

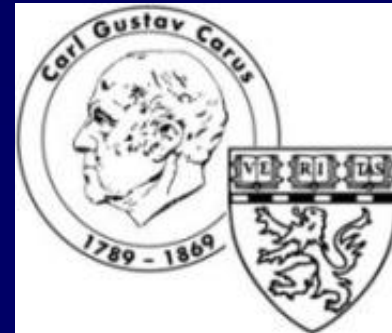
Myelodysplastic Syndromes

- high-risk disease in
a “rather” young patient -

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Patient characteristics

Hb	9.6 g/dL
WBC	2300/μL
Neutrophil count	650/μL
Platelets	54.000/μL
LDH	260 U/L (normal range <240 U/L)
EPO	> 500, no response to EPO
Bone marrow	8.5% blasts, del(7q), del(9q), -18, +21

reduced health, 50 pack-year smoking history, COPD ?

What would you estimate the expected median survival to be for this patient?

< 3 months

3 to 6 months

6 to 12 months

12 to 18 months

18 to 24 months

24 to 36 months

Longer than 3 years

IPSS (International Prognostic Scoring System)

Prognostic variable	Score				
	0	0.5	1.0	1.5	2.0
Bone marrow blasts (%)	< 5	5–10		11–20	21–30
Karyotype*	Good	Intermediate	Poor		
Cytopenias	0/1	2/3			

*Karyotype: good: normal, -Y, del(5q), del(20q); poor: complex (≥ 3 abnormalities) or chr 7 anomalies; and intermediate: other abnormalities.

Score	IPSS subgroup	Median survival (years)
0	Low	5.7
0.5–1.0	Int-1	3.5
1.5–2.0	Int-2	1.2
≥ 2.5	High	0.4

Hb < 10.0 g/dL; ANC < $1.5 \times 10^9/L$; platelet count < $100 \times 10^9/L$

WHO classification-based Prognostic Scoring System (WPSS)

Variable	0	1	2	3
WHO	RA, RARS, del5q-	RCMD, RCMD-RS	RAEB-1	RAEB-2
Karyotype	Good	Intermediate	Poor	-
RBC	no	yes	-	-

* Karyotype: good: normal, -Y, del(5q), del(20q); poor: complex (≥ 3 abnormalities, chr 7 anomalies); and intermediate: other abnormalities.

Score	WPSS group	Median OS (mon)	Median OS (mon)
		Italian cohort	German cohort
0	Very low	103	141
1	Low	72	66
2	Intermediate	40	48
3-4	High	21	26
5-6	Very high	12	9

What would you estimate the expected median survival to be for this patient?

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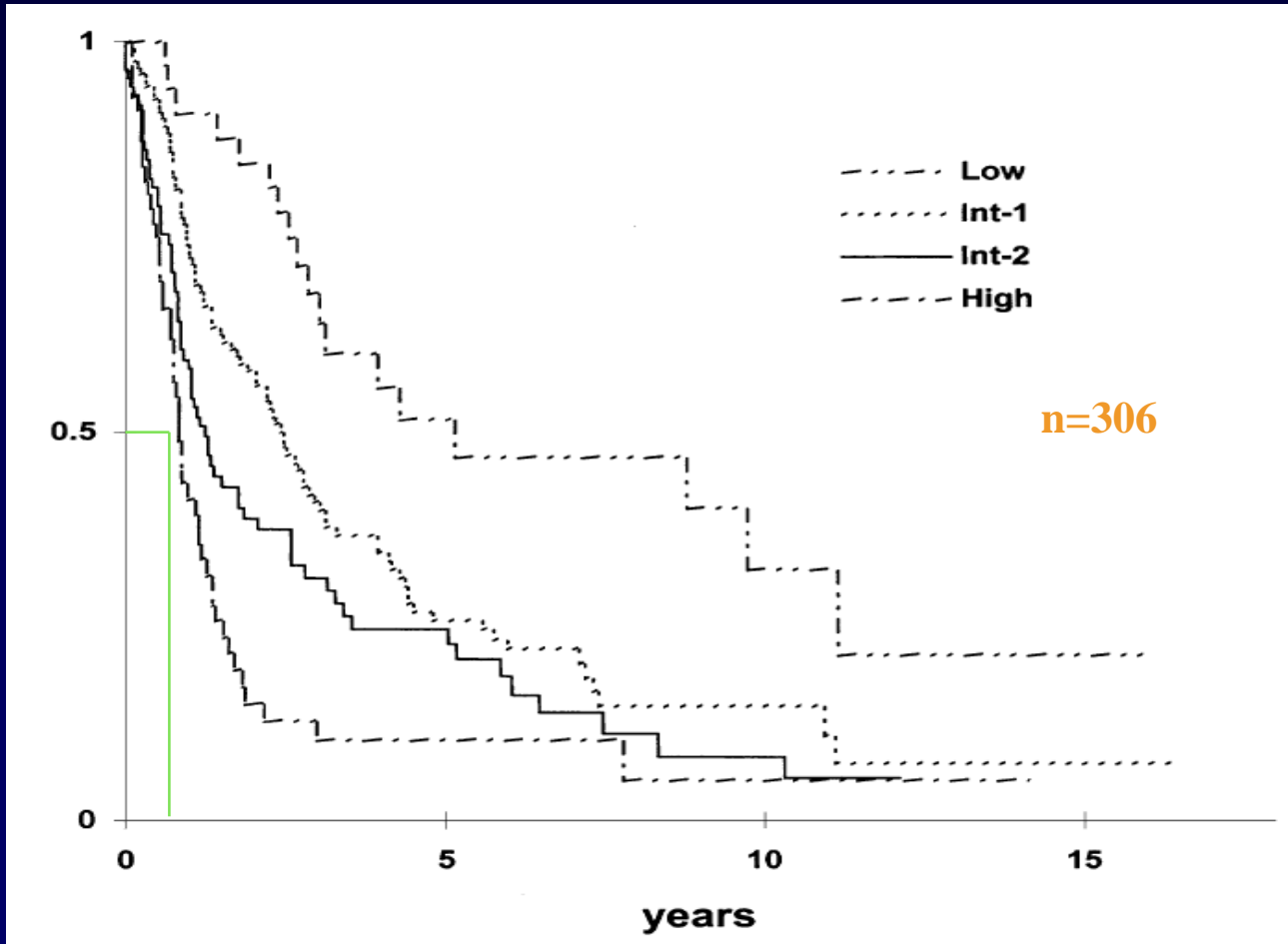
At this point what else would you recommend?

