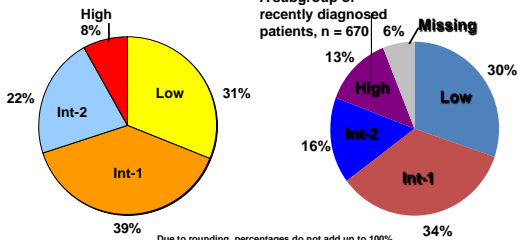


Treating Higher Risk MDS

Bart Scott, M.D.
 Assistant Member, FHCRC
 Assistant Professor, UWMC

IPSS Score Distribution at Time of Diagnosis

Data from 6 consecutive cross-sectional surveys of 101 US hematology and medical oncology specialists from 2005 to 2007 (N = 4,514)

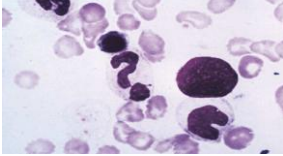


Sekeres MA et al. J Natl Cancer Inst. 2008;100:1542-1551.
 Greenberg et al. Blood 1997;89:2079-2088

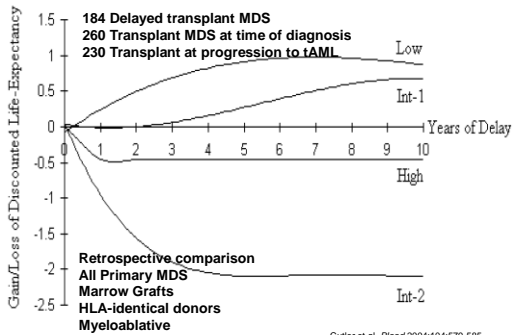
Questions to be Addressed

- When should stem cell transplantation be considered?
- Is induction chemotherapy necessary?
- What non-transplant therapies are available?

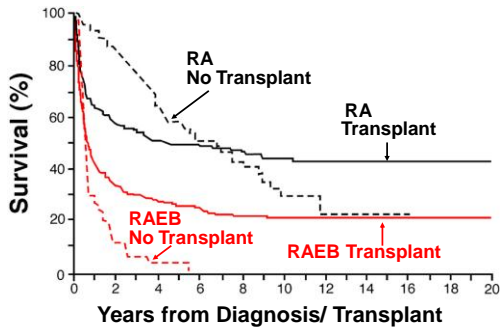
When should allogeneic stem cell transplant be considered?

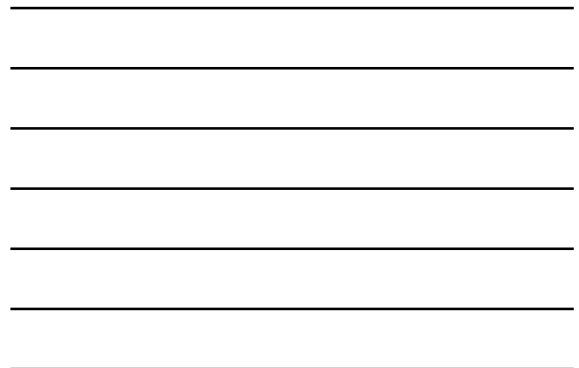
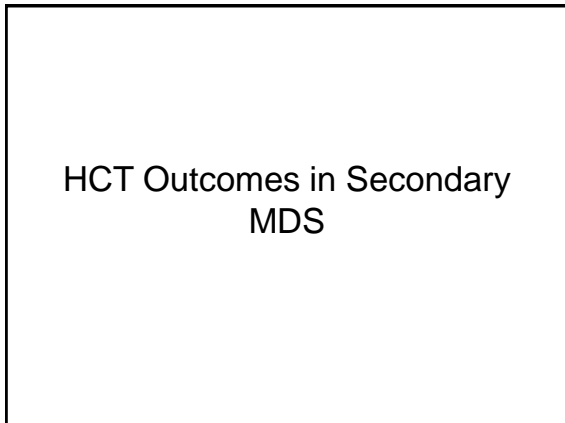
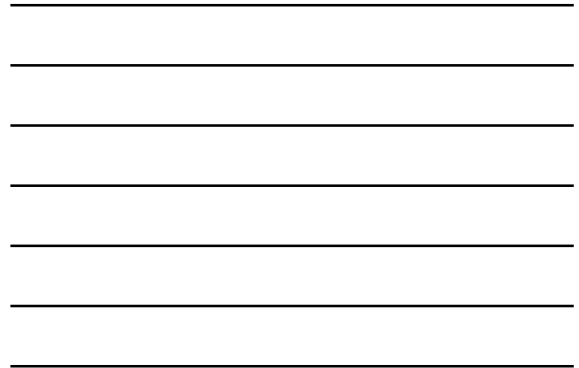
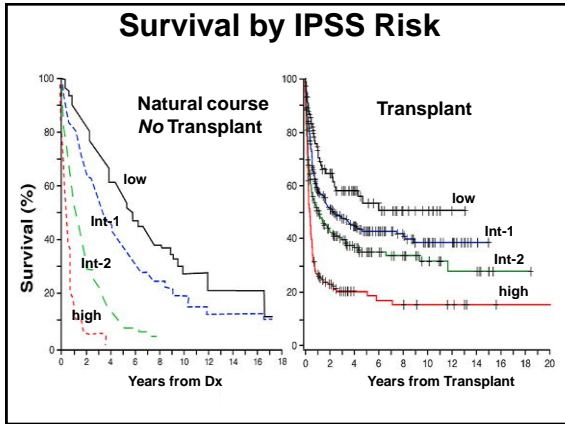


