What do patients recall being told about MDS?

- Survey of 358 patients via AA&MDSIF

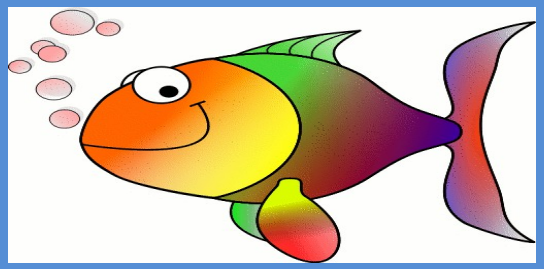


Table 1. Baseline demographics and disease characteristics

Characteristic	$n = 358$
Median (range) age, yrs	65 (19–91)
Male, %	49
Median (range) time since diagnosis, yrs	3 (0–29)
Median (range) time since first detection of abnormal blood profile, yrs	6 (0–59)
IPSS risk category,[a] %	
Low	28
Int-1	39
Int-2	23
High	9
Bone marrow not known, %	42
Cytogenetic status not known, %	28
Cytopenias, %	
Anemia	82
Thrombocytopenia	46
Neutropenia	45
Blood transfusions, %	65
Within 3 mos	52
Treatments in the last 3 mos before survey, %	
Darbepoetin	55
Epoetin	49
Active therapies	
Azacitidine	51
Lenalidomide	39
Decitabine	56
Antithymocyte globulin	11
Stem cell or bone marrow transplantation	10
Enrollment in a clinical trial	24

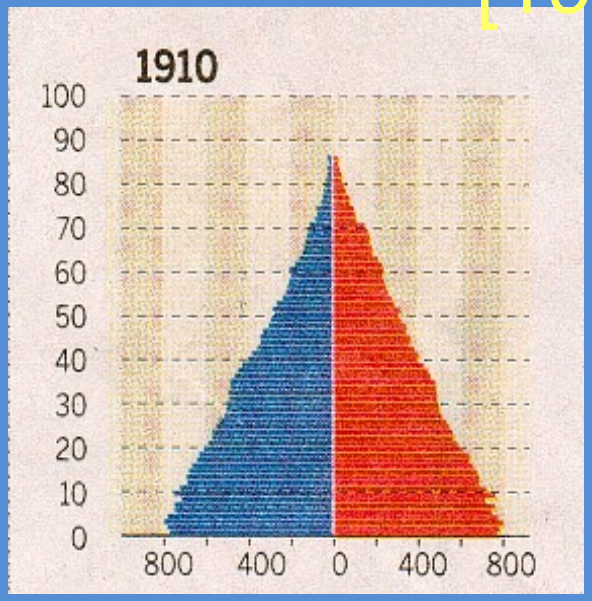
[a]Only 45% of all patients knew their IPSS score.
Abbreviations: Int, Intermediate; IPSS, International Prognostic Scoring System.

