ManagingMDS
Myelodysplastic Syndrome Community

Optimizing Outcomes in High-risk MDS: Current and Emerging Standards of Care

Eunice S. Wang, MD
Chief, Clinical Leukemia Service
Professor, Department of Medicine
Roswell Park Comprehensive Cancer Center
Buffalo, New York

Welcome to *Managing MDS*, I am Dr. Eunice Wang. Today I will present "Optimizing Outcomes in High-Risk MDS: Current and Emerging Standards of Care." In this presentation, I will summarize strategies for optimizing patient selection and treatment using current standards of care and available data from clinical trials. I will also identify indications and optimization for the use of hypomethylating agents (also known as HMAs), and I will also seek to outline emerging data from clinical trial reports focusing on the future directions relevant to the treatment of these high-risk MDS patients.

©2018 MediCom Worldwide, Inc.

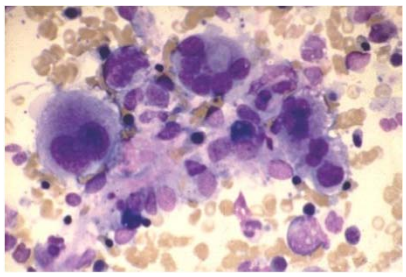
Speaker Disclosure

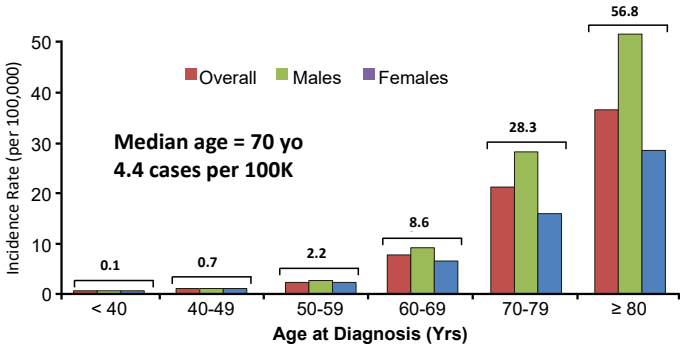
- Advisory activities: AbbVie Inc., Amgen Inc., Arog Pharmaceuticals, Inc., ImmunoGen, Inc., and Pfizer Inc.
- Speakers' bureau: Jazz Pharmaceuticals plc and Novartis AG

These are my disclosures.

©2018 MediCom Worldwide, Inc.

Myelodysplastic Syndrome





- Most often presenting as cytopenias in an older patient
- Clonal hematopoietic disorder with ineffective hematopoiesis
- Mortality due to infection, bleeding, AML transformation

Noone AM, et al. SEER Cancer Statistics Review, 1975-2015, National Cancer Institute. Bethesda, MD, *https://seer.cancer.gov/csr/1975_2015/*, based on November 2017 SEER data submission, posted to the SEER website, April 2018.

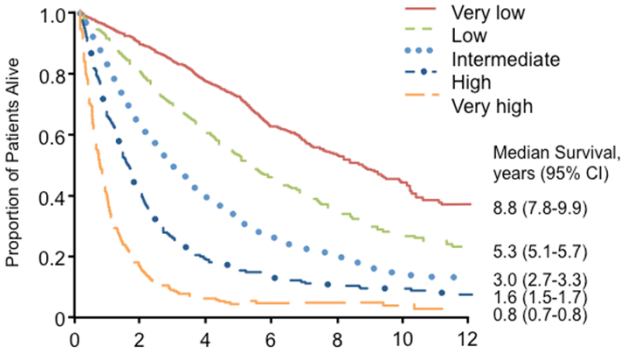
Myelodysplastic syndrome (MDS) most often presents in an older individual as cytopenias. These include most commonly anemias, but also thrombocytopenias and leukopenia or neutropenia. This disorder is a clonal hematopoietic syndrome which is characterized by ineffective hematopoiesis, or lack of ability to produce normal numbers of white cells, red cells, and platelets. This is primarily identified in older individuals with a median age of 70 years old. The incidence rises rapidly as we age, with the majority of patients being diagnosed over the age of 80, and increasing numbers of patients diagnosed in their 70s as well as their 60s. The incidence of MDS in patients under the age of 50 is relatively rare. The majority of these patients will have disease that is progressive, and complications develop due to the lack of effective hematopoiesis; specifically development of life-threatening infections, bleeding, as well as transformation to a more aggressive disease, acute myeloid leukemia. As our population ages in general, we are seeing more and more cases of MDS among older individuals.

©2018 MediCom Worldwide, Inc.

Risk Stratification of MDS: IPSS-R

Parameter	Categories and Associated Scores				
Cytogenetic risk group	Very good	Good	Intermediate	Poor	Very Poor
	0	1	2	3	4
Marrow blast proportion	≤2%	>2% to <5%	5% to 10%	>10%	
	0	1	2	3	
Hemoglobin	≥10 g/dL	8 to <10 g/dL	<8 g/dL		
	0	1	1.5		
Absolute neutrophil count	≥0.8 × 10^9/L	<0.8 × 10^9/L			
	0	0.5			
Platelet count	≥100 × 10^9/L	50 to <100 × 10^9/L	<50 × 10^9/L		
	0	0.5	1		

