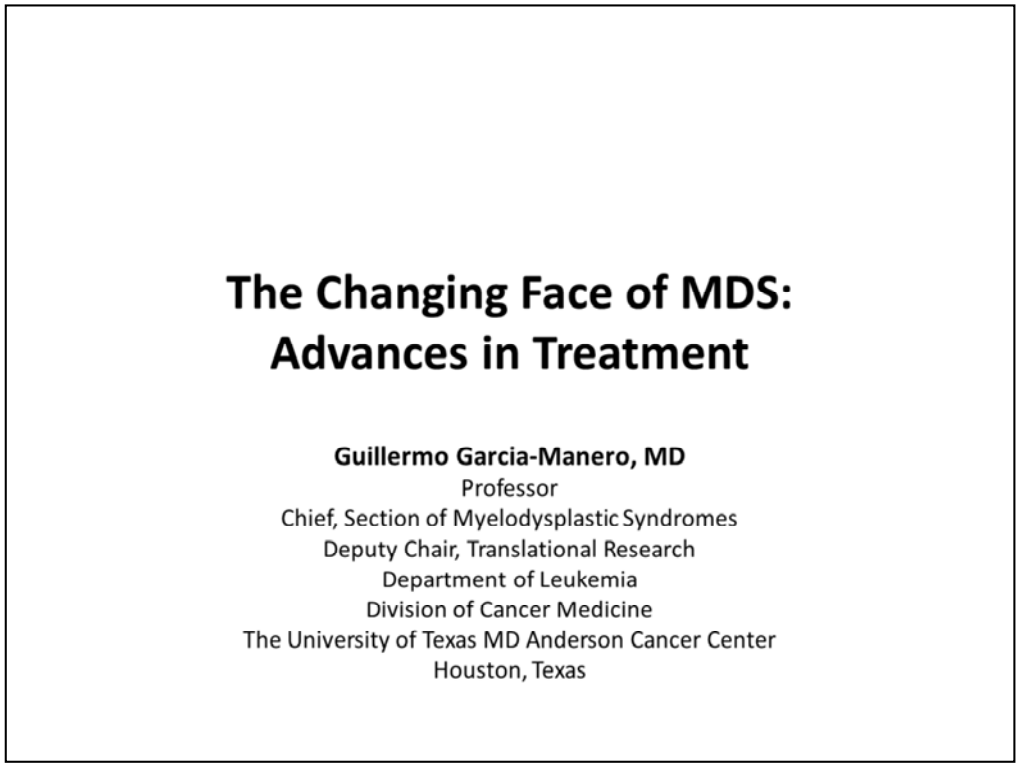
The Changing Face of MDS: Advances in Treatment



Thank you very much again for listening to me. We are going to be talking now in terms of therapy of MDS or "The Changing Face of MDS – Advances in Treatment." My name is Guillermo Garcia-Manero. I am a Professor of Medicine at the University of Texas MD Anderson Cancer Center where I lead the MDS program and I am also the Deputy Chair for Translational Research out here.

So if you listened to my prior talk regarding prognosis and cytogenetic molecular, you see that over the last 10 years we have made quite a bit of progress in understanding this disease and also in terms of how to apply this type of molecular information into the actual care of our patients. Now, we are learning a little bit in treatment discoveries, but I think actually this is going to change in the next couple of years.

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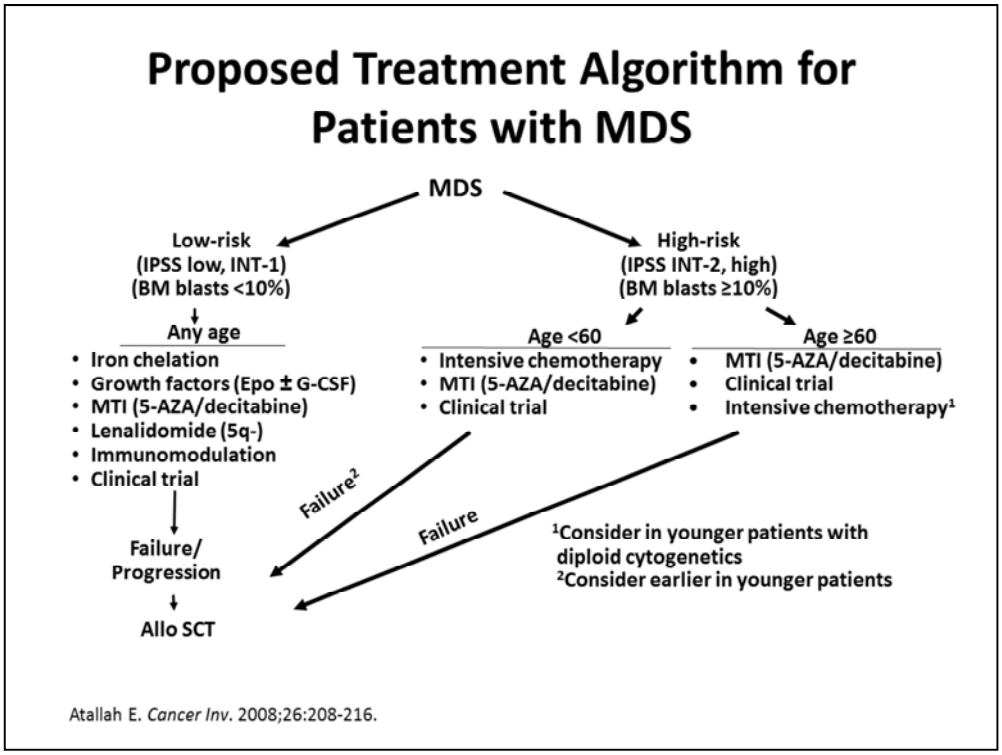

So in this next half an hour or so, I am going to talk to you about what are the major paradigms of therapy of MDS today and hopefully how this is going to change in the near future. So in this slide, this is from a paper that I wrote with Ehab Atallah, who is now in Wisconsin, a few years ago, and we came with kind of like a short NCCN type of guideline that you have there, and what you see is that we divide patients into lower risk and higher risk. In the lower risk, we still talk by IPSS low, intermediate 1. I guess by IPSS-R, this would be low, intermediate 1 and some group of patients with intermediate-risk disease, or to make it easy, perhaps blasts less than 10%. Then for that group of patients the number of interventions that one could think of, like iron chelation, growth factors, although I do not know that nowadays actually we use them very much either as therapeutic intent, but for sure the hypomethylating agents, lenalidomide, immunomodulation, they are basically our standard of care. And then there is a question in terms of when to do or perform an allogeneic stem cell transplant in our patients. Then, you go to the high-risk column. This actually is a little bit more complicated where you may divide patients not only by IPS risk or percentage of blasts, but also by age, and I put in the slide 60. The question is it is now 65, but this is probably depending on the comorbidity and the overall performance of patients, but then, the question there is should you give a hypomethylating agent or should you use induction chemotherapy? And then, the other question that is not answered today is when do you do a stem cell transplantation, at the time of diagnosis, at the time of best response, or at the time when you start losing the response? So, I am going to try to go through these through this talk.

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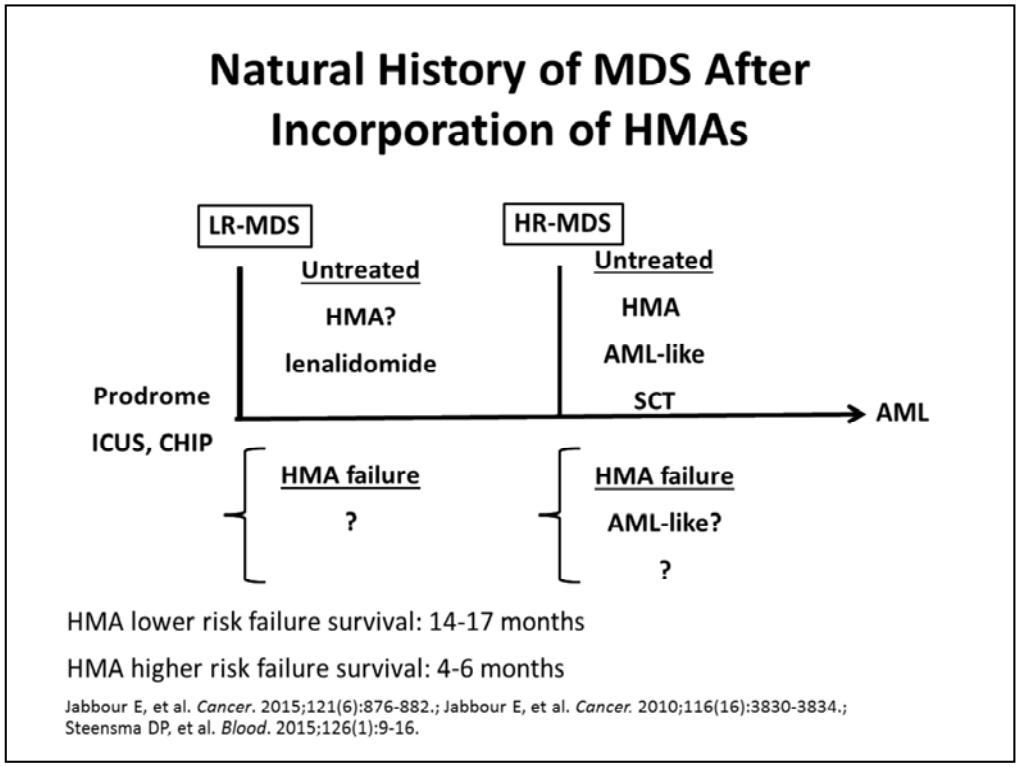
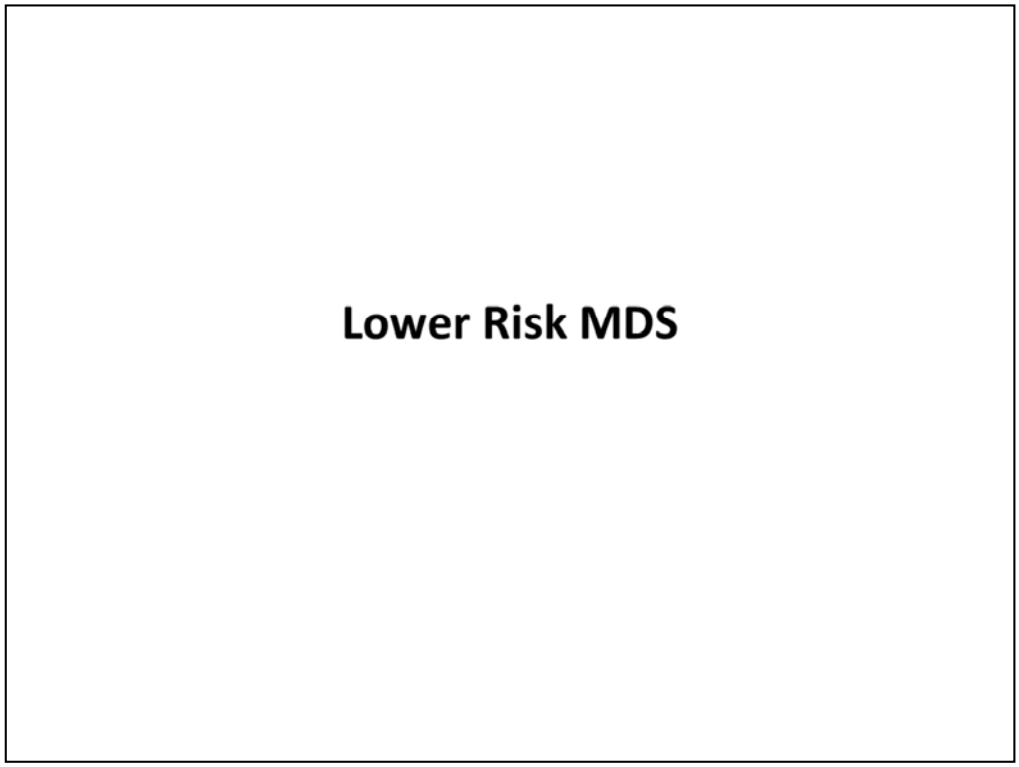