1. Observe further with continued erythropoietin therapy to see what the pace of the MDS will be
2. Decitabine on study (Dacogen®)
3. Azacitidine (Vidaza®)
4. Arsenic trioxide (Trisenox®)
5. Clofarabine on study (Evoltra®)
6. Lenalidomide (Revlimid®)
7. Induction chemotherapy
8. Allogeneic stem cell transplant

Low-Dose ARA-C

	<i>N=59 (100%)</i>
<i>Response</i>	26 (44.1%)
CR	12 (20.3%)
PR	7 (11.9%)
Minor response	7 (11.9%)
Stable disease	12 (20.3%)
Progression to RAEBt	7 (11.9%)
Progression to AML	8 (13.6%)
Death due to MDS	0 (0%)
Toxic death	5 (8.2%)
Other	1 (1.6%)

Intensive Chemotherapy



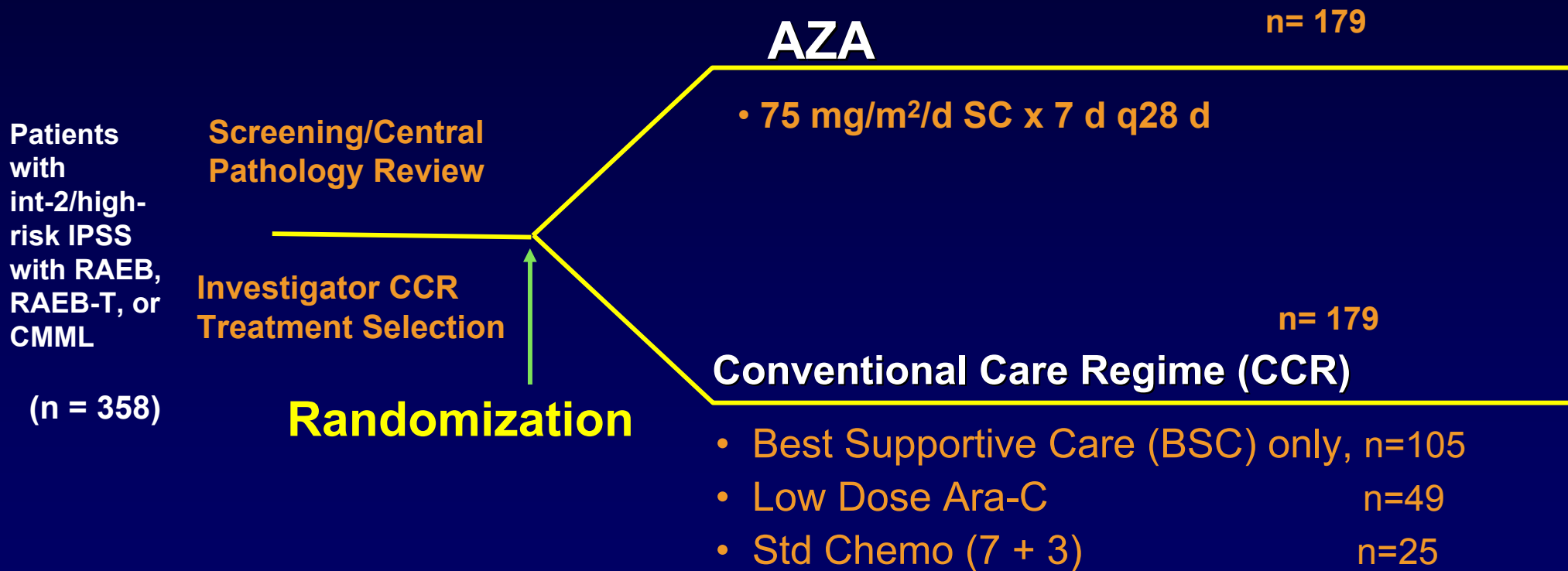
Clofarabine

Response	Clofarabine +			P
	Clofarabine	LD Cytarabine	Total	
	(N=16) N (%)	(N=54) N (%)	(N=70) N (%)	
Complete remission (CR)	5 (31)	34 (63)	39 (56)	0.025
Complete remission with incomplete count recovery (CRi)	0	2 (4)	2 (3)	
Overall response (OR)	5 (31)	36 (67)	41 (59)	0.012
Treatment failure	6 (38)	8 (19)	14 (20)	0.046
Induction mortality	5 (31)	10 (19)	15 (21)	0.276

Azacitidine (Vidaza®)

- DNA hypermethylation common in MDS (p15)
- Azacitidine (5-azacitidine) incorporates into RNA and DNA and can work as a methyltransferase inhibitor
 - promotes hypomethylation of DNA, allowing expression of previously silenced genes
 - SC, IV
 - Azacitidine FDA approved in USA for all MDS FAB subtypes
- Orphan drug in EU

