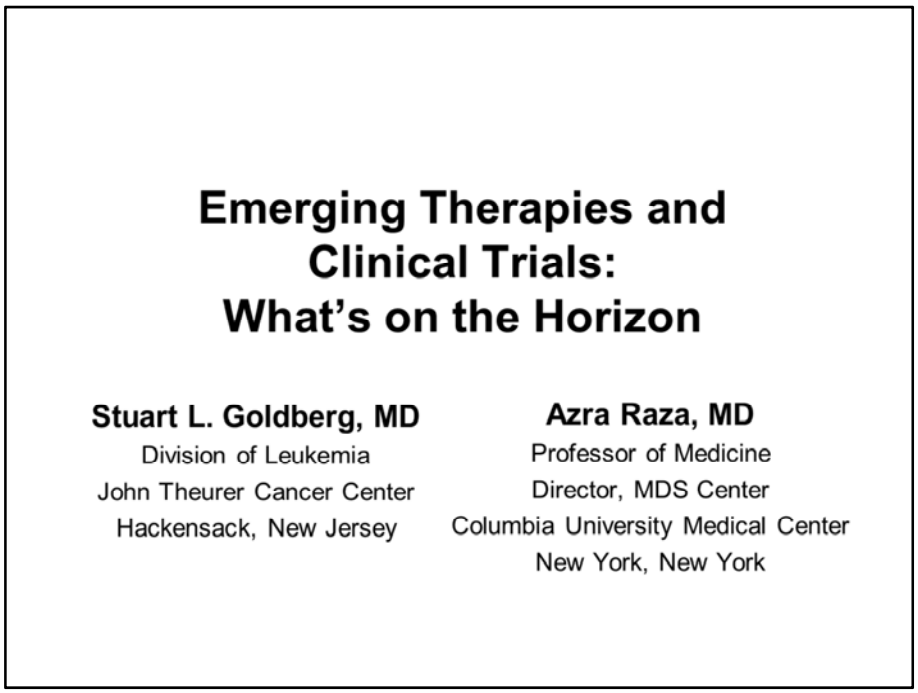
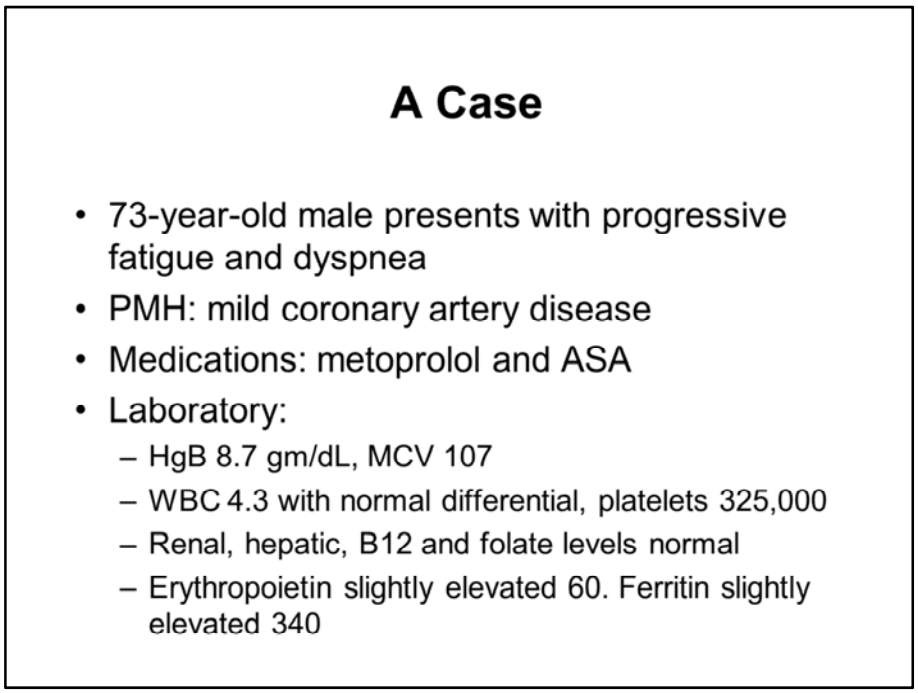
Emerging Therapies and Clinical Trials: What's on the Horizon



Dr. Stuart Goldberg: Hello, I am Dr. Stuart Goldberg from the John Theurer Cancer Center in Hackensack, New Jersey, and I am here with *ManagingMDS.com*. Today, we are going to talk about what is new and what is on the horizon in myelodysplastic syndromes, and I am joined today by one of the true experts in the field.

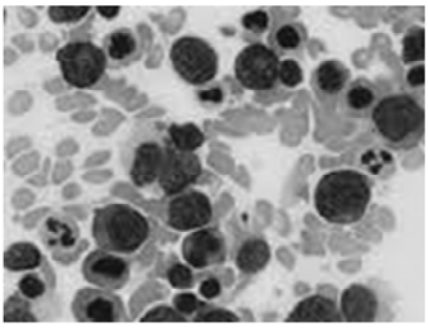
Dr. Azra Raza: Hi, my name is Azra Raza, and I am a professor of medicine and director of the MDS Center at Columbia University in New York.



Dr. Stuart Goldberg: Let's start with a case. I recently saw a 73-year-old gentleman who presented with fatigue and chronic dyspnea. His past medical history was significant for mild coronary artery disease, and he was on a beta-blocker and some aspirin. He saw his family doctor who noted that he had a macrocytic anemia with a normal white count, a normal differential, and a normal platelet count. His renal function, hepatic function, and vitamin studies were all normal. He has slightly elevated erythropoietin level, and his ferritin was slightly elevated upon presentation.

Bone Marrow with Changes of MDS: Refractory Anemia

- Blasts: 0%
- Cytogenetic: 46 XY
- IPSS: low risk
  - Anemia only: score 0
  - Blasts: score 0
  - Cytogenetics: score 0
- R-IPSS: low risk
  - Anemia: score 1
  - Blasts: score 0
  - Cytogenetics "good": score 1



Dr. Stuart Goldberg: He was sent to me for analysis of his macrocytic anemia, and we performed a bone marrow study which revealed changes consistent with a low-grade myelodysplastic syndrome, refractory anemia in the FAB classification system. He had no blast and had normal cytogenetics. His IPSS score was a low risk, and his revised IPSS score was also low risk. Dr. Raza, could you explain to our audience a little about the new classification systems, especially focused on the R-IPSS system?

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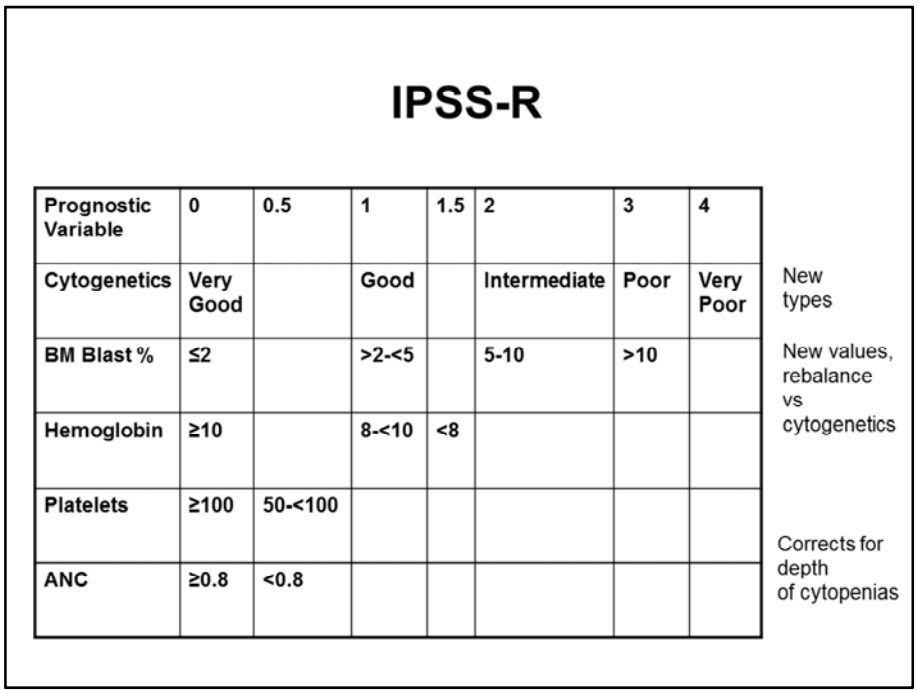

Dr. Azra Raza: Yes. So, when patient walks into our office with myelodysplastic syndrome, the first thing we want to know is really if patient has a chance of living for 10 years or is their life is at risk in 10 months, and this sort of distinction has been made traditionally by using the international prognostic scoring system or IPSS, but over the last 15 years, it was recognized that there were some issues in terms of accuracy of predicting prognosis with this system, so attempts have been made to revise and refine some of the parameters that have been used to segregate patients into various risk categories, and that system was reported in 2012 in *Blood,* and it is called the revised IPSS scoring system. So, the original scoring system took into account three parameters. Number one, what are the cytogenetics; number two, what was the percentage of blasts; and number three, how many blood counts are low. In the revised IPSS system, the same three parameters are looked at but in slightly more elaborate and greater detail.