The next issue, and I think this is critical, is that of course you are going to be classifying your patient based on IPPS or IPSS-R, but practically, I think the slide that I show here is very important, that is you are going to be talking about MDS, thinking about them in four different buckets, low risk versus high risk, that we already discussed, but then, you are going to ask the question, "Has this patient received any prior therapy?" In particular, has the patient had a hypomethylating agent? Has the patient had lenalidomide? Why? Because prognosis of a patient with untreated low-risk disease is different than a patient that has received a hypomethylating agent. Indeed, actually, we call this hypomethylating agent failure and this could be high risk or low risk. And as you see in the slide, the importance is that the patient with high-risk disease with HMA failure has a survival of 4 to 6 months. A patient with low-risk failure has a survival of 14 to 17 months, and the biology of this disease in the front-line versus in the relapsed setting is totally different in the sensitivity, and the chances that this patient will respond to second-line therapy are also different. So, you need to be aware of that when you approach your patients. So, I always tell my fellows that when you approach a patient in the clinic, you think about these automatically and then you say well these are the characteristic cytogenetic, molecular, etc., but you need to have a frame, and I think this is actually a very important one. Of course in the prior talk, I really talked about problems like ICUS or something called CHIP, clonal hematopoiesis of unknown significance, that I kind of alluded earlier where these are people that have mutations in their blood with marrows that are normal or not totally normal that are actually predisposing factors to myelodysplastic syndrome. The question now is whether we are going to consider them or not as a group of patients that we want to treat. I think most of us now of course will observe these patients but in a more closer way than what we used to do a few years ago, and then of course, on the right, at the end of the spectrum you have the group of patients with AML, but this is a different group of patients because these are patients with MDS that will go on to acute myelogenous leukemia.



So, I am going to go through therapies for each one of these buckets. Let's start with low-risk disease, and again, my intention here is not to cover every therapy because this will take quite a bit of time but just to give you some updates or discuss some of the paradigms. Again, I think growth factors and iron chelation may be good supportive tools. I do not particularly see them as primary therapies for most of our patients.

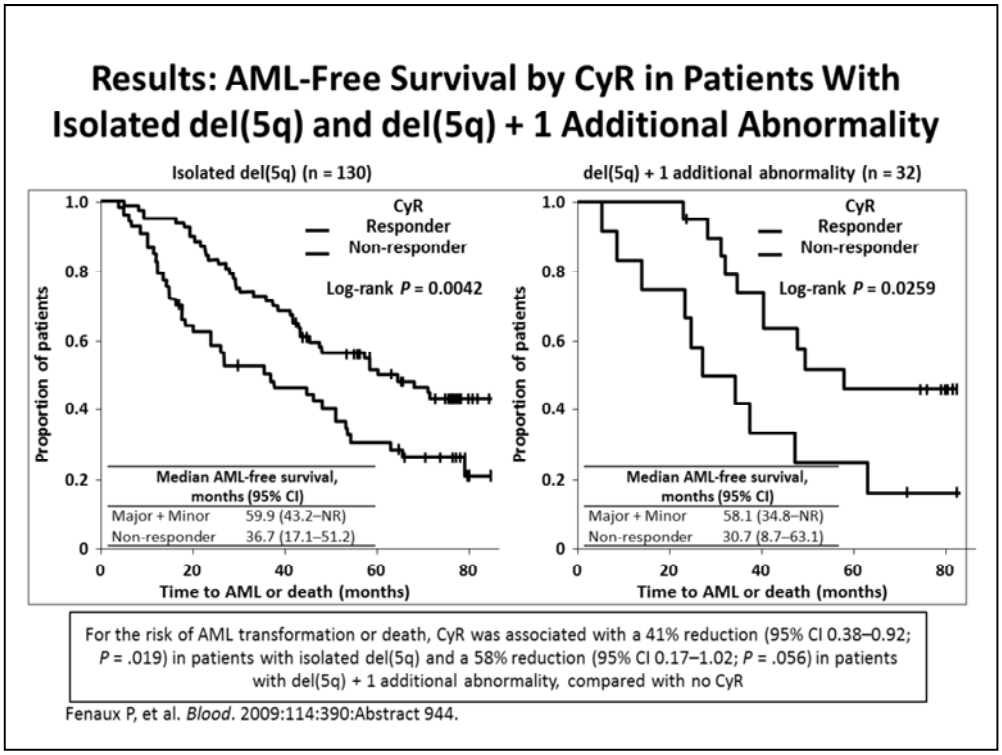
MDS-004: Randomized Phase III of Lenalidomide in Lower Risk del5q MDS

Efficacy	PBO	LEN 5	LEN 10
RBC-TI ≥26 weeks (N, %)	3 (6)	19 (41)	23 (56)
IWG-TI (N, %)	4 (8)	23 (50)	25 (61)
Median time to response (weeks)	0.3 (0.3-24)	3.3 (0.3-12.3)	4.3 (0.3-14.7)
Median Hgb ↑	2.3	5.1	6.3
CCGR+PCGR	0	8 (17)	17 (41)

- Progression to AML: LEN 5 6%, LEN 10 1%, PBO 2%
- Time to AML: 9.3, 5.9 and 3.1 months
- G3-4 neutropenia in LEN 5 74%, LEN 10 75%, PBO 15%
- Discontinuation in LEN 5 16%, LEN 10 9% and PBO 5%

Fenaux P, et al. *Blood*. 2009:114:390:Abstract 944.

I think drugs that are established in this group of patients are agents like, in this case, lenalidomide. This is from the 004 trial published by Dr. Fenaux a number of years ago that really established this drug together with the data from analysis as a standard of care for patients with 5q- MDS. This is an important randomized trial where they compared basically placebo versus lenalidomide at 5 mg versus lenalidomide at 10 mg, and it showed clearly that lenalidomide at 10 mg is the standard and very effective group of patients therapy, particularly for patients with chromosome 5 alteration and those who have platelets over 50,000 or 100,000. In my opinion, the drug has a very little role if you are trying to treat thrombocytopenia or neutropenia, and particularly it is not very active in patients with severe thrombocytopenia. At ASH a couple of years ago, there was data from a randomized trial of lenalidomide in the non-del 5q- group of patients that also showed some activity, but not to the extent that we see here with lenalidomide at 10 mg in this group of patients with lower risk MDS and a 5q- alteration.



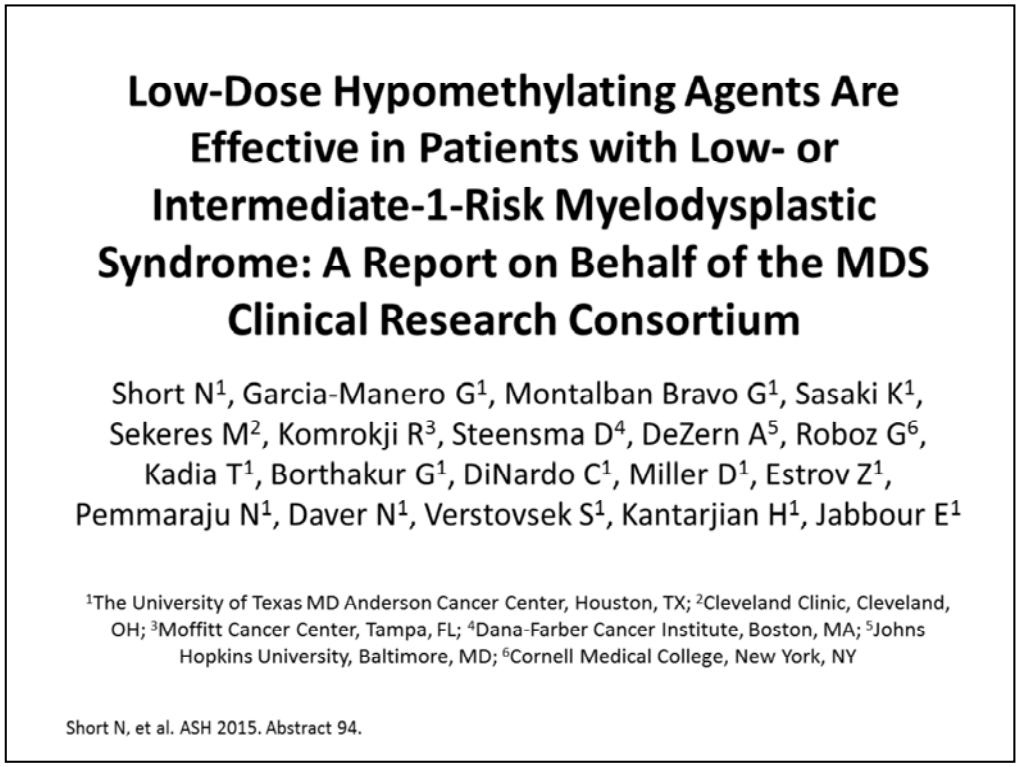
Now, one question that is important is that because these drugs were actually approved on single arm type of trials that we do not really know long-term survival effect of this compound and biomarkers associated with outcomes. So, this paper that was eventually presented by Dr. List and Dr. Sekeres is crucial because it, for instance, correlates outcomes with lenalidomide and achievement of a complete cytogenetic response. So, this is very important because at least you have a landmark in terms of similar to what you do in CML that if you have a patient with 5q- disease that has not achieved a complete cytogenetic response perhaps you may need to look for other alternatives and for sure continue therapy in those patients that achieve this type of complete cytogenetic response similar to what we do in CML and acute myelogenous leukemia.

Phase 1 Oral Aza Study
Response to Therapy (N=41)

Disposition	MDS (N=29) N (%)	CMML (N=4) N (%)	AML (N=8) N (%)
Ongoing	8 (28)	2 (50)	2 (25)
Terminated	21 (72)	2 (50)	6 (75)
Median duration of oral therapy, # of cycles, (range)	6.0 (1–23+)	7.0 (3–17+)	4.5 (1– 14+)
Cycle 7 Response Assessment*	13 (45)	2 (50)	2 (25)
CR / PR / HI	4 (31)	1 (50)	0 (0)
SD	8 (61)	1 (50)	2 (100)†
Progression	1 (8)	0 (0)	0 (0)

* IWG 2003 or 2006
†Subjects did not meet criteria for progression or response by IWG 2003

Now the drugs, at least in our group, we use more frequently are the hypomethylating agents and this actually may be different, for instance, from what they do in Europe where the indication for hypomethylating agent seems to be more on a level for high-risk disease, but here in North America, we have a lot of expertise in using these compounds. This probably all started with the development of oral azacitidine. This is from a *JCO* paper a number of years ago where we did the first phase 1 trial of this compound that is now in a phase 3 trial, and we see actually that oral azacitidine has activity in patients with lower risk disease with responses actually that are close to 40-50%.



