7th South African Symposium on Haematopoietic Stem Cell Transplantation

# MUD SCT for Paediatric AML?

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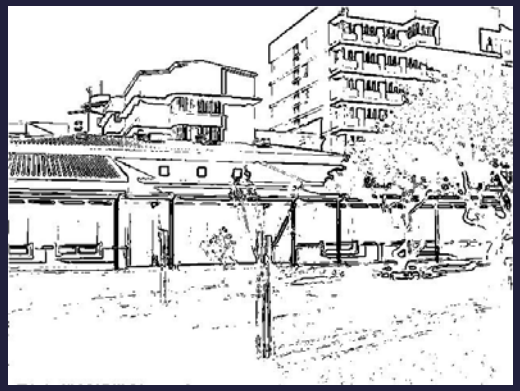


# THE SCENARIO

- A 10 year old boy with M2 acute myelogenous leukaemia presents with a leukocyte count of of 16 x $10^9$/L
  - 30% myeloblasts (CD34+, DLA-DR+, CD33+, CD13+, CD7+)
  - normal male karyotype
  - 46 XY cytogenetics
  - CSF clear
- He achieves remission after induction chemotherapy
- He does not have siblings but the local registry indicated that there are several 10/10 matches available
- Do we transplant?

# TWO QUESTIONS

- ONE

  Is transplant superior to chemotherapy alone? For which patients?

- TWO

  In the absence of a matched sibling donor, do we use a MUD?

# THE EXPERTS IN A NUTSHELL

- In a series of articles in BJH in 2002 comparing MSD to chemotherapy:
  - Statistician … need more data
  - Creutzig (BFM) … good risk: no / high risk: yes
  - Burnett (adult transplanter) … good risk: no / need to capitalise on reduction in relapse risk by improving transplantation effectiveness
  - Chen (CCG) … ONLY t(8;21) and inv16 warrant *allo vs chemo* trial and that alternative donor SCT for poor risk patients may be warranted


Creutzig et al, **BJH 2**002;118:365-377

Wheatley et al, **BJH 2**002;118:351-356

Burnett et al, **BJH 2**002;118:357-364

Chen et al, **BJH 2**002;118:378-384

# SO WHERE'S THE RCT?

- Problems with evaluating the "transplant arm" of a RCT
  - Patients in the transplant arm need to stay in CR long enough to be transplanted
  - Eligible patients may be unsuitable for medical or social reasons
  - Eligible patients may not have a donor
  - Those who do have donors may be better risk patients
- So the best tool we have is to compare those with and without donors

  *… genetic or Mendelian randomisation*
- Most studies show that the lower relapse rate after allogeneic transplantation is offset by more treatment related mortality
- IN PRINCIPLE transplantation should be offered to those with poorer response to chemotherapy and a higher relapse rate (poor risk disease)

Creutzig et al, **BJH 2**002;118:365-377

# CURRENT PAEDIATRIC PRACTICE

- Who is Doing What?
  - BFM
  - MRC
  - CCG, POG, COG
  - Others
- How are the patients faring?
  - Risk assignment
  - Treatment
  - Outcomes

# THE BFM (studies 83/87/93)

- STANDARD RISK
  - M1 or 2 with Auer rods / M3 / $M4_{eo}$
  - Cytogenetics t(8;21), inv16, t(15;17)
  - < 5% blasts on day 15 marrow
- HIGH RISK
  - Other Morphology or Cytogenetics
  - Non-remitters

⇨ TREATMENT STRATEGY

- Transplant for HIGH RISK only … any matched related donor

Creutzig et al, **Leukemia** 2005;19:2030-2042

# THE BFM (studies 83/87/93)

- Results support the risk stratification, including the assignment of favourable morphology without favourable cytogenetics as good risk …

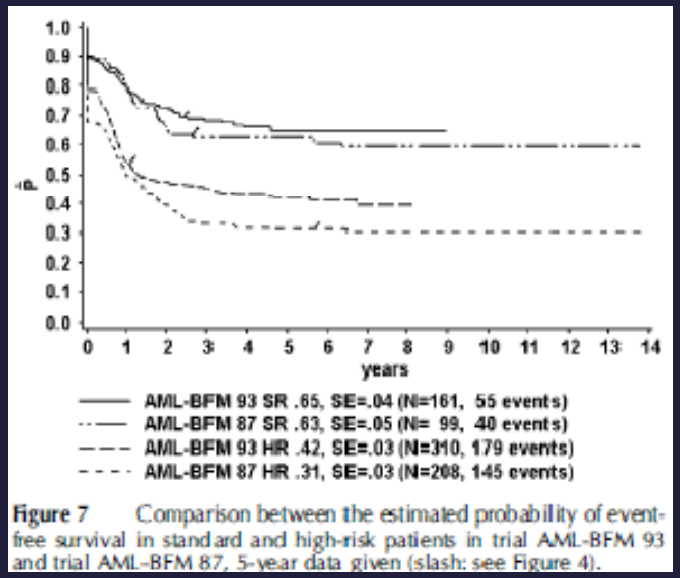



**Figure 7** Comparison between the estimated probability of event-free survival in standard and high-risk patients in trial AML-BFM 93 and trial AML-BFM 87, 5-year data given (slash: see Figure 4).

