Journal reading

-Acute Myeloid Leukemia and Myelodysplastic Syndrome in Older Adult-

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Outline

-Introduction

-Treatment trial

Induction C/T, low-intensity regimen, post-remission therapy

-Prognostic model

Myelodysplastic syndrome

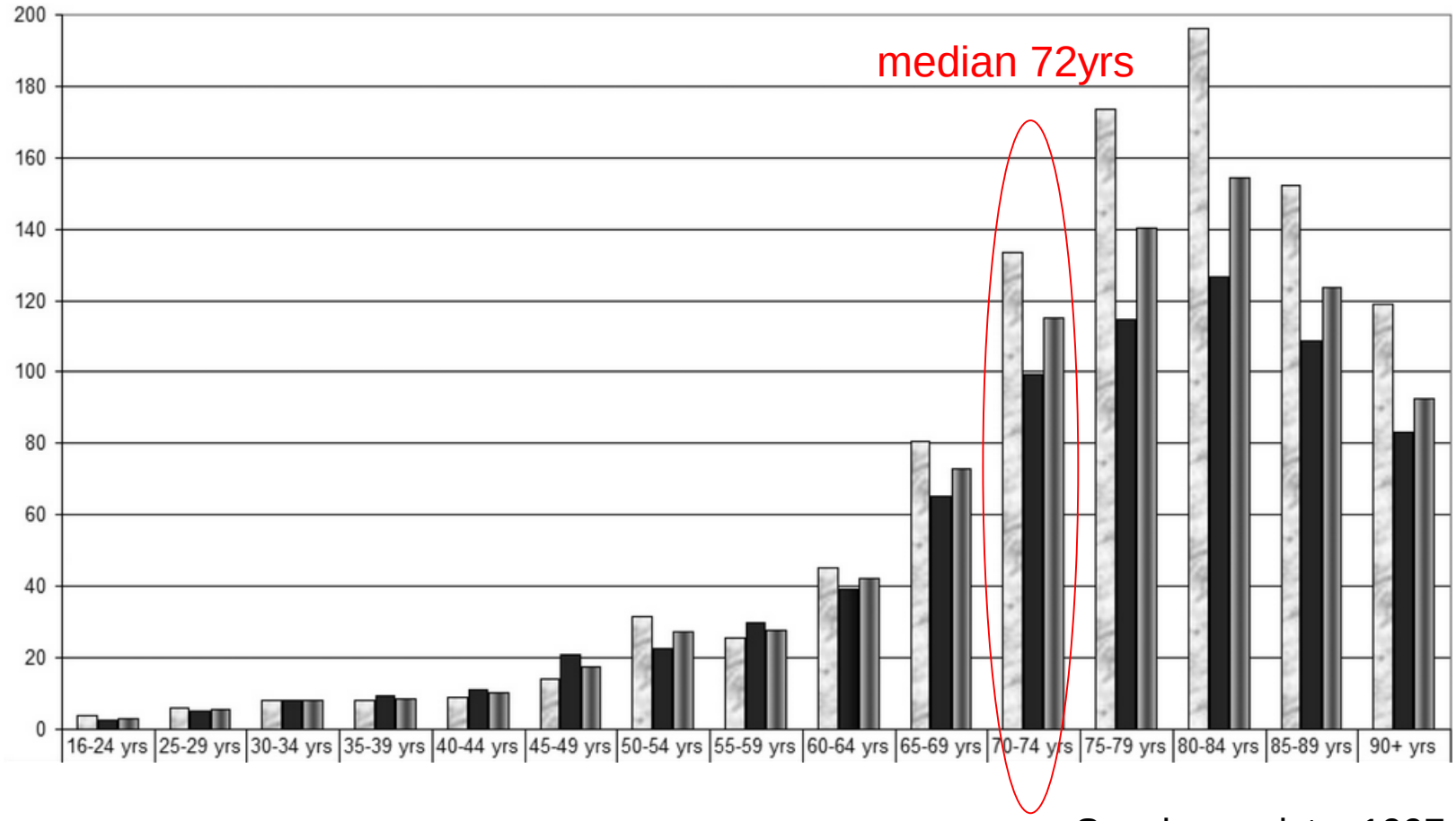
-Introduction

-Prognostic model

-Treatment trial

Azacitidine, Decitabine, Lenalidomide, HSCT

AML is predominantly a disease of elderly!



Sweden registry 1997~2005

AML[hh,fff] ≥60y

PS 0-2

Favorable cytogenetic/ molecular markers without prior MDS/therapy-related AML

Clinical trial
or
Standard-dose cytarabine (100-200 mg/m^2 continuous infusion x 7 days) with idarubicin[hhh] 12 mg/m^2 or daunorubicin[iii] 45-90 mg/m^2 x 3 days or mitoxantrone 12 mg/m^2

decitabine)[jjj]

Therapy-related AML/prior MDS or unfavorable cytogenetic/ molecular markers

Low-intensity therapy (5-azacytidine, decitabine)[jjj]
or
Intermediate-intensity therapy (clofarabine) (category 2B)[kkk]
or
Standard-dose cytarabine (100-200 mg/m^2 continuous infusion x 7 days) with idarubicin[hhh] 12 mg/m^2 or daunorubicin 45-60 mg/m^2 x 3 days or mitoxantrone 12 mg/m^2

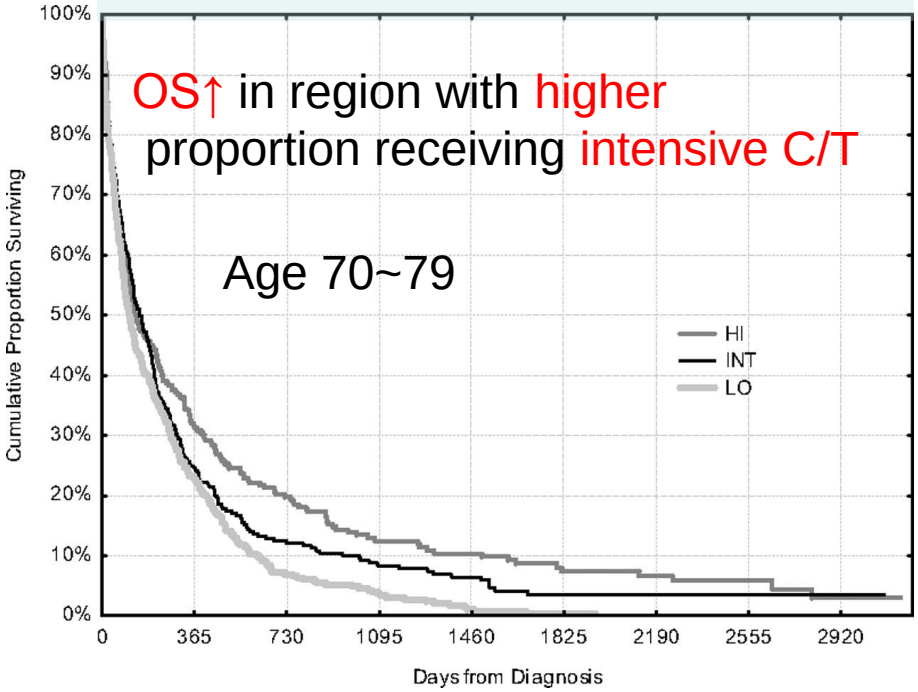
No treatment consensus in p'ts above 60yrs

