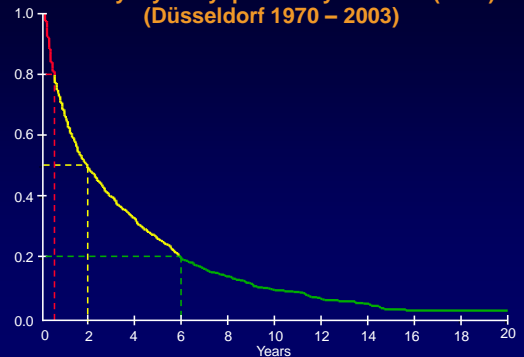


## Case #2 Advanced Myelodysplastic Syndromes: Is There a New Standard of Care?

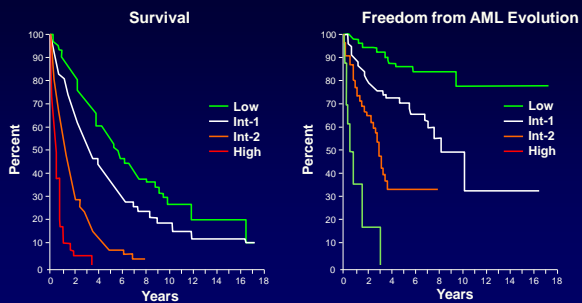
Aristoteles Giagounidis, MD, PhD  
St Johannes Hospital  
Duisburg, Germany



## Cumulative Survival of 1806 Untreated Patients with Primary Myelodysplastic Syndromes (MDS) (Düsseldorf 1970 – 2003)



## International MDS Risk Classification



Greenberg P, et al. *Blood*. 1997;89(6):2079-2088.

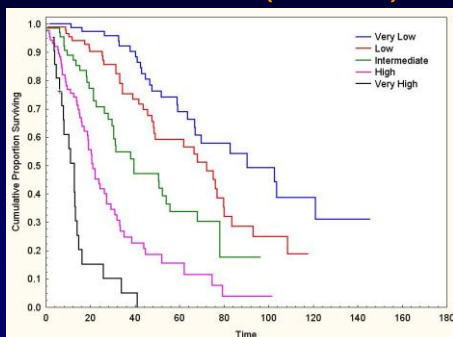
## A WHO-Based Prognostic Scoring System

	Point			
	0	1	2	3
WHO subtype	RA, RARS 5q-	RCMD RCMD-RS	RAEB-I	RAEB-II
Transfusion requirement	None	Regular	-	-
Cytogenetic category	Low	Intermediate	High	

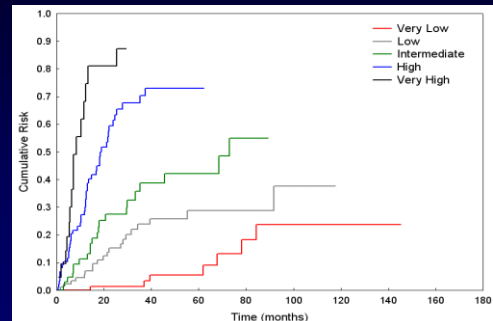
Risk Groups	Score
Very low	0
Low	1
Intermediate	2
High	3-4
Very high	5-6

Malcovati L, et al. *Blood*. 2005;106: Abstract 788.

## A WHO-Based Prognostic Scoring System: Overall Survival (in Months)

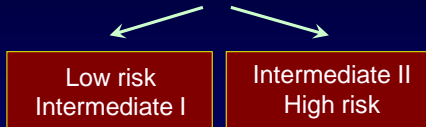


## A WHO-Based Prognostic Scoring System: AML Evolution



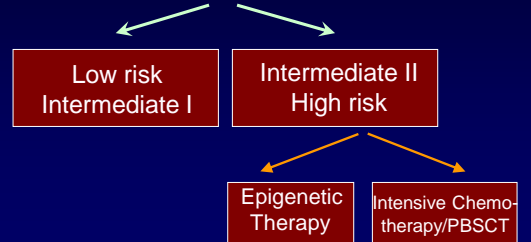
## Treatment Options in Myelodysplastic Syndromes

Risk stratification according to IPSS

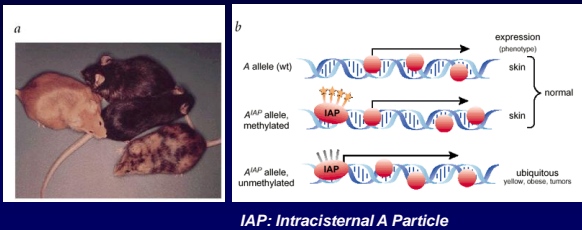


## Treatment Options in Myelodysplastic Syndromes

Risk stratification according to IPSS

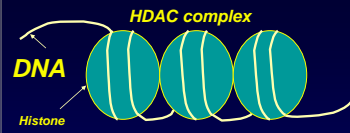


## Epigenetic Modulation

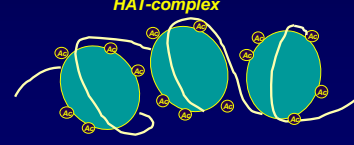


Jaenisch R, et al. *Nat Genet.* 2003;22(Suppl):245-254.