Possible range of summed scores: 0 to 10

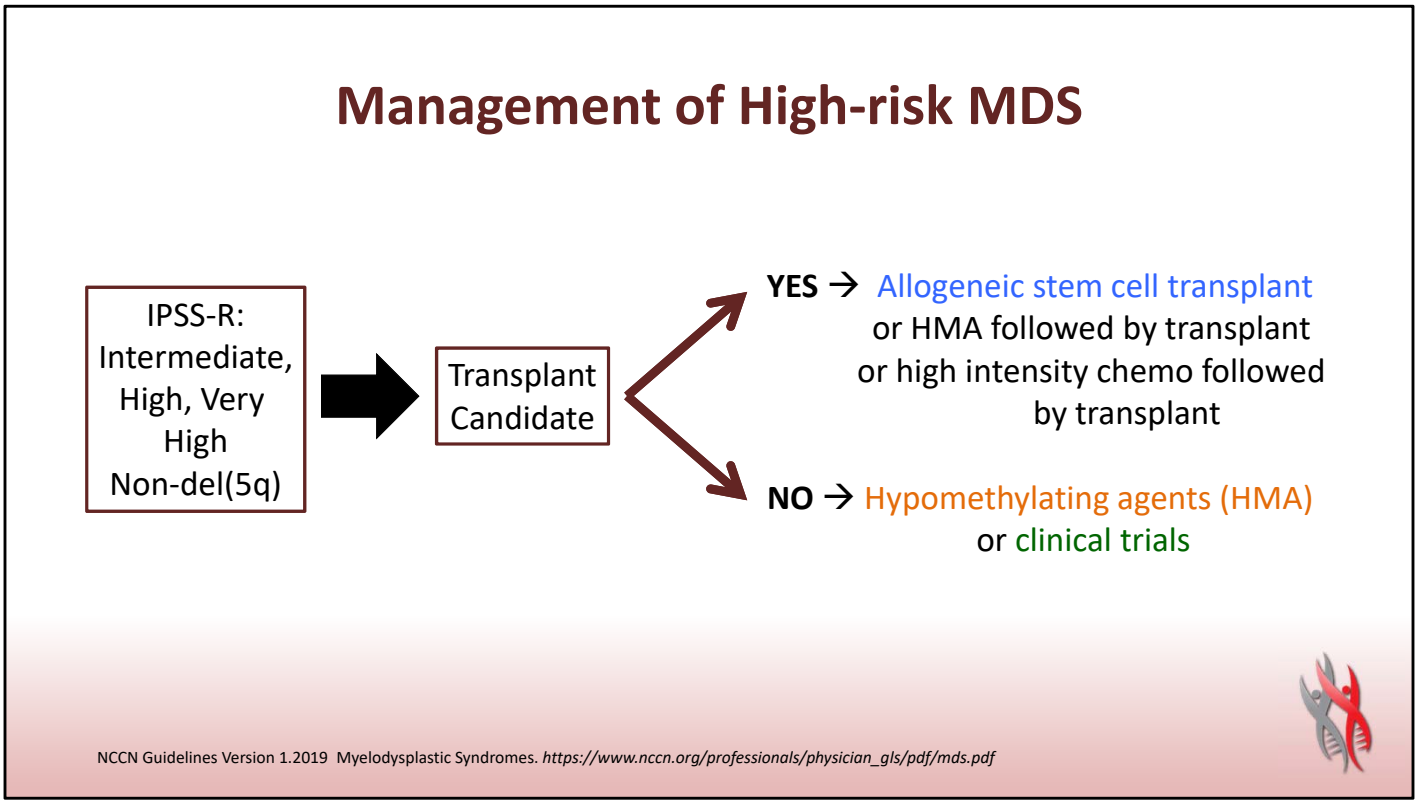


Low risk = very low, low, intermediate
High risk = high, very high

Greenberg PL, et al. *Blood.* 2012;120:2454-2465.2

How do we characterize MDS? Typically, patients are treated based on a strict risk stratification. There have been many prognostic model systems that have been developed to characterize MDS in these older individuals. Among patients that have low-risk MDS, the median overall survival can be as great as 8 to 10 years. However, for patients that have high-risk disease – in general characterized by high numbers of marrow blast counts, poor cytogenetic abnormalities, and severe cytopenias with hemoglobin levels under 8, absolute neutrophil counts under 500, and platelet counts under 50 – the overall survival without treatment can be quite poor, and often is in the range of less than one year. In general, very low- to low/intermediate-risk patients are treated symptomatically, and when cytopenias develop with treatment with growth factors, best supportive care, antibiotics, etc., to maintain quality of life and prevent life-threatening complications.

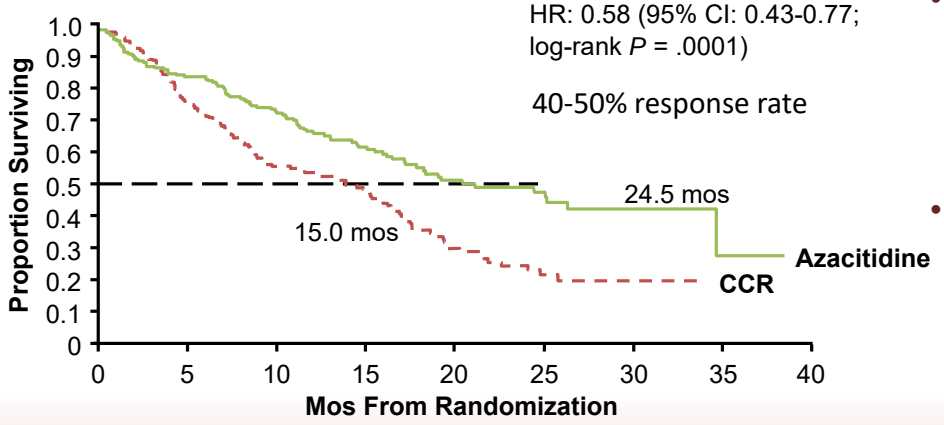
©2018 MediCom Worldwide, Inc.



However, patients that have high-risk MDS are a much higher prognostic category and are at significant risk for development of these potentially life-threatening infectious, bleeding, and AML transformation events. Therefore, the NCCN has outlined these recommendations for the management of these patients. As defined by an IPSS-R score of intermediate, high, or very high, in the absence of del(5q) abnormalities, these high-risk MDS patients should all be considered as candidates for allogeneic stem cell transplantation. Allogeneic stem cell transplantation represents the only curative therapy for high-risk MDS patients. Although only a small proportion of academic centers are actually capable of performing allogeneic stem cell transplantation, this consideration must be entertained in all of our patients because it can have a significant impact on the selection of future treatment options. Patients that are eligible for allogeneic stem cell transplantation should be referred to larger academic centers, and should be considered for what we call bridging therapy with hypomethylating agents or high-intensity chemotherapy followed by a transplantation when a donor is identified and proper arrangements are made. For those elderly or unfit individuals who are not eligible for these types of allogeneic stem cell procedures, standard treatment represents hypomethylating agents or clinical trials with investigational agents.

©2018 MediCom Worldwide, Inc.

Azacitidine Improves Overall Survival of HR-MDS



- Need adequate trial of HMA (4-6 cycles) before assessing response
- Continuous use until clear evidence of loss of response among responders

Fenaux P, et al. *Lancet Oncol.* 2009;10:223-232.

