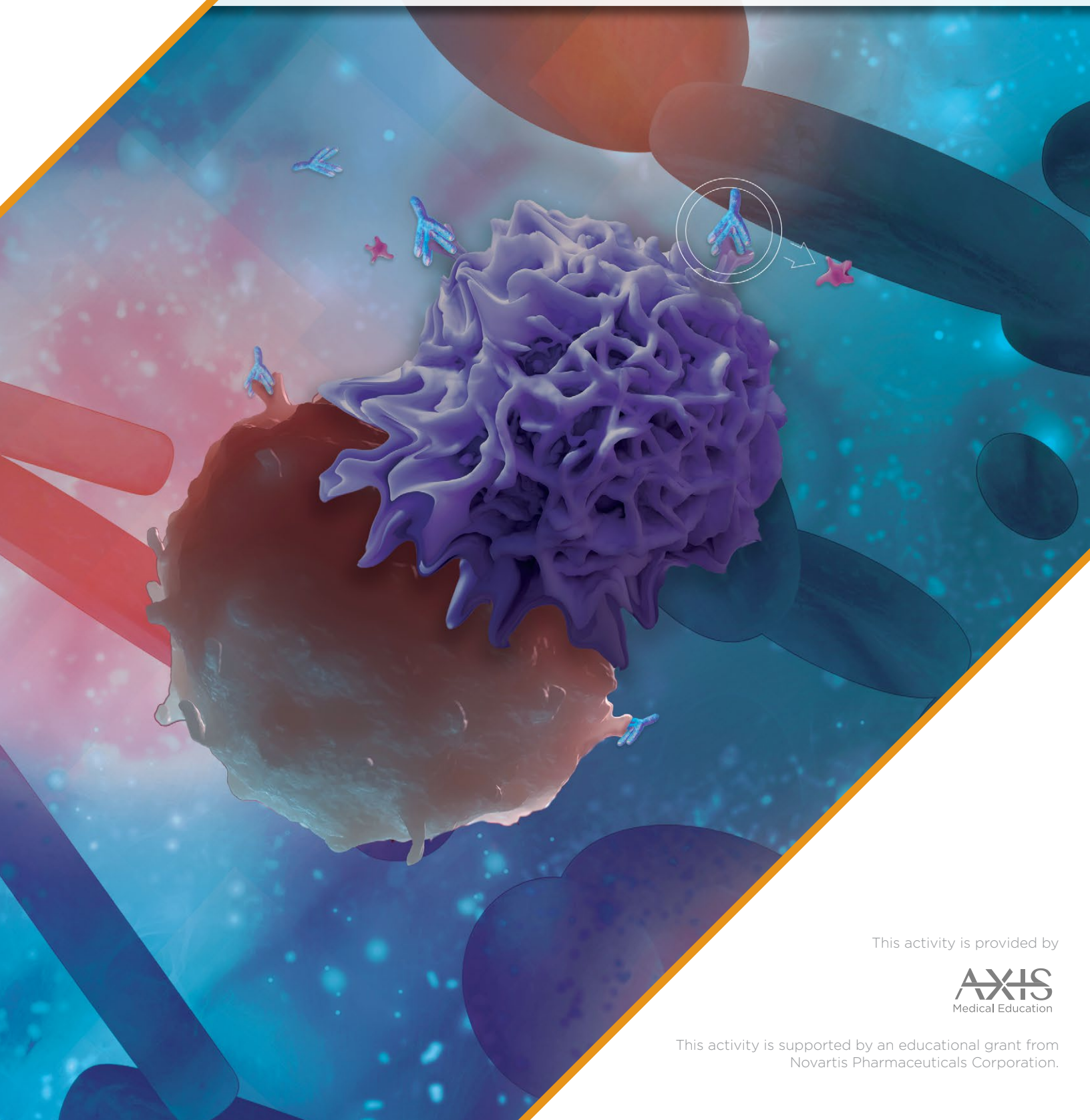
AXIS Medical Education

Harnessing the Power of the Immune System to Manage Higher-Risk MDS

This transcript has been edited for style and clarity and includes all slides from the presentation.



This activity is provided by

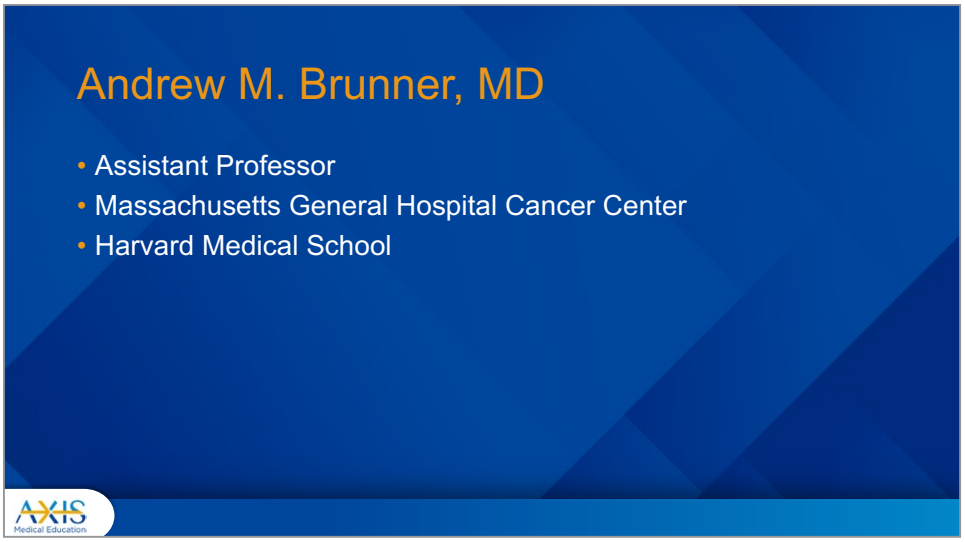
AXIS Medical Education

This activity is supported by an educational grant from Novartis Pharmaceuticals Corporation.

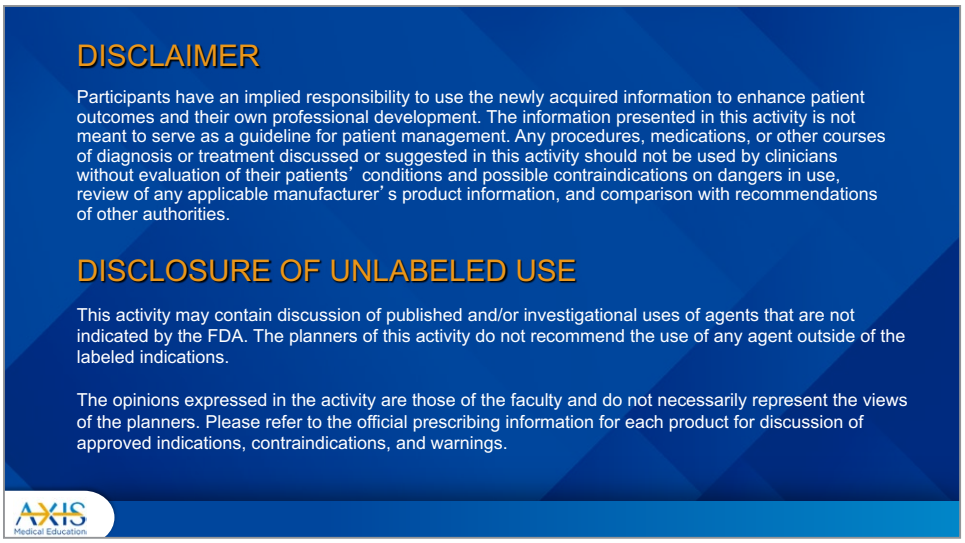
Harnessing the Power of the Immune System to Manage Higher-Risk MDS

Andrew M. Brunner, MD

Andrew M. Brunner, MD: Hello, and welcome to this educational activity entitled, *Harnessing the Power of the Immune System to Manage Higher-Risk MDS*.

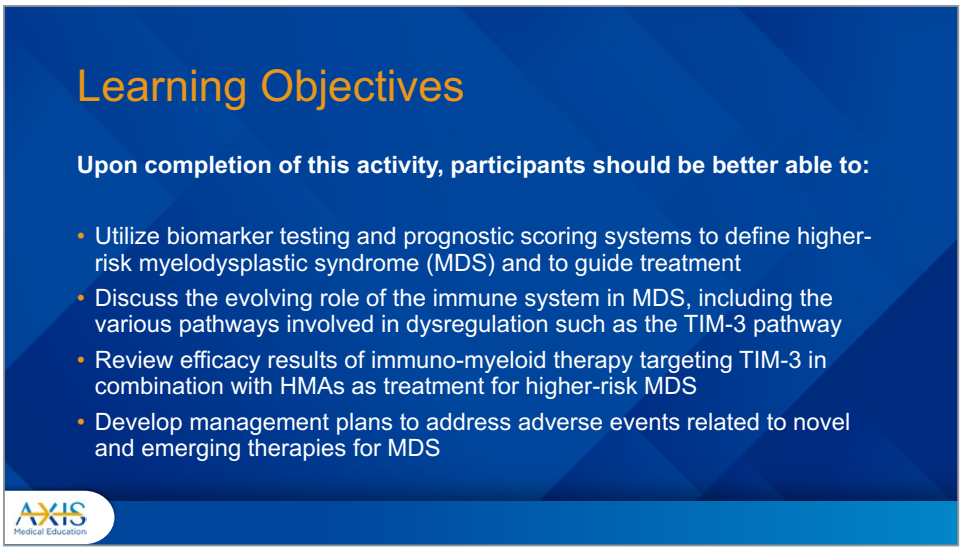


I'm Dr. Andrew Brunner, and I'm an Assistant Professor at Massachusetts General Hospital Cancer Center, and at Harvard Medical School here in Boston, Massachusetts.

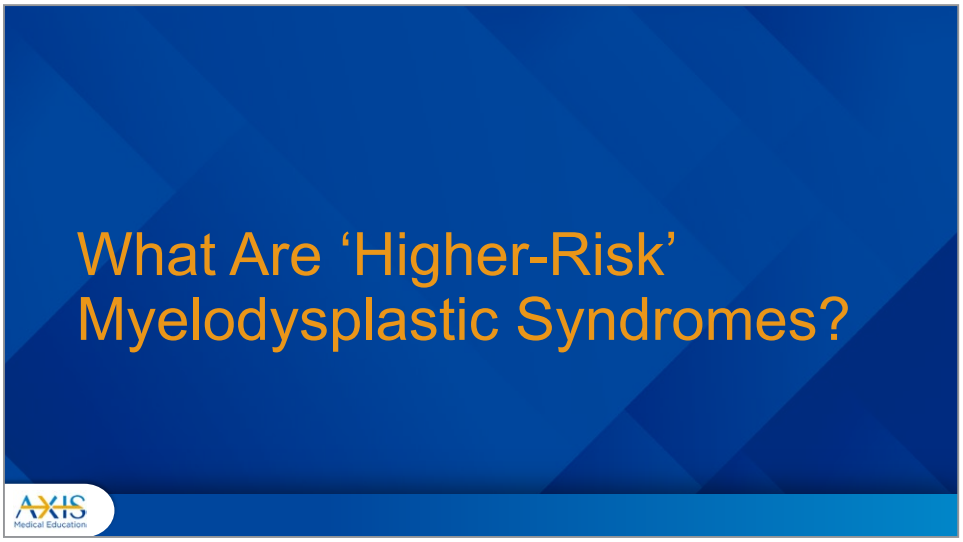


- First, a disclaimer and disclosure, indicating that we may be discussing the off-label use of approved agents, as well as discussing the use of agents that are in clinical development.

- And here are my financial disclosures.



- We have a number of learning objectives. We are planning to discuss how we implement biomarking testing and prognostic scoring systems to define what is higher-risk MDS and help inform treatment of that disease. We're going to discuss the evolving role of the immune system in MDS, including a number of pathways in dysregulation, including TIM3 and CD47. We'll be reviewing results of several immunologic-directed therapies including TIM3, in combination with HMAs, as well as the CD47 inhibiting agents in combination with HMAs for the treatment of higher-risk MDS. And then we'll be discussing management of complications in MDS that might be related both to existing therapies as well as emerging or novel treatments.



- First, how do we define what higher-risk MDS is in the first place?

Patient Presentation

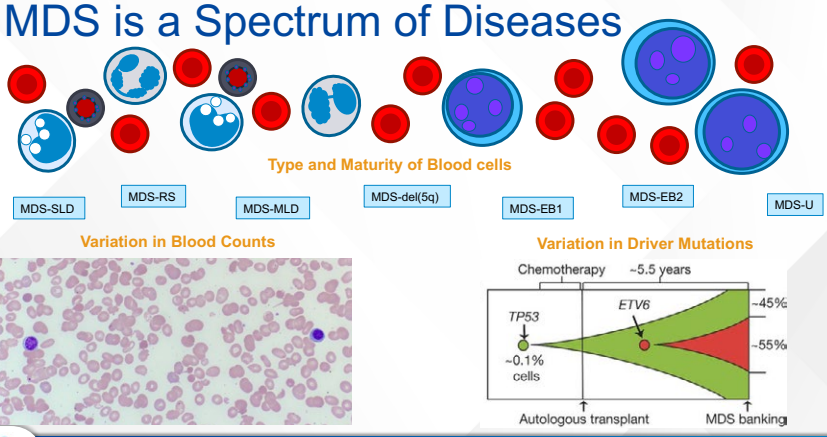
- The clinical features that can be used to identify and characterize high-risk MDS subtypes
- Risk stratification systems based on the modern MDS prognostic models, including IPSS and IPSS-R, along with IPSS-M
- Identifying higher-risk MDS subtypes based on blood counts, percentage of blast cells, cytogenetics, subclonal heterogeneity, hypermethylation of tumor suppressor genes, and unfavorable genetic mutations
- Burden of disease, diagnosis, and biomarker testing in higher risk MDS

AXIS Medical Education

IPSS-M, molecular international prognostic scoring system; IPSS-R, revised international prognostic scoring system; MDS, myelodysplastic syndrome.

So, we have a patient in front of us who presents with a number of symptoms related to their MDS. The most common presenting symptom of MDS is anemia. But many patients will have infectious complications or easy bruising or recurrent bleeding that bring them to medical attention. Often, the progression to medical attention is slow and can be insidious in a number of patients; patients actually have low enough blood counts that they cause clinical problems.

MDS is a Spectrum of Diseases

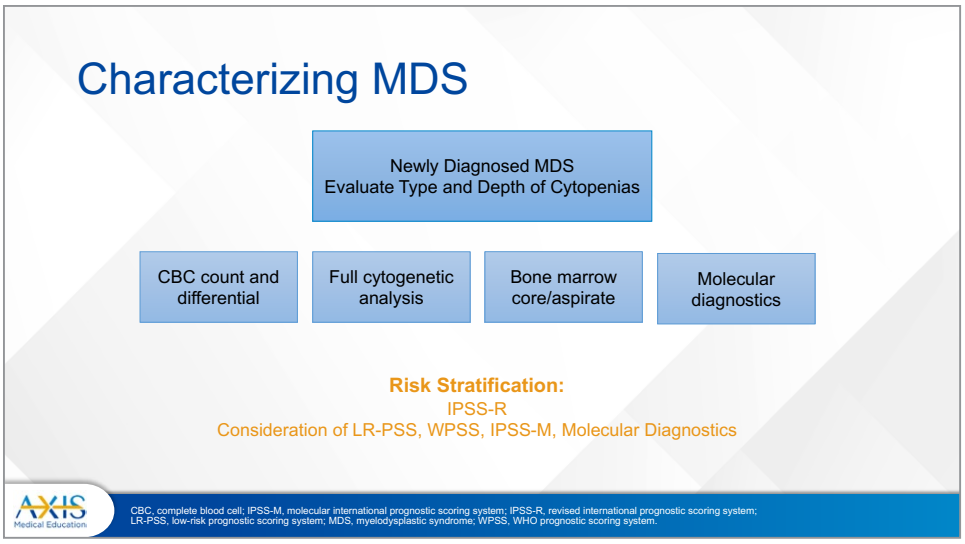


AXIS Medical Education

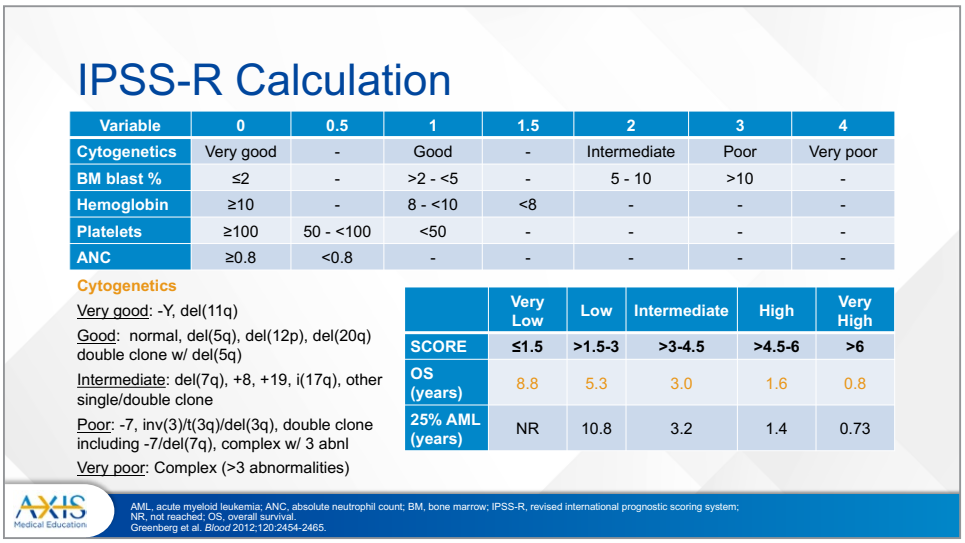
EB, excess blasts; MDS, myelodysplastic syndrome; MLD, multilineage dysplasia; RS, ring sideroblasts; SLD, single lineage dysplasia; U, unclassifiable.
Wong et al. *Nature* 2015;518(7540):552–555.

When we're identifying a case of MDS, and when I meet a patient in clinic, one of the first things I tried to do is understand how to best subclassify their disease. There's a lot of ways that we have to classify MDS. One of the ways that we can subgroup it is by what specific pathological subgroup it is. So, we have been historically using the WHO classification. There are a few new classification systems that have just been proposed and recently published in 2022, the ICCC and the WHO updates.

We use pathological blood count and molecular cytogenetic characteristics of the disease to box that MDS into a group that behaves similar to other patients who have that subtype of disease. One of the first things we do is try to characterize what type of MDS a given patient might have.