Histone deacetylation → Gene silencing



Histone acetylation → Gene transcription



Acetylation

## AZA-001 Phase III Survival Study

AZA 75 mg/m<sup>2</sup>/d x 7 days  
Every 28 days N = 179

Stratify (FAB, IPSS)

N = 358

Eligibility

- RAEB, RAEB-t, CMML
- 10% to 29% blasts
- IPSS: INT-2/High risk

N = 179

Conventional Care Regimen (CCR):

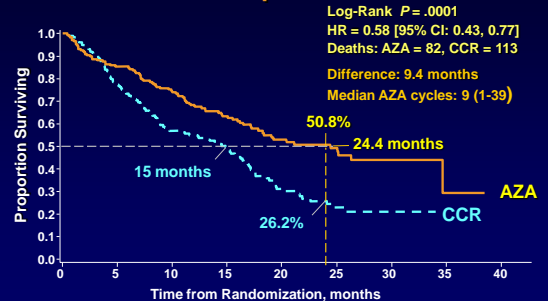
1. BSC only, n = 105
2. Low-dose ara-C, n = 49
3. Induction/consolidation, n = 25

Primary endpoint: Overall survival

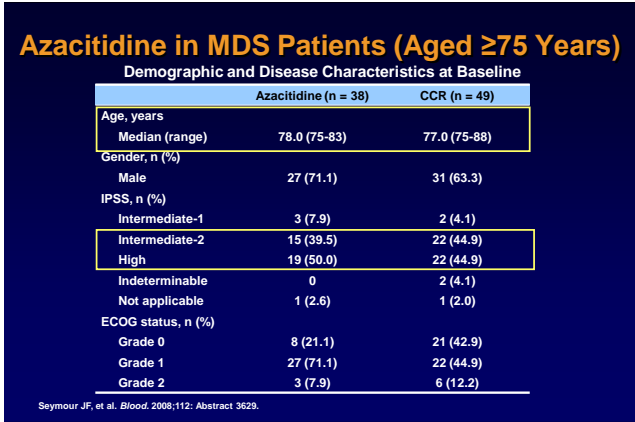
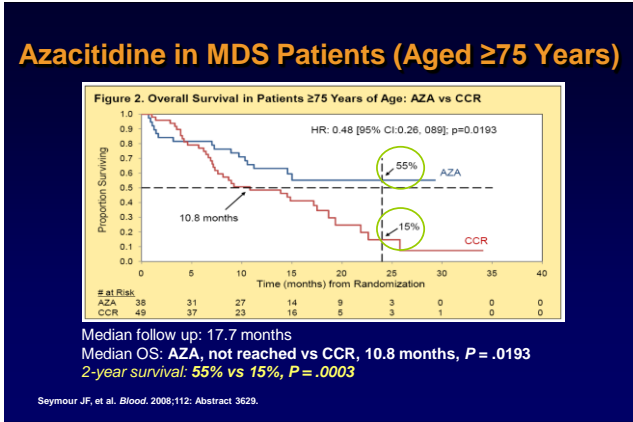
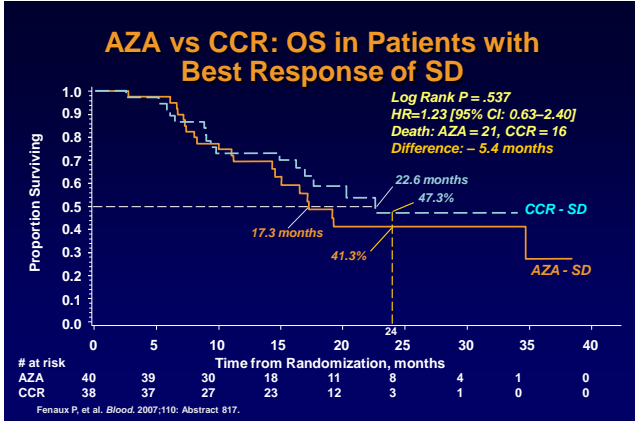
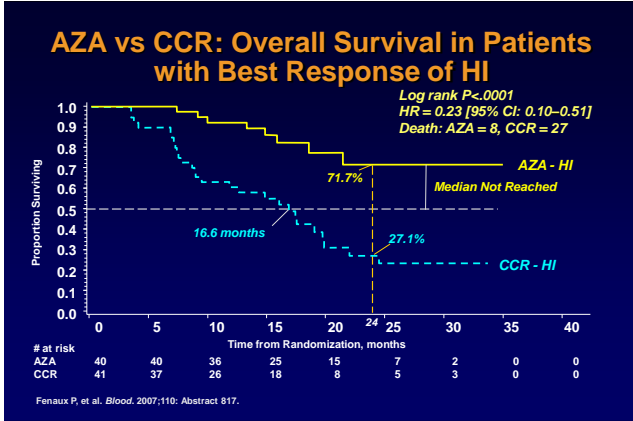
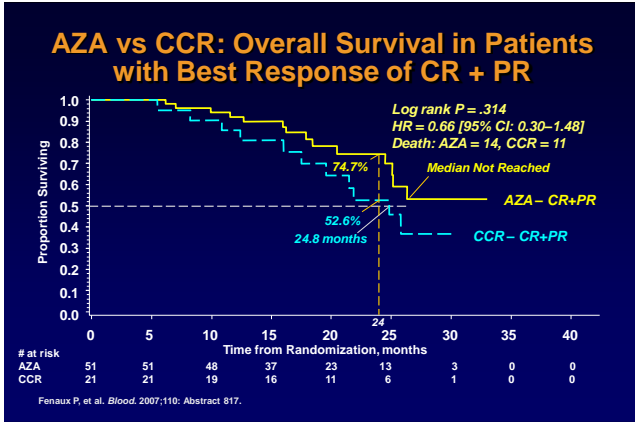
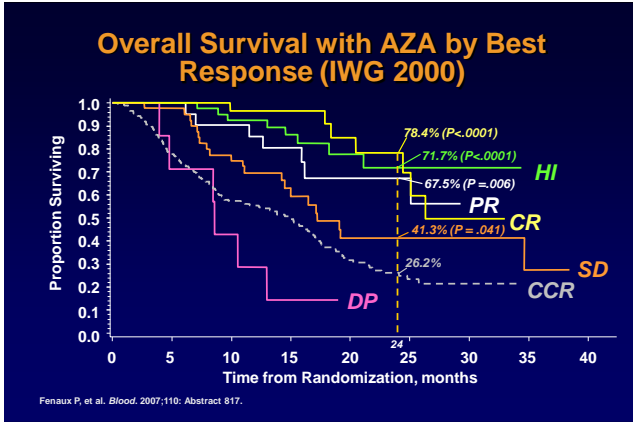
Secondary endpoints: Time to AML, RR, TI, infection, safety