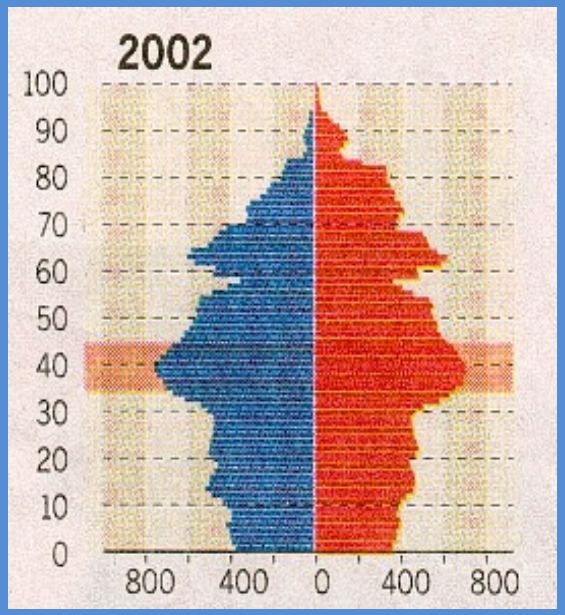
Abnormal blood test

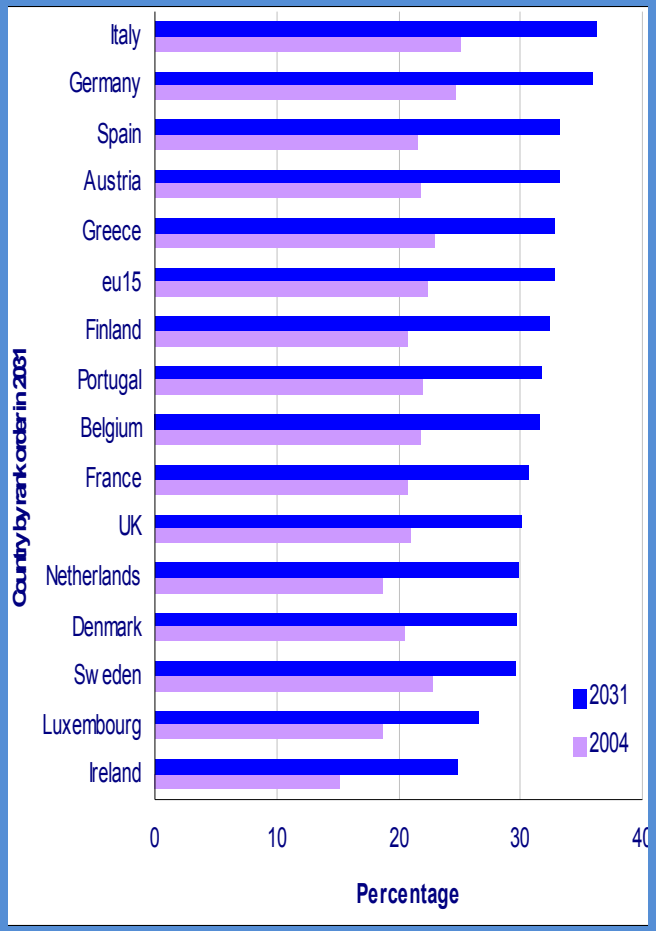
3 YEARS

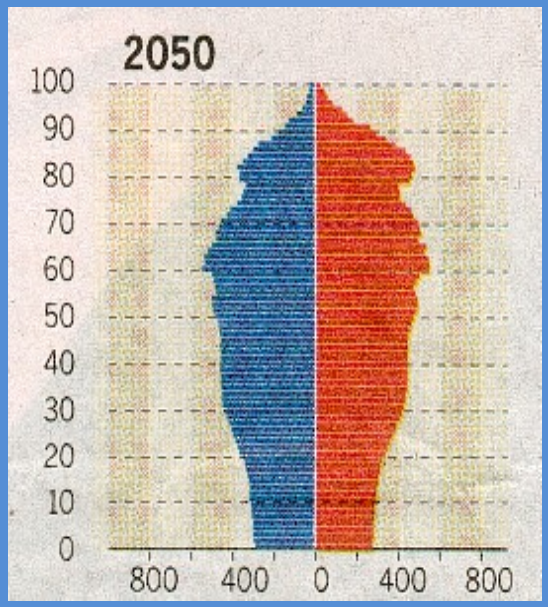
Diagnosis of MDS

Demographics of Germany [1910 – 2050] and Europe





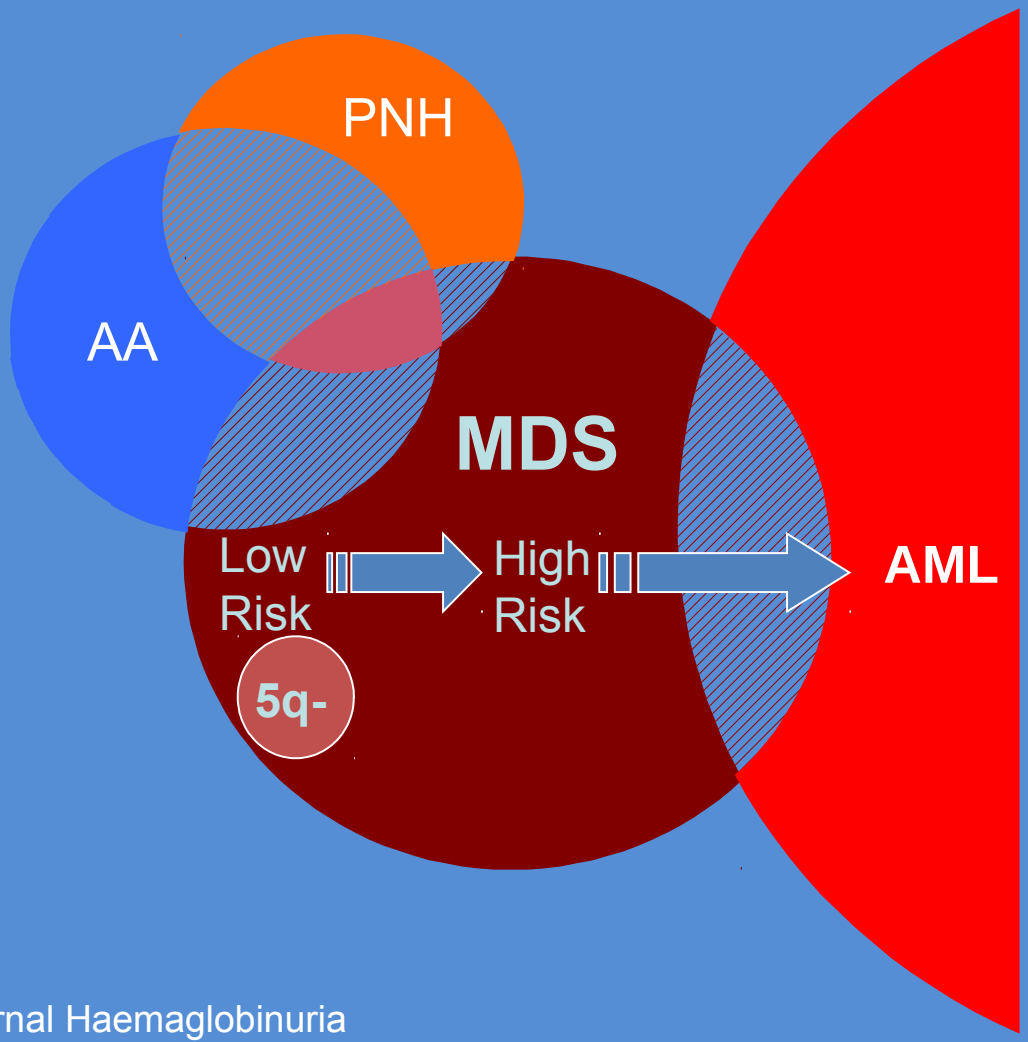




Statistisches Bundesamt, 2002

Eurostat 2004-Percentage of people over age of 60 years in 2031

The Bone Marrow Failure Syndromes



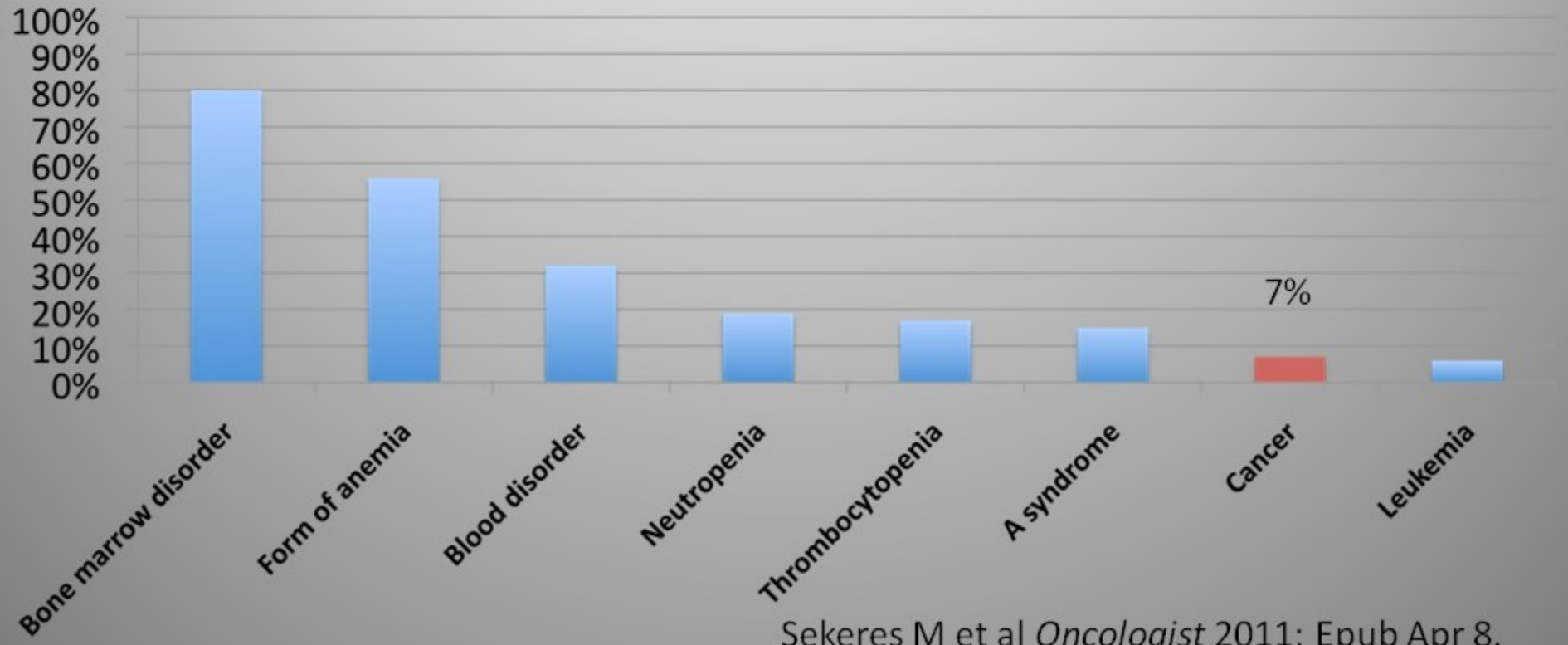
AA – Aplastic Anaemia

PNH – Paroxysmal Nocturnal Haemaglobinuria

Adapted from N. Young

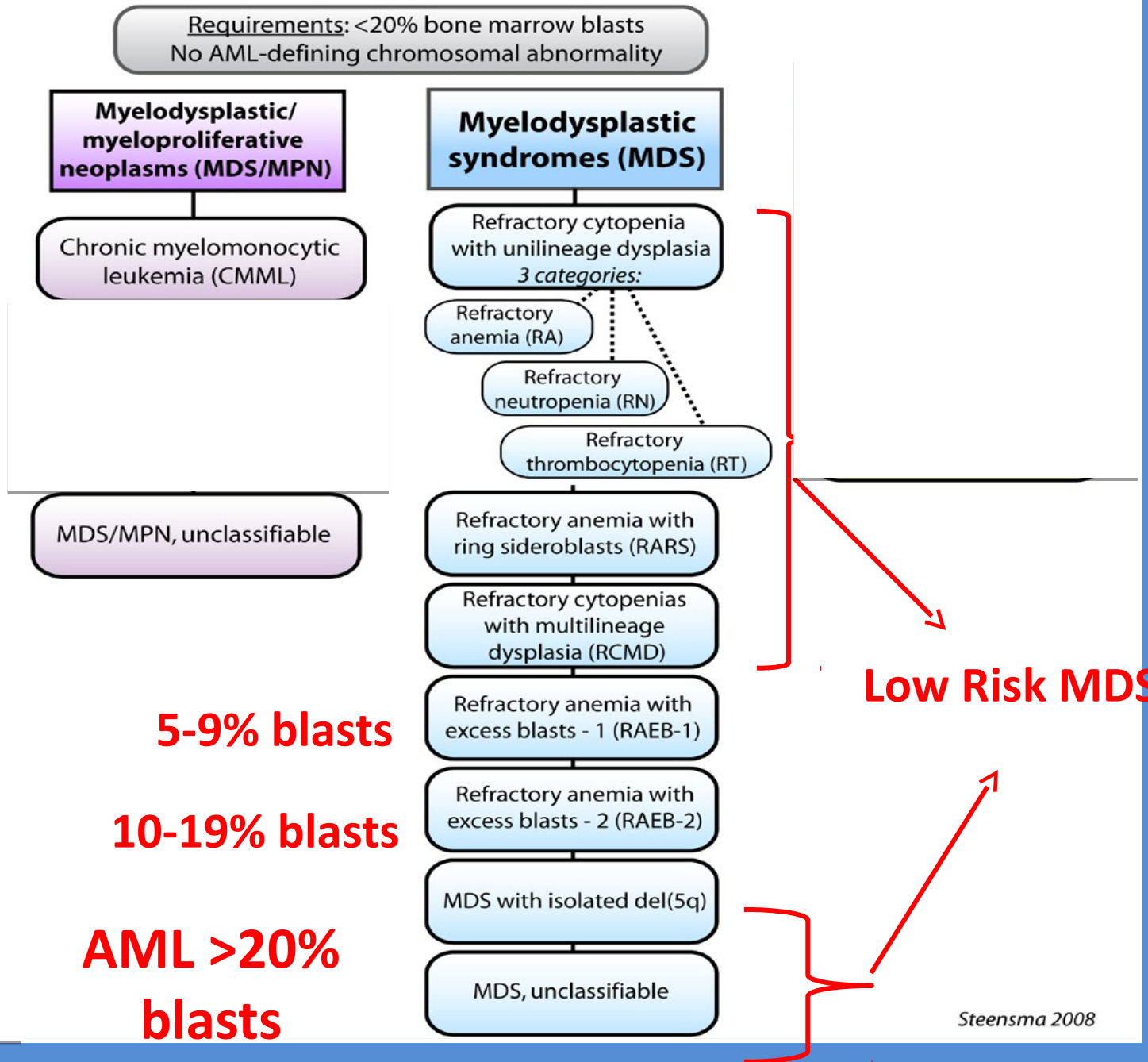
What do patients recall being told about MDS?

- Survey of 358 patients via AA&MDSIF:
  - *How was MDS first described to you?*



Sekeres M et al *Oncologist* 2011; Epub Apr 8.

