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Dr. John Hill, Jr.: Thank you very much for all coming today. It's a pleasure to be here and very nice to see some familiar faces in the audience and just want to reiterate that we're delighted with the support of the MDS Foundation. We really appreciate that and all the support of our colleagues and as well the pharmaceutical support here. I do want to apologize that my slides are not nearly as beautiful as Dr. Lowrey's. Those are fantastic, Chris, and also in the midst of doing this talk we were reminded several times over keep it to 20 minutes or we want to have enough questions. So, I did pare down my slides a bit, but I'm happy to go into detail. So, just if there's a slide and I will pause and discuss with various slides a little bit more than is sort of written on the page. If I'm not mentioning something that comes up, just give a holler. This is informal or at the end certainly ask about it and anyway, hope to be at least as informative as what Dr. Lowrey just spoke about which is very helpful. So, without further ado.

The objectives that I want to leave you with today would be to have an understanding for the basis of both low and high risk Myelodysplastic Syndromes, a general sense of the therapies that are related to these and as Chris mentioned there's a direct extension between the risk of the disease and the therapies that we utilize. So, we'll start out by talking about the risks and then we'll discuss therapies and that should make it a little more clear. I want to leave you with an understanding of the rationale for allogeneic stem cell transplant, what are the indications for that and the eligibility considerations, but I'll be emphasizing a few times over that many patients do very well without allogeneic stem cell transplant. Even though were transplanters here if someone doesn't need a transplant, we're not anxious to push them towards transplant because despite the fact that that has curative potential it has many potential complications and it certainly changes one's life in terms of its complexity and whatnot. So, I want really want to drive home the point that there are strategies both on the transplant realm and the nontransplant realm in treatment and it's important to realize that and every patient is different and every patient deserves a very personalized approach to their therapy based on their own status and their disease status and then finally at the end I'll touch upon some new therapies and the basis of what clinical trials really are.

So, what are the potential consequences of MDS? Dr. Lowrey also mentioned this, but in discussing treatment it's really important to focus on this because this directly relates to how aggressively we treat our patients. So, Chris mentioned the fact that there can be a progressive drop in blood counts and Dr. Meehan mentioned that that can be one cell line, two cell lines or all three cell lines. So, we call this bone marrow failure in our clinical discussions. All we're talking about is the drop in counts. When the white blood cell count drops, there's risk for infection as Chris mentioned. When the red cells or hemoglobin drops that's anemia and patients can be fatigued and short of breath, sometimes light headed, dizzy, have headaches and even chest pain and palpitations and then when the platelets drop, as Chris mentioned that can be a risk for bruising and bleeding. The second major issue just to reiterate what was already discussed is this potential for progression to acute leukemia. This is much less common than marrow failure and the very low risk MDS patients have a minimal risk for progression to AML and we often don't even deal with that discussion or that consideration. Patients with much higher risk MDS where there's a preponderance of blasts that are in their bone marrow on the initial biopsy, those patients we follow those blasts very closely in terms of assessing their risk for development of acute myeloid leukemia and in those patients, in the very highest risk patients, it can be really just months before you're at risk for progressing to acute myeloid leukemia. We've had patients that have needed to get treated in that realm really for almost as if they had AML to knock them back down to sort of an earlier stage, if you will, and then consideration for gentler therapies. So, the goals of MDS therapy are necessarily to counteract and potentially reverse all of these effects.

Well so how do we approach each individual patient with MDS? So, part of it is what I just mentioned, the risks of the disease, but really we have to look at each patient in a personal sense. Ages of MSD, of patients with MDS, can range dramatically. We have patients as young as in their late 30s and 40s that we've diagnosed, not commonly, but it can happen and then, of course, we have patients up to their 80s and even in their early 90s that come in with the disease. Their overall functional status can be very indicative of how they're going to respond to therapy. Of course, we're not going to take someone who's fragile with many other health issues and hit them really hard with therapy. On the other hand when we have a very active person who's quite young in their 40s, 50s, 60s and early 70s and yes, early 70s is considered young in some patients. When we have those patients that are very active and don't have other medical issues, they may desire a very aggressive care and we may be able to do that for them. So, we tailor our approach to the patient's status, the disease aggressiveness, the patient's desires. Some of our patients really want the most aggressive therapy and are willing to take the risks. Other patients really want optimal quality of life and that's the most important thing and that's really important that we ask the patients early on what their desires are and that we respect those and that we work with them because every patient is certainly different.