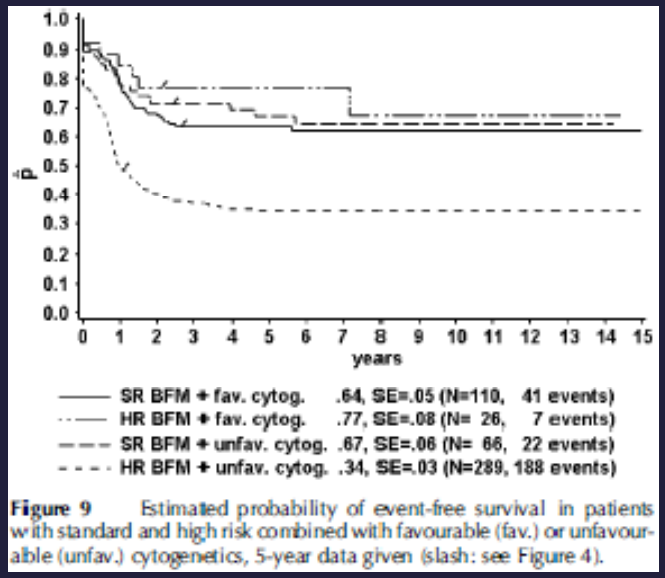



**Figure 9** Estimated probability of event-free survival in patients with standard and high risk combined with favourable (fav.) or unfavourable (unfav.) cytogenetics, 5-year data given (slash: see Figure 4).

- BUT: Analysis of BFM-93 high risk patients showed no advantage of BMT over chemo alone

Creutzig et al, **Blood** 2001;97:3671-3672 and **Leukemia** 2005;19:2030-2042

# MRC AML (studies 10 and 12)

- GOOD RISK
  - t(8;21), inv16, t(15;17) or FAB M3 morphology
  - < 5% blasts on day 15 marrow
- STANDARD RISK
  - All others
- POOR RISK
  - Monosomy 5 or 7, del(5q), abn(3q), MAKA
  - > 15% blasts on day 15 marrow
  - *Presence of FLT3-ITD+ regarded as a poor prognostic factor (FLT3-inhibitor randomisation in adults)*

Gibson et al, **Leukemia** 2005;19:2130-2138

# MRC AML (studies 10 and 12)

- RESULTS BY RISK CATEGORY:

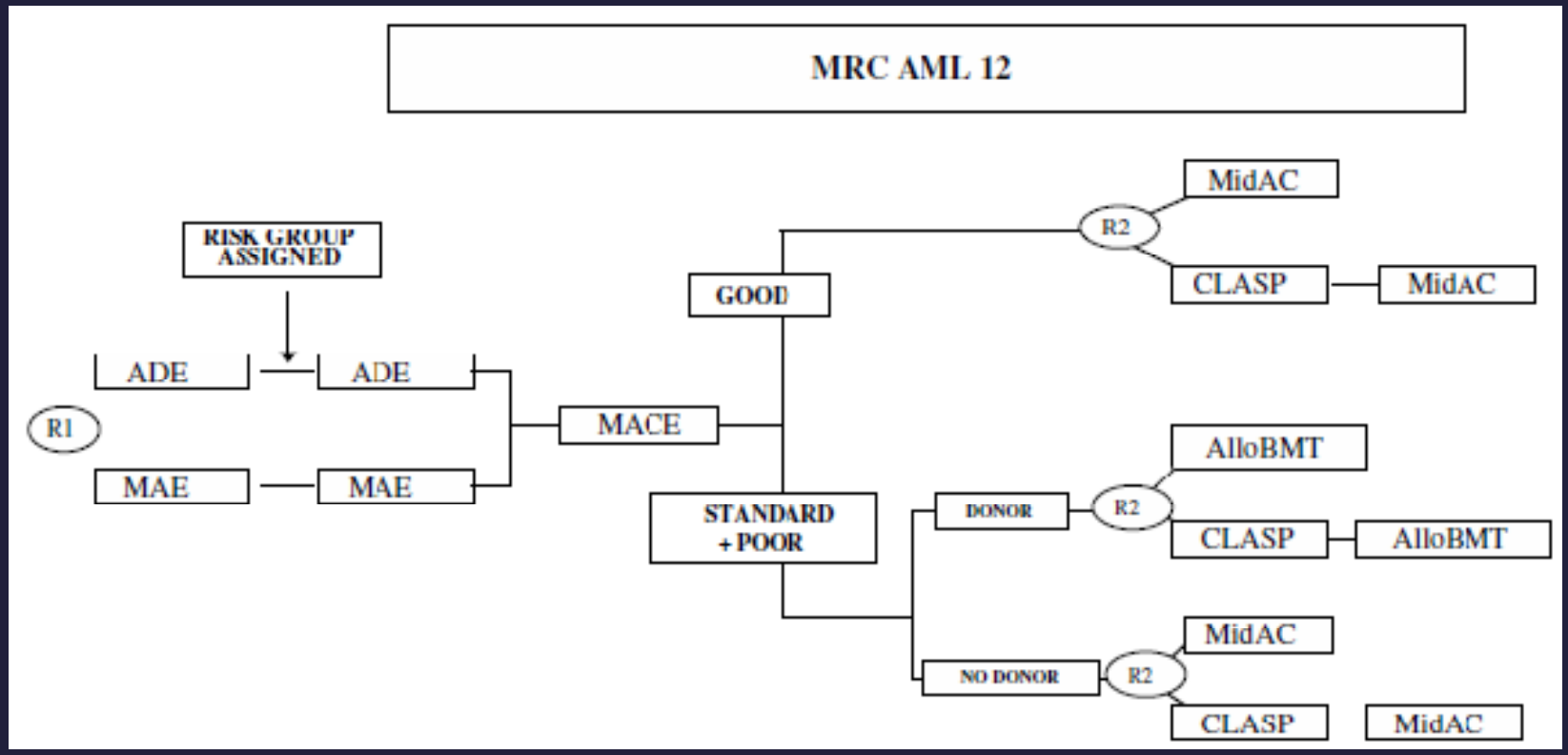
| | AML 10 | | AML 12 | |
|---|---|---|---|---|
| | Number | 5yr OS% | Number | 5yr OS% |
| GOOD RISK | 85 | 79 | | 84 |
| STANDARD RISK | 127 | 60 | | 76 |
| POOR RISK | 49 | 25 | | 47 |

