

Treatment of Adult ALL: Key Issues

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Disparities

- **Paeds: Cure rates in excess of 80-90%**
- **Adults: 90% 1st CR attainment**
- **However-most eventually relapse**
- **LFS: 30-45% at 3-7 years consistent across numerous international studies**

Different Diseases

- **Different diseases**
- **25% Ph+ in adults; 3% in paed**s
- **Different biology. Low risk group (12;21)**
- **Differing protocols**
- **Tolerance to chemotherapy**

Adult vs Children

- **Success in children NOT due to novel drugs**
- **Altering doses and schedule of existing drugs**
- **Adherence to protocol and timing**
- **Mainstay: anthracycline, steroids, vinca alkaloids, alkylating agents, asparaginase, MTX, etoposide**

AYAS (Adolescents and Young Adults)

- ?treated on paediatric protocols?
- 18-?25-35 age group
- Compelling retrospective analysis (Fr/Neth/Swe/UK/Italy) paed vs adult
- Caveats: differing median ages, variations in regimens, small patient size, different BMT criteria
- Finland: identical survivals

AYAs II (Adolescents and Young Adults)

- **CALBG Cancer and Leukaemia Group B) vs CCG (Children's Cancer Group)** *Stock, Blood 08*
- **Identical CR rate but EFS 63% vs 36%**
- **Median age CALBG: 19 while CCG:16**
- **If you look only at 16-17: EFS similar!**
- **Prospective, single arm trials ongoing**
- **No head to head comparisons except for US trial:**
- **Up to age 30: paed vs identical regimen on adult centre**

Chemotherapeutic Protocols

- **MRC UKALL XII / ECOG E2993: prolonged; complicated; asparaginase upfront. Arguably best/largest results across > 100 sites?**
- **HyperCVAD: MD Anderson. Straightforward. Across all subtypes. Alopecia and aspa. during maintenance**
- **LALA; GMALL; PETHEMA**
- **Significant toxicity: how to adjust treatment accordingly**
- **Vincristine: constipation in the elderly; neurotoxicity;**
- **azoles and vincristine and breakthrough fungal infections**

Asparaginase

- **Hepatotoxicity**
- **?more susceptible in Asians**
- **Optimal preparation and dosage still unclear**
- **Peg-L-Asp less immunogenic. No data in adults until recent CALBG trial: Aspa depletion achieved**
- **Dex or pred? Dexa preferred in children. But Dex may be related to Asparaginase (Yang, JCO2008)**
- **FFP replacement and coagulation monitoring: routine in adults. Less in children.**
- **FFP contains asparagine: compromise depletion (Leuk 2008)**
- **Thrombosis a issue rather than bleeding.**

Stratified treatment during induction

- **Depending on risk factors in paediatrics**
- **Balance of efficacy and toxicity**
- **None in adults. Stratification of risk groups only for transplantation**
- **There is no “good risk”**

Transplantation

- **Autologous transplants: Not generally recommended at the moment. Data from MRC and earlier French trials**
- **Autologous transplants plus maintenance or immunotherapy?**
- **Allogeneic: traditionally been demonstrated for high risk group.**
- **LALA: donor vs no donor randomisation. Those with no donor randomised to chemo vs autologous. No benefit from auto. Allos increased DFS for high risk group**