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Updated Cytogenetic Classification for Use in IPSS-R

Risk group	Included karyotypes (19 categories)	Median survival, years	AML evolution, 25%, years
Very good	del(11q), -Y	5.4	NR
Good	Normal, del(20q), del(5q) alone or with 1 other anomaly, del(12p)	4.8	9.4%
Intermediate	+8, del(7q), abnormal 17q, +19, any other single or double abnormality not listed, 2 or more independent clones	2.7	2.5%
Poor	Inv(3)/t(3q)/del(3q), -7, double abnormality include -7/del(7q), complex with 3 abnormalities	1.5	1.7%
Very poor	Complex with >3 abnormalities	0.7	0.7%

Dr. Azra Raza: So, for example, in terms of cytogenetics, we now have divided them into multiple categories which are presented here ranging from very good prognostic categories to a very poor one, and these are all described in detail here along with how the median survival of patients varies from 5.4 years of median in the very good risk group to a very poor prognostic group which is 0.7 years' total survival. Similarly, the percentage of blast has been divided and so not just the number of cytopenias but the profundity of each cytopenia, so for example, was the hemoglobin less than 8 g or was it more than 8 g; what about platelets, were they more than 50000 or less and ANC as well, and based on this revised IPSS system, we think that we have a slightly more accurate predictability. So, a score is a sign to the patient and the risk of survivor is given, but just remember that these are just median survivals for a large group of patients. So, to apply this sort of thing to an individual patient can be a little tricky, and we still have not reached the point where we would be able to predict with absolute accuracy of what is the risk of transformation to AML at risk of death.

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IPSS-R Outcomes by Risk Score

Risk group	Risk score	Median survival, years	Time until 25% of patients develop AML, years
Very low	≤1.5	8.8	Not reached
Low	>1.5-3	5.3	10.8
Intermediate	>3-4.5	3.0	3.2
High	>4.5-6	1.6	1.4
Very high	>6	0.8	0.73

Greenberg PL, et al. *Blood*. 2012;120(12):2454-2465.

Dr. Azra Raza: In this particular slide that you put up, Stuart, shows nicely the time until 25% of patients develop AML in years and you can see the huge difference between the very low and very high-risk group again underscoring the fact that MDS is a very heterogenous disease.

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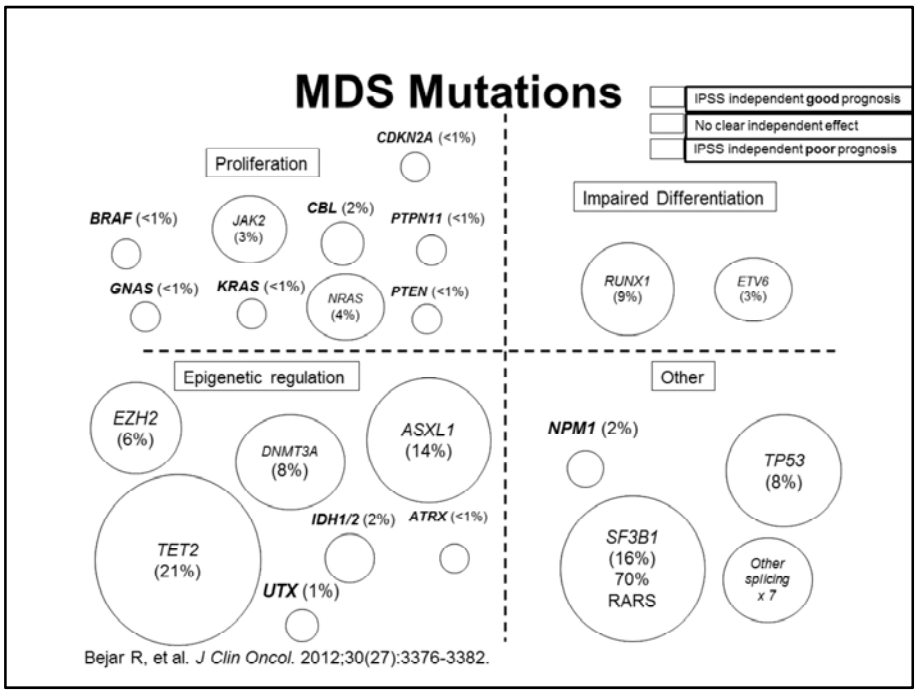

Dr. Stuart Goldberg: Now, certainly, we have learned a lot about cytogenetics in the classical karyotyping, but in the last 5 years, I know there have been a lot of advances in understanding the genomics going beyond just the classical karyotype. As shown on this slide, there are now a number of different mutations that we see in myeloid malignancies, and they are starting to group in myelodysplasia and really even point characteristics of what might be treatment options. I know that your group has done a lot of this work, and may be you could explain a little bit to our audience about MDS mutations and even the exciting work that came out of Dr. Bejar. How we can use this clinically to sort of figure out which might be the best treatment for our patients?

Dr. Azra Raza: So, we have known for many years that the hypomethylating drugs that affect epigenetic regulation appear to work best in patients who have myelodysplastic syndrome, and I think this slide really demonstrates why that is so because the left lower quadrant shows the genes that are found to be affected and mutated in MDS most commonly are those involved in epigenetic regulation. Specifically, Tec2 gene is found to be mutated up to 20% of patients, and more recently a course in 2011 went unsupervised whole exome sequencing was performed. It was discovered to everyone's surprise that perhaps the most common group of genes that are found to be mutated in MDS are splicing factor genes, and the right bottom quadrant of this particular slide shows that splicing factor 3B1 is found to be mutated in 16% of MDS patients but in 70% of RARS patients, and the interesting thing that is not shown on the slide but is true is that 98% of patients who will have SF3B1 mutation will have the presence of ringed sideroblasts in their bone marrow. So, SF3B1 is directly associated with ring sideroblasts whenever it is mutated.

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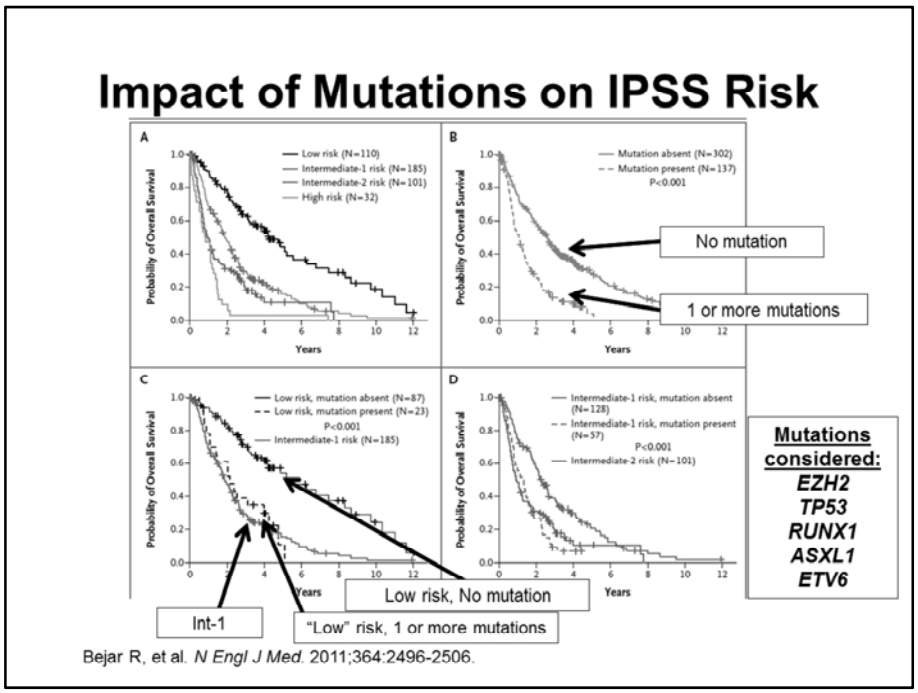

Dr. Azra Raza: Now, going onto the next slide, something interesting that our group has done is we worked with Rafael Bejar and Benjamin Ebert, and this paper was published in *The New England Journal of Medicine* in 2011 where 439 patients with myelodysplastic syndromes and 200 normal controls were looked at, and it was found interestingly that if there were mutations in any one of the five genes which are listed in this yellow panel here, EZH2, P53, RUNX1, ASXL1, and ETV6, then survival is affected. So, for example, if there is no mutation, then survival is better than even if there is a mutation in a single one of these genes as shown in the right upper hand quadrant. Then, if you look at the left lower quadrant, what you see is that if there is a low-risk patient and there is a mutation present, then the survival is almost exactly the same as the survival for intermediate 1 risk disease, and when there is no mutation, then the survival is that of low-risk disease. So, in other words, when there is a mutation present in any one of these five genes, then the survival according to the risk category of IPSS is moved up by 1. So, intermediate 1 with a mutation would become intermediate 2 risk disease, and I think that this is very important because like you mentioned we can now start to use this sort of genomic information along with cytogenetic information and clinical characteristics to better stratify patients into risk categories.

