INDUCTION THERAPY FOR ADULTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA (ALL):
RESULTS OF OVER 1,500 PATIENTS FROM THE INTERNATIONAL ALL TRIAL:
MRC UKALL XII / ECOG E2993

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Short title: Induction therapy in acute lymphoblastic leukemia

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ABSTRACT

The international ALL study was designed to prospectively define the optimal therapy for adults ≤ 60 years with newly diagnosed ALL. All patients received identical induction therapy and 91% achieved a complete remission (CR). Patients ≤ 50 years with a compatible sibling are assigned to an allogeneic transplant; the others are randomized between an autologous transplant or consolidation / maintenance therapy for 2.5 years. Patients who did not achieve a CR after induction had an overall survival of 5% compared with 45% for patients who went into CR. Factors at diagnosis predicting for overall survival and disease-free survival are age (p = .001); white cell count <30,000/µL for B-lineage or <100,000/µL for T-lineage (p = .001) and immunophenotype; T-lineage versus B-lineage (p = .001).

The data demonstrate that achieving a CR with induction therapy is a sine qua non for a long-term survival in adult ALL. Furthermore, the induction regimen is highly efficacious as remission-inducing therapy with >90% response rate. This large database has validated several previously identified independent prognostic factors in ALL such as age, white count at presentation, cytogenetics and immunophenotype. However, the achievement of CR within 4 weeks does not appear to be an independent prognostic factor.
INTRODUCTION

Over the past five decades the results of treatment for childhood ALL have evolved from a median survival of 2 months from diagnosis\(^1\) to overall survival rates that approximate 80% of children with ALL.\(^2,3\) Although the outcome in adults has certainly improved over the same period, the overall long-term survival for adults is only in the range of 30%-40% for patients less than age 60, and is less than 10% for ALL patients over the age of 60 years.\(^4-15\)

Historically, several important risk factors have been recognized. One of the most significant prognostic factors has been the response to the initial treatment. In many studies response to initial therapy has been an overriding prognostic factor regardless of the initial disease features.\(^2,5\) In addition, more recent data suggest that the presence of residual leukemia in the bone marrow on day 7 or 14 has been associated with a worse prognosis, although the published data are predominantly in childhood ALL.\(^16,17\)

Cytogenetic abnormalities are independent prognostic factors in ALL. The most important chromosomal abnormality in ALL is the Philadelphia chromosome characterized by the balanced translocation t(9;22)(q34;q11). Other major cytogenetic abnormalities include t(4;11)(q21;q23) involving the MLL gene; other translocations such as t(8;14), t(1;19) or t(10;14) and other structural abnormalities including 9p, 6q or 12p abnormalities.\(^18,19\) The Philadelphia chromosome can also be detected by the polymerase chain reaction for the bcr-abl fusion protein and is present in 20%-30% of adults with ALL.\(^20-22\) Philadelphia chromosome positivity confers a uniformly poor prognosis with standard chemotherapy.

The initial white cell count at diagnosis is an important prognostic factor reported in every study of ALL.\(^5,9\) An arbitrary cutoff of 30,000/µL for B-lineage ALL or 100,000/µL for T-ALL has often been used in clinical studies.\(^5,14\)
The outcome of therapy for adult ALL is directly dependent on age. There are very few long-term survivors among patients who are over age 60.\textsuperscript{7,8} Although the relationship between the age and prognosis for patients between the age 20 and 60 is a continuum, most clinical studies have chosen an arbitrary age of 30, 35 or 40 years as a cutoff.\textsuperscript{5,6,8,23-25}

The immunophenotype has traditionally been correlated with prognosis,\textsuperscript{5,26,27} although with the advent of molecular diagnostic tools and more intensive therapies this may no longer be an independent prognostic factor.\textsuperscript{14}

Finally, gender has been reported to be an independent prognostic factor with males doing less well than females, possibly due to the impact of testicular relapse. However, these data have been reported in childhood ALL\textsuperscript{28-32} and the applicability to adult ALL remains uncertain.