C/T provide OS benefit over BSC, even among p't age > 80

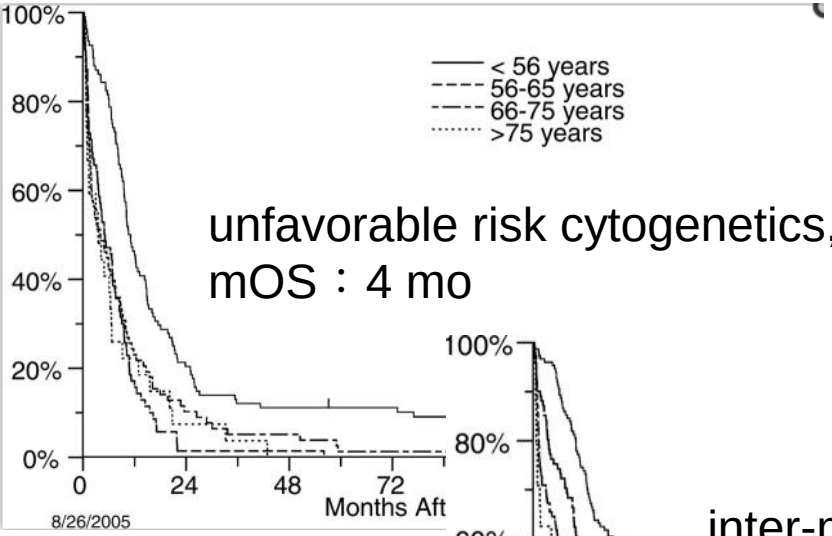
SEER data, 2000~2007

OS	Treated	Untreated
65~69	10 mo	4 mo
70~74	8 mo	3 mo
75~79	6 mo	2 mo
>80's	3 mo	1 mo

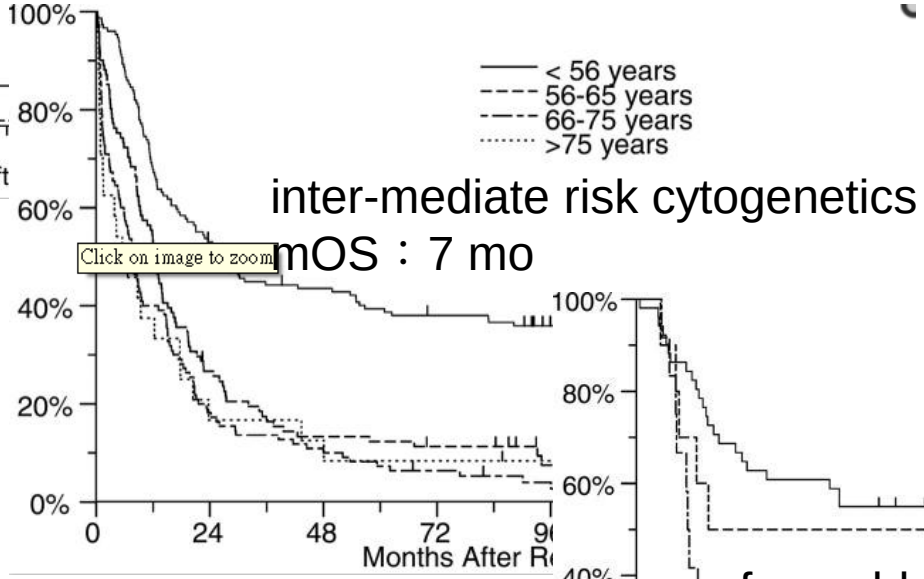
Swedish registry, 1997~2005



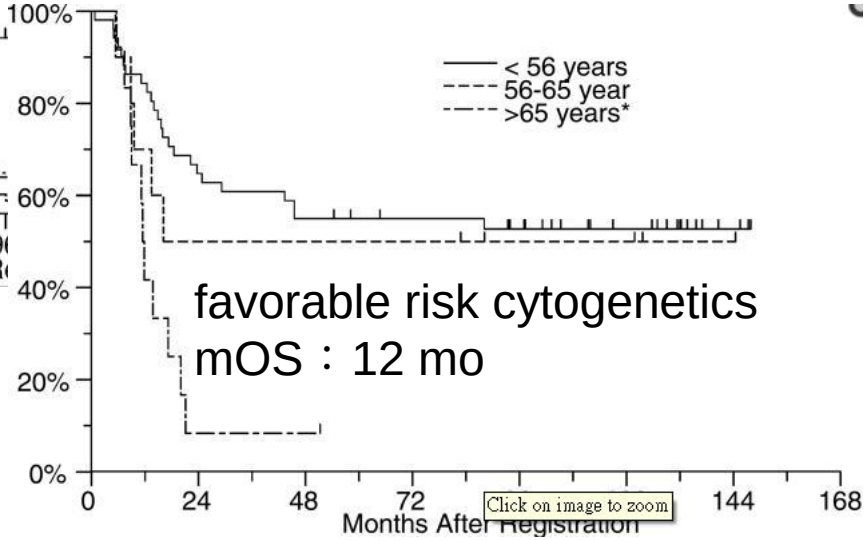
Treatment trial in elderly--SWOG trial



unfavorable risk cytogenetics,
mOS：4 mo



inter-mediate risk cytogenetics
mOS：7 mo



favorable risk cytogenetics
mOS：12 mo

Frederick R. Blood 2006

Besides treatment intolerance, what makes elderly difficult to treat？

-HSC aging =>↓lymphoid genes but↑myeloid genes
↑self renewal and potential to myeloid progenitor cell

- Leukemic blast more likely to be CD34/CD33 +/+ or -/-, translate into poorer OS

