Next Generation Approaches for Evaluation and Treatment of MDS

- Prognosis: IPSS-R
- Molecular characterization of MDS
- Impaired ribosome function & molecular basis of 5q- MDS
- Newer therapeutic agents/ approaches
- Stem cell transplantation

Updated prognostic assessment of MDS: The Revised IPSS (IPSS-R)

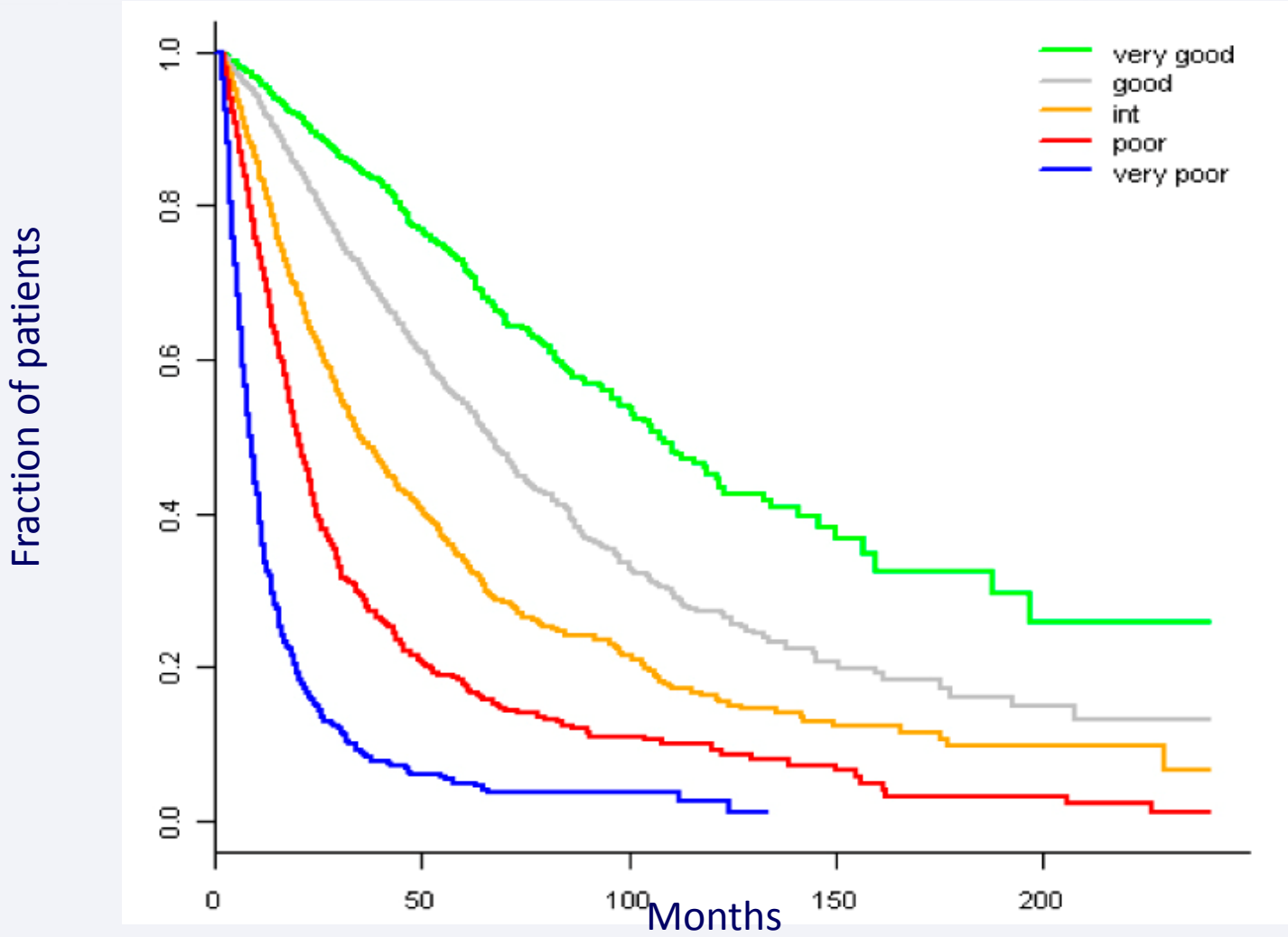
Developed by the International Working Group for Prognosis in MDS (IWG-PM)

Peter Greenberg, MD
Stanford University Cancer Center
for the IWG-PM

MDS Classifications

- 1997 IPSS/IMRAW (FAB): 816 pts/7 DBs
  - Marrow blasts, cytogenetics, cytopenias
- 2001 WHO classification
  - Dysplastic subgroups, RAEB-1,2, del(5q)
- 2007 WPSS: 1165 pts/3 DBs
  - WHO subgroups, IPSS cytogenetics, RBC Txns
- 2001-2011 New features described as possible additional prognostic factors
- New cytogenetic classification: 2900 pts/4 DBs
- 2011 IWG-PM Refined consensus system (IPSS-R)
  - 7012 pts/18 DBs

IPSS-R Survival, n=7012



H. LEE MOFFITT Cancer Center & Research Institute

The End Of Cancer Begins Here.

