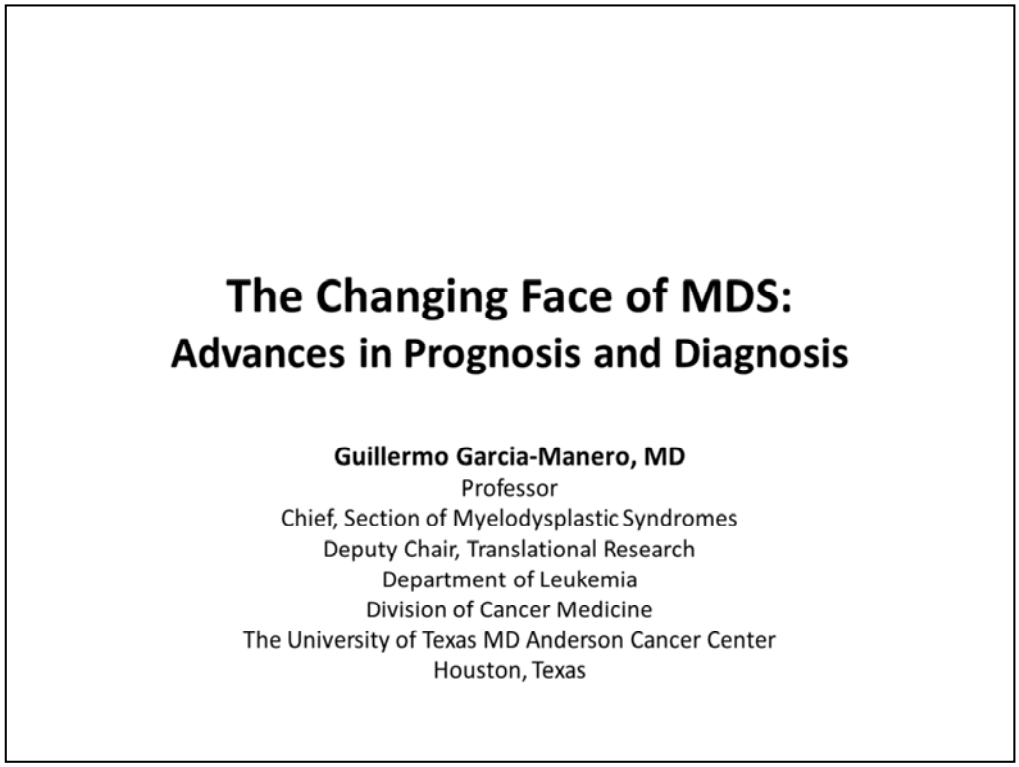
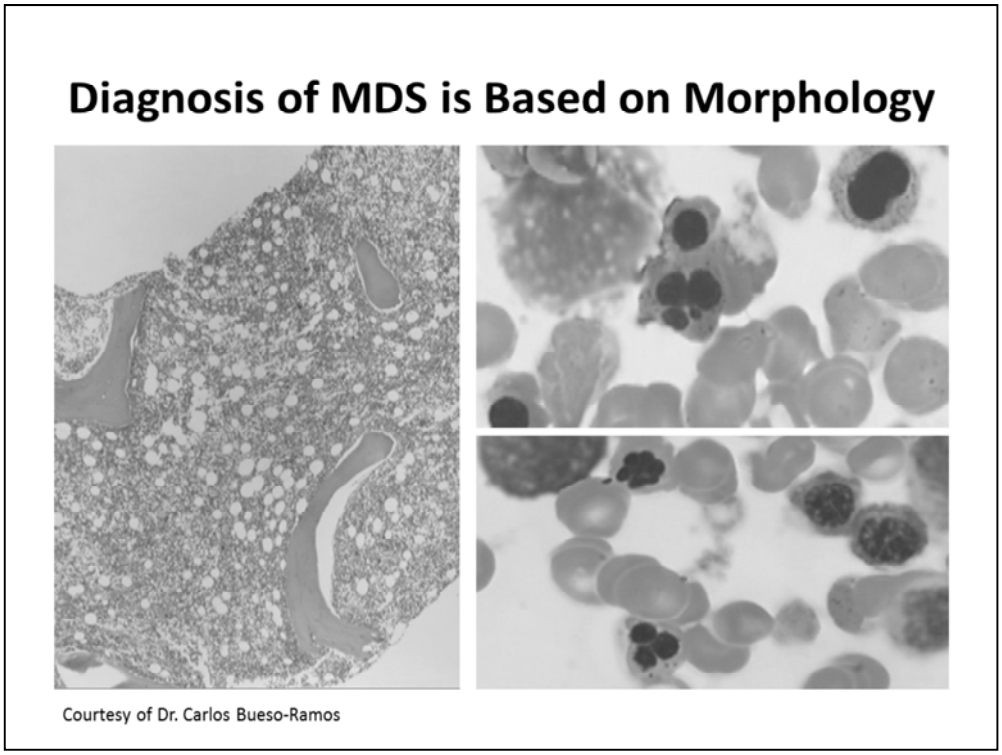
The Changing Face of MDS: Advances in Prognosis and Diagnosis



Hello, my name is Guillermo Garcia-Manero. I am a Professor of Medicine in the Department of Leukemia at the University of Texas MD Anderson Cancer Center in Houston where I am the Head of the Section of Myelodysplastic Syndrome and Deputy Chair for Translational Research. I am happy to be talking to you today about both new aspects of diagnosis and prognosis of this group of disorders that we call myelodysplastic syndromes.

In this presentation, I will outline challenges associated with the diagnosis of MDS, as well as explain the utility of prognostic models and ongoing research into the clinical significance of cytogenetic abnormalities in this group of disorders.



The first thing, and probably one of the most important messages, is that today still, the diagnosis of MDS is based on morphology. So, there is no adjunct test, let's say molecular test or flow cytometry test, that will really make the diagnosis. So today, we still depend on the expert opinion of our morphologists and hematopathologists that can really confirm the diagnosis. So, in this slide, courtesy of Dr. Bueso-Ramos from MD Anderson, you see the characteristic morphological features of patients with MDS. On the left, you see a hypercellular bone marrow. On the right, you see two panels with very dysplastic, in this case, red cells and micromegakaryocytes. Now, this is an obvious case that most pathologists would have no problems in diagnosing, but one of the main issues actually is the morphological diagnosis and some of the subjective aspects that go around this process.

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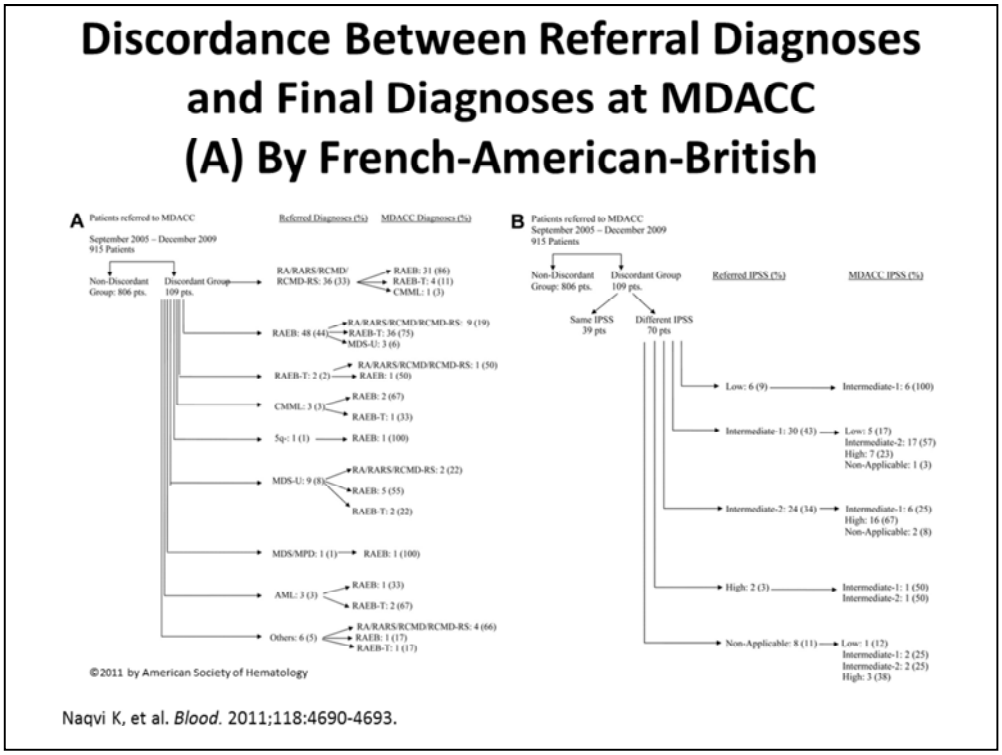
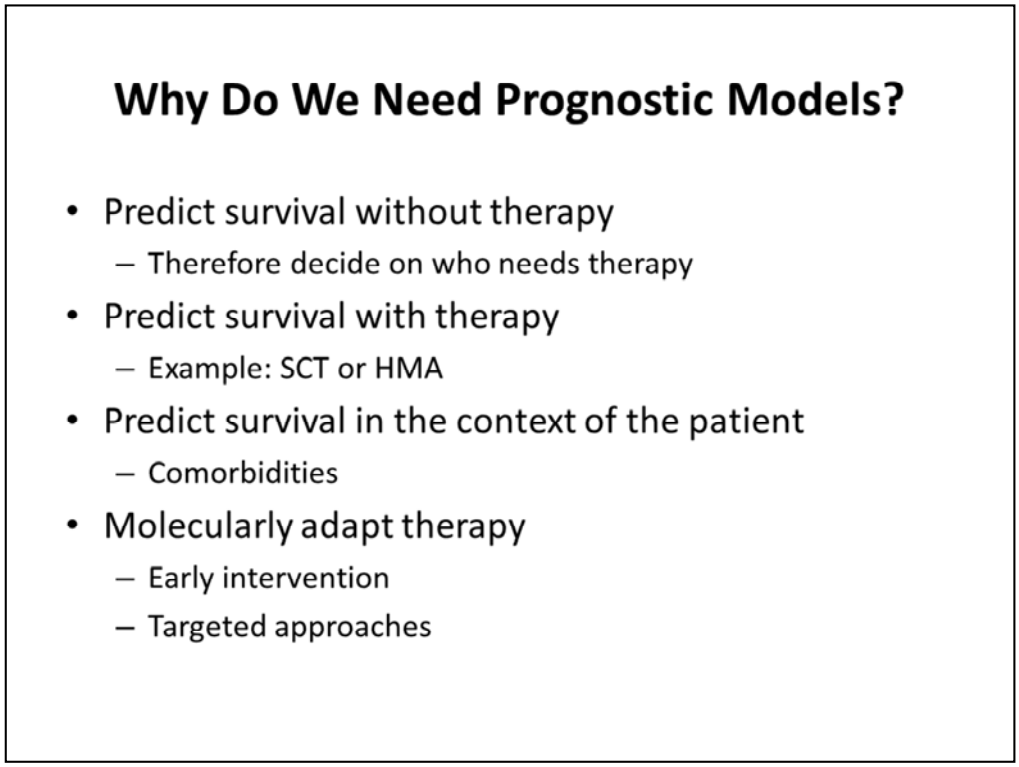
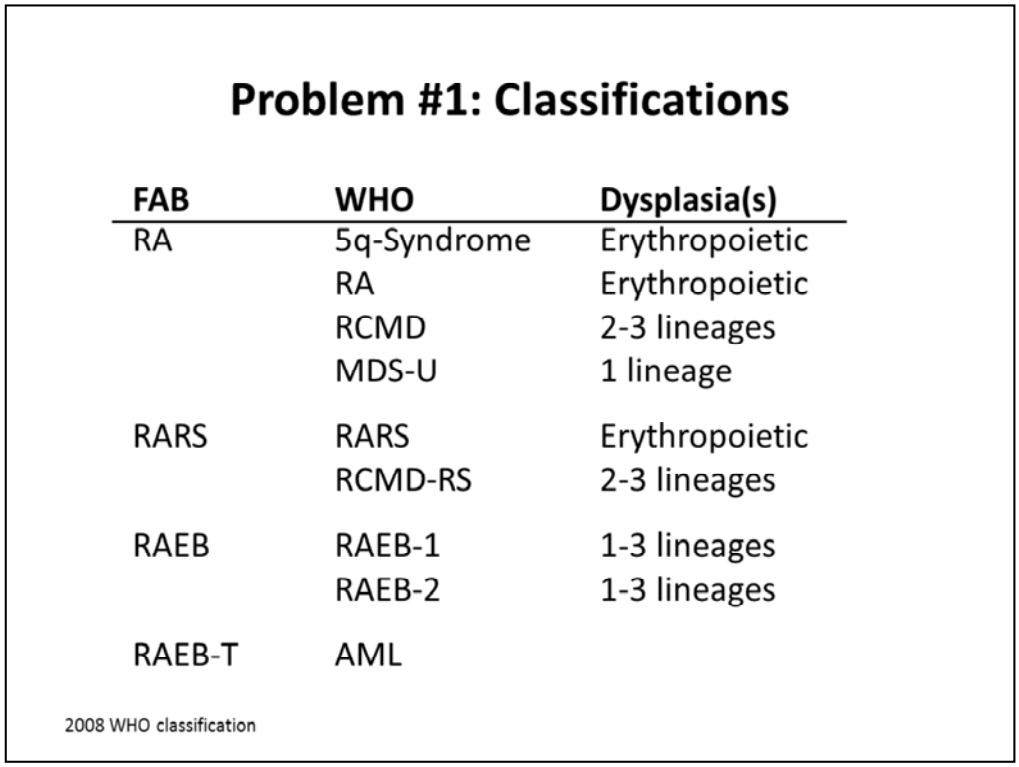


