooks for other people. I mean, just an amazing woman and she told me, she says, "Denise, motion is lotion," and the lady is right. It's good for the bones and it's good for fatigue and especially when someone is running anemic anyway from having myelodysplasia, fatigue is one of the biggest complaints that people can have and the best way to fight fatigue is to be as active as you possibly can and I'm not saying overdo where you feel so wore out the next day, but a good general rule of thumb is about 30 minutes three times a week for people who can walk a little bit each day without overdoing. Avoiding infection. Good hand washing is key and avoiding people who are sick. Do things to lessen your risk of bleeding and even though someone may have a diagnosis of myelodysplasia, we still want people to live the best life that they can and enjoy events that they always have. Rest is important and, of course, looking into community resources that can help you and as mentioned earlier and as you all know because you're here, the MDS Foundation is an amazing resource who is truly devoted to the care of those with myelodysplasia.

Becoming a Partner in Your Own Care. This booklet that you have in front of you can certainly help you with that and as Dr. Savona mentioned earlier, your relationship with your healthcare team is truly a partnership and patient preferences are very, very, very important and it's important to have a healthcare team who you truly believe is passionate about your care. It's important to have a team of people who recognize what myelodysplasia is, know about the science behind it and have an interest in ensuring that your needs are met whether that is referring you to a Center of Excellence, to an academic center to get expertise from someone who sees patients with MDS all day long and someone who has a passion for factors that drive this disease such as through laboratory research and trying to turn it around. So, there's many avenues of help that you can get and it's a matter that you do have a team of people who you trust and who recognizes the value in you success.

So, speaking of tools for success and that is understanding… have some understanding of what myelodysplasia is. It doesn't mean that you have to be truly immersed in all the factors that drive the disease, but important to recognize that even low risk disease is sometimes not so benign even though it's called low risk disease, it can still be a hindrance to people with transfusion dependence. There are some who do fall into that low risk category who are in a watch and wait approach. They do not require transfusions. They get their labs monitored and they're not making any progression toward acute myelogenous leukemia. It's important to know the therapies that are available. It's important to know the therapy that you're on. What is the schedule? What are the side effects and that you also have the information necessary at home to help you manage those effects because you're not going to have your healthcare team in front of you and it's also important to know who to call.

And tab five is a chapter devoted to the MDS plan, Understanding the Diagnosis, what are tools that are available to help and because there… it's really is blank forms that talks about the transfusion diary and I can't stress that enough. Something that's helpful to us as healthcare

providers and especially with being in an academic center and working in partnership with community physicians, I may not always know where patients are getting their blood or how often they're getting it. So, a transfusion diary is very important because how often people are receiving blood product transfusions kind of tells us what's the tempo of the disease. Are things changing? If the transfusion need is becoming less while on therapy or there's nothing that I enjoy hearing more than someone's last transfusion was six weeks ago where they had been getting transfused every two weeks. Then that tells us that there are good changes that are occurring and that people are responding to treatment.

So, keeping up with dates and how many units of blood or how often platelet transfusions are occurring is important and, again, I think all of you have this information and knowing how to reach Audrey, but there it is. There's her contact information and she is certainly a founder with the MDS Foundation and has truly devoted her career to the service of all of us.

Okay. It is lunch time. So when we return, let's plan on spending the next hour, the last hour talking about you and I very much look forward to hearing who you are and talking about how you live with myelodysplasia each day and perhaps hearing from the caregivers as well and sharing information with each other to help everyone in the room live better or live as successful as possible with MDS whether on treatment or not. Any quick questions? Alright. We'll meet up after lunch. Enjoy. One o'clock is our scheduled time back. Thank you.

(Applause)

Denise McAllister: Well, I hope everyone enjoyed lunch and I hope everyone has taken away something away from the morning session. Again, just to recap recognizing the hope for the future, Recognizing that physician scientists and researchers have identified what is believed to be driving features behind this disease and working to try to find therapies to expound on what we already have available and that can significantly make a difference. So, our last 50 minutes, recognizing that the meeting comes to a close at two o'clock is to talk more about strategies of living with myelodysplasia and if you're willing, if we could go around the room to say who is living with myelodysplasia and who is a caregiver, friend or if you don't wish to say anything, just say pass. Whatever you want to say is totally fine and when it comes to strategies for living with myelodysplasia in the book there's book number three which is "Quick Tips." So, that will primarily be our focus for the next few minutes, but of course it really is more about you and recognizing that all of us have something to learn from each other. So, if we could start here at this end as far as if you are a patient living with myelodysplasia, caregiver, friend or if you don't want to say anything just hand it off to the next person.

Dr. Mahon: I'm a caregiver for as many people with MDS at Vanderbilt, the clinic there.