In 1993 the Medical Research Council (MRC) in the United Kingdom together with the Eastern Cooperative Oncology Group (ECOG) in the United States initiated a joint international study, UKALL XII / ECOG 2993, that was designed to prospectively define the optimal therapy for adult patients with newly diagnosed ALL. The study employs uniform induction therapy and early intensification for all patients irrespective of their presumed risk group. The prescribed post-remission therapy is intended to evaluate the role of allogeneic and autologous transplantation versus the more standard protracted consolidation maintenance therapy. Over 1,700 patients have already been registered to this trial and the overall outcome data are available on over 1,500 patients with a median follow-up of 5 years. In this large cohort of patients the results of induction therapy and an analysis of prognostic factors are reported herein.
PATIENTS AND METHODS

The international ALL trial was initiated in 1993 and involves a major transatlantic collaboration between the Medical Research Council (UKALL XII) in the United Kingdom and the Eastern Cooperative Oncology Group (ECOG E2993) in the United States. [Fig. 1] All patients $\geq$15 and less than 60 years old were eligible for this study irrespective of the prognostic factors at presentation, including Ph-positive patients. All patients received the identical induction therapy, irrespective of risk assessment, including CNS prophylaxis and treatment of CNS disease, if present at diagnosis. The study was approved by the Institutional Review Board of each treating center for these studies and informed consent was given according to the Declaration of Helsinki.

Induction Therapy (Table 1)

All patients received phase I of induction (weeks 1-4), which consisted of daunorubicin 60 mg/m$^2$ intravenously (IV) on days 1, 8, 15 and 22; vincristine 1.4 mg/m$^2$ IV on days 1, 8, 15 and 22; L-asparaginase 10,000 IU IV or intramuscularly on days 17-28 and prednisone 60 mg/m$^2$ in divided doses orally on days 1-28; methotrexate 12.5 mg was given intrathecally (IT) on day 15. The L-asparaginase was initially given at a high dose of 10,000/m$^2$, among ECOG patients only, during the years 1993-2000. After the analysis revealed that there was no difference in efficacy, compared with 10,000 IU total, ECOG reverted to the lower dose of L-asparaginase.

Patients went on to phase II of induction, whether or not they had residual leukemia in their marrow at the end of phase I. Phase II (weeks 5-8) consisted of cyclophosphamide 650 mg/m$^2$ IV on days 1, 15 and 29, cytarabine 75 mg/m$^2$ IV on days 1-4, 8-11, 15-18 and 22-25.
mercaptopurine 60 mg/m² was administered orally on days 1-28 and methotrexate 12.5 mg IT was given on days 1, 8, 15 and 22.

A diagnostic spinal tap was performed on all patients. If central nervous system (CNS) leukemia is present at diagnosis then methotrexate IT or via an Omaya reservoir is given weekly until the blast cells are no longer present in the spinal fluid. In addition, 2,400 cGy cranial irradiation and 1,200 cGy to the spinal cord are administered concurrently with phase II. For such patients with CNS leukemia at presentation the intrathecal methotrexate is not administered during phase II.

Patients were evaluated for response at the end of each of the two phases of induction. Those who achieved a complete remission went on to intensification and post-remission consolidation part of the study.

Following induction therapy all patients under 50 years of age who had an HLA-compatible sibling were assigned to an allogeneic transplant. All other patients were randomized between an autologous transplant and standard consolidation / maintenance therapy. For patients who were Ph-positive, a search for a matched unrelated donor was offered, if they did not have a histocompatible family donor.

**Intensification Therapy**

Following this assignment or randomization all patients received intensification with 3 cycles of high-dose methotrexate, 3g/m² IV – given on days 1, 8 and 22 followed by L-asparaginase 10,000 IU on days 2, 9 and 23 and standard leucovorin rescue. Following this intensification patients went on to receive their previously assigned or randomized therapy.
Transplant Regimen

The conditioning regimen for both the allogeneic and autologous transplant patients was identical, consisting of total body irradiation (TBI) for a total dose of 1320 cGy, given twice daily in 6 fractions of 220 cGy on days –6 to –4 followed by etoposide 60 mg/kg IV on day –3.

There was no post-transplant therapy specified for either the allogeneic and autologous transplant patients. The exception was for Ph-positive patients, for whom α-interferon, $3 \times 10^6$ units, was given 3 times a week for 15 months.