Timing of Transplantation



FAB: No Transplant vs. Transplant Outcome





Patient and Transplant Characteristics

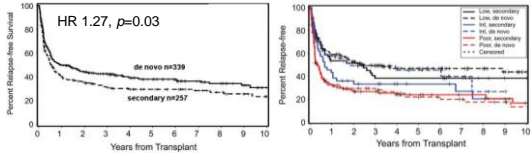
	Secondary MDS/AML	De novo MDS/AML
No. of patients	257	339
Male/female	134/123	200/139
Age range, y (median)	3.1-72.7 (41.2)	1.1-69 (47.3)
Disease category,† no. patients (%)		
RA	82 (32)	90 (27)
RARS	5 (2)	6 (2)
RCMD	—	11 (3)
MDS-U	—	1 (0.3)
Sq-syndrome	—	4 (1)
RAEB-1/2	57 (22)	42 (12)/43 (13)
SM/AML, resp	80 (31)/25 (9)	84 (25)/37 (11)
CMML-1/2	10 (4)	18 (3)/11 (3)
Cytogenetic risk group,‡ no. patients (%)		
Good	70 (27)	196 (49)
Intermediate	48 (18)	53 (15)
Poor	123 (49)	104 (31)
Unknown	18 (8)	16 (5)

	Secondary MDS/AML, no. (%)	De novo MDS/AML, no. (%)
Donor type	257	339
Related		
HLA-phenotypically identical sibling	108 (42)	145 (43)
HLA-antigenetically family member**	28 (11)	20 (6)
Syngeneic twin	2 (1)	4 (1)
Unrelated		
HLA-identical	88 (38)	88 (29)
HLA-mismatched††	24 (9)	72 (21)
Source of stem cells		
Marrow	150 (58)	177 (52)
PBSCs	102 (40)	162 (48)
Cord blood	5 (2)	—
Transplant conditioning regimen		
BU/Flu/CC-2	20 (11)/97 (38)	18 (4)/172 (51)
High-dose TB	83 (32)	122 (36)
FLU/BU	12 (5)	22 (6)
Flu/TB (2/0)	28 (10)	—
Nonrelapse chemotherapy regimen‡‡	14 (5)	10 (3)
Interval from diagnosis to HCT, mo		
0 to 6	148 (58)	138 (41)
7 to 12	69 (27)	95 (28)
13 to 24	29 (11)	56 (17)
Longer than 24	20 (7)	48 (14)
Year of transplantation		
2000 to 2006	116 (45)	147 (43)
1990 to 1999	121 (47)	192 (57)
1980 to 1989	20 (8)	0

