



MDS updates

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9/28/2018

2018 MDS Update

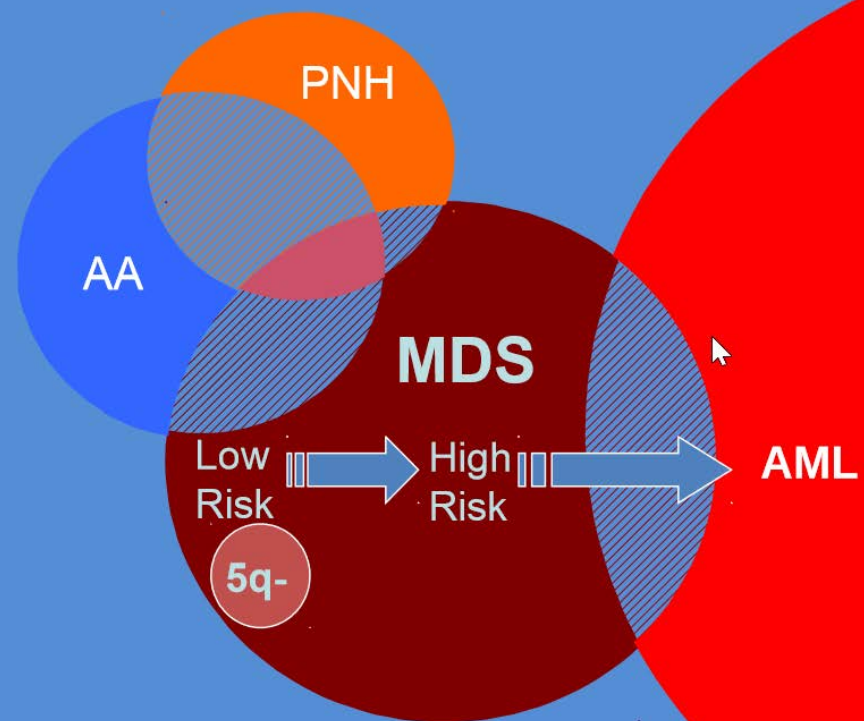
- ▶ Defined by Common Features
 - ▶ Clonal Disorder
 - ▶ Dysplasia
 - ▶ Cytopenias
 - ▶ Transformation to AML
- ▶ Heterogeneous Disease – Heterogeneous Outcomes
 - ▶ Median Survival from 0.8 to 8 years
 - ▶ Differential Response to Therapy
 - ▶ Cytogenetic & Molecular Profiles
 - ▶ Impact of Immunologic & Microenvironment
- ▶ Today: 2018 Updates
 - ▶ Prognosis
 - ▶ IPSS and Beyond
 - ▶ Mutation Profiling
 - ▶ Therapy

What is MDS

- ▶ A Group of Progressive Bone Marrow Disease characterized by:
 - ▶ Failure of the bone marrow to generate normal blood cells
 - ▶ There are 3 main types of blood cells:
 - ▶ Platelets – makes your blood clot
 - ▶ Red Blood Cells - carries oxygen in your blood
 - ▶ White Blood Cells – fights infection
 - ▶ For these cells to carry out their function – they must be produced in adequate numbers and must be normal functioning
 - ▶ In MDS - the cells that are produced are too few in number and are dysfunctional

Risk Factors for MDS

- ▶ Older age – uncommon in people younger than 50
 - ▶ Most cases found in people 70-80 years of age
- ▶ Sex – more common in men
 - ▶ Reason unclear – thought it might have to do with men being more likely to smoke or be exposed to certain chemicals in the workplace
- ▶ Cancer Treatment – prior treatment with chemotherapy
- ▶ Genetic syndromes
 - ▶ Fanconi anemia
 - ▶ Diamond Blackfan anemia
 - ▶ Shwachman-Diamond syndrome
 - ▶ Familial platelet disorders
 - ▶ Severe congenital neutropenia
 - ▶ Dyskeratosis congenital
- ▶ Familial MDS – gene mutation
- ▶ Smoking
- ▶ Environmental exposures
 - ▶ High-dose radiation
 - ▶ Long-term workplace exposure to benzene and other chemicals used in the petroleum and rubber industries