A National Cancer Institute Comprehensive Cancer Center

At the University of South Florida

Molecular Characterization of MDS Risk & Predisposition

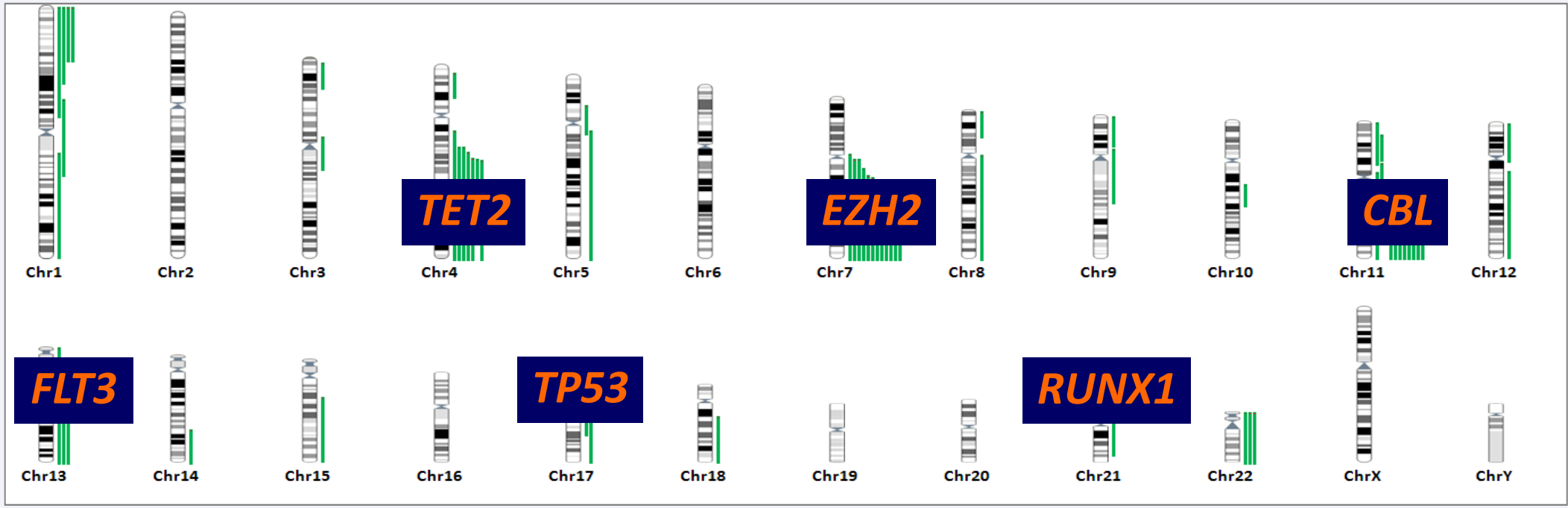
Alan List, MD

H. Lee Moffitt Cancer Center & Research Institute

Tampa, FL, USA

Regions of Likely aUPD in MDS

- SNP 6.0 analysis; n=148
- 63 tracts of copy neutral runs of homozygosity >20Mb in 46 (31%) cases
- 17 different chromosomes; 7 recurrent regions



Ernst et al., Nat Genet. 2010;42:722-6

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

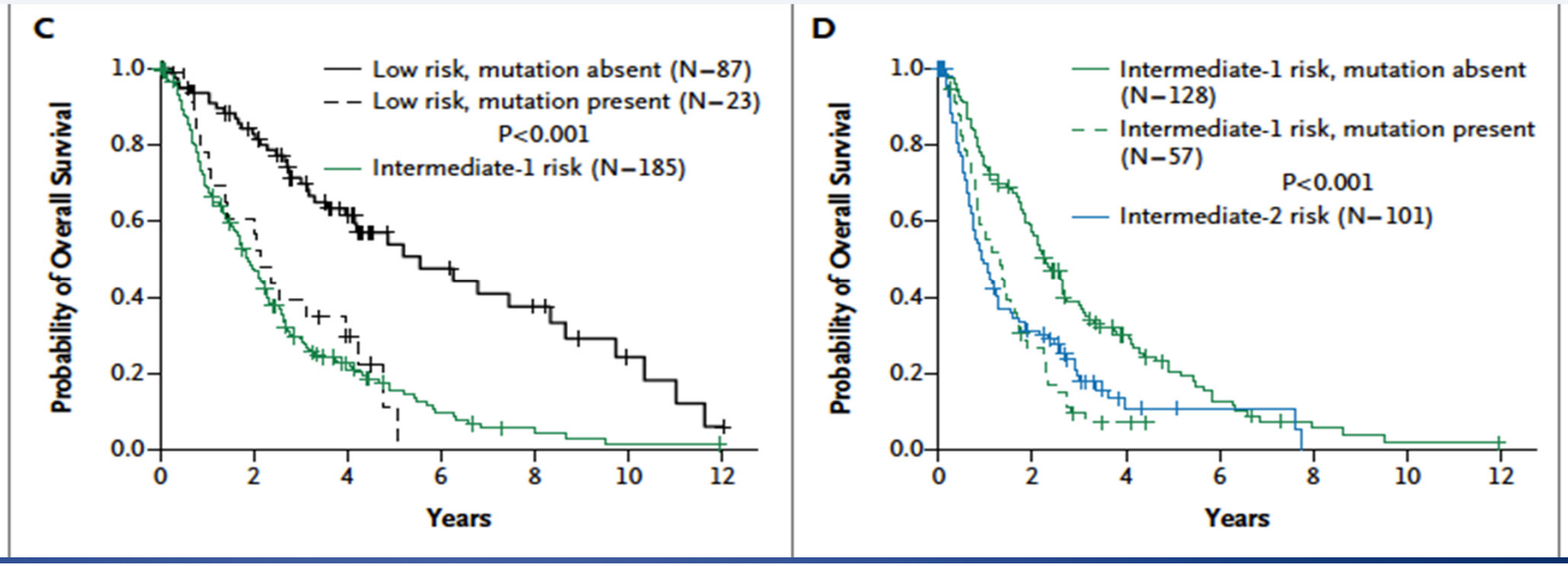
Clinical Effect of Point Mutations in Myelodysplastic Syndromes