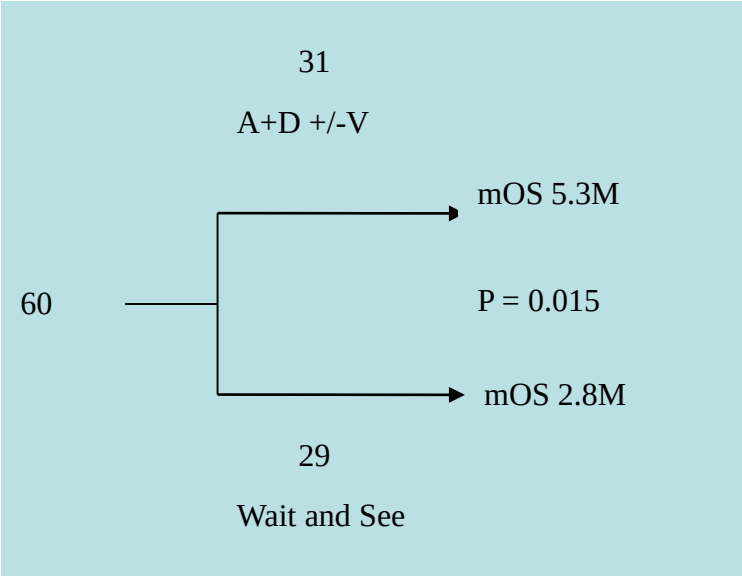
- more poor-risk karyotypes

- blast less likely apoptosis after treatment(MDR1)

Induction C/T in the elderly--IC

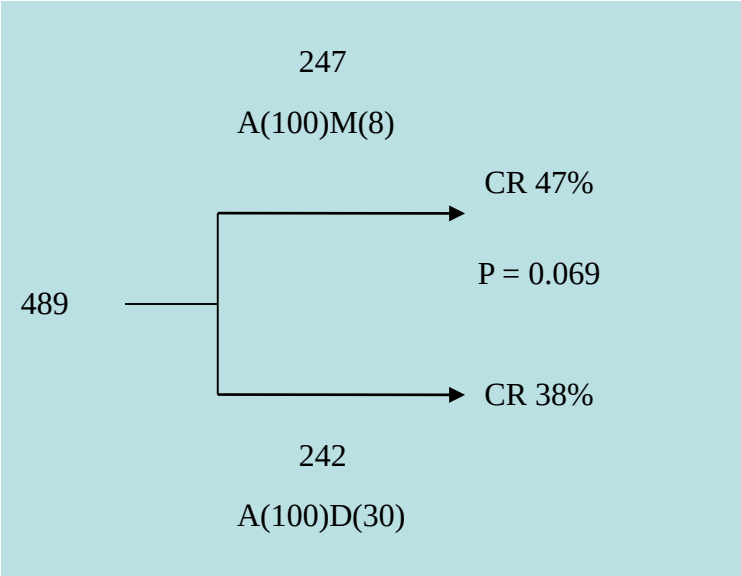
- Remission induction

C/T VS supportive care (>65's)



Lowenberg G. JCO 1989

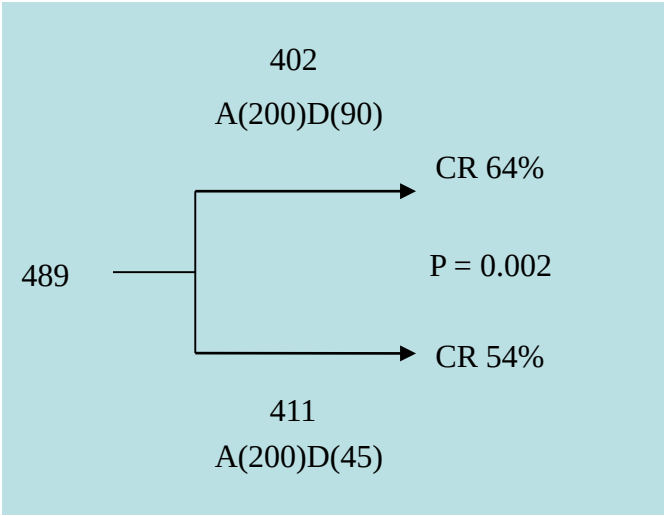
- Mitoxantron VS Daunomycin(>60's)



Lowenberg G. JCO 1998

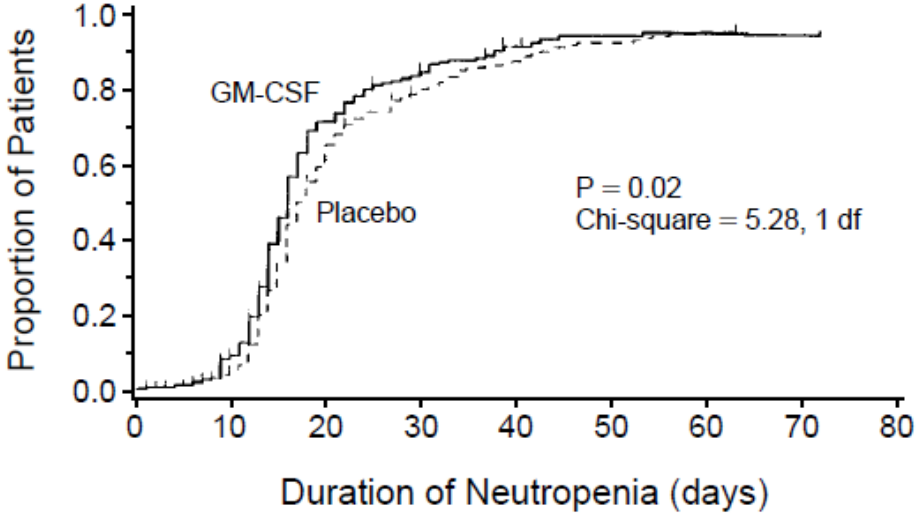
Induction C/T in the elderly--IC

- High dose Daunorubicin in elderly with AML(60's~83's)
- Benefit in age between 60's to 65's, CR(73% VS 51%), OS(38% VS 23%)

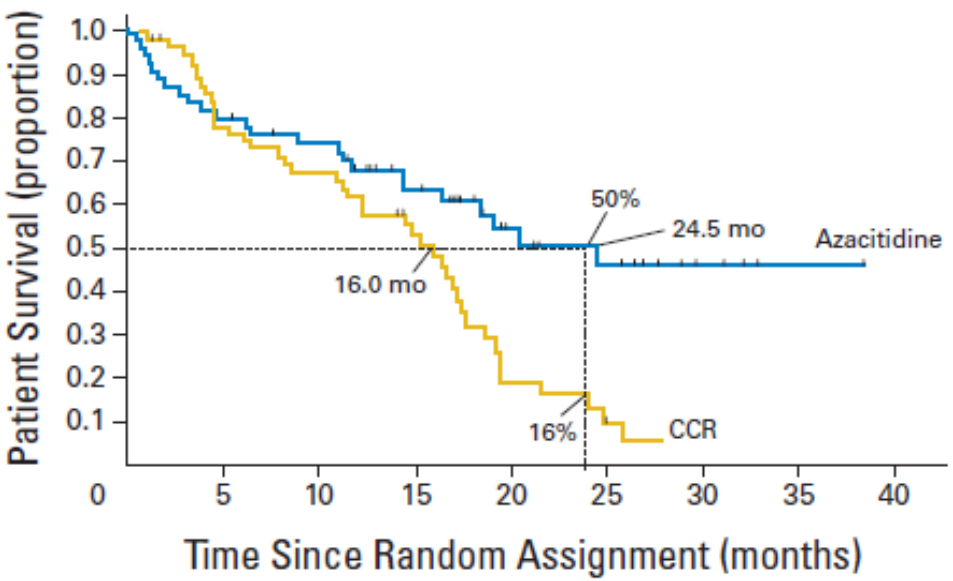


Lowenberg G. NEJM 2009

- non-selective G-CSF priming(age > 60's) did not ↑regrowth of leukemia or↑CR
- median duration of neutropenia 15d VS 17d, not translate into improvement of TRM