AA – Aplastic Anaemia

PNH – Paroxysmal Nocturnal Haemoglobinuria

Classification

- ▶ MDS is classified into several different subtypes based on the following features:
 - ▶ Blood cell counts
 - ▶ Percentage of blasts in the bone marrow
 - ▶ Risk that it will turn into AML
- ▶ It is also classified as either primary MDS or secondary MDS.
- ▶ MDS is given a stage called an IPSS-R score.
 - ▶ These classifications help doctors plan treatment and predict a patient's prognosis, which is the chance of recovery.

Primary/Secondary MDS

- ▶ Primary MDS is much more common than secondary MDS.
 - ▶ About 80% of people with MDS have primary MDS.
 - ▶ In primary MDS, no apparent risk factors can be found.
 - ▶ This may also be called *de novo* MDS.
- ▶ Secondary MDS occurs because of damage to the DNA from chemotherapy or radiation therapy previously given to treat another medical condition.
 - ▶ MDS can develop 2 to 10 years after such treatment.
 - ▶ Secondary MDS is often associated with more complex chromosomal abnormalities.

MDS Subtypes

WHO 2016 Classification of Subtypes

- ▶ **Refractory anemia (RA).**
 - ▶ White blood cell counts and platelet counts are healthy.
 - ▶ There are less than 5% blasts found in the bone marrow.
 - ▶ This subtype of MDS does not often turn into AML.
- ▶ **Refractory anemia with ringed sideroblasts (RARS).**
 - ▶ People with this subtype of MDS have anemia, similar to those with RA, except more than 15% of the red blood cells are sideroblasts.
 - ▶ A sideroblast is a red blood cell in which the iron in the cell appears to be in a ring around the center of the cell where the genes are found, called the nucleus.
 - ▶ The white blood cell and platelet counts are usually healthy.
 - ▶ People diagnosed with RARS have a low risk of developing AML.
- ▶ **Refractory cytopenia with multilineage dysplasia (RCMD).**
 - ▶ In this subtype, people have less than 5% blasts and less than 15% ringed sideroblasts in the bone marrow.
 - ▶ The other bone marrow cells look abnormal when viewed under the microscope.
 - ▶ At least 2 of the blood cell counts are low.
 - ▶ RCMD may eventually turn into AML.

MDS Subtypes - continued

- ▶ **Refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD-RS).**
 - ▶ This subtype is similar to RARS, in which people have anemia and more than 15% sideroblasts.
 - ▶ The other bone marrow cells also look abnormal when viewed with a microscope.
 - ▶ At least 2 types of blood cell counts are low.
 - ▶ RCMD-RS may eventually turn into AML.
- ▶ **Refractory anemia with excess blasts (RAEB).**
 - ▶ People with RAEB can have decreases in all or some of their blood cell counts.
 - ▶ There are less than 5% blast cells in the blood and 5% to 20% blasts in the bone marrow.
 - ▶ People with more than 20% blasts in the bone marrow are diagnosed with AML.
 - ▶ People with RAEB may also have lower white blood cell and platelet counts.
 - ▶ About 40% of people diagnosed with RAEB eventually develop AML.
- ▶ **Myelodysplastic syndrome, unclassified (MDS-U).**
 - ▶ People diagnosed with this subtype have decreased numbers of white blood cells, red blood cells, or platelets, but do not have the specific signs of the other MDS subtypes.
- ▶ **MDS associated with isolated del(5q).**
 - ▶ People with this subtype have anemia and fewer than 5% blasts, and genetic material is missing from chromosome 5.