- These results affected transplant decision-making thus …

Gibson et al, **Leukemia** 2005;19:2130-2138

# MRC AML 12

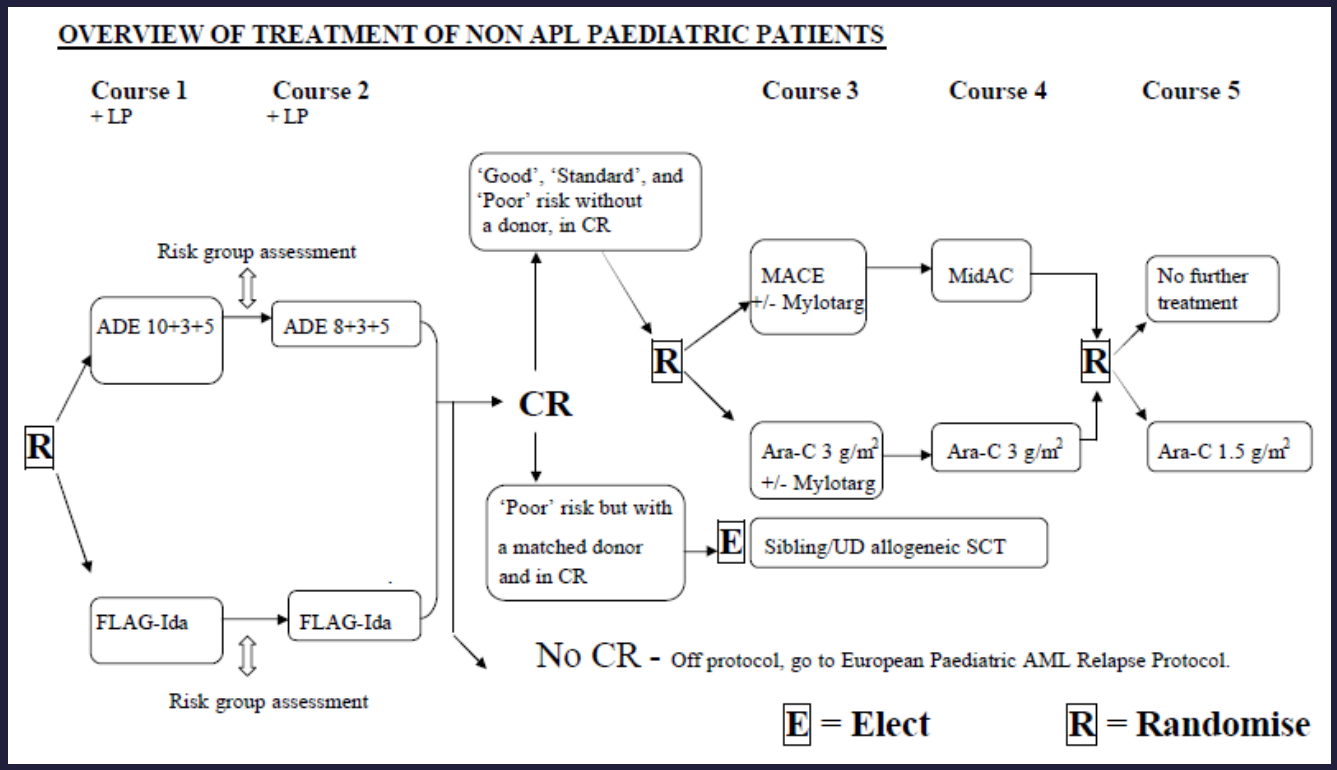
- MSD SCT randomisation (Donor/No-donor) for Standard and Poor Risk




Gibson et al, **Leukemia** 2005;19:2130-2138

# MRC AML 15

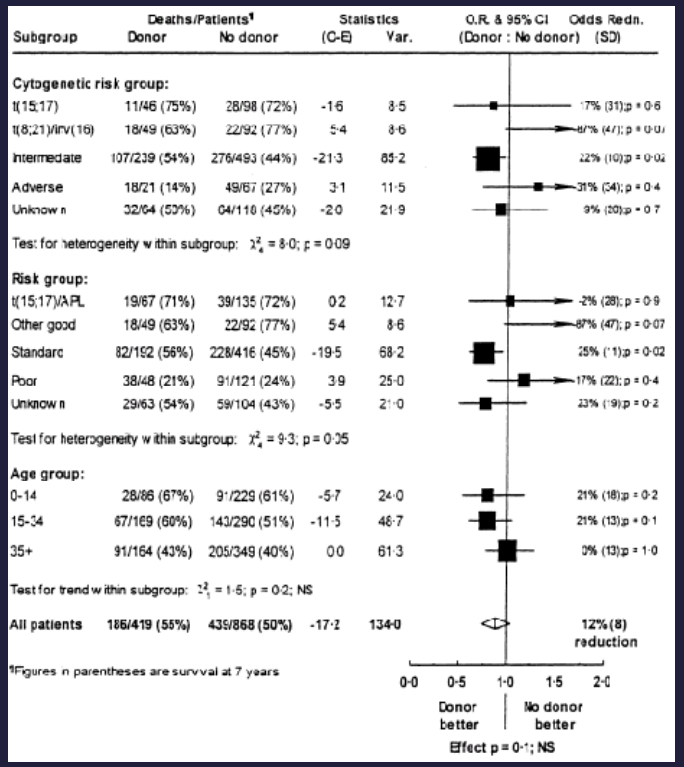
- MSD SCT randomisation (Donor/No-donor) for Poor Risk ONLY