So, other medical conditions as I mentioned could be important. The ability to tolerate different therapies. The overall goals of treatment really is central to any consideration of therapy for

patients and then the relative risk of their MDS as I mentioned for the issues that we discussed, bone marrow failure and acute leukemia.

Well, what about this risk of disease that we keep talking about? So, it's hard to address that without mentioning the fact that there are these scoring systems for MDS and I really trying to keep it away from a lot of difficult read graphs and numbers and that sort of thing, but the old traditional scoring system was called the International Prognostic Scoring System. That is still utilized, but a revised IPSS has now really been utilized a bit more in the past few years and it's a bit more inclusive. There are two purposes for this both to determine the relative risk and the prognosis in terms of the patient's risk for developing acute leukemia and developing bone marrow failure where really the counts are so low as to be the high risk for infection, bleeding and fatigue and then therefore to guide therapy and to guide the goals of treatment.

So these risks, these scoring systems are based on the three factors that you've been becoming familiar with. The percent blasts in the bone marrow. So, percent cells that are essentially leukemia type cells, but which we all have five percent or fewer. So, if you're diagnosed with MDS and you have five percent or fewer blasts then you would get a zero score for this and that's favorable. You don't have any excess blasts. If you're someone that has six to nine percent blasts there's a term called refractory anemia with excess blasts or RAEB, again, you don't have to remember all this, but this may ring some bells for people that have heard that term. RAEB1 means you've got up to 10 percent blasts in the marrow and then if you basically got 11 percent to 19 percent you're RAEB2 and so that's the more advanced form of MDS based on the blast count, but you're still less than 20 percent because as Dr. Lowery mentioned when there are 20 percent blasts in the marrow that's leukemia. So, you can envision that if you have RAEB2 with 17 percent blasts in the marrow you're getting close to tipping over into acute leukemia and that's the scenario where you'd be treated fairly aggressively if you're able to tolerate that therapy. Giving these examples just for you to get some insight into how we utilize the IPSS score and that translates into therapy.

Likewise we look at chromosome changes. When patients have their initial bone marrow biopsy, we look at the karyotype that Chris mentioned and cytogenetics and a normal cytogenetic would be 46 chromosomes of XY for men and XX for women. If we see that there's some abnormal changes in the chromosomes then that starts to give us a sense of higher risk for development of leukemia related complications and worsening bone marrow failure in the MDS setting. So, cytogenetics is another factor that we look at in addition to the percent blasts and then the final risk or the final component that we look at to establish this score is the low counts and how many of these are present. Is it just one of the three cells lines, white count, red count or hemoglobin and platelets or are all of the three cell lines involved? And again, I want to emphasize that these are fairly crude indicators not completely black and white and the point that I would make about that is that we're often seeing patients that come in and there's a chuckle in the office because the patient might say, "Well, gee, doc. Based on the IPSS score that I had two years ago, wasn't I supposed to develop leukemia last year?" and we'd say, "Yes," but the patient's nowhere near

developing leukemia. So, these, again, are crude indicators but you have to start somewhere and someone getting diagnosed with MDS is certainly going to want to know am I low risk, am I intermediate risk or am I on the higher end and this is the place to start.

So again, not to get too numerical and too detailed in ways that would be confusing, but this is the old score system. So, this is the traditional scoring system. You can see that the low risk score is at zero, the higher risk score is at two and then this is the more updated revised system and it runs from 1.5 to greater than six. I'm only showing this so you guys have some sense of what we're talking about with these scores and if at some point your physician tells you that you have a score of three to 4.5 you can appreciate that that that's intermediate risk and therefore the treatment that's recommended will be commensurate with that score. Again, crude indicators, but at least a place to start rather than telling a patient we have no idea what your risk is at least we have some sense of being able to give them some idea that you have a very low risk of evolution to acute leukemia in the next several months or you have a relatively higher risk and therefore let's talk about treatment that deals with this appropriately.