Consolidation / Maintenance Therapy

Patients randomized to consolidation / maintenance therapy receive CNS prophylaxis, if leukemia was not present at diagnosis. Intrathecal cytarabine, 50 mg, is given weekly for 4 weeks together with 2,400 cGy cranial irradiation. In addition, 50 mg of intrathecal cytarabine is given on four occasions 3 months apart during maintenance therapy.

This non-transplant post-remission therapy includes 4 cycles of consolidation followed by maintenance therapy. Cycle 1 of consolidation consisted of cytarabine 75 mg/m² IV on days 1-5; etoposide 100 mg/m² IV on days 1-5; vincristine 1.4 mg/m² IV on days 1, 8, 15 and 22 and dexamethasone 10 mg/m² was administered orally on days 1-28.

Cycle 2 started 4 weeks after cycle 1 and consisted of cytarabine 75 mg/m² IV on days 1-5 and etoposide 100 mg/m² IV on days 1-5.
Cycle 3 was started 4 weeks after cycle 2. It consisted of daunorubicin 25 mg/m² IV on days 1, 8, 15 and 22, cyclophosphamide 650 mg/m² IV on day 29, cytarabine 75 mg/m² IV on days 31-34 and 38-41 and thioguanine 60 mg/m² orally on days 29-42.

Cycle 4 of consolidation was identical to cycle 2 and was to begin 8 weeks after conclusion of cycle 3.

Maintenance therapy consisted of vincristine 1.4 mg/m² i.v. every 3 months, prednisone 60 mg/m² orally for 5 days every 3 months, daily 6-mercaptopurine 75 mg/m² orally per day and methotrexate 20 mg/m² orally or i.v. once a week for two and a half years. The maintenance therapy was to continue for a total of two and a half years from start of intensification.

Table 2 outlines the prognostic risk factors used in this study for analyses of the results for Ph-negative patients. Ph-positive patients were considered the highest risk group and their therapy included also the option of a matched unrelated donor transplant (Fig. 1). Patients who were Ph-negative were considered at high risk if they had any of the following: age ≥ 35 years; time to CR > 4 weeks or WBC > 30,000/µL for B-lineage ALL and > 100,000/µL for T-lineage ALL. Ph-negative patients who had none of these risk factors were considered to be at standard risk.

**Statistical Considerations**

The main analyses are of survival and of disease-free survival defined as time to death or to relapse or death, respectively. Actuarial event percentages were calculated by the Kaplan-Meier methods. For patients without an event, observation was censored at the last contact date. The log rank method was used for initial univariate comparisons between groups.
Multivariate analysis was performed by logistic regression (for complete remission), or Cox regression (for survival and event-free survival) using the SAS statistical package.

Prognostic variables examined were Philadelphia-chromosome status, age, gender, white blood cell count, immunophenotype and time to first remission. All were treated as categorical variables for most analyses, but additional multivariate analyses were done with age and WBC as continuous variables. The purpose was not to define new prognostic variables, but to verify known ones and to suggest groups which might be used in the future for subgrouping treatment comparisons, particularly where the balance of risk and benefit may change over subgroups, such as transplant versus chemotherapy.

RESULTS

As of December 31, 2004 a total of 1713 patients were registered to the study; however, the results presented include only mature data as of October 2003 that were available for 1,521 patients who had completed induction therapy and in whom the remission status was known.

Induction

Table 3 summarizes the overall results from induction therapy. The complete response (CR) was 91% for all 1,521 patients and was 93% for the 1,153 Ph-negative patients and 83% for the 293 Ph-positive patients. For the 533 Ph-negative patients with standard risk (based only on age and WBC at diagnosis) the CR rate was 97% and it was 90% for the 590 Ph-negative patients at high risk. At the time of collection of data for this report the Ph status was unknown for 75 patients (5%).

Overall Survival
The overall survival rate, at 5 years for all patients in this study was 38%, 41% for Ph-negative patients and 25% for Ph-positive patients. (Fig. 2)

Fig. 3 describes the overall survival for the 22 patients who did not achieve a CR on this study – i.e. following two phases of induction. The overall survival in this small group was only 5% compared with 45% overall survival for Ph-negative patients who achieved complete remission on the study.

Toxicity.