AML15 Paediatric Guidance V3 July 2006

# MRC AML 10 – TRANSPLANT RESULTS

- Review of transplant in CR1 …
- Powerful antileukaemic effect offset by
  - TRM
  - Better salvage rate after chemo only
- NO survival advantage to BMT in children




Burnett et al, **BJH** 2002;18:385-400

# US CCG TRIALS

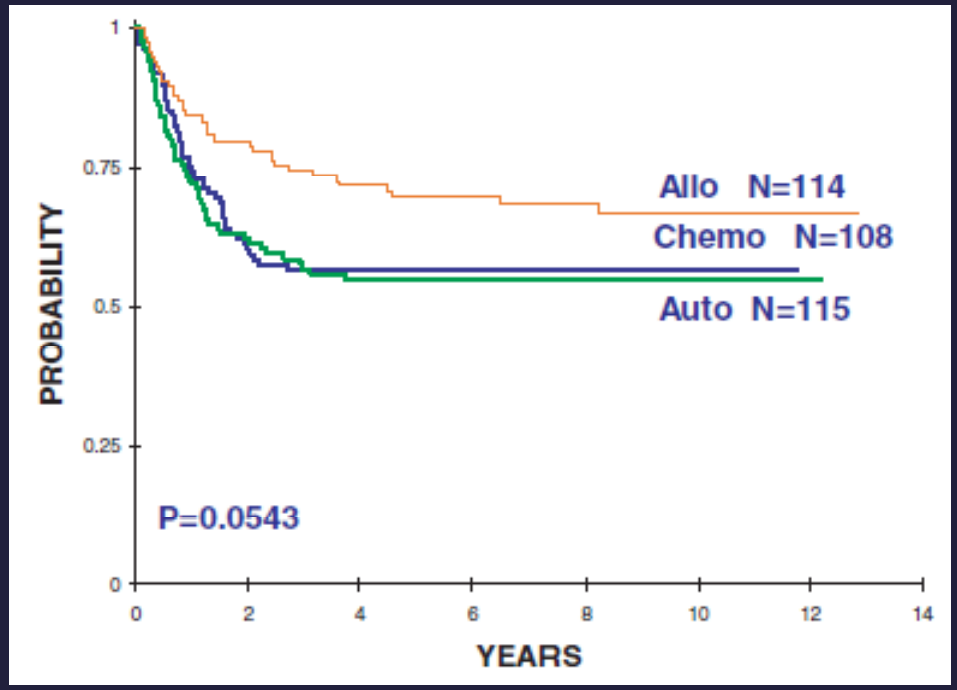
- Americans took an entirely different approach:
- All children with AML (excluding APL) in first remission with a MSD were transplanted …

**Table 1** Sequential CCG studies of AML

| *Study* | *251* | *213* | *2861* | *2891* | *2941* |
|---|---|---|---|---|---|
| Years | 1979–1983 | 1985–1989 | 1988–1989 | 1989–1995 | 1995–1996 |
| *N* | 355 | 355 | 84 | 617 | 53 |
| Induction therapy | '7+3' (C+R) | '7+3' (C+R) *vs* DCTER ('Denver') | DCTER (IT) | DCTER IT *vs* ST $N=398^{a}$ $N=209^{a}$ | Ida-DCTER (IT) *vs* Ida-CTER (IT) |
| Consolidation/maintenance Chemotherapy | 8 – drug cyclic (Aza, C, Car, MP, MTX, P, V, T) *vs* 5 – drug cylic (Aza, C, CTX, V, T) | HDC +5 – drug cylic (Aza, C, CTX, V, T) | | HDC | HDC[b] |
| Stem cell transplant | Allo CTX SD TBI | Allo CTX FTBI | Allo or auto BU/CTX | Allo or auto BU/CTX | Allo BU/CTX |
| GVHD prophylaxis | MTX | CSA, SCMTX | MTX | MTX | MTX |

Alonzo et al, **Leukemia** 2005;19:965-970

# US CCG TRIALS




- Results showed superior survival for Donor vs No donor with the exception of children with inversion 16
- BUT on the strength of MRC data current COG trials are not transplanting children with inv 16 or t(8;21) in CR1

Alonzo et al, **Leukemia** 2005;19:965-970

# WHAT ABOUT OTHER GROUPS?

- France, Italy, the Netherlands, the Nordic countries …
- Generally transplant non-APL AML with MSD in CR1
- Only the Italians claim better long term OS for Allo over Auto or Chemo alone
- A single centre in Spain reports excellent results using BFM based chemotherapy induction, and then transplanting all poor risk patients in CR1 (either by auto or allo) … they showed an OS of 73% for this group …
  - Toxic deaths were only 5.9% for allos and 3.2% for autos

Ortega et al, **Stem Cell Transplantation** 2003;88:290-299

# AND WHEN WE POOL THE DATA?

- Combined data from POG, CCG and the MRC comparing MSD SCT to chemotherapy alone for paediatric AML in CR1:
  - 1373 patients
  - Better OS for those receiving BMT (62% vs 51%)
  - Better OS for the standard risk group only (58% vs 39%) where the risk of relapse was greatly reduced