2008 World Health Organization (WHO) Classification of Chronic Myeloid Neoplasms



MDS Classification – The *Ultimate* Simplification

- **Lower Risk** **(Survival 3-10 years, low rate of AML)**
  - RA, RARS
  - RCUD, RCMD
  - MDS-U, MDS del (5q)
  - IPSS Low, Int-1 (Score 0-1.0)

- **Higher Risk** **(Survival <1.5 years, high rate of AML)**
  - RAEB (-1, -2)
  - IPSS Int-2, High (Score ≥ 1.5)

International Prognostic Scoring System version 1.0 (1997)

	Score				
Prognostic Variable	0	0.5	1.0	1.5	2.0
Marrow blasts (%)	<5%	5-10%	--	11-20%	21-30%
Karyotype class*	Good	Intermediate	Poor	--	--
# of cytopenias**	0 or 1	2 or 3	--	--	--

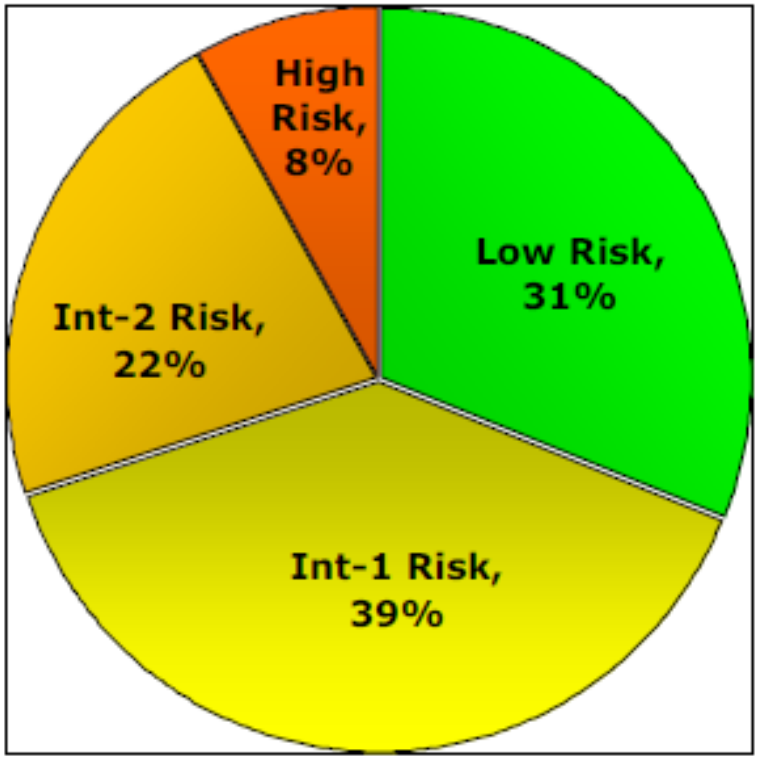
***Karyotypes**: Good = normal, -Y, del(5q) alone, del(20q) alone; Poor = chromosome 7 abnormalities or complex; Intermediate = other karyotypes