Dr. Stuart Goldberg: And I think it is also important to recognize for our viewers that these genomic profiles are available in commercial laboratories. So, it is not just researchers and academics that have the opportunity to do this. The most commercial laboratories are now offering these tests.

Dr. Azra Raza: One other additional thing is that because there is 100% concordance between blood and bone marrow, these genomic tests can be performed from the peripheral blood. You do not need a bone marrow to look for these mutations.

Dr. Stuart Goldberg: I think that is a very important feature that sometimes I see second opinions, and they destroy the standard chromosomes, they come out normal, and you are trying to do the IPSS or the IPSS-R, and you are trying to make a decision of do I start the treatment or not. Sometimes, sending off the peripheral blood rather than putting the patient through another bone marrow, that peripheral blood can tell you if there is a genomic mutation that upstages patient and maybe push to start treatment earlier or pushes us toward the bone marrow transplant or doing something that is a little more aggressive.

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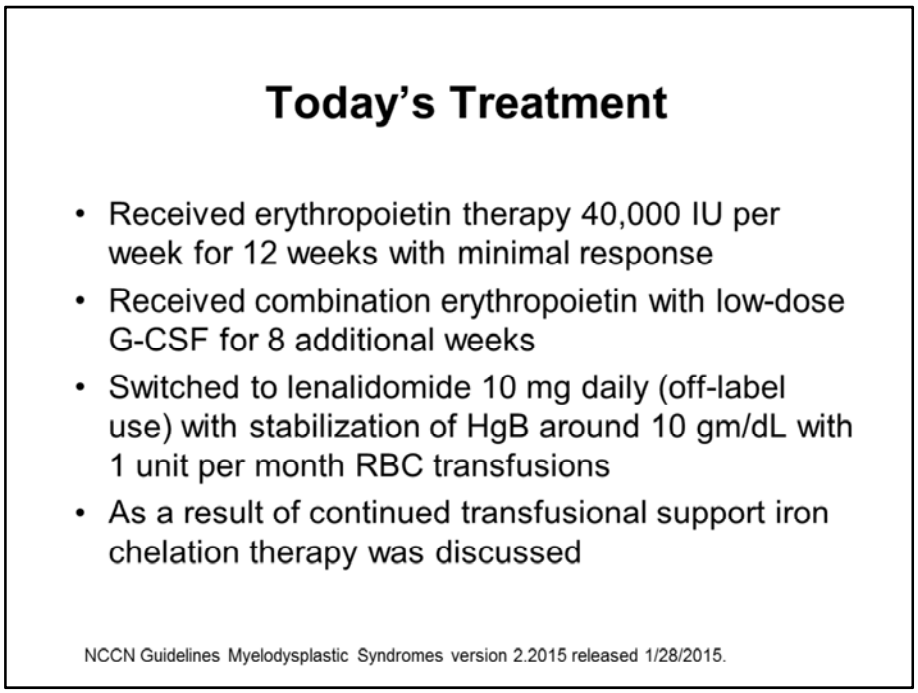

Dr. Stuart Goldberg: So, let's turn to our case again, and what are the therapies that we are sort of used to, I would call "today's treatment". So, this gentleman had a low-grade MDS. His major problem was anemia. So, we started him on erythropoietin using 40,000 units a week, and we gave it weekly for 12 weeks to see if he was going to respond, but unfortunately, his hemoglobin barely budged. We then added low-dose G-CSF to our cocktail thinking that two growth factors might be better than one, and there is a good data from the Scandinavians that we can see improvement in patients who have had a minimal response to erythropoietin, but after that, our patient still was very anemic, still requiring transfusions. So, we went ahead and used an off-label use of lenalidomide 10 mg a day as hemoglobin stabilized around 10 g, although he needed occasional unit of blood. Because he was continuing the transfusions, we offered him iron chelation therapy, and that is what we do today, but I know, Dr. Raza, at the ASH meetings that were just held in San Francisco, there were a lot of exciting abstracts about new therapies and even changing some of the ways we think about treating the low-grade patient. I was just wondering if you could comment on some of the major findings of that meeting.

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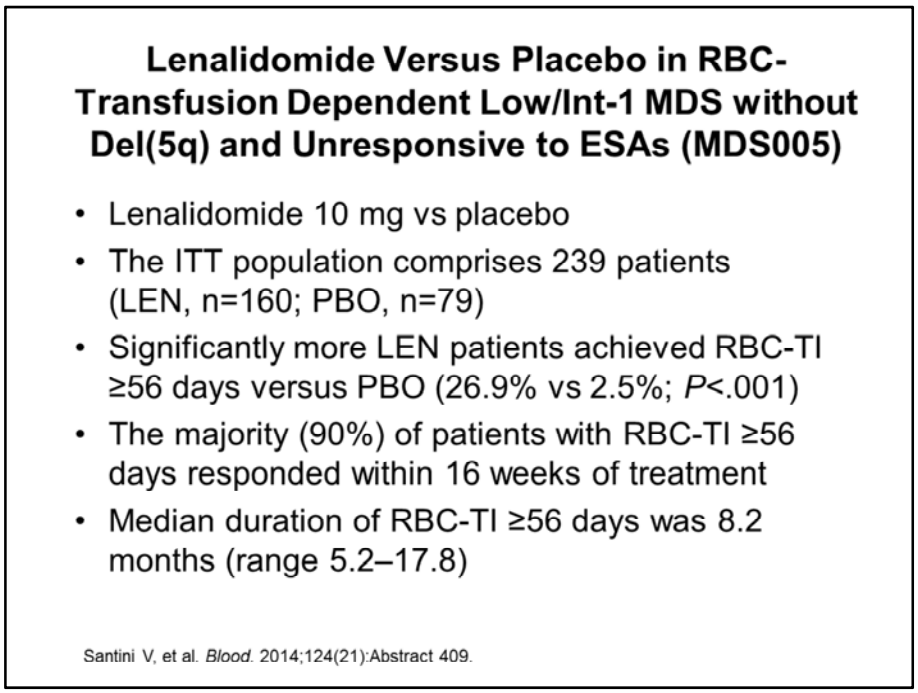

Dr. Azra Raza: Yes. So, one very important study that was presented was the use of lenalidomide in non-deletion 5q patients, and these patients were once again transfusion dependent belonging to low or intermediate 1 risk MDS and unresponsive to erythroid stimulating agents. This was a large placebo controlled trial in which 239 patients were entered, and specifically, what was found was that the most of patients as noted were transfusion dependent, and next slide shows that patients who received the lenalidomide at 10 mg, there was a 26.9% of patients achieved transfusion independence whereas in the placebo group, there was really nothing significant. So, this study actually completely confirmed what was already reported back in 2008 from the Celgene 002 trial which was also conducted in non-deletion 5q MDS patients and showed the 26% transfusion independence rate. So, with this study exactly paralleling the results of transfusion independence, I think it will become very much more of a common practice if not leading to FDA approval for this particular set of patients, but I think this was a very important study that was presented at the ASH meeting.

Dr. Stuart Goldberg: I know that many of our viewers commonly use lenalidomide off-label, and this study will probably give you some support if you have insurance questions. I know that we often use lenalidomide for the non-5q minus patients, and now we have a randomized comparative trial that shows a benefit in that group.

Dr. Azra Raza: Yes, exactly.