Meta-analysis

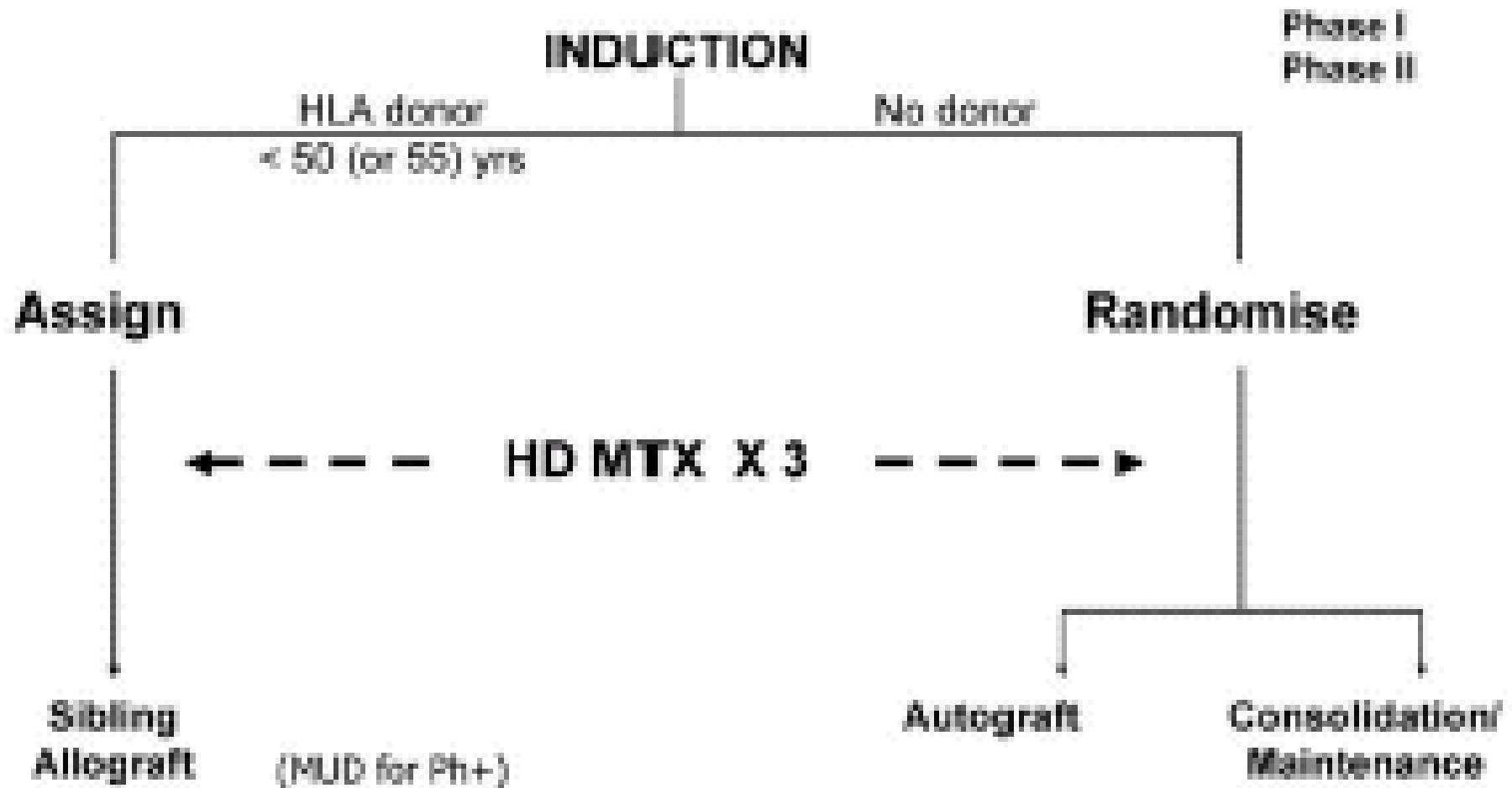
- Yanada et al (Cancer 2006): 7 studies involving 1274 patients. Donor vs no donor. Better survival for those with a donor and high risk
- No effect of autologous transplants
- Hahn T et al (BBMT 2006): Allo-BMT in 1st CR for high risk demonstrates survival benefit

In adults with standard-risk acute lymphoblastic leukemia, the greatest benefit is achieved from a matched sibling allogeneic transplantation in first complete remission, and an autologous transplantation is less effective than conventional consolidation/maintenance chemotherapy in all patients: final results of the International ALL Trial (MRC UKALL XII/ECOG E2993)

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A MRC UKALL XII / ECOG 2993



Why Standard risk and not high?

