TREATMENT OF ADULT AML

Jean-Luc Harousseau

On behalf of the GOELAM

1) Induction treatment

2) Prognostic factors

3) Post-remission therapy

4) Novel agents

5) Elderly patients

INDUCTION TREATMENT

Gold standard **DNR + ARA-C**
3 + 7

Variables

- **Doses of DNR (40-50mg/m² vs 60-90mg/m²)**
- **IDR vs DNR**
- **Doses of ARA-C (100mg/m² vs 200mg/m²)**
- **Duration of ARA-C Tx (7D vs 10D)**
- **Addition of 6 TG or VP 16 (DAT,TAD,ADE…)**

INDUCTION TREATMENT

In patients with de novo AML and up to 60 years of age

1) Thanks to improvement in supportive care (antibiotics, antifungal agents, transfusions…) toxic death rate is usely < 5%

2) CR rate is currently 80-85%

- to show significant improvement would need large number of patients

-but varies according to cytogenetics

CR RATE ACCORDING TO CYTOGENETICS

MRC experience *(A. Burnett)*

Cytogenetics	N	CR (%)
t(8;21)	332	98
Inv (16) / t(16;16)	193	92
Normal	1066	88
+8	210	82
t(11q23)	212	88
abn 5 or 7	276	64

INDUCTION TREATMENT

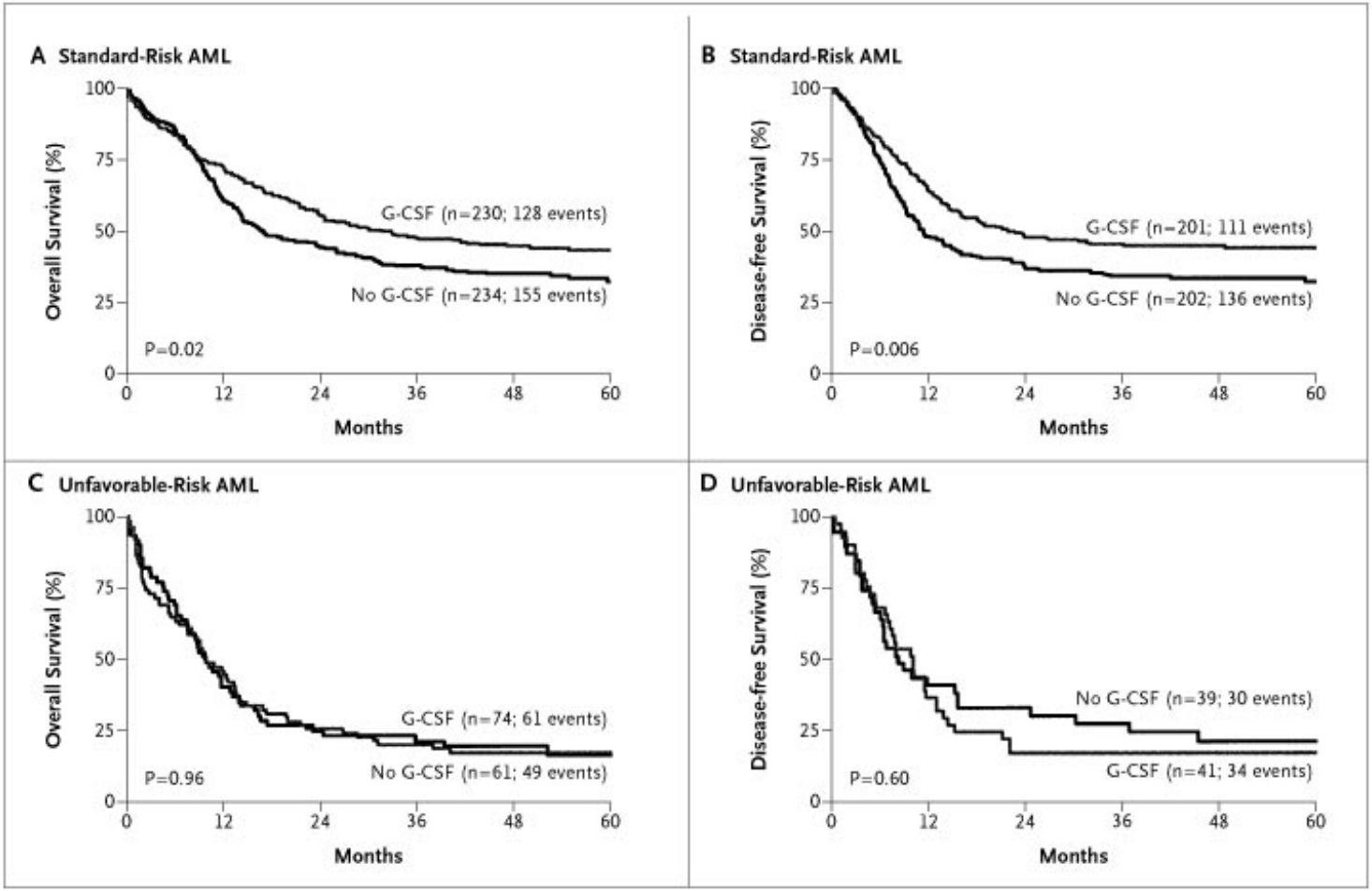
- Myeloid growth factors
- mdr modulation
- High dose ARA-C
- Timing of 2nd course
- Addition of novel agents (Mylotarg) ?

MYELOID GROWTH FACTORS

- After induction treatment
  - reduction of time to neutrophil recovery (2-6 D)
  - usually reduction of the hospitalisation duration
  - no impact on outcome

- Priming
  - 9 randomized studies with G-CSF and GM-CSF
  - Witz *(Blood 98)* 2 y DFS in pts aged 55-65
  - Lowenberg *(NEJM 03)* 4-yr DFS and OS ↗
    in standard risk AML

G-CSF PRIMING DURING INDUCTION THERAPY



Löwenberg *et al. New Engl J Med* 2003;349:743–52

MDR MODULATION

- **Pgp expression** is associated with power outcome *(Marie 91, Pirker 91, Campas 92)*
  - with other adverse prognostic factors
  - is frequent in elderly patients

- **Mdr modifiers**
  - only one positive study with cyclosporine in high-risk AML (List 2001) but 3 negative
  - 3 randomized studies with PSC-833 were prematurely stopped

GOELAM2 TRIAL

- 425 pts aged 15-60

- Quinine 300mg/kg during induction and 2 intensive consolidations
    - no difference in CR, DFS or SV
    - in a subgroup of 54 patients with positive rhodamine efflux : 85% CR with quinine vs 48%

-mdr modifiers could be useful in pts with functional pgp

HIGH-DOSE ARA-C

	BISHOP Blood 96		Weick Blood 96	
	301 pts 15-60 y denovo		493 pts < 65 y De novo ou secondary	
	BD 100mg/m²/ CI x7	HD 3g/m² (J1,3,5,7)	SD 200mg/m²/ CIx7	HD 2g/m²x2 J1-6
% CR	74	71	58	55
CR Med dur	12 m	45 m		
5-yr DFS (%)	24	49	< 50y 21 50-64 9	33 21
5-yr SV (%)	25	31	< 50y 22 50-64 11	32 13

TIMING OF 2nd COURSE

- At the end of aplasia (or on D 30)

- According to bone marrow evaluation on D 15

- Intensive *(Büchner 99, Woods 96, Castaigne 04)*
    - Timed sequential
    - Double induction

1) Induction treatment

2) Prognostic factors

3) Post-remission therapy

4) Novel agents

5) Elderly patients

PROGNOSTIC FACTORS

- Related to the patient
    - PS
    - age (+++)
- Related to ATCD (de novo / secondary)
- Related to initial characteristics
    - Tumor load (clinical, WBC, LDH)
    - Cytologic (M3, M2-M4 / M6-M7)
    - Phenotype (CD34, pgp)
    - Cytogenetics (+++)
    - Molecular biology
- Treatment
    - CR in 2 courses
    - D15 bone marrow blasts

PROGNOSTIC IMPACT OF KARYOTYPE

	Pts	Favorable	Intermediate	unfavorable
MRC	1612	t(8;21) t(15;17) inv(16)	All others Including 11q23 Abnormalities	Complex -5, (del 5q) -7 abnormalities of 3q
EBMT	999	t(8;21) Abnormalities of 16	t(15;17) Pseudidiploid hyperdiploid or diploid	Abnormalities of 5 and/or 7 Abnormalities of 11q hypodiploid
SWOG/ECOG	609	Abnormalities of 16 t(8;21)	Normal +8, -y, +6, del (12p)	-5, del (5q) -7, del (7a) Inv 3 Complex abnormalities of 11q, 20q, 21q Del (9q) t(6;9), t(9;22) Abn 17p

Outcome according to hierarchical cytogenetic classification

	n	CR (%)	ID (%)	RD (%)	RR (%,5yrs)	OS (5yrs)
t(15;17)	569	88	11**	2**	23**	69**
t(8;21)	332	98**	2**	0**	22**	70**
inv(16)/t(16;16)	193	92*	8	0*	35*	61*
t(9;22)	31	71**	6	23**	92**	5**
t(6;9)	28	82	4	14	84**	30
t(11q23)	212	88	7	5	50	46
inv(3)/t(3;3)	44	35**	19	47**	80**	6**
t(3;5)	21	95	5	0	47	43
t(12p13)	25	48**	16	36**	63	25**
abn(11p13~5)	22	91	5	5	33	49
t(8p11)	13	92	0	8	21	66
normal	1066	88	7	5	48	45

**p<0.01, **p<0.001,* Chi-squared test or Fisher exact test (CR/ID/RD), log rank test (RR & OS)

Outcome according to hierarchical cytogenetic classification

	n	CR (%)	ID (%)	RD (%)	RR (%,5yrs)	OS (5yrs)
abn(16q22~24)	35	83	11	6	40	46
-5/5q/-7/7q	276	64**	9	27**	70**	16**
7q, no adverse	45	91	2	7	57	30
+4	30	90	10	0	73	18*
+11	28	70**	4	26**	70	20*
+8	210	82*	6	12	53	37**
del(9q)	36	91	9	0	37	47
+21	47	81	5	14	73	38
del(11)(q23)	24	87	9	4	79**	26
abn(3q)	25	67*	14	19	89**	8**
Other	373	78**	12*	11	48	37*
normal	1066	88	7	5	48	45

**p<0.01, **p<0.001,* Chi-squared test or Fisher exact test (CR/ID/RD), log rank test (RR & OS)

CBF AML

Cytogen abn	t(8;21)	Inv(16) t(16;16)
Fusion gene	AML_1/ETO	CFBβ/MYH_{11}
FAB	M_2	M_4eo
Frequency	7-8 %	4 %

Rare after 60 years

t(8;21) PROGNOSIS

	N	CR (%)	OS 5 y (%)
MRC*	332	92**	70
Bloomfield	84	89	50
N'Guyen	161	96	59

* AML_{10} et AML_{12} (3453 pts)
** 2% induction deaths

PROGNOSIS inv(16)/t(16;16)

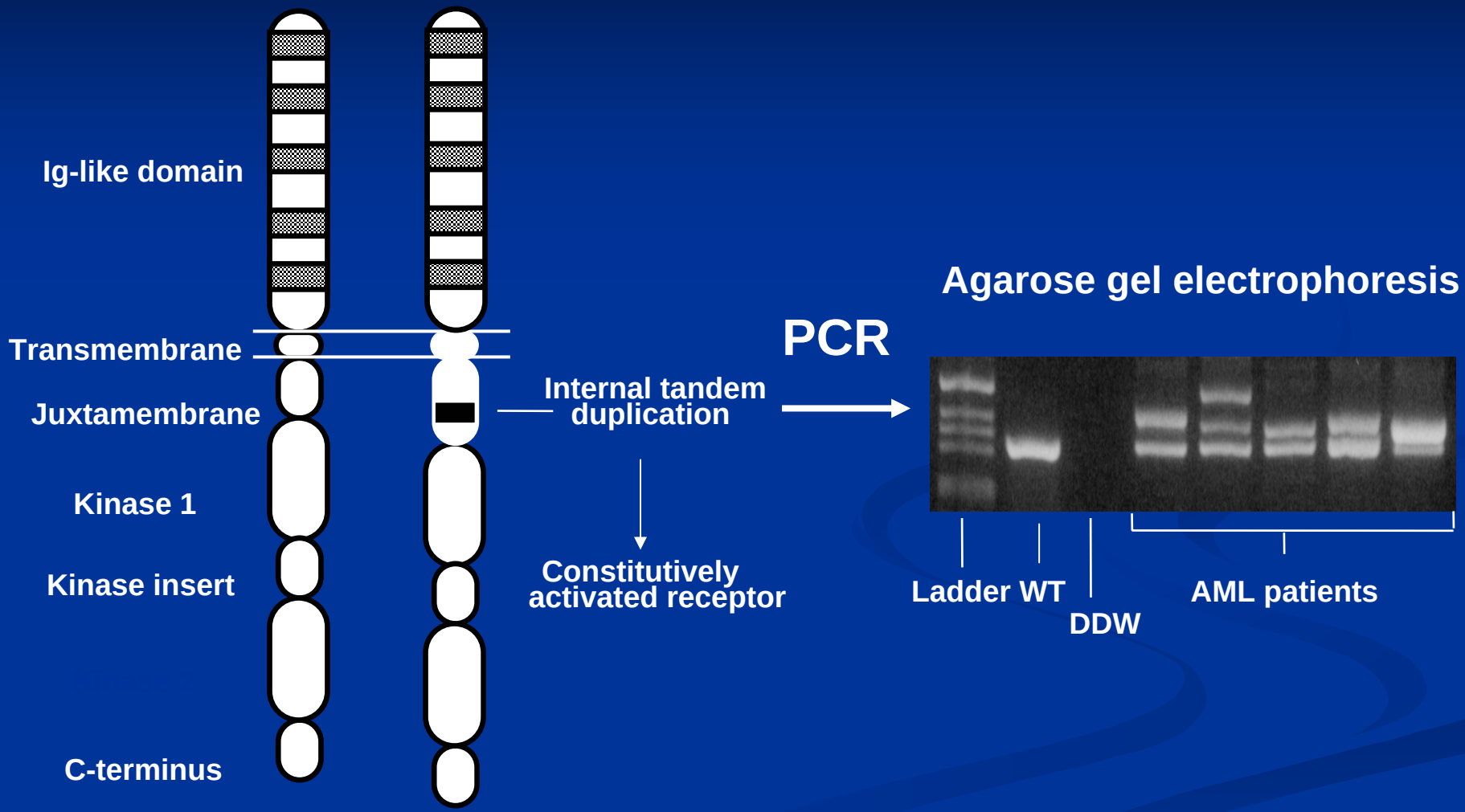
	N	CR (%)	PR (%)	OS (%)
MRC*	193	92**	35	61
Delaunay	110	93	42	58