Denise McAllister: This is Dr. Mahon who we have heard about earlier. It's a pleasure.

(Applause)

Q31: I'm a daughter of a patient with MDS.

Q32: And I'm the patient with MDS.

Q33: And I'm the husband of the patient.

Denise McAllister: You're an important person. I'm glad you're here. Thank you.

Q34: I actually am with a pharmaceutical company called Eli Lilly based in Indianapolis and I live just south of Nashville, but I'm here just to learn more about the disease and really appreciate Michael's talk and your talk and just interacting with the patients and their caregivers and guys are awesome and it's very inspiring to me to be here.

Denise McAllister: Well, thank you for coming. I'm glad you're here.

Q35: What Eli make for MDS?

Q34: We have one molecule that's moving into phase three trial in MDS that Michael did not talk about, but we're hopeful that we can get the trial going at Vanderbilt in the future.

Denise McAllister: For you to come and have an interest is really great. Thank you.

Q36: I'm the wife of a newly diagnosed MDS patient.

Q37: I was an MDS patient, but I had a bone marrow transplant and it will be five years in July and the graft versus host has been my problem that I'm given with currently and it's with the lungs. So, it's not a good one to have of the complications, but I'm dealt what I'm dealt and God's got a plan for me somewhere. I'm here.

Denise McAllister: And you're obviously a survivor. I'm glad you're here. Thank you.

(Applause)

Q38: And I'm her husband and caregiver.

Q37: He is the best caregiver. I would't be here if it wasn't for him to taking very good care of me.

Q38: That's for sure.

Denise McAllister: Thank you for coming.

Q39: I'm (Attendee) and I'm MDS patient recently diagnosed in November and I'm doing great on Vidaza.

Denise McAllister: Very good.

Q40: Caregiver. Easy caregiver.

Q39: Excellent.

Q41: Daughter of MDS patient.

Q42: I'm a daughter of MDS patient.

Q43: I support my wife and (inaudible 2:31:24).

Q44: MDS patient.

Q45: Team member here.

Q46: Friend of the MDS patient. I was diagnosed at the end of December.

Q47: Friend.

Q48: Of the MDS patient.

Q49: I'm a patient, a long time patient.

Q50: I've got patience. I'm a caregiver. She's a nurse and she didn't need a whole lot of care, but she's pretty much been a strong patient.

Denise McAllister: So, she's been a champion in her own care. Is that what I'm getting?

Q50: A champion in her own care. She's been wonderful.

Denise McAllister: So when it comes to strategies, I certainly have heard from this morning the fatigue can be quite overwhelming and I know I've had people tell me that they may get up, put a load of laundry into the washer and have to go and lay down. They hear the washer stop, they may get up, put the laundry from the washer into the dryer and have to go back and lay down or perhaps someone gets winded and tired just taking their garbage cans to the end of the road and then, of course, when their blood counts get better they automatically feel better. So, when it

comes to the fatigue, what are some of the strategies as people living with myelodysplasia, what are you doing that you find helpful and as caregivers what are some of your observations? Anyone care to…?

Q51: (inaudible 2:33:23) even though I don't want to do it I exercise and I do as long as I can because I get worn out very quickly. I used to exercise for an hour and a half to two hours and now if I make it 30 minutes I'm lucky, but that makes me feel so much better the next few hours before the next exhaustion comes on and I really want to ask a question too about chemo brain because I don't know whether I'm getting old or if I'm just getting forgetful, but is there such an animal?

?: Yes.

Q51: I don't feel so bad.

?: Yes, plus the age problem.

Denise McAllister: Specifically with regards to Vidaza, it is what we call a hypomethylating agent, but it also has those cytotoxic properties to it as an agent. In general in oncology hematology care, there is something that is described as chemo brain and I tend to hear more about it from people who have solid tumor cancers who have been on chemotherapies maybe days at a time or they may get treated every two weeks or every weeks for an extended period of time, but it is something that is very real and it's something that's very well published in the literature. Some people may describe it as a fogginess. Some people may describe it where their thought process just is not as clear. Some people say it's just and out forgetfulness where they write notes to try to help them remember what they want to complete throughout the day. It's not necessarily an interference to someone's function. It's a hindrance. People describe it more as a hindrance. In some of the data that we read in patients it may start to clear up within months of chemotherapy stopping or treatment stopping. Some of the literature states it may be a year before people really start to notice a difference. When it comes to disciplines or when it comes oncology care being a multidisciplinary team approach, there are folks out there who offer services called brain fitness and so that may be something to look into. On my side of town, it is covered by Medicare and it is covered by insurance where people can get tested as far as their brain function and their recall and those sorts of things. So, when it comes to medicines to try to make a difference, I'm unaware of it. It really is about trying to do what you can to keep your brain active and that's where brain fitness and analysis can be helpful. I see some people working puzzles. Some people do a lot of reading just to try to keep their brain function going. Dr. Mahon, do you have anything to add to that? Since you're here, I'll rely on you as well.

