Myelodysplastic Syndromes

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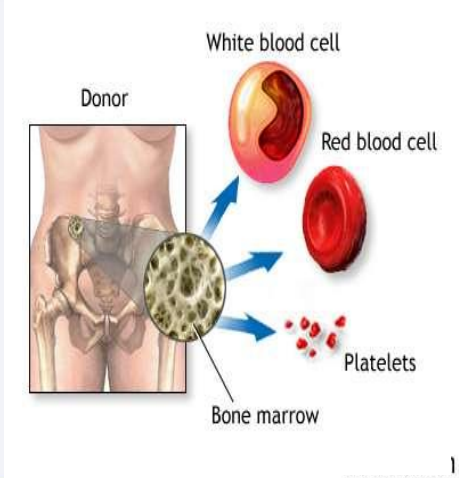
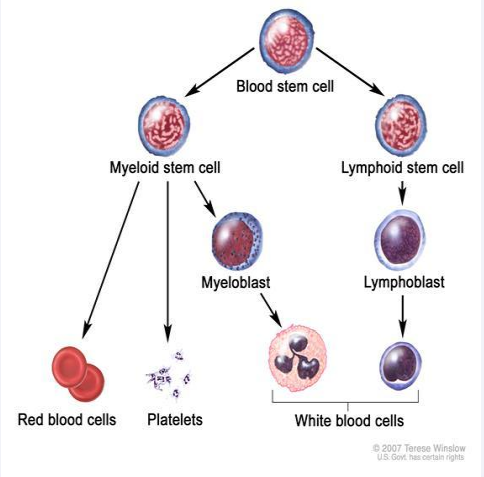
Normal Blood and Bone Marrow





What is MDS

- Myelodysplastic Syndromes (MDS) are a group of diverse bone marrow disorders in which the bone marrow does not produce enough healthy blood cells.

What is MDS

- Myelodysplastic syndromes-
  - Myelo- prefix means marrow
  - Dysplasia-refers to the abnormal shape and appearance — or morphology — of the blood cells.
  - Syndromes means a set of symptoms that occur together.
- MDS has been known as “smoldering leukemia,” “preleukemia” or “oligoleukemia.”
  - These terms may be misleading by implying that MDS is only problematic after it has evolved to AML.
  - MDS can progress such that the abnormal blast cells take over the marrow and the disease “evolves” into AML.

What is MDS

- MDS originates from mutations in a normal stem cell in the marrow
- In MDS, the blood stem cells do not mature into healthy blood cells. The immature blood cells do not function normally and either die in the bone marrow or soon after they enter the blood.
- Normally, immature cells known as “blasts” make up less than five percent of all cells in the marrow. In Some MDS patients, blasts comprise more than five percent of the cells.
- The number of blast cells from cases with lower proportions of blast cells to cases with higher proportions of blast cells—is one of the principal determinants of disease severity.

What is MDS

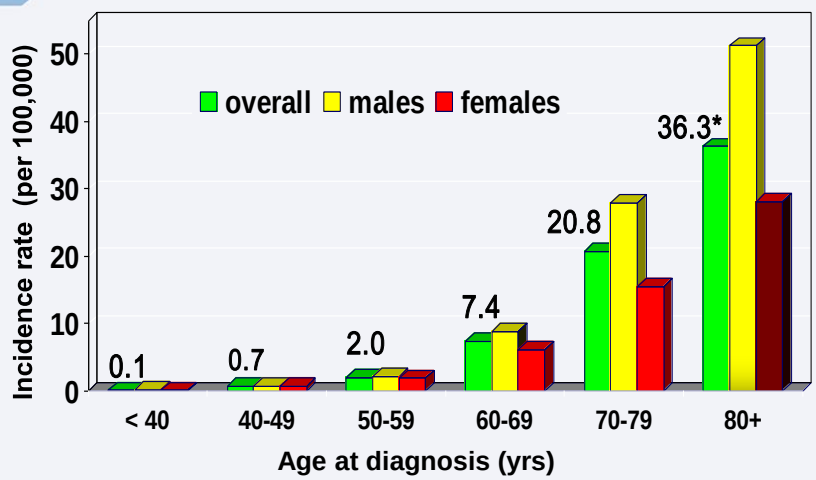
- Is MDS a “cancer” ?
  - MDS is a diagnosis of cancer.
  - Cancer means that a mutation of a normal cell leads to the development of cells that no longer behave normally.
  - MDS is spectrum of disorders

How common is MDS

- One of the most common hematological malignancies “Blood cancers”.
- At least 10,000 new cases in the united states diagnosed every year.
- Majority of patients are above age of 60.
- Slightly more in males.

MDS incidence Rates in USA by Age and Gender

SEER & NAACR Databases



Rollison and List et al, Blood 2008:112:41.

* p for trend = 0.01

What Causes MDS?

- The exact causes of MDS are unknown in majority of patients.
- Senescence “aging” of stem cells plays major role in developing MDS.
- MDS may be “primary” (also called “de novo”) or “secondary” (cases that arise following treatment with chemotherapy and radiotherapy for other cancers, such as lymphoma, myeloma or breast cancer).

What Causes MDS?

- Repeated exposure to the chemical benzene—which damages the DNA of normal stem cells—is another predisposing factor in MDS development.
  - Benzene in cigarette smoke is now the most common known cause of exposure to this toxin.
  - Benzene is also found in certain industrial settings. However, the stringent regulation of its use has diminished benzene exposure in the workplace.

What causes MDS

- There are no known food or agricultural products that cause MDS.
- Alcohol consumed on a daily basis may lower red blood cell and platelet counts, alcohol does not cause MDS.
- No evidence exists to suggest that MDS is contagious disease; thus, MDS cannot be transmitted to loved ones.
- MDS is not inherited. In fact, it is a very rare occasion when family members, including siblings, are diagnosed with MDS.

What are the Symptoms of MDS?

- In the early stages of MDS patients may experience no symptoms at all. A routine blood test may reveal reduced blood counts.
- Patients with blood cell counts well below normal, experience definite symptoms related to low blood counts.

ANEMIA = LOW RED CELL COUNT

- The majority of MDS patients are anemic.
- Anemic patients generally experience fatigue.
- Anemia varies in its severity:
  - Mild anemia, patients may feel well or just slightly fatigued.
  - Moderate anemia, almost all patients experience some fatigue, which may be accompanied by heart palpitations, shortness of breath, and pale skin.
  - Severe anemia, almost all patients appear pale and report chronic overwhelming fatigue and shortness of breath.
- Because severe anemia reduces blood flow to the heart, older patients may be more likely to experience cardiovascular symptoms, including chest pain.