So, what about treatment options? Well, there're really three categories of treatment that we look at as we've been talking about the same theme based on patient condition and disease risk – supportive care, low intensity and high intensity. For the lowest risk MDS, the goal is quality of life benefit. Again, trying to minimize shortness of breath, fatigue, trying to reduce the number of infections if possible or the risk for that, reduce any kind of bleeding and so this appropriately strategizes therapy to the patients that are at that low risk. We don't need a hammer if we're dealing with a relatively low risk patient who's not having particular risk for leukemia or particularly severe cytopenias or low counts. So, this is another important point. There are some patients who have been diagnosed with MDS and are being followed for whom no treatment is really warranted. That's just to say that their drop in counts may be very mild. They're not dependent on transfusions. Their degree of anemia is mild enough that they're not really having symptoms from it. They're not bleeding. They're not having infections and there's really no imminent risk for any kind of evolution to acute leukemia and it's important to identify those patients because why treat someone if they don't need the treatment just yet and there are patients out there, therefore, that are living their lives quite comfortably off of therapy but being followed closely so that when the time comes that they need some treatment, we'll be able to provide that for them.

For those patients who begin to drop their counts and require some supportive care, red blood cell transfusions play a major role in the quality of life for those patients who… particularly who have anemias with hemoglobin less than seven to eight and have some of these symptoms. There's an agent called EPO. Erythropoietin is a hormone that the kidneys typically produce that tells the bone marrow to send more red blood cells to the body because the hemoglobin is too low and in recent years we've been able to come up with a recombinant EPO called Procrit that's in injectable form to be able to stimulate the bone marrow to increase the red blood cell marrow production and many of you probably heard of Procrit and maybe even received it. There are

certain guidelines under which Procrit should not be given just because there could be clotting risk and things like that. So, it's not for everybody and it's not an indication that should be taken lightly because of the potential complications, but it certainly helped many patients. Likewise platelet transfusions for folks that have platelets typically less than 20,000 the outpatient setting or if there's frequent nosebleeds or other bleeding and then in a similar vein Thrombopoietin is like Erythropoietin, but it stimulates the production of platelets from the bone marrow and there are agents called TPO agonists that basically turn on the bone marrow to produce more platelets and so in some patients have received platelet transfusions, but they have developed antibodies to that and they may no longer benefit from that or for other reasons they may be more appropriate to receive these TPO agonists and so the ultimate goal is increasing the platelet number produced from the bone marrow and then in addition there's a drug called EMACAR, epsilon aminocaproic acid that suffice it say it deals with the coagulation system in such a way as to make sure that people aren't over anticoagulated. So, it can help in terms of bleeding risk typically at the mucosal sites like mucus membranes of the nose. So again, patients that have MDS with frequent nose bleeds may do well with a little bit of EMACAR to minimize that risk.

And then finally in patients whose white blood cell count cell line is low and is typically neutropenic, a term that refers to a low absolute neutrophil count in with which you may be familiar and certainly increases your risk for infection. In the setting of neutropenia giving growth factor we call that Neupogen or Neulasta is one that lasts for two weeks and that's a bit more shall I say aggressive to give Neulasta. So, most patients are on, say, a couple times a week of Neupogen and this is designed to increase the white blood cell count and the absolute neutrophil count enough to keep the neutrophils above 500 so people aren't at risk for infections. So all of these, again, are given to the lowest risk patients or the patients who are frail enough that we really can't give them more aggressive therapy and they serve to enhance the quality of life in terms of functional status and minimize risk for development of some of these other complications.