Chang, C. et al. Blood 2007;110:1379-1387



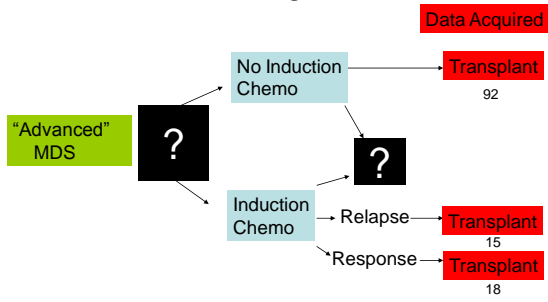
Relapse Free Survival



Chang, C. et al. *Blood* 2007;110:1379-1387

Is Induction Chemotherapy Necessary?

Design

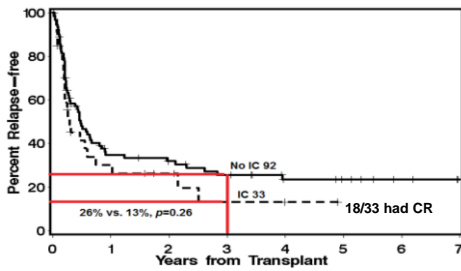


Patient Characteristics

Characteristic	Induction Chemotherapy	
	Yes	No
No. of patients	33	92
Age, range (median), y	2-64 (45)	3-69 (50)
Gender, M/F, no. of patients	17/16	59/33
Etiology, no. of patients (%)		
De novo	28 (84)	60 (65)
Secondary	5 (15)	32 (35)
Disease duration, range (median), mo	1-43 (6)	1-62 (6)
FAB stage, no. of patients (%)		
RAEB	3 (9)	62 (67)
RAEB-T	6 (18)	22 (24)
IAM	24 (73)	8 (9)
IPSS risk group, no. of patients (%)		
Low	0	1 (1)
Intermediate-1	10 (30)	20 (22)
Intermediate-2	8 (24)	37 (40)
High	15 (45)	33 (36)
Not scored†	0	12
Donor, no. of patients (%)		
HLA-identical sibling	16 (48)	46 (50)
Alternative related donor‡	0	3 (4)
HLA-identical unrelated	17 (52)	43 (46)
Source of Stem Cells, no. of patients (%)		
Peripheral Blood	18 (55)	27 (29)
Bone Marrow	15 (45)	65 (71)
Conditioning Regimen (%)		
FluCy	21 (64)	55 (60)
BuTBI	12 (36)	37 (40)

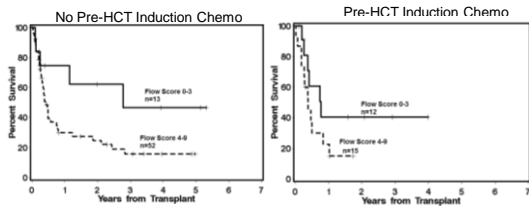
Scott et al. *Biol Blood Marrow Transplant* 2005;11:65-73

Induction Chemo vs. No Induction Chemo Relapse-Free Survival



Scott et al. *Biol Blood Marrow Transplant* 2005;11:65-73

Impact of Flow Score on Survival

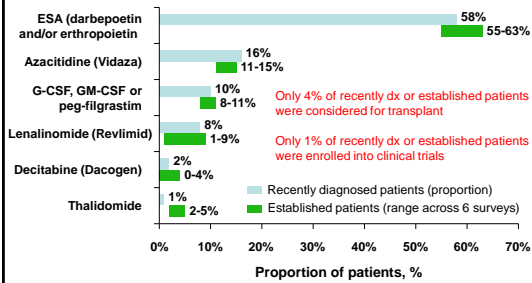


Scott et al. *Biol Blood Marrow Transplant* 2005;11:65-73

What non-transplant therapies are available?