- Beyond simply morphologic assessment and assessing a patient by the pathology, we also try to characterize disease according to what's going to happen to that patient. And so anytime somebody comes to clinic with a possible new MDS, we'll do lab work to identify the type and depth of their cytopenias, it involves a CBC and differential, we do a full karyotype of patients, we get a bone marrow core and aspirate. And we also do a broad panel of molecular diagnostics. Molecular testing is increasingly important in both the classification of MDS, the diagnosis of MDS, as well as the risk stratification.



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	-	-	-	-	-

Cytogenetics

Very good: -Y, del(11q)

Good: normal, del(5q), del(12p), del(20q) double clone w/ del(5q)

Intermediate: del(7q), +8, +19, i(17q), other single/double clone

Poor: -7, inv(3)/t(3q)/del(3q), double clone including -7/del(7q), complex w/ 3 abnl

Very poor: Complex (>3 abnormalities)

	Very Low	Low	Intermediate	High	Very High
SCORE	≤1.5	>1.5-3	>3-4.5	>4.5-6	>6
OS (years)	8.8	5.3	3.0	1.6	0.8
25% AML (years)	NR	10.8	3.2	1.4	0.73

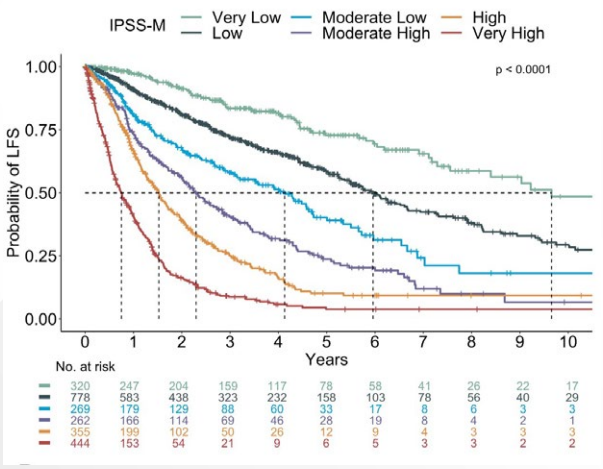
- Recently, we have relied upon the IPSS-R to best classify patients as far as their disease risk, meaning what's going to happen to them after the diagnosis and what is the likeliness that will need to intervene.

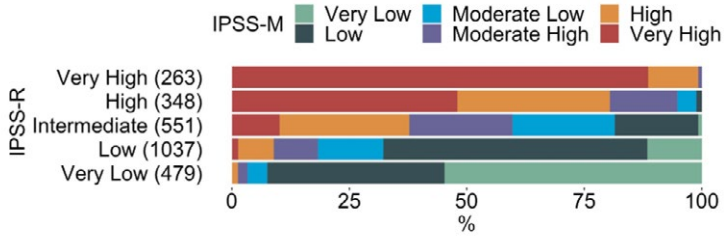
  There are a lot of other tools that I use in practice. Depending on the scenario, so for lower-risk patients, I might try to further classify them, there's a low-risk prognostic scoring system. The IPSS is a nice scoring system that has prognostic information across the history of disease.

  And recently published was the IPSS-Molecular that incorporates many of the same risk factors that are used in IPSS-R, but also uses molecular profile of MDS to better characterize what is likely to happen to that patient.

  Here is the IPSS-R and how each variable in that scoring system is weighted. We score, or prognosticate based on generally three things: how low the blood counts are. This uses hemoglobin, platelets, and neutrophil count, to try to add a certain amount of risk. You can imagine, people who have lower blood counts, have an increased amount of risk; people whose blood counts are more stable may not have as much risk. It uses blast percentage in the bone marrow. And so similarly, a higher percentage of blasts, makes sense that they would be at higher risk of progressing to leukemia, or having a complication or disease and having a low or normal blast count is lower risk of those endpoints. The big advantage that IPSS-R had over prior scoring systems, and one that we still use now is that it collected cytogenetic information on many patients. So we get very granular risk based on cytogenetics. Shown here is how there are categories between very good, good, intermediate, poor, and very poor features of the cytogenetic analysis that may influence the risk of progression or death.

IPSS-M





- Poor LFS, OS, and AML transformation:
  - TP53 multi-hit mutations (7%)
  - MLL PTD (2.5%)
  - FLT3 mutations (1%)
- More favorable clinical course:
  - SF3B1, depending on commutations

AML, acute myeloid leukemia; IPSS-M, molecular international prognostic scoring system; LFS, leukemia-free survival; OS, overall survival; PTD, partial tandem duplication.
Bernard et al. ASH Annual Meeting & Exposition, December 2021, Abstract 61.

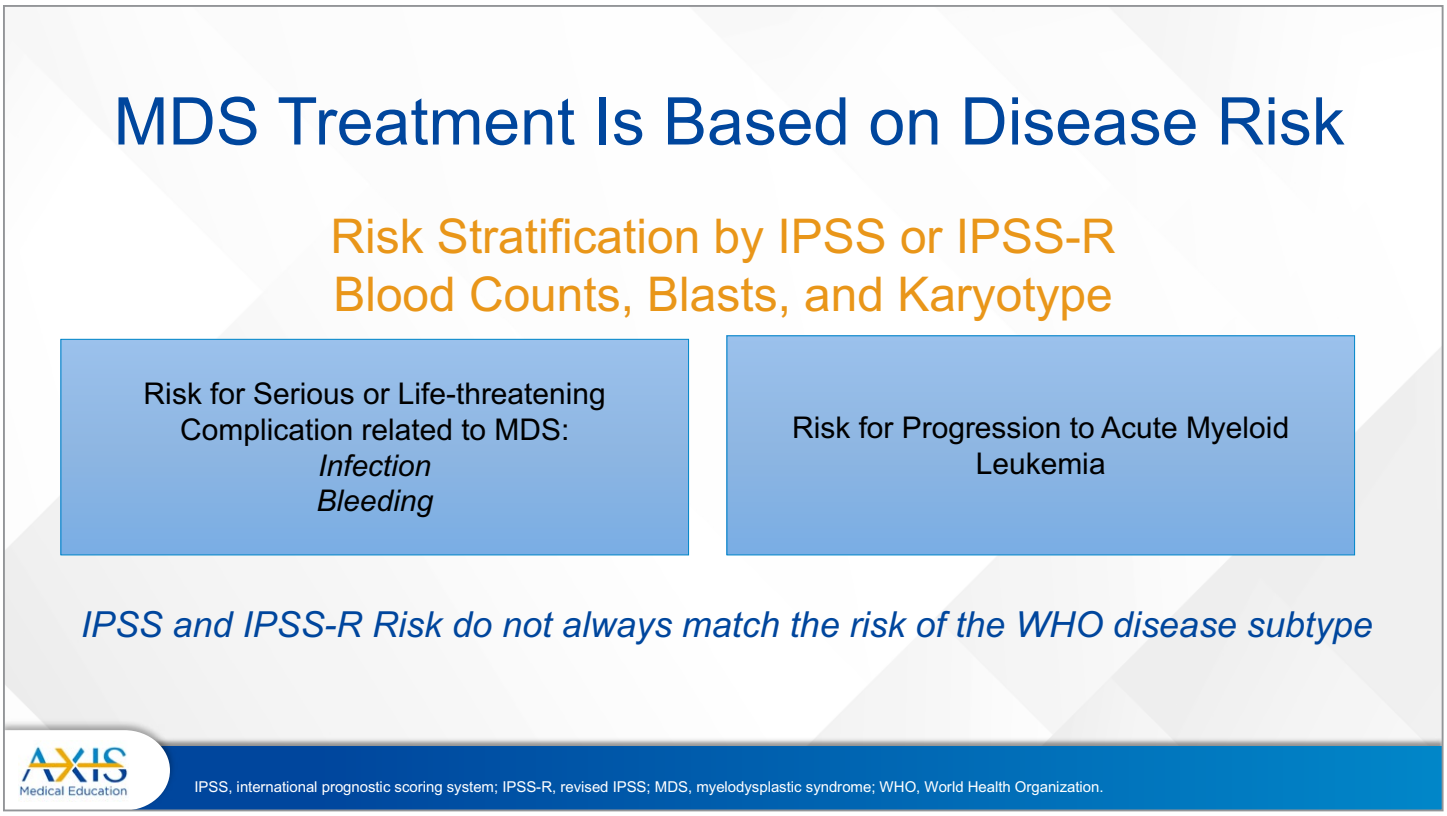
Recently published is the molecular IPSS, which adds on to many of the features of the IPSS-R, also molecular profile. And you can see here in the Kaplan-Meier curve, that this risk stratification system does a very good job at distinguishing patients who are going to live with disease. These patients are older, and so in the very low risk group. They essentially coexist with their disease. That's an important feature to find, because these are patients where you can really predict that they'll have a long period of disease and that management of symptoms or side effects of the MDS itself are probably more relevant. It also does a very good job at predicting patients who have a very high risk of a complication of their disease within months. So more than half of patients in the very high-risk group have either progressed to leukemia or died within months after diagnosis. This is a high-risk group that needs intervention early.

And then there's a wide spread of patients that have different courses of disease according to their risk. It nicely bifurcates patients into three higher risk groups, where within two and a half years, they will have complications of disease. And, three lower-risk groups where their risk of immediate progression is relatively lower.

The number of mutations stand out. These coexist with some of the work that had been done prior to this analysis. The presence of P53 multi-hit mutations are very poor risk in this dataset. And, identify a patient subgroup that's high risk of leukemia or of death from their disease in the near term.

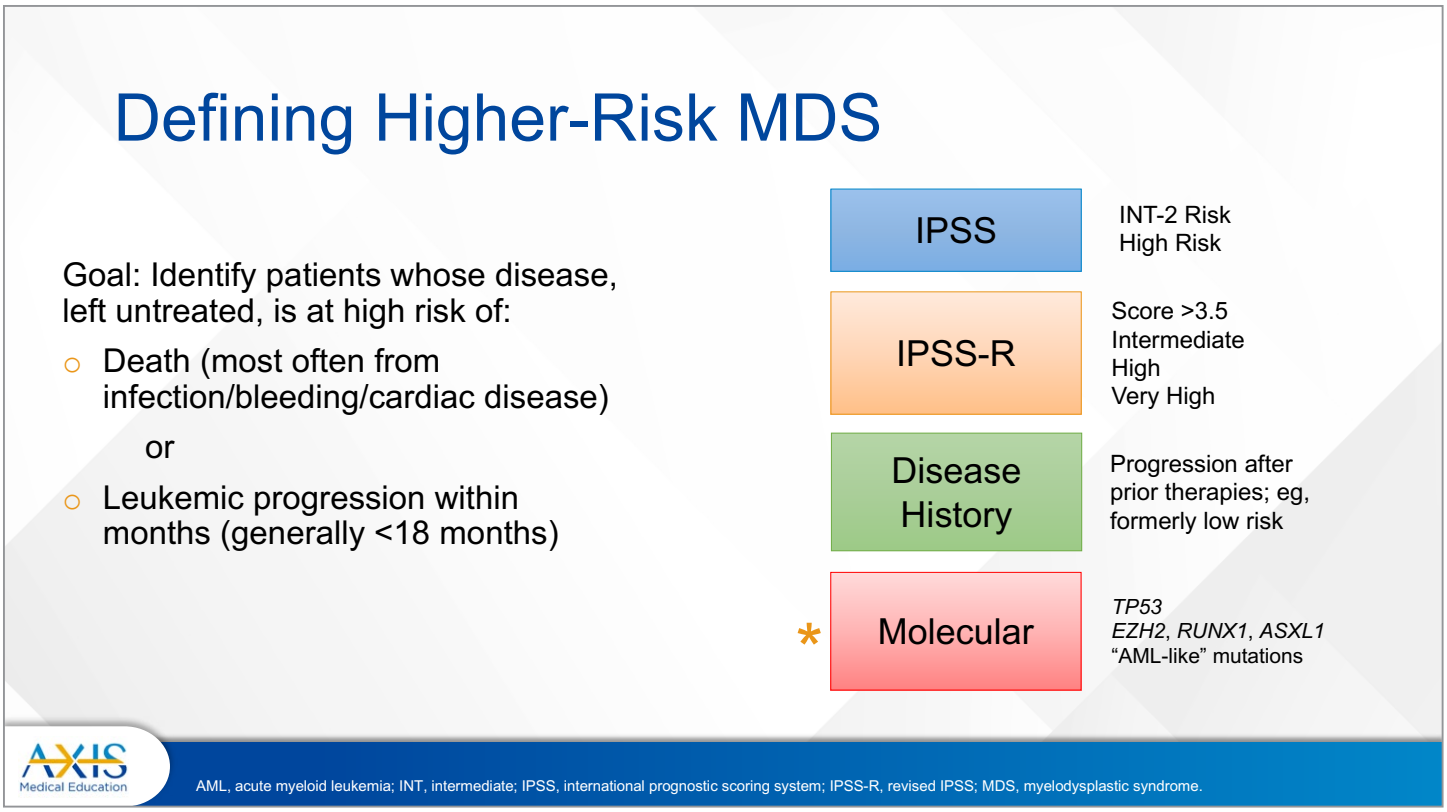
And there are rare subgroups, although when you look at a population level, they really add up. For instance, with MLL-PTD, or with *FLT3* mutations, they also are at risk of disease worsening or progression to leukemia.

There are also patients that we confirm from this data have a more favorable clinical course. So SF3B1 mutations, in particular, certain, SF3B1 mutations that don't have certain higher risk of mutations. These patients live a long time with their disease and their management really differs from people who are going to have complications within a year.



So when I meet a patient with MDS, I'm really trying to prognosticate what's going to happen to you in the coming year. Do I need to treat you, to try to impact your disease, or are you going to coexist with this? So I risk stratify patients. And then I really think about this—do you have a risk of a serious or life-threatening complication, infection and bleeding being the most, immediate problems generally from the cytopenias themselves? Or do you have a risk of progressing to acute myeloid leukemia?

It's important to recognize that all these scoring systems are imperfect. They don't always line up. And especially as we learn more, I often am using multiple scoring systems, especially for people who don't seem to "be behaving," as we expect from their disease risk. So, if monitoring somebody over time, they don't seem to fall into that low-risk group that you think they are, it may be that using a different, scoring system does identify a higher-risk feature that merits consideration are some different approaches to treatment.

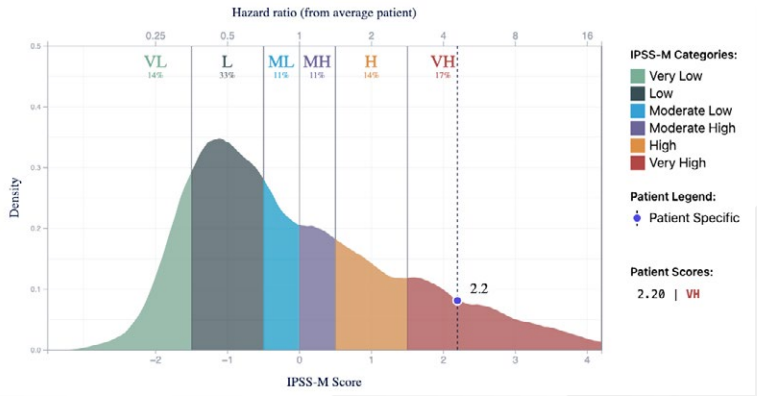


So how do we define what is higher-risk MDS, and what to do with those patients. Really, we want to find patients where the benefit from chemotherapy or transplant outweighs the risks of the toxicities of those therapies themselves. And so again, using all these metrics, most of our trials with azacitidine were based on the old IPSS score. So that'd be intermediate 2 or high-risk patients. Those patients are the ones who benefited most from azacitidine. But there are other ways that we think about it. So, patients with IPSS-R score greater than 3.5, patients in the top three IPSS-M risk categories, patients whose disease has progressed from prior therapy, especially patients who thought were low risk that they have now had their disease progress on multiple lines of therapy. And in particular, the role of molecular mutations that impact risks like *TP53*, AML-like mutations like *FLT3* or MLL-PTD.

Higher-Risk MDS Case

Patient JB:

- 80-year-old woman with progressive anemia
- CBC and differential with WBC 2, ANC 0.6, Hgb 8 g/dL, platelets 45
- Bone marrow biopsy: hypercellular, 12% CD34+ blasts, no ring sideroblasts
- Cytogenetics: 46,XX,del7q
- Molecular studies: mutations in *BCOR*, *CBL*, *U2AF1*

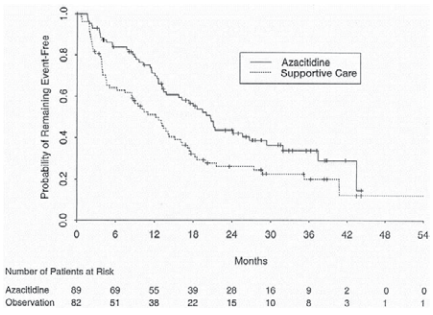


ANC, absolute neutrophil count; CBC, complete blood cell; Hgb, hemoglobin; IPSS-M, Molecular International Prognostic Scoring System; WBC, white blood cells.
Bernard et al. ASH Annual Meeting & Exposition, December 2021, Abstract 61.

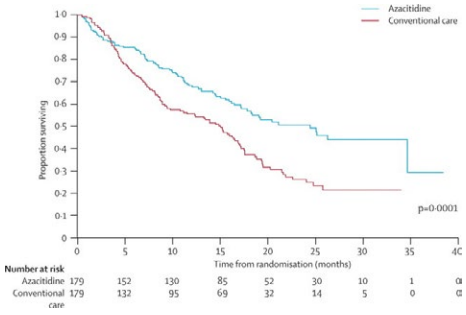
Here's an example of a patient I might see in clinic. Patient JB is an 80-year-old woman. She comes to clinic, she's had a progressive anemia, again, the most common presenting symptom being anemia. She has a blood count, showing that her white count is 2. She has a fairly low neutrophil count 600. Her hemoglobin is at 8 grams per deciliter, and she has a platelet count of 45. If you look at her blood counts, the most immediate potentially symptomatic blood count is probably her hemoglobin. But you do have to consider if her platelets are further dropping, does she have a bleeding diathesis that you haven't explored yet. She may have some shortness of breath that brings her in. Prompt to get a bone marrow biopsy. She has a hypercellular marrow, there are 12% CD34-positive blasts, no ring sideroblasts. And on her cytogenetic analysis, she has 46, XX with a del 7q identified. So if you look at her molecular studies, she had a panel, tested at baseline, and she has mutations identified in BCOR, CBL, and U2AF1.