*AML_{10} et AML_{12} (3453 pts)
** 8% induction deaths

PROGNOSTIC FACTORS in CBF AML

- t(8;21) - Age *(Grimwade Blood 2001)*
  - EM involvement *(Byrd JCO 97)*
  - CD56 positivity *(Baer Blood 97)*
  - WBC *(O'Brien Blood 89)* *(N'Guyen Blood 02)*
- inv (16) - Age
  - Platelets (Delaunay Blood 03)
- Both - KIT mutations (mut KIT 17 and 8) (Paschka JCO 06)

Internal tandem duplication of the FLT3 gene



FLT-3 TANDEM DUPLICATIONS

	N of cases	% with FLT-3 TD	CR%*	Inferior OS*	Inferior EFS*
Kiyoi 99	201	23	-	0.008	0.006
Kottaridis 01	854	27	78 vs 84	0.001	0.001
Schnittger 02	1003	20	70 vs 70	NS	0.007
Thiede 02	979	20	71 vs 67	NS	NS
Frohling 02	224**	32	65 vs 76	0.0001	0.007

* Compared to AML without FLT-3 TD
** with normal cytogenetics

NPM MUTATIONS

- Recently described *(Falini NEJM 2001)*
- The most frequent molecular abnormality in AML (30%)
- At least 15 different mutations (3 of them : 95% of cases)
- Found in 50% of patients with normal karyotype
- Correlation between NPM mutations and cytoplasmic NPM expression on paraffin-embedded biopsies (Falini Blood 2006)

- Can be used to evaluate MRD (RQ-PCR) *(Schnittger ASH 2005, Thiele ASH 2005, Saglio ASH 2005)*

NPM MUTATIONS

- Associated with higher WBC counts and with FLT3-ITD
-In multivariate analysis,associated with

FAVORABLE OUTCOME

- *higher CR rate*
- *longer EFS and RFS*
- *longer OS*

(Verhaak Blood 05,Schnittger Blood 05,K.Dohner Blood 05,Bardet Leukemia 06)

-But only IN THE ABSENCE of Flt3 ITD
- Impact on the indication of Allo SCT ?

NEW GENETIC PROGNOSTIC FACTORS

	Frequency	Prognosis	Author
P53 mutation	4.5%	UNF	*Nakano 2000*
MLL PTD	8% (normal karyotype)	UNF	*Döhner 2002*
Bcl2 and WT1 ↗	36%	UNF	*Karakas 2002*
EVI 1 ↗	10%	UNF	*Van Waalwijk 2003*
BAALC↗		UNF	*Baldus 2003*
CEBP α mutation	11% (NK)	FAV	*Preudhomme 2002*

1) Induction treatment

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ABMT / ICC

In the nineties several groups have prospectively compared ABMT and ICC (Zittoun 95,Harousseau 97,Burnett 98,Cassileth 98 ,Ravindranath 96,Woods 01)

No evidence that unpurged ABMT is superior to the best available CT.Recent attempts with PBSC do not appear to improve results

Lower RR but higher TD rate with ABMT

→ Only benefit: shorter time to hematopoietic recovery

ALLOGENEIC BMT IN AML

- **Most effective antileukemic treatment**
  - **Myeloablative preparative regimen**
  - **GVL effect**

- **High incidence of severe procedure-related toxicity**
  - **High transplant-related mortality**
  - **Indicated only in patients < 55 yo**

- **Impact of allo BMT has been analyzed in large series (EORTC AML 10,MRC AML 10 & 12)** on an intent-to-treat basis (donor/no donor)

ALLO vs AUTO

EORTC-GIMEMA (AML10) *Suciu Blood 2003*

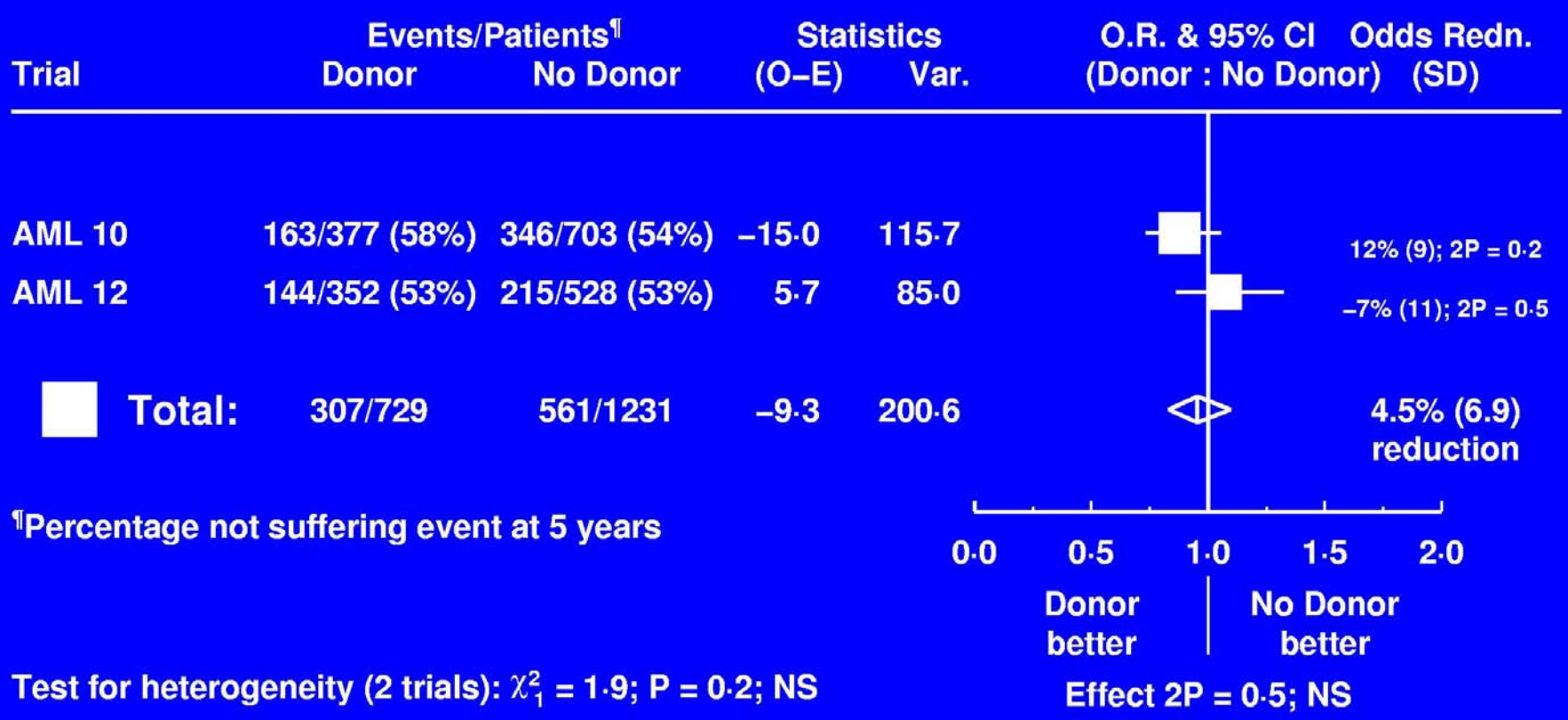
734 pst in CR1 < 46 yo

	293* sibling donor	441** no donor	p value
4yr DFS	52%	42%	0.044
4 yr SV*	58%	51%	0.18
RR	30%	52%	<0.0001
Death in CR	17%	5%	<0.0001

Intent to treat analysis

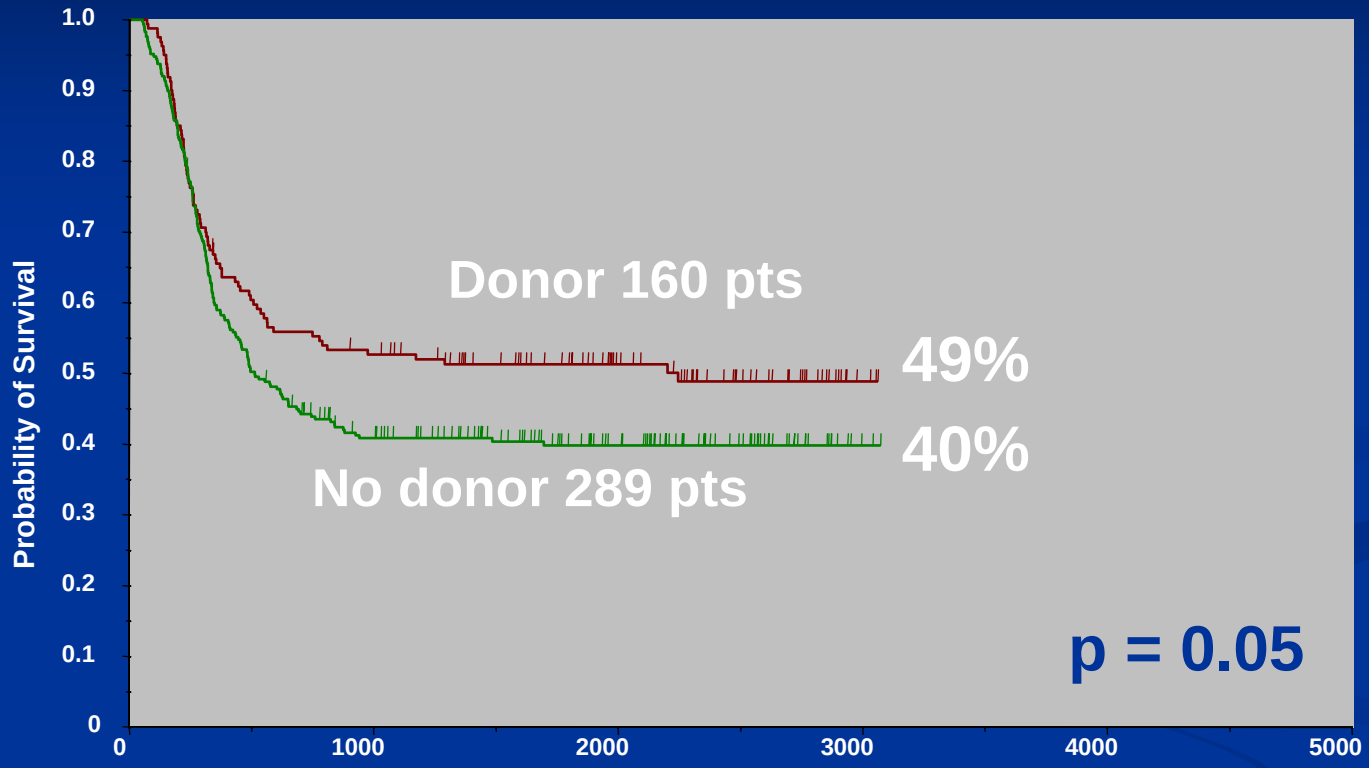
* Allo performed in 69% cases ** auto performed in 56% cases

