Speakers
Steven Gore, MD
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Dr. Steven Gore: It's great to see you all. I'm Steve Gore. I'm a faculty here at Johns Hopkins in hematologic malignancy for another month and a half and I go to different horizons up in the Northeast. I'm going to be moving to Yale after 26 years here. So, I want to keep this extremely informal because I think people come to these things with all different agendas and they give me a topic to talk about that I have set up which we can talk about or not talk about. So, please feel free to throw out questions and if we don't get through all the slides, I'm totally okay with that. Whatever. So, this is a talk where… can everyone see the slides okay with the lights on?

We're going to talk about how we're changing our patient care based on our research. I'd like to start with a case, a patient whom I treated about 10 years ago on a subsequent clinical trial to the one you were on, but similar and this was a young gentleman who had been treated for testicular cancer in 1998, treated with radiation, and had normal blood counts in 2003, but in 2004 was found to have a very low white blood cell count with a very low and neutrophil count for those of you who are familiar with that. That's the infection fighting white cells. He was anemic with a hemoglobin of 9 and had low platelets or thrombocytopenic with the platelets of 44,000 and he had a bone marrow which showed Myelodysplastic Syndrome what we would call refractory anemia with excess blasts which is a high grade Myelodysplastic Syndrome and he had 10 percent blasts in his bone marrow. We would now call that RAEB2 because of the 10 percent blasts. They studied the chromosomes in his bone marrow. You can see that there's a lot of things written which means that this is what we'd call a complex abnormality because there's 1, 2, 3, 4, 5, 6, 7 at least 8, 9, at least 9 different broken chromosomes in his cells and in those days we used to call prognosticate using something called the International Prognostic Scoring System. Many doctors still use it, but it's really no longer up date to date and in the IPSS system there were 4 risk groups and he was in the highest risk category. Well, he liked to golf and weight lift, a very fit guy and wasn't about to… didn't really want to start treatment over the summer and we had this clinical trial that we were very excited about that he wanted to wait for. So, we thought we'd be up in the fall, up and running in the fall, and he was very happy waiting and he didn't have any bone marrow transplant options at that time. So anyway, he came back in November when we got the trial open and now his white count was less than 1,000 and he had an ANC of 0, platelets 3,000. This is very severe and now his disease had progressed to where he had 50 percent blasts, so we would put this in the category of acute leukemia. Now, I can talk about why I wish we never changed the name to acute leukemia because maybe I will stop for a second and do that because the acute… the things that we call acute leukemia associated with Myelodysplastic Syndrome where they grow out of Myelodysplastic Syndrome really are very dissimilar from all the other acute leukemias that we treat and patients and doctors including hematologists don't really appreciate that and so everyone, I think, I think this system puts peoples' focus on everyone's afraid when am I going to have acute leukemia and it's not like that. It's like 1 day you have 5 percent blasts, someday you'll have 7 percent blasts, some day you're going to have 9 percent blasts, some day you'll have 18 percent blasts. Your body doesn't know and at some point we're going to change the name based on your blast count, but it's not like your disease has changed and I think that if you can think of this is just being 1 spectrum. I think that these things that we call acute leukemia should be called VVVBMDS, very, very, very

bad MDS because that's what it is. Well, I'm serious because then we would… it would just make more sense and we wouldn't get into this freaky thing about oh my God, I have leukemia today! It's like MDS is a kind of leukemia. We can talk about that, too. So anyway, but anybody would recognize this 50 percent blast as being advanced enough and his chromosomes are worse and he was the first patient on this trial which involved Azacitidine which now is FDA approved as Vidaza. It wasn't FDA approved in those days and he got a 10 day schedule. It's probably similar to something you got which is something we've developed here, a lower doses for longer, and he got an experimental drug called MS275. It's now called Entinostat and it's still investigational but very excited because it's been given breakthrough status by the FDA meaning it's on a fast track for approval and I'm pretty excited for the company that's developing that drug. This is an oral drug that we're hoping would make the Azacitidine work better.

Entinostat. I don't believe there's any MDS studies going on with Entinostat currently. So, he started the treatment in November. He had a yeast infection in December and then came in coughing up blood with pneumonia and positive blood cultures and in January he was having fevers again and his esophageal infection was worsening despite antifungal medication and his infiltrates in his lung were worse and he was so sick after about 3 weeks in the hospital that he ended up going to subacute rehab. If any of you who have dealt with rehab, subacute rehab is really nursing home. It's like you're not strong enough to be in the real inpatient acute rehab. This is a guy who, like I said, was lifting weights several months before and I was really worried that we had had our investigator hats on a little too tight and when I saw him and he told me he really wanted the summer off, I should of said don't wait for the clinical trial. You got trouble. So, I was a little worried about my ethical status. Well, his wife was extremely proactive and the nursing home didn't want to administer experimental drugs, but in those days Azacitidine when we got it from the NCI could be self injected and thousands of people reconstituted Azacitidine Vidaza at home and injected themselves. That was standard until the lawyers got involved and told the drug company they shouldn't develop it that way. It's unfortunate. So, she was just self injecting him and so she convinced them to let him stay on the trial because he'd have 3 cycles and we had told her that for Vidaza, for Azacitidine, it takes 4 to 6 cycles to see a response and so here he had gone through all the pain with no chance for gain. So, they let her do that and they start sending us the labs and reticulocyte count, these are the young red cells that are made in the bone marrow and show up in the blood transiently. So if people make reticulocytes, it means their body is making red cells and a lot of hematologists forget to measure it and most patients have never heard of it. So, we like to measure the reticulocyte count to see if the red cells are kicking in. So, the arrows show when he got cycles of treatment. So and the scales are different on these 3 maps, but here's the reticulocyte count. First cycle, second cycle, you can see is basically making no reticulocytes and at the fourth cycle, all of a sudden he's making reticulocytes. Now platelets, the 3 cycles previous, are off the map, but you can see his platelet count is very, very low and then after the fourth cycle, his platelet count shoots way up. Similar to his white blood cell count, totally in the toilet until the fourth cycle and his white count goes up. This was 2005 now and he developed a complete remission and his chromosome's normalized and he stayed… Question?

Q1: I just wanted to (inaudible 8:25).

Dr. Steven Gore: On Azacitidine which is Vidaza plus this experimental drug that he was taking orally, Entinostat, MS275. So, he still didn't have a bone marrow transplant option in those days although nowadays he would have and he stayed in remission about 2 or 3 years on treatment, did a lot of motivational speaking at leukemia society functions, so was really one of the greatest people I know and unfortunately relapsed with an aggressive leukemia from which he couldn't achieve remission and eventually succumbed to his disease and I like to do these lectures in his honor because I've learned so much from him and his wife, but also I think it's highly relevant today because in those days, we were just starting to, here at Hopkins, study the possibility of doing transplants with matched… with relatives who are half matched. So in those days you needed either a full matched or find an unrelated donor who was fully matched and if you couldn't, you were… you basically had no options and in those days our half matched thing was so half baked, in my opinion even though our transplanters were very enthusiastic, but I didn't feel that I could legitimately send a patient of mine to that who was otherwise still waiting for an unrelated donor who was salvageable in my opinion. That was really for the worst of the worse, but the truth is that now we think of these half matched transplants as being comparable or potentially even superior to fully sibling match. So if were he treated now, we would have taken him straight from remission to a half matched sibling transplant he probably would have been cured or at least he would have had a 50 – 60 percent chance of being cured. So anyway, this is why people need to put this faith in clinical trials because this is just less than 10 years ago. This is 8 years ago, a man who unfortunately died of a terrible disease probably would have been cured today and it's because of our wonderful, brave patients who are willing to go out on a limb and get these half matched transplants out of desperation back then and like I said, I wouldn't send my patients to that because I felt like if you had any other option, but we've gotten a long way in a short period of time. Jayshree?

Jayshree Shah: How many (inaudible 10:47)?

Dr. Steven Gore: Hundreds.

Jayshree Shah: For MDS.

Dr. Steven Gore: Oh, I don't know the number for MDS, but our total number is hundreds and of them probably 50 to 70 are MDS I'm guessing. So, I didn't update my risk stratification slides I don't think. Maybe I did.

Jayshree Shah: I have one updated.