CMML and JMML

- ▶ In addition to the 7 MDS subtypes:
 - ▶ Types of blood cancers that the WHO classifies as “mixed myelodysplastic/myeloproliferative diseases.”
 - ▶ Chronic myelomonocytic leukemia (CMML)
 - ▶ Juvenile myelomonocytic leukemia (JMML)
 - ▶ Unlike other types of MDS in which blood counts are low, white blood cell counts are higher in these subtypes.
 - ▶ Both CMML and JMML begin after a change, or mutation, happens in a type of blood cell called a monocyte.
 - ▶ CMML generally occurs in people ages 65 to 75.
 - ▶ JMML is most common in children younger than 6.
 - ▶ Treatment is similar to MDS and can include chemotherapy and/or stem cell transplantation

IPSS-R System

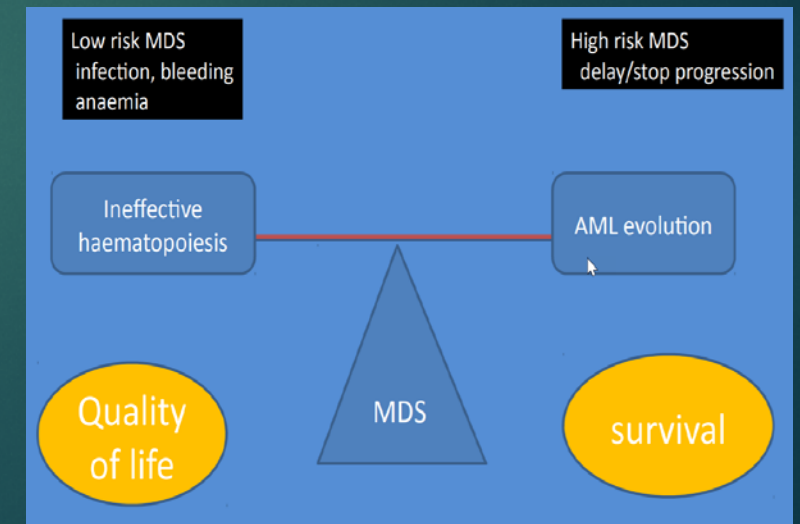
- ▶ The revised International Prognostic Scoring System (IPSS-R) is another classification system used by doctors to help predict a person's risk of developing AML and overall survival.
- ▶ The IPSS-R looks at factors such as the percentage of blasts found in the bone marrow, type and extent of chromosomal changes, and levels of hemoglobin found in red blood cells, platelets, and a type of white blood cell called neutrophils.
- ▶ Poor prognostic factors include:
 - ▶ Certain types and higher numbers of chromosomal changes
 - ▶ Higher percentage of blasts in the bone marrow
 - ▶ Low levels of hemoglobin, platelets, and neutrophils
- ▶ The total IPSS-R score places people with MDS into 5 distinct groups:
 - ▶ Very low risk
 - ▶ Low risk
 - ▶ Intermediate risk
 - ▶ High risk
 - ▶ Very high risk
- ▶ People with MDS who have a lower IPSS-R score have the best outlook for survival and need less aggressive treatment.
 - ▶ For patients with lower IPSS-R scores, overall survival rates tend to be lower when they need red blood cell transfusions.
 - ▶ A red blood cell transfusion is a procedure in which blood or blood cells from 1 person are given to another person.
- ▶ A person diagnosed with a high-risk subtype of MDS and whose IPSS-R score is high usually needs more intensive treatment.

Prognosis



Prognosis for MDS: A Key Element to Care

- ▶ Patients
 - ▶ Set expectations
- ▶ Physicians
 - ▶ Guide treatment decision
- ▶ HSCT
 - ▶ Does benefit surpass risk?
- ▶ Treatment Guidelines
 - ▶ Recommendations based on risk of disease
- ▶ Clinical Trials
 - ▶ Objective description study participants
 - ▶ Risk stratification helps determine appropriateness of trial participation
 - ▶ Certain agents may benefit certain groups of patients over others:
 - ▶ Revlimid (low risk, isolated anemia, 5q minus syndrome)
 - ▶ Azacitadine: goals different for different subgroups:
 - ▶ Overall survival advantage for high risk patients
 - ▶ Particularly effective for del 7