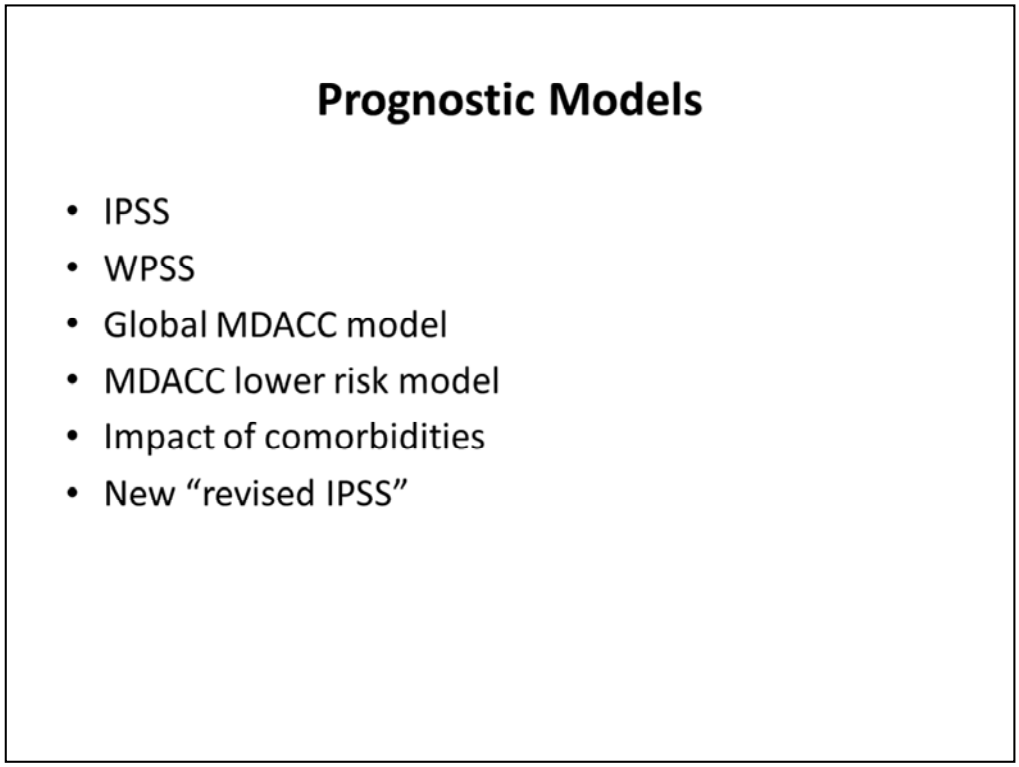
This is quite important because if you go to the next slide, in a paper that we published now 3 or 4 years ago in *Blood* with detailed analysis where we correlated the inside diagnosis with the outside material that we had acquired in close to 900 patients evaluated at MD Anderson. So, when a patient is referred to our institution, we tend to ask the patients or the referring physicians to send us the original slides, not just the paper reports. So, this project came because I actually had the idea that perhaps we could omit the bone marrow that we perform here at MD Anderson that is obviously painful, expensive, and so forth, and it may actually delay a little bit the time that I need to make a decision or intervention. But actually what we found in this paper, and I do not think you can read that in the slide, but the structure of this analysis is that we could actually find a discrepancy in the diagnosis between MD Anderson and outside in almost 15-20% of the patients. The paper actually rated this a little bit lower because the reviewers of the paper had various strict criteria in that regard, but I can tell you that on a practical basis, probably in close to 15-20% of these patients that are referred to us, there is an issue with the diagnosis. This is not to say that the MD Anderson pathologist is better than the pathologist outside. It is to say basically that perhaps from the time these patients are diagnosed to the time they are referred, etc., something happens to them that results in changes in their morphology and final diagnosis, but this is crucial. Imagine actually that all of a sudden you said that in 20% of cases with breast cancer there was a discrepancy, this will be a big news in every newspaper. The corollary of this for you is that when you have a patient that is referred to you, even if they have had a bone marrow performed at MD Anderson, or whatever best referring center in your community, you may want to make sure actually that you have proper morphological diagnosis because you are going to be making your decision based on this data. So, I think this is very important and actually perhaps one of the most difficult aspects of treating these patients, where you need to have access to an expert hematopathologist that has expertise in myelodysplastic syndrome and can help you actually with a final diagnosis. So, this is a very important aspect of the care of our patients.



Once you have morphological assessment, then you need to prognosticate your patients, and actually the patient is going to ask you "What is my survival and what are my expectations?" You have to ask yourself, actually, why do you need these need prognostic models and what are you going to get out of these prognostic models? So in this slide actually I summarized things that may be obvious but you need to understand when you ask these questions. So, some of these prognostic models, for instance, may allow you to help predict survival without therapy. The patient will ask you "Okay, what happens if I do not do any thing with this disease?" Another model may actually allow you to predict survival in the context of a specific therapy. For instance, "I want to know what happens if I receive a stem cell transplantation or a hypomethylating agent." Then, the other classifications that may allow you to have a global view of prognosis based not only on the disease but on intrinsic characteristics of the patient, let's say comorbidities. And then of course, as we move into the field of genomics in this disease, we are able to molecularly adapt therapy based on some of the impact in prognosis of specific gene mutations that then in turn allow you to have targeted therapeutic approaches.



Now, this issue of classifications has been something problematic over the last I would say 15 years or so, and it starts first by this issue that the morphological classifications, as I started saying, are not easy. So now, we have the latest update. Actually, this is just a new one that was just released by the World Health Organization, and as you can see basically that there has been a little bit of change over the last 10 years in terms of what we call MDS versus AML based on the percentage of blasts from 20% to 30%, and again issues that are very specific to morphological characteristics of this disease that, again, require very expert morphological diagnosis, for instance in differentiating if your patient has an issue with one, two, or three lineages. I am not sure that these are things that hematologists, for instance, have the capacity to do unless he or she is trained and works in a very large practice focusing on this group of patients.



Now, in terms of prognostic models, there are multiple. Some of them are outdated, for instance the IPSS, although I have to say that I still use IPSS in my clinic. Why? Because I still can memorize it and most of the drugs that we used were approved under this IPSS classification that basically divided patients into low or intermediate 1, intermediate 2, and high, and we will call patients lower risk if they have low or intermediate 1 and higher risk if they have intermediate 2 or high-risk disease. So, again, I do not think that you will be officially using IPSS to prognosticate patients, but I think most of us still use the IPSS classification to at least decide on therapeutic alternatives. I do not know that people, at least in North America, use the WPSS, this European model, nor actually we were able to gain a lot of traction with the global MD Anderson model even probably these models were more potent than the IPSS program. There are a couple of models that we use very frequently like the MD Anderson lower risk model. I think I showed you some data with comorbidities, and of course we understand that now we have the new Revised-IPSS or RPSS that this actually will be a standard prognostic model, although this model is significantly more complex to use than IPSS, and also I think that we need to understand how we use these new prognostic criteria in the context of the actual therapeutic alternatives that we have for our patients right now.

IPSS Underestimates Prognostic Impact of Poor CG in MDS

- IPSS: score 1.5 for blasts ≥10%, 2.0 for blasts >20%; poor CG score only 1.0
- 2,124 patients; median survival time (MST) 37 months

Parameter	#	Change of MST from overall median (mos)
Blasts <5%	609	+ 20.5
Good CG	768	+ 18
Blasts 5 - 10%	231	– 9.5
Int. CG	222	– 9.5
Blasts 11 - 20%	160	– 20
Poor CG	212	– 26
Blasts 21 - 30%	92	– 26

Haase VH. *Blood*. 2006;108:Abstract 252.

So, one of the issues with the IPSS that actually was identified more than a decade ago by European investigators is the fact actually that the error bar, or in a way the survival prognostication, actually was not very precise. So, it was a good model to group patients together, but there is actually quite a bit of variability in terms of predicted survival based on specific characteristics. And this is illustrated in this slide, where, for instance, you see that for a group of patients with MDS the change in median survival time or MST was actually +20.5 months depending on the percentage of blasts, +18 depending on cytogenetics, and so forth. So, there were characteristics that were associated with very good prognosis and some of them with very bad prognosis, but we are talking basically an error bar that will go +/- 20 months, that could be actually the overall survival of the patient. So, it was clear from this data that we needed better classifications even though the IPSS has served us very well for a long period of time, and again very democratic, very simple system to basically use.