What about low intensity therapies? Well again, as the risk for MDS increases a little bit for complications, patients are going to be considered for additional therapies. So, this I should also point out these are noncurative therapies but they're therapies designed to enhance quality of life benefit and to stabilize the disease. So, the first group of agents is the hypomethylating agents and there are two primary agents – 5Azacitidine, the trade name of which is Vidaza and Decitabine, the trade name which is Dacogen and these are available as outpatient modalities. They can be given either intravenously or subcutaneously in the outpatient setting, typically Monday through Friday in the clinic. They're given over about a half an hour and there are three days off… I'm sorry. Three weeks off during which time counts are monitored because just like any chemotherapy agent counts do drop after this, but the patients generally tolerate this quite well and then come in three weeks later for their next cycle. So, it's generally given at 28 day cycles. We certainly have patients that are on this therapy for months to years with the benefit being that these hypomethylating agents interact with the DNA in such a way to disable the cells and in that way have a benefit and in patients that have done well after, say, four to six cycles

and clearly it's benefiting their MDS, we may keep them on this indefinitely and even move out treatments to every six weeks or so. This really serves two functions. For patients who are not ultimate candidates for an allogeneic stem cell transplant this serves as a very good maintenance to just keep the disease stable for as long as possible until other therapies are warranted. For patients who are feasible candidates and who desire pursuit of an allogeneic stem cell transplant, either of these agents can serve as a nice bridge to a transplant. So, we'll often keep patients on this if they're very stable and just wait for a hint that things are starting to maybe move into the next phase and then decide that we're going to take someone to transplant, but if you're destined to be stable for, say, a year or two on Decitabine or 5Azacitinidine there's no reason to take someone to transplant early when they could have had two years of relatively comfortable living and coming into the clinic periodically but avoiding going to a transplant that soon.

Any questions about these agents or what I just said? Yes?

Q1: You just made two comments. One that if they're stable on like a Vidaza for a year, but then you also indicted that you could be on this for several years.

Dr. John Hill, Jr.: Well, I guess I wouldn't want to say several years, but more than… several months to a year or two. We've had patients that whether they're transplant candidates or not they respond very well to this therapy and the disease is stable for quite a while. Quite a while meaning several months or a year or two. If at some point the disease starts to progress and they're not a candidate for a transplant then we would go to additional therapies, nontransplant therapies, to try to stabilize their disease. If they are a candidate for a transplant we would move to transplant fairly quickly. The idea is to not have them progress significantly before a transplant, but if we get a hint that things are starting to move along that would be a time to transition to transplant, but if you're destined for a year or two of stability on one of these agents, it's definitely in your best interest to not have to go to a transplant right now.

Q1: Thank you.

Dr. John Hill, Jr.: The next group of agents are the immunomodulatory agents or what we call IMiDs and Lenalidomide/Revlimid is really the primary one that's been utilized with MDS. Certainty Thalidomide being another one. That's played a role, but Lenalidomide has been… really revolutionized treatment especially for a subset of patients who manifest something called the 5Q- syndrome. So when we look at those cytogenetics that Dr. Lowery mentioned, if there's a deletion of chromosome five on cytogenetic pattern there are some other factors that also play into it, but those patients are referred to as manifesting the 5Q- syndrome and we know that in particular Lenalidomide is very effective in treating those patients. If they manifest that cytogenic abnormality along with others, there's still a role for using Lenalidomide in that they may still have a reasonable response. Lenalidomide is also used in patients without 5Q- syndrome, but the efficacy is not as good, but we still use that as a daily oral agent for many patients with MDS. Now, it bears mentioning that Lenalidomide/Revlimid has many, many

effects at the cellular level. When it was first discovered, we know that the primary effectiveness was noted to be antiangiogenic meaning that it starved… it starves tumors of blood supply that otherwise would continue to feed the tumor whether it's in the MDS setting or other settings, but that's really just the tip of the iceberg in terms of MDS. This also has many other cellular functions. It inhibits something called TNF alpha, tumor necrosis factor alpha, which is at play in the proliferation of these cells. There are interleukins six and one and 12 that are also at play in terms of what's happening to stimulate these abnormal cells and it can suppress that. It also plays a role in working with the patient's immune system, the T cells, in terms of tumor surveillance and suppression and so that can be an issue and then finally there's something called natural killer cells that also play a role in trying to ameliorate the tumor response or the aggression of these tumors of MDS and it also plays a role in effecting that. So, there are four or five levels that which the IMiDs work in the cell to try to improve thigs with MDS.

