

# Is there a role for autologous stem cell transplantation in the treatment of acute myelogenous leukaemia?



*The University of  
Cape Town*

*Leukaemia Unit*



UCT

*Groote Schuur  
Hospital*

*Division of  
Haematology*

N Novitzky, V Thomas, C. Du Toit, A.  
McDonald.

# Therapy of AML

- Induction Therapy

- Combination chemotherapy
- Cytarabine
  - High, low, Intermediate...
- Daunorubicin
  - ✦ Thioguanine
  - ✦ Etoposide

- Optimal treatment schedule unknown

- 5+1
- 7+3
- 10+ 3
- TAD-HAM
- Hi D-Arac
  - ✦ FLAG (+ida)

- Optimal post-remission management unclear

- Standard 7+3
- High dose Cytarabine (2-4 courses)
- Autologous stem cell transplant
- Allogeneic stem cell transplant
  - ✦ Need stem cell donor

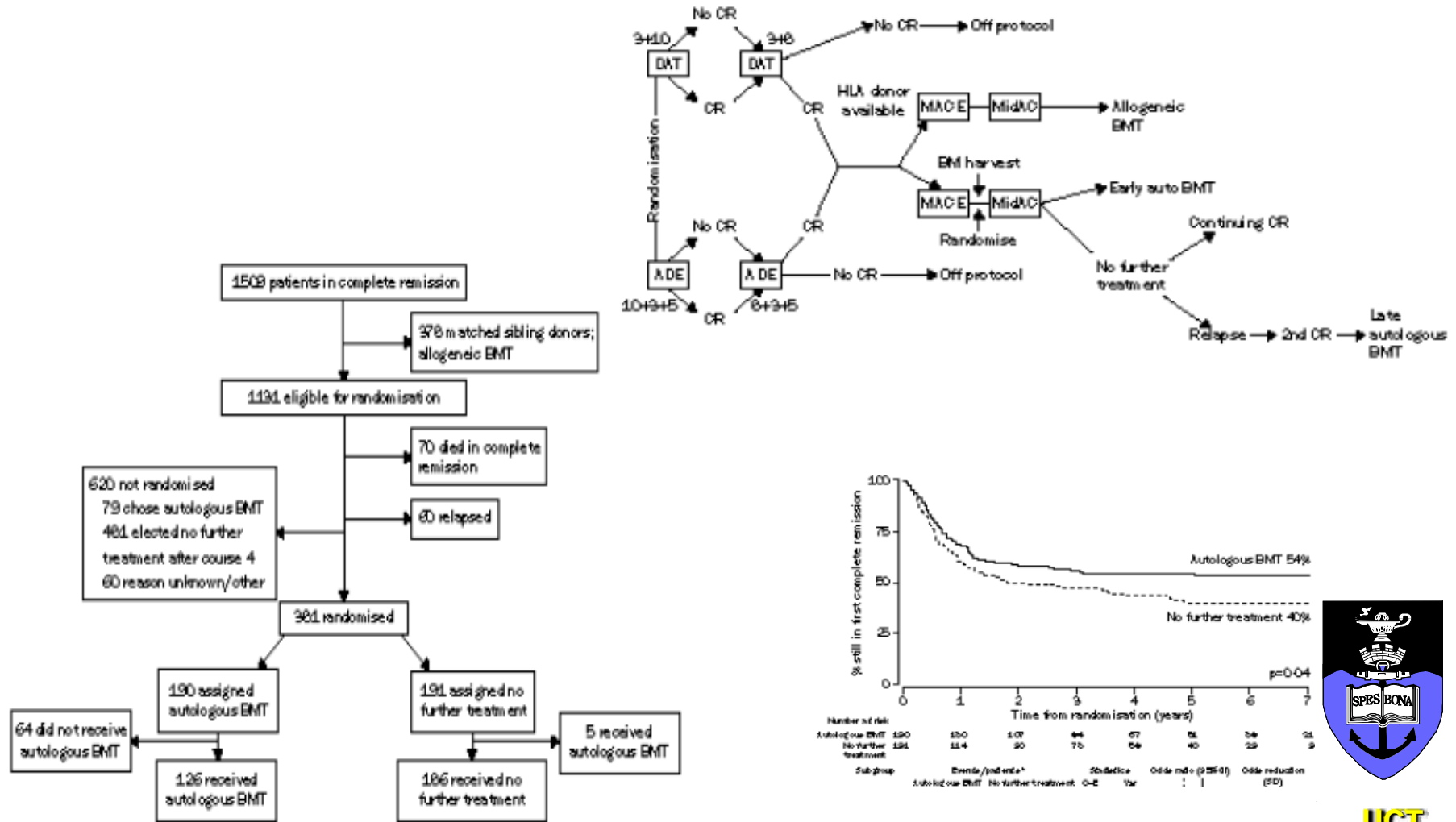


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# Randomised comparison of addition of autologous bone-marrow transplantation to intensive chemotherapy for acute myeloid leukaemia in first remission: results of MRC AML 10 trial

Alan K Burnett, Anthony H Goldstone, Richard M F Stevens, Ian M Hann, John K H Rees, Richard G Gray, Keith Wheatley, for the UK Medical Research Council Adult and Children's Leukaemia Working Parties\*

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# Treatment Schedule



	CTR-IV (1990-1998)		CTR-V (1998-2008)	
	Drugs	Schedule	Drugs	Schedule
<b>Induction</b>	Etoposide Cytarabine Daunorubicin	100 mg/m <sup>2</sup> d for 7 days 100 mg/m <sup>2</sup> c.i. d for 7 days 45 mg/m <sup>2</sup> , days 1, 2 & 3.	Etoposide Cytarabine Daunorubicin	100 mg/m <sup>2</sup> d for 7 days 100 mg/m <sup>2</sup> c.i. d for 7 days 75 mg/m <sup>2</sup> , days 1, 2 & 3.