Rafael Bejar, M.D., Ph.D., Kristen Stevenson, M.S., Omar Abdel-Wahab, M.D., Naomi Galili, Ph.D., Björn Nilsson, M.D., Ph.D., Guillermo Garcia-Manero, M.D., Hagop Kantarjian, M.D., Azra Raza, M.D., Ross L. Levine, M.D., Donna Neuberg, Sc.D., and Benjamin L. Ebert, M.D., Ph.D.

ABSTRACT

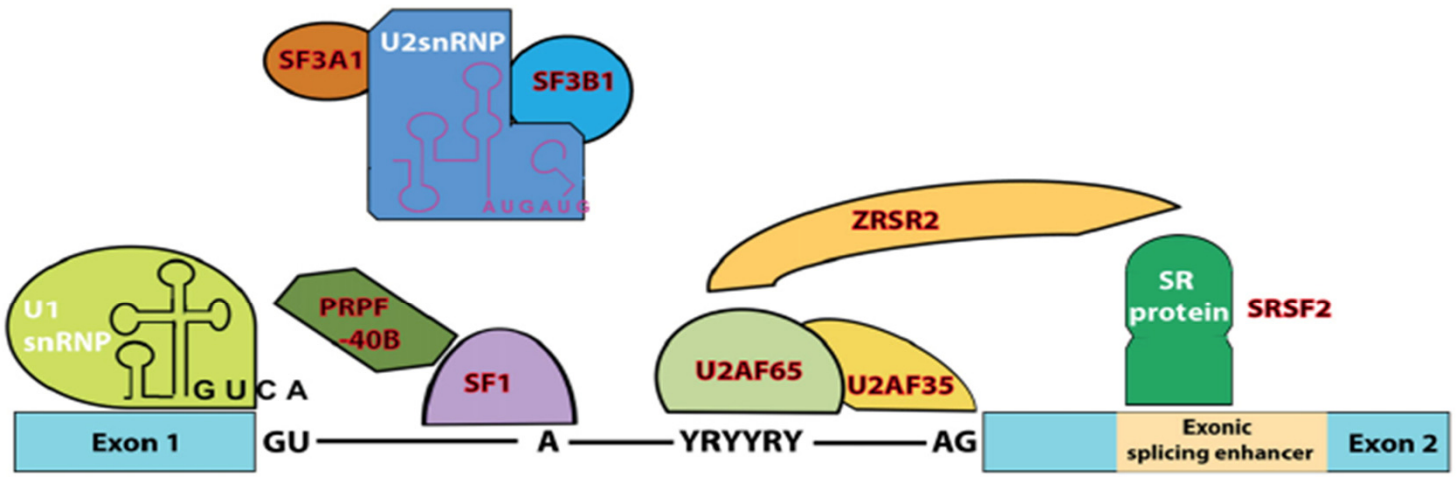
BACKGROUND

Myelodysplastic syndromes are clinically heterogeneous disorders characterized by clonal hematopoiesis, impaired differentiation, peripheral-blood cytopenias, and a risk of progression to acute myeloid leukemia. Somatic mutations may influence the clinical phenotype but are not included in current prognostic scoring systems.