AML 10 & 12: Overall Survival Donor vs No Donor



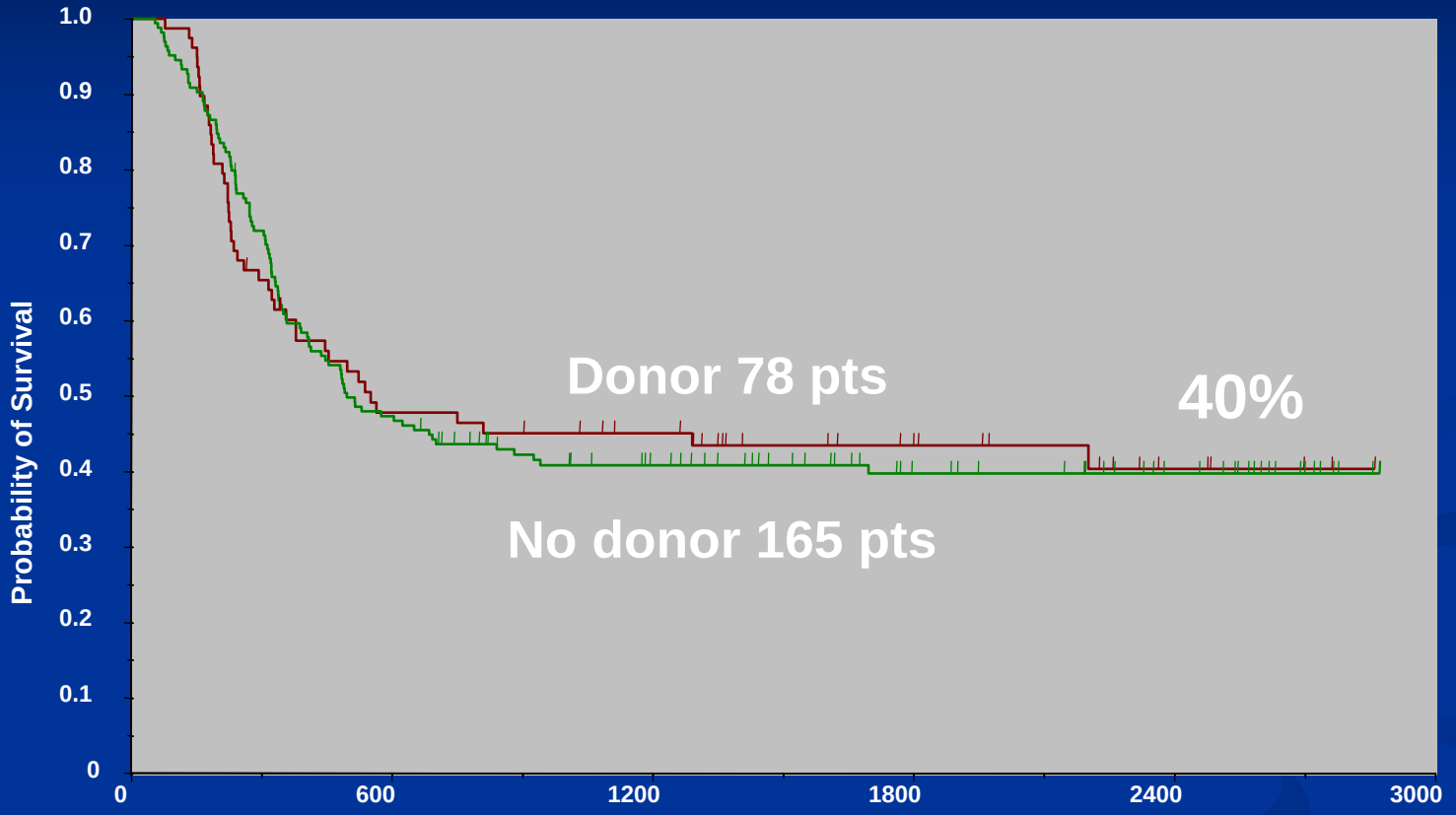
DONOR VS NO DONOR

DFS



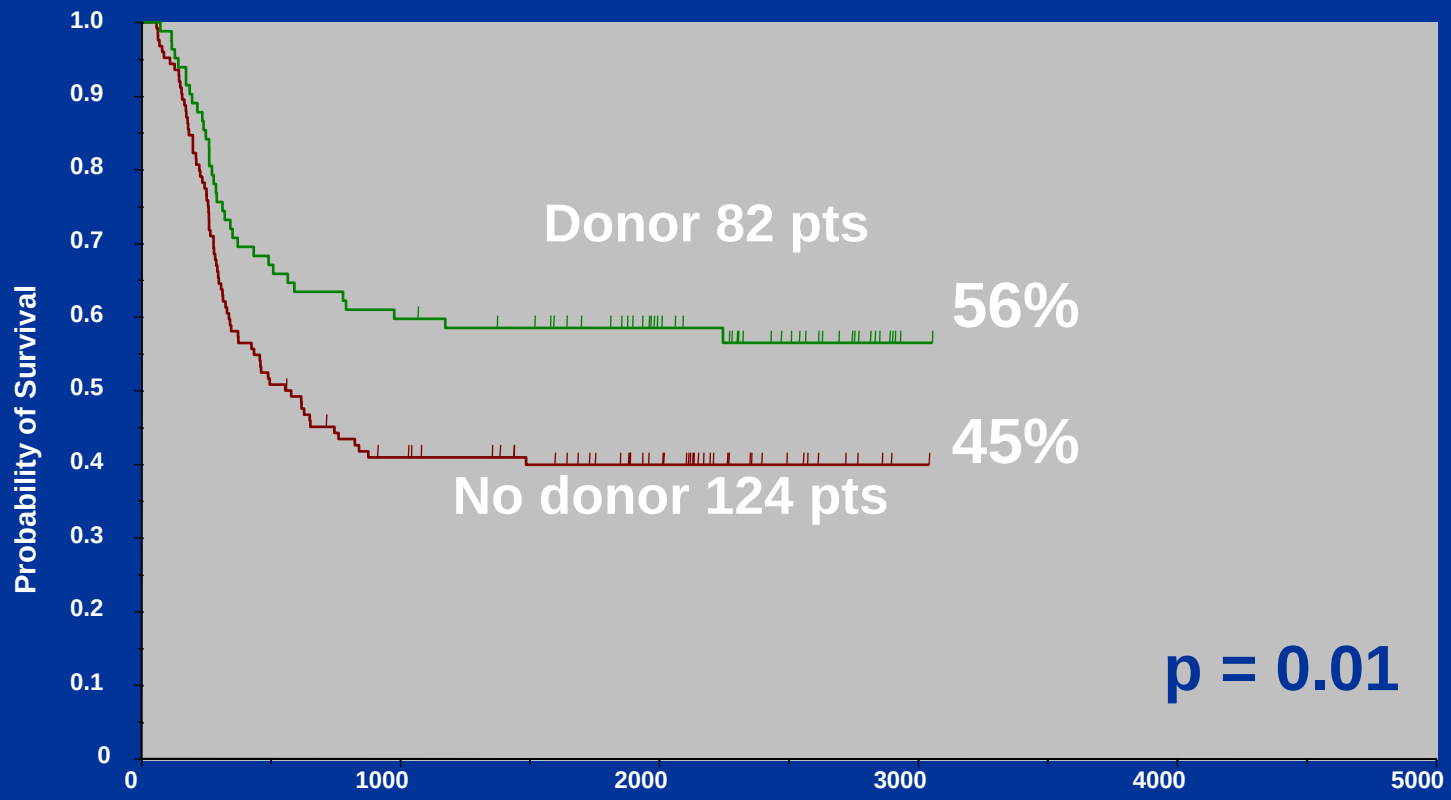
DONOR VS NO DONOR GOELAM 1

DFS



DONOR VS NO DONOR GOELAM 2

DFS

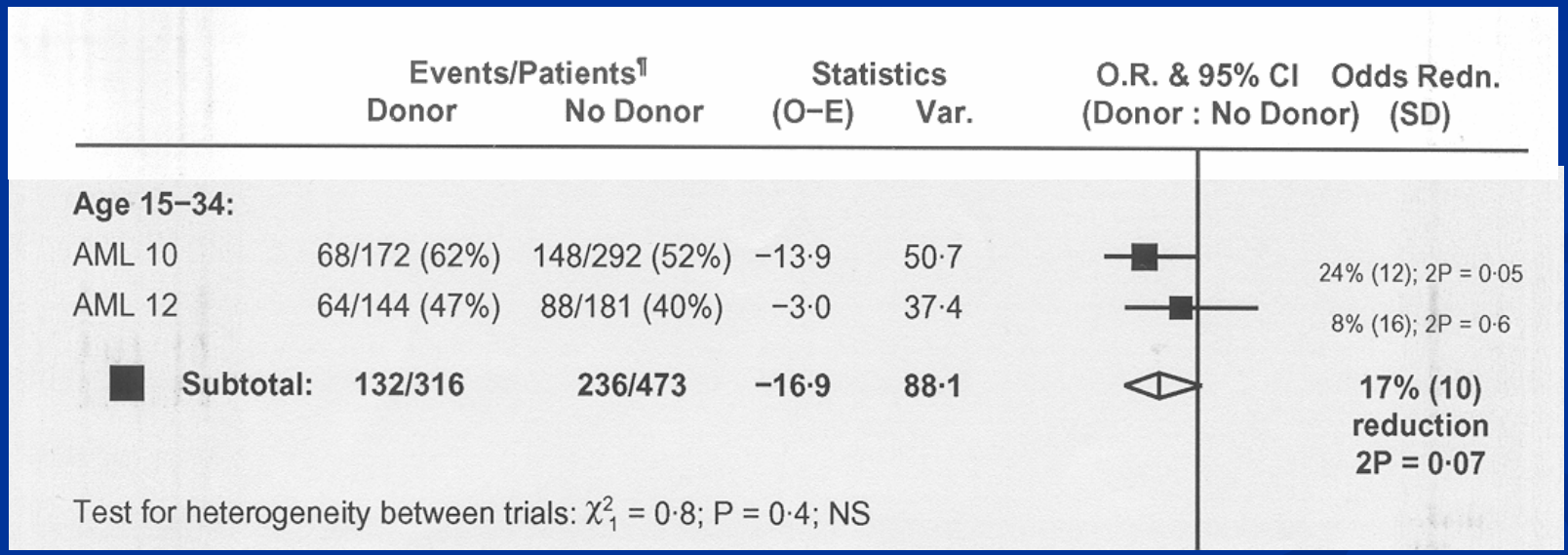


ALLO VS AUTO
INFLUENCE OF AGE

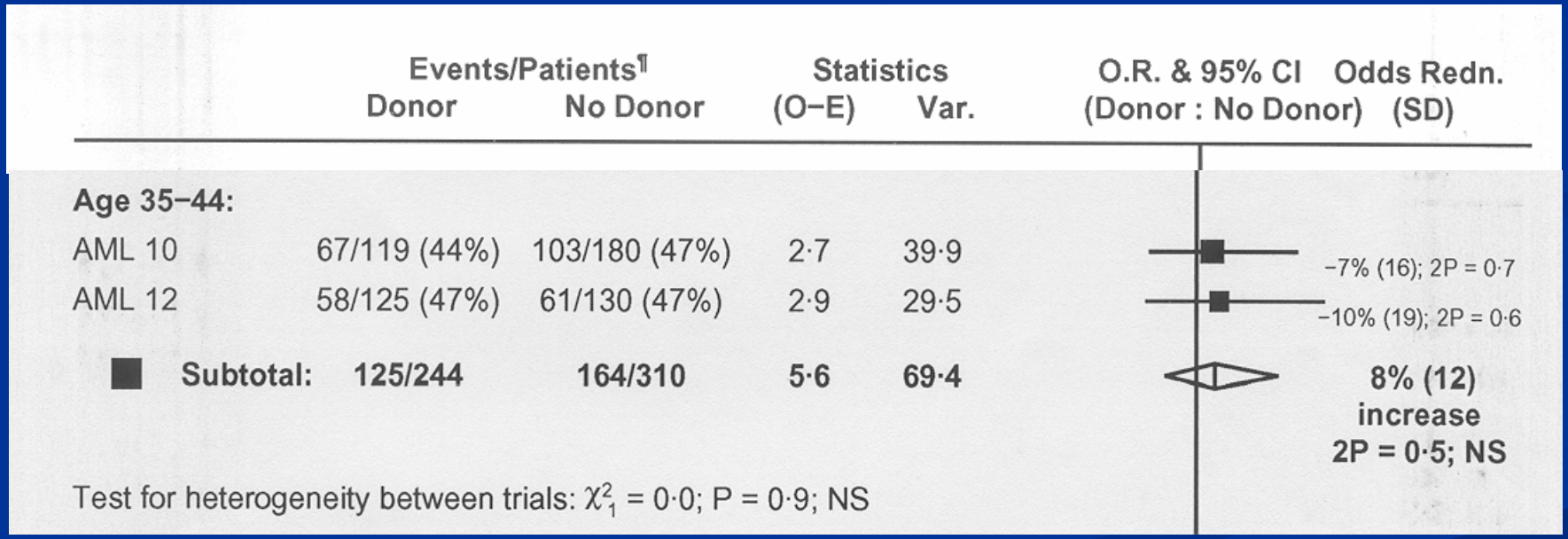
EORTC-GIMEMA (AML 10) *Suciu Blood 2003*
4 – yr DFS Intent to treat Analyis

Donor	No donor	p-value
15-26 (67) 55%	(114) 41%	0.07
26-35 (88) 55%	(88) 38%	0.06
36-45 (138) 49%	(185) 46%	0.85

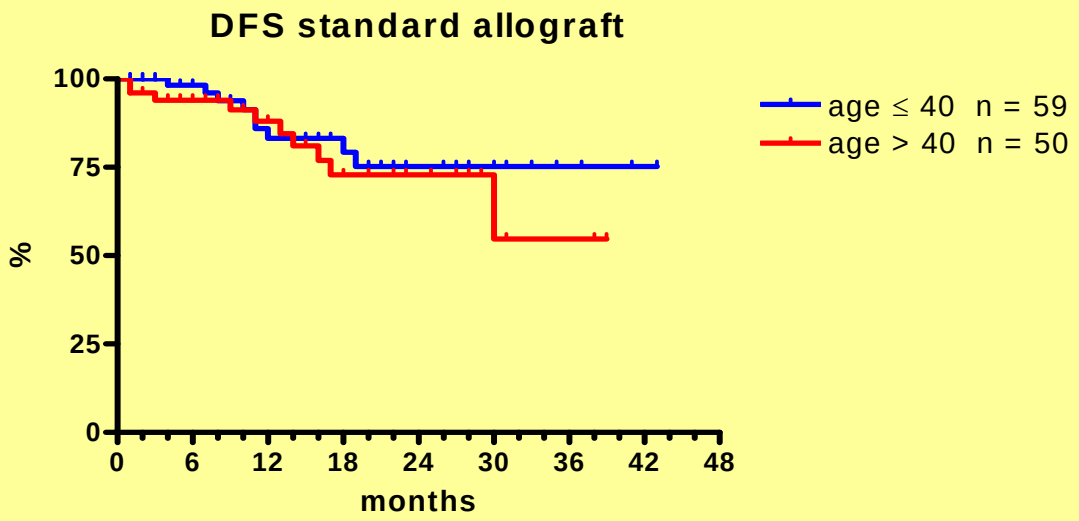
AML 10 & 12
Donor vs no donor comparisons
Overall survival stratified by age



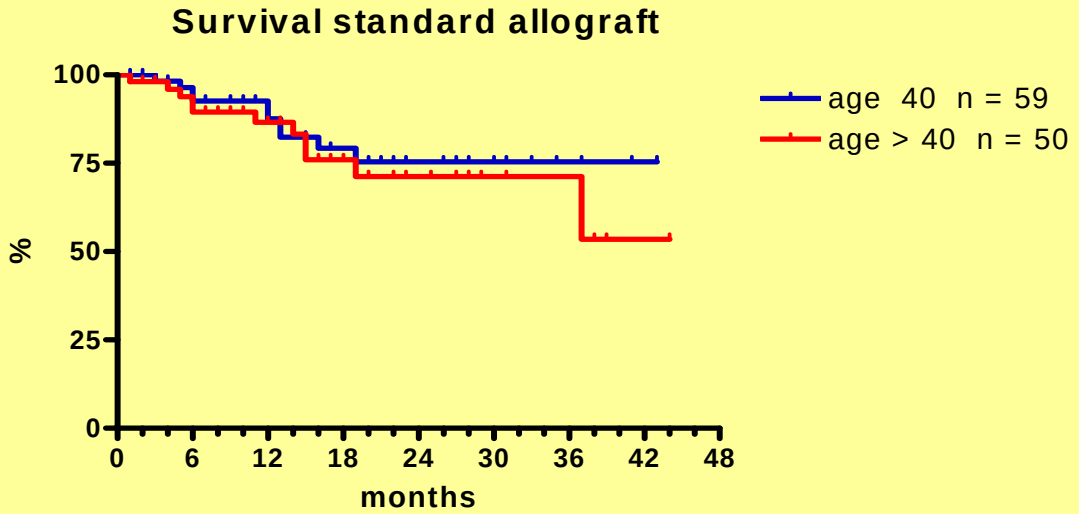
AML 10 & 12
Donor vs no donor comparisons
Overall survival stratified by age



Standard allografting does not result in poorer DFS or survival above 40 years of age