Now, I think it is important to think about panel-based testing, for instance, in this scenario, especially as it impacts prognosis, and with these new scoring metrics that involve a number of mutations in assessing the risk. You'll notice that *BCOR*, *CBL*, and *U2AF1*, at least right now do not have an approved therapeutic target. Even though there are some that are in clinical trials to try to target these. The main benefit of getting this mutation profile is to allow you to get a better understanding of her disease risk. And indeed, by incorporating these mutations into her risk profile, you can estimate that she has very high-risk MDS that, within a year, her risk of progression to leukemia or of dying of some complication of her MDS is quite high, and that you'd want to start some form of treatment for her.

Higher-Risk MDS: Hypomethylating Agents



CALGB 9221: OS 20 mo (AZA) vs. 14 mo (Conventional Care)



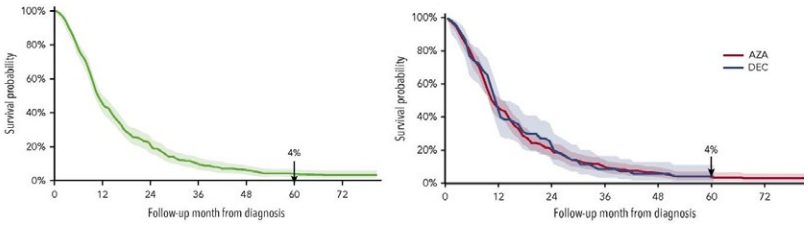
AZA001: OS 21.1 mo (AZA) vs. 15.0 mo (Conventional Care)

CALGB, Cancer and Leukemia Group B; AZA, azacytidine; OS, overall survival; mo, months.
Silverman et al. *J Clin Oncol.* 2002;20(10):2429-2440; Fenaux et al. *Lancet Oncol.* 2009;10(3):223-232.

- Higher-risk MDS, the backbone of therapy remains the use of the so-called hypomethylating agents or DNA methyltransferase inhibitors. The AZA-001 trial built upon an older CALGB study that showed that azacitidine has a survival benefit compared to conventional care. Patients could receive either transfusion support, AML-like chemotherapy, or low-dose cytarabine in the AZA-001 arm. And there was a survival benefit in that trial that has yet to be improved upon in phase 3 clinical trials in MDS.

  Azacitidine, and to another degree, decitabine, remain our standards of care in MDS. And a lot of effort has been ongoing to try to identify ways to improve upon the therapy that they offer.

HMAs in Myelodysplastic Syndromes

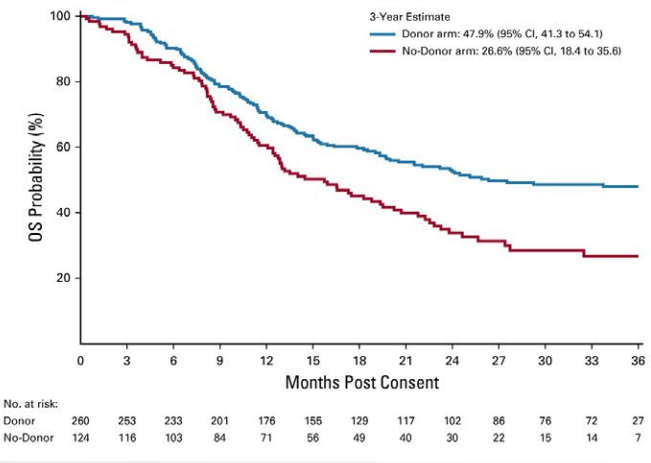


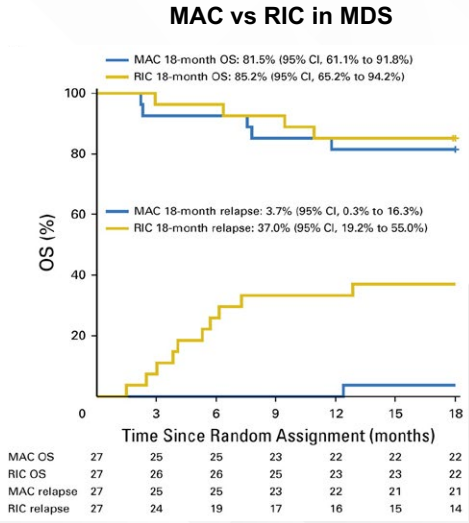
SEER-Medicare, all patients, irrespective of MDS disease risk

AZA, azacitidine; DEC, decitabine; HMAs, hypomethylating agents; MDS, myelodysplastic syndrome; SEER, Surveillance, Epidemiology, and End Results.
Zeidan et al. *Blood* 2018;131:818-821.

- Although they remain our standard backbone therapies, and they do provide a survival benefit compared to patients who don't receive hypomethylating agents, it is also true that they are imperfect therapies. This is a nice analysis looking at the 5-year survival of patients who start on either azacitidine or decitabine in the US populations or population-based registry analysis, and it showed that by 5 years, under 5% of people are alive. And so even though we institute these therapies for our patients, we really have to move the marker to a higher point, because the reality is that this 5-year survival is worse than many other cancers. And we have yet to really improve upon it.

Role of Transplant





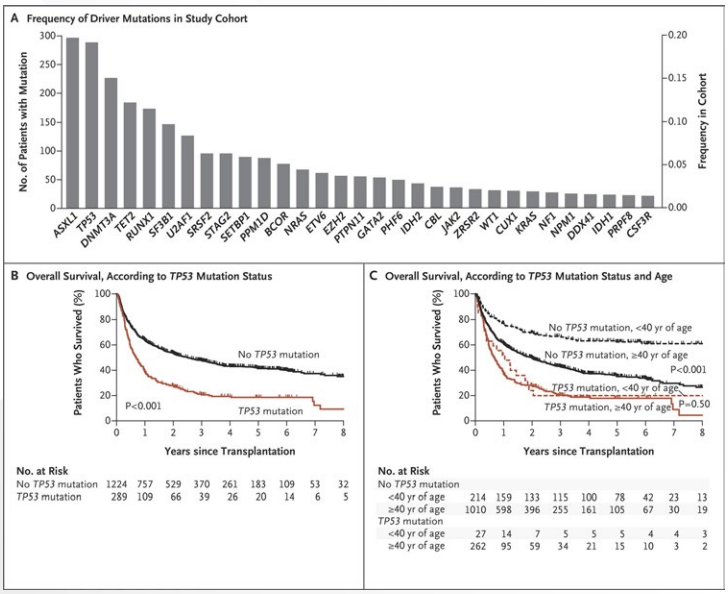
MAC, myeloablative conditioning; MDS, myelodysplastic syndrome; RIC, reduced-intensity conditioning; OS, overall survival.
BMT CTN 1102. Nakamura et al. *J Clin Oncol*. 2021;39(3):3328-3339; Scott et al. *J Clin Oncol*. 2017;35(11):1154-1161.

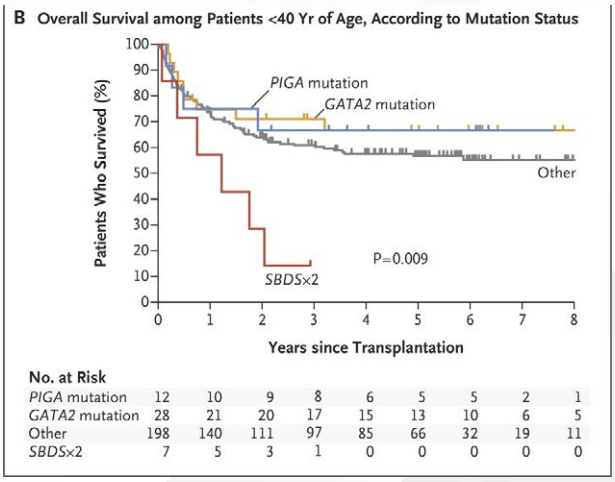
- So how can we? Well, we've known for some time that allogeneic transplant seems to be a potential therapy for many patients with MDS, especially as we learn how to more safely administer transplant to patients who are older. Median age of patients with MDS in their 70s. So, being able to extend transplant to select patients who are older really has a big impact in our thinking about MDS and higher-risk MDS in particular.

There have been some nice studies recently showing that patients who undergo transplant, go into transplant early. So early referral to transplant, within the first several months after higher-risk MDS diagnosis, shown here from the BMT CTN 1102 trial, can be associated with improved survival. Those patients who were able to go with a donor to transplant early on show early separation and survival curve that persists throughout this study.

We also have learned that we can extend conditioning regimens more safely to older patients. So shown here is a trial randomizing myeloablative conditioning compared to reduced intensity conditioning in patients with MDS show that survival is fairly similar, although patients who are receiving a reduced-intensity transplant do have a higher rate of cumulative relapse.

Mutations and Transplant



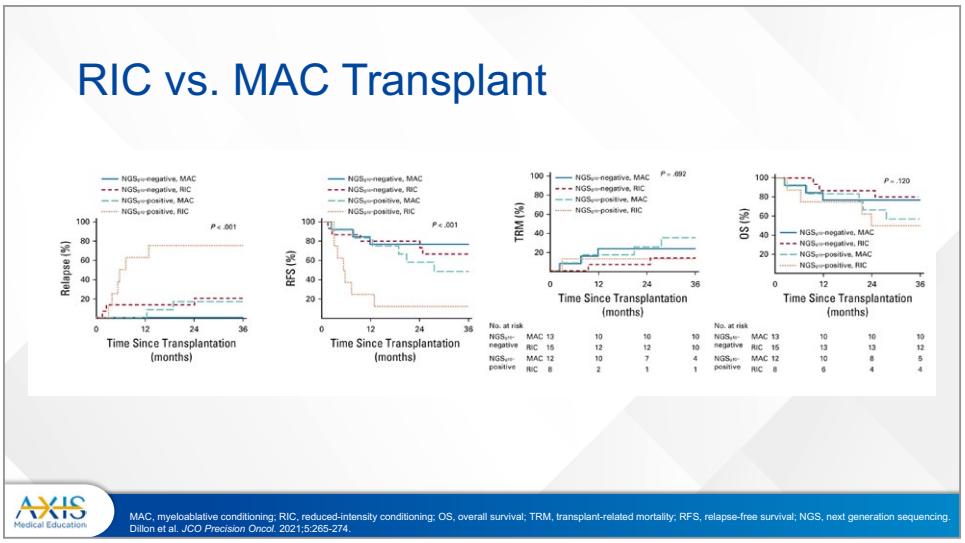


Does pre-transplant therapy/response impact post-transplant outcomes?

Lindsley et al. *N Engl J Med*. 2017;376:536-547.

- So how do we further refine use of transplant in MDS patients? And this is particularly relevant to higher-risk MDS patients. Well, one thing that we can do is we can understand how mutation profiles influence transplant outcomes. So shown here is a nice study. This also utilized the CIBMTR dataset to evaluate how pre-transplant mutation profile impacts post-transplant outcomes.

  One of the things that we find here that we also see in the upfront diagnosis, is that patients with *TP53* mutations, they remain a high-risk patient cohort, even with transplant. They really need new approaches to treatment. Similarly, there are certain high-risk mutations for younger patients that are worth evaluating. Again, bringing to light how our understanding of the clonal profile of MDS plays an increasing role in how we tailor therapy down the line. And also identifies patients who really need new treatments at diagnosis with transplant and perhaps even after transplant.

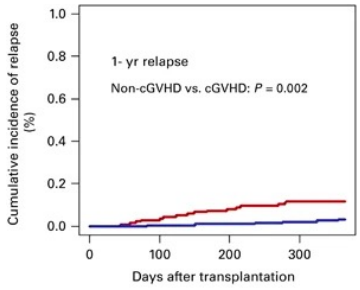


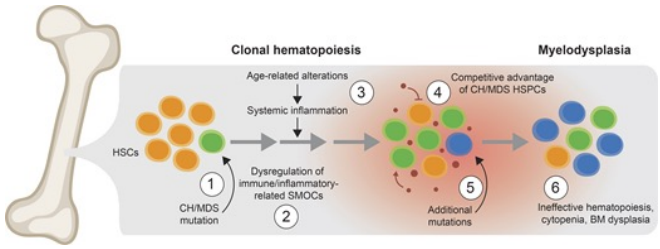
- We're getting hints, at how to improve upon transplant or how to identify even high-risk patients that may benefit more. One of those things is if we are going to use a reduced-intensity conditioning regimen, we just saw that those patients have a higher rate of post-transplant relapse. And can we do something to improve their disease control pre-transplant to try to yield a better post-transplant outcome? And so shown here is a nice analysis of that, that same study that randomized patients to reduced intensity versus myeloablative conditioning. It showed that patients who have myeloablative conditioning, their pre-transplant molecular burden doesn't seem to matter as much, um, in predicting post-transplant relapse. However, for patients who received a reduced-intensity conditioning regimen, which again are the majority of patients who undergo transplant with MDS, most patients are older. So if you're going to consider a transplant, many of them would be better candidates, or may only be candidates for reduced-intensity regimens. Those patients who have a higher disease burden pre-transplant, really do have a higher rate of relapse.

- How do we improve upon our current therapeutic repertoire for high-risk MDS?

Altered Immunity in MDS

- How the altered immune system may play a therapeutic role in MDS
- How an altered immune system may impact MDS pathogenesis





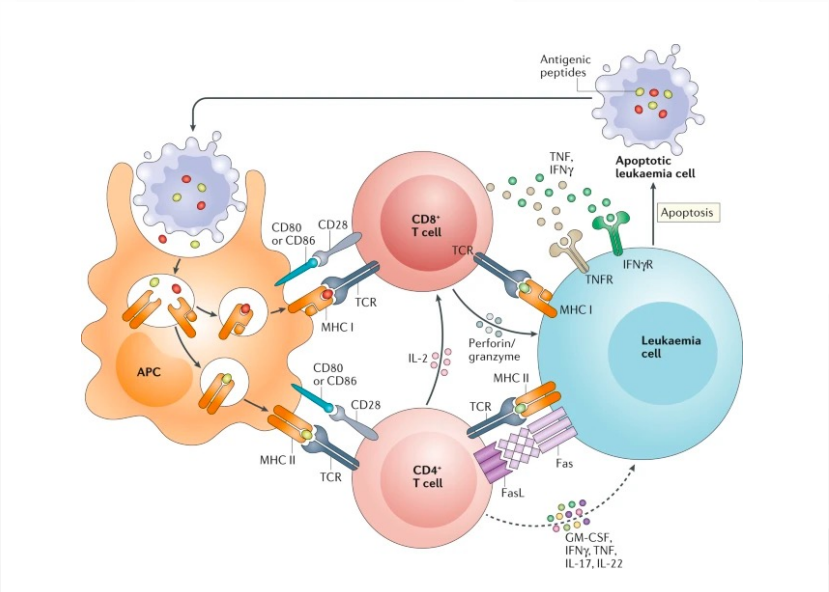
BM, bone marrow; cGVHD, chronic GVHD; GVHD, graft vs host disease; MDS, myelodysplastic syndrome; HSCs, hematopoietic stem cells; CH, clonal hematopoiesis; SMOCs, supramolecular organizing centers; HSPCs, hematopoietic stem and progenitor cells.
Mo et al. *Bone Marrow Transplant.* 2015;50:127-133; Trowbridge et al. *J Exp Med.* 2021;218:e20201544.

One of the things that I'm going to talk about in particular is how we can think of the immune system in MDS. Transplant we spent some time on because it is one of the ways in which we most manipulate the immune system. It's our original immunotherapy to replace the immune system completely, replace the bone marrow, and to evoke some sort of graft-versus-leukemia effect.

And so how can we use what we've learned over the last decades in the care of MDS to try to identify novel therapeutics and in particular immune-based therapies for this disease? And so we know that as mentioned, there is evidence that after transplant, one of the ways in which transplant may be effective at long-term cures in MDS, not just the intensity of treatment that you can deliver pre-transplant with conditioning therapy, and not just the fact that you've replaced the bone marrow with a "healthier" bone marrow, but there is also likely a graft-versus-leukemia effect. And we see this indirectly, for instance, through the way in which chronic graft-versus-host disease seems to be associated with lower rates of relapse, not just in AML and other cancers, but also in MDS patients who are transplanted for MDS who develop some degree of chronic graft-versus-host disease. Those patients do seem to have lower rates of long-term relapse. And so that's one way in which we can try to manipulate the immune surveillance. This is graft-versus-leukemia effect. But even in patients who don't have a donor graft, can we manipulate the existing T cells to act more like donor cells and elicit some sort of intrinsic T cell versus leukemia effect?

Then we also are increasingly understanding how alterations in our immune system, loss of immune surveillance, chronic inflammation, how all of these play a role in the expansion of and progression of MDS. And I think that where this has really become an interesting field, is our understanding of clonal hematopoiesis. As we get better and better tools, we see that more and more people will have some degree of clonal hematopoiesis that can be characterized as we age, and that something changes when we get into our 60th, 70th year of life, where suddenly those clonal populations can expand and become a dominant producer of our blood. And so, while they expand, and they become a larger section of our blood that's produced by that clonal population, they're also not as good at it. So we have a higher and higher percentage of our blood made by this same clone. And yet, we become more and more anemic or thrombocytopenic. In a certain subset of patients that then go on to frankly, progress or present with MDS.

Allogeneic Transplant and MDS/AML



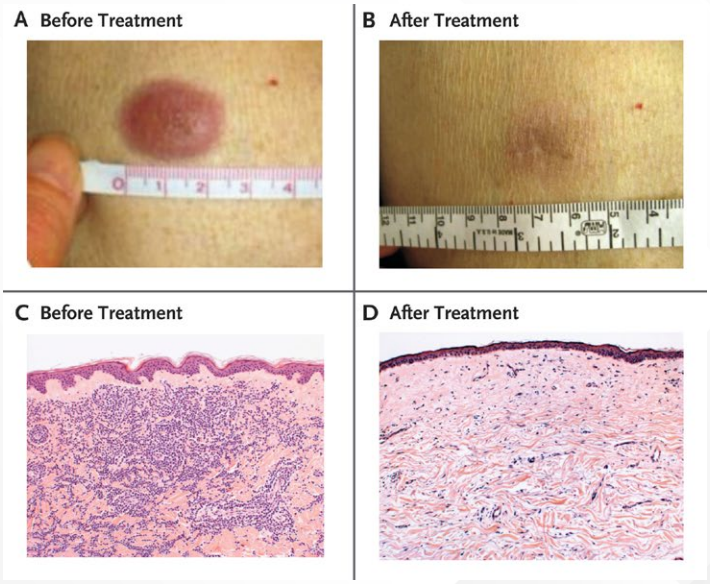
AML, acute myeloid leukemia; APC, antigen-presenting cell; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; MDS, myelodysplastic syndrome; TCR, T-cell receptor; TNF, tumor necrosis factor.
Blazar et al. *Nat Rev Clin Oncol*. 2020;17:475-492.

