20th International Congress & Scientific Seminar 2019

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Specialty: Haematology
Designation: Professor and Head
Working station: Dhaka Medical College & Hospital

Bangladesh Society of Medicine
For comprehensive patient care and education


MDS

Incidence of MDS in Bangladesh

- Incidence of MDS in the country: No authentic data is available.
- Unpublished data: 58 MDS patients among 386 bone marrow examinations.
- Outcomes/survival rates:
  - Low risk patients have better outcome.
  - High risk group outcome is poor. BMT option is available.
- Anemia:
  - Transfusion support is good.

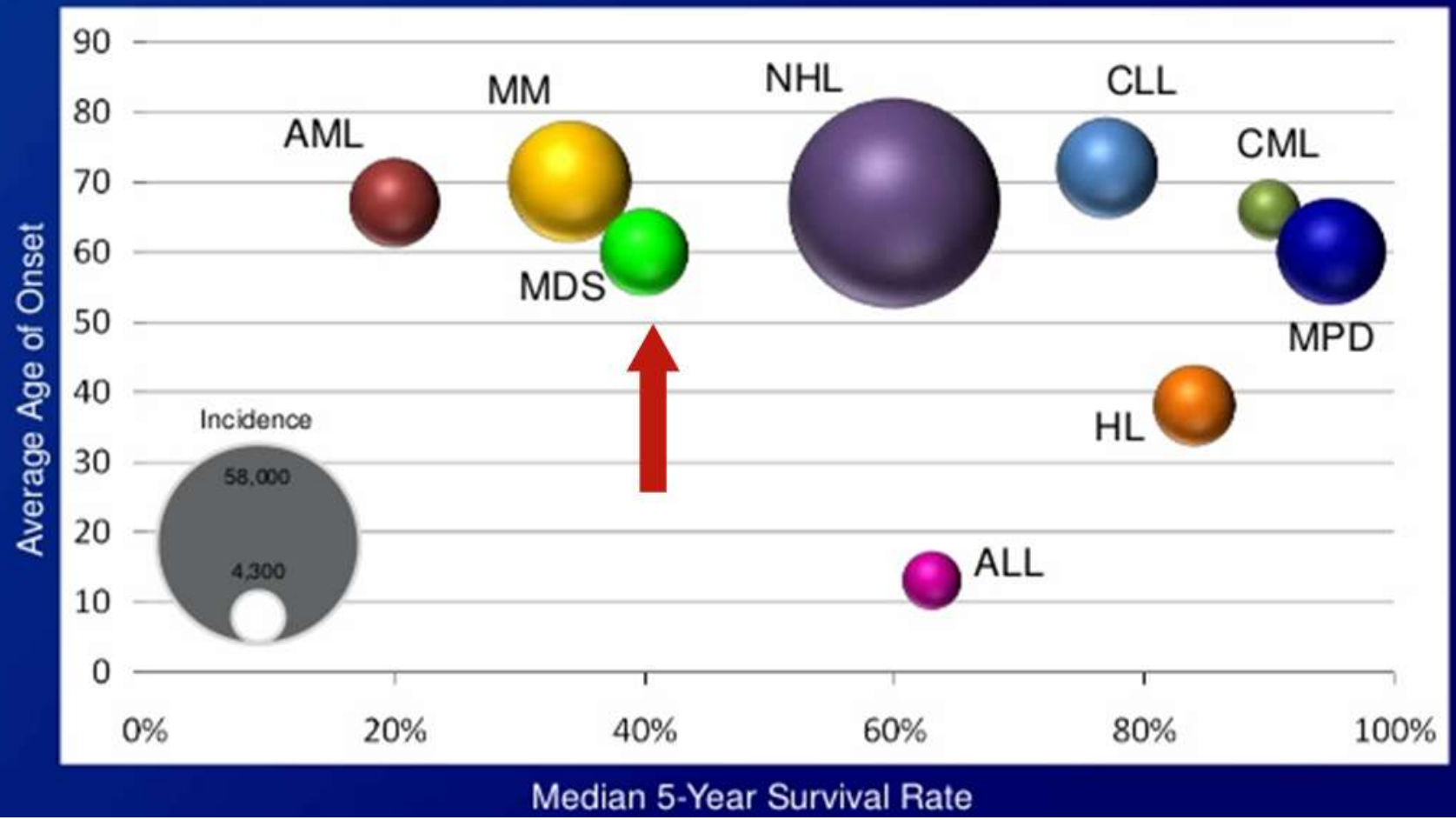
Available Diagnostic and Therapeutic Capabilities in Bangladesh

- Diagnosis:
  - Morphology and Trephine biopsy
  - Flowcytometry & Immunohistochemistry in selected hematological center.
  - Karyotyping & FISH for MDS panel from neighboring countries.
- Risk stratification:
  - IPSS-R

Available Treatment Regimen

- **Low risk:**
  - **Transfusion support**
    - Epo
    - Darbepoetin
    - G-CSF
    - TPO-RA
- **High risk:**
  - -Azacitidine
  - -Decitabine
  - -Thalidomide
  - -Allo-HSCT
- **5q-**
  - -Lenalidomide

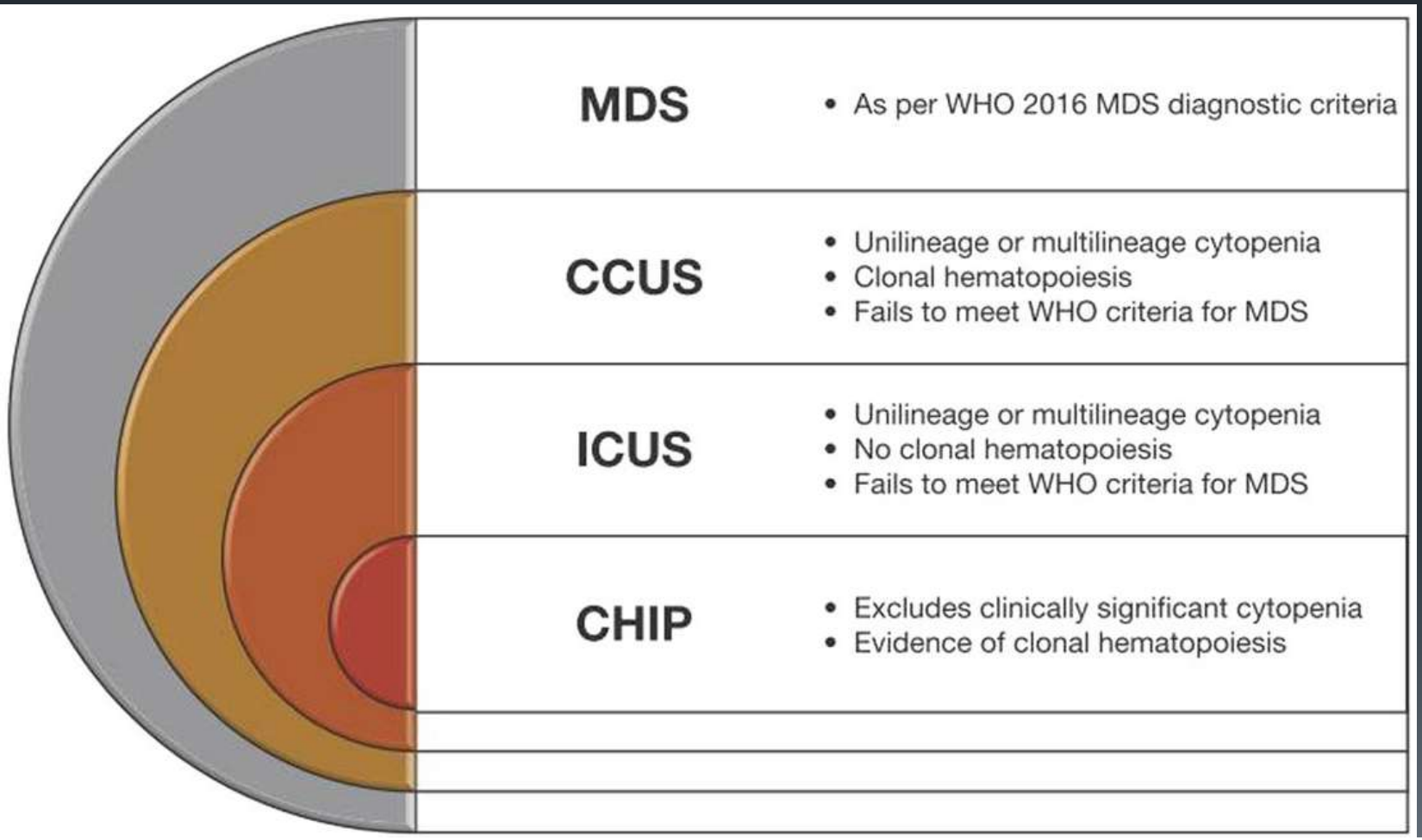
Comparison of Blood Cancers by Survival, Age of Onset, and Incidence



Myelodysplastic syndromes

- MDS are a heterogeneous group of myeloid malignancies characterized by
  - ✓ Cytopenia
  - ✓ Dysplastic morphology
  - ✓ Ineffective hematopoiesis
  - ✓ Propensity for progression to AML

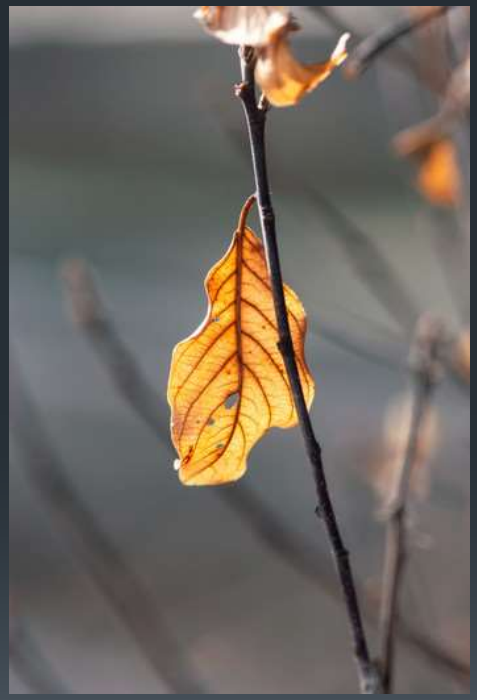
MDS, CCUS, ICUS, CHIP



DISCUSSION

- NGS panel helps in ruling out a clonal disorder
- It has a high negative predictive value
- In recent publications, mutations were detected in 90% of pts with WHO-defined MDS
- However, a very small proportion of pts with MDS may have negative results even on NGS panel
- Follow-up should unfold such cases or give an alternative diagnosis

MDS: Subtypes



- Adult vs pediatric
- Primary vs secondary
- Immune MDS vs the rest
- Lower risk vs higher risk
- De Novo vs Relapsed
- Hypoplastic MDS
- MDS MPN syndrome
- MDS with myelofibrosis

Learning Objectives

- Outline recent improvements in risk stratification for patients with MDS.
- Identify recent advances in therapeutic options for lower risk and higher risk MDS patients.
- Novel investigational therapies for tremendous unmet medical need to improve outcome.

Making a diagnosis of Myelodysplastic Syndromes (MDS)

- At least one cytopenia:
  - Hb<11 g/dl, or
  - ANC <1500µL, or
  - Platelets <100*10^9/L

MDS "decisive" criteria

>10% dysplastic cells in 1 or more lineages

5-19% blasts or

Abnormal Karyotype typical for MDS.

Exclude other causes of cytopenias and morphological changes.

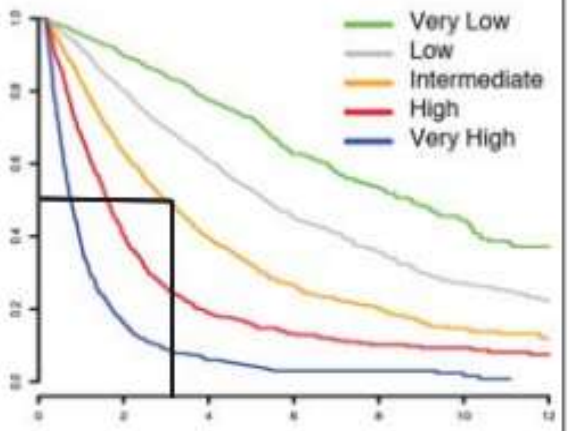
- Vitamin B12/folate deficiency
- HIV or other viral infection
- Copper deficiency
- Alcohol abuse
- Medications (esp. Methotrexate, Azathioprine, recent chemotherapy).
- Autoimmune conditions (ITP, Felty syndrome, SLE etc.)
- Congenital syndromes (Fanconi anemia etc.)
- Other hematological disorders (aplastic anemia, LGL disorders, MPN etc.)

The first step toward an individual prognostication

Prognosis by the Revised IPSS (IPSS-R)

Prognostic Variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very Good		Good		INT	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					

Risk Category	
Very Low	≤ 1.5
Low	> 1.5 - 3
Intermediate	> 3 – 4.5
High	> 4.5 - 6
Very High	>6

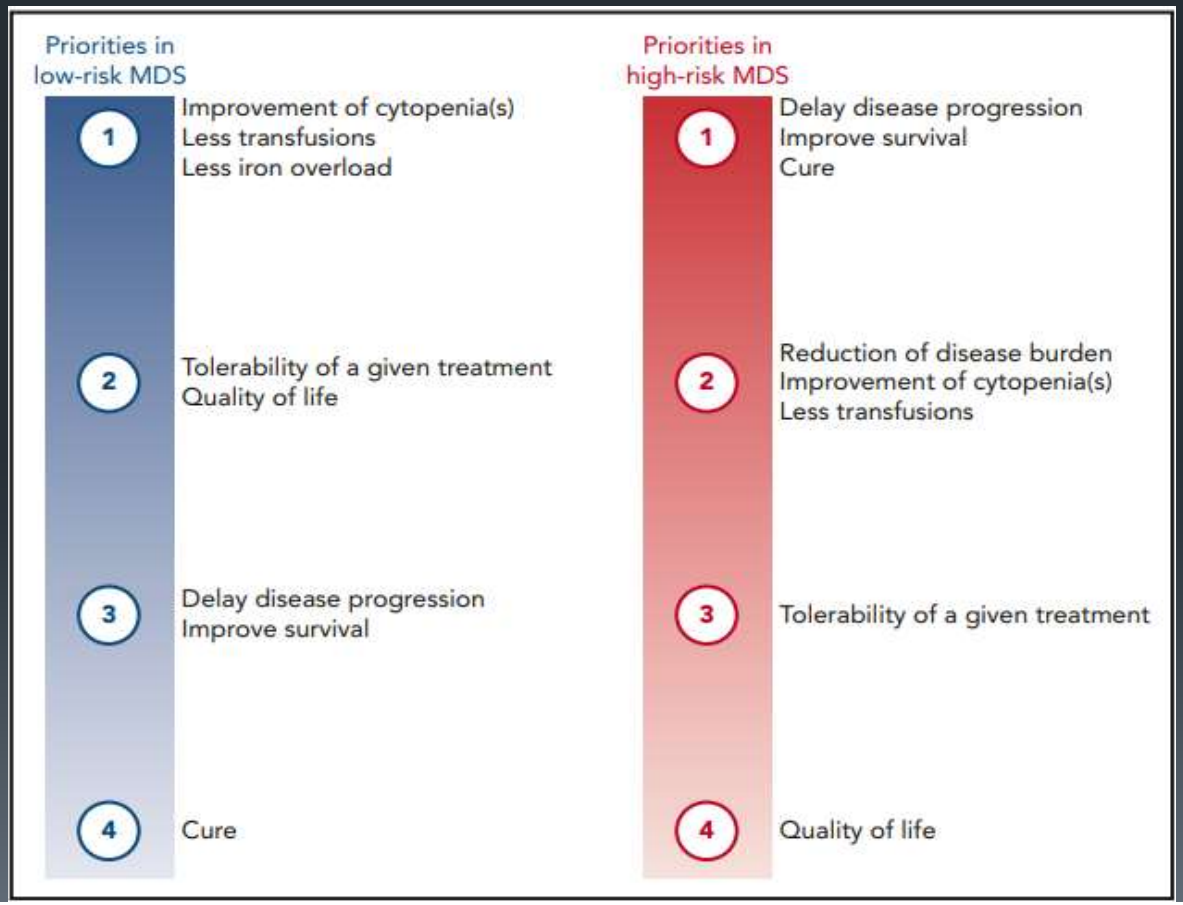


IPSS: Int-1, median OS: 42 months
IPSS-R: INT, median OS: 36 months
Actual survival: 12 months