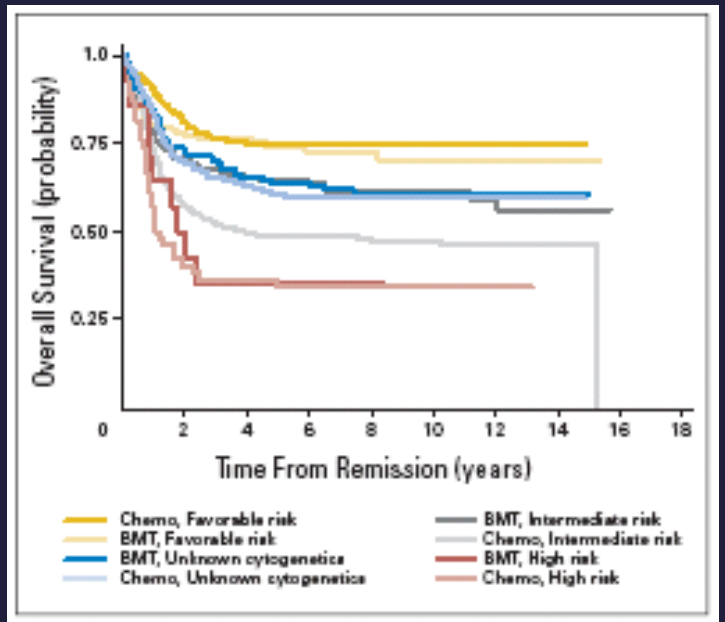



Fig 1. Estimated overall survival stratified by risk group and postremission treatment. Chemo, chemotherapy; BMT, bone marrow transplantation.


Woods et al, **Blood** 2001;97:56-62

Horan et al, **J Clinical Oncology** 2008;26:5797-5801

# AND WHEN WE POOL THE DATA?

- This has been reiterated in a recent article in PBC …

**TABLE I. Controlled Comparisons of Allogeneic BMT Versus Other Postremission Modalities in Childhood AML**

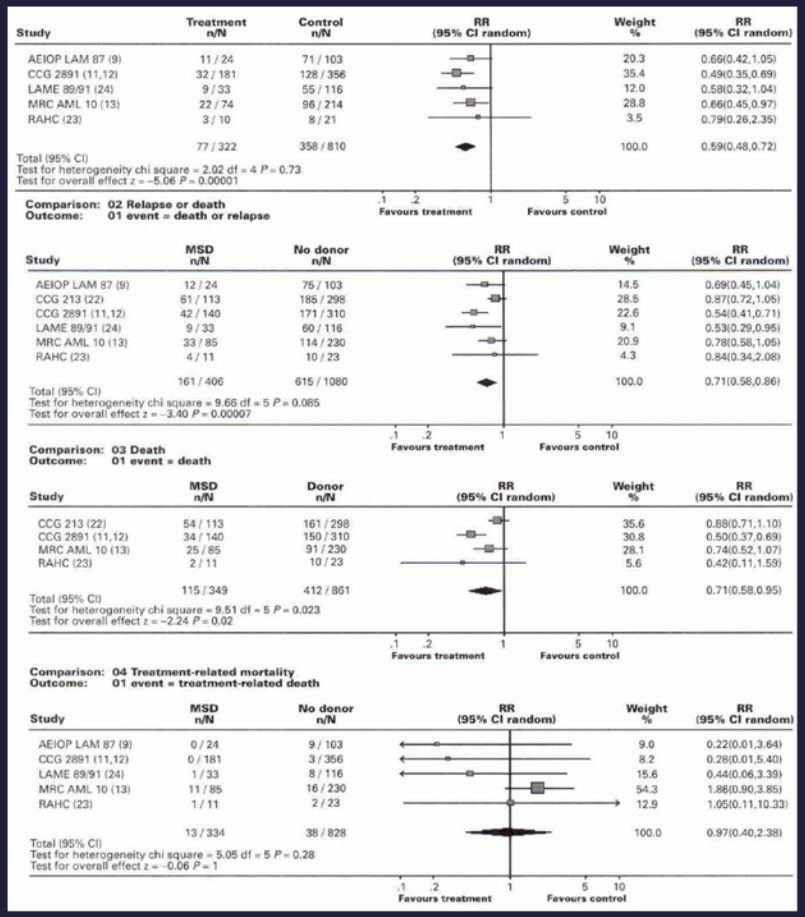
| Group, year | N | Allo outcome (%) | Auto outcome (%) | Chemo outcome (%) | Comment |
|---|---|---|---|---|---|
| CCG 79–83 | 341 (90%) | 47 | | 34 | Surv at 8 years $P < 0.05$ |
| CCG 85–89 | 411 (94%) | 52 | | 46 | Surv at 5 years $P = 0.13$ |
| AEIOP 87–90 | 96 (76%) | 51 | 21 | 27 | DFS at 5 years $P = 0.03$ |
| POG 88–93 | 321 (58%) | 52 | 38 | 36 | DFS at 3 years $P = 0.01/0.06$ Surv $P = 0.007/0.15$ |
| UKCCG 88–95 | 315 (NA) | 70 | | 60 | Surv at 7 years (time adjusted) $P = 0.10$ |
| CCG 89–94 | 537 (82%) | 60 | 48 | 53 | Surv at 8 years $P = 0.002/0.05$ |

Woods, **Pediatric Blood and Cancer** 2006;46:565-956

# AND PAEDIATRIC META-ANALYSIS?

- Paediatric Meta-analysis …
  - Patients < 21 years from 1985 to 2000
  - AML in CR1
  - Donor / No donor studies (6) or RCTs comparing Auto to Chemo (4)
- Conclusions …
  - AlloBMT reduces relapse (by 18%)
  - AlloBMT improves OS (by 15%)
- They commented:

  *"Difference between MRC-10 and the others is the increased TRM"*




Bleakley et al, **Bone Marrow Transplantation** 2002;29:843-852

# WHAT ABOUT MUD ALLO SCT ARE WE GETTING BETTER AT IT?

- Italian adult study of 1180 consecutive leukaemia and lymphoma patients receiving Allo SCT over FOUR time periods … starting before 1990 and ending in 2002.