- High TRM/NRM for high risk group going for allogeneic transplant: 36% at 2 years. Only 19% in standard risk
- High risk group may have older cohort of patients. Poorer tolerance to myeloablation.
- Blunts the effect of an allo-transplant
- Cut off age for transplant 54: older group than other trials
- High risk: too aggressive and difficult to salvage
- ?T cell depletion: its effect

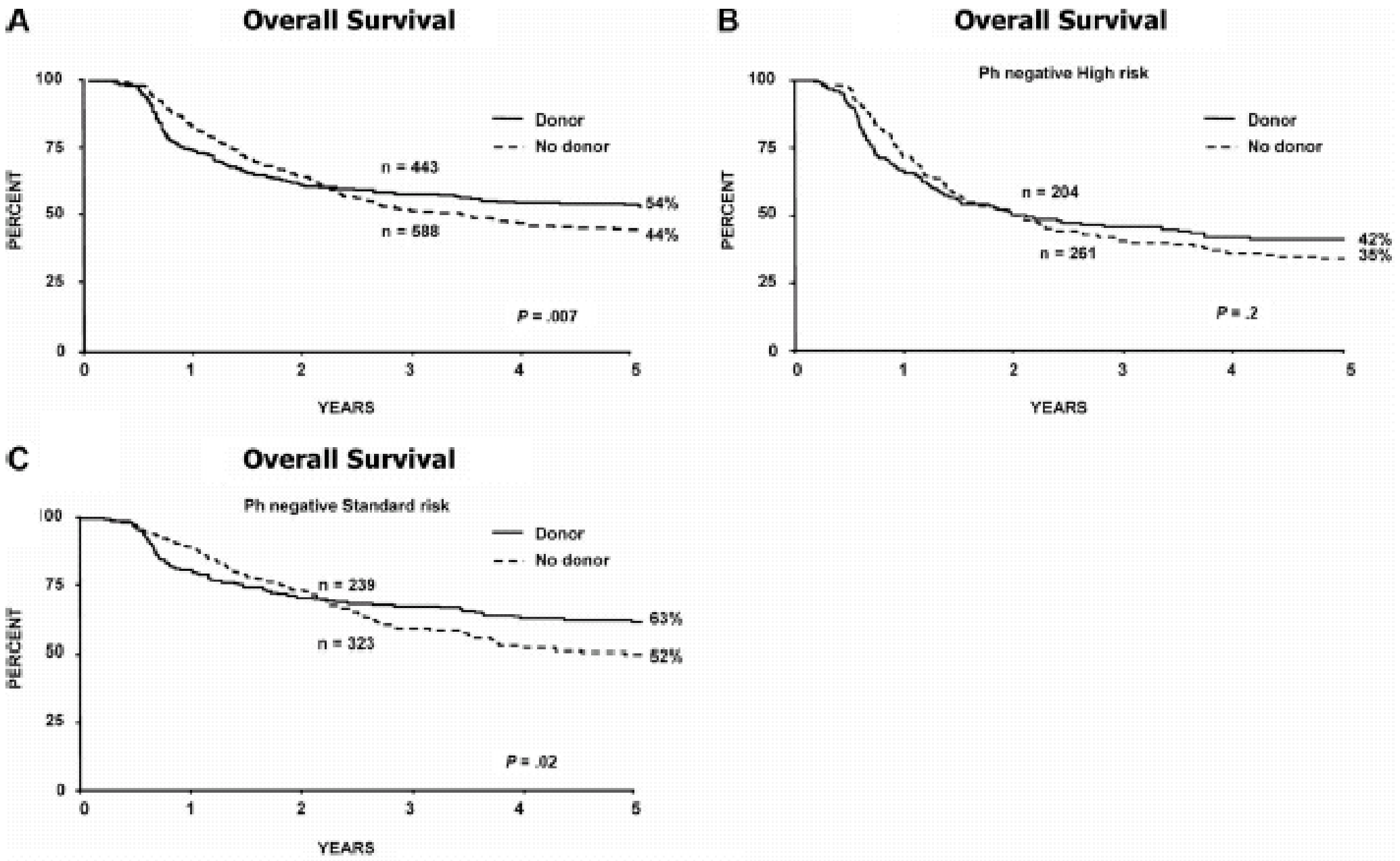
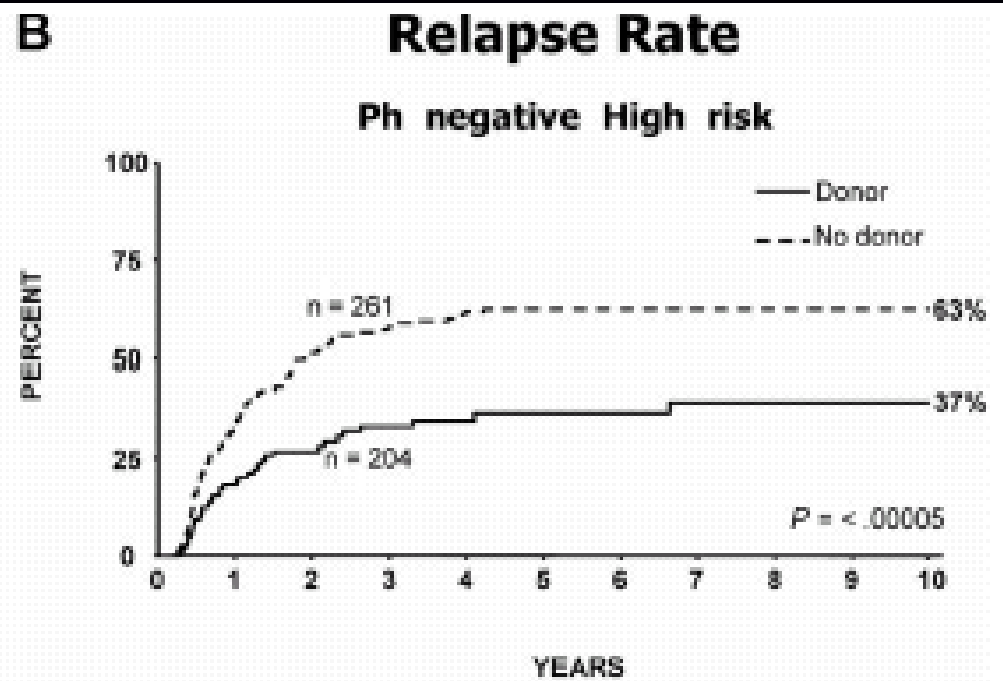
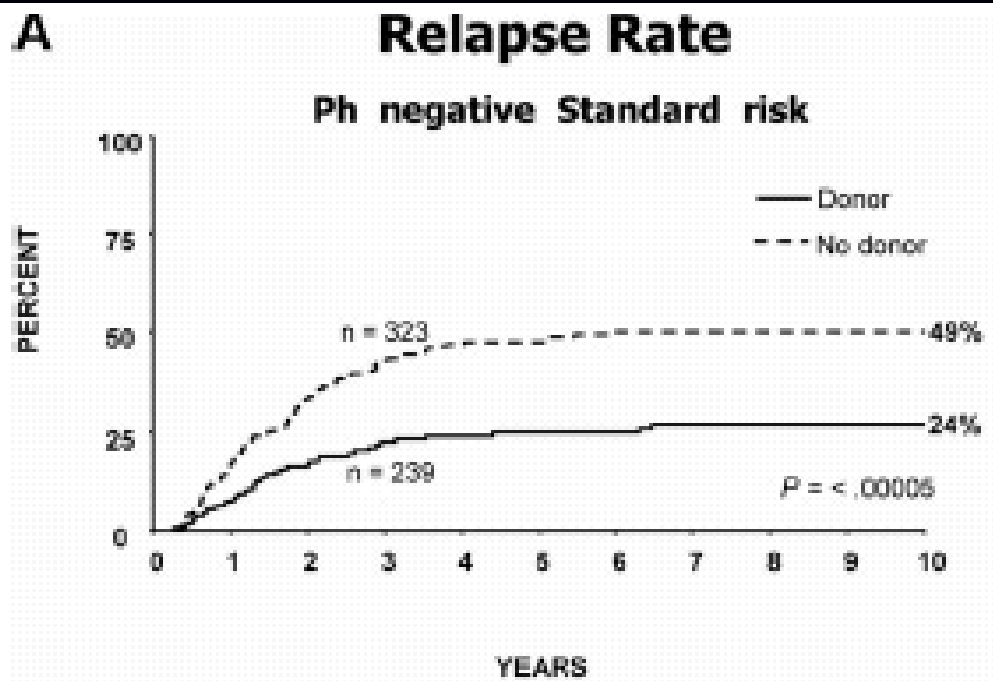