Standard of care treatment for high-risk MDS patients consists of azacitidine therapy. Azacitidine is a hypomethylating agent that has been demonstrated in the phase 3 randomized control study to result in a significant survival benefit of over seven months, as compared with best supportive care in these specific patients. As shown here the hazard ratio of 0.58, and a *P*-value of .0001 signify the significance of this finding. For this reason, azacitidine is considered the gold standard. It is important, however, in managing these patients to remember that these patients should receive an adequate trial of hypomethylating agents before response is assessed. In many studies this consists of at least 4 to 6 or even 8 cycles of hypomethylating therapy before a lack of hematologic response or stable disease is documented by counts or by bone marrow assessment. Once a documented response has occurred with improvement in cytopenias, decreased transfusion dependence, and decreased complications, the standard of care with azacitidine is to continuously administer this agent on a monthly basis until a lack of response develops. It is important to continue the therapy without cease because this therapy is not curative, and the survival benefit is only seen with continued administration.

©2018 MediCom Worldwide, Inc.

Improving Upon Front-line HMA in High-risk MDS

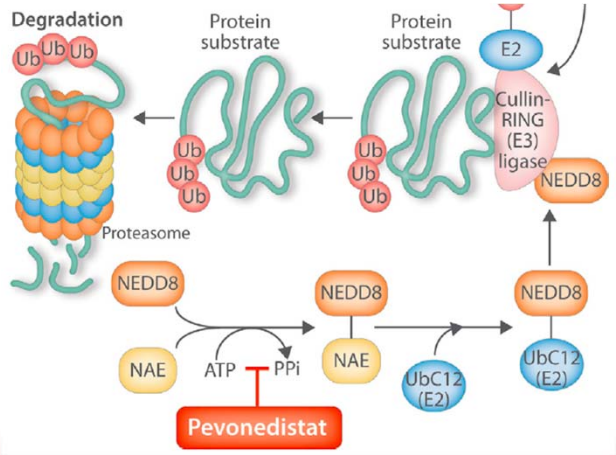
- Phase 3 trial of pevonedistat + azacitidine vs azacitidine alone as first-line therapy for HR-MDS (PANTHER study: NCT03268954)
- A combination study of PF-04449913 (glasdegib) and azacitidine in untreated MDS, AML, and CMML patients (BRIGHT 1012: NCT02367456)
- Phase 3 of ASTX727 in intermediate- and high-risk MDS (Ascertain: NCT03306264)

How can we improve upon front-line hypomethylating therapy for high-risk MDS patients? When considering hypomethylating therapy, one must keep in mind that in addition to the fact that this therapy is not curative, not all patients respond. Studies have shown that between 40% to 60% of high-risk MDS patients will benefit from hypomethylating therapy, but anywhere from 30% to 40% of patients may have primary failure to hypomethylating therapy. For this reason, a number of studies are currently investigating the benefit of adding investigational agents onto a backbone of azacitidine to further improve upon these numbers in terms of prolonged overall survival and maintenance of hematologic responses. Some of these trials are listed here.

One trial is the phase 3 trial of pevonedistat and azacitidine versus azacitidine alone as first-line therapy for high-risk MDS patients. This is also known as the PANTHER study. A second study is investigating the use of a hedgehog inhibitor, glasdegib, plus azacitidine in untreated MDS, AML and CML patients in the phase 2 study. Lastly, there is a phase 3 study of ASTX727 in intermediate high-risk MDS patients in the Ascertain trial.

©2018 MediCom Worldwide, Inc.

Pevonedistat in Front-line HR MDS Patients

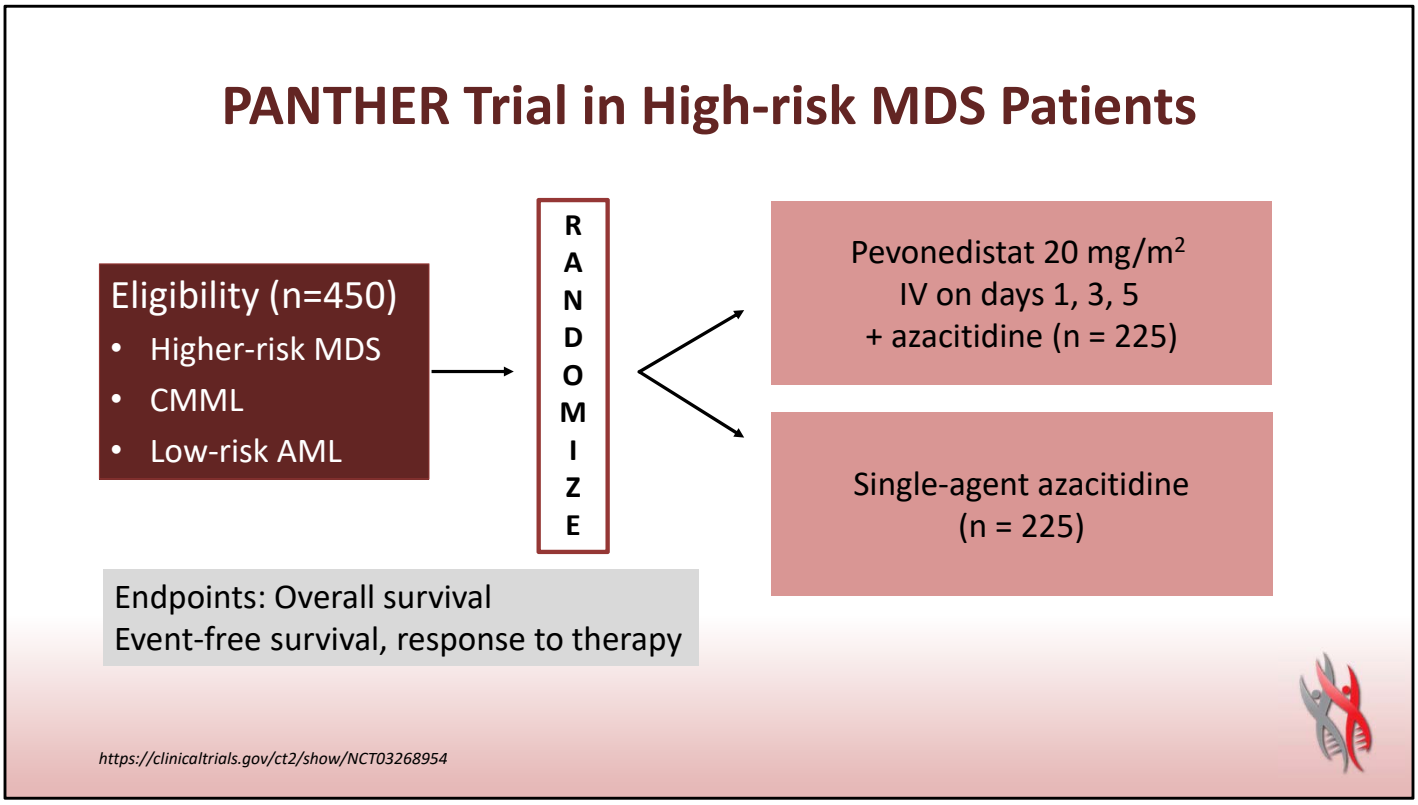


- Small molecule inhibitor of NEDD8 (neural cell developmentally down-regulated 8) activating enzyme
- Suppression of ubiquitin ligases leads to inhibition of DNA replication
- Synergistic effects in combination with azacitidine in preclinical assays

Fathi A. *Blood* 2018;131:1391-1392.