Low-intensity regimen



No. of patients at risk

Azacitidine	55	43	38	26	15	10	4	1	0
CCR	58	43	36	22	6	3	0	0	0

-N =113, median age > 70

-Aza(75) VS BSC

-mOS：24.5m VS 16m, P 0.005

-2yr survival：50% VS 16%, P 0.001

-↓transfusion for RBC(41% VS 18%), but not for PLA

-most common grade 3 or 4 hematological AE: Hb↓, ANC↓, PLA↓

Fenaux et al. JCO 2010

Low-intensity regimen

- Low dose Ara-C VS hydroxyurea

- 217 p't, primarily > 60's, unfit for IC

-↑remission rate(18% VS 1%),↑OS due to↑duration of CR(80wks VS 10wks)

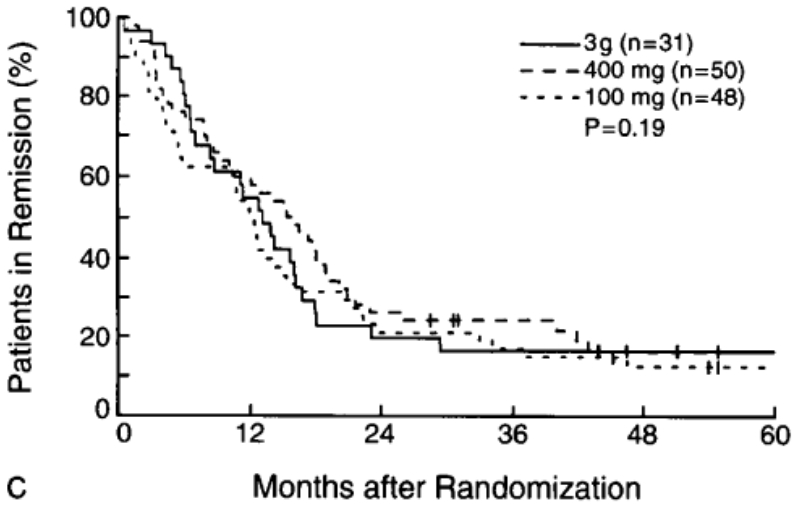
- p't with adverse cytogenetics did not benefit

Post-remission therapy

- HiDAC VS standard dose

-4yr-survival(52% VS 40%)

-no benefit in p’ts age > 60’s



Robert J. NEJM 1994

- RIC allo-HSCT in adults

-CIBMTR, N= 1080

-12% AML p’t &10% MDS p’t > 65’s

-OS and DFS were not significantly worse in older p’t

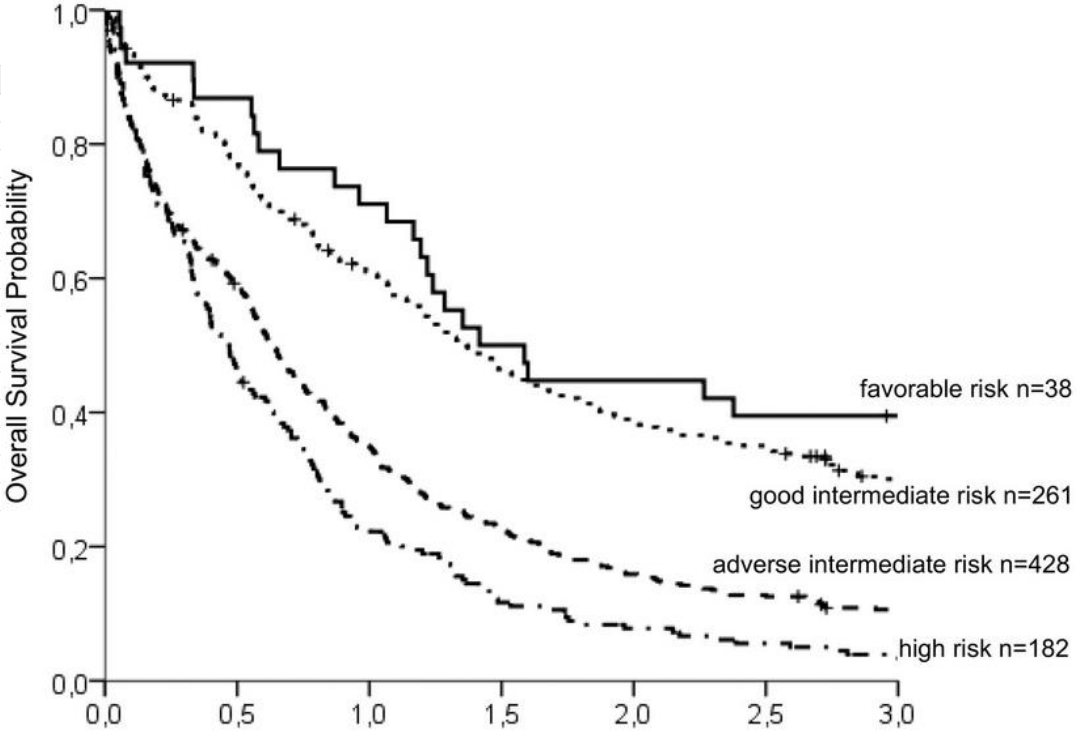
-older age alone should not be contraindication to HST

Prognostic model

-age > 60's, 1996~2004, N =909

-Karyotype, LDH, age, WBC count, CD34 expression as weighted factor

Parameter/subgroup	
CD34 expression	
Less than or equal to 10%	0
More than 10%	2
WBC	
Less than or equal to 20/μL	0
More than 20/μL	2
Age, y	
Less than or equal to 65	0
More than 65	3
LDH	
Less than or equal to 700 U/L	0
More than 700 U/L	4
***NPM1* status**	
Wild-type	0
Mutated	−2



Prognostic model

-age > 70’s, N= 446, HAD- based induction C/T

-adverse risk factor for 8-w mortality：age > 80’s, complex karyotype, Cr > 1.3, ECOG PS

No. of adverse factors	No. of patients (%)	8-wk mortality, %	CR, %	Survival		
				Median, mo	2-y, %	3-y, %
0	122 (28)	16	57	11.3	30	22
1	170 (40)	31	52	5.3	15	7
2	100 (23)	55	29	1.5	7	6
≥ 3	38 (9)	71	16	0.5	0	0

Kantajian H. Blood 2010

Prognostic model

Other predictive model

-Charlson comormidity index(CI)