IPSS-R

- ▶ Bone marrow blast percentage –
 - ▶ ≤ 2 (0 points)
 - ▶ >2 to <5 (1 point)
 - ▶ 5 to 10 (2 points)
 - ▶ >10 (3 points)
- ▶ Karyotype –
 - ▶ Very good karyotype (0 points) includes $-Y$ or $\text{del}(11q)$
 - ▶ Good karyotype (1 point) includes normal karyotype, $\text{del}(5q)$, $\text{del}(12p)$, $\text{del}(20q)$, or a double abnormality including $\text{del}(5q)$
 - ▶ Intermediate karyotype (2 points) includes $\text{del}(7q)$, $+8$, $+19$, $i(17q)$, and any other single or double independent clones
 - ▶ Poor karyotype (3 points) includes -7 , $\text{inv}(3)/\text{t}(3q)/\text{del}(3q)$, double abnormalities including $-7/\text{del}(7q)$, or three abnormalities
 - ▶ Very poor karyotype (4 points) includes complex karyotype (≥ 3 abnormalities)
- ▶ Hemoglobin (g/dL) –
 - ▶ ≥ 10 (0 points)
 - ▶ 8 to <10 (1 point)
 - ▶ <8 (1.5 points)
- ▶ Platelets (cells/microl) –
 - ▶ $\geq 100,000$ (0 points)
 - ▶ 50,000 to 100,000 (0.5 points)
 - ▶ $<50,000$ (1 point)
- ▶ Absolute neutrophil count (cells/microl) –
 - ▶ ≥ 800 (0 points)
 - ▶ <800 (0.5 points)

Risk Scoring

Risk Category	Risk Score
Very Low	≤ 1.5
Low	$\geq 1.5 - 3$
Intermediate	$> 3 - 4.5$
High	$> 4.5 - 6$
Very High	> 6

Risk Category – Survival

Risk Score	Median Survival
Very Low	8.8 year
Low	5.3 years
Intermediate	3 years
High	1.6 years
Very High	0.8 years

Risk of MDS → AML

Risk Category	Risk of AML
Very Low	3%
Low	14%
Intermediate	33%
High	54%
Very High	84%

Approaches to Care

- ▶ NCCN Guidelines
 - ▶ Clinically relevant cytopenias
 - ▶ Age <60; >60
 - ▶ Performance Status
 - ▶ Prognostic Risk Category
 - ▶ Lower risk (VL, L, Intermed): Goal Hematologic Improvement
 - ▶ High Risk (Intermed, H, VH): Goal alter natural history (survival, delay, progression to AML)
 - ▶ Consider if HSCT Candidate – goal is cure
 - ▶ Prognostic risk category
 - ▶ Age, Performance Status
 - ▶ Donor options

MDS: Allogeneic Stem Cell Transplantation

- ▶ Remains only curative approach
 - ▶ 40% long-term disease free survival
 - ▶ 20% transplant related mortality
- ▶ Candidates for Reduced Intensity approaches including “fit” patients into their early 70’s
- ▶ IPSS: Intermediate Risk-II or greater
- ▶ Role of Hypomethylating agent/chemotherapy pre-HSCT debated

Treatment Options

- ▶ Immune suppression
- ▶ Targeted therapy
 - ▶ **Luspatercept** blocks cellular proteins that are part of the TGF-beta superfamily
 - ▶ **Rigosertib**
 - ▶ **Imetelstat**, a telomerase inhibitor
 - ▶ **Pevonedistat**, an NAE inhibitor
 - ▶ **Selinexor**, an XPO1 inhibitor
 - ▶ **Glasdegib**, a smoothened (SMO) inhibitor
- ▶ Stem cell transplant

Low Risk MDS

- ▶ Primarily goal of Treatment is Supportive – improve symptoms and quality of life
 - ▶ Transfusions
 - ▶ Iron Chelation
 - ▶ Growth factors
 - ▶ Antibiotics
 - ▶ Lenalidomide (del5q +/- 1 cytogenetic abnormality)
 - ▶ Hypomethylating agent (aza, decitabine)
 - ▶ Immunosuppressive therapy
 - ▶ Clinical Trial