<b>Consolidation</b>	Etoposide Cytarabine Daunorubicin	100 mg/m <sup>2</sup> d for 7 days 100 mg/m <sup>2</sup> c.i. d for 7 days 45 mg/m <sup>2</sup> , days 1, 2 & 3. X 2	Etoposide Cytarabine Daunorubicin	100 mg/m <sup>2</sup> d for 7 days 100 mg/m <sup>2</sup> c.i. d for 7 days 60 mg/m <sup>2</sup> , days 1, 2 & 3. X 1
<b>Post Remission Therapy</b>	Allogeneic or autologous transplantation		Allogeneic or autologous transplantation	



# Objectives of the Study

- Primary objectives:
  - Remission rate (CR: <5% blasts)
  - Rate of response with 1 course of therapy
- Secondary objectives
  - Proportion of patients undergoing stem cell transplantation
  - Outcomes after SCT
    - ✦ Allogeneic
    - ✦ Autologous
  - Causes of treatment failure
  - Overall survival
- Objectives of the current study (patients undergoing SCT)
  - Retrospectively review the outcome transplantation
  - Determine proportion of surviving patients
  - Review prognostic risks factors and define appropriate therapy in the South African context



# Patients and Methods



- Inclusion criteria

- Age 13-65
- Primary AML
- No contraindications for SCT

- If HLA id. Sibling available: allo SCT

- If HLA id. Sibling not available: Auto SCT

- Exclusion criteria

- AML evolving from MDS/MPO or chemotherapy/radiation
- HIV infection
- Severe organ dysfunction
- History of recent myocardial infarction or active cardiac disease
- APL (FAB M3)
- Unable to mobilise enough CD34+ cells



# Conditioning for Transplantation

- Radiation based conditioning

- TBI (fractionated) 1200 cGy
- TLI (fractionated) 600 "
- Cyclophosphamide 120 mg/kg
  - ✦ Neutropenic fever prophylaxis
  - ✦ Blood product support

- Chemotherapy based conditioning

- Busulfan 12 mg/kg
- Melphalan 140 mg/m<sup>2</sup>
- Cyclophosphamide 120 mg/kg
  - ✦ Neutropenic fever prophylaxis
  - ✦ Blood product support