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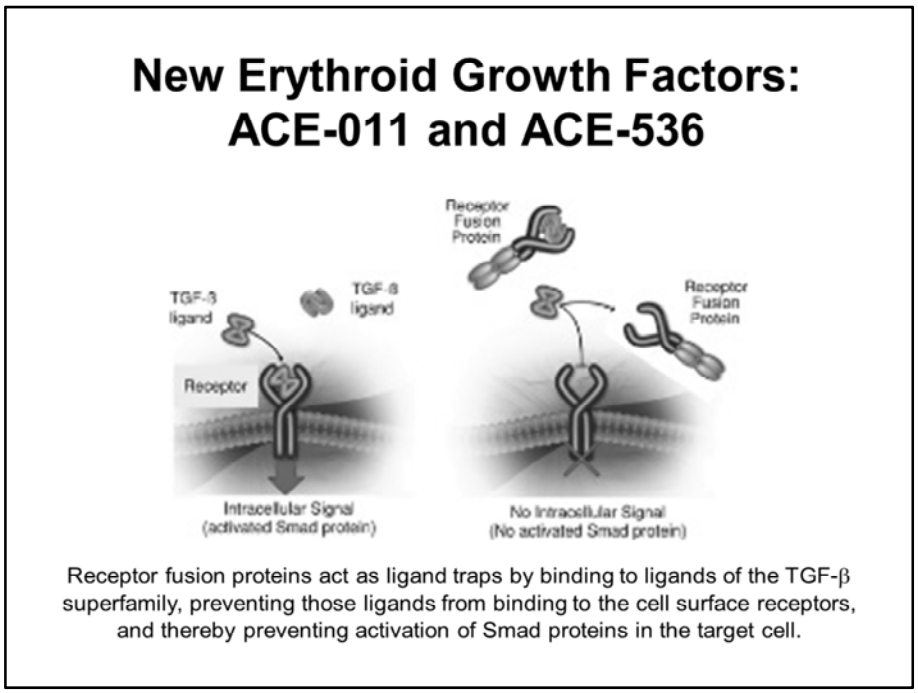

Dr. Stuart Goldberg: So, our patient was treated with erythropoietin and did not have a response. The question now is, "Is Epo the best growth factor for this disease?" I know that at the ASH meetings, and I know that in your own research, you have looked at new erythroid growth factors. Specifically, I know I have sent a couple of patients over to you for ACE-001, sotatercept, and this was also a very early study on
ACE-536. Could you explain these new growth factors to our audience?

Dr. Azra Raza: Yes. So, this is a very interesting novel class of agents that have been developed and that seemed to affect erythroid differentiations in the much later stages. So, for example, in the basophilic stage of early erythroblasts, that is where these growth factors work, and in reality, these are receptors that are fused with IgG at their intracellular end. So, the extracellular domain of the receptor belongs to really the TGF beta family of receptors, and that is a superfamily with the over 40 ligands. So, the receptor is able to bind the ligand, one of these 40 TGF beta family members, but once the ligand is bound to the receptor, then because the intracellular domain is now replaced by an IgG molecule, so what happens is that the whole thing gets dragged to macrophages and the cell is removed. So, what we are saying is that by giving these fusion proteins as working as ligand traps, we are able to have an anti-TGF beta effect, and what was done initially was to develop these agents as bone morphogenetic proteins, but in that setting when it was given to myeloma patients, they found that many patients increased their hemoglobin levels to dramatic values such as 17 and 18 g of hemoglobin, and so, it was then of course proposed that we should be giving it for anemic patients, and the first study has been done in thalassemia patients and then of course moved on to MDS. So, ACE-011 is sotatercept, and ACE-536 which was just reported in this ASH meeting is a recombinant fusion protein, and in this study, patients who were treated had an increase in mean hemoglobin level of more than 1.5 g over 8 weeks, and patients actually can become transfusion independence.

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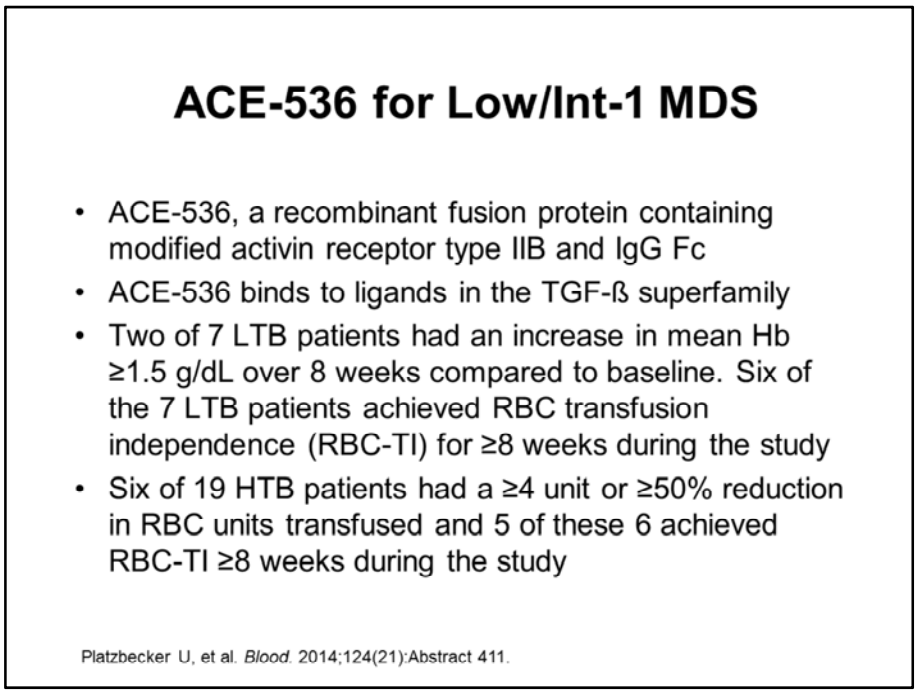

Dr. Azra Raza: The ACE-536 study which was reported at this ASH meeting showed that 6 of 19 patients had more than 4 units or 50% reduction in their transfusion requirements, and 5 of these 6 achieved RBC transfusion independence after 8 weeks during the study.

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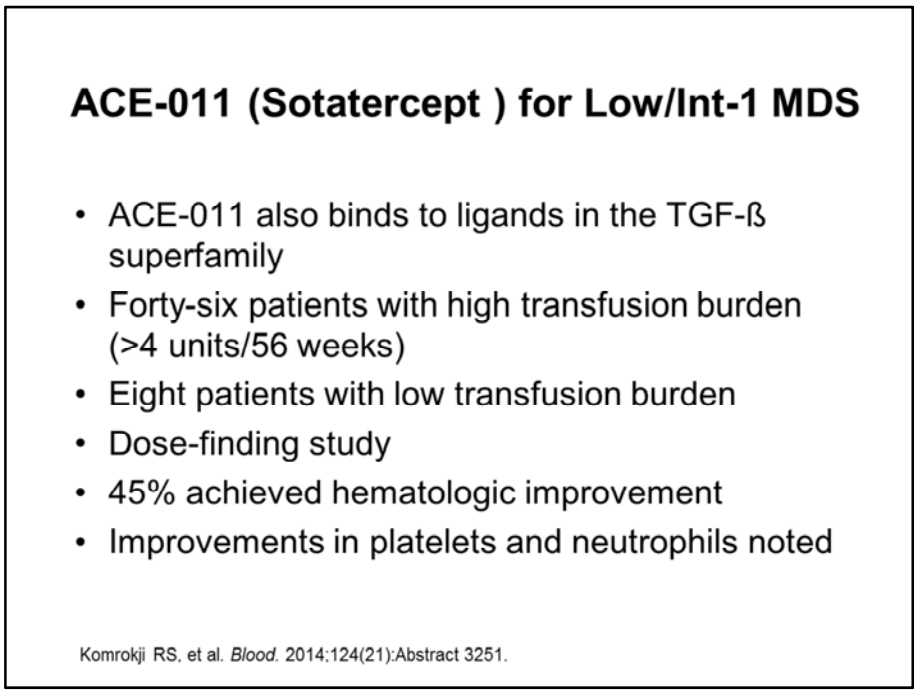

Dr. Azra Raza: So, there is a very exciting new development because here is an agent that is given subcutaneously every 3 weeks, very easy to give, really minimal side effects or very tolerable side effects, and appears to be decreasing transfusion requirements as well as patients developing complete transfusion independence in response to it. Even improvements in platelets and neutrophils were noted in this study, but the study is right now ongoing and we hope will lead to a Phase 3 trial very soon with both ACE-011 and ACE-536.