NEUTROPENIA=LOW WHITE CELL COUNT

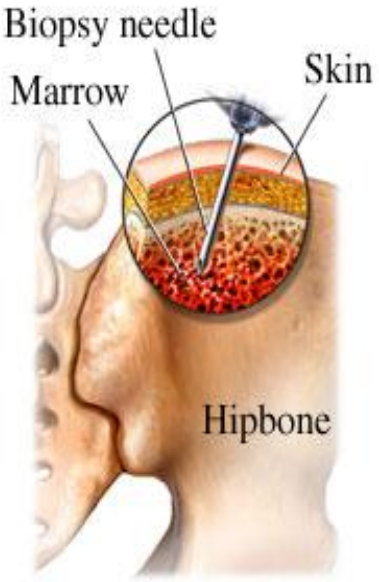
- A reduced white cell count lowers the body's resistance to bacterial infection.
- Patients may be susceptible to:
  - skin infections
  - sinus infections
  - lung infections
  - urinary tract infections
- Fever may accompany these infections.

THROMBOCYTOPENIA=LOW PLATELET COUNT

- Patients with thrombocytopenia have an increased tendency to bruise and bleed even after minor bumps and scrapes.
- Nosebleeds are common and patients often experience bleeding of the gums, particularly after dental work.

What Tests are used to diagnose MDS?

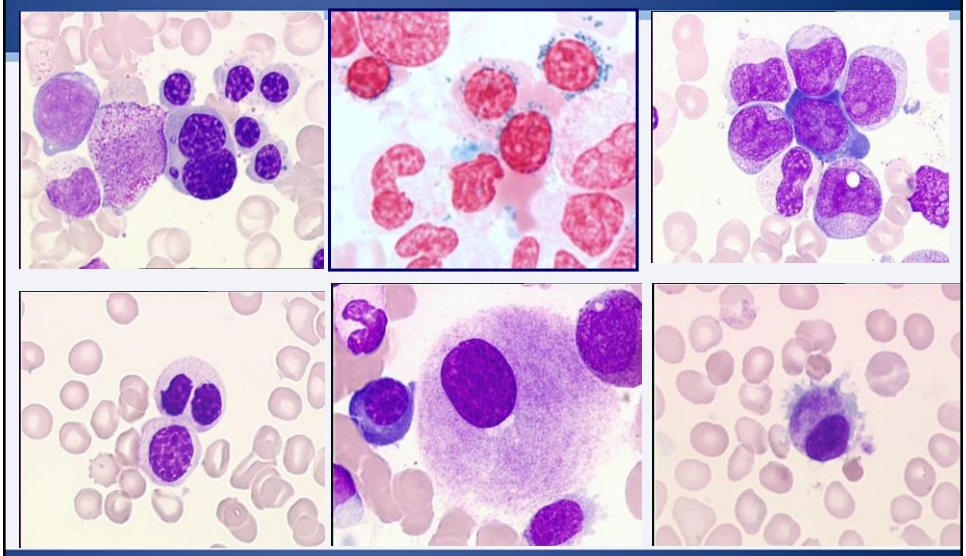
- Blood counts.
- Peripheral Blood smear
- Bone marrow aspirate and biopsy
- Cytogenetic Testing
- FISH
- Other tests ordered
  - Vitamin b12 level
  - Folate
  - Iron and ferritin
  - Serum erythropoietin level.



Diagnosis of MDS

- An experienced hematopathologist should examine the peripheral blood smear and bone marrow.
- Diagnosis of MDS is made if
  - Patient has persistent cytopenia.
  - Demonstration of increased “blasts”.
  - Demonstration of “dysplasia”.
  - Demonstration of certain cytogenetic abnormalities.

Cytologic Dysplasia:



Courtesy of Dr List and Bennett

Cytogenetics

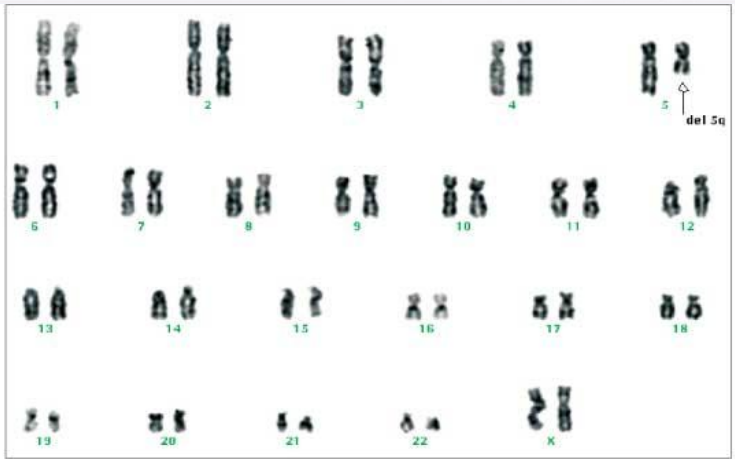
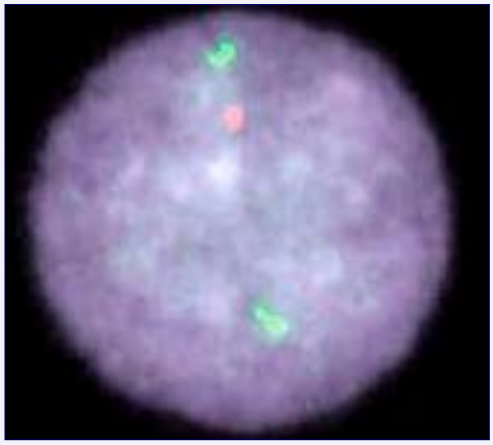


Fig. 2 *—G-banded karyotype obtained from the myelodysplastic syndrome patient at diagnosis: 46, XX, del(5)(q13;q33). The arrow shows the chromosomal abnormality*

del(5q) by FISH



FISH with probe for 5p (green) and probe for 5q (red)

Reprinted with permission from Heaney ML, Golde DW. *N Engl J Med.* 1999;340:1649

What type of MDS do you have?