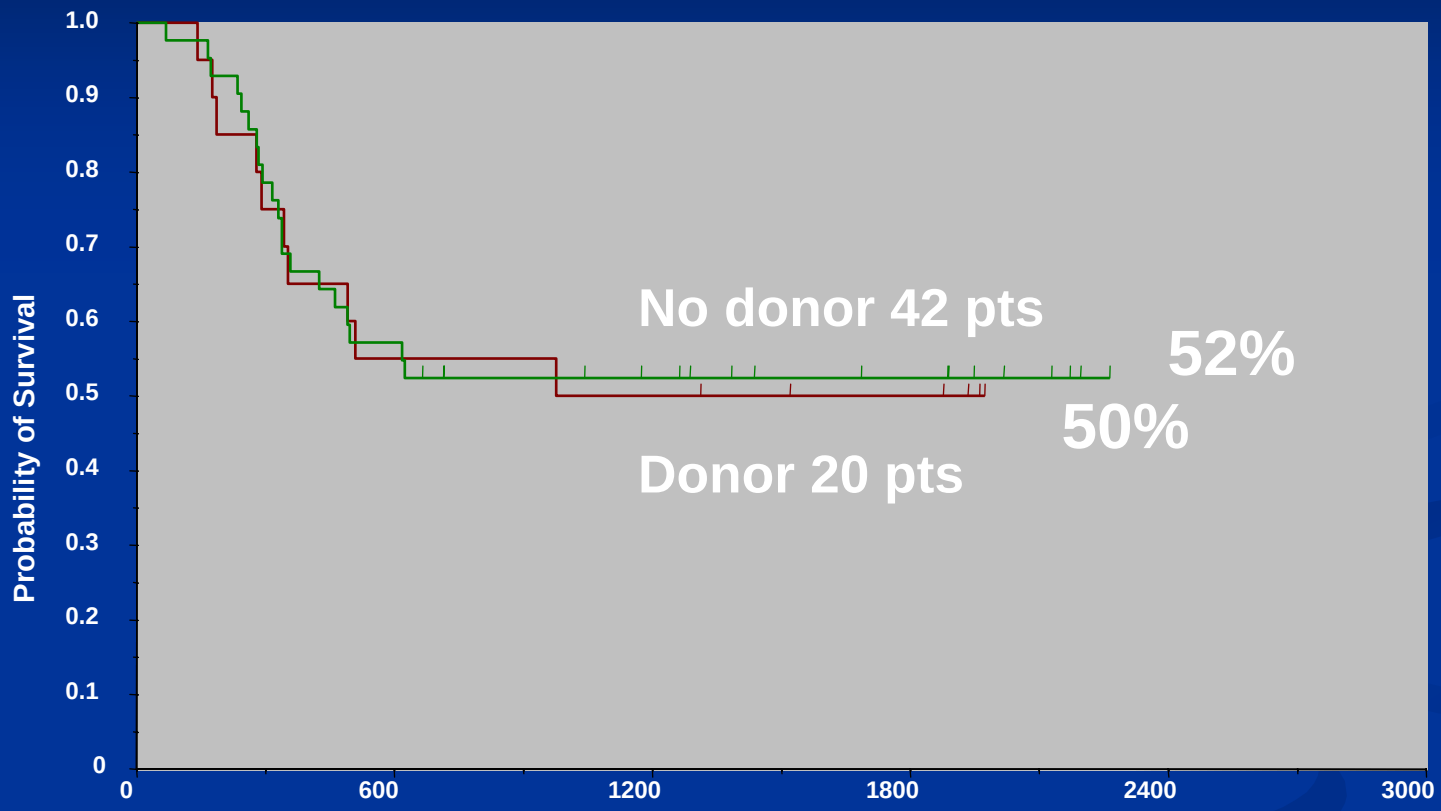


Median DFS
age ≤ 40 = NR
age > 40 = NR
p = 0,46



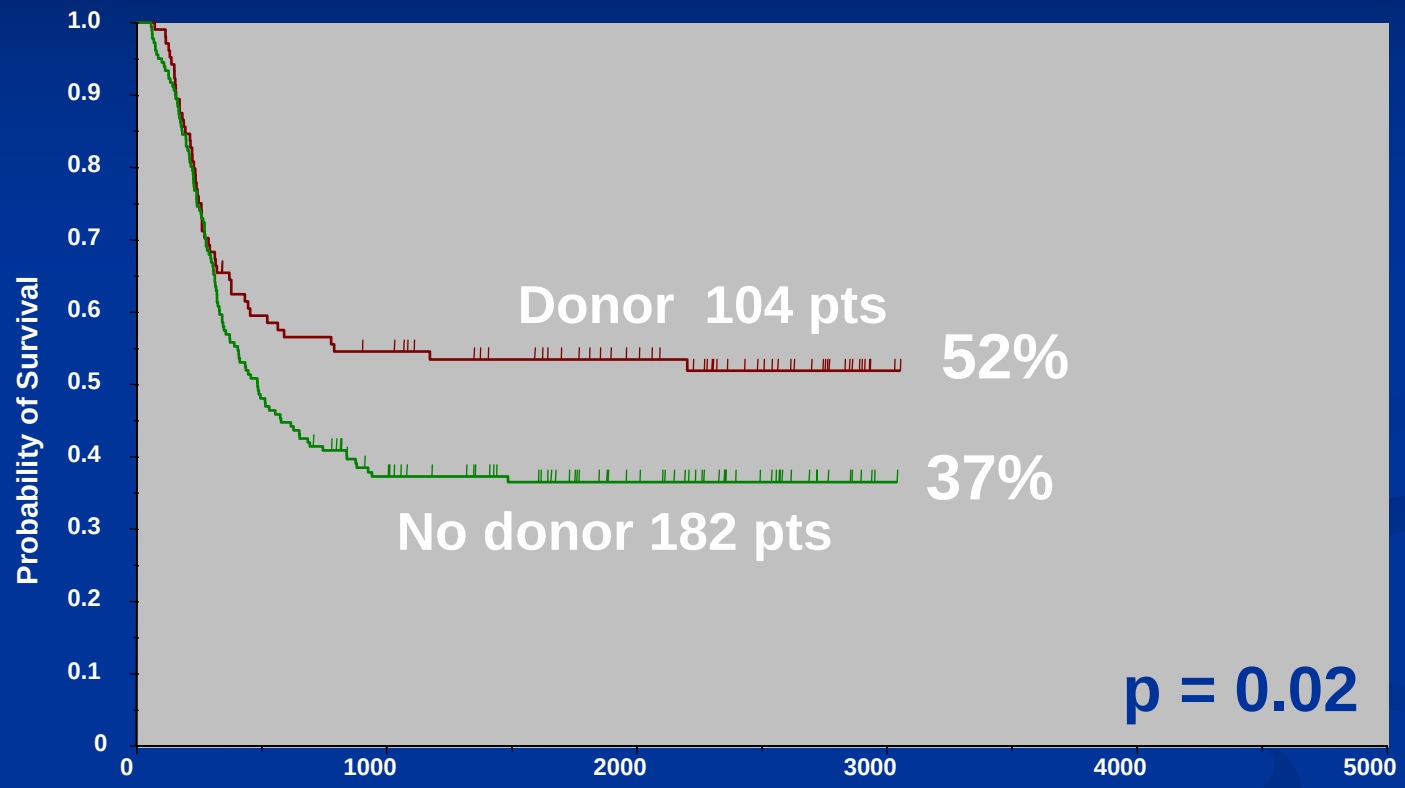
Median survival
age ≤ 40 = NR
age > 40 = NR
p = 0,51

INFLUENCE OF CYTOGENETICS CBF



INFLUENCE OF CYTOGENETICS CBF EXCLUDED

DFS



CAN WE IMPROVE THE RESULTS OF ALLOGENEIC BMT

1)Reduce toxicity

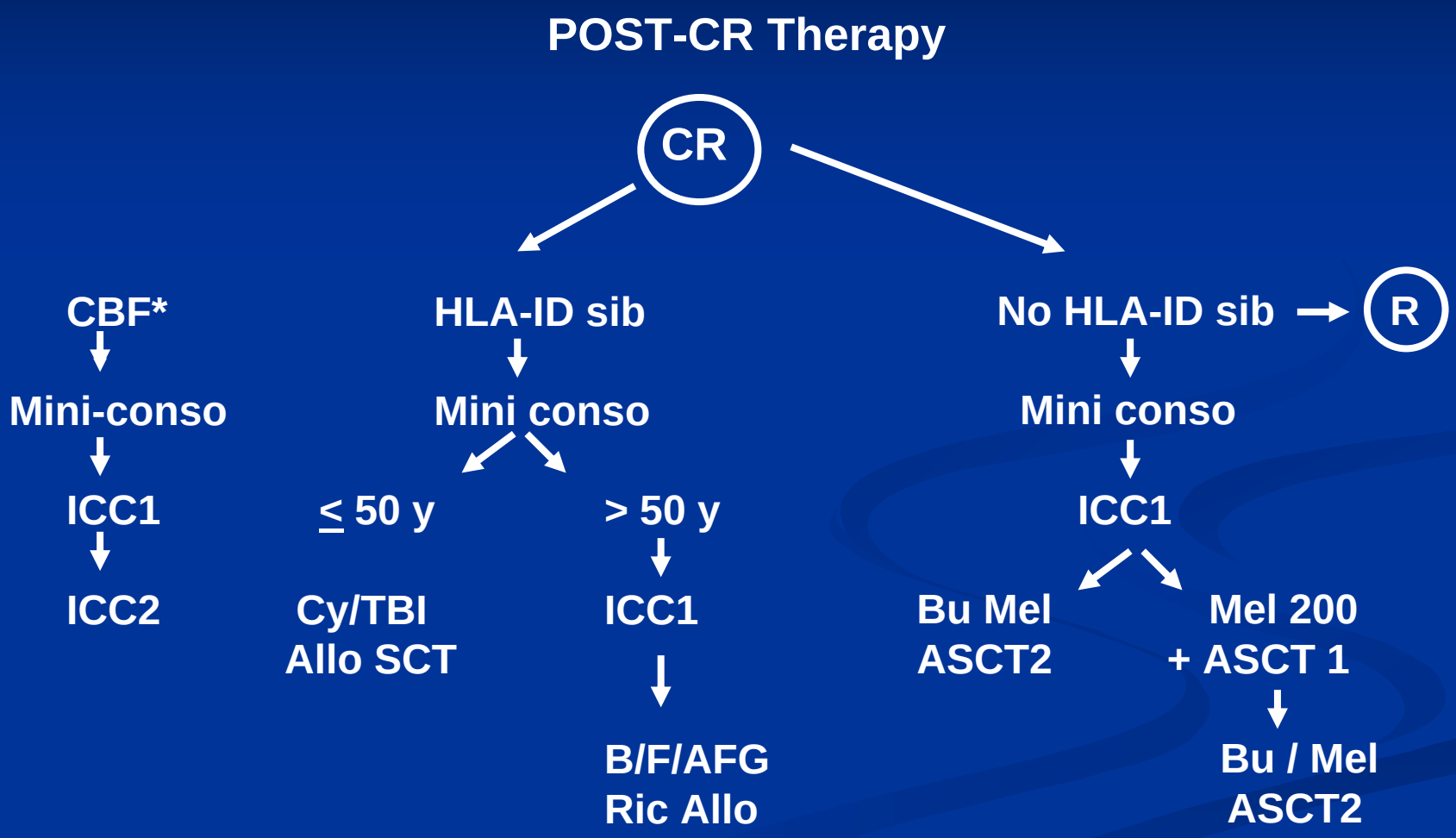
Better control of GVH and infectious complications

- reduced intensity conditioning
- PBSC
- cord blood (double)

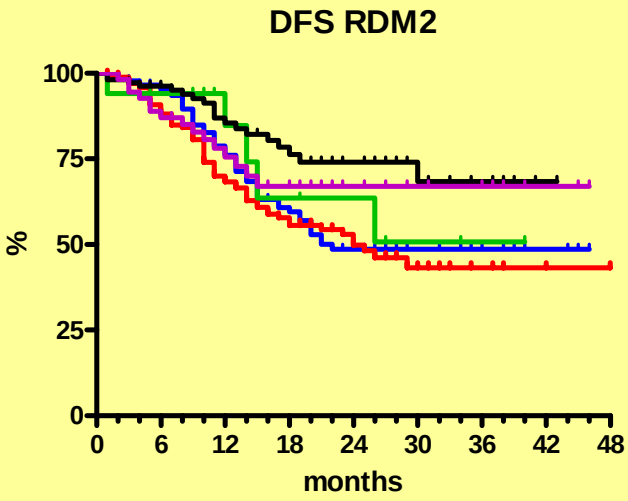
2)Reduce relapse in high-risk patients

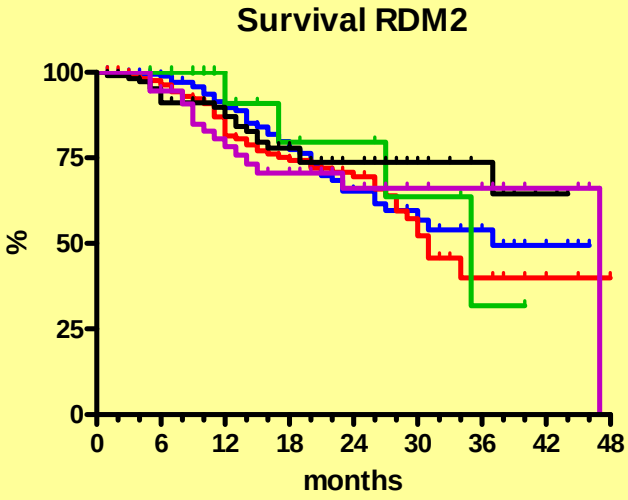
- matched unrelated donors ?