The overall mortality in induction, defined as from time of registration to the study, was 4.7% (54 out of 1153) for Ph-negative patients and 5.5% (16 out of 293) for Ph-positive patients. 29 patients died from infection, the most important being Aspergillus (7 patients). 5 patients died from hemorrhage (3 pulmonary and 2 cerebral), 2 patients died from thromboses (possibly related to l-asparaginase) and one patient died from tumor lysis. The remaining 10 patients died from causes described as multi-organ failure which may also have been related to an infectious etiology.

Prognostic Factors.

Fig 4 demonstrates the overall superiority among Ph-negative patients who had standard risk versus those at high risk. The differences are significant whether assessing this from diagnosis or from the point when complete remission has been achieved.

778 patients achieved complete remission during the 4 weeks of phase I of induction. The 5-year survival for this group is 46%. For the 157 patients who required more than one cycle of induction to achieve CR, i.e., more than 4 weeks, the 5-year survival was 41% (Fig. 5). This difference is not significant by univariate or multivariate analysis.
Fig. 6 illustrates the overall survival for Ph-negative patients by age. There is a decreasing survival with increasing age with a significant cutoff at age 35 (p = <.0001).

Fig. 7 illustrates the overall survival by immunophenotype with a significant slight advantage for the overall group with T-lineage compared to the group with B-lineage (p = .001).

Table 4 summarizes the overall risk factors that were significant by multivariate analyses for Ph-negative patients either for the achievement of complete remission or for the overall survival and disease-free survival. For the achievement of CR, age ≥ 35 years and gender were the only significant factors. For overall survival and disease-free survival, age ≥ 35 years; WBC at presentation of 30,000/µL for B-lineage ALL and 100,000/µL for T-lineage and immunophenotype were significant risk factors. Table 5 summarizes the results of multivariate logistic or Cox regression analysis with age and WBC as continuous variables. Time to achievement of complete remission was not an independently significant risk factor here. Analyzing the data by censoring at transplant, performed at any time, made little difference to the effect of age and WBC and, more importantly, did not affect the lack of independent significance of time to achievement of complete remission.

Table 6 summarizes the overall prognostic factors in this study. The best group is the Ph-negative patients who are at low risk, for whom the long-term overall survival was 55%. Ph-negative patients who had one adverse risk factor (either age >35 years or high WBC) had an overall survival of 34%. On the other hand, Ph-negative patients who were older than 35 years and had a WBC > 100,000/µL at presentation, were considered to be at very high risk with an overall survival of only 5%; worse than the Ph-positive group as a whole.
DISCUSSION

In this report no attempt is made to analyze the post remission therapies, as the study is ongoing. The data are based solely on results of induction therapy, irrespective of the post remission therapy assignment or randomization. With such a large database the aim of this report is to examine long-established prognostic factors and see whether these can be validated in this ongoing trial. Furthermore, the results of induction therapy in this transatlantic study, involving more than 100 participating centers, have been described.

The thrust of this report has focused on results for Ph-negative patients; reference to the Ph-positive patients was only made in passing for comparative purposes. The study itself has already been closed for Ph-positive patients and the preliminary details of this have been reported.34

The complete response rate of 93% for Ph-negative patients is certainly at least as good as anything that has been published for such patients. However, caution is necessary in interpreting long-term outcome based on the complete response rate, as the overall survival and disease-free survival may be influenced to the same or greater degree by the type and intensity of post-remission therapy. Nevertheless, this high response rate confirms the efficacy of this induction regimen, with its relatively low toxicity, allowing for a very high percentage of patients to receive post-remission therapy. The fact that patients who did not achieve a complete remission at the end of induction did so poorly (Figure 3) demonstrates that for any realistic hope of survival it is critical that complete remission be achieved with induction therapy.