FAB classification	Bone Marrow Blasts	Peripheral Blood Blasts	Ringed Sideroblasts
Refractory Anemia (RA)	<5%	<1%	<15%
Refractory anemia with ringed sideroblasts (RARS)	<5%	<1%	>15%
Refractory anemia with excess blasts (RAEB)	5%-20%	<5%	Variable
Refractory anemia with excess in blasts in transformation (RAEB-T)	21%-30%	>5%	Variable
Chronic myelomonocytic leukemia (CMML)	≤20%	<5%	Monocytosis >1000/μl

What type of MDS do you have ?

WHO	MDS cases %	Peripheral blood	Bone marrow
Refractory anemia (RA)	5-10%	Anemia <1% blasts	Erythroid dysplasia < 10 % myeloid or megakaryocytic dysplasia < 5% blasts < 15% sideroblasts
Refractory anemia with ring sideroblasts (RARS)	10-15%	Anemia < 1% blasts	Erythroid dysplasia < 10 % myeloid or megakaryocytic dysplasia < 5% blasts >15% sideroblasts Abnormal sideroblasts are defined by 5 or more iron granules where the granules encircle one third or more of the nucleus.
Refractory cytopenia with multilineage dysplasia (RCMD)	24%	Bi-or pancytopenia < 1%blasts	Dysplasia in > 10% of the cells in 2 or more cell lines < 5% blasts in BM < 15% sideroblasts
Refractory anemia with multilineage dysplasia and ring sideroblasts (RCMD-RS)	15%	Bi-or pancytopenia < 1%blasts	Dysplasia in > 10% of the cells in 2 or more cell lines < 5% blasts in BM > 15% sideroblasts
Refractory anemia with excess blasts type I & II (RAEB-1 & RAEB II)	40%	Cytopenia Type I: 1-5% blasts Type II: 6-19% blasts	Uni or multilineage dysplasia Type I 5-9% blasts Type II 10-19% blasts
5 q syndrome	?	Anemia Normal or elevated platelets < 5% blasts	Normal or increased megakaryocytes < 5% blasts
MDS unclassified (MDS-U)	?	Cytopenia <1% blasts	unilineage dyplasia of myeloid or megakaryocytic line < 5% blasts

Who Severe is the MDS: IPSS

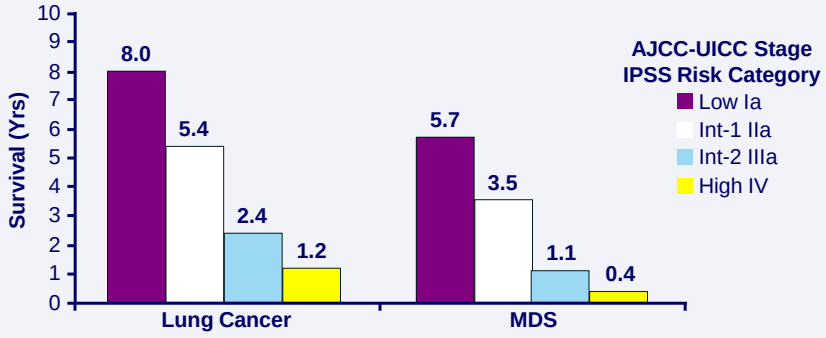
	Score Value				
Prognostic variable	**0**	**0.5**	**1.0**	**1.5**	**2.0**
Bone marrow blasts	< 5%	5% to 10%	--	11% to 20%	21% to 30%
Karyotype*	Good	Intermediate	Poor	--	--
Cytopenias†	0/1	2/3	--	--	--

	Total Score					
	0	**0.5**	**1.0**	**1.5**	**2.0**	**≥ 2.5**
Risk	Low	Intermediate I		Intermediate II		High
Median survival, yr	5.7	3.5		1.2		0.4

*Good = normal, -Y, del(5q), del(20q); intermediate = other karyotypic abnormalities; poor = complex (≥ 3 abnormalities) or chromosome 7 abnormalities.
†Hb < 10 g/dL; ANC < 1800/μL; platelets < 100,000/μL.

Greenberg P et al. Blood. 1997;89:2079-2088.

Life expectancy is shorter for US patients with MDS than those with lung cancer*†[1,2]



*Adjusted for age (lung cancer, median 66 yrs; MDS, median 69 yrs) and risk/stage.[1,2]
†All histological subtypes.[1,2]

1. Greenberg P, et al. Blood. 1997;89:2079-2088. Erratum in Blood. 1998;91:1100.
2. Adebonojo SA, et al. Chest. 1999;115:1507-1513.

MD Anderson Risk Model

Simplified MDS Risk Score (0-15 Points)

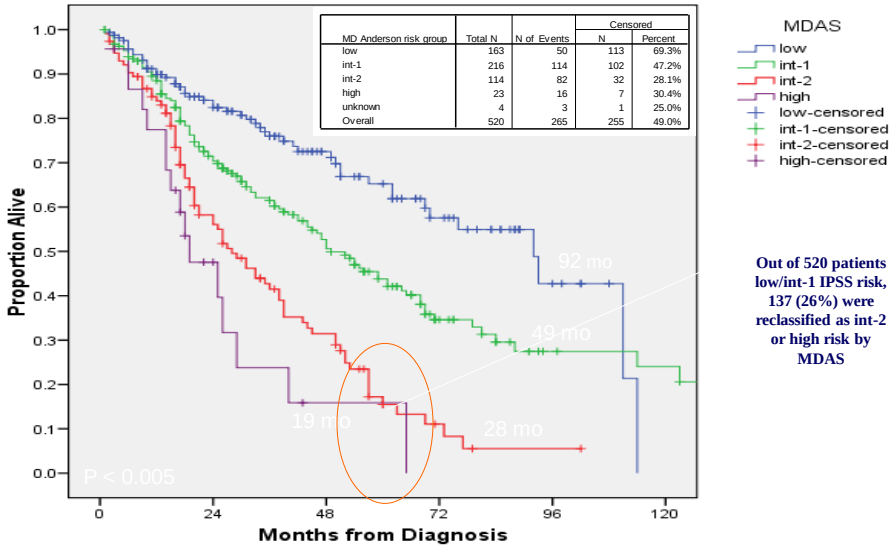
Prognostic Factor	Coefficient	Points
PS > 2	0.267	2
Age, yrs		
60-64	0.179	1
≥ 65	0.336	2
Platelets, × 10^9/L		
< 30	0.418	3
30-49	0.270	2
50-199	0.184	1
Hemoglobin < 12 g/dL	0.274	2
BM blasts, %		
5-10	0.222	1
11-29	0.260	2
WBC > 20 × 10^9/L	0.258	2
Karyotype		
Chromosome 7 Abn or complex ≥ 3 Abns	0.479	3
Prior transfusion, yes	0.107	1

Estimated OS by 4 Levels of Prognostic Score Points

Score	n (%)	Survival		
		Median, Mos	3 Yr, %	6 Yr, %
0-4	157 (16)	54	63	38
5-6	227 (24)	25	34	13
7-8	233 (24)	14	16	6
≥ 9	341 (36)	6	4	0.4

Kantarjian H et al. *Cancer*. 2008;113:1351-1361.