** **Cytopenias**: Hb < 10 g/dL, ANC <1800/uL, platelets <100,000/uL

From Greenberg P et al *Blood* 1997; 89:2079-2089 (correction 1998; 91:1100)

IPSS Risk Categories: Patient Distribution And Outcomes

Score sum	IPSS Risk Category	Median survival for over age 60 group (years)	Time until 25% get AML (years)
0	Low	5.7	9.4
0.5-1.0	Int-1	3.5	3.3
1.5-2.0	Int-2	1.2	1.1
>=2.5	High	0.4	0.2



Patient Distribution

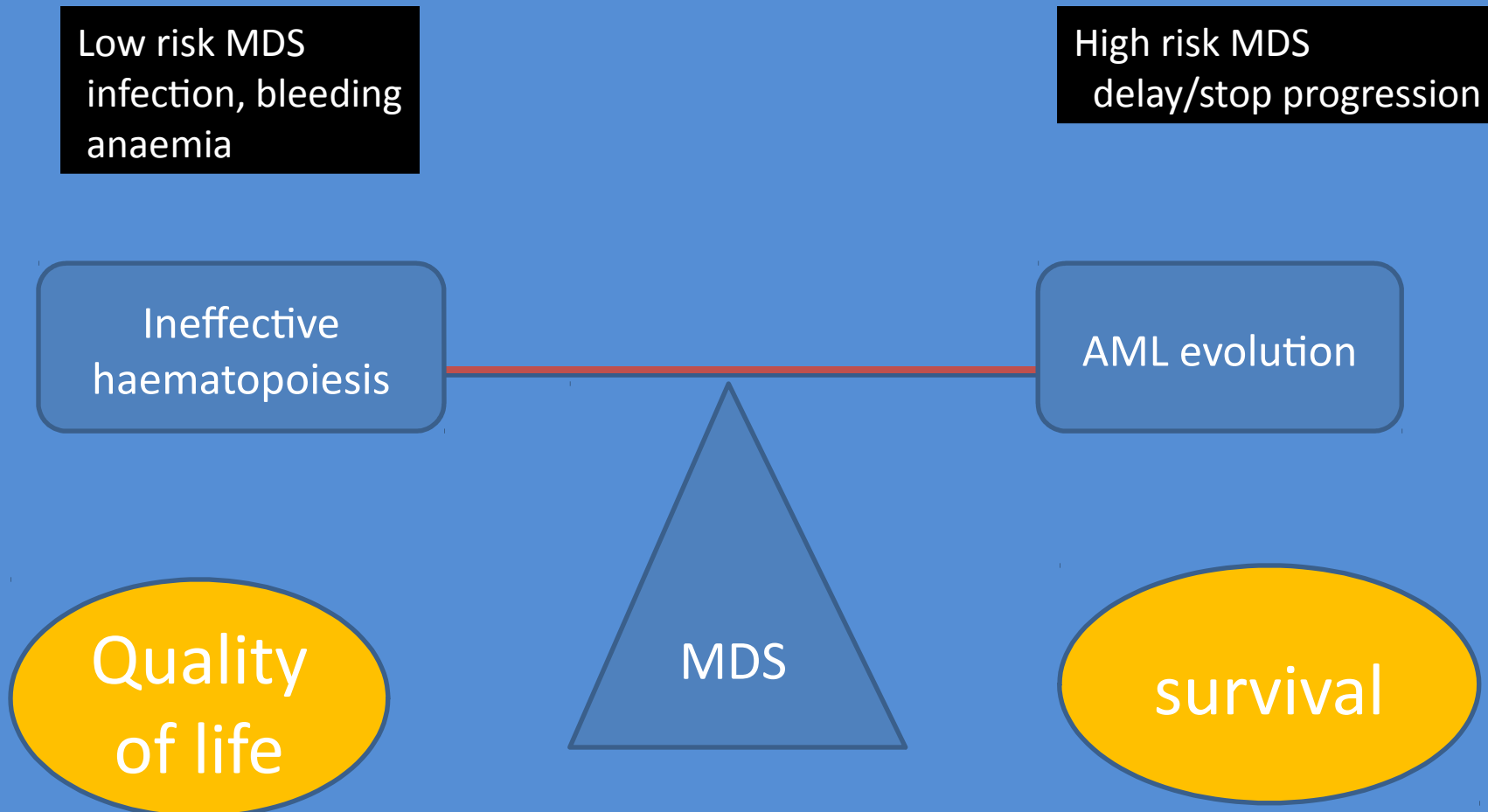
From Greenberg P et al *Blood* 1997; 89:2079-2089 (correction 1998; 91:1100)

CMML (chromic myelomonocytic leukaemia)

- Not CML!!

Variable
Age > 65 years
WBC > 15 × 10^9/L
Anemia, yes*
Platelets < 100 × 10^9/L
ASXL1 mutated, yes

Therapeutic goals



This is a Hard Truth

The only therapy capable of curing MDS is a bone marrow transplantation.

All other therapies improve blood counts, minimize transfusions, or improve quality of life.

If your blood counts and quality of life are fine, and you don't need transfusions, you may not need therapy.

Medications Currently Commonly Used for Patients with MDS

FDA Approved for MDS-Related Indications

Hypomethylating agents / DNA methyltransferase inhibitors / epigenetic drugs

Azacitidine (Vidaza ®)
Approved May 2004

Decitabine (Dacogen ®)
Approved May 2006

Immunomodulatory drug (iMiD)

Lenalidomide (Revlimid ®)
Approved December 2005

Iron chelators

Deferasirox (Exjade ®)
Approved November 2005

Deferoxamine (Desferal ®)
Approved 1968

FDA Approved for Other Indications

Blood cell (hematopoietic) growth factors

Red cell growth factors

Epoetin alfa (Procrit ®)

Darbepoetin alfa (Aranesp ®)

White cell growth factors

Filgrastim, G-CSF (Neupogen ®)

Pegfilgrastim (Neulasta ®)

Platelet growth factors

Romiplostim (NPlate ®)

Eltrombopag (Promacta ®)

Immunosuppressive drugs

Thalidomide, androgens, other biologics

Chemotherapy or stem cell transplant

Supportive care

Red cell transfusion	Anaemia causing symptoms
Platelet transfusion	Low platelets-bleeding & bruising Planned surgical operation
Erythropoietin	Anaemia
Granulocyte-colony stimulating factor	Infections associated with low white count
Antibiotic	Infections
Iron chelation therapy	Patients with low-risk disease with high transfusion requirement

Incidence of RBC Transfusion Dependence In MDS

IPSS Category	Proportion RBC Transfusion Dependent
Low Risk	**39%**
Intermediate-1 Risk	**50%**
Intermediate-2 Risk	**63%**
High Risk	**79%**

Brechignac S et al *Blood* 2004 104;236b (abstract 4716)

Red Cell Transfusion…The good

- Improves the oxygen carrying ability and improves symptoms
- Many patients will develop symptoms due to anaemia
- Red cell transfusion is the commonest way anaemia is treated
- The number and frequency may vary, but generally needs increase over time