Dr. Steven Gore: Do you? Okay. With the IPSSR, the WPSS. Good. So this is the old International Prognostic Scoring System and it looked basically at the marrow blasts and the chromosomes and how many of your blood counts are low. Now you can see that you could have zero low blood counts and still have MDS and you'd say, "Well that doesn't make any sense. I thought MDS was all about low blood counts," but that's because the cytopenias or low blood counts are very strictly defined. So, platelets of 140,000 are not normal, but they wouldn't count in this counting system. You'd have to be less than 100,000 to get a point for that. So, it's like the old fashioned Chinese restaurants, 1 from column A, 2 from column B, but you add up your points and you come into 1 of these 4 risk groups. Again, we don't use this system. We shouldn't

be using this system any longer, but these are called survival curves for those of you who are not familiar with them and I think they're useful as patients to be able to interpret survival curves because some people like to look on the Internet or look at some of the medical literature or if your physician wants to show you things like this it's helpful and in the survival curve, the X axis is time, in this case 19 years, and when you're starting, hopefully, everybody's alive. So at time equals zero, 100 percent of the people are alive and unfortunately as people expire or pass on, the curve drops down. So here in this low risk group, it's 7 years about half of the people have passed on, but you can see here at 18 or 19 years, 20 percent of the people are still alive and so on and so there are these 4 risk categories and we've gotten much better about this because you can see well, you tell me I'm in this intermediate 1 group and there's a group of people that seem to live forever potentially out here, but people are still dying up here and if you're making decisions about your life you'd probably rather know if you're a person who's going to die earlier or not because somebody up here might really want a stem cell transplant. Somebody's going to live just fine without a stem cell transplant may not want to take the risk.

I'm going to skip that.

So, what does this mean as a patient? So, in the IPSS like I say is not the most up to date system. I can get you some slides or maybe Jayshree will, but the bottom line similarly your doctor can use very simple information from your blood and bone marrow test to give you some idea of how long your disease is likely to remain stable and this information is very helpful in choosing therapies and planning your life. I personally use the WPSS scoring system that was developed, let's see what my next slide is. No. The WPSS scoring system stands for World Health Organization Prognostic Scoring System. It's very unpopular in the United States because it was developed by Europeans and peoples' egos are crushed and it's very easy. It involves your pathologic diagnosis that the pathologist will give you based on your bone marrow and blood studies, your chromosomes, I think, and whether or not… and your hemoglobin. It's very simple. Three… I may be forgetting… Three things, right? The good thing about the WPSS scoring system that's different from every other scoring system is that when the statisticians, what they do is they take hundreds of patients' data and they do statistical modeling to predict survival and in the WPSS system, they programmed it so that if a patient was getting worse, they kept them in the model and they would move them from 1 group to another. All these other systems only are really based on how you are diagnosis. So in the IPSS or even the new IPSSR, the revised IPSS, it's not really meant to tell you how you are 3 years into the disease. So it's really only meant to tell you what to expect from the beginning. With the WPSS, you can calculate your WPSS any time and it's still relevant. So, I like the WPSS now. Since the IPSSR and believe me I get made fun of in the United States among that powers that be when they say, "You're using the WPSS when there's this IPSSR." The IPSSR, first of all, you need a computer. It's like it's got 12 different groups and 5 different points and I can't possibly retain it and my phone app doesn't have it on, I can't have WPSS on it.

Jayshree Shah: (inaudible 15:48) patients that have that connection (inaudible 15:50).

Dr. Steven Gore: For the IPSSR? Maybe I have to download a new one then, but anyway so in the past year since the IPSSR has come out for every new patient that I have, I calculate both the WPSS and the IPSSR. I have not once found one that differs. They're exactly the same and the

WPSS is so much easier. There's five risk groups now – intermediate, high, low and very high and very low. So very high risk, high risk, intermediate risk, low risk and very low risk. So anyway, so I like the WPSS, but if your doctor is using the IPSSR that's fine, too.

Okay. What are the goals of therapy in MDS? They need to be individualized both because there's a lot of variability between the diseases that we lump together as MDS and patients have different goals. A 35 year old patient may have a very different set of goals from a 75 old patient. I have 75 year olds who want to be much more aggressive than some 50 year old patients, which kind of surprised me because it's not how I would be, but it's not for me. It's not my life. It's their life. It's not my drama. It's their drama. So obviously, we would like to improve everyone's survival if we can. We almost more importantly we need to control symptoms if people are symptomatic. We like to improve their blood counts. We want to decrease the risk of their disease getting worse whether we choose to call that AML, of VVVBMDS and we'd like to improve quality of life and this is a slide that a bunch of put together, oh, probably 13 years ago, 12 years ago and it's still… and it's been modified, but that's really still the way I approach patients with MDS. So the overall question is is this patient now or will this patient ever be a candidate for stem cell transplant because that's our only curative therapy. What goes into that decision? Well, a lot of it has to do with patient goals and attitude. Is this a patient who really wants to be aggressive with a chance of being cured? Is this patient overall healthy enough to undergo more intensive therapy? That has a lot to do what we call comorbidities or other diseases. So if you have long standing diabetes and obviously which is not well controlled, say, and heart disease and so on and a lot of chronic illnesses, well, it's going to be pretty hard for you to tolerate a transplant probably, but age per se not so much. So many centers now are doing transplants through age 75. Above age 75, very rarely. Certainly here at Hopkins, we pretty much won't. The Fred Hutchinson occasionally will. So is this patient now, will this patient ever be, does this patient want to be considered as a stem cell transplant candidate and either way we then look at what risk category they fit into. Again, this slide was made with IPSS, but we could make it with any of the risk categories and we have 1 set of treatments that we offer to lower risk patients and for higher risk patients, their choices are really Vidaza and/or allotransplant or clinical trial and we'll walk through some of this.

So that tells me I'm probably talking about the high risk diseases first.

So, why do I talk about Vidaza and not Dacogen? Some of you may be on Dacogen, nothing wrong with it. The reason I talk about Vidaza and not Dacogen because these are very similar drugs although they're not exactly not identifiable. They're both drugs that people tend to call hypomethylating agents. They work on a chemical modification of DNA called methylation. This isn't my area of expertise and I'm not convinced that that's how they're working. So, I call them DNA methyltransferase inhibitors because that's the enzyme the inhibit. It doesn't really matter. You can call them Aza drugs. Anyway, both drugs have been studied in randomized trials looking at their outcome and survival in high risk MDS patients and Vidaza improved survival and Dacogen didn't in 2 different studies. So everybody would like… wanted to believe that the 2 drugs were the same. Certainly the drug companies wanted you to believe that, people to believe that, and the studies we looked at survival with Dacogen used a different dosing schedule than the one which is commonly used now, but the one that's commonly used now has never been tested in a survival study. So if a patient asks me which one should I take? If they have high

risk MDS, I say, "Well, if your goal is to improve your survival, the only one we know that does that is Vidaza," and I don't really understand why anybody chooses Dacogen because to me it's just not the right choice not to say there's anything wrong with it because I do think in my heart of hearts they're probably very similar, but those are the data and I like to base my treatment on data. So in the Azacitidine survival trial which was actually started after Vidaza got FDA approved, but was being planned by the Pharmion Company because they didn't expect to get full approval and they knew that for European approval they were going to have survival data not just showing that the drug improved blood counts. Patients were seen by their doctor and their doctor chose 1 of these 3 usual regiments for them either best supportive care meaning they would get transfusions and things like Procrit like that or in Europe it was very popular to give and certainly in certain countries like France low doses of a chemo called Cytarabine. This is a very old fashioned MDS therapy that we don't tend to do very much in the US or some patients might get selected to get very aggressive leukemia style, acute leukemia style, chemotherapy. So in Europe, these 3 were felt to be all legitimate standard care and so the doctor would choose and say, "Mr. Smith, not on this trial I would give you intensive chemo, but if you want to be on the trial, we're going to randomize you between the intensive chemo and Vidaza," or, "Ms. Jones, in your case my standard treatment for you would just be to give you transfusions. In your case if you go on this trial, we're going to randomize you between Vidaza and transfusions." So they really wanted to randomize people between Azacitidine and what the doctor would do for them anyway. It was really like what's on the ground, what really is happening? Not something we made up and remember we talked about survival curves. Everyone starts alive and unfortunately not everybody continues to live. These are high risk MDS patients including a group that now gets lumped into the leukemia side, the more VVVBMDS. It used to be lumped in MDS. So, people with 20 to 30 percent blasts in their bone marrow and you can see that at 2 years of follow up that the number of people alive in the Vidaza arm was twice that of people getting any of the combination of the other arms and this is what established survival improvement and you can see the average survival was improved by a couple years or 15 months here anyway. So, this is how we know that Vidaza actually improved survival not just improves blood counts. It improves the blood counts in 50 percent of the patients who received the drug as well.