Survival by MDAS in Patients with Low/int-1 risk IPSS



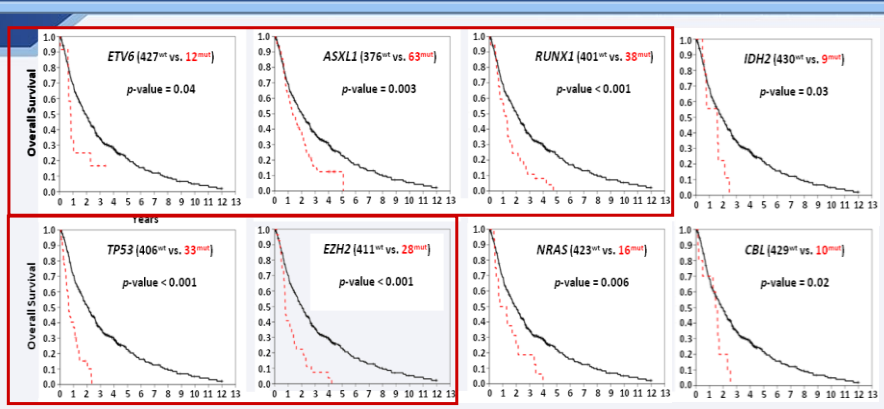
Out of 520 patients low/int-1 IPSS risk, 137 (26%) were reclassified as int-2 or high risk by MDAS

American society of Hematology 52nd annual meeting, December 2010, Orlando, Florida. Abstract # 444

IPSS Modifying Factors

Age and comorbidity	Low/Int-1
Secondary MDS	Natural history
Cytopenia severity	Low/Int-1
Transfusion dependence	Low/Int-1
BM pathology	Number of dysplastic lineages, ALIP, PB CD34+%, fibrosis
Other chromosome abnormalities	• Favorable: -12/12p • Unfavorable: 3q36, +11/11q23, t(4q), t(5q)
Other factors	• LDH • Iron overload

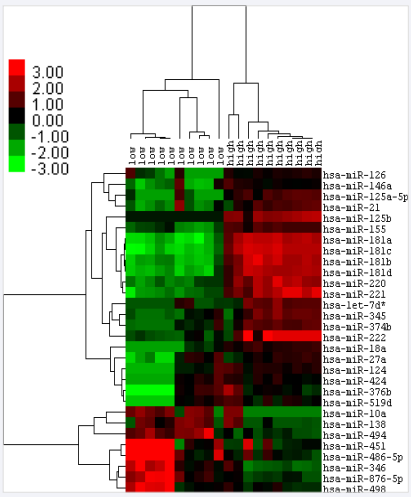
Gene Point Mutations - Independent Predictors of Overall Survival



- Multivariable analysis, mutations of *TP53* (HR, 2.48), EZH2 (HR, 2.13), ETV6 (HR, 2.04), RUNX1 (HR, 1.47), and ASXL1 (HR, 1.38) were ***independent predictors of ↓OS vs. age, sex, IPSS***.

Bejar R, et. al. ASH 2010; 300a.

MiRNA Signature Distinguishing High vs. Low Risk MDS



High vs. Low Risk miR Signature

Fold-Change	miRNA
22.7187	hsa-miR-181c
19.9457	hsa-miR-181a
14.2479	hsa-miR-181b
13.8795	hsa-miR-181d
12.0695	hsa-miR-221
4.99144	hsa-miR-376b
4.27432	hsa-miR-125b
3.61955	hsa-miR-155
2.79939	hsa-miR-130a
0.13911	hsa-miR-486-5p

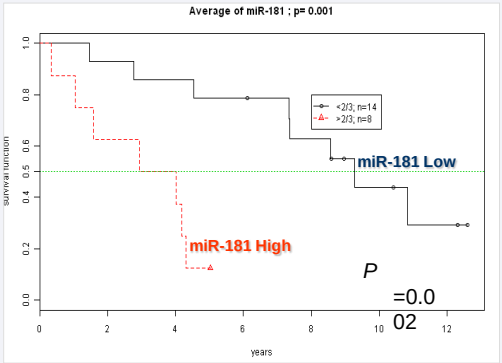
This signature is predictive (misclassification error rate, after 10-fold CV, <0.01)

30 miRNAs out of 68 selected for Heat Map with statistically significant difference p< 0.05. HR= 10; LR=

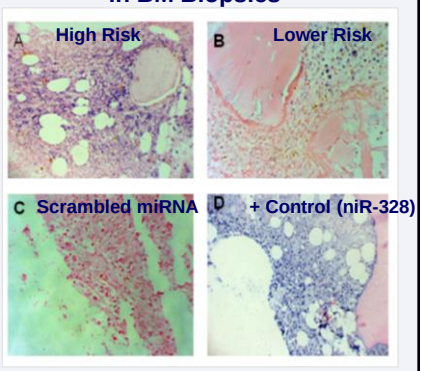
Sokol L & List AF. Brit J Haematol 2011.

Kaplan-Meier OS Estimate in IPSS Low/Int-1 MDS by miR-181 Family Expression.

Q-rtPCR [N=22]



MiRNA-181b *In Situ* Hybridization in BM Biopsies



Sokol L & List AF. Brit J Haematol 2011.

Treatment of Lower Risk MDS

When do we need to treat?

- The goal of treatment in lower risk MDS is to improve blood counts and alleviate related symptoms.
- In asymptomatic patients with adequate counts treatment may not be needed or indicated.
- Majority of patients will need treatment for anemia and to reduce or eliminate red blood cell transfusion.
- Occasionally treatment is directed to improve platelets or neutrophils.

Supportive Care

- RBC transfusions are used for anemic patients who experience fatigue and/or shortness of breath. The frequency varies from patient to patient.
- MDS patients who require periodic red cell transfusions typically receive two units. Most of doctors will transfuse RBC if hemoglobin is less than 8 g/dl.
- There are several concerns related to RBC transfusions
  - Iron overload
  - Risk of retaining excess fluid
  - Transmission of infection
- Despite the concerns, red cell transfusions improve the quality of life for patients with symptomatic anemia.
- Some patients may need platelets transfusion.