AZA-001 Phase III: Study design



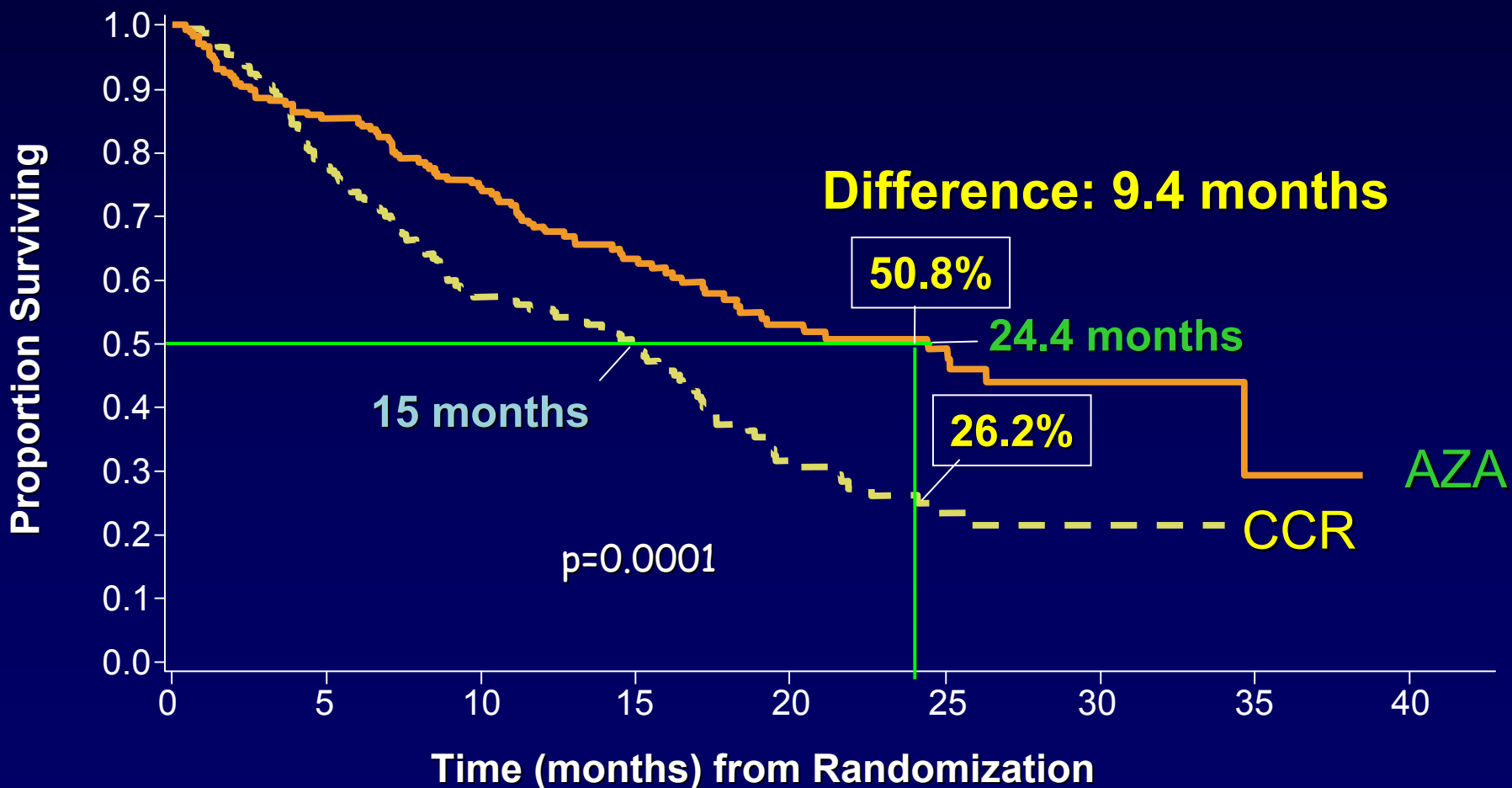
Primary endpoint: OS



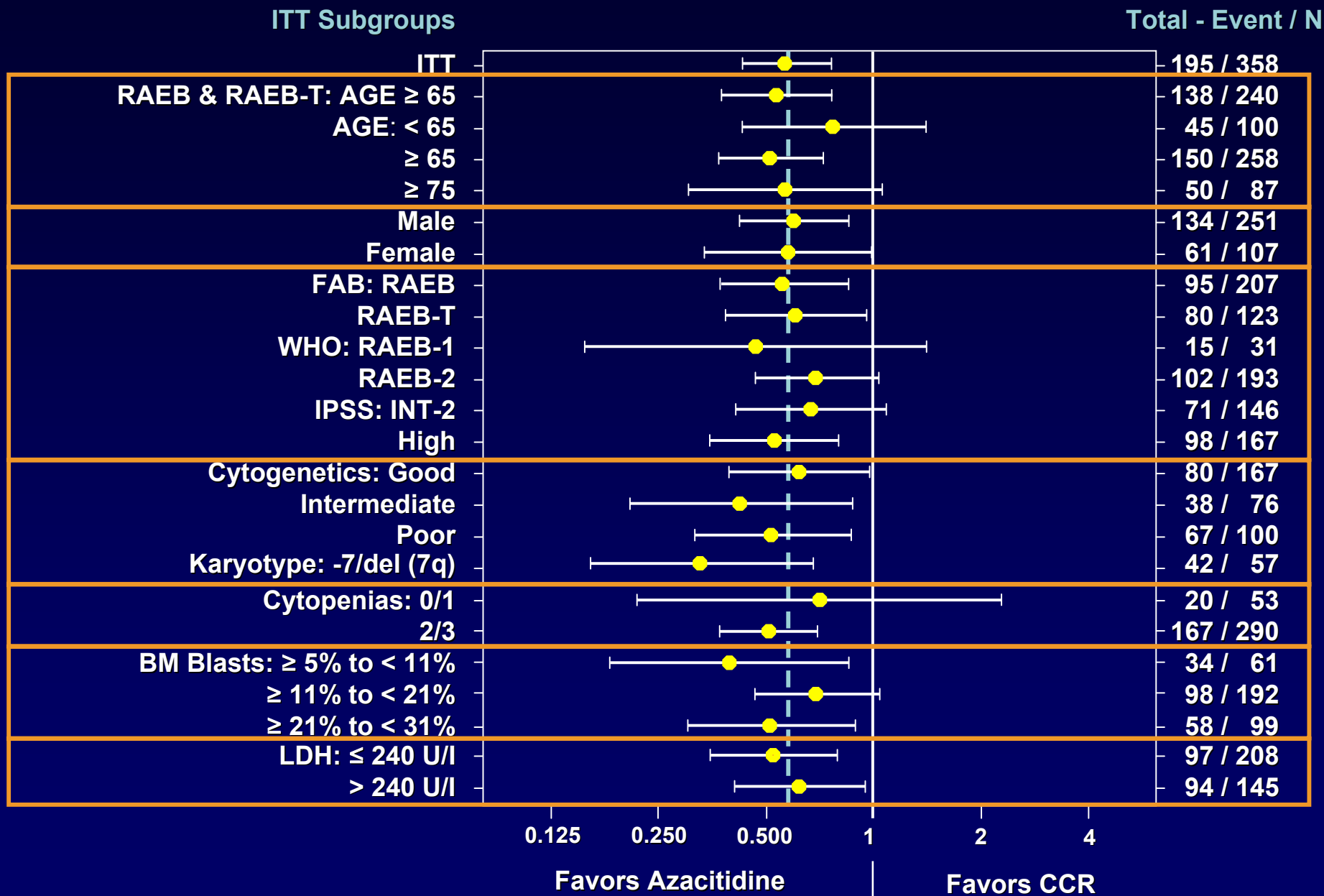
AZA-001 Phase III

	AZA	CCR	P-value
	%	%	AZA vs. CCR
CR+PR (%)	29	12	0,0001
CR	17	8	0,02
PR	12	4	0,009
SD	42	39	0,329
HI	49	29	0,0001
Time to AML (months)	26.1	12.4	0,004
Transf.-indep. (%)	45	11	0,0001