Pevonedistat in front-line high-risk MDS patients is a novel agent which functions by inhibition of NEDD8. NEDD8 stands for neural cell developmentally down-regulated 8-activating enzyme. This enzyme plays a key role in the suppression of the ubiquitin-ligases which lead to inhibition of DNA replication. Blockage of this NEDD activating enzyme therefore would be postulated to result in epigenetic release of tumor suppressor genes and restoration of normal function in patients with high-risk MDS. In the preclinical setting, synergistic activity between pevonedistat and azacitidine has been demonstrated and has led to the design of a phase 3 trial.

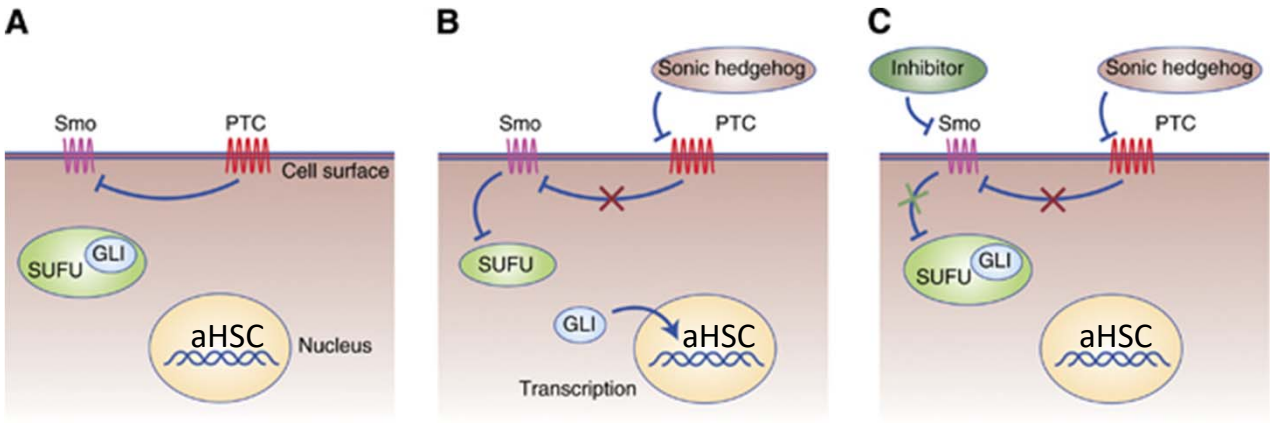
©2018 MediCom Worldwide, Inc.



The PANTHER trial in high-risk MDS is exploring whether pevonedistat given IV on days 1, 3 and 5 added to azacitidine offers any clinical benefit for the treatment of front-line high-risk MDS patients over single-agent azacitidine. Eligibility for this trial includes not only higher-risk MDS but also CMML patients and lower-risk AML patients. It is estimated that up to 450 patients will be randomized on this study. The primary endpoints of this study will be, again, overall survival benefit as compared to azacitidine alone, event-free survival, and evidence of therapeutic responses.

©2018 MediCom Worldwide, Inc.