Dr. Mahon: No, I think I agree with everything you said. I think when… Vidaza and Dacogen, all these different types of treatments or even if it's transfusion support and these are things that have very fundamental side effects that we're still sorting out. I think this loss of energy and the

weak, for example, or the week or so after Azacitidine or Decitabine. I hear that a lot from folks going through the same therapies and what I think has worked best for the people I notice who are coping best to my mind are those that stick to a schedule. Your comment is well taken about an exercise plan. Even if the stamina is not what it was, say, five years ago having sort of a dedicated time where you are going to focus on your wellbeing and your activity, I think, has a payoff for the rest of the month and the rest of the day. Along those lines, I think making sure you get adequate sleep. Everything that you had on your slide up a little bit earlier, taking care of all of you not just fixating on oh, I'm going to go in for my chemo treatment and then sleep the rest of the day. Keep in good sleep hygiene. If you need a nap, so be it. Take a nap but make sure that you're getting the bulk of your night at sleep… bulk at your sleep at night and trying to maintain some sense of normalness to your day and to your schedule. That's what I think works best.

Denise McAllister: Something that Dr. Mahon just reminded me of is it clearly is recommended and please don't shoot the messenger here, but if you do take naps during the day to not nap any more than 30 minutes to an hour at the most because that is known to interfere with your ability to sleep well at night and I hear the fatigue and some people tell me that they can wake in the mornings and feel like they never slept and, of course, the more that people want to sit and want to rest because their body… they feel like that's what their body needs, in the long run that certainly is not helpful when it comes to overcoming the fatigue. So definitely to incorporate exercise is important and I tell patients that they don't have to do 30 minutes at one time, they don't have to do 15 minutes at one time to walk, even if they go 10 minutes knowing that they have to come back or go as far as they can and maybe do that again later in the day. So remember what my patient told me at 91 motion is lotion. It's good for the bones, it's good for the joints, it's good for the mind. It's good for the heart. It's good for the lungs. Any other thoughts that you want to share what you do that may be helpful for someone else?

Q52: I still have a question. Besides (inaudible 2:39:26) do people lose appetite? Is this common because that's one thing my dad leading up to his diagnosis. The (inaudible 2:39:39) my God, I cannot move one step, but prior to that (inaudible 239:45) he kind of gradually losing appetite. Is this something…?

Denise McAllister: Does anyone care to comment on that in the room what your experience has been? You will certainly have folks who will admit to a decrease appetite. Some people are not moving around a whole lot. They're not just not burning a lot of calories and they just don't have an interest in eating. The loss of appetite can be there and we can certainly see it sometimes in people's weight, but the other caveat to that is we can actually see people gain weight while on therapy. So because folks are on therapy and because people are diagnosed with myelodysplasia not everyone loses weight, but certainly in analysis that was done actually by the MDS Foundation looking at the quality of life while living with myelodysplasia weight loss was certainly something that was highlighted among people living with myelodysplasia.

Q53: It was one of the first things that happened to my husband had absolutely no interest in food and that was before Vidaza and weight got worse with Vidaza. She really lost track of things and that started before the next symptom was passing out for her (inaudible 2:41:08). So, that loss of appetite was one of her symptoms.

Denise McAllister: And sometimes with people feeling so tired or perhaps they're short of breath as a result of the anemia that they just don't feel like eating. The appetite just is not there, but that was something that was… it's something that is classic among people with myelodysplasia that was particularly highlighted in the MDS analysis. Were you going to say something? Yes, ma'am.

Q54: I'm old. I'm 70.

Denise McAllister: You don't look it.

Q54: I have a little trouble with my balance, but I still try to walk every day and I have a treadmill in the… not in the refrigerator…

Q55: In the living room.

Q54: In the living room and I watch TV and that helps take my mind off my problems as I'm walking, but I think it has helped.

Q55: And she does up to a mile a day.

Denise McAllister: Oh, my gosh. Congratulations. That's really good. Yes, ma'am.

Q55: It's not a little bit.

Q56: Can I ask you a question? Does the MDS Foundation have any referrals to any kind of grief counseling or anything like that?

Denise McAllister: That's a very good question. Audrey or Tracey, would one of you like to address that?