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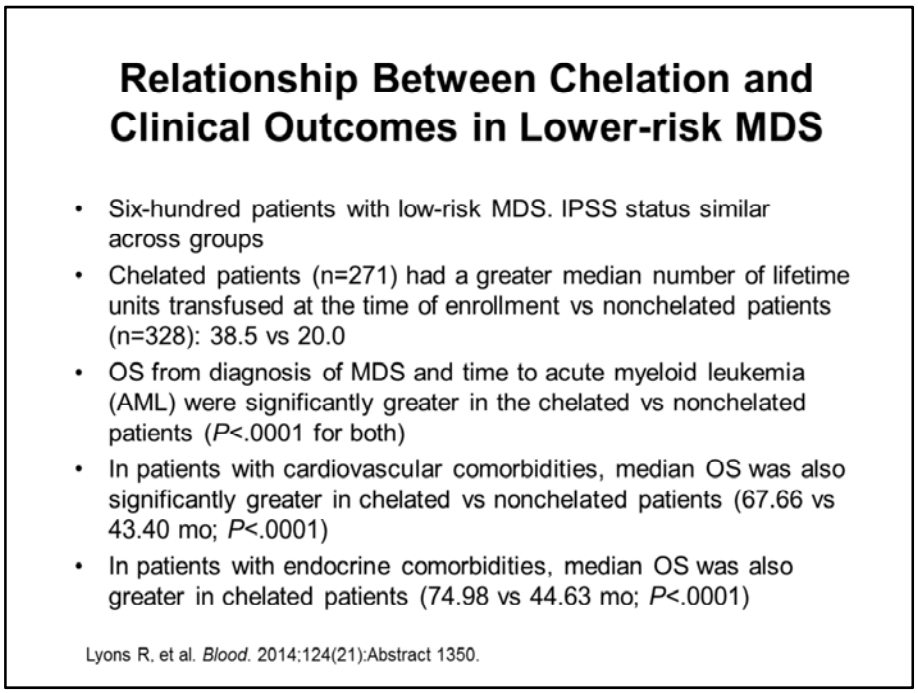
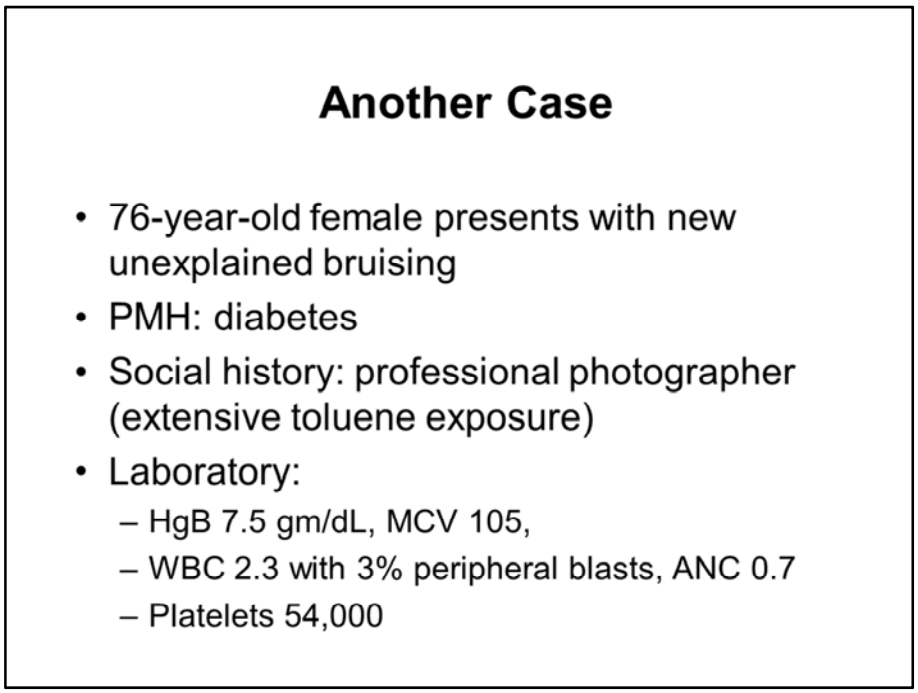


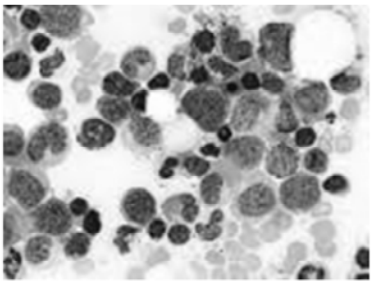
Dr. Stuart Goldberg: I think one of the studies that I was interested in is the relationship between chelation therapy and outcomes. We have known that patients who receive blood transfusions often will build up iron in their critical organs, and the studies that I published a couple of years ago, we saw the patients who received multiple transfusions had a higher rates of developing cardiac disease and higher rates of diabetes, but we have never really been able to show in a prospective manner that using chelation therapy improves those outcomes in part because we do not have a randomized trial. My colleague, Dr. Lyons, looked at over 600 patients with low-risk MDS in a prospective manner but in an observational fashion. Patients were not randomized; 271 patients were given chelation therapy, and 328 patients did not receive chelation therapy. The patients who were chelated were the ones who were receiving many more transfusions, and what they saw was that in these two groups the patients who had low-risk disease, the overall survival as well as the time to developing leukemia were both significantly improved in the group that received chelation therapy even though they were both low IPSS at the time of entering the trial. We also saw that the patients who received chelation therapy had lower cardiovascular morbidities and mortalities and the group that received the chelation therapy who had endocrine comorbidities also had improvement in their overall survival. So, once again, in not a prospective randomized trial but in an observational study with a large group of patients, we are starting to get a hint that chelation therapy may affect the ability to control iron overload in critical organs and change the clinical outcomes for some of our patients. I think this would get some support for those of you who believe in chelation therapy. I know it is still a controversial area in the world of MDS, but I think that this type of large study may push us a little bit more in that direction.



Dr. Stuart Goldberg: So, let me turn to another case. I saw another 76-year-old woman who came in with unexplained bruising. She had diabetes, and she was a professional photographer who had extensive toluene exposure. She also had a macrocytic anemia. She had a low ANC and a low white count with a few circulating blasts, and she had some moderate thrombocytopenia.

Bone Marrow with Changes of RAEB-2

- Blasts: 12%
- Cytogenetic: 45 XX, -7
- IPSS: high risk
  - 3-line cytopenia: score 0.5
  - Blasts: score 1.5
  - Cytogenetics: score 1
- R-IPSS: very high
  - Cytopenias: score 2.5
  - Blasts: score 3
  - Cytogenetics "poor": score 3



Dr. Stuart Goldberg: Her bone marrow showed a higher grade MDS and RAEB-2, refractory anemia with excess blasts type 2, with 12% blasts and the cytogenetics were monosomy 7. Using the IPSS scoring system, the classical one that we are all familiar with, she had three lines of cytopenias, she had some blasts, and she had bad cytogenetics, so she fell into a high risk as a type, a high risk category, and under the new IPSS-R that Dr. Raza explained, she fell into the so-called very high risk category because she was fairly cytopenic, she had a lot of blasts, and she had poor-risk cytogenetics. .

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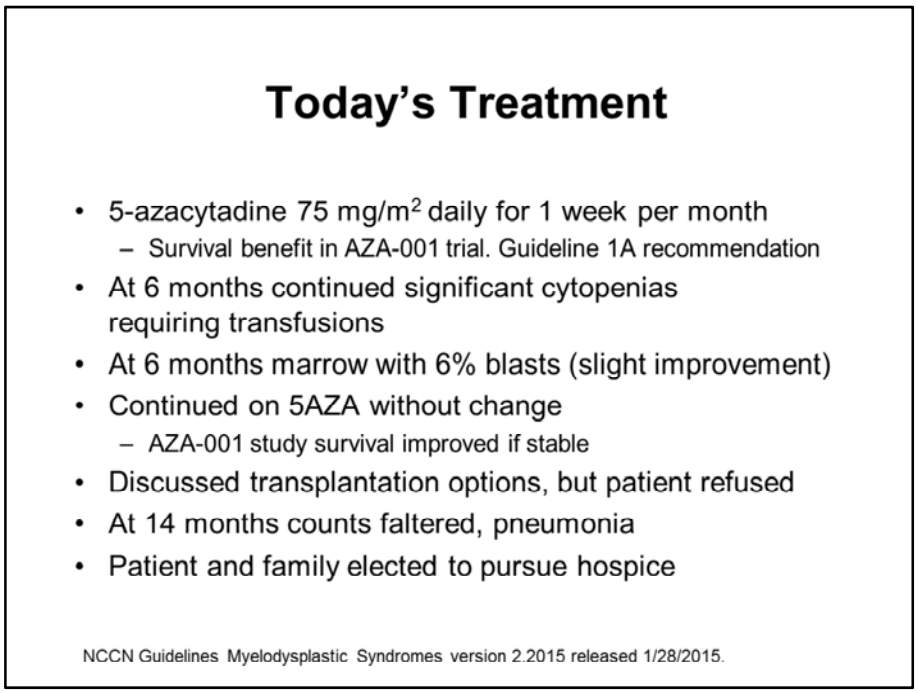

Dr. Stuart Goldberg: So, under today's treatment for our patient with intermediate risk of 2 or high-risk disease based on the AZA-001 trial which is a category 1 recommendation, we would use 5-azacitidine 1 week per month. We know that there is a survival benefit for the patients with intermediate- and high-risk disease if we use a hypomethylating agent. At 6 months, however, after a good trial of this medication, she still had cytopenias and was requiring transfusions. We repeated the bone marrow at 6 months, and her blasts had gone down slightly to 6%. Based on the AZA-001 trial though because she was not showing evidence of disease progression, we decided to continue her on 5 days of azacitidine because in the AZA-001 trial if you were stable, that is if you were not showing evidence of true progression, you actually benefited from a standpoint of survival. We did talk to her about transplant, but she was older, little frail, and she decided not to pursue that. Unfortunately by 14 months into the treatment, her count started to fall when she developed pneumonia and then at that point she elected to pursue hospice. So Dr. Raza, this is a standard way to treat a high-risk patient. What were some of the newer things at ASH meetings about the higher risk patients?