Figure 5. Overall survival from diagnosis for donor versus no-donor for Ph-negative patients censoring at first remission autologous transplantation. Estimation of the effect of sibling donor transplant versus chemotherapy in (A) all patients; (B) high-risk patients; and (C) standard-risk patients.



ALL-Allogeneic benefits

- **Allogeneic BMT till now only for 2nd CR and high risk 1st CR only**
- **Allogeneic BMT benefits overall even with age bias accounted for (53% vs 45% at 5yrs OS) in Ph- ALL, NO benefit for Auto BMT**
- **Benefit is seen for Std Risk**
- **Dutch study: Cornelissen (Blood 2009): allo benefit in standard risk 60% at 5 years**

ALL-Conclusions

- **Allogeneic BMT is Rx of choice for younger std risk ALL in 1st CR**
- **?Moving to transplanting the older and intensive paed's chemo for the younger?**
- **High risk young patients – consider matched MUD**
- **High Risk and older ALL – consider RIC**
- **TBI a key component of conditioning.**
- **Etoposide/TBI vs Cyclo/TBI. Marks et al (Blood 2006**
- **Preventing relapse important. Salvage often poor (MRC and French)**

Is there a GvL

- **Less than modest success with DLIs**
- **Haploidentical KIR mismatched transplants: impressive results with AML only: NOT ALL**
- **However-relapse rates much lower for those transplanted in the MRC trial**

Reduced Intensity

- **Mohty: Retrospective EBMT data**
- **97 patients: 1/3 1st CR. Rest 2nd CR/refractory**
- **3 year OS: 57% for 1st CR patients**
27% for 2nd/3rd CR, 20% refractory
- **Japanese series on 33 patients: OS30%**
- **Minnesota: Weisdorf Blood 2009. High risk**
- **OS 50%; relapse 36%**
- **Small series; high risk, some previous myeloablative**

Cytogenetics/Molecular

- **Age>35; High B count (30,000); T (100,000)**
- **Cytogenetics most important (MRC; Blood 2007 and SWOG, Blood2008). Supercede age**
- **Ph+; (4;11); complex; hypodiploid**
- **Molecular: Notch signalling in T-ALL 50%**
- **Notch indispensable for T cell development**
- **May confer a better prognosis**
- **Targeted treatment (GSIs): small molecule gamma secretase inhibitors. GI toxicity and low anti-leukaemic activity.**
- **Genome wide SNP analysis in B ALL: Pax5 in 32%; B related genes 40%**

New Drugs

- **Clofarabine: inhibits DNA polymerase and disrupts mitochondrial membranes**
- **Nelarabine in T-ALL**
- **Pro drug of guanine arabinoside**
- **1.5g/m² D1,3,5 21 day cycle**
- **31% CR rate. Grade 4 cytopenias**

CD22; epigenetic modifiers

Where is the new
Rituximab?