- Despite [1] increasing patient age
  [2] more unrelated transplants (alternative donors 3.5% to 50%)
  [3] patients with more advanced disease
  - TRM in SCT post CR1 decreased: 34%, 25%, 21%, 6%
  - TRM in SCT post CR2 was little changed: 37%, 35%, 30%, 25%

- So we are getting better at Allo SCT and unrelated transplantation!
- SUPPORTED BY CIBMTR DATA SHOWN YESTERDAY! *(Apperley)*

Bacigalupo et al, **Haematologica** 2004;89:1238-1247

# AND MUD SCT IN CR1 … ARE WE JUSTIFIED?

- US adult review cites as reasons for improvement of MUD SCT …
  - More precise HLA donor matching
  - Safer myeloablation (substituting fludarabine for one of the alkylators)

- Describing a cohort of 56 adult patients …

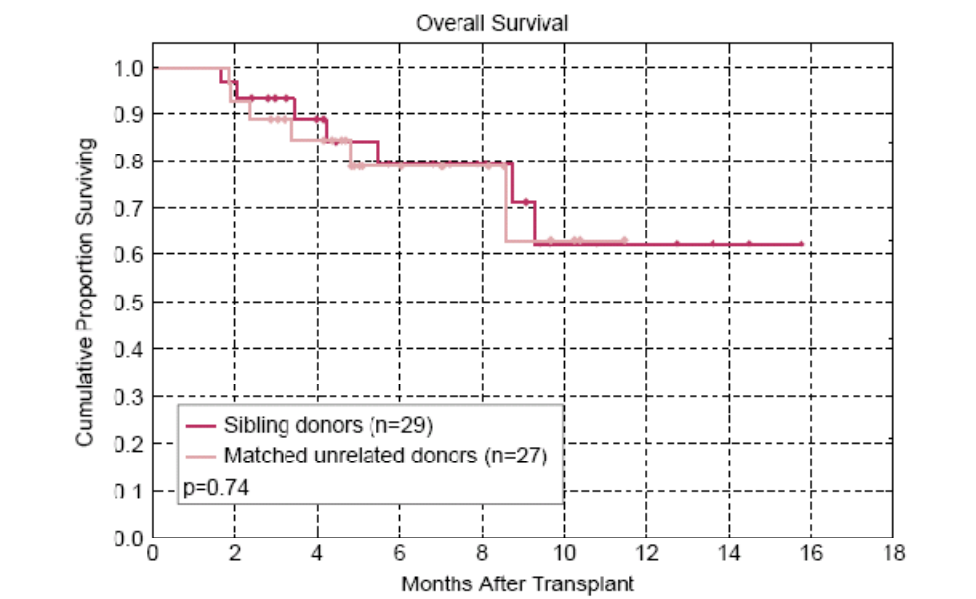


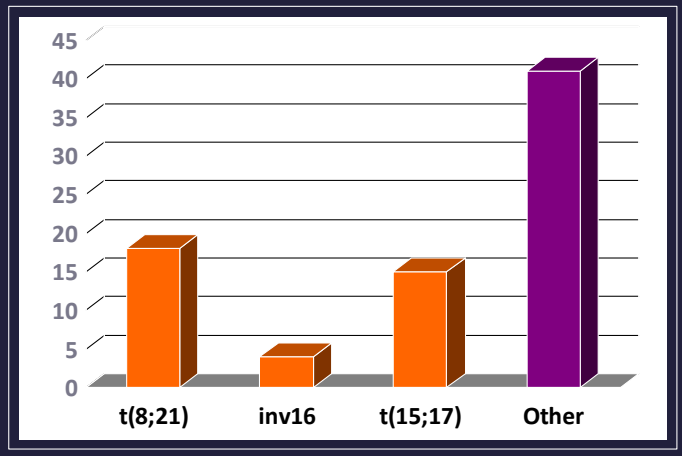

**Figure 1.** Overall survival of HLA matched sibling or unrelated donor transplants for malignancy after condition with Flu/Bu IV targeted to 800–1000 ng/ml $C_{ss}$.

Anasetti et al, **Best Practice and Research Clinical Haematology** 2006;19:321-328