Low-Dose Hypomethylating Agents Are Effective in Patients with Low- or Intermediate-1-Risk Myelodysplastic Syndrome: A Report on Behalf of the MDS Clinical Research Consortium

Short N[1], Garcia-Manero G[1], Montalban Bravo G[1], Sasaki K[1], Sekeres M[2], Komrokji R[3], Steensma D[4], DeZern A[5], Roboz G[6], Kadia T[1], Borthakur G[1], DiNardo C[1], Miller D[1], Estrov Z[1], Pemmaraju N[1], Daver N[1], Verstovsek S[1], Kantarjian H[1], Jabbour E[1]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Cleveland Clinic, Cleveland, OH; [3]Moffitt Cancer Center, Tampa, FL; [4]Dana-Farber Cancer Institute, Boston, MA; [5]Johns Hopkins University, Baltimore, MD; [6]Cornell Medical College, New York, NY

Short N, et al. ASH 2015. Abstract 94.

So, while we hope that at some point we will have a hypomethylating agent in an oral version, at MD Anderson, we have been interested actually on developing lower dosage schedules of either decitabine and/or azacitidine, and an example actually is this paper that we presented at ASH last year where we looked at the results of a randomized trial comparing low-dose decitabine versus azacitidine, and in this part of the presentation because of the design of the study, we were not able to show actually one versus the other, but we could give a composite view of outcomes, and I think actually this data is quite remarkable in lower risk MDS.

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Low-Dose HMAs in LR-MDS: Response

Response	N (%)
CR	33 (36)
mCR	8 (9)
HI	13 (14)
ORR	54 (59)
SD	31 (34)
PD	6 (7)

- Median time to best response: 2 months (range: 1-20)
- Median number of cycles received: 9 (range: 2-32)

Short N, et al. ASH 2015. Abstract 94.

So, we see a complete remission rate close to 40%, overall response rate close to 60% with significant improvement in transfusions in our patients, and this is actually with attenuated doses of decitabine and azacitidine.

Low-Dose HMAs in LR-MDS: Cytogenetic Response (N=38)

Cytogenetic Response	N (%)
CCyR	8 (21)
PCyR	11 (29)
NR	19 (50)

Short N, et al. ASH 2015. Abstract 94.

Importantly, this is associated with a complete cytogenetic response rate over 20%. I do not know if people are aware that these hypomethylating agents actually have this capacity in our patients,

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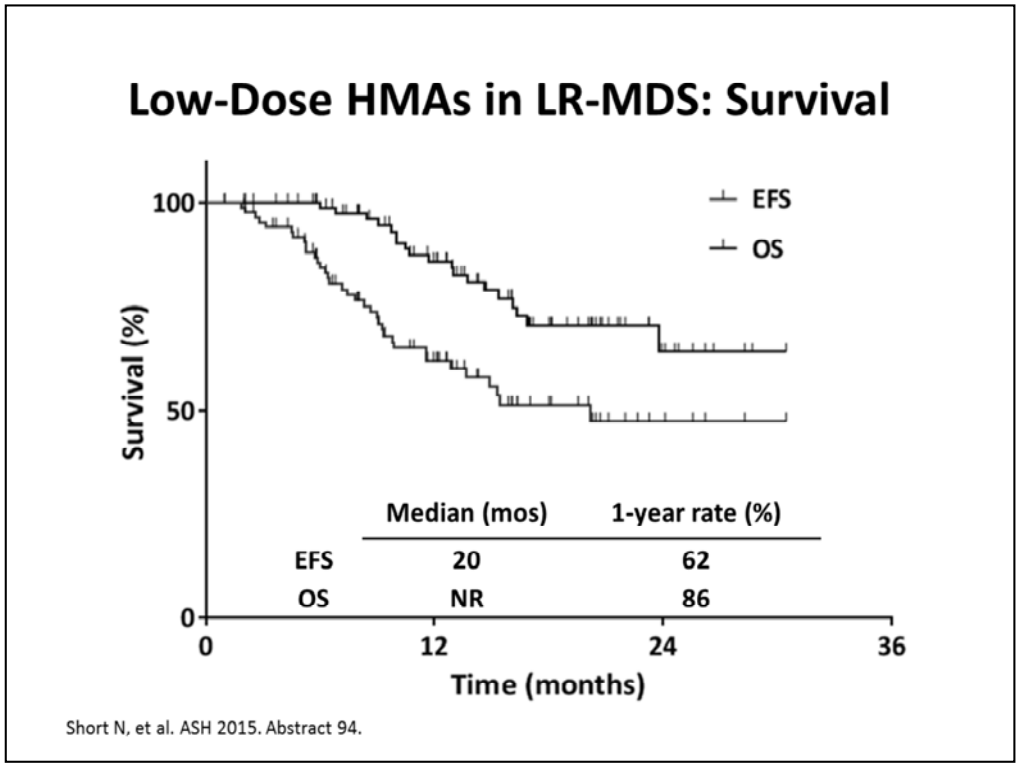
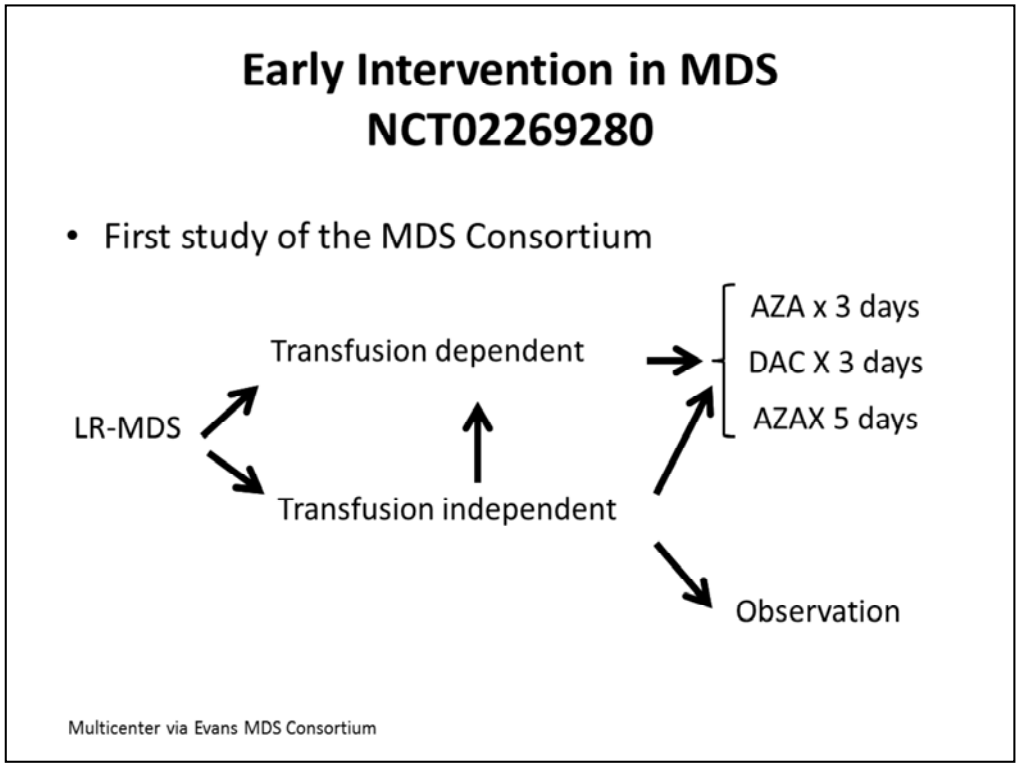
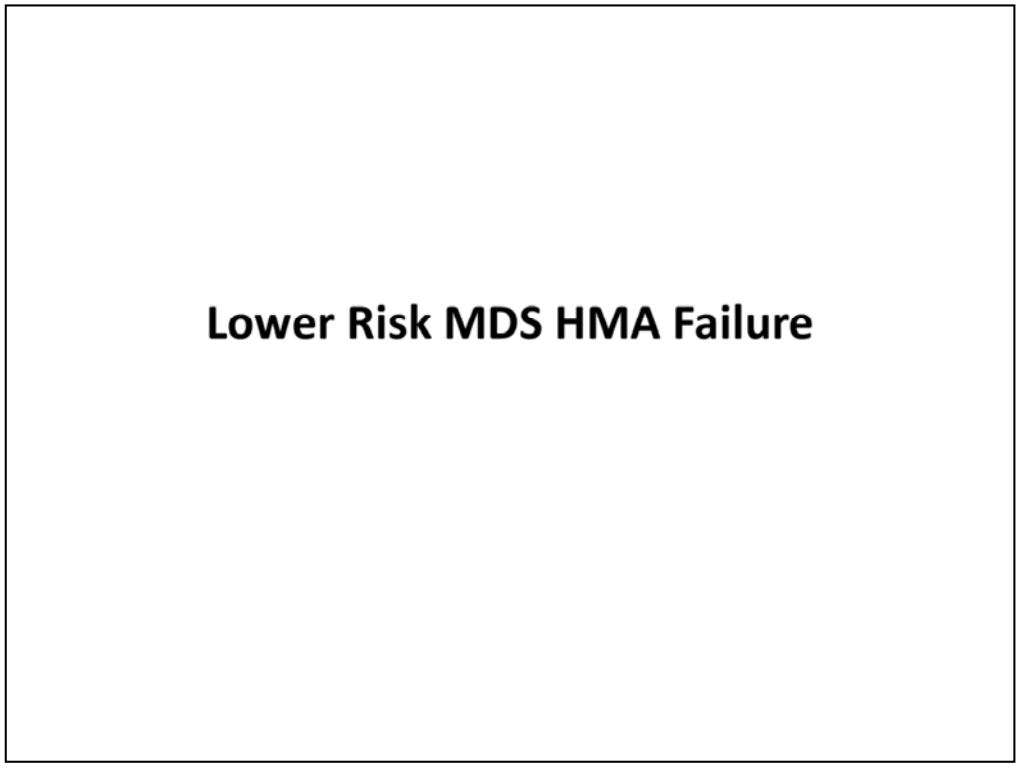


and this actually translates in a group of patients with what we call low-risk and high-risk features that I alluded to in my prior presentation to very acceptable median survivals that are in excess of what we will predict from the MD Anderson data, and you see that in the blue curve in this slide. So, we are now very much considering these as the standard approach for our patients, and what we are talking about, for instance, are doses of decitabine of 20 mg/m^2 daily x3 days, azacitidine 50 to 75 mg/m^2 for 3 days instead of 5- or 7-day type of schedule, and we have very good results with this type of approach.



This actually has led to a clinical trial that is open in North America through the MDS Consortium where we are basically having a strategy of early intervention for our patients and randomize patients between transfusion dependency and transfusion independency, and we randomized them into low-dose azacitidine, low-dose decitabine, standard azacitidine, or observation for those patients that are transfusion independent. The study is ongoing. We have right now close to 100 patients on this trial. This study actually may be a very important one in the next few years to guide us in terms of when and in who and what type of therapy we should use in this group of patients, and I think it is going to lead the way to basically the development of new oral hypomethylating agents that are basically now in phase 1 and phase 2 studies in this disease.