Ph+ ALL

- **Previously uniformly poor: majority do go into CR but often relapse during treatment**
- **BMT standard of care**
- **MRC: unrelated vs sibling. No difference**
- **Addition of imatinib (400-800mg) to frontline has improved more sustained CR BUT**
- **Without BMT—will still relapse**
- **Addition of Imatinib: upfront vs consolidation. Superior for upfront but OS similar**
- **No randomised trials**

Ph+ ALL

- **Stem cell not fully targeted.**
- **Post transplant imatinib**
- **Molecular monitoring post transplant felt to be of great utility**
- **Other kinases besides tyrosine involved: Src kinase**
- **Use of Dasatinib promising but thus far, short term FU**
- **DFS for Ph+ ALL currently running at 40-50%.**
- **Currently better than Ph neg high risk**
- **TKI resistance conferring mutations common**
- **Imatinib not thought to increase transplant mortality**

Minimal Residual Disease

- **Minimal Residual Disease: established in children (Cave NEJM 1998). Predictor of relapse. Less so in adults**
- **Germans: standard risk group. Rapid decline in MRD. 3 year relapse 0% (Bruggemann, GMALL)**
- **Sensitive. T cell and IgH rearrangements**
- **Laboratory technique and skill important. Published guidelines**
- **MRD post treatment predicting relapse less clear cut**

Other Issues

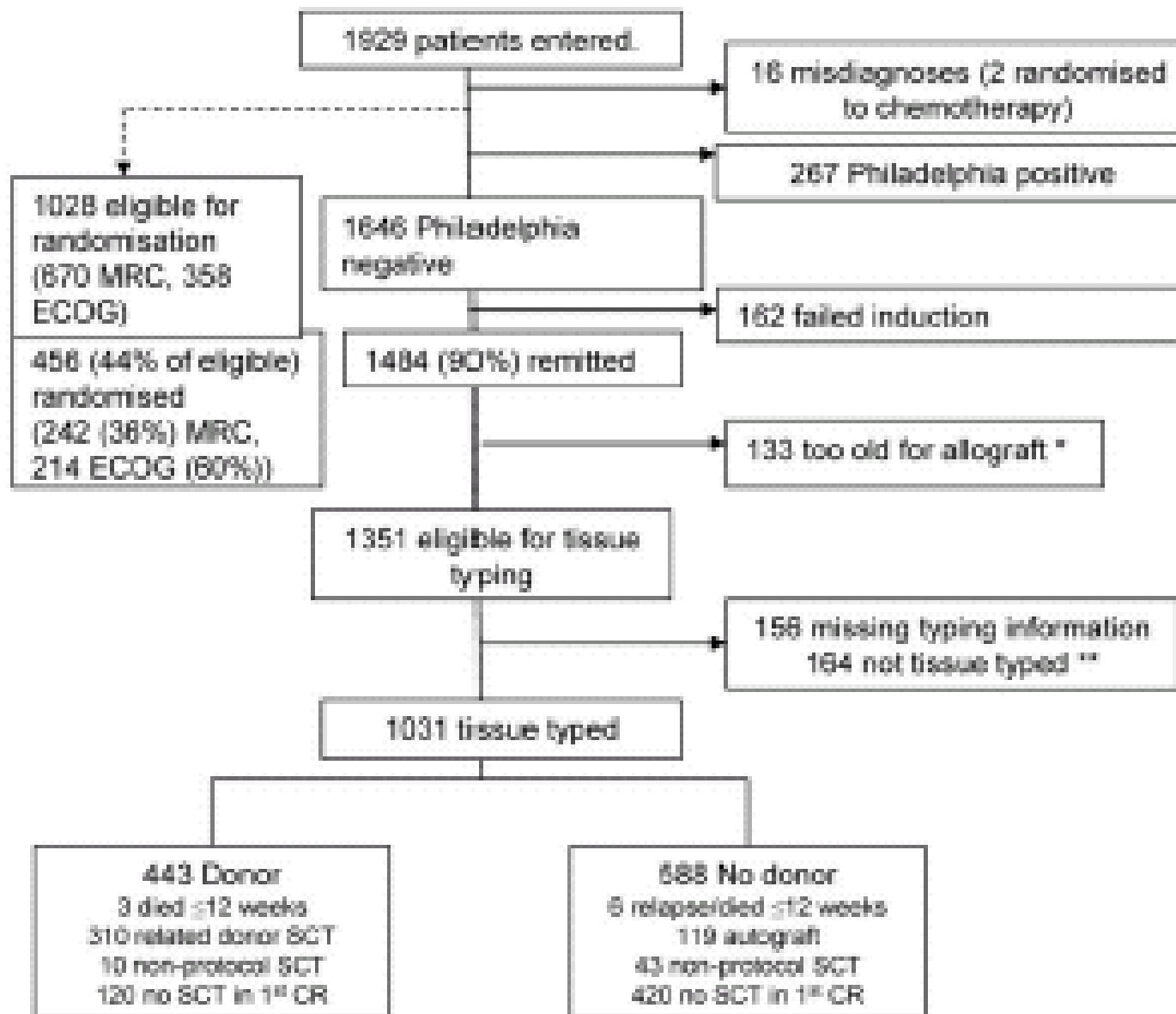
- **Speed of response: d7 response or d28. does that allow for stratification? Time to CR not a prognostic factor in MRC (Blood 05) but is in the LALA-87 trial**
- **Elderly?60. Often not addressed in trials. What shall we do?**
- **Cell Therapy: NK cells; CIK cells**

