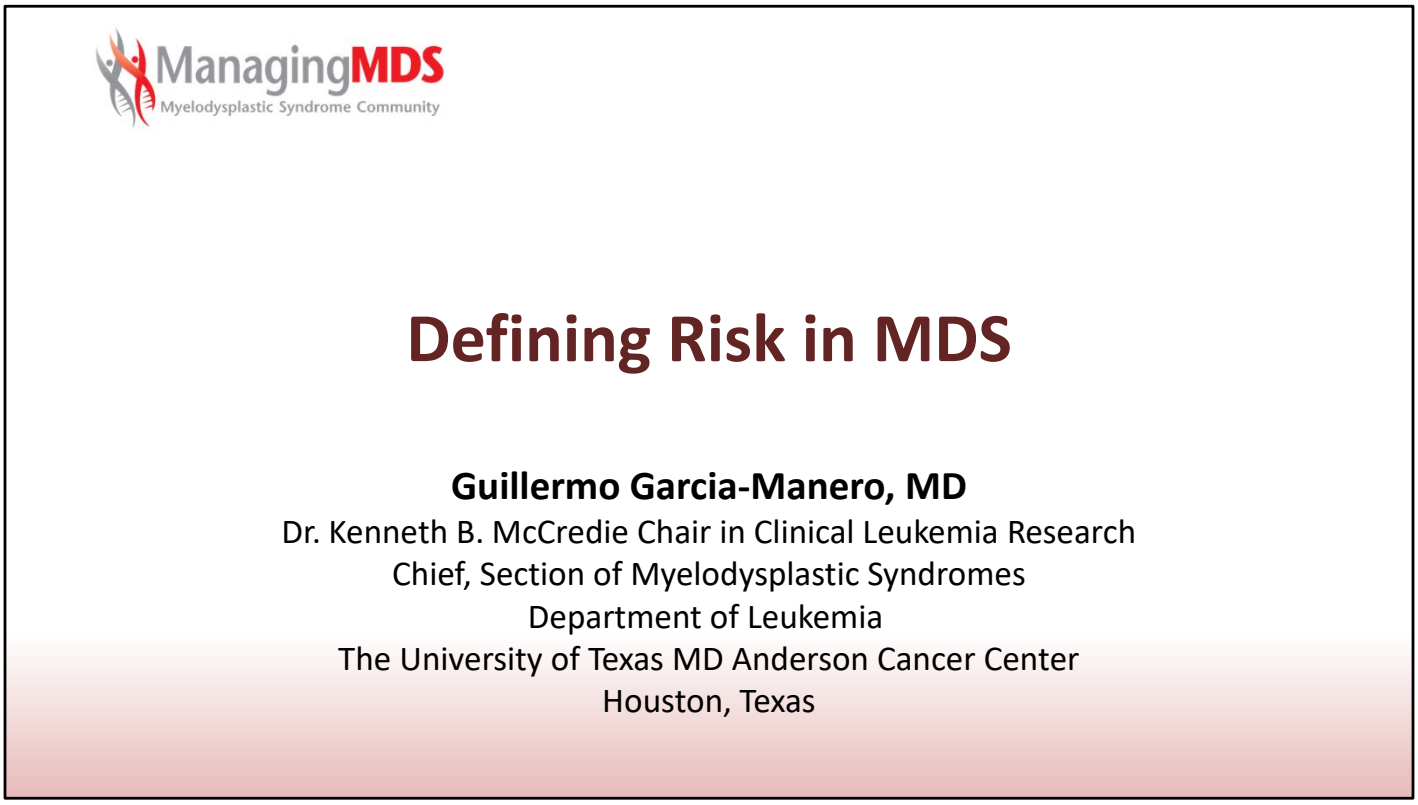

Welcome. My name is Guillermo Garcia-Manero from the Department of Leukemia at The University of Texas MD Anderson Cancer Center. Today, we're going to discuss how to calculate the IPSS-R score in patients with myelodysplastic syndrome. To do so, we're going to use a hypothetical case.