Glasdegib: Inhibitor of Smo in Hedgehog Pathway

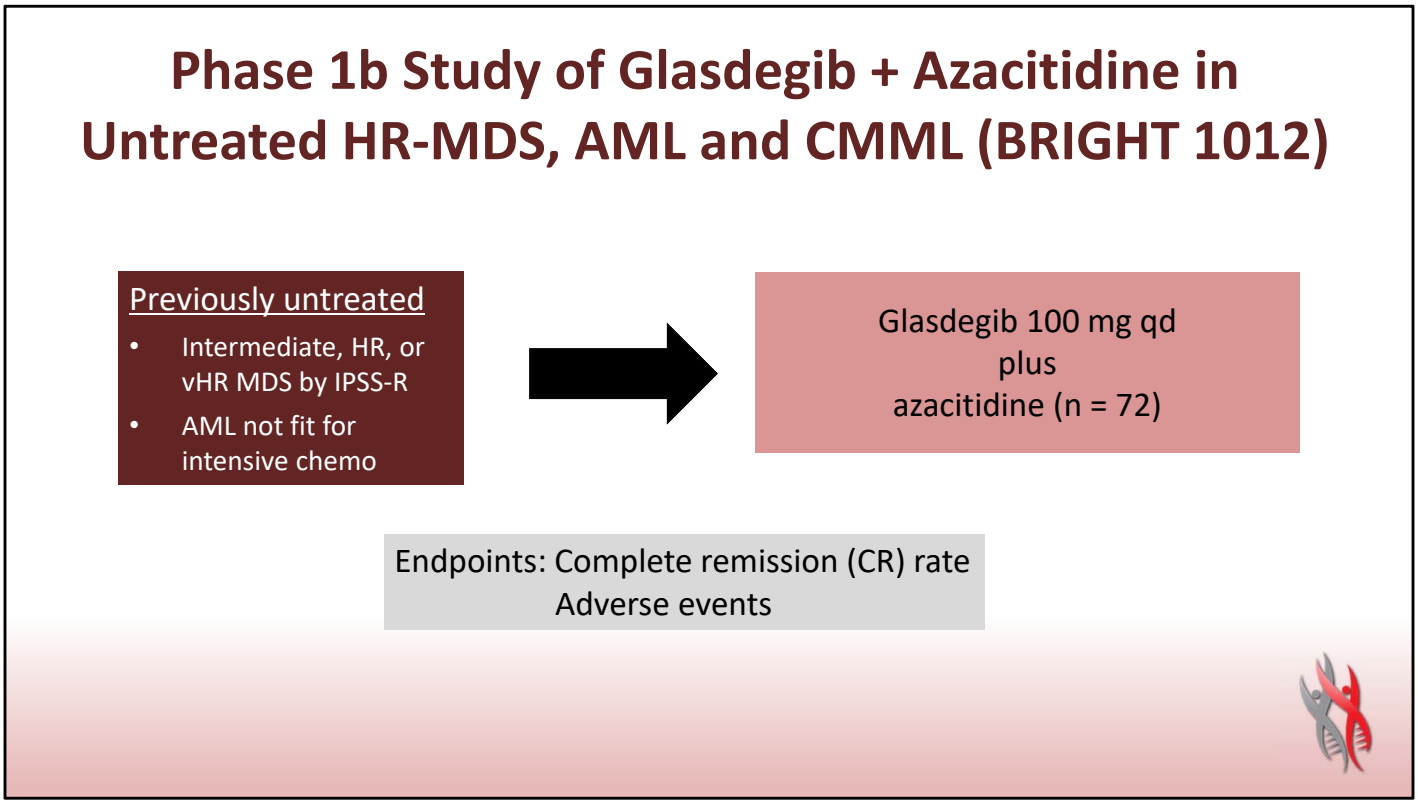


aHSC=abnormal hematopoietic stem cells responsible for MDS; Smo=smoothened
Lear J, et al. *Brit J Cancer.* 2014;111(8):1476-1481.

Glasdegib is an inhibitor of smoothened involved in the hedgehog pathway. Hedgehog is an important signaling pathway which is believed to be responsible for the maintenance and self-renewal of hematopoietic stem cells, as well as leukemic stem cells and dysfunctional myeloid stem cells which are believed to be the root cause of underlying MDS. Prior studies have shown that although azacitidine can alter epigenetic and hypomethylating mechanisms and improve upon the hematologic ineffectiveness seen in MDS, azacitidine alone has no effect on the underlying stem cell biology. Therefore, inhibitors of smoothened have the ability to restore DNA replication and restore and potentially restrict the abnormal stem cells which are the etiology of these high-risk MDS patients.

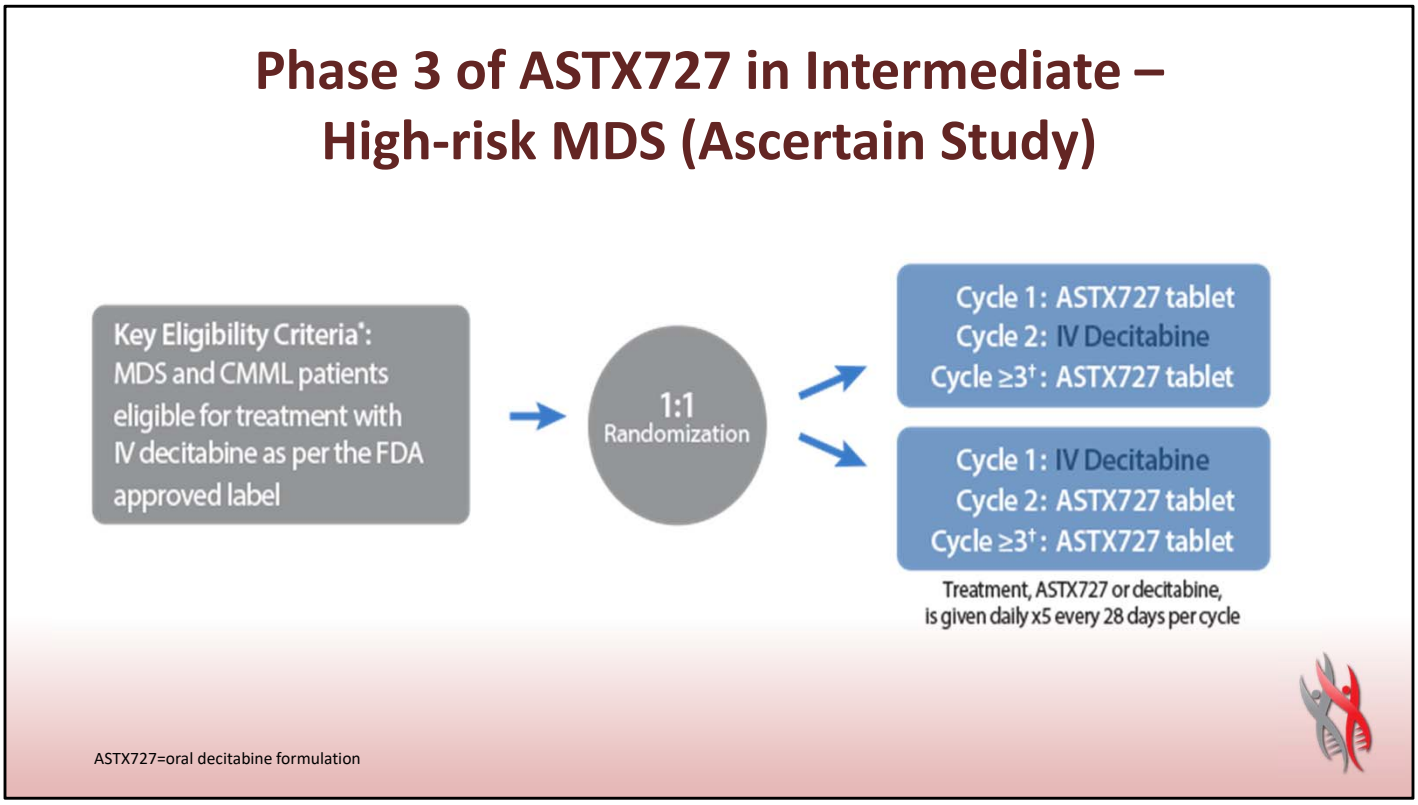
©2018 MediCom Worldwide, Inc.

Phase 1b Study of Glasdegib + Azacitidine in Untreated HR-MDS, AML and CMML (BRIGHT 1012)



The current trial is investigating the use of glasdegib plus or minus azacitidine, again, in newly diagnosed, untreated high-risk MDS, AML, and CMML patients. In this study, patients will be randomized to receive the hedgehog inhibitor plus azacitidine versus single-agent azacitidine, with the same endpoints of overall survival, event-free survival, and response to therapy.

©2018 MediCom Worldwide, Inc.