Spliceosome abnormalities in MDS

A

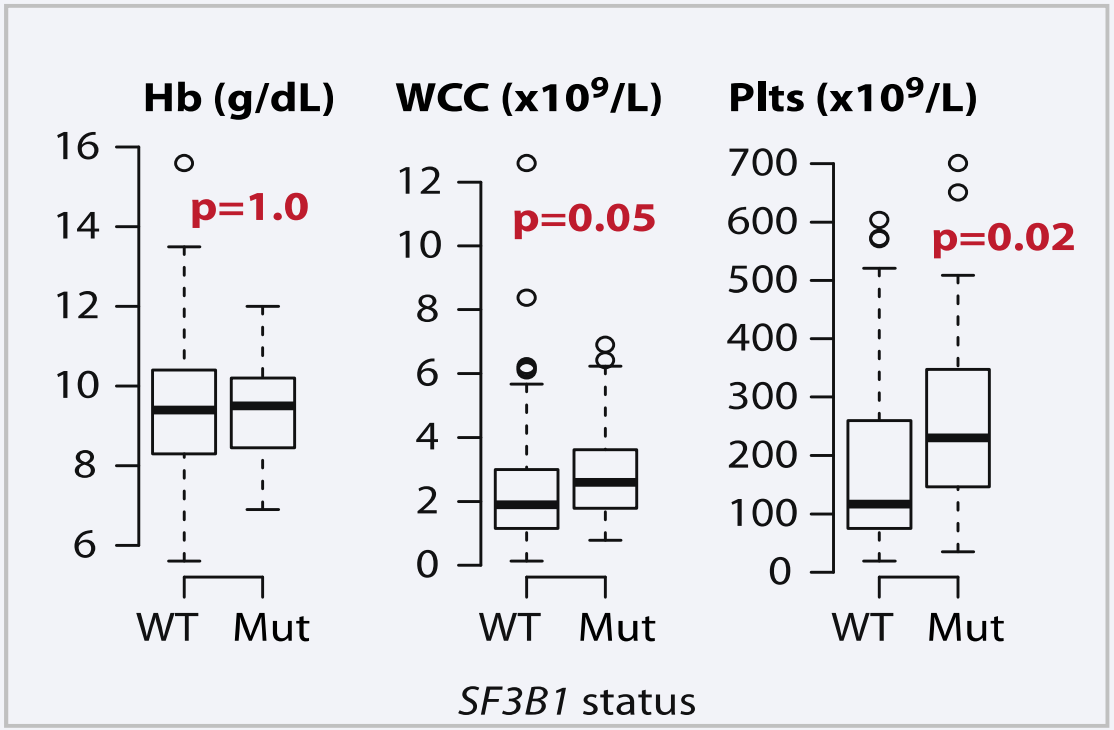


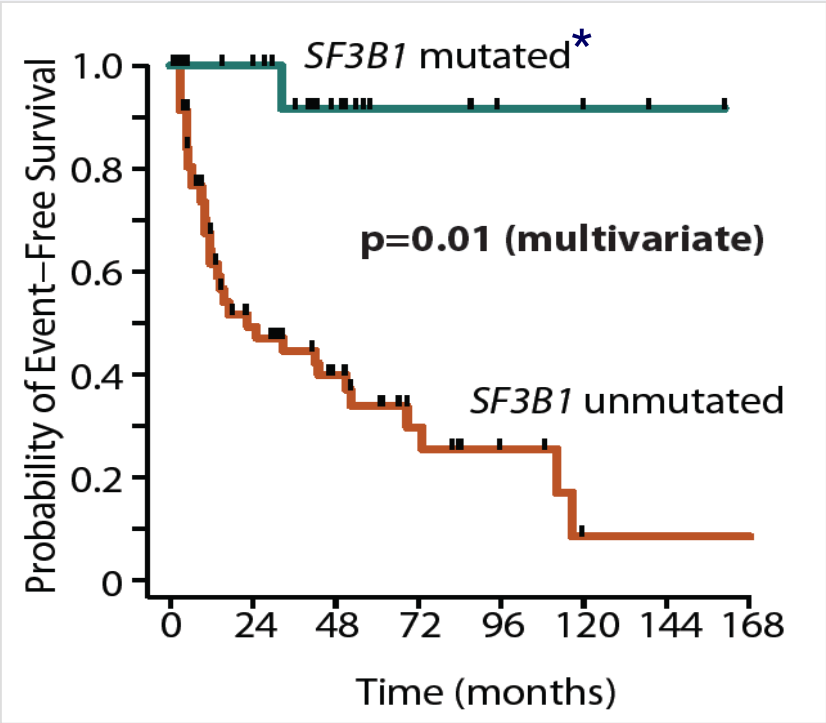
B

Gene	Mutation Description	Mutational Frequency[1]								
		RARS/ RCMD-RS	MDS without RS	CMML	t-MDS/ sAML	*De novo* AML	MPN	ALL[2]	NHL[2]	CLL[2]
SF3B1	Predominant heterozygous missense mutations at K700, R625, and H662.	57 - 75.3%	6 - 20%	4.5 - 5%	4.8%	2.6 - 5%	3 - 4%	nd	nd	5%
SRSF2	Recurrent heterozygous missense mutations at P95.	1.5%	11.6%	28.4%	6.5%	0.7%	1.9%	—	—	nd
U2AF35	Recurrent heterozygous missense mutations at S34 and Q157.	—	11.6%	8.0%	9.7%	1.3%	1.9%	—	—	nd
ZRSRS2	Missense, nonsense and frameshift mutations throughout the open-reading-frame.	1.4%	7.7%	8.0%	1.6%	0.7%	1.9%	nd	nd	nd
SF3A1	Missense mutations throughout the open-reading-frame.	—	1.3%	1.1%	1.6%	0.7%	—	nd	nd	nd
PRPF40B	Missense mutations throughout the open-reading-frame.	—	1.9%	—	1.6%	0.7%	1.9%	nd	nd	nd
U2AF65	Missense mutations throughout the open-reading-frame.	—	0.6%	1.1%	—	—	—	nd	nd	nd
SF1	Missense mutations in the proline-rich C-terminal domain.	—	1.3%	—	—	—	1.9%	nd	nd	nd