Hoeks et al, Abstract 424

- ▶ Iron Chelation therapy in low risk MDS
- ▶ Prospective observational study in 2205 registry patients in Europe
 - ▶ 205 received iron chelation:
 - ▶ 154 deferasirox
 - ▶ 39 deferoxamine
 - ▶ 12 deferiprone
 - ▶ Iron Chelation therapy recipients were younger, had better performance scores and fewer comorbidities
 - ▶ Median time on treatment was 13 months (range 3-42)
- ▶ Control group was 657 non-chelated patients

Luspatercept

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Purchase

Luspatercept for the treatment of anaemia in patients with lower-risk myelodysplastic syndromes (PACE-MDS): a multicentre, open-label phase 2 dose-finding study with long-term extension study

[Prof Uwe Platzbecker, MD](#) • [Prof Ulrich Germing, MD](#) • [Prof Katharina S Götze, MD](#) • ...

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[Show footnotes](#)

Published: September 01, 2017 • DOI: [https://doi.org/10.1016/S1470-2045\(17\)30615-0](https://doi.org/10.1016/S1470-2045(17)30615-0) •



52 completed base study
32 entered extension study (24 rollover, 8 with interruption)
13 low transfusion burden
19 high transfusion burden


Luspatercept - Low Risk MDS with Anemia


- ▶ Ligand trap that blocks TGF beta signaling
- ▶ Subcutaneous injection every 3 weeks
- ▶ Phase 2 study excluded concurrent ESA or lenalidomide use prior hypomethylating agents


Baseline Characteristics	N=88
Age – years, median age, range	72 (29-90)
Prior ESA treatment , n(%)	45 (51%)
Baseline EPO <200U/L, n(%)	43 (49%)
RS+ n(%)	56 (64%)
IWG HI-E evaluable	N=88
Hemoglobin (g/dL) median(range)	8.3 (6-10)
RBC-TI evaluable	N=60
Transfusion burden (units/8 weeks) median(range)	4 (2-18)

Response Rates	IWG HI-E n/N (%) N=88	RBC-TI n/N (%) N=60
All Patients	44/88 (50%)	23/60 (38%)
ESA-naïve	21/43 (49%)	12/25 (48%)
Prior ESA	23/45 (51%)	11/35 (31%)
Baseline EPO <200U/L		
RS+	23/35 (66%)	13/21 (62%)
Non-RS+	4/8 (50%)	1/4 (25%)
Baseline EPO 200-500 U/L		
RS+	7/12 (58%)	3/8 (38%)
Non-RS+	4/8 (50%)	3/5 (60%)
SF-38:l mutation		
Mutated	29/43 (67%)	14/29 (48%)
Wild-type (WT)	10/31 (32%)	8/22 (36%)

Mutation analysis population N=75 (75 HI-E evaluable, 52 TI evaluable) 1 patient had unknown SF381 status

- 
- ▶ Luspatercept (ACE-536) is a novel fusion protein that blocks transforming growth factor beta (TGF β) superfamily inhibitors of erythropoiesis.
 - ▶ International Prognostic Scoring System-defined low or intermediate 1 risk myelodysplastic syndromes or non-proliferative chronic myelomonocytic leukaemia (white blood cell count $<13\,000/\mu\text{L}$), and had anaemia with or without red blood cell transfusion support.
 - ▶ Patients received luspatercept subcutaneously once every 21 days at dose concentrations ranging from 0.125 mg/kg to 1.75 mg/kg bodyweight for five doses (over a maximum of 12 weeks).
 - ▶ The primary endpoint was the proportion of patients achieving modified International Working Group-defined haematological improvement-erythroid (HI-E), defined as a haemoglobin concentration increase of 1.5 g/dL or higher from baseline for 14 days or longer in low transfusion burden patients, and a reduction in red blood cell transfusion of 4 or more red blood cell units or a 50% or higher reduction in red blood cell units over 8 weeks versus pre-treatment transfusion burden in high transfusion burden patients