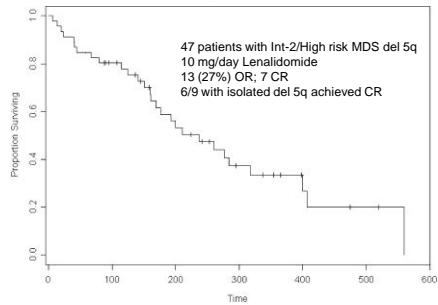
U.S. treatment approaches to MDS

Overall proportion of recently diagnosed patients (n = 670) and range of established patients across six surveys (n = 3844) taking specific types of therapies at the time of the survey



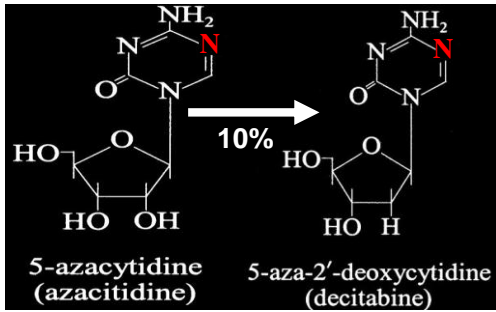
Sekeres, et al. J National Cancer Inst. 2008;100:1542.

Overall Survival Int-2/High Risk MDS Lenalidomide (Revlimid®)

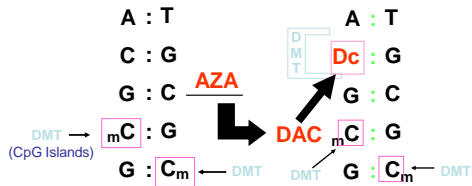


Adès, L. et al. Blood 2009;113:3947-3952

Cytosine Analogs



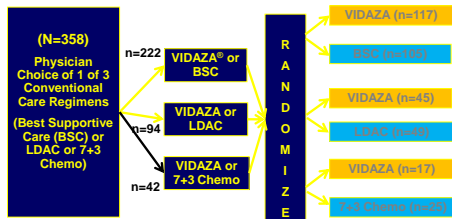
Methyltransferase Inhibitor (MTI) Induces DNA Hypomethylation and Gene Activation



- Azacitidine (AZA) is incorporated into DNA *in lieu* of cytosine residue
- Inactivates DMT
- Leads to formation of newly synthesized DNA with unmethylated cytosine residues
- Results in hypomethylation and transcription of previously quiescent genes

Silverman L. *The Oncologist*. 2001;6(55):9-14.

AZA-001 Randomization Schema



Fenaux et al. *Lancet Oncol* 2009;10:223-32

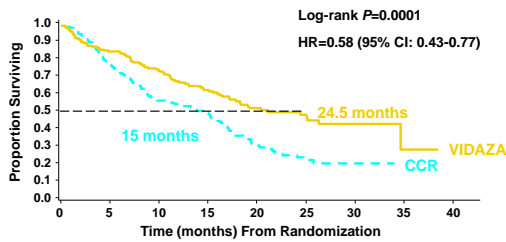
AZA-001 Trial: Baseline Clinical Characteristics*

	CCR Regimens N=179				
	VIDAZA® N=179	CCR N=179	BSC, Only N=105	LDAC N=49	7+3 Chemo N=25
Age					
Median (yrs)	69	70	70	71	65
≥65 (%)	68.1	76.0	77.1	85.7	52.0
FAB (%)					
RAEB	58.1	57.5	64.8	51.0	40.0
RAEB-T	34.1	34.6	28.6	38.8	52.0
CMMoL	3.4	2.8	3.8	2.0	0
IPSS (%)					
Int-1	2.8	7.3	8.6	4.1	8.0
Int-2	42.5	39.1	43.8	42.9	12.0
High	45.8	47.5	43.8	42.9	72.0
WHO (%)					
RAEB-1	7.8	9.5	12.4	6.1	4.0
RAEB-2	54.7	53.1	57.1	49.0	44.0
CMMoL-1	0.6	0	0	0	0
CMMoL-2	5.6	2.8	2.9	0	8.0
AML	30.7	32.4	25.7	40.8	44.0

*Numbers may not add up to 100%, some patient information unknown

Fenaux et al. *Lancet Oncol* 2009;10:223-32

AZA-001 Trial: VIDAZA® Significantly Improves Overall Survival (OS)

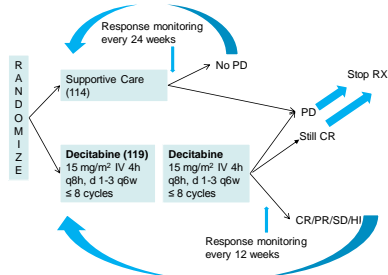


Fenaux et al. *Lancet Oncol* 2009;10:223-32

CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat.