Red Blood cells Growth Factors

Erythropoietin or EPO (Epogen®, Procrit®) and Darbepoietin (Aranesp®)

- The “recombinant” form of this natural growth factor is used to treat symptoms associated with anemia; it stimulates the bone marrow to produce red blood cells.
- The treatment is most likely to benefit patients whose natural (blood serum) EPO level is below 500 and who do not need frequent transfusions.
- Patients who are unresponsive to EPO alone may derive additional benefit when EPO is combined with other growth factors that stimulate the bone marrow to produce white blood cells.
- Recombinant EPO, epoietin, is available as two different brand-name drugs: Epogen® and Procrit®. Darbepoetin (Aranesp®) is a different form of, erythropoietin that is longer acting.
- Response rate vary from 20-40%, usually an initial trial is given for 6-8 weeks. If patient responds the duration of response averages 12-18 month.

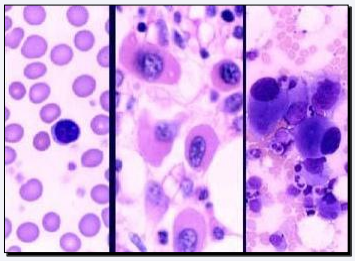
- In 2007, the FDA issued an advisory about the safety of epoietin and darbepoietin use in patients with cancer who were anemic but not undergoing active treatment with chemotherapy.
- It is important to note that the affected patients *did not have MDS.*
- These products have been safely used in a large number of MDS patients and long-term data have not shown any negative effect on either survival or progression to AML.

Deletion 5q31 in MDS

- Interstitial chromosome 5q deletion is the most common chromosome abnormality in MDS
- Two CDRs: 5q31->q32 (1.5 Mb); 5q33 (5q- syndrome)
- **5q-Syndrome' – Van den Berghe 1974**

WHO

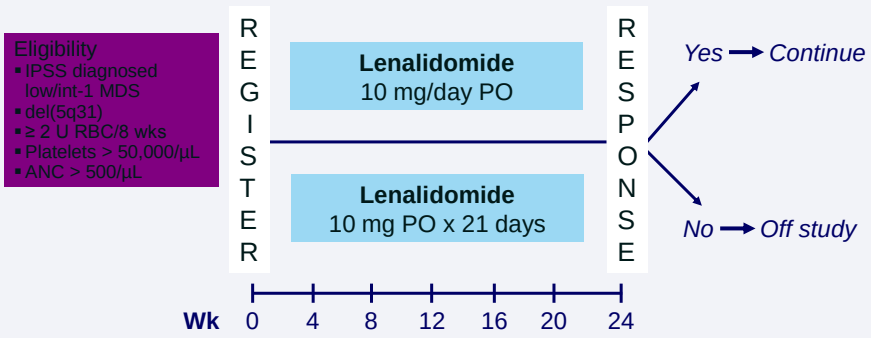
- Isolated 5q deletion
- Severe hypoplastic anemia
- Mild leukopenia
- Normal or elevated platelets
- Atypical megakaryocytes
- Indolent natural history
- –<5% blasts



From Vardiman JW. ASH Image Bank.

Van den Berghe H, et al. Nature 1974; 251:427. Lai F, et al. Genomics 2001; 71: 235.
Jaju RJ, et al. Genes Chrom Cancer 1998; 22:251

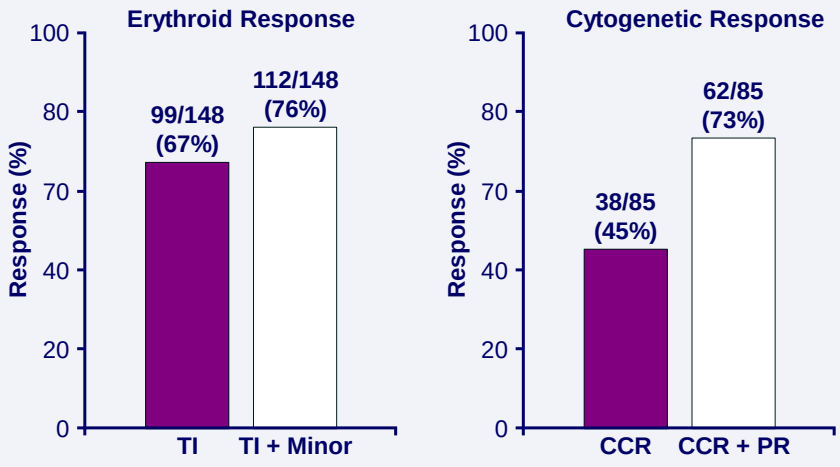
Lenalidomide in MDS With 5q Deletion



Primary endpoint: transfusion independence
Secondary endpoints: duration of TI, cytogenetic response, minor erythroid response, pathologic response, safety

List AF, et al. N Engl J Med. 2006;355:1456-1465.

MDS-003: Response to Lenalidomide Therapy



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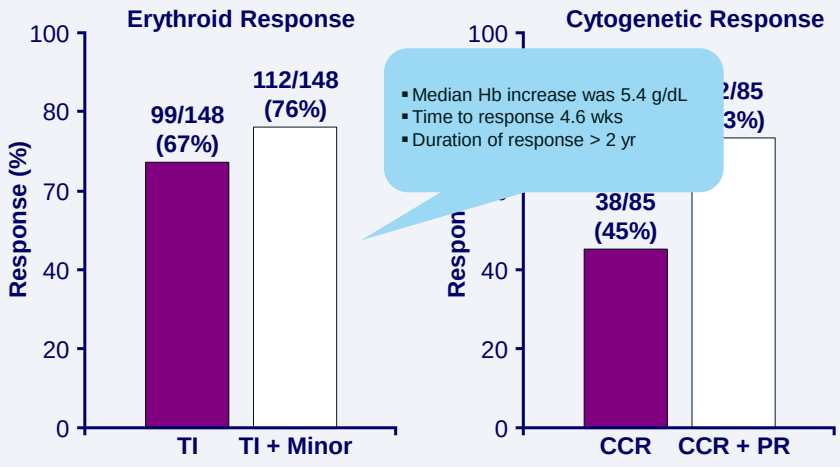
MDS-003: Response to Lenalidomide Therapy



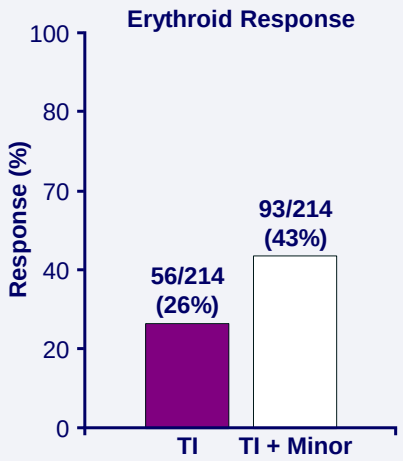
List AF, et al. N Engl J Med. 2006;355:1456-1465.