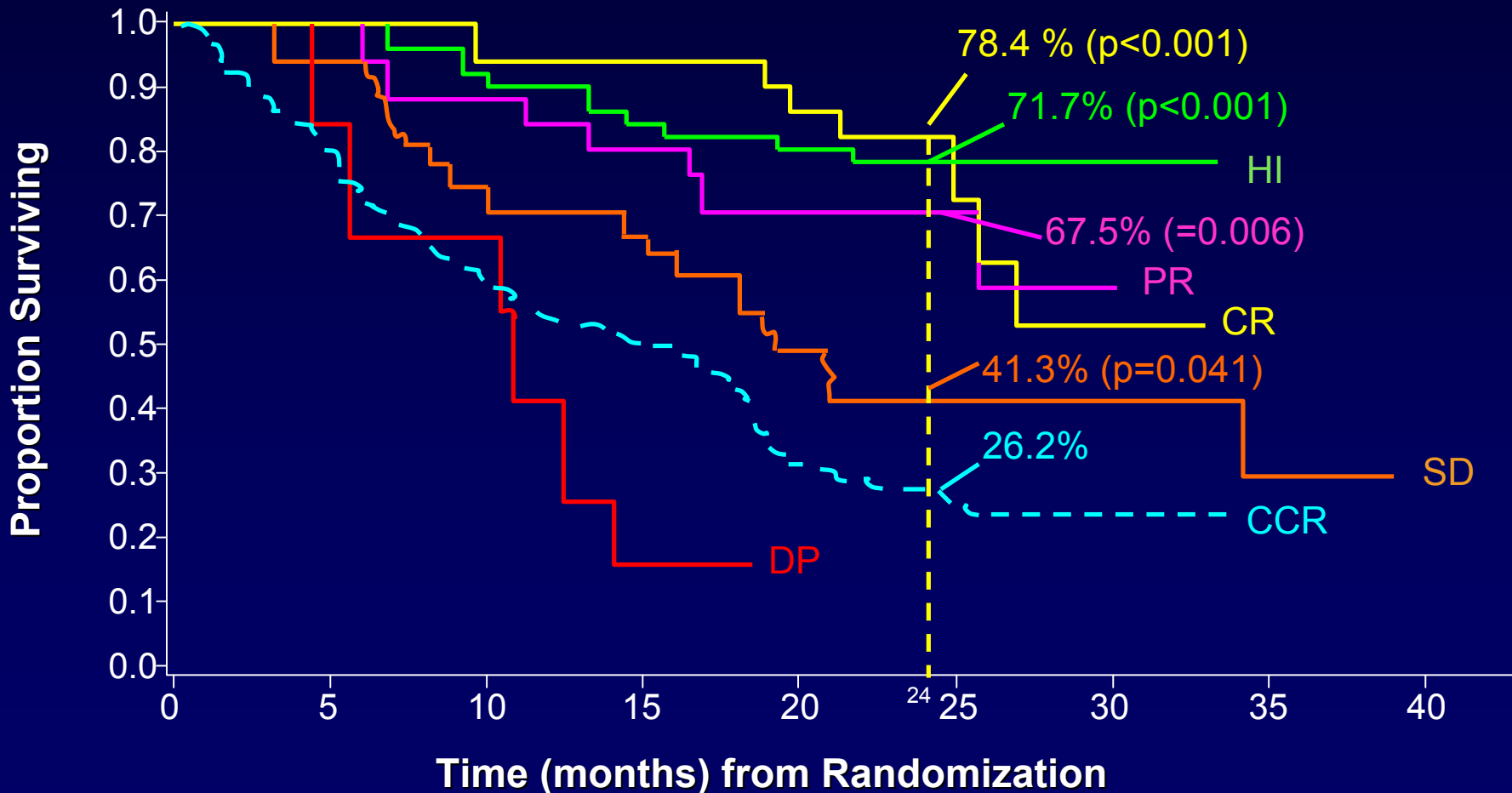
AZA-001 Phase III



5-AZA Superior in All Risk Groups



AZA vs CCR (all patients): OS according to response



Decitabine (Dacogen®)

- **Decitabine (5-aza-2'-deoxycytidine) gets incorporated into DNA and acts as a methyltransferase inhibitor**
 - promotes hypomethylation of DNA, allowing expression of previously silenced genes
 - IV, SC
- **FDA approved in USA for all subtypes**
- **Orphan drug in EU**