A third trial under investigation is looking at a novel oral decitabine formulation. In contrast to azacitidine, decitabine has been shown to be effective in inducing responses in high-risk MDS patients, but it has not been shown to result in overall survival benefit in the randomized phase 3 setting. Other practitioners have preferred decitabine because it is a 5-day administration in the treatment of high-risk MDS as opposed to a 7-day subcutaneous administration required for azacitidine. However, many individuals, particularly older individuals which represent the majority of our patients in high-risk MDS, would prefer an oral formulation. Therefore, this agent has been shown in earlier studies to have similar pharmacokinetics to the IV decitabine, and therefore is being investigated as a potential alternative and more easily tolerated and administered hypomethylating agent in this particular setting. In this trial, patients with high-risk MDS or CMML who are eligible for treatment will be randomized to receive either IV decitabine or oral decitabine, alternating with the other formulation in cycle 2 followed, by oral administration of the oral decitabine tablet continuously. The outcomes are overall survival, therapeutic responses, and event-free survival.

©2018 MediCom Worldwide, Inc.

Outcome of MDS Patients after HMA Failure is Poor

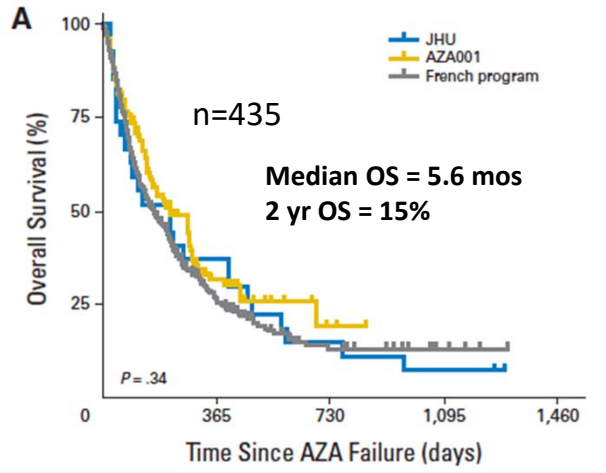


Table 4. Analysis of Prognostic Factors of Survival After AZA Failure for Patients Treated for High-Risk MDS and Former RAEB-T

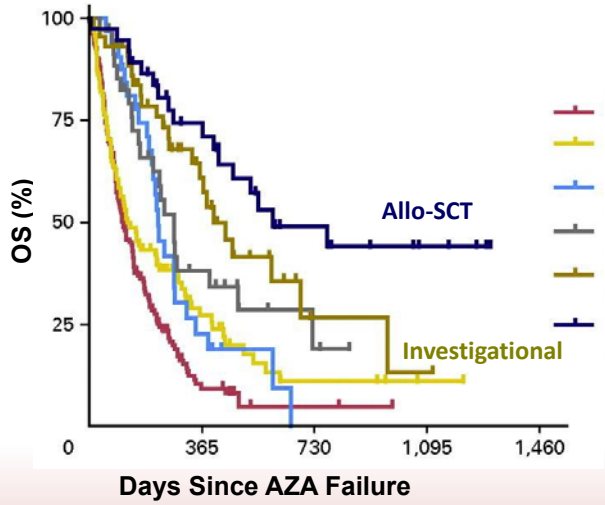
	Univariate Analysis			Multivariate Analysis		
Variable	Median OS (months)	95% CI	*P*	HR	95% CI	*P*
Age as continuous variable			.002	1.02 per year	1.01 to 1.03	.02
Sex						
Female	8	5.2 to 10.3	.04	1		.005
Male	5.5	4.7 to 6.8		1.42	1.12 to 1.82	
Cytogenetic risk						
Favorable	8	6.5 to 9.7	.003	1		
Intermediate	7.3	4.9 to 9.4		1.18	0.85 to 1.62	.32
High risk	4.6	3.7 to 5.8		1.96	1.48 to 2.59	< .001
BM blasts before AZA, %						
< 10	7.9	5.6 to 10.3	.01	1		.004
10-29	5.2	4.8 to 7.3		1.5	1.14 to 1.99	
Response to AZA						
No	4.6	3.9 to 6.3	.007	1		< .001
Yes	7.4	6.5 to 9.3		0.67	0.53 to 0.85	

Prébet T, et al. *J Clin Oncol.* 20112;29(24):3322-3327.

As we know, hypomethylating therapy with azacitidine for the treatment of high-risk MDS patients is not a curative strategy. What is the outcome of MDS patients once they have either been refractory to hypomethylating therapy or developed a resistance to hypomethylating therapy? Overall, as this graphic shows you, the outcome of high-risk MDS patients after failing and hypomethylating agents remains very, very poor. The median overall survival is measured in approximately 5 to 7 months and the two-year overall survival of patients failing hypomethylating agents is only about 10% to 20%. Things that can contribute as well include male gender and unfavorable cytogenetics; but overall, once the patient has developed hypomethylating failure, the search would then need to be initiated for the next line of therapy.

©2018 MediCom Worldwide, Inc.

Transplant is Best Salvage Rx After HMA Failure



Type of Salvage	N	ORR	Median OS, Mos
Unknown	165	NA	3.6
Best supportive care	122	NA	4.1
Low-dose chemotherapy	32	0/18	7.3
Intensive chemotherapy	35	3/22	8.9*
Investigational therapy	44	4/36	13.2*†
Allogeneic transplantation	37	13/19	19.5*†

*Univariate analysis (log-rank test) showed significant differences between palliative care and intensive chemotherapy (CT; $P = .04$), investigational therapy (IT; $P < .001$), or allogeneic stem-cell transplantation (ASCT; $P < .001$). †There was also a significant difference between intensive CT and IT ($P = .05$) and intensive CT and ASCT ($P = .008$). The difference between IT and ASCT reached borderline significance ($P = .09$)

Prébet T, et al. *J Clin Oncol.* 20112;29(24):3322-3327.

What would be the best therapy for patients who are failing standard hypomethylating agents? As shown here, allogeneic stem cell transplantation offers the best possibility of long-term benefit in this particular setting. As shown here, allogeneic stem cell transplantation for patients who have failed HMAs results in a median overall survival of almost 20 months. Best supportive care, in contrast, is only estimated to have a survival benefit of about 4 months at best. Low-dose chemotherapy with either low-dose cytarabine or potentially a second hypomethylating agent is thought to be largely ineffective with an overall survival of only 7 months. Intensive chemotherapy which has been tried in the past for these patients is similarly not very beneficial and is associated with high mortality and morbidity. If a patient is not eligible for allogeneic stem cell transplantation it is important to note that the next best option remains investigational therapy, and combinations of investigational agents have consistently been shown in this setting to result in the second-best treatment outcome following allogeneic transplantation.

©2018 MediCom Worldwide, Inc.