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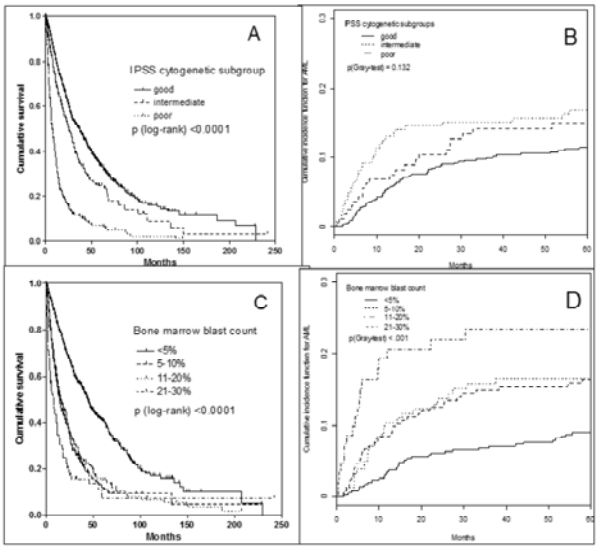
Comorbidities in MDS: Multivariate Survival Model with Risk Score

Prognostic Factor		Coefficient	Score
Age	>65	0.582	2
Comorbidity score (ACE -27)	Mild or moderate	0.301	1
	Severe	0.782	3
IPSS	Int 2	0.512	2
	High	0.769	3

*Score points were obtained by dividing estimated coefficients by 0.3

As we moved, actually, we started to realize that not only these models were not very precise but that we were also missing other issues that may be either molecular features or, in this slide for instance, characteristics related to the patients that could have a very significant impact on the outcome of our patients. One actually that is very important is comorbidities. Of course, MDS is a disease of older individuals that may have actually other conditions, let's say diabetes, hypertension, other cancers, and we were interested in this paper published in *JCO* a few years ago in the understanding of how comorbidities actually impacted on survival of these patients. So, we developed a model that is shown here where we put together IPSS comorbidity score by a classification known as ACE-27, and then age, and as you can see on the right column, each one of them will have a specific weight, and we were able actually to prognosticate in a very powerful way using characteristics that are related to the disease and to the patients what will be the expected survival of our patients with MDS. And I think this data actually is critical because it gives you the opportunity to come with a realistic view of outcomes for patients not just based on the disease characteristics but also on other issues related to their own health.

Weighting of Cytogenetics in Relation to BM Blast Counts in IPSS

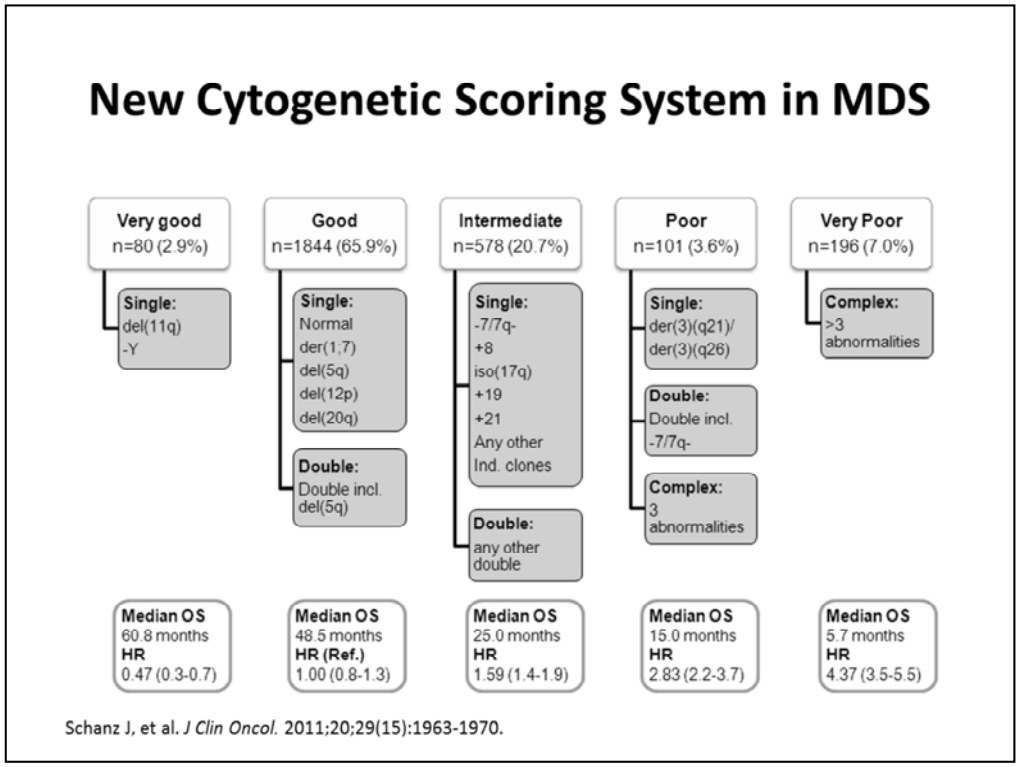


Category	OS (months)	OS (HR)
Poor (IPSS)	7.5	3.2
Complex (non 5/7)	7.4	3.0
Complex (5/7)	5.6	5.4
Blasts (21-30%)	7.4	3.2

Figure 1 A-D.
Overall survival and cumulative risk of AML-transformation in IPSS cytogenetic and FAB bone marrow blast count subgroups (univariate analysis; patients treated with supportive care exclusively)

Schanz J, et al. *J Clin Oncol.* 2011;20;29(15):1963-1970.

Then, around 4 or 5 years ago, as you can see in the slide, we moved to important concepts that is actually to me interesting that we did not really see this earlier, that cytogenetics have a very deep and powerful impact in the behavior of this disease. And this is a paper that was published in *JCO*, and as you can see in the slide, particularly in the box in the right upper corner, you see actually that we could compute survival based on let's say IPSS, but in particular cytogenetics. So, if you look at where it says category then survival, poor-risk disease survival 7.5 months, you have complex 7.4, but for instance if you have complex with an alteration of chromosome 5 from 7, survival actually is around 5 to 6 months. And this actually could be in the context of group of patients with a low percentage of blasts. Indeed actually if you go below to those patients with 21-30% blasts, survival is around 7 months. So, it was obvious from this paper that cytogenetic information had a very important weight in prognosticating these patients, and this actually has allowed us to move earlier in the course of this disease to initiate therapy, meaning in patients that perhaps have a lower percentage of blasts or not so significant cytopenias, just because they have very complex karyotypes, that are associated with a poor prognosis.



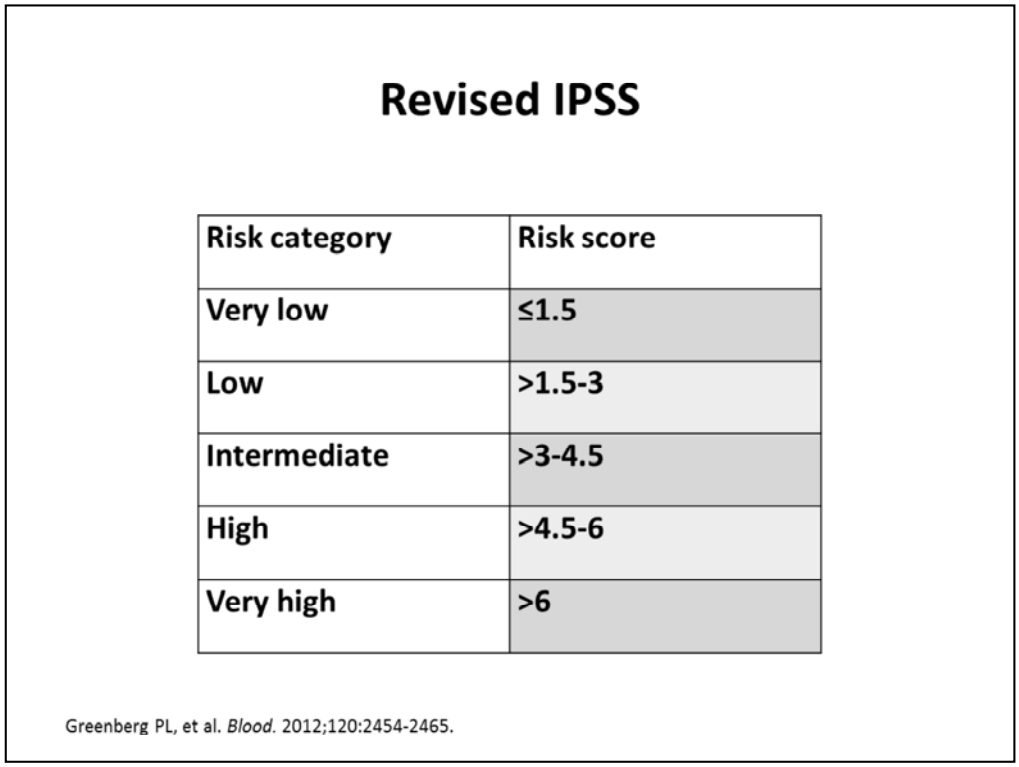
So, this is very important, and this concept actually is what led to what is basically the major risk outfall of the IPSS-R classification, that is the new cytogenetic scoring system in MDS. Now, I cannot memorize this and I spend my days just taking care of people with MDS and AML, so there are tools out there in the internet, I guess, that allow you to compute this because this is difficult to memorize, but it gives you basically now what is the accepted cytogenetic structure or scoring system for MDS. And what you see is that now this is divided into five subsets of patients—very good, good, intermediate, poor, and very poor, and each one has specific alteration. So, very good will be people that have a -Y or a deletion of 11q. In the very poor contact group, you have those with more than three abnormalities, and then in between. Although I was part of this effort, my issue is actually with this intermediate subset where they are calling -7 intermediate and so forth, and I think that what we learned is that the intermediate subset actually may be a highly heterogenous group of patients with some patients with intermediate-risk disease that have good outcomes and then some patients with intermediate-risk disease that actually have a little bit of poorer prognosis. So this, in my opinion, intermediate group may be a little bit more difficult group of patients to understand their behavior based on this particular classification.

Revised IPSS

Prognostic Variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good	—	Good	—	Intermediate	Poor	Very poor
BM blast, %	≤2	—	>2% - <5%	—	5%-10%	>10%	—
Hemoglobin	≥10	—	8 - <10	<8	—	—	—
Platelets	≥100	50 - <100	< 50	—	—	—	—
ANC	≥0.8	<0.8	—	—	—	—	—

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

But no matter what my opinion is on this, basically this has now become the standard classification, and if you are informing a case in your medical records, you are going to be asked actually to describe what are the characteristics based on this Revised-IPSS. This paper is now 3 to 4 years out, led by multiple authors basically all over the world, and again similar to the IPSS, you have the cytogenetics, the percentage of blasts, hemoglobin, platelets, and neutrophil count, and then each one of these characteristics gives you points from 0 to 4, and then basically you are able to build a prognostic scoring based on the cumulative number of points based on blasts, hemoglobin, platelets, and your neutrophil count. This is actually not dissimilar to the IPSS, but what is dissimilar is that you have an intermediate subgroup, and again, the cytogenetic classification now is significantly more complex or more robust than the prior IPSS classification.



And then basically you would call a patient very low risk if they have less than 1.5 points, low if they have 1.5 to 3 points, intermediate if they have 3 to 4.5 points, high if it is 4.5 to 6, and very high if they have more than 6 points.