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Case

A 78-year-old male is referred to you for severe pancytopenia. You perform a marrow examination that shows the following:

- 2% blasts
- Complex cytogenetics (more than 3 changes) including an alteration of chromosome 17
- Hemoglobin 6 g/dL
- Platelet count was 15Ku/dL
- ANC 0.5 ku/dL
- NGS panel showed a p53

This is a 78-year-old man that is referred to you for severe pancytopenia. You perform a marrow examination that shows the following: 2% blasts; complex cytogenetics, meaning more than three changes, including an alteration of chromosome 17. Hemoglobin of 6 grams; a platelet count of 15,000; ANC 0.5. In addition, you perform a next-generation sequencing panel that shows a mutation on the p53 gene.

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Case

Based on the results of the marrow exam, your calculated IPSS-R score is:

- Very low (<1.5 points)
- Low (1.5 to 3 points)
- Intermediate (>3 to 4.5 points)
- High (>4.5 to 6 points)
- Very high (>6 points)

Based on this, your calculated IPSS-R score is: Very low, meaning less than 1.5 points; Low, 1.5 to 3 points; Intermediate, more than 3 to 4.5 points; High, more than 4.5 points to 6; Very high, more than 6 points. I ask the audience to please calculate the score.

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Defining Risk in MDS

Medullary Blasts, %

≤2	0
>2 to <5	+1
5 to 10	+2
>10	+3

If we review the data that we obtained from the bone marrow examination, this patient has 2% blasts,

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Defining Risk in MDS

Medullary Blasts, %

≤2	0
>2 to <5	+1
5 to 10	+2
>10	+3

that will give him 1 point by the IPSS-R.

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Defining Risk in MDS

Cytogenetic Group

Very Good: del(11q) or –Y	0
Good: normal karyotype, del(20q), del(5q), del(12q), or double including del(5q)	+1
Intermediate +8, del(7q), i(17q), +19, or any other single or double independent clone	+2
Poor: -7, inv(3)/t(3q)/del(3q), double including -7/del(7q), or complex (3 abnormalities)	+3
Very Poor: complex >3 abnormalities	+4

Has complex cytogenetics,

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Defining Risk in MDS

Cytogenetic Group

Very Good: del(11q) or –Y	0
Good: normal karyotype, del(20q), del(5q), del(12q), or double including del(5q)	+1
Intermediate +8, del(7q), i(17q), +19, or any other single or double independent clone	+2
Poor: -7, inv(3)/t(3q)/del(3q), double including -7/del(7q), or complex (3 abnormalities)	+3
Very Poor: complex >3 abnormalities	+4

that will give him 4 points.

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Defining Risk in MDS

Hemoglobin, g/dL (g/L)

≥10 (≥100)	0
8 to <10 (80 to <100)	+1
<8 (<80)	+1.5

Has severe anemia with a hemoglobin of 6,

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Defining Risk in MDS

Hemoglobin, g/dL (g/L)

≥10 (≥100)	0
8 to <10 (80 to <100)	+1
<8 (<80)	+1.5

that will give him 1.5 points;

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Defining Risk in MDS

Platelets, $\times 10^3/\mu L$ ($10^9/L$)

≥100	0
50 to <100	+0.5
<50	+1

a platelet count less than 50,

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Defining Risk in MDS

Platelets, $\times 10^3/\mu L$ ($10^9/L$)

≥100	0
50 to <100	+0.5
<50	+1

that will be 1 point.

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Defining Risk in MDS

ANC, $\times 10^3/\mu L$ ($10^9/L$)	
≥0.8	0
<0.8	+0.5

ANC, 0.5,

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Defining Risk in MDS

ANC, $\times 10^3/\mu L$ ($10^9/L$)	
≥0.8	0
<0.8	+0.5

that will give him 0.5 points for a total of 8 points.

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Defining Risk in MDS

ANC, $\times 10^3/\mu L$ ($10^9/L$)

≥0.8	0
<0.8	+0.5

NGS panel showed a p53 = NO POINTS

Of note, the mutation of the p53 gene, although associated with very poor prognosis, is not part of the IPSS-R so it does not count.

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Defining Risk in MDS

IPSS-R Score

8 points	Very-high risk	The patient will need active therapy based on an HMA and should be considered for a clinical trial

Therefore, the answer is 8 points, that is associated with very high-risk disease and very poor prognosis. Therefore, this patient will need active therapy based on a hypomethylating agent, and should also, in addition, be considered for a clinical trial.