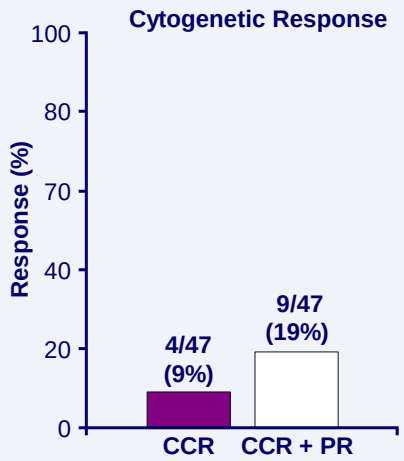
MDS-002/003: Treatment-Related Adverse Events

Grade ≥ 3 Adverse Events, %	Non-Del(5q)	Del(5q)
Thrombocytopenia	**20**	**44**
Neutropenia	**25**	**55**
Pruritus	1	3
Rash	4	6
Diarrhea	1	3
Fatigue	4	3

List AF, et al. N Engl J Med. 2006;355:1456-1465.
Raza A, et al. Blood. 2008;111:86-93.

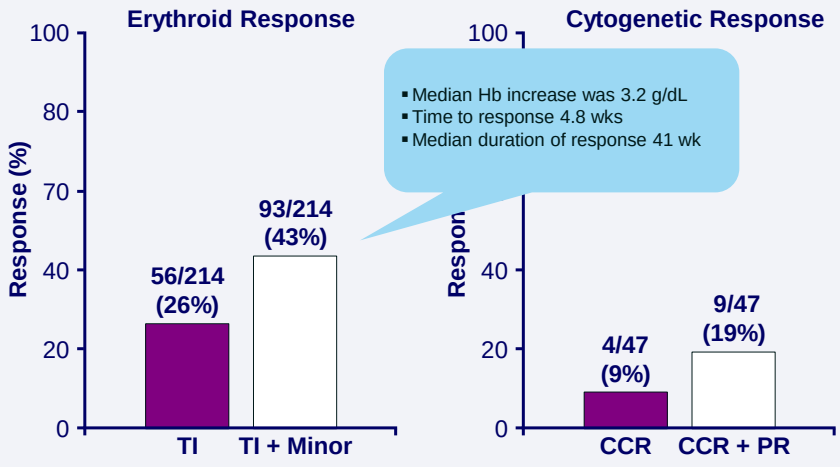
MDS-002: Response to Lenalidomide Therapy





Raza A, et al. Blood. 2008;111:86-93.

MDS-002: Response to Lenalidomide Therapy

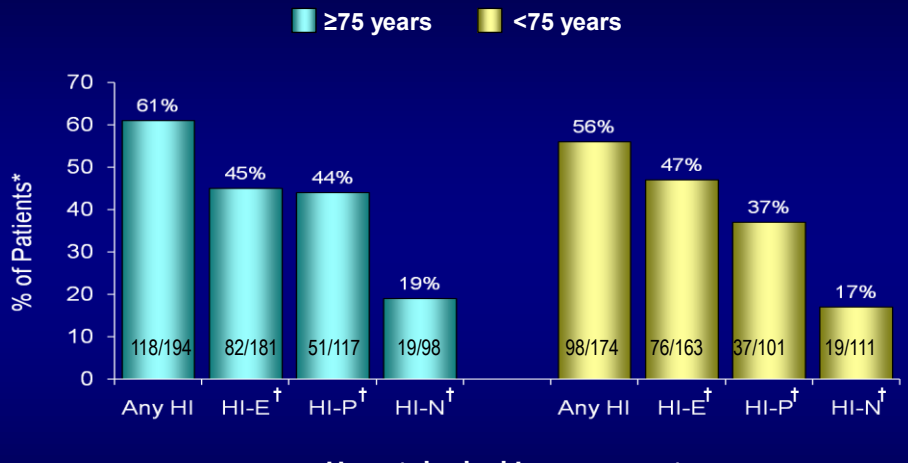


Raza A, et al. Blood. 2008;111:86-93.

Hypomethylating Agents

- Two medications approved by FDA
  - Azacitidine: first FDA approved drug for MDS
  - Decitabine
- Administered subcutaneously or intravenously.
- Low dose chemotherapy with unique mechanism of action.
- In general well tolerated.
- Response rates 40-50%.

Hematologic Improvement



Hematological Improvement

Any HI = major + minor responses; individual cell lines show major responses only
* Ongoing pts with <56 days on-study were excluded
† Individual cell line denominators include only pts eligible for improvement

Komrokji et al, EHA 2010

Randomized Phase II Study of Alternative Azacitidine Dose Schedules

Study Design (N = 151)

Eligibility
- All FAB
- Cytopenia
- ECOG PS: 0-3

A. 5-2-2: 75 mg/m^2
N = 50

B. 5-2-5: 50 mg/m^2
N = 51

C. 5: 75 mg/m^2
N = 50

x 6

IWG 2000 HI

12 Cycles
AZA x 5d
q4-6 wks

Lyons RM, et al. J Clin Oncol. 2009;27:1850-1856.