So, what does this mean for you as a patient? For high risk MDS patients, Vidaza Azacitidine doubles the number of patients alive at 2 years compared to other common treatment strategies. Now, here's the trouble that I have with patients or that patients have with me more likely is that I'm giving people Vidaza and as you'll see it takes 4 to 6 months to know if it's working and I encourage people to be patient. So now it's 6 months and their counts are still not so terrific. Welcome. They're still getting transfusions. We'll do a bone marrow test. It looks stable, but it ain't improved and you know Vidaza, they're coming into the clinic 7 days a month for the shots unless I finagle somebody for them to self inject that I still do when I can and then they're coming in for transfusions. To me, it's still a lot and they say, "Oh, doctor. I know I'm doing better. I feel I'm doing better. You tell me it's improving my survival," so we really wanted to know who in this trial was surviving longer. Every… you know was the whole group surviving longer or just the people who were showing clinical benefit and so we did a lot of statistical analyses and first of all we took the patients who had any kind of blood improvement at 3 months in either arm. So on this graph, you've got the patients who no matter what treatment they were getting had some improvement at 3 months and those patients who had improvement and we're getting Aza survived longer than those patients who were getting 1 of the control arms

and had improvement. So, improvement on Vidaza seemed like that was better. Now, what about people who had improvement or better at 6 months? Same thing. Those patients who at 6 months were improved in the control arm survived much less well than those people who had improvement on Aza at 6 months. You can see the people on Aza were doing pretty well if they were out 6 months and improving. The same with 9 months. Now, what if your best response at 3 months was that you were stable? No improvement, but not worse. Well, the advantage here looks like it's still to Aza, but don't forget some of these Aza patients between 3 and 6 months are going to start responding and so when you look at 6 months at those people who are stable in either arm, the survival curves are exactly the same. So, let me just go over that. So, the people who are stable at 6 months and not improved, we can't say that they're necessarily doing any better than the people in the control arm who are stable. Now, the company which is now Celgene had us do some hand wavy kind of things that are probably true which suggest that the group that's stable in the control arm is not as sick a group to start with as the group that was stable on the Vidaza arm and so that being stable for that group is more of a big deal than being stable these other guys, but I think that's hand wavy and we submitted the paper the first time with that and the reviewer said, "Phht. Take that out," and we did. So when I see a patient like the one I told you about just a minute ago who was stable at 6 months and not improved, I just have a frank discussion with them. I say, "I don't know if it's helping you live longer. It might be, but the data doesn't let us know that and if you feel that you're doing better and you don't mind being getting the shots 7 days a month, we can continue because we have no reason not to unless we have…" I might encourage them to go on a clinical trial or do something different depending on what their goals are and the researcher that I was mentioning before, Tiana, fully believed in that study that I showed you that my patient, John, was on that in the patients who we thought were not responding in that study if you didn't have an improvement after 6 months, you had to stop. She fully believed that there were a bunch of patients when we stopped, they just got worse and a lot of clinicians have that experience or issue. I don't know what your experience is that there are patients we don't know are doing better. They're not doing better but when you stop the Aza, they seem to get very worse.

Jayshree: I think it's also individually based on (inaudible 27:37), but I think moreso my patients they've always expressed that they become transfusion independent. That was a big decision making kind of a point for that…

Dr. Steven Gore: The transfusion independence, those are responders. So for sure those people should stay on.

Jayshree: Yeah. I agree with you that way, but they definitely regress if you stop the medication and it's declined (inaudible 28:05).

Dr. Steven Gore: So we don't really know what the best management is for those people who are stable at best, but what I would say is that most of us agree that if you're on Vidaza or Dacogen and you are improving you should not stop the drug as long as it's working. The biggest mistake the doctors make, that patients make, is they say, "You've been in remission for 6 months, let's stop it," because once… because it always comes back and you won't respond to Vidaza or Dacogen the next time. For sure you won't and the survival of those patients so far with those

treatments we have right now is unfortunately not very good. So if you're responding to Vidaza or Dacogen, you should stay on it as long as it's helping and as long as you're tolerating it.

Q2: Why wouldn't you respond if you went back on it again?

Dr. Steven Gore: It just did because there's mutations in your bone marrow we presume. It's like when you give antibiotics for tuberculosis. You hear a lot about multi-drug resistance to TB because people don't take their drugs regularly, so you let the mutations get in. It's like that we think, but we don't really understand that. It's a great question. If we understood that we might be able to fix it.

So, what do these graphs mean for you? If your blood counts have improved while on Azacitidine or Dacogen, any of your blood counts, that could be your white count, your platelet count or reds then it's likely that the drug, that Aza is improving your length of survival. We don't know with Dacogen, but I, again, if you're responding to Dacogen, I'm not telling you to switch. Such patients should remain on Aza as long as it seems to be helping. If after 6 or more cycles of Aza and, again, you can substitute Dacogen your situation is stable, it's not clear whether the drug is improving your survival or not and the decision to remain on Azacitidine or not if your best outcome is stable disease should be made with your doctor as an individual.

So they looked specifically at the patients who fall into those VVVBMDS category in the same trial and the Aza patients did better than the people in the control group. So it's not limited to people who have just MDS.

Okay. Decitabine we talked about that but it was not shown to improve survival. So, Decitabine has not been shown to improve survival on Harry's patients compared to best supportive care, but the impact of the currently most commonly used dose in schedule of Decitabine on patient survival has not been tested. Decitabine is Dacogen. Dacogen is the brand name.

Okay. I told you that it takes a few months to know if you're responding to either of these drugs and this is from that same Aza 001 trial that I've been talking about that showed that Azacitidine improves survival and you can see that when we look at just improving the blood counts, 50 percent of people will have improvement of 1 or more of their counts within 2 cycles, but that 87 percent of the clinical responses show up within 6 cycles. That means that there's 13 percent of the responses still show up between 6 and 12 cycles. So, if you're stable at 6 months, you might say, "Steve, you told me that I've still got 15 percent chance or whatever. It's still 15 percent of the responders are going to show up. So, why didn't stay on it?" I wouldn't argue with you if you're tolerating it well.

Q2: What patients (inaudible 31:20) actually (inaudible 31:22)

Dr. Steven Gore: So, there you go.

Q3: It depends on the amount (inaudible 31:29).

Dr. Steven Gore: It's my experience that those late responses tend not to be as good. It's just kind of my… I don't know if that's really true, but that's kind of my punch. They don't tend to last as long.

Time to best response. Fifty percent of them the best response is at 4 cycles, again. To get 100 percent of the best responses, you're out at about 14 – 15 cycles and this is just to show you how it goes on a patient. Here's a platelet counts on a patient getting Azacitidine. Red is bad. Green is good. Stop and go, right? So, the platelet count. You can see this patient is getting platelet transfusions because platelet count goes up then it goes down, it goes up, transfusion and so the patient's fourth cycle, fifth cycle still getting transfused. Sixth cycle all of a sudden her platelet counts normalize. It took 6 cycles. Neutrophils, low, low, low. It doesn't come up into the normal range until the ninth cycle. So, it just shows you how slow it goes. It takes a long time to respond to these drugs. Improving the blood counts may take up to a year.

This is an older slide. To just show you how we use these different treatments. Growth factors are things like Procrit and Aranesp. That's Erythropoietin and Darbepoetin. They mainly are used to improve red cell counts and transfusion and we can talk about how we select patients for that. Lenalidomide is Revlimid. It's an oral drug and it's indicated for patients who have a low risk MDS with a chromosome 5 abnormality. It's extremely effective in those patients. It improves transfusion and induces transfusion independence in about two-thirds of those patients. It's not very active in patients who don't have that abnormality, but has about a 25 percent response rate in low risk patients who don't have a 5, chromosome 5 abnormality, but we know that improves anemia. Occasionally, it makes the chromosomes go normal and we don't know if it improves survival. Again, a lot of my colleagues assume that it does for those patients whose chromosomes get better, but I don't think we really have any data that supports that. Decitabine or Dacogen improves blood counts, may delay progression to worse forms of MDS and leukemia. So far, it doesn't seem to improve survival based on the old schedule, but we don't know about in the new schedule. It might be a good way of getting people's blast counts down to get them ready for transplant and if we have time to talk about transplant, again, I don't know which slides are coming up. Azacitidine we know it does improve survival for high risk patients. It can also be used to get ready for people ready for transplant. Transplant is the only curative therapy.

So now, we're going to talk about lower risk. Oh, good. I don't know what we're doing next. It's been awhile since I've looked at these slides. Sorry. I talked about the study that we did using this oral experimental drug called Entinostat that first guy was on and we wanted to see and this is why research is so important because our study here looked like the responses were like off the wall great that much higher than you expect with Vidaza alone. So, we wanted to do a randomized trial. People are always afraid of randomized trials because all they're going to get is the placebo or they're not going to get treated. Most randomized trials in cancer involve active drugs and they're randomizing between 2 different things, but it's always legit to want to know if you're getting a placebo. In this trial, I told you but you probably don't remember that in this Aza study, we were using lower doses of Aza for longer, 10 days instead of 7. There's reasons to think that that's maybe a better way to give the drug based on how we think the drug is working. So, but nobody had ever studied that schedule of Aza really, the 10 day schedule. So, we felt like needed to compare this combination to the 10 day schedule. So, we did a national trial that I ran

and for awhile it was called Entinostat was called Syndax 275. We randomized between our 10 day schedule of Vidaza and the 10 day schedule with this oral drug Entinostat for 6 cycles and our goal was to double the number of patients whose blood counts not only improved but went into the normal range. So, these are people whose blood counts were totally normal, which with Vidaza alone is about 15 percent. So, we wanted to get 30 percent of the people with normal blood counts and the way it worked was the Aza alone people, we got that. The 10 day of Aza seemed to double the number of people who had normalized blood counts compared to the standard 7 day and the combination, not so much. The number is actually 28 percent in the revised data. These arms weren't statistically meant to be compared. So, we can't say that the combination was worse, but we certainly can't say that the combination was better. So, that was disappointing, but and we tried to get the national groups to adopt this 50 times 10 schedule for our future research. While everyone thought this was an interesting finding, it hasn't moved that way unfortunately. So, but Azacitidine isn't curing people. So, we still need to make it better and right now we don't have a lot of great new drugs, so people are still focusing on ways of making Azacitidine better through combination therapies. Yeah.