Now, low-risk MDS failure is complicated, and I cannot offer you a lot of drugs outside the context of a clinical trial, but at least, I can tell you first of all what the drug history is.

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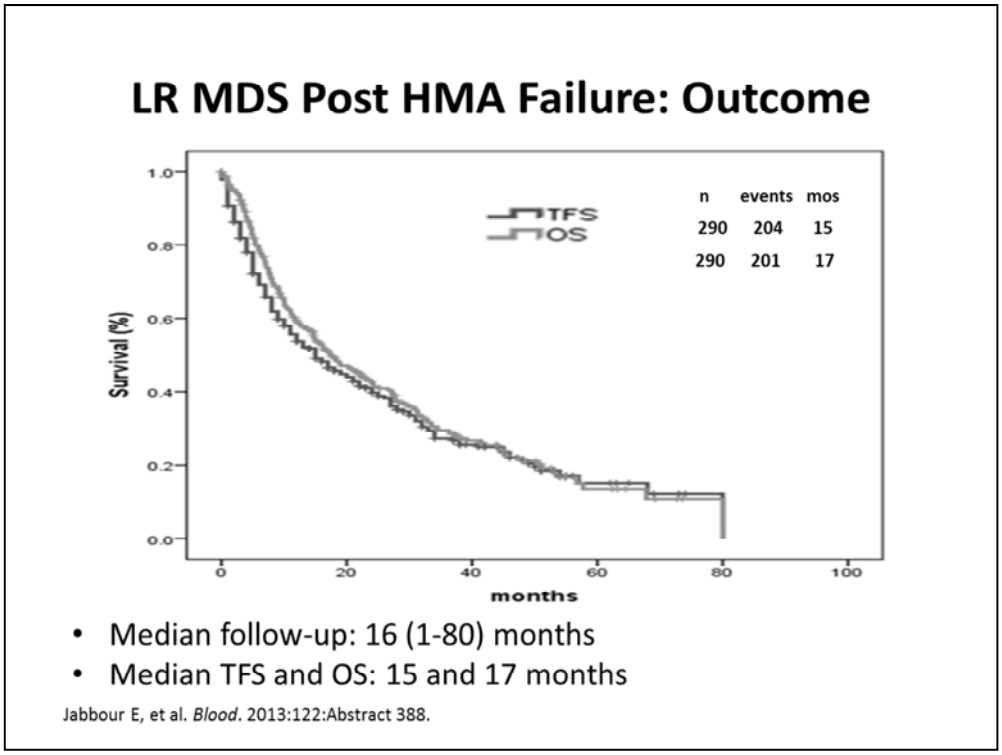


So, here you see the survival of patients with low-risk MDS after HMA failure and it is a survival of around 14 to 17 months. Again, your patients are not going to succumb tomorrow, but they are not going do well for a long period of time, and these today are patients that probably are candidates for investigational clinical trials,

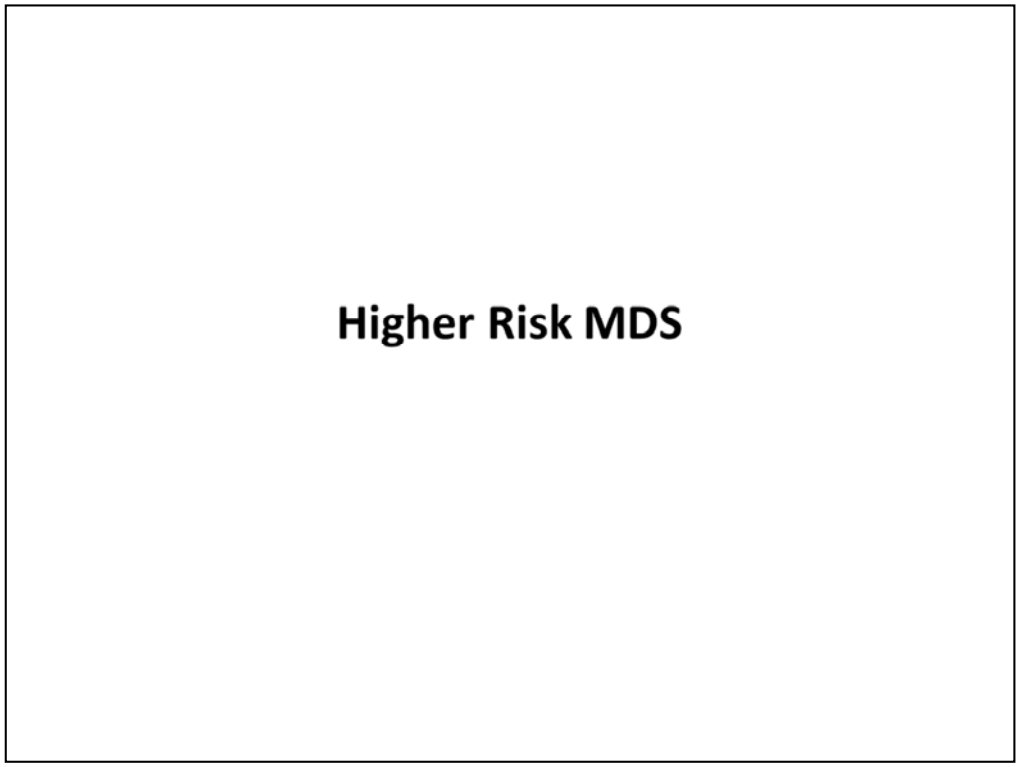
LR MDS Post HMA Failure: Salvage Therapy

Salvage	N (%)	% Response
No therapy	90 (31)	NA
Conventional	83 (29)	18
Stem cell transplantation	26 (9)	62
Investigational	91 (31)	16

- Conventional therapies included cytarabine-based regimen and HMA

Jabbour E, et al. *Blood*. 2013:122:Abstract 388.

but importantly, this is a subset of patients that may be actually a good group to consider for allogeneic stem cell transplant. So, this is data that we presented at ASH and published subsequently, and as you see, actually the group or the therapy that does the best are those that go for stem cell transplant. So, in my opinion, actually this is a subset of patients with low risk HMA failure that do particularly well with stem cell transplantation.



What about high-risk disease?

Hypomethylators vs Intensive Chemo Rx in MDS with 10-30% Blasts

- 330 patients: 93 (28%) Rx with HMA and 237 (72%) with chemo Rx

Parameter	HMA	Intensive Chemo Rx	*P* value
% CR + CRp	42	60	.01
Median Rem. dur. (mos)	14.7	14.7	
% 8-week mortality	10	13	
Median OS (mos)	18.8	14.6	.32

- MVA: worse survival with chemo Rx

Nazha A. *Blood*. 2013;122:Abstract 2788.

Of course, still the standard is the hypomethylating agent. The question is, is it better in some patients to give induction chemotherapy with an acute leukemia type program? This is a presentation a couple of years ago also at ASH where we compared induction versus hypomethylating agents. There is actually no major difference in terms of outcomes, and if anything, there is a trend toward better survival with the hypomethylating agent, of course with less toxicity. So, I think that by and large most of our patients are treated with the lesser intense type of approach. Now, are there differences, is there anyway where I will treat a patient with chemotherapy with MDS or a younger patient with MDS to whom I will not give induction chemotherapy? And the answer is yes. So for instance, if a patient has a very complex karyotype, regardless of the age and let's say a p53 mutation, I would probably not give chemotherapy unless the patient is very proliferative and I need to control the disease very fast. In contrast actually, I may consider induction chemotherapy for a specific group of patients with diploid cytogenetics and some features at the genomic level that may predict for higher response rate with chemotherapy and lately for instance have come across some patients with like 10-15% blasts with an MPN1 mutation that perhaps could do better with chemotherapy, although this has not really been tested in any prospective type of way.

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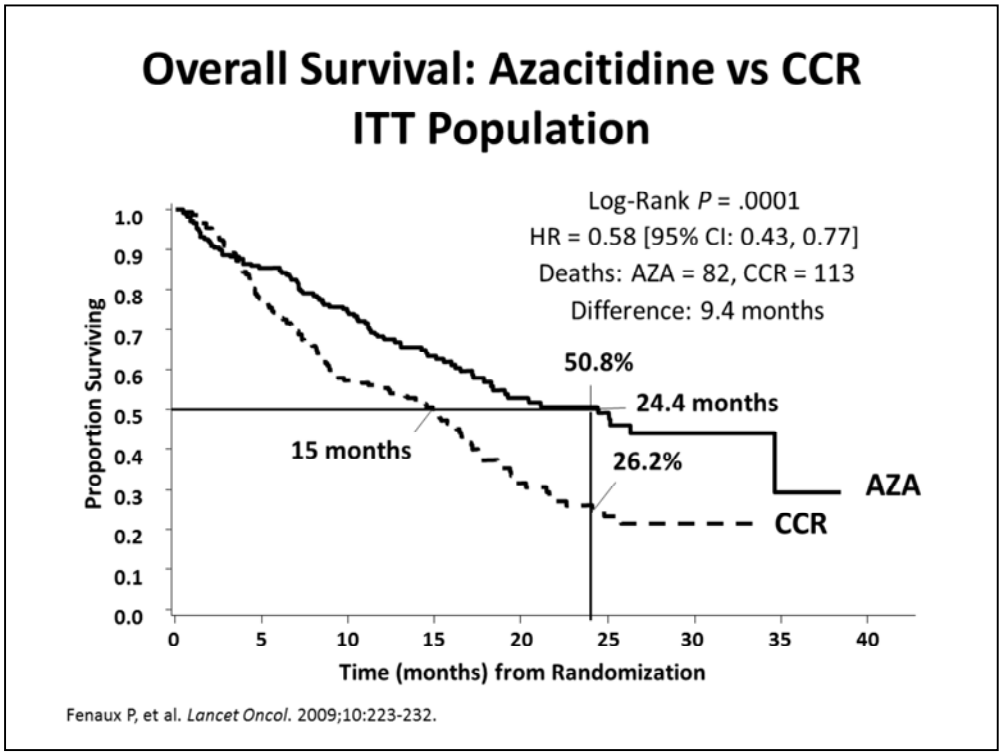

The standard, therefore, today is still hypomethylating agents. This is the data from 2010. This still is the best standard that we have. This is from the randomized trial of azacitidine in high-risk MDS, the very important paper by Pierre Fenaux which clearly shows that azacitidine improves survival of these patients in a very significant fashion, and this has not really changed, and this is again the standard of care for most of our patients in the front-line care.

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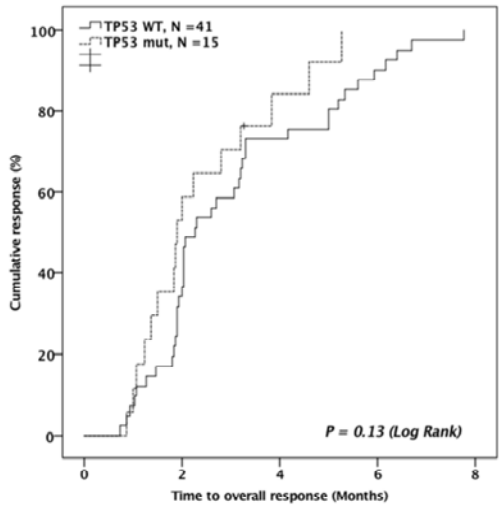
TP53 Mutation Effect on HMA Therapy in MDS



Takahashi K, et al. *Oncotarget*. In Press.; Takahashi K, et al. *Blood*. 2015;126:Abstract 1663.