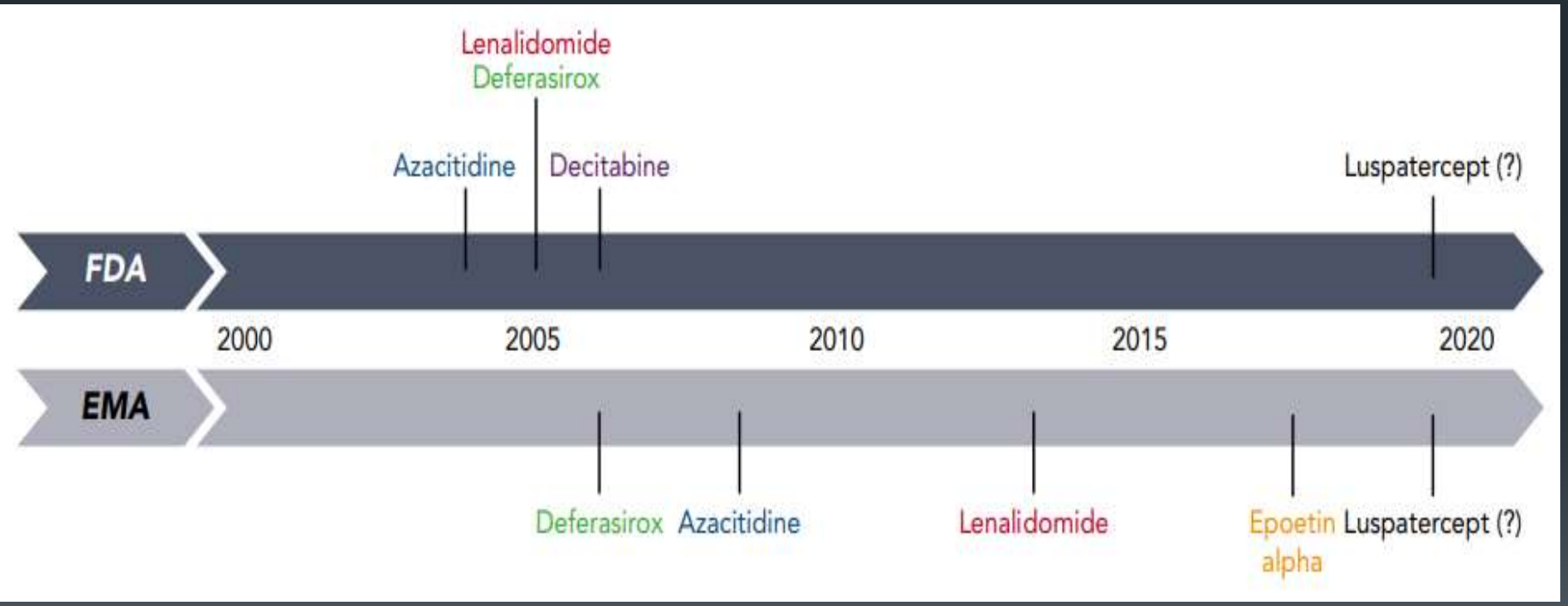
American Society of Hematology

Greenberg et al. 2012. Blood 120:2454

Ranking of potential goals of care in patients with either low- or high risk MDS.



Historical time scale of registration of therapeutic agents for MDS in the EU and United States



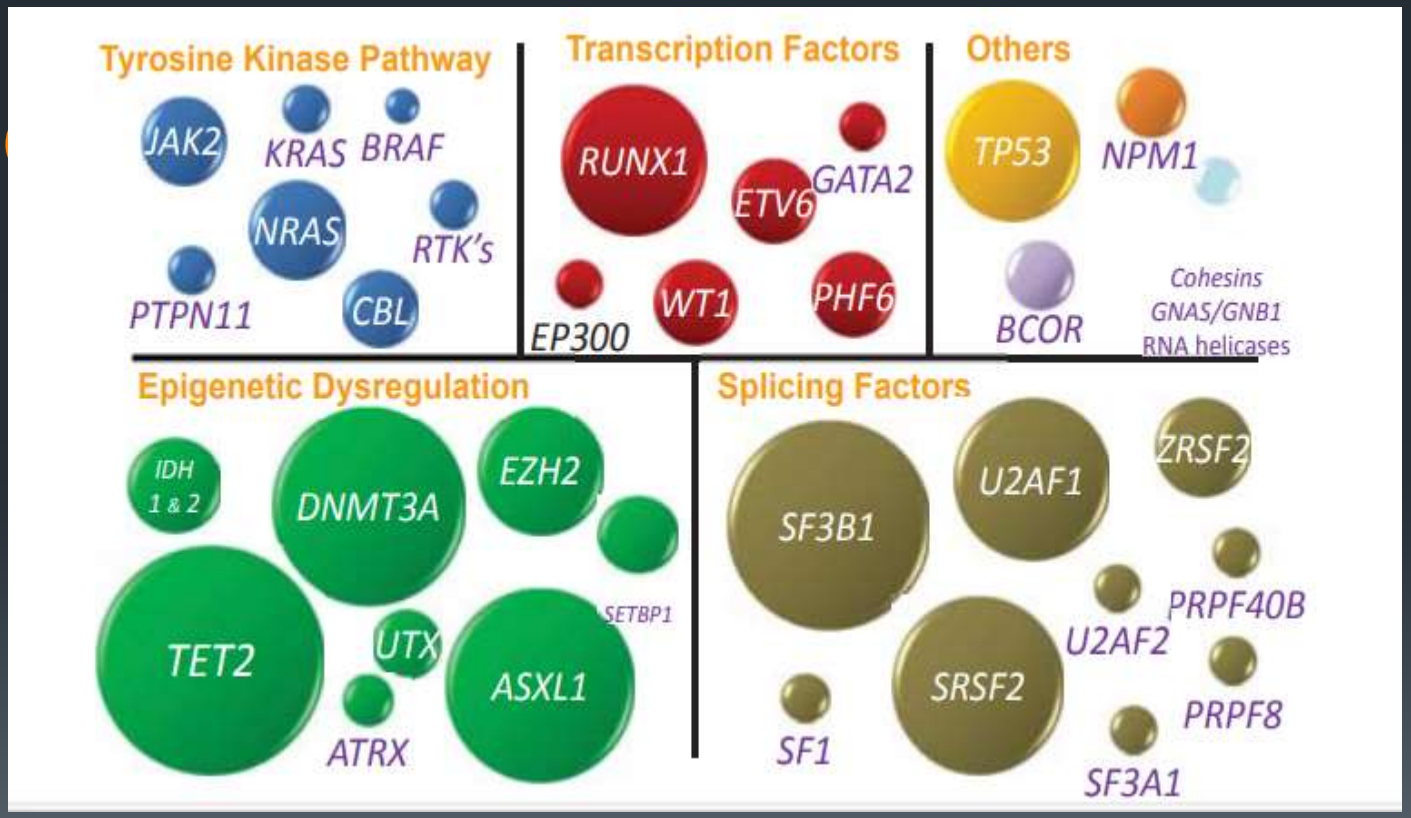
Luspatercept is shown as a potential novel drug, which is hoped to get approved in low-risk MDS in the near future

MDS : Molecular biology

About

40 Recurrently

Mutated Genes


Tyrosine Kinase Pathway
JAK2
KRAS
BRAF
NRAS
RTK's
PTPN11
CBL
Transcription Factors
RUNX1
ETV6
GATA2
EP300
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PHF6
Others
TP53
NPM1
BCOR
Cohesins
GNAS/GNB1
RNA helicases
Epigenetic Dysregulation
IDH 1 & 2
DNMT3A
EZH2
TET2
UTX
ASXL1
SETBP1
ATRX
Splicing Factors
SF3B1
U2AF1
ZRSF2
PRPF40B
U2AF2
SRSF2
PRPF8
SF1
SF3A1

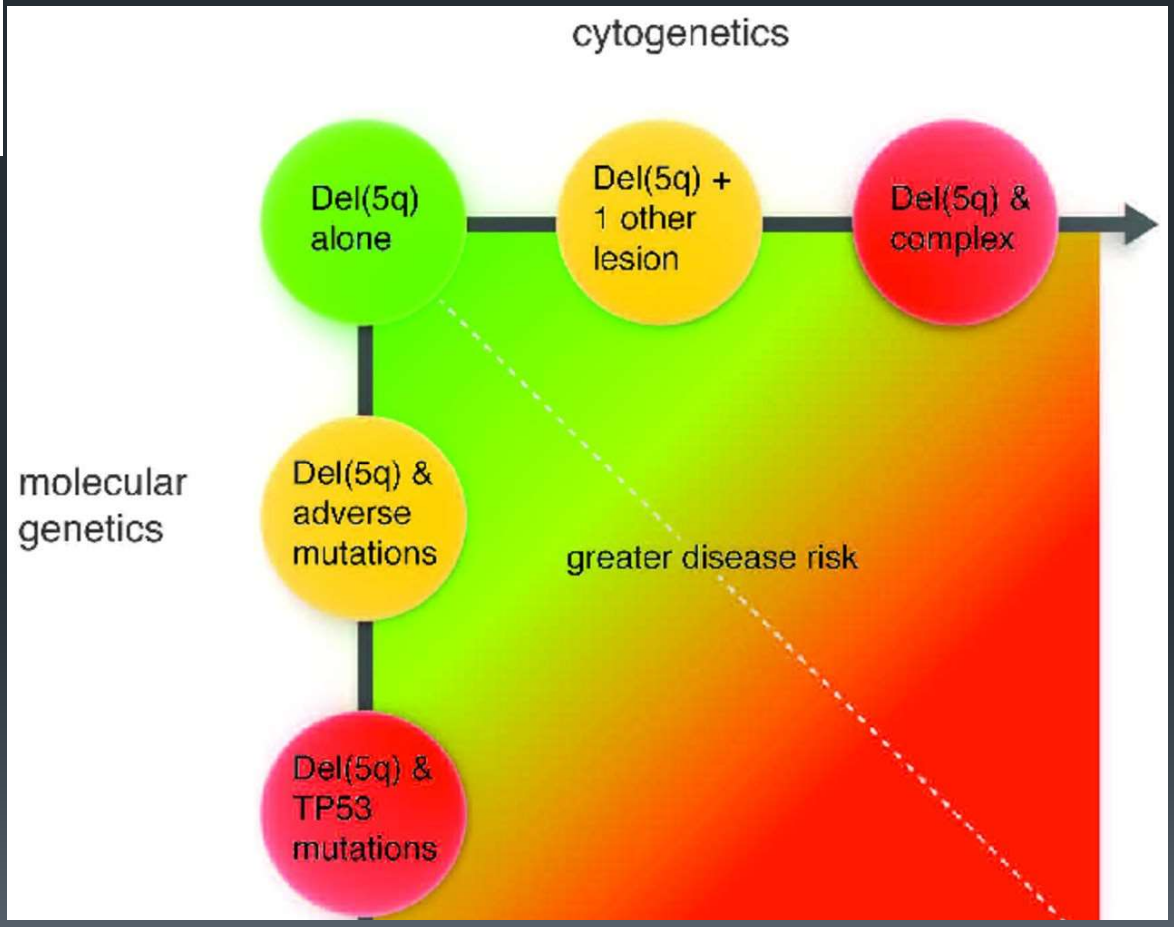
Pathogenesis of MDS

- Somatic mutations in almost every MDS patient.
- Spliceosome gene mutations and comutations involving TET2, DNMT3A, or ASXL1 are highly predictive for disease evolution.
- Unfavorable mutations (TP53, ASXL1, RUNX1, EZH2, HTV6) may indicate a more intensive surveillance strategy so treatment extending to allo-HSCT.

p53

Genome

Guardian


cytogenetics
Del(5q) alone
Del(5q) + 1 other lesion
Del(5q) & complex
molecular genetics
Del(5q) & adverse mutations
greater disease risk
Del(5q) & TP53 mutations

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

TP53 Mutations in Low-Risk Myelodysplastic Syndromes With del(5q) Predict Disease Progression

Martin Jädersten, Leonie Saft, Alexander Smith, Austin Kulasekararaj, Sabine Pomplun, Gudrun Göhring, Anette Hedlund, Robert Hast, Brigitte Schlegelberger, Anna Porwit, Eva Hellström-Lindberg, and Ghulam J. Mufti

See accompanying editorial on page 1937 and article on page 1963

From the Department of Medicine, Center for Experimental Hematology, and Department of Pathology and Oncology, Karolinska Institutet, Stockholm, Sweden; King's College London School of Medicine, London, United Kingdom; and Institute of Cell and Molecular Pathology, Hannover Medical School, Hannover, Germany.

Submitted July 24, 2010; accepted December 1, 2010; published online ahead of print at www.jco.org on April 25, 2011.

A B S T R A C T

Purpose

To determine the frequency of *TP53* mutations and the level of p53 protein expression by immunohistochemistry (IHC) in low-risk myelodysplastic syndromes (MDS) with del(5q) and to assess their impact on disease progression.

Patients and Methods

Pre- and postprogression bone marrow (BM) samples from 55 consecutive patients with International Prognostic Scoring System low risk (n = 32) or intermediate-1 risk (n = 23) were studied by next-generation sequencing of *TP53*. IHC for p53 was performed on 148 sequential BM samples.