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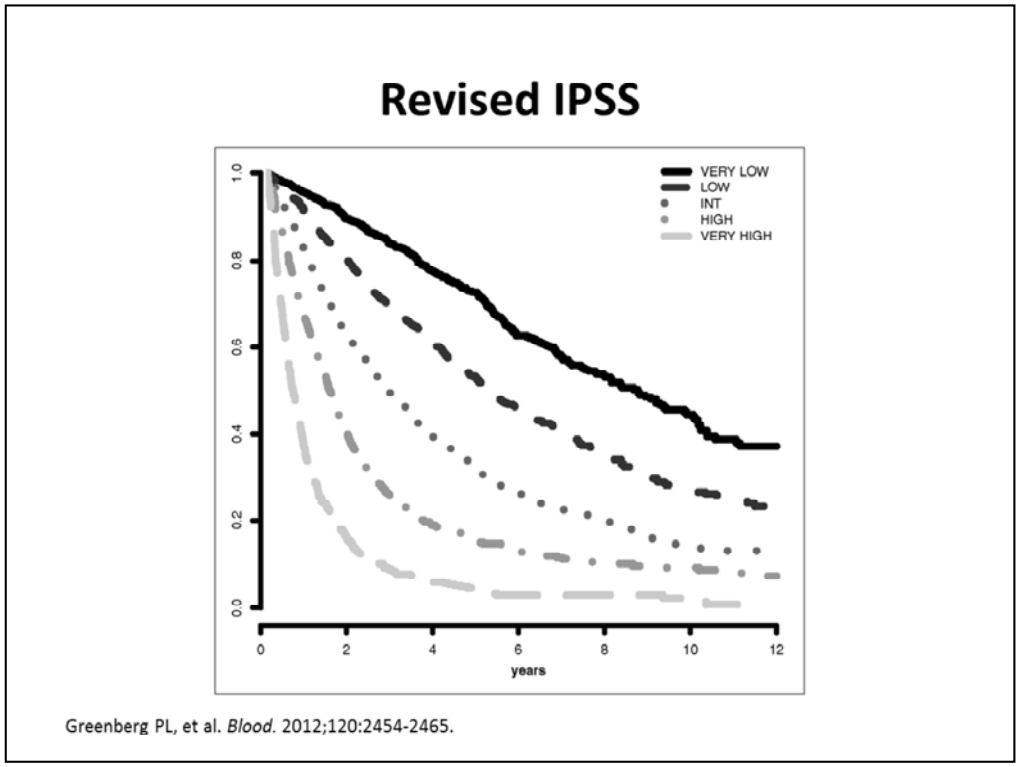
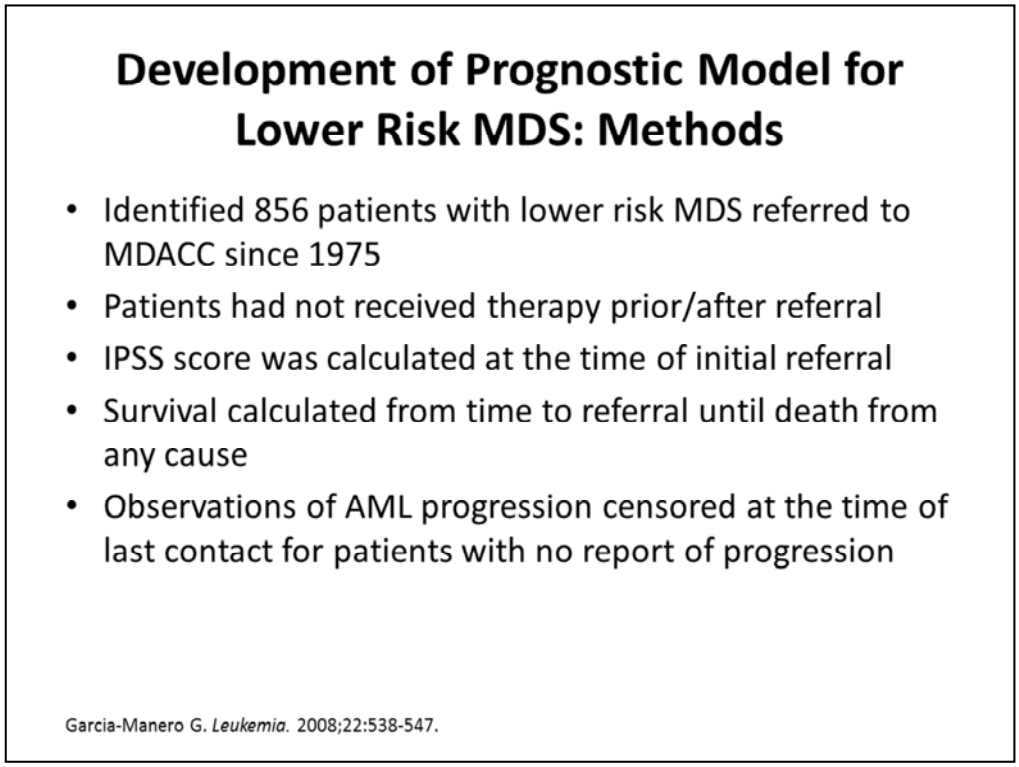


Then of course, this translates into different survival trends, and as you can see in this Kaplan-Meier plot you have a group of patients up there in the top with thick black bar with median survivals that could be over a decade, and then a group of patients in the very high-risk subset that basically have a very dismal prognosis with a behavior not dissimilar to what you see in patients with acute myelogenous leukemia or other very aggressive type of conditions.



Now, my group has been particularly interested in developing lower risk systems. Why? Because I think that we need to start going back to identifying these patients earlier in the course of the disease and this slide tells you a little bit of rationale of why and how we developed a very powerful model looking at the prognosis of patients with lower risk MDS.

Multivariate Analysis Parameters

Adverse Factor	Coefficient	*P* value	Assigned Score
Unfavorable cytogenetics	0.203	<0.0001	1
Age ≥60 years	0.348	<0.0001	2
Hgb <10 (g/dL)	0.216	<0.0001	1
Plt <50 x 10^9/L	0.498	0.0001	2
50-200 x 10^9/L	0.277		1
BM blasts ≥4%	0.195	0.0001	1

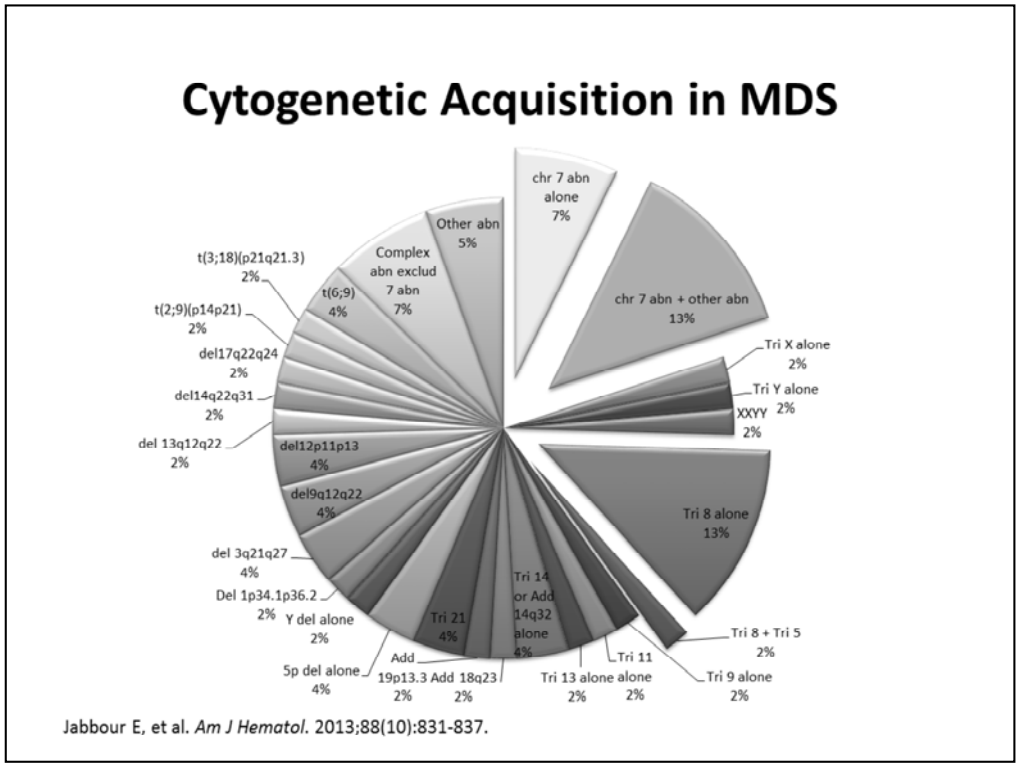
Garcia-Manero G. *Leukemia.* 2008;22:538-547.

The system actually is very simple. We look at cytogenetics, again, the age, hemoglobin, platelets, and if you see on the right column again, you see they assign a score. What you do basically is you add those points and you could go from like I guess 0 point to maximum of 6 to 7 points,

Proposed Categories: Estimated Survival

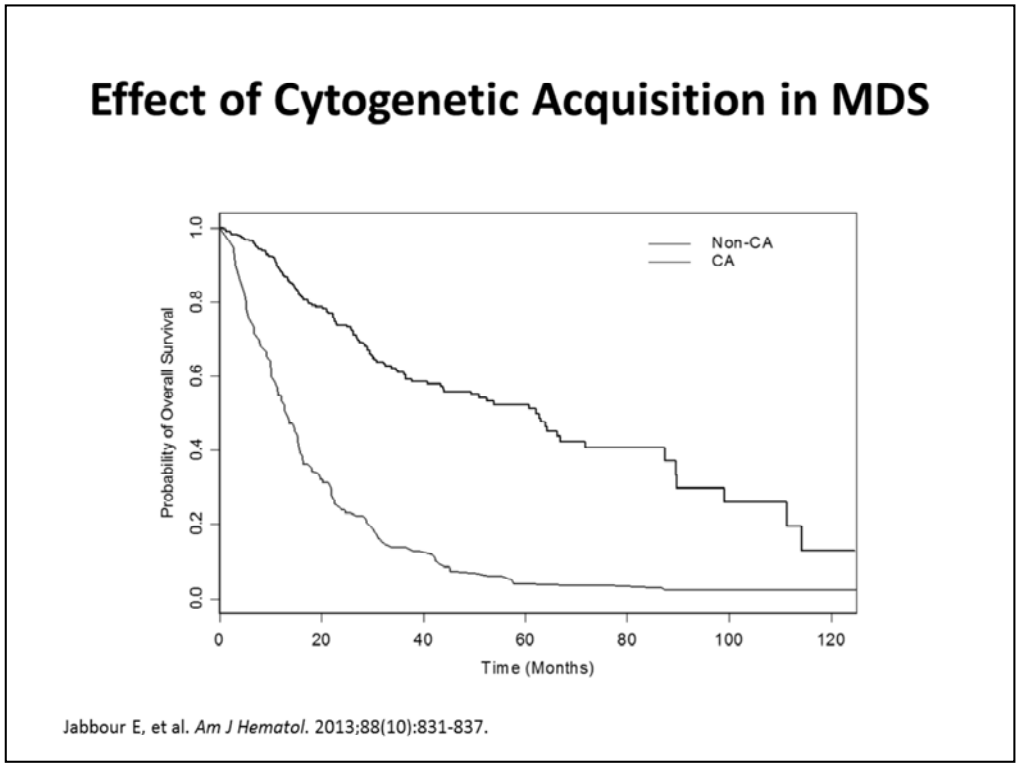
Score	N	Median (months)	4-year survival (%)	Category
0	11	NR	78	1
1	58	83	82	
2	113	51	51	
3	185	36	40	2
4	223	22	27	
5	166	14	9	3
6	86	16	7	
7	13	9	NA	

and then basically as you see here, someone with a score of 0 will have a 4-year survival close to 80% and no median survival, and again, this is very important for you to understand this is in people with low and intermediate 1 disease. Those with 6 to 7 points, they have a survival less than a year and basically nobody will be long-time survival of this disease. And this group of patients actually that in your practice you may be calling low risk and you may be initially offering observation. One of the things that we are doing in our practice is now actually initiate therapy a little bit early on in the context of this disease, particularly if you are in this group of patients with what we call low-risk/high-risk disease.