# Stem cell Harvesting



- Bone marrow transplants
  - Collection by multiple aspirations
  - Buffy coat collected on IBM 2190
  - T-cell depletion
- PBPC transplants
  - Mobilization with G-CSF 5-10 ug daily, for 5-6 days
  - Aphaeresis until CD34+ > 2 x 10<sup>6</sup>/kg
- GvHD prophylaxis: T-cell depletion
  - Campath antibodies used *in vitro*
    - ✦ 1-2mg/10<sup>10</sup> cells
  - For PBPC grafts post transplant immunosuppression with cyclosporin for 90 days
- Autologous mobilisation of CD34+
  - Cyclophosphamide 60 mg/kg or Etoposide 2 gr/m<sup>2</sup>
  - Filgrastim 300-600 ug/day
  - Large volume apheresis
  - Cryopreservation of the product
    - ✦ Controlled rate freezer



# Presentation Parameters



	All Patients N= 157	CTR-IV N= 71	CTR-V N= 86	P=
Age	35 (14-60)	33.5 (15-61)	36 (14-58)	NS
Sex (F/M)	78/79	39/32	39/47	NS
Hb g/dL	8.2(2.1-15)	9 (2.1-13.8)	7.2 (2.6-11.8)	0.07
WCC x 10 <sup>9</sup> /L	16.5 (0.6-414.5)	13.4 (0.6-179)	16.8 (0.7-145.6)	NS
Blasts x 10 <sup>9</sup> /L	7.27 (0-187)	4 (0-69)	8 (0-99)	NS
Platelets x 10 <sup>9</sup> /L	45.5 (3-2732)	48.5 (0-99)	40 (6-2732)	NS
LDH	672 (130-4185)	533 (166-3122)	750 (240-1499)	0.07
Cytogenetics	N= 68	N= 28	N= 42	NS
Favourable		24%	22%	
Intermediate		55%	49%	
Unfavourable		21%	29%	
PS	2 (1-4)	2 (1-4)	2 (1-4)	NS



# Response to Therapy



Initial Therapy	CTR-IV N= 71	CTR-V N= 86
Complete remission CR 1 <sup>st</sup> course	44 (62%) 33	67 (78%; p= 0.02) 58
In CR failed to get SCT	15 (34%) 2 refused further Tx 2 cardiac dysfunction 2 platelet refractoriness 3 persistent infection 5 relapsed 1 unknown	21 (31%) 5 refused further Tx 2 cardiac dysfunction 5 sepsis 7 relapsed 1 failed SCT collection
Underwent SCT	29	45
Allogeneic	11	23
Autologous	18	22