This study confirmed the importance of age as an important prognostic factor for adult ALL and is in the line with previous studies of ALL.2,5,6,8-10,13,14,23-25,35,36
Achievement of a complete response within 4 weeks of therapy has been a time honored prognostic factor for adult patients with ALL. This was carefully analyzed in this study both by univariate and multivariate analyses. The achievement of a complete remission at the end of induction or 4 weeks of therapy could not be confirmed as an independent prognostic factor, either by univariate or multivariate analyses. Although this result may appear surprising at first, it must be remembered that the 4-week cutoff is an arbitrary one and does not preclude the notion that an early response to therapy confers a better prognosis. Recent reports in childhood ALL have suggested that a very early response within 7-14 days is associated with the best prognosis, however, this has never been prospectively confirmed in adult ALL, although some therapeutic strategies in the most recent protocols have attempted to use the very early response as a prognostic factor for risk-adapted therapy.

It is clearly recognized that prognostic factors are dependent on post-remission therapy no less than induction therapy. In contrast to most prior studies, this trial included transplants as a major post-remission modality. In theory, this may have blunted the importance of certain classic prognostic factors, especially time to complete remission. However, an analysis of the data, censoring at transplantation performed at any time, did not materially alter the significance of the prognostic factors or, more importantly, the lack of significance of time to complete remission.

The data clearly indicate the superiority of outcomes of Ph-negative patients over the outcomes of those with the Ph-positive abnormality. While other cytogenetic features clearly have prognostic significance – most important being t(4;11), t(8;14), t(1;19), t(10;14) as well as other structural abnormalities such as 9p, 6q, -7 or +8, 12p – these factors were not prospectively written into this study when this was designed in the early 1990s. This analysis has therefore been limited to the Ph-negative group as a whole. Cytogenetic analysis, however,
is a mandatory part of this study and the data will be collected and reported at the end of this study.

In this study gender was an independent predictive factor for complete remission although not for an overall survival and disease-free survival. Somewhat surprisingly, males did better than females which is in contrast to published data in childhood ALL.\textsuperscript{28-32} It is not known whether this is related to a higher incidence of testicular relapse in childhood ALL or is associated with the higher frequency of T-ALL in children. Furthermore, in one study of adult ALL males had an inferior outcome.\textsuperscript{24}

Immunophenotyping has long been considered a critical part of the diagnostic evaluation of patients with ALL.\textsuperscript{26,32} Until recently, the prognostic usefulness of immunologic classification has been reproduced in virtually every study. While a detailed immunophenotypic analysis of patients in this study will be performed at the closure of this trial, in this report the available data at this time permit only a more limited comparison of the overall T-lineage versus B-lineage looking at the entire group as a whole. The limitation of this is recognized and a more complete analysis of the immunophenotype at various stages of maturation will ultimately provide more accurate prognostic information. Cytogenetic and molecular classification may, in the future, supersede immunophenotyping as a critical diagnostic tool. Already in one very recent report, immunophenotyping was not an independently significant prognostic factor.\textsuperscript{14}

Looking at the overall prognosis among all groups of patients it was noted that Philadelphia chromosome negative patients who were older than 35 years and had a white count over 30,000/µL for B-lineage or over 100,000/µL in T-lineage, had an extremely poor prognosis which was even worse than the Ph-positive group as a whole (Table 6). This, of course, has not been compared with the Ph-positive patients who have similar features. But these data suggest that alternative therapies should be considered for this group. It is likely that allogeneic
transplants from alternative donors will also be incorporated in future trials for these patients at very high risk.

Newer therapies are continually being proposed for adult ALL and some recent data suggest that intensifying the early phases of therapy may impact on survival. Such advances – if they are confirmed in large prospective studies – will further refine the prognostic information and the selection of appropriate therapies for adults. Furthermore, molecular information, including studies of minimal residual disease at early time points as well as advances in genomics are likely to further define the best prognostic factors in ALL. Until these newer modalities have been confirmed in prospective studies, the more traditional prognostic factors continue to guide current therapy of adult ALL.

Other current studies also question whether specific age groups may benefit from more intensified treatment regimens. These approaches, if confirmed in prospective studies, may also impact on the future therapy of ALL.

In summary, the data described in this study have reported on one of the largest studies ever conducted in adult ALL based on data from multiple institutions in two large cooperative groups in both sides of the Atlantic. The achievement of an overall CR rate of over 90% in this study (93% for Ph-negative patients) is higher than previously reported in large studies. Defining the prognostic factors described in this study may have particular relevance, especially in light of the fact that of all the current large studies this prospective trial has more intensive post-remission therapies (allogeneic or autologous transplantation) than others. Furthermore, every single patient (apart from the Ph-positive patients) received the identical therapy throughout induction and post-remission therapy, irrespective of their risk groups. Finally, in
contrast to previously published data, time to complete remission could not be demonstrated in this study to be an independently significant prognostic factor.
REFERENCES


FIGURE LEGENDS.