So how do we understand how this evolving change in our immune surveillance and the inflammatory microenvironment? How does that permit the progression of MDS? And so, one of the ways that we might learn how to use the immune system in MDS is by thinking of how allogeneic transplant interacts with MDS and AML cells to elicit a graft-versus-leukemia effect and what role that plays in the prevention of relapse.

If we understand how we get that effect from allogeneic transplant, can we then take that effect and try to use it in MDS or other myeloid neoplasms to try to teach our own intrinsic T cells, not cells that get donated, but teach our own T cells how to recognize leukemic progenitors and how to eradicate them? And so you can see here an example of how our understanding of the allogeneic transplant interacts with CD8- and CD4-positive T cells, but also with antigen-presenting cells, as well as other cells that are involved in innate and adaptive immunity. These can include macrophages. These can include NK cells.

As we learn more about it, we are understanding that it's really an orchestra that we're having many different cell populations activated against the leukemic cells to maintain disease control.

Immune Checkpoint Inhibition in MDS/AML



AML, acute myeloid leukemia; MDS, myelodysplastic syndrome.
Davids et al. *N Engl J Med*. 2016;375:143-153.

And so that idea that we can reactivate the immune system has been explored somewhat, especially in the post-transplant setting. This was an interesting paper, now about 8 years ago, where patients who had MDS or AML received immune checkpoint inhibition. This was with a CTLA-4 inhibitor, ipilimumab. A number of patients had responses perhaps some of the most interesting though, were a number of patients with AML or MDS who had relapse in the skin or extramedullary disease. And after administering checkpoint inhibitor, that seemed to recover graft-versus-leukemia effect and eradicate these sites of extramedullary disease.

This was one of the first clinical examples that fueled the field to try to understand how can we better use the immune system as a therapeutic in the treatment of MDS or AML.

Challenges with Canonical ICIs in MDS

Response	Arm A (azacitidine + durvalumab) (N = 42)		Arm B (azacitidine) (N = 42)		*P*
	No. (%)	95% CI	No. (%)	95% CI	
ORR (CR + PR + mCR + HI)	26 (61.9)	47.22-76.59	20 (47.6)	32.51-62.72	.1838
CR	3 (7.1)	0.00-14.93	4 (9.5)	0.65-18.40	
mCR	15 (35.7)	21.22-50.21	8 (19.0)	7.17-30.92	
PR	0		0		
HI only	8 (19.0)	7.17-30.92	8 (19.0)	7.17-30.92	
SD	6 (14.3)		3 (7.1)		

Median OS (11.6 months vs 16.7 months; $P = .74$)

Median PFS (8.7 months vs 8.6 months; $P = .93$)

AXIS Medical Education

CR, complete response; HI, hematologic improvement; mCR, median CR; MDS, myelodysplastic syndrome; ICI, immune checkpoint inhibitor; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease.
Gerds et al. *Blood Adv*. 2022;6(4):1152-1161.

Since that time, we've started to test a number of canonical ICIs or immune checkpoint inhibitors in MDS. Canonical, meaning agents that are directed toward either CTLA-4, or toward PD-1 and PD-L1. These were some of the earlier discovered targets in solid tumors. A lot of our experience in MDS or AML, or other blood cancers with the use of immune checkpoint inhibitors really came out of the solid tumor experience and trying to recapitulate that in hematologic malignancies.

Here's an example of a randomized trial. And I think that this illustrates one of the difficulties that we have with directly incorporating some of the discoveries that have been found in solid tumors. You can see that there was no significant difference between these two arms. One of these arms was azacitidine with durvalumab added to it, and the other was azacitidine alone.

The overall response rate was not significantly different. There's a numerically higher number of patients who responded in a combination arm. But those responses are really driven by an increase in the number of patients who had a marrow CR. And I think this illustrates how challenging it is for us to characterize our responses in MDS into meaningful responses.

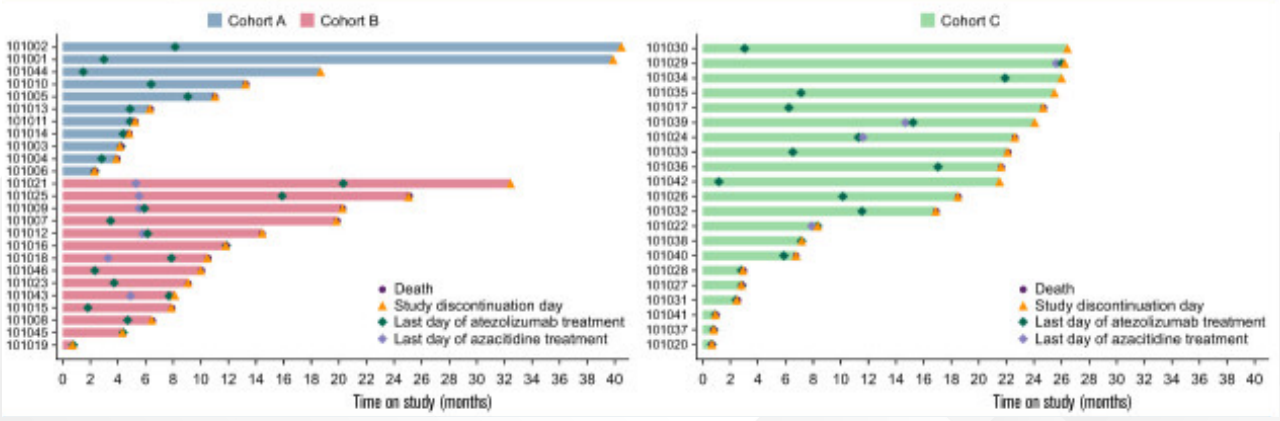
A marrow CR means that you had increased blasts, typically, and that they have decreased by at least half to less than 5%. But it doesn't have any necessary linking to the improvement in blood counts as well. And so it's challenging because it's hard to know, are these patients benefited by the use of this therapy combination?

If you look at them marrow CR rate, if they have suppression of their blasts, does that translate into anything meaningful? And one of the ways to assess it is really by looking at survival, seeing that there was no real difference between overall survival or progression-free survival. So even though there may be some variability in response, again, not significant in this study.

Having an early randomized study that looks at the combination as a checkpoint inhibitor, compared to azacitidine alone really helps to flush out what we would expect with these agents.

Challenges with Canonical ICIs in MDS

- The combination of atezolizumab plus azacitidine in HMA-naïve patients was associated with high early mortality rates, which led to early study termination
- Atezolizumab alone or in combination with azacitidine had limited clinical activity in patients with MDS previously exposed to HMAs, although this was without excessive or unexpected toxicity



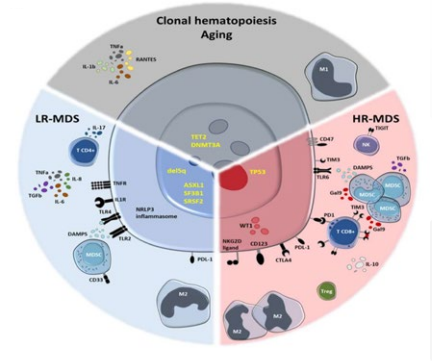
Atezo, atezolizumab; AZA, azacytidine; HMA, hypomethylating agent; ICI, immune checkpoint inhibitor; IV, intravenous; MDS, myelodysplastic syndrome.
Gerds et al. *Blood Adv*. 2022;6(4):1152-1161.

Another challenge with immune checkpoint inhibitors in MDS is shown here. In this study, atezolizumab was added to azacitidine. This was a front-line study. And it was on the same premise of looking at whether we could not just give azacitidine, but also somehow stimulate the immune system to better control disease long term.

Here are several cohorts of patients and their treatment history. A high number of patients had either toxicity from the combination, and so had to come off of treatment with atezolizumab relatively early in the course. Or, patients who had early deaths, and kind of prohibiting the full administration of drug.

And so, from these studies, I think what we've learned is that we can't simply directly translate discoveries that might be found in solid tumors or other cancers directly into our treatment paradigm of MDS, that we need to be a little bit more thoughtful of how the disease, interacts with the immune system. Also, what toxicity profiles our patients with MDS, again, mostly in their 70s, are able to tolerate.

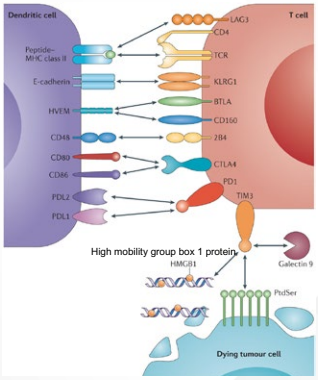
Immune Key Hubs Involved in Early Stages, Low-Risk MDS, and High-Risk MDS



HR, high risk; LR, low risk; MDS, myelodysplastic syndrome; NK, natural killer; MDSC, myeloid-derived suppressor cells.
Comont et al. *Diagnostics* 2021;11(11):982.

- At the same time, we've learned that as we age, we have a number of changes in our immune system that coexist even just with aging itself. So you don't need to develop a blood cancer to see a number of alterations in your inflammatory profile. We see changes in TNF, alpha, IL1 levels in patients. I think that increasingly, we've understood how these inflammatory microenvironment may actually permit expansion of mutated clones in our bone marrow, and may play a role in the direct pathogenesis of MDS. If not in facilitating ongoing clonal expansion over time.

Clinical Blockade of PD-1 and LAG3: Potential Mechanisms of Action

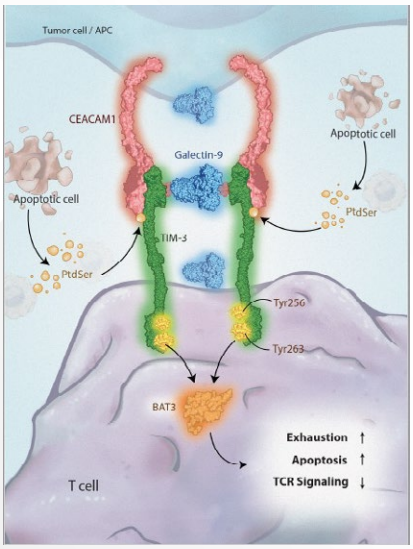


MHC, major histocompatibility; PD-1, programmed-death 1; LAG3, lymphocyte activating 3.
Nguyen and Ohashi. *Nat Rev Immunol.* 2015;15:45-56.

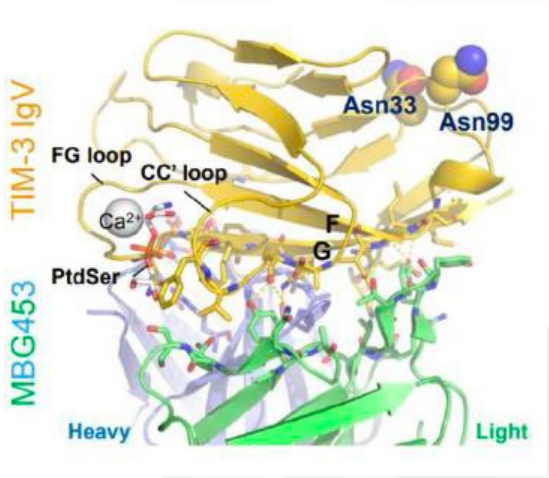
- That's led us to ask, well, is there a way that we can target some of these newer markers in the immune system, inflammatory cytokines or their receptors, cells themselves? And can we inhibit those as a way of targeting both the microenvironment and possibly the MDS blasts themselves? So some of the cells that interact with MDS have led to the discovery of some new targets, not just PD-1 and PD-L1, CTLA-4, but a number of markers that may be more relevant directly to MDS. One of those markers is a cell surface marker called TIM3.

  TIM3 is normally part of a natural feedback loop, when a T cell recognizes a tumor cell, and kills it. As more tumor cells die, they release a number of ligands to interact with TIM3, phosphatidylserine, galectin-9, and those result in a suppressive phenotype in the T cells. So basically, telling the T cells, your job here is done, you've killed the tumor cell.

T-cell Immunoglobulin Domain and Mucin Domain 3



Sabatolimab (MBG453)

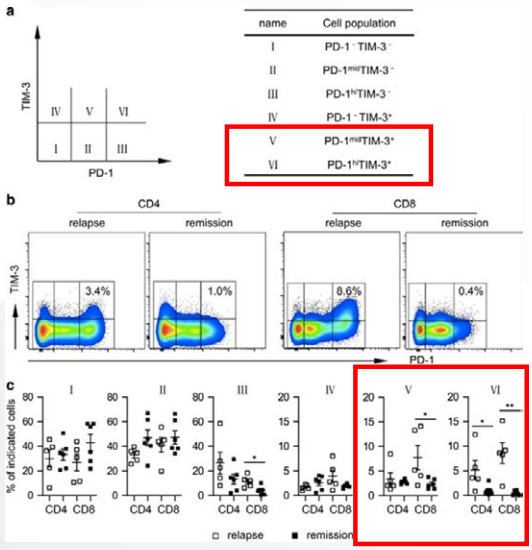


APC, antigen-presenting cell; TCR, T-cell receptor.
Sabatos-Peyton C. MBG453: A high affinity, ligand-blocking anti-TIM-3 monoclonal mAb. AACR 2016.

- What we have recently discovered is that TIM3, or T cell immunoglobulin domain and mucin domain-3, appears to be expressed on a number of our immune cells. It's also aberrantly expressed on leukemic progenitors. And this aberrant expression may be a target that we can utilize in MDS.

Here's a nice little diagram of TIM3 on the surface of a T cell. So again, it interacts with a dying tumor cell. And one of the ways in which, plays a role is when a tumor cell's dying, it binds to galectin-9 or phosphatidylserine. And then that increases this exhaustion phenotype in the T cells to downregulate the T cell response. If you inhibit that interaction, could you actually improve immune surveillance of leukemic progenitors or other tumor cells and improve upon their treatment? So, there's some evidence that perhaps TIM3 plays a role in immune escape through that mechanism.

TIM3/PD-1 Expression and Post-HCT Relapse



- Increase in PD-1+/TIM3+ CD8 T-cells at relapse
- Consistent with immune evasion and TIM3 upregulation playing a potential role

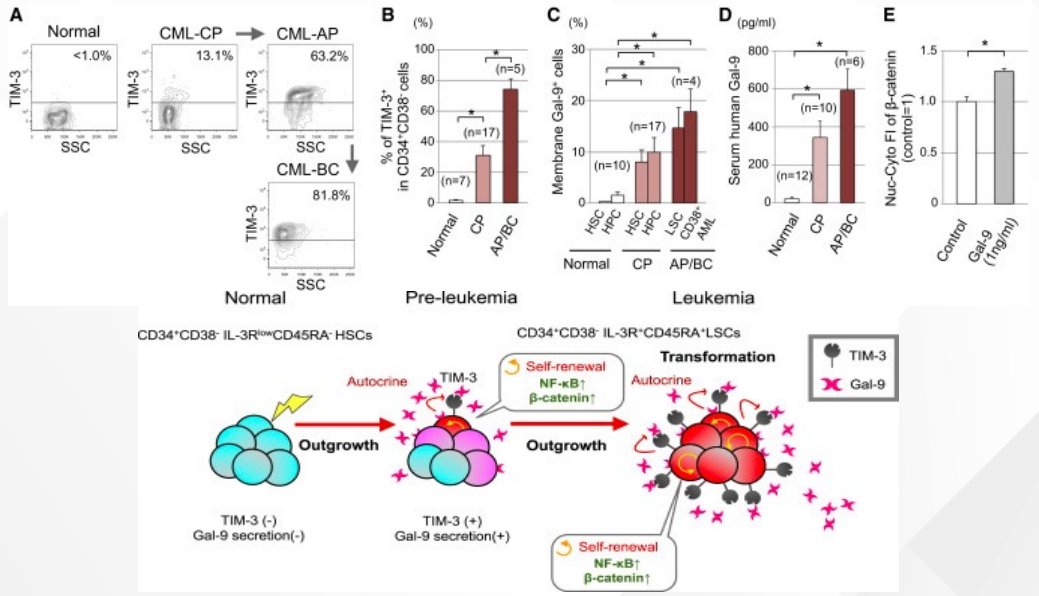
AXIS Medical Education

HCT, hematopoietic stem cell transplantation; PD-1, programmed-death 1; TIM3, T-cell immunoglobin mucin-3.
Kong et al. *Blood Cancer J.* 2015;5(7):e330.

- Here's a study looking at patients who are relapsed after transplant. So again, in transplant, you've got donor T cells that are thought to have some role in identifying any residual leukemic progenitors or MDS progenitors, surveilling for those and then eradicating them with a graft-versus-leukemic effect.

  In patients who relapse after transplant, it's been noted that they seem to have an increase in PD-1 and TIM3 expression on the donor T cells. While not conclusive evidence, it is suggested that there is some degree of immune escape that plays a role in relapse after transplant that you lose whatever graft-versus-leukemia effect may be there.

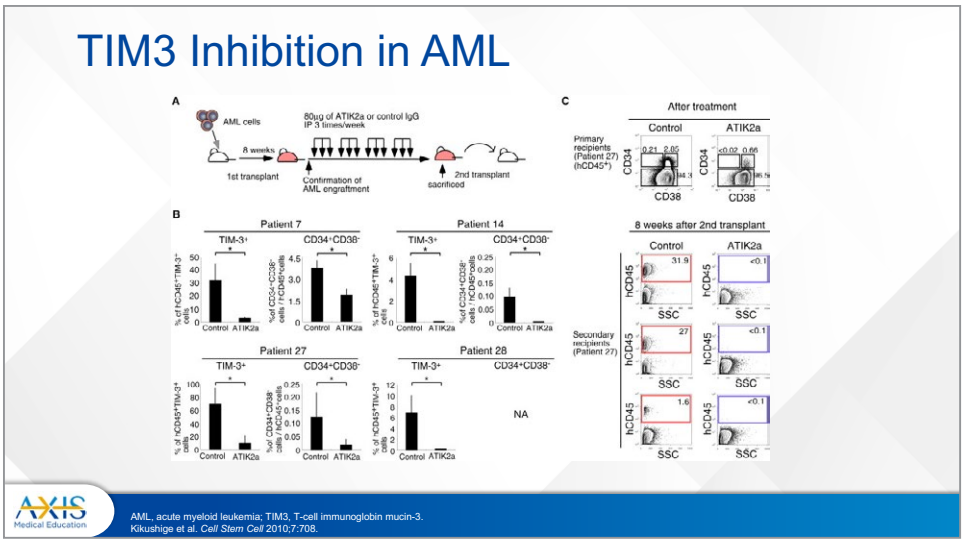
TIM3 Expression on Leukemic Progenitors



CML-CP, chronic myelogenous leukemia-chronic phase; CML- AP, chronic myelogenous leukemia-accelerated phase; CML-BC, chronic myelogenous leukemia-blast crisis; HSCs, hematopoietic stem cells; LCSs, leukemic stem cells; TIM3, T-cell immunoglobin mucin-3.
Kikushige et al. *Cell Stem Cell* 2015;17(3):341-352.