Q4: So, are you doing the 10 day of treatment with anybody or…?

Dr. Steven Gore: I do do it with some patients. I have a hard time… So, I try to get my patients who I'm going to treat with Aza on a clinical trial. That's my default because I think it's so important which doesn't use a 10 day schedule and lately I've been doing it less, but there was a time when I was doing it a lot. Why don't I? Again, I'd feel like of the pudding really still needs to be a randomized trial although I do believe the data. So, yeah. Anyway, I think our… one of our most interesting combinations right now is a combination of Aza with Lenalidomide. That's Vidaza plus Revlimid. Now, this was developed by Dr. Sekeres at Cleveland Clinic and he's a young protégé of mine and when he started this trial, I said, "Mikkael, that is the stupidest thing I've ever heard of." I can be kind of blunt, and I said, "You know, you have no biology behind it. There's no reason to think… we don't have any idea how Revlimid works. Why would just… Just because A has some activity and B has some activity, now A plus B. That's what you're doing." Well, it turns out it's fantastically active. So, good for him and I'm very proud of him. We're not doing this thing anymore, so we won't talk about it.

Vorinostat. Vorinostat is a drug which goes by the brand name Zolinza and it's very similar to the Entinostat that I talked about. Same idea that we think it's going to help Vidaza work better. This has been studied by Dr. Silverman in New York primarily and Dr. Garcia Manero at MD Anderson and as you'll see both of these trial… both of these treatments are in the current national trial. MGCDL103 is another one of the stat drugs. It's mostly Entinostat and these are not really active anymore. So this is the new national frontline study. It's for high risk MDS. It's run by Dr. Sekeres in the Southwest Oncology Group from Cleveland Clinic. There are about 250 centers in the United States participating including our own. It's for patients with high risk MDS and it randomizes people. So, people get randomly assigned by the computer to getting 7 days Aza which is standard or Aza plus Revlimid or Aza plus Vorinostat and if I had high risk MDS and I could get to a center and I was going to start Aza, you can't have had Aza before. If I was going to start Aza, I would want to be on the study because I don't know… a lot of people say why don't I just have my doctor give the combination. Well, you could do that if the insurance will pay for it but maybe the combination really is harmful. Like I said, we thought our

combination was the best thing since sliced bread and we did the randomized trial. It turned it was no worse, but no better. So, I really… the only we make progress is by doing clinical trials. Again, there's no placebos here. Everyone's getting active treatment.

Well, people all want to know about can you take Azacitidine orally? I've been lucky enough to be involved with a series of studies sponsored by Celgene developing an oral version of Vidaza and which is moving forward, a lot slower than it should have because their corporate strategy is one that's based on profitability really I'm afraid to say and marketability and not getting the drug out to patients as early as it could be because we could have had this drug approved 5 years ago, this oral Vidaza, I'm afraid and it will eventually get approved. So, this slide is just to show you… remember I talked about this DNA methylation thing. Just know that when there's blue on this thing it means that that DNA methylation thing has been reversed somewhat. So, we gave patients a standard 7 days of shots of Aza and we looked at their bone marrow and peripheral blood cells in terms of changing this methylation thing around and you can see that around the 15th day, there's a lot of blue which means it was having that affect and then we did the same thing with 7 days of oral Vidaza and you can see the same genes had the same thing happen. So, it just means that the oral Vidaza is getting in and it's doing the same thing to the genes that the shots do. You get less in your blood than with the oral, but remember I told you that maybe it's better to give a lower dose for longer. That's why the 10 day thing is so attractive. So, what we're developing with the oral drug is now a 14 day schedule and our preliminary data are very exciting. Now, there is a national trial. It's actually a global trial that they're doing to try to get… it's going to be for FDA registration and the European registration for oral Vidaza. That's a placebo control trial. So in that trial, it's patients with low and intermediate risk MDS who are transfusion needing and have lowish platelets. That's a group that's a little higher risk than the lowest risk and those patients are being randomized to oral Vidaza or placebo and I didn't open that trial because my patients wouldn't go on that trial and I don't blame them because if you can get Vidaza standard, why risk being on a placebo. To me… You can say well, they're lower risk. We don't know that is improving survival. I respect the company. It's a good study. In Europe, these patients can't get Vidaza because it's not approved for that indication. So, that's the only way they can get Vidaza, go on the study. There's unethical about it, but I can't offer that to a patient here in the United States if I can give Vidaza. Yeah.

Q5: So, Vidaza is not available in Europe right now?

Dr. Steven Gore: Vidaza is available in Europe but not for lower risk patients. They have much stricter regulation about following the approval indication. Here in the United States once something is FDA approved, we can give it for any indication as long as the insurance will pay for it and that's getting tougher, but in Europe if it's not indicated for that you can't give it. Yeah.

Q6: Can you (inaudible 43:43 - 43:48)

Dr. Steven Gore: Yeah. I'm not done yet. Okay. Any questions more about this?

Clofarabine is a chemo drug that's been pushed in for MDS. Treating MDS like acute leukemia, a high risk MDS can get about 50 percent of the patients into a remission. The remissions are

good. The treatment is toxic and the remissions don't last very long. So, I only do this if I need to get the blast down to get somebody to transplant. That's my personal practice. Clofarabine is one way to do it. I don't think it's any better or worse than any other chemo. It's much more expensive, but that was kind of hot for awhile. There's a thing called Telik Telintra. Ezatiostat is what it's called now. It probably has brand name. There's some clinical trials going on with it. I don't know if any of you have been offered it. To me, it's… I'm not really impressed with to be honest with you, but, again, it's a decent clinical trial. Nothing I'd go out of my way to get. This thing, Onconova 1910 is goes by the name Rigosertib now and I have to give this company, Onconova, a lot of credit because they had been given this drug and they showed that it lowered the blast counts in the marrow for a lot of patients, but nobody's blood counts improved, almost nobody's blood counts improved. Now, is that a benefit to the patient? I don't know. So, they actually did a study which we did participate in which randomized people to get this drug or supportive care to see if getting this drug and lowering the blast count thereby improved survival and if it does that's a great thing and that will help us know what to do with the people with Vidaza who are reducing blast counts, but not improving blood counts. So, that study we're waiting for the data. There is an oral version of this drug which is being studied in low risk patients. It does seem to improve red cells in some patients and it's well tolerated. Sapacitabine is another sort of chemo drug that I'm not too excited about. Now, somebody asked about Eltrombopag right? So, Romiplostim, there's a lot more data about this. This is called N plate. These are… this and Eltrombopag are growth factor treatments for platelets and the only thing you should know about Romiplostim is that it makes the blasts go up and that's giving everyone the willy's. So, the blasts usually come down again when you stop it. So, I don't think anybody's using N plate for platelets honestly, but there was a study that showed that in people getting Aza, Romiplostim or N plate could stop the platelets from going down as low as they did but that's not usually a problem for most patients. So, I don't use N plate. Now, Eltrombopag, I actually wanted to put in some slides, but there's nothing published with Eltrombopag. Eltrombopag is an oral drug. It goes by the name Promacta and is approved for the indication of low platelets based on the immune system being overactive what we call ITP. Immune thrombocytopenic Purpura, ITP, and there is some in vitro data, laboratory data, that maybe it slows down the growth of leukemia cells. That would be good. So, there have been some studies in MDS. There is some activity in terms of improving platelet count. It's not that much like 20 to 30 percent improved platelet counts. It does seem in some patients to promote scar tissue formation in the bone marrow called bone marrow fibrosis, myelofibrosis. So, I almost never use Eltrombopag outside of a clinical trial. I have been trying to get it for a patient who really needs it and I can't get her insurance to pay for it because there was this kind of a strict black box thing don't give it to patients with MDS because we don't know if it's safe, but the trials with Romiplostim specifically for MDS are going to be released soon and I don't know what the company is doing in terms of getting an indication in MDS. I don't mean to say I think it's unsafe. I just think that its safety is not validated and it's ethicacy is not that great. I think this is my last slide and then there's probably a few other things we should touch upon, but I'll try to be as open as I can. There's a new drug Sotatercept that's being developed by Celgene. It's pretty exciting. It serves as… It was made as kind of a sponge to soak up this drug… this hormone called Activin or Activin but it turns out that Activin is the family of growth hormones called TGF beta and we know TGF beta inhibits red cell production in some people with MDS. So for people with cancer, nonMDS cancer who've gotten this drug, it's been very effective in improving their anemia and so now it's being developed in MDS to see if it's soaking up this TGF beta. It's

another way of promoting red cell growth and it's a very well tolerated drug. You give it once every 3 weeks. It's pretty good. So, that's an open trial right now. We didn't talk about bone marrow stem cell transplant. We didn't talk about growth factors. I've got plenty of slide shows that I can bring slides up if any of those is something you want to talk about or we can talk about them without slides because I was asked to talk about new treatments, but I'm really totally open to talking about whatever you want to talk about. Please.