-HCT-CI

Age > 55, HCT-CI most significant for OS and ED

Age < 55, karyotype most significant for OS and ED

Djunic I. Hematology 2012

-ADLs

MDS-introduction

Epidemiology

-15000~20000 US patients annually

- > 80% are age > 70's

Peter L. Blood 2012

Table 3. IPSS-R prognostic score values

Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good	—	Good	—	Intermediate	Poor	Very poor
BM blast, %	≤ 2	—	> 2%- < 5%	—	5%-10%	> 10%	—
Hemoglobin	≥ 10	—	8- < 10	< 8	—	—	—
Platelets	≥ 100	50-< 100	< 50	—	—	—	—
ANC	≥ 0.8	< 0.8	—	—	—	—	—

Table 4. IPSS-R prognostic risk categories/scores

Risk category	Risk score
Very low	≤ 1.5
Low	> 1.5-3
Intermediate	> 3-4.5
High	> 4.5-6
Very high	> 6

Table 2. MDS Cytogenetic Scoring System

Prognostic subgroups, % of patients	Cytogenetic abnormalities	Median survival,* y	Median AML evolution, 25%,* y	Hazard ratios OS/AML*	Hazard ratios OS/AML†
Very good (4%*/3%†)	−Y, del(11q)	5.4	NR	0.7/0.4	0.5/0.5
Good (72%*/66%†)	Normal, del(5q), del(12p), del(20q), double including del(5q)	4.8	9.4	1/1	1/1
Intermediate (13%*/19%†)	del(7q), +8, +19, i(17q), any other single or double independent clones	2.7	2.5	1.5/1.8	1.6/2.2
Poor (4%*/5%†)	−7, inv(3)/t(3q)/del(3q), double including −7/del(7q), complex: 3 abnormalities	1.5	1.7	2.3/2.3	2.6/3.4
Very poor (7%*/7%†)	Complex: > 3 abnormalities	0.7	0.7	3.8/3.6	4.2/4.9

Prognostic model

- IPSS-R (N = 7012, median age 71)

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(N = 7012, median age 71)

mOS from 8.8 (very low) to 0.8 years(very high)

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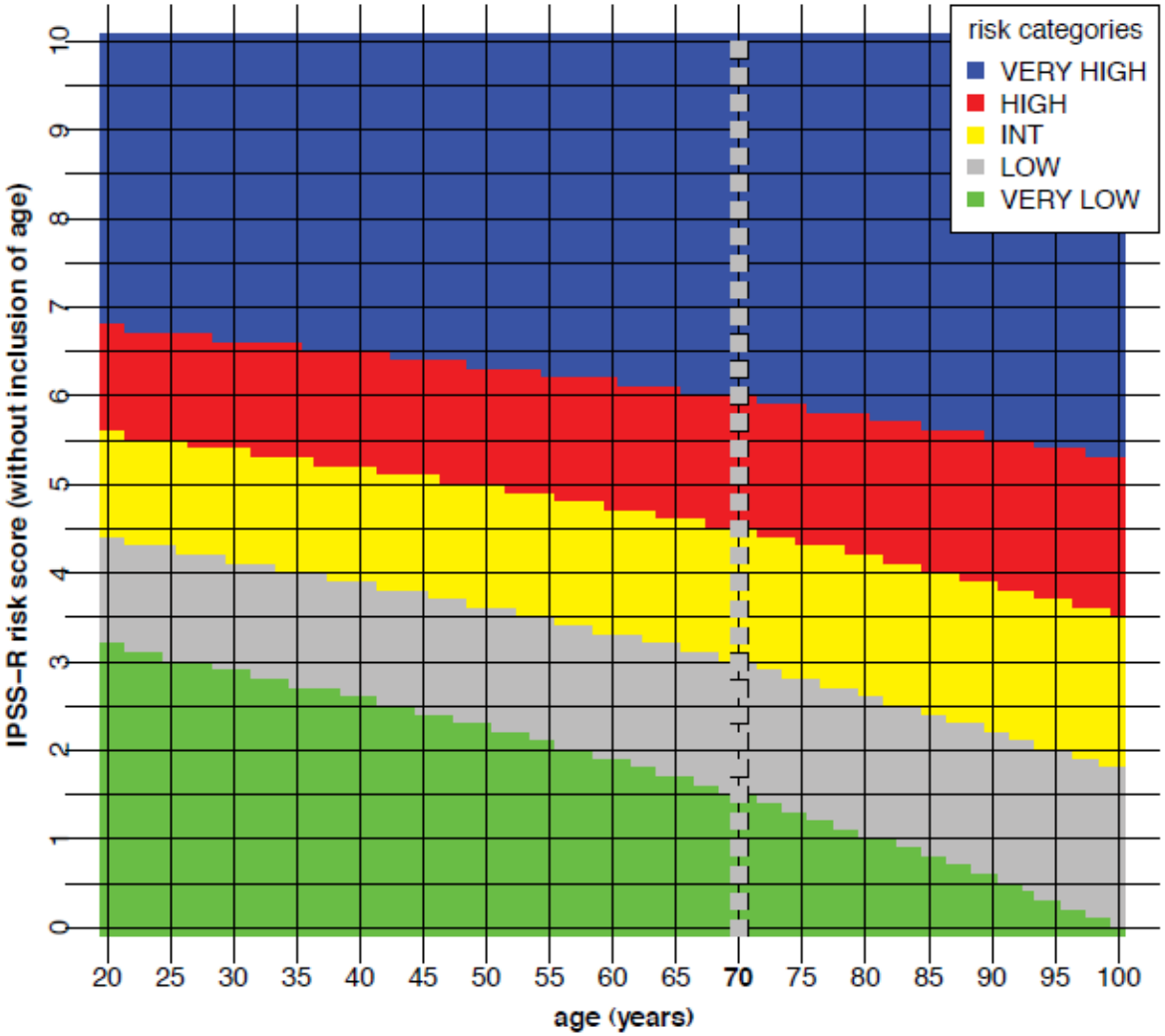
Very poor (7%*/7%†)	Complex: > 3 abnormalities	0.7	0.7	3.8/3.6	4.2/4.9