# WHAT ABOUT RCCH?

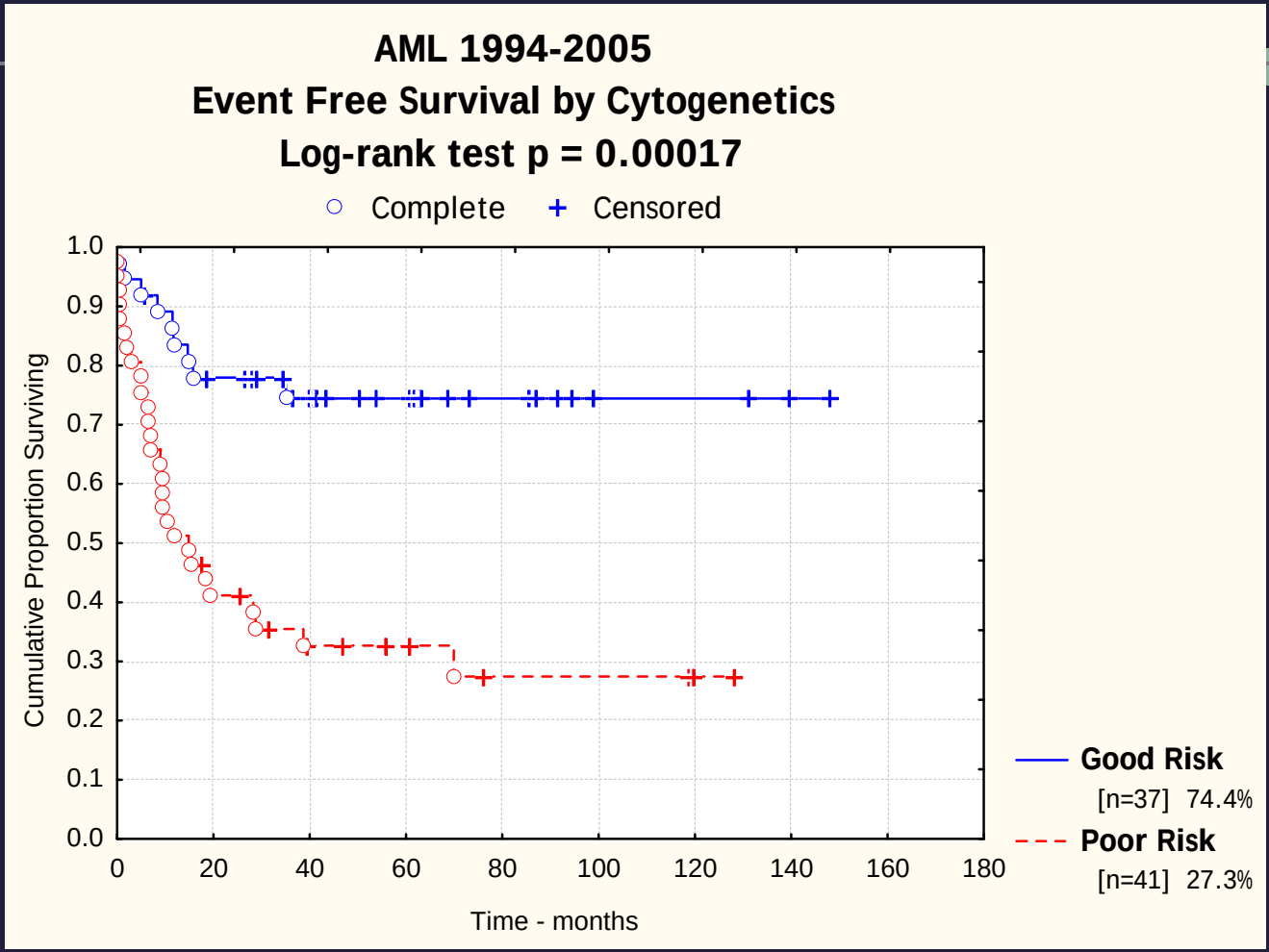
- AML 1994-2005
- Chemotherapy was modified BFM-87

- Patients
  - Good risk (37) … t(8;21)  inv16  t(15;17)
  - Standard and Poor risk (41) …
    Normal / other cytogenetics 34
    MLL gene 4 / MAKA 3
    (Non-remitters 2)