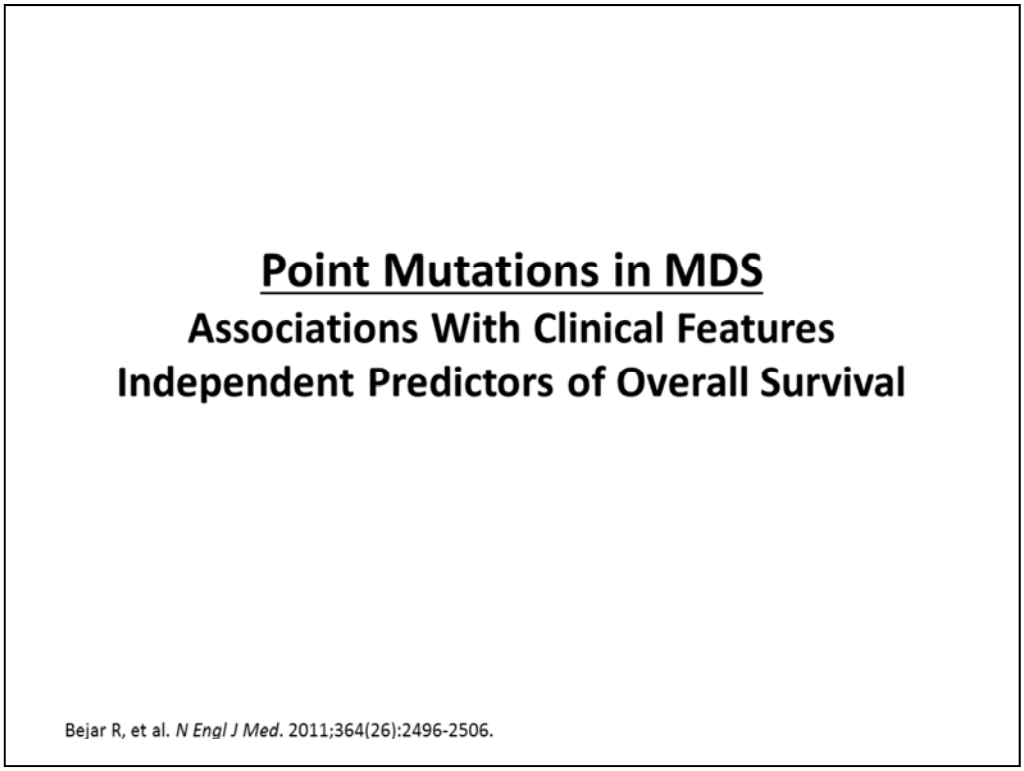


Jabbour E, et al. *Am J Hematol*. 2013;88(10):831-837.

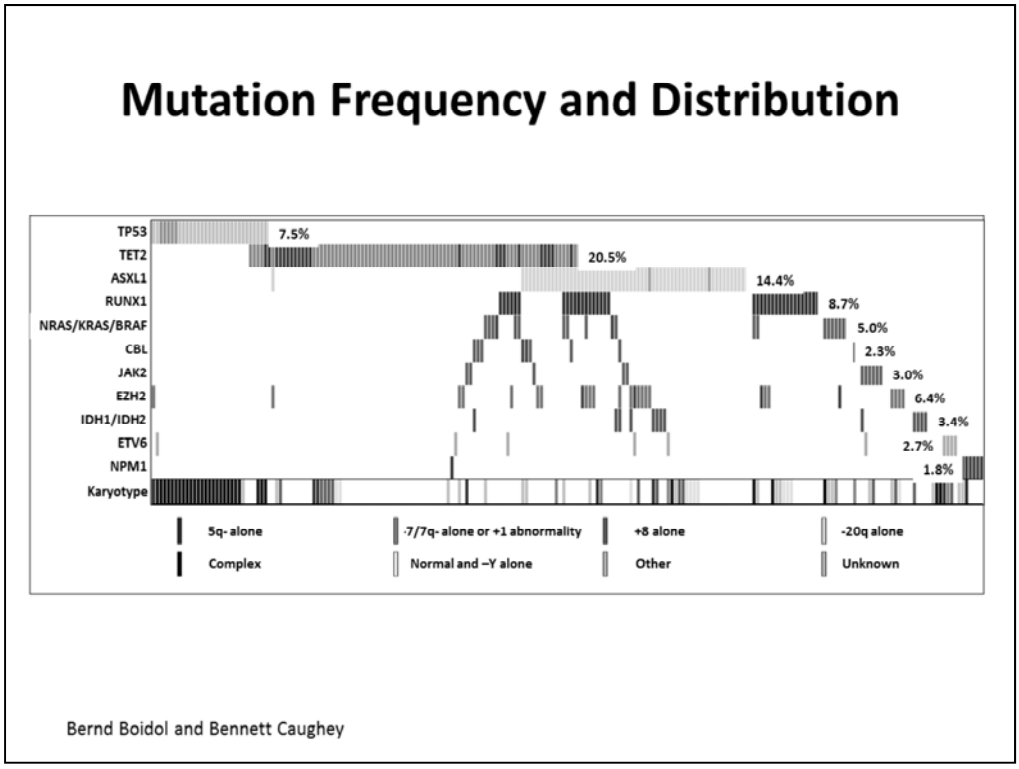
Now, this presentation has a little bit of interesting cytogenetics, and I wanted to put out this slide. This paper was subsequently published in *Leukemia Research*, but I can tell you that these chromosomal abnormalities in MDS are not static. It is not that you check them one time, and they are going to be the same for the rest of the life of the patient. Indeed actually they are really highly viable, and what we showed in this analysis is that it is not uncommon. Indeed, it happens in around a third of the patients that you will see variability in the cytogenetic profile, something we call cytogenetic acquisition, and that is actually associated with very poor prognosis. Now, we do not see a pattern, as you can see on this pie diagram here on this slide. So, you see quite a bit of variability, but this is not an infrequent process, and my point out of this slide is that perhaps when you reevaluate these patients periodically once in a while when you repeat the bone marrow, it would also be acceptable to perform a cytogenetic analysis so you make sure that you know exactly with what you are dealing at the cytogenetic level at that particular time.



And this is a slide from this paper where we basically show the survival based on this clonal acquisition. So, on top, on the black line, you see those patients that are stable in terms of cytogenetic abnormalities, and then in red you see those patients that have a cytogenetic change with very poor prognosis and actually a high rate of transformation to acute myelogenous leukemia. So, you have to think about this dynamic influence of cytogenetics when assessing your patients with MDS.



Then finally over the last few years, we have had quite a bit of significant effort in terms of mutational analysis in MDS. In 2011, my group with that of Ben Ebert published in *The New England Journal of Medicine*, this paper looking at point mutations in MDS,



and we were able to come with probably the first map of genomic alterations in this disease, and you see in this diagram for instance that you have a group of patients with p53 mutation on the left and then distribution of TET2 mutations and so forth.

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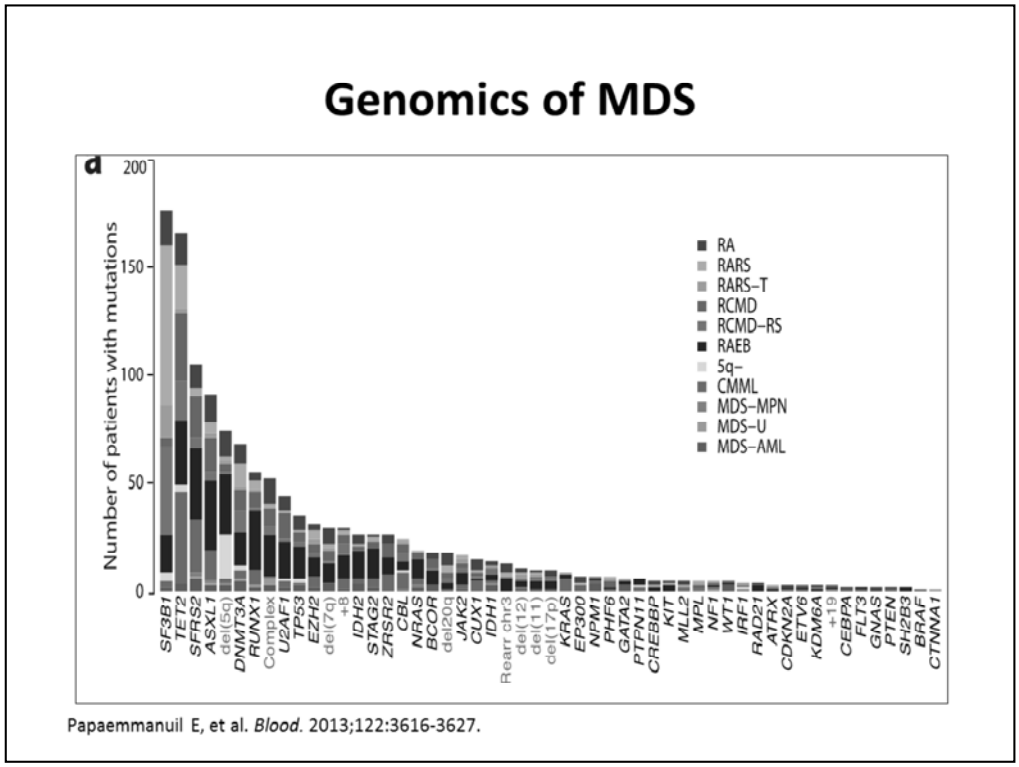

Papaemmanuil E, et al. *Blood*. 2013;122:3616-3627.

Now, when we did this, we had basically a limited knowledge in terms of the number of genes that were mutated in this disease and so forth, and over the last decade or so, we basically have gained quite a bit of knowledge in terms of mutations in MDS, and I think the best example is this paper by Elli Papaemmanuil published in *Blood* from the European Consortium out of Cambridge University where you probably have what is now accepted as the molecular genomic mutational landscape of myelodysplastic syndrome. And you see that for instance in the left on the first column that the most frequently mutated gene is SF3B1. These are genes involved in splicing, and then basically around 20 to 30 genes probably will cover most patients with MDS. Now, you see at the right of the graph that there are some genes that happen to be mutated in 1% or 2% of the cases. The reality is that we do not know, actually, what is the impact of the meaning of this type of mutation and how you will use this kind of data in clinical practice. What we know now is that there is a core group of genes, splicing genes, IDH, p53, TET2, EZH2 that may allow you actually to either prognosticate patients and/or decide on therapeutic alternative for your particular patient.

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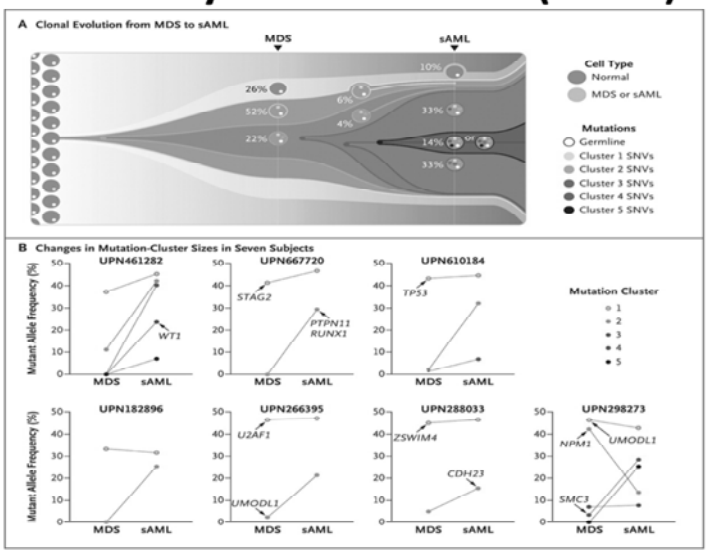
Clonal Progression from MDS to Secondary Acute Myeloid Leukemia (sAML)



MDS=myelodysplastic syndrome

Walter MJ, et al. *N Engl J Med*. 2012;366:1090-1098.