- Sense of Altruism for donors- all voluntary

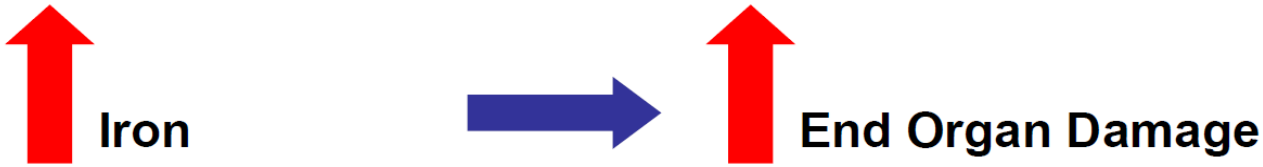
……The bad

- Costly and decreasing donor pool
- Impacts on QOL, hospital attendances
- Transfusion reaction, infections and alloimmunisation
- Each unit has 250 mg of elemental iron

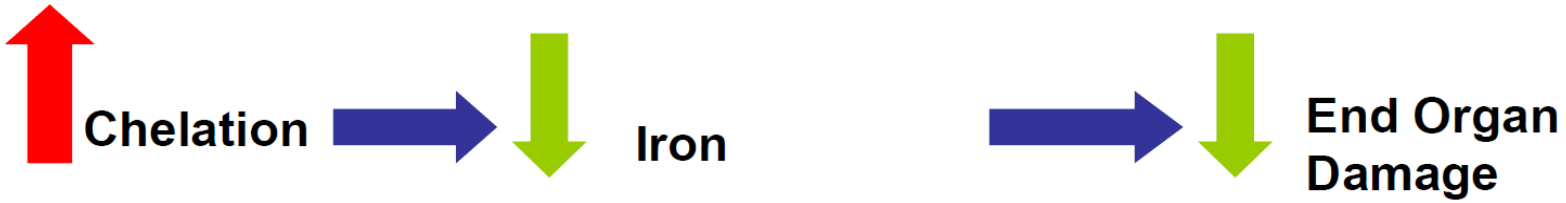
Chelation Clinical Guidelines

- Many organizations have guidelines for iron monitoring and iron chelation in MDS
  - At least 8 different guidelines in the last 10 years
  - Only partially evidence-based
- In general, these guidelines suggest:
  - **Periodic serum ferritin monitoring**, supplemented by other techniques for assessing iron burden
  - Consideration of iron chelation when patient has **persistent ferritin >1000 ng/mL** or other evidence of iron overload such as MRI, and lower-risk MDS
  - Start thinking about iron overload after **20-50 units RBCs**

And now Iron in MDS?…



Therefore…



Platelet transfusion-Liquid Gold

- Platelet transfusion should be reserved for patients with bruising or bleeding symptoms
- Planned surgery, dental extraction may also need to be covered by platelet transfusion

Therapy in low risk MDS

- Squeeze every ounce of production out of the remaining functional bone marrow cells by ERYTHROPOIETIN(EPO) and GROWTH FACTORS(eg GCSF)injections

ESAs/GF in MDS: Who Responds?

Treatment response score

s-epo	<100	+2
U/L	100–500	+1
	>500	–3
Transf	<2 units/m	+2
U RBC/m	= or >2 units/m	–2

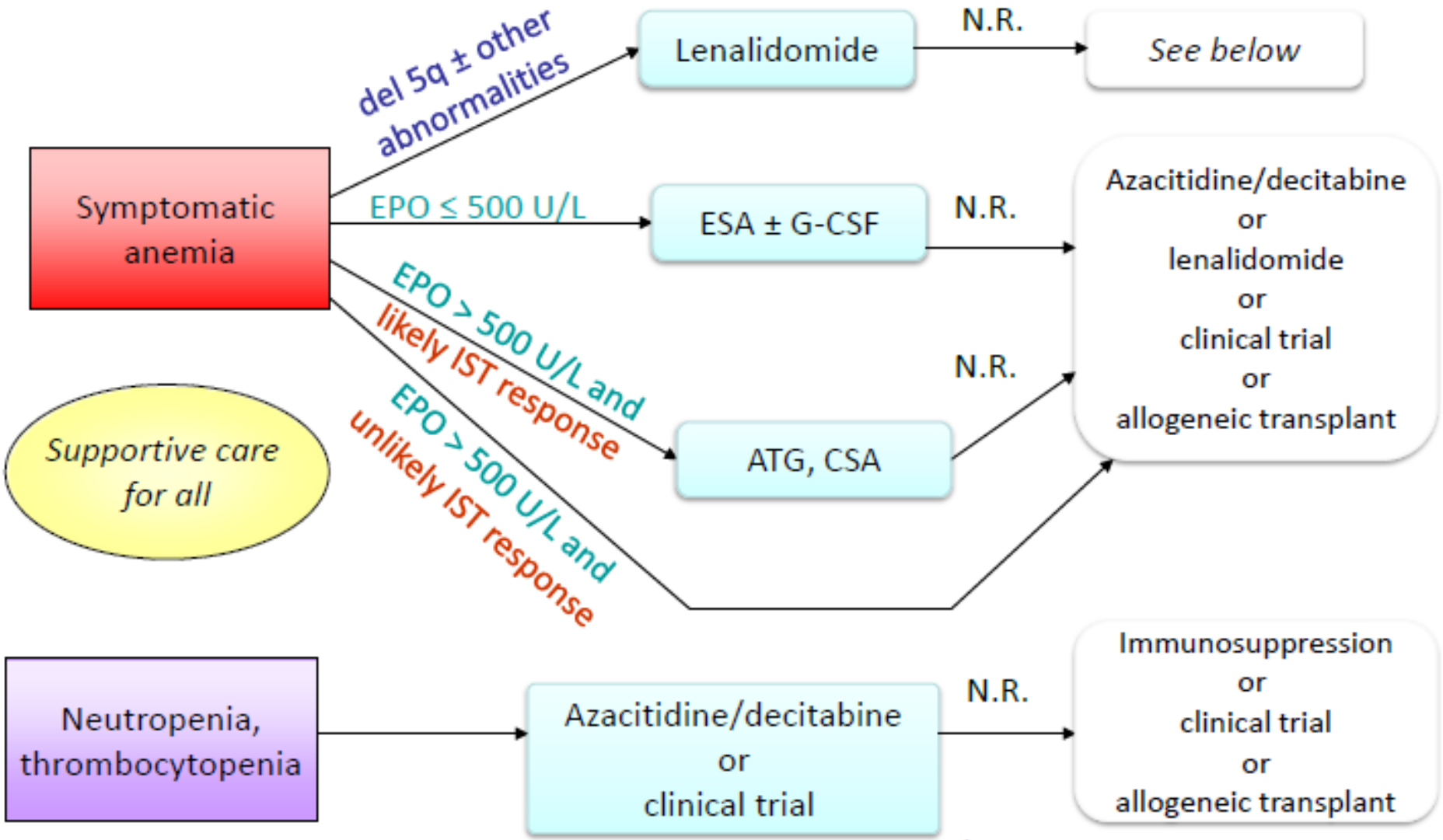
Hellström-Lindberg E et al. *Br J Haematol*. 2003;120:1037

Therapy in low risk MDS

- Blocks the effects of nasty cytokines (chemicals produced in excess by abnormal bone marrow cells which can kill the normal cells)

eg. Lenalidomide
ATG(horse or rabbit)

NCCN guidelines: lower-risk MDS (IPSS Low/Intermediate-1 Risk Groups)



Based on v.2 2011; www.nccn.org

High risk MDS

- Replace the bone marrow (and immune system)
  - Bone marrow transplant
  - Chemotherapy
  - Azacitidine/Decitabine
  - Clinical trials/ novel agents

Goal of Therapy: Higher-risk MDS

Prevent methyl groups from inactivating tumor suppressor genes and be directly cytotoxic – kill those bad cells!