Audrey: I don't usually refer patients to grief counseling, but we just developed a new support group (inaudible 2:42:38) in the last year and a half. It's called Our MDS Family Coping and Caring Group. Actually, it's a series of lections and I usually will and that's geared more towards living with the new normal and helping families cope. Whether I invite someone… We're having one on April 25 in Philadelphia, but this something we maybe can start doing in different regions just like we're doing this type of patient day. So, I'll get working on that. If that's something that you think you might like I'll definitely focus on that for you guys and it's actually run by the

spouse of someone who is very dear and near to us, Bob Weinberg, who had MDS and was on our Board of Directors. He was with a very prestigious law firm and he was on our board and would lend his law expertise to the foundation free of charge. So, this is something that Rochelle wanted to do. It was her idea and we made it so. So for instance, in April at… It was her favorite restaurant with Bob. Every year in the spring we have it at the White Dog Café in Philadelphia. This year I invited an oncology dietician. So, she'll address keeping strong for the fight. We try to change it up. In the summer we had an (inaudible 2:44:08) Margate summer home and last year I actually had a yoga instructor come. They did… and a holistic nurse. They did a prayer circle. They learned breathing exercises. So, even maybe a grief counselor might be a great choice to do at another one, but I'm definitely open to suggestions and this kind of brings up the other thing. The survey that we handed out to everyone, we need your opinions so that we can improve our programs. These events like Denise is doing today will always happen and this is the way we do it. The agenda with a doctor and a nurse from our Nurse Leadership Board, but we also have our MDS Family Coping and Caring events, but we rely on your comments to make our programs better. So, we appreciate any comments that you give us today.

Denise McAllister: Thank you.

?: (inaudible 2:45:03) she didn't offer something locally or that we found it first. The leukemia and Lymphoma Society at Gilda's Club here in Nashville. They have some support groups and because it kind of all falls in that umbrella of blood cancers and things.

Audrey: And maybe we can work with them. I mean, we're open to…

?: They don't have a specific MDS support group.

Audrey: Exactly and this is where, of course, we are the only international foundation devoted to MDS. So, I'd like to create one and then let's open it up again. So, we were doing this one in Philadelphia that I don't see any reason why… and Tracy, maybe this is something we can work on it together to get something and to do. Thank you for the idea. We'll definitely keep that in mind.

Q57: I have a question. I would really address it to you. How many MDS patients do you see at Vanderbilt?

Dr. Mahon: So, and I've been at Vanderbilt three – three and a half years now. There's been a real increase year over year. I've been… Dr. Savona has joined us as well since I've joined. It appears that it's several hundred. I think it's about 200 people a year coming in at some point in their diagnosis whether that's they're coming to have their diagnosis made, they're being referred for low blood counts and we do a bone marrow test, whether that's folks who been diagnosed by their hematologist locally wherever that may be and they've received treatment with Vidaza, Dacogen, maybe they had a response, maybe they didn't, but they're looking for

other therapies. There are people that come specifically for bone marrow transplant or for a clinical trial or just for another opinion just to see what the other options may or may not be. It's close to 200 a year, but when I started it was roughly half of that and similar research universities have similar numbers. Certainly, Vanderbilt is still a growing program in the field of MDS, but we certainly got the… I think some of the expertise. You all got a chance to hear Dr. Savona speak about the growing, the expanding clinical trial network that he's built up and working with a lot of the universities and a lot of the hospitals in the area as well. They have about 200.

Q58: This is a lot, but I'm going to say it and (inaudible 2:47:35). Since we don't have a support group up here in Nashville for MDS to like encourage each other, if anybody would like to exchange phone numbers please come and see me and I'll give you my number.

Denise McAllister: I'd like to go back and expound on your question about support groups and are there any that are specifically sponsored by the MDS Foundation. There are support groups going on all across the United States for multiple cancers. There are some that are happening specifically for hematologic malignancies. There are some that are happening specifically for people living with myelodysplasia. There are patients who have started their own support group. So, certainly it's about finding what's available in your area in which you live recognizing that people have come from all over. Some of the local hospitals, for example, will have support groups that meet generally about once a month or once every other month. So, it's about finding a group who you feel that you can identify with and take pearls away from and the MDS Foundation also has clear guidelines for how to help develop an MDS support group and it can be as general or as detailed as you want it to be. There's specific phases that are outlined to try to help start a support group within your area. So, to visit support groups because they are out there whether it's tied to the local hospital, some churches may have support groups that are happening. Some smaller clinics may have support groups that are going on. So, it's a matter of seeking out what's there. Someone mentioned a leukemia and lymphoma society. They definitely have support groups that go on in areas throughout the United States. They're very active in the area in which I live. So to think about starting a support group in an area where there's not one, that is certainly something that I know can be of value to a lot of people. I also want to thank you for your comments and that is on the chemo brain, the weight loss, asking about those things, fatigue, depression. People definitely go through situations in their life that's not so easy to deal with and certainly what's important to recognize are the signs of depression and, again, when you look at the Quick Tips book three on page 20, there's the definition of depression as well as things that you can do and I won't go through each of these because you can certainly read them at your leisure, but one is recognizing if your mood is not what is should be, it's okay. It's normal to be depressed about a change in health. What we don't want to have happen is that feeling of downness or that really just down feeling last for an extended period of time and then what is important is to reach out for help and it's also important to connect with other people who perhaps have the same diagnosis and to talk with someone who's gone through it just as what we're here today for and a comment that you made about the imbalance. That's something that is really very important. In older adults, one of the number one reasons why people fall is an