The other issue very similar to what we were talking earlier in terms of cytogenetics is that these molecular alterations are not static. Again, they change with time and this is a beautiful paper from Matt Walter in *The New England Journal of Medicine* from Washington University where they showed actually how these clones in terms of mutations change in time during the course of the disease. So, there is quite a bit of dynamism in this process, and this means actually that this disease is basically changing and you either treat it or the disease progresses. So, again, this is very important information and you need to be aware that the mutational or cytogenetic landscape is not going to be the same at baseline compared to basically other endpoints as the disease progresses.

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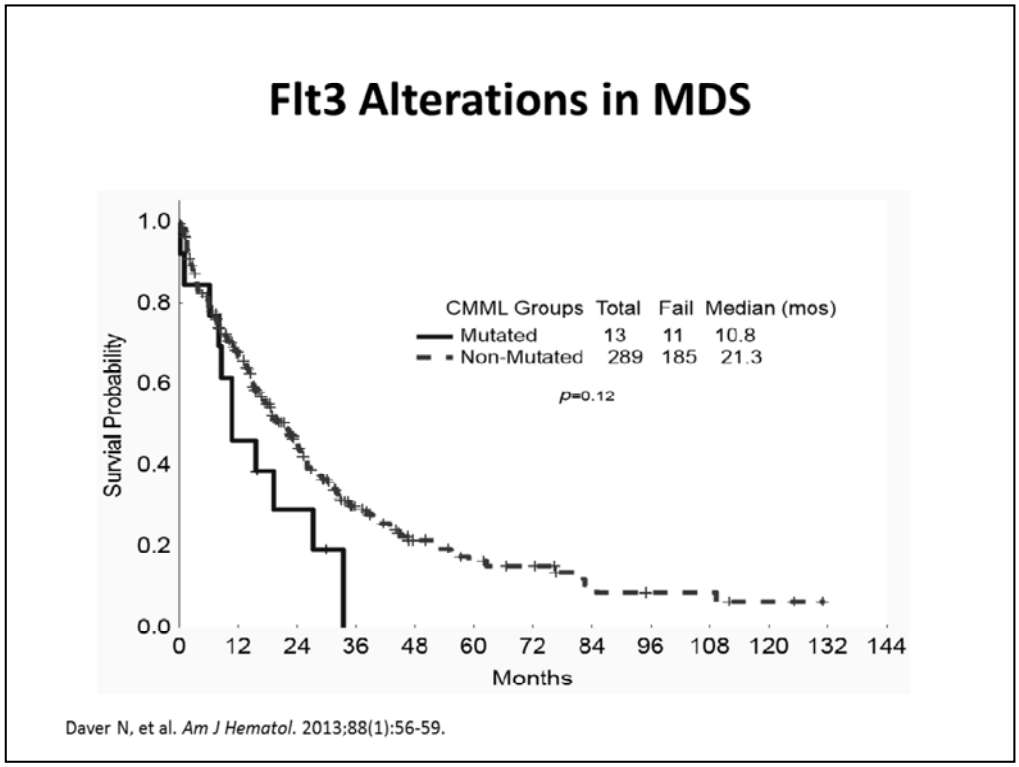
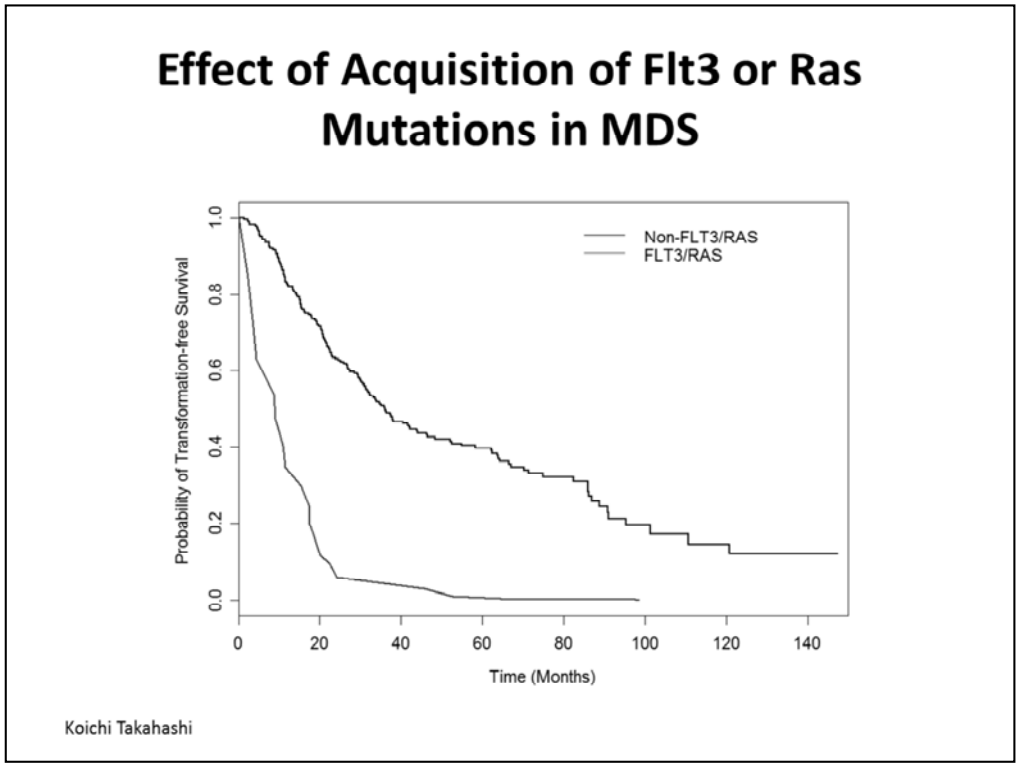


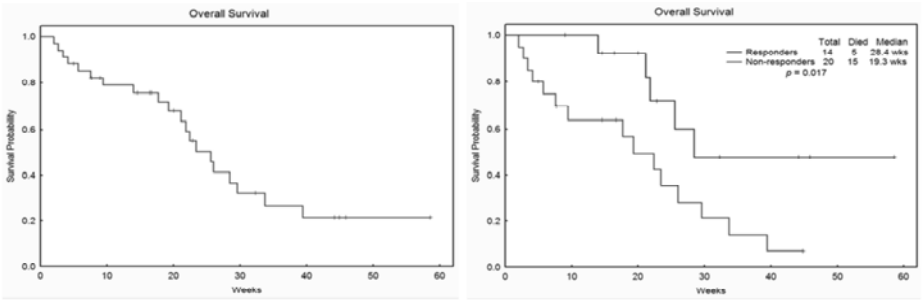
A very important example is shown here. So, a few years ago, we did analysis looking at FLT3 in MDS, and as I think most of us know, we agreed that FLT3 mutations in this particular disease are not very common. Maybe 2% or 3% of the cases will have this mutation at the beginning,



but what we noticed actually is that in a subset of patients, actually in around 20% of the patients, there is an acquisition of FLT3 mutations in these patients, also of RAS by the way, and that when that happens actually the disease changes, and actually you see that before the patients have transformed to acute myelogenous leukemia. This is very important because it is going to predict for a more aggressive course of this disease but also it may allow you for therapeutic interventions for instance adding a FLT3 inhibitor for a patient that has started to transform on a hypomethylating agent. So, this type of data is very important not only to prognosticate the patient but also actually to treat the individual one.

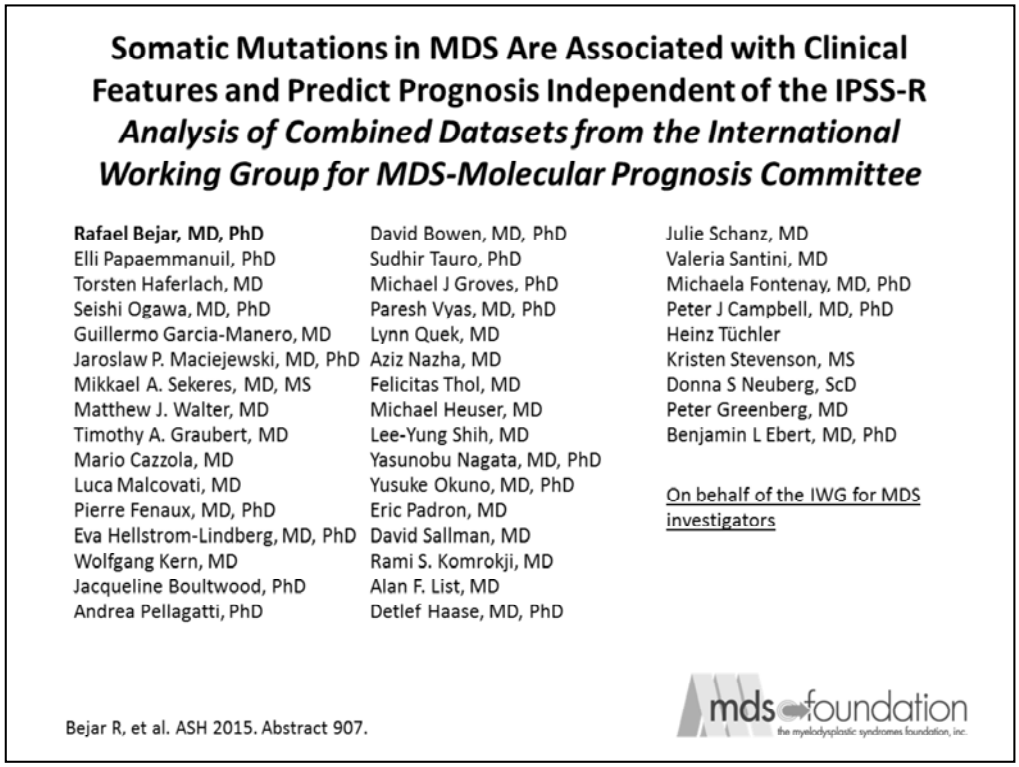
5AZA + Sorafenib – Outcomes and Survival

Parameter	N=37 (%)	
Median no. cycles received, [Range]	3, [1 – 18]	
Median follow-up in weeks, [Range]	24, [5 – 71]	
Response		
CR	6 (16)	
CRi	10 (27)	
PR	1* (3)	
NR	18 (49)	**46%**
Died	2 (5)	
Median no. cycles to response, [Range]	3, [1 – 4]	
4-week mortality	1 (3)	
8-week mortality	1 (3)	