Peter L. Blood 2012

Prognostic model

Age posed more impact on lower risk group than on higher risk group



MDS-Therapy

G-CSF plus EPO support

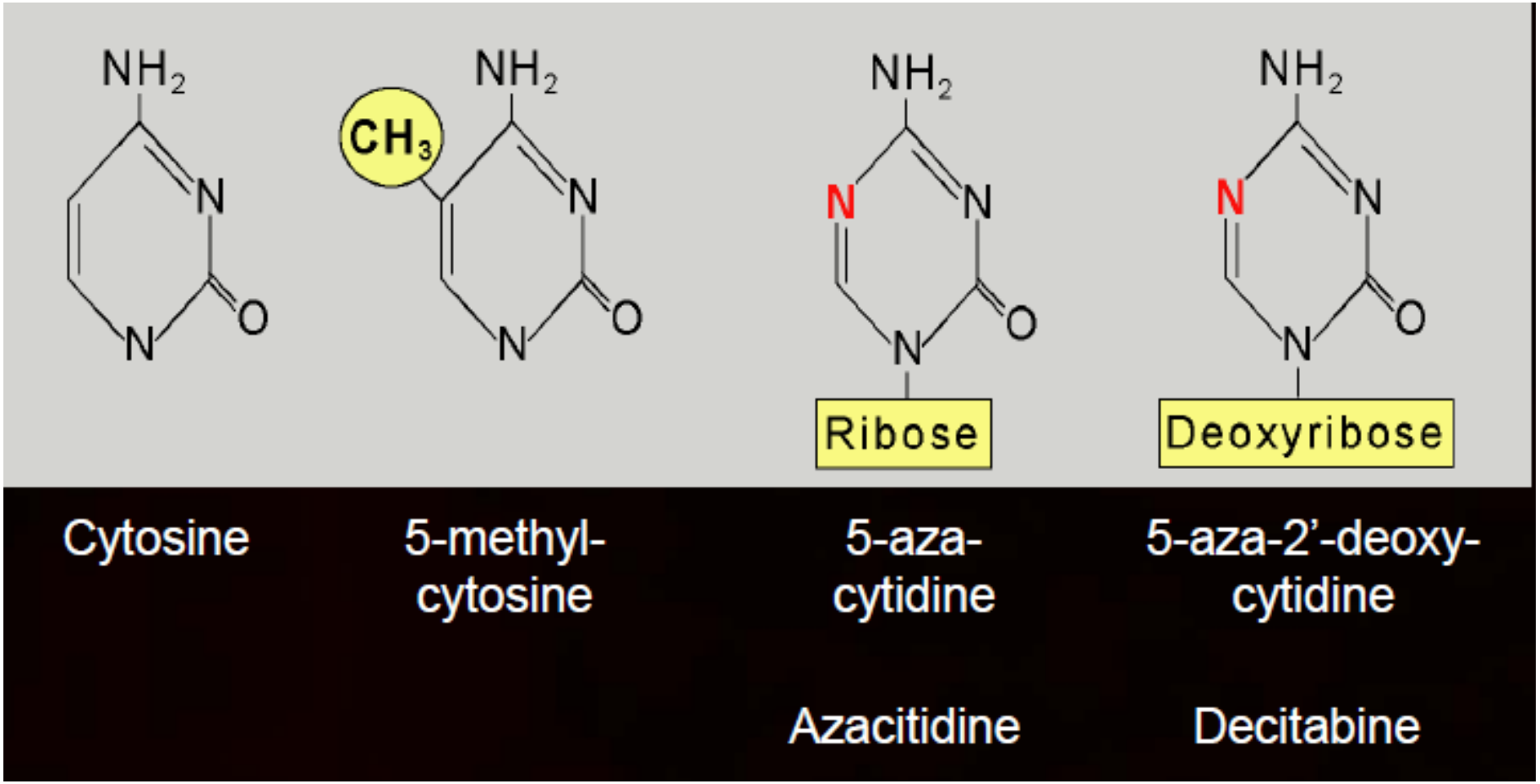
- ↑OS(HR 0.61, P 0.002) in low risk MDS p't and low transfusion demand(< PRBC 2u/month)
- not increased risk of leukemic transformation

Martin J. JCO 2008

Hypomethylating agent

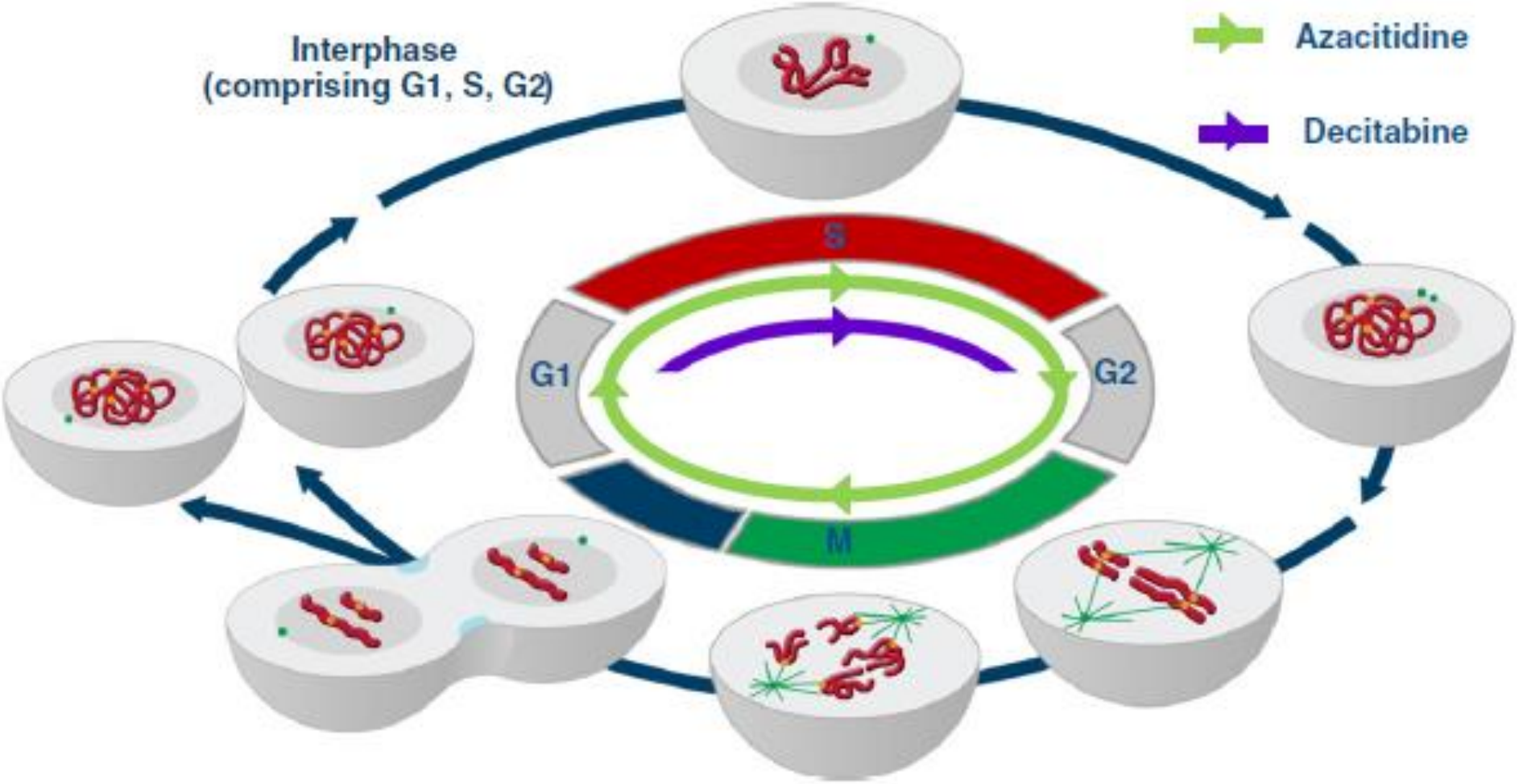
- Azacitidine
- Decitabine

Hypo-methylating agent



Santini et al, Ann int Med 2001

Hypo-methylating agent



New Science Press, Sunderland, MA; 2007.