Any questions about Revlimid or this type of treatment?

The next group is the immunosuppressive agents. Certainly you've all heard of Prednisone, anti-thymocyte globulin is another one that's used less frequently and what I would say about this is two comments. There is an autoimmune basis for myelodysplasia in terms particularly of the bone marrow failure part of it. It's not expressed in the same way by all patients. In those patients that might have a more prominent autoimmune basis for their marrow failure, Prednisone would be relatively more effective and there's certainly a subset of patients that we term hypoplastic MDS. So, some patients will come in. They'll present in a manner that looks like aplastic anemia which is basically a disorder where the bone marrow is completely empty. So, you saw the slides that Dr. Lowery had up here of a typical MDS marrow and the cells are angry looking. They're abnormal looking and you may see a preponderance of blasts, you may not, but in this type of situation you see an empty bone marrow and we're sometimes fooled to thinking well that's aplastic anemia, but we typically in many cases will at least give the patient consideration for a trial of Prednisone because if it turns out that it's a hypoplastic MDS rather than the classic aplastic anemia those patients may very well respond because there's a particularly high autoimmune basis for this. So, that's really the role for Prednisone in most cases in this setting and then just to reiterate these low intensity agents, they're low risk, well tolerated and it can improve counts and quality of life but not cure you.

What about the high intensity therapies? Well, this is clearly for patients who are manifesting high risk disease and also who can handle more aggressive therapy and these are generally provided on the inpatient setting. So, it requires admission to the hospital, sometimes long hospital stays. In most cases if we're talking about AML induction therapy, it's going to be a month in the hospital and what we end up doing basically is patients with increased blasts, I already mentioned this group, RAEB1 or 2, refractory anemia with excess blasts. Those are patients that have high risk for imminent development of AML. We sometimes just go ahead and treat them as if they had AML because they're close enough to tipping over into AML and the classic first induction therapy that we use for AML is called seven and three. It's seven day s of a

drug called Cytarabine and three days of a drug called Daunorubicin and so seven and three is utilized quite often in patients with very high risk MDS especially the RAEB2 type and the goal is to knock them back down so that the blast count is less than five percent ideally or at the very least less than 10 percent. So, they're back down to an RAEB1. Now, in some cases that doesn't work and there's even one person in the audience for whom that didn't work and we went to something called GCLACK (sp? 29:26) right here and that actually did very well they were back down to no excess blasts and then underwent a successful transplant. So, this actually served as a bridge to transplant to reverse the disease, put it back I a stable situation and then allow the patient to go to transplant. What we don't want to ever do is to take someone to transplant with imminent AML because if you've got excess blasts and we take you to transplant part of what we have to do with an allogeneic stem cell transplant is give immunosuppression so that you don't reject the donor cells and that can actually cause the disease to flourish and we don't want to end up having infuse the donor cells and the now the patient's got acute leukemia and now we're scrambling to try to figure out how to treat it.

So, as you probably gather this is sort of another talk in and of itself but there are a couple things on the next slide that I'll mention. It's important to note that this is a potentially curative modality for select MDS patients and yes, we do take patients up to age 75 years. That would be a very robust patient in their 70s who could tolerate a transplant and so, of course, we have to look at our patients very carefully and I'll talk about that again in a little bit and just to digress for a second it used to be that allogeneic stem cell transplant utilized high dose chemotherapy for everyone and then we realized that there's something called a graph versus tumor benefit where essentially the donor cells help to mop up the disease in addition to replacing the marrow and then we realized that we could provide this even with gentler forms of conditioning therapy. So, hence the ability to give transplants to patient up to 75 years or so when previously we could only do it with patients in their 50s. Again, with higher intensity therapy there's higher risk and yet a potential cure for the disease with the transplant. So, chemotherapy is not curative, but it offers more rapid disease control. Transplant's potentially curative, but both of them offer higher risk to the patient.