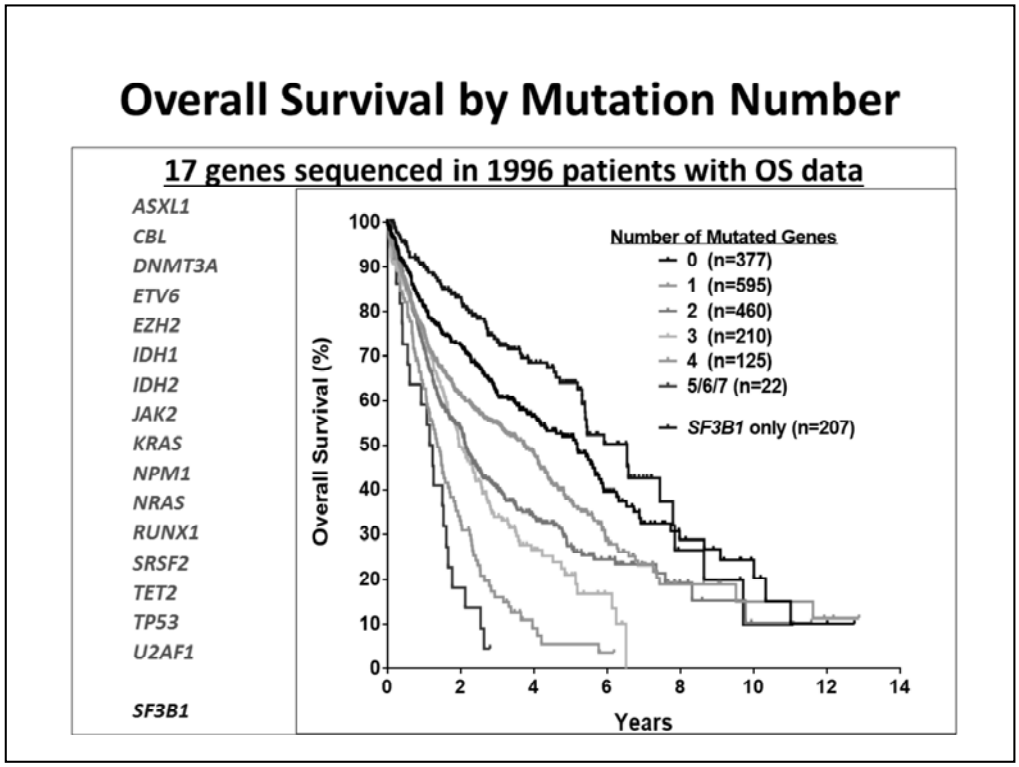


This is actually data from Farhad Ravandi here at MD Anderson showing that if you combine azacitidine with sorafenib you get close to a 40% or 50% response rate with actually long-lasting responses, and of course, the advent of second-generation or FLT3 inhibitors are going to be very important in this type of combination.

The Changing Face of MDS: Advances in Prognosis and Diagnosis

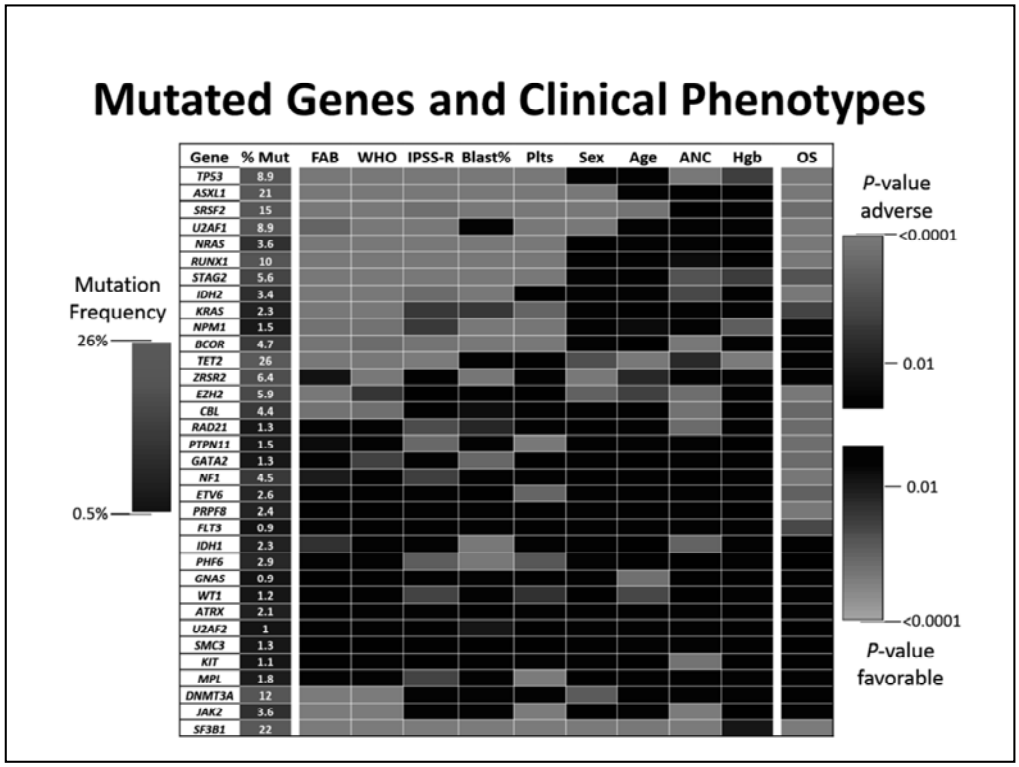


Now in the last couple of years, there has been an effort actually to start compiling this kind of data into more classic type of classifications, and here what you see is the presentation from us last year where again the members of the IPSS-R were able to put together whatever molecular data they had with IPSS.



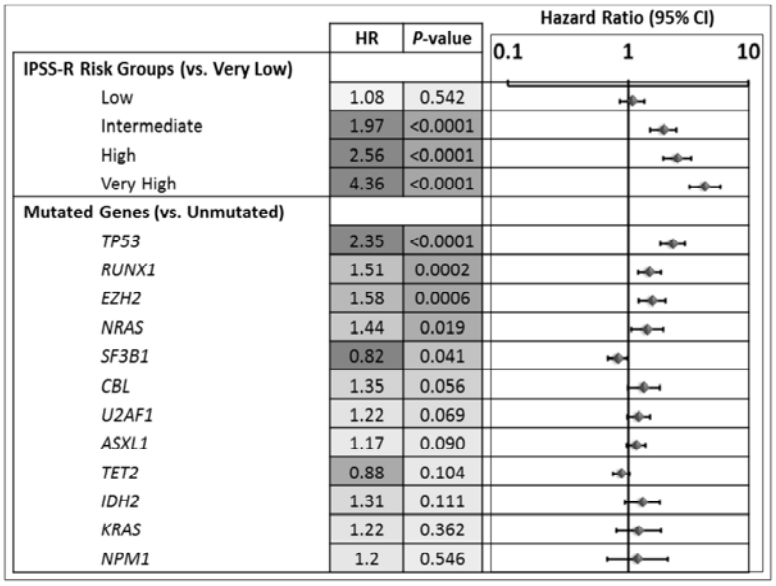
And in this presentation, again, you see for instance the impact on prognosis in patients with MDS based on the number of mutations. So, you have one gene, two genes, three genes, etc. So, for instance, in blue, you see that if you have a mutation on SF3B1 you do very well, but in the other hand, if you have five, six, or seven mutations, the patients do not do very well. So, this actually is going to be very important in terms of putting these prognostic classifications together with molecular data.

The Changing Face of MDS: Advances in Prognosis and Diagnosis



I am going to show you some examples in terms of distribution of particular mutations with FAB, WHO, and IPSS-R. This is a complex slide, but this is basically what is happening where we are trying to put together these IPSS-R or IPSS type classification with molecular annotation in an attempt to come with more prognostic and more robust type of systems.

Final Multivariable Survival Model

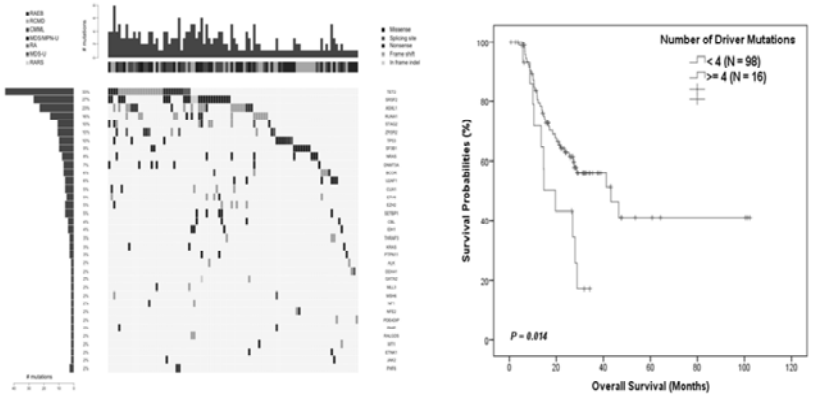


	HR	*P*-value
IPSS-R Risk Groups (vs. Very Low)		
Low	1.08	0.542
Intermediate	1.97	<0.0001
High	2.56	<0.0001
Very High	4.36	<0.0001
Mutated Genes (vs. Unmutated)		
TP53	2.35	<0.0001
RUNX1	1.51	0.0002
EZH2	1.58	0.0006
NRAS	1.44	0.019
SF3B1	0.82	0.041
CBL	1.35	0.056
U2AF1	1.22	0.069
ASXL1	1.17	0.090
TET2	0.88	0.104
IDH2	1.31	0.111
KRAS	1.22	0.362
NPM1	1.2	0.546

Again for instance, this is just giving you hazard ratios for specific mutational events in these patients. So this in the future, and I am not taking 10 years from now, in the near future is going to be actually how you are going to be prognosticating our patients with this disease.

Clinical Implications of Genomics in MDS

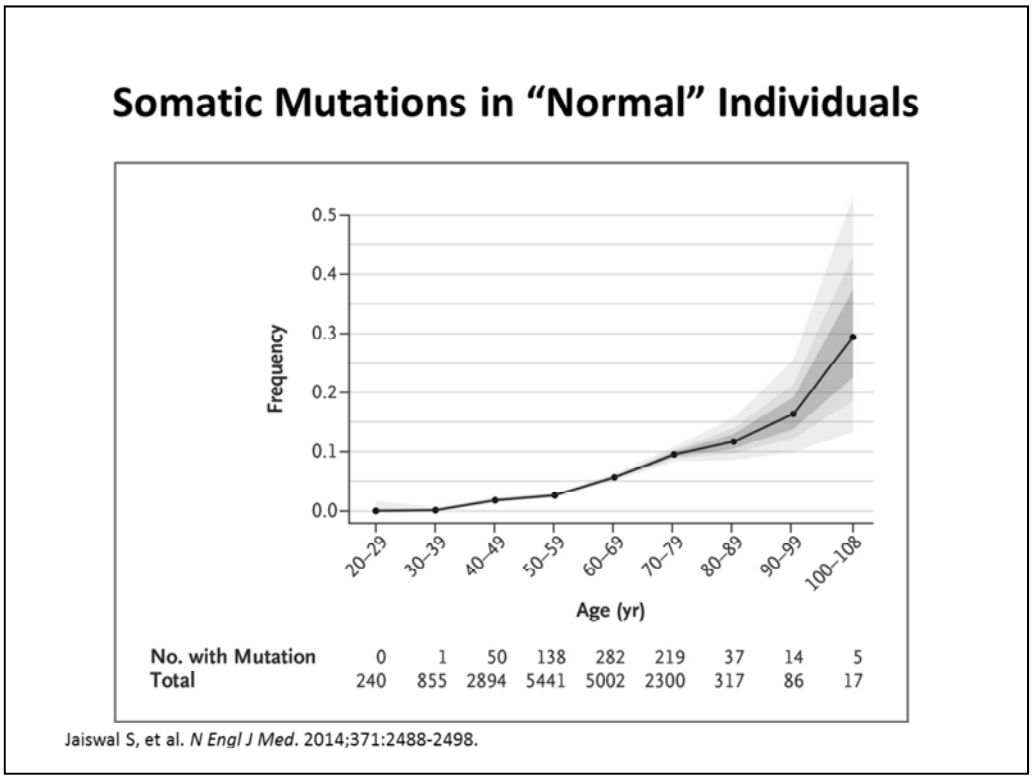
- Whole exome sequencing of 114 untreated MDS patients
- Independent prognostic value of *TP53* mutations
- Four or more driver mutations independently prognostic in MDS



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

This is from my paper we just published a few months ago in *Oncotarget* where we performed full genome sequencing in little bit over 100 patients, and very similar to the data I just showed you we see for instance that you if do have more than four mutations, these patients do particularly worse than other groups of patients. So, I think that this type of molecular annotation is going to add but actually not substitute the type of information we get from cytogenetic type of analysis.