Q7: (inaudible 49:21 – 49:50).

Dr. Steven Gore: Oh. Yes. We did and so Procrit is a brand name for a synthetic version of a hormone your kidney makes called erythropoietin. Your kidney is your sensor, it's your body's sensor of your hemoglobin level and when your hemoglobin is low the kidney knows that it wants more hemoglobin to get more oxygen to the kidney, so it makes this hormone called erythropoietin or we call it EPO because patients don't like to say erythropoietin and it's hard to spell. So, the kidney makes EPO and EPO tells the red cell precursor cells in the bone marrow to reproduce and that's how you regulate your hemoglobin thermostat. Now most people with MDS, their kidneys do this just fine. So, most people with MDS they're anemic and their kidneys know it so they make lots of EPO and so they're… we can measure the level of EPO in their blood. We call it the EPO level and it's high. In patients whose EPO level is high, we can give more EPO till the cows come home, but their cells are bathed in EPO and the problem is their cells aren't responding to it. They're defective cells. That's part of the MDS. So, we've learned that if we're selecting patients for treatment with EPO, what we call an ESA, an erythropoietic stimulating agent which can be either Procrit or Aranesp. So, it's Erythropoietin or Darbepoetin. EPO or Darbepoetin. If your erythropoietin level is high, it's very… it's confusing because everybody with MDS will have a high EPO level compared to normal because everyone's anemic. That's normal. So what we're saying is inappropriately low to the level of anemia. So if you're anemic and your EPO level is 200 or less, you're very likely to respond to Procrit or Darbepoetin, Aranesp. Above 500 not a chance. Two hundred to 500 probably also not a chance, but it's worth a try sometimes for the right patient. Now, which one? So, there's a lot of pharmaco politics here. Let me say first of all that most doctors give Procrit the way they were taught to do it for people who are getting chemo for breast cancer. In those… that dose is 40,000 units weekly and it's not enough for most patients who have… for almost any patient with MDS. So, people who are getting 40,000 units of Procrit for a week which is standard are… who have MDS are not going to respond. Period. Mostly. The dose which has been shown… That's a little more complicated. So minimally, people need 60,000 units a week. Many people need 80,000 units or 90,000 week. Insurance balks at this and doctors get lazy and because we're really exhausted by all this regulatory stuff and so I'm not trying to disparage anybody but it's not worth getting Procrit 40,000 a week. Now if you're getting it and it's working, more power to you. So, I start with… I have actually a way that I calculate it but I usually start with 60,- or 80,000 units a week if people are going to respond, I decrease it. The reason I tend to use Aranesp, again to your point, which is Darbepoetin which is a longer acting synthetic version is because, again, the standard dose of Aranesp for people who have used for treating breast patient is not adequate. That's like every other week at 3 weeks. The dose which has been shown to be the best that's been studied is 300 micrograms weekly. It's a very high dose of Aranesp. Usually for breast cancer or whatever, 200 every other week. So, 300 weekly. I like Aranesp because I can give everybody the same dose and it's once a week and I'm done. I don't have to worry

about twice a week. Now, you ask about the addition of Neupogen. Neupogen is called GCSF or Filgrastim is its generic name. It's a granular cell growth factor, a neutrophil growth factor. Why would I give it to somebody with anemia? Because we think that the red cell precursors in the bone marrow, the GCSF or Neupogen, makes them more sensitive to the EPO and that's been shown to be effective for some patients particularly patients with ring sideroblasts, RARS which is a low grade form that some of you may have. People with low grade… with RARS never respond to Procrit alone. Ever. Ever. Ever. And I've had a lot patients who have been on Procrit till the cows came home from another doctor who have RARS and as soon as we put… add Neupogen they respond. That's the group that really Neupogen in my opinion. One of the reasons that I like Darbepoetin or Aranesp is because there's no indication that adding Neupogen is necessary. So for me, it's a little bit one stop shopping. I'm lazy. I can give 300 micrograms a week of Aranesp and I feel like I'm doing a good job and if it works… it takes about 12 weeks to know if you're going to respond to any of these growth factors. So a 12 week trial is usually adequate. Now that said, my wife and I did a study did a study using data from Medicare and it turns out much to my surprise and there's a Greek study that showed people might respond if you give Procrit for like 30 weeks and they may not respond till late and everyone says, "Oh, that's a European, southern European study. What do they know?" Well, it turns out when you look at the Medicare data and the way we monitor whether people respond is by seeing if they're getting blood transfusions because the claims data tells you what they're getting, what the patients are getting. You don't know a lot about their disease but you know what their getting. It turns out that there are patients that we found in the Medicare database who were getting transfusions and were getting Procrit for 12 weeks, still getting transfusions, blah, blah, blah and then out of 30 weeks they actually stopped getting transfusions. So it turns out for some patients anyway, keeping going for longer makes sense. In that study, we also show that it looks like Darbepoetin was probably a little better that Aranesp was probably a little better. Not a randomized trial.

Q8: (inaudible 56:05 – 56:12)

Dr. Steven Gore: No. That's for solid tumors. That's its indication. That's what it's FDA approved for, but it's not being studied in MDS.

Q8: (inaudible 56:20 – 56-27).

Dr. Steven Gore: Oh. Totally different. So these words are scary and they just have a name. So blast cells are the most immature cells in the bone marrow. They look like acute leukemia cells and everybody has them because our youngest cells in the bone marrow are blast cells and then they mature and they turn into different cells. We could call them Joe cells or Steve cells or brown cells or red cells or green cells or star cells. We call them blast cells. That's what they're called and as MDS gets worse the percentage of cells in the bone marrow which are blasts increases and that's because in early MDS, the bone marrow is working overtime, but the cells are stupid and they're maturing abnormally and as the disease gets worse, the cells get stupider and stupider and they forget how to mature and as they forget how to mature, the blasts pile up. That's blasts. Sideroblasts are red cell precursors. Red cell grandparent cells that when you stain the iron in the cells, they have this real pretty little ring and the ring represents the part of the cells called mitochondria which over accumulate iron for some reason in this select subset of

patients and the way… you don't know if you have ring sideroblasts unless somebody did an iron stain on your bone marrow. That is something which should be done standardly in the evaluation of the bone marrow so with people with MDS it's sometimes forgotten. So, that's ring sideroblasts. You had a question about Campeth. Yeah. Is that okay?

Q9: Yes. I was just wondering how much (inaudible 58:05).

Dr. Steven Gore: Sideroblasts are not dangerous at all, but in order to have the disease called RARS, refractory anemia with ring sideroblasts you need at least 15 percent of the red cells to be ring sideroblasts and you can't have increased regular blasts, myeloblasts. So if you have 15 percent ring sideroblasts but you have 7 percent blasts, you don't have RARS, you have RAEB, refractory anemia with excess blasts. In order to have RARS, refractory anemia with ring sideroblasts, 15 percent of your red cell precursors need to be ring sideroblasts and you can't have an increase in the other kind of blast, the myeloblasts. So if you have 15 percent ring sideroblasts, but 7 percent myeloblasts, you don't have RARS. You have refractory anemia with excess blasts which is a higher risk disease. Campeth is an antibody that's immunosuppressive. It affects the cells called lymphocytes and there's a whole different set of treatments that I haven't talked about targeting the immune system which in my opinion the immune system is clearly disregulated in some patients with MDS and some of their manifestations of low blood counts are because their immune cells are overactive and chewing up some of the cells. It's not the majority of patients with MDS. There's also a group of MDS patients, at least they'll be currently called MDS, that overlap with a disease called aplastic anemia. These tend to be patients what's called hypocellular MDS where there's way too few cells in the bone marrow, not too many. Somewhere in this spectrum are patients who respond to drugs which inhibit T cells which are lymphocytes and the drugs which are used in those cases the strongest one is antithymocyte globulin. It's a horse serum. It's given in the hospital that we use to treat aplastic anemia. There's a drug called Cyclosporine which is used to prevent kidney transplant rejection and Campeth is a very immunosuppressive drug which also is used in those circumstances. The place that's most interested in these kinds of treatments is the National Institutes of Health which is an aplastic anemia center and their MDS program, I think, grew out of aplastic anemia treatment and they're very good at it and the Moffitt Cancer Center in Tampa also is very interested in this. I don't use these therapies very much because I don't know which are the patients to offer it to. I can't figure out who they are, but there's clearly a group of patients that does respond to treatments which target the immune system. Please.

Q10: I'm not sure I heard you correctly.

Dr. Steven Gore: I probably wasn't clear.

Q10: No. It's probably my hearing (inaudible 1:01:11). Did you say that when you use… I can't pronounce these drugs, Araset?

Dr. Steven Gore: Aranesp. Areset is for the treatment of Alzheimer's Disease.