- **Azacitidine (Vidaza)**
- **Decitabine (Dacogen)**

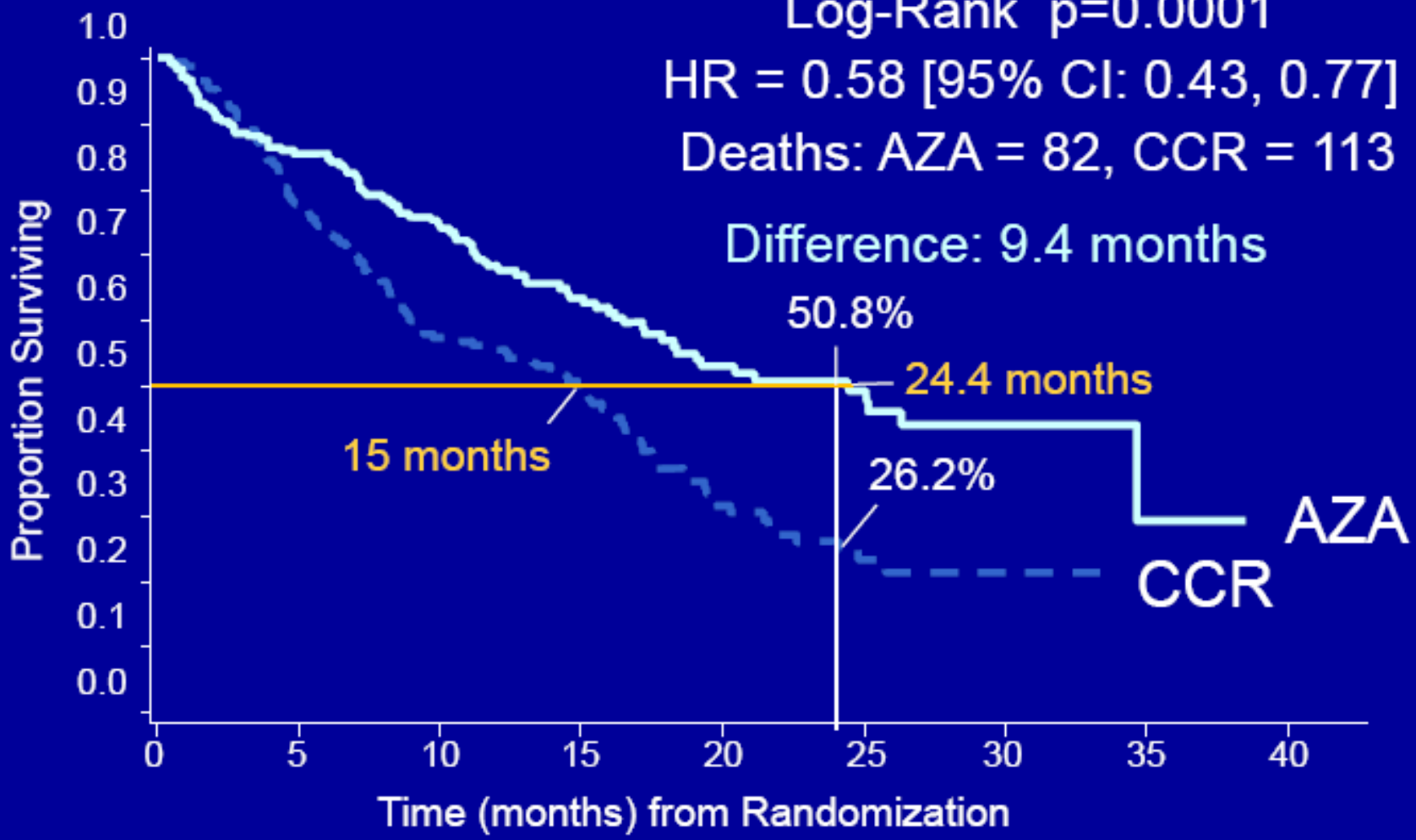
Azacitidine in high-risk MDS

It has been suggested that azacitidine may switch on important anti-cancer genes

Reduced red cell transfusion
Improvement in survival
Less chance of MDS deteriorating
Results not influenced by patient age, blast cells, karyotype

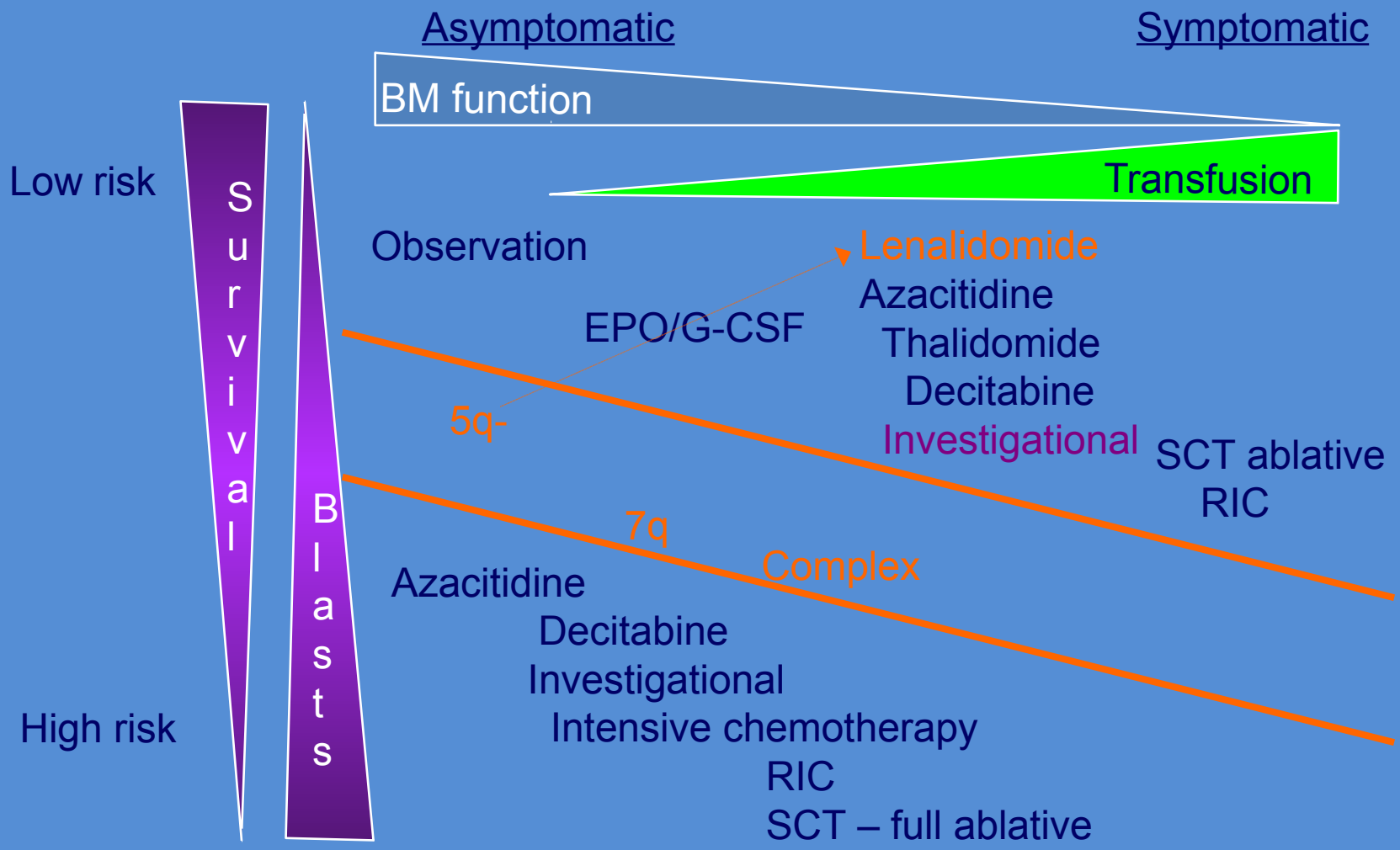
Administered as injection into skin
For high risk patients ineligible for transplantation