2001 TRIAL
DE NOVO AML ≤ 60 y



Standard allografting results in better DFS
No benefit from HDM 200

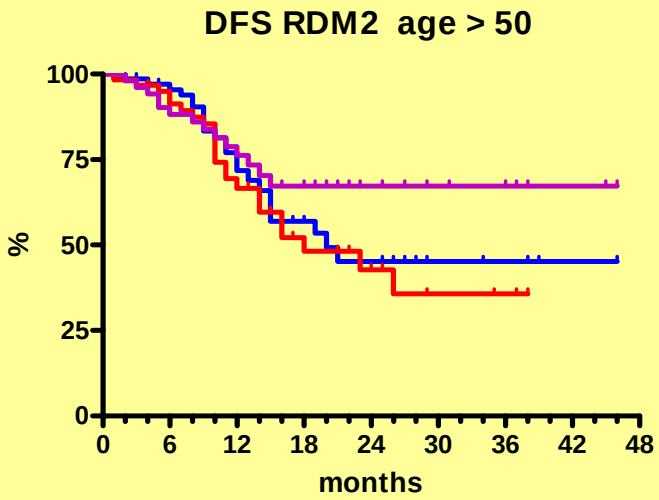




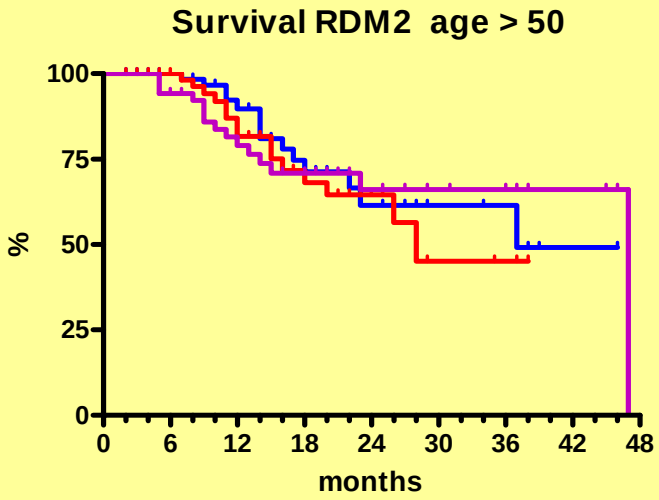
Median DFS
A = 22 months
B = 24 months
C = NR
M = NR
m = NR
M vs A or B p < 0,01
m vs A or B p > 0,10
A vs B p = 0, 37

Median survival
A = 37 months
B = 31 months
C = 35 months
M = NR
m = 47 months
M vs A or B p > 0,15
m vs A or B p > 0,50
A vs B p = 0, 43

RIC Allo compared to Auto in patients over 50 years of age



Median DFS
A = 20 months
B = 18 months
m = NR
p > 0,10



Median survival
A = 37 months
B = 28 months
m = 47
p = NS

1) Induction treatment

2) Prognostic factors

3) Post-remission therapy

4) Novel agents

5) Elderly patients

AML
NOVEL AGENTS

CLASS	AGENT	TARGET
Antibodies	Gemtuzumab	CD33
MDR inhibitors	PSC833, Zosuquidar	P-gp
FT inhibitors	Tipifarmib, Lonafarnib	Ras, others ?
FLT3 inhibitors	PKL 412, CEP 701, MLN518, SU 11248	FLT3 ITD
HDAC inhibitors	Valproid acid, depsipeptide, SAHA	HDAC
Antiangiogenic agents	Bevacizumab	VEGF
Proteasome-inhibitors	Bortezomib	NF-KB
Apoptosis-inhibitors	Genasense	Bcl2

CD33 AS A TARGET FOR AML

- Expressed in 80–90% of patients with AML
- Not a prognostic marker in AML
- Absent in pluripotent stem cells and non-hematologic tissues
- Expressed on > 50% of marrow cells (e.g. myeloid stem cells, progenitor cells, mature cells)
- > 10,000 copies per cell
- Suggests possibility to target these cells while sparing most normal cells and pluripotent stem cells

Bernstein *Leukemia* 2000;14:474–5

GEMTUZUMAB OZOGAMICIN : ANTIBODY-TARGETED CHEMOTHERAPEUTIC AGENT

- Recombinant humanized anti-CD33 antibody
- Conjugated to the highly potent cytotoxic antitumor antibiotic calicheamucin,CD33 antigen is internalized, and toxin liberated in acidic microenvironment causes double-stranded DNA breaks and cell death

MYLOTARG - PHASE II PIVOTAL TRIALS

3 studies (1 in pts >60 y)

. CD33-positive AML (>80% CD33+ blasts)
.1st untreated relapse
. CR1 > 6 months
. > 18 y.o.

Mylotarg 9 mg/m2 2-hr IV inf for up to 3 doses (14-28 days between doses)

188 pts

→ 16% CR + 13% CRp

MYLOTARG Phase II trials

- Hematologic toxicity (median time to neutrophil and platelet recovery 41 d and 38 d respectively)

  In the majority of cases, hospitalization is required for myelosuppression-induced complications

- Concerns regarding hepatic toxicity (with or without HSCT)

  Risk of VOD if Allo after (Interval GO-Allo should be >120 d)

- Approved in the US for the treatment of relapsed AML in the elderly

MYLOTARG – Current development

-In combination with chemotherapy

- in relapsed AML (eg Midam)
- in newly diagnosed pts

(ongoing trials :MRC,SWOG …)

- due to the risk of hepatic toxicity, doses have to be reduced (one course ,3-6 mg/ m2)

- As a single agent in elderly patients (EORTC)

TIPIFARNIB IN AML
SUMMARY

- Clinical efficacy in poor-risk AML
  - Previously untreated elderly pts withpoor-risk (15% CR Lancet 2004)
  - Relapsed / refractory (4% CR Harousseau 2004)
- Well tolerated, oral administration
- Currently developped mostly as induction treatment in elderly patients unfit to undergo CC (AML 301randomized trial)
- Other potential uses
  - Maintenance TX
  - Combination with chemotherapy

FLT3 INHIBITORS

- FLT3 overexpressed in 50% AML

- Constitutive activation in 35% cases
  - internal tandem duplication 25-30%
  - point mutations 7%

- Modest clinical results as a single agent
  → Reductions of blood / BM blasts in patients with activating mutations

- Currently tested in combination with chemotherapy

1) Induction treatment

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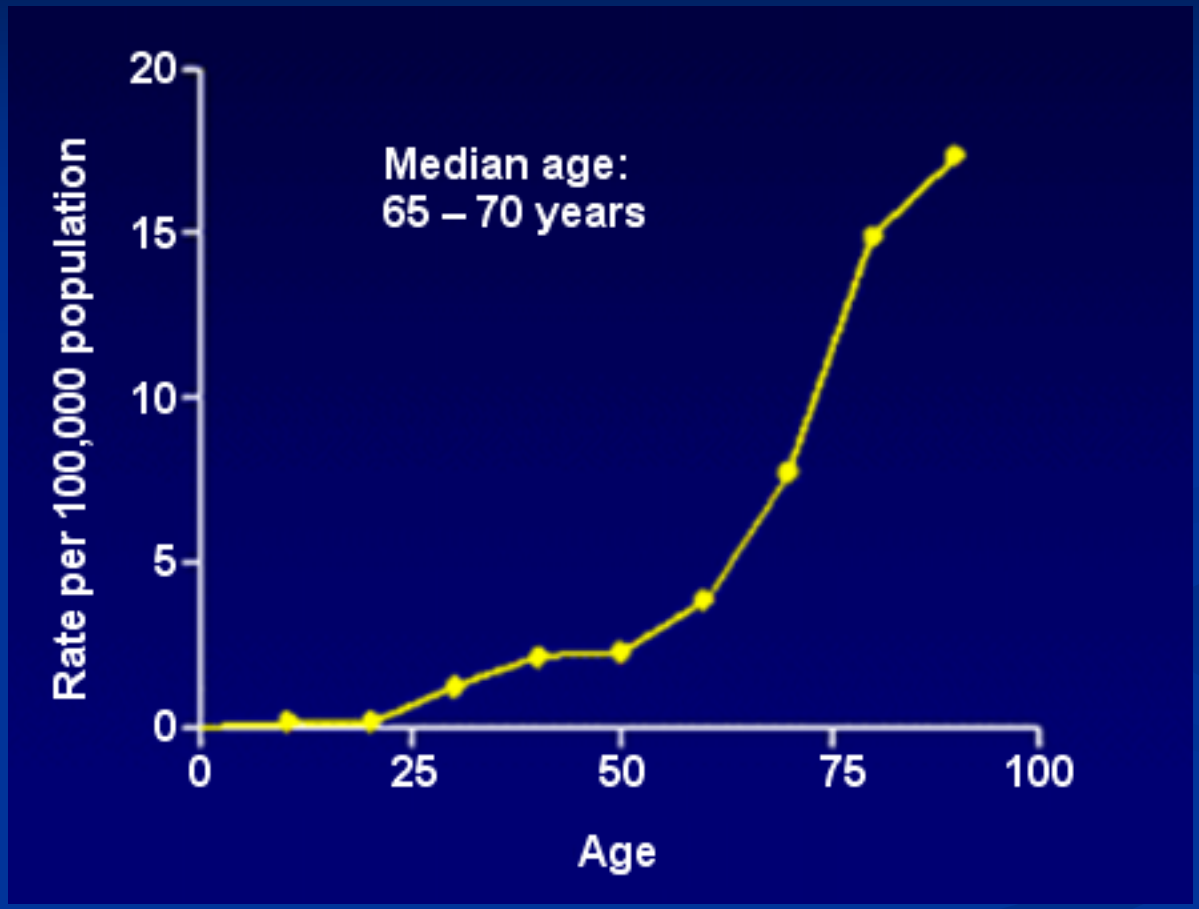
AGE-RELATED INCIDENCE OF AML



Extrapolation for UK
In 2031 + 38% AML in patients > 60 y due to ↗ life expectancy (Yin 1991)

Adapted from Wingo *et al. Cancer J Clin* 1995;45:8–30

AML IN ELDERLY
CURRENT STATUS

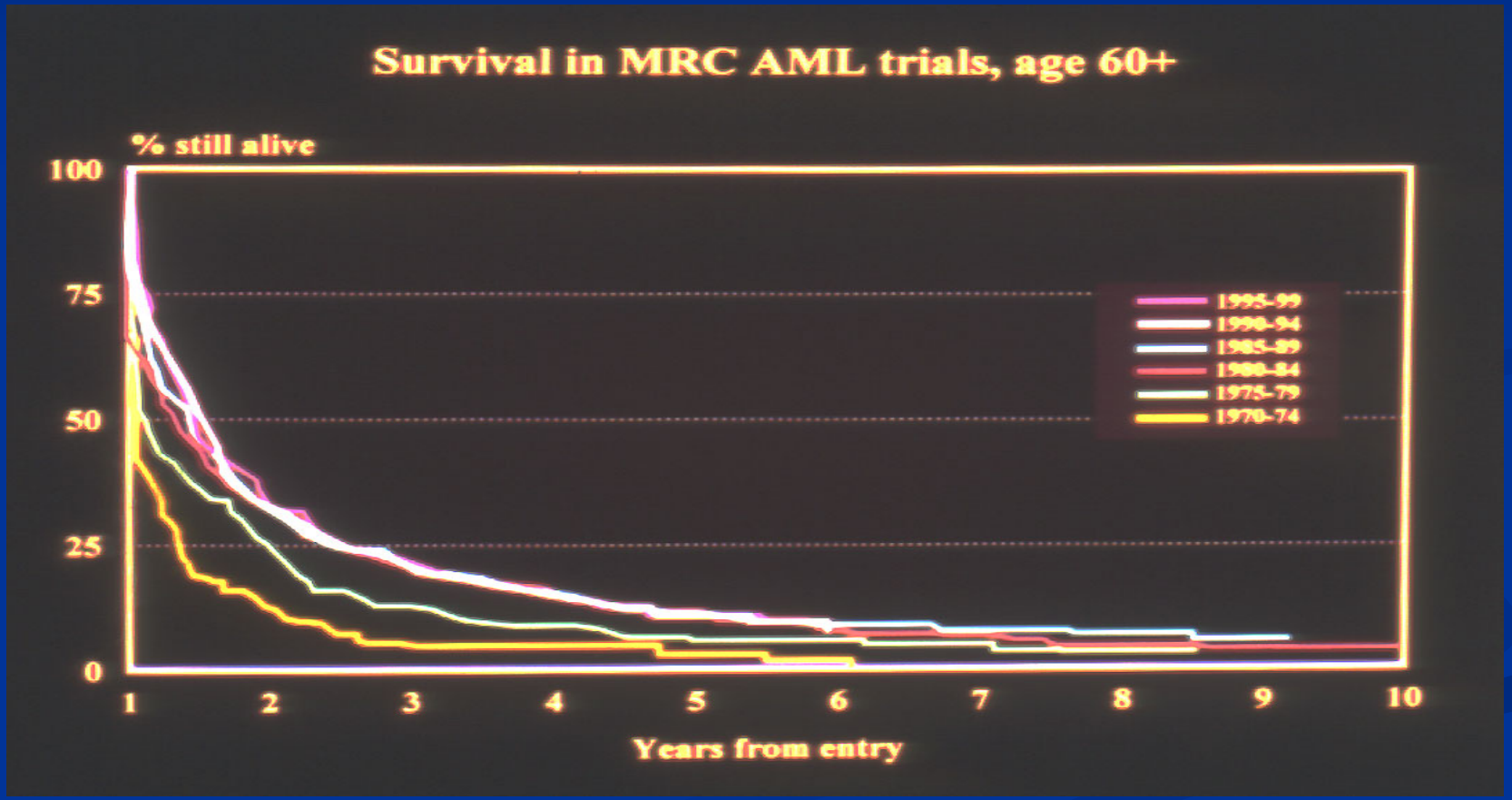
- A dilemna :poor prognosis related to
  - Patients clinical conditions
  - Leukemia characteristics