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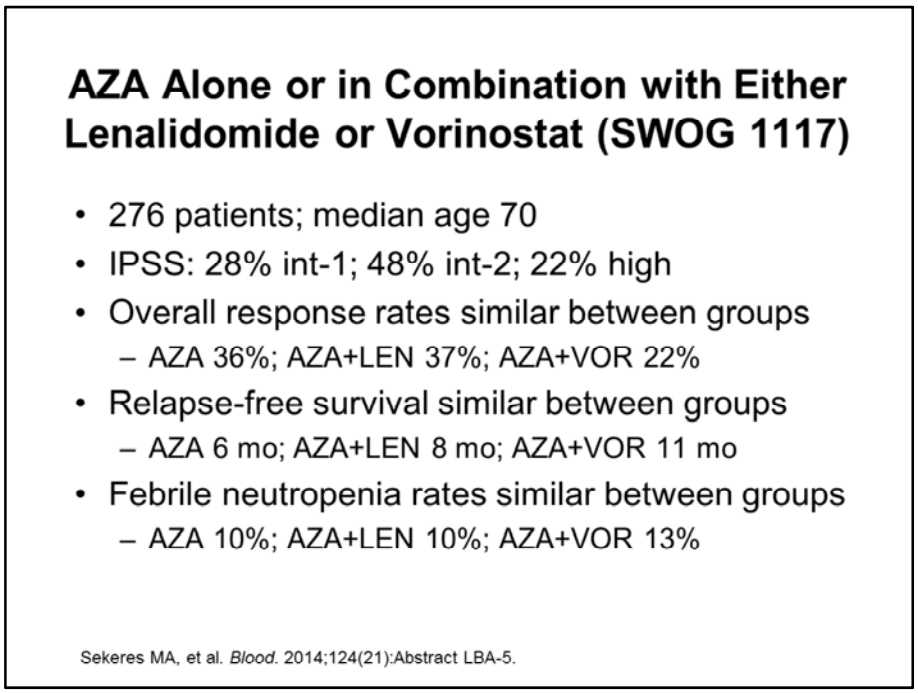
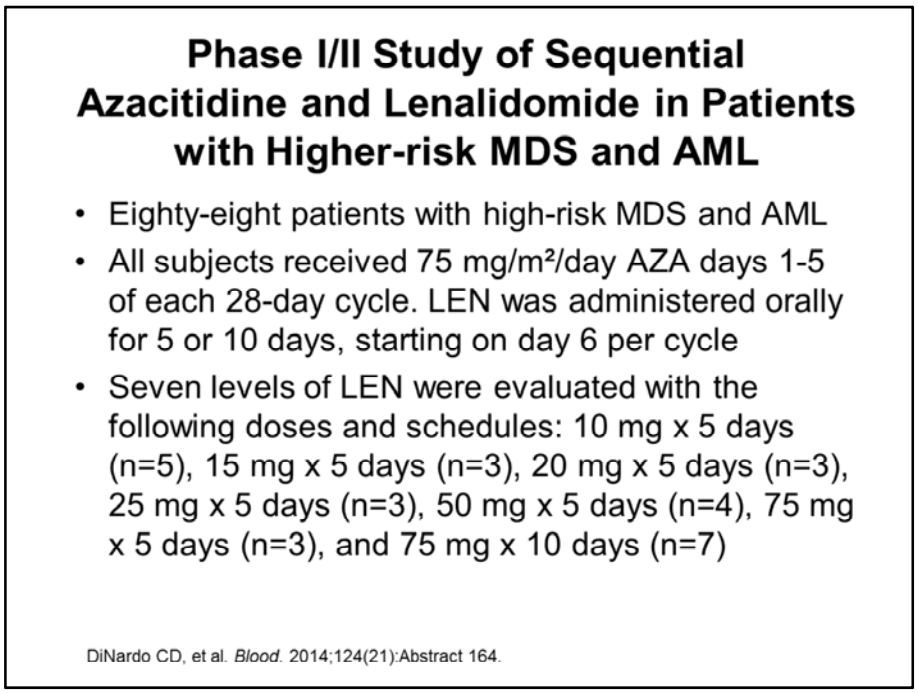


Dr. Azra Raza: High-risk patients, especially very high-risk patients, really require early aggressive intervention. If there is a transplant possibility, we transplant them of course. If transplant is not available, then as you mentioned hypomethylating agent is the first way to go, but in that phase, the next options so far are really limited to clinical trials, and some of the interesting results that were presented at this ASH meeting included combination trials. So, for example, in this particular study from SWOG, azacitidine was given either alone or in combination with lenalidomide or in combination with vorinostat which is an HDAC inhibitor, and 276 patients with a median age of 70 were entered in this trial, and interestingly, the overall response rate really was similar in all the three groups. The relapse-free survival seemed to be almost the same as well and so were the febrile neutropenia rates. So, the survival rates really were around 20-35% for each of the groups.



Dr. Azra Raza: Now, another study that was presented is 88 patients are admitted in this Phase 1 and Phase 2 study of sequential azacitidine and then lenalidomide, once again higher risk patients or AML patients, and all of them received are azacitidine for 5 days and then lenalidomide administered orally for 5 or 10 days starting right after azacitidine finished.

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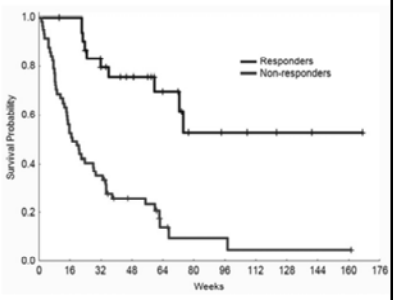
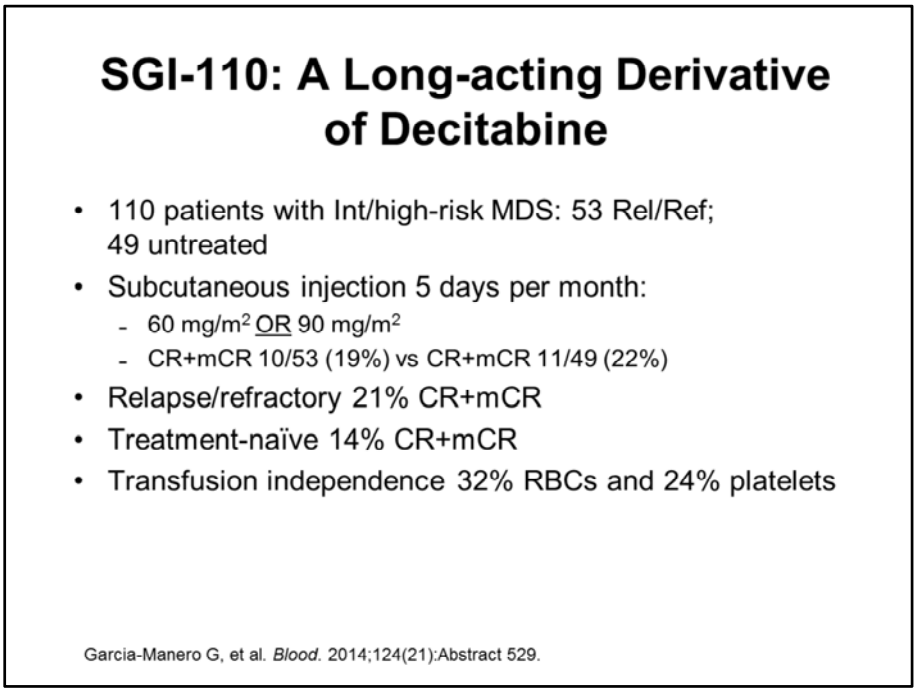
- In the entire cohort, overall response rate (ORR) was 35% with median overall survival (OS) of 33 weeks (range 1-172)
- In responding patients (n=31), median overall survival had not been reached with a median follow-up time of 57 weeks