Fenaux P, et al. *Blood.* 2007;110: Abstract 817.

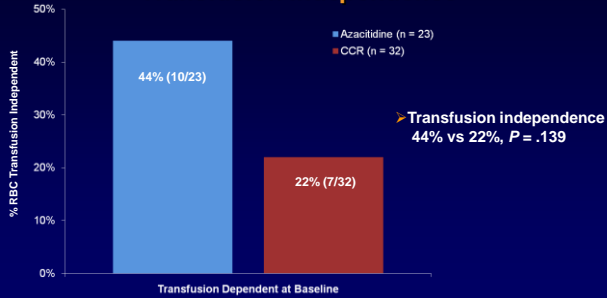
## Overall Survival: Azacitidine vs CCR ITT Population



Fenaux P, et al. *Blood.* 2007;110: Abstract 817.

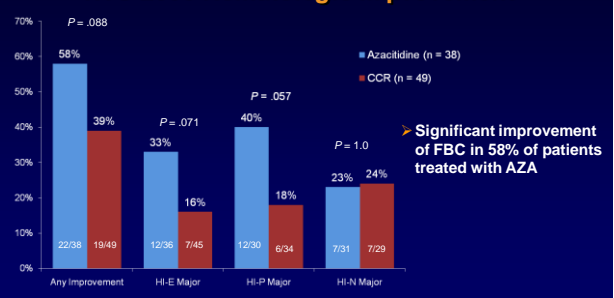


### Azacitidine in MDS Patients (Aged ≥75 Years) Transfusion Independence



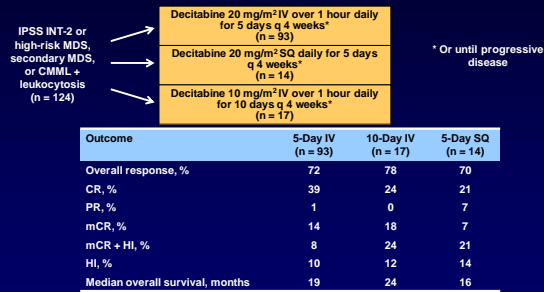
Seymour JF, et al. *Blood*. 2008;112: Abstract 3629.

### Azacitidine in MDS Patients (Aged ≥75 Years) IWG 2000 Hematologic Improvement



Seymour JF, et al. *Blood*. 2008;112: Abstract 3629.