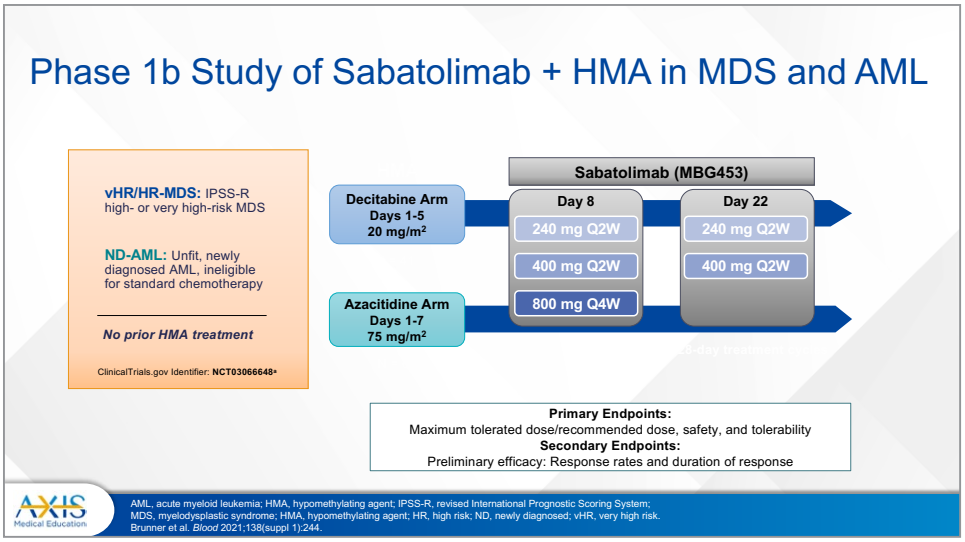
- Another aspect of TIM3, not just this role that it plays on T cells makes it an interesting molecule, is that also appears to be expressed on the leukemic progenitors themselves. There's some data to suggest that TIM3 may actually even be able to help us distinguish between a leukemic progenitor or leukemic stem cell and distinguish that from an otherwise healthy hematopoietic progenitor. There's this expression of TIM3 on the cell surface that may be a marker to distinguish the two, and may also play some role in these cells, and leukemic progenitor progression.

  Here is an interesting study. This is a CML model. But there were also other models where you see progression from chronic to accelerated to blast phase disease. And during that progression from chronic to accelerated to blast phase disease, you see an increase in the percentage of stem cells that have TIM3. So, is TIM3 signaling somehow important in that progression state? One of the ways in which it's proposed that it is important is that potentially TIM3 results in a self-renewal autocrine stimulation loop, so that blasts that express TIM3, release galectin-9, that binds to the TIM3 and somehow allows these blasts to persist and expand. And so, does TIM3 expression have to do perhaps, with clonal progression over time?



- It's been explored therapeutically in certain preclinical models, whether targeting TIM3, may be able to actually be a therapeutic avenue in AML. Again, with the idea that TIM3 might be aberrantly expressed on leukemic progenitors.

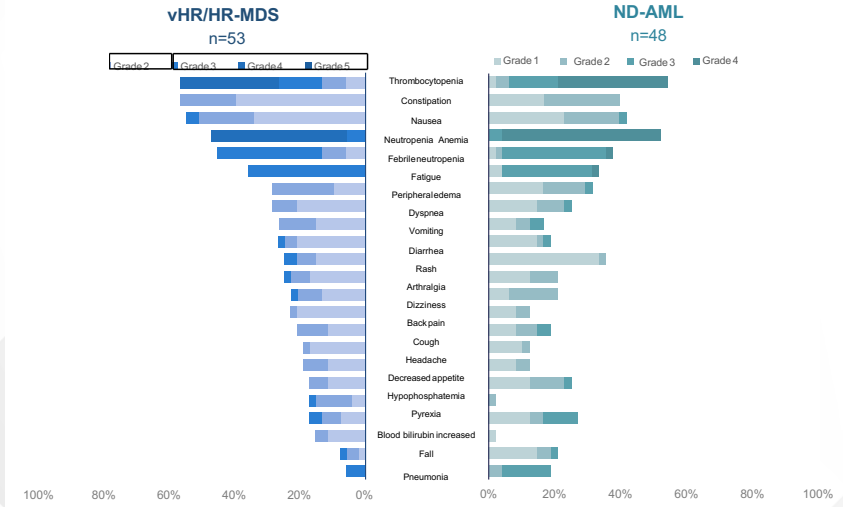
  This is a model where mice were transplanted with leukemic cells, and then either received antibody to TIM3 injected several times a week or received control antibody. So other IgG and then went to subsequent transplant and were evaluated for their ability to serially transplant. And what it found is that giving IgG alone did not seem to have any effect on the ability to serially transplant these mice. But if you gave a TIM3 antibody presumably interrupting the self-renewal loop, that you could no longer serially transplant these mice, suggesting, yes, that perhaps this target has something to do with the persistence and expansion of leukemic progenitors in myeloid neoplasia.



- I was involved in a study along with a number of other investigators looking at TIM3 antibody. So, sabatolimab and combining it with hypomethylating agents in MDS and AML. This was a study that was looking at patients who had very high-risk or high-risk MDS, as well as patients with newly diagnosed AML. And they're treated with decitabine or azacitidine, combined with escalating doses of the antibody sabatolimab, as administered in escalating doses on day 8 or 22 of a 28-day treatment cycle. And really, the initial goal was just to see could we safely combine these two agents and to get a sense of maybe signals about how it influences responses.

Most Commonly Occurring Adverse Events

(≥15% in either population, regardless of relationship to treatment)



vHR/HR-MDS and ND-AML AEs

- Most common reported AEs were cytopenias, GI symptoms, fatigue
- Low rate of sabatolimab dose modification:
  - 1/101 (1%) patients had dose reduction
- 38/101 (38%) patients had dose interruption (cycle delay >7d) due to AE
  - No patient with vHR/HR-MDS and only 3 with ND-AML discontinued treatment due to an AE
- One patient with neutropenic colitis reported as suspected to be related to study treatment died of septic shock. No other treatment-related deaths were reported
- No DLTs in vHR/HR-MDS and only 1 in ND-AML

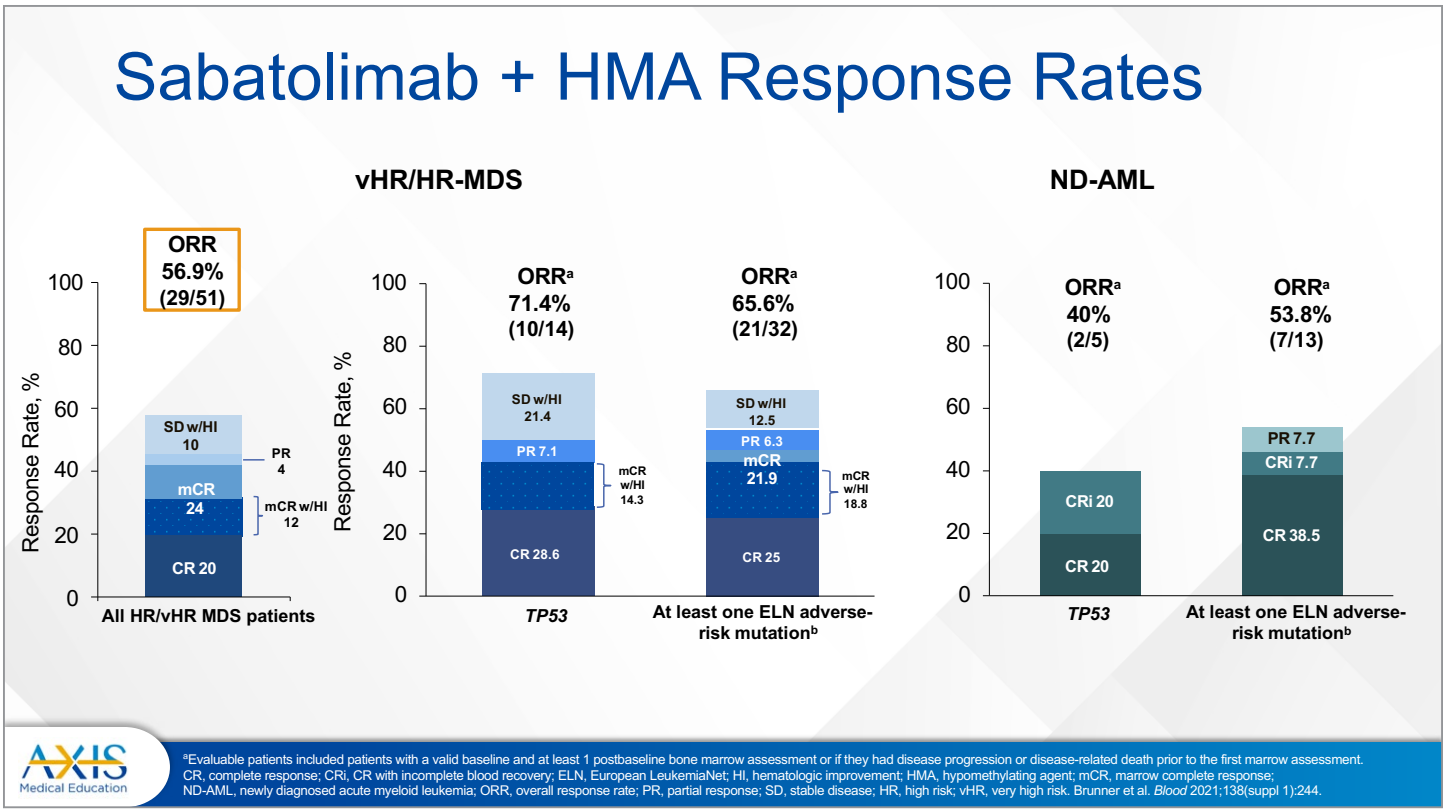
AXIS Medical Education

AEs, adverse events; ND-AML, newly diagnosed acute myeloid leukemia; DLT, dose-limiting toxicities; IPSS-R, revised International Prognostic Scoring System; MDS, myelodysplastic syndrome; HMA, hypomethylating agent; HR, high risk; vHR, very high risk.
Brunner et al. *Blood* 2021;138(suppl 1):244.

In the study, we were able to combine the two agents and we could manage adverse events as they arose. Shown here, are the most commonly occurring adverse events in the study. So predominant adverse events, again, this was in combination with azacitidine or decitabine, really were thrombocytopenia, neutropenia, anemia, and febrile neutropenia. It's always hard in combinations to know what impact the second agent has on the overall profile. But it's encouraging that there was a very low rate of dose modification of sabatolimab, only 1 out of 101 patients had a dose reduction. And there were a number of patients who had dose interruptions. So, a delay of a week or more, due to some toxicity. But no patients really discontinued therapy with MDS and only 3 of the AML patients actually discontinued treatment due to an AE.

While those are indirect measures, it does show that we can administer these two together and that patients can stay on them for a long time.

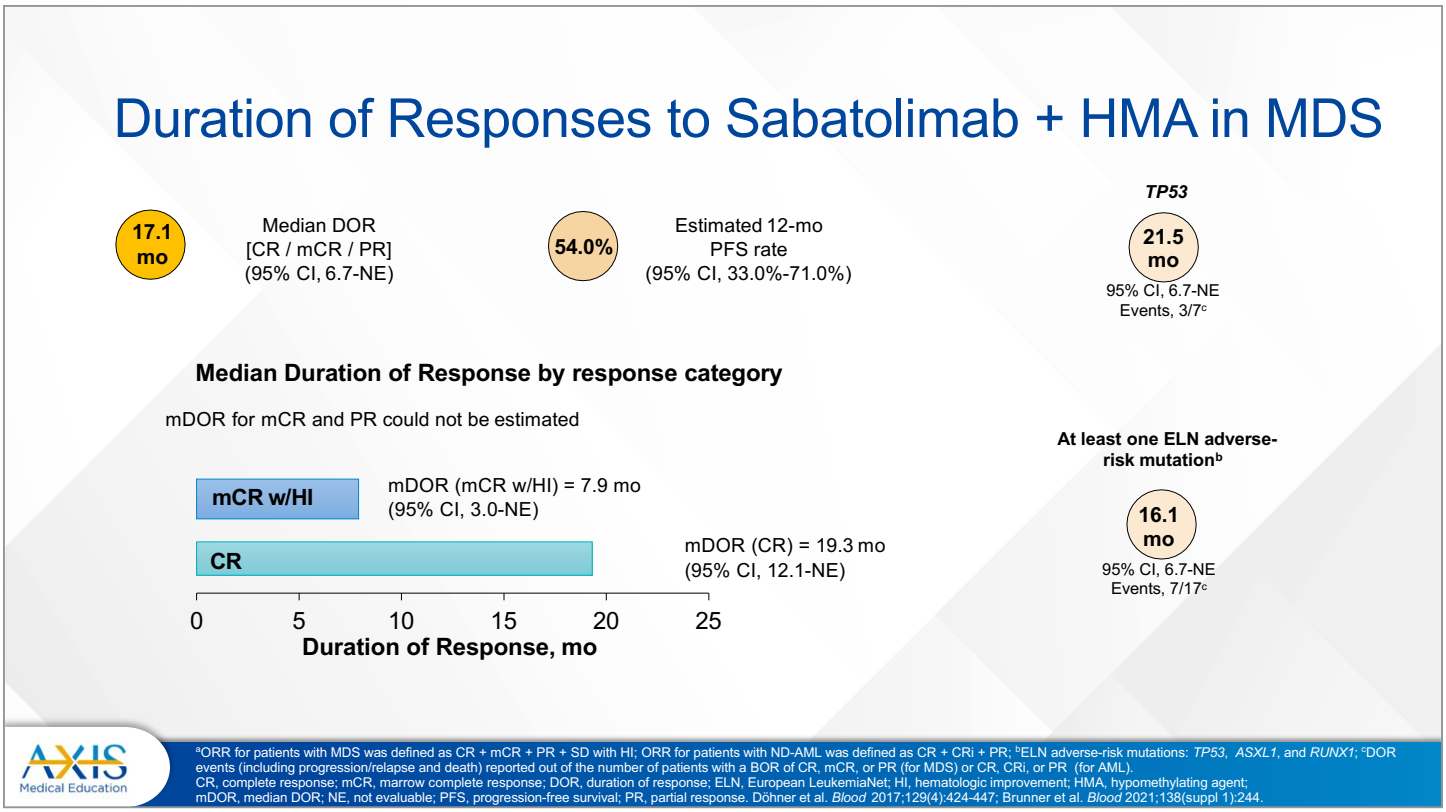
There was one patient who had neutropenic colitis that was suspected to possibly be related to study treatment. No other deaths were attributed to treatment. Again, there's only one DLT and AML, none in the MDS cohort of this study.



- If we look at the response rates, we kind of the first metric you're going to get out of any study is the response to therapy. Shown here is the overall response rate across the MDS patients of 57%, so 29 out of 51 patients, about 20% of those with remission. Another 24% with marrow CR, half of those patients having hematologic improvement, 4% with PR and 10% with stable disease but with hematologic improvement.

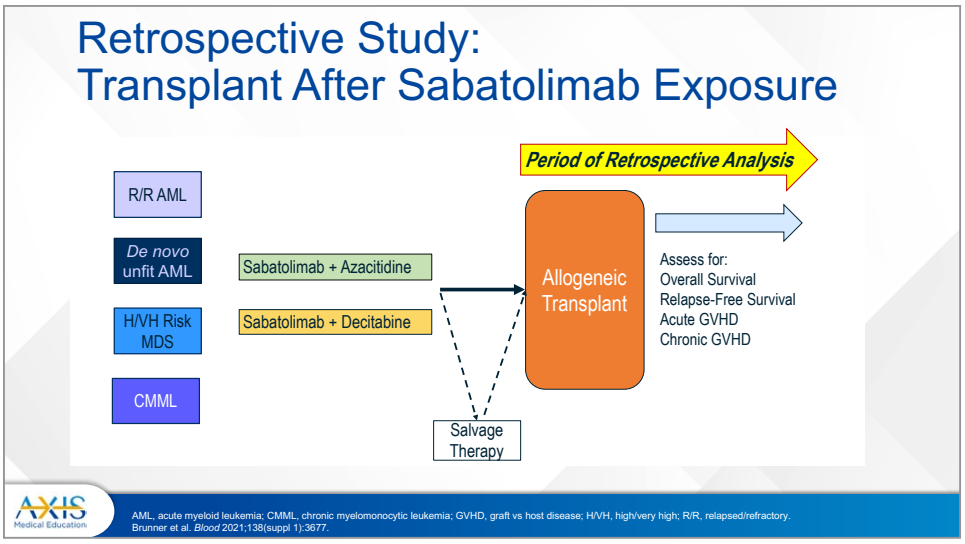
  We looked at some of the higher-risk mutation subgroups within this cohort. In a relatively small study, so hard to lump a lot of patients together just yet. But of those patients with *TP53* mutations or patients who had a high-risk ELN mutation with MDS, these patients did not seem to have variation in their chances of response compared to the overall cohort.

  Shown here also is that an AML cohort based on mutation. And again, fairly similar responses, regardless of mutation profile for the AML patients as well.