Current standard of care in treating patients with MDS

LR-MDS

- IPSS low/intermediate-1
- IPSS-R very low, low, intermediate up to 3.5 points

AIM

- Improving cytopenia(s) to prevent complications, such as bleeding and severe infections.
- Decreasing transfusion burden and iron over load.
- Improving quality of life.

Intensified surveillance strategy

- **Indicators**
  - worsening of cytopenia
  - An increasing number of circulating or bone marrow blasts.
  - Science of cytogenetic or molecular evolution.

Lower risk Vs Higher risk

Different risk MDS have different goals

- Lower risk MDS have long survival but problem of cytopenia, chiefly transfusion dependency
- Goal of therapy is to make pt transfusion free
- Higher risk MDS have a short survival, very high risk of evolution to AML and death
- Goal of therapy is to prevent evolution to AML, extend life & if possible, cure the disease

Treatment of Anemia

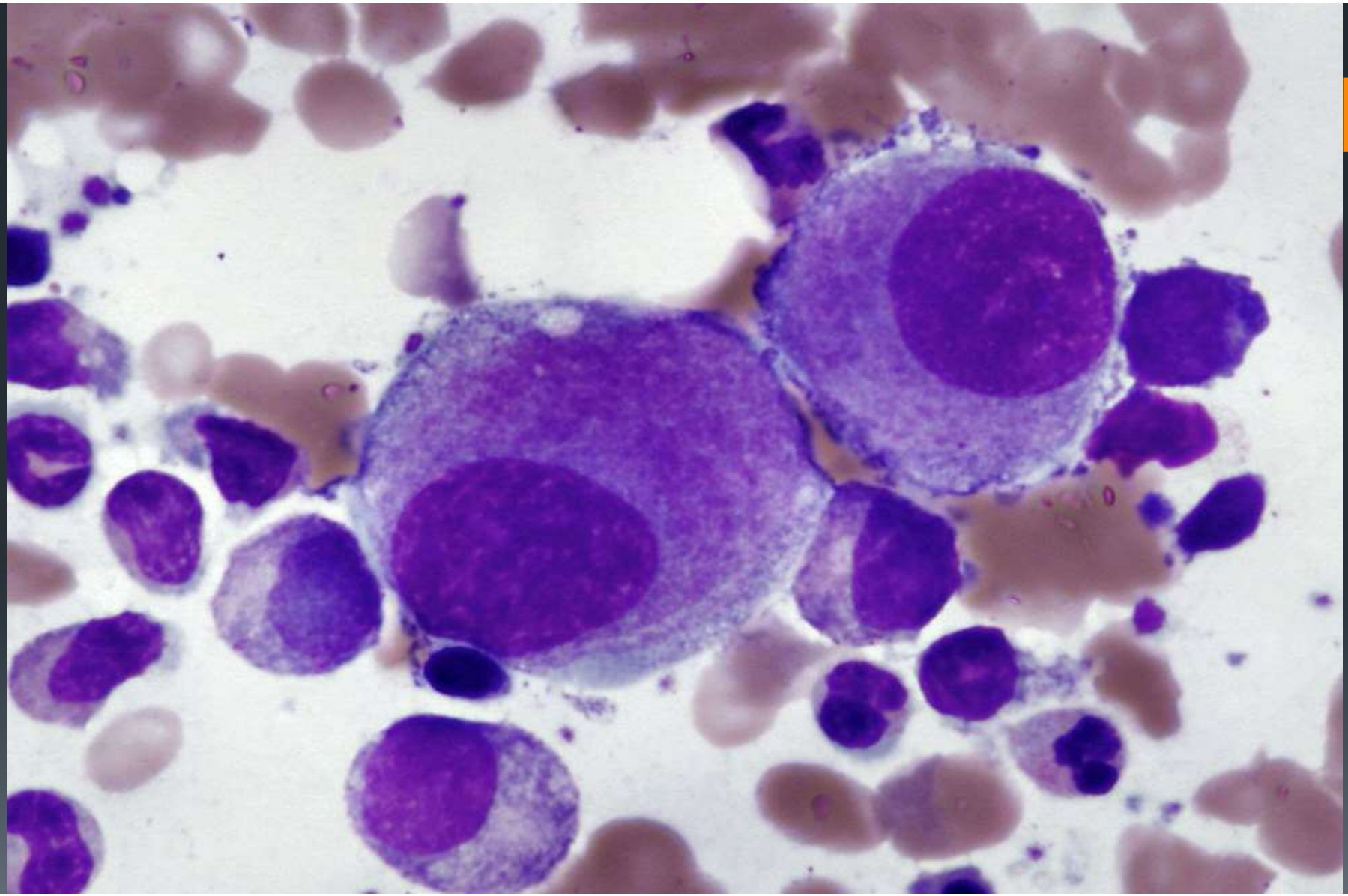
- Majority of patients require regular red blood cell transfusion. This results in iron overload and requires substantial human as well as financial resourses.
- Treatment with ESAs ((ie, Recombinant erythropoietin (EPO) or darbepoetin (DAR))as single agents is the standard of care.
- <500 iu/L endogenous EPO level and a transfusion burden <4 U with in a 8 weeks period.
- The addition of granulocyte colony stimulating factor with single agent ESA, is of particular benefit to patients with ring sideroblasts.

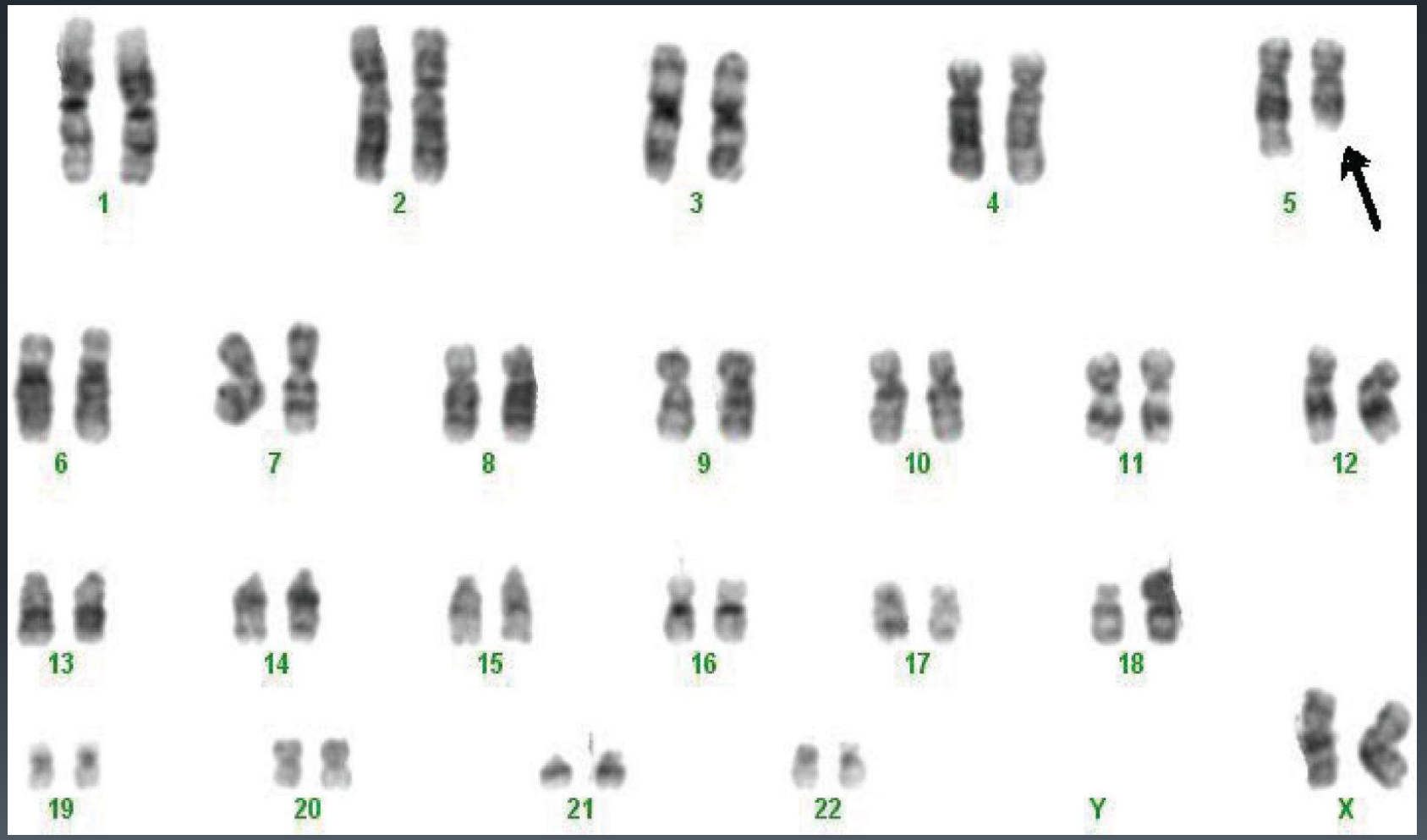
Targeting anemia in genetically defined de(5q) MDS

- Lenalidomide is the treatment of choice and results in erythroid responses in 70% of patients.
- Lenalidomide in non-del(5q) patients with RBC-TD refractory to ESAs results in erythroid responses in 27% of patients.
- The combination of lenalidomide & ESA significantly improved erythroid response rate.

Case study

- Ferdous Ara, 71 Y, Chittagong
- Refractory macrocytic anaemia–10 months
- Thrombocytosis ($805x10^9/L$)
- Transfusion dependent
- Characteristic MK cells in the marrow
- Hypolobated & eccentrically placed nucleus
- Almost no blasts (<0.5%)

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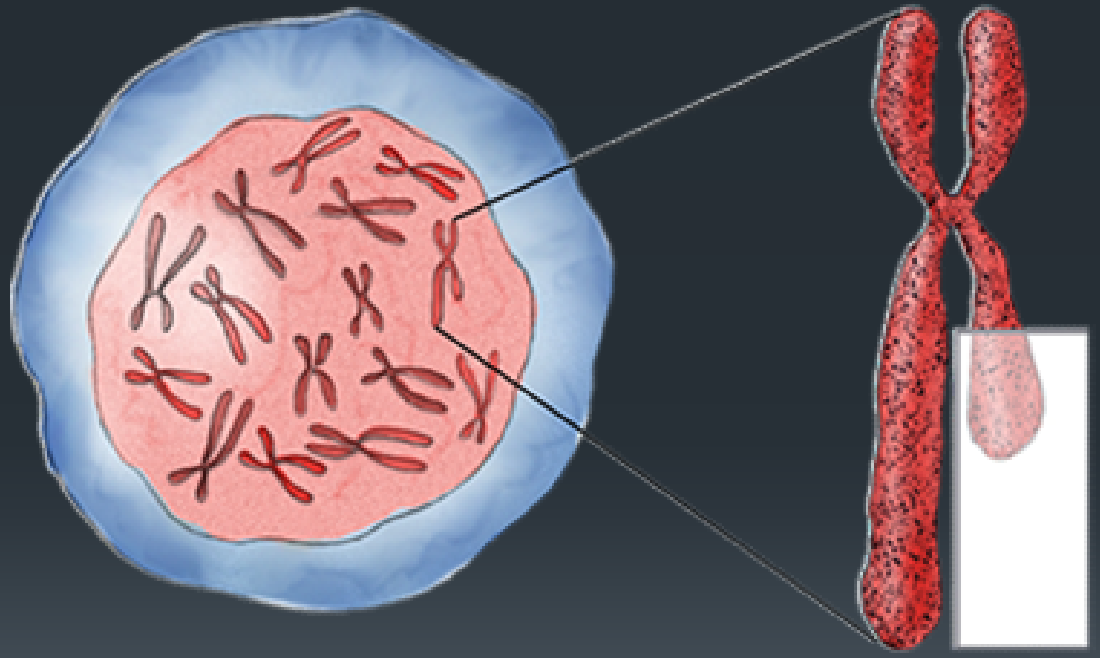
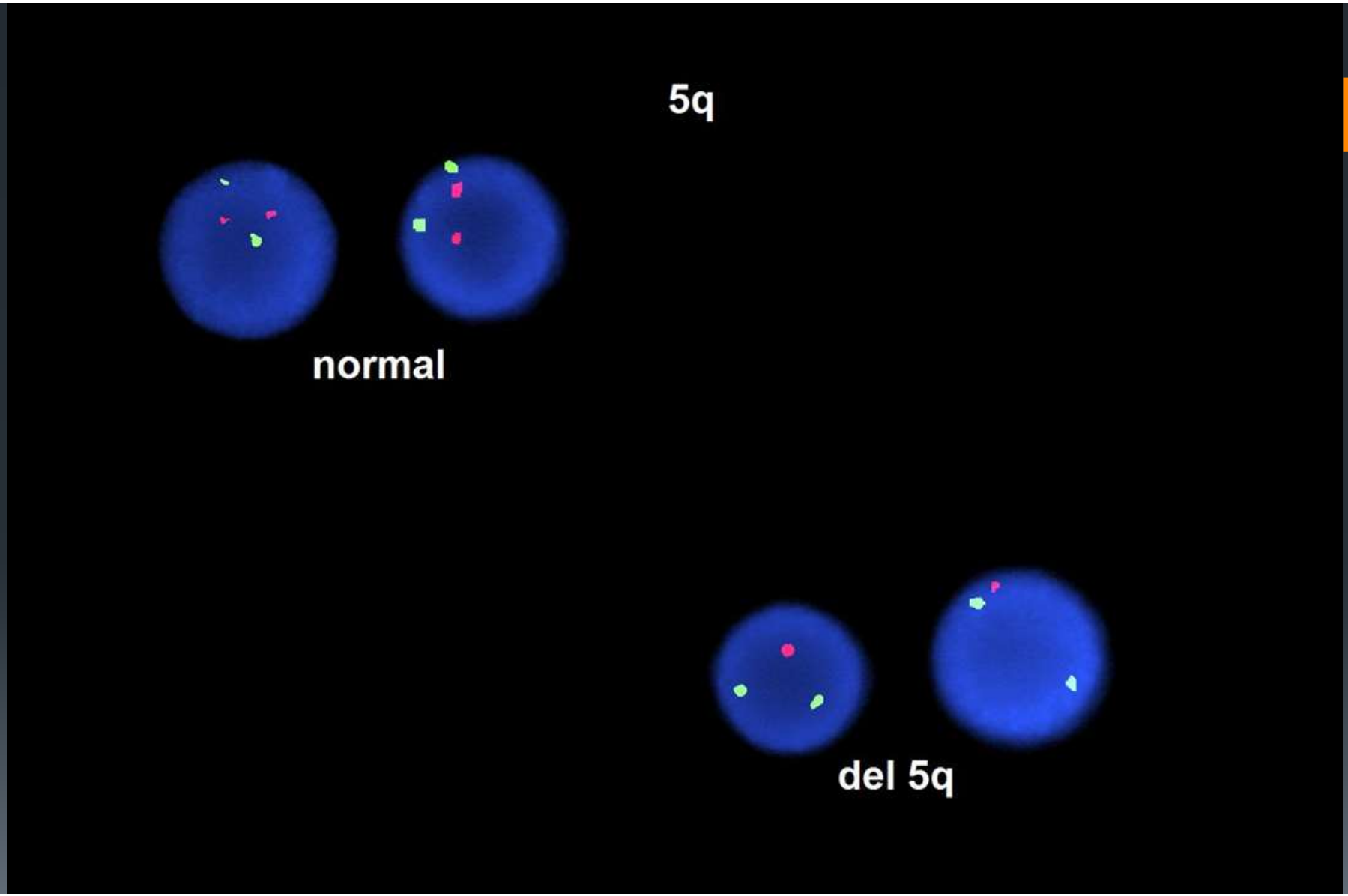