imbalance and as we get older and especially if being anemic or perhaps in a more weakened condition than what we're accustomed to being, it's those quick movements that can create an imbalance such as turning around too quickly or if folks are used to being very robust in their movements recognize that you might need to slow down and pay attention to that because that is how most falls occur in older adults. It's as a result of an imbalance. There are physical therapy departments out there, not all of them are created equal. So, it definitely is about networking with your healthcare team to see who stands out in a crowd. There is in-home physical therapy and occupational therapy departments available or organizations available that is covered by insurance, but once again they're not all created equal. So, you definitely want someone who stands out in a crowd to help with balance and to help lessen someone's risk for falls. So, thank you. You ask very good questions. Yes, sir?

Q59: I have a couple of questions I'd like to address with Dr. Mahon. Are there any cautions that are recommended immediately following the five day course of Vidaza like one should not drive and one should not fly and one should whatever?

Dr. Mahon: Not specifically.

Q59: But might be directly related to the fatigue if there is such.

Dr. Mahon: I think especially as this is a chronic treatment, you know, month one, month two, etc., I think over the course of the one to two months on those types of medications, you get a sense of how your body responds. I will tell you in my experience, many, many people or oftentimes their spouses tell me that the week after the infusions are done tend to be when the energy is lowest. That's not true for everyone, not by any means, but if you are one of those folks who notices that don't plan a massive family reunion for that week right after. Don't set yourself up for situations where you are trying to keep commitments that may be physically are difficult to keep, but short of that there's not specific things as far as avoiding crowds or not being able to be on transport, whatever. Now if your white blood count is low, the neutropenia, I think it's very important to focus on general smart, good hand washing, etc. if you are at higher risk of infection. Many physicians and nurses if they're treating someone whose white blood count is particularly low whether they're on Azacitidine or whichever or not we'll sometimes even prescribe pill preventative antibiotics if those neutrophils, those white blood cells, are very low, but outside of that I think just common sense types of maneuvers. Stay away from people who you know to be sick. That sort of thing.

Denise McAllister: And to add to that and it's not even just travel. It could be doing anything whether you're going to the grocery store. It's important and that's part of building your own MDS plan and that is knowing what are your labs. That can be a driver of what you do. If your platelet counts are low and you're traveling or going somewhere you might need to keep that in mind that you might require a platelet transfusion or it might alter your travels at that point, your plans may change. So 1) it's about building your own plan, knowing what your labs are, getting

direction from your healthcare team and to further, germs, I mean, forgive me I may go a bit overboard, but what I've learned tips from other patients is something that I forget about, for example, is when eating out, menus. Menus can be very dirty and so it may be the fact that when you're out and about make sure you carry antibacterial gel with you and when you go to the grocery store and you're using that cart. If there's a wipe there, just clean it off. Before you get into your own vehicle maybe even use your antibacterial wipe or gel. So if you're on the plane, clean the area around you. Some people tell me that they'll turn the air off just so that that air is not blowing on them and we have something known as the air tamer that this… which I had no knowledge with this gentlemen tells me he has not been sick in two years living with myelodysplasia and on therapy and doing a lot of travel that maybe something to filter the air around him in planes. So, it's about using good common sense, knowing what your lab results look like and just being knowledgably for whether you do travel or if you stay locally in your own home and the precautions to take.

Q59: I have another question relative to travel and that is regarding anemia and altitude. Is it recommended or a worthwhile consideration to request some pack cells before I go to Colorado or higher elevations for a period of time?