- No recent improvement

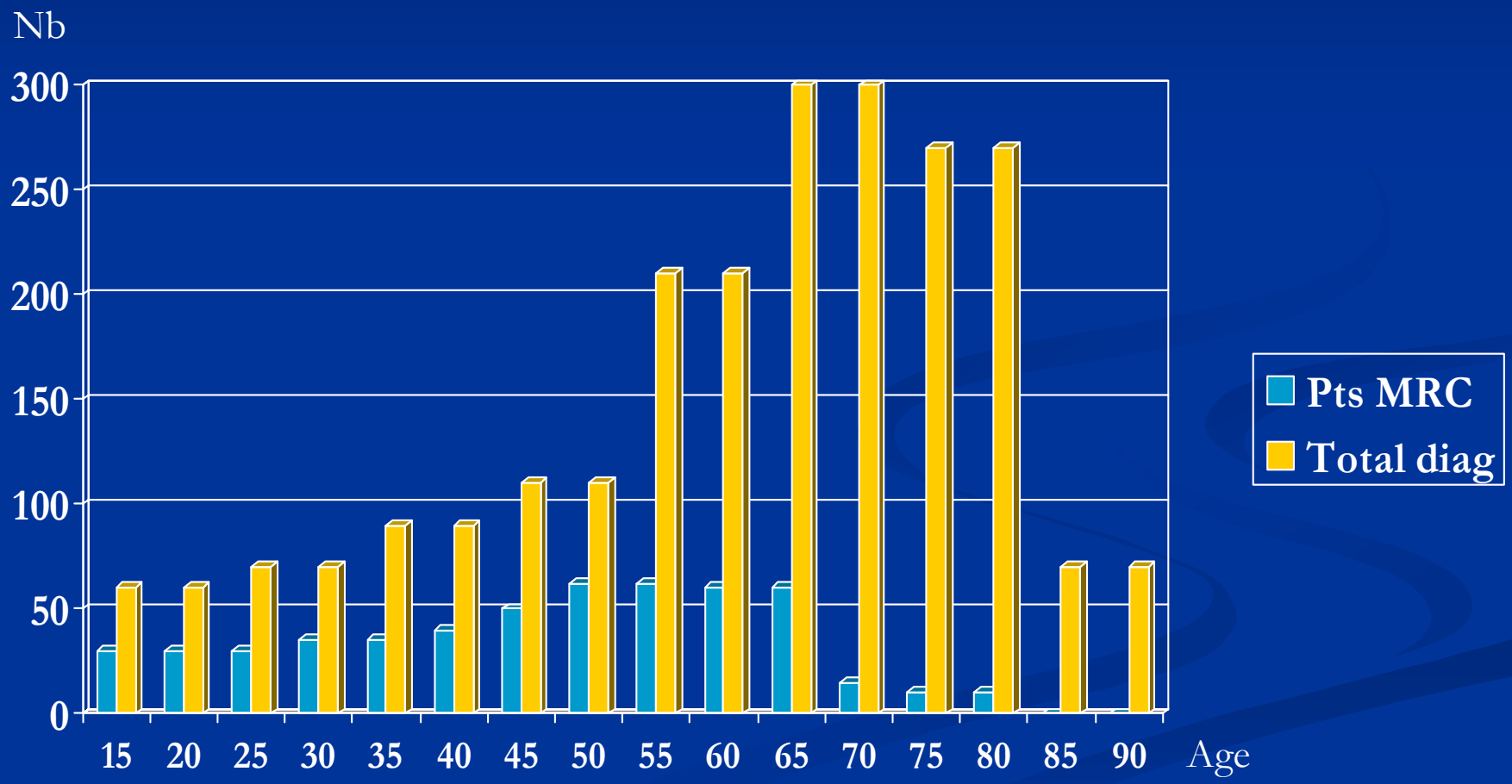
  - Select patients according to initial characteristics

  - Test novel agents

Survival in the United Kingdom Medical Research Council AML trials 1970–1999 for patients aged ≥ 60 years



INCLUSION RATE INTO MRC CLINICAL TRIALS



CLINICAL MANAGEMENT OF PATIENTS WITH AML

INTENSIVE THERAPY → curative intent

the aims are to achieve and maintain CR whatever the risks (and the costs)

First choice for pts with a good PS and with an acceptable cure rate

ATTENUATED DOSE → quantity + quality of life

the aims are also to achieve CR and/or to prolong survival but with reduced risks (and costs ?)

First choice for pts with a poor PS

PALLIATIVE APPROACH (or no referal to specialized centers)

AML IN ELDERLY
CURRENT STATUS

- A dilemna :poor prognosis related to
  - Patients clinical conditions
  - Leukemia characteristics

- No recent improvement

  - Select patients according to initial characteristics

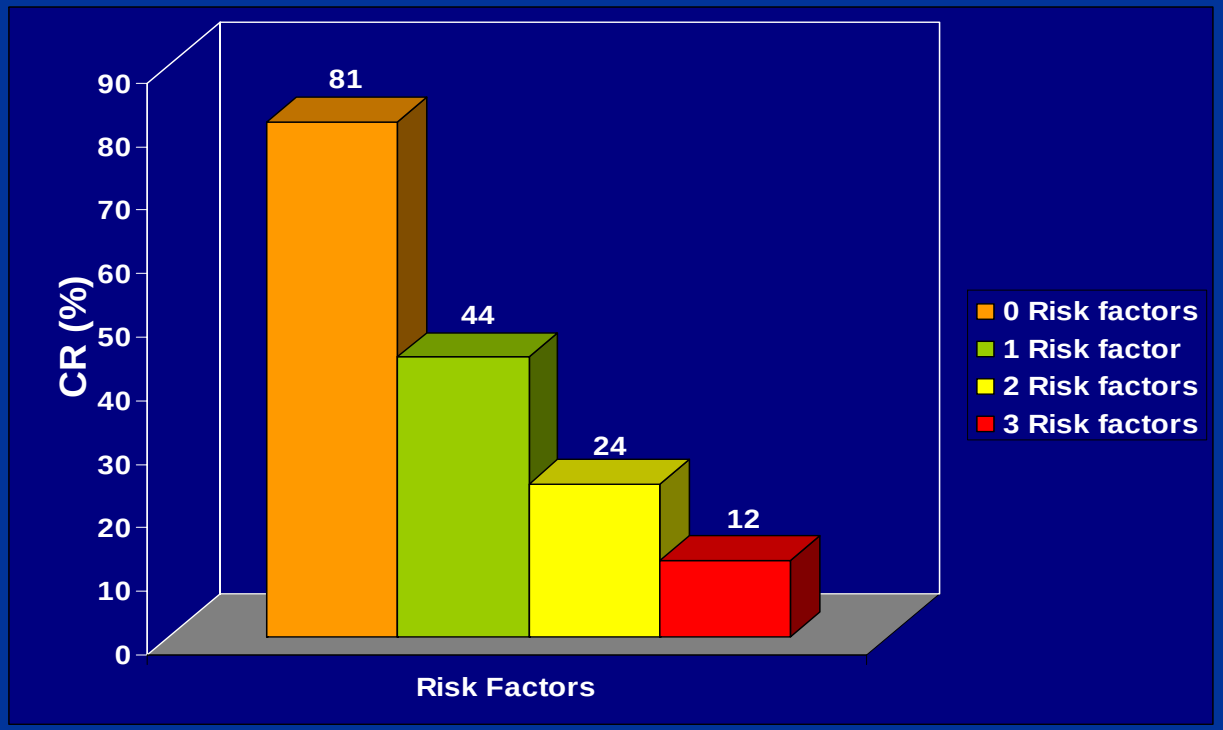
  - Test novel agents

AML : PROGNOSTIC INDICATORS

- Age
- Blast karyotype
- MDR phenotype
- Previous history of hematologic disorder
- Previous history of radiation or chemotherapy
- FAB classification
- CD34 expression
- PS, albumin level,comorbidities,geriatric assessment

CR RATE IN 234 ELDERLY PATIENTS WITH AML WITH 3+7 INDUCTION THERAPY (SWOG 9031)

- Unfavorable cytogenetics/CD34 phenotype
- MDR expression
- Antecedent hematologic disease/MDS



Leith *et al. Blood* 1997;89:3323–9

CLINICAL MANAGEMENT OF PATIENTS WITH AML

Intensive therapy → curative intent

the aims are to achieve and maintain CR whatever the risks (and the costs)

First choice for pts with a good PS and with an acceptable cure rate

Attenuated dose → quantity + quality of life

the aims are also to achieve CR and/or to prolong survival but with reduced risks (and costs ?)

First choice for pts with a poor PS

Test novel agents → Alone or in combination with LD ARA-C

Palliative approach or no referal to specialized centers

AML in poor-risk elderly pts

LD ARA-C vs Hydroxyurea *(AML 14 Burnett)*

-LD ARA-C 20mg x 2 / 10 every 4 - 6 w
+ ATRA (randomized :no benefit)

- 204 pts **129 WHO < 2**
155 > 65 A
53 LA II
28 MDS

- Higher CR rate **15/94 vs 1/92**

- Longer SV (HR 0,61 p=0,001)

- No difference in toxicity and supportive care

AML IN ELDERLY
CURRENT STATUS

- A dilemna :poor prognosis related to
  - Patients clinical conditions
  - Leukemia characteristics

- No recent improvement

  - Select patients according to initial characteristics

  - Test novel agents

GEMTUZUMAB OZOGAMICIN : PATIENTS AGED ≥ 60 YEARS (n = 101)

CR1 duration (months)	RR (%)	Median survival (months)
3–6	10	2.7
6–12	26	4.4
> 12	39	9.7

Larson *et al. Leukemia* 2002;16:1627–36

NOVEL AGENTS

ZARNESTRA (J.Lancet ASH 05)

- Tipifarnib 600 mg x 2 / 21 d ,1-3 w off
  → 4 cycles if CR

- 148 evaluable pts
  - med age 73 (34-85)
  - unf Karyo 47%
  - ATCD MDS 79%

- CR 18% (34% CR + PR)
  pts > 75 y 20% (30%)
  CR med duration 6.4 m
  med SV of CR pts 14 m (overall SV 5.6 m)

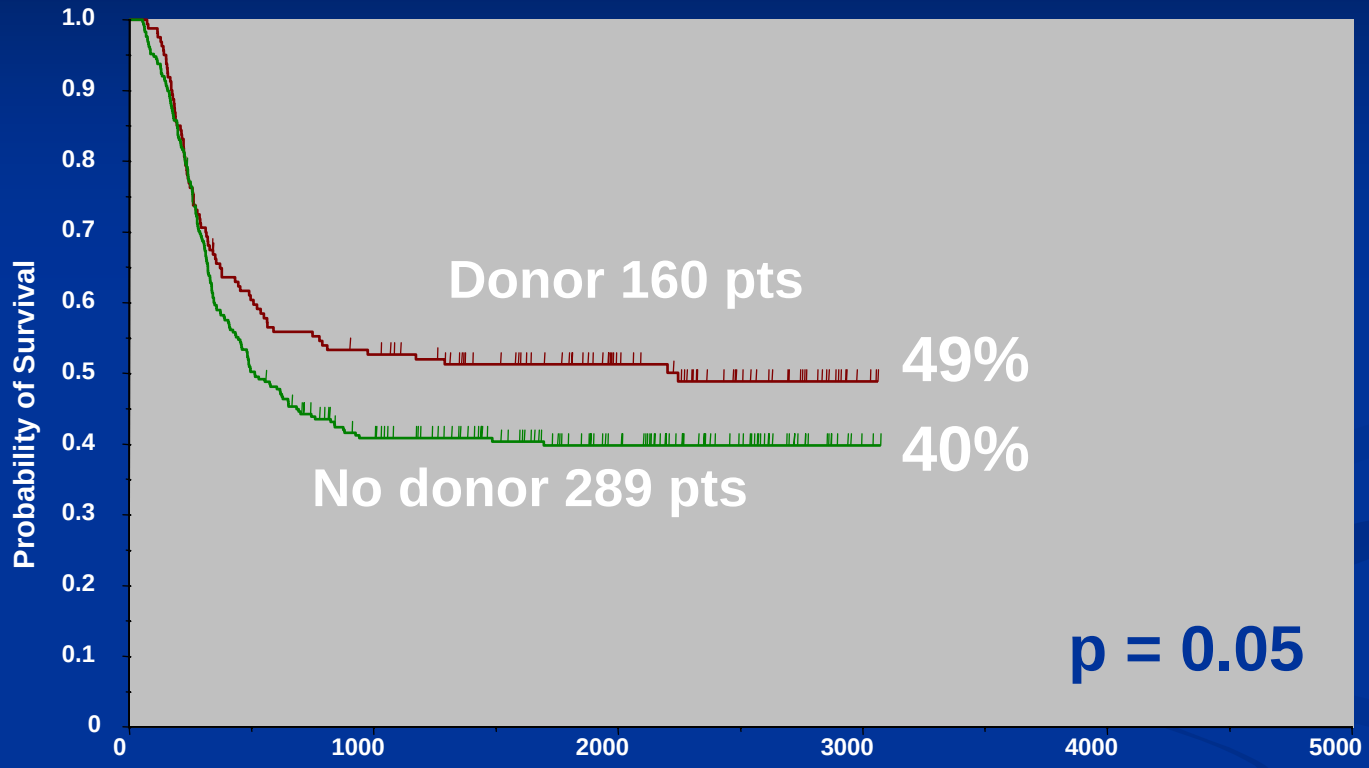
NOVEL AGENTS CURRENTLY TESTED IN POOR-RISK ELDERLY

- Farnesyltransferase inhibitors (randomized study vs best supportive care)
- New cytotoxic agents (Clofarabine,Cloretazine)
- DNA-hypomethylating agents (e.g. 5-azacytidine, decitabine)
- Histone deacetylase inhibitors (e.g phenylbutyrate,depsipeptide,SAHA)
- Flt3 inhibitors