5q
normal
del 5q

Chromosome 5q- syndrome

Del (5q) Syndrome

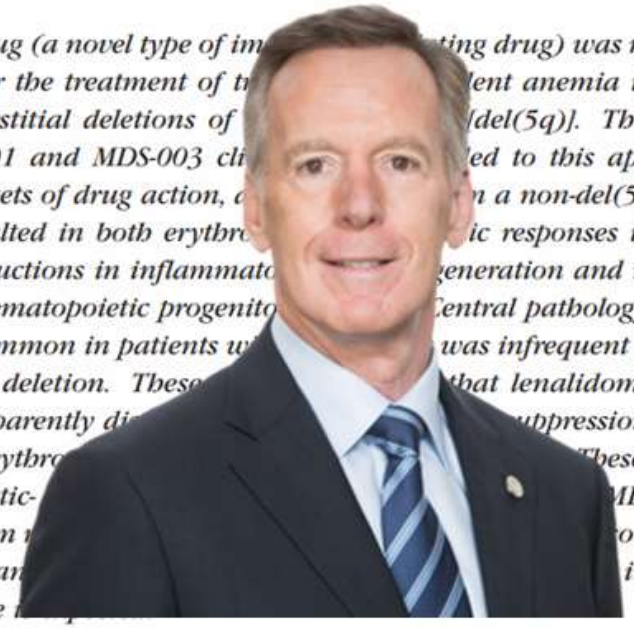
- Elderly female
- Macrocytic anaemia, thrombocytosis
- Marrow resembles PRCA
- Characteristic megakaryocytes
- Low risk of progression to leukaemia
- Relatively better prognosis
- Targeted therapy

Alan List

The NEW ENGLAND JOURNAL of MEDICINE 2006 N Engl J Med 2006; 355:1456-1465

Lenalidomide: Targeted Anemia Therapy for Myelodysplastic Syndromes

Alan F. List, MD, Amanda F. Baker, PharmD, PhD, Sylvan Green, MD, and William Bellamy, PhD



Lenalidomide, an IMiD® drug (a novel type of im ting drug) was recently approved by the US Food and Drug Administration for the treatment of t lent anemia in patients with myelodysplastic syndromes (MDS) and interstitial deletions of /del(5q)]. This review examines the clinical experience from the MDS-001 and MDS-003 cli ed to this approval, the results of biological correlates supporting the targets of drug action, a n a non-del(5q) multicenter study (MDS-002). Lenalidomide treatment resulted in both erythr ic responses in the majority of patients with del(5q), accompanied by reductions in inflammato eneration and marrow microvessel density and improvement in primitive hematopoietic progenito Central pathology review showed that resolution of cytologic dysplasia was common in patients w was infrequent in erythroid-responding patients without the chromosome 5 deletion. These that lenalidomide promotes erythropoiesis in lower-risk MDS, with two apparently di uppression of the ineffective del(5q) clone and promotion of effective erythr These studies identified lenalidomide as a highly active erythropoietic- MDS patients who otherwise would not be expected to benefit from t ommon adverse reactions include dose-dependent neutropenia an in patients with del(5q) in whom early suppression of the clone

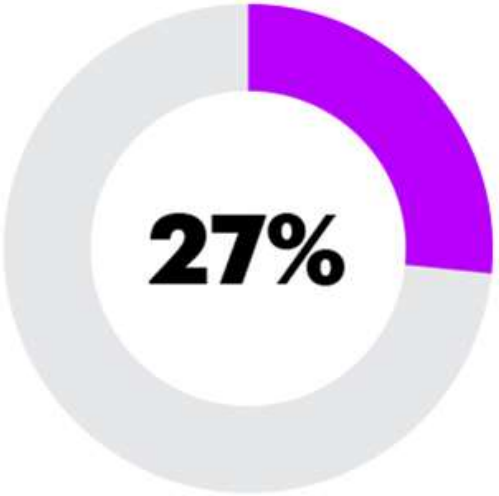
Lesson Learnt

- Refractory anaemia, macrocytosis, elderly woman
- Must do Karyotyping / FISH for del (5q)
- Look for del (17p)
- If negative, do molecular testing for TP53 mutation
- Len is a targeted therapy for this group
- TP53 mutation is predictor of Len failure

Lesson learnt

- Refractory anaemia, macrocytosis, elderly woman
- Must do Karyotyping / FISH for del (5q)
- Look for del (17p)
- If negative, do molecular testing for TP53 mutation
- Len is a targeted therapy for this group
- TP53 mutation is predictor of Len failure
- Does Len work in pts without 5q- ?

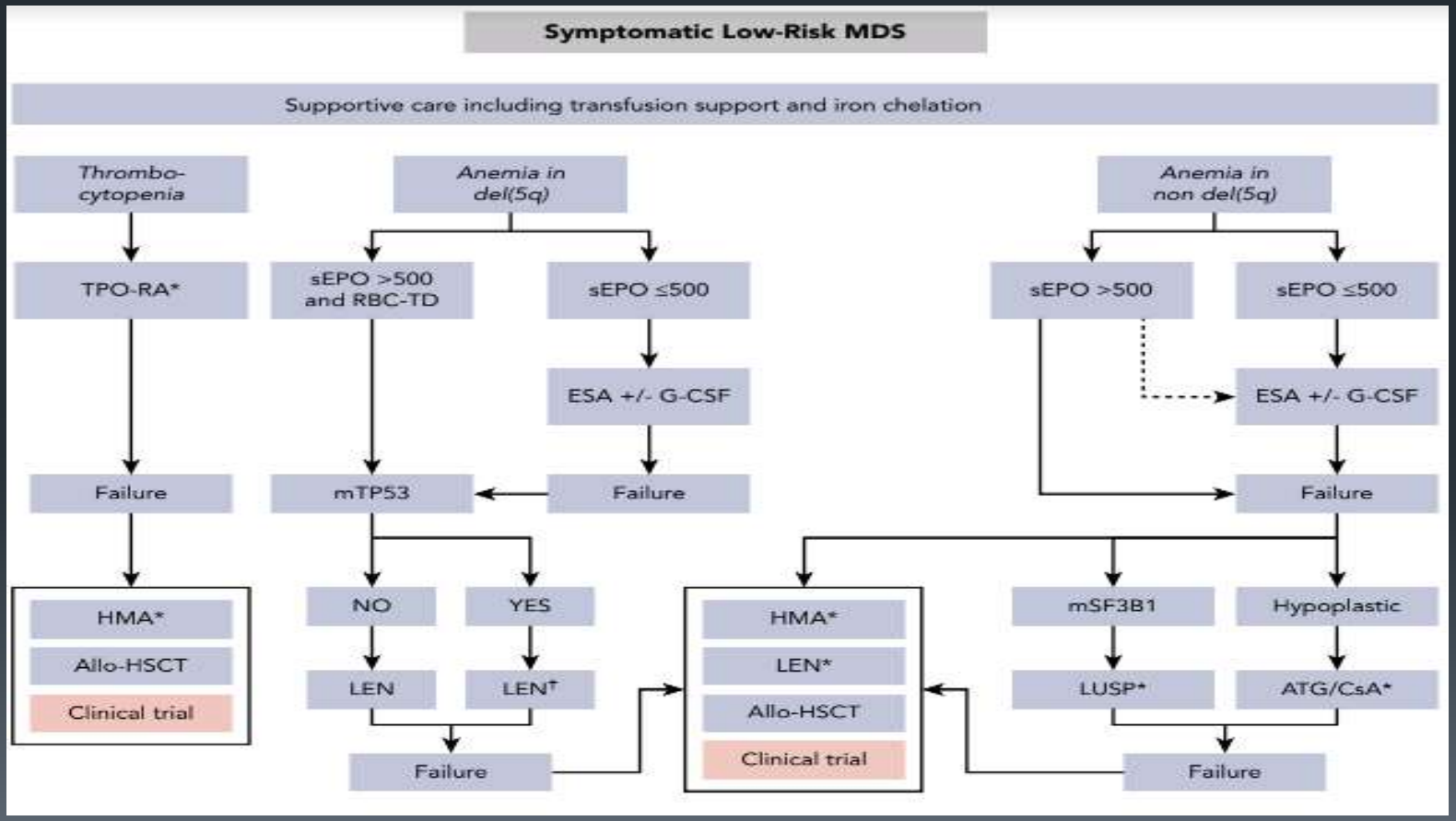
yes



Supportive care using iron chelation

- 250 mg iron per RBC unit accumulates
- Iron chelating drug is deferasirox
- Chelation should be started when serum ferritin level at least >1000 ng/ml.
- 36.4% risk reduction in event-free survival defined by-
  - Worsening cardiac function
  - Hospitalization for congestive heart failure
  - Liver function impairment
  - Liver cirrhosis
  - Transformation to AML

Therapeutic algorithm in LR-MDS patients



Immunosuppressive Agents

- Profound immune dysregulation contributing to ineffective hematopoiesis.
- ATG with or without CSA shows trilineage response rates ranging from 16 % - 67% .
- Predictors of response
  - MDS single lineage dysplasia
  - Hypoplastic bone marrow.
  - DR15 HLA type.
  - Younger age <60 years.

ATG/CSA still recommended

- In hypoplastic MDS & normal karyotype
- Failing with growth factors
- Very high response rates of 72% using the anti-CD52 antibody (Alemtuzumab).

HMAs

- Dose reduced HMAs also have some activity in LR-MDS.
- First-line low-dose HMA treatment with 3 days of decitabine (DAC) resulted in a 32% red blood cell transfusion independence rate.

Allo-HSCT

- A recent study by the European Society for Blood and Bone Marrow Transplantation in 246 IPSS low/intermediate-1 patients demonstrated 3-year survival rates of 58% accompanied by a 30% overall nonrelapse mortility rate.

Appropriate candidates

- Life-threatening infection
- Severe thrombocytopenia
- RBC-TD
- Certain poor-risk molecular abnormalities.

Novel approaches to treat anemia in LR-MDS

- Erythropoiesis-maturating agents (EMAs)
- Luspatercept (ACE-536) has recently shown promising ability to increase hemoglobin with limited toxicity in a phase 2 study in LR-MDS patients.
- Indications-
  - LR-MDS patients with RS-MDS
  - *SF3B1* mutation
  - Refractory to or not eligible for ESA

Treatment of Thrombocytopenia

- Apart from disease modifying therapies such as HMAs, platelet transfusions and TPO-receptor agonists (TPO-RA) are currently the only reasonable treatment options.
- Eltrombopag a small molecular TPO-RA showed 47% platelet responses.
- Romiplostim only 36% platelet response.
- Transient elevation of peripheral blasts in 10% of patients.
- Both can be safely used in patients with no excess of blasts (<5%).

Case study

- Khuda Baksh, 63Y, Rajshahi, 2018
- Low risk MDS (Hb: 4.5 g/dl)
- Transfusion dependent – 1 year
- No evidence del (5q)
- S. EPO was > 750 u/L
- His transfusion requirement was 4 bags per month
- He was offered Len as an option which he accepted
- He is transfusion free for last 18 months with last Hb of 10.8 g/dl (2 weeks ago)

2016

VOLUME 34 · NUMBER 25 · SEPTEMBER 1, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized Phase III Study of Lenalidomide Versus Placebo in RBC Transfusion-Dependent Patients With Lower-Risk Non-del(5q) Myelodysplastic Syndromes

Valeria Santini, Antonio Almeida, Aristoteles Giagounidis, Stefanie Gröpper, Anna Jonasova, Norbert Vey, Ghulam J. Mufti, Rena Buckstein, Moshe Mittelman, Uwe Platzbecker, Ofer Shpilberg, Ron Ram, Consuelo del Cañizo, Norbert Gattermann, Keiya Ozawa, Alberto Risueño, Kyle J. MacBeth, Jianhua Zhong, Francis Séguy, Albert Hoenekopp, C.L. Beach, and Pierre Fenaux

Len in non-del(5q) MDS

Lenalidomide gives sustained transfusion free

life to 26.9 % of transfusion-dependent

low-risk non-del(5q) pts

Case study

- Abdul Jabbar, 73 years, Comilla, 2019
- Saw us for symptomatic anaemia of 6 months
- He was incapacitated & wanted help
- He had IHD, COPD, DM
- Hb was 6.8 g/dl
- H/o 6 packed cells in last 6 months
- MDS-RA, no del (5q) with S.EPO of 180 u/L

Erythropoiesis stimulating agents

Case study

- He was a perfect case for treatment with ESA
- This was in view of :
- Low endogenous EPO-level (< 500 u/L)
- Low transfusion requirement i.e. < 2 units/month
- Inj EPO 40,000 units was given, SC, once a week
- Hb ↑ to 9.6 g/dl by 8th week
- It ↑ to 10.3 g/dl by 12th week

Case study

- He became asymptomatic, free from transfusion started enjoying outdoor activities, socializing & has started going to club as well
- We have now followed him up for 26 months
- Last week his Hb was 12.8 g/dl & we have reduced his dose of EPO to 10,000 units every wk

Response predictors

- S EPO < 250 u/L or at least < 500 u/L
- Less blood requirement i.e. < 2 units/month
- Starting of ESA early in the course of disease
- Absence of 5q-
- Presence of up to 2 mutations
- Absence of ring sideroblasts
- Absence of SF3B1

1. Park, S et al. JCO. 2017. 35; 1591-97
2. Moyo V et al. Annals of Hematology. 2008. 87; 527-36
3. Fenaux P et al. Annals of Oncology. 2014. 25; 57-69

Erythropoietin

- Fortunately, 80% of low-risk MDS have S. EPO level of below 200 u/L & another 10% have it below 500 u/L
- Hence treatment can be tried even without EPO level
- The efficacy of ESA dose and frequency dependent
- Side effects are minimal
- One should aim at Hb of around 10-11 g/dl & dose reduction may be done in responding pts

1. Park, S et al. JCO. 2017. 35; 1591-97
2. Moyo V et al. Annals of Hematology. 2008. 87; 527-36
3. Fenaux P et al. Annals of Oncology. 2014. 25; 57-69

Erythropoietin

- Responses occur within 2 months of starting ESA
- These are seen in 20-40% of pts
- Dose can be raised to 60,000 U
- Those with inadequate response should receive additional G-CSF
- These rescue another 20% of pts