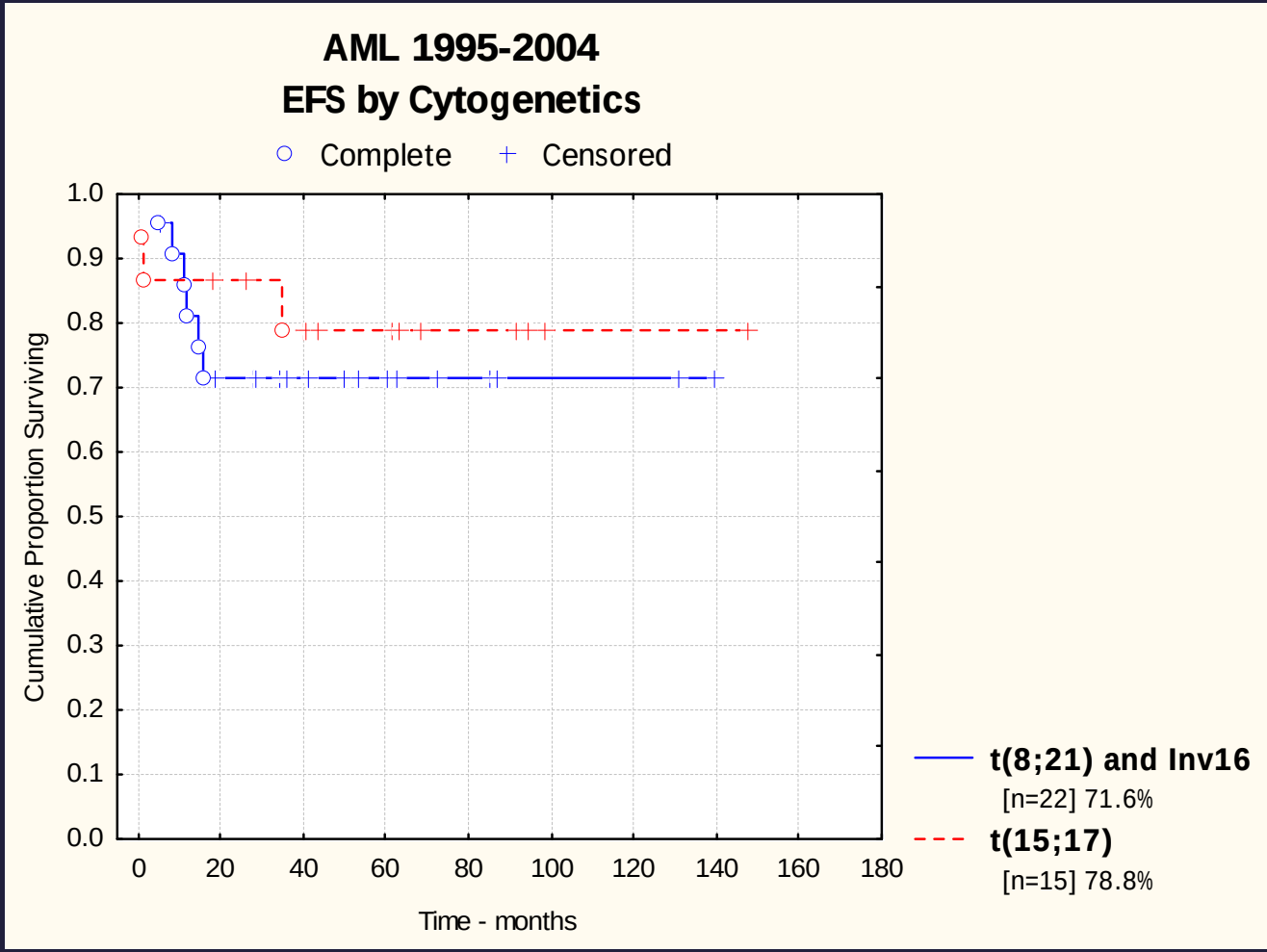

- Allo SCT for any standard or poor risk patient with a matched sib donor
  - 8 patients with matched sibs:
  - 3 good risk patients ADF in CR1
  - 2 SCT in CR1 – both ADF  1 CBT in CR2 – DD
  - 2 were not transplanted - relapsed before SCT or did not achieve CR2

# OUTCOMES for AML 1994-2005



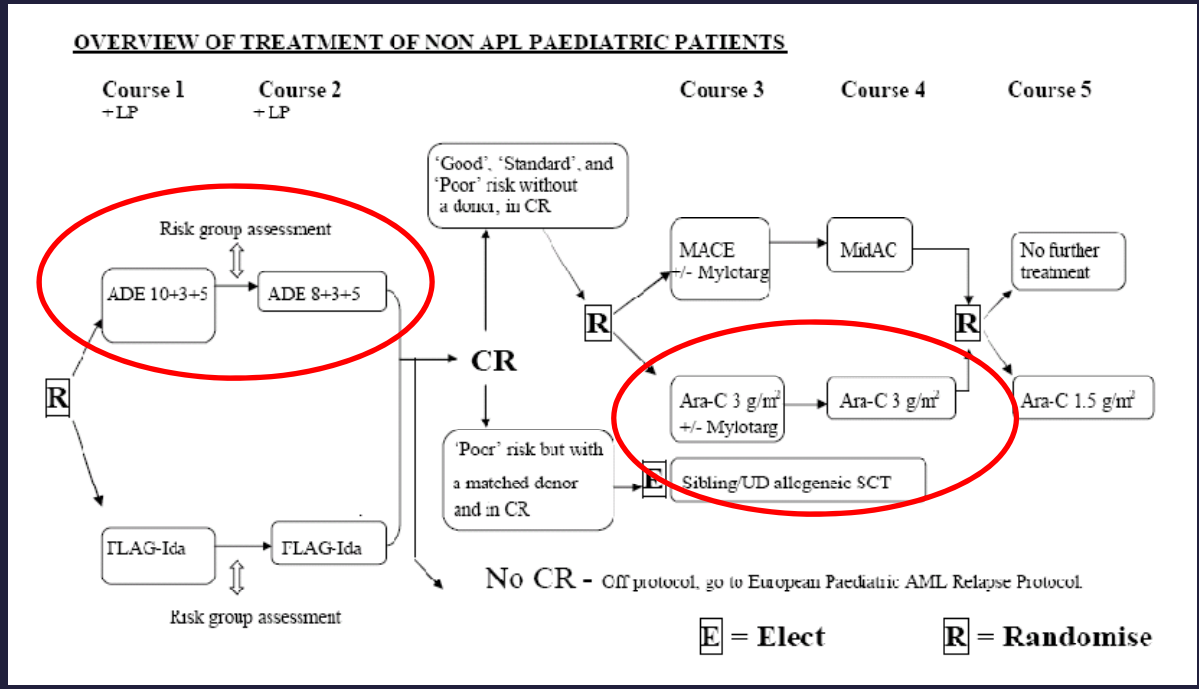

- Notably survival for M1,2 and 4 without favourable cytogenetics was 5/13 or 38%, making them at least standard if not poor risk.

# OUTCOMES for AML 1994-2005



# SO WHAT HAVE WE DONE?

- Outcomes for poor risk AML were poor
- Strategies to improve outcomes are:
  - More intensive chemotherapy: high dose AraC arm of MRC AML 15




  - MUD SCT for selected cases in CR1 if we can find a local donor

# NOW WHAT ABOUT THIS GUY?

- A 10 year old boy with M2 acute myelogenous leukaemia presents with a leukocyte count of 16 x $10^9$/L
  - 30% myeloblasts (CD34+, DLA-DR+, CD33+, CD13+, CD7+)
  - normal male karyotype
  - 46 XY cytogenetics
  - CSF clear
- RISK ASSIGNMENT: STANDARD
- *As an aside … CD7+ with normal cytogenetics suggests he may have CCAAT enhancer binding protein α (CEBPA) mutation but it's not specific and there's no data in paediatrics to consider it GOOD RISK!*

# OPTIONS?

- MRC AML 15 high dose AraC arm (MUD SCT if necessary in CR2)
- MUD SCT in CR1

# WE CHOOSE …

- MRC AML 15 high dose AraC arm (MUD SCT if necessary in CR2)

- MUD SCT in CR1