We have been interested on looking at characteristics associated with outcomes from a paper published recently where for instance we showed that having a p53 mutation does not affect outcome, at least in terms of response with the hypomethylating agent.

TET2 and Response to Azacitidine

	Including SD with HI		Excluding SD with HI	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Mutated TET2	5.92 (1.05–33.33)	0.044	5.92 (1.43–24.39)	0.014
Cytogenetic Risk				
Intermediate	0.24 (0.06–0.98)	0.048	2.41 (0.60–9.71)	0.22
Poor	0.33 (0.11–0.95)	0.040	2.11 (0.68–6.45)	0.19
Previous therapy	1.56 (0.47–5.15)	0.47	0.47 (0.13–1.65)	0.24

Itzykson R, et al. *Leukemia*. 2011;25:1147-1152.

Other investigators, for instance, have claimed that having a mutation on TET2 may be associated with better response to these hypomethylating agents, but the reality is that we do not really have a good biomarker for response to hypomethylating agents, that still makes us basically treat everybody and adapt therapy depending on toxicity and response.

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3-Arm Dosing Study Data
Decitabine Responses By Treatment Arm

Schedule	No. CR/Total
20 mg/m^2 IV × 5 days*	15/32 (47%)
20 mg/m^2 SQ × 5 days	4/14 (28%)
10 mg/m^2 IV × 10 days	4/17 (24%)
Total	23/63 (37%)

*20 mg/m^2 IV × 5 days statistically superior to other 2 arms

Kantarjian H, et al. *Blood*. 2006;109(1):52-57.

Decitabine is another drug that is approved in the United States for MDS, developed here by Dr. Hagop Kantarjian at MD Anderson. We worked quite a bit in terms of different doses and schedules. The standard for us will be decitabine at a dose of 20 mg/m^2 daily to 5 days. Again, this drug has taken perhaps a little bit of second place compared to azacitidine because it was never shown to improve survival in randomized clinical trials, although there are probably multiple explanations of why that happened and it is a drug that we commonly use in our group.

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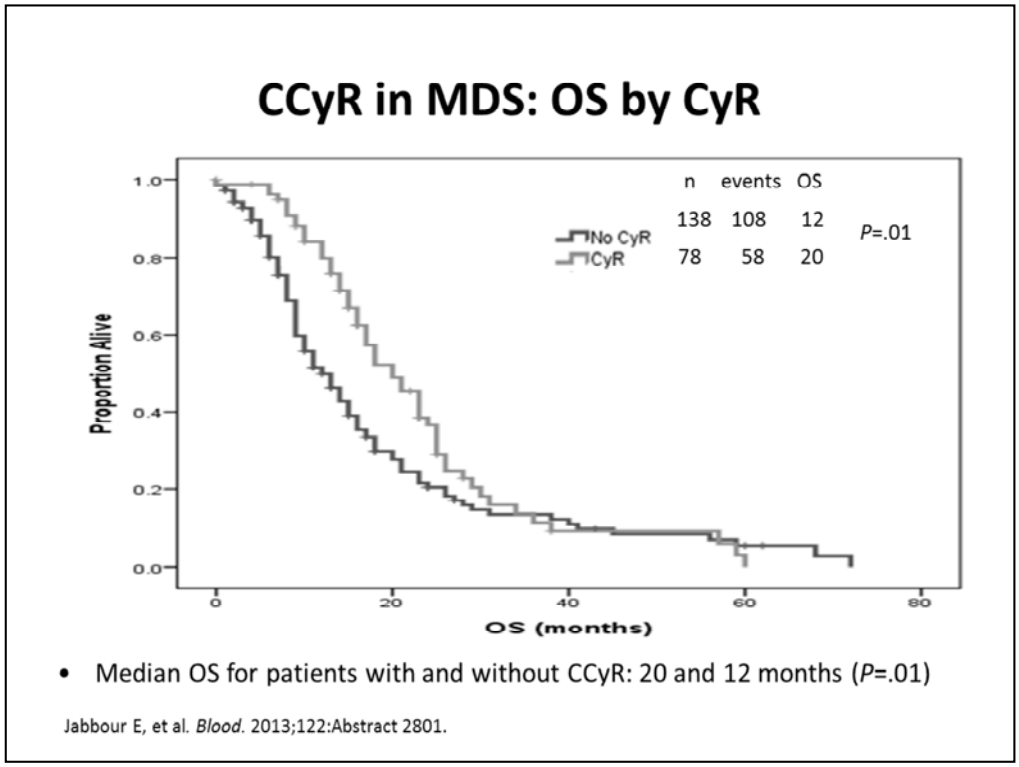
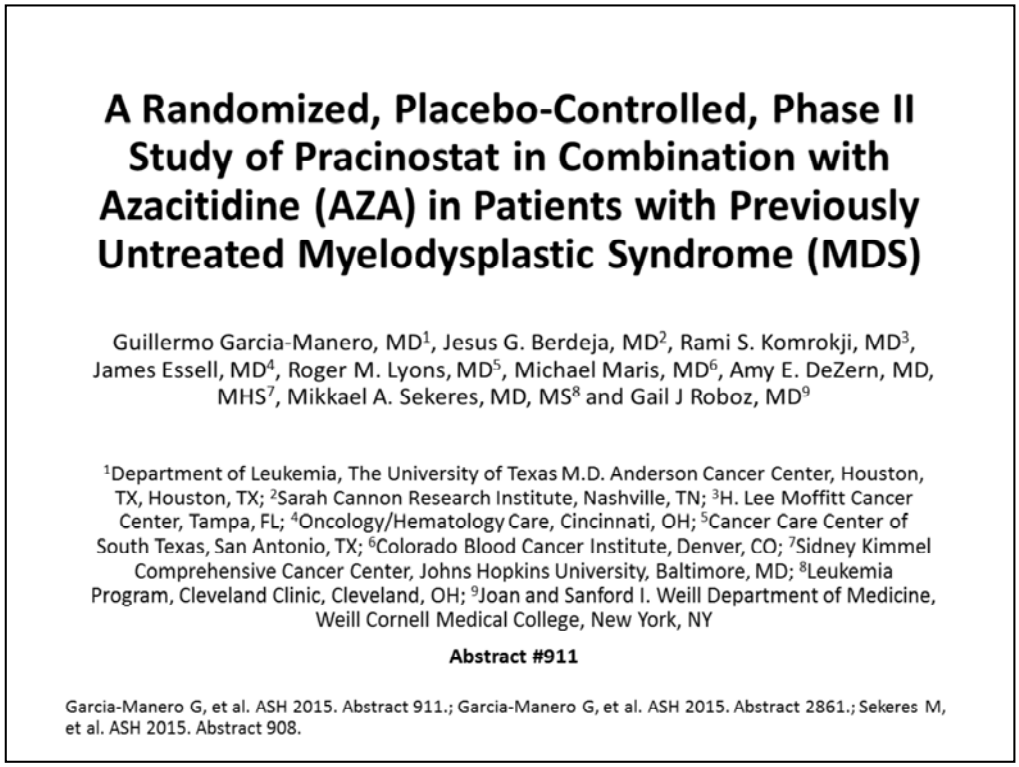


Now, what is interesting about this hypomethylating agent is that some people at least when I talk have a view of these are more like palliative type of approaches, but actually these drugs if used with some expertise are quite powerful. Here, I show you data where we again show the complete cytogenetic response rate of close to 20%. The French group at ASH a couple of years had the same data. So, you have a group of patients that may benefit from this type of strategies, and again, you have a group of patients, maybe 10-15% of them, that may be long-term survivors with the hypomethylating agent if you are able to use these drugs chronically. That is very important, basically, this concept of do not stop this compound because then the disease will become HMA failure and you will have a hard time basically treating those patients.



A Randomized, Placebo-Controlled, Phase II Study of Pracinostat in Combination with Azacitidine (AZA) in Patients with Previously Untreated Myelodysplastic Syndrome (MDS)

Guillermo Garcia-Manero, MD[1], Jesus G. Berdeja, MD[2], Rami S. Komrokji, MD[3], James Essell, MD[4], Roger M. Lyons, MD[5], Michael Maris, MD[6], Amy E. DeZern, MD, MHS[7], Mikkael A. Sekeres, MD, MS[8] and Gail J Roboz, MD[9]

[1]Department of Leukemia, The University of Texas M.D. Anderson Cancer Center, Houston, TX, Houston, TX; [2]Sarah Cannon Research Institute, Nashville, TN; [3]H. Lee Moffitt Cancer Center, Tampa, FL; [4]Oncology/Hematology Care, Cincinnati, OH; [5]Cancer Care Center of South Texas, San Antonio, TX; [6]Colorado Blood Cancer Institute, Denver, CO; [7]Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD; [8]Leukemia Program, Cleveland Clinic, Cleveland, OH; [9]Joan and Sanford I. Weill Department of Medicine, Weill Cornell Medical College, New York, NY

Abstract #911

Garcia-Manero G, et al. ASH 2015. Abstract 911.; Garcia-Manero G, et al. ASH 2015. Abstract 2861.; Sekeres M, et al. ASH 2015. Abstract 908.

We have worked quite a bit with doublets, for instance AZA and lenalidomide, and AZA and HDAC inhibitors. I am not sure what is going to happen with HDAC inhibitors. This is a presentation that I had at ASH this past year with the third-generation HDAC inhibitor called pracinostat, very active combination in acute myelogenous leukemia, but in this randomized trial in myelodysplastic syndrome.