Azacitidine

	N/mAge	group	regimen	2yr survival	AE (G3/4 neutropenia)
France Pierre F. (AZA-001 trial)	N=358 mAge 69	Int-2/high risk MDS (35% AML)	AZA(75) VS CCR	51% VS 26%	90%
USA John F.	N=87 All > 75yrs	Int-2/high risk MDS (1/3 AML)	AZA(75) VS CCR	55% VS 15%	61%
Spanish Xicoy B.	N=107 All > 75yrs	55% Int-2/ high risk MDS, 6% AML	Variable AZA regimen	34%, (40% TI)	29% delay cycle

AZA-AML-001 Study

- Vidaza for elderly AML, blast > 30%

- age > 65's , N = 448
- Aza(75) VS CCR
- OS：12.1 VS 6.9m(P=0.019)
- 1yr-survival 47% VS 34%
- AE

Grade III or IV AE	Hb↓	ANC↓	Febrile neutropenia	PLA↓
BSC	5%	5%	28%	5%
AZA	16%	26%	28%	24%
LDAC	23%	25%	30%	28%
IC	14%	33%	31%	21%

Decitabine

DACO-16 study

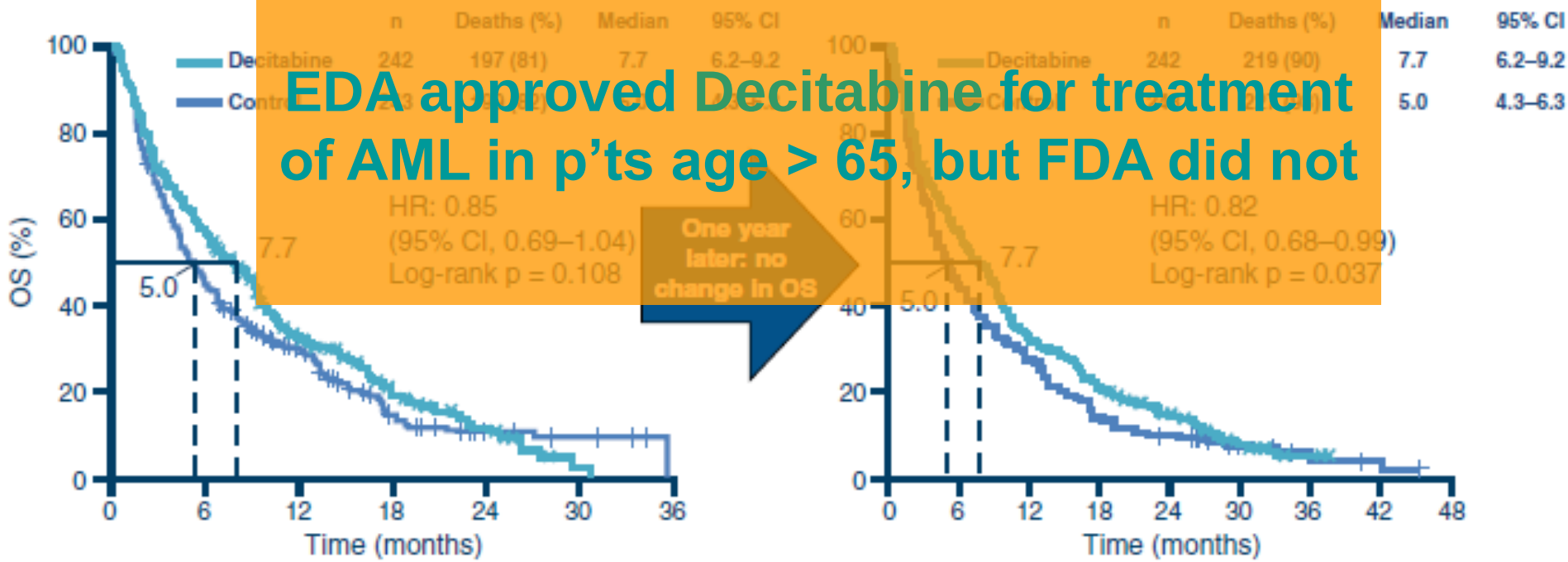
- Inclusion：N=485, age > 65’s, PS 0~2
- Decitabine(20) VS CCR(LDAC & BSC)
- CR plus CRp：17.8% VS 7.8%
- mOS：7.7m VS 5.0m(HR 0.85, P 0.108→HR 0.82, P 0.037 after 1yr)

Decitabine

DACO-16 study

Prespecified analysis in study protocol: October 2009

Unplanned ad-hoc exploratory analysis: October 2010



EDA approved Decitabine for treatment of AML in p'ts age > 65, but FDA did not

Lenalidomide

MDS-003 study, a phase 2 trial, N=148

-↓transfusion need(76%) in Low/Int-1 risk MDS p’ts with del(5q)