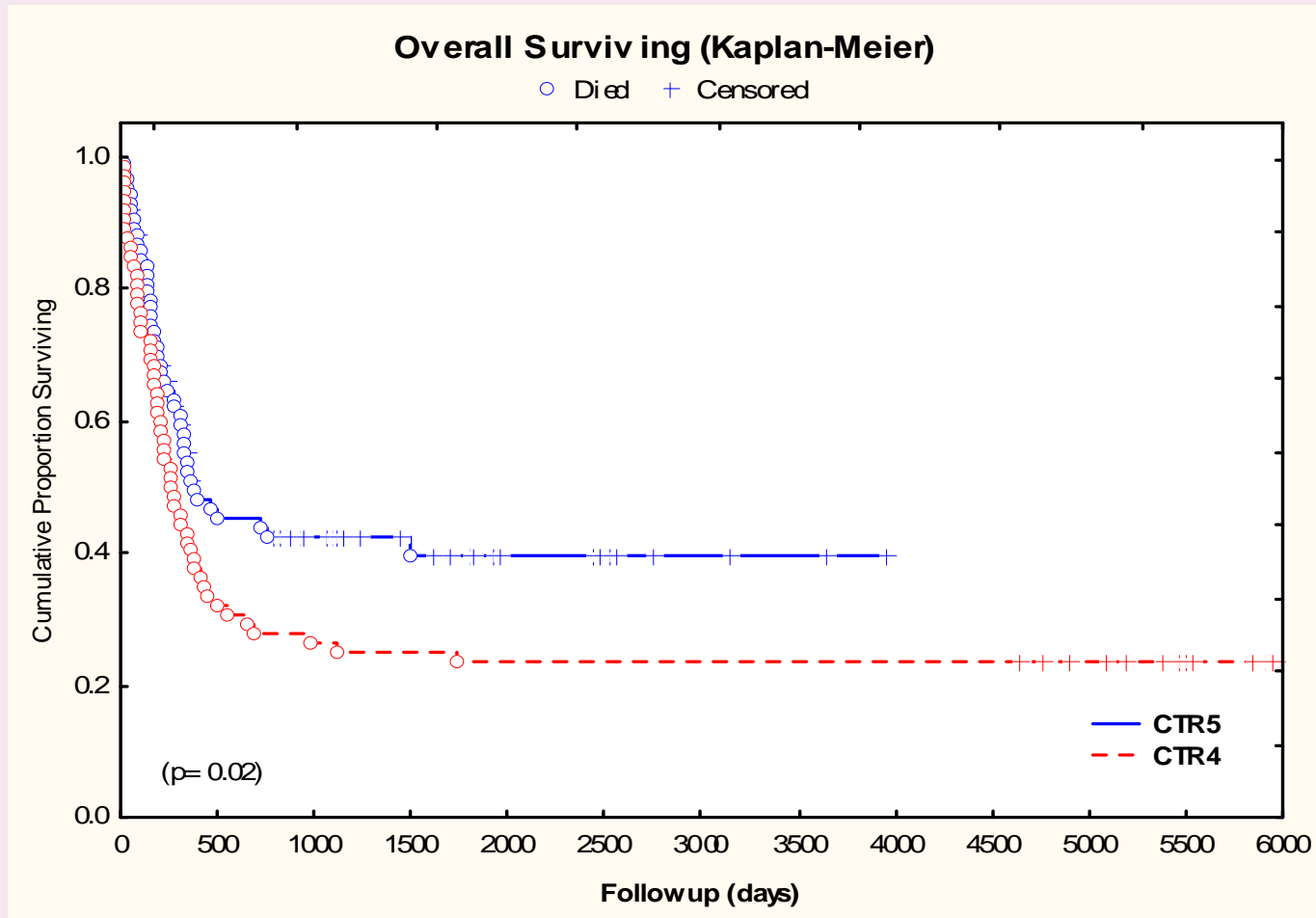
# Stem Cell Transplantation



All: 74/111	Auto SCT N= 39	Allo SCT 35
Age	34 (14-65)	36 ( 15-58)
Females/Males	17	16
PS	2 (1-3)	2 (1-2)
CTR-IV/CTR-V	18 / 22	11 / 24
Cytogenetic risk		
Low	11 (28%)	8 (28%)
Intermediate	22 (56%)	17 (49%)
High	6 (16%)	10 (23%)
Hb g/dL	8.2 (5.9-15)	7.7 (6-15)
WCC x 10 <sup>9</sup> /L	16.15 (0.72-414.5)	7.7 (6-15)
Blasts x 10 <sup>9</sup> /L	7.77 (0-80)	4.45 (0-80)
Plts x 10 <sup>9</sup> /L	42 (17-2032)	38 (17-2732)
LDH i.u.	630 (180-1150)	313 (130-2121)
Median time to transplantation	69(41-402)	88(53-238)