1. Park, S et al. JCO. 2017. 35; 1591-97
2. Moyo V et al. Annals of Hematology. 2008. 87; 527-36
3. Fenaux P et al. Annals of Oncology. 2014. 25; 57-69

Darbepoetin

- Dose of Darbe is 500 u SC once every 3 weeks
- This becomes more convenient as the injections are only once every 3 weeks
- However, it is a bit more expensive

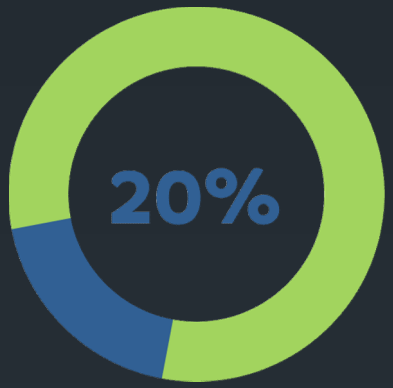
Recommendations

- ESA therapy should be the first-line treatment of anaemia in pts with lower-risk MDS
- Those who benefit the most are the one with base line EPO level of <500 IU/L & without del(5q)

Lesson learnt

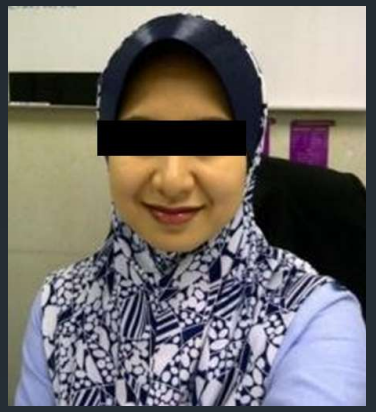
- ESA is the treatment for low-risk MDS
- It should be started at the earliest
- Dose of EPO is 40-60,000 U SC once weekly
- Dose of Darbe is 500 ug SC every 3 weeks
- Responses are seen in 20-40% of subjects
- It should be continued for minimum of 8 weeks
- Responses can last for years
- It spares transfusion dependent life

Len + ESA in non-del (5q) MDS



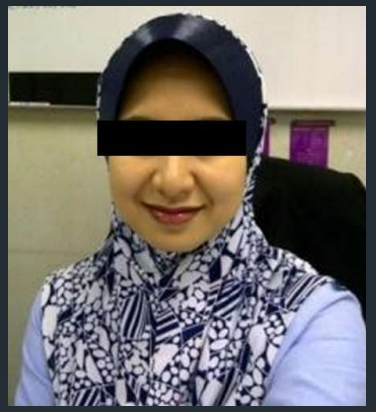
- In pts of lower risk MDS with Len failure, addition of ESA helps
- This combination works in 20% of pts
- Median duration of response is 16 months

Case study



- Nahida, 47 y, Saver
- Symptomatic for 3 months
- Anaemia, thrombocytopenia
- Hypoplastic MDS (two-lineage dysplasia)
- S. EPO > 750 u/L
- PNH studies: positive with 1.2% clone
- Karyotyping: Trisomy 8, no del (5q)
- No evidence of SF3B1

Case study



- She was treated with horse ATG + CsA
- Three months later, she was transfusion free & as of today, we have a follow up of 11 months
- The response has been sustained
- She was a perfect case lower risk MDS treated by immunomodulation using ATG + CsA

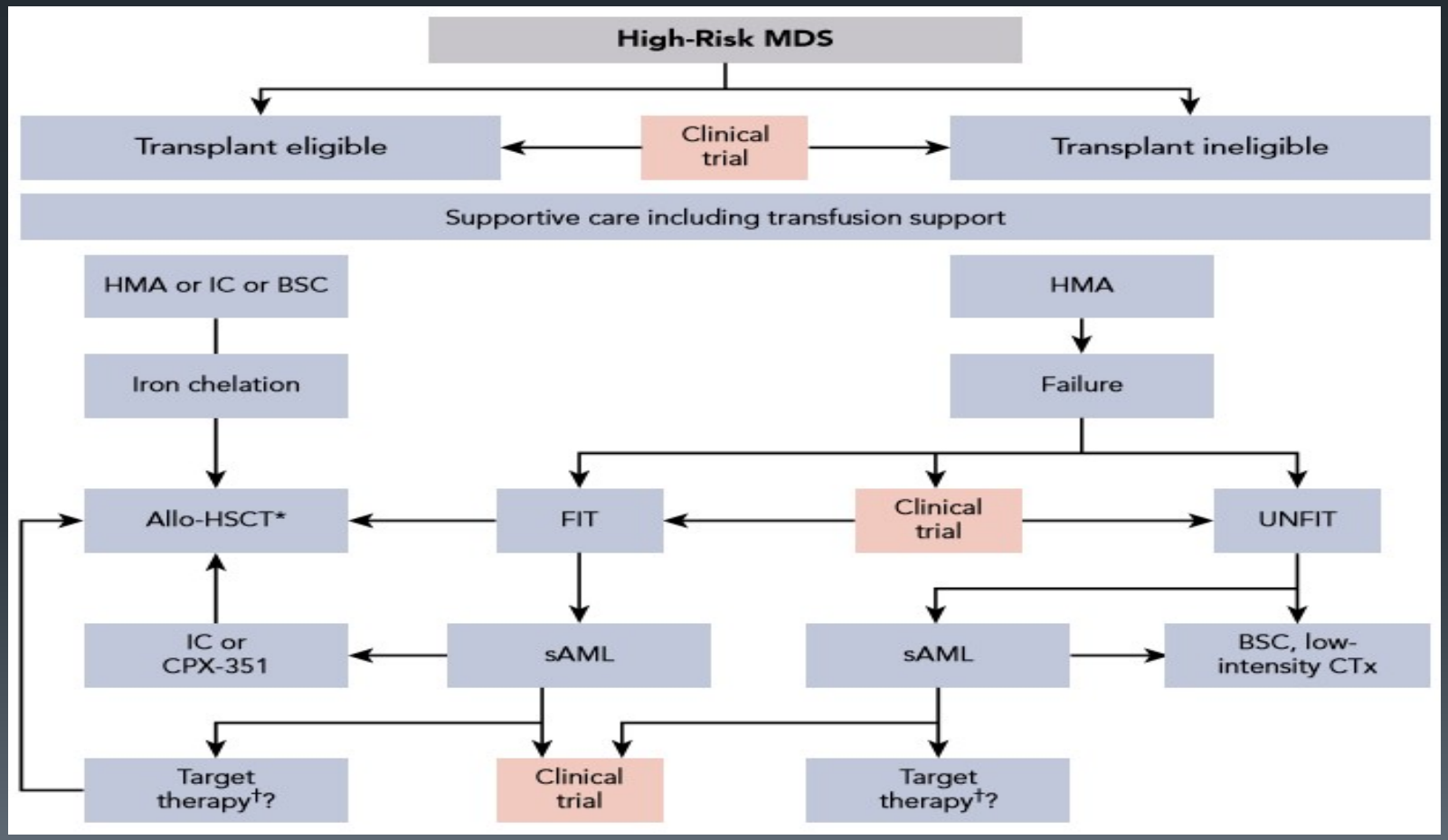
Response predictors

- Young pt < 60 years
- Female
- Short duration of transfusion dependency
- Hypoplastic MDS
- Trisomy 8
- Small PNH clone
- HLA-DR15
- Absence of RARS
- Absence of SF3B1

HR-MDS

- Principal aim of treatment
  - ✓Modify the natural course of disease
  - ✓Limiting disease progression and
  - ✓Improving survival rates.

Therapeutic algorithm in HR-MDS patients.



First-line HMAs

- HMAs (AZA and DAC) represent the only approved therapeutics and current standard of care.
- The registration trial showed a significant survival benefit (24.5 vs 15 months) of AZA compared with standard of care including intensive chemotherapy.

Clinical Markers of worse survival

- Presence of peripheral blasts
- Poor performance status
- High transfusion burden
- Poor risk cytogenetics

Allo-HSCT: Indication and timing

- Patients with intermediate-2 or HR-MDS by IPSS criteria should be considered for allo-HSCT at the time of diagnosis.
- Older patients receiving reduced intensity conditioning (RIC) validated when based on the IPSS-R.
- Pretransplant comorbidities taken into consideration using the HSCT-specific comorbidity index.

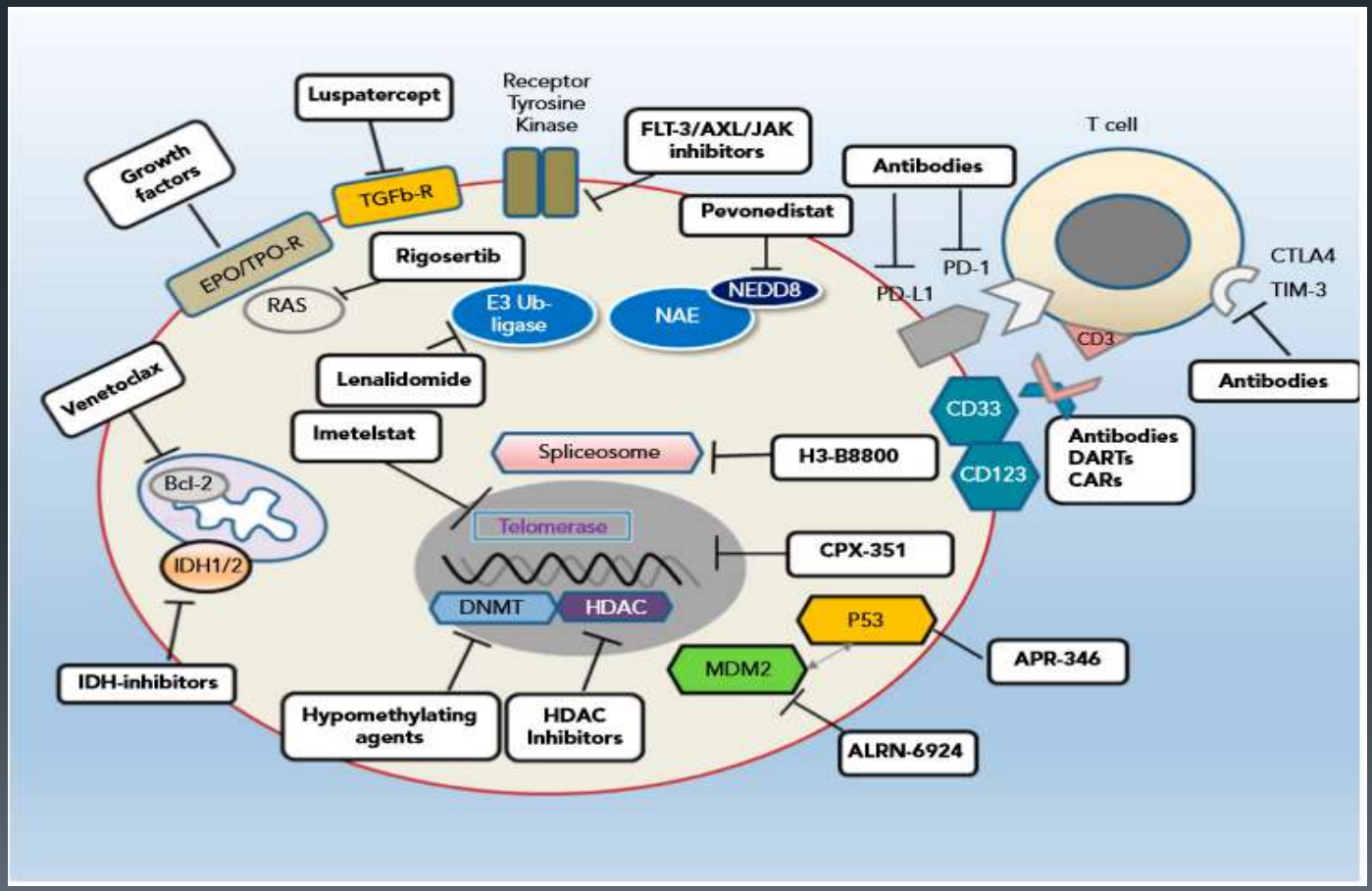
Allo-HSCT: Indication and timing

- Oral AZA is currently under investigation as maintenance therapy following allo-HSCT in HR-MDS or AML patients.
- The availability of CPX-351 may potentially lead to a renaissance of intensive chemotherapy.
- HMAs are currently used to at least “bridqe” the time up to the identification of a compatible donor.
- The development of RIC regimens has allowed the successful application of allo-HSCT in older patients with MDS.

Iron Chelation before allo-HSCT

- Elevated labile plasma iron levels before allo-HSCT predict an increased incidence of infection related nonrelapse mortality (33% vs 7%) and a decreased overall survival in patients with AML or MDS.
- Therefore, eligible patients should receive appropriate iron chelation before allo-HSCT.

Standards and perspectives of therapeutic options in patients with MDS



Novel Concepts in the treatment of HR-MDS

- Second-generation HMAs
  - HMA's action is S-phase dependent.
  - The new-generation DNA hypomethylating drug is guadecitablne.
  - This drug is currently in phase 3 clinical trials for elderly patients with-MDS failing HMAs.