Trials with Decitabine

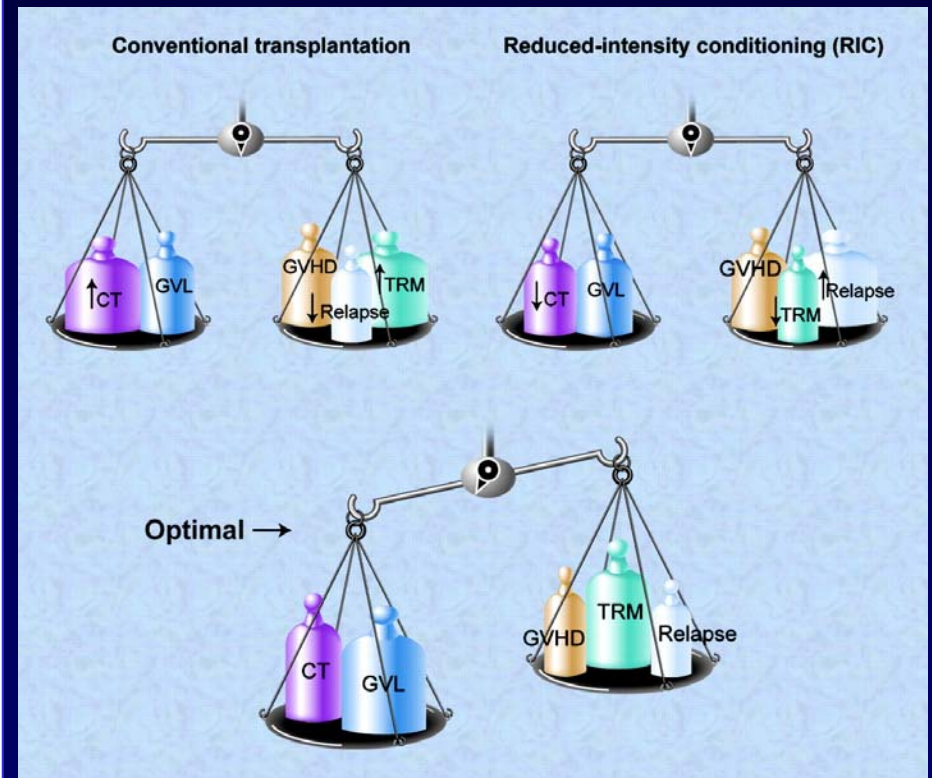
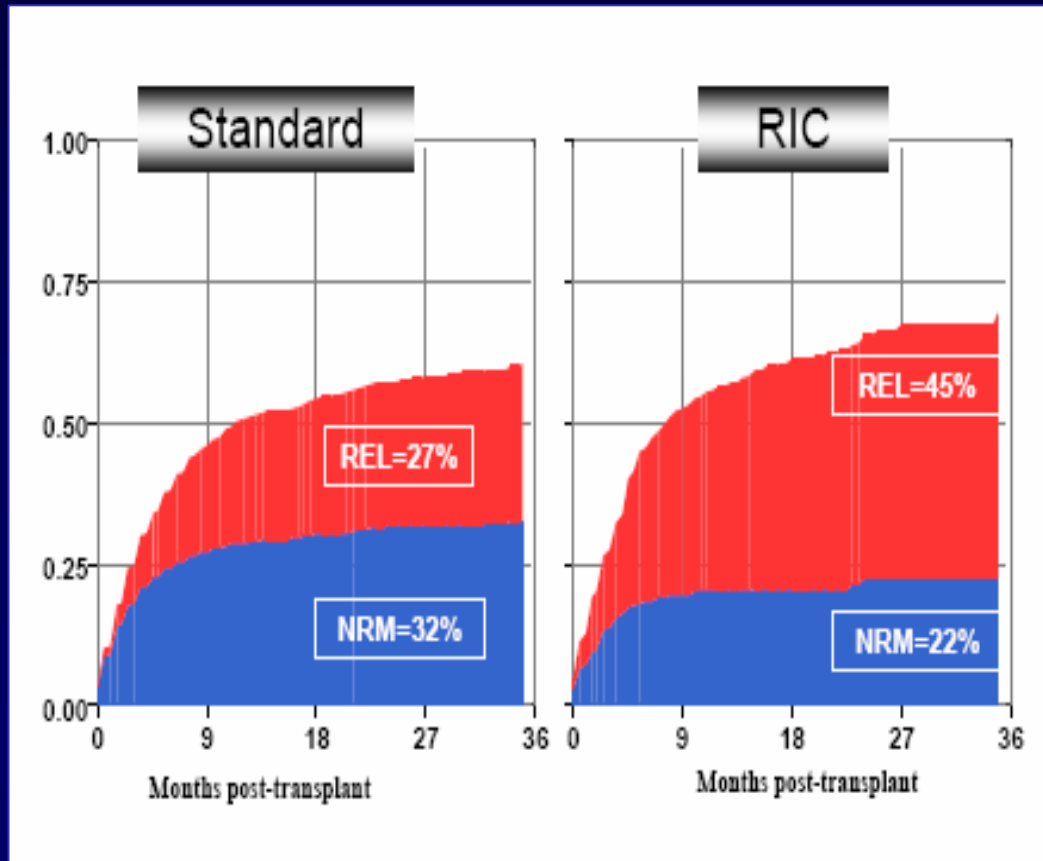
Characteristic	European phase II			US phase III
	91-01	95-11	97-19	D-0007
n	29	66	87	89
CR + PR, %	45	26	26	17
CR, %	28	21	22	9
PR, %	17	5	5	8
Hematological improvement,	7	12	15	13
% ORR	52	38	41	30
Median duration of CR + PR, days	217	250	146	288
Median no. of cycles	4	4	4	3