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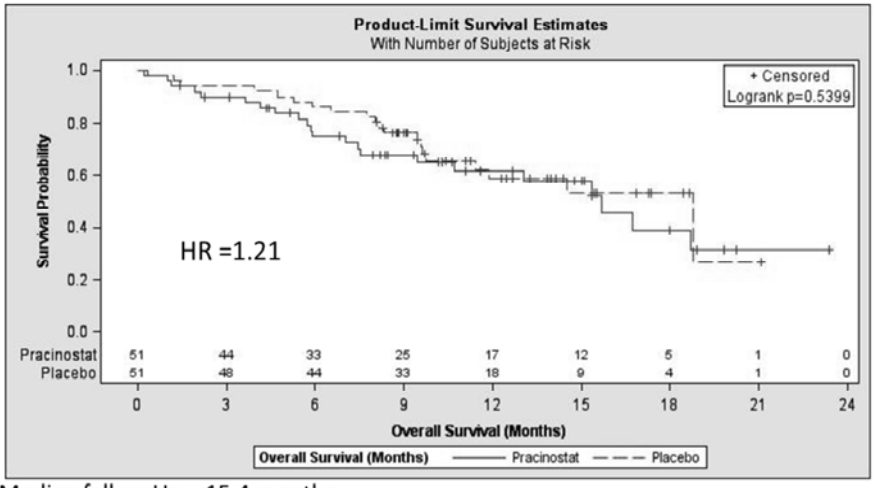
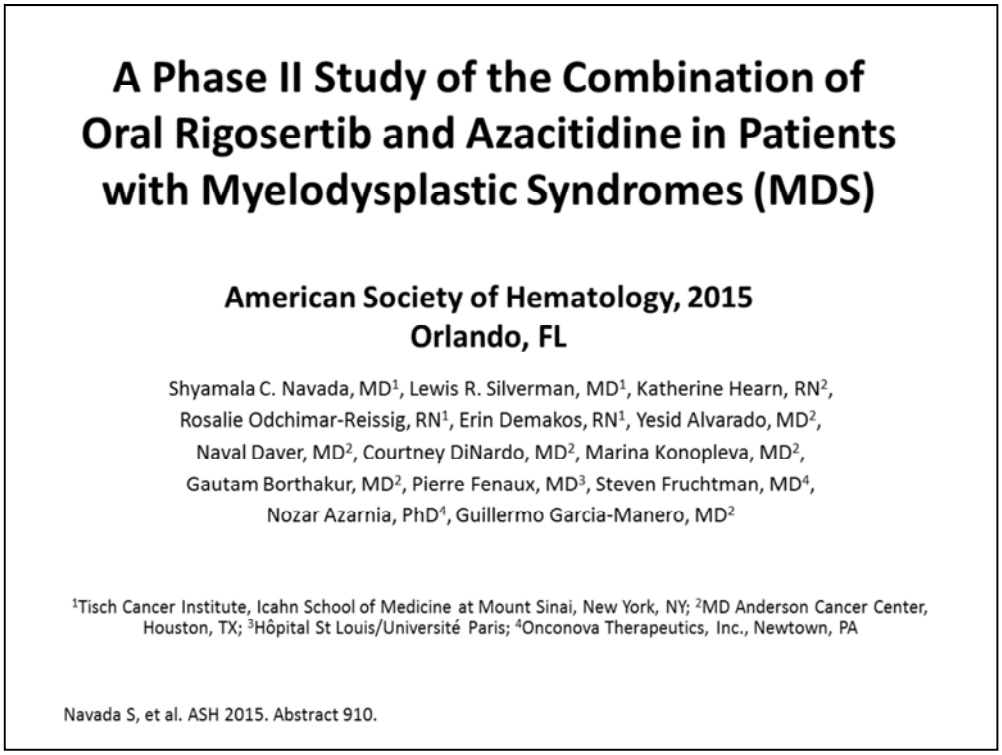
Aza + Pracinostat in MDS: Overall Survival



Median follow Up = 15.4 months
One-year survival: Pracinostat = 57.1%
Placebo = 57.4%

Garcia-Manero G, et al. ASH 2015. Abstract 911.; Garcia-Manero G, et al. ASH 2015. Abstract 2861.; Sekeres M, et al. ASH 2015. Abstract 908.

Basically, we were not able to show a survival difference in this group of patients and actually very good outcomes, again with single-agent azacitidine in the community, suggesting that we are overall now getting very experienced and actually very good at using this type of hypomethylating agents in our practices.



A Phase II Study of the Combination of Oral Rigosertib and Azacitidine in Patients with Myelodysplastic Syndromes (MDS)

American Society of Hematology, 2015
Orlando, FL

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Navada S, et al. ASH 2015. Abstract 910.

There is another doublet combining, for instance, oral rigosertib with azacitidine. This was presented again at ASH this year.

The Changing Face of MDS: Advances in Treatment

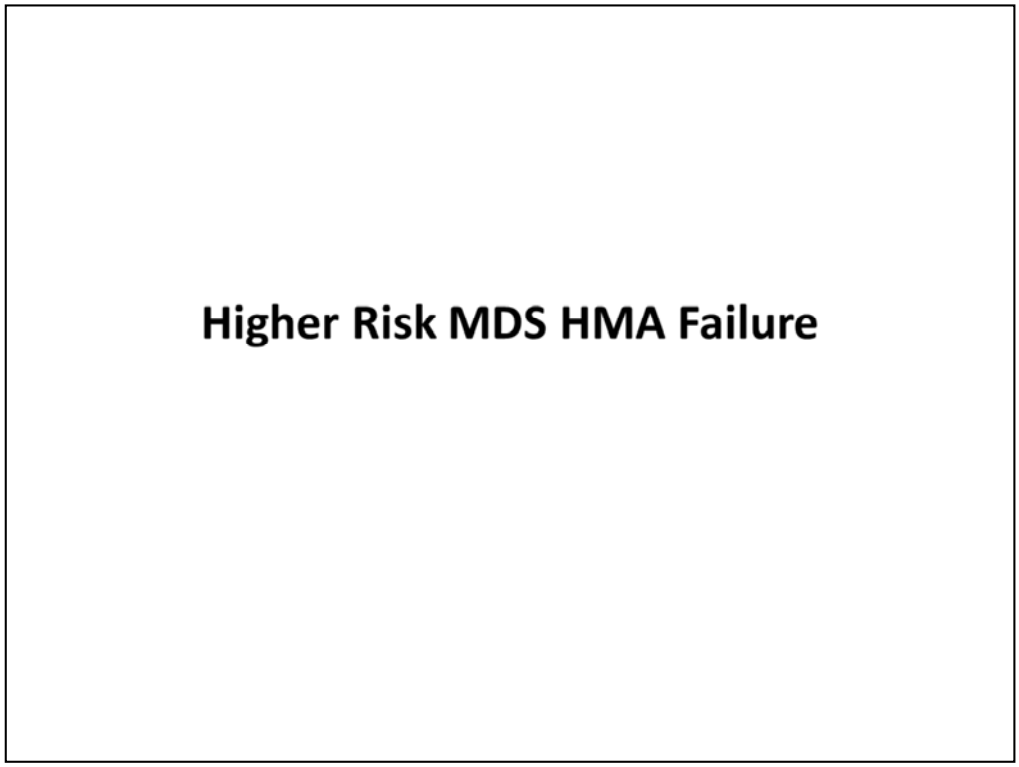
Efficacy Results

Number of MDS patients treated		37
Evaluable for response (8 Ph1, 22 Ph2)		30
Overall response		23 (77%)
Hematologic response*	Complete remission	6 (20%)
	Partial remission	0
	Marrow CR	16 (53%)
	Stable disease	6 (20%)
	Progressive disease	1 (3%)
Hematologic improvement*		1 (3%)
Not evaluable		3 (10%)
Too early to evaluate		4 (13%)
Median duration of treatment (months)		4 (1-27+)

* Per IWG 2006

Navada S, et al. ASH 2015. Abstract 910.

The data shows a very high response rate, although oral rigosertib is a drug that is still in development. We are going to need a little bit more information in terms of how one will design a phase 2 or phase 3 trial with this group of patients.



So, because we have now such a great expertise in using hypomethylating agents, and we are really learning in terms of the chronic use and not to stop therapies, that relates that this group of patients with higher risk MDS is becoming one of our major subset of patients, at least in referral centers.

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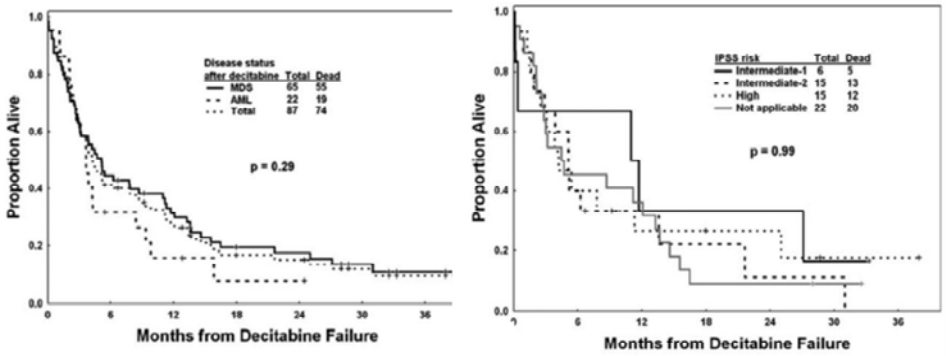
MDS After Hypomethylating Agent-based Therapy: Urgent Need to Develop Novel Combination Approaches



Jabbour E, et al. *Cancer.* 2010;116(16):3830-3834.

This is very important because the prognosis of patients with higher risk MDS after HMA failure is poor. This is shown from this work by Elias Jabbour a number of years ago where we clearly showed that the survival is around 4 to 6 months. And again, these are patients that do not respond to another hypomethylating agent. They do not do well with induction chemotherapy. So, these are a particular difficult groups of patients with this disease and a very active area of research.

So, we conducted a phase 3 trial. It was published in *Lancet Oncology* a couple of months ago with intravenous rigosertib against the best supportive care, and this was actually the first phase 3 trial for patients with HMA failure.

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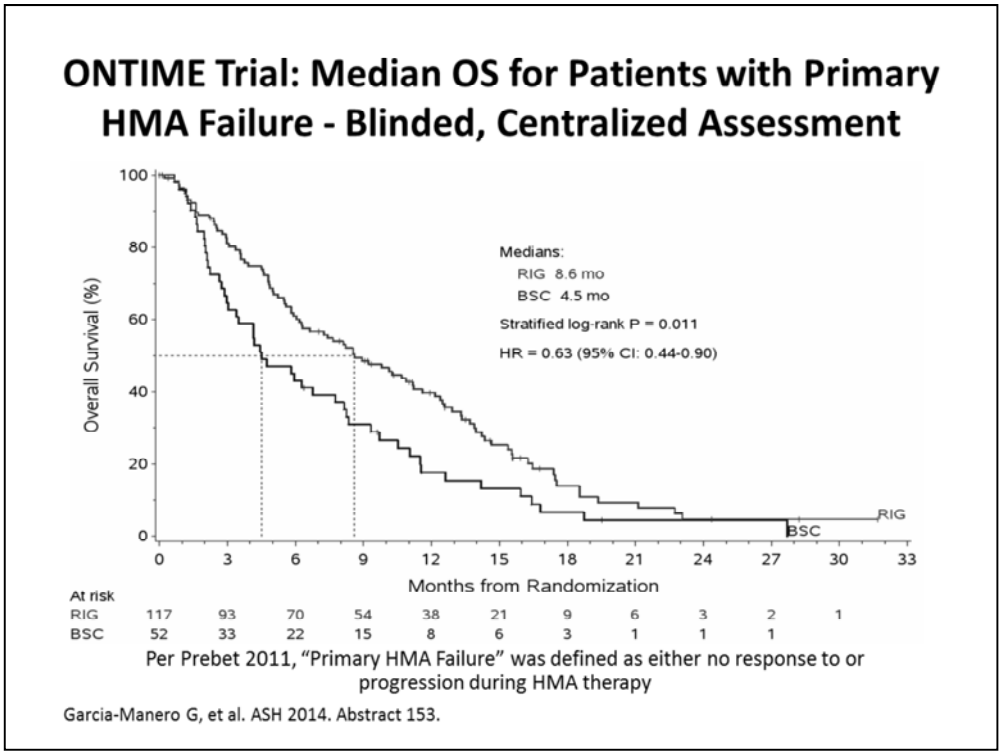

We were not able to basically beat the expected threshold in terms of survival that we had planned on the original trial, but actually we saw that rigosertib with minimal toxicity was associated with a trend toward better survival in a subset of patients with MDS high-risk failure. And you see that, for instance, survival of 8.6 months versus 4.5 months in this group of patients, particularly in what we call primary failure. So, these are patients that have not responded to the hypomethylating agent. So again in the global picture with MDS, we were not able to show the benefit, but when we looked at the specific subsets, those with primary failure disease actually benefited in terms of survival with rigosertib.