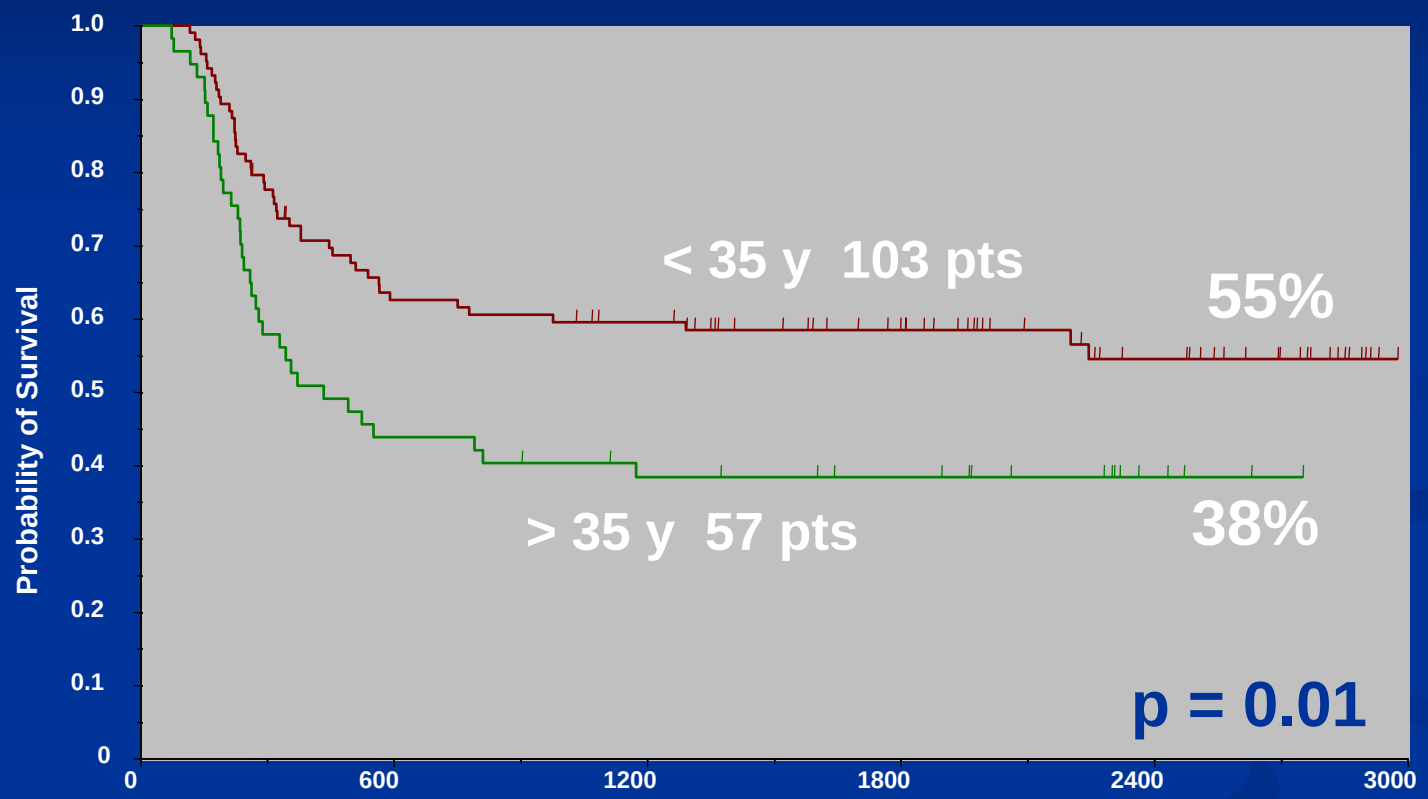
Nantes

DONOR VS NO DONOR

DFS

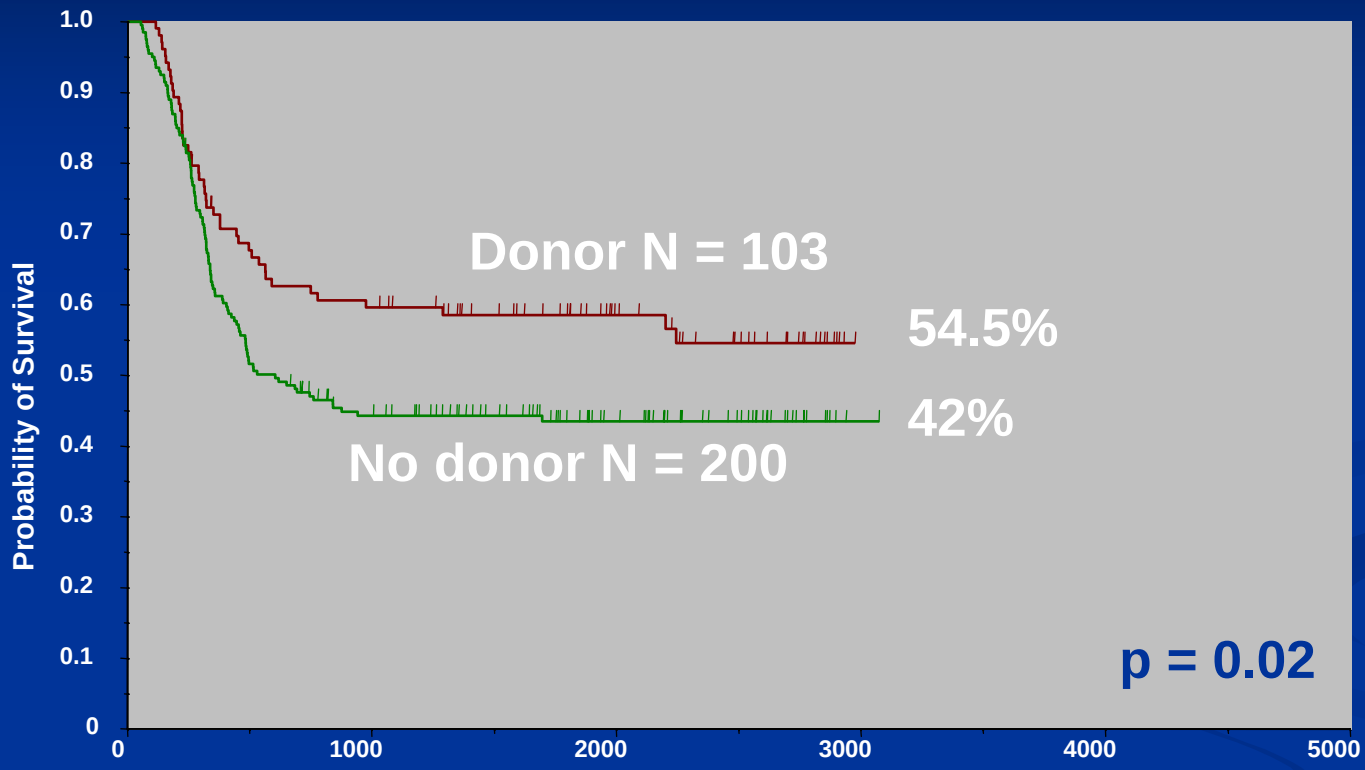


INFLUENCE OF AGE



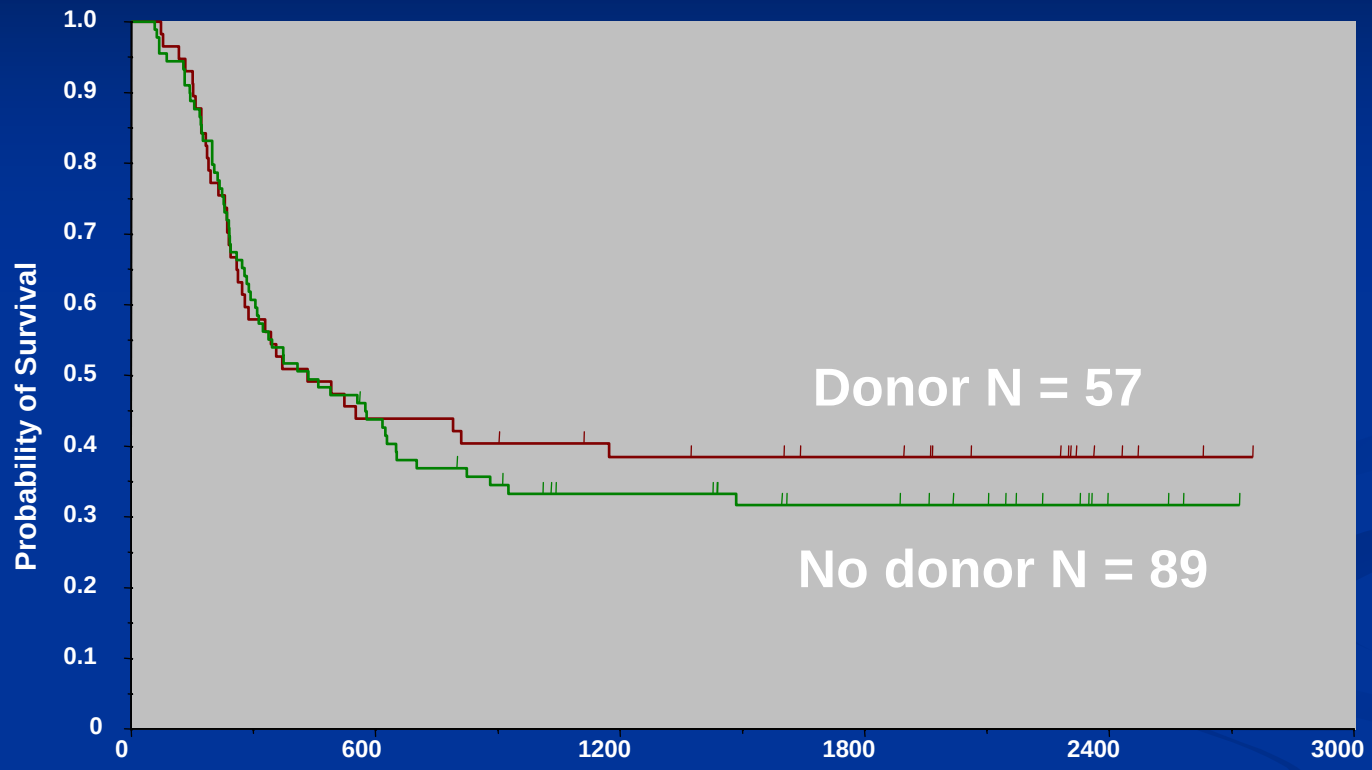
INFLUENCE OF AGE PATIENTS ≤ 35

DFS



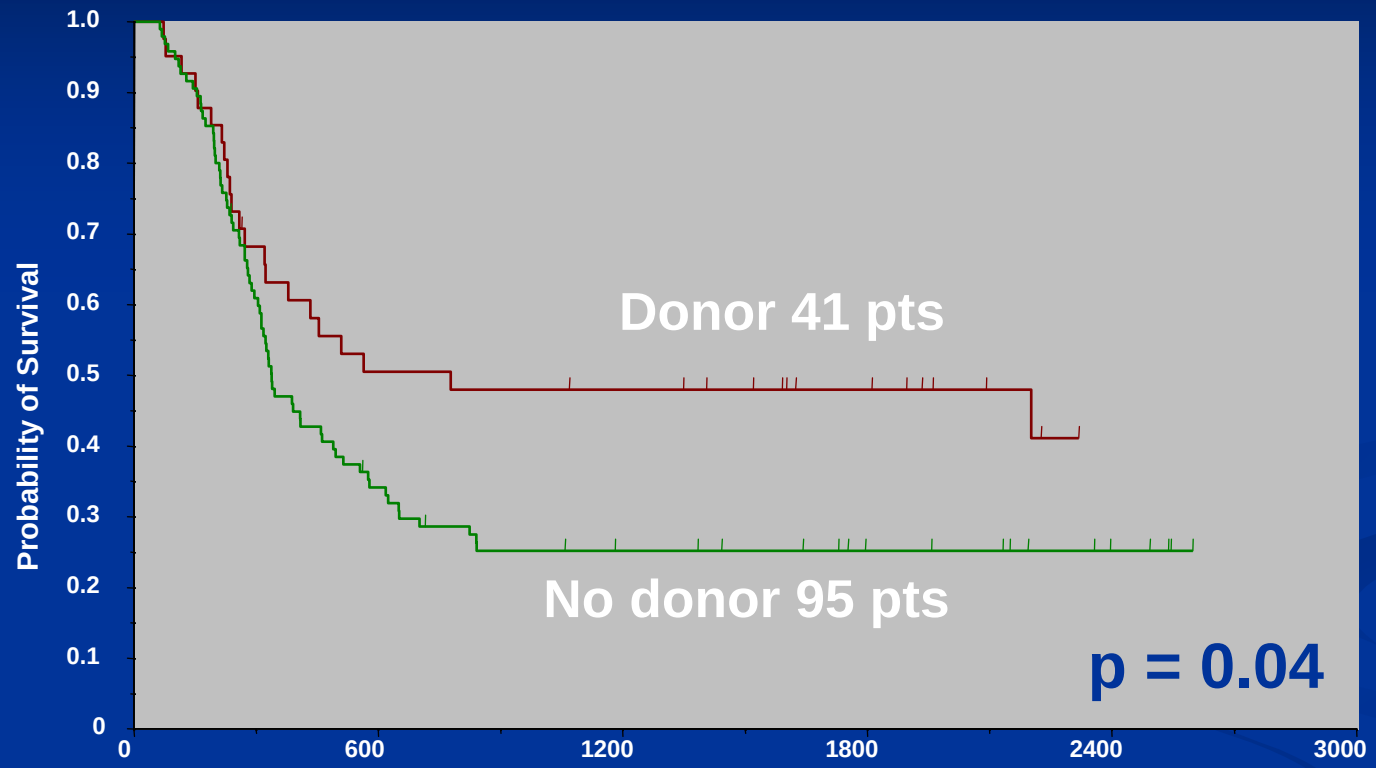
INFLUENCE OF AGE PATIENTS > 35

DFS

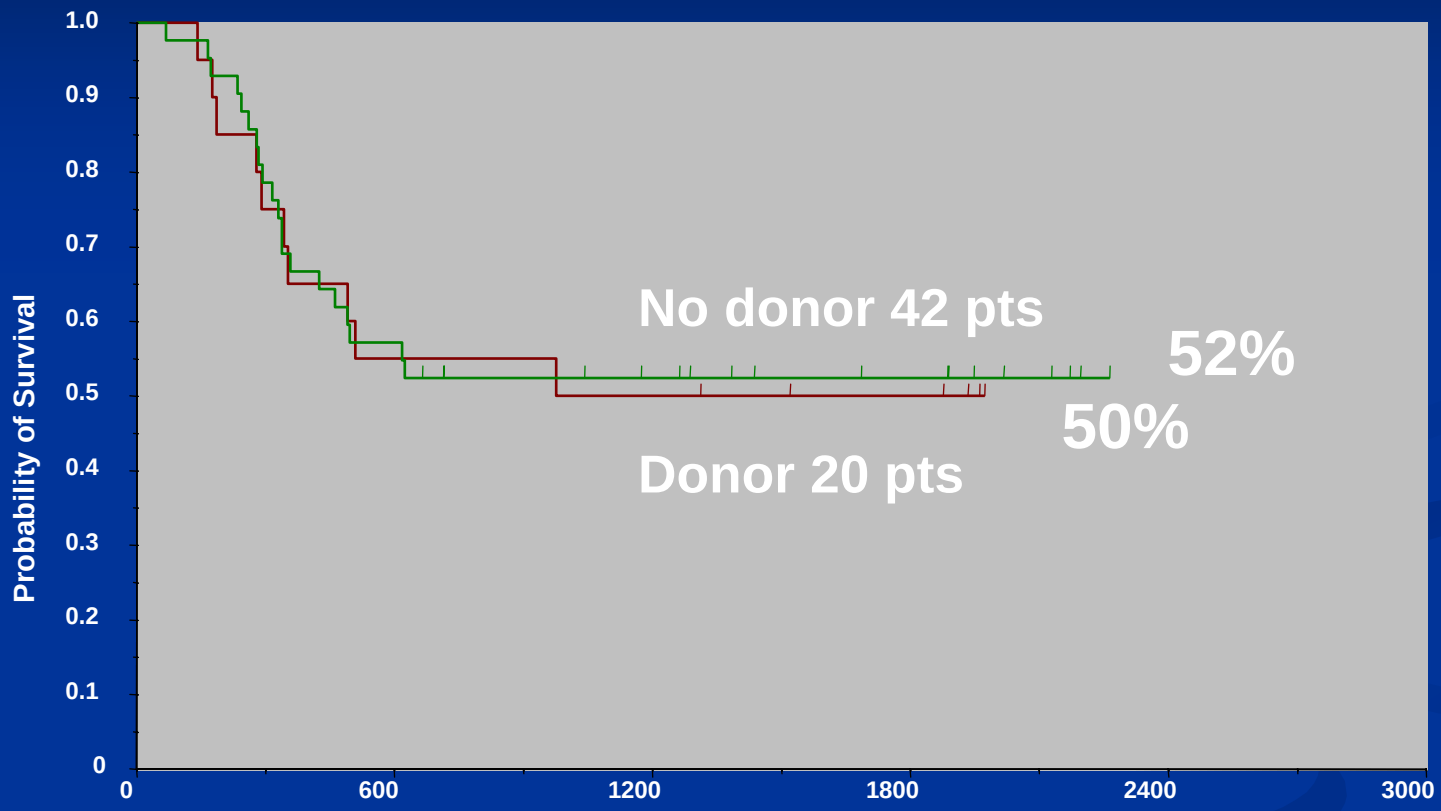


INFLUENCE OF WBC COUNT WBC > 30 000

DFS



INFLUENCE OF CYTOGENETICS CBF



CONCLUSION
GOELAM 1 and 2 TRIALS

- Overall allo SCT is superior to other types of post-CR therapy (autologous SCT or ICC)