Clinical Trials in MDS Failing HMA Therapy

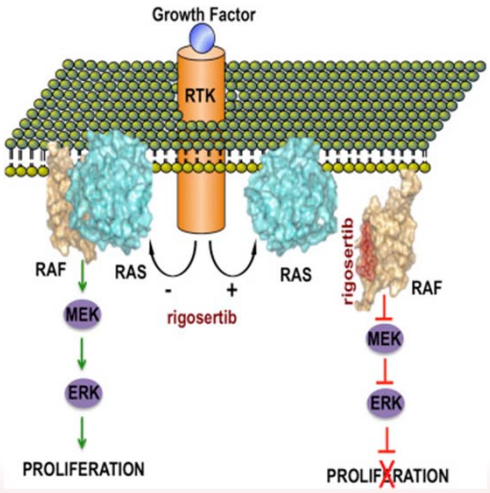
- Phase 3, international, randomized, controlled study of rigosertib + best supportive care versus physician's choice of treatment + best supportive care in patients with MDS after failure of a hypomethylating agent (INSPIRE: NCT02562443)

- Phase 2 study of Selective Inhibitor of Nuclear Export (SINE), selinexor in patients with myelodysplastic syndromes (NCT02228525)

What are some of the agents that we're looking at in this setting? There are a couple of phase 3 clinical trials that are in development, one of which is the INSPIRE trial. The INSPIRE trial is investigating the benefit of rigosertib plus best supportive care versus physician's choice in care in patients who have MDS which has failed a prior hypomethylating agent. There is also a phase 2 study of a novel mechanistic agent, selinexor, also in patients with HMA failure.

©2018 MediCom Worldwide, Inc.

Rigosertib: Mechanism of Action in MDS



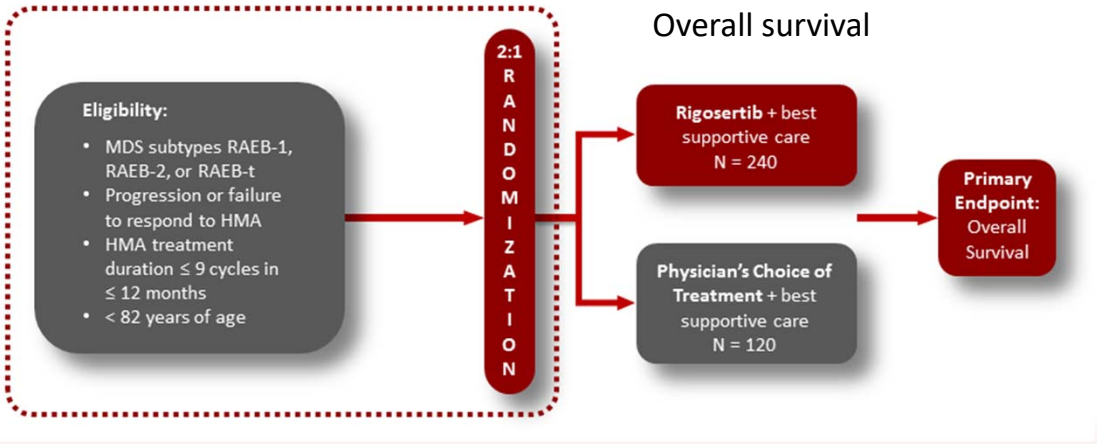
- Rigosertib acts as a RAS mimetic
  - Binds to the RAS-binding domains of multiple RAS effects
  - Blocks downstream signaling cascades including PI3K and RAF
  - Inhibits MEK-ERK pathway
  - Anti-proliferative effects

Athuluri-Divakar SK, et al. *Cell.*2016,165:643-655.

One of the novel agents under investigation for the treatment of MDS patients who have failed prior hypomethylating agents is rigosertib. Rigosertib is a novel agent which acts as a RAS mimetic. RAS is involved in oncogenesis and in the etiology of many solid and hematologic malignancies. Rigosertib binds to the RAS binding domains of the receptor tyrosine kinase and effectively blocks downstream signaling through the receptor tyrosine kinase, involving pathways including PI 3-kinase and the MEK-ERK pathway. Overall, in the preclinical setting, rigosertib has been shown to result in antiproliferative effects and to be beneficial for the treatment of MDS patients who have failed hypomethylating agents in the phase 2 setting.

©2018 MediCom Worldwide, Inc.

INSPIRE Trial in HMA-failure MDS Patients
International Trial of Phase 3 Rigosertib



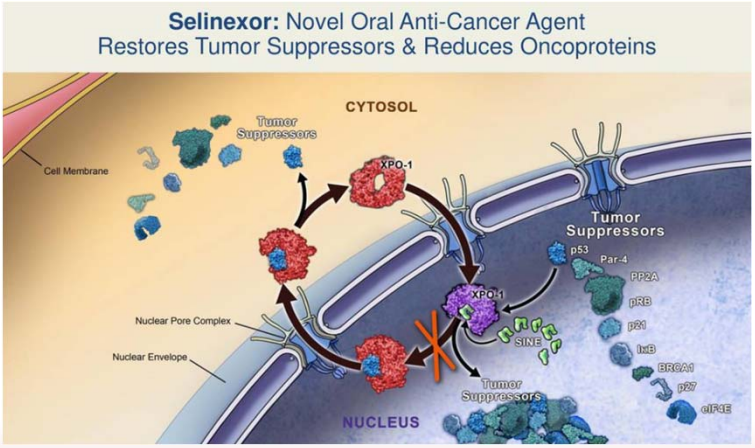
https://www.onconova.com/clinical-trials/; www.clinicaltrials.gov, identifier: NCT02562443.

The current INSPIRE trial in HMA failure MDS patients is examining the potential clinical benefit of rigosertib plus best supportive care versus physician's choice of therapy in patients with high-risk MDS who have progressed or failed to respond to hypomethylating agents. In this trial, the hypomethylating duration must be less than or equal to 9 cycles (or under 12 months) and the primary endpoint of this trial will be overall survival benefit. Patients in this trial are being randomized at over 200 sites internationally with the 2:1 ratio favoring the rigosertib arm as opposed to the best supportive MD choice arm.

©2018 MediCom Worldwide, Inc.