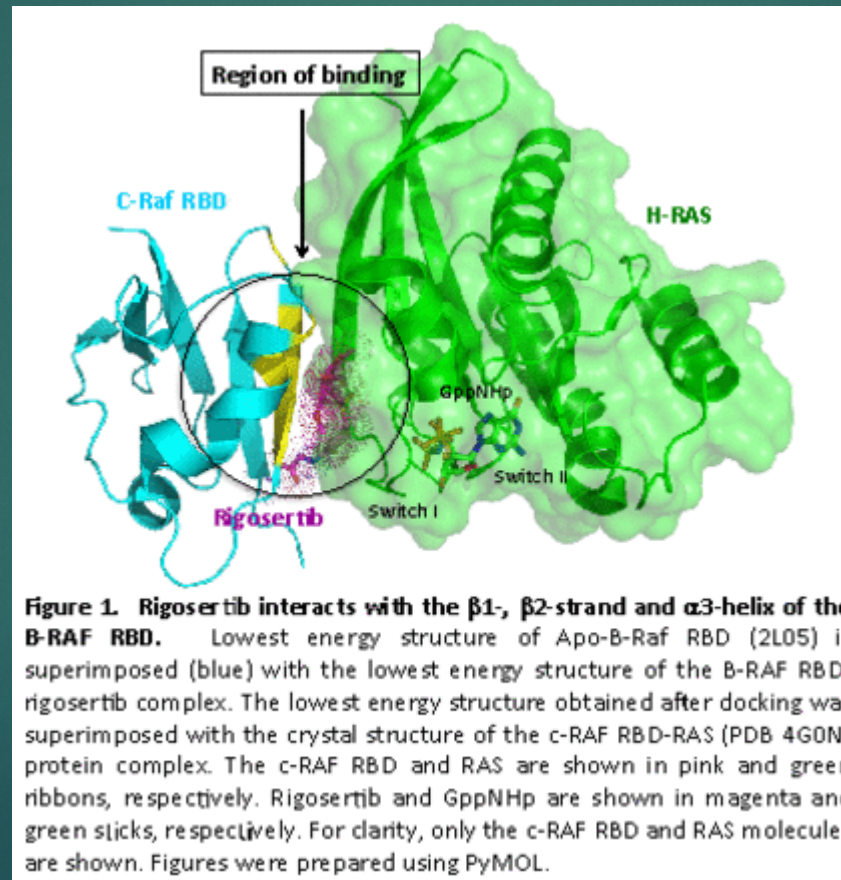
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- ▶ patients receiving higher dose luspatercept concentrations (0.75–1.75 mg/kg) achieved HI-E versus two (22% [95% CI 3–60]) of nine receiving lower dose concentrations (0.125–0.5 mg/kg). Three treatment-related grade 3 adverse events occurred in one patient each: myalgia (one [2%]), increased blast cell count (one [2%]), and general physical health deterioration (one [2%]). Two of these treatment-related grade 3 adverse events were reversible serious grade 3 adverse events: one patient (2%) had myalgia and one patient (2%) had general physical health deterioration.