Novel combination partners of HMAs

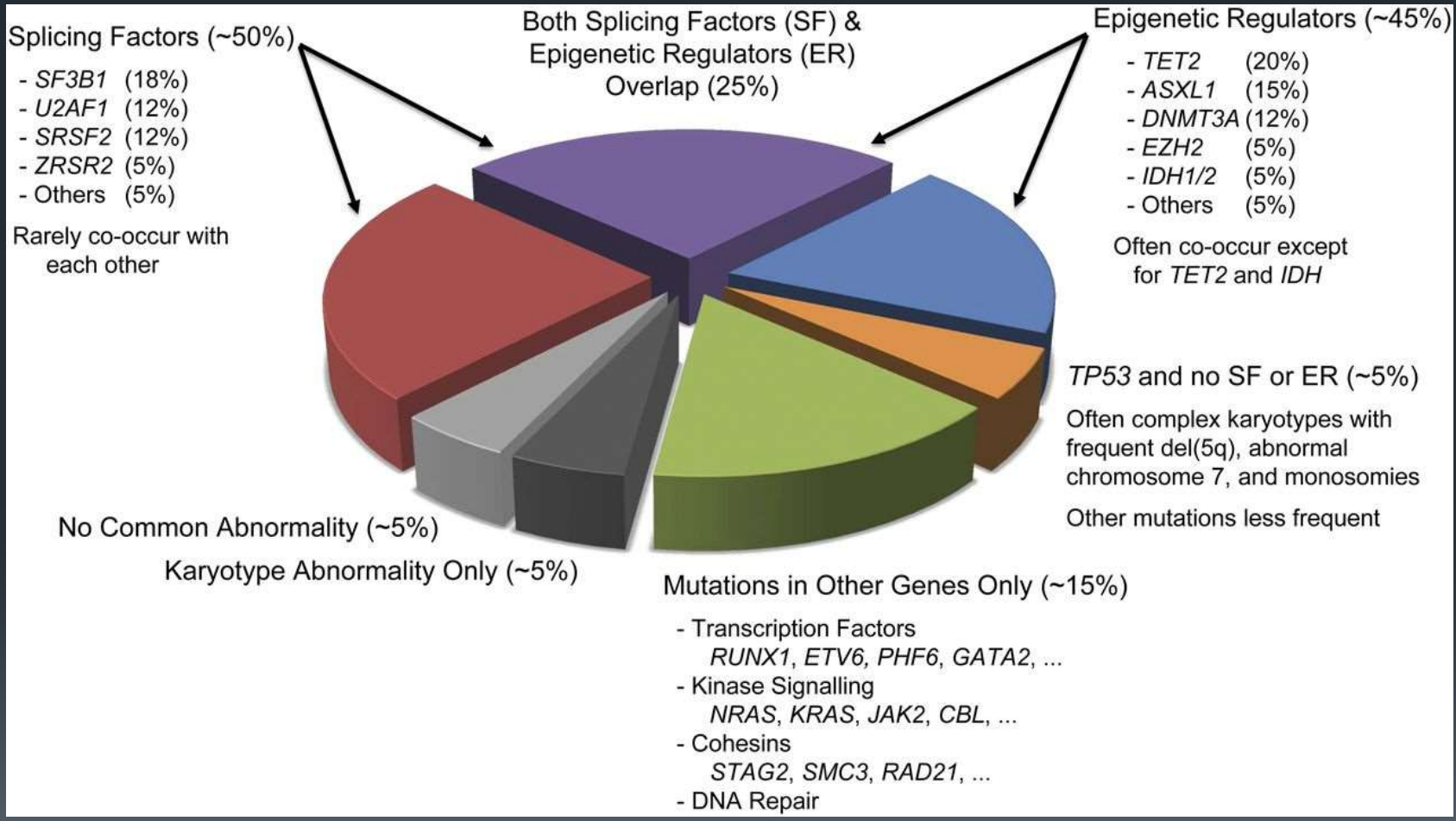
- Combination of AZA with either lenalidomide, vorinostat, or eltrombopag did not show any benefit compared with AZA alone.
- Pevonedistat, a novel inhibitor of the NEDD8 activating enzyme, has shown synergistic and antileukemaic activity with AZA in preclinical AML models.
- IDH mutations are quite common in MDS (10% to 15% of patients)
- IDH1 or IDH2 inhibitors (enasidenib, ivosidenib) in relapsed AML including a small MDS subgroup are promising (ORR 59%).

Novel combination partners of HMAs

- Combination of venetoclax with AZA in patients with HR-MDS including HMA failure is currently recruiting.
- The combination HMAs with different immune-checkpoint inhibitors also as second-line therapy.

Targeting TP53

- Outcomes for patients with
  - HR-MDS and a TP53 gene mutation are generally poor even after allo-HSCT.
  - A 10-day regimen of DAC showed very good efficacy in patients with TP53-mutated MDS or AML.

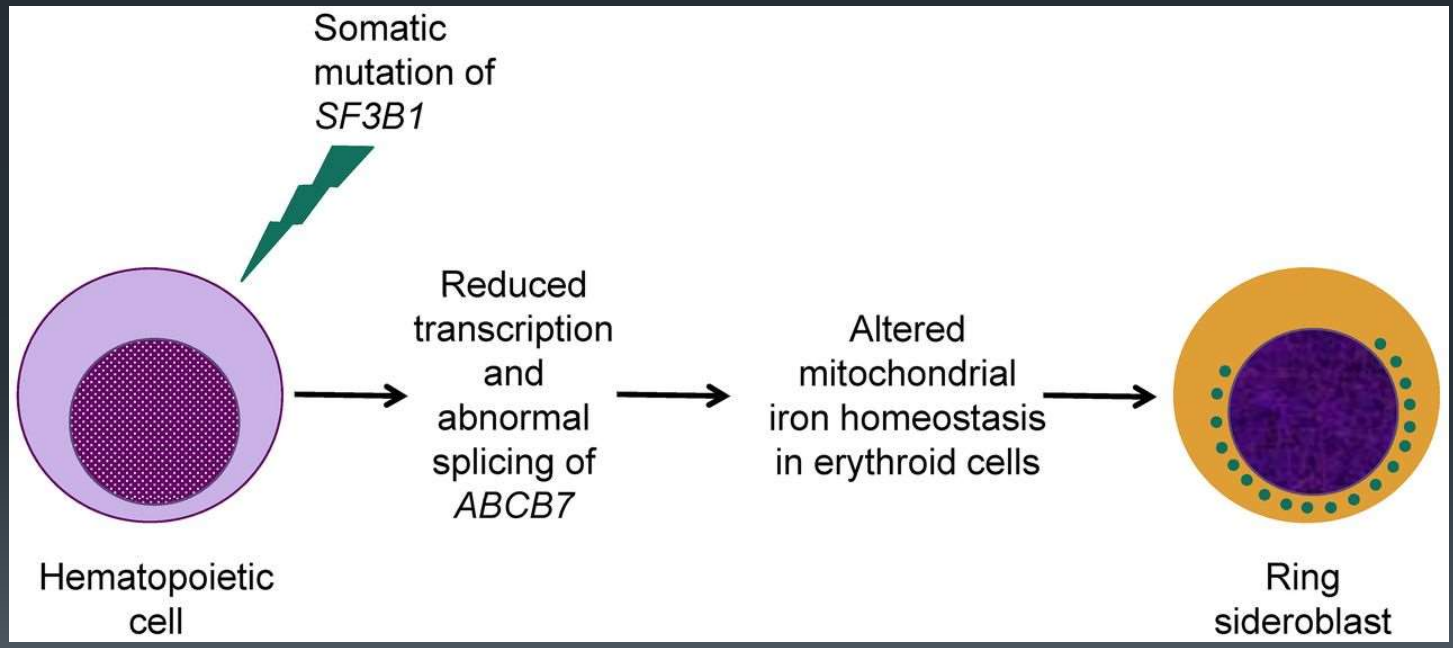

Splicing Factors (~50%)
- SF3B1 (18%)
- U2AF1 (12%)
- SRSF2 (12%)
- ZRSR2 (5%)
- Others (5%)
Rarely co-occur with each other
Both Splicing Factors (SF) & Epigenetic Regulators (ER) Overlap (25%)
Epigenetic Regulators (~45%)
- TET2 (20%)
- ASXL1 (15%)
- DNMT3A (12%)
- EZH2 (5%)
- IDH1/2 (5%)
- Others (5%)
Often co-occur except for TET2 and IDH
TP53 and no SF or ER (~5%)
Often complex karyotypes with frequent del(5q), abnormal chromosome 7, and monosomies
Other mutations less frequent
No Common Abnormality (~5%)
Karyotype Abnormality Only (~5%)
Mutations in Other Genes Only (~15%)
- Transcription Factors
RUNX1, ETV6, PHF6, GATA2, ...
- Kinase Signalling
NRAS, KRAS, JAK2, CBL, ...
- Cohesins
STAG2, SMC3, RAD21, ...
- DNA Repair

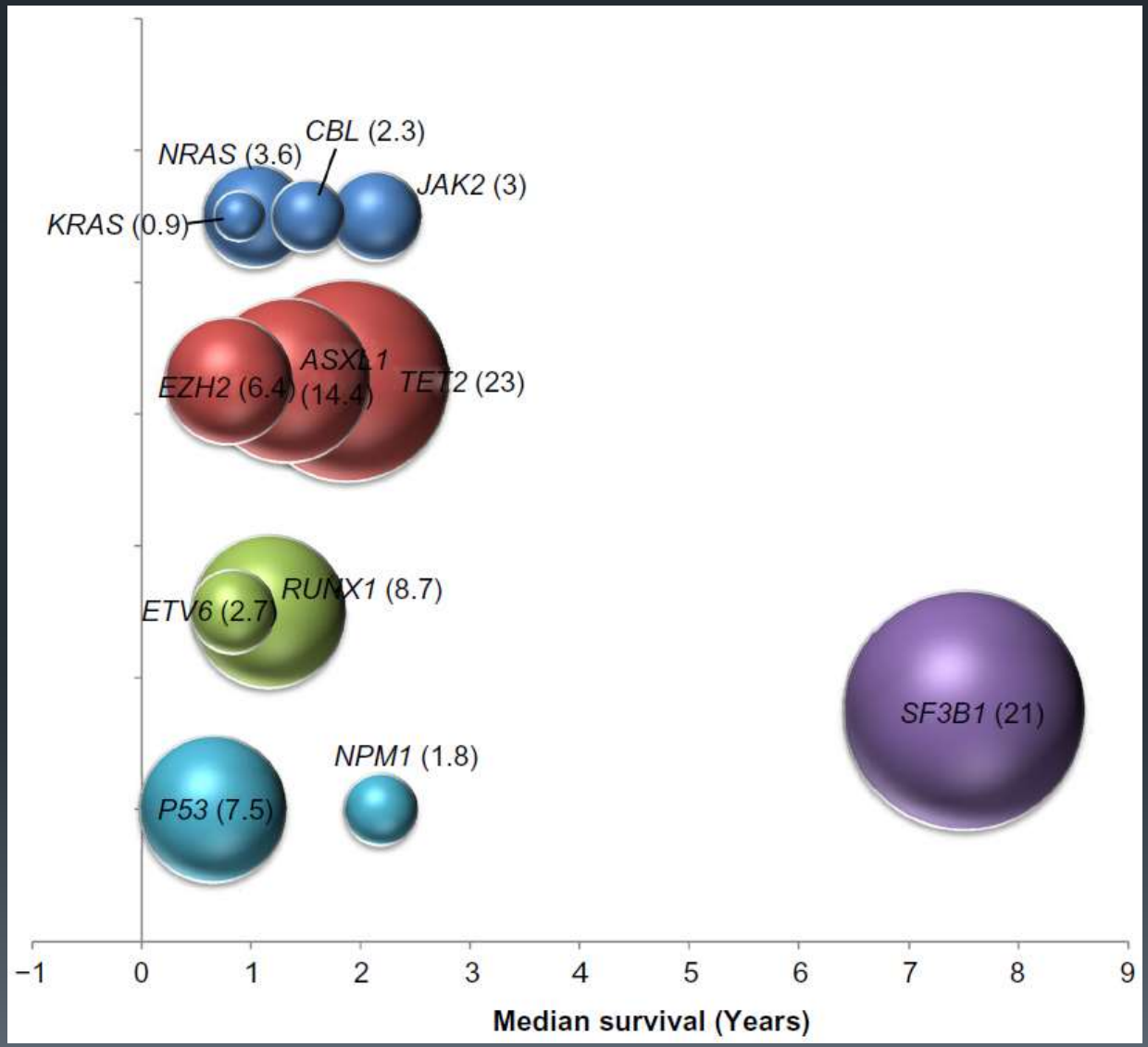
	Frequency of mutations (%)	Gene function	Prognosis
SF3B1	15–30%	Spliceosome	Favourable?
TET2	15–25%	DNA hydroxymethylation	Neutral
ASXL1	10–20%	Histone modifications	Unfavourable
RUNX1	5–15%	Transcription factor	Unfavourable
TP53	5–10%	Transcription factor	Unfavourable
DNMT3A	5–10%	DNA methylation	Unfavourable?
NRAS, KRAS	5–10%	Signal transduction	Unfavourable (low-risk syndromes)
SRSF2	5–10%	Spliceosome	Unfavourable
U2AF1	5–10%	Spliceosome	Unfavourable (low-risk syndromes)
BCOR-L1	5–6%	Transcription repressor	Unfavourable
ZRSR2	5%	Spliceosome	Neutral?
EZH2	3–7%	Histone modifications	Unfavourable
ETV6	3%	Transcription factor	Unfavourable
JAK2	3–4%	Signal transduction	Favourable?
IDH1, IDH2	4–5%	DNA hydroxymethylation and histone modifications	Unfavourable
UTX	1–2%	Histone modifications	Unfavourable?

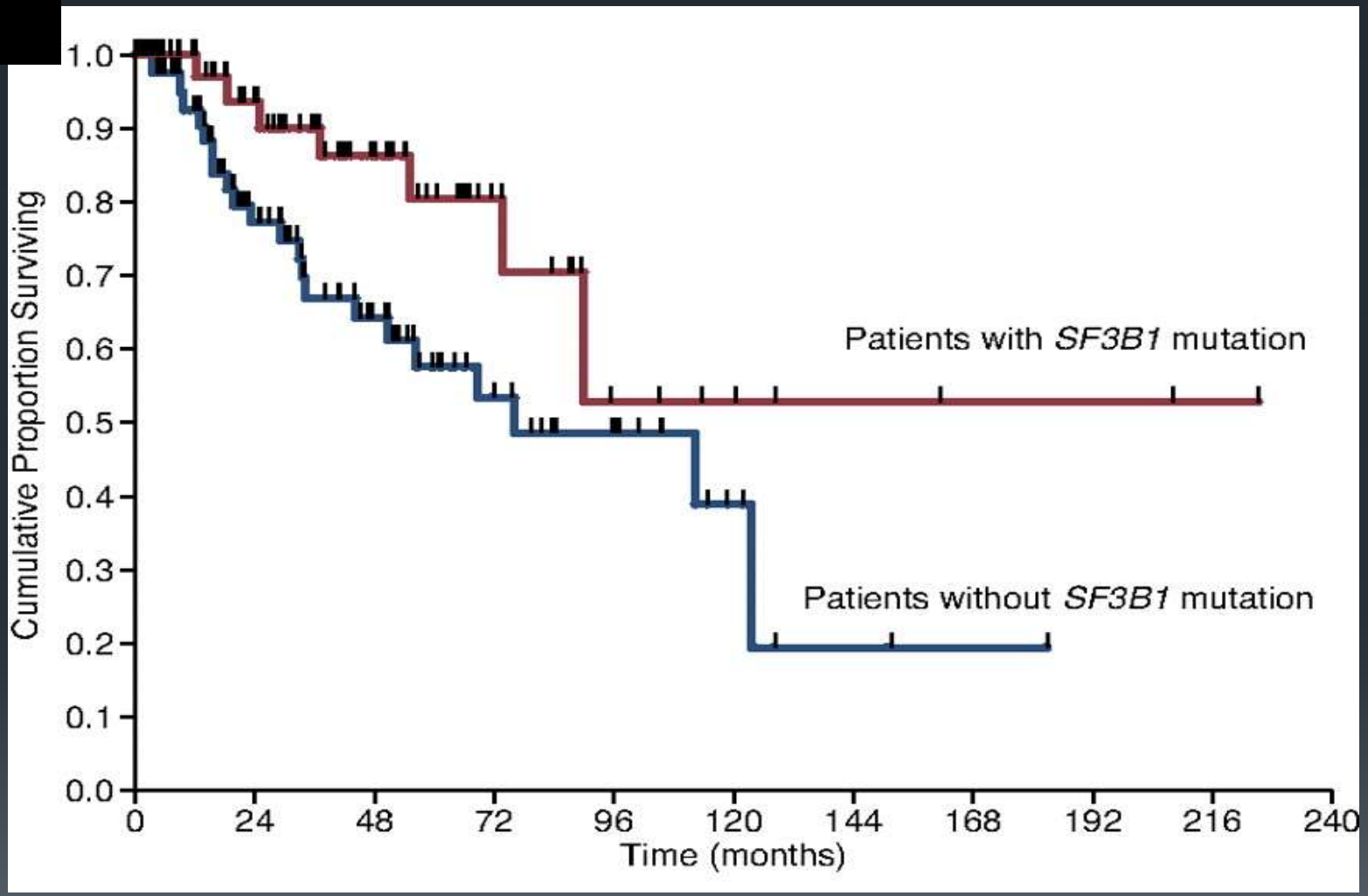
SF3B1 mutation

- SF3B1 mutation is a splicesome mutation
- It is a common mutation (15-30%)
- It has favorable prognosis
- It is seen in 65% of pts with MDS-RS
- If SF3B1 mutation is present, MDS-RS can be diagnosed with merely 5% of ring sideroblasts
- MDS-RS is now molecularly defined by WHO