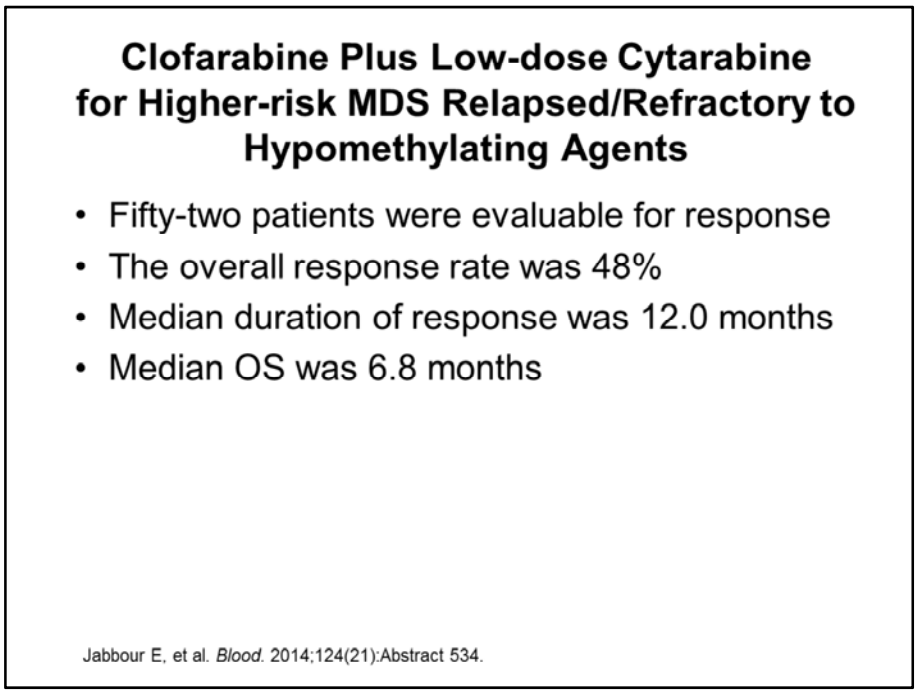
DiNardo CD, et al. *Blood*. 2014;124(21):Abstract 164.

Dr. Azra Raza: The confusing thing about this trial was that there were many, many subgroups where dosage of lenalidomide was being tried, but in the entire cohort, the overall response rate was 35% with a median survival of 33 weeks. However, even though that sounds quite discouraging, the one thing to note is that in the patients who responded which were 31 of these 88 patients, the median overall survival has not been reached, and the followup time is already 57 weeks. So, it seems that the response rate is about a third of the patients, but those who respond appeared to be improving their survival.



Dr. Azra Raza: Then, the next slide shows an interesting development in using a long-acting derivative of decitabine SGI-110. In this study which was restricted once again to intermediate- to high-risk MDS patients, 100 patients were entered in the trial, and 53 had relapsed/refractory disease whereas 49 were previously untreated. Patients received 5 days subcutaneously of SGI-110 at 60 mg/m^2 or 90 mg/m^2, and the complete response rate was 19% versus 22% in the two dosing groups. For relapsed and refractory patients, there was 21% complete response rate, and for treatment-naive patients, it was 14%. So, in fact, it seems that patients who have previously received a hypomethylating agent, have relapsed, and have refractory disease can respond to SGI-110. Transfusion independence and platelet transfusion independents were both achieved in substantial number of patients, 32% red cell transfusion independent and 24% platelet transfusion independent. Again, this is quite impressive.

Emerging Therapies and Clinical Trials: What's on the Horizon

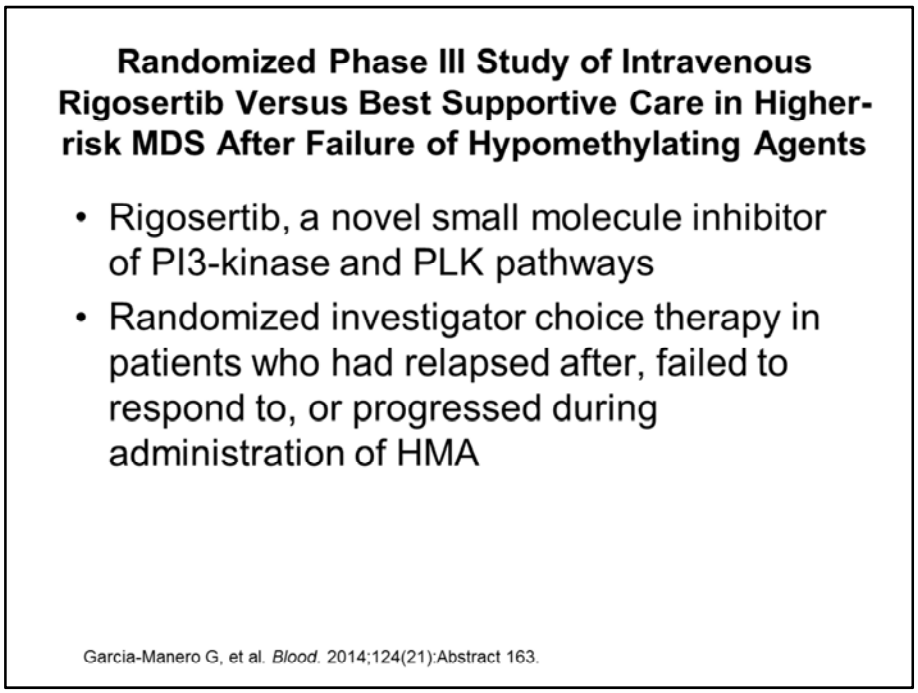


Dr. Azra Raza: In addition, at this ASH meeting once again, chlorthalidone with or without low-dose Ara C was reported for high-risk MDS relapsed and refractory to hypomethylating agents. 52 patients were evaluable for response rate was 48%. The median duration of response was 12 months, and overall survival was 6.8 months, but survival for those patients who responded was median of 16 months actually. So, clofarabine seems to be a very interesting and encouraging possibility for this very high-risk group of patients who have already failed hypomethylating drugs. Remember the group that we are dealing with really does not have many options, so to have some of these options available even through clinical trials right now is quite encouraging.

Dr. Stuart Goldberg: For a brand new patient who walks in the door, who has a high-grade MDS based on the studies that you just showed us, would you combine a hypomethylating agent with either lenalidomide or with an HDAC inhibitor as part of your initial therapy or do you think the SWOG study says that we should wait a little bit longer?

Dr. Azra Raza: I think unfortunately what the SWOG study showed is that there is no difference whether you give the drug alone or in combination with either lenalidomide or vorinostat. So, no, I think for a brand new patient who walks in the door, still the best treatment is a hypomethylating agent alone first of all and then if they fail that, then one of these possibilities that are being reported and the most exciting one right now we mentioned so far is the SGI-110 because that seems to be effective even though it is a hypomethylating agent itself, it is just longer acting decitabine, yet it seems to be helping patients who have failed previous hypomethylating technique. So, I think that as long as a strategy is working, so hypomethylating agent and then followed by the longer acting hypomethylating agent and then I would go to either a combination trial or completely different agent like rigosertib.

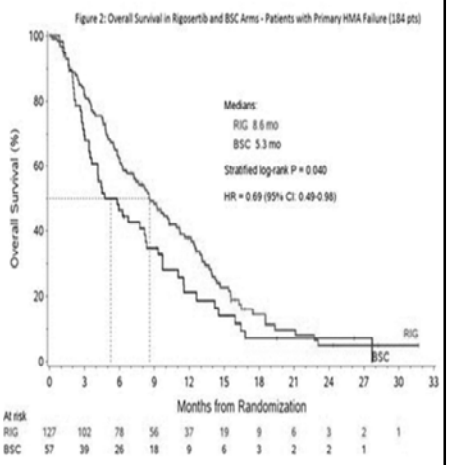
Emerging Therapies and Clinical Trials: What's on the Horizon



Dr. Azra Raza: In this particular randomized Phase 3 study of rigosertib that was presented, actually it turned out to be a study that did not meet its primary endpoint, but there were some very interesting things that were presented. So, this a dual kinase inhibitor that in this setting was given to patients who had high-risk MDS in a 2:1 randomized study with patients either receiving the drug or receiving best supportive care, and patients could also receive low-dose Ara C on this.