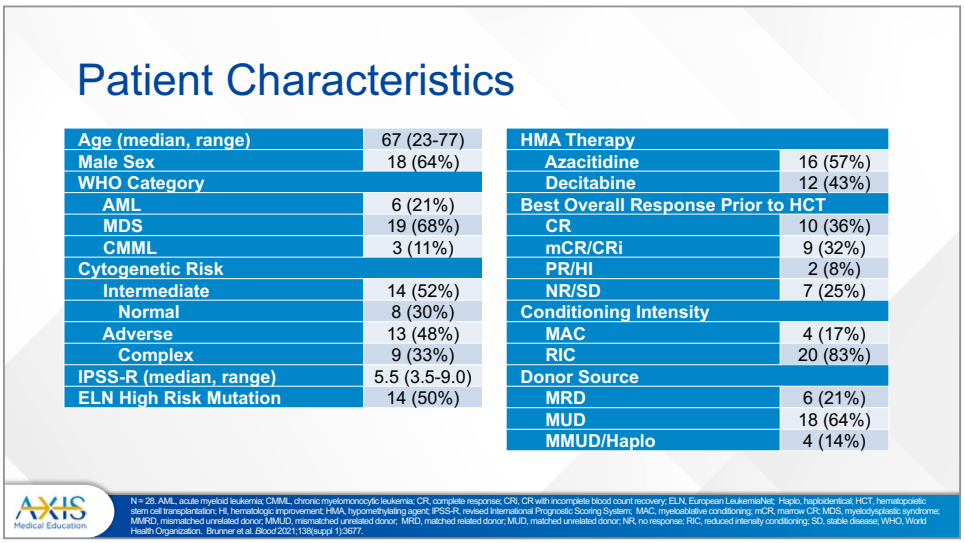


- The duration of responses to this combination shown here and median duration of response across the cohort was 17 months, with a little over half patients not progressing by 1 year. The duration of response varied according to the quality of response. So patients who had a remission, had a median duration of response of 19 months, and the upper limit not reached. Whereas patients who had marrow CR and hematologic improvement, their median duration was about 8 months. Again, with a long tail on that, too few patients to really interpret fully, so this has been analyzed in future studies as well.

An interesting finding that will need to be followed up is whether patients who had *TP53* mutations or ELN high-risk mutation, they had also long durations of responses TP53 21 months, and ELN high-risk 16 months. So if that really does hold true and perhaps suggest areas of further evaluation in this combination.



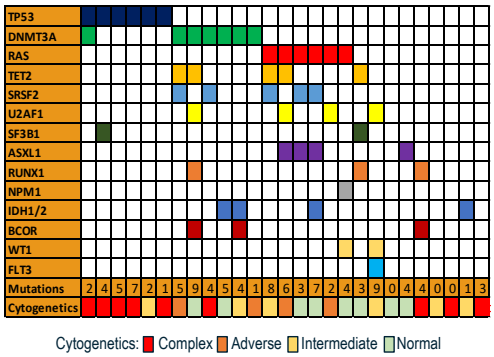
- Independently, we've looked at what happens to these patients who receive sabatolimab and then go on to transplant. And as a relatively small cohort, but one of the things you might worry about in patients who are receiving any immune-directed therapy is do they have toxicity after transplant when we're manipulating the immune system. Antibody therapies linger, and so you do want to take into account whether that has any impact. We identified patients who had been on this trial for any indications of relapsed refractory AML, unfit de novo AML, higher-risk MDS, CMML who had received sabatolimab in combination, and then, gone on to transplant.



- We found that many of the patients were older, median age 67, up to 77, being transplanted. The largest group of the cohort had MDS, but enriched for high-risk features, which is what you would expect from the way the trial enrolled. A third of them had a CR, but many patients proceeded to transplant with less than CR responses to the sabatolimab plus HMA regimen that they received.

  As expected, most patients had reduced intensity conditioning, again not being associated with we worry about higher risk of relapse and higher-risk subject cohorts. And most were unrelated donor.

Molecular Profiling Identified Several Very High-Risk Molecular Features



Brunner et al. *Blood* 2021;138(suppl 1):3677.

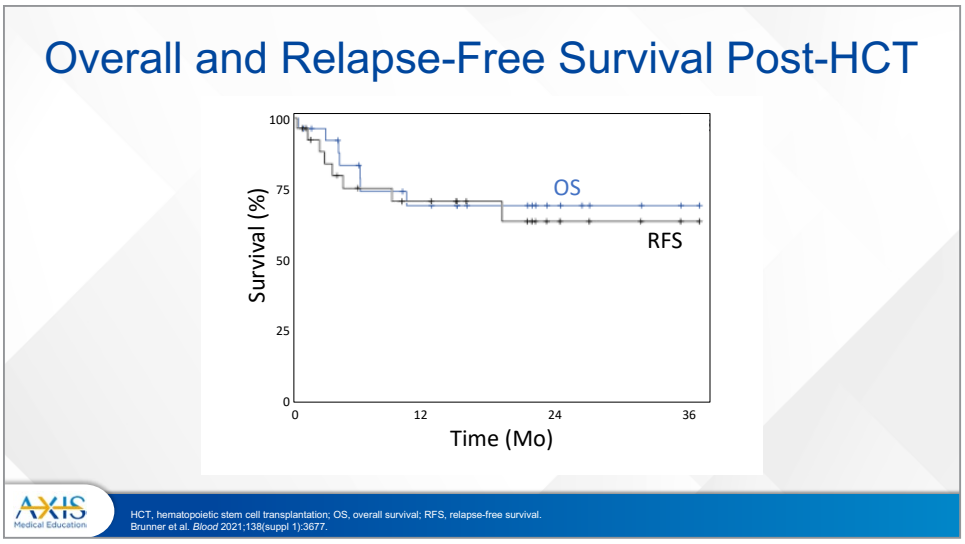
- Here's the mutation profile of the cohorts. It's hard to lump together a group that had like-enough mutations to look specifically at one mutation group. We did have 6 patients each either with a *TP53* mutation or with a RAS pathway mutation. I bring those up because those have been identified previously as groups that have a high rate of relapse after transplant. So while certainly we're not powered to fully evaluate whether those patients actually do better than might be expected historically, we might at least get some insight into these mutation groups.

Investigator Reported GVHD Events

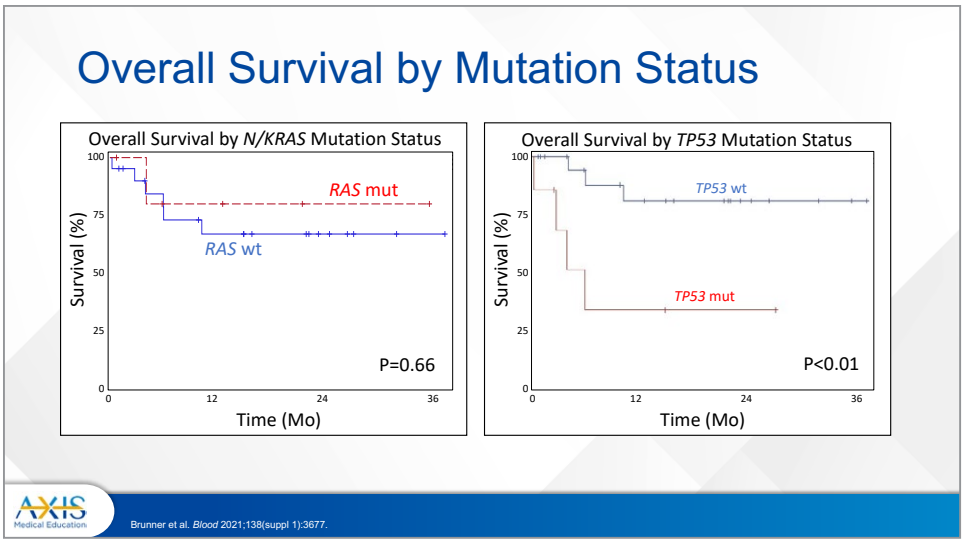
- Acute GVHD was seen in 16 patients; maximum grade 3-4 aGVHD occurred in 4 patients:
  - 2 patients with stage 4 GI disease, 1 with stage 3 GI disease, and 1 patient with stage 4 skin GVHD
  - One patient died on hospice after G4 aGVHD
- Chronic GVHD requiring systemic immunosuppression was seen in 8 patients, none of which have died or relapsed
- One patient also received spartalizumab (PD-1) and had grade 2 skin aGVHD and no cGVHD

aGVHD, acute graft vs host disease; cGVHD, chronic GVHD; GI gastrointestinal; PD-1, programmed-death 1.
Brunner et al. *Blood* 2021;138(suppl 1):3677.

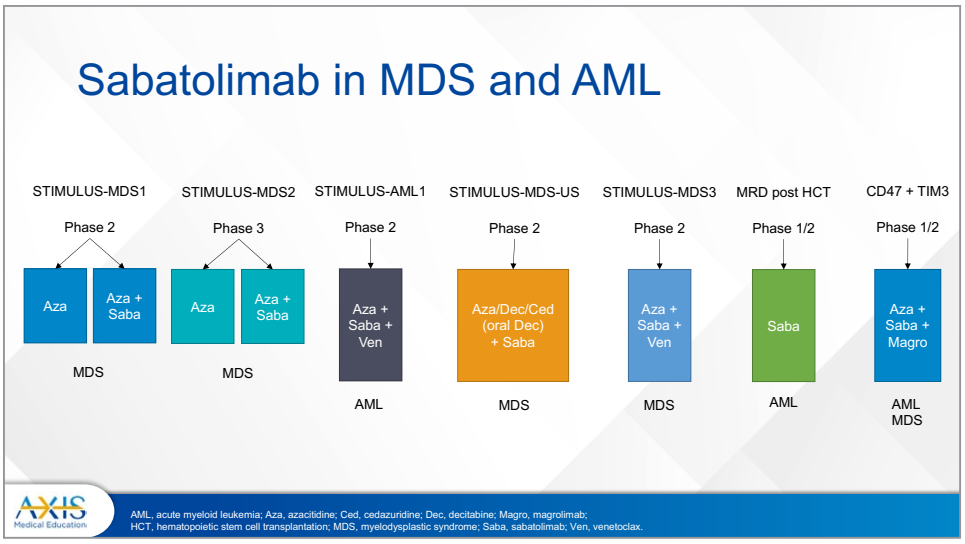
- So GVHD being of paramount concern with any post-transplant regimen that has had prior immune checkpoint inhibition, we saw acute GVHD in 16 of the patients, but very few with grade 3 or 4 acute GVHD, only 4. Chronic GVHD requiring immunosuppression occurred in 8 patients, and they all have not died or relapsed the time of the data cut. Of note, 1 patient also received a PD-1 inhibitor, had some grade 2 skin GVHD.



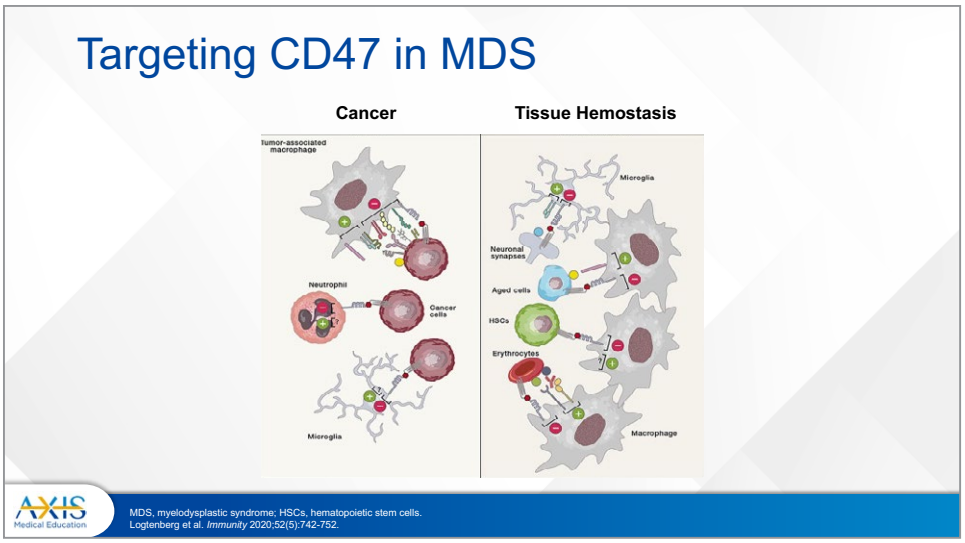
- Here is the survival and relapse-free survival curve. With a median follow-up of about 2 years, reasonable outcomes of survival somewhere around 70% of patients alive. And largely survival nearing the relapse rate. And so, I think encouraging data that this can be administered.



- We did not see a clear difference according to *RAS* mutation. *TP53*, again, hard to assess completely. They appeared to do more poorly than *TP53* wild-type patients, so it remains a challenging group. But some patients were able to have longer term survival.



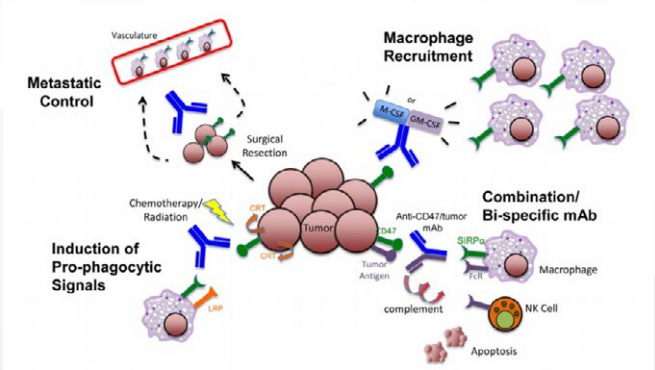
- Sabatolimab is being evaluated across a number of MDS and AML trials, including several randomized studies in phase 2 and phase 3 setting that we're looking forward to seeing some of that data reported out. But then also as triplets; our experience in the doublet setting suggests that the profile can be added to others. So it'll be interesting to see whether that remains true for venetoclax combinations or magrolimab combinations that are on the horizon.



- While TIM3 represents one way in which we are targeting the immune system in MDS, there are other advanced studies looking at other immune targets. And the other major one is probably CD47. CD47, it may play an important role in MDS immune surveillance. We know that in cancer, CD47 indicates don't-eat-me signal that may be expressed by tumor cells to help them evade macrophage surveillance.

  This is an important marker on healthy cells as well. Perhaps the most relevant to MDS is that aging red blood cells express CD47, which means that they persist in our circulation longer, but also means that we have to consider CD47-expressing tissues when we administer an antibody to this target.

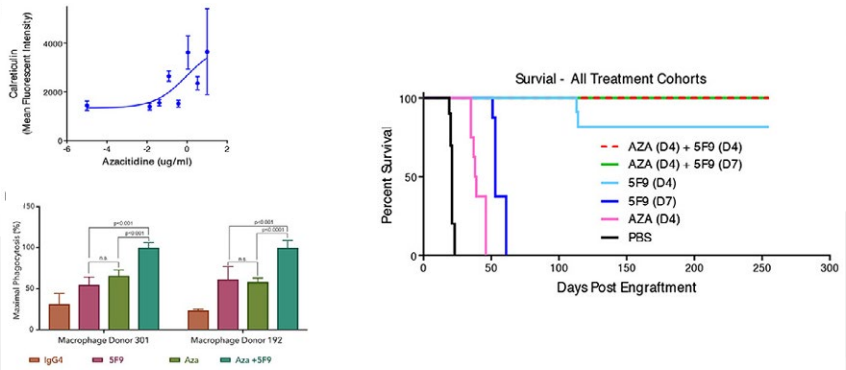
Targeting CD47 in MDS



mAb, monoclonal antibody; MDS, myelodysplastic syndrome; NK, natural killer.
Chao et al. *Curr Opin Immunol*. 2012;24(2):225-232.

- If we think about how CD47 may have a role in MDS tumor cells typically would express CD47 as a way to evade macrophages. Macrophages have CIRP alpha on their cell surface and this interacts with CD47. And that interaction kind of downregulates macrophage-directed phagocytosis. Administering an antibody that blocks that interaction can then help stimulate macrophages and result in control of CD47 expressing cells.

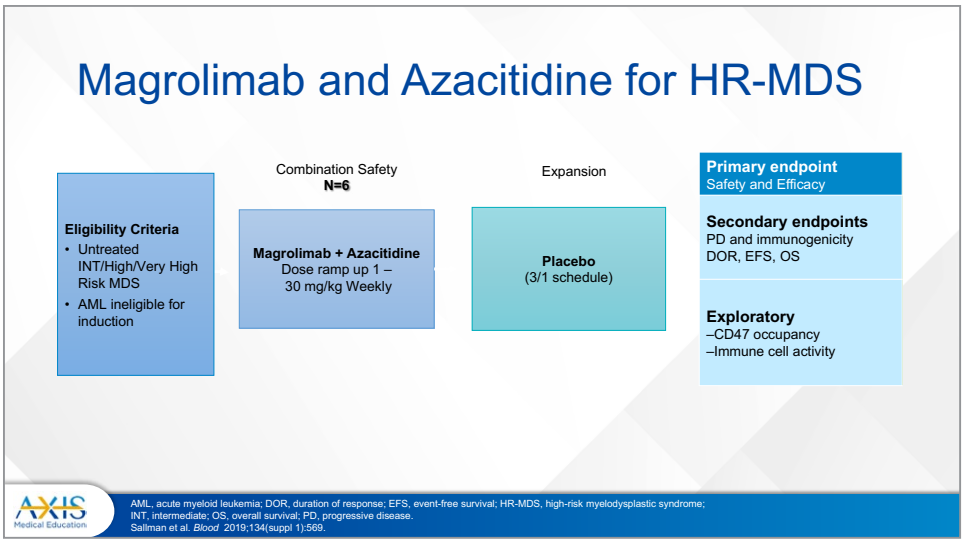
CD47 and Azacitidine



AZA, azacytidine; PBS, phosphate buffered saline.
Chao et al. *Front Oncol*. 2020;9:1380.

- It was shown here that CD47 administration in combination with azacitidine seems to have a distinct synergy. In this experiment, 5F9 is the CD47 molecule. And you can see here in a number of leukemic cells that administering azacitidine alone or 5F9 alone seems to have maybe a little bit of survival benefit compared to administering saline. But the combination in this model really shows the best survival.

  If you look at reasons why this may occur, one of those is thought to be that CD47 upregulates the azacitidine upregulates calreticulin. And then that upregulation of calreticulin serves as a marker to stimulate the macrophage-induced phagocytosis.



- Magrolimab and azacitidine are being explored in high-risk MDS. This is data from one of the earlier studies, a single-arm study looking at untreated intermediate, high, or very high-risk MDS patients or patients with AML ineligible for induction. It did a ramp-up of magrolimab and azacitidine to confirm safety and then expanded patients to evaluate safety and efficacy, overall survival, as well as looking at CD47 occupancy or activity of immune cells after administration.