SF3B1 Mutation




CBL (2.3)
NRAS (3.6)
JAK2 (3)
KRAS (0.9)
ASXL1 (14.4)
EZH2 (6.4)
TET2 (23)
RUNX1 (8.7)
ETV6 (2.7)
SF3B1 (21)
NPM1 (1.8)
P53 (7.5)
−1
0
1
2
3
4
5
6
7
8
9
Median survival (Years)


Cumulative Proportion Surviving
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
24
48
72
96
120
144
168
192
216
240
Time (months)
Patients with SF3B1 mutation
Patients without SF3B1 mutation

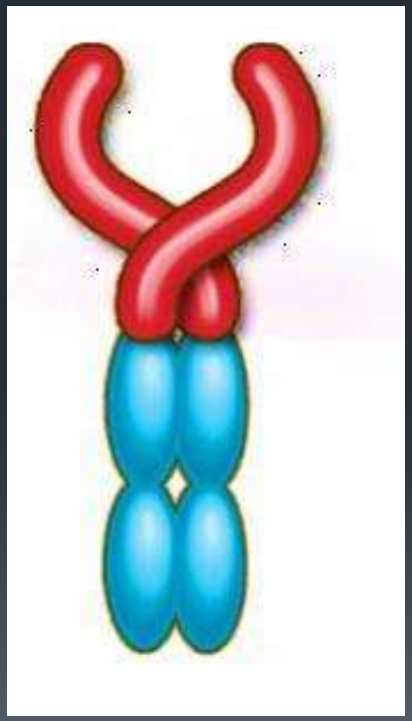
SF3B1 Mutation

- The hematological parameters of SF3B1 mutations identify a distinct subset of MDS pts with homogeneous features
  - Elderly age
  - higher platelet count
  - Pure erythroid dysplasia
  - Ring Sideroblasts

SF3B1 mutation

- Less or no blasts cells
- lower IPSS risk score
- Leukemia free survival
- Less impact on the OS

Luspatercept



Luspatercept

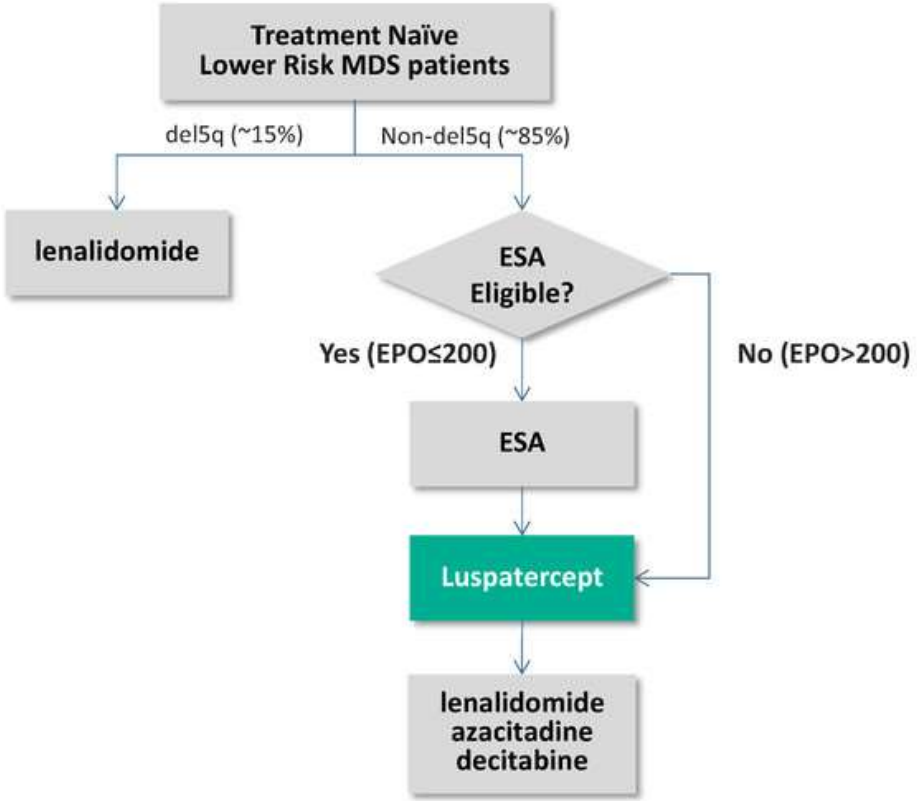
- It is a transforming growth factor-β (TGF-β) ligand trapping molecule
- It targets later stages of erythropoiesis
- It has a remarkable & durable effect on anemia of low-risk MDS specially MDS-RARS

Luspatercept

- It is given SC once every 21 days
- Dose: 0.75 -1.75 mg/kg, 5 doses over 12 weeks and if effective, it can be continued up to 5 years or even more
- Results : Median increase in Hb of 2g/dl in 3 months which is sustained for 36 months or more

Vision for Luspatercept in Lower Risk MDS Patients Following MEDALIST Phase 3 Trial

ACCELERON



Case study

- Arif Istiak, 52 y, Lucknow
- Smoker, alcoholic
- Significant anaemia
- Frequent infections
- Thrombocytopenia
- Trilineage dysplasia
- MDS-RAEB1(Blasts 7%)
- Cytogenetics: Normal

Case study

- He was offered HMA vs 7+3 followed by BMT
- However, there was confusion between HMA vs 7+3
- Multiple consultants, different opinions
- MDS specific NGS 16-gene panel was ordered

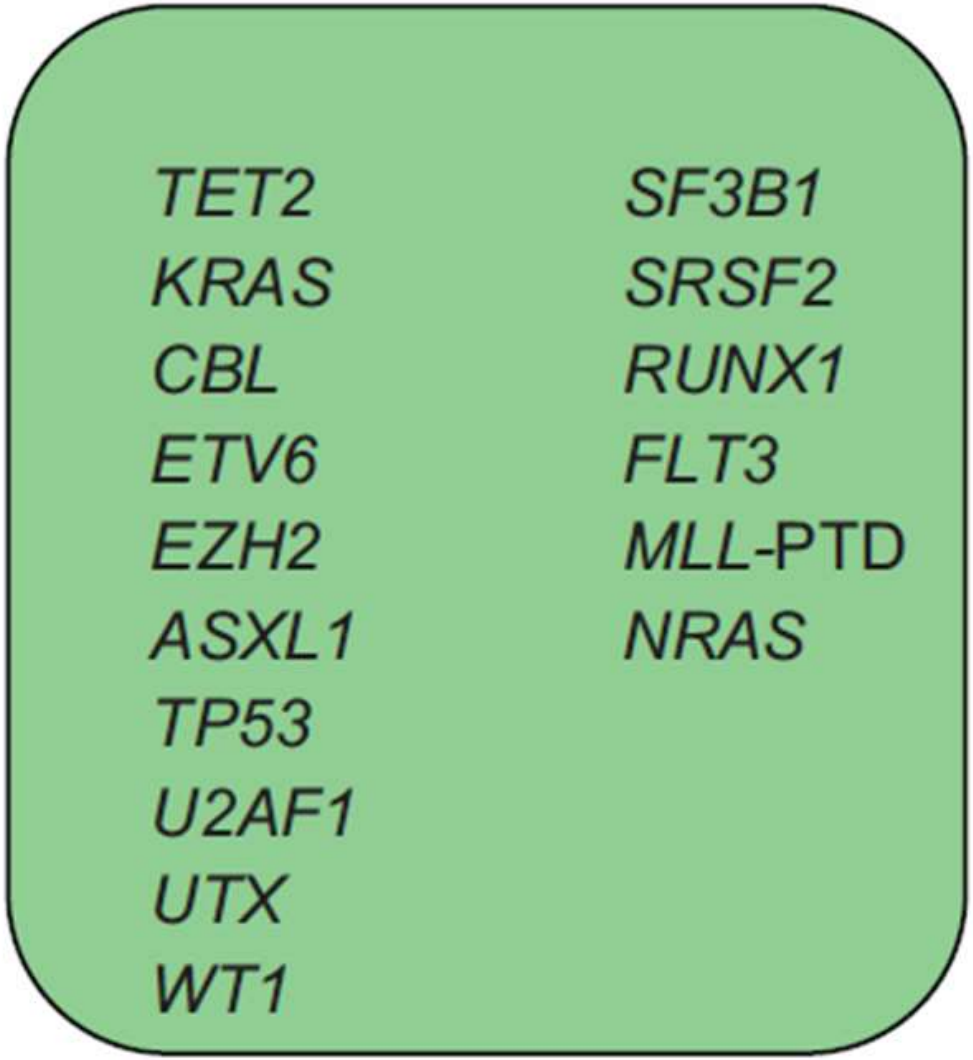
Myeloid malignancies specific NGS 70-gene panel

ABL1	*ASXL1*	*ATRX*	*BCOR*	*BCOR1*	*BRAF*	*CALR*
CBL	*CBLB*	*CBLC*	*CDKN2A*	*CEBPA*	*CSF3R*	*CUX1*
DNMT3A	*EGLN1*	*EPAS1*	*EPOR*	*ETV6*	*EZH2*	*FBXW7*
FLT3	*GATA1*	*GATA2*	*GNAS*	*HRAS*	*IDH1*	*IDH2*
JAK1	*JAK2*	*RTEL1*	*KDM6A*	*KIT*	*KMT2A/ MLL-PTD*	*KRAS*
MEK1	*MPL*	*MYD88*	*NLRP3*	*NOTCH1*	*NPM1*	*NRAS*
PDGFRA	*PHF6*	*PML*	*PTEN*	*PTPN11*	*RAD21*	*RUNX1*
SETBP1	*SF3B1*	*SMC1A*	*SMC3*	*SRSF2*	*STAG2*	*TET2*
TP53	*U2AF1*	*VHL*	*WT1*	*ZRSR2*	*DDX41*	*TERC*
TERT	*DKC1*	*USB1*	*CTC1*	*NOP10*	*NOP2*	*TINF2*

Tier 1

Tier 2

Tier 3



16

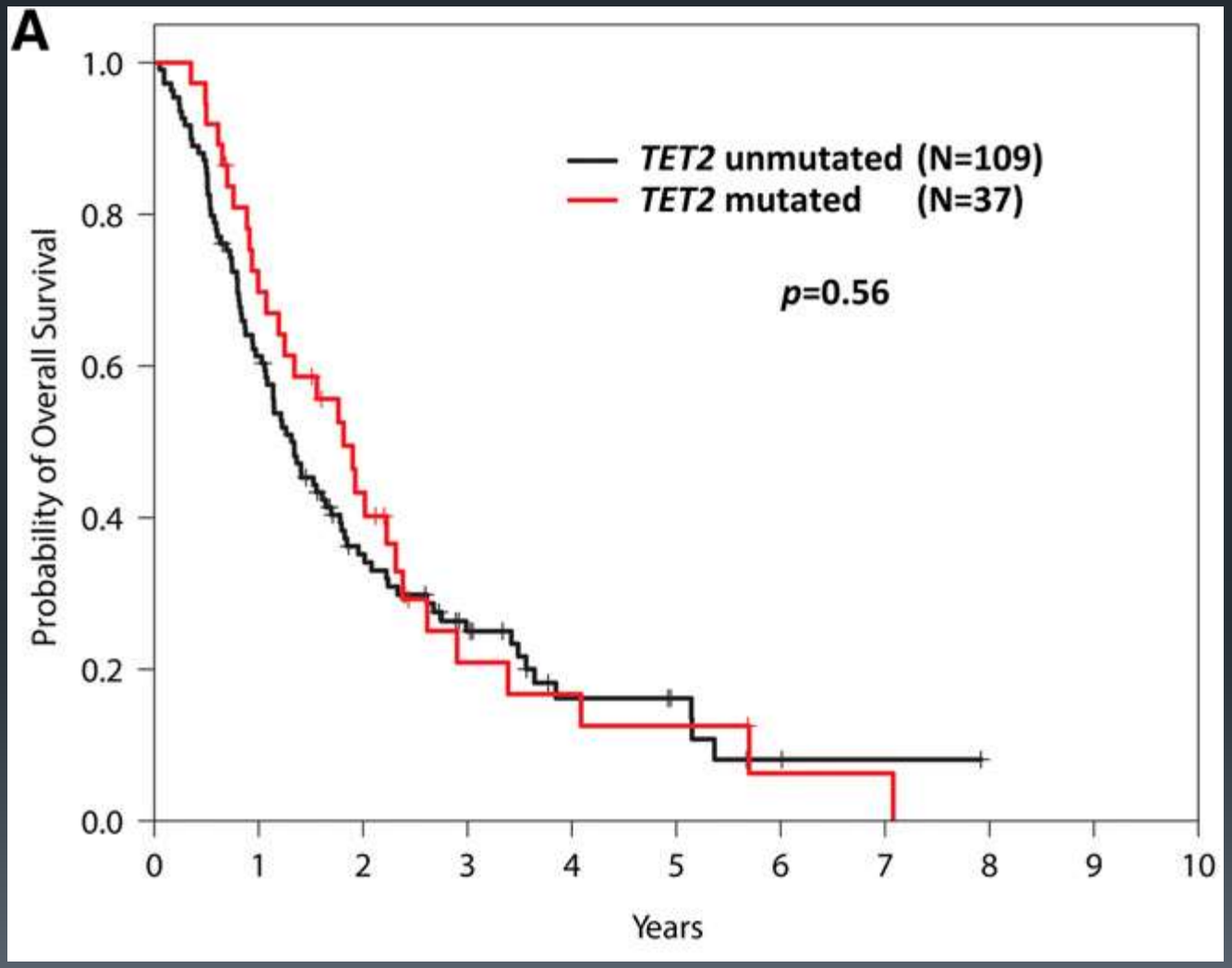
MDS specific

NGS 16-gene

panel

Arif Istiak

- Arif Istiak had 3 mutations
  - TET2
  - ASXL1
  - TP53


A
1.0
0.8
0.6
0.4
0.2
0.0
Probability of Overall Survival
TET2 unmutated (N=109)
TET2 mutated (N=37)
p=0.56
0
1
2
3
4
5
6
7
8
9
10
Years