**Figure 1.** A simplified overall schema of the study.

**Figure 2.** Overall survival for all patients in this study (a) and by Ph status (b).

**Figure 3.** Overall survival for all patients in CR and for the 22 patients who did not achieve CR at the end of induction therapy.

**Figure 4.** Patients who were in standard risk had a far better overall survival from diagnosis, including all patients (a) or those who achieved CR (b).

**Figure 5.** Overall survival by time to achieve a CR.

**Figure 6.** Overall survival by age.

**Figure 7.** Overall survival by immunophenotype.
# Table 1

MRC UKALL XII / ECOG E2993 – Induction Therapy

## Phase I (weeks 1-4)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daunorubicin</td>
<td>60mg/m²</td>
<td>IV</td>
<td>Days 1, 8, 15 and 22</td>
</tr>
<tr>
<td>Vincristine</td>
<td>1.4mg/m²</td>
<td>IV</td>
<td>Days 1, 8, 15 and 22</td>
</tr>
<tr>
<td>L-asparaginase</td>
<td>10,000 units</td>
<td>IV or IM</td>
<td>Days 17 → 28</td>
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<tr>
<td>Prednisone</td>
<td>60mg/m²</td>
<td>PO</td>
<td>Days 1 → 28</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>12.5mg</td>
<td>IT</td>
<td>Day 15</td>
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## Phase II (weeks 5-8)

<table>
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<th>Drug</th>
<th>Dose</th>
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</thead>
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<tr>
<td>Cyclophosphamide</td>
<td>650mg/m²</td>
<td>IV</td>
<td>Days 1, 15 and 29</td>
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<tr>
<td>Cytarabine</td>
<td>75mg/m²</td>
<td>IV</td>
<td>Days 1 → 4, 8 → 11, 15 → 18, 22 → 25</td>
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<td>6-mercaptopurine</td>
<td>6mg/m²</td>
<td>PO</td>
<td>Days 1 → 28</td>
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<tr>
<td>Methotrexate</td>
<td>12.5mg</td>
<td>IT</td>
<td>Days 1, 8, 15 and 22</td>
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Table 2: Risk factors used for this study

*Ph-neg ALL – Risk assignment*

<table>
<thead>
<tr>
<th>High Risk</th>
<th>Standard Risk</th>
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<tr>
<td>Any of the following:</td>
<td>None of the following:</td>
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<tr>
<td>Age &gt; 35 years</td>
<td></td>
</tr>
<tr>
<td>Time to CR &gt; 4 weeks</td>
<td></td>
</tr>
<tr>
<td>WBC &gt; 30,000/μL (B Lineage)</td>
<td></td>
</tr>
<tr>
<td>&gt;100,000/μL (T Lineage)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-----</td>
</tr>
<tr>
<td><strong>All patients</strong></td>
<td>1,521</td>
</tr>
<tr>
<td><strong>Ph-positive</strong></td>
<td>293</td>
</tr>
<tr>
<td><strong>Ph-negative</strong></td>
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<td>(i) All patients</td>
<td>1,153</td>
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<td>(ii) Standard risk*</td>
<td>533</td>
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<tr>
<td>(iii) High risk*</td>
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</tr>
<tr>
<td>(iv) Unknown</td>
<td>30</td>
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* Risk stratification at diagnosis based on age and WBC only
Table 4: Risk Factor shown to be significant  
**MRC UKALL XII / ECOG E2993**  

### Risk Factors by Multivariate Analysis for Ph negative patients CR

<table>
<thead>
<tr>
<th>Age</th>
<th>CR Percentage</th>
<th>vs</th>
<th>Age  ≥  35</th>
<th>CR Percentage</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 35</td>
<td>630/651 (96%)</td>
<td>vs</td>
<td>Age ≥ 35</td>
<td>305/344 (89%)</td>
<td>&lt; .0001</td>
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<tr>
<td>Male</td>
<td>587/619 (95%)</td>
<td>vs</td>
<td>Female</td>
<td>348/383 (91%)</td>
<td>.04</td>
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### Overall Survival and Disease Free Survival