Randomized Phase III Study of Low-Dose Decitabine (Dacogen®) for Patients With Higher-Risk MDS

- Eligibility criteria:**
- Intermediate-1,2 or high-risk MDS or CMML
 - Age ≥ 60 years
 - Blast cell count 11%-30% or ≤ 10% with poor risk cytogenetics
 - ECOG PS 0-2



Lübbert et al. *J Clin Oncol* 2011;29:1987-1996

Patient characteristics

	Supportive care N=114	Decitabine N=119
Age median (range)	70 (60-86) y	69 (60-90) y
≥ 75 yrs	30%	28%
Male/female	64% / 36%	64% / 36%
ECOG PS 0-1	85%	88%
2	15%	12%
FAB RA/RARS	9%	7%
RAEB	56%	51%
RAEB-t	31%	34%
CMML	4%	8%

Lübbert et al. J Clin Oncol 2011;29:1987-1996

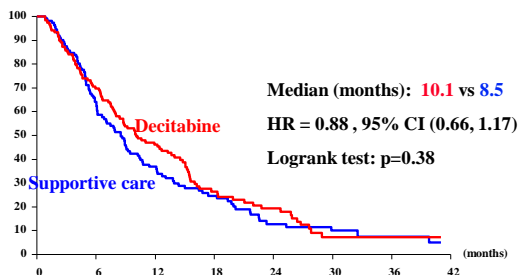
Reason for going off-protocol

	Supportive care N=114 (100%)	Decitabine N=119 (100%)
Normal completion	19 (16.7%)	31 (26.1%)
Progression of disease	55 (48.2%)	40 (33.6%)
Toxicity	NA	19 (16.0%)
Prolonged cytopenia	NA	5 (4.2%)
Death	17 (14.9%)	11 (9.2%)
Refusal	14 (12.3%)	6 (5.0%)
Protocol violations	5 (4.4%)	3 (2.5%)
Ineligible	1 (0.9%)	1 (0.8%)
Other	3 (2.6%)	3 (2.5%)

Median time to off-study: **112 days** vs **180 days**

Lübbert et al. J Clin Oncol 2011;29:1987-1996

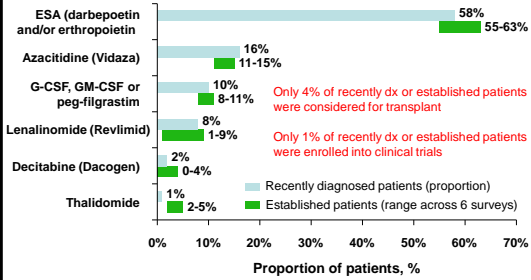
Overall Survival Decitabine (Dacogen)



Lübbert et al. J Clin Oncol 2011;29:1987-1996

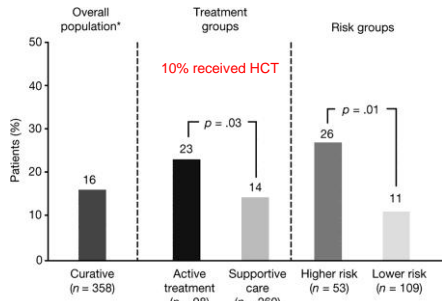
U.S. treatment approaches to MDS

Overall proportion of recently diagnosed patients (n = 670) and range of established patients across six surveys (n = 3844) taking specific types of therapies at the time of the survey



Sekeres, et al. J National Cancer Inst. 2008;100:1542.

Percentage of patients who believed their most current treatment would be curative, in the overall population and according to treatment group and risk group. *30% were uncertain and 54% did not believe that treatment would be curative.



Sekeres M A et al. The Oncologist 2011;16:904-911