Dr. Mohan: So, it's an interesting question. It actually comes up more often than you might think. Oftentimes the cutoffs that we think about for routine sort of management of MDS every physician practice or clinic group or hospital group kind of has their own cutoff but it tends to be a hemoglobin less than 8 or 8.5 or sometimes 9. Those tend to be the times we're thinking about pack cells anyway. So if for example, our hemoglobin count was eight and we're planning to about hop a plane across country, it might be a good idea to get your counts checked in the days leading up to that trip, for example, but I don't think it needs to be specifically done… as a general rule, I don't think it needs to be done specifically for travel unless you're already in a situation where you might be requiring transfusions whether on a regular basis or just an intermittent basis. I think it's common sense, well, if I'm going to be traveling for two weeks and I usually require blood transfusions every two and a half weeks, let's deal with it beforehand, so that we don't… we avoid some sort of mini crisis situation while traveling where we don't have those networks of nurses and docs and folks that know us already and on the line, just building off your point earlier, I think even when we're worried about… certainly, infection is a risk we worry about blood counts are low with MDS and I think there are ways to work around that whether it's sanitizing our area and that's fine. It's your health. You can do that. Who cares if someone's looking at you on the plane and you're wiping down the armrest, so be it, but I think there's ways to make small adjustments in our day to day life and still be able to be out there and live our life, but do it safely as well. If you want to go to the movies, but you're worried about being in a big crowd, go at off times. If you want to go to the new restaurant in town and if you know it's already hard enough to get a reservation at seven o'clock, go at four. There's so many ways that you can still be out there living your life, but also not being in those big crowds. If you want to go to church and I used to say sit in the… you can just sit in the back but that seems to be more crowded… so, you can sit up front. So, there are all these small changes that you can make

in the way you live your life, but still be able to live your life and those changes will be a little bit different for all of us based on what we want to do or what we're trying to accomplish whether that's at work or we want to have time with our family or whatever it might be, but you're smart people. You can adjust this how you see fit for your own life.

Q60: But that altitude, Dr. Savona mentioned that. It's something to do with the altitude?

Dr. Mahon: Yeah.

Q60: What if you're living up there for three weeks? Does that have any correlation with this at all?

Dr. Mahon: So, these red blood cells. I mean, at the most basic functional level they're carrying oxygen throughout our system and so when we're already in altitudes and climates that where the oxygen is "thin," it may be a bit more pronounced if you're already anemic and you have that hemoglobin of, say, 7 ½ - 8, I think some of the side effects of the anemia whether that's fatigue, whether that's in some cases light headedness or in some extreme cases even chest pain, I think those can become more pronounced. So, but again I think the numbers as far as the actual blood counts, the numbers where that becomes a concern are already the numbers where we should be thinking about blood transfusions anyway. So if your hemoglobin is 11 and you're off to Denver for two weeks, I don't know that that would necessarily change our management at least as far as the medical journals go, I no one's been able to show that getting a transfusion when you're hemoglobin's already 11 is going to make anyone do any better or any worse. I'm sorry that I don't have anything more specific for the altitude, but that's what we know.

Denise McAllister: Any other comments to share with the group or questions or strategies what works for you that others might benefit from?

Q61: You know, when you're diagnosed everybody's got some suggestion to give you or I've heard this works and this works or whatever. As far as supplements or anything like that…

Q62: Probiotics.

Q61: Probiotic. I mean, pros/cons?

Q62: I had parabiotic, antifungal and antiviral that I have to take when my blood counts are at different levels. If I'm neutropenic, I go with antifungal and antibiotic, but that's supposedly removes something from your gut that you need probiotics to redo yet the doctor says don't take probiotics. I'm really confused because the neutral people say take the nutrients and the docs tell you not to take anything they don't tell you to take. So, you're in the middle.

Denise McAllister: You're right and, you, again, you raise a very, very, very good point. When it comes to probiotics and gastroenterologists that's not something that has really been widely promoted. However, certainly when people take antimicrobials, it can reduce the natural flora in the gut and people can do better by taking probiotics. My experience has been especially in people with hemalignancies and that is if people to choose to take a probiotic we recommend that it be a pill rather the probiotics that have to be kept refrigerated because those can be of a live culture. Some people say that it can help if in developing diarrhea to take a probiotic might help with that. It's not something that at least in my history in hemalignancies care that we around promoting, but in some folks it certainly can make a difference. I have more people not taking a probiotic than those who do, but if you take one and feel that it helps you then that's okay.

Dr. Mahon: Just make sure your doc knows that if you are doing it… One of the things that we do pay attention to the providers is medication interactions and that includes not just medications that are prescribed but supplements and sometimes even over the counter things. So if there is something you are using, please let your provider know.

Denise McAllister: If you, again, go to the Tips for Success on page 11 when it comes to diarrhea it definitely addresses probiotic supplements as something that can be done, but I always appreciate when I'm going over a medication list in the clinic with my patients, a medication list just is not the prescribed medications. That includes any vitamins, minerals, herbs, things that people are taking because sometimes those things can definitely interfere with the therapeutic management and so if that's a possibly we certainly want to know it. So, just be sure to have an open communication with your healthcare team about that. Thank you.

Q63: I do have a question. Is acupuncture okay with this particular cancer because when I had cancer before, I was told not to do it?