Selinexor: Selective Inhibitor of Nuclear Export (SINE)

- Phase 2 study of Selective Inhibitor of Nuclear Export (SINE), selinexor in patients with myelodysplastic syndromes

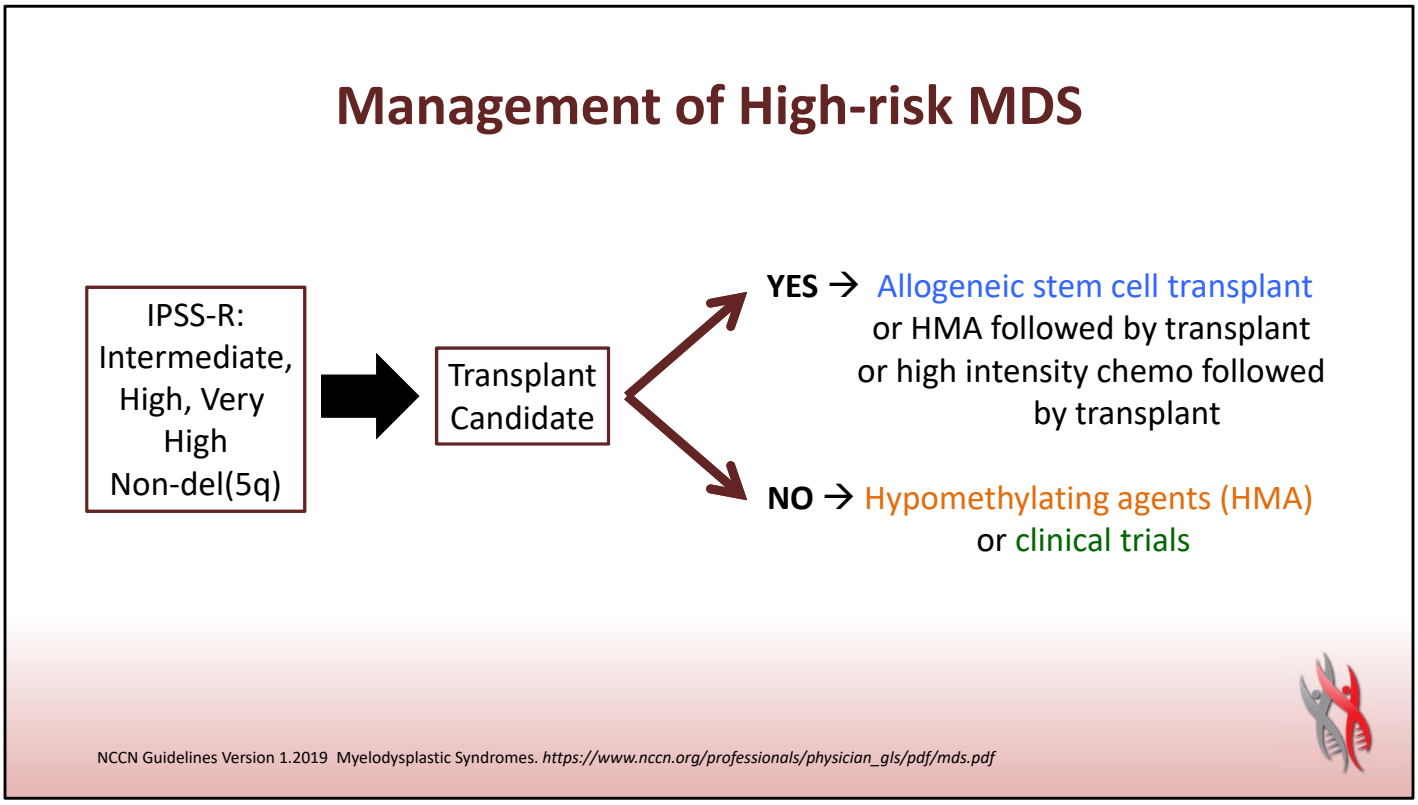


©2016 Karyopharm Therapeutics Inc.

https://seekingalpha.com/article/4058161-karyopharms-selinexor-drive-substantial-growth

Another agent which is being examined for the treatment of high-risk MDS patients who have failed prior hypomethylating agents is a newer agent selinexor. Selinexor is a unique agent that functions as a selective inhibitor of nuclear export, or SINE. This novel oral anticancer agent, by blocking this nuclear export mechanism, is designed to restore tumor suppressive function and to decrease the production and function of multiple oncoproteins, which are the basis of tumor genesis in both MDS and other malignancies.

©2018 MediCom Worldwide, Inc.



To summarize, the overall management of high risk MDS involves, first, identification of the risk stratification of these patients to determine which patients would most benefit from these particular interventions. Secondly, once patients have been classified as having intermediate, high, very high, or a non-del(5q) MDS, these patients should be considered for whether they are candidates for allogeneic stem cell transplantation. Patients that are considered candidates for allogeneic stem cell transplantation should be referred to academic medical centers for further consideration and screening as well as donor selection. These patients should receive some sort of interim or bridge therapy with either hypomethylating therapy or even intensive chemotherapy, followed by subsequent stem cell transplantation. For those patients who are unfit, elderly, or otherwise considered unsuitable for allogeneic stem cell transplantation, the standard of care remains hypomethylating therapy with azacitidine, or consideration of clinical trial intervention.

©2018 MediCom Worldwide, Inc.

Key Points

- Risk stratification important to identify HR-MDS patients
- Standard of care = allogeneic transplant vs HMA therapy
- HMA (Aza) failure prolongs survival but not curative
- Future directions
  - HMA plus novel agent combinations for new diagnosis HR-MDS
  - Novel agents for MDS patients failing HMA

To conclude, I would like to leave you with these key takeaway points. Optimization of outcomes on high-risk MDS patients involves several steps. One is the appropriate risk stratification of patients to identify those patients at particularly high risk of progression, with estimated overall survival rates measured in the 6- to 8-month range. Following identification of these high-risk patients, the next step would be to consider standard of care options. These would include whether the patient is a candidate for allogeneic stem cell transplantation versus whether they should receive standard of care hypomethylating agents, or referral for possible consideration of clinical trial. Patients who exhibit primary resistance to hypomethylating agents, or develop secondary resistance after multiple cycles of therapy, should be referred for investigational therapies given the very poor outcome of these individual patients. Given the fact that none of our current therapeutic approaches with the exception of allogeneic stem cell transplantation will be curative in this patient population, much is going on in the future clinical development of novel agents to further improve the clinical outcomes for this difficult-to-treat patient population. Trials in the phase 3 setting examining agents such as rigosertib have been developed to further improve the prognosis for high-risk MDS patients by adding drugs on top of the azacitidine in the front-line setting. Alternatively, patients who have failed hypomethylating therapy are eligible to receive therapy, investigational agents in this setting, given their overall survival is measured in only a mere few months. Thank you very much for viewing this activity.

©2018 MediCom Worldwide, Inc.