O. Abdel-Wahab and R. Levine Cancer Cell 2011

Clinical Significance of SF3B1 Mutations

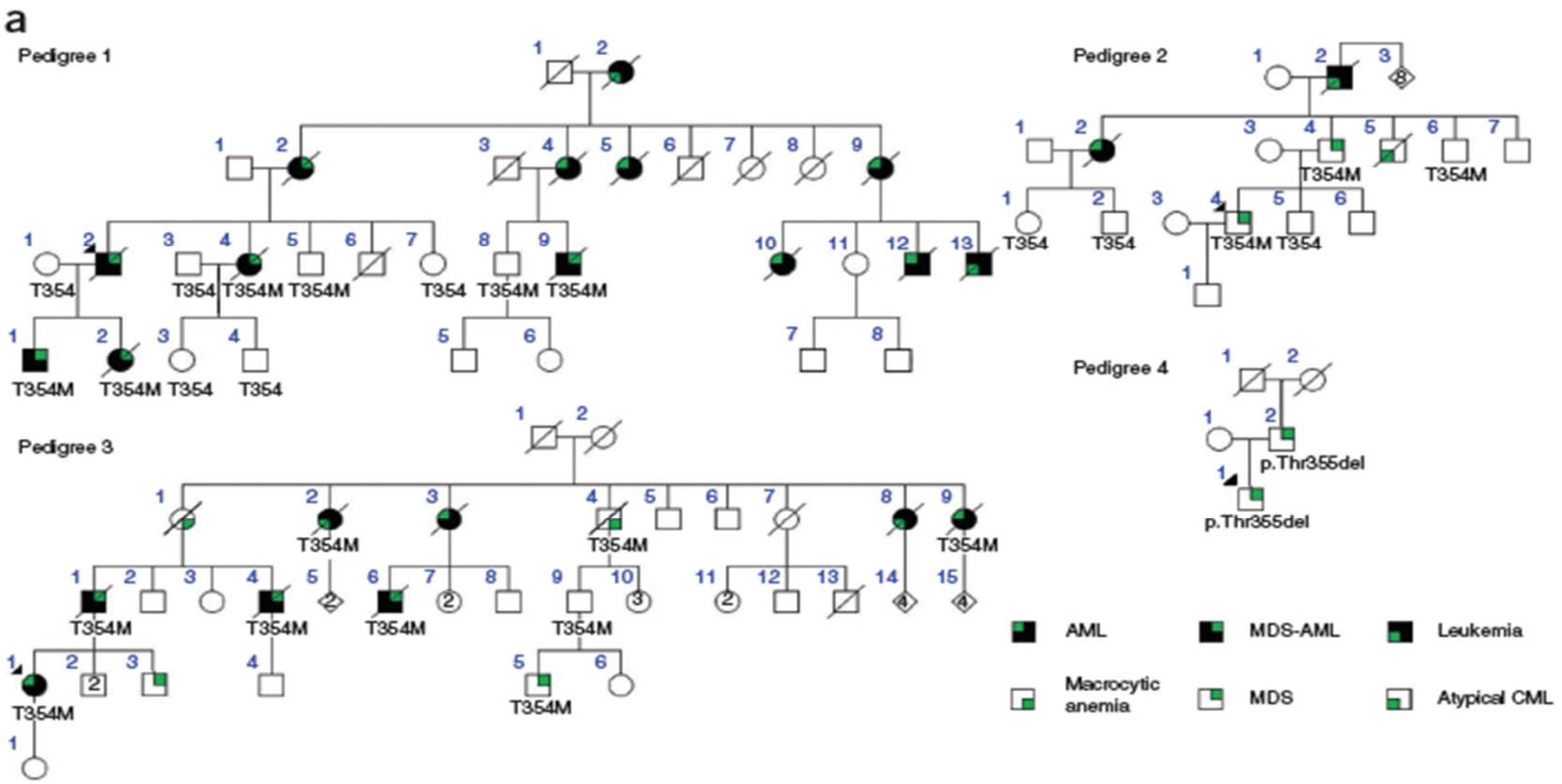




*Prolonged EFS independent of age, gender and karyotype.

Papaemmanuil E, et al. NEJM 2011; 365: 1384.

Familial MDS

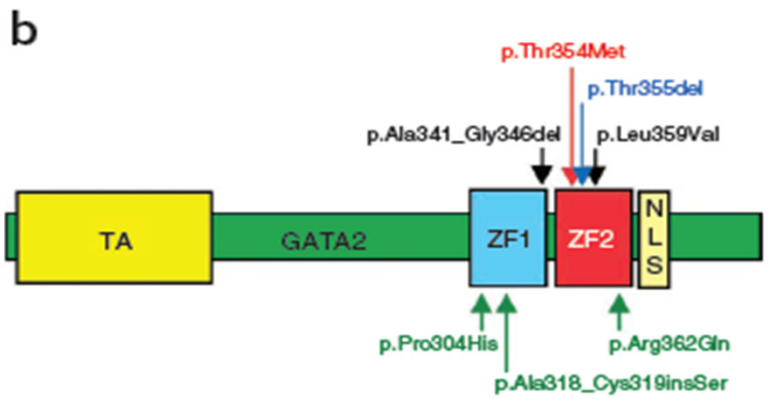


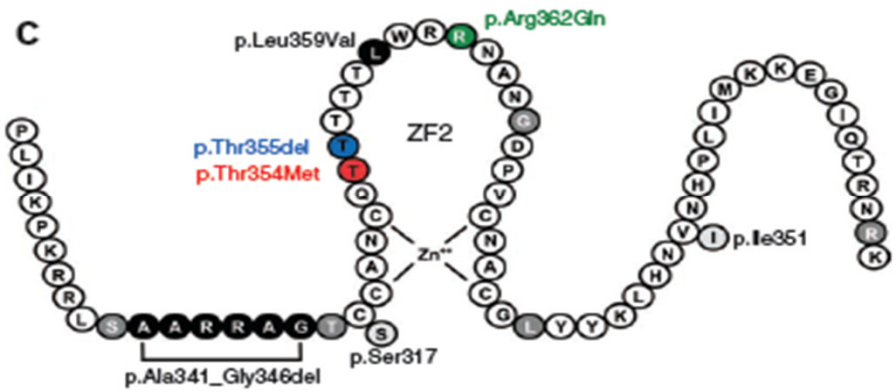
LETTERS

nature genetics

Heritable *GATA2* mutations associated with familial myelodysplastic syndrome and acute myeloid leukemia