Denise McAllister: That's a very, very, very good question and I'm probably not the best person to answer that, but I have certainly read some information or talked to people when it comes to Chinese medicine who are from China and they, I think, and again I don't have the best knowledge about this, but I think that there's some ideation that if there is cancer that by giving acupuncture that might not be the best approach. However, what I can tell you is that there are studies going on looking at acupuncture and symptom management in oncology care.

Q63: I know it helps with fatigue.

Denise McAllister: Correct. Peripheral neuropathy is one. Pain is one. So, I think it's about talking with your healthcare team, getting their option if they feel that that is something that is safe for you and see who they recommend or where cancer patients go in the area for acupuncture just to make sure that you have someone who's well trained. In the center where I work, there is an acupuncturist there as a matter of fact and there also NIH studies going on

looking at acupuncture and symptom management in oncology care. So, something to talk with your healthcare team about.

Dr. Mahon: And just as an aside. I think two things relevant to that issue specific for folks dealing with MDS. If we're particularly neutropenic, if our white blood count is particularly low, I suppose there's a theoretical risk we can worry about and higher risk of infection even though I know these needles are very small. I think the more practical matter as well is that sometimes with MDS whether on or off treatment the platelet count can be very low and, again, are we introducing a risk a bleeding even with these fine needles. The same reason why I tell my folks that I see who have very low platelet counts are requiring transfusion for it. Avoid deep tissue massages and these sorts of things. At very low platelet counts, it does not take much to cause bleeding and that's just a practical thing to consider when we're looking at these sort of support mechanisms.

Denise McAllister: It's about tailoring individualized care for you and that even includes complementary alternative therapies.

Q64: Kind of on that same line, just made me think of it. What about essential oils, treatment with essential oils?

Denise McAllister: Tell me more about what that essential oils. Tell me what that entails.

Q64: Well, it's a new thing that's on the horizon. A girl that I work with and (inaudible 3:06:49) companies that provides them and they're supposed to help with blood pressure and (inaudible 3:06:55) oils and you (inaudible 3:06:57) and Franken scents and I like different combinations of days that you put on the back of your neck or your feet or whatever and it's supposed to help those things. I didn't know if there was anything bad about them.

Denise McAllister: Well, when it comes to essential oils it actually sounds quite relaxing. I do not have any knowledge of that. Yes, ma'am?

Q65: I heard (inaudible 3:07:24) Sirius radio sometimes doctors radio NYU Medical Center doctors were discussing the essential oils just recently on one of the programs and they said be very careful becomes some of the essential oils if you apply it directly to your body and I forget which one they said it was, it can actually go into the skin and affect other medications. So anytime you're doing anything with essential oils or something like that if you're on medication then your body absorbs it into the bloodstream, you can affect. So you need to discuss that with your doctor and they said it's (inaudible). It may seem like it's a topical thing but it is absorbed into the body.

Denise McAllister: I could not have said it better myself because I was going to suggest to have a discussion again with the healthcare team. When people approach me about therapies or

complementary alternative medicine, if I don't know the answer and there's so many things out there that are new that are coming up or perhaps ancient therapies that have been around for years, but they're reemerging. If I don't know the answer, I will do research at reputable sites to figure it out or consult with someone else who's more knowledgeable in that area than I am and ask for help to see if this is something that's safe. So I think really no matter what you're considering, it's important to talk with your healthcare team and verify that is something that is safe for you and something or the benefit outweighs any risk. I like partnering with you. Do you have anything to add?

Dr. Mahon: I think that was well said and I can't claim to have any specific experience with essential oils. I'm sorry.

Denise McAllister: It sounds really nice, but when you hear what was an advertisement about possibly being absorbed into the skin it may not be something that's so good after all.

Q66: The way I see it might help your (inaudible 3:09:20) when I take my Vidaza shots, I use primrose all along the injection points and it tends to clear the inflammation up and the itching and all the side effects and it's hard to find. You can't just get it at Walgreen or Walmart. They have a dotcom. I'm not promoting that, but (inaudible 3:09:40)

Q67: Just go to Amazon.

Q66: Yeah, but it does really progresses the healing.

Denise McAllister: That is actually something that a lot of folks have adopted specifically with primrose oil to help lessen the irritation of the cellulitis type picture that sometimes people can develop as a result of the Vidaza injections. I'm unaware of any adverse effects regarding that and that is something that is out there and published and it's even in here. So, you're hitting... when it comes to strategies for patients and caregivers and living with myelodysplasia and side effects of therapy, you're hitting on a lot of good points.

Q68: A question regarding elective surgery and MDS patient and the timing of it, when to go for it. Obviously, if it's necessary only. Any feelings or recommendations? A side question is even if my platelets are within reasonable range, say, 90,000 and white cells are five, hemoglobin nine, say.