EORTC DAC trial

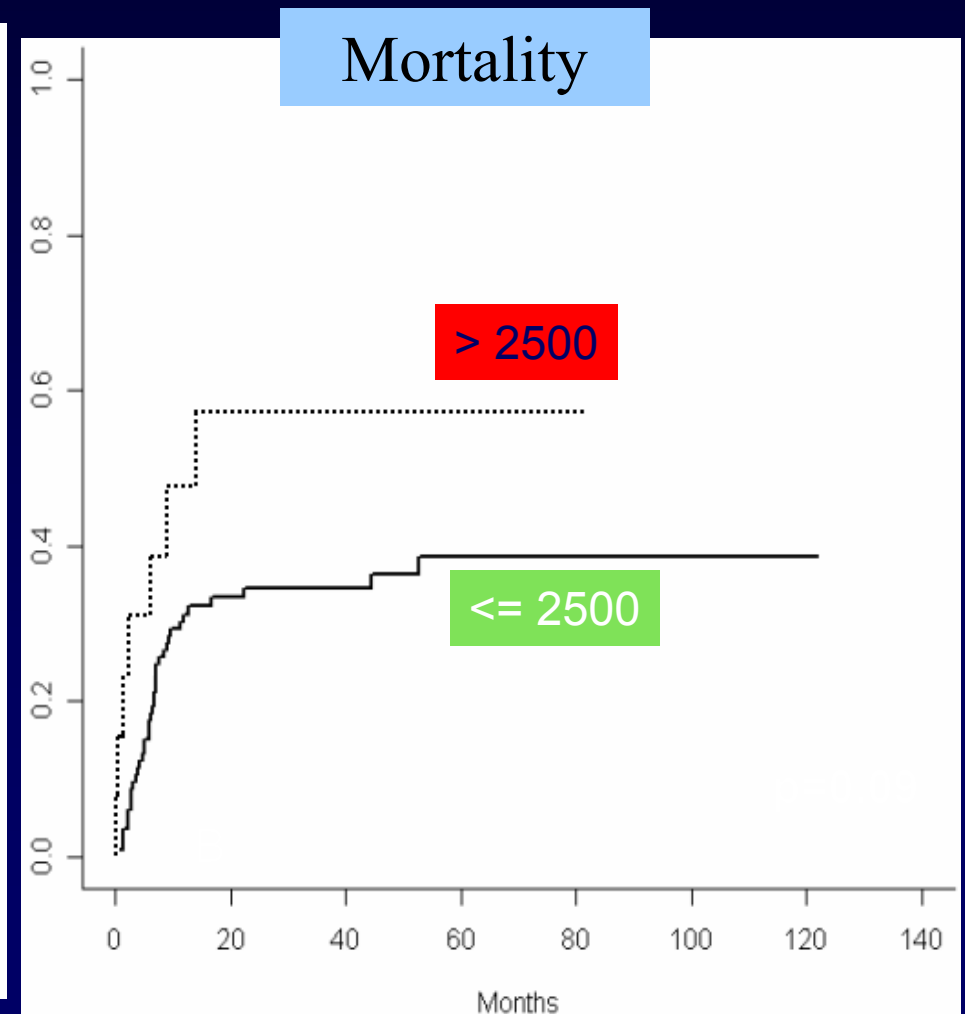
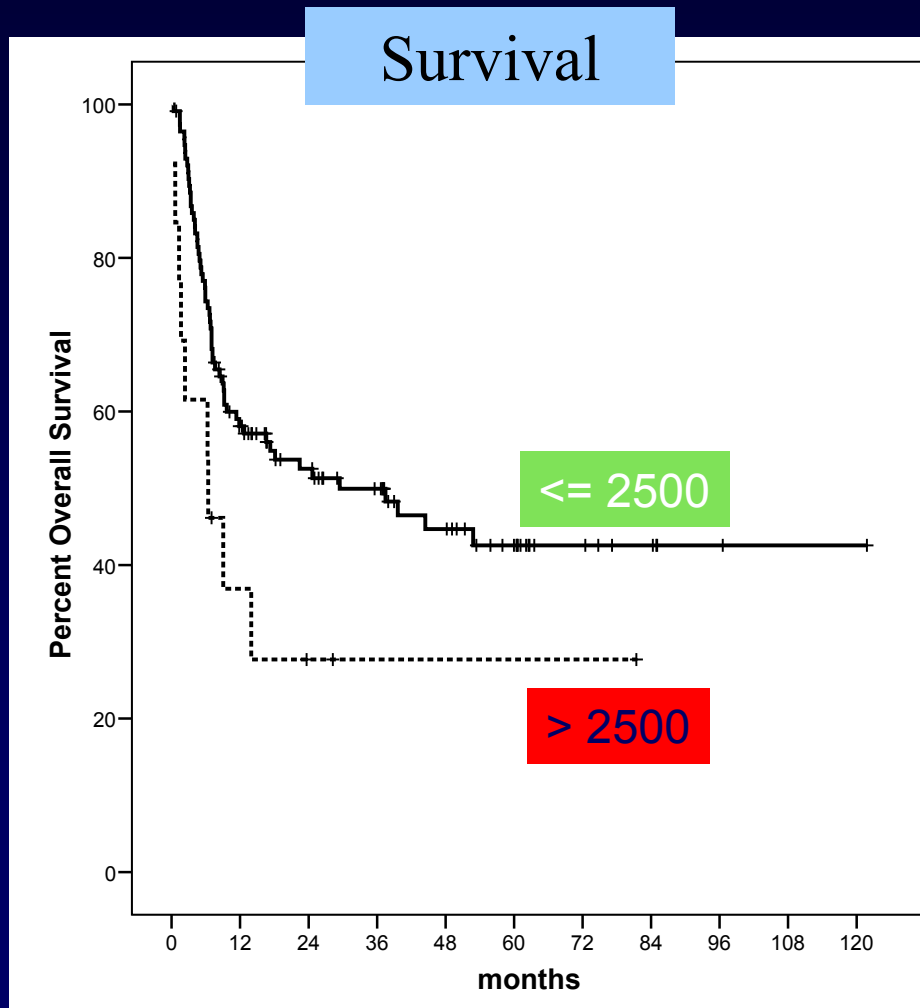
- HR MDS > 60 years
- 15 mg/m² over 4 hours tid for 3 days
- Max. 8 cycles
- Randomized vs BSC