Study group	Study name	range, y	Study type	Main study question/aim
GIMEMA (Italy)	GIMEMA0904	15-60	Phase IV	Intensification of post-remission therapy in high-risk ALL according to MRD monitoring.
GMALL (Germany)	GMALL02	> 55	Phase IV	Reduced-dose chemotherapy plus rituximab.
GMALL (Germany)	GMALL01	15-65	Phase IV	Efficacy and tolerability of intensified induction and consolidation with subsequent therapy stratified to relapse risk. MRD-based evaluation of therapy continuation.
GMALL (Germany)	GMALL03	15-65	Phase IV	Efficacy and tolerability of intensified induction and consolidation in combination with rituximab with subsequent therapy stratified to relapse risk. MRD-based evaluation of therapy continuation.
NILG (Italy)	09/00	15-65	Phase IV	Variable intensity of post-remission therapy according to MRD.
PETHEMA (Spain)	LAL-RI/96	≥ 15	Phase IV	Improving outcome by chemotherapy intensification in adults not for HSCT in CR1.
PETHEMA (Spain)	LAL-AR-03	30-60	Phase IV	Protocol for high-risk ALL to evaluate chemotherapy or allogeneic HSCT according to early cytological response and MRD post-consolidation.
GRAALL (France)	GRAALL 2005	18-59	Randomized Phase III	Risk stratified. Randomizations between standard vs. intensified cyclophosphamide during late intensification/rituximab vs. no rituximab during induction and consolidation.
JALSG (Japan)	ALL202-O	25-64	Randomized Phase III	High-dose (3 g/m ²) vs. intermediate dose (1.5 g/m ²) MTX during most remission therapy
NCRI (UK) Children's Cancer and Leukaemia Group	UKALL2003	1-24	Randomized Phase III	Age-stratified. For 16-24 years, MRD-based randomizations to more intensive therapy.
NCRI (? with ECOG and SWOG)	UKALL14/E2907*	20-65	Randomized Phase III	Rituximab, epratuzumab, or both vs. standard chemotherapy
PALG (Poland)	PALG 5-2007	16-60	Phase III	To demonstrate that individualized therapy according to risk factors and monitoring of MRD results in improved outcome.
SWOG	SWOG	> 60	Randomized Phase III	Liposomal vincristine compared to conventional vincristine.
GMALL (Germany)	GMALL06	≥ 18	Phase II	Liposomal cytarabine in patients with CNS relapse.
GMALL (Germany)	GMALL07	≥ 18	Phase II	Tolerability of CAMPATH in relapsed T-cell ALL.
JALSG (Japan)	ALL202-U	15-24	Phase II	Feasibility of a pediatric-based treatment in young patients.
NCRI (UK)	MARALL	20-65	Phase II	Humanized antiCD20 plus antiCD22 plus chemotherapy in relapsed ALL.
Dana-Farber/Harvard (US)	06-254	18-50	Phase II	Safety and efficacy of a pediatric regimen including pegylated L-asparaginase.
CALGB (US) with COG (US)	CALGB 10403/ AALL0232	16-29	Phase II	Efficacy and tolerability of a pediatric regimen in patients up to the age of 30.
MDACC	2006-0328	No restrictions	Phase II	Hyper-CVAD with nelarabine in untreated T ALL.
MDACC	ID02-230	No restrictions	Phase II	Modified Hyper-CVAD with or without rituximab.
MDACC	ID02-229	No restrictions	Phase II	Hyper-CVAD and rituximab (for Burkitt-type).
SWOG	SWOGS0333	18-64	Phase II	Toxicity of an induction and consolidation schedule. Prognostic value of MRD. Gene expression studies.