Denise McAllister: Neutrophil count adequate?

Q68: Yes. What are the considerations for elective surgery?

Dr. Mahon: So, I think the key in the situation... So, those blood counts that you mention are reasonable for the vast majority of surgical procedures, but the key for any of these whether it's

minor abdominal surgery or skin surgery, whether it's something more extensive like a knee replacement or whatever, I think the key is your surgeon being aware that you have MDS and then your hematologist speaking with the surgeon. I think that's the key making sure that that connection happens so that 1) the surgeon knows what to expect, knows to check that CBC blood count preoperatively not afterward so that there's no surprises. Say sometimes when the blood counts are… the white blood count is a little bit on the low side that might affect the surgeon's and the anesthesiologist's thought process as far as antibiotics after surgery. If the platelet count is kind of on the borderline of whatever their threshold is for this kind of procedure they may elect to do a prophylactic platelet transfusion the night before or the morning of that same surgery before a knee injection or something like that. So, it's making sure that the surgeons are aware to look for this and then making sure they close the lid with your hematologist. That's the key. No one likes surprises.

Q69: One of the problems we had this winter was that (Attendee) developed nosebleeds and it wouldn't heal and that's when we discovered that her platelets were down around 7,000 and she started getting platelets. So, something brought on the problem.

Q70: I got my nose…

Q69: Packed.

Q70: … packed, but when you burn it.

Q69: Oh, cauterized.

Q70: Thank you.

Denise McAllister: Did that take care of it?

Q69: It slowed it for the time being.

Denise McAllister: When the platelet count drops like that bleeding is certainly a risk and to recognize signs or symptoms of a low platelet count one can certain be easy bruising here in the setting of without trauma, bruising that occurs spontaneously or what we call petechiae which are those little red dots. They're about the size of a needle head and they can be in a cluster and we can tend to see them on the belly, we can see them on the arms, we can see them on the legs, bleeding when that hasn't occurred before such as even with brushing your teeth. The gums start to bleed or bleeding from the nose of what you're talking about which you hadn't had before. It's important that when the platelets are low to not do anything to put yourself at risk for bleeding and things to consider are like not straining to have a bowel movement, for example. You may need to start a stool softener, for example, just to keep that from happening and, again, what you highlight when it comes to strategies for living with myelodysplasia, thrombocytopenia is listed.

So, anemia, neutropenia, thrombocytopenia, fever, tracking of the blood counts is very important and keeping track of transfusion requirements, the dates and how many units, diarrhea, constipation, nausea, vomiting, injection site reaction, skin rashes, fatigue, anxiety, depression and when to call the healthcare provider. When it comes managing symptoms, we're very, very fortunate that today we have a good repertoire of antimicrobials. Back in the '80s when I was initially immersed in care of hemalignancies, for example, we only had one fungal medicine. Today, we have multiple. When it comes to IV access back then we only had two lines to choose from. Today, we have multiple with multiple lumens if needed. It comes to blood banking. We have great blood banking procedures in place now to ensure that people get red blood cells when they need it or platelets when they need it. So, and you have access to your own local physicians as well as you know that you have access to physicians that are at a Center of Excellence with myelodysplasia care. Recognizing, walking into this room today you probably didn't expect to hear about the science of some of the driving features that have been discovered when it comes to myelodysplasia, but yet you recognize that there's teams of people nationally as well as internationally who are devoted to trying to change the natural history of this disease and get people in a position with myelodysplasia where we do have cures even outside of transplant with drugs. So, living today with myelodysplasia. It's not easy. I know it's not easy and I hear it from all of you of how it's not easy, but I also hear how you have the courage and the stamina to keep going every day and you tap into the resources that are available to you and certainly being here today at this MDS Foundation forum is a good example of that and even some of you who are so inspired recognizing that there's a need for more support and even considering starting a support group. So as a very passionate oncology nurse practitioner who I generally care about each of you, I care about your well-being and what a nice surprise to have you in the audience to collaborate with in this last hour of this forum. I wish we had more time, but staying on time with our program two o'clock was the deadline, so that has come to a close. If you need anything, do not hesitate to reach out and, of course, you have Tracy and Audrey with the MDS Foundation who are just a phone call way or an E-mail away and I'm the same and I'm sure that Dr. Mahon is as well. If you need us we're here and I'm grateful to all of you for coming and I wish you all much success and keep going because it's working well for you. You're here. Thank you.

(Applause)

?: Thank you, Denise, and please help me join in thanking Denise.

(Applause)

Denise McAllister: My pleasure.

?: Some housekeeping notes here for everyone that parked their car. I'll hand these out to you and all you have to is fill it and you will not have to pay for parking. So, I'll pass (inaudible 3:28:27).