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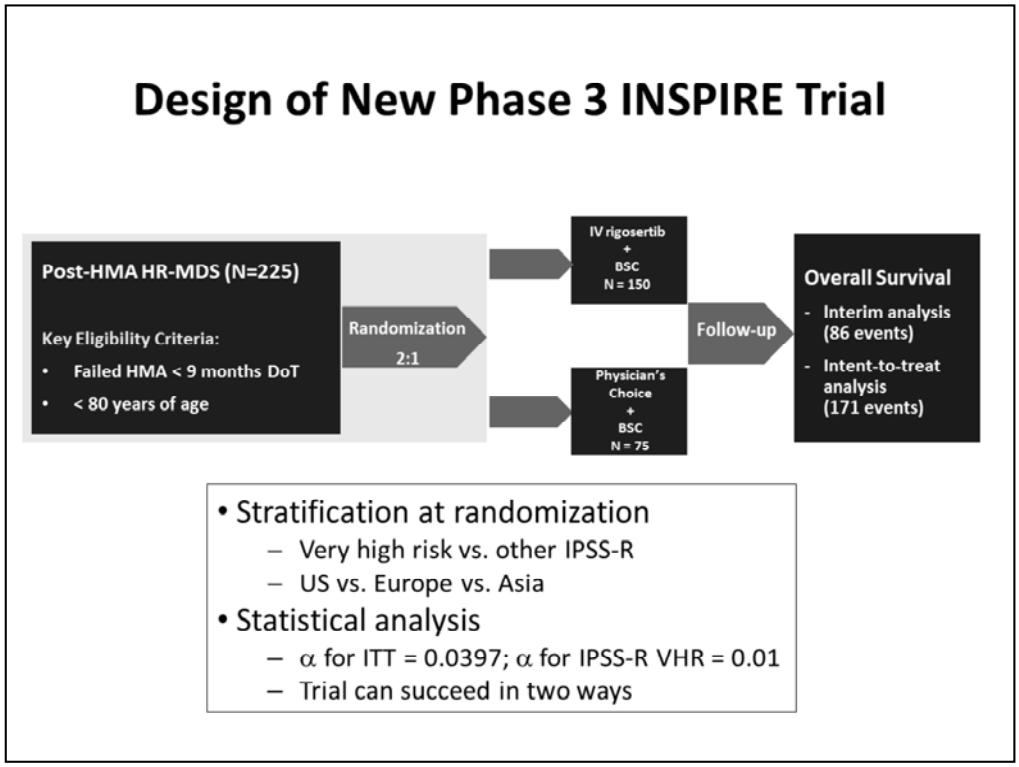
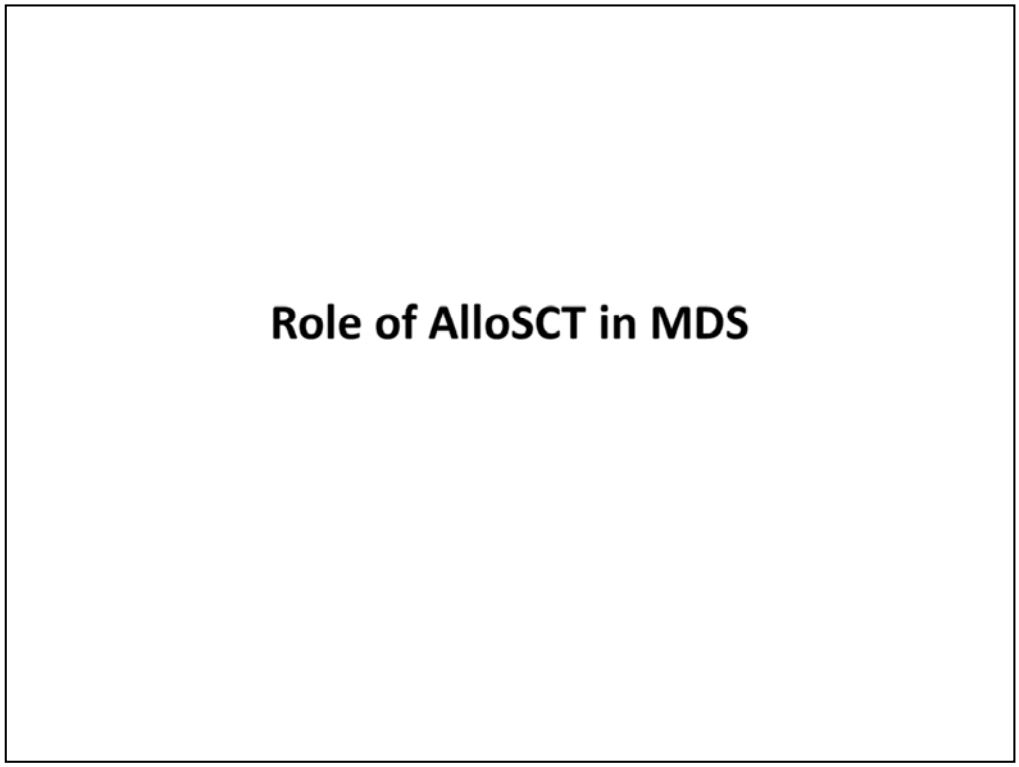


This has led to a second phase 3 trial of this compound. It is called INSPIRE, and here, we are targeting basically this group of patients with primary failure that are the ones who benefited the most. The study actually is already open worldwide. There are around 10 to 15 patients already in the study, and hopefully this could be one of the new leads in this disease.

CLO and LDAC in HR MDS Post HMA: Response (N=61)

Best Response	N (%); Median [range]
Complete response	10 (15)
Marrow CR	9 (14)
CRp	3 (5)
Partial response	1 (2)
Hematologic improvement	4 (6)
Overall response rate	27 (44)
# Cycles to best response	1 [1-7]
Early death	1 (2)

Now, once in a while, one is in a situation where you do not have genomic information or clinical trial, and the question is, is there something that I could do off protocol? We actually have quite significant expertise using very low doses of clofarabine with low-dose AraC, particularly in patients with a diploid cytogenetic. So, this is from a presentation at ASH this past year where we see actually an overall response rate of around 40-50% and survival rates that are higher than expected in this group of patients, but again, this drug is not approved for myelodysplastic syndrome. You may use this as a compassionate use in this group of patients with hypomethylating agent, high-risk failure, if they are diploid.



Then to conclude the talk, I would like to talk a couple of minutes in terms of the role of allogeneic stem cell transplant. This is a little bit controversial. I think this is also based on the expertise of each local center. I think that the data from these two slides I am going to show that were published by the IBMTR eventually in the *JCO* really clarify what is my current position in terms of transplant in this group of patients.

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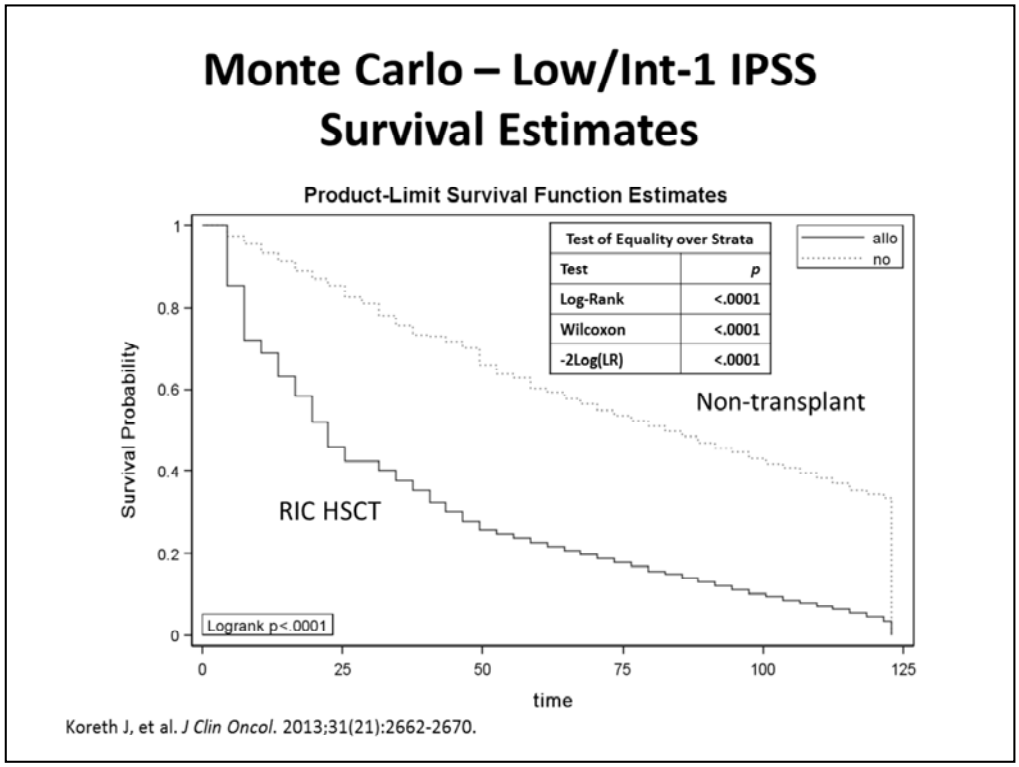

So, in lower risk disease by IPSS, meaning low or intermediate 1, if you look at this graph, the survival is inferior to the group of patients transplanted upfront. Now, early on, I said that there is a group of patients with low-risk disease that do well with transplant if they are HMA failures, but based on these data, I do not see any reason to transplant anybody regardless of age early on in the course of the disease.

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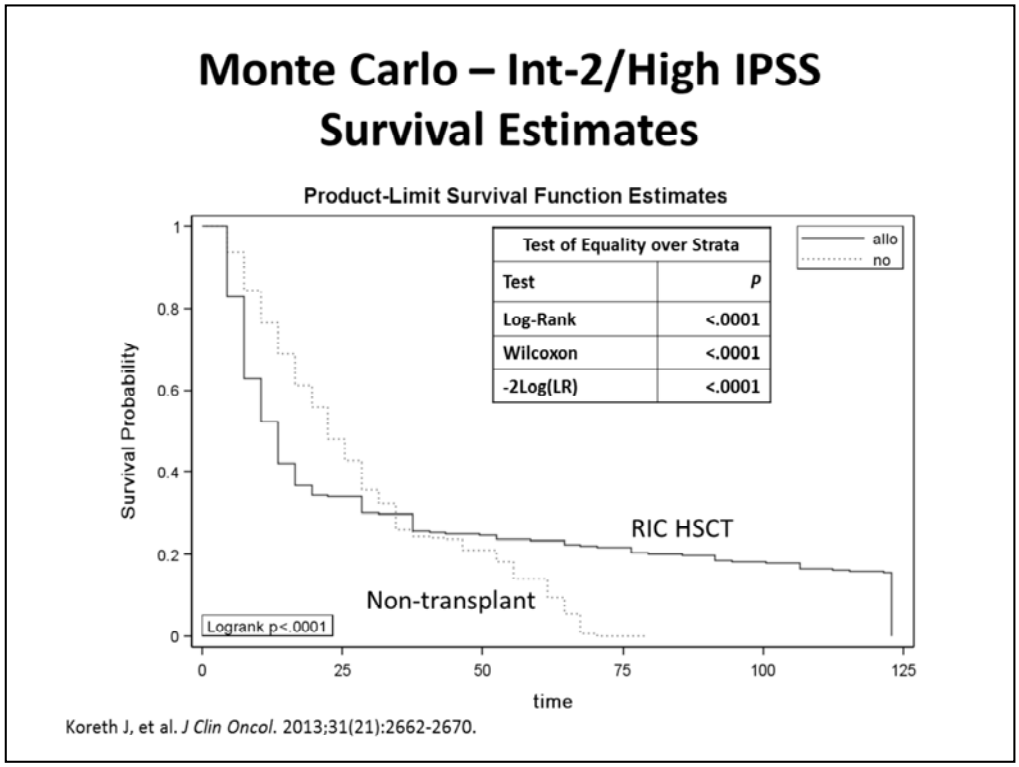

The second is actually the role of transplant in high-risk patients, and here, the conclusion is that transplant improves survival of these patients, although I am not sure it is curative. You basically have long-term outcomes in around one-third of these patients or a little bit less, but if you look at this graph, you see that the hypomethylating agent crosses the transplant basically past 25 months. So, you are looking at a group of patients with very stable disease that apparently can be cured with transplantation, but I do not think that they represent the bulk of patients with MDS, and one of the things that I will be interested in will be in actually understanding who are these patients that are cured with this disease because then we could basically omit this very aggressive type of approach for patients that may have early complication from the trial.