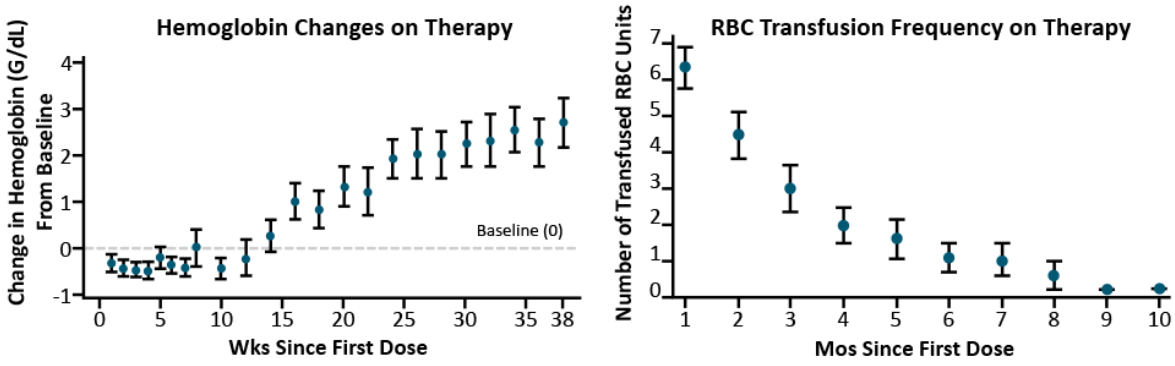
Patient Characteristics

Characteristic	1L MDS 5F9+AZA (N=35)	1L AML 5F9+AZA (N=27)
Median age (range)	70 (47-80)	74 (60-89)
ECOG Performance Status: 0 1 2	13 (37%) 21 (60%) 1 (3%)	9 (33%) 16 (59%) 2 (7%)
Cytogenetic Risk: Favorable Intermediate Poor Unknown/missing	0 10 (29%) 23 (66%) 2 (6%)	0 2 (7%) 18 (67%) 7 (26%)
WHO AML classification: MRC Recurrent abnormalities Therapy-related NOS	–	19 (70%) 2 (7%) 1 (4%) 5 (19%)
WHO MDS classification: RS and single/multi-lineage dysplasia Multilineage dysplasia Excess blasts Unclassifiable/unknown/missing	3 (9%) 6 (17%) 19 (54%) 7 (20%)	–
IPSS-R (MDS): Intermediate High Very High Unknown/missing	11 (31%) 18 (51%) 5 (14%) 1 (3%)	–
Therapy-related MDS Unknown/missing	11 (31%) 1 (3%)	–
Harboring a *TP53* mutation	4 (11%)	11 (41%)

AML, acute myeloid leukemia; AZA, azacitidine; ECOG PS, Eastern Cooperative Oncology Group performance status; IPSS-R, revised International Prognostic Scoring System; MDS, myelodysplastic syndrome; MRC, myelodysplasia related changes; NOS, not otherwise specified; RS, ring sideroblasts; WHO, World Health Organization; 1L, first line; 5F9, magrolimab.
Sallman et al. *Blood* 2019;134(suppl 1):569.

- Here are the patient characteristics of both arms. The MDS arm and the AML arm. Since this report, there have been additional patients enrolled. As you might expect, patients were older, with MDS and AML. Patients tended to have unfavorable risk disease, a majority of patients in MDS having poor risk cytogenetics. And the majority of patients having high or very high IPSS-R scores, or very high-risk. There were also a number of patients that were enrolled to this study with therapy-related disease, and a relatively high number of patients who are enrolled with a *TP53* mutation, which is important, because it may lend some insight into where this is being evaluated.

Hemoglobin and Transfusions with Magrolimab and Azacitidine



RBC, red blood cell.
Sallman et al. *Blood* 2019;134(suppl 1):569.

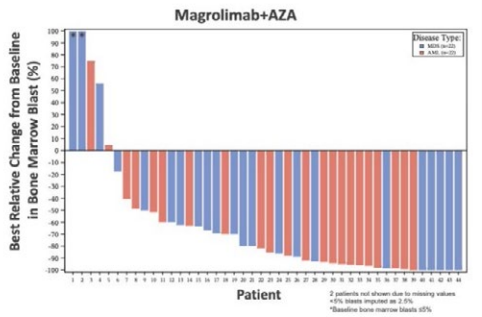
- One of the things to know with using a CD47-directed therapy, and probably the most relevant for if this therapy becomes approved in clinical practice is that, again, CD47 is expressed on aging red cells. And so, the administration of magrolimab results in an initial drop in hemoglobin. And that can vary a lot. Some patients will have relatively mild drop, but some patients with the first dosing can have a more significant hemolysis and need fairly intensive transfusion support. Being prepared for that is important if you're taking care of patients who are on this combination.

  The transfusion support needed drops pretty dramatically after the first few doses. Once you've cleared these "old, older" CD47-positive red cells, you do not see as much hemolysis. But, it is important. I, for instance, reach out to my blood bank, let them know that I'm going to have a CD47 patient, they do need to know that to be able to type and crossmatch so that you can then be prepared for potential transfusion support that's transient but relevant.

CD47 “Don’t Eat Me” Checkpoint

Anti-Leukemic Activity is Observed with Magrolimab + AZA in MDS and AML

Best Overall Response	1L MDS (N = 24)	1L AML (N=22)
ORR	22 (92%)	14 (64%)
CR	12 (50%)	9 (41%)
CRi	-	3 (14%)
PR	0	1 (5%)
MLFS/marrow CR	8 (33%) 4 with marrow CR = HI	1 (5%)
Hematologic improvement (HI)	2 (8%)	-
SD	2 (8%)	7 (32%)
PD	0	1 (5%)



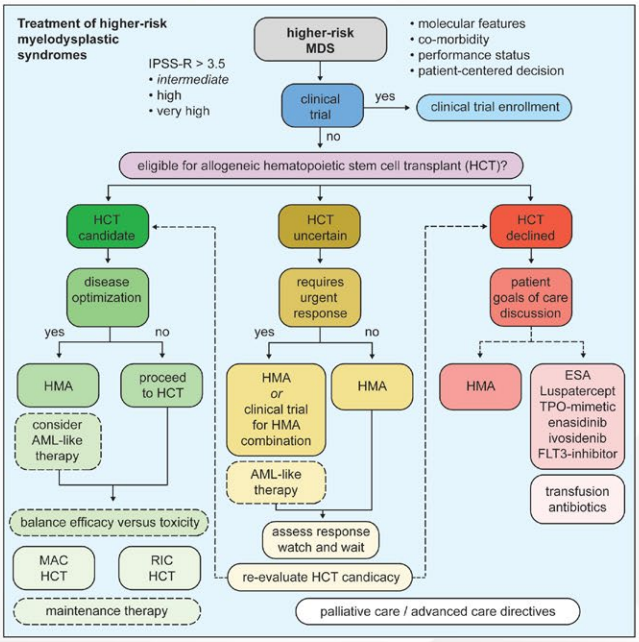
- Magrolimab + AZA induces a 92% ORR (50% CR) in MDS and 64% ORR (55% CR/CRi) in AML
- Median time to response is 1.9 months, more rapid than AZA alone
- Magrolimab + AZA efficacy compares favorably to AZA monotherapy

AXIS Medical Education

Response assessments per 2006 IWG MDS criteria and 2017 AML ELN criteria; Patients with at least one post-treatment response assessment are shown, all other patients are on therapy and are too early for first response assessment, except for 2 MDS patients not evaluable (withdrawal of consent) and 3 AML (1 AE, 2 early withdrawal). *Not applicable
1L, first line; AML, acute myeloid leukemia; AZA, azacitidine; CR, complete response; CRi, CR with incomplete blood count recovery; HI, hematologic improvement; MLFS, morphologic leukemia-free state; MDS, myelodysplastic syndrome; ORR, overall response rate; PR, partial response; SD, stable disease, PD, progressive disease. Sallman et al. *Blood* 2019;134(suppl 1):569.

▶ What kind of activity have we seen with this agent? Most of the activity reported to date is from the single-arm study showing really mostly response rates as well as some preliminary signals for survival. The overall response rate seems to be high, especially in MDS. There's an encouraging rate of remissions reported in the trials that have been presented so far. Many patients will have also a reduction in the blasts in the marrow. I think that an integrated response here is important, but that many patients can have benefit from this. Also survival. Preliminary survival signals seem to be encouraging. There's just an update shown at EHA, a single-arm survival on this combination. What we need and what we're really hoping for in MDS in general is more data from phase 2 and phase 3 studies to identify what kind of survival patterns we see, if there's particular subgroups that benefit most. And just to get a sense of how it might compare to azacitidine monotherapy.

Treatment of Higher-Risk MDS



AML, acute myeloid leukemia; ESA, erythropoiesis-stimulating agent; HCT, hematopoietic stem cell transplantation; HMA, hypomethylating agent; IPSS-R, revised International Prognostic Scoring System; MAC, myeloablative conditioning; MDS, myelodysplastic syndrome; RIC, reduced intensity conditioning; TPO, thrombopoietin. Brunner and Aubrey, in press. Courtesy of Andrew M. Brunner, MD.

This is a good chance to reflect on where we stand in treatment of higher-risk MDS. Higher-risk MDS is defined in many ways. For example, with our patient that we were discussing earlier, she was older, she had a number of high-risk features, including increased blasts, she had pancytopenia, and she had a high-risk cytogenetic abnormality, del 7q, as well as a number of mutations that bestowed higher risk to her disease as well. When you meet somebody who has these features, you worry, and if I don't do anything, or if left untreated, they're likely to have a complication within the coming months or within a year.

Based on that, this is the way I often think about patients. Again, outcomes remain unsatisfactory, regardless of what treatment we choose right now in MDS. So, I think it's always appropriate to consider a clinical trial at any stage of treatment.

The first question I am often asking is, can this patient get through an allogeneic transplant? And would they be a candidate for that? Because even though that is also not curative for all patients, it does provide a longer-term benefit for those patients who are otherwise able to proceed. In evaluating them, age is associated with a number of features that may prohibit transplant, but age itself, I don't always consider a contraindication. So, I do try to work very closely with my transplant team to have somebody evaluated early on in the diagnosis of MDS that has higher-risk features.

If they are a candidate, I am wondering, is there a way I can optimize their disease? Transplant doesn't happen overnight. Even though I don't want to really delay proceeding to transplant, many patients will proceed to some form of chemotherapy prior as you wait for the transplant to be prepared. If I'm choosing to start some form of chemotherapy before transplant, I might think about whether they have AML-like features, or other features that would make me intensify my treatment based on the patient's substrate as well. Can they handle this kind of intensification? Or is it too toxic? And then also thinking about what kind of transplant are they going to get if they're going to reduced-intensity transplant? Is it worth thinking about optimizing the disease more or doing something after transplant to try to prevent relapse? Typically, that would also still be in the context of a clinical trial.

If I'm not sure about transplant, maybe I am just meeting them,

it's a little unclear how active or whether that's in their goals, then I'm often thinking about well, how urgently do I need a response? Most of the time, this is not going to be extremely urgent in MDS, and we're going to start with standard HMA if I don't have a trial option.

Sometimes, particularly with people who have an AML-like profile, I might consider AML-like therapy. And I think this is reflected in how we are recategorizing some of the MDS cohorts. For instance, for patients who have MDS, but also have an NPM1 mutation, I have been typically treating them more like AML. And I think that's reflected in how some of our WHO and ICCC guidelines have changed the classification of MDS and AML to potentially recognize that there are some AML-like mutations that really merit more of an AML-directed therapy.

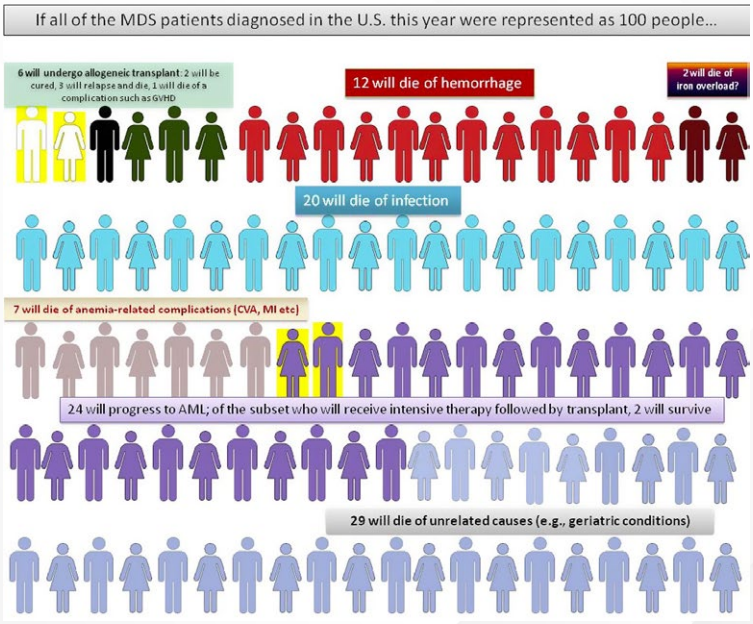
So, I might assess the response, watch and wait, see how well they do on treatment. Some patients will do great and you're reevaluating whether maybe I should go to transplant. Some patients will not do well with therapy, and maybe you'll be glad that you didn't try to go through an intensive transplant with them.

Some patients, transplant's not really their goal. And while we know that is azacitidine then is really the only therapy associated with survival in that space in a phase 3 setting. Many patients will have differing goals. For some people, even azacitidine may not be a therapy that they wish to pursue.

So I think that there is an expanding repertoire and nuance to how we manage patients outside of the transplant setting.

The reality though is that we have a very challenging disease. And while we really are hoping to identify some new therapies, especially ways to use what has succeeded. So, if not everybody can go to transplant, can we get some of the graft-versus-leukemia effect from that by using immunological target in MDS. The reality is that many patients really will still have suboptimal outcomes.

Clinical Outcomes for Patients with MDS



AXIS Medical Education

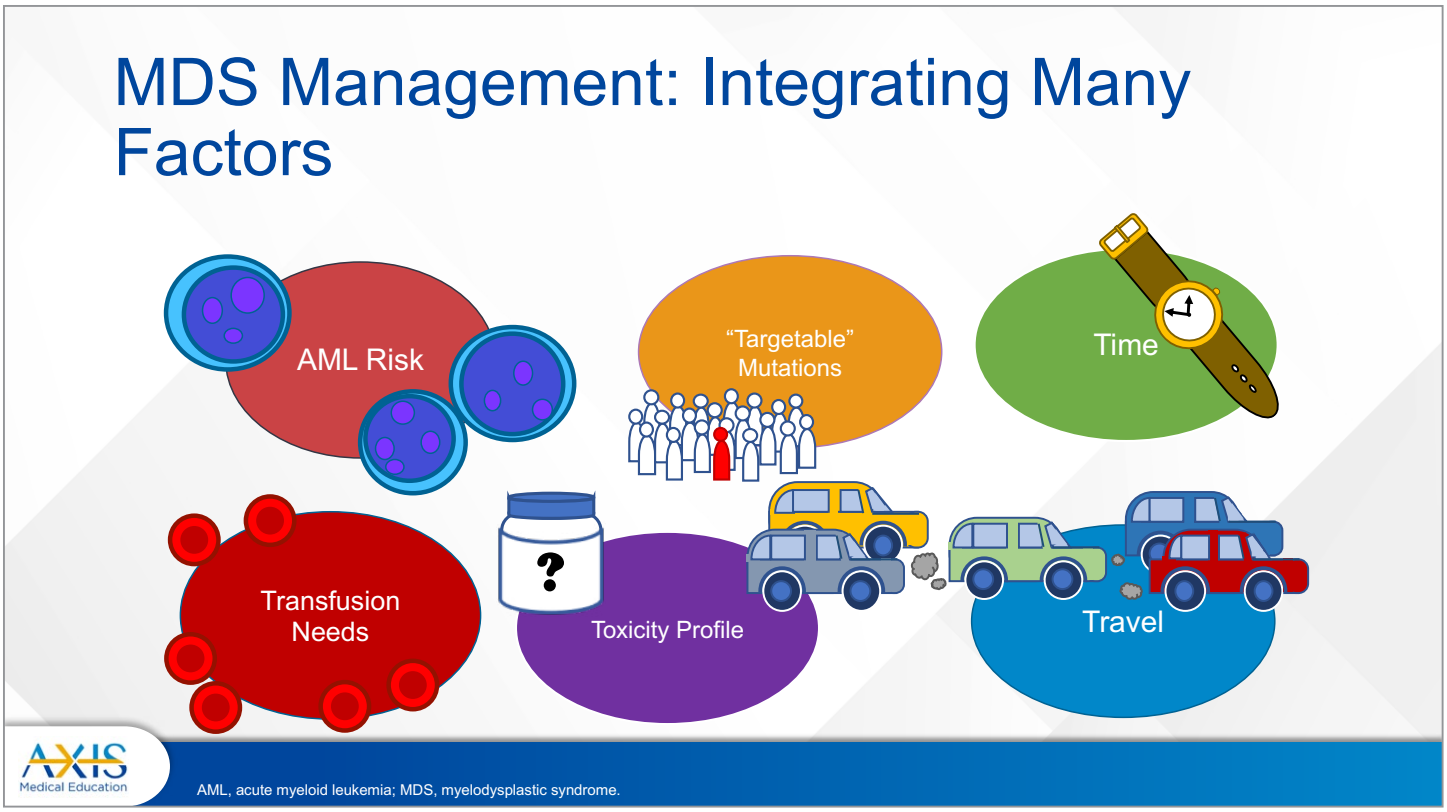
AML, acute myeloid leukemia; CVA, cerebrovascular accident; MDS, myelodysplastic syndrome; MI, myocardial infarction.
Steensma. *Leuk Lymphoma* 2016;57(1):1-8.

This is an interesting infographic as published in *Leukemia and Lymphoma* by Dr. Steensma, a way to think about what happens to patients after they get diagnosed with MDS. And the reality is that, unfortunately, many of them will die, some will die from their disease, either from bleeding or infection. Some will die from progression to leukemia and die after leukemic progression.

Many of our patients, they're older, they have other comorbidities, many will die from comorbid conditions. It's important to recognize that, for instance, cardiovascular disease plays a big risk factor for our patients and can be limiting for how we manage them.

Even though I spent a lot of time talking about transplant, and I'd certainly like to get that therapy to more patients, the reality is very, very few patients actually go on to receive allogeneic transplant. Of the 100 who have MDS, only 6 of them will actually go to transplant. And, even with transplant, very few will be cured.

So we have a long way to go. And we have a long way to try to assess how do better for our patients.