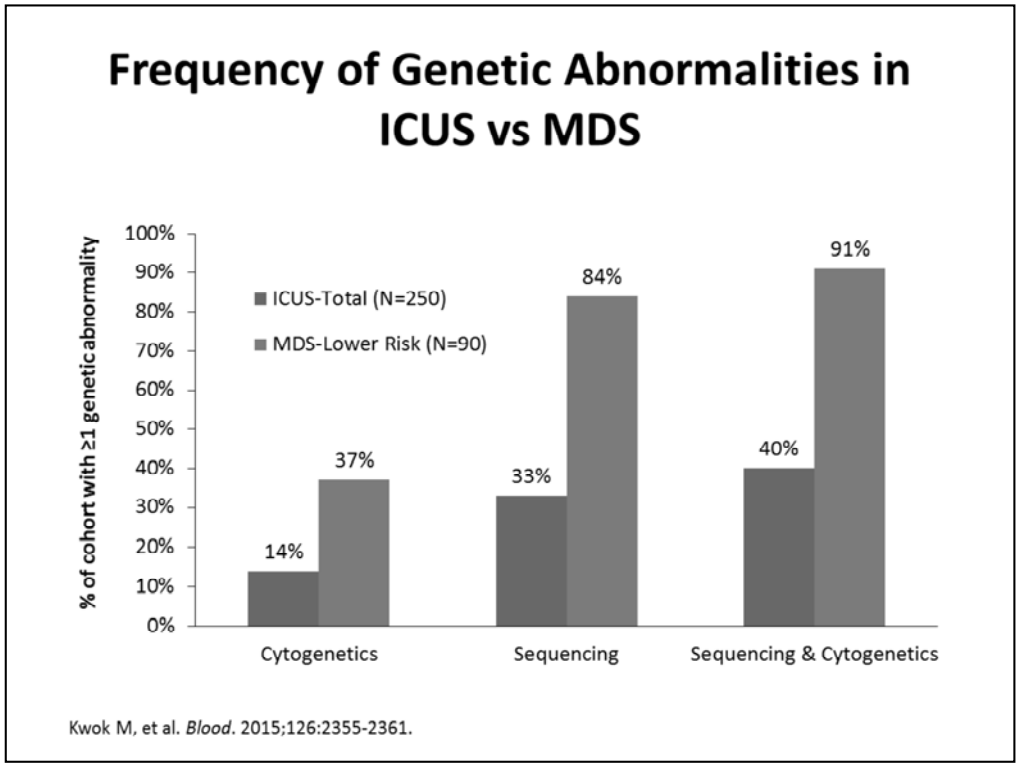
The Changing Face of MDS: Advances in Prognosis and Diagnosis



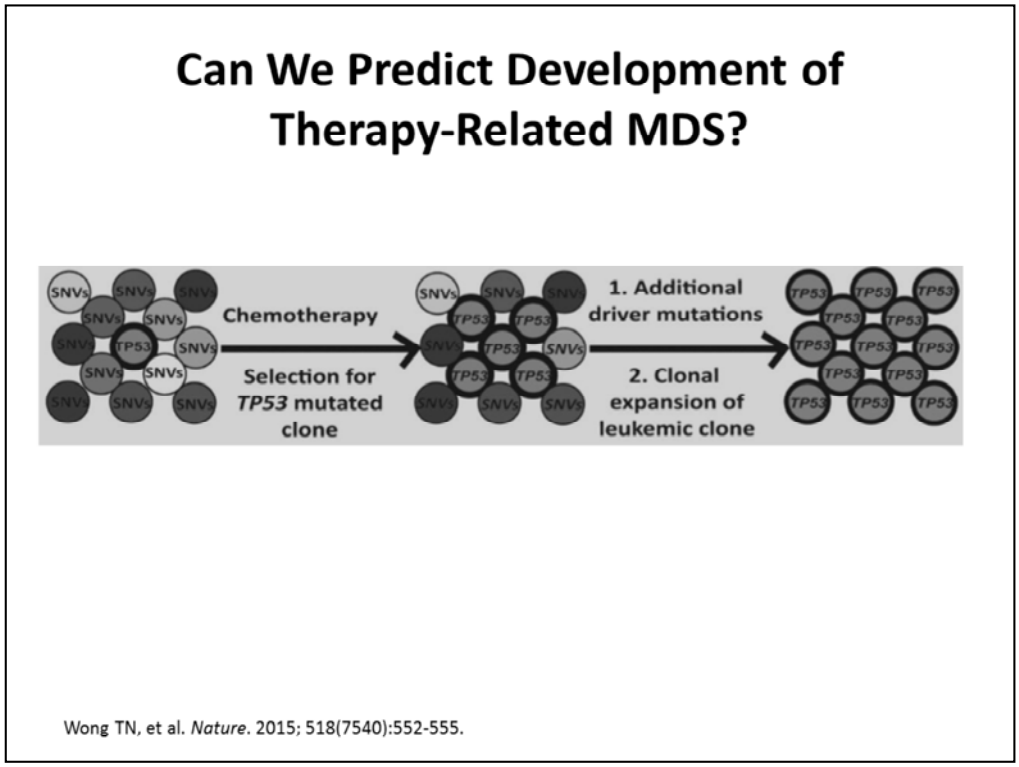
Jaiswal S, et al. *N Engl J Med*. 2014;371:2488-2498.

Now, this genomic data is also having an impact on something that I think could be transformative, and this comes from two major papers published in *The New England Journal of Medicine* in 2014 where these groups in Boston demonstrated that "normal individuals," by that we mean like healthy people, as we age actually carry these kinds of mutations that we see in leukemia in their peripheral blood. So, you see this graph, this is very rare when you are a kid in your 20s but as you get older, particularly once you are beyond 60 years of age, a fraction of these patients from 10% to 30% of them actually may have some of these mutations in their peripheral blood, and what these investigators showed was that this was associated with an increased risk of developing myeloid malignancies. So, this is very important because it may allow us for some type of preventive type of strategies. I think that this data is of great importance.

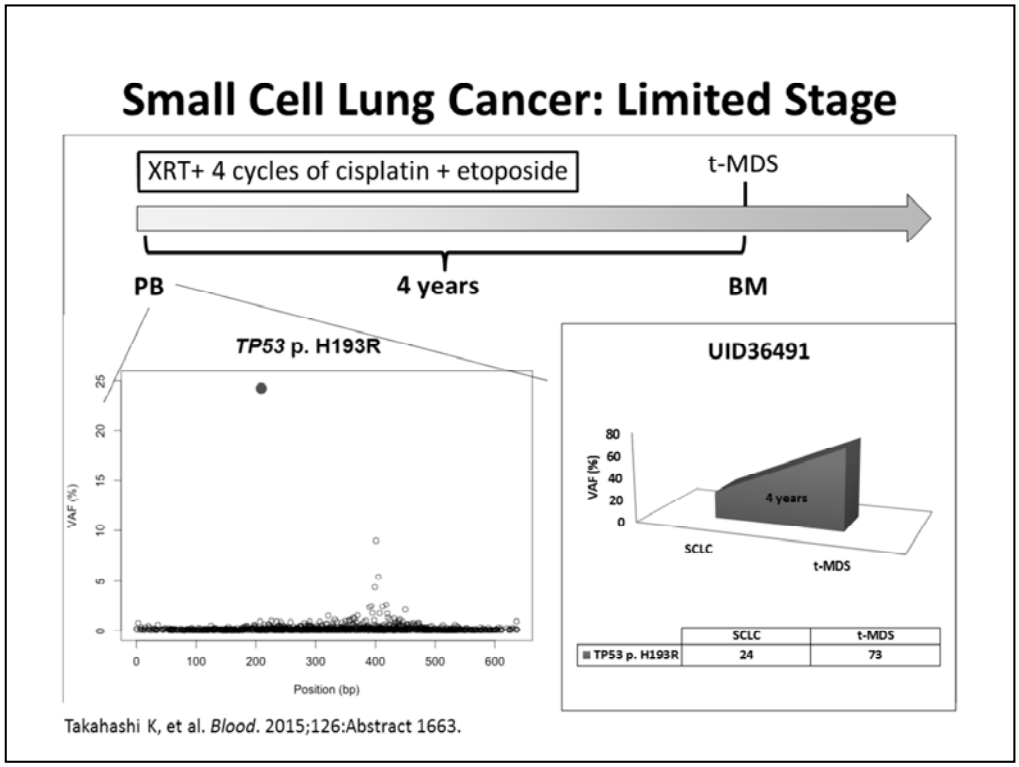
The Changing Face of MDS: Advances in Prognosis and Diagnosis



And indeed actually at ASH and in a secondary paper published in *Blood* a few months ago, these investigators from actually a commercial company showed that patients with ICUS, or idiopathic, cytopenia of unknown significance, these are people that they are not totally normal in their bone marrow morphology but they cannot be labeled as MDS at that time, actually have a higher number of mutations in their bone marrow. Again, suggesting that this is perhaps a pre-MDS type of a stage and that the knowledge in terms of mutations may help us very much in terms of understanding or predicting their natural history.



This actually goes further into actually a very important group of patients with therapy-related myelodysplastic syndrome, and this is a crucial paper published last year by the group at Washington University again in *Nature* where they saw clearly in a small group of patients that there are some patients that have a clone that is involved in the development of leukemia before they see any chemo or radiation therapy for the primary disease. So, let me explain this because this may be a little bit complicated right now the way it is coming in this context. So, we know that for instance if you treat patient with lymphoma with chemoradiation therapy or autologous transplant they are at high risk of developing therapy-related AML or MDS, and we always thought that this was because the chemoradiation therapy will damage the genome of the cells. What these investigators in St. Louis showed is actually that indeed you could track mutations before these patients got any chemoradiation therapy, and this then suggested that there was not just DNA damage that was induced in this process, it is basically some process that is involved with clonal expansion once you treat these patients with chemoradiation therapy. So what you see in this slide is that on the left, this is the bone marrow before the patient gets any chemotherapy. Then, the patient gets chemotherapy and there is a selection for increased number of clones that carry this P53 mutation, and then with time a few years later, this will fully occupy the bone marrow and then cause the leukemia. So, I think this is a very important aspect because, again, it may allow us to predict the detection of this patient or at least decide who may be at risk,



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

and indeed actually we just presented at EHA data on 14 patients at MD Anderson where we were able to have blood before they got any chemoradiation therapy, bone marrow at the time lymphoma diagnosis, and then at the time of leukemia development and/or other solid tumors, and we see basically the same phenomenon. So, this is an example of a patient with lung cancer where we can track a p53 mutation before this patient gets any chemoradiation therapy and then the patient goes on to develop leukemia. So, I think this is going to be transformative for the assessment of these patients with therapy-related myeloid disorders.

And then with that, I would like to conclude this talk. I am very thankful for your attention and please join me in the next activity that we have titled "The Changing Face of MDS – Advances in Treatment" where I will discuss how I treat patients with MDS today in 2016. Thank you very much.