- 67% transfusion dependence, median duration 2.4 yrs

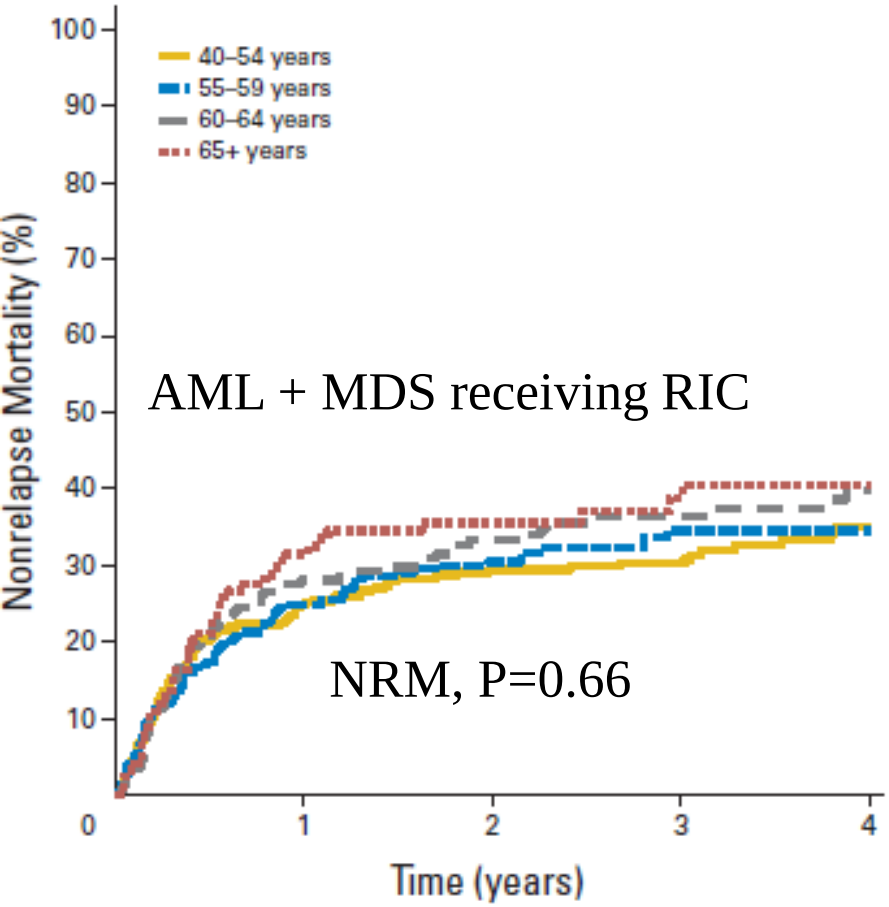
- Median time to response：4.6 wks

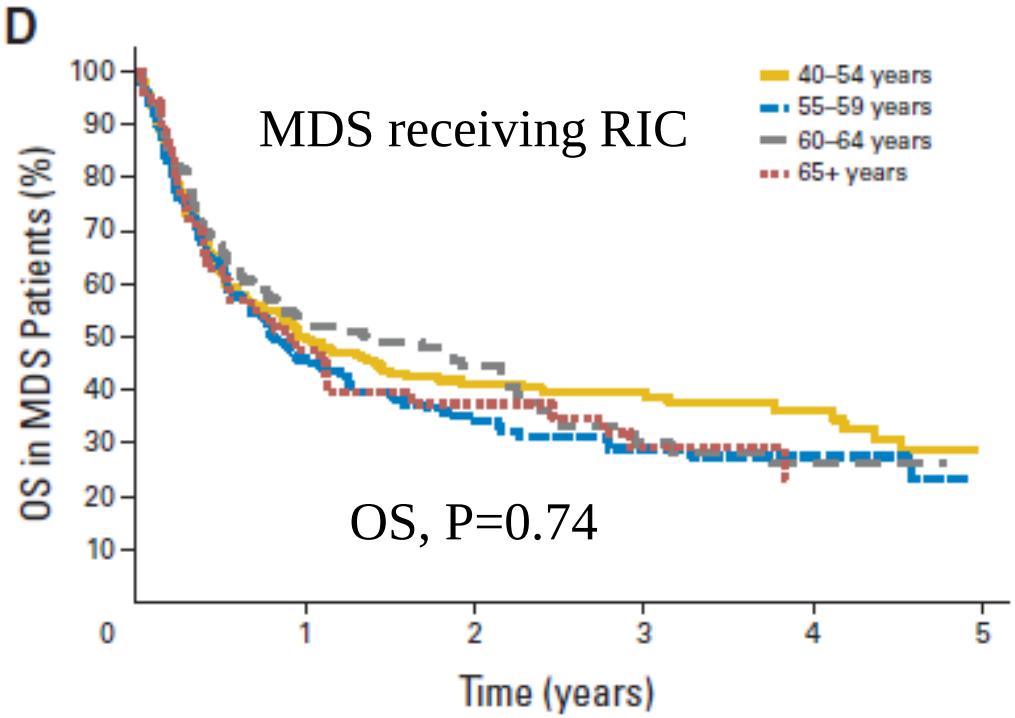
- AE：myelosuppression, 84% p’ts need dose reduction

NEJM 2006

HSCT in the elderly

CIBMTR(1995~2005, N=1080)

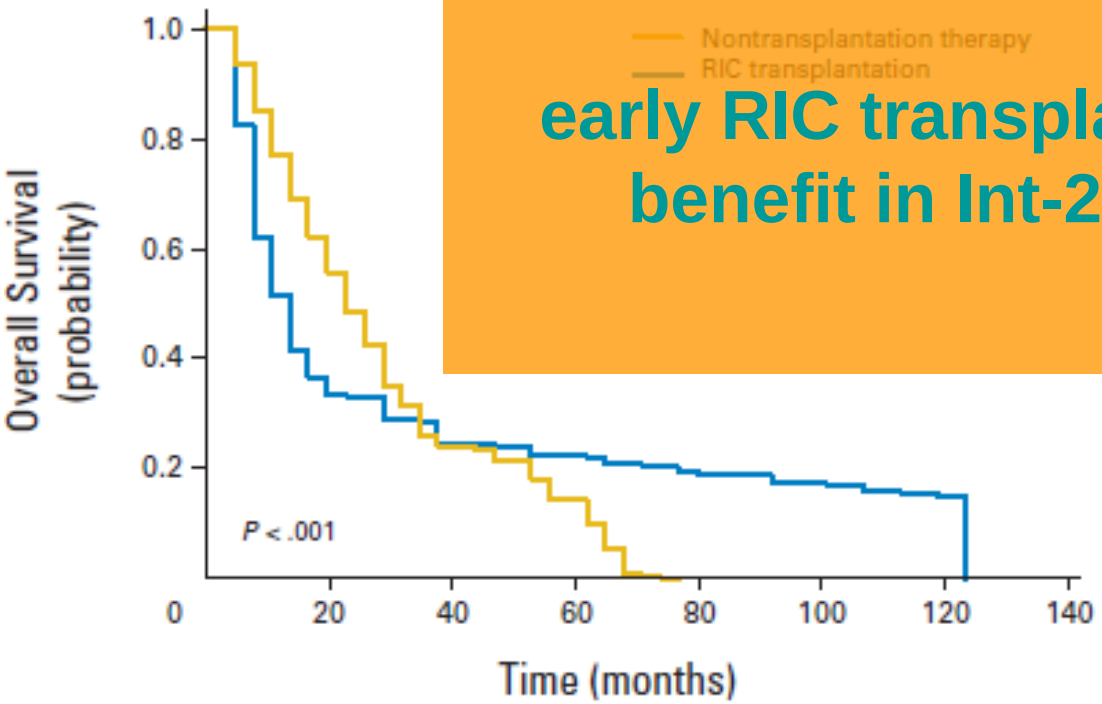




HSCT in the elderly

CIBMTR, DFCI, FHCRC

-Inclusion：N=514, age 60~70, De Novo MDS



early RIC transplant offers survival benefit in Int-2/high IPSS MDS

Koreth J. JCO 2013

Unresolved problem

- Trial targeting less fit patients not been addressed
- Optimal duration of therapies to balance disease control and QoL
- Timing to begin treatment in lower-risk patients
- The role of transplantation needs to be further defined

Thanks for your attention