Q10: … that Neupogen was not necessary (inaudible 1:01:18).

Dr. Steven Gore: So, there's one study where if people didn't respond to Aranesp, Neupogen could be added based on this other data and there wasn't any evidence that any of those people responded better when Neupogen was added. So, we don't have any evidence that Neupogen adds anything to Aranesp, so I don't do it. We know for Procrit as many as half the responses require the addition of Neupogen. So, I'd rather give 1 shot, not 2 shots. So, that's why I give the max dose of Aranesp to see if it works, work from there. That's my practice. It's not to say it's right. To me it's quick and easy and I like to be simple. Keep it simple. Yeah.

Q11: (inaudible 1:01:59) work, can you go back to Neupogen and (inaudible 1:02:03)?

Dr. Steven Gore: Well, I'm not sure I'm understanding. Are you talking about somebody who's getting Neupogen and Procrit? If you're getting it and it's working, I'd stay with it. I wouldn't switch.

Q11: (inaudible 1:02:13) it doesn't work. (inaudible 1:02:20) Neupogen and Procrit.

Dr. Steven Gore: Yeah and it's working?

Q11-a: I don't know.

Q11: I don't think so. They would go to this Aranesp it would be better…

Dr. Steven Gore: No. I think the main thing to do is get one of them and get the right dose. If you're getting the right dose and it's not working, just give it up otherwise you're just supporting the drug companies. If you're still getting transfusions every three weeks, whatever you're taking isn't working.

Q11: (inaudible 1:02:42) every four weeks transfusions.

Dr. Steven Gore: Yeah. If you're getting growth factors and you're still getting regular transfusions the growth factors are not…

Q11: (inaudible 1:02:48) only get 30,000.

Dr. Steven Gore: Well, 30,000 is… you might as well take vitamins. Thirty thousand, I'm sorry to say is nothing.

Q11: (inaudible 1:02:58 – 1:03:03)

Dr. Steven Gore: Say it again.

Q11: (inaudible 1:03:05 – 1:03:12)

Dr. Steven Gore: No. I don't think so. I think that the people who are best candidates for Procrit or Aranesp are the people who've never been transfused. So, it's most effective when you don't yet need transfusions and you say why would I want to take a drug that I don't need

transfusions? That's because we know that people whose hemoglobin is above 10 have better quality of life. That's been studied. So, somebody's 9 ½, say a lot of docs won't transfuse them which I think is right, but might start Aranesp or Procrit because if we can get their hemoglobin to 12, they're going to feel better. So, I can't speak for all the other doctors. Most of us would rather not transfuse unless we need to.

Q12: One of your slides said how (inaudible 1:03:56) increase risk of (inaudible 1:03:57 - 1:04:02).

Dr. Steven Gore: Well, the only thing we know that prevents progression is Vidaza. The only thing that we know improves survival is Vidaza, but how do we improve survival overall for people who want to be aggressive is by getting the blast count down either with Vidaza or Dacogen or chemotherapy and transplanting. That's how we cure people.

Q13: Is it true that tonic water or quinine could lower your platelet count (inaudible 1:04:33)?

Dr. Steven Gore: If you like tonic water drink tonic water. The question is whether tonic water or quinine can decrease your platelet count. I suspect rarely it can. If you have MDS I wouldn't worry about tonic water.

Q14: It (inaudible 1:04:47) cramps though.

Dr. Steven Gore: It's good for cramps. Right.

Q15: (inaudible 1:04:51)

Dr. Steven Gore: Do you mind of we go over a little bit because…

Jayshree: No, not at all (inaudible 1:04:56)

Dr. Steven Gore: Because I'm in no rush if you're no rush if they're no rush.

Jayshree: Not in a rush. I think I want them to see a lot of the questions for (inaudible 1:05:01) because he's an expert.

Dr. Steven Gore: Okay. Please.

Q16: It's really a very personal question to my symptom. My father died of sideroblastic anemia. I have some sideroblasts, just a few. What I'm finding since I've gotten MDS is that if my normal iron blood level, my iron blood levels are normal.

Dr. Steven Gore: Your blood iron levels.

Q16: My blood. Thank you. (inaudible 1:05:41).

Dr. Steven Gore: Remind me to talk about iron also.

Q16: But what I'm finding is that if I eat food high in iron, I mean if I have a cup of oatmeal, two hours later I get these horrible cramps in my muscles. It's what's in the food that has iron. I also have that if I drink 16 bottles of water it will tend to lessen it.

Dr. Steven Gore: So if I may, I really think we need to keep this discussion away from personal symptoms. I can't do diag… No, no, no. That's fine. Everyone wants to do that and I don't feel it's helpful for everybody and I don't feel that I can really be responsible as a physician that way. So, I would talk to your doctor about that. You had a question.

Q17: Yeah. I know that you haven't gotten into transplants yet, but my question is you're saying you want to get patients ready for to be able to get a transplant.

Dr. Steven Gore: If that's what they want. I said that it's up to the patient. Right?

Q17: I feel that patient wants to get a transplant, under what conditions would they be of (inaudible 1:06:55). I mean, once they've been getting…

Dr. Steven Gore: So, I think… So, here's what I'll tell you is that I think that… hold on a sec. So, I think that the decision about transplant of whether you're going to consider transplant needs to be a part of the initial treatment decision so and that's what docs don't do right. What are the goals of the starting treatment? Why are we starting treatment right now? Is it palliative goal? That means does it make you feel better or is it a survival goal? If it's a survival goal what is the package that's going to get you to be cured if that's what you want. That has to be decided from the get go. So, Mr. Schwartz would like to be transplanted, but he's 80 years old, bless his heart. Ain't going to happen and if he's got a low grade MDS, I'm not going to pull out Vidaza right now. I'm going to wait till he needs it. I'm going to give him growth factors and I'm going to give him whatever I want to do. You know, So, but, Mr. Smith is healthy 70 year old, feels like he's got the rest of his life to live, blah, blah, blah and he's got a high risk MDS or let's say he's got an intermediate risk MDS and he's got the gusto and he's otherwise healthy, I'd say, "Okay. Well, let's wait until you need Vidaza based on it turning into high risk or being more transfusion dependent and once we start Vidaza, we're going to work you up for transplant and if you respond well to Vidaza and you still want the transplant, do the transplant."

Q18: How does… Can you define responding well to Vidaza?

Dr. Steven Gore: Well, the best responses have normal blood counts or improvement in blood counts and decreasing blasts are the two things I'm… one thing I wanted to show you but can you keep doing questions while I'm… You had one over there, right?

Q19: Let's say you had (inaudible 1:09:19 – 1:09:21)

Dr. Steven Gore: Uh-huh. Gotcha.

Q19: (inaudible 1:09:25 – 1:09:40)

Dr. Steven Gore: That's fine. Here we go. So again, I don't want to be specific about individual things. So, here's what I'd say about that. There's a question of one question is if you're on Vidaza and it's not working should you switch to Dacogen or vice versa and the answer I say is no. If you had a good treatment regimen with either Dacogen or Vidaza, the other isn't going to work. There's a little bit of data that is not worth talking about. If you had really good 6 months of one or the other, it's not working, it's not working. Somebody's trying to get their transplant and they need to get their blasts down and their blasts haven't come down after Dacogen or Vidaza, I would talk to them about doing something else like leukemia chemotherapy in the hospital, Clofarabine or Cytarabine based therapy if the goal is to get to transplant and you need to get the blast down. That's what we do here or a clinical trial to… Let me just spend a couple minutes showing you a couple transplant slides. This is a slide from good colleague, Corey Cutler at Harvard, who tries to illustrate the kind of risk benefit to transplants. So again, these are survival curves and people get a transplant, unfortunately the transplant kills people off. So, these people have inferior survival because they rolled the dice and they lost. People who don't get transplant don't die there, but don't get cured and so they continue to die. The people who are cured of transplant, now this is drawn very optimistically where most people are cured of the transplant. Unfortunately for MDS it's not really the case. Most people who get transplant are not cured, but you can see that people who get transplanted some people lose their lives unnecessarily, you lose time, but eventually the people who are cured gain the rest of their lives back and here's the sad truth about transplant for people who've had high risk MDS is that people who've had high risk MDS only about 30 or 40 percent of them is cured. So you could say well that's horrible or you could say that's great and I talk to patients about this every day and everyone sees it differently. Like well, I'll take my 30 percent chance it gets to zero percent chance. Other people say, "You know what? If it's a 30 percent chance, I'm going to Hawaii," and those are both fine if it's the right decision for the person. Chance of dying from transplant for most patients depending on what kind of transplant and I don't mean dying right away, but I mean dying as a complication of the transplant over 2 year, say, it's got to be figured at 20 percent. This slide is a little old. So, 30 percent chance of being cured, 20 percent chance of dying and then about a 50 percent chance of surviving but not being cured. So, you go through it and you're still not cured. What happens if you relapse after a transplant? Well, even if you've had Vidaza or Dacogen before a transplant even if it hasn't worked sometimes once you've been engrafted with somebody else's things, Aza actually can turn your graft on for a whole different reason and it can… so you relapse after a transplant or you don't get cured after a transplant. You get Vidaza and you go into remission. Sometimes we can give booster cells from the donor called donor lymphocyte infusion and that can cure some of the patients who weren't cured the first time around and… let's go back. This was some older data from Seattle which used this, the Fred Hutchinson Cancer Research Center which are the people with the lowest risk MDS are the most likely to be cured. So, here are patients with very low risk MDS and about 70 percent of them is cured with transplant. Higher risk only about 30 percent. So, why wouldn't you want to be transplanted when you're low risk? We don't… nobody transplants low risk MDS anymore. Why not? Well, remember that slide about the loss of life. Right? This one. You don't want to be in this group that died unnecessarily. So, Dr. Cutler who made that slide did an analysis where they asked a question what would be the survival of a group of 100 people who were transplanted… this is with a full transplant not a mini transplant, matched sibling kind of vanilla transplant if you transplanted them when their risk was low versus risk was high or if you waited… or if you waited some time. So in people with the lowest risk MDS, their survival