Christopher N Hahn[1,2], Chan-Eng Chong[1,2,14], Catherine L Carmichael[3,14], Ella J Wilkins[3,13], Peter J Brautigan[1], Xiao-Chun Li[1], Milena Babic[1], Ming Lin[1], Amandine Carmagnac[3], Young K Lee[1], Chung H Kok[4,5], Lucia Gagliardi[1], Kathryn L Friend[6], Paul G Ekert[7], Carolyn M Butcher[4,5], Anna L Brown[5], Ian D Lewis[2,5], L Bik To[2,5], Andrew E Timms[8], Jan Storek[9], Sarah Moore[1], Meryl Altree[10], Robert Escher[3,13], Peter G Bardy[5], Graeme K Suthers[10,11], Richard J D'Andrea[2,4,5,15], Marshall S Horwitz[8] & Hamish S Scott[1–3,12,15]





Ribosome function and the molecular biology of the 5q-syndrome

Jackie Boultwood

LLR Molecular Haematology Unit
John Radcliffe Hospital
Oxford

ARTICLES

nature medicine

A p53-dependent mechanism underlies macrocytic anemia in a mouse model of human 5q– syndrome

Jillian L Barlow[1,4], Lesley F Drynan[1,4], Duncan R Hewett[1,4], Luke R Holmes[1,4], Silvia Lorenzo-Abalde[1],

ARTICLES

nature medicine

Identification of miR-145 and miR-146a as mediators of the 5q– syndrome phenotype

Daniel T Starczynowski[1,2], Florian Kuchenbauer[1], Bob Argiropoulos[1], Sandy Sung[1], Ryan Morin[1], Andrew Muranyi[1], Martin Hirst[1], Donna Hogge[1], Marco Marra[1], Richard A Wells[3], Rena Buckstein[3], Wan Lam[1,2], R Keith Humphries[1,4] & Aly Karsan[1,2]