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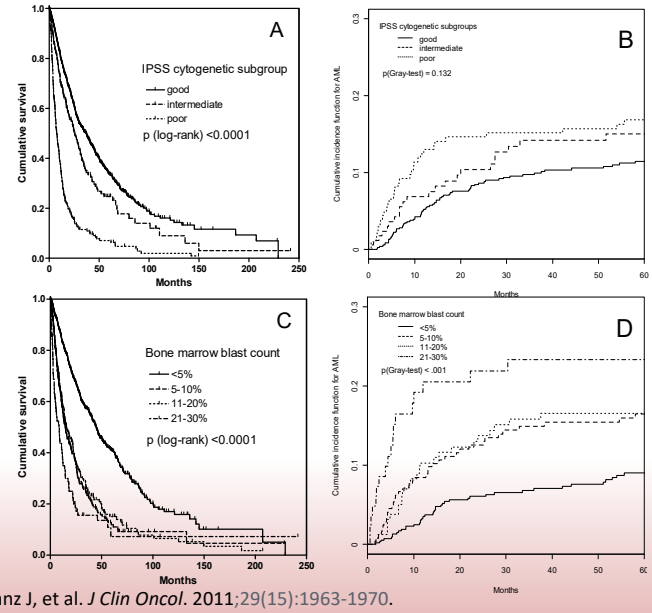
Defining Risk in MDS

Weight of Cytogenetics in Relation to Bone Marrow Blast Count 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;29(15):1963-1970.

The evolution of the IPSS-R comes from original data in the mid-2000s, mainly from the German and MD Anderson groups, that shows that in MDS, cytogenetic alterations had more prognostic weight potentially than that of percentage blasts, that is the characteristic that we traditionally use to allocate risk in our patients.

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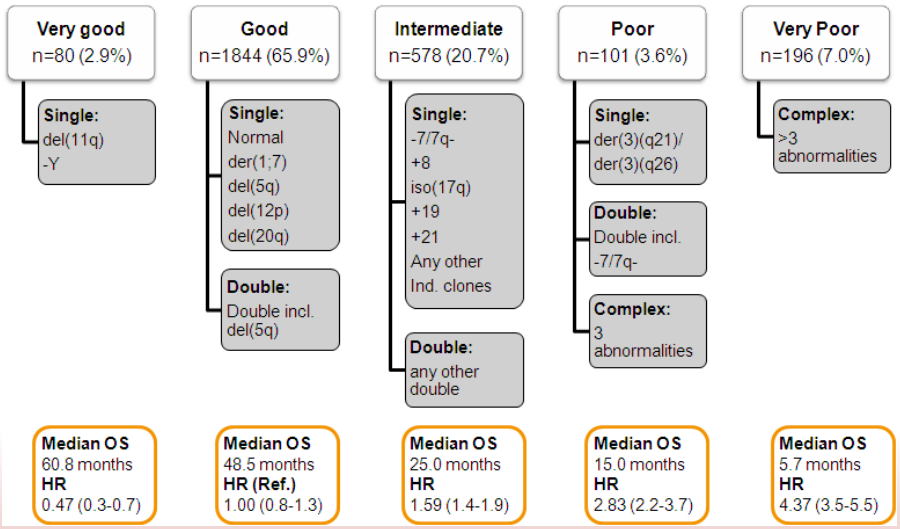
Defining Risk in MDS

Cytogenetic Scoring System in MDS



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

That led to a very large international consortium that developed the cytogenetic scoring system that serves as the scaffold for the IPSS-R. In this system, patients are divided into five cytogenetic categories, from very good, to very poor, good, intermediate, and poor.

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Revised IPSS

- Presented Edinburgh 2011
- N >7000 patients
- German/Spanish cytogenetics
  - 5 instead of 3 subsets
- ANC 0.8
- 5 categories

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

That data was then incorporated into the Revised-IPSS that was originally presented in Edinburgh in 2011, a very large international effort, including more than 7,000 patients, that used the cytogenetic scoring system. The main differences with the IPSS is that the IPSS-R had five subsets, from very low to very high, as opposed to the three that the IPSS had originally, and we had different categories or cutoffs for blast percentage, ANC, and, of course, the cytogenetic alterations that I just described.

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Defining Risk in MDS

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

As you can see on the regional publication, there are different points allocated to these characteristics of cytogenetics, percentage of blasts, hemoglobin, platelets, and ANC.