Overall Survival: Azacitidine vs CCR ITT Population



Fenaux P, et al. *Blood*. 2007;110(11):817a.

Treatment algorithm for patients with MDS*



Silverman LR in Cancer Medicine 7th ed. 2006.

Myelodysplasia
Intensive treatment

Bone marrow transplant should be considered when 'curative' therapy is thought to be appropriate.

Key issues for patients:

Motivated, and deemed fit for BMT

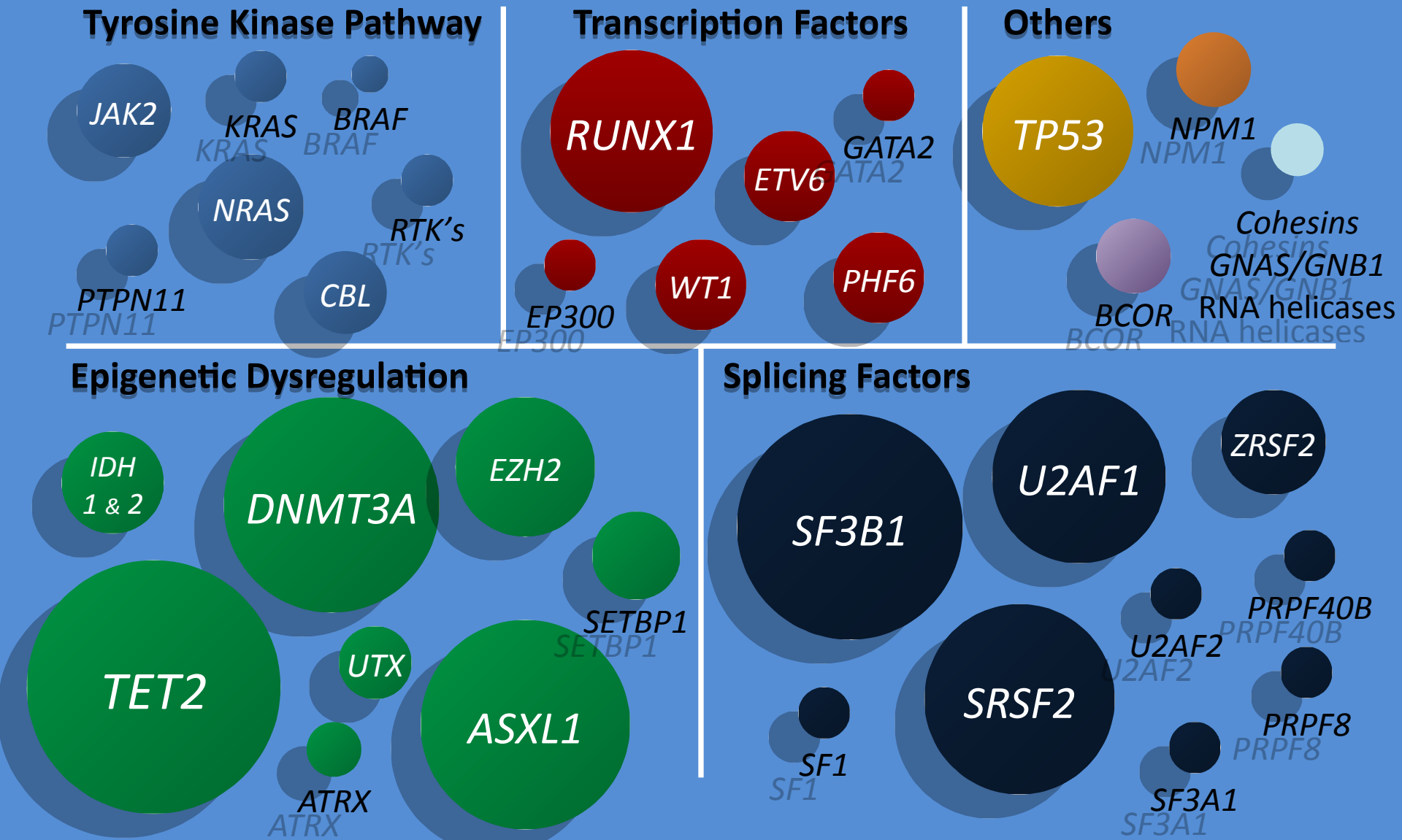
'High-risk' MDS, with disease under control

Appropriate counselling regarding outcomes, risks, and intensive long- term follow-up