Combinational therapy and newer agents in MDS- my perspective

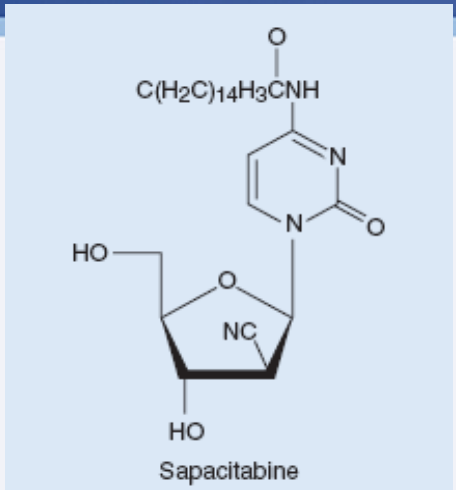
Prof Ghulam .J.Mufti

MDS foundation

ASH 2011

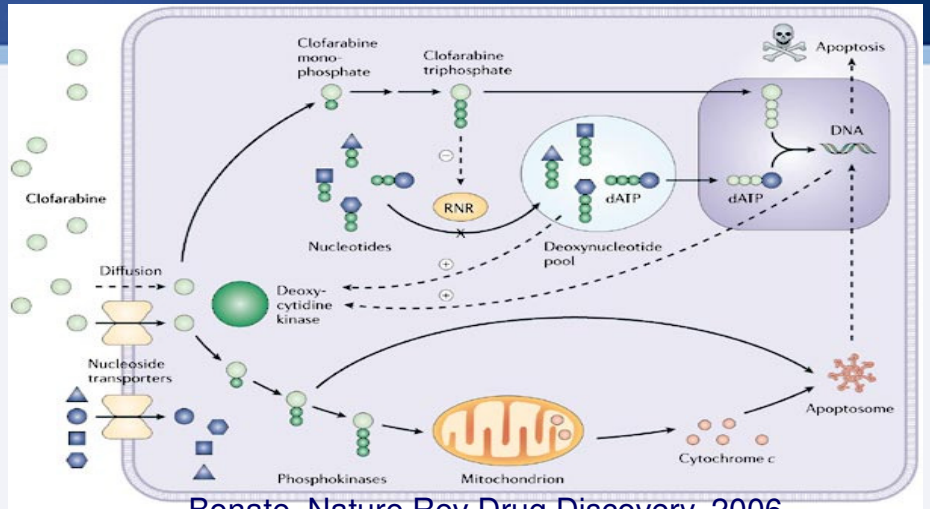
NOVEL Nucleoside analogues

SAPACITABINE



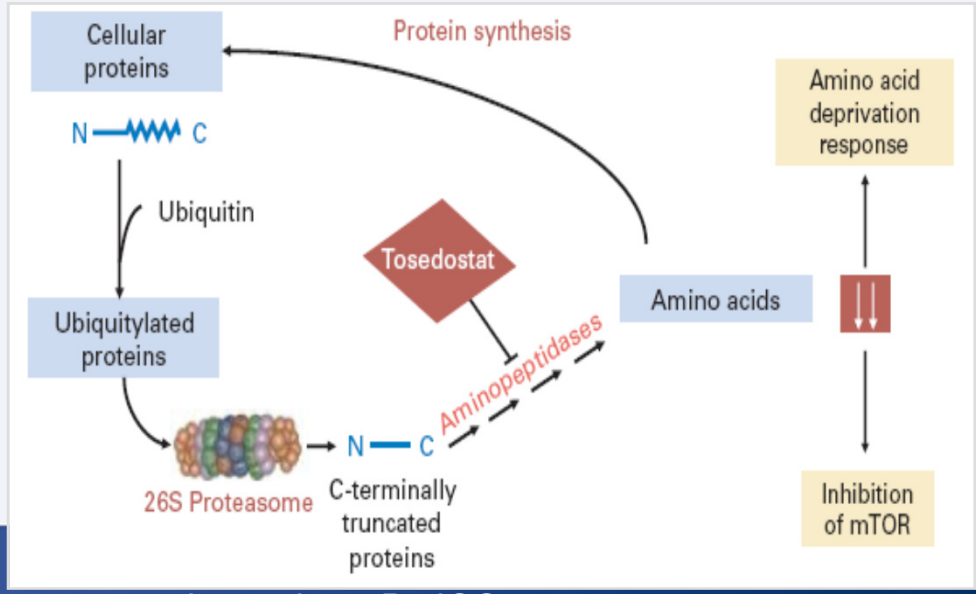
Sapacitabine

CLOFARABINE



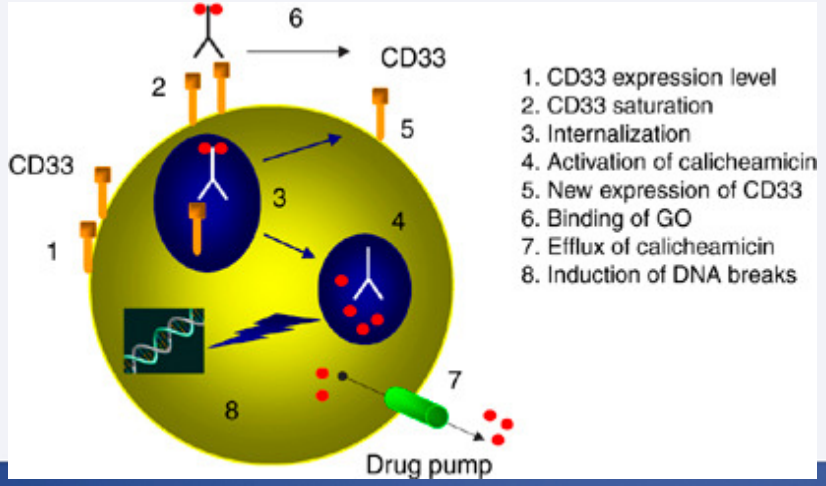
Bonate, Nature Rev Drug Discovery, 2006

Tosedostat-Aminopeptidase inhibitor



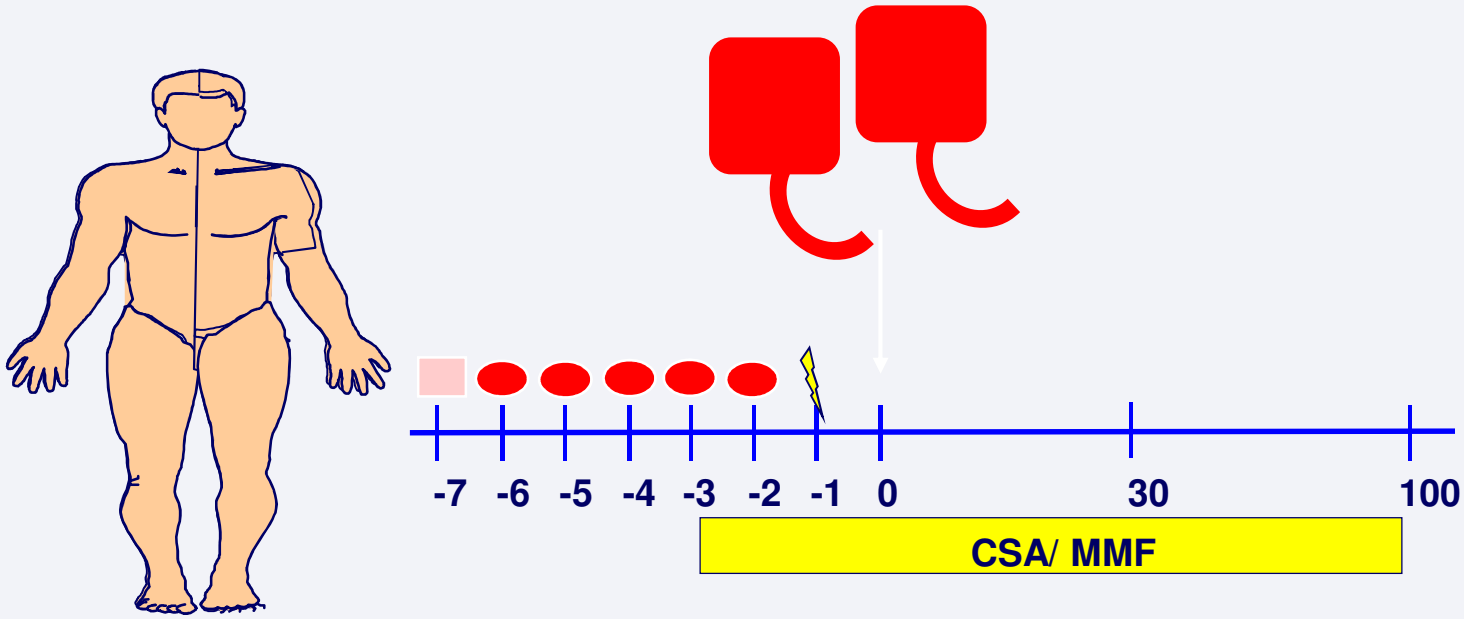
Lowenberg B, JCO 2010.