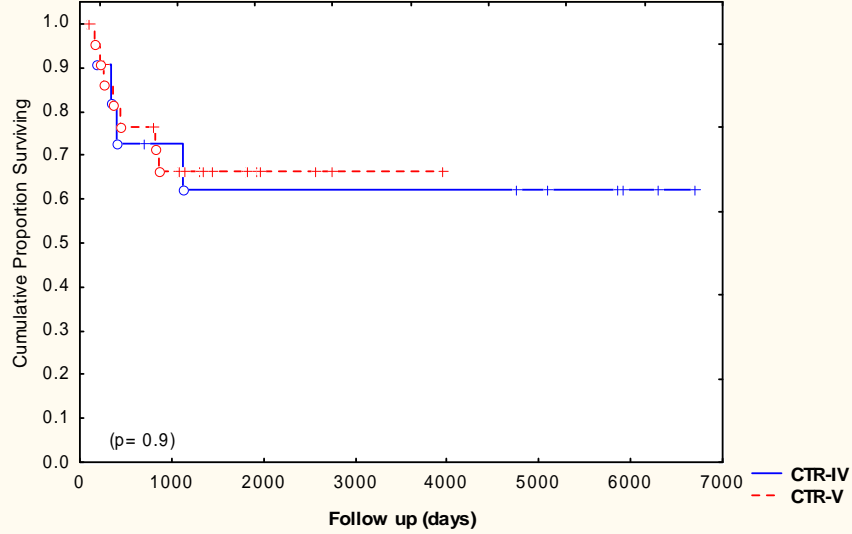


# Treatment Outcome



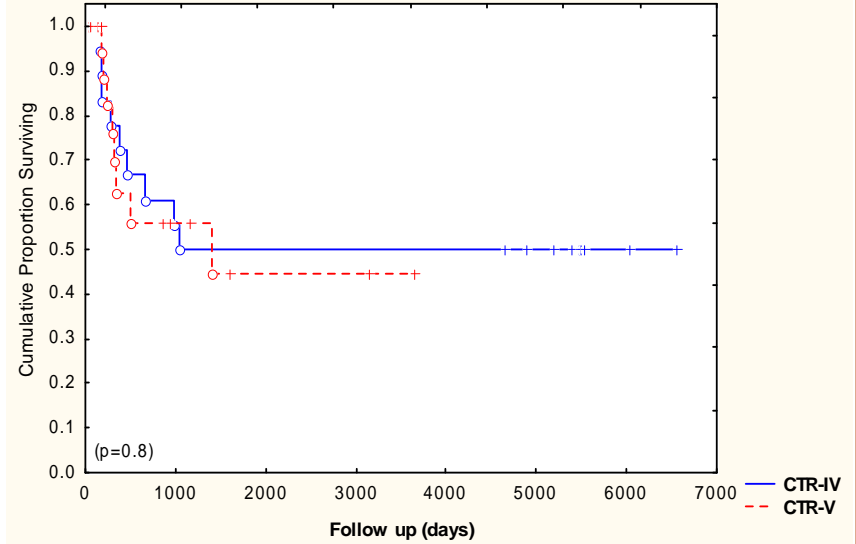
### Allogeneic Stem Cell Transplantation Outcome According to Trial

○ Complete + Censored



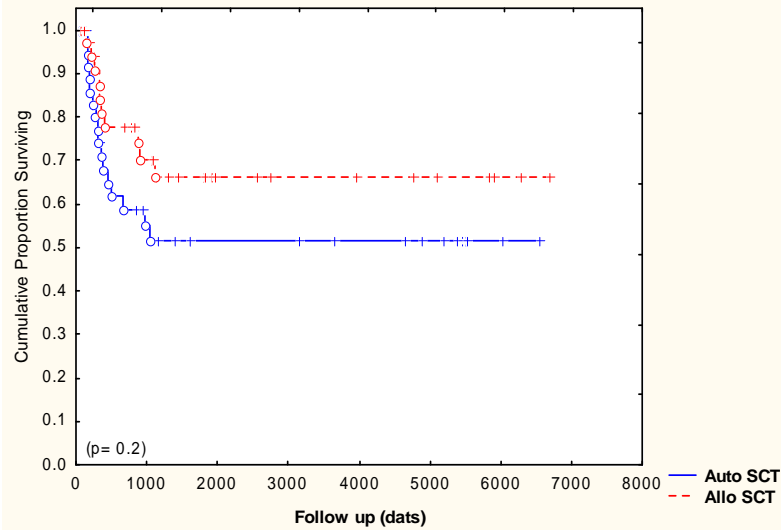
### Autologous Stem Cell Transplantation Survival According to Trial