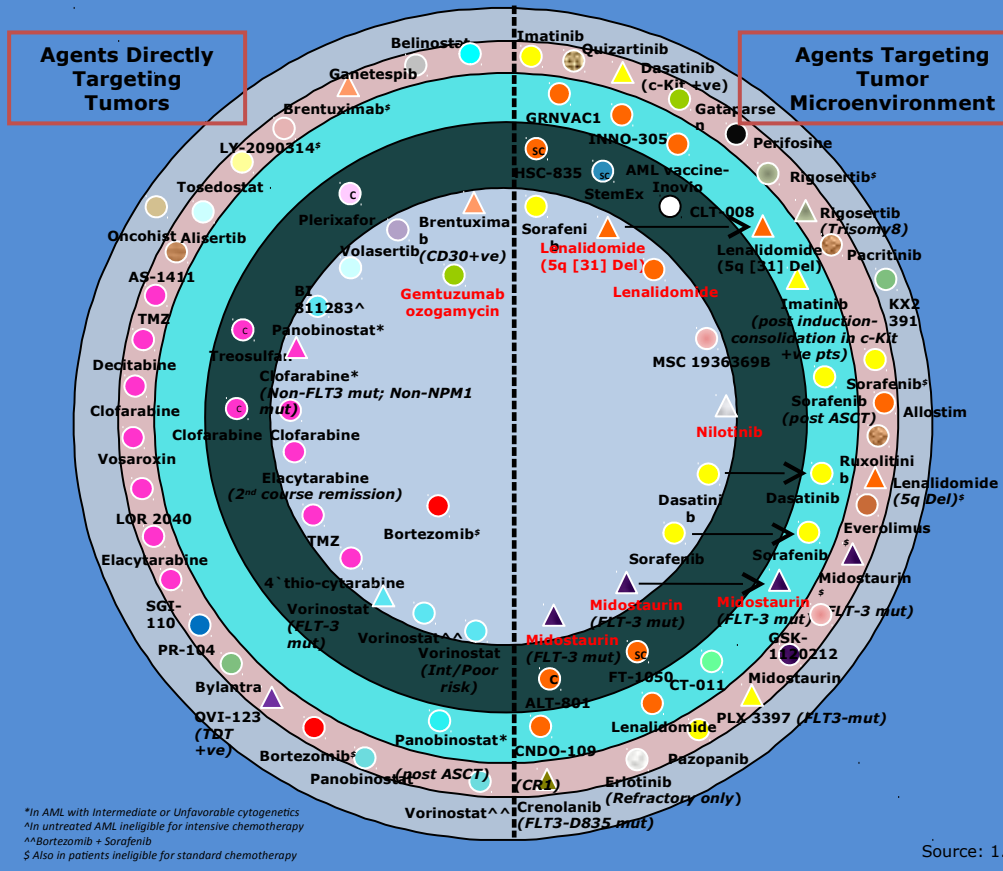
Newer developments

- Genes, genes and more genes
- New risk scoring system-IPSS-R
- Oral azacitdine
- Newer targeted therapy/personalised medicine
- Lenalidomide approved for 5q- syndrome (cancer drug fund and also NICE approved)
- CMML- what is it??

Gene Mutations in MDS



Agents in clinical development for AML/MDS



Line Of Therapy	Biomarker Status
No Line Defined	No Biomarker
Induction/Consolidation	
Transplant Related	
C Conditioning	Biomarker Driven
SC Stem Cells	
Maintenance	
Refractory/Relapse	

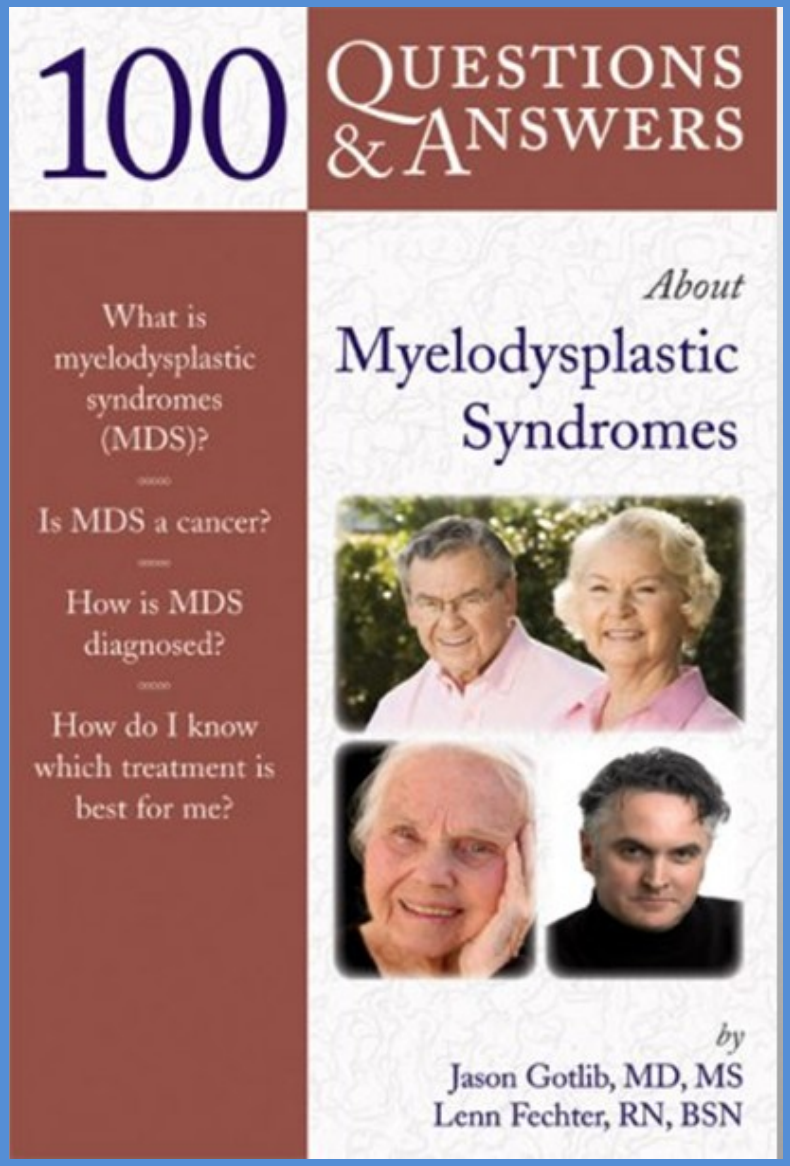
Mechanism of Action	
1	Aurora kinase inhibitor
1	GSK 3 Beta inhibitor
1	HSP 90 inhibitors
1	CD33 linked immunoconjugate
3	HDAC inhibitors
1	PLK-1 antagonist
1	Proteasome inhibitor
1	Amino peptidase inhibitor
9	DNA inhibitors
1	KIF11 protein inhibitor
1	Pyruvate dehydrogenase stimulant
1	RNA synthesis inhibitor
1	Tubulin polymerization inhibitors
1	Guanosine-rich oligonucleotide aptamer
1	Hypoxia and AKT1C3 activated alkylator
	Akt-inhibitor
1	Bcr-abl tyrosine kinase inhibitor
1	BIRC5 protein inhibitor
1	CXCR4 receptor antagonist
1	Dual Src kinase and pre-tubulin inhibitor
1	Dual TKI-FLT3 and KIT inhibitor
1	EGFR inhibitor
1	FLT-3 inhibitor
2	Janus kinase inhibitor
2	MEK inhibitor
1	mTOR inhibitor
5	Multi TKI
1	PDCD 1 protein inhibitor
1	PDGFR inhibitor
1	PI3K inhibitor
8	Immunomodulators
1	Supportive Care

*In AML with Intermediate or Unfavorable cytogenetics
^In untreated AML ineligible for intensive chemotherapy
^^Bortezomib + Sorafenib
$ Also in patients ineligible for standard chemotherapy

Source: 1. ADIS Insight; 2.TrialTrove; 3.Company Website

Conclusion

- MDS is more common than we think!
- Delay therapy until symptoms develop or needing transfusions
- Treatment based on the risk of disease- low risk versus high risk
- Optimistic future-novel drugs in early phase clinical trials
- Personalised gene sequencing and individualised therapy-THE FUTURE !!



MDS UK Patient Support Group

Prof Ghulam Mufti

Staff and patients at Kings College Hospital

LEUKAEMIA & LYMPHOMA RESEARCH

Beating Blood Cancers