So, I'm going to say a couple things about transplant here and then we'll move on to the end of the talk just because there's just too much to say about it, but trying to hit the high points and I'm happy to talk with folks after or answer questions. So, what's the rationale for an allogeneic stem cell transplant? Well, we're replacing the disease, the diseased bone marrow with healthy donor marrow and we're invoking this graph versus tumor or graph versus MDS benefit meaning that in addition to essentially replacing the marrow with the healthy donor cells, that's only the first part of the process. The stem cells replace the diseased stem cells because remember this is a stem cell disorder. The healthy stem cells from the donor replace the diseased stem cells of the recipient, but then the donor T cells and the aftermath of the transplant, those donor T cells exert a graph versus MDS effect that over time helps to eliminate the remaining MDS. It takes time. It's not a quick fix, but we see in patients that undergo an allo transplant that with successive bone marrow biopsies after the fact that when this works the way it's supposed that the bone

marrow becomes normalized. So, that's the graph versus MDS effect. What are the indications? Well, clearly high risk MDS due to progressive marrow failure or progression towards AML. So, either one of those cases, but remember it has to be in eligible patients, patients that first want to have a transplant and secondly are healthy enough to endure it. So, the best way to sort of sum that up is to say otherwise healthy, active patients up to age 75 who desire this form of therapy, have good organ function, have stable MDS after chemotherapy and have an available caregiver support. So, we really… a family member or a friend that can be sort of a 24/7 caregiver in most scenarios is really mandatory.

And then just some list of important issues/considerations regarding marrow before we move onto the next slide. So, this is a complicated process. It's the marathon. It's not a quick fix and there are many factors that can affect the outcome. Patient age and pre-transplant status. The disease status at transplant. This has held up. The IPSS score and there are other scores that we take into effect that may even be more telling, but the IPSS score basically does translate into how one is apt to do after transplant in terms of relapse and whatnot. It's important to note that donor availability is different for each patient and the degree of HLA matching. Some of our patients don't have a HLA match, either sibling or unrelated and we have to do a cord blood transplant or things like that. So, there are just different variables here. The conditioning regimen for transplant varies depending on the patient's ability to tolerate it and how aggressive the disease has been and then, of course, there are potential complications – infection, graph versus host disease and just to mention graph versus host disease is sort of the flip side of the graph versus tumor effect. The benefit of graph versus tumor means that the donor T cells help mop up the disease. The down side is that when those donor T cells start to react against tissue, host tissue, your GI tract, your skin, your liver that can be a significant complication. So, it can be hard to try to steer thing in the right direction and people can get into issues with GVHD, but in most cases it's treatable, but it could certainly be life threatening and then patient and caregiver compliance can be a pretty important factor. We want you people to be coming back weekly initially and then we gradually space that out, call in when you're not feeling well, when there's a change in status and that sort of thing. So again, just to emphasize it's not for everybody. It's a long complicated process, but increasing numbers of patients are in remission and living with good quality life after an allogeneic stem cell transplant.

I think this is my next to last slide for those that are getting antsy.

So, what I wanted to highlight here. There are many different agents that are being considered and there are combination therapies. I really wanted you to have an appreciation for the fact that through clinical trials and other testing there are agents that are on the horizon that are really being brought to the fore essentially from the lab to the clinic almost on a monthly basis. I've highlighted those here that are particularly have been shown particular promise and I should add that in hematology oncology circles, a response rate of 30 to 40 percent is actually quite good. We never get 90 to 100 percent. It's very rare. So while if you're child or your grandchild comes home and I says, "I got 40 percent on my quiz," that's not so good. It's pretty good in our circle.

So, these are all agents that if we have these at our disposal we're feeling like we got several things that we can help to utilize for our patients. Many of these are targeted agent and that's sort of a wave to which we're moving in this field. We're understanding more about what underlies the development of cancer and what causes the cells to evade chemotherapy and we're getting more specific therapies, more targeted therapies that can really go right to a specific protein or other site and essentially intervene.