without transplant if they're less than 60 is 12 years, but if you transplant them early their average survival is only 6 years. So, you can see why we don't like to transplant those patients right away and if you wait until their disease gets worse, their average survival is 7 years. So, it's better because we didn't kill people off unnecessarily. Does that make sense? For the intermediate risk without transplant, their average survival less than 60 was 5 years. Early transplant again took away life, but if we waited until they progressed, we didn't lose life in the same way. Now, that wasn't true with the high risk patients. Now, these data… so with the high risk patients there wasn't any benefit to waiting but these data were before we had Vidaza and Dacogen. So, that's up in the air, too, but the bottom line is we don't transplant lower risk patients. That means when we're transplanting patients, the patients in whom we're transplanting can't expect those 60 percent survival rates. For an individual patient if you're waiting your chance of being cured later is less than had you been cured, but at least you've had those 5 or 6 years where you haven't died and that's how most of us say, "Well, you can't be cured if you're dead."

Q20: (inaudible 1:15:37)

Dr. Steven Gore: Yeah. That's a word that I… if any of my patients who's been here will know that I never use that word with patients because I think it's a really terrible misnomer, so I'm sorry I brought it up but a lot of you guys know the word mini transplants. That's why I said it. So, the correct word is nonablative transplant. So, myelo. Myelo means bone marrow. Myelodysplastic. Funny looking bone marrow. Meylo is bone marrow. Myeloblasts. Bone marrow blast. Right. Meylo is bone marrow. Ablate means to get rid of. Myeloablative. The bone marrow is gotten rid of. That's the standard transplant where you drop the nuclear bomb chemo on the patient, we fry their stem cells. If we don't give them a stem cell product, they don't recover. They have what's called aplastic anemia where the bone marrow isn't working. That's a myeloablative, a standard old fashioned kind of stem cell transplant. Reduced intensity transplants are what tends to be called mini transplants because it's easier to say and people don't want to take time to explain to their patients just like I didn't and the best word is nonablative meaning that it doesn't fry the bone marrow stem cells. If I gave you the chemotherapy or chemo and radiation for a nonablative so called mini transplant and I didn't give you a stem cell product, your bone marrow would recover with your own stem cells, your own same disease. So, without… If you reject the transplant, you're no worse off for wear, but nonablative transplants are ways of getting stem cell products into patients safely with fewer deaths up front making transplant available to older patients, sicker patients and now it's becoming more and more clear that maybe it's just as good as a full transplant. We don't really know that, but that's what I meant when I said mini transplant, but I don't like to use the term 'mini' because it sounds like you can go to Target and get one or Walmart and get one and there's nothing mini about them that people get plenty sick, people die from them, there's a 20 percent mortality. It's not a piece of cake. That's why they're not really mini.

Q21: (inaudible 1:17:38)

Dr. Steven Gore: Well, like I say here at Hopkins we do half matches. We do half matches routinely and that's being done around the world now.

Q22: (inaudible 1:17:47)

Dr. Steven Gore: Half? Half of 100 percent would be full match. Fifty percent is half match. Five out of 10 means anybody's child if it's biologically theirs and not the plumber's or the milkman's is a half match. Nobody likes my milkman joke anymore. I have offended my patient… I have one patient that said, "We really didn't like it when you said that thing about the milkman because we were really offended. We would never do that with the milkman." Are you kidding me? Are you kidding me? I said we have patients where it turned out to be the milkman and I have to say that because you do the typing and you say it's 100 percent they're going to be a half match. It's like, "Oh, Joey was a zero match." Well, you said that everybody has a half match. Oh.

Q23: (inaudible 1:18:29) a half match for nonablative as well as…

Dr. Steven Gore: Yup. We started with non ablative. That's how we started it.

Q24: (inaudible 1:18:37) are there any child that should be a full match?

Dr. Steven Gore: If you are the biological parent, your child is a half match as is your parent.

Q24: (inaudible 1:18:46)

Dr. Steven Gore: No if you're sibling, you have 25 percent of being a full match, a 25 percent of being a nonmatch and a 50 percent chance of being a half match. So everybody if you have siblings, a sibling you have 75 percent chance depending on of having a half match. So, we can get donors, if you're willing to have a half match, we can get donors for almost everybody as long as you have a living first degree relative, you almost certainly have a half match and the outcomes are great. I'm a believer now as you can hear.

Q25: (inaudible 1:19:20).

Dr. Steven Gore: Cousins are much less likely to be half match. We're doing a lot of mismatches now and now we're talking into real experimental stuff, but if there's no biologic… we also do mismatched unrelateds now. There's all sorts of… There's nobody who shouldn't be able to get a transplant because of donor anymore. If your doctor tells you that well they don't do it that way. That's fine, but you can get referred to a center that does. The big centers are doing all sorts of transplants now and then there's cord blood that we haven't talked about, umbilical cord blood.

Q26: You said a full match… A full match somebody matches half the person?

Dr. Steven Gore: Is there.. can there be a full match? Sure with a sibling, with a first degree sibling. Each sibling is a 25 percent chance of being a full match. Yeah. No, there are full matches who are unrelated donors. We don't think that. We think that our outcomes with half match related donors is equal or better than full matched unrelated donors, but we haven't proven that yet. I saw a hand here.

Q27: My question was they have the National…

Dr. Steven Gore: Registry.

Q27: If you can find a full match that is not better than having a sibling match (inaudible 1:20:25).

Dr. Steven Gore: I don't think we know which is better. The Hopkins transplanter's bias would be that there is no data that suggests that the full matched unrelated donor is better. The standard of care would be to use the full unrelated donor. Now, it takes time to find a donor on the registry. So for many of our patients, not so much with our MDS patients, but some of our other diseases, they don't really have the time to look because it takes 90 to 100 days to get a donor. So for those patients being able to turn to a half match…

Q27: If you had the time would the unrelated registry 100 percent be better than a sibling (inaudible 1:21:03)

Dr. Steven Gore: We don't have any data to suggest that one's better than the other. So, not necessarily

Q27: This is for the (inaudible 1:21:10)

Dr. Steven Gore: Either.

Q27: I'm 71 years old…

Dr. Steven Gore: You would not get a full transplant. You would get a nonablative transplant, but we do plenty in your age group.

Q28: Do you do it at 80?

Dr. Steven Gore: No.

Q28: Is there age cutoff?

Dr. Steven Gore: Seventy-five here at Hopkins.

Q29: I'm going to go back to the infusions. If you're getting (inaudible 1:21:32)

Dr. Steven Gore: Transfusions you mean? Are we talking about transfusions? The Red cell transfusions?

Q29: Can you start those (inaudible 1:21:39)?

Dr. Steven Gore: Yeah. So, I would measure your EPO level and if your EPO level is low and you have a lower risk disease then you may be a candidate for growth factors.

Q30: Why is it that you said that (inaudible 1:22:00 – 1:22:02)?

Dr. Steven Gore: Well, transfusions are expensive. Transfusions have a risk of transmitting hepatitis viruses and other things and transfusions are associated with iron overload and I'm so glad you reminded me to talk about iron because I asked somebody to remind me. So, iron. We eat iron and we get it in blood transfusions. There's 50 mgs of iron, I think, of elemental iron with every unit of red cells and the body has no mechanism of getting rid of iron. So it piles up in the storage systems of the body. In a disease, a genetic disease called thalassemia where kids get huge numbers of red cells. We know that unless you use something to get rid of the iron they go into heart failure and they develop diabetes and they develop a pituitary dysfunction and liver dysfunction and it's always been thought that probably patients who are long term survivors of MDS are at risk of those complications as well if they're in a chronic transfusion program. Well in the old days, the drug that we had to get rid of iron was this nasty drug called Desferal that you had to stick a needle under your skin and pump it in 8 hours a night and, frankly, very few people wanted to do that and we had no data in MDS patients that getting too much iron was really bad for them. Anecdotally, we might have a patient or 2 that got a lot of iron and developed liver trouble and we proved it was from the iron, but overall, we really couldn't find that. So then Novartis developed an oral drug which is called Exjade Deferasirox and they really did a lot of promotion to get all these MDS patients to be taking this iron chelater, this Exjade Deferasirox and many of us were very skeptical about that. So my rubric would be, my practice would be if you've had 20 units of red cells, lifetime 20 units and you're still getting red cells, we should probably put you on Deferasirox because we don't know any better not to, but if you don't tolerate it or your insurance won't pay for it, we won't worry about it. So my wife and I, it's a good team, went to this big database and we looked at the use of Deferasirox in patients with MDS who had gotten 20 units of blood and to the best it's not a perfect study, but the best we can control for everything it looks like those patients who are getting Deferasirox or Exjade for at least 13 weeks are living longer and for every week longer than 13 weeks that they're taking Exjade they're living longer. So, I've become a believer in chelation for people who getting red cells. That's one reason don't like to give red cells because they don't want to get iron buildup. I'm not saying everyone needs to be on Exjade, we haven't proven that, but I think there's now better data that if you're getting a lot of red cells you probably should be chelating your iron.