“The data did not demonstrate a statistically significant advantage of Dacogen treatment on median survival compared to BSC, the primary endpoint of the study. However, response rates were similar to those observed in other clinical trials of Dacogen in patients with MDS”

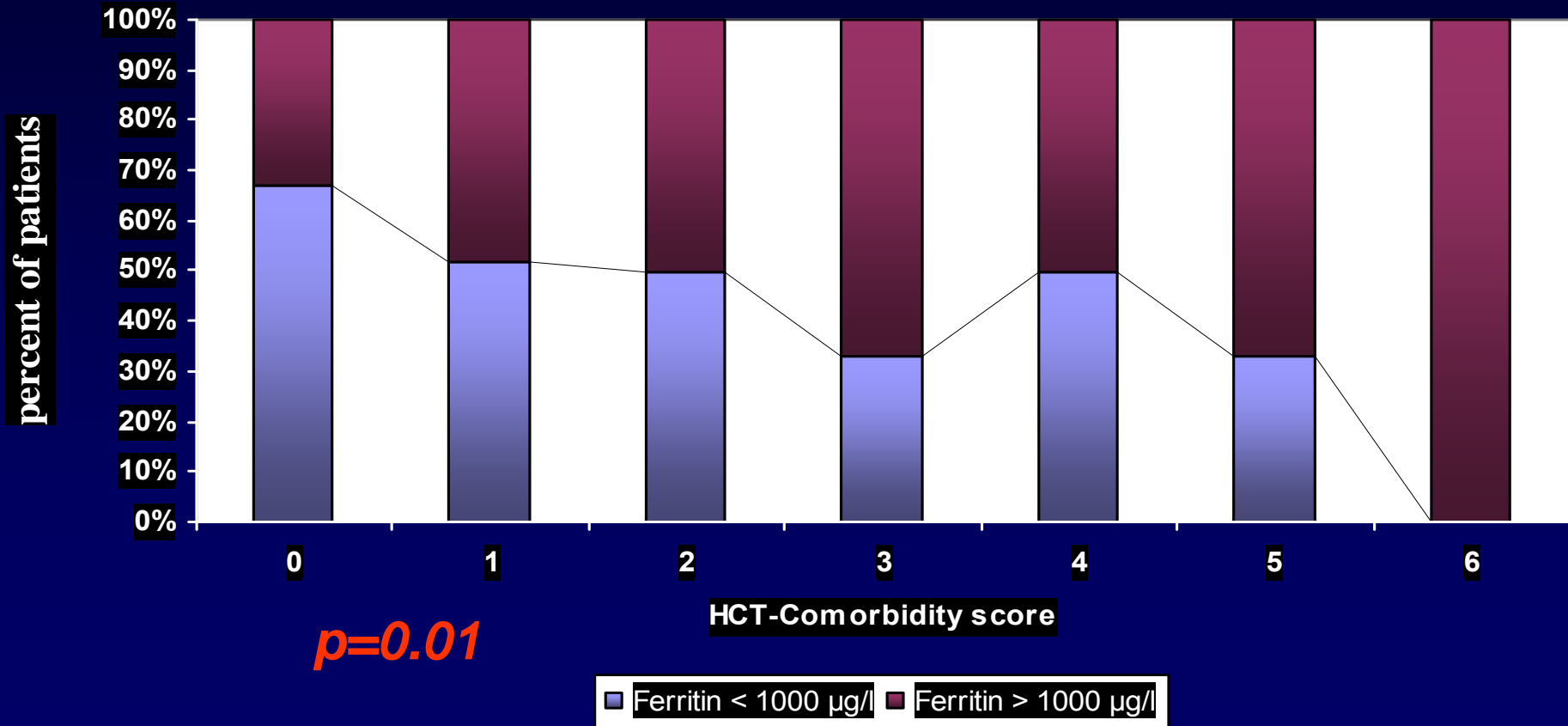
Reduced vs. Myeloablative Conditioning – Low TRM, Higher Relapse



Role of Ferritin Prior to Allo Tx with Myeloablative Conditioning in MDS



Ferritin and Comorbidity Score



At this point what else would you recommend?

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- Induction chemotherapy
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- Discontinue EPO
- Go for DNA-methyltransferase inhibitor until disease progression
- Otherwise consider inclusion into a clinical trial
- Unlikely a candidate for allo Tx (age, comorbidities)