Any questions about these or other agents?

And then the final thing I would say is just a note about clinical trials. So, you probably heard mention of clinical trials. At one point or another people may have said would you like to go on a trial and this really just explains sort of what that means. We're a relatively small center. Some centers are much larger, but one of the things that can happen is we have cooperative groups. We have several hospitals that join together to form what's called a cooperative group and then there are trials that are initiated through that cooperative group and so if you can imagine if you have 10 different centers and each center puts patients on a central trial you can get 500 or 1,000 patients to go on a trial and that's how we answer really important questions about cancer therapy. So, this is a mechanism for providing new agents to a patient population such as MDS patients so as to most accurately obtain information about the safety and efficacy of each therapy. It's done much more appropriately and with checks and balances in this way and then one example of the benefit and this refers to what we call a phase three trial. In some settings this may allow a new treatment regimen to be compared to the best current regiment with determination that the new regimen is an improvement over the current best standard. This is an important way in which progress in cancer therapy can move forward. So, I have to acknowledge this is a relatively rare event that this happens, but it certainly happens periodically and we're able to say, "Gee, we thought Revlimid was the best treatment for low risk MDS patients who require therapy beyond supportive care," but now we have the trial where they just compared Revlimid to something else and we found that that was better and so now we're able to tell our patients we're not going to put you on Revlimid. We're going to put you on something better than that. So, this has been occurring in this field for the last several years and has allowed us to move forward and so it's a little bit of a plug for why we'd like to initiate clinical trials here when we can and why we recommend patients who will at least consider it. Again, a clinical trial isn't for everybody the same way transplant's not for everybody and… but it's something to think about and we hope to move the field forward with these.

This summarizes actually the treatment schema. It really reiterates what I've already said. Am I low on time? Okay. So, this is in your packet and you can see that it basically this is low risk MDS. This is high risk MDS and you can follow it through, but I'm happy to talk about this individually with you after and I just want to end with on a hopeful note I think it's important to emphasize that people don't go into hematology oncology because it's a glamorous field. We go into it because at one time or another whether we're physicians, nurses, other social support workers, other folks, we've had some sense of generally contact with a person with cancer or a

family with cancer, something and it's been really positive rather than being frightening or well, it can be frightening, but it's been invigorating in some sense and so there's a lot of hope among cancer providers and certainly in our group we're kind of a glass half full bunch and I want to mention that in the context of discussion about a really tough disease that can potentially be fatal, but can also give people a good quality of life even in the nontransplant setting for many months or even years and the notion of living with cancer is really no longer one that's sort of foreign. We like to think of this process as something if we can make MDS like diabetes or high blood pressure, a chronic condition that you can live with that doesn't significantly adversely affect your quality of life and hopefully doesn't threaten your life then that would be our goal and so on that note I just want to thank everyone for coming and take any questions.

Q2: Actually, I have two questions. One is about graph versus host. Since I have it, will it ever go away? Will it stay with you for the rest of your life? I know it can get worse. Question number two, can your MDS return?

Dr. John Hill, Jr.: Okay. So first question and some of this relates a little bit to the type of graph versus host disease that people have and I can be more specific but basically it used to be felt that GVHD if you sort of managed it long enough with kind of burn out at a certain point and that still can be true, say for instance, a cutaneous graph versus host disease that is not the type that causes sclerodermatitis changes. Other things like ocular GVHD and oral GVHD. Those generally if they're well controlled often get better over time and then kind of are not an issue. Something like pulmonary graph versus host disease which can be a very serious problem that's not something that if someone has that then it's just going to get better. We try to support that as much as possible, but that kind of doesn't go away. So, it depends on the severity of the GVHD and what organ system is involved and then MDS can it come back? You mean after a transplant?

Q2: Yes.