Is there a role for GO ?



Pagano,Oncogene, 2007.

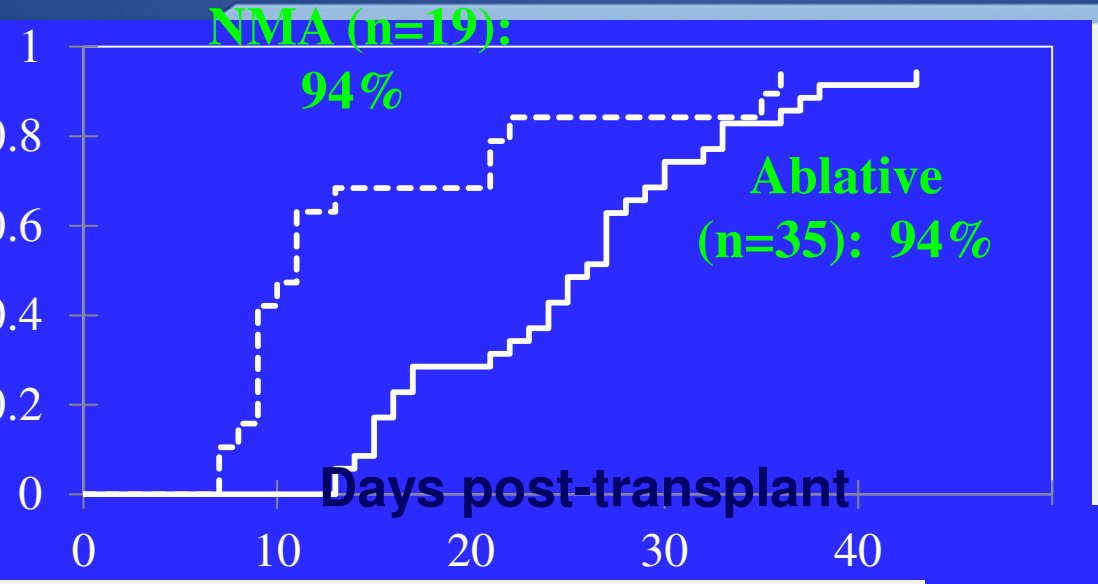
Advances in HSCT for MDS: Cord Blood Transplantation & RIC



Juliet N. Barker, MBBS (Hons), FRACP
Associate Attending
Director Cord Blood Transplant Program
Memorial Sloan-Kettering Cancer Center

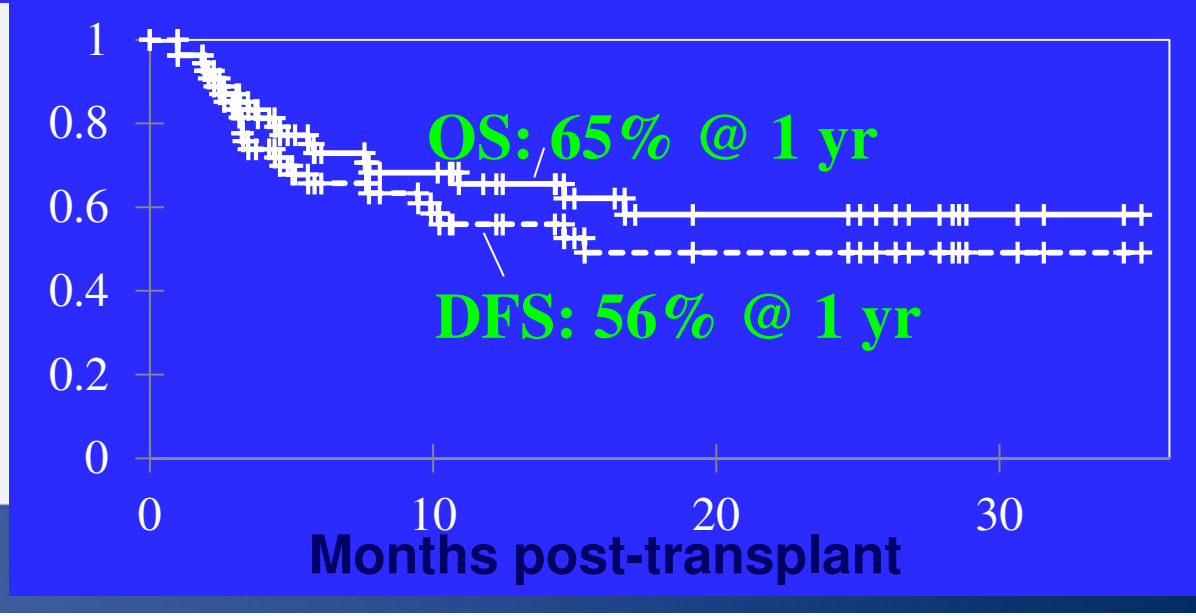
MSK Double Unit CBT: Engraftment & Survival

N = 54, median 42 yrs (range 7-66), high risk heme malignancies



One unit wins. High rates of sustained neutrophil engraftment despite low cell dose of engrafting unit.

Promising survival.



Barker et al, BBMT 2009

About the Foundation

Who Are We?

The Myelodysplastic Syndromes Foundation, Inc., was established in 1994 by an international group of physicians and researchers to provide education about MDS to physicians and patients, support for MDS research, patient support, and advocacy.

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