Ph+ ALL

Study group	Study name	range, y	Study type	Study questions
European Intergroup	EsPhALL	1-17	Randomized Phase II/III	Good-risk patients imatinib vs. no imatinib Poor-risk, all get imatinib. All get HSCT if donor available, includes umbilical cord blood.
GRAALL (France)	GRAAPh02/2015	15-59	Randomized Phase III	Hyper-CVAD/standard Imatinib vs. "imatinib-based"
EWALL (Pan-European)	EWALLPh	> 65	Phase II	Dasatinib with low-dose chemotherapy.
GIMEMA (Italy)	LAL1205	≥ 15	Phase II	Dasatinib as induction therapy.
GMALL (Germany)	Imatinib/MRD/01/01	≥ 15	Phase II	Benefit of imatinib in induction.
GMALL (Germany)	GMALL STI1517-elderly 01/02	≥ 55	Phase II	Single-agent imatinib effectiveness and tolerability.
JALSG (Japan)	Ph+ ALL2008	15-64	Phase II	Intensified imatinib and chemotherapy during post-remission therapy.
MDACC	2006-0478	18-64	Phase II	Dasatinib with hyper-CVAD.
MRC/ECOG (UK/USA)	UKALLXII/ECOG 2993	15-65	Phase II	Benefit of imatinib in induction. Evaluation of sib/MUD HSCT. Benefit of imatinib as post HSCT. Maintenance.
CALGB	CALGB 10001	—	Phase II	Chemotherapy and imatinib followed by allogenic or autologous HSCT.

LESSENING DISPARITIES?

B**PATIENT FLOW DIAGRAM**

* age at entry ≥ 50 (original trial) or > 55 (revised trial)

** 130 no available siblings, 14 clinician choice (4 considered too old), 8 patient choice, 6 early death, 2 admin (insurance), 4 unknown reason

The trial recruited patients between 1993 and 2006. All patients from 15 to 59 years of age with newly diagnosed ALL, including Ph positive, received identical induction therapy, irrespective of risk assessment, including central nervous system (CNS) prophylaxis and treatment of CNS disease, if present at diagnosis. In 2003, the upper age limit of the study was raised to 64 years and for an allogeneic transplantation was raised to 54 from 49 years. All patients who had an HLA-matched sibling donor were assigned to receive an allogeneic transplant. Patients with the Philadelphia chromosome could also receive a matched unrelated donor transplant. Those who did not have an HLA-matched sibling donor, or were older than 50 years or (later) 55 years, were randomized to receive a single autologous transplant or consolidation/maintenance therapy. Prior to receiving the assigned or randomized therapy, all patients received intensification with high-dose methotrexate. In this study, patients older than 35 years or those with a high WBC count at presentation ($\geq 100 \times 10^9/L$ for B lineage and $\geq 30 \times 10^9/L$ for T lineage) along with all patients with the Philadelphia chromosome were deemed to be high risk. All the others were classified as standard risk. Time to remission was not an independent risk factor in this

C**Non-Relapse Mortality (%)**

	3 months	6 months	1 year	2 years
High Risk				
Donor	1.5	7.3	26.0	35.8
No Donor	1.2	2.0	10.3	13.6
Standard Risk				
Donor	0.4	3.4	17.6	19.5
No Donor	0.3	1.2	5.3	6.9