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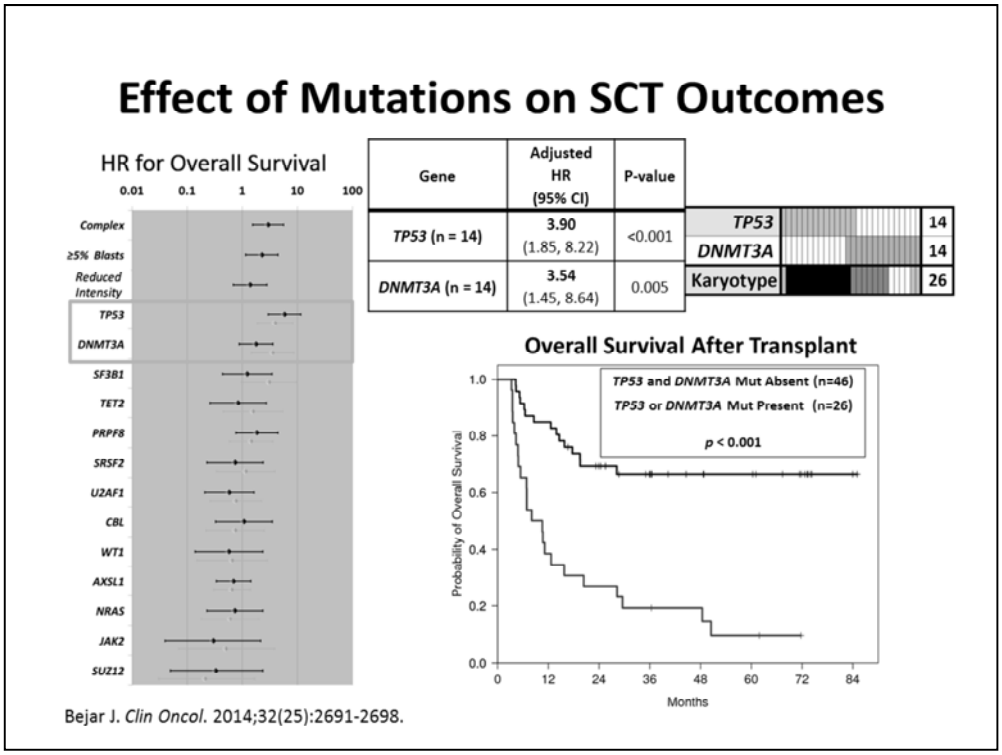

What is interesting actually is that the genomic data has helped us more actually in understanding who are these patients that benefit or not from the transplant, and this is a very important paper by Dr. Bejar in *JCO* where they showed, for instance, that if you have a mutation on p53 and/or DNMT3A, your patient is not going to do well with transplant. Now, I am not saying that you should not transplant these patients. What we are saying actually is that the outcome is going to be worse, and therefore anticipate and perhaps come with a strategy for this group of patients.

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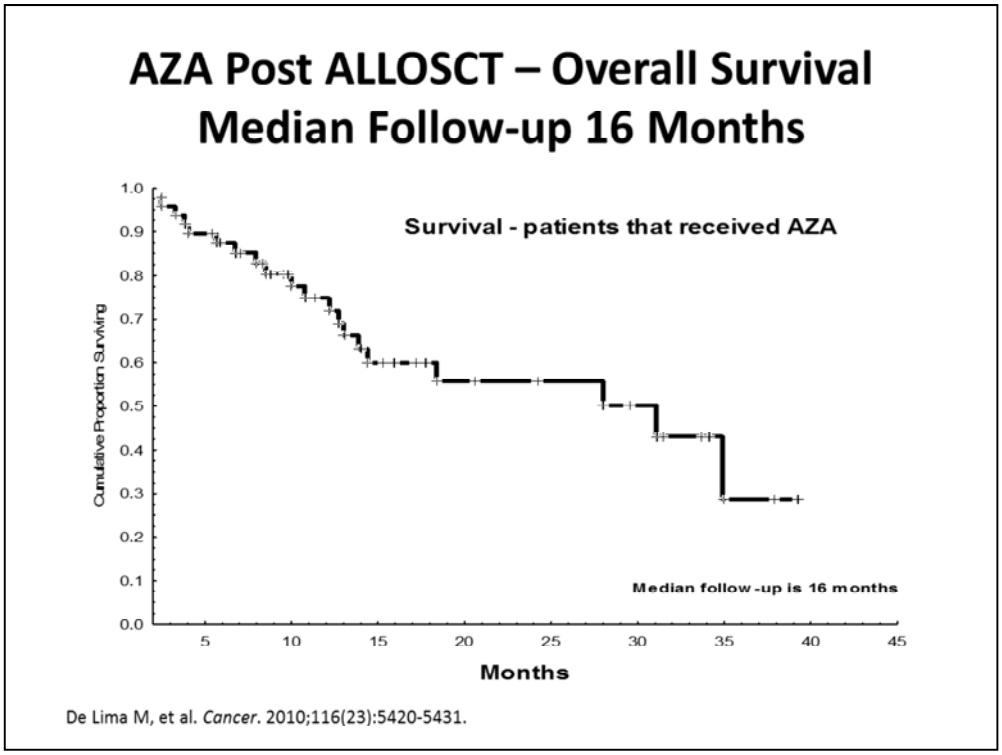
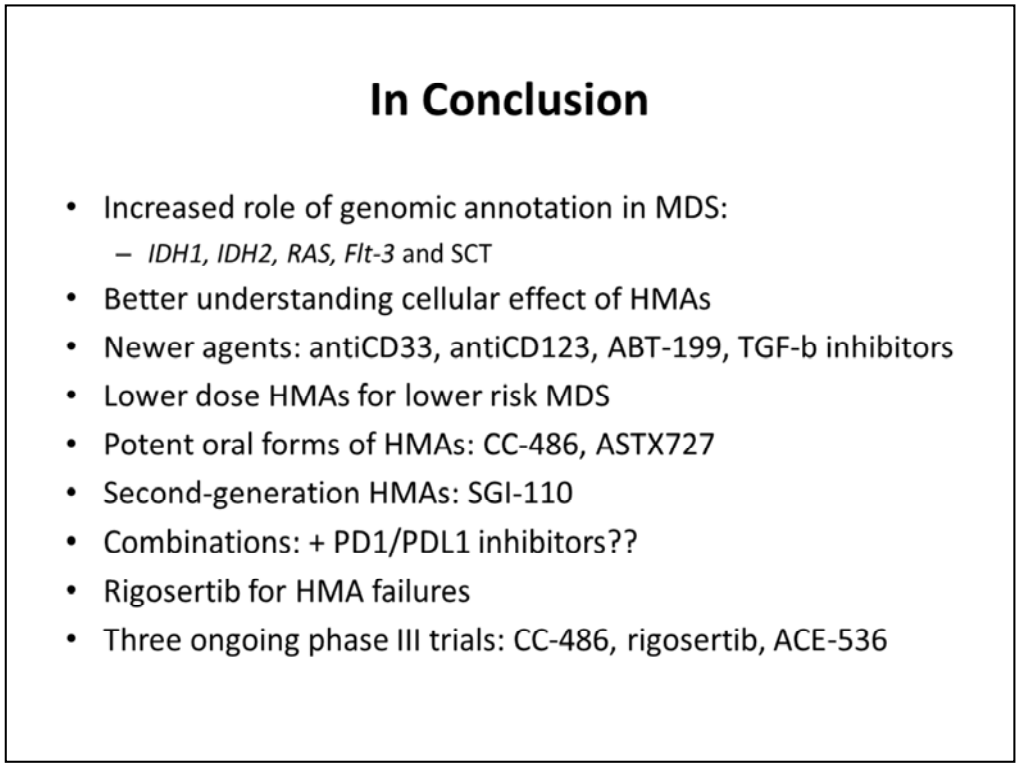


One of the strategies in a way probably similar to what the myeloma doctors do in their total therapy type of approach is the use of maintenance therapy with hypomethylating agents after transplant. This is an old paper now by Marcos de Lima when he was here at Anderson where we gave low doses of azacitidine in the posttransplant setting with actually improved outcomes. And there is now a number of clinical trials that are following this lead, randomizes to therapy and no therapy in this context, and I think this is going to be actually a very important tool, and it is actually becoming now a standard of care for our patients, particularly if they have high-risk features after their transplantation.



Now to conclude, I want to tell you a little bit of what I said in these two talks. First is to emphasize that there is actually an increased role for genomic annotation in MDS. Genes that are important are IDH1, IDH2, RAS, FIT3, and for sure p53, ECH2, and the role of this information in transplantation that I just mentioned a minute ago. I think that, and I did not discuss this in the talk, but there is quite a bit of data helping us understand better the role of hypomethylating agents at the cellular level, not just molecularly. There is a number of new compounds that are coming, drugs that block anti-CD33, CD123, very exciting data with venetoclax or ABT-199, recently approved in chronic lymphocytic leukemia, new TGF-beta modulators like ACE-536, ACE-11 that are going to be very important in lower risk disease. We discussed quite a bit the role of lower doses of hypomethylating agents in lower risk MDS. These are standard in my group. There are a number of potent oral inhibitors like CC-486, this is oral azacitidine, and ASTX727, this is an oral form of decitabine. I think these drugs are going to have an important role in MDS. There are second-generation hypomethylating agents coming like SGI-110, this is actually in a major phase 3 trial in AML and soon in MDS, and there is quite a bit of data actually linking checkpoint inhibitors with hypomethylating agents. So, there are many clinical trials looking at combinations with PD-1 and PD-L1 inhibitors. We discussed the data with rigosertib, and I want to bring to your attention that at least right now we have three ongoing phase 3 trials worldwide like oral azacitidine, rigosertib, and ACE-536 for refractory anemia with ring sideroblasts. So, I think in the next 2 or 3 years we are going to probably have many more phase 2/phase 3 trials that are going to lead to the approval of new drugs that together with developments in AML at the level of genomic annotation and targeted therapy are really going to transform how we take care of our patients and of course better use of stem cell transplantation and better stratification of our patients. And with that, I would like to basically conclude and thank you for this opportunity. Thank you very much.