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Defining Risk in MDS

Revised IPSS

Risk category	Risk score
Very low	≤1.5
Low	>1.5-3
Intermediate	>3-4.5
High	>4.5-6
Very high	>6

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

Again, patients with very low-risk disease will be those having less than 1.5 points; low will be more than 1.5 to 3; intermediate, more than 3 to 4.5; high, more than 4.5 to 6; and very high, more than 6. Our patient, unfortunately, had 8 points.

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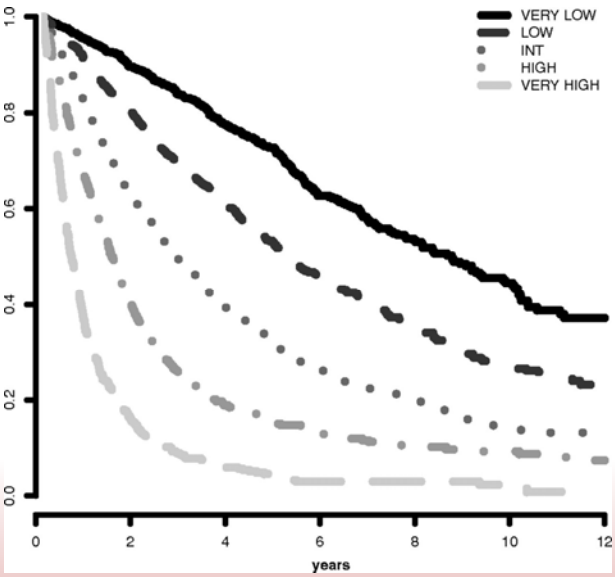
Defining Risk in MDS

Revised IPSS



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

If we look at the Kaplan-Meier plots for survival, those patients with very high risk of disease rarely survive a year with this condition.

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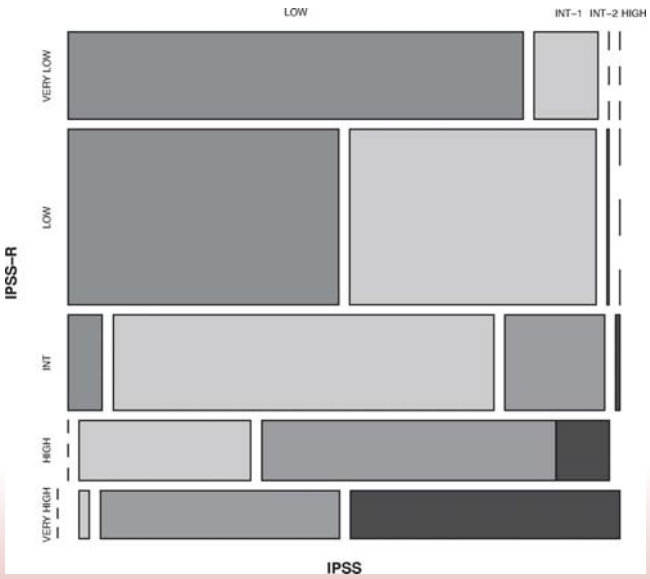
Defining Risk in MDS

Revised IPSS



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

It's also important to notice that when we match the IPSS with the IPSS-R, we see significant differences. This case actually illustrates this, because this patient by the traditional IPSS will have an intermediate risk of disease, mainly because of the low percentage of blasts, and their survival actually will be predicted to be better than what he will really be if you use the IPSS-R, again, mainly based on the cytogenetic alterations that this patient now has.

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Remarks and Conclusion

- IPSS-R gives more prognostic weight to cytogenetics than blast percentage
- By IPSS, score will be 1.5 (int-2)
- NGS not yet incorporated

Therefore, in conclusion, the IPSS-R gives more prognostic weight to the cytogenetics as opposed to the blast percentage. It's a more refined and precise way to prognosticate our patients. Please note that in this particular patient, the next-generation sequencing has not been included. This patient had a p53 mutation that we know is associated with very poor prognosis. We're awaiting a very large international effort that hopefully will incorporate these molecular alterations detected by next-generation sequencing into the IPSS-R. This is the so-called molecular IPSS, that hopefully will come at some point soon and will give us even a more efficient and robust prognostic scoring system for our patients. With that, I want to thank you for your attention.

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