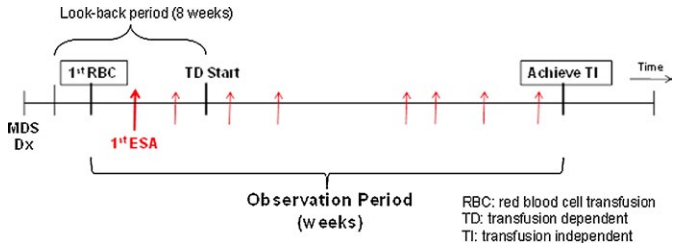
I think another challenge for our patients with MDS is that managing them is not a straightforward task. When you can't make blood, you really are dependent on the healthcare system. We talk a lot about the worry that you might die or progress to leukemia. And certainly, those are concerns but perhaps just as impactful on MDS care is the amount of time that patients have to spend in clinic. They basically have a second home. If you have to recognize that these patients, they have to travel to clinic, that might be hours to get to a specialized MDS center. Even if they don't have to travel so far, they have to wait for a type and cross when they have to spend a half a day to get red cells or platelets. They may be admitted to the hospital with infections.

I think it is a challenge when I have patients who have higher-risk disease, but the toxicity of starting on azacitidine can seem insurmountable.

An area where we're evolving in MDS, that other myeloid diseases as well as other cancers are a little bit more advanced, is through targets in mutation targets. *IDH1, IDH2, FLT3*, these are some mutations that are seen more often in AML. There are subsets of patients with MDS that will have them. You can argue whether how much like MDS or AML that patient actually is. But, there are far too few patients who have an actionable target in MDS right now. A lot of our research tries to identify new targets, but still, we have too little to offer.

And I think transfusion burden, like this 80-year-old patient who I saw in clinic, she presented because of anemia. And even though she has a lot of risk factors to her disease, the one that's going to cause her symptoms first is her anemia. And that burden of transfusions and how that impacts her life can be really deleterious for our patients.

Transfusion Burden in MDS

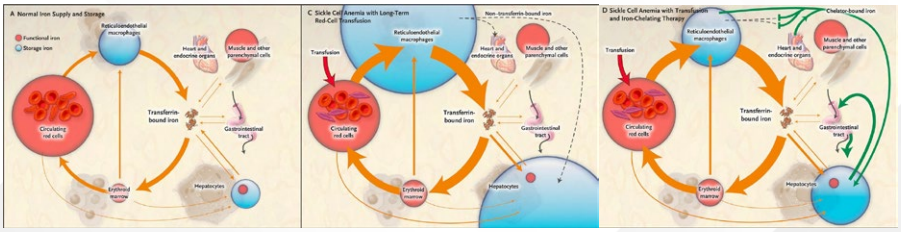


Duong et al. *Leukemia Res.* 2015;39(6):586-591.

- For instance, here is an example of that transfusion burden in MDS. Here we look back prior to starting treatment and we try to see how many transfusions you need, and then observe how patients do over time. It's an imperfect art. What we decide is a benefit can be really challenging to see.

  Giving people enough time on therapy can also be a challenge. When we use cytotoxics, like is azacitidine or decitabine, especially as we start to add additional cytotoxic agents, it can be really difficult to know, how much benefit am I giving a patient if they still are heavily transfusion dependent?

Iron Overload From Transfusions



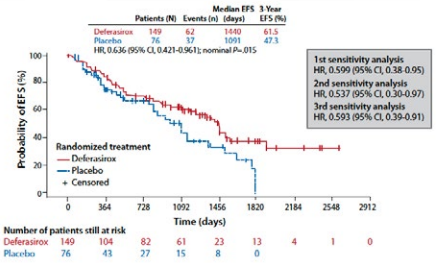
Brittenham et al. *N Engl J Med.* 2011;364:146-156.

- How much does that impact their quality of life? And perhaps not just their quality of life, but how does that burden of transfusions also impact the rest of their body? So, in patients who receive multiple transfusions, you often get iron deposition in heart, liver, you can get it built up in other organs. Patients can have complications that start to involve endocrine organs, diabetes, hypothyroidism, and it can be challenging to know how to weigh that iron overload compared to the therapies.

Iron Chelation: TOLESTO

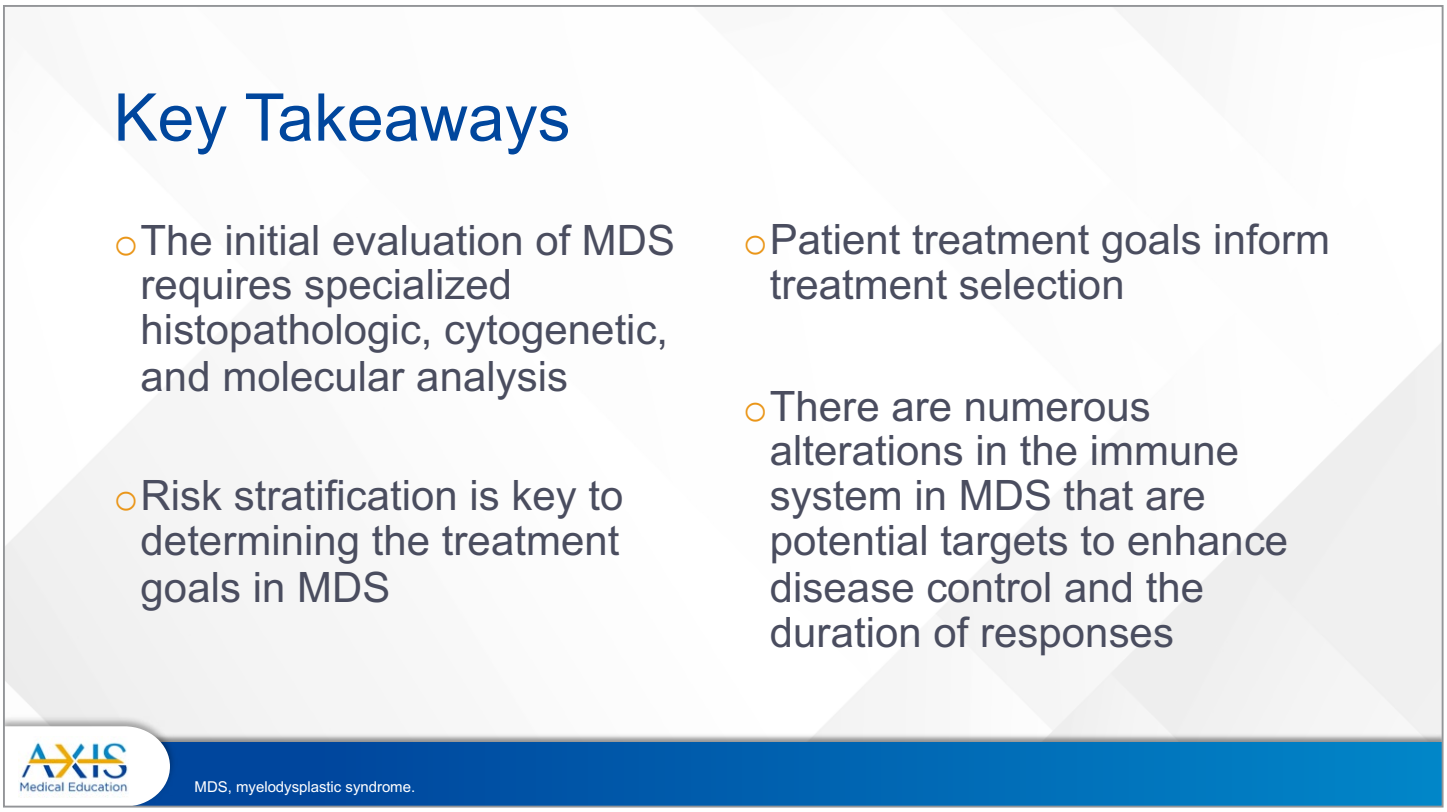
- Patients with Low/Intermediate-1 MDS randomized to deferasirox or placebo

Event	Deferasirox	Placebo
Death	32.2%	32.9%
AML	6.7%	7.9%
CHF Hospitalization	0.7%	3.9%
Liver Impairment	0.7%	1.3%
Cardiac function decline	2.3%	2.6%



AML, acute myeloid leukemia; CHF, congestive heart failure; EFS, event-free survival; MDS, myelodysplastic syndrome.
Angelucci et al. *Clin Adv Hematol Oncol.* 2019;17(2):4-6.

- It's often difficult to maintain people on iron chelation when they're on another chemotherapy. So, we often find ourselves trying to identify ways where we can treat patients for their symptom burden. But having to estimate that based on how long they're going to live with disease. And so, iron, chelation, for instance, may have a better role—even though iron burden probably is a problem in higher-risk disease. Iron chelation requires time. So patients who are going to live with their disease, lower-risk MDS, may have better benefit from iron chelation than patients who have higher-risk disease. And if we can extend response durations, should we start to think about some of these supportive measures in MDS at the same time.



- With that, we've talked about a lot of the management of patients with MDS, we've talked about some of the real challenges that patients who have MDS face, not just with the diagnosis, but also with management of symptoms and comorbid conditions that may arise during treatment. The initial evaluation of MDS is a specialized histopathological cytogenetic molecular analysis. And it's by using all those elements that we get a predictive risk score. There are many scores available, each one has strengths and weaknesses, each one is getting more and more refined over time.

The way I think about risk prognostication in MDS is I'm really trying to make sure that I'm not missing a high-risk feature for a patient and that I'm providing care that aligns with their likely natural history. So, for patients who are going to live with their disease a lot, my main goal is to reduce the impact of complications and to try to keep them doing as much of their routine as possible.

But many patients have higher-risk disease, that does pose a more immediate threat to them with many dying within a year. And really then, modification. So, some sort of therapy that modifies the natural history of disease is the treatment that really is mainstay.

And I think something that we're learning about in addition to new targets for MDS, in addition to new combinations of therapy, perhaps borrowed from AML, is that MDS arises in a state of immune dysfunction. And that this may play a role both in progression of disease as well as may provide targets that we can employ in the treatment of MDS. A big goal would be to try to employ some sort of therapies that can teach our immune system to better control disease for longer. And a number of these alterations are being explored right now.

Clinical Trial Summary

Therapy	Target	Combination	Trial	Phase	Status (July 2022)
Magrolimab	CD47	+ azacitidine	ENHANCE NCT04313881	3	Recruiting
Sabatolimab	TIM3	+ HMA	STIMULUS-MDS1 NCT03946670	2	Active, not recruiting
		+ azacitidine	STIMULUS-MDS2 NCT04266301	3	Active, not recruiting
		+ azacitidine and venetoclax	STIMULUS-MDS3 NCT04812548	2	Recruiting
		+ HMA	STIMULUS-MDS-US NCT04878432	2	Recruiting
		+ siremadlin (HDM201)	NCT03940352	1b	Recruiting

HMA, hypomethylating agent; TIM3, T-cell immunoglobin mucin-3.

- The main drugs that are being used at this time in late-stage trials are those agents that are targeting TIM3 and CD47.

Thank You

Thank you for participating in this activity!

- And so with that, I'd like to thank you for participating in this activity and appreciate your attention.

REFERENCES

Angelucci E, Li J, Greenberg P, et al. Iron chelation in transfusion-dependent patients with low- to intermediate-1-risk myelodysplastic syndromes: a randomized trial. *Ann Intern Med*. 2020;172(8):513-522

Bernard E, Tuechler H, Greenberg PL, et al. Molecular International Prognosis Scoring system for myelodysplastic syndromes. Abstract #61. Presented at the 2021 American Society of Hematology Annual Meeting, December 11, 2021.

Blazar BR, Hill GR, Murphy WJ. Dissecting the biology of allogeneic HSCT to enhance the GvT effect whilst minimizing GvHD. *Nat Rev Clin Oncol.* 2020;17:475-492.

Brittenham GM. Iron-chelating therapy for transfusional iron overload. *N Engl J Med.* 2011;364:146-156

Brunner AM, Esteve J, Porkka K, et al. Efficacy and safety of sabatolimab (MBG453) in combination with hypomethylating agents (HMAs) in patients (pts) with very high/high-risk myelodysplastic syndrome (vHR/HR-MDS) and acute myeloid leukemia (AML): final analysis from a phase Ib study. *Blood* 2021;138(suppl 1):244.

Brunner AM, Traer E, Vey N, et al. Allogeneic hematopoietic cell transplantation outcomes of patients with R/R AML or higher-risk MDS treated with the TIM-3 Inhibitor MBG453 (sabatolimab) and hypomethylating agents. *Blood* 2021;138:3677.

Chao MP, Takimoto CH, Feng DD, et al. Therapeutic targeting of the macrophage immune checkpoint CD47 in myeloid malignancies. *Front Oncol*. 2020;9:1380.

Chao MP, Weissman IL, Majeti R. The CD47-SIRPα pathway in cancer immune evasion and potential therapeutic implications. *Curr Opin Immunol.* 2012;24(2):225-232.

Comont T, Treiner E, Vergez F. From immune dysregulations to therapeutic perspectives in myelodysplastic syndromes: a review. *Diagnostics* 2021;11(11):982.

Davids MS, Kim HT, Bachireddy P, et al. Ipilimumab for patients with relapse after allogeneic transplantation. *N Engl J Med.* 2016;375:143-153.

Dillon LW, Gui G, Logan BR, et al. Impact of conditioning intensity and genomics on relapse after allogeneic transplantation for patients with myelodysplastic syndrome. *JCO Precision Oncol*. 2021;5:265-274.

Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood* 2017;129(4):424-447

Duong VH, Baer MR, Hendrick F, et al. Variations in erythropoiesis-stimulating agent administration in transfusion-dependent myelodysplastic syndromes impact response. *Leukemia Res.* 2015;39(6):586-591.

Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. *Lancet Oncol*. 2009;10(3):223-232.

Gerds AT, Scott BL, Greenberg P, et al. Atezolizumab alone or in combination did not demonstrate a favorable risk-benefit profile in myelodysplastic syndrome. *Blood Adv.* 2022;6(4):1152-1161.

Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. *Blood* 2012;120:2454-2465

Kikushige Y, Miyamoto T, Yuda J, et al. A TIM-3/Gal-9 autocrine stimulatory loop drives self-renewal of human myeloid leukemia stem cells and leukemic progression. *Cell Stem Cell* 2015;17(3):341-352.

Kikushige Y, Shima T, Takayanagi S, et al. TIM-3 is a promising target to selectively kill acute myeloid leukemia stem cells. *Cell Stem Cell* 2010;7:708-717.

Kong Y, Zhang J, Claxton DF, et al. PD-1(hi)TIM-3(+) T cells associate with and predict leukemia relapse in AML patients post allogeneic stem cell transplantation. *Blood Cancer J.* 2015;5(7):e330.

Lindsley RC, Saber W, Mar BG, et al. Prognostic mutations in myelodysplastic syndrome after stem-cell transplantation. *N Engl J Med.* 2017;376:536-547.

Logtenberg MEW, Scheeren FA, Schumacker TN. The CD47-SIRPα immune checkpoint. *Immunity* 2020;52(5):742-752.

Mo X-D, Xu L-P, Zhang X-H, et al. Chronic GVHD induced GVL effect after unmanipulated haploidentical hematopoietic SCT for AML and myelodysplastic syndrome. *Bone Marrow Transplant.* 2015;50:127-133

Nakamura R, Saber W, Martens MJ, et al. Biologic assignment trial of reduced-intensity hematopoietic cell transplantation based on donor availability in patients 50-75 years of age with advanced myelodysplastic syndrome. *J Clin Oncol.* 2021;39(3):3328-3339.

Nguyen LT, Ohashi PS. Clinical blockade of PD1 and LAG3--potential mechanisms of action. *Nat Rev Immunol.* 2015;15:45-56.

Sabatos-Peyton C, Longmire T, Baker L, Patel N. Dual modes of action for anti-TIM-3 antibody MBG453 in myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML): preclinical evidence for immune-mediated and anti-leukemic activity. *J Immunother Cancer* 2020;8(suppl 3):A465.

Sallman DA, McLemore AF, Aldrich AL, et al. TP53 mutations in myelodysplastic syndromes and secondary AML confer an immunosuppressive phenotype. *Blood* 2019;134(suppl 1):569.

Scott BL, Pasquini MC, Logan BR, et al. Myeloablative versus reduced-intensity hematopoietic cell transplantation for acute myeloid leukemia and myelodysplastic syndromes. *J Clin Oncol.* 2017;35(11):1154-1161.

Silverman LR, Demakos EP, Peterson BL, et al. Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the cancer and leukemia group *B. J Clin Oncol.* 2002;20(10):2429-2440.

Steensma DP. Graphical representation of clinical outcomes for patients with myelodysplastic syndromes. *Leuk Lymphoma* 2016;57(1):17-20.

Trowbridge JJ, Starczynowski DT. Innate immune pathways and inflammation in hematopoietic aging, clonal hematopoiesis, and MDS. *J Exp Med*. 2021;218:e20201544.

Wong TN, Ramsingh G, Young AL, et al. Role of TP53 mutations in the origin and evolution of therapy-related acute myeloid leukaemia. *Nature* 2015;518(7540):552–555.

Zeidan AM, Stahl M, Hu X, et al. Long-term survival of older patients with MDS treated with HMA therapy without subsequent stem cell transplantation. *Blood* 2018;131:818-821.

About AXIS Medical Education, Inc.

AXIS Medical Education, Inc. is a full-service continuing education company that designs and implements live, web-based, and print-based educational activities for healthcare professionals. AXIS provides convenient opportunities to engage learners based on their individual learning preferences through a full spectrum of educational offerings.

The executive leadership of AXIS combines 75 years of experience in adult learning theory, curriculum design/implementation/assessment, continuing education accreditation standards, and medical meeting planning and logistics. Our team has a deep understanding of the governing guidelines overseeing the medical education industry to ensure compliant delivery of all activities. AXIS employs an experienced team of medical and scientific experts, medical writers, project managers, meeting planners, and logistics professionals. This team is dedicated to meeting the unmet educational needs of healthcare professionals, with the goal of improving patient outcomes.

AXIS believes that partnerships are crucial in our mission to deliver timely, relevant, and high-quality medical education to healthcare professionals. To that end, AXIS partners with other organizations and accredited providers to offer added expertise and assist in expanding access to our educational interventions. AXIS also partners with numerous patient advocacy organizations to provide recommended patient education and caregiver resources in specific disease areas. AXIS finds value in these partnerships because they complement our core clinical curriculum with validated and relevant supplemental resources for busy clinicians and their patients.

The mission of AXIS is to enhance the knowledge, skills, competence, and performance of the interprofessional healthcare team to ensure patients receive quality care, resulting in improved patient outcomes. We engage healthcare professionals in fair-balanced, scientifically rigorous, expert-led certified educational activities designed to foster lifelong learning that is applicable to clinical practice and patient-centered care.

To learn more and to see our current educational offerings, visit us online at www.AXISMedEd.com.

AXIS
Medical Education