### Low-Dose Decitabine in Intermediate Risk, High Risk, or Noncategorized MDS



Kantarjian H, et al. *Blood*. 2007;110: Abstract 115.

mCR = marrow complete response

### Phase II Study of Decitabine 20 mg/m<sup>2</sup> IV Administered Daily for 5 Days q 4 Weeks

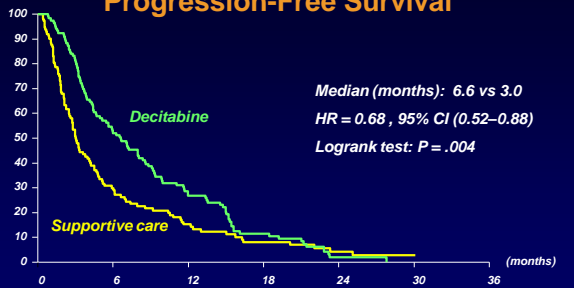
#### ITT Preliminary Response Data (n = 99)

IWG 2006 Criteria	ITT (n=99), %
CR	17
mCR	15
PR	0
HI	18
SD	24

- Time to improvement in patients with clinical improvement (≥HI) was rapid: 82% by cycle 2
- ≥Grade 3 adverse events: neutropenia 37%; thrombocytopenia 22%; anemia 21%; febrile neutropenia 17%; and pancytopenia 5%

Sleensma DP, et al. *Blood*. 2007;110: Abstract 1450.

### Progression-Free Survival

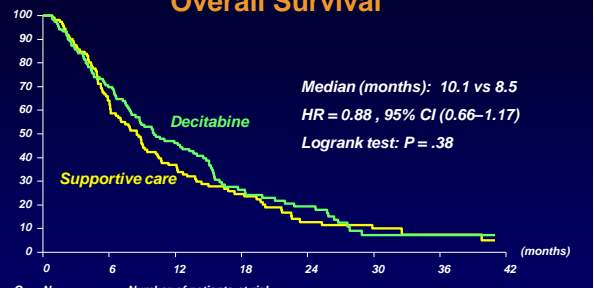


O	N	Number of patients at risk:				
105	114	33	15	7	3	1
113	119	62	32	11	2	0

— Supportive care  
— Decitabine

WijerMans P, et al. *Blood*. 2007;110: Abstract 226.

### Overall Survival



O	N	Number of patients at risk:					
96	114	71	38	22	10	6	3
99	119	83	53	24	15	4	4

— Supportive care  
— Decitabine

WijerMans P, et al. *Blood*. 2007;110: Abstract 226.

## Intensive Post-Study Treatment

	Supportive care N = 114 (100%)	Decitabine N = 119 (100%)
No/Not applicable	86 (75%)	86 (75%)
Without AML	15 (13%)	19 (16%)
5-azacytidine	3	3
Induction chemo	4	8
AlloSCT	8	8
After AML	13 (11%)	10 (8%)
5-azacytidine	1	1
Induction chemo	9	5
AlloSCT	3	4

WijerMans P, et al. *Blood*. 2007;110: Abstract 226.

## A Phase I/II Study of Decitabine and Valproic Acid in Patients with Leukemia and MDS

- 6 MDS, 48 sAML patients (median age 60 years)
- Treatment with low-dose decitabine and valproic acid (both 10 days)
- 10/53 patients showed a complete response (19%)
- *In vivo* demethylation/reactivation of p15 gene
- *In vivo* histone acetylation

Garcia-Manero G, et al. *Blood*. 2006;108(10):3271-3279.

## Phase I Trial of Vorinostat and Azacitidine in MDS and AML

- *In vitro* synergism for HDAC inhibitors and demethylating agents
- 28 patients treated, 20 MDS, 8 AML, median age 68 years
- 8 patients withdrew therapy
- 82% of evaluable patients responded: 12 CR(i) (55%), 1 PR (5%), 5 HI (23%), 2 SD (9%)
- 10 of 16 high-risk patients responded: 7 CR(i), 3 HI
- Mean of 6 cycles given
- Abnormal cytogenetics persisted in 57%

Silverman LR, et al. *Leuk Res*. 2009;33:S135-S136.

## Clofarabine in MDS

- Clofarabine 40 → 30 mg/m<sup>2</sup> PO daily x 5
- Clofarabine 30 vs 15 mg/m<sup>2</sup> IV daily x 5

Parameter	Clofarabine Oral	Clofarabine IV		Total
		30	15	
Treated	24	16	20	60
%CR	29	25	35	30
%CRp	8	13	15	12
%HI	13	-	-	5
%OR	50	38	50	47
6 deaths (10%); renal failure 7 (12%)				

Faderl S, et al. *Blood*. 2008;112: Abstract 222.

## Therapeutic Options in MDS