- However allo SCT is not superior

In patients with good risk disease

CBF AML

WBC < 30000/mm3

In patients > 35 y (toxicity)

In LAM2001 trial

CBF were excluded

RIC allo was proposed to patients aged 50-60

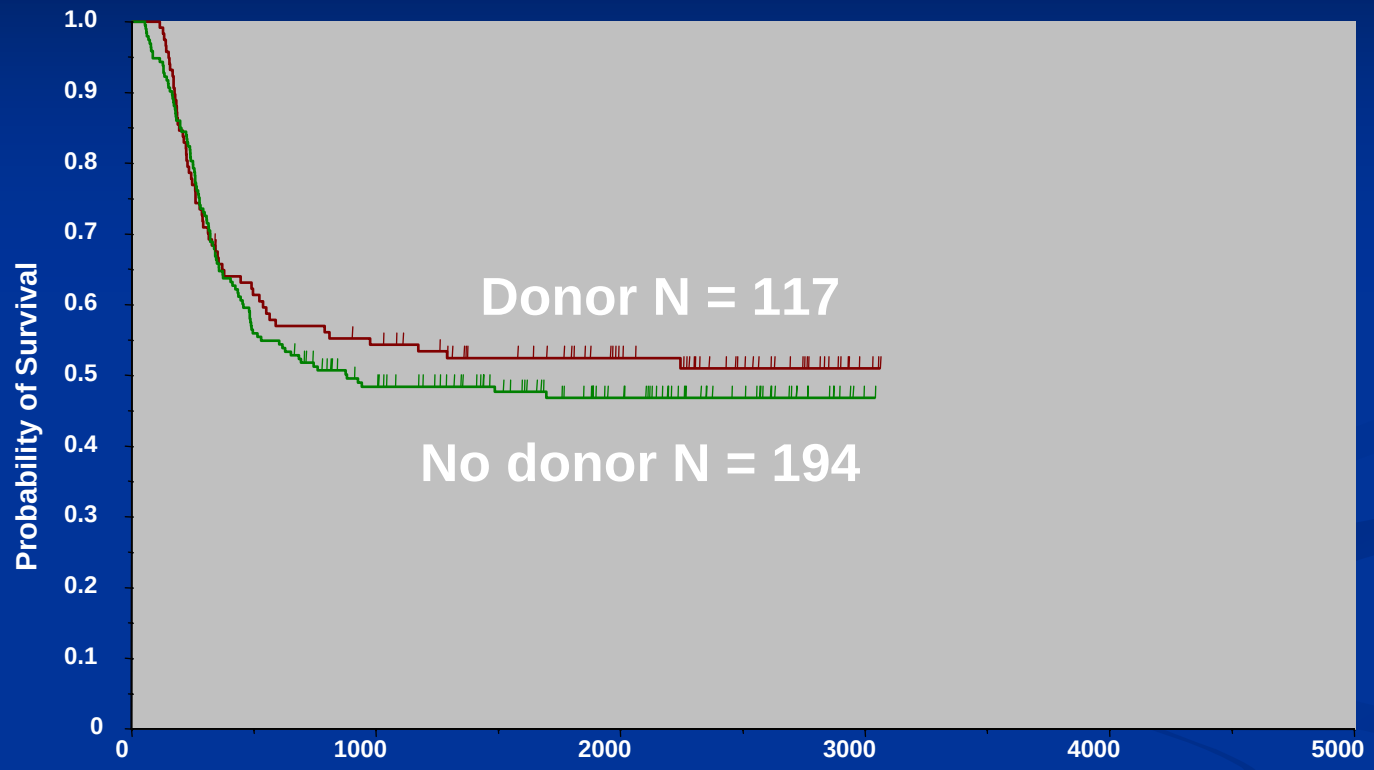
COMPARISON AMBT / ICC
RELAPSE RATE AND TOXIC-DEATH

	Relapse (%)		Toxic death (%)	
	ABMT	ICC	ABMT	ICC
Adult studies				
Zittoun 95	41	57	10	6
Harousseau 97	45	59	13	3
Burnett 98*	37	58	12	4
Cassileth 98	48	61	14	3
Pediatric studies				
Ravindranath 96	31	58	15	3
*Woods** 01*	45	45	5	4

*Autologous BMT was compared to no further treatment after 4 courses of intensive chemo
** Bone marrow was purged with 4 HC in the autologous transplantation arm.

INFLUENCE OF WBC COUNT WBC < 30 000

DFS



AML
NOVEL AGENTS

CLASS	AGENT	TARGET
Antibodies	Gemtuzumab	CD33
MDR inhibitors	PSC833, Zosuquidar	P-gp
FT inhibitors	Tipifarmib, Lonafarnib	Ras, others ?
FLT3 inhibitors	PKL 412, CEP 701, MLN518, SU 11248	FLT3 ITD
HDAC inhibitors	Valproid acid, depsipeptide, SAHA	HDAC
Antiangiogenic agents	Bevacizumab	VEGF
Proteasome-inhibitors	Bortezomib	NF-KB
Apoptosis-inhibitors	Genasense	Bcl2

LAM SUJET AGE
Phase II

CLOFARABINE ***(Burnett 869)***

30mg/m² IV J1-5 tous les 28 J

- 28 pts (soit > 70A soit 60-70 avec cardiopathie)
2 caryo def
→ 59% RC après cycle 1
reconstitution : PN : 285 plaq 25 J

CEP 701 (inhibiteur FLT3) ***(864)***

Po 50mg/J x 28 J puis 80mg/J x 28 J

- 24 pts (mêmes critères d'inclusion) status FLT3
→ 3/4 FLT3 mutés ont une réponse hémato
→ 3/12 WT ont une réponse hémato
→ Pas de RC

LAM SUJET AGE
RESULTATS TRAITEMENT

- Taux de RC : 35 à 65%
  variable en fonction du taux de LAM de mauvais pc

- Survie prolongée : 5 à 15%

- Définir le type de traitement en fonction :
  âge lui-même
  EG et comorbidités
  caractéristiques leucémie

ROLE OF ALLO BMT IN AML

- Good risk cytogenetics
  → not indicated in CR1

- Intermediate risk
  → indicated in CR1 (MRC)
  → different definitions (MRC / EORTC)
  → novel prognostic parameters
- Poor risk
  → poor prognosis even with allo

RISK ADAPTED TREATMENT IN YOUNGER PATIENTS WITH DE NOVO AML

Risk classification based upon cytogenetic profiles

→ **Define Tx strategy according to risk**

Specific molecularly defined entities

→ **New strategies (targeted to molecular abnormalities Flt-3)**

NEW APPROACHES IN AML

- New chemotherapy regimens (Clofarabine, Troxacitabine,cloretazine)
- Direct drug-resistance modulation (Zosuquidar)
- Anti-angiogenic (e.g. Thalidomide)
- Immunotherapeutic approaches
- Cell signaling modulation

RANDOMIZED TRIALS COMPARING ASCT AND ICC OS

	Pts	Auto	Chemo	p
Adult studies				
Zittoun 95	990	56	46	0.43
Harousseau 97	535	50	54	0.72
Burnett 98*	196	57	45	0.2
Cassileth 98	808	43	52	0.05
Pediatric studies				
Ravindranath 96	666	40	44	0.10
*Woods** 01*	887	48	53	0.21

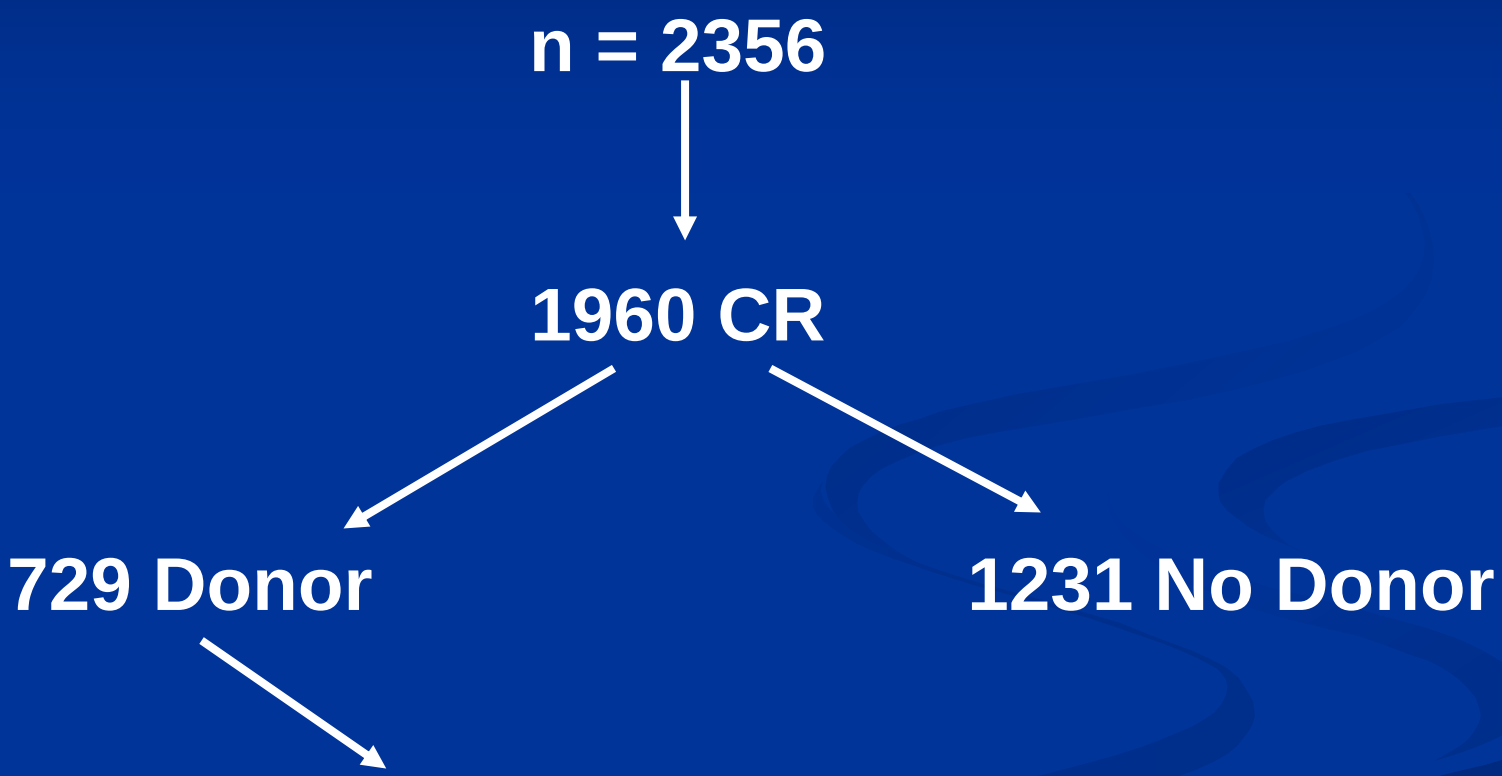
*Autologous BMT was compared to no further treatment after 4 courses of intensive chemo
** Bone marrow was purged with 4 HC in the autologous transplantation arm.
Number of patients is shown in parenthses

RANDOMIZED TRIALS COMPARING ASCT AND ICC DFS

	Pts	Auto	Chemo	p
Adult studies				
Zittoun 95	990	48 (128)	30 (126)	0.05
Harousseau 97	535	44 (86)	40 (78)	0.41
Burnett 98*	196	53 (190)	40 (191)	0.04
Cassileth 98	808	35 (116)	35 (117)	0.77
Pediatric studies				
Ravindranath 96	666	38 (89)	36 (115)	0.20
*Woods** 01*	887	42 (177)	47 (179)	0.31

*Autologous BMT was compared to no further treatment after 4 courses of intensive chemo
** Bone marrow was purged with 4 HC in the autologous transplantation arm.
Number of patients is shown in parenthses

AML10 and AML12 Recruits <45 years



ALLO BMT
INDICATIONS

- Results of allo BMT are inferior in patients > 35 (MRC, EORTC, GOELAM)
  → No difference between donor / no donor in this age cohort
- No significant difference between donor and no donor for CBF leukemias
- Results for other cytogenetic subgroup depend on cytogenetic classification
  . EORTC allo superior in bad risk
  . MRC allo superior in intermediate-risk