(*Blood*. 2014;124(17):2705-2712)

Regular Article

MYELOID NEOPLASIA

TET2 mutations predict response to hypomethylating agents in myelodysplastic syndrome patients

Rafael Bejar,[1] Allegra Lord,[2] Kristen Stevenson,[3] Michal Bar-Natan,[4] Albert Pérez-Ladaga,[1] Jacques Zaneveld,[5] Hui Wang,[5] Bennett Caughey,[1] Petar Stojanov,[6] Gad Getz,[6] Guillermo Garcia-Manero,[7] Hagop Kantarjian,[7] Rui Chen,[5] Richard M. Stone,[4] Donna Neuberg,[3] David P. Steensma,[4] and Benjamin L. Ebert[2,6]

[1]Division of Hematology and Oncology, University of California San Diego Moores Cancer Center, La Jolla, CA; [2]Division of Hematology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [3]Department of Biostatistics and Computational Biology and [4]Department of Medical Oncology, Division of Hematological Malignancies, Dana-Farber Cancer Institute, Boston, MA; [5]Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX; [6]Broad Institute of Harvard and Massachusetts Institute of Technology, Cambridge, MA; and [7]Department of Leukemia, University of Texas MD Anderson Cancer Center, Houston, TX

Gelsi-Boyer *et al. Journal of Hematology & Oncology* 2012, **5**:12
http://www.jhoonline.org/content/5/1/12

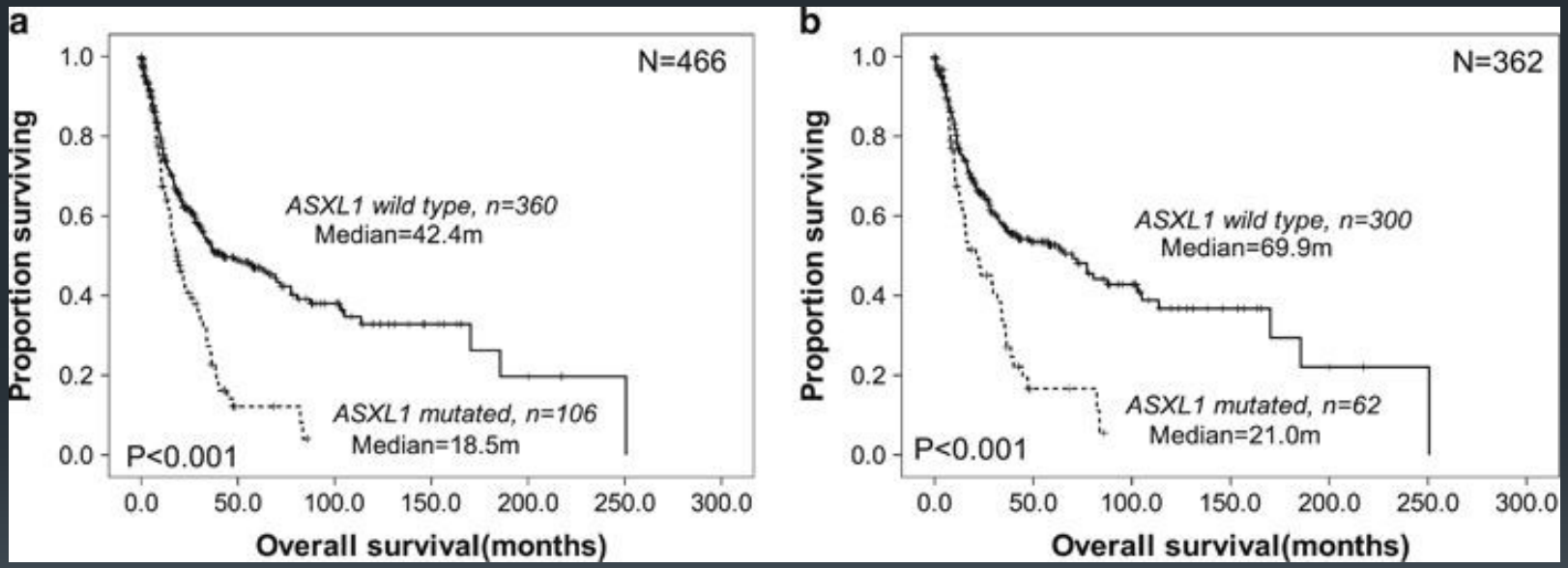
JOURNAL OF HEMATOLOGY & ONCOLOGY

REVIEW

Mutations in *ASXL1* are associated with poor prognosis across the spectrum of malignant myeloid diseases

Véronique Gelsi-Boyer[1,2,3,4*], Mandy Brecqueville[1,2], Raynier Devillier[1,2], Anne Murati[1,3], Marie-Joelle Mozziconacci[1,3] and Daniel Birnbaum[1]

ASXL1 mutation & Prognosis



p53 : The anti-cancer gene

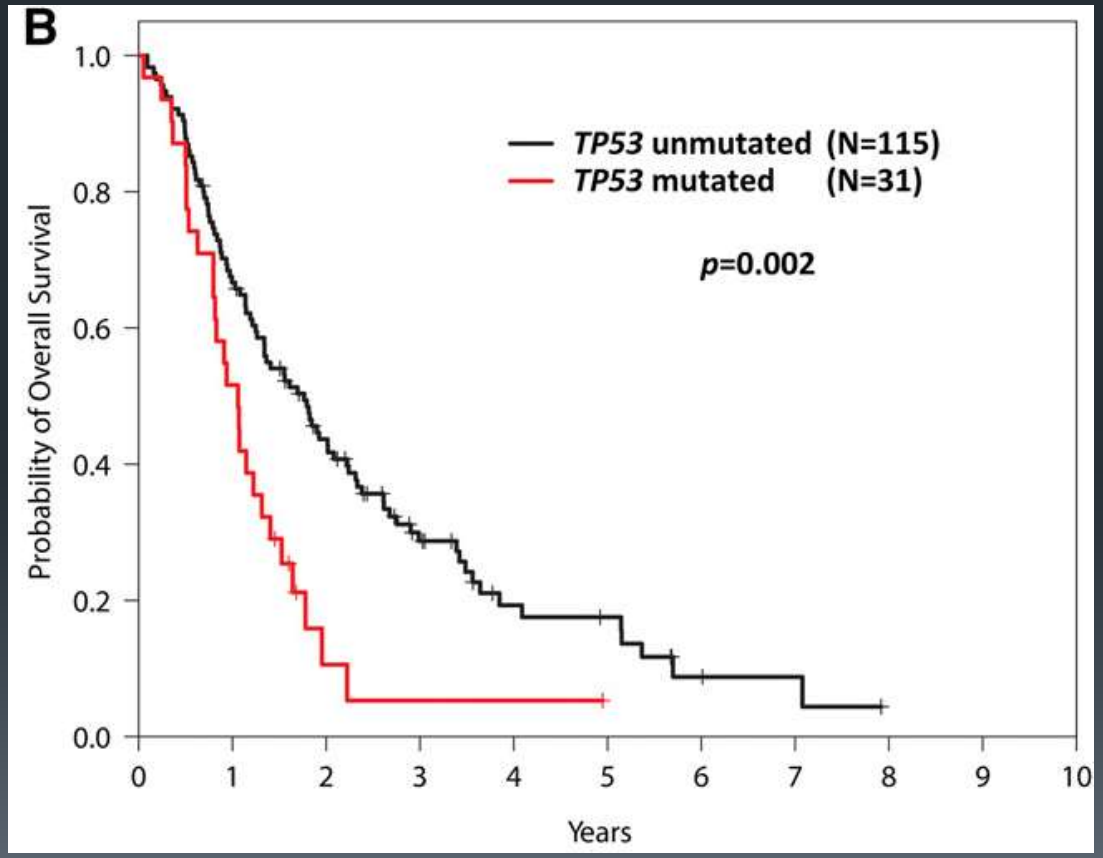
- The first tumour suppressor gene
- It is located on chromosome 17p
- Its job is to eliminate abnormal cells
- Thus, it prevents tumour development
- It is the guardian of genome

TP53 mutated MDS

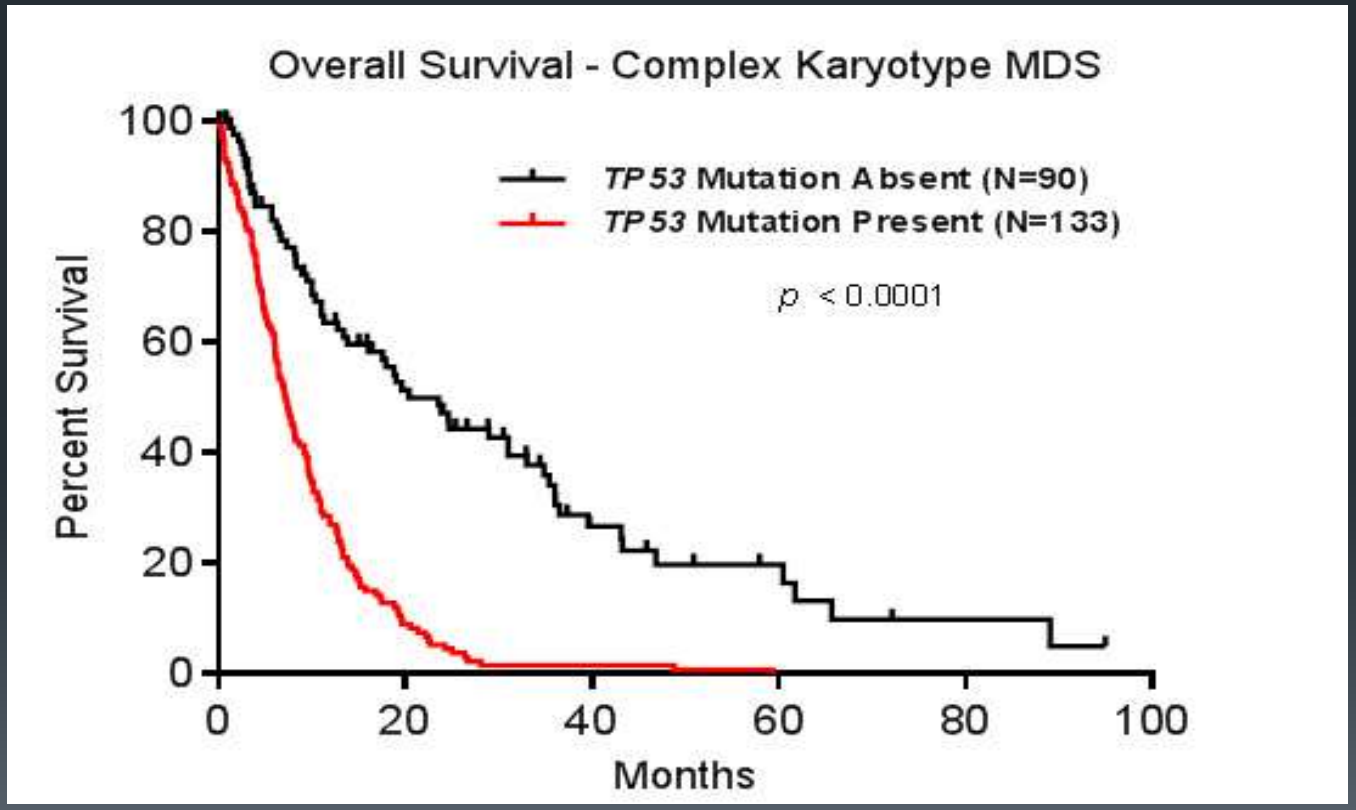
- TP53 mutated MDS pts have many adverse disease features ie Excess blasts, thrombocytopenia and complex karyotypes
- MDS with complex karyotypes without TP53 have better survival similar to those not having complex karyotypes

Haferlach T, Nagata Y. Leukemia. 2014;28:241-7
Shlush LI, Zandi S et al. Ntaure. 2014;506:328-33

TP53 mutation & Prognosis



Effect of TP53 Mutation with Complex Karyotype



haematologica 2014; 99:e181

Response to azacitidine is independent of p53 expression in higher-risk myelodysplastic syndromes and secondary acute myeloid leukemia

The demethylating agent azacitidine (AZA) is currently the standard of care for patients with higher-risk myelodysplastic syndromes (MDS) not eligible for allogeneic stem cell transplant (HSCT). Although approximately 50% of patients show a response to AZA it is not currently possible to accurately predict which patients will respond. In addition, higher-risk MDS frequently progress to secondary acute myeloid leukemia (sAML) within months, even in the

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 24, 2016 VOL. 375 NO. 21

TP53 and Decitabine in Acute Myeloid Leukemia and Myelodysplastic Syndromes

J.S. Welch, A.A. Petti, C.A. Miller, C.C. Fronick, M. O'Laughlin, R.S. Fulton, R.K. Wilson, J.D. Baty, E.J. Duncavage, B. Tandon, Y.-S. Lee, L.D. Wartman, G.L. Uy, A. Ghobadi, M.H. Tomasson, I. Pusic, R. Romee, T.A. Fehniger, K.E. Stockerl-Goldstein, R. Vij, S.T. Oh, C.N. Abboud, A.F. Cashen, M.A. Schroeder, M.A. Jacoby, S.E. Heath, K. Luber, M.R. Janke, A. Hantel, N. Khan, M.J. Sukhanova, R.W. Knoebel, W. Stock, T.A. Graubert, M.J. Walter, P. Westervelt, D.C. Link, J.F. DiPersio, and T.J. Ley

10-day course of Decitabine

- Pts with MDS who have cytogenetic abnormalities associated with unfavorable risk, *TP53* mutations, or both have favorable clinical response and robust (but incomplete) mutation clearance after receiving serial 10-day courses of Decitabine

VOLUME 32 · NUMBER 25 · SEPTEMBER 1 2014

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Somatic Mutations Predict Poor Outcome in Patients With Myelodysplastic Syndrome After Hematopoietic Stem-Cell Transplantation

Rafael Bejar, Kristen E. Stevenson, Bennett Caughey, R. Coleman Lindsley, Brenton G. Mar, Petar Stojanov, Gad Getz, David P. Steensma, Jerome Ritz, Robert Soiffer, Joseph H. Antin, Edwin Alyea, Philippe Armand, Vincent Ho, John Koreth, Donna Neuberg, Corey S. Cutler, and Benjamin L. Ebert

Conclusion:

Mutations in *TP53*, *TET2*, or *DNMT3A* identify patients with MDS with shorter OS after HSCT

teacher

The mediocre teacher tells. The good teacher explains. The superior teacher demonstrates. The great teacher inspires.

Arthur Ward


Thank You!