Emerging Therapies and Clinical Trials: What's on the Horizon

- 2.3-mo improvement in median OS was found in the overall (ITT) population (8.2 mo rigosertib vs. 5.9 mo BSC)
- Among the 184 patients with primary HMA failure, the median OS was 8.6 mo in the rigosertib arm (N=127) vs. 5.3 mo in the BSC arm (N=57), HR=0.69, *P*=.040
- Primary endpoint for entire study not met
- Encouraging results in subgroup with primary failure to respond to HMAs and IPSS-R very high subgroups



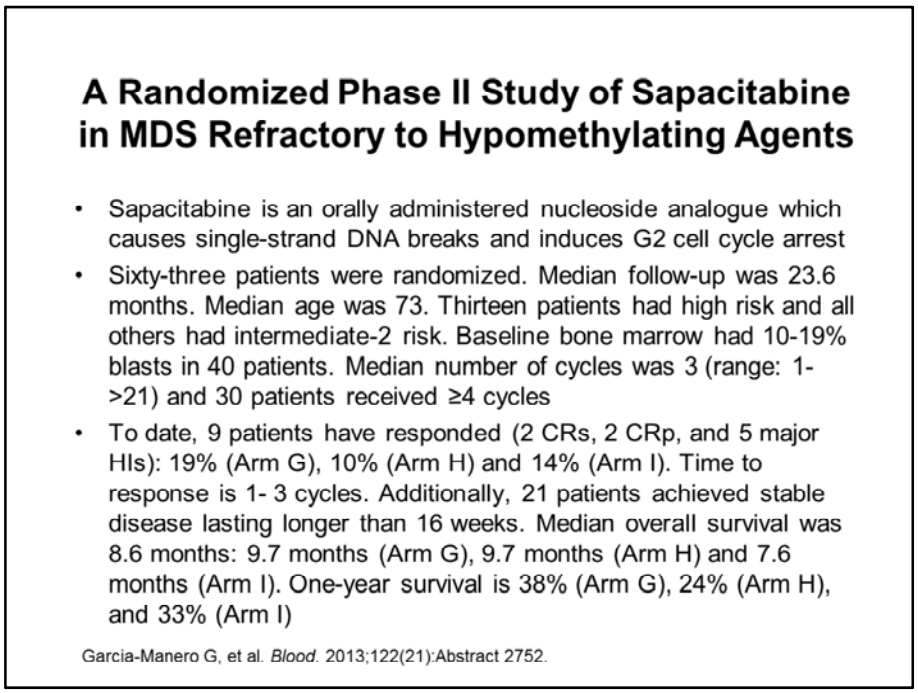
Garcia-Manero G, et al. *Blood*. 2014;124(21):Abstract 163.

Dr. Azra Raza: What was found in the trial was that the median overall survival for the intent to treat population was not very statistically different between the rigosertib and the best supportive care. However, amongst the 184 patients with primary hypomethylating agent failure, median overall survival was 8.6 months in the rigosertib arm and 5.3 months in the best supportive care arm, and this was statistically significant. So, why the primary endpoint for this entire study was not met? It seems that patients are primary HMA, so there is a difference between patients who are primary versus secondary HMA failures. Primary failures are those who never responded to the hypomethylating agent, and secondary failures are those who responded and then stopped responding. So, for primary HMA failures, it is an interesting thing to see that rigosertib appears to be effective in a statistically significant way in this subgroup and what it is suggesting is that patients who are failing hypomethylating agents or primary failures really need a completely differently strategy of treatment, a strategy that is provided by this kinase inhibitor. So, in this sense, the subgroup of primary HMA failure had encouraging responses to hypomethylating agents.

Dr. Stuart Goldberg: So, I know our center participated in that trial, and we found it little cumbersome to have the patients with the IV continuous infusion, but I know that your center has been pioneering an oral version of rigosertib in patients with lower grade disease. The data has not been shown yet, but could you share us any insight that you have with these drugs when it is given as an oral drug?

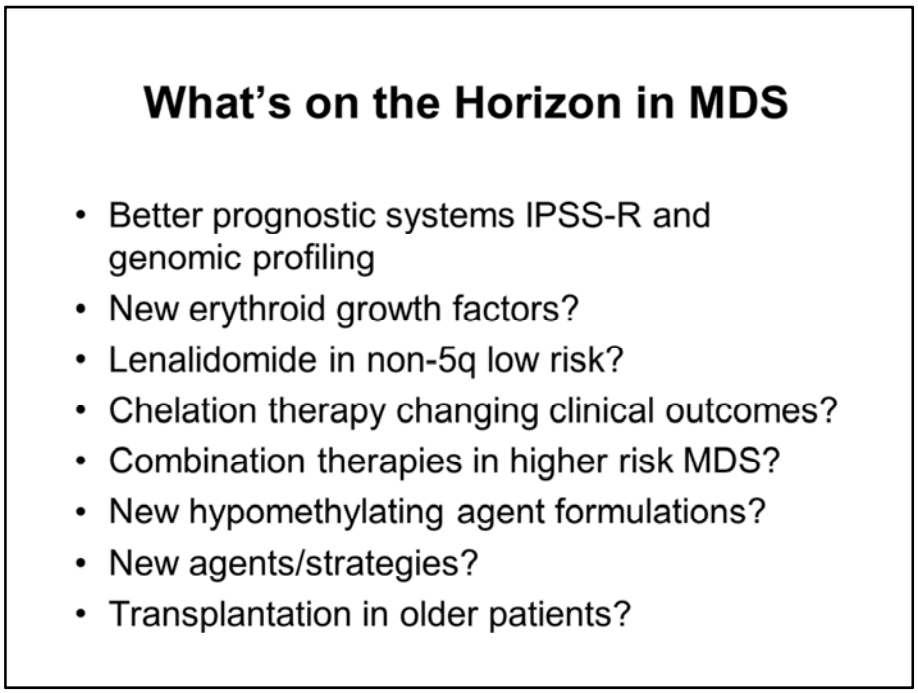
Dr. Azra Raza: So far, the oral drug, Stuart, has mainly been restricted to patients who have had low-risk disease and only in a Phase 1 and in a Phase 2 trial, and in low-risk MDS patients, we have reported a response rate between 30% and 40% of transfusion independence. Especially, there seems to be some synergy with an erythroid stimulating agents with rigosertib. So, I do think that the oral drug presents a very nice alternate substitute for the cumbersome intravenous 72-hour infusion that is given through a pump, but so far, we do not have this drug tested in the setting really of higher risk MDS patients. I do think that in the next trial it is shown that for the subgroup of patients with primary HMA failure and high-risk MDS for whom rigosertib turns out to be the treatment of choice once they fail hypomethylating agents, then I do think that better trial of the oral agent compared to the intravenous agent will be very much desirable.

Emerging Therapies and Clinical Trials: What's on the Horizon



Dr. Stuart Goldberg: One of my favorite drugs in the AML world has been an oral drug called sapacitabine which is a nucleoside analog, and for those of you who are watching, there is a large randomized registration trial comparing sapacitabine against decitabine in the AML patient, the elderly patient. Hopefully, that is on a regulatory pathway, but at the recent meetings and we have heard a little bit about using this oral drug in patients with MDS that have been refractory to hypomethylating agents. So, I know in this trial which we participated in, we saw 63 patients who are randomized to a variety of different dosing and strategies. We did see some improvement in hematopoiesis in patients who had refractory to hypomethylating agents and control of the leukemia blast, this being more of a leukemia type drug and that led to longer survivals than we might have predicted in a patient who is already refractory to hypomethylating agent.

Emerging Therapies and Clinical Trials: What's on the Horizon



Dr. Stuart Goldberg: So, I guess to sort of summarize, the question is really what is on the horizon. At this conference, we have talked about some of the better prognostic scoring systems that are coming out and the role of genomic profiling. We have mentioned a little about erythroid growth factors. We all know that we have used lenalidomide in patients with 5q and now there is some data on the non-5q setting, a little bit more about chelation therapy, certainly for the high-risk patients combination therapies or new formulations of hypomethylating agents and then truly new agents and then obviously we do not want to forget transplantation which we did not cover. Dr. Raza, do you have any final comments on things that you think are going to be changing the way we practice medicine for older patients with MDS in the next 5 years or so?

Dr. Azra Raza: I would like to just make two points here, Stuart. One is that it is very discouraging to note that the last drug that was approved for the treatment of MDS was 10 years ago, and really, we do not see too many new strategies, completely normal strategies coming onboard even now for myelodysplastic syndromes, but I think that the noble insights that are being developed into the genomics, for example, all these splicing factor mutations, all the new mutations and epigenetic genes that are being identified, and as agents are being developed, I think that in the next 5 to 6 years we will see quite a dramatic turnaround in this discouraging scenario, but the last point I do want to make here is that the IPSS scoring system which gives us really not the risk of developing leukemia but the risk of dying for a patient is a very important point for hematologists, our colleagues, to appreciate that for very low and low-risk MDS patients, the risk of leukemia is 17% to 20%, but for very high-risk patients and high-risk patients, it is not like 80% and 90%, it is still 35-36%. So, in another words, what I am saying is that the patients are dying of MDS at a very rapid rate in high-risk MDS. They still die of their disease. So, their disease is MDS which causes increasing profundity of cytopenias, and so, I think that drugs have to be developed for high-risk MDS to target the MDS clone rather than always worrying about how do we stop development of leukemia, that is only in a third of the patients, and I think in the next 5 or 6 years you are going to start seeing that.

Dr. Stuart Goldberg: Well. Thank you very much. I hope you have enjoyed this presentation on what is on the horizon in MDS. This is Dr. Stuart Goldberg with Dr. Raza for *ManagingMDS.com.* For more information on this disease, check out the website.