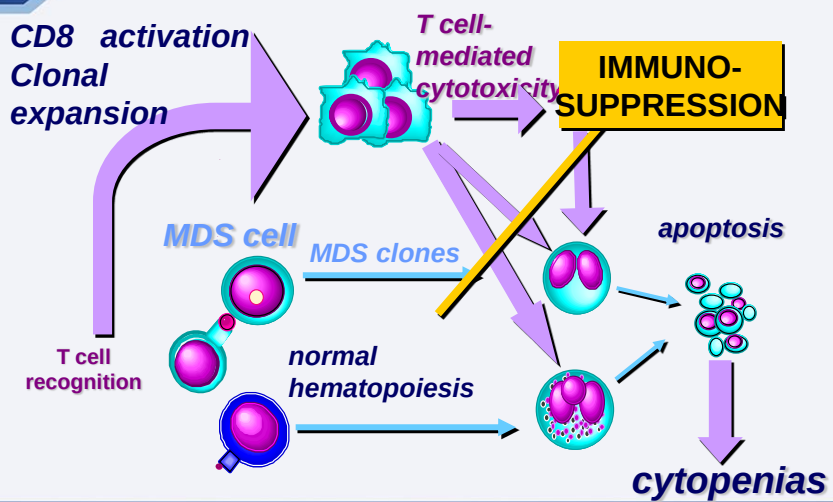
Frequency of Major HI

Lineage HI in Evaluable Pts,* n (%)	5-2-2 (n = 50)	5-2-5 (n = 51)	5d (n = 50)
$Erythroid_{Ma}$	19/43 (44)	19/43 (44)	20/44 (46)
RBC-TI	**12/24 (50)**	**12/22 (55)**	**15/25 (64)**
$Platelet_{Ma}$	12/28 (43)	8/30 (27)	11/22 (50)
Any HI	22/50 (44)	23/51 (45)	28/50 (56)
$Neutrophil_{Ma}$	4/23 (17)	4/23 (17)	9/24 (38)
Heme AEs > Gr 3	**33/50 (66)**	**24/48 (50)**	**17/50 (34)**
AE Tx delay	**34/50 (68)**	**30/48 (63)**	**17/50 (34)**

*IM

Lyons RM, et al. J Clin Oncol. 2009;27:1850-1856.

Ineffective Hematopoiesis in MDS
Immuno-Pathogenesis



A. John Barrett – NHLBI 2005.

Immunosuppressive Therapy (IST) in MDS
NHLBI Response Predictive Variables (N=82)[1]

- Age < 60 years*
- RA vs other FAB
- Karyotype (+8 WT1)[2]
- Hypocellular marrow
- HLA-DR15 allele*
- PNH phenotype
- RBC transfusion duration*

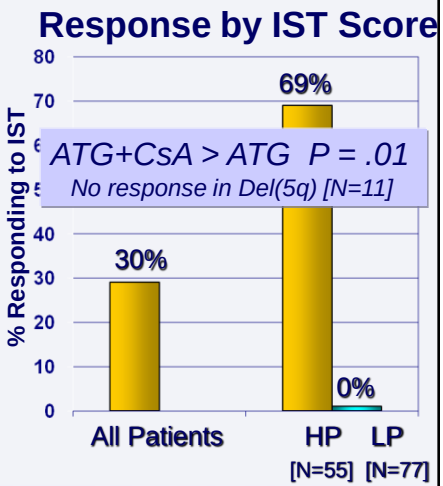
Independent Variables
- Age
- Duration transfusion dependent
- HLA-DR15

*Multivariate significance[1,3]

1. Sauntharajah Y, et al. Blood. 2002;100(5):1570-1574.
2. Sloand E, et al. ASH 2004. Abstract 1431.
3. Sauntharajah Y, et al. Blood. 2003;102(8):3025-3027

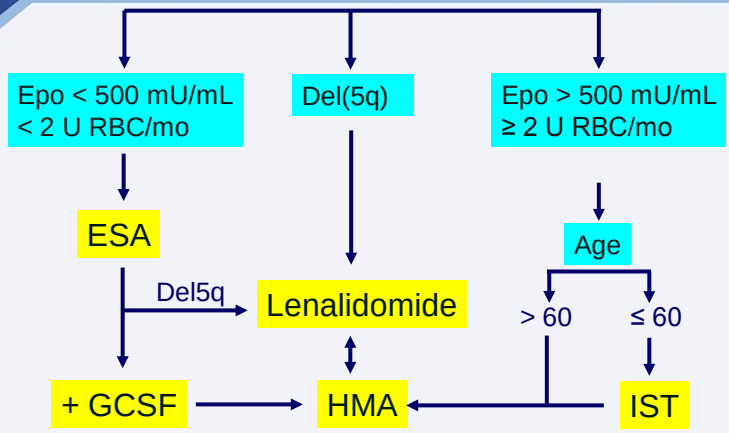
NHLBI IST Response Score & Survival
Validation Set (IST Date: 1998-2004)

Patient characteristic	Number (%) (N = 129)
IST	
ATG	74 (57.4)
ATG+CsA	42 (32.6)
CsA	13 (10.1)
IPSS status	
Low	16 (12.4)
Int-1	94 (72.9)
Int-2	13 (10.1)
High	6 (4.7)



Sloand EM, et al. J Clin Oncol. 2008;26:2505-2511

Anemia Management Algorithm 2011



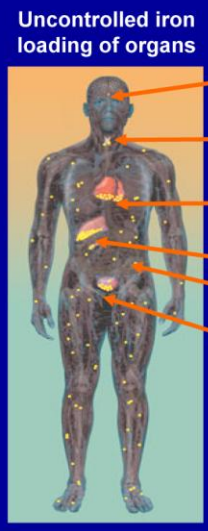
EPO, serum erythropoietin; ESA , erythropoiesis-stimulating agents; GCSF, granulocyte colony-stimulating factor; HMA, hypomethylating agents; IST, immunosuppressive therapy; RBC, red blood cells.

List AF. Hematology. 2007.

Iron Overload

- One unit of blood contains 200-250 mg of iron.
- After 15-20 units of RBC transfusion patients develop iron overload.