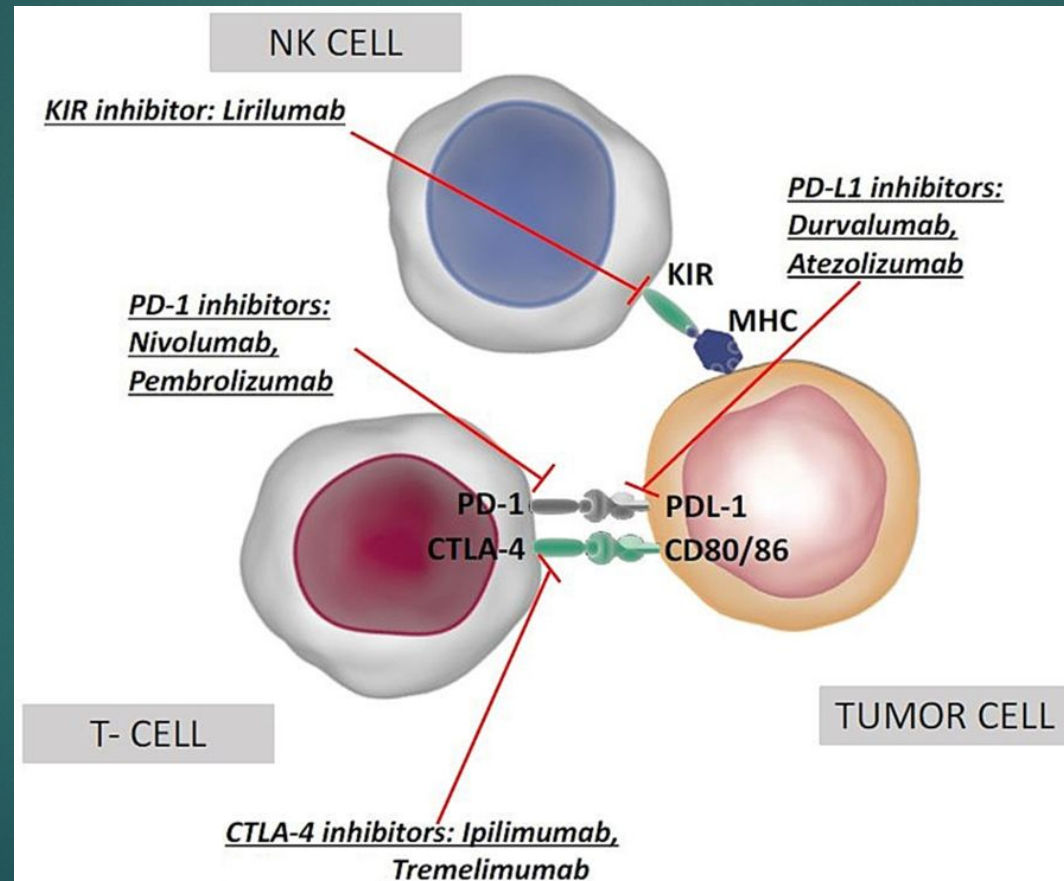
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- ▶ Luspatercept was well tolerated and effective for the treatment of anaemia in lower-risk myelodysplastic syndromes and so could therefore provide a novel therapeutic approach for the treatment of anaemia associated with lower-risk myelodysplastic syndromes; further studies are ongoing.

Rigosertib

- ▶ Rigosertib is a small molecule inhibitor of RAS effector pathways used in low risk, transfusion dependent MDS
 - ▶ 82 patients enrolled in a Phase 2 study
 - ▶ Median age 70
 - ▶ 54 (66%) had received prior ESA
 - ▶ Dosing was twice a day, continuous or intermittent
 - ▶ ESA was permitted as well

Binding of Rigosertib to RBDs





A Genomic Predictive Signature for Rigosertib in Lower Risk MDS Derived By Integrating Clinical Response, Mechanism of Action Data and Simulation

Steven M. Fruchtman, Abdullah Mahmood Ali, Michael E. Petrone, Patrick Simon Zbyszewski, Benjamin Hoffman, Shireen Vali, Neeraj Kumar Singh, Shahabuddin Usmani, Himanshu Grover, Taher Abbasi, and Azra Raza

Blood 2016 128:5535;



ELSEVIER

Leukemia Research

Volume 64, January 2018, Pages 10-16



Research paper

A phase 1/2 study of rigosertib in patients with myelodysplastic syndromes (MDS) and MDS progressed to acute myeloid leukemia

Shyamala C. Navada ^a  , Steven M. Fruchtmann ^b , Rosalie Odchimar-Reissig ^a , Erin P. Demakos ^a ,
Michael E. Petrone ^b , Patrick S. Zbyszewski ^b , James F. Holland ^a , Lewis R. Silverman ^a 

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Jun 28, 2018


Celgene and Acceleron Announce Luspatercept Achieved Primary and Key Secondary Endpoints in Phase III 'MEDALIST' Study in Patients with Low-to-Intermediate Risk Myelodysplastic Syndromes

*Results showed significant improvement in red blood cell
transfusion independence compared to placebo*