Dr. John Hill, Jr.: Absolutely. MDS is like any other malignancy. It's like leukemia, lymphoma, that sort of thing. So, it's dependent upon initially going into transplant with control of the disease, having an optimal graph versus MDS effect, maintaining the stability of your graph, not having a scenario where you reject the graph that sort of thing. There are a lot of checks and balances that have to remain there and the longer that someone is in remission after transplant the more likely they're going to stay that way and hopefully that's reassuring to our patients rather than wondering, gee, when is the next shoe going to drop, but certainly no one can tell you that you're home free or that you're cured. We don't use the 'cure' word because we just can't know. Again, if you're in remission for years and years, you're most likely going to stay that way and that's the best that we can tell you, but it is true in most cases.

Q3: If it does return after stem cell transplant, does it come back in a more severe type or…?

Dr. John Hill, Jr.: That's great question. Hopefully based on being monitored closely, if it starts to come back it's detected relatively early on and some more treatment can be started such that it doesn't suddenly come back in, say, a leukemic form or something like that. So, it's not that that can't happen. Sometimes diseases just come back very aggressively, but in most cases if there is good monitoring and checks and balances we detect it early because the counts start going down or we see some evidence of something different and then are able to hopefully utilize more treatment.

Q4: Is it cancer?

Dr. John Hill, Jr.: MDS is cancer. That's a great question.

Q5: You got to be careful I think with that because it's actually not a cancer, but it's a series of cancers, lung cancer, breast cancer (inaudible 46:11).

Dr. John Hill, Jr.: At one meeting, so I think there is a debate and if you have some changes in the bone marrow early on and we might say it's not although at a recent ASH meeting someone got up and said, "We should stop dancing around the issue and we should tell our patients that this is an evolving cancer of the bone marrow." Now again, I think there are many different issues if you lined up 10 hematologists, but that person raised a good point. I think sometimes patients don't leave the office understanding that it can be as severe as it is because MDS has so many different descriptions of it.

Q6: Exactly what are the new therapeutic agents? Are they chemo type pill or what?

Dr. John Hill, Jr.: So, that's a good question. So, many of them are oral agents. There's something called a histone deacetylase inhibitors that are in the group and both alone and in combination with the IMiDs. There are epidermal growth factor receptor inhibitors. So, there are various inhibitory agents that often will inhibit one part of a particular biologic cycle. Some of those are oral. Some of those are intravenous. It's hard to answer your question in a yes or no form. Yes, are they oral? Some are oral, some are intravenous.

Q6: Now, are they available now?

Dr. John Hill, Jr.: Well, most of them are still in clinical trials. The results that I gave on that slide of those response rates were largely based on recent clinical trials and so in many instances having shown some efficacy they're going to be more available, but remember that if things aren't FDA approved for a certain use they're hard to get to the clinic unless it's on a clinical trial. So, the optimal thing would be if there's a large clinical trial and our center's involved in it and you can get that agent via that sort of thing. Ultimately if they are so effective that they become FDA approved then it's much easier. Then we just bring them to the clinic.

Q7: Could you (inaudible 48:44) RARS and RAES?

Dr. John Hill, Jr.: Sure. So, and I had a slide on the various subtypes that I thought it was going to be… kind of make people dizzy, but refractory anemia or refractory anemia with ringer sideroblasts are two of the early stages of MDS. Refractory anemia with excess blasts 1 and 2 are a little bit more down the line. So, they're higher risk and that's because you start to see evidence of increased blasts in the bone marrow. Six to 10 percent, 11 to 19 percent. So, refractory anemia with ring sideroblasts or RARS, you don't see excess blasts and you see some what's called ring sideroblasts in the marrow and so that's why it has that name, but it's lower down on in the terms of risk.

Dr. Kenneth Meehan: Thank you Dr. Hill. We're going to take a 10 minute break and after that break we're going to have sort of the four physicians sit up here for ask the expert panel and then lunch will be served at noon. So, let's take a 10 minute break and we have a number of questions that were submitted electronically, but if anyone else has any questions if you want to write them down just hand them to one of us, etc. and we'll go from there. So, let's say a 10 minute break. We'll be back in about 10 minutes approximately. Thank you, everyone.