○ Died + Censored



### Survival According to Type Transplant

○ Died + Censored



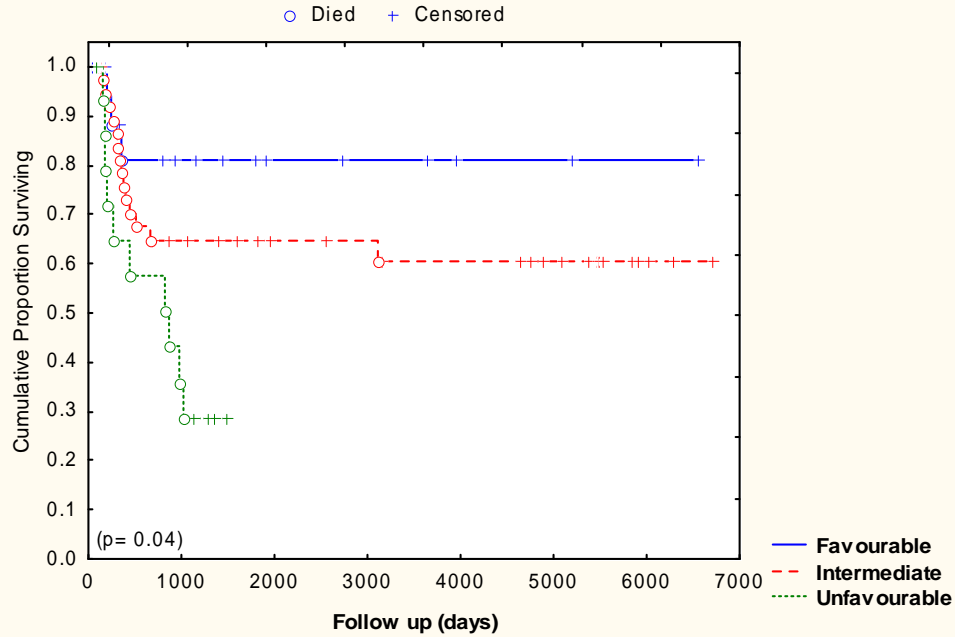
# Stem Cell Transplantation



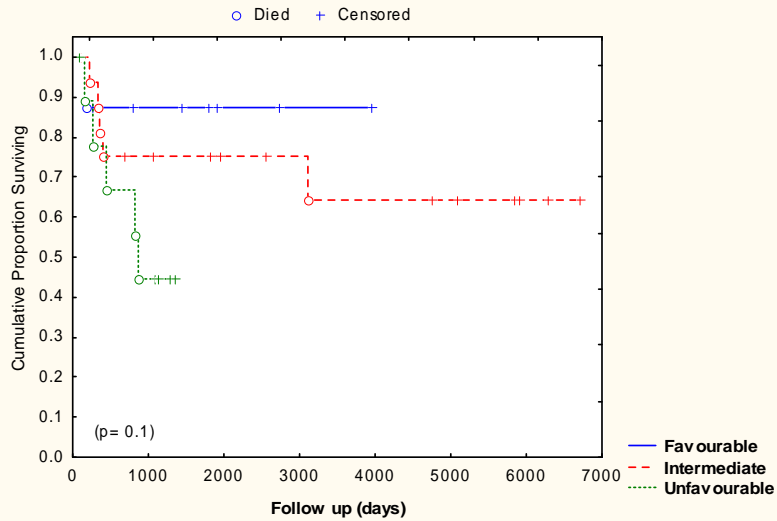
Outcome of SCT	Auto SCT N= 39	Allo SCT= 35
Non relapse mortality	7 (17%)	5 (14%)
VOD	1	1
BM failure	1	
Malignancy	1	4(2)
Infections	4	2
GvHD>1		
Relapses	9 (31%)	7 (23%)
Alive	23 (51%)	23 (66%)
OS	1609 (149- 6558)	1819 (83-6704)
Man-U-Whitney	Dysplasia Cytogenetics PS More than 1 induction course Blasts LDH	Dysplasia Cytogenetics PS More than 1 course
Cox Regression analysis	Cytogenetics (p= 0.012) LDH (p= 0.0019)	Cytogenetics (p= 0.012)