Q31: (inaudible1:24:49 – 1:24:53)

Dr. Steven Gore: That would be my preference. Yeah. I usually tell them to take iron free multivits.

Q32: Have you ever heard of anything called vitamin K and (inaudible 1:25:03)?

Dr. Steven Gore: Well, vitamin D has been studied and anecdotally it helps some peoples' blood counts. Vitamin K helps blood clotting, but I don't know of anything helping blood counts.

Q33: Is it possible that (inaudible 1:25:15) the chelation is that (inaudible 1:25:18 – 1:25:19)?

Dr. Steven Gore: Yeah. So, that's the big question, but my wife is a very sophisticated economist actually. She's a health economist and so we've done this very, very sophisticated modeling that actually weights the data based on the likelihood of prescribing chelation at any time. It's the best you can do, but it corrects for everything we can including our interpretation of what the statistical likelihood of a doctor prescribing chelation for that patient and once you do all that it still seems to be improving survival. That's the best we can do without a randomized trial, but that's… you know something. That's good. That's much higher than I usually talk to… Most doctors don't get that. Yeah.

Q34: (inaudible 1:26:05) the studies we're doing so (inaudible 1:26:07)

Dr. Steven Gore: Okay. Good.

Q34: I may be getting off track a little bit.

Dr. Steven Gore: That's alright.

Q34: … opinion. The cause of MDS among many things is a toxin and exposure to benzene.

Dr. Steven Gore: Well, that is one cost. The question is benzene exposure.

Q34: And toxic chemicals. So, can MDS in your opinion be linked to the spray and herbicide Agent Orange?

Dr. Steven Gore: My opinion is absolutely Agent Orange is a cause of MDS and one of the great scandals and shame of our Veteran's Administration is that they have refused MDS. They accept CLL, Chronic Lymphocytic Leukemia which is much less data about Agent Orange and it is… I was actually going to be working with Senator Inouye who was very passionate about this before he got sick. This is a scandal in our country that veterans, Vietnam veterans, have been exposed to Agent Orange are developing MDS are not getting compensated. This is horrific and I've written letters for patients. What's that?

Q34: I've been denied my service (inaudible 1:27:20).

Dr. Steven Gore: I'm very sorry about that. This is a national scandal in my opinion.

Q35: (inaudible 1:27:29) ever come off (inaudible 1:27:31) or once you're on it you're on it.

Dr. Steven Gore: It stops working eventually. The average time that it's working is about two years.

Q35: (inaudible 1:27:37 – 1:27:40)

Dr. Steven Gore: Yeah. Well so unlike Dacogen or Vidaza, we don't… there's also safety rules about you can't give it when the hemoglobin is too high. So, you can stop Procrit or Aranesp if, God forbid, your hemoglobin gets too high which doesn't really apply to our patients usually like over 12. They don't usually respond that well. Then you stop it and you wait till it goes down, you start it again, they keep responding.

Q36: (inaudible 1:28:01 – 1:28:05)

Dr. Steven Gore: They can have very low cholesterol levels. That's a little piece of anecdotal, not anecdotal, it's a little minutia that most people don't know about that the leukemia and bone marrow disorders reduce the cholesterol levels. So people who used to have to take statins often don't when they get MDS.

Q36: (inaudible 1:28:19 – 1:28:22)

Dr. Steven Gore: I'm sorry. The question was about… the question is about whether MDS reduces triglyceride levels and I said that sometimes it reduces cholesterol levels. I haven't seen that with triglycerides.

Q37: Oh, but it sometimes (inaudible 1:28:35).

Dr. Steven Gore: People who have been on statins sometimes don't need them once they get MDS. It's just one of those interesting facts, Ripley's Believe it or Not. Yeah.

Q38: (inaudible 1:28:46) Do you get the healthy (inaudible 1:28:48) does your MDS attack the healthy blood, too? Usually that too? (inaudible 1:28:57)

Dr. Steven Gore: No. No, no, no.

Q38: If you get a blood transfusion it should actually be your red blood count should get better.

Dr. Steven Gore: It should. Right. Unless you're making antibodies to red blood cells which some people who've been chronically transfused to. They develop antibodies and as your MDS is more persistent, your red… the duration of affect of your red cell transfusions will go less. So, you might used you needed it every six weeks then you needed it every three weeks. Also, your bone marrow isn't making as much red cells. Your spleen might get bigger and the spleen starts to chew up the blood.

Q39: Do you recommend to your patients (inaudible 1:29:33 – 1:29:35)

Dr. Steven Gore: No. Exercise is good. Eat what you like. Anything else?

Q40: (inaudible 1:29:42) MDS focuses the neutropenic diet.

Dr. Steven Gore: Yeah. Well, that's been disproven. The neutropenic diet has been disproven. It's not effective. It never was. It's total BS. Eat what you want. Eat what you like. Absolutely. You should peel your fruit probably.

Q41: Well, I wash.

Dr. Steven Gore: Wash or peel because we worry about fungus and stuff, but…

Q42: (inaudible 1:30:09)

Dr. Steven Gore: So, cats have can have toxoplasmosis. So, cat liter should not be dealt with and if you're severely amino compromised. Dogs are fine.

Q43: What is severely compromised?

Dr. Steven Gore: Like if you've had a transplant. Jayshree's getting on the mark.

Jayshree: Well, the reason is because I think I want to stay on quue (inaudible 1:30:35).

Dr. Steven Gore: Absolutely. Very good. Well, you should. So, let's do it and I'm going to stick around. So, I can stick around during lunch or at least at the beginning of lunch and we'll get more questions. Okay? The wonderful young woman named Amy Duzern (sp? 1:30:53) is taking over my role (inaudible 1:30:57) of this MDS (inaudible 1:31:01 – 1:31:25)

Jayshree: Thank you, Dr. Gore.

Dr. Steven Gore: You are welcome.

Jayshree: So, I'm sure you possibly may need a restroom break or… You've been talking for an hour and a half over here. My name is Jayshree. I'm a nurse practitioner. I work at Hackensack University Medical Center and I'm from Jersey, state up north over there. I'm very proud to participate in and work with MDS Foundation as a volunteer nurse to educate, to teach, to answer your questions and talk and get your feedback as patients and caregivers that are here today. I understand there's some patients that could not be here because they're still going through a different type of treatments or they're not feeling well and what so but we have other representatives here like Ms. Diana here. I didn't get to go around yet to get everybody's story. I know some patients and their caregivers from other forums that they've come to. First of all, I just want to say thank you for coming today and sharing your stories with us. We're very excited that you are here because want to get feedback from you as patients and caregivers to help our foundation, MDS Foundation, that I collaborate with to making it better in regards to giving resources, supplies, any kind of connections, patient care support, anything to start up something in regards to MDS. Just wanted to go over a couple of things with you. There was a questionnaire that was in the binder. If you guys get a chance, please help us fill it out because we're getting data. We're collecting data from you as a patient or a caregiver to feedback to improve or make changes. So when you have a chance during a few minutes of downtime if you can fill that out that will be great.

Q44: Is that the same questionnaire that was online?

Jayshree Shah: Yes, it is. So, you may get it as a paper or online. Either way. Deb had sent it by E-mail to probably everybody here who gave her an E-mail and she's going to send it again in case you don't get a chance to fill it out. There's also end of visit meeting evaluation and just going over what did you think about this meeting overall. Do you want it a little bit longer to have more questions answered? Do you want some other kind of a person coming in to give their expertise or what's out. So, we want to gain feedback on this and the last but not least we do have a cook book that Deb has. It's called *Annie's Sweet Tooth*. I think it's $10. Is that right? If anybody's interested in a cookbook and learning or getting new recipes or what so feel free to speak to Deb about that. I have a good 40, maybe half an hour timeframe of a lecture. Does anybody need to use the restroom? It's right down the door. Why don't we take 5 minutes? Is that okay? And then come back and I'll do a quick spiel and then we'll have lunch. I may not finish and I'll continue on after lunch.