<table>
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<th>Age</th>
<th>vs</th>
<th>Age  ≥  35</th>
<th>p-value</th>
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<tr>
<td>Age &lt; 35</td>
<td></td>
<td>Age ≥ 35</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>WBC (30,000 B-lineage, 100,000 T-lineage)</td>
<td></td>
<td></td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>T-lineage</td>
<td>vs</td>
<td>B-lineage</td>
<td>.001</td>
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Table 5: Multivariate logistic or Cox regression analysis with age and WBC as continuous variables

<table>
<thead>
<tr>
<th></th>
<th>Risk factor</th>
<th>Odds ratio/ Hazard ratio</th>
<th>p-value</th>
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<tbody>
<tr>
<td><strong>CR</strong></td>
<td>Age</td>
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<td>&lt; .0001</td>
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<tr>
<td></td>
<td>Gender</td>
<td>0.631</td>
<td>.048</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>Age</td>
<td>1.027</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td><strong>Survival</strong></td>
<td>WBC</td>
<td>1.002</td>
<td>&lt; .0001</td>
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<tr>
<td></td>
<td>B or T lineage</td>
<td>0.770</td>
<td>.018</td>
</tr>
<tr>
<td><strong>Disease Free</strong></td>
<td>Age</td>
<td>1.021</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td><strong>Survival</strong></td>
<td>WBC</td>
<td>1.002</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td></td>
<td>B or T lineage</td>
<td>0.738</td>
<td>.0047</td>
</tr>
<tr>
<td>Prognostic Group</td>
<td>Age Criteria</td>
<td>WBC Criteria (T-cell)</td>
<td>WBC Criteria (B-cell)</td>
</tr>
<tr>
<td>-----------------</td>
<td>-------------</td>
<td>-----------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Ph-neg - low risk</td>
<td>Age &lt; 35  AND WBC &lt; 100,000</td>
<td>or 30,000 (B-cell)</td>
<td></td>
</tr>
<tr>
<td>Ph-neg - intermediate risk</td>
<td>Age &lt; 35 AND WBC &gt; 100,000</td>
<td>or 30,000 (B-cell)</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td>Age ≥ 35  AND WBC &lt; 100,000</td>
<td>or 30,000 (B-cell)</td>
<td></td>
</tr>
<tr>
<td>Ph-positive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ph-neg - very high risk</td>
<td>Age &gt; 35  AND WBC &gt; 100,000</td>
<td>or 30,000 (B-cell)</td>
<td></td>
</tr>
</tbody>
</table>
MRC UKALL XII / ECOG E2993

INDUCTION

- HLA donor < 50yrs
- No donor or > 50yrs

Phase I
Phase II

MUD
Ph+

Assign

Randomise

- Autograft
- Consolidation / Maintenance

HD MTX X 3

- Allograft
- Autograft

Consolidation/Maintenance

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Overall Survival

At risk: 1521

Fig 2(a)
Fig 3

Ph Negative

- CR
- No CR on study

( but alive at end of induction )

n=935

n=22

45%

5%

Time (Years)

Percent
Fig 4(a)
Fig 5

Ph Negative

- CR < 4 weeks (phase I)
- CR ≥ 4 weeks

Percent

Time (Years)

n=778
46%

n=157
41%

Univariate
Multivariate
p = .2
p = .5
Fig 6
Fig 7

- T Lineage
- B Lineage

Percent vs. Time (Years)

- n=190, 48%
- n=627, 41%

p = .003 (multivariate)
Induction therapy for adults with acute lymphoblastic leukemia (ALL): results of over 1,500 patients from the international ALL Trial: MRC UKALL XII / ECOG E2993

Jacob M Rowe, Georgina Buck, Alan K Burnett, Raj Chopra, Peter H Wiernik, Susan M Richards, Hillard M Lazarus, Ian M Franklin, Mark R Litzow, Niculae Ciobanu, H G Prentice, Jill Durrant, Martin S Tallman and Anthony H Goldstone

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