Consequences of Iron Toxicity[1]



Pituitary
Impaired growth,[2] infertility

Parathyroid
Hypoparathyroidism[1]

Heart
Cardiomyopathy, cardiac impairment[1]

Liver
Hepatic cirrhosis[1]

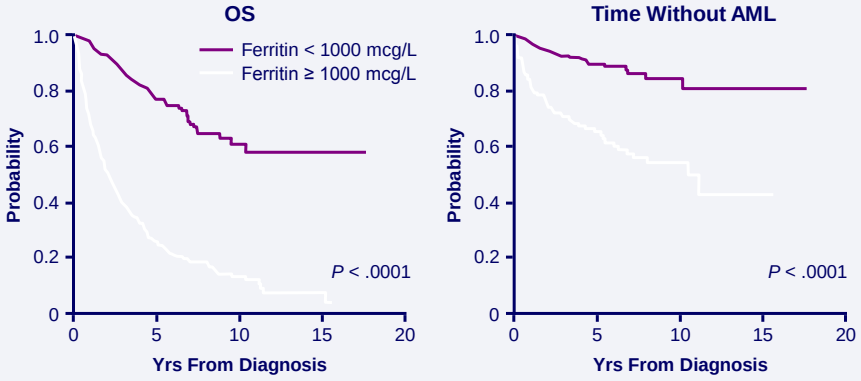
Pancreas
Diabetes mellitus[1]

Gonads
Hypogonadism[1,2]

1. Andrews NC. *N Engl J Med.* 1999;341:1986-1995. 2. Porter JB. *Br J Haematol.* 2001;115:239-252.

Serum Ferritin Is Predictive of Survival and Risk of AML in MDS

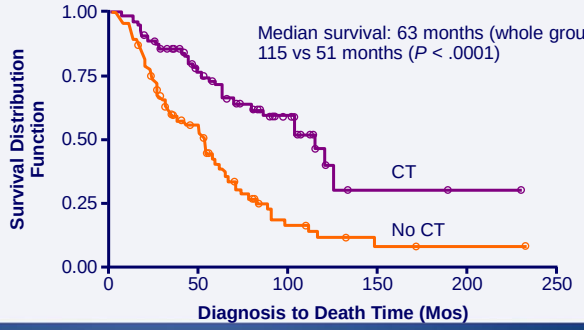
Development of transfusional iron overload is a significant independent prognostic factor for overall survival and evolution to AML



Sanz G, et al. 2008 ASH. Abstract 640.

Iron Chelation Therapy and Survival

- OS significantly better for patients who received iron chelation therapy
- Results consistent across all subgroups analyzed (IPSS low and intermediate-1, sex, age)



Rose C, et al. ASH 2007. Abstract 249.

MDS Patients Who Are Likely to Benefit Most From Management Iron Overload

Characteristic	NCCN[1]	MDS Foundation[2]
Transfusion status	• Received 20-30 packed RBC units • Continuing transfusions	• Transfusion dependent, requiring 2 units/month for > 1 year
Serum ferritin level	• > 2500 µg/L	• 1000 µg/L
MSD risk	• IPSS: Low- or Int-1	• IPSS: Low- or Int-1 • WHO: RA, RARS and 5q-
Patient profile	• Candidates for allografts	• Life expectancy > 1 year and no comorbidities that limit progress • A need to preserve organ function • Candidates for allografts

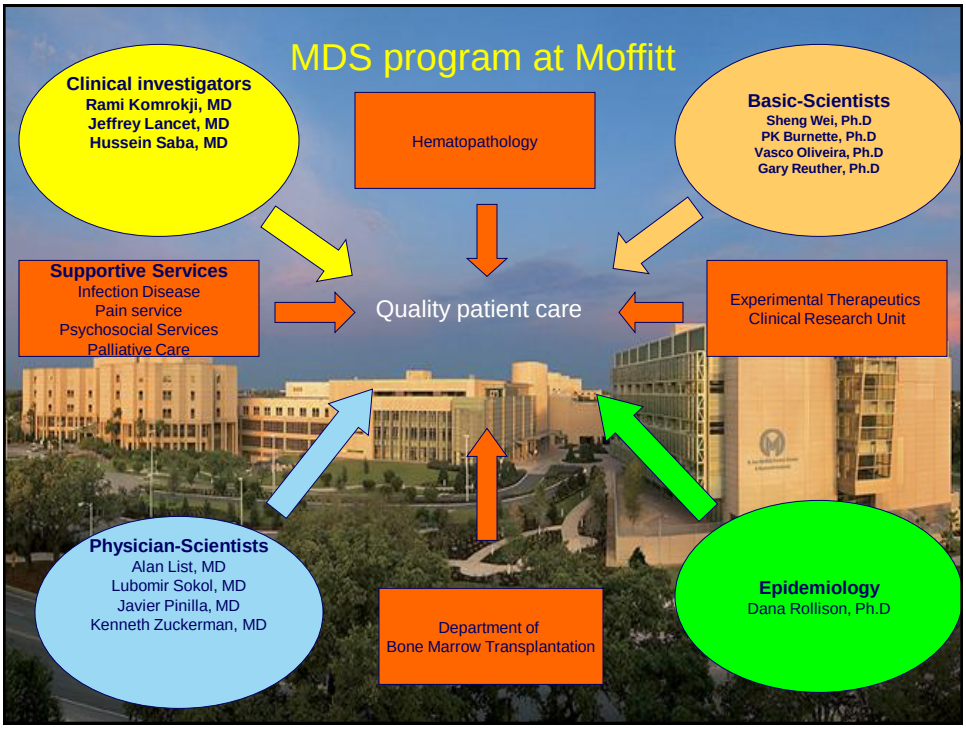
1. NCCN Clinical Practice Guidelines in Oncology. 2. Bennett JM. J Hematol. 2008;83:858-861.

Comparison of chelators

Property	DFO	Deferiprone	Deferasirox
Usual dose (mg/kg/day)	25–60	75	20–30
Route	sc, iv (8–12 hours, 5 days/week)	Oral 3 times daily	Oral Once daily
Half-life	20–30 minutes	3–4 hours	12–16 hours
Excretion	Urinary, fecal	Urinary	Fecal
Adverse effects	Local reactions, ophthalmologic, auditory, growth retardation, allergic	Gastrointestinal disturbances, agranulocytosis/ neutropenia arthralgia	Gastrointestinal disturbances, rash, mild non-progressive creatinine increase
Status	Licensed	Licensed outside US/Canada	Licensed

Moffitt Cancer Center Lower Risk MDS Clinical Trials – 2011

	Treatment	Trial Design
ECOG/	LEN ±epoetin alfa	Phase III
MCC/FL MDS Consortium	LEN + Prednisone	Phase II
MCC	Array 614	Phase I/II
MCC	Eltrombopag	Phase I/II
MCC	Thymoglobulin	Phase II
MCC	Siltuximab	Phase II
MCC	Sotatercept	Phase II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Jeffrey Lancet, MD
Hussein Saba, MD
Hematopathology
Basic-Scientists
Sheng Wei, Ph.D
PK Burnette, Ph.D
Vasco Oliveira, Ph.D
Gary Reuther, Ph.D
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Infection Disease
Pain service
Psychosocial Services
Palliative Care
Quality patient care
Experimental Therapeutics
Clinical Research Unit
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