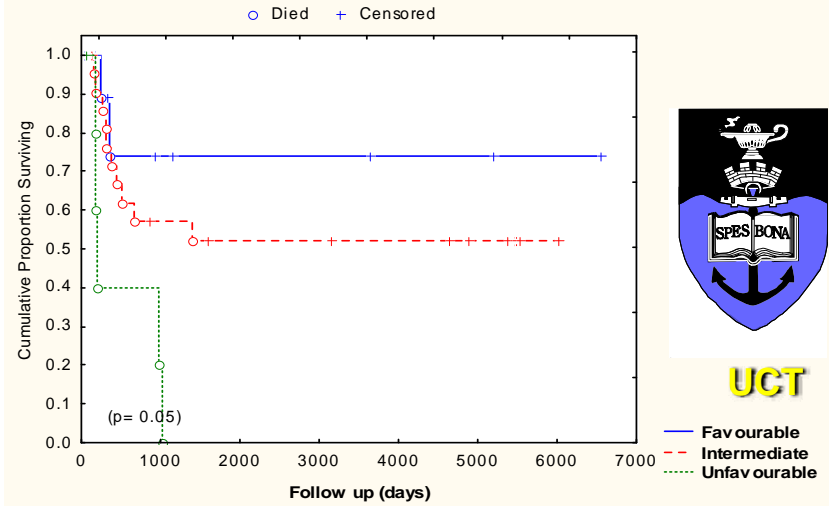
### Stem Cell Transplantation Survival According to Cytogenetic Risk



### Allogeneic Transplantation Survival According to Cyrogenetic Risk



### Autologous Stem Cell Transplantation Survival According to Cytogenetic Risk



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# Conclusions:



- 1) Despite a proactive approach 1/3 of patients in CR 1 did not received the intended intensification
- 2) Cytogenetic profile is confirmed as a critical prognostic factor in de novo AML
- 3) Autologous stem cell transplantation is very effective consolidation therapy for patients with low cytogenetic risk
- 4) Patients undergoing Auto and Allo SCT appear to have similar outcome in intermediate risk cytogenetic group
- 5) Auto SCT has little protective role in patients with adverse karyotype AML



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## Treatment of primary acute myeloid leukemia: results of a prospective multicenter trial including high-dose cytarabine or stem cell transplantation as post-remission strategy

SALUT BRUNET  
JORDI ESTEVE  
JOAN BERLANGA  
JOSEP M. RIBERA  
JAVIER BUENO  
JOSEP M. MARTÍ  
JOAN BARGAY  
RAMON GUARDIA  
ANTONI JULIÀ  
ALBERT GRANENA  
EMILI MONTSERRAT  
JORGE SIERRA  
FOR THE CETLAM  
COOPERATIVE GROUP  
(GRUPO COOPERATIVO DE  
ESTUDIO Y TRATAMIENTO DE  
LAS LEUCEMIAS AGUDAS Y  
MIELODISPLASIAS), SPAIN

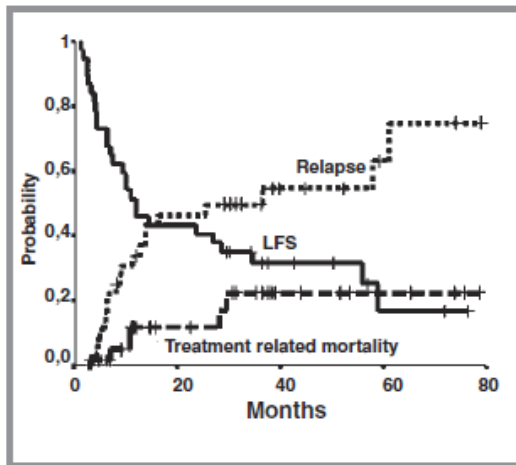


Figure 4. Leukemia-free survival since CR, relapse and TRM in patients > 50 years old according to the intention to treat with autologous transplantation (n=37).

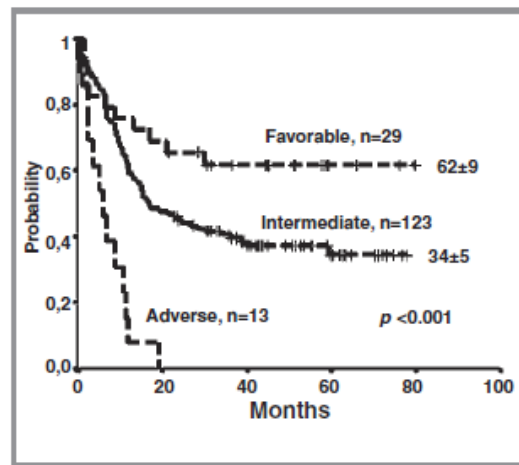


Figure 5. Overall survival according to cytogenetics at diagnosis.