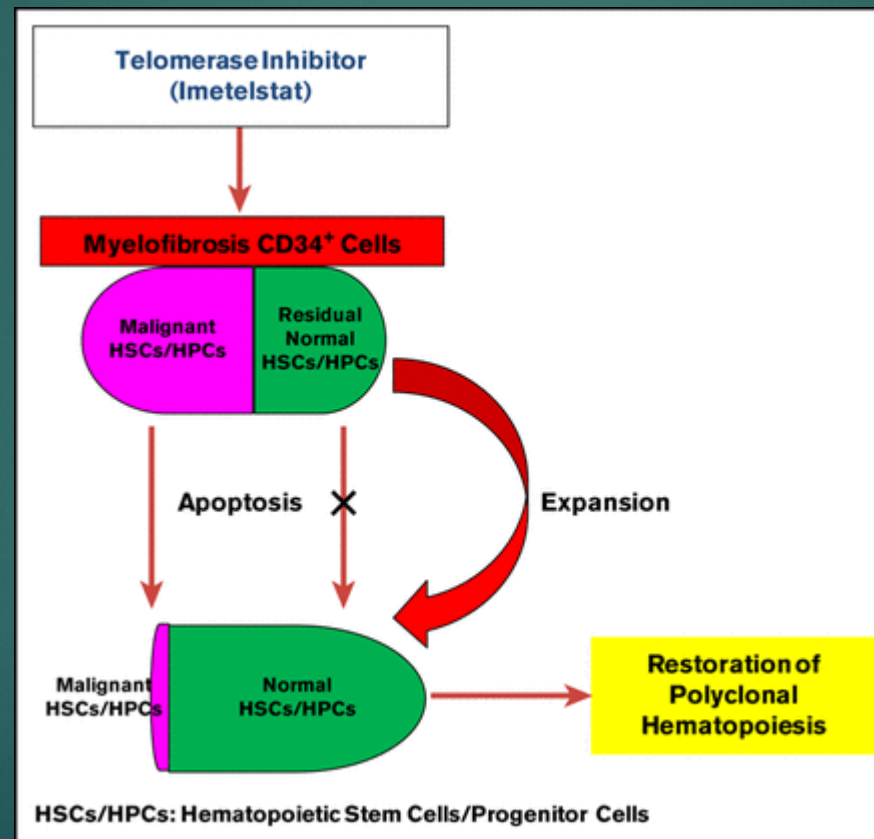
*Safety profile generally consistent with previously
published data*

Regulatory submissions planned in the United States and Europe in the first half of

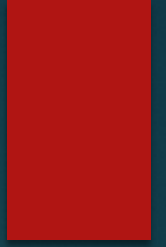
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- ▶ MEDALIST evaluated the efficacy and safety of luspatercept versus placebo in patients with IPSS-R very low, low or intermediate risk myelodysplastic syndromes (MDS) with chronic anemia and refractory to, intolerant of, or ineligible for treatment with an erythropoietin-stimulating agent (ESA), ring sideroblast-positive and require frequent RBC transfusions.
 - ▶ In addition to achieving the primary endpoint of the study, luspatercept also met the key secondary endpoint of demonstrating a highly statistically significant improvement in RBC transfusion independence of at least 12 consecutive weeks during the first 24 weeks. Modified hematologic improvement-erythroid (IWG mHI-E), a meaningful secondary endpoint, was also achieved.
 - ▶ Adverse events observed in the study were generally consistent with previously published data.
 - ▶ “This result from the phase III MEDALIST trial demonstrates the potential clinical benefit of luspatercept as an erythroid maturation agent for the treatment of chronic anemia in patients with low-to-intermediate risk MDS,” said Jay Backstrom, M.D., Chief Medical Officer for Celgene. “Based on these results, we look forward to preparing the dossier for global regulatory submissions and also investigating the clinical potential of luspatercept in ESA-naïve, low-to-intermediate risk MDS patients through the initiation of our phase III COMMANDS study.”

Imetelstat



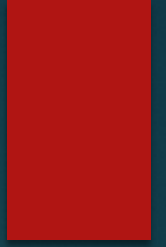
Pevonedistat



Selinexor



Glasdegib





Questions

Thank you